

Introducing Deep Eutectic Solvents to Polar Organometallic Chemistry: Chemoselective Addition of Organolithium and Grignard Reagents to Ketones in Air**

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Dedicated to Professor Bill Clegg on the occasion of his 65th birthday

Abstract: Despite their enormous synthetic relevance, the use of polar organolithium and Grignard reagents is greatly limited by their requirements of low temperatures in order to control their reactivity as well as the need of dry organic solvents and inert atmosphere protocols to avoid their fast decomposition. Breaking new ground on the applications of these commodity organometallics in synthesis under more environmentally friendly conditions, this work introduces deep eutectic solvents (DESs) as a green alternative media to carry out chemoselective additions of ketones in air at room temperature. Comparing their reactivities in DES with those observed in pure water suggest that a kinetic activation of the alkylating reagents is taking place, favoring nucleophilic addition over the competitive hydrolysis, which can be rationalized through formation of halide-rich magnesiate or lithiate species.

Grignard and organolithium reagents are exceptionally valuable organometallic reagents in synthesis. Boasting extremely high reactivities, primarily because of the high polarity of their metal–carbon bonds, these reagents are indispensable to any laboratory where synthetic chemistry is carried out.^[1] Amongst their numerous applications, their addition reactions to ketones is one of the most versatile and fundamental methodologies to generate new C–C bonds

allowing access to tertiary alcohols.^[2] However, the chemoselectivity of these processes can be seriously compromised by formation of undesired reduction and/or enolization products, resulting from competing β -hydride elimination and deprotonation reactions, respectively.^[3] Modern synthetic alternatives to overcome these unwanted side reactions include the use of inorganic salt additives (such as CeCl_3 , FeCl_2 , or ZnCl_2),^[4] as well as the in situ generation of magnesiate (LiMgR_3) complexes by mixing Grignard reagents with alkyllithiums.^[5] Aiming to boost the nucleophilicity of these organometallic reagents, as well as activating the carbonyl substrates, most such approaches still require the restriction of low temperatures (ranging from 0 to -78°C) to allow chemoselective control of the reaction. Furthermore, the use of dry ethereal solvents and inert atmosphere protocols is mandatory to avoid fast degradation of these polar reagents, which can react violently with air or moisture. These experimental constraints can greatly hamper their synthetic usefulness in scale-up industrial processes. Thus development of novel synthetic methodologies to use these reagents under green conditions,^[6,7] compatible with the presence of water and air, without having a detrimental effect in performance is the monumental challenge in polar organometallic chemistry.

Building new bridges between traditional polar organometallic synthesis and green chemistry, by pioneering the use of Grignard and organolithium reagents in deep eutectic solvents (DESs), herein we report remarkable progress towards meeting this challenge which allows chemoselective alkylation of aliphatic and aromatic ketones to be conducted in air at room temperature and without the need of volatile organic solvents (VOCs).

DESs have emerged in synthesis as a new family of green solvents which find widespread applications in a variety of areas, spanning electrochemistry, biocatalysis, metal extraction, material chemistry, purification of biodiesel to metal-catalyzed organic reactions.^[8] DESs are mostly obtained by mixing a quaternary ammonium salt with a hydrogen-bond donor that can form a complex with the halide anion of the ammonium salt. A popular choice to prepare DESs is the low-cost and readily available ammonium salt choline chloride (ChCl , Figure 1),^[9] which in combination with biorenewable and environmentally benign hydrogen-bond donors [that is, glycerol (Gly), lactic acid (LA), urea or water, Figure 1] can form an eutectic mixture.

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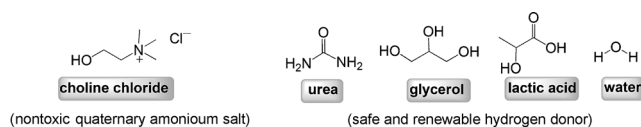


Figure 1. Components used in the synthesis of the DESs employed as solvent in this work.

