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Enantioselective Synthesis of Succinimides by Michael Addition of Aldehydes to Maleimides Organocatalyzed by Chiral Primary Amine-Guanidines

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Dedicated to the memory of Professor Balbino Mancheño

Keywords: Organocatalysis / Asymmetric catalysis / Michael addition / Aldehydes / Enantioselectivity

The monoguanylation of (1*S*,2*S*)- and (1*R*,2*R*)-cyclohexane-1,2-diamine affords chiral primary amine-guanidines that are used as chiral organocatalysts in the enantioselective Michael addition of aldehydes, particularly α,α-disubstituted aldehydes, to maleimides. The reaction is carried out in the presence of imidazole, as an additive, in aqueous *N*,*N*-dimethylformamide, as the solvent, and affords the corresponding enantioenriched succinimides in high or quantitative yields with enantioselectivities up to 96 % *ee*. Theoretical calculations (DFT and M06–2X) suggest a different hydrogen-bonding coordination pattern between the maleimide (C=O) and the catalyst (NH groups) is responsible for the enantioinduction switch that is observed when the reaction is carried out using primary amine-guanidines versus primary amine-thioureas as the organocatalysts.

Introduction

Maleimides are an important class of compounds that have been successfully used in different asymmetric organocatalytic transformations.[1] Particularly, the organocatalytic functionalization of maleimides provides easy access to chiral-substituted succinimide derivatives, which are of interest because of the occurrence of the succinimide moiety in natural products and some clinical drug candidates.[2] In addition, succinimides can be transformed into other important compounds such as γ-lactams,[3] which are important in the treatment of epilepsy,[4] HIV,[5] neurodegenerative disease, and depression.[6]

The enantioselective Michael addition of carbon nucleophiles to maleimides is probably the most direct method to prepare enantioenriched succinimides using an organocatalytic approach.[1] Frequently, this has been achieved by using pronucleophiles that contain highly acidic α hydrogens and employing chiral bifunctional compounds as organocatalysts that contain both an acidic moiety and a tertiary amine.[1] Thus, enantioinduction is achieved after the formation of the transition state, which involves the close coordination of the maleimide and the enolate that is generated by deprotonation with a basic tertiary amine. However, pronucleophiles, such as aldehydes, that contain α-hydrogens that cannot be deprotonated by tertiary amines require formation of the carbon nucleophile through other catalytic systems. Thus, the first enantioselective conjugate addition of aliphatic aldehydes to *N*-aryl-substituted maleimides used α,α-diphenylprolinol silyl ether as an organocatalyst.[7] The corresponding succinimides were obtained with very high enantioselectivity through a proposed transition state that involved the formation of an enamine through the reaction of the secondary amine with the aldehyde. However, the use of α,α-disubstituted aldehydes as pronucleophiles resulted in much lower enantioselectivities.

Therefore, other organocatalysts suitable for use with the challenging α,α-disubstituted aldehydes to give enantioenriched succinimides that contain contiguous quaternary-tertiary carbons were subsequently developed.[1] The most common and successful have been those that incorporate both primary amine and thiourea moieties,[8] such as the trifluoromethylated primary amine-thioureas **1**,[8a,8b] **2**,[8a,8b] and **3**[8e] as well as beyerane-containing thiourea **4**.[8f] However, noncovalent bifunctional organocatalysts based on the use of the primary amine of amino acids, combined with acid additives, have also been successfully used.[9]

The use of chiral guanidines as organocatalysts has noticeably grown in recent years as researchers have taken advantage of their strong basic character and coordinating capabilities.[10] However, their use has been rather limited with regard to their application as organocatalysts in enan-

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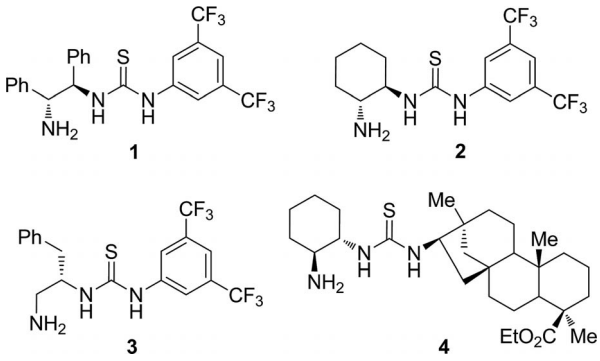
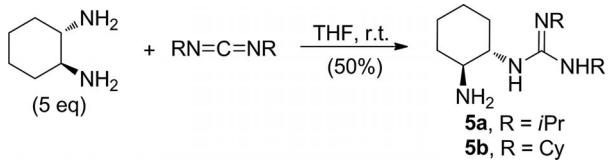


tioselective Michael additions of carbon nucleophiles to maleimides. Only enantioselective processes that involve the deprotonation of some pronucleophiles that contain highly acidic α-hydrogens have been reported.[10] The use of aldehydes remaining unexplored.

Recently, we reported the use of new chiral primary amine-guanidines as organocatalysts in the enantioselective addition of α,α-disubstituted aldehydes to maleimides to give the opposite enantioselectivity to that obtained when related thioureas were used.[11] Herein, we present a full account of the use of these new amine-guanidines as chiral organocatalysts in the asymmetric Michael addition of aldehydes to maleimides to give enantioenriched succinimides, the improvement of the enantioselectivity, and the investigation of the origin of the enantioinduction by employing theoretical calculations.

