Origin of Catalysis and Regioselectivity of Lewis Acid-Catalyzed Diels-Alder Reactions with Tropone


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Abstract
We have studied the uncatalyzed and Lewis acid (LA)-catalyzed cycloaddition reaction between tropone and 1,1-dimethoxyethene using dispersion-corrected relativistic density functional theory (DFT). The LA catalysts BF₃, B(C₆H₅)₃, and B(C₆F₅)₃ efficiently accelerate both the competing [4+2] and [8+2] cycloaddition reactions by lowering the activation barrier up to 12 kcal mol⁻¹ compared to the uncatalyzed reaction. Our study reveals that the LA catalyst promotes both cycloaddition reaction pathways by LUMO-lowering catalysis and demonstrates that Pauli-lowering catalysis is not always the operative catalytic mechanism in cycloaddition reactions. Judicious choice of the LA catalyst can effectively impart regiocontrol of the cycloaddition: B(C₆H₅)₃ furnishes the [8+2] adduct while B(C₆F₅)₃ yields the [4+2] adduct. We discovered that the regioselectivity shift finds its origin in the ability of the LA to absorb distortion by adopting a trigonal pyramidal geometry around the boron atom.

Keywords: Activation Strain Model • Cycloaddition • Density functional calculations • Lewis acids • Reactivity • Regioselectivity
Introduction
The Diels-Alder reaction is one of the most widely employed reactions in organic synthesis because it holds the potential to form a six-membered ring with up to four stereocenters in a single reaction step.\(^1\) The inverse electron demand (IED) [4+2] Diels-Alder reaction typically involves electron-poor dienes, such as the widely utilized tropone.\(^2\) Nevertheless, tropone can, due to its extended \(\pi\)-electronic system, also engage in many higher-order cycloaddition reactions, for instance, the competing [6+2],\(^3\) [6+3],\(^4\) [6+4],\(^5\) [6+6],\(^6\) [8+2],\(^7\) and [8+3]\(^8\) cycloadditions. In this way, several bridged 3D molecular structures can be formed. Constructing a target compound in a regioselective fashion when tropone is involved is highly desirable. For example, it was recently shown that the regioselectivity of the reaction between tropone and 1,1-diethoxyethene can be efficiently steered by a judicious selection of the Lewis acid (LA) catalyst to form either the [4+2] cycloadduct or [8+2] cycloadduct (Scheme 1).\(^9\) Specifically, when the LA triphenylborane is employed, the [8+2] cycloadduct is formed, whereas for tris(pentafluorophenyl)borane the [4+2] cycloadduct is selectively formed. Despite the experimental evidence on the LA-induced regioselectivity of inverse electron demand Diels-Alder reactions, the origin of the regioselectivity shift is still unresolved.

![Scheme 1](image)

**Scheme 1.** Lewis acid (LA)-catalyzed cycloaddition reaction between 1,1-diethoxyethene and tropone forming the [4+2] and [8+2] cycloadducts with their experimentally determined regioselectivity ratios estimated by crude \(^1\)H NMR.\(^9\)

Until recently, it was commonly accepted that Lewis acids catalyze Diels-Alder reactions via lowering the LUMO of the activated dienophile, which gives rise to a smaller normal electron demand (NED) HOMO\(_{\text{dienene}}\)–LUMO\(_{\text{dienophile}}\) orbital energy gap and hence more stabilizing orbital interactions.\(^10\) Over the last few years, however, we discovered that this rationale behind LA-catalyzed Diels-Alder reactions is incorrect. We found, instead, that the catalytic effect of LAs on Diels-Alder reactions is determined by a reduction of destabilizing
two-center four-electron Pauli repulsion between the occupied $\pi$-molecular orbitals of the reactants.\textsuperscript{[11]} Furthermore, the LA also increases the asynchronicity of the DA reaction, thereby leading to an additional lowering of the Pauli repulsion as well as a reduction of the destabilizing activation strain. This \textit{Pauli-lowering catalysis} concept has been shown to apply to a diverse set of other organic reactions as well.\textsuperscript{[12, 13]}

