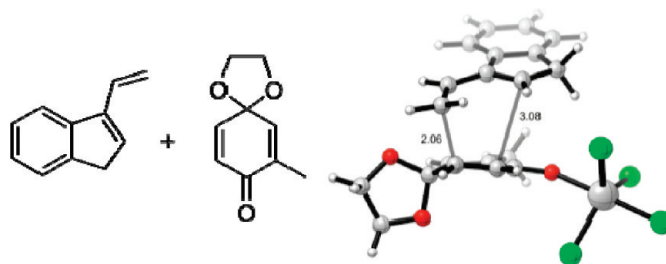# Origins of the Regioselectivities in the Diels−Alder Reactions of Vinylindenes with 1,4-Quinone Monoketal and Acrolein Dienophiles

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Computations with density functional theory (B3LYP/6-31G(d)) have elucidated the origins of regioselectivities in the Diels−Alder reaction of vinylindene with a 1,4-quinone monoketal reaction that was employed as the key step in the synthesis of fluostatin C. Frontier Molecular Orbital theory and an electrostatic model are applied to the reactions of alkyl-substituted and vinylindene dienes with 1,4-quinone monoketal and acrolein dienophiles. Regiochemical results that deviate from expectation are explained by a progression from electronic to steric control upon the addition of a Lewis acid catalyst.

Introduction

Danishefsky and co-workers recently reported the use of a Diels−Alder reaction as the key step in the synthesis of fluostatin C.[1] The results exemplified the subtle forces that control the regiochemical outcome of cycloadditions of this type. These insights were melded into a program that led to a remarkably concise total synthesis of fluostatin. In this paper, we seek to explicate the key issues of the cycloaddition. The synthetic pathway involves the Ti(IV)-catalyzed cycloadditions of vinylindenes (**1**) to 1,4-quinone monoketals (**2**) (Scheme 1a). With the substitution patterns shown, the presumed electrophilic position of the dienophile (the β carbon to the carbonyl carbon) reacts with the unsubstituted end of the diene to yield products **3**. Corey et al. observed similar regioselectivity in the reaction of 1,3-pentadiene (**4**) with dienophiles **2**, which was also performed in the presence of a Ti(IV) catalyst (Scheme 1b).[2] This type of product,

which results from the reaction of the unsubstituted terminus of the diene with the electrophilic portion of the dienophile, is collectively referred to herein as product A. The alkyl group (here, methylene in **1** or methyl in **4**) is apparently controlling the regiochemistry, since the phenyl of **1** would activate the substituted diene terminus.

Remarkably, the literature shows that when substituted acrolein dienophiles were employed, the opposite regioselectivity was observed, i.e., product B was obtained. Upon reaction of vinylindenes **1** with methacrolein (**6a**) in the presence of the same catalyst and under identical reaction conditions, the adducts obtained resulted from the reaction of the unsubstituted, electrophilic end of the dienophiles with the substituted terminus of the diene (Scheme 1c).[1] Similarly, Loh and co-workers observed the same regiochemical preference for product B when performing a Diels−Alder reaction of similar dienes **8** and acrolein dienophiles **6** in the presence of a different Lewis acid catalyst (Scheme 1d).[3]

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(2) Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1559–1562.

(3) Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2539–2541.

