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Deep eutectic solvents meet safe, scalable and sustainable hydrogenations enabled by aluminum powder and Pd/C†

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A general, safe and scalable reductive protocol, based on the *in situ* generation of H_2 from aluminum and water, has been developed in deep eutectic solvents for the reduction of many organic compounds under Pd-catalysis. The methodology has been efficiently applied to the multigram-scale synthesis of benzindopyrine as an active pharmaceutical ingredient.

The hydrogenation of organic molecules is one of the most employed synthetic transformations in both academic research and industrial applications. The formation of ubiquitous C–H, O–H and N–H bonds has been achieved by countless synthetic methodologies mostly based on catalytic hydrogenations[1] or the employment of metal hydrides[2] because of their general applicability, and less frequently on organic[3] and inorganic reagents or dissolving metals for specific requests.[4]

Although these methods could be very efficient from a synthetic point of view, they often pose many environmental issues such as the generation of large amounts of waste, the use of harmful reagents and toxic volatile solvents, and the employment of harsh reaction conditions.[4]

The addition of hydrogen gas to functional groups under the heterogeneous metal catalysis is one of the most eco-friendly methods for the reduction of organic molecules, because of the elevated atom economy and the ease of catalyst recovery. Alongside these important benefits, some critical drawbacks, related to the use of gaseous H_2, must be considered. In particular, molecular hydrogen: (a) has a very broad flammability range and it requires only 0.02 mJ of energy to ignite when mixed with air;[5] (b) requires suitable containers for transport and storage; (c) requires appropriate reactors when the process occurs at high pressures; (d) derives principally by natural gas reforming, a technique with a huge energy demand and large emission of greenhouse gases (principally CO_2).[6] Alternatively, the *in situ* generation of molecular hydrogen could be considered as a safer and greener way for the hydrogenation of organic molecules.

In this field, in the past few decades extensive studies have been performed based on the use of nickel–aluminum alloys for hydrogenations in an aqueous medium.[7] Despite remarkable catalytic activity, Ni/Al alloys are not ideal in a sustainable chemistry scenario because they are pyrophoric and require to be handled under an inert atmosphere; moreover, they are suspected to cause lung cancer in humans.[8]

Although water represents the greener solvent among all others, the use of aluminum in an aqueous medium, for the reduction of organic compounds, can be critical from the hazard point of view. The reaction between Al and H_2O is highly exothermic, having an enthalpy of formation of about −280 kJ per mol of H_2 produced at temperatures below 100 °C.[9] This aspect can be dangerous when the reaction is performed on a large scale, since, in principle, it gets progressively harder to remove heat as the reaction is scaled up.[10] Furthermore, the narrow solubility of organic reagents in water, often reduces the reaction efficiency. The addition of surfactants can increase the productivity of a water-based reaction,[11] but serious pollution issues must be addressed since surfactants are often nonbiodegradable and dangerous for the environment.[12]

It is important to underline that the reaction between aluminum and water can be initially inhibited by the presence of a thin protective film of aluminum oxide (Al_2O_3), that naturally covers the particle surface of the pure Al metal. Such oxide, which does not dissolve in water, prevents the effective contact between water and aluminum, and makes hydrogen

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†Electronic supplementary information (ESI) available: General experimental procedures and copies of ^{1}H and ^{13}C-NMR spectra of compounds **2a–o**, **4–6**. See DOI: https://doi.org/10.1039/d2gc00636g

production inadequate for synthetic purposes. The activation of the aluminum surface, in wet chemistry, has been classically accomplished by using aqueous solutions of hydroxide[7,13a] or chloride[13b] ions. Among physical methods, it is the remarkable work of Török that used the mechanical action of ultrasound for the disruption of the aluminum oxide film to generate H_2 and to perform the reduction of many organic molecules under the catalytic activity of palladium.[13c]

