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On the mechanism of catalytic enantioselective hetero-Diels–Alder reactions of carbonyl compounds catalyzed by chiral aluminum complexes—a concerted, step-wise or Mukaiyama–aldol pathway

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Abstract—The mechanism for the hetero-Diels–Alder reaction of benzaldehyde with Danishefsky's diene catalyzed by various types of achiral and chiral aluminum complexes has been studied from a theoretical point of view using semi-empirical and ab initio calculations. The uncatalyzed reaction proceeds as a concerted reaction with an unsymmetrical transition state. The catalytic reaction has been studied using first $(MeO)_2AlMe$, followed by (*S*)-BINOL-AlMe as the catalysts, and the transition states and intermediates have been calculated for different reaction paths. The catalyst activates benzaldehyde making the carbon atom in the carbonyl functionality more electrophilic. Attempts to calculate a concerted reaction path failed. However, a two-step process, the first step being a nucleophilic attack of the activated diene to the carbonyl carbon atom, with a transition-state energy of up to 13 kcal mol^{-1}, depending on the catalyst and calculation method used, was found to take place leading to an aldol-like local energy-minimum intermediate. The second step, the ring-closure, which has a significantly lower transition-state energy leads to the hetero-Diels–Alder adduct. The mechanistic aspects of the catalytic hetero-Diels–Alder reaction is discussed on the basis of the calculations. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The hetero-Diels–Alder (HDA) reaction of carbonyl compounds with dienes is a convenient synthetic procedure for the preparation of six-membered heterocyclic compounds. In recent years an intensive effort has been performed to achieve asymmetric HDA reactions,[1] and especially has the synthetic development of catalytic enantioselective HDA reactions been in focus, while the number of mechanistic studies is limited.[2]

The basic idea in performing these reactions in a catalytic enantioselective manner is to use the Lewis-acid properties for coordination to the carbonyl compound leading to its activation, and the chiral ligand, which is coordinated to the Lewis acid, to direct the three-dimensional approach of the diene to one of the faces of the carbonyl compound. A variety of chiral Lewis-acid complexes can catalyze the HDA reaction of carbonyl compounds with dienes.[3] The choice of catalyst is dependent on the carbonyl compound. For unactivated aldehydes, especially chiral aluminum and boron, and chiral early transition- and lanthanide metal complexes are suitable catalysts.[3,4] These catalysts can be considered as hard-Lewis acid complexes.

For the reaction of e.g. benzaldehyde with activated dienes, such as the Danishefsky-type dienes, different reaction courses can take place depending on the chiral Lewis-acid catalyst used. Two mechanistic pathways have generally been taken into account (i) a traditional HDA-cycloaddition reaction or (ii) formation of the HDA adduct via a Mukaiyama–aldol reaction pathway followed by the cyclisation step as outlined in Fig. 1.[1i,3b,c,5] In several cases the Mukaiyama–aldol intermediate has been isolated and characterised and shown to undergo a ring-closure reaction leading to the HDA adduct. The traditional HDA-cycloaddition reaction pathway can also take different reaction courses, either as a concerted reaction with an unsymmetrical transition state, or as a step-wise mechanism.

The different reaction paths are dependent on especially the Lewis-acid properties, however, only very limited insight into the mechanism of catalytic enantioselective HDA reactions is available. Compared to the numerous theoretical calculations on the normal-Diels–Alder reaction, only very few theoretical studies of HDA reactions have been performed.[2] Furthermore, theoretical studies of the Lewis-acid catalyzed HDA reactions are even more limited. Houk et al. have for the reaction of formaldehyde with 1,3-butadiene calculated the C–C and C–O bond lengths to be 2.133 and 1.998 Å, respectively, in the transition state.[2b] This reaction was also investigated with the formaldehyde

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Keywords: catalysis; hetero-Diels–Alder; aluminum; aldehydes; dienes; calculations; mechanism.

