A Modular, Argon-Driven Flow Platform for Natural Product Synthesis and Late-Stage Transformations

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Abstract: A modular flow platform for the synthesis of natural products and their analogs was designed. To access different reaction setups with a maximum of flexibility, interchangeable 3D-printed components serve as backbone. By switching from conventional liquid- to gas-driven flow, reagent and solvent waste is minimized which translates into an advantageous sustainability and economy profile. To enable inert conditions, practical “Schlenk-in-flow” techniques for the safe handling of oxygen- and moisture sensitive reagents were developed. Adopting these techniques, reproducible transformations in natural product synthesis were achieved.

In recent years, flow chemistry has been elevated from a prerogative of petrochemical industry to a technology of enormous value for chemical synthesis.[1] As flow reactors show outstanding heat and mass transfer, flow chemistry has recently been outlined as primary key for sustainable manufacturing.[2] Transformations viewed impracticable under batch conditions can be enabled by the precise reaction control of flow reactors while offering improved scalability.[1,3] Despite the advantages of flow chemistry, virtually all endeavors towards more complex molecules are still performed in batch.

As our research program focuses on the synthesis of natural products and their analogs, we envisaged to implement flow chemistry to expand our synthetic options and overcome scalability and reproducibility issues.[4] Indeed, the transfer of protocols from one chemist to another has been realized a critical point, with some even perceiving a “reproducibility crisis”.[5]

With most commercial flow reactors, established equilibration protocols lead to partial loss of substrate on small scale. When air- and moisture-sensitive reactions are performed, flow reactors are either dried with several reactor volumes of the reagents or by flushing with anhydrous solvent before dissolved reactants are injected.[1a,3c,6,7] While in principle, reactions with minute quantities can be performed by using chip reactors with capillaries of an inner diameter of 100−250 µm, clogging by precipitating solids limits feasible transformations and scalability.[1a] Employing more robust tube reactors (inner diameter 0.8−1.6 mm), precipitates can often be kept in turbid flow.[8] In liquid-driven flow, a transient between sample solution and solvent forms resulting in dispersion phenomena at front and back of the injected sample and leads to hard-to-predict reaction outcome in these segments. Therefore, the pre- and postrun are discarded and only the product obtained under steady state conditions is collected, the yield is corrected likewise. (Figure 1A).[1a]

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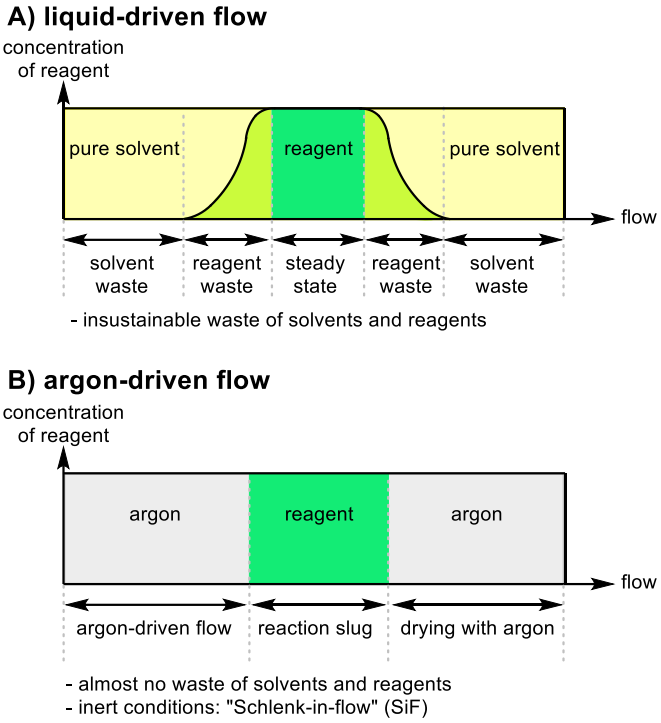


Figure 1. A) Liquid-driven flow resulting in dispersion phenomena between pure solvent and reagent solution. B) Argon-driven, segmented flow regime of reagent solution without dispersion.

