

Mechanistic and enantioselectivity insights into a chiral phosphoric acid-catalyzed asymmetric aza-pinacol rearrangement to synthesis doleine

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A comprehensive mechanistic study on the chiral phosphoric acid catalyzed an enantioselective asymmetric aza-pinacol rearrangement of 4-chloro-*N*-(2-(3'-hydroxy-1'-phenylspiro[cyclopentane-1,2'-indolin]-3'-yl)ethyl) (**1a**) is investigated at the M06-2X/6-311+G(d,p) level. Our computational results suggest that the whole catalytic cycle proceeds through dehydration of **1a**, enantioselective aza-pinacol rearrangement, intramolecular cyclization and catalyst regeneration to deliver the fused indoline product. The aza-pinacol rearrangement is the key stereocontrolling step of the title reaction. The chiral catalyst controls the orientation of the transition states of the enantioselective step through two potential binding sites between the bifunctional chiral phosphate and the aza-ortho-xylylene intermediate. Moreover, theoretical studies identified that the multiple C—H $\cdots$ π , C—H $\cdots$ O, and C—H $\cdots$ N hydrogen bonds and N—H $\cdots$ O[−] electrostatic interactions between the substrates and the arms as well as functional oxygen anion of the chiral catalyst (*R*)-**4c** play a crucial role in determining the stereochemical outcomes. And the strong N—H $\cdots$ O[−] interaction in the major transition state was found to contribute to the high levels of enantioselectivity. Additionally, the predicted enantiomeric excess (*ee*) of 89% based on the 6.3 kJ·mol^{−1} energy difference between the enantioselective **TS-2-major** and **TS-2-minor** is in agreement with the experimental results of 90%.

Chiral phosphoric acid catalysis; aza-pinacol rearrangement; enantioselective; density functional theory

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1. Introduction

Heterocyclic compound, also called heterocycle, any of a major class of organic chemical compounds characterized by the fact that some or all of the atoms in their molecules are joined in rings containing at least one atom of an element other than carbon (such as nitrogen, oxygen, and sulfur). Heterocycles constitute the largest and most diverse family of organic compounds. Among them, nitrogen-based heterocycles receive the greatest attention, as they are of great importance to life science. Since, they are abundant in nature and widely existing as structural subunits in bioactive natural products, pharmaceuticals, agrochemicals, dyes, cosmetics, and functional materials.^[1-6] Of the myriad heterocycles known to man, the indole ring stands foremost for its remarkably versatile chemistry, its enormous range of

biological activities, and its ubiquity in terrestrial and marine environments.^[7-8] Due to the important applications of indole scaffolds, various synthetic methods have been developed to access indole moieties.^[9-13] However, developing methods to rapidly and directly construct these valuable scaffolds are still a big challenge. Pinacol^[14-17] and related semipinacol^[18-23] rearrangements have been extensively used in the total synthesis of natural products.^[24-27] Moreover, aza-pinacol rearrangement is a powerful approach for making nitrogen-containing heterocycles and natural alkaloids, however, it is rarely reported.^[28-32] This mainly arises from the weak driving force compared with the pinacol rearrangement and the relatively high activity of the rearrangement product (imine or iminium). Thus, the development of aza-pinacol rearrangement as synthetic methods remains a significant challenge.

Zhou et al. reported an asymmetric hydrogenation of the active intermediate generated from aza-pinacol rearrangement where the rearrangement itself is a racemic process.^[33]

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Interestingly, this was so far the only report with respect to the enantioselective asymmetric version of aza-pinacol rearrangement. In an exquisite demonstration, Zu and co-workers have reported the first catalytic enantioselective asymmetric aza-pinacol rearrangement^[34]. The reaction catalyzed by chiral phosphoric acid (*R*)-SPINOL proceeds with high yield (83% to 99%) and enantioselectivity (88% to 91%) on indolyl substrates. This methodology has been exploited in the key step toward the asymmetric synthesis of a key intermediate to the natural product minfiensine and the identification of a chiral lead reported by Wang and co-workers^[35-37] to fight antibiotic resistance. In this study, we have utilized computational methods to provide a detailed mechanistic insight into this important reaction. Thus, we took chiral phosphoric acid ((*R*)-**4c**) catalyzed an enantioselective asymmetric aza-pinacol rearrangement of 4-chloro-*N*-(2-(3'-hydroxy-1'-phenylspiro[cyclopentane-1,2'-indolin]-3'-yl)ethyl)benzenesulfonamide (**1a**) as a model system (See Figure 1) to explore the detailed mechanism. We wish to present (a) a detailed mechanistic picture of the action of the chiral catalyst in substrate activation, (b) the key intermediates and transition states involved in the catalytic cycle so as to understand the most likely mechanism, (c) the molecular insights into how the chiral catalyst works in the stereocontrolling step, and (d) the origin of enantioselectivity in the formation of the products.

