Tetrahedron: *Asymmetry* 25 (2014) 1091–1094

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

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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ARTICLE INFO

Article history:
Received 6 May 2014
Accepted 19 June 2014

ABSTRACT

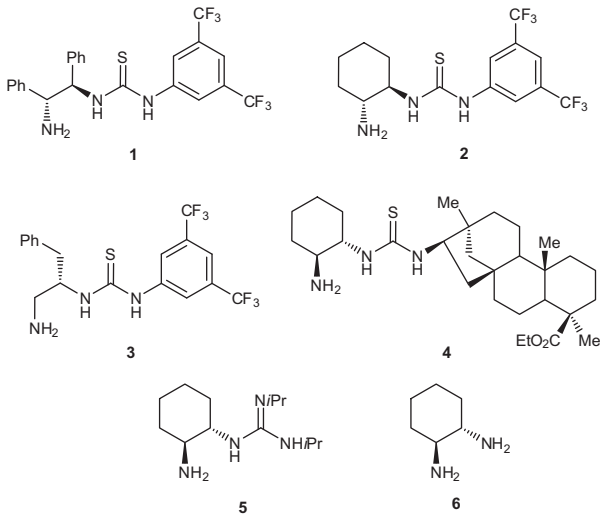
Enantiomerically pure mono-*N*-Boc-protected *trans*-cyclohexa-1,2-diamines are used as organocatalysts for the enantioselective conjugate addition of α,α-disubstituted aldehydes to maleimides. Using a single enantiomer of the organocatalyst, both enantiomeric forms of the resulting Michael adducts bearing a new quaternary stereocenter are obtained in high yields, by only 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 method for 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 that are important in the treatment of cancer,[4] epilepsy,[5] HIV,[6] neurodegenerative disease, and depression.[7]

Carbon nucleophiles suitable for enantioselective conjugate additions 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 organo catalysts that are 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 the 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 enantioselective Michael additions of these 'difficult' α,α-disubstituted aldehydes to maleimides, giving high enantioselections in the corresponding succinimides.[10] Some examples include the primary amine–thioureas **1**,[10a,b] **2**[10a,b] and **3**,[10e] the beyerane-containing thiourea **4**,[10f] the primary amine–guanidine **5**,[10h,j] and even the simple *trans*-cyclohexa-1,2-diamine **6**.[10k]



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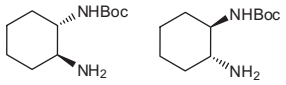
http://dx.doi.org/10.1016/j.tetasy.2014.06.014
0957-4166/

When dealing with enantioselective organocatalysis, as with any asymmetric catalysis, opposite enantiomeric products are typically obtained by using opposite enantiomeric organocatalysts. However, switching the enantioselectivity of an organocatalyst just by varying the reaction conditions, although potentially very interesting, is not an easy matter. Thus, only a few examples of switching the enantioselectivity of an organocatalyzed process by changing the 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-pyrrolidine methanol[17] as organocatalysts, as well as conformationally flexible peptidic[18] and guanidine/bisthiourea species.[19]

Herein we report how a change in the solvent in the enantioselective addition reaction of the particularly 'difficult' α,α-disubstituted aldehydes to maleimides allows a single enantiomer of *N*-Boc-monoprotected *trans*-cyclohexa-1,2-diamines to be employed as an organocatalyst for the synthesis of both enantiomers of the final succinimides.

2. Results and discussion

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



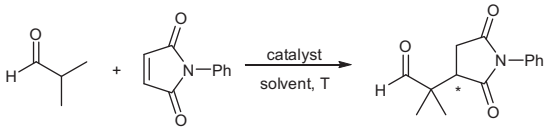
7 *ent*-**7**

The use of a 20 mol % loading of **7** in toluene as solvent at room temperature gave succinimide (*S*)-**10aa** in almost quantitative yield of 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 (*S*)-**10aa** with a higher ee, 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, (*S*)-**10aa** was obtained with 63% and 75% ee, respectively (Table 1, entries 4 and 5).

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

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 explored lowering the organocatalyst loading. Thus, the amount of organocatalyst **7** was decreased to 10 and 5 mol % using both solvents (Table 1, entries 11–14); higher

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



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

Entry	Catalyst (mol %)	Solvent	*T* (°C)	*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.

