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A Bipyridine-Palladium Derivative as General Pre-Catalyst for Cross-Coupling Reactions in Deep Eutectic Solvents

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Abstract. A versatile and DES-compatible bipyridine palladium complex has been developed as a general pre-catalyst for different cross-coupling reactions (Hiyama, Suzuki-Miyaura, Heck-Mizoroki and Sonogashira) in deep eutectic solvents. Hydrogen bond capacity of the ligand allows to keep the excellent level of results previously obtained in classical organic solvents. Palladium pre-catalyst showed a high catalytic activity for many cross-coupling reactions, demonstrating a great versatility and applicability. Also, this methodology employs sustainable solvents as a reaction medium and highlights the potential of DES as alternative solvents in organometallic catalysis.

The catalyst and DES were easily and successfully recycled. The formation of PdNPs in DES has been confirmed by TEM and XPS analysis and their role as catalyst by mercury test. The dynamic coordination of bipyridine-type ligand in the palladium complex formation has been studied via UV/Vis.

Keywords: Cross-coupling, Green chemistry, Hydrogen bonds, Ligand design, Palladium.

Introduction

Transition-metal catalyzed cross-coupling reactions comprise one of the most important classes of synthetic transformations in modern organic chemistry, providing chemists with an exceptionally powerful tool for the construction of carbon-carbon (C-C) bonds including *sp*²-*sp*² ones. These methods have been extensively used both in academic and industrial areas, including natural product synthesis, material science, pharmaceutical and fine chemical production.^[1]

Over the years, numerous protocols for cross-coupling reactions have been reported. However, most of these transformations are performed in hazardous and toxic volatile organic solvents (VOCs). The use of appropriate solvents for chemical transformations is becoming increasingly important for the sustainable development of the chemical industry. Therefore, intensive research efforts have been made to develop protocols with less ecological footprint.^[2]

Deep eutectic solvents (DES), are generally referred to combinations of two or three safe and

inexpensive components. These components can engage in reciprocal hydrogen-bonding interactions to form an eutectic mixture that has a melting point far lower than that of the individual components, owing to self-association. DES are important alternatives to volatile organic solvents, due to their interesting properties and benefits such as low cost, no flammability, recyclability, low vapor pressure, ease synthetic accessibility, benign and safe nature along with renewability and biodegradability.^[3]

Although, the application of neoteric media in metal-catalyzed reactions has undergone a tremendous growth in recent years,^[4] only a few catalytic systems were able to carry out cross-coupling reactions using sustainable solvents and there are even less reports about cross-coupling processes in DES media (Scheme 1). So, the design and synthesis of organometallic complexes compatible with DES (hydrogen bond interactions) together with keeping the catalytic activities obtained in organic solvents, is still a real challenge in order to make this methodology useful for industry.

The first reported use of DES was described by König and co-workers when they synthesized biaryls using palladium-catalyzed Suzuki-Miyaura coupling

reaction in a mannitol-DMU- NH_4Cl mixture.^[5] A few months later, the same group published the use of sugar-urea-salts melts as solvent for Stille reactions,^[6] and also Heck and Sonogashira cross-coupling reaction using sugar and L-carnitine based melts. In all these cases, the studied scope was very limited and each reaction needed different palladium pre-catalyst, as well as DES.^[7] Our research group reported cationic phosphine palladium-catalyzed cross-coupling reactions in DES media with lower catalytic amounts, but this catalytic system was not suitable for the Hiyama coupling reaction.^[8] Although, a pincer-type palladium catalyst was effective for the aforementioned reaction.^[9]

Scheme 1. Previous work of cross-coupling reactions in DES.

Recently, Capriati and co-workers published Suzuki-Miyaura coupling reactions using aryltrifluoroborates in DES^[10] and the combination of a Suzuki cross-coupling reaction and an enzymatic transamination in DES has been reported,^[11] but none of them were active pre-catalysts to all typical cross-coupling processes. Nearly for each cross-coupling reaction a different pre-catalyst is used.