Results and Discussion

The primary amine-guanidines **5a** and **5b** that were employed in this study were directly prepared in 50% yield by monoguanylation of (1*S*,2*S*)-cyclohexane-1,2-diamine (5 equiv.) with diisopropylcarbodiimide and dicyclohexylcarbodiimide, respectively, in tetrahydrofuran (THF) at room temperature for 48 h (see Scheme 1).



Scheme 1. Preparation of primary amine-guanidines **5**.

These primary amine-guanidines **5** were used as organocatalysts in the enantioselective Michael addition of aldehydes to *N*-substituted maleimides. First, the search for the optimal reaction conditions was tackled, and the reaction of isobutyraldehyde (**6a**) to *N*-phenylmaleimide (**7a**) was chosen as the model (see Table 1). Thus, the reaction between these two compounds was organocatalyzed by primary amine-guanidine **5a** (20 mol-%) and carried out in toluene at room temperature to afford succinimide (*R*)-**8aa** in 51% yield and 76%*ee* (determined by chiral HPLC, see the Exp. Section; see Table 1, Entry 1). The *R* stereochemistry for this compound was assigned by using chiral HPLC analysis and comparing the elution order of the corresponding enantiomers with the data in the literature.[8b] The same reaction conditions were employed with primary amine-guanidine **5b** as the catalyst to result in a higher isolated yield of (*R*)-**8aa**, but only 48%*ee* (see Table 1, Entry 2). Therefore, the optimization study was continued with **5a** as the organocatalyst.

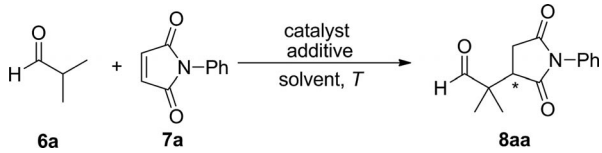
Other solvents, such as acetone, *tert*-butyl methyl ether (TBME), nitromethane, and methanol were employed, but the observed enantioselection for (*R*)-**8aa** was much lower than when toluene was used (see Table 1, Entries 3–6). The use of *N*,*N*-dimethylformamide (DMF) as the solvent increased the enantioselectivity of (*R*)-**8aa** to 82%, but with a moderate yield (see Table 1, Entry 7), whereas the use of water as the solvent increased the isolated yield and reaction rate, and only slightly decreased the enantioselection (see Table 1, Entry 8). Therefore, we assayed combinations of DMF/water as the reaction solvent (see Table 1, Entries 9–11) to obtain quantitative yields of (*R*)-**8aa** with the highest enantiomeric excess value of 88% by using a 2:1 (v/v) mixture of DMF/water (see Table 1, Entry 10).

Once the most appropriate reaction solvent was found (DMF/water, 2:1, v/v), we lowered the reaction temperature to 15 °C with the expectation of increasing the enantioselectivity, but the enantiomeric excess value remained essentially unchanged as the reaction rate diminished considerably (see Table 1, Entry 12). Lowering the reaction temperature even more practically stopped the reaction. In addition, lowering the catalyst loading to 10 mol-% diminished the reaction rate and slightly decreased the enantioselectivity of (*R*)-**8aa** (see Table 1, Entry 13).

Subsequently, we explored the possible effect of the presence of some additives. Thus, the addition of benzoic acid (20 mol-%) to the reaction mixture slightly reduced the enantioselection for (*R*)-**8aa**, although it increased the reaction rate (see Table 1, Entry 14). We also employed basic compounds as additives, considering reported observations that their presence accelerates catalytic cycles when enamine-forming organocatalysts are involved.[12] Thus, the addition of triethylamine (20 mol-%) considerably diminished the reaction time, but afforded a lower enantioselection for (*R*)-**8aa** (see Table 1, Entry 15). Furthermore, the addition of 20 mol-% of other organic bases such as 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) increased the reaction rate, but still gave a lower *ee* value for (*R*)-**8aa** compared to when no additive was provided (see Table 1, Entries 16 and 17).

Nevertheless, the addition of 20 mol-% of imidazole to the reaction mixture not only increased the reaction rate and gave a quantitative yield of (*R*)-**8aa** but also afforded an *ee* value of 86%, a similar value to that obtained without the basic additive (see Table 1, Entry 18). Under these last conditions, the reaction temperature was then decreased to 0 °C to allow the isolation of succinimide (*R*)-**8aa** in quantitative yield with 91%*ee* (see Table 1, Entry 19). Thus, the addition of imidazole as an additive allowed for a decrease in the reaction temperature and an increase in the enantioselectivity compared to when no additive was provided.[11]

