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# On the Origin of the Stereoselectivity in Organocatalysed Reactions with Trimethylsilyl-Protected Diarylprolinol

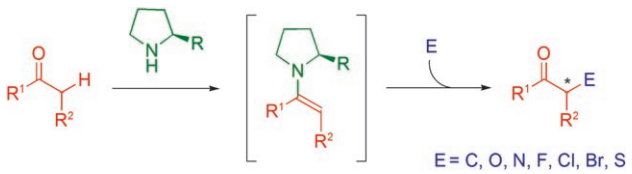
**Peter Dinér, Anne Kjærsgaard, Mette Alstrup Lie, and Karl Anker Jørgensen*[a]**

**Abstract:** The origin of the enantioselectivity in the TMS-protected (TMS = trimethylsilyl) prolinol-catalysed α-heteroatom functionalisation of aldehydes has been investigated by using density functional theory calculations. Eight different reaction paths have been considered which are based on four different conformers of the TMS-protected prolinol–enamine intermediate. Optimisation of the enamine structures gave two intermediates with nearly the same energy. These intermediates both have an *E* configuration at the C=C bond and the double bond is positioned *anti* or *syn*, relative to the 2-substituent in the pyrrolidine ring. For the four intermediates, the chiral TMS-protected-diaryl substituent effectively shields one of the faces of the reacting C=C bond in the enamine intermediate. A number of transition states have been calculated for the enantioselective fluorination by *N*-fluorobenzenesulfonimide (NFSI) and based on the transition-state energies it has been found that the enantioselectivity depends on the orientation of the C=C bond, being *anti* or *syn*, relative to the 2-substituent on the pyrrolidine ring, rather than the approach of the electrophilic fluorine to the face of the reacting carbon atom in the enamine which is less shielded relative to the face with the highest shielding. The calculated enantiomeric excess of 96% *ee* (*ee* = enantiomeric excess) for the fluorination reaction corresponds well with the experimentally found enantiomeric excess—97% *ee*. The transition state for the α-amination reaction with the same type of intermediate has also been calculated by using diethyl azodicarboxylate as the amination reagent. The implication of the intermediate structures on the stereoselection of α-functionalisation of aldehydes is discussed.

**Keywords:** density functional theory · enamine · enantioselection · mechanism · organocatalysis

## Introduction

In the last few years, the research field of organocatalysis has become a hot topic in organic chemistry.[1] The rediscovery of the proline-catalysed direct aldol reaction by List, Lerner and Barbas[2] was the starting point for a groundbreaking development of highly stereoselective organocatalysed transformations. Since then, several different protocols for carbon and heteroatom α-functionalisations of aldehydes and ketones, including aldol[3] and Mannich[4] reactions, amination,[5] oxygenation,[6] fluorination,[7] chlorination,[8] bromination[9] and sulfenylation and selenylation[10] reactions have been developed by using proline, as well as other chiral secondary amines and chiral imidazolidinones as the catalysts (Scheme 1).




Scheme 1. Organocatalytic carbon and heteroatom α-functionalisation of aldehydes and ketones.

An important aspect of organocatalytic α-functionalisation reactions is to understand the activation of the carbonyl compound, and in particular how the stereoselectivity is controlled in the bond-forming step. The mechanism of the organocatalysed electrophilic addition of carbonyl compounds to the proline-enamine intermediate has been investigated by computational chemistry mainly by Houk et al.[11]

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The calculations show that the reaction proceeds by means of a hydrogen-bond-directed Brønsted acid catalysis and that the proton from the carboxylic acid group in proline is important for the determining the stereochemical outcome of the reaction. The hydrogen bonding in the transition state directs the electrophile approach from above to the *Re* face of the enamine intermediate, and hence, yields the *R* configuration of the optically active product formed (Figure 1a).

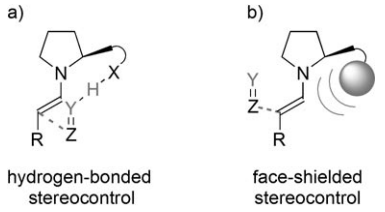
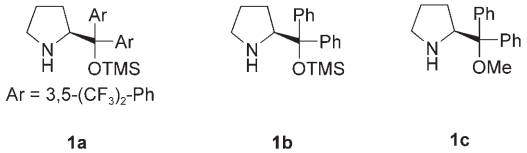


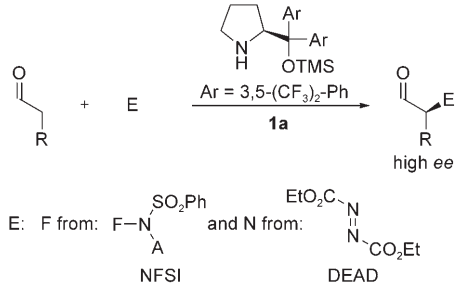

Figure 1. a) Hydrogen-bonded stereocontrol. b) Face-shielded stereocontrol.

