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Deep eutectic solvents as H_2-sources for Ru(II)-catalyzed transfer hydrogenation of carbonyl compounds under mild conditions

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ABSTRACT

The employment of easily affordable ruthenium(II)-complexes as pre-catalysts in the transfer hydrogenation of carbonyl compounds in deep eutectic media is described for the first time. The eutectic mixture tetrabutylammonium bromide/formic acid = 1/1 (TBABr/HCOOH = 1/1) acts both as reaction medium and hydrogen source. The addition of a base is required for the process to occur. An extensive optimization of the reaction conditions has been carried out, in terms of catalyst loading, type of complexes, H_2-donors, reaction temperature and time. The combination of the dimeric complex [RuCl(*p*-cymene)-μ-Cl]$_2$ (0.01–0.05 eq.) and the ligand dppf (1,1′-ferrocenediyl-bis(diphenylphosphine)ferrocene) in 1/1 molar ratio has proven to be a suitable catalytic system for the reduction of several and diverse aldehydes and ketones to their corresponding alcohols under mild conditions (40–60 °C) in air, showing from moderate to excellent tolerability towards different functional groups (halogen, cyano, nitro, phenol). The reduction of imine compounds to their corresponding amine derivatives was also studied. In addition, the comparison between the results obtained in TBABr/HCOOH and in organic solvents suggests a non-innocent effect of the DES medium during the process.

1. Introduction

The catalytic reduction of carbonyl compounds by means of dihydrogen (H_2) [1] or H_2-donors is a fundamental reaction for the preparation of alcohols [2–4]. Therefore, the preparation of catalysts for the selective reduction of C=O bonds is a topic of relevant interest both for the academic research and application in industry. A deep insight into the literature shows how the fine tuning of the ligands around the metal center allows the carbonyl group to be hydrogenated chemo- and stereoselectively. Among the large number of known catalysts, complexes bearing metal centers belonging to the Platinum group have emerged during the last decades. Starting from the end of the 90s, great deal of attention has been devoted to Ru(II)-complexes, as its oxidation state can be easily stabilized by various ligands (e.g. phosphanes, amines), providing in the end highly robust and active catalytic species [5]. Moreover, compared with other so-called high-precious transition metals, ruthenium represents the best compromise between cost and catalytic efficiency. In particular, $RuCl_2(P)_2$(diamine) e $RuCl_2$(PP)(diamine) (P = phosphane, PP = diphosphane), developed by Noyori's group, are excellent catalysts for selective homogeneous hydrogenation of different ketone substrates [6]. Also, using the proper combination of chiral diphosphane and diamine is possible to perform asymmetric hydrogenation of carbonyl compounds for the production of chiral alcohols with high enantiomeric excess. Nowadays, *trans*-$RuCl_2$(BINAP) (1,2-diamine) systems under H_2 pressure are employed in the industry for the asymmetric reduction of C=O bonds [5]. Simultaneously, to avoid the risks implied with the use of high-pressure H_2, transfer hydrogenation (TH) processes employing easily accessible small molecules as hydrogen sources (e.g. ethanol [7], 2-propanol [8], glycerol [9,10] or formic acid and its salt derivatives [11]) have been developed. Thus, great efforts have been devoted to potentiate ligand and catalyst design for accessing efficient and active Ru(II)-complexes in the TH reaction [12]. On this regard, several protocols have been developed for the synthesis of Ru-based catalysts [13] containing bidentate phosphines and bidentate nitrogen ligands, bearing 2-(aminomethyl)pyridine (ampy) and their successful application in the selective reduction of the C=O functionality of ketones and aldehydes [14]. Several modifications of the ligand set around the metal

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center, by altering the ampy scaffold [15–18] and the introduction of the CO molecule on the ruthenium atom [19–21], accomplished by some of the authors have led to the obtainment of even more efficient complexes for the TH of carbonyl compounds. Moreover, when a chiral diphosphine is employed, these complexes are also able to catalyze the asymmetric reduction of carbonyl compounds to secondary alcohols with high optical purity [22,23]. Recently, Ru-phosphine complexes bearing the framework of 4-substituted-2-(aminomethyl)benzo[*h*]quinoline have been developed by Facchetti et al. [14], showing high activity in the TH of commercial-grade aldehydes, the TH being promoted by different H_2-sources, such as 2-propanol [24], formic acid/triethylamine mixtures, sodium formate and ammonium formate [25]. Remarkably, low catalyst loadings down to 0.001 mol% were reached, employing substrates and solvents not previously pre-treated or distilled [26].

TH of carbonyl compounds are usually carried out in Volatile Organic Compounds (VOCs), which present serious environmental issues. Several attempts to replace expensive and toxic media in catalytic processes have been made, for instance using biomass decomposition derivatives (e.g. 2-methyltetrahydrofuran, cyrene), supercritical carbon dioxide, perfluorinated solvents and Ionic Liquids (ILs) [27]. In this scenario, Deep Eutectic Solvents (DESs) have arisen as a feasible alternative to VOCs since 2003 [28]. DESs are usually composed by a hydrogen bond acceptor (HBA), typically an ionic compound (i.e. inorganic or organic salt) and one or more hydrogen bond donors (HBDs), e.g. polyols, carboxylic acids or amine derivatives, combined in a specific molar ratio. These mixtures show a dramatically lower melting point with respect to its single constituents. This is likely due to the peculiar structural association of the components through a thick network of hydrogen bonds. DESs possess a large number of distinctive and useful properties, e.g. nearly no vapor pressure, nonflammability, immiscibility with many organic solvents and, in most cases, they are often liquid at room temperature. In addition, compared to ILs and most VOCs, DESs are less expensive, moisture sensitive and toxic, thus showing a higher degree of environmental benignity [29]. For these reasons, they have extensively been used as reaction media for several organic transformations, namely alkylation, condensation and multicomponent [30], organometallic reactions [31–33], carbon-carbon bond formation [34] and bio-catalyzed processes [35]. In some cases, DES components have also shown to react with other molecules present in the environment, thus proving their versatility both as reaction media and reagents [30].

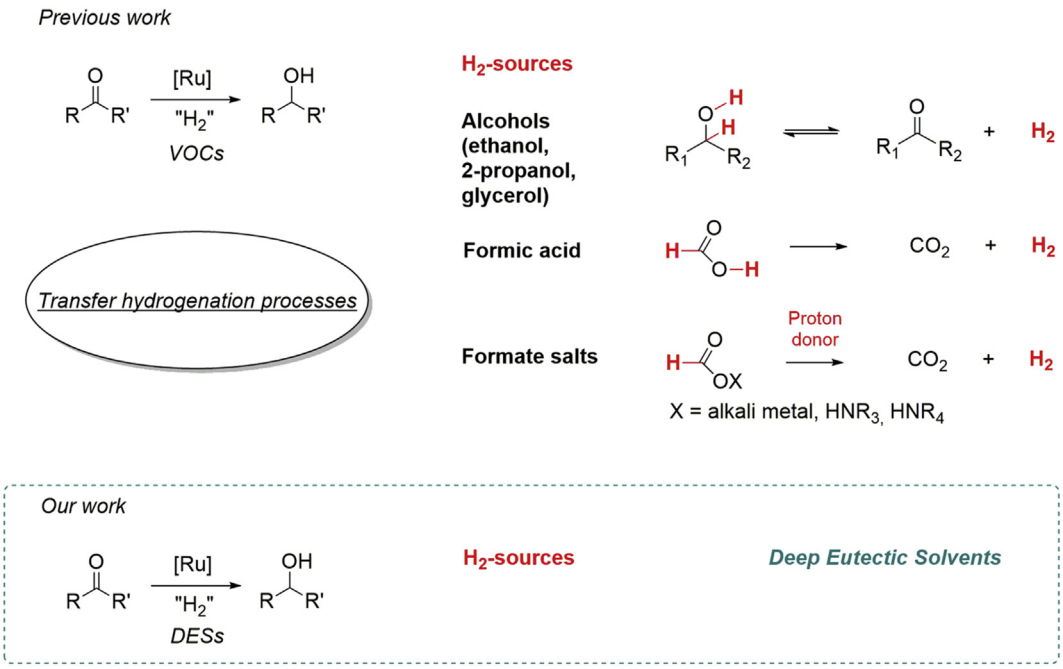
Lately, special attention has been addressed to the pursuit of sustainable catalytic reactions [36–39], and especially to transition metal mediated processes in DESs, with applications in Pd-catalyzed cross-coupling [40], Cu-catalyzed Ullmann type [41], Ru-catalyzed redox isomerization [42] and metathesis reactions [43] It is worth mentioning that García-Álvarez and co-workers performed a cascade Ru(IV)-catalyzed isomerization of allylic alcohols and asymmetric bio-TH catalyzed KRED enzymes, in buffered cholinium chloride-based DESs [44]. Notwithstanding the elegance of the concurrent reactions, the procedure entails the use of the expensive $NADP^+$, which has to be continuously converted into the actual H_2-source NADPH by dehydrogenation of 2-propanol into acetone during the process. During the last two decades, the synthesis and characterization of DESs containing molecules which in principle can work as H_2-donors in transition metal catalyzed processes, e.g. glycerol and formic acid, has witnessed a significant boost, however their use as such has been neglected so far. As a matter of fact, *no reports* of transition metal catalyzed TH of carbonyl compounds in DESs acting as media or H_2-donors in in homogeneous conditions are present in the literature.

