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Harnessing Thin Film Continuous Flow Assembly Lines

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Abstract

Inspired by nature's ability to construct complex molecules through sequential synthetic transformations, we have developed an assembly line synthesis of α-aminophosphonates. In this approach, simple starting materials are continuously fed through a thin-film reactor where the intermediates accrue molecular complexity as they progress through the flow system. Flow chemistry allows rapid multi-step transformations to occur *via* reaction compartmentalization, an approach not amenable to using conventional flasks. Thin film processing can also access facile *in situ* solvent exchange to drive reaction efficiency, and through this method, α-aminophosphonate synthesis requires only 443 s residence time to produce 3.22 g h^{-1}. Assembly line synthesis allows unprecedented reaction flexibility and processing efficiency.

Let It Flow - Multi-Step Assembly Line Syntheses

A rapid continuous flow assembly line synthesis of an α-aminophosophonate was achieved using thin film vortex fluidics. The effectiveness of this transformation was only possible due to reaction compartmentalization and an *in situ* solvent exchange. Continuous flow assembly lines allow reactions to be performed in optimal conditions to drive reaction efficiency.

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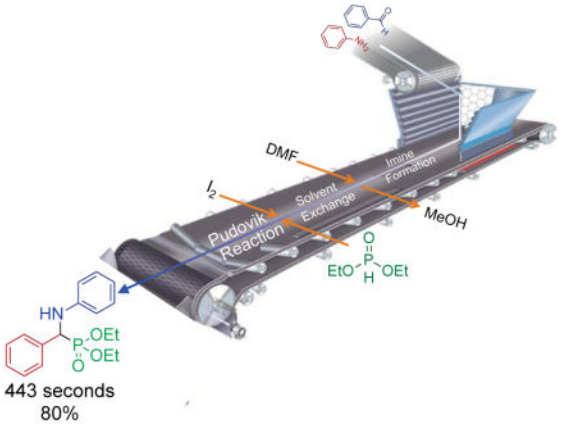
Supporting information for this article is given via a link at the end of the document.



Keywords

Flow Chemistry; Multi-step Transformations; Reaction Telescoping; α-Aminophosphonates; Thin Film Chemistry

Plants and microbes synthesize a highly diverse range of polyketide natural products through multi-step enzymatic processes. Polyketide intermediates pass from one active site to another, building up molecular complexity in an assembly line fashion.[1] Through iterative modifications to a transferable skeleton, this process of substrate channeling avoids intermediate stockpiling. Such enzymatic pathways prevent reactive species from diffusing back into bulk solution to avoid side reactions and also increase reaction efficiency.[2] As an analogous laboratory process, multi-step continuous flow has opened new horizons in organic synthesis.[3]

Reaction telescoping applies multiple transformations to a single scaffold without intermediate isolation and purification. Although examples of reaction telescoping have been reported in round bottom flasks, continuous flow may improve the efficiency of such multi-step transformations.[3a,4] Round bottom flasks cannot easily isolate reagents, reactions and intermediates. In contrast, continuous flow can compartmentalize reactions for specific amounts of time as governed by flow rates. This synthetic tactic can improve product yields and reaction safety by avoiding the buildup of reactive intermediates.[5]

Recently, our efforts have focused on applying thin films for continuous flow syntheses.[6] The vortex fluidic device (VFD) mediates organic transformations in thin films ≈250 μm thick. Rapid rotation of an angled sample tube confines liquid reagents into a dynamic thin film without reactor clogging. Here, vortexing, micromixing, and vibrations can have dramatic effects on covalent and non-covalent bond formation.[6b,7] These conditions have benefited both single-step synthetic transformations and a thin film assembly line synthesis of lidocaine.[6a] This low yielding proof of concept with lidocaine, has now matured into a high yielding and well-understood system.

α-Aminophosphonates are bioisosteres of amino acids. These well-studied pharmacophores appear in a large number of pharmaceuticals including antibiotic,[8] antiviral[9] and

antitumor compounds.[10] Our laboratories recently became interested in these molecules for single molecule enzymatic and biosynthesis experiments. As we required large quantities of such compounds, a rapid continuous flow approach was developed. This continuous flow setup simplified reaction scale-up, as the process reported here can be run for long times without intervention to yield large quantities of material using a relatively small footprint VFD.

Two common synthetic routes access α-aminophosphonates. The first method applies a two-step process - imine synthesis and then addition of a functionalized phosphite. The imine is isolated before the second reaction, termed the Pudovik reaction.[11] The Kabachnik-Fields reaction avoids imine isolation through a three-component coupling reaction with an amine, aldehyde/ketone, and a functionalized phosphite (Figure 1A).[12] The versatility of a three-component reaction makes it ideal for translation into a continuous flow assembly line process. Here, we also avoid imine isolation, harnessing optimal conditions for each individual step to improve overall reaction efficiency.

