

The present document is the Post-Print version of the article entitled "Deep Eutectic Solvents Meet Safe, Scalable and Sustainable Hydrogenations Enabled by Aluminum Powder and Pd/C", *Green Chem.*, 2022, 24, 4388, DOI: 10.1039/d2gc00636g. The final version of the manuscript can be found at the following link <https://doi.org/10.1039/d2gc00636g>.

Deep Eutectic Solvents Meet Safe, Scalable and Sustainable Hydrogenations Enabled by Aluminum Powder and Pd/C

Received 00th January 20xx,
Accepted 00th January 20xx

Francesco Messa,^a Giuseppe Dilauro,^{a,b} Andrea Nicola Paparella,^a Lavinia Silvestri,^c Guido Furlotti,^c Tommaso Iacoangeli,^c Serena Perrone^{*,a} and Antonio Salomone^{*,d}

DOI: 10.1039/x0xx00000x

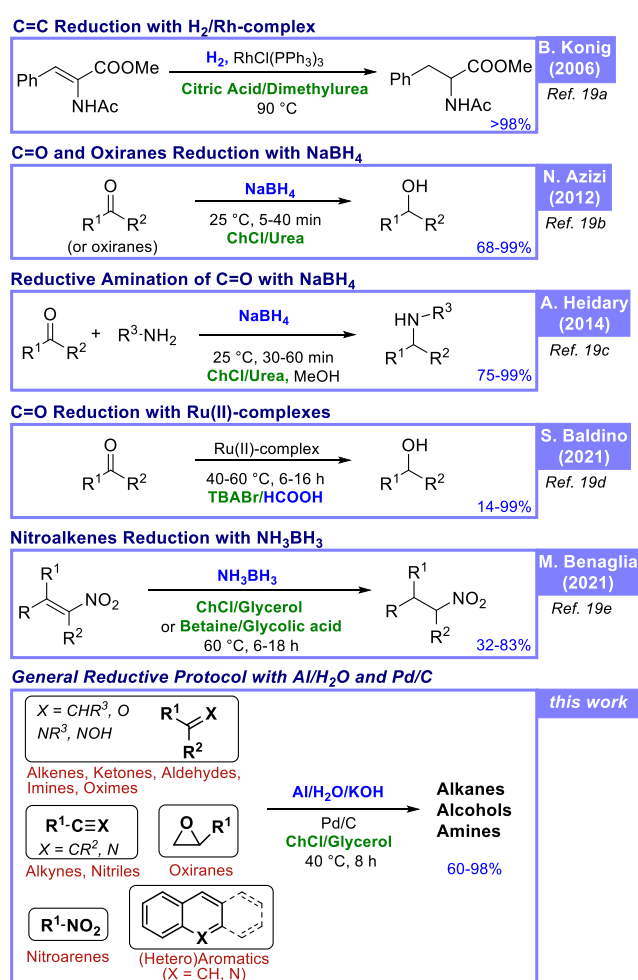
A general, safe and scalable reductive protocol, based on the *in-situ* generation of H₂ from aluminum and water, has been developed in Deep Eutectic Solvents for the reduction of many organic compounds under the Pd-catalysis. The methodology as been efficiently applied to the multigram-scale synthesis 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 hydrogenations¹ or the employment of metal hydrides² because of their general applicability, and less frequently with organic³ 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, 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 H₂, 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

Figure 1. Reductive methodologies performed in Deep Eutectic Solvents.



^a Dipartimento di Scienze e Tecnologie Biologiche ed Ambientali, Università del Salento, Prov.le Lecce-Monteroni, I-73100 Lecce (Italy).

^b Dipartimento di Farmacia-Scienze del Farmaco, Università degli Studi di Bari "Aldo Moro", Consorzio C.I.N.M.P.I.S., Via E. Orabona 4, I-70125 Bari (Italy).

^c Angelini Pharma S.p.A. Via Guardapasso, 1, 04011 Aprilia, (Italy)

^d Dipartimento di Chimica, Università degli Studi di Bari "Aldo Moro", Consorzio C.I.N.M.P.I.S., Via E. Orabona 4, I-70125 Bari (Italy).