2. Computational methods

All calculations were carried out using the Gaussian 09 program package.^[38] The geometries were optimized using the M06-2X density functional in conjunction with the 6-31G(d,p) basis set.^[39-41] Fully optimized geometries of all stationary points were characterized by frequency calculations in order to verify that the transition states (TSs) have one and only one imaginary frequency for the desired reaction coordinate. The intrinsic reaction coordinate (IRC) calculations^[42-43] were performed at the same level to further verify that the TS on the potential energy surface connects to the desired minima on either side of the first-order saddle point. Solvent effects, in dichloroethane (DCE), were evaluated at the M06-2X/6-311+G(d,p) level using the gas phase

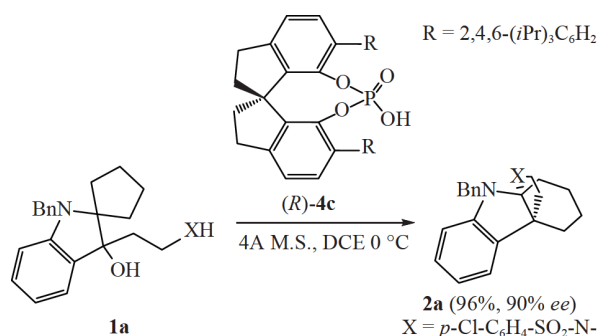


Figure 1 Reaction conditions of the asymmetric aza-pinacol rearrangement of **1a**

optimized geometries.^[44] Solvation energies were calculated by self-consistent reaction field using the SMD solvation model that employs quantum mechanical charge densities of solutes.^[45] The discussions are presented based on the Gibbs free energies obtained at the SMD_{DCE}/M06-2X/6-311+G(d,p) level of theory. The images of the computed structures are illustrated *via* CYLview software^[46].

Additional analysis of the transition states has been performed by examining the topological distribution of electron density. The atoms in molecules (AIM) formalism^[47-49] and noncovalent interaction analysis^[49-50] have been employed to gain more insights into the important noncovalent interactions present in the stereocontrolling transition states. Topological analyses of electron densities were carried out using Bader's atoms in molecules formalism wherein bond critical paths and bond critical points were identified. An interacting pair of atoms is characterized by the presence of a bond path and a bond critical point (bcp) along the bond path. The shared electron density shows a minimum at the bcp. The value of the electron density at such bcps can be regarded as proportional to the strength of the interaction.

3. Results and discussion

The proposed mechanism^[34] of the title reaction proceeds *via* three steps involving (1) the dehydration of the tertiary alcohol to form aza-ortho-xylylene intermediate through hydrogen bonding complex with the chiral phosphoric acid, (2) subsequent enantioselective aza-pinacol rearrangement, (3) followed by ring closure to deliver the fused indoline product. Two pathways (major and minor pathways) were investigated according to the chirality of substrate. The Gibbs free energy profile for the catalytic cycle is shown in Figure 2.

3.1 Conformational analysis for catalyst spinol (*R*)-**4c**

For catalyst spinol (*R*)-**4c**, the orientation of the isopropyl group measured as H(1)—C(2)—C(3)—C(4) dihedral angle

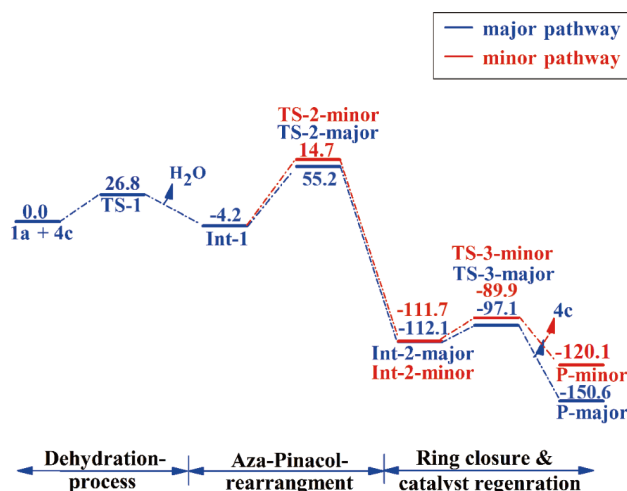


Figure 2 Computed free-energy profile (in kJ·mol⁻¹) for the asymmetric aza-pinacol rearrangement

can either be 0° or 180° as shown in Figure 3. And the free energy difference between **CPA1** and **CPA2**, **CPA3** as well as **CPA4** is less than $15.0 \text{ kJ}\cdot\text{mol}^{-1}$, thus leading to a total of four possible conformations for each transition state.

3.2 Step 1: Dehydration of the tertiary alcohol

A total of three different substrate geometries for substrate **1a** were investigated with different relative orientations of the $-\text{CH}(1)$, $-\text{NH}$ and $-\text{OH}$ groups. As a result, three different activation modes **Com1**, **ComA**, and **ComB** between the catalyst (*R*)-**4c** and **1a**, with a total of 12 conformations were located as shown in Figure 4. **Com1** enjoys the formation of two hydrogen bonds (H-bonds) ($\text{N}-\text{H}\cdots\text{O}(2)$

and $\text{O}-\text{H}(2)\cdots\text{O}(3)$), on the contrary, three different H-bonds ($\text{N}-\text{H}\cdots\text{O}(2)$, $\text{C}-\text{H}(1)\cdots\text{O}(2)$, and $\text{O}-\text{H}(2)\cdots\text{O}(3)$) present in **ComA**, and two ($\text{C}-\text{H}(1)\cdots\text{O}(1)$ and $\text{O}-\text{H}(2)\cdots\text{O}(3)$) in **ComB**. As shown in Figure 2, the first step in the catalytic cycle begins with the spinol (*R*)-**4c** catalyzed dehydration of the tertiary alcohol **1a**, leading to the formation of aza-ortho-xylylene intermediate **Int-1**, a total of 12 transition state structures were obtained (See Figure 5). The lowest energy structures of transition states **TS-1**, **TS-1-A**, and **TS-1-B** with different relative orientations of the H(1), H(2) atoms, the $-\text{NH}$ and the $-\text{OH}$ groups are shown in Figure 6. Conformation **TS-1** corresponds to the lowest energy pathway of $26.8 \text{ kJ}\cdot\text{mol}^{-1}$. The lowest energy structure enjoys the formation of $\text{C}-\text{H}(1)\cdots\text{O}(1)$, $\text{C}-\text{H}(1)\cdots$

