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Gas-Free Amino- and Alkoxycarbonylation of Aryl Iodides in a Bioinspired Deep Eutectic Solvent with $Mo(CO)_6$ as a Safe CO Source

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The Pd-catalyzed amino- and alkoxycarbonylation of aryl iodides has been exploited, for the first time, in a bioinspired Deep Eutectic Solvent and under gas-free conditions, by using $Mo(CO)_6$ as the CO source. The method allows for the preparation of carboxylic amides and esters in high yields (up to 99%), short reaction time (2 h) and under mild reaction conditions (80 °C), with a low catalyst loading (2.5 mol%). Noteworthy, in the case of *N*-hexylbenzamide, it has been demonstrated that both the catalyst and DES can be used for four consecutive runs, with a moderate decrease of catalytic efficiency. The methodology has been also applied to the preparation of an Active Pharmaceutical Ingredient used for the treatment of human scabies and lice.

Introduction

The Pd-catalyzed carbonylation of organic halides is one of the most powerful strategies for the direct incorporation of a carbonyl moiety into an organic compound.[1–4] The carbonylation reaction is a multicomponent process which allows the direct synthesis of a variety of important carbonyl compounds, including carboxylic acids, esters, amides, and ketones. It is also commonly used in the production of heterocyclic compounds.[5–7] Following its initial report by R.F. Heck in 1974,[8] this methodology has gained significant interest and attention in recent years, not just in academic research but also in industry, where it has become a crucial tool for the production of fine chemicals and pharmaceutical ingredients; therefore, its effectiveness and versatility have made it a relevant method for industrial applications.[9] It is important to recognize that catalytic carbonylations offer both valuable synthetic applications and promote sustainable practices. By allowing for the combination of an electrophile, carbon monoxide, and a nucleophile in a single synthetic step, catalytic carbonylations minimize waste generation and eliminate the need for intermediate isolation. Additionally, this process maximizes the atom economy, in line with the principles of green chemistry.[10,11]

Historically, carbonylation reactions were conducted under high pressure of toxic carbon monoxide, thus requiring specialized laboratory equipment such as steel autoclaves. Recognizing the potential dangers associated with this approach, alternative methods have been developed to replace gaseous CO with its precursors or sources. This has led to a safer and more accessible implementation of these reactions in a variety of experimental protocols: formic acid,[12] alkyl- and arylformates,[13] *N*-formylsaccharin,[14] chloroform,[15] acyl chlorides,[16] carbon dioxide,[17] silanecarboxylic acid[18] and metal carbonyls[19–21] have been successfully employed as synthetic equivalents of gaseous CO. Among metal carbonyls, the potential of molybdenum hexacarbonyl to facilitate carbonylation reactions has recently attracted significant consideration due to its ability to provide a safe, practical, and a manageable solid source of carbon monoxide.[22] $Mo(CO)_6$ can release CO either through thermic treatment,[23] or ligand exchange with several Lewis bases such as DBU,[24] piperidine,[25] or MeCN.[26]

In an effort to identify environmentally friendly and safe replacements for conventional Pd-catalyzed carbonylation procedures relying on gaseous CO, a remarkable research study has been conducted that exploits the utility of $Mo(CO)_6$ as carbon monoxide source.[22]

Regarding the most notably and sustainable carbonylation methods of general applicability, in 2014, the group of Lam and Lo described a versatile microwave-assisted carbonylation of

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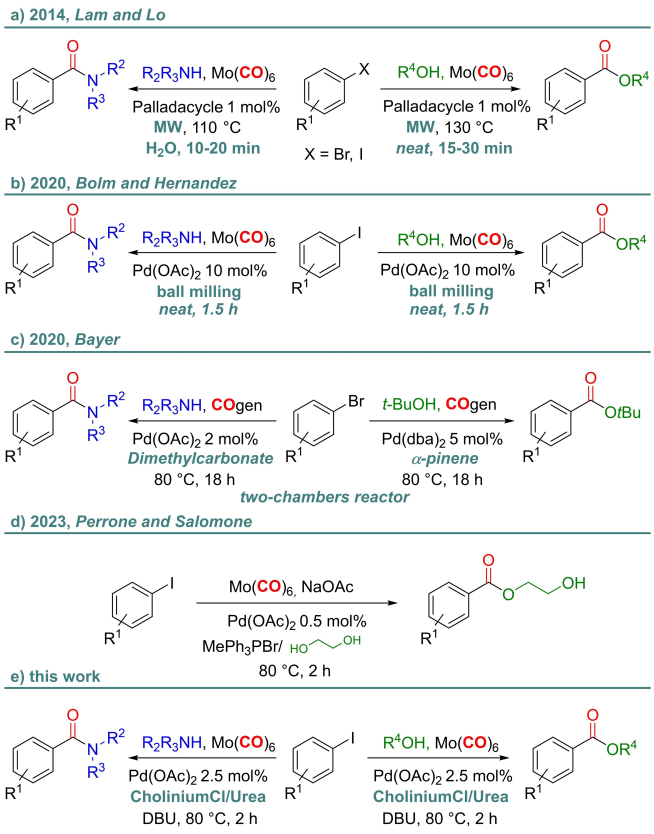
aryl bromides and iodides with alcohols or amines, in water or under neat conditions. The process led to the synthesis of esters and amides thanks to the synergy between $Mo(CO)_6$, as CO source, and a fluorinated oxime-based palladacycle, as the catalyst. The catalytic system also showed an excellent recyclability (Scheme 1a).[27]

