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.*

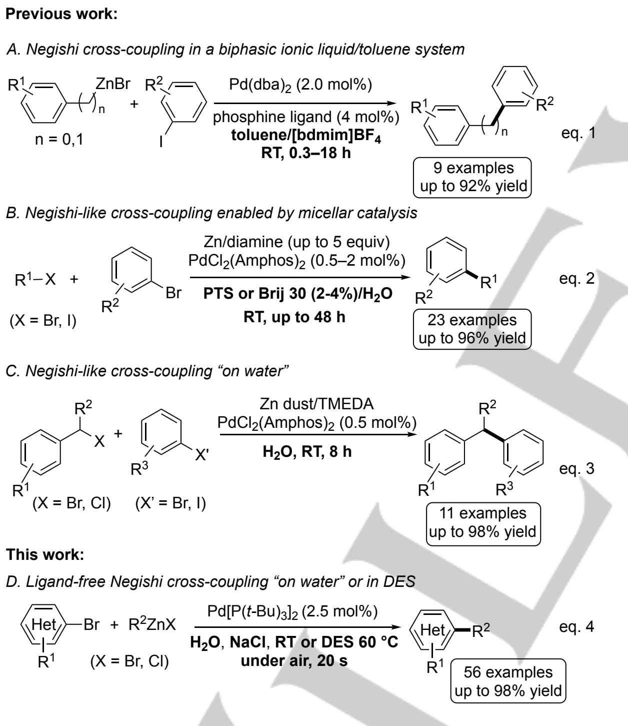
The Negishi coupling (NC) represents a versatile and valuable Ni- or Pd-catalyzed cross-coupling reaction of organozinc compounds with various halides or pseudo-halides to forge new carbon–carbon bonds between the sp^3, sp^2, or sp carbon atoms.[1] Because of their higher functional group tolerance when 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[2] and of advanced electronic, optical, electrochemical, and magnetic materials.[3] 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 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.[4] 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), γ-valerolactone, Deep Eutectic Solvents (DESs)],[5] and aqueous media.[5f,6]

Pd-catalyzed NC in unconventional solvents are less common.[7] In 1997, Knochel and co-workers described the Pd-catalyzed cross-coupling of organozinc bromides with aryl iodides in a biphasic toluene/perfluorinated mixture.[8a] 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 1-butyl-2,3-dimethylimidazolium tetrafluoroborate [bdmim][BF_4] in the presence of $Pd(dba)_2$, with an ionic phosphine as the catalyst (Scheme 1A, eq. 1).[8b] In recent years, Lipshutz and co-workers have reported Zn-mediated cross-coupling reactions between alkyl and aryl or alkenyl halides promoted by micelles in water with surfactants (Scheme 1B, eq. 2).[9] Functionalized diarylmethanes and allylated benzenes could also be successfully prepared “on water” at room temperature (RT, 25°C) (Scheme 1C, eq. 3).[10] 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^2) NC at C–Br can also be achieved within 5 min, working at RT in air in a toluene/THF mixture, when using the bench-stable dinuclear Pd(I) complex [{(P*t*-Bu_3)PdI}$_2$] as a catalyst, while its counterpart, the bromide-bridged Pd(I) species, is an air-sensitive complex.[11]

As part of our ongoing research in DES and water chemistry, we recently reshaped some transition metal-catalyzed cross-coupling reactions, like the Suzuki-Miyaura,[12a,b] the Sonogashira,[12c] and the Ullmann-Goldberg couplings,[12d,e] and the aminocarbonylation of aryl iodides[12f] in bioinspired eutectic mixtures, and set up the direct Pd-catalyzed 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.[12g] 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 1D, eq. 4).

