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Theoretical studies of the direct anti-Mannich reactions catalyzed by chiral 3-trifluoromethanesulfonamido-pyrro-lidine

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Abstract

Density functional calculations have been performed to study the stereoselectivities in the direct anti-Mannich reactions catalyzed by chiral 3-trifluoromethanesulfonamido- pyrroli- dine. Transition states of the stereochemistry- determining C-C bond-forming step with the enamine intermediate addition to the imine for the subject Mannich reactions are reported. BH and HLYP/6-31G** calculations provide a good explanation for the anti-diastereoselectivities in the chiral pyrrolidine-based amino sulfonmide- catalyzed Mannich reactions. Calculated and observed diastereomeric ratio and enantiomeric excess values are in reasonable agreement.

1. Introduction

The asymmetric Mannich reaction is one of the most powerful carbon-carbon bond-forming reactions in the construction of chiral buildingblocks for the synthesis of structurally complex molecules, e.g. natural products or non-natural drug molecules [1]. 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. and Barbas et al.[3] that proline could act as a catalyst in direct threecomponent Mannich reactions, organocatalytic direct asymmetric Mannich-type reactions have been a highly active research area, and thus many metalfree chiral catalysts [3-9], which include Brønsted acid [4a,4b], cinchona alkaloids [4c,4d], proline derivatives and linear amino acid derivatives [5-9], have been developed for this transformation, all attempting to reach high levels of efficiencies and to widen the scope of substrates. Over the past years, excellent *syn* diastereo- and enan- tioselectivity were achieved employing (*S*)- proline and its derivatives, cinchona alkaloids and several acyclic α-amino acids [3-5]. Therefore, new routes which allow high enantio- and diastereo- *anti*-Mannich

