Organolithium Chemistry

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Exploiting Deep Eutectic Solvents and Organolithium Reagent Partnerships: Chemoselective Ultrafast Addition to Imines and Quinolines Under Aerobic Ambient Temperature Conditions

Cristian Vidal, Joaquín García-Álvarez,* Alberto Hernán-Gómez, Alan R. Kennedy, and Eva Hevia*

In memory of Jose Barluenga

Abstract: Shattering the long-held dogma that organolithium chemistry needs to be performed under inert atmospheres in toxic organic solvents, chemoselective addition of organolithium reagents to non-activated imines and quinolines has been accomplished in green, biorenewable deep eutectic solvents (DESs) at room temperature and in the presence of air, establishing a novel and sustainable access to amines. Improving on existing methods, this approach proceeds in the absence of additives; occurs without competitive enolization, reduction or coupling processes; and reactions were completed in seconds. Comparing RLi reactivities in DESs with those observed in pure glycerol or THF suggests a kinetic anionic activation of the alkylating reagents occurs, favoring nucleophilic addition over competitive hydrolysis.

Nucleophilic addition of organolithium derivatives to carbonyl compounds (e.g., ketones or aldehydes) is a common methodology to access new C-C bonds allowing synthesis of functionalized alcohols.^[1] Contrastingly, their use as nucleophiles to transform imines to amines via direct 1,2addition processes has been significantly less developed.^[2] Reduced electrophilicity of the C=N group, competitive abstraction of acidic α -hydrogens to give azaenolates and possible formation of reductive coupling side-products are some mitigating factors, which can compromise the chemoselectivity of this approach.^[3] Strategies undertaken to overcome these limitations include the use of Lewis acids (e.g., AlMe₃, LiBr)^[4,5] as additives that can activate the organic substrate and of alternative alkylating reagents such as magnesium zincates ([MgCl][ZnR₃]) which appear more chemoselective than conventional common RLi or RMgX reagents.^[1,2] However, all these protocols, as with nearly all

[*]	Dr. C. Vidal, Dr. J. García-Alvarez
	Laboratorio de Compuestos Organometálicos y Catálisis (Unidad
	Asociada al CSIC), Departamento de Química Orgánica e Inorgánica
	(IUQOEM), Facultad de Química, Universidad de Oviedo
	33071, Oviedo (Spain)
	E-mail: garciajoaquin@uniovi.es
	Dr. A. Hernán-Gómez, Dr. A. R. Kennedy, Prof. E. Hevia
	WestCHEM, Department of Pure and Applied Chemistry
	University of Strathclyde
	Glasgow, G1 1XL (UK)
	E-mail: eva.hevia@strath.ac.uk
	Supporting information for this article can be found under:

Supporting information for this article can be found under http://dx.doi.org/10.1002/anie.201609929. methods using polar organometallics, require restrictive reaction conditions. This includes use of inert atmospheres, dry oxygen-free organic solvents and in many cases low temperatures (-78 °C) in order to avoid intermediate degradation and side reactions.^[6] Thus, running polar organometallic chemistry under aerobic and/or hydrous conditions is the ultimate challenge to synthetic chemists.^[7] As an opening gambit towards this target, we recently pioneered use of green and biorenewable deep eutectic solvents (DESs) combining ammonium salt choline chloride (ChCl) with water or glycerol (Gly) (Figure 1) showing they can activate Grignard



Figure 1. Components of DES mixtures used in this study.

and organolithium reagents to promote room temperature chemoselective ketone alkylation/arylation reactions.^[8] Moreover, air could be tolerated in these additions. Subsequent insightful studies by Capriati reported lithiation of diaryltetrahydrofurans in ChCl-based DESs under air, finding it competitive with protonolysis as well as RMgX- and RLimediated additions to γ -chloroketones to furnish 2,2-disubstituted tetrahydrofurans.^[9] Taking organolithium DES chemistry into new, more taxing territory, here we describe the chemoselective addition of organolithium compounds to both imines and quinolines in DESs under air as a novel sustainable methodology to amines. This has wide implications as amine synthesis has been identified as a key area in green chemistry for pharmaceutical manufacturers.^[10]

