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Deep Eutectic Mixtures as Reaction Media for the Enantioselective Organocatalyzed α-Amination of 1,3-Dicarbonyl Compounds

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Abstract: The enantioselective α-amination of 1,3-dicarbonyl compounds has been performed using deep eutectic solvents (DES) as a reaction media and chiral 2-amino benzimidazole-derived compounds as a catalytic system. With this procedure, the use of toxic volatile organic compounds (VOCs) as reaction media is avoided. Furthermore, highly functionalized chiral molecules, which are important intermediates for the natural product synthesis, are synthetized by an efficient and stereoselective protocol. Moreover, the reaction can be done on a preparative scale, with the recycling of the catalytic system being possible for at least five consecutive reaction runs. This procedure represents a cheap, simple, clean, and scalable method that meets most of the principles to be considered a green and sustainable process.

Keywords: asymmetric organocatalysis; α-amination; benzimidazole; deep eutectic solvents; natural products; green chemistry

1. Introduction

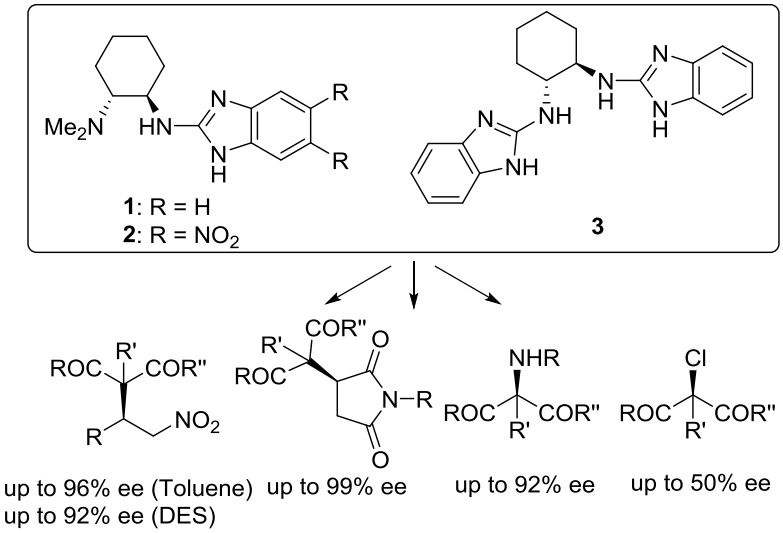
Asymmetric organocatalysis is an extremely attractive methodology for the preparation of functionalized chiral molecules and natural products, since small organic compounds are used as catalysts under very mild and simple reaction conditions [1–3]. Due to the lack of a metal element in the catalyst, organocatalytic methods are often used to prepare compounds that do not tolerate metal contamination such as pharmaceutical products. Asymmetric organocatalysis has become such an effective method of maintaining sustainability in organic synthesis as it provides many advantages, such as accessibility, low molecular weight, inexpensive catalysts and reduced toxicity.

Among the limited number of available green solvents, [4,5] deep eutectic solvents (DES) [6–12] maintain consistency within different criteria, such as availability, non-toxicity, inexpensiveness, high recyclability and low volatility. A deep eutectic solvent is a mixture between two or more components, one acting as hydrogen bond acceptor and the other as donor, having a melting point lower than the melting point of each one of the components. This behavior is due to hydrogen bond interactions between the acceptor and donor species. The use of DES as a reaction media is considered a new and expanding topic, which further assists and advances the importance of green chemistry. Recently, the association of these reaction media with asymmetric organocatalyzed processes [13,14] has been envisaged as a new and bright approach to advance sustainable processes.

Additionally, significant developments have been reached in the asymmetric electrophilic α-amination of carbonyl compounds through metal- or organo-catalyzed processes during recent

years [15–19]. In fact, chiral carbonyl derivatives bearing stereogenic α-amine substitution are widely distributed among pharmaceutically active compounds. In particular, the organocatalyzed asymmetric α-amination of prochiral 1,3-dicarbonyl compounds have received great interest, since the resulting functionalized chiral molecules can be further elaborated allowing the synthesis of chiral biologically active natural products. However, this process remains unexplored with DES as reaction media.

