

Steps forwards towards the substitution of conventional solvents in the Heck-Mizoroki coupling reaction: glycerol-derived ethers and DES as reaction media.

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13 reaction: glycerol-derived ethers and DES as reaction
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40 **ABSTRACT**

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42 Glycerol-derived ethers and their eutectic mixtures with two renewable ammonium salts (**ChCl**
43 and **N00Cl**) are effectively used as new green solvents for the immobilization of PVP-Palladium
44 nanoparticles. Those air-stable, selective and recoverable catalytic systems are applied in the
45 benchmark Heck-Mizoroki coupling reaction between iodobenzene and *n*-butyl acrylate in order
46 to evaluate the influence of the different solvation properties of the solvent on the reaction results.
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54 The HBD ability (α acidity) of the solvent seems to play a crucial role in the reaction selectivity.
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Keywords: *Glycerol ethers, DES, green solvents, Pd-NPs, Heck-Mizoroki, IL*

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INTRODUCTION

The development of green solvents emerges as a key point to achieve sustainable processes. The need of replacing the traditional organic solvents is motivated by their non-renewable origin and their unfavorable properties such as flammability, volatility and toxicity.¹ Among a plethora of green solvents, water,² bio-based solvents,³ fluoruous solvents,⁴ supercritical and gas-expanded fluids (SCFs)⁵ and ionic liquids (ILs)^{6,7} have attracted great attention. However, nowadays research is focused on bio-based solvents in order to overcome some drawbacks such as the low volatility and solubility of organic compounds in the case of water, the availability and toxicity of fluorinated solvents, the technical requirements in the use of SCFs, or the toxicity, cost and hard synthesis of ILs.^{5,8-10} Among them, glycerol,¹¹⁻¹³ and its versatile derivatives such as glycerol esters, ketals, carbonates and ethers are standing out as useful bio-solvents.^{13,14}

Green and efficient methodologies for the synthesis of glycerol monoethers,¹⁵⁻¹⁷ and also di- and triethers,¹⁸⁻²⁰ have been recently developed. Interestingly, the physical-chemical properties of these glycerol-derived ethers can be easily tuned by modifying the number or the nature of the substituents, thus offering a wide range of properties values.¹⁸⁻²¹ Besides they present a very low ecotoxicity,^{22,23} which make them suitable for different applications, for example the solubilization of natural products in water,²⁴ or as alternative media for enzymatic catalysis.²⁵

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3 Among bio-based solvents, Deep Eutectic Solvents (DES) or in general Low Melting Mixtures
4 (LMM) are emerging as green alternative to ionic liquids.^{26 27–29} Glycerol has been profusely used
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6 in the formulation of DES with different properties, standing out glyceline (mixture of choline
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8 chloride and glycerol in a 1:2 molar ratio).^{30,31} More recently, glycerol derivatives such as mono-
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10 and diethers have also been included as the HBD component in this kind of ionic solvents.²¹
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15 The use of neoteric solvents in catalysis is essential to improve the sustainability of the catalytic
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17 processes. Among them, metal-catalyzed cross-coupling reactions, outstanding Suzuki-Miyaura,
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19 Heck-Mizoroki and Sonogashira, can be considered as one of the most powerful organic synthetic
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21 tool with industrial interest.³² The importance of the solvent in these processes has been recently
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23 highlighted by Sherwood et al.³³
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27 Palladium catalysts, including homogeneous or supported Pd(II) complexes, play a key role in
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29 this kind of organic strategies.^{34,35} Outstanding results have also been achieved by using palladium
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31 nanoparticles (Pd-NPs) grafted onto solid supports such as clays, microporous polymers, graphene
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33 and carbon-based materials.³⁶ Some of these systems have shown very good recoverability in
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35 solvent-free Heck-Mizoroki reaction between iodobenzene and *n*-butyl acrylate.^{37,38}
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39 Steps forwards have been taken and a different approach from solid supports is being envisaged
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41 with the use of neoteric solvents for the immobilization and stabilization of NPs and as reaction
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43 media for catalytic coupling reactions. Thus bioalcohols, including glycerol and its derivatives
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45 such as 1,2-propanediol or diacetin,^{12,39} other bio-based solvents as 2-MeTHF, ethyl lactate or γ -
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47 valerolactone,^{33,39} water,^{35,40} ILs,^{41–44} and DES,^{27,45} are being applied in those reactions with
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49 promising results. Unfortunately, the use of these solvents often requires the presence of co-
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51 solvents in order to increase the solubility of the substrates or alternative reaction activation
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53 methods,³⁹ e.g. microwaves when using Laponite®/Pd-NPs immobilized onto an ionic liquid.⁴⁶
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3 In this work we focus on the study of the influence of the nature of the glycerol derived solvent
4 in the Pd-NPs catalyzed benchmark the Heck-Mizoroki coupling reaction between iodobenzene
5 and *n*-butyl acrylate. The use of glycerol-derived solvents both as stabilizers and reaction media
6 for the design of recoverable Pd-NPs catalytic systems for the Heck-Mizoroki coupling reaction is
7 also envisaged.
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14 15 **EXPERIMENTAL SECTION**

16 17 18 **Materials and methods**

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20 Glycidol, glycerol, 3-chloropropane-1,2-diol, *n*-butyl acrylate, triethylamine, palladium (II)
21 acetate, PVP, *n*-decane, *n*-pentane, octanol, [bmim]PF₆ and deuterated solvents were purchased
22 from Sigma–Aldrich. Methanol, ethanol, isopropanol and potassium hydroxide were purchased
23 from Scharlab. Iodobenzene, 2,2,2-trifluoroethanol, butanol, 1-hexanol, phenol and choline
24 chloride were purchased from AlfaAesar. All the products, except potassium hydroxide, were
25 purchase as reagent grade. Alcohols were dried and distilled over CaH₂ previous to use.
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35 Conversions and reaction yields were determined by Gas Chromatography (GC) using a Hewlett
36 Packard 7890 Series II chromatograph equipped with a column of phenyl silicone 5.5% (Zebron
37 ZB-5HT Inferno 30 m × 0.25 mm × 0.25 μm) and helium as carrier gas, and provided with a Flame
38 Ionization Detector (FID). GC temperatures programs are gathered in the Supplementary
39 Information.
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47 48 **Preparation of the glycerol-derived solvents**

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50 For the synthesis of the glycerol **R00** monoethers, the catalyst, potassium hydroxide (20% mol),
51 was completely dissolved in the corresponding dried alcohol (15:1 mol with respect to glycidol)
52 in a round bottomed flask. Then the mixture was heated at 65 °C and stirred under argon and the
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glycidol (1 mol) was added dropwise for 15 minutes. The reaction was monitored by extracting samples that were neutralized with 0.3 M HCl previous to injection in GC. After total consumption of glycidol, the temperature was cooled down to 25 °C, KOH neutralized with 0.3 M HCl and the salts filtered off. All the glycerol monoethers were purified by vacuum distillation except in the case of 3-phenoxy-1,2-propanediol (**Ph00**). This compound was purified by column chromatography (SiO₂/ hexane/AcOEt 40:60). The solvents were fully characterized by spectroscopic techniques (see Supplementary Information).

