1 *Review*

2,3 Recent Advancements in the Utilization of *s*-Block Organometallic Reagents in Organic Synthesis with Sustainable Solvents

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Abstract: This mini-review offers a comprehensive overview of the advancements made over the last three years in utilizing highly polar *s*-block organometallic reagents (specifically, RLi, RMgX, and RNa compounds) in organic synthesis run under bench-type reaction conditions. These conditions involve exposure to air/moisture and are carried out at room temperature, with the use of sustainable solvents as reaction media. In the examples provided, the adoption of *Deep Eutectic Solvents* (*DESs*) or even water as non-conventional and protic reaction media has not only replicated the traditional chemistry of these organometallic reagents in conventional and toxic volatile organic compounds under Schlenk-type reaction conditions (typically involving low temperatures of -78 °C to 0 ºC and a protective atmosphere of N_2 or Ar), but has also resulted in higher conversions and selectivities within remarkably short reaction times (measured in sec/min). Furthermore, the application of the aforementioned polar organometallics under bench-type reaction conditions (at room temperature/under air) has been extended to other environmentally responsible reaction media, such as more sustainable ethereal solvents (*e.g.*, CPME or 2-MeTHF). Notably, this innovative approach contributes to enhancing the overall sustainability of *s*-block-metal-mediated organic processes, thereby aligning with several key principles of *Green Chemistry*.

Keywords: Organolithium; Organomagnesium; Organosodium; Green Chemistry; Deep Eutectic Solvents; Water

1. Introduction

Highly polar organometallic reagents based on *s*-block elements, basically organolithium (RLi) [1-5], organomagnesium (RMgX or R_2Mg) [6-8], and organosodium compounds (RNa) [9-12], stand out as some of the most reliable and extensively employed reagents in organic synthesis. Among these polar organometallic compounds, RLi reagents have played a pivotal role as indispensable tools since their discovery by Schlenk and Holz in 1917 [13]. Following this groundbreaking work, and owing to the contributions of other pioneers in the field (such as Ziegler [14], Wittig [15], and Gillman [16-17]), continuous advancements in the synthesis and use of these highly reactive reagents have expanded their applications across various domains of synthetic organic chemistry. These include lithium-halogen exchange processes, metalation reactions, Pd-catalyzed C-C coupling protocols, and anionic polymerization reactions [1-5]. Consequently, it is not surprising that over 95% of methodologies employed in the total syntheses of natural products rely on RLi reagents in at least one step [5].

The attractiveness of RLi reagents to synthetic organic chemists lies in their: *i*) high and rich reactivity; *ii*) commercial availability (typically sold as hydrocarbons or ethereal solutions); and *iii*) affordable prices. However, their inherent high reactivity also presents certain challenges, primarily related to the tendency of RLi compounds to react with organic solvents, thereby requiring the use of low temperatures (ranging from 0 to -78 ºC). Notably, it is well-documented that THF undergoes decomposition (reverse cycloaddition reaction) in the presence of *n*-BuLi at room temperature [18]. For even more reactive *s*-BuLi or *t*-BuLi, this decomposition reaction occurs much more rapidly, thereby requiring storage/manipulation at temperatures below 0 ºC [19]. Furthermore, owing to the high polarity of the C–M bond (M = Li, Na, or Mg), additional side reactions, such as hydrolysis/oxidation, become prominent. Consequently, the use of these polar organometallic compounds requires: *i*) the use of rigorously dried, aprotic, toxic, and volatile organic compounds (*VOCs*) as solvents; and *ii*) an inert atmosphere (usually N_2 or Ar) to prevent side reactions in the presence of moisture or oxygen.

Contrary to conventional wisdom, recent innovations in *s*-block polar organometallic chemistry [20-27] have challenged established norms. It has been demonstrated that polar organolithium (RLi) and Grignard (RMgX) reagents can be effectively used: *i*) in the presence of air; *ii*) in sustainable, protic, non-toxic, and non-dried solvents (such as water or *Deep Eutectic Solvents* (*DESs*) [28]); and *iii*) at room temperature. This groundbreaking approach not only reduces costs but also minimizes waste generation and energy consumption, contributing to a more sustainable use of fossil resources. Furthermore, the application of aerobic and non-dried reaction conditions for RLi/RMgX has also been reported in flow processing [29-33] and solid-phase synthesis [34]. Additionally, the use of more sustainable ethereal solvents (*e.g.*, 2-methyltetrahydrofuran (2-MeTHF) [35,36] or cyclopentyl methyl ether (CPME) [37]) has broadened the possibilities for employing these common s-block metal reagents under atmospheric conditions and in the presence of moisture.

At this point, it is crucial to highlight that, beyond the sustainable perspective, the utilization of bench-type reaction conditions (presence of air/moisture at room temperature) in synergistic conjunction with the aforementioned unconventional, protic, and polar reaction media (water, *DES*) or sustainable ethereal solvents (2-MeTHF/CPME) in polar organometallic chemistry has yielded significant advantages. This approach has, indeed, enabled: *i*) notable improvements in reaction times (on the scale of sec/min); *ii*) enhanced yields/selectivities in well-established chemical transformations; and *iii*) the discovery of novel reactions/mechanistic pathways that cannot be replicated in traditional, dry, and toxic volatile organic compounds (*VOCs*) as solvents [20-27].

In the case of protic polar solvents (water and *DESs*), these empirical observations have been so far connected to the exceptional chemical and physical properties of these non-conventional solvents, which can exert a strong influence on: *i*) the position of chemical equilibria; *ii*) the reaction rates in both heterogeneous and homogeneous protocols; and *iii*) the overall outcome of the synthetic organic process under study [38-52]. In this context, a thorough review of the scientific literature, focusing specifically on the pair formed by RLi/RMgX reagents and water, unequivocally demonstrates that the intentional (or adventitious) addition of catalytic or stoichiometric amounts of water favors various main-group-mediated organic protocols by: *i*) speeding up the desired reaction [53]; *ii*) enhancing a lithium/halogen exchange protocol [54,55]; or *iii*) improving the enantiomeric excess in asymmetric protocols [56].

With this idea in mind, our focus in this review is on recent advancements (since 2021) in the use of *s*-block polar organometallic reagents under aerobic/ambient conditions, when employing sustainable reaction media such as *DESs*, water, 2-MeTHF, or CPME as solvents. This review is structured into distinct sections, each highlighting various types of reactivities: *i*) chemoselective double addition of RLi/RMgX reagents into esters in *DESs* or water at room temperature and in the absence of a protective atmosphere [57]; *ii*) the potential implementation of RLi/RMgX reagents under continuous, stable, and

safe reaction conditions in flow at room temperature, assisted by *DESs* [58]; *iii*) rapid addition of *s*-block organometallic reagents to CO_2-derived cyclic carbonates at room temperature, under air, and in 2-MeTHF [59]; *iv*) one-pot/two-step modular double addition of different highly polar organometallic reagents (RLi/RMgX) into nitriles to produce asymmetric tertiary alcohols under aerobic/room-temperature and in neat conditions [60]; *v*) fast addition of RLi reagents to amides in environmentally friendly CPME, at ambient temperature and under air [61]; *vi*) highly efficient and selective fast addition of *in situ* generated lithium amides (obtained via an acid-base reaction between *n*-BuLi and the desired primary amine) into carbodiimides (R-N=C=N-R) or nitriles (R-C≡N) in 2-MeTHF or CPME [62]; *vii*) Directed *ortho*-Metalation (D*o*M) or anionic Fries rearrangement of O-arylcarbamates promoted by lithium amides under aerobic conditions in sustainable reaction media (*DESs*/CPME) [63]; *viii*) Pd-catalyzed cross-coupling reactions of RLi reagents with *o*-benzenedisulfonimides [64]; *ix*) electrophilic trapping of *in situ* generated organosodium intermediates (RNa) in *DESs* or in pure water, at room temperature and under air [65]; and *x*) neopentyl sodium (NpNa)-promoted sodium-halogen exchange of aromatic products or direct deprotonation of terminal alkynes, under mild conditions [65]. Additionally, a final section of this review summarizes ongoing efforts to design hybrid one-pot tandem protocols aimed at synergistically combining aerobic polar s-block organometallic chemistry in green solvents with: *i*) enzymatic aqueous synthetic protocols, such as oxidations of secondary alcohols into ketones [66] or biodeoximation of ketoximes [67]; *ii*) organic procedures, including acetylation of diols [68] or tetrahydropyranylation of alcohols, promoted by Brønsted-type acidic *DES*s [69]; and *iii*) Cu-catalyzed oxidation of primary alcohols into the corresponding aldehydes in *DESs* or water [70].
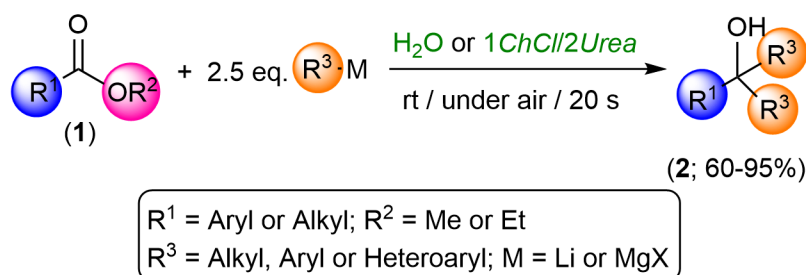
2. Addition of RLi/RMgX reagents into different electrophiles in Green Solvents

A groundbreaking study conducted by Hevia and García-Álvarez research teams in 2014 [71] has brought forth a novel perspective on the potential utilization of highly polar *s*-block organometallic reagents (RLi/RMgX) within more environmentally friendly reaction conditions. Specifically, we explored the feasibility of conducting reactions at room temperature, in the presence of air and moisture, achieved through the use of choline chloride (*ChCl*)-based eutectic mixtures [72] as green and innovative solvents. Our investigation demonstrated that these *DESs* promoted ultrafast (2-3 sec) and chemoselective additions of organometallic reagents into ketones. By comparing the reactivity of RMgX and RLi reagents in these *ChCl*-based *DESs* with that observed in pure water as a reaction medium, we proposed a mechanism involving a kinetic activation, most probably taking place through the formation of highly-nucleophilic and halide-rich anionic magnesiate ($[RMgCl_2]^-$) or lithiate ($[LiCl_2R]^{2-}$) species, thereby promoting their nucleophilic addition into ketones, while minimizing undesired side reactions such as enolizations and hydrolysis. Building upon this seminal example, the scope of unsaturated electrophiles, amenable to fast and chemoselective addition in *DESs*, was then extended to include: *i*) imines [73,74]; *ii*) nitriles [75,76]; and *iii*) aldehydes/epoxides [77]. This expansion broadens the potential applications of *DESs* as green solvents in organic synthesis, opening avenues for sustainable and efficient reactions across diverse substrates.

2.1. Chemoselective addition of polar organometallic reagents (RLi/RMgX) to esters under air, at room temperature and using either water or ChCl-based eutectic mixtures as reaction media

Recently, our research endeavors have expanded upon the previously discussed nucleophilic addition of RLi/RMgX reagents in green solvents, leading to the development of a novel, straightforward, and highly efficient synthetic protocol. This protocol enables the production of symmetric tertiary alcohols (**2**) with exceptional yields reaching up to 95%. The method involves a rapid (20 sec) and chemoselective double addition of various highly-polar *s*-block reagents (RLi/RMgX) to esters **1**, working at room temperature and under ambient air conditions. Notably, the biorenewable 1*ChCl*/2Urea eutectic mixture or pure water are employed as sustainable reaction media [57] (Scheme 1).

It is crucial to highlight that this methodology exhibits several key features: *i*) it demonstrates a broad scope, accommodating both aromatic and aliphatic substituents in the starting ester **1**, as well as a variety of organometallic reagents (including *n*-BuLi, *i*-PrLi, PhLi, 2-ThienylLi, MeLi, PhMgCl, MeMgCl, or EtMgBr); *ii*) it obviates the need for isolating intermediate ketones, streamlining the synthetic pathway; and *iii*) it proves applicable to the synthesis of *A*ctive *P*harmaceutical *I*ngredient (*API*)-type organic products, exemplified by the synthesis of *S*-trytil-L-cysteine—an influential Eg5 inhibitor. This advancement underscores the versatility and practicality of our synthetic approach, contributing to the sustainable and efficient synthesis of valuable organic compounds [57].