Nitrogen-based ligands have received less attention compared to phosphines or NHCs in palladium-catalyzed cross-coupling reactions. However, the lower cost of nitrogen-based ligands compared with phosphines make them attractive alternative systems.^[12]

With all these precedents, and our experience in the use of DES in other Pd-catalyzed organic reactions,^[13] a new amino-bipyridine-palladium complex has been successfully applied for the first time as a general and efficient pre-catalyst to a broad cross-coupling reactions under heterogeneous conditions (including Hiyama, Suzuki-Miyaura, Heck-Mizoroki, and Sonogashira) with a great compatibility with DES due to its intrinsic capacity of hydrogen bond formation with the solvent.

Results and Discussion

Our investigations started with the synthesis and characterization of the novel bipyridine-palladium complex. Ligands **3** were synthesized following a literature procedure, and simple metalation with PdCl_2 led to the formation of complexes **4** (Scheme 2).^[14]

Scheme 2. Bipyridine-palladium catalyst synthesis.

Once we prepared and characterized the palladium complexes (see ESI), they were tested in different cross-coupling reactions starting by the Hiyama reaction. Different palladium sources were evaluated as pre-catalysts for the reaction between 4-bromoacetophenone (**5a**) and trimethoxyphenylsilane (**6**; Table 1). Prior to these studies we proved that the reaction without catalyst failed (entry 1). After this control experiment, catalyst **4a** was evaluated using

different catalytic amounts of complex **4a** (entries 2-3) obtaining higher yield with 1 mol% of catalyst.

Table 1. Optimization of the catalyst.

Entry	Catalyst (x mol%)	Yield (%) ^{a)}
1	-	0
2	4a (1 mol%)	88
3	4a (0.5 mol%)	75
4	PdCl ₂ (1 mol%)	58
5	PdCl ₂ (1 mol%) + 3a (1:1)	30
6	4a (1 mol%) + 3a (1:1)	0
7	(2,2'-bipyridine)dichloropalladium(II) (1 mol%)	5
8	4b (1 mol%)	54

^{a)} Yield determined by GC using tridecane as the internal standar

In order to prove the importance of the presence of the ligand **3a**, PdCl₂ was employed as solely pre-catalyst (entry 4) and in the presence of ligand **3a** (entry 5) obtaining 58 or 30% yield, respectively. Surprisingly, pre-catalyst **4a** with an excess of ligand **3a** inhibited the reaction (entry 6). The amino group of bipyridine moiety proved to be relevant as the use of (2,2'-bipyridine)dichloropalladium(II) as catalyst

under the same reaction conditions yielded only 5% of the product (entry 7). The use of dimethylaminobipyridine palladium complex **4b** as pre-catalyst also gave lower yield (entry 8), showing that the presence of the free amino group in pre-catalyst **4a** enhanced its activity, probably due to its interaction as a hydrogen donor with the DES structure. This cooperative effect established by hydrogen-bond network within the DES and the ligand has been previously described by García-Álvarez *et al.* in the isomerization of allylic alcohols in DES.^[15]

Once the best pre-catalytic system was established, a study to find the best reaction conditions was performed (Table 2). The reaction was performed at different temperatures, obtaining better results at 100 °C (entries 1-2). Then, we tried a sort of bases (entries 3-8), founding out that sodium bicarbonate (2 equiv.) provided the best yield (entry 7). The reaction without base did not take place (entry 9). Finally, different hydrophilic (entries 7, 10-14) and hydrophobic (entries 15-16) eutectic mixtures and also, pure glycerol and water (entries 17-18) were tested as solvents, with the best results being obtained in ChCl:glycerol (1:2; entry 7).

Once the optimum reaction conditions were established, the substrate scope was studied (Table 3). Different activated and deactivated aryl bromides were cross-coupled with trimethoxyphenylsilane (**6**). In general, very good isolated yields were obtained for biaryls **7** regardless of the electronic nature of the employed aryl bromide (entries 1-7).

Table 2. Optimization of the reaction conditions.