Recently, diarylprolinol ethers **1a**–**c** were introduced as new chiral secondary amine catalysts.[12–14] These new organocatalysts, including also the imidazolidinones developed




by MacMillan et al.,[15] do not possess a Brønsted acid functionality, but they still promote electrophilic additions and substitutions via enamine intermediates. The diarylprolinol ethers show a remarkable generality as organocatalysts as they can catalyse a large number of different types of reactions with excellent stereoselectivity.[12] These reactions include α-,[16] β-[17] and γ-functionalisation of aldehydes,[18] and also several multi-step and domino reactions.[19,20] For the direct α-functionalisation of aldehydes, it has been postulated that the stereoselectivity is controlled by face-shielding of the *Re* face of the enamine intermediate leaving the *Si* face available for attack (Figure 1b), rather than inducing the enantioselectivity by means of hydrogen bonding (Figure 1a).

Due to the recent success of the TMS-protected diarylprolinol catalyst **1a**, we found it interesting to computationally investigate the origins of the stereoselectivity by density functional theory calculations.[21] In this paper, we present a computational investigation of the transition states involved in the stereoselective electrophilic α-addition, by studying the α-fluorination of aldehydes with *N*-fluorobenzenesulfonimide (NFSI) as the fluorination reagent, and also possible transition states for the α-amination by using diethyl azodicarboxylate (DEAD; Scheme 2).




Scheme 2. Direct α-fluorination and α-amination by using TMS-protected diarylprolinol catalyst **1a** (*ee* = enantiomeric excess).

## Results and Discussion

The stereochemical outcome of the α-functionalisations of aldehydes depends on the approach of the electrophile to the enamine and to which conformer of the enamine intermediate the electrophile adds (Figure 2). For example, if the electrophile approaches from below (*Si* face) the enamine **2a**, with an *E* configuration of the double bond and with the double bond *anti* to the 2-substituent in the catalyst, the reaction yields a product with a *S* configuration. However, if the electrophile attacks from the above face (*Re* face) of the enamine **2a**, the *R* product is obtained. As seen in Figure 2, the enamine intermediate can be present in four different conformers, which originate from the two possible configurations of the double bond in the enamine, *E* or *Z*, and from whether the reacting double bond is positioned *syn* or *anti* relative to the 2-substituent in the pyrrolidine ring. This gives a total of eight different diastereomeric transition states for the electrophilic reaction with the enamine intermediate as outlined in Figure 2.

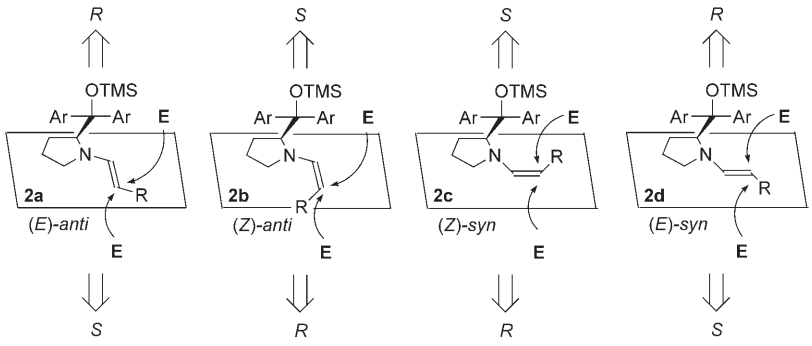



Figure 2. The four different enamine intermediates.

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**Intermediates**: Initially, we investigated the geometries and energies of the different enamine intermediates **2a–d** shown in Figure 3 at the B3LYP/6-31G(d)[21,22] level of theory, to eliminate some of the possible transition states that could be involved in the reaction. The total energies of the enamine conformers are given in Table 1.