R¹ = Aryl or Alkyl; R² = Me or Et
R³ = Alkyl, Aryl or Heteroaryl; M = Li or MgX

Scheme 1. Synthesis of symmetric tertiary alcohols (**2**) through double addition of RLi/RMgX reagents into esters (**1**) in the eutectic mixture 1*ChCl*/2Urea or water, working under air and at room temperature (rt).

2.2. Continuous, stable, and safe organometallic reactions in flow at room temperature assisted by Deep Eutectic Solvents

Continuous flow technologies have gained widespread acceptance in the realm of organic chemistry, emerging as a highly dependable synthetic approach, particularly when dealing with highly reactive reagents in both laboratory and industrial settings [30-33;78,79]. Elevating this concept to new heights, Hevia, Torrente-Murciano *et al.* have presented a groundbreaking contribution [58] by introducing the first continuous, stable, and secure synthetic operation involving RLi/RMgX reagents in flow under ambient conditions with remarkable moisture tolerance and resistance to clogging. A contextualization and summary of the key aspects of this paper has also been published [80].

This innovation capitalizes on the utilization of two distinct *ChCl*-based eutectic mixtures, namely 1*ChCl*/2Urea or 1*ChCl*/2*Gly* (*Gly* denotes glycerol). Notably, the implementation of these eutectic mixtures eliminates the need for temperature control or the use of an inert atmosphere. Through the integration of a multi-phase, segmented-flow microfluidic system (depicted in Figure 1), the researchers observed a significant enhancement in mixing and heat transfer. This improvement is attributed to the secondary vortices within the droplets and the high surface-area-to-volume ratio, resulting in stable and secure operations. This novel protocol was successfully applied to the synthesis of alcohols and imines through the addition of various organometallic species to different ketones and imines. The adaptability and efficiency demonstrated by this continuous flow method mark a significant stride in the advancement of synthetic methodologies, offering a robust and reliable approach for diverse chemical transformations.
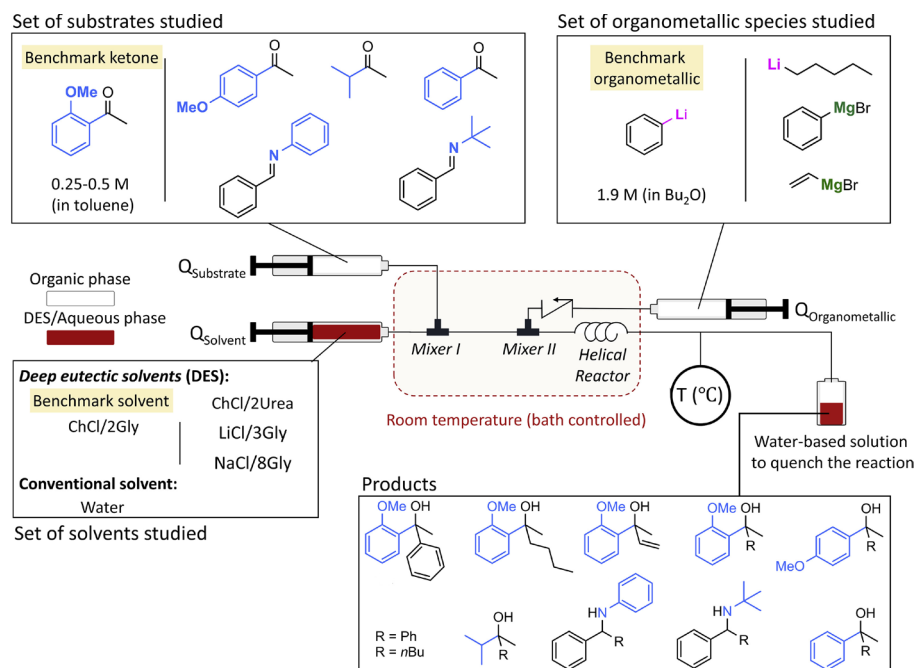
Figure 1. Synthesis of alcohols and amines through the addition of RLi/RMgX reagents using continuous bi-phasic flow platform at room temperature and in the absence of protecting atmosphere [Reproduced with permission from ref. 58 Copyrigth (2023) Cell Press].

2.3. Fast addition of s-block organometallic reagents to CO₂-derived cyclic carbonates at room temperature, under air, and in 2-MeTHF

In a collaborative effort involving some of us and Elorriaga, Castro-Osma *et al.* [59], we drew inspiration from an earlier refined method reported by Jessop, Snieckus, and their colleagues. This method, focused on the conversion of C1 feedstock (specifically, sodium methyl carbonate), utilizing *s*-block polar organometallic reagents (RLi/RMgX) in dry organic solvents under Schlenk-type conditions, with extended reaction times (24 h) [81]. Building on this foundation, we decided to explore the use of cyclic carbonates (derived from CO_2, a sustainable feedstock) as biorenewable electrophiles capable of undergoing ultrafast (3 sec) addition of RMgX/RLi reagents, as illustrated in Scheme 2.

Remarkably, our investigations revealed that under optimal conditions—employing 2-MeTHF as a sustainable reaction medium or working in the absence of external *VOCs* (neat conditions)—and conducting reactions at room temperature in the presence of air and moisture, cyclic carbonates **3** could be efficiently converted into tertiary alcohols **4**, symmetric ketones **5**, or *β*-hydroxy esters **6** through direct addition of polar organometallic alkylating or arylating reagents (RMgX/RLi). This innovative approach not only significantly shortens reaction times, but also demonstrates the versatility of cyclic carbonates as renewable electrophiles in the synthesis of diverse chemical products.
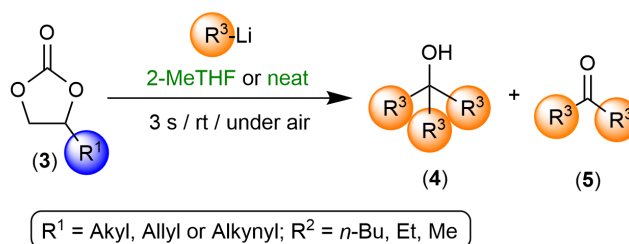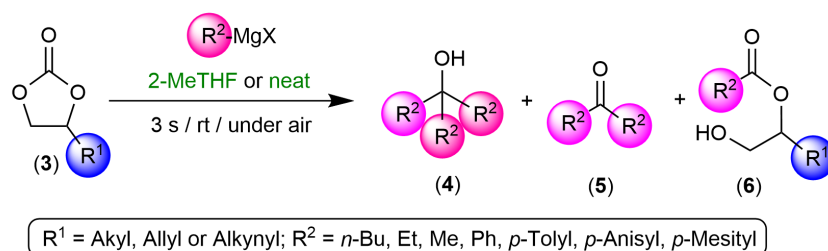
Scheme 2. Fast addition of polar *s*-block organometallic reagents (RLi/RMgX) into cyclic carbonates (**3**) to produce: *i*) highly substituted tertiary alcohols (**4**); *ii*) symmetric ketones (**5**); or *iii*) *β*-hydroxy esters (**6**), at room temperature (rt), under air, and in 2-MeTHF or in neat conditions.

In the same study, we successfully devised a hybrid one-pot/two-steps tandem protocol [82]. This innovative approach seamlessly integrates the aluminum-catalyzed insertion of CO_2 into propylene epoxide (**7**) with the subsequent chemoselective and rapid addition of an organolithium reagent (EtLi) to the transiently formed cyclic carbonate **3a**. Notably, this protocol eliminates the need to isolate or purify the reaction intermediate [83], thus representing a direct and sustainable method for converting CO_2 into tertiary alcohol **4a** (Scheme 3).
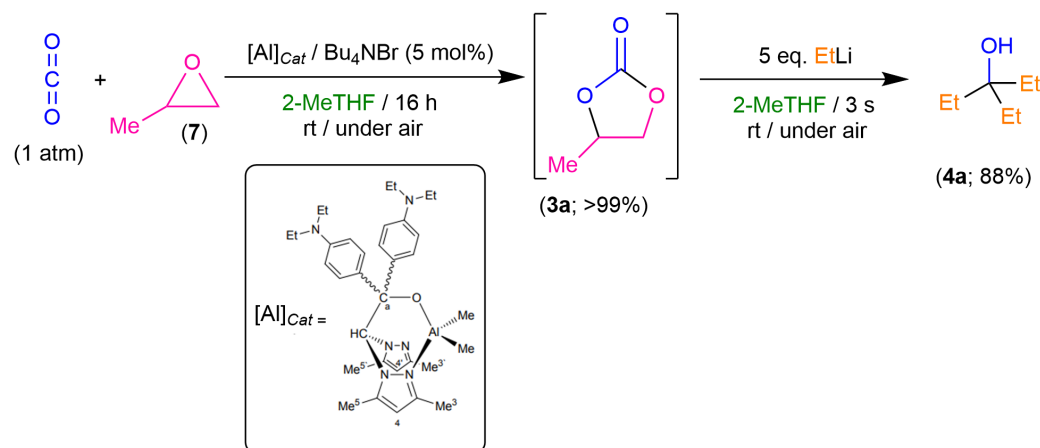
Scheme 3. Hybrid one-pot/two-step tandem protocol to convert CO_2 into tertiary alcohol **4a** by combining the cycloaddition of CO_2 and propylene oxide (**7**) with the subsequent fast addition of EtLi to cyclic carbonate **3a** at room temperature (rt), under air, and using 2-MeTHF as solvent.

2.4. One-pot/two-step modular double addition of different highly polar organometallic reagents (RLi/RMgX) into nitriles to produce asymmetric tertiary alcohols under aerobic/room-temperature and in neat conditions

In the pursuit of designing one-pot/two-step protocols leveraging *s*-block organometallic reagents (RLi/RMgX) under bench-type reaction conditions (room temperature and without the need for a protective atmosphere) with an emphasis on neat conditions (*the*

best solvent is no solvent) [84], our collaborative efforts, led by Elorriaga, Carrillo-Hermosilla, and some of us, drew inspiration from the pioneering work of Capriati and colleagues that had previously demonstrated the double addition of RLi/RMgX reagents into nitriles, yielding tertiary carbinamines in water at room temperature [74]. Building on our prior knowledge of RLi-mediated conversion of nitriles into ketones under air/moisture and at room temperature [76], we decided to revisit and expand this field.

Our newly developed one-pot modular tandem protocol began with the fast and chemoselective addition of various RLi reagents (ranging from aliphatic and silylated to aromatic or heteroaromatic groups) to a diverse array of nitriles (**8**; accommodating both aromatic and aliphatic substituents). This process took place under bench-type and neat conditions, eliminating the need for external *VOCs*. This first step generated the corresponding lithiated imines **9**, which, following acidic hydrolysis (using a saturated NH₄Cl aqueous solution), yielded the desired ketones **10**.

