

Previews

Polar organometallic chemistry meets deep eutectic solvents in flow

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Polar organometallic chemistry in water and deep eutectic solvents (DESs) have recently captured the attention of chemists. In this issue of *Chem*, Torrente-Murciano, Hevia, and co-workers pioneer the first continuous and safe handling of organometallic reagents in (aqueous) DESs with an easy setup and without clogging problems at room temperature.

Organometallic chemistry undoubtedly plays a vital role across a wide spectrum of science. It still remains a core subject in the pursuit of all those “grand challenges” (e.g., energy, materials, and health) toward which priorities are tending more and more, despite the lack of champions for it among granting agencies worldwide. At the same time, the environmental concerns imposed by current society are forcing chemists to reshape long-established paradigms, while concepts such as bio-renewable resources or sustainability are being rapidly implemented in the chemical industry. Thus, continuous innovation is needed starting from novel, fundamental advances toward the implementation of the 12 principles of green chemistry according to the European Green Deal agenda. But what would make organometallic chemistry (more) sustainable? Organic solvents are among the most responsible for most waste generated in the chemical industries and laboratories. For these reasons, and to balance the diminution of oil supplies, there is a pressing need for the development of renewable solvents not based on crude petroleum toward a concept of circular rather than linear economy. In this vein, the routine use in organometallic chemistry of solvents that are safer, renewable, and recyclable would certainly represent a first step forward in fighting the threat

coming from climate change. But when considering polar organometallic reagents belonging to the s-block elements, there are additional restrictions, as their use typically requires the employment of low temperature (−78°C or lower), inert atmosphere, and strictly anhydrous volatile organic compounds (VOCs) because of their notorious air and moisture sensitivity due to their high basic character.

Recent groundbreaking studies from a few laboratories worldwide, however, have shown that the principles and the rules governing the world of “conventional” solvents might indeed be different from those applicable to “unconventional” solvents when it comes to dealing with polar organometallic reagents. Organolithium compounds, for example, have been proven to undergo fast nucleophilic addition to carbonyl derivatives, imines, and nitriles (within a few seconds of reaction time), and even direct Pd-catalyzed cross-coupling reactions with aryl halides, when working in water or in protic bio-based solvents like the so-called deep eutectic solvents (DESs).^{1–5} DESs represent an emerging class of bio-renewable solvents. They can be readily prepared by mixing and heating two or three safe and nature-inspired components able to engage in reciprocal hydrogen bond interactions. Thus, no

waste is generated in the process, and no purification is required. Water and DESs, both characterized by strong and extended H-bond networks, are key players in the work of Torrente-Murciano, Hevia, and co-workers. In this issue of *Chem*, the authors have reported that the switch of polar organometallic chemistry from batch to flow is feasible also when working with choline chloride (ChCl)-based eutectic mixtures as reaction media, and this, in turn, enables organometallic reactions to be run continuously and safely, and most importantly, at room temperature and with high moisture tolerance and clogging resistance.⁶

There are a number of benefits of using continuous-flow chemistry. These include (1) better control and reproducibility of reactions by modulating key reaction parameters such as mixing, heating, and residence time; (2) accessibility to a wider range of reaction variables; (3) an improved safety process, especially in the case of hazardous, exothermic, or otherwise energetic reactions; and (4) an easy optimization and scale-up of chemical processes. Continuous flow-processing of organolithium reactions in VOCs, however, generally requires cryogenic conditions and is often plagued by clogging problems caused by insoluble lithium salts formed either as reaction byproducts or by undesired hydrolysis of the organometallic lithium species.⁷

A key aspect of the engineered system setup by Torrente-Murciano, Hevia, and co-workers in this issue of *Chem* is the adoption of a microfluidic biphasic segmented flow consisting in a sequence of droplets containing the