Entry	Base (x equiv.)	Solvent	Yield (%) ^{a)}	Entry	Base (x equiv.)	Solvent	Yield (%) ^{a)}
1	K ₂ CO ₃ (2 equiv.)	ChCl:glycerol (1:2)	0 ^{b)}	10	NaHCO ₃ (2 equiv.)	ChCl:urea (1:2)	7
2	K ₂ CO ₃ (2 equiv.)	ChCl:glycerol (1:2)	83	11	NaHCO ₃ (2 equiv.)	ChCl:ethylene glycol (1:2)	20
3	K ₃ PO ₄ (2 equiv.)	ChCl:glycerol (1:2)	70	12	NaHCO ₃ (2 equiv.)	Ph ₃ PMeBr:glycerol (1:2)	7
4	Na ₂ CO ₃ (2 equiv.)	ChCl:glycerol (1:2)	23	13	NaHCO ₃ (2 equiv.)	AcChCl:urea (1:2)	0
5	NaOAc (2 equiv.)	ChCl:glycerol (1:2)	68	14	NaHCO ₃ (2 equiv.)	Guanidine:glycerol (1:1)	0
6	NaF (2 equiv.)	ChCl:Glycerol (1:2)	30	15	NaHCO ₃ (2 equiv.)	Decanoic acid:menthol (1:2)	0
7	NaHCO ₃ (2 equiv.)	ChCl:glycerol (1:2)	88	16	NaHCO ₃ (2 equiv.)	Decanoic acid:TBAB (2:1)	0
8	NaHCO ₃ (1 equiv.)	ChCl:glycerol (1:2)	74	17	NaHCO ₃ (2 equiv.)	Glycerol	55
9	-	ChCl:glycerol (1:2)	0	18	NaHCO ₃ (2 equiv.)	H ₂ O	5

^{a)} Yield determined by GC using tridecane as the internal standar ^{b)} Reaction performed at 50 °C.

4-Chloroacetophenone was also tested but the desired product was not obtained.

Table 3. Scope of the Hiyama reaction.

Ar-Br 5	+ PhSi(OMe) ₃ 6	$\xrightarrow[\text{NaHCO}_3 \text{ (2 equiv.)}, 100^\circ\text{C}]{\text{4a (1 mol\%)}ChCl:glycerol (1:2), 16 \text{ h}}$	Ar-R 7
Entry	Ar	Product	Yield (%) ^{a)}
1	4-(MeCO)C ₆ H ₄	7a	88 ^{b)}
2	4-(O ₂ N)C ₆ H ₄	7b	90 ^{c)}
3	4-FC ₆ H ₄	7c	88
4	Ph	7d	95
5	4-MeC ₆ H ₄	7e	73
6	4-HOC ₆ H ₄	7f	70
7	4-MeOC ₆ H ₄	7g	33
8	3-pyridyl	7h	67
9	3-furyl	7i	80
10	CH ₂ Ph	7j	89

^{a)} Isolated yield after flash chromatography. ^{b)} Reaction performed during 1 h. ^{c)} Reaction performed during 2 h.

Table 4. Optimization of the reaction conditions.

Entry	Catalyst (x mol%)	Solvent	Yield (%) ^{a)}
1	4a (1 mol%)	ChCl:glycerol (1:2)	87
2	4a (1 mol%)	Decanoic acid:menthol (1:2)	98
3	4a (0.5 mol%)	Decanoic acid:menthol (1:2)	62
4	4a (1 mol%)	ChCl:urea (1:2)	33
5	4a (1 mol%)	Decanoic acid:TBAB (2:1)	16
6	4a (1 mol%)	ChCl:ethylene glycol (1:2)	93
7	4a (0.5 mol%)	ChCl:ethylene glycol (1:2)	64
8	4a (1 mol%)	Ph ₃ PMeBr:glycerol (1:2)	0
9	4a (1 mol%)	ChCl:oxalic acid (1:1)	0
10	4a (1 mol%)	ChCl:L-tartaric acid (1:1)	0
11	4a (1 mol%)	ChCl:L-malic acid (1:1)	4
12	4a (1 mol%)	Decanoic acid:menthol (1:2)	99 ^{b)}
13	4a (1 mol%)	ChCl:ethylene glycol (1:2)	91 ^{b)}
14	4a (1 mol%)	Ethylene glycol	88 ^{b)}
15	4a (1 mol%)	H ₂ O	89 ^{b)}
16	PdCl ₂ (1 mol%)	ChCl:ethylene glycol (1:2)	85 ^{b)}
17	PdCl ₂ (0.5 mol%)	ChCl:ethylene glycol (1:2)	48

^{a)} Yield determined by GC using tridecane as the internal standard ^{b)} Reaction performed in 1 h.

