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Hydrogen bond-mediated organocatalytic enantioselective reduction of nitroalkenes in deep eutectic solvents

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ABSTRACT

The catalytic enantioselective reduction of β,β-disubstituted nitroalkenes was performed in deep eutectic solvents, avoiding the use of volatile organic compounds (VOCs) as reaction medium. The desired enantioenriched nitroalkanes were obtained in high yields and high enantiomeric excesses, up to 90%, by a metal-free, hydrogen bond-mediated catalytic methodology, with a convenient experimental protocol that could be successfully applied to a gram-scale reaction.

1. Introduction

Chemists all over the world work to develop new green synthetic methodologies and to design sustainable industrial processes. In this context, since solvents account for 80% of the total volume of chemicals employed for chemical synthesis, a paradigm shift from conventional solvents to sustainable solvents [1] is highly desirable.

The combination of green solvents with organocatalysis [2], a metal-free strategy, offers a further opportunity to address the problem of sustainability in organic synthesis [3]. Several works about asymmetric organocatalysed reactions in alternative reaction media appeared in the literature recently [4].

In particular, ionic liquids (ILs), deep eutectic solvents (DESs), supercritical fluids (SCFs), liquid polymers (glycols and glymes) and biodegradable solvents from renewable sources were studied [5]. Among the aforementioned alternatives, DESs are particularly attractive for their low health and environmental risks, and for their low vapor pressure; moreover, their preparation is straightforward and it doesn't require any purification [6]. Despite the remarkable advantages linked to the use of DESs, the field of asymmetric organocatalyzed reactions is still underdeveloped in such reaction media [7].

One of the first example was reported by de María and co-workers in 2014 [8]. They disclosed the possibility to run a tandem biocatalysed and organocatalysed enantioselective aldol reaction between aromatic aldehydes and acetaldehyde, generated in situ from vinyl acetate. A couple of years later, our group [9] explored the activity of chiral primary amines, 9-amino-9-deoxy-*epi*-cinchona derivatives, as organocatalysts, to promote reactions via enamine, dienamine and iminium ion formation in Choline chloride-based eutectic mixtures. Later, Alonso and co-workers studied the use of a chiral 2-aminobenzimidazole as the catalyst to achieve the enantioselective Michael addition of 1,3-dicarbonyl compounds to β-nitroalkenes [10] and α-amination of 1,3-dicarbonyl compounds [11].

Herein we report our efforts to implement the catalytic enantioselective reduction of β,β-disubstituted nitroalkenes published by List [12] and further studied by Bernardi and co-workers [13] and our group [14], using deep eutectic solvents instead of traditional solvents. Remarkably, a major challenge of the present work is to efficiently perform a reaction in which the catalyst, the substrate and the reductant interact with each other through a hydrogen bonds network, in a reaction medium made in turn of hydrogen bonds connections.

2. Results and discussion

Our investigation started with a catalyst screening (Table 1) for the reduction of (*E*)-1-nitro-2-phenyl-1-propene (**1**).

Among the already known bifunctional catalysts we tested four different chiral thiourea-based organocatalysts [15] in choline chloride/glycerol 1:2 DES (Scheme 1) as reaction medium; the results are reported in Table 1. We were pleased to see that good levels of enantioselectivity were achieved with three of the four examined catalysts. The *tert*-leucine derivative catalyst **A** promoted the reduction in 84% e. e.

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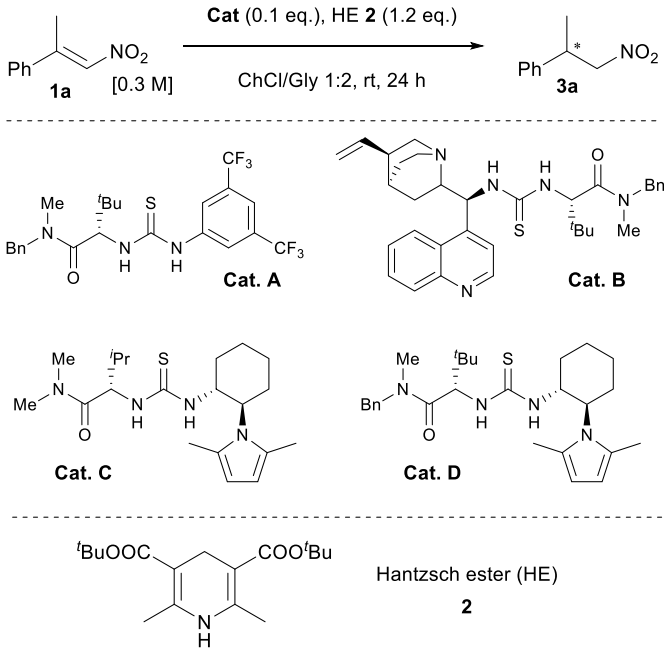
Table 1
Preliminary catalyst screening.
(a) Isolated yields of the product. (b) Enantiomeric excess of the product was determined by HPLC on chiral stationary phase.