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

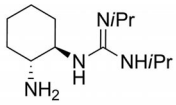


6a 7a 8aa

Entry	Catalyst [mol-%]	Additive [mol-%]	Solvent	T [°C]	t [d]	% Yield[a]	% *ee*[b]
1	**5a** (20)	–	PhMe	25	2	51	76 (*R*)
2	**5b** (20)	–	PhMe	25	2	90	48 (*R*)
3	**5a** (20)	–	acetone	25	2	47	57 (*R*)
4	**5a** (20)	–	TBME	25	2	12	64 (*R*)
5	**5a** (20)	–	$MeNO_2$	25	2	30	46 (*R*)
6	**5a** (20)	–	MeOH	25	2	15	68 (*R*)
7	**5a** (20)	–	DMF	25	2	55	82 (*R*)
8	**5a** (20)	–	H_2O	25	1	70	80 (*R*)
9	**5a** (20)	–	DMF/H_2O[c]	25	2	99	85 (*R*)
10	**5a** (20)	–	DMF/H_2O[d]	25	2	99	88 (*R*)
11	**5a** (20)	–	DMF/H_2O[e]	25	2	99	84 (*R*)
12	**5a** (20)	–	DMF/H_2O[d]	15	3	88	87 (*R*)
13	**5a** (10)	–	DMF/H_2O[d]	25	3	99	83 (*R*)
14	**5a** (20)	$PhCO_2H$ (20)	DMF/H_2O[d]	25	1	99	84 (*R*)
15	**5a** (20)	NEt_3 (20)	DMF/H_2O[d]	25	0.7	67	73 (*R*)
16	**5a** (20)	DABCO (20)	DMF/H_2O[d]	25	0.7	99	80 (*R*)
17	**5a** (20)	DBU (20)	DMF/H_2O[d]	25	0.7	73	76 (*R*)
18	**5a** (20)	imidazole (20)	DMF/H_2O[d]	25	0.7	99	86 (*R*)
19	**5a** (20)	imidazole (20)	DMF/H_2O[d]	0	2	99	91 (*R*)
20	*ent*-**5a** (20)	imidazole (20)	DMF/H_2O[d]	0	2	98	91 (*S*)

[a] Isolated yield after flash chromatography. [b] Enantioselectivity and absolute stereochemistry determined by chiral HPLC analysis (see ref.[8b]). [c] 1:1, v/v. [d] 2:1, v/v. [e] 4:1, v/v.

Expecting to achieve the opposite enantioinduction, we prepared primary amine-guanidine *ent*-**5a** in 51% yield by following the same procedure as in the case of its enantiomeric counterpart **5a**, but starting from (1*R*,2*R*)-cyclohexane-1,2-diamine. This primary amine-guanidine was employed as the organocatalyst in the model reaction between isobutyraldehyde and *N*-phenylmaleimide under the previously mentioned reaction conditions to yield enantiomeric succinimide (*S*)-**8aa** in 98% yield and 91%*ee* (see Table 1, Entry 20).



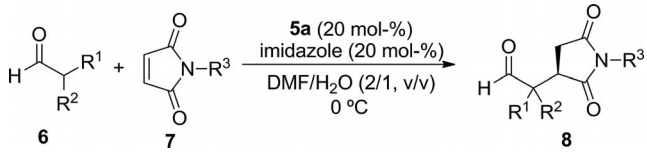
ent-**5a**

Once the optimized reaction conditions were established [**5a** (20 mol-%), imidazole (20 mol-%), DMF/water (2:1, v/v), 0 °C], we proceeded to extend the application of this organocatalytic methodology to other aldehydes and maleimides (see Table 2). Thus, when isobutyraldehyde was treated with *N*-phenylmaleimides that contain halogen substituents on the phenyl ring, such as a chloro group at the 3- and 4-position (i.e., **7b** and **7c**, respectively) or a bromo group at the 4-position (i.e., **7d**), the enantioselectivity of the quantitatively obtained succinimides (*R*)-**8ab**, (*R*)-**8ac**, and (*R*)-**8ad** increased to 95, 92, and 96%, respectively (see Table 2, Entries 2–4). When an electron-releasing methoxy group was present on the phenyl ring of the maleimide, as in the case of **7e**, the enantioselectivity of the corresponding succinimide (*R*)-**8ae** decreased to 89% (see Table 2, Entry 5). In addition, the presence of a 4-acetoxy group, as in maleimide **7f**, gave rise to succinimide (*R*)-**8af** with 94%*ee* (see Table 2, Entry 6).

Maleimides without an *N*-aryl group were also used for the conjugate addition with isobutyraldehyde. Thus, *N*-benzylmaleimide (**7g**) quantitatively afforded the corresponding succinimide (*R*)-**8ag** with 87%*ee*, and *N*-methylmaleimide (**7h**) provided Michael adduct (*R*)-**8ah** quantitatively with 89%*ee* (see Table 2, Entries 7 and 8). Furthermore, simple maleimide (**7i**) yielded succinimide (*R*)-**8ai** with an enantiomeric excess value of 84% in quantitative yield (see Table 2, Entry 9). However, an oxygenated analogue such as maleic anhydride gave no reaction.

