

Catalysis of 6 π Electrocyclizations**

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The synthetic power of pericyclic reactions has greatly increased with the emergence of catalytic variants. Indeed, catalysis in cycloadditions^[1] and sigmatropic rearrangements^[2] is now well established. General methods for the catalysis of electrocyclizations, however, have remained elusive, with the notable exception of the Nazarov cyclization.^[3] The development of such methods would enable electrocyclizations to occur under milder conditions and create the possibility of catalytic asymmetric variants. Herein, we report the first examples of catalytic 6 π electrocyclizations and provide a detailed investigation into the mechanism of these reactions.

Experimental and computational studies have shown that the rate of 6 π electrocyclizations can be influenced by varying the electronics of the substituents on the triene.^[4–7] Electron-

withdrawing groups located in the 2-position of hexatriene systems have been observed to lower their electrocyclization energy barriers,^[6,7] sometimes by as much as 10 kcal mol^{–1}.^[7,8] We envisioned exploiting this effect to catalyze 6 π electrocyclizations by the coordination of a Lewis acid to a Lewis basic electron-withdrawing group located in the 2-position of a hexatriene system. This coordination should increase the electron-withdrawing effect of the substituent, thereby decreasing the electrocyclization energy barrier.

We began our investigations by computationally assessing the viability of this approach in the catalysis of 6 π electrocyclizations. Hexatriene systems with methyl ester substituents at all possible positions and orientations were modeled by density functional theory (Figure 1). A proton, serving as the simplest Lewis acid, was bonded to the carbonyl oxygen

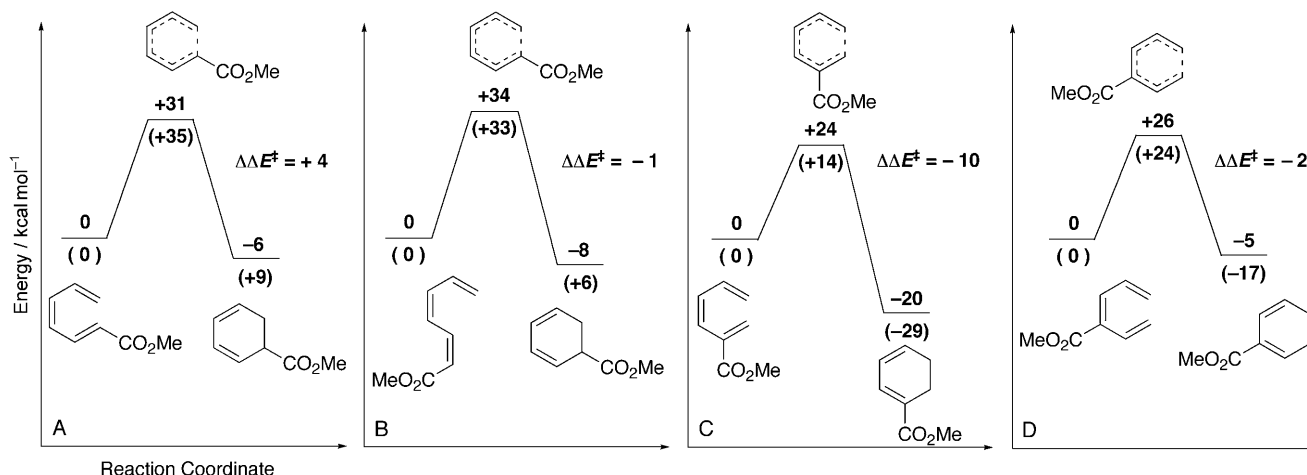


Figure 1. Relative electronic energies (kcal mol^{–1}) of the thermal (numbers above line) and cprotonated carbonyl group (numbers below line) electrocyclization pathways computed at the B3LYP/6-31G** level of theory. 1-substituted trienes (A and B); 2-substituted triene (C); 3-substituted triene (D).^[10]