SCHEME 1. Diels−Alder Reactions of (a) Vinylindenes and 1,4-Quinone Monoketals, (b) 1,3-Pentadiene and 1,4-Quinone Monoketals, (c) Vinylindenes and Methacrolein, and (d) Other Dienes and Acroleins[1−3]
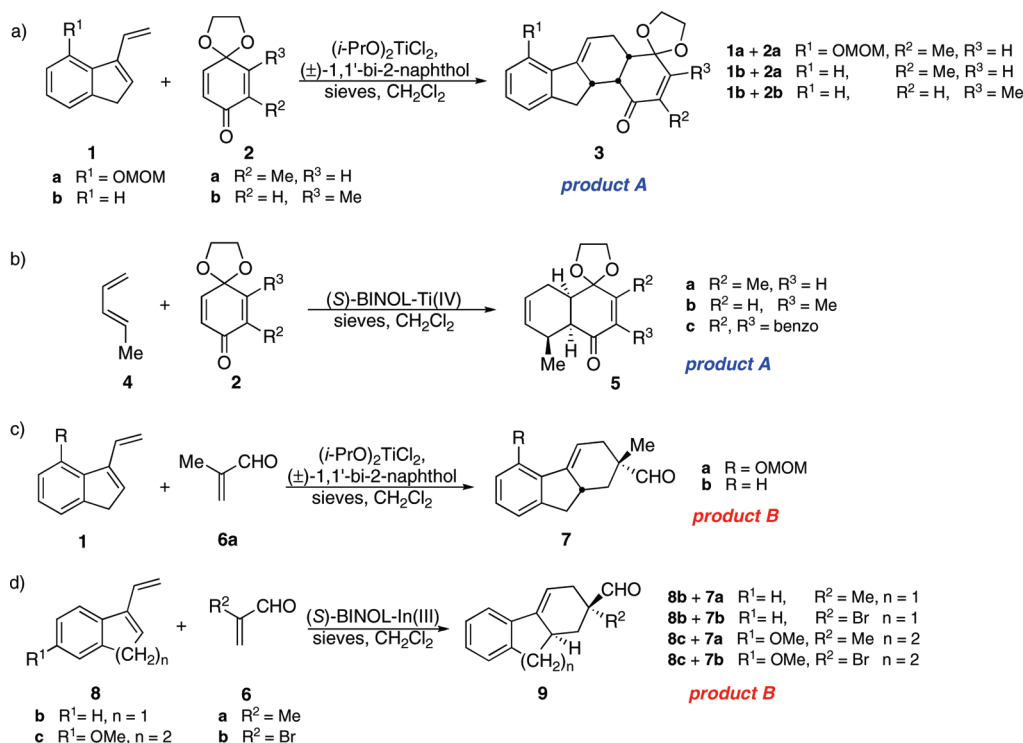
Although these examples are the most similar to the reactions being explored in this paper, there have also been other reactions of 1,2-disubstituted dienes that can give insight into these interesting regioselectivity preferences. The Diels−Alder reactions of related dienes, such as vinyl-cyclohexenes, were studied by various groups as early as the 1950s. The uncatalyzed reactions of 1-methyl-2-vinyl-4-hy-droxycyclohexene with cyclohexenones by Stork et al.,[4] vinylcyclohexene with propiolic acid by Nazarov and co-workers,[5] and vinylcyclohexene with 1-formylcyclohexene by Bergmann et al.[6] all provide products analogous to product A as the major product, with the unsubstituted terminus of the diene attacking the most electophilic termi-nus of the dienophile. Pitea and co-workers obtained similar results with the reactions of vinylcyclohexene with benzo-quinones.[7]

The use of a Lewis acid catalyst was found to be able either to enhance the regiochemical preference or to reverse the regioselectivity of the preferred adduct in a variety of reac-tions. For the reactions of vinylcyclohexenes with substi-tuted benzoquinones, there is a complete reversal of the preferred regioselectivity in the presence of $BF_3 \cdot Et_2O$.[8] In the addition of unsymmetrically disubstituted dienes to acroleins, the ratio of regioisomers obtained was enhanced from ∼10:1 to ∼50:1 when $BF_3 \cdot Et_2O$ or $MgBr_2 \cdot Et_2O$ was

added to the reaction mixture.[9] Hendrickson and co-workers demonstrated that the cycloadditions of 1,3-pentadiene (**4**) or vinylcyclohexene with quinone dienophiles provided dif-ferent regioisomeric products depending upon whether $BF_3 \cdot Et_2O$ or $TiCl_4$ was used as a catalyst.[10] Furthermore, Alston et al. found that complexation of the dienophile with a Lewis acid catalyst alters both the primary and secondary orbital interactions, which can result in changes in regiopre-ference.[11] More recently, in the total syntheses of galbulimi-ma alkaloid GB 13[12] and himandrine,[13] Mander and co-workers used 1′-OTBS substituted vinylcyclohexenes as dienes in Diels−Alder reactions that resulted in the assembly of the skeletons of these natural products. These reactions preferentially gave product A in the presence of the Lewis acid catalyst Yb(thd)₃. It is also notable that for bis-peri-cyclic Diels−Alder reactions, the shape of the potential energy surface as well as the products obtained are altered upon addition of a Lewis acid catalyst.[14]

