

Synthetic Approaches to 4-(Hydroxymethyl)benzoates and Cyclophanes

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Introduction:

The Diels-Alder reaction is known as a 4+2 cycloaddition because a conjugated diene having 4 pi electrons combines with a dienophile having 2 pi electrons to produce a cyclohexene ring.

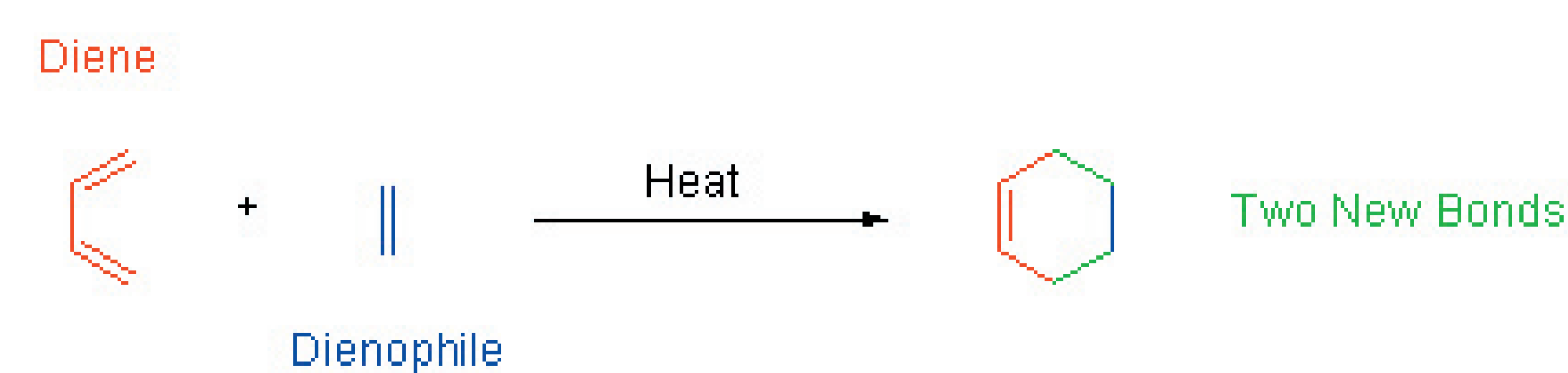


Figure 1. A diene (red) and a dienophile (blue) undergo Diels-Alder cycloaddition to form a cyclohexene ring (new bonds in green).

In a typical Diels-Alder reaction, the diene is the electron-rich species, so electrons are donated from its highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) of the electron-poor dienophile.

