Introducing Glycerol as a Sustainable Solvent to Organolithium Chemistry: Ultrafast Chemoselective Addition of Aryllithium Reagents to Nitriles under Air and at Ambient Temperature

María J. Rodríguez-Alvarez,[a] Joaquín García-Álvarez,*[a] Marina Uzelac,[b] Michael Fairley,[b] Charles T. O'Hara,[b] and Eva Hevia*[b]

Abstract: Edging closer towards developing air and moisture compatible polar organometallic chemistry, the chemoselective and ultrafast addition of a range of aryllithium reagents to nitriles has been accomplished by using glycerol as a solvent, at ambient temperature in the presence of air, establishing a novel sustainable access to aromatic ketones. Addition reactions occur heterogeneously ("on glycerol conditions"), where the lack of solubility of the nitriles in glycerol and the ability of the latter to form strong intermolecular hydrogen bonds seem key to favouring nucleophilic addition over competitive hydrolysis. Remarkably, PhLi exhibits a greater resistance to hydrolysis working "on glycerol" conditions than "on water". Introducing glycerol as a new solvent in organolithium chemistry unlocks a myriad of opportunities for developing more sustainable, air and moisture tolerant main-group-metal-mediated organic synthesis.

Introduction

Celebrating the 100 year anniversary since Schlenk and Holtz's discovery of them in 1917, organolithium compounds have been and remain pivotal to the development of synthetic chemistry.[1] Staple reagents in academic laboratories worldwide, these centurions are in high demand in chemical industries that require manipulation of aromatic scaffolds (e.g., agrochemicals, pharmaceuticals).[2] This extensive utilisation reflects the high reactivity (and associated oxophilicity) of their Li@C bonds owing largely to the substantial polarity separation between lithium and carbon. To control this reactivity therefore necessitates the imposition of severely restrictive protocols (e.g., moisture- and oxygen-free organic solvents, inert atmospheres, low temperatures, etc.).[1] Thus, running organolithium chemistry under aerobic and/or hydrous conditions, without the need of scrupulously dry toxic organic solvents, is one of the ultimate challenges for synthetic chemists working in this area.[3]

Making inroads towards meeting this challenge, our groupshave uncovered the potential of deep eutectic solvents (DESs), combining the non-toxic and biorenewable ammonium salt choline chloride (ChCl), [Me$_3$NCH$_2$CH$_2$OH]$^+$Cl$^{\ominus}$ with water or glycerol (Gly),[4] as alternative green reaction media for highly polarised organometallic compounds.[5,6] Thus, we have reported the chemoselective alkylation of ketones by RMgX and RLi reagents at ambient temperature, under air and in protic DESs, a trio of conditions seemingly incompatible with polar organometallics, yet bizarrely these offer improved yields and better selectivities than under standard inert atmosphere protocols (Scheme 1).[5a] Interestingly, we have found the same behaviour
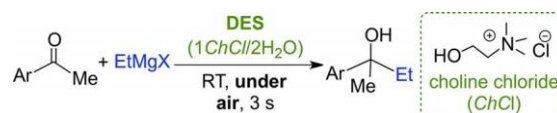
Scheme 1. Addition of RMgX reagents to ketones under air at ambient temperature by using ChCl-based DESs.[5a]

for the chemoselective nucleophilic arylation/alkylation of non-activated imines.[6] The DESs' success has been attributed to the possible formation of kinetically activated mixed-ammonium ate salts by co-complexation of the polar reagents (RLi or RMgX) with choline chloride (ChCl). In parallel with these studies, Capriati and co-workers[7] have demonstrated that Grignard and organolithium reagents can smoothly undergo nucleophilic additions to g-chloroketones or imines "on water",[8] competitively with protonolysis, under batch conditions at ambient temperature and in the presence of air.

Biomass-derived solvents [e.g., 2-methyltetrahydrofuran (Me-THF), lactic acid, g-valerolactone or glycerol] are also emerging as greener alternatives to volatile organic compounds (VOCs) in organic synthesis.[9] Obtained as a major by-product of the biodiesel industry,[10] glycerol (Gly) is a particularly appealing green solvent.[11] Thus, along with its exceptional physicochemical properties (i.e., high boiling point and polarity; low toxicity and flammability) and its ability to dissolve both inorganic or organic compounds,[11] recent reports have shown that using Gly as a solvent can improve the selectivity/efficiency of organ- ic transformations.[12] Nevertheless, despite these key advantag-es, Gly has never been used as a solvent in organolithium chemistry, probably as a consequence of the common assump-tion that these polar reagents will rapidly decompose in this solvent through reaction with its acidic alcohol groups.

