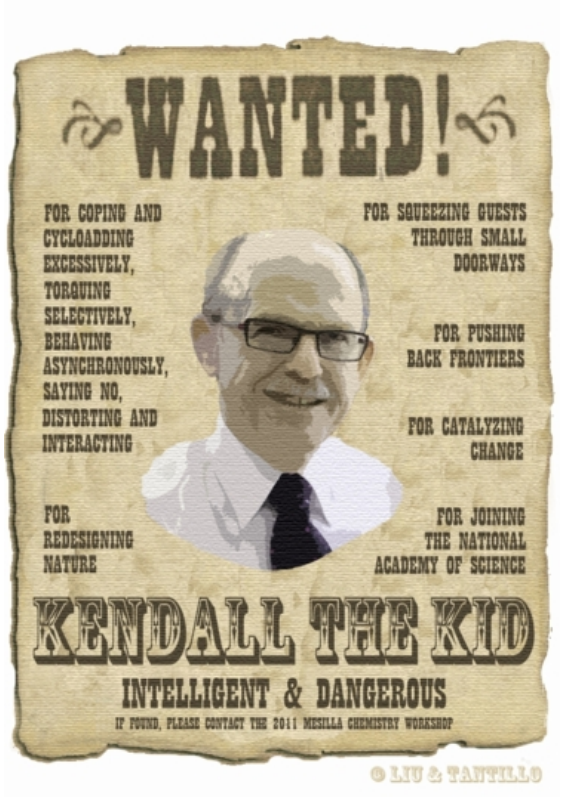
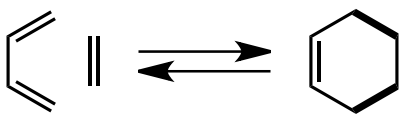
Electrocyclizations and Torquoselectivity



MacMillan Group Meeting
Andrew Capacci
4/24/13

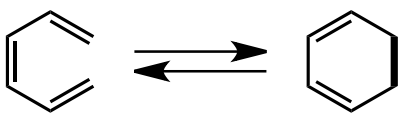
Pericyclic Reactions

Classes of pericyclic reactions



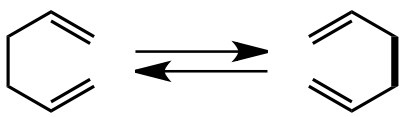
Cycloaddition Reactions

$\Delta\sigma = \pm 2$
$\Delta\pi = \pm 2$



Electrocyclic Rearrangements

$\Delta\sigma = \pm 1$
$\Delta\pi = \pm 1$



Sigmatropic Rearrangements

$\Delta\sigma = 0$
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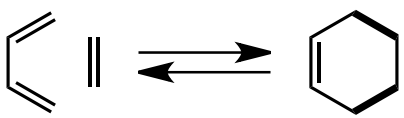
Pericyclic Reactions

Classes of pericyclic reactions



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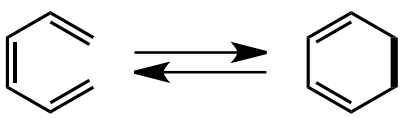

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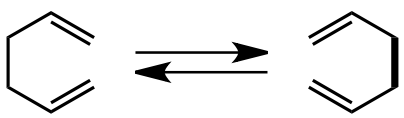

Sigmatropic Rearrangements

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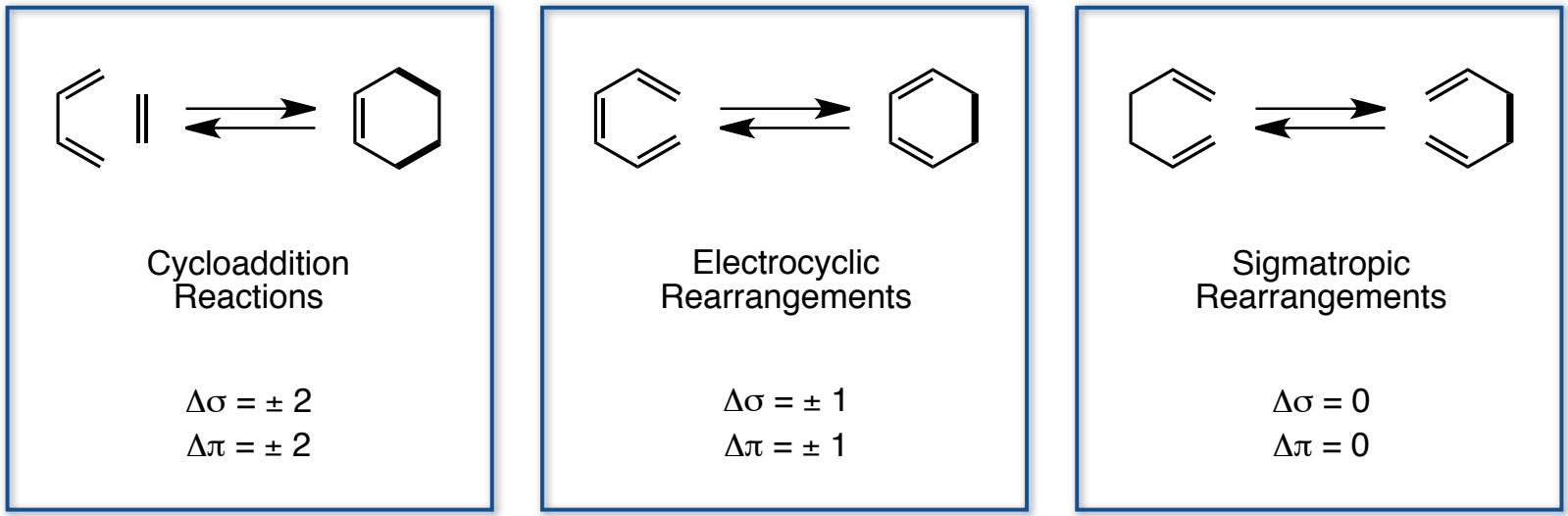
What is a pericyclic reaction?

Pericyclic Reactions

- Classes of pericyclic reactions



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- A concerted reaction wherein the transition state is characterized as having a cyclic array of interacting orbitals.

Pericyclic Reactions

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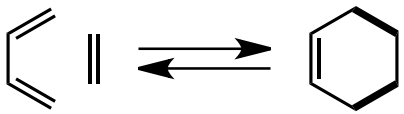

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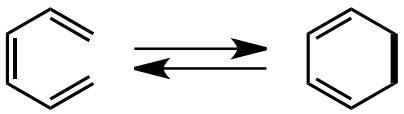

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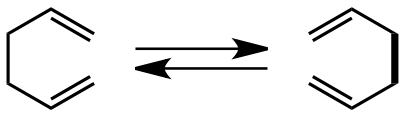

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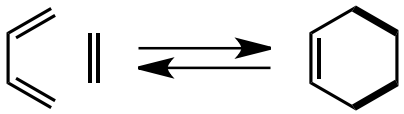

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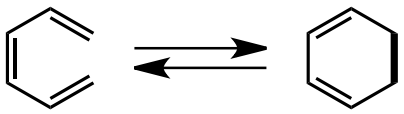

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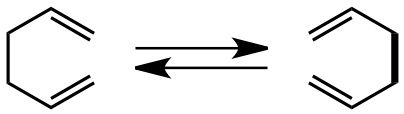

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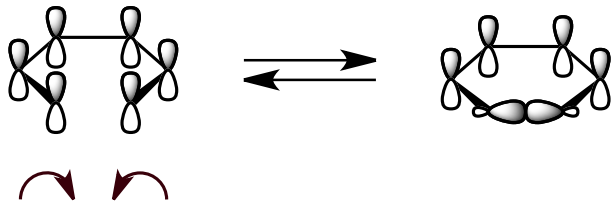
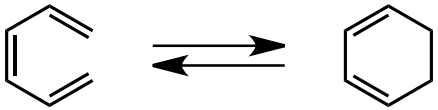
- Basic look at orbital motion:



disrotatory ring-closure

Electrocyclic Reactions

- What other systems participate in electrocyclic reactions?



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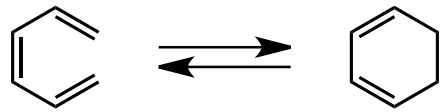

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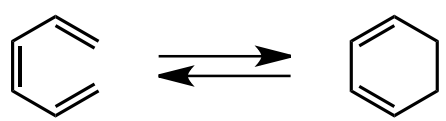

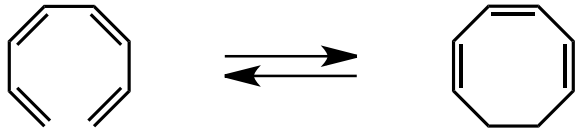

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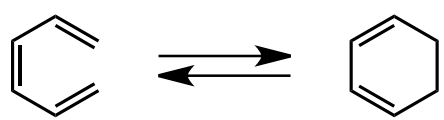

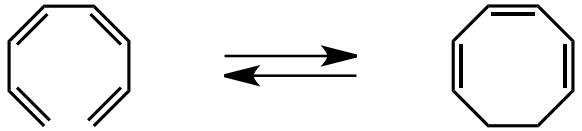

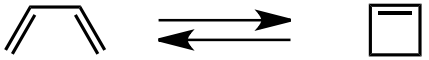

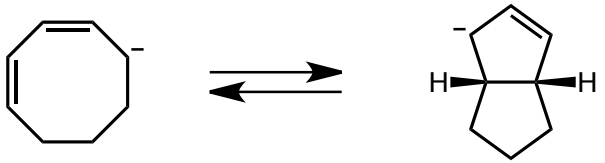

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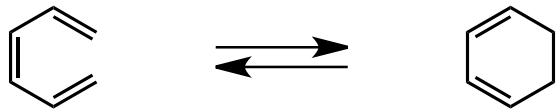

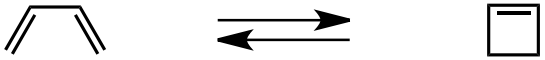

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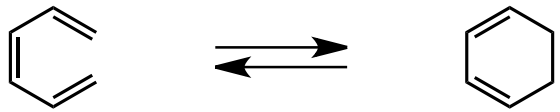

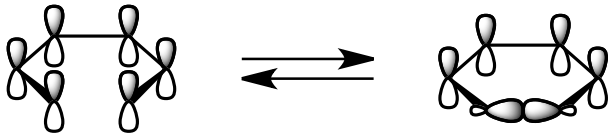

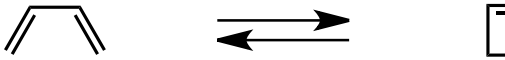

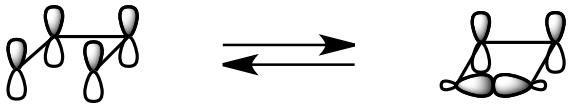

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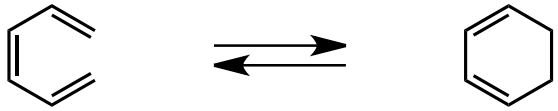
Electrocyclic Reactions

- What other systems participate in electrocyclic reactions?

- Higher order systems also undergo electrocyclic rearrangement in the same manner

Frontier Molecular Orbital Analysis

- Taking a closer look at the electrocyclization



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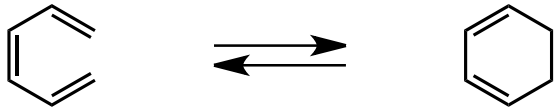

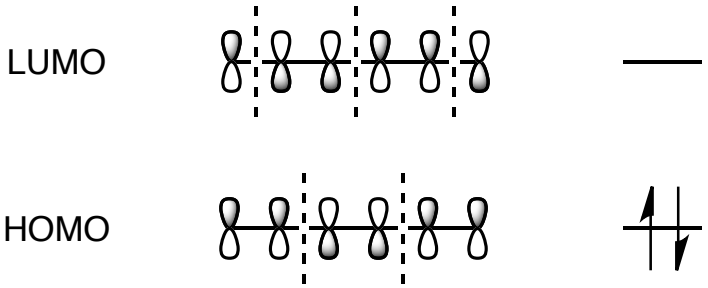

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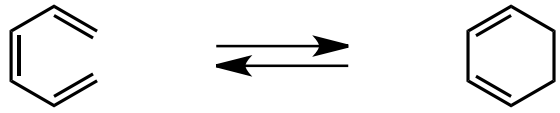

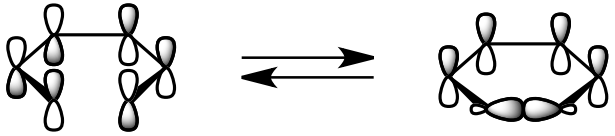

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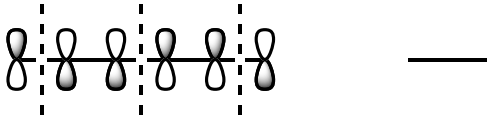

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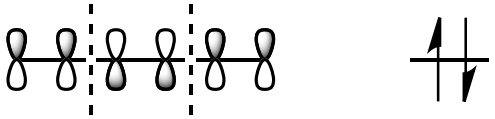

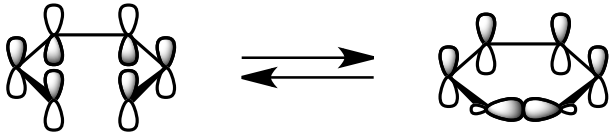

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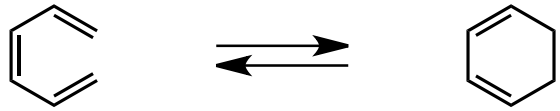

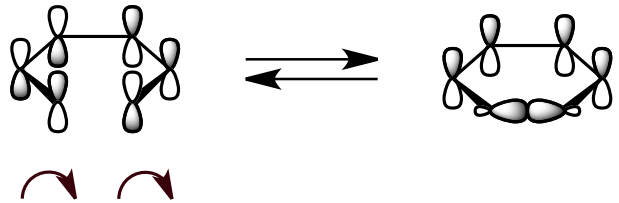

conrotatory
ring-closure

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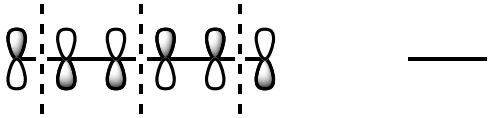

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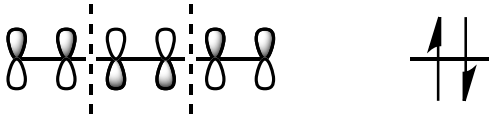

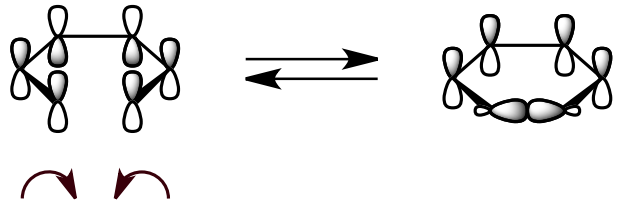

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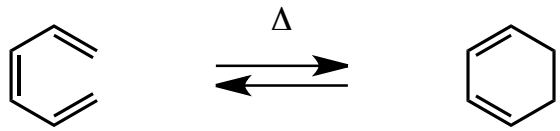

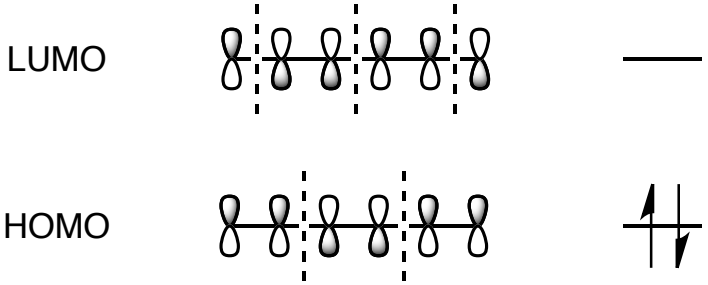

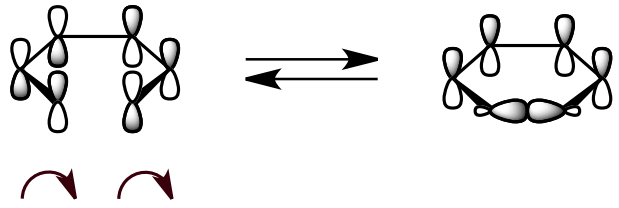

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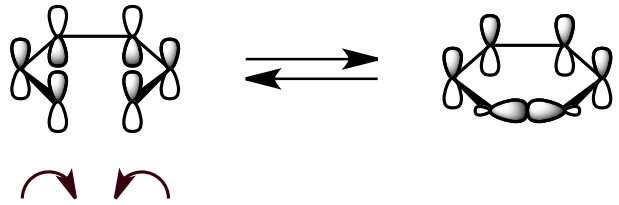

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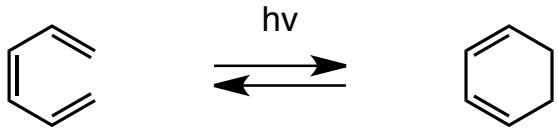

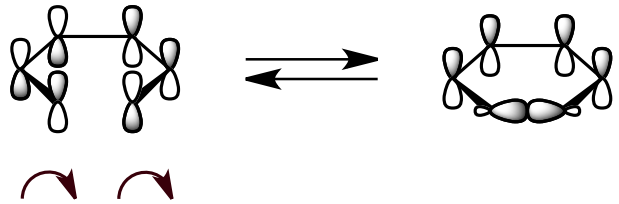

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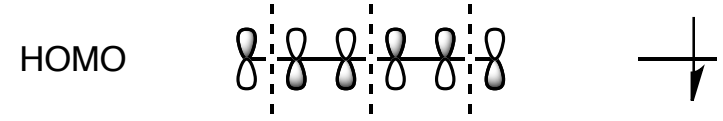