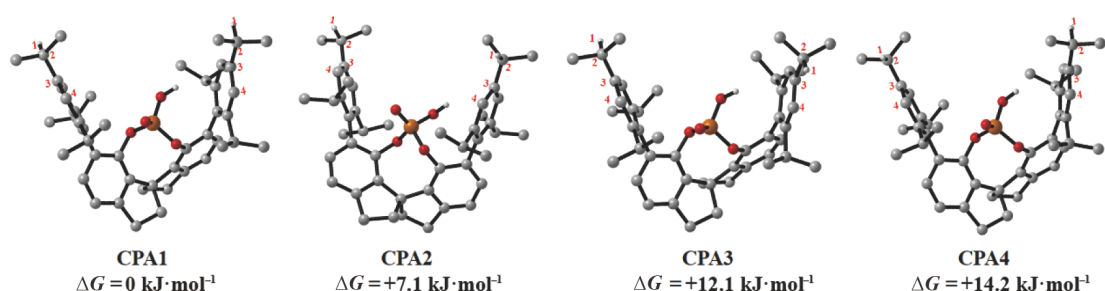


Figure 3 The structures of **CPA1**, **CPA2**, **CPA3**, and **CPA4**. Only selected hydrogen atoms are shown for improved clarity

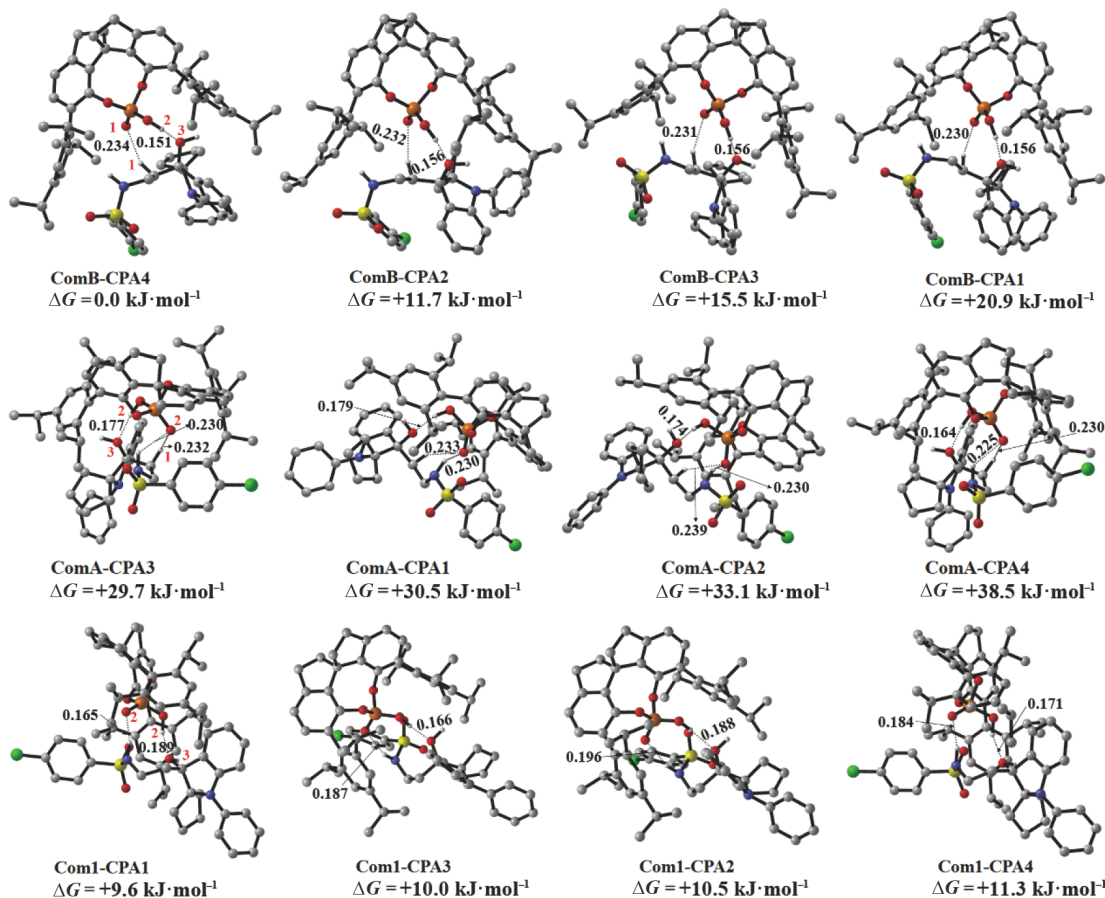


Figure 4 Optimized geometries for different conformations of substrate **1a** combination with catalyst (*R*)-**4c**. N: blue, C: gray, O: red, H: white, S: yellow, and Cl: green. Only selected hydrogen atoms are shown for improved clarity