To start this work addition of the Grignard reagent vinylmagnesium bromide to 2'-methoxy-acetophenone (**1a**) was examined at room temperature, in air, using different stoichiometries, (entries 1–3, Table 1) in the eutectic mixture 1ChCl/2Gly. Remarkably, the almost instantaneous formation

Table 1: Study of the addition reaction of vinylmagnesium bromide to 2'-methoxy-acetophenone (**1a**) in different deep eutectic solvents.^[a]

Entry	Grignard [mmol] ^[b]	Eutectic mixture	Yield [%] ^[c]
1	1	1ChCl/2Gly	20
2	1.5	1ChCl/2Gly	43
3	2	1ChCl/2Gly	78
4	2	1ChCl/2EG	55
5	2	1ChCl/2H ₂ O	57
6 ^[d]	2	1ChCl/2Urea	67
7 ^[d]	2	1ChCl/2LA	30
8 ^[e]	2	1ChCl/2Gly	60

[a] Reactions done in air at room temperature using 1 g of DES. Reaction time 2–3 s. 1 mmol of the ketone used. [b] A commercially available 1.0 M solution of vinylmagnesium bromide in THF was used. [c] Determined by GC and ¹H NMR spectroscopy. [d] Addition of the Grignard reagent to urea or LA was also seen. [e] Ethereal solvent removed by exhaustive evacuation.

of the relevant tertiary alcohol **2a** was observed in all cases, finding a significantly improved yield of 78 % when two equivalents of the Grignard reagents were employed (entry 3). Replacing Gly by other H-bond donors like ethylene glycol (EG, entry 4) or water (entry 5) led to lower conversions. In all cases the formation of **2a** occurs chemoselectively with no side products observed in the crude reaction mixture (only unreacted starting material **1a**). Remarkably, when the reaction was carried out using water as a solvent, **2a** was obtained in a diminished 21 % yield, indicating that the addition reaction to **2a** must be significantly slower under these conditions than with the DES, which translates in a greater degree of hydrolysis of the organometallic reagent.^[10] Interestingly, using H-donors bearing carbonyl functionalities to generate the DES mixtures [urea (entry 6) or lactic acid (LA, entry 7)] has a negative effect in the overall chemoselectivity of the addition process, yielding **2a** in 67 and 30 % respectively, along with products generated by addition of Grignard reagent to the C=O bond of these H-donor molecules.^[11] Crucially the use of Schlenk techniques (N₂ or Ar atmosphere) or low temperatures (0 °C) is not required. In this sense and since DESs have high heat capacities, low

temperatures are not needed to cool the reaction (but often mandatory for ethereal solvents). Although attempts to generate the Grignard reagent in the eutectic mixture 1ChCl/2Gly failed, isolated vinylmagnesium bromide also reacts with the aromatic ketone **1a** in the pure eutectic mixture (without ethereal co-solvents), although the yield is lower (60 %, entry 8) than when a commercial ethereal solution of the Grignard reagent was employed.

Encouraged by these initial findings, which glimpse the potential that 1ChCl/2Gly and 1ChCl/2H₂O have as green solvents for the chemoselective addition of Grignard reagents to ketones under standard bench experimental techniques, we then assessed the scope of this methodology extending our studies to a range of Grignard reagents with both aromatic and aliphatic ketones (Table 2). Similarly to the experiments

Table 2: Addition of various Grignard reagents to ketones **1a–1c** in ChCl-based eutectic mixtures.^[a]

Entry	R ¹	R ²	R ³	DES	Yield [%] of 2 ^[b]
1	<i>o</i> -(MeO)C ₆ H ₄	Me	vinyl	1ChCl/2Gly	2a 78
2	<i>o</i> -(MeO)C ₆ H ₄	Me	vinyl	1ChCl/2H ₂ O	2a 57
3	<i>o</i> -(MeO)C ₆ H ₄	Me	Et	1ChCl/2Gly	2b 64
4	<i>o</i> -(MeO)C ₆ H ₄	Me	Et	1ChCl/2H ₂ O	2b 73
5	Ph	Ph	vinyl	1ChCl/2Gly	2c 69
6	Ph	Ph	vinyl	1ChCl/2H ₂ O	2c 44
7 ^[c]	Ph	Ph	Et	1ChCl/2Gly	2d 24 [46]
8 ^[c]	Ph	Ph	Et	1ChCl/2H ₂ O	2d 19 [46]
9	CH ₃ (CH ₂) ₂	Me	vinyl	1ChCl/2Gly	2e 79
10	CH ₃ (CH ₂) ₂	Me	vinyl	1ChCl/2H ₂ O	2e 87
11	<i>o</i> -(MeO)C ₆ H ₄	Me	ethynyl	1ChCl/2Gly	2f 77
12	<i>o</i> -(MeO)C ₆ H ₄	Me	ethynyl	1ChCl/2H ₂ O	2f 72