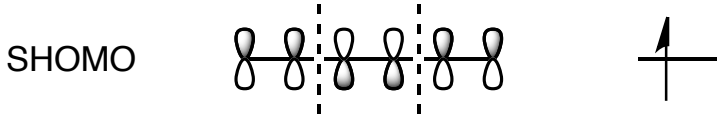

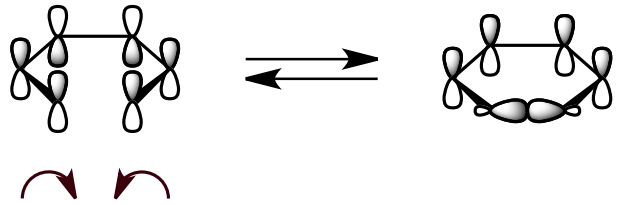

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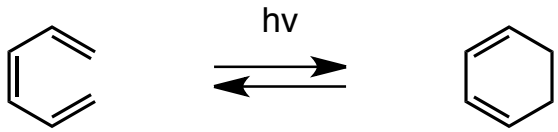
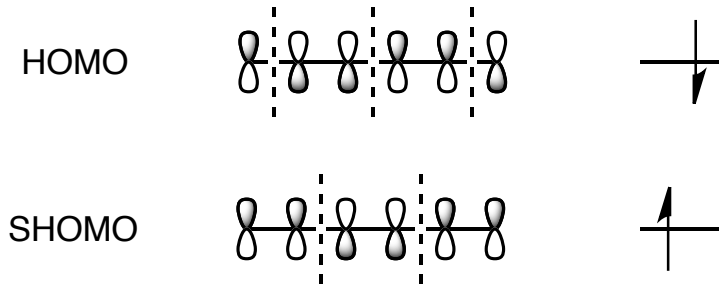
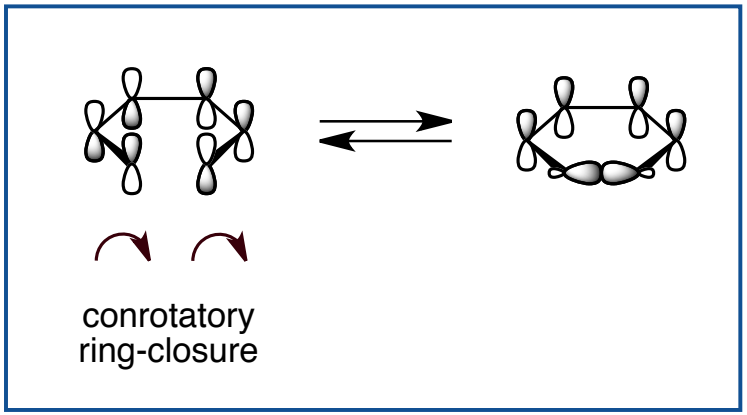
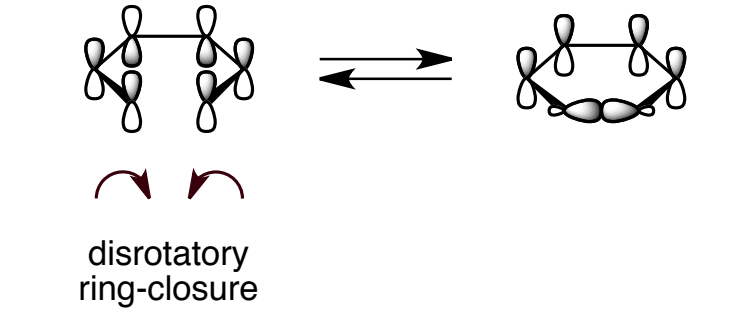
Frontier Molecular Orbital Analysis

- Taking a closer look at the electrocyclization









Frontier Molecular Orbital Analysis

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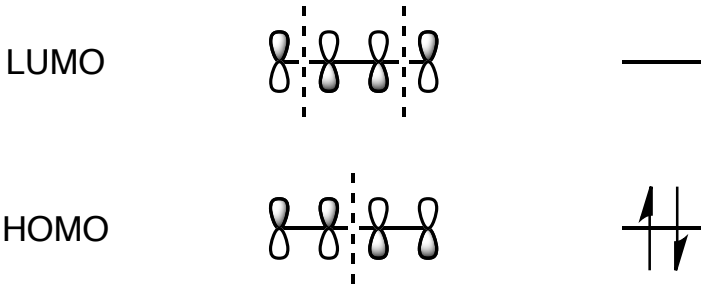

Frontier Molecular Orbital Analysis

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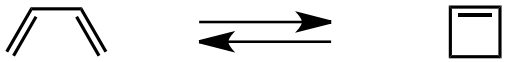

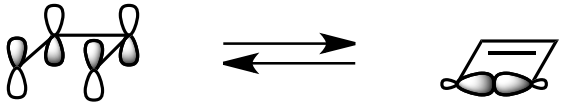

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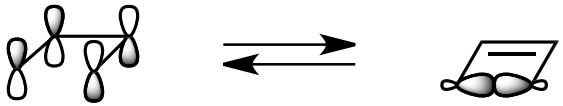
HOMO



Frontier Molecular Orbital Analysis

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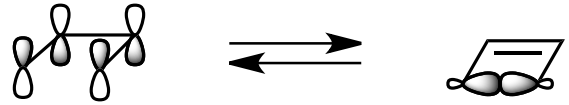

conrotatory
ring-closure

LUMO

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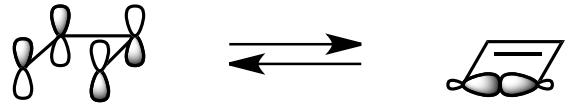

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Frontier Molecular Orbital Analysis

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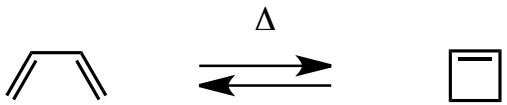

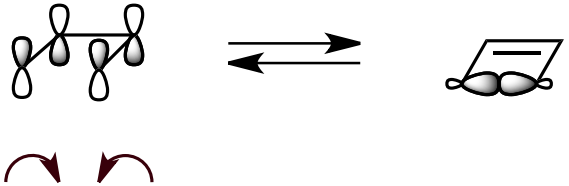

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ring-closure

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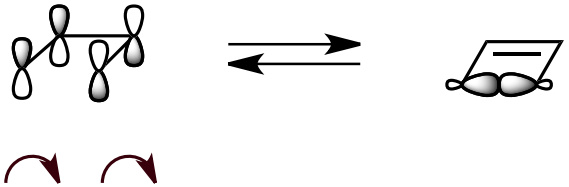

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Frontier Molecular Orbital Analysis

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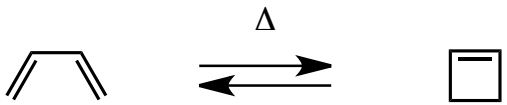

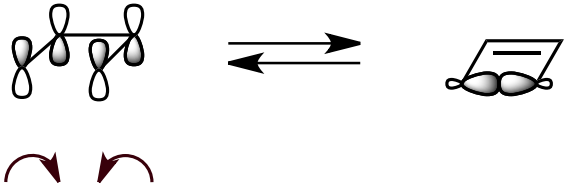

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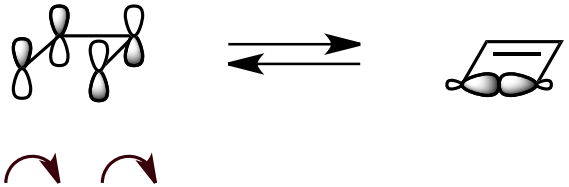

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Frontier Molecular Orbital Analysis

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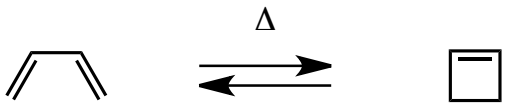
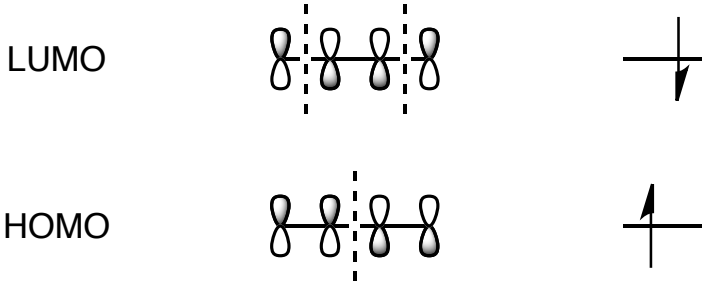
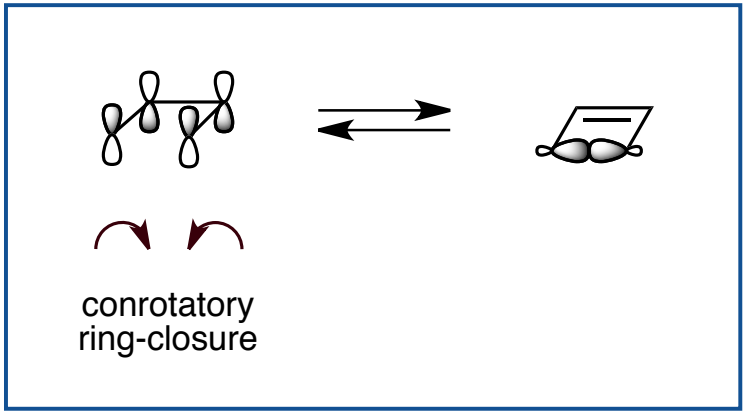
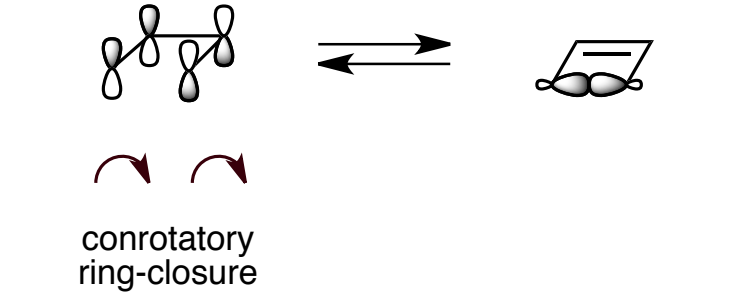


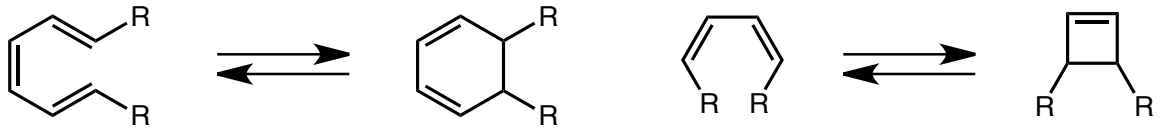






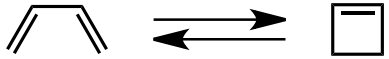
Frontier Molecular Orbital Analysis

- FMO analysis derived rules for electrocyclization



thermal reaction	disrotatory	conrotatory
photochemical reaction	conrotatory	disrotatory

Hückel / Möbius Analysis

- Alternative method for analysis of pericyclic reactions
  - Model reaction: 

Hückel / Möbius Analysis

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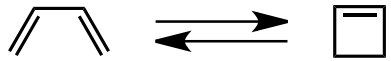

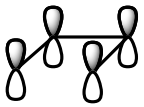

Hückel / Möbius Analysis

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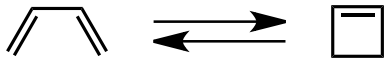

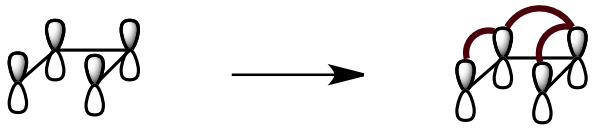

Hückel / Möbius Analysis

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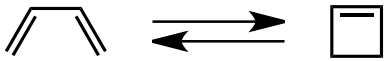

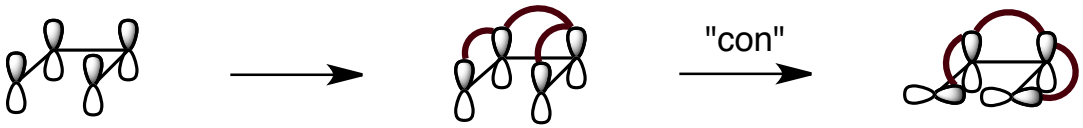

Hückel / Möbius Analysis

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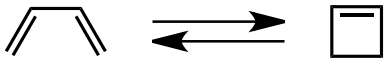

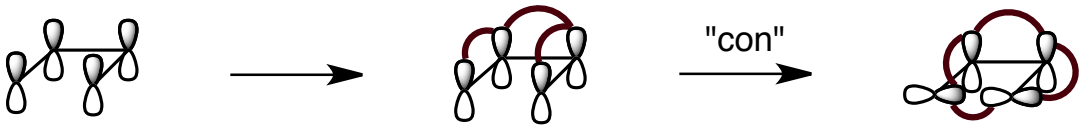

Hückel / Möbius Analysis

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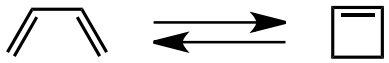

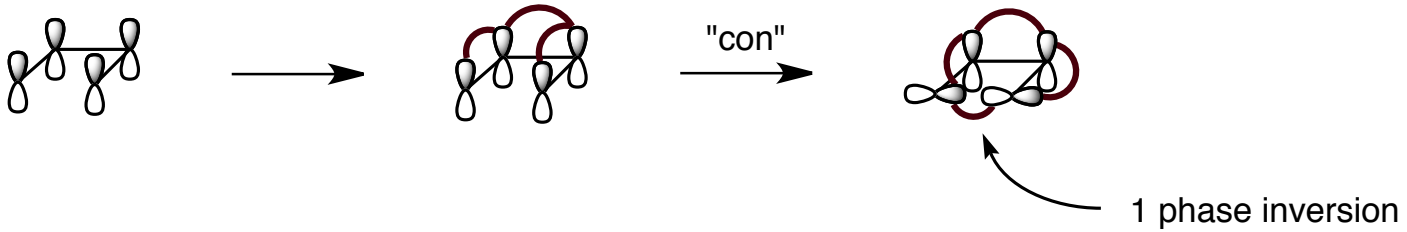

Hückel / Möbius Analysis

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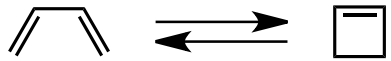
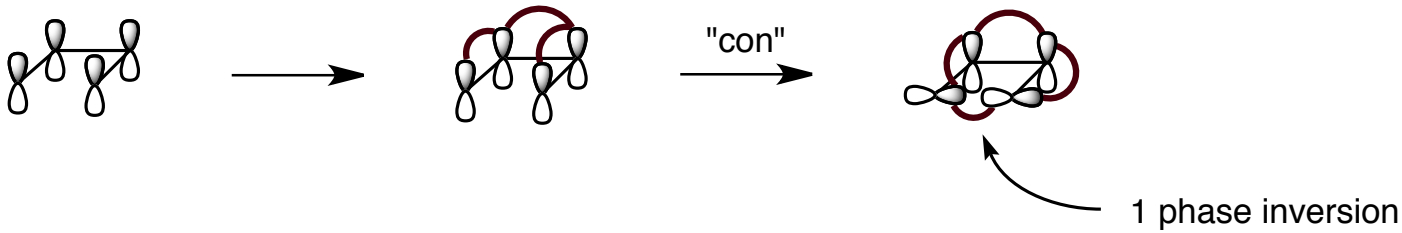




Phase inversions:

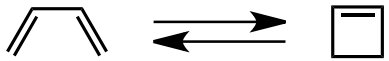
odd = Möbius

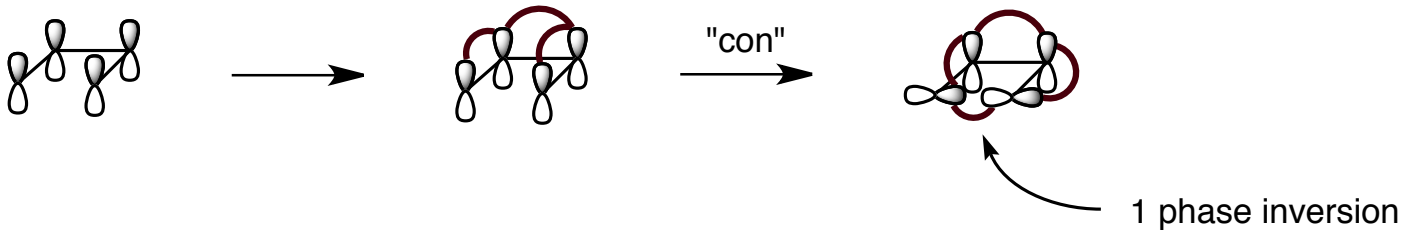
even = Hückel

Hückel / Möbius Analysis

- Alternative method for analysis of pericyclic reactions

- Model reaction:



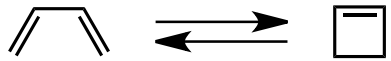


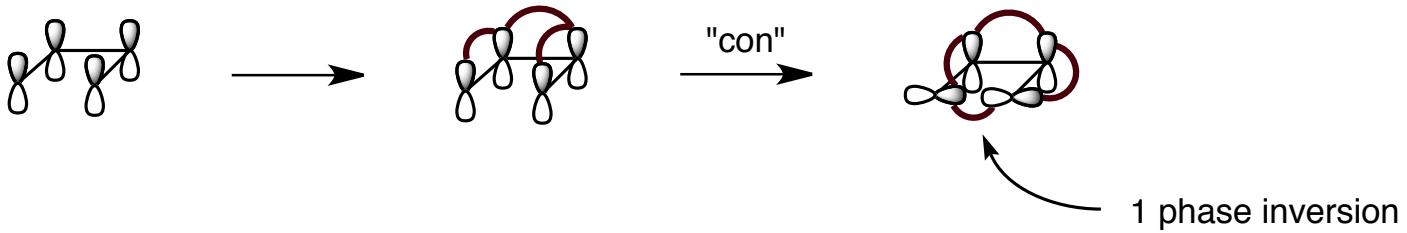
	Aromatic	Anti-aromatic	Phase inversions:
Hückel	4q+2	4q	odd = Möbius
Möbius	4q	4q+2	even = Hückel

Hückel / Möbius Analysis

- Alternative method for analysis of pericyclic reactions

- Model reaction:





	Aromatic	Anti-aromatic	Phase inversions:
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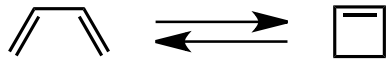
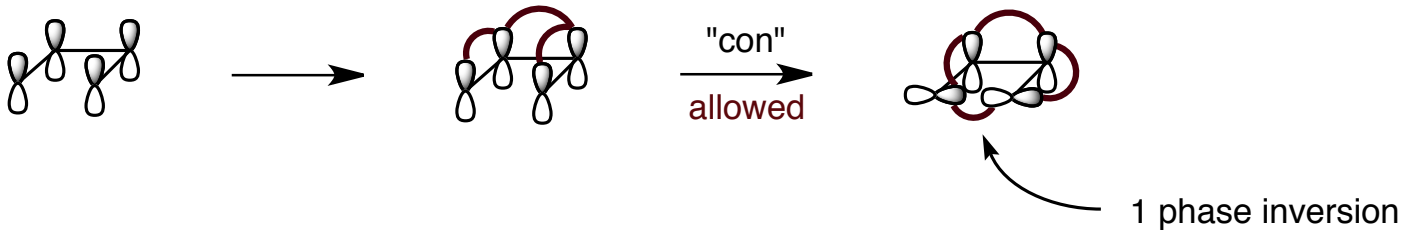
- Aromatic allowed thermally, Anti-aromatic allowed photochemically

Hückel / Möbius Analysis

- Alternative method for analysis of pericyclic reactions

- Model reaction:





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Hückel / Möbius Analysis

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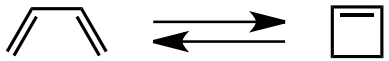

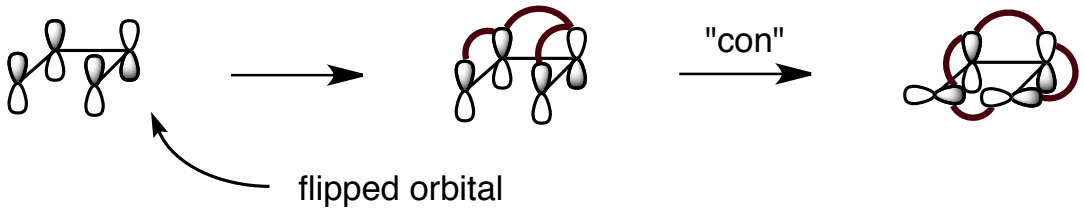

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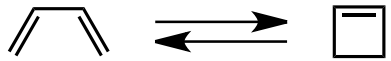