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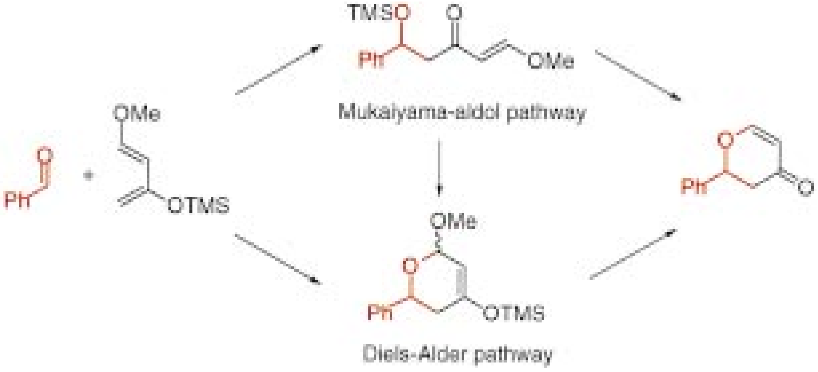
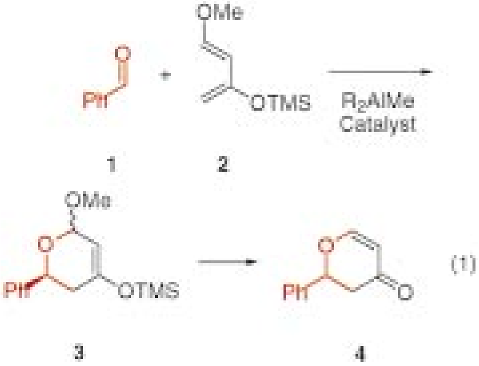


Figure 1. The two different reactions pathways for the reaction of benzaldehyde with Danishefsky's diene leading to the HDA adduct via a traditional Diels–Alder pathway or formation of the adduct via a Mukaiyama–aldol pathway.

oxygen atom coordinated to BH_3 as a model for a Lewis acid.[2b] Two transition states were located, one with BH_3 *exo*, and one *endo*, relative to the diene. The former has the lowest energy and the calculated transition-state structure is much less symmetrical than the transition state in the absence of a Lewis-acid catalyst. The transition state of the BH_3-catalyzed reaction has significant zwitterionic character, with a partial positive charge of 0.37 on the diene and a negative charge on the formaldehyde-oxygen atom of -0.65 and -0.28 on BH_3. The coordination of the carbonyl-oxygen atom to BH_3 makes the carbonyl group an acceptor of negative charge, and the O–B bond length in the transition state is 0.12 Å shorter compared with the BH_3-formaldehyde complex, indicating a tighter complexation in the transition state. At the highest level of calculations (MP2/6-31G*), the activation energy is 8.9 kcal/mol, which is 12.0 kcal/mol lower in energy than the uncatalyzed reaction.

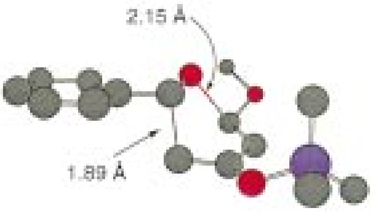
This paper will present the first theoretical investigation of the mechanism of the catalytic enantioselective HDA reaction of benzaldehyde **1** with Danishefsky's diene **2** leading to the HDA-adduct **3** (Eq. (1)). The mechanism, concerted *vs*. step-wise, or Mukaiyama–aldol reaction course for the uncatalyzed reaction and the reaction in the presence of both achiral and chiral aluminum complexes will be presented in the following (for theoretical details see Methods).



(1)

2. Results and discussion

Starting with the uncatalyzed reaction of benzaldehyde **1** with Danishefsky's diene **2**, there are in principle eight different transition states for the reaction of **1** with **2**; two for each of the two regioisomers, an *exo* and *endo* approach for each of the two regioisomers, and each of these giving two different enantiomers. The latter will not be considered for the uncatalyzed reaction. The calculated transition-state structure for the lowest-energy path using AM1 calculations[6] is shown in **5** (color code: carbon: grey; oxygen: red; silicon: purple; hydrogen atoms omitted for clarity). The transition-state energy for the concerted reaction of **1** with **2** leading to *exo*-**3** (optimized structure shown below) is calculated to be 27 kcal mol^{-1} relative to the reactants, while the transition-state energy for the reaction leading to *endo*-HDA adduct is calculated to be 28 kcal mol^{-1}. Based on the small energy difference it is thus not possible to distinguish between the two transition states on the basis of the present calculations. For the transition-state structure **5**, the C–C and C–O bond lengths are 1.89 and 2.15 Å, for the concerted HDA reaction of **1** with **2**, respectively. Attempts to form the zwitterionic aldol transition-state intermediate in the absence of stabilization by the aluminum catalyst (vide infra), resulted in either separation to the reactants or a collapse to the HDA-adduct, hence no transition state could be found for this zwitterionic intermediate in the uncatalyzed reaction.