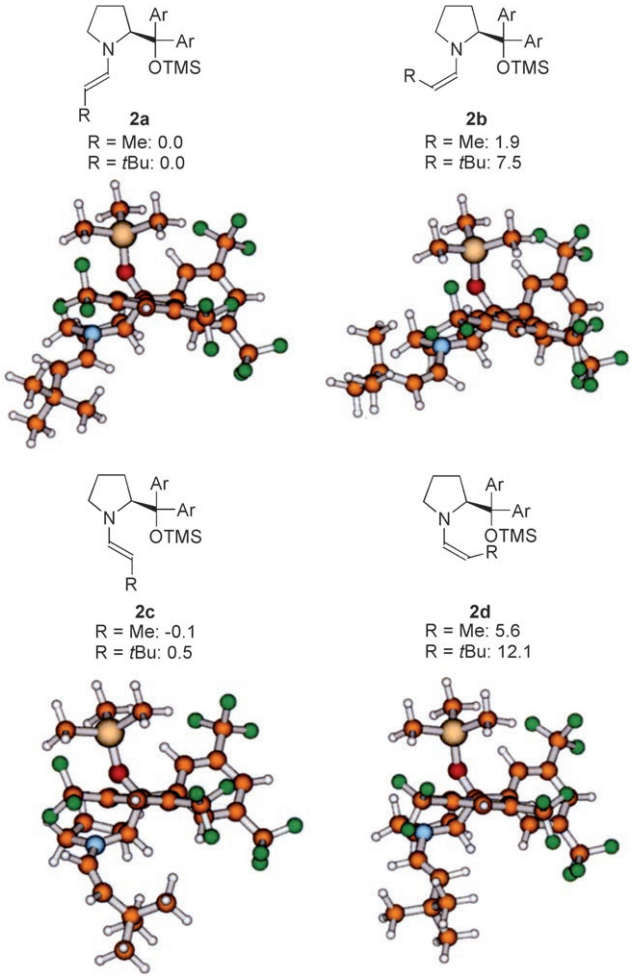


Figure 3. Optimized structures of the four different intermediates.

Table 1. Electronic and free energies of the enamine conformers at the B3LYP/6-31G(d) level of theory.

| | $E_{elec}$ [Hartree][a] | $\Delta E_{elec}$ [kcal mol$^{-1}$] | $G$ [Hartree][a] | $\Delta G$ [kcal mol$^{-1}$] |
|---|---|---|---|---|
| Me-**2a** | −2662.77511 | 0[b] | −2662.348422 | 0 [b] |
| Me-**2b** | −2662.77189 | 2.0[b] | −2662.345334 | 1.9[b] |
| Me-**2c** | −2662.77471 | 0.2[b] | −2662.348587 | −0.1[b] |
| Me-**2d** | −2662.76656 | 5.3[b] | −2662.339576 | 5.6[b] |
| *t*Bu-**2a** | −2780.71586 | 0 [c] | −2780.208647 | 0 [c] |
| *t*Bu-**2b** | −2780.70466 | 7.0[c] | −2780.196673 | 7.5[c] |
| *t*Bu-**2c** | −2780.71614 | −0.2[c] | −2780.207834 | 0.5[c] |
| *t*Bu-**2d** | −2780.69646 | 12.2[c] | −2780.188082 | 12.1[c] |

[a] Absolute energies and free energies for calculated compounds. [b] Energies are given relative to Me-**2a**. [c] Energies are given relative to *t*Bu-**2a**.

The free energies of the different enamine intermediates from propanal and catalyst **1a** show that the enamines Me-**2a** (0 kcal mol$^{-1}$) and Me-**2c** (−0.1 kcal mol$^{-1}$) containing an *E* configuration of the double bond are more stable than the enamines Me-**2b** (1.9 kcal mol$^{-1}$) and Me-**2d** (5.6 kcal mol$^{-1}$) with a *Z* configuration. This difference in free energy originates from the steric repulsion between the methyl group and the protons adjacent to the nitrogen atom in the pyrrolidine ring. This is confirmed by an increase in relative free energy for enamine *t*Bu-**2b** and *t*Bu-**2d** compared to enamine *t*Bu-**2a** (7.5 and 12.1 kcal mol$^{-1}$, respectively) upon exchanging of the methyl group with the much more sterically demanding *tert*-butyl group. The calculations thus suggest that the two major enamine conformers present in a reaction mixture are the enamines intermediates **2a** and **2c**.