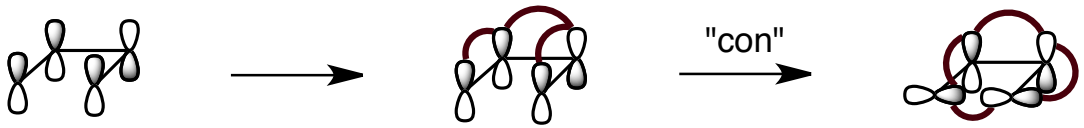

2 phase inversions

	Aromatic	Anti-aromatic	Phase inversions:
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Möbius	4q	4q+2	even = Hückel

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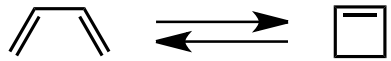
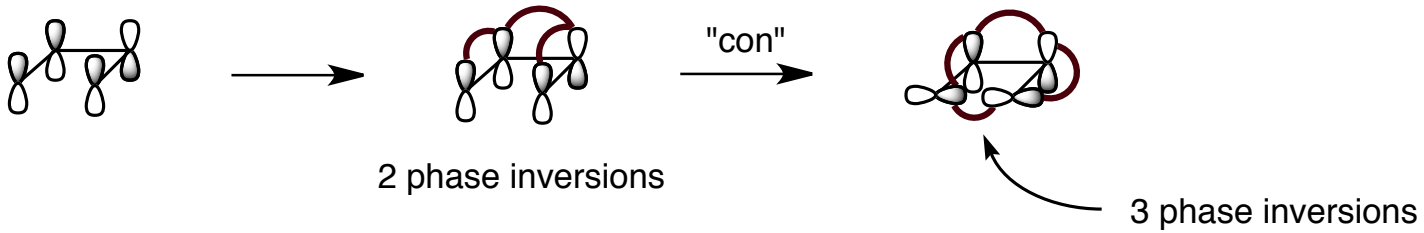
Hückel / Möbius Analysis

- Alternative method for analysis of pericyclic reactions

- Model reaction:





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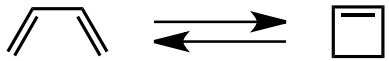
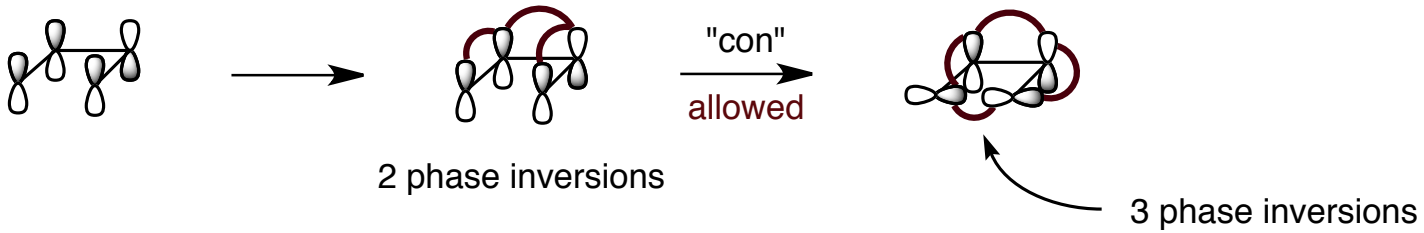
Hückel / Möbius Analysis

- Alternative method for analysis of pericyclic reactions

- Model reaction:





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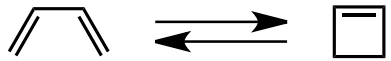

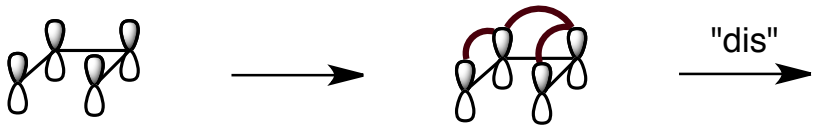

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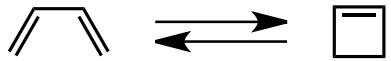

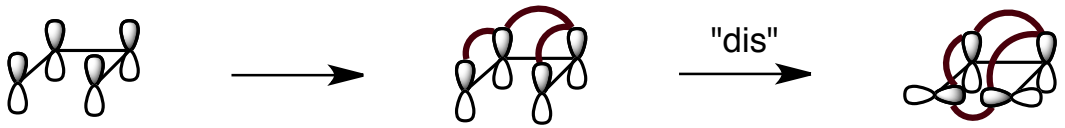

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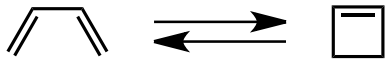

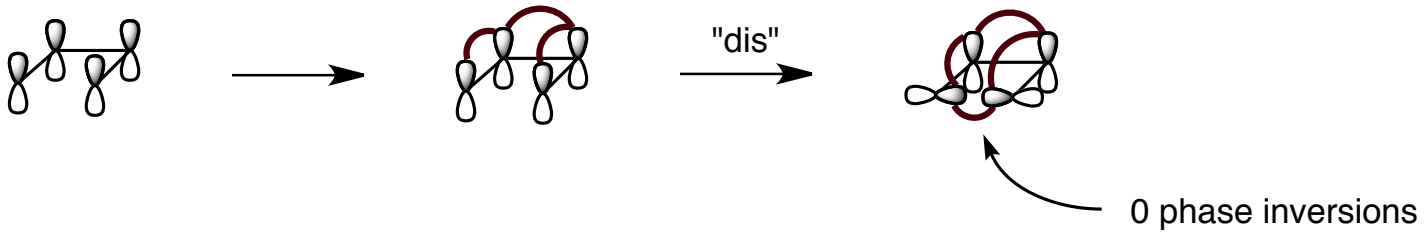

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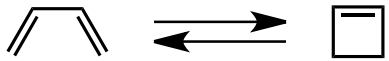

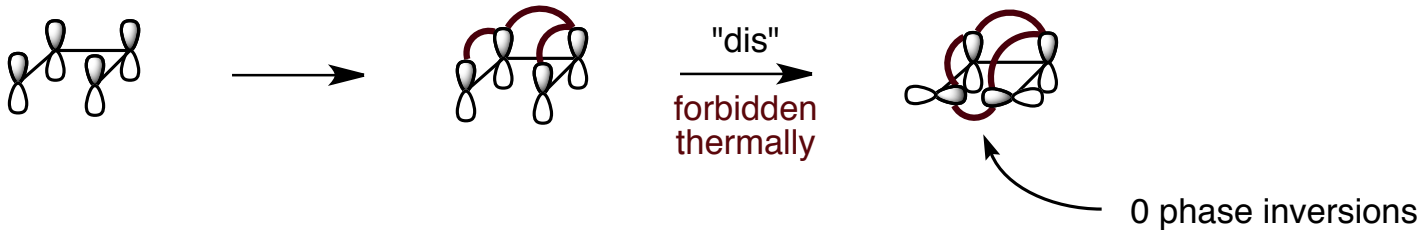

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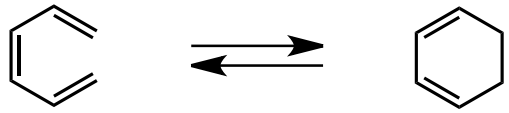

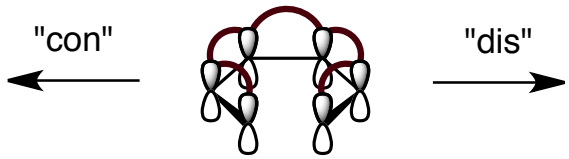

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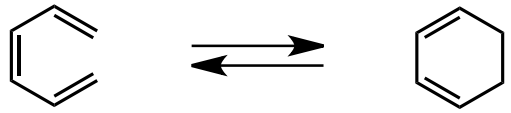

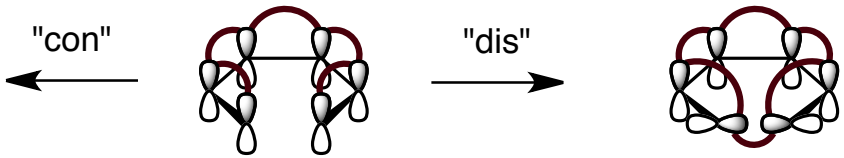

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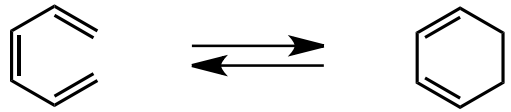

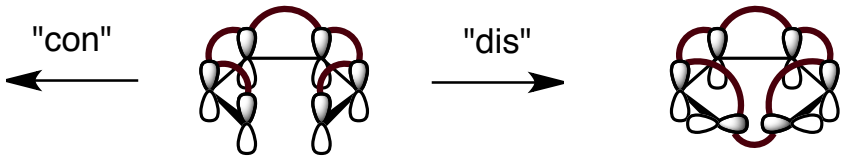

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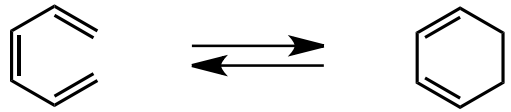

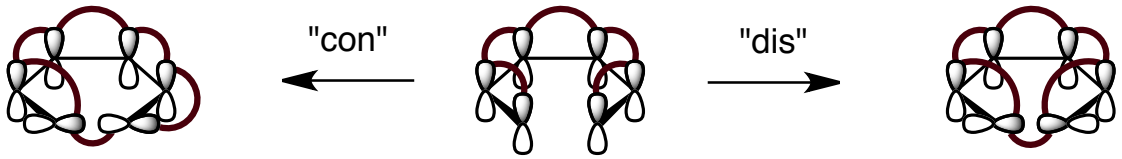

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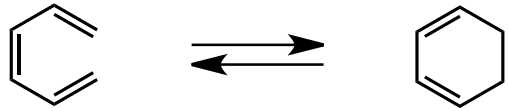

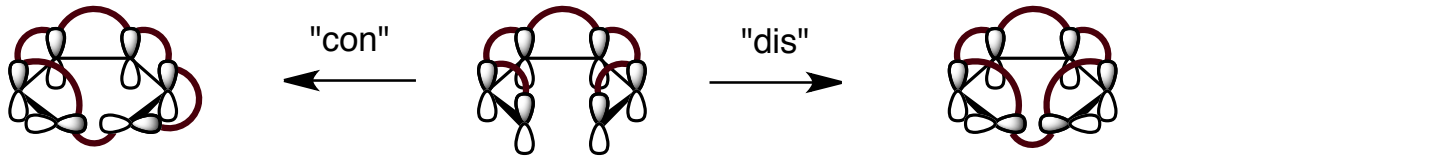

1 phase inversion,
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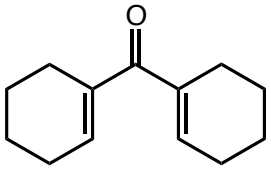
Nazarov Cyclization through Electrocyclization

- The Nazarov reaction follows typical $4e^-$ electrocyclic behavior



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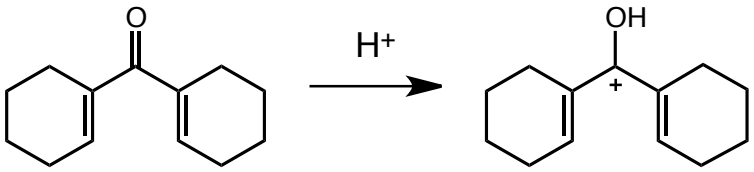

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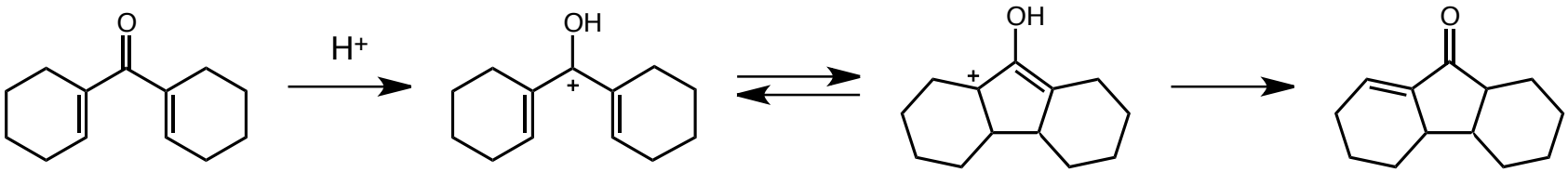

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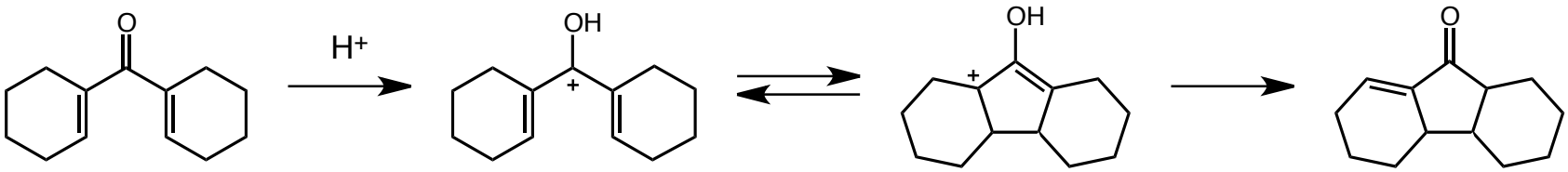

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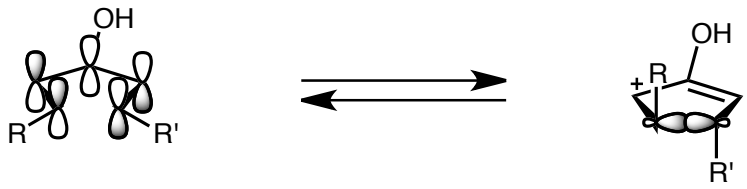

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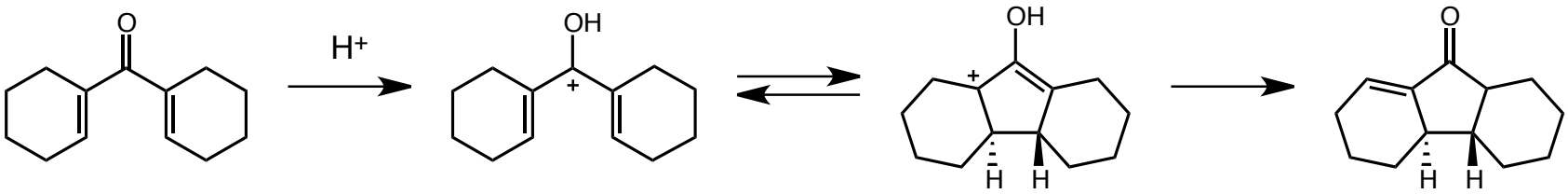

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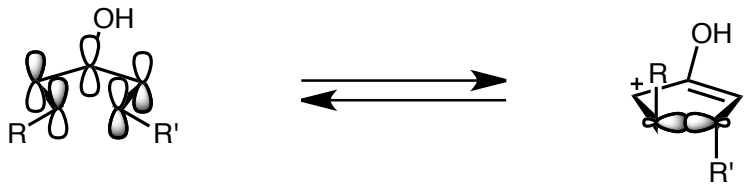

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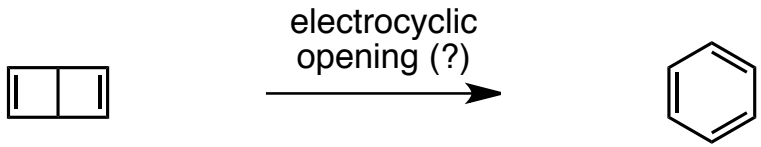

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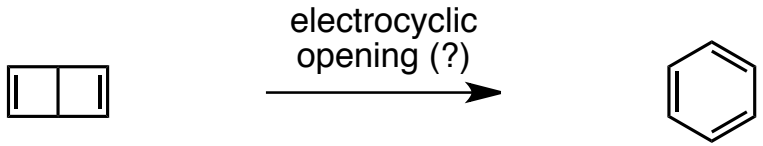

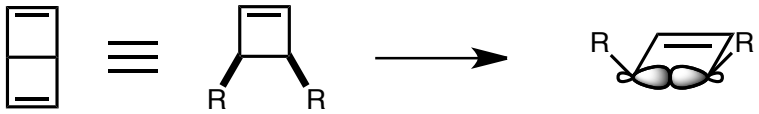

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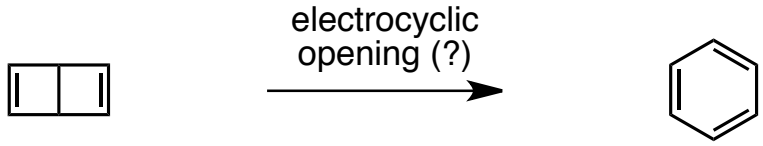

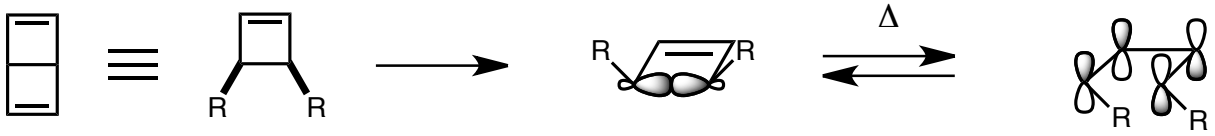

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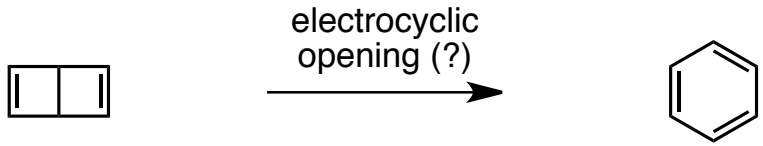

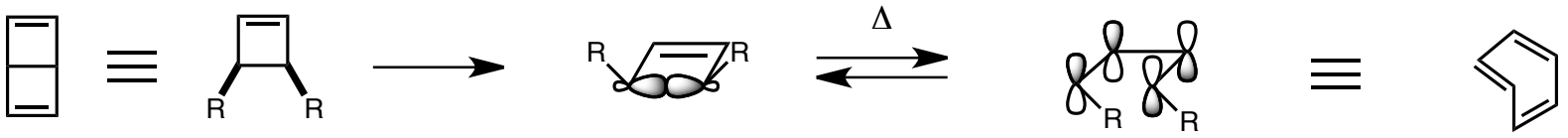

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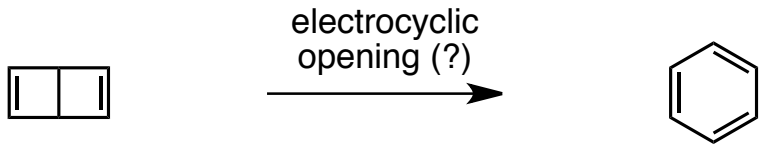

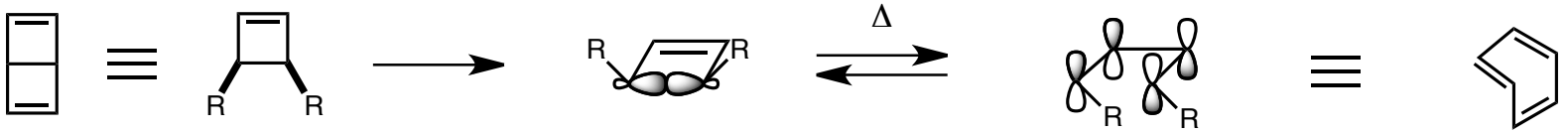

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- The alternative, disrotatory opening does occur but is only allowed photochemically

Torquoselectivity in Electrocyclic Reactions

- What is a "torquoselective" reaction?