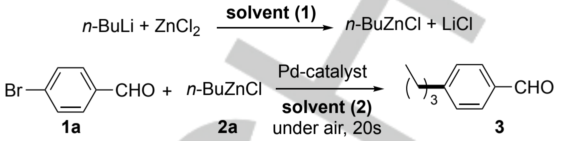
Our first investigation focused on the C(sp^3)–C(sp^2) cross-coupling between 4-bromobenzaldehyde (**1a**) (0.2 mmol) and *n*-BuZnCl (**2a**) (3 equiv) as a model system for the preparation of educt **3**. We chose the same reaction conditions, which allowed for the streamlining of alkyl-aryl couplings when aryl halides were reacted with organolithium reagents using bulk water.[12g] Organozinc **2a** was, in turn, freshly prepared by mixing and stirring an equimolar amount of *n*-BuLi (2.0 M in cyclohexane) and dry $ZnCl_2$ in THF under a nitrogen atmosphere.[1] The resulting solution was rapidly cannulated to a suspension of **1a** and Pd[P(*t*-Bu)$_3$]$_2$ (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).[13]



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.

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.[12g,14] 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[5a] or CPME[15] (Table 1, entries 2,3), whereas lower yields (79–84%) were obtained in other ethereal solvents, like Et_2O and *t*-butyl methyl ether (TBME) (Table 1, entries 4,5). The calculated turnover frequency was 7.14 × 10^3 h^{-1} for **1a** (see ESI).

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



Entry	Solvent (1)	Solvent (2)	Pd-catalyst	Yield [%][b]
1	THF	H_2O, NaCl	Pd[P(*t*-Bu)$_3$]$_2$	98[c]
2	2-MeTHF	H_2O, NaCl	Pd[P(*t*-Bu)$_3$]$_2$	98[c,d,e]
3	CPME	H_2O, NaCl	Pd[P(*t*-Bu)$_3$]$_2$	98[c]
4	Et_2O	H_2O, NaCl	Pd[P(*t*-Bu)$_3$]$_2$	84[c]
5	TBME	H_2O, NaCl	Pd[P(*t*-Bu)$_3$]$_2$	79[c]
6	2-MeTHF	H_2O, NaCl	Pd[P(*t*-Bu)$_3$]$_2$	72[c,f]
7	2-MeTHF	H_2O, NaCl	$PdCl_2$	12[c]
8	2-MeTHF	H_2O, NaCl	Pd(dba)$_2$	5[c]
9	2-MeTHF	H_2O, NaCl	Pd(OAc)$_2$	12[c]
10	2-MeTHF	H_2O, NaCl	Pd(OAc)$_2$	91[c,g]
11	2-MeTHF	H_2O, NaCl	Pd[P(*t*-Bu)$_3$]$_2$	59[c,h]
12	2-MeTHF	H_2O, NaCl	Pd[P(*t*-Bu)$_3$]$_2$	71[c,i]
13	2-MeTHF	ChCl/Gly	Pd[P(*t*-Bu)$_3$]$_2$	42[c]
14	2-MeTHF	ChCl/urea	Pd[P(*t*-Bu)$_3$]$_2$	57[c]
15	2-MeTHF	ChCl/urea	Pd[P(*t*-Bu)$_3$]$_2$	91[j,k]
16	2-MeTHF	ChCl/Fru[l]	Pd[P(*t*-Bu)$_3$]$_2$	68[j]
17	2-MeTHF	ChCl/Sor[m]	Pd[P(*t*-Bu)$_3$]$_2$	76[j]
18	2-MeTHF	Gly	Pd[P(*t*-Bu)$_3$]$_2$	10[j]

