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Intramolecular Diels–Alder Reactions of Cycloalkenones: Stereoselectivity, Lewis Acid Acceleration, and Halogen Substituent Effects

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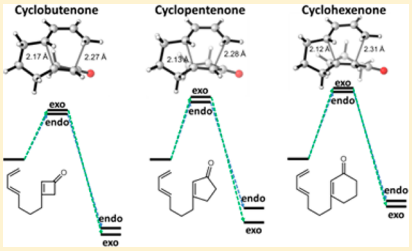
Supporting Information

ABSTRACT: The intramolecular Diels–Alder reactions of cycloalkenones and terminal dienes occur with high endo stereoselectivity, both thermally and under Lewis-acidic conditions. Through computations, we show that steric repulsion and tether conformation govern the selectivity of the reaction, and incorporation of either BF_3 or α-halogenation increases the rate of cycloaddition. With a longer tether, isomerization from a terminal diene to the more stable internal diene results in a more facile cycloaddition.



INTRODUCTION

Diels–Alder reactions of cycloalkenone dienophiles with a variety of dienes are powerful synthetic tools.[1] Cyclobutenone has been shown to be a potent dienophile[2,3] with greater reactivity than five- and six-membered cycloalkenones. This has been attributed to the ease of out-of-plane distortion of cyclobutenone, so as to more easily achieve the transition state geometry for cycloaddition.[4] Intramolecular Diels–Alder reactions of cycloalkenones are reliable methods to generate fused polycycles.[5] We have performed a computational study to rationalize the high stereoselectivity of the reactions shown in Figure 1 as well as describe the positive effect of incorporating a Lewis acid catalyst and an α-bromo substituent. We have also explored an unanticipated diene isomerization that occurs along with cycloaddition, regardless of cycloalkenone ring size.

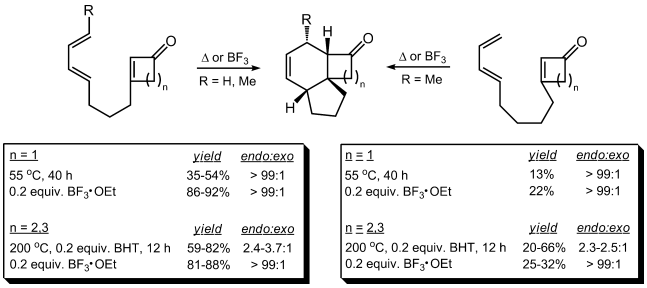


Figure 1. Summary of experimental results for the intramolecular Diels–Alder reaction of cycloalkenones.[5]

COMPUTATIONAL METHODS

Geometry optimizations were conducted in the gas phase using the M06-2X hybrid meta-GGA density functional.[6] Through the inclusion of a local spin kinetic energy density term in the exchange-correlation functional and extensive parametrization, M06-2X has been shown to be effective at modeling kinetics and thermochemistry, particularly where nonlocal dispersion interactions play a non-negligible role.[7] We have shown previously that it is possible to obtain relatively accurate activation and reaction energies for cycloadditions at the M06-2X/6-31G(d) level of theory.[8] Values in the text and figures are for the standard state of the gas phase (1 atm). Brinck has recently shown this level also yields geometries for asynchronous Diels–Alder transition structures in agreement with those obtained at the CCSD/6-31+G(d) level.[9] Frequency analysis was performed to verify the nature of each stationary point, with transition structures (TSs) and minima possessing a single and zero imaginary frequencies, respectively. Intrinsic reaction coordinate (IRC) scans were conducted when necessary to ensure the TSs led to the correct minima. All calculations were performed using Gaussian 09.[10]

RESULTS AND DISCUSSION

Danishefsky and co-workers have recently reported a series of intramolecular Diels–Alder reactions of cycloalkenones.[5] As shown in Figure 1, the endo:exo selectivity of the fused tricycles

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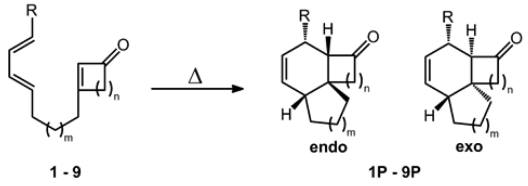
Table 1. Computed Reaction and Activation Free Energies and Enthalpies (kcal/mol) for the Thermal Diels–Alder Cycloaddition of Cycloalkenones 1–9