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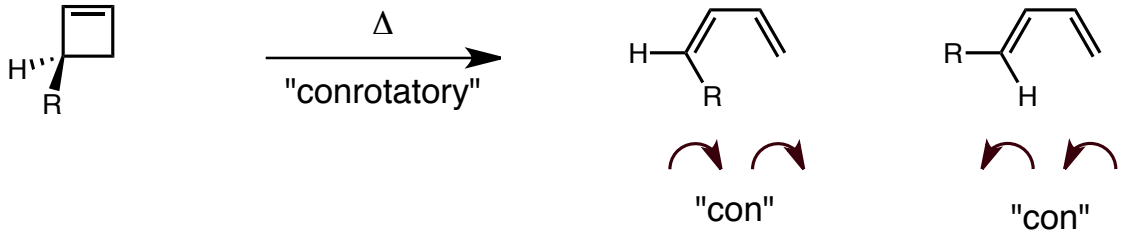

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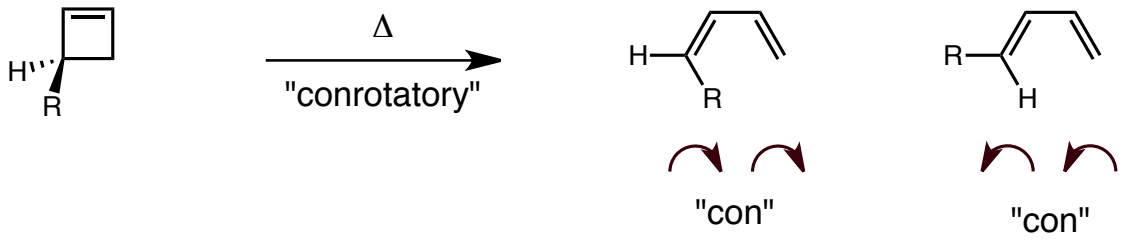

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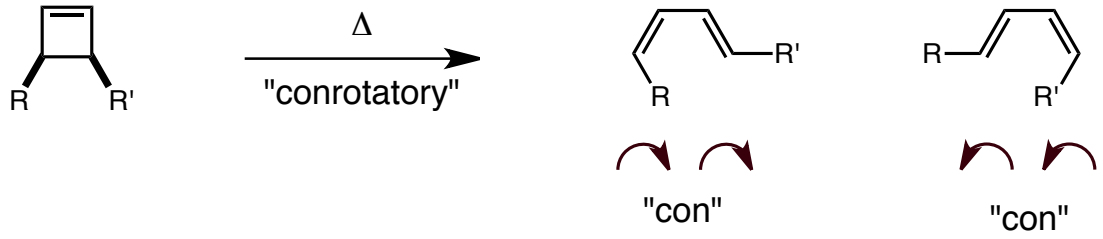

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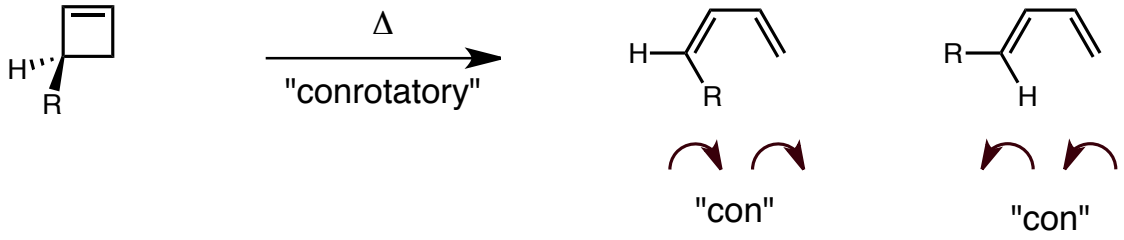

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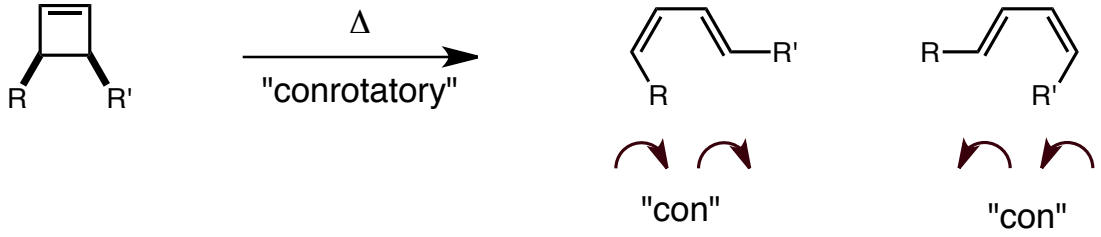

How does differential substitution effect the direction of opening?

Torquoselectivity in Electrocyclic Reactions

- Unusual examples of torquoselectivity could not be explained using FMO analysis

<0.2% >99.8%

only ~1 kcal/mol energy difference

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R =		
	Et:	68 : 32
	i-Pr:	65 : 35
	t-Bu:	32 : 68
	Ph:	30 : 70

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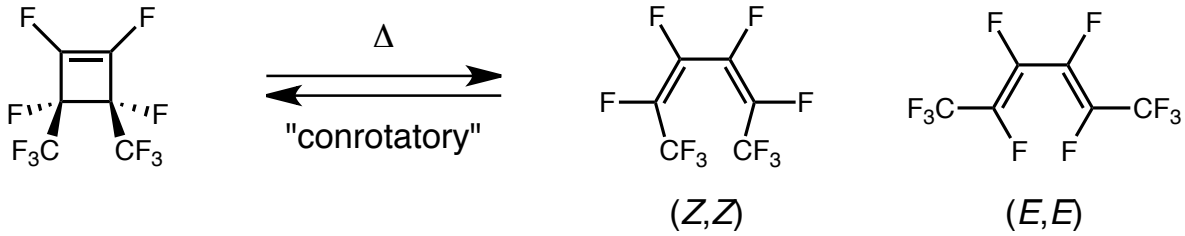

(*Z*,*Z*) (*E*,*E*)

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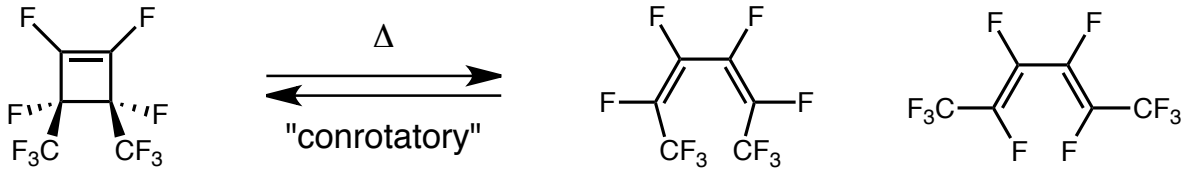

(*Z*,*Z*) (*E*,*E*)

E_a = 30.5 kcal/mol E_a = 49.7 kcal/mol

k_{ZZ}/k_{EE} (at 112 °C): 1.9 x 10^9

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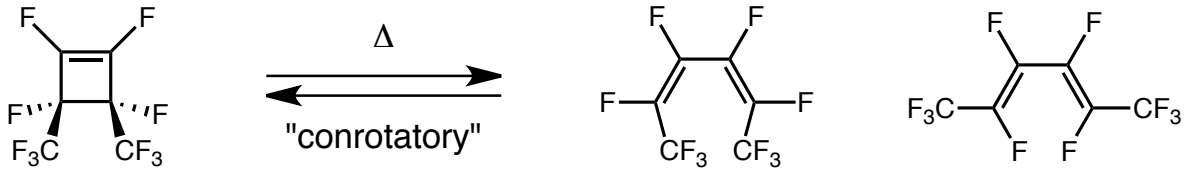


(*Z*,*Z*) (*E*,*E*)

E_a = 30.5 kcal/mol E_a = 49.7 kcal/mol

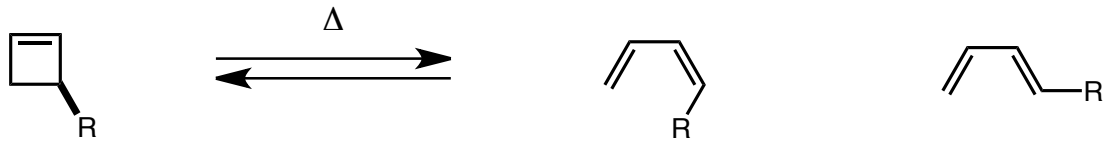
k_{ZZ}/k_{EE} (at 112 °C): 1.9 x 10^9

  - Sterics are clearly not the dominant factor in determining direction of rotation

Dolbier, W. R., Koroniak, H., Burton, D., Bailey, A. R., Shaw, G. S., Hansen, S. W. *J. Am. Chem. Soc.*, **1984**, *106*, 1871.

Torquoselectivity in Electrocyclic Reactions

- Further thermodymanic analysis towards a rational for torquoselectivity
  - Substituent preference for outward rotation determined



"inward" "outward"

Kirmse, W., Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1984**, *106*, 1989.
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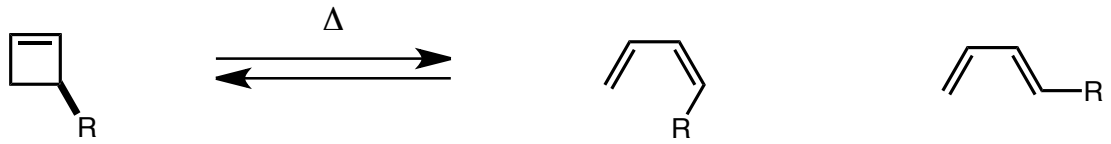

"inward" "outward"

Substituent	E_a (kcal/mol)	E_{rel} (R–H, kcal/mol)
H	32.5	0

Kirmse, W., Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1984**, *106*, 1989.
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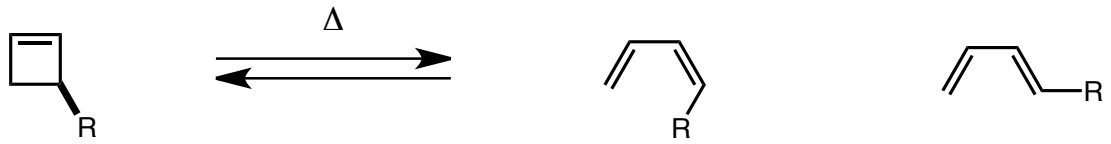

"inward" "outward"

Substituent	E_a (kcal/mol)	E_{rel} (R–H, kcal/mol)
H	32.5	0
Me	31.6	–0.9

Kirmse, W., Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1984**, *106*, 1989.
Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1985**, *107*, 2099.

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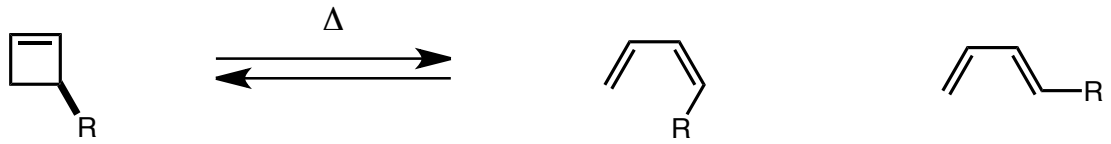

"inward" "outward"

Substituent	E_a (kcal/mol)	E_{rel} (R–H, kcal/mol)
H	32.5	0
Me	31.6	–0.9
Cl	29.4	–3.1
OAc	27.8	–4.7

Kirmse, W., Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1984**, *106*, 1989.
Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1985**, *107*, 2099.

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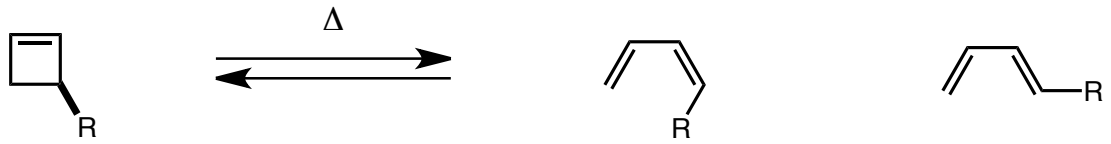

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Substituent	E_a (kcal/mol)	E_{rel} (R–H, kcal/mol)
H	32.5	0
Me	31.6	–0.9
Cl	29.4	–3.1
OAc	27.8	–4.7
OEt	23.5	–9.0

Kirmse, W., Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1984**, *106*, 1989.
Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1985**, *107*, 2099.

Torquoselectivity in Electrocyclic Reactions

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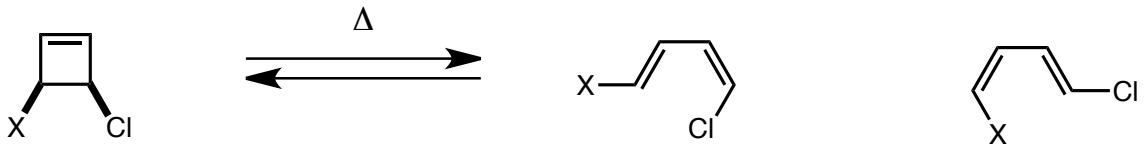

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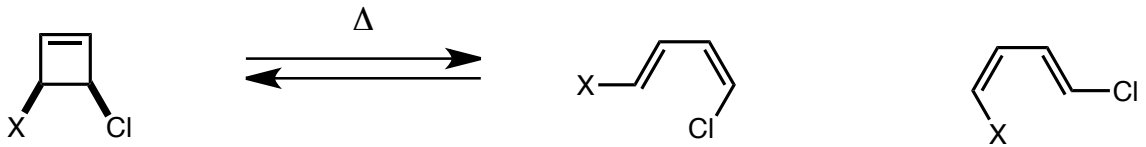

"inward" "outward"

Substituent	E_a (kcal/mol)	E_{rel} (X–H, kcal/mol)
H	29.4	0

Kirmse, W., Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1984**, *106*, 1989.
Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1985**, *107*, 2099.

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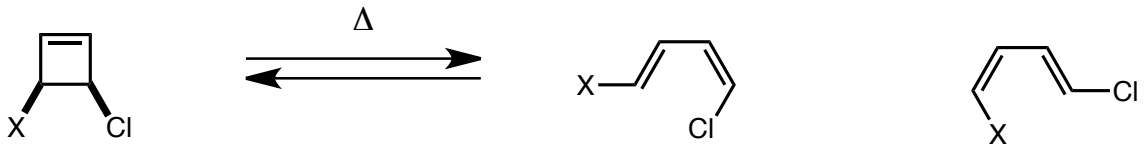

"inward" "outward"

Substituent	E_a (kcal/mol)	E_{rel} (X–H, kcal/mol)
H	29.4	0
Me	31.6	+2.2
Cl	35.6	+6.2

Kirmse, W., Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1984**, *106*, 1989.
Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1985**, *107*, 2099.

Torquoselectivity in Electrocyclic Reactions

- Further thermodymanic analysis towards a rational for torquoselectivity
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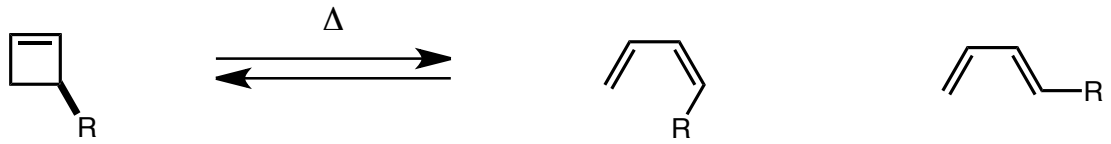

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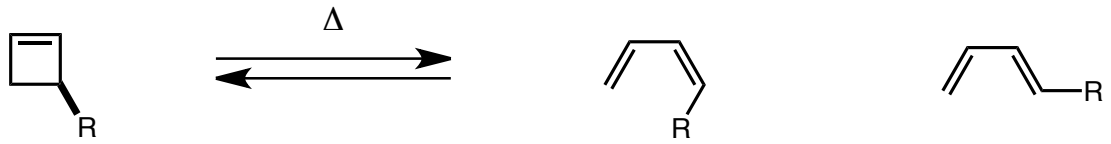

"inward" "outward"

Substituent effect on E_a:

Substituent	inward (kcal/mol)	outward (kcal/mol)
Me	+3	–1
Cl	+6	–3
OAc		–5
OR	+5	–9

Kirmse, W., Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1984**, *106*, 1989.
Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1985**, *107*, 2099.

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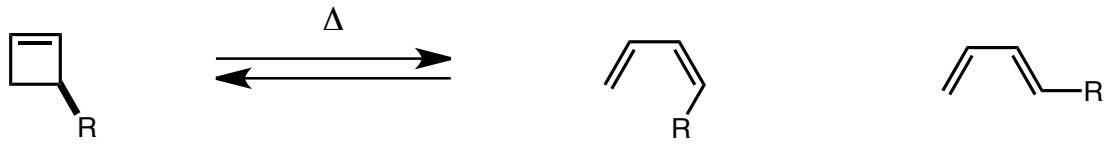

"inward" "outward"

Substituent effect on E_a:

Substituent	inward (kcal/mol)	outward (kcal/mol)	$E_{out} - E_{in}$ (kcal/mol)
Me	+3	–1	–4
Cl	+6	–3	–9
OAc		–5	
OR	+5	–9	-14

Kirmse, W., Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1984**, *106*, 1989.
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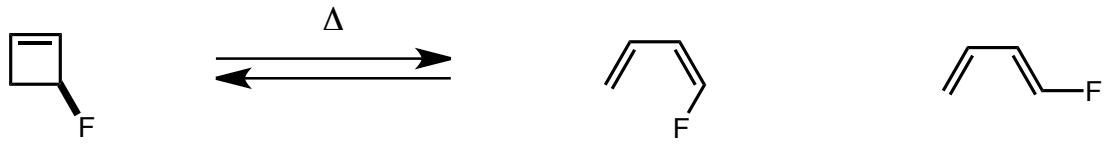

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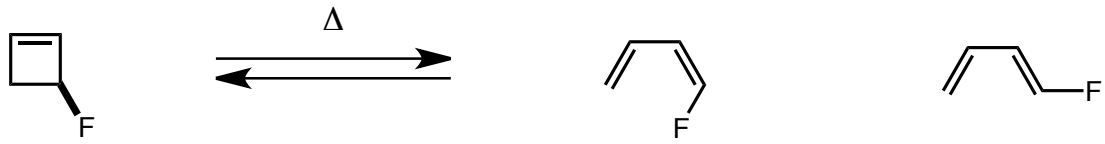

"inward" "outward"

~13 kcal/mol preference
for outward TS (calculated)

Kirmse, W., Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1984**, *106*, 1989.
Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1985**, *107*, 2099.