Continuous flow synthesis in a VFD offers several advantages. First, vigorous vortexing in thin films can drive evaporation of H_2O,[7a] a by-product during imine formation, thus, accelerating the reaction. Second, translating a three-component reaction into a continuous flow system could facilitate reaction telescoping through solvent-specific reaction confinement for the individual steps.

First, conditions for each reaction step were optimized to limit reaction residence times whilst maintaining high product yields (Figure 1A, S1–S8). After optimization, the total reaction time for imine formation and the Pudovik reaction was only 5.5 min, far shorter than the time often required for the equivalent reactions, in a single solvent system, in a round bottom flask.

Solvents play a crucial role in reaction rates, and multi-step processes can be hindered in round bottom flasks with a single solvent. Solvent specificity testing for both the imine and Pudovik reaction revealed opposite preferences for the two reactions. Ideal imine formation conditions feature polar protic solvents, yet the Pudovik reaction favors DMF at 50 °C. Reversing the two reaction conditions resulted in low to undetectable yields (Figure S9). To generate a rapid two-step process in continuous flow required using optimal solvents for each synthetic step.

Thin film processing allows facile *in situ* solvent exchange. Even high boiling solvents such as DMSO (189 °C bp) can be removed at RT (25 °C) through high surface to volume ratios and vortexing. This approach allows imine synthesis to take place in methanol, and then rapid methanol evaporation with simultaneously addition of DMF accelerates the Pudovik reaction. Although continuous flow distillation has been briefly developed for microfluidic devices,[13] these devices accommodate low flow rates of μL/min, where as the VFD processes at mL/min. Thus, rapid, facile and simple *in situ* solvent exchange, an hitherto unsolved problem in thin film continuous flow synthesis, was required to increase reaction efficiency. To help plan future multi-step continuous reactions, a useful series of solvent evaporation rates were derived (Figure S11 and Table S1). Having demonstrated near

quantitative α-aminophosphonate synthesis in 5.5 min with individual steps, we next compiled both reactions into a continuous flow system. Three continuous flow setups illustrate evolution towards a simplified system for facile assembly line synthesis.

First, a continuous flow system was constructed with three VFDs serially linked by pumps. The first device in the sequence mediates RT imine formation in 187 s (0.80 mL/min flow rate, 95% conversion to product). This reaction mixture is then passed into a second consecutive VFD for *in situ* solvent exchange of methanol for anhydrous DMF over 187 s. The DMF must be anhydrous to avoid rapid imine hydrolysis in the presence of I_2. Thus, the reaction mixture was passed through a $MgSO_4$ plug before entering the third consecutive VFD. Here, the Pudovik reaction occurs at 50 °C in the presence of catalytic I_2 (20 mol%) for a residence time of 469 s. Heating a rapidly rotating sample tube required the development of a controllable heating unit. For this we developed a modular heating unit that spans temperatures from RT to 250 °C (Figure S10). Overall, this process yielded 87% conversion to product with a fluid residence time of only 843 s (Figure 2A).

Quenching the reaction mixture after the transformation allows accurate reaction analysis. Also, careful control over the rate of H_2O addition to quench the reaction drives solidification of the product, α-aminophosphonate. This precipitation allows a straightforward isolation (Figure S12).

The next continuous flow setup compressed the system towards a molecular assembly line synthesis requiring only a single VFD. First, imine synthesis and *in situ* solvent exchange were combined in a single device. The first 10.25 cm of the sample tube mediates imine formation and the second half allows methanol evaporation and DMF addition. In combining these steps efficiently, the sample tube was heated to 50 °C which increased the rate of methanol evaporation. Overall, this process yielded 79% conversion to product with a decreased fluid residence time of 827 s, and a smaller reactor footprint (Figure 2B).

In the third continuous flow system, the three distinct steps were combined into a single VFD, creating a true assembly line process. This approach allows each step to be compartmentalized to a specific point in the sample tube. Using a single sample tube, imine synthesis occurs at RT over the first 4.5 cm, avoiding increased methanol evaporation at 50 °C. As more reagents are added, the fluid proceeds up the sample tube into the heated compartment. Next, methanol evaporates and DMF is added. A low flow rate of compressed air facilities the *in situ* solvent exchange that is necessary for a rapid Pudovik reaction. Finally, the reaction mixture proceeds to points 8.0 cm and 10.5 cm along the sample tube where diethylphosphite (DEP) and I_2 are added respectively. I_2 must be added after the DEP otherwise a reaction occurs to produce a number of new phosphorous products (monitored by ^{31}P NMR, non-characterized reaction). This reaction mixture then reacts over the final 9.5 cm of the sample tube at 50 °C. Overall, this process yielded 80% conversion to product in a fluid residence time of only 443 s (Figure 2C).