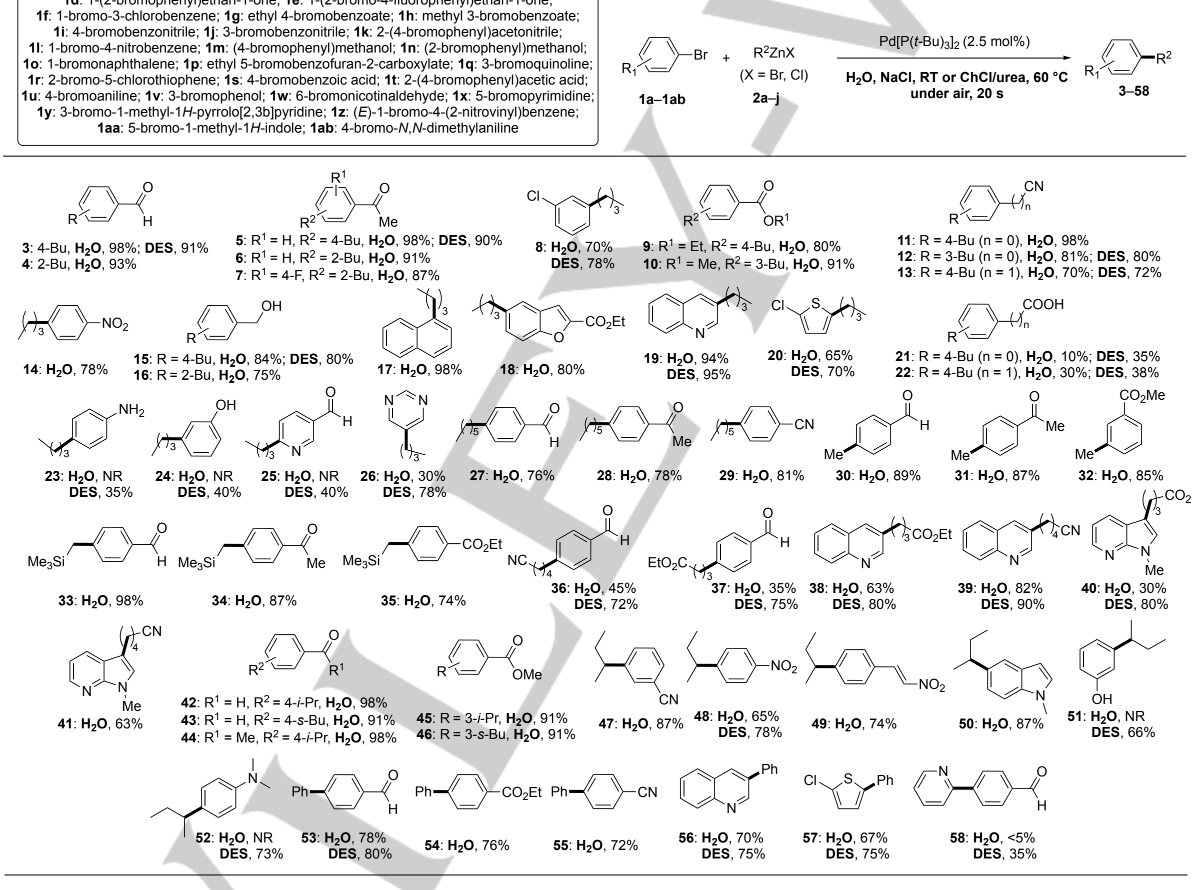
[a] Reaction conditions: 1.0 g DES or 1 mL deionized H_2O per 0.2 mmol of **1a**; **2a**: 3 equiv; NaCl: 1 equiv; Pd-catalyst: 2.5 mol%. ChCl/Gly (1:2 mol mol^{-1}); ChCl/urea (1:2 mol mol^{-1}); ChCl/Fru (3:2 w w^{-1}); ChCl/Sor (1:1 mol mol^{-1}). [b] Yield of isolated product. [c] 25°C. [d] With no additional solvent, **3** was isolated in 32% yield. [e] 93% yield: 100 mL deionized H_2O 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.

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 rapidly.[16a–f] In Negishi couplings, in particular, lithium halides 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.[16g] Further screening of the Pd-catalysts [e.g., $PdCl_2$, $Pd(dba)_2$, and $Pd(OAc)_2$] have revealed a strong dependence on the Pd-source, as the yield of **3** was not higher than 12%, whereas the combination of $Pd(OAc)_2$ 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^{-1}) and ChCl/urea (1:2 mol mol^{-1}) 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 $Pd[P(t\text{-}Bu)_3]_2$ (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 in ChCl/urea (100 g) (Table 1, entries 2,15) (see ESI for details).

