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## Cross-Coupling Reactions

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## Scalable Negishi Coupling between Organozinc Compounds and (Hetero)Aryl Bromides under Aerobic Conditions when using Bulk Water or Deep Eutectic Solvents with no Additional Ligands

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In memory of Professor Victor Snieckus

**Abstract:** Pd-catalyzed Negishi cross-coupling reactions between organozinc compounds and (hetero)aryl bromides have been reported when using bulk water as the reaction medium in the presence of NaCl or the biodegradable choline chloride/urea eutectic mixture. Both  $C(sp^3)$ - $C(sp^2)$  and  $C(sp^2)$ - $C(sp^2)$  couplings have been found to proceed smoothly, with high chemoselectivity, under mild conditions (room temperature or 60°C) in air, and in competition with protonolysis. Additional benefits include very short reaction times (20 s), good to excellent yields (up to 98%), wide substrate scope, and the tolerance of a variety of functional groups. The proposed novel protocol is scalable, and the practicability of the method is further highlighted by an easy recycling of both the catalyst and the eutectic mixture or water.

he Negishi coupling (NC) represents a versatile and valuable Ni- or Pd-catalyzed cross-coupling reaction of organozinc compounds with various halides or pseudo-halides to forge new carbon-carbon bonds between the sp<sup>3</sup>, sp<sup>2</sup>, or sp carbon atoms.<sup>[1]</sup> Because of their higher functional group tolerance when compared to polar organometallic compounds of the s-block elements (e.g., Grignard and the organolithium reagents), the low-cost of preparation, and low toxicity, these organozinc reagents have found common use in the fields of natural products or drug motifs<sup>[2]</sup> and of advanced electronic, optical, electrochemical, and magnetic materials.<sup>[3]</sup> However, owing to their high reactivity (due to their strong basic character that often results in C-Zn bond protonolysis), organozincs remain air and moisture sensitive reagents, so their coupling reactions have been traditionally carried out by

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using rigorously aprotic and dry volatile organic compounds (VOCs), and under an inert atmosphere.

Increasing environmental awareness has pressured chemists, both in academia and in industry, to become more proactive in addressing public concerns that are related to the environmental effects of reagents, products, and solvents during their use and as waste, and to drive the field of synthetic chemistry toward more green practices.<sup>[4]</sup> In this vein, the past decade has witnessed a flourish in the number of papers dealing with transition metal-catalyzed cross-coupling reactions run in less environmentally impactful reaction media, such as bio-based solvents [e.g., glycerol, 2-methyltetrahydrofuran (2-MeTHF),  $\gamma$ -valerolactone, Deep Eutectic Solvents (DESs)],<sup>[5]</sup> and aqueous media.<sup>[5f,6]</sup>

Pd-catalyzed NC in unconventional solvents are less common.<sup>[7]</sup> In 1997, Knochel and co-workers described the Pd-catalyzed cross-coupling of organozinc bromides with aryl iodides in a biphasic toluene/perfluorinated mixture.<sup>[8a]</sup> A few years later, the same group also reported the coupling between preformed aryl- or benzylzinc bromides and aryl iodides in the biphasic solvent system toluene/ionic liquid 1butyl-2,3-dimethylimidazolium tetrafluoroborate [bdmim]- $[BF_4]$  in the presence of Pd(dba)<sub>2</sub>, with an ionic phosphine as the catalyst [Scheme 1 A, Eq. (1)].<sup>[8b]</sup> In recent years, Lipshutz and co-workers have reported Zn-mediated crosscoupling reactions between alkyl and aryl or alkenyl halides promoted by micelles in water with surfactants [Scheme 1B, Eq. (2)].<sup>[9]</sup> Functionalized diarylmethanes and allylated benzenes could also be successfully prepared "on water" at room temperature (RT, 25°C) [Scheme 1 C, Eq. (3)].<sup>[10]</sup> Common to all of these procedures is the use of a diamine ligand, like N, N, N', N'-tetramethylethylendiamine (TMEDA), which has proved to be crucial to the success of the technology, presumably by functioning as an activator of the Zn surface toward the insertion into an alkyl halide, or as a stabilizer of the transient organozinc species. Of note, Schoenebeck and co-workers have recently shown that chemoselective  $C(sp^2)$ -C(sp<sup>2</sup>) NC at C-Br can also be achieved within 5 min, working at RT in air in a toluene/THF mixture, when using the benchstable dinuclear Pd<sup>I</sup> complex [{(Pt-Bu<sub>3</sub>)PdI}<sub>2</sub>] as a catalyst, while its counterpart, the bromide-bridged Pd<sup>I</sup> species, is an air-sensitive complex.<sup>[11]</sup>