Various heteroaromatic bromides were used in good results (entries 8 and 9) and even, benzyl bromide gave a satisfactory 89% yield (entry 10). Different alkyl bromides (1-bromopentane and 1-bromododecane) and allylic bromide were employed with no results.

The Suzuki-Miyaura reaction was also evaluated (Table 4). Preliminary optimization studies showed that the optimal temperature was 100 °C and the best base was K₂CO₃. Different eutectic mixtures were tested, obtaining unsatisfactory results in two hydrophilic DES (entries 4 and 8), an hydrophobic mixture (entry 5) and some NADES (entries 9-11). Better yields were obtained in hydrophilic DES ChCl:glycerol (87% yield), and ChCl:ethylene glycol (93% yield) and, as well as, in the hydrophobic DES decanoic acid:menthol (98% yield; entries 1, 2 and 6). Although the best result was obtained with the hydrophobic mixture decanoic acid:menthol (entry 2), the purification step was more tedious due to the presence of a large amount of menthol after the work-up process. Also, pure ethylene glycol and water were employed but with higher yields being obtained in ChCl:ethylene glycol mixture (entries 13-15). The use of PdCl₂ salt as pre-catalyst (entries 16-17) or the use of lower amounts of catalyst (entries 3, 7 and 17) led to worse results (compare entries 7 and 17). However using a high amount of the pre-catalyst, the difference in activity between PdCl₂ and **4a** is not so significant (compare entries 13 and 16).

With the optimal conditions in hand, we explored the scope of the reaction with a variety of aryl bromides **5** and boronic acids **8** (Table 5). Regarding to aryl bromides, slightly higher yields of the desired coupled products were obtained in the presence of electron-withdrawing groups (entries 1-3).

Table 5. Scope of the Suzuki-Miyaura reaction.

Entry	Ar	R	Product	Yield (%) ^{a)}
1	4-(MeCO)C ₆ H ₄	H	7a	91 ^{b)}
2	4-(O ₂ N)C ₆ H ₄	H	7b	65
3	4-FC ₆ H ₄	H	7c	54
4	Ph	H	7d	20
5	4- ⁱ BuC ₆ H ₄	H	7k	20
6	4-HOC ₆ H ₄	H	7f	42
7	4-MeOC ₆ H ₄	H	7g	46
8	3-pyridyl	H	7h	55
9	2-thienyl	H	7l	50
10	3-quinoliny	H	7m	53
11	4-(MeCO)C ₆ H ₄	3-Me	7n	53
12	4-(MeCO)C ₆ H ₄	4-F	7o	57
13	4-(MeCO)C ₆ H ₄	4-HO	7p	70
14	4-(MeCO)C ₆ H ₄	2-MeO	7q	72

^{a)} Isolated yield after flash chromatography ^{b)} Reaction performed in 1 h.

Aryl bromides bearing electron-donating groups gave low to moderate yields (entries 4-7). Heteroaromatic bromides were tested, leading to moderate yields (entries 8-10). Then, various boronic acids were coupled with 4-bromoacetophenone giving moderate to good yields (entries 11-14), with superior yields being achieved in the case of those substrates having electron-donating groups.

The Heck-Mizoroki cross-coupling reaction was also tested (Table 6). The reaction was performed using different DES as sustainable solvent at 100 °C, obtaining the best result in ChCl:ethylene glycol mixture (entry 1). It was observed that the reaction time could be significant reduced just by heating up the reaction, obtaining similar yields at 120 °C (compare entries 1 and 8).

Table 6. Optimization of the reaction conditions.

Entry	T (°C)	t (h)	Solvent	Yield (%) ^{a)}
1	100	24	ChCl:ethylene glycol (1:2)	94
2	100	24	ChCl:glycerol (1:2)	83
3	100	24	ChCl:urea (1:2)	0
4	100	24	AcChCl:ethylene glycol (1:2)	51
5	100	24	Ph ₃ PMeBr:glycerol (1:2)	82
6	100	24	Decanoic acid:menthol (1:2)	0
7	100	24	Decanoic acid:TBAB (2:1)	0
8	120	6	ChCl:ethylene glycol (1:2)	93

^{a)} Yield determined by GC using tridecane as the internal standard.

Based on above results, we attempted the cross-coupling reactions of various aryl iodides **9** with methyl acrylate **10** (Table 7).