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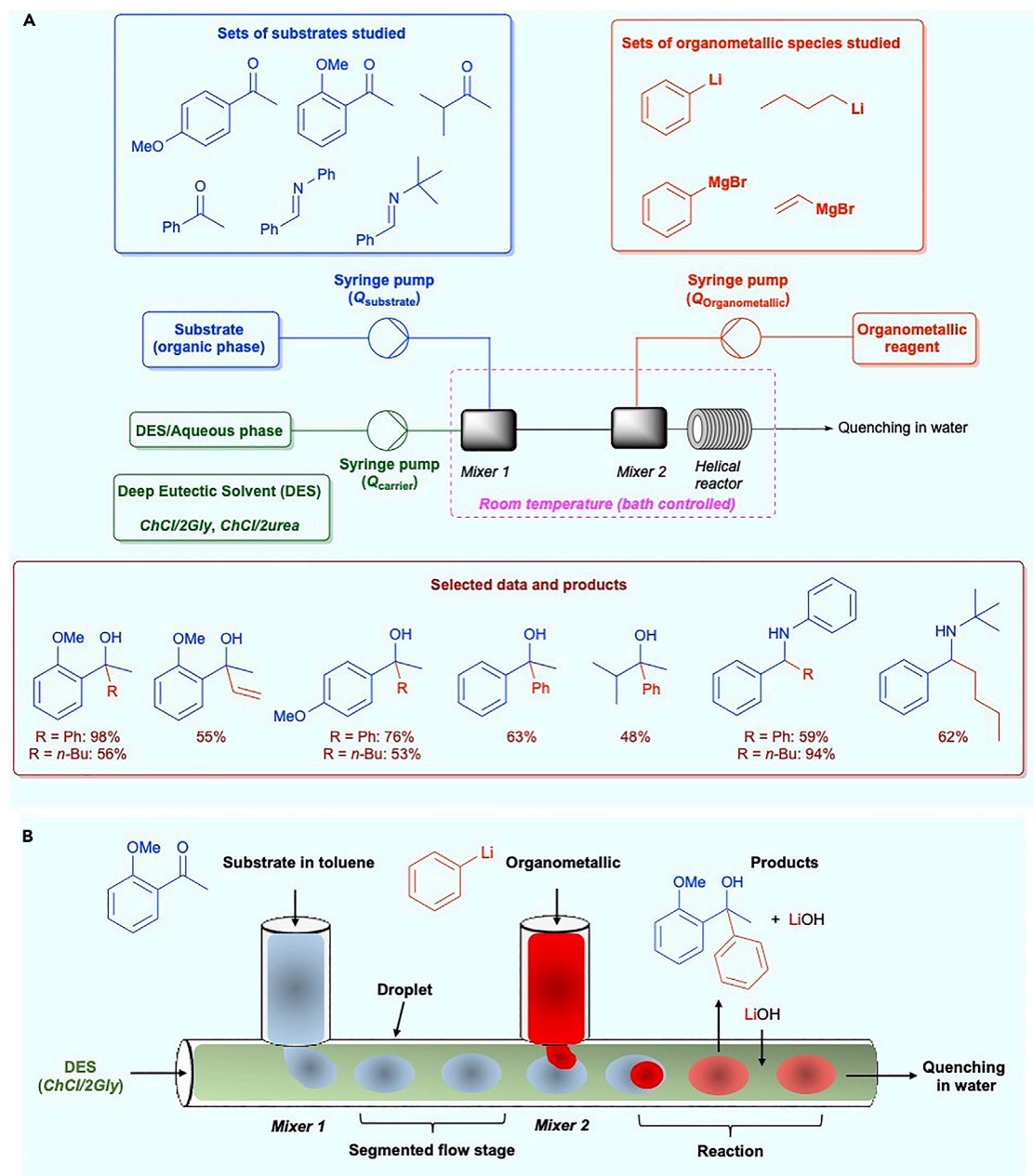


Figure 1. Continuous organometallic reactions in flow assisted by deep eutectic solvents

(A) Reactions between polar organometallic reagents and carbonyl derivatives or imines at room temperature enabled by a continuous biphasic flow platform.

