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

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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] Contrariwise, their use as nucleophiles to transform imines to amines via direct 1,2-addition 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 zinicates (MgCl[ZnR₂]) which appear more chemoselective than conventional common RLi or RMgX reagents. [6] However, all these protocols, with nearly all 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 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 RLi-mediated 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
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)methylamines in toluene,[10] yields 2a in a modest 36% yield (entry 11). Even anionically activated lithium magnesiate LiMg₂Bu₃ 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 1,2-addition process.

Our previous work related the enhanced reactivity of polar organometallics in DESs with studies on the addition of RMX reagents to ketones in organic solvents, where chemoselectivity can be enhanced by adding substoichiometric amounts of ammonium salt N⁺Bu₄Cl⁻. We attributed this to forming kinetically activated mixed ammonium magnesiate salts. Studies here reacting PhLi with 1a in THF in the presence of N⁺Bu₄Cl suggest the formation of related mixed ammonium lithiacte 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 lithiacte complex 5 (Scheme 2(ii)), whose constitution was established by ¹H DOSY NMR experiments (see SI). Contrastingly, using PhLi the addition reaction occurs quantitatively to form amide [(THF)₂LiNPh(CH₂Ph₃)] (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
that though the formation of reactive ammonium salt is widespread and attracts widespread interest yielding amines (In contrast, we found that under the same debate in cyclohexane), and phenyllithium. Using conventional methods, limited to date only.

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 1ChCl/2Gly 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 (2a–e) in excellent yields (86–95%). Results are particularly remarkable with sterically demanding ‘BuLi and ‘BuLi, 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-attracting 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 reagents to aza-aromatic heterocyclic compounds which takes place with concomitant deaeromatization of the heterocycle. The synthesis of 2-substituted dihydroquinolines, through adding RLi reagents to quinoline, is a commonly used methodology for the production of tetrahydroquinoline-containing alkaloids. Using conventional methods limited by low temperatures, an inert atmosphere and scrupulously dry solvents, these reactions usually yield mixtures of re- aromatized 2-substituted quinoline and C2- and C4-dihydroquinolines. In contrast, we found that under the same optimized reaction conditions (1ChCl/2Gly 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 quinoline and C2- and C4-dihydroquinolines. 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...
Table 3: Addition of organolithium (RLi) reagents to quinolines in the eutectic mixture 1ChCl/2Gly.[a]

| Reaction | R1 | R2Li
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[a] Reactions were performed under air, at room temperature using 1 g of the eutectic mixture 1ChCl/2Gly. 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 facilitate 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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[13] It should be noted that benzaldehyde (the hydrolyzed product of imine 1a) was not formed in the reaction using eutectic mixture 1ChCl/2H₂O.

[14] A similar behavior has been noted by us for the addition of RMgX to ketones using DESs, see Ref. [8].


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