Stereoselectivities in α- and β-Amino Acids Catalyzed Mannich Reactions Involving Cyclohexanone

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Abstract The effects of two different amino acid catalysts on the stereoselectivities in the direct Mannich reactions of cyclohexanone, *p*-anisidine and *p*-nitrobenzaldehyde were studied with the aid of density functional theory. Transition states of the stereo-determining C—C bond-forming step with the addition of enamine intermediate to the imine for the *L*-proline(α-amino acid) and (*R*)-3-pyrrolidinecarboxylic acid(β-amino acid)-catalyzed processes were reported. B3LYP/6-31G** calculations provide a good explanation for the opposite *syn vs*. *anti* diastereoselectivities of these two different kinds of catalysts(*syn*-selectivity for the α-amino acid catalysts, *anti*-selectivity for the β-amino acid catalysts). Calculated and observed diastereomeric ratio and enantiomeric excess values are in reasonable agreement.

Keywords *Syn*- and *anti*-Mannich reaction; Stereoselectivity; Amino acid; Transition state

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1 Introduction

The direct asymmetric Mannich reaction is one of the most important C—C bond-forming reactions. As a result of its great usefulness in pharmaceutical chemistry and natural product syntheses, the development of catalytic asymmetric Mannich reactions has received increased attention in recent years[1—9]. In particular, since the pioneering finding by List *et al*.[2,4] and Barbas *et al*.[1] that proline could act as a catalyst in direct three-component Mannich reactions, organocatalytic direct asymmetric Mannich-type reactions have been a highly active research area, and thus many metal-free chiral catalysts[1—9] have been developed for this transformation, all attempting to reach high levels of efficiencies and to widen the scope of substrates. Among the various organocatalysts, different amino acids and their derivatives have drawn great attention[4—9] and an intriguing stereochemical observation has been made: when cyclohexanone was used as the Mannich donor, α-amino acids *e.g.*, proline[4], serine and alanine etc.[5] catalyzed the direct asymmetric Mannich reactions with *syn*-selectivity, while β-amino acids *e.g.*, (*R*)-3-pyrrolidinecarboxylic acid[6—8] and 3-amino-butrric acid, and so on[9] provided the opposite diastereoselectivity to give the *anti*-Mannich products. This interesting observation that different amino acid catalysts lead to opposite *syn vs. anti* diastereoselectivities calls for mechanistic and theoretical investigations. To the best of our knowledge, although great efforts have been made to the general understanding of the mechanism of enamine catalytic reactions[10—12], there are no other systematic theoretical investigations concerning the different diastereoselectivity of different α- and β-amino acids-catalyzed Mannich reactions of ketones, *p*-anisidine and *p*-nitrobenzaldehyde. Moreover, since cyclohexanone is a very useful donor, and its Mannich reactions catalyzed by different amino acids have been evaluated by several laboratories[4—9]. Therefore, to extend our understanding of the mechanism and stereoselectivity of the enamine catalytic reactions, the present theoretical study is performed to address the question: what is the origin of the opposite *syn-anti* diastereoselectivities in the α- and β-amino acids-catalyzed direct asymmetric Mannich reactions involving cyclohexanone as the donor?

2 Computational Methods

All ground state and transition state(TS) geometries were located by density functional theory(DFT) and the B3LYP hybrid functional[13]. The standard 6-31G** basis sets were employed throughout. All transition state geometries were fully optimized and characterized by frequency analysis. Bulk effects of the solvent dimethyl sulfoxide(DMSO) for the different amino acids-catalyzed processes on the enamine mechanism have been taken into account by means of a dielectric continuum represented by the polarizable conductor calculation model(CPCM)[14], with united-atom Kohn-Sham(UAKS) radii.

