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Towards a Sustainable Synthesis of Amides: Chemoselective Palladium-catalysed Aminocarbonylation of Aryl Iodides in Deep Eutectic Solvents

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Palladium-catalysed aminocarbonylation of (hetero)aryl iodides has, for the first time, been accomplished in deep eutectic solvents as environmentally benign and recyclable media, under mild conditions. The reactions proceed with good substrate scope, and a variety of amides have been synthesized in yields up to 98%.

Transition-metal-catalysed carbonylation reactions have become a cornerstone of modern organic synthesis, whether it is in academia or in industry, for the one-pot synthesis of a variety of carbonyl-containing functionalities such as carboxylic acids, esters, ketones, aldehydes, amides, and thus for the preparation of high value-added organic molecules useful for our daily life.¹ A common feature of all Pd-catalysed carbonylation of halogenated or triflate aromatic hydrocarbons, however, is the use of toxic, volatile organic compounds (VOCs) (e.g., toluene, 1-butanol, DMF, dioxane), and heating the mixture at a temperature of or higher than 100 °C.^{1a,2} Milder temperatures (60–100 °C) have recently been introduced only for ionic liquids,^{3a,b} and for microwave-assisted homogeneous and heterogeneous processes.^{3c}

Increasingly, stringent environmental legislation and urgent action to address the climate crisis have generated a pressing need for cleaner methods of chemical production.⁴ In particular, the progressive replacement of extensively used conventional and hazardous VOCs in favour of safe, environmentally responsible and bio-renewable solvents is holding a key interest, and has become a topic of interdisciplinary research.⁵ Such a replacement also minimises the emission of effluents in the chemical industry, and contributes to bridge the divide between industrial applications and the fundamental chemistry. Accordingly, the so-called Deep Eutectic Solvents

(DESS) (also known in the literature as Low Melting Mixtures, LMMs) have become to emerge as a new, unconventional class of reaction media in green synthesis. DESSs are combinations of two or three safe, inexpensive, and nature-inspired components able to engage in reciprocal hydrogen bond interactions to form an eutectic mixture with a melting point much lower than that of either of the individual components. Compared to conventional VOCs, DESSs show high thermal stability, non-flammability and practically no vapour pressure, therefore low volatility. Typical DES components [e.g., choline chloride (ChCl), urea, glycerol (Gly), natural carboxylic acids, amino acids and carbohydrates, polyalcohols] come from renewable sources. Thus, their biodegradability is extraordinarily high, and their toxicity is non-existent or very low. DESSs also display high tunable solvent properties by simply changing the nature and the molar ratio of the components.⁶

From the perspective of green chemistry, although the application of these neoteric solvents in several fields of sciences has experienced an exponential growth particularly in the last years,⁶ Pd-catalysed reactions in DESSs have received much less attention.⁷ Building on recent findings in Pd-catalysis,⁸ and as part of our ongoing efforts to develop environmentally benign synthetic and catalytic protocols using a multiple bond-forming approach⁹ or unconventional reaction media,¹⁰ herein, we disclose a sustainable, chemoselective route to amides by exploiting the direct carbonylation reaction of (hetero)aryl iodides in DESSs. Notable features of our report include: (i) phosphine-free and mild conditions, (ii) absence of VOCs, (iii) easy isolation of products, and (iv) efficient recycling of both DES and catalyst.

Our investigation started with 1-chloro-3-iodobenzene (1.0 mmol) (**1a**) and EtOH (6.0 mmol) (**2a**) as model substrates to synthesize ethyl 3-chlorobenzoate **3aa** under a pressure of CO (Table 1). When the reaction was run in THF (5 mL) using Pd(PPh₃)₄ (5 mol%) as catalyst, NEt₃ (3.0 mmol) as base, under a CO atmosphere (27 atm) for 12 h and gently heating at 60 °C, **3aa** was isolated in 50% yield, with the remaining mass balance being starting material only (Table 1, entry 1). When performed in the eutectic mixture Gly/ChCl (2:1 mol mol⁻¹), under the same

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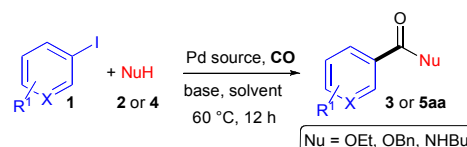
Electronic Supplementary Information (ESI) available: Experimental details for the synthesis and characterization of new compounds and copies of their NMR spectra. See DOI: 10.1039/x0xx00000x

