FULL PAPER

Solvent-induced reversal of the enantioselectivity in the synthesis of succinimides by addition of aldehydes to maleimides organocatalyzed by carbamate-monoprotected 1,2-diamines

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A simple change in the polarity of the solvent allows obtaining both enantiomers of substituted succinimides in the enantioselective conjugate addition reaction of aldehydes, mainly α,α -disubstituted, to maleimides organocatalyzed by chiral carbamate-monoprotected *trans*-cyclohexa-1,2-diamines. Using a single enantiomer of the organocatalyst, both enantiomers of

the resulting Michael adducts are obtained in high yields, only by changing the reaction solvent from aqueous DMF (up to 84% *ee*) to chloroform (up to 86% *ee*). Theoretical calculations are used to justify this uncommon reversal of the enantioselectivity, revealing two transition state orientations of distinct polarity which are differently favoured in polar or apolar solvents.

Introduction

In enantioselective organocatalysis, as in any asymmetric catalysis, opposite enantiomeric products are typically obtained using opposite mirror images of the organocatalysts. However, being able to switch the enantioselectivity of an organocatalyzed reaction only by changing the reaction conditions is an exciting matter of high potential interest. One of the main reasons is that having both enantiomeric forms of certain organocatalysts can be difficult or costly.

Although not frequent, there are some reported examples of enantioselective organocatalyzed reactions where both enantiomers are obtained using a single mirror configuration of the catalyst. These results are always unexpected and serendipitous.^[1] Thus, a few examples of switching the enantioselectivity of an organocatalyzed process by changing counteranions in the catalyst,^[2] adding bases,^[3] acids^[4] or other additives^[5] or even by light irradiation,^[6] have been reported.

However, a more simple change would be just modifying the reaction solvent, and some examples of solvent-dependent enantioselectivity reversal have been reported. Thus, an inversion of the enantioselectivity was discovered in the enantioselective Michael addition of dimethyl malonate to chalcone organocatalyzed by a quininium ammonium salt, when changing the reaction medium from conventional organic solvents to ionic liquids.^[7] In addition, a solvent-dependent enantioinduction reversal was observed when using the imidazolidinone salt **1** as organocatalyst in the Michael addition of an indol to acroleine for the synthesis of a pyrroloindoline.^[8] Later, α,α -phenylprolinol silyl ether **2** was shown to organocatalyze the enantioselective α -phenylselenenylation of isovaleraldehyde, revealing a change in the sense of the enantioselectivity when changing the polarity of the solvent.^[9] The reversal of the enantioselectivity of this α -phenylselenenylation reaction influenced by the solvent, has also been reported using polystyrene-supported imidazolidinone **3** as recoverable organocatalyst.^[10]

Moreover, an inversion of the enantioselectivity induced by a change in the solvent has been observed in the enantioselective Michael addition of cyclohexanone to chalcones using 1-ethyl-3-methylimidazolium-(*S*)-2-pyrrolidinecarboxylic acid salt as organocatalyst.^[11] Furthermore, some conformationally flexible organocatalyst have been used in solvent-dependent enantioswitched reactions, as the peptidic system **4** in the aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde,^[12] and the bistiourea/guanidine **5** in a recent Mannich-type addition of malonates to *N*-Boc-protected aldimines.^[13] No explanation justifying why a particular enantiomer of the final product is obtained using a solvent and the opposite using other has been given in any of the reported cases.

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Among the huge array of enantioselective organocatalyzed reactions, those leading to enantioenriched substituted succinimides have shown interest in the last years. These compounds are present in natural products and some clinical drug candidates,^[14] and can be transformed into γ -lactams,^[15]

which are subunits for the design of pharmaceutical agents important in the treatment of cancer,^[16] epilepsy,^[17] HIV,^[18] neurodegenerative disease and depression.^[19]

The most direct and easy way of preparing enantioenriched succinimide moieties is by organocatalytic enantioselective Michael addition of carbon nucleophiles to maleimides.^[20] These carbon nucleophiles can be generated by α -deprotonation of pro-nucleophiles using chiral bifunctional organocatalysts bearing both a basic tertiary amine and an acidic moiety able to coordinate the maleimide.^[20] However, when aldehydes are used as pro-nucleophiles, tertiary amines are not basic enough for generating an enolate, and the enantioselective Michael addition reaction is carried out by using amine-bearing organocatalysts suitable to form a transient enamine with the reacting aldehyde.^[21]