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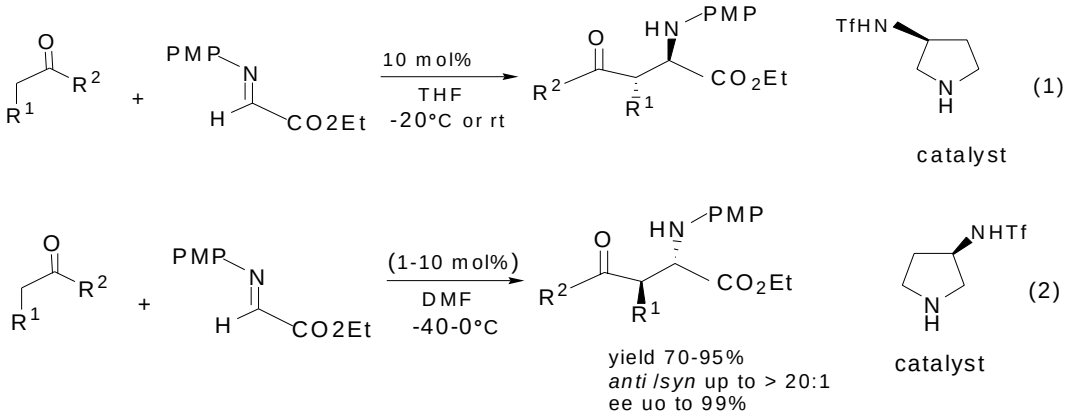
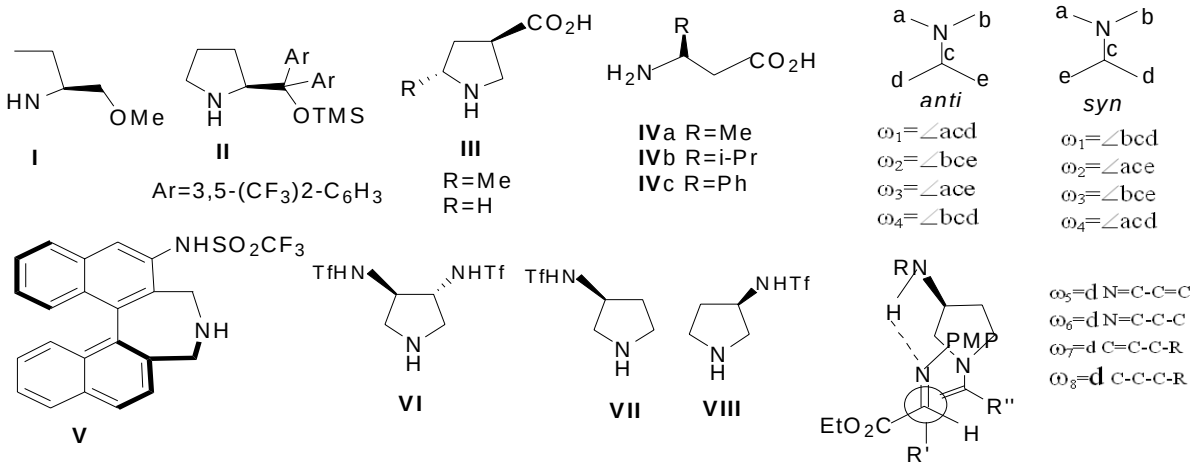
reactions become to be an appealing area and have received much research interest [6-9]. The first *anti*-selective asymmetric Mannich reaction between unmodified aldehydes and N-PMP- protected α-imino ethyl glyoxylate was reported by Córdova and Barbas in 2002 using 20% mol of (*S*)-2-methoxymethyl-pyrrolidine (SMP) (catalyst I in Scheme 1) as catalyst [7a]. The reactions give the products in good yields (44-78%) with *anti*-selectivity ranging from 1:1 to >19:1 dr and good enantioselectivities (74-92%ee). Later, Jorgensen et al. [8b] and Córdova et al. [7b] have also reported the similar catalyst of α,α-diarylprolinol siyl ether (catalyst II in Scheme 1) in the same direct catalytic Mannich-type reactions which afford the products with highly *anti*- and enantio-selectivities. The mechanism of those organo-catalyzed *ani*-Mannich process represents the concept of the new asymmetric induction strategy and has proposed to be controlled by the efficient steric shielding instead of the commonly used hydrogen-bonding concept [10]. Very recently, Barbas's group has designed the new pyrrolidine derivatives of *β*-amino acid catalysts e.g. (*3R, 5R*)-5-methyl-3- pyrrolidine-carboxylic acid and (*R*)-3-pyrrolidinecarboxylic acid (catalyst III in Scheme 1) for the *anti*-selective Mannich-type reactions of aldehydes and ketone with imine [6d-6f]. The *anti*-Mannich products were obtained with high stereoselctivities. Thereafter, Córdova and coworkers have also reported the primary amine containing acyclic β^3-amino acids (catalyst IV in Scheme 1)-catalyzed direct asymmetric *anti*-selective Mannich-type reactions between ketones and α-imino ester with high diastereo- and enantioselectivity (up to >19:1 dr, 88-99%ee) [6k]. Above two experimental results indicate that the position of the carboxylic acid functionality e.g. *α* or *β* in the amino acids catalysts directs the stereoselection of the reaction. Besides all above important *anti*- Mannich reactions, Maruoka and co-workers have designed a new type of axially chiral amino sulfonamide catalysts (catalyst V-VI in Scheme 1) [6a-6b], which has a rigid and readily derivatizable binaphthyl backbone, for the highly *anti*-selective asymmetric Mannich reaction between different aldehydes and N-PMP-protected α-imino glyoxylates. However, this compound is limited in the Mannich reaction mainly with linear aldehydes as donor. To circumvent this limitation, pyrrolidine-based amino sulfonamides (catalyst VII in Scheme 1) have been successfully developed by Maruoks's group for the Mannich reactions [6c]. High diastereo- and enantiose- lectivities were obtained with different aldehydes and ketones as Mannich donors (*eq*.1). Interestingly, Pouliquen and Blanchet [9] have also reported the excellent performance of the same 3-trifluoromethane- sulfonamido- pyrroli- dine catalysts (catalyst VIII in Scheme 1) for the direct *anti*-selective Mannich reactions between glyoxylate imine and various aldehyde or ketone (*eq*.2). The only difference between the catalysts of Maruoka's and Blanchet's is that they are enantiomers as shown in eq1-2. The broad scope and the easily available properties observed in the experiment reflect the superiority of this type of catalyst.