(B) Schematic representation of the flow system for the addition of PhLi to *o*-methoxyacetophenone including an initial segmented flow formation stage followed by a reaction stage.

substrate (e.g., carbonyl compounds and imines) in toluene surrounded by an immiscible DES-containing carrier phase. The two immiscible solutions are pumped by two syringes, with a controlled flow rate ($Q_{\text{substrate}}$ and

Q_{carrier}), into a first micromixer (mixer 1). Then, the organometallic reagent is introduced downstream with a selected flow rate ($Q_{\text{organometallic}}$) into a second micromixer (mixer 2) (Figure 1A). The goal is the injection of the organome-

tallic species into the droplet, which is the reaction vessel (Figure 1B). By increasing $Q_{\text{substrate}}$, both the droplet size and the number of droplets per unit volume increase, while the presence of the organometallic species

dispersed in DES-containing carrier phase decreases, and thus most of the organometallic species can be incorporated into the substrate droplet through coalescence with a higher yield. For example, under optimized conditions (up to $Q_{\text{carrier}}/Q_{\text{substrate}}$ 2/18), the addition of PhLi to *o*-methoxyacetophenone (organic phase: toluene; carrier phase: ChCl/2glycerol [Gly]) takes place with 100% selectivity at room temperature, delivering the desired adduct in up to 98% yield within a 35 s of residence time (Figures 1A and 1B). At the same time, the proposed system provides an efficient heat-management platform; a boost in temperature (enthalpy of the reaction calculated by calorimetry: 143 kJ/mol) is prevented not only by the high surface-to-volume ratio typical of micro-reactors but also probably by the higher volumetric heat capacity of DESs (ChCl/2Gly: $2.64 \text{ j mL}^{-1} \text{ K}^{-1}$) than of the organic phase (toluene: $1.7 \text{ j mL}^{-1} \text{ K}^{-1}$). Thus, there is no need to use sophisticated reactors with a size from 10^{-6} to 10^{-3} or to greatly reduce the residence time to less than seconds, such as when one wants to tame extremely fast and exothermic reactions in a highly controlled manner, according to the guidelines of "flash chemistry."⁸

All in all, the joint combination of DES and a segmented flow (1) ensures a long-term stable operation of the device; (2) allows the meeting between the substrate and the organolithium reagent in a continuous and safe way; (3) improves mixing and heat transfer, enabling safe operations at room temperature; and (4) also promotes a fast transfer of potentially insoluble lithium salts from the organic to the DES phase thanks to an intimate contact achieved between the two phases, thereby avoiding the problem of clogging. Clogging usually takes place when the reaction between the organometallic species and the electrophile is faster than the dispersion/dissolution rate of

in-situ-formed salts by the carrier phase. Interestingly, a thorough investigation of the impact of different flow rates ($Q_{\text{carrier}}/Q_{\text{substrate}}$) and water content on the reaction performance disclosed that even with an aqueous eutectic mixture of ChCl/2Gly (up to 50 mol % H₂O), the reaction proceeds well and without clogging when the $Q_{\text{carrier}}/Q_{\text{substrate}} > 10/10$. Thus, with a judicious choice of the reaction conditions, even organolithium reagents can be re-engineered, coaxing them to selectively react with the substrate rather than with water, which mainly acts as a carrier phase and not as a quenching reagent!

Different DESs, however, cannot be freely interchanged with each other on equal terms. This is because of their surface tensions and viscosity potentially differently impacting the stability of the corresponding segmented flow and the droplet size and periodicity. The different solubility behavior of DESs toward lithium salts can represent an additional problem. The authors have ascertained that while a ChCl/2urea mixture can alternatively be used as a DES (though with slightly lower performance than ChCl/2Gly), the same does not hold good when switching to LiCl/3Gly or NaCl/8Gly, which are too viscous to guarantee a stable flow. The practicability of the methodology has been demonstrated by screening a range of organolithium and organomagnesium reagents, ketones, and imines. Variability in yields suggests that an optimization of the hydrodynamics of the system studied can be potentially useful in order to make effective the mixing of the organometallic species with substrate droplets and to minimize its decomposition (Figure 1A).

