Peer-reviewed version available at Catalysts 2018, 8, 217; doi:10.3390/catal8050217

Article

Enantioselective Organocatalyzed α-Amination of 1,3-Dicarbonyl Compounds in Deep Eutectic Mixtures

Diego Ros Ñíguez, Pegah Khazaeli, Diego A. Alonso,* and Gabriela Guillena*

Departamento de Química Orgánica and Instituto de Síntesis Orgánica (ISO), Facultad de Ciencias, Universidad de Alicante. Apdo. 99, E-03080 Alicante, Spain.

* Correspondence: diego.alonso@ua.es (D.A.A.); gabriela.guillena@ua.es (G.G.); Tel.: +34-965909841 (D.A.A.); +34-965902888 (G.G.)

Abstract: The enantioselective α-amination of 1,3-dicarbonyl compounds has been performed using a catalytic system based on deep eutectic solvents (DES) and chiral 2-amino benzimidazole-derived organocatalysts. This procedure avoids the use of toxic volatile organic compounds (VOCs) as a reaction medium, providing access to highly functionalized chiral molecules, which are important intermediates for the natural product synthesis, in a selective and efficient manner. Furthermore, the reaction can be performed on a large scale and recycling the catalytic system is possible for at least five times, leading to a clean, cheap, simple, and scalable procedure that meets most of the criteria required to be a green and sustainable process.

Keywords: Asymmetric organocatalysis; Benzimidazole; α-Amination; Deep eutectic solvents; Green chemistry, Natural Products

---

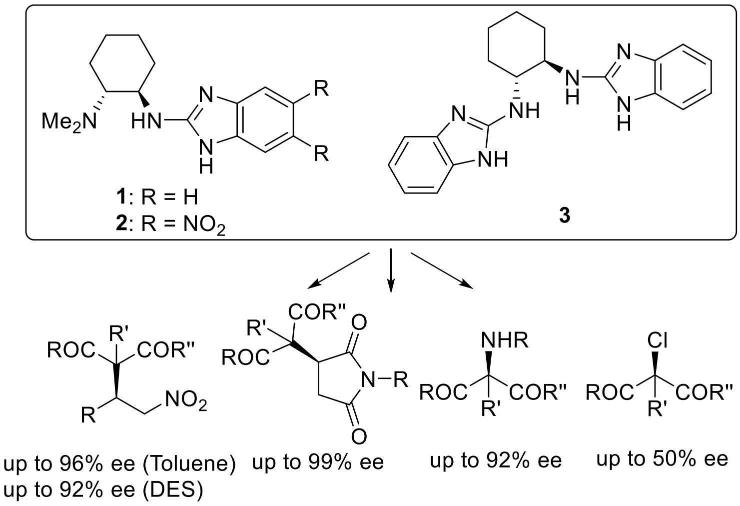
1. Introduction

Asymmetric organocatalysis is an extremely attractive methodology for the synthesis of functionalized chiral molecules and natural products since small organic molecules 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 and inexpensive catalysts and reduced toxicity.

On the other hand, among the limited number of available green solvents [4,5] deep eutectic solvents (DES)[6-12] maintain consistency within different criteria's, such as non-toxicity, inexpensive, high recyclability and availability and low volatility. The use of DES as reaction media is then considered a new and expanding topic, which further assist and advance the importance of green chemistry. Recently, the combination of asymmetric organocatalyzed reactions with DES[13,14] as reaction medium has been highlighted as a promising approach for the development of sustainable processes.

On the other hand, significant advances have been achieved in the metal-catalyzed or organocatalytic asymmetric electrophilic α-amination of carbonyl compounds with during the past years [15-19]. In fact, chiral carbonyl derivatives bearing stereogenic α-amine substitution are widely distributed among pharmaceutically active compounds. Particularly interesting is the organocatalyzed asymmetric α-amination of prochiral 1,3-dicarbonyl compounds, since the resulting functionalized chiral molecules can be further elaborated allowing the synthesis of chiral biologically active natural products. However, this process remains unrealized using DES as reaction medium.

Our research group has demonstrated 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 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 medium [29].



Scheme 1. Chiral benzimidazoles in asymmetric organocatalysis.

