ACS Sustainable Chemistry & Engineering

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Letter

Biobased Functional Ionic Liquids for a Novel Approach to Sonogashira Coupling in the Absence of Copper and External Bases

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Cite This: https://doi.org/10.1021/acssuschemeng.6c00237

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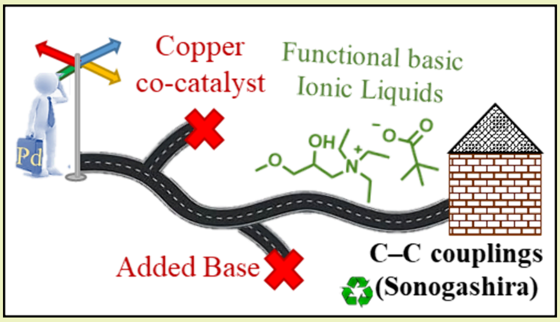

ABSTRACT: We report the first use of functional renewable ionic liquids, with favorable ecotoxicological profiles toward representative microorganisms, in efficient and recoverable nanoparticle-based catalytic systems to promote copper-free Sonogashira coupling reactions in the absence of externally added bases. These systems, based on palladium nanoparticles immobilized on glycerol-derived $[N_201]X$ ionic liquids bearing basic anions, achieved the coupling of differently substituted substrates in 1 h. Contrarily, analogous ionic liquids without basic character and classic imidazolium ionic liquids —$[BMIm]PF_6$— were not active for the test reaction at all, even if a large excess of an external base was added. Different product selectivities were observed, as a function of the different hydrophilic nature (and water content) of the ionic liquid. Therefore, this novel approach improves the catalytic results under milder conditions and minimizes waste generation, as observed in the green metrics determined for the benchmark process, offering a more sustainable and effective alternative in cross-coupling transformations.

KEYWORDS: *Functional ILs, Cu-free Sonogashira, glycerol, renewable, nanocatalysts, toxicity*

INTRODUCTION

Metal-catalyzed cross-coupling reactions represent nowadays one of the most powerful tools for the sustainable preparation of high-value organic chemicals.[1,2] Most of these processes require the use of bases to promote the limiting step.[3] Nevertheless, to circumvent the need of strong bases, the Sonogashira cross-coupling reaction, between a terminal alkyne and aryl or vinyl halides, can be catalyzed by the combination of palladium and copper.[4] Similar mechanisms involving Pd/palladacycle linked by a multistep transmetalation process have been proposed for Cu-free reactions.[5] Because this is a field of intense study, a growing number of copper-free catalysts have been developed, but always requiring the addition of external bases.[6,7]

Ionic liquids (ILs) have been deeply studied as reaction media in C–C coupling reactions.[8−10] This is a consequence of the capacity of ionic solvents to both solvate reagents and stabilize metal catalysts.[10−13] However, traditional ILs have important limitations, such as high cost, well-identified ecotoxicity issues, and difficult scaling-up and purification processes.[14−16] Nevertheless, a new generation of biobased ILs, more benign, and from renewable sources, has been developed in the recent years.[17,18]

Although green molecular solvent/base blends have been described in the literature,[19,20] in this letter we report, for the first time, the use of functional ILs derived from glycerol, of renewable origin, accessible, with benign toxicological profile, and presenting basic character, to actively promote —in a recyclable process— the Pd nanoparticle-catalyzed Sonogashira coupling, as a benchmark reaction, in the absence of copper and any externally added base.