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

1a: 4-bromobenzaldehyde; **1b**: 2-bromobenzaldehyde; **1c**: 1-(4-bromophenyl)ethan-1-one; **1d**: 1-(2-bromophenyl)ethan-1-one; **1e**: 1-(2-bromo-4-fluorophenyl)ethan-1-one; **1f**: 1-bromo-3-chlorobenzene; **1g**: ethyl 4-bromobenzoate; **1h**: methyl 3-bromobenzoate; **1i**: 4-bromobenzonitrile; **1j**: 3-bromobenzonitrile; **1k**: 2-(4-bromophenyl)acetonitrile; **1l**: 1-bromo-4-nitrobenzene; **1m**: (4-bromophenyl)methanol; **1n**: (2-bromophenyl)methanol; **1o**: 1-bromonaphthalene; **1p**: ethyl 5-bromobenzofuran-2-carboxylate; **1q**: 3-bromoquinoline; **1r**: 2-bromo-5-chlorothiophene; **1s**: 4-bromobenzoic acid; **1t**: 2-(4-bromophenyl)acetic acid; **1u**: 4-bromoaniline; **1v**: 3-bromophenol; **1w**: 6-bromonicotinaldehyde; **1x**: 5-bromopyrimidine; **1y**: 3-bromo-1-methyl-1*H*-pyrrolo[2,3b]pyridine; **1z**: (*E*)-1-bromo-4-(2-nitrovinyl)benzene; **1aa**: 5-bromo-1-methyl-1*H*-indole; **1ab**: 4-bromo-*N*,*N*-dimethylaniline



[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^{-1})]; 1 equiv NaCl; 3 equiv **2**. NR = no reaction.

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),[5b,f] as it was found that the substrates with functional groups containing hydrogens, whose acidity was comparable to that of water, were unresponsive under micellar conditions.[9c] All of these products could not be prepared by subjecting *n*-BuLi, in place of **2a**, to the Pd-catalyzed cross-coupling reactions "on water", as reported.[12g] Different (hetero)aromatics, like 1-bromonaphtalene (**1o**), 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 cross-coupled 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 (**1s**,**t**), reacted poorly (**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^{-1}) 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).[17] 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_3SiCH_2ZnCl (**2d**), (4-cyanobutyl)ZnBr (**2e**), and (4-ethoxy-4-oxobutyl)ZnBr (**2f**) underwent a smooth cross-coupling 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.[18] 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.[9c] 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 **1l** 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.[19] No cross-coupling was observed when 3-bromophenol (**1v**) or the electron-rich 4-bromoaniline 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.[5b,f,12g,20] Thus, they can advantageously and complementarily be used in organometallic chemistry. Finally, the C(sp^2)–C(sp^2) coupling between PhZnCl (**2i**) and **1a**, **1g**, **1i**, **1q**, and **1r** also proceeded uneventfully, providing the expected educts **53**–**57** in a 70–78% 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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Keywords: organozinc compounds • water chemistry • deep eutectic solvents • cross-coupling reactions • heterogeneous catalysis

[1] a) D. Haas, J. M. Hammann, R. Greiner, P. Knochel, *ACS Catal.* **2016**, *6*, 1540; b) C. Diner, M. G. Organ, in *Organic Reactions* (Eds.: S. E. Denmark, L. E. Overman), John Wiley & Sons, Inc., **2020**, vol. 100, chap. 1, p. 1.

[2] a) Y. Koseki, T. Sugimura, K. Ogawa, R. Suzuki, H. Yamada, N. Suzuki, Y. Masuyama, Y. Y. Lin, T. Usuki, *Eur. J. Org. Chem.* **2015**, 4024; b) J. E. Tungen, M. Aursnes, J. Dalli, H. Arnardottir, C. N. Serhan, T. V. Hansen, *Chem. Eur. J.* **2014**, *20*, 14575; c) Z. Hu, X.-J. Wei, J. Handelmann, A.-K. Seitz, I. Rodstein, V. H. Gessner, L. J. Gooβen, *Angew. Chem.* **2021**, doi: 10.1002/ange.202016048; *Angew. Chem. Int. Ed.* **2021**, doi: 10.1002/anie.202016048.

[3] S. Huo, R. Mroza, J. Carroll, *Org. Chem. Front.* **2015**, *2*, 416.

[4] a) B. H. Lipshutz, S. Ghoral, *Green Chem.* **2014**, *16*, 3660; b) B. H. Lipshutz, F. Gallou, S. Handa, *ACS Sustain. Chem. Eng.* **2016**, *4*, 5838; c) S. Sharma, J. Das, W. M. Braje, A. K. Dash, S. Handa, *ChemSusChem*, **2020**, *13*, 2859.

