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Chiral 2-Aminobenzimidazoles in deep eutectic mixtures: recyclable organocatalysts for the enantioselective Michael addition of 1,3-dicarbonyl compounds to β-nitroalkenes

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ABSTRACT: A catalytic system based on deep eutectic solvents and chiral 2-amino benzimidazole organocatalysts is used to promote the enantioselective addition of 1,3-dicarbonyl compounds to β-nitrostyrenes. This procedure avoids the use of toxic VOC as reaction medium, providing access to highly functionalized chiral molecules in a selective and efficient manner. Furthermore, the reaction can be performed on a large scale and the recyclability of the catalytic system is possible at least for four times, leading to a clean, cheap, simple and scalable procedure that meets most of the criteria required to be a green and sustainable process. NMR studies have

confirmed the key role of the hydrogen-bonding interactions between the DES and the chiral organocatalyst, which allow their recovery and the recyclability of the system.

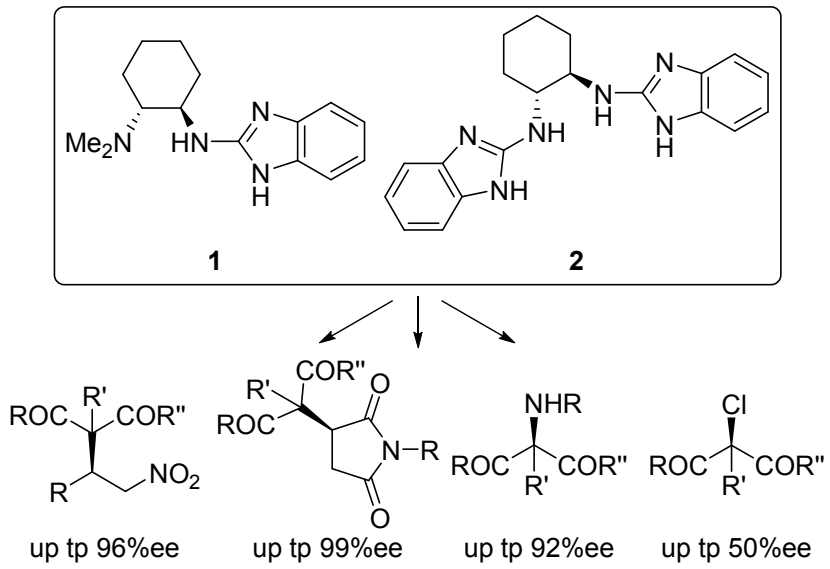
KEYWORDS Asymmetric Organocatalysis, Benzimidazole, Deep Eutectic Solvents, Green Chemistry, Conjugate Addition

Introduction

Organic chemistry needs strategies to make products in a greener, efficient, selective, safe and economic manner. Accounting for these strategies, recently, the combination of asymmetric organocatalyzed reactions with deep eutectic solvents (DES) as reaction media has been highlighted as a promising approach for the development of sustainable processes.[1-5]

The asymmetric conjugate addition to α,β-unsaturated organic substrates is a powerful and well-known method to synthesize structurally complex chiral molecules through C-C or C-X (X = O, N, S, etc) bond formation.[6-9] Among all the array of asymmetric Michael reactions, the conjugate addition of carbon nucleophiles to electron-poor alkenes is one of the most important ways of creating C-C bonds.[10,11] Particularly, the asymmetric organocatalyzed conjugate addition of carbon nucleophiles to α,β-unsaturated nitroolefins has recently attracted considerable attention, due to the possibility to set multiple stereocenters in a single synthetic operation usually employing mild conditions.[12-22] Furthermore, the final enantioenriched γ-nitrocarbonyl compounds are important building blocks which can be easily transformed into compounds of interest.[23]

Recently, our research group has demonstrated the usefulness of chiral 2-aminobenzimidazole derivatives **1** and **2** as organocatalysts in the asymmetric Michael addition of malonates, β-ketoesters, and 1,3-diketones to nitroolefins[24] and maleimides[25-27] as well as for the asymmetric α-chlorination[28,29] and α-amination[30] of these interesting nucleophiles (Scheme 1). Usually, due to the bifunctional Brønsted-base/hydrogen-bonding ~~activation~~ nature of catalysts **1** and **2**, very high enantioselectivities have been observed in the studied reactions using volatile organic solvents (VOCs) such as toluene or diethyl ether.



Scheme 1. Chiral benzimidazoles in asymmetric organocatalysis.

In organocatalyzed processes, the use of VOC as a reaction medium has inherent advantages. However, the negative impact on the environment and health of VOC due to their volatile nature, non-biodegradability, flammability and toxicity, has led to the search for alternative media to perform these and other chemical transformations.[31,32] Consequently, organocatalyzed reactions have been extensively studied under solvent-free conditions,[33,34] water[35] and ionic liquids,[36] among other alternative media.[37] However, the use of DES as a reaction medium for asymmetric

organocatalyzed processes has been only reported for the aldol reaction[38-42] and conjugated additions,[43,44] with the choice of the DES and design of the organocatalyst shown to be crucial to achieve good results and enable the organocatalyst recycling.