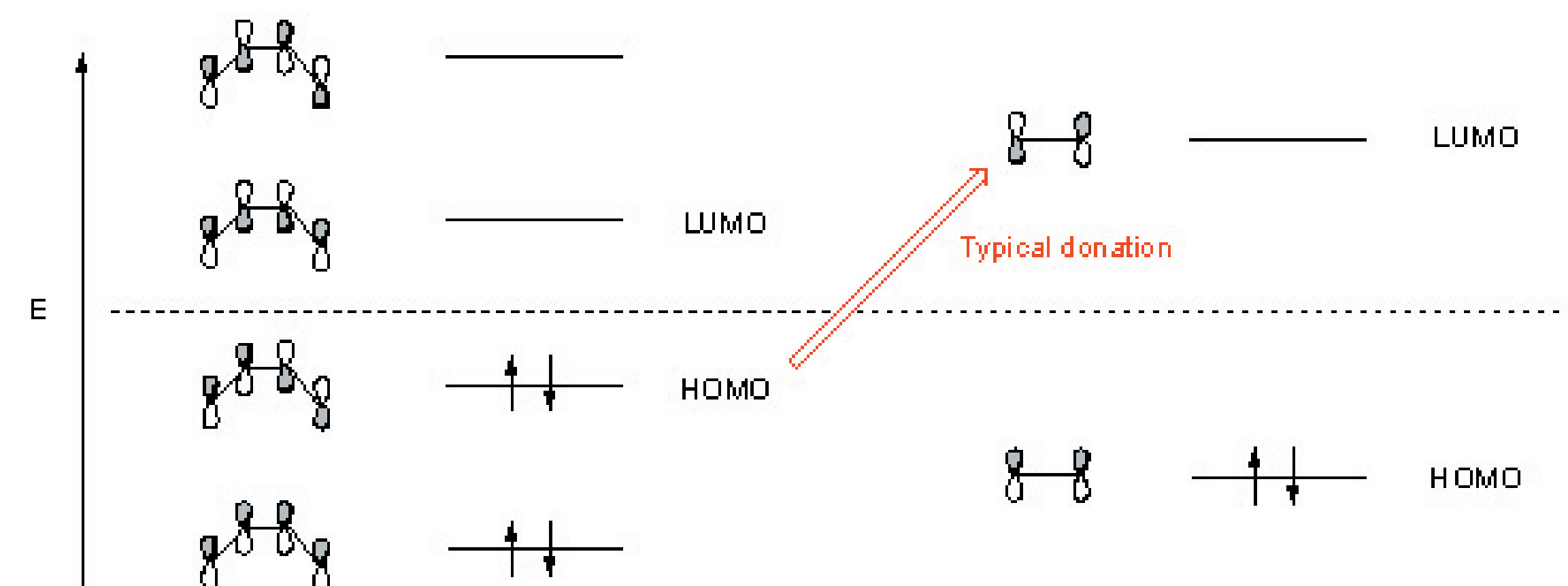


Figure 2. In a typical Diels-Alder reaction, the HOMO of the diene donates electrons to the LUMO of the dienophile.

In an inverse electron demand Diels-Alder reaction, the donation is reversed because the diene is electron poor and the dienophile is electron rich.

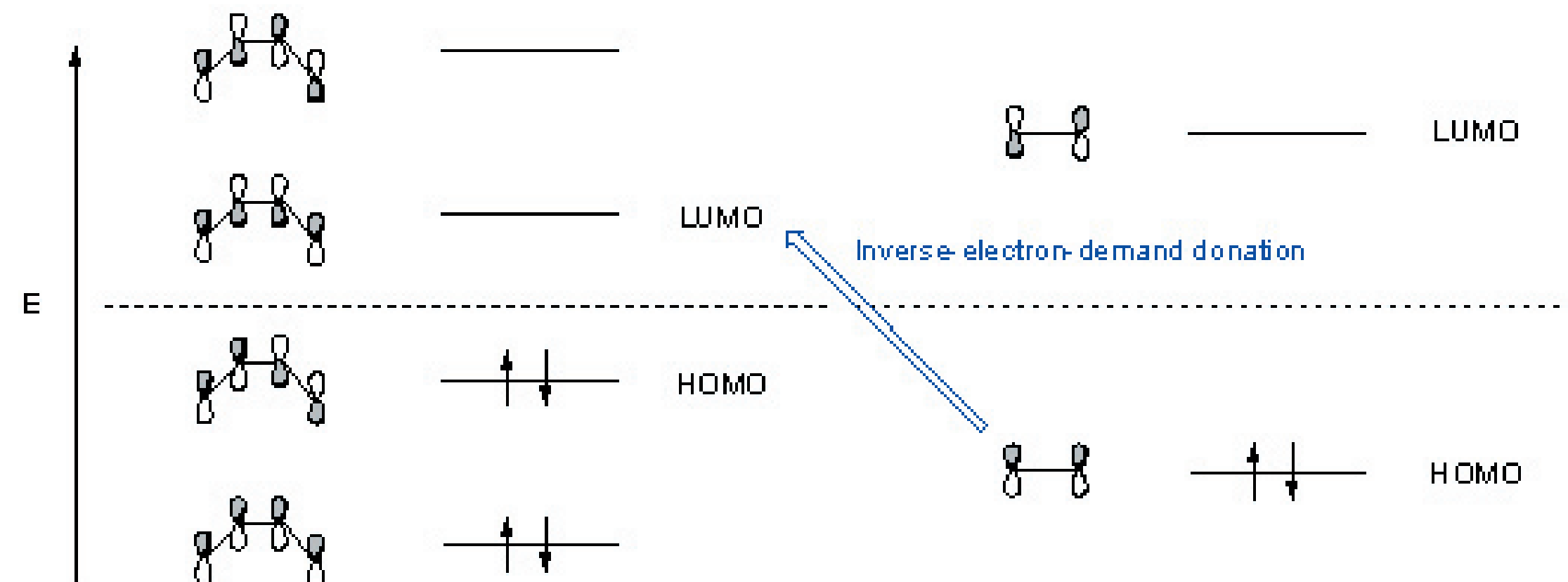


Figure 3. In the inverse-electron-demand Diels-Alder reaction, the HOMO of the dienophile donates electrons to the LUMO of the diene.

