



# Introducing Water and Deep Eutectic Solvents in Organosodium Chemistry: Chemoselective Nucleophilic Functionalizations in Air

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Dedicated to Professor Dieter Seebach on the occasion of his 85<sup>th</sup> birthday

**Abstract:** Advancing the development of perfecting the use of polar organometallics in bio-inspired solvents, we report on the effective generation in batch of organosodium compounds, by the oxidative addition of a C–Cl bond to sodium, a halogen/sodium exchange, or by direct sodiation, when using sodium bricks or neopentylsodium in hexane as sodium sources. C(sp<sup>3</sup>)-, C(sp<sup>2</sup>)-, and C(sp)-hybridized alkyl and (hetero)aryl sodiated species have been chemoselectively trapped (in competition with protonolysis), with a variety of electrophiles when working “on water”, or in biodegradable choline chloride/urea or L-proline/glycerol eutectic mixtures, under hydrous conditions and at room temperature. Additional benefits include a very short reaction time (20 s), a wide substrate scope, and good to excellent yields (up to 98 %) of the desired adducts. The practicality of the proposed protocol was demonstrated by setting up a sodium-mediated multigram-scale synthesis of the anticholinergic drug orphenadrine.

## Introduction

Since the beginning of the 20<sup>th</sup> century, alkali-metal-mediated transformations have greatly contributed to the burgeoning field of synthetic organometallic chemistry, through the functionalization of a polarized carbon–metal bond with an electrophile.<sup>[1]</sup> In contrast to the well-established and developed organolithium chemistry,<sup>[2]</sup> organosodium chemistry (OC) has lagged behind, mainly because of the high reactivity and low thermostability of these organometallic species.<sup>[3]</sup> In some of the earliest

studies, organosodium compounds were referred to as simple intermediates in Wurtz reactions, and their direct preparation from sodium and organo-halides was believed impossible. It was only in 1933 that Gilman and Wright prepared 3-furylsodium (potassium) by reacting 3-iodofuran with a sodium-potassium alloy over a period of 2 weeks.<sup>[4]</sup> Bockmühl and Ehrhart were probably the first to prepare phenylsodium by reaction of sodium wire with chlorobenzene.<sup>[5]</sup>

The use of finely divided sodium (10 to 30 microns), in hydrocarbon media, later allowed for the preparation of other (hetero)arylsodium compounds.<sup>[6]</sup> The generation of such sodium dispersion (SD), however, has always proved to be somewhat troublesome, as it has required the metal fusion (105 °C), apparatus to have high-speed stirring motors (up to 18000 rpm), and effective temperature control.<sup>[7]</sup> Another downside aspect of OC is that organosodium compounds, owing to their saltlike character, neither readily dissolve in nonpolar solvents, nor show stability in ethereal solvents. Thus, despite the low-cost and the great availability of sodium in the Earth's crust and oceans, progress in OC has remained dormant for over 80 years.<sup>[8]</sup>

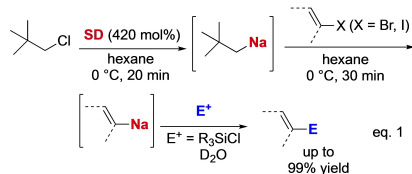
The grounds for a renaissance of OC in modern synthetic organic chemistry have recently been laid by Collum, Chiba, Knochel, Hevia, Takai and Asako, and Lu, who independently investigated the structure and reactivity of sodium amides,<sup>[9]</sup> amide-directed *ortho*- and lateral C–H sodiation,<sup>[10]</sup> sodiation of (hetero)arenes in a continuous flow,<sup>[11]</sup> benzylic arylation of toluenes,<sup>[12]</sup> organosodium-based catalytic cross-coupling reactions,<sup>[13]</sup> and ligand-catalyzed organosodium-mediated carbonyl methylenations,<sup>[14]</sup> respectively. Takai and Asako have also reported that in situ prepared neopentylsodium (from neopentyl chloride and reactive SD in paraffin oil at ≈26 wt % concentration) enables efficient halogen/sodium exchange reactions, and thus the obtainment of a variety of (hetero)aryl- and alkenylsodium compounds at 0 °C, which can undergo trapping reactions with silyl chlorides and D<sub>2</sub>O [Scheme 1A, Eq. (1)].<sup>[15]</sup> By accessing hexane-soluble (2-ethylhexyl)sodium from 3-(chloromethyl)heptane when using a sodium-packed-bed reactor under continuous flow conditions, Knochel and co-workers successfully generated arylsodium and laterally sodiated intermediates, which could be batch quenched with a variety of electrophiles [Scheme 1B, Eq. (2)].<sup>[16]</sup>

