Solvent-Dependent Enantioswitching in the Michael Addition of α,α-Disubstituted Aldehydes to Maleimides Organocatalyzed by Mono-*N*-Boc-Protected Cyclohexa-1,2-Diamines

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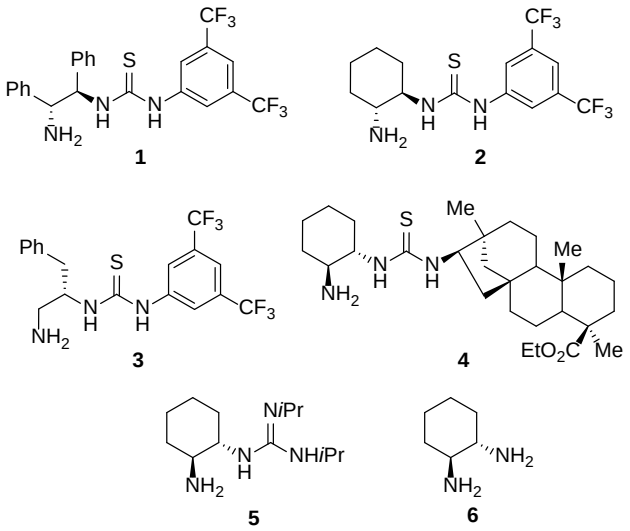
Abstract— Enantiomerically pure mono-*N*-Boc-protected *trans*-cyclohexane-1,2-diamines are used as organocatalysts for the enantioselective conjugate addition of α,α-disubstituted aldehydes to maleimides. Using a single enantiomer of the organocatalyst, both enantiomeric forms of the resulting Michael adducts bearing a new quaternary stereocenter are obtained in high yields, only by changing the reaction solvent from chloroform (up to 86% *ee*) to aqueous DMF (up to 84% *ee*).

1. Introduction

The organocatalytic enantioselective Michael addition of carbon nucleophiles to maleimides is the most direct and easy way of preparing enantioenriched succinimide moieties,[1] which are present in natural products and some clinical drug candidates.[2] Moreover, succinimides can be transformed into γ-lactams,[3] which are privileged structural subunits for the design of pharmaceutical agents important in the treatment of cancer,[4] epilepsy,[5] HIV,[6] neurodegenerative disease and depression.[7]

Carbon nucleophiles suitable for the enantioselective conjugate addition to maleimides can be generated by α-deprotonation of pro-nucleophiles using chiral bifunctional organocatalysts bearing both an acidic moiety and a tertiary amine.[1] Coordination of the maleimide and the enolate generated after deprotonation to the chiral organocatalyst leads to an enantioselective process. However, when aldehydes are used as pro-nucleophiles, tertiary amines are not basic enough for the efficient generation of an enolate, and these organocatalysts cannot be employed. In this case, the enantioselective Michael addition reaction can be carried out by using amine-bearing organocatalysts suitable to form a transient enamine with the reacting aldehyde,[8] thus creating a chirality-inducing transition state after coordination with the maleimide. The first organocatalytic Michael addition of aliphatic aldehydes to *N*-aryl-maleimides used α,α-phenylprolinol silyl ether as organocatalyst, although α,α-disubstituted aldehydes resulted in much lower enantioselectivities.[9]

Taking into consideration this enamine-forming approach, different bifunctional primary amine-bearing organocatalysts have been applied to the enantioselective Michael addition of these "difficult" α,α-disubstituted aldehydes to maleimides, giving high enantioselections of the corresponding succinimides.[10] Some examples are the primary amine-thioureas **1**,[10a, 10b] **2**[10a, 10b] and **3**,[10e] the beyerane-containing thiourea **4**,[10f] the primary amine-guanidine **5**[10h, 10j] and even the simple *trans*-cyclohexa-1,2-diamine **6**.[10k]