Taking an important step further on our journey to develop more sustainable polar organometallic chemistry, here we pres-ent a breakthrough in the addition of aryllithium reagents to aromatic nitriles to access a range of bis(aryl) ketones under air, at ambient temperature by introducing Gly as an environ-mentally benign solvent for these reaction classes. For compar-ison, the reactions have also been assessed by using water as a solvent.

Results and Discussion

To begin, we selected as a model reaction the addition of phe-nyllithium (PhLi) to benzonitrile[13] (1 a) at ambient tempera- ture, in air and by using different stoichiometries in Gly as sol-vent (Scheme 2). Remarkably, the high yield (85 %) and almost instantaneous (3 s) formation of benzophenone imine (2 a) was observed when 2 equivalents of PhLi were used. It is important to note that firstly, using a larger excess of PhLi (2.5–3.0 equiv-alents) does not improve the yield of benzophenone imine (2 a), but produces small amounts of biphenyl and phenol as by-products; and secondly, that formation of the tertiary carba-mine (triphenylmethanamine) through double addition of PhLi to benzonitrile was not observed.[14] However, the most re-markable aspect of this reaction is that the use of inert-atmos-phere Schlenk techniques or low temperatures, that is, stan-dard reaction conditions for manipulating organolithium re-agents, is not required.

One-pot acidic hydrolysis[15] of 2a led to the formation of benzophenone (3 a) in an 83% yield under standard bench conditions (Table 1, entry 1). Thus, we envisioned that a modu-lar combination of the PhLi addition to nitriles in Gly with the in situ hydrolysis of the relevant imine should allow us to
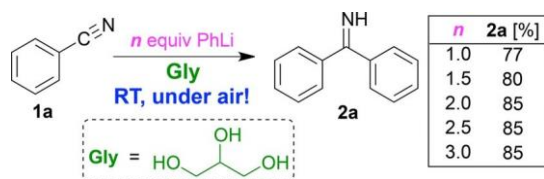
Scheme 2. Study of the addition reaction of PhLi to benzonitrile (1a) by em-ploying different stoichiometries in Gly as solvent (yields determined by GC analysis of reaction mixtures by using a calibration curve).

Table 1. Addition reaction of polar organometallic reagents (RM) to ben-zonitrile (1a) in different green solvents.[a]

Entry	RM[b]	Solvent	Ketone	Yield [%][c]
1	PhLi	Gly	3a	83
2	PhLi	1ChCl/2Gly	3a	71
3	PhLi	H2O	3a	79
4	PhLi	ethylene glycol	3a	53
5	PhLi	MeOH	3a	8
6	PhLi	Gly (without stirring)	3a	51
7	PhLi	Me-THF	3a	47
8	nBuLi	Gly	3b	22
9	PhMgBr	Gly	3a	traces
10	PhMgBr	Me-THF	3a	3

[a] Reactions were performed under air, at ambient temperature and using 0.5 g of the solvent and 0.5 mmol of benzonitrile (1a) was utilised throughout. [b] Commercial solution of PhLi (1.9 m in dibutyl ether), nBuLi (1.6 m in hexanes) and PhMgBr (1.0 m in THF) were used. [c] Yields deter-mined by ^{1}H NMR spectroscopy by using CH2Br2 as an internal standard.

design a straightforward, one-pot method to prepare a library of structurally diverse ketones under mild, simple and environ-mentally friendly reaction conditions (see Table 1 and Table 2).

