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Adding Crystals to Minimize Clogging in Continuous Flow Synthesis

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Abstract:

For many carbon-carbon and carbon-nitrogen bond-forming reactions, the stoichiometric formation of inorganic salt crystals limits continuous flow synthesis by causing precipitation, agglomeration, and ultimately clogging of the reactor. We describe a new method of mitigating uncontrolled clogging by adding crystals into the reactant stream. Adding seed crystals of the inorganic salt byproduct shifts the crystallization from uncontrolled nucleation to controlled heterogeneous growth. Reactions with the addition of high quality crystals show less agglomeration compared to the unseeded reaction. We realize the formation of high quality seeds using multiple methods including filtration and settling. Modelling enables balancing of the reaction rate and deposition of the salt onto seed crystals to prolong reactor operating times without clogging.

Introduction:

Continuous flow synthesis is well known in production of commodity chemicals, and small scale analogs are finding increasing use in fine chemicals, pharmaceuticals, and nanomaterials under the term, flow chemistry. The enhanced heat and mass transfer rates present in small scale continuous flow systems enable efficient and safe chemical synthesis. [1-7] However, reactions that involve solids present challenges for continuous flow methods. Solids may be present in the reaction as reagents, intermediates, byproducts or as the product.[8-21] In batch systems, forced convective

mixing allows the use of solids during reactions. However, lack of convective mixing and the small reactor cross sectional area in continuous flow systems increases the probability that solids clog the channel, leading to an early termination of the process. In organic synthesis, numerous reactions that are pharmaceutically and industrially relevant involve the formation of stoichiometric amounts of inorganic crystalline salts,[12, 22] which precipitate in organic solvents and ultimately clog small-scale reactors (with millimeter or submillimeter diameters), sometimes irreversibly. Minimizing clogging will help open up additional opportunities for continuous flow synthesis.

Numerous methods have been explored to mitigate solid clogging in microreactors, such as addition of solvents that dissolve salts, use of pressure pulses, application of ultrasonication, or changing the synthesis to not create solids.[12, 17, 19, 23-25] For example, Buchwald et al. have used a fluid-fluid biphasic packed bed reactor for C-N cross coupling, where the aqueous portion dissolved the salt byproduct.[23] However, using secondary fluids only to dissolve salts can reduce the throughput of the reaction, and care has to be taken to ensure adequate mass transfer rates to the secondary fluid phase. Changing synthetic conditions can also remove the solid formation issue, but is harder to generalize across different chemistries. The use of different reactors can also reduce the impact of solid formation.[26, 27] For example, the use of miniature CSTR cascades can be used to realize continuous flow production with solid byproducts.[26] Ultrasonication can cause a rise in the temperature in the reactor, changing the chemical reaction rate.[12] Moreover, these methods require additional processing equipment, and increase the system complexity. In this work, we approach the issue of clogging from a conceptually and technically different perspective, namely, that of crystal engineering.

It is well known that the nucleation and growth of crystals is dependent on the supersaturation of the molecules or ions, and the classical crystallization mechanism has been verified for KCl salt crystals.[28] The low solubility of KCl in solvents generally used for C-N bond formation reactions (like tetrahydrofuran) causes a large nucleation rate of KCl crystallites, through homogeneous or heterogeneous nucleation pathways. However, a competition between nucleation and growth exists in this system. We hypothesize a proportion of the KCl formed during the reaction can grow on the KCl seed crystals. This 'seeding' technique has been previously utilized to shift crystallization systems from nucleation to growth in multiple materials, including pharmaceutical compounds, and inorganic materials.[29-32]

The research outlined in this paper involves using this hypothesis to increase reactor lifetime. Seeded crystal growth to prevent clogging in continuous flow systems has not been explored before. Instead of avoiding the formation of crystalline solids, we add more solids in the form of seed crystals to suppress uncontrolled nucleation, and allow for the KCl formed during the reaction to grow onto the seed crystals. The seed crystals acts as a sink for the inorganic salt produced in the reaction, resulting in a decreased supersaturation profile, reducing secondary nucleation and fractal-like crystallites, thereby reducing agglomeration and clogging in the reaction region. We show the effectiveness of seeded crystallization strategy to reduce clogging during the pharmaceutically relevant palladium (Pd) catalyzed C-N bond formation reactions. This effectiveness is shown by both reactor performance, and the morphology of the crystals that are obtained in typical reactor conditions with and without seeds. Finally, to study the possibility of whether modelling can be utilized to predict the size and amount of seed crystals that need to be added into the reactor, a model is developed to balance the salt formation and deposition onto the

seeds as a function of reaction conditions and seed crystal number and morphology. **Experimental Section:**

Materials:

Aniline, 4-chloroanisole, sublimed grade potassium tert-butoxide (KOtBu), potassium chloride (KCl), and 2-methyltetrahydrofuran (mTHF) (Sigma-Aldrich Corporation) were used as purchased. Methylated Brett Phos Palladium catalyst (N-Me-BP-Pd) were prepared according to literature procedures.[33]

Potassium Chloride Seed Formation:

KCl crystallites with upper size of 35 μm were obtained by grinding KCl powder using a mortar and pestle, followed by dry sieving using a 35 μm stainless steel mesh sieve (WS Tyler). Crystallites were suspended in mTHF by continuous stirring at 1600 rpm (Dyla-Dual Hot Plate Stirrer, VWR International).