Herein, we describe the use of chiral benzimidazole derivatives as organocatalysts in the Michael addition of 1,3-dicarbonyl compounds to nitroalkenes using DES as reaction medium, showing that an appropriate design of the catalyst and choice of DES are crucial to achieve high yields, diastereo- and enantioselectivities.

Materials and Methods

General procedure for the preparation of Deep Eutectic Solvents. The two components of the DES, with the corresponding molar ratio, were added to a round bottom flask and the mixture was stirred for 60 minutes at 80 °C to afford the corresponding deep eutectic solvent. Then, the mixture was cool-down to room temperature and ~~it~~ was stored under argon atmosphere.

*General procedure for the conjugate addition of diethyl malonate to β-nitrostyrene catalyzed by **5**. Synthesis of **3a**.* Catalyst **5** (5.22 mg, 0.015 mmol, 10 mol%) and β-nitrostyrene (22.4 mg, 0.15 mmol) were dissolved in a mixture of choline chloride and glycerol (ChCl/Gly, 1/2 molar ratio, 0.2 mL) and kept under stirring for 10 minutes at rt. Then, the mixture was cooled-down to 0 ºC and diethyl malonate (50 μL, 0.30 mmol) was added. The reaction was vigorously stirred during 4 days at 0 ºC. After this period, water (3 mL) was added to the mixture and the reaction product was extracted with EtOAc (3×5 mL). The collected organic phases were dried over anhydrous $MgSO_4$ and, after filtration, the solvent was evaporated under reduced pressure to give crude **3a**. Purification by flash column chromatography on silica gel (hexane/EtOAc: 4/1) afforded pure

3a. The enantiomeric excess was determined by chiral HPLC analysis (Chiralpack AD, hexane/*i*PrOH: 90/10, 1 mL/min).

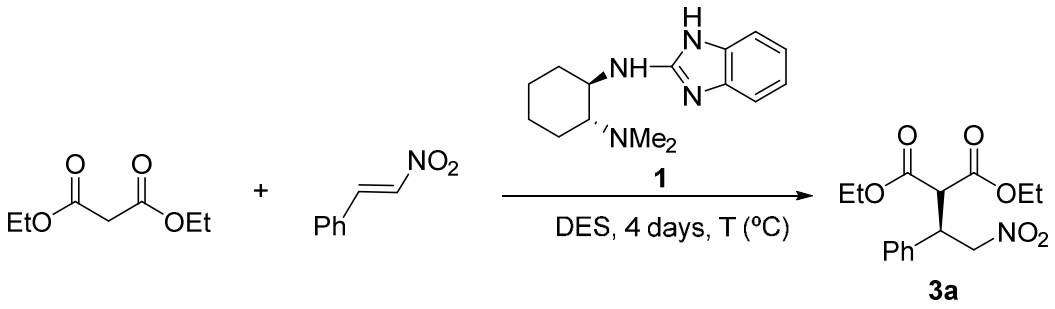
Recycling experiments. A mixture of catalyst **5** (5.22 mg, 0.015 mmol) and β-nitrostyrene (22.4 mg, 0.15 mmol) in ChCl/Gly (1/2 molar ratio, 0.2 mL) was stirred for 10 minutes at rt. Then, the mixture was cooled-down to 0 ºC and diethyl malonate (50 μL, 0.30 mmol) was added. The reaction was vigorously stirred for 4 days at 0 °C. After this period, the corresponding organic solvent was added (3 mL) and the mixture was stirred for 10 minutes at rt. The stirring was stopped to allow phase separation and the upper organic layer was removed. This extractive procedure was repeated two more times and the combined organic extracts were washed with water (3×5 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford the crude reaction product. The residual volatile organic solvent present in the DES/catalyst phase was removed under vacuum evaporation. Then, the next reaction cycle was performed with the DES containing catalyst **5**, adding fresh β-nitroestyrene and diethyl malonate. This reaction mixture was subjected again to the above-described procedure and further reaction cycles were repeated using the recycled deep eutectic solvent phase.

Results and discussion

Our group has previously shown that chiral benzimidazole **1** efficiently catalyzes the Michael addition of 1,3-dicarbonyl compounds to nitroolefins in toluene through a bifunctional Brønsted-base/hydrogen bonding activation.[24] In order to study the possibility of replacing toluene by a more sustainable solvent, we focused our attention on the **1**-catalyzed conjugate addition of diethyl malonate to β-nitrostyrene as a model reaction in different DES (Table 1). Initially, no reaction was observed under catalyst-free conditions at room temperature in two DES based on