In this work, we have performed a comprehensive computational study to pinpoint both the origin of regioselectivity and the origin of catalysis of the LA-catalyzed IED Diels-Alder reactions experimentally investigated by Yamamoto \textit{et al}.\textsuperscript{[9]} Given the current computational capacity and state-of-the-art analysis tools available, computational studies have the ability to provide deep and unparalleled insight into the mechanistic action of organocatalysts.\textsuperscript{[14]} To that end, we have analyzed and compared the uncatalyzed and LA-catalyzed [4+2] (IED Diels-Alder reaction) and [8+2] cycloaddition reactions between 1,1-dimethoxyethene (E) and tropone (T) (Scheme 2) by means of the activation strain model (ASM)\textsuperscript{[15]} of reactivity, in combination with Kohn-Sham molecular orbitals\textsuperscript{[16]} theory, and the matching canonical energy decomposition analysis (EDA).\textsuperscript{[17]} 1,1-dimethoxyethene was used as a model system instead of 1,1-diethoxyethene to reduce the conformational flexibility of the ethoxy groups. First, we study the catalytic effect of the LAs on the reactivity of the [8+2] and [4+2] cycloadditions. Thereafter, we examine and pinpoint the origin of the regioselectivity of $\text{B(C}_6\text{H}_5)_3$ and $\text{B(C}_6\text{F}_5)_3$.

\begin{center}
\begin{tabular}{|c|}
\hline
LA = none, BF$_3$, B(C$_6$H$_5$)$_3$, B(C$_6$F$_5$)$_3$
\hline
\end{tabular}
\end{center}

\textbf{Scheme 2.} The uncatalyzed and LA-catalyzed cycloaddition reactions between 1,1-dimethoxyethene (E) and tropone (T) that were computationally analyzed.
Computational method

Computational Details

All calculations were performed utilizing the Amsterdam Density Functional (AMS2021.104) software package.\textsuperscript{[18]} For all computations and analyses, the generalized gradient approximation (GGA) functional BP86\textsuperscript{[19]} was used augmented by Grimme’s D3 dispersion correction\textsuperscript{[20]} using the damping function proposed by Becke and Johnson\textsuperscript{[21]}. The basis set employed, denoted TZ2P, is of triple-\(\zeta\) quality and augmented with two sets of polarization functions on each atom.\textsuperscript{[22]} Scalar relativistic effects were accounted for using the zeroth-order regular approximation (ZORA).\textsuperscript{[23]} This level is referred to as ZORA-BP86-D3(BJ)/TZ2P, and has been proven to be accurate in calculating relative trends in activation barriers and energies, as well as in performing the activation strain and energy decomposition analysis for cycloaddition reactions.\textsuperscript{[11,24]} The accuracies of the integration grid (Becke grid)\textsuperscript{[25a]} and the fit scheme (Zlm fit)\textsuperscript{[25b]} were set to VERYGOOD. All geometries were optimized without any symmetry constraint. Equilibrium and transition state geometries were verified by means of vibrational analysis\textsuperscript{[26]} to assess the nature of all structures where local minima presented real frequencies while transition structures had a single imaginary frequency. Furthermore, the character of the normal mode associated with the imaginary frequency has been analyzed to ensure it was associated with the correct reaction mode: the formation of the C–C bond between the reactants. A rigorous conformational search was performed to identify the lowest energy transition state of the regioselective step for the cycloaddition reaction between LA–T and E. The potential energy surfaces of the studied Diels-Alder reactions of the lowest energy transition states were obtained using intrinsic reaction coordinate (IRC) calculations\textsuperscript{[27]} and were analyzed with the aid of the PyFrag 2019 program.\textsuperscript{[28]} All structures were illustrated by using CYLview.\textsuperscript{[29]} 

Activation Strain Model and Energy Decomposition Analysis

Quantitative analyses of the potential energy surfaces associated with the studied reactions were obtained by means of the activation strain model (ASM) of chemical reactivity.\textsuperscript{[15]} The ASM is a fragment-based approach built upon the concept that the energy of a reacting system (i.e. the potential energy surface) can be described with respect to, and understood in terms of the characteristics of the original reactants. It examines the rigidity of the original reactants, the extent of their deformation during the reaction, and their capability to interact as the reaction proceeds. In this model, the potential energy surface \(\Delta E(\zeta)\) is decomposed into the total strain
energy, $\Delta E_{\text{strain}}(\zeta)$, and interaction energy, $\Delta E_{\text{int}}(\zeta)$ in which these values are projected onto a reaction coordinate $\zeta$ that is critically involved in the transformation [Eq. (1)]:

$$\Delta E(\zeta) = \Delta E_{\text{strain}}(\zeta) + \Delta E_{\text{int}}(\zeta)$$  \hspace{1cm} (1)