KCl crystallites with an upper size of 5 μm were obtained by first grinding the KCl as received, then dry sieving with a 35 μm stainless steel mesh sieve. These crystallites were then suspended in mTHF. A 5 μm syringe filter (VWR International) was used to isolate KCl crystallites with an upper size limit of 5 μm. The crystal stock solution was enriched by evaporating mTHF. The concentration and average size of the crystal seeds were measured by using a Countess II cell counter (Beckman Coulter Incorporated).

KCl crystallites with an upper bound of 7 μm were prepared by using the settling method. The received KCl were ground using a mortar and pestle and then dry sieved with a 35 μm stainless steel mesh sieve. These crystallites were suspended in mTHF. After stirring the crystallites at 1600

rpm, the crystals were allowed to settle. The settling time was determined such that the top half of the 40 mL vial would contain crystallites smaller than 7 μm. The top portion of the suspension was removed gently without disturbing the settled crystals. The crystal solution was enriched by evaporating mTHF. The crystal size was measured using scanning electron microscopy (SEM). Sodium Bromide (NaBr) seed crystals were created and characterized using the same method.

General procedure for Pd-catalyzed amination reactions:

A 20 mL vial with a PTFE screw top cap (VWR International), equipped with a magnetic stirbar, was charged with dodecane (51.1 mg, 0.1 mmol), aniline (279.4 mg, 3 mmol), 4-chloroanisole (513.2 mg, 3.6 mmol) and the stock solution of KCl seed crystals (0-1 mL). This solution was sparged with Argon for 30 min to ensure removal of dissolved Oxygen. Argon-sparged mTHF was added to bring the final solution volume to 6.0 mL. In another 20 mL vial with a PTFE screw top cap, the N-Me-BP-Pd catalyst (27.6 mg, 0.03 mmol) was added along with a magnetic stirbar. This vial was evacuated and backfilled with Argon a total of 3 times. Reagent solution from the first vial was added to this vial under positive Argon pressure to make up solution 1. This solution was connected to the reactor using a flow pump (Asia Flow Pump, Syrris).

An oven dried vial with a PTFE screw top cap was evacuated and backfilled with Argon, and then charged with KOtBu (0.505 g, 45 mmol). The vessel was evacuated and backfilled with Argon, and mTHF was added to bring the final volume of the solution to 6 mL (solution 2). After vigorous mixing, this solution was loaded into a Normject plastic syringe (10 mL) and filtered through a PTFE membrane filter (0.4 μm porosity, VWR International) into an oven dried 20 mL vial with a PTFE screw top cap that had been purged with argon. Solution 2 was then loaded into a stainless steel syringe (8 mL, Harvard Apparatus). This system was connected to the reactor.

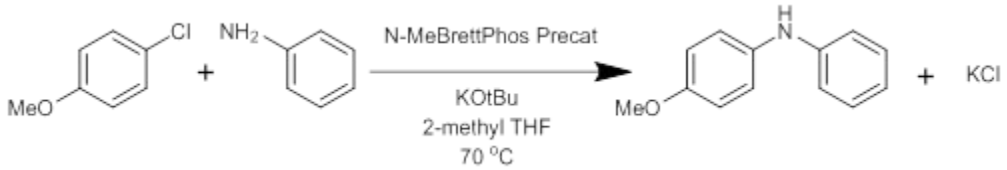
A Teflon reactor (perfluoroalkoxy alkane (PFA), 1/16" OD x 0.04" ID x 3'- 6' Idex Corporation) was inserted into a spiral aluminum frame (Proto Labs) and heated to the specified temperature (60 - 90 ^{o}C)on a hot plate (VWR International). All fluidic connects were made using ¼ in.-28 PTFE fittings. Flowrate and pressures were allowed to stabilize to a steady state (3 reactor volumes) and a sample was collected for the duration of the experiment. The product stream was collected under argon, into water or mTHF. An aliquot of the organic layer was mixed in a vial containing water, KCl and ethyl acetate. The organic layer from this vial was isolated and run in a gas chromatography (GC) system (6890 Series, Agilent Technologies). Sample yields were measured by GC analysis of the organic layer, relative to the dodecane internal standard. Mass spectroscopy of the product showed the product to be 4-methoxy-N-phenylaniline.[12]

Optical characterization and scanning electronic microscopy (SEM):

Optical characterization of the crystal seeds were performed using the Countess II Cell Counter (Beckman Coulter Incorporated). 10 μL of the stock solution of KCl crystal seeds were loaded onto a cell counter chip. SEM characterization of the crystal seeds required loading and drying 100 μL of the crystal seed stock solution as a uniform layer onto 1 cm^2 carbon tape attached on a sample pin. The samples were measured on the Zeiss Merlin High Resolution SEM (Zeiss). To characterize the KCl byproduct after the reaction, 100 μL of the reaction solution was diluted in 900 μL mTHF, and 100 μL of the diluted solution was loaded onto 1 cm^2 carbon tape attached on a sample pin. Evaporation of Au (5-10 nm) on the samples ensured a conductive layer for ease of imaging.