experimental conditions, such coupling proved less effective (**3aa**: 35% yield; Table 1, entry 2). Upon switching to LMM L-lactic acid/D-glucose (5:1 mol mol⁻¹), no coupling was observed (Table 1, entry 3). The product **3aa** was obtained in moderate yield (58%) by employing urea/ChCl (2:1 mol mol⁻¹) as eutectic mixture and NEt₃ (3.0 mmol) as base (Table 1, entry 4). Further screening of catalysts/bases to boost the transformation revealed a negligible dependence on both the Pd-source and the nature of base, the yields of **3aa** being in the range of 45 to 56% (Table 1, entries 5–8). On the other hand, a lower pressure of CO (10 atm) almost completely suppressed the formation of the coupling product (**3aa**: <5%; Table 1, entry 9). By performing ethoxycarbonylation or (benzyloxy)-carbonylation (**2b**: BnOH) with CO (27 atm) at 60 °C in urea/ChCl of variously substituted aryl iodides **1b–d**, or of electron-deficient heteroaromatic rings (e.g., 3-iodopyridine, **1e**), unsatisfactory outcomes resulted, with yields of the expected adducts **3ba**, **3cb**, **3db**, and **3ea** of up to 41% (Table 1, entries 10–13). However, despite the low isolated yields of esters, it was noted that starting substrate **1a** was completely consumed in all the above alkoxycarbonylation reactions. We questioned at this point whether DES components themselves, in competition with alcohols, might trigger alternative acylation processes. Thus, we focused on the use of more nucleophilic species, such as amines. To our delight, the reaction of **1a** (1.0 mmol) with *n*-BuNH₂ (6.0 mmol) (**4a**) under a pressure of CO (27 atm) for 12 h, at 60 °C and using Pd(OAc)₂ (5 mol%) as catalyst and K₂CO₃ (3.0 mmol) as base, straightforwardly led to the desired aminocarbonylated product **5aa** in high yield (93–98%) either in a Gly/ChCl or in a urea/ChCl eutectic mixture (Table 1, entries 14,15). By changing the solvent to pure glycerol, however, the yield of **5aa** dropped down to 27%, most probably because of the high viscosity of the medium (Table 1, entry 16). The use of DMF or water (heterogeneous conditions) as reaction media was also less satisfactory (**5aa**: 46–75% yield; Table 1, entries 17,18).¹¹

To examine the scope and limitations of the reaction, various functionalised (hetero)aryl iodides and different primary and secondary amines were tested (Table 2). The carbonylative coupling between **1a** and piperidine (**4b**) or 2-aminopyridine (**4c**) took place smoothly, either in a ChCl/urea (1:2) (DES A) or in a ChCl/Gly (1:2) (DES B) eutectic mixture, and provided the desired products **5ab** and **5ac** in 92–96% yields (Table 2). The direct carbonylation of an acyl-containing aryl iodide (**1b**) with **4a** gave the expected adduct **5ba** in up to 51% yield (DES A); an inspection of the crude (GC-MS analysis) revealed the formation of an imine as a by-product. The aminocarbonylation reaction was less efficient in the absence of an electron-withdrawing group on the phenyl ring. Indeed, the coupling of **1c** with **4a**, under a carbon monoxide pressure, provided **5ca** in 60% vs. 93% yield, as in the case of **5aa** (Tables 1,2). On the other hand, an electron-deficient nitrogen heterocycle, such as 3-iodopyridine (**1e**), proved to be a competent partner, and underwent aminocarbonylation with assorted *N*-nucleophiles [**4a**, **4c**, and aniline (**4d**)] delivering the corresponding adducts **5ea**, **5ec** and **5ed** in excellent yields (86–95%) (Table 2). The direct carbonylation of **1e** in the presence of a secondary amine (**4b**) was less favourable and furnished

product **5eb** in 57% yield (Table 2). Despite the lower yield, however, the sustainable preparation of compounds of the type of **5eb**, which are nicotinamide derivatives, appears very interesting since these carbon scaffolds are known for their important pharmacological activities such as cytotoxicity,¹² the inhibition of succinate dehydrogenase,¹³ and of gastric H⁺/K⁺-ATPase.¹⁴ When an aryl iodide bearing a nitro group (**1f**) and amine **4a** were jointly submitted to this carbonylative protocol, coupling product **5fa** was delivered in 58% yield, however, with the reduction of the nitro group to amino group.¹⁵

Table 1. Alkoxycarbonylation and aminocarbonylation of aryl iodides **1** in various solvents.^a



