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Theoretical Investigations on the Mechanism of Hetero-Diels–Alder Reactions of Brassard's Diene and 1, 3-Butadiene Catalyzed by a Tridentate Schiff Base Titanium(IV) Complex

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Abstract: The mechanism of the hetero-Diels–Alder reactions of Brassard's diene and 1,3-butadiene catalyzed by a titanium(IV) complex of a tridentate Schiff base was investigated by DFT and ONIOM methods. The calculations indicate that the mechanism of the reaction is closely related to the nucleophilicity–electrophilicity between diene and carbonyl substrates. A stepwise pathway is adopted for Brassard's diene, and the step corresponding to the formation of the C–C bond is predicted to be the rate-determining step with a free-energy barrier of 8.4 kcal mol^{-1}. For 1,3-butadiene, the reaction takes place along a one-step, two-stage pathway with a free-energy barrier of 14.9 kcal mol^{-1}. For Brassard's diene as substrate, the OCH_3 and $OSi(CH_3)_3$ substituents may play a key role in the formation of the transition state and zwitterionic intermediate by participating in charge transfer from Brassard's diene to formaldehyde. The combination of the phenyl groups at the amino alcohol moiety and the *ortho-tert*-butyl group of the salicylaldehyde moiety in the chiral tridentate Schiff base ligand plays an important role in the control of the stereoselectivity, which is in agreement with experimental observations.

Keywords: cycloaddition · density functional calculations · reaction mechanisms · Schiff base ligands · titanium

Introduction

The hetero-Diels–Alder (HDA) reaction is a very convenient protocol for constructing six-membered partly saturated heterocycles, which can be used as starting materials for the total synthesis of many natural products and other highly functionalized heterocycles.[1] Among these important compounds, chiral 5,6-dihydropyran-2-one or α,β-unsaturated δ-lactone derivatives are key structural subunits of natural products with a wide range of biological activity, such as antifungal and antitumor.[2]

From the synthetic viewpoint, the HDA reaction of electron-rich 1,3-dimethoxy-1-(trimethylsiloxy)butadiene (Brassard's diene)[3] with suitable aldehydes or ketones is one of the most convenient ways to produce δ-lactones.[4a–c] As compared to Danishefsky's diene, however, only a few cases of HDA reactions involving Brassard's diene were reported,[4] while the reaction mechanism is still uncertain theoretically. Midland and co-workers performed reactions of Brassard's diene with various α-alkoxy aldehydes in the presence of [Eu(hfc)$_3$] (hfc = 3-heptafluoropropylhydroxymethylencamphorato), $MgBr_2$, or Et_2AlCl, and obtained products with moderate to high enantioselectivities.[4f–i] An experimental investigation by Togni and co-workers indicated the efficiency of vanadium(IV) complex catalysts for the reaction of Brassard's diene and cinnamaldehyde.[4j] A chelation-control model was proposed to provide a possible explanation for the stereochemical outcome of the cycloaddition of an α-alkoxy aldehyde with Brassard's diene.[4h] Recently, Feng et al. verified experimentally that tridentate Schiff base ligands with Ti(O*i*Pr)$_4$ or Cu(OTf)$_2$ were effective for the HDA reaction of Brassard's diene and aromatic aldehydes, which follows the Diels–Alder pathway to afford the corresponding α,β-unsaturated δ-lactone derivatives in moderate yields and excellent enantioselectivities (up to 90 yield and 99 % *ee*).[4a–c,1g] In addition, some small organic molecules, such as TADDOL derivatives, can also be used as catalysts to synthesize the corresponding δ-lactone derivatives by the hydrogen-bonding activation HDA reaction of Brassard's diene.[4k]

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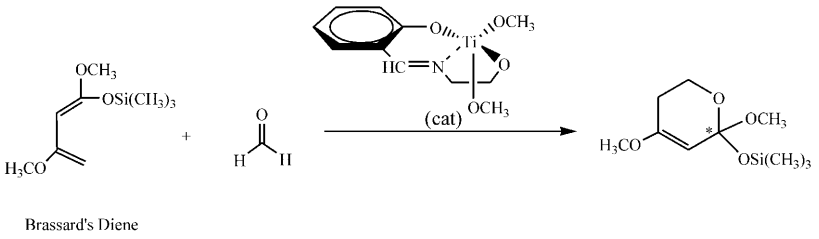
With regard to mechanistic aspects of the HDA reaction,[5,6] Danishefsky et al. proposed that the products could be formed by two different reaction paths: 1) the traditional Diels–Alder-type cycloaddition reaction and 2) formation of the HDA adduct by a Mukaiyama aldol reaction path, depending especially on the Lewis acid catalyst employed.[7] In addition, coordination of chiral ligands such as BINOL and its derivatives,[8] bis(oxazolines),[9] and salen[10] to metal centers could provide a chiral environment for enantioselective control of the reaction. Jørgensen and co-workers investigated the HDA reaction of benzaldehyde with Danishefsky's diene catalyzed by an aluminum complex using the AM1 method.[5e] They concluded that the reaction proceeds along a Makaiyama aldol two-step pathway catalyzed by $(MeO)_2AlMe$, which is very different from the concerted pathway in the absence of catalyst. In BH_3-[5c] or BF_3-catalyzed[5a] HDA reactions, coordination of Lewis acid catalysts to formaldehyde increased the asynchronicity and charge separation of transition states and allowed for a concerted and a stepwise mechanism in the reaction. The theoretical investigation performed by Yamada and co-workers indicated that increasing cationic character of the cobalt atom and coordination of a Lewis base to the central metal atom decrease the activation energy and improve the enantioselectivity of the HDA reaction catalyzed by cobalt complexes.[5b] A cationic oxazaborolidine Lewis acid catalyst was shown to change the reaction mechanism from concerted to stepwise and lowered the activation barriers in the DA reaction between 2-methylacrolein and cyclopentadiene according to DFT calculations by Li and co-workers.[6a]