Results and Discussion:

The Pd-catalyzed C-N bond forming reaction is widely pursued in the production of intermediates, active pharmaceutical ingredients (API), and natural products.[34-37] We study the coupling of aniline and 4-chloroanisole using a Pd catalyst, with the N-Me-Brett Phos ligand, to form 4-methoxy-N-phenylaniline as the product **(Scheme 1).**[38] This reaction produces a stoichiometric amount of salt as byproduct, in this case, potassium chloride (KCl). KCl is insoluble in 2-methyltetrahydrofuran (mTHF), the solvent used to carry out the reaction. The reaction is complete in minutes, resulting in fast rates of salt formation, which can easily clog microfluidic or millifluidic systems utilized in continuous flow synthesis.[13, 17, 26]



Scheme 1: Pd-catalyzed amination of an aryl chloride with aniline.

A single-phase tube-based continuous flow system is employed to study clogging of this reaction. In a typical experiment, the reagents aniline and 4-chloroanisole, along with the catalyst N-Me-BP-Pd, are delivered to the reactor using a syringe pump, and the base KOtBu is delivered from a stainless steel syringe driven by a syringe pump (**Figure 1**). The reagent streams are mixed in a T-junction and are delivered to a heated reactor. The sample is then collected in a vial downstream.

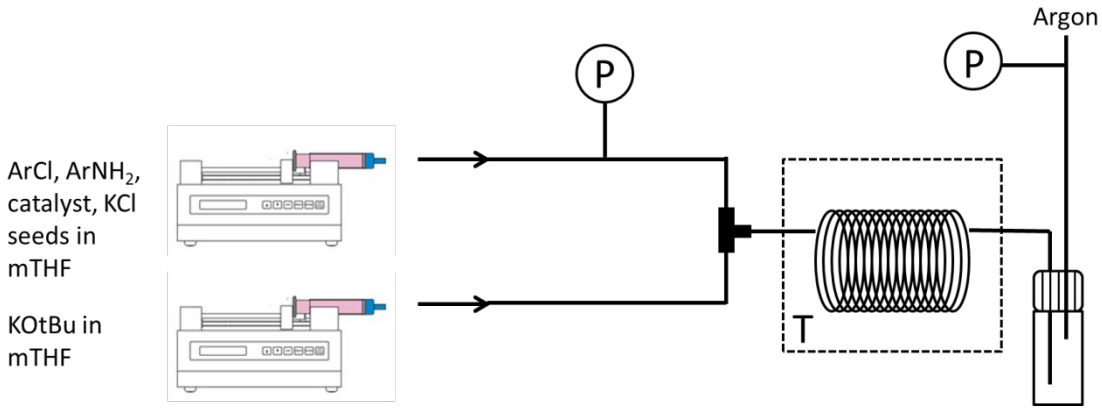


Figure 1: Experimental setup used to carry out the flow chemistry and clogging experiments.

In our strategy, adding crystal seeds of the salt increases the rate of crystal growth due to the increased surface area, while having the additional benefit of lowering supersaturation, and thus lowering the rate of crystal nucleation.[39] SEM of a representative product stream after dilution and drying shows different salt crystal morphologies with and without crystal seeds present in the reaction. In the control reaction without seeds, fractal-like KCl crystal morphology is observed (**Figure 2a**). We hypothesize that the high degree of supersaturation that occurs during the reaction causes uncontrolled nucleation of numerous KCl crystallites, which then aggregate to form fractal structures.[40, 41] These structures have a larger surface area per unit mass compared to compact KCl crystals, leading to more inter-particle collisions and interactions. The combination of numerous secondary crystallites and increased interactions leads to larger agglomerates[42], which causes flow resistance in the continuous flow system, eventually resulting in clogging.

