Unprecedented Nucleophilic Additions of Highly Polar Organometallic Compounds to Imines and Nitriles Using Water as a Non-Innocent Reaction Medium

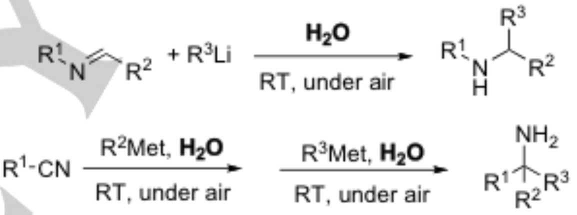
Giuseppe Dilauro,[†] Marzia Dell'Aera,[†] Paola Vitale, Vito Capriati,* and Filippo Maria Perna

Dedicated to Professor Roald Hoffmann on the occasion of his 80th birthday

Abstract: In contrast to classic protocols carried out under inert atmospheres with dry volatile organic solvents and often low temperatures, we report that the addition of highly polar organometallic compounds to non-activated imines and nitriles proceeds quickly, efficiently, and chemoselectively with a broad range of substrates at room temperature and under air with water as the only reaction medium, providing secondary amines and tertiary carbinamines with yields up to >99%. The significant solvent D/H isotope effect observed for the on-water nucleophilic additions of organolithiums to imines suggests that the on-water catalysis arises from proton transfer across the organic–water interface. The strong intermolecular hydrogen bonds between water molecules may play a key role in disfavouring protonolysis, which occurs extensively in other protic media such as methanol. This work lays the foundation for reshaping many fundamental s-block metal-mediated organic transformations in water.

The discovery and the introduction of organolithium and Grignard reagents in organic synthesis at the beginning of the twentieth century became, over the years, a beacon of opportunity to create thousands of new organic compounds by carbon–carbon bond formation because of the high polarity of their metal–carbon bonds.[1] The utilization of these reagents, however, typically requires strictly anhydrous and aprotic volatile organic solvents, inert atmospheres, and often low temperatures (–78 °C), owing to the notorious air- and moisture-sensitivity of s-block organometallic compounds.[1d]

The chemistry of polar organometallic compounds in unconventional, biorenewable reaction media (*e.g.*, "Deep Eutectic Solvents", DESs) has opened up new, intriguing, and unexpected opportunities in synthesis, not only from a "green" standpoint, but also from a mechanistic perspective.[2–5] Organic syntheses run at organic-liquid water interfaces with water-insoluble reactants (i.e., "on-water") are also a fascinating area of research.[6] Building on our recent findings on the nucleophilic addition of Grignard and organolithium reagents to carbonyl derivatives under "heterogeneous" conditions in water,[5c] we present the first successful addition of highly polar organometallic compounds at room temperature (RT) and under air to imines and nitriles *using water as the only reaction medium without further additives*, thereby crossing the considerable divide between traditionally allowed and textbook-prohibited reactions (Scheme 1). These routes provide access to secondary amines and tertiary carbinamines, which are often components of bioactive compounds, synthetic materials, and useful "building blocks" for natural products and active pharmaceutical ingredients (APIs).[7] An alternative, sustainable approach to amines has recently been established by Hevia and García-Álvarez by reacting organolithium reagents with imines and quinolines in choline-chloride-based DESs. A kinetic anionic activation of the alkylating reagent was suggested to take place with choline chloride, which favoured nucleophilic addition over competitive protonolysis.[4b]



Scheme 1. Organometallic nucleophilic additions to imines and nitriles using water, at RT and under air.