The regioselectivities of Diels−Alder reactions and other cycloadditions have been rationalized and predicted by using frontier molecular orbital theory[15] and with electrostatic

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TABLE 1.   Transition State Energetics for the Model Systems (B3LYP/6-31G(d), kcal/mol)[a]

	$\Delta H^{\ddagger}$ $(\Delta G^{\ddagger})$			
	TS(A)	TS(B)	TS(A)TiCl$_4$	TS(B)TiCl$_4$
4 + 2a	**20.4 (35.6)**	26.4 (41.2)	**11.5 (26.3)**	18.4 (33.5)
4 + 6a	**19.2 (33.3)**	24.1 (38.0)	**10.9 (24.6)**	15.1 (29.9)
4 + 6b	**13.4 (27.8)**	19.1 (33.1)	**4.9 (19.4)**	9.5 (24.0)
4 + 6c	**17.8 (32.0)**	22.1 (35.8)	**9.2 (23.3)**	13.6 (27.8)
10 + 2a	20.5 (35.4)	**20.2 (34.8)**	12.1 (26.9)	**11.4 (26.5)**
10 + 6a	19.5 (33.3)	**17.6 (31.0)**	10.7 (24.8)	**7.6 (21.2)**
10 + 6b	14.6 (28.4)	**12.3 (26.0)**	5.3 (19.9)	**2.1 (16.0)**
10 + 6c	17.3 (31.4)	**16.3 (29.9)**	9.1 (23.5)	**6.1 (20.2)**
11 + 2a	**18.2 (33.7)**	23.8 (39.6)	**10.4 (24.5)**	13.1 (28.1)
11 + 6a	**16.8 (31.0)**	20.5 (34.7)	**8.6 (22.4)**	10.9 (24.8)
11 + 6b	**8.6 (22.4)**	15.5 (29.9)	**2.6 (17.0)**	5.0 (11.6)
11 + 6c	**14.7 (29.6)**	18.6 (32.8)	**6.5 (21.1)**	9.2 (23.6)
1b + 2a	*17.8 (32.1)*	*23.8 (38.5)*	*8.8 (22.8)*	*13.1 (27.2)*
1b + 6a	*16.9 (30.1)*	*17.9 (30.2)*	*9.0 (21.8)*	*7.4 (19.9)*
1b + 6b	*11.4 (24.7)*	*12.2 (25.1)*	*4.3 (17.6)*	*1.5 (14.5)*
1b + 6c	*15.4 (28.7)*	*16.6 (29.3)*	*7.5 (20.3)*	*5.7 (18.4)*

[a]For each reaction, energetics corresponding to the preferred product are shown in bold. The reactions that deviate from expectation based upon electronic preferences are highlighted in italic.

potential models.[16] Donor or conjugating substituents at the 1-position of dienes cause the 4-position to have the largest HOMO coefficient and the most negative electrostatic potential, so that either theory predicts the 4-position of the diene will bond to the most electrophilic terminus of the dienophile. Substituents at the 2-position of a diene activate the 1-position of the diene. The greater influence of substituents at the 1-position of dienes as compared to the 2-position has been considered.[17] In the cases described here, the 1 and 2 positions of the diene are substituted by different types of groups; the aryl substituent is expected to be a more powerful director than an alkyl, but the substituent at the 2-position is expected to have a smaller effect than that at the 1-position, which leads to some ambiguity about which group will have the dominant influence on regioselectivity.

We undertook a computational study in order to explain the puzzling experimental results obtained with vinylindene. All computations were performed with the B3LYP density functional with the 6-31G(d) basis set in Gaussian03.[18]

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(17) (a) *Pericyclic Reactions*; Marchand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1977; Vol. 2, pp 181–271. (b) An excellent example of the dominance of a 1-substituent (methyl) over a 2-substituent (trimethylsiloxy) can be found in a coriolin synthesis: Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1980**, *102*, 2097–2098.

(18) Frisch, M. J. et al. *Gaussian03*, Revision C.02; Gaussian, Inc., Wallingford, CT, 2004.