This practice results in a high material loss percentage for small amounts, making this procedure unsuitable for late-stage applications in natural product synthesis. Contrarily, in a segmented liquid-gas flow, distinct sample regimes are formed and dispersion effects are reduced (Figure 1B).[9,10]

As commercially available flow devices were mostly not suitable for argon-driven flow, we aimed to overcome this technical limitation by designing an easy-to-assemble flow platform not dependent on unsustainable drying with solvents and without associated material loss.[10] Typically, the synthesis of complex molecules requires a broad spectrum of different reaction types and setups: fast reactions conducted at low temperatures, slow reactions at elevated temperatures, and photoreactions under irradiation. Thus, we aimed for a modular design of our platform to provide a maximum of flexibility. Secondly, testing reactions with a few milligrams should be equally feasible as should be scale-up to several grams of substrate. Finally, we decided to avoid HPLC pumps as they are prone to fouling and clogging by precipitation.[1a,7] Our platform design is based on commercially available parts (tubes, valves, etc.) and a backbone of 3D-printed components to lower the reproduction barrier (for a detailed assembly guide, see the Supporting information).[12]

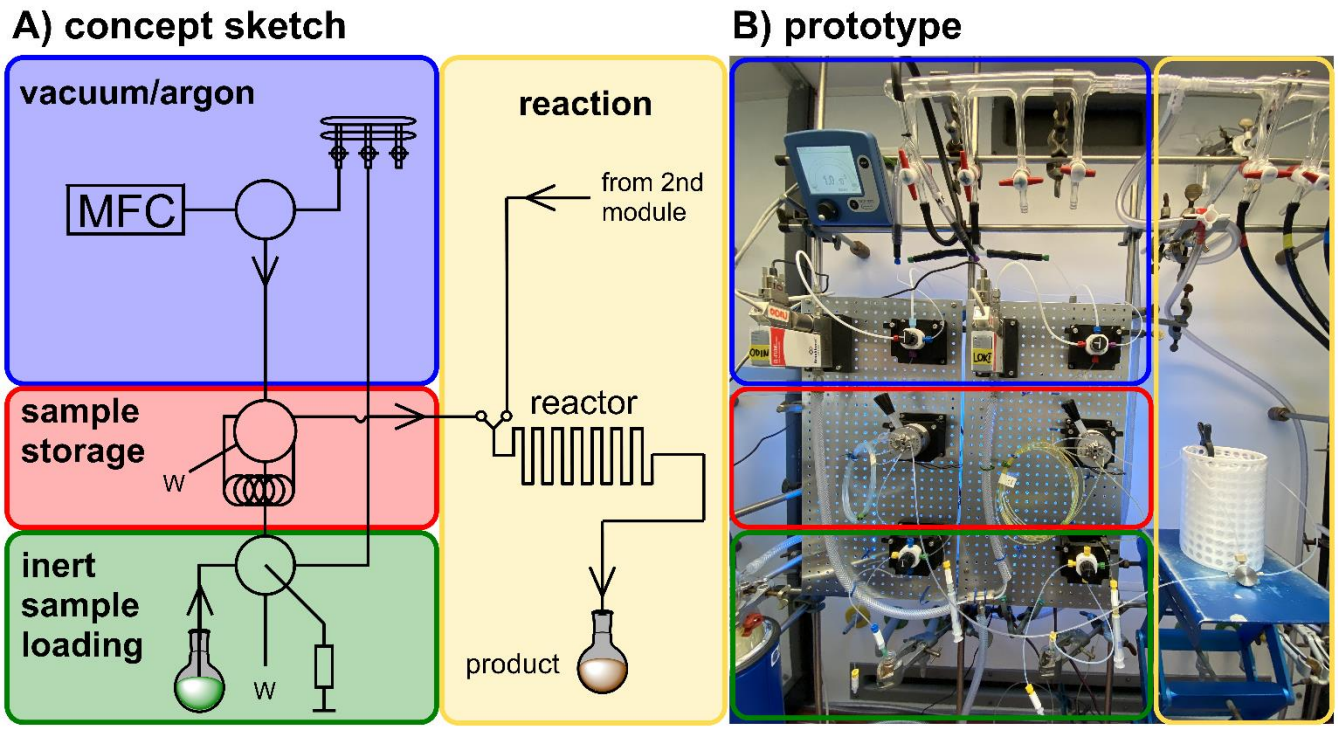


Figure 2. A) Concept sketch of the flow platform consisting of modules for vacuum/argon supply (blue), sample storage (red), inert sample loading (green), and reactor (yellow). The reactor is merged with the reagent feed of a second unit (not shown). B) Prototype of the flow platform consisting of two units with corresponding modules. MFC = mass flow controller; W = waste.