We elected to study the reaction between commercially available, water-insoluble aldimine **1a** and *n*-BuLi as a model system for the preparation of amine **2a** (Table 1). First, 1.4 equiv. of *n*-BuLi were rapidly spread over a suspension of **1a** (0.50 mmol) in water (1 mL) under air with vigorous stirring at RT to generate an emulsion (vortex). The mixture became orange red upon addition of the organolithium, and turned colourless after a few seconds. Dilution with 1 mL of cyclopentyl methyl ether, followed by filtration, evaporation, and chromatography of the resulting residue led to product **2a** with a 96% yield (Table 1, entry 1). Pleasingly, the reaction could also be scaled-up; by reacting 5.5 mmol of **1a** in 10 mL of water with 1.4 equiv. *n*-BuLi, amine **2a** formed in quantitative yield (>99%), and was isolated by simply evaporating the organic phase without further purification (Table 1, entry 2). Notably, due to the poor electrophilicity of the iminic carbon atom, organolithium additions hardly proceed in conventional ethereal or hydrocarbon solvents in the absence of additives, and are often plagued with competitive reduction, enolization, or coupling reactions.[8]

Recent reports have revealed that the yields and efficiencies of on-water reactions can be influenced by the volume and surface area of organic droplets, and thus by the physical mixing parameters (*e.g.*, stirring speeds, shaking, sonication).[9] When the organolithium addition was performed under gentle

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[*] Dr. Giuseppe Dilauro, Dr. Marzia Dell'Aera, Dr. Paola Vitale, Dr. Filippo M. Perna, Prof. Vito Capriati
Dipartimento di Farmacia-Scienze del Farmaco, Università di Bari "A. Moro", Consorzio C.I.N.M.P.I.S., Via E. Orabona 4, I-70125 Bari, Italy
E-mail: vito.capriati@uniba.it

[†] These authors contributed equally to this work.

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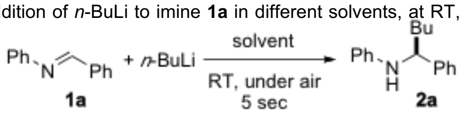
stirring so as to minimize the area of interface without mixing the organic and aqueous phases (i.e., static droplets) the yield of **2a** dropped to 66% (Table 1, entry 3).

Table 1. Addition of *n*-BuLi to imine **1a** in different solvents, at RT, and under air.[a]



Entry	Solvent	**2a** yield%[b]
1	H_2O (vortex)	96
2	H_2O (vortex)	>99[c]
3	H_2O (gentle stirring)	66
4	D_2O (vortex)	57
5	MeOH (vortex)	15
6	H_2O (vortex)	20%[d]

[a] Typical experimental conditions: *n*-BuLi (1.4 equiv.) was added at RT and under air to a suspension/solution of imine **1a** (0.50 mmol) in 1.0 mL of solvent. [b] Isolated yield. [c] Imine **1a** (5.5 mmol), 10 mL of H_2O. [d] To 1.0 mL of water, *n*-BuLi and imine **1a** were sequentially added at RT and under air.

On-water catalysis is not well understood.[6d,e] Jung and Marcus first proposed that on-water catalysis arises from *trans*-phase H-bonding by “dangling” (that is free, not H-bonded) OH groups at the water interface to H-bond acceptors in organic transition states.[10] Beattie and McErlean later proposed that a proton transfer across the organic-water interface could be the source of such phenomena.[11a] These authors provided compelling evidence for this hypothesis by measuring a strong solvent D/H isotope effect for on-water aromatic aza-Claisen rearrangements of allyl aryl amines.[11b]

