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Experimental and Theoretical Studies on the Hydrogen-Bond-Promoted Enantioselective Hetero-Diels−Alder Reaction of Danishefsky's Diene with Benzaldehyde

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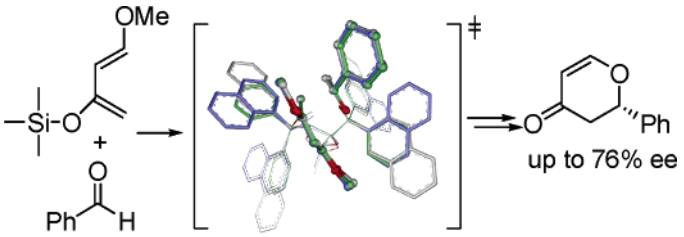

The enantioselective hetero-Diels−Alder (HDA) reaction of Danishefsky's diene with benzaldehyde has been achieved catalytically by a series of α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) derivatives through hydrogen-bonding activation, affording 2-phenyl-2,3-dihydro-4*H*-pyran-4-one after trifluoroacetic acid workup in moderate yield and good enantioselectivity. The α,α′-aryl substituents in the TADDOL molecules are found to exert a significant impact on both the activity and the enantioselectivity of the catalysis. In combination with the experimental investigations, the mechanism of the present reaction has also been studied theoretically using the ONIOM (B3LYP/6-31G*:PM3) method with *trans*-1,3-dimethoxy-1,3-butadiene as the model for Danishefsky's diene. In agreement with the experimental findings, the calculation results indicate that this TADDOL-catalyzed HDA reaction proceeds via a concerted mechanism through an asynchronous and zwitterionic transition structure (TS). The carbonyl group of benzaldehyde is activated by forming an intermolecular hydrogen bond with one of the hydroxy groups of TADDOL. Meanwhile, the intramolecular hydrogen bond between the two hydroxy groups in TADDOL is found to facilitate the intermolecular hydrogen bonding with benzaldehyde. The sense of asymmetric induction is well-rationalized by the analysis of the relative energies of TADDOL-complexed TSs, while the different stereocontrol capabilities exhibited by TADDOLs in the reaction can be qualitatively established on the basis of the structural features of their corresponding TSs.

Introduction

The enantioselective hetero-Diels−Alder (HDA) reaction of carbonyl compounds with 1,3-dienes represents one of the most important methods for the construction of optically active six-membered oxo heterocycles with extensive applications in natural or unnatural product synthesis.[1] Various chiral Lewis acid catalysts have been developed for the catalysis of this type of reaction.[2] Since the pioneering work by Rawal et al. in 2003,[3] the enantioselective HDA reaction promoted by a hydrogen bond using diol compounds as the chiral Bronsted acids has become a topic of interest in asymmetric organocatalysis.[4−6] In these catalytic systems, the hydrogen-bonding interaction between the hydroxyl group of the diol catalyst and the carbonyl group of the substrate is considered to be the main driving force of the catalysis. Here, the orientation of the α-aryl substituents in the catalysts, such as TADDOL[7a,8] (α,α,α′,α′-tetraaryl-1,3-dioxolan-4,5-dimethanol), provides a chiral environment for the enantioselective control of the reaction. An interesting phenomenon

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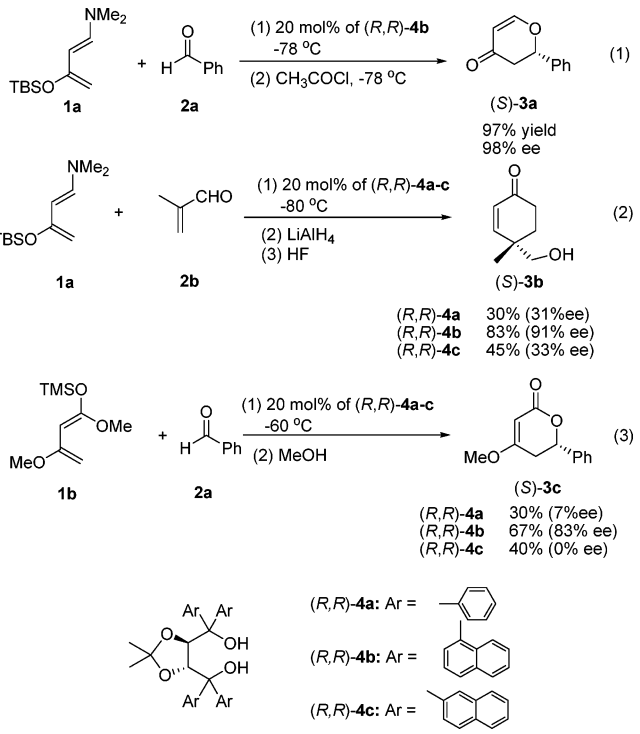
is that naphth-1-yl-TADDOL (**4b**) exhibits remarkably superior performance compared to that of its analogues, such as phenyl-TADDOL (**4a**) or naphth-2-yl-TADDOL (**4c**), in several HDA or DA reactions in terms of both activity and enantioselectivity (eq 1−3). For example, Rawal demonstrated that TADDOL (*R*,*R*)-**4b** is the best catalyst for the HDA reaction of diene **1a** with benzaldehyde (**2a**), affording (*S*)-**3a** in 97% yield with 96% ee (eq 1).[3] In the catalysis of the all-carbon Diels−Alder reaction of diene **1a** with methacrolein (**2b**), TADDOL (*R*,*R*)-**4b** (91% ee, 83% yield) is much more efficient than (*R*,*R*)-**4a** (31% ee, 30% yield) or (*R*,*R*)-**4c** (45% ee, 33% yield) (eq 2).[4c] We found that the HDA reaction of Brassard's diene (**1b**) with **2a** under the catalysis of (*R*,*R*)-**4b** afforded (*S*)-**3c** in 67% yield with 83% ee (eq 3).[5b] On the contrary, the use of (*R*,*R*)-**4a** or (*R*,*R*)-**4c** as the catalyst for the same reaction only resulted in a low yield of product **3c** in almost racemic form.