Recently, systems in which a Schiff base is combined with a transition metal have been found to serve as excellent catalysts for various asymmetric reactions.[11] Therefore, theoretical investigations of reactions catalyzed by Schiff base complexes have attracted considerable attention.[5b] However, few analyses of the reaction pathways catalyzed by Schiff base titanium(IV) complexes as Lewis acids catalysts in the HDA reaction have been performed.[11c,d,4a,b] In addition, mechanistic investigations involving Brassard's diene are very limited as far as we know. To understand the mechanism of the HDA reaction between Brassard's diene and benzaldehyde and get useful information on asymmetric induction of the Lewis acid, theoretical investigations on the detailed mechanism of the reaction between Brassard's diene and benzaldehyde catalyzed by tridentate Schiff base titanium(IV) complexes were performed with the B3LYP[12] and ONIOM[13] methods in the present work.

Computational Details

For the present system, a complete DFT analysis would be difficult, owing to very bulky structural elements. Therefore, models were employed to probe the mechanism of the HDA reaction of benzaldehyde (PhCHO) and Brassard's diene catalyzed by tridentate Schiff base titanium (IV) complex catalysts (Scheme 1).



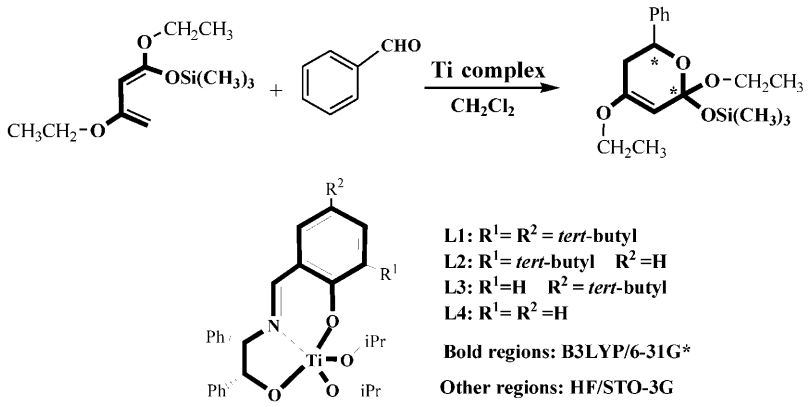
Scheme 1. Model system for HDA reaction.

For the model system, all calculations were performed with the hybrid DFT method B3LYP as implemented in the Gaussion 03 program package.[14] Geometries were fully optimized with the 6-31G* basis set and characterized by frequency analysis. The vibrational mode analysis corresponding to the unique imaginary frequency was adopted to confirm the relationship between intermediates and transition states. To obtain further insight into the electronic properties of the present system, natural bond orbital (NBO)[15] analysis was also performed. To understand the mechanism of reaction, a DFT analysis based on the reactivity indices (electrophilicity index ω and nucleophilicity index N)[6b,d,16,17] of reactants involved in these cycloadditions were also performed by computing the B3LYP/6-31G* HOMO and LUMO energies at the ground-state of molecules. The effect of solvent on the reaction was considered by employing the self-consistent reaction field (SCRF) method based on the polarized continuum model (PCM)[18] at the B3LYP/6-311G** level. The calculated total energies and relative energies for stationary points corresponding to reactants are listed in Table S1 in the Supporting Information. Unless otherwise specified, the single-point energies obtained in CH_2Cl_2 are used in the discussion.

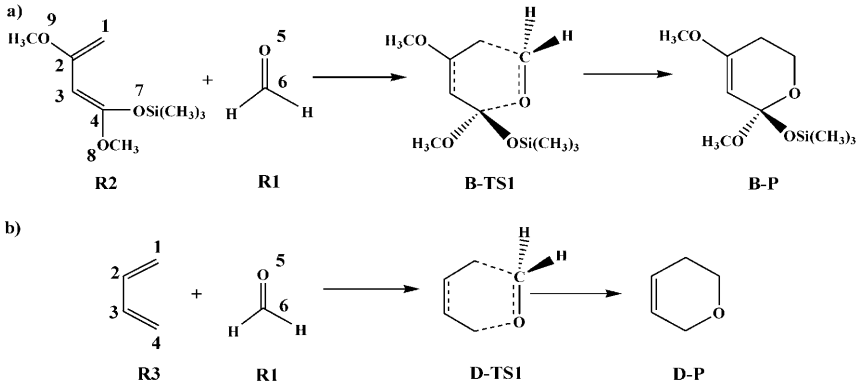
On the basis of the results obtained from the model system, the actual reaction was further considered. With a view to computational costs, the ONIOM method was used to simulate the asymmetric reaction system in the present study (the layering of the system is shown in Scheme 2). The internal region was treated with hybrid functional B3LYP and 6-31G* basis set. The remainder of the system was optimized at the HF/STO-3G level. The bonds between atoms in the core and outer layers were broken and saturated by hydrogen atoms (link atoms) for the higher level part of the ONIOM calculation on the core system. Each transition state was characterized by analysis of the vibrational mode corresponding to its unique imaginary frequency. The calculated total energies and relative energies for stationary points corresponding to reactants are listed in Table S2 in the Supporting Information.