Despite the above exciting results observed for catalyst VII and VIII with amino sulfonamide functionality, the interesting reversal of the diastereoselectivity when switching the catalyst from the popular (*S*)-proline to the new type of catalyst of amino sulfonamides VII or VIII calls for mechanistic and theoretical investigations. To the best of our knowledge, although great effort has been made to the general understanding of the mechanism of enamine catalytic reactions [10-13], there are no other theoretical investigations concerning this *anti*-Mannich processes involving the type of chiral pyrrolidine-based amino sulfonamide catalyst. Hence, to extend our understanding in the mechanism and stereoselectivity of the enamine catalytic reactions, the present theoretical study is performed to explain the



Scheme 1 shows the different *anti*-selective catalysts for Mannich reaction mentioned above.

Scheme 1



Catalysts used in the *anti*-selective Mannich reaction

definition of dihedral angles of enamine intermediate and transition state

origin of the chiral amino sulfonamide-catalyzed *anti*-selectivity in the Mannich reaction involving aldehyde and ketone as the donors.

2. Computational Methods

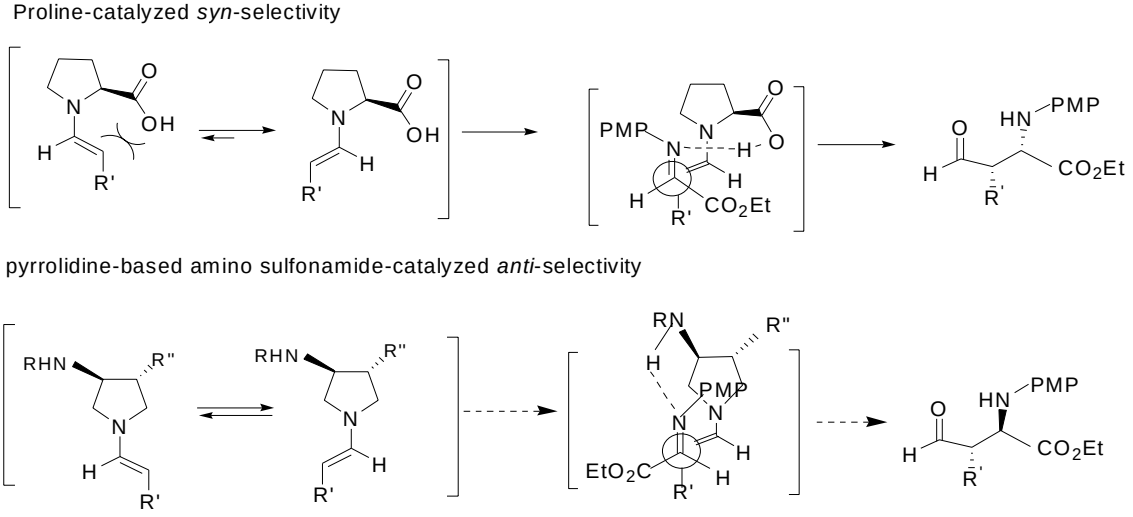
All ground state and transition state (**TS**) geometries were located using density functional theory (DFT) and the BH and HLYP hybrid functional [14] since this functional has satisfactorily reproducing the experimental results in several organocatalyzed Mannich reactions [15]. The standard 6-31G** basis sets were employed throughout. All TS geometries were fully optimized and characterized by frequency analysis. The bulk effects of the solvent (THF) on the enamine mechanism have been taken into account by means of a dielectric continuum represented by the polarizable conductor calculation model (CPCM) [16], with united–atom Kohn-Sham (UAKS) radii. The single-point continuum calculations were done upon the optimized gas phase geometries with a dielectric constant ε=7.58 for THF. All calculations were carried out using the Gaussian 03 program [17].