Ketone 3a was obtained in comparable yields when using bulk Gly as a solvent and its chloride-based eutectic mixture 1 ChCl/2 Gly (83 and 71 % yield, respectively, entries 1 and 2, Table 1). It should be noted that benzonitrile (1 a) is sparingly soluble in both reaction media, and the reactions take place under heterogeneous conditions, when a completely immisci-ble ethereal solution of PhLi is added to a suspension of 1a in Gly. A similar scenario has been reported by Capriati and co-workers when using organolithium and Grignard reagents in heterogeneous aqueous media,[7] with addition reactions taking place "on water" conditions,[8] rather than in the reac-tion medium, preferentially furnishing the relevant addition products instead of the hydrolysis of the organometallic re-agent. "On water" reactions are thought to occur at the organ-ic/liquid water interface with water insoluble reactants.[8c] To try to verify this "on glycerol" assumption, we ran in parallel three sets of reactions under the previously optimised reaction conditions (2 equiv of PhLi, ambient temperature and under air). Thus, first we replace glycerol by the another protic medium (water, entry 3) in which benzonitrile is insoluble.[7b] Under these "heterogeneous" conditions, the expected ketone 3a could also be produced in good yields (79 %, entry 3), with-out observing the expected protonation of PhLi as a compet-ing process. Moreover and in the same line, we observed ex-perimentally a direct relationship between the solubility of benzonitrile in other protic and alcoholic reaction media [ethyl-ene glycol (EG) partially soluble; MeOH totally soluble] and re-action yield (53 and 8 %, respectively, entries 4 and 5), which suggests a key role for the solubility of the reactant in promot-ing these addition reactions. The ability of these alcohols to engage in hydrogen bonding should also be considered, with

that of MeOH being significantly more limited than those reported for Gly or water,[16] which can also favour the competing hydrolysis of PhLi over the addition process. Thus, using Me-THF as a solvent, in which 1a is completely soluble, under air and at ambient temperature, afforded 3a in a 47% yield (entry 7).

Further support for "on Gly" reactivity was found when PhLi addition to 1a was performed in Gly with no stirring. Previous reports have shown that the yields of "on water" reactions can be affected by stirring/agitation effects as they can influence the volume and surface area of the organic droplets.[8c] Under these conditions, the yield for 3a dropped to 51% (entry 6).

The reactivity of 1a with other polar organometallics (RLi or RMgX) under the optimised reaction conditions (2 equiv, ambient temperature, under air) was also investigated by using glycerol as solvent. In this sense, an aliphatic and more basic organolithium reagent (nBuLi, entry 8) yielded the expected butylated ketone 3b in a modest 22 % yield. Replacing Gly by water afforded 3b in a slightly improved 37 % yield. These findings contrast with recent work by Capriati and co-workers for additions of alkyl organolithiums (e.g., nBuLi) to nitriles under "on water" conditions, which in the presence of allyl Grignard reagents allows access to tertiary carbimines.[7b]

The less reactive Grignard reagent PhMgBr failed to produce 3a under the optimised reaction conditions (entry 9), suggest- ing that the higher polarity of Li@C bonds in RLi reagents (versus C@Mg bonds) is crucial for success in the addition pro- cess.[17] This lack of reactivity was also observed when using Me-THF under air at ambient temperature (entry 10). Remarka- bly, the reaction of PhLi with PhCN can also be scaled-up to 5 mmol scale (using 5 g of Gly as a solvent), yielding ketone 3a in a 87% yield (see Figure S12 in the Supporting Informa- tion for details).

Stimulated by these preliminary results, we next assessed the scope of this methodology by extending our studies to a range of nitriles (1 a–i) when using Gly or water as solvents. As shown in Table 2 and regardless of the solvent employed, in most cases, the nitriles tested led to the efficient and almost instantaneous (3 s) addition reaction with high chemoselectivi- ty, as only unreacted nitrile and the final ketone (3 a–j) were observed in the reaction crudes. Comparing the yields ob- served when using water and Gly as a solvent an interesting trend emerges. For liquid aromatic nitriles (entries 1–8, Table 2) excellent and comparable yields are observed for both reaction media (76–86 %). However, for solid nitriles (entries 9–16), greater ketone conversions are observed for water than for Gly. Thus, for example, using (p-OMe)C₆H₄CN formed 3f in a modest 32% yield in Gly versus 84 % in water (entries 9 and 10). This difference could be attributed to the different solubili-ties that these solid nitriles may display in the different sol- vents employed. Nevertheless, the results summarised in Table 2 indicate an excellent substrate scope and functional group tolerance, without observing other competing side reac-tions taking place under the conditions investigated. Steric ef-fects on the substitution of the nitrile do not seem to have a major role, observing comparable yields in both solvents when ortho-, meta- and para-tolunitrile were employed (entries 3–6