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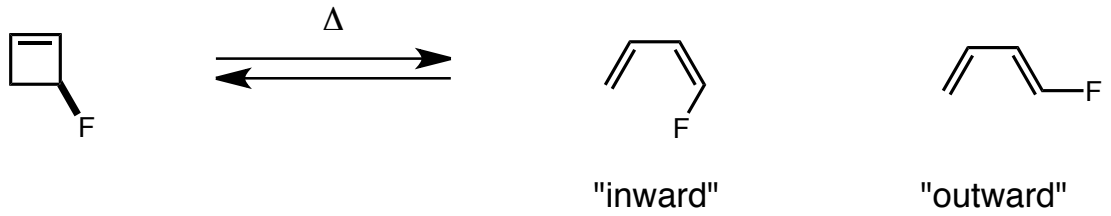

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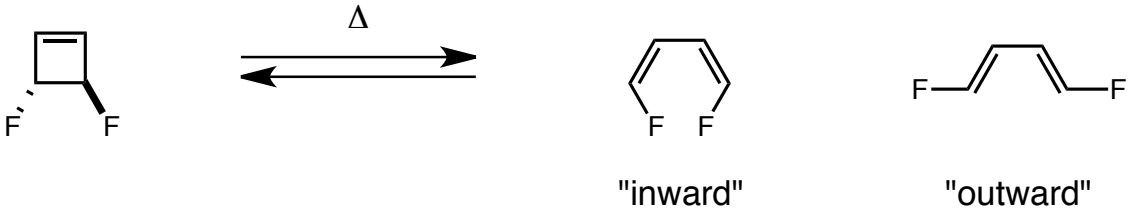

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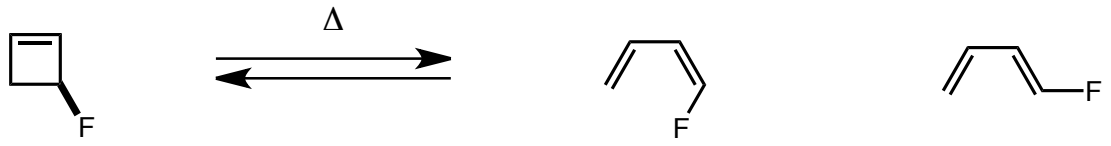
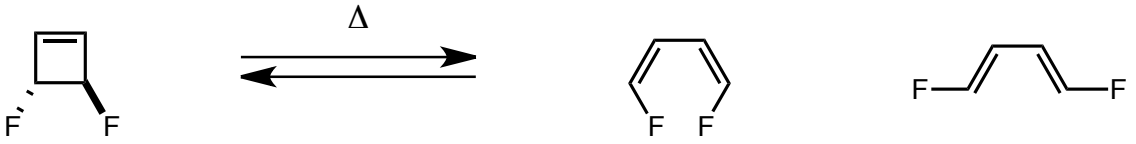


"inward" "outward"

~13 kcal/mol preference
for outward TS (calculated)



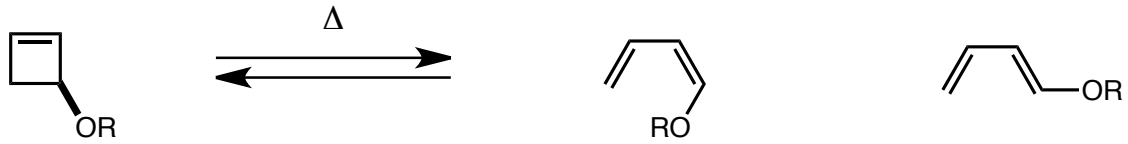
"inward" "outward"

~29 kcal/mol preference
for outward TS (calculated)

Kirmse, W., Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1984**, *106*, 1989.
Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1985**, *107*, 2099.

Torquoselectivity in Electrocyclic Reactions

- Transition state analysis of torquoselective electrocyclic opening



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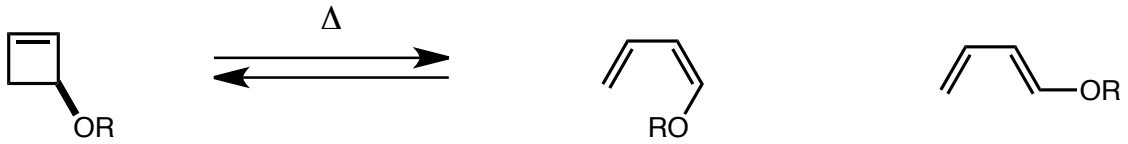
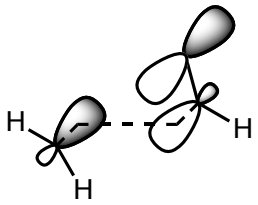
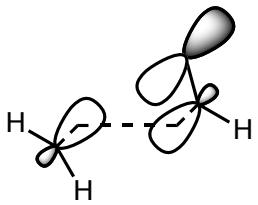


inward TS



LUMO



HOMO

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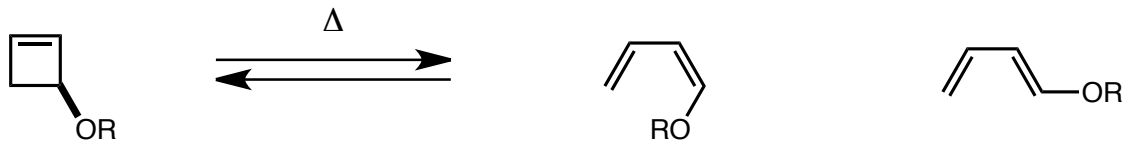
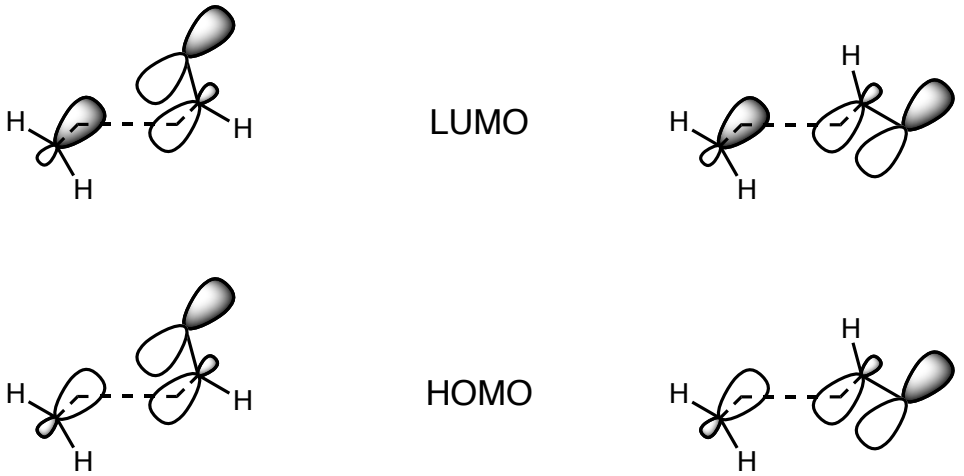


inward TS

outward TS



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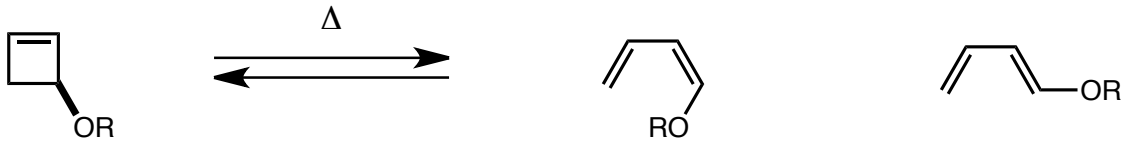

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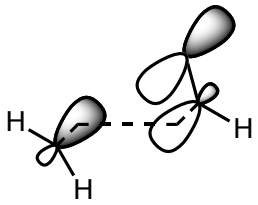
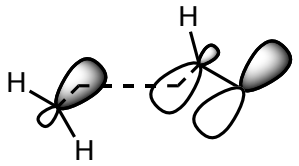
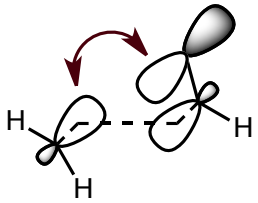


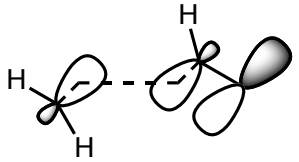
LUMO



Unfavorable 4e⁻ interaction of p-orbital with σ



HOMO



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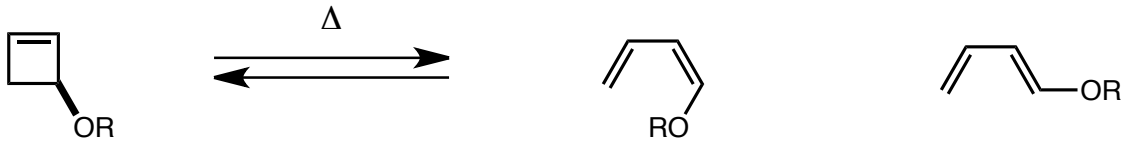
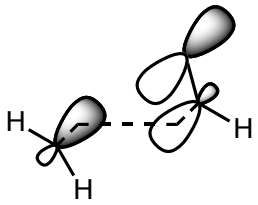
Torquoselectivity in Electrocyclic Reactions

- Transition state analysis of torquoselective electrocyclic opening



inward TS

outward TS



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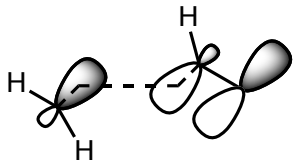
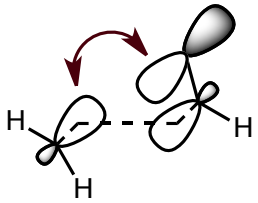


Stabilization of TS through σ* / p-orbital overlap

Unfavorable 4e⁻ interaction of p-orbital with σ



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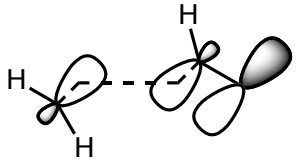

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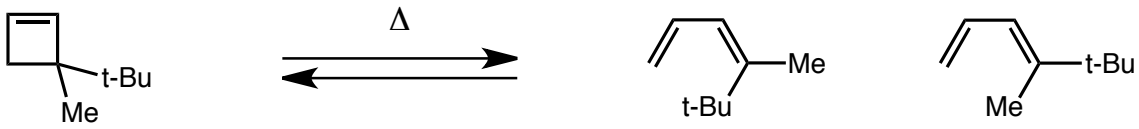
Torquoselectivity in Electrocyclic Reactions

- Unique control arises from torquoselective reactivity



30 : 70

Dolbier, W. R., Koroniak, H., Houk, K. N., Sheu, C. *Acc. Chem. Res.*, **1996**, *29*, 471.
Houk, K. N., Spellmeyer, D. C., Jefford, C. W., Rimbault, C. G., Wang, Y., Miller, R. D. *J. Org. Chem.*, **1988**, *53*, 2125.

Torquoselectivity in Electrocyclic Reactions

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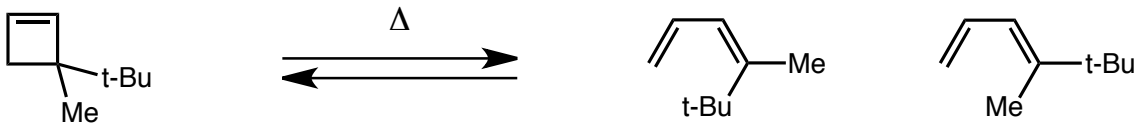

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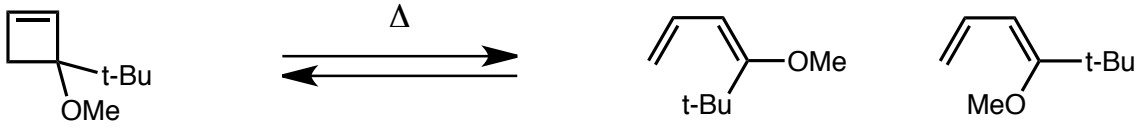
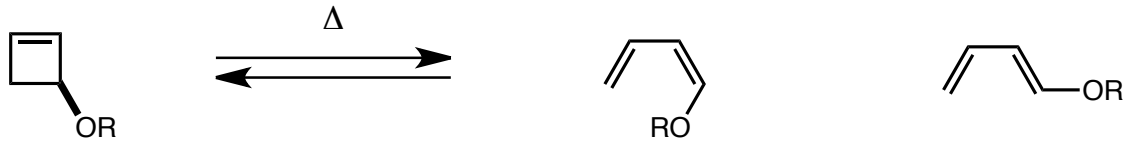


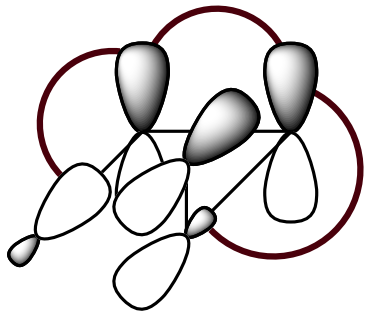
> 99 : 1

Dolbier, W. R., Koroniak, H., Houk, K. N., Sheu, C. *Acc. Chem. Res.*, **1996**, *29*, 471.
Houk, K. N., Spellmeyer, D. C., Jefford, C. W., Rimbault, C. G., Wang, Y., Miller, R. D. *J. Org. Chem.*, **1988**, *53*, 2125.

Torquoselectivity in Electrocyclic Reactions

- Transition state analysis of torquoselective electrocyclic opening





Kirmse, W., Rondan, N. G., Houk, K. N. *J. Am. Chem. Soc.*, **1984**, *106*, 1989.
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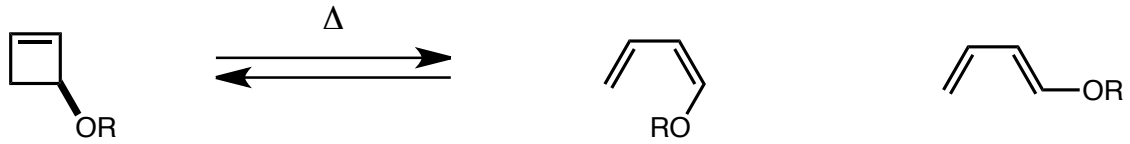

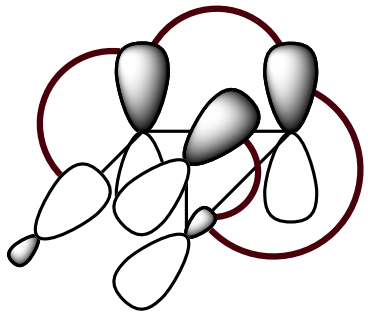

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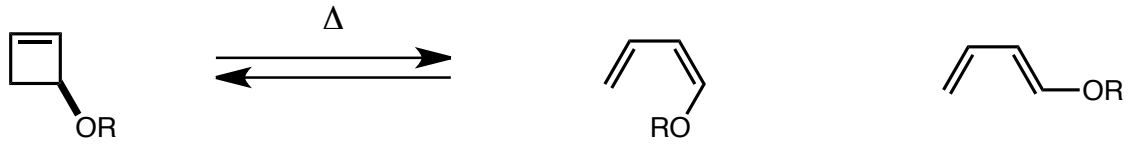

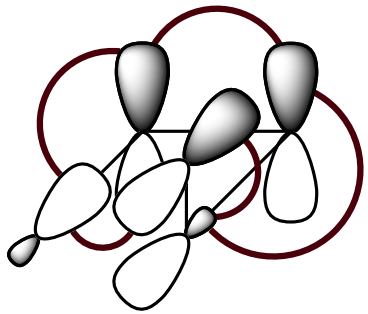

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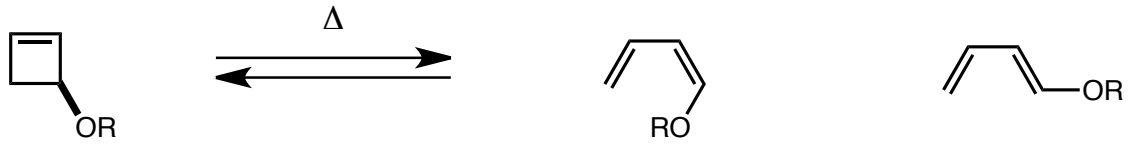

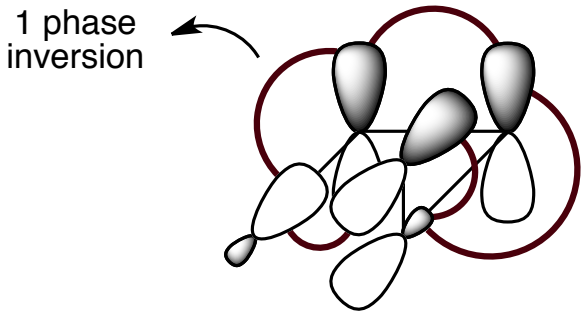

6 e⁻, Möbius array

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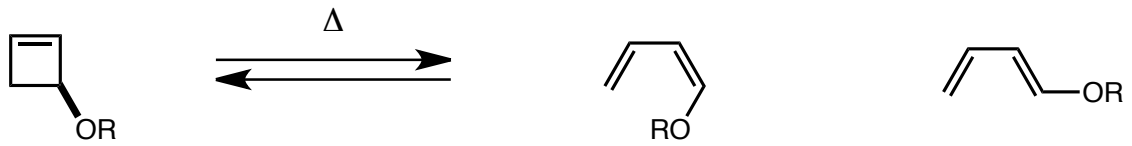

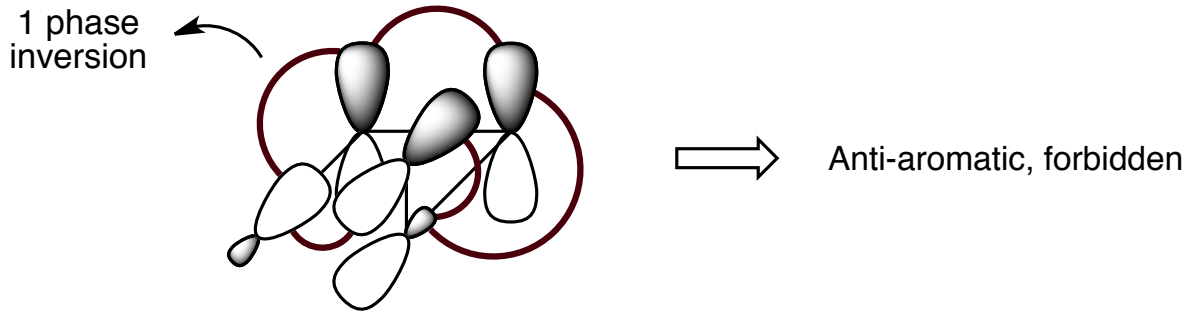

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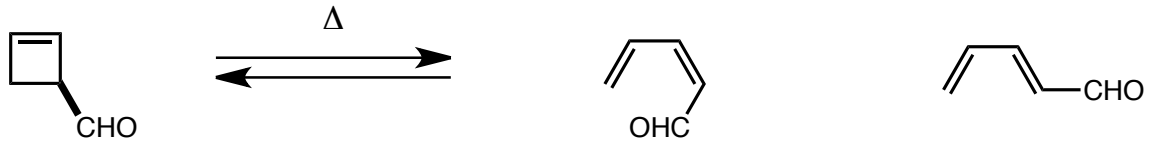

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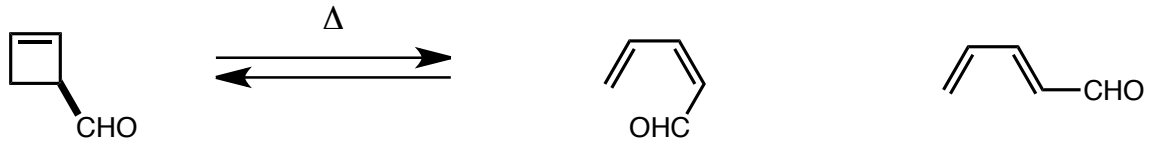