Results and Discussion

The calculations indicate that the reactions of Brassard's diene (Scheme 3a) and 1,3-butadiene (Scheme 3b) with formaldehyde in the absence of catalysts take place by a one-step, two-stage mechanism, which leads to the formation of the corresponding cycloadducts through transition states **B-TS1** and **D-TS1**, respectively. The lengths of the forming C1−C6 and C4−O5 bonds of 1.997 and 2.142 Å in **D-TS1** and 1.891 and 2.508 Å in **B-TS1**, suggest that both



Scheme 2. Layering of the catalytic reaction system catalyzed by chiral tridentate Schiff base titanium(IV) complex.



Scheme 3. Pathways of the HDA reaction for Brassard's diene (a) and 1,3-butadiene (b) with formaldehyde in the absence of catalysts.

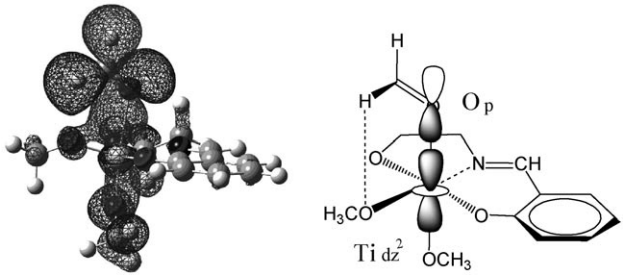
D-TS1 and **B-TS1** are asynchronous transition states associated with a two-stage mechanism. These results are similar to those from theoretical investigations on the reaction of formaldehyde with 1,3-butadiene by Houk et al.[5c] and on the polar Diels–Alder reaction by Domingo and co-workers.[16a] The present calculations indicate that Brassard's diene exhibits higher reactivity than 1,3-butadiene, which is verified by the lower free-energy barriers (10.8 kcal mol^{-1} for Brassard's diene vs. 17.6 kcal mol^{-1} for 1,3-butadiene) in the reaction.

Recent studies on DA reactions by Domingo and co-workers have shown that the electrophilicity and nucleophilicity indices defined within the framework of DFT are powerful tools for correctly explaining the electronic activation of the reagents involved in polar Diels–Alder reactions.[16] Table 1 shows the static global properties, which include electronic chemical potential μ, chemical hardness η, global electrophilicity ω, and global nucleophilicity N of Brassard's diene, 1,3-butadiene, and formaldehyde. Since the electronic chemical potential of dienes (−0.0789 a.u. for Brassard's diene and −0.1270 a.u. for 1,3-butadiene) are higher than that of electrom-deficient formaldehyde (−0.1553 a.u.), charge transfer during a polar HDA reaction will occur from diene to formaldehyde. Compared with 1,3-butadiene, Brassard's diene with higher nucleophilicity index (N= 4.27 eV) should be more reactive as nucleophile than 1,3-butadiene (N=2.83). The $\Delta\omega$ of 1.03 eV for the Brassard's diene/formaldehyde pair indicates the reaction will have a highly polar character, which is in agreement with pronounced charge-transfer character at the TS (0.65 e for Brassard's diene and 0.19 e for 1,3-butadiene). Furthermore, NBO analysis indicates that the negative charge accumulated on the terminal C1 atom of Brassard's diene is remarkably larger than that for 1,3-butadiene (−0.611 vs. −0.505). This is favorable for the interaction between Brassard's diene and formaldehyde in an HDA reaction. As a result, Brassard's diene is more reactive than 1,3-butadiene.

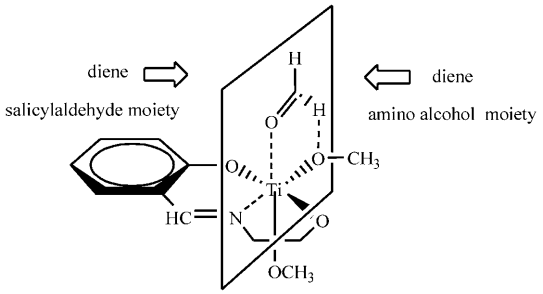
In our investigation, a non-chiral tridentate Schiff base model was employed to probe the possible reaction mechanism in detail, in particular to identify the rate-determining steps (RDS) for the entire HDA reaction. The five-coordinate tridentate Schiff base titanium complex **cat** is initially formed when the Schiff base ligand interacts with Ti(O*i*Pr)$_4$. This Ti complex can be regarded as the active species in the HDA reaction, and was investigated theoretically in our previous work.[19] Next, the external aldehyde coordinates to the titanium center to form the six-coordinate Ti complex **COM** (Scheme 4). The NBO analysis indicates that an orbital interaction exists between the p orbital of the O atom and the d_{z^2} orbital of the Ti atom, which leads to a decrease in the Wiberg bond index of the C=O bond (from 1.929 to 1.839). In such an electronic rearrangement, coordination of aldehyde to the

Table 1. Electronic chemical potential μ, chemical hardness η, global electrophilicity ω, and global nucleophilicity N for tridentate Schiff base titanium(IV) complex **COM**, formaldehyde, Brassard's diene, and 1,3-butadiene.

Reactant	μ [a.u.]	η [a.u.]	ω [eV]	N [eV]
COM	−0.1339	0.1479	1.65	3.46
formaldehyde	−0.1553	0.2264	1.45	1.82
1,3-butadiene	−0.1270	0.2084	1.05	2.83
Brassard's diene	−0.0789	0.1992	0.42	4.27



Scheme 4. Orbital interaction between the O atom of formaldehyde and the Ti atom in the six-coordinate tridentate Schiff base titanium complex **COM**.



Scheme 5. Attack of diene on formaldehyde from the salicylaldehyde moiety and amino alcohol moiety sides.