In 2020, Bolm, Hernandez and co-workers reported a very fast mechanochemical carbonylation of aryl iodides under the catalysis of a palladium-phosphine complex. The method afforded carboxylic esters and amides in moderate to excellent yields. The pressure was monitored in real-time and the results indicated that the transfer of the CO ligand from $Mo(CO)_6$ to the active catalytic Pd-species occurred rapidly and without significant release of CO gas (Scheme 1b).[28]

A deep study, conducted in 2020 by Bayer and colleagues, showed a new method for performing a Pd-catalyzed carbonylation of aryl bromides using renewable solvents as reaction media, such as limonene, dimethylcarbonate, and α-pinene. This route, involving the use of 9-methyl-9*H*-fluorene-9-carbonyl chloride (COgen) as the source of carbon monoxide, was carried out under mild reaction conditions (80 °C), and resulted in moderate to excellent yields of aromatic amides, and esters. The methodology required a two-chamber reactor, with one chamber dedicated to the release of CO from COgen, which was run in a petroleum-derived solvent (1,4-dioxane), Scheme 1c.[29]



Scheme 1. Sustainable Pd-catalyzed carbonylations in green solvents, or neat conditions, with alternative sources of carbon monoxide.

In light of the latest findings, it is essential to encourage the development of innovative techniques for the carbonylation of organic compounds that eliminate the need for hazardous CO gas. These methods should prioritize safety, affordability, and atom economy, while maintaining high process efficiency.

Our recent research efforts have been dedicated to the advancement of sustainable synthetic methodologies using two distinct approaches; the first one involves the use of multiple bond-forming strategies,[30–33] while the second approach focuses on the replacement of toxic and volatile organic solvents, derived from petroleum, with Deep Eutectic Solvents (DESs).[34–40] These eutectic mixtures represent a promising new class of environmentally friendly polar solvents, often derived from bio-renewable sources, and with various applications in sustainable chemistry.[41]

Results and Discussion

Our research group previously reported the first aminocarbonylation of aryl iodides with pressurized gaseous CO in cholinium chloride-based DESs.[42] Moreover, we have recently described the first alkoxycarbonylation of iodo arenes in methyltriphenylphosphonium bromide/ethylene glycol (EG) eutectic mixture, which led to an easy preparation of ethylene glycol esters, by using molybdenum hexacarbonyl as the CO source (Scheme 1d).[43]

As a natural evolution of these studies, to improve both the sustainability and the general applicability of the carbonylation methodology in eutectic mixtures, herein we report a novel gas-free alkoxy- and aminocarbonylation process. Compared to our recent work,[43] this method allows an efficient synthesis of both carboxylic esters and amides, by employing the nature-inspired, sustainable, and easy to recycle cholinium chloride (ChCl)/urea DES (Scheme 1e).

This gas-free reaction, catalyzed by $Pd(OAc)_2$, is performed in the bioinspired ChCl/urea (1 : 2) eutectic mixture, at a low temperature (80 °C) and exploits the power of $Mo(CO)_6$ as a safe source of CO (Scheme 1e).

Our investigation started by performing the carbonylative coupling between iodobenzene **1a** and piperidine **2a**, in ChCl/urea (1 : 2) as the green reaction medium, to obtain *N*-benzoylpiperidine **3aa**. The catalytic system was composed by $Pd(OAc)_2$ (5.0 mol%) and $MePPh_2$ (20 mol%), whereas the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.5 mmol) ensured the CO release from $Mo(CO)_6$; in these experimental conditions, the target amide **3aa** formed, after 2 hours, in moderate yield (60%, Table 1, entry 1). The reaction without DBU (Table 1, entry 2) did not afford the target product **3aa**, although in the presence of an excess of both $MePh_2P$ (1.0 mmol) and piperidine **2a** (3.0 mmol), thus evidencing the importance of a strong Lewis base for the CO release from Mo complex.

