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# Advancing Air- and Moisture-Compatible s-Block Organometallic Chemistry Using Sustainable Solvents

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*Dedicated to all past and current Spanish Organometallic Researchers on the occasion of the 40th Anniversary of the "Grupo Especializado de Química Organometalica (GEQO)" from the "Real Sociedad Española de Química (RSEQ)".*

Challenging conventional wisdom that s-block organometallic reagents such as Grignard or organolithiums need to be used under protecting inert atmosphere ($N_2$ or Ar), employing dry organic solvents with a strict temperature control, this Minireview focusses on recent advances on the use of these commodity reagents while operating under air, at room temperature and in the presence of moisture. Key for the success of these approaches has been the use of the following sustainable solvents: *i*) water; *ii*) *Deep Eutectic Solvents (DESs)*; or *iii*) biomass-derived polyols (like glycerol) or ethereal solvents [*i.e.*, 2-MeTHF or cyclopentyl methyl ether (*CPME*)]. The versatility of these air and moisture compatible synthetic protocols has been demonstrated for a myriad of key organic transformations, including nucleophilic additions of RLi/RMgX reagents to unsaturated organic molecules (*i.e.*, ketones, imines, esters, amides or nitriles) as well as *ortho*- and lateral lithiation of aromatic substrates, Pd catalysed cross-couplings and anionic polymerisation of styrenes. Extension of these studies to lithium amides ($LiNR_2$) or phosphides ($LiPPh_2$) has enabled the development of more sustainable and efficient methods for C–N and C–P bond forming processes. These unconventional s-block metal mediated transformations have also been successfully incorporated in one-pot tandem processes in combination with transition-metal and organo-catalysis. Remarkably, in some cases the conversions and chemoselectivities observed are superior to those detected in common toxic organic solvents, while working under inert atmosphere conditions with strict temperature control. The key role played by the choice of solvent in these transformations and how it can affect the constitution of the s-block organometallic species present in solution is also discussed.

## 1. Introduction

Since the pioneering works by Victor Grignard and Philippe Barbier (organomagnesium derivatives, 1900)[1] and Wilhelm Schlenck and Johanna Holtz (organolithium compounds, 1917),[2] polar s-block organometallic chemistry has become a pivotal instrument in the toolbox of synthetic organic chemists. Used in academic synthetic laboratories worldwide, they are especially in high demand for functionalising aromatic and heterocyclic compounds and so are indispensable in the chemical industry (*e.g.*, for the manufacture of agrochemicals, electronic materials, pharmaceuticals and other medicines). Part of their popularity lies in their high reactivity, as a consequence of the large (for lithium)[3] to medium (for magnesium)[4] polarity of their metal-carbon bonds. However, controlling this high reactivity can be challenging and side reactions such as hydrolysis/oxidation of reagents, decomposition of intermediates, unwanted rearrangements, and functional group attacks are common. In order to overcome some of these limitations, polar organometallic reagents are usually employed at very low temperatures (−78 °C) and the use of strict inert atmosphere conditions and carefully dried organic solvents is paramount to this type of chemistry. These problems in controlling the selectivity of these reagents can also lead to the formation of complex mixtures and poor product yields, which necessitate additional separation steps and generate lots of waste. These limitations can greatly impact large scale processes in industry due to the extra costs and time incurred in solving these problems. In addition, hazardous volatile organic compounds (*VOCs*) used as common solvents in polar organometallic chemistry still represent 80–90 wt.% of the non-aqueous materials used in a typical chemical manufacturing process despite their toxicity, high flammability, non-biodegradability and tendency to accumulate in the atmosphere.[5] Furthermore,

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the recovery of these toxic and flammable organic compounds only reaches 50 to 80 % in most of the cases.[6]

Advances in *Green Chemistry*[7] have made giant steps towards addressing some of these challenges as well as others imposed by today's society (which are related with the limited availability of our natural resources and its consequences). Thus, great efforts have focussed on the design of organic processes that can take place: *i*) under aerobic ambient conditions and

Sergio E. García Garrido studied chemistry at the University of Oviedo and received his PhD degree in 2005 under the supervision of Prof. José Gimeno and Dr. Victorio Cadierno working in the chemistry of organometallic complexes of ruthenium(II) and ruthenium(IV), as well as their application in different catalytic processes of interest. After a postdoctoral stay (2005–2007) at the School of Chemistry of Southampton University (Southampton, UK), working under the supervision of Prof. Philip A. Gale in the field of supramolecular chemistry and its application to the recognition of anions, he rejoined the Department of Organic and Inorganic Chemistry of Oviedo University, first as contracted researcher (2008), later as a Ramón y Cajal researcher (2009–2013), Lecturer (2014–2018) and finally as Senior Lecturer (Associate Professor) in Inorganic Chemistry, position that he currently holds. His current lines of work focus on the chemistry of organometallic complexes and the development of new supramolecular structures as well as their applications in homogeneous and heterogeneous catalysis. He is coauthor of more than 50 articles in international journals and 7 book chapters.

Alejandro Presa Soto was born in Gijón (Asturias, Spain) in 1976. He obtained his PhD at the University of Oviedo (2005) working in the synthesis and catalytic activity of chiral polyphosphazene copolymers under the supervision of Prof. G. Carriedo and Prof. F. J. García-Alonso. After exploring the self-assembly of crystalline block copolymers in work with I. Manners in Bristol, he returned to the University of Oviedo in 2010 first as a Juan de la Cierva researcher, and later as a Ramón y Cajal research fellow. Currently he is Associate Professor of Inorganic Chemistry and his research interest is focused on the synthesis and self-assembly of polyphosphazene-based block copolymers and the development of novel chemical transformations involving the formation of C-heteroatom bonds under sustainable reaction media. He has authored more than 50 scientific publications including 3 book chapters.

Eva Hevia received both her MSci degree in Chemistry and her Ph.D. degree from the Universidad de Oviedo (Spain) in 1998 and 2002 respectively. After a three-year position at the University of Strathclyde (Glasgow, UK) working as a Marie Curie Fellow with Professor Robert Mulvey, in 2006 she took up a Royal Society University Research Fellowship and Lectureship there. Subsequently she was promoted to Full Professor in 2013. In February 2019, Eva moved to the University of Bern to take up a full professorship in Inorganic Chemistry. Research in her group focuses on polar organometallic chemistry at the crossroads of inorganic, organic, and green chemistry. Eva is an elected fellow of the European Academy of Sciences and her research has been recognised with several awards including the 2017 RSC Corday-Morgan Prize, and the 2019 GEQO Research Excellence Award.

Joaquín García Álvarez studied chemistry at the University of Oviedo and received his PhD degree in 2005 under the supervision of Prof. José Gimeno and Dr. Victorio Cadierno studying the coordination of iminophosphorane ligands in arene-Ru(II) fragments. Then, he joined the group of Prof. Robert E. Mulvey at the University of Strathclyde in Glasgow (Scotland, United Kingdom) working for two years and a half in the field of main group chemistry (alkali-metal-mediated-metallation). In 2008, he returned to the University of Oviedo as a postdoctoral researcher, thanks to the award of a contract from the regional program "Clarín" of the Principado de Asturias. The current focuses of his research are: i) the study of metal-catalysed (Ru, Cu, Pd, Au) and metal-mediated (Li, Mg) organic reactions using environmentally friendly solvents [water and Deep Eutectic Solvents (DESs)] as reaction media; and ii) the design of one-pot processes combining either metal-, organo- and bio-catalysis. This research has been recognised over the last years with the award of a postdoctoral contract "Juan de la Cierva" in 2009, and more recently (2012), with a postdoctoral contract "Ramón y Cajal". In 2017, he was promoted to an Assistance Professor position, and more recently (2018) to an Associate Professor position. He has published more than 75 scientific articles and is coauthor of twelve book chapters on Organometallic Chemistry and Catalysis in unconventional reaction media. In 2016, he received the Prize "GEQO-Young Scientist Award"; in 2017 the "Beca Leonardo a Jóvenes Investigadores y Creadores Culturales" from BBVA fundation; and in 2018 the "Green Chemistry For Life Grant Programme" awarded by PhosAgro/UNESCO/IUPAC.


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with energy efficiency (*i.e.*, room temperature and atmospheric pressure); *ii*) using sustainable solvents;[8] and *iii*) under safe conditions (for both human beings and the environment). However, until recently, progress made towards upgrading s-block organometallic chemistry to these greener conditions have been limited, since *a priori*, the cannon of this type of chemistry is incompatible with these conditions (*vide supra*).