Ti complex increases the electrophilicity of the carbonyl compound and favors the reaction through a more polar process.

In the following step, Brassard's diene can approach formaldehyde alternatively from the amino alcohol side or the salicylaldehyde side, leading to formation of a C–C bond in **a-B-IM2** and **s-B-IM2** via transition states **a-B-TS1** or **s-B-TS1**, respectively (Scheme 5). The calculations predict free-energy barriers of 8.4 and 8.2 kcal mol^{-1}, respectively. As shown in Figure 1, in **a-B-TS1**, the C1–C6 distance of 2.051 Å is shorter than that in **s-B-TS1** (2.091 Å). Simultaneously, the C6–O5 bonds are elongated remarkably (from 1.206 Å to 1.278 Å for **a-B-TS1** and to 1.267 Å for **s-B-TS1**), which indicates activation of the C=O bond of formaldehyde. Meanwhile, NBO analysis indicates that the Wiberg bond index for the forming C–C bond is larger and that for the C=O bond is smaller in **a-B-TS1** (0.446 and 1.374, respectively) than in **s-B-TS1** (0.396 and 1.431, respectively). The C1–C6 and C4–C5 distances are 1.589 and 2.928 Å for **a-B-IM2** and 1.587 and 3.126 Å for **s-B-IM2**. According to NBO analysis, the net charge on the Ti carbonyl complex framework is −0.76 e in **a-B-IM2** and −0.78 e in **s-B-IM2**. These large values, which are in agreement with the larger dipole moment of the TSs (8.89 D for **a-B-IM2** and 7.32 D for **s-B-IM2**), indicate that both **a-B-IM2** and **s-B-IM2** exhibit zwitterionic character. Next, six-membered ring addition products **a-B-P** and **s-B-P** are formed via transition states **a-B-TS3** and **s-B-TS3**, respectively. The calculations predict that the free-energy barriers for this ring-closure step are 5.8 and 7.3 kcal mol^{-1}, respectively. The interaction between C4 and O5 in **a-B-TS3** is stronger than that in **s-B-TS3**, which was verified by the larger Wiberg bond index (0.344 vs. 0.338) and the shorter distance between C4 and O5 (1.983 vs. 1.990 Å).

We also investigated the mechanism of reaction between 1,3-butadiene and formaldehyde catalyzed by the tridentate Schiff base titanium(IV) complex for comparison with that of Brassard's diene. The calculations indicate that the reaction follows the same one-step, two-stage pathway. The TS in which attack of 1,3-butadiene occurs from the amino alco-

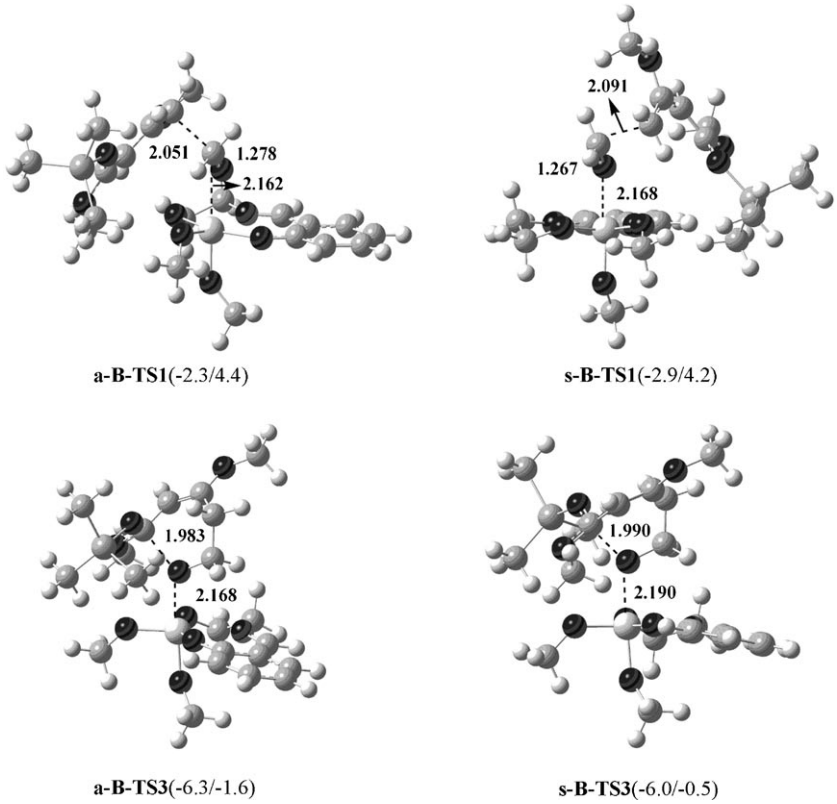


Figure 1. Optimized geometries and relative energies/relative Gibbs free energies [kcal mol^{-1}] for the transition states involved in the HDA reaction between Brassard's diene and formaldehyde catalyzed by a tridentate Schiff base titanium(IV) complex.

hol side (**a-D-TS1**) is lower in relative energy than its isomer **s-D-TS1**, in which 1,3-butadiene approaches the carbonyl group of formaldehyde from the salicylaldehyde side. As shown in Figure 2, **a-D-TS1** and **s-D-TS1** are asynchronous with longer distances (2.494–2.509 Å) between aldehyde oxygen and diene carbon atoms, while the distances between aldehyde carbon and diene carbon are relatively short (1.869–1.848 Å). The activation free-energy barriers are 14.9 kcal mol^{-1} for **a-D-TS1** and 16.0 kcal mol^{-1} for **s-D-TS1**. After the TSs, the products coordinated to the Ti complex are formed. The resulting system proceeds in a dissociative manner to release the product with recovery of the catalyst.