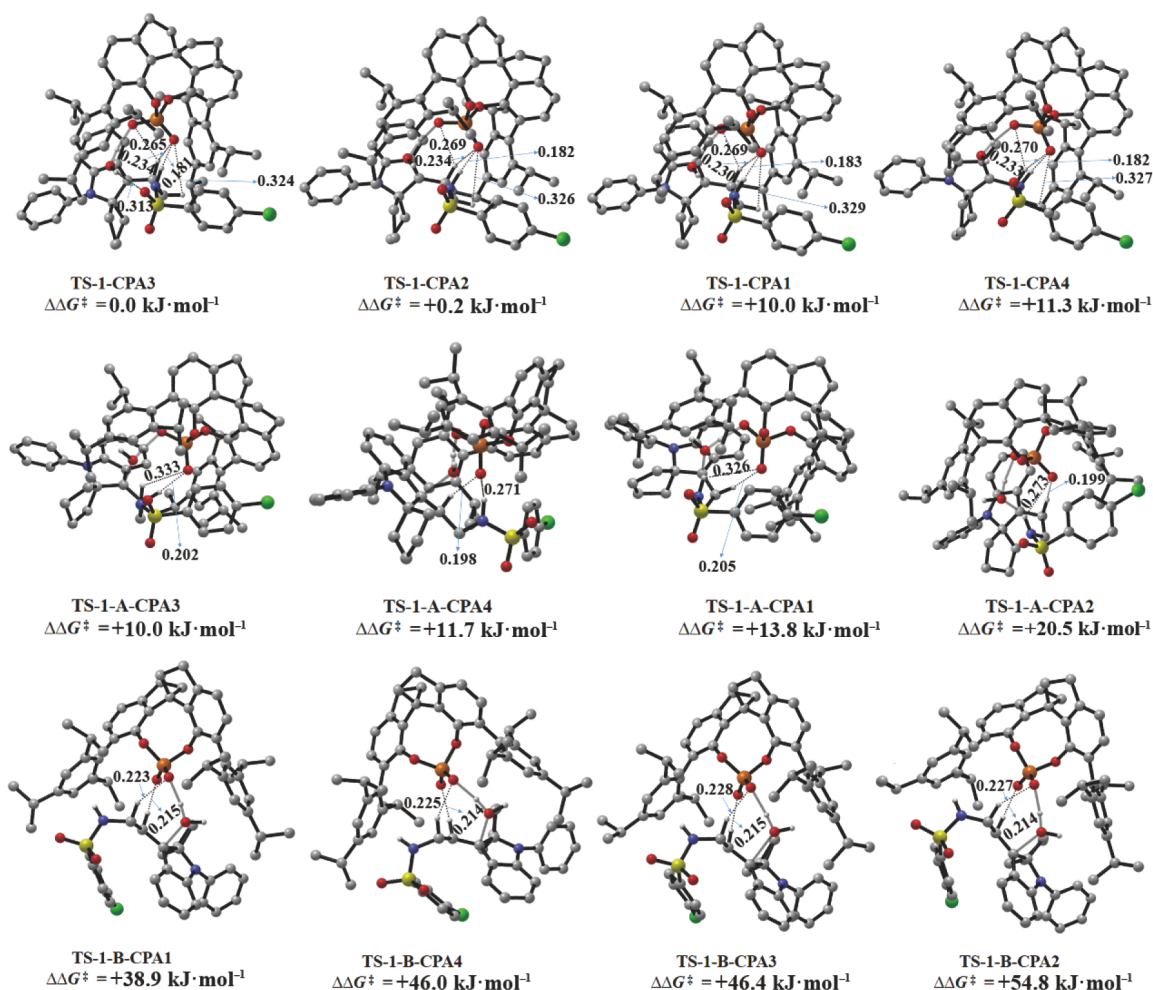


Figure 5 Optimized geometries for different conformations of transition states **TS-1**, **TS-1-A**, and **TS-1-B** of the dehydration process. N: blue, C: gray, O: red, H: white, S: yellow, and Cl: green. Only selected hydrogen atoms are shown for improved clarity.

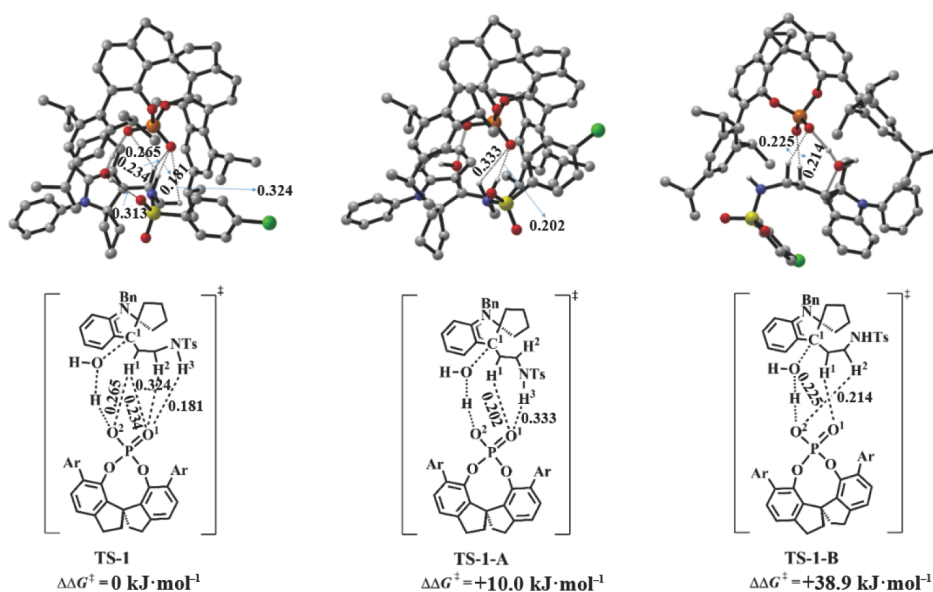


Figure 6 TS structures for the lowest energy conformations of transition states **TS-1**, **TS-1-A**, and **TS-1-B**. Key hydrogen-bonding interactions are shown in nm