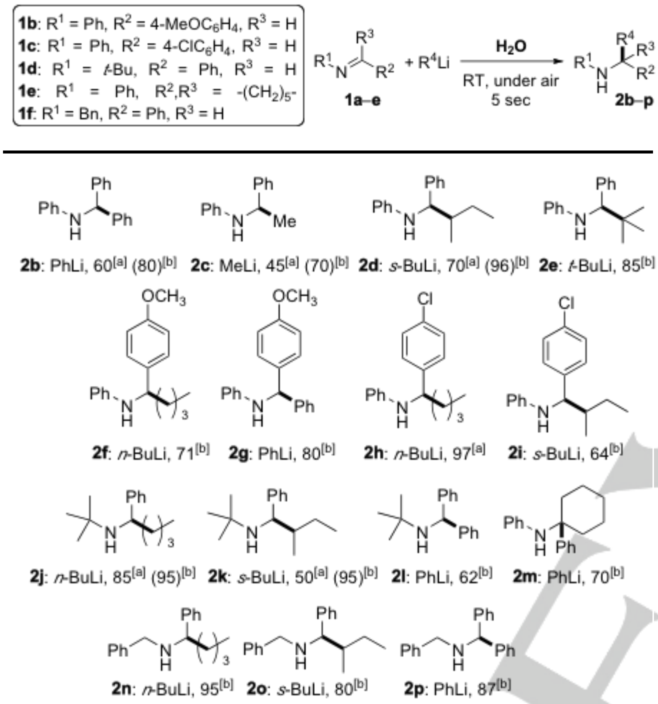
We recently posited that interfacial H-bonding to water-insoluble carbonyl compounds embedded at the organic-water interface may provide catalytic impetus for on-water nucleophilic additions promoted by Grignard and organolithium reagents. This was supported by low deuterium isotope values for on-H_2O and on-D_2O.[5c,6d,e] More basic nucleophilic sites in organic molecules, however, are known to facilitate proton transfer across the water organic interface.[6e] This postulate was experimentally surveyed in the addition of *n*-BuLi to **1a** by setting up another reaction identical in every respect to the one described above (Table 1, entry 1), but with D_2O as the aqueous phase. After 5 s, the reaction was worked up, and the product was isolated and quantified. Remarkably, a significant solvent deuterium isotope effect was detected: the yield of **2a** dropped considerably to 57% vs. 96% for the on-H_2O reaction (Table 1, entry 4). These reproducible data are consistent with a *proton transfer at the water-organic interface (cleavage of an O–D bond) in the rate-limiting step*, and thus with the active participation of water.[12] On the other hand, upon replacing water with MeOH, a higher degree of protonation was observed as the formation of **2a** was suppressed dramatically (15% yield) (Table 1, entry 5). The stronger intermolecular hydrogen bonds of water compared to those of MeOH may play a key role in shielding the organometallic reagent from competitive protonolysis.[5c] The more limited ability of MeOH to engage in intermolecular hydrogen bonds may also contribute to the less efficient activation of the azomethine moiety towards nucleophilic addition. Some experimental evidence suggests that protonolysis of organolithium compounds by protic media does not occur as rapidly as anticipated.[13] To investigate this aspect, in a challenging, seemingly counterintuitive experiment, we first spread *n*-BuLi (1.4 equiv.) over water (1 mL) and then added imine **1a** (0.55 mmol) after 5 s. Astonishingly, amine **2a** formed with a 20% yield (Table 1, entry 6). Thus, the water quenching was not instantaneous, and the organolithium had a sufficient lifetime (a few seconds) to add to the azomethine moiety.

The scope of suitable imine derivatives and commercially available organolithium reagents was explored (Table 2). To our delight, the optimized conditions for the synthesis of **2a** could be successfully applied to many combinations, indicative of the considerable generality of the reaction. For example, 1.4 equiv. of PhLi and **1a** provided amine **2b** with a 60% yield. Pleasingly, as similarly observed in the addition to carbonyl compounds,[5c] by increasing the amount of the organometallic reagent to 3 equiv., the final yield increased to 80%. The use of other aliphatic, commercially available organolithium reagents, ranging from MeLi to *s*-BuLi and even *t*-BuLi led to desired adducts **2c**–**e** in satisfactory yields (1.4 equiv.: 45–70%; 3 equiv.: 70–96%). When an aryl-substituted imine with an electron-donating group (**1b**) was used as a substrate, adducts **2f**,**g** could be isolated in 71–80% yields by employing 3 equiv. of *n*-BuLi or PhLi. A chloro-substituted arylimine (**1c**) was equally tolerated, and produced desired amines **2h**,**i** within good yields (64–97%) when reacted with *n*-BuLi (1.4 equiv.) and *s*-BuLi (3 equiv.). The formation of the latter adducts highlights further opportunities for subsequent functionalization by cross-coupling reactions. Sterically hindered *N*-*t*-butyl-substituted imine **1d** readily participated in the reaction, and delivered amines **2j**–**l** in 62–95% yields when 3 equiv. of *n*-BuLi, *s*-BuLi, or PhLi were used. Notably, enolizable cyclohexylidene imine **1e** also served as a competent reaction partner providing amine **2m** with a 70% yield upon reaction with PhLi (3 equiv.). An *N*-benzyl-substituted imine (**1f**) could also be used to produce **2n**–**p** at excellent yields of 80–95% with 3 equiv. of *n*-BuLi, *s*-BuLi, or PhLi. We also explored the effectiveness of using Grignard reagents. The addition of 1.4 equiv. of PhMgCl or *i*-PrMgCl·LiCl (turbo-Grignard reagent) to **1a** on water proved to be ineffective. When the highly reactive (allyl)MgCl was alternatively used, however, the expected *N*-(1-phenylbut-3-enyl)aniline (**2q**) could be isolated in reasonable yields (1.4 equiv.: 40%; 3 equiv.: 75%) (see SI). We did not investigate this type of reaction further.