Entry	Solvent ^b	Pd source	R ¹	NuH	3 or 5aa yield (%) ^c
1	THF ^d	Pd(PPh ₃) ₄	1a : 3-Cl ^e	2a : EtOH	3aa : 50 ^f
2	Gly/ChCl	Pd(PPh ₃) ₄	1a : 3-Cl ^e	2a : EtOH	3aa : 35 ^f
3	LMM	Pd(PPh ₃) ₄	1a : 3-Cl ^g	2a : EtOH	NR ^{g,h}
4	urea/ChCl	Pd(PPh ₃) ₄	1a : 3-Cl ^e	2a : EtOH	3aa : 58 ^f
5	urea/ChCl	Pd/C	1a : 3-Cl ^e	2a : EtOH	3aa : 45 ^f
6	urea/ChCl	Pd(PPh ₃) ₄	1a : 3-Cl ^e	2a : EtOH	3aa : 55 ^h
7	urea/ChCl	Pd/C	1a : 3-Cl ^e	2a : EtOH	3aa : 52 ^h
8	urea/ChCl	Pd(OAc) ₂	1a : 3-Cl ^e	2a : EtOH	3aa : 56 ^f
9	urea/ChCl	Pd(OAc) ₂	1a : 3-Cl ^e	2a : EtOH	3aa : <5 ^{f,i}
10	urea/ChCl	Pd(OAc) ₂	1b : 4-Ac ^{e,j}	2a : EtOH	3ba : 25 ^h
11	urea/ChCl	Pd(OAc) ₂	1c : H ^k	2b : BnOH	3cb : 28 ^h
12	urea/ChCl	Pd(OAc) ₂	1d : CO ₂ ET ^e	2b : BnOH	3db : 41 ^h
13	urea/ChCl	Pd(OAc) ₂	1e : H ^k	2a : EtOH	3ea : 21 ^h
14	Gly/ChCl	Pd(OAc) ₂	1a : 3-Cl ^e	4a : BuNH ₂	5aa : 93 ^{h,l}
15	urea/ChCl	Pd(OAc) ₂	1a : 3-Cl ^e	4a : BuNH ₂	5aa : 98 ^h
16	Gly	Pd(OAc) ₂	1a : 3-Cl ^e	4a : BuNH ₂	5aa : 27 ^h
17	DMF	Pd(OAc) ₂	1a : 3-Cl ^e	4a : BuNH ₂	5aa : 46 ^h
18	H ₂ O	Pd(OAc) ₂	1a : 3-Cl ^e	4a : BuNH ₂	5aa : 75 ^h

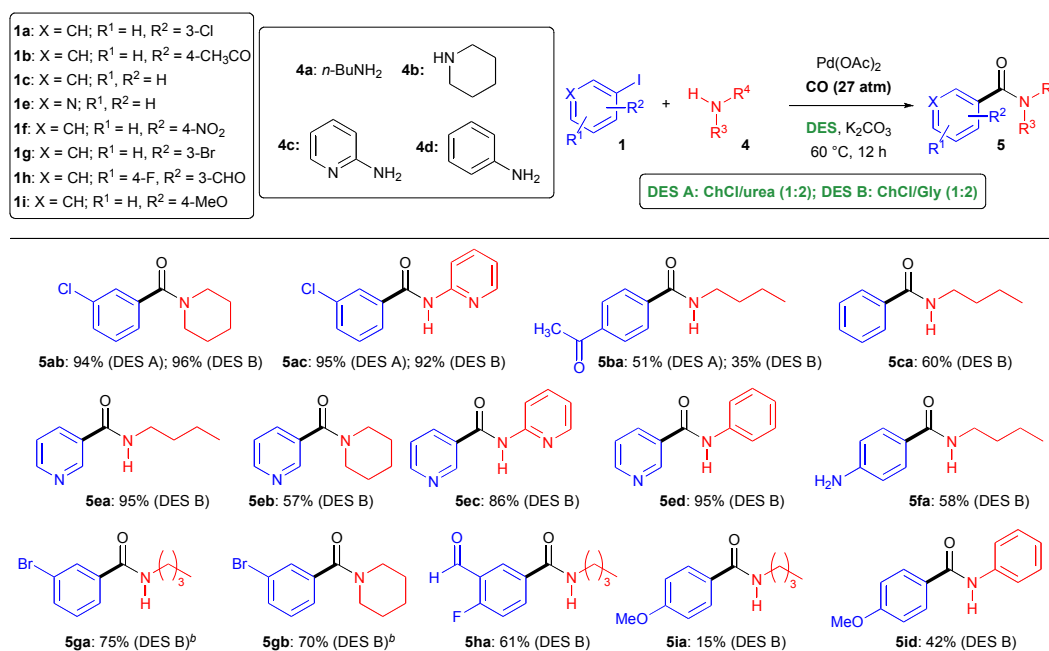
^a Reaction conditions: (hetero)aryl iodide (1.0 mmol), alcohol or *n*-BuNH₂ (6.0 mmol), base (3.0 mmol), Pd source (5 mol% in Pd; Pd/C: 1 mol% in Pd), CO (27 atm), DES or LMM (2 g), 60 °C, 12 h. All reactions were run in duplicate. ^b Gly/ChCl (2:1 mol mol⁻¹); LMM: L-lactic acid/D-glucose (5:1 mol mol⁻¹); urea/ChCl (2:1 mol mol⁻¹). ^c Calculated by ¹H-NMR analysis of the crude reaction mixture using an internal standard technique (NMR internal standard: dimethylsulfone). ^d 5 mL. ^e X = CH. ^f Base = NEt₃. ^g NR = no reaction. ^h Base = K₂CO₃. ⁱ Reaction performed under 10 atm CO. ^j Ac = CH₃CO. ^k X = N. ^l The yield of **5aa** dropped down to 15% when using NaOAc as the base.