For the preparation of the glycerol-derived eutectic solvents, salts were mixed with the glyceryl **R00** monoether in a 1:2 molar ratio and stirred under argon at 70 °C for 10 hours until a homogeneous colorless liquid was obtained, assuring the HBA/HBD ratio by ¹H-NMR. Previously, the ammonium salts, choline chloride (**ChCl**) was recrystallized from absolute ethanol, filtered off and dried under vacuum and or *N,N,N*-triethyl-2,3-dihydroxypropan-1-aminium chloride (**N00Cl**) was prepared according to our previously described methodology.²¹ The ammonium salts were then mixed with glyceryl **R00** monoether in a 1:2 molar ratio and stirred under argon at 70 °C for 10 hours the until a homogeneous colorless liquid was obtained, assuring the HBA/HBD ratio by ¹H-NMR.

Synthesis and immobilization of the palladium nanoparticles

Suspensions of PVP-Pd-NPs (3 mM) were prepared as described elsewhere.⁴⁷ For immobilizing the Pd-NPs, 1 mL of the prepared suspension was mixed with 1 mL of the desired glyceryl ether, DES, glycerol or IL ([bmim]PF₆) and stirred for several minutes in a Schlenk flask. Finally, ethanol was totally eliminated under vacuum and moderated stirring obtaining the PVP-Pd-NPs/solvent catalytic systems (0.3% Pd). Pd/NPs systems were analyzed by TEM micrograph using a JEOL-2000 FXII microscope.

General procedure for the miscibility tests

The miscibility tests were carried out in triplicate by mixing and stirring 0.5 mL of a weighed glyceryl solvent with 0.5 mL of the organic solvent (*n*-pentane, AcOEt, DE, etc.). Then the two phases were separated, evaporating the organic solvent under reduced pressure and quantifying in both phases the final weight of the glycerol derivative and, in the case of DES, the HBA/HBD ratio.

General procedure for Heck-Mizoroki coupling reactions

1 mL of the PVP-Pd-NPs previously immobilized onto the glycerol-derived solvent (3 mM Pd) was placed into a 20 mL Schlenk flask. Then a reaction mixture formed by 0.1 mL of iodobenzene (0.9 mmol), 0.2 mL of *n*-butyl acrylate (1.4 mmol) and 0.3 mL of triethylamine (2.17 mmol) was added. The closed Schlenk flask was stirred and heated at 100 °C in a silicone oil bath for 4 hours. After this time, the system was cooled down and the mixture was extracted with *n*-pentane (2 × 10 mL and 2 × 5 mL) at 65 °C using vigorous stirring and at least 20 minutes periods between each extraction. Finally, the catalytic system was dried under vacuum previous to a new reaction cycle. The purification of the products was carried out by column chromatography.

***n*-Butyl (*E*)-3-phenylprop-2-enoate:** Colorless liquid; b.p. 245 °C; $t_R = 8.42$ min. **¹H-NMR** (DMSO-*d*₆, 400 MHz): δ 7.69-7.73 (m, 2H,), 7.65 (d, 1H, $J_{trans} = 16.1$ Hz), 7.40-7.44 (m, 3H), 6.63 (d, 1H, $J_{trans} = 16.0$ Hz), 4.15 (t, 2 H, $J = 6.6$ Hz,), 1.62 (quint, 2H, $J = 6.9$ Hz), 1.36 (sext, 2H, $J = 7.4$ Hz), 0.90 (t, 3H, $J = 7.4$ Hz). **¹³C-NMR** (DMSO-*d*₆, 100 MHz, APT): δ 166.2 144.3, 134.0, 130.4, 128.9, 128.3, 118.1, 63.7, 30.3, 18.7, 13.5. **HRMS** (ESI⁺): m/z (calc.) = 227.1043,

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3 m/z (found) = 227.1047 [M+Na⁺]. **IR**: ν 3000, 2880, 1750, 1630, 1490, 1440, 1180 cm⁻¹. **GC-MS**
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5 (EI) m/z : 204 [100%, M⁺].
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8 **Biphenyl**: White solid; t_R = 6.20 min. **¹H-NMR** (DMSO-d₆, 400 MHz): δ 7.64-7.70 (m, 4H), 7.44-
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10 7.50 (m, 4H), 7.37 (tt, 2H, J_o = 7.3 Hz, J_m = 1.2 Hz). **¹³C-NMR** (DMSO-d₆, 100 MHz, APT): δ
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12 140.2, 128.9, 127.4, 126.7. **IR**: ν 3033, 1477, 725 cm⁻¹. **GC-MS** (EI) m/z : 154 [100%, M⁺], 76,
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20 RESULTS AND DISCUSSION