the 1/2 molar ratio mixtures ChCl/Gly and ChCl/Urea (Table 1, entries 1 and 2). Next, the **1**-catalyzed reaction was studied in these solvents using different catalyst loadings (1-20 mol%) and concentrations (Table 1, entries 3-8). As shown, excellent conversions (>95%) and enantioselectivities between 50 and 65% were obtained, being the best enantioselectivity achieved when using ChCl/Gly (1/2) as solvent and 10 mol% of **1** (entry 5). Using this catalyst loading, the model conjugate addition was performed using other DES (Table 1, entries 9-15). Complete conversions were observed in all cases. However, only using ChCl/Malic acid, ChCl/Glu and Glu/Malic acid as reaction media, the best enantioselectivity (75% ee) for compound **3a** was achieved (Table 1, entries 9, 11, and 12). To compare, the model conjugate addition reaction was carried out in pure glycerol and in toluene as solvents (Table 1, entries 16 and 17), affording compound **3a** in good yields and similar enantioselectivities (73 and 75% ee, respectively). The observed selectivities are in agreement with the previously reported by our group using VOCs as solvents in the absence of acid co-catalysts.[24] The most selective DES were used to perform the model conjugate addition at 0 ºC. As depicted in Table 1, an improvement of the enantioselectivity of the reaction was observed at 0 ºC for all the tested solvents (entries 18-22, 80-83% ee), although only the mixtures ChCl/Gly (1/2) and ChCl/Urea (1/2) afforded complete reaction conversion (entries 18 and 19). Finally, when the reaction was tested using 1 mol% of **1** in both eutectic solvents, no product was detected (Table 1, entries 23 and 24).

Table 1. **1**-Catalyzed addition of diethyl malonate to β-nitrostyrene. Reaction conditions optimization.



Entry	**1** (mol%)/[M]	DES (molar ratio)	T (ºC)	Conv. (%)[a]	*ee* (%)[b]
1	(0)/[0]	ChCl/Gly (1/2)	25	0	0
2	(0)/[0]	ChCl/Urea (1/2)	25	0	0
3	(20)/[0.150]	ChCl/Gly (1/2)	25	>95	55
4	(20)/[0.150]	ChCl/Urea (1/2)	25	>95	50
5	(10)/[0.075]	ChCl/Gly (1/2)	25	>95	65
6	(10)/[0.075]	ChCl/Urea (1/2)	25	>95	60
7	(1)/[0.0075]	ChCl/Gly (1/2)	25	>95	60
8	(1)/[0.0075]	ChCl/Urea (1/2)	25	>95	60
9	(10)/[0.075]	ChCl/Malic acid (1/2)	25	>95	75
10	(10)/[0.075]	ChCl/Malonic acid (1/1)	25	>95	0
11	(10)/[0.075]	ChCl/Glucose (1/1)	25	>95	75
12	(10)/[0.075]	Glucose/Malic acid (1/1)	25	>95	75
13	(10)/[0.075]	ChCl/Resorcinol (1/1)	25	>95	20
14	(10)/[0.075]	AcCh/Urea (1/2)	25	>95	53
15	(10)/[0.075]	ChCl/H_2O (1/2)	25	>95	63
16	(10)/[0.075]	Gly	25	>95	73
17	(10)/[0.075]	Toluene	25	>95	75
18	(10)/[0.075]	ChCl/Gly (1/2)	0	>95	80
19	(10)/[0.075]	ChCl/Urea (1/2)	0	>95	80
20	(10)/[0.075]	ChCl/Malic acid (1/2)	0	50	83

21	(10)/[0.075]	ChCl/Glucose (1/1)	0	88	80
22	(10)/[0.075]	Glucose/Malic acid (1/1)	0	20	82
23	(1)/[0.0075]	ChCl/Gly (1/2)	0	-	-
24	(1)/[0.0075]	ChCl/Urea (1/2)	0	-	-

[a] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [b] Determined by chiral HPLC analysis (Chiralpack AD, hexane/^{i}PrOH: 90/10) of the crude reaction mixture.

In order to explore the influence of the catalyst structure in the reaction outcome, under the optimized reaction conditions (catalyst loading 10 mol%, ChCl/Gly (1/2) or ChCl/Urea (1/2) as solvents at 0 °C), the activity and selectivity of different chiral benzimidazole-derived organocatalysts in the model addition of diethyl malonate to β-nitrostyrene was studied (Table 2). All tested chiral catalysts showed high activity affording complete reaction conversion in both solvents. However, enantioselectivities varied notably depending on the electronic and/or steric nature of the chiral organocatalyst. The best results were obtained using the new benzimidazole derivative **5**, which afforded **3a** in a 91% ee in ChCl/Gly and 90% ee in ChCl/Urea (Table 2, entries 5 and 6). The presence on the benzimidazole ring of two strong electron-withdrawing nitro groups could probably account for the improvement of the selectivity of the process; due to an increase in the hydrogen-bonding ability of **5** and therefore the interaction with the DES structure. This was confirmed with chiral organocatalyst **6**, where the electron-donating ability of the amino group reduced the selectivity of the process in both DES affording **3a** in a lower enantioselectivity (67% ee, Table 2, entries 7 and 8). To further analyze the electronic effect observed in the asymmetric conjugate addition, the correlations of ln([*R*]/[*S*]) with Hammett constants of the *para*-substituents (σ-para) were conducted using the Hammett equation ln([R]/[S]) = ρ σ + c.[45] As depicted in Figure 1, the enantiomeric ratio [ln([*R*]/[*S*])] correlates with the *para* Hammett constant with ρ = 0.9483, R = 0.9606 (Figure 1).