In contrast, the initial seeds added in the reaction stream serve as a sink for the KCl produced during the reaction, and lead to a shift of the KCl crystal morphology from a fractal-like system to a more compact structure (**Figure 2b**). As the KCl growth onto the seed crystals creates relatively compact structures, aggregation of KCl is reduced compared to the control reaction, even if the

total mass of KCl produced is the same. Lowered aggregation leads to minimized clogging events in the small scale reactor. Real-time optical observation of the reactor also shows the different crystal morphologies with and without the addition of initial crystal seeds **(Supplementary Video 1, 2)**. In the control reaction, collisions between crystallites cause the formation of larger agglomerates (**Figure 2c**). In contrast, the reaction with seed crystals show smaller crystals and aggregated particles, leading to less collisions and agglomeration (**Figure 2d).**

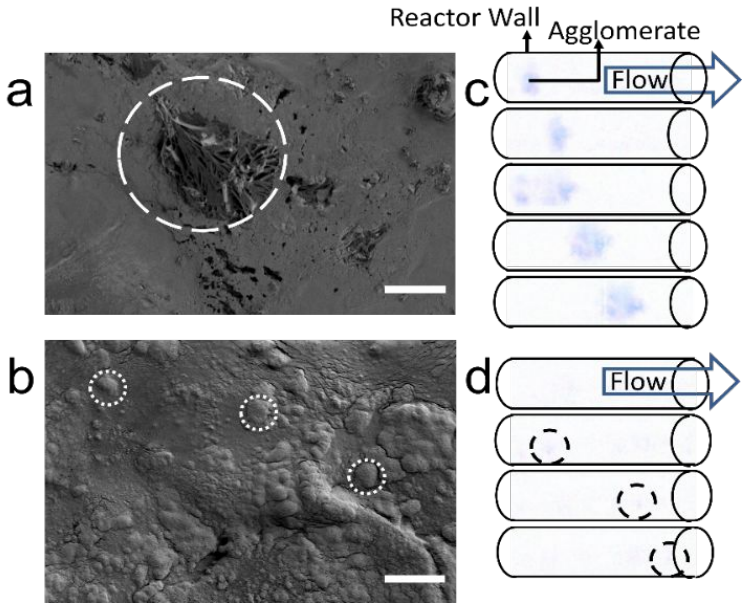


Figure 2: Scanning electron microscope (SEM) and in situ optical microscope images showing KCl crystal morphology from the reaction stream. (a) Fractal-like morphology observed in reaction stream without crystal seeds. Scale bar is 50 µm. 5-10 nm gold was evaporated on the substrates to obtain contrast and reduce charging. (b) Compact crystallite morphology observed in reaction stream with crystal seeds. Scale bar is 50 µm. 5-10 nm gold was evaporated on the substrates to obtain good contrast. (a),(b) 0.25 M reagents (80 ^{o}C, 400 µL flowrate and residence time (t_R) = 2 min). (c) In situ optical images show the progression of agglomeration in the reactor. Image was processed for clarity by enhancing the contrast

between the solution and the salt crystals, and removing the solvent color. (d) In-situ optical image of reaction with seeds, no agglomeration is observed. Small crystals are outlined in the picture. Image was processed for clarity by enhancing the contrast between the solution and the salt crystals, and removing the solvent color. (c),(d) 0.25 M reagents (80 °C, 200 µL flowrate and t_R = 2 min).

Initially, 35 µm KCl seed crystals are created using dry sieving. These sieved seeds are weighed, suspended in the solvent, and delivered into the reactor with the base. The effect of increasing the crystal seed amount on reactor clogging is determined by the pressure increase inside the reactor. A rapid increase in pressure is indicative of clogging and the interruption of flow. As an initial study, we perform an acid-base reaction with and without seed crystals, with benzoyl chloride as the acid and potassium tert-pentoxide as the base (**Table 1**). Without any seed crystals, the pressure drop increases rapidly and the reactor clogs within 5 reactor volumes (**Supplementary Figure S1a**). Adding 0.05 and 0.10 mg/mL seed crystals extends the reactor lifetime to 8 and 15+ reactor volumes, respectively. However, when the initial seed loading is increased to 0.2 mg/mL, reactor clogging occurs within 8 reactor volumes. These data suggest that an optimal seed loading concentration is necessary to extend reactor lifetime.

KCl Seed Concentration (mg/mL)	Reactor Volumes Until Clog	
	Average	Std. Dev.
0	4.8	0.3
0.05	8.0	
0.1	16.5	3.5
0.2	7.2	1.2

Table 1: Reactor volumes until clogging occurs during 0.1 M acid-base reaction in a small scale reactor (at 62.5 µL/min and room temperature, t_R = 4 min). Addition of 35 µm KCl seeds extends reactor lifetime. An optimal amount of seed addition exists at 0.1 mg/mL.

The Pd-catalyzed amination of aniline and 4-chloroanisole is carried out next to study the effect of KCl seed loading on reactor clogging behavior on a pharmaceutically relevant reaction, at a concentration of 0.25 M and 70 °C, at a flowrate of 90 µL/min (Residence time (T_R) = 4 min). In the control reaction, without the seeds, the reactor clogs within 4 residence volumes (**Table 2, Supplementary Figure S1b**). A seed loading of 0.05 mg/mL is found to extend the lifetime of the reactor by a factor of 2.5. However, when the seed loading is increased to 0.1 mg/mL, the reactor clogs within 5 reactor volumes. These results indicate that an optimal seed loading is required to prevent clogging and extend the reactor lifetime. It is possible that because of the large initial seed crystal size, a dense initial suspension can promote clogging.

