

RESEARCH ARTICLE

Indium-mediated allylation of carbonyl compounds in deep eutectic solvents

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This study describes, for the first time, the in situ generation of indium organometallic reagents in environmentally friendly deep eutectic solvents (DESS). The allylation process of different carbonyl compounds is achieved mediated by indium metal and using cheap allyl chloride derivatives. The unique DES properties allow to perform the reaction at room temperature and under air, obtaining yields ranging from 45% to 99%. It is possible to recycle the reaction medium for at least four consecutive cycles without much decrease of the observed results. Also, a linear correlation between the yield of the reaction and the density of the DESSs is observed.

KEYWORDS

allylation, green chemistry, indium, solvent effects, sustainability

1 | INTRODUCTION

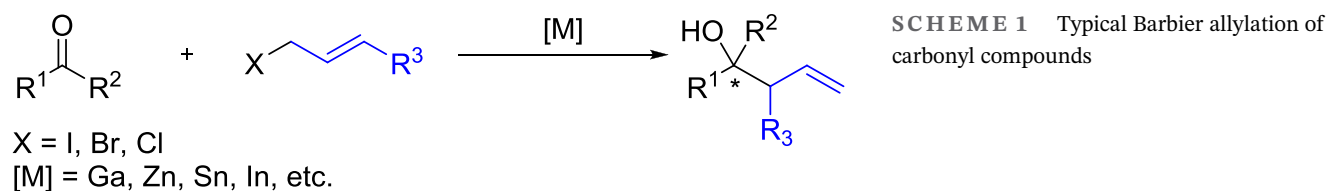
The allylation of carbonyl compounds via allylmetal reagents is one of the most valuable transformations in Organic Synthesis because it creates a new C—C bond and a stereocenter.^[1] The presence of a C—C double bond in the resulting homoallylic alcohols is very interesting leading to highly functionalized compounds, suitable for the synthesis of natural and pharmaceutical compounds. This type of compounds has played an essential role in organic chemistry for the development of novel chemical structures. For instance, antitumor agents, such as leucascandrolide A, or psychostimulants, such as (–)-lobeline, possess this kind of structural feature.^[2] The allylation process of carbonyl compounds

has been described with different metals (Ga, Zn, Sn, etc.), with indium reagents offering several advantages, because they are minimally toxic, compatible with a great variety of functional groups, and stable to air and moisture (Scheme 1).^[3] This Barbier-type allylation process has been previously performed in classical organic solvents,^[4a,b] water,^[4c,d] ionic liquids (ILs),^[4e–k] and under solvent-free conditions.^[4l–n]

Despite water might be seemed as a sustainable solvent, its use has some disadvantages including incompatibility of several functional groups and high cost in the treatment of residual streams.^[5] Some ILs have been found to be toxic and nonbiodegradable, with also several synthetic steps involving nonsustainable procedures being required for their

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**TABLE 1** Optimization of the reaction conditions

Entry	Solvent (mol:mol)	T (°C)	X	Yield (%) ^a
1	ChCl:glycerol (1:2) ^b	90	Br	80
2	ChCl:ethylene glycol (1:2) ^b	90	Br	99
3	ChCl:urea (1:2) ^b	90	Br	79
4	AcChCl:acetamide (1:2) ^b	90	Br	45
5	ChCl:urea (1:2) ^b	25	Br	36
6	ChCl:glycerol (1:2) ^b	25	Br	58
7	Decanoic acid:TBAB (2:1)	25	Br	23
8	Decanoic acid:menthol (1:2)	25	Br	33
9	ChCl:ethylene glycol (1:2) ^b	25	Br	99
10	AcChCl:acetamide (1:2) ^b	25	Br	62
11	ChCl:ethylene glycol (1:2) ^b	25	Cl	75, 99 ^c
12	AcChCl:acetamide (1:2) ^b	25	Cl	35, 99, ^c 14, ^d 0, ^e 67, ^f 56, ^g 34, ^h 21, ⁱ 10, ^j 34 ^{k, l}
13	ChCl:glycerol (1:2) ^b	25	Cl	68 ^l
14	ChCl:urea (1:2) ^b	25	Cl	50 ^l
15	MePPh ₃ Br:glycerol (1:2)	25	Cl	20 ^l
16	ChCl:L-malic acid (1:1) ^b	25	Cl	0
17	ChCl:D-galactose (5:2) ^b	25	Cl	0