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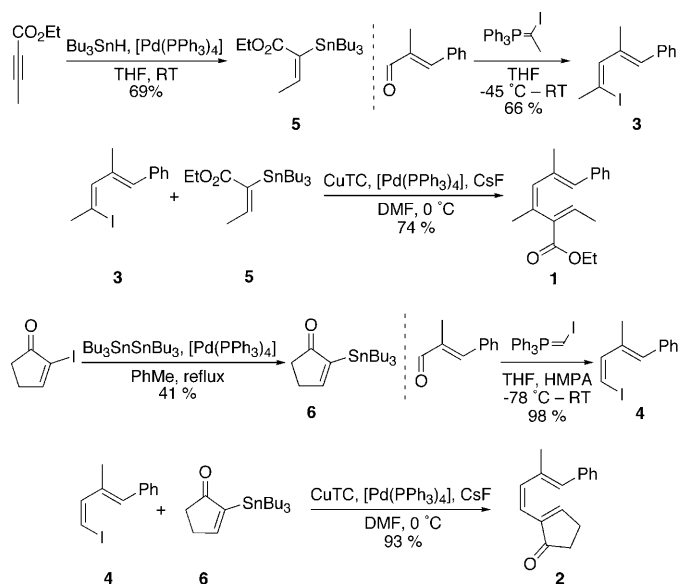
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atom at the lone pair *anti* to the hexatriene.^[9] As seen in Figure 1, these calculations predict a slight increase and decrease of the electrocyclization energy barrier for the (*E,Z*)- and (*Z,Z*)-1-carbomethoxy-substituted hexatriene systems (Figure 1 A and B), respectively. Calculations additionally predict a small decrease of the electrocyclization energy barrier for the 3-substituted system (Figure 1 D). However, we found that the electrocyclization energy barrier is predicted to decrease by 10 kcal mol^{–1} upon protonation of the 2-carbomethoxy-substituted triene system (Figure 1 C). An intrinsic reaction coordinate search in both directions from the protonated electrocyclization transition state of this system suggests that the catalyzed pathway is a concerted process, as no stationary points other than the transition state were located between the protonated triene and protonated cyclohexadiene.

Encouraged by these results, we focused our synthetic efforts on hexatriene systems with carbonyl-containing substituents at the 2-position—specifically triene substrates **1** and **2** (see Scheme 1 and the Supporting Information).^[11] A Stork–Zhao olefination furnished (*Z*)-vinyl iodides **3** and **4**, which were coupled with stannanes **5** and **6**, respectively. Modified Liebeskind coupling conditions allowed the synthesis of triene substrates **1** and **2** under mild conditions.^[12]



Scheme 1. Synthesis of triene substrates **1** and **2**. DMF = *N,N*-dimethylformamide, HMPA = hexamethylphosphoramide, TC = thiophene-2-carboxylate.

Triene **1** cyclizes thermally to *cis*-substituted cyclohexadiene **7** (Figure 2). This reaction proceeds quantitatively (on the basis of ¹H NMR analysis) with a half-life of four hours at 50 °C. After investigating a variety of Lewis acids (see the Supporting Information) we found that dimethylaluminum

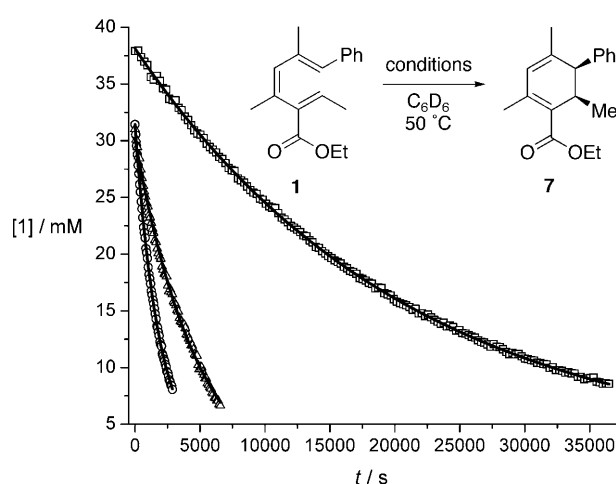


Figure 2. Kinetic plots (with first order exponential decay fits) and half-lives of the electrocycloization of **1** at 50 °C in the presence and absence of Me₂AlCl. ○: 1 equiv Me₂AlCl, *t*_{1/2} = 21 min; △: 0.43 equiv Me₂AlCl, *t*_{1/2} = 41 min; □: thermal, *t*_{1/2} = 4 h.

chloride (Me₂AlCl) was an excellent catalyst for this reaction. The addition of one equivalent of Me₂AlCl resulted in a significant rate increase, giving a half-life of 21 minutes at 50 °C. The reaction in the presence of Me₂AlCl yields *cis*-cyclohexadiene **7**, indicating that the catalyzed reaction also proceeds by the expected thermal disrotatory pathway.^[13]

A plot of the observed first-order rate constant for the electrocycloization of **1** to **7** in [D₆]benzene at constant initial substrate concentration versus varying Me₂AlCl concentration is shown in Figure 3. For a reference, the thermal first-