Table 2. Addition of PhLi to various nitriles (1a–i) on glycerol or water.[a]

| Entry	R@CN[b]	Product	Solvent	Yield [%][c]
1	Ph	3a	Gly	83
2	Ph	3a	H₂O	79
3	(m-Me)C₆H₄	3c	Gly	81
4	(m-Me)C₆H₄	3c	H₂O	82
5	(o-Me)C₆H₄	3d	Gly	87
6	(o-Me)C₆H₄	3d	H₂O	80
7	(o-F)C₆H₄	3e	Gly	76
8	(o-F)C₆H₄	3e	H₂O	86
9	(p-OMe)C₆H₄	3f	Gly	32
10	(p-OMe)C₆H₄	3f	H₂O	84
11	(p-Me)C₆H₄	3g	Gly	63
12	(p-Me)C₆H₄	3g	H₂O	90
13	(p-Br)C₆H₄	3h	Gly	24
14	(p-Br)C₆H₄	3h	H₂O	59
15	(2-CF₃-4-F)C₆H₃	3i	Gly	43
16	(2-CF₃-4-F)C₆H₃	3i	H₂O	76
17	n-hexyl	3j	Gly	60
18	n-hexyl	3j	H₂O	65

[a] Reactions were performed under air, at ambient temperature and using 0.5 g of the solvent. A commercial solution of PhLi (1.9 m in dibutyl ether) was added. [b] 0.5 mmol of the desired nitrile (1a–i) was utilised throughout. [c] Yields determined by ¹H NMR spectroscopy by using CH₂Br₂ as an internal standard.

and 11 and 12). The addition of PhLi to a purely aliphatic nitrile (hexanenitrile) furnished the aryl-alkyl-substituted ketone (1-phenylhexan-1-one, 3j) in either Gly (60%, entry 17) or water (65%, entry 18) whereas no addition product can be detected when acetonitrile is employed. This lack of reactivity is consis-tent with the high solubility of this nitrile in both solvents, pre-cluding "on water" or "on Gly" conditions.[18] It should be noted that contrastingly, hexanenitrile does not dissolve in Gly. Recent reports have revealed along with increasing yields, a considerable rate acceleration can be observed in "on water" reactions when water insoluble reagents are stirred vigorously for a short period of time in pure water.[7b,8] Although this "on water" catalysis is still to be fully understood, it has been pro-posed that trans-phase hydrogen bonding at water/organic in-terfaces, promoted by "dangling" OH groups can be responsi-ble.[19] Later studies by Beattie and McErlean and co-workers suggest an alternative explanation, attributing this "on water" effect to a proton transfer across the organic/water inter-phase.[20]

For Gly, studies using broadband vibrational sum frequency generation (VSFG) spectroscopy have shown that, unlike water, the surface of pure Gly is almost "flat" without the presence of "dangling" OH groups to protrude out into the vapour phase.[21] However, analysis of salty NaBr and NaI Gly solutions have revealed that bromide and iodide anions perturb the in-terfacial Gly organisation in a similar manner to that found in aqueous halide salt solutions, leading to an increase of the "dangling" OH groups at the interphase. This made us ponder whether if by using salty Gly solutions we could mimic the ketone conversions observed in water, focusing particularly on

the reaction of (p-OMe)C₆H₄CN and PhLi, which works well in water but poorly in neat Gly (84 % vs. 32 % yields for ketone 3 f, Table 2, entries 9 and 10; Scheme 3). Interestingly, when using a 1:8 NaCl to Gly molar ratio solution[22] as a reaction
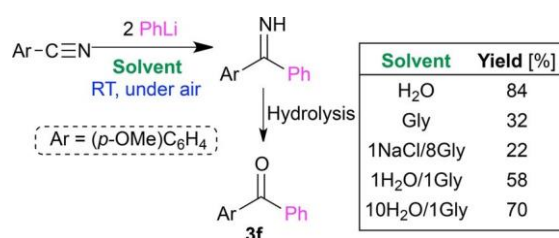
Scheme 3. Assessment of the formation of 3f in NaCl/Gly and H₂O/Gly mixtures. Yields determined by ¹H NMR spectroscopy by using CH₂Br₂ as an internal standard.

medium led to slightly lower conversions than when using neat Gly, affording 3f in a modest 22 % yield (see the Support- ing Information for details), suggesting that perturbing the interfacial Gly organisation does not seem to affect the efficiency of the addition process (Scheme 3). Further support was found when performing the addition of PhLi to PhCN in this salty Gly solution, which gave ketone 3a in a 76 %, only slightly lower than when using neat Gly (83 %, Table 2, entry 1).