entry	SM	*m*	*n*	R	$\Delta G^{\ddagger}$endo	$\Delta G^{\ddagger}$exo	$\Delta H^{\ddagger}$ endo	$\Delta H^{\ddagger}$ exo	ΔG_{rxn} endo	ΔG_{rxn} exo	$k_{endo/exo}$
1	**1**	1	1	H	20.8	21.5	15.6	16.4	−32.2	−33.7	3.2
2	**2**	1	2	H	25.8	26.9	19.7	21.0	−21.8	−28.0	5.8
3	**3**	1	3	H	27.3	28.0	21.5	22.1	−19.9	−21.9	3.5
4	**4**	2	1	H	21.7	22.8	16.0	16.7	−40.0	−38.9	6.5
5	**5**	2	2	H	25.0	26.3	18.4	19.7	−26.9	−32.0	9.0
6	**6**	2	3	H	26.8	27.3	20.3	20.7	−26.8	−25.1	2.4
7	**7**	1	1	Me	20.4	21.0	14.3	14.7	−29.0	−31.4	2.5
8	**8**	1	2	Me	24.4	25.4	18.4	19.7	−17.9	−24.4	5.5
9	**9**	1	3	Me	25.8	27.0	19.7	21.1	−14.5	−20.5	7.6

was investigated as a function of cycloalkenone ring size (four-, five-, and six-membered rings were considered) and for both thermal and Lewis acid-catalyzed cycloadditions. Here, we initially examine the uncatalyzed, thermal reaction of these cycloalkenones and then consider the influence of BF_3 on the [4 + 2] cycloaddition.

Endo Selectivity and an Unexpected Isomerization. The computed activation and reaction free energies of the (uncatalyzed) thermal intramolecular Diels–Alder reactions of cycloalkenones **1**–**3** were calculated and summarized in Table 1. These substrates contain a 3-carbon tether between the diene and dienophile, forming a fused cyclopentane ring as a result of the cycloaddition. In all cases (entries 1–3), the endo product is kinetically favored, ranging from 0.7 kcal/mol for cyclobutenone **1** and cyclohexenone **3** to 1.1 kcal/mol for cyclopentenone **2**. As expected, the activation barrier of 20.8 kcal/mol for the Diels–Alder reaction of cyclobutenone is substantially lower than that for its larger-ring counterparts (Figure 2). The higher barriers associated with **2** and **3** necessitate higher reaction temperatures. The theoretical preference for the endo adduct in each case agrees with experiment, although the preference is underestimated for substrate **1**, where only the endo product is observed at 55 °C.

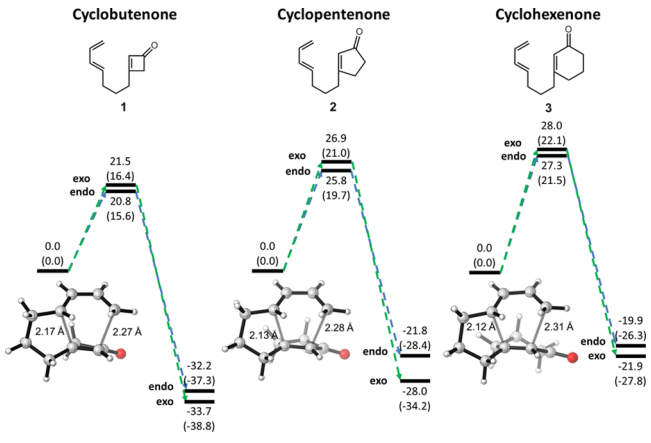


Figure 2. Reaction coordinate diagrams for reactions of 3-carbon-tethered cycloalkenones **1**–**3**. Free energies (enthalpies) are in kcal/mol. Endo transition structures are shown.

Temperatures of 200 °C were needed for reactions of cycloalkenones **2** and **3**, where an approximately 3:1 endo:exo ratio was observed for each.[5]

Endo selectivity in Diels–Alder reactions has been studied extensively in the past, rationalized through secondary orbital interactions between the π-orbitals of the diene and the carbonyl moieties.[11] However, the importance of these interactions has been questioned in recent years.[12] A distortion-interaction model has been used to explain the endo preference of the intermolecular cycloaddition between cyclic dienes and cycloalkenones.[4] Furthermore, the steric clash between the C_{sp3}–H of the cycloalkenone and the hydrogen of the internal double bond destabilizes the exo transition state, as shown for cyclobutenone **1** in Figure 3. This steric strain is

