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Editor's choice paper

Theoretical studies of stereoselectivities in the direct organocatalytic Mannich reactions involving ketimine

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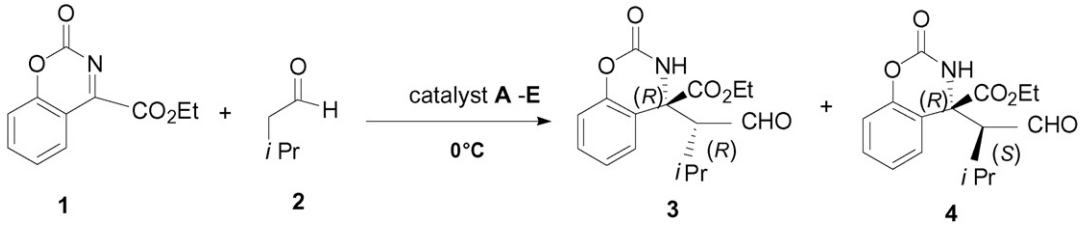
ABSTRACT

Quantum mechanics calculations have been performed to study the stereoselectivities in the direct Mannich reactions catalyzed by different chiral secondary amine catalysts. The effects of two kinds of catalysts, (*S*)-1-(2-pyrrolidinylmethyl) pyrrolidine and proline on the diastereoselectivities of the direct Mannich reactions between ketimine and aldehyde have been studied with the aid of the BH and HLYP method. Transition states of the stereochemistry-determining C—C bond-forming step with the enamine intermediate addition to the ketimine for the subject reactions are reported. These theoretical calculations provide a good explanation for the opposite diastereoselectivities of these two different kinds of catalysts. Calculated and observed diastereomeric ratio and enantiomeric excess values are in good agreement.

1. Introduction

The direct asymmetric Mannich reaction is one of the most important C—C bond-forming reactions in the construction of optically active nitrogen containing compounds, such as amino acids, amino alcohols, amino carbonyls and their derivatives. 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 [1–7]. In particular, since the pioneering finding by List et al. and Barbas et al. [2] 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 [3–7], which include Brønsted acids [3a,3b], cinchona alkaloids [3c,3d], proline derivatives and linear amino acid derivatives [4–7], have been developed for this transformation, all attempting to reach high levels of efficiencies and to widen the scope of substrates. For these organo-catalyzed direct asymmetric Mannich and Mannich-type reactions, both *syn*- [2] and *anti*-selective methods [5] that afford products with high enantioselectivity have been reported. However, despite the tremendous amount of work and effort devoted to the development of efficient and versatile Mannich reactions, the structure of the electrophile has been limited to imines derived from aldehydes (aldimine), although substrates of ketimine (imine derived from ketone) such as α-substituted α-ketimino esters would constitute an interesting template for the synthesis of quaternary α- and β-amino acids. Recently, Jørgensen et al. [7a] have reported the first organocatalytic enantioselective Mannich reaction of ketimines and unmodified aldehydes (Eq. (1)).



For catalyst A, 84% yield, 3/4 = 1:8, 82% ee; for catalyst B, 56%~99% yield, 3/4 = 2:1~>20:1,86%~92% ee; for catalyst C, 11% yield, 3/4 > 20:1, 7% yield; for catalyst D, trace yield; for catalyst E, 39% yield, 3/4>20:1, 80% ee. (1)

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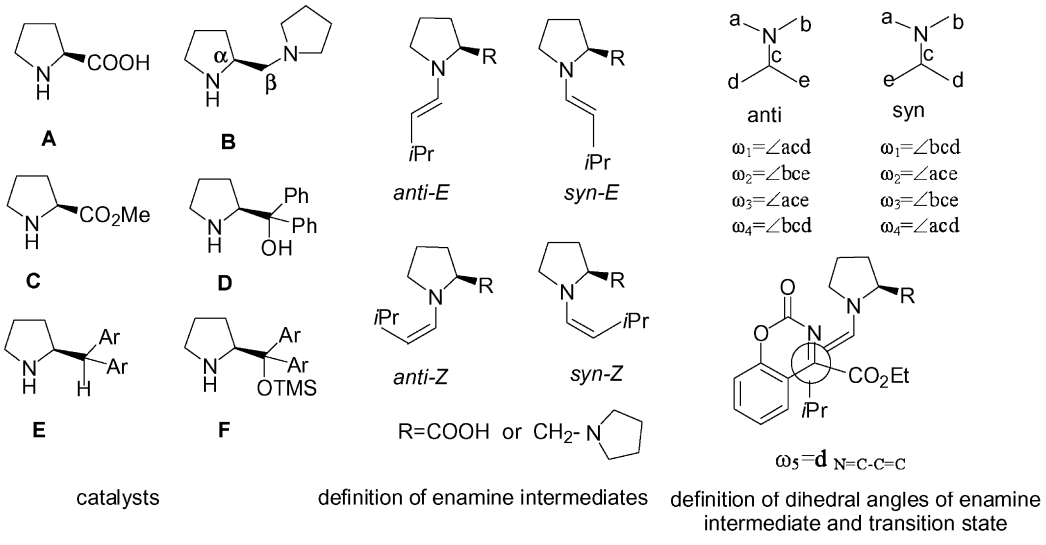
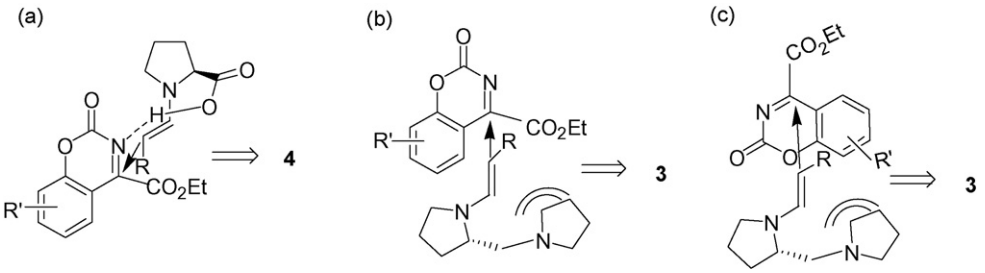


Scheme 1.