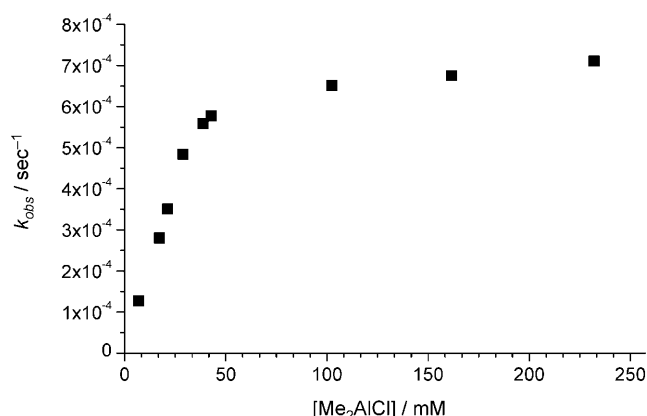


Figure 3. Saturation in Me₂AlCl. Conditions: [**1**] = 40 mM, in C₆D₆ at 50 °C.

order rate constant in [D₆]benzene at this temperature is 4.75(4) × 10^{−5} s^{−1}. The data in Figure 3 provide clear evidence of catalytic turnover—the rate of the reaction is increased at catalyst loadings greater than 17 mol % (*k*_{obs} = 1.27(4) × 10^{−4} s^{−1}), and all the kinetic data fit a first-order exponential model. A plot of the logarithm of the rate constant versus the logarithm of the Me₂AlCl concentration at sub-stoichiometric catalyst loadings yields a straight line with a slope of 0.88(4), indicating the reaction is first order in catalyst (see the Supporting Information). Also evident in Figure 3 is the fact that the rate increase begins to level off at approximately one equivalent of the catalyst, suggesting tight binding of the catalyst to the triene substrate.

The nature of the catalyst–substrate binding was additionally investigated by conducting a ¹H NMR titration of **1** with Me₂AlCl at 10 °C. A shift in all resonances of the ¹H NMR spectrum of **1** is observed (see the Supporting Information). This shift levels off at approximately one equivalent of Me₂AlCl for all resonances, which provides additional evidence for an energetically favorable 1:1 binding of Me₂AlCl to **1**.

A substrate-saturation curve was assembled to measure the order in the substrate, to extract a Michaelis constant, and to determine the rate acceleration for the catalyzed reaction (Figure 4). A plot of the logarithm of the initial reaction velocity versus the logarithm of the initial substrate concentration (where [**1**] < [Me₂AlCl]) yields a straight line with a slope of 0.99(3), indicating the reaction is first order in triene **1** (see the Supporting Information). The substrate-saturation curve also provides additional evidence for the high affinity of

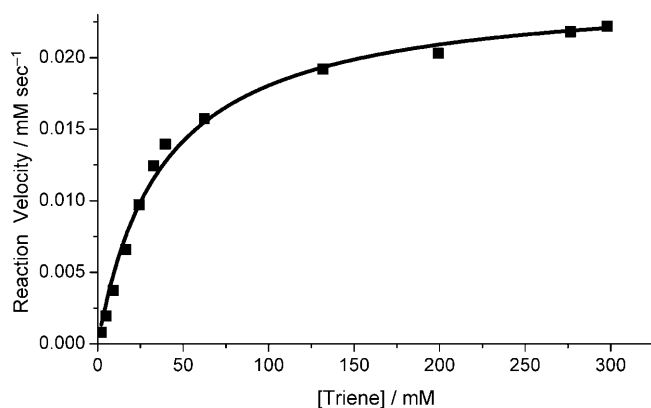
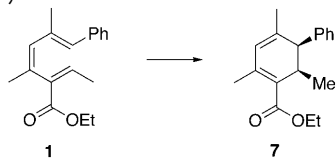


Figure 4. Saturation in **1** (fit to the Michaelis–Menten equation). Conditions: $[\text{Me}_2\text{AlCl}] = 40 \text{ mM}$, in C_6D_6 , at 50°C .

Me_2AlCl for **1**, as this curve can be fit to the Michaelis–Menten equation to give a Michaelis constant of $38(3) \text{ mM}$. Furthermore, a first-order rate constant (k_{cat}) of $6.2(2) \times 10^{-4} \text{ s}^{-1}$ for the electrocyclization of the Me_2AlCl -bound substrate at 50°C can be extracted, which is in excellent agreement with the data obtained under catalyst-saturation conditions (Figure 3). This data represents a 13-fold rate increase of the catalyzed 6π electrocyclization over that of the thermal reaction (thermal $k_{\text{obs}} = 4.75(4) \times 10^{-5} \text{ s}^{-1}$ at 50°C).