Other α,α-disubstituted aldehydes were employed as the pronucleophile in the organocatalyzed Michael addition to *N*-phenylmaleimide. Thus, the reaction with 2-ethylbutanal (**6b**) gave succinimide (*R*)-**8ba** with 95%*ee*, whereas cyclopentanecarbaldehyde (**6c**) and cyclohexanecarbaldehyde (**6d**) gave the corresponding succinimides (*R*)-**8ca** and (*R*)-**8da**, respectively, each with 93%*ee* (see Table 2, Entries 11 and 12). Moreover, the use of α-monosubstituted aldehydes such as propanal (**6e**) and 3-phenylpropanal (**6f**) quantitatively afforded Michael adducts (*S*,*R*)/(*R*,*R*)-**8ea** and (*S*,*R*)/(*R*,*R*)-**8fa**, respectively, as mixtures of diastereomers with enantiomeric excess values of 87 and 79%, respectively, for the major isomer (see Table 2, Entries 13 and 14).

Table 2. Michael addition of aldehydes to maleimides organocatalyzed by chiral primary amine-guanidine **5a**.

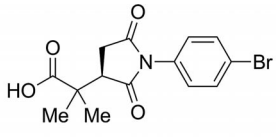


6 7 8

Entry	Aldehyde			Maleimide		*t* [d]	Succinimide	% Yield[a]	% *ee*[b,c]
	R^1	R^2	No.	R^3	No.				
1	Me	Me	**6a**	Ph	**7a**	2	(*R*)-**8aa**	99	91
2	Me	Me	**6a**	3-ClC_6H_4	**7b**	3	(*R*)-**8ab**	99	95
3	Me	Me	**6a**	4-ClC_6H_4	**7c**	3	(*R*)-**8ac**	99	92
4	Me	Me	**6a**	4-BrC_6H_4	**7d**	2	(*R*)-**8ad**	97	96
5	Me	Me	**6a**	2-$MeOC_6H_4$	**7e**	2	(*R*)-**8ae**	95	89
6	Me	Me	**6a**	4-$AcOC_6H_4$	**7f**	2	(*R*)-**8af**	98	94
7	Me	Me	**6a**	Bn	**7g**	2	(*R*)-**8ag**	99	87
8	Me	Me	**6a**	Me	**7h**	2	(*R*)-**8ah**	99	89
9	Me	Me	**6a**	H	**7i**	1	(*R*)-**8ai**	99	84
10	Et	Et	**6b**	Ph	**7a**	4	(*R*)-**8ba**	85	95
11	–$(CH_2)_4$–		**6c**	Ph	**7a**	4	(*R*)-**8ca**	92	93
12	–$(CH_2)_5$–		**6d**	Ph	**7a**	4	(*R*)-**8da**	90	93
13	H	Me	**6e**	Ph	**7a**	1	(*S*,*R*)/(*R*,*R*)-**8ea**	99[d]	87:87
14	H	Bn	**6f**	Ph	**7a**	1	(*S*,*R*)/(*R*,*R*)-**8fa**	99[e]	79:74

[a] Isolated yield after flash chromatography. [b] Enantioselectivity determined by chiral HPLC analysis. [c] Absolute configuration determined by chiral HPLC analysis and the order of elution of the enantiomers (see Exp. Section and Supporting Information). [d] Mixture of diastereomers is 1.2:1, determined by ^{1}H NMR (300 MHz) in the reaction crude. [e] Mixture of diastereomers is 1.9:1 as determined by ^{1}H NMR analysis (300 MHz) of the crude reaction mixture.

The absolute configurations of the known succinimides were assigned by using chiral HPLC analysis and the elution order of the enantiomers compared to the data in literature (see Supporting Information), whereas the configurations of the new succinimides were assigned by analogy. In addition, aldehyde (*R*)-**8ad** was converted into acid (*R*)-**9ad** upon standing in the open air for several days. Crystallization of this compound in *n*-hexane/AcOEt afforded crystals, which were used for X-ray crystal structure analysis (see Figure 1). The assigned *R* stereochemistry was confirmed by the Sheldrick least-squares refinement of the structure, which gave a Flack parameter of $x = 0000(13)$.



(*R*)-**9ad**

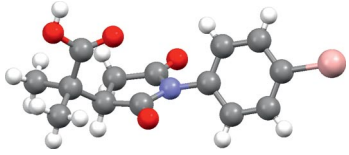
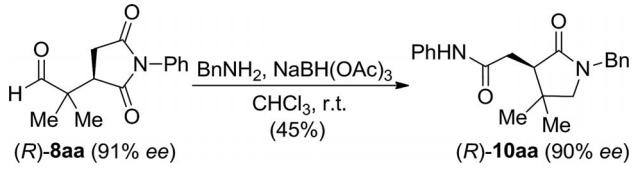


Figure 1. X-ray crystal structure of (*R*)-**9ad**.

To exemplify the synthetic usefulness of the succinimides **8**, their transformation into γ-lactams was carried out by a one-pot, tandem reductive amination/lactamization sequence.[3] Thus, enantioenriched crude succinimide (*R*)-**8aa** (91%*ee*), which was obtained by evaporation of the solvent from the Michael addition of isobutyraldehyde and *N*-phenylmaleimide (see Table 2, Entry 1), was dissolved in chloroform and treated with benzylamine and sodium triacetoxyborohydride. The subsequent spontaneous cyclization reaction afforded lactam (*R*)-**10aa** in essentially the same enantioselectivity (90%*ee*) as the starting succinimide (see Scheme 2).