When the catalyst loading was reduced to 2.5 mol%, a decrease of **3aa** yield was observed (52%, Table 1, entry 3). Interestingly, in the absence of the phosphine ligand, the amide formation increased up to 60%, although the Pd-loading

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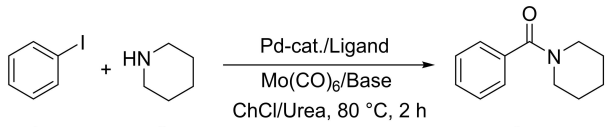
Table 1. Screening of the reaction conditions for the aminocarbonylation of iodobenzene **1a** with piperidine **2a** and $Mo(CO)_6$, in ChCl/urea (1:2) DES.[a]



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

entry	Base	Ligand	Pd-Cat. [mol%]	**3aa** Yield [%][b]
1	DBU	$MePh_2P$	$Pd(OAc)_2$ (5)	60
2[c]	–	$MePh_2P$	$Pd(OAc)_2$ (5)	0
3	DBU	$MePh_2P$	$Pd(OAc)_2$ (2.5)	52
4	DBU	–	$Pd(OAc)_2$ (2.5)	60
5[d]	DBU	–	$Pd(OAc)_2$ (2.5)	78
6[d,e]	DBU	–	$Pd(OAc)_2$ (2.5)	84
7[d]	DBU	–	$PdCl_2$ (2.5)	12
8[d]	DBU	–	Pd/C (2.5)	3
9[d]	DBU	–	$Pd(OAc)_2$ (1.0)	43
10[d]	NaOAc	–	$Pd(OAc)_2$ (2.5)	46
11[d]	KOH	–	$Pd(OAc)_2$ (2.5)	50
12[d]	K_2CO_3	–	$Pd(OAc)_2$ (2.5)	37
13[f]	DBU	–	$Pd(OAc)_2$ (2.5)	46

[a] Reaction conditions: iodobenzene **1a** (0.5 mmol), piperidine **2a** (1.5 mmol) $Mo(CO)_6$ (0.5 mmol), Pd-cat (2.5–5 mol%), base (1.5 mmol), $MePh_2P$ ligand (20 mol%), ChCl/urea (1/2 mol/mol, 2 mL), at 80 °C for 2 hours. (ChCl = Cholinium Chloride) [b] Calculated via ^1H NMR analysis of the crude reaction mixture using the internal standard technique (NMR internal standard: dimethyl sulfone). [c] Reaction performed with 1.0 mmol of $MePh_2P$ and 3.0 mmol of **2a**. [d] Reaction performed in 1 mL of DES. [e] Reaction performed with 0.25 mmol of $Mo(CO)_6$. [f] Reaction performed in CPME (1.0 mL). Beside the expected amide **3aa**, also 1-phenyl-2-(piperidin-1-yl)ethane-1,2-dione was detected and quantified (17% yield) by ^1H NMR and EI-MS analyses on the crude reaction mixture.

remained unchanged (2.5 mol%) (Table 1, entry 4). By halving the volume of DES to 1 mL (Table 1, entry 5) and the amount of $Mo(CO)_6$ to 0.25 mmol (Table 1, entry 6), the process reached a satisfying efficiency, producing the target amide in 84% yield, in a reaction time of only 2 hours and at 80 °C.

The use of different sources of Pd (i.e., $PdCl_2$ and Pd/C) suggested the peculiar catalytic activity of the $Pd(OAc)_2$ in the eutectic mixture; in fact, only traces of the product **3aa** were detected in the crude mixture (Table 1, entries 7–8).

With the aim to reduce the catalyst loading (1.0 mol%, Table 1, entry 9) or to replace DBU with greener alternatives (i.e., NaOAc, KOH, K_2CO_3, Table 1, entries 10–12), unsatisfactory outcomes resulted, affording the expected amide **3aa** in a 37–50% yield.

The use of a non-protic ethereal solvent, such as the biomass- derived CPME, was also investigated but with a lower result (Table 1, entry 13): only 64% of the starting iodide **1a** was converted, after 2 hours at 80 °C, providing the target product **3aa** in 46% yield. Moreover, EI-MS and ^1H-NMR analyses of the crude reaction mixture revealed the presence of a by-product (17% yield), probably deriving from the double carbonylation reaction of starting iodide **1a**; the by-product was identified as the 1-phenyl-2-(piperidin-1-yl)ethane-1,2-dione and quantified by internal standard technique (17% yield).

Furthermore, the optimized protocol (Table 1, entry 6) was applied to carbonylative coupling between bromobenzene and piperidine, but unfortunately the expected amide **3aa** was not formed. Even by increasing the reaction temperature to 100 °C and doubling the reaction time (4 h), only traces of the target product were detected in the crude reaction mixture.

Amides are widely spread in nature and technology. Polypeptides and many synthetic polyamides like the plastics Nylons, Aramid, Twaron, and Kevlar are polymers whose monomers are connected by amidic bonds.[44] Moreover, it is worthwhile to note that the amide scaffold constitutes one of the most valuable pharmacophores in medicinal chemistry research. Paracetamol, penicillin, for examples, are well known drugs including amide moiety in their structure.[45,46]

Once the optimal reaction conditions were found (Table 1, entry 6), by varying the aryl iodide and amine components, the scope of this novel aminocarbonylation protocol in a green eutectic mixture was probed. The results are summarized in Scheme 2.