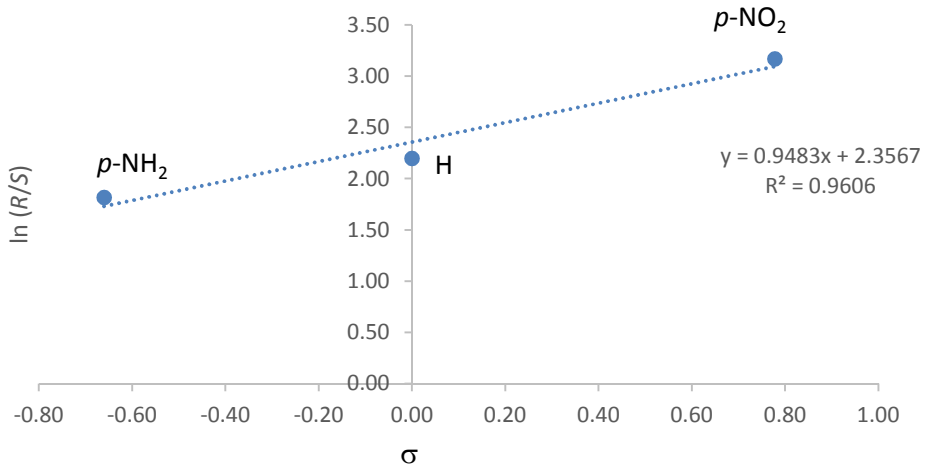
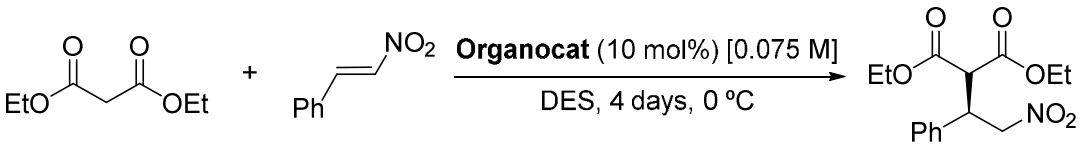
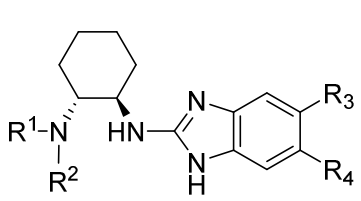


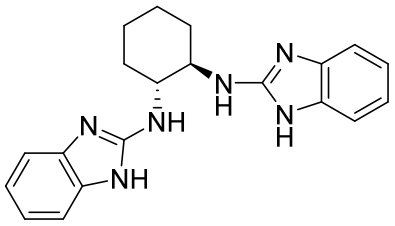
Figure 1. Hammett plots in the asymmetric conjugate addition reaction catalyzed chiral benzimidazoles.

The sterically congested C_2-symmetric chiral benzimidazole **2** afforded racemic **3a** in ChCl/Gly (Table 2, entry 9) while only a 30% ee was observed in the mixture ChCl/Urea (Table 2, entry 10). These results confirmed the importance of a good balance between the electronic and the steric properties of the organocatalyst, in order to obtain a good selectivity in the conjugate addition. The positive effect of acid co-catalysts, such as TFA, in the selectivity of chiral benzimidazole organocatalysts in conjugate addition reactions has been previously demonstrated by our group.[24-27] However, as depicted in Table 2 (entries 11-13), no improvement was observed when adding TFA, benzoic acid or water as additives (10 mol%) to **5** in the studied model reaction.

Table 2. Conjugate addition between diethyl malonate and β-nitrostyrene. Catalyst study.







2

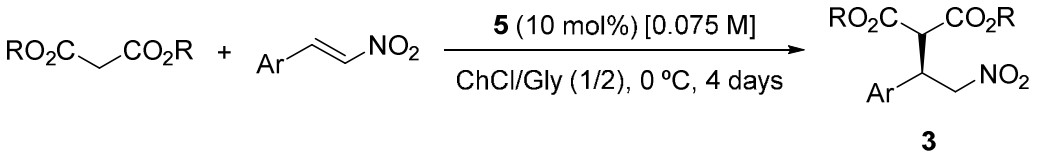
1, R_1, R_2 = Me; R_3, R_4 = H
4, R_1 = R_2 = R_3 = R_4 = H
5, R_1, R_2 = Me; R_3, R_4 = NO_2
6, R_1, R_2 = Me; R_3 = NH_2; R_4 = H

