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A Glycerol-Based Deep Eutectic Solvent as Natural Medium and Organic Reductant for Homocoupling of (Hetero)Aryl Chlorides: a Green Route to 2,2′-Bipyridine and Biaryl Scaffolds

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A glycerol-based Deep Eutectic Solvent (DES) enables the Pd-catalyzed activation of (hetero)arylchlorides and promotes the formation of 2,2′-bipiyridines and biaryls through an Ullmann-type homocoupling in smooth experimental conditions (80 °C) with $Ca(OH)_2$ as a green base and Pd/C as heterogeneous catalyst. Noteworthy, the coupling does not need the addition of external reducing agents, like metals, since the glycerol present in the DES acts as a safe and green organic reductant. The heterogeneous catalytic system (DES-Pd/C) showed to be easily recyclable and has been applied to the sustainable synthesis of the Abametapir drug.

Introduction

Over the years, an enormous amount of research has been devoted to the Ullmann coupling, namely a copper-mediated homocoupling reaction of (hetero)aryl halides, intensively applied to the preparation of symmetrical (hetero)biaryls. Since the first report by Ullmann,[1] many modified approaches, built on the catalytic activity of transition metals such as Pd, Ni, Mn, Au, Co and Fe, have been described.[2] The broad interest in such a methodology belongs to the utility of its products, the biaryls, a family of organic compounds with important applications as precursors of liquid crystals[3a] components of semiconducting complexes,[3b] and rigid fragments in drug design.[3c]

Among biaryls, a special role is played by 2,2′-bipyridines employed as metal ligands by virtue of their extraordinary coordination properties and redox stability; in addition, they show benchtop stability unlike other conventional metal ligands such as phosphines, carbenes or ferrocenes.[4] Many other fascinating applications have also been associated to 2,2′-bipyridines, employed with success as key-structures in chiral molecular recognition,[5a,b] luminescent devices,[5c,d] as well as in photonics and optoelectronics.[5e,f]

As part of our research on Pd-catalyzed reactions and sustainable synthetic processes in Deep Eutectic Solvents (DESs),[6] we focused our attention on the development of ligand-free catalytic systems for aryl chlorides activation. The replacement of organic iodides and bromides with the corresponding chlorides, is beneficial from a sustainability point of view, because aromatic chlorides are cheaper, easier to prepare and bench-stable. In addition, by considering that the formation of an Ullmann product releases in the environment at least two equivalents of halide anion, it can be deduced that the employment of chloro(hetero)arenes could result in a higher grade of sustainability, due to the less environmental impact of chloride ion.[7]

Despite decades of research dedicated to the Ullmann-type couplings of 2-iodo and 2-bromo-substituted pyridines,[8] few methodologies focused on the homocoupling of 2-chloropyridines have been published to date (Figure 1).

In 2013, an impressive work by Sakurai disclosed a general Ullmann-type coupling of chloropyridines at 35 °C under the

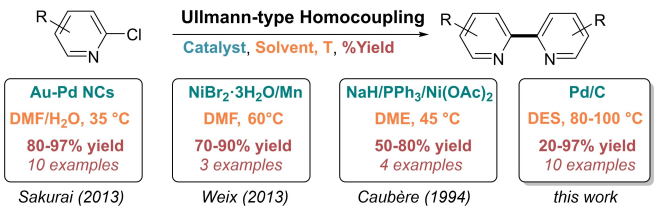

Figure 1. Overview of the Ullmann-type homocoupling on 2-chloropyridines.

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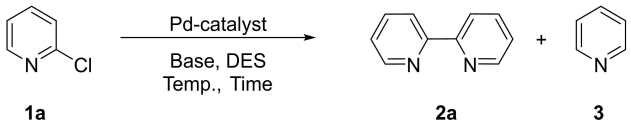
catalysis of bimetallic Au–Pd alloy nanoclusters (NCs) stabilized by poly(*N*-vinylpyrrolidone) (Figure 1).[9a] In the same year, Weix found that $NiBr_2 \times 3H_2O$ enabled the dimerization of a small number of 2-chloropyridines in DMF at 60 °C, with Mn^0 as reductant, for the synthesis of specific bidentate ligands (Figure 1).[9b] In 1994, Caubère realized that a Ni-based catalyst, obtained from *t*-BuOH, NaH, $Ni(OAc)_2$ and PPh_3, enabled the formation of 2,2′-bipyridines in DME at 45 °C (Figure 1).[9c] Few other authors recently reported the specific synthesis of 2,2′-bipyridine by Pd-catalyzed homocoupling of 2-chloropyridine.[10]