In contrast to the overwhelming majority of effort devoted to the synthetic aspects of HDA reactions of carbonyl compounds with dienes, the number of theoretical and mechanistic studies is limited.[9] In a study, McCarrick et al. used ab initio methods to model the reaction between formaldehyde and 1,3-butadiene.[9b−c] While the uncatalyzed reaction was found to



proceed via a concerted pathway with an unsymmetrical transition structure (TS), coordination of the Lewis acid BH_3 to formaldehyde not only makes it much more reactive, but also increases the asynchronicity and charge separation (zwitterionic character) in the TS, making a stepwise mechanism favored in solution. Later, Jørgensen and co-workers reported a semiempirical AM1 study on the mechanism of the HDA reaction of

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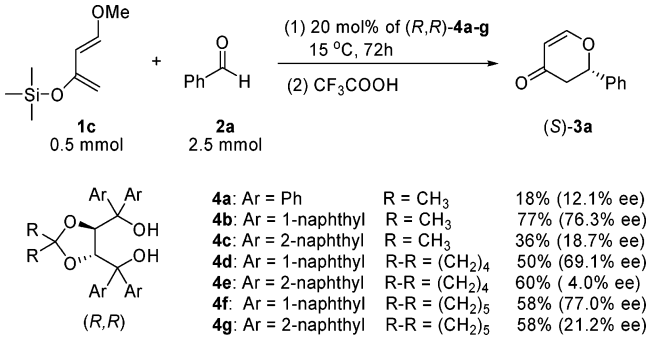
SCHEME 1. Enantioselective HDA Reaction of Danishefsky's Diene (1c) with Benzaldehyde (2a) Catalyzed by TADDOL Derivatives



benzaldehyde with Danishefsky's diene catalyzed by aluminum complexes.[9e] The results indicated that a concerted pathway is most likely in the absence of a catalyst, while a Makaiyama-aldol two-step pathway operates the reaction catalyzed by $(MeO)_2AlMe$. Intrigued by Rawal's experimental observation that hydrogen-bonding solvents such as chloroform or alcohols can greatly enhance the HDA reaction between **1a** and ketonic substrates, Domingo and Andres recently studied the model HDA reaction between *N*,*N*-dimethyl-1-amino-3-methoxy-1,3-butadiene and acetone promoted by hydrogen-bonding interaction(s) with the solvent (chloroform) molecule(s) using density functional theory (DFT) at the B3LYP/6-31G* level.[9g] The results suggested that the feasibility of Rawal's cycloadditions is not only a consequence of the increase of the electrophilicity of the ketone by the explicit solvation, but also attributable to the strong nucleophilic character of the substituted butadiene **1a**.

To clarify the effect of the hydrogen-bonding interaction and the impact of aryl groups in the TADDOL-catalyzed enantioselective HDA reaction of diene with carbonyl compounds and to gain a deeper understanding of the mechanistic aspects of the catalysis, herein we report our results on the experimental and computational studies of the hydrogen-bond-promoted enantioselective HDA reaction of Danishefsky's diene (**1c**) with benzaldehyde (**2a**; Scheme 1). Although this reaction represents one of the most important C−C bond-forming reactions in asymmetric catalysis,[2] it has not yet been furnished by hydrogen-bonding activation.

Results and Discussion

Experimental Studies on the TADDOL-Catalyzed Enantioselective HDA Reaction of Danishefsky's Diene with Benzaldehyde. A variety of α,α,α′,α′-tetraaryl-substituted TADDOL derivatives (**4a**−**g**, Scheme 1), synthesized according to the published procedure,[5b] were tested for their catalytic efficiency in the HDA reaction of Danishefsky's diene (**1c**) with benzaldehyde (**2a**). Typically, the reactions were run at room temperature for 72 h under solvent-free conditions with a TADDOL-catalyst loading of 20 mol %, followed by workup with trifluoroacetic acid (TFA). As shown in Scheme 1, under otherwise identical conditions, the HDA product 2-phenyl-2,3-dihydro-4*H*-pyran-4-one (**3a**) was obtained in varying yields and ee values, depending on the structures of the TADDOLs used. The reaction of Danishefsky's diene (**1c**, 1.0 mmol) with benzaldehyde (**2a**, 0.5 mmol) in the presence of 20 mol % of **4a** proceeded to give 2-phenyl-2,3-dihydro-4*H*-pyran-4-one in 18% yield with 12.1% ee. Remarkably, all the TADDOL derivatives with 1-naphthyl substituents were superior to those having 2-naphthyl or phenyl rings. Moreover, the change of the R group in the backbone of TADDOL from methyl (**4b**) to 1,4-butylene (**4d**) or 1,5-pentylene (**4f**) affected the enantioselectivity slightly. Among the three 1-naphthyl-substituted catalysts **4b, 4d**, and **4f, 4b** turns out to be the best one in terms of both enantioselectivity and reactivity.