Note: Reaction conditions: **1a** (0.25 mmol), allyl halide **2** (0.5 mmol), and indium powder (0.5 mmol) in 0.5 ml of solvent were stirred at different temperatures for 16 h.

^aYield determined by CG using 4,4'-di-*tert*-butylbiphenyl (DTBB) as internal standard.

^bChCl stands for choline chloride; AcChCl stands for acetylcholine chloride; TBAB stands for tetrabutylammonium bromide.

^c28 mol% of NH₄Cl or NH₄OAc were added.

^d28 mol% of KOAc were added.

^e28 mol% of NaOAc were added.

^f20 μl of acetic acid were added.

^g14 mol% of NH₄Cl were added.

^h14 mol% of NH₄OAc were added.

ⁱ28 mol% of NaCl were added.

^j28 mol% of LiCl were added.

^kZinc powder was used instead of indium powder.

^l28 mol% of NH₄Cl was added.

preparation.^[6] Solvent-free conditions might not be widely applicable, because solvents allow the heat and mass transfer, thus playing a crucial role in the reaction outcome. In addition, they stabilize some

transition states and even govern the selectivity of the reaction.^[7] Therefore, the search for sustainable solvents for these Barbier-type allylation reactions remains in demand.

Deep eutectic solvents (DESs) are generally referred to as combinations of two or more safe and inexpensive components forming liquid eutectic mixtures mainly due to electrostatic and hydrogen bond interactions between components, with a melting point far lower than that of the ideal mixture. DESs have interesting properties and benefits in terms of sustainability, such as low cost, low vapor pressure, nonflammability, and benign and safe nature along with renewability and biodegradability.^[8]

Although several studies using organometallic reagents under aerobic conditions in DESs have already been reported,^[8a,9] in most of the cases, the organometallic reagents were synthesized previously under standard conditions, including inert atmosphere and using typical volatile organic solvents. To the best of our knowledge, only a recent study has reported the use of highly reactive lithium phosphides generated in situ in choline chloride-based eutectic mixtures under aerobic conditions.^[9d] Herein, it is described for the first time the allylation reaction by the in situ generation of the organometallic reagent in DESs, employing low reactive allyl chlorides as a source of nucleophilic alkylating agents. Different carbonyl compounds were used as electrophiles performing the reaction at room temperature and under air atmosphere. The obtained results were similar and even better than those previously described in organic solvents, water, and ILs.

2 | RESULTS AND DISCUSSION

The study started with the optimization of the reaction conditions employing acetophenone (**1a**), allyl halides (**2**), and indium powder as a model reaction under Barbier conditions (Table 1). Several DESs were tested as solvent for this transformation at 90°C, obtaining promising results (Entries 1–4). Unfortunately, low yields were observed when the reaction was carried out at room temperature employing both hydrophilic (Entries 5 and 6) and hydrophobic DESs (Entries 7 and 8). Only when choline chloride:ethylene glycol (1:2) or acetylcholine chloride:acetamide (1:2) were used as solvents, good results were achieved (Entries 9 and 10). Thus, it was decided to test these two DESs employing allyl chloride instead of allyl bromide. It is well known that allyl chlorides are cheaper and more stable than allyl bromides, although their reactivity is lower, being the reaction more challenging. As expected, product **3a** was obtained with lower yields. The addition of ammonium salts has been reported to have a positive impact on this type of reaction under aqueous conditions.^[10] Therefore, we decided to study the impact of the addition of the ammonium acetate in both choline chloride:ethylene glycol (1:2) and

acetylcholine chloride:acetamide (1:2) mixtures. When 28 mol% of ammonium acetate was added, compound **3a** was obtained in both mixtures with excellent yields (Entries 11 and 12, footnote c).

