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Organocatalytic enantioselective conjugate addition of aldehydes to maleimides in deep eutectic solvents

Jesús Flores-Ferrándiz, Rafael Chinchilla *

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

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ABSTRACT

The conjugate enantioselective addition of aldehydes, mainly α,α-disubstituted, to maleimides leading to enantioenriched succinimides, has been achieved in recyclable deep eutectic solvents at room temperature. Enantiomerically pure carbamate-monoprotected *trans*-cyclohexane-1,2-diamines are used as organocatalysts, affording high yields and up to 94% *ee* of the final succinimides. The product can be extracted from the deep eutectic solvent, which retains the chiral organocatalyst, allowing both the solvent and catalyst to be reused.

1. Introduction

Over the last few years, enantioselective organocatalysis has established itself as a crucial synthetic tool when the stereoselective preparation of compounds of interest is intended.[1] Thus, the use of small chiral metal-free molecules as catalysts is environmentally advantageous if the synthetic procedure is designed to be scaled-up. However, some disadvantages still hamper the consideration of enantioselective organocatalysis as a common methodology in chemical industry. Among them are the frequent use of rather large amounts of organocatalyst, something that makes its recovery and reuse an important matter, as well as the usual necessity of employing conventional hazardous volatile organic compounds as solvents to achieve the highest enantioselections.

Recently, attention has been focused in the use of deep eutectic solvents in organic synthesis as an alternative to volatile organic compounds.[2] A deep eutectic solvent is a combination of two or three components which interact through hydrogen bonds, to form a eutectic mixture with a melting point lower than the individual components.[3] Deep eutectic solvents are non-volatile, have a low ecological footprint, are inexpensive and easy to recycle, and are nowadays promising 'green' alternatives to conventional solvents.

Despite these potential advantages, the use of deep eutectic solvents in enantioselective organocatalyzed reactions remains very scarce. The first reported example of an asymmetric organocatalyzed reaction with deep eutectic solvents employed in fact a tandem enzyme-proline derived combination.[4] Only two very recent publications can be considered 'purely organocatalytic', involving 9-amino-9-deoxy-*epi*-quinine[5] and proline[6] as chiral organocatalysts.

Enantioselective organocatalysis has been successfully employed for the preparation of enantioenriched succinimides,[7] which are interesting compounds in natural products and drug candidates.[8] Succinimides can be easily transformed into γ-lactams,[9] which are important in the design of pharmaceutical agents.[10]

The most direct method for preparing enantioenriched succinimides in an organocatalytic fashion is by the enantioselective conjugate addition of carbon nucleophiles to maleimides.[7] The nucleophile can be generated by deprotonation of a carbon pro-nucleophile using chiral basic amine-containing organocatalysts. However, when aldehydes are used as pro-nucleophiles, an α-deprotonation with just an organic base is not feasible. In this case, an enamine-forming strategy using chiral organocatalysts bearing a primary or secondary amine is employed.[11] Thus, many enamine-forming chiral organocatalysts have been reported for the enantioselective conjugate addition of aldehydes, to maleimides.[12]

We have previously reported the use of single enantiomers of carbamate-monoprotected *trans*-cyclohexa-1,2-diamines **1** as chiral organocatalyst in the conjugate addition of aldehydes, particularly the challenging α,α-disubstituted, to maleimides.[12q,r] As mentioned previously, a common disadvantage of this type of enantioselective organocatalytic procedure is the use of non-recoverable volatile organic compounds. Herein we report how deep eutectic solvents can be used in this enantioselective addition reaction, reusing both solvent and organocatalyst.

* Corresponding author. Tel.: +34 965903822; fax: +34 965903549.
E-mail address: chinchilla@ua.es (R. Chinchilla).