Results and Discussion

To understand why different dienophiles react with similar dienes to give opposite regioisomers, a series of Diels−Alder reactions was modeled computationally (Table 1, top). Both the *exo* and *endo* transition states were computed for all reactions studied. The *endo* transition structures were lower in energy in all cases, presumably as a consequence of favorable secondary orbital and electrostatic interactions. Dienes **4**, **10**, and **11** were chosen to help examine the effect of an alkyl group (methyl) at the 1-position of the diene, a phenyl group at the 2-position of the diene, and a combination of both substituents, respectively. The diene in question, vinylindene (**1b**), was also studied. The 1,4-quinone monoketal **2a** and a series of acroleins (**6a**−**c**) were chosen as the corresponding dieonophiles. Ti(IV) chloride was used as a model Lewis acid for all reactions.

The activation and reaction energies of both the uncatalyzed and catalyzed reactions are shown in Table 1. For clarity, this table is divided into sections, with each part demonstrating the reactivity of a single diene with the given series of dienophiles. With dienes **4** and **11**, the formation of product A is favored in all cases for both the uncatalyzed and TiCl$_4$ catalyzed reactions, indicating that the methyl group at the 1-position of the diene still controls the regiochemical outcome even with an aromatic group at the 2-position. When diene **10** was employed, product B was predicted to be formed preferentially, indicating that the phenyl group is controlling the regioselectivity. When considering vinylindene **1b** as the diene, product A is predicted in all uncatalyzed
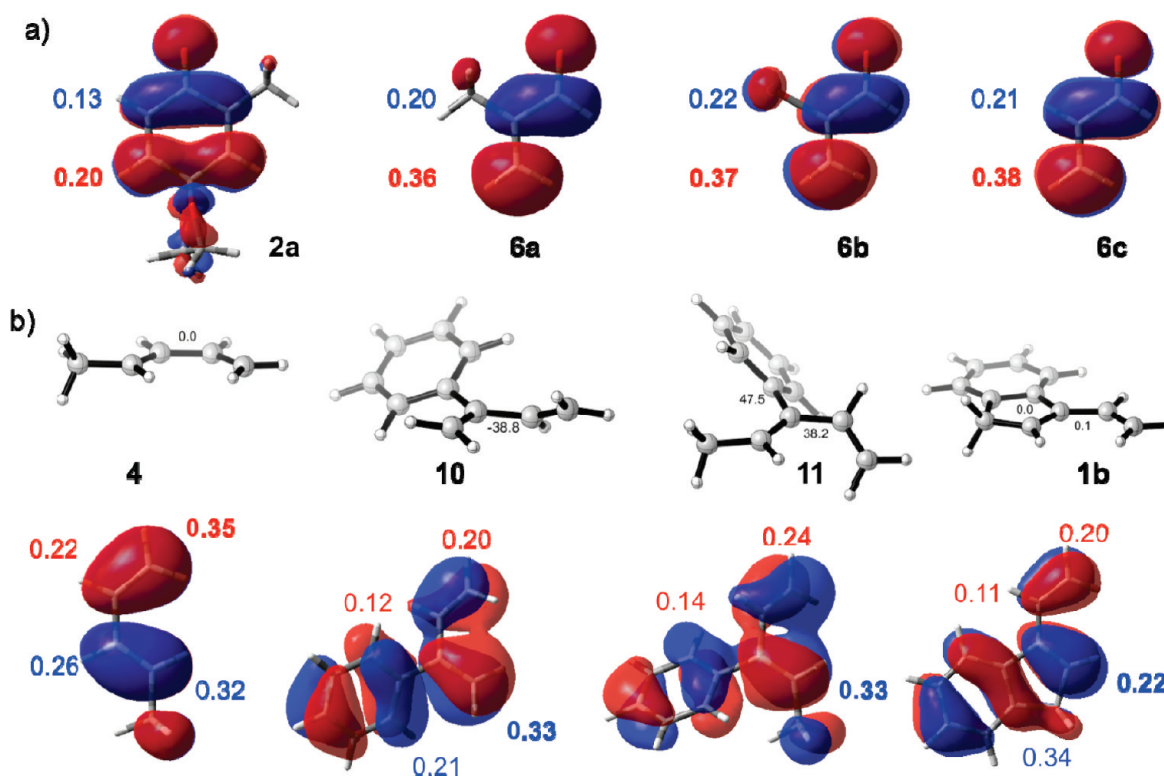
FIGURE 1. (a) LUMO coefficients of model dienophiles. The blue numbers correspond to the carbon α to the carbonyl, and the red numbers to the β carbon. (b) Computed structures and HOMOs coefficients of model dienes. The two red numbers correspond to the termini on the top of the structures and neighboring diene positions, and the blue numbers to the termini on the bottom and the neighboring position. Dihedral angles about diene C2−C3 are shown in deg; B3LYP/6-31G(d) density functional.