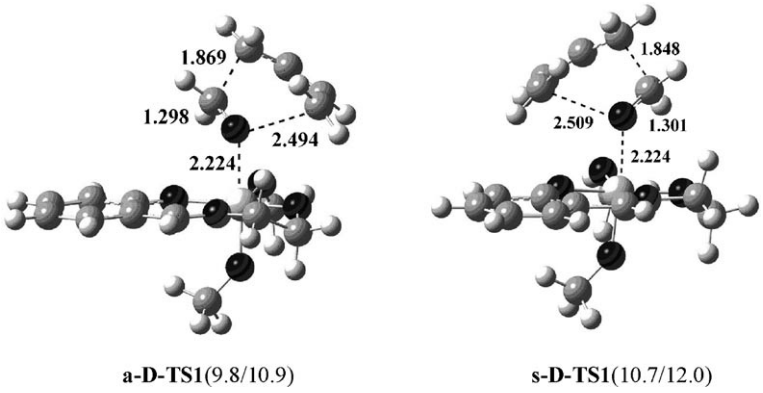


Figure 2. Optimized geometries and relative energies/relative Gibbs free energies [kcal mol^{-1}] for the transition states involved in the HDA reaction between 1,3-butadiene and formaldehyde catalyzed by a tridentate Schiff base titanium(IV) complex.

As shown in Figure 3, for Brassard's diene, the reaction takes place in a stepwise way, and the reaction step corresponding to formation of **a-B-IM2** is predicted to be the RDS in CH_2Cl_2 with free-energy barriers of 8.4 kcal mol^{-1}. In contrast to Brassard's diene, the reaction of 1,3-butadiene follows a one-step, two-stage pathway with an activation free-energy barrier of 14.9 kcal mol^{-1}. In comparison with the background reaction, the energy barrier decreases remarkably for both Brassard's diene and 1,3-butadiene in the presence of the Ti complex catalyst. According to analysis of reactivity indices, the coordination of tridentate Schiff base titanium(IV) complex to the carbonyl oxygen atom of formaldehyde leads to electrophilic activation of formaldehyde ($\omega = 1.65$ eV). The increase in electrophilicity index of formaldehyde on coordination to the Lewis acid increases $\Delta\omega$ of the catalyzed reaction and favors the HDA reaction through a more polar process.[16a,d] The net effect leads to increased charge transfer from diene to formaldehyde–catalyst complex **COM** in the transition state. Meanwhile, the increased population of the antibonding orbital of BD*(π)C6–O5 suggests activation of the C=O bond. As a result, the reaction is accompanied by lowering of the activation barrier in the presence of the Ti complex catalyst.

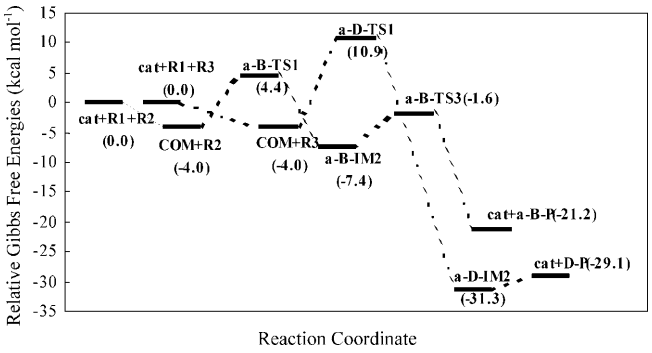


Figure 3. Relative Gibbs free-energy profiles for the model reactions of Brassard's diene and 1,3-butadiene with formaldehyde catalyzed by a tridentate Schiff base titanium(IV) complex (reaction pathway for diene approaching to formaldehyde from amino alcohol side).

On the other hand, according to the Hammond postulate, the transition state of the reaction involves large structural changes and significant electronic reorganizations.[20] Polar Diels–Alder reactions are characterized by the dominant nucleophile–electrophile interaction,[16a–b] which is related to the charge transfer at the corresponding TS. To probe the evolution of electronic population along the reaction and further understand the different electronic details between Brassard's diene and 1,3-butadiene in the presence of the Ti complex, charge transfer and orbital interactions between six-coordinate Ti complex **COM** and the diene moiety were analyzed. The calculations indicate that formation of the two intermediates (**a-B-IM2** and **a-D-IM2**) is closely related to the variation of charge on the diene and Ti carbonyl complex framework. Figure 4a displays the evolution of charge on the diene moiety as the reaction proceeds along the intrinsic reaction coordinate (IRC).[21] During formation of **a-B-IM2**, the positive charge in the diene moiety increases monotonically with accompanying formation of a C–C bond for Brassard's diene. Besides, the large stabilization energies [LpO9→BD*(π)C1–C2 (41.1 kcal mol^{-1}), LpO7→BD*(π)C3–C4 (38.9 kcal mol^{-1})and LpO8→BD*(π)C3–C4 (37.5 kcal mol^{-1})] indicate that the dominant interaction occurs between the OCH_3 and $OSi(CH_3)_3$ groups and the C=C bonds of Brassard's diene in **a-B-TS1**. The calculations also indicate that the interaction between the OCH_3 and $OSi(CH_3)_3$ substituents and the diene skeleton is further strengthened in Brassard's diene during formation of the C–C bond, which is verified by the increasing trend of the Wiberg bond indices between O and C atoms in Brassard's diene for formation of **a-B-IM2** via **a-B-TS1**, as shown in