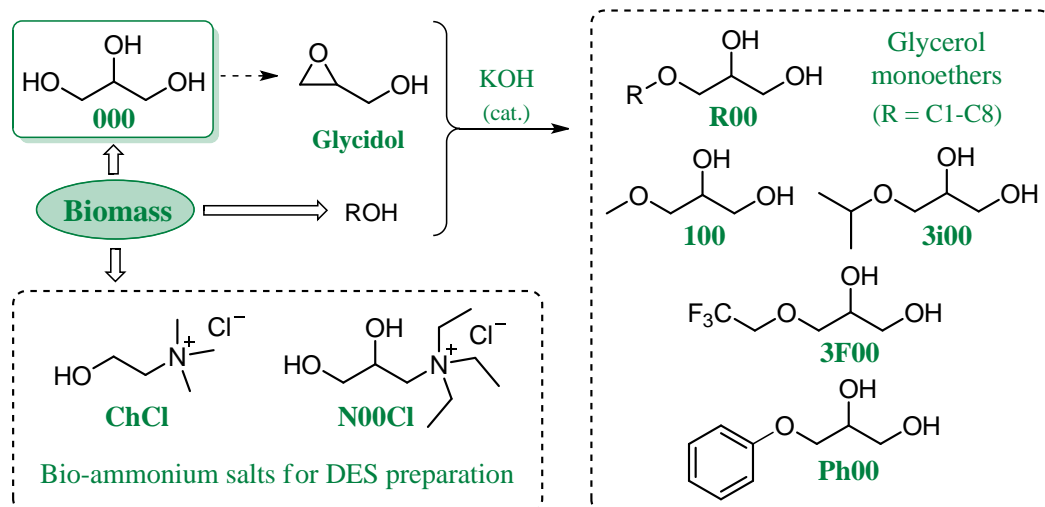
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23 Design and preparation of the selected glycerol-derived solvents

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26 First, a selection of glycerol-derived solvents, including differently substituted glyceryl
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28 monoethers, **R00**, and their eutectic mixtures with two ammonium salts as HBA, **ChCl** and **N00Cl**
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30 (see Scheme 1), were prepared in order to have a set of solvents with different properties and
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32 solvation abilities. Glyceryl monoethers, bearing in C₁ methoxy (**100**), ethoxy (**200**), isopropoxy
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34 (**3i00**), butoxy (**400**), hexyloxy (**600**), octyloxy (**800**), 2,2,2-trifluoroethoxy (**3F00**) and phenoxy
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36 (**Ph00**) groups, were synthesized starting from glycidol by means of basic catalysis with total
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38 atomic economy, as described in our previous work.¹⁶ Glyceryl diethers and triethers were a priori
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40 not considered for the study attending to the higher volatility and hydrophobicity criteria (see
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42 miscibility study). Eutectic's type mixtures (henceforth DES) were prepared by mixing at 70 °C
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44 the corresponding ammonium salts (ChCl or **N00Cl**) with the previously synthesized glyceryl
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46 ethers (**R00**), in a 1:2 HBA/HBD molar ratio. An ionic liquid [bmim]PF₆ was also tested in sake
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48 of comparison.
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54 **Scheme 1.** Synthesis of the selected glycerol-derived solvents.
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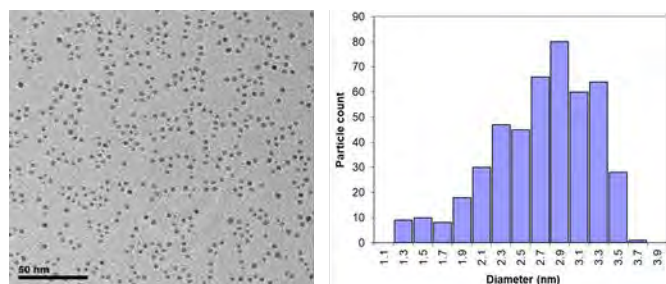


Preparation and dispersion of PVP-Pd-NPs into the different reaction media

Poly-*N*-vinylpyrrolidone (PVP)-Pd nanoparticles (NPs) were prepared according to a straightforward procedure based on the chemical reduction of H_2PdCl_4 to Pd(0), using PdCl_2 as metallic precursor, ethanol as reductive agent and PVP as polymeric stabilizer. These reaction conditions allow the reduction of the palladium, provoking the change of the ethanolic solution coloration from yellow to black, as well as the nucleation and growth of the forming NPs.

This effective and fast methodology led to the synthesis of spherical-shaped and homogeneous PVP-Pd-NPs (see Figure 1), with an average size of 2.7 ± 0.6 nm. In addition, the synthesized NPs showed a good stability, maintaining their aspect and catalytic activity for long periods (even years), which facilitated the storage and utilization without any need of an inert or reductive atmosphere. Once synthesized, Pd-NPs were dispersed onto the selected glycerol-derived solvents, as well as, for sake of comparison, onto a standard ionic liquid, 1-butyl-3-methylimidazolium ($[\text{bmim}]\text{PF}_6$). Thus, the PVP-Pd-NPs ethanolic solutions were mixed and stirred with the desired amount of each glycerol-derived solvent, until the obtaining of a homogeneous suspension. Then ethanol was slowly evaporated, affording the dispersion of the

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3 NPs in the neoteric solvent, thus avoiding palladium agglomeration. These resulting PVP-Pd-
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5 NPs/solvent systems were also homogeneous and presented a long stability under air.
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17 **Figure 1.** TEM micrograph and size distribution of the Pd-NPs synthesized in this study.
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19 20 21 **Miscibility study for the choice of the optimal extraction solvent**

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24 After preparing the catalytic systems and previous to the catalytic study, it is necessary to find out
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26 the best extraction solvent for quantitatively recovery of the desired reaction products without
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28 altering the catalytic system, that is, without extracting neither the Pd-NPs nor the solvent. To this
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30 effect a miscibility study was carried out, by mixing the different glyceryl media with measured
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32 amounts of selected common organic solvents, including *n*-pentane, diethyl ether (DE), ethyl
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34 acetate (AcOEt) and methyl isobutyl ketone (MIBK), and measuring the extracted amount of the
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36 glyceryl ether and the remaining HBA/HBD ratio in the case of DES.
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41 In general, as it can be seen in Figure 2, glyceryl ethers were miscible with dipolar organic
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43 solvents, but not with aliphatic or aromatic hydrocarbons as *n*-pentane or toluene (all the solvent
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45 abbreviations are gathered in the Supplementary Information). However, even using apolar
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47 solvents most of the monoethers (**200**, **400**, **500**, **600** or **800**), as well as the glyceryl diethers and
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49 triethers, were increasingly extracted. This fact prompted us to discard these media for pursuing
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51 the catalytic tests, despite their suitability for stabilizing the Pd-NPs. In order to preserve the
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53 catalytic systems during the reaction product extraction step, **100**, **300** and **3F00** monoethers, as
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well as glycerol, **000**, and their corresponding eutectic mixtures were selected for the catalytic study.