† Footnotes relating to the title and/or authors should appear here.

Electronic Supplementary Information (ESI) available: General experimental procedures and copies of ¹H and ¹³C-NMR spectra of compounds **2a-o**, **4-6**. See DOI: 10.1039/x0xx00000x

for transport and storage; c) requires appropriate reactors when the process occurs at high pressure; d) derives principally by the natural gas reforming, a technique with a huge energy demand and a large emission of greenhouse gases (principally CO₂).⁵ 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 decades extensive studies have been performed based on the use of Nickel-Aluminum alloys for the hydrogenations in aqueous medium.⁷ Despite a remarkable catalytic activity, Ni/Al alloys are not ideal in a sustainable chemistry scenario because they are pyrophoric and require to be handled under inert atmosphere; moreover, they are suspected to cause lung cancer in humans.⁸

Although the water represents the greener solvent at all, the use of aluminum in aqueous medium, for the reduction of organic compounds, can be critical from the hazard point of view. The reaction between Al and H₂O is highly exothermic, having an enthalpy of formation of about -280 kJ per mol of H₂ produced at temperatures below 100 °C.⁹ This aspect can be dangerous when the reaction is performed in 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 (Al₂O₃), that naturally covers the particle surface of pure Al metal. Such oxide, which does not dissolve in water, prevents the effective contact between water and aluminum, and makes hydrogen production inadequate for synthetic purposes. The activation of 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 remarkable the work of Török that used the mechanical action of ultrasounds for the disruption of the aluminum oxide film to generate H₂ 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 strategy¹⁴ and the substitution of toxic volatile organic solvents, deriving from petrol, with the 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 the hydrogen generation from aluminum, could be the continual removal of the adherent oxide layer from the metal surface. Since DESSs have been reported to be very efficient solvents in the dissolution of metal oxides,¹⁷ we thought that the system aluminum/DES 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 DESSs in the last two decades,¹⁸ very few examples of reductions in such green ionic liquids are known to date (Figure 1): in 2006 König hydrogenated for the first time a C-C double bond in DES

Table 1 (T1). 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 ₂ O (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 ₂ CO 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	<i>t</i> -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), H₂O, Pd/C (0.05 mmol of Pd, 10 mol%) 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); ZnCl₂/Urea (1/3.5 mol/mol); ChCl/Gly = Cholinium Chloride/glycerol (1/2 mol/mol). ^c The **1a** conversion (%) equals to (mol of **1a** consumed/starting mol of **1a**)x100 and has been calculated via ¹H 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 ¹H NMR analysis (27% yield). ^e Reaction time: 4 hours. ^f Traces of **2a** were detected by GC-MS analysis of the crude reaction mixture.

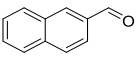
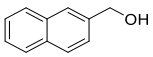

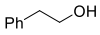




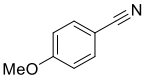
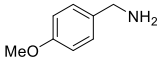

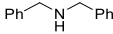
(Citric Acid/Dimethylurea) by using the Wilkinson's catalyst and H₂ but the reaction was applied to just one compound.^{19a} More recently, few authors studied the reduction of aldehydes, ketones and oxiranes by using NaBH₄^{19b,c} or exploited the activity of a diphosphine-bridged Ru(II)-complex in TBABr/HCOOH,^{19d} an eutectic mixture acting both as reaction medium and hydrogen source. Nitroalkenes have been selectively reduced to nitroalkanes by using NH₃BH₃ in nature-derived deep eutectic solvents, too (Figure 1).^{19e} However, the most used strategy to reduce organic compounds in DES, remains the biocatalysis.^{19f-i}

Our initial study began with the reduction of 4'-methylacetophenone **1a**, as a model substrate, in 2 grams of a deep eutectic solvent composed by 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, also T1).

