Chiral Pyrrolidine-Pyrazole Catalyzed Enantioselective Michael Addition: a Mechanistic Study by Computational Methods

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Asymmetric synthesis to provide enantiomerically pure compounds is a promising research area in the field of organic chemistry. Especially, the asymmetric Michael addition is very widely used and viable strategy for the carbon–carbon (C–C) bond formation.1,2 Organo-catalyzed asymmetric Michael addition reactions have been developed recently and attracted significant attention in the area of asymmetric synthesis because of their prospective applications.3 This reaction represents one of the most efficient pathways for the C–C bond formation in synthetic organic chemistry. Many proline derivatives, such as proline–triazole,4 pyrrolidine-pyridine,5 pyrrolidine-sulfonamide,6 and pyrrolidine-pyrazole7 have been employed as efficient organocatalysts for asymmetric Michael addition. These organic catalysts are applied not only to the Michael addition reactions, but also to the other reactions, such as Aldol reactions, and Domino process. A large number of cyclic ketones and nitroolefins as Michael donors and Michael acceptors, respectively were used in this process, which proceeds with very good enantioselectivity and diastereoselectivity.7

In the present computational mechanistic study, cyclohexanone (1) and trans-β-nitrostyrene (2) were chosen as Michael donor and Michael acceptor, respectively. Achiral (S)-pyrrolidine-pyrazole (3) catalyst, which has shown excellent catalytic cycle in the Michael addition of carbonyl compounds to various nitroolefins with very good enantio- and diastereo-selectivities (up to 99% ee), was chosen as the organic catalyst. The reaction between cyclohexanone (1) and trans-β-nitrostyrene (2) yielded the Michael adduct (4) (Scheme 1).

Four possible transition geometries related to the C–C bond formation step of the reaction (vide supra) were investigated by employing the density functional theory (DFT), both in the presence and absence of an acid additive. Insights on the diastereo- and enantio-selectivities in the formation of Michael adduct were gained by the transition state analysis. This reaction proceeds through a mechanism involving the initial formation of an enamine between the cyclohexanone and pyrrolidine-pyrazole catalyst with the simultaneous loss of one water molecule. As the enamine formation and the hydrolysis of the Michael adduct (Figure 1) are rapid and have no effect on the rate and stereoselectivity of the reaction,8 this study focused on the transition states involved in the rate-limiting C–C bond formation step, the nucleophilic attack of the enamine on trans-β-nitrostyrene. Figure 1 presents the mechanism of this reaction from the earlier reports7.

The two transition states arising from the approach of trans-β-nitrostyrene to the diastereotopical Re and Si faces of the anti-enamine are represented as TSA, and TSB, respectively. Similarly, the other two transition states are formed with syn-enamine and represented as TSC, and TSD. The formation of four transition states and corresponding products are shown in the Scheme 2.

The structures of the transition states were computed using the B3LYP hybrid functional9 in combination with 6-31G (d,p) basis set, by employing Gaussian 09 software.10 All the ground state geometries and transition state geometries were characterized by harmonic vibrational frequency analysis. All the reported energies include the zero-point vibrational energy (ZPVE) corrections. The stationary points of the transition states were confirmed by vibrational frequency analysis, ensuring only one imaginary frequency.

Herein, a comprehensive mechanistic investigation was undertaken using DFT methods and the transition states were located successfully at the B3LYP/6-31G(d,p) level. Table 1 lists the relevant computational data of the four transition states. From the results, it was observed that TS_A (anti-Re) is energetically more stable than TS_B, TS_D, and TS_C. Experimentally observed anti diastereoselectivity was predicted successfully in this study using the DFT methods. The anti diastereoselectivity and Re stereoselectivity were experimentally determined by 1H

Scheme 1. Asymmetric Michael addition of cyclohexanone and trans-β-nitrostyrene catalyzed by Pyrrolidine-pyrazole.
In summary, the transition state formed when the anti-enamine was approached with the Re-face of nitrostyrene (TS\textsubscript{A}) is lower in energy than the other three transition states. The earlier theoretical reports are in favor of TSA with other organic catalysts, whereas the same time, the transition state, TSC, is higher in energy than the other three transition states. The DFT studies of the transition states provided more insight into the reaction pathway. The differences in the energies of the transition states result in high enantio- and diastereo-selectivities.

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Supporting Information. Additional information (absolute energies, relative energies, and geometries of the transition states) is available in the online version of this article.

Table 1. Absolute energies (Hartrees) and imaginary frequencies of the four transition states in the presence of an acid additive.

<table>
<thead>
<tr>
<th>Transition State</th>
<th>Absolute Energy (au)</th>
<th>Imaginary Frequency (cm\textsuperscript{-1})</th>
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<tbody>
<tr>
<td>TSC</td>
<td>−1224.439325 (11.6)</td>
<td>220.1</td>
</tr>
<tr>
<td>TSD</td>
<td>−1224.449675 (5.1)</td>
<td>214.5</td>
</tr>
<tr>
<td>TSB</td>
<td>−1224.453833 (2.5)</td>
<td>221.6</td>
</tr>
<tr>
<td>TSA</td>
<td>−1224.457770 (0.00)</td>
<td>172.2</td>
</tr>
</tbody>
</table>

* Relative energies (kcal/mol) are given in the parentheses.

References