In this equation, the total strain energy, $\Delta E_{\text{strain}}(\zeta)$, is associated with the rigidity and the structural deformation of the reactants from their equilibrium structure to the geometry they adopt at the coordinate of $\zeta$ during the reaction. On the other hand, the interaction energy, $\Delta E_{\text{int}}(\zeta)$, is related to the electronic structure of the reactants and their spatial orientation and accounts for all mutual chemical interactions between the deformed reactants. The total strain energy can be further decomposed into the strain energies corresponding to the deformation of 1,1-dimethoxyethane $\Delta E_{\text{strain,E}}(\zeta)$ and the deformation of the LA–tropone complex $\Delta E_{\text{strain,LA–T}}(\zeta)$ [Eq. (2)]:

$$\Delta E_{\text{strain}}(\zeta) = \Delta E_{\text{strain,E}}(\zeta) + \Delta E_{\text{strain,LA–T}}(\zeta)$$  \hspace{1cm} (2)

The strain energy of the LA–tropone complex can even be further decomposed, see Supporting Information for a detailed description. To obtain a deeper insight into the physical mechanism behind $\Delta E_{\text{int}}(\zeta)$, we utilized our canonical energy decomposition analysis (EDA).\textsuperscript{[17]} In the EDA scheme, the $\Delta E_{\text{int}}(\zeta)$ is decomposed, within the framework of Kohn-Sham DFT, into four physically meaningful energy terms [Eq. (3)]:

$$\Delta E_{\text{int}}(\zeta) = \Delta V_{\text{elstat}}(\zeta) + \Delta E_{\text{Pauli}}(\zeta) + \Delta E_{\text{oi}}(\zeta) + \Delta E_{\text{disp}}(\zeta)$$  \hspace{1cm} (3)

Herein, the electrostatic interaction, $\Delta V_{\text{elstat}}(\zeta)$, corresponds to classical electrostatic interaction between the unperturbed charge distributions of the deformed reactants and is usually attractive. The Pauli repulsion, $\Delta E_{\text{Pauli}}(\zeta)$, compromises for the destabilizing interaction between occupied closed-shell orbitals of both deformed reactants due to the Pauli principle. The orbital interaction, $\Delta E_{\text{oi}}(\zeta)$, accounts for polarization and charge transfer between the fragments. The dispersion term $\Delta E_{\text{disp}}$ corresponds to the dispersion corrections as introduced by Grimme \textit{et al.}\textsuperscript{[20]}

Both the activation strain and energy decomposition analyses were carried out along the intrinsic reaction coordinate (IRC) projected onto a critical geometry parameter, which is,
in this study, the shortest of the two newly forming C···C bonds between 1,1-dimethoxyethene and tropone. This particular geometry parameter undergoes a well-defined change during the reaction going from the reactants via the transition state to the cycloadduct and has been shown to be a valid reaction coordinate for studying cycloaddition reactions.\textsuperscript{11,12}

**Results and Discussion**

**Reaction Profiles**

First, we analyze the interaction of the Lewis acids (LAs) with the carbonyl oxygen of tropone (T) in the LA–T complex (see Tables S1 and S2 for a detailed analysis). We find that the most favorable binding mode is between the LA and the lone pair orbitals of the carbonyl oxygen of T. Naturally, the LA can also potentially interact with the C=C bonds of T and E, and to the methoxy group of E. These binding modes are, however, energetically less favorable than the binding to the carbonyl oxygen of T (Table S2) and hence not included in the analysis of the Diels–Alder reaction.