The first organocatalytic Michael addition of aliphatic aldehydes to *N*-aryl-maleimides used α,α -phenylprolinol silyl ether as organocatalyst, although the “difficult” α,α -disubstituted aldehydes resulted in much lower enantioselectivities.^[22] Since then, different chiral bifunctional primary amine-bearing organocatalysts have been applied to the enantioselective Michael addition of these α,α -disubstituted aldehydes to maleimides leading to enantioenriched succinimides, most of them being primary amine-thioureas,^[23] although primary amine-guanidines,^[24] amino acids,^[25] amino acids combined to amine-thioureas,^[26] amines,^[27] or 1,2-diamines^[28] have also being used.

In this paper, we present how just a simple change in the reaction solvent can produce a reversal in the enantioselectivity in the conjugate addition of aldehydes to maleimides organocatalyzed by chiral carbamate-monoprotected *trans*-cyclohexa-1,2-diamines.^[29] In this way, a single enantiomeric form of a simple organocatalyst can be employed for the preparation of both enantiomeric forms of the corresponding substituted succinimides. The origin of this uncommon solvent-dependent enantioswitching can be explained by theoretical calculations.

Results and Discussion

We attempted to explore the behaviour of chiral mono-*tert*-butoxycarbonyl (Boc)-protected diamine **6** as primary amine-containing bifunctional organocatalyst for the enantioselective conjugate addition reaction of aldehydes to *N*-substituted maleimides. This Boc-containing amine **6** was obtained following a reported procedure consisting of reaction of (1*S*,2*S*)-cyclohexa-1,2-diamine with 1 equivalent of hydrogen chloride, followed by subsequent treatment with di-*tert*-butyl carbonate.^[30] The enantioselective Michael addition of isobutyraldehyde to *N*-phenylmaleimide was chosen as a model reaction for testing the efficiency of **6** as organocatalyst (Table 1).

Initially, primary amine **6** (20 mol-%) was used in toluene as solvent at room temperature, affording succinimide (*S*)-**9aa**

almost quantitatively in 67% *ee* (Table 1, entry 1). The absolute configuration for **9aa** was determined according to the order of elution of their corresponding enantiomers in chiral HPLC (see Experimental).^[24b] When hexane was used as solvent, the enantioselectivity for (*S*)-**9aa** increased up to 73%, whereas the use of ethyl ether afforded a lower *ee* (Table 1, entries 2 and 3). In addition, when CH₂Cl₂ and CHCl₃ were employed as solvents, 63% and 75% *ee*'s for (*S*)-**9aa**, respectively, were observed (Table 1, entries 4 and 5).

Unexpectedly, when DMF was used as solvent the enantioselectivity of the process reversed totally, obtaining the opposite succinimide (*R*)-**9aa** in 62% *ee* in high yield although in a much lower reaction rate (Table 1, entry 6). The use of solvents such as 1,4-dioxane or acetone afforded also (*R*)-**9aa** in lower *ee*'s (Table 1, entries 7 and 8). When water was the solvent, the reaction rate of the reaction increased considerably, affording (*R*)-**9aa** almost quantitatively although in only 32% *ee* (Table 1, entry 9). Therefore, combining the highest *ee* and reaction rate, we explore the use of mixtures of DMF/H₂O as reaction solvent. Thus, different DMF/H₂O v/v ratios were assayed (Table 1, entries 10-12), a DMF/H₂O 2/1 v/v ratio affording (*R*)-**9aa** in 90% yield and 84% *ee* (Table 1, entry 11).

Once the most appropriate solvent for achieving a reversal in the enantioselectivity was established [CHCl₃ for (*S*)-**9aa** and DMF/H₂O 2/1 v/v for (*R*)-**9aa**], we decide lowering the organocatalyst loading. Thus, both solvents were used with 10 and 5 mol-% organocatalyst loadings (Table 1, entries 13-16), observing the higher enantioselections for the (*S*) and (*R*) stereoisomers when a loading of 10 mol-% of **6** was used [86% *ee* for (*S*)-**9aa** and 84% *ee* for (*R*)-**9aa**] (Table 1, entries 13 and 14). Lowering the reaction temperature down to 0 °C showed a diminished enantioselectivity for **9aa** (Table 1, entries 17 and 18).