Coumalic acid derivatives can be electron-poor dienes. Since these dienes contain a ring and an additional ring is formed during the reaction, the initial products are bicyclic compounds.¹

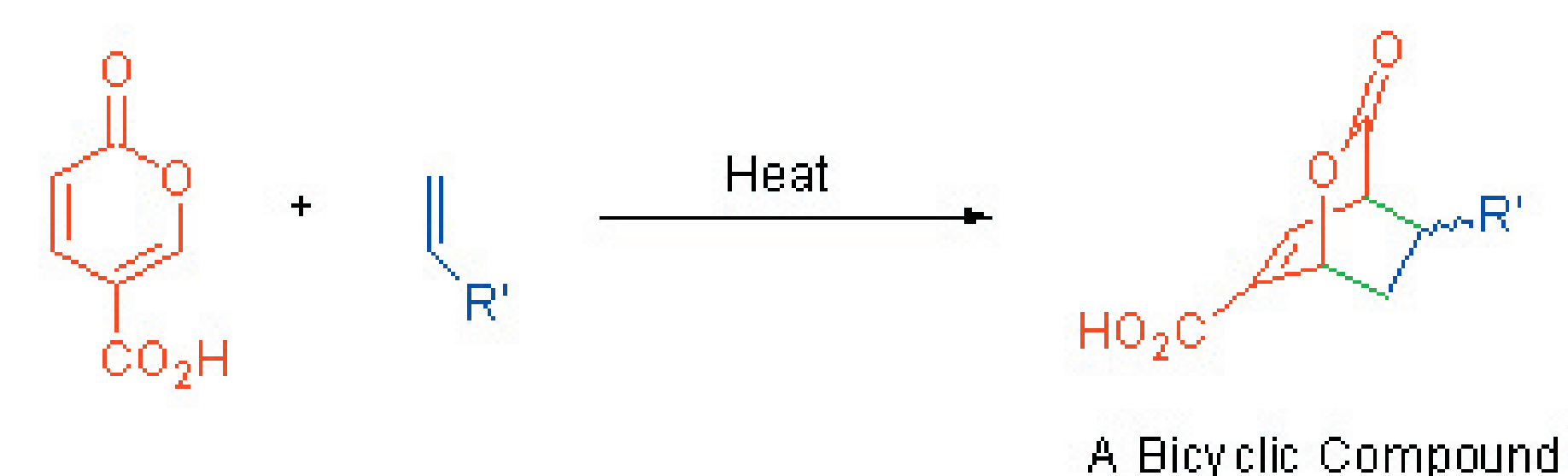
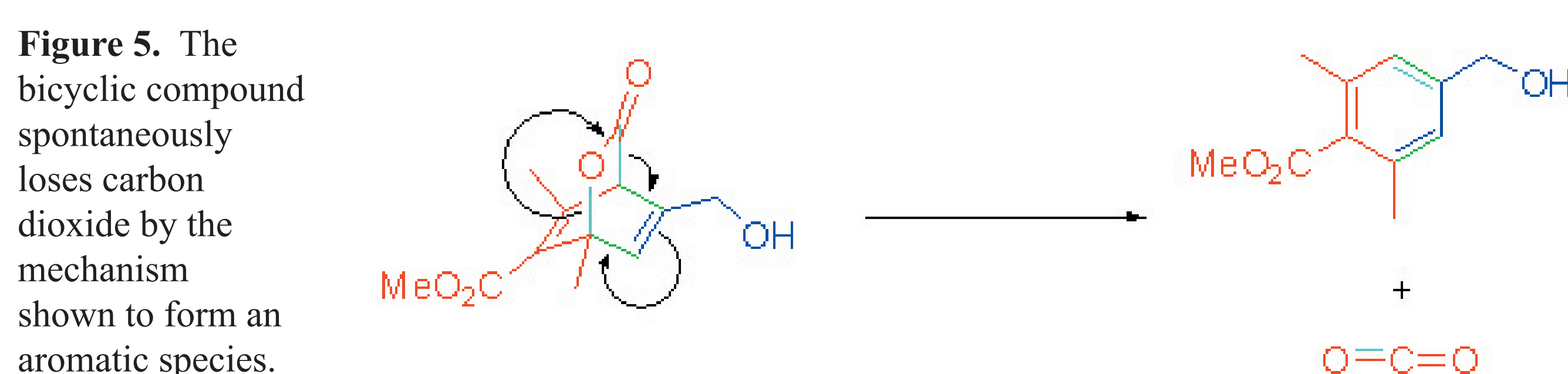