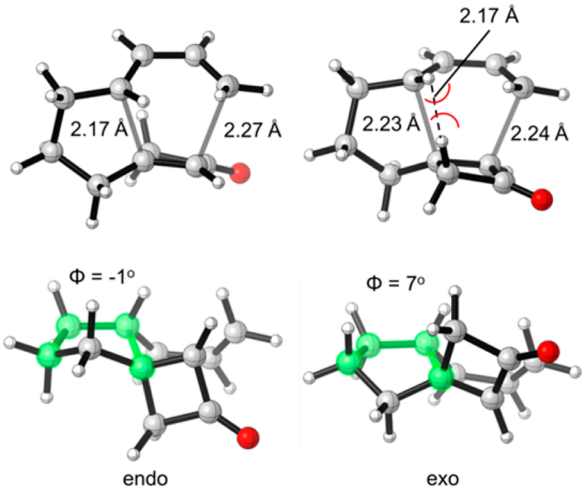


Figure 3. Transition structures for the cycloaddition of cyclobutenone **1**. Steric clash between hydrogens is shown in red. Dihedral carbons are highlighted in green.

absent in the endo transition state. A similar rationale was used to explain the cis/trans selectivity of the parent 1,3,8-nonatriene [4 + 2] cycloadditions, which were investigated both experimentally and theoretically.[13]

The tether linking diene and dienophile moieties can play a sizable role in the transition state conformations in intra-

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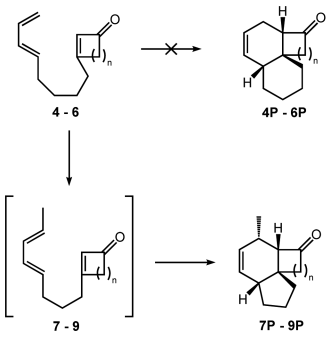
molecular reactions. Distortion of the carbon tether is a large contributor to the activation energy in previously studied intramolecular Diels–Alder and nitrone cycloadditions.[14] An analogous argument can be used for these cycloalkenone systems. The forming cyclopentane ring in the endo transition state of **1** more closely resembles the ideal envelope conformation, with four of the carbons essentially lying in one plane (dihedral angle $\Phi = -1°$). In the exo case, the four carbons are slightly distorted out of plane by 7°, causing more strain in the transition state. This deviation, along with steric strain, provides an explanation of the observed endo selectivity.

Adding an extra carbon to the tether does not alter the kinetically favored product (entries 4–6); the endo products are still preferred. The endo transition states are lower in energy than the corresponding exo transition states by 0.5–1.3 kcal/mol and are predicted to yield results similar to those of compounds **4**–**6**. However, the 6,6-fused cycloadducts were not experimentally observed.[5] Rather, the products formed were 6,5-fused systems, those in which the initial butadiene had isomerized to methyl-substituted analogues of **1**–**3** (Figure 4).



Substrate	Product	LA yield	Thermal yield (endo:exo)
n = 1	4	7P	22%	13%
n = 2	5	8P	25%	66% (2.5:1)
n = 3	6	9P	32%	20% (2.3:1)

Figure 4. Proposed mechanism to account for the formation of cycloadducts **7P**–**9P** from cycloalkenones **4**–**6**. Experimental data from the Danishefsky group are shown.[5]

It is interesting to note that early quenching of the reaction revealed no isomerized reactants **7**–**9**.[5,15] Preliminary studies using 1,3-hexadiene suggest that a similar diene migration occurs in intermolecular cases (see below). With this in mind, we also calculated the energetics of the cycloadditions of **7**–**9** (entries 7–9).

The Diels–Alder reactions of isomerized butadienes **7**–**9** are predicted to be more facile than those of the corresponding cycloalkenones **4**–**6** by 0.6–1.3 kcal/mol, translating to about a 10-fold higher reaction rate (Figure 5). Additionally, dienes **7**–**9** are 3.3–3.9 kcal/mol more stable than **4**–**6**. The free energy difference between TSs in Figure 5 of 4.6–5.1 kcal/mol accounts for the absence of product **4P**–**6P**. Diene isomerization should be independent of cycloalkenone ring size and, according to our results, should rapidly convert substrates **4**–**6** to the thermodynamically favored internal dienes **7**–**9**, which subsequently react to form the experimentally observed **7P**–**9P**.

