Tetrahedron: *Asymmetry* 23 (2012) 1625–1627

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

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

Enantioselective Michael addition of α,α-disubstituted aldehydes to maleimides organocatalyzed by chiral primary amine-guanidines

Angel Avila, Rafael Chinchilla *, Carmen Nájera *

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

ARTICLE INFO

Article history:
Received 16 October 2012
Accepted 8 November 2012

ABSTRACT

New primary amine-guanidines derived from the monoguanylation of (1*S*,2*S*)- and (1*R*,2*R*)-cyclohexane-1,2-diamine have been prepared and used as chiral organocatalysts for the enantioselective conjugate addition of α,α-disubstituted aldehydes to maleimides. The corresponding Michael adducts bearing a new stereocenter were generally obtained in high or quantitative yields and with good enantioselectivities (up to 93% *ee*).

1. Introduction

The synthesis of enantiomerically enriched substituted succinimides is currently an interesting topic, as these compounds have important biological activities[1] and are precursors of interesting substances.[2] For instance, succinimides can be easily transformed into γ-lactams, a subunit widely distributed among biologically interesting natural products.[3]

Probably the most direct way of preparing enantiomerically enriched substituted succinimides is performing the enantioselective Michael addition reaction of a carbon-centered nucleophilic species onto a maleimide, a process which can be carried out organocatalytically.[4] In general, the organocatalysts employed have a basic character, therefore being able to deprotonate species bearing acidic hydrogens, and thus generating the nucleophile. This deprotonation is much more difficult in the case of substrates bearing low-acidity hydrogens, such as simple ketones or aldehydes. In this case, the reaction can be performed using chiral amines as organocatalysts, which are amenable to generate a transient chiral enamine responsible for asymmetric outcome of the process. Amino acid derivatives has been used for this process,[5] as well as chiral diamine monosulfamides.[6] Particularly good yields and enantioselectivities in the conjugate addition of aldehydes to maleimides have been obtained using a protected diarylprolinol as the organocatalyst,[7] although the enantioselection achieved using α,α-dialkylated aldehydes such as isobutyraldehyde was only moderate.

This limitation prompted the search for new chiral amine -bearing organocatalysts amenable to carry out the Michael addition reaction of disubstituted aldehydes to maleimides with a high enantioselection. Thus, several bifunctional primary amine thiourea organocatalysts have been developed and applied to the enantioselective Michael addition of α,α-disubstituted aldehydes to maleimides, giving excellent results.[8] However, a drawback of the use of these organocatalysts, particularly on a large scale, is that their best performance is achieved employing chlorinated solvents.

Chiral guanidines have been shown to be interesting systems for achieving asymmetric transformations when used as organocatalysts.[9] However, their use in the enantioselective Michael addition reaction of carbon nucleophiles to maleimides is limited to the reaction of malonates or 1,3-dicarbonyl compounds,[10] as well as dithiomalonates,[10a] 3-benzyl-substituted oxoindoles,[11] or anthrones[12] as nucleophile precursors, due to their easy deprotonation by the basic guanidine. No examples exist on the use of chiral guanidine derivatives for performing this conjugate reaction to maleimides with aldehydes.

Herein we report the synthesis of new chiral primary amine-guanidines and their use as organocatalysts for the direct enantioselective reaction of particularly difficult α,α-disubstituted aldehydes to maleimides.

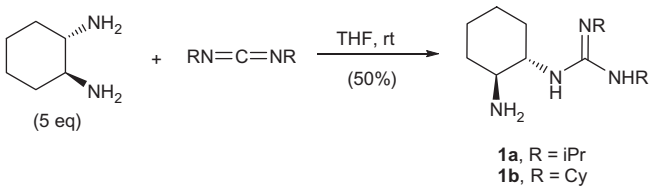
2. Results and discussion

Chiral primary amine-guanidines **1a** and **1b** were prepared in 50% yield by the reaction of (1*S*,2*S*)-cyclohexane-1,2-diamine (5 equiv) with diisopropylcarbodiimide and dicyclohexylcarbodiimide, respectively, in THF at room temperature for 48 h (Scheme 1).

These primary amine-guanidines **1** were then used as organocatalysts in the model Michael conjugate addition of isobutyraldehyde to *N*-phenylmaleimide under different reaction conditions (Table 1). Thus we tested diisopropyl-containing amine guanidine **1a** as the organocatalyst (20 mol %) in this model transformation, using toluene as the solvent at room temperature. The addition adduct (*R*)-**4aa** was obtained in 51% conversion (300 MHz ^{1}H NMR)

* Corresponding authors. Tel.: +34 96 5903728; fax: +34 96 5903549.
E-mail addresses: chinchilla@ua.es (R. Chinchilla), cnajera@ua.es (C. Nájera).