During recent studies related to the green hydrogenations[11a] of organic compounds in DES,[11b] a sustainable alternative to ionic liquids, we subjected the 4-chloronitrobenzene to the optimized reduction protocol [Al (10 equiv), KOH (10 equiv), H_2O (400 μL), Pd/C (5 mol%) in Cholinium Chloride (ChCl)/Glycerol (2 g)]. Surprisingly, the major product of the reaction was not the expected 4-aminochlorobenzene, but the benzidine (40% yield), a clear proof that an Ullmann-type homocoupling (UtH) promoted the biaryl bond formation.

Results and Discussion

With the aim of studying the reactivity of chloro(hetero)arenes in DES and exploiting it for the sustainable synthesis of 2,2′-bypiridine scaffolds, 2-chloropyridine **1a** was chosen as the model substrate and subjected to the Pd activity in various ionic eutectic mixtures (DES A-D, Table 1).

Table 1. Optimization of the Pd-catalyzed homocoupling reaction of 2-chloropyridine **1a** in Deep Eutectic Solvents.[a,b]



1a **2a** **3**

Entry	DES	Base	Pd-cat (mol%)	**1a** %conv.	**2a** %yield	**3** %yield
1[c]	A	KOH	Pd/C (5)	100	32	60
2[c]	B	KOH	Pd/C (5)	88	12	57
3[c]	C	KOH	Pd/C (5)	98	16	73
4[c]	D	KOH	Pd/C (5)	40	0	32
5[c]	A	KOH[d]	Pd/C (5)	80	20	52
6[c]	A	NEt_3	Pd/C (5)	74	0	63
7[c]	A	*t*-BuOK	Pd/C (5)	83	20	55
8[c]	A	K_3PO_4	Pd/C (5)	63	29	32
9[c]	A	$Ca(OH)_2$	Pd/C (5)	50	31	15
10[e]	A	$Ca(OH)_2$	Pd/C (5)	81	48	18
11[e]	**A**	**$Ca(OH)_2$**	**Pd/C (10)**	**100**	**75**	**23**
12[e]	A	$Ca(OH)_2$	Pd/Al_2O_3(10)	100	22	71
13[e]	A	$Ca(OH)_2$	$Pd/BaSO_4$(10)	100	23	68
14[e]	Gly	$Ca(OH)_2$	Pd/C (10)	100	45	33

[a] Reaction conditions: **1a** (0.5 mmol), base (5.0 mmol), Pd-catalyst (5 or 10 mol%), DES (2.0 g), at 40 or 80 °C, for 12 hours. The yields and conversions are calculated via GC analysis. **2a** could also be isolated by liquid-liquid extraction (see ESI). [b] DES A = Cholinium Chloride/Glycerol or ChCl/Gly (1/2 mol/mol), DES B = ChCl/Urea (1/2 mol/mol), DES C = Tetrabutylammonium bromide/Ethylene glycol (1/2 mol/mol); DES D = Methyltriphenylphosphonium bromide/Ethylene Glycol (1/5 mol/mol). [c] 40 °C. [d] 2.5 mmol of base. [e] 80 °C.

First evidence, the use of an external reductant was not essential for the UtH: after 12 h, at 40 °C in the presence of KOH and 5 mol% of Pd/C, without Al and H_2O, the reaction provided the expected bipyridine **2a** in 32% yield, although the dehalogenation of substrate was preferred (entry 1).

The nature of DES had a somewhat important effect on the UtH: ChCl/Urea or Tetrabutylammonium/Ethylen glycol (EG) caused a drastic decrease in homocoupling product (entries 2,3), while the methyltriphenylphosphonium bromide/EG completely inhibited the UtH (entry 4); in all three cases the pyridine **3** had formed again as the major product (32-73%, entries 2–4).