Our research group has established the practicality of bifunctional chiral 2-aminobenzimidazole derivatives [20,21] **1** and **3** (Scheme 1) as efficient organocatalysts in the asymmetric conjugate addition of 1,3-dicarbonyl compounds to nitroolefins [22] and maleimides [23,24] as well as in the α-functionalization [25–28] of these interesting nucleophiles using volatile organic solvents (VOCs) as a reaction medium. More fascinating, we have also demonstrated that the catalytic system based on the deep eutectic solvent choline chloride/glycerol and chiral 2-aminobenzimidazole organocatalysts **2** efficiently promotes the enantioselective addition of 1,3-dicarbonyl compounds to β-nitrostyrenes, avoiding the use of toxic VOC as reaction media [29].



Scheme 1. Chiral benzimidazoles in asymmetric organocatalysis.

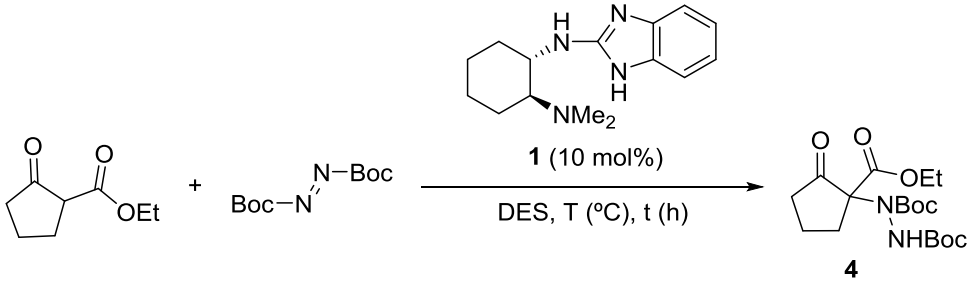
For asymmetric organocatalyzed processes, the use of DES as a reaction medium has been barely studied, with the aldol reaction [30–34] and conjugated addition [13,29,35] being the main focus. For these processes a rational design of the organocatalyst and the right choice of the DES has shown to be critical to obtain good results and allow organocatalyst recycling.

Herein, the use of chiral benzimidazole derivatives as organocatalysts for the electrophilic α-amination of 1,3-dicarbonyl compounds using DES as reaction media is presented.

2. Results and Discussion

Initially, the electrophilic α-amination of ethyl 2-oxocyclopentane-1-carboxylate with di-*tert*-butyl azodicarboxylate (DBAB) in the presence of catalyst 1 (10 mol %) in different choline chloride-based DES was investigated at 25 and 0 °C (Table 1). In general, good conversions and higher enantioselectivities were obtained at 0 °C, especially when using ChCl/urea (94%, 78% ee) and ChCl/glycerol (94%, 80% ee) as reaction media (Table 1, entries 2 and 6). The reaction time of the reaction was initially 4–5 h, however it was reduced to 1 h using ultrasounds (360 W) at 25 °C. The reduction in reaction time by the use of ultrasounds was previously observed in other related systems (i.e., ionic liquids), being attributed to physical-chemical effects [36,37]. As shown in Table 1, entries 12 and 13, under these conditions compound **4** was obtained with similar enantioselectivities with only a small erosion of the reaction conversion.

Table 1. Asymmetric α-amination of ethyl 2-oxocyclopentane-1-carboxylate with di-*tert*-butyl azodicarboxylate (DBAB). Deep eutectic solvents (DES) study.