As part of our ongoing research in DES and water chemistry, we recently reshaped some transition metalcatalyzed cross-coupling reactions, like the Suzuki-MiyaurPrevious work:



*Scheme 1.* Negishi coupling in ionic liquids (A), enabled by micellar catalysis (B), "on water" with Zn/TMEDA without micelles (C), and

"on water" or in DESs without additional ligands (D). RT = room temperature.

a,<sup>[12a,b]</sup> the Sonogashira,<sup>[12c]</sup> and the Ullmann-Goldberg couplings,<sup>[12d,e]</sup> and the aminocarbonylation of aryl iodides<sup>[12f]</sup> in bioinspired eutectic mixtures, and set up the direct Pdcatalyzed cross-coupling between organolithiums and (hetero)aryl halides, by using bulk water as a non-innocent reaction medium in the presence of NaCl as a cheap additive.<sup>[12g]</sup> Herein, we report the Pd-catalyzed NC between (hetero)aryl bromides and organozinc halides, and compare the outcome of the reactions both in DESs and in water/NaCl. In particular, we showcase that these reactions work well *i*) in air under mild conditions (RT or 60 °C), *ii*) in the absence of additional ligands, and *iii*) with short reaction times (20 s), and exhibit a broad substrate scope (56 examples) and a high chemoselectivity, with the desired educts prepared in good to excellent yields (up to 98%) [Scheme 1 D, Eq. (4)].

Our first investigation focused on the  $C(sp^3)-C(sp^2)$  crosscoupling between 4-bromobenzaldehyde (1a) (0.2 mmol) and *n*-BuZnCl (2a) (3 equiv) as a model system for the preparation of educt 3. We chose the same reaction conditions, which allowed for the streamlining of alkyl-aryl couplings when aryl halides were reacted with organolithium reagents using bulk water.<sup>[12g]</sup> Organozinc 2a was, in turn, freshly prepared by mixing and stirring an equimolar amount of *n*-BuLi (2.0 M in cyclohexane) and dry ZnCl<sub>2</sub> in THF under a nitrogen atmosphere.<sup>[1]</sup> The resulting solution was rapidly cannulated to a suspension of 1a and Pd[P(*t*-Bu)<sub>3</sub>]<sub>2</sub> (2.5 mol%) as a catalyst in deionized water (1 mL, pH 6) containing NaCl (1 equiv), while under air and vigorous stirring (10 min) at RT, in order to generate an emulsion (vortex).<sup>[13]</sup> During this time, the color of the mixture changed from slightly yellow to dark orange. This color change was attributed to the formation of an active form of the catalyst.<sup>[12g,14]</sup> After 20 s reaction time, the mixture was extracted with cyclopentyl methyl ether (CPME), and to our delight, the desired product **3** was isolated in a quantitative yield (Table 1, entry 1). Pleasingly, the observed data could be reproduced by preparing the organozinc **2a** in more environmentally responsible solvents, like 2-MeTHF<sup>[5a]</sup> or CPME<sup>[15]</sup> (Table 1, entries 2,3), whereas lower yields (79–84%) were obtained in other ethereal solvents, like Et<sub>2</sub>O and *t*-butyl methyl ether (TBME) (Table 1, entries 4,5). The calculated turnover frequency was  $7.14 \times 10^3$  h<sup>-1</sup> for **1a** (see ESI).

By simply mixing **1a** and **2a** with no additional solvent, **3** was isolated in 32% yield only, whereas in the absence of NaCl dehalogenated benzaldehyde **1a** was isolated as a by-product in up to a 26% yield (Table 1, entries 2,6). Detailed theoretical and experimental investigations by Amatore, Jutand, Shaik, Organ and Koszimowski have related the so-called "halide effect" to the formation of Pd-ate complexes, which are presumed to have a high reactivity toward the aryl halides, and to undergo an oxidation addition more rap-idly.<sup>[I6a-f]</sup> In Negishi couplings, in particular, lithium halides

**Table 1:** Pd-catalyzed cross-coupling of 4-bromobenzaldehyde (1 a) with n-BuZnCl (2 a) in different solvents under air.<sup>[a]</sup>