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,

Table 2 (T2). Substrate scope of the aluminum-based reduction of variously functionalized organic compounds under Pd/C catalysis in DES.^a

Substrate (1) $\xrightarrow[\text{ChCl/Gly, H}_2\text{O, 40 }^\circ\text{C, 8 h}]{\text{Al, KOH, Pd/C (5 mol\%)}}$ Product (2)

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), H₂O (400 μ L), 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.

only 26% of ketone converted to alcohol, although with high selectivity (24% yield of **2a**, T1, 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 1.4–1.8 M, depending on the batch.²⁰ The addition of 25 μ L of water had a negligible improvement of **2a** yield (28%, T1, entry 2). By gradually increasing the amount of water, up to 400 μ L, a linear increase of **2a** amount was observed, until the conversion and the yield reached the optimal values of >98% and 96%, respectively (T1, entries 3-5).

A short exploration of the deep eutectic mixture components was then executed. By switching the nature of H-bond acceptor from ChCl to TBAB, ZnCl₂ or K₂CO₃ 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%, T1, 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 ZnCl₂/Urea and K₂CO₃/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 for the reductive system, giving the benzylic alcohol **2a** in only 40% yield (T1, entry 9); as described for the previous entries, part of the substrate was converted in by-products that were not possible to extract from DES.

Having ascertained that 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 the substrate conversion and reaction selectivity stayed very high, also by performing the hydrogenation at 40 $^\circ$ C (T1, entry 10) and even

by halving the catalyst loading (5 mol%, T1, 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 **1a** conversion (44%, T1, entry 12). Moreover, a further decrease of Pd/C to 2.5 mol% was responsible of a dramatic lowering of **2a** yield (21%, T1, entry 13). As expected, the role of Pd-catalyst is essential: the reduction of **1a** without Pd/C gave only traces of alcohol **2a** (<5% yield, T1, entry 14).

The importance of the “green” ionic medium has been also 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 the better result (4-71%, T1, entries 15-17). It is important to highlight that the exothermic reaction between Al and KOH/H₂O 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 T1, entry 11), the versatility of our reductive protocol in DES was investigated, by employing variously functionalized organic substrates; the results are summarized in Table 2 (also T2).

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%, T2, 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 (T2, entry 3). Similarly, the C–N double bond of imine **1e**, typically less susceptible of reduction, was efficiently transformed in the secondary benzylic amine **2e** (97%, T2, entry 4). The primary benzylic amine **2f** was instead produced in 68% yield by subjecting the 4-methoxybenzylideneamine **1f** to the aluminum/KOH/DES system, under the Pd/C catalysis (T2, entry 5). When the oxime **1g** has been used as the substrate, the reducing protocol caused a something different result: dibenzylamine **2g** was isolated as the major product (86%, T2, entry 6). Such compound probably arises from dehydroxylation of **1g** to the unstable NH-imine that, undergoing both hydrolysis to benzaldehyde and reduction to benzylamine, afforded **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 isolated π -system of *N*-allylaniline **1h** showed to be a straightforward task affording the *N*-propylaniline **2h** in 87% yield (Table 3, also T3, entry 1). Even more efficient was the hydrogenation of conjugated π -systems of stilbenes (*E*)-**1i** and (*Z*)-**1i**: in both cases the 1,2-diphenylethane **2i** was formed in very high yield (95% and >98% respectively, T3, entries 2-3). The feasibility of the methodology respect to a carboxylic acid was then proved; we were pleased to find that (*E*)-cinnamic

Table 3 (T3). Substrate scope of the aluminum-based reduction of various C-C double and triple bonds under Pd/C catalysis in DES.^a

$$\text{Substrate (1)} \xrightarrow[\text{ChCl/Gly, H}_2\text{O, 40 }^\circ\text{C, 8 h}]{\text{Al, KOH, Pd/C (5 mol\%)}} \text{Product (2)}$$