Figure 4. The dienophile (blue) attacks coumalic acid, the diene (red), to form a bicyclic compound. This cycloaddition can be depicted as an inverse-electron-demand Diels-Alder reaction. The new bonds are shown in green.

If the dienophile is an alkyne, the initial bicyclic adduct is a 1,4-diene, and the extrusion of carbon dioxide can produce an aromatic ring.^{2,3}



The Diels-Alder reaction can be catalyzed by a species that interacts with a reactant in such a way that the HOMO-LUMO energy gap is reduced. In the inverse electron demand Diels-Alder reaction of coumalic acid derivatives, a catalyst that can hydrogen bond to the diene carbonyl could stabilize the LUMO thereby facilitating the reaction.

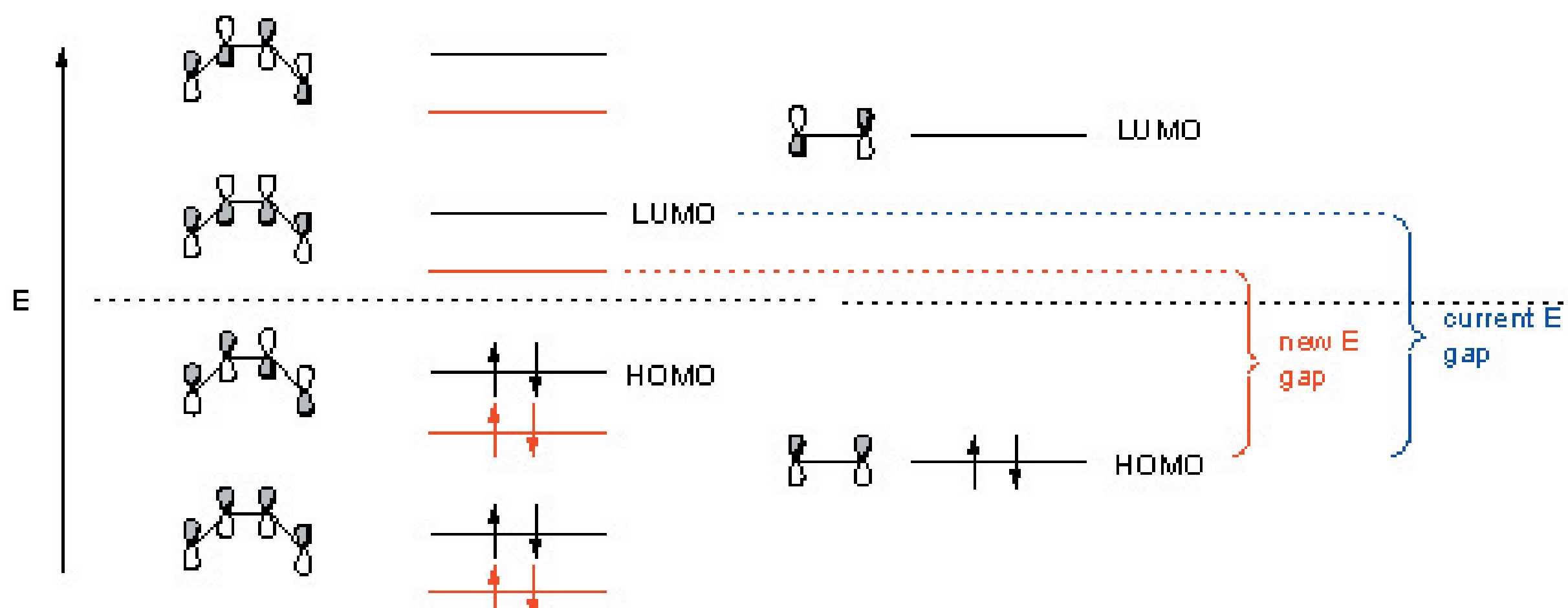


Figure 6. Black lines indicate E levels prior to interaction with the catalyst, and red lines indicate the E levels upon interaction with the catalyst.

These catalysts act as electron-withdrawing groups for the diene, making it more electron poor and therefore more likely to accept donation of electrons from the dienophile.⁴