<i>n</i> -BuLi + ZnCl₂				
	Br-CHO +	n-BuZnCl solve 2a under	talyst ent (2) air, 20s	сно 3
Entr	y Solvent (1)	Solvent (2)	Pd-catalyst	Yield [%] <sup>[b]</sup>
1 2 3 4 5 6 7 8 9 10 11 12 13 14	THF 2-MeTHF CPME Et <sub>2</sub> O TBME 2-MeTHF 2-MeTHF 2-MeTHF 2-MeTHF 2-MeTHF 2-MeTHF 2-MeTHF 2-MeTHF	$H_2O$ , NaCl $H_2O$ , NaCl	$\begin{array}{c} Pd[P(t\text{-}Bu)_{3}]_{2}\\ Pd[P(t\text{-}Bu)_{3}]_{2}\\ Pd[P(t\text{-}Bu)_{3}]_{2}\\ Pd[P(t\text{-}Bu)_{3}]_{2}\\ Pd[P(t\text{-}Bu)_{3}]_{2}\\ Pd[P(t\text{-}Bu)_{3}]_{2}\\ PdCl_{2}\\ Pd(dba)_{2}\\ Pd(dba)_{2}\\ Pd(OAc)_{2}\\ Pd(OAc)_{2}\\ Pd[OAc)_{2}\\ Pd[P(t\text{-}Bu)_{3}]_{2}\\ Pd[P(t\text{-}Bu)_{3}]_{2}\\ Pd[P(t\text{-}Bu)_{3}]_{2}\\ Pd[P(t\text{-}Bu)_{3}]_{2}\\ Pd[P(t\text{-}Bu)_{3}]_{2}\\ Pd[P(t\text{-}Bu)_{3}]_{2}\\ Pd[P(t\text{-}Bu)_{3}]_{2}\\ \end{array}$	98 <sup>[c]</sup> 98 <sup>[c,d,e]</sup> 98 <sup>[c]</sup> 84 <sup>[c]</sup> 79 <sup>[c]</sup> 72 <sup>[c,f]</sup> 12 <sup>[c]</sup> 12 <sup>[c]</sup> 91 <sup>[c,g]</sup> 59 <sup>[c,h]</sup> 71 <sup>[c,i]</sup> 42 <sup>[c]</sup>
15 16 17 18	2-MeTHF 2-MeTHF 2-MeTHF 2-MeTHF	ChCl/urea ChCl/Fru <sup>[I]</sup> ChCl/Sor <sup>[m]</sup> Gly	Pd[P(t-Bu) <sub>3</sub> ] <sub>2</sub> Pd[P(t-Bu) <sub>3</sub> ] <sub>2</sub> Pd[P(t-Bu) <sub>3</sub> ] <sub>2</sub> Pd[P(t-Bu) <sub>3</sub> ] <sub>2</sub>	91 <sup>(j,k)</sup> 68 <sup>(j)</sup> 76 <sup>(j)</sup> 10 <sup>(j)</sup>

[a] Reaction conditions: 1.0 g DES or 1 mL deionized H<sub>2</sub>O per 0.2 mmol of **1a**; **2a**: 3 equiv; NaCl: 1 equiv; Pd-catalyst: 2.5 mol%. ChCl/Gly (1:2 mol mol<sup>-1</sup>); ChCl/urea (1:2 mol mol<sup>-1</sup>); ChCl/Fru (3:2 w/w); ChCl/ Sor (1:1 mol mol<sup>-1</sup>). [b] Yield of isolated product. [c] 25 °C. [d] With no additional solvent, **3** was isolated in 32% yield. [e] 93% yield: 100 mL deionized H<sub>2</sub>O per 27 mmol of **1a**. [f] Without NaCl, dehalogenated **1a** was isolated in a 26% yield. [g] Pd-catalyst: 5 mol%, Q-Phos: 20 mol%. [h] Organozinc: 2 equiv. [i] Pd-catalyst: 1 mol%. [j] 60 °C. [k] 86% yield: 100 g DES per 27 mmol of **1a**. [l] Fru: D-fructose. [m] Sor: D-sorbitol.