Next, we examined the addition of organometallics to nitriles, using bulk water as the only reaction medium, aimed at preparing tertiary alkyl primary amines (termed carbinamines) via a two-step, one-pot procedure. Generally, this addition is limited to the first step, as the second one, involving the corresponding poor electrophilic metallated imines generated in the first step, is more challenging. In only a few isolated cases, it was reported that Grignard reagents add twice to nitriles in conventional solvents to form tertiary carbinamines, as in the case of allyl Grignard reagents with α-alkoxy nitriles.[14a,b] On the other hand, tetrahydropyridine derivatives were the main products when allyl

Grignard reagents were reacted with aromatic nitriles.[14c] The use of very harsh conditions, microwave heating, and Lewis acids such as titanium alkoxides, somewhat expanded the scope of the reaction so as to include two different organometallic nucleophiles and less reactive nitriles.[14d] Aside from some exceptions, however, chemical yields and selectivities were generally modest, and long reaction times (up to 24 h) were usually required for the second addition.[14e]

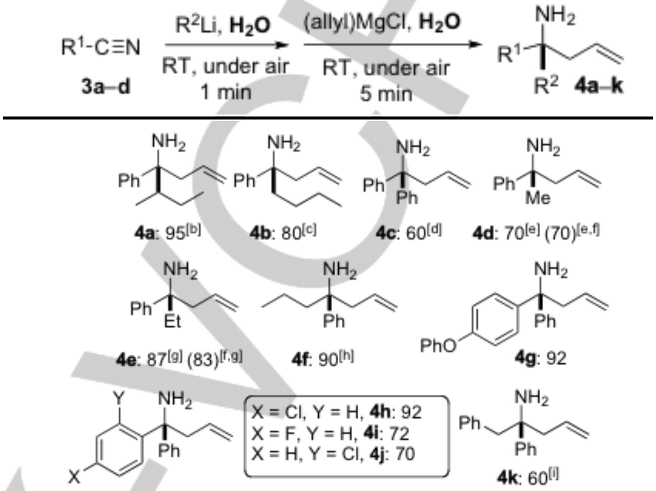
Table 2. Addition of organolithium reagents to imines **1a–f** on water, under air, and at RT, affording amine derivatives **2b–q**.



[a] 1.4 equiv. of R^4Li (isolated yields, %). [b] 3.0 equiv. of R^4Li (isolated yields, %).