3. Results and Discussion

Actually, Maruoka's *anti*-Mannich studies are based on their original hypothesis (Scheme 2) [6c]: when L- proline is used as the catalyst, the observed *syn*-selectivity of the product results from the *anti*-enamine conformation reacting with the *si* face of the imine in the C-C bond forming step, which has been proposed and confirmed by Barbas, List [3], and Houk [11] et al. for the catalytic enantioselective Mannich reactions. While for the Maruoka's chiral pyrrolidine-based amino sulfonamide catalyst,

the proton donor functional group switched from α- position to the β-position, and therefore both enamine conformations of *anti* and *syn* may be similarly favored. However, the key for the formation of the *anti*-Mannich product is that the *syn*-enamine approaching the *re* face of imine should advance the C-C bond formation predominantly since the nucleophilic carbon of *anti*-enamine should be too far from the imine electrophilic carbon to form a bond which activated by the more remote acidic proton. This means the reaction selectivity has been changed from *syn* to *anti* due to the reaction face of enamine being reversed from that of the proline-catalyzed process (**Scheme 2**).

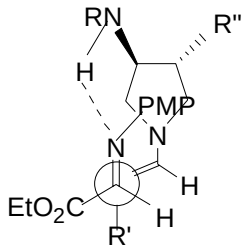
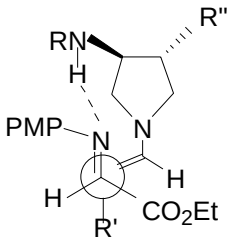
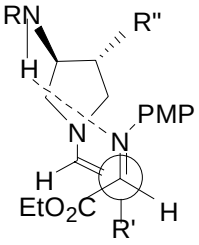
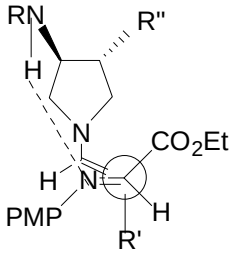
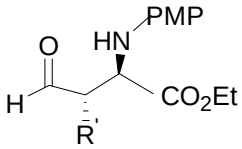
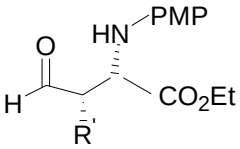
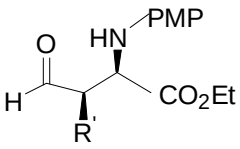
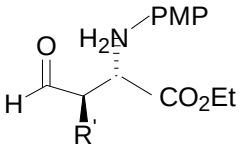
Scheme 2



On the basis of their design considerations, we then performed the density functional theory calculations on the stereochemistry-determining step of 3-trifluoromethanesulfonamido-pyrrolidine-catalyzed Mannich reactions. We have used catalyst VII shown in Scheme 1 as the prototype catalysts, and Eq.1 as the model reaction (for simplicity, propionaldehyde and cyclohexanone were chosen as the prototype donors in Eqs.1). The notation used for the transition states in the calculation has also been shown in Scheme 1.

Analogous to the previous investigations of the enamine-catalyzed aldol and Mannich reactions [10-13], we focused our attention on the TSs for the enamine attack to the imine. This is expected to be the stereochemistry-controlling step of the reaction and thus was studied in order to understand the observed diastereo- and enantioselectivities. Since (*Z*)-imine is much higher in energy than (*E*)-imine, and (*Z*)-enamines are also more than 20kJ/mol higher in energy than their counterparts of (*E*)-enamines, then the reactive channels involving the (*Z*)-enamine and (*Z*)-imine can be safely excluded in the discussion of the stereoselectivities. Therefore, only four possible pathways corresponding to the *syn-E* and *anti-E* orientation of the enamine double bond relative to the the sulfonamide group and the two diastereoisomeric approach modes to the *si* and *re* faces of imine acceptor have been investigated in the reaction (shown in Scheme 3). The transition state structures corresponding to four stereoisomers that are *syn*- and *anti*-diastereomeric pairs of enantiomers for the reaction of the enamine of propionaldehyde and N-PMP-protected α-imino methyl glyoxylate have been illustrated in Figure 1. The similar TSs involving the enamine of cyclohexanone have shown in Figure 2**.** The notation used for the TSs, for example, '*anti*' in '*anti-re*' is consistent with previous conventions, '*re*' denotes as the *re* face of imine.