EXPERIMENTAL SECTION

All reagents used in this work were purchased of analytical grade from Sigma-Aldrich and Alfa Aesar. ILs were synthesized according to our previously optimized methodology.[18] All of the ILs were characterized by ^1H NMR and HRMS, determining their water content by TGA. ^1H-, ^{13}C-, and ^{19}F NMR spectra ($[d_6]$DMSO, δ ppm, J Hz) were obtained by using a Bruker AV-400 instrument with TMS as the standard. High-resolution mass spectroscopy was carried out in a Bruker MicroTof-Q, by electrospray ionization (HRMS-ESI). The impact of glycerol-derived ILs on microbial growth was tested by broth microdilution in which *Escherichia coli*, *Staphylococcus epidermidis*, and *Saccharomyces cerevisiae* were exposed to a range of ILs concentrations. Due to the letter nature of this article, the detailed synthesis of glycerol-derived ILs, their characterization and spectra,

Received: January 7, 2026
Revised: March 11, 2026
Accepted: March 12, 2026

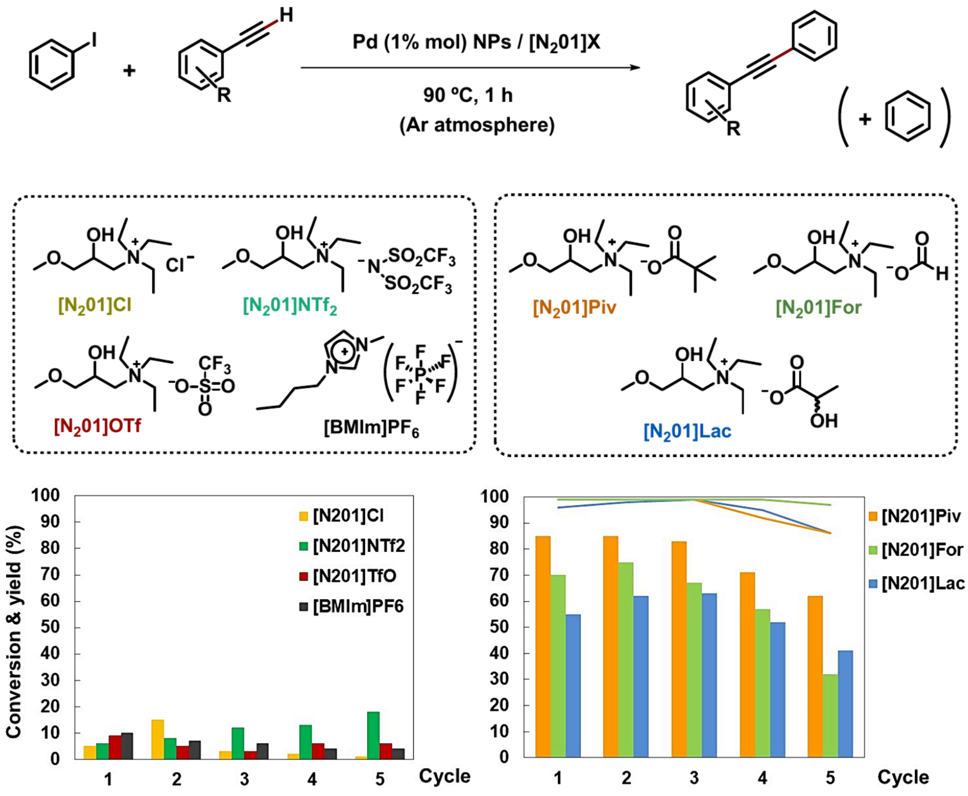

Figure 1. Results in the copper-free Sonogashira reaction between iodobenzene **1** and phenylacetylene **2** catalyzed by Pd NPs (1 mol %) over ILs without (left) and with (right) basic character. Iodobenzene **1** conversions are represented by lines and product **3** yields by solid bars.

the preparation and characterization of catalytic systems, the cross-coupling reaction procedure and analysis, the green metrics calculations, and the toxicological study are fully detailed in the Supporting Information.

RESULTS AND DISCUSSION

First, the biobased ILs were prepared at the large-scale through a recently developed sustainable methodology starting from a glycerol-based platform molecule.[18,21] Different anions presenting an intrinsic basic nature, such as pivalate (Piv), lactate (Lac), and formate (For), together with anions with no basic character, such as chloride (Cl), triflate (OTf), and bistriflimide (NTf$_2$), were combined with the glycerol-based [N$_2$01] triethylammonium cation (Figure 1, Table S-1). The studied ILs are thus renewable, liquid, and stable in a wide temperature range, presenting tunable properties through modifications of the cation chain and the selected anion.[18]

Stable and recoverable catalytic systems were designed by immobilizing spherical palladium nanoparticles (Pd NPs), with an average size of 1.4 ± 0.4 nm (Figure S-16), in glycerol-derived ILs. These designer systems can remain in the air for extended periods without the nanoparticles agglomerating.