Significantly, without any intermediate isolation or purification, the second step of our protocol facilitated the addition of a second RLi reagent to ketones **10**. This occurred even in the presence of an acidic reaction medium, at room temperature, and under ambient air (Scheme 4). Employing this innovative tandem methodology, we achieved the fast, direct, and selective conversion of nitriles into the corresponding tertiary alcohols **11** in moderate to excellent yields [60]. Notably, we successfully demonstrated the scalability of this protocol, establishing it as an environmentally-friendly synthetic tool for the efficient synthesis of non-symmetric tertiary alcohols from nitriles. This process operates under bench-type reaction conditions and avoids the use of external organic solvents.
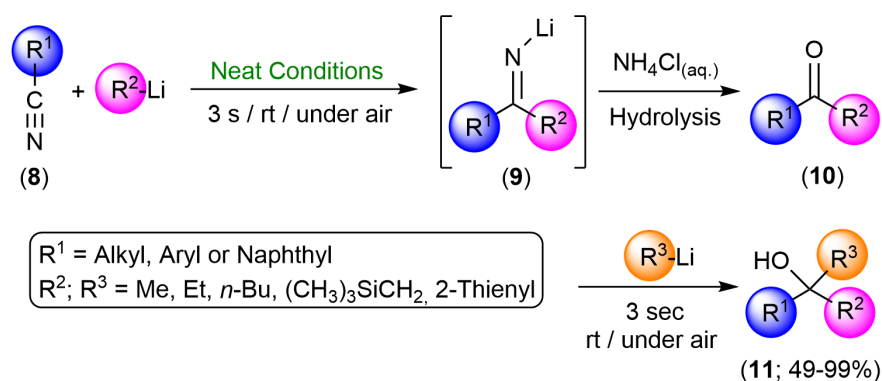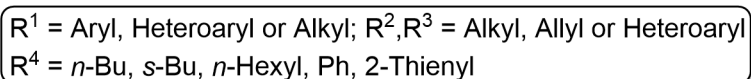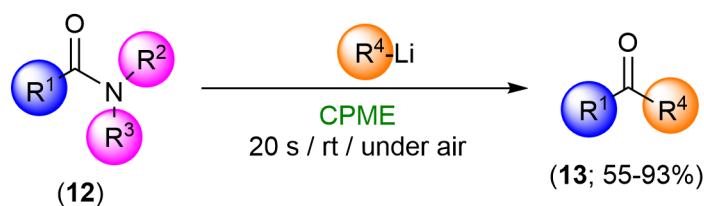

Scheme 4. One-pot/two-steps modular double addition of RLi reagents into different nitriles (**8**) under air, at room temperature (rt) and in the absence of any additional/external solvent to produce tertiary alcohols **11**.

2.5. Addition of organolithium reagents (RLi) into amides as a general and fast route to ketones using CPME as sustainable solvent under aerobic ambient conditions

In their pioneering investigation focusing on the application of *t*-BuLi to facilitate the D*o*M of hindered benzamides under bench-type reaction conditions (room temperature and in the presence of air), and utilizing 1*ChCl*/2*Gly*:CPME mixtures as sustainable reaction media [85], Capriati, Prandi, Blangetti, and co-workers found that substituting *t*-BuLi with less-hindered organometallic reagents, which are more inclined to induce addition reactions rather than the metalation process, led to the synthesis of aromatic ketones alongside the corresponding di-*n*-butylated symmetric tertiary alcohol—a by-product anticipated in a double addition protocol [86].

Building upon this experimental insight, the same researchers embarked on a systematic investigation to devise a novel synthetic protocol enabling the chemoselective conversion of amides **12** into the desired aromatic ketones **13** using polar organometallic reagents. This process was designed to operate under bench conditions, employing CPME as a sustainable solvent [61]. The authors discovered that the nucleophilic acyl substitu-

tion reaction (S$_N$Ac) of aliphatic and (hetero)aromatic amides **12** could be efficiently promoted by various organolithium reagents, such as *n*-BuLi, *s*-BuLi, *n*-HexylLi, PhLi, or 2-ThienylLi (Scheme 5). This nucleophilic substitution takes place rapidly (within 20 sec), with good product yields (up to 93%), and exhibits high chemoselectivity, avoiding the formation of over-addition by-products. Notably, this methodology demonstrates remarkable tolerance for a broad substrate scope of substituents. It is also worth mentioning that: *i*) both DFT calculations and NMR investigations substantiated the observed experimental results; and *ii*) the reported methodology was shown to be recyclable and amenable to scale-up, thereby enhancing its practical utility.

R^1 = Aryl, Heteroaryl or Alkyl; R^2,R^3 = Alkyl, Allyl or Heteroaryl
R^4 = *n*-Bu, *s*-Bu, *n*-Hexyl, Ph, 2-Thienyl

Scheme 5. Synthesis of ketones **13** through the nucleophilic acyl substitution (S$_N$Ac) reaction between aliphatic and (hetero)aromatic amides **12** and aliphatic and (hetero)aromatic organolithium reagents in CPME, at room temperature (rt) and under air.

2.6. Fast and selective addition of in situ generated lithium amides (LiNR$_2$) into carbodiimides (R-N=C=N-R) or nitriles (R-C≡N) in 2-MeTHF or CPME under air and at room temperature

In the preceding sections of this review, the examples discussed primarily involved the formation of new C–C bonds through the fast and selective addition of RLi/RMgX reagents to various organic electrophiles, working at room temperature and under ambient air conditions [57-61]. However, in previous collaborative efforts with Hevia and co-workers, some of us reported on the synthesis of new C–N bonds using lithium amides (LiNR$_2$) as nucleophiles. Specifically, we explored: *i*) the direct transamidations of esters or highly activated *N*-Boc-protected amides [87]; and *ii*) the moisture-promoted hydroamination of vinylarenes [88]. Notably, both reactions were performed under aerobic ambient temperature conditions, employing 2-MeTHF as a sustainable solvent.

Building upon this chemistry, Elorriaga, Carrillo-Hermosilla, and some of us then extended these investigations to the addition of *in situ*-generated lithium amides LiNHR (prepared *via* an acid-base reaction between *n*-BuLi and the desired primary amines RNH$_2$ **14**) into two distinct nitrogenated and unsaturated organic electrophiles—carbodiimides (**15**; R-N=C=N-R) or nitriles (**16**; R-C≡N). This extension was carried out at room temperature, without the need for a protective atmosphere, and utilizing either 2-MeTHF or CPME as sustainable solvents [62].

For carbodiimides **15**, optimal yields of the desired guanidines **17** were achieved when 2-MeTHF was employed as the solvent. Conversely, the use of CPME was essential to obtain the corresponding amidines **18** when using aromatic nitriles **16** as electrophiles (Scheme 6). Importantly, our one-pot/two-step synthetic protocols demonstrated versatility in accommodating various functional groups, present in both the starting amine **14** and the electrophiles **15,16**. This approach resulted in a diverse array of *N*-containing and highly substituted organic products **17,18** obtained in good to excellent yields and under more environmentally-friendly reaction conditions.
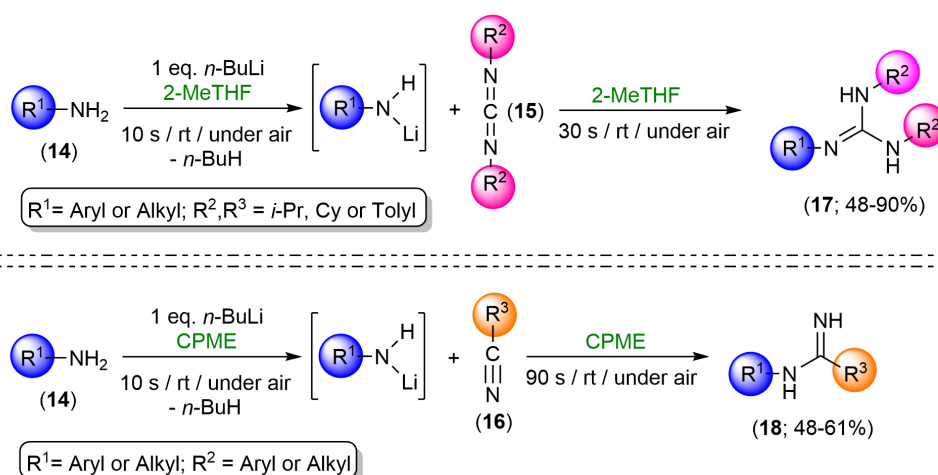
Scheme 6. One-pot/two-step protocol for the synthesis of guanidines **17** and amidines **18** using different amines **14**, *n*-BuLi and the corresponding carbodiimides **15** or nitriles **16** as electrophiles, working at room temperature (rt) in the presence of air and in 2-MeTHF or CPME as a sustainable solvent.

3. Directed *ortho*-Metalation or anionic Fries rearrangement of *O*-arylcarbamates promoted by lithium amides under aerobic conditions in sustainable reaction media (*DESs*/CPME)

Despite the notable advancements in the rapid and selective nucleophilic addition of RLi/RMgX reagents into various unsaturated organic electrophiles using sustainable solvents and bench-type reaction conditions [57-63], the exploration of the behavior of RLi/RMgX reagents as bases in greener reaction media is still in its early stages. The limited research in this area can be attributed to the conventional wisdom that polar organolithium or organomagnesium compounds would readily undergo protonation in the presence of unconventional protic solvents like water or *DESs*.

Although the nucleophilic character of RLi or RMgX reagents in *ChCl*-based *DESs* can be augmented through two strategies: *i*) co-complexation with an ammonium salt, leading to the formation of the corresponding anionic lithiates ([LiCl$_2$R]$^{2-}$) or magnesiates ([RMgX$_2$]$^-$); and/or *ii*) hydrogen-bond interactions within a heterogeneous mixture under vigorous stirring, the classical deprotonation/electrophilic trapping protocol involves the generation of a highly reactive carbanionic intermediate (C-Li), which requires a proton-free environment to prevent undesired re-protonation reactions, leading to the recovery of the unreacted starting material.

The initial hurdle of working with protic *DESs* was successfully overcome by Capriati and co-workers by: *i*) achieving the D*o*M of diaryltetrahydrofurans, followed by trapping with various electrophiles [89]; and *ii*) running a one-pot tandem lateral lithiation/alkylative ring opening of *o*-tolyltetrahydrofurans [90], both conducted in the presence of protic *DESs* as the reaction medium. Building on these pioneering efforts, Prandi, Blangetti, and co-workers expanded the scope of lithiation/electrophilic trapping in the presence of *DESs* to: *i*) the aforementioned D*o*M and subsequent electrophilic trapping of hindered carboxamides [85]; and *ii*) the heteroatom-directed lateral lithiation of substituted toluene derivatives [91].
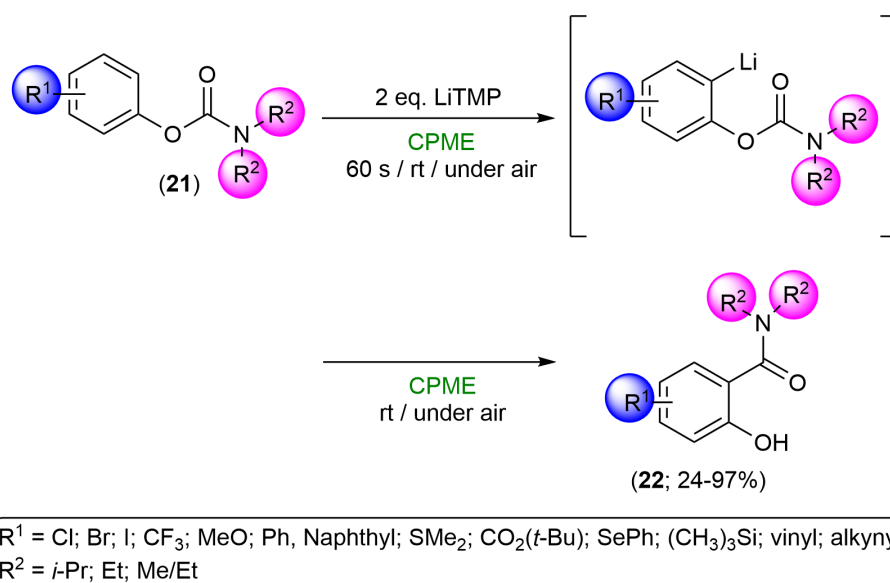
Subsequently, the same research team delved into *N,N*-dialkyl-*O*-phenylcarbamates, revealing an intriguing dichotomy in the behavior of these aromatic organic products based on: *i*) the reaction temperature (0 ºC or room temperature); *ii*) the nature of the organolithium reagents used (LiTMP *vs* s-BuLi); and *iii*) the reaction media employed (pure CPME *vs* mixtures of CPME/DESs) [63]. Aromatic carbamates are conventionally recognized as excellent directors for D*o*M protocols, enabling clean metalation at their *ortho*-position at low temperatures. This facilitates their chemoselective and straightforward

functionalization after the corresponding electrophilic quenching [92]. Additionally, in the absence of an external electrophile, the aryl anion undergoes a rapid intramolecular carbamoyl transfer upon gradual warming to room temperature, a process known as anionic *ortho*-Fries rearrangement [93]. This process yields the corresponding salicylamides, which can also be utilized in subsequent D*o*M protocols. In light of these considerations, Prandi and co-workers found that the optimal conditions for a selective D*o*M functionalization of phenylcarbamate **19** (avoiding Fries rearrangement) involves: *i*) working at low temperatures (0 °C) in the presence of air/moisture; *ii*) using *s*-BuLi as the organolithium reagent; and *iii*) employing an equimolecular mixture of the eutectic mixture 1*ChCl*/2*Gly* and CPME (Scheme 7). This results in the formation of the corresponding *ortho*-functionalized carbamates **20** in moderate to good yield. Lastly, it is noteworthy that this protocol allows for the use of different trapping electrophiles, leading to the formation of various C–C or C–heteroatom bonds [84].