We subdivided the flow platform into different modules (Figure 2A). One module constitutes an interface between a standard laboratory vacuum/argon manifold, a mass flow controller (MFC), and the other modules (Figure 2A, blue box). The MFC provides an adjustable argon flow to drive the reagents, while the vacuum/argon manifold allows to evaporate solvents, dry the system in vacuum, and flush it with argon.

As the volumetric flow rate provided by the MFCs is dependent on the pressure in the system,[13] we linked the MFCs with pressure sensors. Using an Arduino microcontroller, the argon flow rate of the MFCs is continuously corrected allowing to compensate undesired pressure buildup or drop. The MFCs are controlled using a script written in LabVIEW with an easy-to-handle graphical user interface (GUI; program provided as Supporting Information).[14]

The core of the second module is an HPLC injection valve to store reagent solutions on a sample loop in loading position (Figure 2A, red box). By injection into the argon stream provided by the MFC, a reaction slug is formed (Figure 1B) and pumped through the reactor.

We designed a third module to allow safe handling of air- and moisture sensitive reagents such as organometallics (Figure 2A, green box). This module provides an interface between reagent solution, vacuum/argon module and the sample storage module. With this module, well-established Schlenk techniques can be translated to “Schlenk-in-flow” (SiF).

In total, each flow unit consists of three valves that are interchangeable and ordered on a perforated plate. This setup was duplicated to allow for more complex reaction setups with more than one reactant.

To prove oxygen-free conditions using SiF, we used Ti(III) complex **1** as an indicator, which has a deep blue color in anaerobic solution and is oxidized to yellow-green Ti(IV) complex **2** when exposed to small amounts of oxygen.[15] When SiF was used, a solution of **1** could be loaded on a sample loop without a color change. Without using SiF, almost immediate color change to yellow-green was observed indicating the presence of detrimental amounts of oxygen in the system.

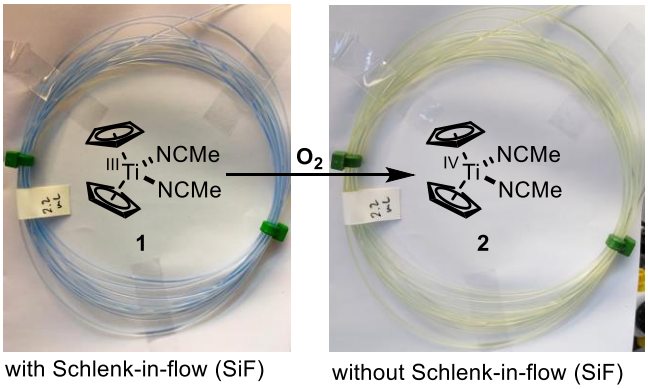
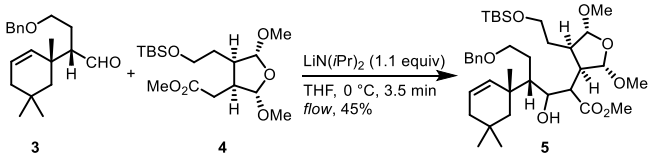


Figure 3. Sample loops with solution of Ti(III) complex **1** when SiF was applied previous to injection of **1** (left) and when no SiF was performed previous to injection of **1** (right) resulting in partial oxidation to Ti(IV) complex **2**.

Then, we investigated the efficiency of establishing anhydrous conditions using SiF. Thus, the system was first flushed with water and then dried either by SiF or by just flushing with argon. Anhydrous tetrahydrofuran (THF, H_2O content <5 ppm) was then loaded on a sample loop, pumped through a 4 mL reactor, and collected for Karl Fischer titration. When only flushed with argon for 15 min, THF with a water content of >2000 ppm was collected. When using SiF, the collected tetrahydrofuran contained only 14 ppm of residual H_2O, meaning that the water content increased by only 9 ppm after passing through two valves and 7 m of tubing. With this general proof of concept, we then moved our attention to applications of our flow platform in typical examples of natural product synthesis.

