

## PAPER

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# Copper-catalyzed Goldberg-type C–N coupling in deep eutectic solvents (DESSs) 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 (DESSs) 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 DESSs 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.

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## 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 it: (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 coordi-

nation 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 reactions 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 (DESSs).<sup>16</sup> These environmentally friendly and tunable eutectic mixtures can be obtained by mixing and heating two (binary DESSs) or

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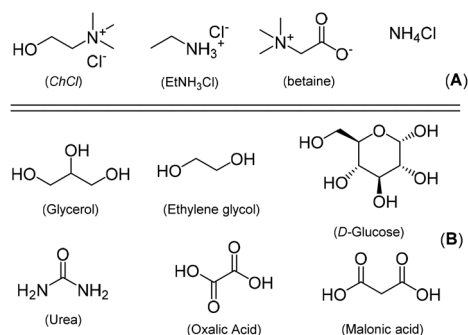
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†Dedicated to Professor Robert E. Mulvey on the occasion of his 60th birthday. A truly inspiring pioneer and model for mixed-metal main-group organometallic chemists worldwide.

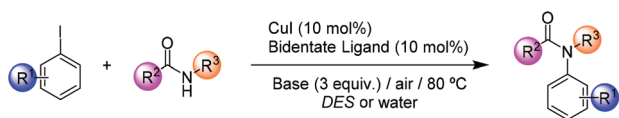
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**Fig. 1** Hydrogen-bond-acceptors (HBAs, **A**) and hydrogen-bond-donors (HBDs, **B**) usually employed in the synthesis of sustainable Deep Eutectic Solvents (DESS).

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**, Fig. 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 acid (**B**, Fig. 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>

Despite the large number of Pd-catalyzed C–C coupling reactions successfully run in different eutectic mixtures (*e.g.*, Sukuzi, Heck, Stille, Sonogashira and Hiyama-type couplings),<sup>15c,e–h,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 halides 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 <sup>t</sup>BuOK) 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 in water.

## 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 <sup>t</sup>BuOK (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

**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 (DESS or water)<sup>a</sup>

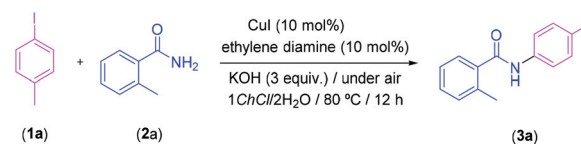
| Entry | X  | Solvent                 | T (°C) | Ligand <sup>b</sup> | Base (%)                        | Yield <sup>c</sup> (%) |
|-------|----|-------------------------|--------|---------------------|---------------------------------|------------------------|
| 1     | I  | 1ChCl/2Gly              | 80     | L1                  | <sup>t</sup> BuOK               | 66                     |
| 2     | I  | 1ChCl/2Gly              | 60     | L1                  | <sup>t</sup> BuOK               | 41                     |
| 3     | I  | 1ChCl/2Gly              | 100    | L1                  | <sup>t</sup> BuOK               | 72                     |
| 4     | I  | 1ChCl/2Gly              | 80     | L1                  | —                               | 0                      |
| 5     | I  | 1ChCl/2Gly              | 80     | —                   | <sup>t</sup> BuOK               | 10                     |
| 6     | I  | Gly                     | 80     | L1                  | <sup>t</sup> BuOK               | 51                     |
| 7     | I  | 1ChCl/2Urea             | 80     | L1                  | <sup>t</sup> BuOK               | 74                     |
| 8     | I  | 1ChCl/2Urea             | 80     | L1                  | —                               | 0                      |
| 9     | I  | 1ChCl/2Urea             | 80     | L2                  | <sup>t</sup> BuOK               | 72                     |
| 10    | I  | 1ChCl/2Urea             | 80     | L3                  | <sup>t</sup> BuOK               | 0                      |
| 11    | I  | 1ChCl/2Urea             | 80     | L4                  | <sup>t</sup> BuOK               | 9                      |
| 12    | I  | 1ChCl/2Urea             | 80     | L5                  | <sup>t</sup> BuOK               | 20                     |
| 13    | I  | 1ChCl/2Urea             | 80     | L6                  | <sup>t</sup> BuOK               | 27                     |
| 14    | I  | 1ChCl/2Urea             | 80     | L7                  | <sup>t</sup> BuOK               | 37                     |
| 15    | I  | 1ChCl/2Urea             | 80     | L8                  | <sup>t</sup> BuOK               | 2                      |
| 16    | I  | 1ChCl/2Urea             | 80     | L9                  | <sup>t</sup> BuOK               | 10                     |
| 17    | Br | 1ChCl/2Urea             | 80     | L1                  | <sup>t</sup> BuOK               | 8                      |
| 18    | Cl | 1ChCl/2Urea             | 80     | L1                  | <sup>t</sup> BuOK               | 0                      |
| 19    | I  | 1Bet/1Urea              | 80     | L1                  | <sup>t</sup> BuOK               | 60                     |
| 20    | I  | 1ChCl/2H <sub>2</sub> O | 80     | L1                  | <sup>t</sup> BuOK               | 80                     |
| 21    | I  | H <sub>2</sub> O        | 80     | L1                  | <sup>t</sup> BuOK               | 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> | 0                      |
| 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                      |