E = CH$_3$I; PhC(=O)H; HC(=O)N(CH$_3$)$_2$; I$_2$; S$_2$(CH$_3$)$_2$; (CH$_3$)$_3$SiI
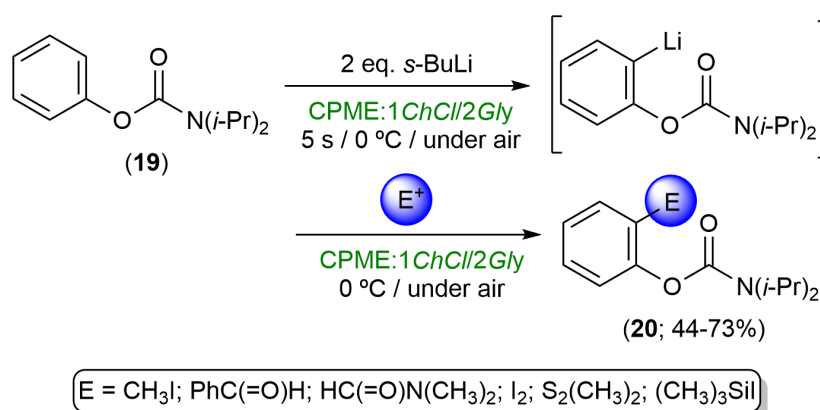
Scheme 7. D*o*M/electrophilic trapping of *N,N*-diisopropyl-*O*-phenylcarbamate (**19**) working at 0 °C, in mixtures 1*ChCl*/2*Gly*:CPME and in the presence of air/moisture.

In their comprehensive study [63], Prandi *et al.* successfully identified optimized reaction conditions for achieving a chemoselective anionic *ortho*-Fries rearrangement in a series of phenyl *N,N*-diisopropyl and *N,N*-diethyl carbamates **21**, encompassing a diverse range of functionalities on the aromatic ring (Scheme 8). The Fries-type reaction conditions consistently involved: *i*) the use of CPME as a solvent, thus excluding *DESs*; *ii*) operating under ambient air conditions at room temperature; and *iii*) utilizing a freshly prepared solution of LiTMP (TMP = 2,2,6,6-tetramethylpiperidine) as the metalating agent, as opposed to carbanionic RLi reagents. Employing this set of conditions yielded the desired salicylamides **22** in nearly quantitative yields within remarkably short reaction times (60 sec). Of particular significance, the authors demonstrated the practical applicability of their protocol in the pharmaceutical industry by showcasing the synthesis of: *i*) an acetylcholinesterase inhibitor (*AChEI*) used in the treatment of Alzheimer's disease; and *ii*) the blockbuster drug acetaminophen (Paracetamol).

R^1 = Cl; Br; I; CF$_3$; MeO; Ph, Naphthyl; SMe$_2$; CO$_2$(*t*-Bu); SePh; (CH$_3$)$_3$Si; vinyl; alkynyl
R^2 = *i*-Pr; Et; Me/Et

Scheme 8. Anionic Fries rearrangement of *O*-arylcarbamates **21** promoted by LiTMP in the presence of air/moisture in CPME at room temperature (rt).

4. Pd-catalyzed C-C coupling reactions using RLi reagents in green solvents

Since Murahashi groundbreaking work on the potential application of direct organolithium-promoted cross-coupling reactions in organic synthesis [94], RLi reagents have found extensive utility as coupling partners in Pd-catalyzed C-C processes. However, the adoption of these RLi organometallic compounds in C-C cross-coupling protocols in environmentally friendly and protic solvents has long been overlooked by synthetic organic chemists. This neglect stemmed from the perceived high susceptibility of these polar reagents to hydrolysis reactions in protic media.

In 2016, Feringa and co-workers reported a chemoselective Pd-catalyzed C-C coupling protocol involving PhLi (2-10 equiv) and 1-bromonaphthalene as partners, utilizing a protic *DES* as the reaction medium at room temperature. Under these conditions, the final C-C coupling product was obtained in moderate to good yields (28–53%), and within a short reaction time (10 min) [95]. Building upon this work, Capriati and co-workers then demonstrated the feasibility of promoting Pd-catalyzed C(sp^3)–C(sp^2), C(sp^2)–C(sp^2), and C(sp)–C(sp^2) cross-coupling reactions between RLi reagents and a variety of (hetero)aryl halides (Cl, Br), that occurred competitively with protonolysis when using water as a non-innocent reaction medium (*on water* conditions) and NaCl as a cheap additive. All the reactions proceeded within a reaction time of 20 sec, in yields of up to 99%, at room temperature and under ambient air conditions. The proposed protocol was also scalable and the catalyst and water could easily be recycled up to 10 times, with an *E*-factor as low as 7.35 [96].

In a more recent development in 2023, Dughera and Antenucci expanded the application of RLi reagents in protic solvents to the study of Pd-catalyzed coupling reactions involving the use of arenediazonium *o*-benzenedisulfonimides **23** (instead of the traditionally used aryl halides) and aryl/heteroaryl organolithium reagents. Reactions were conducted in the eutectic mixture formed by KF and glycerol (1KF/6*Gly*) using Pd[P(*t*-Bu)$_3$]$_2$ as the catalyst (Scheme 9). Operating at room temperature and in the presence of air, the desired biaryl products **24** were obtained after short reaction times (5 min) and with moderate to good yields (27–80%) [64].
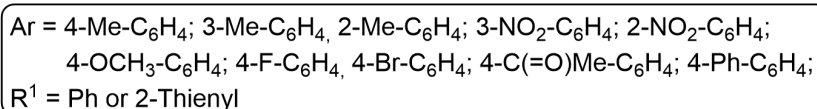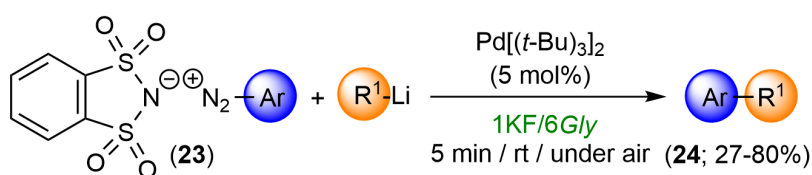
Scheme 9. Pd-catalyzed cross-coupling reactions between arenediazonium *o*-benzenedisulfonimides (**23**) and organolithium reagents in the eutectic mixture 1KF/6*Gly*, at room temperature (rt) and under air.

5. Organosodium chemistry (RNa) in green solvents

Organosodium reagents (RNa) stand out for their highly reactive Na-C bonds, potentially rivaling or even surpassing the reactivity of the previously mentioned organolithium reagents [9,10]. However, their increased reactivity often encounters significant challenges, including poor solubility in common organic solvents and limited stability. These limitations have historically restricted their application in organic synthesis. Nevertheless, in recent years, the resurgence of RNa-promoted organic synthesis can be attributed to the integration of sustainability concepts, such as the fact that sodium is more abundant (earth crustal abundance 22,700 ppm) than lithium (abundance 18 ppm) [97], thus reigniting the interest in sodium-promoted synthetic chemistry.

Capitalizing on the heightened reactivity and distinctive regioselectivities observed for RLi/RMgX reagents in protic and non-conventional solvents—such as water or eutectic mixtures—under ambient conditions and in the presence of air, Capriati and co-workers sought to extend this chemistry to organosodium reagents (RNa) [65]. To achieve this goal, the authors devised a method to generate highly reactive $C(sp^3)$, $C(sp^2)$, and $C(sp)$ organosodium reagents *in situ* using hexane as a solvent. This synthetic protocol relies on the oxidative addition reactions of C–Cl bonds, originating from both aryl and alkyl organochlorides (R-Cl, **25**) and metallic sodium supplied as sodium bricks (*SBs*). The resulting organosodium intermediates, denoted as RNa (**26**), were then promptly (within 20 sec) subjected to an electrophilic trapping protocol.

This trapping reaction successfully took place in two distinct *DESs*—namely, 1*ChCl*/2Urea and 1*Pro*/3*Gly* (*Pro* = L-proline)—or even in pure water. All reactions were run at room temperature and in the presence of air/moisture, yielding the final organic products **27** in good to almost quantitative yields (58–98%). Importantly, the electrophilic quenching process was found to be favored over the undesired competing hydrolysis reaction, as shown in Scheme 10 [65]. This innovative approach opens new avenues for the application of organosodium reagents in more sustainable organic syntheses, bridging the gap between their high reactivity and the challenges associated with their practical utility.
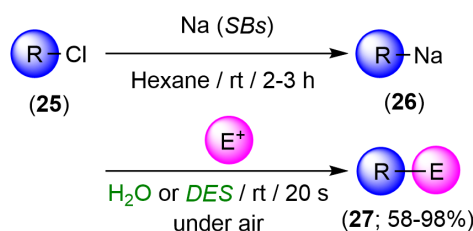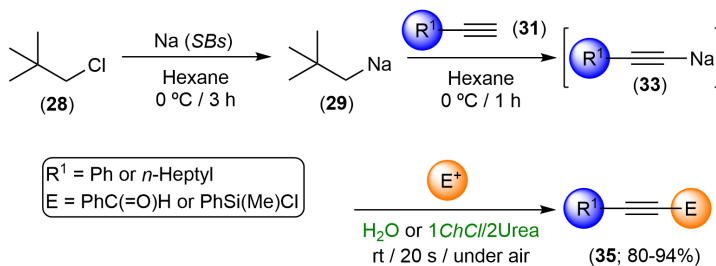
Scheme 10 Oxidative addition reactions of C-Cl bonds into metallic sodium [sodium Bricks (*SBs*)], at room temperature (rt), and in hexane, followed by an electrophilic trapping protocol in water or *DES*, under air and at room temperature.

Furthermore, within the same study [65], Capriati and co-workers employed the previously optimized procedure to synthesize neopentyl sodium (NpNa; **29**) through the oxidative addition reaction involving the C-Cl bond of neopentyl chloride (NpCl; **28**) and the aforementioned *SBs* in hexane. The *in situ* generated **29** exhibited remarkable versatility, facilitating either sodium-halogen exchange reactions with aryl bromides (**30**) or direct deprotonation of terminal alkynes (**31**) under mild conditions (at 0 °C in hexane; Scheme 11). The resulting organosodium species **32**,**33** could be easily intercepted using a variety of simple electrophiles, either in water or in the eutectic mixture 1*ChCl*/2Urea, with all reactions performed at room temperature and in the presence of air.
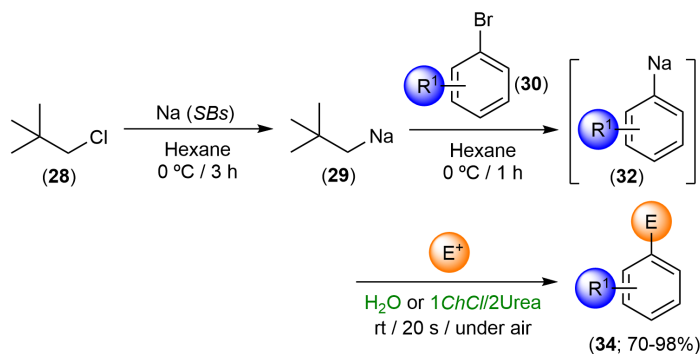
**Scheme 11** Oxidative addition reactions of C-Cl bonds from NpCl (**28**) into metallic sodium [Sodium Bricks (*SBs*)], at room temperature (rt), and in hexane, followed by an electrophilic trapping protocol with aryl bromides (**30**) or direct deprotonation of terminal alkynes (**31**) in water or *DES*, under air and at rt, to give adducts **34** and **35**, through sodiated intermediates **32** and **33**, respectively.