When dealing to enantioselective organocatalysis, as in any asymmetric catalysis, opposite enantiomeric products are typically obtained by using opposite enantiomeric organocatalysts. However, switching the enantioselectivity of an organocatalyst just by variation of the reaction conditions, although potentially very interesting, is not an easy matter. Thus, a few examples of switching the enantioselectivity of an organocatalyzed

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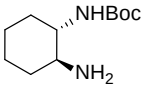
process by changing counteranions of the catalyst,[11] adding bases,[12] acids[13] or other additives[14] or even by light irradiation,[15] have been reported. In addition, examples of changing the enantioselectivity of organocatalyzed reactions simply by changing the reaction solvent are scarce, and limited to the use in some particular cases of some chiral unsupported[16a] and supported[16b] MacMillan's imidazolidinones or α,α-diphenyl-2-pyrrolidinemethanol[17] as organocatalysts, as well as conformationally flexible peptidic[18] and guanidine/bisthiourea species.[19]

We report in this paper how a change in the solvent in the enantioselective addition reaction of the particularly "difficult" α,α-disubstituted aldehydes to maleimides allows employing a single enantiomer of *N*-Boc-monoprotected *trans*-cyclohexa-1,2-diamines as organocatalysts for the synthesis of both enantiomers of the final succinimides.

2. Results and discussion

The (1*S*,2*S*)-cyclohexane-1,2-diamine (**6**) was chosen as chirality source, performing its mono-*N*-protection with the *tert*-butoxycarbonyl (Boc) group by means of a procedure consisting of reaction of **6** with 1 eq of hydrogen chloride (2M, Et_2O) and subsequent treatment with di-*tert*-butyl carbonate.[20] The obtained chiral mono-Boc-protected diamine **7** was explored as primary amine-containing organocatalyst for the model enantioselective Michael addition of isobutyraldehyde to *N*-phenylmaleimide, under different reaction conditions (Table 1).



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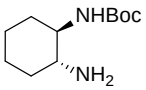
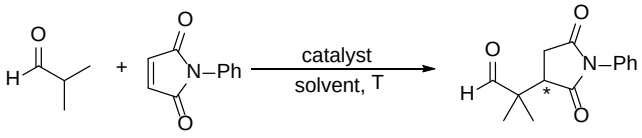


ent-**7**

Thus, the use of a 20 mol% loading of **7** in toluene as solvent at room temperature gave rise to an almost quantitative yield of the succinimide (*S*)-**10aa** in 67% *ee* (Table 1, entry 1). The absolute configuration was determined according to the order of elution of the corresponding enantiomers in chiral HPLC (see experimental).[10j] Changing the solvent to hexane gave a higher *ee* of (*S*)-**10aa**, whereas the use of ether as solvent lowered the enantioselectivity (Table 1, entries 2 and 3). When CH_2Cl_2 and $CHCl_3$ were employed as solvents, 63% and 75% *ee*'s of (*S*)-**10aa**, respectively, were observed (Table 1, entries 4 and 5).

However, it resulted surprising that when DMF was used as solvent the enantioselectivity of the process switched totally, allowing to obtain the opposite (*R*)-**10aa** in 62% *ee* (Table 1, entry 6). The use of water as solvent increased considerably the reaction rate, affording also (*R*)-**10aa** almost quantitatively in 2h although in only 32% *ee* (Table 1, entry 7). Therefore, we explored the possible use of mixtures of DMF/H_2O as solvents, something that has resuted effective when primery amine-guanidines have been used as organocatalysts in this reaction.[10h, 10j] Thus, different DMF/H_2O v/v ratios were assayed (Table 1, entries 8-10), a 2/1 v/v ratio affording (*R*)-**10aa** in 90% yield and 84% *ee* (Table 1, entry 9).

Table 1. Screening and optimization of the reaction conditions for the enantioswitched Michael addition reaction.



