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Reactivity of Polar Organometallic Compounds in Unconventional Reaction Media: Challenges and Opportunities

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This paper is gratefully dedicated to the memory of Dr. Guy Lavigne

Abstract: Developing new green solvents in designing chemical products and processes or successfully employing the already existing ones is one of the key subjects in Green Chemistry and is especially important in Organometallic Chemistry, which is an interdisciplinary field. Can we advantageously use unconventional reaction media in place of current harsh organic solvents also for polar organometallic compounds? This Microreview critically analyses the state-of-the-art on this topic and showcases recent developments and breakthroughs which are becoming new research directions in this field. Because metals cover a vast swath of the periodic table, the content is organised into three Sections discussing the reactivity of organometallic compounds of s-, p- and d-block elements in unconventional solvents. The richness of bibliography reported witnesses the genuine, burning thirst for a deeper knowledge of this field, and forecasts an ever-bright future for Organometallics in Green Chemistry.

1. Introduction

“There are times when one can sense a sea change, a shift in the order of things that is profound and fundamental”.[1] A silent, but contagious revolution is taking place in the way of thinking and practising Organometallic Chemistry (OC) by academic and industrial groups worldwide, which is mainly driven by new insights, needs, and evidence on the horizon. OC plays an essential role across a wide spectrum of science, technology, medicine and industry, with a heavy impact on the environment, and still remains a core subject within the “grand challenges” or “big themes” (e.g. energy, materials, medicine) towards which priorities and policy often focus.

International strategies launched by institutions and organizations, such as The American Chemical Society’s (ACS) Green Chemistry Institute Pharmaceutical Roundtable (GCIPR), strive for the need to replace conventional hazardous volatile organic compounds (VOCs) in favour of safe, green and biorenewable reaction media that are not based on crude petroleum.[2] One large area of consumption of petroleum-based chemicals in chemical transformations is, indeed, solvents used as reaction media, which account for 80–90% of mass utilization in a typical pharmaceutical/fine chemical operational process. Thus, the solvent itself is often a critical parameter especially in drug product manufacturing and is as well responsible for most waste generated in the chemical industries and laboratories.[3]

Following these considerations, some of the most critical and intriguing questions that arise are: Can we get traditional organic solvents out of organometallic reactions?[4] Can we use protic, recyclable, biodegradable, and cheap unconventional solvents also for highly reactive organometallic compounds? Answering these questions would not only mean to break new ground towards sustainable solutions to the aforementioned challenges, but it could also be rewarding from an intellectual point of view in order to investigate to what extent a certain organometallic compound does not react with the intended unconventional solvent and, if that is the case, to explain why this occurs.

In this Microreview, recent selected contributions published in the literature tackling the above timely topics have been highlighted, but seminal references have also been critically analysed. The contents are organized into three main sections with subheadings according to the nature of the Metal-Carbon (M-C) bond. The impact played by unconventional solvents (e.g., water, deep eutectic solvents, ionic liquids, and supercritical CO₂) on the chemistry of compounds of s-, p- and d-block elements has been discussed. Topics that have recently been reviewed are not further detailed here.

2. Organometallic compounds of s-block elements

Within the periodic table, the s-block elements are the 14 elements contained in the first two columns (Groups 1A and 2A) plus helium. They are unified by the fact that their valence electrons are in an s orbital, and are very reactive due to highly polar M-C bonds. In this section, we will deal with the reactivity of organolithium and Grignard (organomagnesium) reagents in unconventional solvents.

2.1. Reactivity in protic reaction media (water and deep eutectic solvents)

Organolithium and Grignard reagents are among the most useful and versatile organometallic compounds in chemical synthesis, and functionalised organometallic species are very useful intermediates for the synthesis of many organic non-natural and natural products.[5] Opening chapters in classic organic textbooks, however, emphasise the need of the strict control of anhydrous conditions and the use of water-free reaction media for the successful handling of organometallic

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compounds with highly polarised M–C bonds. Thus, at first sight, it might sound ridiculous to think to a protic solvent (e.g. water) as a potential “additive” (or, even worse, as a full component) for reaction media for carrying out s-block-metal-mediated organic transformations as these organometallics are extremely sensitive to traces of air and moisture. Nevertheless, a perusal of the modern and present-day literature reveals, from time to time, some “perplexing” reactions strangely “accelerated” by water. These deserve consideration and still need an explanation.

One of the first examples reported is the following. In order to label aromatics via hydrolysis of organometallic intermediates with tritiated water (T₂O), Taylor made the observation that the most convenient way for the preparation of tritiated arenes was the addition of n-BuLi to a mixture of a bromoarene and wetted (T₂O) sodium-dried Et₂O. This result is consistent with a lithium-bromine exchange reaction surprisingly occurring “at least as fast and most probably faster” than the expected reaction of n-BuLi with T₂O (Scheme 1).[7] The relative rates of deprotonation and of halogen-lithium exchange by organolithium compounds, however, have been a matter of controversy in the following years.[8]

![Scheme 1. Preparation of 9-tritium-labelled antracene.](image)

Lithium carboxylates 1 are known to react with organolithium compounds 2 in Et₂O to give high yields of the corresponding ketones 3 after considerable time of reflux (at least 24 h). Under these conditions, tertiary alcohols 5 are not usually formed. However, if the reflux time is shorter (e.g. 30 min), mixtures of ketones 3 and tertiary alcohols 5 are alternatively produced upon quenching with H₂O. This result implies that the excess organolithium 2 reacts during the hydrolysis with part of the ketone, which is formed by the hydrolysis of the intermediate adduct 4, faster than it reacts with water (Scheme 2).[8] In highlighting these results,[10] Keith Smith finally commented: “Shall we await the day when reactions of organolithiums are routinely performed in aqueous solution?”

In general, Lewis basic solvents increase the reactivity of organolithiums as they become an integral part of the organolithium aggregate and, once used as additives or ligands, they sometimes proved to be effective in contributing to the optimization of organolithium reactions.[11]

![Scheme 2. Preparation of ketones and tertiary alcohols by reacting organolithium compounds with lithium carboxylates.](image)

For instance, in the asymmetric LDA-mediated synthesis of the anticancer Lonafarnib 8, a unique water effect on the enantioselectivity was discovered. In the key alkylation step, an LDA–THF complex in cyclohexane was added to a toluene solution containing the tricyclic substrate 6, the chiral norephedrine-based mediator, and the alkylating agent 7. Counter-intuitively, the highest ee (95%) and the best yield (95%) in 8 were achieved once one equivalent of water was sequentially added to the above reaction mixture, then compensated by an additional equivalent of LDA. In the absence of water, both the ee and the yield in 8 dramatically dropped down to 50% (Scheme 3).[12] As an additional example, carboalumination of alkenes has been proved to occur within minutes at −23 °C (and is fast even at −70 °C) in the presence of stoichiometric amounts of water leading stereoselectively to alkenes.[13] To understand this water effect is extremely important to study the interaction of water with organometallic compounds.