<table>
<thead>
<tr>
<th>LA–T</th>
<th>[4+2]</th>
<th>[8+2]</th>
<th>[4+2]/[8+2]\textsuperscript{[c]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>–6.5 (4.5)</td>
<td>–4.6 (6.8)</td>
<td>&lt;1:99</td>
</tr>
<tr>
<td>TS</td>
<td>8.1 (22.9)</td>
<td>5.4 (19.0)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>–18.1 (−1.4)</td>
<td>–20.5 (−5.1)</td>
<td></td>
</tr>
<tr>
<td>BF\textsubscript{3}–T</td>
<td>–9.3 (2.8)</td>
<td>–8.7 (4.8)</td>
<td></td>
</tr>
<tr>
<td>TS1</td>
<td>–4.3 (10.8)</td>
<td>–5.0 (10.1)</td>
<td>24:76</td>
</tr>
<tr>
<td>INT</td>
<td>–6.5 (9.9)</td>
<td>–8.9 (7.3)</td>
<td></td>
</tr>
<tr>
<td>TS2</td>
<td>–1.8 (14.7)</td>
<td>–8.1 (9.5)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>–10.7 (6.5)</td>
<td>–11.1 (4.8)</td>
<td></td>
</tr>
<tr>
<td>B(C\textsubscript{6}H\textsubscript{5})\textsubscript{3}–T</td>
<td>–9.6 (4.2)</td>
<td>–10.4 (3.0)</td>
<td></td>
</tr>
<tr>
<td>TS1</td>
<td>–3.7 (11.1)</td>
<td>–4.7 (10.4)</td>
<td>22:78</td>
</tr>
<tr>
<td>INT</td>
<td>–6.4 (10.5)</td>
<td>–8.7 (7.6)</td>
<td></td>
</tr>
<tr>
<td>TS2</td>
<td>–5.0 (10.8)</td>
<td>–3.2 (14.6)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>–12.8 (4.1)</td>
<td>–7.6 (10.0)</td>
<td></td>
</tr>
<tr>
<td>B(C\textsubscript{6}F\textsubscript{5})\textsubscript{3}–T</td>
<td>–9.7 (3.7)</td>
<td>–6.7 (7.4)</td>
<td></td>
</tr>
<tr>
<td>TS1</td>
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<td>–3.0 (12.3)</td>
<td>70:30</td>
</tr>
<tr>
<td>INT</td>
<td>–5.6 (10.0)</td>
<td>–6.9 (9.4)</td>
<td></td>
</tr>
<tr>
<td>TS2</td>
<td>–3.4 (12.8)</td>
<td>–1.7 (15.3)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>–11.0 (7.7)</td>
<td>–6.2 (10.6)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Computed at ZORA-BP86-D3(BJ)/TZ2P. \textsuperscript{[b]} See Figures S1–S5 for complete reaction profiles and Figure S6 for transition state structures (TS1). \textsuperscript{[c]} The computed [4+2]/[8+2] ratios were calculated using the Arrhenius equation based on the difference of the Gibbs free energy barriers.\textsuperscript{30}
Next, we focus on the [4+2] and [8+2] cycloaddition reactions between LA–T and E. Table 1 contains the energies of the stationary points of the [4+2] and [8+2] reaction profiles relative to the energy of the separate optimized reactants. The schematic reaction energy profiles of the LA-catalyzed [4+2] and [8+2] cycloaddition reactions are shown in Figure S1 and Figure S2, respectively. In line with previous studies on LA-catalyzed Diels-Alder reactions,[11, 31] we find that LAs not only lower the activation barrier, but also affect the reaction mode, even to the extent that the otherwise concerted reaction pathways become stepwise. The uncatalyzed [4+2] and [8+2] cycloaddition reactions follow a concerted asynchronous reaction mode while the LA-catalyzed cycloadditions proceed, for all LA catalysts, in a stepwise manner. For both, the [4+2] and [8+2] cycloaddition reaction, the C–C\textsubscript{a} bond formation at the \(\alpha\)-carbon of LA–T is ahead of the second bond formation, which are the C–C\textsubscript{γ} bond formation and C–O bond formation of the [4+2] and [8+2] cycloaddition reaction, respectively. Overcoming the first activation barrier is the regioselectivity determining step and in most cases the rate determining step, and we will, therefore, solely focus on this reaction step (See Figure S6 in the Supporting Information for the transition state structures).[32] The uncatalyzed reaction has the highest activation barrier of 8.1 kcal mol\(^{-1}\) and 5.4 kcal mol\(^{-1}\) for the [4+2] and [8+2] cycloaddition reactions, respectively, while coordination of a LA to tropone lowers the activation barrier up to –4.3 kcal mol\(^{-1}\) and –5.0 kcal mol\(^{-1}\) for the [4+2] and [8+2] cycloadditions, respectively, when catalyzed by BF\(_3\).