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), H₂O (400 μ L), 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

acid **1j** could be reduced quantitatively in a very short time (30 min) at 80 °C (>98% yield, T3, entry 4). The C–C triple bonds were also fully hydrogenated: alkynol **1k** and the 1,3-butadiyne derivative **1l** were efficiently reduced to the corresponding products **2k** and **2l** in yields up to >98% (T3, 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, T3, 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 heterosubstituted carbocyclic compounds. With this objective in mind, we applied our protocol to quinoline **1n** and 9-anthraldehyde **1o**; in the case of *N*-heterocycle the hydrogenation occurred as expected, furnishing the partially dearomatized product **2n** in satisfactory yield (75%, T3, entry 8). Of note, the 1,2,3,4-

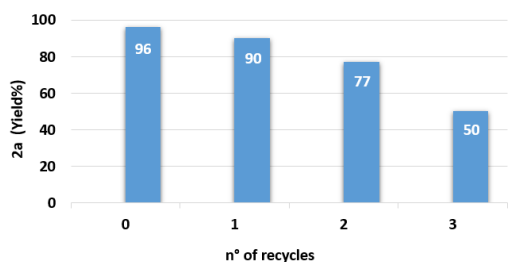
tetrahydroquinoline core is a very important building block for the synthesis of a large family of biologically active compounds.²¹ When polycyclic aldehyde **1o** was reduced, a peculiar transformation happened: beside the planned dearomatization of the central aromatic ring, a deformylation reaction also occurred. Probably, after the dearomatization step, a reduction of 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%, T1, 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%, Figure 1, number of recycles=0), leaving the catalyst in the eutectic mixture. Upon the addition of new, fresh reagents (Al, KOH, H₂O and **1a**, see ESI), the catalyst and the reaction medium (DES) could be reused for additional reaction runs. As shown in Figure 1, the activity of 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 n° 3 the reduction experienced a more consistent drop of efficiency, being halved the formation of target product **2a** (50% yield). 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 in the aluminum activation by removing the superficial layer of Al₂O₃, we performed the reduction of ketone **1a** in the optimized reaction conditions reported (T1, entry 11) but in the absence of KOH, an additive able to activate the aluminum by breaking the Al₂O₃ shield.^{7,13a} In such new conditions, the product **2a** formed in only 4% yield (see ESI, Table S1, entry 1), although the high substrate conversion (92%). The absence of KOH likely caused a lower rate of H₂ production and consequently allowed the formation of by-products such as the acetals derived from **1a** and glycerol.

We then chosen a model substrate less inclined to side reactions such as the (*E*)-cinnamic acid **1j**. Treatment of **1j** in the optimized reaction conditions, but in the absence of KOH, afforded 3-phenylpropionic acid **2j** in good yield (70%, see ESI Table S1, entry 2) with a 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, the hydrogenation in ChCl/Gly without KOH was also tested on nitrobenzene **1d** and (*E*)-stilbene **1i**.

In both cases, an appreciable amount of reduced products **2d,i** had formed (32-43%, see ESI, Table S1, entries 4,5) suggesting that the activity of aluminum in DES is significant. In addition, the solubility (*S*) of Al₂O₃ in ChCl/Gly was briefly investigated; at 40 °C, alumina dissolves in DES nearly five times more than in water (*S*_{DES} = 0.72 ppm, *S*_{water} = 0.16 ppm, see ESI for further experimental details). These experimental evidences

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

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 DES medium or in pure water, under optimized conditions (T1, 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 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 raised very slowly and reached the maximum value (108 °C) after 12 minutes (see 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 on 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.

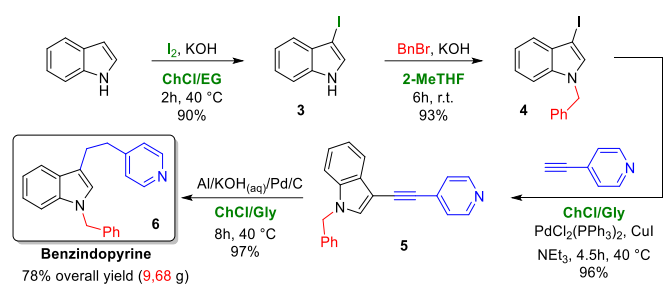
First planned transformations of indole consisted in its C_3 -iodination and *N*-benzylation. We attempted to perform such synthetic steps in a one-pot²⁴ fashion but, unfortunately, the benzylation of DES components proved to be always preferred. Hence, the iodination reaction was firstly carried out in ChCl/EG , on 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-iodo indole **4** in excellent yield, after isolation by crystallization (93% yield, 11.15 g, Scheme 1).