KCl Seed Concentration (mg/mL)	Reactor Volumes Until Clog	
	Average	Std. Dev.
0	3.5	0.7
0.05	9.6	5.3
0.1	4.8	

Table 2: Reactor volumes until clogging occurs during a Pd-catalyzed amination reaction, with reaction conditions of 90 µL/min and 70 °C. Seeds were 35 µm or smaller. Addition of 35 µm KCl seeds extends reactor lifetime. An optimal amount of seed addition exists at 0.05 mg/mL.

Next, we use smaller seeds so that the KCl formed during the reaction would be presented with a larger surface area for crystal growth, while keeping the seed mass (and volume) constant. In order

to reduce the size of seed crystals added into the reagent, we use a 5 µm syringe filter to obtain seed crystals with an upper size of 5 µm. The mass of the crystallites present in the filtered suspension cannot be easily measured as it is impossible to resuspend the seed crystallites after drying the sample completely. Therefore, an optical counting method is used to measure the concentration of the seed crystallites. Crystals smaller than 2 µm cannot be counted using this method, leading to an undercounting of seed loading. Using this lower bound of the seed crystal concentration, we study the effect of the seed crystals on the Pd-catalyzed amination of aniline and 4-chloroanisole, at a concentration of 0.25 M and 90 °C, with a flowrate of 200 µL/min (t_R = 2 min). **Table 3** and **Supplementary Figure S1c** shows the result of adding smaller seed crystals. The control reaction clogs the reactor within 5 reactor volumes, while the reaction with 100,000 seed crystals/mL shows no clogging for the duration of the reaction in all cases. This result further validates our hypothesis that adding seed crystals causes the KCl formed during reaction to grow compactly on the seed crystals, resulting in fewer clogging events. However, syringe filtration of KCl crystals is a slow and cumbersome process and cannot be easily scaled for industrial production.

	KCl Seed Concentration (Crystals/mL)	Reactor Volumes Until Clog	
		Average	Std. Dev.
Control	0	5.0	0.6
Filtration	$1x10^5$	14.4*	5.3
Settling	$9.3x10^6$	12.2	4.0

Table 3: Reactor volumes until clogging occurs during a Pd-catalyzed amination reaction at reaction conditions of 200 µL/min and 80 °C. Seeds were 5 µm or smaller when isolated by filtration and counted using optical techniques, or 7 µm or smaller, when isolated by settling

and counted using scanning electron microscopy. *No clogging occurred when the filtered seeds were used, and the reaction was run until starting materials were used completely.

Settling is an easier method of creating seed crystals of a similar size range as the filtered crystals. After dry sieving the crystallites with a mesh filter of 35 µm, the KCl seeds are suspended in the solvent, and allowed to settle. The settling velocity of different sized KCl crystallites can be calculated as

$$w = \frac{g(\rho_p - \rho)D_p^2}{18\mu} \tag{1}$$

Here w is the settling velocity, g is gravitational acceleration, ρ_p is the KCl density, ρ is the solvent density, D_p is the KCl seed crystal diameter, and μ is the solvent viscosity. Crystallites smaller than 7 µm are obtained and concentrated by drying the mTHF using an argon stream. The seed crystal size distribution with a lower limit of 100 nm is measured using scanning electron microscopy (SEM) **(Figure 3b)**. The size distribution of the KCl seed crystals show the majority of the crystallites are smaller than 1 µm , below the optical counting limit of conventional optics based particle counters (**Supplementary Figure S2**).

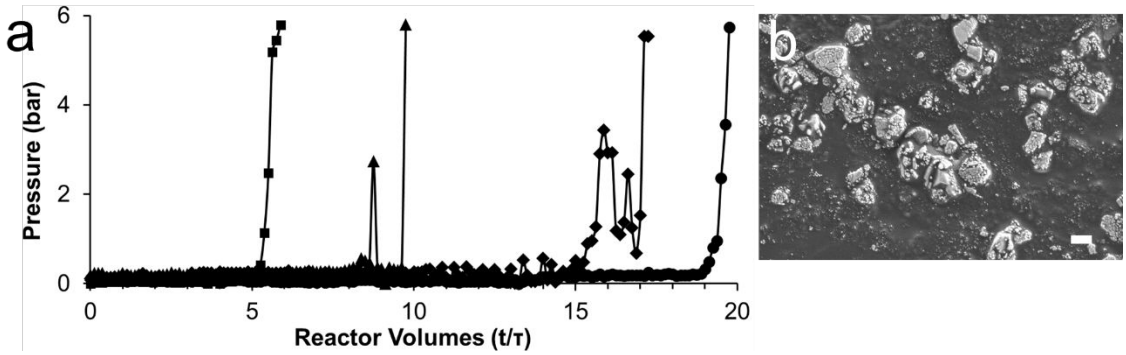


Figure 3: (a) Pressure drop data showing clogging behavior. Reaction with < 7 µm sized seeds, 9.3x10^6 seeds/mL, counted using SEM (at 200 µL/min and 80 ^{o}C). The mixing region before the reagents reach the reactor are sonicated to ensure that seeds do not settle at the start of the reaction. However, clogging occurs at 20 reactor volume (80 min) in the system without reaction. Legend: -■- Control, -▲- Control with sonication, -♦- 9.3x10^6 Seed crystals/mL, -●- Reactants without catalyst (i.e., no reaction). (b) SEM images of KCl seed crystals obtained by using the settling method. Scale bar is 2 µm.