Unanticipated diene isomerizations accompanying the Diels–Alder cycloaddition have been reported in other systems.[16] For example, Grieco observed a similar transformation when performing an IMDA reaction with acyclic enones.[16a] The presence of 10% camphorsulfonic acid in highly polar media allowed for a protonation/deprotonation mechanism to be confidently proposed, even without detection of any isomerized diene. Observed isomerizations of octadecatrienoates prior to Diels–Alder cycloaddition had previously been rationalized by Hase through a series of 1,5-hydride shifts and *E*/*Z* olefin isomerizations under high temperatures and long reaction times.[16b] Likewise, Gordon observed thermal 1,5-hydrogen shifts in various alkenyl maleates en route to the construction of the decalin core of mniopetals.[16c]

In our cycloalkenone systems, a 1,5-hydrogen shift to account for the isomerization is highly unlikely, since the relative stereochemistry of the observed cycloadducts is consistent with cyclization of *E*,*E*-diene precursors, which are not directly accessible via intramolecular 1,5-hydride transfer. Although we are not yet certain as to how the isomerization occurs, it is very likely to be proceeding under catalysis by an acidic agent rather than by thermal means.

Two potential types of mechanistic scenarios warrant consideration: First, it may be that a presently unknown catalytic species, generated exclusively in the course of the isomerization reaction but not in reactions that commence with the preformed methyl diene substrates, is capable of promoting

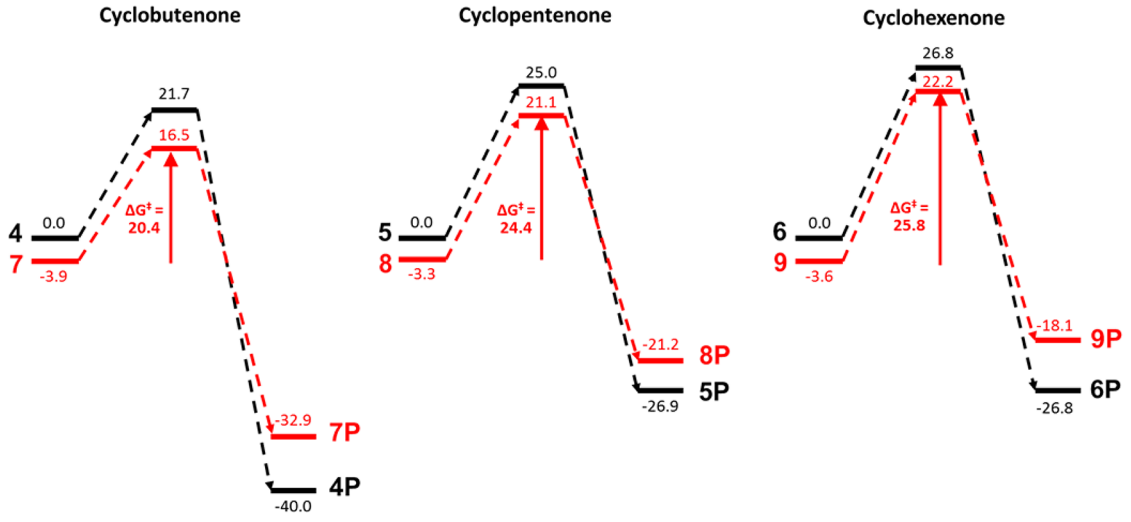


Figure 5. Energy profile comparison of 4-carbon-tethered cycloalkenones **4**–**6** and possible isomerized intermediates **7**–**9**. Only the endo pathways are shown for each substrate. All free energy values are in kcal/mol.

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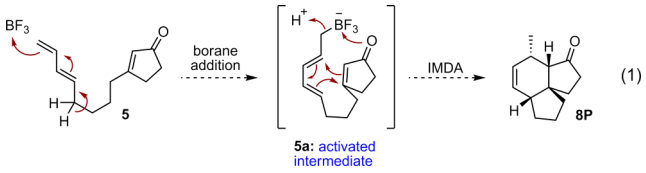
rapid IMDA cyclization. In other words, perhaps when we start with the methyl dienes (**7**–**9**), we are not duplicating all of the collateral agents present when the methyl dienes are generated via isomerization (cf., **4**–**6** → **7**–**9**). For instance, in principle the isomerization of **5** might conceivably lead to the generation of HBF_4 (or HF) in amounts greater than are present when one starts directly with substrate **8**. If such a hypothetical agent accelerated the IMDA cycloaddition, the apparent anomaly could be explained.

Upon further consideration of the problem, an alternative type of solution presented itself (eq 1). While highly



(1)

conjectural, the notion addresses a broader question than this particular BF_3-driven IMDA curiosity. Applied to the case at hand, perhaps BF_3 reacts with terminal diene **5** to produce, following (or concurrent with) deprotonation at C_5, the *trans*-dienyl methylfluoroborate **5a**; recent studies have shown that Lewis acids are capable of van der Waals interactions with alkenes,[17] with some able to catalyze olefin migrations and cis/trans isomerizations.[18] Were that to transpire, the resulting diene substructure would be highly activated to engage the dienophile in an IMDA cycloaddition (perhaps further facilitated by transfer of the boron from C→O), culminating in protonation at carbon to generate the observed **8P**. We must again emphasize the speculative nature of this sort of rationalization of the failure to identify intermediates **7**–**9** in the conversion of **4**–**6** to **7P**–**9P**. It is also well to underscore that the particular progression shown in eq 1 is one of a family of related possibilities, which share a common integrating concept: that during the course of BF_3-induced conversion of **4**–**6** to **7**–**9**, there is produced a molecular entity that is particularly prone to undergo IMDA.

