The C(sp³) friendly processes, and no functionalization step is needed. Various strategies for transition-metal-catalysed C–H activation have been of significant interest, as they are environmentally benign and catalytically efficient in industrial and academic research due to their biological and pharmaceutical applications, such as anticancer agents, enzyme inhibitors, ligand receptors and therapeutic agents. Tetrahydroisoquinolines are widely present in Nature. The synthesis of different tetrahydroisoquinolines using choline chloride:ethylene glycol as a deep eutectic solvent (DES) and copper(II) oxide impregnated on magnetite as a catalyst has been accomplished successfully. The copper catalyst amount is the lowest loading ever reported. The presence of DES showed to be essential since the reaction in the absence of this medium did not proceed. A direct relationship was found between the conductivity of DES medium and the yield obtained. The DES and the catalyst could be reused up to ten times without any detrimental effect on the yield of the reaction, with the aerobic conditions making the protocol highly sustainable, where the only waste is water.

Introduction

Tetrahydroisoquinolines are widely present in Nature. The synthesis of these compounds has been paid much attention in industrial and academic research due to their biological and pharmaceutical applications, such as anticancer agents and anticonvulsant agents, enzyme inhibitors, ligand receptors and therapeutic agents. Tetrahydroisoquinolines are widely present in Nature. The synthesis of different tetrahydroisoquinolines using choline chloride:ethylene glycol as a deep eutectic solvent (DES) and copper(II) oxide impregnated on magnetite as a catalyst has been accomplished successfully. The copper catalyst amount is the lowest loading ever reported. The presence of DES showed to be essential since the reaction in the absence of this medium did not proceed. A direct relationship was found between the conductivity of DES medium and the yield obtained. The DES and the catalyst could be reused up to ten times without any detrimental effect on the yield of the reaction, with the aerobic conditions making the protocol highly sustainable, where the only waste is water.

The C–C bond formation via C–H activation is one of the most challenging reactions in organic synthesis. Various strategies for transition-metal-catalysed C–H bond activation have been of significant interest, as they are environmentally friendly processes, and no functionalization step is needed. The C(sp³)–H bond activation at the α-position of nitrogen has been widely used in different transformations. The key step in this transformation, is the generation of an iminium intermediate assisted by the lone pair of the nitrogen atom, via a single-electron transfer (SET) mechanism.

For this purpose an important number of different methods have been developed, with metal-catalysed protocols being well established. Different catalysts derived from vanadium, iron, copper, ruthenium, rhodium, palladium, antimony, iridium or gold, among others have been recently introduced. In all cases, the protocols needed a highly reactive oxidizing agent such as peroxides or high oxygen pressure.

Moreover, the lack of recyclability, and the high catalyst loading (5–20 mol%) made these protocols unsustainable for large chemical production. The metal-free version using organic radical promoters, recently published, has similar drawbacks. Within the framework of green chemistry, solvents occupy a strategic place. In order to be qualified as a green medium, the components of this solvent have to meet different criteria such as availability, non-toxicity, biodegradability, recyclability, inflammability, renewability and low price, among others. DES (Deep Eutectic Solvent) is an environmentally benign alternative to hazardous (organic) solvents and, in many cases, might replace them. DESs are liquid systems formed from a eutectic mixture of a solid Lewis or Brønsted acids and bases which can contain a variety of anionic and/or cationic species. These two components are capable of self-association, often through a strong bond interaction, to form an eutectic mixture with a melting or phase transition point lower than that of each individual component. The properties of a solvent, such as conductivity, viscosity, vapour pressure and thermal stability can be fine-tuned by appropriately choosing the mixture components, with the large-scale preparation being feasible. Besides these interesting advantages, the application of DES in organic synthesis is in its infancy, with the related metal-catalysed process being nearly unknown. Only very recently, the superparamagnetic CuFeO₂ has been used as a catalyst for the multicomponent synthesis of imidazo[1,2-a]pyridines in DMU-citric acid medium.

Here, we introduced a recyclable copper-impregnated magnetite catalyst for the C–H activation in choline chloride: ethylene glycol as medium using bio-renewable air as the only oxidizing agent.
Results and discussion

To start with this study, 2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (1a) and phenylacetylene (2a) using copper impregnated on magnetite as a catalyst was selected as the model reaction for the optimization of the conditions (Table 1).