4

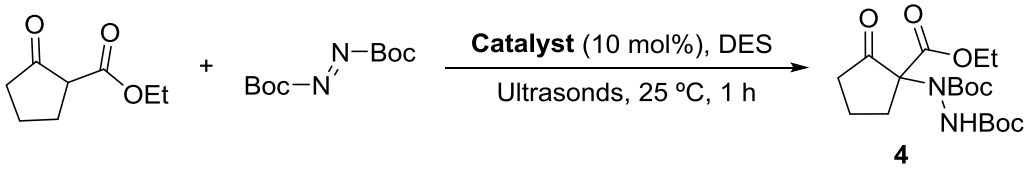
Entry	DES	T (°C)	t (h)	Conversion (%) [1]	Ee (%) [2]
1	ChCl/Urea: 1/2	25	5	61	77
2	ChCl/Urea: 1/2	0	5	94	78
3	AcChCl/Urea: 1/2	25	5	64	72
4	AcChCl/Urea: 1/2	0	5	55	75
5	ChCl/Glycerol: 1/2	25	5	94	73
6	ChCl/Glycerol: 1/2	0	5	94	80
7	ChCl/Ethyleneglycol: 1/2	25	5	78	72
8	ChCl/Ethyleneglycol: 1/2	0	5	84	70
9	ChCl/Malic acid: 1/1	25	5	<5	nd
10	ChCl/Tartaric acid: 1/1	25	5	64	76
11	ChCl/Tartaric acid: 1/1	0	5	58	77
12	ChCl/Urea: 1/2	25 [3]	1	92	76
13	ChCl/Glycerol: 1/2	25 [3]	1	80	80

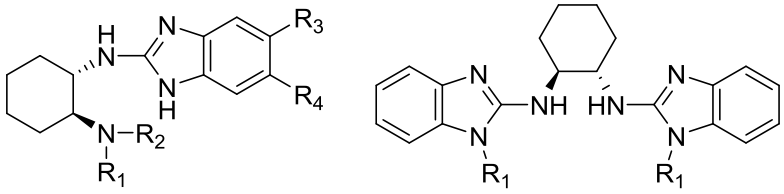
[1] Reaction conversion towards **4** determined by GC analysis. [2] Enantiomeric excess determined by chiral HPLC analysis. [3] Reaction performed under ultrasounds irradiation (360 W).

The optimization of the reaction medium resulted in the understanding that choline chloride/glycerol and choline chloride/urea were the best solvents to go forward with the conditions study using ultrasound irradiation at 25 °C. Next, the influence of the catalyst structure in the reaction results was studied: for this purpose, a series of several chiral benzimidazole-derived organocatalysts (as well other type of organocatalysts such as thiourea or sulphonamide derivatives, see Figure S1 in Supplementary Material) were tested in the α-amination model reaction under the optimized conditions using choline chloride/urea and choline chloride/glycerol as reaction media.

In both solvents, all chiral catalysts tested showed high performance achieving high reaction conversions (70–95%). However, different results concerning the enantioselectivities were encountered depending on the steric and/or electronic nature of the chiral organocatalyst. Chiral derivative **2**, containing two strong electron-withdrawing nitro groups lead to the best results, giving product **4** in 84% ee in ChCl/urea and 82% ee in ChCl/glycerol (Table 2, entries 3 and 4). The presence of two nitro groups on the benzimidazole ring increases the hydrogen-bonding ability of **2** and as a consequence the interaction with the DES structure, leading to an improvement of the selectivity of the electrophilic amination. Conversely, a strong decrease in the enantioselectivity of the process was observed when using the sterically congested C_2-symmetric chiral benzimidazoles **3** and **6**, which afforded compound **4** with enantiomeric excess ranging from 33 to 44% (Table 2, entries 7–10). It can be concluded that in order to obtain good selectivity in the amination addition, it is crucial to have good correlation between the steric and electronic properties within the organocatalyst [38].

Table 2. Asymmetric α-amination of ethyl 2-oxocyclopentane-1-carboxylate with DBAB. Catalyst study.