Intrigued by this lack of information on the subject and, given our experience in ruthenium catalyzed processes [13] and DES synthesis [45,46] and applications [32–34], we envisaged the possibility to investigate the Ru(II)-catalyzed TH of commercial-grade carbonyl compounds to their corresponding alcohols in DESs which could behave both as reaction media and H_2-donors (Scheme 1).

2. Results and discussion

Combinations of easily accessible Ru(II)-complexes and ligands were screened in order to explore the catalytic performances in the selected DES. All the DESs employed in this study have been chosen among those in which at least one of the components can in principle act as H_2-donor molecule (Table 1), i.e. the cholinium ion and glycerol for DES-1 and DES-3, the cholinium fragment for DES-2 and formic acid for DES-5. Regarding DES-4, all its components could behave as H_2-sources (see Scheme 1). Also, they are all liquids at room temperature (Table 1). The aforementioned compounds could be activated by Ru(II)-complexes in the presence of a base [8]. The Ru(II) pre-catalysts **1**–**4** (Fig. 1) were chosen based on their structural simplicity and easy availability. The catalytic TH reactions were performed using acetophenone as a model substrate (Scheme 2).

Initially, DES-1 was tested with Ru(II)-complexes **1**–**4** in the TH of acetophenone, using KOH as a strong base to promote the TH. No significant conversion was attained at different temperatures (40–100 °C, Table 2, entries 1–4). When pre-catalyst **4** was combined in situ with the robust diphosphane ligand dppf at 100 °C, 20% of 1-phenylethanol was attained after 24 h (Table 2, entry 5), suggesting a crucial effect of the presence of the dppf ligand for the catalysis. Since system **4**/dppf showed partial conversion, it was tested with DES-2 and -3, having in common either ChCl or Gly as H_2-sources with DES-1. Unfortunately, also in these cases, the TH did not occur after several hours even at high temperatures, (Table 2, entries 6–8). As regards DES-4, bearing HCOOH as H_2-source, no conversion was attained at 40 °C with **4** (Table 2, entry 9), whereas system **4**/dppf (1/2, 0.03/0.06 eq.), afforded only partial formation (16%) of 1-phenylethanol (Table 2, entry 10). Since the generation of reduction equivalents from HCOOH usually requires weaker bases than the C–H activation of alcohols, the TH was carried out in the presence of triethylamine (NEt_3) [48]. Employing analogous conditions, bifunctional type catalyst **3** gave poor conversion (15%) after several hours (Table 2, entry 11). The conversion dramatically increased in DES-5 using **4** (0.03 eq.) as pre-catalyst (50% after 16 h at 60 °C, entry 12), suggesting a better compatibility of **4** with DES-5 system with respect to DES-4. On the other hand, we observed that in DES-5 the consumption of HCOOH and the accumulation of the remaining TBABr (mp = 103 °C) led to a heterogenous system, which could present reproducibility issues. In this case, the use of an additive to homogenize the system was required for maintaining mild reaction conditions. The partner of choice was cyclopentyl methyl ether (CPME), due to its higher biocompatibility [49] and stability [50] with respect to other ethereal media, such as tetrahydrofuran (THF) and 2-methylTHF. Then, with the aim to improve the catalytic activity, the effect of additional diphosphine ligands which could stabilize **4** in the DES environment was studied. Low or no appreciable conversions were achieved combining **4** (0.03 eq.) with the bidentate ligands (0.03 eq.) dppe (31%), dppp (36%) and dppb (0%) (Table 2, entries 13–15), as with highly rigid Xantphos (0.03 eq.), attaining only 14% of alcohol product (Table 2, entry 16). More satisfying results were obtained with dppf (0.03 eq.), reaching 60% conversion in 16 h (Table 2, entry 19). By increasing the catalyst loading (**4**/dppf = 1/1, 0.05 eq.) and the amount of H_2-source (7 eq.), 92% of 1-phenylethanol was attained in 12 h (Table 2, entry 18). In order to understand the role of the diphosphine ligand, acetophenone was



Scheme 1. Ru-catalyzed Transfer Hydrogenation of carbonyl compounds promoted by (a) "classical" H_2-sources; (b) Deep Eutectic Solvents as H_2-sources.

Table 1
Selected DESs for this study.

DES	HBA[a]	HBD1[b]	HBD2[b]	HBA/HBD/1/HBD2[c]	m.p. (°C)
DES-1	ChCl	Gly	–	1/2/0	− 40 [47]
DES-2	ChCl	Urea	–	1/2/0	12 [28]
DES-3	TBABr	Gly		1/1/0	Not reported[d]
DES-4	ChCl	HCOOH	Gly	1/1/1	Not reported[d]
DES-5	TBABr	HCOOH	–	1/1/0	Not reported[d]

[a] Hydrogen bond acceptor: ChCl = cholinium chloride, TBABr = tetrabutylammonium bromide.
[b] Gly = glycerol.
[c] Molar ratio.
[d] Liquid at 25 °C.

subjected to the TH using **4**/dppf = 1/2, 0.05/0.10 eq. Interestingly, doubling the amount of dppf negatively affected the catalytic activity, achieving only 60% of conversion (Table 2, entry 19). Since the presence of oxygen may be deleterious for the Ru(II)-hydride species involved in the TH, especially over prolonged reaction times, the TH was carried out under N_2 atmosphere, after careful degassing DES-5. Curiously, under inert atmosphere the conversion was 87%, in line with the data obtained under open air conditions (Table 2, entry 20). As a matter of comparison we also briefly investigated Ru(II) systems **1**–**4** and DES-1–2 as media, performing the THs using external H_2-sources, such as HCOOH/NEt_3 mixtures. Low or no appreciable conversion of acetophenone was attained with all the H_2-donors employed (see supplementary data, Table S2).

It is worth pointing out that the system $RuCl_2$(ampy)(dppb) **3**, which has proven to be a highly active pre-catalyst in the TH of carbonyl compounds in basic 2-propanol [14], is unable to mediate the TH in all cases, hinting that a detrimental impact of the DESs on the catalytic system occurred. This fact may be ascribed to the action of the DES system towards **3**, which could trap the complex within its network, through the strong hydrogen bonding interactions with the amine portion around the ruthenium center. On the other hand, the less active Ru(II)-diphosphane complexes

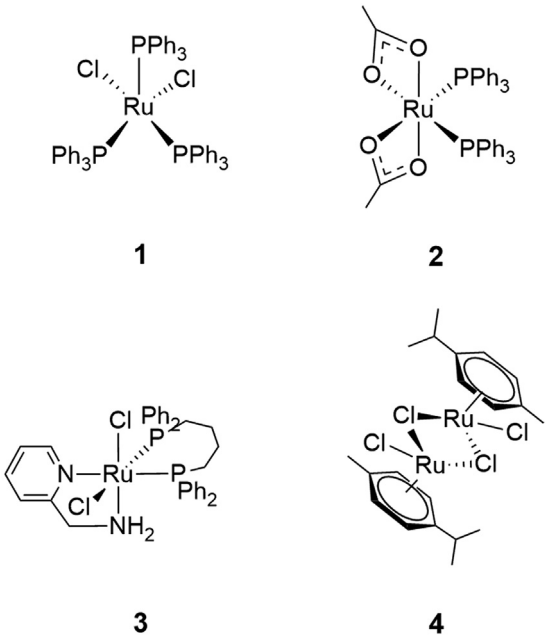
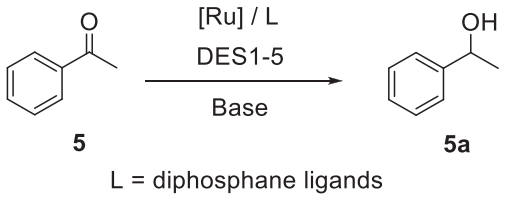


Fig. 1. Structures of the Ru(II)-complexes employed in this work.



Scheme 2. TH of acetophenone **5** catalyzed by ruthenium complexes **1**–**4**.

Table 2
Screening of the reaction conditions for the TH of **5** to **5a** using DESs as H_2-sources.