Table 7. Scope of the Heck-Mizoroki reaction.

Entry	Ar	Product	Yield (%) ^{a)}
1	4-(O ₂ N)C ₆ H ₄	11a	93
2	4-(MeCO)C ₆ H ₄	11b	67
3	4-F ₃ CC ₆ H ₄	11c	95
4	Ph	11d	90
5	2-MeC ₆ H ₄	11e	66
6	4-MeC ₆ H ₄	11f	79
7	2-HOC ₆ H ₄	11g	84
8	4-MeOC ₆ H ₄	11h	86
9	1-naphthyl	11i	94

^{a)} Isolated yield after flash chromatography.

The couplings of aryl iodides with an electron-withdrawing substituent at *para*-position with methyl acrylate afforded good (entry 2) to excellent yields (entries 1 and 3). Unactivated iodides or bearing electron-donating substituents gave similar results (entries 4 and 7-9) except for 2-methyl and 4-methyl derivatives that led to slightly lower yields (entries 5 and 6).

Finally, the catalytic activity of pre-catalyst **4a** in the copper-free Sonogashira reaction was evaluated (Table 8). To find the optimal conditions, the Sonogashira cross-coupling between iodobenzene (**9d**) and phenylacetylene (**12**) in DES as a model reaction was examined. Initially, different DES were tested (entries 1-5) and Ph₃PMeBr:glycerol was emerged as the best reaction medium (entry 5). Also, different organic and inorganic bases were examined (entries 6-9 and 11), obtaining the best results with *i*Pr₂NH (entry 9) and K₂CO₃ (entry 11). To evaluate which base gave better yield, higher catalytic amount of **4a** was employed (2 mol%) in longer reaction times (entries 10 and 12); showing that the organic base (*i*Pr₂NH) was the best (entry 10).

Table 8. Optimization of the reaction conditions.

Entry	Base	t (h)	Solvent	Yield (%) ^{a)}
1	<i>i</i> Pr ₂ NH	2	ChCl:ethylene glycol (1:2)	30 ^{b)}
2	<i>i</i> Pr ₂ NH	2	ChCl:urea (1:2)	33 ^{b)}
3	<i>i</i> Pr ₂ NH	2	AcChCl:ethylene glycol (1:2)	20 ^{b)}
4	<i>i</i> Pr ₂ NH	2	ChCl:glycerol (1:2)	32 ^{b)}
5	<i>i</i> Pr ₂ NH	2	Ph ₃ PMeBr:glycerol (1:2)	55 ^{b)}
6	NaOAc	2	Ph ₃ PMeBr:glycerol (1:2)	6 ^{b)}
7	Na ₂ CO ₃	2	Ph ₃ PMeBr:glycerol (1:2)	33 ^{b)}
8	K ₃ PO ₄	2	Ph ₃ PMeBr:glycerol (1:2)	54 ^{b)}
9	<i>i</i> Pr ₂ NH	2	Ph ₃ PMeBr:glycerol (1:2)	61
10	<i>i</i> Pr ₂ NH	16	Ph ₃ PMeBr:glycerol (1:2)	80 ^{c)}
11	K ₂ CO ₃	5	Ph ₃ PMeBr:glycerol (1:2)	68 ^{c)}
12	K ₂ CO ₃	16	Ph ₃ PMeBr:glycerol (1:2)	71 ^{c)}
13	<i>i</i> Pr ₂ NH	16	Ph ₃ PMeBr:glycerol (1:2)	84 ^{d)}

^{a)} Yield determined by GC using tridecane as the internal standard. ^{b)} Reaction performed at 80 °C. ^{c)} Reaction performed with **4a** (2 mol%). ^{d)} Reaction performed with **4a** (3 mol%).

Finally, a higher catalytic amount (3 mol%) afforded the coupled product **13a** with the best yield achieved (84%; entry 13).