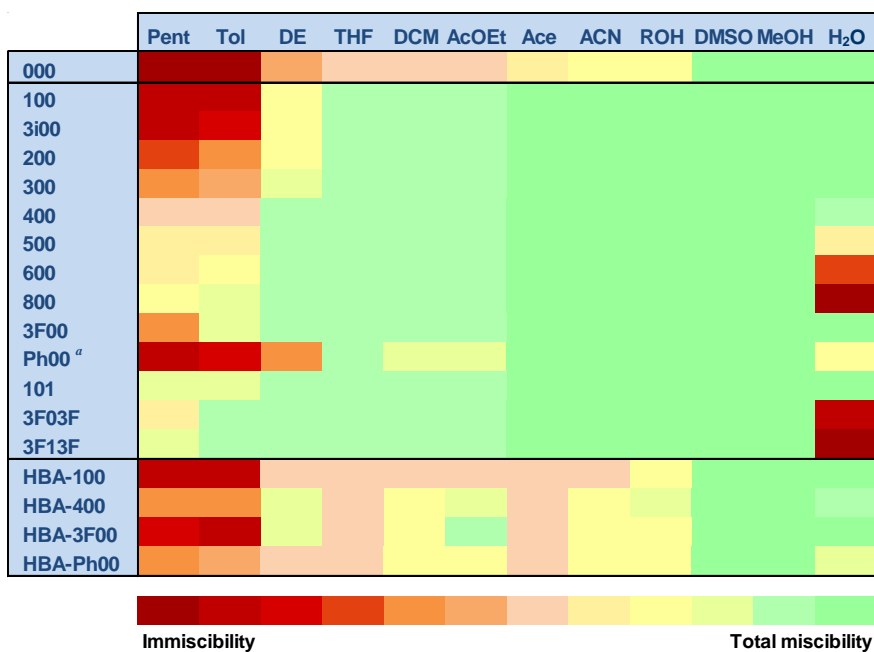


Figure 2. Miscibility of the glycerol solvents (row) versus organic solvents or water (column). ^a Solubility of Ph00 (solid).

A deeper study of the extraction of the selected solvents reveals that in the case of DES, the use of polar solvents as MIBK or AcOEt favors the extraction of the HBD monoether component, modifying the initial HBA/HBD ratio from 1:2 to even 30:1, and thus destroying the eutectic mixture. When using slightly polar solvents, such as diethyl ether, less than 6 wt% of the **R00** component was extracted in the case of glycerol, short-chained and fluoruous **R00** monoethers and aromatic (**Ph00**) ether mixtures. Finally, when using a hydrocarbon as *n*-pentane less than 2 wt% of the solvent was extracted in all the cases, guaranteeing the DES stability throughout the extraction process. For this reason, in this study, *n*-pentane was selected as the optimal extraction solvent in all the cases, that is **000**, **100**, **3i00**, **3F00** and **Ph00** monoethers and their mixtures with both ammonium salts, **ChCl** and **N00Cl**.

Catalytic study in the benchmark Heck-Mizoroki coupling reaction

PVP-Pd-NPs immobilized in glycerol-derived solvents were tested in the benchmark Heck-Mizoroki reaction between iodobenzene and *n*-butyl acrylate, in the presence of triethylamine (Scheme 2).

Scheme 2. Benchmark Heck-Mizoroki reaction between iodobenzene and *n*-butyl acrylate, catalyzed by PVP-Pd-NPs immobilized onto glycerol derived solvents.

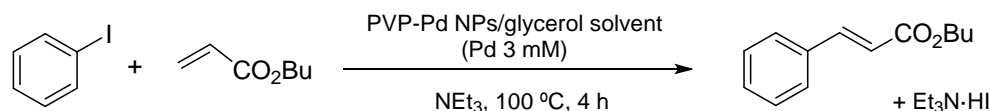


Table 1 gathers iodobenzene conversions and product yields obtained in the benchmark reaction with the different solvent systems. At 100 °C and using 0.3% mol total Pd in 1 mL of solvent, iodobenzene conversions over 95% were achieved within 4 hours in all the cases, except when using glycerol as solvent. Shorter reaction times were not enough for providing total conversions, thus reaction time was fixed in 4 hours for further reactions.

Table 1. Results of Pd-NPs catalyzed reaction of iodobenzene with *n*-butyl acrylate in glycerol-derived solvents.^a

Solvent	Conversions (%) ^b					Yields (Selectivities) (%) ^{b,c}				
	Cycle 1	2	3	4	5	Cycle 1	2	3	4	5
[bmim]PF₆	100	100	100	92	93	97 (97)	93 (93)	93 (93)	86 (93)	87 (93)
Glycerol	22	89	100	100	100	18 (82)	69 (83)	93 (93)	54 (54)	93 (93)
100	100	100	100	100	100	98 (98)	89 (89)	89 (89)	91 (91)	93 (93)
3i00	98	100	100	100	100	98 (100)	99 (99)	99 (99)	92 (92)	93 (93)
3F00	95	100	100	100	100	90 (95)	86 (86)	88 (88)	85 (85)	81 (81)
ChCl-000	100	100	100	100	100	99 (99)	99 (99)	94 (94)	93 (93)	95 (95)
ChCl-100	100	100	100	96	95	98 (98)	97 (97)	95 (95)	92 (96)	89 (94)
ChCl-3F00	100	100	100	98	96	99 (99)	95 (95)	93 (93)	83 (85)	61 (64)
N00Cl-000	98	100	100	100	97	97 (99)	100(100)	99 (99)	98 (99)	96 (99)
N00Cl-100	100	100	100	100	100	100(100)	100(100)	96 (96)	96 (96)	86 (86)
N00Cl-3i00	100	100	100	100	100	99 (99)	99 (99)	100(100)	95 (95)	97 (97)

N00Cl-3F00	100	100	100	100	100	100(100)	92 (92)	91 (91)	81 (81)	52 (52)
N00Cl-Ph00	100	100	100	100	100	100(100)	84 (84)	75 (75)	126(126)	85 (85)

^a **Reaction conditions:** 0.9 mmol iodobenzene, 1.4 mmol *n*-butyl acrylate and 2.2 mmol triethylamine, 0.3% mol total palladium in 1 mL of the neoteric solvent, at 100 °C during 4 hours. ^b Results determined by gas chromatography using *n*-decane as standard. ^c Regio- and stereoselectivity to *n*-butyl cinnamate were 100% in all the cases. All the results are the average of at least two parallel reactions.

