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Theoretical studies of stereoselectivities in the direct *syn*- and *anti*-Mannich reactions catalyzed by different amino acids

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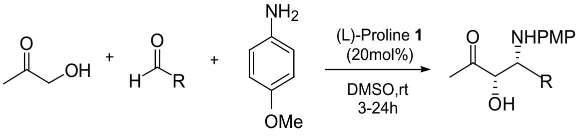
ABSTRACT

Quantum mechanics calculations have been performed to study the stereoselectivities in the direct *anti*- and *syn*-Mannich reactions catalyzed by different amino acids. The effects of two kinds of amino acid catalysts, L-proline (secondary) and L-tryptophan (primary), on the diastereoselectivity and enantioselectivity of the direct Mannich reactions between α-hydroxyacetone, *p*-anisidine, and *p*-nitrobenzaldehyde have been studied. Transition states of the stereochemistry-determining C–C bond-forming step with the enamine intermediate addition to the imine for the proline- and tryptophan-catalyzed processes are reported. These theoretical calculations provide a good explanation for the opposite *syn* diastereoselectivities versus *anti* diastereoselectivities of these two types of catalysts (*syn*-selectivity for the secondary cyclic amino acids such as proline and *anti*-selectivity for the acyclic primary amino acids such as tryptophan). Calculated and observed diastereomeric ratio and enantiomeric excess values are in good agreement.

1. Introduction

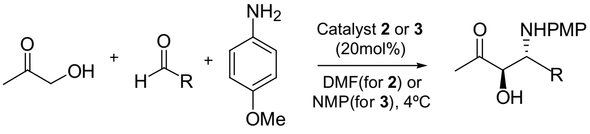
Chiral 1,2-amino alcohols are common structural motifs that occur frequently in natural products and in biologically active molecules.[1] Recently, significant efforts have been applied toward the development of direct catalytic asymmetric approaches to the construction of this unit based on the addition of unmodified α-hydroxyketones to imines in Mannich-type reactions.[2,3] Although Shibasaki and Trost have provided access to both *syn*- and *anti*-1,2-amino alcohols using metal-based catalysis,[2] the development of highly diastereo- and enantioselective organocatalytic approaches remains an important challenge and an appealing area.[3] List et al. reported the first L-proline **1**-catalyzed direct Mannich reactions between unmodified hydroxyacetone, *p*-anisidine, and various aldehydes to generate *syn*-1,2-amino alcohols in excellent regio-, diastereo-, and enantioselectivities Eq. 1.[3a–c]



(1)

R = *i*-Pr: 57% yield, *syn* :*anti* = 17:1, 65%ee;
R = *p*-$NO_2C_6H_4$: 92%yield, *syn* :*anti* = 20:1, >99%ee

Since List et al. showed that L-proline could act as a catalyst in direct three-component Mannich reactions, many new organocatalytic systems[4,5] have been developed attempting to reach high levels of efficiencies and to widen the scope of substrates. However, in all of these enamine-catalyzed Mannich-type reactions, highly enantioselective organocatalytic strategies have been mainly limited to *syn*-selectivity and there are only a few examples of *anti*-selective direct catalytic asymmetric Mannich reactions.[5] As a result, the new routes to the *anti*-selective direct Mannich reactions are more challenging and have received much research interest.[5] Recently, Barbas et al. have developed a simple and efficient strategy to obtain highly enantiomerically enriched *anti*-1,2-amino alcohols through direct asymmetric Mannich reactions involving unmodified α-hydroxyketones and 4-nitrobenzaldehyde Eq. 2.[3d] In these novel asymmetric Mannich reactions, primary amine containing-amino acids such as L-tryptophan **2** and *O*-*t*Bu-L-threonine **3** were used as catalysts and desired *anti*-amino alcohols were obtained in good yields with excellent dr (up to 15:1) and ee (up to 98% ee).[3d]



R =*p*-$NO_2C_6H_4$: for catalyst **2 (L-Tryptophan)**, 95%yield, *anti* :*syn* = 12:1, 95%ee;
for catalyst **3 (O-tBu-L-Threonine)**, 85%yield, *anti* : *syn* > 15:1, 98%ee.

(2)

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Later, highly diastereoselective and enantioselective direct organocatalytic *anti*-selective Mannich reactions employing *N*-tosylimines were also reported by Lu et al.[5i] In these novel asymmetric reactions, a primary amino acid (L-threonine-derived catalyst) was used as a catalyst and the desired *anti*-1,2-amino alcohols were obtained with high dr and ee.