Our recent interests are mainly related to the development of sustainable synthetic methodologies using two approaches, the multiple bond-forming strategy[14] and the substitution of toxic volatile organic solvents, derived from petrol, along with deep eutectic solvents (DESs),[15] a new class of green media with many fascinating applications in sustainable chemistry.[16] We moved from the consideration that a key point to induce and maintain hydrogen generation from aluminum, could be the continual removal of the adherent oxide layer from the metal surface. Since DESs have been reported to be very efficient solvents for the dissolution of metal oxides,[17] we thought that the aluminum/DES system could represent, in the presence of small amounts of water, a promising medium for the green reduction of organic compounds. To limit the environmental impact of the method, the cheapest source of palladium (Pd/C) has been chosen as the metal catalyst. Of note, despite the huge number of general synthetic protocols efficiently performed in DESs in the last two decades,[18] very few examples of reductions in such green solvents are known to date (Fig. 1): in 2006 Konig hydrogenated for the first time a C–C double bond in DES (citric acid/*N,N*′-dimethylurea) by using the Wilkinson's catalyst and H_2 but the reaction was applied to just one compound.[19a] More recently, few authors studied the reduction of aldehydes, ketones and oxiranes by using $NaBH_4$,[19b,c] or exploited the activity of a diphosphine-bridged Ru(II)-complex in TBABr/HCOOH,[19d] an eutectic mixture acting both as a reaction medium and hydrogen source. Nitroalkenes have been selectively reduced to nitroalkanes by using NH_3BH_3 in nature-derived deep eutectic solvents, too (Fig. 1).[19e] However, the most used strategy to reduce organic compounds in DES, remains biocatalysis.[19f–j]

Our initial study began with the reduction of 4′-methyl acetophenone **1a**, as a model substrate, in 2 grams of a deep eutectic solvent composed of ChCl/Gly, in the presence of aluminum powder (10 equiv., −325 mesh), KOH (10 equiv.), and palladium on charcoal (Pd/C, 10 mol%) as the catalyst. The reaction has been conducted under vigorous magnetic stirring (300 rpm) at 80 °C for 8 hours (Table 1).

We first analyzed the relationship between the amount of water and the formation yield of alcohol **2a**. By performing the reaction with ChCl/Gly, without any external addition of water, only 26% of ketone converted to alcohol, although with high selectivity (24% yield of **2a**, Table 1, entry 1). The low conversion yield could be ascribed to the low concentration of water, constitutionally present in the DES and quantified in the range of 1.4–1.8 M, depending on the batch.[20] The addition of 25 μL of water had a negligible improvement in **2a** yield (28%, Table 1, entry 2). By gradually increasing the amount of water,

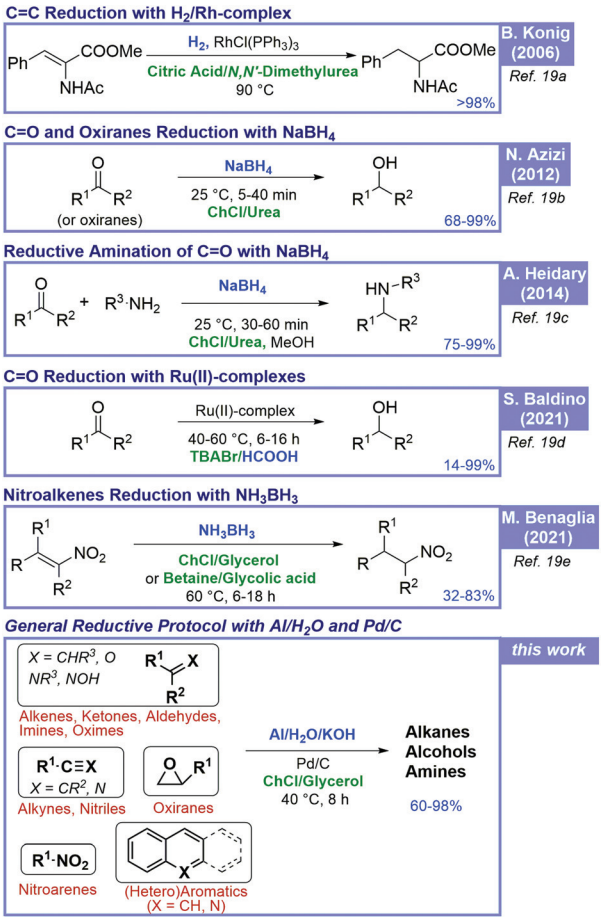


Fig. 1 Reductive methodologies performed in deep eutectic solvents.