Initially, the reaction was performed using different DESs (entries 1–6), obtaining the best result with the mixture choline chloride (ChCl): ethylene glycol (1:2) (entry 4), with the only by-product observed being the corresponding lactam 4a. Then, the amount of catalyst was evaluated obtaining similar results when the loading was decreased (entry 7). However, a further decrease of catalyst loading down to 0.37 mol% (entry 8) led to lower yield. Increasing the amount of copper to 3.64 mol% (entry 9) the yield could be improved. It should be pointed out that even this high amount of copper catalyst is one of the lowest metal catalyst loadings reported so far in the literature. The addition of only one equivalent of alkyn led to the decrease of the reaction yield (entry 10), and the addition of an excess of alkyn did not improve it (entry 11). The study of the temperature of reaction was carried out obtaining, after seven days of reaction at room temperature, a full conversion of the starting material (entry 12). Increasing the temperature up to 100 °C decreased the yield (entry 13).

![Fig. 1 Obtained yield in different solvents.](Image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuO–Fe3O4 (1.82)</td>
</tr>
<tr>
<td>2</td>
<td>CuO–Fe3O4 (1.82)</td>
</tr>
<tr>
<td>3</td>
<td>CuO–Fe3O4 (1.82)</td>
</tr>
<tr>
<td>4</td>
<td>CuO–Fe3O4 (1.82)</td>
</tr>
<tr>
<td>5</td>
<td>CuO–Fe3O4 (1.82)</td>
</tr>
<tr>
<td>6</td>
<td>CuO–Fe3O4 (1.82)</td>
</tr>
<tr>
<td>7</td>
<td>CuO–Fe3O4 (0.91)</td>
</tr>
<tr>
<td>8</td>
<td>CuO–Fe3O4 (0.37)</td>
</tr>
<tr>
<td>9</td>
<td>CuO–Fe3O4 (0.37)</td>
</tr>
<tr>
<td>10</td>
<td>CuO–Fe3O4 (0.37)</td>
</tr>
<tr>
<td>11</td>
<td>CuO–Fe3O4 (0.37)</td>
</tr>
<tr>
<td>12</td>
<td>CuO–Fe3O4 (0.37)</td>
</tr>
<tr>
<td>13</td>
<td>CuO–Fe3O4 (0.37)</td>
</tr>
<tr>
<td>14</td>
<td>CuO–Fe3O4 (0.37)</td>
</tr>
<tr>
<td>15</td>
<td>CuO–Fe3O4 (0.37)</td>
</tr>
<tr>
<td>16</td>
<td>CuO–Fe3O4 (0.37)</td>
</tr>
<tr>
<td>17</td>
<td>CuO–Fe3O4 (0.37)</td>
</tr>
<tr>
<td>18</td>
<td>CuO–Fe3O4 (0.37)</td>
</tr>
</tbody>
</table>

Table 1 Optimization of the reaction conditions

The reaction was carried out under argon atmosphere (entry 14) obtaining a very low yield, highlighting the capital role of oxygen in the air as the final oxidizing agent. To finish with the optimization of the reaction conditions, the reaction was tested using LED irradiation (photoredox conditions), microwave irradiation and an ultrasound bath (entries 15–17), but the yield did not improve. Finally, the reaction was repeated in ethylene glycol obtaining a modest result (entry 18).

To prove the essential role of DES [ChCl : (CH2OH)2], other VOC solvents were tested as reaction medium (Fig. 1). In all cases a mixture of products 3a and 4a was obtained in a ratio

Conversion determined by $^1$H-NMR. $^c$ Reaction carried out using compounds 1a (0.5 mmol) and 2a (1 mmol) in 1 mL of DES. $^d$ Reaction carried out using compounds 1a (0.5 mmol) and 2a (0.5 mmol) in 1 mL of DES. $^e$ Reaction carried out using 1a (0.5 mmol) and 2a (2.5 mmol) in 1 mL of DES. $^f$ 99% of conversion after 7 days of reaction. $^g$ Reaction carried out under an argon atmosphere. $^h$ Reaction carried out using visible LED light irradiation. $^i$ Reaction carried out under microwave irradiation for 10 h at 80 W. $^j$ Reaction carried out under ultrasound bath for 8 h.
close to 1 : 1, highlighting the role of DES for minimizing the lactam formation. It should be pointed out that when the reaction was performed in 1,4-dioxane as a solvent the main product was 4a.

