

## Copper-catalyzed Goldberg-type C–N coupling in Deep Eutectic Solvents (DESs) and water under aerobic conditions

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An efficient and selective N-functionalization of amides is first reported via a CuI-catalyzed Goldberg type C–N coupling reaction between aryl iodides and primary/secondary amides run either in Deep Eutectic Solvents (DESs) or water as sustainable reaction media, under mild and bench-type reaction conditions (absence of protecting atmosphere). Higher activities were observed in an aqueous medium, though the employment of DESs expanded and improved the scope of the reaction to include also aliphatic amides. Additional valuable features of the reported protocol include: i) the possibility to scale up the reaction without any erosion of the yield/reaction time; ii) the recyclability of both the catalyst and the eutectic solvent up to 4 consecutive runs; and iii) the feasibility of the proposed catalytic system for the synthesis of biologically active molecules.

### 1. Introduction

The search for organic transformations catalyzed by first-row, cheap and earth-crust abundant transition metals is nowadays playing a pivotal role in synthetic organic chemistry.<sup>1</sup> In this sense and within the coinage metals group (Cu, Ag and Au),<sup>2</sup> copper occupies a prominent and strategic position as: i) is an essential metal in biology<sup>3</sup> and presents moderate toxicity;<sup>4</sup> ii) displays a versatile reactivity with rich and diverse redox chemistry [possibility to access different oxidations states: Cu(0); Cu(I); Cu(II) or even Cu(III)];<sup>5</sup> iii) can allocate in its coordination sphere either soft (containing P- and S- donor atoms) as Cu(I) or hard donor ligands (like O and N) as Cu(II); and iv) can participate in both  $\sigma$ - or  $\pi$ -interactions with unsaturated organic substrates (alkenes or alkynes). Thus, it is not surprising to find a plethora of applications for Cu-based catalysts in several hot-topic areas of catalysis spanning cross-coupling reactions<sup>6</sup> and asymmetric synthesis.<sup>7</sup> As for C–N bond formations,<sup>8</sup> typical Cu-catalyzed cross-coupling processes like the Ullmann<sup>9</sup> or the Goldberg<sup>10</sup> reactions are reputed by organic chemists as key and valuable synthetic tools for the formation of C–N bonds either in academic or in industrial laboratories all over the world,<sup>8</sup> especially considering the ongoing depletion of petroleum reserves and the severe environmental problems associate with their use. Thus, the employment of sustainable reaction media in organic synthesis is today highly sought after in order to fulfill one of the most important Principles of Green Chemistry.<sup>11</sup> In this context, it is worth mentioning that 80–90% of the mass balance of chemical reaction is directly related with the volatile organic solvents (VOCs) employed, either used as a bulk reaction medium or in the usually required isolation/purification steps.<sup>12</sup>

In this vein, we have recently reported on a variety of highly selective and effective transition-metal-catalyzed organic transformations promoted by Ru,<sup>13</sup> Au,<sup>14</sup> or Pd<sup>15</sup> complexes, which have been performed in a new family of sustainable reaction media, that is the so-called Deep Eutectic Solvents (DESs).<sup>16</sup> These environmentally friendly and tunable eutectic mixtures can be obtained by mixing and heating two (binary DESs) or even three (ternary DESs) components that are amenable to interact through a tridimensional hydrogen-bond-type network, which is established between hydrogen-bond-acceptor components [HBAs, usually biorenewable quaternary ammonium salts like choline chloride (ChCl)<sup>17</sup> (A, Figure 1)] and hydrogen-bond-

donors [HBDs, typically natural polyols (like glycerol (Gly), ethylene glycol (EG), sugars, urea derivatives and biorenewable carboxylic acids (e.g., oxalic, malonic or citric acid (B, Figure 1)].<sup>18</sup> At this point, it is important to remark that DESs have been today used as privileged sustainable solvents in a wide variety of chemical applications.<sup>19</sup>

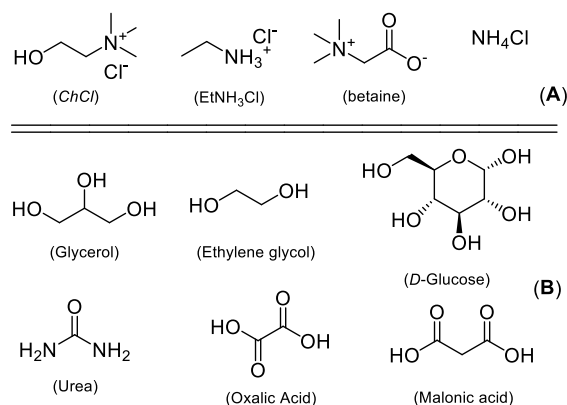
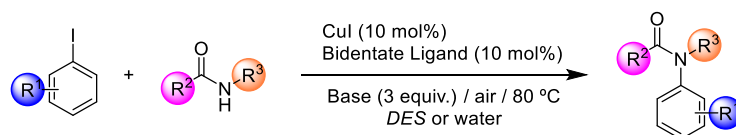


Figure 1. Hydrogen-bond-acceptors (HBA, top) and hydrogen-bond-donors (HBD, down) usually employed in the synthesis of sustainable Deep Eutectic Solvents (DESs).