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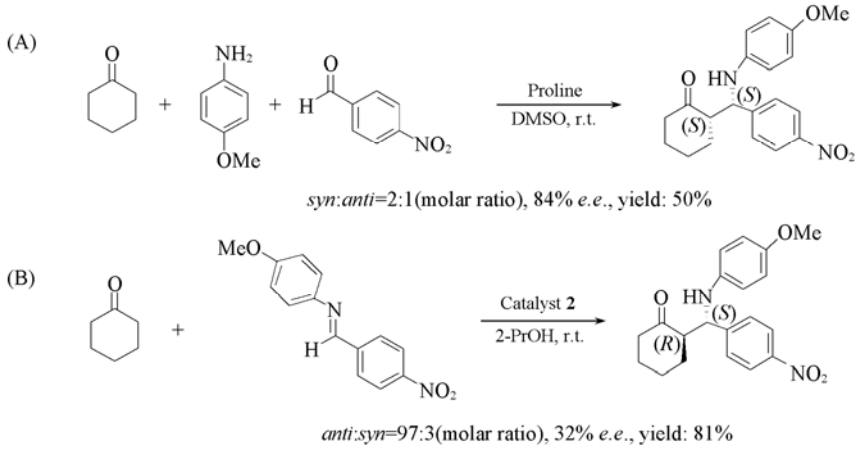
The single-point continuum calculations were done upon the optimized gas phase geometries with a dielectric constant ε=46.7 for DMSO. All calculations were carried out with the Gaussian 03 program[15].

3 Results and Discussion

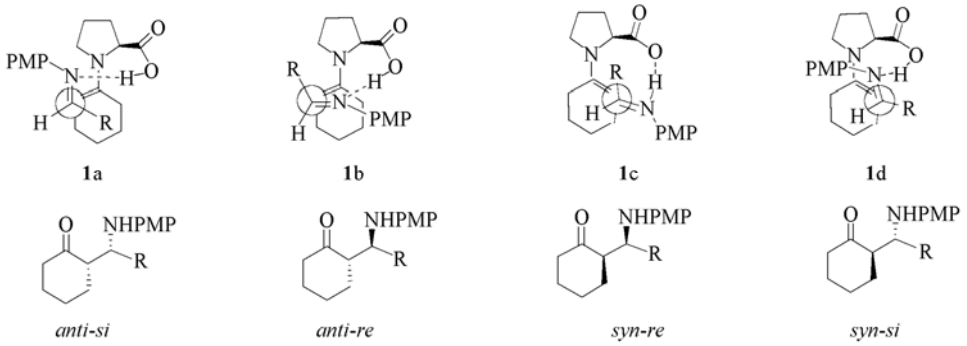
To investigate the α- and β-amino acids catalyzed asymmetric direct Mannich reactions involving cyclohexanone, we have used α-amino acid *e.g.*, *L*-proline(catalyst **1**) and β-amino acid *e.g.*, (*R*)-3-pyrrolidinecarboxylic acid(catalyst **2**) as the prototype catalysts, and Scheme 1 illustrated the model reactions of the α- and β-amino acid catalyzed processes(denoted as A and B).



Scheme 1 Model Mannich reaction

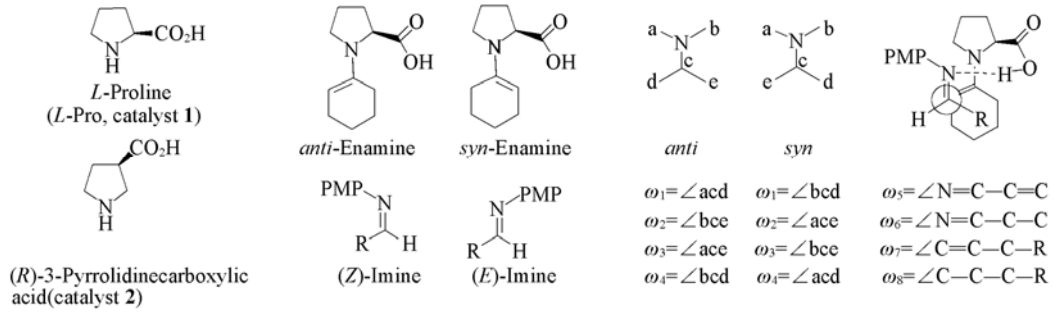
(A) α-Amino acid catalyzed process; (B) β-amino acid catalyzed process.

Analogous to the previous investigation of the enamine-catalyzed Mannich reactions[10—12], we focused our attention on the TSs for the enamine attack to the imine. This is expected to be the stereo-controlling step of the reaction and thus to be studied to understand the observed diastereo- and enantio-selectivities. This step leads to the formation of two stereogenic centers, resulting in four possible stereoisomers(Scheme 2, proline as the model).