0957-4166/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetasy.2012.11.002

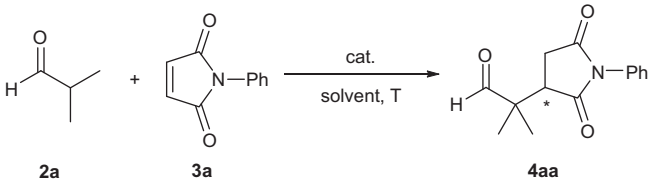


Scheme 1. Preparation of primary amine guanidines **1**.

and 76% *ee* (chiral HPLC) (Table 1, entry 1). Its (*R*) absolute configuration was determined by comparison of the elution order of the corresponding enantiomers in chiral HPLC with those in the literature.[8b] However, when dicyclohexyl-containing primary amine guanidine **1b** was used as the organocatalyst under the same reaction conditions, only 48% *ee* for adduct (*R*)-**4aa** was detected, although in a much higher yield (Table 1, entry 2). Therefore, we continued the search for the optimum reaction conditions using organocatalyst **1a**.

Other solvents were then assayed. Nitromethane and methanol were also used as solvents at room temperature, although a lower enantioselection was observed in both cases, as well as lower yields (Table 1, entries 3 and 4). When DMF was employed as the solvent, the enantioselection of the process increased up to 82% for adduct (*R*)-**4aa**, although in 55% yield after 2 d (Table 1, entry 5). However, the yield for this model reaction rose up to 70% after 1 d reaction time when using water as the solvent at room temperature, with compound (*R*)-**4aa** being obtained in 80% *ee* (Table 1, entry 6). Therefore, the combination of DMF/H_2O was explored as the solvent mixture at room temperature, employing different DMF/H_2O ratios. Thus, a DMF/H_2O 1/1 v/v gave rise to a quantitative yield after 2 d reaction time, with (*R*)-**4aa** being obtained with 85% *ee* (Table 1, entry 7). The use of a mixture of DMF/H_2O 2/1 v/v as solvent increased the enantioselectivity up to 88% *ee* while keeping quantitative yield (Table 1, entry 8). Further lowering the amount of water in the mixture was not beneficial, as the use of a DMF/H_2O 4/1 v/v mixture afforded a lower enantioselection (84% *ee*) (Table 1, entry 9). Moreover, the addition of an additive such as benzoic acid (20 mol %) to the reaction mixture did not improve the yield or enantioselectivity of the process.

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



2a **3a** **4aa**

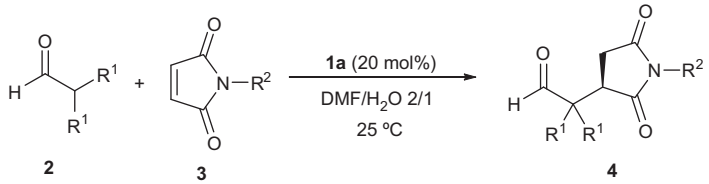
Entry	Cat. (mol %)	Solvent	*T* (°C)	*t* (d)	Yield[a] (%)	*ee*[b] (%)
1	**1a** (20)	PhMe	25	2	51	76 (*R*)
2	**1b** (20)	PhMe	25	2	90	48 (*R*)
3	**1a** (20)	$MeNO_2$	25	2	30	46 (*R*)
4	**1a** (20)	MeOH	25	2	15	68 (*R*)
5	**1a** (20)	DMF	25	2	55	82 (*R*)
6	**1a** (20)	H_2O	25	1	70	80 (*R*)
7	**1a** (20)	DMF/H_2O[c]	25	2	99	85 (*R*)
8	**1a** (20)	DMF/H_2O[d]	25	2	99	88 (*R*)
9	**1a** (20)	DMF/H_2O[e]	25	2	99	84 (*R*)
10	**1a** (20)	DMF/H_2O[d]	15	3	88	87 (*R*)
11	**1a** (10)	DMF/H_2O[d]	25	3	99	83 (*R*)
12	*ent*-**1a** (20)	DMF/H_2O[d]	25	2	99	87 (*S*)

[a] Isolated yield (^{1}H NMR, 300 MHz).
[b] Enantioselectivities determined by chiral HPLC.[14] Absolute stereochemistry determined by the reported order of elution of the enantiomers in chiral HPLC.[8b]
[c] 1/1, v/v.
[d] 2/1, v/v.
[e] 4/1, v/v.