<sup>a</sup> 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. <sup>b</sup> L1 = ethylene diamine; L2 = *N,N*-dimethylethylenediamine; L3 = glycine; L4 = L-proline; L5 = 2,2′-bipyridine; L6 = (1*R*,2*S*)-cyclopentane-1,2-diamine; L7 = (1*R*,2*S*)-cyclohexane-1,2-diamine; L8 = benzene-1,2-diamine; L9 = (1*R*,2*S*)-2,3-dihydro-1*H*-indene-1,2-diamine. <sup>c</sup> Yield determined by HPLC.

**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.

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 *t*BuOK, 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 and 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 *t*BuOK 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%) was achieved also in 1ChCl/2H<sub>2</sub>O by performing the coupling reaction on a 2.5 mmol scale (Scheme 2).<sup>25</sup>

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 con-



**Scheme 2** Cul-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).

ditions (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 and 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 iodo-aryl partners containing different substituents [4-Me (**1a**) or 3-MeO (**1c**); Table 2, entries 9–11]. Finally, in order to promote an efficient

**Table 2** Cul-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<sup>a</sup>

| Entry | R <sup>1</sup>      | R <sup>2</sup> /R <sup>3</sup> | Solvent                 | Yield <sup>b</sup> (%) |
|-------|---------------------|--------------------------------|-------------------------|------------------------|
| 1     | 4-Me ( <b>1a</b> )  | 2-Me-Ph/H ( <b>2a</b> )        | H <sub>2</sub> O        | 92 (85, <b>3a</b> )    |
| 2     | H ( <b>1b</b> )     | 2-Me-Ph/H ( <b>2a</b> )        | H <sub>2</sub> O        | 95 (90, <b>3b</b> )    |
| 3     | 3-OMe ( <b>1c</b> ) | 2-Me-Ph/H ( <b>2a</b> )        | H <sub>2</sub> O        | 81 (74, <b>3c</b> )    |
| 4     | 4-Me ( <b>1a</b> )  | 3-MeO-Ph/H ( <b>2b</b> )       | H <sub>2</sub> O        | 88 (83, <b>3d</b> )    |
| 5     | H ( <b>1b</b> )     | 3-MeO-Ph/H ( <b>2b</b> )       | H <sub>2</sub> O        | 99 (95, <b>3e</b> )    |
| 6     | H ( <b>1b</b> )     | 2-F-Ph/H ( <b>2c</b> )         | H <sub>2</sub> O        | 74 (68, <b>3f</b> )    |
| 7     | 4-Me ( <b>1a</b> )  | 2-F-Ph/H ( <b>2c</b> )         | H <sub>2</sub> O        | 64 (57, <b>3g</b> )    |
| 8     | H ( <b>1b</b> )     | Ph/Me ( <b>2d</b> )            | H <sub>2</sub> O        | 70 (65, <b>3h</b> )    |
| 9     | 4-Me ( <b>1a</b> )  | Et/H ( <b>2e</b> )             | 1ChCl/2H <sub>2</sub> O | 99 (92, <b>3i</b> )    |
| 10    | H ( <b>1b</b> )     | Et/H ( <b>2e</b> )             | 1ChCl/2H <sub>2</sub> O | 62 (60, <b>3j</b> )    |
| 11    | 3-OMe ( <b>1c</b> ) | Et/H ( <b>2e</b> )             | 1ChCl/2H <sub>2</sub> O | 45 (42, <b>3k</b> )    |

<sup>a</sup> 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. <sup>b</sup> Yield determined by HPLC. Isolated yields after column chromatography in brackets.

mass transfer in the synthesis of compounds **3g**, **3j** and **3k** (Table 2, entries 7, 10 and 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.

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>16c</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>

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 a 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.

### 3. 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.

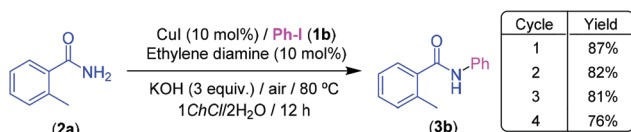
Furthermore, we demonstrated: (i) the possibility to scale up the reaction without observing any erosion of the yield/reaction time; (ii) the successful recycle of both the catalyst and the eutectic solvent up to 4 consecutive runs; and (iii) the competence of our catalytic system for the synthesis of 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

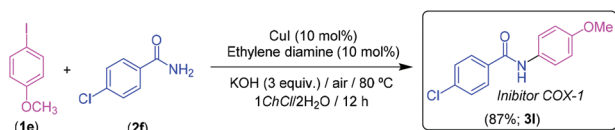
There are no conflicts to declare.

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**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.



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

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