Gratifyingly, our computations correctly recover the experimentally observed reactivity trends.[9] From the computed ratios between the [4+2] and [8+2] cycloaddition reactions, we establish that the [8+2] adduct is formed when utilizing B(C\(_6\)H\(_5\))\(_3\) and the [4+2] adduct with B(C\(_6\)F\(_5\))\(_3\) (Table 1 and Scheme 1). Besides the [4+2] and [8+2] cycloaddition pathways shown in Scheme 2, we have also studied the cycloaddition reactions forming the other possible structural isomers of the [4+2] and [8+2] cycloadduct, as well as the formation of the [6+2] cycloadduct (Scheme S1). These cycloadditions go, however, with higher activation barriers and are thus not competitive with the experimentally observed [4+2] and [8+2] cycloadducts (Table S3). For this reason, they are excluded from the further analyses.
Origin of catalysis

In this next section, we examine the physical factors that lead to the enhanced reactivity of the LA-catalyzed compared to the uncatalyzed cycloaddition reactions, by applying the activation strain model (ASM).\(^{15}\) Figure 1a shows the activation strain diagrams (ASDs) of the uncatalyzed and BF\(_3\)-catalyzed \([4+2]\) cycloaddition reaction along the IRC projected on the shorter of the two newly forming C–C bonds between \(E\) and LA–T. The ASDs of the other catalysts, \(i.e., \) B(C\(_6\)H\(_5\))\(_3\) and B(C\(_6\)F\(_5\))\(_3\), as well as the \([8+2]\) reaction pathways possess the same features and are provided in Figures S7–S9 of the Supporting Information. The enhanced reactivity of the BF\(_3\)-catalyzed compared to the uncatalyzed reaction originates exclusively from a more stabilizing interaction energy (\(\Delta E_{\text{int}}\)). The strain energy, on the other hand, shows a trend that opposes the trend in activation barrier and hence is not responsible for the reactivity trend. To understand why the interaction energy is more stabilizing for the BF\(_3\)-catalyzed reactions, we have carried out an energy decomposition analysis (EDA).\(^{17}\) Decomposing the interaction energy reveals that the trend in interaction energy is solely determined by the orbital interactions (Figure 1b). Interesting, and in contrast with our previous studies,\(^{11}\) the Pauli repulsion of the uncatalyzed and the BF\(_3\)-catalyzed reactions are nearly superimposed along the entire reaction pathway and, therefore, not responsible for the observed catalysis.

Figure 1: a) Activation strain analyses and b) energy decomposition analyses of uncatalyzed and BF\(_3\)-catalyzed \([4+2]\) cycloaddition reactions between \(E\) and LA–T, where the transition states are indicated with a dot and the energy terms along the IRC are projected on the shorter of the two newly forming C–C bonds between \(E\) and LA–T computed at ZORA-BP86-D3(BJ)/TZ2P. The \(\Delta E_{\text{disp}}\) is constant along the reaction coordinate and is omitted for clarity.
Figure 2. Molecular orbital diagrams with orbital energy gaps and overlaps for a) the inverse electron demand (IED) $\pi$-HOMO$_{E}$−$\pi$-LUMO$_{LA-T}$ interaction; and b) normal electron demand (NED) $\pi$-LUMO$_{E}$−$\pi$-HOMO$_{LA-T}$ interaction of the uncatalyzed and BF$_3$-catalyzed [4+2] cycloaddition reactions between $E$ and LA−T, computed at consistent geometries along the IRC ($C_{\alpha,E} \cdots C_{\alpha,LA-T} = 1.958$ Å) at ZORA-BP86-D3(BJ)/TZ2P.