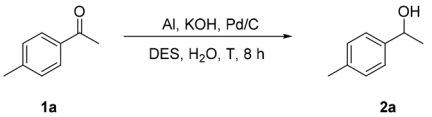
up to 400 μL, a linear increase in the **2a** amount was observed, until the conversion and the yield reached the optimal values of >98% and 96%, respectively (Table 1, entries 3–5).

A short exploration of the deep eutectic mixture components was then executed. By switching the nature of the H-bond acceptor from ChCl to TBAB, $ZnCl_2$ or K_2CO_3 a constant trend was ascertained: in all cases, the substrate conversion was almost complete but associated with a low yield of reduced product **2a** (5–29%, Table 1, entries 6–8). In the case of TBAB/EG, the acetal between **1a** and EG formed as a by-product (27% yield). In the case of $ZnCl_2$/urea and K_2CO_3/Gly, we were unable to extract from DES the side products, suggesting the formation of very polar molecules highly soluble in water.

The change of the H-bond donor from glycerol to urea was also detrimental to the reductive system, giving benzylic alcohol **2a** in only 40% yield (Table 1, entry 9); as described in the previous entries, part of the substrate was converted to by-products that were impossible to extract from DES.

Having ascertained that the ChCl/Gly mixture remains the most suitable medium for our reductive system, the possibility to decrease the reaction temperature and the catalyst loading, was investigated. Pleasingly, we found that substrate conver-

Table 1 Screening of DES, water content, temperature and catalyst loading in the reduction of the model substrate **1a** with aluminum under Pd/C catalysis[a]



Entry	DES[b]	H_2O (μL)	T (°C)	Pd/C loading (mol%)	**1a** Conversion[c] (%)	**2a** Yield[c] (%)
1	ChCl/Gly	—	80	10	26	24
2	ChCl/Gly	25	80	10	30	28
3	ChCl/Gly	100	80	10	41	37
4	ChCl/Gly	200	80	10	64	60
5	ChCl/Gly	400	80	10	>98	96
6	TBAB/EG	400	80	10	93	5[d]
7	$ZnCl_2$/urea	400	80	10	>98	29
8	K_2CO_3/Gly	400	80	10	86	10
9	ChCl/urea	400	80	10	>98	40
10	ChCl/Gly	400	40	10	>98	95
11	ChCl/Gly	400	40	5	>98	96
12	ChCl/Gly	400	40	5	44	41[e]
13	ChCl/Gly	400	40	2.5	23	21
14	ChCl/Gly	400	40	—	<5	<5[f]
15	*t*-BuOH	400	40	5	>98	71
16	DMF	400	40	5	90	4
17	Toluene	400	40	5	>98	28

[a] Reaction conditions: **1a** (0.5 mmol), Al (5.0 mmol), KOH (5.0 mmol), H_2O, Pd/C in DES (2.0 g), under vigorous magnetic stirring for 8 hours. [b] TBAB/EG = Tetrabutylammonium bromide/ethylen glycol (1/4 mol/mol); ChCl/urea = Cholinium chloride/urea (1/2 mol/mol); $ZnCl_2$/urea (1/3.5 mol/mol); ChCl/Glyl = Cholinium chloride/glycerol (1/2 mol/mol). [c] The **1a** conversion (%) equals to (mol of **1a** consumed/starting mol of **1a**) × 100 and has been calculated *via* ^{1}H NMR analysis of the crude reaction mixture using an internal standard technique (NMR internal standard: dimethyl sulfone). [d] The cyclic acetal between **1a** and EG was also detected and quantified by ^{1}H NMR analysis (27% yield). [e] Reaction time: 4 hours. [f] Traces of **2a** were detected by GC-MS analysis of the crude reaction mixture.

sion and reaction selectivity remained very high, also by performing the hydrogenation at 40 °C (Table 1, entry 10) and even by halving the catalyst loading (5 mol%, Table 1, entry 11). The latter is a relevant aspect considering that it is not unusual, for hydrogenation reactions, to use a Pd loading up to 10 mol%. In contrast, the shortening of the reaction time to 4 hours caused a low conversion of **1a** (44%, Table 1, entry 12). Moreover, a further decrease of Pd/C to 2.5 mol% was responsible for a dramatic lowering of **2a** yield (21%, Table 1, entry 13). As expected, the role of the Pd-catalyst is essential; the reduction of **1a** without Pd/C gave only traces of alcohol **2a** (<5% yield, Table 1, entry 14).