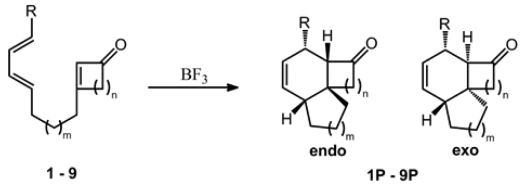
In future research, we hope to explore this question, which may well go to the broader issue of olefin isomerization by apparent Lewis, rather than protonic, acids. We also hope to continue our studies into the energetics and new synthetic applications of IMDA reactions to build molecular complexity in a concise fashion.

The Effect of Lewis Acid BF_3. Lewis acids are able to activate enone dienophiles, lowering the activation barrier in the Diels–Alder reactions of enones.[19] The calculated energetics for the Lewis acid-catalyzed reactions of cycloenones **1**–**9** are shown in Table 2. BF_3 was used as the Lewis acid, modeled after the experimental conditions in the Danishefsky lab.[5] Coordination to each lone pair of the oxygen was considered, and the lowest energy conformations are reported here. The coordination of BF_3 to the cycloalkenone oxygen increases the electrophilic nature of the β-carbon, resulting in a more asynchronous cycloaddition. As shown in Figure 6, the difference in length between the forming C–C bonds in the endo transition states increases from 0.10–0.19 Å in the thermal reactions to 0.38–0.46 Å in the presence of BF_3. This increase in electrophilicity of the β-carbon consequently enhances the favorable interaction with the nucleophilic carbon of the diene, lowering the activation barriers of all transition states. In contrast, the reaction free energies are largely unaffected, implying that Lewis acids comparably stabilize the reactant enones and product ketones.

The stereoselectivity of the reaction is amplified in the presence of acid, as noted earlier;[20] with BF_3, the endo transition state becomes substantially more favorable relative to the exo transition state in all cases (~2.8 kcal/mol). Because of the asynchronous nature of the Lewis acid-catalyzed reaction, the forming σ-bond that is shared by the fused rings is shorter than under thermal conditions. This intensifies the steric clash between the hydrogens in the exo transition state, thus increasing the preference for the endo transition state. For instance, the H–H bond distance in the Lewis acid-catalyzed exo transition state for cyclobutenone **1** is reduced to 2.08 Å from the 2.17 Å in the thermal exo transition state shown earlier. The larger steric strain causes the kinetically favored endo product to be formed exclusively, as found in experiment.[5]

Comparing the kinetics of the 4-carbon-tethered substrates (entries 4–6) with their isomerized counterparts (entries 7–9) demonstrates that Lewis acid catalysis now greatly favors the cycloaddition of the latter by upward of 3 kcal/mol for the

Table 2. Computed Reaction and Activation Free Energies (kcal/mol) of the Lewis Acid-Catalyzed Diels–Alder Cycloaddition of Cycloalkenones 1–9



entry	SM	*m*	*n*	R	$\Delta G^{\ddagger}$ endo	$\Delta G^{\ddagger}$ exo	$\Delta H^{\ddagger}$ endo	$\Delta H^{\ddagger}$ exo	ΔG_{rxn} endo	ΔG_{rxn} exo	$k_{endo/exo}$
1	**1**	1	1	H	14.5	17.1	8.0	11.0	−32.0	−33.6	83.0
2	**2**	1	2	H	19.6	23.5	13.1	16.9	−18.4	−23.5	703.2
3	**3**	1	3	H	19.4	22.2	13.6	16.4	−20.7	−22.4	115.0
4	**4**	2	1	H	15.9	17.0	9.2	11.1	−40.5	−38.5	7.1
5	**5**	2	2	H	20.2	22.4	13.2	15.8	−26.1	−27.0	44.6
6	**6**	2	3	H	22.2	23.3	15.3	16.4	−25.3	−23.5	6.5
7	**7**	1	1	Me	10.6	14.1	4.3	7.5	−29.9	−31.6	365.7
8	**8**	1	2	Me	17.2	20.8	9.9	13.4	−15.6	−21.3	414.8
9	**9**	1	3	Me	17.1	20.9	10.5	14.7	−14.4	−19.8	578.6