Most notably, we were pleased to find that, besides the carbonylation reaction with piperidine (**2a**) as nucleophile, various amines, both aliphatic and aromatic, were smoothly coupled with iodobenzene **1a**, affording the corresponding amides **3aa**–**3af** in moderate to excellent yields (61-99%). Particularly, the simple long-chain primary *n*-hexylamine **2b** was proved to be a suitable substrate for our carbonylative protocol, obtaining the amide **3ab** in quantitative yield. When primary aliphatic *N*-nucleophiles, such as the 2-amino-2-methylpropan-1-ol **2c** and cyclohexanamine **2d**, were employed, the aminocarbonylation process led to the desired amides **3ac**–**3ad** in moderate yield (61–69%). This protocol worked efficiently also with the benzylamine **2e** and the aniline derivative **2f**, giving the products **3ae** and **3af** in 95% and 91% yield, respectively. The presence of electron-withdrawing (Cl) or electron-donating (OMe) groups on the phenyl moiety of the aryl iodide does not affect the trend of the process, both with primary and secondary aliphatic amines, leading to the desired amide derivatives **3ba**, **3bd** and **3ca** in 76–86% yields. Moreover, also the sterically hindered 1-iodonaphthalene **1d** can be successfully applied to our carbonylative method, achieving **3da** in a 77% yield.

In order to prove the functional group tolerability of the method, the carbonylative protocol was applied to 4'-iodoacetophenone **1e**, bearing a reactive functionality, obtaining the corresponding amides **3ee** in 86% yield. Also the use of an heteroaryl substrate such as the 3-iodopyridine **1f**, led to the nicotinamide derivative **3fe** in a satisfactory 75% yield.

Therefore, encouraged by the excellent results obtained with these gas-free aminocarbonylation reactions, we proceeded to use the same catalytic system for the alkoxycarbonylation of aryl halides, in ChCl/urea (1:2) green medium, to afford esters.

Esters are widespread in nature, as well as widely employed both for industrial and medical applications.[47] Several million tons of polyesters (i.e., polyethylene terephthalate, acrylate esters, cellulose acetate) are produced industrially every year[47] and they represent the largest classes of synthetic lubricants on the commercial market.[48] Moreover, because of their pleasant aroma, they are commonly used as fragrances.

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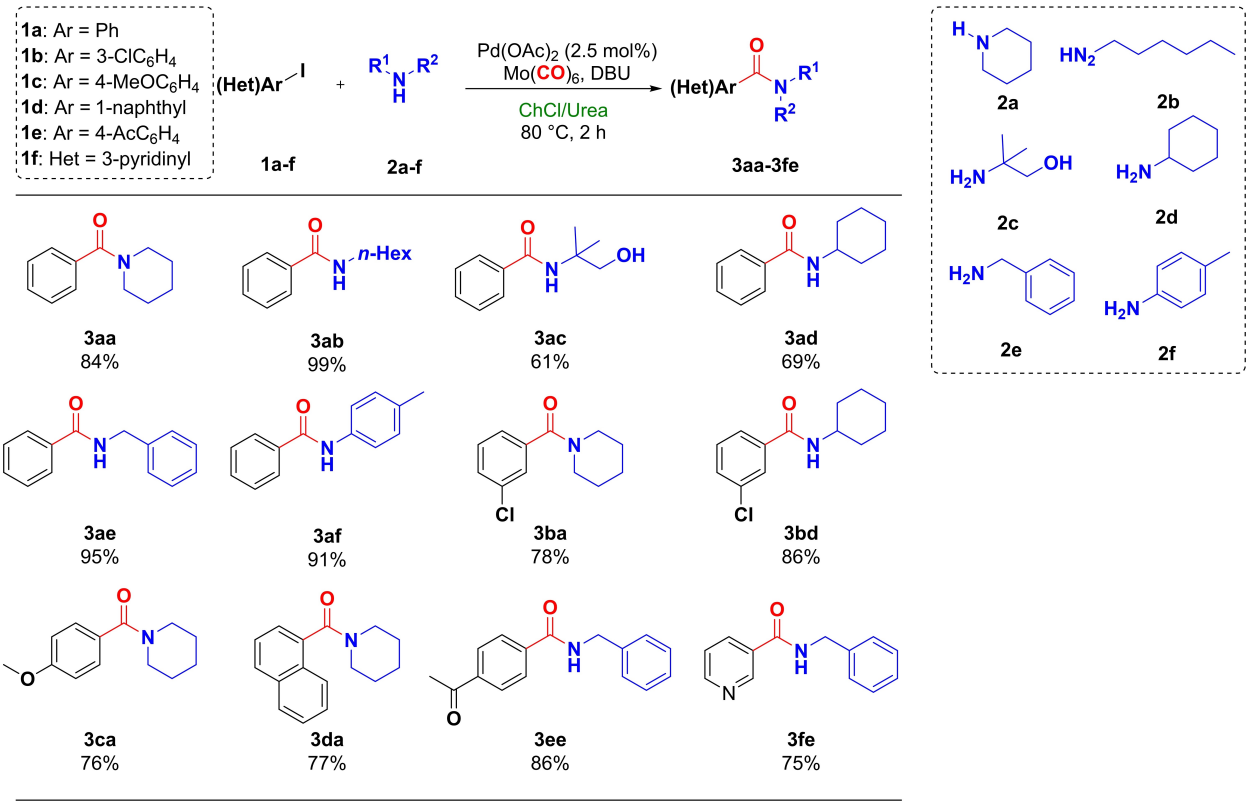