The above observation that these asymmetric Mannich reactions can be catalyzed by secondary amine-containing amino acids (e.g., proline) with stereochemistry opposite to those catalyzed by the primary amine-containing amino acids (tryptophan or *O*-*t*Bu-L-threonine) called for mechanistic and theoretical investigations. It is well known that quantum mechanical calculations are an important tool in elucidating the reaction mechanism and the stereoselectivity. In most cases, good agreement between the theoretical results and experimental observations was obtained.[6] Recently, the secondary amine-containing amino acids (e.g., proline and pipecolic acid)-catalyzed asymmetric direct Mannich reactions have been studied by density functional theory methods.[7] In a series of pioneering contributions,[7,8] Houk et al. have established that the Mannich reactions, similar to the amino acids-catalyzed aldol reactions,[8,9] also proceed via enamine intermediates and that the transition states for the crucial C–C bond-forming step (nucleophilic addition of the enamine intermediate to an electrophilic imine) show an arrangement of the reacting atoms that is stabilized by a hydrogen-bonding interaction between the acidic proton of the carboxylic acid moiety in amino acids and the nitrogen atom of the electrophile imine. On the basis of this concept, the diastereo- and enantioselectivity have been successfully rationalized and predicted for the proline- and pipecolic acid-catalyzed Mannich reactions.[7]

To the best of our knowledge, although great effort has been made toward the general understanding of the mechanism of enamine catalytic reactions,[7–9] there are no other theoretical investigations concerning the *anti*-selectivity of the primary amino acid-catalyzed Mannich reaction between α-hydroxyketones, *p*-anisidine, and *p*-nitrobenzaldehyde. Therefore, to extend our understanding in the mechanism and stereoselectivity of enamine catalytic reactions, the present theoretical study has been performed to address the question: what is the origin of the opposite (*syn* vs *anti*) diastereoselectivities in the secondary amine-containing and primary amine-containing amino acid-catalyzed direct Mannich reactions involving α-hydroxyketones as the donor?

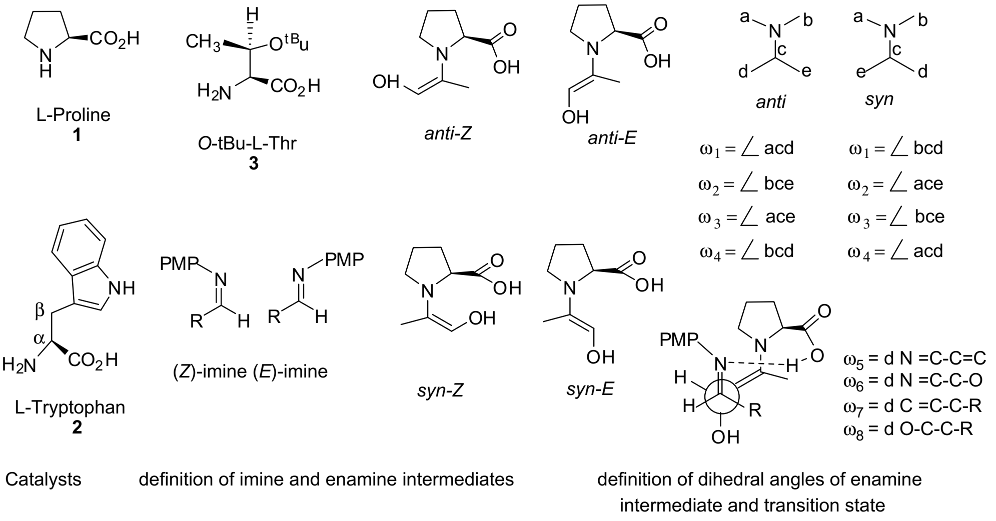
2. Computational methods

All ground state and transition state geometries were located using density functional theory (DFT) and the BH and HLYP hybrid functional.[10] The standard 6-31G* basis sets[11] were employed throughout. All transition state geometries were fully optimized and characterized by frequency analysis. In some cases, the intrinsic reaction coordinate (IRC) pathways were traced in order to verify the energy profiles connecting the transition structure to the two desired minima of the proposed mechanism. Furthermore, to check the validity of the results at the above computational level, we have reoptimized several important transition states employing the 6-31G** basis sets for comparison. The bulk effects of the solvent DMSO for the L-proline-catalyzed and L-tryptophan-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),[12] with united-atom Kohn-Sham (UAKS) radii. The single-point continuum calculations were done upon the optimized gas phase geometries with a dielectric constant $\varepsilon = 46.7$ for DMSO. All calculations were carried out using the GAUSSIAN 03 program.[13]

3. Results and discussion

To investigate the secondary amine-containing and primary amine-containing amino acid-catalyzed asymmetric direct Mannich reactions involving α-hydroxyketones, we used L-proline **1** and L-tryptophan **2** as the protype catalysts, and Eqs. 1 and 2 as the model reactions. Scheme 1 shows these catalysts and the notation used for the enamine, imine intermediate, and transition states.

Analogous to the previous investigation of the enamine-catalyzed aldol and Mannich reactions,[7–9] we focused on the transition states for the enamine attack to the imine. This was expected to be the rate-determining and the stereochemistry-controlling step of the reaction, and thus was studied in order to understand the observed diastereo- and enantioselectivities. We have considered several stereochemical pathways for this step. First, the enamine intermediate may in principle have a *Z*- or *E*-configuration and the enamine double bond may be oriented *syn* and *anti* relative to the carbonyl acid group of the title amino acids (Scheme 1). Second, the imine may also have a *Z*- or *E*-configuration (Scheme 1). Third, the different diastereomeric approach modes to the *re* and

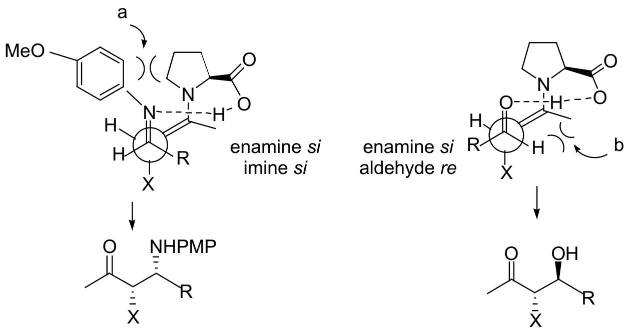


Scheme 1.

si faces of the enamine and of the imine should be considered. Consistent with the previous theoretical studies,[7–9] only transition states that involve hydrogen bonding between the carboxylate and the imine were considered here.