Entry	*Catalyst*	*Yield*[(a)]	Ee[(b)]
1	**A**	80%	84%
2	**B**	63%	<5%
3	**C**	88%	70%
4	**D**	52%	56%



Scheme 1. Catalysts screening.

At rt and was selected for the following tests.

An extensive study of the reaction media was undertaken (Scheme 2), different Deep Eutectic Solvents mixtures were investigated and the results are collected in Table 2.

At first, achiral reaction media were studied (entries 1–4); good yields (70–80%) and enantiomeric excesses (up to 84% for the (S) enantiomer, as expected) were achieved. We next evaluated the use of DESs with chiral components (entry 5–9). The enantioselectivity of the reaction dropped in the case of entries 5 and 6, when (L)-lactic acid containing mixtures were employed; using two diastereomeric DES - ((L)-malic acid with (D)-proline and (L)-proline, entries 8 and 9) the product was isolated with good enantiomeric excess in the favour of the same enantiomer, clearly indicating that only the chiral catalyst is playing an active role in defining the stereochemical outcome of the reaction. Indeed, the reaction in a chiral medium catalysed by an achiral thiourea led to the formation of a racemic product (entry 15). At last, the reaction was tested in some polar protic solvents (entry 10–12); in water and glycerol the product was still obtained in higher than 80% e. e., while, when methanol was employed, the enantiomeric excess dramatically dropped. It should be noted that in all cases, with the exception of the reaction of entry 12, all the components resulted suspended in the reaction medium (see

Table 2
Reaction medium screening.

Entry	*Reaction medium*	*Yield*[a]	Ee[b]
1	Choline Chloride/Glycerol 1:2	80%	84%
2	Choline Chloride/Urea 1:2	77%	65%
3	Betaine/Glycerol 1:2	76%	72%
4	Betaine/Glycolic acid 1:2	70%	78%
5	Choline Chloride/(L)-lactic acid 1:3	25%	34%
6	(L)-menthol/(L)-lactic acid 1:2	62%	<5%
7	(L)-proline/(L)-lactic acid 1:4	76%	54%
8	(D)-proline/(L)-malic acid 1:2 (80 °C)	59%	78%
9	(L)-proline/(L)-malic acid 1:2 (80 °C)	65%	75%
10	Water	61%	80%
11	Glycerol	68%	86%
12	Dry MeOH	38%	30%
13	Choline Chloride/Glycerol 1:2 +10% water	70%	79%
14	Choline Chloride/Glycerol 1:2 + 20% water	75%	75%
15 [c]	(D)-proline/(L)-malic acid 1:2 (80 °C)	51%	<5%

[a] Isolated yields of the product.
[b] Enantiomeric excess of the product was determined by HPLC on chiral stationary phase.
[c] Reaction run in the presence of achiral catalyst *N,N*-di (3,5-ditrifluoromethylphenyl) thiourea.

Supporting Information for a picture), thus suggesting that the reaction is probably taking place at the interface between the organic reactants phase and the reaction medium. Finally, it was shown that the best DES (Choline Chloride/Glycerol 1:2) well tolerates up to 20% of water in the DES mixture, with not significant difference in the stereochemical outcome of the reaction (entries 13–14).

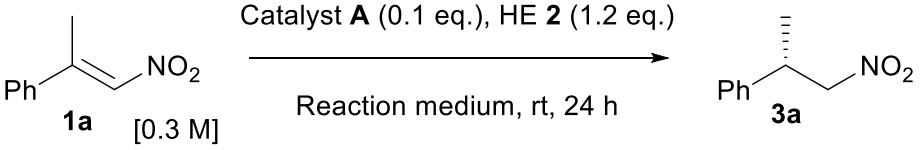
To complete the reaction conditions optimization, the influence of the substrate concentration was also assessed. In order to better evaluate it, we conducted the study using betaine/glycolic acid (1:2) as reaction medium. A substrate concentration of 0.30 M assured the best result in terms of chemical yield, while the variation in the concentration did not influence the enantiomeric excess (Table 3).