Moving from our previous experience on Pd-catalyzed Sonogashira reactions in eutectic mixtures,^{15c} we studied the coupling between the indole derivative **4** and 4-ethynylpyridine in ChCl/Gly medium, which already proved to

be one of the best choices for such transformation. We started our investigation with the help of a statistic tool, the well-known strategy called 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 factors that we take into consideration for the DoE were the following: 1) amounts of 4-ethynylpyridine, NEt_3 , $\text{PdCl}_2(\text{PPh}_3)_2$, CuI and DES; 2) temperature; 3) time; 4) rate of mechanical stirring (see ESI). Following the DoE outcomes, the reaction between of 1 equiv. of indole **4**, 2.5 equiv. of 4-ethynylpyridine, 2.5 mol% of $\text{PdCl}_2(\text{PPh}_3)_2$, 15 mol% of CuI

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

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 in the experimental conditions previously optimized (T1, entry 11). Alkyne **5** was subjected to the system composed by $\text{Al}/\text{KOH}/\text{H}_2\text{O}$ in ChCl/Gly at 40 °C, under the catalysis of Pd/C (5.0 mol%) for 8 hours. With our satisfaction, it was found that the method resulted once again very efficient, affording 9.68 grams of the pharmacologically active target Benzindopyrine (97% yield, Scheme 1), corresponding to a 78% overall yield on four synthetic steps, a notable improvement in the synthetic method 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 resulted of general application, 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 catalyst has been proved for a model reaction for at least three consecutive runs, with a reasonable preservation of Pd activity. The methodology has been then applied to the multi-gram synthesis of a pharmacologically relevant target, the antipsychotic Benzindopyrine, prepared in 78% overall yield starting from

indole. Of note, all the synthetic steps for the preparation of the target molecule were performed in Natural Deep Eutectic Solvents or “green media” deriving from renewable sources, so representing a virtuous synthetic pathway aimed at drastically minimize the use of toxic and volatile organic solvents deriving from fossil fuels.

Conflicts of interest

“There are no conflicts to declare”.

Acknowledgements

We gratefully acknowledge Mr. Francesco Monno for its valuable contribution to the experimental section.