In the first run, selectivity towards the desired product, *n*-butyl cinnamate, was in between 95%–100% with all the glyceryl ethers and DES media except when using glycerol. It is noteworthy that regio- and stereoselectivity were 100% in all the cases.

In order to evaluate the utility of the different solvent systems for the Pd-NPs recovery, their reuse in 5 consecutive runs was evaluated. For this, first the optimization of the extraction protocol of the organic products of the reaction was carried out, choosing pentane as extraction solvent, and studying several extractant volume, temperatures and time. Maximum amounts of the reaction products were extracted at 65 °C using *n*-pentane (2 × 10 mL and 2 × 5 mL), and the Pd-NPs immobilized onto the IL or the glycerol-derived solvent were applied to a new catalytic cycle by just adding new reagents.

Concerning the extraction process effectiveness, it strongly depended on the temperature, the solvent volume and the stirring time and rate. Once experimental procedure was optimized, the quantitative recovery of the *n*-butyl cinnamate, as well as the triethylamine and non-reacted substrates was achieved without removing palladium from the catalytic system. It is important to note that *n*-butyl cinnamate yields were determined after the extraction process, so results gathered in Table 1 represent both the reaction cinnamate yield and the effectiveness of extraction procedure of the organic products from the reaction medium.

As it can be seen in Table 1, all the Pd-NPs suspended onto glycerol-derived solvents provided conversions from 95% to 100% for 5 consecutive runs, while using the IL [bmim]PF₆ a progressive

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3 decay from 100% to 92% was observed. In the case of the reaction in pure glycerol, an increase of
4 conversion from 22% to 100% in three runs was detected. These results seem to indicate the need
5 of an activation period of the catalyst in the case of the glycerol system, which is probably due to
6 diffusional limitations caused by the high viscosity of this solvent.
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13 A close look at the reaction yields and selectivities upon recovery shows an influence of the
14 nature of the solvent. Two effects can be seen. First depending on the use of a glycerol-derived
15 ether either alone or in a DES, and second the influence of the nature of the glyceryl ether
16 component when using DES systems. Table 1 shows that the best results in the reaction between
17 iodobenzene and *n*-butyl acrylate were obtained when using DES (**N00Cl-000**, **N00Cl-R00**, **ChCl-**
18 **000** and **ChCl-R00**). This can be evidenced by comparing the results for one glycerol-derived
19 ether (**100**). As shown in Figure 3, Pd-NPs immobilized in **N00Cl-100** provided the best yields
20 (over 95% in 4 consecutive runs), followed by the ones in **ChCl-100** media, **100** alone, and all the
21 three provided better yields than the IL [bmim]PF₆. When comparing the influence of the nature
22 of the glyceryl ether on the reaction yields when using for example **N00Cl-R00** mixtures (Figure
23 4), the best results were obtained using glycerol (**000**), **3i00**, **100** as the HBD component in the
24 mixtures. Albeit, when using fluororous (**3F00**) or phenoxy (**Ph00**) glycerol derivatives, poorer
25 selectivities upon recovery were observed.
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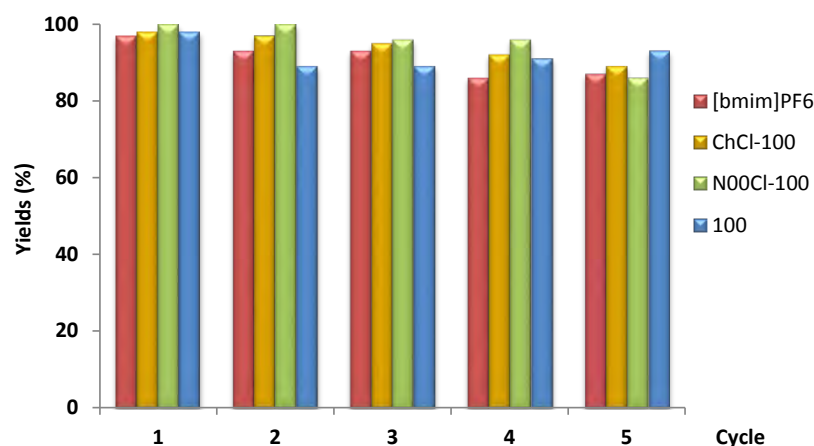


Figure 3. *n*-Butyl cinnamate yields in the reaction catalyzed by Pd-NPs immobilized systems in the different families of solvents studied.

In the case of using **N00Cl-Ph00** medium, as can be seen in Figure 4, cinnamate yields did not follow a systematic trend. This was due to a non-optimum product extraction that provided non-reproducible yields, even over 100% for the fourth cycle. This behavior was probably provoked by the higher viscosity of this solvent compared to the rest at the extraction temperature (159 cSt versus 20–120 cSt of the other DES or 5–10 cSt of **R00** monoethers).

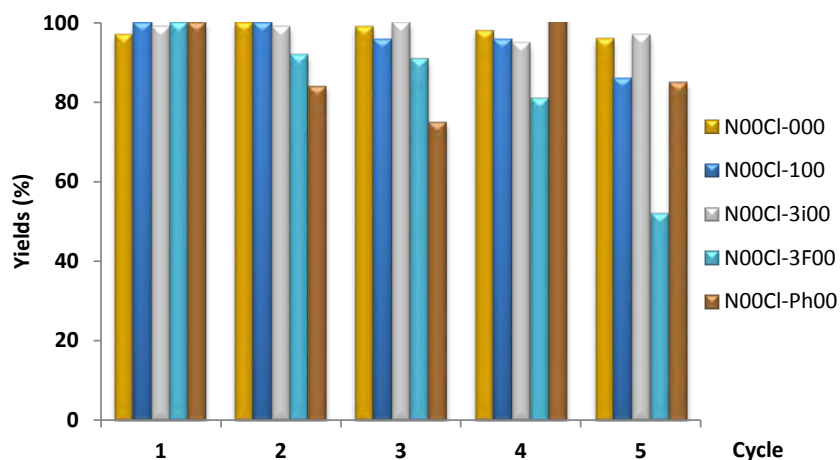


Figure 4. Influence of the nature of the glyceryl ether (HBD component) in the yields of *n*-butyl cinnamate upon recovery of the Pd-NPs catalytic systems.