For comparison, we also assessed this reaction by using H₂O/Gly mixtures for the reaction of (p-OMe)C₆H₄CN and PhLito form ketone 3 f. As shown in Scheme 3, using a 1:1 mixture gave 3f in an 58 % yield, which is greater than that observedin neat Gly but lower than in neat water. Contrastingly, using a 10 H₂O/1 Gly mixture led to the formation of 3f in an improved 70 % yield (see the Supporting Information for details). Although these differences could be related to the different dynamics of the complex hydrogen-bonding networks in thesemixtures,[23] the different solubilities of the solid nitrile (p- OMe)C₆H₄CN in these solvent systems may also be key.

Next, we extended this greener and air-tolerant protocol to other aryllithium reagents, containing both electron-donating [Me (entries 1 and 2); MeO (entries 5 and 6)] or electron-withdrawing [CF₃ (entries 7 and 8)] substituents (Table 3). Thus, benzonitrile (1 a) was chosen as the benchmark reagent for this study working under the previously optimised reaction conditions (2 equiv of RLi, ambient temperature, under air) with Gly or water as the reaction media. As previously ob- served in Table 2, addition reactions took place instantaneously (3 s) to benzonitrile, furnishing the non-symmetric diarylke- tones 3 c, k–m in good yields (43–95 %) and remarkable che- moselectivities, as no by-products were seen in the reaction crudes. In general, for these reactions, Gly appeared to be a su-perior solvent, with the most noticeable effect on the yield of3l, which decreases drastically from 93 % when using Gly to45 % in water (entries 5 and 6, Table 3).

Despite these similar performances in water and Gly, a key difference between these solvents is the greater resistance to- wards hydrolysis of ArLi in the latter. This was evident when PhLi was added to the solvent and allowed to stir for 15 s before introducing nitrile 1 a. Astonishingly, although only

Table 3. Addition of different aryllithium (ArLi) reagents to benzonitrile (1a) "on" glycerol or water.[a]

| Entry	ArLi[b]	Product	Solvent	Yield [%][c]
1	(m-Me)C₆H₄	3c	Gly	86
2	(m-Me)C₆H₄	3c	H₂O	79
3	(m-F)C₆H₄	3k	Gly	59
4	(m-F)C₆H₄	3k	H₂O	69
5	(o-OMe)C₆H₄	3l	Gly	93
6	(o-OMe)C₆H₄	3l	H₂O	43
7	[3,5-(CF₃)₂]C₆H₃	3m	Gly	79
8	[3,5-(CF₃)₂]C₆H₃	3m	H₂O	77

[a] Reactions were performed under air, at ambient temperature and using 0.5 g of the solvent and 0.5 mmol of benzonitrile (1a) was utilised throughout. [b] See the Experimental Section for the synthesis of ArLi. [c] Yields determined by ¹H NMR spectroscopy by using CH₂Br₂ as an internal standard.

traces of 3a were detected when water was employed, in Gly 3a is formed in a 74% yield (Scheme 4), which is comparable to that observed when the order of addition is reversed (83 %, Table 2, entry 1).
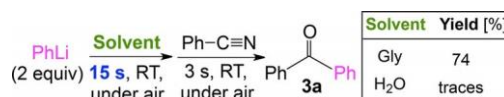
Scheme 4. Assessment of the formation of 3a in water and Gly when the order of addition of reagents is reversed. Yields determined by ¹H NMR spectroscopy by using CH₂Br₂ as an internal standard.

Intrigued by these findings, we pondered whether Gly could also be used as a solvent for the addition of aryllithiums to ke-tones under air, a reactivity that we have previously reported by using water and Gly-based DESs.[5a] Pleasingly, tertiary alco-hols 4 a–c were obtained in good yields (56–80 %) as the result of the chemoselective arylation of benzophenone, acetophe-none and trifluoromethyl acetophenone, respectively, when using PhLi (2 equiv) and bulk Gly as the reaction media (Scheme 5).
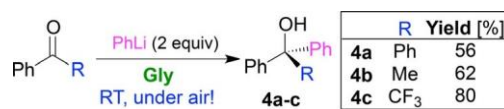
Scheme 5. Addition of PhLi to different ketones in Gly, at ambient tempera-ture and in the presence of air. Yields determined by ¹H NMR spectroscopy by using CH₂Br₂ as an internal standard.