We then explored the influence of the presence of additives, using an optimized 10 mol-% loading of organocatalyst **6** and CHCl₃ and DMF/H₂O 2/1 v/v as enantioswitching solvents. Thus, hexanedioic (HDA) or benzoic acids were used as additives (10 mol%) but no increasing in the enantioselection for any enantiomer was observed (Table 1, entries 19-22). In addition, imidazole was also used as additive (10 mol%), as its presence has proven beneficial in this Michael addition reaction,^[24b] but also lower enantioselectivities for both enantiomers of **9aa** were observed (Table 1, entries 23 and 24).

Attempting to achieve opposite enantioselections to those obtained using organocatalyst **6**, we obtained its enantiomer *ent*-**6**, following an identical procedure but starting from (1*R*,2*R*)-cyclohexa-1,2-diamine. Using this mono-Boc-protected diamine *ent*-**6** as organocatalyst, under the most convenient reaction conditions [10 mol-% organocatalyst loading, room temperature, CHCl₃ or DMF/H₂O 2/1 v/v as solvents], the expected opposite enantioselections were observed [(*R*)-**9aa** using CHCl₃ as solvent and (*S*)-**9aa** using DMF/H₂O 2/1 v/v] (Table 1, entries 25 and 26).

Table 1. Screening and optimization of the reaction conditions for the reversal of the enantioinduction in the Michael addition reaction.

7a + 8a $\xrightarrow[\text{solvent, T}]{\text{cat. additive}}$ 9aa

Entry	Catalyst [mol-%]	Additive [mol-%] ^[a]	Solvent	T [°C]	t [h]	% Yield ^[b]	% ee ^[c]
1	6 (20)	-	PhMe	25	20	98	67 (S)
2	6 (20)	-	Hexane	25	14	85	73 (S)
3	6 (20)	-	Et ₂ O	25	14	95	32 (S)
4	6 (20)	-	CH ₂ Cl ₂	25	20	95	63 (S)
5	6 (20)	-	CHCl ₃	25	20	99	75 (S)
6	6 (20)	-	DMF	25	44	94	62 (R)
7	6 (20)	-	Dioxane	25	50	85	58 (R)
8	6 (20)	-	Acetone	25	44	92	57 (R)
9	6 (20)	-	H ₂ O	25	2	97	32 (R)
10	6 (20)	-	DMF/H ₂ O ^[d]	25	17	94	70 (R)
11	6 (20)	-	DMF/H ₂ O ^[e]	25	20	90	84 (R)
12	6 (20)	-	DMF/H ₂ O ^[f]	25	24	88	80 (R)
13	6 (10)	-	CHCl ₃	25	20	97	86 (S)
14	6 (10)	-	DMF/H ₂ O ^[e]	25	20	95	84 (R)
15	6 (5)	-	CHCl ₃	25	40	95	76 (S)
16	6 (5)	-	DMF/H ₂ O ^[e]	25	40	93	82 (R)
17	6 (10)	-	CHCl ₃	0	48	94	70 (S)
18	6 (10)	-	DMF/H ₂ O ^[e]	0	48	91	82 (R)
19	6 (10)	HDA (10)	CHCl ₃	25	22	98	78 (S)
20	6 (10)	HDA (10)	DMF/H ₂ O ^[e]	25	20	86	80 (R)
21	6 (10)	PhCO ₂ H (10)	CHCl ₃	25	22	93	78 (S)
22	6 (10)	PhCO ₂ H (10)	DMF/H ₂ O ^[e]	25	22	84	80 (R)
23	6 (10)	Imidazole (10)	CHCl ₃	25	22	97	78 (S)
24	6 (10)	Imidazole (10)	DMF/H ₂ O ^[e]	25	22	90	77 (R)
25	<i>ent</i> - 6 (10)	-	CHCl ₃	25	20	97	84 (R)
26	<i>ent</i> - 6 (10)	-	DMF/H ₂ O ^[e]	25	20	94	83 (S)
27	12 (10)	-	CHCl ₃	25	24	98	81 (S)
28	12 (10)	-	DMF/H ₂ O ^[e]	25	24	94	78 (R)
29	13 (10)	-	CHCl ₃	25	48	97	86 (S)
30	13 (10)	-	DMF/H ₂ O ^[e]	25	48	96	78 (R)

[a] HDA: Hexanedioic acid. [b] Isolated yield after flash chromatography. [c] Enantioselectivities and absolute stereochemistry determined by chiral HPLC (Ref. 24b) in the reaction crude. [d] 1/1, v/v. [e] 2/1, v/v. [f] 4/1, v/v.