This beneficial effect might be due to the presence of acetate or ammonium ions in the reaction mixture or to a change in the pH of the reaction that could help in the stabilization of the involved indium species as it has been previously described.^[11] Therefore, the effect of the addition of several acetate salts and acetic acid was evaluated in acetylcholine chloride:acetamide (1:2) mixture, which presents less toxicity in higher concentrations than choline chloride:ethylene glycol mixture.^[12] Poor yields or no reaction were obtained when potassium acetate or sodium acetate or acetic acid in 70 mol% were added to the reaction mixture (Entry 12, footnotes d–f, respectively). The effect of the amount of ammonium salt was also tested. The reaction was run with different quantities, obtaining the best results with 28 mol% (Entry 12, footnote c). It is worthy to note that better results were obtained by using a 14 mol% of ammonium chloride instead of ammonium acetate (Entry 12, footnotes g and h). Recently, it has been demonstrated that simple NaCl can enhance the efficiency of organozinc and organolithium compounds in sustainable solvents.^[9e,13] Therefore, the addition of NaCl and LiCl instead of ammonium chloride was considered. Unfortunately, poor yields were obtained in both cases (Entry 12, footnotes i and j, respectively).

It is well known that similar Barbier transformations have already been performed using Zn instead of In^[14]; thus, the use of Zn powder was also tested, but moderate yield was obtained (Entry 12, footnote k). In sight of these results, the rest of the DESs were also evaluated by adding 28 mol% of ammonium salt to the reaction mixture, affording compound **3a** with poor to moderate yields (Entries 13–15). Finally, we tried to perform the enantioselective process by using chiral DESs such as choline chloride:(*S*)-malic acid (1:1), choline chloride:(*S*)-lactic acid (1:2), choline chloride:(2*R,R*)-tartaric acid (1:0.5), (*S*)-proline:(*S*)-malic acid (1:1), or choline chloride:*D*-galactose (5:2). Unfortunately, in all the cases, no reaction was observed recovering the starting material (see, for instance, Entries 16 and 17).

A parallel study of the reaction progress with time, with both ammonium acetate and chloride, was carried out (Table 1, Entry 12). Similar results were obtained in both cases, being the reaction completed after 12 h (Table 2, Entries 1–4). It was decided to use ammonium chloride instead of ammonium acetate because it is cheaper and easier to handle. Finally, a study of the ratio of indium and allyl chloride was performed. All the attempts to change the ratio between indium and allyl

TABLE 2 Optimization of the reaction time and equivalents of the reagents

Entry	Time (h)	Yield (%) ^a	
		NH ₄ Cl	NH ₄ OAc
1	1	0	0
2	3	64	65
3	8	88	86
4	12	98	95
5	12	65, ^b 60, ^c 55, ^d 0 ^e	-

Note: Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), NH₄Cl or NH₄OAc (28 mol%), and indium powder (0.5 mmol) in 0.5 ml of acetylcholine chloride:acetamide (1:2) were stirred at room temperature. Bold characters were used to highlight the best conditions.

^aYield determined by CG using DTBB as internal standard.

^b1.5 equiv. of **2a** and indium powder.

^c1.5 equiv. of **2a** and 1 equiv. of indium powder.

^d1 equiv. of **2a** and indium powder.

^eNo indium powder was used.

chloride were unsatisfactory with a significant drop in the yield being observed (Table 2, Entry 5, footnotes b–d). As it was expected, no reaction occurred when it was carried out in the absence of indium powder (Table 2, Entry 5, footnote e).