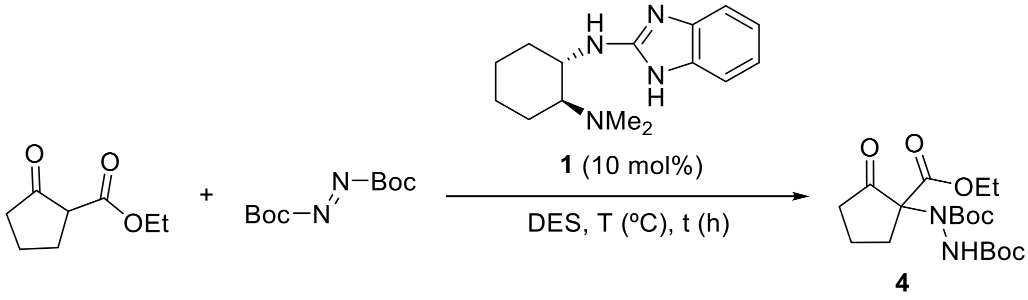
The use of DES as a reaction medium for asymmetric organocatalyzed processes has been barely studied being the aldol reaction [30-34] and conjugated additions[13,29,35] the main targets with the choice of the DES and design of the organocatalyst shown to be crucial to achieve good results and enable the organocatalyst recycling.

Herein, we describe the use of chiral benzimidazole derivatives as organocatalysts in the electrophilic α-amination of 1,3-dicarbonyl compounds using DES as reaction medium.

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 medium (Table 1, entries 2 and 6). The reaction time of the reactions (4-5 h) could be reduced to only 1 hour using ultrasounds (360 W) at 25°C. 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 DBAB. DES study.



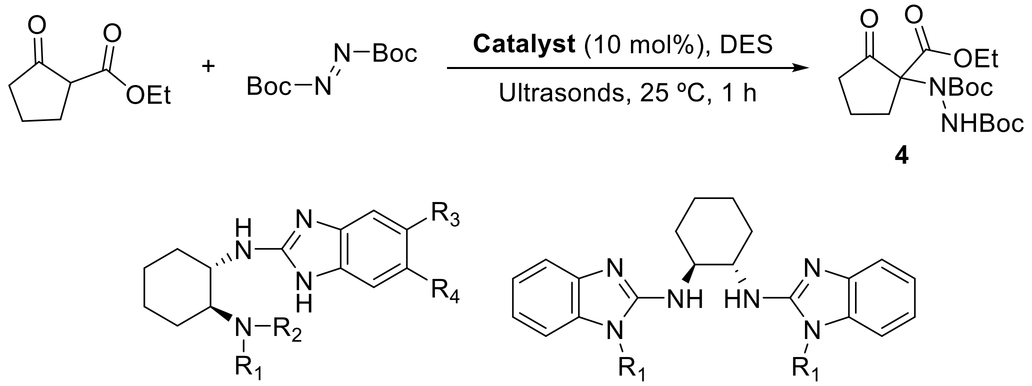
Entry	DES	T (ºC)	t (h)	Conversion (%)[1]	Ee (%)[2]
1	ChCl/Urea: 1/2	25	5	61	77

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. Then, in order to explore the influence of the catalyst structure in the reaction, a series of different chiral benzimidazole-derived organocatalysts were tested in the model α-amination reaction under the optimized conditions using choline chloride/urea and choline chloride/glycerol as reaction medium.