Despite the large number of Pd-catalyzed C–C coupling reactions successfully run in different eutectic mixtures (e.g., Suzuki, Heck, Stille, Sonogashira and Hiyama-type couplings),<sup>15c,e-g,20</sup> there are only few examples, independently reported by Shaabani<sup>21</sup> and Capriati<sup>22</sup> research groups, which illustrate the possibility to perform the Cu-catalyzed Ullman-type C–N coupling between aryl iodides and primary or secondary amines in sustainable eutectic mixtures. Conversely, as far as we are aware, the corresponding counterpart studies on the Cu-catalyzed Goldberg-type C–N coupling in DESs have been totally neglected.<sup>23</sup> Accordingly, we decided to fill this gap by studying the C–N coupling reaction of aryl halides with either aromatic or primary and secondary aliphatic amides (Scheme 1): i) in different DESs or water as sustainable solvents; ii) under mild and bench-type reaction conditions (presence of air and lower reaction temperature); and iii) using different bases (KOH or tBuOK) and bidentate ligands (like ethylene diamine, glycine, L-proline, bipyridine). The robustness of the proposed methodology was further highlighted by successful recycling studies of the catalytic system and its application in drug synthesis.



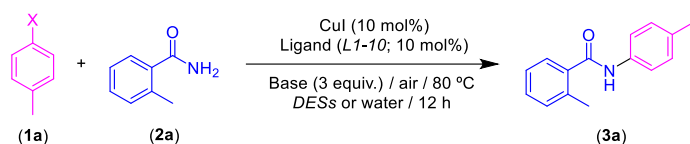
Scheme 1. CuI-catalyzed Goldberg-type C–N coupling of aryl iodides with primary/secondary amides under air in DES or aqueous media.

## 2. Results and Discussion

We started our investigation by exploring sustainable reaction media (DESs or water) useful to design a Cu-catalyzed Goldberg-type C–N coupling under milder and bench-type reaction conditions. We elected to study, as a model reaction, the CuI-catalyzed (10 mol%) coupling of 4-iodotoluene (1a) with 2-methylbenzamide (2a) in the archetypical eutectic mixture 1ChCl/2Gly, in the absence of protecting atmosphere (under air) and at 80 °C. Building on

previously reported studies on Goldberg-type C–N couplings,<sup>23</sup> we decided to use ethylene diamine (L1) (10 mol%) and tBuOK (3 equiv.) as a base. After 12 h reaction time, we observed the formation of the desired secondary amide 3a in moderate yield (66%), but with a complete chemoselectivity. No side products were observed in the crude reaction mixture aside from unreacted starting materials (1a and 2a) (Table 1, entry 1). At this point, it is important to note the significant effect of the temperature on the outcome of the catalytic reaction. Indeed, the yield of 3a dropped to 41% when the temperature was lowered down to 60 °C (Table 1, entry 2). On the other hand, enhancement of the reaction temperature up to 100 °C only produced a moderate increase of the yield of 3a (72%, Table 1, entry 3). We also found that the suppression of either the external base (Table 1, entry 4) or the bidentate ligand ethylene diamine (L1) (Table 1, entry 5) produced a loss of the catalytic activity or a dramatic decrease of the 3a yield, respectively. Finally, in accordance with previous studies on transition-metal-catalyzed organic reaction in ChCl-based eutectic mixtures,<sup>14</sup> the Goldberg-type C–N coupling was similarly found to proceed at higher rates in the 1ChCl/2Gly eutectic mixture than in pure glycerol (Table 1, entry 6), thus highlighting the positive effect of this quaternary ammonium salt in the catalytic procedure when synergistically combined with Gly.

Table 1. CuI-catalyzed Goldberg type C–N coupling between 4-iodotoluene (1a) and 2-methylbenzamide (2a) under air and at 80 °C in different sustainable solvents (DESSs or water).<sup>a</sup>

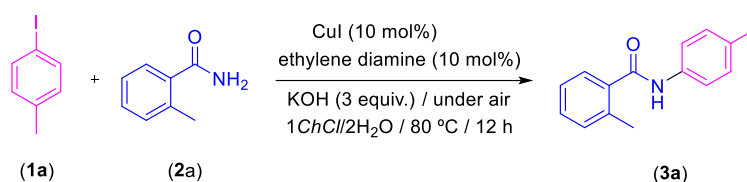


Entry	X	solvent	T (°C)	Ligand <sup>b</sup>	Base (%)	Yield (%) <sup>c</sup>
1	I	1ChCl/2Gly	80	L1	tBuOK	66
2	I	1ChCl/2Gly	60	L1	tBuOK	41
3	I	1ChCl/2Gly	100	L1	tBuOK	72
4	I	1ChCl/2Gly	80	L1	-	0
5	I	1ChCl/2Gly	80	-	tBuOK	10
6	I	Gly	80	L1	tBuOK	51
7	I	1ChCl/2Urea	80	L1	tBuOK	74
8	I	1ChCl/2Urea	80	L1	-	0
9	I	1ChCl/2Urea	80	L2	tBuOK	72
10	I	1ChCl/2Urea	80	L3	tBuOK	0
11	I	1ChCl/2Urea	80	L4	tBuOK	9
12	I	1ChCl/2Urea	80	L5	tBuOK	20
13	I	1ChCl/2Urea	80	L6	tBuOK	27
14	I	1ChCl/2Urea	80	L7	tBuOK	37
15	I	1ChCl/2Urea	80	L8	tBuOK	2