[a] Reactions performed under air, at room temperature using 1 g of the DES. Reaction time 2–3 s. 1 mmol of ketone used. Commercially available 1.0 M solutions of the relevant Grignard reagents in THF (2 mmol) were employed. [b] Determined by GC and ¹H NMR spectroscopy. [c] Formation of diphenylmethanol (**3**), resulting from the reduction reaction was also observed, with yields displayed in brackets.

compiled in Table 1, the addition reactions in both eutectic mixtures were completed in exceptionally short reaction times (2–3 seconds), with in most cases a high degree of selectivity, recovering only unreacted ketone. An exception was the reaction of EtMgCl with benzophenone (**1b**) (entries 7 and 8, Table 2) where the corresponding reduction product (diphenylmethanol, **3**) was also formed.^[12] Considering first the two different eutectic mixtures employed, although no direct correlation was found between the H-bond donor component of the DESs (Gly or water) and the outcome of the reaction, in general, better yields for the corresponding alcohols **2** were obtained in the Gly-containing eutectic mixture (odd entries in Table 2). Using vinylmagnesium bromide as an alkenylating reagent tertiary alcohols **2a**, **2c**, and **2e** can be effectively obtained from reactions with 2'-methoxy-acetophenone (**1a**) (entries 1 and 2), benzophenone (**1b**) (entries 5 and 6), and aliphatic ketone 2-pentanone (**1c**)

(entries 9 and 10), respectively. Similarly ethynylmagnesium bromide reacts with **1a**, affording **2f** in a 77 and a 72 % yield depending on the eutectic mixture employed (entries 11 and 12). Confronting the same ketone with EtMgCl, where β -hydride transfer (reduction) is more plausible, led exclusively to addition product **2b** in 64 and 73 % yields (entries 3 and 4 using 1ChCl/2Gly and 1ChCl/2H₂O), although when benzophenone was employed, secondary alcohol **3** was the major product (entries 7 and 8, Table 2), while ethyl adduct **2d** was obtained in modest yields, similar to those previously reported for the same reaction using dry THF as solvent at 0 °C.^[4c]

Theoretical and experimental studies monitoring the addition reactions of carbonyl compounds by Grignard reagents, using neat water as a solvent, have shown that while for allyl Grignard reagents additions take place at a comparable rate to those of the competing hydrolysis processes,^[10] alkyl analogs, such as BuMgCl, are much more kinetically retarded (addition reaction is up to 10⁵ times slower),^[13] and therefore protonation occurs preferentially, yielding only trace amounts of addition products. This behavior contrasts sharply with the reactions mentioned above with EtMgCl and **1a** where in both eutectic mixtures (1ChCl/2Gly and 1ChCl/2H₂O), the tertiary alcohol **2b** is the major product (entries 3 and 4 Table 2), hinting at some type of kinetic activation of the Grignard reagent may be occurring using the DESs. Furthermore in this case the conversions observed for **2b** are greater than that found when **1a** is reacted at –78 °C in dry THF under strictly inert atmosphere techniques (45 %). Germane to this work, Song has recently shown that catalytic amounts of ammonium salt NBu₄Cl in THF solutions of Grignard reagents can greatly enhance the chemoselectivity of addition reactions, minimizing formation of enolization and reduction products.^[14] The authors proposed that substoichiometric amounts of the salt can shift the position of the Schlenk equilibrium of Grignard reagents to form dinuclear R₂Mg·MgX₂ species which would favor addition. Since a main component in the eutectic mixtures employed in this work is an ammonium salt, a related activation effect can be operative. To explore this possibility more, we reacted choline chloride (ChCl) with various amounts of the Grignard reagent Me₃SiCH₂MgCl in THF solvent. However, because of the poor solubility of this ammonium salt in this organic solvent, no reaction was observed. In contrast, the addition of one equivalent of Grignard to the slightly more soluble NBu₄Cl afforded a solution that deposited crystals of magnesiate $[(NBu_4)^+ \cdot (THF)MgCl_2(CH_2SiMe_3)]^-$ (**4**) in a 87 % yield.