Entry	**Organocat**	DES (molar ratio)	Conv. (%)[a]	*ee* (%)[b]
1	**1**	ChCl/Gly (1/2)	>95	80
2	**1**	ChCl/Urea (1/2)	>95	80
3	**4**	ChCl/Gly (1/2)	>95	40
4	**4**	ChCl/Urea (1/2)	>95	60
5	**5**	ChCl/Gly (1/2)	>95	91
6	**5**	ChCl/Urea (1/2)	>95	90
7	**6**	ChCl/Gly (1/2)	>95	67
8	**6**	ChCl/Urea (1/2)	>95	67
9	**2**	ChCl/Gly (1/2)	>95	0
10	**2**	ChCl/Urea (1/2)	>95	30
11	**5**[c]	ChCl/Gly (1/2)	-	-
12	**5**[d]	ChCl/Gly (1/2)	>95	91
13	**5**[e]	ChCl/Gly (1/2)	>95	91

[a] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [b] Determined by chiral HPLC analysis (Chiralpack AD, hexane/^{i}PrOH: 90/10) of the crude reaction mixture. [c] The reaction was performed in the presence of TFA (10 mol%) as co-catalyst. [d] The reaction was performed in the presence of $PhCO_2H$ (10 mol%) as co-catalyst. [e] The reaction was performed in the presence of H_2O (10 mol%) as co-catalyst.

Under the optimized reaction conditions, the scope of the **5**-catalyzed Michael addition was examined (Table 3). Initially, it was demonstrated that the size of the ester group of the malonate had a marginal effect on the selectivity of the Michael adducts (Table 3, entries 1-3). However, using the most sterically hindered isopropyl malonate, the yield of the reaction was lower (Table 3, entry 3). Then, different β-nitrostyrenes were also tested in the addition with diethyl malonate achieving good enantioselectivities and high yields for all tested substrates. As shown in entries 4-7, irrespective of the electronic nature of the aromatic substituent, excellent yields and good enantioselectivities (80-90%) were observed for the corresponding Michael adducts **3**. Finally, the reaction of diethyl malonate with (*E*)-2-(2-nitrovinyl)thiophene gave **3g** in excellent yield and enantioselectivity (Table 3, entry 7).

Table 3. Conjugate addition of dialkyl malonates to nitroalkenes catalyzed by **5**.[a]



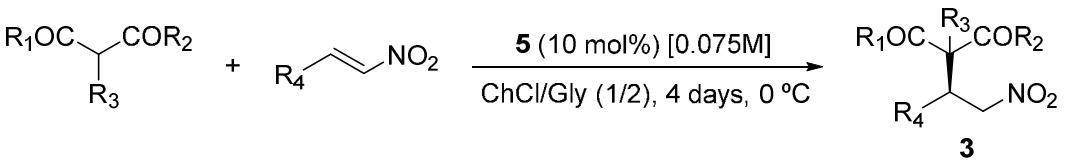
3

Entry	R	Ar	**No.**	Yield (%)[b]	*ee* (%)[c]
1	Et	Ph	**3a**	83	91
2	Me	Ph	**3b**	88	91
3	*i*-Pr	Ph	**3c**	63	90
4	Et	4-ClC_6H_4	**3d**	84	80
5	Et	2,4-$(Cl)_2C_6H_3$	**3e**	86	90
6	Et	4-MeC_6H_4	**3f**	87	85
7	Et	2-Thienyl	**3g**	85	90

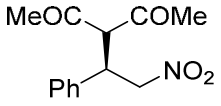
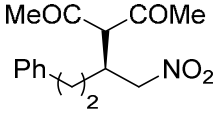
[a] Reaction conditions: nitroolefin (0.15 mmol), dialkyl malonate (0.30 mmol), catalyst **5** (0.015 mmol), ChCl/Gly (1/2 molar ratio, 0.2 mL), 0 °C, 4 days. [b] Isolated yield after flash chromatography. [c] Determined by chiral HPLC analysis of the crude reaction mixture (see SI for conditions).

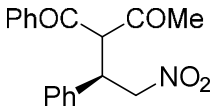
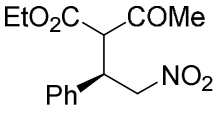
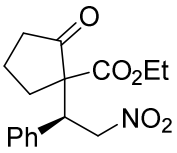
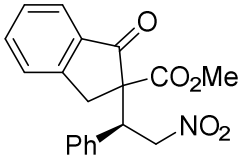
The efficiency of **5** in the conjugate addition to nitroalkenes was further evaluated with other 1,3-dicarbonyl compounds and nitroalkenes (Table 4). For instance, acetylacetone afforded, after reaction with β-nitroestyrene and (*E*)-4-phenyl-1-nitro-1-butene, compounds **3h** and **3i** in moderate to good yields and moderate enantioselectivities (77 and 67% ee, respectively). The conjugate addition of acyclic non-symmetrical 1,3-diketones, such as the reaction of 1-phenylbutane-1,3-dione with β-nitrostyrene (Table 4, entry 3), proceeded with low diastereoselectivity, to afford *ca.* a 1/1 diastereomeric mixture of compound **3j** with a 65% ee. In the case of the conjugate addition of acyclic β-ketoesters such as ethyl 3-oxobutenoate to β-nitrostyrene catalyzed by **5**, the ester moiety seemed to have little influence on the selectivity of the process, since good enantioselectivities for both diastereoisomers of **3k** were achieved (79% and 81% ee, Table 4, entry 4). α-Substituted β-ketoesters were also tested in the conjugate addition to β-nitrostyrene, affording adducts **3l** and **3m** with moderate yields and low to moderate enantioselectivities (Table 4, entries 5 and 6).