The Diels-Alder reaction applied in this way can be used in a novel synthesis of paracyclophanes. Paracyclophanes contain an aromatic core in which the para positions are tethered by an aliphatic chain. Paracyclophanes are useful in the study of strain and pi stacking and are also present in some natural products.^{5,6} A paracyclophane could be produced by an inverse electron demand Diels-Alder reaction in which a coumalate is tethered to an alkyne, which serves as the dienophile. The initial reaction will form a bicyclic compound that will spontaneously extrude carbon dioxide, producing an aromatic ring tethered at the para positions.

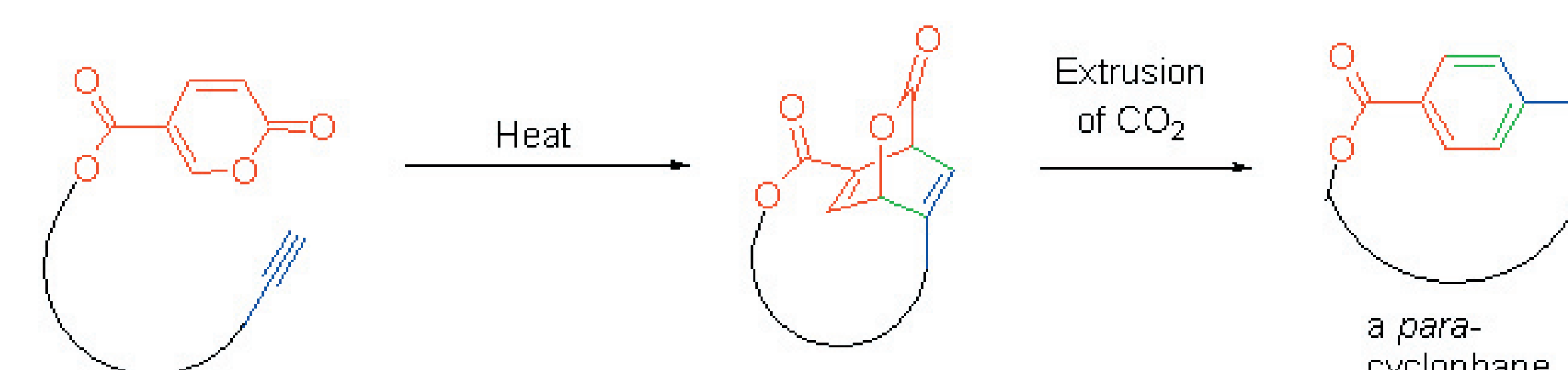


Figure 7. Paracyclophane formation proceeds via an analogous pathway, differing only in the tether between the diene and dienophile.

Experimental:

Previous investigations by Vosburg, Scherer, and Leonard⁷ suggested that hydroxy acids could be effective catalysts of the cycloaddition of methyl isodehydroacetate and propargyl acetate. Several additional catalysts were screened in order to probe the specific requirements for catalysis. The effect of 2,3-dimethylsuccinic acid, succinic acid, citric acid, and lactic acid on the reaction between methyl isodehydroacetate and propargyl acetate in a pressure tube heated at 180 °C was investigated. Data points were taken at 4, 7, and 10 hours using GC/MS to analyze percent completion.