We then explored the possibility of achieving this solvent-dependent reversal of the enantioselectivity using chiral *trans*-cyclohexa-1,2-diamines monoprotected with other carbamates as organocatalysts. We choose the frequently used benzyloxycarbonyl (Cbz) and fluorenylmethoxycarbonyl (Fmoc) protecting groups. Thus, the Cbz- and Fmoc-monoprotected diamines **12** and **13**, respectively, were prepared after reaction of the *N*-Boc-monoprotected diamine **6** with the corresponding chloroformates to give diprotected compounds **10** and **11**, followed by final trifluoroacetic acid (TFA)-induced *N*-Boc-deprotection (Scheme 1).

Scheme 1. (i) CbzCl (for **10**) or FmocCl (for **11**), aq NaHCO₃, dioxane, rt; (ii) TFA, CH₂Cl₂, rt; (iii) NH₄OH, CH₂Cl₂, rt.

These Cbz- and Fmoc-monoprotected chiral diamines **12** and **13**, respectively, were also assayed as organocatalyst in the model Michael addition reaction, using the most convenient reaction conditions determined above [10 mol-% organocatalyst

loading, room temperature, CHCl₃ or DMF/H₂O 2/1 v/v as solvents] (Table 1, entries 27–30). Again, it was observed the reversal in the enantioselectivity of the process when using CHCl₃ [(*S*)-enantiomer] or DMF/H₂O 2/1 v/v [(*R*)-enantiomer] as solvents. Thus, when mono-Cbz-protected diamine **12** was used as organocatalyst, enantioselectivity values of 81% for (*S*)-**9aa** and 78% for (*R*)-**9aa** were obtained (Table 1, entries 27 and 28). In addition, the use of Fmoc-containing primary amine **13** as organocatalyst afforded a similar enantioselectivity for (*S*)-**9aa** than when using the Boc-derivative **6** but in a much longer reaction time, whereas a lower one for (*R*)-**9aa** (Table 1, entries 29 and 30).

Once the most effective organocatalyst and reaction conditions [**6** (10 mol-%), CHCl₃ for (*S*)-enantiomer and DMF/H₂O 2/1 v/v for (*R*)-enantiomer, rt] were established, we explored the extension of this organocatalytic solvent-dependent methodology to other aldehydes and maleimides (Table 2). As in the case of the model reaction, the absolute configuration of the known resulting succinimides was assigned according to the elution order of their enantiomers in chiral HPLC when compared to the literature (see Experimental).

Thus, when CHCl₃ was used as solvent, isobutyraldehyde reacted with *N*-phenylmaleimides bearing halogens on the phenyl ring, such as a chloro atom at the 3- and 4-position (**8b**

and **8c**) or a bromo atom at the 4-position (**8d**), and the succinimides (*S*)-**9ab**, (*S*)-**9ac** and (*S*)-**9ad** were obtained in 38, 60 and 70% *ee*, respectively (Table 2, entries 3, 5 and 7). However, when DMF/H₂O 2/1 v/v was the reaction solvent, adducts (*R*)-**9ab**, (*R*)-**9ac** and (*R*)-**9ad** were isolated in 76, 74 and 70% *ee* (Table 2, entries 4, 6 and 8). In addition, when an acetyl or a methoxy group was present onto the phenyl ring of the maleimide, as in the case of **8e** and **8f**, the enantioselectivities for the corresponding enantiomeric succinimides (*S*)-**9ae**/*(R)*-**9ae** and (*S*)-**9af**/*(R)*-**9af** were 40/80% and 76/74%, respectively, depending on the use of CHCl₃ or DMF/H₂O 2/1 v/v as solvents (Table 2, entries 9–12).