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, $R_1 = Me$

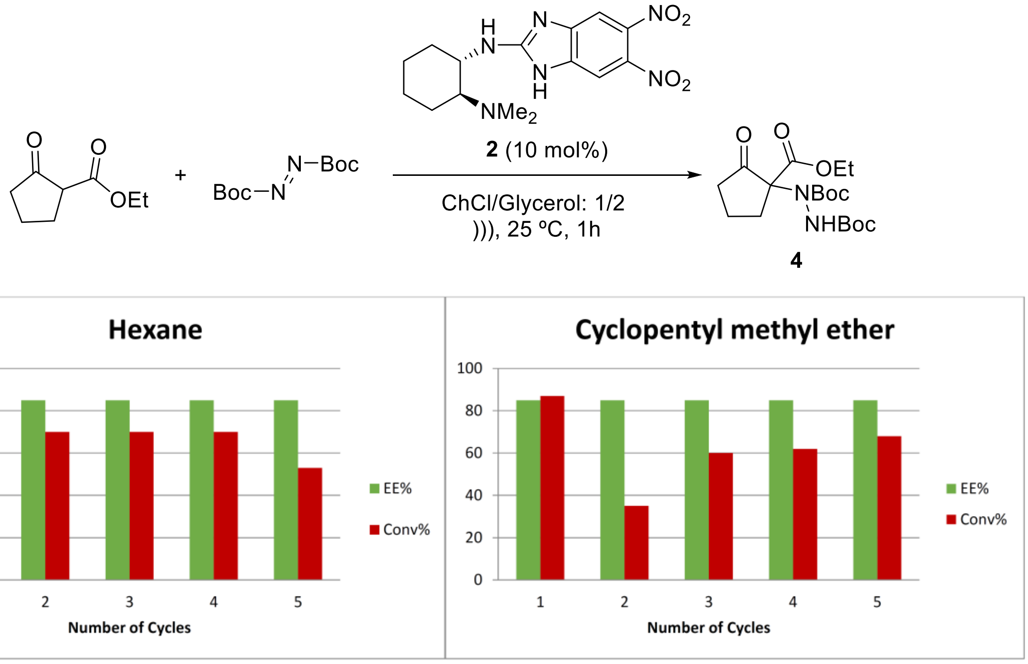
Entry	**Catalyst**	DES	Conversion (%)[1]	Ee (%)[2]
1	**1**	ChCl/Urea: 1/2	92	76
2	**1**	ChCl/Glycerol: 1/2	80	80
3	**2**	ChCl/Urea: 1/2	85	**84**
4	**2**	ChCl/Glycerol: 1/2	90	**82**
5	**5**	ChCl/Urea: 1/2	95	74
6	**5**	ChCl/Glycerol: 1/2	70	78
7	**3**	ChCl/Urea: 1/2	90	40
8	**3**	ChCl/Glycerol: 1/2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

Peer-reviewed version available at *Catalysts* **2018**, *8*, 217; doi:10.3390/catal8050217

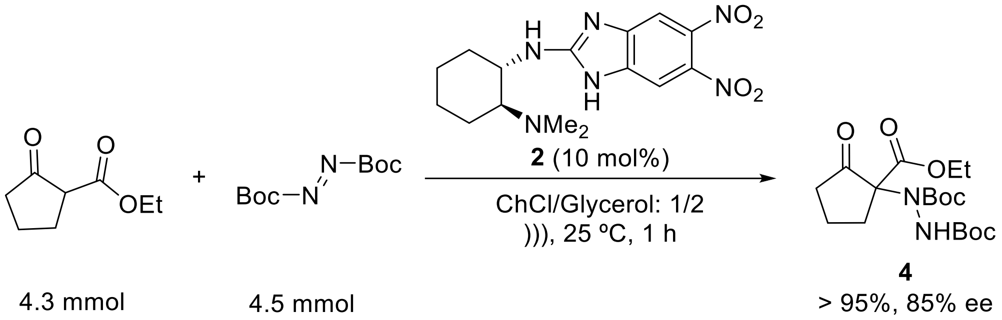
All chiral catalysts tested showed high performance achieving high reaction conversions (70-95%) in both solvents. However, enantioselectivities varied notably depending on the electronic and/or steric nature of the chiral organocatalyst. The best results were obtained using the chiral benzimidazole derivative **2**, containing two strong electron-withdrawing nitro groups, which resulted in **4** in a 84% ee in ChCl/urea and 82% ee in ChCl/glycerol (Table 2, entries 3 and 4). The presence on the benzimidazole ring of two nitro groups could probably account for the improvement of the selectivity of the electrophilic amination due to an increase in the hydrogen-bonding ability of **2** and therefore the interaction with the DES structure. 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). These latter results established 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 amination addition [36].

The recyclability of organocatalyst **2** and the eutectic liquid was performed in the model reaction under the optimized reaction conditions (Scheme 2). For this purpose, the extraction ability of hexane and cyclopentyl methyl ether was tested with the aim of separating the unreactive reagents and reaction products from the DES/chiral organocatalyst mixture. As shown in Scheme 2, the recovered catalyst was used in five consecutive runs while still maintaining high enantioselectivity but with reduced activity. Furthermore, a 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.