![Scheme 3. Stereoselectivity achieved in the key alkylation step by adding water.](image)

We have always been taught about the crucial role played by water in Life Sciences. Among its properties, it is worth mentioning its extraordinary capability to engage in strong intermolecular hydrogen bonding with a plethora of Lewis acid and basic sites, thereby promoting a self-organization in supramolecular ordered structures. Could the water play a similar role in organometallic compounds? Careful, systematic, and controlled hydrolysis studies performed by Roetsky and coworkers of kinetically stabilised Group 13 trialkyl compounds, supported by spectroscopic and crystallographic evidences, have led to the isolation and the structural characterization of interesting intermediate oligomeric compounds that eventually result in final polycrystalline metalloxene clusters.[14] More recent work disclosed the synthesis of organoaluminum hydroxides and of three-in-one clusters comprising two tetranuclear aluminophosphate units and a tetrameric alumino hydroxide unit. These examples testify that water plays a major role also in organometallic chemistry contributing to the coordination sphere of the metal, and promoting intermolecular interactions and extensive self-assembly.

What about the “role of water” in the reactions of organometallic compounds of s-block metals? The hydrolysis of organolithium compounds by water or other proton donors is often assumed to be a very simple process yielding
quantitatively the corresponding organic acid and LiOH.\(^{[17]}\) As a matter of fact, it may not be as simple as is commonly believed. The rate of protonation of Et\(_2\)O solution of PhLi and PhCH\(_2\)Li and their O-deuteriated analogues by water or alcohols, for instance, shows small isotope effects (1.0–1.5), which implies that the rate-determining step is the displacement of Et\(_2\)O from the organolithium compound by the oxygen of the “acid”.\(^{[18]}\)

Could water act as a polar ligand towards Li\(^+\) centres? The first lithiated organic compound containing water as a ligand was published by Wright and co-workers.\(^{[19]}\) Lithiation of 2-mercaptobenzoxazole, in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA) and H\(_2\)O (both adventitious and deliberately added to the reaction mixture), produced the monomeric complex 9 (Figure 1) exhibiting a strong hydrogen bonding between one proton of the coordinated H\(_2\)O and the polarised sulphur centre of the organic anion, rather than a protonated Li–OH···SH species.

Such a molecular structure, as suggested by the authors, can be viewed as a model for how hydrolysis of organolithium compounds might take place. Analogously to what has been ascertained in the case of organoalanes,\(^{[14]}\) this process might proceed as well via preliminary organolithium–water complex formation followed by proton transfer to the carbanion.

![Figure 1. Molecular structure of the complex (9) between lithiated 2-mercaptobenzoxazole and TMEDA.](image)

The relative rate of these processes, however, might also be influenced by the nature of the aggregate involved because of the strong structure-reactivity relationship in organolithium compounds.\(^{[18,21]}\) These findings were then also extended to alkaline-earth metal complexes,\(^{[20]}\) with the synthesis of aqua complexes carried out by “assembling” H\(_2\)O ligands via solid metal hydroxides in a hydrocarbon solvent and in the presence of a Lewis base.

![Figure 2. Molecular structure of the 1:1:1 complex (10) among lithiated malonodinitrile, TMEDA, and H\(_2\)O.](image)

The first structural characterisation of an H\(_2\)O-containing complex of the lithium salt of an organic molecule containing an acidic C–H bond was also reported.\(^{[21]}\) The three-dimensional polymeric structure 10 depicted in Figure 2 discloses an intriguing complex of lithiated malonodinitrile, TMEDA, and H\(_2\)O in a 1:1:1 molar ratio. What is remarkable here is (a) the lack of TMEDA–Li interactions which is unprecedented in lithium chemistry especially considering that TMEDA is a bidentate ligand compared to water, which should favor complexation to lithium, and (b) the ability of each water molecule to engage simultaneously in hydrogen bonding to two TMEDA molecules (donor function) and to two lithium atoms (acceptor function) (Figure 2).

The intrinsic reactivity of a series of monomeric allylmetals with water and carbonyl compounds has been recently addressed by a theoretical study.\(^{[22]}\) Interestingly, calculations suggest that intrinsic kinetic preference of allylation over hydrolysis correlates quite well with the reactivity of hydrolysis. That is, a higher activation energy of hydrolysis corresponds to a higher kinetic preference toward allylation. However, the sole polarity of the C–M bond does not fully account for the reactivity of hydrolysis, but both nucleophilicity of the allylmetal and thermodynamic driving forces are likely significantly to contribute to the barrier of hydrolysis. Data relative to the organometallic compounds of the s-block elements also suggest that both \(\pi\)-complexes of Li and polarised \(\sigma\)-complexes of MgBr\(_2\) may hydrolyse or allylate preferentially, depending on the employed experimental conditions. In particular, calculations for the reaction of allylMgBr with water and acetone show that both activation energies of hydrolysis (4.5 kcal/mol) and allylation (5.7 kcal/mol) are quite similar. This competition was later experimentally investigated by Madsen and Holm.\(^{[23]}\) When
allylMgBr was reacted with either acetone or PhCHO in the presence of water (inverse addition), the yields of the corresponding addition products were found to be 91 and 75%, respectively. Grignard reagents are complex mixtures of the Schlenk components alkylaryl)magnesium halide, dialkyl(diaryl)magnesium, and magnesium halide salt, solvated by an ethereal solvent, and undergoing very fast chemical exchange in solution (Scheme 4).\[56]\[24]\[24]

\[2\text{RMgBr} \rightleftharpoons \text{R}_2\text{Mg} + \text{MgBr}_2\]

Scheme 4. The Schlenk equilibrium.

The potential impact of protic solvents in the above functionalisations was further investigated employing the so-called “deep eutectic solvents” (DESs). The concept of DESs was first introduced by Abbott and co-workers to describe the formation of a liquid eutectic mixture (mp 12 °C) starting from two solid materials with high melting points: choline chloride (ChCl, mp 133 °C) and urea (mp 302 °C) in a ratio 1:2 (1ChCl/2Urea).\[26] DESs are today generally defined as combinations of two or three safe and inexpensive components which are able to engage in hydrogen bond interactions with each other to form an eutectic mixture with a melting point lower than either of the individual components.\[27] ChCl, in particular, is nowadays one of the widespread ammonium salt used for the synthesis of DESs. The latter (also known as vitamin B\(_2\)) is produced on the scale of million metric tons per year (ca. 2 €/Kg) as an additive for chicken feed and has many other applications. Thanks to their low ecological footprint and attractive low price, DESs have now become of growing interest both at academic and industrial levels especially for their unusual solvent properties. It is worth noting that the concept of DESs is quite different from that of traditional ionic liquids (ILs) (vide infra) because the former are not entirely composed of ionic species, and can also be obtained from non-ionic species.\[27]

Both nucleophilic additions and substitutions proved to be effective in such eutectic mixtures providing the expected adducts in good yields and competitively with protonolysis.\[25] Adduct 12, for example, could now be recovered with a yield of 40% upon adding an Et\(_2\)O solution of 11-Li to acetone (6 equiv) in a ChCl-Gly (1:2) eutectic mixture at room temperature and under air (Scheme 6). Similarly, the addition reaction of a CPME solution of 11-Li to benzophenone, run either in a ChCl-Gly (1:2) or in a ChCl-urea (1:2) DES mixture, gave the hydroxalkylated compound 13 in both cases in 75% yield. Chlorodiphenylphosphine also successfully underwent nucleophilic substitution in ChCl-urea (1:2) leading the phosphonylethyl derivative 14 in 75% yield. Remarkably, once a commercial pentane solution of t-BuLi (1.9 equiv) was rapidly spread out over a mixture of 11-H (1 equiv) in CPME and ChCl- Gly (1:2), at 0 °C, under air, and under vigorous stirring, and quenched after 1 min reaction time with neat DMF (2 equiv), the formylated adduct 15 could be isolated in 90% yield (Scheme 6).
The chemoselective nucleophilic addition of organolithium and Grignard reagents to ketones in ChCl-based eutectic mixtures was in depth investigated by Hevia, Garcia-Álvarez and co-workers.[20] A range of the above reagents (19) could successfully be added, under air and at room temperature, to aromatic and aliphatic ketones 18 in both ChCl–Gly (1:2) and ChCl–H₂O (1:2) mixtures, thereby affording the corresponding tertiary alcohols 20 in good yields (up to 90%) and competitively with protonolysis (Scheme 8).