Scheme 3 Different TS arrangements of enamine and imine along the forming C-C bond that generate the four diastereomers.

a	**b**	**c**	**d**
			
syn-re	*syn-si*	*anti-re*	*anti-si*
			

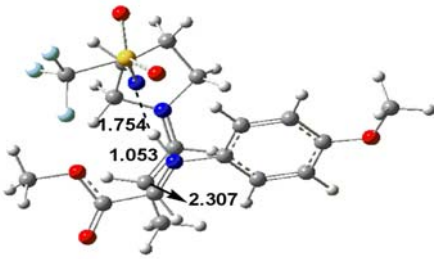
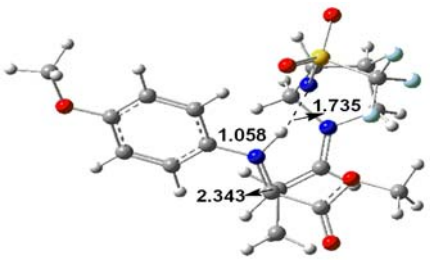
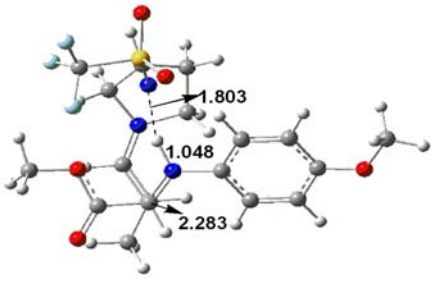
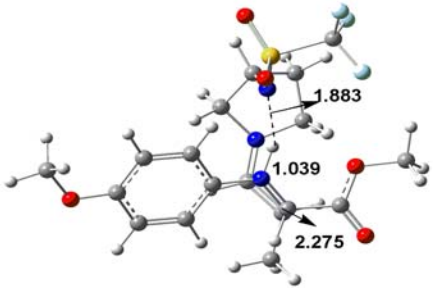
1a	**1b**
ΔH = 0.0 (0.0) kJ/mol	**ΔH = 12.3 (14.1) kJ/mol**
	
$\omega_{1\text{-}4}$ = -8, -4, 180, 168 $\omega_{5\text{-}8}$ = 13, 11, 137, 139	$\omega_{1\text{-}4}$ = -3, -10, -178, 166 $\omega_{5\text{-}8}$ = 77, -159, -50, 73
1c	**1d**
ΔH = 5.8 (5.1) kJ/mol	**ΔH = 12.4 (11.7) kJ/mol**
	
$\omega_{1\text{-}4}$ =14, 14, -159, -173 $\omega_{5\text{-}8}$ = -66, 171, 61, -62	$\omega_{1\text{-}4}$ = 13, 11, -158, -178 $\omega_{5\text{-}8}$ = -3, -128, -131, 106

Figure 1. BH and HLYP/6-31G** optimized transition structures that lead to the four different diastereoisomers. Relative energies for the reaction of the (S)-3-enamine of propionaldehyde with imine are shown. CPCM values in THF are shown in parentheses. Distances are given in angstroms and angles are in degree.

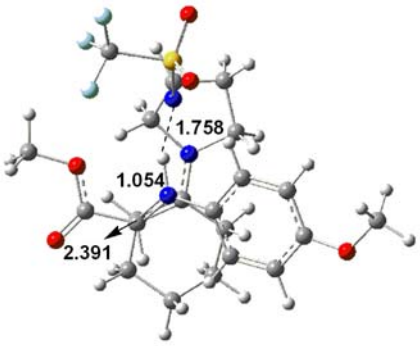
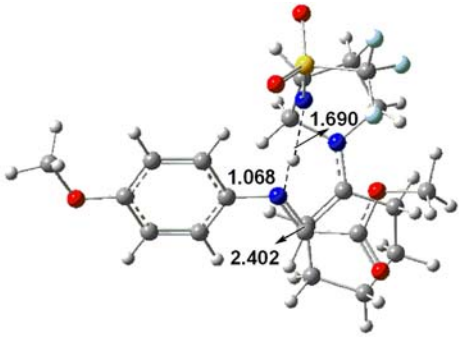
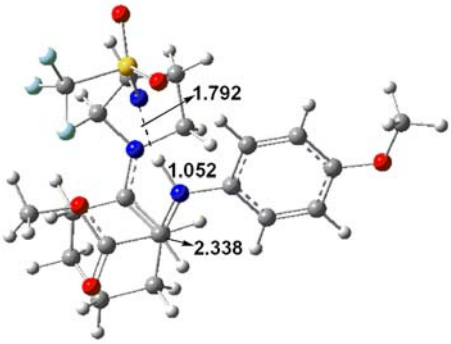
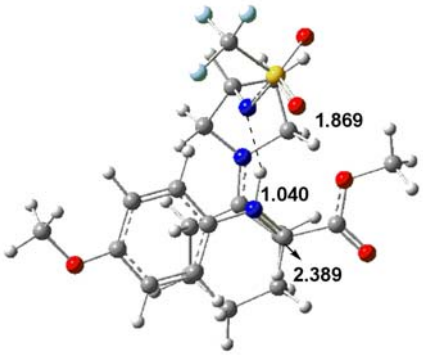
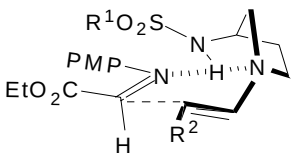
2a	2b
ΔH = 0.0 (0.0) kJ/mol	**ΔH = 9.9 (12.6) kJ/mol**
	