cases. However, for the catalyzed reactions, product A is preferred with the 1,4-quinone monoketal dienophile **2a**, but the opposite regiochemistry is predicted for the acrolein dienophiles. Since the computed catalyzed results are in agreement with experiment, the remaining goal of this study is that of explaining why the catalyst alters the preferred regiochemistry when acrolein dienophiles are utilized.

The molecular orbitals (MOs) of the starting materials were computed in order to apply frontier molecular orbital (FMO) theory to these reactions. The computed orbitals and their corresponding coefficients are shown in Figure 1. The lowest unoccupied molecular orbitals (LUMOs) are shown in Figure 1a. As expected, the larger MO coefficient (shown in bold) is at the carbon that is β to the carbonyl groups; the same trend applies to dienophiles complexed with the TiCl$_4$ catalyst (not shown). The carbon β to the carbonyl is predicted to be the electrophilic center of each dienophile.

The highest occupied molecular orbitals (HOMOs) of the dienes are shown in Figure 1b. The largest coefficient is at the unsubstituted terminus for diene **4**, and at the end closer to the phenyl ring for diene **10**, which is in accord with the expectation that the terminus activated by methyl or phenyl is the most nucleophilic "center." Diene **1b** has the largest HOMO coefficient at the terminus β to the phenyl groups, the substituted diene terminus; in terms of HOMO coefficients, this end should be more nucleophilic. This is contrary to experimental results, where the unsubstituted terminus is apparently the most nucleophilic locus when 1,4-quinone monoketals were used as dienophiles. However, the terminal

coefficients are almost identical (0.22 and 0.20), so that FMO control is expected to be small.

The electrostatic potentials (ESPs) of the starting materials were next evaluated; electrostatic effects can also contribute to regioselectivities. The nucleophilic terminus is the unsubstituted terminus for dienes **4**, **11**, and **1b** (Figure 2b). The differences are not large, but are consistent with the idea that the ESP is the result not only of the π electrons of the diene, but also of the through-space interactions with the substituents.[19] As expected, the electrophilic terminus of each dienophile is at the unsubstituted terminus, which is β to the carbonyl. Electrostatic interactions are in accord with all experimental and computational results except for the catalyzed reactions of vinylindenes with acrolein dienophiles, which involve union of the substituted terminus of diene **1b** with the β-carbon of the dienophile.

The transition state geometries were inspected with a view to elucidating the dramatic change in regioselectivity when a Lewis acid catalyst is added for the reactions of vinylindenes such as **1b** with acrolein dienophiles **6a**−**c**. The reactions of 1,3-pentadiene (**4**) with 1,4-quinone monoketal **2a** (Figure 3) and methacrolein **6b** (Figure 4) as well as the reaction of **1b** with **2a** (Figure 5) are all examples of reactions that have the same regiochemical outcome with and without catalyst and follow the favored frontier MO and electrostatic interactions. The reaction of **1b** with **2a** does not involve the reaction of termini predicted by frontier MO theory, because the substituted

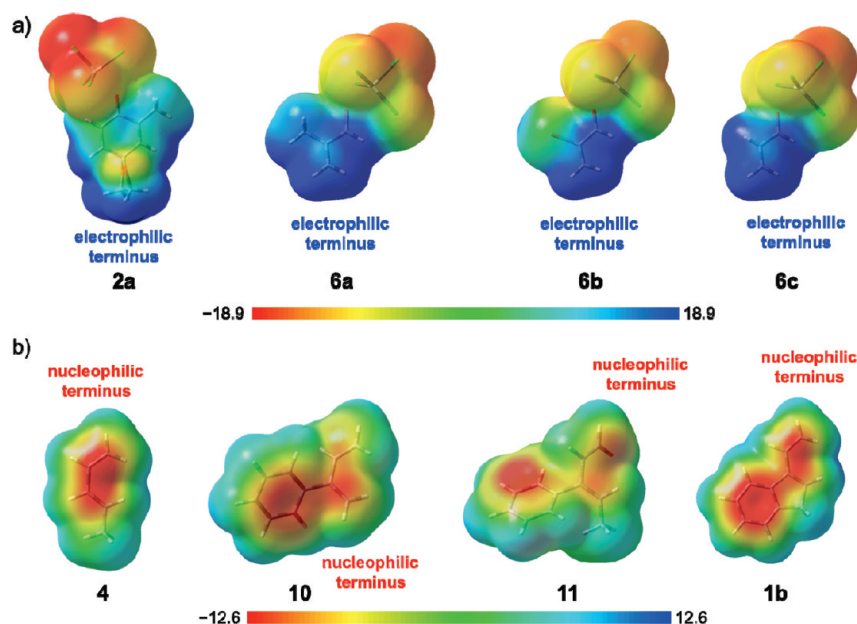(19) Wheeler, S. E.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10854–10855.