Scheme 2. Recycling studies.

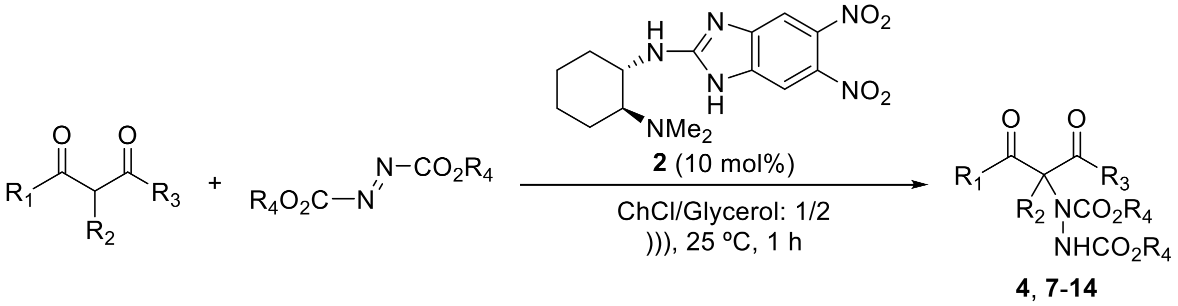
The efficiency and synthetic utility of **2** in ChCl/glycerol was further evaluated by performing a gram-scale experiment (4.3 mmol of ethyl 2-oxocyclopentane-1-carboxylate) for the synthesis of compound **4** which was obtained in a 95% yield and 85% ee (Scheme 3).

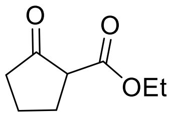
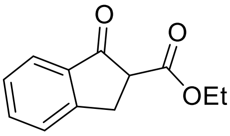
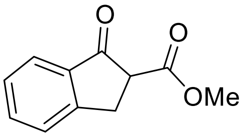
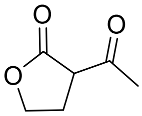


Scheme 3. Gram-scale α-amination of ethyl 2-oxocyclopentane-1-carboxylate catalyzed by **2**.

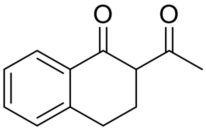
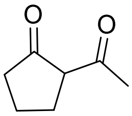
Lastly, the influence of different electrophiles and nucleophiles were assessed during the scope of the reaction. For this purpose, the different reactions were carried out under the optimized conditions using ChCl/glycerol as solvent (Table 3). Regarding the electrophile, an important steric effect 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.

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



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

Peer-reviewed version available at *Catalysts* **2018**, *8*, 217; doi:10.3390/catal8050217

8		BocN=NBoc	**13**	68	25
9		BocN=NBoc	**14**	75	53

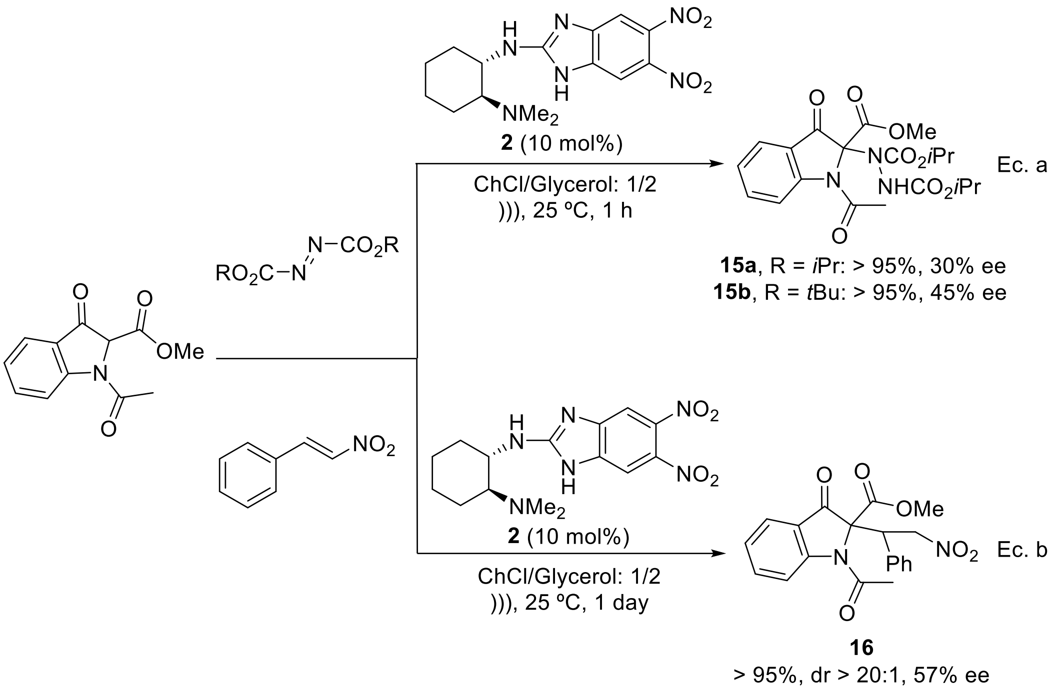
[1] Isolated yield after flash chromatography. [2] Enantiomeric excess determined by chiral HPLC analysis.