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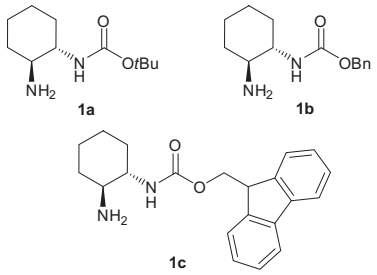


2. Results and discussion

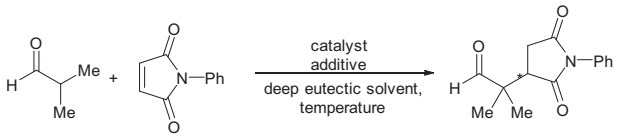
The carbamate-monoprotected *trans*-cyclohexane-1,2-diamines **1** were prepared from (1*S*,2*S*)-cyclohexane-1,2-diamine, as previously described.[12r] The derivative monoprotected with the *tert*-butoxycarbonyl (Boc) group **1a** was primarily chosen as the chiral enamine-forming organocatalyst in the model enantioselective conjugate addition reaction of isobutyraldehyde **2a** to *N*-phenylmaleimide **3a**, in different deep eutectic solvents (Table 1).

Thus, the use of a 10 mol % loading of **1a** in the deep eutectic solvent formed by choline chloride and urea (ChCl/urea, 1/2 molar ratio, see Section 4) at room temperature, gave rise after 24 h to a 90% yield of succinimide (*R*)-**4aa**, but with only 36% *ee* (Table 1, entry 1). The absolute configuration was determined according to the order of elution of the corresponding enantiomers in chiral HPLC (see Section 4).[12r] When the urea component of the deep eutectic solvent was changed to glycerol (ChCl/Gly, 1/2 molar ratio), a higher *ee* for (*R*)-**4aa** was obtained (52%, Table 1, entry 2). Higher enantiomeric excesses were obtained when using ethylene glycol (ChCl/ethylene glycol, 1/2 molar ratio) (64% Table 1, entry 3), or resorcinol (ChCl/resorcinol, 1/1 molar ratio) (67%, Table 1, entry 4).

When the employed deep eutectic solvent was the combination of tetra-*n*-butylammonium bromide (TBAB) and Gly (TBAB/Gly, 1/3 molar ratio), (*R*)-**4aa** was obtained in 85% yield and with 66% *ee* (Table 1, entry 5). However, the best results were obtained using as deep eutectic solvent the combination Ph_3MePBr/Gly (1/2 molar ratio), which afforded the final adduct in 96% yield and with 72% *ee* (Table 1, entry 6). Thus, this last deep eutectic solvent was used for the rest of our studies.

According to the literature, the presence of acid additives is frequently beneficial to this reaction.[12b,f,o,s] Therefore, we decided to evaluate the influence of an acid component. Thus, when hexanedioic acid (HDA) was added (10 mol %) to the reaction mixture, the reaction rate increased noticeably, as well as the enantioselection of the reaction, with (*R*)-**4aa** being obtained in 95% yield in only 8 h with an excellent 92% *ee* (Table 1, entry 7). The presence of other diacids, such as oxalic or phthalic acid, as additives gave much lower yields and enantioselectivities (Table 1, entries 8 and 9). When benzoic acid was added, the reaction yield was high and the enantioselection reached 86% (Table 1, entry 10). However, the addition of 3,4-dimethoxybenzoic acid gave the best results, affording adduct (*R*)-**4aa** with 94% *ee* and in 97% isolated yield (Table 1, entry 11). This enantioselectivity is remarkable, as values of only up to 86% were observed when using conventional volatile organic compounds as solvents.[12r] The presence of a strong electron-withdrawing group in the aromatic ring of the acid additive, as in the case of 4-nitrobenzoic acid, led to slightly lower enantioselectivity (Table 1, entry 12). The addition of bases such as imidazole or 4-*N*,*N*-dimethylaminopyridine (DMAP), which has

Table 1
Optimization of the reaction conditions in the model enantioselective conjugate addition in deep eutectic solvents