Table 4. Conjugate addition of 1,3-dicarbonyl compounds to nitroalkenes catalyzed by **5**.[a]



3

Entry	Product structure	**No.**	Yield (%)[b]	*dr* (%)[b]	*ee* (%)[d]
1		**3h**	91	-	77
2		**3i**	46	-	67

3		**3j**	96	57/43	65/65
4		**3k**	85	55/45	79/81
5		**3l**	66	58/42	<5/69
6		**3m**	52[e]	65/35	55/73

[a] Reaction conditions: nitroolefin (0.15 mmol), dialkyl malonate (0.30 mmol), **5** (0.015 mmol), ChCl/Gly (1/2 molar ratio, 0.2 mL), 0 °C, 4 days. [b] Isolated yield after flash chromatography. [c] Determined by ^{1}HNMR analysis of the crude reaction mixture. [d] Determined by chiral HPLC analysis of the crude reaction mixture (see SI for conditions). Diastereomeric mixtures were not separated when isolating the reaction product. [e] 1 equiv. of nucleophile was used.

Next, the recyclability and reuse of organocatalyst **5** was studied as well as the eutectic liquid in the model addition of diethyl malonate to β-nitrostyrene under the optimized reaction conditions (Table 2, entry 5). For this purpose, the extraction ability of 2-methyltetrahydrofuran (2-MeTHF), *tert*-butyl methyl ether (TBME), diethyl ether and hexane was tested with the aim of separating the unreactive reagents and reaction products from the DES/chiral organocatalyst mixture. As depicted in Figure 2, good conversions and enantioselectivities were observed for the two first runs irrespective of the extracting solvent used. However, the reaction conversion decreased in the third and the forth reaction cycles as far as ethereal solvents are concerned (Figures 2a-c). Especially with diethyl ether where no conjugate addition was observed after the third cycle (Figure 2b). ^{1}H-NMR analysis of the collected ethereal fractions, demonstrated the presence of the final Michael product and traces of the chiral organocatalyst (see SI). This partial extraction of the chiral organocatalyst by the ethereal solvents explains the reduction of the

catalytic activity of the DES/**5** system over the cycles. Fortunately, when the recycling was performed with hexane (where **5** is not soluble), high conversion and selectivity were achieved in the all the tested reaction cycles (Figure 2d).

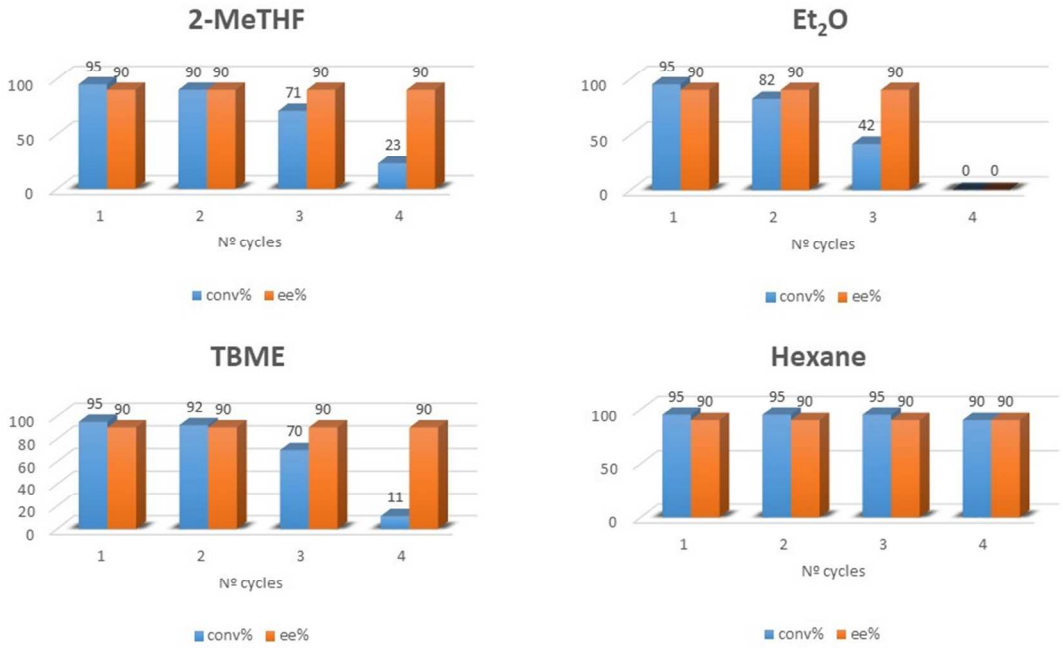


Figure 2. Recycling studies.