Model predictions provide insight into the impact of different seed crystals on the surface area available for KCl deposition, and the possible maximum amount of KCl deposition onto the crystals (**Figure 4**). Dry sieved crystals have a larger initial size (< 35 µm), which results in a low count of seeds (~ 600 crystals/mL) that can be added into the reagent stream before the seeds promote faster clogging, which also means a low initial surface area for KCl deposition (**Supplementary Table S1**). The low initial surface area and the low crystal count limits the total KCl that can be deposited onto the seed crystals, as the crystal deposition rate scales linearly with both crystal count and surface area.

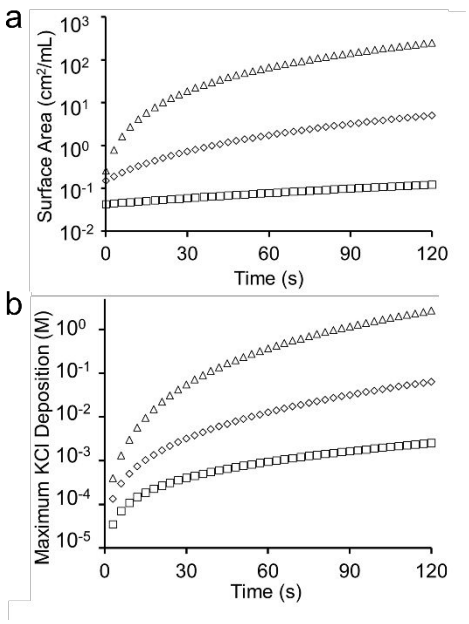


Figure 4: (a) Seed crystal surface area evolution assuming 0.1 µm/s growth rate. (b) Potential KCl deposition possible on seed crystals assuming 0.1 µm/s crystal growth rate. Legend: □ Dry Sieved Seeds, ◊ Filtered Seeds, Δ Settled Seeds.

When the seed crystals are created using filtration and are counted optically, the initial surface area available for KCl deposition increases by a factor of three (**Supplementary Table S1**). More importantly, ~100,000 crystals/mL filtered seed crystals can be added without clogging, instead of ~1,000 crystals/mL of dry sieved seed crystals. However, if the reaction is completed in a short residence time (t_R = 2 min), only 25 % of the KCl produced during a 0.25 M reaction can be deposited onto the seed crystals due to a lack of surface area.

If the settling method is used and the seed crystals are accurately counted using SEM, the seed crystal concentration can be increased to 6 - 10 million crystals/mL, with an average initial size of 800 nm. The full amount of KCl formed during the reaction can be potentially deposited onto these seed crystals, even at short residence times (t_R = 2 min). The relation between surface area present

for crystal growth and the uptake potential of the seed crystals in the 3 methods of seed preparation is represented in **Figure 4**, assuming a 0.1 μm/s KCl crystal growth rate. This growth rate was chosen because it theoretically yields crystals of similar size to the final crystallites observed in SEM images.

The seed crystals obtained through settling are added to the Pd-catalyzed amination of aniline and 4-chloroanisole at a concentration of 0.25 M and 80 ^{o}C, with a flowrate of 200 μL/min (t_R = 4 min). **Figure 3** shows that with ~9×10^6 seed crystals/mL clogging occurs at 17 reactor volumes (68 min), while the control systems without or with sonication at the mixing region clogs at 5 and 10 reactor volumes, respectively. Importantly, the clogging of the seeded reactor occurs at the mixing region, and not the reactor itself. To explore why the mixing region clogs, a control was run without any seeds or catalyst. This reaction stream still clogs at the mixing region within 20 reactor volumes (**Figure 3**). X-ray diffraction (XRD) of the unreacted, mixed reagent stream showed the existence of potassium hydroxide, which indicates that there is water present in the system that reacts with the potassium tert-butoxide and forms KOH in the mixer (**Supplementary Figure S3**).

We hypothesize that without seed addition, the supersaturation profile that develops during the reaction causes the formation of numerous small crystallites, due to the formation of large amounts of the byproduct in a solvent with a low solubility. Due to the rapid formation of these crystallites, we observe dendritic growth. These uncontrolled crystal nucleation events give rise to a non-compact morphology. Although both compact and non-compact crystal morphologies (**Supplementary Figure S4**) are created in the unseeded reactor, we hypothesize that the larger surface area of the dendritic morphologies enable interactions between separate particles, and allow for the formation of larger multi-crystalline aggregates.[43] These aggregates, in turn, have a

slower velocity compared to the surrounding fluid due to their mass, enabling more particle aggregation until a clog is created in the reactor.