1, $R_1 = R_2 = Me$; $R_3 = R_4 = H$
2, $R_1 = R_2 = Me$; $R_3 = R_4 = NO_2$
5, $R_1 = R_2 = R_3 = R_4 = H$

3, $R_1 = H$
6, $R_1 = Me$

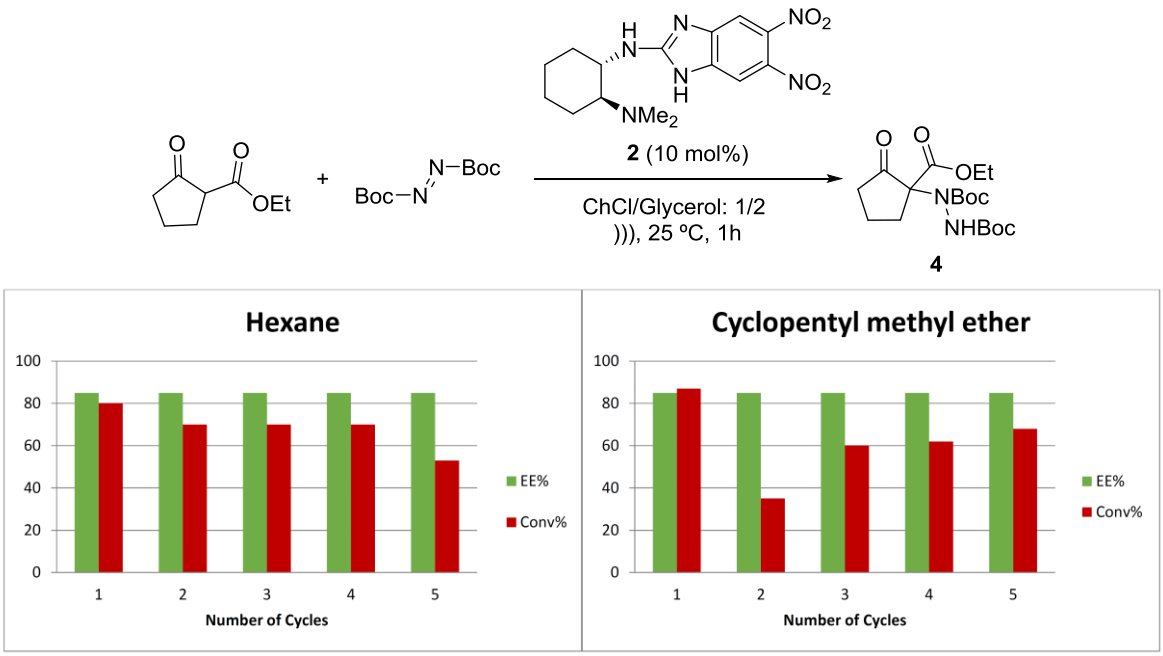
Entry	Catalyst	DES	Conversion (%) [1]	Ee (%) [2]
1	**1**	ChCl/Urea: 1/2	92	76
2	**1**	ChCl/Glycerol: 1/2	80	80
3	**2**	ChCl/Urea: 1/2	85	84
4	**2**	ChCl/Glycerol: 1/2	90	82
5	**5**	ChCl/Urea: 1/2	95	74
6	**5**	ChCl/Glycerol: 1/2	70	78
7	**3**	ChCl/Urea: 1/2	90	40
8	**3**	ChCl/Glycerol: 1/2	95	44
9	**6**	ChCl/Urea: 1/2	92	40
10	**6**	ChCl/Glycerol: 1/2	91	33

[1] Reaction conversion towards **4** determined by GC analysis. [2] Enantiomeric excess determined by chiral HPLC analysis.

The recyclability of organocatalyst **2** and the eutectic liquid was performed in the model reaction under the optimized reaction conditions (Scheme 2). Therefore, to separate the DES/chiral organocatalyst mixture from the unreactive reagents and reaction products, hexane and cyclopentyl methyl ether were tested as extractive media. As shown in Scheme 2, the product was extracted and most of the catalyst remained in the DES, with the mixture being recovered and reused in five consecutive reaction runs, maintaining high enantioselectivity but with a decreased activity. Furthermore, vigorous stirring is mandatory when performing the extraction of the products to obtain a good recyclability results. For instance, in the second cycle of the cyclopentyl methyl ether recovering sequence (Scheme 2), a standard stirring was used and therefore a decrease in the conversion was observed. However, for the third run, again a vigorous stirring was applied and the conversion of the process was almost recovered.