In these asymmetric Mannich reactions, a series of chiral secondary amines (catalyst A–E in Scheme 1) were used as catalysts and optically active quaternary α-amino acid derivatives were formed in high yields (72–99%) with optical purities ranging from 83 to 98%ee. More importantly, a very interesting reversal of the diastereoselectivity was observed when the carboxylic acid functionality of L-proline (catalyst A) was substituted for a non-acidic or basic substituent (catalysts B–E). For example, as shown in Eq. (1), the major Mannich product **4** was obtained in the L-proline-catalyzed process while product **3** predominated when using B–E as the catalysts. In their original work, Jørgensen et al. have proposed the plausible transition states for those Mannich reactions and explained the origin of the different diastereoselectivities for (*S*)-1-(2-pyrrolidinylmethyl) pyrrolidine (catalyst B) and proline-catalyzed processes (Scheme 2).

As illustrated in Scheme 2a, the observed stereoselectivity with L-proline as the catalyst results from the *si*-face of ketimine attacking the *re* face of the *anti*-(*E*)-enamine, which is in good agreement with the transition state models proposed by Barbas [2d, 2e], List [2a–2c], and Houk et al. [8] for the catalytic enantioselective Mannich reaction of imines derived from glyoxylic aldehydes. Their pioneering theoretical and concomitant experimental studies of proline and other common organocatalysts-catalyzed aldol, Mannich and other related reactions [8–10], have established that the hydrogen-bonding interaction between the acidic proton of the carboxylic acid in the enamine intermediate and the oxygen or nitrogen atom of the electrophile plays an important role in achieving the high asymmetric induction. In contrast, when the new type of organocatalyst B which lacks of such hydrogen-bonding donor properties was used as the catalyst, Jørgensen et al. have proposed a linear transition state in which the *si* face of the *anti*-(*E*)-enamine intermediate approaches the *si* face of the imino electrophile to explain the observed opposite stereochemistry to proline (Scheme 2b). They thought that such kind of arrangement of the reaction partners would minimize the steric repulsion in the C—C bond-forming step and made **3** to be the major Mannich product.

This very interesting reversal of the diastereoselectivity when switch the catalyst from proline to the other pyrrolidine derivatives with the carboxylic acid functionality substituted for a non-acidic or basic substituent was also reported by Córdova et al. in their earlier work of the first (*S*)-2-methoxymethylpyrrolidine (SMP)-catalyzed highly *anti*-selective Mannich-type reactions of unmodified aldehydes with N-PMP-protected α-imino ethyl glyoxylate [6a]. Very recently, they have also examined another catalyst (α,α-diphenylprolinol silyl ether, catalyst F shown in Scheme 1)) in the same direct catalytic Mannich-type reactions which afford the products with highly *anti*- and enantioselectivities [6b]. It is worthwhile to emphasize that the performance of catalyst F was first investigated by Jørgensen's group in the reactions of α-amination, α-fluorination, α-bromination, and α-sulfenylation of aldehydes, Mannich reactions, and Michael conjugation additions [7b]. The above reactions also reveal an very important phenomenon: the absolute configuration of the product or the diastereoselectivity for the reaction obtained with catalyst F are always opposite to those generated with L-proline, although the absolute configuration of the catalysts is the same. Obviously, all of above studies suggest a new strategy in the design of the organic catalysts for direct asymmetric Mannich reactions and related transformation: in the process of the electrophile approaching to the enamine intermediate, the asymmetric induction may be con-



Scheme 2. A schematic representation of the approach of the ketimine to two enamine intermediates that accounts for the observed diastereoselectivities: (a) reaction occurs at the *si* face of the imine and the *re* face of the enamine; (b) reaction occurs at the *si* face of the imine and the *si* face of the enamine (linear TS); (c) reaction occurs at the *si* face of the imine and the *si* face of the enamine.

trolled by the efficient steric shielding instead of the commonly used hydrogen-bonding concept.

The concept of the new asymmetric induction strategy call 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, especially for the organo-catalyzed aldol, Mannich and other related transformations involving enamine intermediate. In most cases, the diastereo- and enantioselectivity have been successfully rationalized and predicted [8–10]. To the best of our knowledge, although great effort has been made to the general understanding of the mechanism of enamine catalytic reactions [8–10], there are no other theoretical investigations concerning the process involving the new type of catalysts which lack of the acidic proton or hydrogen bond donor. Furthermore, ketimines are in general less reactive towards nucleophilic additions on the C=N bond than aldimines owing to their low electrophilicity and increased steric hindrance, and the literature lacks theoretical investigation for the mechanism of the organo-catalyzed asymmetric Mannich reactions of ketimines. It is, therefore, intriguing to determine the behavior of ketimine theoretically in these conversions and to gain an insight into the stereochemistry. Hence, to extend our understanding in 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 diastereoselectivities when the carboxylic acid functionality was substituted for a non-acidic or basic substituent in the direct Mannich reactions involving ketimine as the acceptor?