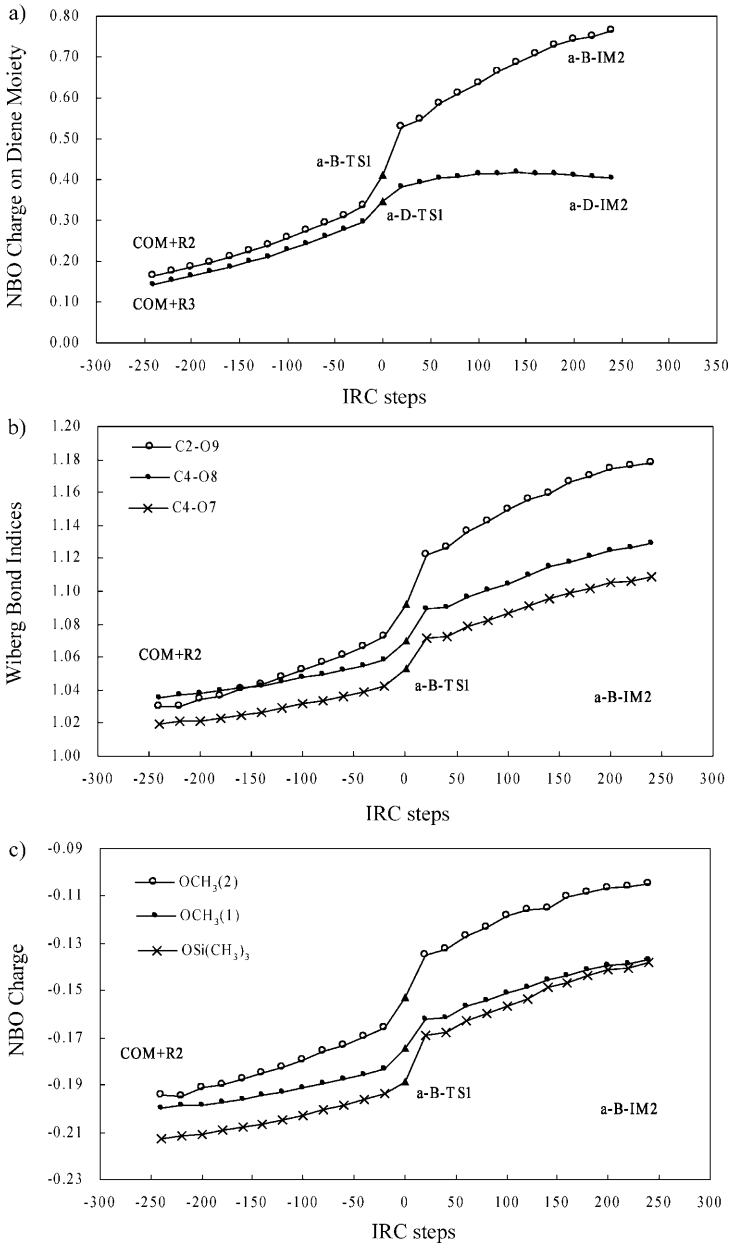


Figure 4. Evolution of charge populations and Wiberg bond indices in the formation of the C–C bond in the reaction of Brassard's diene and 1,3-butadiene with formaldehyde catalyzed by Ti complex. In c) $OCH_3(1)$ and $OCH_3(2)$ are the substituents at the C4 and C2 positions of Brassard's diene, respectively.

Figure 4b. Correspondingly, the charge accumulated on the OCH_3 and $OSi(CH_3)_3$ groups decreases gradually, which indicates increasing charge transfer from OCH_3 and $OSi(CH_3)_3$ groups to the formaldehyde moiety in this step (shown in Figure 4c). As a result, the charge populations on the 2p orbital of O in formaldehyde keep increasing concomitantly with formation of C–C bond (see Figure S1 in the Supporting Information).

On the contrary, the charge-transfer process in the formation of **a-D-IM2** is very different from that in the formation of **a-B-IM2** discussed above. Initially, charge transfer from 1,3-butadiene to formaldehyde decreases the charge on 1,3-butadiene. With formation of the second C–O bond there is a slight decrease in charge transfer as a consequence of a retrodonation process. As shown in Figure 4a, the range of charge variation in the diene moiety in the formation of **a-D-IM2** is significantly narrower than in the formation of **a-B-IM2** (ca. 0.27 vs. ca. 0.60). The net charge transfer of 0.35 e in **a-D-TS2** is smaller than that in **a-B-TS2** (0.41 e). These phenomena can be attributed to the electron-donating properties of the OCH_3 and $OSi(CH_3)_3$ groups. After formation of the first C–C bond, the lack of negative charge in 1,3-butadiene results in charge transfer from O5 of formaldehyde to the C4 atom, which is verified by the increased orbital interaction between O5 and C4 after the TS and before formation of the C–O bond. As a result, the charge population in the 2p orbital of O5 atom decreases along with formation of C–O bond (see Figure S1 in the Supporting Information).

Therefore, the mechanism of the HDA reaction catalyzed by tridentate Schiff base titanium(IV) complex **cat** is substrate-related. The electronic features of both reagents play a central role in development of the reaction. For Brassard's diene as substrate, the OCH_3 and $OSi(CH_3)_3$ substituents may play the key role for formation of the transition state by participating in charge transfer from Brassard's diene to formaldehyde. In addition, they are favorable for stabilization of the charges of opposite sign in zwitterionic intermediates, and hence the reaction takes place by a two-step mechanism via a zwitterionic intermediate instead of a one-step two-stage one. Meanwhile, the increased nucleophilic character of Brassard's diene with electron-releasing substituents, together with the increase in electrophilic character of formaldehyde by coordination to the Ti complex, results in an enhancement of the charge transfer that is accompanied by a lowering of the activation barrier.