3.1. L-Proline-catalyzed process

Eq. 1 illustrated the *syn*-selectivity of the proline-catalyzed Mannich reaction involving unmodified hydroxyacetone performed by List et al.[3a–c] Excellent diastereo- and enantioselectivity were obtained for the *p*-nitrobenzaldehyde. Thus, the reaction between hydroxyacetone, *p*-anisidine, and *p*-nitrobenzaldehyde has been chosen as a model to investigate the stereoselectivities addressed with **proline** catalyst. In their original work, List et al. proposed plausible transition states for the Mannich reaction and explained the origin of the different stereoselectivitiy for the **proline**-catalyzed aldol and Mannich reactions (Scheme 2).[3b,c] As illustrated in Scheme 2, the main aldol products result from a *re*-enantiofacial attack on the aldehyde of the *si* face of an (*E*)-enamine, whereas Mannich products are formed via *si*-face attack on an (*E*)-imine of the *si* face of an (*E*)-enamine, since the attack of the imine *re*-face would result in an unfavorable steric interaction between the pyrrolidine and aromatic ring. Therefore, in the aldol reaction, *anti*-diastereoselectivity is observed, while *syn*-selectivity is found in the corresponding Mannich reactions. Later, theoretical investigations[7] for the proline- and its derivatives-catalyzed Mannich reactions by Houk et al. have confirmed the above hypothesis.



Scheme 2. Opposite enantiofacial selectivities in aldol and Mannich transition states.

Although the computational studies of the proline-catalyzed Mannich reactions between aldehyde and *N*-*p*-methoxyphenyl-protected α-imino ethyl glyoxylate have been performed,[7a] for the sake of comparison with the primary amino acid-catalyzed process, we carried out a theoretical calculation of the proline-catalyzed Mannich reaction between hydroxyacetone, *p*-anisidine, and *p*-nitrobenzaldehyde. We first explored the relative energies of (*E*)-imine and (*Z*)-imine (Scheme 1), and the results indicate that (*Z*)-imine is about 33.5 kJ/mol higher in energy than (*E*)-imine. Inclusion of the solvent effect enlarges the energy difference to 35.3 kJ/mol. This large energy difference means that the reactive channels involving the (*Z*)-imine can be safely excluded in the discussion of the primary and secondary amino acids-catalyzed direct Mannich reactions. Then four isomers of the enamine intermediates formed between proline and hydroxyacetones (Scheme 1) were considered. The relative free energies between different isomers are shown in Table 1 (CPCM values in DMSO are presented in parentheses). Contrary to the hypothesis by List et al.,[3a–c] the (*Z*)-enamine is slightly more stable than the (*E*)-enamine with the vinylamine framework distorting greatly to avoid the steric hindrance between the methylene in the pyrrolidine ring and the hydroxyl group. There is only a slight energy difference between the different isomers. The inclusion of the solvent effect only slightly affects the stabilization of the four isomers with the *anti*-(*Z*)-enamine still being the most stable one.

Table 1
Relative free energies[a] (kJ/mol) of different isomers of proline- and tryptophan-enamine of α-hydroxyacetone

	anti-Z	*anti-E*	*syn-Z*	*syn-E*
Enamine–proline	0.0(0.0)	6.8(6.8)	6.8(6.9)	6.4(8.9)
Enamine–tryptophan	0.0(0.0)	11.0(6.6)	5.3(1.4)	6.1(3.1)

[a] CPCM values in DMSO are shown in parentheses.

