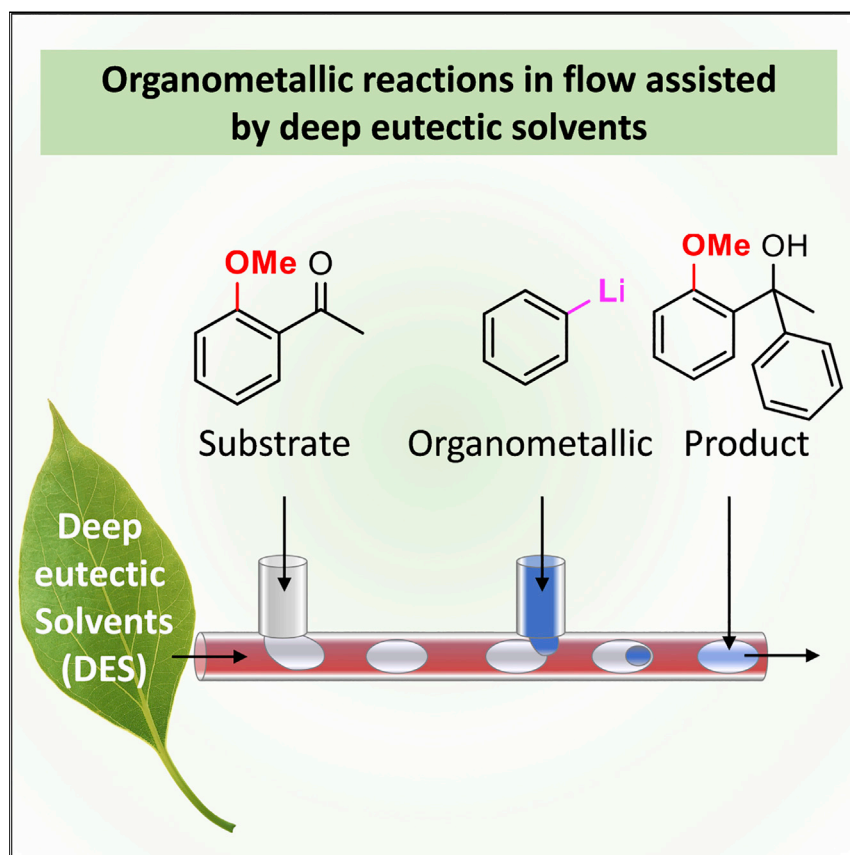


Article

Continuous, stable, and safe organometallic reactions in flow at room temperature assisted by deep eutectic solvents



This work presents the foundation for the continuous, safe, and stable manufacturing of pharmaceutical and aromatic compounds using organometallic reagents at room temperature and in atmospheric conditions instead of the strict oxygen-free and cryogenic (-30°C to -70°C) conditions currently required. This innovation is possible thanks to the presence of deep eutectic solvents in optimized droplet microreactor systems, with a direct impact on the energy requirements of the system.

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Highlights

Continuous, stable, and safe operation of organometallic reactions

Green deep eutectic solvents lead to high moisture tolerance

DESs avoid clogging in organometallic reactions under ambient conditions

Hydrodynamics of the two-phase system are key to maximize yield



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Article

Continuous, stable, and safe organometallic reactions in flow at room temperature assisted by deep eutectic solvents

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SUMMARY

This work demonstrates the first continuous, stable, and safe operation of organometallic reactions in flow under ambient conditions with high moisture tolerance and clogging resistance. The addition of deep eutectic solvents (DESs), such as glyceline (choline chloride/glycerol) and reline (choline chloride/urea), overcomes the previous limitations associated with the need for cryogenic conditions (long residence times and high energy requirements) and clogging. The immiscibility of the different solvents leads to a segmented flow where the reactive organic substrates are dispersed in a continuous DES-containing carrier phase. This system provides intimate contact between solvents, favoring the dissolution of lithium species (by-product) into the DES phase, avoiding the clogging under a wide range of conditions. In addition, the microfluidic scale provides excellent heat management (recirculation flow patterns) and a high surface area/volume ratio, enabling safe operation. The benefits of DESs were studied with a selection of two organolithiums and two organomagnesium reagents, and different imine/ketone substrates.

INTRODUCTION

Organolithium reagents are commodity organometallics used daily in synthetic laboratories around the world.¹ This near-ubiquitous utilization reflects the exceptionally high reactivity of their Li–C bonds due to the polarity separation within them.^{2,3} However, their exceptional reactivity also imposes severe drawbacks on their applications. They cannot come in contact with air or water and must be used in stringently dry, toxic organic solvents and at extremely low temperatures (below -50°C), which are employed to control the reaction selectivity.⁴ Breaking down the formidable barrier between organometallic and aerobic/aqueous chemistry, the chemoselective addition of organolithium reagents to non-activated imines, ketones, and nitriles under air, in the presence of moisture, and at room temperature has been recently reported, replacing toxic conventional ethereal solvents with green, non-toxic and bio-renewable deep eutectic solvents (DESs) and glycerol (Gly).^{5–13} These studies have revealed the key role played by these DES combinations, which promote the kinetic activation of the organolithium reagents, facilitating these transformations to take place under conditions typically forbidden in polar organometallic synthesis and leading to exceptional selectivity without the need for external additives. Water molecules have been observed in some landmark studies to act as donor ligands for lithium^{14,15} and potassium^{16,17} complexes rather than leading to direct hydrolysis. In some studies, it has been shown that DESs and Gly offer a better performance than water due to their lower acidity and lower miscibility with the organic phase.^{6–9,12}

THE BIGGER PICTURE

Hardly any pharmaceutical or aromatic chemical is currently manufactured without the use of organometallic reagents. Yet, this chemistry is incompatible with air, trace moisture, and aqueous solvents. Very recently, this forbidding barrier between organometallic and aerobic/aqueous chemistry has been removed by replacing solvents with green, non-toxic, and bio-renewable deep eutectic solvents. The present work reports the safe, stable, and continuous operation of this chemistry using microreactors, without the need for oxygen-free techniques or energy-intensive cryogenic conditions, thanks to the segmented/droplet system created by deep eutectic solvents, paving the way to potentially transform manufacturing. This innovation, enabled by an interdisciplinary approach between chemistry and engineering, will lead to more sustainable processes aligned with several of the UN Sustainable Development Goals.