2. Computational methods

All ground state and transition state (TS) geometries were located using density functional theory (DFT) and the BH and HLYP hybrid functional [11] since this functional has satisfactorily reproducing the experimental results in several organo-catalyzed Mannich reactions [12]. The standard 6-31G* basis sets [13] were employed throughout. All TS geometries were fully optimized and characterized by frequency analysis. To check the validity of the results at the above computational level, we have reoptimized several important TSs employing the 6-31G** basis sets for comparison. The bulk effects of the solvent CH_2Cl_2 for the different chiral secondary amines-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. The single-point continuum calculations were done upon the optimized gas phase geometries with a dielectric constant $\varepsilon = 8.93$ for CH_2Cl_2. All calculations were carried out using the Gaussian 03 program [15].

3. Results and discussion

To investigate the different chiral secondary amines-catalyzed asymmetric direct Mannich reactions involving ketimine, we have used L-proline (catalyst A) and chiral diamine (*S*)-1-(2-pyrrolidinylmethyl) pyrrolidine (catalyst B) as the prototype catalysts, and Eq. (1) as the model reactions. Scheme 1 shows these catalysts and the notation used for the enamine intermediate, and TSs.

Analogous to the previous investigations of the enamine-catalyzed aldol and Mannich reactions [8–10], we have focused on the TSs for the enamine attack to the imine. This is 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. Firstly, 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 R group shown in Scheme 1. Secondly, the different diastereomeric approach modes to the *re* and *si* faces of the enamine and of the imine should be considered.

Table 1
Relative free energies[a] (kJ/mol) of different isomers of (*S*)-1-(2-pyrrolidinylmethyl) pyrrolidine- and proline-enamine of isovaleraldehyde.

	anti-E	syn-E	anti-Z	syn-Z
Enamine-diamine	0.5 (0.0)	0.0 (1.7)	8.6 (9.5)	16.1 (22.9)
Enamine-proline	4.6 (4.8)	0.0 (0.0)	10.2 (11.4)	10.8 (16.6)

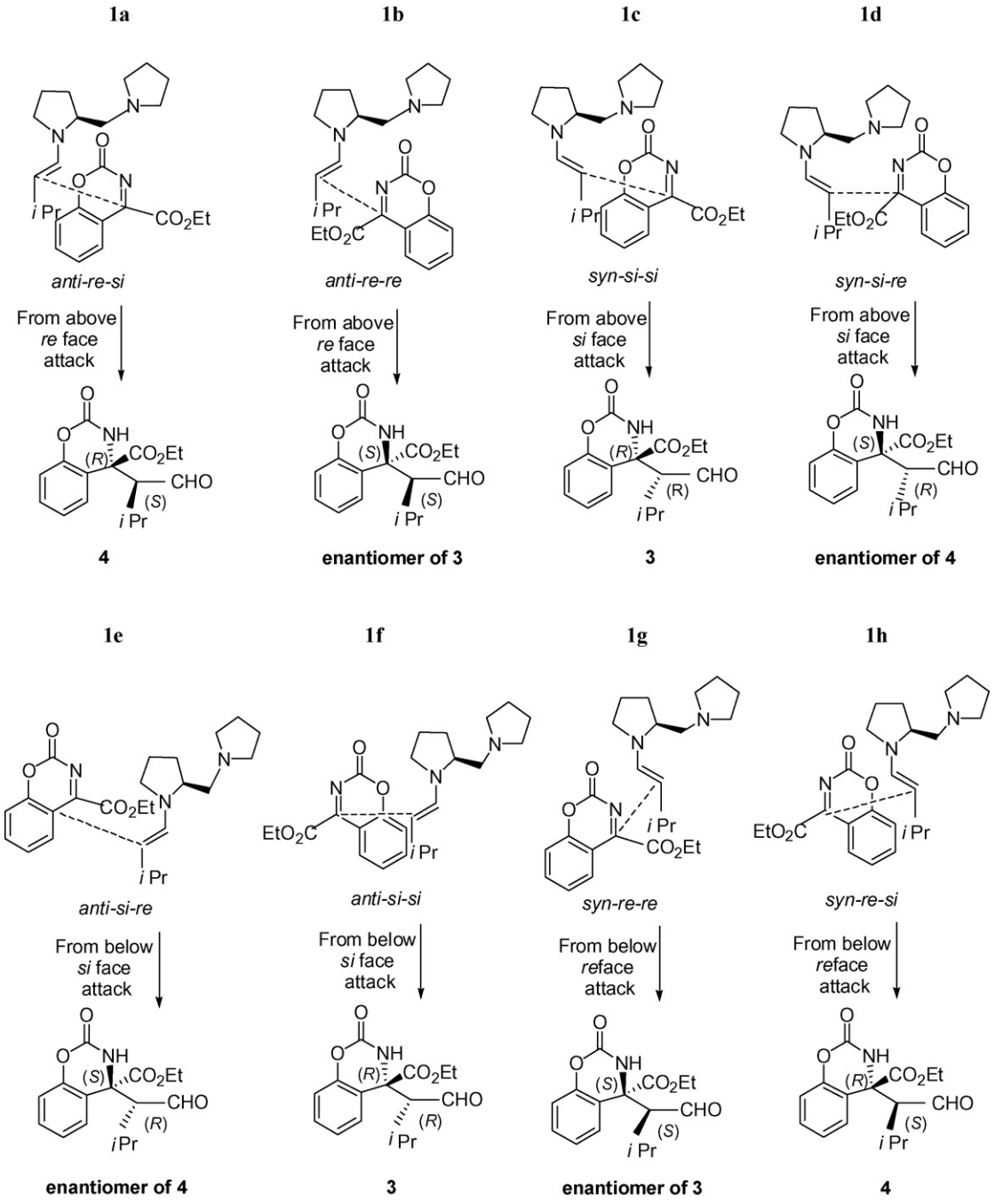
[a] CPCM values in CH_2Cl_2 are shown in parentheses.