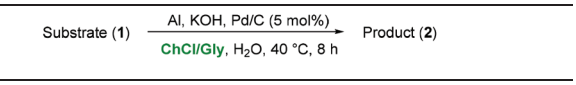
The importance of the "green" ionic medium has also been assessed by replacing the ChCl/Gly mixture with representative and conventional organic solvents such as toluene, DMF and *t*-BuOH. In all cases, the conversion of model ketone **1a** was very high but the hydrogenated product **2a** formed in a lower yield, with the alcoholic medium (*t*-BuOH) showing a better result (4–71%, Table 1, entries 15–17). It is important to highlight that the exothermic reaction between Al and KOH/H_2O caused the boiling of the organic solvents with the formation of highly toxic and flammable vapours, an unsafe scenario never experienced when deep eutectic solvents were used.

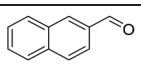
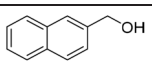
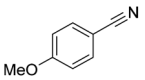
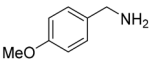
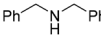
After optimizing the reaction conditions (reported in Table 1, entry 11), the versatility of our reductive protocol in DES was investigated by employing variously functionalized organic substrates and the results are summarized in Table 2.

Naphthaldehyde **1b** and styrene oxide **1c** could be smoothly reduced affording the corresponding primary alcohols **2b** and **2c** in high to excellent isolated yields (76–95%, Table 2, entries 1–2). Of note, the highly regioselective oxirane opening suggests a radical pathway of the transformation, probably flowing through a benzylic radical as a key intermediate. A set of nitrogenated compounds was then reduced to obtain valuable aromatic and aliphatic amines. Nitrobenzene **1d** was hydrogenated quantitatively affording the aniline **2d** in >98% yield (Table 2, entry 3). Similarly, the C–N double bond of imine **1e**, typically less susceptible to reduction, was efficiently transformed into the secondary benzylic amine **2e** (97%, Table 2, entry 4). The primary benzylic amine **2f** was instead produced in 68% yield by subjecting 4-methoxybenzonitrile **1f** to the aluminum/KOH/DES system under Pd/C catalysis (Table 2, entry 5). When oxime **1g** was used as the substrate, the reducing protocol caused a somewhat different result; dibenzylamine **2g** was isolated as the major product (86%, Table 2, entry 6). Such a compound probably arises from dehydroxylation of **1g** to the unstable NH-imine that undergoes both hydrolysis to benzaldehyde and reduction to benzylamine, affording **2g** as the reductive amination product.

Having proved the applicability of the methodology to several important functionalities, our attention moved to the hydrogenation of C–C double and triple bonds. The reduction of the isolated π-system of *N*-allylaniline **1h** showed to be a straightforward task affording *N*-propylaniline **2h** in 87% yield (Table 3, entry 1). Even more efficient was the hydrogenation

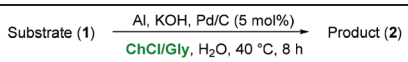
Table 2 Substrate scope of the aluminum-based reduction of variously functionalized organic compounds under Pd/C catalysis in DES[a]

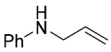
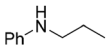
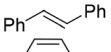
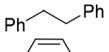
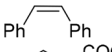
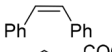
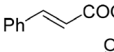
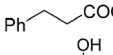
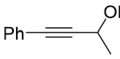
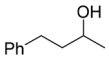
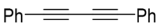
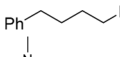
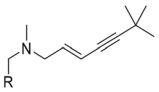
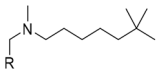
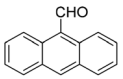
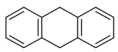


Entry	1	Substrate	Product	2 Yield[b] (%)
1	**1b**			**2b** (95)
2	**1c**			**2c** (76)
3	**1d**			**2d** (>98)
4	**1e**			**2e** (97)
5	**1f**			**2f** (68)
6	**1g**			**2g** (86%)

[a] Reaction conditions: **1a–g** (0.5 mmol), Al (5.0 mmol), KOH (5.0 mmol), H_2O (400 μL), Pd/C (0.025 mmol of Pd, 5.0 mol%) in DES ChCl/Gly (2.0 g), under vigorous magnetic stirring for 8 hours. [b] Isolated yield after column chromatography.