With the optimal conditions in hand (Table 2, Entry 4), the scope of this transformation was evaluated (Table 3). First, different ketones were used with excellent to quantitative yields being obtained when electron-withdrawing groups were attached to the aromatic ring of the aryl ketones (Entries 2 and 3). Conversely, a lower yield was observed when an electron-donating substituent was present in the ketone (Entry 4). An excellent yield was achieved employing 4-phenylacetophenone as a substrate (Entry 5). Good yield was obtained employing an aryl ketone bearing a substituent at *meta*-position (Entry 6). The reaction was also compatible with longer carbon chain ketones and benzophenone, obtaining the expected allylated product with good results (Entries 7 and 8). Cyclic ketones (α -tetralone and cyclohexanone) were also compatible substrates, affording results from good to excellent (Entries 9 and 10). The similarity in the obtained results using acetophenone and α -tetralone seems to indicate the low basicity of the generated nucleophile.^[15] An α,β -unsaturated carbonyl compound (2-cyclohexenone) was also employed, and no conjugate addition was observed, being the reaction selective, obtaining exclusively 1,2-addition product with a good

yield (Entry 11). This result seems to indicate the hard behavior of the generated nucleophile. Then, several aldehydes were also tested as electrophiles, obtaining in all the cases excellent results (Entries 12–14). Next, different substituted allylic chlorides were evaluated with moderate to good yields being obtained. The reaction was compatible with methyl 2-(chloromethyl)acrylate (**2b**) obtaining product **3o** with moderate yield (Entry 15). The corresponding double addition was observed when methallyl dichloride (**2c**) was made to react as Y-aromatic nucleophile source with different ketones, affording product **3p** and **3q** with moderate yields (Entries 16–18). When crotyl chloride (**2d**) was used, a mixture of diastereoisomers was achieved with the major one being the *anti*-isomer (Entry 19). When cinnamyl chloride (**2e**) was used, a single diastereoisomer was formed in moderate yield (Entry 20).

For γ -substituted allyl chloride derivatives (**2d** and **2e**), the addition gave the γ -*anti*-adducts, as a major or sole diastereoisomer. Based on the stereochemical outcome observed, a cyclic Ireland-transition state was proposed as the expected pathway, leading to the *anti*-product as the major one (Scheme 2). The results obtained in both cases are in concordance with those previously reported in the literature.^[16]

Finally, mixture of isomers and homopropargylic and allenyl alcohols (**5** and **6**) were obtained in 81% overall yield, in a 25:75 ratio, respectively, when propargylic

TABLE 3 Scope of the reaction employing different carbonyl and allylic compounds

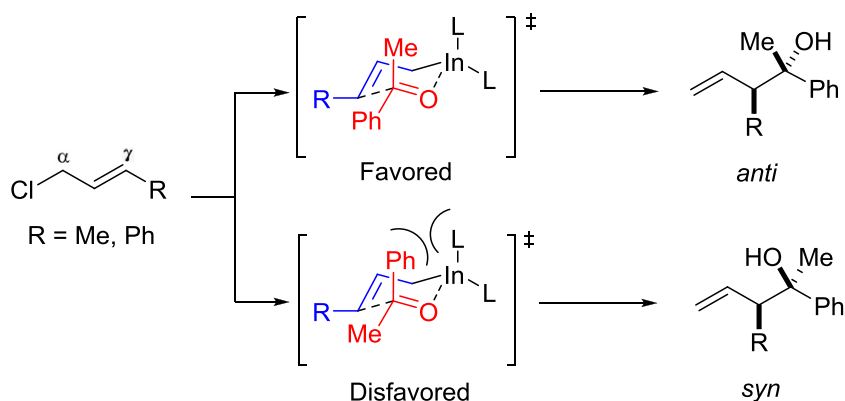
Entry	R ¹	R ²	R ³	R ⁴	R ⁵	Product	Yield (%) ^a
1	Ph	Me	H	H	H	3a	95
2	<i>p</i> -FC ₆ H ₅	Me	H	H	H	3b	99
3	<i>p</i> -CF ₃ C ₆ H ₅	Me	H	H	H	3c	90
4	<i>p</i> -MeOC ₆ H ₅	Me	H	H	H	3d	56
5	4-Biphenyl	Me	H	H	H	3e	90
6	<i>m</i> -MeC ₆ H ₅	Me	H	H	H	3f	80
7	Ph	Et	H	H	H	3g	88
8	Ph	Ph	H	H	H	3h	71
9	-[1,2-C ₆ H ₄ (CH ₂) ₃]-		H	H	H	3i	85
10	-(CH ₂) ₅ -		H	H	H	3j	90
11	C ₅ H ₈		H	H	H	3k	80
12	Ph	H	H	H	H	3l	99
13	Furyl	H	H	H	H	3m	90
14	C ₆ H ₁₁	H	H	H	H	3n	90
15	Ph	Me	COOMe	H	H	3o	45
16 ^b	-(CH ₂) ₅ -		CH ₂ Cl	H	CH ₂ C(OH)C ₆ H ₁₁	3p	47
17 ^b	-(CH ₂) ₄ -		CH ₂ Cl	H	CH ₂ C(OH)C ₅ H ₉	3q	55
18 ^b	Et	Et	CH ₂ Cl	H	CH ₂ C(OH)Et ₂	3r	58
19	Ph	Me	Me	H	Me	3s	75
20	Ph	Me	Ph	H	Ph	3t	52