Two possible pathways for the enantioselective addition of Danishefsky's diene to aldehydes have been reported: Mukaiyama aldol condensation versus concerted [4+2] cycloaddition.[2d] Presently, the isolation and characterization of the reaction intermediate would provide useful information in this respect (Scheme 2). The ^1H NMR spectral identification of the isolated primary product formed by the reaction of **1c** with **2a** in the presence of **4b** prior to CF_3COOH treatment suggests that the [4+2] cycloadduct is formed exclusively (see Figure S1 in Supporting Information), supporting a concerted cycloaddition mechanism (Scheme 2).

Computational Methods: For the present system, a complete DFT[10] analysis would be impractical, owing to the very bulky structural elements, such as the α,α,α′,α′-tetraaryl groups of the TADDOL catalysts. On the other hand, the use of semiempirical approaches would very likely be flawed by an imperfect description of the critical parameters in the TSs, which may result in a poor estimation of the effect of structural elements in the catalyst on the activity and enantioselectivity. The ONIOM (B3LYP/6-31G*:PM3) method[11] appears to be the best choice for the present case: the critical parts of the reacting system can be relatively accurately described using DFT calculation at the B3LYP/6-31G*[12,13] level, while the effects of the different aryl substituents of the TADDOLs can be accounted for by a semiempirical PM3[14] treatment. To further reduce the computational cost, we utilized the *trans*-1,3-dimethoxy-1,3-butadiene (**5**; Figure 1) as the working model of Danishefsky's diene (**1c**). The energies of all stationary points (including the B3LYP/6-31G*:PM3 optimized geometries) were calculated by DFT at the B3LYP/6-31G* level.

The calculations were performed using the Gaussian 98 program.[15] The two geometry layers of the ONIOM calculation are denoted as the high layer and the low layer, as depicted in Figure 1, where the high layer is the level on the core layer and the low layer is the level on the whole system. The core layer contains the reactive part of the catalytic system: benzaldehyde, the model diene (**5**) and *trans*-4,5-bis(hydroxymethyl)-1,3-

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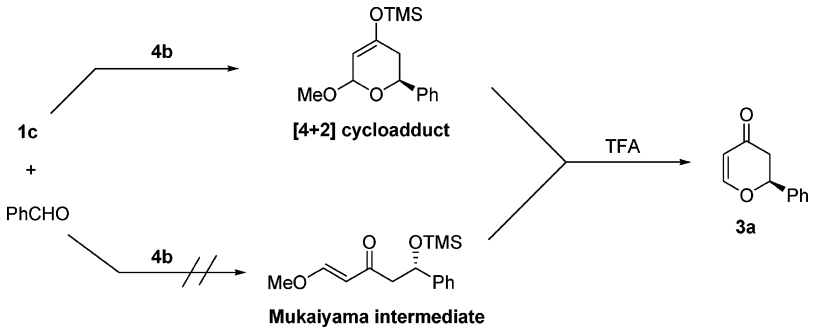
SCHEME 2. Mukaiyama Aldol vs Concerted [4+2] Cycloaddition Pathways



dioxacyclopentane (with hydrogen atoms replacing four aryl rings and two methyl groups of the TADDOL molecule). For this high layer, we used DFT with Becke's three-parameter hybrid functional (B3),[12] and the Lee, Yang, and Parr correlation functional (LYP).[13] The low layer is modeled at the semiempirical PM3[14] level. In the calculations, the TSs were characterized by vibration frequency calculations that showed one and only one imaginary frequency corresponding to motions along the reaction coordinate under consideration. Single-point calculations at the B3LYP/6-31G* level were done on the geometries located at the ONIOM level (or, in the cases of uncatalyzed reactions, pure DFT). All atomic charges were from the natural population analysis (NPA).[16]

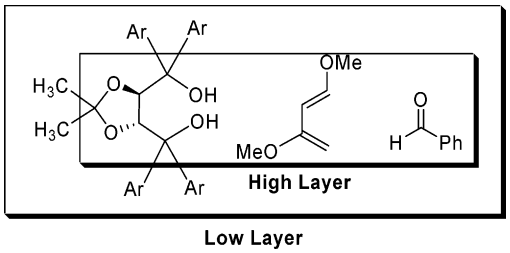


FIGURE 1. The two geometry layers of the reaction system in the ONIOM calculation.

Because the carbonyl group of benzaldehyde possesses two possible hydrogen-bond-acceptor sites (lone pair cis or trans to the phenyl group) and each TADDOL molecule has two potential hydrogen-bond-donor sites, the benzaldehyde may interact with either one or both of its lone pairs to the TADDOL's hydroxyl proton through single or double hydrogen bonding (**A**, **B**, or **C**, respectively, in Figure 2). Although double-hydrogen-bonding activation has been used as an efficient tool for the catalysis of the reactions of carbonyl compounds,[5a,17] the existence of an intramolecular hydrogen bond between the two hydroxyl groups has been one of the well-known structural features of TADDOL molecules.[5b,7a,8] Accordingly, coordination pattern **C** can be safely excluded. For coordination modes **A** and **B**, it was found that structure optimization calculations starting from the initial structure **A** or **B** always end up with the mode **A** configuration, thus only the trans mode **A** is feasible. Remarkably, **A** is also consistent with many observed crystal structures of analogous TADDOL−carbonyl compound adducts.[5b,7a,8]

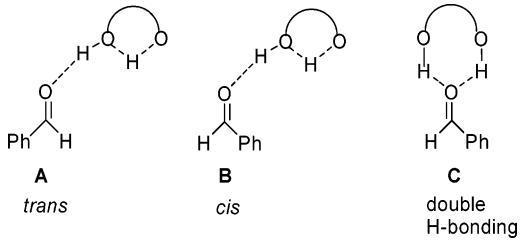


FIGURE 2. Possible intermolecular hydrogen-bonding patterns between benzaldehyde and TADDOL.

