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Water and Sodium Chloride: Essential Ingredients for Robust and Fast Pd-catalysed Cross-Coupling Reactions between Organolithiums and (Hetero)aryl halides

Giuseppe Dilauro, Andrea Francesca Quivelli, Paola Vitale, Vito Capriati,* and Filippo Maria Perna

Dedication ((optional))

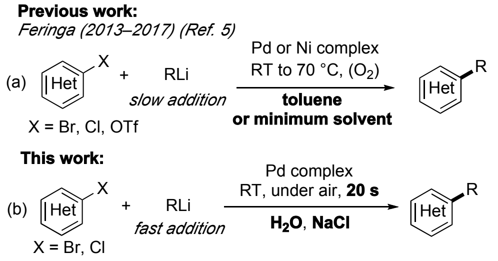
Abstract: *Direct palladium-catalysed cross-couplings between organolithiums and (hetero)aryl halides (Br, Cl) proceed fast, cleanly and selectively at room temperature in air, with water as the only reaction medium and in the presence of NaCl as a cheap additive. Under optimised reaction conditions, a water-accelerated catalysis is responsible for furnishing Csp^3–Csp^2, Csp^2–Csp^2, and Csp–Csp^2 cross-coupled products, competitively with protonolysis, within a 20 s reaction time, in yields of up to 99%, and in the absence of undesired dehalogenated/homocoupling side-products even if it starts from challenging secondary organolithiums. It is worth noting that the proposed protocol is scalable and the catalyst and water can easily and successfully be recycled up to 10 times, with an E-factor as low as 7.35.*

Selective formation of carbon-carbon bonds via transition metal-catalysed cross-coupling reactions had revolutionised the field of organometallic chemistry in the 70s, leading to three Nobel Prizes shared by nine individuals during the period 2001–2010.[1] The straightforward conversion of readily available organolithium compounds into cross-coupling products has long represented a challenge because of the high reactivity of these organometallic reagents.[2] The direct metal-catalysed stereospecific synthesis of olefins from vinyl halides and alkyllithiums was first reported in 1975 by Murahashi: inert atmosphere, long reaction time, toxic and volatile organic compounds (VOCs) (benzene), and Pd(0) compounds used in stoichiometric amount were strictly required.[3] It was not until 2010 that Yoshida and co-workers documented the first integrated Br-Li exchange of aryl bromides with *n*-BuLi with a selective, faster Muharashi coupling with other aryl bromides (and then with vinyl halides) in a flow microreactor.[4]

The Muharashi coupling has been recently revisited by Feringa and co-workers who reported optimised protocols for performing direct cross-coupling of alkyl-, alkenyl-, and (hetero)aryllithium reagents with a variety of aryl and alkenyl (pseudo)halides as electrophilic partners catalysed by either palladium or nickel complexes.[5] To avoid the notorious lithium-halogen exchange and homocoupling side reactions, the key factors were (a) the use of a non-polar solvent (toluene) or solventless conditions in combination with a Pd-catalyst containing bulky electron rich ligands [e.g., Pd/P(t-Bu$_3$)$_3$], and (b) the *slow addition* of a (diluted) solution of the organolithium reagent to the reaction mixture.[5a–g] Rapid cross-couplings of organolithiums with a range of aryl bromides were also achieved in toluene at room temperature (RT) by purging the mixture with pure oxygen, which favoured the *in situ* generation of active palladium nanoparticles (Scheme 1a).[5h]

The use of highly polar organometallic compounds of s-block elements in environmentally benign, bio-inspired protic solvents (water, glycerol, the so-called deep eutectic solvents, DESs) represents one of the most formidable challenges in the field of organometallics.[6] Recent years, however, have witnessed the flourishing of *greener* and selective polar organometallic and catalytic methodologies truly compatible with nature-based solvents like DESs[7] and water.[8]

We herein disclose that Pd-catalysed direct cross-coupling reactions can be efficiently and cleanly realized by a *fast addition* of organolithium compounds to a variety of (hetero)aryl halides (Br, Cl) by working under "on water" conditions and in the presence of NaCl as an additive, with the expected adducts being isolated in good to excellent yields (up to 98%) and with a broad substrate scope (Scheme 1b). It is to be noted that these processes (a) are run at RT and under air, and (b) end within 20 s.