On the other hand, when an optimized amount of crystalline seeds are added into the reactor, the crystal surface allows for crystal growth, instead of just nucleation of numerous crystallites as in the unseeded reactor. As the nucleation rate is a strong function of supersaturation, a small decrease in supersaturation can have a strong impact on the nucleation rate.[44] Thus, the reduction of new crystallites and the growth of seeds, lead to the formation of more compact structures than the dendritic aggregates seen in the unseeded case. The compact structures reduce clogging events, as multi particle aggregation becomes less likely.

The high concentrations of salt produced during the reaction allows for roughened growth on the seed surface. Thus, it is possible for these surface to serve as secondary nucleation sites as well. However, we show that even less compact seed morphologies, like that of NaBr (Supplementary Figure S6), can reduce the clogging issues when a NaBr producing C-N bond formation reaction is used (Supplementary Figure S7). Therefore, we also show that the seed crystal method is effective on other Pd-catalyzed amination reactions that produce chemically different salt byproducts such as NaBr (**Supplementary Figures S5-S7**).

A priori prediction of the optimum concentration is difficult, as many factors can influence the crystallization kinetics, including the reactor type, temperature, flow rate, crystal structure, and any morphological modification that the reactants or products/byproducts may cause. However, the modelling performed here balances the formation and deposition rates for a given reaction and byproduct, and can thus be used to optimize seed size and loadings for different concentrations and temperatures for the same reaction.

The kinetics of KCl production and deposition on seed crystals were modelled to obtain insights into the clogging behavior. The KCl production rate was quantified based on experiments (**Supplementary Figure S8**). The KCl deposition rate is the rate at which the produced KCl is absorbed onto the surface of the seed crystals, modeled by assuming a linear growth rate of the KCl crystals (0.1 μm/s) at full KCl saturation (more details in S1 of Supplementary Information).

Figure 5a shows the relationship between the KCl production rate and the deposition rate during the residence time of the fluid in the reactor. The KCl production rate decreases over time, as reactants are consumed. On the other hand, the KCl deposition rate increases over time, as the seed crystals grow larger (leading to a larger surface area), while the linear growth rate remains constant. This creates a temporal mismatch between the production and deposition rate, and the difference leads to an initial accumulation of KCl in the reactor. The KCl accumulation peaks at 25 seconds, when KCl production rate equals the deposition rate (**Figure 5b,c**). Beyond 25 seconds, the excess amount of KCl gradually dwindles as the KCl deposition rate outweighs the KCl generation rate, until the accumulated KCl is completely consumed at 60 seconds. After 60 seconds, the KCl deposition rate should simply match the KCl generation rate, so that the incremental amount of KCl generated at this point is instantaneously absorbed by the seed crystals. In summary, before 60 seconds, the KCl deposition is the rate-limiting step for crystal growth, and after 60 seconds, the KCl generation becomes the rate-limiting step for crystal growth.

Our simulation results also indicate how the seed crystals can be utilized to achieve better results to avoid clogging. Namely, it is best to match the KCl production rates with the KCl deposition rates so that the amount of excess KCl built up in the interim is minimized. Rate matching can be accomplished by several methods: (1) We could slow down the reaction rate, but it is not advisable to do so as the production of product is stoichiometric with the KCl production; (2) We could

increase the total amount of seed crystals, but there is also an upper limit, as too much seed crystals alone can cause clogging; (3) It is also possible to optimize the seed crystal addition by injecting progressively into the reaction stream at different concentrations; (4) Finally, external additives that limit crystal aggregation can be investigated.[45]