Such a concomitant reductive carbonylation of aromatic nitro compounds is very attractive as it paves the way for the synthesis of amino-substituted benzamides, which are not easy to be straightforwardly prepared. Remarkably, the carbonylation of 1-bromo-3-iodobenzene (**1g**), run in the presence of either a primary amine (**4a**) or a secondary amine (**4b**), led to the chemoselective reaction of the aryl iodide functionality to provide **5ga** (75% yield) or **5gb** (70% yield), respectively, leaving the bromide unreacted, and thus available for further functionalisation (Table 2). The use of the benzaldehyde derivative **1h** was also tolerated, and furnished

the valuable formyl-fluorobenzamide **5ha** (61% yield) by carbonylative coupling with **4a**. The presence of an electron-donating group (MeO) in the starting aryl iodide (**1i**) was

detrimental to the reaction outcome as the yields of amides produced in the coupling with **4a** and **4b** were poor (**5ia**: 15%; **5id**: 42%) (Table 2).¹⁶

Table 2 Synthesis of amides **5** via aminocarbonylation of (hetero)aryl iodides **1** in deep eutectic solvents.^a



^a Reaction conditions: (hetero)aryl iodide (1.0 mmol), amine (6.0 mmol), K₂CO₃ (3.0 mmol), Pd(OAc)₂ (5 mol %), CO (27 atm), DES (2.0 g), 60 °C, 12 h. The yields reported are for products isolated and purified by column chromatography. ^b Reaction time: 3 h.

Both the Pd-catalyst and DES could be easily recycled. The aminocarbonylation of iodoarene **1a** with amine **4a** in ChCl/urea (1:2) was chosen as a model reaction, since it provided almost quantitative yield of the corresponding coupling product **5aa** (Table 1, entry 15). Upon completion of the first coupling, in-flask extraction with AcOEt afforded product **5aa** (98% yield, Figure 1, number of recycles = 0), but leaving the active palladium species in the eutectic mixture. The DES phase was then dried under vacuum until constant weight. Then, upon simply adding new, fresh reagents (**1a**, **4a**, and K₂CO₃), the catalyst and DES could be successfully re-used for further reactions. As shown in Figure 1, the catalyst remained active over 5 cycles, albeit with a drop in the chemical yield of **5aa** of up to 34%. The recycling efficiency was improved by using the less viscous ChCl/Gly (1:2) eutectic mixture and Pd/C (1 mol%) as the catalyst, in the presence of K₂CO₃.¹⁷ In this case, the chemical yield of **5aa** dropped down to only 14% in the fourth and up to 24% in the fifth cycle.

In summary, Pd-catalysed aminocarbonylation of (hetero)aryl iodides can be performed under remarkably mild conditions (60 °C) using biodegradable eutectic mixtures as environmentally responsible reaction media in place of toxic and hazardous VOCs.

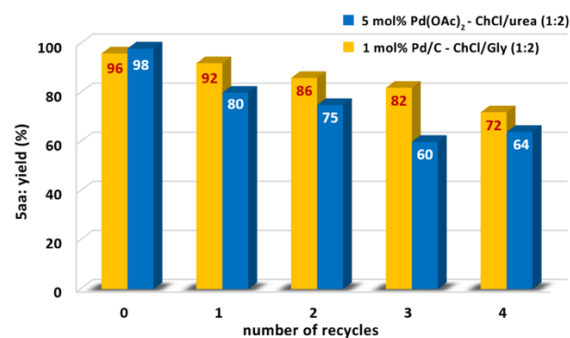


Figure 1 Recycling of Pd(OAc)₂ (5 mol%) or Pd/C (1 mol%) and DES in the coupling reaction between 1-chloro-3-iodobenzene (**1a**) and *n*-BuNH₂ (**4a**).

The proposed protocol (a) does not require additional ligands, (b) is highly chemoselective towards the aryl carbon-iodine bond cleavage, (c) tolerates various functional groups (with the exception of nitro group which is *in-situ* reduced to a valuable amino group), (d) proceeds with good reaction efficiency especially starting from electron-deficient (hetero)aryl iodides, and (e) allows an effective recycling of both DES and catalyst. Efforts towards clarifying the “active” role played by DES components in promoting carbonylation reactions, and in tuning the activity of the Pd-catalyst, will surely help to expand even more the substrate scope with respect to other nucleophiles.

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Conflicts of Interest

There are no conflicts to declare.

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