< 2% observed

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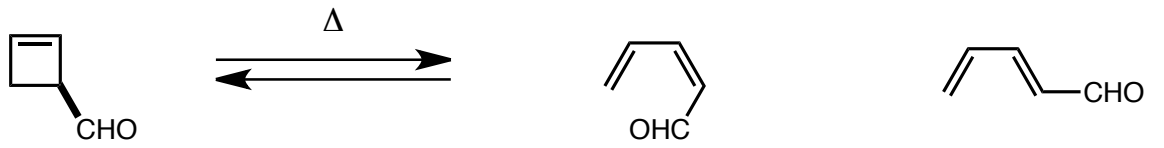

< 2% observed

inward TS

outward TS

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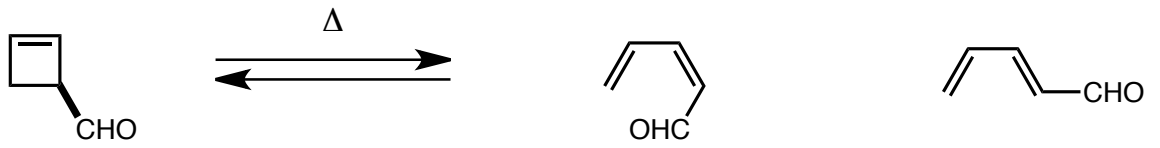

< 2% observed

inward TS

outward TS

Favorable 2e⁻ interaction of p-orbital with σ

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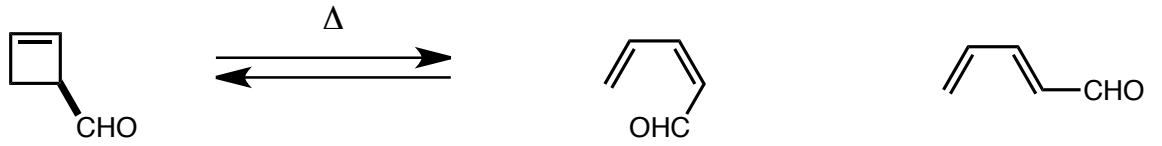

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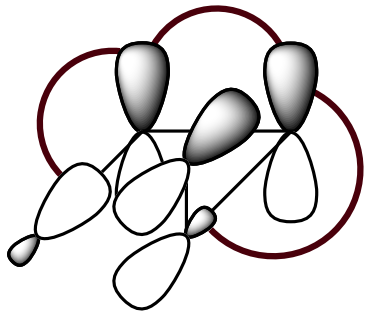

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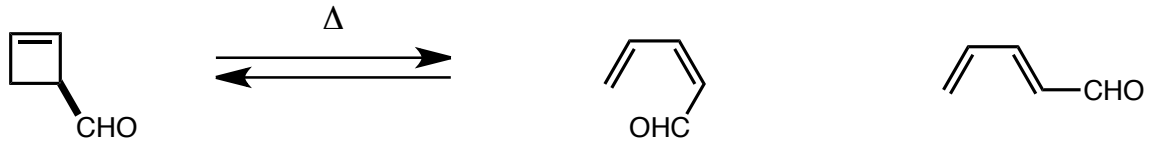

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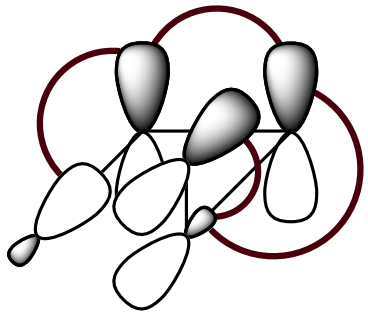

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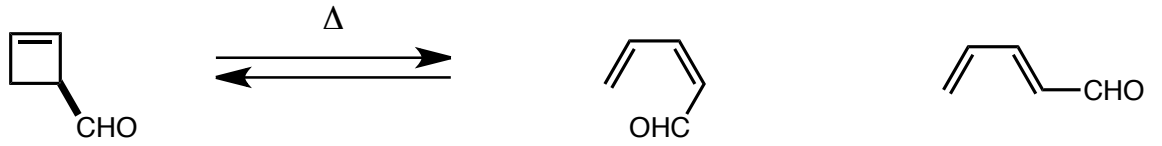

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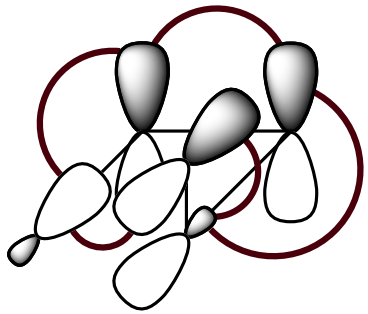

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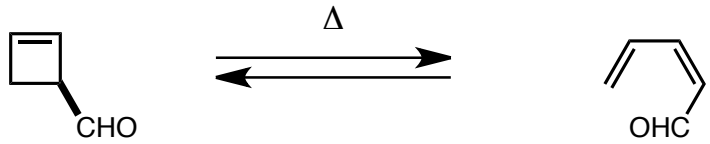

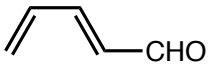

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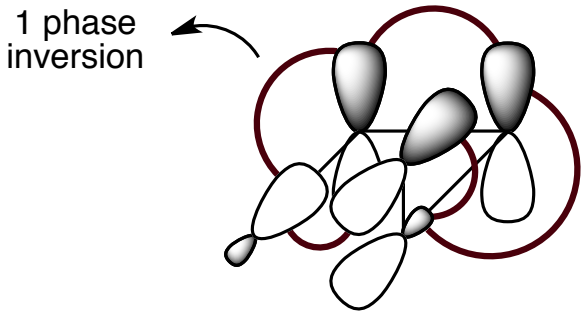

4 e^-, Möbius array

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Torquoselectivity in Electrocyclic Reactions

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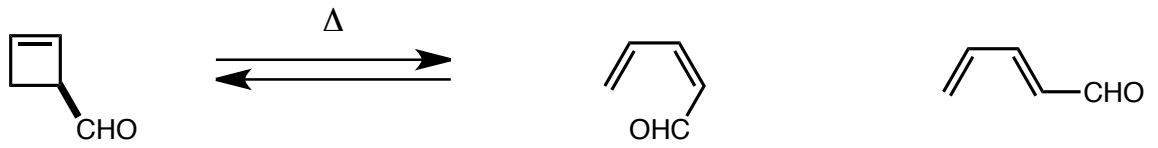

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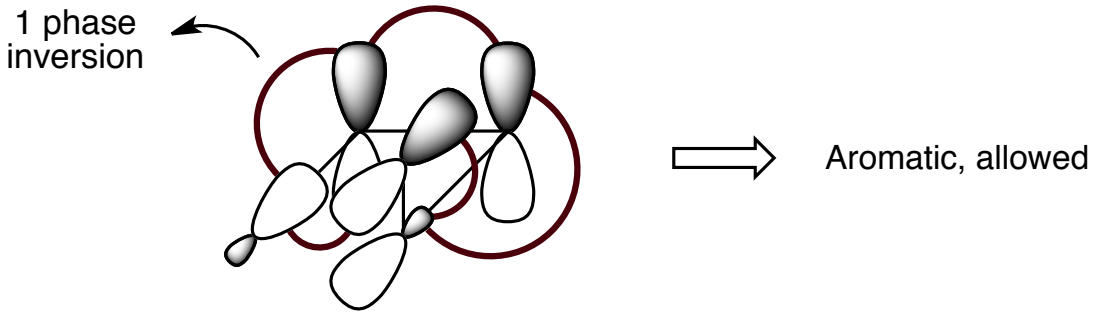

Aromatic, allowed

4 e^-, Möbius array

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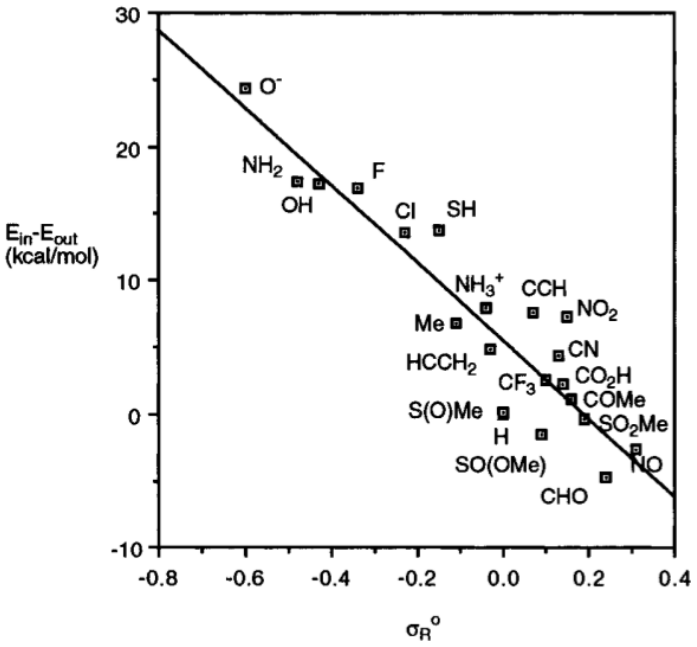

- Linear relationship between in-out preference and Taft substituent parameter for π-donating or accepting ability

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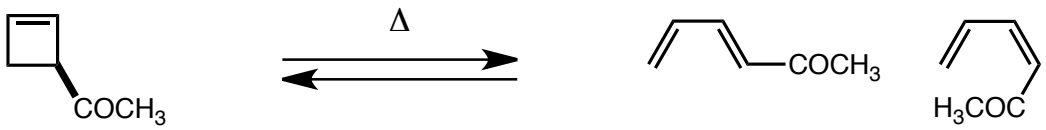

Benzene, Δ: 66 : 34

Niwayama, S., Houk, K. N. *Tetrahedron Lett.*, **1993**, *34*, 8, 1251.

Torquoselectivity in Electrocyclic Reactions

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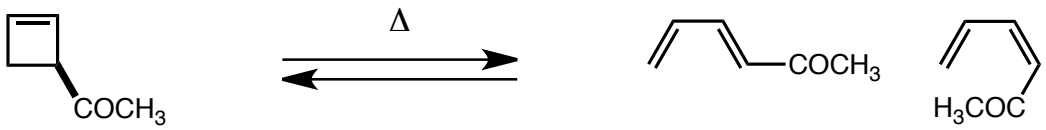

Benzene, Δ:	66 : 34
ZnI_2/Na_2CO_3, Benzene, Δ:	17 : 83

- Increasing acceptor strength increases inward torquoselectivity

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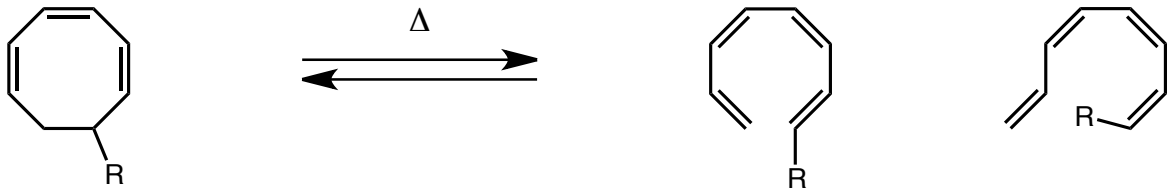
Torquoselectivity in Electrocyclic Reactions

- Additional examples of torquoselective effects



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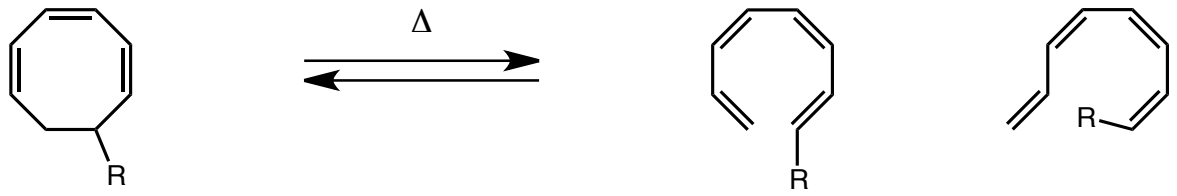

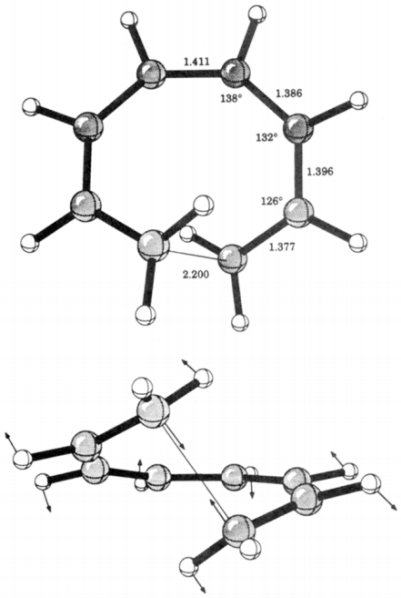

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- Electronic effects in elecrocyclization are minimal; steric effects dominate

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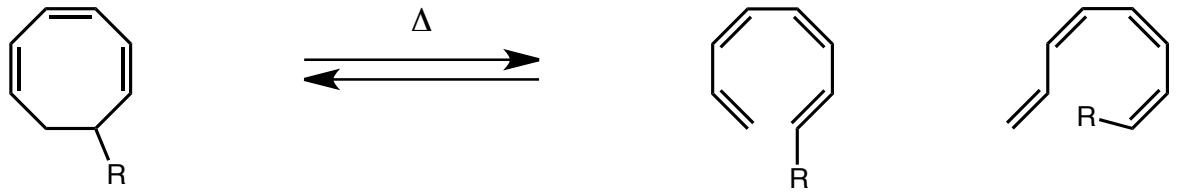

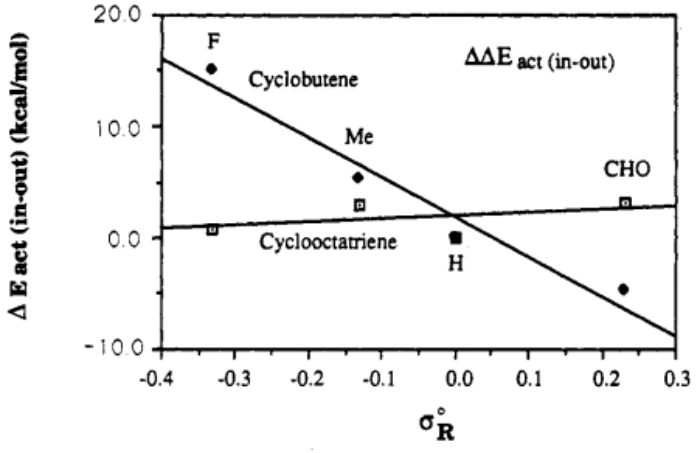

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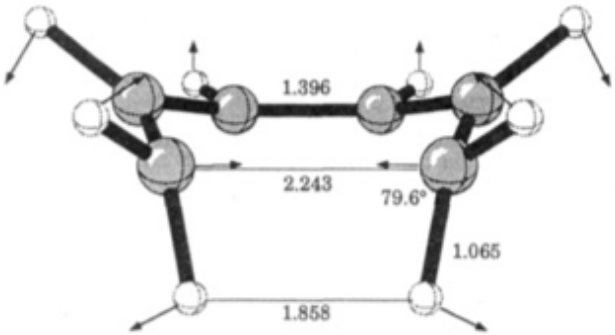

- Hexatrienes undergo disrotatory thermal electrocyclization

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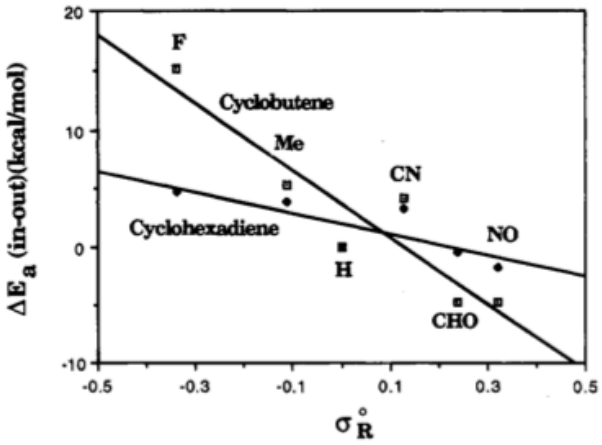

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Torquoselectivity in Electrocyclic Reactions

- Additional examples of torquoselective effects

inward TS outward TS

LUMO

HOMO

- Additional steric repulsion in inward transition state vs cyclobutene
- Reduced overlap with σ bond decreases electronic contribution

Thomas, B. E., Evenseck, J. D., Spellmeyer, D. C., Houk, K. N. *J. Org. Chem.*, **1995**, *60*, 7134.

Torquoselectivity in Electrocyclic Reactions

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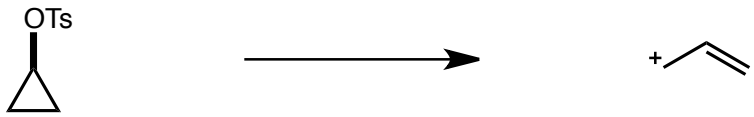

DePuy, C. H. *Acc. Chem. Res.*, **1968**, *1*, 33.
Faza, O. N., López, C. S., Álvarez, R., de Lera, A. R. *Org. Lett.*, **2004**, *6*, 905.