3.1. (S)-1-(2-pyrrolidinylmethyl) pyrrolidine-catalyzed process

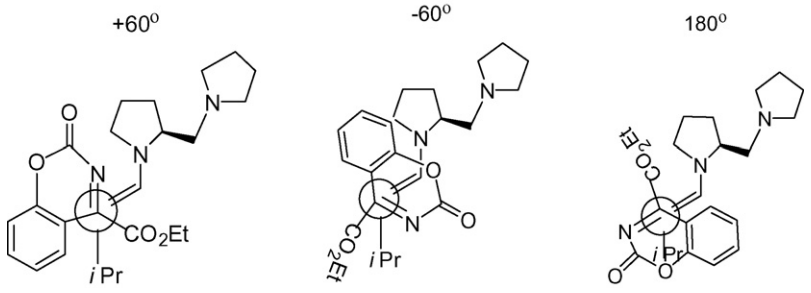
We first explored the different isomers of the enamine intermediates formed between catalyst B and isovaleraldehyde **2**. Since the enamine can rotate about the C_α-C_β (α and β shown in Scheme 1) and the C—N bond, and the five-membered pyrrolidine ring have different orientations, thus more isomers have been considered. Table 1 only lists the relative energies for the four most stable isomers (CPCM values in CH_2Cl_2 are presented in parentheses). Whether in the gas phase or in solution phase, there is only a slight energy difference between the *anti*- and the *syn*-isomers of the (*E*)-enamine. As expected, (*E*)-enamine is more stable than (*Z*)-enamine, and inclusion of the solvent slightly affects the energy difference. In addition, since *anti*-(*Z*)-enamine is only 8.6 kJ/mol higher in energy than the most stable one, the reactive channels involving the (*Z*)-enamine can not be safely excluded in the discussion of the stereoselectivity. Therefore, we have considered several reactive channels involving the (*Z*)-enamine. However, in all cases, the TSs involving (*Z*)-enamine are computed to be more than 26 kJ/mol higher in energy than the most stable one, and are, therefore, not discussed further.

Eight TS orientations involving (*E*)-enamine that generate four stereoisomers have been envisioned in Scheme 3. The notation used for the TSs, for example, '*anti*' in 'anti-*re*-*si*' is consistent with previous conventions, '*re*' denotes as the *re* face of enamine, while '*si*' means the *si* face of imine. These TSs can be divided into two types that differ in the attack on the opposite face of enamine intermediate (Type I: **1a-1d**, above face attack, Type 2: **1e-1h**, below face attack), which means that products generated by TSs **1e-1h** are enantiomers of those by TSs **1a-1d** correspondingly. In addition, for each of these TSs shown in Scheme 3, the enamine and the imine may adopt three different staggered arrangements about the forming C—C bond, resulting in three rotameric TSs. For example, three representative arrangements of these TSs of **1a** are shown in Scheme 4. Moreover, the conformational flexibility of the CO_2Et group in ketimine and the *i*-Pr group in enamine dramatically increases the number of the possible TSs. Hence, there are a large number of TSs to be considered computationally. As an example, eight TS structures corresponding to the attack mode of **1f** which lead to the experimentally observed major product **3** are illustrated in Fig. 1. These include three rotameric TSs about the forming C—C bond (**1f**, **1f-1**, and **1f-2**), three corresponding TSs arising from the different orientation of the CO_2Et group in **1f**, **1f-1**, and **1f-2** (**1f-3**, **1f-4**, and **1f-5**), and another two TSs corresponding to the different conformation of *i*-Pr in 1f (**1f-6** and **1f-7**). We have also performed similar calculations for the TSs leading to the other product isomers (corresponding to the modes of **1b-1h** shown in Scheme 3). For simplicity, only the optimized lowest energy TSs for each arrangement are presented in Fig. 2.

Among these eight lower energy TSs in Fig. 2, the most favored one **1f** involving the attack of the back face of *anti*-(*E*)-enamine to the *si* face of ketimine, which leads to the experimentally observed



Scheme 3. Eight TS arrangements of (*E*)-(*S*)-1-(2-pyrrolidinylmethyl) pyrrolidine-enamine and ketimine along the forming C—C bond that generate the four diastereomers.



Scheme 4. Three rotameric TSs of **1a** involving the C=N group of ketimine with dihedral angles of ±60° and 180° relative to the C=C bond of the enamine.