Entry	Catalyst (mol %)	Additive (mol %)	Deep eutectic solvent (molar ratio)[a]	*T* (°C)	*t* (h)	Yield[b] (%)	*ee*[c,d] (%)
1	**1a** (10)		ChCl/urea (1/2)	25	24	90	36 (*R*)
2	**1a** (10)		ChCl/Gly (1/2)	25	24	94	51 (*R*)
3	**1a** (10)		ChCl/ethylene glycol (1/2)	25	24	46	64 (*R*)
4	**1a** (10)		ChCl/resorcinol (1/1)	25	24	72	67 (*R*)
5	**1a** (10)		TBAB/Gly (1/3)	25	24	85	66 (*R*)
6	**1a** (10)		Ph_3MePBr/Gly (1/2)	25	24	96	72 (*R*)
7	**1a** (10)	HDA (10)	Ph_3MePBr/Gly (1/2)	25	8	95	92 (*R*)
8	**1a** (10)	Oxalic acid (10)	Ph_3MePBr/Gly (1/2)	25	8	28	72 (*R*)
9	**1a** (10)	Phthalic acid (10)	Ph_3MePBr/Gly (1/2)	25	8	58	72 (*R*)
10	**1a** (10)	$PhCO_2H$ (10)	Ph_3MePBr/Gly (1/2)	25	8	96	86 (*R*)
11	**1a** (10)	$3,4\text{-}(OMe)_2C_6H_3CO_2H$ (10)	Ph_3MePBr/Gly (1/2)	25	8	97	94 (*R*)
12	**1a** (10)	$4\text{-}O_2NC_6H_3CO_2H$ (10)	Ph_3MePBr/Gly (1/2)	25	8	95	90 (*R*)
13	**1a** (10)	Imidazole (10)	Ph_3MePBr/Gly (1/2)	25	8	94	66 (*R*)
14	**1a** (10)	DMAP (10)	Ph_3MePBr/Gly (1/2)	25	8	90	50 (*R*)
15	**1a** (20)	$3,4\text{-}(MeO)_2C_6H_3CO_2H$ (20)	Ph_3MePBr/Gly (1/2)	25	8	94	92 (*R*)
16	**1a** (5)	$3,4\text{-}(MeO)_2C_6H_3CO_2H$ (5)	Ph_3MePBr/Gly (1/2)	25	24	89	86 (*R*)
17	**1a** (10)	$3,4\text{-}(MeO)_2C_6H_3CO_2H$ (10)	Ph_3MePBr/Gly (1/2)	10	8	10	66 (*R*)
18	**1b** (10)	$3,4\text{-}(MeO)_2C_6H_3CO_2H$ (10)	Ph_3MePBr/Gly (1/2)	25	8	94	88 (*R*)
19	**1c** (10)	$3,4\text{-}(MeO)_2C_6H_3CO_2H$ (10)	Ph_3MePBr/Gly (1/2)	25	8	93	90 (*R*)
20	*ent*-**1a** (10)	$3,4\text{-}(MeO)_2C_6H_3CO_2H$ (10)	Ph_3MePBr/Gly (1/2)	25	8	95	94 (*S*)

[a] Abbreviations: ChCl = choline chloride; DMAP = 4-*N*,*N*-dimethylaminopyridine; Gly = glycerol; HDA = hexanedioic acid; TBAB = tetra-*n*-butylammonium bromide.
[b] Isolated yield after flash chromatography.
[c] Enantioselectivity determined by chiral HPLC.
[d] Absolute configuration assigned by the order of elution of the enantiomers in chiral HPLC.

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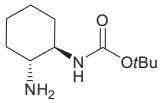
been shown to accelerate catalytic cycles when enamine-forming organocatalysts are involved,[13] gave good yields, but low enantioselectivities (Table 1, entries 13 and 14).

The synergistic role played by the acidic additive, when combined with the organocatalyst, in speeding up the reaction and in increasing both the yield and the *ee* is noteworthy. Perhaps a chiral H-bonded chelated cluster with maleimide may be playing a role in exalting its electrophilic character, thereby facilitating the nucleophilic attack by the aldehyde.

Once the most convenient deep eutectic solvent (Ph_3MePBr/Gly, 1/2 molar ratio) and additive [3,4-$(OMe)_2C_6H_3CO_2H$, 10 mol %) were established, we next studied the influence of the amount of organocatalyst **1a**. Increasing the loading of **1a** up to 20 mol % showed almost no influence on the yield or enantioselectivity for adduct (*R*)-**4aa**, whereas decreasing it to 5 mol % gave rise to a lower yield and *ee* in a much longer reaction time (Table 1, entries 15 and 16). Lowering the reaction temperature down to 10 °C resulted in a very slow reaction rate and an enantioselection of only 66% (Table 1, entry 17).