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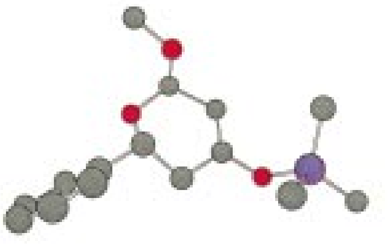


exo-3

The course of the HDA reaction of benzaldehyde **1** with

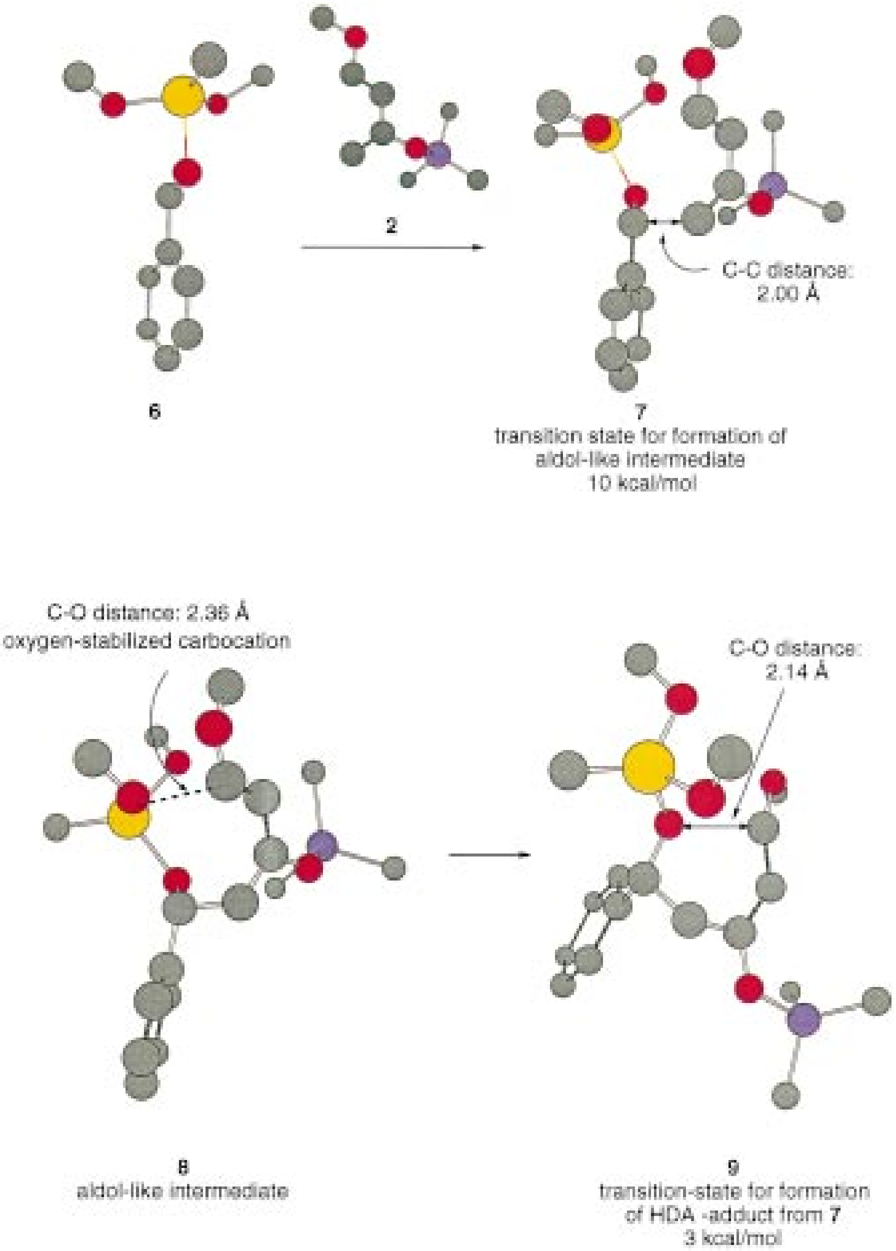


Figure 2. Reaction of benzaldehyde **1** activated by $(MeO)_2AlMe$, **6**, with Danishefsky's diene **2** along the Lewis acid aldol-like pathway. Structure **7** is the transition state for the formation of the Lewis acid aldol-like intermediate **8**, while **9** is the transition state for the formation of the HDA adduct **3b**. Color code: carbon: grey; oxygen: red; silicon: purple; aluminum: yellow.

Danishefsky's diene **2** was studied next in the presence of various aluminum catalysts using AM1 calculations.[6] In the following the main attention will be focused on the reaction catalyzed by the $(MeO)_2AlMe$ and the (*S*)-BINOL-AlMe catalyst. Benzaldehyde **1** is able to coordinate in a monodentate fashion to the $(MeO)_2AlMe$ catalyst and the structure of the activated benzaldehyde **6** is shown in Fig. 2. The coordination of **1** to $(MeO)_2AlMe$ leads to changes of the carbonyl group both structurally and electronically and the major changes are given in Table 1.

It appears from the results in Table 1 that the C–O bond length is increased from 1.23 Å in benzaldehyde **1** to 1.26 Å in the **1**-$(MeO)_2AlMe$ complex **5**. There are three significant

Table 1. Structural and electronic changes of the carbonyl fragment of benzaldehyde **1**, and **1** coordinated to $(MeO)_2AlMe$ (6)

	Ph-CHO	Ph-CHO–$(MeO)_2AlMe$ **6**
C–O (Å)	1.23	1.26
HOMO (eV)	−9.98	−9.98
LUMO (eV)	−0.44	−1.12
c(C)-LUMO[a]	0.37	0.50
c(O)-LUMO[b]	−0.37	−0.40
q(C)[c]	0.21	0.26
q(O)[c]	−0.32	−0.33

[a] MO coefficient on carbon atom of the carbonyl group.
[b] MO coefficient on oxygen atom of the carbonyl group.
[c] Charge on the atoms in the carbonyl group.

changes taking place in terms of electronic properties: (i) the LUMO of **1** is lowered from -0.44 eV in the uncoordinated case to -1.12 eV for **6**, (ii) the LUMO atomic coefficient of the carbon atom of the carbonyl group changes from 0.37 in **1** to 0.50 for **2**, and (iii) the charge on the carbon atom of the carbonyl group changes from 0.20 to 0.26 by coordination of the Lewis acid. These electronic changes account for the activation of **1** by coordination to the aluminum catalyst, and it is especially notable that the carbonyl carbon atom becomes more polarized—more electrophilic—by the coordination to $(MeO)_2AlMe$.