DESs are composed of eutectic mixtures of acids and bases (Brønsted or Lewis) and may contain different cationic and anionic species. Among different classes of DESs, a group called type III eutectics, which are comprised of an ammonium salt (most commonly choline chloride [ChCl]) and hydrogen bond donors (HBDs), have emerged as a promising class of solvents in chemical research due to their low cost, environmental friendliness, and biodegradability, and the tunability of their physicochemical characteristics. For instance, properties such as heat capacity and solubility of inorganic salts can be tuned by selecting the HBDs (a wide range are available; e.g., urea, ethylene glycol, and carboxylic acids).¹⁸ In addition, low acidity offers a broad set of beneficial functions to manage hazards and synthetic hurdles.^{19–26} Profiting from these unique features, our studies have demonstrated that DESs, such as choline chloride:glycerol in 1:2 molar ratio (ChCl/2Gly), enable air- and temperature-sensitive organometallic reactions at room temperature in open flasks.^{6–8,27,28} It has been reported that DESs also allow polymerization of styrenes in the air using organolithium reagents.¹²

Employing these new possibilities in flow promises fast-to-deploy processes for the preparation of fine chemicals by minimizing contact with air and moisture (e.g., chemicals on-demand).^{3,23,29,30} Due to poor mixing, and slow heat and mass transfer rates, traditional manufacturing technologies (using stirred tanks or tubular reactors) face difficulties in efficiently handling organometallic syntheses.²⁹ In this context, microfluidic reactor technology offers a viable solution to attain high mass transfer rates and better mixing (high contact area between fluids) and to facilitate heat transfer (high contact area between fluids and wall) by confining the reaction medium to micro- and milli-fluidic channels.^{23,31} Nevertheless, the high level of reactivity, sensitivity to air/moisture, and heat management of such fast and exothermic processes present a number of challenges.^{23,30} Functionalization using organometallics typically involves the generation of inorganic salts that are insoluble in organic media.³² In these syntheses (both in batch and flow), the production yield and selectivity are extremely sensitive to the local reaction environment. In addition, as the reactions are extremely fast (less than 5 s in batch),^{6,8} temperature and concentration gradients quickly develop within the reactor leading to an uncontrollable and unsafe process. For instance, Knochel and co-workers have successfully performed deprotonative metalation in flow conditions. This includes the development of protocols for the lithiation of aromatic C–H bonds followed by transmetalation in anhydrous tetrahydrofuran.³² More recently, researchers were also able to activate similar bonds with sodium and potassium diisopropylamide (see Power et al.⁴ for additional examples of organometallic chemistry in flow).^{33,34} Yoshida and colleagues have been able to perform highly complex and elegantly useful reaction protocols utilizing lithiation in microfluidic systems, both via deprotonation and halogen-metal exchange strategies.^{35–39} It should be noted that all these studies involve the use of volatile organic solvents.

In this work, we demonstrate the novel application of biodegradable and non-toxic DESs enabling the addition of main group organometallics to C=X double bonds while addressing the most pressing issues of deploying organometallics in flow; that is, clogging, temperature control, a need for inert atmospheres, and safety.^{3,23,29} This work pioneers organometallic syntheses in flow at room temperature with high reaction yields, even in the presence of moisture. This is achievable with ease of operation and a high level of safety with minimal preparation and precautions during the synthesis. As a prototypical challenge, the addition reactions of several main groups of organometallic species to different ketones and imines were investigated. Clogging-free operation and heat management were achieved by implementing a multi-phase, segmented-flow regime by generating isolated reaction

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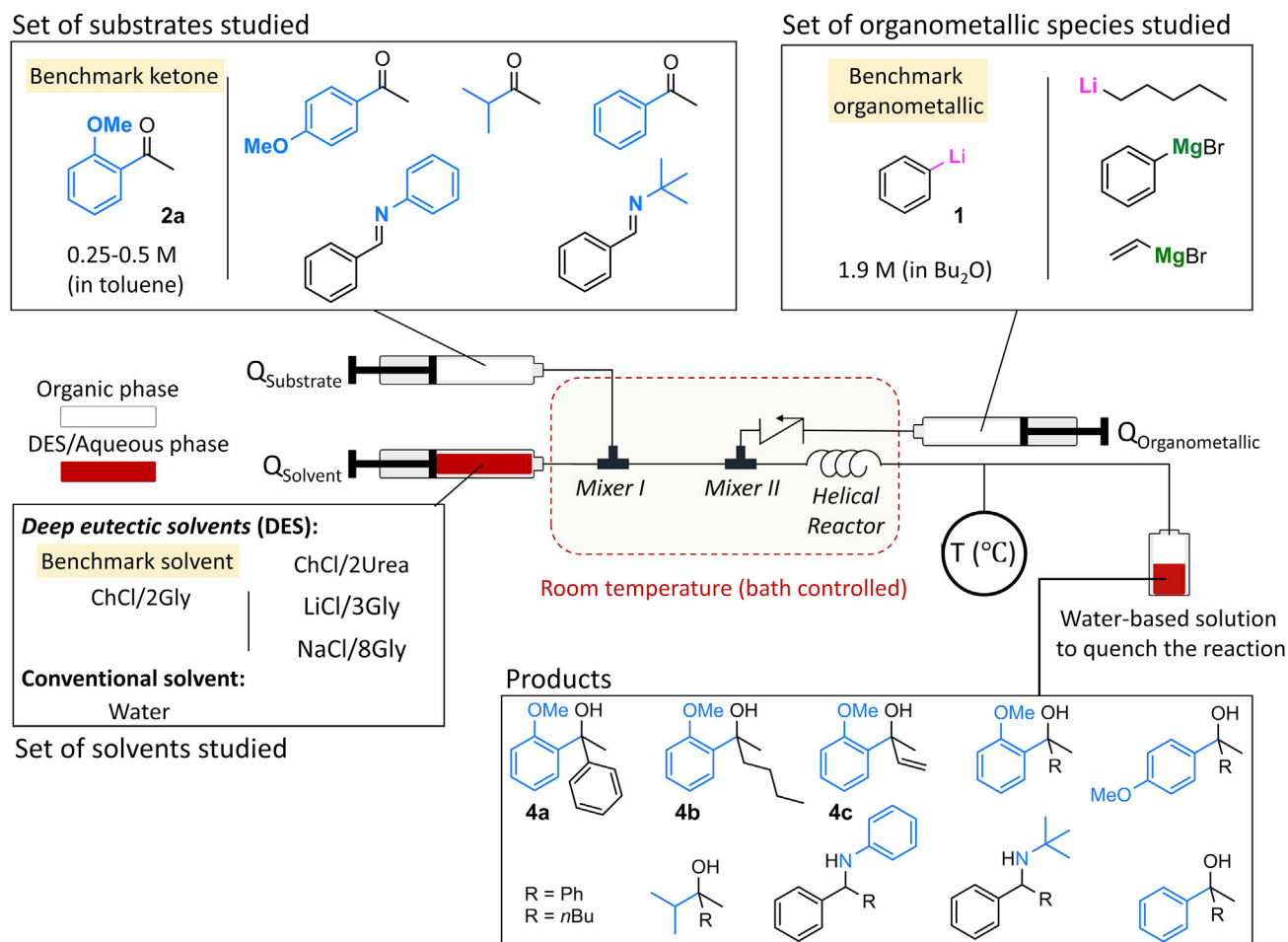