16	I	1ChCl/2Urea	80	L9	tBuOK	10
17	Br	1ChCl/2Urea	80	L1	tBuOK	8
18	Cl	1ChCl/2Urea	80	L1	tBuOK	0
19	I	1Bet/1Urea	80	L1	tBuOK	60
20	I	1ChCl/2H <sub>2</sub> O	80	L1	tBuOK	80
21	I	H <sub>2</sub> O	80	L1	tBuOK	85
22	I	H <sub>2</sub> O	80	L1	KOH	92
23	I	H <sub>2</sub> O	80	L1	Cs <sub>2</sub> CO <sub>3</sub>	
24	I	H <sub>2</sub> O	80	L1	K <sub>2</sub> CO <sub>3</sub>	11
25	I	H <sub>2</sub> O	80	L1	K <sub>3</sub> PO <sub>4</sub>	4

a General conditions: reactions performed under air, at 60–100 °C using 0.5 mmol of 1a and 2a in 1 mL of the desired solvent. b L1 = ethylene diamine; L2 = N,N-dimethylethylenediamine; L3 = glycine; L4 = L-proline; L5 = 2,2'-bipyridine; L6 = (1R,2S)-cyclopentane-1,2-diamine; L7 = (1R,2S)-cyclohexane-1,2-diamine; L8 = benzene-1,2-diamine; L9 = (1R,2S)-2,3-dihydro-1H-indene-1,2-diamine. c Yield determined by HPLC.

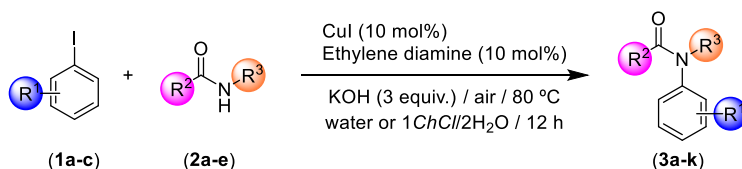
Next, we decided to study the effect of different HBDs forming the eutectic mixture on the outcome of the catalytic reaction. To this end, we firstly replaced the natural polyol Gly by urea to form the so-called eutectic mixture reline (1ChCl/2Urea).<sup>18</sup> Under the aforementioned conditions (80 °C, 10 mol% of CuI, 10 mol% of L1, 3 equiv. of tBuOK, under air), we observed an increase of the yield of 3a (74%), while maintaining the total chemoselectivity of the reaction (Table 1, entry 7). Probably, this result could be related to the enhanced basic character of the eutectic mixture 1ChCl/2Urea when compared with 1ChCl/2Gly.<sup>24</sup> At this point, we explored: i) the possibility to run the reaction in the absence of base, but no reaction was observed (Table 1, entry 8); ii) the effect of different chelating ligands (10 mol% of L1–L9), with the best result obtained by the ethylene diamine (Table 1, entries 9–16); iii) the influence of the halogen atom present in the aromatic coupling partner (4-Br- or 4-Cl-toluene), observing a decrease in the yield of the process (Table 1, entries 17,18); and iv) the employment of a different HBA, detecting a decrease of the catalytic activity when using betaine (Bet, Table 1, entry 19). To finish with the parametrization studies on the role of HBD of the eutectic mixture, we decided to extend our studies to the prototypical HBD present in nature, that is water, thus using the eutectic mixture 1ChCl/2H<sub>2</sub>O as a solvent. In this case, we found an increased catalytic activity (80%; Table 1, entry 20). This enhancement could even be improved using bulk water as the solvent (85%; Table 1, entry 21). Finally, a yield as high as 92% could be achieved when switching from tBuOK to KOH (Table 1, entry 22), while the use of carbonate- or phosphate-containing inorganic bases considerably decreased the activity of the catalytic system (Table 1, entries 23–25). At this point, it is worth noting that a similar yield (90%) in this aqueous medium was achieved also by performing the coupling reaction on a 2.5 mmol scale (Scheme 2).<sup>25</sup>



Scheme 2. CuI-catalyzed Goldberg type C–N coupling between 4-iodotoluene (1a) and 2-methylbenzamide (2a) for the scaled-up synthesis of 3a (reaction performed on a 2.5 mmol scale).

Since the use of water was associated to the best catalytic performance, we decided to expand the scope of this reaction to the coupling of a library of amides 2a–e (aliphatic/aromatic, secondary/primary amides containing either electron-donor or electron-withdrawing groups) with a variety of substituted aryl iodides (1a–c), under the previously optimized catalytic conditions (80 °C, 10 mol% of CuI, 10 mol% of ethylene diamine, 3 equiv. of KOH and under air; see Table 2). As for aromatic amides, the presence of electron-donating substituents in the aromatic ring, like methyl (2a) or methoxy (2b) groups, gave rise to the corresponding secondary amides 3a–e in good to quantitative yields (81–99%, Table 2, entries 1–5) when 4-iodotoluene (1a), 4-iodobenzene (1b) or 3-iodoanisole (1c) were employed as coupling partners. However, the presence of electron-withdrawing substituents in the aromatic ring of the amide, like in the case of 2-fluorobenzamide (2c), produced a slight erosion in the yield of the corresponding secondary amides 3f,g (64–74%; Table 2, entries 6–7). This catalytic system also tolerates the use of secondary amides, like N-methylbenzamide (2d) giving rise to the expected tertiary amide 3h in good yield (70%; Table 2, entry 8). One of the main drawbacks of our aqueous catalytic system is related to the fact that aliphatic amides proved to be totally unreactive. Pleasantly, switching water for the 1ChCl/2H<sub>2</sub>O eutectic mixture, we observed moderate to good coupling yields (up to 99%) of aliphatic propionamide (2e) with several iodoaryl partners containing different substituents [4-Me (1a) or 3-MeO (1c); Table 2, entries 9–11]. Finally, in order to promote an efficient mass transfer in the synthesis of compounds 3g, 3j and 3k (Table 2, entries 7 and 10–11), we performed the coupling reaction under ultrasonic irradiation using a conventional ultrasound bath operating at 35 KHz and 160 W.<sup>26</sup> However, the use of these new reaction conditions did not improve the yield/reaction times previously observed in any of the studied cases.