Entry	[Ru]/eq.	Ligand/eq.[a]	H_2 source	Base/eq.	Additive	T (°C)	Time (h)	Conv. (%)[b]
1	**1**/0.03	–	DES-1	KOH/0.3	–	100	24	2
2	**2**/0.03	–	DES-1	KOH/0.3	–	100	24	0
3	**3**/0.03	–	DES-1	KOH/0.3	–	100	24	0
4	**4**/0.03	–	DES-1	KOH/0.3	–	100	24	2
5	**4**/0.03	Dppf/0.06	DES-1	KOH/0.3	–	100	24	20
6	**4**/0.03	Dppf/0.06	DES-2	KOH/0.3	–	60	24	0
7	**4**/0.03	Dppf/0.06	DES-2	KOH/0.3	–	80	24	0
8	**4**/0.03	Dppf/0.06	DES-3	KOH/0.3	–	100	24	2
9	**4**/0.03	–	DES-4	NEt_3/3.3[c]	–	40	24	0
10	**4**/0.03	Dppf/0.06	DES-4	NEt_3/3.3[c]	–	40	24	16
11	**3**/0.03	–	DES-5	NEt_3/3.3[c]	–	60	20	15
12	**4**/0.03	–	DES-5	NEt_3/3.3[c]	–	60	16	50
13	**4**/0.03	Dppe/0.03	DES-5	NEt_3/3.3[c]	CPME[d]	60	16	31
14	**4**/0.03	Dppp/0.03	DES-5	NEt_3/3.3[c]	CPME[d]	60	16	36
15	**4**/0.03	Dppb/0.03	DES-5	NEt_3/3.3[c]	CPME[d]	60	16	0
16	**4**/0.03	Xantphos/0.06	DES-5	NEt_3/3.3[c]	CPME[d]	60	16	14
17	**4**/0.03	Dppf/0.03	DES-5	NEt_3/3.3[c]	CPME[d]	60	16	60
18	**4/0.05**	**Dppf/0.05**	**DES-5**	**NEt_3/7[c]**	**CPME[d]**	**60**	**12**	**90**
19	**4**/0.05	Dppf/0.10	DES-5	NEt_3/7[c]	CPME[d]	60	16	60
20[e]	**4**/0.05	Dppf/0.05	DES-5	NEt_3/7[c]	CPME[d]	60	12	87

[a] dppe = 1,2-bis(diphenylphosphino)ethane; dppp = 1,3-bis(diphenylphosphino)propane; dppb = 1,4-bis(diphenylphosphino)butane; dppf = 1,1′-ferrocenediyl-bis(diphenylphosphine)ferrocene; Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.
[b] Conversion was determined by GC-MS or NMR analysis.
[c] Triethylamine (NEt_3) was added in 1/1 molar ratio with respect to the DES employed.
[d] CPME = cyclopentyl methyl ether was used in 1/1 ratio (V/V) with respect to DES-5.
[e] Reaction performed under N_2 atmosphere, after carefully degassing DES-5.

resulted much more efficient in DES-5 than in VOCs.

In order to inspect the impact of the eutectic mixture in the reaction, the TH of acetophenone was carried out under the same reaction conditions using a freshly prepared mixture of HCOOH/NEt_3 = 1/1 (7 eq.) in CPME, 2-MeTHF and toluene in the absence of DES-5, obtaining no appreciable conversion in all cases after 8 h (Table 3, entries 1, 2 and 3, respectively). Moreover, when HCOOH and TBABr (1/1) in CPME were reacted with an equimolar amount of NEt_3 in the presence of **4**/dppf, no significant transformation of acetophenone to 1-phenylethanol was achieved (Table 3, entry 4), strongly indicating that the employment of the eutectic mixture TBABr/HCOOH resulted in a non-innocent effect in the TH process with respect to the simple "blending" of the two components.

The base appeared to be an important parameter in the TH process. In our attempt to evaluate its influence on the catalytic system, different amounts and types of organic and inorganic bases were then tested (Table 4). Initially, decreasing the amount of NEt_3 with respect to DES-5 to a 1/2 ratio (*cf.* Table 1, entry 18), no transformation occurred under the usual reaction conditions (Table 4, entry 1). When 0.2 and 0.5 eq. of the strong base KOH were employed, 42 and 78% conversions were observed (Table 4, entries 2 and 3, respectively), whereas increasing its amount to 1 and 7 eq., the catalytic activity was dramatically reduced (14 and 28% of 1-phenylethanol, entries 4 and 5, respectively). Poor conversion (30%) was also obtained employing the strong organic base DBU (Table 4, entry 6), whereas no transformation was attained when the TH was performed in the absence of a base (Table 4, entry 7), revealing that the presence of NEt_3 was mandatory for achieving significant catalytic activity in the DES environment.

With the aim to prove the feasibility of the best system found, entailing the combination **4**/dppf in 1/1 molar ratio (Table 1, entry 20), the corresponding pre-formed complex was then synthesized, by reacting **4** with dppf (1/1) in CPME at 80 °C and isolating after 3 h

Table 4
TH of **5** to **5a** catalyzed by system **4**/dppf (1/1, 0.05 eq.) in DES-5 (7 eq.) at 60 °C after 16 h (CPME as the addtive): the effect of the base.

Entry[a]	Base/eq.	Conv. (%)[b]
1	NEt_3/3.5[c]	0
2	KOH/0.2	42
3	KOH/0.5	78
4	KOH/1.0	14
5	KOH/7.0	28
6	DBU/7.0[d]	30
7	None	0

[a] Reaction performed employing CPME in 1/1 ratio (V/V) with respect to DES-5.
[b] Conversion was determined by NMR analysis.
[c] Triethylamine (NEt_3) was added in 1/2 molar ratio with respect to DES-5.
[d] DBU = 1,5-diazabiciclo[5.4.0]undec-7-ene, added in 1/1 molar ratio with respect to DES-5.

Table 3
TH of **5** to **5a** catalyzed by system **4**/dppf in different VOCs at 60 °C after 10 h.

Entry	[Ru]/eq.	Ligand/eq.	H_2 source	Base/eq.	Solvent	Conv. (%)[a]
1[b]	**4**/0.05	Dppf/0.10	HCOOH/NEt_3[c]	–	CPME	0
2[b]	**4**/0.05	Dppf/0.10	HCOOH/NEt_3[c]	–	2-MeTHF	0
3[b]	**4**/0.05	Dppf/0.10	HCOOH/NEt_3[c]	–	Toluene	0
4	**4**/0.05	Dppf/0.05	HCOOH + TBABr[d]	NEt_3/7[e]	CPME	3

[a] Conversion was determined by NMR analysis.
[b] Reaction performed under N_2 atmosphere, after carefully degassing the selected solvent.
[c] A freshly prepared mixture of HCOOH/NEt_3 = 1/1 (7 eq.) was used.
[d] An equimolar mixture of HCOOH/TBABr in CPME was used in place of DES-5.
[e] Triethylamine (NEt_3) was added in 1/1 molar ratio with respect to the H_2-source employed.

the diphosphine-bridged complex [$RuCl_2$(*p*-cymene)$_2$-*μ*-dppf] **6** [51] by filtration in very good yield (90%). Readily synthesized **6** was then employed to further refine the reaction conditions (Table 4).

When the amount of **6** was reduced to 0.03 and 0.04 eq., the conversion decreased to 47 and 53% (Table 5, entries 1 and 2, respectively). Also, the reaction temperature plays a crucial role. At 40 °C, with 0.05 eq. of **6**, TH of acetophenone only reaches 68% conversion in 20 h (Table 5, entry 3)). At 60 °C, 60% of conversion is obtained in 4 h (Table 5, entry 4), and 92% in 8 h in good yield (84%), showing that the pre-formed complex **6** give comparable catalytic performances with respect to in situ system **4**/dppf (*cf.* Table 1, entry 18). Also, the DES/substrate and NEt_3/substrate ratios revealed to be crucial for the outcome of the reaction, reaching the best result when equal to 7/1 (corresponding to a NEt_3/DES = 1/1 m ratio).

In addition, further investigations were performed for better understanding the catalytic behaviour of **6** within the DES-5/NEt_3 system. When DES-5, CPME, **6** and NEt_3 were heated at 60 °C for 6 h, a change in the physical state of the biphasic system was observed together with a vigorous gas evolution (likely CO_2), leading to a heterogenous dispersion (likely TBABr) in CPME (Scheme 3a). After addition of acetophenone, the TH resulted in the recovery of the unreacted starting material, hinting that HCOOH was previously decomposed by the catalytically active Ru(II)-species. On the other hand, maintaining DES-5, CPME and NEt_3 under the same conditions and then adding acetophenone and **6** to the clear biphasic system, the final mixture was obtained with 90% conversion (Scheme 3b), suggesting a moderate robustness of the system DES-5/NEt_3 and that the base has no detrimental effect on DES-5 in the absence of the catalyst.