We initiated our studies with poorly water-soluble benzonitrile (PhCN) (**3a**). **3a** (1 mmol) was suspended in 1 mL of water and stirred vigorously to generate an emulsion. When the aqueous mixture was treated with 3 equiv. of *s*-BuLi and 3 equiv. of *n*-BuLi after 1 min of stirring, a mixture of 2-methyl-1-phenylbutan-1-one (70%) and 1-phenyl-pentan-1-one (30%) was isolated with complete consumption of the starting material. Mindful of this observation, emphasis was then placed on the use of more reactive allyl Grignard reagents in combination with organolithiums. Pleasingly, when **3a** was treated under vigorous stirring with 3 equiv. of *s*-BuLi and 3 equiv. of (allyl)MgCl after 1 min in water, tertiary carbinamine **4a** was isolated with a 95% yield, whereas 2-methyl-1-phenylbutan-1-one formed at a less than 5% yield (by ^{1}H NMR analysis) (Table 3). When subjected to this two-step, one-pot protocol, assorted aliphatic and aromatic organolithium reagents such as MeLi, *n*-BuLi, PhLi, and EtLi (3 equiv.) afforded the corresponding allyl-substituted tertiary carbinamines **4b**–**e** in satisfactory yields (60–87%), with modest amounts of the corresponding ketones (17–35% yield) (Table 3). Benzonitrile derivatives with electron-donating (*p*-PhO), electron-withdrawing (*p*-Cl and *o*-Cl), or fluorine groups afforded adducts **4g**–**j** in 70–92% yields by employing 3 equiv. of either PhLi or (allyl)MgCl. To emphasize the versatility of the protocol, aliphatic substrates were also screened.

Table 3. Addition of organometallics to nitriles **3a**–**d** on water, at RT and under air affording tertiary carbamines **4a**–**k**.[a]



[a] Isolated yields (%). [b] 2-Methyl-1-phenylbutan-1-one also formed in less than 5% yield. [c] 1-Phenylpentan-1-one also formed with a 20% yield. [d] Benzophenone also formed with a 35% yield. [e] Acetophenone also formed with a 30% yield. [f] PhLi and (allyl)MgCl were sequentially added to MeCN or EtCN. [g] Propiophenone was also isolated with a 13–17% yield. [h] Butyrophenone also formed with a 10% yield. [i] Benzyl phenyl ketone also formed with a 40% yield.

When PhLi and (allyl)MgCl (3 equiv.) were added sequentially (time interval: 1 min) to a *solution* of acetonitrile (MeCN) (**3b**) (1 mmol) or propionitrile (EtCN) (**3c**) (1 mmol) or butyronitrile (PrCN) (**3d**) in water, the double nucleophilic addition again took place, thereby offering direct and complementary access to the corresponding tertiary allyl amines **4d**–**f** in 70–90% yields (Table 3). Thus, both in-water and on-water methodologies could be applied to the synthesis of tertiary carbamines.[6c] On the other hand, the yield of **4e** decreased dramatically to 12% upon sequential addition of PhLi (3 equiv.) and (allyl)MgCl (3 equiv.) to **3c** in MeOH (propiophenone was produced with a 88% yield). $PhCH_2CN$ could be converted into amine **4k** with a 60% yield when sequentially treated with PhLi and (allyl)MgCl (3 equiv.). Other Grignard reagents (*e.g.*, MeMgCl, EtMgCl, or PhMgCl) proved to be ineffective for this transformation.

In summary, nucleophilic addition of Grignard and organolithium reagents to imines and nitriles, *en route* to secondary amines and tertiary carbinamines, can be conveniently carried out *using bulk water as a privileged reaction medium*, working under air, at RT, with vigorous stirring. Although in-depth mechanistic studies are needed to unveil the intriguing role played by water, aqueous polar organometallic chemistry has potential to become an attractive and powerful tool in several other fundamental and applied organic processes.

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Keywords: azo compounds • Grignard reagents • nucleophilic addition • organolithiums • water chemistry

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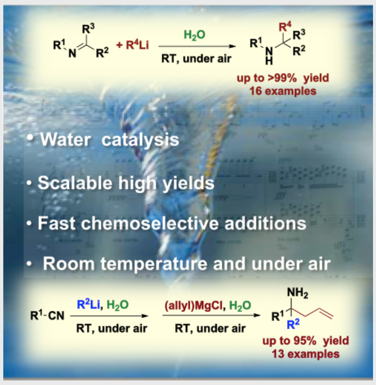
Symphony between organolithiums and water: The title reactions allow unprecedented access to secondary amines and tertiary carbinamines in very good yields using water as the only reaction medium. These reactions, which proceed quickly, smoothly, and chemoselectively at room temperature and under air, open exciting opportunities for using highly polar organometallics in other fundamental and applied transformations in aqueous media.



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