Table 2. CuI-catalyzed Goldberg type C–N coupling between different aryl iodides (1a–c) and several aromatic/aliphatic amides (2a–e), in water or 1ChCl/2H<sub>2</sub>O, under air and at 80 °C.a

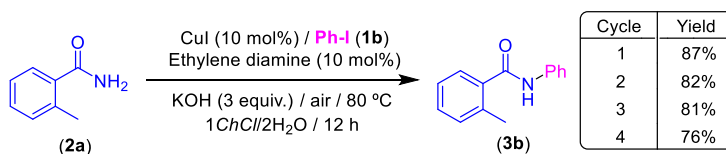


Entry	R1	R2/R3	solvent	Yield (%) <sup>b</sup>
1	4-Me (1a)	2-Me-Ph/H (2a)	H <sub>2</sub> O	92 (85, 3a)
2	H (1b)	2-Me-Ph/H (2a)	H <sub>2</sub> O	95 (90, 3b)
3	3-OMe (1c)	2-Me-Ph/H (2a)	H <sub>2</sub> O	81 (74, 3c)

4	4-Me (1a)	3-MeO-Ph/H (2b)	H <sub>2</sub> O	88 (83, 3d)
5	H (1b)	3-MeO-Ph/H (2b)	H <sub>2</sub> O	99 (95, 3e)
6	H (1b)	2-F-Ph/H (2c)	H <sub>2</sub> O	74 (68, 3f)
7	4-Me (1a)	2-F-Ph/H (2c)	H <sub>2</sub> O	64 (57, 3g)
8	H (1b)	Ph/Me (2d)	H <sub>2</sub> O	70 (65, 3h)
9	4-Me (1a)	Et/H (2e)	1ChCl/2H <sub>2</sub> O	99 (92, 3i)
10	H (1b)	Et/H (2e)	1ChCl/2H <sub>2</sub> O	62 (60, 3j)
11	3-OMe (1c)	Et/H (2e)	1ChCl/2H <sub>2</sub> O	45 (42, 3k)

a General conditions: reactions performed under air, at 80 °C using 0.5 mmol of 1a–c and 2a–e and 3 equiv. of KOH in 1 mL of the desired solvent. b Yield determined by HPLC. Isolated yields after column chromatography in brackets.

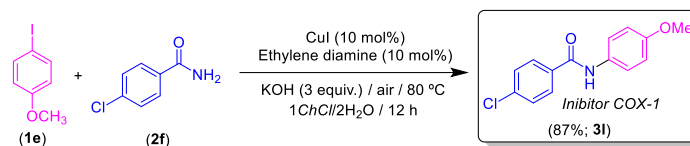
In the framework of a sustainable catalysis,<sup>27</sup> the lifetime of a catalytic system and its level of reusability are key factors that could improve the environmental footprint of a given catalytic system.<sup>28</sup> In this sense, and taking into account the feasibility of recycling eutectic mixtures in metal-catalyzed organic reactions,<sup>16e</sup> we decided to investigate the reusability of our catalytic system taking, as a model reaction, the CuI-catalyzed Goldberg-type coupling between iodobenzene (1b) and 2-methylbenzamide (2a), at 80 °C, in the presence of ethylene diamine (10 mol%) as a ligand and KOH (3 equiv.) as a base, under air and using the eutectic mixture 1ChCl/2H<sub>2</sub>O as a reaction medium (Scheme 3). Under these conditions, the desired amide 3b was isolated in 87% yield after 12 h reaction time. Subsequent extraction of the resulting crude with a sustainable green solvent like cyclopentyl methyl ether (CPME)<sup>29</sup> and concomitant addition of fresh reagents, allowed us to recycle the catalyst and the DES successfully up to three consecutive runs with only a negligible erosion of the final yield of 3b (Scheme 3). In order to provide metrics to support the “greenness” profile of the reported methodology, we have calculated the Sheldon’s environmental factor (E-factor) (total mass of waste/mass of product),<sup>30</sup> finding a value of 15,<sup>31</sup> which is within the recommended range for fine chemicals (5–50).<sup>30</sup>



Scheme 3. CuI-catalyzed Goldberg type C–N coupling between iodobenzene (1b) and 2-methylbenzamide (2a) under air and at 80 °C in the eutectic mixture 1ChCl/2H<sub>2</sub>O: recycling studies.