With these results in our hands, our attention was then devoted to broaden the scope of the reaction, applying the setup procedure to a series of different ketones (Scheme 4), containing diverse functional groups, i.e. alkyl moieties, aryl bearing electron-withdrawing and electron-donating groups and heterocycles (Table 6).

The alkyl-alkyl ketones 2-decanone **7** and cyclohexanone **8** were reduced to 2-decanol **7a** and cyclohexanol **8a** respectively, with 66 and 100% conversion (Table 6, entries 1 and 2). The conversion of alkyl-aryl ketones was very high in the case of 1-(3-bromophenyl) ethan-1-one **9** and 4-acetylbenzonitrile **10** (Table 6, entries 2 and 3) to 1-(3-bromophenyl)ethan-1-ol **9a** and 4-(1-hydroxyethyl)benzonitrile **10a**, respectively. It is worth pointing out that system **6**/DES-5 resulted chemoselective towards hydrogenolysis of the relatively weak carbon-bromine bond. The TH of **10** occurred with complete consumption of the starting material, although not totally chemoselective, likely due to the reduction of the cyano functionality. Unfortunately, the presence of an unidentified alcohol side product was detected, as inferred from NMR measurements (see Supplementary material). High conversion was attained in the TH of 1-indanone (2,3-dihydro-1*H*-inden-1-one) **11** to the corresponding alcohol **11a** (84%) under the same reaction conditions. The TH of benzophenone **12** afforded 74% conversion after 16 h at 60 °C (Table 6, entry 6). It is interesting to notice that the reduction of **12**, in the same conditions, gave 60% of conversion in only 6 h, suggesting that catalyst deactivation occurred slowly (Table 6, entry 6). When 4-nitrobenzophenone **13** was subjected to the TH under the same reaction conditions, total consumption of the starting ketone was observed in 16 h. Unfortunately, the reaction in this case was not totally chemoselective, as the NO_2 group was reduced to NH_2. NMR analysis of the crude showed a mixture of 4-nitrodiphenylmethanol **13a** (67%) and 4-aminobenzophenone **13b** (28%) and 4-aminodiphenylmethanol **13c** (5%) (Table 6, entry 7). The unusual high amount of **13b** was unexpected, as Ru(II)-complexes have been reported to be more selective towards the C═O moiety with respect to NO_2 functionality [11]. In fact, only very recently, efficient reduction of nitro to amino group mediated by half-sandwich Ru(II)−NHC complexes in the presence of ammonia borane adduct as H_2-source has been reported [52]. The reduction of enones was also performed, to test the selectivity of the system for the carbonyl group in the presence of a conjugated carbon-carbon double bond. Cyclohex-2-en-1-one **14** is totally reduced both at the C═C and at the C═O moieties (Table 6, entry 8) to **8a**, as already observed for analogous substrates in Ru(II)-catalyzed TH [53], while the TH of benzylideneacetone (4-phenylbut-3-en-2-one) **15** showed 93% conversion, giving a mixture of three products, i.e. 4-phenylbut-3-en-2-ol **15a** (19%), 4-phenylbutan-2-ol, **15b** (51%) and 4-phenylbutan-2-one **15c** (30%) (Table 6, entry 9). These results indicate that a concurrent Ru-promoted redox isomerization of the allylic alcohol product firstly formed to the C−C saturated ketone may occur, leading to the total reduction product eventually (Scheme 5a). On the other hand, the extension of the conjugated system led to an enhancement of the selectivity towards the carbon-carbon double bond formal reduction: in the case of dibenzylideneacetone **16**, the major product was the saturated carbonyl compound (Table 4, entry 10) in which both the C═C moieties resulted hydrogenated (Scheme 5b). Unfortunately, the TH of 2-acetylpyridine and 4-acetylpyridine was unsuccessful and no conversion was observed at 40 °C, with 0.05 eq. of **6** after 4 h (Table 6, entries 11 and 12). This fact can be ascribed to the strong coordinating ability of the pyridine substrates, which probably forms a relatively stable complex with the Ru-species present in the reaction environment, preventing the catalyst to react in the catalytic cycle.

The recovery of the products generally ranged from moderate to excellent, showing clean crude mixtures in all cases, as inferred from NMR analyses (see supplementary data). Poor recovery of the alcohol product only in the TH of 4-acetylbenzonitrile, likely due to concurrent reduction/hydrolysis processes.

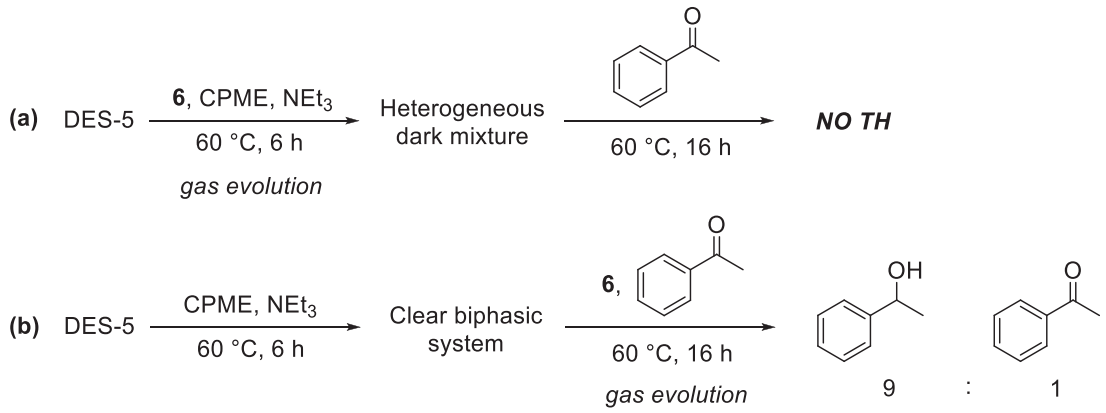
Encouraged by the results obtained for the TH of ketone substrates, we then turned our attention to the reduction of aldehydes to their corresponding alcohols, considered the greater electrophilicity of aldehydes (Scheme 6), thus we expected both the catalytic system to be more active and to need lower catalyst loadings and to apply milder reaction conditions for the TH to occur.

The TH of citronellal **19** attained 100% of conversion with 0.01 eq. of **6** after 6 h (Table 7, entry 1), as well as the reduction of benzaldehyde **20** under the same reaction conditions (Table 7, entry 2). The TH of terephthalaldehyde **21** gave total conversion, affording a mixture of monoalcohol/dialcohol in about 1/1 ratio after 6 h, whereas extending the reaction time to 15 h, double reduction to 1,4-phenylenedimethanol **21a** was observed (Table 7, entry 3). The TH of *p*-methoxybenzaldehyde **22** employing 0.05 eq. of **6**, after 16 h, at 60 °C attained complete conversion, as well as vanillin **23** was totally transformed into vanillyl alcohol **23a** under the same reaction conditions (Table 7, entries 4 and 5). It is worth pointing

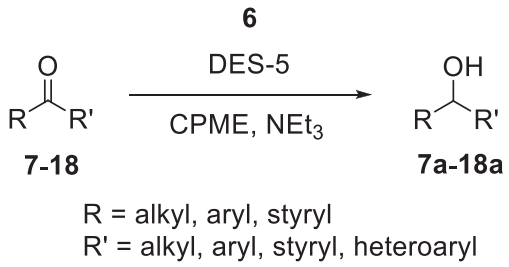
Table 5
Optimization of the loading percentage of [$RuCl_2$(*p*-cymene)$_2$-*μ*-dppf] **6**, reaction temperature and time in DES-5 (7 eq.), NEt_3 (7 eq.) as base and CPME as the additive, in the TH of **5** to **5a**.

Entry	Eq. [Ru]	Temperature (°C)	Time (h)	Conversion (%)[a]
1	0.03	60	20	47
2	0.04	60	20	53
3	0.05	40	20	68
4	0.05	60	4	60
5	0.05	60	8	92 (84)[b]

[a] The conversion was determined by NMR analysis.
[b] Internal yield was determined by ^{1}H NMR spectroscopy.



Scheme 3. TH of acetophenone in DES-5 after pre-heating of the system with (a) and without (b) complex **6**.



Scheme 4. TH of ketones catalyzed by **6** in the presence of DES-5.