The efficiency and synthetic utility of **2** in ChCl/glycerol was further evaluated by performing a gram-scale experiment (4.3 mmol of ethyl 2-oxocyclopentane-1-carboxylate) for the synthesis of compound **4** which was obtained in a 95% yield and 85% ee (Scheme 3).

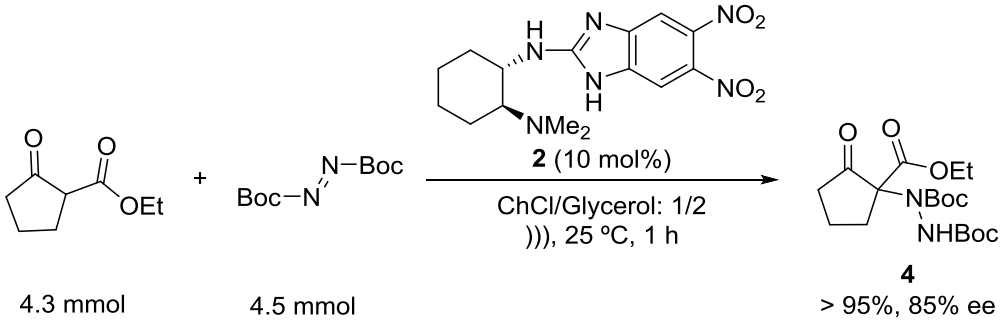
Lastly, the influence of different electrophiles and nucleophiles were assessed during the scope of the reaction. For this purpose, the different reactions were carried out under the optimized conditions using ChCl/glycerol as solvent (Table 3). Regarding the electrophile, an important steric effect was observed, being compound **4** obtained with the best enantioselectivity when using di-*tert*-butyl azodicarboxylate (DBAB) as electrophile (Table 3, entry 3). This electrophile was used for further studies.



Scheme 2. Recycling studies.

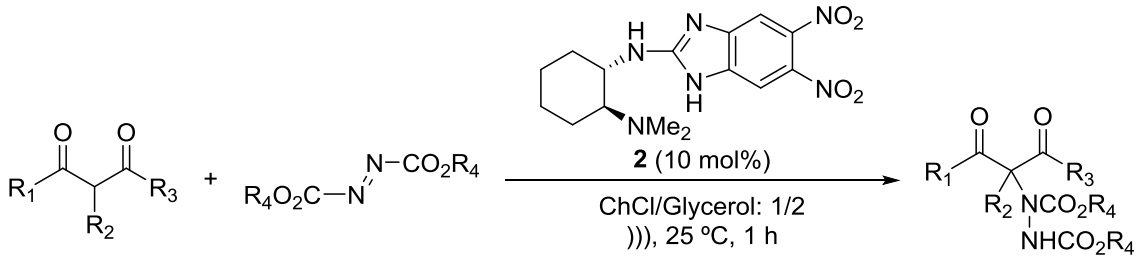
The α-amination of other β-ketoesters such as, ethyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate, methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate, and 3-acetyldihydrofuran-2(3*H*)-one was also assessed (Table 3, entries 5–7). In general, good isolated yields were obtained with low enantioselectivites (13 to 36% ee). Better enantioselection was observed in the α-amination with DBAB of 1,3-diketones, especially in the case of 2-acetylcyclopentan-1-one (Table 3, entry 9), which afforded compound **14** in a 75% isolated yield and 53% enantiomeric excess.

Due to accessibility, as well as green considerations, enantioselective organocatalysis has proved to be one of the most efficient approach towards the synthesis of drugs and natural products [39–43]. In particular, the organocatalytic functionalization of indolin-3-one has been recently studied since this type of heterocycles are commonly found in an ample range of biologically active natural alkaloids [44–48]. As depicted in Scheme 4 (Equation (a)), the **2**-catalyzed electrophilic α-amination of methyl 1-acetyl-3-oxoindoline-2-carboxylate [49] in ChCl/glycerol (1/2) as solvent under the optimized reaction conditions gave compound **15** in excellent yields and moderate enantioselectivities (**15a**: R = *i*Pr, 30% ee; **15b**: R = *t*Bu, 45% ee).