Table 3 Substrate scope of the aluminum-based reduction of various C–C double and triple bonds under Pd/C catalysis in DES.[a]



Entry	1	Substrate	Product	2 Yield[b] (%)
1	**1h**			**2h** (87)
2	(*E*)-**1i**			**2i** (95)
3	(*Z*)-**1i**			**2i** (>98)
4	**1j**			**2j** (>98)[c,d]
5	**1k**			**2k** (96)
6	**1l**			**2l** (>98)
7	**1m**[e]			**2m** (92)
8	**1n**			**2n** (75)
9	**1o**			**2o** (60)

[a] Reaction conditions: **1h–o** (0.5 mmol), Al (5.0 mmol), KOH (5.0 mmol), H_2O (400 μL), Pd/C (0.025 mmol of Pd, 5.0 mol%) in DES ChCl/Gly (2.0 g), under vigorous magnetic stirring for 8 hours. [b] Isolated yield after column chromatography. [c] Reaction time = 30 min. [d] When performed without KOH the product **2j** was obtained in 70% yield. [e] R = 1-naphthyl.

of conjugated π-systems of stilbenes (*E*)-**1i** and (*Z*)-**1i**; in both cases 1,2-diphenylethane **2i** was formed in very high yield (95% and >98% respectively, Table 3, entries 2–3). The feasibility of the methodology with respect to a carboxylic acid was then proved; we were pleased to find that (*E*)-cinnamic acid **1j** could be reduced quantitatively in a very short time (30 min) at 40 °C (>98% yield, Table 3, entry 4). The C–C triple bonds were also fully hydrogenated: alkynol **1k** and the 1,3-butadyine derivative **1l** were efficiently reduced to the corresponding products **2k** and **2l** in yields of up to >98% (Table 3, entries 5–6).

Intrigued by the possibility to apply this reductive protocol to the transformation of pharmaceutically relevant molecules, we then explored the hydrogenation of the antimycotic drug terbinafine **1m**. The reduction occurred smoothly also in this case (92% yield, Table 3, entry 7), tolerating the presence of a bulky group (*t*-butyl) bonded to the triple bond.

The reduction of aromatic rings is a very useful methodology to obtain cyclohexane derivatives, as well as hetero-substituted carbocyclic compounds. With this objective in mind, we applied our protocol to quinoline **1n** and 9-anthraldehyde **1o**; in the case of the *N*-heterocycle hydrogenation occurred as expected, furnishing the partially dearomatized product **2n** in satisfactory yield (75%, Table 3, entry 8). Of note, the 1,2,3,4-tetrahydroquinoline core is a very important building block for the synthesis of a large family of biologically active compounds.[21] When polycyclic aldehyde **1o** was reduced, a peculiar transformation occurred; besides the planned dearomatization of the central aromatic ring, a deformylation reaction also occurred (Table 3, entry 9). Probably, after the dearomatization step, a reduction of the carbonyl moiety took place, affording the corresponding potassium alkoxide that promptly fragmented in formaldehyde and (9,10-dihydroanthracen-9-yl) potassium, a very stable bis-benzylic anion precursor of **2o**.

Additionally, the recyclability of both DES and catalyst was evaluated. Pd-catalyzed reduction of ketone **1a** in ChCl/Gly was chosen as the model reaction, since it provided almost quantitative yield of the alcohol **2a** (96%, Table 1, entry 11). After 8 hours the crude mixture was extracted with cyclopentyl methyl ether (CPME), considered a versatile eco-friendly solvent for applications in synthetic chemistry;[22] alcohol **2a** was recovered in excellent yield (96%, Fig. 2, number of recycles = 0), leaving the catalyst in the eutectic mixture. Upon the addition of new, fresh reagents (Al, KOH, H_2O and **1a**, see the ESI†), the catalyst and the reaction medium (DES) could be reused for additional reaction runs. As shown in Fig. 2, the activity of the catalyst remained almost unchanged in the first recycle (90% of **2a** yield) and underwent a slight deactivation during the second recycle (77% of **2a** yield). From the recycle no 3 the reduction experienced a more consistent decrease of efficiency, the formation of target product **2a** (50% yield) being halved. Such behaviour could be ascribed to the increased quantity of inorganic salts accumulated in the reaction medium during the consecutive runs.