(*R*)-**8aa** (91% *ee*) (*R*)-**10aa** (90% *ee*)

Scheme 2. Synthesis of γ-lactam (*R*)-**10aa** from enantioenriched succinimide (*R*)-**8aa** by a tandem reductive amination/lactamization sequence.

The sense of the enantioinduction achieved in this organocatalyzed reaction by using the primary amine-guanidines **5** is rather unexpected. Thus, the observed *R* stereochemistry of all the formed succinimides **8**, which was achieved by employing organocatalyst **5a** that was derived from (1*S*,2*S*)-cyclohexane-1,2-diamine, is the same as that observed by using primary amine-thiourea **2** as the organocatalyst, which was obtained from the enantiomeric (1*R*,2*R*)-cyclohexane-1,2-diamine.[8b] This would indicate that the reaction with **2** as the organocatalyst occurs through a different transition state, which leads to the opposite mode of stereoinduction.

To obtain further insight into the origin of the observed enantioselectivity that was achieved by these primary

amine-guanidines as well as the intriguing switch in the enantioselectivity that occurs with the thiourea versus the guanidine, we carried out theoretical calculations[13] to detail the H-bonding activation patterns during the crucial C–C bond-forming transition state. Structure optimizations were performed at the B3LYP/6-311+G** level and single point energies were obtained at the M06–2X/6-311+G** level, in both cases taking into account the solvent (water, IEFPCM) effects. We examined the reaction between substrates **6a** and **7a** in the presence of the two catalysts thiourea **2** and guanidine **5a**. We assume that the reaction is initiated by the formation of a reactive enamine intermediate between the free NH_2 group of the catalyst and the aldehyde. Hydrogen-bonding interactions should then occur between maleimide and the NH functions (one or two NH) of the thiourea or guanidine moieties. As expected, the first computational results show that the thiourea activates the maleimide substrate in the transition state to afford the *R* enantiomer preferentially [see Figure 2, 8.3 kcal/mol (*R*) vs. 14.9 kcal/mol (*S*)]. The formation of two H-bonds in the transition state to give *R* and only one H-bond in the transition state to give *S* appears to be a partial explanation for this preference. A closer analysis of the structures indicates that the thiourea in TS_1-S is slightly distorted to accommodate the H-bond with maleimide, which might induce the corresponding energy penalty.

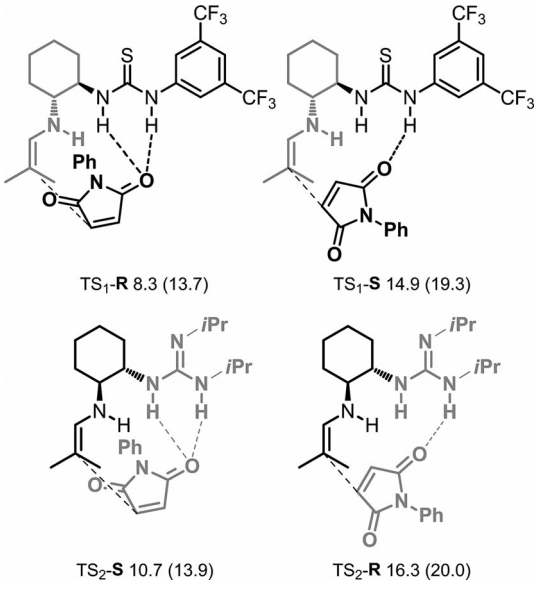


Figure 2. Hydrogen-bonding activation using thiourea **2** and guanidine **5a**. Gibbs Free energy (*G*) values computed at M06-2X/6-311+G** (water) level. Values in parenthesis correspond to the B3LYP method.

In addition, we found that a similar disposition of the NH groups in the guanidine would lead to a similar enantiomeric preference (see Figure 2), and the transition state TS_2-S (10.7 kcal/mol) appeared to be highly favored over the transition state TS_2-R (16.3 kcal/mol). The fact that **2** and **5a** belong to the opposite enantiomeric series (see Figure 2) must be noted, and, thus, the computational preference of thiourea **2** for *R* is equivalent to the preference of guanidine **5a** for *S*. This is obviously in contradiction with the experimental results, which show a large enantiomeric excess in favor of the *R* form with both catalysts. We assumed that a different activation pattern was necessary to explain these experimental facts. In this regard, we found that the two main conformations of a cyclohexyl-guanidine model (see Figure 3, G-1 and G-2) do not present their NH groups in the parallel disposition necessary for the double H-bonding activation (which is the case in the TS_2 transition state), but instead, the two NH groups are pointing in opposite directions. In sharp contrast, the cyclohexyl-thiourea model presents two main conformations (T-1 and T-2) of similar energies, and one of them displays the necessary disposition of the NH groups to attain the TS_1-type structures.[14]

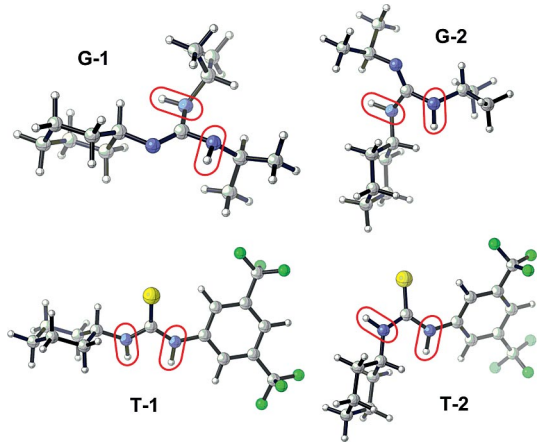


Figure 3. Most stable conformations for the models of cyclohexyl-guanidine (G-1 and G-2) and cyclohexyl-thiourea (T-1 and T-2).

