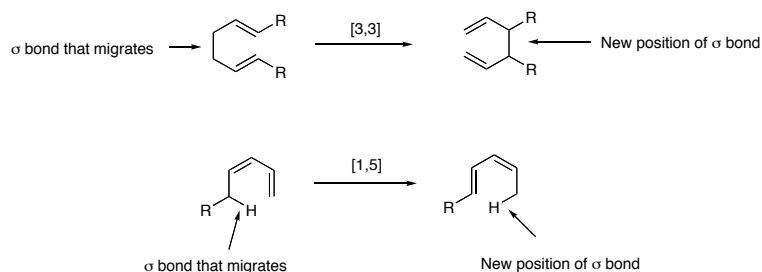


Pericyclic Reactions - Continued

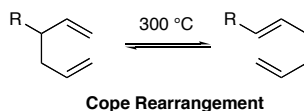
Sigmatropic Rearrangements

Definition: A sigmatropic rearrangement is defined as an intramolecular rearrangement of a σ bond, adjacent to one or more π systems, to a new position in a molecule, with the π systems becoming reorganized in the process.



Cope Rearrangements

Thermal rearrangement of 1,5-dienes to isomeric 1,5-dienes:

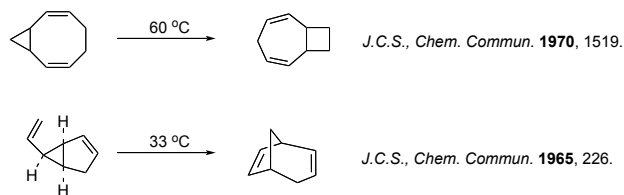


Specific value for modern organic synthesis:

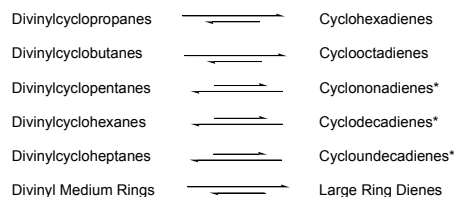
- Parent Cope involves no requirement for acid or base catalysis and can thus accommodate a wide variety of functional groups.
- One of the most powerful methods of synthesis of medium rings.
- Due to the highly ordered cyclic TS, the reaction is extremely stereospecific. Two unsymmetrical double bonds and two asymmetric centers are translated to four new elements of stereochemistry, usually with near quantitative symmetric transmission.

The development of the **oxy-Cope** and **anionic oxy-Cope** reactions has greatly extended the utility of the Cope rearrangement by allowing easier access to diene substrates, lowering the temperature required for rearrangement, and producing carbonyl substrates irreversibly.

- Ring strain:



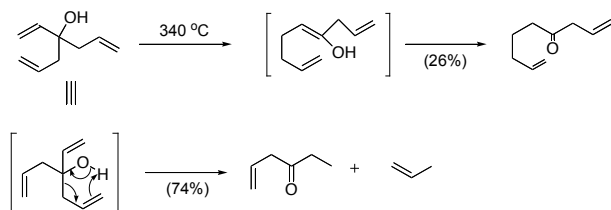
Effect of Ring-Size on the Cope-Equilibrium of 1,2-Divinyloalkanes:



*The equilibrium lies in the opposite direction in the irreversible oxy-Cope reaction.

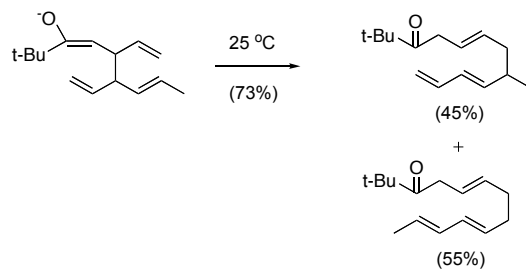
Characteristics of the oxy-Cope rearrangement:

- Substrate is easily prepared by Grignard addition to a carbonyl compound.
- Oxy-Cope is irreversible.
- Product has two different functional groups.
- Competing fragmentation of the substrate via a thermal retro-ene reaction:

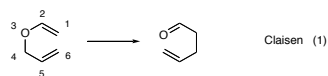


Characteristics of the anionic oxy-Cope rearrangement:

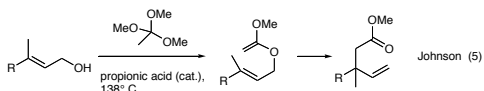
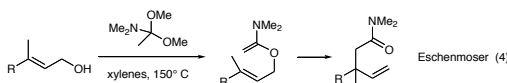
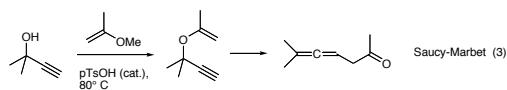
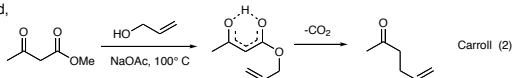
- Enormous rate accelerations (10^{10} - 10^{17}).
- Sodium and, especially, potassium alkoxides are most effective.
- The primary effect of the alkoxide is to weaken the C,C-single bond, rather than stabilizing the TS. The effect is seen in the gas phase as well as in solution.
- Both donor and acceptor groups should increase the rate (B. K. Carpenter, *Tetrahedron* **1978**, *34*, 1877):

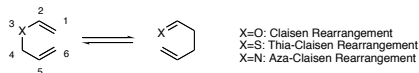
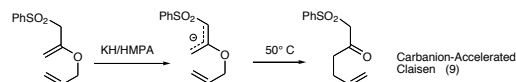
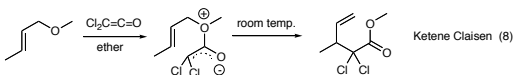
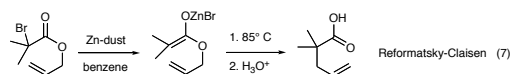
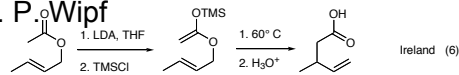


Claisen Rearrangements

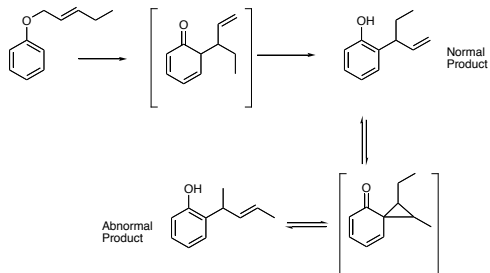
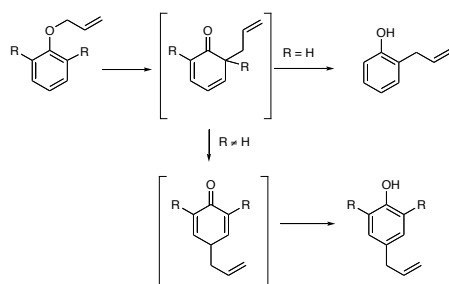


- Wipf, P. In *Comprehensive Organic Synthesis*; B. M. Trost, I. Fleming and L. A. Paquette, Ed.; Pergamon: Oxford, 1991; Vol. 5; pp 827-874.





The Aromatic Claisen Rearrangement

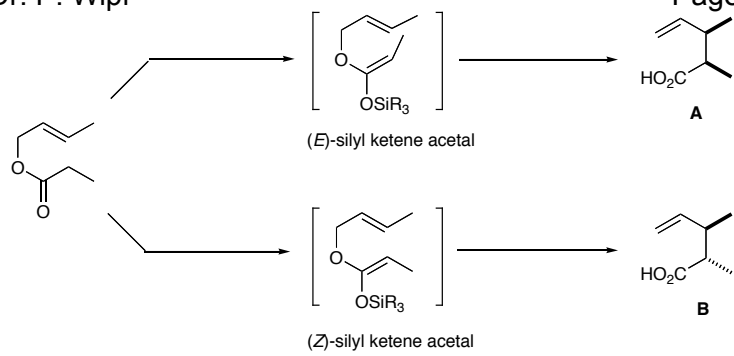


The Ireland Silyl Ester Enolate Rearrangement

Several factors contribute to the versatility of the ester enolate Claisen rearrangement. Among these are the ability to use a stoichiometric combination of the alcohol and the acid components, the relatively low temperature of the pericyclic process that allows for the assembly of complex, highly functionalized structures, and the transformation of a carbon-oxygen into a carbon-carbon bond that lends itself easily to the assembly of contiguous quaternary centers.