Conclusions

We have demonstrated that, like water, Gly can function as an environmentally friendly reaction medium for the ultrafast and chemoselective addition of aryllithium reagents to nitriles

under standard bench reaction conditions (ambient temperature and under air), which for almost a century have been out of bounds in polar organometallic chemistry. Notably, working under heterogeneous conditions (as the starting nitriles are insoluble in Gly or water) allowed the smooth nucleophilic addition of organolithium reagents to nitriles either "on glycerol" or "on water", respectively. Moreover, the unprecedented use of Gly (a low-cost and renewable feedstock) in polar organometallic chemistry unlocks countless scenarios for developing more sustainable main-group-mediated organic syntheses.

Experimental Section

General procedure for the addition reactions of PhLi with nitriles in alternative solvents

Syntheses were performed under air and at room temperature. In a glass tube, the appropriate nitrile (0.5 mmol) was added to the corresponding alternative solvent (0.5 g) under air, followed by the addition of PhLi (1 mmol) at room temperature, and the reaction mixture was stirred for 2–3 s. The reaction was then stopped by addition of a saturated solution of the Rochelle salt (sodium potassium tartrate tetrahydrate). The reaction mixture was transferred to a round-bottom flask, 2 m HCl (5 mL) was added and heated at 100 8C for 30 min. After cooling down to room temperature, the reaction mixture was neutralised by addition of $NaHCO_3$ and the organic products were extracted with dichloromethane (3 V 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. Yields of the reaction crudes were determined by ^1H NMR methodology by using dibromomethane as an internal standard. The identity of obtained ketones 3a,[24] 3b,[25] 3c,[24] 3d,[24] 3e,[24] 3f,[24] 3g,[24] 3h,[24] 3j,[26] 3k,[27] 3l[24] and 3m[28] was assessed by comparison of their ^1H and ^{13}C NMR spectroscopic data with those reported in the literature. Compound 3i was isolated and fully characterised, see the Supporting Information for details. All reactions were done in triplicate to ensure good reproducibility of the obtained yields.

General procedure for the synthesis of aryllithium reagents

In addition to commercially available PhLi, other aryllithium reagents were tested as reagents that can undergo addition to benzonitrile. These were prepared under protective argon atmosphere by using standard Schleck techniques and solvent dried by heating to reflux over sodium benzophenone ketyl and then distilledunder nitrogen prior to use. To a diethyl ether solution of the chosen aryl iodide (6 mmol in 2.2 mL of Et_2O) at @78 8C, n-butyllithium (6 mmol, 1.6 m in hexanes) was added drop-wise. The reaction mixture was warmed up and stirred at room temperature for 2 h before it was used as a 1 m solution of aryllithium reagent for the addition reactions. The following additions were, as described above, performed under air in triplicate.

General procedure for the addition reactions of PhLi with ketones in glycerol

Syntheses were performed under air and at room temperature. In a glass tube, the appropriate ketone (0.5 mmol) was dissolved in glycerol (0.5 g) under air, to which PhLi (1 mmol) was added at room temperature, and the reaction mixture was stirred for 2–3 s. The reaction was then stopped by addition of a saturated solutionof the Rochelle salt (sodium potassium tartrate tetrahydrate) and

organic products were extracted with dichloromethane (3 V 5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. Yields of the reaction crudes were determined by ^1H NMR spectroscopy by using dibromomethane as an internal standard. The identity of obtained tertiary alcohols 4a,[29] 4b[30] and 4c[31] was assessed by comparison of their ^1H and ^{13}C NMR spectroscopic data with those reported inthe literature.

Comparison of the stability of phenyllithium in glycerol and water

Phenyllithium (1 mmol, 0.53 mL, 1.9 m solution) was added to glycerol or water (0.5 g) and stirred under air. After 15 s, benzonitrile (0.5 mmol, 0.051 g) was added under air at room temperature and the reaction mixture was stirred for 2–3 s. The reaction was then stopped by addition of a saturated solution of the Rochelle salt and the product was hydrolysed, isolated, identified and quantified as previously described.

[1] For an insightful frontier article on the pivotal role of organolithium chemistry, see: V. Capriati, F. M. Perna, A. Salomone, *Dalton Trans.* 2014, *43*, 14204.