Eight reactive channels corresponding to four stereoisomers that are *syn*- and *anti*-diastereomeric pairs of enantiomers for the reaction of the proline-enamine of hydroxyacetone and *N*-*p*-methoxyphenyl-protected imine of *p*-nitrobenzaldehyde have been considered. Although the imine and enamine may adopt different staggered arrangements about the forming bond, on the basis of the pioneering computational studies,[7–9] only the lowest energy transition states leading to the four products have been illustrated in Figure 1. The notation used for the transition states, for example, '*anti*' and '*E*' in '*anti*-(*E*)-*si*-*re*' is consistent with previous conventions, '*si*' denotes the *si* face of enamine, while '*re*' means the *re* face of imine. The corresponding transition states occurring on the opposite side of the proline ring which lack hydrogen bonding stabilization are not considered. As shown in Figure 1, all of the transition states have the carboxylic acid proton completely transferred to the imine, with the forming C–C single-bond having lengths of 2.2–2.4 Å and the forming C–N iminium bond having lengths of 1.33 Å. This substantial ionic interaction between an iminium and the carboxylate is the common feature of the proline-catalyzed Mannich reactions proposed by Houk's group.[7] Among these transition states, consistent with the hypothesis by the experimental work,[3b,c] transition states involving an (*E*)-enamine are more stable than their counterparts involving (*Z*)-enamine. The most stable one involving the attack of the *anti*-(*E*)-enamine to the *si*-face of imine **1a** leads to the (3*S*,4*R*)-*syn*-1,2-amino alcohol, which is indeed the major product observed experimentally. The (3*R*,4*R*)-diastereoisomer is mainly formed through transition state **1b** corresponding to the *anti*-(*Z*)-enamine attacking the *si* face of the imine, which lies 6.9 kJ/mol higher in energy than the most stable one **1a** in the gas phase. This free energy difference increases to 7.1 kJ/mol when the solvent effect is taken into account. Thus, the high *syn*-diastereoselectivity (dr = 20:1) can be explained. The (3*R*,4*S*)-enantiomer generated from the attack of *syn*-(*E*)-enamine to the *re* face of imine also requires a higher free energy barrier (14.3 kJ/mol in the gas phase, 17.6 kJ/mol in DMSO), which is in good agreement with the experimental results (>99% ee).

To validate the above results at the BH and HLYP/6-31G* computational level, we have reoptimized several important transition states (**1a**, **1b**, and **1g**) using the 6-31G** basis sets. The calculated free energy differences between **1a** and **1b**, and between **1a** and **1g** are 6.9 and 15.1 kJ/mol, respectively, which indicates that the enlarged basis sets lead to similar results with those employing the 6-31G* basis sets. Therefore, our calculations at the 6-31G* basis sets level can produce reliable results.

To further verify the reliability of our computational results, the differences in the calculated free activation enthalpies $\Delta\Delta G^{\neq}$ have been used to predict the absolute stereoselectivities such as the associated enantiomeric excess (ee) and diastereomeric ratio (dr) from the absolute rate theory, $\ln(k_{anti}/k_{syn}) = \Delta\Delta G^{\neq}/RT$. Table 2 lists the corresponding $\Delta\Delta G^{\neq}$, ee, and dr values in the gas phase and in DMSO solution, and compares them with the available experimental data.[3b,c] As shown in Table 2, whether in the gas phase or in DMSO, there is obviously excellent agreement between

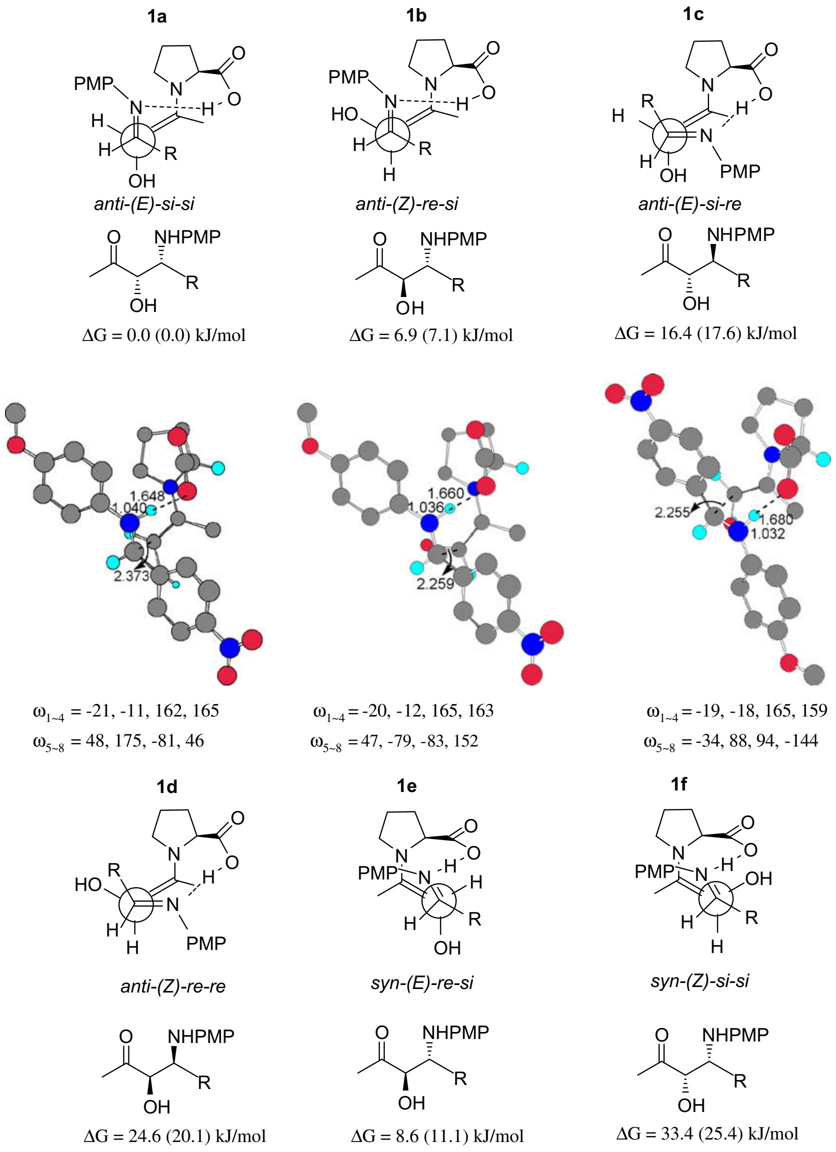


Figure 1. Transition structures and relative free energies at BH and HLYP/6-31G* level for the reaction of the proline-enamine of hydroxyacetone with *N*-PMP imine of *p*-nitrobenzyaldehyde. Values in parentheses including solvation energies in DMSO using the CPCM/UAKS model. Different transition state arrangements of imine and enamine along the forming C–C bond that generate the four diastereoisomers are shown. For clarity, some of the hydrogen atoms at the periphery are omitted.

the predicted and observed stereoselectivities for the proline-catalyzed Mannich reaction.