The reaction of benzaldehyde **1** coordinated to $(MeO)_2AlMe$ (**5**) with Danishefsky's diene **2** was investigated next. Several attempts to calculate a transition-state structure for a concerted reaction path leading to the HDA-adduct failed. However, a transition state **7** was easily located for the reaction path leading to the Lewis-acid coordinated aldol-like intermediate outlined in Fig. 2. The transition-state energy for **7** is calculated to be 10 kcal mol^{-1} relative to the separated reactants and the energy corresponds very well with the transition-state energy for the BH_3-catalyzed HDA reaction of formaldehyde with 1,3-butadiene.[2b] The structure of **7** shows clearly that **2** attacks the coordinated benzaldehyde in a nucleophilic addition-like reaction (aldol-like mechanism) with formation of the C–C bond between the carbonyl-carbon atom and the methylene-carbon atom of **2**. The C–C bond length in the transition state is calculated to be 2.00 Å. From transition state **7** (Fig. 2) the Lewis-acid coordinated aldol-like intermediate **8** is formed. The total energy of **8** is the same as the total energy of **6** and **2**. One of the oxygen atoms of the $(MeO)_2AlMe$ catalyst is of importance for stabilizing the intermediate **8** (Fig. 2). The bond length between this oxygen atom in $(MeO)_2AlMe$ and the sp^2-hybridized cationic-carbon atom in the diene species is calculated to be 2.36 Å. We have also calculated the reaction path for the same reaction using $AlMe_3$ as the Lewis acid catalyst and in this case the total energy of the Lewis-acid coordinated aldol-like intermediate was calculated to be 9 kcal mol^{-1} higher in energy relative to **8**. The transition-state energy for the formation of this intermediate is 18 kcal mol^{-1}, compared to 10 kcal mol^{-1} for transition state **7**. The higher energy of both the aldol-like intermediate and the transition-state energy for the formation of this intermediate shows the importance of the oxygen atoms of $(MeO)_2AlMe$ for the former reaction and for stabilizing the intermediate.