Catalyst	Percent product after 4 hours	Percent product after 7 hours	Percent product after 10 hours
Uncatalyzed	33	53	58
Citric acid	60	74	78
Succinic acid	40	59	70
Lactic acid	45	56	66
2,3-Dimethyl Succinic acid	25	42	58

Table 1. This chart shows the percent product, calculated by GC/MS, as a function of time in the reaction of methyl isodehydroacetate and propargyl acetate with varying catalytic conditions.

Citric acid was the most effective catalyst for this reaction. Its structure could allow it to coordinate to the carbonyl of methyl isodehydroacetate by way of two hydrogen bonds resulting in a 7-membered ring.

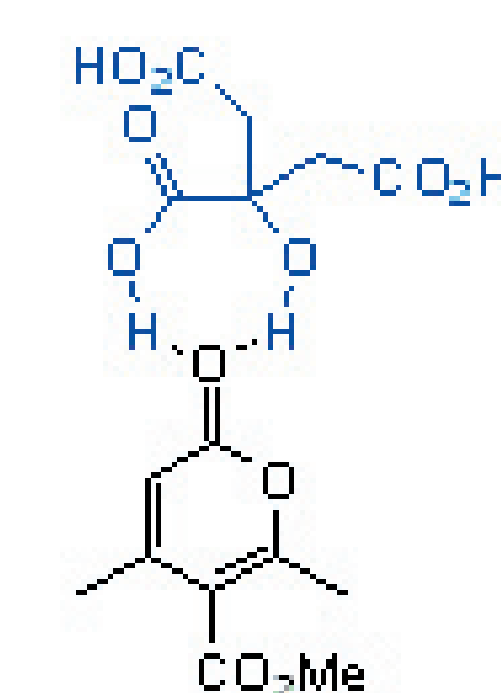


Figure 8. Citric acid could coordinate to a coumalic acid derivative via a 7-membered, cyclic hydrogen bonding array to lower its energy, therefore catalyzing an inverse-electron-demand Diels-Alder reaction.

The geminal dialkyl (Thorpe-Ingold) effect favors a conformation that allows for this dual hydrogen bonding. Citric acid is, therefore, a logical choice for catalysis of Diels-Alder reactions for the synthesis of cyclophanes.

This first step toward the synthesis of the paracyclophane was to convert coumalic acid into coumalyl chloride by refluxing with thionyl chloride.

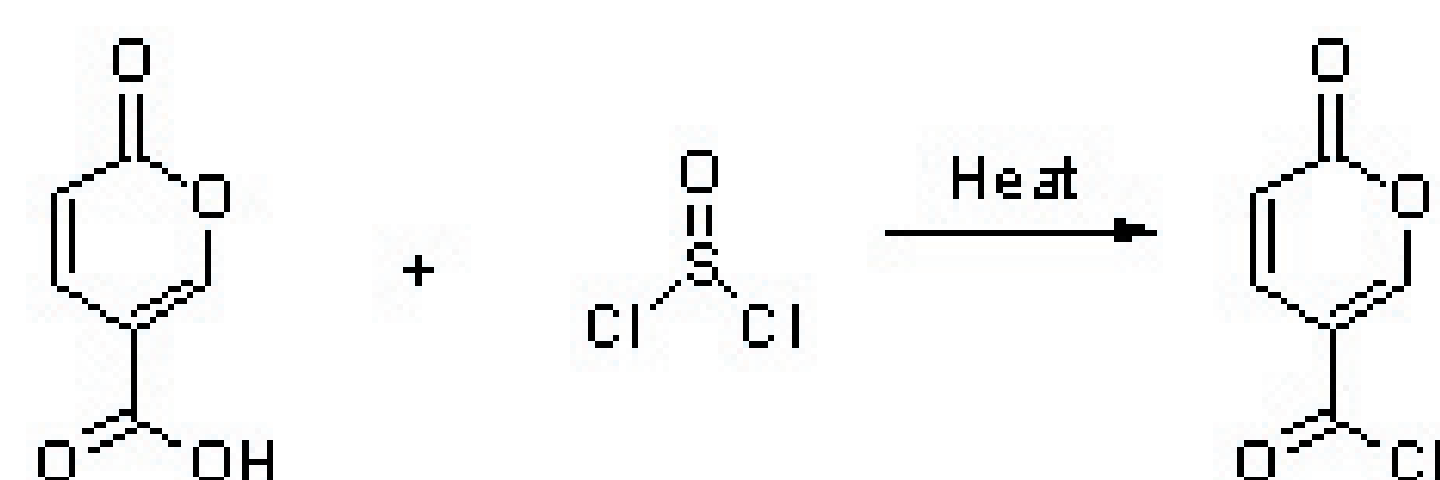


Figure 9. The reaction of coumalic acid and thionyl chloride to form coumalyl chloride was the first step in the synthesis of a paracyclophane.