This study examined adding RLi reagents to a range of imines at room temperature, in air, using DESs as solvents.^[11] The scope of this green approach considered: 1) the DES combination, 2) the organometallic reagent; and 3) the imine. Firstly we assessed the reaction of commercially available "BuLi with aromatic imine *N*-benzylideneaniline (**1a**) using different stoichiometries (entries 1–4, Table 1) in the eutectic

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Table 1: Study of the addition reaction of organometallic reagents (RM) to *N*-benzylideneaniline (**1** a) in different DESs^[a,b]

	$Ph \frac{1}{1a}$	+ RM	$\begin{array}{c} \underline{ESs} \\ \underline{HN}^{Ph} \\ \underline{R} \\ \underline$)
Entry	RM ^[b]	[mmol] ^[b]	Solvent	Yield [%] ^{[c}
1	"BuLi	1.3	1 ChCl/2 Gly	91
2	"BuLi	1.4	1 ChCl/2 Gly	95
3	"BuLi	1.8	1 ChCl/2 Gly	97
4	"BuLi	2	1 ChCl/2 Gly	98
5	"BuLi	1.4	1 ChCl/2 EG	66
6	"BuLi	1.4	1 ChCl/2 H₂O	54
7	"BuLi	1.4	H ₂ O	22
8	"BuLi	1.4	Gly	38
9	"BuMgCl	1.4	1 ChCl/2 Gly	1
10 ^[d]	"BuMgCl	1.4	1 ChCl/2 Gly	8
11	"Bu ₂ Mg	1.4	1 ChCl/2 Gly	36
12	LiMg ⁿ Bu ₃	1.4	1 ChCl/2 Gly	72

[a] Reactions were performed under air, at room temperature and using 1 g of DES. Reaction time 3 s. 1 mmol of the imine **1 a** was always used. [b] Commercial solutions of "BuLi ($1.6 \, \text{m}$ in hexanes), "BuMgCl ($1.0 \, \text{m}$ in THF) or dibutyImagnesium ($1.0 \, \text{m}$ in hexanes) were used. LiMg"Bu₃ was prepared in situ by mixing equimolar amounts of "BuLi and "Bu₂Mg in hexane. [c] Determined via ¹H NMR data using dibromomethane as internal standard. [d] ZnCl₂ ($10 \, \text{mol}\%$) was added to the reaction mixture.

mixture 1 ChCl/2 Gly (1:2 mol/mol). Remarkably, under conditions incompatible with conventional organolithium chemistry, almost quantitative formation of amine (**2a**) was observed employing only slight excess of "BuLi (1.4 equiv, entry 2), in a very short reaction time (2–3 s). Advantages of this approach are that: 1) no additives are required to achieve high conversions; 2) competitive enolization, reduction or coupling reactions were not observed,^[12] 3) edging closer to stoichiometric conditions, a slight excess of "BuLi gave full conversion to the desired amine **2a**, even though hydrolysis could be expected in the protic solvent; and 4) no imine decomposition was seen in the eutectic mixture.

Next we assessed the effect of different ChCl-based DESs on this 1,2-addition reaction. Interestingly, replacing Gly for HBDs ethylene glycol (EG, entry 5) and water (entry 6) lowers the yield of amine **2a** (to 66 and 54%, respectively). Notwithstanding, although the addition process is less efficient, its excellent chemoselectivity is maintained, without forming by-products, as only unreacted imine 1a and amine 2a were seen in the reaction crudes (see the Supporting Information (SI)).^[13] Contrastingly, when using HBDs containing carbonyl functionalities (such as urea or lactic acid), complex mixtures of products were observed from adding "BuLi across the C=O bond of these H-donor molecules, along with traces of 2a.^[14] Crucially, the use of inertatmosphere Schlenk techniques or low temperature (0 to -78 °C), mandatory when these additions are carried out in ethereal solvents, are not required using DESs (these solvent mixtures have a high heat capacity, so low temperatures are not needed to cool reactions).^[15] The propensity of the DES mixture to favor "BuLi addition to **1a** over its competing hydrolysis is illustrated in entries 7 and 8 of Table 1, whereas using neat H_2O or Gly, in the absence of ammonium salt ChCl, furnishes **2a** in lower 22 and 38% yields, respectively.