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 [37-41]. In particular, the organocatalytic functionalization of oxindoles have been recently studied since this type of heterocycles are commonly found in a wide range of biologically active natural alkaloids [42-46]. As depicted in Scheme 4 (Ec. a), the **2**-catalyzed electrophilic α-amination of methyl 1-acetyl-3-oxoindoline-2-carboxylate [47] in ChCl/glycerol (1/2) as solvent under the optimized reaction conditions led to compounds **15** in excellent yields and moderate enantioselectivities (**15a**: R = *i*Pr, 30% ee; **15b**: R = *t*Bu, 45% ee).

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 [48] (Scheme 4, Ec. b).

Peer-reviewed version available at Catalysts 2018, 8, 217; doi:10.3390/catal8050217



Scheme 4. Asymmetric organocatalyzed functionalization of methyl 1-acetyl-3-oxoindoline-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, using $CDCl_3$ as solvent and 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, being the samples introduced through a GC chromatograph Agilent 6890N 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 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 HPLC analyses were performed on an Agilent 1100 Series (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 a ultrasons P-Selecta instrument at 360 W.

3.2. Synthesis of Catalyst **2**

Peer-reviewed version available at Catalysts 2018, 8, 217; doi:10.3390/catal8050217

Catalyst **1** [49] (50 mg, 0,2 mmol, 1 equiv.) was dissolved in concentrated H_2SO_4 (0,2 mL, 98%) and stirred vigorously for 5 minutes; after this time concentrated HNO_3 (0,4 mL, 65%) was carefully added to the mixture at –20 °C. Then, the reaction was stirred at room temperature for 16 hours. 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 ºC (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); HRMS calcd. for $C_{13}H_{13}N_5O_4$ [M^+-$NHMe_2$] 303.0968, found 303.0964.

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. Then, di-*tert*-butylazodicarboxylate (36.8 mg, 0.16 mmol) was added. The reaction was vigorously stirred with ultrasounds 1 hour. 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 with ultrasounds for 1 hour. 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 performed in deep eutectic solvents formed by the choline chloride/glycerol or choline chloride /urea combinations. The procedures are clean, simple, cheap, scalable and safe. Furthermore, the catalyst and reaction media can be recovered and reused at least five times, achieving high and similar enantioselectivities. This procedure, as well as the conjugate addition to β-nitrostyrene, has been applied to the synthesis of two natural product precursors. All these facts conclude 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.

Supplementary Materials: The following are available online at

Acknowledgments: Financial support from the University of Alicante (UAUSTI16-03, UAUSTI16-10, VIGROB-173), the Spanish Ministerio de Economía, Industria y Competitividad (CTQ2015-66624-P) is acknowledged.

Author Contributions: Diego Ros Ñíguez and Pegah Khazaeli performed the synthetic works. Gabriela Guillena and Diego A. Alonso designed the experiments of the project and supervised the whole studies reported in the manuscript. Diego Ros Ñíguez, Pegah Khazaeli, Gabriela Guillena and Diego A. Alonso wrote the manuscript**.**

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

References and Notes

[1] Mahrwald, R. *Enantioselective organocatalyzed reactions*. Springer: Dordrecht, The Nertherlands, 2011.