We also found an interesting correlation between the DES conductivity and the yield of the desired product (Fig. 2), in such a way that a higher conductivity affords a better yield. Since an iminium intermediate is generated in the reaction media, a better conductivity means an easier movement of ions that could explain the increase in the yield. Nevertheless, the correlation between obtained yields and conductivities of VOC solvents and of water did not fit with the aforementioned plot. It should be pointed out that the reaction using ChCl : 1,2-propanediol : water (1 : 1 : 1, conductivity 12.09 mS cm\(^{-1}\)) or ChCl : glycerol : water (1 : 2 : 1, conductivity 13.78 mS cm\(^{-1}\)) gave the product 3a in 46 and 53% yield respectively. Although these two mixtures have higher conductivity than the previous DES used, the presence of water changed the direct proportion between yield and conductivity probably due to the highly nucleophilic character of water.

Once the optimal conditions were determined, the reaction was repeated with a variety of catalysts prepared by the simple impregnation protocol\(^{24}\) (Table 2). The reaction without a catalyst gave a poor yield (entry 2). Then, the activity of the support was evaluated using magnetite as the unique catalyst. Nanoparticles or microparticles of magnetite (entries 3 and 4) were used with the results showing the inactivity of the support, reaching a low conversion of product and highest amount of compound 4a, as the only by-product detected by GC-MS. Once the activity of magnetite was tested, different metal oxides impregnated on magnetite (entries 5–17) were evaluated as catalysts, observing that none of them gave better results than the copper catalyst (entry 1). After that, different copper salts were tested (entries 18–20), obtaining moderate to good results, but poorer than the one obtained by the heterogeneous copper oxide impregnated on magnetite.

After that, the addition of a mixture of CuO and Fe\(_3\)O\(_4\), was evaluated (entry 21), obtaining a decrease in the conversion compared to the impregnated catalyst, which seems to be related to a synergic effect between the metal oxide and support in the catalyst.

In order to establish the reusability of the catalyst and DES, the reaction with nitromethane (see Table 5, entry 1) was repeated under standard conditions (Fig. 3). When the reaction was completed, the mixture was extracted with cyclopentyl methyl ether, recently reported as a potential green alternative solvent.\(^{25}\) All organic compounds were removed and the mixture of DES and catalyst, lower phase in the decantation, was reused under the same reaction conditions. This catalytic