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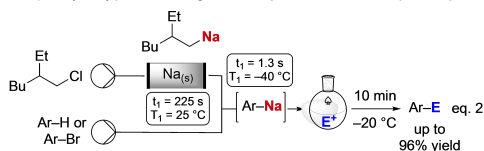
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## Previous work:

A. Halogen-sodium exchange between aryl/alkenyl halides and neopentylsodium using a sodium dispersion (SD) (ref. 15a)

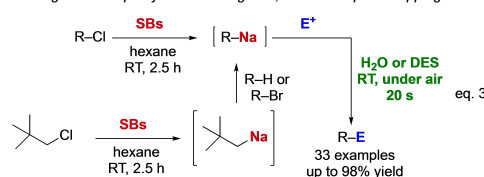


B. Br/Na exchange or directed metalation in continuous flow with (2-ethylhexyl)sodium using a sodium-packed-bed reactor (ref. 16a)



## This work:

C. Oxidative addition of a C-Cl bond to Na with sodium bricks (SBs), directed sodiation or Br/Na exchange with neopentylsodium using SBs, and electrophilic trapping "on water" or in DES in air



**Scheme 1.** Electrophilic trapping of sodiated organic species in batch, when using a sodium dispersion (A), in a continuous flow, when using a sodium-packed-bed reactor (B), in batch under air, "on water", or in DES, when using sodium bricks (C). RT = room temperature.

The progressive and successful use over the years of highly polar organometallic compounds of s- and d-block elements in protic, nature-inspired solvents (for instance, water, glycerol, and deep eutectic solvents, DESs) have been contributing to nurturing new catalytic and stoichiometric synthetic pathways, thereby advancing the knowledge in this intriguing field of research.<sup>[17]</sup> Building on our interest in developing a truly sustainable polar organometallic chemistry in water and in DESs,<sup>[17e,f,i,k,l,n,o]</sup> we herein disclose a general and simplified method for organosodium preparation in batch starting from cheap sodium bricks (SBs), showcasing that sodiated organic compounds (generated by the oxidative addition of a C-Cl bond to sodium, a halogen/metal exchange, or by direct deprotonation) can be successfully intercepted by a variety of electrophiles *i)* working "on water"<sup>[18]</sup> or in DES<sup>[19]</sup> at room temperature (RT) and under air, *ii)* with short reaction times (20 s), and *iii)* with a broad substrate scope, with the desired adducts isolated with good to excellent yields (up to 98%) [Scheme 1C, Eq. (3)].

## Results and Discussion

The initial investigations were conducted toward the preparation of *o*-sodiated anisole (**2**) by the oxidative addition of a C-Cl bond to sodium, when using *o*-chloroanisole (**1a**) and a commercially available SD (25 wt % concentration)<sup>[20]</sup> as the sodium source, according to the protocol of Takai and Asako.<sup>[13]</sup> To this end, SD (2.2 equiv) was added to a solution of **1a** (0.39 mmol) in dry hexane (1.5 mL) under N<sub>2</sub>,