Notes and references

- S. Nishimura, *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*, Wiley, New York, 2001
- J. Seyden-Penne, *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, 2nd edition. Wiley-VCH, New York, 1997.
- D. Wang and D. Astruc, *Chem. Rev.*, 2015, **115**, 6621.
- M. Hudlicky, “Reductions in Organic Chemistry”, Ellis-Horwood and Wiley, Chichester, 1984, ch. 2–4, pp. 13–35.
- R. Ono and T. Oda, *J. Phys. Conf. Ser.*, 2008, **142**, 012003
- P. L. Spath and M. K. Mann, *Life Cycle Assessment of Hydrogen Production via Natural Gas Steam Reforming*, United States, <https://doi.org/10.2172/764485>.
- (a) H. Cho, C. Schäfer and B. Török, *Curr. Org. Synth.*, 2016, **13**, 255. (b) L. K. Keefer and G. Lunn, *Chem. Rev.*, 1989, **89**, 459.
- G. Genchi, A. Carocci, G. Lauria, M. S. Sinicropi and A. Catalano, *Int. J. Environ. Res. Public Health* 2020, **17**, 679.
- Refers to the following chemical equation: $2\text{Al} + 6\text{H}_2\text{O} \rightarrow 3\text{H}_2 + 2\text{Al}(\text{OH})_3$ and has been calculated with *HSC Thermodynamic Software*. See: J. Petrovic and G. Thomas, *Reaction of Aluminum with Water to Produce Hydrogen - 2010 Update*, <https://doi.org/10.2172/1219359>.
- Levin, D. (2014), *Managing Hazards for Scale Up of Chemical Manufacturing Processes*, ACS Symposium Series, Vol. 1181, Chapter 1, pp 1-71.
- M. Cortes-Clerget, J. Yu, J. R. A. Kincaid, P. Walde, F. Gallou and B. H. Lipshutz, *Chem. Sci.*, 2021, **12**, 4237.
- M. Jackson, C. Eadsforth, D. Schowanek, T. Delfosse, A. Riddle and N. Budgenk, *Env. Toxicol. Chem.*, 2016, **35**, 1077.
- (a) G. Liu, H. Zhao, J. Zhu, H. He, H. Yang, T. Thiemann, H. Tashiro and M. Tashiro, *Synth. Commun.*, 2008, **38**, 1651.; (b) W. Li, T. Cochell and A. Manthiram, *Sci. Rep.* 2013, **3**, 1229; (c) C. Schäfer, C. J. Ellstrom, H. Cho and B. Török, *Green Chem.* 2017, **19**, 1230.
- (a) M. Capua, S. Perrone, F. Bona, A. Salomone and L. Troisi, *European J. Org. Chem.*, 2017, **2017**, 1780; (b) S. Perrone, A. Caroli, A., G. Cannazza, C. Granito, A. Salomone, and L. Troisi, *Tetrahedron Lett.*, 2015, **56**, 2773; (c) S. Perrone, M. Capua, A. Salomone and L. Troisi, *J. Org. Chem.*, 2015, **80**, 8189; (d) S. Perrone, A. Salomone, A. Caroli, A. Falcicchio, C. Citti, G. Cannazza and L. Troisi, *Eur. J. Org. Chem.*, 2014, **2014**, 5932.
- (a) G. Dilauro, C. S. Azzollini, P. Vitale, A. Salomone, F. M. Perna and V. Capriati, *Angew. Chem. Int. Ed.*, 2021, **60**, 10632; (b) L. Cicco, J. A. Hernández-Fernández, A. Salomone, P. Vitale, M. Ramos-Martín, J. González-Sabín, A. Presa Soto, F. M. Perna, V. Capriati and J. García-Álvarez, *Org. Biomol. Chem.*, 2021, **19**, 1773; (c) F. Messa, G. Dilauro, F. M. Perna, P. Vitale, V. Capriati and A. Salomone, *ChemCatChem*, 2020, **12**, 1979; (d) P. Vitale, L. Cicco, F. Messa, F. M. Perna, A. Salomone and V. Capriati, *Eur. J. Org. Chem.*, 2019, **2019**, 5557; (e) F. Messa, S. Perrone, M. Capua, F. Tolomeo, L. Troisi, V. Capriati and A. Salomone, *Chem. Commun.*, 2018, **54**, 8100; (f) S. Perrone, M. Capua, F. Messa, A. Salomone and L. Troisi, *Tetrahedron*, 2017, **73**, 6193.
- E. L. Smith, A. P. Abbott and K. S. Ryder, *Chem. Rev.*, 2014, **114**, 21, 11060–11082.