![Table 2 Optimization of the catalyst](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>3a (^b) (%)</th>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>3a (^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuO–Fe(_3)O(_4) (3.64)</td>
<td>95 (3)</td>
<td>12</td>
<td>IrO(_2)–Fe(_3)O(_4) (0.26)</td>
<td>33 (47)</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>6 (20)</td>
<td>13</td>
<td>PtO/PtO(_2)–Fe(_3)O(_4) (1.08)</td>
<td>33 (7)</td>
</tr>
<tr>
<td>3</td>
<td>Nano-Fe(_3)O(_4) (259.15)</td>
<td>0 (34)</td>
<td>14</td>
<td>Au(_2)O(_3)–Fe(_3)O(_4) (0.28)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>4</td>
<td>Micro-Fe(_3)O(_4) (259.15)</td>
<td>15 (48)</td>
<td>15</td>
<td>PdO/Cu–Fe(_3)O(_4) (3.05/1.79)</td>
<td>35 (28)</td>
</tr>
<tr>
<td>5</td>
<td>CoO–Fe(_3)O(_4) (2.83)</td>
<td>4 (31)</td>
<td>16</td>
<td>NiO/Cu–Fe(_3)O(_4) (1.82/1.76)</td>
<td>78 (2)</td>
</tr>
<tr>
<td>6</td>
<td>NiO–Fe(_3)O(_4) (2.06)</td>
<td>30 (30)</td>
<td>17</td>
<td>VO(_2)–Fe(_3)O(_4) (1.13)</td>
<td>37 (8)</td>
</tr>
<tr>
<td>7</td>
<td>RuO(_2)–Fe(_3)O(_4) (2.64)</td>
<td>8 (28)</td>
<td>18</td>
<td>CuCl(_2) (8.3)</td>
<td>88 (5)</td>
</tr>
<tr>
<td>8</td>
<td>Rh(_2)O–Fe(_3)O(_4) (0.84)</td>
<td>0 (45)</td>
<td>19</td>
<td>CuO (4.04)</td>
<td>46 (10)</td>
</tr>
<tr>
<td>9</td>
<td>PdO–Fe(_3)O(_4) (2.43)</td>
<td>46 (7)</td>
<td>20</td>
<td>Cu(OAc)_2 (3.64)</td>
<td>80 (6)</td>
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<tr>
<td>10</td>
<td>Ag(_2)O–Fe(_3)O(_4) (2.5)</td>
<td>13 (0)</td>
<td>21</td>
<td>CuO (3.64) + Fe(_3)O(_4) (255.26)</td>
<td>51 (9)</td>
</tr>
<tr>
<td>11</td>
<td>OsO(_2)–Fe(_3)O(_4) (1.03)</td>
<td>5 (21)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^{a}\) Reaction carried out using compounds 1a (0.5 mmol) and 2a (1 mmol) in 1 mL of DES. \(^{b}\) Yield determined by \(^1\)H-NMR, yield of oxidised compound 4a in brackets.
The mixture could be recycled up to 10 times without any decrease in the yield. When just the catalyst was recovered, by magnetic decantation, and fresh solvent was used, the obtained yield showed an important decrease, pointing out the sharp decrease of the catalyst after 4 reaction cycles. In fact, the ICP-MS analysis of the crude reaction solution showed the leaching of a small amount of copper (14.2 ppm; 3.6% of the initial amount) and iron (0.30 ppm; 0.001% of initial amount), the values were completely different from the reported solubility of these metal oxides (3.68 ppm for CuO and 10.85 ppm for Fe₃O₄). The higher solubility in DES of copper species seems to show that the heterogeneous catalyst is only a reservoir of highly active copper clusters. To try to understand more this effect, the standard reaction was performed as usual (Table 2, entry 1) and, after 36 h, only the catalyst was removed by magnetic decantation, with the yield of 3a being estimated in 40% by GC-MS. The mixture was heated again for 36 h, and after the usual work up the yield of compound 3a increased up to 65%, with the oxidised by-product 4a reaching 25%. At the end of the first cycle, the catalyst was removed, by magnetic decantation, as well as the organics by cyclopentyl methyl ether extraction (yield of compound 3a 93%). Then, the used DES medium was employed alone in other cycles (without catalyst) and the final product 3a was obtained in 52% (29% for by-product 4a). These two experiments showed that there was a partial leaching of active species, capable of performing the oxidative step. However, and due to the great amount of by-product, these leached species seemed to be less effective to catalyze the final nucleophilic addition.

In order to study the effect of the reaction conditions on the copper heterogeneous catalyst, the nanosize distribution of the copper nanoparticles was measured after one reaction cycle. A uniform size distribution was found, 60% of nanoparticles have an average size between 2–4 nm. In the fresh catalyst 63% of nanoparticles have an average size between 2–6 nm, showing a small overall decrease in the particle size with the reaction cycles which is in concordance with a partial solubilization–read sorption of copper species (Fig. 4).

The XPS and Auger Electron Spectroscopy (AES, see ESI†) studies of the catalyst showed the transformation of the initial Cu(0) onto the corresponding copper(I) oxide and Cu(OH)₂ in the recycled catalyst (Fig. 5) with CuO being the main species in both cases. These changes in particle size as well as the initial oxidation state did not seem to affect the activity of the catalyst, since it could be reused ten times without losing its activity.

Once the best conditions were established, the scope of the reaction was evaluated. First of all, different pro-electrophiles were tested by modifying the nitrogen substituent at the tetrahydroisoquinoline ring (Table 3). The reaction was carried out with different N-substituted substrates. When the substituent was an aryl group, bearing both, electron-withdrawing or electron-donating groups (entries 1 and 3), the results were excellent. In the case of phenyl derivatives, the yield was moderate. On the other hand, when the reaction was carried out with the free amine or with a strong electron-withdrawing group such as tosyl, the reaction did not take place at all (entries 4 and 5), recovering the starting material unchanged.
Having studied the scope of pro-electrophiles, we tested a variety of alkynes as pro-nucleophiles (Table 4). Once again, the reaction took place obtaining moderate to good yields when the alkyne had an electron-rich (entry 1) or electron-poor (entries 2–5) aryl substituents. Not only aryl substituents were tested, but also olefinic and aliphatic ones (entries 6–9) and the reaction still worked smoothly. It has to be pointed out that, in the case of using a dialkyne, the reaction was selective in such a way that only one of the two alkynes reacted (entry 8).