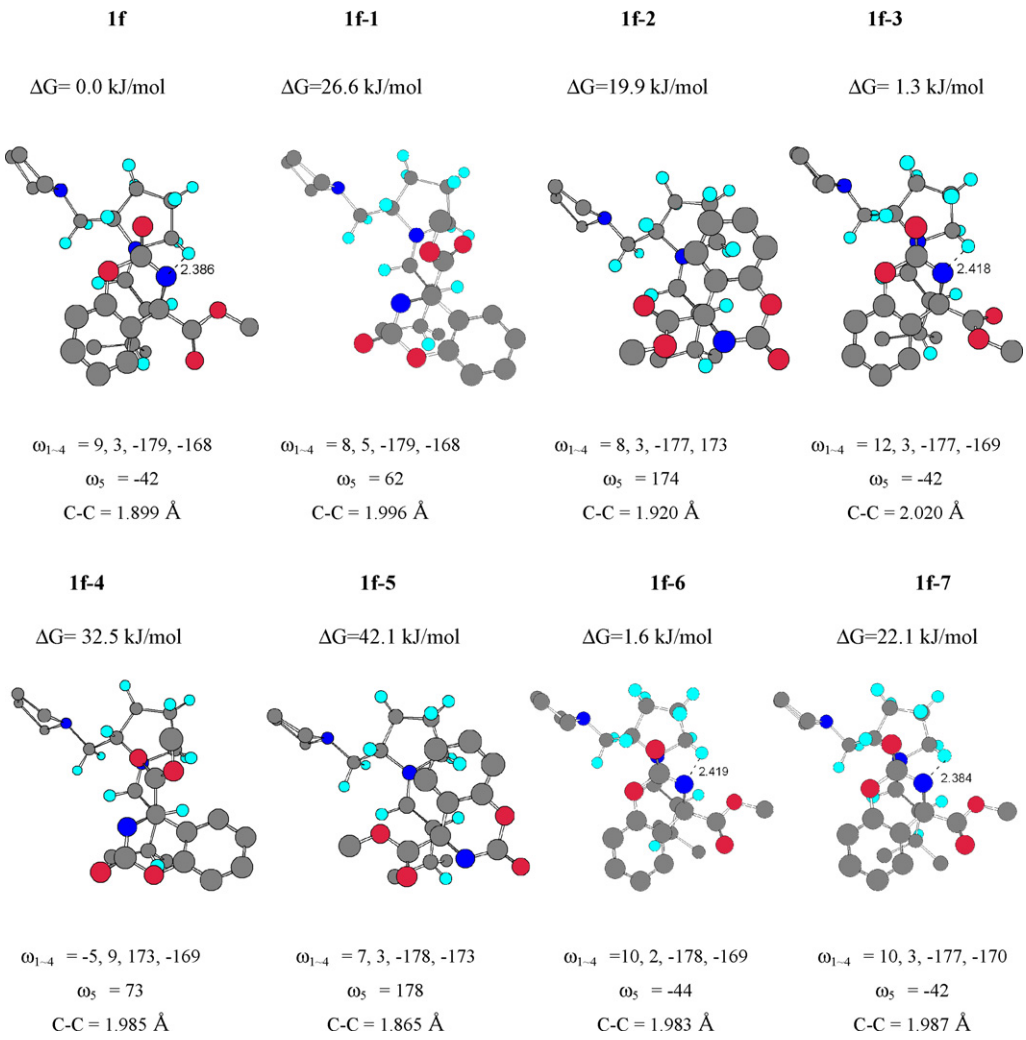


Fig. 1. Eight possible transition structures that generate the major product 3 from the *si* face of enamine attacking the *si* face of imine for the reaction of the (*S*)-1-(2-pyrrolidinylmethyl) pyrrolidine-enamine of aldehyde **2** with ketimine **1**. Relative free energies at BH and HLYP/6-31G* level are also shown. For clarity, some of the hydrogen atoms at the periphery are omitted.

major product of **3**. The minor product of diastereoisomer **4** mainly generated from the above *re* face attack to *anti*-(*E*)-enamine of the *si* face of ketimine (**TS 1a**) requires a higher free energy barrier (4.1 kJ/mol in gas phase, and 6.5 kJ/mol in CH_2Cl_2), thus the diastereoselectivity (dr = 2:1–15:1 in CH_2Cl_2) [7a] can be explained. The enantiomer of product **3** is mainly formed through TS **1b** corresponding to the front face of *anti*-(*E*)-enamine attacking the *re* face of ketimine, which lies 4.8 kJ/mol higher in energy than the most stable one in the gas phase. This free energy difference increases to 6.7 kJ/mol when the solvent effect is taken into account, which is in good agreement with the experimental results (86–88%ee in CH_2Cl_2) [7a].

To validate the above results at the BH and HLYP/6-31G* computational level, we have reoptimized above eight important TSs shown in Fig. 2 using the 6-31G** basis sets. The calculated free energy differences are also listed in Fig. 2, which indicate 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.