Next, overnight hydrolysis of **10** with bromotrimethylsilane (BTMS) and quenching with wet methanol yielded the free acid, **11** (100%). Translating these conditions to the confined mode operation of the VFD generated a further opportunity for reaction optimization.

Increasing the concentration of **10** (0.78 M) and BTMS (5.0 eq.) provided quantitative yields in 1 h at RT. Adding this reaction mixture to 3:1 MeOH: H_2O precipitates **11** in 7.5 min as a white powder. This approach avoids tedious chromatography and the generation of a copper salt that may result from the stabilizing copper present in the BTMS.

As demonstrated previously, processing in the VFD allows high boiling solvents to be removed at RT. DMSO evaporation in a round bottom flask to generate the product as a solid material is not practical. However, using thin films allowed solidification of **11** (400 mg) from DMSO at RT (10 h, 8 krpm, Figure S13).

Mimicking nature to create complex molecules through assembly lines challenges modern synthetic methods. Conventional methods, for example, cannot perform the necessary reaction isolation required for efficient reaction telescoping. Overcoming this hurdle requires a toolbox of approaches to perform efficient multi-step transformations. Developing a continuous flow thin film reactor allowed a high yielding, and rapid multi-step transformation that benefited from *in situ* solvent exchange. In addition to VFD-mediated approaches, conventional and biosynthetic flow chemistry could further advance the frontiers of synthetic chemistry, especially when applied in complimentary fashions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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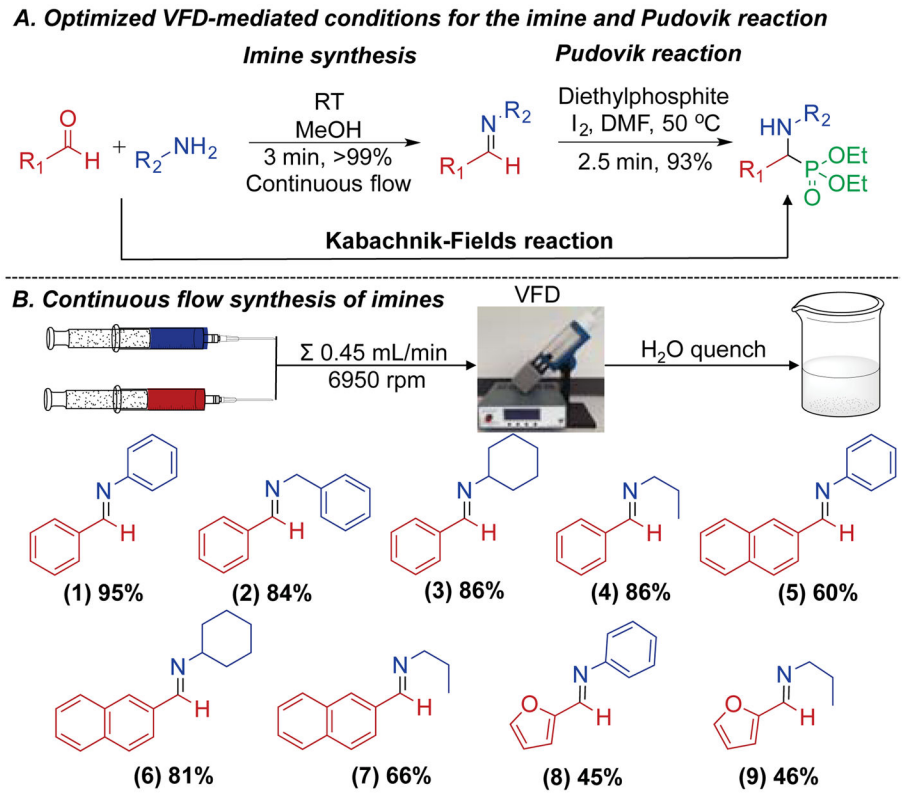

Figure 1. Optimized conditions for the imine and Pudovik reactions that encompass the three-component Kabachnik-Fields coupling

A) The three-component Kabachnik-Fields reaction is a combination of imine formation and then the Pudovik reaction. Above, we detail optimized conditions for both reactions. **B)** The VFD-mediated continuous flow conditions allow a general approach to the synthesis of imines. Optimized conditions required a total flow rate (Σ) of 0.45 mL/min for a 5.35 min residence time in a 20 mm diameter hydrophobic sample tube inclined at 45° and rotating at 6950 rpm. Imines **8** and **9** contain a furfural moiety, which consequently decreased yields due to spurious polymerization.