Note: Reaction conditions: carbonyl compound **1** (0.25 mmol), allyl chloride **2** (0.5 mmol), NH₄Cl (28 mol%), and indium powder (0.5 mmol) in 0.5 ml of acetylcholine chloride:acetamide (1:2) were stirred at room temperature for 12 h.

^aIsolated yield.

^bCarbonyl compound **1** (0.5 mmol), allyl chloride **2c** (0.25 mmol), NH₄Cl (28 mol%), and indium powder (0.25 mmol) in 0.5 ml of acetylcholine chloride:acetamide (1:2) were stirred at room temperature for 12 h.

SCHEME 2 Ireland-transition state for the allylation of carbonyl compounds



chloride (**4**) was used as a nucleophilic source (Scheme 3).

The recycling of the DES and NH_4Cl was attempted because it is a crucial point for the sustainability of the process.^[17] Extraction of the organic compounds using immiscible organic solvents, such as 2-methyltetrahydrofuran (2-MeTHF, a renewable solvent), was performed.^[18] The mixture of DES and NH_4Cl was reused, after being vacuum dried, performing a new reaction cycle under the same reaction conditions. It was possible to recycle the DES and NH_4Cl up to four cycles, even though a slight decrease in the reaction yield was observed (Figure 1). Because the reaction yield dropped from 99% to 65% in the fifth cycle, in the sixth cycle, fresh NH_4Cl was added to the reaction medium, along with the other reagents. An improvement of the reaction yield was observed, but it was lower than in the first run. This slight decrease in the results might be due to the accumulative presence of different salts and the regarding metal, affecting the DES structure.

In order to gain insight into the possible mechanism of the reaction, several control experiments were performed. When 2.0 equivalents of TEMPO were added as a radical quencher, the reaction under standard conditions did not take place and the desired product **3a** was not observed. Possible TEMPO adducts were analyzed, and the formation of 2,2,6,6-tetramethylpiperidin-1-ol was observed by GC-MS (Scheme 4), which seems to indicate the formation of radical species.^[19] This is in concordance with a mechanism involving a radical pathway for the generation of allylmetal species, as it is stated previously in the literature.^[20]

In addition, the evolution of reagents/products versus reaction time was also studied. At the beginning of the reaction, the amount of allyl chloride derivative **2e** (cinnamyl chloride) decreased; meanwhile, the ketone **1a** remained unchanged; and the final product **3t** could not be detected by GC of the hydrolyzed reaction crude mixture. After an induction period of about 1 h and a half, product **3t** started to be formed, indicating the generation of radical species in the medium prior to the formation of product **3t** (Figure 2).