- a) A. P. Abbott, G. Capper, D. L. Davies, K. J. McKenzie and S. U. Obi, *J. Chem. Eng. Data*, *J. Chem. Eng. Data* 2006, **51**, 4, 1280; b) N. Rodriguez Rodriguez, L. Machiels and K. Binnemans, *ACS Sustain. Chem. Eng.*, 2019, **7**, 3940; c) I. M. Pateli, D. Thompson, S. S. M. Alabdullah, A. P. Abbott, G. R. T. Jenkin and J. M. Hartley, *Green Chem.*, 2020, **22**, 5476.
- Q. Zhang, K. de Oliveira Vigier, S. Royer and F. Jérôme, *Chem. Soc. Rev.*, 2012, **41**, 7108–7146; b) J. García-Álvarez, E. Hevia and V. Capriati, *Eur. J. Org. Chem.*, 2015, **31**, 6779–6799; c) P. Liu, J.-W. Hao, L.-P. Mo and Z.-H. Zhang, *RSC Adv.* 2015, **5**, 48685; d) D. A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I. M. Pastor and D. J. Ramón, *Eur. J. Org. Chem.* 2016, **4**, 612; e) J. García-Álvarez, E. Hevia and V. Capriati, *Chem. Eur. J.* 2018, **24**, 14854; f) L. Cicco, G. Dilauro, F. M. Perna, P. Vitale and V. Capriati, *Org. Biomol. Chem.*, 2021, **19**, 2558.
- For chemical reductions in DES, see: a) G. Imperato, S. Hoger, D. Lenoir, B. König, *Green Chem.*, 2006, **8**, 1051; b) N. Azizi, E. Batebi, S. Bagherpoura and H. Ghafari, *RSC Adv.*, 2012, **2**, 2289; c) D. Saberi, J. Akbari, S. Mahdudi, Akbar Heydari, *J. Mol. Liq.*, 2014, **196**, 208. d) M. Cavallo, D. Arnodo, A. Mannu, M. Blangetti, C. Prandi, W. Baratta and S. Baldino, *Tetrahedron*, 2021, **83**, 131997; e) C. Faverio, M. F. Boselli, P. C. Gonzalez, A. Puglisi, M. Benaglia, J. Beilstein. *Org. Chem.*, 2021, **17**, 1041. For enzymatic reductions in DES, see: f) V. Gotor-Fernandez and C.E. Paul, *J. Biotechnol.*, 2019, **293**, 24–35P; g) Vitale, F. Lavolpe, F. Valerio, M. Di Biase, F.M. Perna, E. Messina, G. Agrimi, I. Pisano and V. Capriati, *Reac. Chem. Eng.*, 2020, **5**, 859–864; h) P. Vitale, F.M. Perna, G. Agrimi, I. Pisano, F. Mirizzi, R.V. Capobianco and V. Capriati, *Catalysts*, 2018, **8**, 55; i) P. Vitale, V.M. Abbinante, F.M. Perna, A. Salomone, C. Cardellicchio and V. Capriati, *Adv. Synth. Catal.*, 2017, **359**, 1049; l) P. Vitale, A. Digeo, F.M. Perna, G. Agrimi, A. Salomone, A. Scilimati, C. Cardellicchio and V. Capriati, *Catalysts*, 2017, **7**, 37.
- The initial content of water in ChCl/Gly has been determined by FT-IR technique following the methodology published in: F. Milano, L. Giotta, M. R. Guascito, A. Agostiano, S. Sblendorio, L. Valli, F. M. Perna, L. Cicco, M. Trotta and V. Capriati, *ACS Sustain. Chem. Eng.*, 2017, **5**, 7768.
- a) Scott, J.D.; Williams and R.M. *Chem. Rev.* 2002, **102**, 1669; b) K. Abe, T. Saitoh, Y. Horiguchi, I. Utsunomiya, and K. Taguchi. *Biol. Pharm. Bull.* 2005, **28**, 1355; c) H. R. Lin, M. K. Safo and D. J. Abraham, *Bioorg. Med. Chem. Lett.* 2007, **17**, 2581.
- U. Azzena, M. Carraro, L. Pisano, S. Monticelli, R. Bartolotta and V. Pace, *ChemSusChem*, 2019, **12**, 40.
- a) C. Guerey, F. Audiau, A. Champseix, A. Uzan, G. Le Fur and J. Rataud, *J. Med. Chem.*, 1980, **23**, 1306; b) A.P. Gray and W. L. Archer *J. Am. Chem. Soc.* 1957, **79**, 3554; c) L.D. Hankoff, L. Rudorfer and H.M. Paley, *J. New Drugs*, 1962, **2**, 167.
- P. Barbie and U. Kazmaier, *Org. Biomol. Chem.* 2015, **13**, 9267–9275.
- V. Pace, P. Hoyos, L. Castoldi, P. Domínguez de María, and A.R. Alcántara, *ChemSusChem* 2012, **5**, 1369.
- D.F. Emiabata-Smith, D. L. Crookes, and M.R. Owen, *Org. Process Res. Dev.* 1999, **3**, 281.