Making a seemingly impossible step change possible, recent studies from our groups and others, have shown that by replacing conventional toxic organic solvents (*i.e.*, THF or toluene) with other sustainable reaction media (such as *Deep Eutectic Solvents*, water, glycerol, 2-MeTHF or cyclopentyl methyl ether) it is possible to use these commodity s-block metal reagents under air and in the presence of moisture. Furthermore, on many occasions, under these conditions, greater performances and selectivities of the s-block organometallic reagents are observed. Overall, these innovations have rendered an even greater scenario, where the development of more environmentally benign synthetic procedures has unveiled greater chemical behaviours.

This Minireview summarises some of these studies on the use of s-block polar organometallic reagents in aerobic/ambient conditions when using sustainable reaction media (like *Deep Eutectic Solvents*, water, glycerol, 2-MeTHF or cyclopentyl methyl ether) as solvent. Specifically, the Minireview is divided in different sections, which showcase different type of reactivities. This includes: *i*) chemoselective nucleophilic addition of RLi/RMgX to carbonyl compounds (like ketones,[9] imines,[10] esters,[11] amides[12]) or nitriles;[13] *ii*) regioselective *ortho*- or lateral lithiation of aromatic amides[12a] and aryltetrahydrofurans,[14] respectively; *iii*) formation of new C-heteroatom bonds (C–X) by using lithium amides ($LiNR_2$)[15] or phosphides ($LiPPh_2$);[16] *iv*) the anionic polymerisation of styrenes;[17] and *v*) cross-coupling reactions of RLi with aryl halides.[18] In addition, a section is included summarising current efforts to design one-pot tandem protocols in which aerobic polar s-block organometallic chemistry in green solvents can be synergically amalgamated with either metal-[12a,19] or organocatalysed[20] synthetic processes.

The overarching aim of this Minireview is to inform and inspire other synthetic chemists who use this fundamental type of reagents on a regular basis, finding it a helpful resource towards the development of air and moisture compatible, sustainable s-block organometallic chemistry.[21] Approaching this area from a metal-focussed perspective, a special effort has been made to correlate the reactivities observed in these solvents with the possible constitution of the organometallic intermediates in these unconventional solvents.

## 2. Aerobic Addition/Substitution Reaction of s-Block Organometallic Reagents (RLi/RMgX) to Carbonyl Compounds in Sustainable Solvents

### 2.1. Chemoselective addition of RMgX/RLi reagents to ketones and esters in *DESs* and water

While the use of organolithium and Grignard reagents in bulk water and other unconventional solvents (*DES*s, glycerol, etc) is a recent innovation,[9–20] some previous precedents in the literature have hinted at the influence of water on the reactivity of these commodity organometallic reagents. Thus, in 1975 Taylor reported the reaction of *n*-BuLi with bromoarenes using Na-dried solvent wetted with $T_2O$ at −70 °C as an efficient method to access tritiated arenes.[22a] In parallel advances in inorganic chemistry have shown that water can actually be a suitable donor ligand in organolithium and organopotassium chemistry.[22b–d] Thus, in 1990 Wright and co-workers reported the lithiation of 2-mercaptobenzoxazole in the presence of TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylene diamine) and $H_2O$ which furnished [($C_6H_4OCSN$)Li(TMEDA)($H_2O$)] where the coordinated molecule of water forms a strong H-bond between one of its protons and the polarised C=S bond of the ligand.[22b] Scheyer and co-workers reported the structure of [LiCH$(CN)_2$($H_2O$)(TMEDA)]$_\infty$] resulting from the lithiation of malonitrile followed by addition of TMEDA and water. Forming an intricate three dimensional polymeric structure, TMEDA does not coordinate to the Li atoms, whereas each water molecule binds simultaneously to TMEDA (via H-bonding) and to the lithium cations (acting as a Lewis base).[22c] More recently Stalke and co-workers have reported the synthesis and structural authentication of a novel water-containing organopotassium complex (Figure 1) which was found to be surprisingly robust towards hydrolysis.[22d] $^1$H NMR titration experiments in deuterated THF using variable amounts of water revealed that full hydrolysis of this compound was only observed after one week using 114 equivalents of water.[22d]

Building on these exciting precedents, our first studies focussed on the addition of Grignard reagents to ketones to access tertiary alcohols. It should be noted that previous work by Holm and Madsen has shown that allyl Grignard reagents

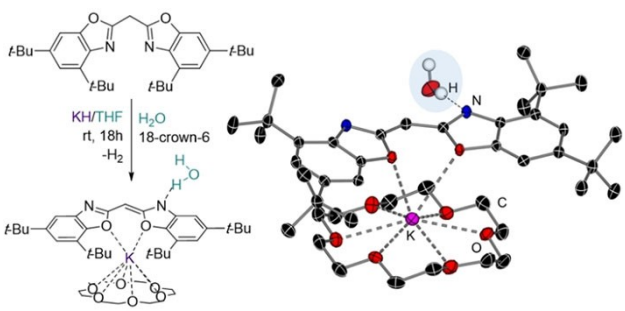


**Figure 1.** Synthesis and asymmetric unit of [(18-crown-6)K{(4,6-*t*Bu-$OCNC_6H_2)_2CH$}·$H_2O$].[22d]


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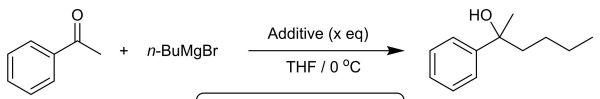
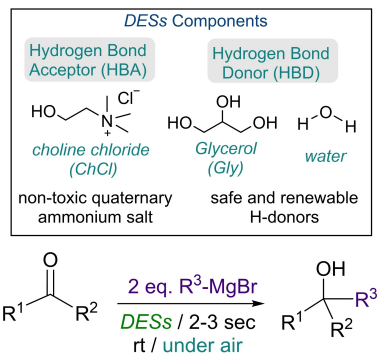
can add to acetone in the presence of water.[23] Key for the success of this approach was that the rate of the ketone addition was comparable to that of protonation of the Grignard reagent in water. However, its substrate scope was very limited, and using more reactive reagents such as *n*-BuMgCl only traces of the addition product were observed. On the other hand, studies by Song and co-workers described the activation effect of quaternary ammonium salts [like N(*n*-Bu)$_4$Cl or N(*n*-Bu)$_4$Br] and diglyme on the addition of Grignard reagents to ketones in THF.[24] Thus, when the addition of *n*-BuMgBr is performed in the absence of any additive the obtained yield for the desired tertiary alcohol is 49%. The simple addition of the ammonium salts N(*n*-Bu)$_4$Cl/N(*n*-Bu)$_4$Br to the reaction media (using either stoichiometric or catalytic amounts) triggered a remarkable increase of the yield of the addition reaction (up to 91%) (Scheme 1). In the same line, the addition of a tridentate donor ligand (*i.e.*, diglyme) to the reaction media clearly improves the yield of the final tertiary alcohol up to 75%. While the authors acknowledge that the presence of the ammonium salt or the diglyme can affect the position of the Schlenk equilibrium for the Grignard reagents, the exact activating effect of this additive remained concealed.

Inspired with these precedents and with the aim of developing more sustainable Grignard mediated reactions, we pondered if we could export this ammonium salt activating




| additive | yield(%) |
|---|---|
| - | 49 |
| N(*n*-Bu)$_4$Br (0.1 eq) | 89 |
| N(*n*-Bu)$_4$Br (1 eq) | 91 |
| Diglyme (1.5 eq) | 75 |

**Scheme 1.** Observed improvement of the reaction yield in the addition of Grignard reagents to ketones when ammonium salt N(*n*-Bu)$_4$Br or diglyme are employed as additives.[24]




**Scheme 2.** Ultrafast and chemoselective addition of RMgX reagents to ketones under air, at room temperature using *ChCl*-based eutectic mixtures as reaction media.[9a]

effect to the use of non-toxic and biodegradable ammonium-salt-based *Deep Eutectic Solvents* (*DESs*) (Scheme 2).[25] These neoteric, sustainable and tunable reaction media can be easily obtained just by mixing two naturally occurring compounds that are able to interact through a tridimensional hydrogen-bond-type network, which is established between an hydrogen-bond-acceptor component and its corresponding hydrogen-bond-donor counterpart. In particular for this study, we used *DESs* containing the biorenewable quaternary ammonium salt choline chloride (*ChCl*)][26] and different hydrogen-bond-donors such as glycerol (*Gly*), ethylene glycol (*EG*), urea or even water (Scheme 2).[25]