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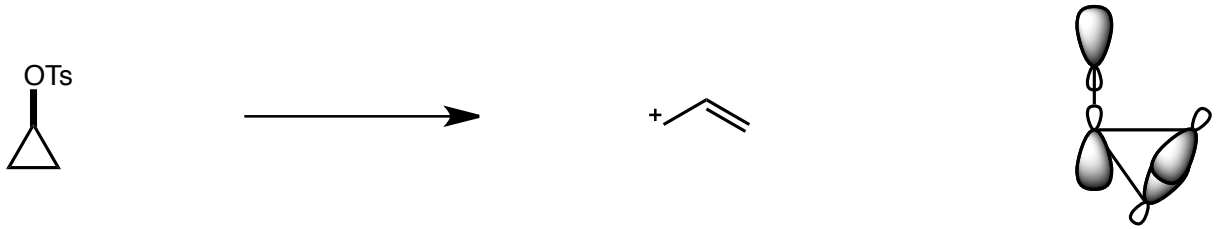

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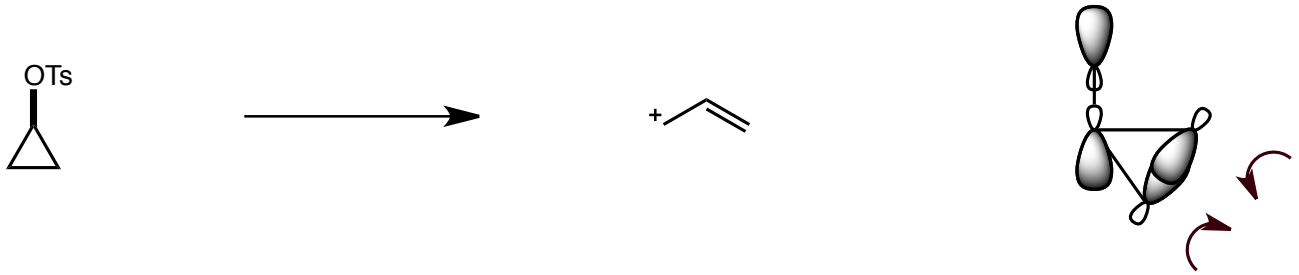

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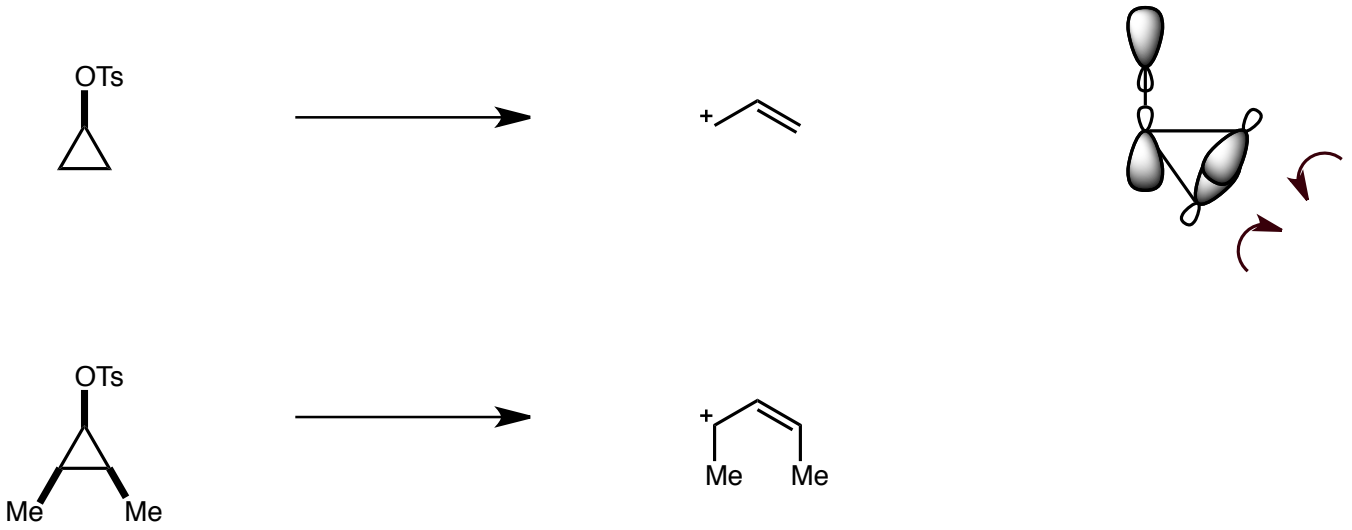

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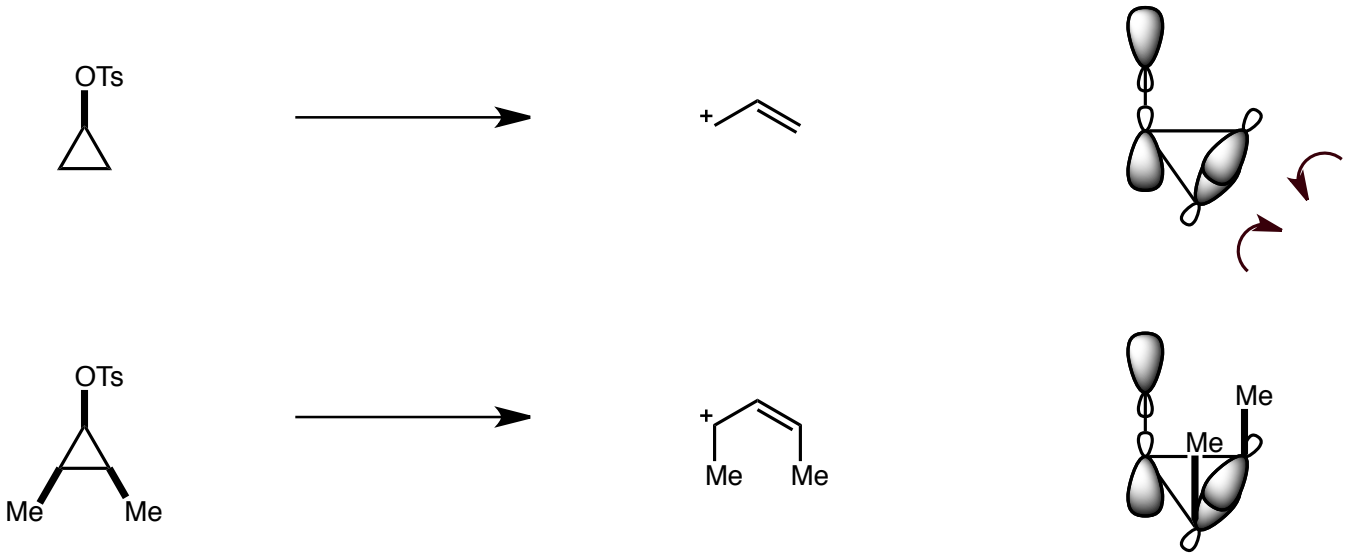

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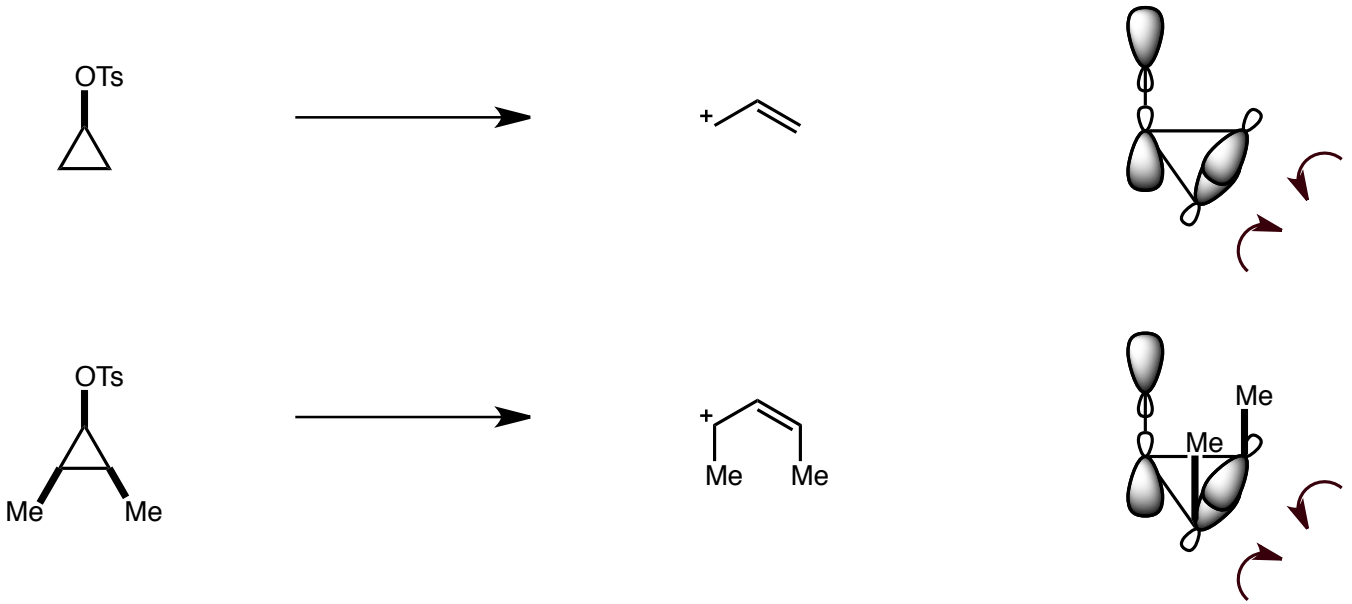

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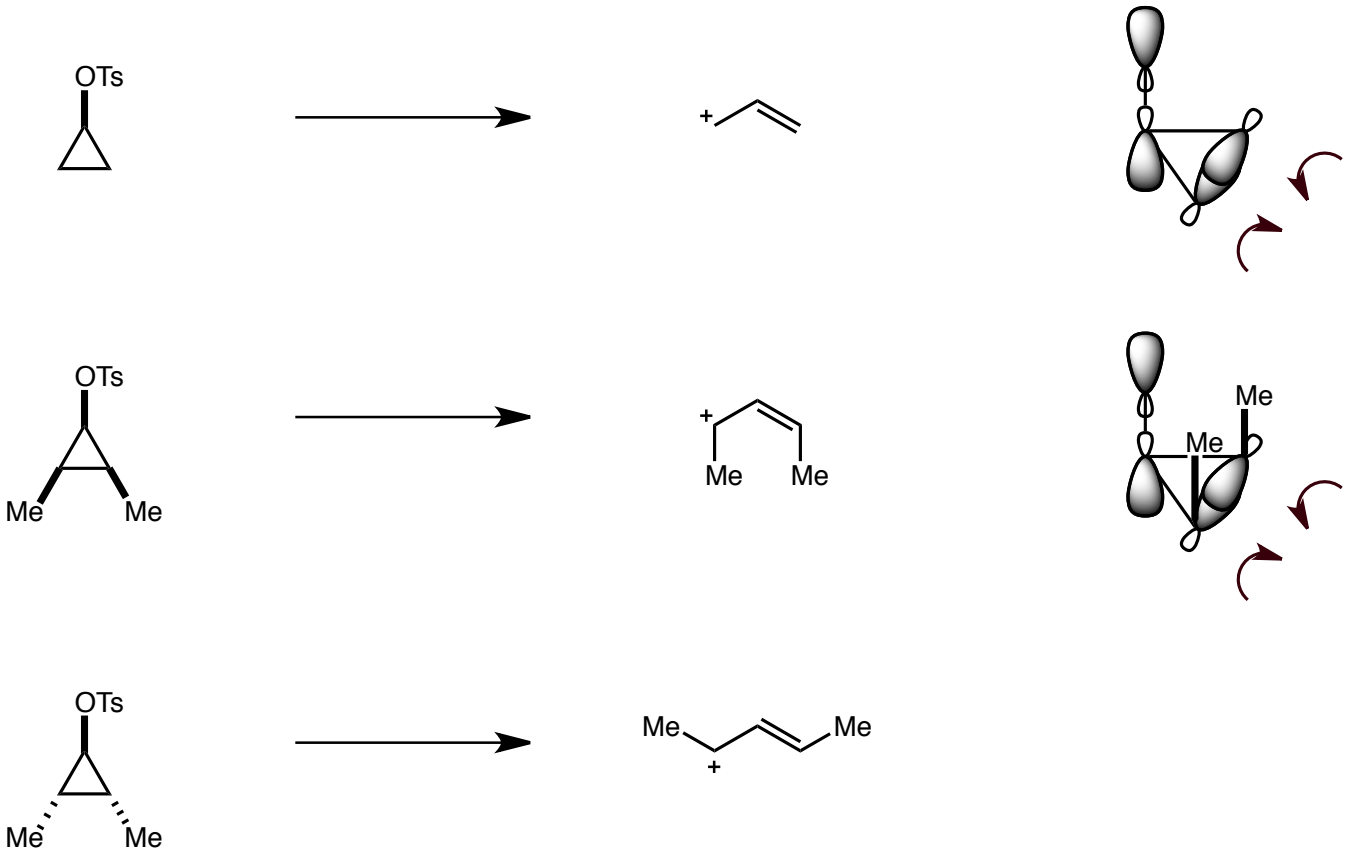

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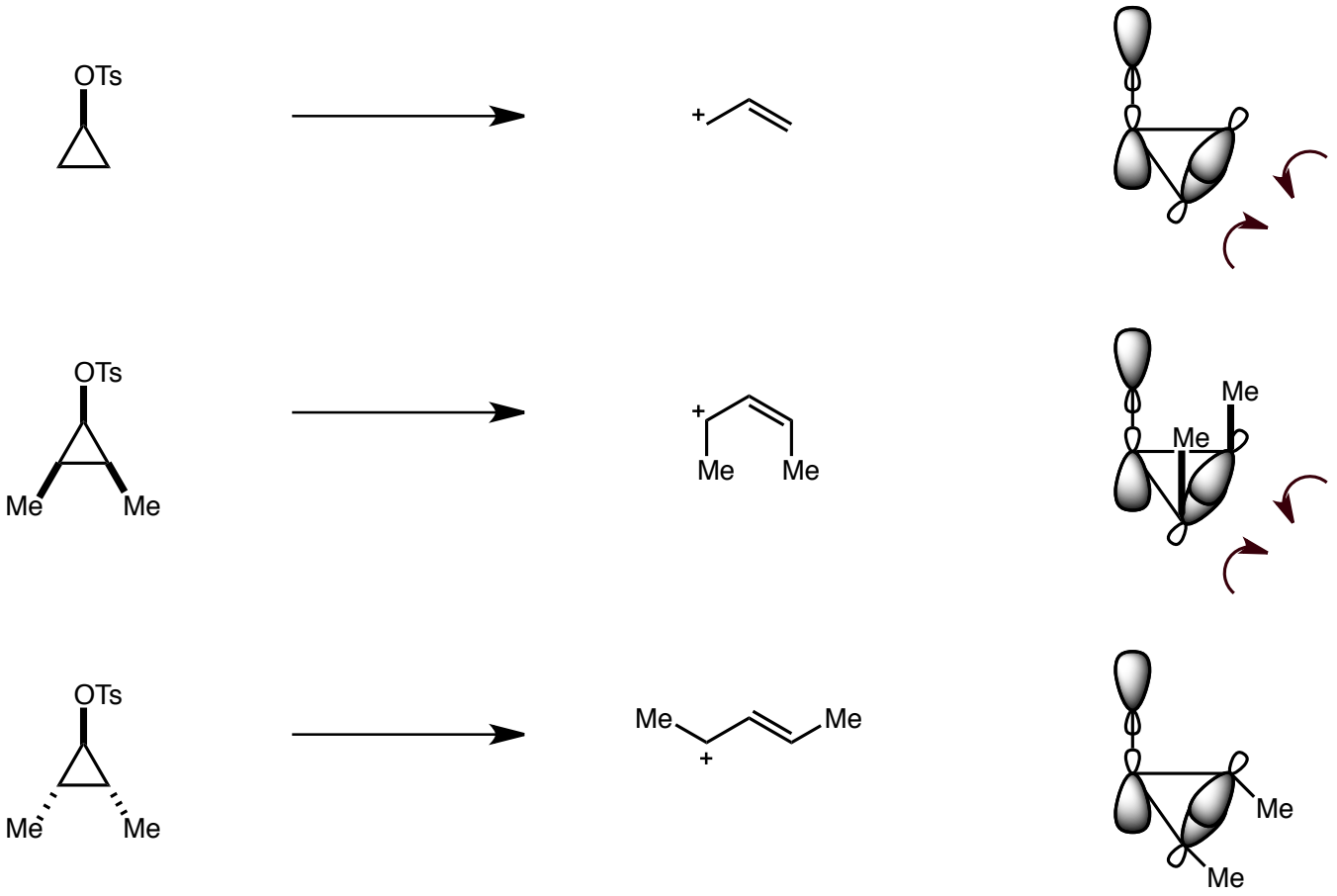

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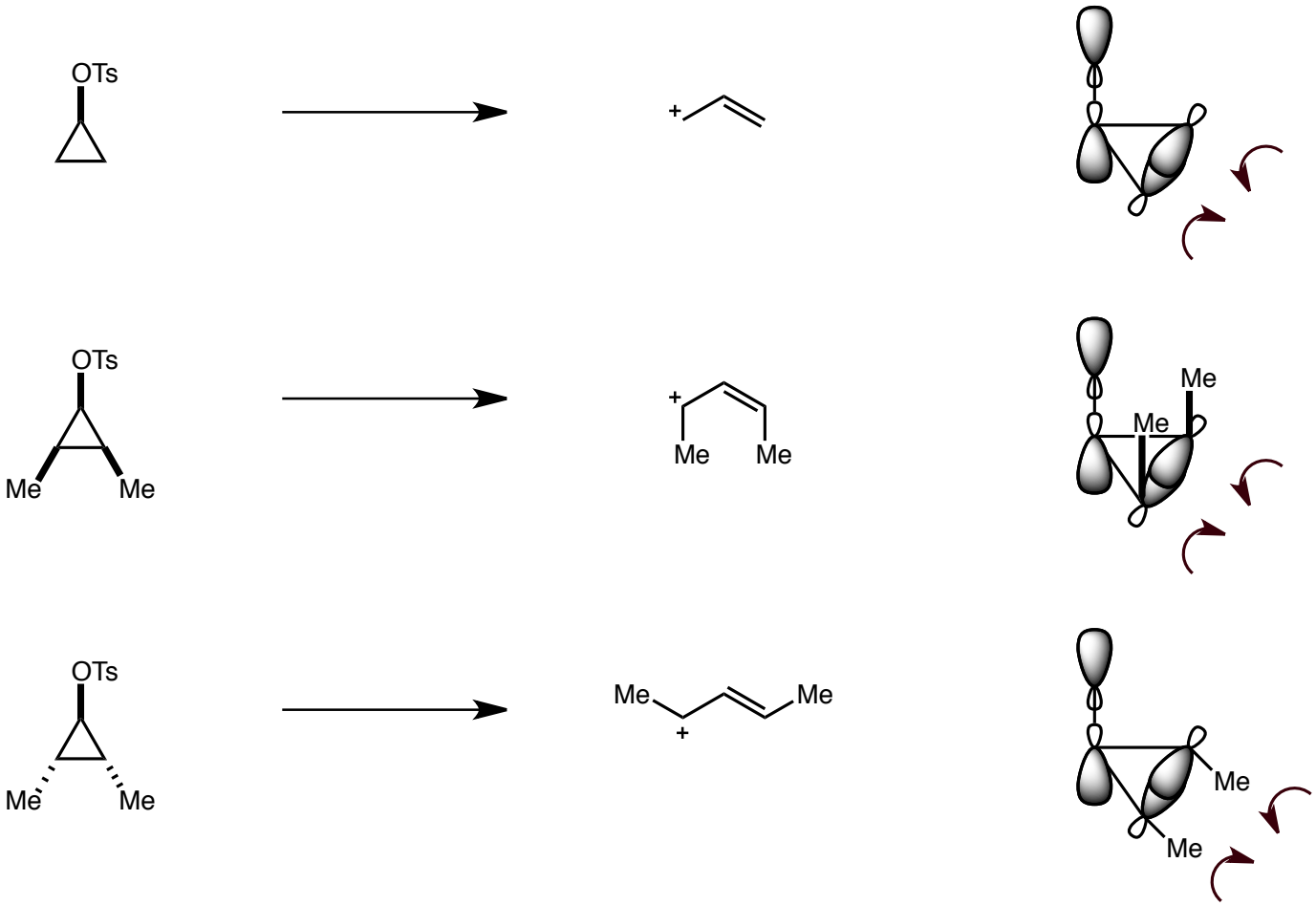