Highlighting the exciting potential of these green solvents, when the addition order of the reagents is reversed and "BuLi is introduced firstly to the eutectic mixture, which is stirred for 15 s under air before adding imine **1a**, product **2a** is obtained in a remarkably high 89% yield. Astonishingly, even if a oneminute interval is left between these reagents, the yield of **2a** is still good at 63%, emphasising the kinetic stability of "BuLi in this green solvent. Indeed, it is only after 3.5 min when the formation of **2a** is almost totally suppressed (Scheme 1).



Scheme 1. Assessing the time-dependent formation of **2a** when the order of addition of reagents is reversed.

The reactivity of **1a** with other polar organometallics under the optimized reaction conditions was also investigated. "BuMgCl failed to produce **2a**, even when ZnCl₂ was employed as an additive (entries 9 and 10). Using "Bu₂Mg, which has recently shown promise for addition to bis-(aryl)methylimines in toluene,^[16] yields **2a** in a modest 36% yield (entry 11). Even anionically activated lithium magnesiate LiMgⁿBu₃ showed reduced reactivity (72%, entry 12), suggesting that under these conditions, the high polarity of Li–C bonds in RLi reagents is crucial for success of the 1,2addition process.

Our previous work related the enhanced reactivity of polar organometallics in DESs with studies on the addition of RMgX reagents to ketones in organic solvents, where chemoselectivity can be enhanced by adding substoichiometric amounts of ammonium salt NⁿBu₄Cl.^[8] We attributed this to forming kinetically activated mixed ammonium magnesiate salts. Studies here reacting PhLi with 1a in THF in the presence of NⁿBu₄Cl suggest the formation of related mixed ammonium lithiate species. However, in this case, these compounds appear to be extremely reactive in THF solutions, having a negative effect on addition chemoselectivity. Thus NMR monitoring of the reaction revealed the formation of lithium but-3-en-1 oxide 4, resulting from α -deprotonation and subsequent ring-opening of THF (50% yield) along with ammonium lithiate complex 5 (Scheme 2(i)), whose constitution was established by ¹H DOSY NMR experiments (see SI). Contrastingly, using PhLi the addition reaction occurs quantitatively to form amide [(THF)₃LiNPh(CHPh₂)] (3), whose structure was elucidated by X-ray crystallography (Scheme 2(ii) and SI). This significant increase in the basicity of PhLi in THF on the addition of N"Bu₄Cl contrasts with results observed using DESs, where no substantial metallation of the glycerol (HBD component of the DES) is seen, hinting

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Scheme 2. Deleterious effect of ammonium salt on addition reaction between imine **1 a** and phenyllithium.

that though the formation of reactive ammonium lithiate species (via anionic activation by possible co-complexation with ChCl) can explain high efficiency of the addition reactions, other subtle effects such as the choice of HBD component or the nature of the ammonium salt employed should also play an important role in tuning the chemoselectivity of the reaction. Moreover, the different HBD abilities of water and alcohols cannot be disregarded, as recently shown by Capriati for "in water" RMgX mediatedadditions to γ -chloroketones.^[9c] Advancing the understanding of the interactions between the different components of DESs attracts widespread interest and debate,^[11a] and to date only the structure of the DES reline (1ChCl/2Urea) has been elucidated using neutron diffraction.^[17]

Encouraged by these findings we then ran the reaction using other RLi reagents and imines, to probe the scope of this transformation (see Table 2). For each substrate tested, the addition reaction in the eutectic mixture 1 ChCl/2 Gly was complete in a very short reaction time (3 s) and with high selectivity, as only unreacted imine and the desired amine (2a-s) were observed in the reaction crudes (see SI). Imine 1a was chosen as the benchmark to study the addition of different organolithium reagents. Thus, under the previously optimized reaction conditions (1.4 equiv of RLi, room temperature, under air, Table 1) both aliphatic ("BuLi, MeLi, 'BuLi, 'BuLi) and aromatic (PhLi) organolithium reagents successfully add to imine 1a yielding amines (2ae) in excellent yields (86-95%). Results are particularly remarkable with sterically demanding ^sBuLi and ^tBuLi, which in general have a greater tendency to undergo β -hydride elimination, especially when employed at room temperature. But here, they chemoselectively produce amines (2c,d and 2h,i, 80–94% yield), without need of a large excess of RLi (1.4 equiv) or long reaction times (3 s). The method also offers an excellent substrate scope, showing similar amine conversions for N-aryl- or N-alkyl-substituted aldimines (Table 2). High chemoselectivity is also apparent as electron-withdrawing (Br; 2m, 2q and 2s) and electron-donating substituents (MeO or Me; 2k, 2l, 2n, 2o, 2p and 2r) are tolerated on imine Ar groups, without observing possible competing processes such as Li–Br exchange (2m, 2q and 2s) or α -metallation.