The synthetic utility of the catalytic methodology was confirmed by a gram-scale experiment (6.7 mmol of the Michael acceptor, 5 mol% of **5**) for the synthesis of compound **3a** which was obtained in a 90% ee and a 96% yield (Scheme 2).

Scheme 2. Gram-scale experiment.

In order to search for the molecular interactions involved between chiral organocatalyst **5** and the ChCl/Gly DES, we conducted an NMR study (Figure 3). Initially, we obtained the ^{1}HNMR spectra of catalyst **5**[46] (Figure 3a) and the DES (ChCl/Gly: 1/2, Figure 3b) in DMSO-d_6 where the most important ^{1}H resonances were assigned.[47,48] Then, in a separate experiment, 40 mg of **5** (0.11 mmol) were dissolved in 0.1 mL of the DES (ChCl/Gly: 1/2). A sample of this mixture was also analyzed by NMR (DMSO-d_6). The ^{1}HNMR spectrum of the resulting mixture (**5**+DES) is shown in Figure 3c where, in general, no strong chemical shift changes were observed for catalyst **5**. Only signal peak broadening was detected for those protons from **5** involved in exchange and/or strong H-bonding interactions with the eutectic mixture (H^2).

The existence of hydrogen-bond interactions[49] between DES components has been previously observed in different mixtures by using 2DNMR experiments[47,48,50] and neutron diffraction techniques.[51] Similar close-proximity relationships through space were detected in a NOESY experiment carried out over the **5**/ChCl-Gly mixture (see SI) using a DMSO-d_6 as solvent. In Figure 4 is represented a proposal based on the observed NOESY interactions between the two DES components and the chiral organocatalyst with the choline chloride component.