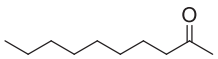
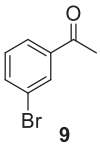
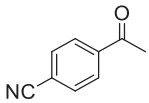
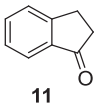
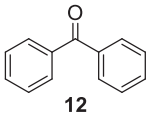
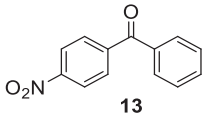
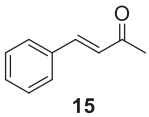
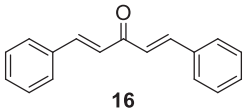
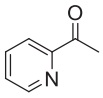
out that the reduction of **23** by means of ruthenium catalyzed TH is not an easy goal to be achieved. Up to date, only one example of Ru-catalyzed TH of **23** has been reported [54]. Strangely, 4-(dimethylamino)benzaldehyde **24** resulted in the recovery of the unreacted starting material after 19 h, suggesting that the substrate may poison the catalytically active species. In fact, no examples are present in the literature reporting an inhibited catalytic activity of Ru(II)-complexes in the presence of aminoaldehydes. On the contrary, when bearing electron-withdrawing groups such as nitro, cyano and acetyl groups with respect to the carbonyl, the reduction proceeded with total conversion of the substrates (Table 7, entries 7, 8 and 9, respectively). The reduction of 4-nitrobenzaldehyde **25**, 4-formylbenzonitrile **26** and 3-acetylbenzaldehyde **27** to their corresponding alcohols occurred from moderate to high chemoselectivity of the catalytic system towards the carbonyl moiety. Nitro and cyano functionalities resulted unchanged by the TH (Table 7, entries 7 and 8), indicating that the lack of chemoselectivity observed for ketone substrates may be caused by the higher temperatures employed (*cf.* 4-acetylbenzonitrile and 4-nitrobenzophenone, Table 6, entries 4 and 6), whereas **27** underwent partial reduction of the ketone moiety (Table 7, entry 9). The alicyclic enal (1*R*)-(−)-myrtenal **28** gave a mixture of products differently reduced at the carbon-carbon double bond and at the carbonyl moieties in a 15/85 ratio (Table 7, entry 10). We observed a similar lack of selectivity on (*E*)-α-methylcinnamaldehyde **29** (Table 7, entry 11), obtaining a mixture of 2-methyl-3-phenylprop-2-en-1-ol **29a** and 2-methyl-3-phenylpropan-1-ol **29b** with 4/1 ratio, respectively, as inferred from NMR measurements. As already pointed out for ketone substrates (Table 6, entries 9–10), this is probably due to an isomerization process occurring after the TH on the C=O functionality took place (Scheme 5a). The preferential reduction of the aldehyde C=O over the conjugated C=C functionality was previously disclosed by some of the authors in the Ru(II)-catalyzed TH promoted by ammonium formate [25]. We finally investigated the feasibility of the reaction in the presence of different heterocyclic substituents. The catalytic system was also effective in the reduction of five membered-ring heterocycles. 2-Furfural **30** and 5-HMF (5-(hydroxymethyl)furan-2-carbaldehyde) **31** were efficiently transformed into 2-furfurol **30a** and (furan-2,5-diyl)dimethanol **31a**, respectively, with 0.025 eq. of **6**, at 40 °C after 6 h (Table 7, entries 12 and 13, respectively). Also, the TH 1-methylpyrrole-2-carbaldehyde **32** to (1-methylpyrrol-2-yl)methanol **32a** occurred in 16 h (Table 7, entry 14), under the same reaction conditions, as well as for thiophene-2-carbaldehyde **33** (Table 7, entry 15). Unfortunately, the TH of pyridine-2-carbaldehyde **34** and pyridine-4-carbaldehyde **35**, instead, attained no transformation to the corresponding alcohols (Table 7, entries 16 and 17, respectively). The reason may be likely the same as for the pyridyl ketones (vide infra and *cf.* Table 6, entries 11 and 12). Similarly for the ketone substrates, all the alcohol products were collected from low to excellent yields, showing remarkably clean crude mixtures in all cases, as inferred from NMR analyses (see Supplementary data). In some cases low amounts of the expected alcohols were achieved with hydrolysable (Table 7, entry 8) or highly polar (Table 7, entries 3, 9 and 13) products, suggesting that the methodology may need some refinments for enhancing the recovery of the carbinols.

Finally, to test the ability of the catalytic system on different carbon-heteroatom unsaturations, the TH of *N*,2-diphenylethane-1-imine **36** to *N*-benzylaniline and (*E*)-*N*,1-diphenylethan-1-imine **37** was also tested, achieving 99 and 52% of conversion, respectively, in 18 h at 60 °C (0.05 eq. of **6**, Scheme 7).

3. Conclusions

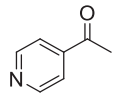
This work reports on the study of the Ru(II)-catalyzed TH of carbonyl substrates to their corresponding alcohols in DESs used both as media and as H_2-source under mild conditions (40–60 °C). The methodology is new, straightforward and simple and proceeds smoothly with commercial-grade substrates and solvents in open air, without the use of inert gases or the need for further purification of the reactants and the solvents. Our study demonstrated that the easily achievable complex [$RuCl_2$(*p*-cymene)$_2$-*μ*-dppf] was able to efficiently catalyze the TH of several carbonyl substrates, in the presence of the eutectic mixture TBABr/HCOOH and of triethylamine as the base, obtaining in most cases total conversions and clean crude mixtures. The TH process required an additive in order to maintain the system homogeneous under mild conditions. Notably, eco-friendly CPME was found to be the best partner of choice. As expected, aldehydes showed higher reactivity than ketones, which needed harsher reaction conditions to reach elevated

Table 6
Reduction of ketone substrates to their corresponding alcohols catalyzed by **6** (0.05 eq.) in DES-5, NEt_3 (7 eq., 1/1 with respect to DES-5) as base and CPME as the additive, at 60 °C.

Entry	Ketone	Time [h]	Conversion (%)[a]
1	 **7**	16 16	66 87 (57)[b]
2	 **8**	16	100 (48)
3	 **9**	16	97 (89)
4	 **10**	16	100 (28)[c]
5	 **11**	16	84 (67)
6	 **12**	6 16	60 74 (72)
7	 **13**	16	>99[d]
8	 **14**	16	100 (98)[e]
9	 **15**	10	94[f]
10	 **16**	16	>99[g]
11[h]	 **17**	4	0

(*continued on next page*)

Table 6 (*continued*)

Entry	Ketone	Time [h]	Conversion (%)[a]
12[h]	 **18**	4	0

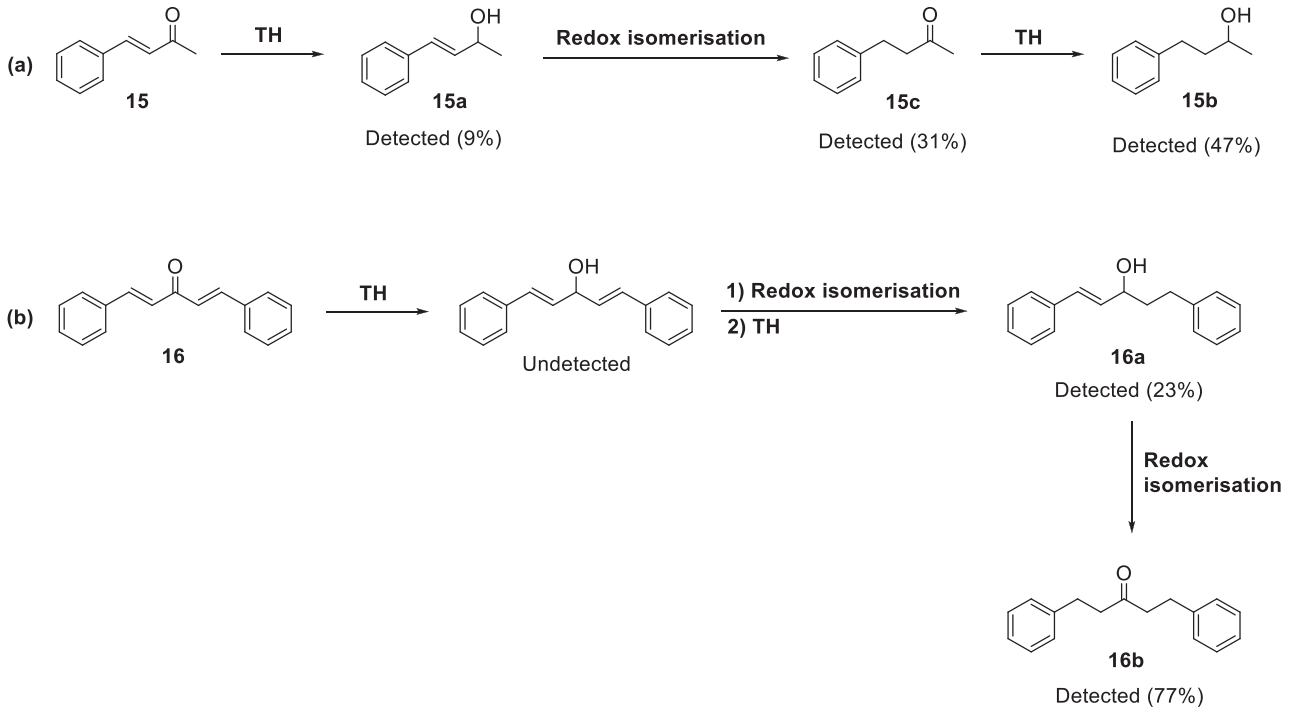
[a] Conversion and internal yield (i.y.) in parentheses were determined by ^{1}H NMR spectroscopy (see Supplementary material for details).
[b] Reaction performed at 80 °C.
[c] Two products were observed: 4-(1-hydroxyethyl)benzonitrile as the main product and an unidentified side product.
[d] Three products were observed: 4-nitrodiphenylmethanol **13a** (38% i.y.), 4-aminobenzophenone **13b** (10% i.y.) and 4-aminodiphenylmethanol **13c** (1% i.y.).
[e] Total reduction of both the C=C and C=O bonds was observed.
[f] Three main products were observed: 4-phenylbutan-2-ol **15b** (47% i.y.), 4-phenylbutan-2-one **15c** (31% i.y.) and 4-phenylbut-3-en-2-ol **15a** (9% i.y.).
[g] Two main products were observed: 1,5-diphenylpentan-3-one **16b** (77% i.y.) and 1,5-diphenylpent-1-en-3-ol **16a** (23% i.y.).
[h] Reaction performed at 40 °C.