Scheme 1. Direct cross-coupling reactions between organolithiums and (hetero)aryl halides (a) in toluene or minimum solvent, (b) "on water", in the presence of NaCl, at RT and under air.

As a part of our program that is aimed at exploring the boundaries of metal-,[7e–h,8h] organo-,[9a,b] and bio-catalysis[9c,d] when using unconventional solvents, we became initially eager to investigate the usefulness of DESs[10] as sustainable reaction media for direct cross-coupling reactions between organolithiums and aryl halides.

We decided to study the C*sp*^{3}–C*sp*^{2} cross-coupling reaction between *n*-BuLi (2.0 M in cyclohexane) and 1-bromonaphthalene **1a** (0.2 mmol) as a model system for the preparation of adduct **2aa** using Pd[P(t-Bu)$_3$]$_2$ (5 mol%) as a catalyst. Unsatisfactory results in terms of conversion and/or selectivity were obtained in DESs formed between choline chloride (ChCl) and urea or glycerol (Gly) even with an excess of *n*-BuLi (3 equiv) (Table 1, entries 1,2). However, the only side product isolated was the dehalogenated naphthalene **3aa**,

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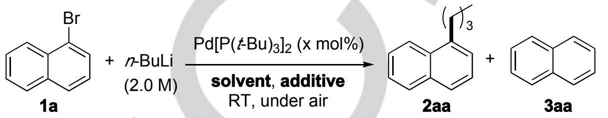
presumably arising from a competing β-hydride elimination/olefin dissociation pathway rather than from a Br-Li exchange as in the absence of the Pd-catalyst, only the starting aryl bromide was quantitatively recovered.[5d] Upon changing the hydrogen bond donor to ethylene glycol (EG), oxalic acid (OxA), L-lactic acid (LA) or malic acid (MA), the ratio **2aa**:**3aa** could only be improved up to 2:1 (Table 1, entries 3–6). In all cases studied, *n*-BuLi was rapidly added in one portion to the mixture of catalyst and **1a**, which were pre-mixed for 10 min. During this time, the catalyst slowly changed its colour from yellow to dark orange. A turn of the catalyst (Pd[P(*t*-Bu)$_3$]$_2$) solution in toluene to red was similarly observed by Feringa upon purging the mixture with molecular oxygen. This was attributed to the formation of an active form of the catalyst.[5h]

There is nowadays an increasing interest in developing coupling reactions using more environmentally friendly solvents. For instance, as for palladium-catalysed transformations, water has been shown to boost catalysis by promoting the migratory insertion and by accelerating the often rate-determining oxidative addition step and the displacement of labile ligands.[11] Thus, we switched to water as the solvent. When *n*-BuLi (3 equiv) was rapidly added in one portion to a suspension of **1a** (0.2 mmol) and Pd-catalyst in deionized water (1 mL, pH 6.0) under air with vigorous stirring at RT to generate an emulsion (vortex), an almost 1:1 mixture of **2aa** and **3aa** was isolated, but with a quantitative conversion (Table 1, entry 7). This time, by lowering the pH to 2.0 with HCl, a 2:1 mixture in favour of **2aa** was obtained, the overall conversion yield being 92% (Table 1, entry 8). However, when H_2SO_4 was used in place of HCl (pH = 2) the formation of **2aa** was suppressed dramatically (15% yield) (Table 1, entry 9). Thus, when using water, we anticipated that the chloride ion would play a key role in favouring the cross-coupling reaction.