With the aim to shed light on the role of DES, supposed to be crucial for aluminum activation by removing the superficial layer of Al_2O_3, we performed the reduction of ketone **1a** under the optimized reaction conditions reported (Table 1, entry 11) but in the absence of KOH, an additive able to activate aluminum by breaking the Al_2O_3 shield.[7,13a] Under such new conditions, product **2a** formed in only 4% yield (see the ESI, Table S1, entry 1†), although with high substrate conversion (92%). The absence of KOH likely caused a lower rate of H_2 production and consequently allowed the formation of by-products such as the acetals derived from **1a** and glycerol.

We then chose a model substrate less inclined to side reactions such as the (*E*)-cinnamic acid **1j**. Treatment of **1j** under the optimized reaction conditions, but in the absence of KOH, afforded 3-phenylpropionic acid **2j** in good yield (70%, see the ESI, Table S1, entry 2†) with 98% conversion of **1j**. Of note, the same reaction performed in water gave only traces of the expected product **2j** (<2% yield, Table S1, entry 3†). Moreover,

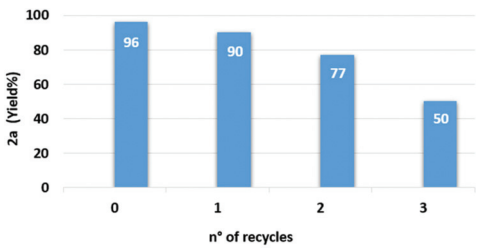


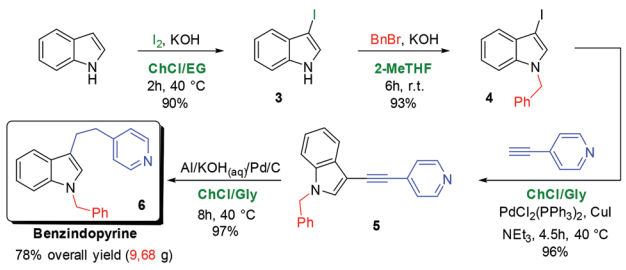
Fig. 2 Recycling of Pd/C and DES in the hydrogenation of ketone **1a** to alcohol **2a**.

the hydrogenation in ChCl/Gly without KOH was also tested on nitrobenzene **1d** and (*E*)-stilbene **1i**.

In both cases, appreciable amounts of reduced products **2d, i** were formed (32–43%, see the ESI, Table S1, entries 4 and 5†) suggesting that the activity of aluminum in DES is significant. In addition, the solubility (*S*) of Al_2O_3 in ChCl/Gly was briefly investigated; at 40 °C, alumina dissolves in DES nearly five times more readily than in water (S_{DES} = 0.72 ppm, S_{water} = 0.16 ppm, see the ESI for further experimental details†). These experimental pieces of evidence suggested that the ionic medium might participate in the activation of aluminum by eliminating part of the Al_2O_3 coating. However, the addition of KOH to DES makes the methodology more efficient for synthetic purposes.

Furthermore, a preliminary hazard test of the protocol was carried out; the internal temperature of the reaction mixture was monitored during the hydrogenation of ketone **1a** in the DES medium or in pure water, under optimized conditions (Table 1, entry 11). When the reduction was performed in water the temperature of the medium reached its maximum value (100 °C) in only 4 seconds after the addition of the last reagent (KOH). Such a violent boiling of the solvent combined with a fast H_2 evolution caused a hazardous and undesirable bumping of the reaction mixture. When the reduction was performed in DES, the temperature of the medium increased very slowly and reached the maximum value (108 °C) after 12 minutes (see the ESI, Graph S1†). The negligible volatility of the ionic solvent and its low thermal conductivity ensured a somewhat safe reaction.