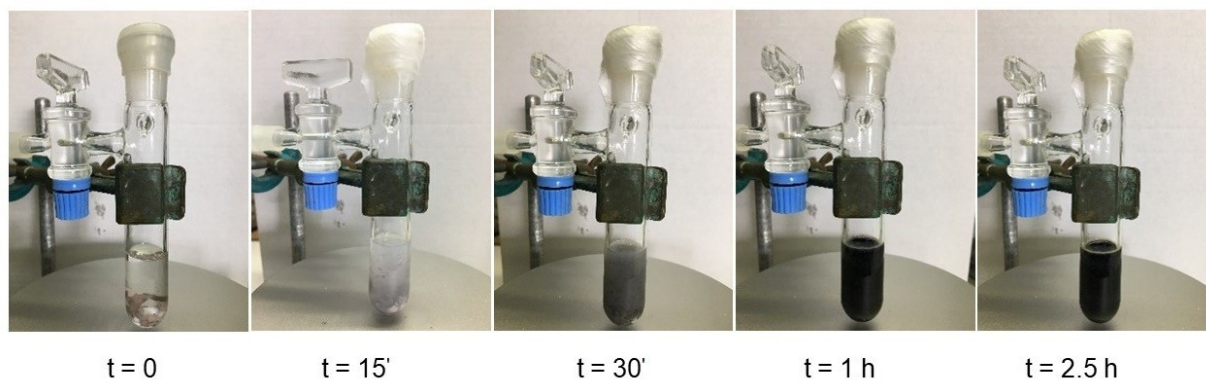
and the corresponding dispersion was kept under magnetic stirring at 0 °C. After 20 min, this dispersion was rapidly spread with a syringe over a suspension of PhCHO (**3a**) (0.2 mmol) in deionized water (1 mL, pH 6.0), and under air, with vigorous stirring at RT, to generate an emulsion (vortex).<sup>[17f,i,o]</sup> After the extraction with cyclopentyl methyl ether (CPME),<sup>[21]</sup> the analysis of the mixture revealed the formation of the desired adduct **4a** (41 % yield), along with a mixture of by-products, among which benzyl alcohol, benzoic acid, and benzyl ether (Table 1, entry 1). We envisaged that the presence of a residual sodium dispersion might be responsible for the formation of the above by-products.<sup>[22]</sup> After settling the sodium suspension for 2 min, before taking the supernatant, the yield of **4a** increased up to 81 % (Table 1, entry 2). The SD was then replaced by SBs (6.4 mmol), that is to say, with small pieces of sodium that were cut off from sodium lumps, which were first washed with hexane (2 mL), and then immediately added to dry hexane (4 mL) under an inert atmosphere in a Schlenk tube with a magnetic stirrer. After adding substrate **1a** (1.6 mmol), the mixture was left stirring at RT, and the consumption of **1a** was constantly monitored. The color gradually got darker over time up to pitch black (Figure 1). After 2.5 h, the stirring was halted, the excess sodium was allowed to settle at the bottom of the Schlenk tube (1 min), and the dark supernatant jelly-like suspension (1.8 equiv, 0.9 mL) was rapidly added in one portion to a suspension of **3** (0.2 mmol) in water (1 mL), under vigorous stirring at RT,

**Table 1:** Sodiation of **1** and electrophilic trapping of **2** with PhCHO (**3a**) in different solvents and conditions, under air.<sup>[a]</sup>

Reaction scheme showing the sodiation of **1** (X = Cl, Br, I) with Na source in hexane at 2.5 h, RT, yielding **2** (Na). **2** then reacts with PhCHO (**3a**) in solvent for 20 s, RT under air, yielding **4a**.

Entry	Na source	Solvent	<b>4a</b> yield [%]
1	SD <sup>[b,c]</sup>	H <sub>2</sub> O	41 <sup>[d]</sup>
2	SD <sup>[b,c]</sup>	H <sub>2</sub> O	81 <sup>[e]</sup>
3	SBs <sup>[c,f]</sup>	H <sub>2</sub> O	82 <sup>[e]</sup>
4	SBs <sup>[f,g]</sup>	H <sub>2</sub> O	17 <sup>[d]</sup>
5	SBs <sup>[f,h]</sup>	H <sub>2</sub> O	24 <sup>[d]</sup>
6	SBs <sup>[c,i]</sup>	H <sub>2</sub> O	91 <sup>[e]</sup>
7	SBs <sup>[c,i]</sup>	ChCl/urea	83 <sup>[e]</sup>
8	SBs <sup>[c,i]</sup>	Pro/Gly	94 <sup>[e]</sup>
9	SBs <sup>[c,i]</sup>	Gly	46 <sup>[d]</sup>

[a] Reaction conditions: 1.0 g DES, or 1 mL deionized H<sub>2</sub>O; 0.2 mmol of **3a**; SD: 2.2 equiv; SBs: 4.0 equiv; ChCl/urea (1:2 mol mol<sup>-1</sup>); L-proline (Pro)/Gly (1:2 mol mol<sup>-1</sup>); RT = room temperature; entries 2–9: the sodium suspension was settled for 1–2 min (see main text). [b] 1.5 mL hexane, 0.39 mmol of **1a**; sodiation temperature and time: 0 °C, 20 min. [c] **1a**. [d] Yield determined by <sup>1</sup>H NMR analysis of the crude reaction mixture in the presence of the internal standard CH<sub>2</sub>Br<sub>2</sub>. [e] Yield of isolated product. [f] 1.6 mmol of **1a** in 4 mL hexane (0.4 M hexane solution), 1.8 equiv (0.36 mmol, 0.9 mL) of **2**. [g] **1b**. [h] **1c**. [i] 1.6 mmol of **1a** in 2.7 mL hexane (0.6 M), 1.8 equiv (0.36 mmol, 0.60 mL) of **2**.



**Figure 1.** Sodiation of **1a** over time starting from a suspension of sodium bricks in hexane.

and under air. Adduct **4a** could be isolated in an 82 % yield (Table 1, entry 3).