Using choline-chloride-based eutectic mixtures containing glycerol (1*ChCl*/2*Gly*) or water (1*ChCl*/2H$_2$O), we found that a variety of Grignard reagents (alkyl-, vinyl- and ethynyl magnesium bromides) can rapidly undergo selective addition to both aromatic or aliphatic ketones, under bench type reaction conditions (room temperature and under air). Reactions take place in just 3 seconds and the relevant substituted tertiary alcohols are obtained in good to excellent yields (up to 87%).[9a] It should be noted that the reactions require the use of two equivalents of the RMgBr reagent, but they occur with an excellent control of the chemoselectivity, without observing the formation of other by-products resulting from competing reduction or enolisation processes. Demonstrating the key role of the *DESs*, in the absence of the quaternary ammonium-salt *ChCl* (that is using bulk water as solvent), the addition process almost shuts down, with the yield dramatically decreasing to 10%. This experimental observation suggested a possible kinetic activation of the Grignard reagents favored by *ChCl* (in good agreement with previous studies reported by Song).[24] Trying to shed some light in this activation process, we studied the co-complexation of several Grignard reagents with N(*n*-Bu)$_4$Cl. We use this ammonium salt due to its solubility in THF. Combining X-ray crystallographic studies with DOSY NMR experiments, we could establish the formation of mixed ammonium magnesiate [{N(*n*-Bu$_4$)}$^+${RMgCl$_2$}$^-$] species (Figure 2).[9a]

Since the formation of this mixed ammonium magnesiate species occurs via co-complexation of the ammonium salt and the Grignard reagent using an ethereal solvent (THF), it is not possible to ascertain if the same type of co-complexation is in operation when using *DESs* containing *ChCl* as solvent. Nevertheless, it could be expected that these type of anionic

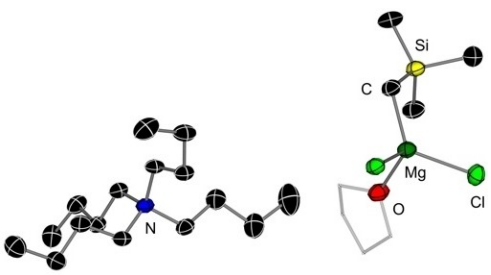



**Figure 2.** Molecular structure of ammonium magnesiate [{N(*n*-Bu$_4$)}$^+${(Me$_3$SiCH$_2$)MgCl$_2$(THF)}$^-$] obtained by co-complexation of N(*n*-Bu$_4$)Cl and Me$_3$SiCH$_2$MgCl in THF.[9a]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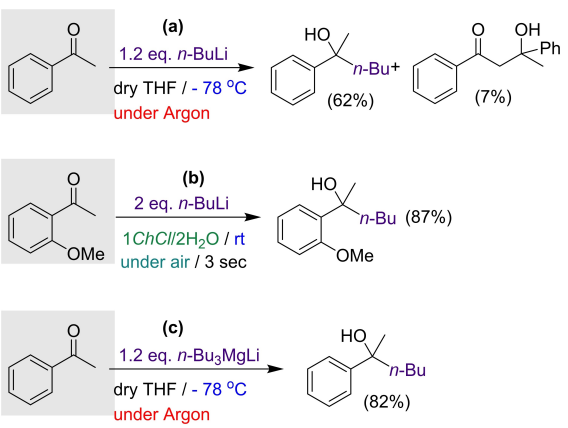
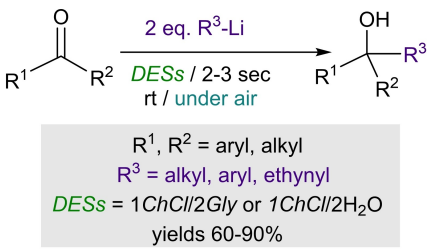
magnesiate species will exhibit enhanced nucleophilic power in comparison with that of neutral Grignard reagents.[27] This could explain, to certain extent, the fast reactivity observed in these additions, favoring the addition reactions over competing hydrolysis processes. Notwithstanding other factors should also be taken into account, as for example the activation of the substrate by the formation of H-bonding with the H-bond donor component of the *DES* (water or *Gly*). Furthermore, as the Grignard reagents used in this study were purchased from commercial sources as THF solutions, and the employed *DESs* and THF are not miscible, the heterogeneous character of these reactions may also play an important role (*vide infra* for reaction "*on-water*" conditions).[28]

Building on these promising results using RMgX reagents, we next extended these studies to highly polar organolithium reagents. The greater polarity of the M–C bond in these systems in comparison to RMgX reagents, generally imposes the use of cryogenic conditions (−78 °C), in order to control their chemoselectivity.[3] For example Ishihara and co-workers have previously reported the addition of *n*-BuLi to acetophenone, working at −78 °C, under protecting atmosphere and using dry THF as solvent. As depicted in Scheme 3a and employing these Schlenk-type reaction conditions, the authors observed the formation of a mixture of products containing the expected tertiary alcohol in a 62% yield along with the undesired aldol condensation by-product.[29] Contrastingly, when we repeated this reaction (but using 2-methoxy-acetophenone as electrophile) under air, at room temperature and employing 1*ChCl*/$2H_2O$ (Scheme 3b) the corresponding tertiary alcohol is obtained as the only product of the reaction, in an increased 87% yield. These findings show that using these unconventional reaction conditions not only it is possible to improve the performance of the organometallic reagent but also to increase the chemoselectivity of the addition process. Again, and as previously proposed for Grignard reagents, we rationalise these experimental observations in terms of an activation effect of *n*-BuLi in the presence of the quaternary-ammonium-salt (*ChCl*). In this case, whilst we were not able to obtain X-ray quality crystals from the reaction, both monodimensional ($^1$H, $^{13}$C, and $^7$Li) and bidimensional (DOSY) NMR studies hint at the possible *in-situ* formation of anionic lithiate ($[LiCl_2R]^{2-}$) as a probable active species, in which two chloride anions coming from the *ChCl* are now coordinated to the lithium atom. Although it should be noted that these experiments have been carried out using N(*n*-$Bu_4$)Cl as a mimic of *ChCl* and the solvent employed is deuterated THF. Related to the formation of reactive *ate* species, Ishihara and co-workers have also reported that lithium magnesiate (*n*-Bu)$_3$MgLi can offer greater chemoselectivities for the alkylation of ketones than conventional organolithium reagents using THF as a solvent (see Scheme 3c, using in this case acetophenone as the organic substrate).[29] Thus, these experimental observations reveal the key double role of *ChCl* in this transformation, being at the same time: *i*) the hydrogen-bond acceptor needed for the synthesis of the eutectic mixture; and *ii*) the halide source that can facilitate the *in-situ* formation of more activated and nucleophilic lithiate species.

Thrilled by these observations, we next assessed the scope of the RLi addition reaction in terms of the nature of both the organolithium reagents and the ketones employed as organic electrophiles (see Scheme 4). Thus, alkyl-, aryl- or alkynyl-based organolithium reagents can be successfully and chemoselective added to ketones (either aliphatic or aromatic groups are tolerated) after only 3 seconds of reaction, giving rise to the corresponding highly substituted tertiary alcohols in good to almost quantitative yields. It should be noted that similar conversions were observed using either 1*ChCl*/$2H_2O$ or 1*ChCl*/2*Gly* as *DESs*. However, when the same reactions were carried out replacing the relevant *DES* by neat water only traces of the addition product were observed, highlighting again the importance of *DES* as part of the reaction medium.[9a] At this point, it is important to mention that in those cases in which the desired alcohols are obtained as solids (for example aromatic alcohols derived from benzophenone) the final products could be isolated just by simple adding of a brine aqueous solution to the eutectic mixture media, which favoured the precipitation of the desired tertiary alcohols. Therefore, these organic products could be isolated directly through filtration without using organic and toxic *VOC* solvents. For those cases in which the final products are obtained as oils/liquids, a liquid/liquid extraction with environmentally friendly and biomass-based ethereal solvents (like 2-MeTHF or CPME) could be also employed.




**Scheme 3.** Comparative studies on the addition of organolithium reagents into ketones employing either traditional Schlenk-type (**a**, **c**)[29] or *DESs*-type reaction conditions (**b**).[9a]




**Scheme 4.** Ultrafast and chemoselective addition of organolithium reagents (RLi) to ketones under air, at room temperature and using *ChCl*-based eutectic mixtures as reaction media for the synthesis of tertiary alcohols.[9a]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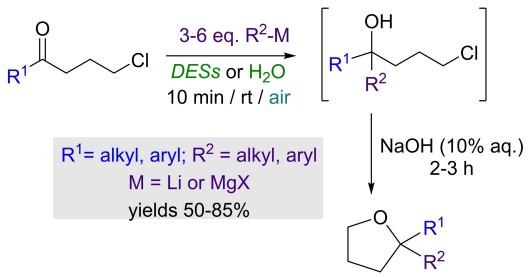
Contemporary to our work and going one step further, Capriati and co-workers reported the design of a one-pot/two-steps protocol that combines the chemoselective nucleophilic addition of alkyl/aryl Grignard (RMgX) or organolithium (RLi) reagents to aryl/alkyl $\gamma$-chloroketones, under bench-type (room temperature and in the presence of air) and heterogeneous conditions (water or *DESs* were used as sustainable solvents, Scheme 5), with the concomitant cyclisation of the *in-situ* obtained aryl/alkyl $\gamma$-chloroalcohols, thanks to the addition of an aqueous solution of NaOH (10%) to the reaction crude.[9b] By employing this protocol, the authors were able to produce 2,2-disubstituted tetrahydrofurans in good yields (up to 85%) working "*on-water*"[28] or "*on-DESs*" heterogeneous conditions (as the aryl/alkyl $\gamma$-chloroketones employed are sparingly soluble in water or *DESs*). Interestingly, this work also showed that water/*DESs* mixture cannot be simply replaced by bulk alcohols (MeOH) as solvent, suggesting that the strong and tridimensional intermolecular hydrogen bond stablished between water/*DESs* and the substrate may play a pivotal role in the studied transformation. This special H-bonding scenario can induce not only the activation of the C=O bond on the substrate towards the nucleophilic addition but also shield the organometallic reagent from competitive hydrolysis processes.