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3 Results in Figure 4 demonstrate the possibility of reusing the catalytic systems by just extracting
4 reaction products from the catalytic media. Only in the case of using **3i00** systems, some additional
5 amount of monoether should be added in order to avoid Pd-NPs agglomeration. Fortunately, this
6 solvent addition does not seem to trigger the catalyst deactivation (see the **N00Cl-3i00**
7 recoverability results in Table 1).
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12 Summarizing, PVP-Pd-NPs immobilized in all the glycerol-derived media, except when using
13 fluorous derivatives, provided excellent results in the benchmark coupling reaction, surpassing the
14 selectivity, catalytic activity and recoverability obtained using the ionic liquid [bmim]PF₆ or pure
15 glycerol. In addition, the utilization of eutectic mixtures instead of glycerol or **R00** glycerol-
16 derived ethers provided the best yields and selectivities, additionally stabilizing the palladium
17 nanoparticles and minimizing solvent losses in the extraction step.
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22 Above all this, product yields herein described are higher than many of the ones gathered in the
23 literature for the same Heck-Mizoroki reaction catalyzed by supported Pd-NPs,⁴⁷ or palladium
24 catalysts in DES media such as reline or glyceline,⁴⁵ using lower amounts of catalyst and reducing
25 the reaction temperature and time. Finally, the good stability of the presented catalytic systems,
26 never observing the black palladium precipitation, also allowed to carry out an air tolerant
27 catalysis.
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30 31 32 **Influence of the nature of the solvent in the activity, selectivity and recoverability of the** 33 **catalyst** 34 35

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38 Although good results are obtained in most of the cases, some decay in selectivity was observed,
39 particularly when using **3F00** containing systems. This prompted us to study the influence of the
40 nature of the solvent in the reaction results in order to better design recoverable catalytic systems.
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42 To better compare, Table 2 gathers accumulated Turnover Number (TON) of the catalytic systems
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in the different reaction media for five consecutive runs (see Figure S-54 for graphical representation).

Table 2. Accumulated TON for all the different studied solvent systems.

Solvent	Accumulated TON	Solvent	Accumulated TON
[bmim]PF ₆	1354	N00Cl-000	1455
Glycerol	971	N00Cl-100	1420
100	1366	N00Cl-3i00	1455
3i00	1429	N00Cl-3F00	1236
3F00	1277	N00Cl-Ph00	1321
ChCl-000	1426		
ChCl-100	1399		
ChCl-3F00	1280		

As it has been previously stated, catalytic activity and selectivity in the Heck-Mizoroki coupling reaction, are affected by the polarity of the reaction medium.³³

Reaction results, conversion and selectivity, are influenced by the solvation of the chemical species of the reaction pathways, namely reagents, transition states, intermediates and products. As it has been evidenced by DFT calculations as it has been presented by Zhao and coworkers for S_N2 or tautomerization reactions.^{48,49}

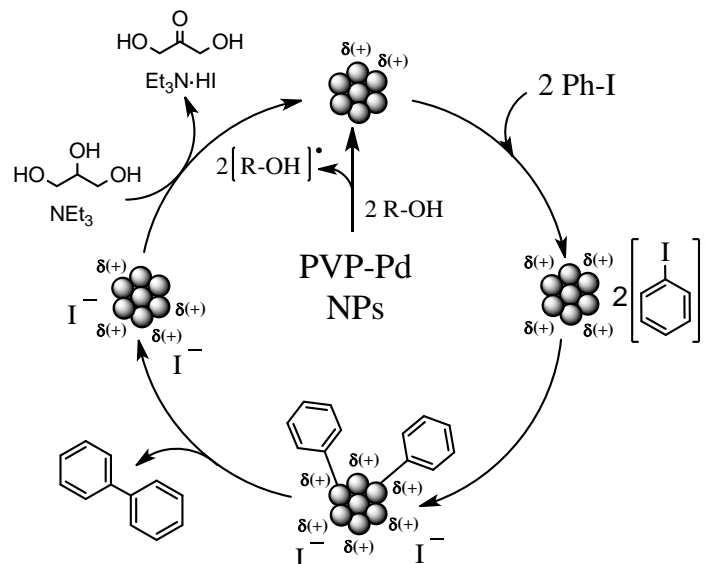
We first analyzed this effect on iodobenzene conversions (Table 2). In the case of glycerol, its polarity limited the solubility of the hydrophobic substrates and its high viscosity provoked diffusion limitations to the reaction components in the medium. In our study, this was evidenced by lower conversions and lower accumulated TONs. In the case of glycerol derivatives and

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3 [bmim]PF₆, the total conversions seem to indicate a good solvation of the organic substrates and
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5 products.
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9 It can be concluded that in our study conversion is not affected by the nature of the solvent when
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11 miscibility and viscosity problems are avoided.
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14 Taking into account the observed 100% in regio- and stereoselectivity in all the cases, selectivity
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16 changes upon recovery are caused by a reduction in chemoselectivity due to the concurrence of two
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18 competitive reactions, whose products were detected and characterized by GC-MS. First, traces of
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20 a biarylated coupling product could be detected in some of the systems, mainly the ones containing
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22 **3F00** ether. The formation of this diphenylpropenoate is due to the fact that the reaction product
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24 is also an olefin which can compete with the *n*-butyl acrylate in the π -coordination to Pd, thus
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26 entering into the catalytic cycle. Nevertheless, this by-product was detected in very low amounts
27
28 probably due to the use of an excess of *n*-butyl acrylate and a minor reactivity of cinnamate. Hence,
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30 the main reaction by-product detected was biphenyl. Very small amounts, under 3%, of this by-
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32 product were found with fresh catalyst in all the solvent systems, but increasing biphenyl amounts
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34 were detected upon recovery in some of the media, especially in the ones containing the **3F00**
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36 fluororous derivative.
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42 **Scheme 3.** Proposed mechanism for the iodobenzene homocoupling reaction catalyzed by palladium
43 nanoparticles in the presence of acidic **R00** as promoter inspired in the mechanism of Gómez and
44 coworkers.⁵⁰
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In order to explain this behavior, we have proposed a mechanism for the biphenyl formation (Scheme 3), inspired in the one described by Favier et al. for Pd-NPs catalyzed iodobenzene homocoupling in glycerol.⁵⁰ According to this mechanism, a molecule able to accept the single-electron transference, responsible for the Pd activation, is needed. Therefore, the “acidity” of the alcohol, in our case the glyceryl ether or glycerol, should strongly influence the homocoupling mechanism activation. For this reason, the strong electro-withdrawing trifluoroethoxy groups in **3F00** and its mixtures, would favor the homocoupling reaction and thus the biphenyl formation, as it was experimentally observed. It is also interesting to say that total conversions of iodo- and bromobenzene to biphenyl were observed for the same Pd NPs solvent systems in the absence of *n*-butyl acrylate, thus evidencing that this homocoupling reaction takes place in these glycerol derived media. Hence, cross-coupling reaction would not be dependent on the solvent, taking place quantitatively in those cases solvents where iodobenzene homocoupling reaction is less favored.