Having ascertained the general applicability of the present methodology, we were then interested in its application to the "green" synthesis of a pharmacologically relevant molecule. We focalized our attention on benzindopyrine (known also as pyrbenzindole, Scheme 1), a valuable structural motif showing sedative and antipsychotic activities thanks to the inhibition of serotonin reuptake in the pre-synaptic space.[23] As shown in Scheme 1, starting from indole, we optimized a multigram-scale synthesis of such a valuable molecule by means of a synthetic strategy mainly based on a Sonogashira coupling followed by the reduction of the C–C triple bond of the internal alkyne **5**; of note, all transformations were performed in green media.



Scheme 1 Multigram synthesis of the antipsychotic benzindopyrine in green media.

The first planned transformations of indole consisted of its C_3-iodination and *N*-benzylation. We attempted to perform such synthetic steps in a one-pot[24] fashion but, unfortunately, the benzylation of DES components proved to be always preferred. Hence, the iodination reaction was firstly carried out in ChCl/EG, starting from 4.73 g of indole to afford the 3-iodoindole **3** in 90% yield (8.74 g, Scheme 1). The following treatment of crude **3** with benzyl bromide in 2-methyl tetrahydrofuran (2-MeTHF), a biomass-derived green solvent,[25] afforded the expected *N*-benzyl-3-iodoindole **4** in excellent yield, after isolation by crystallization (93% yield, 11.15 g, Scheme 1).

Moving from our previous experience on the Pd-catalyzed Sonogashira reactions in eutectic mixtures,[15c] we studied the coupling between the indole derivative **4** and 4-ethynylpyridine in a ChCl/Gly medium, which already proved to be one of the best choices for such transformations. We started our investigation with the help of a statistical tool, the well-known strategy called the design of experiments (DoE).

DoE has been extensively applied to chemical processes for the optimization of large-scale reactions, however, it can be readily applied also to reactions on smaller scales.[26]

The reaction parameters that we take into consideration for the DoE were as follows: (1) amounts of 4-ethynylpyridine, NEt_3, $PdCl_2(PPh_3)_2$, CuI and DES; (2) temperature; (3) time; and (4) rate of mechanical stirring (see the ESI†). Following the DoE outcomes, the reaction between 1 equiv. of indole **4**, 2.5 equiv. of 4-ethynylpyridine, 2.5 mol% of $PdCl_2(PPh_3)_2$, 15 mol% of CuI and 3.5 equiv. of NEt_3 in ChCl/Gly at 40 °C for 4.5 hours, with a mechanical stirring speed of 300 rpm was performed, leading to the expected alkyne **5**, isolated after crystallization in 96% yield (9.76 grams, Scheme 1).

Finally, the reduction step has been performed under the experimental conditions previously optimized (Table 1, entry 11). Alkyne **5** was subjected to the system composed of Al/KOH/H_2O in ChCl/Gly at 40 °C, under the catalysis of Pd/C (5.0 mol%) for 8 hours. To our satisfaction, it was found that the method once again proved to be very efficient, affording 9.68 grams of the pharmacologically active target benzindopyrine (97% yield, Scheme 1), corresponding to a 78% overall yield in four synthetic steps, a notable improvement in the synthetic method with respect to the 18% yield reported in the literature.[23a]

Conclusions

In summary, we described a novel reductive methodology performed in ChCl/Gly a bio-based, non-toxic deep eutectic solvent. The reaction acquires safe connotations because it avoids the use of harmful reagents or high-pressure reactors, being based on *in situ* generation of hydrogen from Al powder and small amounts of basic water, under the catalysis of cheap Pd/C. The method is of general applicability, allowing the hydrogenation of C–O, C–N, N–O and C–C multiple bonds, as well as the ring opening of an oxirane, and the dearomatization of quinoline and anthracene derivatives. The recyclability

of both DES and the catalyst has been proved for a model reaction for at least three consecutive runs, with reasonable preservation of Pd activity. The methodology has been then applied to the multi-gram synthesis of a pharmacologically relevant target, the antipsychotic benzindopyrine, that was prepared in 78% overall yield starting from indole. Of note, all the synthesis steps for the preparation of the target molecule were performed in natural deep eutectic solvents or "green media" derived from renewable sources, so representing a virtuous synthetic pathway aimed at drastically minimizing the use of toxic and volatile organic solvents derived from fossil fuels.

Conflicts of interest

There are no conflicts to declare.

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