Scheme 2 Four transition state arrangements of proline-enamine and imine along the forming C—C bond that generates the four diastereoisomers

Thus several stereochemical pathways for this step have to be considered. First, the double bond of enamine may be oriented *syn* and *anti* relative to the carbonyl acid group of the title amino acid(Scheme 3). Second, imine may also have a *Z* or *E* configuration(Scheme 3). However, (*Z*)-imine was computed to be more than 30 kJ/mol higher in energy than (*E*)-imine, which means that the reactive channels involving the (*Z*)-imine can be safely excluded in the discussion of the amino acids-catalyzed direct Mannich reactions. Third, the different diastereomeric approach modes to the *re* and *si* faces of enamine



Scheme 3 Catalysts and notations used for enamine, imine intermediate, and transition states

and those of imine should be considered. Consistent with the previous theoretical studies[10—12], the corresponding transition states occurring on the opposite face of the pyrrolidine ring for the secondary amino acids-catalyzed process, which lack the favorable hydrogen bonding interactions between the carboxylate and the imine, are expected to have higher activation energies. Hence, we have investigated only four possible pathways in each reaction as shown in Scheme 2(proline as the model). In addition, for each of the orientations that generate different stereoisomers, the cyclohexene of the enamine can adopt two different conformations *e.g.*, chair-like and boat-like conformations. As expected, our calculated results show that the TSs involving the boat conformation are much more unstable than those involving chair conformation and are, therefore, not discussed further.

3.1 *L*-Proline-catalyzed Process

Scheme 1 illustrates the *syn*-selectivity of the proline-catalyzed Mannich reaction involving cyclohexanone performed by List *et al.*[4] and moderate diastereo- and enantioselectivities were obtained for the *p*-nitrobenzaldehyde. This reaction was chosen as the model to investigate the stereoselectivities addressed with proline catalyst. We first explored the different isomers of the enamine intermediates formed between proline and cyclohexanone. The relative energies of different isomers showed that *syn*-enamine is 6.3 kJ/mol more stable than the *anti*-enamine, which is arising from the large steric hindrance between the methylene in the six-membered ring and the carbonyl acid group in *anti*-conformation. Inclusion of solvent effect only slightly affects the stabilization of different isomers(7.0 kJ/mol) with the *syn*-conformer still being the most stable one.

The transition state structures corresponding to four stereoisomers that are *syn*- and *anti*-diastereomeric pairs of enantiomers for the reaction of the proline enamine of cyclohexanone and *N*-*p*-methoxyphenyl-protected(N-PMP) imine of *p*-nitrobenzaldehyde have been illustrated in Fig.1. The notation used for the TSs, for example, '*anti*' in '*anti-si*' is consistent with previous conventions, '*si*' denotes the *si* face of imine. As shown in Fig.1, all of the transition states have the carboxylic acid proton completely transferred to the imine, with the formed C—C single bond lengths of 0.21—0.23 nm and the hydrogen bond lengths of NH···O of 0.15—0.17 nm. This substantial ionic interaction between an iminium and the carboxylate is the common feature of proline-catalyzed Mannich reactions proposed by Houk's group[10,11]. Among these transition states, consistent with the hypothesis by the experimental work and the previous theoretical results, the most stable one involving the attack of the *anti*-enamine to the *si*-face of imine(**1**a) leads to the(2*S*,*3S*)-enantiomer, which is indeed the major product observed experimentally. The *anti*-diastereoisomer is mainly formed through the transition state **1**d corresponding to the *syn*-enamine attacking the *si* face of imine, which is 5.2 kJ/mol higher in energy than the most stable one **1**a in the gas phase. This free energy difference decreases to 2.7 kJ/mol when the solvent effect is taken into account. Thus the low *syn*-diastereoselectivity(*d.r.*=2:1) can be well explained. The relative free energies between different transition states($\Delta\Delta G$) can be used to predict the product ratios and consequently the stereoselectivities and the associated *e.e. and d.r.* from absolute rate theory, $\ln(k_1/k_2)=-\Delta\Delta G/RT$. Furthermore, the enantiomeric excess (*e.e.*,%) and the diastereomeric ratio (*d.r.*) can be calculated as follows: $e.e.(\%)=\frac{[R]-[S]}{[R]+[S]}\times 100\%$, $d.r.=\frac{[S*S]}{[S*R]}$.