After the study of alkynes, as pro-nucleophiles, was completed, we decided to check other types of reagents (Table 5), such as nitroalkanes (entry 1), heterocycles (entry 2), phosphonates (entry 3), silyl enol ethers (entry 4), ketones (entries 5 and 6) and fluoroborates (entry 7), proving that this methodology can be applied to a wide range of substrates with very different properties and obtaining similar results. It should be noted that both, silyl enol ether and ketone (entries 4 and 5) afford the same product 3r but with different diastereomeric ratios. Only the starting material alongside a small amount of by-product 4a was detected from the crude of the reaction, when a moderate or low yield of product was obtained.

### Experimental

**General**

XPS analyses were carried out on a VG-MicrotechMutilab. XRD analyses were carried out on a Bruker D-8 Avance diffractometer with a Göbel mirror, a high temperature chamber (up to 900 °C), an X-ray generator Kristallography K 760-80F (3 kW, 20–60 kV and 5–80 mA).

The TEM images were obtained on a JEOL, model JEM-2010 equipped with an X-ray detector Oxford INCA Energy TEM 100 for microanalysis (EDS). XRF analyses were obtained on a Philips Magix PRO (PW2400) X-ray spectrometer equipped
with a rhodium X-ray tube and a beryllium window. BET iso-
therms were carried out on an Autosorb-6 (Quantachrome),
neglecting N₂. The melting points were obtained by using a Reich-
ert Thermovar apparatus. The NMR spectra were recorded on a
Bruker AC-300 (300 MHz for ¹H and 75 MHz for ¹³C) using
CDCl₃ as a solvent and TMS as an internal standard for ¹H and
¹³C; chemical shifts are given in δ (parts per million) and
coupling constants (J) in hertz. FT-IR spectra were recorded on a
JASCO 4100LE (Pike Miracle ATR) spectrophotometer. Mass
spectra (EI) were recorded at 70 eV on a Shimadzu QP-5000
spectrometer, giving fragment ions in m/z with relative intensi-
ties (%) in parentheses. The chromatographic analyses (GLC)
were carried out on a Hewlett Packard HP-5890 instrument
equipped with a flame ionization detector and 12 m HP-1
capillary column (0.2 mm diam, 0.33 mm film thickness, OV-1
stationary phase), using nitrogen (2 mL min⁻¹) as a carrier gas,
Tinjector = 275 °C, Tdetector = 300 °C, Tcolumn = 60 °C (3 min) and
60–270 °C (15 °C min⁻¹), P = 40 kPa. Thin layer chromato-
graphy (TLC) was carried out on Schleicher & Schuell F4100/LS
254 plates coated with a 0.2 mm layer of silica gel; detection
was carried out by UV₂₅₄ light. Column chromatography was
performed using silica gel 60 of 40–63 mesh. All reagents were
commercially available (Acrros, Aldrich, Fluorochem) and were
used as received. The ICP-MS analyses were carried out on a
Thermo Elemental VG PQ-ExCell spectrometer. The elemental
analysis was performed on an Elemental Microanalyser
Thermo Finnigan Flash 1112 Series.

Synthetic procedures

General procedure for the preparation of CuO-Fe₃O₄ cata-
lyst. To a stirred solution of CuCl₂ (1 mmol, 130 mg) in de-
ionized water (120 mL) was added commercially available
Fe₃O₄ (4 g, 17 mmol, powder <5 μm, BET area: 9.86 m² g⁻¹).
After 10 minutes at room temperature, the mixture was slowly
basified with NaOH (1 M) until pH was around 13. The
mixture was stirred in air for one day at room temperature.
After that, the catalyst was filtered and washed several times
with deionized water (3 × 10 mL). The solid was dried at
100 °C for 24 h in a standard glassware oven, obtaining there-
after the expected catalyst.

General procedure for the preparation of DES. A mixture of
hydrogen-bond donor and hydrogen-bond acceptor, with the
previously specified molar ratio, was added in a round bottom
flask under an inert atmosphere. The mixture was stirred for
60 minutes in a T range between 65 and 80 °C obtaining the
corresponding DES.