[2] Berkessel, A.; Gröger, H. *Asymmetric organocatalysis - from biomimetic concepts to applications in asymmetric synthesis*. Wiley-VCH: Weinheim, Germany, 2006.

[3] Dalko, P. *Enantioselective Organocatalysis*. Wiley-VCH: Weinheim, Germany, 2007.

[4] Clarke, Coby J.; Tu, Wei-Chien; Levers, Oliver; Brohl, Andreas; Hallett, Jason P., Green and Sustainable Solvents in Chemical Processes. *Chem. Rev*. **2018**, *118*, 747-800.

[5] Kerton, F. M. (2016). Solvent Systems for Sustainable Chemistry. In Encyclopedia of Inorganic and Bioinorganic Chemistry. John Wiley & Sons.

[6] Liu, Y.; Friesen, J. B.; McAlpine, J. B.; Lankin, D. C.; Chen, S.-N.; Pauli, Guido F., Natural Deep Eutectic Solvents: Properties, Applications, and Perspectives. *J. Nat. Prod.* **2018**, *81*, 679-690.

[7] Zhang, Q.; De Oliveira Vigier, K.; Royera, S.; Jerome, F., Deep eutectic solvents: syntheses, properties and applications. *Chem. Soc. Rev.* **2012**, *41*, 7108-7146.

[8] García-Álvarez, J. Deep eutectic solvents and their applications as new green and biorenewable reaction media. In Handbook of Solvents; Wypych, G., Ed.; ChemTec Publishing: Toronto, Canada, 2014, Vol. 2, p 813-844.

[9] Guajardo, N.; Müller, C. R.; Schrebler, R.; Carlesi, C.; Domínguez de María, P. Deep eutectic solvents for organocatalysis, biotransformations, and multistep organocatalyst/enzyme combinations. *ChemCatChem*, **2016**, *8*, 1020–1027.

[10] Alonso, D. A.; Baeza, A.; Chinchilla, R.; Guillena, G.; Pastor, I. P.; Ramón, D. J. Deep Eutectic Solvents: The Organic Reaction Medium of the Century. *Eur. J. Org. Chem*. **2016**, *2016*, 612–632.

[11] García-Álvarez, J. Deep Eutectic Mixtures: Promising Sustainable Solvents for Metal-Catalysed and Metal-Mediated Organic Reactions. *Eur. J. Inorg. Chem.* **2015**, *2015*, 5147–5157.

[12] García-Álvarez, J.; Hevia, E.; Capriati, V. Reactivity of Polar Organometallic Compounds in Unconventional Reaction Media: Challenges and Opportunities. *Eur. J. Org. Chem.* **2015**, *2015*, 6779–6799.

[13] Massolo, E.; Palmieri, S.; Benaglia, M.; Capriati, V.; Perna, F. M., Stereoselective organocatalysed reactions in deep eutectic solvents: highly tunable and biorenewable reaction media for sustainable organic synthesis. *Green Chem.* **2016**, *18*, 792-797.

[14] Branco, L. C.; Faisca Phillips, A. M.; Marques, M. M.; Gago, S.; Branco, P. S. Recent advances in sustainable organocatalysis. *In Recent Advances in Organocatalysis;* Karame, I.; Srour, H., Eds.; InTech: Rijeka, Croatia, 2016, pp. 141-182: ISBN: 978-953-51-2673-7.

[15] Genet, J.-P.; Creck, C.; Lavergne, D. In Modern Amination Methods; Ricci, A., Eds.; Wiley-VCH: Weinheim, 2000; Chapter 3.

Peer-reviewed version available at *Catalysts* **2018**, *8*, 217; doi:10.3390/catal8050217

[16] Amino Group Chemistry: From Synthesis to the Life Sciences; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2008.

[17] Janey, J. M., Recent Advances in Catalytic, Enantioselective α-Aminations and α-Oxygenations of Carbonyl Compounds. *Angew. Chem. Int. Ed*. **2005**, *44*, 4292-4300.

[18] Smith, A. M. R.; Hii, K. K., Transition Metal Catalyzed Enantioselective α-Heterofunctionalization of Carbonyl Compounds. *Chem. Rev.* **2011**, *111*, 1637-1656.