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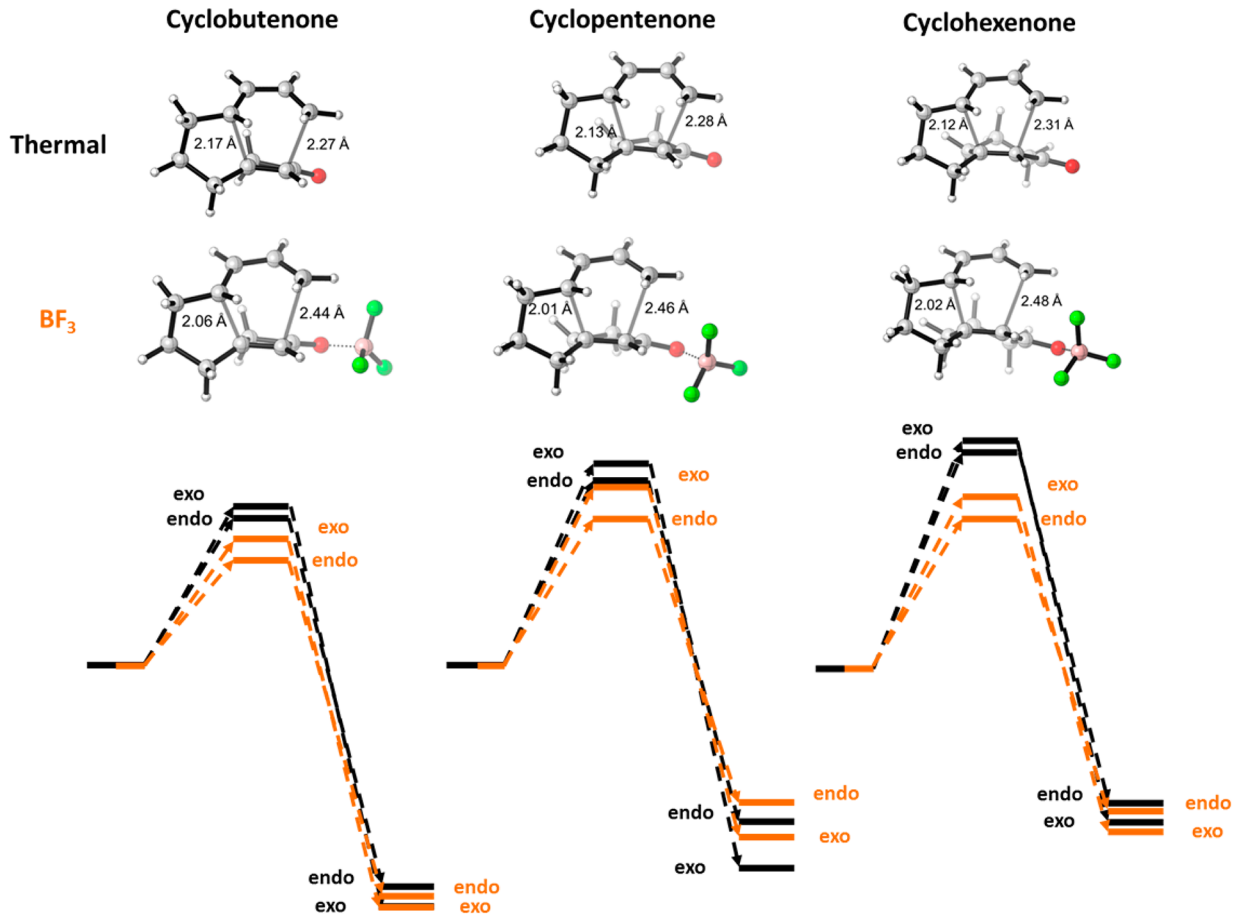

Figure 6. Energy profile comparison of the thermal (black) and BF_3-catalyzed (orange) reactions of cycloalkenones **1**–**3**. Endo transition states are shown. Respective starting points have been scaled to 0.

endo transition states. The activation barrier for isomerized cyclobutenone **7** remarkably drops to 10.6 kcal/mol, lower than typically expected for pericyclic reactions. This results from the synergistic contributions of the increase in polarization from BF_3-coordination and the intrinsic preference of the isomerized internal-diene cycloaddition over terminal-diene cycloaddition, also exhibited in the uncatalyzed reaction.