[5] a) S. Santoro, F. Ferlin, L. Luciani, L. Ackermann, L. Vaccaro, *Green Chem.* **2017**, *19*, 1601; b) J. García-Álvarez, E. Hevia, V. Capriati, *Chem. Eur. J.* **2018**, *24*, 14854; c) *Deep Eutectic Solvents: Synthesis, Properties, and Applications* (Eds: D. J. Ramón, G. Guillena), Wiley-VCH, Weinheim, **2019**, pp. 1–384; d) F. M. Perna, P. Vitale, V. Capriati, *Curr. Opin. Green Sust. Chem.* **2020**, *21*, 27; e) S. E. Hooshmand, R. Afshari, D. J. Ramón, R. S. Varma, *Green Chem.* **2020**, *22*, 3668; f) L. Cicco, G. Dilauro, F. M. Perna, P. Vitale, V. Capriati, *Org. Biom. Chem.* **2021**, doi: 10.1039/d0ob02491k.

[6] a) J. García-Álvarez, E. Hevia, V. Capriati, *Eur. J. Org. Chem.* **2015**, 6779; b) F. Zhou, C.-J. Li, *Chem. Sci.* **2019**, *10*, 34; c) M. Cortes-Clerget, J. Yu, J. R. A. Kincaid, P. Walde, F. Gallou, B. H. Lipshutz, *Chem. Sci.* **2021**, doi: 10.1039/d0sc06000c.

[7] J. Sherwood, J. H. Clark, I. S. J. Fairlamb, J. M. Slattery, *Green Chem.* **2019**, *21*, 2164.

[8] a) B. Betzemeier, P. Knochel, *Angew. Chem.* **1997**, *109*, 2736; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2623; b) J. Sirieix, M. Oßberger, B. Betzemeier, P. Knochel, *Synlett* **2000**, 1613.

[9] a) A. Krasovskiy, C. Duplais, B. H. Lipshutz, *J. Am. Chem. Soc.* **2009**, *131*, 15592; b) A. Krasovskiy, C. Duplais, B. H. Lipshutz, *Org. Lett.* **2010**, *12*, 4742; c) C. Duplais, A. Krasovskiy, B. H. Lipshutz, *Organometallics* **2011**, *30*, 6090.

[10] a) C. Duplais, A. Krasovskiy, A. Wattenberg, B. H. Lipshutz, *Chem. Commun.* **2010**, *46*, 562; b) V. Krasovskaya, A. Krasovskiy, A. Bhattacharjya, B. H. Lipshutz, *Chem. Commun.* **2011**, *47*, 5717.

[11] a) M. Aufiero, T. Scattolin, F. Proutière, F. Schoenebeck, *Organometallics* **2015**, *34*, 5191; b) I. Kalvet, G. Magnin, F. Schoenebeck, *Angew. Chem.* **2017**, *129*, 1603; *Angew. Chem. Int. Ed.* **2017**, *56*, 1581.

[12] a) G. Dilauro, S. M. García, D. Tagarelli, P. Vitale, F. M. Perna, V. Capriati, *ChemSusChem* **2018**, *11*, 3495; b) V. Pelliccioli, G. Dilauro, S. Grecchi, S. Arnaboldi, C. Graiff, F. M. Perna, P. Vitale, E. Licandro, A. Aliprandi, S. Cauteruccio, V. Capriati, *Eur. J. Org. Chem.* **2020**, 6981; c) F. Messa, G. Dilauro, F. M. Perna, P. Vitale, V. Capriati, A. Salomone, *ChemCatChem* **2020**, *12*, 1979; d) A. F. Quivelli, P. Vitale, F. M. Perna, V. Capriati, *Front. Chem.* **2019**, *7*, 723; e) L. Cicco, J. A. Hernández-Fernández, A. Salomone, P. Vitale, M. Ramos-Martín, J. González-Sabín, A. Presa-Soto, F. M. Perna, V. Capriati, J. García-Álvarez, *Org. Biom. Chem.* **2021**, doi: 10.1039/D0OB02501A; f) F. Messa, S. Perrone, M. Capua, F. Tolomeo, L. Troisi, V. Capriati, A. Salomone, *Chem. Commun.* **2018**, *54*, 8100; g) G. Dilauro, A. F. Quivelli, P. Vitale, V. Capriati, F. M. Perna, *Angew. Chem.* **2019**, *131*, 1813; *Angew. Chem. Int. Ed.* **2019**, *58*, 1799.