Scheme 2. Scope of Pd-Catalyzed carbonylative coupling between aromatic iodides **1a–f** and amines **2a–f** in ChCl/urea (1:2) as green medium and $Mo(CO)_6$ as a safe CO source. Reaction conditions: aryl iodide (0.5 mmol), amine (1.5 mmol), $Pd(OAc)_2$ (2.5 mol%), $Mo(CO)_6$ (0.25 mmol), DBU (1.5 mmol), ChCl/urea (1/2 mol/mol, 1.0 mL), 80 °C, 2 h. Isolated yields are reported.

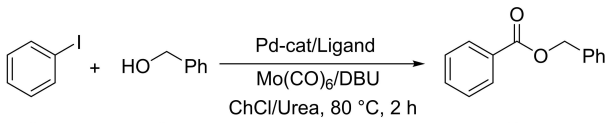
In a model reaction, iodobenzene **1a** was treated with benzyl alcohol **4a**, in the presence of $Pd(OAc)_2$, $Mo(CO)_6$ and DBU as the base. After 2 hours at 80 °C, the expected benzyl benzoate **5aa** formed in only 22% (Table 2, entry 1). Even by doubling the Pd loading, the yield of the desired ester remained unchanged (22%, Table 2, entry 2).

Notably, we found that the presence of a phosphine ligand in the mixture was a key factor in this alkoxycarbonylation process: the experimental results described in entries 3–4 provided evidence that the addition of Ph_3P or $MePh_2P$ as catalyst ligands significantly improved the ester formation, resulting in a **5aa** yield of 65% and 67%, respectively.

The increase in the alcohol **4a** concentration resulted in an enhancement of the **5aa** yield (79%, Table 2, entry 5), thus suggesting that a competition between the hydroxylated DES component (cholinium chloride) and the nucleophile is operative in our carbonylative coupling. With the aim to reduce the amount of noble metal involved in the process, we lowered the DES volume (1 mL, Table 2, entry 6) and found that with only 2.5 mol% loading of catalyst and 10 mol% of $MePh_2P$, the ester **5aa** formed in satisfactory yield (70%). The catalytic activity of a preformed Pd^{II}-phosphine complex was also tested (Table 2, entry 7), but with less satisfactory results, as the benzyl benzoate **5aa** was obtained in 55% yield.

The best experimental conditions for this gas-free alkoxycarbonylation of **1a** in the ChCl/urea (1:2) medium, with $Mo(CO)_6$ and $Pd(OAc)_2$, were finally given by those ones reported in Table 2, entry 8 (86% of **5aa** yield).

Table 2. Screening of the reaction conditions for the alkoxycarbonylation of iodobenzene **1a** with benzyl alchohol **4a** and $Mo(CO)_6$ in ChCl/urea (1:2) DES.[a]



entry	**4a** (mmol)	Pd-ligand	Pd-Cat. [mol%]	**5aa** Yield [%][b]
1	1.5	–	$Pd(OAc)_2$ (2.5)	22
2	1.5	–	$Pd(OAc)_2$ (5)	22
3	1.5	Ph_3P	$Pd(OAc)_2$ (5)	65
4	1.5	$MePh_2P$	$Pd(OAc)_2$ (5)	67
5	3	$MePh_2P$	$Pd(OAc)_2$ (5)	79
6[c,d]	1.5	$MePh_2P$	$Pd(OAc)_2$ (2.5)	70
7[d]	1.5	–	$Pd(PPh_3)_2Cl_2$ (2.5)	55
8[c,d]	3	$MePh_2P$	$Pd(OAc)_2$ (2.5)	86

[a] Reaction conditions: iodobenzene **1a** (0.5 mmol), benzyl achohol **4a** (1.5 mmol), Pd-cat (2.5–5 mol%), $Mo(CO)_6$ (0.5 mmol), DBU (1.5 mmol), $MePh_2P$ (0–20 mol%), ChCl/urea (1/2 mol/mol, 2.0 mL). [b] Calculated via ^1H NMR analysis of the crude reaction mixture using the internal standard technique (NMR internal standard: dimethyl sulfone). [c] Reaction performed with 10 mol% of $MePh_2P$. [d] Reaction performed in 1.0 mL of DES.

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Any attempt to replace DBU with a greener base, or to reduce the catalyst loading, resulted detrimental for the **5aa** yield (see ESI, Table S1).

It is important to note that, among the synthetized esters, benzyl benzoate **5aa** represents a valuable organic product. First studied medically in 1918,[49] it is listed in the World Health Organization's List of Essential Medicines[50] for the treatment of human scabies and lice.[51]

With the aim to explore the applicability of the present method, we also performed the synthesis of API **5aa** on a gram scale. Under the best conditions shown in Table 2 (entry 8), and starting from 1.0 grams of iodobenzene **1a**, we were pleased to find that, despite scaling up the reaction by a factor of 10, the yield of benzyl benzoate remained almost unchanged, affording the benzoate **5aa** in 82% yield.