Another particularly important aspect of the Ireland rearrangement is that, through an efficient control of ketene acetal geometry, a highly reliable and predictable transfer of stereochemistry from starting material to product can be realized. Deprotonation of crotyl ester with LDA in THF leads, via the selective formation of the kinetically favored (Z)-ester enolate, upon silylation to the (E)-silyl ketene acetal. After rearrangement at 65°C and mild hydrolysis of the silyl ester, a 87 : 13 ratio of g,d-unsaturated acids is isolated in 79% yield. These two products can be obtained in a 19 : 81 ratio by using 23%HMPA/THF as a solvent system for the generation of the thermodynamically favored (Z)-silyl ketene acetal via the corresponding (E)-lithium enolate.

Wipf, P., "Claisen rearrangements." In B. M. Trost, I. Fleming and L. A. Paquette, editors. Comprehensive organic synthesis. Vol 5. Oxford: Pergamon; 1991. p. 827-874.

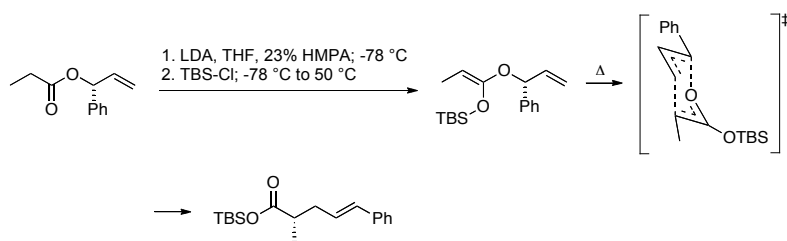
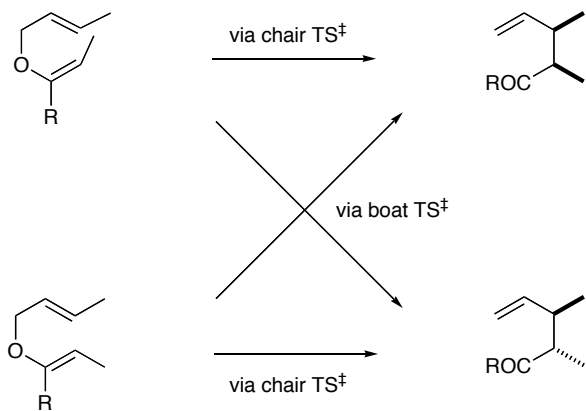
**A : B**

LDA, THF;
 TMSCl; Δ ;
 NaOH/H₂O; 79%

87 : 13

LDA, THF/23% HMPA;
 TMSCl; Δ ;
 NaOH/H₂O; 73%

19 : 81



Woodward-Hoffmann Rules

Among the theories that are commonly used to analyze pericyclic reactions, three are generally considered to be the most useful:

1. **Fukui's Frontier MO interactions.** This analysis applies HOMO-LUMO interactions as well as orbitals close to HOMO & LUMO, and it is more intuitive than the original orbital symmetry arguments.

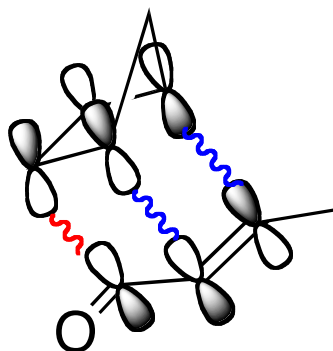
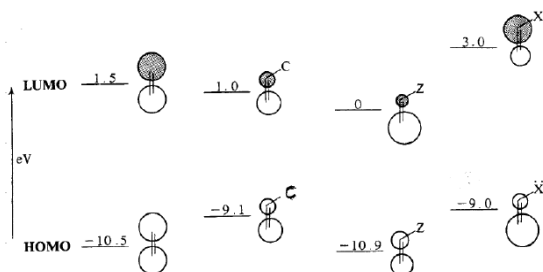
$$\Delta E = \underbrace{\sum_{ab} (q_a + q_b) \beta_{ab} S_{ab}}_{\text{Closed-Shell Repulsion}} + \underbrace{\sum_{k<l} \frac{Q_k Q_l}{\epsilon R_{kl}}}_{\text{Coulomb Interaction}} + \underbrace{\sum_r^{\text{occ.}} \sum_s^{\text{unocc.}} - \sum_s^{\text{occ.}} \sum_r^{\text{unocc.}} \frac{2(\sum_{ab} c_{ra} c_{sb} \beta_{ab})^2}{E_r - E_s}}_{\text{Frontier Orbital Interaction}}$$