Finally, we decided to apply our methodology to the synthesis of biologically active molecules. Our target was 4-chloro-N-(4-methoxyphenyl)benzamide (3l), which belongs to the N-arylbenzamide class of cyclooxygenase (COX-1) selective inhibitors (Scheme 4).<sup>32</sup> We envisaged as a key step to access this secondary amide, a CuI-catalyzed Goldberg-type C–N coupling between 4-iodoanisole (1e) and 4-chlorobenzamide (2f), under the previously optimized reaction conditions in the 1ChCl/2H<sub>2</sub>O eutectic mixture (Scheme 4), finding that the desired secondary amide 3l chemoselectively formed in 87% yield. As a final point, it is worth

mentioning that the biologically active compound 3l was isolated in the same yield (87%) when working on a 2.5 mmol scale.



Scheme 4. Synthesis of the biologically active aromatic secondary amide 3l through CuI-catalyzed Goldberg type C–N coupling between 4-iodotoluene (1e) and 4-chlorobenzamide (2f), under air and at 80 °C in the eutectic mixture 1ChCl/2H<sub>2</sub>O.

## Conclusions

In summary, we have developed the first Cu-catalyzed Goldberg-type C–N coupling working in ChCl-based Deep Eutectic Solvents and water. The utilization of these sustainable reaction media allowed us to carry out this coupling process: i) under milder reaction conditions (80 °C; temperatures as high as 110 °C are usually required); ii) employing bench-type settings (presence of air); and iii) with high chemoselectivity, as a variety of coupling partners with different electron-donating or electron-withdrawing substituents are tolerated. The inactivity of the catalytic system in water when using aliphatic amides was overcome upon simple switching of water for a water-based eutectic mixture, that is 1ChCl/2H<sub>2</sub>O.

Furthermore, we demonstrated: i) the possibility to scale up the reaction without observing any erosion of the yield/reaction time; ii) the successful recycle of both the catalyst and the eutectic solvent up to 4 consecutive runs; and iii) the competence of our catalytic system for the synthesis of biologically active organic molecules. Overall, this methodology provides a synthetic tool for the efficient, sustainable and selective formation of C–N bonds, which is an important endeavour in the field of metal-catalyzed organic transformations.

## Conflicts of interest

There are no conflicts to declare.

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#### Notes and references

- 1 (a) B. Su, Z.-C. Cao and Z.-J. Shi, *Acc. Chem. Res.*, 2015, 48, 886; (b) J. Miao and H. Ge, *Eur. J. Org. Chem.*, 2015, 7859; (c) M. D. Kärkäs and B. Åkermark, *Dalton Trans.*, 2016, 45, 14421; (d) D. Wang and D. Astruc, *Chem. Soc. Rev.*, 2017, 46, 816; (e) J. V. Obligation and P. J. Chirik, *Nat. Rev. Chem.*, 2018, 2, 15.
- 2 (a) B. Lipshutz and Y. Yoshinori, *Chem. Rev.*, 2008, 108, 2793; (b) A. M. Echavarren, N. Jiao and V. Gevorgyan, *Chem. Soc. Rev.*, 2016, 45, 4445; (c) H. V. Huynh, Group 11 Metal-NHC Complexes, in *The Organometallic Chemistry of N-Heterocyclic Carbenes*, (ed. H. V. Huynh), John Wiley & Sons Ltd, Hoboken, USA, 2017.
- 3 R. A. Festa and D. J. Thiele, *Curr. Biol.*, 2011, 21, R877.
- 4 With exclusion of iron, copper is considered the less toxic 1st row transition metal: (a) A. J. Hickman and M. S. Sanford, *Nature*, 2012, 484, 177; (b) S. D. McCann and S. S. Stahl, *Acc. Chem. Res.*, 2015, 48, 1756.
- 5 Cu catalysts can trigger either two-electron or radical-promoted transformations: R. Trammell, K. Rajabimoghadam and I. García-Bosch, *Chem. Rev.*, 2019, 119, 2954.
- 6 *Copper-Mediated Cross-Coupling Reactions*, (eds. G. Evans and N. Blanchard), John Wiley & Sons Ltd, Hoboken, USA, 2014.
- 7 *Copper Catalyzed Asymmetric Synthesis*, (eds. A. Alexakis, N. Krause and S. Woodward), Wiley-VCH Verlag GmbH & Co. KgaA, Weinheim, Germany, 2014.
- 8 The transition-metal-catalyzed C–N bond formation allows the construction of a wide variety of N-containing building blocks with a plethora of applications ranging from pharmaceutical and agrochemical to chemistry of natural products and material sciences. For outstanding book chapters and reviews on C–N couplings, see: (a) A. R. Muci and S. L. Buchwald, *Practical Palladium Catalysts for C–N and C–O Bond Formation*, in *Cross-Coupling Reactions* (ed. N. Miyaura), *Topics in Current Chemistry*, vol 219, pp 131-209, Springer, Berlin, Heidelberg, Germany, 2002; (b) L. Jiang and S. L. Buchwald, *Palladium-Catalyzed Aromatic Carbon-Nitrogen Bond Formation*, in *Metal-Catalyzed Cross-Coupling Reactions* (eds A. de Meijere and F. Diederich), Wiley-VCH Verlag GmbH & Co. KgaA, Weinheim, Germany, 2004; (c) J. Bariwal and E. Van der Eycken, *Chem. Soc. Rev.*, 2013, 42, 9283; (d) *Amination and Formation of sp<sup>2</sup> C–N Bonds*, (eds. M. Taillefer and D. Ma), Springer, New York, USA, 2014; (e) P. Ruiz-Castillo and S. L. Buchwald, *Chem. Rev.*, 2016, 116, 12564; (f) J. Luo and W.-T. Wei, *Adv. Synth. Catal.*, 2018, 360, 2076.
- 9 (a) F. Ullmann, *Ber. Dtsch. Chem. Ges.*, 1903, 36, 2382; (b) F. Ullmann and P. Sponagel, *Ber. Dtsch. Chem. Ges.*, 1905, 38, 2211.
- 10 I. Goldberg, *Ber. Dtsch. Chem. Ges.*, 1906, 39, 1691.
- 11 (a) P. T. Anastas and J. C. Warner, *Green Chemistry Theory and Practice*, Oxford University Press, Oxford, UK, 1998; (b) A. S. Matlack, *Introduction to Green Chemistry*, Marcel Dekker, New York, USA, 2001; (c) M. Poliakov, J. M. Fitzpatrick, T. R. Farren and P. T. Anastas, *Science*, 2002, 297, 807; (d) M. Lancaster, *Green Chemistry: An Introductory Text*, RSC