8a **9a** **10aa**

Entry	Catalyst (mol%)	Solvent	*T* (ºC)	*t* (h)	Yield (%)[a]	*ee* (%)[b]
1	**7** (20)	PhMe	25	20	98	67 (*S*)
2	**7** (20)	Hexane	25	14	85	73 (*S*)
3	**7** (20)	Et_2O	25	14	95	32 (*S*)
4	**7** (20)	CH_2Cl_2	25	20	95	63 (*S*)
5	**7** (20)	$CHCl_3$	25	20	99	75 (*S*)
6	**7** (20)	DMF	25	44	94	62 (*R*)
7	**7** (20)	H_2O	25	2	97	32 (*R*)
8	**7** (20)	DMF/H_2O[c]	25	17	94	70 (*R*)
9	**7** (20)	DMF/H_2O[d]	25	20	90	84 (*R*)
10	**7** (20)	DMF/H_2O[e]	25	24	88	80 (*R*)
11	**7** (10)	$CHCl_3$	25	20	97	86 (*S*)
12	**7** (10)	DMF/H_2O[d]	25	20	95	84 (*R*)
13	**7** (5)	$CHCl_3$	25	40	95	76 (*S*)
14	**7** (5)	DMF/H_2O[d]	25	40	93	82 (*R*)
15	**7** (10)	$CHCl_3$	0	48	94	70 (*S*)
16	**7** (10)	DMF/H_2O[d]	0	48	91	82 (*R*)
17	*ent*-**7** (10)	$CHCl_3$	25	20	97	84 (*R*)
18	*ent*-**7** (10)	DMF/H_2O[d]	25	20	94	83 (*S*)

[a] Isolated yield after flash chromatography.

[b] Enantioselectivities and absolute stereochemistry determined by chiral HPLC.

[c] 1/1, v/v.

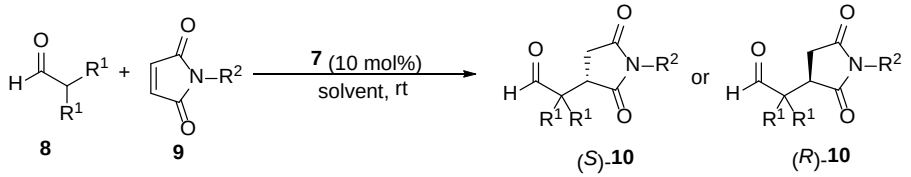
[d] 2/1, v/v.

[e] 4/1, v/v.

Once the most appropriate solvents for achieving opposite enantioselectivities were selected [$CHCl_3$ for (*S*)-**10aa** and DMF/H_2O 2/1 v/v for (*R*)-**10aa**], we explore lowering the organocatalyst loading. Thus, the amount of organocatalyst **7** was diminished to 10 and 5 mol% using both solvents (Table 1, entries 11-14, observing the higher enantioselections for the (*S*) and (*R*) stereoisomers when a loading of 10 mol% was used [86% *ee* for (*S*)-**10aa** and 84% *ee* for (*R*)-**10aa**] (Table 1, entries 11 and 12). Using this optimized 10 mol% organocatalyst loading, we lowered the reaction temperature down to 0 ºC, but no increasing in the stereoselectivity of the reaction was observed in any case (Table 1, entries 15 and 16).

Attempting to achieve opposite enantioselections to those obtained using organocatalyst **7**, we prepare its corresponding enantiomer *ent*-**7** following the same procedure but starting from (1*R*,2*R*)-cyclohexane-1,2-diamine. When this mono-*N*-Boc-protected diamine *ent*-**7** was used as organocatalyst under the most convenient reaction conditions [10 mol% organocatalyst loading, room temperature, $CHCl_3$ or DMF/H_2O 2/1 v/v as solvent], the expected opposite enantioselections than when using **7** were observed [(*R*)-**10aa** using $CHCl_3$ as solvent and (*S*)-**10aa** using DMF/H_2O 2/1 v/v] (Table 1, entries 17 and 18).

Table 2. Solvent-dependent enantioswitched Michael addition of aldehydes to maleimides organocatalyzed by mono-Boc-protected 1,2-diamine **7**.