The optimised geometries of enamine intermediates **2b–d** presented in Figure 3 also show that the "upper face" of the enamines is effectively shielded by the 2-substituent of the catalyst and therefore an attack to this side by the electrophile was only considered to the enamine **2a**. Furthermore, the attack from below to enamine **2d** was ruled out due to the high energy of this enamine intermediate.

**Fluorination**: The organocatalytic direct enantioselective α-fluorination of aldehydes was presented within a few weeks in 2005 by four different research groups.[7a–d] The work by Enders et al.[7a] focused on the use of Selectfluor for the α-fluorination of both aldehydes and ketones, while the other approaches for the direct enantioselective α-fluorination of aldehydes used NFSI (see Scheme 2) as the fluorinating reagent.[7b–d] In the present work, we have investigated the transition states involved in the α-fluorination of aldehydes by using NFSI and catalyst **1a**. Due to the volatile nature of the fluorinated aldehyde compounds, the aldehydes used experimentally contained a bulky group and, therefore, 3,3-dimethylbutanal was used in the computational investigation of the α-fluorination. The intermediates used for the fluorination reaction were **2a–c** (R = *t*Bu) and the four optimised transition state structures are shown in Figure 4.

The transitions states were optimised at the B3LYP/6-31G(d) level of theory. The transition states considered include three transition states in which the enamine intermediates *t*Bu-**2a–c** are attacked from the less shielded "lower side", and one transition state in which enamine *t*Bu-**2a** is attacked from the more shielded "upper side". The absolute and relative energies for the transition states are given in Table 2. The calculations show that the lowest transition state energy (**TS3a**, −4495.64374 Hartree) involved in the fluorination with NFSI, occurs by attack to the *Si* face of the enamine *t*Bu-**2a**, leading to the *S* configuration of the chiral product. The second most stable transition state found (**TS3c**) is 2.4 kcal mol$^{-1}$ higher in energy than **TS3a** and occurs by fluorination to the *Re* face of enamine *t*Bu-**2c**, leading to the (*R*)-configured product. The energy difference between **TS3a** and **TS3c** (2.4 kcal mol$^{-1}$) corresponds to an enantiomeric excess in favour of the *S* product of

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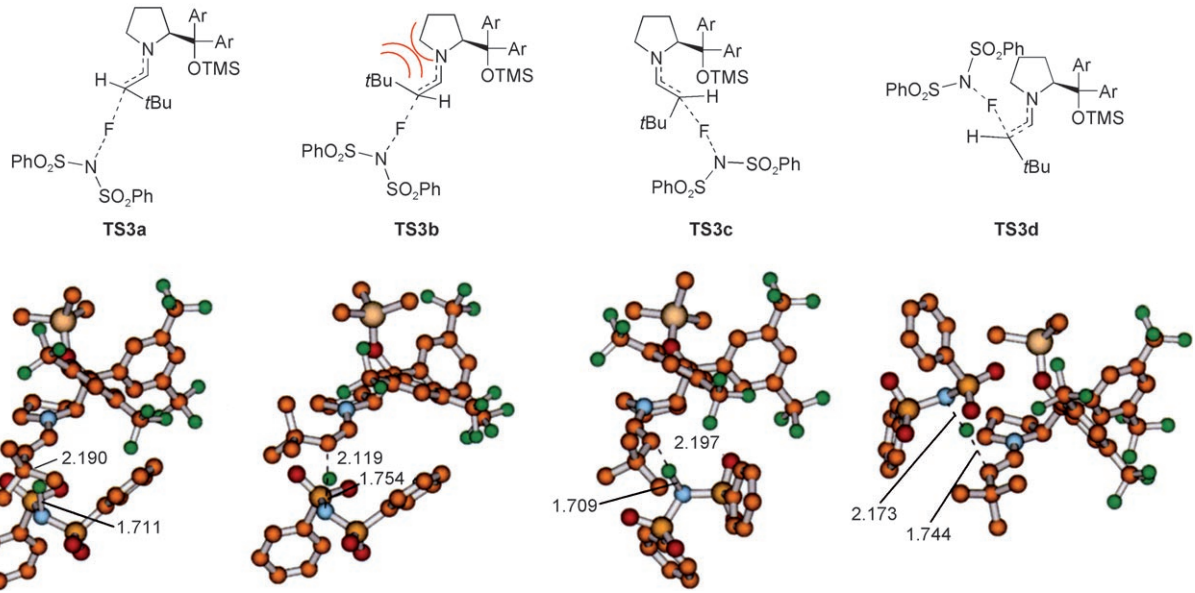


Figure 4. Structures of four different transition states for the α-fluorination of 3,3-dimethylbutanal by using catalyst **1a** at the B3LYP/6-31G(d) level of theory. Hydrogen atoms are omitted for clarity.