FIGURE 2. Electrostatic potential maps of (a) dienophiles complexed with TiCl$_4$ and (b) dienes (B3LYP/6-31G(d), kcal/mol).

4 + 2a TS(A)
20.4 (*35.6*)

4 + 2a TS(B)
26.4 (*41.2*)

4 + 2a TS(A) TiCl$_4$
11.5 (*26.3*)
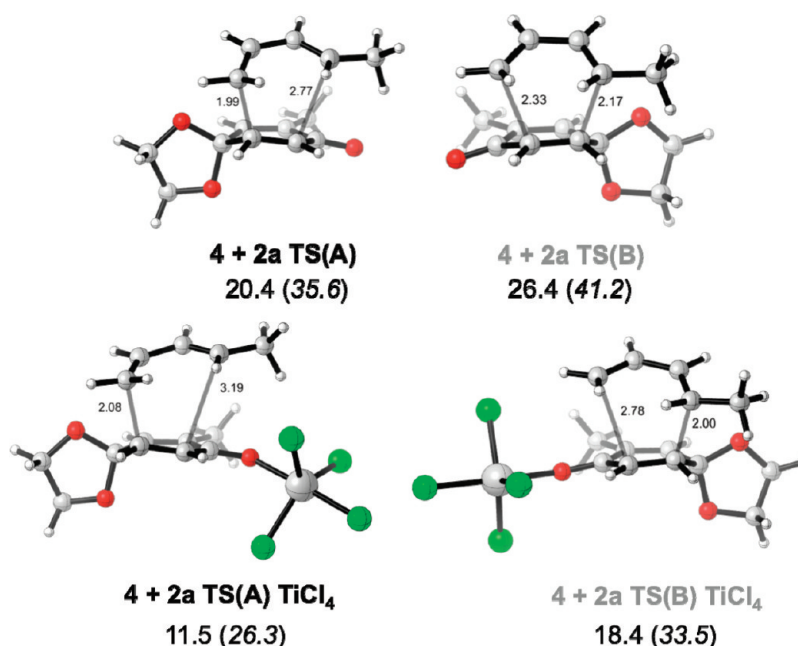
4 + 2a TS(B) TiCl$_4$
18.4 (*33.5*)

FIGURE 3. Transition structures for the reaction of 1,3-pentadiene (**4**) with 1,4-quinone monoketal **2a** without catalyst (top) and with TiCl$_4$ (bottom). The energetically favored transition state is labeled in black, while the higher energy structure is labeled in gray. $\Delta H^{\ddagger}$ ($\Delta G^{\ddagger}$), kcal/mol; B3LYP/6-31G(d) density functional. Distances are given in Å.

terminus has the largest HOMO coefficient, but instead follows the model of electrostatic interactions. In the energetically favored transition state, the "nucleophilic" end of the dienes reacts with the electrophilic end of the dienophiles in setting the regiochemical orientation of the cycloaddition.