6. One-pot tandem hybrid combinations of RLi reagents with other synthetic organic tools in water or *Deep Eutectic Solvents* (*DESs*)

The findings presented in this review challenge the conventional notion that organolithium (RLi), Grignard (RMgX), or organosodium (RNa) reagents must be exclusively handled under stringent Schlenk-type conditions, and in the absence of protic solvents [57–65]. This paradigm shift creates new opportunities for developing innovative and environmentally friendly one-pot tandem hybrid protocols under greener reaction conditions, utilizing sustainable and protic reaction media. These tandem hybrid protocols hold the promise of seamlessly integrating highly efficient main-group-mediated organic transformations, run in protic and unconventional solvents, with other synthetic techniques available to organic chemists, such as homogeneous catalysis promoted by transition metals, enzymes or organocatalysts. For instance, some of us have previously demonstrated the feasibility of combining the addition of RLi/R_2Mg reagents with: *i*) the Ru(IV)-catalyzed redox isomerization of allylic alcohols in *DESs* [98]; and *ii*) the organocatalytic oxidation of secondary alcohols into ketones, a process performed in aqueous media [99].

6.1. Design of one-pot hybrid chemoenzymatic protocols which rely on the use of RLi/RMgX reagents in aqueous media

Following our previous success in combining RLi reagents with organocatalyzed oxidations of secondary alcohols in water under bench-type reaction conditions [99], we extended our investigation by introducing a novel chemoenzymatic hybrid one-pot tandem protocol. In this approach, the biocatalytic oxidation of secondary alcohols **36**, catalyzed by a commercially available laccase from *Trametes Versicolor* [100], was fruitfully integrated through a sequential one-pot/two-step procedure, eliminating the need for intermediate isolation/purification steps. This protocol was specifically designed to efficiently combine the rapid and selective addition of RLi reagents into the transiently formed ketones **37** [66]. Notably, the addition of RLi reagents into ketones **37** occurs under biocatalytic conditions, involving: *i*) water/CPME mixtures as the reaction medium at room temperature; *ii*) TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) as a co-factor; and *iii*) aerial O_2 as a co-oxidant (Scheme 12). Interestingly, the less reactive Grignard reagents (RMgX) underwent complete protonolysis under these conditions. Finally, the non-symmetric tertiary alcohols **38** were obtained in good to almost quantitative yields (65–96%).

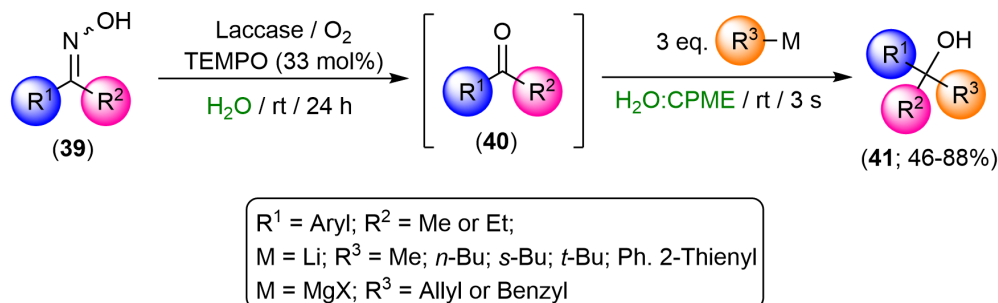R^1 = Aryl; R^2 = Me or Et; R^3 = Me; *n*-Bu; *s*-Bu; *t*-Bu; Ph
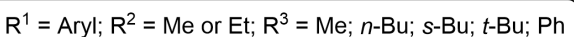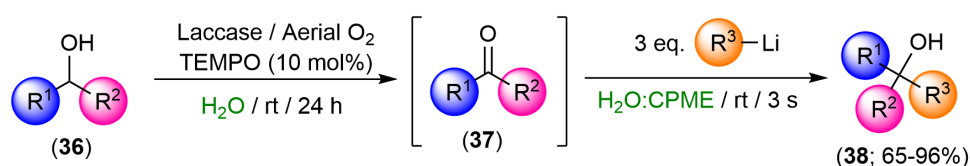
Scheme 12 One-pot tandem hybrid combination of the biocatalytic oxidation of secondary alcohols (promoted by the system Laccase/TEMPO) with the chemoselective addition of RLi reagents, at room temperature (rt), in the presence of air and in aqueous media.

After detailing the successful integration of RLi reagents and laccases in aqueous media under bench-type reaction conditions, and considering the feasibility of laccases from *Trametes Versicolor* to trigger deoximation reactions in an aqueous environment and under bench-type conditions [101], the same authors chose to extend their investigation. In a sequential hybrid protocol, they combined the biocatalytic deoximation of aromatic ketoximes **39** with the subsequent addition of RLi reagents into the transiently formed ketones **40**. This innovative one-pot/two-step procedure takes place in aqueous media, at room temperature, and in the presence of air, yielding the desired tertiary alcohols **41** in moderate to good yields (46–88%). Importantly, this entire process does not require the

employment of isolation or purification steps [67]. Moreover, this hybrid approach demonstrated exceptional adaptability, marking its capacity to accommodate less reactive Grignard-type organometallic reagents (RMgX), a novel feat in this domain of chemistry (Scheme 13).

R^1 = Aryl; R^2 = Me or Et;
M = Li; R^3 = Me; *n*-Bu; *s*-Bu; *t*-Bu; Ph. 2-Thienyl
M = MgX; R^3 = Allyl or Benzyl

Scheme 13 One-pot tandem hybrid combination of the biocatalytic deoximation of ketoximes (promoted by the system Laccase/TEMPO) with the chemoselective addition of RLi/RMgX reagents, at room temperature (rt), in the presence of air and in aqueous media.

6.2. Combination of Brønsted-Acidic-DESs promoted organic protocols with the addition of RLi reagents

Brønsted-type acidic *DESs* represent a versatile class of eutectic mixtures widely employed as promoters/catalysts in various organic transformations encompassing a broad spectrum, ranging from Claisen-Schmidt procedures and Friedel-Craft acylations to esterification reactions, biodiesel production, or multicomponent condensation reactions [102-103]. Notably, these *DESs* are composed by utilizing naturally occurring carboxylic acids as hydrogen-bond donors. In this realm of research, Prandi, Blangetti, and their co-workers have recently showcased the integration of Brønsted-acidic-*DESs* in the chemistry of protecting groups for aldehydes/ketones or alcohols. They have further demonstrated the feasibility of combining this chemistry with subsequent RLi-mediated synthetic transformations, thus delineating two distinct telescoped approaches for one-pot tandem procedures involving organolithium reagents under more sustainable conditions. In the first case, Prandi and co-workers demonstrated the effectiveness of using a malonic acid (*Mal*) containing eutectic mixture (1*ChCl*/1*Mal*) as both environmentally-friendly solvent and promoter for the selective acetalization reaction of diols with carbonyl compounds, working at room temperature, in air, and with short reaction times [68]. In this work, the authors chose *p*-formyl methyl benzoate **42** as the ideal substrate for the design of a hybrid tandem protocol (as contains both aldehyde and ester functional groups in its structure), to synthesize the target compound **45**. In this approach, the more electrophilic aldehyde function needed protection towards the addition of *n*-BuLi. Thus, **42** was firstly converted into acetal **43** in the presence of neopentyl glycol by using (1*ChCl*/1*Mal*) as promoter/solvent. The *in situ* obtained acetal **43** was directly utilized (without the need of any halfway isolation/purification protocol) in the subsequent step, which involves the addition of *n*-BuLi under ambient air conditions (CPME was added as a co-solvent to facilitate vigorous stirring) to produce the tertiary alcohol **44**. Finally, the desired product **45** was obtained just by a simple and straightforward acidic work-up with 61% overall yield over the three sequential steps (Scheme 14).
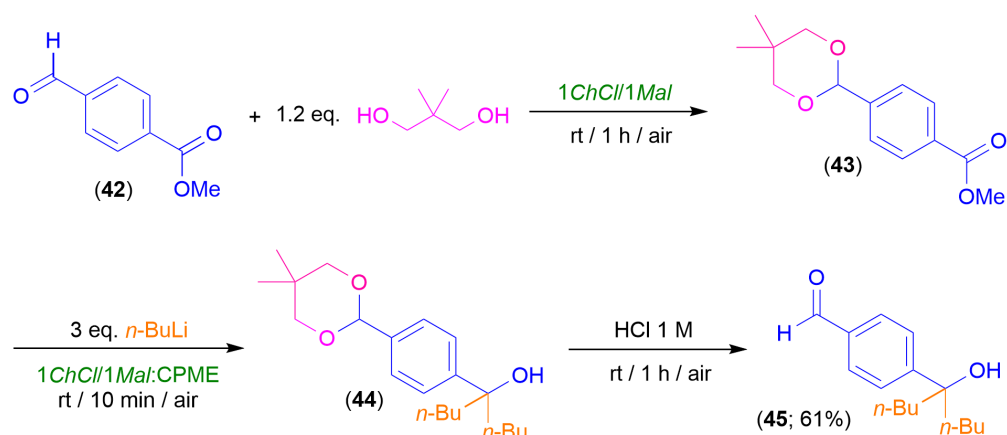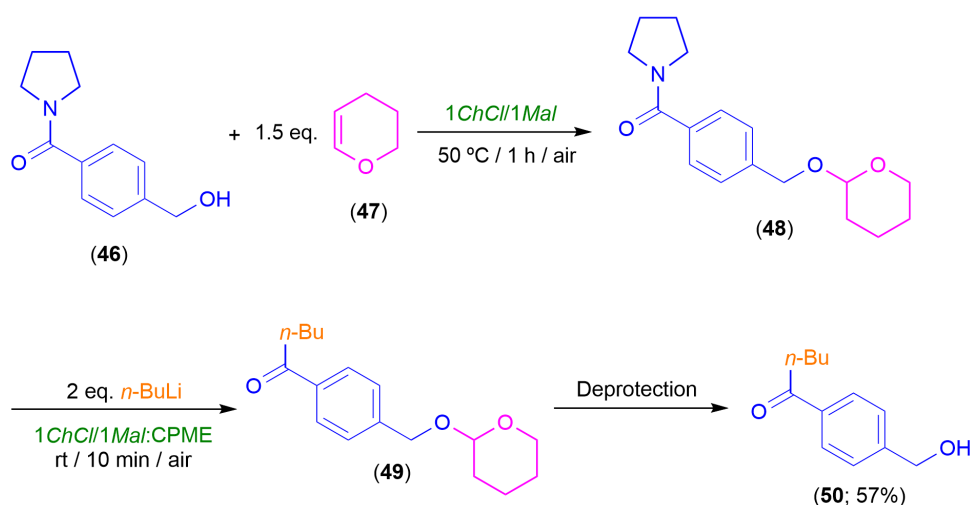
Scheme 14 One-pot tandem hybrid combination of acetalization reaction of neopentyl glycol with *p*-formyl methyl benzoate (**42**) (promoted by the eutectic mixture 1*ChCl*/1*Mal*) with the chemoselective addition of *n*-BuLi into acetal **43**, working at room temperature (rt), in the presence of air and in the mixture 1*ChCl*/1*Mal*:CPME as reaction medium, to give hydroxylated benzaldehyde **45** through the hydrolysis of acetal derivative **44**.

Secondly, in a closely related study [69], the same authors expanded the scope of this telescoped chemistry by demonstrating the feasibility of combining acidic-*DES*-promoted tetrahydropyranylation of primary alcohols (a process occurring under air, within short reaction times, and exhibiting exceptional chemoselectivity) with the subsequent addition of RLi reagents in the presence of the acidic eutectic mixture. In this context, Prandi and co-workers outlined a hybrid one-pot tandem protocol for converting benzyl alcohol **46** into the desired hydroxylated valerophenone **50** (Scheme 15). The initial step of this hybrid tandem transformation involves the conversion of alcohol **46** into the corresponding pyranyl derivative **48** by treating **46** with 3,4-dihydro-2*H*-pyran (**47**) in the eutectic mixture 1*ChCl*/1*Mal* at 50 °C and under air. The subsequent addition of *n*-BuLi to the *in situ* generated intermediate **48** in a heterogeneous CPME/*DES* mixture triggers the expected S$_N$Ac, resulting in ketone **49**. After a final deprotection step, the corresponding valerophenone **50** is obtained with an overall yield of 57% (Scheme 15). Importantly, this hybrid protocol was extended to other benzylic alcohols containing ester or nitrile groups in their structures.