Table 2. Electronic and free energies of the transitions states for the fluorination and amination of enamine intermediates at the B3LYP/6-31G(d) level of theory.

| | $E_{elec}$ [Hartree][a] | $\Delta E_{elec}$ [kcal mol$^{-1}$] | $G$ [Hartree][a] | $\Delta G$ [kcal mol$^{-1}$] |
|---|---|---|---|---|
| **TS3a** | −4495.64374 | 0[b] | −4494.95051 | 0[b] |
| **TS3b** | −4495.62701 | 10.5[b] | −4494.93099 | 12.2[b] |
| **TS3c** | −4495.63998 | 2.4[b] | −4494.94589 | 2.9[b] |
| **TS3d** | −4496.70807 | 9.5[b] | −4494.93807 | 7.8[b] |
| **TS4a** | −3347.09756 | 0[c] | −3346.48961 | 0[c] |
| **TS4b** | −3347.09731 | 0.2[c] | −3346.48628 | 2.0[c] |

[a] Absolute and free energies for calculated compounds. [b] Energies are given relative to **TS3a**. [c] Energies are given relative to **TS4a**.

96% *ee*, which is in agreement with the experimentally obtained result (97% *ee*).[7b]

In the transition states, the fluorine atom is transferred from the nitrogen atom in NFSI to the carbon atom in the enamine in a "$S_N2$-like" substitution. The electrophilic fluorine is only partly transferred in the transition state, that is, the fluorine atom is positioned closer to the nitrogen atom in NFSI than to the carbon atom in the enamine, 1.711 compared to 2.190 Å, respectively, in **TS3a**, which suggests an early transition state. A major geometrical difference between the two most stable transition states leading to the *S* and *R* products, is that the most stable transition state **TS3a** has a staggered configuration of the substituents relative to the C–F-forming bond and the F–N-breaking bond, while a more eclipsed arrangement is seen for transition state **TS3c**. The transition state **TS3b**, with a *Z* configuration of the enamine double bond is much higher in relative energy, 10.5 kcal mol$^{-1}$, relative to transition state **TS3a**. This large difference in relative energy reflects the difference in energy that is calculated for the enamine intermediates. An attack from the "upper side" (*Re* face) of the enamine *t*Bu-**2a** is also disfavoured (**TS3d**, 9.5 kcal mol$^{-1}$) due to the effective screening of the enamine-part of the molecule by the two aryl and OTMS (TMS = trimethylsilyl) groups of the chiral catalyst.

According to the energies of the two lowest transition states for the α-fluorination reaction the two competing pathways for the enantioselection are the addition of fluorine from the less shielded face to the enamines **2a** and **2c** (transition states **TS3a** and **TS3c**), rather than the enantioselectivity originating from a more favourable approach to the *Si* face ("from below") in **2a** compared to the approach from the more sterically shielded "upper" face (*Re*) in the same intermediate. The two intermediates **2a** and **2c** can be formed either directly by reaction of the TMS-protected diarylprolinol **1a** with the aldehyde or they can be interconverted through a rotation of the N–C bond in the enamine. We have calculated this rotation barrier to be 6.5 kcal mol$^{-1}$ between the two enamine intermediates **2a** and **2c**. These two intermediates have very similar energy (for R = *t*Bu: $\Delta G = 0.5$ kcal mol$^{-1}$) and with the relatively low rotation barrier, a fast interconversion between the **2a** and **2c** is feasible. In Scheme 3, the two enamines are schematically shown along with the calculated transition-state energies of the two different fluorinated iminium ions with opposite absolute configuration.