Publishing, Cambridge, UK, 2002; (e) R. A. Sheldon, I. W. C. E. Arends and U. Henefeld, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, Germany, 2007.

12 (a) D. J. C. Constable, C. Jiménez-González and R. K. Henderson, *Org. Process Res. Dev.*, 2007, 11, 133; (b) J. H. Clark and S. J. Tavener, *Org. Process Res. Dev.*, 2007, 11, 149; (c) P. G. Jessop, *Green Chem.*, 2011, 13, 1391; (d) T. Laird, *Org. Process Res. Dev.*, 2012, 16, 1; (e) B. H. Lipshutz, *Chem.*, 2018, 4, 2004.

13 (a) C. Vidal, F. J. Suárez and J. García-Álvarez, *Catal. Commun.*, 2014, 44, 76; (b) L. Cicco, M. J. Rodríguez-Álvarez, F. M. Perna, J. García-Álvarez and V. Capriati, *Green Chem.*, 2017, 19, 3069; (c) L. Cicco, N. Ríos-Lombardía, M. J. Rodríguez-Álvarez, F. Morís, F. M. Perna, V. Capriati, J. García-Álvarez and J. González-Sabín, *Green Chem.*, 2018, 20, 3468; (d) N. Ríos-Lombardía, M. J. Rodríguez-Álvarez, F. Moris, R. Kourist, N. Comino, F. López-Gallego, J. González-Sabín and J. García-Álvarez, *Front. Chem.*, 2020, 8, 139.

14 (a) M. J. Rodríguez-Álvarez, C. Vidal, J. Díez and J. García-Álvarez, *Chem. Commun.*, 2014, 50, 12927; (b) C. Vidal, L. Merz and J. García-Álvarez, *Green Chem.*, 2015, 17, 3870; (c) M. J. Rodríguez-Álvarez, C. Vidal, S. Schumacher, J. Borge and J. García-Álvarez, *Chem. Eur. J.*, 2017, 23, 3425.

15 (a) R. Mancuso, A. Maner, L. Cicco, F. M. Perna and V. Capriati, *Tetrahedron*, 2016, 72, 4239; (b) F. Messa, S. Perrone, M. Capua, F. Tolomeo, L. Troisi, V. Capriati and A. Salomone, *Chem. Commun.*, 2018, 54, 8100; (c) G. Dilauro, S. M. García, D. Tagarelli, P. Vitale, F. M. Perna and V. Capriati, *ChemSusChem*, 2018, 11, 3495; (d) B. Saavedra, J. M. Pérez, M. J. Rodríguez-Álvarez, J. García-Álvarez and D. J. Ramón, *Green Chem.*, 2018, 20, 2151; (e) S. Ghinato, G. Dilauro, F. M. Perna, V. Capriati, M. Blangetti and C. Prandi, *Chem. Commun.*, 2019, 55, 7741; (f) G. Dilauro, A. F. Quivelli, P. Vitale, V. Capriati and F. M. Perna, *Angew. Chem. Int. Ed.*, 2019, 58, 1799; (g) F. Messa, G. Dilauro, F. M. Perna, P. Vitale, V. Capriati and A. Salomone, *ChemCatChem*, 2020, 12, 1979.

16 For general reviews or book chapters that cover the use of Deep Eutectic Solvents (DESs) in transition-metal-catalyzed organic transformations see: (a) J. García-Álvarez, *Eur. J. Inorg. Chem.*, 2015, 5147; (b) J. García-Álvarez, E. Hevia and V. Capriati, *Eur. J. Org. Chem.*, 2015, 6779; (c) P. Liu, J.-W. Hao, L.-P. Mo and Z.-H. Zhang, *RSC Adv.*, 2015, 5, 48675; (d) D. A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I. M. Pastor and D. J. Ramón, *Eur. J. Org. Chem.*, 2016, 612; (e) C. Vidal and J. García-Álvarez, *Metal-Promoted Organic Transformation in DES, in Deep Eutectic Solvents: Synthesis, Properties, and Applications* (eds. D. J. Ramón and G. Guillena), Wiley-VCH, Weinheim, Germany, 2019.