$\omega_{1\text{-}4}$ =-11, -8, 173, 168 $\omega_{5\text{-}8}$ = 17, 142, 142, -92	$\omega_{1\text{-}4}$ =-9, -15, 174, 163 $\omega_{5\text{-}8}$ = 84, -149, -44, 83
2c	**2d**
ΔH = 5.7 (6.3) kJ/mol	**ΔH = 13.1 (15.8) kJ/mol**
	
$\omega_{1\text{-}4}$ =-21, 24, -161, -155 $\omega_{5\text{-}8}$ = -71, 162, 57, -70	$\omega_{1\text{-}4}$ =13, 21, -171, -156 $\omega_{5\text{-}8}$ = -6, -130, -131, 105

Figure 2. BH and HLYP/6-31G** optimized transition structures that lead to the four different diastereoisomers. Relative energies for the reaction of the (S)-3-enamine of cyclohexanone with imine are shown. CPCM values in THF are shown in parentheses. Distances are given in angstroms and angles are in degree.

As shown in Figure 1 and Figure 2, all of the transition states have the acidic proton completely transferred to the imine, with the forming C-C single bond having lengths of 2.20-2.40 Å. This substantial ionic interaction between an iminium and the TfN^- is the common feature of the proline-catalyzed Mannich reactions proposed by Houk's group [11]. The C-C lengths at the process involving propionaldehyde are slightly shorter than those associated with cyclohexanone. Furthermore, Blanchet et. al [9] have proposed a rigid transition state involving a three-centered hydrogen bond as shown in Scheme 4. However, we could not find the evidence for the favorable hydrogen bond interaction between the nitrogen atom of the pyrrolidine ring and the NH of the sulfonamide group. Only the two-centered common hydrogen bond which is usually presented in the aldol and Mannich reaction has been found during the calculation.

Scheme 4 Postulated transition state involving a three-centered hydrogen bond by Blanchet et. al.



Among the four TSs for the 3-trifluoromethanesulfonamido-pyrrolidine-catal

yzed process, whether for the reactions involving propionaldehyde or the cyclohexanone, the most stable one 1a or 2a involves the attack of the *syn*-enamine to the *re* face of imine, which leads to the experimentally observed major (2*R, 3S*)-*anti*-product. The (2*R*, 3*R*)-diastereoisomer is mainly formed through TS **1c** (TS**2c**) corresponding to the *anti*-(*E*)-enamine attacking the *re* face of imine, which lies 5.8 (5.7) kJ/mol higher in energy than the most stable one **1a (2a)** in the gas phase. This energy difference changes to 5.1(6.3) kJ/mol when the solvent effect is taken into account. Thus the observed *anti/syn* ratio (14:1 for propionaldehyde and >20:1 for cyclohexanone) can be explained. The (2*S, 3R*)-enantiomer generated from the attack of the *anti*-(*E)*-enamine to the *si* face of imine also requires a higher energy barrier (12.4 and 13.1kJ/mol in the gas phase, 11.7 and 15.8 kJ/mol in THF), which is in good agreement with the experimental results (98%ee and 99ee%).