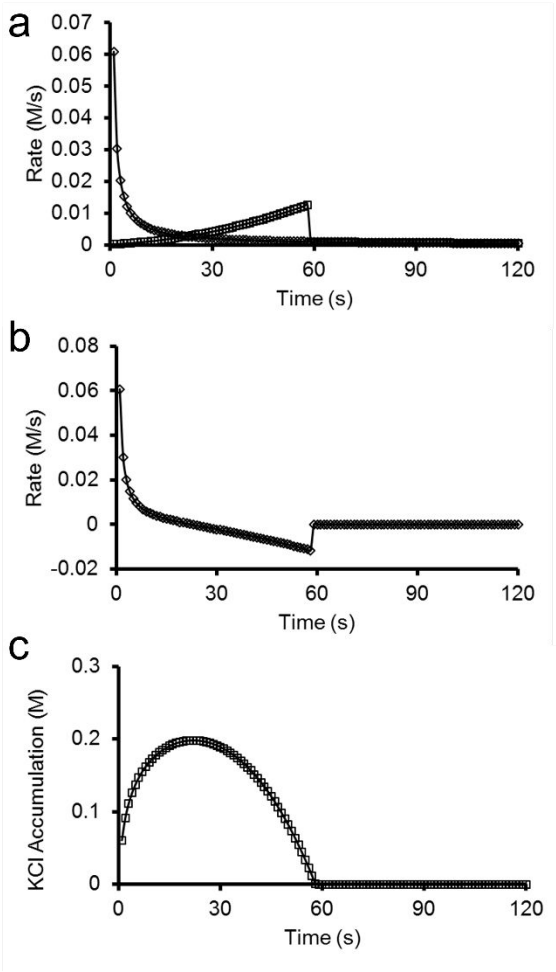


Figure 5: (a) Modelling KCl production rate and deposition rate. Production rate matches the deposition rate at 25 s. Legend: -◊- KCl production rate, -□- KCl deposition rate (b) Difference of production and deposition rates. All accumulated KCl can be deposited on the

crystals by 60 s. (c) KCl accumulation in the reactor based on the production and deposition rates.

Conclusion:

In this work, we show that crystal growth control in flow chemistry could extend the continuous flow reactor lifetime compared to the unseeded reactors. Preliminary experiments with an acid base salt formation reaction showed extended reactor lifetimes without clogging. For the C-N bond forming reaction, as higher reagent concentrations were desired, larger seed crystals surface area was required while still minimizing the total volume of seed crystals added. In order to do this, better techniques of obtaining smaller seed crystals (sieving and settling) as well as better techniques for counting seeds (SEM based particle counting) were utilized.

It was observed that reactions that form stoichiometric amounts of solids could have their crystal morphology shifted to a compact form instead of fractal-like agglomerates. Different methods of seed crystal formation and seed crystal counting were explored. Settling the crystal seeds and counting using SEM were most useful in measuring seed crystal concentration accurately. Theoretical calculations on solid production and deposition rates showed that clogging could be mitigated by the use of smaller crystals, such that each crystallite could grow to have a larger surface area without an initial increase in solid mass, or by slowing the reaction rate such that the crystals could grow to have a larger surface area for KCl deposition.

Ultrasonication is a more general method of limiting clogging, since it can be utilized when non-crystalline materials (such as polymers) cause clogging, as well as when multiple crystalline byproducts are created within one reactor. However, ultrasonication based de-clogging systems

have their own difficulty. In particular, continuous sonication has been shown to change the kinetics of reactions due to localized temperature increases.[12]

The proposed crystal engineering technique can work in conjunction with sonication techniques to extend reactor lifetimes. As clogging is most likely to occur in narrow junctions, it is possible to sonicate bends and narrowed regions of the reactor to ensure no clogging occurs.[46] On the other hand, over long, continuous reactors of constant diameter, it is less feasible to sonicate the entire reactor. However, as crystallization and aggregation is a stochastic mechanism, there is a possibility of clogging occurring in this region. We envision the crystal engineering technique described here to reduce clogging in this reactor region.

Crystal engineering can also be useful if further modification of the byproduct or the product is necessary. For example, the concepts developed here can be utilized to crystallize the product itself, providing an easy in-line purification and separation technique. With the ease of forming and adding seed crystals, this method could become a tool alongside sonication, oscillating flows, and pressure pulses to mitigate clogging effects of salt forming reactions in microfluidic and small-scale reactors.

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Conflict of Interest Disclosure:

The authors declare no competing financial interest.

Supplementary information description:

S1. Methodology of KCl Simulation

Figure S1: Pressure drop traces showing clogging behavior.

Figure S2: Crystal size distribution of settled seeds measured using SEM.

Figure S3: X-ray diffraction of reagents and products.

Figure S4: SEM of unseeded reactor final crystal morphology.

Figure S5: Second Pd-catalyzed C-N bond formation reaction scheme with sodium bromide as salt byproduct.

Figure S6: Sodium bromide (NaBr) seed crystals made through sieving, imaged using SEM.

Figure S7: Pressure drop for NaBr producing reaction.

Figure S8: Conversion of reaction used to simulate reaction rate.

Table S1: Seed crystal characteristics.

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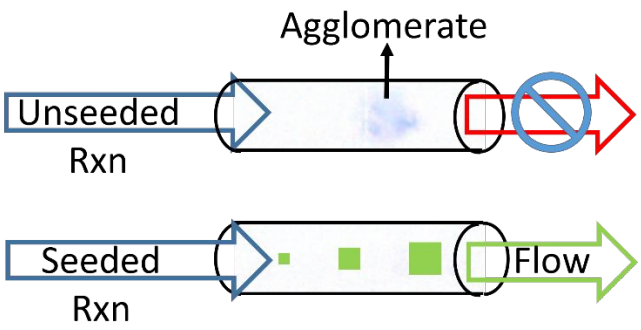

Adding seed crystals of crystalline byproducts during a continuous flow synthesis promotes the growth of compact, high quality crystals instead of agglomerates. These compact crystals are less likely to clog the reactor, extending the reactor lifetime for the carbon-nitrogen bond forming reaction.