O(2), C—H(2)···O(1), and N—H(3)···O(1) between the substrate and the catalyst. Conformation **TS-1-A** was found to be 10.0 kJ·mol⁻¹ higher in energy than that of the **TS-1**. This structure does not exist C—H(2)···O(1) and

C—H(1)···O(2) H-bonds, but it shows H-bonds C—H(1)···O(1) and N—H(3)···O(1) between hydrogen H(1) of the —NH group and the phosphate. Conformation **TS-1-B** was found to be 38.9 kJ·mol⁻¹ higher in energy than **TS-1**.

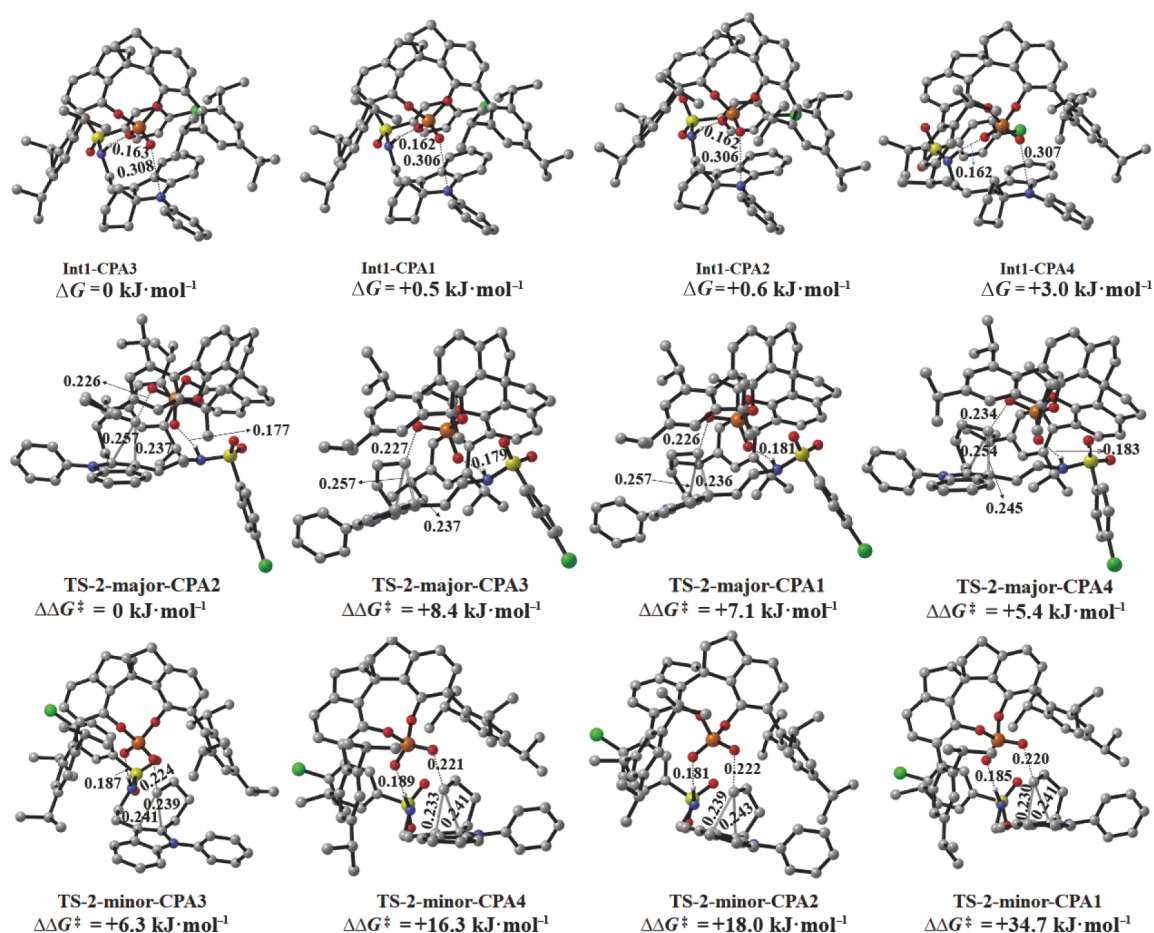


Figure 7 Optimized geometries for different conformations of aza-ortho-xylylene intermediate **Int-1** and transition states **TS-2-major** and **TS-2-minor** of aza-pinacol rearrangement. N: blue, C: gray, O: red, H: white, S: yellow, and Cl: green. Only selected hydrogen atoms are shown for improved clarity

This structure shows the formation of $\text{C}—\text{H}(1)\cdots\text{O}(1)$ and $\text{C}—\text{H}(2)\cdots\text{O}(2)$ H-bonds. The latter two conformations **TS-1-A** and **TS-1-B** impede the formation of the secondary H-bonds. Thus, the following discussion is based on the most stable conformation of **TS-1**.