The origin of the more stabilizing orbital interactions for the BF$_3$-catalyzed [4+2] cycloaddition reaction is further investigated by performing a Kohn-Sham molecular orbital (KS-MO)$^{[16]}$ analysis at the consistent geometries obtained from the IRC where the distance of the shorter forming C•••C bond is 1.958 Å (Figure 2). Performing this analysis at a consistent point along the reaction coordinate (near the transition state structures), rather than on the individual transition state structures, assures that the analyses are not skewed by the location of the transition state.$^{[33]}$ We looked into the inverse electron demand (IED) and normal electron demand (NED) interactions between $E$ and LA−T, and noticed a significant strengthening in the IED interaction that causes the more stabilizing orbital interactions for the BF$_3$-catalyzed compared to the uncatalyzed reaction. The primary IED interaction occurs between the $\pi$-HOMO of $E$, which is located on the reactive C=C double bond, and $\pi$-LUMO of LA−T, as shown in Figure 2a, and becomes more stabilizing from the uncatalyzed to BF$_3$-catalyzed reaction due to a smaller energy gap of 2.0 eV to 1.4 eV, respectively. The LA induces a $LUMO$-lowering effect and therefore a smaller energy gap. The main NED interaction occurs between the $\pi$-LUMO of $E$ and $\pi$-HOMO of LA−T, see Figure 2b. The NED interaction is slightly destabilized as going from the uncatalyzed to BF$_3$-catalyzed...
cycloaddition reaction, because of a larger energy gap for the uncatalyzed (3.9 eV) than for the BF$_3$-catalyzed (6.0 eV) cycloaddition and a larger orbital overlap of 0.06 compared to 0.04, respectively. A LA catalyst, such as BF$_3$, induces charge transfer from T making the carbonyl oxygen effectively more electronegative. This leads to polarization of orbital amplitude towards the more electronegative oxygen and the LA catalyst, which results into the slightly smaller NED orbital overlap. Besides that, the reduced Coulomb repulsion between the electrons causes stabilization of all energy levels and thus not only lowering the LUMO$_{LA-T}$, but also the lower laying HOMO$_{LA-T}$, which results in the larger NED energy gap. So, the IED interaction is more stabilizing for the LA-catalyzed than the uncatalyzed cycloaddition reaction, while the opposite holds for the NED interaction. However, the magnitude and significance of the NED interaction in the uncatalyzed reaction is already much smaller compared to the IED interaction. Therefore, the weakening in NED interaction is insignificant compared to the strengthening in the IED interaction and cannot counteract the gain in the significantly larger IED. This results in overall more stable orbital interactions for the LA-catalyzed than the uncatalyzed [4+2] cycloaddition reaction (IED-Diels-Alder reaction).\[34\] Note that this phenomenon has not been observed in Lewis acid-catalyzed NED Diels-Alder reactions, since in that situation the strengthening of the NED orbital interaction is effectively counteracted by the weakening of the IED orbital interaction, resulting in similar orbital interactions for both the uncatalyzed and LA-catalyzed NED Diels-Alder reaction.\[11\]

Surprisingly, in the present study, the Pauli repulsion is nearly identical for the uncatalyzed and LA-catalyzed cycloaddition reactions and hence is not responsible for the catalysis (Figure 1b). In our recent work, all of our studied NED Diels-Alder reactions have found that the catalytic effect of the Lewis acid is not caused by the strengthening of the orbital interactions but by the reduction of Pauli repulsion between the occupied $\pi$-molecular orbitals of the reactants (Pauli-lowering catalysis).\[11\] This raises the question: why is the Pauli repulsion similar for the uncatalyzed and LA-catalyzed [4+2] and [8+2] cycloaddition reactions? To answer this, we study the Pauli repulsive orbital interaction between the key occupied $\pi$-molecular orbitals of the reactants. We indeed found that the LA polarizes the $\pi$-molecular orbitals of T away from the reactive carbon atoms towards the LA, which should cause a diminished Pauli repulsion (Figure S11). However, an additional Pauli repulsion between the LA itself and E is obtained (Table S4), which cancels out the diminished Pauli repulsion between T and E, and results in a similar Pauli repulsion in the uncatalyzed and LA-catalyzed reaction.
Regioselectivity