**Scheme 15** One-pot tandem hybrid protocol based on the combination of the tetrahydropyranylation of benzyl alcohol **46** (promoted by the eutectic mixture 1*ChCl*/1*Mal*) followed by a subsequent S$_N$Ac (promoted by *n*-BuLi), working at room temperature (rt), in the presence of air and in the mixture 1*ChCl*/1*Mal*:CPME used as solvent, to give hydroxylated valerophenone **50** through the hydrolysis of acetal **49**.

6.3. Combination of a Cu-catalyzed oxidation of primary alcohols into aldehydes with the addition of RLi reagents in DES

The conceptualization of hybrid one-pot tandem protocols, combining transition-metal-catalyzed organic processes with main-group-mediated synthetic transformations, has garnered significant interest in the scientific community as both methodologies represent fundamental pillars in the toolkit of synthetic organic chemistry. However, instances of these hybrid transformations utilizing protic and environmentally friendly reaction media, such as water and *DESs*, are still relatively scarce. In this context, some of us have previously reported the successful integration of the Ru(IV)-catalyzed redox isomerization of allylic alcohols into the corresponding carbonyl compounds with a concurrent, rapid, and chemoselective addition of RLi/R$_2$Mg reagents in *ChCl*-based eutectic mixtures, yielding the corresponding tertiary alcohols in a sequential tandem protocol [98]. In a subsequent study, Prandi, Capriati, and co-workers successfully combined the lithiation/iodation process of aromatic amides with a consecutive Pd-catalyzed Suzuki-Miyaura cross-coupling reaction using various borates/boronic acids as coupling partners in mixtures of 1*ChCl*/2*Gly*:CPME [85].

More recently, in 2022, following these seminal studies, some of us explored the combination of the chemoselective oxidation of benzyl alcohol (**51**) into benzaldehyde (**52**) using the Cu(II)-based oxidative catalytic system CuCl$_2$/TMEDA/TEMPO (TMEDA = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine) under sonication (US). This was followed by the subsequent addition of RLi/RMgCl reagents, run in the presence of air and employing water or the eutectic mixture 3*Fruc*/2Urea (*Fruc* = D-fructose) as more sustainable reaction media [70]. Through this hybrid protocol, the primary alcohol **51** could be directly transformed into the desired secondary alcohols **53** in moderate to good yields, using bench-type reaction conditions and without the need for any intermediary isolation/purification steps (Scheme 16).

M = Li; R^1 = *n*-Bu or Me
M = MgCl; R^1 = *n*-Bu or Allyl
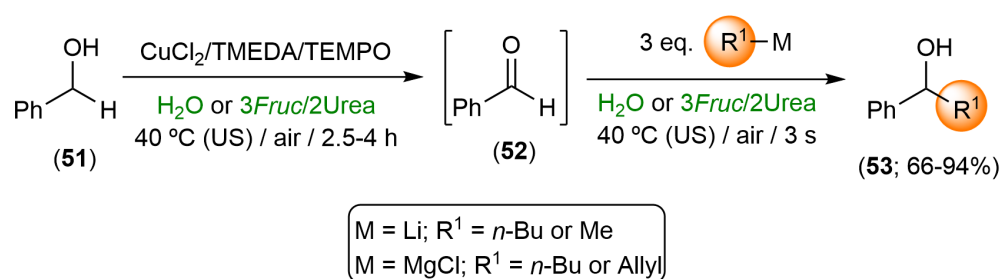
Scheme 16 One-pot tandem hybrid combination consisting in a Cu(II)-catalyzed oxidation of benzyl alcohol (**51**) into benzaldehyde (**52**) with the subsequent addition of RLi/RMgCl reagents, using water or the eutectic mixture 3*Fruc*/2Urea as green solvents, to give secondary alcohol **53**.

7. Conclusions

Polar organometallic reagents, belonging to the *s*-block elements (RLi, RMgX, or RNa), play a crucial role in synthetic chemistry, being widely employed for the functionalization of organic molecules owing to the high polarity of their M–C bonds. However, their application is typically constrained by the requirement for low temperatures, the use of dry, toxic organic solvents, and the need for protective inert atmospheres to prevent rapid decomposition. Traditionally, the challenge of conducting organolithium, organosodium, or organomagnesium chemistry, under aerobic and/or hydrous conditions, and in the absence of dry toxic solvents, has been considered insurmountable. Nevertheless, this review showcases that recent work from various research groups worldwide is expanding the field of research related to the use of highly polar organometallic reagents

under bench-type reaction conditions (room temperature and in the absence of a protective atmosphere) and in more sustainable reaction media, such as water, Deep Eutectic Solvents (*DESs*), or greener ethereal solvents (2-MeTHF or CPME).

The examples reviewed not only underscore the sustainability of the transformations, but also reveal that the unique chemoselectivities and enhanced performance achieved under these greener and milder reaction conditions cannot be replicated using traditional Schlenk-type synthetic techniques with dry *VOCs*. Furthermore, the possibility of integrating these methods with enzymes or transition-metal catalysis introduces an array of opportunities for designing innovative hybrid one-pot protocols under environmentally friendly reaction conditions. Thus, the progress compiled in this review represents a substantial advance toward making polar organometallic chemistry more sustainable, and provides a versatile platform for diverse and greener synthetic pathways.

An interplay of factors seems to be responsible for the outcome of the previously described reactions and the missing protonolysis of polar organometallic reagents when employed in strongly hydrogen-bonded associated media like water and *DESs* [21-27]. A recent computational investigation carried out by Koszinowski and Rahrt, aimed at addressing the experimental observation of how organozinc reagents survive instantaneous protonolysis in protic media, also disclosed the significance of achieving favorable kinetics despite to a less favorable thermodynamics [104].

For sure, the structure and dynamical properties of water and *DESs* are more complex than expected, and reactions of polar organometallic compounds of s-block elements across the "oil-water/*DES*" interface may represent another example of *compartmentalization* in organic synthesis [105]. Indeed, the use of *I*nterphase-*R*ich *A*queous *S*ystems (*IRAS*) are known to promote and guide organic reactions [106]. A deeper understanding of phenomena taking place at such an interface, when polar organometallics meet water or *DESs*, will enable full exploitation of this chemistry for novel and exciting transformations, working under conditions that no one would have ever envisioned adopting before!

Conflicts of Interest: "The authors declare no conflict of interest."

References

1. Clayden, J. *Organolithiums: Selectivity for Synthesis*, Pergamon, Oxford, UK, 2002.
2. *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I. Eds.; Wiley, Chichester, UK, 2005.
3. Capriati, V.; Perna, F. M.; Salomone, A. "The Great Beauty" of Organolithium Chemistry: a Land Still Worth Exploring. *Dalton Trans.* **2014**, *43*, 14204–14210.
4. Luisi, R.; Capriati, V. *Lithium Compounds in Organic Synthesis: from Fundamentals to Applications*, John Wiley & Sons, Weinheim, Germany, 2014.
5. Wietelmann, U.; Klett, J. 200 Years of Lithium and 100 Years of Organolithium Chemistry. *Z. Anorg. Allg. Chem.* **2018**, *644*, 194–204.
6. Garst, J. F.; Soriaga, M. P. Grignard reagent formation. *Chem. Soc. Rev.* **2004**, *248*, 623–652.
7. *The Chemistry of Organomagnesium Compounds*; Rappoport, Z., Marek, I. Eds.; Patai Series, Wiley, Chichester, UK, 2008.
8. Seyferth, D. The Grignard Reagents. *Organometallics* **2009**, *28*, 1598–1605.
9. Seyferth, D. Alkyl and Aryl Derivatives of the Alkali Metals: Useful Synthetic Reagents as Strong Bases and Potent Nucleophiles. 1. Conversion of Organic Halides to Organoalkali-Metal Compounds. *Organometallics* **2006**, *25*, 2–24.
10. Robertson, S. D.; Uzelac, M.; Mulvey, R. E. Alkali-Metal-Mediated Synergistic Effects in Polar Main Group Organometallic Chemistry. *Chem. Rev.* **2019**, *119*, 8332–8405.
11. Woltornist, R. A.; Ma, Y.; Algera, R. F.; Zhou, Y.; Zhang, Z.; Collum, D. B. Structure, Reactivity, and Synthetic Applications of Sodium Diisopropylamide. *Synthesis* **2020**; *52*, 1478–1497.

12. Anderson, D. E.; Tortajada, J. A.; Hevia, E. New Frontiers in Organosodium Chemistry as Sustainable Alternatives to Organo-lithium Reagents. *Angew. Chem. Int. Ed.* **2023**, *62*, e202313556.

13. Schlenk, W.; Holtz, J. Über die einfachsten metallorganischen Alkaliverbindungen. *Ber. Dtsch. Chem. Ges.* **1917**, *50*, 262–274.

14. Ziegler K.; Colonius, H. Untersuchungen über alkali-organische Verbindungen. V. Eine bequeme Synthese einfacher Lithium-alkyle. *Justus Liebigs Ann. Chem.* **1930**, *479*, 135–149.

15. Wittig, G.; Leo, M. Über das Tetraphenyl-o-xylylen. *Ber. Dtsch. Chem. Ges.* **1931**, *64*, 2395–2405.

16. Gilman, H.; Zoellner, E.; Selby, W. An Improved Procedure for the Preparation of Organolithium Compounds. *J. Am. Chem. Soc.* **1932**, *54*, 1957–1962.

17. Gilman, H.; Moore, F. W.; Baine, O. Secondary and Tertiary Alkyllithium Compounds and Some Interconversion Reactions with Them. *J. Am. Chem. Soc.* **1941**, *63*, 2479–2482.

18. Gilman, H.; Haubein, A.; Hartzfeld, H. The Cleavage of Some Ethers by Organolithium Compounds. *J. Org. Chem.* **1954**, *19*, 1034–1040.

19. Bates, B.; Kroposki; L.; Potter, D. Cycloreversions of anions from tetrahydrofurans. Convenient synthesis of lithium enolates of aldehydes. *J. Org. Chem.* **1972**, *37*, 560–562.

20. For previous revisions in this field the interested readers are also encouraged to consult references [21-27].

21. García-Álvarez, J. Deep Eutectic Mixtures: Promising Sustainable Solvents for Metal-Catalysed and Metal-Mediated Organic Reactions. *Eur. J. Inorg. Chem.* **2015**, 5147–5157.

22. García-Álvarez, J.; Hevia, E.; Capriati, V. Reactivity of Polar Organometallic Compounds in Unconventional Reaction Media: Challenges and Opportunities. *Eur. J. Org. Chem.* **2015**, 6779–6799.

23. García-Álvarez, J.; Hevia, E.; Capriati, V. The Future of Polar Organometallic Chemistry Written in Bio-Based Solvents and Water. *Chem. Eur. J.* **2018**, *24*, 14854–14863.

24. Hevia, E. Towards a Paradigm Shift in Polar Organometallic Chemistry. *Chimia* **2020**, *74*, 681–688.

25. Gentner, T. X; Mulvey, R. E. Alkali-Metal Mediation: Diversity of Applications in Main-Group Organometallic Chemistry. *Angew. Chem. Int. Ed.* **2021**, *60*, 9247–9262.

26. Perna, F. M.; Vitale, P.; Capriati, V. Synthetic Applications of Polar Organometallic and Alkali-Metal Reagents Under Air and Moisture. *Curr. Opin. Green Sustain. Chem.* **2021**, *30*, 100487.

27. García-Garrido, S. E.; Presa Soto, A.; Hevia, E., García-Álvarez, J. Advancing Air- and Moisture-Compatible *s*-Block Organometallic Chemistry Using Sustainable Solvents. *Eur. J. Inorg. Chem.* **2021**, 3116.