The X-ray crystal structures[18] of TADDOLs **4a**, **4b**, and **4c** were taken as the starting geometries for all the calculations involving these compounds, respectively, and the hydrogen-bonded molecular complex between **4a** and DMF[5b] was taken as the model of the interaction pattern between catalyst and substrate by replacing DMF with benzaldehyde. For comparison, four computational models were constructed, as shown in Scheme 3. Model I corresponds to the uncatalyzed HDA reaction between diene **5** and benzaldehyde **2a**. The influence of the hydrogen bonding on the reactions in the presence of different TADDOL catalysts, including **4a**, **4b**, or **4c**, were studied by means of models II, III, and IV, respectively.

Uncatalyzed Reaction: To rationalize the enantioselectivity of the TADDOL-catalyzed HDA reaction between Danishefsky's diene with benzaldehyde, eight possible diastereomeric TSs resulting from different regio-, exo-, endo-, and enantioselectivities should in principle be considered for extensive analysis. For the uncatalyzed reaction, no enantioselectivity needs to be considered, and the cycloaddition reaction between the model diene **5** and the benzaldehyde **2a** can take place along two regio-isomeric channels: the ortho and the meta (Model I shown in Scheme 3). The ortho channel corresponds to the C1−

(15) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

(16) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735.

(17) For examples of the activation of carbonyl compounds by double hydrogen bonding, see: (a) Hine, J.; Linden, S.-M.; Kanagasabapathy, V. M. *J. Org. Chem.* **1985**, *50*, 5096. (b) Kelly, T. R.; Mechani, P.; Ekkundi, V. S. *Tetrahedron Lett.* **1990**, *31*, 3381.

(18) The crystal structures corresponding to CCDC-236876, CSD reference codes YONVEC and YONVAY, are used for the starting geometries of **4a**, **4b**, and **4c**, respectively.

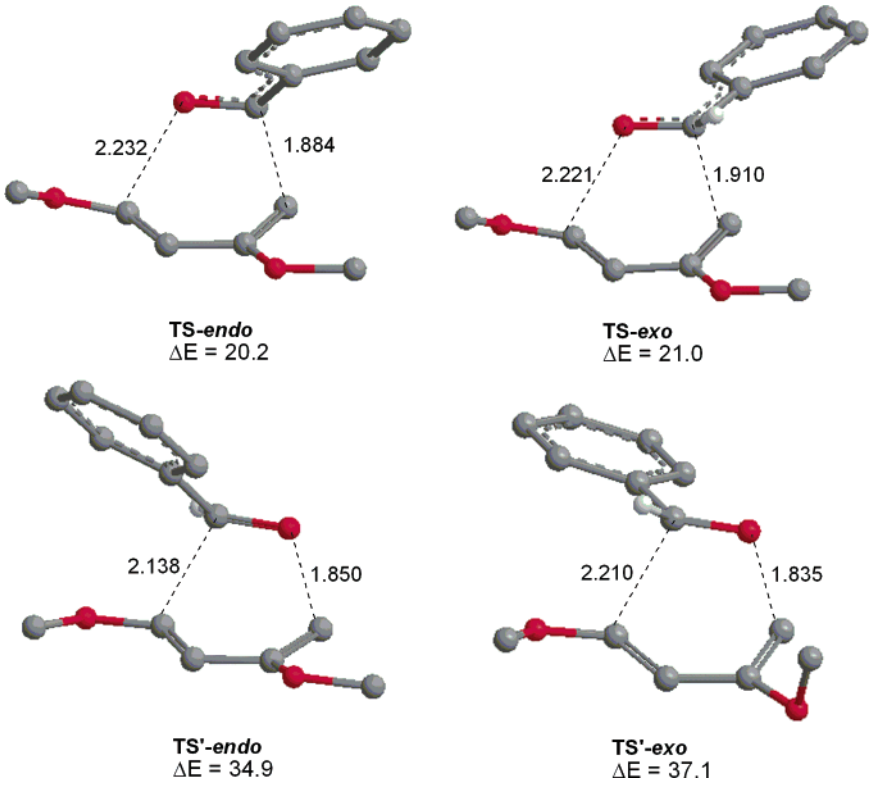
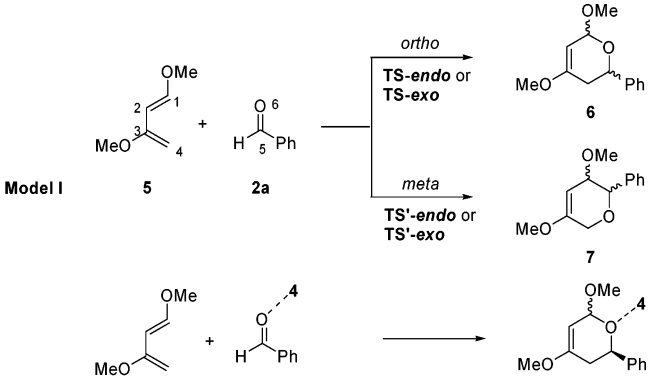


FIGURE 3. B3LYP/6-31G* optimized TSs and the activation energies (Δ*E*, kcal/mol) corresponding to the two channels (ortho and meta) for the uncatalyzed HDA reaction between diene **5** and benzaldehyde **2a**. The bond lengths involved in the TSs are given in angstroms.