**Amination**: The TMS-protected diarylprolinol **1a** is also an effective catalyst for the α-amination of aldehydes in high yields and enantioselectivities,[13] leading to a slight improvement in yield and enantioselectivity compared to the use of proline as the catalyst.[5c,e]

To understand the mechanism for the α-amination of aldehydes by using **1a** as the catalyst, we have also studied

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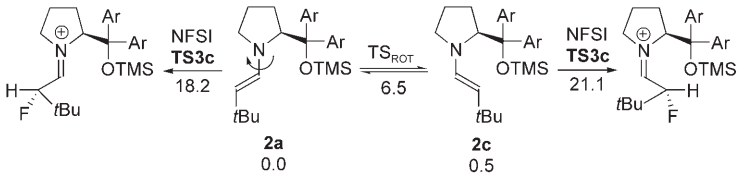


Scheme 3. Rotation around the N–C bond leading to the enantiomers in the fluorination of the enamine intermediates **2a** and **2c** and transition-state free energies (kcal mol$^{-1}$) for the fluorination of these intermediates.

the transition states for the amination of the enamine intermediate for the addition of diethyl azodicarboxylate (DEAD) to Et-**2a** in order to account for the experimentally observed (*S*)-α-aminated aldehyde product.

The two transition states **TS4a** and **TS4b** shown in Figure 5 correspond to two different approaches of the nitrogen atoms in DEAD in the addition step to the enamine intermediate. In transition state **TS4a**, nitrogen atom N1 is approaching the enamine from below with nitrogen atom N2 pointing away from the catalyst, while in transition state **TS4b**, nitrogen atom N1 is pointing towards the pyrrolidine part of the catalyst. Transition state **TS4a** is an earlier transition state compared to **TS4b** as the forming C–N bond distance in the former transition state is 0.138 Å closer compared to the latter. The calculated energies of the transition states show also that the early transition state **TS4a** has the lowest free energy—2.0 kcal mol$^{-1}$ lower than **TS4b**. The calculated forming C–N bond length is similar to the calculated C–N bond length in the transition states for the addition of DEAD to the γ-position to the dienamine intermediate formed from the TMS-protected diarylprolinol **1a** and an α,β-unsaturated aldehyde.[18]

## Conclusion

We have investigated the TMS-protected diarylprolinol-catalysed α-functionalisation of aldehydes computationally at the DFT level of theory. The calculation of the most stable structures of the enamine intermediates, formed by reaction of the TMS-protected diarylprolinol and aldehydes, show that two intermediates, both with an *E* configuration of the double bond, but in which the reacting carbon atom in the enamine part is oriented *syn* or *anti*, relative to the 2-substituent of the catalyst, have nearly similar energy. Calculation of the transition-state structures for the enantioselective fluorination of these two intermediates, as well as others, gave the lowest transition-state energy for fluorination of the (*E*)-*anti* intermediate to be 2.9 kcal mol$^{-1}$ lower in energy than fluorination of the (*E*)-*syn* intermediate. These transition-state energies were found to be significantly lower in energy than the other transition structures calculated. The enantiomeric excess, calculated to be 96% *ee* on the basis of the difference in transition-state energies, corresponds in enantioselectivity to experimental observation (97% *ee*). The electrophile approaches the reactive carbon atom from the same side (below) relative to the catalyst in the (*E*)-*anti* and (*E*)-*syn* intermediates and it is suggested that the enantioselection originates from different populations of these two transition states, rather than from an approach of the electrophile from the more sterically shielded side (upper). The mechanism for the direct α-amination has also briefly been discussed.

## Acknowledgements

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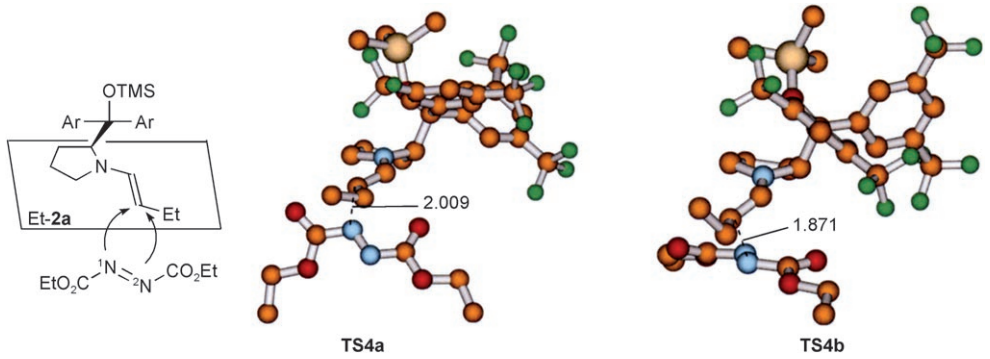


Figure 5. Structures of the two transition states for the α-amination of butanal by using catalyst **1a** leading to the *S* product at the B3LYP/6-31G(d) level of theory.

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