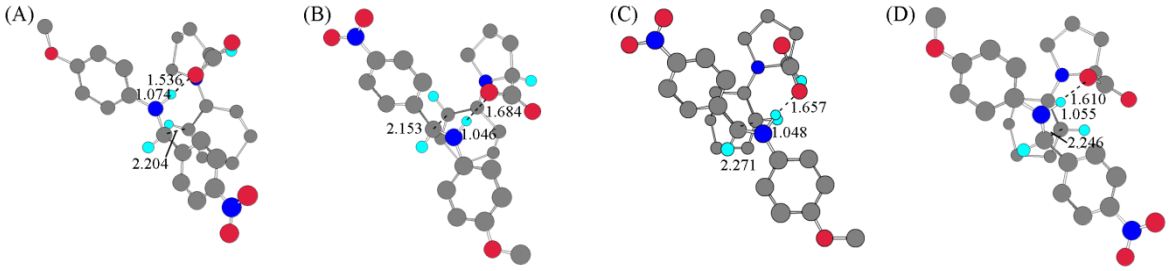


Fig.1 Transition state structures and relative free energies at B3LYP/6-31G level for the reaction of proline enamine of cyclohexanone with N-PMP imine of *p*-nitrobenzyaldehyde**

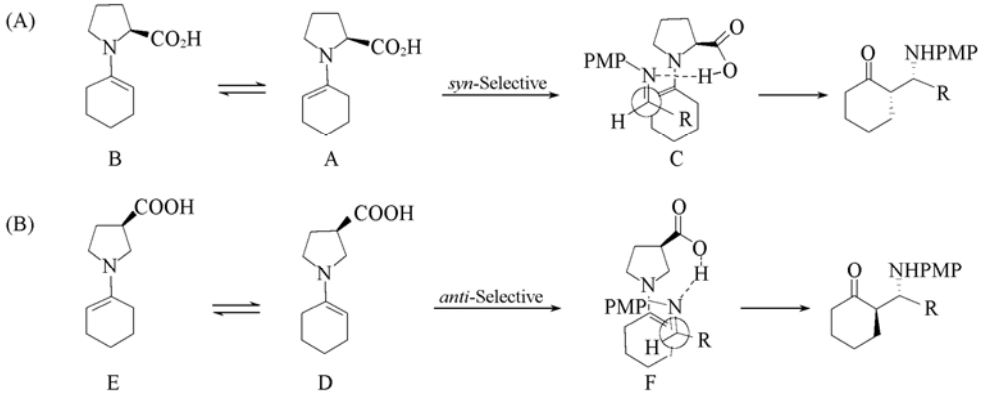
Values in the parentheses including solvation energies in DMSO based on the CPCM/UAKS model. For clarity, some of the hydrogen atoms at the periphery are omitted. Color code: C: black; N: blue; O: red; H light blue. Bond lengths are in nm and angles in degree. (A) **1**a, *anti-si*; G_{rel}=0.0(0.0) kJ/mol; $\omega_{1—4}$=−24°, −14°, 159°, 163°; $\omega_{5—8}$=46°, 173°, −84°, 44°; (B) **1**b, *anti-re*; G_{rel}=8.7(12.7) kJ/mol; $\omega_{1—4}$=−17°, −21°, 168°, 155°; $\omega_{5—8}$=−19°, 106°, 110°, −125°; (C) **1**c, *syn-re*; G_{rel}=12.7(16.0) kJ/mol; $\omega_{1—4}$=14°, 4°, −168°, −174°; $\omega_{5—8}$=−125°, 107°, 3°, −124°; (D) **1**d, *syn-si*; G_{rel}=5.2(2.7) kJ/mol; $\omega_{1—4}$=−18°, 10°, −165°, −167°; $\omega_{5—8}$=−29°, −155°, −157°, 78°.

The (2*R*, *3R*)-enantiomer generated from the attack of *syn*-enamine to the *re* face of imine(**1**c) also requires a higher free energy barrier(12.7 kJ/mol in gas phase, 16.0 kJ/mol in DMSO), which is somewhat overestimation over the experimental result(84% *e.e.*)[4]. However, the absolute error can be tolerable and the diastereoselectivity is reproduced satisfactorily.