SCHEME 3. Computational Models Used for TADDOL-Catalyzed HDA Reactions between the Model Butadiene 5 and Benzaldehyde 2a



O6 and C4−C5 bond-forming process, whereas the meta channel corresponds to the C1−C5 and C4−O6 bond formations. For the two regioisomers, each has an exo and endo approach. Therefore, four potentially viable TSs (TS-endo and TS-exo for the ortho channel; TS′-endo and TS′-exo for the meta channel) need to be considered for Model I.

Consistent with the calculation results reported previously by Houk et al.,[9b,c] Jørgensen et al.,[9e] and Domingo and Andres[9g] on analogous model reactions, DFT calculations on Model I at the B3LYP/6-31G* level indicated that the uncatalyzed reaction proceeds via a concerted but asynchronous pathway (Figure 3), and no zwitterionic intermediate or TS corresponding to the Mukaiyama aldol type pathway could be located. The energy of the located TS for the meta route is 14 kcal/mol higher than that of the ortho channel, which is consistent with frontier molecular orbital theoretical expectation.[19] Therefore, the meta channels associated with the cycloaddition in models II, III, and IV can be excluded. For the ortho channel of Model I, the TS-endo is calculated to be about 0.8 kcal/mol more stable than that of the TS-exo.[20] For the slightly favorable TS, TS-endo, the lengths of the forming C−C and C−O bonds are 1.884 and 2.232 Å, respectively, indicating the asynchronous nature of the bond-forming process.

TADDOL-Catalyzed Reactions: For the reactions between diene **5** and benzaldehyde−TADDOL adducts **2a···4a−c** (Models II, III, and IV), the attempts to find the zwitterionic aldol-like intermediates again proved to be unsuccessful, thus excluding the Mukaiyama stepwise pathway for the present reaction. This is in agreement with experimental observations. The TSs for a concerted reaction pathway leading to the HDA adducts **6···4a−c** were located. Their corresponding TSs are denoted as TS-(*re*)-**4a**/TS-(*si*)-**4a** (Model II), TS-(*re*)-**4b**/TS-(*si*)-**4b** (Model III), and TS-(*re*)-**4c**/TS-(*si*)-**4c** (Model IV), respectively, depending on the direction of the suprafacial attack of diene **5** to the *re* or *si* face of the hydrogen-bonded benzaldehyde (**2a···4a−c**; Scheme 3 and Figure 4).

Unlike the uncatalyzed counterpart, the TADDOL **4b**-catalyzed HDA reaction between **5** and **2a** exhibited a clear preference for the endo over the exo approach. The calculated relative energies for the exo TSs TS-*exo*-(*si*)-**4b**/TS-*exo*-(*re*)-**4b** (16.3 and 13.5 kcal/mol, respectively) are significantly

(19) Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 4094.
(20) It is difficult to predict the endo/exo preference of the reaction on the basis of such a small energy difference.

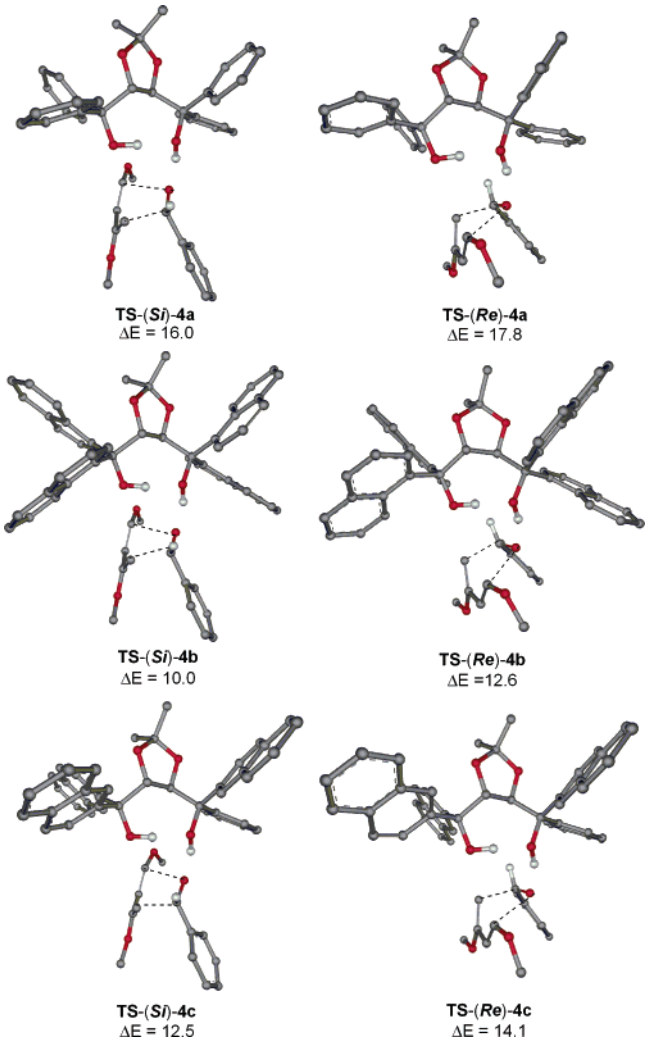


FIGURE 4. TSs involved in the reactions (endo mode) of model diene **5** with **2a** in the presence of **4a**, **4b**, or **4c** and their activation energies (ΔE, kcal/mol).

higher than those of the endo ones TS-*endo*-(*si*)-**4b**/TS-*endo*-(*re*)-**4b** (10.0 and 12.6 kcal/mol, respectively; see Supporting Information), presumably caused by the more severe steric repulsions present in the exo TSs.[21] Therefore, the contribution of the exo approach of the diene in the catalytic system can be negligible. In the following discussion, only the endo TSs are considered.