A detailed mechanistic rationalization of the beneficial effect of halide ions on palladium catalysis has been provided by Bäckvall, Amatore, Jutand, and others.[12a–e] In particular, detailed DFT calculations and theoretical analysis performed by Shaik and co-workers have shown that an "apparently innocuous additive" such as a chloride ion may have a strong impact on the catalytic cycle triggered by a Pd(0)L$_2$ (L = phosphine) complex by forming an anionic complex while keeping a small P–Pd–P angle, which is a prerequisite for a low activation barrier to oxidative addition[12d] Recently, the formation and the role played by Pd^0 and Pd^{II} ate complexes in cross-coupling reactions have been thoroughly investigated by Koszinowski and co-workers via spectroscopic/spectrometric studies.[12f,g] By running the on-water coupling reaction in the presence of 3 equiv of either LiCl or the cheapest NaCl as an additive, adduct **2aa** formed in 98% yield as a sole product (Table 1, entries 10,11). To our delight, the effectiveness of such a cross-coupling was still maintained (**2aa**: 98%) with 1.1 equiv *n*-BuLi, 1 equiv NaCl, and at a loading of the catalyst as low as 2.5 mol% (Table 1, entry 12). Most importantly, it took only 20 s at RT to achieve full conversion with a turnover frequency of 14.54 × 10^3 h^{-1} (see Supporting Information). By decreasing the amount of NaCl up to 10 mol%, however, the **2aa**:**3aa** ratio became 70:15 (85% conversion). Thus, working under heterogeneous conditions, the concentration of NaCl solution is important. Notably, the rate of addition of the organolithium reagent was also of utmost importance; the yield of **2aa** dropped considerably to 45% when *n*-BuLi (1.1 equiv) was added dropwise to the reaction mixture (Table 1, entry 13) (see Supplementary Movies). Finally, we also ascertained that the presence of dissolved oxygen in water was crucial to speed up the reaction most probably by generating an active form of the catalyst.[5h] Indeed, when water was first deoxygenated with the freeze-pump-thaw cycling technique and argon purging, **2aa** could be isolated in 32% yield (Table 1, entry 14).

Table 1. Pd-catalysed cross-coupling of 1-bromonaphthalene **1a** with *n*-BuLi in different solvents, at RT, and under air.[a]



Entry	Solvent	Additive	Conv. (%)	**2aa**:**3aa**[b]
1	urea/Gly[c,d]	–	12	3:9
2	ChCl/Gly[c,d]	–	89	20:69
3	EG/ChCl[c,d]	–	Full	54:46
4	OxA/ChCl[c,d]	–	82	53:29
5	LA/ChCl[c,d]	–	90	55:35
6	MA/ChCl[c,d]	–	60	60:30
7	H_2O (pH 6)[c,d]		Full	55:45
8	H_2O (HCl, pH 2)[c,d]	–	92	61:31
9	H_2O (H_2SO_4, pH 2)[c,d]	–	15	>98:<2[e]
10	H_2O (pH 6)[c,d]	LiCl (3 equiv)	Full	>98:<2[f]
11	H_2O (pH 6)[c,d]	NaCl (3 equiv)	Full	>98:<2[f]
12	H_2O (pH 6)[g,h]	NaCl (1 equiv)	Full	>98:<2[f]
13	H_2O (pH 6)[g,h,i]	NaCl (1 equiv)	45	>98:<2[j]
14	H_2O (pH 6)[g,h,k]	NaCl (1 equiv)	32	>98:<2[l]
15	MeOH[g,h]	NaCl (1 equiv)	Full	<2:>98[f]

[a] Reaction conditions: 1.0 g DES or 1 mL deionized H_2O per 0.2 mmol of **1a**; Gly/ChCl (2:1, mol mol^{-1}); urea/ChCl (2:1, mol mol^{-1}); EG/ChCl (3:1, mol mol^{-1}); OxA/ChCl (3:1, mol mol^{-1}); LA/ChCl (3:1, mol mol^{-1}); MA/ChCl (1:1, mol mol^{-1}). To a pre-mixed (10 min) suspension of aryl bromide **1a** and the Pd-catalyst in DES or H_2O, *n*-BuLi was quickly added at RT and under air; reaction time: 20 s. [b] Ratio determined by ^{1}H NMR analysis of the crude reaction mixture in the presence of the internal standard CH_2Br_2. [c] *n*-BuLi: 3 equiv. [d] Pd-catalyst: 5 mol%. [e] 15% isolated yield. [f] 98% isolated yield. [g] *n*-BuLi: 1.1 equiv. [h] Pd-catalyst: 2.5 mol%. [i] *n*-BuLi was added in 10 min at RT and under air. [j] 45% isolated yield. [k] The mixture was deoxygenated, and the reaction was run under argon. [l] 32% isolated yield.

Upon replacing water with MeOH, only the dehalogenated product **3aa** was quantitatively recovered (Table 1, entry 15). The latter reasonably formed further to a fast β-hydride elimination process as no reaction was observed in this solvent in the absence of the Pd-catalyst. Further screening of catalysts were unsuccessful (see Supporting Information).