With the optimal catalyst loading, additive, deep eutectic solvent and reaction temperature determined, we next explored the organocatalytic behaviour of the other chiral carbamate-monoprotected *trans*-cyclohexane-1,2-diamines **1b** and **1c**, bearing a benzyloxycarbonyl (Cbz) and a fluorenylmethoxycarbonyl (Fmoc) protecting group, respectively. Their performance in the model reaction was not superior to **1a**, affording adduct (*R*)-**4aa** in good yields, but with lower enantioselectivities (Table 1, entries 18 and 19). Finally, we carried out a blank reaction in absence of organocatalyst **1** but in the presence of an additive, and observed no reaction.

In order to achieve opposite enantioselectivities to those obtained using organocatalyst **1a**, we obtained its enantiomer *ent*-**1a**, following an identical procedure but starting from (1*R*,2*R*)-cyclohexane-1,2-diamine.[12r] By using this mono-Boc-protected diamine as the organocatalyst, under the most convenient reaction conditions [*ent*-**1a** (10 mol %), 3,4-$(OMe)_2C_6H_3CO_2H$ (10 mol %), Ph_3MePBr/Gly (1/2 molar ratio), rt], the expected enantiomeric adduct (*S*)-**4aa** was obtained in identical absolute values of opposite enantioselectivity than when using **1a** as the organocatalyst (Table 1, entry 20).



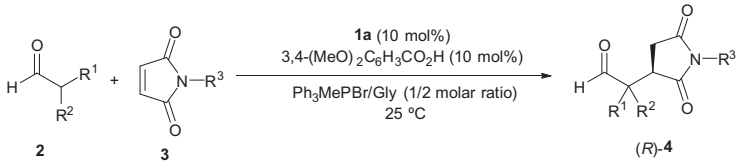
ent-**1a**

We subsequently explored the extension of the procedure to other aldehydes and *N*-substituted maleimides, by employing the above mentioned optimized reaction conditions (Table 2). As in the case of the model reaction, the absolute configuration of the resulting succinimides was assigned according to the elution order of their enantiomers in chiral HPLC when compared to the literature.[12r]

Thus, when isobutyraldehyde was reacted with *N*-phenylmaleimides bearing halogens on the phenyl ring, such as a chloro or a bromo atom at the 3- or 4-positions **3b**, **3c** and **3d**, the corresponding succinimides (*R*)-**4ab**, (*R*)-**4ac** and (*R*)-**4ac** were obtained in high yields and with 70, 87 and 86% *ee*, respectively (Table 2, entries 2–4). In addition, when an acyl group was present on the phenyl ring of the maleimide, as in the case of **3e**, the enantioselectivity for the corresponding succinimide (*R*)-**4ae** was 72% *ee* in a slightly lower yield (Table 2, entry 5). A similar enantioselectivity for (*R*)-**4af** was observed when an electron-releasing group, such as a methoxy, was present at the 4-position **3f** (Table 2, entry 6)

Non-*N*-arylated maleimides were also employed for the conjugate addition with isobutyraldehyde. Thus, *N*-benzylmaleimide **3g** and *N*-methylmaleimide **3h** gave succinimides (*R*)-**4ag** and (*R*)-**4ah** in high yields but with moderate 63 and 66% *ee*, respectively (Table 2, entries 7 and 8). In addition, the simple maleimide **3i** was also used as a Michael acceptor, affording (*R*)-**4ai** in 90% yield and with 67% *ee* (Table 2, entry 9).

Table 2
Enantioselective conjugate addition of aldehydes to maleimides organocatalyzed by **1a** in a deep eutectic solvent



2 **3** (*R*)-**4**

Entry	Aldehyde			Maleimide		*t* (h)	Adduct No.	Yield[a] (%)	*ee*[b,c] (%)
	R^1	R^2	No.	R^3	No.				
1	Me	Me	**2a**	Ph	**3a**	8	(*R*)-**4aa**	97	94
2	Me	Me	**2a**	3-ClC_6H_4	**3b**	8	(*R*)-**4ab**	95	70
3	Me	Me	**2a**	4-ClC_6H_4	**3c**	8	(*R*)-**4ac**	96	87
4	Me	Me	**2a**	4-BrC_6H_4	**3d**	8	(*R*)-**4ad**	95	86
5	Me	Me	**2a**	4-AcC_6H_4	**3e**	8	(*R*)-**4ae**	90	72
6	Me	Me	**2a**	2-$MeOC_6H_4$	**3f**	8	(*R*)-**4af**	93	70
7	Me	Me	**2a**	Bn	**3g**	8	(*R*)-**4ag**	91	63
8	Me	Me	**2a**	Me	**3h**	8	(*R*)-**4ah**	94	66
9	Me	Me	**2a**	H	**3i**	8	(*R*)-**4ai**	90	67
10	Et	Et	**2b**	Ph	**3a**	12	(*R*)-**4ba**	60	43
11	$-(CH_2)_4-$		**2c**	Ph	**3a**	8	(*R*)-**4ca**	96	87
12	$-(CH_2)_5-$		**2d**	Ph	**3a**	10	(*R*)-**4da**	93	31
13	Me	Ph	**2e**	Ph	**3a**	20	(*S*,*R*)/(*R*,*R*)-**4ea**	87[d]	85/10
14	H	Me	**2f**	Ph	**3a**	16	(*R*,*R*)/(*S*,*R*)-**4fa**	90[e]	50/50