All of these catalytic systems were applied to a palladium-catalyzed benchmark reaction, the copper-free Sonogashira coupling reaction (also known as Heck-Cassar-Sonogashira reaction) between iodobenzene **1** and phenylacetylene **2** (Figure 1). Optimized reaction conditions (90 °C, 1.5 equiv of alkyne, Pd 1 mol %, Argon atmosphere, and 1 h reaction time) were used. When catalytic systems were applied, whose IL did not have a basic nature, such as Pd NPs/[N$_2$01]Cl, diphenylacetylene **3** yields under 10% were obtained for 5 reaction cycles (Figure 1, left). In order to avoid possible problems of substrate solubilization in the ILs or coordination of the Cl$^-$ anion to palladium, the systems Pd NPs/[N$_2$01]NTf$_2$ and Pd NPs/[N$_2$01]OTf were studied. However, in both cases, similar results were observed. Finally, using a typical commercial hydrophobic imidazolium IL, the resulting system Pd NPs/[BMIm]PF$_6$ did not improve the yields, which also remained below 10%.

Contrarily, when using catalytic systems based on ionic liquids having an intrinsic basic character, such as Pd NPs/[N$_2$01]Piv, Pd NPs/[N$_2$01]For, and Pd NPs/[N$_2$01]Lac, in the absence of any externally added base, total iodobenzene **1** conversions and diphenylacetylene **3** yields up to 85% were observed (Figure 1, right). These catalytic systems were recovered and reused for 5 reaction cycles without significant loss of catalytic activity, especially for the case of the system Pd NPs/[N$_2$01]Piv.

It is important to highlight that, in the case of using the "non-basic" ILs, the addition of a 6:1 molar excess of external strong bases did not barely promote the coupling reaction. More interestingly, in the case of the ILs with basic nature, we observed that the addition of an external base to the reaction medium barely caused an additional favorable effect on the catalytic activity. As introduced above, this basic IL nature comes from the presence of the pivalate anion, which is the conjugate base of the weak carboxylic acid pivalic (Figure 1). Mårtensson and co-workers investigated *p*-substituted phenylacetylenes and 4-iodobenzotrifluoride as coupling partners using a copper-free Pd$_2$(dba)$_3$·CHCl$_3$−AsPh$_3$ catalyst.[22] In this work, the electron-poor alkynes and the phenyl acetylene **2** were hypothesized to react via a pathway in which the key step would be the proton transfer from an uncharged complex to produce a Pd-acetylide intermediate (Figure 2b up), showing the important role of the base in the alkyne deprotonation.