Upon replacing hexane with other solvents (e.g., toluene, THF, 2-MeTHF, CPME) the yield of **4a** was suppressed dramatically (up to 16%; see Supporting Information), polycyclic aromatic hydrocarbons (e.g., triphenylene) being the main byproducts in the case of ethereal solvents.<sup>[23]</sup> The corresponding aryl bromide and iodide (**1b**, **c**) proved to be less effective as the yield of **4a** dropped to 17 and 24 %, respectively (Table 1, entries 4, 5). After many screenings (see Supporting Information), the optimal reaction conditions were found when 1.8 equiv (0.60 mL) of a 0.6 M hexane suspension of **2** (1.6 mmol in 2.7 mL) were used in the reaction with **3a**, which provided adduct **4a** with a 91 % yield (Table 1, entry 6). At this point, it must be noted that by quickly adding a hexane suspension of **2** (1.8 equiv, 1.6 M) to a solution of **3a** (0.2 mmol) in hexane (1 mL), under N<sub>2</sub>, the addition reaction slackened off considerably, with **4a** forming in up to 20 % yield after a 20 min reaction time, whereas 40 % of **3a** remained unreacted (<sup>1</sup>H NMR analysis). Working with no additional solvents (neat conditions), the yield of **4a** was even lower (12 %, 20 min under N<sub>2</sub>), with **3a** being recovered in 70 % yield (<sup>1</sup>H NMR analysis). Thus, the rapid one-shot addition of sodiated arene to a suspension of **3a** in water, when vigorously stirred at RT, and under air, was crucial for the success of the reaction.

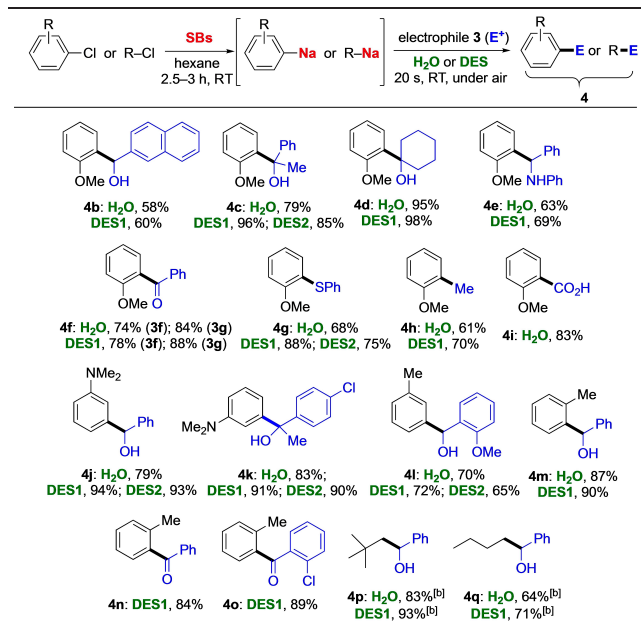
Although water and DESs share many physicochemical properties (e.g., non-flammability, thermal stability, negligible vapor pressure, strong hydrogen-bond network),<sup>[19]</sup> they sometimes offer complementary performances as far as the reactivity of organometallic compounds is concerned.<sup>[17i,n,o]</sup> Upon switching water for some representative DESs [e.g., choline chloride (ChCl)/glycerol (Gly) (1:2 and 1:3 molar ratios), ChCl/urea (1:2), L-proline (Pro)/Gly (1:3), D-sorbitol/ChCl (1:1), L-lactic acid/ChCl (2:1), ChOAc/urea (1:2), Gly/FeCl<sub>3</sub>·6H<sub>2</sub>O (1:3), D-fructose/urea (3:2 w/w)], the best yields of **4a** were achieved with the ChCl/urea (83 %) and Pro/Gly (94 %) eutectic mixtures (Table 1, entries 7, 8) (see Supporting Information) On the other hand, by changing the solvent to pure Gly, the yield of **4a** dropped to 46 % (Table 1, entry 9). A possible alkali-

metal effect was also investigated. To this end, a 0.52 M solution of *o*-lithiated anisole was prepared by subjecting **1b** (0.65 mmol) to a bromo-lithium exchange with *n*-BuLi (0.65 mL, 2.0 M in hexanes) in hexane (0.6 mL) at 0 °C for 10 min.<sup>[24]</sup> After an additional stirring at RT for 20 min, 1.6 equiv (0.61 mL) of the resulting solution were rapidly spread out over a suspension of **2a** (0.2 mmol) either in water (1 mL) or in a ChCl/urea mixture (1:2 mol mol<sup>-1</sup>) (1.0 g), while working at room temperature, under air and vigorous stirring. Adduct **4a** again formed in good yields: 84 % in water and 86 % in DES (<sup>1</sup>H NMR analysis).