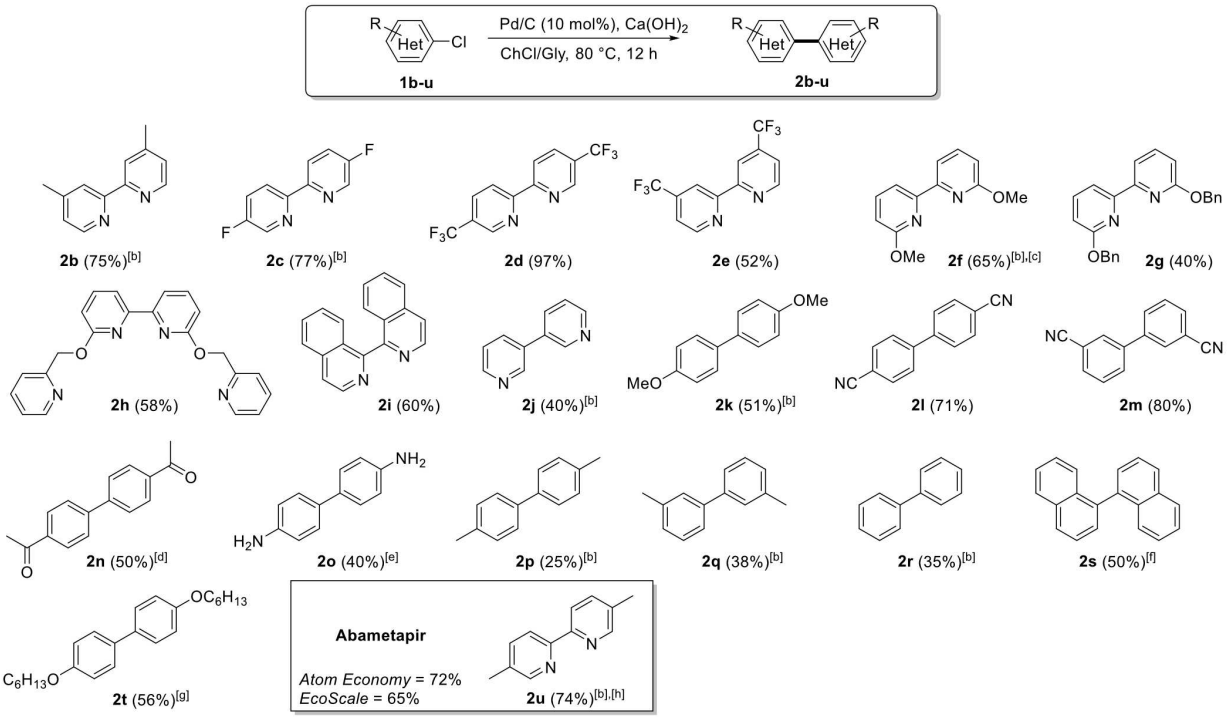
The excess of base, as well as its nature, are noteworthy for the bipyridine formation: when halving the amount of KOH (entry 5) the target product **2a** formed in a lesser extent. The employment of a weaker organic base (NEt_3) was totally useless for the UtH, on the contrary, tBuOK gave slightly better results but still lower than KOH (entries 6–7). The experiment with K_3PO_4 (entry 8) allowed the formation of bipyridine **2a** in a slightly better selectivity but with an unsatisfactory conversion of substrate (63%) in 12 hours at 40 °C. The coupling selectivity was significantly improved when $Ca(OH)_2$ was used (entry 9); the expected bipyridine **2a** formed as the major product, even though with a limited conversion of **1a**.

By increasing the reaction temperature to 80 °C and the Pd-loading up to 10 mol% (entries 10–11),[12] we found the best reaction conditions; the 2,2′-bipyridine **2a** could be prepared in 75% yield, with an increased selectivity respect to the dehalogenation process (23% yield of **3,** entry 11).

The carbon support showed to be crucial for the coupling in DES: by using Pd/Al_2O_3 or $Pd/BaSO_4$ the expected UtH product **2a** was produced in only 22–23% yield (entries 12–13) and the dehalogenative pathway was again the preferred one.

When the optimal experimental conditions (entry 11) were applied to **1a** in pure glycerol, bipyridine **2a** formed in no more than 45% yield, thus suggesting that the ionic character of DES had a notable and positive effect on the outcome of the process (entry 14).

The reductive homocoupling developed for model substrate **1a** was then applied to a wide range of chloroarenes **1b**–**u** (Scheme 1). Substrates having a 4-methyl or a 5-fluoro substituent reacted smoothly and afforded the corresponding 2,2′-bipyridines **2b,c** in good yields (75–77%). The presence of a CF_3 group in 5-position promoted the best UtH, allowing the formation of **2d** in 97% yield. The same substituent, but positioned on the carbon 4, gave a lower yield in product **2e** (52%). Electron rich substituents, such as methoxy and benzyloxy, were well tolerated furnishing products **2f,g** in moderate yields (40-65%). Of note, in the case of **2f** we found that at 80 °C the dechlorination pathway was favourite (**2f** yield 43%, 2-methoxypiridine yield 50%). The reaction selectivity could be improved by increasing the temperature to 100 °C obtaining the bipyridine **2f** in 65% yield. With satisfaction, it was also found that the decoration of starting 2-chloropyridine with a 2-pyridinylmethoxy group, in 6-position, afforded the valuable and new polydentate ligand **2h** in 58% yield.