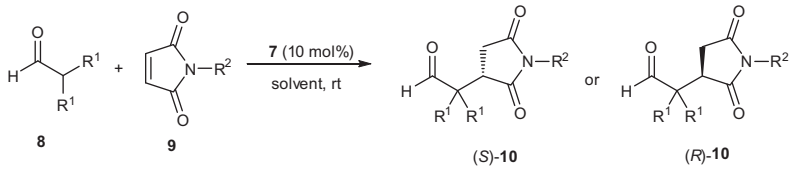
enantioselections were observed for the (*S*)- and (*R*)-stereoisomers when a loading of 10 mol % was used [86% ee for (*S*)-**10aa** and 84% ee for (*R*)-**10aa**] (Table 1, entries 11 and 12). Using this optimized 10 mol % organocatalyst loading, we lowered the reaction temperature to 0 °C, but no increase in the stereoselectivity of the reaction was observed (Table 1, entries 15 and 16).

Attempting to achieve opposite enantioselections to those obtained using organocatalyst **7**, we prepared the corresponding enantiomer *ent*-**7** following the same procedure but starting from (1*R*,2*R*)-cyclohexa-1,2-diamines. When mono-*N*-Boc-protected diamine *ent*-**7** was used as the 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 to those obtained 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).

In order to determine whether the observed ee for (*R*)-**10aa** changed during the process, the model reaction of aldehyde **8a** and maleimide **9a** in the presence of organocatalyst **7** (10 mol %) was carried out in DMF/H_2O 2:1 v/v with reaction times of 4, 8, and 12 h. In all cases the ee for (*R*)-**10aa** remained at 84%, the same value as to when the reaction was completed. In an attempt to rule out whether the change in the enantioselectivity was due to the former evolution of the final product, product (*R*)-**10aa** (84% ee) was combined with organocatalyst **7** (10 mol %) in $CHCl_3$ as the solvent at room temperature. After stirring for 20 h, 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 extended 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]

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



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-AcC_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.[22]
[c] Absolute configuration assigned by the order of elution of the enantiomers in chiral HPLC.[23]

Thus, when $CHCl_3$ was used as the solvent, isobutyraldehyde reacted with *N*-phenylmaleimides bearing halogens on the phenyl ring, such as a chloro or a bromo atom at the 4-position of **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). When an acetyl group was present on 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 the solvent, 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 of $CHCl_3$ and DMF/H_2O 2:1 v/v as the reaction solvent (53% and 68% ee, respectively) (Table 2, entries 9 and 10). Maleimide (**9f**) was also used as a Michael acceptor and afforded (*S*)-**10af** (50% ee) when using $CHCl_3$ as the 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. 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). Cyclopentane-**8c** and cyclohexane carbaldehyde **8d** gave almost quantitative amounts of succinimides (*S*)-**10ca** and (*S*)-**10da** with 49% and 14% ee, respectively, when $CHCl_3$ was the reaction solvent, while (*R*)-**10ca** and (*R*)-**10da** were obtained with 61% and 35% ee, respectively when using DMF/H_2O 2:1 v/v (Table 2, entries 15–18).

3. Conclusion

It can be concluded that the 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 the (*S*)- or (*R*)-enantioenriched forms of the Michael adducts can be obtained by employing a single mirror form of the organocatalyst, by simply changing the reaction solvent from chloroform to aqueous *N*,*N*-dimethylformamide. Further studies devoted to gaining insight into the origin of this solvent-induced stereoselectivity switch, as well as extending this methodology to other organocatalysts and substrates are currently underway.

Acknowledgments

We thank the financial support from the Spanish Ministerio de Economía y Competitividad (Project CTQ2011-24151), FEDER, the COST Action CM0905 'Organocatalysis', and the University of Alicante.

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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 aldehyde **8** (0.4 mmol) and the reaction was stirred at rt until completion (TLC). A solution of 2 M HCl (10 mL) was then added and the mixture was extracted with EtOAc (3 × 10 mL). The organic phase was washed with water (2 × 10 mL), dried ($MgSO_4$), filtered, and evaporated (15 torr). The resulting crude was purified by flash chromatography (hexane/AcOEt) to afford adducts **10**, which gave consistent spectroscopic data with those reported in the literature.[10j]
22. *Enantioselectivities were determined by HPLC using n-hexane/2-propanol mixtures as eluant and the following chiral columns:* Chiralcel OD-H for **10aa**, **10ab**, **10ac, 10ca**, **10da**, Chiralpak AS-H for **10ad**, **10ae**, **10ba**, and Chiralpak AD-H for **10af**. Reference racemic samples of adducts **10** were obtained by performing the reaction using 4-methylbenzylamine (20 mol %) as the organocatalyst in toluene as the solvent at room temperature.
23. The absolute configurations for adducts **10** were determined according to the described order of elution of their enantiomers in chiral HPLC.[10j]