Next we extended this greener and air-compatible protocol to the even more challenging addition of organolithium Table 2: Addition of organolithium (RLi) reagents to imines in the eutectic mixture 1 ChCl/2 Gly. $^{\rm [a]}$



[a] Reactions were run under air, at room temperature using 1 g of the eutectic mixture 1 ChCl/2 Gly. Reaction time 3 s. 1 mmol of imine was always used. Commercial solutions of "BuLi (1.6 M in hexanes), MeLi (1.6 M in diethyl ether), ⁵BuLi (1.4 M in cyclohexane), ⁵BuLi (1.9 M in pentane) and PhLi (1.8 M in dibutyl ether) were used. Yields were determined by ¹H NMR data using dibromomethane as internal standard.

reagents to aza-aromatic heterocyclic compounds which takes place with concomitant dearomatization of the heterocycle. The synthesis of 2-substituted dihydroquinolines, through adding RLi reagents to quinoline, is a commonly used methodology for the production of tetrahydroquinolinecontaining alkaloids.^[18] Using conventional methods limited by low temperatures, an inert atmosphere and scrupulously dry solvents, these reactions usually yield mixtures of rearomatized 2-substituted quinoline and C2- and C4-dihydroquinolines.^[19] In contrast, we found that under the same optimized reaction conditions (1 ChCl/2 Gly as solvent, at room temperature in air, 1.4 equiv RLi in Table 3) aliphatic (MeLi, 'BuLi, 'BuLi) organolithium reagents add instantaneously (5 s) to quinoline to furnish exclusively C2-substituted dihydroquinolines 6a-d. Although reaction yields are moderate (30-54%), chemoselectivities are remarkable, as no by-products were seen in reaction crudes, only unreacted quinoline and target 2-substituted dihydroquinolines (see SI).

In summary, this work has shown that replacing conventional toxic ethereal solvents by green, biorenewable deep

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Table 3: Addition of organolithium (RLi) reagents to quinolines in the eutectic mixture 1 ChCl/2 Gly.^[a]



[a] Reactions were performed under air, at room temperature using 1 g of the eutectic mixture 1 ChCl/2 Gly. Reaction time 5 s. 1 mmol of quinoline was always employed. Commercial solutions of MeLi (1.6 m in diethyl ether), 'BuLi (1.4 m in cyclohexane), and 'BuLi (1.9 m in pentane) were used. Yields were determined by ¹H NMR data using dibromomethane as internal standard.

eutectic solvents facilitates the successful chemoselective addition of organolithium reagents to imines and quinolines under standard bench experimental conditions (room temperature and under air), thus edging closer towards reaching aerobic/hydrous polar organometallic chemistry and at the same time advancing main-group based green chemistry.

Experimental Section

Full experimental details and copies of NMR spectra are included in the Supporting Information. CCDC 1503241 contains supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Keywords: deep eutectic solvents · green chemistry · imines · organolithium reagents · salt activation

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Communications

Organolithium Chemistry

- C. Vidal, J. García-Álvarez,*
- A. Hernán-Gómez, A. R. Kennedy,
- E. Hevia* _____ **IIII**-**IIII**

Exploiting Deep Eutectic Solvents and Organolithium Reagent Partnerships: Chemoselective Ultrafast Addition to Imines and Quinolines Under Aerobic Ambient Temperature Conditions



The green(air), the better! Moving closer to the dream of hydrous/aerobic organolithium chemistry, replacing toxic organic solvents by green and biorenewable deep eutectic solvents (DESs) enables regioselective addition of organolithium reagents to non-activated imines at room temperature in air.