Scheme 1. Scope of the Pd-catalyzed homocoupling of (hetero)aryl chlorides **2b**–**u** in a glycerol-based DES.[a]
[a] Reaction conditions: **1b**–**u** (0.5 mmol), Pd/C (10 mol%), $Ca(OH)_2$ (5.0 mmol), ChCl/Gly (1/2 mol/mol) 2.0 g at 80 °C for 12 h. Yields were calculated after product isolation by column chromatography, unless otherwise specified. [b] Product isolated by liquid-liquid extraction (see ESI). [c] T = 100 °C (43% yield at 80 °C). [d] 48 hours [e] From 1-chloro-4-nitrobenzene. **2o** formed in 22% yield when starting from 4-chloroaniline **1o** [f] KOH (5.0 mmol) was used as the base. **2s** was isolated in 35% yield when $Ca(OH)_2$ was employed. [g] Starting form 1-bromo-4-hexyloxybenzene. [h] T = 100 °C.

Interestingly, also the 2-chloroquinoline **1i** could be dimerized without any modification of the method. The reaction furnished the 2,2′-bisquinoline **2i** in 60% yield; such molecular scaffold has been recently suggested as a candidate for the treatment of transmissible spongiform encephalopathies.[13] Compound **1j**, reacted less efficiently than the corresponding 2-substituted isomer **1a**; in fact, the 3,3′-bipyridine **2j** formed in no more than 40% yield. After this initial survey on the UtH of chloropyridines, we then investigated the possibility that the present methodology could also promote the homocoupling reaction of other chlorinated aromatic systems such as chlorobenzene derivatives (Scheme 1). In a first attempt, 4-chloroanisole was subjected to the UtH protocol previously optimized for the *N*-heterocycles: after 12 hours at 80 °C the substrate **1k** was fully converted affording the expected biphenyl derivative **2k** in 51% yield, beside a not negligible amount of dechlorinated starting material (anisole, 35% yield).

Various efforts were performed to improve the selectivity of the homocoupling: we investigated the palladium source [$Pd(OH)_2$/C, $PdCl_2$, $Pd(tBu_3P)_2$], the catalyst support ($BaSO_4$, Al_2O_3, $CaCO_3$), the base [DBU, K_3PO_4, NaOH, KOH, $Ba(OH)_2$], the Deep Eutectic Solvent (ChCl/Urea, $MePh_3PBr$/EG, TBAB/Gly). However, the best experimental conditions persisted those already described for chlorinated *N*-heterocycles (see ESI, Table S2, for further details).

The protocol worked well with electron withdrawing groups, as observed when 4-chloro and 3-chlorobenzonitrile were subjected to the UtH affording products **2l** and **2m** in 71% and 80% yields, respectively. When 4-chloroacetophenone **1n** was used as the substrate, the conversion was almost quantitative and the biaryl **2n** could be isolated in 50% yield and only 5% of acetophenone was detected in the crude reaction mixture. In this peculiar case, the remaining ketone **1n** was converted into a mixture of acetals with glycerol (detected by LC-MS).

The synthesis of 4,4′-diaminobiaryl **2o** (benzidine), showed to be a challenging task. Starting form 4-chloroaniline, **2o** formed in only 20% yield, underlying that the presence of a strong electron-donating group favoured the dechlorination, in fact, aniline formed in 50% yield. Anyway, the benzidine **2o** could be prepared in 40% yield starting from 1-chloro-4-nitrobenzene, as described before. The coupling of substrates with alkyl groups progressed more slowly under the standard

conditions, causing a reduced selectivity of the process: isomeric 4,4′- and 3,3′-dimethyl biphenyls **2p** and **2q** formed in 25% and 38% yields, respectively. Also chlorobenzene was dimerized with a similar efficiency (**2r** yield 35%). Despite the absence of an activating electron withdrawing group on the aromatic rings, 1-chloronaphthalene could be smoothly homocoupled in 50% yield by using KOH. When standard conditions were used the product **2s** could be obtained in only 35% yield. The use of an arylbromide was also tested on 1-bromo-4-hexyloxybenzene **1t**. As expected, the UtH proceeded efficently providing biaryl **2t** in 56% yield. Also in this case, the dehalogenation process was operative and hexyloxybenzene formed in appreciable quantities (23% yield).