3.3 Step 2: Enantioselective aza-pinacol rearrangement

The second step is the aza-pinacol rearrangement, which is the key stereocontrolling step in the catalytic cycle. It occurs *via* the $\text{C}(2)—\text{C}(3)$ bond breaking and the $\text{C}(1)—\text{C}(3)$ bond formation to produce the enantioselective aza-pinacol rearrangement intermediate **Int-2-major** and **Int-2-minor**, and eight TSs structures were located (See Figure 7). The chiral catalyst controls the orientation of the transition states of this step through two potential binding sites between the bifunctional chiral phosphate and the aza-ortho-xylylene intermediate. Thus two transition states **TS-2-major** and **TS-2-minor** have been located for the major and minor pathways. The relative free energy of the lowest energy structure for transition state **TS-2-minor** is found to be $6.3 \text{ kJ}\cdot\text{mol}^{-1}$ higher than that of **TS-2-major**. The calculated enantioselectivity is 89%, which is in agreement with the experimental value of 90%. Moreover, the $\text{C}(2)—\text{C}(3)$ breaking bond lengths (0.257 and 0.239 nm) are slightly

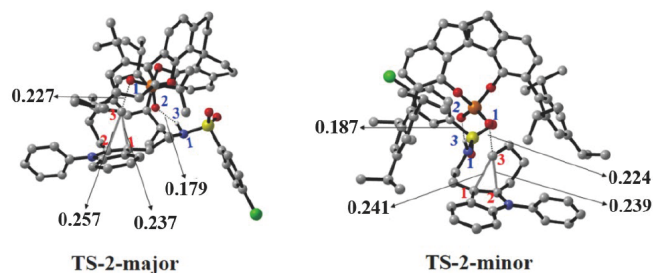


Figure 8 Optimized structures for the most reasonable conformations of transition states **TS-2-major** and **TS-2-minor**. Key hydrogen-bonding interactions are shown, with their corresponding bond distances in nm. Noncritical hydrogen atoms omitted for clarity

longer than the $\text{C}(1)—\text{C}(3)$ forming bond (0.237 and 0.241 nm) in **TS-2-major** and **TS-2-minor**, respectively (See Figure 8). The strong electrostatic interactions of $\text{N}(1)—\text{H}(3)\cdots\text{O}(1)^-$ and $\text{C}(1)\cdots\text{C}(3)$ (0.179/0.237 nm) in the major transition state **TS-2-major** compared to those (0.187/0.241 nm) in **TS-2-minor** favor the major pathway.

3.4 Step 3: Ring closure

The third step is the $\text{C}(2)—\text{N}(1)$ bond formation and the $\text{H}(3)$ transfer from $\text{N}(1)$ to $\text{O}(2)$ to afford the desired fused indoline product and regenerate the catalyst. The in-

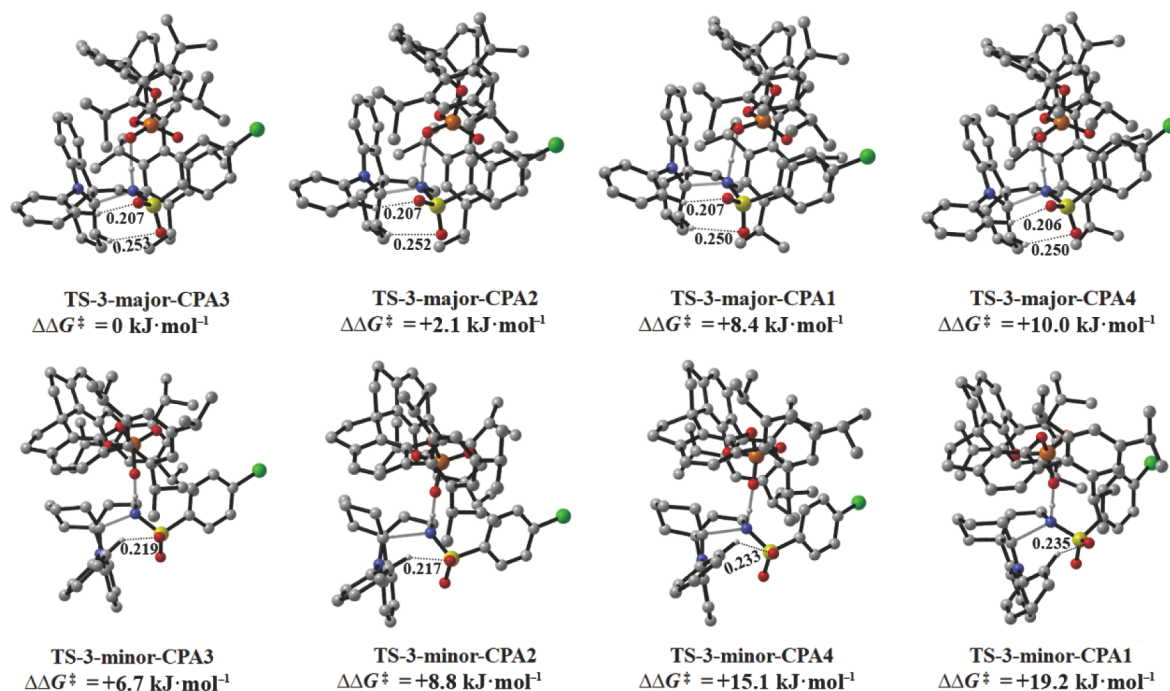


Figure 9 Optimized geometries for different conformations of ring-closure transition states. N: blue, C: gray, O: red, H: white, S: yellow, and Cl: green. Only selected hydrogen atoms are shown for improved clarity

tramolecular cyclization and H(3)-shift take place in a concerted manner *via* transition states **TS-3-major** and **TS-3-minor**, eight TS structures were located (See Figure 9). The corresponding energy barriers of the lowest energy structures for **TS-3-major** and **TS-3-minor** are 15.1 and 21.8 kJ·mol⁻¹, respectively. A closer structures inspection of these two transition states (See Figure 10), one can note that **TS-3-major** enjoys additional stabilization due to the presence of two favorable H-bonds interactions C—H(4)···O(4) (0.207 nm) and C—H(5)···O(5) (0.253 nm) arising from the oxygen atoms of the sulphonyl group. Whereas, **TS-3-minor** has only one hydrogen bond C—H(4)···O(4) (0.219 nm). Such differences in these noncovalent interactions contribute to the relative energy order of the enantiomeric transition states and hence give more energetic advantage to transition state **TS-3-major** of the major pathway over **TS-3-minor** of the minor pathway.