To survey the scope and versatility of catalyst **4a** in the Sonogashira reaction, diverse aryl halides **9** were coupled with terminal alkynes (**12**) under the optimal reaction conditions (Table 9). Good yields were obtained using electron-withdrawing and electron-neutral aryl iodides (entries 1, 3, 5, 7 and 8). Different aryl bromides were tested obtaining moderate to good yields in the presence of electron-withdrawing groups (entries 4 and 6) and a lower yield with bromobenzene (entry 2). In this case, the electronic nature of the aromatic ring had a notable impact, obtaining lower yields with electron-donating aryl iodides (entries 9-12). Aliphatic terminal alkynes and heteroaryl iodides were also tested (entry 13 and 14). Ethynylcyclohexane was cross-coupled with 1-iodo-4-nitrobenzene obtaining a moderate yield (48%; entry 13) and surprisingly, electron rich thienyl derivative gave a good result (entry 14).

Table 9. Scope of the Sonogashira reaction.

$\text{Ar-X} + \text{R} \xrightarrow[\text{Ph}_3\text{PMeBr:glycerol (1:2), 16 h}]{\text{4a (3 mol\%)}, \text{ } ^i\text{Pr}_2\text{NH (2 equiv.)}, 60^\circ\text{C}}$				
Entry	Ar/X	R	Product	Yield (%) ^a
1	Ph/I	Ph	13a	84
2	Ph/Br	Ph	13a	11
3	4-(O ₂ N)C ₆ H ₄ /I	Ph	13b	90
4	4-(O ₂ N)C ₆ H ₄ /Br	Ph	13b	85
5	4-(MeCO)C ₆ H ₄ /I	Ph	13c	91
6	4-(MeCO)C ₆ H ₄ /Br	Ph	13c	71
7	4-F ₃ CC ₆ H ₄ /I	Ph	13d	83
8	4-FC ₆ H ₄ /I	Ph	13e	56
9	2-MeC ₆ H ₄ /I	Ph	13f	29
10	4-MeC ₆ H ₄ /I	Ph	13g	54
11	4-MeOC ₆ H ₄ /I	Ph	13h	15
12	2-H ₂ NC ₆ H ₄ /I	Ph	13i	64
13	4-(O ₂ N)C ₆ H ₄ /I	C ₆ H ₁₁	13j	48
14	2-thienyl/I	Ph	13k	74

^a) Isolated yield after flash chromatography.

Then, we decided to study the recyclability of our catalytic system, which is considered to be a crucial point for the sustainability of many industrial processes.^[16] For this purpose, after the completion of the reactions, the mixture was extracted with 2-MeTHF^[17] (a renewable VOC solvent) to remove all organic compounds, and the mixture of DES and catalyst was reused under the same reaction conditions. The catalyst remained active and could be efficiently recycled up to 5 consecutive cycles in Hiyama and Suzuki reactions. In the case of Heck and Sonogashira reactions, the catalyst could be recycled only 3 consecutive cycles (Figure 1).

Figure 1. Recyclability of the system.

It should be pointed out that precipitate of palladium black was also observed during the sequence of the reactions, which might explain the progressive decrease of activity detected during the recycling of the catalyst by formation of inactive species. However, the fact that a good catalytic activity was still detected after 3 or 5 runs suggested that DES components played a possible stabilizing role on the formed PdNPs.^[18] To confirm this fact, after the completion of the reaction (first cycle), the remaining mixture was analyzed by TEM (Transmission Electron Microscopy; Figure 2). As expected, palladium clusters were observed with an average of 4.16±1.10 nm diameter (Hiyama conditions), 3.17±0.69 nm diameter (Suzuki-Miyaura conditions), 1.81±0.40 nm diameter (Heck conditions) and 1.66±0.33 nm diameter (Sonogashira conditions), confirming the presence of PdNPs in all cross-coupling reactions. These data permitted to calculate that about 1919, 848, 156 and 118 palladium atoms constituted the average cluster, respectively.^[19]

Figure 2. TEM images of PdNPs after the first cycle of the Hiyama (A), Suzuki-Miyaura (B), Heck (C) and Sonogashira (D) reactions.

XPS (X-ray Photoelectron Spectroscopy) analysis was performed to confirm the oxidation state of the catalyst after the catalytic reactions (Figure 3). This analysis showed that part of the initial palladium(II) was reduced to palladium(0).

Figure 3. A) XPS of pre-catalyst **4a** before the reaction, B) XPS of palladium catalyst after the reaction.