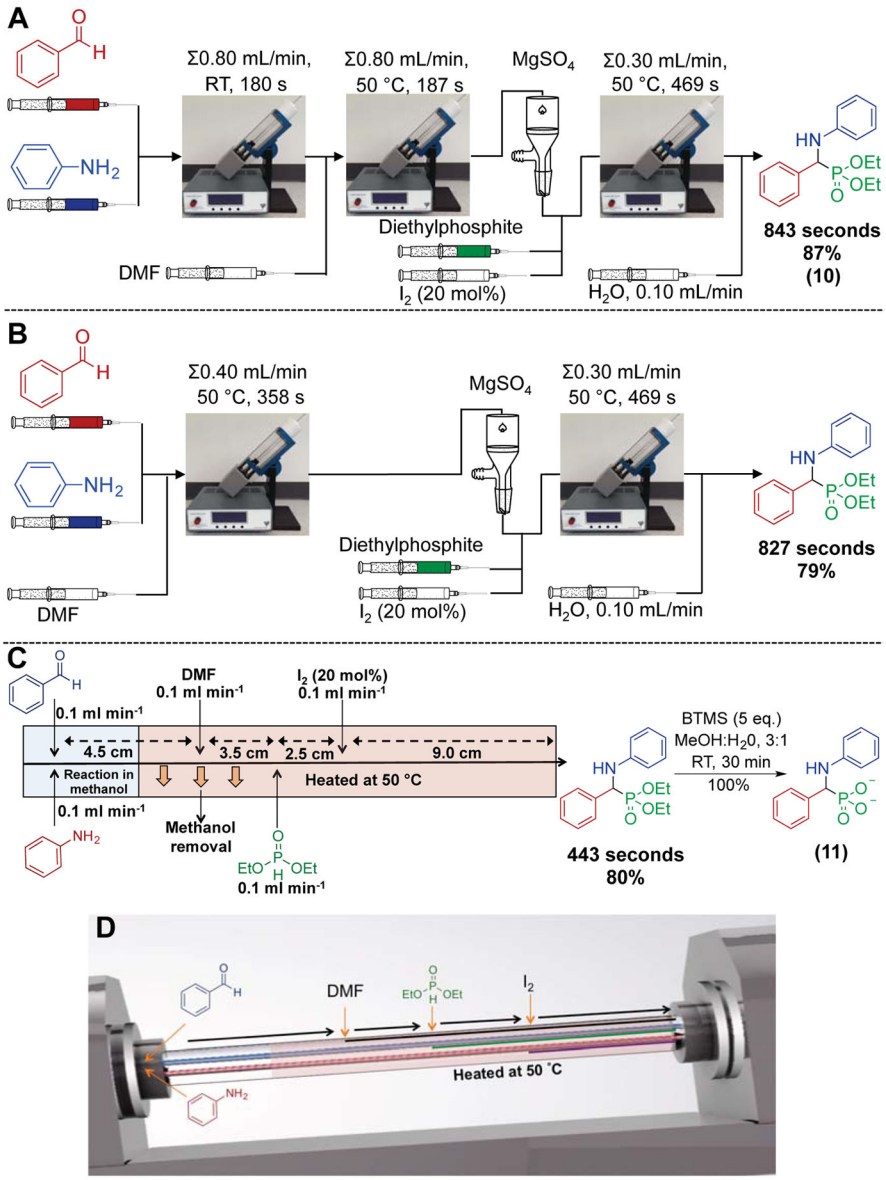

Figure 2. Evolution of continuous flow approaches towards a molecular assembly line synthesis of an α-aminophosphonate, 10

A) Here, three sequential VFDs are serially linked by automated syringe pumps. The first VFD accelerates imine synthesis, the second the *in situ* solvent exchange, and the third the Pudovik reaction at 50 °C. The reaction mixture is then collected and immediately quenched with a feed of H_2O. **B)** Here, two sequential VFDs are serially linked by automated syringe pumps. Imine synthesis and the *in situ* solvent exchange at 50 °C were combined into a single VFD to decrease reaction apparatus footprint, and fluid residence time. **C and D)** The molecular assembly line approach using a single VFD can produce the α-aminophosphonate **10**. Here, benzaldehyde and aniline are added to the bottom of the sample tube where they react for a total distance of 4.5 cm, with a gentle flow of air (65.0 SCCM (cm^3min^{-1})) passing over the thin film at 3.0 cm to facilitate MeOH removal from the rotating tube. At the same sample tube height, anhydrous DMF is added for *in situ* solvent exchange. Next, at

an 8.0 cm distance, DEP is added, followed by I_2 (20 mol% in DMF) at 10.5 cm from the bottom of the sample tube. The reacting mixture then proceeds at 50 °C for the rest of the sample tube length (9.0 cm). Upon exiting the device, the reaction mixture is quenched by H_2O. The Supplementary Information provides additional photographs of the system and instructions for reactor set up.