To explore the origin of the stereoselectivity of the HDA reaction of Brassard's diene catalyzed by the tridentate Schiff base titanium(IV) complex, chiral ligand **L1** was used for investigation of the actual reaction system. Based on the results obtained on the model reaction above, theoretical calculations in this section were performed at the ONIOM-(B3LYP/6-31G*:HF/STO-3G) level (see Computational Details). When benzaldehyde interacts with the chiral tridentate Schiff base titanium(IV) complex, two distinct intermediates can be initially formed, denoted **L1-O-IM-up** and **L1-O-IM-down** in Figure 5. According to the calculations, **L1-O-IM-up**, in which benzaldehyde is axially coordinated to the Ti center above the pseudoplane of the Schiff base ligand and *anti* arrangement with the phenyl rings of the amino alcohol moiety, is 3.3 kcal mol^{-1} lower in energy. Thus, the formation of **L1-O-IM-up** would be more favorable in the entrance of the reaction in terms of energy and geometry.

As shown in Figure 5, the H atom of benzaldehyde in the coordinated substrate is orientated toward the isopropoxyl group by a hydrogen bond in **L1-O-IM-up** and **L1-O-IM-down**. As a result, there are four possible routes of attack

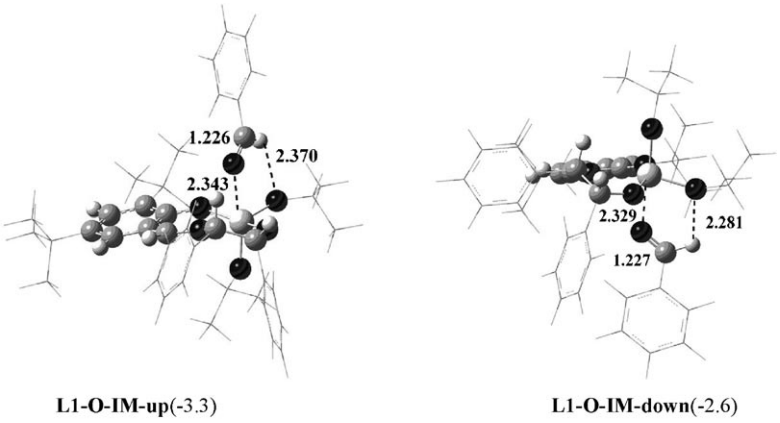


Figure 5. Optimized structures for the intermediates in the HDA reaction catalyzed by Ti complex. Energies relative to the reactants [kcal mol^{-1}] calculated at the ONIOM (B3LYP/6-31G*:HF/STO-3G) level are listed in parentheses.

when a diene approaches benzaldehyde. The bulky *tert*-butyl groups on the salicylaldehyde moiety of the Schiff base may increase the hindrance of *Si* face of benzaldehyde in **L1-O-IM-up** and the *Re* face of benzaldehyde in **L1-O-IM-down**. Meanwhile, the two large phenyl groups at the amino alcohol moiety would also play a crucial role by shielding the *Si* face of the reacting carbonyl group, and hinder approach of the diene to the *Si* face in **L1-O-IM-down**. Therefore, the geometrical analysis of six-coordinate Ti complexes identifies kinetically favorable *Re* attack of the diene on benzaldehyde of **L1-O-IM-up** in the following C–C formation step.

Starting from **L1-O-IM-up** and **L1-O-IM-down**, four transition sates are located theoretically when the attack of diene on the *Re* or *Si* face of benzaldehyde is considered, which are denoted as **L1-TS-*Re*-up**, **L1-TS-*Si*-up**, **L1-TS-*Re*-down**, and **L1-TS-*Si*-down** (Figure 6). As expected, the calculations predict that the lowest energy transition state is **L1-TS-*Re*-up**, which corresponds to *Re* attack on benzaldehyde to produce final *R* product (see Table S2 in the Supporting Information). For **L1-TS-*Re*-up**, the phenyls groups at the amino alcohol moiety are below the pseudo-plane of the Schiff base. Brassard's diene approaches benzaldehyde from the side of the amino alcohol moiety, avoiding steric repulsion with the bulky *tert*-butyl *ortho* and *para* substituents of the salicylaldehyde moiety. Meanwhile, the OSi-$(CH_3)_3$ group of Brassard's diene is far away from other groups connected directly to the Ti center. Compared with **L1-TS-*Re*-up**, **L1-TS-*Si*-up** suffers more steric hindrance from *tert*-butyl groups at the salicylaldehyde moiety of the Schiff base and therefore is kinetically disfavored. The calculations predict that the relative energy for **L1-TS-*Si*-up** is 8.5 kcal mol^{-1} higher than that of the corresponding **L1-TS-*Re*-up** in the gas phase. The competing transition state to produce the *S* product is identified as **L1-TS-*Si*-down**. For **L1-TS-*Si*-down**, Brassard's diene attacks benzaldehyde from the side of the salicylaldehyde moiety. Owing to pronounced steric repulsion between the benzaldehyde substrate and the phenyl groups of the Schiff base, the relative energy of **L1-TS-*Si*-down** is 3.6 kcal mol^{-1} higher than that of its analogue **L1-TS-*Re*-up**, and this suggests that