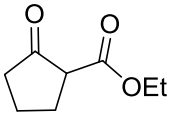
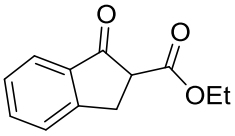
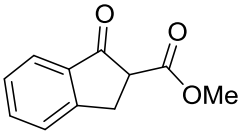
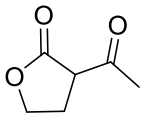
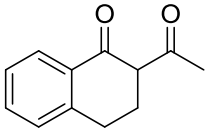
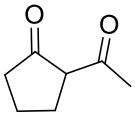


Scheme 3. Gram-scale α-amination of ethyl 2-oxocyclopentane-1-carboxylate catalyzed by **2**.

Table 3. Asymmetric α-amination catalyzed by **3**. Reaction scope.

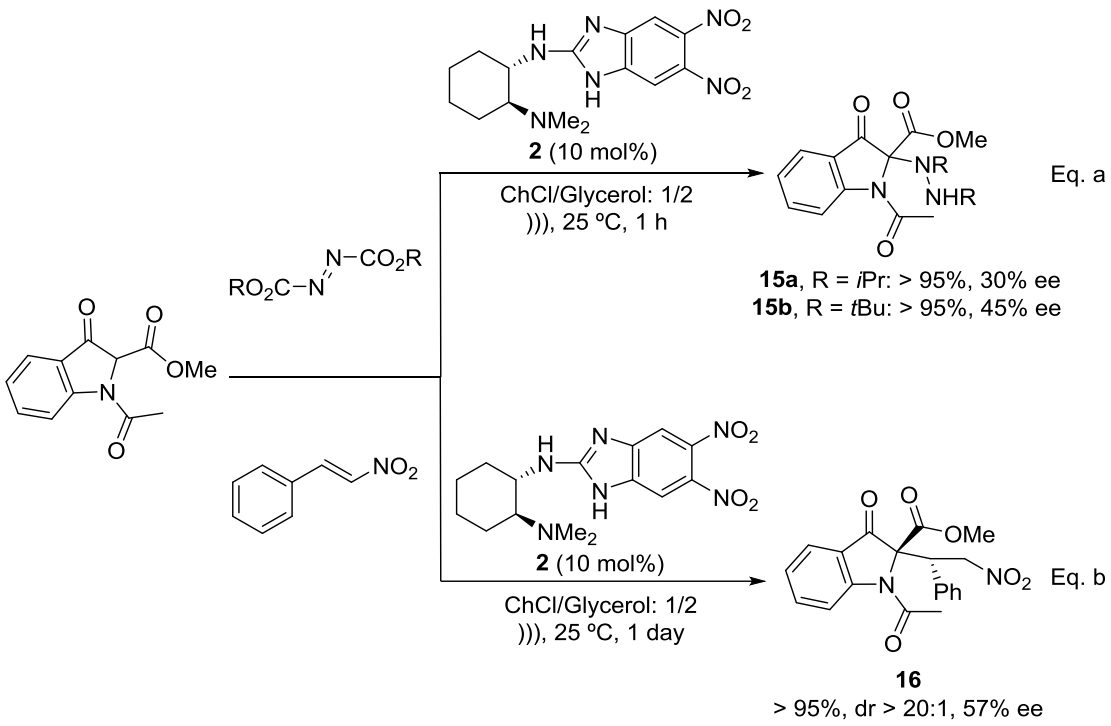


4, **7-14**

Entry	Dicarbonyl	Azodicarboxylate	Product	Yield (%) [1]	Ee (%) [2]
1		BocN=NBoc	**4**	78	85
2		*i*PrO$_2$CN=NCO$_2$*i*Pr	**7**	52	60
3		EtO$_2$CN=NCO$_2$Et	**8**	76	65
4		BnO$_2$CN=NCO$_2$Bn	**9**	0	nd
5		BocN=NBoc	**10**	66	36
6		BocN=NBoc	**11**	65	35
7		BocN=NBoc	**12**	65	13
8		BocN=NBoc	**13**	68	25
9		BocN=NBoc	**14**	75	53

[1] Isolated yield after flash chromatography. [2] Enantiomeric excess determined by chiral HPLC analysis.