Non-*N*-arylated maleimides were also used for the conjugate addition with isobutyraldehyde. Thus, *N*-benzylmaleimide (**8g**) afforded the enantiomeric succinimides (*S*)-**9ag** and (*R*)-**9ag** in high yields and in 30 and 72% *ee*, depending on the solvent used (Table 2, entries 13 and 14). Similarly, *N*-methylmaleimide (**8h**) gave the (*S*)- and (*R*)-enantiomer of adduct **9ah** when CHCl₃ and DMF/H₂O 2/1 v/v were the reaction solvents (53 and 68% *ee*, respectively) (Table 2, entries 15 and 16). In addition, the simple maleimide (**9i**) was also used as Michael acceptor, affording (*S*)-

9ai (50% *ee*) using CHCl₃ as solvent, and (*R*)-**9ai** (70% *ee*) when the solvent was DMF/H₂O 2/1 v/v (Table 2, entries 17 and 18).

Other α,α -disubstituted aldehydes were employed for this enantioswitched organocatalyzed Michael addition reaction to *N*-phenylmaleimide. Thus, 2-ethylbutanal (**7b**) afforded succinimides (*S*)-**9ba** (55% *ee*) and (*R*)-**9ba** (68% *ee*) using CHCl₃ and DMF/H₂O 2/1 v/v as solvents, respectively (Table 2, entries 19 and 20). In addition, cyclopentane- (**7c**) and cyclohexanecarbaldehyde (**7d**) gave almost quantitative amounts of succinimides (*S*)-**9ca** and (*S*)-**9da** in 49 and 14% *ee*, respectively, when CHCl₃ was the reaction solvent, whereas (*R*)-**9ca** and (*R*)-**9da** in 61 and 35% *ee*, respectively, were isolated using DMF/H₂O 2/1 v/v as solvent (Table 2, entries 21–24). Moreover, the use of a α -monosubstituted aldehyde such as propanal (**7e**) in the two solvents, allowed obtaining the Michael adducts (*R,S*)/(*S,S*)-**9ea** and (*S,R*)/(*R,R*)-**9ea**, respectively, as mixtures of diastereomers, with enantioselections up to 36 and 76%, respectively, for the major isomer [Table 2, entries 25 and 26, see footnotes d) and e)].

Table 2. Solvent-dependent reversal of the enantioinduction in the Michael addition of aldehydes to maleimides organocatalyzed by *N*-Boc-monoprotected 1,2-diamine **6**.

Reaction scheme: Aldehyde **7** (R¹, R²) + Maleimide **8** (R³) $\xrightarrow[\text{solvent, rt}]{\text{6 (10 mol-%)}}$ Succinimides (*S*)-**9** or (*R*)-**9**.

Entry	Aldehyde			Maleimide		Solvent	<i>t</i> [h]	Succinimide	% Yield ^[a]	% <i>ee</i> ^[b,c]
	R ¹	R ²	No.	R ³	No.					
1	Me	Me	7a	Ph	8a	CHCl ₃	20	(<i>S</i>)- 9aa	97	86
2						DMF/H ₂ O 2/1	20	(<i>R</i>)- 9aa	95	84
3	Me	Me	7a	3-ClC ₆ H ₄	8b	CHCl ₃	30	(<i>S</i>)- 9ab	99	38
4						DMF/H ₂ O 2/1	30	(<i>R</i>)- 9ab	96	76
5	Me	Me	7a	4-ClC ₆ H ₄	8c	CHCl ₃	30	(<i>S</i>)- 9ac	99	60
6						DMF/H ₂ O 2/1	30	(<i>R</i>)- 9ac	97	74
7	Me	Me	7a	4-BrC ₆ H ₄	8d	CHCl ₃	30	(<i>S</i>)- 9ad	99	70
8						DMF/H ₂ O 2/1	30	(<i>R</i>)- 9ad	98	70
9	Me	Me	7a	4-AcC ₆ H ₄	8e	CHCl ₃	26	(<i>S</i>)- 9ae	92	40
10						DMF/H ₂ O 2/1	26	(<i>R</i>)- 9ae	15	80
11	Me	Me	7a	2-MeOC ₆ H ₄	8f	CHCl ₃	32	(<i>S</i>)- 9af	90	76
12						DMF/H ₂ O 2/1	32	(<i>R</i>)- 9af	92	74
13	Me	Me	7a	Bn	8g	CHCl ₃	22	(<i>S</i>)- 9ag	93	30
14						DMF/H ₂ O 2/1	22	(<i>R</i>)- 9ag	90	72
15	Me	Me	7a	Me	8h	CHCl ₃	21	(<i>S</i>)- 9ah	94	53
16						DMF/H ₂ O 2/1	21	(<i>R</i>)- 9ah	91	68
17	Me	Me	7a	H	8i	CHCl ₃	17	(<i>S</i>)- 9ai	94	50
18						DMF/H ₂ O 2/1	17	(<i>R</i>)- 9ai	88	70
19	Et	Et	7b	Ph	8a	CHCl ₃	48	(<i>S</i>)- 9ba	70	55
20						DMF/H ₂ O 2/1	48	(<i>R</i>)- 9ba	93	68
21	-(CH ₂) ₄ -		7c	Ph	8a	CHCl ₃	30	(<i>S</i>)- 9ca	99	49
22						DMF/H ₂ O 2/1	30	(<i>R</i>)- 9ca	96	61
23	-(CH ₂) ₅ -		7d	Ph	8a	CHCl ₃	48	(<i>S</i>)- 9da	96	14
24						DMF/H ₂ O 2/1	48	(<i>R</i>)- 9da	96	35
25	H	Me	7e	Ph	8a	CHCl ₃	23	(<i>S,S</i>)/(<i>R,S</i>)- 9ea	95 ^[d]	36/28
26						DMF/H ₂ O 2/1	23	(<i>R,R</i>)/(<i>S,R</i>)- 9ea	96 ^[e]	76/73

