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-pyrazole[7] 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 diastereoselectivities (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 forming 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 reports[7].

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 TS_A, and TS_B, respectively. Similarly, the other two transition states are formed with *syn*-enamine and represented as TS_C, and TS_D. 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 functional[9] 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 [1]H
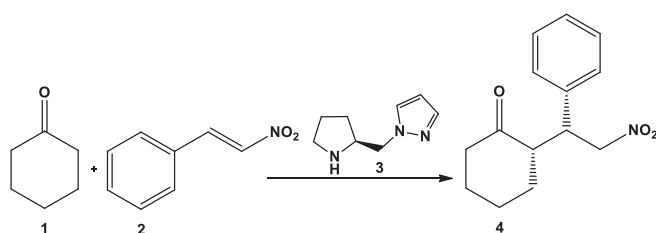
Scheme 1. Asymmetric Michael addition of cyclohexanone and *trans*-β-nitrostyrene catalyzed by Pyrrolidine-pyrazole.
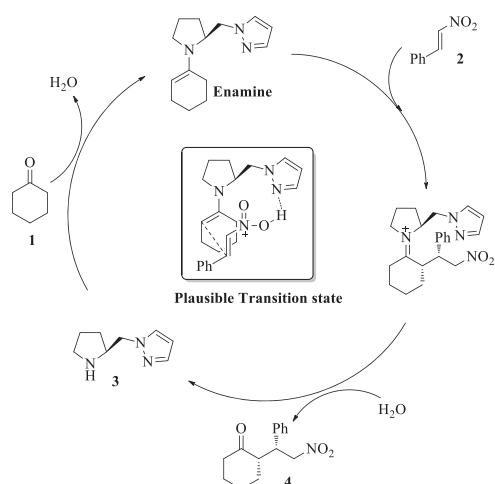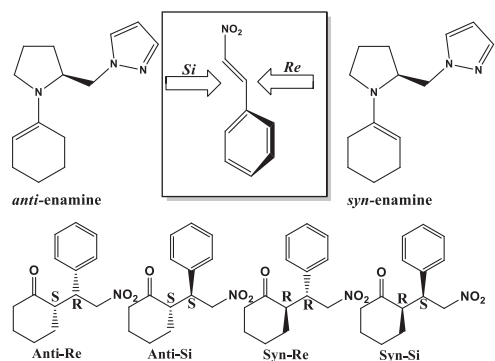
Figure 1. Reaction mechanism of asymmetric Michael addition of cyclohexanone and *trans*-β-nitrostyrene catalyzed by pyrrolidine-pyrazole.

Scheme 2. Stereochemical representation of the formation of four transition states and the corresponding products.

NMR, and chiral HPLC analysis, respectively.[7] The distance between the bond forming carbon atoms in the optimized TS$_A$ (2.455 Å) is highest, whereas, it is lowest (2.268 Å) in the case of TS$_C$. The prominent spatial distance between the two species in the TS$_A$ reduces the steric hindrance and gives a lower energy barrier. The steric hindrance caused by the low spatial distance in TS$_C$, could be responsible for the high energy barrier. The observed characteristic imaginary frequency in each transition state was visualized, which was associated with the new C–C bond to be formed. The same series of calculations were also performed in the absence of an acid additive (proton). The transition state TS$_A$ was found to have the lowest energy barrier, even in the absence of an acid additive. The earlier theoretical reports are in favor of TS$_A$ with other organic catalysts, supporting the reliability of the present simulation results.[3] Figure S1 of the Supporting information compares the activation energies of the four transition states.

In summary, the transition state formed when the anti-enamine was approached with the Re-face of nitrostyrene (TS$_A$) is lower in energy than the other possible transition states in the presence and absence of an acid additive, which proved the reaction proceeds through TS$_A$. At the

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

	Absolute energy (au)[a]	Frequency (i) (cm^{-1})
TS$_C$	−1224.439325 (11.6)	220.1
TS$_D$	−1224.449675 (5.1)	214.5
TS$_B$	−1224.453833 (2.5)	221.6
TS$_A$	−1224.457770 (0.00)	172.2

[a] Relative energies (kcal/mol) are given in the parentheses.

same time, the transition state, TS$_C$, 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.

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

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