3.2 (*R*)-3-Pyrrolidinecarboxylic Acid-catalyzed Process

As shown in Scheme 1(B), Barbas *et al.*[8] have reported the *anti*-selective organocatalytic Mannich reactions with unmodified cyclohexanone as donor to install the *anti*-amino ketone products with high diastereoselectivities (*anti*:*syn*=97:3), but *e.e.* values were moderate(32% *e.e.*, reaction condition was not optimized for this reaction). In their experiments, the *β*-amino acid of (*R*)-3-pyrrolidinecarboxylic acid was used as the catalyst. The *anti*-Mannich studies were based on their original hypothesis(Scheme 4): with proline, the observed *syn*-selectivity of the product resulted from the *anti*-enamine conformation A reacting with the *si* face of the imine(transition

state C) in the C—C bond forming step. When the carboxylic group switchs from α-position to the β-position, both enamine conformations E and D may be similarly favored, however, only conformation D should advance the C—C bond formation through transition state F since the nucleophilic carbon of enamine conformation E should be too far from the imine electrophilic carbon to form a bond. This means the reaction selectivity has been changed from *syn* to *anti* due to the reaction face of enamine being reversed from that of enamine in the proline-catalyzed process.



Scheme 4 Opposite diastereoselectivities in the α- and β-amino acid-catalyzed processes

(A) Proline-catalyzed *syn*-selectivity; (B) (*R*)-3-pyrrolidinecarboxylic acid catalyzed *anti*-selectivity.

On the basis of their design considerations, we then performed the density functional theory calculations on the (*R*)-3-pyrrolidinecarboxylic acid-catalyzed Mannich reactions with cyclohexanone as the donor. Similarly, the different isomers of the (*R*)-3-pyrrolidinecarboxylic acid-enamine of cyclohexanone were first explored and the relative energies at B3LYP/6-31G** level show that *anti*- and *syn*-enamine of catalyst **2** have nearly the same energies(the energy difference: 0.4 kJ/mol), which is in consistent with the hypothesis by Barbas *et al.*[8]. The inclusion of the solvent effect only slightly changes the energy difference(0.2 kJ/mol) between different isomers.

Fig.2 shows the transition state structures of the C—C bond-forming step in the (*R*)-3-pyrrolidinecarboxylic acid catalyzed processes. As shown in Fig.2, the most favored one is **2**d, which leads to the experimentally observed major product of (2*S*,3*R*)-*anti*-amino ketone. The (2*R*,3*S*)-enantiomer is mainly formed through transition state **2**b that is 10.7 kJ/mol higher in energy, which is somewhat overestimation over the experimental results(32% *e.e.*). This may be due to the fact that the reaction condition was not optimized for this reaction. The (2*S*,3*S*)-diastereoisomer generated from TS **2**a requires a higher energy barrier(7.1 kJ/mol in gas phase, and 8.5 kJ/mol in DMSO), thus reasonably explaining the high *anti* diastereoselectivity(*d.r.*=97:3).

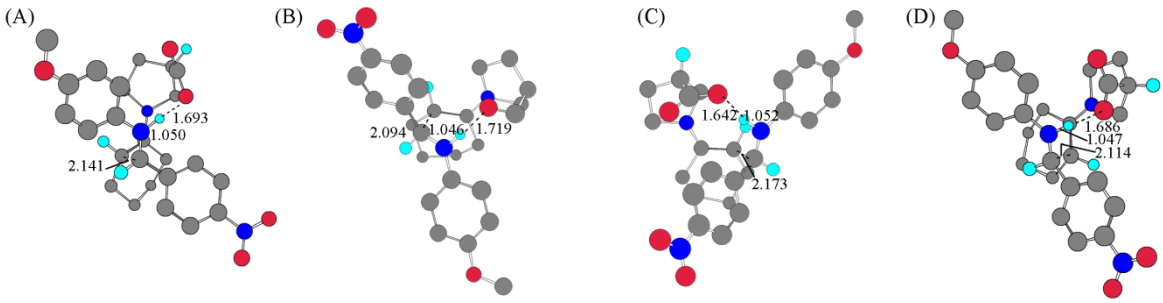


Fig.2 Transition state structures and relative free energies at B3LYP/6-31G level for the reaction of the catalyst 2-enamine of cyclohexene with N-PMP imine of *p*-nitrobenzyaldehyde**