In Figure 6, the transition structures for the reactions of vinylindene **1b** with acrolein dienophile **6a** are shown. This is an example of a case when the predicted regiochemistry switches when a catalyst is added, and the catalyzed reaction gives anomalous regioselectivities. When the TiCl$_4$ complexes with the carbonyl of the acrolein, the steric bulk of

the electron-withdrawing group on the dienophile increases. For the reaction to proceed through the transition state that would be electronically favorable (as predicted by electrostatic effects), the bulky catalyst and the fused substituent on the diene are required to be syn at the transition state. To avoid steric clashes, the dienophile portion of the catalyzed transition state (**1b** + **6a TS(A) TiCl$_4$**) is distorted from planarity, with a C−C−O−Ti dihedral angle of 159.3°. The transition state that leads to the opposite regioisomer does not have such potential steric repulsions and geometric distortions (C−C−O−Ti dihedral angle of 175.4°). We

4 + 6a TS(A)
19.2 (*33.3*)

4 + 6a TS(B)
24.1 (*38.0*)

4 + 6a TS(A) TiCl₄
10.9 (*24.6*)

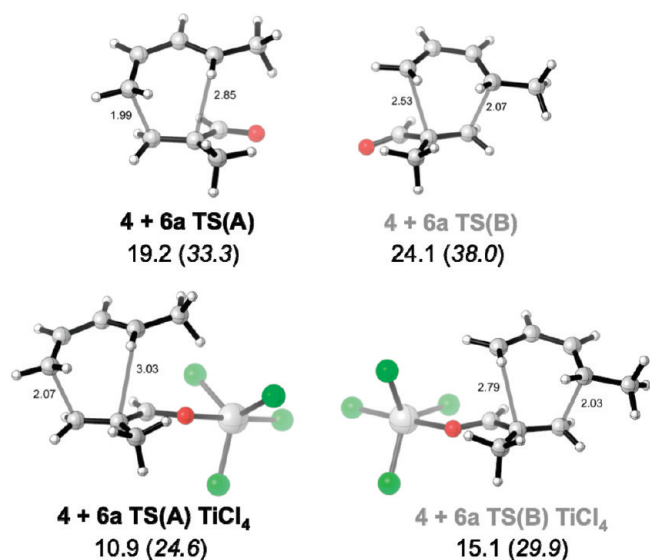**4 + 6a TS(B) TiCl₄**
15.1 (*29.9*)

FIGURE 4. Transition structures for the reaction of 1,3-pentadiene (**4**) with methacrolein **6a** without catalyst (top) and with TiCl₄ (bottom). The energetically favored transition state is labeled in black, while the higher energy structure is labeled in gray. $\Delta H^{\ddagger}$ ($\Delta G^{\ddagger}$), kcal/mol; B3LYP/6-31G(d) density functional. Distances are given in Å.

1b + 2a TS(A)
17.8 (*32.1*)

1b + 2a TS(B)
23.8 (*38.5*)

1b + 2a TS(A) TiCl₄
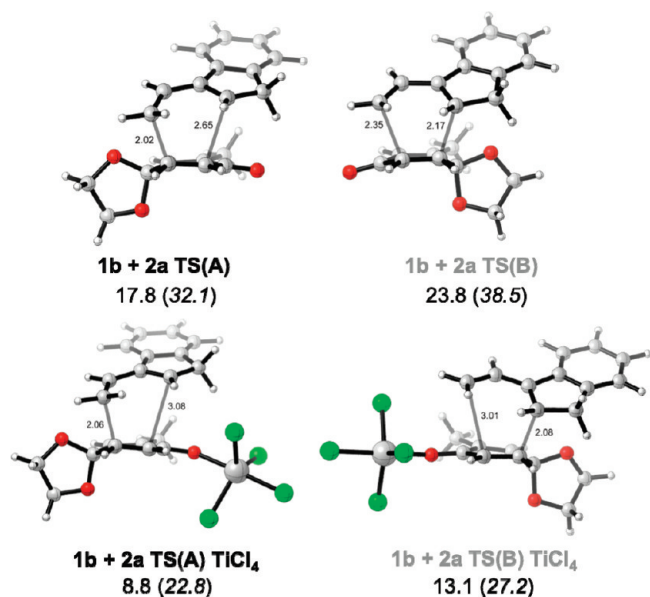8.8 (*22.8*)

1b + 2a TS(B) TiCl₄
13.1 (*27.2*)

FIGURE 5. Transition structures for the reaction of vinylindene **1b** with 1,4-quinone monoketal **2a** without catalyst (top) and with TiCl₄ (bottom). The energetically favored transition state is labeled in black, while the higher energy structure is labeled in gray. $\Delta H^{\ddagger}$ ($\Delta G^{\ddagger}$), kcal/mol; B3LYP/6-31G(d) density functional. Distances are given in Å.

surmise that the uncatalyzed reaction is controlled by anticipated electronic effects, but the catalyzed reaction is controlled by steric effects.