17 2-Hydroxyethyl-tri(methyl)ammonium chloride (choline chloride, ChCl), which is produced in million of tons/year, has been described as an essential micro- and human nutrient within the Recommended Dietary Allowance (RDA) of 50 mg: J. K. Blusztajn, *Science*, 1998, 284, 794.

18 The term Deep Eutectic Solvent (DES) was firstly coined by A. P. Abbott et al. to describe the eutectic mixture formed by mixing choline chloride (ChCl) with urea in a 1:2 molar ratio (1ChCl/2Urea). This eutectic mixture (reline) is liquid at room temperature (melting point 12 °C), while its isolated solid components have higher melting points (urea: 133 °C; ChCl: 302 °C): A. P. Abbott, G. Capper, D. L. Davies, R. K. Rasheed and V. Tambyrajah, *Chem. Commun.*, 2003, 70.

19 For general reviews and books dealing with the use of Deep Eutectic Solvents as sustainable reaction media in different fields of chemistry, see: (a) A. P. Abbott, R. C. Harris, K. Ryder, C. d'Agostino, L. Gladden and M. D. Mantle, *Green Chem.*, 2011, 13, 82; (b) C. Ruß and B. König, *Green Chem.*, 2012, 14, 2969; (c) Q. Zhang, K. de Oliveira Vigier, S. Royer and F. Jérôme, *Chem. Soc. Rev.*, 2012, 41, 7108; (d) D. Carriazo, M. C. Serrano, M. C. Gutiérrez, M. L. Ferrer and F. Del Monte, *Chem. Soc. Rev.*, 2012, 41, 4996; (e) M. Francisco, A. van den Bruinhorst and M. C. Kroon, *Angew. Chem. Int. Ed.*, 2013, 52, 3074; (f) G. Yu and F. Jérôme, *Chem. Soc. Rev.*, 2013, 42, 9550; (g) A. Paiva, R. Craveiro, I. Aroso, M. Martins, R. L. Reis and A. R. C. Duarte, *ACS Sustainable Chem. Eng.*, 2014, 2, 1063; (h) D. V. Wagle, H. Zhao and G. A. Baker, *Acc. Chem. Res.*, 2014, 47, 2299; (i) E. L. Smith, A. P. Abbott and K. S. Ryder, *Chem. Rev.*, 2014, 114, 11060; (j) J. García-Álvarez, E. Hevia and V. Capriati, *Chem. Eur. J.*, 2018, 24, 14854; (k) *Deep Eutectic Solvents: Synthesis, Properties, and Applications* (eds. D. J. Ramón, G. Guillena), Wiley-VCH, Weinheim, Germany, 2019; (l) F. M. Perna, P. Vitale and V. Capriati, *Curr. Opin. Green Sust. Chem.*, 2020, 21, 27. For recent works dealing with the use of DESs in organic synthesis see: (m) J. Xu, W. Huang, R. Bai, Y. Queneau, F. Jérôme and Y. Gu, *Green Chem.*, 2019, 21, 2061; (n) Z. Cao, Q. Zhu, Y.-W. Lin and W.-M. He, *Chin. Chem. Lett.*, 2019, 30, 2132; (o) M. Li, F. Wu and Y. Gu, *Chin. J. Catal.*, 2019, 40, 1135. For recent use of DESs in solar technology, photosynthesis and electrochemistry, see: (p) C. L. Boldrini, N. Manfredi, F. M. Perna, V. Trifiletti, V. Capriati and A. Abbotto, *Energy Technol.*, 2017, 5, 345; (q) C. L. Boldrini, N. Manfredi, F. M. Perna, V. Capriati and A. Abbotto, *Chem. Eur. J.*, 2018, 24, 17656; (r) C. L. Boldrini, N. Manfredi, F. M. Perna, V. Capriati and A. Abbotto, *ChemElectroChem*, 2020, 7, 1707; (s) F. Milano, L. Giotta, M. R. Guascito, A. Agostiano, S. Sblendorio, L. Valli, F. M. Perna, L. Cicco, M. Trotta and V. Capriati, *ACS Sustainable Chem. Eng.*, 2017, 5, 7768; (t) L. Millia, V. Dall'Asta, C. Ferrara, V. Berbenni, E. Quartarone, F. M. Perna, V. Capriati and P. Mustarelli, *Solid State Ionics*, 2018, 323, 44.

20 (a) G. Imperato, S. Höger, D. Lenoir and B. König, *Green Chem.*, 2006, 8, 1051; (b) G. Imperato, R. Vasold, and B. König, *Adv. Synth. Catal.*, 2006, 348, 2243; (c) F. Illgen and B. König, *Green Chem.*, 2009, 11, 848; (d) X. Marset, A. Khoshnood, L. Sotorriós, E. Gómez-Bengoia, D. A. Alonso and D. J. Ramón, *ChemCatChem*, 2017, 9, 1269; (e) X. Marset, S. De Gea, G. Guillena and D. J. Ramón, *ACS Sustainable Chem. Eng.*, 2018, 6, 5743; (f) B. Saavedra, N. González-Gallardo, A. Meli and D. J. Ramón, *Adv. Synth. Catal.*, 2019, 361, 3868; (g) S. E. Hooshmand, R. Afshari, D. J. Ramón and R. S. Varma, *Green Chem.*, 2020, 22, 3668; (h) L. Cicco, G. Dilauro, F. M. Perna and V. Capriati, *Org. Biom. Chem.*, 2021, DOI: 10.1039/D0OB02491K.