[2] a) *The Chemistry of Organolithium Compounds* (Eds.: Z. Rappoport, I. Marek), Patai Series, Wiley, Chichester, 2004; b) J. Clayden, *Organolithiums: Selectivity for Synthesis*, Pergamon, Oxford, 2002.

[3] J. García-Álvarez, E. Hevia, V. Capriati, *Eur. J. Org. Chem.* 2015, 6779, and references therein.

[4] For recent reviews on DESs, see: a) M. Francisco, A. van den Bruinhorst, M. C. Kroon, *Angew. Chem. Int. Ed.* 2013, *52*, 3074; *Angew. Chem.* 2013, *125*, 3152 ; b) E. L. Smith, A. P. Abbott, K. S. Ryder, *Chem. Rev.* 2014, *114*, 11060; c) J. García-Álvarez, *Eur. J. Inorg. Chem.* 2015, 5147; d) D. A. Alonso, A. Baeza, C. Chinchilla, R. G. Guillena, I. M. Pastor, D. J. Ramón, *Eur. J. Org. Chem.* 2016, 612.

[5] a) C. Vidal, J. García-Álvarez, A. Hern#n-Gómez, A. R. Kennedy, E. Hevia, *Angew. Chem. Int. Ed.* 2014, *53*, 5969; *Angew. Chem.* 2014, *126*, 6079; b) L. Cicco, M. J. Rodríguez-Álvarez, F. M. Perna, J. García-Álvarez, V. Capriati, *Green Chem.* 2017, *19*, 3069.

[6] C. Vidal, J. Garc⎱a-]lvarez, A. Hern#n-Gómez, A. R. Kennedy, E. Hevia, *Angew. Chem. Int. Ed.* 2016, *55*, 16145; *Angew. Chem.* 2016, *128*, 16379.

[7] a) L. Cicco, S. Sblendorio, R. Mansueto, F. M. Perna, A. Salome, S. Florio, V. Capriati, *Chem. Sci.* 2016, *7*, 1192; b) G. Dilauro, M. Dell'Aera, P. Vitale, V. Capriati, F. M. Perna, *Angew. Chem. Int. Ed.* 2017, *56*, 10200; *Angew. Chem.* 2017, *129*, 10334– 10337. c) For related studies using DESs, see also: V. Mallardo, R. Rizzi, F. C. Sassone, R. Mansueto, F. M. Perna, A. Salo- mone, V. Capriati, *Chem. Commun.* 2014, *50*, 8655; d) F. C. Sassone, F. M. Perna, A. Salomone, S. Florio, V. Capriati, *Chem. Commun.* 2015, *51*, 9459.

[8] a) A. Chanda, V. V. Fokin, *Chem. Rev.* 2009, *109*, 725; b) R. M. Butler, A. G. Coyne, *J. Org. Chem.* 2015, *80*, 1809; c) R. N. Butler, A. G. Coyne, *Org. Biomol. Chem.* 2016, *14*, 9945.

[9] a) V. Pace, P. Hoyos, L. Castoldi, P. Dom⎱nguez de Mar⎱a, A. R. Alc#ntara, *ChemSusChem* 2012, *5*, 1369; b) J. Yang, J.-N. Tan, Y. Gu, *Green Chem.* 2012, *14*, 3304; c) D. M. Alonso, S. G. Wettstein, J. A. Dumesic, *Green Chem.* 2013, *15*, 584.

[10] The biodiesel industry produces a large excess of glycerol (ca. 100 kg of glycerol per ton of biodiesel): N. Rahmat, A. Z. Abdullah, A. R. Mo- hamed, *Renewable Sustainable Energy Rev.* 2010, *14*, 987.

[11] a) Y. Gu, F. J8rôme, *Green Chem.* 2010, *12*, 1127; b) A. E. D⎱az-]lvarez, J. Francos, B. Lastra-Barreira, P. Crochet, V. Cadierno, *Chem. Commun.* 2011, *47*, 6208; c) F. Chahdoura, I. Favier, M. Gómez, *Chem. Eur. J.* 2014, *20*, 10884.