As a result, the TS_2 transition states were probably not responsible for the activation exerted by the guanidine. Indeed, after an important conformational search, a pair of structures (see Figure 4, TS_3-R and -S) were located in which the activation of the maleimide is achieved by a single NH bond pointing towards the reaction center as the other NH bond points towards the external face of the catalyst (see Figure 3, similar to G-1). One such transition state (TS_3-R) shows the overall lowest activation energy found with **5a**, which is in agreement with the experimental results and predicts the correct *R* enantiomer. Examination of the energies of the different transition states in Figures 2 and 4 leads to the conclusion that the *R* enantiomer arises from TS_3-R (8.9 kcal/mol), whereas the *S* enantiomer arises from TS_2-S (10.7 kcal/mol). These data were obtained by the M06-2X method, which correctly predicted the experimental results. Although B3LYP showed a similar overall trend, it afforded less conclusive data, as it showed closer energies for both enantiomers (14.1 kcal/mol in TS_3-R and 13.9 kcal/mol in TS_2-S).

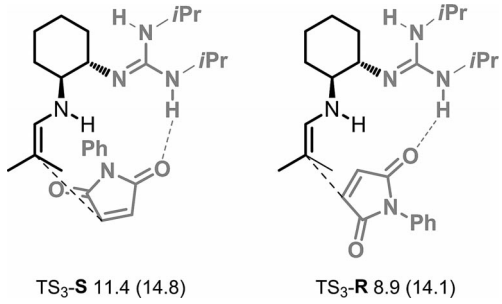


Figure 4. Hydrogen-bonding activation using primary amine-guanidine **5a** (G-1-type conformation). Gibbs Free Energy (*G*) values computed at M06-2X/6-311+G** (water) level. Values in parenthesis correspond to the B3LYP method.

Conclusions

We conclude that primary amine-guanidines, which are prepared by a simple monoguanylation of enantiomerically pure *trans*-cyclohexane-1,2-diamine, act as organocatalysts in the enantioselective conjugate addition of aldehydes, including α,α-disubstituted aldehydes, to different maleimides to give enantiomerically-enriched succinimides. High yields and enantioselectivities were achieved by carrying out the reaction in aqueous solvents and in the presence of imidazole as a rate-accelerating additive. The enantioselectivity obtained is opposite in sense to those reported when primary amine-thioureas are employed as organocatalysts. Theoretical calculations suggest different hydrogen-bonding coordination patterns between the organocatalyst and the maleimide in the case of the primary amine-guanidines and amine-thioureas. For the primary amine-guanidine, a more favorable transition state occurs when the maleimide is oriented in the opposite direction to its transition state position with the primary amine-thiourea, and, thus, after internal attack of the enamine intermediate, these reactions give opposite enantioselection results.

Experimental Section

General Methods: All the reagents and solvents were of the best grade available and used without further purification. Specific rotations were measured with a Perkin–Elmer 341 polarimeter. IR data were collected with a Nicolet Impact 400D-FT spectrometer. The ^{1}H and ^{13}C NMR spectroscopic data were recorded at 25 °C with a Bruker AC-300 at 300 and 75 MHz, respectively, with TMS as the internal standard. MS (EI, 70 eV) were performed with Agilent MS 5973 (DIP) and HP MS-GC 5973A equipment. HRMS analyses were carried out with a Finnigan MAT 95S. The absolute configurations of adducts **8** were determined by chiral HPLC analysis and the order of elution of their enantiomers. The absolute configurations of new adducts **8af** and **8ai** were assigned by analogy. Reference racemic samples of adducts **8** were obtained by performing the reaction with 4-methylbenzylamine (20 mol-%) as the organocatalyst in toluene at 25 °C.

CCDC-930978 [for (*R*)-**9ad**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Preparation of Primary Amine-Guanidines: To a solution of (1*S*,2*S*)-cyclohexane-1,2-diamine (for **5a** and **5b**, 5.71 g, 50 mmol) or (1*R*,2*R*)-cyclohexane-1,2-diamine (for *ent*-**5a**, 5.71 g, 50 mmol) in THF (10 mL) was added diisopropylcarbodiimide (for **5a** and *ent*-**5a**, 10 mmol) or dicyclohexylcarbodiimide (for **5b**, 10 mmol), and the mixture was stirred at room temp. for 2 d. The solvent was evaporated (15 Torr), and CH_2Cl_2 (20 mL) was added. The solution was extracted with HCl (2 M solution, 3 × 10 mL), and the aqueous phase was basified with NaOH (2 M solution) until the pH ≈ 9. Water was evaporated in vacuo (15 Torr), and MeOH was added (50 mL). The solution was dried with $MgSO_4$ and filtered, and the solvents were evaporated in vacuo (15 Torr). The crude residue was purified by column chromatography (CH_2Cl_2/MeOH, 8:2, v/v) to afford **5a** (1.20 g, 50%), **5b** (1.60 g, 50%), or *ent*-**5a** (1.22 g, 51%).