[a] Isolated yield after flash chromatography. [b] Enantioselectivities determined by chiral HPLC in the reaction crude. [c] Absolute configuration assigned by the order of elution of the enantiomers in chiral HPLC (See Experimental). [d] Mixture of diastereomers 1.4/1 determined by ¹H NMR (300 MHz) in the reaction crude. [e] Mixture of diastereomers 1.2/1 determined by ¹H NMR (300 MHz) in the reaction crude.

Attempting to rule out that the change in the enantioselectivity could be a consequence of a former evolution of the initially formed product, the succinimide (*R*)-**9aa** obtained in 84% *ee* (Table 2, entry 2) was stirred in the presence of organocatalyst **6** (10 mol-%), in CHCl₃ as solvent at room temperature. After 20h, the initial succinimide (*R*)-**10aa** was recovered unaltered. In addition, the model reaction of aldehyde **7a** to maleimide **8a** in the presence of the organocatalyst **6** (10 mol-%) in DMF/H₂O 2/1 v/v was carried out during 4, 8, and 12h, the enantioselectivity for (*R*)-**9aa** being kept in 84%.

In order to get further insight into the origin of this solvent-dependent enantioselectivity reversal, we carried out theoretical calculations of the reaction of the phenylmaleimide **8a** and isobutyraldehyde **7a** in the presence of primary-amine catalyst **6**. Different computational conditions were envisioned (see Computational methods section), in the gas phase, in implicit solvents (water and chloroform), and also in the presence of a discrete number of explicit water molecules, in an attempt to resemble the experimental conditions as close as possible, since the results are highly dependent on the reaction medium. Preliminary studies showed that, as expected, the initial formation of an enamine between catalyst and aldehyde is followed by the nucleophilic attack to the maleimide, according to Seebach's synclinal model (*endo* attack, Figure 1).^[31] A key feature of this model is that the reacting face of the enamine diastereospecifically attacks only one of the faces of the maleimide. That is, the lower face of the enamine (from our point of view in Figure 1) is reacting with the *Re*-face of the maleimide, and the upper face of the enamine must react with the *Si*-face of the maleimide. It means that each face of the enamine produces only one of the final enantiomeric products. This fact is crucial to understand the following discussion, which can be based solely on the reacting face of the enamine. Meanwhile, the *exo* approaches, like the one involving the lower face of the enamine and the *Si*-face of the maleimide (Figure 1), are much higher in energy and can be safely discarded.

Figure 1. Faces of enamine and maleimide reacting through Seebach's synclinal model.