Does Isomerization Occur in the Intermolecular Case? Further studies were performed to gain insight into the fine balance of cycloaddition versus diene migration. The BF_3-catalyzed intermolecular cycloadditions of 1,3-hexadiene **10** and isomeric 2,4-hexadiene **15** with cyclobutenone and cyclopentenone were computed (Figure 7). Only the endo transition states were considered, because we have previously demonstrated that these are favored over the exo counterparts. Cycloaddition with **10** theoretically leads to two regioisomers, with the ethyl substituent on the cyclohexene either proximal (**13a**/**14a**) or distal (**13b**/**14b**) to the carbonyl; computations predict that formation of **13a**/**14a** is preferred by greater than 4 kcal/mol. It is of interest to note that in the intramolecular examples, the tether dictates the regiochemistry of the reaction, forming products with the distal alkyl group analogous to the disfavored **13b**/**14b**.

Reactions of cycloalkenones with isomerized diene **15** occur with lower barriers with respect to unisomerized diene **10**, implying that any incidence of diene isomerization will lead to cycloaddition and formation of products **16** and **17**. Preliminary experimental results from the Danishefsky lab suggest that the reaction of **10** with cyclobutenone results only in direct Diels–Alder product **13a**, while reaction with cyclopentenone yields a 1.6:1 ratio of **14a** to isomerized **17** (see the Supporting Information). Presumably the 13.6 kcal/mol barrier for the cycloaddition of **10** and **11** is lower than that for diene isomerization, which in turn should be lower than the 15.9 kcal/mol barrier seen for the intramolecular Diels–Alder reaction of **4** (Table 2, entry 4), because only isomerized product is observed in that case. Hence, the barriers for diene isomerization should be about 15 kcal/mol for isomerization to take place prior to Diels–Alder cycloaddition.

The Effect of a Bromine Substituent. The Danishefsky group found that incorporation of a vinyl bromide or chloride at the α position of the cycloalkenones increases their reactivity in intermolecular Diels–Alder reactions.[21] This effect should extend to the analogous IMDA reactions, and thus we have modeled the reaction between 2-bromocyclobutenone and a tethered diene (Figure 8). The influence of halogen substituents on dienes in Diels–Alder reactions has been studied by us and other groups,[8a,22] but the investigations of the effects of α-halogenated enones have been limited to intermolecular cases.[23]

As compared to the thermal cycloaddition of the parent cyclobutenone, the reaction barriers decrease and the reactions become more exothermic following vinylic halogenation. This "halogen effect" was previously observed in our work on halofuran cycloadditions with Padwa.[22a] Additionally, the preference of the endo transition state is increased from 0.7

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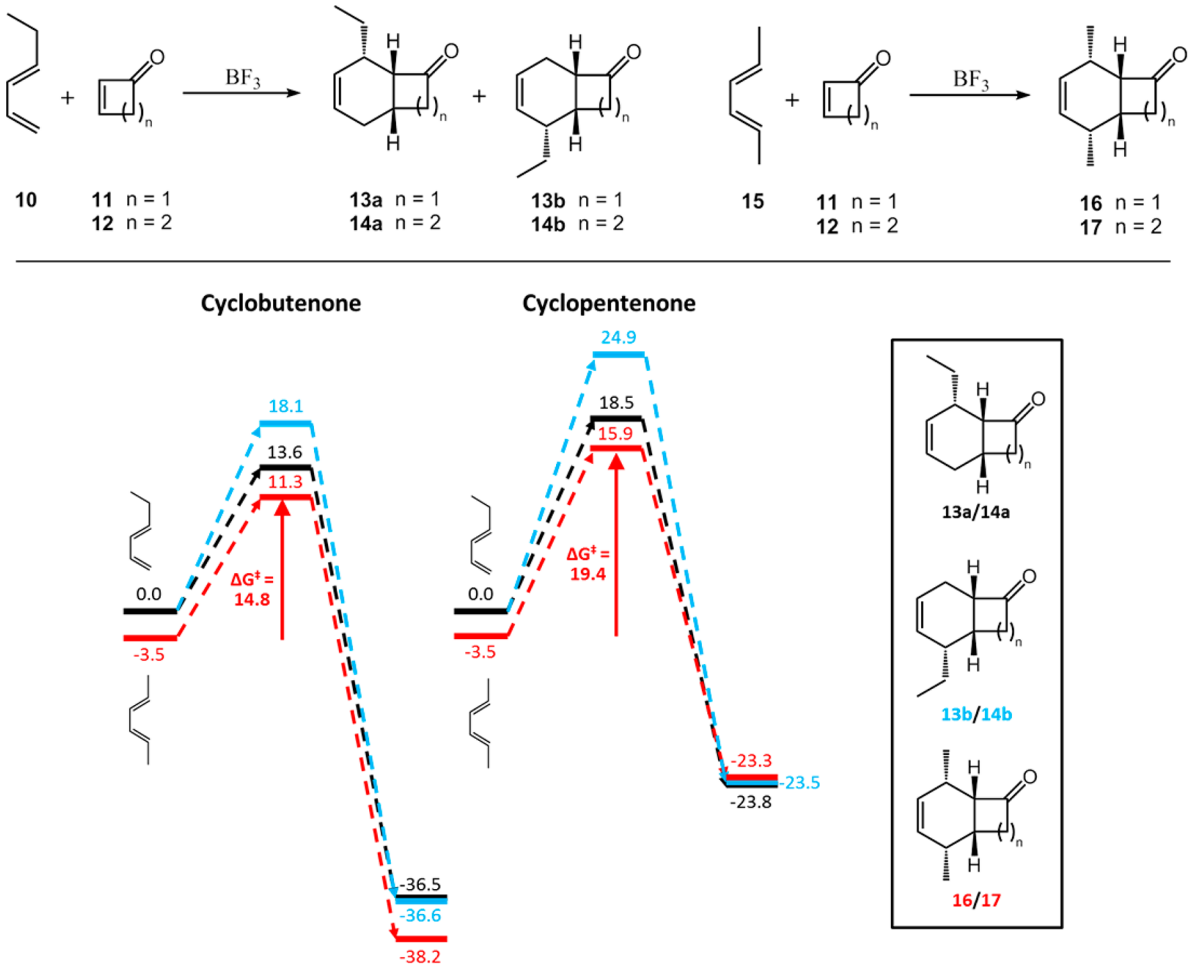