Under the optimal conditions (Table 2, entry 8), different aryl iodides and alcohols were tested to showcase the substrate scope of this novel alkoxycarbonylation methodology, employing $Mo(CO)_6$ as a safe CO surrogate and the sustainable eutectic mixture ChCl/urea (1:2) as the solvent. At first, different primary and secondary aliphatic alcohols were selected as *O*-nucleophilic partners in the carbonylation process. As shown in Scheme 3, in the reaction with iodobenzene **1a**, 3,3-dimethylbutan-1-ol **4b** was conveniently transformed to the corresponding ester **5ab**, obtained in good yield (83%). Also the primary alcohol **4c** reacted well with **1a**, giving the target ester **5ac** in high yield (92%)

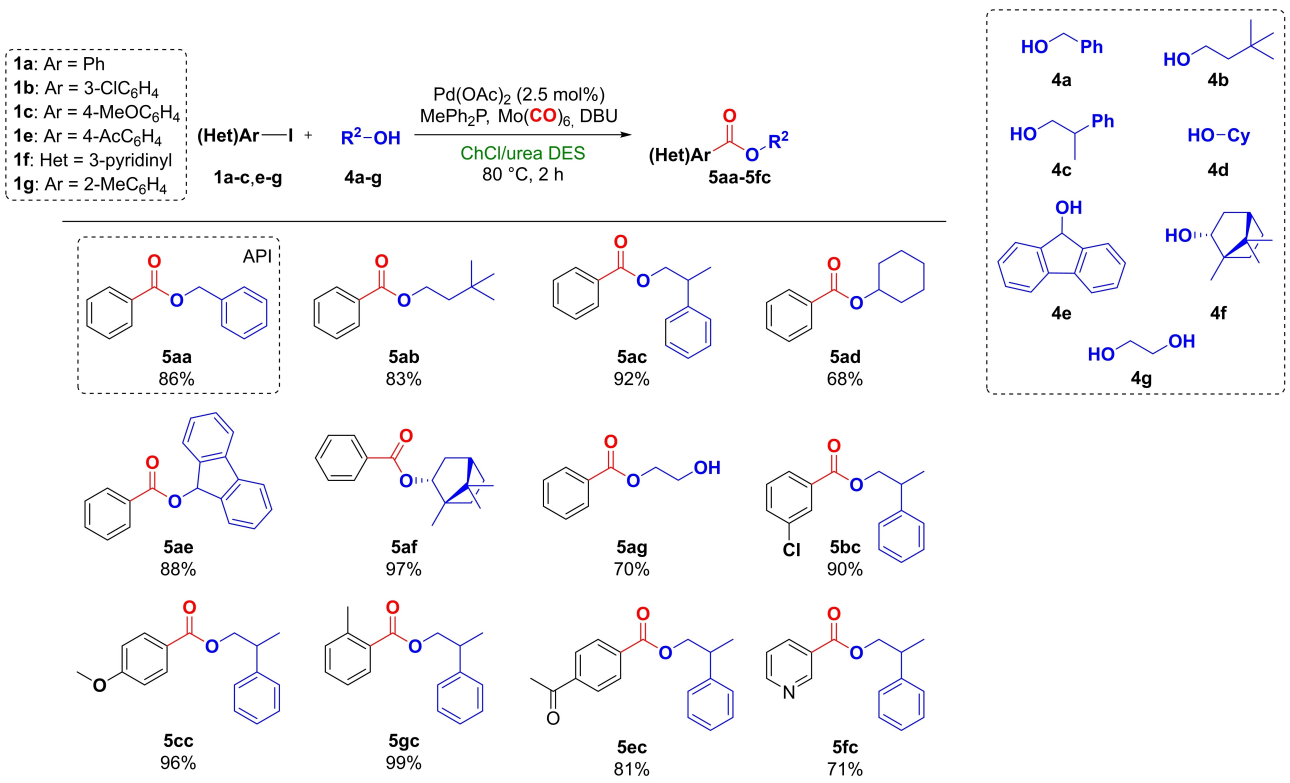
Compared to primary alcohols, the secondary cyclohexanol **4d** was proven to be less efficient in the alkoxycarbonylation process, achieving the ester **5ad** in a 68% yield. However, with the use of other secondary alcohols, such as the hindered 9*H*-fluoren-9-ol **4e** and (+)-borneol **4f**, the protocol worked smoothly, affording the corresponding esters **5ae**-**5af** in excellent yields (88-97%). Moreover, the diol EG (**4g**) was employed in the alkoxy carbonylation of the halide **1a**, albeit the desired EG-derivative **5ag** formed in moderate yield (70%). In this case traces of the diester product were detected in the mixture (by GC-MS).

The presence of electron-withdrawing (e.g. Cl) or electron-donating (e.g. Me- and MeO-) substituents on the aryl iodide, did not influence significatively the efficiency of the process, resulting in the synthesis of the esters **5bc**–**5cc** and **5gc** in high yields (90–99%).