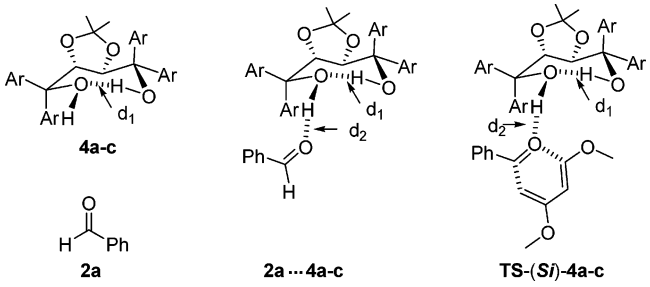
Figure 4 shows the TSs (endo approach) of the HDA reactions of model diene (**5**) with benzaldehyde (**2**) catalyzed by **4a**−**c** (Model II−IV) and their corresponding activation energies, obtained from B3LYP/6-31G*//B3LYP/6-31G*:PM3 calculations on *re*- or *si*-face attack of the model diene (**5**) to **4a**−**c**-activated benzaldehyde. The values of the activation energies, ΔE, were calculated on the basis of the total energies of the stationary points. As can be seen from the figure, the activation energies of the reactions in the presence of **4a, 4b**, and **4c** were reduced by 4.2, 10.2, and 7.7 kcal/mol, respectively, in comparison with that of the uncatalyzed reaction (20.2 kcal/mol, see Figure 3) in terms of their preferential TSs (endo approach, *si*-face attack). Although the reductions in the activation energy by the hydrogen-bonding activation of the benzaldehyde may be somewhat overestimated due to the negligence of solvent effects, it can be qualitatively concluded that the reactions are accelerated by the catalysts and the catalytic efficiency is in the order **4b** > **4c** > **4a**. In each case, the *si*-TS is found to be more stable than the competing *re*-TS, thus, correctly accounting for the observed (*S*) sense of asymmetric induction in the experiments. A comparison among the values of the *si*-TS and *re*-TS energy differences for TS-**4b** (2.6 kcal/mol), TS-**4a** (1.8 kcal/mol), and TS-**4c** (1.6 kcal/mol) can predict the relative trend of the stereocontrol capability of TADDOL **4a**, **4b**, and **4c**; that is, **4b** should be superior to both **4a** and **4c**, while the latter two remain at essentially the same level. Indeed, as shown in Scheme 1, the reaction of benzaldehyde with Danishefsky's diene in the presence of 20 mol % of **4b** afforded the cycloadduct **6** in 77% yield with 76.3% ee (*S*), while using **4a** (18% yield, 12% ee (*S*)) or **4c** (36.5% yield, 19% ee (*S*)) yields modest results. However, it should be noted that these energy differences should not be over-interpreted in elucidating the stereochemical outcome of the experiment. Although the energy difference between the *si*-TS and the *re*-TS of Models II and IV when **4a** and **4c** are utilized as the catalysts (1.8 and 1.6 kcal/mol, respectively) are high enough to expect good enantioselective control of the catalysis; the enantiomeric excesses of the products observed in the actual reaction systems are very low. This might be attributed to the various possible sources of errors associated with the calculation, such as approximations of the model substrate, inaccuracies of methods, and complex reaction conditions different from those of calculation. Moreover, low reactivity of the catalysis is expected for both TS-(*si*)-**4a** and TS-(*si*)-**4c** as a result of their relatively high activation energy barriers. Under such circumstance, the background reaction may become more competitive with the catalytic process. Indeed, the reaction of **1c** with **2** in the absence of any catalyst under otherwise identical reaction conditions gave racemic product **3a** in 10% yield. Therefore, these calculation results of the activation energies of the reactions are well-consistent with the dramatic differences of the catalytic activities and the enantioselectivities of catalysts **4a**−**c** observed in the experiments despite difficulty in quantitative predictions.

The NPA[16] indicates that there is a considerable charge transfer from the donor diene **5** to acceptor **2a**, complex **2a**···**4a**, **2a**···**4b**, or **2a**···**4c** in the TSs for all the model reactions. The values of the charge transfer from **5** to the benzaldehyde system are 0.27 e (endo TS), 0.47 e (TS-(*si*)-**4a**), 0.49e (TS-(*si*)-**4b**), and 0.47e (TS-(*si*)-**4c**), respectively. These data show that these TSs have some zwitterionic character, and the formation of the hydrogen bond at the carbonyl oxygen atom facilitates the charge transfer in the reaction process. The fact that the hydrogen-bond interaction results in larger stabilizations in the TSs than for reactants can be explained by the large stabilization of the negative charge that is developed at the carbonyl O6 oxygen atom during nucleophilic attack.

A comparison of the TS geometries can provide clues for understanding the differences in the catalytic activity of TADDOLs **4a**−**c** in the title reaction. Table 1 shows the calculated intra- and intermolecular O−H···O hydrogen bond distances in free TADDOLs **4a**−**c**, TADDOL−benzadehyde complexes

(21) Similar preference and interpretation for an endo orientation can also be found in the Lewis-acid-catalyzed HDA reaction between Danishefsky's diene and aldehydes; for examples, see: (a) Danishefsky, S. J.; Larson, E.; Ashkin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246. (b) Simonsen, K. B.; Svenstrup, N.; Roberson, M.; Jorgensen, K. A. *Chem.*—*Eur. J.* **2000**, *6*, 123.