With these satisfactory conditions in place, we focused our attention on the generality of this process, by exploring the scope of the reaction, both as regards the substrate and the electrophile. When using aryl chloride **1a** as the model, the nucleophilic addition of the resulting arylsodium species **2** to 2-naphthaldehyde (**3b**), acetophenone (**3c**), enolizable cyclohexanone (**3d**) and *N*-benzylideneaniline (**3e**), led to satisfactory yields of the adducts **4b–e**, both in water (58–95 %) and DESs (60–98 %) (Table 2). The reaction of **2** with the Weinreb amide *N*-methoxy-*N*-methylbenzamide (**3f**) afforded the aromatic ketone **4f** in a 74–78 % yield, when working in water or in Pro/Gly. The yield of **4f** could be increased up to 88 % when **2** was reacted with benzonitrile (**3g**) in Pro/Gly, after hydrolysis of the crude product on silica gel. The nucleophilic substitution of **2** on diphenyl disulfide (**3h**) and CH<sub>3</sub>I (**3i**) also proceeded smoothly, thereby providing aryl sulfide **4g** and *o*-methylanisole (**4h**) in very good yields [**4g**: 68 % in water, 75–88 % in DES; **4h**: 61 % in water, 70 % in Pro/Gly]. *o*-Anisic acid (**4i**) could be isolated in an 83 % yield by the reaction of **2** with solid CO<sub>2</sub> (**3j**) in water (Table 2).

Our second task was to expand the nucleophile scope. The oxidative addition reaction of the C–Cl bond of 3-chloro-*N,N*-dimethylaniline (**1d**) to sodium with SBs, followed by the addition of the corresponding sodiated species (1.8 equiv) to a suspension of **3a** or 4-chlorobenzaldehyde (**3k**) in water/DES, cleanly afforded the adducts **4j** and **4k** in remarkable yields (water: 79–83 %; DES: 90–94 %). 3-Chlorotoluene (**1e**) and 2-chlorotoluene (**1f**) could also be easily sodiated and reacted with 2-methoxybenzaldehyde (**3l**) and **3a** to give diaryl secondary alcohols **4l,m** in a 70–

**Table 2:** Oxidative addition reactions of C–Cl bonds of organochlorides to sodium with sodium bricks, at room temperature, and in hexane, followed by trapping reactions with electrophiles **3** “on water”, or in DES, under air.<sup>[a]</sup>



[a] Yield of isolated product; suspension concentration: 1.6 mmol Ar(R)Cl in 2.7 mL hexane (0.6 M); SBs: 6.4 mmol; sodiated species: 1.8 equiv (0.36 mmol, 0.60 mL); electrophile: 0.2 mmol; 1.0 mL deionized water (pH 6.0) or 1.0 g DES [DES1 Pro/Gly (1:2 mol mol<sup>-1</sup>); DES2: ChCl/urea (1:2 mol mol<sup>-1</sup>)]; RT=room temperature; SBs: sodium bricks. [b] Sodiation time: 3 h; temperature: 0 °C.

87% yield in water and a 65–90% yield in DES. Impressively, the nucleophilic acyl substitution of both benzoyl chloride (**3m**) and 2-chlorobenzoyl chloride (**3n**) by *o*-sodiated toluene chemoselectively provided the benzophenone derivatives **4n,o** in an 84–89% yield in Pro/Gly with effective suppression of the notorious over-addition reaction, which usually takes place when using organometallic reagents of the s-block elements. Of note, trapping reactions were successful also when using solid electrophiles such as **3b, 3e**, and **3l**.

Neopentyl chloride (**1g**) and even the sensitive 1-chlorobutane (**1h**) with  $\beta$ -hydrogens proved to be competent reaction partners as well, and their sodiated derivatives could be intercepted by **3a** to give the alkyl-aryl secondary alcohols **4p,q** in a 64–83% yield in water and a 71–93% yield in Pro/Gly (Table 2). Unfortunately, some aryl chlorides [e.g., *p*-chloroanisole, 1-chloro-4-(trifluoromethyl)benzene] did not undergo any oxidative addition reaction of their C–Cl bonds to Na when using SBs under the above conditions. We, thus, investigated alternative sodiation approaches.