Previous studies have demonstrated that neutral radical pairs are highly influenced and affected by solvent viscosity and density, among other factors.^[21] Thus, it

was postulated that a solvent “cage radical pair” is produced when radical species are involved in the reaction, and this “cage” is treated as a “hole” in the solvent itself. Consequently, escaping from this “pocket” is mainly determined by the density of the surrounding molecules of the solvent. Therefore, the behavior of the radical species might be related to the density and viscosity of the solvent and that could determine the possibility of radicals to escape from the “pocket.”^[21] In order to corroborate whether the densities and viscosities of the DESs could have a significant impact on the reaction output, a correlation was carried out (Figure 3).

According to the aforementioned mechanism, a linear relationship between the densities and the yield of the reaction was observed, indicating that the higher density the DES has, the lower yield is obtained (Figure 3, left). A similar tendency between the viscosity of the DES and the yield of the reaction product was also observed, although a linear relationship could not be drawn, probably due to the use of macroviscosity values instead of microviscosity ones, which are better parameters to predict radical recombination efficiencies.^[23] The viscosity of the DES employed has an important role in the reaction output, because a significant drop in the yield was observed with an increase of the viscosity (Figure 3, right). All these results pointed out that an important factor for the reaction process might be the radical escape from the “cage,” which is highly dependent on the

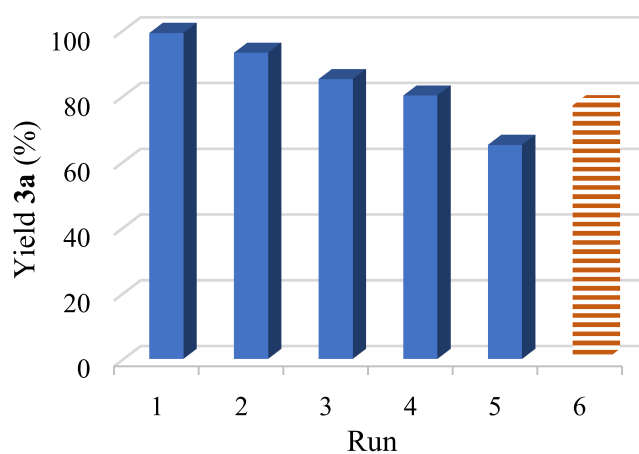
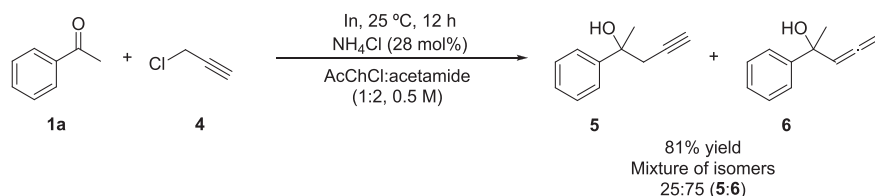