X-ray crystallographic studies established that the molecular structure of **4** (Figure 2) is surprisingly a monomer, comprising a well-defined magnesiate anion, made up of a Mg atom which binds terminally to an alkyl group, two chlorines, and a THF molecule, and a tetrabutylammonium counterion. ¹H DOSY NMR studies on solutions of **4** in [D₈]THF confirmed that this structure is retained. These results suggest that these activating effects of the ammonium salts in THF solutions may be best rationalized in terms of the formation of an anionic species which should have an enhanced nucleophilic power over that of a neutral Grignard reagent. The use

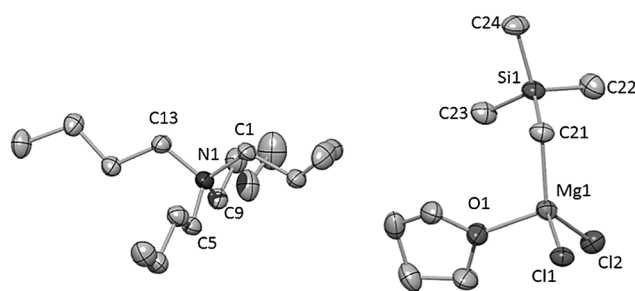


Figure 2. Molecular structure of **4**. Displacement ellipsoids are drawn at the 50 % probability level. Hydrogen atoms have been omitted for clarity.

of highly reactive magnesiate species as chemoselective reagents for additions to ketones has been previously described, but as far as we are aware, this involves the in situ formation of a bimetallic reagent, by co-complexation of the Grignard reagent with an organolithium.^[5] These lithium magnesiates exhibit greater kinetic reactivities and unique selectivity profiles, unmatched by conventional magnesium reagents.^[15] Although the formation of a similar compound to **4** using ammonium salt ChCl present in the DESs employed in this work could not be demonstrated, the possibility of the participation of more nucleophilic magnesiate species in the addition reactions described in Tables 1 and 2 cannot be disregarded. This would imply that ChCl may have a double role in these processes, as a component of the DES mixture employed but also as part of organometallic alkylating reagent, being a halide source.

To probe the scope of DESs in terms of the nature of the polar organometallic reagent employed we then studied the reactivity of ketones **1a–c** with a series of organolithium reagents (Table 3). The large increase in the polarity of the metal–carbon bonds in these commodity reagents when compared with organomagnesium compounds, generally imposes the use of much lower temperatures in order to control their selectivity.^[1] Thus, for example the addition of BuLi to acetophenone should be performed at –78 °C in THF, and even so the tertiary alcohol is obtained in a 62 % yield along with 7 % yield of the unwanted aldol condensation product.^[5] Contrastingly, under the previously optimized reaction conditions used for Grignard reagents (ChCl-based eutectic mixtures as solvent, at room temperature in air; Table 3), BuLi can be added instantaneously to 2-methoxyacetophenone (**1a**) to give tertiary alcohol **2g** in impressive yields (60–82 %, entries 1, 2, and 3) without forming any other by-products. We believe this makes our study unique in that it is the first to report the successful coexistence of organolithium reagents and green solvents within the same solution. Again and as previously demonstrated for Grignard reagents, the addition reaction of BuLi is orders of magnitude faster than its protonation by water, ethylene glycol or glycerol present in the DES. Showing the general applicability of this approach, chemoselective butylation was also observed for the exclusively aliphatic ketone **1c** (entries 6 and 7 in Table 3) in either Gly- or water-containing eutectic mixtures. Diverging from the low conversions observed in the reactions of EtMgCl with benzophenone (**1b**) (entries 7 and 8 in Table 2),

Table 3: Addition of organolithium (RLi) reagents to ketones **1a–1c** in CHCl₃-based eutectic mixtures.^[a]

entry	R ¹	R ²	R ³	DES	Yield [%] of 2 ^[b]
1	<i>o</i> -(MeO)C ₆ H ₄	Me	Bu	1ChCl/2Gly	2g 71 ^[e]
2	<i>o</i> -(MeO)C ₆ H ₄	Me	Bu	1ChCl/2H ₂ O	2g 82
3	<i>o</i> -(MeO)C ₆ H ₄	Me	Bu	1ChCl/2EG	2g 60
4 ^[c]	Ph	Ph	Bu	1ChCl/2Gly	2h 75 (12)
5 ^[c]	Ph	Ph	Bu	1ChCl/2H ₂ O	2h 68 (9)
6	CH ₃ (CH ₂) ₂	Me	Bu	1ChCl/2Gly	2i 73
7	CH ₃ (CH ₂) ₂	Me	Bu	1ChCl/2H ₂ O	2i 85
8	<i>o</i> -(MeO)C ₆ H ₄	Me	Ph	1ChCl/2Gly	2j 80
9	<i>o</i> -(MeO)C ₆ H ₄	Me	Ph	1ChCl/2H ₂ O	2j 82
10	Ph	Ph	Ph	1ChCl/2Gly	2k 81
11	Ph	Ph	Ph	1ChCl/2H ₂ O	2k 85
12	CH ₃ (CH ₂) ₂	Me	Ph	1ChCl/2Gly	2l 72
13	CH ₃ (CH ₂) ₂	Me	Ph	1ChCl/2H ₂ O	2l 90
14 ^d	CH ₃ (CH ₂) ₂	Me	ethynyl	1ChCl/2H ₂ O	2m 84