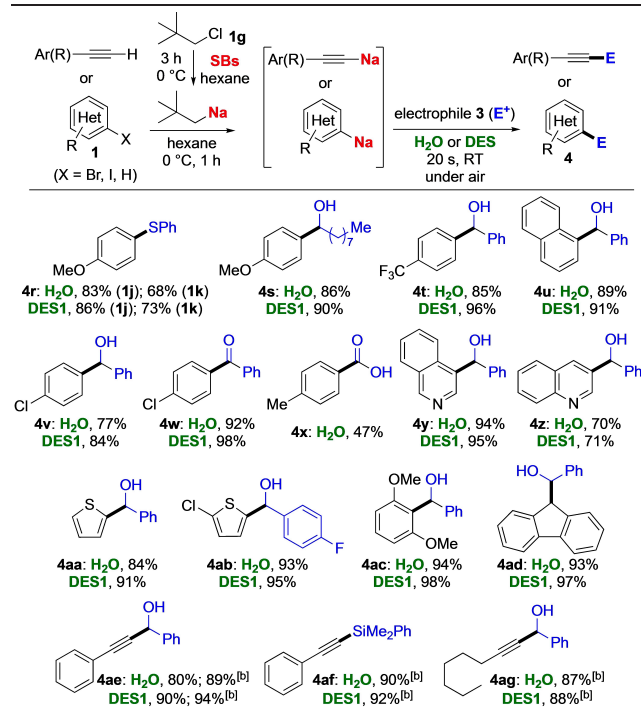
Inspired by the work of Takai and Asako,<sup>[15a]</sup> we investigated the ability of neopentylsodium, when prepared from **1g** and SBs (rather than using finely dispersed sodium), to induce the halogen-sodium exchange reaction on aryl halides. To this end, **1g** (1.6 mmol) was added to a suspension of SBs (6.4 mmol) in hexane (2.7 mL) (0.6 M

hexane suspension), and the resulting mixture was stirred for 3 h at 0 °C. Again, the color progressively darkened to pitch black. Then, *p*-chloroanisole (**1i**) (1.6 mmol) was added, and the mixture was additionally stirred at 0 °C for 1 h. After this time, the stirring was halted, the excess sodium was allowed to settle for 1 min, and the black supernatant suspension (1.8 equiv, 0.36 mmol, 0.60 mL) was rapidly added to a suspension of **3h** (0.2 mmol) in water (1 mL), under vigorous stirring at RT, and under air. No reaction took place. The <sup>1</sup>H NMR analysis of the crude reaction mixture revealed unreacted **1i**. This is consistent with the poor reactivity of **1i** also towards neopentylsodium. Pleasingly, upon switching to *p*-bromoanisole (**1j**), the desired phenyl sulfide **4r** formed in an 83% yield in water and an 86% yield in Pro/Gly (Table 3).

Slightly lower yields of **4r** (water: 68%; Pro/Gly: 73%) were achieved starting from *p*-iodoanisole (**1k**) as the substrate. Sodiated anisole from **1j** was also trapped with nonanal (**3o**) to give adduct **4s** in an 86% yield in water and a 90% yield in Pro/Gly (Table 3).

Therefore, this procedure's scope was explored to include a variety of (hetero)aryl bromides. 1-Bromo-4-(trifluoromethyl)benzene (**1l**), 1-bromonaphthalene (**1m**), 1-bromo-4-chlorobenzene (**1n**) underwent a chemoselective Br/Na exchange with neopentylsodium to give, upon reac-

**Table 3:** Br(I)/Na exchange of aryl bromides (iodides), and deprotonation reactions induced by neopentylsodium in hexane, followed by trapping reactions with electrophiles “on water”, or in DES, under air.<sup>[a]</sup>

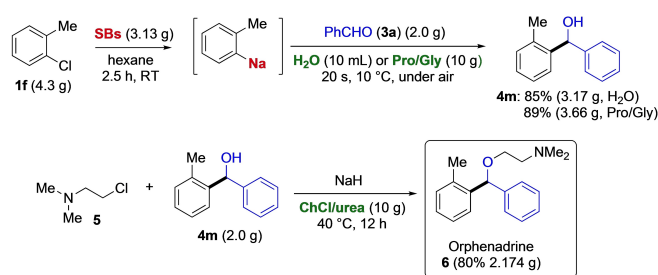


[a] Yield of isolated product; suspension concentration: 1.6 mmol **1g** in 2.7 mL hexane (0.6 M); SBs: 6.4 mmol; 1.6 mmol ArBr(H); sodiated species: 1.8 equiv (0.36 mmol, 0.60 mL); electrophile: 0.2 mmol; 1.0 mL deionized water (pH 6.0) or 1.0 g DES1 [Pro/Gly (1:2 mol mol<sup>-1</sup>)]; [b] Sodiated species generated by a direct deprotonation with SBs; RT=room temperature; SBs: sodium bricks.