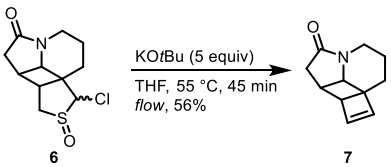
In our previously reported synthesis of anti-MRSA agent (+)-darwinolide,[16] one of the key steps was an aldol coupling of aldehyde **3** and ester **4** to give β-hydroxy ester **5** (Scheme 1). Using sodium bis(trimethylsilyl)amide as base and performing the reaction at −78 °C for 4 h afforded **5** in 42% yield.

The reproducibility of this reaction in batch became a concern with the need for careful control of reaction conditions. In flow, deprotonation of ester **4** with lithium diisopropylamide at 0 °C was complete within 30 sec. Subsequent aldol reaction with aldehyde **3** proceeded within only 3 min at the same temperature providing key intermediate **5** in a reproducible yield of 45%.



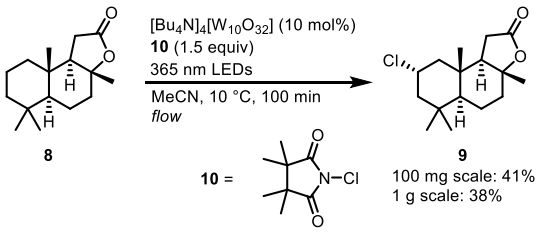
Scheme 1. Preparation of β-hydroxy ester **5** by aldol reaction of aldehyde **3** and ester **4** in flow. TBS = *tert*-butyldimethylsilyl.

Secondly, we investigated the Ramberg−Bäcklund contraction of our recent total synthesis of aspidodispermine.[17] Addition of potassium *tert*-butoxide initiated the ring contraction of α-chlorinated sulfoxide **6** to cyclobutene **7**. Despite screening of bases and reaction conditions, this transformation proceeded in batch at 23 °C for 14 h with a moderate yield of 43%. As highly reactive and unstable sulfur monoxide was released in this transformation, side reactions diminished the yield. Thus, we aimed for reducing the reaction time by fast heating in a tube reactor employing a back-pressure regulator to maintain stable flow rates. After optimization of parameters, heating of the reaction mixture to 55 °C for 45 min followed by an immediate quench with 1 M aqueous HCl resulted in an improved yield of 56% in flow.



Scheme 2. Ramberg−Bäcklund contraction of α-chlorinated sulfoxide **6** to cyclobutene **7** in flow.

As a third example, we chose (+)-sclareolide (**8**) to emulate a late-stage C−H functionalization.[18] Recently, decatungstate emerged as a sustainable photocatalyst for the functionalization of unactivated C−H bonds.[19] We envisaged that a favorable photon transfer in flow could accelerate site-selective chlorination of (+)-sclareolide (**8**) through decatungstate catalysis.



Scheme 3. Site-selective C−H chlorination of (+)-sclareolide (**8**) catalyzed by decatungstate in flow. LED = light-emitting diode.

Employing electron-rich chlorine source **10**[20] at 10 °C gave 2α-chloro-sclareolide (**9**) in a yield of 41% within 100 min using a 3D-printed photoreactor (for details, see the Supporting Information). To prove scalability, this transformation was repeated on gram scale and gave a similar yield of 38%.

In conclusion, we designed a modular flow platform using a backbone of 3D-printed parts and commercially available electronics. Electronic parts are controlled using Arduino microcontrollers and a script written in LabVIEW providing a graphical user interface. The developed SiF (Schlenk-in-flow) techniques offer robust procedures for performing flow reactions under exclusion of air and moisture. By driving reagents with argon instead of solvent, distribution phenomena are suppressed, saving both reagents and solvents. To demonstrate the benefit of our flow system, the key steps of two natural product syntheses previously reported by our groups were realized in flow. Finally, a sustainable flow protocol for the site-selective chlorination of (+)-sclareolide employing decatungstate as photocatalyst was developed. We believe, this initial report will spark the interest of other research groups in our flow platform and enable further natural product synthesis projects.

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Keywords: flow chemistry • C−H activation • late-stage modification • natural products • total synthesis

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