On the other hand, 2,2-disubstituted oxindole **16**, which is a precursor of biologically active molecules containing indolin-3-ones with a quaternary stereocenter at the 2-position, such as Brevianamide A, Austamide, among others, has been prepared with excellent yield and diastereoselectivity and a 57% ee by the **2**-catalyzed conjugate addition of methyl 1-acetyl-3-oxoindoline-2-carboxylate to β-nitrostyrene [50] (Scheme 4, Equation (b)). The use of Takemoto´s thiourea type catalyst for this transformation led to compound 16 with similar results (>95%, dr > 20:1, 63% ee).



Scheme 4. Asymmetric organocatalyzed functionalization of methyl 1-acetyl-3-indol-2-carboxylate in DES.

3. Materials and Methods

3.1. General

Unless otherwise noted, all commercial reagents and solvents were used without further purification. Reactions under argon atmosphere were carried out in oven-dried glassware sealed with a rubber septum using anhydrous solvents. Melting points were determined with a hot plate apparatus and are uncorrected. ^{1}H-NMR (300 or 400 MHz) and ^{13}C-NMR (75 or 101 MHz) spectra were obtained on a Bruker AC-300 or AC-400(Bruke Corporation, Villerica, MA., USA), using $CDCl_3$ as solvent and tetramethyl silane (TMS) (0.003%) as reference, unless otherwise stated. Chemical shifts (δ) are reported in ppm values relative to TMS and coupling constants (*J*) in Hz. Low-resolution mass spectra (MS) were recorded in the electron impact mode (EI, 70 eV, He as carrier phase) using an Agilent 5973 Network Mass Selective Detector spectrometer (Agilent Technologies, Santa Clara, CA, USA), being the samples introduced through a GC chromatograph Agilent 6890N (Agilent Technologies, Santa Clara, CA, USA) equipped with a HP-5MS column [(5%-phenyl)-methylpolysiloxane; length 30 m; ID 0.25 mm; film 0.25 mm]. IR spectra were obtained using a JASCO FT/IR 4100 spectrophotometer (Jasco Analytical Spain, Madrid, Spain) equipped with an ATR component; wavenumbers are given in cm^{-1}. Analytical TLC was performed on Merck aluminium sheets with silica gel 60 F254. Analytical TLC was visualized with UV light at 254 nm Silica gel 60 (0.04–0.06 mm) was employed for flash chromatography whereas P/UV254 silica gel with $CaSO_4$ (28–32%) supported on glass plates was employed for preparative TLC. Chiral High-performance liquid chromatography (HPLC) analyses were performed on an Agilent 1100 Series (Agilent Technologies, Santa Clara, CA, USA), (Quat Pump G1311A, DAD G1315B detector and automatic injector) equipped with chiral columns using mixtures of hexane/isopropanol as mobile phase, at 25 °C. The asymmetric reactions were sonicated in an ultrasounds P-Selecta instrument at 360 W.