This switch in regioselectivity is not seen upon addition of the catalyst to the other reactions for two reasons. The first factor is that there is not a strong steric preference for one of the regioisomeric transition states in other reactions. For the reactions with **2a**, there is no clearly preferred steric product because there are bulky groups on both ends of the
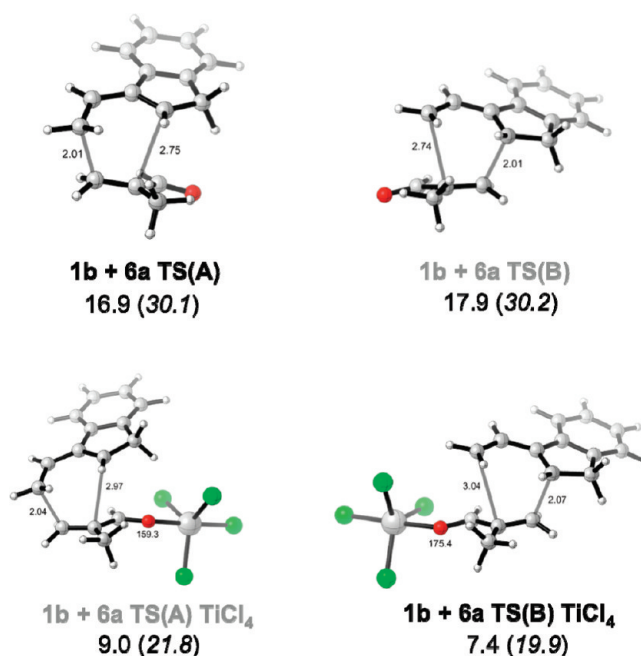

1b + 6a TS(A)
16.9 (*30.1*)

1b + 6a TS(B)
17.9 (*30.2*)

1b + 6a TS(A) TiCl₄
9.0 (*21.8*)

1b + 6a TS(B) TiCl₄
7.4 (*19.9*)

FIGURE 6. Transition structures for the reaction of vinylindene **1b** with methacrolein (**6a**) without catalyst (top) and with TiCl₄ (bottom). The energetically favored transition state is labeled in black, while the higher energy structure is labeled in gray. $\Delta H^{\ddagger}$ ($\Delta G^{\ddagger}$), kcal/mol; B3LYP/6-31G(d) density functional. Distances are given in Å, and C−C−O−Ti dihedral angles are given in deg.

dienophile. For the reaction of 1,3-pentadiene (**4**) with acrolein **6a**, there should be a steric preference for product B, but the electronically favored product A is both observed and theoretically predicted. However, there is a second factor that plays a role in this reversal of regioselectivity for the reaction of **1b** and **2a** in the presence of TiCl₄. The other uncatalyzed transition states have large differences in energy between regioisomeric transition states (~4−6 kcal/mol, Figures 4 and 5); however, for the uncatalyzed reaction of **1b** and **2a**, the $\Delta\Delta H^{\ddagger}$ is only 1.0 kcal/mol (Figure 6). Whereas electronic effects dictate the regiochemical outcome for most reactions, the small difference in regioisomeric transition states for the reaction of vinylindene **1b** with methacrolein enables steric effects to control the regiochemistries of these reactions.

Conclusions

Model reactions have been employed to explain the observed regioselectivities of Diels−Alder reactions of alkyl-substituted and vinylindene dienes with 1,4-quinone monoketal and acrolein dienophiles. FMO theory does not alone explain all observed results, but electrostatic effects do correlate with most experimentally observed regioselectivities. In addition, results that are seemingly anomalous based on electrostatic interactions−the reactions of vinylindene dienes with acrolein dienophiles−are explained by a switch from electronic to steric control upon the addition of a Lewis acid catalyst.

Program) and the UCLA Dissertation Year Fellowship. The computations were performed with use of the UCLA Academic Technology Services (ATS) Hoffman Beowulf cluster, as well as the California NanoSystems Institute (CNSI) Beowulf cluster.

Supporting Information Available: Discussion of dienophile models, complete ref 4, absolute energies, and Cartesian coordinates of stationary points. This material is available free of charge via the Internet at http://pubs. acs.org.