[19] Zhou, F.; Liao, F.-M.; Yu, J.-S.; Zhou, J., Catalytic Asymmetric Electrophilic Amination Reactions to Form Nitrogen-Bearing Tetrasubstituted Carbon Stereocenters. *Synthesis* **2014**, *46*, 2983-3003.

[20] Khose, V. N.; John, M. E.; Pandey, A. D.; Karnik, A. V., Chiral benzimidazoles and their applications in stereodiscrimination processes. *Tetrahedron: Asymmetry* **2017**, *28*, 1233-1289.

[21] Nájera, C.; Yus, M., Chiral benzimidazoles as hydrogen bonding organocatalysts. *Tetrahedron Letters* **2015**, *56*, 2623-2633.

[22] Almaşi, D.; Alonso, D. A.; Gómez-Bengoa, E.; Nájera, C., Chiral 2-Aminobenzimidazoles as Recoverable Organocatalysts for the Addition of 1,3-Dicarbonyl Compounds to Nitroalkenes. *J. Org. Chem.* **2009,** *74*, 6163-6168.

[23] Gómez-Torres, E.; Alonso, D. A.; Gómez-Bengoa, E.; Nájera, C., Conjugate Addition of 1,3-Dicarbonyl Compounds to Maleimides Using a Chiral C2-Symmetric Bis(2-aminobenzimidazole) as Recyclable Organocatalyst. *Org. Lett.* **2011,** *13*, 6106-6109.

[24] Gómez-Torres, E.; Alonso, D. A.; Gómez-Bengoa, E.; Nájera, C., Enantioselective Synthesis of Succinimides by Michael Addition of 1,3-Dicarbonyl Compounds to Maleimides Catalyzed by a Chiral Bis(2-aminobenzimidazole) Organocatalyst. *Eur. J. Org. Chem*. **2013**, *2013*, 1434-1440.

[25] Gómez-Martínez, M.; Alonso, D. A.; Pastor, I. P.; Guillena, G.; Baeza, A., Organocatalyzed Assembly of Chlorinated Quaternary Stereogenic Centers, *Asian J. Org. Chem.* 2016, *5*, 1428-1437.

[26] Sánchez, D.; Baeza, A.; Alonso, D., Organocatalytic Asymmetric α-Chlorination of 1,3-Dicarbonyl Compounds Catalyzed by 2-Aminobenzimidazole Derivatives. *Symmetry*, **2016**, *8*, 3-13.

[27] Trillo, P.; Gómez-Martínez, M.; Alonso, D. A.; Baeza, A., 2-Aminobenzimidazole Organocatalyzed Asymmetric Amination of Cyclic 1,3-Dicarbonyl Compounds. *Synlett*, **2015**, *26*, 95-100.

[28] Benavent, L.; Puccetti, F.; Baeza, A.; Gómez-Martínez, M., Readily Available Chiral Benzimidazoles-Derived Guanidines as Organocatalysts in the Asymmetric α-Amination of 1,3-Dicarbonyl Compounds. *Molecules* **2017**, *22*, 1333-1344.

[29] Ñíguez, D. R.; Guillena, G.; Alonso, D. A., Chiral 2-Aminobenzimidazoles in Deep Eutectic Mixtures: Recyclable Organocatalysts for the Enantioselective Michael Addition of 1,3-Dicarbonyl Compounds to β-Nitroalkenes. *ACS Sustain. Chem. Eng.* **2017**, *5*, 10649-10656.

[30] Muller, C. R.; Meiners, I.; Domínguez de María, P. Highly enantioselective tandem enzyme–organocatalyst crossed aldol reactions with acetaldehyde in deep-eutectic-solvents, *RSC Adv.*, **2014**, *4*, 46097–46101.

[31] Muller, C. R.; Rosen, A.; Domínguez de María, P. Multi-step enzyme-organocatalyst C–C bond forming reactions in deep-eutectic-solvents: towards improved performances by organocatalyst design, *Sustain. Chem. Process* **2015**, *3*, 12-20.

[32] Martínez, R.; Berbegal, L.; Guillena, G.; Ramón, D. J. Bio-renewable enantioselective aldol reaction in natural deep eutectic solvents. *Green Chem.*, **2016**, *18*, 1724–1730.