3.5 Molecular origin of the enantiocontrolling factors

To rationalize the stereoelectronic factors that contribute to the differential stabilization of structures of **TS-2-major** and **TS-2-minor**, we further analyze the stereocontrolling transition states related to the aza-pinacol rearrangement step. AIM analysis was employed to identify important non-covalent interactions in the form of bond paths and bond critical points.^[51-57] Electron densities (ρ) at various bond critical points are analyzed to get an approximate measure of the strength of weak noncovalent interactions. The topological maps have been carefully analyzed. The corresponding values of the electron densities at the bond critical points and the estimated E_{HB} values are provided in parentheses,

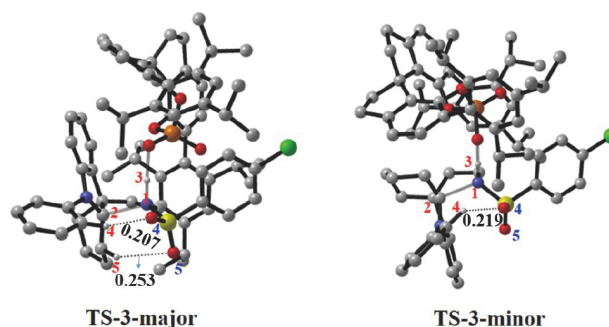


Figure 10 Optimized structures for the lowest energy conformations of transition states **TS-3-major** and **TS-3-minor**. Key hydrogen-bonding interactions are shown, with their corresponding bond distances in nm. Noncritical hydrogen atoms omitted for clarity

respectively, beside the corresponding interatomic contact distances in Figure 11.

Geometries analysis of transition states **TS-2-major** and **TS-2-minor** revealed that three different types of non-covalent interactions C—H···O, C—H··· π , and N—H···O are identified in **TS-2-major**. Whereas four different types C—H···O, C—H··· π , N—H···O and C—H···N are found in **TS-2-minor**. **TS-2-major** evidently exhibits more stabilizing contacts namely the C—H···O interactions ($e^- \rightarrow l$) in comparison to those ($e^- \rightarrow g$) in **TS-2-minor**. The total strength of the C—H···O interactions in **TS-2-major** (0.083 a.u.) is stronger than that in **TS-2-minor** (0.032 a.u.). However, **TS-2-minor** has a more number of C—H··· π interactions and enjoys the presence of C—H···N interaction, and a fairly great N—H···O⁻ interaction (m) in **TS-2-major** (0.179 nm) is stronger than that (m') in **TS-2-minor** (0.185 nm). Underscoring the importance of the pivotal H-

bonding between the amine group of aza-ortho-xylylene intermediate and the chiral catalyst spinol (*R*)-**4c**. Overall, multiple noncovalent interactions seem to provide additional stabilization to **TS-2-major** over that to **TS-2-minor**. The total sum of electron densities at the bond critical points in the lowest energy transition-state **TS-2-major** shows that the total strength of different noncovalent interactions (0.152 a.u., $\sigma \rightarrow \pi$) is higher than that in **TS-2-minor** (0.107 a.u., $\sigma \rightarrow n$). The ρ_{bcp} values for all these interactions lie within the range of 0.002–0.040 a.u.

Exponential relationships between the ρ_{bcp} and the interatomic distance (See Figure 11) are found to be consistent with previous reports for hydrogen bonds^[57–60] or other weak interactions.^[61–64] Furthermore, the estimated E_{HB} absolute values contribute 100.5 kJ·mol^{−1} to the stabilization of **TS-2-major** but only 68.2 kJ·mol^{−1} to the stabilization of **TS-2-minor**. Thus, the cumulative effect of the relative efficiencies of all these interactions gives rise to the vital energy difference of 6.3 kJ·mol^{−1} between the diastereomeric transition states **TS-2-major** and **TS-2-minor**.

After having identified a number of important interatomic noncovalent interactions through the AIM analysis, we examined the details of noncovalent interactions in these

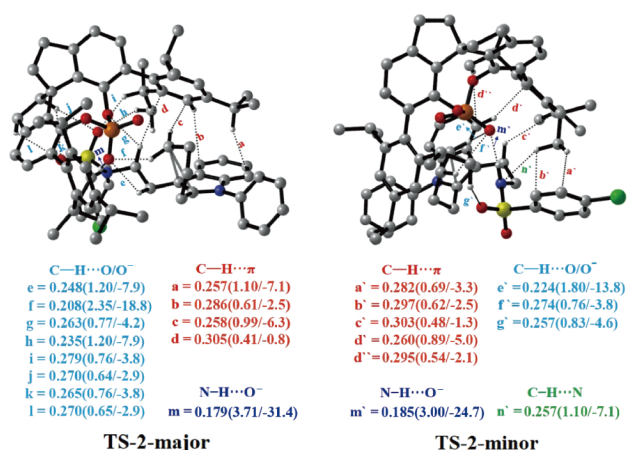


Figure 11 Stereocontrolling transition states for the C—C bond formation. Interatomic contacts that correspond to noncovalent interactions between the catalyst and substrates are in nm, the corresponding electron densities ($\rho \times 10^{-2}$ a.u.) at the bcps, and the estimated E_{HB} values (in kJ·mol^{−1}) are given in parentheses, respectively. Only selected hydrogen atoms are shown for improved clarity