The influence of the reaction temperature was then determined. Thus, when the temperature was lowered to 15 °C using the mixture of DMF/H_2O 2/1 v/v as the solvent, the enantioselection for (*R*)-**4aa** remained essentially the same (87%) when working at 25 °C, while the reaction rate decreased considerably (Table 1, entry 10). In addition, we also explored the influence of lowering the loading of the organocatalyst **1a**. Thus, when the model reaction was performed using **1a** as the organocatalyst in 10 mol % loading, the yield of the process was quantitative after a longer reaction time (3 d), while the enantioselectivity of (*R*)-**4aa** decreased to 83% *ee* (Table 1, entry 11).

Expecting to achieve an opposite enantioselection, we prepared the primary amine guanidine *ent*-**1a** in 50% yield in a similar man-

Table 2
Enantioselective Michael addition of α,α-disubstituted aldehydes to maleimides organocatalyzed by primary amine-guanidine **1a**

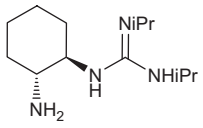


2 **3** **4**

Entry	Aldehyde		Maleimide		*t* (d)	Adduct No.	Yield[a] (%)	*ee*[b,c] (%)
	R^1	No.	R^2	No.				
1	Me	**2a**	Ph	**3a**	2	(*R*)-**4aa**	99	88
2	Me	**2a**	4-BrC_6H_4	**3b**	2	(*R*)-**4ab**	94	93
3	Me	**2a**	4-$AcOC_6H_4$	**3c**	1.5	(*R*)-**4ac**	92	79
4	Me	**2a**	Bn	**3d**	2	(*R*)-**4ad**	99	76
5	Me	**2a**	Me	**3e**	1.5	(*R*)-**4ae**	84	75
6	Me	**2a**	H	**3f**	1.5	(*R*)-**4af**	94	83
7	Et	**2b**	Ph	**3a**	4	(*R*)-**4ba**	99	74
8	$-(CH_2)_4-$	**2c**	Ph	**3a**	4	(*R*)-**4ca**	99	86
9	$-(CH_2)_5-$	**2d**	Ph	**3a**	4	(*R*)-**4da**	99	84

[a] Isolated yield after flash chromatography.
[b] Enantioselectivities determined by chiral HPLC.[14]
[c] Absolute configuration determined by the reported order of elution of the enantiomers in chiral HPLC.[15]

ner to its enantiomer **1a**, although starting from (1*R*,2*R*)-cyclohexane-1,2-diamine. This compound was used as the organocatalyst in a former model Michael reaction using a combination DMF/H_2O 2/1 v/v as solvent at 25 °C, to quantitatively afford the enantiomer (*S*)-**4aa** in essentially the same enantioselectivity (87% *ee*) that when using the enantiomeric guanidine **1a** (Table 1, entry 12).



ent-**1a**

With the most appropriate organocatalyst **1a** and convenient reaction conditions (DMF/H_2O 2/1 v/v as solvent, 25 °C reaction temperature) established, we proceeded to extend the procedure to other α,α-disubstituted aldehydes and maleimides (Table 2).[13] Thus, when isobutyraldehyde reacted with the *N*-phenylmaleimide bearing a bromo at the 4-position of the aromatic ring **3b**, the enantioselectivity of the adduct (*R*)-**4ab** increased to 93% (Table 2, entry 2). When a 4-acyloxy group was present **3c**, adduct (*R*)-**4ac** was isolated with a lower enantioselection (79%) (Table 2, entry 3). In addition, the influence of the other non-aromatic *N*-substituents in the maleimide system was also explored. Thus, the use of *N*-benzylated maleimide **3d** and isobutyraldehyde gave rise to adduct (*R*)-**4ad** in 76% *ee*, a similar value when using *N*-methylmaleimide **3e**, which afforded (*R*)-**4ae** in 75% *ee* (Table 2, entry 5). The use of the simple maleimide **3f**, with no *N*-substituent, yielded the corresponding adduct (*R*)-**4af** in high yield and good enantioselectivity (83%) (Table 2, entry 6).