Figs. 1 and 2 also provide numerical values for several geometric parameters that are relevant for the relative stability of different TSs. These include the lengths of the forming C—C bond, the distances involved in the electrostatic interactions, 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 that represent the different rotamers involving the C=N group of the ketimine relative to the C=C bond of the enamine along the forming C—C bond (ideally ±60° and 180° for staggering conformation, see Schemes 1 and 4). As shown in Figs. 1 and 2, the lengths of the forming C—C bond are generally around 1.9–2.0 Å, thus somewhat shorter than those in the proline and other amino acids-catalyzed Mannich reactions involving aldimine [8]. Further analysis of the geometric arrangements of the above TSs that lead to the four different diastereoisomers allows us to identify the origin of the stereoselectivity in the reaction. The following factors may contribute to the enantioselectivity and diastereoselectivity. First, the different arrangements of the ketimine and the enamine along the forming C—C bond can affect the relative stability of different TSs (ω_5 shown in Scheme 1 and Figs. 1 and 2). Of course, intramolecular electrostatic interaction and steric repulsion may change the ideal arrangement from the staggering to the more eclipsed ones (for example, in Figs 1 and 2, ω_5 have deviated from the ideally ±60° and 180° to different extent). As shown in Fig. 1, the energetically most accessible TSs **1f** ($\omega_5 = -42°$) is much lower in energy than its two rotameric TSs (**1f-1**: $\omega_5 = 62°$, **1f-2**: $\omega_5 = 174°$). Similarly, there is also large energy difference between different rotameric TSs corresponding to the other seven attack modes (**1a-1e** and **1g-1h** shown in Scheme 3), which indicates that the dihedral angles ω_5 involving the C=N group of the ketimine relative to the C=C bond of the enamine

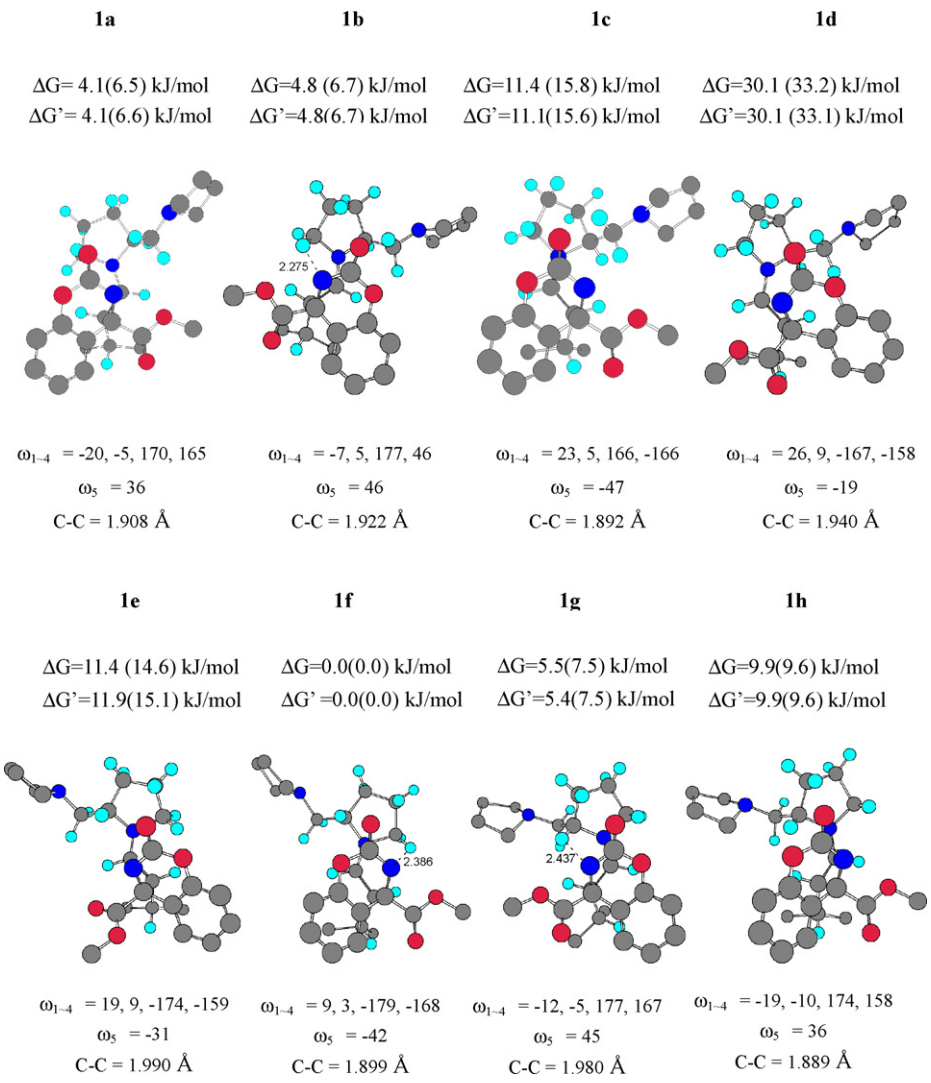


Fig. 2. Eight transition structures that lead to the four different diastereoisomers. Relative free energies ΔG at BH and HLYP/6-31G* level ($\Delta G'$ at 6-31G** level) for the reaction of the (*S*)-1-(2-pyrrolidinylmethyl) pyrrolidine-enamine of aldehyde **2** with ketimine **1** are shown. Values in parentheses including solvation energies in CH_2Cl_2 using the CPCM/UAKS model. For clarity, some of the hydrogen atoms at the periphery are omitted.