conversions to their corresponding alcohols. In general, excellent chemoselectivities were achieved towards the bromo-arene and isolated olefin functionalities, whereas less tolerability was attained towards nitro and cyano groups, especially in the case of ketone substrates. The reduction of the latters appears to be a slower competitive reaction compared to the C=O reduction, usually observed when the TH was carried out at higher temperatures and over long reaction times. α,β-unsaturated carbonyl substrates showed very good conversions but poor chemoselectivies, due to the formal reduction of the conjugated C=C bond. Notably, vanillin was efficiently reduced to vanillyl alcohol with a good recovery of the product, which is not a trivial process to occur in homogenous conditions. Also, imine derivatives were tested, the TH being effective only with the aldimine substrate to its corresponding amine derivative, whereas the ketimine functionality showed modest reactivity towards the hydrogenative system employed. Remarkably, the highly active bifunctional catalysts employed in the TH of carbonyl substrates in VOCs, such as $RuCl_2$(diphosphine)(ampy), are not active in DESs, whereas the use of cheaper (half-sandwich)$RuCl_2$(PP) complexes is very efficient as catalytic system. Moreover, the outcomes obtained strongly indicate a non-innocent impact of the eutectic system TBABr/HCOOH on the Ru(II)-catalyzed TH with respect to the employment of a mere solution of their components, which has not previously been described. Finally, this work introduces for the first time the concept of employing DESs as H_2-sources for transition metal catalyzed reductive reactions, opening a window on the assessment of alternative procedures for hydrogenative processes in non-conventional media. Further investigations on the ensemble Ru(II)/DES are in progress in order to better understand the system for its employment in different organic transformations.

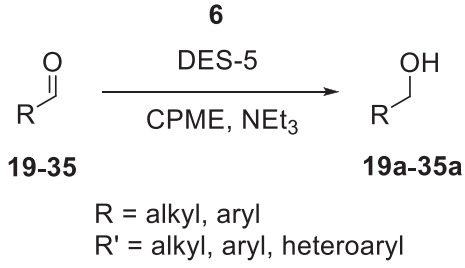
4. Experimental section

4.1. General procedure for the catalytic TH of carbonyl compounds and imines

The selected substrate (0.2–1.0 mmol, 1 eq), [$RuCl_2$(*p*-cymene)$\}_2$-μ-dppf] (**6**) (0.002–0.01 mmol, 0,01–0,05 eq, 2.3–58.3 mg), NEt_3 (1.4–8.6 mmol, 0.2–1.2 mL) and CPME (0.5–1.5 mL) were transferred into a 4 mL vial. The mixture was heated at the selected temperature (40–80 °C) under stirring for ca. 15 min and finally the DES-5 (0.45–1.7 mL) was added. After the addition of the DES, the vial was put into the oil bath and the Teflon® cap pierced with a



Scheme 5. Possible reaction pathways in the TH of **15** (a) and **16** (b).



Scheme 6. TH of aldehydes catalyzed by **6** in the presence of DES-5.

needle to help the emission of the CO_2 produced. The reaction was then leaved to react at the selected temperature from 2 to 24 h, depending on the substrate. The reaction mixture was worked taken up with water (1.5 mL) and extracted with diethyl ether (4 × 1.5 mL), then the combined organic layers washed with brine (1.5 mL). The organic phase was then separated, dried over Na_2SO_4 and filtered. The solvent was removed and the crude was analysed by ^1H and, when pure products were afforded, by ^{13}C NMR spectroscopy.

4.2. NMR data for the TH of ketones

Mixture of 1-phenylethan-1-ol (5a) and acetophenone (5): 92% conversion, 84% yield. ^1H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.50 (d, *J* = 6.5 Hz, 3H, **5a**), 1.97 (br s, 1H, **5a**), 2.61 (s, 3H, **5**), 4.90 (q, *J* = 6.5 Hz, 1H, **5a**), 7.25–7.30 (m, 1H, **5a**), 7.33–7.40 (m, 4H, **5a**), 7.45–7.50 (m, 2H, **5**), 7.55–7.59 (m, 1H, **5**), 7.95–7.98 (m, 2H, **5**).

Mixture of decan-2-ol (7a) and decan-2-one (7): 87% conversion, 57% yield. ^1H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 0.86 (t, *J* = 7.0 Hz, 3H, **7**) superimposed to 0.87 (t, *J* = 7.0 Hz, 3H, **7a**), 1.17 (d, *J* = 6.2 Hz, 3H, **7a**), 1.21–1.34 (m, 22H, **7a** + **7**), 1.34–1.52 (m, 5H, **7a** + **7**), 2.12 (s, 3H, **7**), 2.40 (t, *J* = 7.5 Hz, 2H, **7**), 3.74–3.81 (m, 1H, **7a**).

Cyclohexanol (8a): 100% conversion, 48% yield. ^1H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.22–1.33 (m, 5H), 1.40 (br s, 1H), 1.51–1.57 (m, 1H), 1.70–1.77 (m, 2H), 1.85–1.93 (m, 2H), 3.55–3.69 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ = 24.3, 25.6, 35.7, 70.5.

1-(3-bromophenyl)ethan-1-ol (9a): 97% conversion, 89% yield. ^1H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.47 (d, *J* = 6.5 Hz, 3H), 2.11 (br s, 1H), 4.85 (q, *J* = 6.5 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.26–7.27 (m, 1H), 7.37–7.39 (m, 1H), 7.50–7.55 (m, 1H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, 25 °C): δ = 25.4, 69.8, 122.7, 124.1, 128.7, 130.2, 130.5, 148.3.

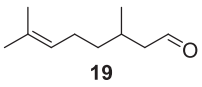
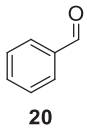
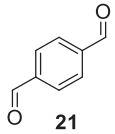
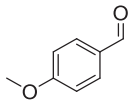
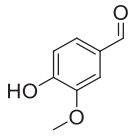
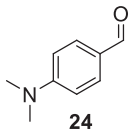
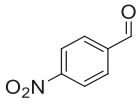
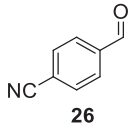
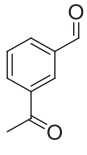
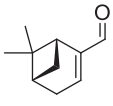
4-(1-hydroxyethyl)benzonitrile (10a): 100% conversion (**10a** + unidentified side product), 28% yield (**10a**). ^1H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.48 (d, *J* = 6.5 Hz, 3H), 2.40 (br s, 1H), 4.94 (q, *J* = 6.5 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 2H).

Mixture of indan-1-ol (11a) and indan-1-one (11): 84% conversion, 67% yield. ^1H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.90–1.98 (m, 1H, **11a**), 2.04 (br s, 1H, **11a**) 2.49 (dddd, *J* = 13.1, 8.3, 6.9, 4.7 Hz, 1H, **11a**), 2.68–2.72 (m, 2H, **11**), 2.79–2.87 (m, 1H, **11a**), 3.06 (ddd, *J* = 16.0, 8.6, 4.7 Hz, 1H, **11a**), 3.13–3.17 (m, 2H, **11**), 5.20–5.26 (m, 1H, **11a**), 7.22–7.30 (m, 3H, **11a**), 7.38 (t, *J* = 7.2 Hz, 1, **11**), 7.42 (d, *J* = 6.6 Hz, 1H, **11a**), 7.49 (d, *J* = 7.7 Hz, 1H, **11**), 7.60 (td, *J* = 7.4, 1.2 Hz, 1H, **11**), 7.77 (d, *J* = 7.7 Hz, 1H, **11**).