Figures 1 and 2 also provide Numerical values for several geometric parameters that are relevant for the relative stability of different TSs. These include the dihedral angles ω1-4 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 ω5-8 that represent the different arrangements of imine and enamine along the forming C-C bond (ideally ideally ±60° and 180° for staggering conformation). As has been pointed out in the previous proline and its derivatives-catalyzed aldol and Mannich process [10-13], the following factors may contribute to the enantioselectivity and diastereoselectivity. First, the stereoselectivity partially arises from the different degrees to which each diastereomeric transition states satisfies iminium planarity. Generally, the more stable TS is always associated with a “more planar” iminum moiety. Comparing the dihedral angles ω1-4 of TS 1a and 1b (2a and 2b) illustrated in Figure. 1(and Figure 2) with their counterparts of 1c and 1d (2c and 2d), we can see that there is more out-of-plane deformation of iminium in 1c and 1d (2c and 2d) than those in 1a and 1b(2a and 2b). This may ultimately determine the relative energies of the various TSs and make 1a (2a) being preferred over 1c(2c), which then subsequently switch the diastereoselectivity from *syn* in the proline-catalyzed process to *anti* in the 3-trifluoromethanesulfonamido-pyrrolidine-catalyzed one. The second factor that regulates the stereoselectivity is the different arrangements of imine and enamine along the forming C-C bond. Of course, intermolecular hydrogen bonding and steric repulsion may change the ideal arrangement from the staggering to the more eclipsed ones (ω5-8 shown in Scheme1 and Figures. 1-2). However, TSs with the more staggering orientation at the reaction center should be preferred over the other ones. These factors combine to affect the relative energies of the various TSs and subsequently the stereoselectivity. In summary, the origin of the *anti*-diastereoselectivities in the direct Mannich reactions when the trifluoromethanesulfonamide functionality is positioned at the more distant β-position can be explained as the direct consequence of the different spatial distance between amino and the hydrogen donor group of the different catalysts leading to two different TSs. In the L-proline catalyzed process, the α-positioned carboxylic acid group allows the *re* face of imine to react via the anti-(E)-enamine predominantly, giving rise to *syn*-isomers. In contrast, the more remote acidic proton in catalyst VII results in the large distortions of the developing iminium from planarity in the reaction of the *re* face of imine approaching the *anti*-(*E*)-enamine to achieve the proton transfer, directs the reaction mainly involving the *syn*-(*E*)-enamine attacking the *re* face of imine and makes the *anti*-isomer to be favored. Our calculated results satisfactorily support Maruoka’s design considerations.

Furthermore, if we compared this phenomenon with that reported by Barbas et.al in their

(*R*)-3-pyrrolidinecarboxylic acid-catalyzed *anti*-selective Mannich reactions [6d-6f], we can draw the conclusion that whether the proton donor is the carbonyl acid group or the amino sulfonamide functionality, the switching of those groups from α to β position would result in the inverse of the diastereoselectivity. Our calculations confirm the hypothesis by Barbas and Maruoka et. al that the position of the proton donor moiety plays a significant role in directing the stereochemical outcome of the organocatalyzed asymmetric Mannich reactions and the tuning of the proper distance between the amino group and the proton donor moiety in the catalyst to direct the stereochemical outcome of the reaction is the useful strategy in the asymmetric synthesis process.

4. Conclusions

The transition structures associated with the C-C bond-formation step of the 3-trifluoromethanesulfonamido-pyrrolidine-catalyzed direct Mannich reactions involving propionaldehyde and cyclohexanone have been studied using BH and HLYP method at the 6-31G** basis set level. For this stereo-controlling step, the reactive channels corresponding to the *syn* and *anti* arrangement of the enamine double bond relative to the amino sulfonamide group, and the two diastereoisomeric approach modes to the *re* and *si* faces of the imine have been studied. Our calculations further confirm the idea that tuning the proper distance between the amino group and the acid moiety in the catalyst can control the main reaction channels and subsequently the stereoselectivities. This is a very useful strategy to achieve different isomers in the asymmetric synthesis process.

Acknowledgement

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