FIGURE 1 Recyclability of the system



SCHEME 3 Reaction between acetophenone and propargylic chloride

SCHEME 4 Reaction under the presence of TEMPO

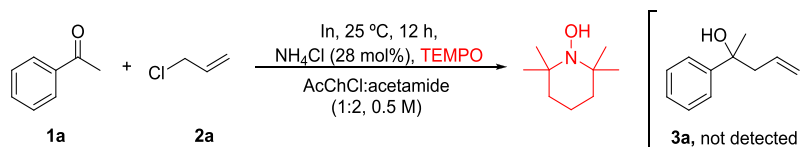


FIGURE 2 Evolution of reagents/products versus time

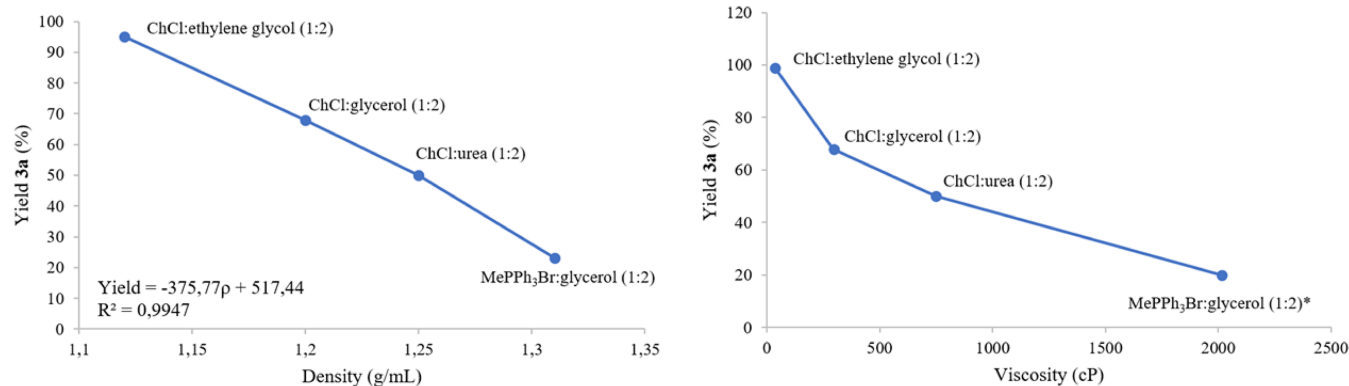
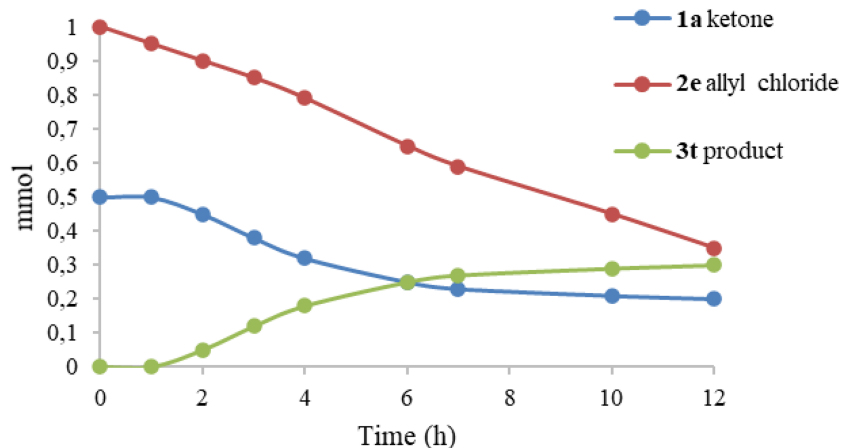


FIGURE 3 Impact of solvent's densities on the yield of the reaction (left). Influence of the viscosity in the yield of the reaction (right). *The density of MePPh₃Br:Gly (1:2) was estimated from values of similar deep eutectic solvents (DESS) described in the literature^[22]

solvent properties, such as density or viscosity. Thus, based on the results observed, it seems that the lower densities and viscosities favor the escape from the “cage,” affording the highest yields.

3 | CONCLUSIONS

In summary, the in situ generation of organoindium reagents and the subsequent addition to different carbonyl compounds has been achieved for the first time in DESs under mild, aerobic conditions showing the high compatibility of DESs with organometallic reagents. In terms of sustainability, it is worthy to mention that the right choice of DES allowed the recyclability of the

reaction at least four consecutive cycles without any significant decrease in the results employing a nontoxic solvent medium. An interesting linear correlation between the densities of the DESs used and the yield of the reaction was observed, pointing out the importance of the choice of DES, a tailor-made solvent, in order to achieve the best results.

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CONFLICT OF INTEREST

The authors declare no competing financial interest.

AUTHOR CONTRIBUTIONS

Nerea González-Gallardo: Formal analysis; methodology. **Beatriz Saavedra:** Formal analysis; methodology. **Gabriela Guillena:** Conceptualization; investigation; methodology. **Diego J. Ramón:** Conceptualization; funding acquisition; investigation; methodology; supervision.

DATA AVAILABILITY STATEMENT

Data are available in the Supporting Information.

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