[12] a) J. Francos, V. Cadierno, *Green Chem.* 2010, *12*, 1552; b) C. Vidal, J. Garc⎱a-]lvarez, *Green Chem.* 2014, *16*, 3515; c) M. Rodr⎱guez-Rodr⎱guez, E. Gras, M. A. Peric⁄s, M. Gómez, *Chem. Eur. J.* 2015, *21*, 18706; d) M. Ro- dr⎱guez-Rodr⎱guez, P. Llanes, C. Pradel, M. A. Peric⁄s, M. Gómez, *Chem. Eur. J.* 2016, *22*, 18247.

[13] Note that in conventional anaerobic organolithium chemistry this reac- tion produces iminolithium compounds with stacked ring structures, see: a) D. Barr, W. Clegg, R. E. Mulvey, R. Snaith, *J. Chem. Soc. Chem. Commun.* 1984, 79; b) D. Barr, W. Clegg, R. E. Mulvey, R. Snaith, K. Wade, *J. Chem. Soc. Chem. Commun.* 1985, 295; c) D. R. Armstrong, D. Barr, W. Clegg, R. E. Mulvey, R. Snaith, K. Wade, D. Reed, *J. Chem. Soc. Dalton Trans.* 1987, 1071.

[14] In contrast, the double addition of RLi/RMgX reagents to nitriles has been recently reported "in water" and "on water" conditions (see ref. [7 b]).

[15] See the Supporting Information for experimental and spectroscopic de- tails.

[16] J. A. Padró, L. Saiz, E. Gu⁄rdia, *J. Mol. Struct.* 1997, *416*, 243.

[17] A similar trend has been previously reported by us in the addition of RMgX to imines in different eutectic mixtures, ref. [6].

[18] Although, in our hands, formation of acetophenone, as the result of ad- dition PhLi to MeCN under the conditions of our study (H_2O or Gly as solvent, room temperature, under air), could not be detected, it should be noted that Capriati and co-workers have reported the sequential ad- dition of PhLi and allylMgCl in water to acetonitrile furnishing the rele- vant tertiary allyl amine in a remarkable 70 % yield, see ref. [7b].

[19] Y. Jung, R. A. Marcus, *J. Am. Chem. Soc.* 2007, *129*, 5492.

[20] a) J. K. Beattie, C. S. P. McErlean, C. W. Phippen, *Chem. Eur. J.* 2010, *16*, 8972; b) K. D. Beare, C. S. P. McErlean, *Org. Biomol. Chem.* 2013, *11*, 2452.

[21] Z. Huang, W. Hua, D. Verreault, H. C. Allen, *J. Phys. Chem. A* 2013, *117*, 6346.

[22] A. P. Abbott, C. D'Agostino, S. J. Davis, L. F. Gladden, M. D. Mantle, *Phys. Chem. Chem. Phys.* 2016, *18*, 25528.

[23] For a molecular dynamics simulation study on hydrogen bonding anal- ysis of glycerol aqueous solutions, see: C. Chen, W. Z. Li, Y. C. Song, J. Yang, *J. Mol. Liq.* 2009, *146*, 23.

[24] M. Li, C. Wang, H. Ge, *Org. Lett.* 2011, *13*, 2062.

[25] J. A. Murphy, A. G. J. Commeureuc, T. N. Snaddon, T. M. McGuire, T. A. Khan, K. Hisler, M. L. Dewis, R. Carling, *Org. Lett.* 2005, *7*, 1427.

[26] J. Ruan, O. Saidi, J. A. Iggo, J. Xiao, *J. Am. Chem. Soc.* 2008, *130*, 10510.

[27] A. T. Biju, F. Glorius, *Angew. Chem. Int. Ed.* 2010, *49*, 9761; *Angew. Chem.* 2010, *122*, 9955.

[28] C. J. Rohbogner, C. R. Diène, T. J. Korn, P. Knochel, *Angew. Chem. Int. Ed.* 2010, *49*, 1874; *Angew. Chem.* 2010, *122*, 1918.

[29] T. Maekawa, H. Sekizawa, K. Itami, *Angew. Chem. Int. Ed.* 2011, *50*, 7022; *Angew. Chem.* 2011, *123*, 7160.

[30] M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc.* 2006, *128*, 9998.

[31] J. R. White, G. J. Price, P. K. Plucinski, C. G. Frost, *Tetrahedron Lett.* 2009, *50*, 7365.

[32] The Fundacion BBVA accepts no responsibility for the opinions, state- ments and contents included in the project and/or the results thereof, which are entirely the responsibility of the authors.