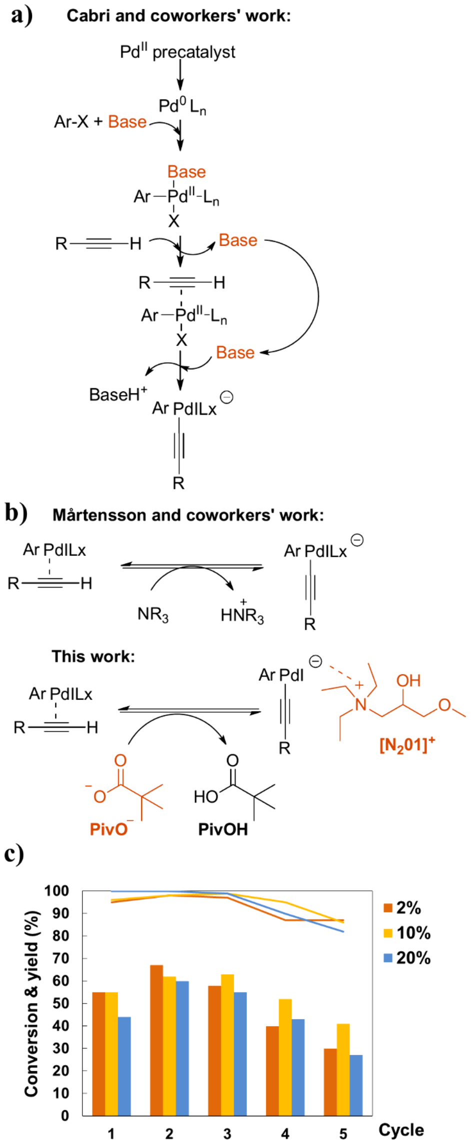

Figure 2. a) Key steps in the neutral mechanism for the copper-free Sonogashira coupling of aryl halides.[23] b) Possible alkyne activation step catalyzed by Pd NPs/[$N_2$01]Piv.[22] c) Effect of IL water content (wt %) in the Pd NPs/[$N_2$01]Lac system (0.5 mmol **1**, Pd 1 mol %, Ar atmosphere, 90 °C, 1 h).

More recently, Cabri and co-workers have proposed alternative mechanisms for couplings promoted by $(PPh_3)_2PdCl_2$.[23] For the case of aryl halides, they propose a neutral mechanism in which the base contributes in the initial reduction of Pd(II) to Pd(0), which may not possibly be the case of our Pd(0) NPs, and also as a ligand in the oxidative addition (Figure 2a).

Among the bases normally used in Sonogashira reactions, secondary and tertiary amines present conjugate cations that usually have a pK_a ranging from 8.3 to 11.2. Given that the pK_a of pivalic acid is 5.03, the activity of this system seems to be quite surprising. However, it is important to highlight a significant advantage of our method: since the base is the solvent anion itself, it is always present in a notable excess (6:1). Undoubtedly, the use of a 6:1 excess of base would favor the reaction, but it probably is not the only reason. In fact, pK_a measurements refer to the behavior in water. In our case, the solvent is ionic; thus, the ionic pairs should weakly increase the Brønsted basic character of pivalate anion to promote the key step (Figure 2b down). This alkyne activation by the IL anion would evidence its active role as a proton-accepting species. Finally, in the case of pivalate and lactate, these anions are poorly coordinated to Pd, thus probably not limiting the catalytic activity of the system. Indeed, it is possible to find interesting precedents in Cu-free Sonogashira reactions, promoted by active palladacycles, occurring in the presence of excess of added [Bu_4N]Ac —in which the basicity of acetate would be comparable to that of pivalate, lactate, and formate anions employed in this study— but not with [H_4N]Ac, in agreement with the above-commented role of the counter-ion.[7,24]

These results indicate that basic ILs act as functional solvents, capable of promoting the reaction on their own. Indeed, to the best of our knowledge, this work represents the first example of a Sonogashira reaction catalyzed by palladium nanoparticles in the absence of copper and externally added bases. Additionally, ILs seem to provide unique Pd speciation and NP stabilization that enhances catalyst recyclability, as widely described in the literature.[10]

It is also interesting to note that different product selectivities were observed as a result of the nature of the basic IL used. While the Pd NPs/[$N_2$01]Piv system provides selectivity values over 80−90%, in the case of the Pd NPs/[$N_2$01]Lac system, selectivities decreased in some cases to 60%. In this case, a side reaction of hydrogen transfer to iodobenzene **1** was observed with the formation of benzene **4**. Having analyzed the experimental results, we can conclude that the differences in the selectivity toward diphenylacetylene **3** are due to the IL anion nature. Thus, when using the glycerol-derived IL with pivalate anion —bearing a *terc*-butyl group in its structure (see Figure 1)— near quantitative selectivities are observed. However, when using the IL displaying a lactate anion, its hydroxyl group was supposed to play an active role in the hydrodeiodination of the Sonogashira substrate **1**, thus decreasing in this case the selectivity toward the desired product and promoting the benzene **4** formation. This effect had been observed in other coupling reactions with iodobenzene **1** when using as reaction medium deep eutectic solvents containing glycerol monoethers with a higher number of hydroxyl groups.[12]

This phenomenon prompted us to study the effect of the water content on the lactate-based catalytic system. Three different scenarios were assessed: 2, 10, and 20 wt %. The water content was controlled by drying the ILs prior to the preparation of the catalytic system and then adding the corresponding amounts of water.