From the $(MeO)_2AlMe$ coordinated aldol-like intermediate **8** there are two possible reaction paths which can give the HDA-adduct **3** (we have not taken the *endo* and *exo* forms into consideration, due to the small energy difference between these products and in transition-state energies (<2 kcal mol^{-1})): (i) the direct formation of the HDA-adduct **3** or (ii) the migration of the TMS-group to the oxygen atom to which the Lewis acid is coordinated, leading to the Mukaiyama–aldol-like intermediate (Fig. 1). The transition state for the direct formation of **3** is presented as **9** in Fig. 2; this transition state has an energy barrier of 3 kcal mol^{-1} relative to intermediate **8**. The energy of the ring-closure HDA-adduct **3** lies at -17 kcal mol^{-1} relative to the reactants. The transfer of the TMS-group, leading to the Mukaiyama–aldol like intermediate, begins from the isomer of **8** where the two oxygen atoms involved are rotated so as to be aligned, and has an energy of 7 kcal mol^{-1} relative to the separated reactants because the catalyst oxygen atoms can no longer stabilise the intermediate. The transition state which follows lies 2 kcal mol^{-1} above the intermediate, or 9 kcal mol^{-1} above the separated species, and the aldol-like product lies 8 kcal mol^{-1} below the reactants.

Both the subsequent barriers are lower in energy than the initial barrier and this principally suggests that intermediate **8** will possess significantly more energy than is needed to cross the second barrier and will likely to be too short-lived to be observed. The reaction is thus stepwise-like in the sense that the reaction path moves through a discrete, local energy-minimum intermediate (**8**), but it is not stepwise in the phenomenological sense that there is a possibility of rotation about a sigma bond in the time before ring closure. In short, the aluminum-catalyzed HDA reaction is a stepwise reaction in which the first step is analogous to the aldol reaction rather than a 'true' HDA reaction with an activated diene, but it remains an HDA reaction in that ring closure is preferred to transfer of the TMS-group.

The calculated transition-state energies for the formation the HDA-adduct **3** show that the highest energy barrier is the initial step, the attack of the terminal methylene carbon atom of Danishefsky's diene **2** to the carbonyl carbon atom of the benzaldehyde coordinated to the Lewis acid. The reason for this change in reaction path compared with the uncatalyzed reaction, which takes place as a concerted unsymmetrical reaction, is suggested to be the change in the electronic structure of the carbonyl bond by coordination to $(MeO)_2AlMe$. This more polarized carbonyl carbon atom makes it probably more susceptible towards a nucleophilic attack—an aldol-like reaction—by the activated diene compared with the concerted reaction path. In Fig. 3 is a schematic representation of the energy changes of reaction path outlined. The results obtained for the change in energy for the HDA reaction of benzaldehyde **1** with Danishefsky's diene **2** in the absence of a catalyst and catalyzed by $(MeO)_2AlMe$ (via intermediate **6**) using AM1 calculations are shown as the red and upper green curve, respectively.