3.2. Synthesis of Catalyst 2

Catalyst **1** [51] (50 mg, 0.2 mmol, 1 equiv.) was dissolved in concentrated H_2SO_4 (0.2 mL, 98%) and stirred vigorously for 5 minutes; concentrated HNO_3 (0.4 mL, 65%) was then carefully added to the mixture at −20 °C. Then, the reaction was stirred at room temperature for 16 h. After this period, the mixture was treated with cold water and basified until pH 8 with a 25% aqueous solution of NH_3. Finally, the aqueous phase was extracted with AcOEt (3 × 20 mL). The collected organic phases were dried over anhydrous $MgSO_4$. After filtration, the organic solvent was removed under reduced pressure to give catalyst **2** without further purification as a red solid (74% yield, 52 mg, 0.15 mmol); mp 110–115 °C (CH_2Cl_2, decomposes); δ_H (300 MHz, $CDCl_3$) 1.19–1.49 (m, 4H, 2 × CH_2), 1.63–1.98 (m, 4H, 2 × CH_2), 2.37 (s, 6H, 2 × Me), 2.51 (m, 1H, $CHNMe_2$), 3.66 (bs, 1H, CHNH),7.49 (s, 2H, ArH); δ_C (75 MHz, $CDCl_3$) 21.7, 24.4, 24.6, 33.2, 39.8, 53.8, 67.8, 108.3, 136.8, 142.0, 161.8; *m*/*z* 348 [M^+, <1%] 128 (10), 126 (11), 125 (100), 124 (25), 84 (64), 71 (24), 58 (20), 44 (10).

3.3. Typical Procedure for the α-Amination Reaction

Catalyst **2** (5.22 mg, 0.015 mmol, 10 mol %) and ethyl 2-oxocyclopentane-1-carboxylate (23.4 mg, 0.15 mmol) were dissolved in a mixture of ChCl/Gly (1/2 molar ratio, 0.2 mL) and kept under stirring for 10 minutes at rt., followed by the addition of di-*tert*-butylazodicarboxylate (36.8 mg, 0.16 mmol). The reaction was vigorously stirred in ultrasounds for 1 h. 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 **4**. Purification by flash column chromatography on silica gel (hexane/EtOAc: 7/3) afforded pure **4** (45.1 mg, 78% yield). δ_H (300 MHz, $CDCl_3$) 1.28 (t, *J* = 7.1 Hz, 3H), 1.59–1.36 (m, 18H), 2.98–1.75 (m, 6H), 4.24 (m, 2H), 6.53 (br s, 1H) ppm). The enantiomeric excess of **4** was determined by chiral HPLC analysis (Chiralpack IA, hexane/EtOH: 96/04, 0.7 mL/min).

3.4. Typical Procedure for the Recovery of the Catalyst in the α-Amination Reaction

A mixture of catalyst **2** (5.22 mg, 0.015 mmol, 10 mol %) and ethyl 2-oxocyclopentane-1-carboxylate (23.4 mg, 0.15 mmol) in ChCl/Gly (1/2 molar ratio, 0.2 mL) was stirred for 10 minutes at rt. Then, di-*tert*-butylazodicarboxylate (36.8 mg, 0.16 mmol) was added. The reaction was vigorously stirred in ultrasounds for 1 h. After this period, the corresponding organic solvent was added (3 mL) and the mixture was stirred for 10 minutes at rt. The stirring was then 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. Then, the next reaction cycle was performed with the obtained DES/**2** mixture, adding fresh ethyl 2-oxocyclopentane-1-carboxylate and di-*tert*-butylazodicarboxylate. This reaction mixture was subjected again to the above-described procedure and further reaction cycles were repeated using the recycled deep eutectic solvent phase.

4. Conclusions

The enantioselective electrophilic α-amination of 1,3-dicarbonyl compounds with diazodicarboxylates catalyzed by the bifunctional chiral 2-aminobenzimidazole-derivative **2** has been carried out in choline chloride/glycerol or choline chloride/urea deep eutectic solvents. The protocols presented are simple, cheap, clean and scalable. Moreover, the recovery and reuse of the catalyst and reaction medium can be performed at least five times, achieving high and similar enantioselectivities. The synthesis of two natural product precursors is possible by the application of this procedure, as well as the conjugate addition to β-nitrostyrene. With these results, it has been shown that the combination of organocatalyzed enantioselective organic processes in deep eutectic solvents as a reaction media are a clear example of a green, bio-renewable and sustainable process.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/8/5/217/s1.

Author Contributions: D.R.Ñ. and P.K. performed the synthetic works. G.G. and D.A.A. designed the experiments of the project and supervised the whole studies reported in the manuscript. D.R.Ñ., P.K., G.G. and D.A.A. wrote the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

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