Table 2 shows as the highest accumulated TON values were obtained in the mixtures containing **000**, **3i00** and **100** derivatives, followed by pure **3i00** and **100** ethers. The lower TON values

observed in **3F00** and **Ph00** systems were due to the decreasing selectivity along the consecutively reaction runs. As it has been previously described, Scheme 3 would explain the progressive decrease in selectivity due to the competitive homocoupling, attending to the acidity/HBD ability of the medium. In fact, good empiric correlations can be found between the accumulated TON in each kind of glycerol-derived medium and its experimental α Kamlet-Taft parameter (Figure 5). Moreover, this effect seems to be less important in the case of **R00** monoethers than in the case of eutectic solvents. In the case of DES, small changes in α values provoke big differences in the accumulated TON values. The lowest TON value for the pure glycerol (**000**) system would be then related not only to its higher viscosity and lower solubility of the reagents as above mentioned, but also to its high α HBD ability.

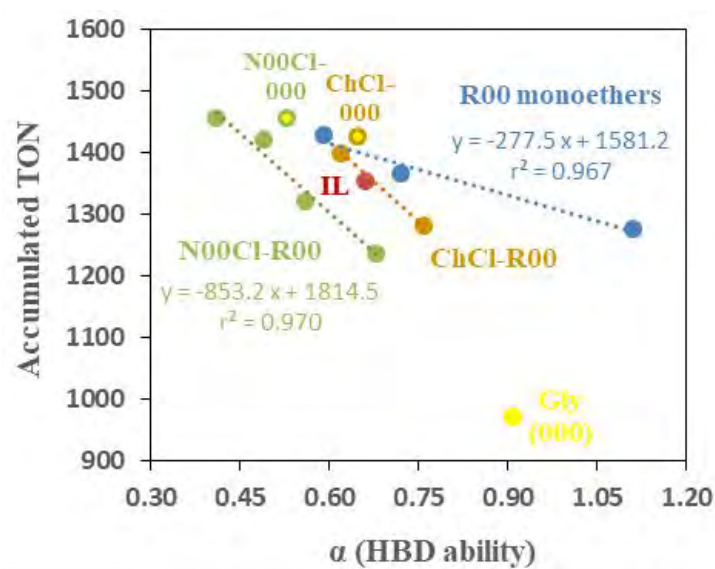


Figure 5. Correlations between the α Kamlet-Taft parameter and the accumulated TON of the immobilized PVP-Pd-NPs catalyst, for the families of glycerol-derived solvents as a function of the R ether substitution.

As it has been stated, in general more dipolar media favor the Heck-Mizoroki coupling reaction.³³ This effect has also been recently described for the reaction between iodobenzene and *n*-butyl acrylate in the case of eutectic solvents.⁴⁵ Figure 6 shows the plot of accumulated TON towards solvent systems total dipolarity (E_T^N Reichardt parameter). This figure evidences that DES

containing glyceryl ethers and glycerol maintain the general trend described in the literature. For example, the most dipolar media (**N00Cl-000** and **ChCl-000**) presented the highest accumulated TONs. In the case of pure **R00** ethers (and glycerol) a perfect inverse correlation ($r^2 = 1.000$) was found between E_T^N and accumulated TON (Figure 6 in blue). It is possible to suggest a reason for this correlation as the E_T^N parameter includes the dipolarity as well as the HBD ability. Thus the most polar ether (**3F00**) presented also the highest α value, counteracting both properties in the resultant catalytic activity. Other minor correlations between TON values and different physical-chemical properties were found (see Supplementary Information), but mainly the HBD ability (dominant factor) and the dipolarity of the medium influenced the catalytic activity and the selectivity.

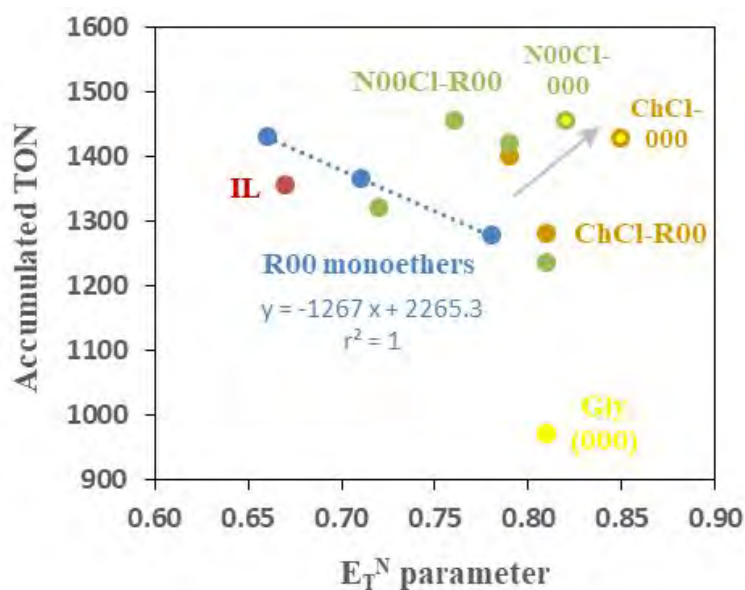


Figure 6. Correlation between accumulated TON of the immobilized PVP-Pd-NPs catalyst and the E_T^N polarity solvatochromic parameter, as a function of the R ether substitution in the glyceryl ether solvent.