Peer-reviewed version available at *Catalysts* **2018**, *8*, 217; doi:10.3390/catal8050217

[33] Fanjul-Mosteirín, N; Concellon, C.; del Amo, V., L-Isoleucine in a choline chloride/ethylene glycol deep eutectic solvent: a reusable reaction kit for the asymmetric cross-aldol carboligation, *Org. Lett.* **2016**, *18*, 4266–4269.

[34] Brenna, D.; Massolo, E.; Puglisi, A; Rossi, S.; Celentano, G.; Benaglia M.; Capriati, V. Towards the development of continuous, organocatalytic, and stereoselective reactions in deep eutectic solvents. *Beilstein J. Org. Chem*. **2016**, *12*, 2620–2626.

[35] Flores-Ferrándiz, J.; Chinchilla, R. Organocatalytic enantioselective conjugate addition of aldehydes to maleimides in deep eutectic solvents, *Tetrahedron: Asymmetry* **2017**, *28*, 302–306.

[36] For the full catalyst optimization study, see the SI.

[37] Merad, J.; Lalli, C.; Bernadat, G.; Maury, J.; Masson, G., Enantioselective BrønstedAcid Catalysis as a Toolfor the Synthesis of Natural Products and Pharmaceuticals. *Chem. Eur.J.* **2018**, *24*, 3925-3943.

[38] Dibello, E.; Gamenara, D.; Seoane, G., Organocatalysis in the Synthesis of Natural Products: Recent Developments in Aldol and Mannich Reactions, and 1,4-Conjugated Additions. *Curr. Organocat.* **2015**, *2*, 124-149.

[39] Sun, B.-F., Total synthesis of natural and pharmaceutical products powered by organocatalytic reactions. *Tetrahedron Lett.* **2015**, 2133–2140.

[40] Yu, J.; Zhou, Y.; Chen, D. F.; Gong, L.-Z., Organocatalytic asymmetric synthesis of chiral nitrogenous heterocycles and natural products. *Pure Appl. Chem.* **2014**, 86, 1217-1226.

[41] Abbasov, M. E.; Romo, D., The ever-expanding role of asymmetric covalent organocatalysis in scalable, natural product synthesis. *Nat. Prod. Rep*. **2014**, *31*, 1318-1327.

[42] Yu, B.; Xing, H.; Yu, D.-Q.; Liu, H.-M., Catalytic asymmetric synthesis of biologically important 3-hydroxyoxindoles: An update. *Beilstein J. Org. Chem.* **2016**, *12*, 1000-1039.

[43] Macaev, F. Z.; Sucman, N. S.; Boldescu, V. V., Selective transformations of isatins to substituted 2-oxindoles. *Russ. Chem. Bull*. **2014**, *63*, 15-25.

[44] Dalpozzo, R.; Bartoli, G.; Bencivenni, G., Recent advances in organocatalytic methods for the synthesis of disubstituted 2- and 3-indolinones. *Chem. Soc. Rev.* **2012**, *41*, 7247-7290.

[45] Badillo, J. J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug. Discov. Devel.* **2010**, *13*, 758-776.

[46] Chauhan, P.; Chimni, S. S., Organocatalytic asymmetric synthesis of 3-amino-2-oxindole derivatives bearing a tetra-substituted stereocenter. *Tetrahedron: Asymmetry*, **2013**, *24*, 343-356.

[47] Yarlagadda, S.; Ramesh, B.; Reddy, C. R.; Srinivas, L.; Sridhar, B., Subba Reddy, B.V., Organocatalytic Enantioselective Amination of 2-Substituted Indolin-3-ones: A Strategy for the Synthesis of Chiral α-Hydrazino Esters. *Org. Lett.* **2017**, *19*, 170-173.

[48] Jin, C.-Y.; Wang, Y.; Liu, Y.-Z.; Shen, C.; Xu, P.-F., Organocatalytic Asymmetric Michael Addition of Oxindoles to Nitroolefins for the Synthesis of 2,2-Disubstituted Oxindoles Bearing Adjacent Quaternary and Tertiary Stereocenters. *J. Org. Chem.* **2012,** *77* (24), 11307-11312.

[49] For the synthesis of catalyst **1** see SI.