An Eyring plot of the thermal reaction reveals activation parameters typical of a carba- 6π electrocyclization (see Table 1 and the Supporting Information).^[5] The Eyring plot of the catalyzed reaction was assembled under saturation conditions (2 equiv Me_2AlCl) to assure that the parameters being measured are those for the electrocyclization of the catalyst-bound triene, without any effect from the pre-equilibrium of the catalyst–triene complex. Under these conditions, a $1.7 \text{ kcal mol}^{-1}$ decrease in the Gibbs free energy of activation is measured (Table 1) for the catalyzed electrocyclization relative to that of the thermal reaction. This value corresponds to a $2.5 \text{ kcal mol}^{-1}$ decrease in the enthalpy of activation, and a $0.8 \text{ kcal mol}^{-1}$ decrease in $T\Delta S^\ddagger$ (298 K), which indicates that the catalysis is primarily enthalpic. Additionally, the data obtained from the Eyring plots can be compared to the data obtained in the substrate-saturation experiments. An 11-fold rate acceleration would be expected at 50°C based on the measured activation parameters. These

Table 1: Activation parameters of the thermal and catalyzed (2 equiv Me_2AlCl) electrocyclizations.



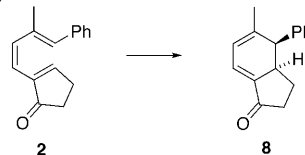
	Thermal	Catalyzed
$\Delta H^\ddagger$ [kcal mol^{-1}]	22.4(5)	20.0(2)
$\Delta S^\ddagger$ [e.u.]	−9.2(4)	−11.8(2)
$\Delta G^\ddagger_{298}$ [kcal mol^{-1}]	25.2(5)	23.5(2)

Conditions: $[\textbf{1}] = 40 \text{ mM}$, in C_6D_6 .

data are in good agreement with the 13-fold rate acceleration that is measured in the substrate-saturation experiments.

The rate of the electrocyclization of **2** to **8** is also substantially increased in the presence of catalytic or stoichiometric amounts of Me_2AlCl (see Table 2 and the Sup-

Table 2: Activation parameters of the thermal and catalyzed (1 equiv Me_2AlCl) electrocyclizations.



	Thermal	Catalyzed
$\Delta H^\ddagger$ [kcal mol^{-1}]	20.3(4)	18.1(1)
$\Delta S^\ddagger$ [e.u.]	−12.4(5)	−11.6(1)
$\Delta G^\ddagger_{298}$ [kcal mol^{-1}]	24.0(5)	21.6(1)

Conditions: $[\textbf{2}] = 40 \text{ mM}$, in C_6D_6 .

porting Information).^[14] A 55-fold rate acceleration is observed for this substrate in the presence of 1 equiv of the Lewis acid at 28°C , and Eyring analysis reveals a $2.4 \text{ kcal mol}^{-1}$ decrease in the Gibbs free energy of activation for the catalyzed process. Again, this catalysis is primarily enthalpic, exhibiting a $2.2 \text{ kcal mol}^{-1}$ decrease in the enthalpy of activation and a $0.2 \text{ kcal mol}^{-1}$ increase in $T\Delta S^\ddagger$ (298 K). This result demonstrates that ketones as well as esters are suitable Lewis-basic groups for catalytic 6π electrocyclizations, and is an indication of the broad synthetic scope of this reaction.

In conclusion, the catalysis of 6π electrocyclizations has been achieved for the first time. Our experimental work confirms the predictions of the density functional theory calculations, which suggest that such catalysis is possible with hexatriene systems substituted in the 2-position with suitable functional groups. We have synthesized trienes **1** and **2** and found that the rates of their electrocyclizations are increased in the presence of Me_2AlCl . The reaction is catalytic in Me_2AlCl , first order in both catalyst and substrate, and exhibits saturation behavior for both catalyst and substrate. The Gibbs free energy of activation for the catalyzed pathway is $1.7 \text{ kcal mol}^{-1}$ lower than that of the thermal pathway for **1**, and $2.4 \text{ kcal mol}^{-1}$ lower for **2**. Efforts towards catalytic asymmetric 6π electrocyclizations, as well as organocatalysis, are currently underway in our laboratories.

Experimental Section

Experimental procedures, kinetic data, and characterization data for products are available in the Supporting Information.

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