Finally, we applied our method to the synthesis of Abametapir (Scheme 1), a metalloproteinase inhibitor recently approved by FDA as an antiparasitic agent.[14] Treatment of 2-chloropicoline **1u** in the standard conditions afforded the product **2u** in 68% yield. We were pleased to find that, by rising the reaction temperature up to 100 °C, the target molecule Abametapir was formed in 74% yield. Of note, the isolation of **2u** was achieved by liquid-liquid extraction, so avoiding the separation by column chromatography. The estimation of two green metrics (Atom economy = 72%, and EcoScale = 65) validated the sustainability of the process (Table 1, see ESI).

Having investigated the scope of the methodology, the chance to recycle both DES and catalyst was than evaluated (Figure 2). The UtH of pyridine **1d** was chosen as the model reaction since it provided quantitatively the bipyridine **2d** (97%, Scheme 1). After treatment of **1d** in the optimal experimental conditions, the crude mixture was extracted with cyclopentyl methyl ether, a green solvent for applications in sustainable chemistry,[15] leaving the Pd-catalyst in the DES; quantitative ^{1}H-NMR revealed that bipyridine **2d** had formed in a very good yield (93%, see ESI).

Upon the addition of fresh reagents [**1d** and $Ca(OH)_2$], the catalyst and the reaction medium (DES) could be efficiently recycled for additional four runs (Figure 2). The activity of the catalyst remained almost unchanged in the first (87% yield) and second recycle (83% yield) and underwent a moderate deactivation during the third (70% yield) and fourth recycles (63%). Only from the fifth recycle the inactivation of catalyst

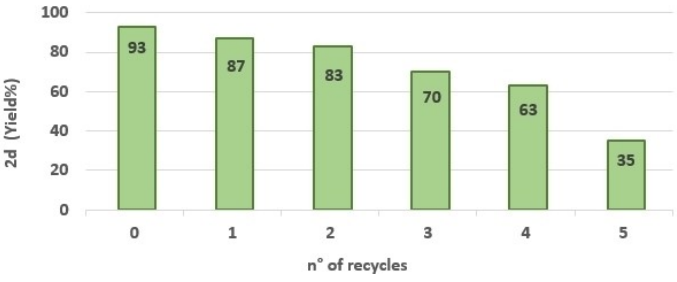
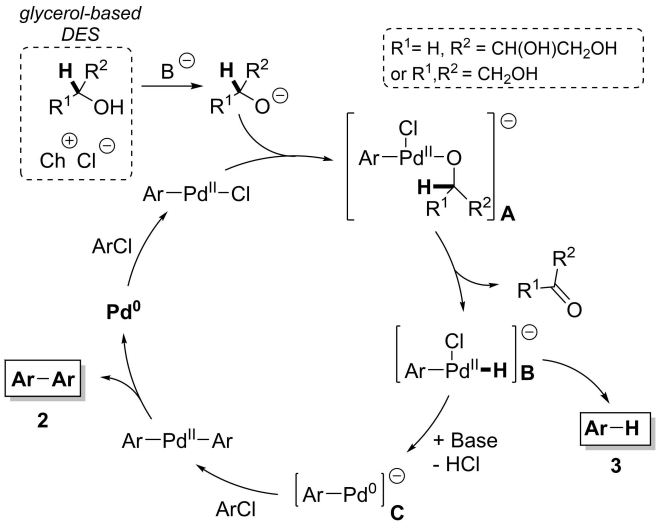


Figure 2. Recycling of Pd/C and DES in the Ullmann-type homocoupling of 2-chloro-5-trifluoromethylpyridine **1d** to afford bipyridine **2d**.



Scheme 2. Proposed reaction mechanism of UtH in a glycerol-based Deep Eutectic Solvent.

was significant as suggested by the halving of **2d** yield (35%, see ESI).