3.2. Tryptophan-catalyzed process

As shown in Eq. 2, Barbas et al. reported the *anti*-selective organocatalytic Mannich reactions using unmodified hydroxyacetone as a donor to install *anti*-1,2-amino alcohols functionality in the products.[3d] In their experiments, the primary amine-containing amino acids such as L-tryptophan **2** and *O*-*t*Bu-L-threonine **3** (Scheme 1) were proved to be efficient catalysts with excellent stereoselectivities. The *anti*-Mannich studies are based on their original hypothesis (Scheme 3): with pyrrolidine-derived catalysts or secondary amines, (*E*)-enamine A intermediates predominate because of the steric interaction in (*Z*)-enamine B. The *syn*-selectivity of the product can be explained by transition state C because the *si* face of the (*E*)-enamine reacts. With primary amines, the (*Z*)-enamine of hydroxyketones E should be predominant over (*E*)-enamines F, when (*Z*)-enamine E reacts with the imine in the C–C bond-forming transition state G, *anti*-Mannich products should form predominantly.

On the basis of their design considerations, we then performed density functional theory calculations on the tryptophan-catalyzed Mannich reaction with hydroxyacetone as the donor and the imine formed between *p*-nitrobenzaldehyde and *p*-anisidine as the acceptor. Similarly, the four isomers of the tryptophan–enamine of hydroxyacetone were first explored, and the relative free energies at BH and HLYP/6-31G* level are also shown in Table 1. Consistent with the hypothesis by Barbas et al.,[3d] the (*Z*)-enamine isomers are more stable than their (*E*)-enamine counterparts. In the *anti*-(*Z*)-enamine isomer, the extra hydrogen bonding formed between the O atom in OH group attached to the enamine double bond and the NH group of amino acid makes it to be the most stable one among them. The inclusion of the solvent effect lowers the energies of the other three isomers, but does not change the stability order.

Unlike the proline-derived enamine intermediate, acyclic primary amino acid enamines can rotate about the C_{α}–N bond, and