More recently in collaboration with Capriati's group, we have also reported an efficient protocol for the synthesis of symmetric tertiary alcohols in excellent yields (up to 98%) but using esters as organic electrophiles (Scheme 6).[11] In this case, the fast (20 sec) and chemoselective double addition of RLi/RMgX reagents (intermediate ketones were not isolated) can be performed in the sustainable choline chloride/urea eutectic mixture (1*ChCl*/2Urea) or in bulk water. This double addition protocol tolerates a wide variety of esters and alkylating/arylating reagents (RLi/RMgX) takes place straightforwardly at room temperature in the presence of air. Finally, demonstrating its synthetic utility, this procedure was applied to the synthesis of some representative *S*-trityl-L-cysteine derivatives, which are a potent class of Eg5 inhibitors.[30]

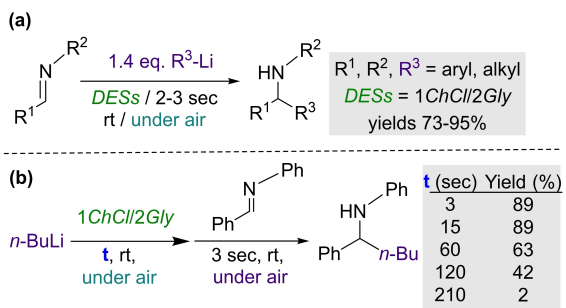



**Scheme 5.** Chemoselective addition of polar organometallic reagents RLi/RMgX) to $\gamma$-chloroketones under air, at room temperature and using either water or *ChCl*-based eutectic mixtures as reaction media for the synthesis of 2,2-disubstituted tetrahydrofurans.[9b]

**Scheme 6.** 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 for the synthesis of symmetric tertiary alcohols.[11]

### 2.2. Chemoselective addition of RMgX/RLi reagents to imines and nitriles in *DESs*, water and glycerol

Imines are generally considered valuable starting materials for the synthesis of amines[31] through the nucleophilic addition of Grignard,[32] organolithium (RLi),[33] organoaluminium ($AlR_3$)[34] or organozinc ($ZnR_2$) reagents.[35] Contrary to the aforementioned case of ketones or esters, the addition of polar main-group reagents to imines has been less explored. This is probably due to: *i*) the reduced electrophilic character of the iminic carbon when compared with their corresponding keto counterparts;[36] and *ii*) the high tendency of imines to suffer undesired side reactions (deprotonation/reduction) in the presence of highly polar organometallics. In order to overcome some of these drawbacks, several protocols have been described in the literature that focused on increasing the electrophilic character of the iminic carbon. Some of these strategies involve the use of electron-withdrawing groups on the substituents on the nitrogen atom; or the activation of the imine group through the addition of Lewis acids to the reaction media. Thus, and bearing in mind the foreseen activation effect of *ChCl*-based eutectic mixtures in the addition of organolithium reagents to ketones and esters (Scheme 4, Scheme 5, Scheme 6),[9,11] some of us decided to test non-activated imines as new electrophilic partners (Scheme 7a).[10a] We found that the addition reaction of either aliphatic or aromatic RLi reagents into the selected non-activated imines took place faster (only 3 sec) than their corresponding hydrolysis process with the protic eutectic reaction medium, giving rise to the desired secondary amines: *i*) with high selectivity (only the starting imines and/or the final




**Scheme 7.** (**a**) Chemoselective addition of organolithium reagents (RLi) to imines under air, at room temperature and using the eutectic mixture 1*ChCl*/2*Gly* as sustainable reaction media for the synthesis of secondary amines; (**b**) Assessing the time-dependent formation of the addition product when the order of addition of reagents is reversed.[10a]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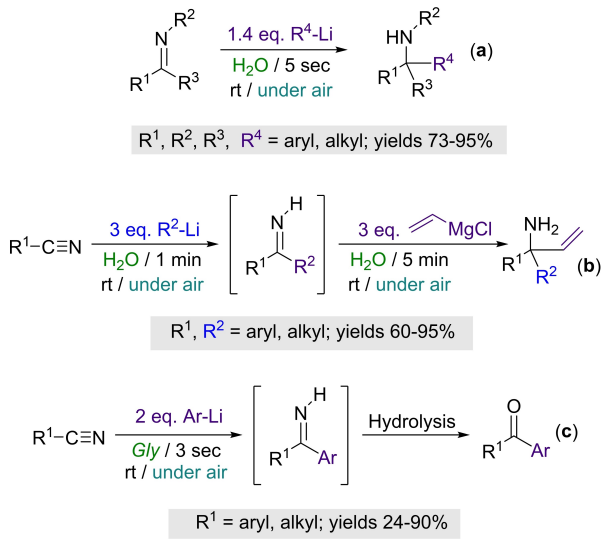
secondary amines were observed in the NMR spectra of the reaction crudes); *ii*) at room temperature and under air; and *iii*) in good to almost quantitative yields (73–95%). Interestingly in this study under the conditions explored, the eutectic mixture 1*ChCl*/2*Gly* proved to be a better choice of solvent than 1*ChCl*/2$H_2O$. Furthermore, by using the 1*ChCl*/2*Gly* mixture it was possible to carry out this alkylation/arylation reactions using just 1.4 equivalents of the relevant organolithium reagents, edging closer to stoichiometric conditions. Moreover, this approach could also be applied for the alkylation of the more challenging quinolines. In this case, while lower yields were observed (18–54%), the reaction takes place with an excellent control of the chemoselectivity, furnishing exclusively the 1,2-addition products. Remarkably, the addition reactions to imines worked well with sterically demanding *s*-BuLi and *t*-BuLi, which in general have a greater tendency to undergo $\beta$-hydride elimination, especially when employed at room temperature.

Astonishingly, when we studied the lifetime of the organolithium reagent in the protic eutectic mixture by reversing the order of addition of reagents (as shown in Scheme 7b for the addition of *n*-BuLi to *N*-Benzylideneaniline), we found that after stirring the organolithium reagent for 15 seconds under air before adding imine, the addition product is still obtained in a remarkably high 89% yield. These findings revealed an unexpected high kinetic stability of *n*-BuLi in the 1*ChCl*/2*Gly* eutectic mixture. In fact, it was only after leaving this reagent in the *DES* for 3.5 minutes exposed to air that the addition to the imine was completely supressed (Scheme 7b).

Further work by Capriati has also shown that water can be used as a solvent to promote the same fast and selective addition of organolithium reagents to imines.[10b] As we previously observed when *ChCl*-based eutectic mixtures were used as sustainable reaction media, the addition of RLi to imines took place "*on-water*" conditions, at room temperature and under air, giving rise to the expected secondary amines in yields up to 99% (Scheme 8a). Additions take place under vortex conditions, by the formation of emulsions resulting from the addition of a commercially available solution of RLi in hexanes to a suspension of the imine substrate in water. Under these heterogeneous conditions it has been previously noted that the efficiency of the "*on-water*" reactions can be influenced by the volume and surface area of the organic droplets.[28] Supporting this interpretation, when the addition was carried out with gently stirring (to minimise the area of interface), the yields for the amine product decreased from 99 to 66%.[10b] Interestingly, when using $D_2O$ as a solvent, a significant H/D isotope effect was revealed. This supports that the observed "*on-water*" behaviour can arise from proton transfer across the organic-water interface. Other highlights of this work from a practical perspective were that reactions can be efficiently carried out in a larger scale (up to 5.5 mmol using 10 mL of water), and also that the relevant amine product can be isolated by simple evaporation of the organic phase, without any further purification.