Having established the optimal reaction conditions (entry 1 Table 2), the reduction of different substrates was investigated.

E-nitrostyrenes bearing both electron-donating and electron-withdrawing substituents were converted to the corresponding nitroalkanes in excellent yields and high enantiomeric excesses (Scheme 3). (*E*)-β-trifluoromethyl-β-nitrostyrene was also successfully reduced to the corresponding trifluoromethyl nitroalkane **3f** employing the same conditions. The reduction of the β,β-dialkylsubstituted nitroalkene **1h** led to the formation of the desired product **3h** with only 60% *ee*, probably due to the lack of π stacking interactions between the alkyl chains and the catalyst [14]. Highest enantioselectivities were obtained for nitrostyrenes featuring a more sterically hindered alkyl substituent at the β-position, such as **1i** and **1j**, in which the β-methyl group was replaced by the bulkier cyclopentyl or *iso*-propyl residues; in those case products **3i** and **3j** were obtained in 87% and 90% e. e. Respectively.

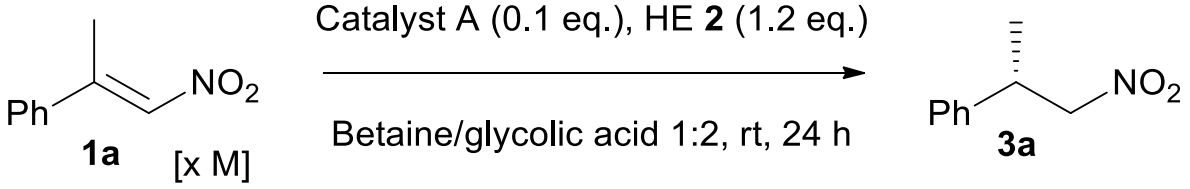
Having demonstrated the scope of the reaction and the versatility toward different substrates, we have attempted to implement a protocol for a gram-scale reaction. The reduction of (*E*)-1-nitro-2-phenyl-1-propene **1a** in choline chloride/glycerol 1:2 was selected to conduce this study.

At first, we worked on the optimization of the product isolation protocol, with the aim of minimizing the use of organic solvent in the work-up. We have tried to selectively extract the nitroalkane and the