Other α,α-disubstituted aldehydes were also assayed in the reaction with *N*-phenylmaleimide. Thus, 2-ethylbutanal **2b** gave rise to the corresponding Michael adduct (*R*)-**4ba** in quantitative yield and 74% *ee* (Table 2, entry 7), whereas the use of cyclopentane- and cyclohexanecarbaldehyde quantitatively afforded adducts (*R*)-**4ca** and (*R*)-**4da** in 86% and 84% *ee*, respectively (Table 2, entries 8 and 9).

The observed (*R*)-sense of enantioinduction in all of the former adducts, achieved when employing catalyst **1a** which derives from (1*S*,2*S*)-cyclohexane-1,2-diamine was unexpected, as the (*R*)-enantiomers have also been obtained when using amino-thioureas as a catalyst obtained from (1*R*,2*R*)-cyclohexane-1,2-diamine.[8b,d] This indicates that a different transition state operates when these amine-guanidines are used compared to the reaction promoted by primary amine-thioureas.

3. Conclusion

It can be concluded that the simple monoguanylation of enantiomerically pure *trans*-cyclohexane-1,2-diamines gives chiral guanidines which contain a primary amino group. These new systems behave as organocatalysts in the enantioselective conjugate addition of α,α-disubstituted aldehydes to different maleimides in an aqueous solvent, with high yields and good enantioselectivities. This is the first reported α-substitution of aldehydes employing amine-guanidines as organocatalysts. Further studies devoted to determine the origin and sense of the enantioselectivity when using these guanidines, as well as expanding their catalytic ability to other substrates are currently underway.

Acknowledgments

We thank for the financial support from the Spanish Ministerio de Economía y Competitividad (projects CTQ2010-20387 and Consolider Ingenio 2010, CSD2007-00006), FEDER, the Generalitat Valenciana (Prometeo/2009/039), and the University of Alicante.