play an important role in the stability of different TSs. For simplicity, the less stable rotameric TSs have been excluded in the further discussion and only eight lowest ones are illustrated in Fig. 2. Furthermore, it should also be emphasized that: contrary to the ideal linear TS proposed by Jørgensen et al. ($\omega_5 = 180^\circ$ in Scheme 2b), its rotameric TS **1f** ($\omega_5 = -42^\circ$ in Fig. 1), which corresponds to the ideal TS ($\omega_5 = -60^\circ$) in Scheme 2c, is calculated to be the most stable one while **1f-2** ($\omega_5 = 174^\circ$ in Fig. 1 corresponding to Scheme 2b) is nearly 20 kJ/mol higher in energy. Second, scrutiny of the geometrical parameters of the eight low-lying TSs in Fig. 2, we can deduce that the favorable electrostatic interaction between the $^{+\delta}$NCH–N$^{\delta-}$ (distances: 2.2–2.4 Å) contributes greatly to the three lowest TSs of **1a**, **1b**, and **1f**, while this favorable interaction is absent in the other higher energy TSs. The third factor that regulates the stereoselectivity arises from the different steric effect in the TSs. Obviously, there is no repulsive interaction between the protecting group of the ketimine and the pyrrolidinylmethyl of the enamine in the TSs occurring at the below face of enamine (**1e-1h** in Fig. 2). However, when the ketimine approaches the enamine from its above face (**1a-1d**), the protecting group of ketimine interacts unfavorably with the pyrrolidinylmethyl, thus leads to the higher energy of the TSs. Finally as has been pointed out previously [8,9], the stereoselectivity partially arises from the different degrees to which each diastereomeric TSs satisfies iminium planarity. The more stable TS is always associated with a "more planar" iminum moiety. For example, there is much less out-of-plane deformation of iminium in the more stable TSs of **1a**, **1b**, and **1f** shown in Fig. 2. In summary, the interplay between these factors ultimately determines the relative energies of the various TSs and the main source of the stereoselectivity is arising from the favorable electrostatic interaction between the $^{+\delta}$NCH–N$^{\delta-}$ and the minimization of the steric repulsion between the protecting group of ketimine and the pyrrolidinylmethyl of the enamine.

3.2. Proline-catalyzed process

Although the computational studies of the proline-catalyzed Mannich reactions have been performed, the investigation has been limited to the reactions involving aldimine [8]. For the sake of comparison with the reaction involving ketimine, we carry out a theoretical calculation of the proline-catalyzed Mannich reaction between isovaleraldehyde **2** and ketimine **1** shown in Eq. (1). Similarly, the four isomers of the proline-enamine were first explored and the relative free energies at BH and HLYP/6-31G* level are also shown in Table 1.The results indicate that the (*E*)-enamine are more stable than their (*Z*)-enamine counterparts and the *syn*-(*E*)-

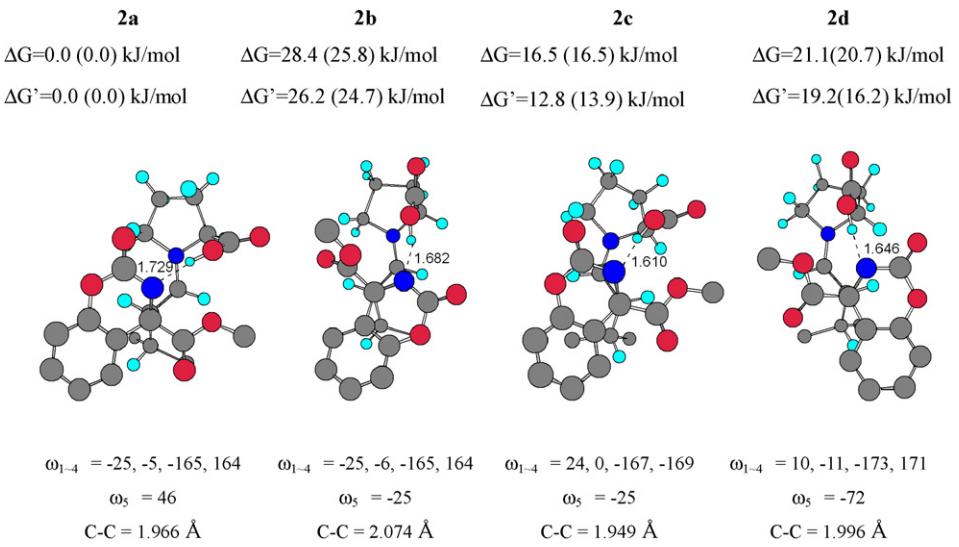


Fig. 3. Transition structures that lead to the four different diastereoisomers. Relative free energies ΔG at BH and HLYP/6-31G* level ($\Delta G'$ at 6-31G** level) for the reaction of the proline-enamine of aldehyde **2** with ketimine **1** are shown. Values in parentheses including solvation energies in CH_2Cl_2 using the CPCM/UAKS model. For clarity, some of the hydrogen atoms at the periphery are omitted.

enamine is the most preferred one among them. The inclusion of the solvent has little effect on the relative energies and the stability order.