have also been found to be responsible for maintaining the longevity of Pd-phosphine catalysts, and for breaking up highly aggregated organometallic species so as to speed up the slow transmetallation step.<sup>[16g]</sup> Further screening of the Pdcatalysts [e.g., PdCl<sub>2</sub>, Pd(dba)<sub>2</sub>, and Pd(OAc)<sub>2</sub>] have revealed a strong dependence on the Pd-source, as the yield of 3 was not higher than 12%, whereas the combination of Pd(OAc)<sub>2</sub> with the ligand Q-Phos provided 3 in a 91% yield (Table 1, entries 7-10). Lower yields (59-71%) were obtained by reducing either the equivalents of the organozinc reagent (up to 2), or the catalyst loading (up to 1 mol%) (Table 1, entries 11,12). Upon switching water for some prototypical choline chloride (ChCl)/glycerol (Gly) (1:2 mol mol<sup>-1</sup>) and ChCl/urea (1:2 molmol<sup>-1</sup>) eutectic mixtures, the yield of **3** dropped down to 42-57 % at RT, whereas it was increased up to 91% in the ChCl/urea mixture at a higher temperature (60°C) (Table 1, entries 13-15). On the other hand, the use of D-fructose or D-sorbitol as the hydrogen bond donor, in a combination with ChCl, was less effective, as this led to the cross-coupled product 3 in a 68-76% yield (Table 1, entries 16,17). Finally, by changing the solvent to pure Gly, the yield of **3** was dramatically decreased (up to 10%) (Table 1, entry 18). It is also worth mentioning that upon mixing 1a (0.2 mmol) with 1-bromobutane (0.6 mmol) in the presence of Zn (1 mmol) and  $Pd[P(t-Bu)_3]_2$  (up to 5 mol%) either in water/NaCl at RT or in ChCl/urea at 60 °C, only starting material was recovered even after 18 h reaction time.

In order to prove the applicability of the method, we also carried out the synthesis of **3** on a 5-gram scale. Under the best conditions of Table 1 (entries 2,15), NC between **1a** (27 mmol, 5 g) and **2a** (81 mmol) resulted in the formation of **3** in a 93% yield (4.068 g) when using water (100 mL) containing NaCl (1.578 g), and in a 86% yield (3.767 g) in ChCl/urea (100 g) (Table 1, entries 2,15) (see ESI for details).

With these satisfactory conditions in place, we sought to capitalize on this process by exploring the scope of the reaction with a variety of (hetero)aryl bromides **1** and organozinc halides **2** (Table 2). With regard to **2a**, very good to excellent yields (70–98%) of the desired coupled products (**3–16**) were obtained when using water for the aryl bromides bearing an aldehyde, a ketone, an ester, a nitrile, an alcohol, or a nitro functional group at the *ortho-*, *meta-*, and *para*-positions, or additional halogens such as fluorine or chlorine. Particularly noteworthy was the lack of sensitivity of the alcohol moiety to the "on-water" reaction conditions (**15**,**16**: 75–84% yield),<sup>[5b,f]</sup> as it was found that the substrates with functional groups containing hydrogens, whose acidity was comparable to that of water, were unresponsive under

Table 2: Pd-catalyzed cross-coupling between (hetero)aryl bromides 1 and organozinc halides 2 "on water" or in DES under air.<sup>[a]</sup>



[a] Yield of isolated product; 0.2 mmol 1 in 1 mL deionized water (pH 6.0) or 1 g DES [ChCl/urea (1:2 mol mol<sup>-1</sup>)]; 1 equiv NaCl; 3 equiv 2. NR = no reaction.

micellar conditions.<sup>[9c]</sup> All of these products could not be prepared by subjecting n-BuLi, in place of 2a, to the Pdcatalyzed cross-coupling reactions "on water", as reported.<sup>[12g]</sup> Different (hetero)aromatics, like 1-bromonaphtalene (10), ethyl 5-bromobenzofuran-2-carboxylate (1p), 3-bromoquinoline (1q) and 2-bromo-5-chlorothiophene (1r), proved to be competent partners as well, and were efficiently crosscoupled with 2a, delivering the corresponding educts 17-20 in a 65–98% yield. On the other hand, the aryl bromides with an increased hydrophilicity bearing a free carboxy, an amino, or an hydroxyl group on the aromatic ring, reacted poorly (1s,t) (21,22: 10–30 % yield), or did not react at all (1u,v) with 2a. The same also held for 6-bromonicotinaldehyde (1w), which was quantitatively recovered at the end of the process, whereas 5-bromopyrimidine (1x) furnished the educt 26 in a 30% yield. However, when the reaction was alternatively carried out in the eutectic mixture ChCl/urea (1:2 mol mol<sup>-1</sup>) at 60°C in air, under heterogeneous conditions, all of the desired products 21-26 could be isolated in a 35-78% yield. Phenolic derivative 24 has been shown to exhibit significant cytotoxic activity against two human oral cancer cell lines (SCC-40 and SCC-29B).<sup>[17]</sup> By transferring these conditions to some representative substrates (1c, 1f, 1j, 1k, and 1m), which had been previously reacted "on water", the expected educts 5, 8, 12, 13, and 15 were produced in almost similar yields (72-90%). Likewise, HexylZnCl (2b), MeZnCl (2c). Me<sub>3</sub>SiCH<sub>2</sub>ZnCl (2d), (4-cyanobutyl)ZnBr (2e), and (4ethoxy-4-oxobutyl)ZnBr (2f) underwent a smooth crosscoupling reaction "on water", with functionalized (hetero)aryl bromides 1a, 1c, 1g-1i, 1q, and 1y to afford the desired products 27-41 in a 30-98% yield. Of note, the yields of compounds 36-40 could be improved considerably from 30-82% to 72-90% by alternatively working in the ChCl/urea eutectic mixture.