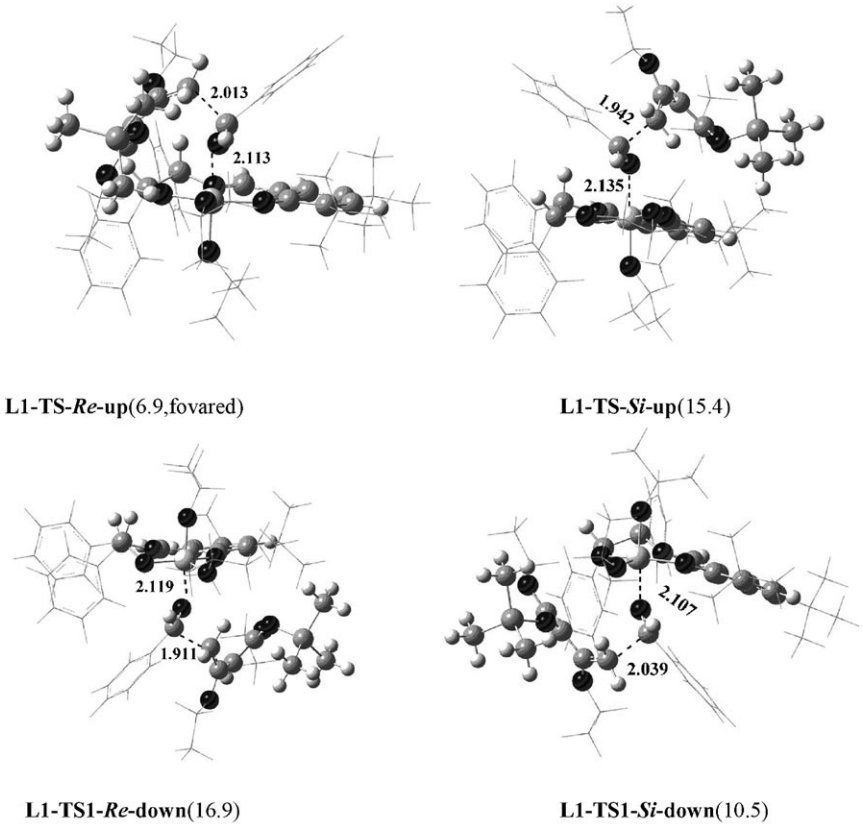


Figure 6. Optimized structures and relative energy [kcal mol^{-1}] for the transition states of the stereocontrolling step in the HDA reaction catalyzed by Ti complex.

the predominant product has the *R* configuration. These results are in qualitative agreement with the experimental observations.[4a–b,k]

Furthermore, to gain insight into the steric effects of the substituents on the stereoselectivity of the reaction, tridentate Schiff base ligands with or without *tert*-butyl groups at the salicylaldehyde moiety were also investigated comparatively. The key transition states in the stereocontrolling step were optimized at the same level. As shown in Table 2 and Table S3 in the Supporting Information, the energy gap between the competing transition states corresponding to the *Si* and *Re* attack is increased significantly when the *ortho* substituent R^1 is changed from H to *tert*-butyl (from **L4** to **L2**). On the contrary, when a *tert*-butyl group replaces an H atom in the *para* substituent R^2 (from **L4** to **L3**), the energy difference of these competing TSs is still slight, and this suggests that the stereoselectivity of the reaction is not sensitive to the R^2 substituent. Therefore, it was reasonable to deduce that the combination of phenyl groups at the amino alcohol moiety and the *ortho-tert*-butyl group of the salicylaldehyde moiety can generate a good chiral ligand environment that controls the stereochemistry of the reaction and leads to high *ee* values, in agreement with the experimental observations.[4a]

Table 2. Differences in relative energy ΔE [kcal mol^{-1}] for the lowest energy transition states corresponding to *Si* and *Re* attack for four ligands and the *ee* values obtained by experimental investigation.[4a]

Ligand	R^1	R^2	ΔE	*ee* [%]
L1	*t*Bu	*t*Bu	3.6	92
L2	*t*Bu	H	3.5	76
L3	H	*t*Bu	0.9	71
L4	H	H	0.9	64

Conclusion

Theoretical analysis of the HDA reaction catalyzed by a tridentate Schiff base titanium(IV) complex reveals the following results:

1) The mechanism of HDA reaction catalyzed by tridentate Schiff base titanium(IV) complex **cat** is closely related to the electrophilic/nucleophilic properties of the substrate. A stepwise pathway is adopted for Brassard's diene, and a one-step, two-stage pathway for 1,3-butadiene. For Brassard's diene as substrate, the OCH_3 and $OSi(CH_3)_3$ substituents may play the key role for formation of the transition state and zwitterionic intermediate by participating in charge transfer from Brassard's diene to formaldehyde.
2) The combination of phenyl groups at the amino alcohol moiety and the *ortho-tert*-butyl group of the salicylaldehyde moiety plays an important role in the control of the stereoselectivity, which is in agreement with experimental observations.

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[17] The global electrophilicity index ω,[16c,16d] which measures the stabilization energy when the system acquires an additional electronic charge ΔN from the environment, is given) in terms of the electronic chemical potential μ and chemical hardness η by the following simple expression: $\omega\ [\mathrm{eV}]=(\mu^2/2\eta)$ Both quantities can be calculated in terms of the HOMO and LUMO electron energies ε_H and ε_L as $\mu\approx(\varepsilon_H+\varepsilon_L)/2$ and $\eta\approx(\varepsilon_H-\varepsilon_L)$. The nucleophilicity index N,[16b] based on the HOMO energies obtained within the Kohn–Sham scheme, is defined as $N=E_{HOMO(Nu)}-E_{HOMO(TCE)}$. The nucleophilicity is taken relative to tetracyanoethylene (TCE) as reference, because it has the lowest HOMO energy in a large series of molecules already investigated in the context of polar cycloadditions.

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