The acid chloride was then added to 10-undecyn-1-ol to form an ester via nucleophilic acyl substitution. This produces a substrate bearing a tethered diene and dienophile.

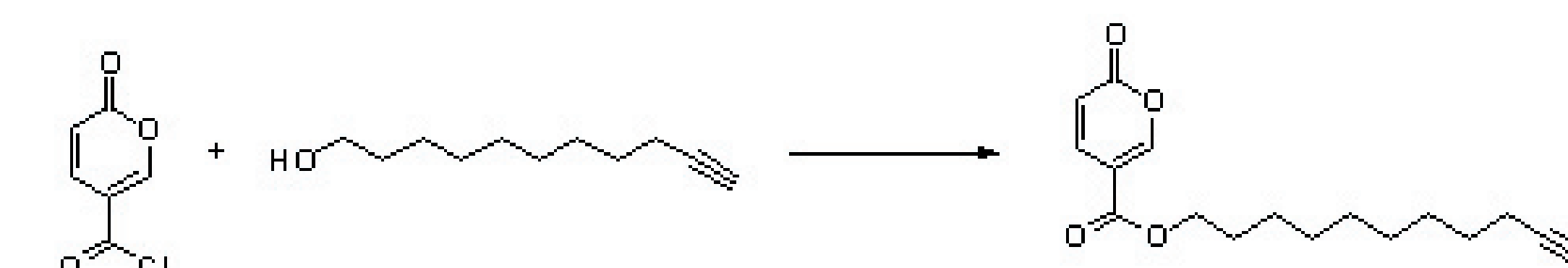


Figure 10. The formation of an ester by the reaction of coumalyl chloride and 10-undecyn-1-ol made the necessary tether between the diene and dienophile to form a paracyclophane.

Column chromatography removed polar impurities and subsequent recrystallization from methanol removed residual 10-undecyn-1-ol from the desired ester. Various concentrations for the intramolecular cycloaddition were then screened. Ethyl acetate was used as the solvent, and the reactions were conducted in pressure tubes at 180°C.

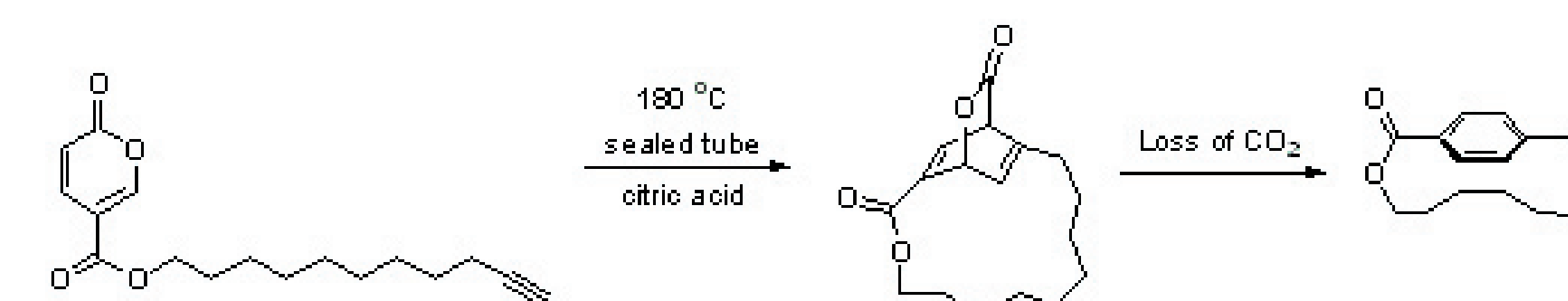


Figure 11. This figure shows the intended Diels-Alder reaction of the tethered diene and dienophile.