tion with **3a** or **3g**, the adducts **4t–w** in a 77–92 yield in water, and in up to a 98 % yield in Pro/Gly. The sodiation of 4-bromotoluene (**1o**), followed by a reaction with **3j** in water, led to the isolation of *o*-toluic acid (**4x**) in a 47 % yield. The exchange procedure could also be successfully extended to heteroaromatic compounds. Indeed, 4-bromoisoquinoline (**1p**), 3-bromoquinoline (**1q**), 2-bromothiophene (**1r**) and 2-bromo-5-chlorothiophene (**1s**), after being subjected to the Br/Na exchange, and reacted with carbonyl electrophiles [**3a** or 4-fluorobenzaldehyde (**3p**)], afforded the anticipated functionalized heterocycles **4y–4ab** in a 70–94 % yield in water and a 71–95 % yield in Pro/Gly. Neopentylsodium was also enlisted to promote a directed metalation at C2 in 1,3-dimethoxybenzene (**1t**) and a lateral metalation in fluorene (**1u**) to produce the adducts **4ac** (94–98 % yield) and **4ad** (93–97 % yield), respectively, after quenching with **3a** (water and Pro/Gly).

Nucleophilic acetylides are commonly prepared from terminal alkynes and strong bases, such as carbanions (mainly organolithium, organomagnesium and organozinc reagents), metalated amides (e.g., LDA, KHMDS), and alkoxides/hydroxides (*t*-BuOK, CsOH). Their generation from alkylsodiums, and their use as nucleophiles for C–C bond forming reactions, is underdeveloped in the literature. In this respect, we have ascertained that direct sodiation of both aromatic and aliphatic terminal alkynes [phenylacetylene (**1v**), 1-octyne (**1w**)] can also be smoothly carried out either by using neopentylsodium, or by a suspension of SBs in hexane, in accordance to the above-described protocol. Quenching reactions with **3a** or phenyldimethylsilyl chloride (**3q**) provided the adducts **4ae–4ag** in an 80–90 % yield in water, and an 88–94 % yield in Pro/Gly (Table 3). Unfortunately, either the direct sodiation of *N,N*-diisopropylaniline or the Br/Na exchange on 3-bromopyridine with neopentylsodium were unsuccessful.

The robustness and the practicality of the above methodologies was assessed by the multigram-scale synthesis of orphenadrine (**6**), which is an anticholinergic chiral drug, whose racemate is used to treat muscle pain, and to help motor control in Parkinson's disease.<sup>[25]</sup> Under the best conditions of Table 1 (entries 6,8), 2-chlorotoluene (**1f**) (4.3 g, 34 mmol) was first subjected to an oxidative addition of the C–Cl bond to sodium triggered by a suspension of SBs (3.13 g) in dry hexane (56.7 mL), while working at RT. The corresponding sodiated species (1.8 equiv, 33.84 mmol, 56.4 mL) was then added with a syringe, over 1 min under air, to a vigorously stirred suspension of **3a** (2.0 g, 18.8 mmol) in water (10 mL) or in Pro/Gly (10 g), while cooling the reaction mixture with a water-bath (10 °C). The desired secondary alcohol **4m** was isolated in an 85 % yield (3.17 g), when working in water, or in an 89 % yield (3.66 g), when using DES. Finally, a suspension of alcohol **4m** (2 g, 10.1 mmol) and 2-chloro-*N,N*-dimethylethan-1-amine (**5**) in ChCl/urea (10 g) was carefully treated with NaH (20.2 mmol), and the resulting mixture was left under stirring at 40 °C for 12 h. After conventional work-up (see Supporting Information), compound **6** was isolated in an 80 % yield (2.174 g) (Scheme 2). Typical metrics applied at First Pass, according to the CHEM21 Metrics Toolkit



**Scheme 2.** Two-step synthesis of orphenadrine (**6**) by trapping *o*-sodiated anisole with **3a**, “on water”, or in DES, and under air, followed by the functionalization of **4m** with amino alcohol **5** in ChCl/urea.