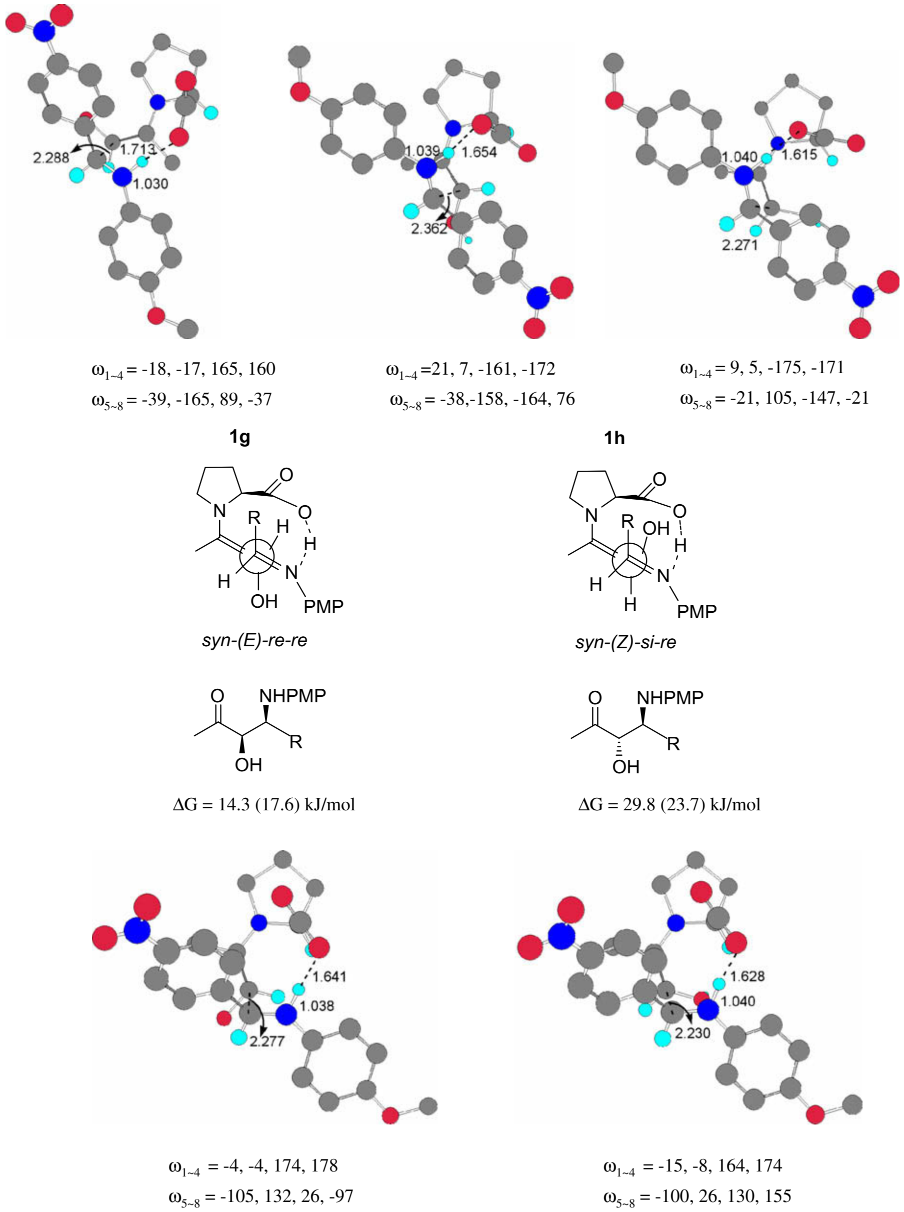


Figure 1. *(continued)*

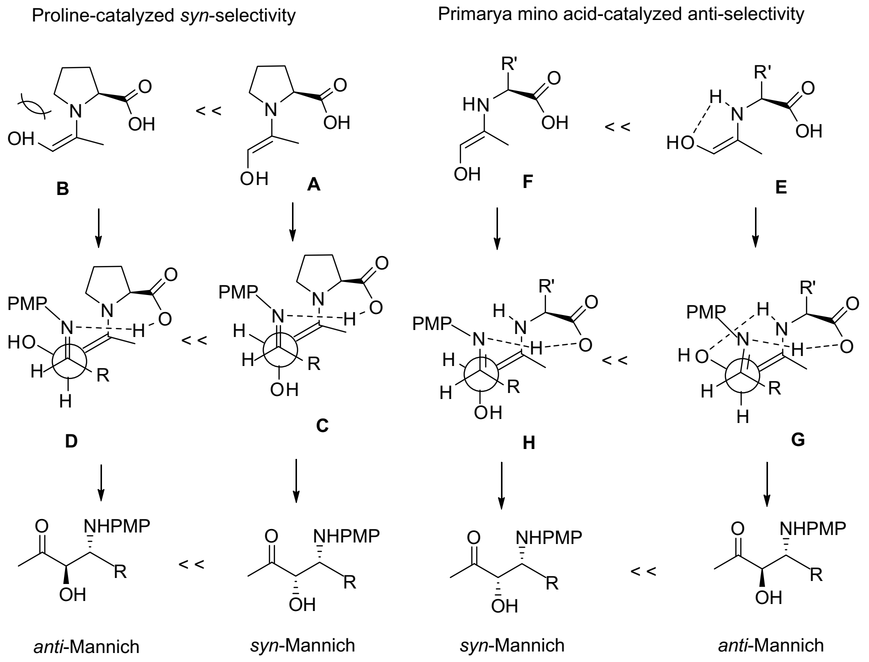
Table 2

Free activation enthalpies $\Delta\Delta G^{\neq}$ (kJ/mol), ee, and dr values versus experimental results

Catalyst	Theory (gas phase)				Theory (DMSO)[a]				Experiment[a]	
	$\Delta\Delta G_1^{\neq}$	ee	$\Delta\Delta G_2^{\neq}$	dr	$\Delta\Delta G_1^{\neq}$	ee	$\Delta\Delta G_2^{\neq}$	dr	ee	dr
Proline	14.3	>99%	6.9	16:1	17.6	>99%	7.1	17:1	>99%	20:1
Tryptophan	15.0	>99%	7.5	20:1	13.7	99%	6.8	15:1	95%	12:1

[a] Experimental data from Refs. 3b–d, respectively.

thus the (*E*)- and (*Z*)-enamines are possible for both *si* and *re* attacks by the imine. Therefore, more transition-state structures have to be considered. Herein, 16 transition state orientations that generate four stereoisomers have been envisioned. More transition states with different arrangement of enamine and imine along the forming C–C bond, which requires much higher activation energies, are not discussed here. These 16 transition states can be divided into two types that differ in the attack on the opposite face of enamine intermediates (Type I: **2a**–**2h**, Type II: labeled by a prime, **2a**′–**2h**′), which means products generated by transition states **2a**′–**2h**′ are enantiomers of those by transition states **2a**–**2h** correspondingly. In all cases, transition states **2a**′–**2h**′ are much higher in energy than their counterparts **2a**–**2h**, which indicates that these reactive channels can be excluded in the calculation of the stereoselectivities (**2a**′ is an exception). The results for the more stable transition states **2a**–**2h** and **2a**′ are shown in Figure 2. Among these nine lower-energy transition states, the most favored one is **2b**, which leads to the experimentally observed



Scheme 3.

major product of the (3*R*,4*R*)-*anti*-1,2-amino alcohol. The (3*S*,4*S*)-enantiomer is mainly formed via transition state **2a**′ that lies 15.0 kJ/mol higher in energy, which is consistent with the experimental results (95%ee). The (3*S*,4*R*)-diastereoisomer requires a higher energy barrier (7.5 kJ/mol), thus explaining the high *anti*-diastereoselectivity (dr = 12:1).