As observed in Figure 2c for the system Pd NPs/[$N_2$01]Lac, the effect of the presence of water is significant in the studied benchmark reaction. The catalytic activity is not affected by the water content (see conversion lines), but the best yields of **3** were obtained for a water presence of 10 wt %. The almost water-free systems showed slightly worse results, probably due to the notably higher viscosity of the reaction medium after drying the ionic liquid,[18] while the systems with higher water content (i.e., 20 wt %) showed a worsened selectivity, as expected due to the above-mentioned side hydrogen transference reaction. Similar conclusions were observed when using the other basic IL systems.

Finally, a scope of differently substituted substrates was studied for the best basic catalytic system, Pd NPs/[$N_2$01]Piv. These results can be observed in Figure 3. In all cases, using aromatic and olephinic alkynes, quantitative iodobenzene **1**

https://doi.org/10.1021/acssuschemeng.6c00237
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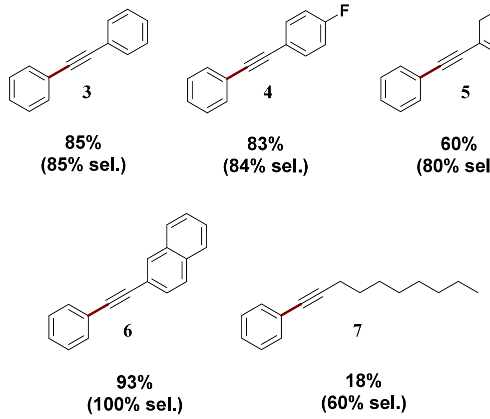

Figure 3. Yields and desired product (**3**–**7**) selectivities in the substrate scope for **1** catalyzed by Pd NPs (1 mol %)/[$N_2$01]Piv in the absence of externally added base (Ar atmosphere, 90 °C, 1 h). The only detected side product is benzene **4**.

conversions were obtained in 1 h, with selectivities of 80–100% toward the desired products (**3**–**6**). We mention that substrates less activated than **1**, such as chlorobenzene and bromobenzene, showed expected low conversions (<15%) under the conditions described.

A study was conducted to evaluate the effectiveness and greenness of the developed methodology in comparison with the state-of-the-art. A selection of works were made on the Sonogashira coupling of arylbenzene **1** and phenylacetylene **2** promoted by copper-free Pd catalysts. Despite most works in the literature using ILs were described using copper cocatalysts,[25] we also included a copper-free $Pd(PPh_3)_2Cl_2$ system immobilized on an IL, tetrabutylphosphonium 4-ethoxyvalerate ($[TBP]_4$EtOV).[26] In general, our base-free method allowed us to obtain a similar diphenylacetylene **3** yield to that of the reported works that use significant excesses of added base —from 1.5 to 3 equiv of potassium carbonate or triethylamine—and, in most cases, in shorter reaction times — 1 h vs 2 to 24 h. Also, in our method, the use of Pd nanoparticles avoids the need of using Pd-activating ligands such as the phosphines in the mentioned IL's work (nonrenewable and with significant environmental impact)[26] or ionic surfactants such as the very recent work of Oftadeh et al.[27]

The full green metrics study is gathered in Table 1 (additional details in Tables S-4 to S-14). The impact of recycling the catalytic system was also evaluated when possible (italic lines in Table 1).