The mercury test was performed in order to check if the generated nanoparticles catalyzed the reaction. The reaction was set up under Hiyama standard conditions and Hg (2.5 equiv.) was added, observing only a 2% of conversion of desired product **7a**. Also, kinetic studies were performed for all cross-coupling reactions observing an induction period with low catalyst loadings in all cases. During this initial period, palladium nanoparticles were not observed by TEM images (see ESI). Only, the nanoparticles isolated from the first Hiyama cycle, after aqueous work-up and centrifugation of the aqueous mixture, were used in a second cycle with fresh solvent and reagents obtaining a slightly decrease in the yield (**7a**, 56%). These results seem to indicate that catalyst **4a** plays a pre-catalyst role and palladium(0) nanoparticles might be the real catalyst for the reaction, and they are generated in the reaction medium.

Experimental UV/Vis titration studies in acetonitrile at different wavelengths revealed that palladium was initially coordinated by two bipyridine ligands **3a** (Figure 4 and ESI). Surprisingly, characterization analysis of the crude mixture of pre-catalyst **4a** synthesized with an excess of ligand **3a**, showed only the presence of one ligand by one palladium atom (see ESI: Complex NMR analysis). Therefore, we began to suspect that the UV/Vis

titration showed the formation of an initial complex with a palladium atom coordinated with two ligands, probably by the more donating nitrogen atoms (NH_2 moiety: A in Figure 5).

Figure 4. Molar ratio = 1:2 (metal:ligand) obtained by UV/Vis titration studies at 224 nm and 222.8 nm.

Figure 5. Different coordination of palladium with ligand **3a**.

Then, this initial complex evolves towards the thermodynamic complex formed by coordination with the two nitrogen atoms of the bipyridine unit (C), probably through an intermediate complex involving the coordination with the amino pyridine subunit of the ligand (Figure 5, coordination B).

To obtain more information about the formation of complex **4a**, an UV/Vis study of the evolution of the coordination of the ligand **3a** ($5 \cdot 10^{-5}$ M in acetonitrile) to palladium salt $[\text{Pd}(\text{MeCN})_2\text{Cl}_2]$ ($2.6 \cdot 10^{-4}$ M in acetonitrile) with the time was carried out, showing that the initial complex ($t = 0$ min) is changing and the final shape ($t = 6$ h) is in consonance with the spectrum of the previously synthesized and isolated complex **4a** ($2.5 \cdot 10^{-4}$ M in acetonitrile; Figure 6).

Figure 6. Evolution of palladium coordination with ligand 3a.

Conclusion

A novel and versatile pre-catalyst has been successfully applied for the first time to common cross-coupling reactions usually performed in toxic dipolar aprotic solvents (Hiyama, Suzuki-Miyaura, Heck-Mizoroki and Sonogashira), in environmentally friendly eutectic mixtures. It is important to note that: (i) the same palladium pre-catalyst is able to catalyze a broad number of cross-coupling reactions, keeping the excellent results obtained in hazardous organic solvents, (ii) the reactions proceed in DES under aerobic conditions, and (iii) the use of DES as a reaction medium allows the catalyst recycling (up to 3 or 5 consecutive times depending on the cross-coupling reaction) without loss of catalytic activity. Different studies showed the dynamic behaviour of palladium complexes as well as its role as pre-catalyst, with nanoparticles of palladium(0) seeming to be the real catalyst. All these results highlight the broad potential of DES as substituents for hazardous organic solvents in any type of cross-coupling reaction, just by choosing the correct pre-catalyst, making organic synthesis more sustainable and reducing its negative impact on the environment.