8 **9** (*S*)-**10** (*R*)-**10**

Entry	Aldehyde		Maleimide		Solvent	*t* (h)	Adduct No	Yield (%)[a]	*ee* (%)[b,c]
	R^1	No.	R^2	No.					
1	Me	**8a**	Ph	**9a**	$CHCl_3$	20	(*S*)-**10aa**	97	86
2					DMF/H_2O 2/1	20	(*R*)-**10aa**	95	84
3	Me	**8a**	4-ClC_6H_4	**9b**	$CHCl_3$	30	(*S*)-**10ab**	99	60
4					DMF/H_2O 2/1	30	(*R*)-**10ab**	97	74
5	Me	**8a**	4-BrC_6H_4	**9c**	$CHCl_3$	30	(*S*)-**10ac**	99	70
6					DMF/H_2O 2/1	30	(*R*)-**10ac**	98	70
7	Me	**8a**	4-$AcOC_6H_4$	**9d**	$CHCl_3$	26	(*S*)-**10ad**	92	40
8					DMF/H_2O 2/1	26	(*R*)-**10ad**	15	80
9	Me	**8a**	Me	**9e**	$CHCl_3$	21	(*S*)-**10ae**	94	53
10					DMF/H_2O 2/1	21	(*R*)-**10ae**	91	68
11	Me	**8a**	H	**9f**	$CHCl_3$	17	(*S*)-**10af**	94	50
12					DMF/H_2O 2/1	17	(*R*)-**10af**	88	70
13	Et	**8b**	Ph	**9a**	$CHCl_3$	48	(*S*)-**10ba**	70	55
14					DMF/H_2O 2/1	48	(*R*)-**10ba**	93	68
15	-$(CH_2)_4$-	**8c**	Ph	**9a**	$CHCl_3$	30	(*S*)-**10ca**	99	49
16					DMF/H_2O 2/1	30	(*R*)-**10ca**	96	61
17	-$(CH_2)_5$-	**8d**	Ph	**9a**	$CHCl_3$	48	(*S*)-**10da**	96	14
18					DMF/H_2O 2/1	48	(*R*)-**10da**	96	35

[a] Isolated yield after flash chromatography.

[b] Enantioselectivities determined by chiral HPLC (Ref. 22).

[c] Absolute configuration assigned by the order of elution of the enantiomers in chiral HPLC (Ref. 23).

In order to determine if the observed *ee* for (*R*)-**10aa** was changing during the process, the model reaction of aldehyde **8a** and maleimide **9a** in the presence of the organocatalyst **7** (10 mol%) was carried out in DMF/H_2O 2/1 v/v during reaction times of 4, 8, and 12h. In all cases the *ee* for (*R*)-**10aa** was kept in 84%, the same value than when the reaction was totally finished. In addition, attempting to rule out that the change in the enantioselectivity was a consequence of a former evolution of the final product, the product (*R*)-**10aa** in 84% *ee* was combined to organocatalyst **7** (10 mol%) in $CHCl_3$ as solvent at room temperature. After 20h stirring, the product (*R*)-**10aa** was recovered with its enantioinduction intact.

With the most effective reaction conditions in hand [**7** (10 mol%), $CHCl_3$ for (*S*)-enantiomer and DMF/H_2O 2/1 v/v for (*R*)-enantiomer, rt] we explored the extension of this organocatalytic solvent-dependent enantioswitching methodology to other aldehydes and maleimides (Table 2).[21] 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.[22,23]

Thus, when $CHCl_3$ was the solvent of choice, isobutyraldehyde reacted with *N*-phenylmaleimides bearing halogens on the phenyl ring, such as a chloro or a bromo atom at the 4-position (**9b** and **9c**), and the succinimides (*S*)-**10ab** and (*S*)-**10ac** were obtained in 60 and 70% *ee*, respectively (Table 2, entries 3 and 5). However, when DMF/H_2O 2/1 v/v was the reaction solvent, adducts (*R*)-**10ab** and (*R*)-**10ac** were isolated in 74 and 70% *ee* (Table 2, entries 4 and 6). In addition, when an acetoxy groups was present onto the phenyl ring of the maleimide, as in the case of **9d**, the enantioselectivities for the corresponding enantiomeric succinimides (*S*)-**10ad** and (*R*)-**10ad** were 40 and 80%, depending on the use of $CHCl_3$ or DMF/H_2O 2/1 v/v as solvents, respectively (Table 2, entries 7 and 8).