For the model reaction studied, the method proposed in this work provides values for the E-factor and process mass intensity (PMI) that are clearly comparable to those of the greenest methods found in the literature, with the exception of the work of Oftadeh et al.[27] However, this study is based on the use of a surfactant-aided homogeneous Pd catalyst that cannot be reused. Interestingly, both parameters, indicating the magnitude of waste generation, are increased in our method to be the best ones after reusing the catalyst for 5 times. As can be seen in Table 1, the atomic economy (AE) of our work is significantly better than the other methods due to the absence of an added base to promote the reaction. Also, the stoichiometric factor (SF) is clearly competitive with the state-of-the-art, only surpassed by the work of Karami et al.[29] Nevertheless, this parameter, mainly affected in our case by the use of analkyne **2** excess, could be easily optimized by recovering this alkyne after the reaction and reusing it in a second reaction cycle. Moreover, it should be noted that, after the catalyst reaches the end of its useful life, Pd is quantitatively recovered by centrifugation, and then both Pd and IL can be recovered separately and reused.

In addition to the favorable metrics and the renewable origin of ILs, we have conducted a preliminary assessment of their toxicological impact. The absence of ecotoxicity of salt [$N_2$00]Cl to several bioindicators,[33] together with the experimental log P values of ILs,[18] seemed to anticipate good ecotoxicological profiles for our ILs. Thus, the impact of glycerol-derived ILs on the microbial growth of Gram-positive and Gram-negative bacteria and a fungal strain was tested over a wide range of concentrations. Average MIC_{90} values for each microbial species are given in Table 2.

Gram-positive bacteria *S. epidermidis* and model fungi *S. cerevisiae* were highly tolerant to the ILs tested, which indicates that our ILs have a low toxicity against these two species under these experimental conditions. Surprisingly, the Gram-negative bacteria was more susceptible to the action of our ILs, since lower concentrations were sufficient to arrest *E. coli* growth, while the growth of the two other microbial species was unaffected. Higher susceptibility of Gram-negative bacteria

Table 1. Green Metrics Analysis of Our Novel Methodology and Comparison with the State-of-the-Art for the Studied Model Reaction

	AE	E	SF	PMI[c]	Catalyst	Solvent	Added base
This work	58%	15.8	1.2	16.8	Pd NPs (1 mol %)	[$N_2$01]Piv	-
a	*58%*	*4.7*	*1.2*	*5.7*			
Barros et al. 2008[28]	40%	185	1.8	186	$Pd(PPh_3)_2$ (5 mol %)	Ethanol	K_2CO_3 (2 equiv)
Orha et al. 2019[26]	44%	15.1	1.3	16.1	$Pd(PPh_3)_2Cl_2$ (0.5 mol %)	$[TBP]_4$EtOV	NEt_3 (1.5 equiv)
b	*44%*	*7.3*	*1.3*	*8.3*			
Karami et al. 2023[29]	40%	20.0	1.1	21.0	PdL_2/TiO_2 (0.5 mol %)	Ethanol	K_2CO_3 (1 equiv)
a	*40%*	*20.4*	*1.1*	*21.4*			
Oftadeh et al. 2025[27]	44%	4.74	1.5	5.74	$Pd(OAc)_2$-$P(NBu_2)_3$ (0.5–2 mol %)	CPME + SDS/H_2O[d]	NEt_3 (3 equiv)
Golovenko et al. 2025[30]	44%	40.6	1.5	41.6	Pd-PDMS (0.1 mol %)	CD_3OD	K_2CO_3 (2.5 equiv)
Ghiglietti et al. 2024[31]	53%[e]	14.5	1.5	15.5	$Pd(OAc)_2$-XPhos (0.75–1.9 mol %)	Aqueous surfactant	NEt_3 (3 equiv)
Pawar et al. 2024[32]	40%	24.8	1.2	25.8	Pd–Fe_3O_4@GO	Isopropanol	K_2CO_3 (1.5 equiv)

[a] Green metrics obtained for the reuse of the catalyst 5 times. [b] Only 4 cycles were available in this work. [c] PMI of reaction is shown in order to make a fair comparison between all methods. [d] Cyclopentyl methyl ether as the solvent and sodium dodecyl sulfate as a surfactant. [e] This AE is increased compared to other methods due to the use of bromobenzene instead of iodobenzene.

https://doi.org/10.1021/acssuschemeng.6c00237

Table 2. Minimal Inhibitory Concentration (MIC$_{90}$) of ILs (%*v*/*v*) against Microbial Species