In the same work, Capriati and co-workers illuminated the way to follow to produce tertiary carbinamines under *greener* reaction conditions by employing a one-pot/two-steps protocol




**Scheme 8.** Addition of highly polar organometallic reagents (RLi/RMgX) to imines or nitriles under air, at room temperature using water[10b] or glycerol[13] (*Gly*) as reaction media for the synthesis of amines or ketones.

based on the double and consecutive addition of organolithium (RLi) and Grignard reagents (RMgX) to nitriles (Scheme 8b).[10b] At this point it is important to note that, in this specific case, both water-soluble ($CH_3CN$) and poorly soluble (PhCN) nitriles proved to be effectively converted into the desired carbinamines. This is a rare example for this type of chemistry, where the outcome of the addition reactions is not dependent on the solubility of the organic electrophile in the employed sustainable and protic eutectic mixture (water or *ChCl*-based eutectic mixtures).

Another sustainable solvent that has emerged as an efficient medium for the arylation of nitriles is glycerol (*Gly*, Scheme 8c).[13] As described in the previous examples using *DESs* or water, these reactions which employ aryl lithiums, are ultrafast (2–3 seconds) and compatible with air and moisture. Arylation of the nitriles generates *in-situ* the relevant NH-imines which can then be converted into the corresponding ketones by hydrolysis in moderate to good yields (24–90%, Scheme 8c).[13] Interestingly, contrasting with the reactivities observed in the studies carried out in water (*vide supra*), when using *Gly*,[37,38] only those nitriles who were insoluble in this solvent were effective towards these arylation processes. These findings suggest that this addition protocol takes place under "*on-glycerol*" conditions. A key difference between the use of ArLi reagents in water or *Gly* is the greater resistance to hydrolysis in the later. Thus, a study reversing the order of addition of the reagents, revealed that if benzonitrile is added to a mixture of PhLi in *Gly* that has firstly been allowed to stir at room temperature, under air, for 15 seconds, benzophenone can still be obtained in a 74% yield (as opposed to 83% when the nitrile is first mixed with *Gly* and then PhLi is introduced). Contrastingly no benzophenone could be detected when the same reaction is performed in water.[13] More recently, expanding even further the synthetic potential of these approaches,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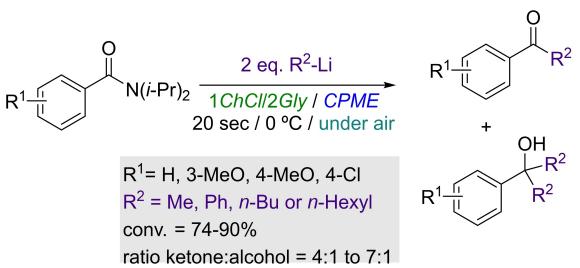
the addition of RLi/RMgX reagents *N*-tert-butanesulfinyl imines using a mixture of *D*-sorbitol/*ChCl* as a solvent has been reported as an environmentally friendly procedure for the preparation of chiral amines of pharmaceutical interest at room temperature and in the presence of air.[10c]

### 2.3. Nucleophilic substitution/addition of organolithium reagents (RLi) to amides in *DESs* or cyclopentyl methyl ether (*CPME*)

Amides are key building blocks in a plethora of different synthetic organic protocols due to their excellent chemical versatility and easy synthesis/accessibility.[39] For the specific case of the reactivity of aromatic amides towards highly polar organometallic reagents (*e.g.*, RLi compounds) basically two major reaction pathways have been reported so far: *i*) metallation on the activated *ortho* position of the aromatic ring (*DoM*, Direct-*ortho*-Metalation); and *ii*) the corresponding nucleophilic substitution of the amine group ($NR_2$) by the incoming carbanion ($R^-$) present in the polar organometallic reagents (RLi).[40] When substitution reactions in aromatic amides are sought by synthetic organic chemists, the employment of less sterically hampered organolithium reagents (with reduced basic character like for example MeLi, PhLi, *n*-BuLi or *n*-HexylLi) is recommended. However, since the transitorily obtained ketones are more reactive than the starting amides, usually over-addition is observed furnishing the relevant symmetric tertiary alcohols.[41] This problem has recently been overcome by Capriati and Prandi by using a mixture of cyclopentyl methyl ether (*CPME*)[42,43] and the *DES* 1*ChCl*/2*Gly* as solvent, which allowed the preparation of the relevant ketones in good yields (Scheme 9).[12a] These products are obtained as mixtures with the corresponding symmetric alcohols, with the best ratios in favour of the ketone product when the reaction mixture is cooled down up to 0 °C. While this approach works well for several commercially available organolithium reagents (MeLi, PhLi, *n*-BuLi or *n*-HexylLi), when *t*-BuLi was employed *ortho*-metalation of the benzamide was observed (see section 3).[12a]

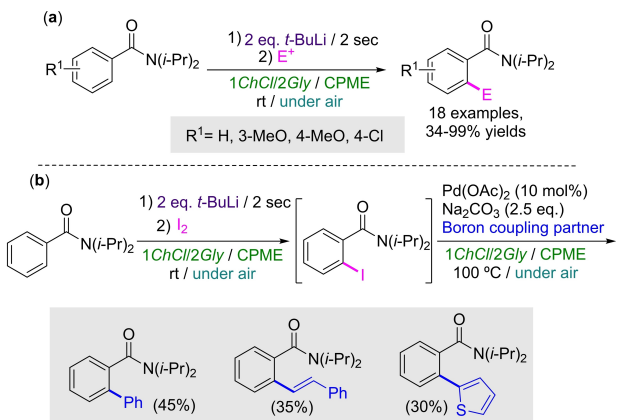
The scope and selectivity of this nucleophilic substitution method has been recently improved by using *CPME* as the only sustainable solvent for this transformation; and increasing the temperature of the reaction from 0 to 25 °C.[12b] Under these optimised conditions nucleophilic acyl substitution of a broad range of aliphatic and hetero(aromatic) amides can be accomplished using a variety of RLi reagents, including *s*-BuLi or thienyl lithium. NMR investigations combined with DFT calculations suggest that these reactions take place *via* the formation of a dimeric tetrahedral intermediate which is stabilised by the coordination of *CPME*.[12b] Demonstrating its sustainability, this approach could also be scaled up to gram scale with subsequent recycling of the solvent and the amine leaving group to prepare additional starting material.




**Scheme 9.** Nucleophilic substitution on *N,N*-diisopropylbenzamides triggered by organolithium reagents using mixtures *DESs*/*CPME*.[12a]

## 3. Regioselective *ortho*- or Lateral-Lithiation of Aromatic Amides and Aryltetrahydrofurans Promoted by Organolithium Reagents (RLi) in Sustainable Solvents

As previously mentioned, amide substituents are strong *ortho*-directing groups, and therefore benzamides are susceptible of metallation.[40] Pioneering work by Prandi and Capriati has recently shown that *t*-BuLi can act as a selecting *ortho*-metallating reagent of *N,N*-diisopropylbenzamides under air, at room temperature, using a mixture of *CPME* and the *DES* 1*ChCl*/2*Gly* (see Scheme 10a), a trio of conditions regarded as completely incompatible with this highly reactive organometallic reagent.[12a] The *in-situ* generated *ortho*-lithiated amides could then be subsequently trapped with a variety of electrophiles such as benzaldehyde, DMF, $I_2$, $S_2Me_2$, or $CD_3OD$ to name just a few (Scheme 10a). Expanding even further the synthetic potential of this approach, the resulting *ortho*-iodo-*N,N*-diisopropylbenzamide can be used as an electrophile for Pd-catalysed cross-couplings with borates/boronic acids compounds in the same *DES* medium as the one employed for the lithiation/iodination step (Scheme 10b). These findings showed for the first time the possibility of performing one-pot, *ortho*-lithiation/Pd-catalysed Suzuki-Miyaura couplings in *DES* mixtures.[12a]




**Scheme 10.** (**a**) Regioselective *ortho*-lithiation of *N,N*-diisopropylbenzamides, at room temperature, in the presence of air and using a *CPME*/*DES* (1*ChCl*/2*Gly*) mixture as reaction media. (**b**) One-pot/two-steps protocol that merges deprotonation/iodation process with an *in-situ* Pd-catalysed Suzuki-Miyaura coupling with different borates/boronic acids.[12a]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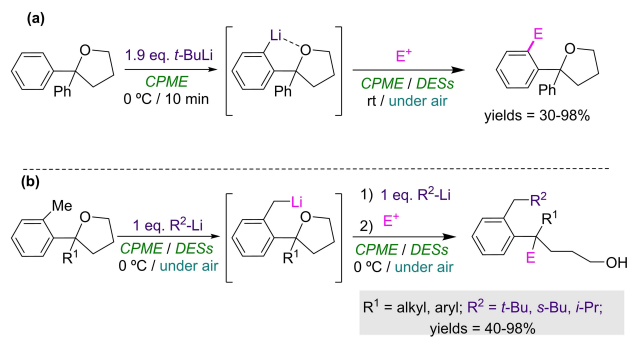
Prior to these studies, Capriati had also reported that *CPME* was an excellent sustainable ethereal solvent to promote regioselective lateral lithiation of 2,2-diaryltetrahydrofurans (Scheme 11a).[14a] In this case, the presence of the tetrahydrofuran ring acts as a directing group for the metalation. Best results were obtained using *t*-BuLi, although in this case reactions had to be performed at 0 °C. Interesting subsequent electrophilic quenching was more selective and efficient when *ChCl*-based eutectic mixtures (1*ChCl*/2*Gly* or 1*ChCl*/2Urea) were used as co-solvents, furnishing the expected products in good yields (up to 98 %). Further extension of this work have demonstrated that the lateral metallation of *o*-tolyltetrahydrofurans can be coupled with a C–C bond formation step.[14b] These processes take place using *CPME*/*DESs* as sustainable reaction media, with the initial regioselective lithiation of the activated benzylic position of the substrate, followed by addition of the second equivalent of the RLi reagent (*s*-BuLi, *i*-PrLi, or *t*-BuLi). This promotes the ring-opening of the furan furnishing the relevant primary alcohol in good to quantitative yields (up to 98 %, see Scheme 11b).