From good to moderate ester yields (81–71%) were also achieved with the employment of the iodide **1e** decorated with a reactive functionality and with the heteroaryl iodide **1f**.

Additionally, a brief investigation was performed to test if our method could allow the recycling of both catalyst and DES.

The Pd-catalysed aminocarbonylation of iodobenzene **1a** with *n*-hexylamine **2b** in ChCl/urea (1:2) was chosen as the model reaction, since it provided almost quantitative yield of the corresponding amide **3ab** (Scheme 2). After the first carbonylation run, the crude mixture was extracted with the biomass-derived solvent 2-MeTHF,[52] affording the product **3ab**



Scheme 3. Scope of Pd-Catalyzed carbonylative coupling between aromatic iodides **1a**–**c**,**e**–**g** and alcohols **4a**–**g** in ChCl/urea (1:2) as green medium and $Mo(CO)_6$ as a safe CO source. Reaction conditions: aryl iodide (0.5 mmol), alcohol (3.0 mmol), $Pd(OAc)_2$ (2.5 mol%), $MePh_2P$ (10 mol%), $Mo(CO)_6$ (0.5 mmol), DBU (1.5 mmol), ChCl/urea (1/2 mol/mol, 1.0 mL), 80 °C, 2 h. Isolated yields are reported.

in a >98% yield (Figure 1, number of cycles = 0), leaving the active catalyst species in the eutectic mixture. The DES phase was then dried under vacuum until a constant weight.

Upon the simple addition of the new, fresh reagents [**1a**, **2b**, $Mo(CO)_6$ and DBU), the catalyst and reaction medium could be easily re-used for additional reaction cycles. As shown in Figure 1, the catalyst remained active for over 4 runs.

Particularly, its activity remained almost unaffected in the first recycle (98% of **3ab** yield) and underwent a gradual deactivation during the second and the third recycles, with 80% and 73% of **3ab** yield, respectively. The recycling efficiency suffered a consistent decrease from the fourth recycle, with a drop down in the chemical yield of the target product up to 12%.

The drop in the reaction efficiency observed during the recycling procedure could be explained as follows. The transformation of $Mo(CO)_6$ and $Pd(OAc)_2$ during the catalytic cycle could produce inorganic solids, which accumulate in the reaction mixture over consecutive runs, thus hindering the stirring and consequently decreasing the efficiency of the process. Additionally, during the successive carbonylation reactions, protonated DBU ($DBU\text{-}H^+$) accumulates in the DES phase. This was confirmed through a careful characterization, by ^1H- and ^{13}C-NMR, of the DES after performing the model reaction (see Supporting Information for more details).

Although lipophilic molecules, like the carbonylation products, can be extracted with 2Me-THF during the workup procedure, the ammonium cation $DBU\text{-}H^+$ stores in the DES phase, thus reducing the medium basicity, known to be a crucial key factor in aminocarbonylation processes.

The possibility that a change in DES composition could be responsible for the decrease in recycling efficiency has also been considered. However, a quantitative ^{13}C-NMR analysis on the ChCl/urea eutectic mixture, after running a model reaction, showed that the DES composition remained unchanged and ruled out this hypothesis (see Supporting Information for further details).

To gain a quantitative understanding of the environmental impact of our carbonylative coupling in DES, for the carbonylative synthesis of *N*-hexyl benzamide **3ab** from iodobenzene **1a** and *N*-hexylamine **2b**, we calculated two green metrics, namely EcoScale and E-factor. Such parameters were then compared with the corresponding ones related to the aminocarbonylations reported in Scheme 1. Based on the green metric analysis, we determined that our methodology exhibited a comparable environmental impact (EcoScale = 44.5) to the procedure reported by Bolm (EcoScale = 47), which was the most sustainable among the compared methods, as indicated by the EcoScale. However, in terms of the E-Factor, our protocol, with a value of 45.5, significantly outperformed all others, making it the most favorable option (see Supporting Informations for further details).

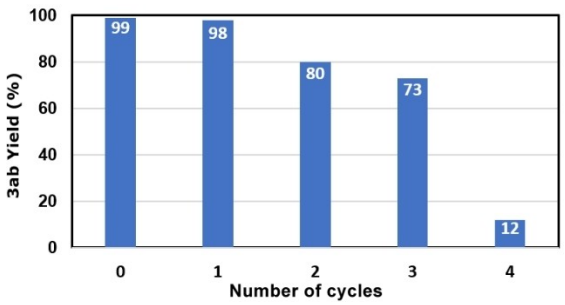


Figure 1. Recycling of $Pd(OAc)_2$ and ChCl/urea (1:2) in the carbonylative synthesis of *N*-hexyl benzamide **3ab** from iodobenzene **1a** and *N*-hexylamine **2b**.