Scheme 8. Chemoselective addition of Grignard and organolithium reagents to ketones in ChCl-based eutectic mixtures.

A comparison of the reactivity profiles of these organometallic reagents in DESs with those in pure water, suggest that a kinetic activation takes place in the former most probably due to the formation of more nucleophilic halide-rich magnesiate or lithiate species further to the reaction of the alkylating reagent with ChCl. Thus, ChCl may be playing a double role in these processes, that is as a component of both the DES mixtures and the new “ate” complexes. This conclusion was supported by X-ray crystallographic studies, multinuclear magnetic resonance investigations, and ¹H DOSY NMR experiments.

In a recent paper, Song showed as well that catalytic amounts of NBu₄Cl in THF solutions of Grignard reagents enhanced the efficiency of addition reactions to carbonyl compounds producing tertiary alcohols in excellent yields, while minimizing the formation of enolization and reduction products.[30] The authors proposed that the presence of this ammonium salt should help to shift the Schlenk equilibrium of Grignard reagents in solution (Scheme 4) to the side of the dimeric species that would favour the addition reaction thanks to the 2:1 complex involved in the six-membered transition state.

2.2 Reactivity in ionic liquids

Generally, the term “ionic liquids” (ILs) stands for liquids composed of poorly coordinated ions with a melting point below 100 °C.[31] At least one ion has a delocalised charge, and one component is organic, which prevents the formation of a stable crystal lattice. They have recently attracted great interest as “greener” alternative to conventional organic solvents because of their thermal stability, non-flammability, easy of recycling, low vapour pressure, and catalytic properties.[32] Their use as solvents for reactions involving organometallic compounds of s-block elements, however, is still in its infancy. One of the most extensively studied class of ILs is based on imidazolium cations with an appropriate counter anion (ImILs), which are known to support many organic transformations.[33] Because of an acidic

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hydrogen substituent at the C-2 position, \( \text{ILs} \) (21) have been shown to react under basic conditions to produce \( N \)-heterocyclic carbenes (NHCs) (22), which are neutral, highly reactive, six-electron species possessing a dicoordinate carbon atom with two nonbonding electrons, and are responsible of many side reactions (Scheme 9).

\[
\begin{align*}
\text{Scheme 9. Formation of a NHC (22) species from an imidazolium cation (21).}
\end{align*}
\]

This problem was overcome by Clyburne and co-workers who showed that dried phosphonium \( \text{ILs} \) 23 are inert towards reactions with strong bases and are not reduced even by potassium metal, thereby representing the first suitable solvents for Grignard chemistry.23 Commercially available THF solutions of PhMgBr, once dissolved in 23 (ratio THF : 23 = 1 : 3), proved to cleanly carry out of benzyl cations, benzene reactions, halogenation, hydroxy(alkylation)arylation, and coupling reactions. Most importantly, competitive deprotonation of 23 to produce the phosphane 24 did not take place (Scheme 10). The inertness of phosphonium cations towards Grignard solutions appears to have primarily a kinetic basis and to be ion dependent: small bases are more prone to deprotonate 23, whereas large bases are more reluctant. Several other causes, however, seem also to contribute to such an inertness; e.g., the bulkiness and the flexibility nature of the cation as well as its electrochemical robustness compared to unsaturated ions.

\[
\begin{align*}
\text{Scheme 10. Possible formation of phosphane 24 by deprotonation of 23.}
\end{align*}
\]

The introduction of an ether oxygen on the side arm of a phosphonium salt (25) contributes to stabilising the organomagnesium reagent, thereby improving the capability of the corresponding IL to act as a solvent even for aliphatic Grignard reagent-mediated reactions (Figure 3).25

\[
\begin{align*}
\text{Figure 3. Phosphonium \text{ILs} with an ether functionality.}
\end{align*}
\]

Walsby and co-workers also demonstrated that while in molecular solvents Grignard reagents react according to nucleophilic pathways, \( \text{ILs} \) are ideal reaction media to promote electron-transfer processes.26 The Kumada-Corriu reaction, which involves the coupling of Grignard reagents with aryl halides mediated by transition metal catalysts (typically nickel or palladium), has been successfully carried out between PhMgBr and aryl halides in the phosphonium \( \text{IL} \) 26 in the presence of a Ni(0) complex of NHC 27 to afford bisaryl derivatives 28 with yields up to 88%, thereby supporting the \textit{in situ} generation of carbene species (Scheme 11). Remarkably, such a reaction even facilitates the activation of C–F bonds.

\[
\begin{align*}
\text{Scheme 11. Kumada–Corriu cross-coupling reaction in the phosphonium \text{IL}.}
\end{align*}
\]

Apart from phosphonium \( \text{ILs} \), also some imidazolium-based \( \text{ILs} \) can withstand the strong basicity of the Grignard reagents. These include \( \text{ILMILs} \) with a phenyl substituent27 and with an isopropyl group28 at the vulnerable C–2 position. Both \( \text{ILs} \) 29 and 30 (Figure 4) have been successfully employed as suitable solvents in reactions involving the addition of aliphatic and aromatic Grignard reagents to aldehydes, ketones and esters affording the expected hydroxyalkylated adducts in good yields (68–83%). These \( \text{ILMILs} \) can be recycled and reused several times without appreciable loss of the same \( \text{IL} \). All attempts, however, to generate Grignard reagents in \( \text{ILs} \) failed. In 2006, Chan and co-workers reported the first example of an organomagnesium species generated directly in the pyridinium-based \( \text{IL} \) 31 having a tetrafluoroborate as a counter ion (Figure 4).29 The reactivity pattern showed towards carbonyl compounds for reactions run in 31, however, was different from that exhibited by Grignard reagents in conventional organic solvents, the yields in the final adducts also being critically dependent on the molar ratio of the reagents and the presence of additives in the reaction mixture. New alkylpyridinium (32) and tetralkylphosphonium (33) \( \text{ILs} \), possessing an ether functionality to provide stabilisation to the Grignard reagent, have been prepared by Scammells and co-workers and evaluated as solvents for Grignard reactions.40 Interestingly, different outcomes have been observed according to the presence or not of an ethereal co-solvent. When the addition reaction to carbonyl compounds was run in \( \text{ILs} \) 32, the expected adducts occurred only in the presence of Et\( _2 \)O, whereas in the absence of this ether an unusual reduction of aldehydes to the corresponding primary alcohols was favoured. On the other hand, aldehydes cleanly reacted with Grignard reagents in \( \text{ILs} \) 33 affording the corresponding addition products only in the presence of Et\( _2 \)O as a co-solvent.
To the best of our knowledge, analogous reactions of organolithium compounds run in ILs always produced decomposition and unidentified products. Because of the broad use of organolithium and Grignard reagents in the pharmaceutical and fine chemical industry, a judicious choice of the reaction solvent is crucial from both safety and environmentally standpoints. In this context, 2-MeTHF (derived from cyclopentene) is emerging “greener” alternatives for organometallic reactions to the common Et$_2$O and THF, and have also proved to be more effective in improving product yield and in suppressing side reactions. The challenge will be the use of commercially prepared Grignard and organolithium solutions directly in the above solvents.