- Coulson, C. A.; Longuet-Higgins, H. C. *Proc. Roy. Soc. A* **1947**, *192*, 16.
- Klopman & Salem (JACS **1968**, *90*, 223, 543, 553).
- Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57.

q_a and q_b
 β and S
 Q_k and Q_l
 ϵ
 R_{kl}
 c_{ra}
 E_r

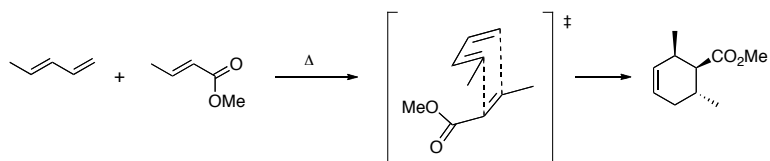
Electron densities in orbitals a and b.
Resonance and overlap integral.
Total charges at atoms k and l.
Local dielectric constant.
Distance between atoms k and l.
Coefficient of atomic orbital a at the molecular orbital r.
Energy of molecular orbital r.

Rather than considering the relative phases, i.e. symmetry, of all orbitals involved during the transformation of reactants into products, the *frontier orbital approach* makes predictions for the outcome of pericyclic reactions based on the *highest occupied molecular orbital* (HOMO) and the *lowest unoccupied molecular orbital* (LUMO). In this, the electrons in the HOMO of one reactant are looked upon as analogous to the outer (valence) electrons of an atom, and reaction is then envisaged as involving the overlap of this (HOMO) orbital with the LUMO of the other reactant. Where, as in electrocyclic reactions, only one species is involved only the HOMO needs to be considered.



If, upon examination of the interactions that occur in the frontier orbitals (HOMO, LUMO if applicable, otherwise only HOMO) the interactions are constructive (of the same phase, the reaction is considered “allowed”).

If the orbital overlap is destructive (i.e. of different phase), then the reaction is “forbidden”.



2. **The Dewar-Zimmerman Theory of Aromatic Transition States.** This analysis is possibly the most general and easiest to apply to a broad range of pericyclic reactions, but it is also the least anchored in fundamental physical principles.

For applying this model, choose a basis set of 2p atomic orbitals for all atoms involved (1s for hydrogens).

After assigning *any* phases to these orbitals (no relationship to MO's is required!), connect the orbitals that interact in the starting materials, before the reaction begins. Allow the reaction to proceed according to the postulated geometry; connect the lobes that begin to interact and were not connected in the starting materials.

Count the number of phase inversions that occur - a phase inversion within an orbital is not counted.

Based on the number of phase inversion of the orbital perimeter, identify the topology of the system:

Odd # of phase inversions: **Möbius topology**

Even # of phase inversions: **Hückel topology**

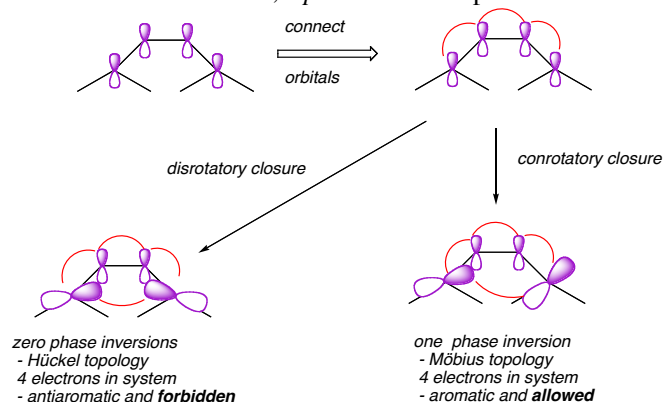
The transition state can now be assigned as antiaromatic or aromatic, based on the number of electrons in the system:

Möbius topology: Aromatic for $4n$, Antiaromatic for $4n+2$

Hückel topology: Aromatic for $4n+2$, Antiaromatic for $4n$

if the transition state is *aromatic*, then the reaction is *thermally* allowed.

If the transition state is *antiaromatic*, a *photochemical* process is required.



Thermal processes involving $4n+2$ electrons will be suprafacial/disrotatory and involve a Hückel-type TS^\ddagger , whereas those involving $4n$ electrons will be antarafacial/conrotatory and the orbital array will be of the Möbius type.