IL [a]	*E. coli*	*S. epidermidis*	*S. cerevisiae*
[N$_2$01]Piv	1.40	45	>45
[N$_2$01]For	2.81	>22.5	22.5
[N$_2$01]Lac	3.03	>12.13	>12.13
[N$_2$01]Cl	11.25	22.5	22.5
[N$_2$01]OTf	11.75	>23.5	>23.5

[a] An IL was considered toxic when MIC$_{90}$ < 10% (orange), harmful when MIC$_{90}$ = 10 − 20% (yellow), and not harmful when MIC$_{90}$ > 20% (green).

than that of Gram-positives had previously been reported for imidazolium and other conventional ILs.[34,35] Some studies suggested that lipopolysaccharides (a molecule present in the cell wall of Gram-negative bacteria only) could mediate interaction between *E. coli* and ILs.[36]

In summary, functional glycerol-derived ILs present good toxicological profiles for representative microbial species, including *S. epidermidis* and *S. cerevisiae*, especially in the case of the least toxic, [N$_2$01]Piv, the IL responsible for the best catalytic performance.

CONCLUSIONS

This work reveals the potential of basic renewable ionic liquids (ILs) as functional solvents, acting as both reaction media and catalytic promoters, in this case due to their intrinsic basic character, and for the first time, in combination with nanoparticle-catalysts. The catalytic systems designed by immobilizing palladium nanoparticles on glycerol-derived ILs bearing basic anions achieved in 1 h the coupling of a scope of differently substituted substrates with 80−100% selectivity, in the absence of copper species and externally added bases. On the contrary, glycerol-derived ILs without basic character, as well as a classic imidazolium IL —[BMIm]PF$_6$—, were not active in the studied coupling reaction, even if a large excess of external base was added. Therefore, the use of functional [N$_2$01]X ionic liquids allows the stabilization, activity, and recycling of the catalyst, minimizing the waste generation thanks to the combination of high catalytic activity and absence of additional bases and cocatalysts. The relevance of this methodology is thus evident in the practical implications, operational simplicity, catalyst recyclability, and simple work-up. Moreover, the green metrics analysis of the method developed using our functional ILs shows comparable or superior greenness to those of previous methods described in the literature, especially when considering the possibility of reusing the catalyst. Finally, the study of antimicrobial activity reveals that functional ILs derived from glycerol, most notably the one exhibiting the best catalytic performance, [N$_2$01]Piv, are not harmful toward representative model bioindicators, including Gram-positive bacteria (*S. epidermidis*) and model fungi (*S. cerevisiae*), thus presenting favorable ecotoxicological profiles. Therefore, our work represents an advance in Green Chemistry principles including 1) Prevention of waste generation; 2) Improvement of atomic economy in Sonogashira reactions by the absence of base; 3 and 12) Less hazardous chemical syntheses; 5) Safer solvents; 7) Renewable feedstocks in the catalytic/solvent systems; and 9) Development of active catalysts. It is expected this novel approach will allow to eliminate the need to add external bases in future works to promote catalytic coupling processes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.6c00237.

Synthesis, structures, and characterization of the functional ionic liquids used in this work, the preparation of the catalytic systems, the characterization of the catalytic systems, the Cross-Coupling reaction procedure, the determination of results and GC calibrations, the green metrics calculations, and the toxicity study details (PDF)

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Funding

This work was financially supported by the Agencia Estatal de Investigación of Spain (PID2021−125762NB-I00) and the Gobierno de Aragón (E37_23R).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was developed within the scope of the project PID2021-125762NB-I00 from Agencia Estatal de Investigación of Spain. Financial support from the Gobierno de Aragón (Research Group E37_23R) is acknowledged. The authors thank the Laboratory of Advanced Microscopy from the Universidad de Zaragoza for their assistance in TEM characterization. L. Torné from the Servicio de Análisis Térmico of CEQMA-Universidad de Zaragoza is acknowledged for her valuable assistance in the determination of the ILs water content.

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