Experimental Section

General. Solvents and reagents were used as obtained from commercial sources and without purification. ^1H NMR (300 MHz) spectra were recorded on Bruker AC-300 NMR spectrometers respectively in proton coupled mode. ^{13}C NMR (75.5 MHz) spectra were recorded on Bruker AC-300 NMR spectrometers respectively in proton decoupled mode at 20 °C; chemical shifts are given in δ (parts per million) and coupling constants (J) in Hertz. Low-resolution mass spectra (EI) were obtained at 70 eV on an Agilent Technologies GC/MS-5973N spectrometer or Agilent 5973 Network spectrometer with Direct Insertion Probe (73DIP-1), giving fragment ions in m/z with relative intensities (%) in parentheses. Infrared spectra were measured on a Jasco FT/IR-4100 Fourier Transform Infrared Spectrometer. Melting points were obtained with a Reichert Thermovar apparatus. XPS analyses were carried out on a VG-Microtech Mutilab. TEM images were obtained on a JEOL, model JEM-2010 equipped with an X-ray detector OXFORD INCA Energy TEM 100 for microanalysis (EDS). The chromatographic analyses (GC) were determined with a Younglin 6100 instrument equipped with a flame ionization detector and 30 m HP-5 capillary column (0.25 mm diam, 0.33 mm film thickness), using nitrogen (2 mL/min) as a carrier gas, $T_{\text{injector}} = 270$ °C, $T_{\text{column}} = 60$ °C (3 min) and 60–270 °C (15 °C/min), $P = 12$ psi. Thin layer chromatography (TLC) was carried out on Schleicher & Schuell F1400/LS 254 plates coated with a 0.2 mm layer of silica gel; detection by UV₂₅₄ light. Column chromatography was performed using silica gel 60 of 40–63 mesh. UV-Vis spectra were recorded in a SHIMADZU UV-1603 apparatus.

General Procedure of Hiyama reaction. To a solution of aryl halide (0.5 mmol), sodium bicarbonate (1 mmol), catalyst **4a** (0.005 mmol) in 1 mL of DES, 0.75 mmol of organosilane was added and the resulting mixture was stirred at 100 °C for 16 h. The mixture was quenched with water and extracted with EtOAc (3 $\times$ 5 mL). The combined organic phases were dried over MgSO_4 , followed by evaporation under reduced pressure to remove the solvent. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate) and/or distillation to give the corresponding products.

General Procedure of Suzuki-Miyaura reaction. To a solution of aryl halide (0.5 mmol), potassium carbonate (0.75 mmol), catalyst **4a** (0.005 mmol) in 2 mL of DES, 0.55 mmol of boronic acid was added and the resulting mixture was stirred at 100 °C for 4 h. The mixture was quenched with water and extracted with EtOAc (3 $\times$ 5 mL). The combined organic phases were dried over MgSO_4 , followed by evaporation under reduced pressure to remove the solvent. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate) and/or distillation to give the corresponding products.

General Procedure of Heck-Mizoroki reaction. To a solution of aryl halide (0.5 mmol), sodium acetate (0.75 mmol), catalyst **4a** (0.005 mmol) in 1 mL of DES, 0.60 mmol of methyl acrylate was added and the resulting mixture was stirred at 120 °C for 6 h. The mixture was quenched with water and extracted with EtOAc (3 $\times$ 5 mL). The combined organic phases were dried over MgSO_4 , followed by evaporation under reduced pressure to remove the solvent. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate) and/or distillation to give the corresponding products.

General Procedure of Sonogashira reaction. To a solution of aryl halide (0.5 mmol), diisopropyl amine (1 mmol), catalyst **4a** (0.015 mmol) in 2 mL of DES, 0.60 mmol of phenylacetylene was added and the resulting mixture was stirred at 60 °C for 16 h. The mixture was quenched with water and extracted with EtOAc (3 $\times$ 5 mL). The combined organic phases were dried over MgSO_4 , followed by evaporation under reduced pressure to remove

the solvent. Products were usually purified by chromatography on silica gel (hexane/ethyl acetate) and/or distillation to give the corresponding products.

General procedure for the preparation of DESs. A mixture of hydrogen-bond donor and hydrogen-bond acceptor, with the previously specified molar ratio, was added in a round bottom flask under an inert atmosphere. The mixture was stirred for 60 minutes in a T range between 65 and 80 °C obtaining the corresponding DES.

General Procedure for Recycling Experiments. The reaction was performed according to the general procedure. Once the reaction was completed, the reaction mixture was cooled to room temperature, and 2-MeTHF (3 x 3 mL) was added to the reaction vessel. The biphasic mixture was stirred for 5 min, and the upper phase (VOC-phase, mainly unreacted organic reagents and products) was separated by decantation and analyzed by GC using tridecane as the internal standard. The eutectic mixture with the remaining PdNPs (bottom phase) was dried under vacuum and was charged again with fresh reagents and base, repeating the process.

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A Bipyridine-Palladium Derivative as General Pre-Catalyst for Cross-Coupling Reactions in Deep Eutectic Solvents

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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