Mixture of diphenylmethanol (12a) and benzophenone (12): 74% conversion, 72% yield**.** ^1H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 2.48 (br s, 1H, **12a**), 5.84 (s, 1H, **12a**), 7.24–7.29 (m, 2H, **12a**), 7.32–7.36 (m, 4H, **12a**), 7.37–7.41 (m, 4H, **12a**), 7.46–7.52 (m, 4H, **12**), 7.57–7.63 (m, 2H, **12**), 7.79–7.85 (m, 4H, **12**).

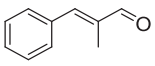
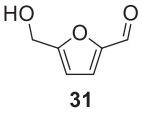
Mixture of 4-nitrodiphenylmethanol (13a), 4-aminobenzophenone (13b) and 4-aminodiphenylmethanol (13c): >99% conversion (**13a** 67%, **13b** 31%, **13c** 2%), yield (**13a** 38%, **13b** 10%, **13c** 1%). ^1H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.26 (s, 2H, **13c**), 3.01 (br s, 1H, **13a**), 4.19 (br s, 2H, **13b**), 5.73 (s, 1H, **13c**), 5.89 (s, 1H, **13a**), 6.62 (d, *J* = 8.4 Hz, 2H, **13c**), 6.65 (d, *J* = 8.6 Hz, 2H, **13b**), 7.12 (d, *J* = 8.4 Hz, 2H, **13c**), 7.27–7.32 (m, 1H, **13a**) superimposed to 7.28–7.38 (m, 5H, **13c**) superimposed to 7.33–7.37 (m, 4H, **13a**), 7.42–7.46 (m, 2H, **13b**), 7.51–7.54 (m, 1H, **13b**), 7.54–7.57

Table 7
Reduction of aldehyde substrates to their corresponding primary alcohols catalyzed by **6** (0.01–0.05 eq.) in DES-5, NEt_3 (7 eq., 1/1 with respect to DES-5) as base and CPME as the additive, at 40 °C.

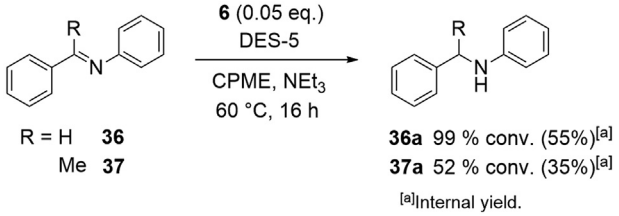
Entry	Aldehyde	[Ru] (eq.)	Time (h)	Conv. (%)[a]
1	 **19**	0.01	6	100 (99)
2	 **20**	0.01	6	100 (85)
3	 **21**	0.01	6 15	99[b] 100 (21)[c]
4[d]	 **22**	0.05	16	98 (94)
5[d]	 **23**	0.05	15	99 (78)
6	 **24**	0.05	8	0
7	 **25**	0.01	4	100 (69)
8	 **26**	0.01	6	100 (14)
9	 **27**	0.01	6	100[e]
10	 **28**	0.025	16	100[f]

(*continued on next page*)

Table 7 (*continued*)

Entry	Aldehyde	[Ru] (eq.)	Time (h)	Conv. (%)[a]
11	 **29**	0.025	16	100[g]
12	 **30**	0.025	6	100 (63)
13	 **31**	0.025	6	99 (28)
14	 **32**	0.025	10	100 (99)
15	 **33**	0.025	10	100 (71)
16	 **34**	0.02	2	0
17[h]	 **35**	0.02	5	0

[a] Conversion and internal yield (i.y.) in parentheses were determined by ^1H NMR spectroscopy (see Supplementary material for details).
[b] A mixture of monoalcohol/dialcohol in 1/1 ratio was observed.
[c] 1,4-Phenylenedimethanol **21a** was observed as a sole product.
[d] Reaction performed at 60 °C.
[e] A mixture of two products was observed: 1-((3-hydroxymethyl)phenyl)ethanone (14% i.y.) and 1-((3-hydroxymethyl)phenyl)ethan-1-ol (3% i.y.).
[f] A mixture of C=O (55% i.y.) and double C=C/C=O reduction (11% i.y.) products was observed.
[g] A mixture of two products was observed: 2-methyl-3-phenylprop-2-en-1-ol **29a** (84% i.y.) and 2-methyl-3-phenylpropan-1-ol **29b** (16% i.y.).
[h] Reaction performed at 30 °C.



Scheme 7. TH of imine derivatives.

(m, 2H, **13a**), 7.66–7.70 (m, 4H, **13b**), 8.13–8.17 (m, 2H, **13a**).

Cyclohexanol (14a): 100% conversion, 98% yield. ^1H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.22–1.33 (m, 5H), 1.40 (br s, 1H), 1.51–1.57 (m, 1H), 1.70–1.77 (m, 2H), 1.85–1.93 (m, 2H), 3.55–3.69 (m, 1H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, 25 °C): δ = 24.3, 25.6, 35.7, 70.5.

Mixture of 4-phenylbut-3-en-2-ol (15a), 4-phenylbutan-2-ol (15b), 4-phenylbutan-2-one (15c) and 4-phenylbut-3-en-2-one

(15): 94% conversion (**15a** 16%, **15b** 49%, **15c** 29%), yield (**15a** 9%, **15b** 47%, **15c** 31%). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.24 (d, *J* = 6.2 Hz, 3H, **15b**), 1.38 (d, *J* = 6.4 Hz, 3H, **15a**), 1.54–1.59 (m, 1H, **15b**), 1.72–1.84 (m, 2H, **15b**), 1.87 (br s, 1H, **15a**), 2.14 (s, 3H, **15c**), 2.39 (s, 3H, **15**), 2.68 (ddd, *J* = 13.8, 9.4, 6.8 Hz, 1H, **15b**), 2.73–2.80 (m, 1H, **15b**) superimposed to 2.77–2.80 (m, 2H, **15c**), 2.90 (t, *J* = 7.7, 2H, **15c**), 3.80–3.87 (m, 1H, **15b**), 4.50 (quint, *J* = 5.6 Hz, 1H, **15a**), 6.27 (dd, *J* = 15.9, 6.4 Hz, 1H, 15**a**), 6.57 (d, *J* = 15.9 Hz, 1H, **15a**), 6.73 (d, *J* = 16.3 Hz, 1H, 15), 7.53 (d, *J* = 16.4 Hz, 1H, **15**) superimposed to 7.10–7.52 (m, 20H, **15** + **15a** + **15b** + **15c**).

Mixture of 1,5-diphenylpent-1-en-3-ol (16a) and 1,5-diphenylpentan-3-one (16b): >99% conversion (**16a** 35%, **16b** 65%), yield (**16a** 23%, **16b** 77%). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.80–1.93 (br s, 1H,**16a**), 1.96–2.09 (m, 2H, **16a**), 2.75 (t, *J* = 7.6 Hz, 4H, **16b**), 2.83 (tdd, *J* = 16.1, 9.4, 6.2 Hz, 2H, **16a**), 2.94 (t, *J* = 7.6 Hz, 4H, **16b**), 4.35 (q, *J* = 6.6 Hz, 1H, **16a**), 6.30 (dd, *J* = 15.9, 6.7 Hz, 1H, **16a**), 6.63 (d, *J* = 15.9 Hz, 1H, **16a**), 7.13–7.50 (m, 20H, **16a** + **16b**).

4.3. NMR data for the TH of aldehydes

3,7-dimethyloct-6-en-1-ol (19a): 100% conversion, 99% yield. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 0.82–1.02 (m, 1H) superimposed to 0.89 (d, *J* = 6.6 Hz, 3H), 1.11–1.21 (m, 1H) 1.28–1.42 (m, 2H), 1.52–1.62 (m, 1H) superimposed to 1.59 (s, 3H), 1.67 (s, 3H), 1.89–2.05 (m, 2H), 3.61–3.72 (m, 1H), 5.08 (dddt, *J* = 7.1, 5.7, 2.8, 1.4 Hz, 1H)·^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 25 °C): δ = 17.7, 19.6, 25,5, 25.8, 29.2, 37.3, 40.0, 61.1, 124.8, 131.3.

Phenylmethanol (20a): 100% conversion, 85% yield. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.92 (br s, 1H), 4.69 (s, 2H), 7.27–7.33 (m, 1H), 7.34–7.39 (m, 4H). ^{13}C{^{1}H}NMR (150 MHz, $CDCl_3$, 25 °C): δ = 65.4, 127.1, 127.8, 128.7, 141.0.