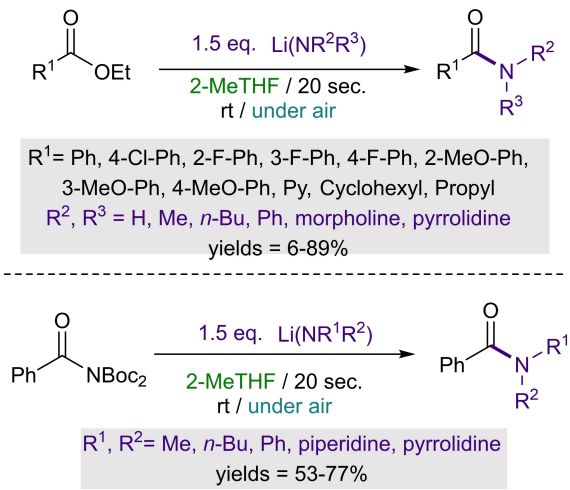
## 4. Aerobic Addition of Lithium Amides $LiNR_2$ to Esters/Amides or Aromatic Olefins in 2-MeTHF as Sustainable Solvent

Along with *CPME*, another biomass derived ethereal solvent which has emerged as an excellent reaction medium for air/moisture compatible transformations of polar organometallics is 2-methyl-THF (2-MeTHF). This solvent can be obtained from furfural in the absence of any petrochemical protocol.[44] Furthermore, its inherent immiscibility with water allows its use in liquid-liquid extractions, thus avoiding the employment of toxic and non-biorenewable *VOCs (Volatile Organic Compounds)* as extraction solvents (*i.e.*, $CH_2Cl_2$) in the purification/isolation steps of the desired final organic products.[45] Several synthetic organic studies have already demonstrated the excellent potential of this solvent for the use of organolithium and organomagnesium reagents, although in most cases reactions still have to be carried out under inert atmosphere conditions.[46] Inspired by this work some of us have investigated the capability of lithium amides ($LiNR_2$) to trigger the amidation of esters under air and using 2-MeTHF as solvent (Scheme 12a).[15a] Reactions take place at room temperature without the need of external additives in just 20 seconds. This methodology tolerates the presence of either electron-withdrawing (halogens) or electron-donating (MeO, Me) groups in both aromatic or purely aliphatic amides. Regarding the lithium amide partner, both aliphatic and aromatic lithium amides were amenable to this approach. High yields and good selectivities were observed. This approach also works for transamidation reactions of $NBoc_2$ substituted amides (Scheme 12b).

Structural and spectroscopic studies revealed that 2-MeTHF plays a key role in these reactions, ensuring full solubilisation of the lithium amides and favouring the formation of small kinetically activated aggregates. Thus, while LiNHPh and $LiNPh_2$ exhibit dimeric structures in the solid state solvated by three and two molecules of 2-MeTHF respectively (Figure 3), DOSY NMR studies are consistent with the formation of trisolvated $[Li(NR_2)(2\text{-MeTHF})_3]$ monomers.[47] Monomer formation should lead to more powerful nucleophilic lithium amides that can react faster with the unsaturated organic substrate (ester or




**Scheme 11.** (**a**) Lateral lithiation and electrophilic quenching of diaryltetrahydrofurans in mixtures *CPME*/*DESs*. (**b**) Organolithium promoted one-pot/two-steps benzylic metalation/ring-opening of *o*-tolyltetrahydrofurans in *CPME*/*DESs* mixtures in the presence of air.[14]




**Scheme 12.** (**a**) Ultrafast amidation of esters or (**b**) transamination of amides by using lithium amides ($LiNR_2$) under aerobic ambient temperature conditions in 2-MeTHF.[15a]

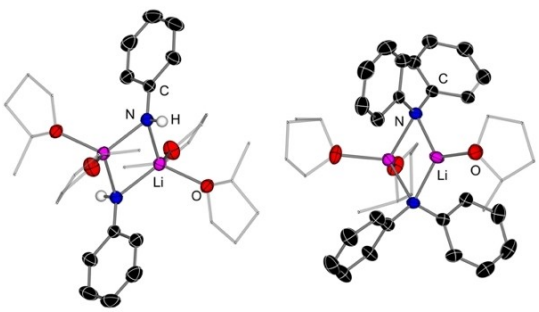


**Figure 3.** Molecular structures of dimeric lithium anilide $[\{Li(NHPh)\}_2(2\text{-MeTHF})_4]$ and lithium diphenylamide $[\{Li(NPh_2)\}_2(2\text{-MeTHF})_3]$.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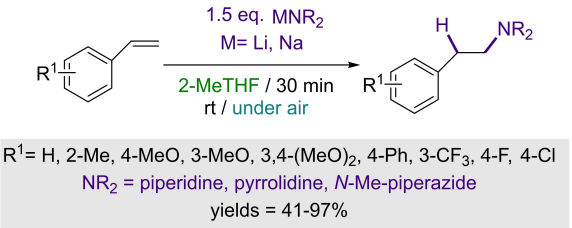
amide) to add across its C=O bond, favoring addition over competing degradation by oxygen or moisture.

These results prompted us to investigate other applications on the use of lithium amides under these unconventional conditions. We next focussed our attention on hydroamination reactions of vinylarenes with alkali-metal amides. Interestingly, while the addition of stoichiometric amounts of lithium amides to these unsaturated organic substrates using dry 2-MeTHF under argon atmosphere promoted the polymerisation of the olefines, when the same reactions were carried under air in the presence of moisture selective hydroamination was observed affording the relevant amines in yields up to 97% after 30 minutes (Scheme 13).[15b] Pushing the limits of this approach, selective hydroamination can be also accomplished using sodium amides, which are orders of magnitude more air and moisture sensitive than their lithium analogues, and typically suffer from lower selectivity.

To explain these findings where the presence of moisture seems to be key for the success of the hydroamination process, NMR monitoring studies combined with DOSY studies suggest that in the presence of ambient moisture some of the lithium amide hydrolyses to generate free amine and also that 2-MeTHF favours the formation of small reactive monomeric aggregates of the lithium amide (as shown in Figure 4 for lithium piperidide, LiPip) which should contribute to the fast reactivity observed in these hydroamination processes. Thus, considering the reaction of LiPip with styrene, under air in the presence of ambient moisture, some Pip(H) can be generated that in turn can coordinates to the lithium amide. This intermediate can then react with styrene to form the insertion intermediate **I**. This can be subsequently quenched by PipH or traces of moisture (Figure 4). However, under strict inert atmosphere conditions, using dry solvents, **I** can react with some free styrene (present in solution due to the equilibrium between LiPip, styrene and **I**) initiating its polymerisation.