[a] Isolated yield after flash chromatography.
[b] Enantioselectivities determined by chiral HPLC.
[c] Absolute configuration assigned by the order of elution of the enantiomers in chiral HPLC.
[d] Mixture of diastereomers 4/1 determined by ^1H NMR (300 MHz) in the reaction crude.
[e] Mixture of diastereomers 1.4/1 determined by ^1H NMR (300 MHz) in the reaction crude.

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Other α,α-disubstituted aldehydes were employed for the organocatalyzed conjugate addition reaction to *N*-phenylmaleimide. Thus, 2-ethylbutanal **3b** afforded succinimide (*R*)-**4ba** with moderate yield and enantioselectivity (Table 2, entry 10). However, cyclopentanecarbaldehyde **2c** gave almost a quantitative yield of (*R*)-**4ca** with 87% *ee* (Table 2, entry 11), something very different than when using cyclohexanecarbaldehyde **2d**, which afforded the corresponding adduct (*R*)-**4da** with an enantioselection of only 31% (Table 2, entry 12). Moreover, when a different α,α-disubstituted aldehyde such as 2-phenylpropanal **2e** was employed, the final adduct was obtained in a 4/1 diastereomeric ratio with an enantioselection of 85% for the diastereomer (*S*,*R*)-**4ea** and 10% for (*R*,*R*)-**4ea** (Table 2, entry 13). Furthermore, the use of an α-monosubstituted aldehyde such as propanal **2f**, allowed us to obtain the adducts as a 1.4/1 mixture of diastereomers, with enantioselections of 50% for (*R*,*R*)- and (*S*,*R*)-**4fa** (Table 2, entry 14).

The possibility of reusing the deep eutectic solvent is the cornerstone of a synthetic methodology performed using these neoteric solvents. Therefore, we explored the reusability of the deep eutectic solvent, and the catalytic system, by carrying out different reaction cycles of the model conjugate addition reaction performed under the best reaction conditions depicted in Table 2, entry 1. Thus, once the reaction was finished, a 4/1 v/v mixture of ethyl ether/*n*-hexane was added and the resulting mixture was stirred vigorously. After the two layers settled down, the upper layer, containing the final adduct, was separated. Attempting to directly reuse the lower deep eutectic solvent layer in other reaction by adding new aldehyde and maleimide resulted in low yields and moderate enantioselectivities of the resulting adduct (*R*)-**4aa**. This was explained after observing the presence of acid additive in the recovered organic layer (NMR). After several attempts, it was found that refreshing the catalytic system by the addition of new additive (but no new chiral organocatalyst) to the recovered deep eutectic solvent allowed us to obtain (*R*)-**4aa** with almost identical enantioselectivity and yield than when used for the first time. Following this recovery procedure, the deep eutectic solvent containing the organocatalyst **1a** could be reused four times without diminishing its enantioinduction (Table 3). However, a fifth reaction cycle led to a decrease in the catalytic activity.

Table 3
Recycle experiments. Yields and *ee*'s of (*R*)-**4aa** after consecutive reaction cycles[a]

Reaction cycle	Yield[b] (%)	*ee*[c] (%)
1	97	94
2	95	94
3	93	93
4	76	92
5	60	84

[a] **1a** (10 mol %), 3,4-$(MeO)_2C_6H_3CO_2H$ (10 mol %), Ph_3MePBr/Gly (1/2 molar ratio), 25 °C, 8 h.
[b] Isolated yield after flash chromatography.
[c] Enantioselectivitity determined by chiral HPLC.