Figure 1. Continuous bi-phasic flow platform to enable organometallic reactions at room temperature

In the first stage, segmented flow is created between the DES or DES/aqueous phase and the organic phase containing the substrate. The organometallic solution is added downstream through a second mixer. The depicted ranges of substrates, solvents, and organometallic compounds were studied. To evaluate the system's bi-phasic properties and hydrodynamics, the selected benchmark system (identified by a light-yellow label) was used as a baseline. The Q_i relates to the flow rate of a given compound, being expressed in mL h⁻¹.

droplets enveloped in the continuous phase of a carrier fluid (typically a DES or its mixture with water) that preferentially wets the channel walls.

RESULTS AND DISCUSSION

Traditional continuous manufacturing technologies are often not suitable for very fast and highly energetic reactions such as organometallic ones, where fast mixing and pin-point hydrodynamic control are needed. These requirements are met herein for the first time by adopting a microfluidic bi-phasic segmented flow reactor (Figure 1). In order to achieve high yields in addition reactions using organometallic reagents over long periods of time without performance degradation at room temperature, a bespoke setup was designed to generate segmented flow, consisting of a sequence of droplets containing the substrate in toluene surrounded by an immiscible carrier phase formed by the DES, usually ChCl/2Gly. Each droplet acts as an individual reactor ready to receive the organometallic species and create a reactive medium (organometallic + substrate). It should be noted that the organic substrates employed in this study are insoluble in ChCl/2Gly, forming emulsions or suspensions.

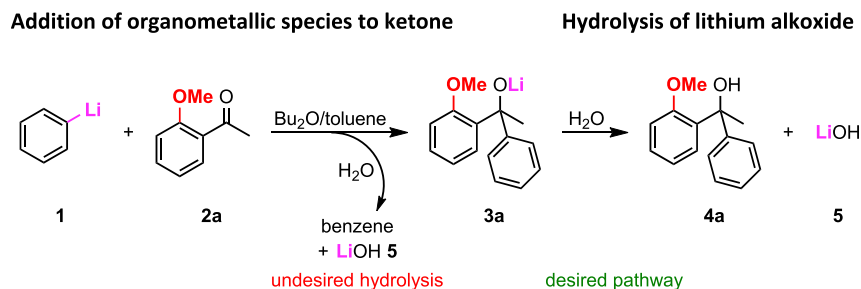


Figure 2. Benchmark reactions

Phenyllithium (PhLi) 1 addition to ketone 2a, which after hydrolysis gives tertiary alcohol 4a and lithium hydroxide 5.

Syringe pumps are used to control the flow of the immiscible solutions containing (1) the DES/aqueous mixture (i.e., ChCl/2Gly) and (2) the substrate organic solution (i.e., ketone 3a solutions in toluene). Once the segmented flow is established, the commercially available organometallic reagent organic solution (i.e., phenyllithium [PhLi] in di-*n*-butylether [Bu₂O]) is introduced downstream. T-connectors are used to facilitate the controllable formation of segmented flow. Perfluoroalkoxy alkane (PFA) tubing provided good chemical compatibility. The system was operated for at least 2.5 times its space-time before collecting samples for yield determination to ensure steady-state conditions.

Representing addition reactions of organometallic reagents to C=X double bonds, we first examined the addition of PhLi 1 to 2'-methoxyacetophenone 2a as a benchmark for testing our bespoke flow microsystem (Figure 2).^{6,8} This reaction produces lithium alkoxides such as 3a as an intermediate, which consequently hydrolyses, liberating the desired tertiary alcohol 4a and lithium hydroxide (LiOH) 5. Such tertiary alcohols are part of several pharmaceutically active ingredients and have seen widespread use in industry and academia.^{40–42}

Reaction yields up to 98% are achieved with 1.25 equivalents of PhLi to substrate ratio, with 100% selectivity within 35 s of residence time without the need for oxygen-free techniques. The product was isolated in yields of 90% by recrystallization in Et₂O. The room temperature conditions favor the fast reaction rate compared with cryogenic conditions which usually require considerably longer residence times on the scale of tens of minutes. By comparison, most of the previous studies using RLi (organolithium) in conventional organic solvents in flow synthesis require cryogenic conditions and can be susceptible to clogging by solid formation. Although the traditional batch synthesis can be performed similarly quickly with high yields, this also typically employs cryogenic conditions and has to be kept under strictly oxygen- and moisture-free conditions.³ On the other end of the spectrum, there are also extremely fast processes available (flash chemistry); however, these require considerable optimization efforts for every reaction at hand.⁴³