**Scheme 13.** Hydroamination of vinylarenes with alkali-metal amides under air and at room temperature, using 2-MeTHF.[15b]

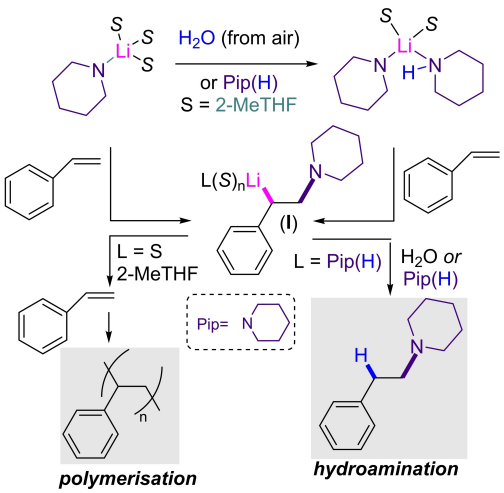
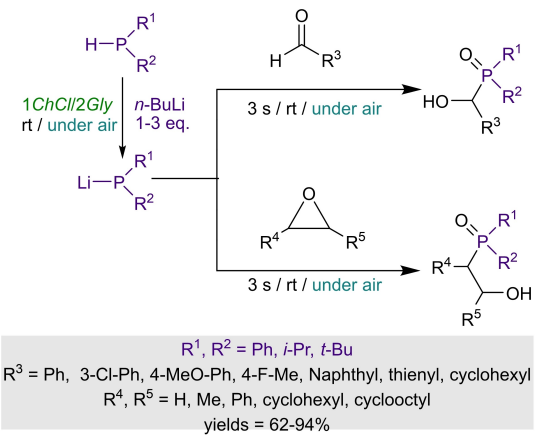



**Figure 4.** Proposed pathway for the reaction of lithium piperidide (LiPip) with styrene in 2-MeTHF showing how the excess piperidine or ambient moisture supply is necessary to favour hydroamination over polymerisation.[15b]

## 5. Chemoselective Aerobic Addition of Lithium Phosphides ($LiPR_2$) to Aldehydes or Epoxides in *DESs*

Demonstrating the versatility of the use of polar s-block organometallic reagents in sustainable reaction media and under bench type reaction conditions, recently we have reported the synthesis of highly polarised lithium phosphides ($LiPR_2$) using choline chloride-based *DESs* as sustainable reaction media, at room temperature and in the presence of air, *via* direct deprotonation of both aliphatic and aromatic secondary phosphines ($HPR_2$) with *n*-BuLi.[16]

Addition of an organic electrophile such aldehydes or epoxides to the *in-situ* generated $LiPR_2$ triggered fast and chemoselective addition processes uncovering an efficient and straightforward method to access $\alpha$- or $\beta$-hydroxy phosphine oxides. Reactions take place under bench-type conditions (air and at room temperature) in good to excellent isolated yields (62–94%). Remarkably, this system tolerates a variety of functional groups in the organic electrophile, being compatible with a variety of both electron-donating and electron-withdrawing substituents in the aldehydes or epoxides (Scheme 14).




**Scheme 14.** Chemoselective and fast addition of $LiPR_2$ to aldehydes and epoxides, at room temperature, under air in *DESs*.[16]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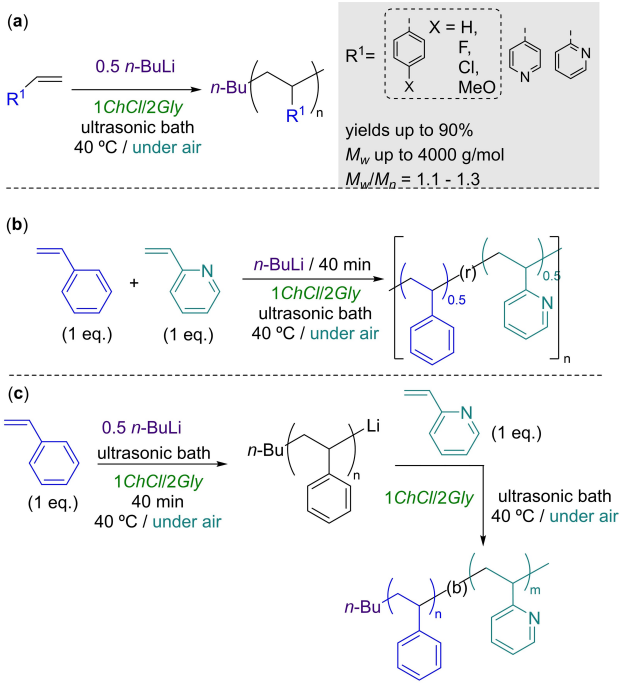
## 6. Anionic Polymerisation of Styrenes Initiated by Polar Organolithium Reagents (LiR) in *DESs* and under Aerobic Conditions

Since the pioneer work by Szwarc and co-workers back in 1956,[48] the anionic living polymerisation of olefin-type monomers promoted by organolithium reagents (RLi) has been considered as the protocol of choice for the selective and well-defined synthesis of styrene-derived polymers [this allows the synthesis of polymers with the desired macromolecular architecture, composition, molecular weight and narrow polydisperisty indexes ($Đ = M_w/M_n \approx 1$)].[49] This anionic polymerisation of olefins, which proceeds *via* an organometallic end-chain propagation sites composed by carbanions with lithium counterions, allows to control the aforementioned polymeric parameters, thus opening the door to create a plethora of complex architectures (comb, graft, dendritic, star, cyclic) with myriad of different applications such as biomedical materials, electronics or stimuli responsive surfaces.[50]

Bearing in mind our previous breakthroughs in the addition of organolithium reagents (RLi) to different unsaturated organic substrates (*i.e.*, ketones,[9] imines,[10] esters,[11] amides[12] or nitriles[13]), some of us decided to focus our attention on the design of an unprecedented organolithium-initiated anionic polymerisation of olefins (styrene-type monomers) in *DESs* and under air. Under these conditions, using *n*-BuLi as initiator, we were able to promote the synthesis of a variety of polyolefins, including polystyrene (*PS*), 4-aryl substituted polystyrenes (*PS-X*; X = F, Cl, MeO), poly(2-vinylpyridines) (*P2VP*) or poly(4-vinylpyridines) (*P4VP*), using in all these cases unpurified monomers as starting materials and performing all the polymerisation reactions in open vials (Scheme 15a).[17] Moreover, the corresponding random (*PS-r-P2VP*; Scheme 15b) or block (*PS-b-P2VP*; Scheme 15c) copolymers were synthesised, thanks to the unexpected stability of the *in-situ* formed polystyryl lithium intermediate towards hydrolysis in the eutectic mixture 1*ChCl*/2*Gly* (up to 1.5 h). In general, all the desired polymers or copolymers were obtained in high yields (up to 90%) and with low polydispersities. Taking another step forward towards developing more sustainable polymerisation processes, we have recently reported the Cu-catalysed *ARGET-ATRP* polymerisation (*Activator ReGenerated by Electron Transfer-Atom Transfer Radical Polymerisation*), under homogenous or heterogeneous conditions, of methyl methacrylate by using the eutectic mixture 1*ChCl*/2*Gly* as sustainable reaction media.[51]

## 7. Fast and Chemoselective Pd-Catalysed Cross-Coupling Reactions between Organolithium Reagents (RLi) and Aromatic/Heteroaromatic Halides in *DESs* or Water

Pd-catalysed C–C or C–X (X = heteroatom) cross-coupling processes are considered one of the most versatile, reliable and




**Scheme 15.** Anionic polymerisation of styrene-type olefins promoted by *n*-BuLi in *DESs* in the presence of air.[17]

chemoselective synthetic protocols within the organic chemist's toolbox.[52] Thus, unsurprisingly, they are amongst the most important methodologies for the synthesis of a wide variety of chemical commodities (*i.e.*, fine chemicals, pharmaceutical products or new materials).[53] For the specific case of the use of *DES* in these Pd-catalysed C–C protocols, a new core of knowledge has been achieved thanks to the pioneering work of different research groups worldwide.[54] Most of these examples use boronic esters or acids, organosilanes or organtin compounds, terminal alkynes, acrylates or anilines as coupling partners with the corresponding aromatic halide. Breaking new ground in this evolving field, more recently Pd-catalysed cross-couplings using organolithium reagents with organic halides in *DESs* have been reported. These studies build on seminal work by Feringa on the fast and selective direct Pd-catalysed C–C coupling processes employing organolithium compounds as partners. Key for the success of this approach is the use of toluene as solvent, employing diluted solutions of the relevant RLi reagents, which is slowly introduced in the reaction mixtures.[55,56] Increasing further the sustainability of this protocol, Feringa *et al* have also studied the coupling between 1-bromonaphthalene and an excess (2–10 eq.) of PhLi catalysed by Pd-PEPPSI-*i*-Pr (10 mol%) in the eutectic mixture 1*ChCl*/2*Gly* at room temperature.[57] Under these conditions it was found that the couplings proceeds with good selectivity but in moderate-low yields (Scheme 16). It should also be noted that the use of neat conditions allowed the authors to design a new highly selective and green Pd-catalysed cross-coupling between organic halides and organolithium reagents, which: *i*) proceeds in short reaction times (10 min); *ii*) can be used under industrially viable catalysts loadings (down to 0.1 mol%);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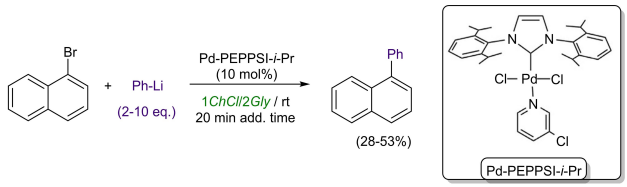



**Scheme 16.** Pd-catalysed direct coupling of 1-bromonaphthalene and PhLi in *DESs*.[57]

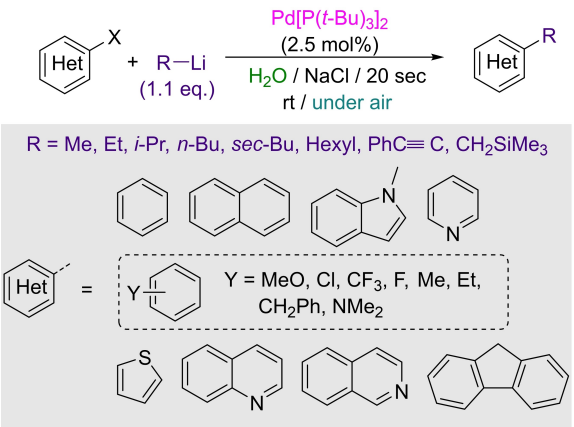
*iii*) presents possible scalability of the process (tested up to 120 mmol); and *iv*) shows exceptionally favourable environmental impact (E factors in several cases as low as 1).