Figure 7. Computed energy diagrams for the Lewis acid-catalyzed intermolecular reactions of cyclobutenone **11** and cyclopentenone **12**. Free energies are in kcal/mol. Only endo transition states were considered.

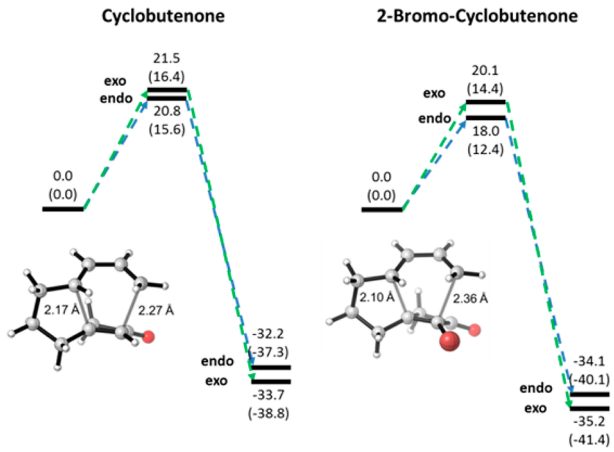

Figure 8. Computed free energy diagrams for cyclobutenone **1** and halogenated analogue 2-bromocyclobutenone **1Br**. Free energies (enthalpies) are in kcal/mol. Endo transition states are shown.

to 2.1 kcal/mol. These changes, along with the larger asynchronicity of the bond formation, are indicative of a more polar transition structure, reminiscent of conducting the reaction in the presence of BF_3. Both α-halogenation and/or coordination of Lewis acidic BF_3 to the carbonyl oxygen increase the electrophilicity of the β-carbon. The M06-2X-computed LUMO energy of cyclobutenone **1** decreases by 0.4 eV upon incorporation of the α-bromine substituent. Furthermore, the thermodynamic preference for electronegative halogens to be attached to more alkylated sp^3-carbons explains the larger exergonicity of the halogenated Diels–Alder products.[8a]

CONCLUSION

We have investigated the intramolecular Diels–Alder reaction of tethered cycloalkenones and butadienes. The high endo selectivity of the reaction observed experimentally arises from strain induced by tether conformation and steric repulsion in the exo transition states. Coordination of a Lewis acid increases the rate of reaction as well as the difference in activation energy of the endo and exo transition states, producing solely the endo product. The lack of anticipated 6,6-fused product with a 4-carbon tether is caused by a facile and thermodynamically favorable diene migration prior the Diels–Alder cycloaddition. The addition of a bromine substituent at the α-position of the enone facilitates both the kinetics and the thermodynamics of the reaction and increases the preference for the endo transition state.

ASSOCIATED CONTENT

Supporting Information

Computational data, including Cartesian coordinates and energies. General experimental protocols and NMR spectra.

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