With these optimised conditions in place, we evaluated the reaction scope by reacting a variety of (hetero)aryl halides (**1**)

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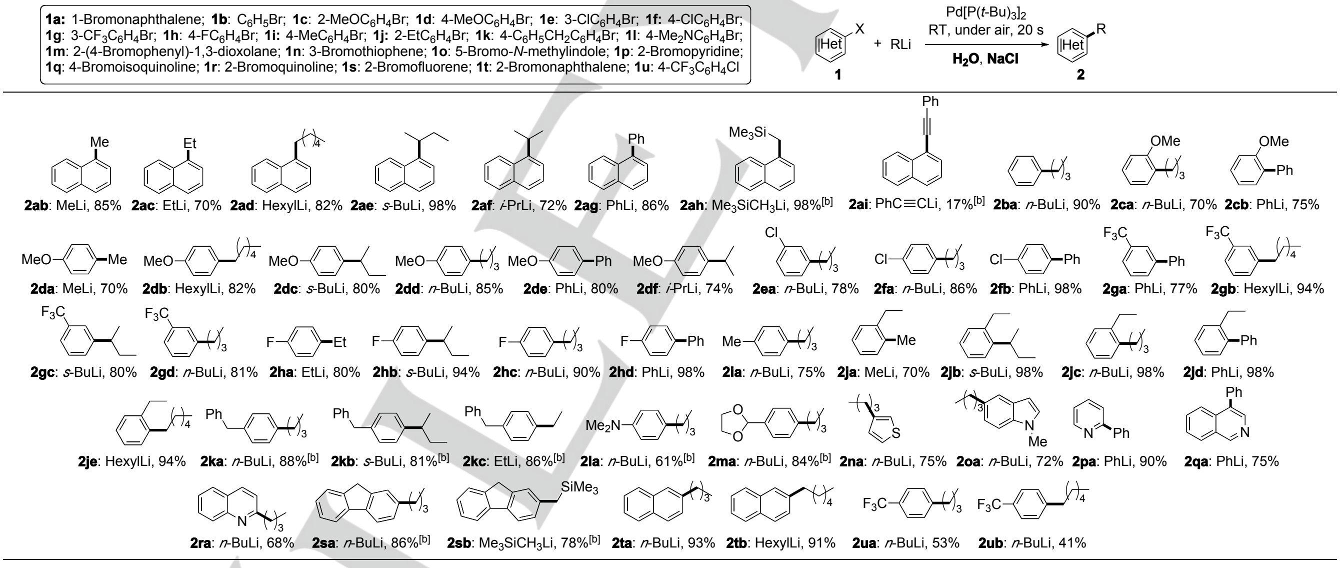
with organolithium reagents (Table 2). Using 1-bromonaphthalene **1a** as our standard, commercially available aliphatic and aromatic organolithium reagents, ranging from MeLi to EtLi, HexylLi, *s*-BuLi, *i*-PrLi PhLi and Me_3SiCH_2Li led the desired coupling products **2ab**–**2ah** with high selectivities and satisfactory yields (70–98%). Of note, it was reported that, when working under solventless conditions, secondary alkyllithiums such as *i*-PrLi and *s*-BuLi were found to only give dehalogenation products.[5g] The C*sp*-C*sp*^{2} coupling between **1a** and (phenylethynyl)lithium (2.2 equiv) also provided the expected adduct **2ai**, albeit in 17% yield. Unsubstituted aryl bromides (**1b**) or decorated with an electron-donating group (MeO) at the *ortho*- (**1c**) or *para*-position (**1d**) provided adducts **2ba**, **2ca**, **2cb**, and **2da**–**2df** in 70–90% yield. Aryl bromides bearing electron-withdrawing groups at the *meta*- and *para*-positions, such as chlorine (**1e**,**f**) and the trifluoromethyl group (**1g**) also effectively participated in the process, delivering adducts **2ea**, **2fa**, **2fb**, and **2ga**–**2gd** in very good yields (77–98%). The presence of a fluorine atom (**1h**) was equally tolerated and produced valuable products **2ha**–**2hd** at excellent yields of 80–98%. Assorted aryl derivatives with "neutral" substituents (methyl, ethyl, benzyl) (**1i**–**k**), a tertiary amino group (**1l**), an acetal moiety (**1m**), electron-rich [3-bromothiophene (**1n**), 5-bromo-*N*-methylindole (**1o**)] and electron-deficient [2-bromopyridine (**1p**), 4-bromisoquinoline (**1q**), 2-bromoquinoline (**1r**)] heterocycles could be efficiently cross-coupled as well to afford the expected adducts **2ia**, **2ja**–**2je**, **2ka**–**2kc**, **2la**, **2ma**, **2na**, **2oa**, **2pa**, **2qa**, and **2ra** in 61–98% yield. 2-Bromofluorene (**1s**) and 2-bromonaphthalene (**1t**) also served as competent reaction partners, delivering products **2sa**, **2sb**, **2ta** and **2tb** in 78–93% yield. Under the above conditions, cross-couplings with aryl chlorides proceeded smoothly only in the presence of electron-withdrawing groups (**1u**), although in moderate yields (**2ua**, **2ub**: 41–53%), whereas functional group tolerance could not be extended to carbonyl derivatives, nitrile, carboxylic acid and ester moieties. The coupling between 1.1 equiv of *n*-BuMgCl or (allyl)MgCl or *i*-PrMgCl·LiCl with **1a** proved to be ineffective. The catalyst and water could be recycled easily. As for the synthesis of **2aa** (Table 1, entry 12), once the stirring was stopped after the 20 s reaction time, VOCs introduced with *n*-BuLi were removed under reduced pressure, leaving the product **2aa** inside the reaction mixture. Then, upon addition of new, fresh reagents, the catalyst and water could be successfully re-used for further reaction runs. The catalyst retained optimum activity over ten cycles, the overall yield of product **2aa** being 97% (357 mg by adding 0.2 mmol substrate each cycle). The associated E-factor for the recycling process was 7.35 (see Supporting Information for details). Finally, we have also carried out a gram scale coupling of **1a** (4.83 mmol, 1 g) with *n*-BuLi (1.1. equiv) in 5 mL water. The reaction proceeded uneventfully at room temperature in air and resulted in the formation of **2aa** in 99% (883 mg) isolated yield.