3. Organometallic compounds of d-block elements

As has been assessed in the Introduction, OC has become a cornerstone of modern organic synthesis, and nowadays hardly any total synthesis endeavour can be envisioned without a key step involving the use of polarised organometallic compounds containing d-block elements, that is the transition metals. These fundamental reagents (most commonly organozinc and organocopper compounds) are able to deliver carbon residues (M–C bonds) from zinc or copper to carbon halides or pseudohalides (C–X), to form new C–C bonds. However, the chemoselectivity of these processes can be seriously compromised by: i) the formation of undesired products, ii) the use of low temperatures (ranging from 0 to –78 °C), and iii) the employment of dry and hazardous ethereal solvents, and inert atmosphere protocols (to avoid fast degradation of the polar reagents). All these experimental restrictions hinder the synthetic application of these polarised species under environmentally-friendly reactions conditions (i.e. at room temperature and in the absence of protecting atmosphere) and their use in the presence of unconventional solvents [e.g., water, ILs, supercritical CO$_2$ (scCO$_2$) or perfluorinated solvents] as reaction media. Despite all these drawbacks, during the last decades the chemistry of polarised organometallic compounds containing d-block elements has crossed the frontiers between their application in modern synthetic organic chemistry and the growing area related to the employment of unconventional solvents. Since the synthesis of the first polarised organozinc compound (ZnEt$_2$) by Wanklyn in 1848, it is well-known that these basic compounds are able to react with several unconventional solvents (like water or scCO$_2$).

This Section covers the progress made in the application of the aforementioned unconventional solvents as reaction media in a variety of organozinc-, organocopper-, and organogold-mediated organic reactions. In particular, the following reactions will be surveyed: i) Reformatsky- and Barbier-type reactions, ii) addition of organozinc derivatives to $\alpha,\beta$-unsaturated carbonylic compounds, iii) cross-coupling reactions of the in situ generated organozinc reagents and organic halides (Negishi coupling), iv) polymerization reactions, v) organogold reactions, and vi) iridium-promoted C–H bond activation reactions.

3.1 Reformatsky reaction in unconventional solvents

The Reformatsky reaction, which involves the treatment of a haloester with a carbonyl compound (ketone or aldehydes) in the presence of Zn (Scheme 12), was the first example of addition of polarised organometallic reagents containing d-block elements to carbonyl compounds. Since its discovery in the 19th century, it was believed that this Zn-mediated addition reaction could only take place under protective atmosphere (using Schlenk techniques) and employing dry organic solvents. However, several examples were then reported in the literature showing the reactions between carbonyl compounds and organic halides, mediated by reactive d-block metals (Zn, Cu), in both wet solvents and pure water.

![Figure 4. ILs employed as alternative reaction media for Grignard reagents.](image-url)
formation of the desired product was observed in the presence of galvinoxyl or hydroquinone (radical scavengers).[51b]  

\[
\begin{align*}
\text{Ph} -\text{H} & + \text{Br} -\text{O} -\text{Ph} \quad \text{Zn} \\
\text{Me} & \quad \text{H}_2\text{O} / \text{RT}
\end{align*}
\]

Scheme 13. Reformatsky-type reaction between benzaldehyde and o-bromopropiophenone in water.  

Not only water, but also other unconventional solvents like ILs have been employed as reaction media for Reformatsky-type reactions. As previously discussed in Section 2.2 of this Microreview, ILs have received much attention as a new class of unconventional solvents during the last decades.[52] To the best of our knowledge, the first Reformatsky reaction in a variety of ILs was reported by Kitazume and co-workers (Scheme 14).[53] The authors studied the Reformatsky reaction: i) between aromatic, aliphatic or alkenyl aldehydes (35) with different halocarbons (36), ii) mediated by metallic Zn, and iii) in the ILs [EtDBU][OTf] (8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate), [BMIM][BF₄] (1-Butyl-3-methylimidazolium tetrafluoroborate), and [BMIM][PF₆] (1-Butyl-3-methylimidazolium hexafluorophosphate). At room temperature, only a moderate yield (52%) of the desired compound 37 was achieved in the IL [EtDBU][OTf]. However, upon heating the reaction to 50 ºC, almost quantitative conversion (93%) in 37 was reached. As has been pointed out in Section 2.2, one of the major advantages associated with the use of ILs as solvents is the possibility of reusing the IL by a simple extraction of the desired organic product (37) with organic solvents.[52,46] In this way, the IL could be recycled up to three consecutive cycles without any loss of activity or selectivity.

\[
\begin{align*}
\text{R}^1\text{O} -\text{H} & + \text{Br} -\text{O} -\text{R}^2\text{R}^3\text{OEt} \quad \text{Zn} \\
\text{IL, 50-60 ºC} & \quad \text{IL, 50-60 ºC}
\end{align*}
\]

Scheme 14. Reformatsky reaction in ILs.  

### 3.2 Barbier reaction in unconventional solvents

The Barbier reaction,[64] which involves the reaction of organic halides and carbonyl compounds in the presence of magnesium, aluminium, zinc, indium, tin or its salts is one of the most important methods for creating C–C bonds and has widespread synthetic applications in organic chemistry.[55] The reaction proceeds via the nucleophilic attack of the in situ generated organometallic compound on the carbonyl electrophile (generally an aldehyde). Since its discovery, there has been considerable attention towards the development of this Zn-mediated reaction in water.[56] In fact, the allylation of aldehydes and ketones under the Barbier conditions usually occurs faster and gives rise to higher yields when water is used as the (co)solvent.[57] In this sense, Li and Chan reported one of the first and innovative allylation reactions of carbonyl compounds promoted by Zn in water (Scheme 15).[58] Again, the presence of water was critical to the success of the coupling step for the formation of 38. Thus, when the reaction was performed in dry conventional ethereal solvents (e.g., Et₂O or THF), poor formation of compound 38 was encountered.

\[
\begin{align*}
\text{I} -\text{Cl} & + \text{R}^1\text{Cl} \quad \text{Zn} \\
\text{H}_2\text{O} / \text{NH}_4\text{Cl} & \quad \text{RT}
\end{align*}
\]

Scheme 15. Zn-mediated Barbier reaction in water.