Figure 3. Activation strain analyses dividing the a) electronic energy in the b) strain energy and c) interaction energy of B(C₆H₅)₃- and B(C₆F₅)₃-catalyzed [8+2] cycloaddition (solid line) and [4+2] cycloaddition (dashed line) reactions between E and LA–T, where the transition states are indicated with a dot and the energy terms along the IRC are projected on the shorter of the two newly forming C–C bonds between E and LA–T. Computed at ZORA-BP86-D3(BJ)/TZ2P.
Lastly, we examine the B(C₆H₅)₃- and B(C₆F₅)₃-catalyzed cycloaddition reactions to understand the difference in regioselectivity between the two LA catalysts. The [8+2] cycloadduct is preferred for the B(C₆H₅)₃-catalyzed cycloaddition reaction, whereas, in contrast, the [4+2] cycloadduct is preferred for the B(C₆F₅)₃-catalyzed reaction. As becomes clear from Figure 3a, and in line with Table 1, for B(C₆H₅)₃ the activation barrier of the [8+2] cycloaddition (solid line) is lower than the barrier of the [4+2] cycloaddition (dashed line). We see just the opposite for B(C₆F₅)₃, where the barrier of the [4+2] cycloaddition reaction is lower than the activation barrier of the [8+2] cycloaddition. It is the lower activation barrier of the B(C₆H₅)₃-catalyzed [8+2] cycloaddition compared to the B(C₆F₅)₃-catalyzed analog (activation barrier of –4.7 and –3.0 kcal mol⁻¹, respectively) that causes the difference in regioselectivity. The electronic energies of the B(C₆H₅)₃- and B(C₆F₅)₃-catalyzed [4+2] cycloadditions are, on the other hand, nearly identical along the entire reaction pathway (activation barrier of –3.7 and –3.5 kcal mol⁻¹, respectively) and hence are not responsible for the difference in regioselectivity (Figure 3a). Next, to understand the difference in activation barriers of the [8+2] cycloadditions, we turned to the ASM of reactivity (Figure 3b, 3c). The lower [8+2] cycloaddition barrier for the B(C₆H₅)₃-catalyzed reaction originates from a less destabilizing strain while the interaction energy is near the transition state similar for both the B(C₆H₅)₃- and B(C₆F₅)₃-catalyzed [8+2] cycloaddition reactions.

**Figure 4.** The strain energy terms (in kcal mol⁻¹) computed for the B(C₆H₅)₃ and B(C₆F₅)₃-catalyzed [8+2] cycloaddition transition state structures (TS1) between E and LA–T at ZORA-BP86-D3(BJ)/TZ2P.

As being the main actor behind the regioselectivity, the strain energy of the [8+2] cycloaddition reactions was investigated further. The difference in strain energy between the B(C₆H₅)₃- and B(C₆F₅)₃-catalyzed reactions originates from the deformation of LA–T with ΔE_{strain,LA–T} of 16.2 and 18.0 kcal mol⁻¹, respectively, while ΔE_{strain,E} is identical for both catalysts (Figure 4). To understand what causes this difference in strain, we further decomposed
the strain of LA–T \((\Delta E_{\text{strain,LA-T}})\) into the strain of the LA \((\Delta E_{\text{strain,LA}})\) and the strain of T \((\Delta E_{\text{strain,T}})\) which revealed that the primary difference between B\((C_6H_3)_3\) and B\((C_6F_3)_3\) lies in \(\Delta E_{\text{strain,LA}}\), that is, the deformation in the LA catalyst. In the [8+2] cycloaddition, deformation of B\((C_6H_3)_3\) requires only 2.9 kcal mol\(^{-1}\), while deformation of B\((C_6F_3)_3\) requires 6.0 kcal mol\(^{-1}\) (Figure 4). For the full energy decomposition, see Figure S13 in the Supporting Information.

Two factors cause the deformation of the LA catalyst. First, during the reaction, a C–O bond is formed between E and the oxygen atom of T to which the LA is bound. The close proximity of E and the LA causes a steric clash, inducing geometrical deformation of the LA (Figure 5). The steric clash is the predominant cause of the difference between the B\((C_6H_3)_3\)- and B\((C_6F_3)_3\)-catalyzed reactions. Besides that, a C–C\(_\alpha\) bond between E and T is formed, causing build-up of negative charge at the oxygen of the carbonyl group of T. This leads to a strengthening and thus shortening of the LA–O bond, which induces a further pyramidalization of the LA. On top of that it amplifies the steric hindrance between de LA and E. Pyramidalization of B\((C_6H_3)_3\) is more facile than for B\((C_6F_3)_3\), due to the relatively weaker B–C bonds in the former.\(^{[35]}\) The average homolytic bond energies\(^{[36]}\) of the B–C bonds in B\((C_6H_3)_3\) and B\((C_6F_3)_3\) are −142.7 and −148.6, respectively. So, deformation of the LA catalyst necessary for the [8+2] cycloaddition requires less energy for B\((C_6H_3)_3\) than for B\((C_6F_3)_3\) causing the [8+2] activation barrier to be lower for the B\((C_6H_3)_3\)-catalyzed reaction than for the B\((C_6F_3)_3\)-catalyzed reaction. This results in a preferred [8+2] cycloaddition for the B\((C_6H_3)_3\)-catalyzed reaction, yet the [4+2] cycloaddition is preferred for the B\((C_6F_3)_3\)-catalyzed reaction.