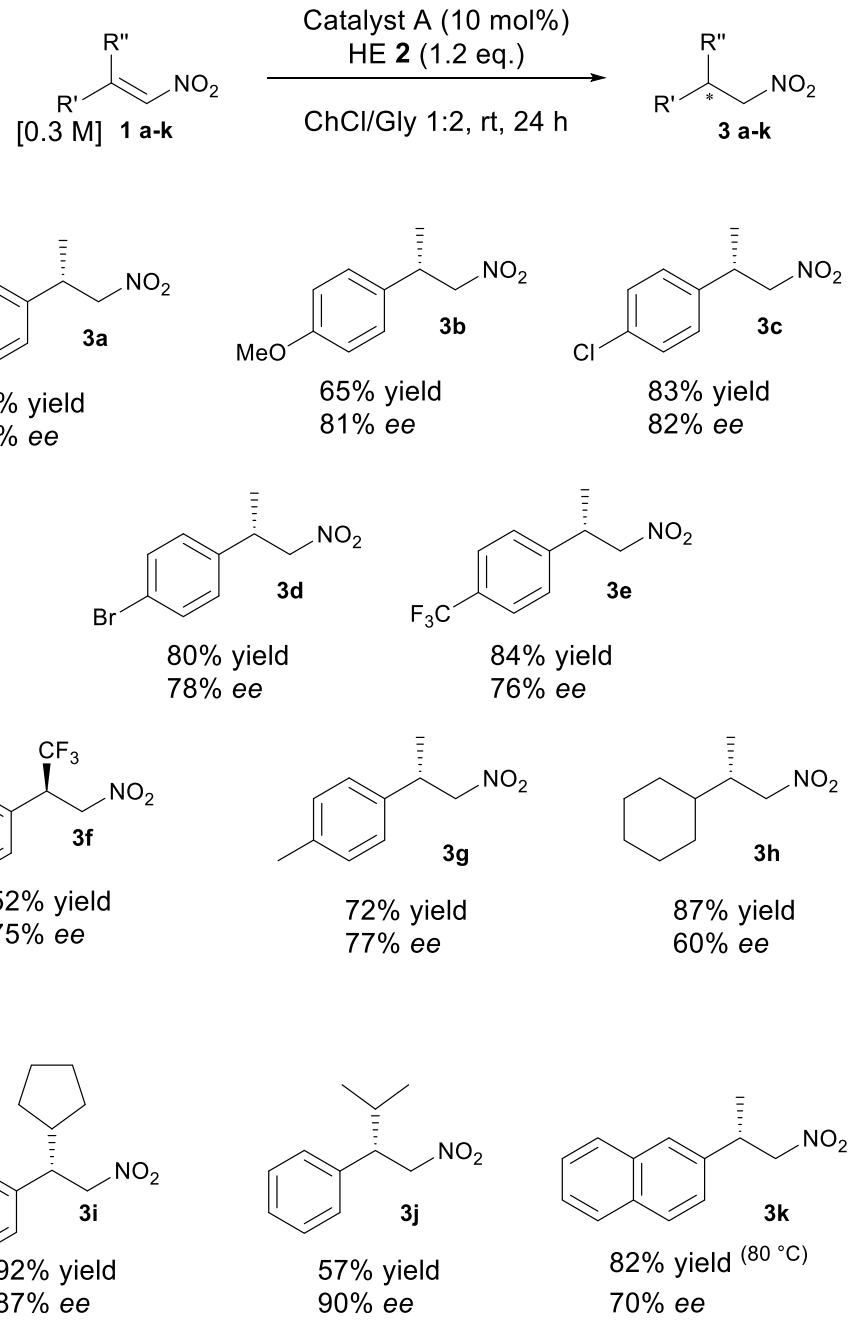


Scheme 2. Reaction media screening.

Table 3
Concentration screening.



Entry	*Concentration*	*Yield*	Ee
1	0.18 M	33%	77%
2	0.30 M	70%	78%
3	0.80 M	49%	79%



Scheme 3. Substrate scope.

pyridine side product, derived from the HE, with the minimum quantity of organic solvent, with the idea of reusing the DES mixture and the catalyst for further reactions. Unfortunately, all the tested solvents (ethyl acetate, methyl-*tert*-butyl ether and cyclopentyl-methyl ether) proved to solubilize also the catalyst, thus preventing the direct reuse of the reaction medium containing the catalyst (for further details See the SI). Next, we tried to separate the product, the catalyst and the pyridine side product by centrifugation, but the viscosity of the reaction medium precluded the possibility to achieve an efficient separation. Therefore, the addition of water to dissolve the DES was mandatory to separate it from the other components.

At last, in the best experimental protocol, aimed to facilitate the isolation of the product, at the end of the reaction the crude mixture was treated with 1:1 20% HCl_{aq}/THF solution and extracted with few ml of AcOEt. After solvent evaporation, a quick filtration of the organic phase on a short silica pad allowed to easily separate the hydrochloride salt of the pyridine derivative and the catalyst from the product, (*S*)-1-nitro-2-phenylpropane **3a**, that was isolated on gram scale in 80% yield and 85% *ee*, a comparable result with the data obtained in the reaction on mg scale.

The recovery of the catalyst was possible, but still presents some issues, since a second chromatography purification was necessary in order to isolate a cleaner catalyst, with only 30% recovery yield. The recycle of the recovered catalyst in a subsequent reaction led to the formation of the desired product in 76% yield and 77% *ee* (see the Supporting Information).

Another protocol was also studied, in order to verify the effect of the acidic treatment on the integrity and the stereochemical efficiency of the chiral organocatalyst. Therefore, at the end of the reaction, after water addition and extraction with AcOEt, a quick filtration on a short silica pad with DCM/Hexanes 3/7 mixture allowed to isolate the product in 85% yield. The recovered impure catalyst **A** (in mixture with traces of unreacted HE and pyridine derived from HE oxidation) was reused without further purification; also in this case, the reaction afforded the product in excellent yields and slightly lower enantioselectivity (88% yield, 78% *ee*).

3. Conclusions

In the landscape of green chemistry, Deep Eutectic Solvents represent an interesting alternative to traditional solvents. The first catalytic enantioselective reduction of nitroalkenes in such solvents mediated by a thiourea-based organocatalyst working through a hydrogen bond network with the reagents was disclosed. The reaction was tested employing eleven different substrates and the desired products were isolated in excellent yields (up to 92%) and very good enantiomeric excesses (up to 90%). A protocol to perform the reduction on gram-scale was also developed, and the reuse of the recovered chiral organocatalyst was established; however, the reaction product was obtained in slightly lower enantioselectivity, clearly indicating that the recovery protocol of the chiral catalyst needs a further work of optimization.

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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tchem.2023.100038.

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