Nowadays, a plethora of Zn-mediated allylation of different electrophiles (e.g., aldehydes, ketones, acetics or dioxolanes) in aqueous conditions is known in the literature, allowing the direct synthesis of homoallylic alcohols under environmentally-friendly reaction conditions.[59] Recently, the spectrum of unconventional solvents available to accomplish this Zn-mediated allylation reaction under green conditions has been enlarged by Leeke and co-workers. These authors reported the employment of supercritical CO₂/H₂O (30 ºC/80 bar) as a renewable solvent mixture to increase the desired allylation reaction with a variety of aryl aldehydes.[60,61]

Not only Zn-mediated allylations,[59] but also propargylations[62] and benzyllations[63] of different carbonyl compounds can be conveniently performed in the presence of water. In recent years, Li and co-workers have expanded the scope of this Barbier-type reaction to the more challenging vinylcarbonyl allylations[64] and arylation[65] with non-activated halides in water. In both the examples cited, the desired aromatic aldehyde suffers the corresponding alkylation or arylation in water, which is mediated by stoichiometric amounts of Zn dust and catalysed by InCl or [Rh(acac)(CO)]₂ (acac = acetylacetone), respectively (Scheme 16). These processes allowed the mild and straightforward synthesis of benzyl alcohols (39) and aryl methanols (40), thereby unlocking one of the last challenges in the field of Barbier-type reactions in water.
Amines could also be conveniently prepared by direct addition of zinc organometallic reagents to imines in the presence of water. Savoia, Umani-Ronchi and co-workers first developed the enantioselective synthesis of homoallylic amines by addition of in situ generated (allyl)ZnBr reagents to imines in a mixture of THF/H₂O.[66] More recently, Naito and co-workers reported the Zn-mediated addition of alkyl iodides to imines in the absence of VOCs by using a saturated NH₄Cl aqueous solution as the solvent.[67] Nitrones 41 can also suffer a Barbier-type alkylation in pure water as the solvent and at room temperature, yielding the corresponding hydroxylamines 42 (Scheme 17).[68]

\[
\begin{align*}
\text{R}^1\text{N}^- &+ \text{R}^2\text{I} + \text{Zn} &\rightarrow \text{R}^1\text{N}H\text{R}^2

\text{Scheme 16. Barbier-type alkylation and amination of aldehydes in water.}
\]

### 3.3 Conjugate addition of organozinc derivatives to **α,β**-unsaturated carboxylic compounds in water

The conjugate 1,4-addition of organometallic compounds to electron-deficient olefins represents one of the most powerful tools currently exploited to create new C–C bonds. Among the various methods available, the most commonly employed strategies involve the use of organometallic species such as Grignard reagents (RMgX) or organolithium (RLi) compounds. However, the use of these highly reactive organometallic derivatives can lead to undesired side reactions (e.g., Wurtz coupling, reduction of the carbonyl compounds, hydrolysis, competitive 1,2-addition, etc.).[69] Thus, dialkyldzinc reagents have dominated the field of copper-mediated enantioselective conjugate addition since their first application in the mid-1990s.[70] From that moment on, several reports have appeared in recent years demonstrating that the addition of stoichiometric or sub-stoichiometric quantities of water increases the rate and/or the enantioslectivity of this organic transformation.[71]

\[
\begin{align*}
\text{R}^1\text{N}^- &+ \text{R}^2\text{I} + \text{Zn} &\rightarrow \text{R}^1\text{N}H\text{R}^2

\text{Scheme 17. Synthesis of hydroxylamines via Barbier-type alkylation of nitrones in water.}
\]

Conjugated 1,4-addition of alkyl halides (R–X) to **α,β**-unsaturated aldehydes, ketones, esters, amides,[76] or nitriles[77] can be mediated in EtOH–H₂O or THF–H₂O mixtures by the combination of Zn and Cu, under sonication conditions. It is worth noting that this methodology has been fruitfully applied to the synthesis of: i) a variety of vitamin D₃ derivatives,[78] ii) dioxolanes,[78] iii) oxazolidinones,[79] and iv) sienefungin analogues.[79] Finally, the intramolecular version of this 1,4-addition reaction mediated by Zn/Cu allowed the straightforward synthesis of the lupinine analogues 45 (Scheme 19).[80,81] Thus, the 1,4-conjugated addition of alkyl halides to **α,β**-unsaturated carbonyl compounds mediated by Zn–Cu mixtures in aqueous media proved to be the key step in the total synthesis of a diversity of natural products.

\[
\begin{align*}
\text{R}^1\text{N}^- &+ \text{R}^2\text{I} + \text{Zn} &\rightarrow \text{R}^1\text{N}H\text{R}^2

\text{Scheme 18. Cu(I)-catalysed conjugate 1,4-addition of Et₃Zn to cyclohexenone (43) accelerated in the presence of water.}
\]

\[
\begin{align*}
\text{R}^1\text{N}^- &+ \text{R}^2\text{I} + \text{Zn} &\rightarrow \text{R}^1\text{N}H\text{R}^2

\text{Scheme 19. Synthesis of lupidine analogue 45 mediated by Zn/Cu under sonication conditions in the presence of water.}
\]

Delapierre and co-workers reported the dramatic beneficial effect of addition of water (0.5 equiv.) in the asymmetric addition of diethylzinc to cyclohexenone (43) catalysed by CuI in the presence of chiral ligands (Scheme 18).[72] Thus, when the reaction was performed in dry CH₂Cl₂ only 55% yield of the desired cyclohexanone (44) was achieved in 45% ee. However, formation of the desired carbonyl compound in higher yield (76%) and enantiomeric excess (ee 61%) was observed upon the addition of sub-stoichiometric amounts of water. The authors proposed that the in situ formation of Zn(OH)₂ (which is a stronger and more effective Lewis acid), activates the carbonyl moiety. This suggestion was confirmed as the direct addition of Zn(OH)₂ to the reaction provided analogous results to those observed with water.[73] Similarly, the addition of sub-stoichiometric amounts of water (0.3-0.33 equiv.) to lithium dimethylcuprate (LiCuMe₂), generated a more reactive and stereoselective reagent for the conjugate addition to linear **α,β**-enones.[74] More recently, Lipshutz and co-workers reported the conjugate addition of in situ generated organocupper reagents to enones[75] in water and at room temperature by using small amounts of commercially available amphiphiles (TPGS-750-M, polyoxyethanyl-α-tocopheryl succinate) that are able to form nanomicelles in water.
3.4 Cross-coupling of in-situ generated organozinc reagents with organic halides (Negishi coupling) in unconventional solvents.

Metal-catalysed cross-coupling reactions between an organic electrophile (typically an organic halide) and an organic nucleophile have developed into a standard component of the armamentarium synthetic chemist’s toolbox for the formation of C–C and C–heteroatom bonds. Palladium-catalysed reactions, which can be generally carried out under milder conditions and with a wider range of substrates than reactions promoted by other metals, clearly meet the challenge. The organic halide can be a sp2 or sp3 hybridised carbon with any halogen or pseudo-halogen leaving group. Different organometallic nucleophiles (e.g., organoboron, organotin, organozinc, organomagnesium) and organic nucleophilic reagents (such as amines, alkynes or alkenes) are routinely used in different cross-coupling reactions. In this Section, the attention will be mainly focused on the Pd-catalysed Negishi coupling (with reference to the cross-coupling reactions of polarised organozinc reagents with organic halides), in different unconventional solvents, like water, ILs and perfluorinated solvents.

Lipshutz and co-workers have almost dominated the field of aqueous Negishi-type cross-coupling reactions by describing a new technology that allows the Pd-catalysed Zn-mediated cross-couplings to be conducted in water and at room temperature, without the need to preform the corresponding organozinc reagent (RZnX). Lipshutz’s approach uses homogeneous micellar catalysis within catalytic nanoreactors formed spontaneously upon dissolution in water of different surfactants (PTS, TPGS, Brj 30, Solutol, SPGS). The scope of this process has been studied in the Pd-catalysed coupling between: i) alkyl halides and aryl or heteroaryl halides (Scheme 20). Lipshutz and co-workers described at the beginning of this millennium the cross-coupling reaction between: ii) alkyl or benzylic halides and alkenyl halides, and iii) benzyl halides and aryl or heteroaryl halides. More recently, Lipshutz and co-workers reported the reduction of alkyl halides, and nitroaromatics in water and at room temperature by using Zn dust in the presence of nanomicelles composed of the aforementioned surfactants.