The concentration for this reaction must be kept relatively low in order to prevent dimerization. The uncatalyzed reactions failed to proceed, so approximately three equivalents of citric acid were added. TLC analysis allowed for convenient tracking of the reaction progress. Column chromatography allowed for separation of the product from residual starting material. A small portion of impure product was isolated. ¹H NMR spectroscopy revealed new aromatic signals, which could be consistent with the structure of the desired product. The identity of the product will be confirmed by further NMR studies and GC/MS analysis.

An ester with a smaller tether was produced from coumalyl chloride and 5-hexyn-1-ol. The substrate with the larger tether would yield a cyclophane which is rather unstrained. The substrate bearing a smaller tether will enable a study of the effect of strain on the reaction. It is possible that dimerization or metacyclophane formation will be competitive pathways in this instance.

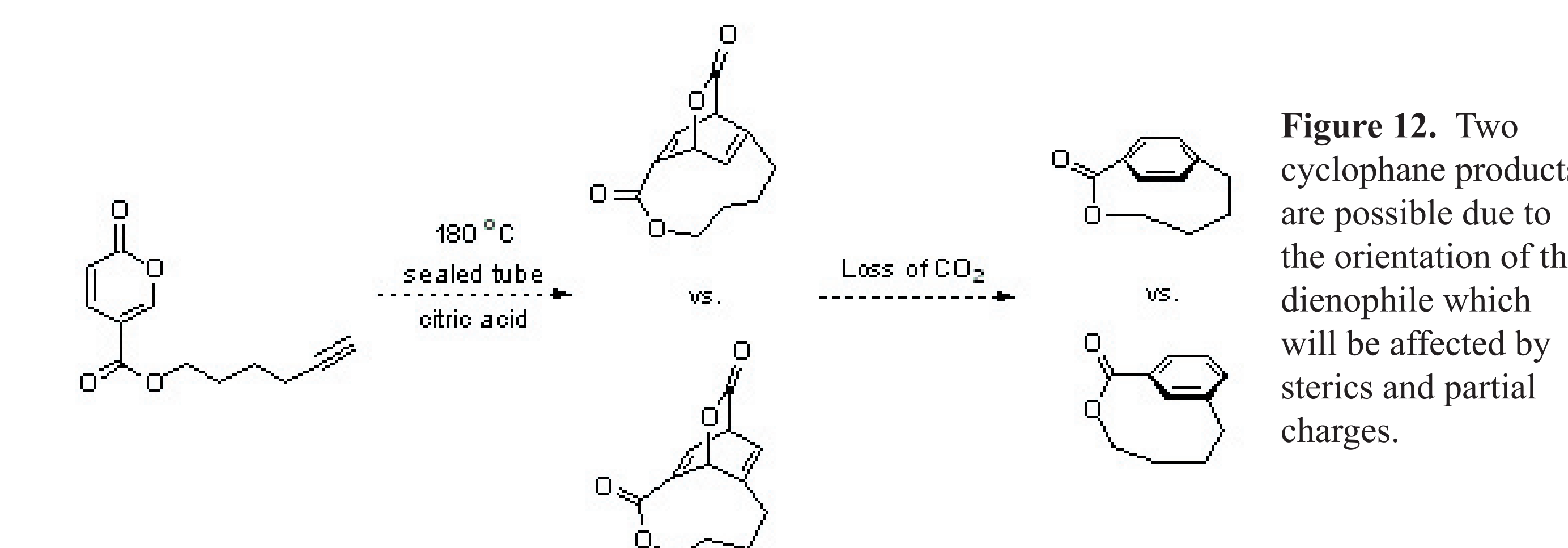


Figure 12. Two cyclophane products are possible due to the orientation of the dienophile which will be affected by sterics and partial charges.

Conclusions:

Key contributions to this project include:

- Identification of citric acid as an effective catalyst for the inverse electron demand Diels-Alder reaction of coumalates and alkynes
- Preparation of two bifunctional substrates for study of the tandem intramolecular cycloaddition-fragmentation

A manuscript of complete research methods and results is in preparation.

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