A key aspect of the system is the introduction of the organometallic species into the segregated substrate-containing droplets. The ideal “meeting mechanism” (or droplet coalescence of organic phases) between both solutions is depicted in Figure 3A. In reality, the perfect integration between reactants is not always achieved periodically. In cases where the organometallic solution (i.e., PhLi) is instead dispersed in the DES-containing phase, it partially hydrolyses in a side reaction with DESs (refer to Figure 2). Thus, the efficient interaction between the organometallic (PhLi) and the substrate solutions dictates the system's performance (i.e., yield and selectivity). Such interaction can be tuned by varying the flow rate (Q) of

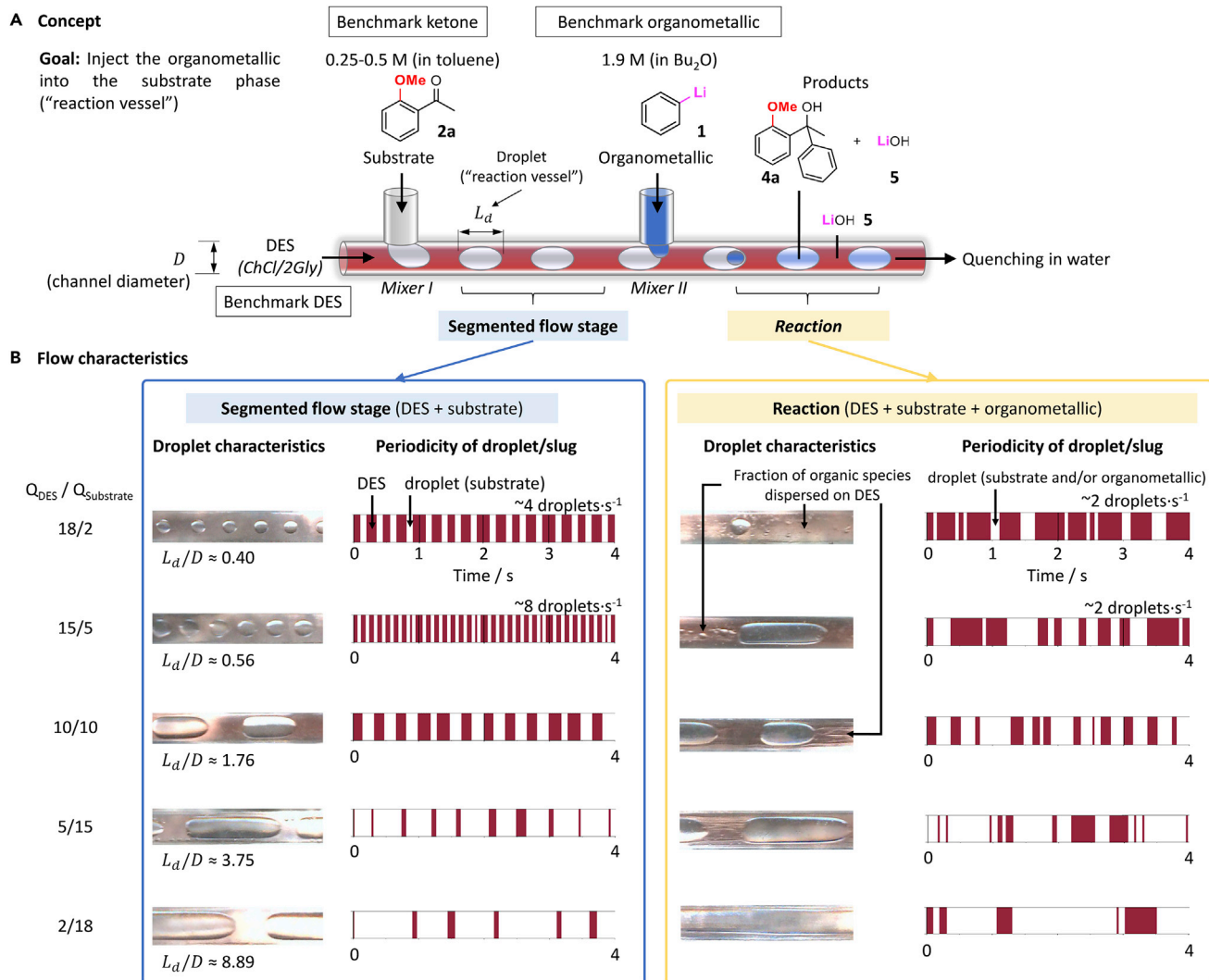


Figure 3. Schematic of the flow system and inspection of the droplet behavior

(A) Graphical representation of the flow system with two defined stages: segmented flow formation stage and reaction stage. The first stage generates the segmented flow between the DES and substrate solutions. The second stage involves the addition of the organometallic solution to the substrate droplet, forming the reactive media.

(B) Droplet behavior at each stage as a function of the flow-rate ratio between DES and substrate solutions ($Q_{Carrier}/Q_{Substrate}$). The periodicity of the droplet/slugs at each stage is graphically represented as white (substrate droplet) on red (DES carrier fluid) strips. The data were obtained by using circular image probes applied to the videos acquired during the experiments. All the visual experiments were done in a non-reactive system to decouple hydrodynamics from reaction effects. In these cases, no substrate was in the organic (toluene) phase, and phenol replaced the organometallic species to mimic the interfacial effects of the organometallic species in dibutyl ether as a safe control experiment. The videos relative to both model flow systems can be accessed in the [supplemental information \(Videos S1 and S2\)](#).

the carrier fluid (DES or its mixture with water, $Q_{Carrier}$) relative to the reactive phases (organometallic and substrate, Q_{PhLi} and $Q_{Substrate}$, respectively), which allows control over the droplet populations.