There is something of magic and an intrinsic beauty in the chemistry of polar organometallics run in unconventional solvents (either in batch or in flow) such as water and DESs. Tangible ad-

vantages often include simplicity of operation and easy setups, fast reactions, and no need of cryogenic conditions or protection from moisture. The same water should no longer be considered a "foe" but rather a "friend" for polar organometallic compounds for its ability to stabilize reagents, products, and transition states, to promote H-transfer reactions and catalysis, and even to be engaged in hydrogen-bonding interactions with metal salts of organic compounds.^{3,5,9} The synthesis of water-containing organometallic potassium complexes, recently reported by Stalke and co-workers, is rather amazing and unexpected!¹⁰ After welcoming the meeting of polar organometallic chemistry and aqueous DESs in flow, which certainly paves the way for a sustainable metal-assisted production of industrially relevant molecules, a fundamental question remains to be answered: what happens at the interface when polar organometallics start liaising with water or DESs? A deeper understanding of these phenomena could be fruitful not only to develop a truly green organometallic chemistry but also to fully exploit the potential of this "new" chemistry!

DECLARATION OF INTERESTS

The author declares no competing interests.

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Hybrid chem-bio production from electricity and CO₂ via two-carbon mediators

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In this issue of *Chem*, Zhang et al. describe a new system for the production of biomass and bioplastic from CO₂ and electricity. Their system is a hybrid chemical and biological system in which the electrochemical system generates a mixture of soluble two-carbon (C₂) mediators to feed the bacterium *Pseudomonas putida*.

We currently face several major global crises, such as climate change, biodiversity loss, and politically undesirable resource dependencies. Renewable-energy technologies and electrification have started to transition our energy system toward becoming independent of carbon and fossil resources. However, apart from the energy system, a large factor in these global issues is the production of carbon-containing chemicals, materials, and food. To fulfill the future demand for carbon-based products, we urgently need to develop sustainable production routes that are based on CO₂ as a carbon feedstock and independent of fossil resources.

An alternative route for carbon-based products is their generation via biological photosynthesis and CO₂ fixation.

Photosynthetic production can be performed by plants, microalgae, or cyanobacteria as raw materials or production systems. However, the relatively low solar-to-product energy-conversion efficiency (typically below 1%) and low carbon-fixation rates in photosynthetic organisms limit their potential.^{1,2} In addition, further upscaling of agricultural land use is challenging given both the amount of available arable land and the already gigantic environmental footprint of agriculture on our planet.

Since the last decade, an alternative CO₂-based production route has been proposed and explored. This so-called “electro-microbial production” route, also referred to as microbial electrosynthesis or artificial photosynthesis, is based on renewable electricity. In this

route, the electrical energy powers hybrid chemical-biological systems to generate carbon-based molecules from CO₂. Technology advances in the field of (electro)chemistry allow for the energy-efficient generation of chemical mediator molecules through electrical energy, such as hydrogen from water, or one-carbon (C₁) molecules, such as carbon mono-oxide, formic acid, or methanol from CO₂. After (electro)chemical catalytic formation toward these mediators, biological processes are well suited to converting such mediators into specific, more complex multi-carbon products. For example, micro-organisms, such as bacteria and yeast, can efficiently convert these mediator molecules into biomass and a diverse array of products; the scope and production performance can be expanded by genetic engineering of these organisms.

Despite the theoretical promise of these hybrid chemical-biological systems and several proof-of-principle studies in recent years,^{3–6} they have so far hardly been upscaled in the real world. This can be partly related to the economic reality of still relatively cheap fossil carbon.

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