In order to test the reliability of the AM1 results we have calculated the HDA reaction of benzaldehyde **1** with Danishefsky's diene **2** catalyzed by $(MeO)_2AlMe$ using ab initio calculations with a RHF/6-31G basis set.[7] The reaction of **1** coordinated to $(MeO)_2AlMe$, intermediate **6**, with **2** shows the same reaction profile as obtained using the AM1 calculations. The reaction profile is presented as the lower green curve in Fig. 3. The transition state (similar to **7**) for the formation of the aldol intermediate (similar to **8**) is calculated be 8 kcal mol^{-1} with the forming C–C bond having a distance of 2.22 Å. The total energy of **8** is -13 kcal mol^{-1}, relative to the starting situation. The formed C–C bond in **8** is calculated to be 1.57 Å, compared to 1.56 Å when using AM1 calculations, while the C–O distance is 3.08 Å, which is slightly longer than the same bond length calculated using AM1 calculations. For the second step an increase in the transition-state energy is found compared to the first step, the transition-state energy is calculated to be -6 kcal mol^{-1} relative to the reactants,

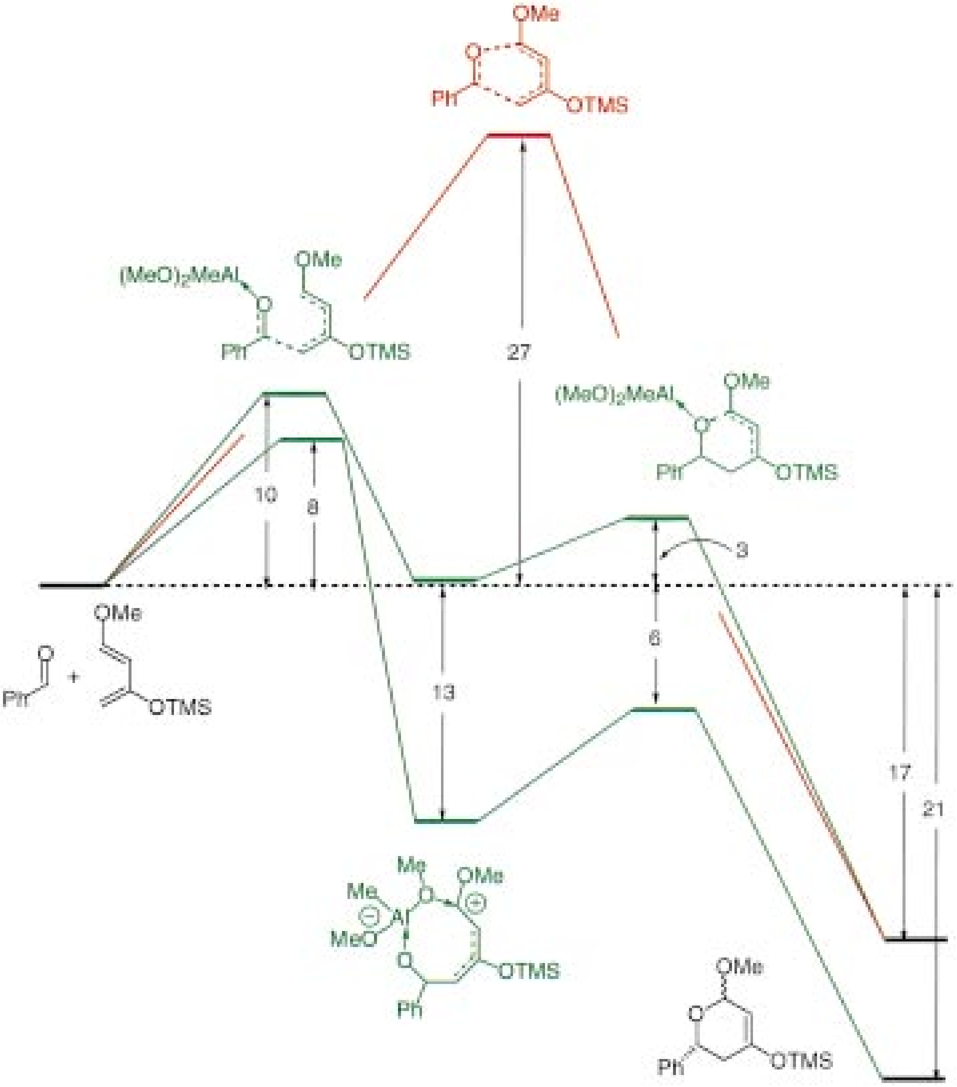
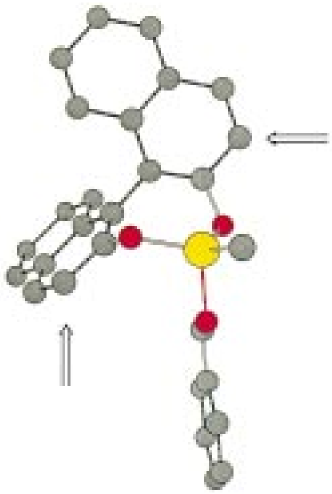