Table 2. Pd-catalysed cross-coupling between (hetero)aryl halides **1** and organolithium reagents on water, at RT and under air.[a]



[a] Isolated yield; 0.2 mmol **1** in 1 mL deionized water (pH 6.0), 1 equiv. NaCl, 1.1 equiv RLi, 2.5 mol% Pd-catalyst. [b] 2.2 equiv RLi.

To summarize, a practical and scalable protocol for performing direct and fast (20 s reaction time) Pd-catalysed C*sp*^{3}–C*sp*^{2}, C*sp*^{2}–C*sp*^{2}, *and* C*sp*–C*sp*^{2} cross-coupling reactions between organolithiums and a variety of (hetero)aryl halides, at RT and under air, and using bulk water as a non-innocent reaction medium and NaCl as a cheap additive, has been developed. Efforts towards improving functional group tolerance are underway and will be reported in due course.

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Keywords: organolithium compounds • cross-coupling reactions • water chemistry • deep eutectic solvents • sustainable chemistry

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Water chemistry

Layout 1:

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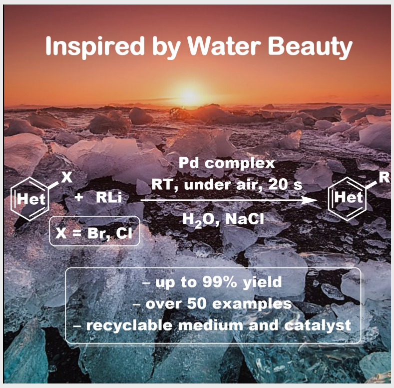
Salt water heals everything! Water with added NaCl was a very effective reaction medium for performing direct and fast (within 20 s) Pd-catalysed cross-coupling reactions between organolithiums and a variety of (hetero)aryl halides, at room temperature and under air. Catalyst and water recyclability and reusability were added advantages of the proposed protocol.



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Water and Sodium Chloride: Essential Ingredients for Robust and Fast Pd-catalysed Cross-Coupling Reactions between Organolithiums and (Hetero)aryl halides

Layout 2:

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((Insert TOC Graphic here))

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