Finally, with the aim to understand the role of DES in this reaction, we endeavored to conduct the carbonylation reaction using a mixture of the biomass-derived CPME, as a sustainable solvent, and either choline chloride or urea as additives (20 wt% respect with CPME). Regrettably, both choline chloride and urea exhibited minimal solubility in this ethereal solvent, significantly hampering the outcome of our experimental efforts. As a result, the two model carbonylative reactions, performed between iodobenzene and piperidine, yielded the amide **3aa** in a similar yield of 40–43%, if compared with the same reaction performed in pure CPME. Based on literature reports, we suppose that the role of DES components is strictly related to the ionic character of cholinium chloride; an aspect that potentially enables the formation of anionic Pd-species, which are considered to act as the authentic catalysts in cross-coupling reactions.[53]

Conclusion

To summarize, we have developed a novel gas-free carbonylation process of general applicability which aims at a more sustainable synthesis of aromatic esters and amides, by using $Mo(CO)_6$ as a safe source of carbon monoxide in ChCl/urea (1:2), an environmentally responsible and bioinspired deep eutectic solvent. This process offers various benefits in comparison to other approaches. These include the use of mild reaction conditions (80 °C), short reaction time (2 h), low catalyst loading (2.5 mol%), no requirement for specialized lab equipment, and the possibility to use both catalyst and DES for at least 4 consecutive runs, with only a modest decrease in the catalytic system's performance. The protocol enables the synthesis of valuable esters and amides in up to 99% yield, including a pharmacologically relevant molecule such as the benzyl benzoate **5aa**, also synthesized on a gram scale. Our future studies will focus on exploring how the DES components could facilitate carbonylation reactions, thereby broadening the range of substrates that could be employed and extending the research to the use of non-noble metal catalysts.

Experimental Section

Synthesis of amides 3aa–3fe by the aminocarbonylation reaction of aryl iodides in ChCl/urea eutectic mixture: In a 10 mL round bottom flask, aryl iodide (**1a–f**, 0.5 mmol), $Mo(CO)_6$ (66.0 mg, 0.25 mmol), amine (**2a–f**, 1.5 mmol) DBU (228.3 mg, 224.0 μL, 1.5 mmol), $Pd(OAc)_2$ (trimeric, FW = 673.46, 2.5 mol%, 0.0125 mmol, 8.4 mg) and ChCl/urea (1:2) DES (1.0 mL) were sequentially added.

The reaction was stirred for 2 hours at 80 °C. After this time, the reaction mixture was cooled to room temperature and water (2.5 mL) and HCl solution (10% v/v) up to pH = 2 were sequentially added. The mixture was then extracted with AcOEt (5 mL × 3) and the reunited organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered through a celite pad and evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel (using as eluent petroleum ether/AcOEt 70/30 to petroleum ether/AcOEt 50/50), obtaining the desired amides **3 aa**–**3 fe** as pure compounds.

Synthesis of esters 5 aa–5 fc by the alkoxycarbonylation reaction of aryl iodides in ChCl/urea eutectic mixture: In a 10 mL round bottom flask, aryl iodide (**1 a**–**c**, **e**–**g**, 0.5 mmol), $Mo(CO)_6$ (132.0 mg, 0.5 mmol), alcohol (**4 a**–**g**, 3.0 mmol) DBU (228.3 mg, 224.0 μL, 1.5 mmol), $Pd(OAc)_2$ (trimeric, FW = 673.46, 2.5 mol%, 0.0125 mmol, 8.4 mg), $MePh_2P$ (10.0 mol%, 0.05 mmol, 10.0 mg, 9.3 μL) and ChCl/urea (1 : 2) DES (1.0 mL) were sequentially added. The reaction was stirred for 2 hours at 80 °C. After this time, the reaction mixture was cooled to room temperature and water (2.5 mL) and HCl solution (10% v/v) up to pH = 2 were sequentially added. The mixture was then extracted with AcOEt (5 mL × 3) and the reunited organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered through a celite pad and evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel (using as eluent petroleum ether/AcOEt 98/2 to petroleum ether/AcOEt 70/30), obtaining the desired esters **5 aa**–**5 fc** as pure compounds.

Supporting Information

Additional references cited within the Supporting Information. [54-74]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: alkoxycarbonylation · aminocarbonylation · Pd-catalysis · deep eutectic solvent · molybdenum hexacarbonyl

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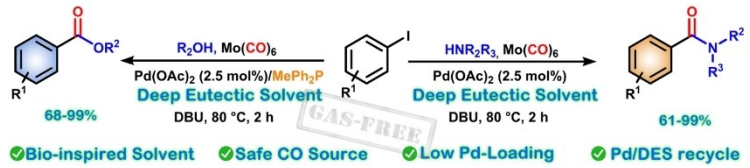

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Gas-Free Amino- and Alkoxycarbonylation of Aryl Iodides in a Bio-inspired Deep Eutectic Solvent with $Mo(CO)_6$ as a Safe CO Source

The synergy between a nature-inspired ionic solvent and $Mo(CO)_6$, as a solid source of carbon monoxide, allowed to develop a Pd-catalyzed amino- and alkoxycarbonylation under mild reaction conditions and with an improved degree of sustainability.