Regarding the reaction mechanism, a dual role of DES was hypothesized. Firstly, thanks to its ionic character, it could stabilize the anionic palladium species (**A**–**C**, Scheme 2) formed along the catalytic cycle, thus justifying the high reactivity of (hetero)aryl chlorides; it is known that ionic liquids are good solvents for arylhalide homocouplings.[16] Secondly, the glycerol could act as a reductant: intermediate **A** undergoes a β-hydride elimination to afford **B** which, after reductive elimination, regenerate the Pd(0) catalyst. This hypothesis is supported by the formation of benzidine **2o** starting from 1-chloro-4-nitrobenzene. In addition, the Pd(II)-mediated oxidation of alcohols is a well-documented reaction[17a] and has been invoked as a key-step in Pd-catalyzed UtH.[17b] In order to prove that also in our system alcohols can act as reducing agents, for the in situ regeneration of the active Pd-species, we performed a control experiment by adding benzyl alcohol (0.2 mL, 1.8 mmol) to the model homocoupling reaction of **1a** (0.5 mmol). After the reaction completion, we found that beside the expected bipyridine **2a** (75% yield) a considerable amount of benzaldehyde was also formed (0.25 mmol, 14% yield), thus substantiating our original hypothesis. In the postulated mechanism, a key role can be also associated to the palladium hydride **B**, that most likely triggers the formation of the unwanted arene **3** (Scheme 2).

Conclusion

In summary, a sustainable ligand-free Pd-catalyzed UtH has been developed in a glycerol-based Deep Eutectic Solvent for the preparation of (hetero)biaryls from (hetero)aryl chlorides. The methodology showed to be useful for the construction of valuable 2,2′-bipyridine scaffolds in smooth experimental conditions (80 °C) with $Ca(OH)_2$ as the base and a cheap source

of palladium (Pd/C). Moreover, the catalyst and the DES can be reused for at least 4 consecutive runs. The protocol has been applied to the synthesis of the pharmacologically relevant Abametapir (**2u**), obtained in 74% yield. Noteworthy, the coupling does not need the addition of external reducing agents, like metals, since the glycerol present in the DES acts as a safe and green organic reductant. Moreover, in all those cases where the dehalogenated substrates can be removed by evaporation, the purification of products can be performed by a simple liquid-liquid extraction, avoiding the highly environmental impact of chromatography. Although, in some cases, the yield of (hetero)biaryls is not excellent, this study highlights the potential of glycerol-based DES as green medium to exploit the catalytic activity of transition metals in their low oxidation states. Further studies are ongoing to clarify the reaction mechanism and to reduce the dehalogenation side reaction.

Experimental Section

General Methods: Deep Eutectic Solvents were prepared by heating, under stirring at 60–80 °C for 10–30 min, the corresponding individual components until a clear solution was obtained. Tetrabutylammonium bromide (TBAB)/Glycerol (Gly) (1 : 4 mol/mol), TBAB/Ethylene glycol (EG) (1 : 2 mol/mol), Methyltriphenylphosphonium bromide ($MePh_3PBr$)/EG (1 : 5 mol/mol), cholinium chloride (ChCl)/Urea (1 : 2 mol/mol), ChCl/Gly (1 : 2 mol/mol). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 400 MHz spectrometer and chemical shifts are reported in parts per million (δ). Dimethyl sulfone has been used as the internal standard for yield determination by ^{1}H-NMR analysis of the crude reaction mixtures.

General procedure for the Pd-catalysed homocoupling of (hetero)aryl halides 1a–t in ChCl/Gly: In a 10 mL round bottom flask, (hetero)aryl halide **1a–t** (0.5 mmol), Pd/C (10 mol%, 0.05 mmol, 53 mg), $Ca(OH)_2$ (5.0 mmol, 370 mg) and DES ChCl/Gly (2.0 g) were sequentially added. The mixture was stirred for 12 h at 80 °C. After this time, the reaction mixture was cooled down to room temperature and water (5 mL) was added. The reaction mixture was extracted with CPME (cyclopentyl methyl ether, 3 mL × 3). The collected organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered through a celite pad, and evaporated under reduced pressure to obtain **2a–c**, **2f**, **2j–k**, **2p–r** as pure compounds. For the other homocoupling products (**2d–e**, **2g–i**, **2l–o**, **2s–t**), after solvent evaporation, the crude was purified by column chromatography on silica gel (petroleum ether/AcOEt 90 : 10 to petroleum ether/AcOEt 50 : 50) to obtain the desired product.

Supplementary Information Summary

Details about general methods, synthetic procedures, spectroscopic data and copies of ^{1}H- and ^{13}C-NMR spectra are provided in the supplementary information.

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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 from the corresponding author upon reasonable request.

Keywords: Biaryls · 2,2′-Bipyridines · Deep Eutectic Solvents · Palladium catalysis · Ullmann coupling

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