The initial optimizations of the enamine-structures showed that in the most stable conformations (**A** and **B**, Figure 2), the NHBoc and the enamine groups are in equatorial positions of the cyclohexane ring. In both cases, the NH moiety of the NHBoc carbamate is pointing *down* from our view. The two conformations differ in the orientations that the NH enamine group can present, pointing *up* (conformation **A**) or *down* (conformation **B**, Figure 2) from the plane of the cyclohexane ring. According to this picture, the fragment NH-C-C-NH shows both NH groups in *anti* (**A**) or *syn* (**B**) relative orientations. The optimization of these structures showed that they are very similar in energy, and both must be taken into account for the transition structure search. In fact, structure **B** is slightly more stable than **A** in CHCl₃ (1.0 kcal/mol difference), whilst they afford the same energy in water, meaning that **A** is slightly better solvated by water than by chloroform. Although with caution, we took these data as a first indication of the solvent dependence of the conformational distribution of the initial structures. We thought

that this effect could be more dramatic during the transition states of the reaction, which are supposed to be quite polar, due to the significant charge transfer that takes place from the enamine to the maleimide.

Figure 2. Most stable conformations of the reacting enamine.

We confirmed this hypothesis in light of the computed transition state activation energies. In conformation **A**, the maleimide could hypothetically approach the two faces of the enamine, like in Figure 3. If the attack takes place from the left side of the enamine, the reaction occurs through **TS-A_R** (*Si* face of maleimide, *R* product), whereas the approach of the maleimide from the right side of the enamine (hypothetical **TS-A_S**) is strongly disfavoured due to steric repulsion with the large Boc group, which is blocking that face. We could not actually find any transition state for that approach without severely distorting the structure. Noteworthy, **TS-A_R** shows a very polar structure, with a high negative charge developing in the maleimide/oxygen atom. Consequently, the polarity of the reaction medium must have a great influence on the activation barrier of the process. Thus, it was not surprising to find that the lowest Free energy for **TS-A_R** corresponds to the structure computed in a water model ($\Delta G^\ddagger = 14.8$ kcal/mol),^[32] whilst chloroform and gas phase models present higher values ($\Delta G^\ddagger = 18.7$ kcal/mol and 20.7 kcal/mol, respectively). Interestingly, **TS-A_R** leads to the formation of the *R* enantiomer, which is experimentally obtained in the polar aqueous media.

Figure 3. Computed activation energies for the transition state **TS-A_R** (corresponding to conformation **A** in Fig. 2) in the gas phase, chloroform and water models. Structures and values were obtained at M06-2X/6-311+G**/M06-2X/6-31G** level of theory.

On the other hand, two transition states were located for conformation **B**, following the two possible approaching trajectories (**TS-B_S** and **TS-B_R**, Figure 4). In **TS-B_S**, the *Re*-face of the maleimide is attacked by the lower face (from our view) of the enamine, whereas in **TS-B_R**, the *Si*-face of the maleimide approaches the upper face of the enamine. Noteworthy, in **TS-B_S**, the maleimide/oxygen and the HNBoc groups are close enough to form an intermolecular hydrogen bond, which stabilizes the developing negative charge in the maleimide/oxygen atom, producing a structure that is much more apolar than **TS-A_R**, and therefore, less sensitive to the surrounding solvent molecules. This effect can be observed in the computed energies for **TS-B_S**, which do not present significant differences between the different solvent models or even in the gas phase (**TS-B_S-water** 17.7,^[32] **TS-B_S-chloroform** 16.0, **TS-B_S-gas phase** 15.8 kcal/mol, Figure 4).

Figure 4. Representations and energies of the transition states **TS-B_S** and **TS-B_R**, corresponding to conformation **B** in Fig. 2. Structures and values were obtained at M06-2X/6-311+G**//M06-2X/6-31G** level of theory.

Meanwhile, if the maleimide approaches the upper face of the enamine in conformation **B**, the corresponding transition state **TS-B_R** is located (Figure 4). In a similar way as **TS-A_R**, the new transition structure is quite polar, and the maleimide/oxygen is better stabilized in the presence of surrounding solvent molecules. Thus, its lowest energy was measured in water (15.2 kcal/mol),^[32] although this value is higher than the one corresponding to **TS-A_R** (14.8 kcal/mol, Figure 3). This increase in the energy is probably due to the higher internal strain that the structure presents as the result of a weak H-bond formed between the enamine NH and the carbamate oxygen atom, which does not participate in the activation of the maleimide.