Finally, it is worth noting that the use of polar protic solvents in the studied Heck-Mizoroki reaction can add an interesting advantage with respect to solvent-less catalysis. After the formation of *n*-butyl cinnamate, it is necessary the reduction of the Pd(II) to Pd(0) in order to restore the

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3 catalytic palladium specie. At that step a base, in this case triethylamine, is used in order to
4 regenerate the catalyst by a reductive elimination, but triethylammonium iodide salt is formed. In
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6 a solvent-free system this concomitant by-product precipitates in the reaction medium and
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8 accumulates over the Pd-NPs, thus reducing their active catalytic surface but also increasing the
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10 NPs stability.³⁸ In our case, Et₃N·HI salt was mostly dissolved in the case of glycerol ethers and
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12 completely dissolved in the case of glycerol-derived DES. This solubilization allows to preserve
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14 all the activity of the catalyst, assuring the stability of the NPs thanks to the hydrogen-bond
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16 supramolecular structure of the solvent. In addition, the salt was never extracted with the reaction
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18 products, avoiding further product purification. Nevertheless, in the case of viscous glycerol (**000**)
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20 and **N00Cl-Ph00** media, the salt was precipitated, thus altering the catalytic activity and hindering
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22 the results reproducibility.
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28 29 **CONCLUSIONS**

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31 The use of glycerol ethers and their eutectic mixtures with two ammonium salts (**ChCl** and **N00Cl**)
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33 as reaction media in the benchmark Heck-Mizoroki coupling reaction between iodobenzene and
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35 *n*-butyl acrylate provided highly active, selective and recoverable Pd-NPs catalytic systems. The
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37 correlations established between the solvent HBD ability with the accumulated TON allowed to
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39 state that, the nature of the HBD compound, both pure or as a component of the DES, seems to
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41 play a crucial role in the reaction chemoselectivity, due to the competence of the iodobenzene
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43 homocoupling reaction.
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49 Finally, in general all the studied systems provided higher yields and TONs than the IL [bmim]PF₆
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51 and pure glycerol, constituting an interesting alternative to the use of ionic liquids in this reaction.
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54 **ASSOCIATED CONTENT**

Supporting Information.

The supporting Information is available free of charge on the ACS Publications website at DOI: [xx.xxxx/acssuschemeng.xxx](https://doi.org/xx.xxxx/acssuschemeng.xxx).

List of abbreviations and solvent acronyms, GC analysis conditions, solvents and coupling products characterization, miscibility data, Heck yields for all the solvents systems and complete relationships between catalytic activity and physical-chemical properties (PDF).

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Notes

The authors declare no competing financial interest.

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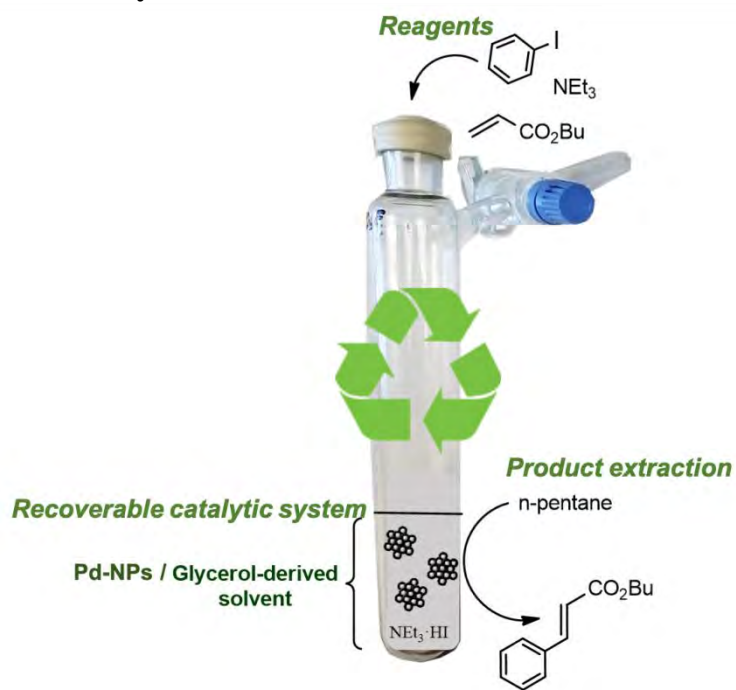
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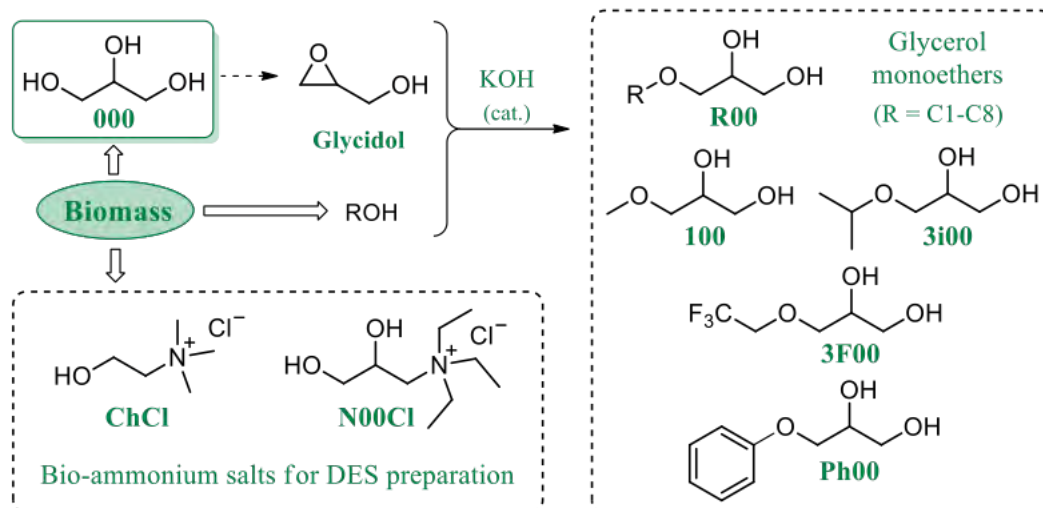
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28 Green derived glycerol ethers and related DES as reaction media in recoverable Pd-NPs catalytic
29 systems for Heck-Mizoroki reactions.
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