1,4-phenylenedimethanol (21a): 100% conversion, 21% yield. ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C): δ = 4.46 (d, *J* = 5.7 Hz, 4H), 5.12 (t, *J* = 5.7 Hz, 2H), 7.25 (s, 4H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6, 25 °C): δ = 62.7, 126.2, 140.9.

Mixture of (4-methoxyphenyl)methanol (22a) and 4-methoxybenzaldehyde (22): 98% conversion, 94% yield. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.92 (br s, 1H, **22a**), 3.80 (s, 3H, **22a**), 3.86 (s, 3H, **22**), 4.60 (s, 2H, **22a**), 6.86–6.90 (m, 2H, **22a**), 6.96–7.00 (m, 2H, **22**), 7.25–7.30 (m, 2H, **22a**), 7.80–7.82 (m, 2H, **22**), 9.84 (s, 1H, **22**).

4-(hydroxymethyl)-2-methoxyphenol (23a): 99% conversion, 78% yield. ^{1}H NMR (600 MHz, acetone-d_6, 25 °C): δ = 3.82 (s, 3H), 4.11 (br s, 1H), 4.50 (s, 2H), 6.78 (s, 2H), 6.96 (s, 1H), 7.52 (br s, 1H). ^{13}C{^{1}H} NMR (150 MHz, acetone-d_6, 25 °C): δ = 56.1, 64.7, 111.4, 115.4, 120.2, 134.8, 146.4, 148.1.

(4-nitrophenyl)methanol (25a): 100% conversion, 69% yield. ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C): δ = 4.60 (d, *J* = 5.7 Hz, 2H), 5.51 (t, *J* = 5.7 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 2H), 8.16 (d, *J* = 8.7 Hz, 2H). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6, 25 °C): δ = 62.0, 123.3, 127.0, 146.3, 150.8.

4-(hydroxymethyl)benzonitrile (26a): 100% conversion, 14% yield. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.95 (br s, 1H), 4.79 (s, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 25 °C): δ = 64.4, 111.3, 119.0, 127.2, 132.5, 146.3.

Mixture of 1-(3-(hydroxymethyl)phenyl)ethan-1-one (27a) and 1-(3-(hydroxymethyl)phenyl)ethan-1-ol (27b): 100% conversion (**27a** 83%, **27b** 17%), yield (**27a** 14%, **27b** 3%). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.50 (d, *J* = 6.5 Hz, 3H, **27b**), 1.69 (br s, 1H, **27b**), 1.93 (br s, 1H, **27b**), 2.08 (br s, 1H, **27a**), 2.61 (s, 3H, **27a**), 4.69 (s, 2H, **27b**), 4.76 (s, 2H, **27a**), 4.91 (q, *J* = 6.5 Hz, 1H, **27b**), 7.24–7.41 (m, 4H, **27b**), 7.46 (t, *J* = 7.6 Hz, 1H, **27a**), 7.58 (d, *J* = 7.6 Hz, 1H, **27a**), 7.87 (d, *J* = 7.7 Hz, 1H, **27a**), 7.95 (s, 1H, **27a**).

Mixture of (1*R*)-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl) methanol (28a) and (6,6-dimethylbicyclo[3.1.1]heptan-2-yl) methanol (298b): 100% conversion (**28a** 85%, **28b** 15%), yield (**28a** 55%, **28b** 11%). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 0.83 (s, 3H, **28a**) superimposed to 0.82–0.86 (m, 1H, **28b**), 0.96 (s, 3H, **28b**), 1.15 (s, 3H, **28b**), 1.16–1.18 (m, 1H, **28a**), 1.28 (s, 3H, **28a**), 1.42–1.48 (m, 2H, **28b**) superimposed to 1.46 (br s, 1H, **28a**), 1.81–1.95 (m, 4H, **28b**), 1.98–2.02 (m, 1H, **28b**), 2.07–2.11 (m, 1H, **28a**), 2.13 (td, *J* = 5.7, 1.5 Hz, 1H, **28a**), 2.20–2.26 (m, 1H, **28a**) superimposed to 2.23–2.26 (m, 1H, **28b**), 2.27–2.33 (m, 1H, **28a**), 2.33–2.37 (m, 1H, **28b**), 2.39 (dt, *J* = 8.6, 5.6 Hz, 1H, **28a**), 3.49–3.61 (m, 2H, **28b**), 3.97 (s, 2H, **28a**), 5.46 (m, 1H, **28a**).

Mixture of (*E*)-2-methyl-3-phenylprop-2-en-1-ol (29a) and 2-methyl-3-phenylpropan-1-ol (29b): 100% conversion (**29a** 83%, **29b** 17%), yield (**29a** 84%, **29b** 16%). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 0.92 (d, *J* = 6.7 Hz, 3H, **29b**), 1.91 (s, 3H, **29a**) superimposed to 1.92 (br s, 1H, **29a**) superimposed to 1.92–1.99 (m, 1H, **29b**), 2.43 (dd, *J* = 13.5, 8.1 Hz, 1H, **29b**), 2.76 (dd, *J* = 13.5, 6.3 Hz, 1H, **29b**), 3.48 (dd, *J* = 10.6, 6.1 Hz, 1H, **29b**), 3.54 (dd, *J* = 10.5, 5.9 Hz, 1H, **29b**), 4.20 (s, 2H, **29a**), 6.54 (s, 1H, **29a**), 7.14–7.21 (m, 5H, **29b**), 7.21–7.25 (m, 1H, **29a**), 7.27–7.31 (m, 2H, **29a**), 7.32–7.37 (m, 2H, **29a**).

Furan-2-ylmethanol (30a): 100% conversion, 63% yield. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.98 (br s, 1H), 4.60 (s, 2H), 6.29 (d, *J* = 3.2 Hz, 1H), 6.34 (dd, *J* = 3.2, 1.8 Hz, 1H), 7.40 (dd, *J* = 1.9, 0.8 Hz, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 25 °C): δ = 57.6, 107.9, 111.1, 142.2, 154.2.

Furan-2,5-diyldimethanol (31a): 99% conversion, 28% yield. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 2.85 (br s, 2H), 4.55 (s, 4H), 6.19 (s, 2H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 25 °C): δ = 57.7, 108.7, 154.2.

(1-methyl-1*H*-pyrrol-2-yl)methanol (32a): 100% conversion, 99% yield. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.47 (br s, 1H), 3.69 (s, 3H), 4.59 (s, 2H), 6.05 (dd, *J* = 3.5, 2.7 Hz, 1H), 6.11 (dd, *J* = 3.6, 1.8 Hz, 1H), 6.62–6.65 (m, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 25 °C): δ = 33.8, 56.9, 106.8, 109.0, 123.7, 131.9.

Thiophen-2-ylmethanol (33a): 100% conversion, 71% yield. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 2.17 (br s, 1H), 4.82 (s, 2H), 6.98 (dd, *J* = 5.0, 3.4 Hz, 1H), 7.00–7.02 (m, 1H), 7.27 (dd, *J* = 5.1, 1.2 Hz, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 25 °C): δ = 60.0, 125.6, 125.7, 127.0, 144.2.

4.4. NMR data for the TH of imines

***N*-benzylaniline (36a)**: 99% conversion, 55% yield. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 4.06 (br s, 1H), 4.36 (d, *J* = 5.7 Hz, 2H), 6.65–6.69 (m, 2H), 6.75 (tt, *J* = 7.3, 1.1 Hz, 1H), 7.19–7.23 (m, 2H), 7.29–7.33 (m, 1H), 7.36–7.42 (m, 4H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, 25 °C): δ = 48.4, 112.9, 117.7, 127.3, 127.6, 128.7, 129.4, 139.5, 148.3.

Mixture of *N*-(1-phenylethyl)aniline (37a) and (*E*)-*N*,1-diphenylethan-1-imine (37): 52% conversion, 35% yield**.** ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.54 (d, *J* = 6.7 Hz, 3H, **37a**), 2.26 (s, 3H, **37**), 4.06 (br s, 1H, **37a**), 4.47–4.55 (m, 1H, **37a**), 6.52–6.56 (m, 2H, **37a**), 6.67 (tt, *J* = 7.3, 1.1 Hz, 1H, **37a**), 6.82–6.85 (m, 2H, **37**), 7.10–7.14 (m, 3H, **37a** + **37**), 7.22–7.28 (m, 1H, **37a**), 7.35–7.36 (m, 2H, **37**), 7.38–7.41 (m, 4H, **37a**), 7.46–7.51 (m, 3H, **37**), 7.99–8.03 (m, 2H, **37**).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.131997.

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