General procedure for the N-arylation of tetrahydroisoquin-
olines.²⁷ Copper(i) iodide (200 mg, 1.0 mmol) and potassium
phosphate (4.25 g, 20.0 mmol) were placed into a 50 mL two-
neck flask. The flask was evacuated and back filled with argon.
2-Propanol (10.0 mL), ethylene glycol (1.11 mL), 1,2,3,4-tetra-
hydroisoquinoline (2.0 mL, 15 mmol) and the corresponding
iodoaryl (10.0 mmol) were added successively by using a
syringe at room temperature. The reaction mixture was heated
at 90 °C for 24 h and then allowed to cool to room tempera-
ture. Diethyl ether (20 mL) and water (20 mL) were then added
to the reaction mixture. The organic layer was extracted with
diethyl ether (2 × 20 mL). The combined organic phases were
washed with brine and dried over sodium sulphate. The
solvent was removed and the residue was purified by column
chromatography on silica gel using hexane/ethyl acetate (20:1)
as an eluent.

Procedure for the preparation of 2-tosyl-1,2,3,4-tetrahydro-
isoquinoline (1d).²⁸ To a mixture of 1,2,3,4-tetrahydroiso-
quinoline (0.2663 g, 2 mmol) and pyridine (0.5 mL),
p-toluene sulfonfonyl chloride (0.46 g, 2.4 mmol) in dry dichloro-
methane (5 mL) was added slowly and stirred at room tempera-
ture for 1 h. The reaction mixture was then washed with
aqueous 1 N HCl (10 mL) and extracted with diethyl ether (2 ×
10 mL). The combined organic phases were washed with water
(10 mL), brine solution (10 mL) and dried over anhydrous
sodium sulphate. The filtered solution was concentrated and
purified by column chromatography to yield 2-tosyl-1,2,3,4-
tetrahydroisoquinoline 1d.

General procedure for the synthesis of compounds 3. To a
stirred solution of the corresponding tetrahydroisoquinoline 1
(0.5 mmol) and a catalyst (100 mg) in 1 mL of DES were added
the corresponding nucleophiles 2 (1 mmol). The resulting
mixture was stirred at 50 °C for 3 days until the end of the reac-
tion. The mixture was quenched with water and extracted with
AcOEt (3 × 5 mL). The organic phases were dried over MgSO₄,
followed by evaporation under reduced pressure to remove the
solvent. The product was usually purified by chromatography
on silica gel (hexane/ethyl acetate) and/or distillation to give
the corresponding product 3. Physical and spectroscopy data,
as well as the literature for known compounds, are given
below.

Procedure for catalyst recycling. The reaction was performed
according to the general procedure. After 3 days, the mixture
was extracted with cyclohexyl methyl ether, dissolving all
organic compounds, in such a way that the mixture of DES
and catalyst remained in the reaction vessel. To the remaining
mixture, nitromethane (or phenylacetylene) and compound 1a
were added, carrying out the reaction again under the same
reaction conditions.

On the other hand, in order to recycle only the catalyst, we
added water to the reaction mixture, dissolving the DES and
decanting the solution with the aid of a magnet, the catalyst
remained in the reaction vessel. Then, fresh DES, nitro-
methane and compound 1a were added to the vessel, carrying
out the new reaction under standard conditions.

Conclusions

In conclusion, we have demonstrated that the appropriate
mixture of DES and copper(i) oxide impregnated on magnetite
is a good catalytic system to perform the cross-dehydrogenative
coupling reaction between tetrahydroisoquinolines with a
broad range of pro-nucleophiles in a highly selective way.
The little amount of copper catalyst used is the lowest copper cata-
lyst loading ever published. A direct proportional relationship
between yield and conductivity was found in the absence of water. The high recyclability of the mixture (solvent + catalyst), as well as the use of cyclopentyl methyl ether for the workup drives this protocol towards Green Chemistry. Moreover, the protocol uses only the oxygen present in air, showing the high activity of the catalytic system and providing the first example of a biorenewable approach, with water being the only stoichiometric waste. All these facts made the sustainability of the whole process extremely high, compared with any other alternative.

Acknowledgements

This work was supported by the Spanish Ministerio de Economía y Competitividad (MICINN; CTQ2011-24151) and the University of Alicante. J. M. P. thanks the MICINN (FPI program) for her fellowship.

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