Pd-catalysed Negishi-type reaction has also been reported in ILs. In this regard, Knochel and co-workers described at the beginning of this millennium the cross-coupling reaction between preformed aryl- or benzylzinc halides (RZnX) and various aryl iodides in the IL [BDMM][BF4] (BDMM = 1-butyl-2,3-dimethylimidazolium), and using as catalytic system the mixture formed by [Pd(dbach2)] an ionic phosphine 46 (Scheme 21). In most cases, the reaction proceeded at room temperature within minutes leading to the desired product in almost quantitative yields. The work up of this reaction is remarkably simple, as the IL phase containing the palladium catalyst can be separated from the organic product simply by extraction with toluene. Attempts to reuse the palladium catalyst showed that after the third cycle, a significant decrease in the yield was observed. The same authors enlarged the scope of unconventional solvents that could be used in the Negishi reaction by describing the Pd-catalysed cross-coupling of organozinc bromides with aryl iodides in perfluorinated solvents.

Highly coordinated dianion-type zincates (Li2ZnR2) were reported in the mid-1990s by Uchiyama and co-workers as a new type of zincate complexes, and added a new dimension to organozincate reagents because they were able to promote bromine-zinc exchange and carbozincation reactions. In this regard, the dilithium tetra-tert-butylzincate [LiZn(t-Bu)4] turned out to be a highly crowded and bulky zincate with an excellent anionic polymerization ability, even in the presence of acidic protons. Uchiyama and co-workers studied the anionic polymerization of N-isopropylacrylamide (NIPAm) using Li2Zn(t-Bu)4 as initiator in both organic solvents and water (Scheme 22). Surprisingly, an interesting solvent effect was found in this polymerization reaction: with THF as the reaction medium, only 8% of the desired polymeric material 47 was obtained after 24 h, whereas the polymer 47 could be isolated in high yields (92–76%) after 3 hours only when protic solvents (like H2O or MeOH) were alternatively used. Upon monitoring the time/yields profile of this polymerization reaction in water, the authors noticed that polymer 47 could be obtained in 92% yield after 15 minutes. The nature of the organometallic compound proved to be crucial as no polymerization reaction took place when Li2Zn(t-Bu)4 was replaced by PhLiBu, ZnCl2, LiCl or LiOH. This Zn-mediated anionic polymerization in water could also be extended to other acryl acid derivatives, such as N,N-dimethylacrylamide (DMA, 74% yield), acrylamide (AM, 84% yield) and 2-hydroxyethylmethacrylate (HEMA, 92% yield). One of the main drawbacks of this Li2Zn(t-Bu)4-mediated polymerization in aqueous media is the impossibility of induce the polymerization of styrene (one of the most important synthetic polymers). In this...
case, deprotonation of the solvent took place before polymerization.\textsuperscript{[92]}  

\[
\begin{array}{c}
\text{OCH} \\
\text{Pr} \\
(N\text{IPAm})
\end{array} \\
\text{H}_2\text{O} / \text{RT}
\]

Scheme 22. Li\textsubscript{2}Zn(t-Bu\textsubscript{4}) catalysed anionic polymerization of N-isopropylacrylamide (NIPAm) in water.

Recently, Higashihara and co-workers reported another possibility for application of zinicate Li\textsubscript{2}Zn(t-Bu\textsubscript{4}) in polymerization reactions, that is through an exchange-cross-coupling process.\textsuperscript{[93]} Thus, when 2-bromo-3-hexyl-5-iodothiophene 48 was treated with Li\textsubscript{2}Zn(t-Bu\textsubscript{4}), the iodine-zinc exchange reaction took place selectively. Upon heating to 60 °C the resultant zinicate 49 with the nickel catalyst [Ni(dppe)Cl\textsubscript{2}] (dppe = 1,2-Bis(diphenylphosphino)ethane), polymerization proceeded in a controlled manner affording poly(3-hexylthiophene) 50 in high yield (80-85%) and low polydispersions (PDIs < 1.2). As analogously observed in the anionic polymerization of N-isopropylacrylamide (NIPAm) in water,\textsuperscript{[91]} the high-molecular-weight polymer 50 could be obtained in a THF solution containing a small amount of water (Scheme 23).

\[
\begin{array}{c}
\text{OCH} \\
\text{Pr} \\
\text{H}_2\text{O} / \text{RT}
\end{array} \\
\text{H}_2\text{O} / \text{RT}
\]

Scheme 23. Halogen-exchange reactions and catalyst-transfer polycoumpoundation for the synthesis of polymer 50 using Li\textsubscript{2}Zn(t-Bu\textsubscript{4}) in the presence of water.

### 3.6 Organogold(I) compounds in Palladium-catalysed cross-coupling reactions in aqueous media

As previously discussed in Section 3.4, Pd-catalysed cross-coupling reactions are usually run with polarised organometallic nucleophiles (e.g., organoborane, organotin, organozinc, organosilane) in VOCs solvents. However, Sarandeses and co-workers have recently expanded the scope of this transformation first employing organogold(I)-phosphine derivatives (RAuPPh\textsubscript{3}) as organometallic nucleophiles in water. Under these conditions, reactions between isolated aryl-, alkynyl-, or alkynyrgold(I)-phosphines and aryl halides or triflates were shown to proceed at room temperature (or at 80 °C) in water/THF mixtures.\textsuperscript{[84]} These Pd-catalysed reactions delivered the corresponding coupling products in good yield and with high chemoselectivity being compatible with free amino or hydroxyl groups present in the electrophile. As a proof of concept, this methodology was then successfully applied also to the preparation of substituted phenylalanine esters under protic conditions (Scheme 24).

### 3.7 Iridium-promoted C–H bond activation in water

Encapsulation of a variety of organometallic complexes into the internal cavity of hydrophilic supramolecular structures constitutes an innovative way to solubilise organometallic derivatives in aqueous media.\textsuperscript{[69]} In this context, Raymond and co-workers have incorporated the cationic iridium complexes ([Ir\textsubscript{III}][PMe\textsubscript{3}]_3[C(OH)\textsubscript{2}][O][OTf]) (R\textsuperscript{2}olefin = ethylene or cis-2-butene) into a supramolecular [Ga\textsubscript{L\textsubscript{1}}] tetrahedral assembly (L = 1,5-bis(2,3-dihydroxybenzoylamino)naphthalene) (Scheme 25). These species formed the host-guest complexes 51 and 52, stabilised by hydrophobic effects as well as by π–π interactions between the coordinated olefin and the π–basic naphthalene walls of the host.\textsuperscript{[96]} The resulting water soluble host-guest systems (51, 52) were then tested in the C–H activation of aldehydes in aqueous media. In order to generate the active iridium species, decoordination of the olefin was preliminary required. The simple heating of the host-guest complexes (45 °C for 51 and 75 °C for 52) facilitated olefin dissociation, thereby allowing the C–H bond activation of the desired aldehyde. Interestingly, evidence for both size and shape selectivity was observed. Small aldehydes (e.g., acetaldehyde) are readily activated, whereas large aldehydes (e.g., benzaldehyde) are too large to fit inside the cavity. Also, the shape of the aldehyde proved to influence the reactivity of the encapsulated host-guest complex. For example, the host-guest complex reacted with isobutyraldehyde with a lower diastereoselectivity than with butyraldehyde. This experimental evidence was attributed to the more spherical shape of the isobutyraldehyde complex when compared to the butyraldehyde one.
4. Organometallic compounds of p-block elements