TABLE 1. Comparison of Hydrogen-Bonding Interactions between Catalysts 4a−c and 2a, as Well as In Preferential TSs

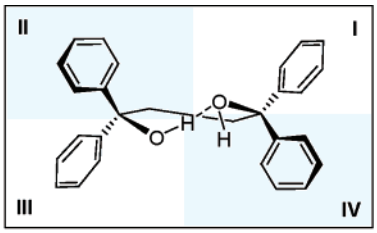


structure	H-bond length (Å) d_1	d_2
4a	1.910	
4b	1.853	
4c	1.900	
2a···4a	1.756	1.842
2a···4b	1.725	1.825
2a···4c	1.752	1.831
TS−(*si*)-**4a**	1.678	1.634
TS−(*si*)-**4b**	1.642	1.612
TS−(*si*)-**4c**	1.675	1.622

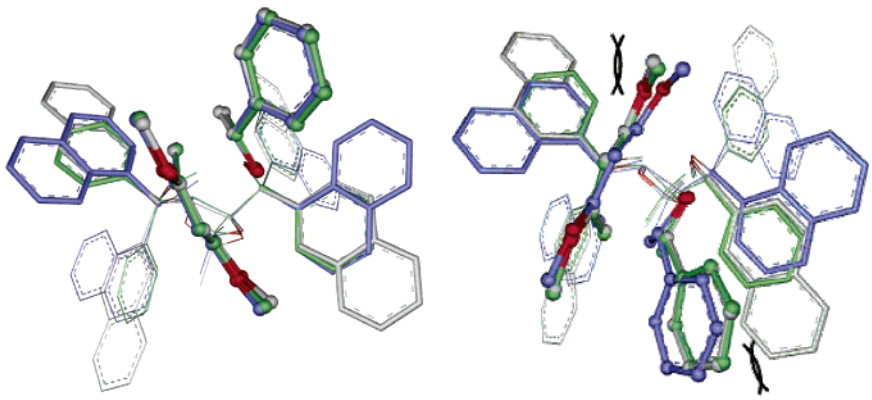
2a···4a−c, as well as for the favorable TSs of TS-(*si*)-**4a**, TS-(*si*)-**4b**, and TS-(*si*)-**4c**. Upon complexation between **2a** and **4a−c**, the length of d_1 in **2a···4a−c** is significantly reduced by about 0.13−0.15 Å compared to those in the free **4a−c**. In going from the complexes to the TSs, the d_2 distance is shortened by about 0.21 Å, while d_1 is also shortened by about 0.08 Å. Thus, both the intra- and intermolecular hydrogen bonds can reinforce each other in the TSs, which can be considered as Bronsted-acid-assisted Bronsted acid (BBA) catalyst systems.[4d] A closer examination indicates that **4b** has a shorter d_1 than **4a** and **4c**. The shortening of d_1 and d_2 in TS-(*si*)-**4b** are also somewhat more significant than those in TS-(*si*)-**4a** and TS-(*si*)-**4c**. Therefore, **4b** can be considered more acidic than **4a** and **4c**, and this causes a larger stabilization of the TS, as discussed above.

Then how can we account for the energetic preference of TS-(*si*)-**4** over TS-(*re*)-**4**? Figure 5a shows a quadrant diagram perspective of the representative TADDOL derivative **4a**, while Figure 5b,c are the overlaid TSs of the *si* or *re* approach for all three TADDOLs **4a−c**, where the overall geometrical features are very similar. In Figure 5a, the phenyl groups in quadrants II and IV extend forward, so these two locations are the hindered quadrants. On the other hand, the other two phenyl rings in quadrants I and III extend backward, providing less-hindered quadrants. A comparison of the two TSs (TS-(*si*)-**4a−c** and TS-(*re*)-**4a−c**) shows that the substrates lie in the less-hindered quadrants I and III in TS-(*si*)-**4a−c**, thus forming a preferential transition state (Figure 5b). In contrast, in the TS-(*re*)-**4a−c**, both substrates are situated at the hindered quadrants II and IV, resulting in the less-stable TSs (Figure 5c). This quadrant map illustrates the steric interactions that occur between the substrates and the catalysts in the TSs and well explains the sense of asymmetric induction observed in the catalysis.

A further question is why catalyst **4b** causes a higher enantioselectivity than either **4a** or **4c**? As mentioned above, the spatial orientation of the aryl groups distributed in the quadrant map is the key point for the enantioselective control of the reaction process. The impact of the aryl groups in TADDOL catalysts on the level of enantioselectivity of the reaction can be addressed by a careful comparison of the different steric hindrances developed in the TSs using the quadrant diagram. Although the superposition of the favorable TSs (TS-(*si*)-**4**) of reactions in the presence of catalysts **4a−c**



(a) Quadrant diagram



(b) *Si*-approach, favored (c) *Re*-approach, disfavored

FIGURE 5. Quadrant diagram perspective of the TADDOL molecule: (a) superposition TSs of the si approach (b) and re approach (c) of the diene, where the TS with the green line represents TS-**4a**, the blue line represents TS-**4b**, and the gray line represents TS-**4c**.

adopt very similar overall structures, the 1-naphthyl groups in TS-(*re*)-**4b** extend more significantly forward in quadrants II and IV than the aryl groups in TS-(*re*)-**4a** or TS-(*re*)-**4c**. Thus, TS-(*re*)-**4b** suffers from a larger steric interaction than TS-(*re*)-**4a** or TS-(*re*)-**4c** and as a result, develops a higher energy barrier for the *re*-face approach. This explains why the catalysis by **4b** results in higher enantioselective induction than those by **4a** and **4c**.