References

1. a Ahmed, S. *Drug Des. Discov.* **1996**, *14*, 77–89; b Curtin, M. L.; Garland, R. B.; Heyman, H. R.; Frey, R. R.; Michaelidies, M. R.; Li, J.; Pease, L. J.; Glaser, K. B.; Marcotte, P. A.; Davidsen, S. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2919–2923.
2. a Katritzky, A. R.; Yao, J.; Qi, M.; Chou, Y.; Sikora, D. J.; Davis, S. *Heterocycles* **1998**, *48*, 2677–2691; b Ballini, R.; Bosica, G.; Cioci, G.; Fiorini, D.; Petrini, M. *Tetrahedron* **2003**, *59*, 3603–3608.
3. Nöth, J.; Frankowski, K. J.; Neuenswander, B.; Aubé, J.; Reiser, O. *J. Comb. Chem.* **2008**, *10*, 456–459.
4. Some recent examples: a Lu, J.; Zhou, W.-J.; Liu, F.; Loh, T.-P. *Adv. Synth. Catal.* **2008**, *350*, 1796–1800; b Zea, A.; Valero, G.; Alba, A.-N. R.; Moyano, A.; Rios, R. *Adv. Synth. Catal.* **2010**, *352*, 1102–1106; c Liao, Y.-H.; Liu, X.-L.; Wu, Z.-J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2010**, *12*, 2896–2899; d Li, X.; Hu, S.-S.; Xi, Z.-G.; Zhang, L.; Luo, S.-Z.; Cheng, J.-P. *J. Org. Chem.* **2010**, *75*, 8697–8700; e Qin, Y.; Yang, G.; Yang, L.; Li, J.; Cui, Y. *Catal. Lett.* **2011**, *141*, 481–488; f Zea, A.; Alba, A.-N. R.; Bravo, N.; Moyano, A.; Rios, R. *Tetrahedron* **2011**, *67*, 2513–2529; g Gómez-Torres, E.; Alonso, D. A.; Gómez-Bengoa, E.; Nájera, C. *Org. Lett.* **2011**, *13*, 6106–6109; h Bai, J.-F.; Wang, L.-L.; Peng, L.; Guo, Y.-L.; Jia, L.-N.; Tian, F.; He, G.-Y.; Xu, X.-Y.; Wang, L.-X. *J. Org. Chem.* **2012**, *77*, 2947–2953.
5. Nugent, T. C.; Sadiq, A.; Bibi, A.; Heine, T.; Zeonjuk, L. L.; Vankova, N.; Bassil, B. S. *Chem. Eur. J.* **2012**, *18*, 4088–4098.
6. a Yu, F.; Sun, X.; Jin, Z.; Wen, S.; Liang, X.; Ye, J. *Chem. Commun.* **2010**, 4589–4591; b Wang, J.; Zhang, M.-M.; Zhang, S.; Xu, Z.-A.; Li, H.; Yu, X.-H.; Wang, W. *Synlett* **2011**, 473–476.
7. Zhao, G.-L.; Xu, Y.; Sunden, H.; Eriksson, L.; Sayah, M.; Cordova, A. *Chem. Commun.* **2007**, 734–735.
8. a Yu, F.; Jin, Z.; Huang, H.; Ye, T.; Liang, X.; Ye, J. *Org. Biomol. Chem.* **2010**, *8*, 4767–4774; b Bai, J.-F.; Peng, L.; Wang, L.-l.; Wang, L.-X; Xu, X.-Y. *Tetrahedron* **2010**, *66*, 8928–8932; c Xue, F.; Liu, L.; Zhang, S.; Duan, W.; Wang, W. *Chem. Eur. J.* **2010**, *16*, 7979–7982; d Miura, T.; Nishida, S.; Masuda, A.; Tada, N.; Itoh, A. *Tetrahedron Lett.* **2011**, *52*, 4158–4160; e Miura, T.; Masuda, A.; Ina, M.; Nakashima, K.; Nishida, S.; Tada, N.; Itoh, A. *Tetrahedron: Asymmetry* **2011**, *22*, 1605–1609; f Ma, Z.-w.; Liu, Y.-x.; Li, P.-l.; Ren, H.; Zhu, Y.; Tao, J.-c. *Tetrahedron: Asymmetry* **2011**, *22*, 1740–1748; g Ma, Z.-W.; Liu, Y.-X.; Zhang, W.-J.; Tao, Y.; Zhu, Y.; Tao, J.-C.; Tang, M.-S. *Eur. J. Org. Chem.* **2011**, 6747–6754.
9. a Ishikawa, T.; Isobe, T. *Chem. Eur. J.* **2002**, *8*, 553–557; b Leow, D.; Tan, C.-H. *Chem. Asian J.* **2009**, *4*, 488–507; c Ishikawa, T. *Chem. Pharm. Bull.* **2010**, *58*, 1555–1564; d Leow, D.; Tan, C.-H. *Synlett* **2010**, 1589–1605; e Fu, X.; Tan, C.-H. *Chem. Commun.* **2011**, 8210–8222.
10. a Ye, W.; Jiang, Z.; Zhao, Y.; Goh, S. L. M.; Leow, D.; Soh, Y.-T.; Tan, C.-H. *Adv. Synth. Catal.* **2007**, *349*, 2454–2458; b Jiang, Z.; Ye, W.; Yang, Y.; Tan, C.-H. *Adv. Synth. Catal.* **2008**, *350*, 2345–2351.
11. Li, L.; Chen, W.; Yang, W.; Pan, Y.; Liu, H.; Tan, C.-H.; Jiang, Z. *Chem. Commun.* **2012**, *48*, 5124–5126.
12. a Peng, B.; Cheng, K.-J.; Ma, D. *J. Org. Chem.* **2000**, *18*, 411–413; b Shen, J.; Nguyen, T. T.; Goh, Y.-P.; Ye, W.; Fu, X.; Xu, J.; Tan, C.-H. *J. Am. Chem. Soc.* **2006**, *128*, 13692–13693.
13. Typical experimental procedure for the enantioselective Michael addition reaction: To a solution of **1** or *ent*-**1a** (0.04 mmol) and **3** (0.2 mmol) in DMF/H_2O (2/1, v/v) (0.5 mL) was added aldehyde **2** (0.4 mmol) and the reaction was stirred at rt until completion (TLC). Water (10 mL) was then added and the mixture was extracted with AcOEt (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) affording adducts **4**.
14. Enantioselectivities were determined by HPLC using *n*-hexane/2-propanol mixtures as eluant and the following chiral columns: Chiralcel OD-H (**4aa**, **4ab**, **4ca**, **4da**), Chiralpak AS-H (**4ac**, **4ae**, **4ba**), and Chiralpak AD-H (**4ad**, **4af**). Reference racemic samples of adducts **4** were obtained by performing the reaction using 4-methylbenzylamine (20 mol %) as organocatalyst in toluene as the solvent at 25 °C.
15. The absolute configuration for the known adducts **4aa**,[8b] **4ab**,[8e] **4ad**,[8b] **4ae**,[8b] **4ba**,[8a] **4ca**,[8c] and **4da**[8c] was determined according to the described order of elution of their enantiomers in chiral HPLC. The absolute configuration of the new adducts **4ac** and **4af** was assigned by analogy.