To verify the calculated results at the DFT/6-31G* basis sets level, the key transition states of **2a, 2b**, and **2a**′ have also been reoptimized at the BH and HLYP/6-31G** level. The related free energy differences between **2a** and **2b**, and between **2a** and **2a**′ are 6.5 and 14.5 kJ/mol, respectively. Hence, it can be concluded that enlarging the basis sets to 6-31G** has little effect on the energy difference between those transition states.

The calculated $\Delta\Delta G^{\neq}$, ee, and dr values in the gas phase and in DMSO solution of the L-tryptophan-catalyzed Mannich reaction are presented in Table 2, along with the observed experimental results.[3d] There is also good agreement between the calculated and the experimental stereoselectivities.

The origin of the opposite *anti* diastereoselectivities versus *syn* diastereoselectivities in primary and secondary amino acids-catalyzed Mannich reactions can be explained by looking at the geometrical arrangements of the transition states (shown in Figs. 1 and 2). Numerical values for several geometric parameters that are relevant for the relative stability of the transition states are provided in these figures. These include the lengths of the forming C–C bond and the hydrogen bond, and the dihedral angles ω_{1-4} that are commonly used to measure the deviation of the developing iminium bond from planarity (ideally 0°, 0°, 180°, and 180°, see Scheme 1), and the dihedral angles ω_{5-8} that represent the different arrangements of imine and enamine along the forming C–C bond (ideally ±60° and 180° for staggered conformation, see Scheme 1). As has been pointed out in the previous proline- and its derivatives-catalyzed aldol and Mannich process,[7–9] the following factors may contribute to the enantioselectivity and diastereoselectivity. First, stereoselectivity partially arises from the different degrees to which each diastereomeric transition state satisfies iminium planarity. Generally, the more stable transition state is always associated with a 'more planar' iminum moiety. The dihedral angles ω_{1-4} illustrated in Figure 2 indicate that primary amino acids can allow a much lower distortion of the enamine systems than with secondary amino acid proline (compare Fig. 2 with Fig. 1). This is because of the conformational flexibility of the acyclic primary amino acids that can allow the C_{α}–N bond to rotate, which subsequently permits the carboxylic moiety to give the proton transfer more easily without need of a large geometric distortion. However, this is not the case for the proline system due to the conformational restraints imposed by the pyrrolidine ring. The second factor that regulates the stereoselectivity is the different arrangements of the imine and enamine along the forming C–C bond. Of course, intermolecular hydrogen bonding and steric repulsion may change the ideal arrangement from the staggered to the more eclipsed ones (ω_{5-8} shown in Scheme 1 and Figs. 1 and 2). However, transition states with the more staggering orientation at the reaction center should be preferred over the other ones. In summary, these factors combine to affect the relative energies of the various transition states and subsequently the stereoselectivity. Furthermore, despite the above interplaying factors, when the calculated transition states for the proline-enamine **1b** and tryptophan–enamine **2b** are compared, transition state **2b** also benefits from an extra hydrogen bonding interaction between the O atom in the OH group of enamine and the NH group of amine. Hence, the considerable steric repulsion between the methylene substituent on the proline nitrogen atom and the OH group in (*Z*)-enamine (in transition state-**1b**) is replaced by the favorable hydrogen bonding interaction in the counterpart of the tryptophan-catalyzed process, which makes the transition state **2b** to be the most stable one, and consequently leads to an inversion in the diastereoselectivity. Therefore, our calculations confirm the hypothesis by Barbas et al.[3d] that the opposite diastereoselectivity found with the secondary amino acid (proline) and primary amino acid (tryptophan) arises from the differential steric repulsion between the substituents on the enamine nitrogen (hydrogen in tryptophan and methylene in proline), with the OH substituent of the (*Z*)-enamine. In the proline-catalyzed Mannich reaction, the steric repulsion with the methylene group destabilized the transition states involving a (*Z*)-enamine, resulting in the transition state involving the *anti*-(*E*)-enamine being predominant. As a consequence, the *syn*-Mannich adducts are proved to be the major prod-