In the segmented flow stage, stable droplets are formed with good periodicity for all the flow-rate ratios tested, from $Q_{Carrier} / Q_{Substrate}$ ratio of 2/18 to 18/2. As depicted in [Figure 3B](#), when increasing the $Q_{Substrate}$ (from 2 to 18 mL/min), the droplet size increases, going from 0.4 to 8.89 (in a dimensionless form, L_D/D , where L_D is the droplet size and D is the reactor diameter). The droplet dynamics are followed using

a probe (Figure 3B), providing information about droplet periodicity and size (represented by white bars in Figure 3). The flow rate of the substrate solution ($Q_{\text{Substrate}}$) can affect both the droplet size as well as the number of droplets per unit volume (i.e., concentration). For example, $Q_{\text{Substrate}}$ of 2 and 5 mL/min led to droplet sizes of 0.40 and 0.56 (L_D/D), respectively, and a simultaneous increase in number from 4 to 8 droplets/s (and consequently velocity from 4.2 to 11.5 mm/s).

In all our experiments, we noticed that upon introducing the organometallic organic stream into the bi-phasic substrate/DES one, the periodic segmented flow regime was disrupted, leading to the formation of a dispersed bi-phasic system, including small and large coalesced droplets (see Figure 3).

When the organometallic phase is integrated into the substrate slug, it results in an increase in the droplet size. On the other hand, when the organometallic phase is introduced into the DES-containing carrier phase, it generates small droplets. The ratio between the number of occurrences depends on the relative flow rates between the three phases. One should note that while the substrate and organometallic phases are miscible in each other, both are immiscible in the DES-containing carrier phase. As the $Q_{\text{Substrate}}$ increases, the presence of organometallic non-reactive droplets dispersed in the DES-containing carrier phase decreases, and most of the organometallic species are incorporated into the substrate droplet, through coalescence (indicated by larger white bars in Figure 3B).

To further examine this phenomenon, we conducted flow observations to assess the interactions between the different streams. To focus on the hydrodynamic features only and de-couple them from the reaction, we designed a non-reactive system where the 1.9 M PhLi solution was replaced with a 1.9 M solution of phenol in toluene, and the substrate solution was replaced with blank toluene. Phenol was chosen to mimic the effect of PhLi due to its dipole moment and similar monomeric molecule size, which we assumed would allow similar interfacial adsorption behavior at the toluene-DES interface (despite their likely different aggregation states in bulk ether solvents). These conditions mimic the ones that were used to perform the reaction, and this set of concentrations is maintained throughout the paper.

Replacing the substrate solution (in toluene) with pure toluene did not affect the formation of a well-defined segmented flow. However, a similar disruption behavior occurred when the organometallic PhLi solution was replaced by the phenol solution, as both of these polar species appear to act as a surfactant, decreasing the surface tension of droplet interfaces and allowing droplets to merge.

Continuous reactions of organometallics with ketones and imines usually suffer from clogging events due to the formation of insoluble lithium salts as the reaction by-product.⁴ In addition, insoluble LiOH is also formed in the reactions that are not performed in strict moisture-free conditions, due to the hydrolysis of the organometallic lithium species. Herein, we demonstrate for the first time the long-term stable operation of these reactions, even under atmospheric conditions, enabled by not only the presence of DESs such as ChCl/2Gly but also the segmented flow, which promotes the transfer of potentially insoluble compounds (such as lithium salts) from the organic phase to the DES phase, enhancing the contact area between both phases.

To demonstrate this, a set of experiments was conducted at room temperature by varying the amount of water in the carrier phase (using ChCl/2Gly and water mixtures

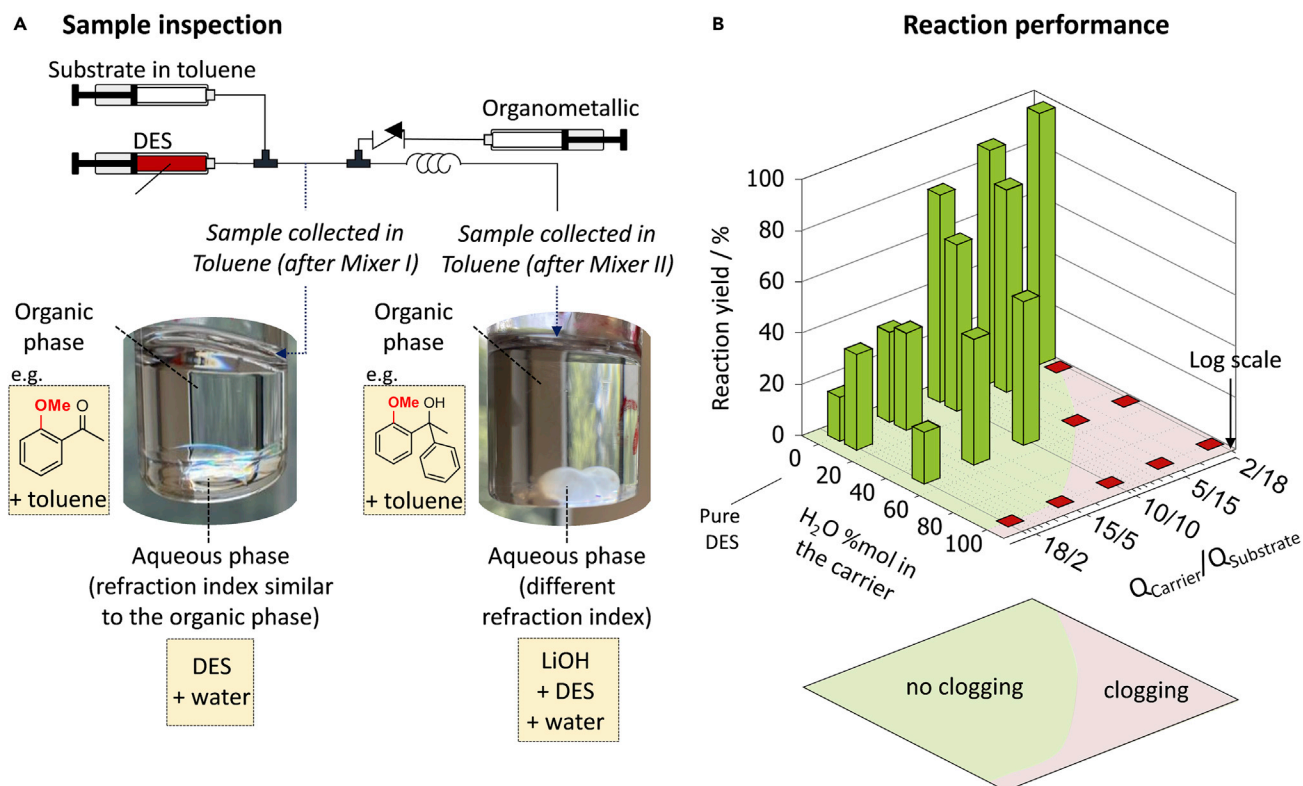


Figure 4. Visual inspection of the outlet content after mixing and reaction performance outcomes

(A) Outlet content after *Mixer I* and *Mixer II* (conditions 50% water, $Q_{\text{Carrier}}/Q_{\text{Substrate}} = 5/15$). The addition of organometallic reagents leads to a clear change in the refraction index of the aqueous phase, demonstrating the dispersion of LiOH and potentially other chemicals in the aqueous phase containing DESs.