In summary, the most significant computational data are that the lowest computed activation energy in water corresponds to **TS-A_R** (14.8 kcal/mol), a polar structure lacking intramolecular H-bond, where the surrounding water molecules are responsible for intermolecular H-bonding activation of the maleimide (Figure 5). **TS-A_R** produces the *R* enantiomer of the product, in agreement with the experimental results in the polar aqueous DMF media (Table 1). Also, the lowest computed activation energy in chloroform is **TS-B_S** (16.0 kcal/mol), a transition structure containing an intramolecular H-bond between the maleimide and the NHBoc groups (Figure 5). This transition state leads to the formation of the *S* enantiomer, once again, in agreement with the experimental data in chloroform (Table 1). Furthermore, these results agree with the common chemical sense, by which intramolecular H-bonds are stronger in apolar solvents, while intermolecular H-bonds with surrounding water molecules are present in aqueous systems.

Figure 5. 3-D representations and energies of the transition states **TS-A_R-water** and **TS-B_S-chloroform**.

Conclusions

It can be concluded that easily prepared carbamate-monoprotected chiral *trans*-cyclohexa-1,2-diamines can be used as organocatalysts in the high-yielding enantioselective conjugate

addition of aldehydes, mainly α,α -disubstituted, to different maleimides, giving rise to a solvent-dependent enantioswitched reaction. Thus, both (*S*)- or (*R*)-enantioenriched forms of the corresponding succinimides can be obtained employing a single mirror form of the organocatalyst, just by changing the reaction solvent from chloroform to aqueous *N,N*-dimethylformamide. Theoretical calculations are able to show the reason for this solvent dependent reversal of enantioselectivity, since the most polar transition state **TS-A_R** presents the lowest energy in water, being responsible for the major formation of the *R* enantiomer, whilst the most apolar transition state **TS-B_S** explains the formation of the *S* enantiomer in chloroform, in agreement with the experimental results.

Experimental Section

General: The synthesis of all organocatalysts, as well as their physical and spectroscopic properties can be found in the Supporting Information. Absolute configuration for adducts **9** was determined according to the described order of elution of their enantiomers in chiral HPLC. Reference racemic samples of adducts **9** were obtained by performing the reaction using 4-methylbenzylamine (20 mol-%) as organocatalyst in toluene as solvent at 25 °C.

Typical Procedure for the Enantioselective Michael Addition

Reaction: To a solution of **6** (0.04 mmol) and **8** (0.2 mmol) in CHCl₃ or DMF/H₂O 2/1, v/v (0.5 mL) was added the aldehyde **7** (0.4 mmol) and the reaction was stirred at rt until completion (TLC). A solution of 2M HCl (10 mL) was added and the mixture was extracted with AcOEt (3x10 mL). The organic phase was washed with water (2x10 mL), dried (MgSO₄), filtered and evaporated (15 torr). The resulting crude was purified by flash chromatography (hexane/AcOEt) affording adducts **9**. Succinimides **9** have already been described.^[24b] Their ¹H NMR and ¹³C NMR data and retention times in chiral HPLC for both enantiomers can be found in the Supporting Information.

Computational Methods: The structures were initially optimized by using density functional theory (DFT) with the B3LYP^[33] and the 6-31G* basis set as implemented in Gaussian 09.^[34] Further re-optimization at M06-2X/6-31G** level of theory^[35] was carried out in order to account for the important dispersion forces in such large systems. The energy values shown in Figures 3 and 4 also include single-point refinements at M06-2X/6-311+G** level on the previously optimized structures (M06-2X/6-31G**), including polarization functions for better description of hydrogen bond activations. Besides, solvation factors were introduced with the IEF-PCM method,^[36] using chloroform or water as indicated in the text and figures.

We also performed single-point calculations at B3LYP/6-311+G** level of theory, and the relative values are similar to those of the M06-2X energies. Therefore, they have not been included in the manuscript, and are collected in the Supplementary Information. The stationary points were characterized by frequency calculations in order to verify that they have the right number of imaginary frequencies.

The intrinsic reaction coordinates (IRC)^[37] were followed to verify the energy profiles connecting each TS to the correct associated local minima.

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