The secondary alkyl organometallic compounds are known to undergo cross-coupling with the aryl bromides to give mixtures of linear and branched products because of a competitive β-hydride-elimination pathway.<sup>[18]</sup> Lipshutz and co-workers detected by NMR no undesired linear products in the crude reaction mixture by promoting the Pd-catalyzed coupling between secondary alkyl bromides and aryl halides in the presence of Zn/TMEDA under micellar conditions.<sup>[9c]</sup> To our delight, the effectiveness of such "on water" coupling reactions was still maintained when using secondary alkylzinc halides in the absence of additional ligands. Indeed, both *i*-PrZnCl (2g) and s-BuZnCl (2h) effectively participated in the process with 1a, 1c, 1h, and 1j, delivering the educts 42-47 in very good yields (87–98%). Conjugated nitro-substituted aryl bromides, like 11 and 1z, and the bromoindole 1aa, were also good substrates, affording the educts 48-50, respectively, in a 65-87 % yield. It is worth noting that the conjugate addition to the activated alkene moiety of 1z did not compete, in contrast to what was observed when using lithium tetraorganozincates.<sup>[19]</sup> No cross-coupling was observed when 3-bromophenol (1v) or the electron-rich 4bromoaniline derivative 1ab were reacted with 2h "on water". Remarkably, upon switching to the eutectic mixture ChCl/urea, the desired products 51,52 could be isolated in a 66-73 % yield. The yield of the nitro derivative 48 could also be improved in DES from 65 to 78%. As testified by the recent literature, although sharing some physicochemical properties (e.g., a strong H-bonded network), water and DES have been proven to be not on the same ground as far as the reactivity of the organometallic compounds is concerned.<sup>[5b,f,12g,20]</sup> Thus, they can advantageously and complementarily be used in organometallic chemistry. Finally, the C(sp<sup>2</sup>)-C(sp<sup>2</sup>) coupling between PhZnCl (2i) and 1a, 1g, 1i, 1q, and 1r also proceeded uneventfully, providing the expected educts 53–57 in a 67–78% yield under the "on water" conditions. Compounds 53, 56, 57 were also prepared in a 75–80% yield in ChCl/urea. On the other hand, the electron-poor 2-pyridylZnBr (2j) resulted a sluggish coupling partner as it provided in the reaction with 1a the educt 58 in a yield not higher than 35% in DES.

Both the Pd-catalyst and the DES ChCl/urea or water could easily be recycled. The cross-coupling of bromoarene 1a with organozinc 2a was chosen as a model reaction, since it provided educt 3 in 91-98% yield. As for catalyst/DES recycling, upon completion of the first coupling, the in-flask extraction with CPME afforded 3 (91% yield, number of recycles = 0), but it left the Pd catalyst in the eutectic mixture. Then, upon adding new, fresh reagents (1a and 2a), the catalyst and DES could be successfully re-used for further reaction runs. The catalyst remained active for over 7 cycles, albeit with a drop in the chemical yield of 3 of up to 29% at the end of the 7th cycle. The strategy for recycling catalyst/ water consisted in removing, after each run, VOCs introduced with organozinc 2a under reduced pressure, and in adjusting the pH value of the resulting mixture at about 6 by using concentrated HCl, leaving the product 3 inside it. The catalyst retained good catalytic activity over four cycles, and the overall yield of product 3 was 86% (see ESI for details).

In conclusion, we have shown that the Pd-catalyzed Negishi coupling of (hetero)aryl bromides with organozinc halides can be accomplished with a wide substrate scope and with very good reaction yields (up to 98%), by using bulk water in the presence of NaCl, or alternatively the environmentally friendly eutectic mixture of ChCl/urea. These reactions are scalable, and they proceed under remarkably mild conditions (RT or 60°C), with short reaction times (20 s) in air, in the absence of additional ligands, and with an easy recycling of both the DES or water and the catalyst. This simple novel protocol complements the traditional and recent approaches to perform Negishi coupling, thereby reinforcing the argument that notoriously moisture-sensitive organometallic reagents can be used under aerobic conditions in protic bio-based solvents like DESs or water.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** cross-coupling reactions  $\cdot$  deep eutectic solvents  $\cdot$  heterogeneous catalysis  $\cdot$  organozinc compounds  $\cdot$  water chemistry

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