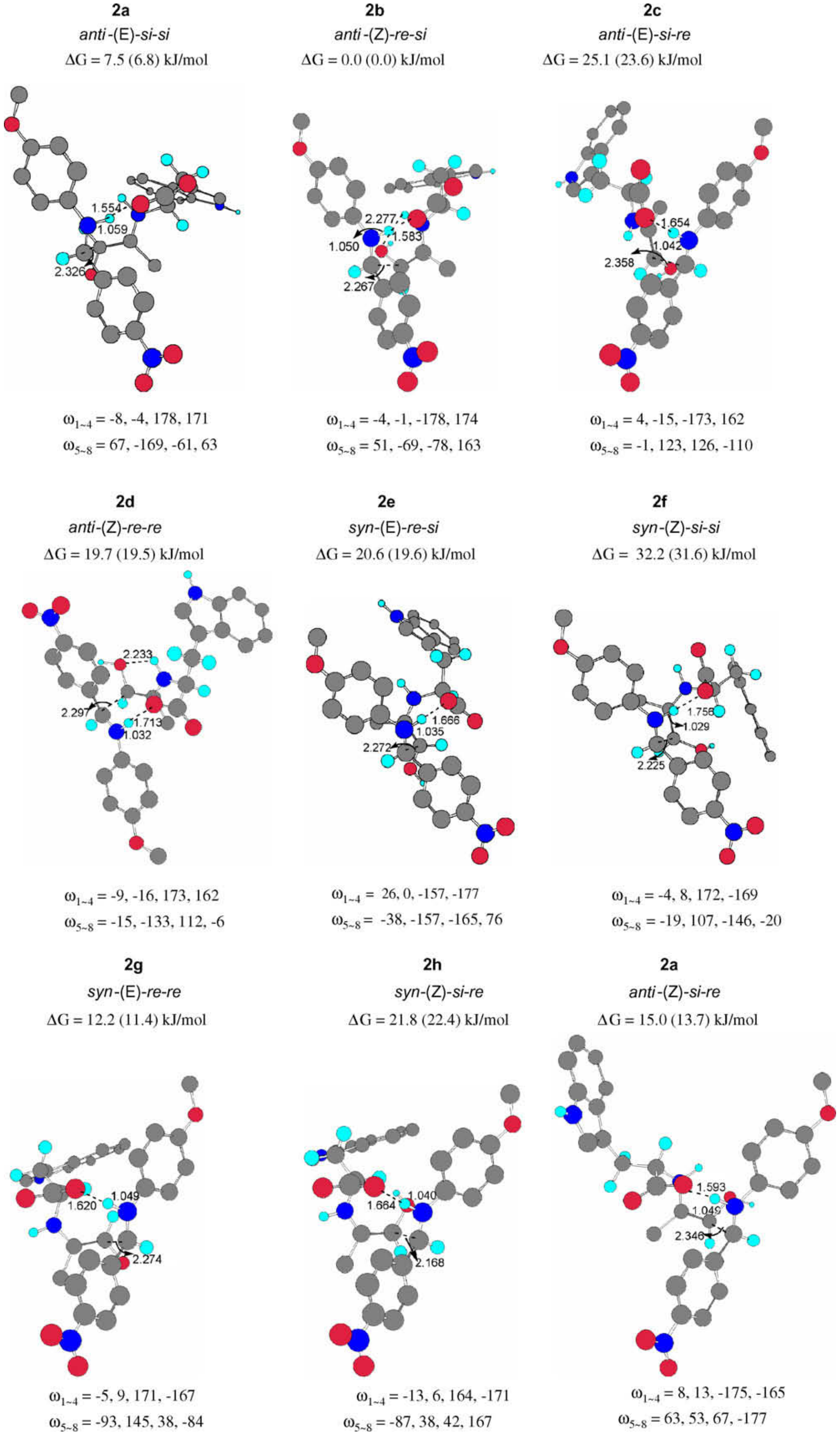


Figure 2. The more stable transition state structures and relative free energies at BH and HLYP/6-31G* level for the reaction of the tryptophan–enamine of hydroxyacetone with *N*-PMP imine of *p*-nitrobenzyaldehyde. Values in parentheses include solvation energies in DMSO using the CPCM/UAKS model. For clarity, some of the hydrogen atoms at the periphery are omitted.

uct. While in the tryptophan-catalyzed reactions (Scheme 3), the favorable hydrogen bonding interaction between the NH group and the OH substituent instead of the unfavorable steric hindrance between OH group and methyl in transition state involving an *anti*-(*Z*)-enamine makes the transition states involving the *anti*-(*Z*)-enamine to be preferred over those involving the *anti*-(*E*)-enamine. This leads to an inversion in the diastereoselectiviy as compared with that of the proline-catalyzed reaction and makes the *anti*-Mannich adducts to be the major product.

3.3. Conclusions

The transition structures associated with the C–C bond formation step of the secondary cyclic amino acid proline- and primary amino acid tryptophan-catalyzed direct Mannich reactions involving hydroxyacetone, *p*-anisidine, and *p*-nitrobenzaldehyde have been studied using BH and HLYP methods at the 6-31G* basis set level. For this stereochemistry-controlled step, all the reactive channels corresponding to the *syn* and *anti* arrangement of the enamine double bond relative to the carboxylic group, and the two diastereoisomeric approach modes to the *re* and *si* faces of the imine, and *re* and *si* attack of tryptophan–enamine have been studied. Our calculations confirm that the opposite *anti* diastereoselectivities versus *syn* diastereoselectivities found with the tryptophan and the proline catalysts arises from the differential steric repulsion between the substituents on the enamine nitrogen (hydrogen in tryptophan and methylene in proline), with the OH substituent of the *Z*-enamine. The favorable hydrogen bonding interaction between the NH group and the OH substituent in transition states involving *anti*-(*Z*)-tryptophon-enamine instead of the steric hindrance between the OH group and the methylene in pyrrolidine ring in transition states involving *anti*-(*Z*)-proline-enamine leads to an opposite diastereoselectivity in these two amino acid-catalyzed Mannich reactions. The calculated diastereomeric ratio and enantiomeric excess are in good agreement with experimental results.

Acknowledgments

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