[a] Reactions performed under air, at room temperature using 1 g of the DES. Reaction time 2–3 s. 1 mmol of ketone used. Commercially available 1.6 M solution in hexane of BuLi and 1.8 M solution in dibutylether of PhLi (2 mmol in all cases) were employed. [b] Determined by GC and ¹H NMR spectroscopy. [c] Formation of the reduction product **3** was also observed. [d] Lithium acetylide ethylenediamine complex in the absence of organic solvents was employed. [e] Removing most of the hexane under vacuum from the commercial BuLi solution did not affect the selectivity of the addition reaction although **2g** was obtained in a slightly lower yield (66%).

the addition of BuLi to this sensitive ketone formed the relevant tertiary alcohol **2h** in much greater yields, although small amounts of reduction product **3** could also be detected in reaction mixtures (entries 4 and 5 in Table 3). Besides aliphatic ones, aromatic organolithium reagents (PhLi) can also be successfully added to both aromatic (entries 8–11 in Table 3) and aliphatic (entries 12 and 13 in Table 3) substrates.^[12] Trying to push our system to its limits, the commercially available solid lithium acetylide ethylenediamine complex (without organic solvent) was added to the reaction mixture containing the water-based DES 1ChCl/2H₂O and 2-pentanone (entry 14 in Table 3). Astonishingly, almost quantitative (84%) formation of the desired propargylic alcohol was seen, confirming that addition can be also performed in pure eutectic mixtures. It should be noted that the same reaction tested using H₂O as a solvent gave ketone **2m** in a modest 7% yield, which hints at a possible activation effect of the organolithium reagent when it is added to the DES mixtures.

To assess the possibility of forming a lithiate complex with ammonium salts, similar investigations to those mentioned for Grignard reagents were carried out. Supporting the formation of a complex, the addition of one molar equivalent of LiCH₂SiMe₃ to a NBu₄Cl suspension in THF gave a solution which on cooling deposited colorless crystals which melt very quickly about –10 °C, precluding their analysis by X-ray crystallography. Multinuclear (¹H, ¹³C, and ⁷Li) magnetic resonance investigations of this solid in [D₈]THF solution supports the formation of a new species (see the Supporting

Information). Although the chemical shifts observed for the resonances for the Li-CH₂ group in ¹H and ¹³C NMR spectra do not differ significantly to those found for LiCH₂SiMe₃ in the same deuterated solvent, there is a distinct change for that seen in ⁷Li NMR spectra, moving from 3.54 ppm in the organolithium precursor to 0.61 ppm in the crystalline product, which is consistent with a marked change in the metal coordination sphere. Interestingly, the integration of the ammonium butyl groups against the monosilyl group revealed a 2:1 NBu₄/CH₂SiMe₂ ratio which would be consistent with forming a dianionic halolithiate [(NBu₄)₂⁺{LiCl₂-(CH₂SiMe₃)²⁻}], where two Cl anions have been transferred to lithium. The addition of LiCl to lithium amides or organolithium reagents has a profound effect on their reactivity. Thus kinetic studies have shown that by adding less than 1 mol % of LiCl to lithium diisopropylamide, its 1,4-addition reaction to unsaturated ethers occurs 70 times faster.^[16] A similar halide-mediated accelerating effect could also favor the addition reaction in DES over the competing protonation process.

In summary, this work introduces deep eutectic solvents as superior green and biorenewable reaction media for highly polar organometallic compounds. As illustrated with both Grignard and organolithium reagents, these eutectic mixtures are the solvents of choice to cross the frontiers between synthetically useful main group chemistry and green solvents. A comparison of the reactivity profiles of these reagents in DES mixtures with those in pure water, suggest that a kinetic activation of the alkylating reagents occurs in the former, favoring nucleophilic addition over the competing hydrolysis process. Building on recent work on the enhanced reactivity of Grignard reagents on the addition of ammonium salts, a plausible rationale may be the in situ formation of anionic halide-rich magnesiate or lithiate species. Clearly, this first crossing opens up a new, much sought after frontier of organolithium chemistry in their practical application under environmentally friendly conditions (green solvents, room temperature, and in the presence of air).

Experimental Section

Full experimental details are included in Supporting Information. CCDC 978224 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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