Non-*N*-arylated maleimides were also employed for the conjugate addition with isobutyraldehyde. Thus, *N*-methylmaleimide (**9e**) gave the (*S*)- and (*R*)-enantiomer of adduct **10ae** depending on the use $CHCl_3$ and DMF/H_2O 2/1 v/v as reaction solvents (53 and 68% *ee*, respectively) (Table 2, entries 9 and 10). In addition, the simple maleimide (**9f**) was also used as Michael acceptor, affording (*S*)-**10af** (50% *ee*) using $CHCl_3$ as solvent, and (*R*)-**10af** (70% *ee*) when the solvent was DMF/H_2O 2/1 v/v (Table 2, entries 11 and 12).

Other α,α-disubstituted aldehydes were employed for the organocatalyzed Michael addition reaction to *N*-phenylmaleimide. Thus, 2-ethylbutanal (**8b**) afforded succinimides (*S*)-**10ba** (55% *ee*) and (*R*)-**10ba** (68% *ee*) using $CHCl_3$ and DMF/H_2O 2/1 v/v as solvents, respectively (Table 2, entries 13 and 14). In addition, cyclopentane- (**8c**) and cyclohexanecarbaldehyde (**8d**) gave almost quantitative amounts of succinimides (*S*)-

10ca and (*S*)-**10da** in 49 and 14% *ee*, respectively, when $CHCl_3$ was the reaction solvent, whereas gave the (*R*)-**10ca** and (*R*)-**10da** enantiomers in 61 and 35% *ee*, respectively, using DMF/H_2O 2/1 v/v (Table 2, entries 15-18).

3. Conclusions

It can be concluded that easily prepared *N*-Boc-monoprotected chiral *trans*-cyclohexa-1,2-diamines can be used as organocatalysts in the high-yielding enantioselective conjugate addition of α,α-disubstituted aldehydes to different maleimides, giving rise to an uncommon solvent-dependent enantioswitched reaction. Thus, both (*S*)- or (*R*)-enantioenriched forms of the Michael adducts can be obtained employing a single mirror form of the organocatalyst, just by changing the reaction solvent from chloroform to aqueous *N*,*N*-dimethylformamide. Further studies devoted to get insight into the origin of this solvent-induced stereoselectivity switch as well as to extend this methodology to other organocatalysts and substrates are now underway.

Acknowledgments

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21. *Typical experimental procedure for the enantioselective Michael addition reaction*: To a solution of **7** or *ent*-**7** (0.04 mmol) and **9** (0.2 mmol) in DMF/H_2O (2/1, v/v) (0.5 mL) was added the aldehyde **8** (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 ($MgSO_4$), filtered and evaporated (15 torr). The resulting crude was purified by flash chromatography (hexane/AcOEt) affording adducts **10**, which gave consistent spectroscopic data with those reported in the literature (Ref. 10j).
22. Enantioselectivities were determined by HPLC using *n*-hexane/2-propanol mixtures as eluant and the following chiral columns: Chiralcel OD-H (**10aa**, **10ab**, **10ac, 10ca**, **10da**), Chiralpak AS-H (**10ad**, **10ae**, **10ba**) and Chiralpak AD-H (**10af**). Reference racemic samples of adducts **10** were obtained by performing the reaction using 4-methylbenzylamine (20 mol%) as organocatalyst in toluene as solvent at room temperature.
23. Absolute configuration for the adducts **10** was determined according to the described order of elution of their enantiomers in chiral HPLC (Ref. 10j).