1-[(1*S*,2*S*)-2-Aminocyclohexyl]-2,3-diisopropylguanidine (5a): Yellow solid; m.p. 165 °C (MeOH/Et_2O). $[\alpha]_D^{20}$ = –46.7 (*c* = 1, MeOH). IR [attenuated total reflectance (ATR)]: $\tilde{\nu}$ = 3252, 3193, 2973, 2934, 2865, 1607, 1389, 1370, 1167, 1132, 733 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ = 3.99 (m, 4 H), 1.94 (m, 1 H), 1.76 (m, 3 H), 1.46 (m, 2 H), 1.34 (m, 1 H), 1.29 (d, *J* = 6.4 Hz, 6 H), 1.28 (d, *J* = 6.4 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 154.2, 56.5, 45.8, 33.7, 25.4, 22.8 ppm. MS (EI, 70 eV): *m*/*z* (%) = 240 (5) $[M]^+$, 144 (100). HRMS (EI): calcd. for $C_{13}H_{28}N_4$ 240.2314; found 240.2308.

1-[(1*S*,2*S*)-2-Aminocyclohexyl]-2,3-dicyclohexylguanidine (5b): White solid; m.p. 184 °C (MeOH/Et_2O). $[\alpha]_D^{20}$ = –39.6 (*c* = 1, MeOH). IR (ATR): $\tilde{\nu}$ = 3242, 3182, 2927, 2855, 1608, 1366, 1343, 1146, 1097, 727 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ = 7.33 (d, *J* = 9.0 Hz, 1 H), 4.02 (m, 1 H), 3.63 (m, 2 H), 3.45 (m, 1 H), 1.87–1.08 (m, 28 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 154.2, 56.6, 52.7, 34.6, 33.9, 33.8, 26.7, 26.2, 26.1, 26.0, 25.4 ppm. MS (EI, 70 eV): *m*/*z* (%) = 320 (2) $[M]^+$, 224 (100). HRMS (EI): calcd. for $C_{19}H_{36}N_4$ 320.2940; found 320.2934.

Typical Procedure for the Enantioselective Michael Addition Reaction: To a solution of **5** or *ent*-**5a** (0.04 mmol), maleimide **7** (0.2 mmol), and imidazole (0.04 mmol) in DMF/H_2O (2:1, v/v, 0.5 mL) was added aldehyde **6** (0.4 mmol), and the mixture was stirred at 0 °C until completion of the reaction (monitored by TLC). HCl (2 M solution, 10 mL) was added, and the mixture was extracted with AcOEt (3 × 10 mL). The combined organic phases were washed with water (2 × 10 mL), dried with $MgSO_4$, filtered, and evaporated (15 Torr). The resulting crude residue was purified by flash chromatography (*n*-hexane/AcOEt) to afford adducts **8**. Succinimides **8aa**,[8b] **8ab**,[8f] **8ac**,[8b] **8ad**,[8f] **8ae**,[8f] **8ag**,[8b] **8ah**,[8b] **8ba**,[8a] **8ca**,[8c] **8da**,[8c] **8ea**,[8b] and **8fa**[3a] have already been described, and their ^{1}H and ^{13}C NMR spectroscopic data and retention times from the chiral HPLC analyses of both enantiomers can be found in the Supporting Information. Full analytical and spectroscopic data as well as the observed retention times from chiral HPLC analyses of new compounds **8af** and **8ai** as well as oxidation product (*R*)-**9ad** are given below.

(*R*)-4-[3-(2-Methyl-1-oxopropan-2-yl)-2,5-dioxopyrrolidin-1-yl]phenyl Acetate (8af): White solid; m.p. 75 °C (*n*-hexane/AcOEt). $[\alpha]_D^{20}$ = +1.1 (*c* = 1, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3055, 2968, 2933, 1703, 1684, 1386, 1260, 1188, 1170, 838, 742 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.49 (s, 1 H), 8.05 (d, *J* = 8.5 Hz, 2 H), 7.44 (d, *J* = 8.5 Hz, 2 H), 3.14 (dd, *J* = 9.6, 5.6 Hz, 1 H), 3.00 (dd, *J* = 18.3, 9.6 Hz, 1 H), 2.63 (dd, *J* = 12.7, 5.6 Hz, 1 H), 2.62 (s, 3 H), 1.38 (s, 3 H), 1.30 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.8,

197.3, 176.6, 174.5, 136.9, 136.0, 129.8, 129.3, 126.7, 48.9, 45.2, 32.2, 26.8, 20.7, 20.1 ppm. MS (EI, 70 eV): *m/z* (%) = 303 (0.02) $[M]^+$, 259 (100). HRMS (EI): calcd. for $C_{16}H_{17}NO_5$ 303.1107; found 303.1134. HPLC analysis (Chiralpak AS-H, λ = 210 nm, *n*-hexane/2-propanol, 75:25, 1.0 mL/min): t_R = 50.2 (minor) and t_R = 67.7 min (major).