(B) Three-dimensional plot summarizing the effect of flow-rate ratio ($Q_{\text{Carrier}}/Q_{\text{Substrate}}$) and water content (%mol) on the yield and stability of the system. Red bars represent the observation of clogging without product collection, and green bars represent a stable operation without clogging. The flow-rate units (Q_{Carrier} , $Q_{\text{Substrate}}$, and Q_{PhLi}) are mL h^{-1} . All the reactions were carried out with 1.25 equivalents of PhLi to substrate (to compensate for any possible PhLi hydrolysis, equivalent to a $Q_{\text{Substrate}} : Q_{\text{PhLi}}$ of 1:3).

with different molar ratios, ranging from 0% to 100%, inclusive). Figure 4 shows a three-dimensional plot covering the reaction yield (based on ketone **2a**) as a function of the water content and the $Q_{\text{Carrier}}/Q_{\text{Substrate}}$.

In the absence of a carrier DES-containing fluid and thus single-phase operation (i.e., non-segmented flow [$Q_{\text{Carrier}}/Q_{\text{Substrate}} = 0/20$]), the organometallic stream (containing PhLi) is in direct contact with the substrate (i.e., ketone) leading to variability in clogging with a high dependence on the start-up routine and dryness of toluene used. Clogging happens when there is a rapid reaction between both species that leads to the fast accumulation of precipitates (e.g., LiOH), which is more rapid than the media dispersion/dissolution rate. Both the intermediate lithium alcoholate **3a** and product alcohol **4a** are highly soluble in the organic phase. On the contrary, the reaction product LiOH (possibly forming alongside other inorganic lithium salts) is not soluble in toluene or DES but is soluble in water. It is noteworthy that in the case of 50%mol DES/water the LiOH is still not soluble, forming a dispersion. The affinity of LiOH toward the solvent media follow water (soluble) > 50% DES (dispersion) > 100% DES (dispersion) > toluene (dispersion). The presence of LiOH in the aqueous phase was visually inspected by changes in the refraction index before and after the reaction with organometallic reagents (clear versus cloudy droplets, Figure 4A), which proves that the aqueous phase is actively removing insoluble

precipitates during the reaction. Attempts to use water as a carrier fluid (100% water content) also resulted in an immediate clogging of the system for all the flow conditions tested ($Q_{\text{Carrier}}/Q_{\text{Substrate}}$). The independence of such clogging events from the flow conditions indicates the rapid formation of insoluble species through the hydrolysis of PhLi in contact with water. As a consequence, no or diminished reaction between the ketone and PhLi takes place. In addition, clogging took place in the T connector (*Mixer II*), where PhLi is in direct contact with water (100%).

On the other hand, when pure DES is used as the carrier fluid (ChCl/2Gly; with a water content of zero), the reaction proceeds without clogging for all the flow conditions tested (Figure 4B). This is a result of the greater dispersion/dissolution of the LiOH and **4a** combination in ChCl/2Gly. Even more interesting is the fact that in the presence of DESs, the system can cope with a large amount of water (up to 50%) without clogging, but only if the $Q_{\text{Carrier}}/Q_{\text{Substrate}} > 10/10$. The set of conditions that allows stable, clogging-free operation is represented at the bottom of the graphic in Figure 4B.

In the absence of clogging, the reaction yield increases as the $Q_{\text{Carrier}}/Q_{\text{Substrate}}$ decreases, achieving values up to 98%. This trend is supported by the previously discussed hydrodynamic behavior in Figure 3B. At high $Q_{\text{Carrier}}/Q_{\text{Substrate}}$ ratios, the probability of coalescence of the organometallic phase into the substrate droplet is low and, in addition, contact of the PhLi directly with the DES leads to its hydrolysis into inactive benzene. Indeed, the PhLi hydrolysis is the main reason for yield losses, as the reaction was found to be chemoselective. Quantitatively, more than 97% selectivity (yield/conversion based on the ketone substrate) was achieved in all cases, and the only detectable side-product was styrene, which we found to originate after the reaction, from protonation by residual HCl in the NMR solvent CDCl_3 . Low reaction yields (~20%) are observed for all the values of $Q_{\text{Carrier}}/Q_{\text{Substrate}} = 18/2$, independently of the amount of water present. When decreasing the $Q_{\text{Carrier}}/Q_{\text{Substrate}}$ ratio, the probability of the PhLi stream being introduced directly into a substrate droplet increases, leading to an increase in reaction yield. In addition, the organometallic phase disrupts the periodic segmented flow, creating a superior chaotic mixing environment (Figure 4B) favoring the reaction yield (up to 98%).

Using the same experimental conditions (1.25 equivalents of PhLi and $Q_{\text{Substrate}} = 3Q_{\text{PhLi}}$), an alternative DES formed by a mixture of choline chloride and urea (ChCl:2urea, so-called reline) presented reaction yields of 73% and 56% for $Q_{\text{Carrier}}/Q_{\text{Substrate}}$ of 10/10 and 15/5, respectively. At a $Q_{\text{Carrier}}/Q_{\text{Substrate}} < 5/10$, the reactor clogged. At 81%, the yield for 10/10 is slightly lower than for ChCl/2Gly. The difference in performance can be explained by the different surface tensions of both DESs,⁴⁴ leading to differences in the segmented flow, droplet size, and periodicity, which consequently translates into a more efficient coalescence mechanism between the PhLi phase and the substrate droplets. Even though this is beneficial to the reaction yield, reline seems to have lower solubility toward lithium salts, which enables a narrower range of conditions ($Q_{\text{Carrier}}/Q_{\text{Substrate}}$ ratios) without clogging. Other DESs, such as LiCl/3Gly and NaCl/8Gly, are too viscous for stable flow and, therefore, they were not further tested. Despite this, we demonstrate that it is possible to use another DES successfully, albeit with careful optimization, considering the hydrodynamic properties of each system.