developed by Clark et al.,<sup>[26]</sup> have also been calculated for the two-step water/DES (ChCl/urea)-based synthetic procedure of orphenadrine (Scheme 2): reaction mass efficiency (RME) 22.3, atom economy (AE) 63.7, optimum efficiency (OE) 35, and process mass intensity (PMI) 51.2 g g<sup>-1</sup>, with the E-factor value being 34.6. These values are in line with those obtained in the synthesis of other active pharmaceutical ingredients (APIs) using environmentally responsible/nature-inspired solvents.<sup>[27]</sup> Calculated production costs of **6**, with reference to raw materials only, are 2.6 €/g (for details, see Supporting Information).<sup>[28]</sup>

## Conclusion

In conclusion, we have reported that C(*sp*<sup>3</sup>)-, C(*sp*<sup>2</sup>)-, and C(*sp*)-hybridized organosodium compounds can be effectively generated in batch by the oxidative addition of a C–Cl bond to sodium, a halogen/Na exchange, or by direct sodiation, when using a suspension of sodium bricks or neopentylsodium in hexane at RT. The rapid one-shot addition of such sodiated organic species to a suspension of the electrophile in water, or in environmentally friendly eutectic mixtures (ChCl/urea or Pro/Gly), under vigorous stirring at RT, and under air, is key for trapping them in a short time (20 s) and chemoselectively with a variety of electrophiles (carbonyl compounds, imines, disulfides, alkyl iodides, Weinreb amides, acyl chlorides, nitriles, solid CO<sub>2</sub>) to furnish valuable functionalized derivatives, in good to excellent yields (up to 98 %). A two-step multigram-scale synthesis of the anticholinergic drug orphenadrine (overall yield: up to 71 % in DESs) is also reported, and some metrics typical of the First Pass CHEM21 Metrics Toolkit and production costs have been calculated.

Reactions of polar organometallic compounds of s-block elements taking place across the “oil-water/DES” interface may represent an example of *compartmentalization* in organic synthesis, as recently suggested by Seebach.<sup>[29]</sup> “Interface-rich aqueous systems (IRAS)” are indeed known to promote and guide chemical reactions.<sup>[30]</sup> However, an interplay of factors represented by complex dynamic equilibria and the aggregation states of the organometallic species involved, catalytic effects at the organic/water interface<sup>[18]</sup> and strong H-bonded networks, may be responsible either for the acceleration these s-block-metal-medi-

ated reactions undergo in unconventional reactions media like water and hydrophilic DESs or for making protons less available for protonolysis processes. Water, in particular, is known to promote H-transfer reactions and catalysis, and does have a unique H-bonding property and a unique surface structure that cannot be mimicked by any other alcohol molecule.<sup>[18f,31]</sup> Remarkably, charge transfer interactions between water and oil molecules have been demonstrated to take place through weak C–H...O H bonds, and have also been found to be responsible for their stabilization. As a result, the H-bonding network is stronger at the oil-water interface than at the air–water interface.<sup>[32]</sup>

The aptitude of water to behave as a ligand for alkali metal cations cannot be overlooked either when discussing the reactivity of the corresponding organometallic complexes in water-containing media. The presence of LiX (X = Cl, Br, Me) in lithium amide mixed aggregates, for example, has been found to be responsible for the introduction of a waterproof-type character in the corresponding complexes,<sup>[33]</sup> while the synthesis of intriguing water-containing and water-stable reactive organopotassium compounds has also been recently reported by Stalke and co-workers.<sup>[17g,h]</sup> After almost sixty years, some thought-provoking questions raised by Avery A. Morton on the *electrophilic* character of hydrocarbon insoluble organosodium compounds should give us pause for reflection.<sup>[34]</sup>

Detailed quantum chemical computations may be surely of help in future supporting studies. Recent investigations performed by Koszinowski, for example, on the gas-phase reactivity of ethylzincate ions toward protonolysis have disclosed that, despite their higher basicity, the zinc-bound ethyl groups of these complexes are protonated significantly less efficiently than their hydroxy counterparts, because of the higher intrinsic barrier associated with the proton transfer.<sup>[17r]</sup>

The routine use of organoalkali reagents in solvents that are safer, renewable, and recyclable, with no need of cryogenic conditions or protection from moisture, not only has tangible benefits on the environment, but also includes simplicity of operations, easy set ups, and fast (and often clean) reactions. Moreover, with respect to Grignard reagents, which are usually prepared in volatile and flammable ethereal solvents, stable (or relatively stable) suspensions of organosodium reagents can also be obtained by simply reacting cheap alkyl and aryl chlorides with sodium or even by direct sodiation in inert hydrocarbon media, thereby making the whole procedure suitable for scaling up processes for industrial purposes. Further investigations in organic synthesis on the use of organosodium reagents across water and DES are under way in our laboratory, and the results will be reported in due course.

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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