Amongst the vast family of organometallic compounds, and within the subgroup of the p-block metals (elements whose valence electrons are in the p orbital), organoaluminium[97] and organotin[98] members play a pivotal role in organic synthesis, finding widespread applications in a myriad of C–C bond-forming processes. Although most of these reactivity studies have been performed using conventional VOCs, the potential of using these commodity organometallic reagents also in unconventional media (including ILs, DESs, scCO₂, and recently also neat water) has already been hinted at by several intriguing studies that will be discussed in this Section. In addition to these two important families of p-block metal reagents, the chemistry and applications of organoindium compounds are receiving increasing attention from the synthetic community, and are thus being rapidly developed. Bearers of an exceptional functional group tolerance and distinctive mild reactivity profiles, these compounds can render unique chemoselectivities in several C–C bond forming reactions which are difficult to achieve using more polar reagents such as organolithium or organomagnesium reagents. Intriguingly and contrasting with the typical extreme moisture sensitivity of these polar organometallics, organoindium reagents can be utilised in aqueous media which allows the functionalisation of water-soluble substrates such as carbohydrates, as well as with the development of greener synthetic methodologies. This unique behaviour was first reported by Li and Chan in 1991 through a seminal study assessing the alkylation reactions of aldehydes and ketones under Barbier conditions in water,[99] and nowadays it constitutes a signature attraction of organoindium chemistry. Of note, the chemistry of these reagents and their applications for the functionalisation of organic molecules (some of them employing aqueous media) have been recently summarised in a comprehensive review by Loh and co-workers.[100] Thus, they will not be covered in this overview.

4.1 Applications of Group 13 organometallic reagents

Organoaluminium reagents have received considerable attention in recent years not only due to their high chemoselective reactivity and exceptional functional group tolerance, but also because of their relative cheapness, ready availability and comparative low toxicity. The polarity of their Al–C bonds makes these commodity reagents extremely air and moisture sensitive, and they usually have to be manipulated under strict inert-atmosphere techniques. Therefore, although at present most of their applications require the use of dry organic solvents, some promising studies have already glimpsed the potential of applying these compounds in ILs as an alternative reaction media. In 2006, Taddei and co-workers have reported the multistep synthesis of isoxazolines using the IL [BMIM][BF₄]₂, where one of the key synthetic steps involves the transformation of an ester into an amide via an aluminium amide. This species is generated in situ by adding a solution of AlMe₃ in toluene to a solution of the ester 53 and benzylamine furnishing 54 in 79% yield (Scheme 26).[101]

![Scheme 26. Ester amidination of isoxazoline 53 with AlMe₃ in the IL [BMIM][BF₄]₂.](image)

More recently, Chen and Liu have shown that aluminium alkyl and arylalkoxy compounds, used widely in polymerization processes, can effectively catalyse the conversion of glucose to HMF (5-hydroxymethylfurfural) using the IL 1-ethyl-3-methylimidazolium chloride, [EMIM]Cl.[102] Trying to shed some light on the constitution of the active Al species involved in this transformation, allylaryloxy aluminium MeAl(OAr)₂ 56 (OAr = 2,6-di-tert-butyl-4-methylphenoxide) was mixed with 55, under the same glucose conversion conditions, and this enabled the isolation and subsequent structural elucidation of the new mixed imidazolium aluminate (ENIM)+{(MeCl)Al(OAr)₂}⁻ 57, where the chloride is now attached to Al (Scheme 27).

![Scheme 27. Formation of imidazolium aluminate 57 by combining aluminium complex 56 with IL 55.](image)

As already alluded to, indium can mediate Barbier-type reactions in water.[99,100] Interestingly, metallic gallium can also be used to promote the alkylation of aldehydes and ketones with allyl bromide in water, affording the relevant homoallyl alcohols in high yields.[103] Similarly, the coupling of indoles and pyrroles with allyl halides can be accomplished in a mixture of water and DMF in the presence of Ga metal using NBu₄Br as an additive.[104] This method in granting access to C3-allylated indole species 58 represents a main-group metal-mediated alternative to other approaches employing Pd catalysts. Interestingly, the choice of solvent is crucial for the success of this transformation as a mixture of products results on using acetone or THF. The effect of NBu₄Br is also remarkable; in fact, the employment of other metal bromides such as MgBr₂ or KBr inhibits the coupling process (Scheme 28).
Oshima has shown that allylgallium reagents, generated in situ via salt metathesis of GaCl₃ and allylmagnesium bromide, promote radical allylation of α-iodo and α-bromo carbonyl compounds in the presence of BEt₃ and under air, using a mixture of THF/hexane and water (Scheme 29). Interestingly, when assessing solvent effects, it was found that without using water as a co-solvent the yields in the formation of 59 were lowered significantly. Although the exact nature of this favourable solvent effect is unclear, the authors suggest the possible involvement of allylgallium hydroxide intermediates, which may be more reactive towards the radical allylation process.

Significantly, indium-mediated allylation reactions cannot only be accomplished using water as the solvent. Alternative reaction media such as ILs and scCO₂ can be employed too. Indeed, Gordon and Ritchey have reported the use of indium metal and allyl bromide for the allylation of a wide range of aldehydes and ketones using IL [BMIM][BF₄]. These reactions can be carried out at room temperature using stoichiometric amounts of In to afford the relevant homoallylic alcohols in yields ranging from 37 to 92%, which, in general, are comparable to those reported using organic solvents or water. Interestingly, this study reveals that, at the end of the reaction, addition of water to quench the putative indium alkoxide intermediate is essential in order to achieve the above yields for the relevant homoallylic alcohols. Using this approach for the allylation of 2-methoxycyclohexanone (60), the level of diastereoselectivity towards the syn product 61, was greater (61:62 ratio = 18:6:1) than using pure water or a THF–water mixture (Scheme 30).

Related to these studies is the work of Chan and co-workers who compared the ability of In, Sn or Zn to mediate the allylation of carbonyl compounds using ILs [BMIM][BF₄] and [EMIM][BF₄]. This study reveals that under ambient temperature conditions each metal can effectively promote the formation of the relevant homoallylic alcohols in the above solvent systems, although the best conversions are observed for Sn.

From a more cost-effective perspective, Hirashita has reported the efficient allylation of carbonyl compounds in ILs using catalytic amounts of In, which can be generated in situ by reduction of InCl₃ (10 mol%) with stoichiometric aluminum. Notably, these reactions occur faster when water is added to the IL [BMIM][PF₆], although it should be noted that when the same approach was employed using neat water as the solvent, the allylation process was completely shutdown. In addition, once In–mediated aldehyde allylation processes are carried out using liquid CO₂ as the solvent, the relevant homoallylic alcohols can be isolated in 38 to 82% yield. This method represents a cleaner and efficient alternative to conventional organic solvents, where the excess of CO₂ can be separated by depressurisation and subsequently be reused.