Figure 3. Schematic representation of the energy change for (i) the uncatalyzed concerted hetero-Diels–Alder reaction of benzaldehyde with Danishefsky's diene, outlined in red; (ii) the $(MeO)_2AlMe$ catalyzed reaction of benzaldehyde with Danishefsky's diene. The upper green curve is the results obtained using AM1 calculations and the lower green curve the results found using ab initio calculations with a RHF/6-31G basis set. All values are in kcal mol^{-1}.

but 7 kcal mol^{-1} relative to the intermediate. It is important to note that both the semi-empirical and ab initio calculations give the same reaction course for the catalytic HDA reaction of benzaldehyde **1** with Danishefsky's diene **2**.

The catalytic HDA reaction of benzaldehyde **1** with Danishefsky's diene **2** has also been investigated in the presence of (*S*)-BINOL-AlMe as the chiral Lewis-acid catalyst using AM1 calculations. The transition states have also been located and this reaction also shows a two-step reaction similar to the reactions catalyzed by the model system $(MeO)_2AlMe$ (see Figs. 2 and 3). Different coordination modes of **2** to (*S*)-BINOL-AlMe have been investigated and the lowest energy structure is outlined in **10**. This structure is very similar to the coordination of **2** to $(MeO)_2AlMe$, **6** and allows one at this point to understand the enantioface selection of this HDA reaction. Introduction of substituents in the 3,3′-position of the (*S*)-BINOL-AlMe catalyst (indicated with an arrow in **10**) will shield the *re*-face of the aldehyde functionality.

We have calculated various approaches of Danishefsky's diene **2** to the benzaldehyde-(*S*)-BINOL-AlMe intermediate **10**. The lowest transition-state energy has been calculated to be 13 kcal mol^{-1} and the structure of this transition state, the reaction step where the chiral center is formed, is shown in **11**. This transition state is very similar to the transition state calculated using $(MeO)_2AlMe$ as the catalyst and the C–C bond length is calculated to be 2.00 Å, similar to the results obtained above. The diene **2** approaches the *si*-face of the carbonyl functionality and this enantioface selection in the HDA reaction is in agreement with the stereoselection obtained in the experimental results.[3a,4a–f,j] The next step in the HDA reaction for the (*S*)-BINOL-AlMe catalyzed reaction is the formation of the intermediate similar to **8**. The calculated structure of this intermediate is also similar to **8** in Fig. 2 and is calculated to be 2 kcal mol^{-1} lower in energy, compared with the starting reactants. The next step, the ring-closure step has a transition-state energy of 4 kcal mol^{-1}, leading to the HDA-adduct, which is 16 kcal mol^{-1} lower in energy than the starting situation.



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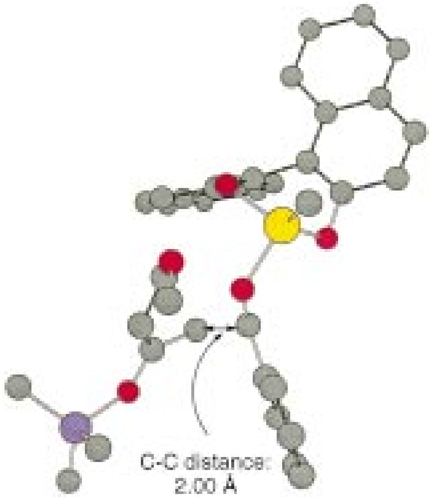

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The reaction path (transition states and intermediate) for the HDA reaction of benzaldehyde **1** with Danishefsky's diene **2** catalyzed (*S*)-BINOL-AlMe using semi-empirical calculations is thus similar to the reaction path obtained for the same reaction catalyzed by the model system $(MeO)_2AlMe$ using both semi-empirical and ab initio calculations.