28. *DESs* are eutectic mixtures of Lewis or Brønsted acids and bases strongly associated with each other, exhibiting a significant depression of freezing points far below that of ideal mixtures (each component has a higher melting point than the mixture). For a recent review in this field, see: Hansen, B. B.; Spittle, S.; Chen, B.; Poe, D.; Zhang, Y.; Klein, J. M.; Horton, A.; Adhikari, L.; Zelovich, T.; Doherty, B. W.; Gurkan, B.; Maginn, E. J.; Ragauskas, A.; Dadmun, M.; Zawodzinski, T. A.; Baker, G. A.; Tucker-man, M. E.; Savinell, R. F.; Sangoro, J. R. Deep Eutectic Solvents: A Review of Fundamentals and Applications. *Chem. Rev.* **2021**, *121*, 1232–1285.

29. For recent revisions on this field, see references 30-32.

30. Nagaki, A. Recent topics of functionalized organolithiums using flow microreactor chemistry. *Tetrahedron Lett.* **2019**, *60*, 150923.

31. Power, M.; Alcock, E.; McGlacken, G. P. Organolithium Bases in Flow Chemistry: A Review. *Org. Process Res. Dev.* **2020**, *24*, 1814–1838.

32. Colella, M.; Nagaki; A.; Luisi, R. Flow Technology for the Genesis and Use of (Highly) Reactive Organometallic Reagents. *Chem. Eur. J.* **2020**, *26*, 19–32.

33. Brucoli, J.; Gariboldi, D.; Puglisi, A.; Rossi, S.; Capriati, V.; Benaglia, M. In Continuo Pd-Catalysed Cross Coupling Reactions of Organolithium Reagents with Aryl Bromides Under Aerobic Conditions. *Eur. J. Org. Chem.* **2024**, e202301289.

34. Franzén, R. G. Utilization of Grignard Reagents in Solid-phase Synthesis: A Review of the Literature. *Tetrahedron* **2000**, *56*, 685–691.

35. 2-MeTHF is considered a biorenewable biomass-derived solvent as it can be produced from furfural without the need for pet-rochemical protocols. Dalvand, K.; Rubin, J.; Gunukula, S.; Wheeler, M. C.; Hunt, G. Economics of Biofuels: Market Potential of Furfural and its Derivatives. *Biomass Bioenergy* **2018**, *115*, 56–63.

36. The immiscibility between water and 2-MeTHF permits its straightforward employment in liquid–liquid extraction (avoiding the use of toxic *VOC* solvents for the purification/isolation of the desired final organic products), thus opening the door to its use as an alternative solvent in organometallic-mediated organic transformations. Monticelli, S.; Castoldi, L.; Murgia, I.; Senatore, R.; Mazzeo, E.; Wackerlig, J.; Urban, E.; Langer, T.; Pace, V. *Monatsh. Chem.*, **2017**, *148*, 37–48.

37. CPME is considered a promising eco-friendly solvent with valuable properties such as low peroxide formation rate, stability under basic and acidic conditions, and relatively high boiling point. De Gonzalo, G.; Álcantara, A. R.; Domínguez de María, P. Cyclopentyl Methyl Ether (CPME): A Versatile Eco-Friendly Solvent for Applications in Biotechnology and Biorefineries. *ChemSusChem* **2019**, *12*, 2083–2097.

38. "*In-water*" or "*on-water*" are considered key concepts for organic reactions performed in water. For fundamental reviews in this field, which indicates the magnitude of this field of research, see references [39-42].

39. Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. "On Water": Unique Reactivity of Organic Compounds in Aqueous Suspension. *Angew. Chem. Int. Ed.* **2005**, *44*, 3275–3279.

40. Hayashi, Y. In Water or in the Presence of Water? *Angew. Chem. Int. Ed.* **2006**, *45*, 8103–8104.

739 41. Chanda, A.; Fokin, V. V. Organic Synthesis "On Water". *Chem. Rev.* **2009**, *109*, 725–748.

740 42. Zuo, Y. J.; Qu, J. How Does Aqueous Solubility of Organic Reactant Affect a Water-Promoted Reaction? *J. Org. Chem.* **2014**, *79*,
741   6832–6839.

742 43. For reviews/books dealing with peculiar dynamic three-dimensional hydrogen-bonded network of water, its colligative struc-
743   ture and its catalytic properties, see references [44-47]

744 44. Ohmine, I.; Saito, S. Water Dynamics: Fluctuation, Relaxation, and Chemical Reactions in Hydrogen Bond Network Rearrange-
745   ment. *Acc. Chem. Res.* **1999**, *32*, 741–749.

746 45. Steiner, T. The Hydrogen Bond in the Solid State. *Angew. Chem. Int. Ed.* **2002**, *41*, 48–76.

747 46. Smith, J. D.; Cappa, C. D.; Wilson, K. R.; Messer, B. M.; Cohen, R. C.; Saykally, R. J. Energetics of Hydrogen Bond Network
748   Rearrangements in Liquid Water. *Science* **2004**, *306*, 851–853.

749 47. Lindström, U. M. *Organic Reactions in Water: Principles, Strategies and Applications*, 1st ed., Blackwell, Oxford, UK, 2007.

750 48. Kubik, S. When Molecules Meet in Water-Recent Contributions of Supramolecular Chemistry to the Understanding of Molec-
751   ular Recognition Processes in Water. *ChemistryOpen* **2022**, *11*, e202200028.

752 49. Cortes-Clerget, M.; Yu, J.; Kincaid, J. R. A.; Walde, P., Gallou, F.; Lipshutz, B. H. Water as the reaction medium in organic
753   chemistry: from our worst enemy to our best friend. *Chem. Sci.* **2021**, *12*, 4237–4266.

754 50. Li, G.; Wang, B.; Resasco, D. E. Water-Mediated Heterogeneously Catalyzed Reactions. *ACS Catal.* **2020**, *10*, 1294–1309.

755 51. Zhou, F.; Hernae, Z.; Li, C.-J. Water—the greenest solvent overall. *Curr. Opin. Green Sustain. Chem.* **2019**, *18*, 118–123.

756 52. Kitanosono, T.; Kobayashi, S. Reactions in Water Involving the "On-Water" Mechanism. *Chem. Eur. J.* **2020**, 9408–9429.

757 53. Addition of RLi/RMgX reagents into different organic electrophiles (*i.e.*, ketones, aldehydes, imines) takes place in the scale of
758   seconds when using protic and polar solvents like water or *DESs*. See references 21–27.

759 54. Taylor, R. A novel preparation of tritium- and trimethylsilyl-labelled aromatics. *Tetrahedron Lett.* **1975**, *16*, 435–436.

760 55. Belaud-Rotureau, M.; Castanet, A.-S.; Nguyen T. H.; Mortier, J. Uncatalyzed CO₂Li-Mediated SNAr Reaction of Unprotected
761   Benzoic Acids *via* Silicon Trickery. *Aust. J. Chem.* **2016**, *69*, 307–313.

762 56. Kuo, S.-C.; Chen, F.; Hou, D.; Kim-Meade, A.; Bernard, C.; Liu, J.; Levy, S.; Wu, G. G. A Novel Enantioselective Alkylation and
763   its Application to the Synthesis of an Anticancer Agent. *J. Org. Chem.* **2003**, *68*, 4984–4987.

764 57. Quivelli, A. F.; D'Addato, G.; Vitale, P.; García-Álvarez, J.; Perna, F. M.; Capriati, V. Expeditious and Practical Synthesis of
765   Tertiary Alcohols from Esters Enabled by Highly Polarized Organometallic Compounds Under Aerobic Conditions in Deep
766   Eutectic Solvents or Bulk Water. *Tetrahedron* **2021**, *81*, 131898.

767 58. Mulks, F. F.; Pinho, B.; Platten, A. W. J.; Andalibi, M. R.; Expósito, A. J.; Edler, K. J.; Hevia, E.; Torrente-Murciano, L., Continuous,
768   Stable, and Safe Organometallic Reactions in Flow at Room Temperature Assisted by Deep Eutectic Solvents. *Chem* **2022**, *8*,
769   3382–3394.

770 59. Elorriaga, D.; de la Cruz-Martínez, F.; Rodríguez-Álvarez, M. J.; Lara-Sánchez, A.; Castro-Osma, J. A.; García-Álvarez, J. Fast
771   Addition of s-Block Organometallic Reagents to CO₂-derived Cyclic Carbonates at Room Temperature, Under Air, and in 2-
772   Methyltetrahydrofuran. *ChemSusChem* **2021**, *14*, 2084–2092.

773 60. Elorriaga, D.; Carrillo-Hermosilla, F.; Parra-Cadenas, B.; Antiñolo, A.; García-Álvarez, J. Aerobic/Room-Temperature-Compat-
774   ible s-Block Organometallic Chemistry in Neat Conditions: A Missing Synthetic Tool for the Selective Conversion of Nitriles
775   into Asymmetric Alcohols. *ChemSusChem* **2022**, *15*, e202201348.

776 61. Ghinato, S.; Territo, D.; Maranzana, A.; Capriati, V.; Blangetti, M.; Prandi, C. A Fast and General Route to Ketones from Amides
777   and Organolithium Compounds under Aerobic Conditions: Synthetic and Mechanistic Aspects. *Chem. Eur. J.,* **2021**, *27*, 2868–
778   2874.

779 62. Elorriaga, D.; Parra-Cadenas, B.; Antiñolo, A.; Carrillo-Hermosilla, F.; García-Álvarez, J. Combination of Air/Moisture/Ambient
780   Temperature Compatible Organolithium Chemistry with Sustainable Solvents: Selective and Efficient Synthesis of Guanidines
781   and Amidines. *Green Chem*. **2022**, *24*, 800–812.

782 63. Ghinato, S.; De Nardi, F.; Bolzoni, P.; Antenucci, A.; Blangetti, M.; Prandi, C. Chemo- and Regioselective Anionic Fries Rear-
783   rangement Promoted by Lithium Amides under Aerobic Conditions in Sustainable Reaction Media. *Chem. Eur. J.* **2022**, *28*,
784   e202201154.

785 64. Antenucci, A.; Dughera, S. Cross-Coupling Reactions between Arenediazonium *o*-Benzenedisulfonimides and Organolithium
786   Reagents in a Deep Eutectic Solvent. *ChemistrySelect* **2023**, *8*, e202303046.

787 65. Dilauro, A. G.; Luccarelli, C.; Quivelli, A. F.; Vitale, P.; Perna, F. M.; Capriati, C. Introducing Water and Deep Eutectic Solvents
788   in Organosodium Chemistry: Chemoselective Nucleophilic Functionalizations in Air. *Angew. Chem. Int. Ed*. **2023**, *62*,
789   e202304720.

790 66. Ramos-Martín, M.; Lecuna, R.; Cicco, L.; Vitale, P.; Capriati. V.; Ríos-Lombardía, N.; González-Sabín, J.; Presa-Soto, A.; García-
791   Álvarez, J. A One-pot Two-step Synthesis of Tertiary Alcohols Combining the Biocatalytic laccase/TEMPO Oxidation System
792   with Organolithium Reagents in Aerobic Aqueous Media at Room Temperature. *Chem. Commun.* **2021**, *57*, 13534–13537.

793 67. Arnodo, D.; Ramos-Martín, M.; Cicco, L.; Capriati, V.; Ríos-Lombardía, N.; González-Sabín, J.; Presa Soto, A.; García-Álvarez,
794   J. From Oximes to Tertiary Alcohols in Water, at Room Temperature and Under Air: a Hybrid One-Pot Tandem Assembly of
795   Enzymatic Deoximation and RLi/RMgX Reagents. *Org. Biomol. Chem.* **2023**, *21*, 4414–4421.

796 68. Arnodo, D.; Meazzo, C.; Baldino, S.; Blangetti, M.; Prandi, C. Efficient and Low-Impact Acetalization Reactions in Deep Eutectic
797   Solvents. *Chem. Eur. J.* **2023**, *29*, e202300820.

69. Arnodo, D.; De Nardo, E.; Ghinato, S.; Baldino, S.; Blangetti, M.; Prandi, C. A Mild, Efficient and Sustainable Tetrahydropyranylation of Alcohols Promoted by Acidic Natural Deep Eutectic Solvents. *ChemSusChem* **2023**, *16*, e202202066.

70. Cicco, L.; Roggio, M.; López-Aguilar, M.; Ramos-Martín, M.; Perna, F. M.; García-Álvarez, J.; Vitale, P.; Capriati, V. Selective Aerobic Oxidation of Alcohols in Low Melting Mixtures and Water and Use for Telescoped One-Pot Hybrid Reactions. *ChemistryOpen* **2022**, *11*, e202200160.