3. Conclusions

It can be concluded that deep eutectic solvents can be used as reusable solvents in enantioselective conjugate additions of aldehydes, mainly α,α-disubstituted, to *N*-substituted maleimides, to afford enantioenriched substituted succinimides. Carbamate-monoprotected *trans*-cyclohexa-1,2-diamines have been employed as enantiomerically pure organocatalysts, with the mono-Boc-substituted derivative affording the best results. The reaction can be carried out in the presence of a carboxylic acid as an additive at room temperature. Once the reaction is completed, the final adduct can be separated by extraction, and the deep eutectic solvent retaining the organocatalyst, can be reused up to four times after the addition of fresh additive, while keeping its enantiodifferentiation activity. These results demonstrate than the use of deep eutectic solvents in enantioselective organocatalytic reactions can result in efficient and green strategies, and afford even better enantioselections than when conventional volatile organic compounds are used.

4. Experimental

4.1. General

All reagents were commercially available and used without further purification. Organocatalysts **1** were obtained as described.[12r] All known adducts **4** were characterized by spectroscopic methods.[12r] Enantioselectivities and absolute configurations were determined on the reaction crude by HPLC analyses[12r] on an Agilent 1100 series equipped with chiral columns (Chiralcel OD-H: **4aa**, **4ab**, **4ac**, **4ad**, **4ca**, **4da**, **4ea**;[12l] Chiralcel AD-H: **4af**; Chiralpak AS-H: **4ae**, **4ah**, **4ba**; Chiralpak AD-H: **4ag**, **4ai**, **4fa**), using mixtures of *n*-hexane/isopropyl alcohol as the mobile phase, at 25 °C. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates and the spots were visualised under UV light. For chromatography we employed Merck silica gel 60 (0.063–0.2 mm).

4.2. General procedure for the preparation of deep eutectic solvents

A mixture of the two components, with the previously specified molar ratio, was added to a round bottom flask and the mixture was stirred for 60 min in a temperature range between 65 and 80 °C, obtaining the corresponding deep eutectic solvent.[14]

4.3. Enantioselective conjugate addition reaction. General procedure

To a mixture of catalyst **1** (0.02 mmol), additive (0.02 mmol), and maleimide (0.2 mmol) in the corresponding deep eutectic solvent (0.5 mL) was added the aldehyde (0.4 mmol) and the reaction was vigorously stirred during the necessary reaction time (TLC, Table 2) at rt. Next 2 M HCl (10 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined organics were washed with aq $NaHCO_3$ (2 × 10 mL), dried ($MgSO_4$) and evaporated (15 torr), and the resulting crude was purified by flash chromatography (hexane/EtOAc gradients) affording adduct **4**.

4.4. Recycling experiments

To a mixture of catalyst **1a** (4.3 mg, 0.02 mmol), 3,4-dimethoxybenzoic acid (3,7 mg, 0.02 mmol), and *N*-phenylmaleimide (34.6 mg, 0.2 mmol) in Ph_3MePBr/Gly (1/2 molar ratio, 0.5 mL) was added isobutyraldehyde (36.5 μL, 0.4 mmol) and the reaction was vigorously stirred for 8 h at rt. After this period, a mixture of ethyl ether/*n*-hexane (4/1, v/v, 3 mL) was added and the mixture was stirred for 2 min. The stirring was stopped to allow for phase separation and the upper organic layer was removed through settling. This extractive procedure was repeated three times. The combined organic extracts were washed ($NaHCO_3$ aq, 10 mL), dried ($MgSO_4$), evaporated (15 torr) and purified by flash chromatography on silica gel (hexane/EtOAc gradients) to yield (*R*)-**4aa**. The deep eutectic solvent layer, where catalyst **1a** remained dissolved, was evaporated in vacuo to remove volatile solvent residues

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(15 torr) and the catalytic system was regenerated by 3,4-dimethoxybenzoic acid addition (3,7 mg, 0.02 mmol). A further run was performed with this deep eutectic solvent, adding new isobutyraldehyde and *N*-phenylmaleimide. This reaction mixture was subjected again to the above described procedure and further reaction cycles were repeated using the same deep eutectic solvent phase.

Acknowledgments

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