Conclusions

In summary, an enantioselective HDA reaction of Danishefsky's diene with benzaldehyde has been achieved under the catalysis of a variety of α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) derivatives through hydrogen-bonding activation, affording 2-phenyl-2,3-dihydro-4*H*-pyran-4-one after TFA workup in moderate yield and good enantioselectivity. It was found that the α,α′-aryl substituents of catalysts significantly impact both the activity and the enantioselectivity of the TADDOL catalysts. A ^{1}H NMR spectrum of the isolated primary adduct demonstrates that the TADDOL-catalyzed reaction proceeds via a concerted pathway. In combination with the experimental investigations, the mechanism of this reaction has also been studied theoretically using the ONIOM method. In agreement with the experimental findings, the calculation results indicate that the carbonyl group of benzaldehyde is activated by forming an intermolecular hydrogen bond with one of the hydroxyl groups of the TADDOL molecule. Meanwhile, the intramolecular hydrogen bond in the catalyst can facilitate the intermolecular hydrogen bonding with the benzaldehyde substrate. The sense of asymmetric induction could be well-rationalized by the analysis of the relative energies of the TADDOL-complexed TSs. The impact of aryl substituents in TADDOL catalysts on the level of enantioselective control of the reaction could be addressed on the basis of the structural features of their corresponding TSs. The information attained from this research will impact the design of a new generation of chiral diol catalysts for asymmetric reactions of carbonyl compounds.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a 300-MHz spectrometer at 25 °C. Chemical shifts were expressed in ppm with TMS as an internal standard ($\delta = 0$ ppm) for ^{1}H NMR. Coupling constants, *J*, are listed in hertz. Optical rotation was measured with a 341 automatic polarimeter. HRMS was taken on a 4.7-tesla FTMS instrument. IR spectra were taken on a FTIR instrument and were reported in cm^{-1}. The enantiomeric excesses were determined by HPLC on a chiral column. All the experiments that were sensitive to moisture or air were carried out under an argon atmosphere using standard Schlenk techniques. Commercial reagents were used as received without further purification unless otherwise noted. Toluene, tetrahydrofuran, and hexane were freshly distilled from sodium benzophenone ketyl and degassed before use.

Syntheses of TADDOLs 4a−g. TADDOL derivatives **4a−d** and **4f−g** were prepared as described in the literature.[5b,7] TADDOLs **4e** were prepared by following a similar procedure.

4e. Yield: 72%; mp 209−211 °C; $[\alpha]^{20}_D$ +107.3° ($c = 1.0$, $CHCl_3$). IR (KBr): ν_{max} 3411, 3217, 3055, 2967, 2899, 1631, 1599, 1504, 1433, 1335, 1274, 1123, 1106, 1019, 902, 817, 792, 758, 745 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.27 (s, 2H), 8.03−7.93 (m, 8H), 7.84−7.74 (m, 6H), 7.59−7.48 (m, 12H), 7.32−7.29 (d, $J = 11.7$ Hz, 2H), 4.96 (s, 2H), 1.75−1.50 (m, 8H). MS (MALDI): 715.3 (M + Na$^+$). HRMS (MALDI): calcd for $C_{49}H_{40}O_4Na$, 715.2489; found, 715.2819. Anal. Calcd for $C_{49}H_{40}O_4$: C, 84.94; H, 5.82. Found: C, 84.67; H, 5.80.

Typical Procedure for TADDOL-Catalyzed Asymmetric Hetero-Diels−Alder Reaction of Danishefsky's Diene and Aldehyde. A 1.5-mL polypropylene microtube was charged with catalyst **4b** (66.6 mg, 0.1 mmol) and freshly distilled benzaldehyde **2a** (265 mg, 2.5 mmol), and the mixture was agitated for 30 min at 15 °C before Danishefsky's diene **1c** (86 mg, 0.5 mmol) was quickly added. The reaction mixture was kept at 15 °C for 72 h, followed by dilution with 5.0 mL of ether and quenching with 10 drops of TFA. The mixture was neutralized with saturated $NaHCO_3$ solution (0.8 mL), and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic phase was dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography with hexanes/ethyl acetate (4:1) as eluent to afford 2-phenyl-2,3-dihydro-4*H*-pyran-4-one (**3a**)[2i] as a colorless liquid (67 mg, 77% yield). IR (liquid film): ν_{max} 3064, 1676, 1596, 1402, 1272, 1228, 1210, 1040, 990, 934, 864, 826, 796, 760, 732, 720, 640, 612 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, $J = 6.6$ Hz, 1H), 7.42−7.36 (m, 5H), 5.51 (dd, $J = 5.7$, 1.2 Hz, 1H), 5.41 (dd, $J = 14.18$, 3.4 Hz, 1H), 2.95−2.84 (m, 1H), 2.68−2.60 (m, 1H). The enantiomeric excess (ee) was determined to be 76.3% in favor of (*S*) by HPLC on Chiralcel OD column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, $t_{R1} = 14.0$ min (*S*, major), $t_{R2} = 18.7$ min (*R*, minor).

The primary cycloadduct generated in the **4b**-catalyzed HDA reaction of **1c** with **2a** was isolated prior to CF_3COOH treatment. The reaction mixture was stirred at 15 °C for 72 h, followed by the evaporation of the solvent in vacuo. The residue was purified by silica gel column chromatography with EtOAc/*n*-hexane = 1:8 as eluent to afford the intermediate, which was identified as the structure of the [2+4] adduct by ^{1}H NMR (See Figure S1 in Supporting Information).

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Supporting Information Available: ^{1}H NMR spectrum of the primary cycloadduct, global electrophilicity analysis of the dienes, and Cartesian coordinates of all of the structures with their computed total energies (16 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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