[13] G. Dilauro, M. Dell'Aera, P. Vitale, V. Capriati, F. M. Perna, *Angew. Chem.* **2017**, *129*, 10334; *Angew. Chem. Int. Ed.* **2017**, *56*, 10200.

[14] D. Heijnen, F. Tosi, C. Vila, M. C. A. Stuart, P. H. Elsinga, W. Szymanski, B. L. Feringa, *Angew. Chem.* **2017**, *129*, 3402; *Angew. Chem. Int. Ed.* **2017**, *56*, 3354.

[15] U. Azzena, M. Carraro, L. Pisano, S. Monticelli, R. Bartolotta, V. Pace, *ChemSusChem* **2019**, *12*, 40.

[16] a) C. Amatore, A. Jutand, *Acc. Chem. Res.* **2000**, *33*, 314; b) X. Lu, *Topics in Catalysis* **2005**, *35*, 73; c) S. Kozuch, C. Amatore, A. Jutand, S. Shaik, *Organometallics* **2005**, *24*, 2319; d) C. Amatore, A. Jutand, G. Le Duc, *Angew. Chem. Int. Ed.* **2012**, *51*, 1379; *Angew. Chem.* **2012**, *124*, 1408; e) K. Böck, J. E. Feil, K. Karaghiosoff, K. Koszinowski, *Chem. Eur. J.* **2015**, *21*, 5548; f) M. Kolter, K. Böck, K. Karaghiosoff, K. Koszinowski, *Angew. Chem. Int. Ed.* **2017**, *56*, 13244; *Angew. Chem.* **2017**, *129*, 13427; for a recent review on the impact of inorganic salts on Negishi coupling, see: g) P. Eckert, S. Sharif, M. G. Organ, *Angew. Chem.* **2021**, doi: 10.1002/ange.202010917; *Angew. Chem. Int. Ed.* **2021**, doi: 10.1002/anie.202010917.

[17] A. Atiya, M. A. Salim, B. N. Sinha, U. R. Lal, *Nat. Prod. Res.* **2020**, doi: 10.1080/14786419.2020.1762186.

[18] S. D. Dreher, P. Dormer, D. Sandrock, G. A. Molander, *J. Am. Chem. Soc.* **2008**, *130*, 9257.

[19] M. Dell'Aera, F. M. Perna, P. Vitale, A. Altomare, A. Palmieri, L. C. H. Maddock, L. J. Bole, A. R. Kennedy, E. Hevia, V. Capriati, *Chem. Eur. J.* **2020**, *26*, 8742.

[20] A. F. Quivelli, G. D'Addato, P. Vitale, J. García-Álvarez, F. M. Perna, V. Capriati, *Tetrahedron* **2021**, *81*, 131898.

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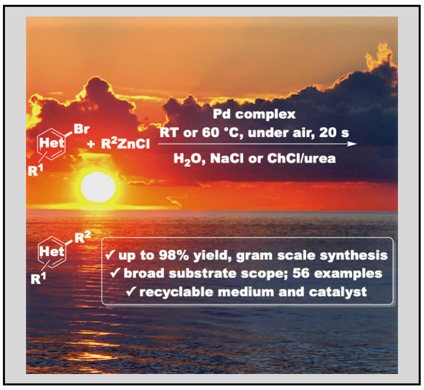

Coupling runs across water and DES: Scalable Pd-catalyzed Negishi cross-couplings between (hetero)aryl bromides and organozinc halides have been developed either by using bulk water, or the choline chloride/urea eutectic mixture as a reaction medium. These processes proceed under mild conditions, short reaction times (20 s) in air, in the absence of additional ligands, with high chemoselectivity and a broad substrate scope, and an easy recycling of both the catalyst and the eutectic mixture or water.

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