This work demonstrates the first continuous and safe operation of organometallic reactions in DESs in flow at ambient conditions, demonstrating moisture tolerance and clogging resistance. Previous attempts required the use of cryogenic conditions and long residence times to account for the slow kinetics under such

conditions, with their associated large energy consumption. One such cryogenic approach reports a similar reaction with the same organometallic reagent (PhLi) to enable the iodation of 4-fluoro-2-(trifluoromethyl)benzonitrile in flow, requiring -70°C for 20 min to facilitate the lithiation step and avoid clogging events.⁴⁵ Indeed, according to a recent review by McGlacken and colleagues,⁴ most flow reactions involving organometallic species have been restricted to cryogenic temperatures between -70°C and -30°C . This is the first time that an organometallic reaction using PhLi was conducted with no clogging events at room temperature in a continuous flow, requiring low residence times (~ 35 s). Some related reactions that were enabled at room temperature have been performed in considerably lower concentrations, while utilizing sub-second residency times and high flow rates or much more complex setups requiring elaborate optimization for avoiding fouling (e.g., in-reactor phase separations and flushing with water).^{46–48} Based on these results, the proposed microreactor system presents an attractive approach for the continuous manufacturing of pharmaceutical and aromatic compounds using organometallic reagents, where production can be simply increased by running the system for longer periods of time, in contrast to batch manufacturing approaches. The further scale-up of production will require careful consideration to ensure that the fluid dynamics of the system are maintained, with the possibility of using reactors working in parallel as a common approach.

In addition, the high surface to volume ratio characteristic of microreactors enables efficient heat management, avoiding the rapid increase of temperature normally associated with the highly exothermic addition reactions of organometallic reagents to C=X double bonds. In particular, our baseline reaction of the addition of phenyl lithium to 2'-methoxyacetophenone has an enthalpy of reaction of 143 kJ/mol (measured by calorimetry; see [supplemental information](#) for details). Indeed, using an infrared thermal camera, we observed a large increase in temperature as soon as the organometallic phase was introduced in the system (*Mixer II*, where organometallic and the segmented substrate/DES meet) associated with the high rate of reaction at room temperature. Such an increase in temperature was also measured by inserting a thermocouple after the T connector. Our attempts to measure the experimental temperature increase show ΔT below 15°C , even at the highest reaction yields where the corresponding adiabatic temperature increase calculations indicated an increase above 40°C . We speculate that the excellent heat management of the system is not only associated with the dissipation of heat across the walls of the reactor favored by the internal fluid recirculations characteristic of segmented flow (i.e., Taylor flow⁴⁹) but also with the high volumetric heat capacity of the DES (ChCl/2Gly, $2.64\text{ J mL}^{-1}\text{ K}^{-1}$) compared with the organic phase (toluene, $1.7\text{ J mL}^{-1}\text{ K}^{-1}$). Therefore, this system enables the increase of substrate concentration without their thermal decomposition when the reaction is carried out at room temperature.

The reaction system can be expanded to a range of different substrates and organometallic compounds. To demonstrate this, we adopted conservative conditions to maximize conversions while replacing the organic solvent with a significant amount of environmentally benign DES. The substrate concentration was halved and the organometallic flow rate was adjusted to 2.5 equivalents ($Q_{\text{Carrier}} / Q_{\text{Substrate}} = 5/5$, carrier phase = ChCl/2Gly and substrate concentration in toluene = 0.25 M). These conditions led to reasonable yields ($>50\%$) while enabling the comparison between the different substrates and organometallic compounds.

Several organolithium and organomagnesium species were screened using commercial solutions of *n*-butyllithium (2.5 M in *n*-hexane), phenylmagnesium bromide

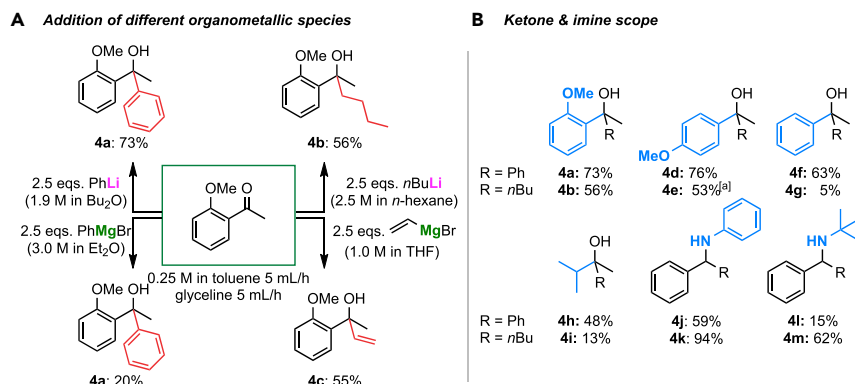


Figure 5. Screening of different organometallic reagents and ketone and imines substrates

(A) Yield obtained using different organolithium and organomagnesium species for their addition to ketone **2a**.

(B) Addition of phenyllithium (Ph) and *n*-butyllithium (*n*Bu) to a range of ketones or imines. ^aBy-product formation was observed with a product selectivity of 90%.

(3.0 M in diethylether), and vinylmagnesium bromide (1.0 M in tetrahydrofuran), with the $Q_{organometallic}$ adjusted to introduce 2.5 equivalents (Figure 5A). The addition of 2'-methoxyacetophenone proceeded smoothly, leading to phenylalcohol (**4a**; 73% yield), *n*-butylalcohol (**4b**; 56% yield), and vinylalcohol (**4c** 55% yield). On the contrary, the addition of the phenyl Grignard reagent only gave a yield of 20% **4a** as a result of poor mixing behavior caused by the formation of bubbles due to the evaporation of the diethylether.