Lastly, one might wonder why the [4+2] cycloaddition does not encounter a higher strain for B\((C_6F_3)_3\) than for B\((C_6H_3)_3\)? In the [4+2] cycloaddition less deformation of the LAs is required because a C–C\(_\gamma\) bond between E and T is formed further away from the LA, compared to the C–O bond in the [8+2] cycloaddition. This means that during the [4+2] cycloaddition less steric hindrance between the \textbf{LA} and \textbf{E} will be built up, and therefore less strain.
Figure 5. The steric clash between E and the LA in the transition state structures for the regioselective step of the B(C₆H₅)₃ and B(C₆F₅)₃-catalyzed [8+2] cycloaddition reactions computed at ZORA-BP86-D3(BJ)/TZ2P.

Conclusions

We have pinpointed the origin of catalysis and [4+2]/[8+2] regioselectivity in the cycloaddition reactions between tropone and 1,1-dimethoxyethene catalyzed by Lewis acids (LA = BF₃, B(C₆H₅)₃, and B(C₆F₅)₃). The binding of a LA to the carbonyl oxygen of tropone leads to a lowering of the activation barrier up to 12 kcal mol⁻¹ compared to the uncatalyzed reaction. In addition, the complete regioselective formation of the [4+2] and [8+2] adduct can be modulated by judicious selection of the LA. The reaction catalyzed by B(C₆H₅)₃ forms the [8+2] cycloadduct while the reaction catalyzed by the fluorinated analog B(C₆F₅)₃ forms the [4+2] cycloadduct.

The origin of the differing regioselectivity between B(C₆H₅)₃ and B(C₆F₅)₃ arises from the ability of the LA catalyst to facilitate the buildup of differing degrees of geometrical deformation. In both the [8+2] and [4+2] cycloadditions the first C–C bond at the α-carbon of tropone is formed. Subsequently, during the [8+2] cycloaddition a C–O bond is formed at the oxygen of tropone, to which the LA is bound, while for the [4+2] cycloaddition a C–C bond is formed further away from the LA. The LA needs to deform heavily in the [8+2] cycloaddition to accommodate for the C–O bond formation. Deformation of B(C₆H₅)₃ requires less energy than deformation of B(C₆F₅)₃ due to weaker B–C bonds, which leads to a lower [8+2] activation barrier for the B(C₆H₅)₃-catalyzed reaction than for the B(C₆F₅)₃ analog. Hence, the B(C₆H₅)₃
catalyzed reaction furnishes the [8+2] cycloadduct, while B(C₆F₅)₃ prefers the [4+2] cycloadduct.

Our activation strain and Kohn-Sham molecular orbital bonding analysis show that a LA lowers the activation barrier of the [4+2] and [8+2] cycloaddition reaction by enhancing the orbital interactions between tropone and 1,1-dimethoxyethene. Binding a LA to tropone results in a stabilization of the LUMO of tropone, which, in turn, reduces the HOMO–LUMO orbital energy gap and hence amplifies the inverse electron demand orbital interaction. The Pauli repulsion remains, in contrast to our recent work,[11] nearly identical for both the uncatalyzed and LA-catalyzed cycloaddition, demonstrating that these catalyzed reactions follow the LUMO-lowering catalysis concept. This work, therefore, reveals that LAs can accelerate organic reactions via LUMO-lowering catalysis and not only via Pauli-lowering catalysis. This phenomenon occurs when the difference between the magnitude of the inverse electron demand and the normal electron demand orbital interactions is sufficiently large in the reaction. Thus, where the LA can induce a LUMO-lowering effect that will not be counterbalanced by the small unfavorable HOMO-lowering effect.

Conflict of interest
There are no conflicts to declare.

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Pick your path! Quantum chemical activation strain analyses reveal how the regioselectivity between [4+2] and [8+2] cycloaddition reactions of tropone can be steered by the use of a Lewis acid, which catalyze the reactions via a LUMO-lowering effect.

References


[30] See the Supporting Information for a detailed description on how the Arrhenius equation was used to compute the [4+2]/[8+2] ratio.


[32] The trends in reactivity emerging from the electronic energy reaction profiles are the same as those found on the Gibbs free energies reaction profile (Figures S1 and S2).


[34] See ref. [11e] for *LUMO-lowering catalysis* in Brønsted acid-catalyzed IED Diels-Alder reaction.


[36] The average homolytic bond energy is the interaction energy between B and the three R groups divided by three.