Values in the parentheses including solvation energies in DMSO based on the CPCM/UAKS model. For clarity, some of the hydrogen atoms at the periphery are omitted. Color code: C: black; N: blue; O: red; H: light blue. Bond lengths are in nm and angles in degree. (A) **2**a, *anti-si*; G_{rel}=7.1(8.5) kJ/mol; ω_{1-4}=–18°, –22°, 164°, 156°; ω_{5-8}=71°, –161°, –61°, 68°; (B) **2**b, *anti-re*; G_{rel}=10.7(14.0) kJ/mol; ω_{1-4}=–6°, –11°, 178°, 165°; ω_{5-8}= –2°, 124°, 128°, –106°; (C) **2**c, *syn-re*; G_{rel}=7.9(11.0) kJ/mol; ω_{1-4}=4°, 5°, –179°, –172°; ω_{5-8}=–92°, 138°, 39°, –91°; (D) **2**d, *syn-si*; G_{rel}=0.0(0.0) kJ/mol; ω_{1-4}=8°, 6°, –177°, –170°; ω_{5-8}= –16°, –143°, –145°, 89°.

Now, the origin of the opposite *syn vs*. *anti* diastereoselectivities in α- and β-amino acids-catalyzed Mannich reactions can be explained by making a scrutiny into the geometrical arrangements of the TSs(shown in Figs.1 and 2). Numerical values for several geometric parameters that are relevant to the relative stability of the TSs are provided in those figures. These include the lengths of the formed C—C bond and the hydrogen bond, and the dihedral angles ω_{1-4} that are commonly used to measure the deviation of the developed iminium bond from planarity(ideally 0°, 0°, 180°, and 180°, see Scheme 3), and the dihedral angles ω_{5-8} that represent the different arrangements of imine and enamine along forming C—C bond(ideally ±60° and 180° for staggering conformation, see Scheme 3). As has been pointed out in the previous proline and its derivatives-catalyzed Mannich process[10—12], the different degrees to which each diastereomeric TS satisfies iminium planarity (ω_{1-4}), combined with the different arrangements adopted by enamine and aldehyde along forming C—C bond(ω_{5-8}) affects

the enantioselectivity and diastereoselectivity. Generally, the "more planar" iminium moiety and the more staggering orientation of imine and enamine at the reaction center are always preferred over the others. For example, when we consider the geometric difference between the TSs of the secondary α- and β-amino acids(comparing Figs.1 and 2), we can see that there is much less distortion of the iminium moiety in TS(**2**d) than in TS (**1**d). This "more planar" property may determine the relative energies of different TSs and switch the diastereoselectivities from *syn* in the α-amino acid-catalyzed Mannich reaction to *anti* in the β-amino acid-catalyzed one.

Therefore, our calculations confirm the hypothesis by Barbas *et al.*[8] that the position of the carboxylic acid moiety plays a significant role in directing the stereochemical outcome of the amino acids-catalyzed asymmetric Mannich reactions. For the α-amino acid-catalyzed processes, the reaction mainly proceed through *anti*-enamine intermediate, giving rise to the *syn*-Mannich product, since the channels involving *syn*-enamine which distorts greatly to achieve the proper proton transfer distance, requires higher activation energy. In contrast, when the acid moiety changed from 2-position to 3-position, the more remoted carboxylic group in the β-amino acid resulted in the "more planar" iminium in the reaction of imine approaching the *syn*-enamine to achieve proton transfer, made the diastereoselectivity alter from *syn* to *anti*. These results also confirm the new strategy that the tuning of the proper distance between the amino group and the acid moiety in the catalyst makes a significant effect on directing the stereochemical outcome of the reaction.

4 Conclusions

The transition state structures associated with the C—C bond-formation step of the α- and β-amino acids-catalyzed direct Mannich reactions involving cyclohexanone have been studied using B3LYP methods at the 6-31G** basis set level. Our calculations confirm that the opposite *anti vs. syn* diastereoselectivities found with β- and α-amino acid catalysts arises from the predominant TSs invoving different enamine isomers. α-Amino acid-catalysts prefer TS involving *anti*-enamine, while β-amino acid-catalysts advance the reaction occurring with the *syn*-enamine and switch the diastereoselectivities frome *syn* to *anti*. Our calculations also confirm the idea that tuning the proper distance between the amino group and the acid moiety in the catalyst can determine the main reaction channels and the subsequent major products. This may be a very useful strategy to achieve different isomers in the asymmetric synthesis.

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