Capriati *et al.* revisited this field by studying the use of water as a solvent and NaCl as additive (Scheme 17).[18] Remarkably, by replacing the *ChCl*-based eutectic mixture by brine and using as catalyst $Pd[P(t\text{-}Bu)_3]_2$ (2.5 mol%), this team was able to: *i*) increase the yield of the final coupling products up to 99%; *ii*) promote different Pd-catalysed C–C coupling protocols [$C(sp^3)$–$C(sp^2)$; $C(sp^2)$ –$C(sp^2)$ or C(sp) –$C(sp^2)$]; *iii*) a-avoid the formation of side products (derived from protonolysis, dehalogenations or homocoupling processes); *iv*) scale-up the coupling reaction; and *v*) recycle the catalytic system up to 10 consecutive times. More recently, the same group has extended the use of the NaCl/water combination or the eutectic mixture 1*ChCl*/2Urea as sustainable reaction media to the Pd-catalysed Negishi coupling of organozinc reagents ($ZnR_2$) with aryl(heteroaryl) halides, working at room temperature or 60 °C and in the presence of air.[58]

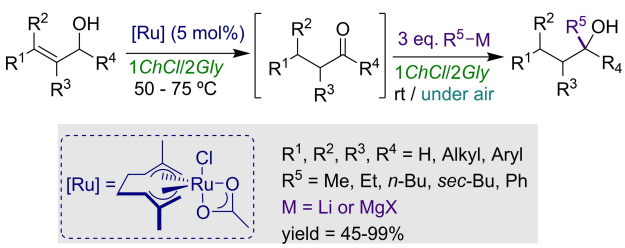
## 8. Design of One-Pot Tandem Protocols Based on Main-Group-Promoted Organic Transformations in *DESs* or Water

During the last decade and in the framework of organic synthesis, the use of one-pot tandem protocols has emerged as a greener alternative to standard and tedious stepwise processes. The main advantages are: *i*) the drastic reduction of isolation and purification steps of intermediates of reaction, minimising both the generation of chemical waste and the required time and energy as well as simplifying the practical aspects of the synthetic procedures; and *ii*) the possibility of working with unstable reaction intermediates, as no isolation of highly reactive and transitory-form species is needed.[59] In most of the cases, the same type of transformational tools (metal-, main-group element-, bio- or organo-catalysts) are used throughout all the tandem process, whereas the number of examples which combine different methodologies is scarce, especially those that also employ sustainable solvents.[60] In this regard, some of us have previously studied the fruitful combination of transition-metal-catalysed organic transformations in water or *DESs* with: the enzymatic and enantioselective bioamination (transaminases, ATA) or bioreduction (ketoreductases, KRED) of *in-situ* generated prochiral ketones;[61a–e] and the biocatalytic decarboxylation of *p*-hydroxycinnamic acids.[61f] Building on the success of these hybrid protocols we have also merged the use in tandem of transition metal-catalysis with polar organometallics in *DESs*. Thus, we have reported an operational simple one-pot method to access tertiary alcohols in excellent yields (up to 99%, Scheme 18) by combining the Ru(IV)-catalysed isomerisation of allylic alcohols into the corresponding ketones (working at 75 °C and in the eutectic mixture 1*ChCl*/2*Gly*) with the chemoselective nucleophilic addition of organolithium (RLi) or organomagnesium ($MgR_2$) reagents. This second step takes place a room temperature and in the presence of air. It should be noted that the corresponding tertiary alcohols are obtained without the need to isolate/purify the ketone intermediate (Scheme 18).[19] Related to these findings, more recently, as previously mentioned in section 3, Prandi, Capriati and co-workers have designed a one-pot/two-steps protocol that merges the lithiation/iodation process of aromatic amides with an *in-situ* Pd-catalysed Suzuki-Miyaura coupling using different borates/boronic acids as coupling partners (Scheme 10b).[12a]

Opening new ground in the combination of greener polar organometallic chemistry with other commonly used synthetic tools in organic synthesis, we have also reported the combination of an organocatalysed oxidation protocol (the AZADO/NaClO mediated oxidation of secondary alcohols into ketones) followed by the nucleophilic addition of organolithium reagents to the transitorily formed ketones, to produce a range of tertiary




**Scheme 17.** Pd-catalysed cross-coupling reactions between organolithium reagents (RLi) and (hetero)aryl halides in salted water as green solvent.[57]




**Scheme 18.** One-pot tandem combination of Ru-catalysed isomerisation of allylic alcohols with regioselective addition of RLi/RMgX reagents in *DESs*.[19]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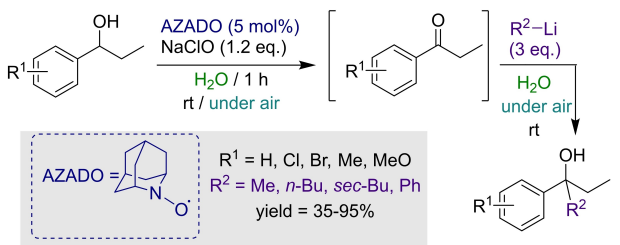
alcohols in a one-pot/two-steps protocol without the need of isolation/purification protocols (Scheme 19).[20] In this case, the organocatalytic oxidation system is not compatible with choline-based eutectic mixtures (as the addition of NaClO to the eutectic reaction media produced immediately the expected formation of $Cl_2$ gas). However, we found that the simple exchange of the chlorine-based eutectic mixture by bulk water as solvent permits the synthesis of the desired highly substituted tertiary alcohols at room temperature and in the presence of air.

## 9. Conclusions and Outlook

Polar organometallic reagents have been and remain pivotal for the development of synthetic chemistry. Exploiting the large polarity of their M–C (M=Li, Mg) bonds, these reagents are used worldwide in industry and academia for the functionalisation of organic molecules. However, despite their enormous synthetic relevance, their use is handicapped by their requirements of low temperature, in order to control their reactivity, as well as the need of dry toxic organic solvents and protective inert atmosphere protocols to avoid their fast decomposition. Thus, running organolithium chemistry under aerobic and/or hydrous conditions, without need of dry toxic organic solvents has been traditionally seen as an insuperable challenge for synthetic chemists. Edging closer towards meeting this challenge, the research summarised in this Minireview shows that by using polar organometallics in sustainable solvents such as *DESs*, water, *Gly*, *CPME* or 2-MeTHF, it is possible to access a broad range of valuable organic molecules while operating under air, in the presence of moisture and at room temperature. These examples of reactivity not only demonstrate the synthetic versatility of working under these unconventional conditions but have also revealed that in some cases unique chemoselectivities and enhanced performances can be accomplished. The possibility of using these methods in tandem with organocatalysis or transition-metal catalysis multiplies opportunities for the design of novel one-pot protocols under greener reactions conditions.

While many challenges are still pending ahead, the number of contributions on the use of polar organometallics in these solvents under air continues to grow at a steady pace, unlocking new opportunities and catching the eye of many synthetic chemists. Advancing the understanding on the constitution of these reagents in these solvents as well as possible substrate/solvent interactions will certainly pave the way towards new innovations in this evolving field. These additional challenges may not be easily met but the prospect of dispensing with the requirement for dry toxic organic solvents or inert atmospheres will have worldwide implications for the practice of polar organometallic chemistry both in academia and industry.




**Scheme 19.** One-pot combination of the AZADO/NaClO organocatalysed oxidation of secondary alcohols with the addition of organolithium reagents (RLi), at room temperature, in the presence of air in aqueous media.[20]

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** Chemoselectivity · Deep eutectic solvents · Green chemistry · Organolithium reagents · Organomagnesium reagents

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