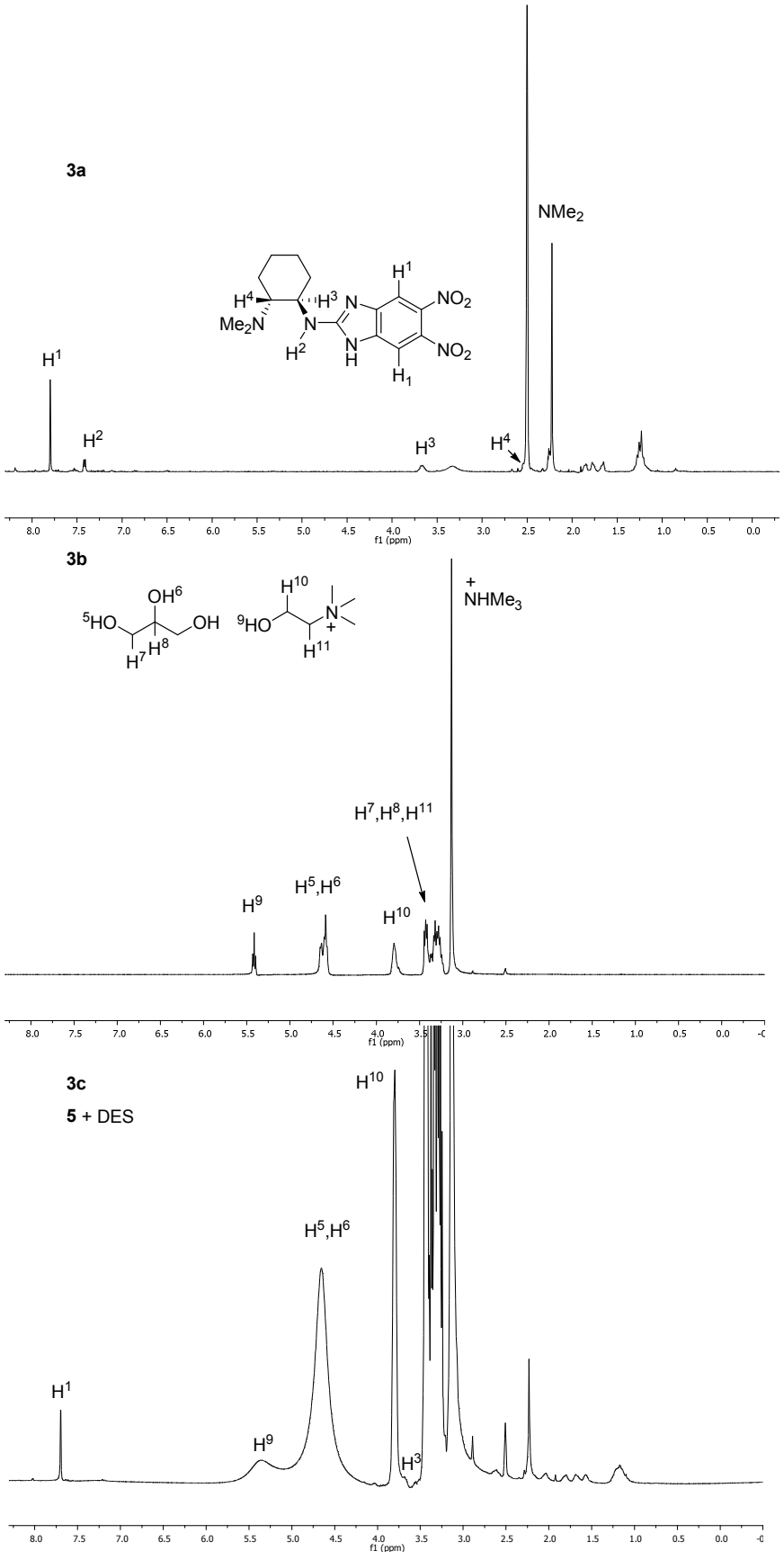

3a
NMe2
H1
H2
H3
H4
Me2N
NO2
NO2
3b
OH6
5HO
OH
H7
H8
9HO
H10
H11
+
NHMe3
H7,H8,H11
H5,H6
H9
H10
3c
5 + DES
H10
H5,H6
H1
H9
H3
f1 (ppm)

Figure 3. [1]HNMR spectra of: a) **5**; b) DES: ChCl/Gly (1/2); c) **5** + DES.

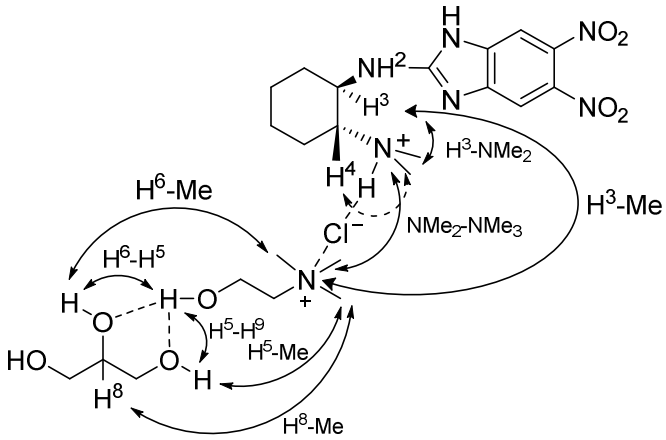


Figure 4. Proposed interaction of chiral organocatalyst **5** with the eutectic mixture. Arrows are used for the observed NOESY correlations.

The enantioselective conjugate addition of 1,3-dicarbonyl compounds to nitrostyrenes catalyzed by the bifunctional chiral 2-aminobenzimidazole-derivative **5** has been performed in a deep eutectic solvent formed by the choline chloride/glycerol combination. The procedures are clean, simple, cheap, scalable and safe. Furthermore, the catalyst and reaction media can be recovered and reused at least four times, achieving similar results. NMR studies have demonstrated the hydrogen-bonding interactions between the DES and the chiral organocatalyst. All these facts pointed out the possibility of carrying out enantioselective organocatalyzed organic reactions using deep eutectic solvents as reaction media, which have been proved to be a clear example of a green, bio-renewable and sustainable process.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and physical and spectroscopic data for the chiral catalysts and the optically active Michael adducts is provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. All authors contributed equally.

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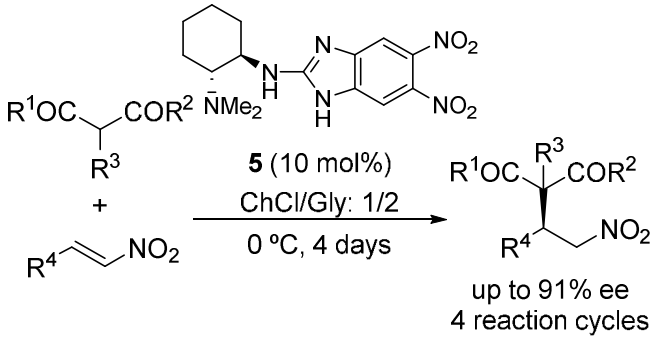
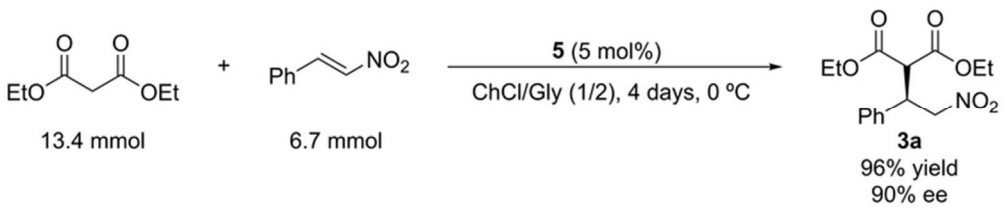
TOC/GRAPHICAL ABSTRACT



SYNOPSIS

Green, bio-renewable and sustainable enantioselective organocatalyzed conjugate addition using deep eutectic solvents made of choline chloride and glycerol as reaction medium.



Scheme 2

32x6mm (600 x 600 DPI)