(*R*)-2-(2,5-Dioxopyrrolidin-3-yl)-2-methylpropanal (8ai): Colorless oil. IR (film): $\tilde{\nu}$ = 3235, 3077, 2973, 2938, 1779, 1698, 1353, 1290, 1179, 804, 659 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.49 (s, 1 H), 8.73 (br. s, 1 H), 3.10 (dd, *J* = 9.4, 5.8 Hz, 1 H), 2.85 (dd, *J* = 18.4, 9.4 Hz, 1 H), 2.51 (dd, *J* = 18.4, 5.8 Hz, 1 H), 1.25 (s, 3 H), 1.23 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.9, 178.3, 176.2, 48.0, 46.3, 32.8, 20.1, 19.4 ppm. MS (EI, 70 eV): *m/z* (%) = 169 (0.66) $[M]^+$, 69 (100). HRMS (EI): calcd. for $C_8H_{11}NO_3$ 169.0739; found 169.0738. HPLC analysis (Chiralpak AD-H, λ = 210 nm, *n*-hexane/2-propanol, 85:15, 1.0 mL/min): t_R = 22.5 (major) and t_R = 30.4 min (minor).

(*R*)-2-[1-(4-Bromophenyl)-2,5-dioxopyrrolidin-3-yl]-2-methylpropanoic Acid (9ad): White solid; m.p. 186 °C (*n*-hexane/AcOEt). $[\alpha]_D^{20}$ = +1.6 (*c* = 1, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3000 (br.), 2986, 1706, 1675, 1491, 1401, 1181, 781, 723 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.58 (m, 2 H), 7.15 (m, 2 H), 3.14 (dd, *J* = 9.5, 5.4 Hz, 1 H), 3.05–2.96 (dd, *J* = 18.1, 5.4 Hz, 1 H), 2.70 (dd, *J* = 18.1, 5.4 Hz, 1 H), 1.54 (s, 3 H), 1.39 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.5, 176.5, 174.5, 132.4, 130.8, 128.1, 122.6, 47.0, 32.6, 24.3, 23.6 ppm. MS (EI, 70 eV): *m/z* (%) = 338 (4.62) $[M]^+$, 57 (100). HRMS (EI): calcd. for $C_{14}H_{14}BrNO_4$ 339.0106; found 339.0128.

One-Pot Michael Addition/Reductive Amination/Lactamization: To a mixture of **1a** (0.08 mmol, 19.2 mg), *N*-phenylmaleimide (0.4 mmol, 69.2 mg), and imidazole (0.08 mmol, 4.8 mg) in DMF/H_2O (2:1, v/v, 0.5 mL) was added isobutyraldehyde (73 μL, 0.8 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 d, and the solvent was evaporated to dryness (15 Torr). The crude residue was dissolved in $CHCl_3$ (3.5 mL), and benzylamine (1 M in $CHCl_3$, 0.8 mL, 0.8 mmol) and sodium triacetoxyborohydride (211.9 mg, 1 mmol) were added. The mixture was stirred at room temp. for 6 h, and the solvent was evaporated in vacuo (15 Torr). To the crude residue was added HCl (2 M solution, 5 mL), and the solution was extracted with $CHCl_3$ (3× 2 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated (15 Torr). The resulting crude residue was purified by flash chromatography (*n*-hexane/AcOEt) to afford γ-lactam (*R*)-**10aa** (60.6 mg, 45%).

(*R*)-2-(1-Benzyl-4,4-dimethyl-2-oxopyrrolidin-3-yl)-*N*-phenylacetamide (10aa): Yellow oil. $[\alpha]_D^{20}$ = +1.6 (*c* = 1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3316, 3262, 2986, 1675, 1491, 1401, 1181, 781, 723 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62 (m, 2 H), 7.41–7-18 (m, 7 H), 7.12–7.01 (m, 1 H), 4.60 (d, *J* = 14.6 Hz, 1 H), 4.38 (d, *J* = 14.6 Hz, 1 H), 3.09 (d, *J* = 9.7 Hz, 1 H), 2.86 (d, *J* = 9.7 Hz, 1 H), 2.81–2.63 (m, 2 H), 2.30 (dd, *J* = 13.4, 0.8 Hz, 1 H), 1.15 (s, 3 H), 0.88 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.4, 170.2, 138.8, 135.7, 128.8, 128.2, 127.9, 123.6, 119.6, 58.9, 50.0, 46.9, 37.9, 34.6, 25.1, 21.8 ppm. MS (EI, 70 eV): *m/z* (%) = 336 (12.79) $[M]^+$, 244 (100). HRMS (EI): calcd. for $C_{21}H_{24}N_2O_2$ 336.1838; found 336.1851. HPLC analysis (Chiralpak AD, λ = 210 nm, *n*-hexane/2-propanol, 80:20, 1.0 mL/min): t_R = 8.6 (major) and t_R = 9.9 min (minor).

Supporting Information (see footnote on the first page of this article): Physical data, ^1H and ^{13}C NMR spectra and data, chiral HPLC data, and description of computational methods and data are included.

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[13] For computational details, see the Supporting Information.
[14] The corresponding T-1-like conformation of the guanidine model lies >3 kcal/mol higher in energy than the G-1 structure and is not competitive.

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