Different ketones and imines were also screened (Figure 5B). Within the acetophenones studied, PhLi generally gave slightly better yields for a range of different ketones, resulting in 73% **4a**, 76% **4d**, and 63% yield of **4f**. Besides, 56% yield of the butyl-substituted alcohol **4b** and 53% of **4e** were found, while the addition of *n*-BuLi to acetophenone only gave **4g** in 5% yield. Polarization of the ketone seems to have a crucial effect on the addition of *n*-BuLi, as seen for the substrate 3-methylbutanone, giving 48% of the phenyl addition product **4h** and only 13% of **4i**. Similar high yields were observed with a range of imines as well; *N*-phenylbenzylimine gave very similar yields compared with 2'-methoxyacetophenone. Yields of 59% were found for **4j** and considerably higher yields of 94% for **4k**. The sterically more hindered, *tert*-butyl-functionalized amine shows reduced yields with both PhLi (**4l**: 15%) and *n*-BuLi (**4m**: 62%). It is important to note that these yields are considerably lower than those achieved in batch conditions (83% and 91%, respectively), indicating that optimization of the hydrodynamics of the system to maximize the effective mixing of the organometallic species in the substrate droplets, minimizing their parallel decomposition when in direct contact with the DES carrier phase, is needed.

Conclusions

This work pioneered the flow production of alcohols and amines from ketones and imines, with a selection of two organolithium and two organomagnesium reagents at room temperature without clogging, enabled by the presence of DESs. We demonstrate that segmented flow between the immiscible DES-containing carrier phase and the dispersed substrate organic phase facilitates stable operation without clogging at room temperature by the dispersion/dissolution of any formed lithium salts (either as by-products of the reaction or by hydrolysis decomposition) in the DES. In addition, the segmented-flow microfluidic system has the added advantage of improved mixing and heat transfer due to the secondary vortices present within

the droplets and high surface-area-to-volume ratio, enabling the stable and safe operation of the reactor at room temperature. Both aspects require the optimization of the hydrodynamics of the system to maximize the contact between the organometallic reagents and the substrate droplets and minimize the decomposition of the organometallic reagents by direct contact with the DES. The ambient conditions, and thus the high reaction rates, moisture tolerance, and stable operation, result in a more attractive process in comparison with processes that apply cryogenic conditions and long residence time, which have a large energy consumption.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Laura Torrente-Murciano (lt416@cam.ac.uk).

Materials availability

This study did not generate new unique reagents.

Data and code availability

The NMR raw data and videos generated during this study have been deposited at University of Cambridge Apollo repository: <https://doi.org/10.17863/CAM.72288> and are publicly available as of the date of publication. All other data reported in this paper will be shared by the lead contact upon request.

Flow reactor setup

The setup consisted of a PFA tubing reactor ($D = 0.76$ mm internal diameter), and ethylene tetrafluoroethylene (ETFE)/PFA fittings. The different streams were introduced using syringe pumps. A solution of the substrate in toluene was introduced via a T-mixer (*Mixer I*) into a stream of the carrier phase (DES) producing a segmented flow regime with the droplets of the organic phase enveloped by the DES. Downstream, a commercial solution of PhLi (1.9 M) in Bu₂O was added using a second T-mixer (*Mixer II*). Subsequently, the addition reaction took place in a tubular microreactor (0.23 mL). The microreactor length (50 cm) allows for an excess of residence time (t_{res} ; in the order of 30–90 s) to ensure the full conversion of the PhLi. The outlet stream was collected into a vial containing water to ensure the full hydrolysis of the hazardous unreacted organo-Li species and to quench the reaction. A check valve was included in the PhLi supply line to prevent the potential backflow into the organometallic-containing stock syringe. Additionally, a syringe containing toluene was connected to this supply line (using a T connector) via a manual valve. This allowed for simple reactor maintenance by flushing all the reactor parts that come into contact with the reactive PhLi.

Preparation of reagent solutions

In a typical experiment, 5.05 mmol of the corresponding ketone were weighed (solids) or volumetrically determined (liquids) and dissolved in 10 mL technical grade toluene in air in a screw-cap vial. The solution was then filled into a 5 mL Luer lock syringe to be mounted on the employed syringe pumps.

Preparation of organometallic solutions

The employed organometallic species were used as commercially available. A positive stream of nitrogen was applied to the commercial container via tubing connected to a needle. A 5 mL Luer lock syringe was then flushed three times with nitrogen before filling with the appropriate amount of the solution, the needle was

removed, and the syringe was quickly attached to the syringe pump and the Luer lock male connector of the microreactor setup.

Product collection

The reactor outlet was collected in a 10 mL glass vial as waste until the reactor volume was flushed 2.5 times its space-time to ensure steady-state operation. Then, a different 10 mL glass vial containing 3 mL of water and a pre-weighed amount of hexamethylbenzene as an internal standard for NMR experiments was used to collect samples for analysis. This approach was used as a safety precaution to quench any unreacted organometallic species in the outlet stream. The organic phase was then diluted with 1.5 mL toluene and a 500 μ L aliquot was taken and the solvent was allowed to evaporate overnight. The remaining mixture of reactant and products was then dissolved in 650 μ L CDCl_3 for quantitative ^1H NMR analysis. The yield and selectivity were determined based on the integral of the remaining reactant, product, and (if any) side-products as used before in literature.⁶

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.chempr.2022.11.004>.

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AUTHOR CONTRIBUTIONS

F.F.M. and B.P. performed the investigation, formal analysis, and writing/editing; A.W.J.P. repeated most experiments to revalidate the results obtained; F.F.M. and A.W.J.P. did the NMR analysis; M.R.A. and A.J.E. introduced F.F.M. to the flow chemistry tools used in the study and aided in the writing of the initial draft. K.J.E., E.H., and L.T.-M. conceived, founded, and managed the project. All the authors analyzed and discussed the results and gave inputs to the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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