Unlike the (*S*)-1-(2-pyrrolidinylmethyl) pyrrolidine-catalyzed process, the pioneering experimental and theoretical studies about the proline-catalyzed direct aldol, Mannich and other related transformations [2,4,8–10] involving enamine intermediate have shown that the proton transfer from the carboxylic acid group of proline to the N or O atom of the electrophile is essential to the high stereoselectivity. Therefore, for the cases that lack such proton transfer process, e.g. TSs occurring from the below face attack to the enamine by the ketimine are expected to be unfavorable and can be safely excluded in the discussion of the stereoselectivity. On the basis of the above discussion involving the (*S*)-1-(2-pyrrolidinylmethyl) pyrrolidine-catalyzed process, only four lowest TSs corresponding to the four stereoisomers that are *syn*- and *anti*-diastereomeric pairs of enantiomers have been shown in Fig. 3. Scrutiny of the geometrical parameters of the TS structures allows us to identify the difference between the aldimine and ketimine involving in the enamine-catalyzed Mannich reaction. The pioneering computational studies of the proline-catalyzed Mannich reactions involve aldimine [8] have established that all of the TSs have the carboxylic acid proton completely transferred to the imine, with the forming C—C single-bond lengths of 2.2–2.4 Å and the hydrogen bond of NH···O having lengths of 1.6–1.9 Å. This substantial ionic interaction between an iminium and the carboxylate is the common features of proline-catalyzed Mannich reactions proposed by Houk's group [8]. However, in the proline-catalyzed Mannich reactions involving ketimine, the TS structures are characterized by a relatively shorter forming C—C bond (about 2.0 Å). Most importantly, the acidic proton of the proline carboxylic acid moiety has not transferred to the imine and only formed the hydrogen bond interaction with the bond lengths in different TSs being 1.6–1.7 Å. This means that the proton transfer is later than the C—C bond-forming process, which is contrary to the previous theoretical results of the Mannich reaction involving aldimine.

Among these four TSs, **1a** involving the *si* face of ketimine attacking the *re* face of *anti*-(*E*)-enamine, requires the lowest activation energy and leads to the experimentally observed major product **4**. The enantiomer of **4** is formed through TS **2d** which corresponds to the *re* face of ketimine attacking the *si* face of *syn*-(*E*)-enamine. This TS structure lies 19.2 kJ/mol (16.2 kJ/mol in CH_2Cl_2) higher in energy, which is consistent with the experimental results (82%ee) [7a], but somewhat overestimated. The diastereoisomer of **3** also requires a higher energy barrier (12.8 kJ/mol in gas phase, and 13.9 kJ/mol in CH_2Cl_2) and there is also somewhat overestimation over the experimental dr value (dr = 8:1) [7a]. However, the absolute error can be tolerable.

Now, the origin of the opposite diastereoselectivities in the direct Mannich reactions when the carboxylic acid functionality of proline catalyst was replaced by a non-acidic substituent can be explained as the direct consequence of the different structure and properties of the two catalysts leading to two different TSs. For the proline-catalyzed process, the hydrogen bonding interaction between the acidic proton of carboxylic acid moiety and the imine directs the reaction mainly occurring at the above *re* face of the enamine and subsequently determines the stereoselectivity. This is in good agreement with the TS model proposed previously [8]. In stark contrast, (*S*)-1-(2-pyrrolidinylmethyl) pyrrolidine (catalyst B) does not have the acidic proton and the hydrogen bonding between the enamine intermediate and the lone pair of electrons on the nitrogen atom of the ketimine can not occur, the new controlling factors should be considered to direct the reaction face of enamine. According to our calculation about the (*S*)-1-(2-pyrrolidinylmethyl) pyrrolidine-catalyzed process, the steric repulsion between the protecting group of ketimine and the pyrrolidinylmethyl group, and the favorable electrostatic interaction between the $^{\delta+}$NCH–N$^{\delta-}$ combine to contribute greatly to the stereoselectivity and direct the reaction mainly occurring from the *si* face of imine attacking the below *si* face of enamine, while the above *re* face attack to enamine is relatively unfavorable because of the steric shielding or lack of the electrostatic interaction. Our calculations confirmed Jørgensen's hypothesis that the reaction mainly occurs at the *si* face of the imine and the *si* face of the enamine (Scheme 2c), but their linear TS model (Scheme 2b) is not supported theoretically. Moreover, it can also be deduced that, when catalyst F of α,α-diarylprolinol silyl ether was used in the Mannich or other related transformations, the steric repulsion between the electrophile and the large aryl and silyl substituents on the α-position of the pyrrolidine ring can efficiently shield the *re* face of the enamine and makes that only the below *si* face can be attacked by the electrophile, e.g. imine in the Mannich reaction. As a consequence, the excellent enantioselectivity can be obtained by the employment of a more bulky chiral amine catalyst. This efficient face shielding strategy has been

successfully applied in many reactions by Jorgensen and Córdova's group [6,7].

4. Conclusions

The transition structures associated with the C—C bond-formation step of the (*S*)-1-(2-pyrrolidinylmethyl) pyrrolidine and proline-catalyzed direct Mannich reactions involving ketimine and aldehyde have been studied using BH and HLYP method 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 enamine have been studied. Our calculations confirm that the opposite diastereoselectivities found with the (*S*)-1-(2-pyrrolidinylmethyl) pyrrolidine and the proline catalysts arises from the different nature of the TS. The hydrogen bond interaction between the acidic proton in proline and the N atom of ketimine makes the above *re* face attack to enamine most preferred while the steric shielding and electrostatic interaction combined to induce the below *si* face attack to enamine most favorable in (*S*)-1-(2-pyrrolidinylmethyl) pyrrolidine-catalyzed process. It can be deduced that the more bulky substituent on the α-position of the pyrrolidine ring would resulting more efficient face shielding and makes the electrophilic attack only occurs from the below *si* face of enamine. The calculated diastereomeric ratio and enantiomeric excess are in good agreement with experimental results.

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