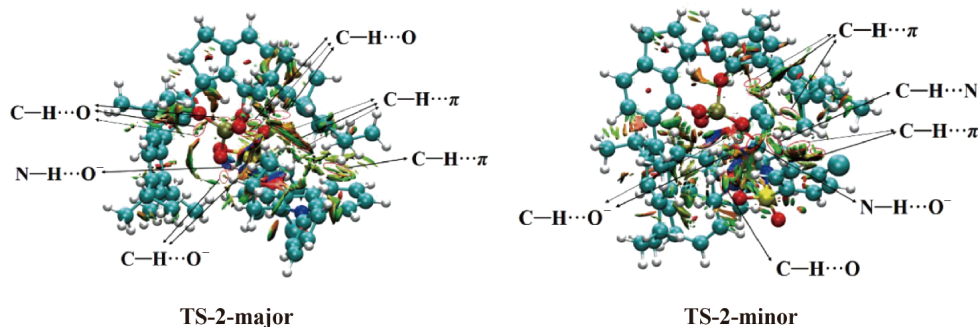


Figure 12 NCI plots for stereocontrolling transition states **TS-2-major** and **TS-2-minor**

transition states. Recently proposed noncovalent interaction index (NCI) plots offer a qualitative mapping of the regions of noncovalent interaction present in a molecule in real space. NCI plots for the stereocontrolling transition states are provided in Figure 12. In the graphical depiction of NCI, strong attractive interactions appear as blue regions, dispersion or weak noncovalent interactions as green regions, and repulsive interactions as red regions. For instance, the noncovalent interactions such as $\text{C—H}\cdots\pi$, $\text{C—H}\cdots\text{O/O}^-$, $\text{N—H}\cdots\text{O}^-$, and $\text{C—H}\cdots\text{N}$ can be noted in the NCI plots. It is clearly gleaned that the $\text{C—H}\cdots\text{O}$ interactions are greater in number in **TS-2-major** than **TS-2-minor**, and the blue and green-colored regions have a more widespread in **TS-2-major**. The differential noncovalent interactions that are present in these stereocontrolling transition states can be regarded as the most important contributing factors to the energy difference between them.

4. Conclusions

In conclusion, we have gained molecular insights into the mechanism and the origin of stereo divergence in the chiral phosphoric acid-catalyzed an asymmetric aza-pinacol rearrangement using DFT (M06-2X) computational tools. Different conformations of the substrate were evaluated, and conformation **TS-1** led to the lowest energy TS because it allows the formation of multiple H-bonds between the substrate and the chiral catalyst (*R*)-**4c**. The aza-pinacol rearrangement is the key stereocontrolling step. Moreover, the origin of enantioselectivity could be traced to the differences in the $\text{C—H}\cdots\pi$, $\text{C—H}\cdots\text{O}$, and $\text{N—H}\cdots\text{O}^-$, and $\text{C—H}\cdots\text{N}$ noncovalent interactions of the transition states **TS-2-major** and **TS-2-minor**. The cumulative effect of these weak noncovalent interactions between the chiral catalyst and the substrate is found to play a vital role in influencing aza-pinacol rearrangement. And a stronger $\text{N—H}\cdots\text{O}^-$ interaction in the major transition state was found to contribute to the high levels of enantioselectivity. The predicted enantioselectivity 89% *ee* is found to be in good agreement with the experimental observations 90% *ee*. These results provide valuable insight into the mechanism of the title re-

action and can be used in the design of more selective catalysts for it and related transformations.

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手性磷酸催化不对称氮杂频哪醇重排合成吡啶的机理和对映选择性研究

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摘要 采用M06-2X/6-311+G**对手性磷酸催化的4-氯-*N*-(2-(3'-羟基-1'-苯基螺[环戊烷-1,2'-吡啶]-3'-基)乙基)(**1a**)的不对称氮杂频哪醇重排反应进行了深入的机理研究。计算结果表明, 整个催化循环经历底物**1a**脱水、对映选择性的氮杂频哪醇重排、分子内环化和催化剂再生得到吡啶产物。氮杂频哪醇重排是该反应的关键立体控制步骤。手性催化剂通过双官能团手性磷酸和氮杂邻二甲苯中间体之间的2个结合位点控制了对映选择性步骤过渡态的取向。重要的是, 理论研究表明底物和手性催化剂的中心官能团上的氧阴离子和臂之间形成的多个C—H $\cdots$ π , C—H $\cdots$ O和C—H $\cdots$ N氢键和N—H $\cdots$ O静电相互作用在决定立体化学结果方面起着关键作用。主要过渡态中强的N—H $\cdots$ O⁻相互作用提高了对映选择性。此外, 对映选择性过渡态之间6.3 kJ·mol⁻¹的能量差所对应的 ee 值为89%, 与实验结果90%非常吻合。

关键词 手性磷酸催化; 氮杂频哪醇重排; 对映选择性; 密度泛函理论