3. Summary

We have in this paper shown by the use of theoretical calculations that the HDA reaction of benzaldehyde with Danishefsky's diene catalyzed by achiral and chiral aluminum complexes takes place as a two-step process. The first is a nucleophile-like attack by the activated diene on the carbonyl-carbon atom of benzaldehyde when coordinated to the catalyst. This leads to a short-lived intermediate where the cationic charge of the diene is stabilized by an association with an oxygen atom of the chiral catalyst. The second step is formation of the HDA adduct by a ring-closure reaction. The mechanism outlined can account for the absolute configuration of the chiral center formed in the HDA reaction when chiral BINOL-AlMe catalysts are applied.

4. Methods

AM1 calculations were performed using the Gaussian 94 program.[6] Hartree–Fock calculations were performed using Jaguar version 4.0.[7]

Following the standard practice, Hessians were calculated at all stationary points to ensure that the minima were characterised by all positive normal modes and the transition states by one negative mode that corresponded to the motion of the proper atoms. In doubtful cases, intrinsic reaction coordinate paths were traced to ensure that the transition state did in fact connect the proper local minima.

The transition states for the second step of the aldol mechanism, the transfer of the TMS-group from the incipient carbonyl to the alcohol moiety, present the difficulty that the potential energy surface is extraordinarily flat. The path was fully characterised for the reaction catalyzed by $(MeO)_2AlMe$ and was found to contain several 'saddle points' with vanishing gradients and one very soft (around −10 wave numbers) negative mode. In view of the fact that the entire path lies very much lower in energy than the initial barrier to formation of the aldol intermediate, the detailed path was not constructed for the reaction catalyzed by (*S*)-BINOL-AlMe. Rather, a simplified technique was used in which the TMS-group was moved from the initial geometry towards the final geometry in steps of 0.1 Å while all other coordinates were relaxed. In this way, the qualitative behaviour of this relatively uninteresting part of the potential energy surface was confirmed without the investment of undue effort.

In a larger sense, however, this difficulty represents an exception to our implicit claim that AM1 is 'accurate enough' to answer the chemical questions at the heart of this paper. Semi-empirical methods such as AM1 possess the same orbital structure as Hartree–Fock and perform well when the transformations being described are dominated by changes in orbital mixing, but becomes less reliable when describing unusual chemical structures. Thus it is hardly surprising that the method proves less than satisfactory in the case where a TMS-cation is being transferred over long distances.

The work in this paper arose as an effort to clarify the underlying mechanism of the title reaction, in support of an investigation of the use of BINOL derivatives as chiral induction agents,[4] hence the initial use of $(MeO)_2AlMe$ as a model for the full (*S*)-BINOL-AlMe catalyst. It was thought that such a model would preserve the essential features of the catalytic system while dramatically decreasing the computational cost. The utility of this model has been confirmed by extending the original work in two directions, the calculation of similar curves with the AM1 method for other aluminum catalysts and the confirmation of the original curves using the more accurate Hartree–Fock method. While the details of the energetic changed, the fundamental topology of the potential energy surface remained in every case: the reaction was initiated by the attack of the activated carbonyl upon one end of the diene to form a locally stable intermediate, followed by ring closure to form the HDA product or by transfer of the TMS-group to form the Mukaiyama–aldol product. In the case of the aluminum catalysts the pathway leading to the aldol precursor has a barrier 4–9 kcal mol^{-1} higher than that leading to the HDA precursor, which is consistent with the finding that no aldol product was observed experimentally.

Total energies obtained by the ab initio calculations using the RHF/6-31G basis set: **1**·(MeO)$_2$AlMe (**5**): −1604.4798 au; **6**: −1604.4658 au; **7**: −1604.4998 au; **8**: −1604.4881 au; **9**: −1604.5118 au.

Acknowledgements

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