71. Vidal, C.; García-Álvarez, J.; Hernán-Gómez, A.; Kennedy, A. R.; Hevia, E. Introducing Deep Eutectic Solvents to Polar Organometallic Chemistry: Chemoselective Addition of Organolithium and Grignard Reagents to Ketones in Air. *Angew. Chem. Int. Ed.* **2014**, *53*, 5969–5973.

72. Deep Eutectic Solvents (*DESs*) are emerging as a new class of biorenewable, save and cheap solvents in organic synthesis. García-Álvarez, J. Deep Eutectic Solvents and Their Applications as New Green and Biorenewable Reaction Media, in *Handbook of Solvents*, *vol. 2, 3rd ed.: Use, Health, and Environment*, Wypych, G. Ed.; ChemTec Publishing, Toronto, Canada, 2019.

73. Vidal, C.; García-Álvarez, J.; Hernán-Gómez, A.; Kennedy, A. R.; Hevia, E. Exploiting Deep Eutectic Solvents and Organolithium Reagent Partnerships: Chemoselective Ultrafast Addition to Imines and Quinolines Under Aerobic Ambient Temperature Conditions. *Angew. Chem. Int. Ed.* **2016**, *55*, 16145–16148.

74. Dilauro, G.; Dell'Aera, M.; Vitale, P.; Capriati, V; Perna, F. M. Unprecedented Nucleophilic Additions of Highly Polar Organometallic Compounds to Imines and Nitriles Using Water as a Non-Innocent Reaction Medium. *Angew. Chem. Int. Ed.* **2017**, *56*, 10200–10203.

75. Cicco, L.; Salomone, A.; Vitale, P.; Ríos-Lombardía, N.; González-Sabín, J.; García-Álvarez, J.; Perna, F. M.; Capriati, V. Addition of Highly Polarized Organometallic Compounds to *N-tert*-Butanesulfinyl Imines in Deep Eutectic Solvents under Air: Preparation of Chiral Amines of Pharmaceutical Interest. *ChemSusChem* **2020**, *13*, 3583–3588.

76. Rodríguez-Álvarez, M. J.; García-Álvarez, J.; Uzelac, M.; Fairley, M.; O'Hara, C. T.; Hevia, E. Introducing Glycerol as a Sustainable Solvent to Organolithium Chemistry: Ultrafast Chemoselective Addition of Aryllithium Reagents to Nitriles under Air and at Ambient Temperature. *Chem. Eur. J.* **2018**, *24*, 1720–1725.

77. Cicco, L.; Fombona-Pascual, A.; Sánchez-Condado, A.; Carriedo, G.; Perna, F. M.; Capriati, V.; Presa Soto, A.; García-Álvarez, J., Fast and Chemoselective Addition of Highly Polarized Lithium Phosphides Generated in Deep Eutectic Solvents to Aldehydes and Epoxides. *ChemSusChem* **2020**, *13*, 4967–4973.

78. Movsisyan, M.; Delbeke, E. I. P.; Berton, J. K.; Battilocchio, C.; Ley, S. V.; Stevens, C.V. Taming Hazardous Chemistry by Continuous Flow Technology. *Chem. Soc. Rev.* **2016**, *45*, 4892–4928.

79. Kockmann, N.; Thené, P.; Fleischer-Trebes, C.; Laudadio, G.; Noël, T. Safety Assessment in Development and Operation of Modular Continuous-Flow Processes. *React. Chem. Eng.* **2017**, *2*, 258–280.

80. Capriati, V. Polar organometallic chemistry meets deep eutectic solvents in flow. *Chem* **2022**, *8*, 3159–3174.

81. Hurst, T. E.; Deichert, J. A.; Kapeniak, L.; Lee, R.; Harris, J.; Jessop, P. G.; Snieckus, V. Sodium Methyl Carbonate as an Effective C1 Synthon. Synthesis of Carboxylic Acids, Benzophenones, and Unsymmetrical Ketones. *Org. Lett.* **2019**, *21*, 3882–3885.

82. In most of the cases, one-pot tandem protocols rely on the use of the same synthetic organic tool (transition metals, organocatalysts, enzymes or main-group reagents) throughout all the tandem process. However, the corresponding hybrid counterparts, which merged together different synthetic techniques, is still in its infancy. Ye, R.; Zhao, J.; Wickemeyer, B. B.; Toste, F. D.; Somorjai, G. A. Foundations and Strategies of the Construction of Hybrid Catalysts for Optimized Performances. *Nat. Catal.* **2018**, *1*, 318–325.

83. The design of one-pot tandem protocols has attracted great attention in the portfolio of organic synthesis, as alternative routes to obtain the desire final products under greener conditions and without the need of tedious and time/energy consuming stepwise processes. Hayashi, Y. Time and Pot Economy in Total Synthesis. *Acc. Chem. Res.* **2021**, *54*, 1385–1398.

84. This phrase was coined by P. T. Anastas and J. C. Warner, which are considered the fathers of the *Green Chemistry* concept. Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*, Oxford University Press, New York, USA 1998.

85. Ghinato, S.; Dilauro, G.; Perna, F. M.; Capriati, V.; Blangetti, M.; Prandi, C. Directed *ortho*-Metalation–Nucleophilic Acyl Substitution Strategies in Deep Eutectic Solvents: the Organolithium Base Dictates the Chemoselectivity. *Chem. Commun.* **2019**, *55*, 7741–7744

86. Transitorily obtained ketones are more reactive than the starting amides and usually suffer from over-addition reactions to furnish the corresponding symmetric tertiary alcohols. Sureshbabu, P.; Azeez, S.; Muniyappan, N.; Sabiah, S.; Kandasamy. J. Chemoselective Synthesis of Aryl Ketones from Amides and Grignard Reagents via C(O)–N Bond Cleavage under Catalyst-Free Conditions. *J. Org. Chem.* **2019**, *84*, 11823–118385.

87. Fairley, M.; Bole, L. J.; Mulks, F. F.; Main, L.; Kennedy, A. R.; O'Hara, C. T.; García-Alvarez, J., Hevia, E. Ultrafast Amidation of Esters Using Lithium Amides Under Aerobic Ambient Temperature Conditions in Sustainable Solvents. *Chem. Sci.* **2020**, *11*, 6500–6509.

88. Mulks, F. F.; Bole, L. J.; Davin, L.; Hernán-Gómez, A.; Kennedy, A.; García-Álvarez, J.; Hevia, E. Ambient Moisture Accelerates Hydroamination Reactions of Vinylarenes with Alkali-Metal Amides under Air. *Angew. Chem. Int. Ed.* **2020**, *59*, 19021–19026.

89. Mallardo, V.; Rizzi, R.; Sassone, F. C.; Mansueto, R.; Perna, F. M.; Salomone, Capriati, V. Regioselective Desymmetrization of Diaryltetrahydrofurans via Directed *ortho*-Lithiation: an Unexpected Help from Green Chemistry. *Chem. Commun.* **2014**, *50*, 8655–8658.

90. Sassone, F. C.; Perna, F. M.; Salomone, A.; Florio, S.; Capriati, V. Unexpected Lateral-Lithiation-Induced Alkylative Ring Opening of Tetrahydrofurans in Deep Eutectic Solvents: Synthesis of Functionalised Primary Alcohols. *Chem. Commun.* **2015**, *51*, 9459–9462.

91. Arnodo, D.; Ghinato, S.; Nejrotti, S.; Blangetti, M.; Prandi, C. Lateral Lithiation in Deep Eutectic Solvents: Regioselective Functionalization of Substituted Toluene Derivatives. *Chem. Commun*. **2020**, *56*, 2391–2394.

92. Snieckus, V. Directed *ortho* Metalation. Tertiary Amide and *O*-carbamate Directors in Synthetic Strategies for Polysubstituted Aromatics. *Chem. Rev.* **1990**, *90*, 879–933.

93. Korb, M.; Lang, H. The Anionic Fries Rearrangement: a Convenient Route to *ortho*-Functionalized Aromatics. *Chem. Soc. Rev.* **2019**, *48*, 2829–2882.

94. Murahashi, S.; Yamamura, M.; Yanagisawa, K.; Mita, N.; Kondo, K. Stereoselective Synthesis of Alkenes and Alkenyl Sulfides from Alkenyl Halides using Palladium and Ruthenium Catalysts. *J. Org. Chem.* **1979**, *44*, 2408–2417.

95. Pinxterhuis, E. B.; Giannerini, M.; Hornillos, V.; Feringa, B. L. Fast, Greener and Scalable Direct Coupling of Organolithium Compounds with no Additional Solvents. *Nat. Commun.* **2016**, *7*, 11698.

96. Dilauro, G.; Quivelli, A. F.; Vitale, P.; Capriati, V.; Perna, F. M. Water and Sodium Chloride: Essential Ingredients for Robust and Fast Pd-Catalysed Cross-Coupling Reactions between Organolithium Reagents and (Hetero)aryl Halides *Angew. Chem. Int. Ed.* **2019**, *58*, 1799–1802.

97. Anderson, D. E.; Tortajada, A.; Hevia, E. New Frontiers in Organosodium Chemistry as Sustainable Alternatives to Organolithium Reagents. *Angew. Chem. Int. Ed.* **2023**, *62*, e202313556.

98. Cicco, L.; Rodríguez-Álvarez, M. J.; Perna, F. M.; García-Álvarez, J.; Capriati, V. One-pot sustainable synthesis of tertiary alcohols by combining ruthenium-catalysed isomerisation of allylic alcohols and chemoselective addition of polar organometallic reagents in deep eutectic solvents. *Green Chem*. **2017**, *19*, 3069–3077.

99. Elorriaga, D.; Rodríguez-Álvarez, M. J.; Ríos-Lombardía, N.; Morís, F.; Presa Soto, A.; González-Sabín, J.; Hevia; E.; García-Álvarez, J. Combination of organocatalytic oxidation of alcohols and organolithium chemistry (RLi) in aqueous media, at room temperature and under aerobic conditions. *Chem. Commun.* **2020**, *56*, 8932–8935.

100. Laccases are copper-containing enzymes belonging to the group of oxidoreductases. In nature, laccases are involved in biological processes such as lignification in plants or lignin degradation in fungi, and catalyze the oxidation of substrates such as phenols, polyphenols and anilines by means of four-electron transfer processes while reducing O_2 to water. Wellington, K. W. Application of Laccases in Organic Synthesis: A Review, in *Green Chemistry*, Luque, R. Ed.; Nova Science Publishers Inc, New York, USA, 2014.

101. González-Sabín, J.; Ríos-Lombardía, N.; García, I.; Vior, N. M.; Braña, A. F.; Méndez, C.; Salas, J. A.; Morís, F. Laccase-Catalysed Biotransformation of Collismycin Derivatives. A Novel Enzymatic Approach for the Cleavage of Oximes. *Green Chem.* **2016**, *18*, 989–994.

102. Ünlu, A. E.; Arikaya, A.; Takaç, S. Use of Deep Eutectic Solvents as Catalyst: A Mini-Review. *Green Process Synth*. **2019**, *8*, 355–372.

103. Hooshmand, S. E.; KumarI, S.; Bahadur, I.; Singh, T.; Varma, R. S. Deep Eutectic Solvents as Reusable Catalysts and Promoter for the Greener Syntheses of Small Molecules: Recent Advances. *J. Mol. Liq.* **2023**, *371*, 121013.

104. Rahrt, R.; Koszinowski, K. *C* versus *O* Protonation in Zincate Anions: A Simple Gas-Phase Model for the Surprising Kinetic Stability of Organometallics, *Chem. Eur. J.* **2023**, *29*, e202203611.

105. Seebach, D. No Life on this Planet Without PHB. *Helv. Chim. Acta* **2023**, *106*, e202200205.

106. Serrano-Luginbühl, S.; Ruiz-Mirazo, K.; Ostaszewski, R.; Gallou, F.; Walde, P. Soft and dispersed interface-rich aqueous systems that promote and guide chemical reactions. *Nat. Chem. Rev.* **2018**, *2*, 306–327.