21 A. Shaabani and R. Afshari, *J. Colloid Interface Sci.*, 2018, 510, 384

22 A. F. Quivelli, P. Vitale, F. M. Perna and V. Capriati, *Front. Chem.*, 2019, 7, 723.

23 For recent examples on Cu-catalyzed Goldberg type C–N couplings in either volatile organic solvents or water, see: (a) A. Klapars, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, 124, 7421; (b) Y. Z. Huang, J. Gao, H. Ma, H. Miao and J. Xu, *Tetrahedron Lett.*, 2008, 49, 948; (c) Z. Q. Zhu, S. Xiang, Q. Y. Chen, C. Chen, Z. Zeng, Y. P. Cui and J. C. Xiao, *Chem. Commun.*, 2008, 5016; (d) B. Sreedhar, R. Arundhati, P. Linga Reddy and M. L. Kantam, *J. Org. Chem.*, 2009, 74, 7951; (e) S. Jammi, S. Sakthivel, L. Rout, T. Mukherjee, S. Mandal, R. Mitra, P. Saha and T. Punniamurthy, *J. Org. Chem.*, 2009, 74, 1971; (f) C. T. Yang, Y. Fu, Y. B. Huang, J. Yi, Q. X. Guo and L. Liu, *Angew. Chem. Int. Ed.*, 2009, 48, 7398; (g) K. Swapna, S. N. Murthy and Y. V. D. Nageswar, *Eur. J. Org. Chem.*, 2010, 6678; (h) A. M. Thomas and G. Anilkumar, *Mini Rev. Org. Chem.*, 2015, 12, 3; (i) M. Bollenbach, P. G. V. Aquino, J. X. de Araújo-Júnior, J.-J. Bourguignon, F. Bihel, C. Salomé, P. Wagner and M. Schmitt, *Chem. Eur. J.*, 2017, 23, 13676.

- 24 (a) A. Pandey, R. Rai, M. Pal and S. Pandey, *Phys. Chem. Chem. Phys.*, 2014, 16, 1559; (b) J. García-Álvarez, *Deep Eutectic Solvents and Their Applications as New Green and Biorenewable Reaction Media*, in *Handbook of Solvents, Vol. 2: Use, Health, and Environment* (ed. G. Wypych), 3rd ed., ChemTec Publishing, Toronto, Canada, 2019.
- 25 For more information, see Electronic Supplementary Information (ESI).
- 26 Ultrasonic irradiation has been previously employed to improve the yield/reaction time in organic transformations performed in DESs. For a recent example see: C. Wu, H.-J. Xiao, S.-W. Wang, M.-S. Tang, Z.-L. Tang, W. Xia, W.-F. Li, Z. Cao and W.-M. He, *ACS Sustainable Chem. Eng.*, 2019, 7, 2169
- 27 In modern organic synthesis, catalysis is considered as a key concept for sustainability; see: G. Rothenberg, *Catalysis*, Wiley-VCH, Weinheim, Germany, 2008.
- 28 (a) *Catalyst Separation, Recovery and Recycling. Chemistry and Process Design* (eds. D. Cole-Hamilton and R. Tooze), Springer, Dordrecht, The Netherlands, 2006; (b) *Recoverable and Recyclable Catalyst* (ed. M. Benaglia), Wiley, Chichester, UK, 2009.
- 29 U. Azzena M. Carraro, L. Pisano, S. Monticelli, R. Bartolotta and V. Pace, *ChemSusChem*, 2019, 12, 40.
- 30 R. A. Sheldon, *Green Chem.*, 2007, 9, 1273.
- 31 For more details on the E-factor calculation, see ESI.
- 32 Cyclooxygenase-1 (COX-1) is an emerging target for prevention and treatment of atherosclerosis and ovarian epithelial cancer: (a) T. Daikoku, D. Wang, S. Tranguch, J. D. Morrow, S. Orsulic, R. N. DuBois and S. K. Dey, *Cancer Res.*, 2005, 65, 3735; (b) P. Vitale, A. Panella, A. Scilimati and M. G. Perrone, *Med. Res. Rev.*, 2016, 36, 641; (c) P. Malerba, B. C. Crews, K. Ghebreselasie, C. K. Daniel, E. Jashim, A. M. Aleem, R. A. Salam, L. J. Marnett and Md. J. Uddin, *ACS Med. Chem. Lett.*, 2020, 11, 1837. Although the inhibition of COX-1 is involved in gastrointestinal side effects of nonsteroidal anti-inflammatory drugs (NSAIDs), some N-arylbenzamides exhibit strong analgesic effects as COX-1-selective inhibitors without causing gastric damage; see: (d) H. Kakuta, X. Zheng, H. Oda, S. Harada, Y. Sugimoto, K. Sasaki and A. Tai, *J. Med. Chem.*, 2008, 51, 2400.
- 33 The Fundación BBVA accepts no responsibility for the opinions, statements and contents included in the project and/or the results thereof, which are entirely the responsibility of the authors.