### 4.2. Applications of organotin reagents

Finding widespread applications in cornerstone synthetic methods (Stille coupling, radical reactions, allylations, etc.), organotin compounds are a family of versatile organometallic reagents. Part of their popularity stems from their thermal stability and relatively straightforward preparations combined with their robustness to hydrolysis and oxidation. Furthermore, these reagents are also compatible with a myriad of organic
functional groups, showing an excellent balance between stability and reactivity. However, despite such an impressive synthetic background, one of their main drawbacks is related to their toxicity and the difficulties associated with the removal of residues from the final products. Some of the strategies developed to try to overcome this limitation include the use of organotin reagents supported by ILs. These reagents can be easily prepared by treating imidazole derivative SnBu with Mel or EtBr forming the IL supported tin reagent 66 that, in turn, can be used in Stille cross-coupling reactions, under solvent-free conditions and without the addition of additives or ligands, thereby affording a range of bis(aryl) compounds of the kind of 67 in good yields (Scheme 32).

Furthermore, it is possible to recycle the tin compound/catalyst system at the end of the reaction by extracting the organic products with an organic solvent. By treating the IL phase containing the halogenotin-supported ionic liquid 68 with PhLi, it is possible to generate the arylating starting material 66 (Figure 5). These organotin reagents can also be used as effective catalysts for the reductive amination of aldehydes and ketones using PhSiH₃. Reactions can also be carried out under solvent-free conditions, which facilitate the purification of the final products and minimise problems caused by tin contamination.

It should also be noted that allylation reactions and Stille couplings, two of the most powerful synthetic applications of organotin reagents, have also been investigated using ILs as alternative reaction media to organic solvents. Under these conditions, successful allylation methods of aldehydes and ketones have been reported using several tin reagents, including Sn metal, SnCl₂ or tetra(allyl)tin. These reactions offer an excellent substrate scope and can be carried out at room temperature. Even more importantly, in many cases, the IL can be efficiently recycled without any further purification, thus making these protocols more environmentally benign. Moreover, using tetra(allyl)tin it is possible to activate all-four allyl groups towards their transfer to the carbonyl substrates, thereby maximizing the atom-economy of the process Related to this work is that by Kobayashi and co-workers who described a silica-gel-supported scandium system with an IL acting as a heterogeneous catalyst to efficiently promote several C–C bond-forming processes, including the allylation of ketones using tetra(allyl)tin (Scheme 33). Intriguingly, this study shows that the key to success of this novel approach is the combination of a silica-gel-supported metal catalysts with an IL, which creates a hydrophobic reaction environment in water.
This drawback can be overcome by using Pd nanoparticles as catalysts rather than molecular palladium species. The versatility and tuneability of ILs allows the stabilisation of nanoparticles, protecting them from agglomeration, while increasing the robustness to oxidation and hydrolysis of the nanoscale catalyst surface thanks to the formation of a protective shell. In these reactions, Pd nanoparticles act as catalyst reservoirs, while the active catalytic species are molecular Pd complexes, which can be leached out from the surface of the nanoparticle. A wide range of ILs have been assessed for this type of Stille coupling, containing a variety of cations (e.g., pyridinium, imidazolium, tetraalkyl ammonium). Notably, Dyson has shown that the use of nitrile functionalised ILs improved significantly the stability of the catalytic systems allowing their efficient recycling and minimising catalyst leaching. Employing Pd nanoparticles stabilised by tetraalkyl ammonium salts bearing long alkyl chains as catalyst, Nacci and co-workers have reported efficient Suzuki and Stille cross-couplings involving a wide range of halide aryls, including aryl chlorides, whose applications in these type of processes can be particularly challenging due to their reduced reactivity.

DESs have also been successfully employed in Stille alkylations and biaryl synthesis. König and co-workers have reported that using low-melting mixtures of sugar, urea and inorganic salts as solvents it is possible to promote the fast and efficient Pd-catalysed alkyl transfer of tetraalkyl stannanes (Scheme 35). Using conventional organic solvents, the transfer of simple alkyl groups requires instead special conditions including the use of toxic solvents such as HMPA or DMF. The smooth formation of coupling products 70 (Scheme 35) using this alternative method has been attributed to the high polarity and nucleophilic character of the DES combinations employed. Biaryl 71 can also be prepared in almost quantitative yields using this approach, which works well with both electron-poor and electron-rich aryl bromides (Scheme 35). Interestingly, the catalyst load can be reduced to 0.001 mol% and the catalyst-solvent mixture can be recycled up to three times. An added advantage to this approach is the simple work up and the ease at which products are isolated employing these melt mixtures; in fact, upon adding water, the organic products precipitate as amorphous solids and can be separated by filtration.

Although traditionally Stille couplings are carried out in organic solvents, the stability that aryl stannanes exhibit to air and moisture has allowed the development of alternative methods using water as the solvent. For example, Wolf has reported an effective Stille cross-coupling methodology using a wide range of aryl chlorides and aryl bromides. Using an air-stable and water-soluble Pd-phosphinous acid catalyst, the synthesis of several bis(aryl) compounds can be accomplished in good to high yields, using neat water as the solvent and without the need of an organic co-solvent.
Using water as the solvent, a simple and efficient one-pot methodology has been developed by Duan and co-workers: with \( \text{Pd}(\text{PPh}_3)_4 \) as a catalyst, effective cross-coupling of a variety of aryl and heteroaryl bromides/iodides could be accomplished.\(^{[12]}\) This method requires the use of microwave irradiation and involves the sequential stannylation followed by a Stille cross-coupling process, as depicted in Scheme 37 for the synthesis of 73.

Scheme 37. Open-pot stannylation/Stille cross-coupling sequential reactions.

5. Conclusions

Overall, it is clear from the examples discussed in this Microreview that the employment of unconventional reaction media in the chemistry of \( s-, p- \), and \( d- \) block elements is taking the stage today transforming everything and everyone. In a world with dwindling petroleum resources, organometallic scientists are slowly but firmly nurturing their own ability to improve the environmentally friendliness of chemical processes so as to produce the best and original “green organometallic chemistry”. The reticence to carry out the reactions of polar organometallic reagents under air, at room temperature, and in protic reaction media is also destined to fade away. The water itself, which is the most abundant and the only natural solvent on Earth, as well as the main traditional allied of biochemical processes, should no longer be considered a “foe” for organometallic compounds, but a “friend” to win.

The change in thinking will be the key to shift definitively our own paradigms and convictions. This will require a complete redesign of the experimental conditions, a deeper understanding of organometallic mechanisms and reactivities, and a close collaboration between theoreticians and experimental inorganic and organic researchers. In addition, fostering stronger industry/academic partnerships will expedite the transfer of new knowledge and emerging “greener technologies” to the marketplace to finally see realized in topical areas of science which they were simply considered not long ago as “fragile and visionary ideas”. Now that the first seeds are being planted, it would be expected and desirable that this infant field would grow up and develop quickly beyond our present concepts, and that the lion’s share of organometallic transformations (stoichiometric, catalytic, and asymmetric applications) be designed and carried out mainly according to the “Green Chemistry” regulations. Until today, we have developed an extraordinary ability to adapt to our expectations. It is time now to adapt our expectations to fit the environment needs, hoping this may also lead to new scientific findings and to the disclosure of novel and unpredictable aspects of organometallic reactivity in the years to come!

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Stepping towards ideal polar organometallic processes! This Microreview provides a reliable evidence of the unstoppable transition of polar organometallic chemistry towards greener protocols, mainly represented by unconventional solvents. This contributes to make organometallic chemistry even more sustainable and prepares the ground for new, stimulating research.