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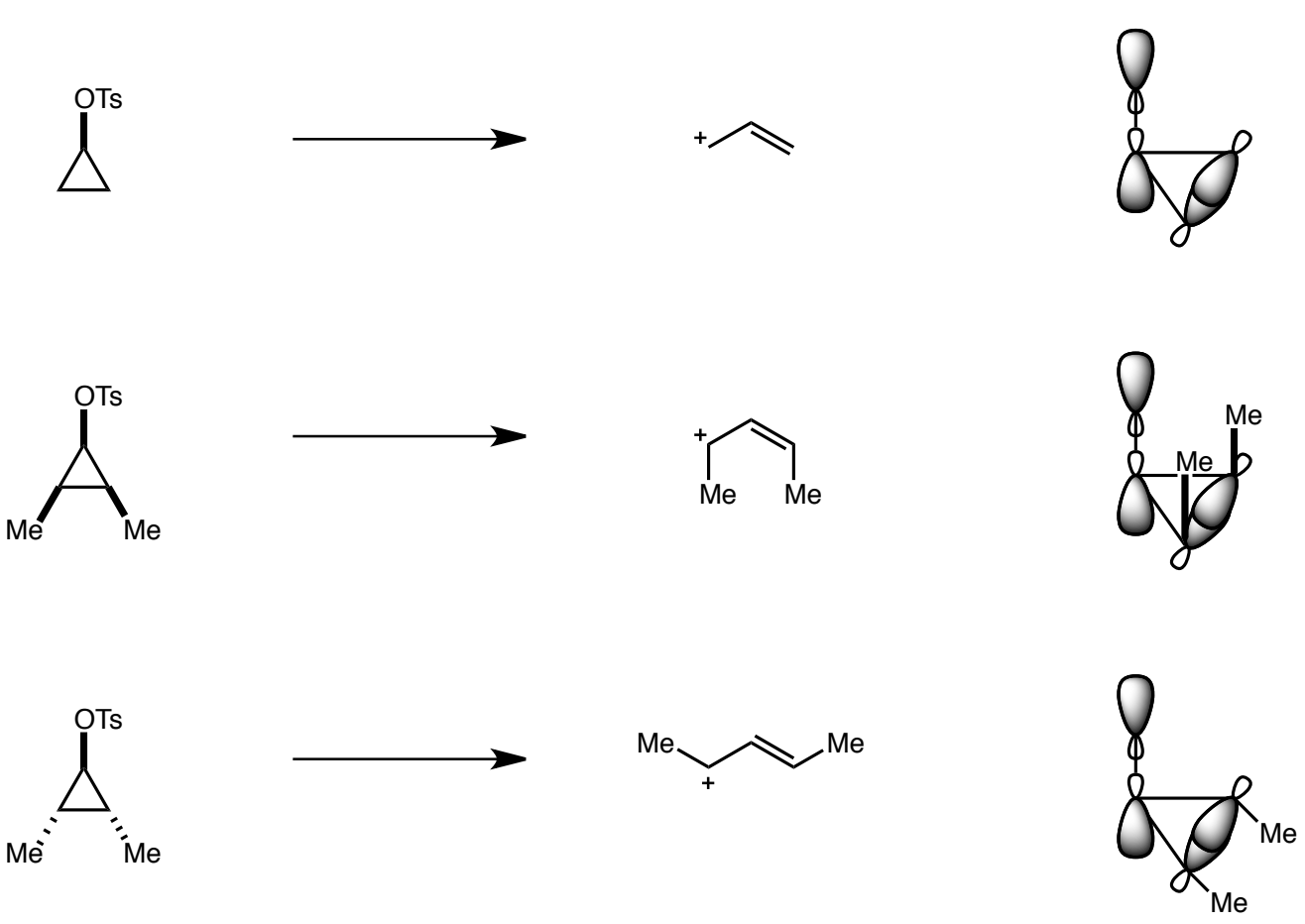

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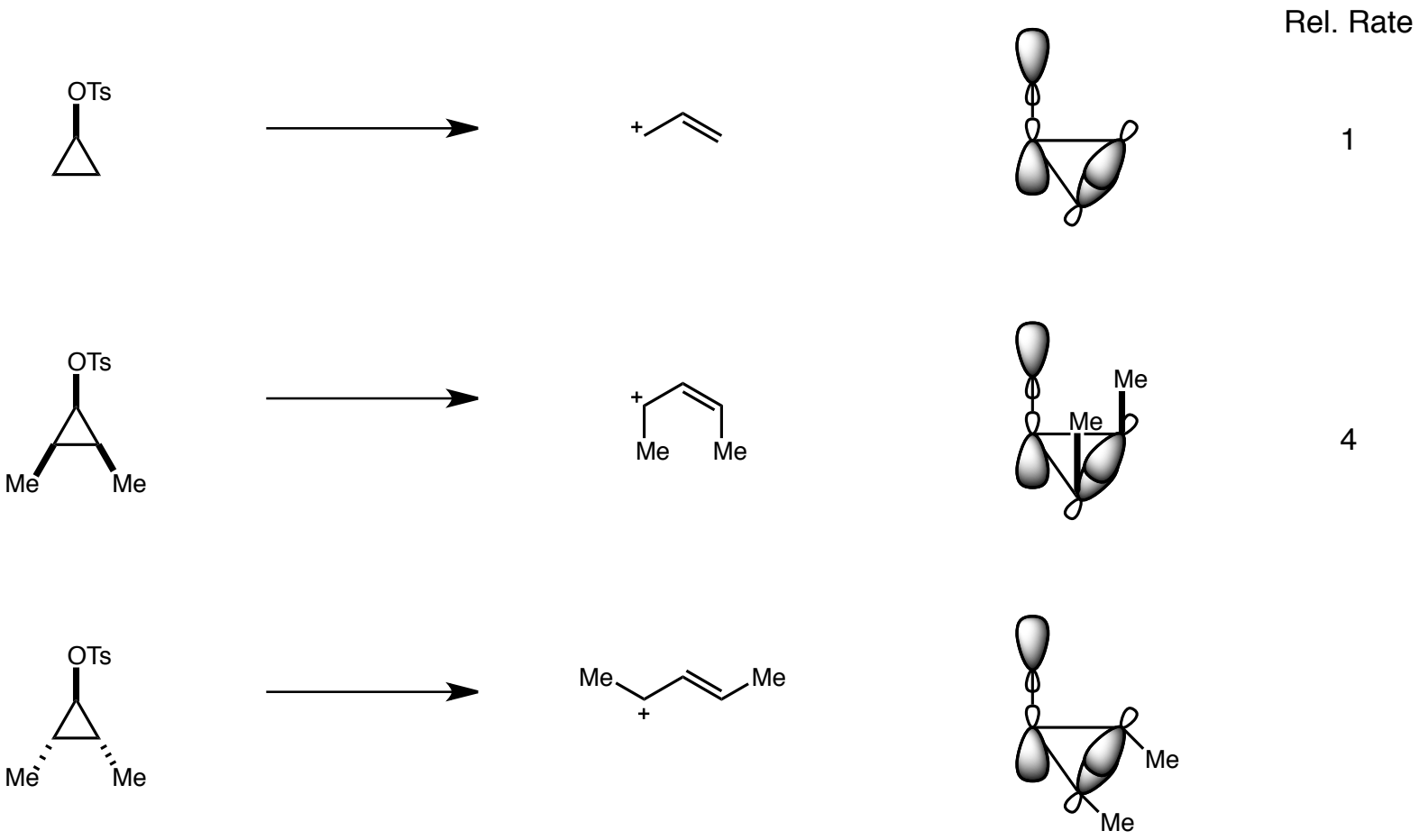

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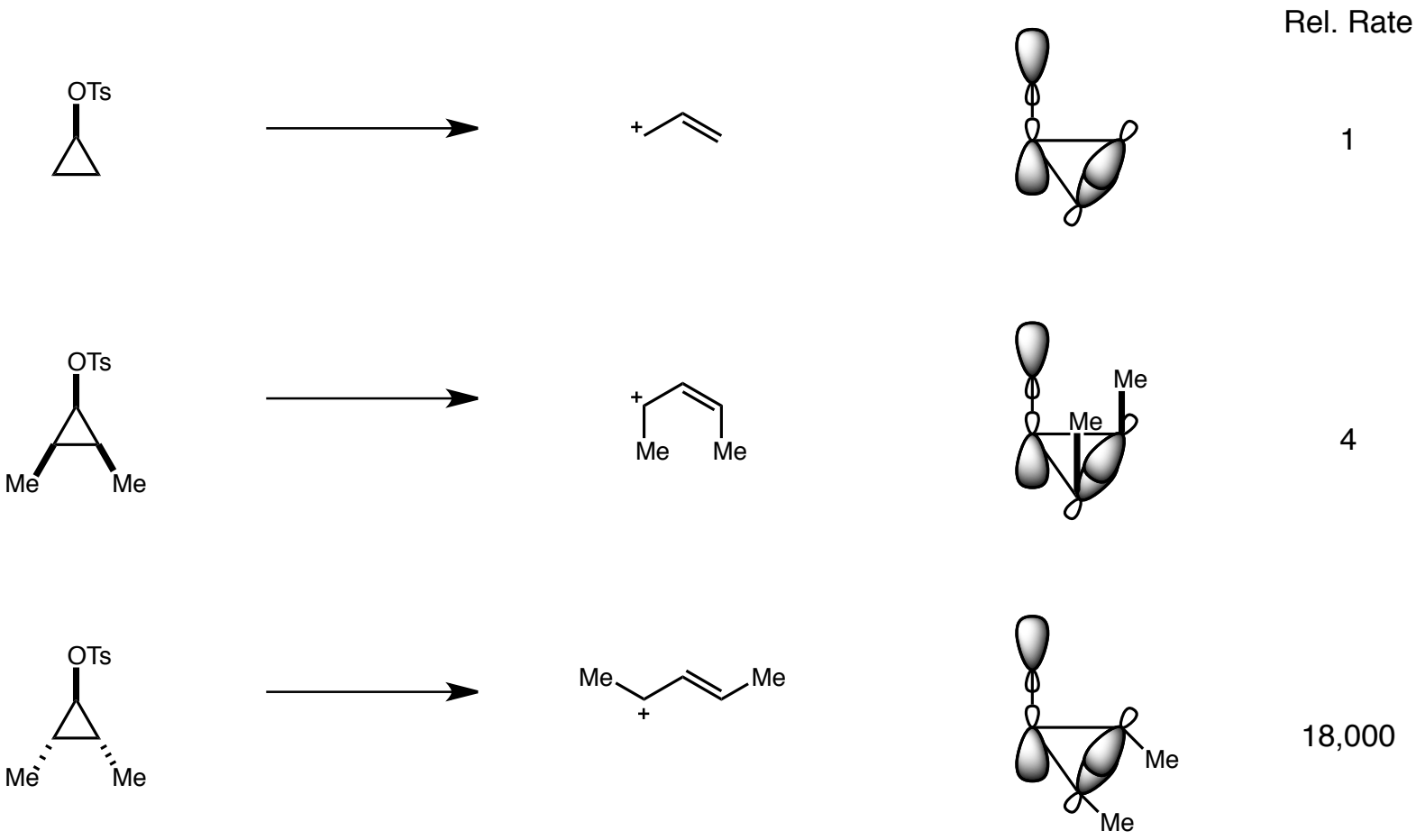

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Electrocyclic Reactions

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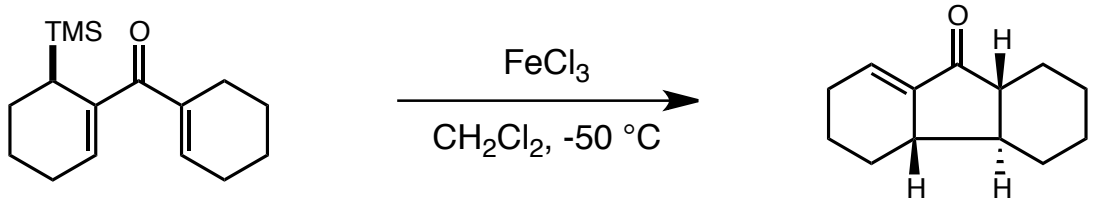

88% *ee*

88% *ee*
58% yield

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Electrocyclic Reactions

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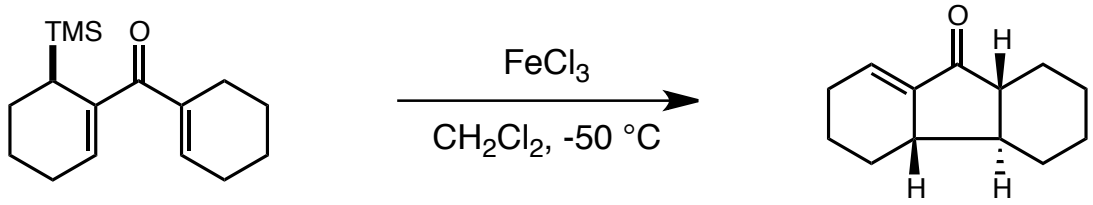

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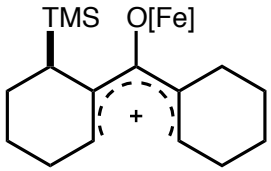

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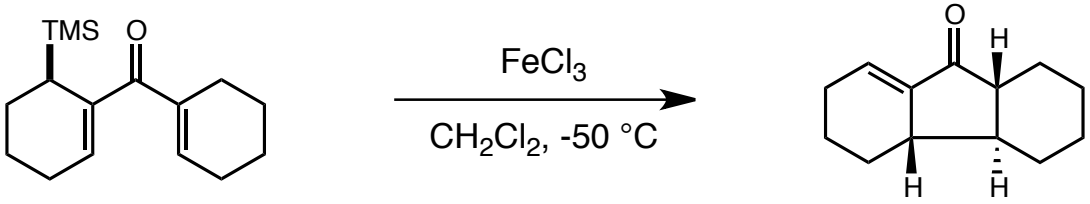

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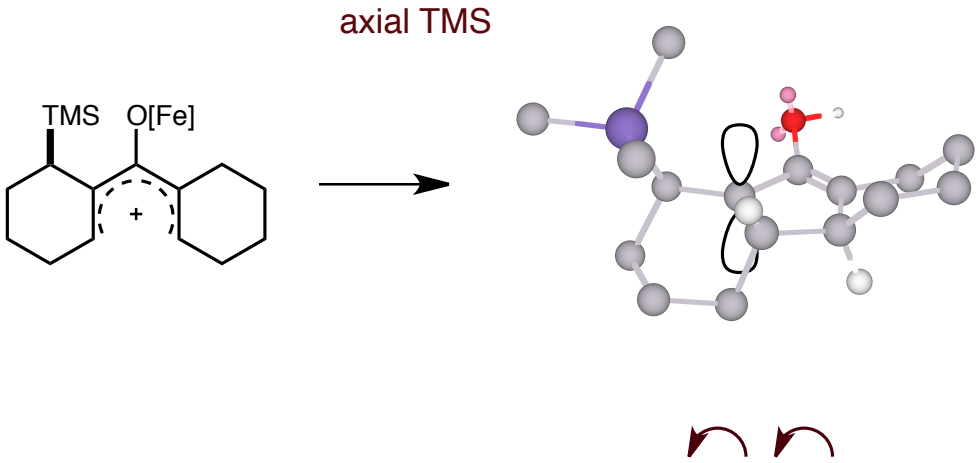

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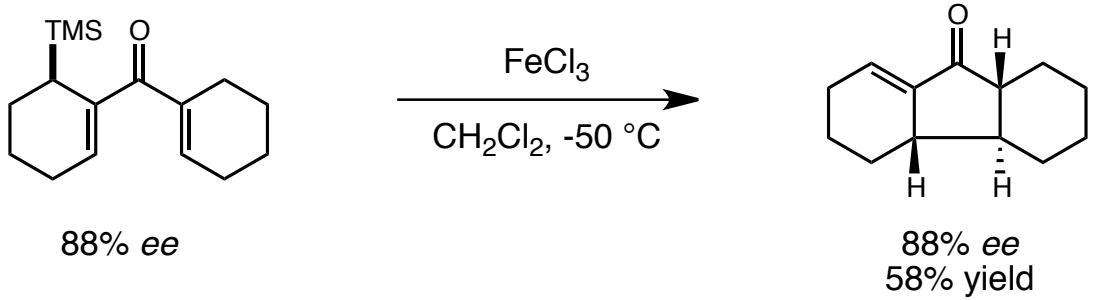

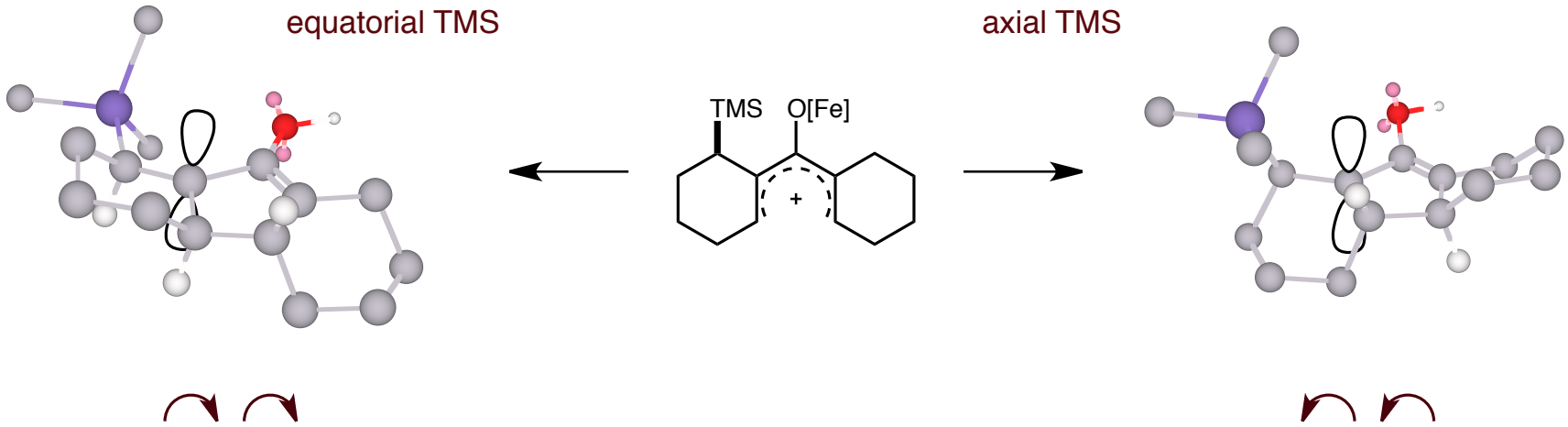

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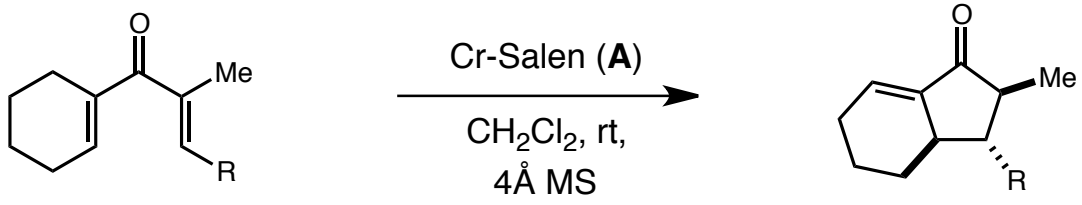
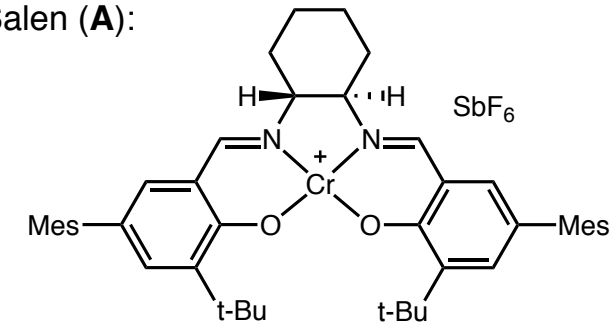


55-78% yield
80-90% *ee*
R = Alkyl, Aryl

Cr-Salen (**A**):



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Electrocyclic Reactions

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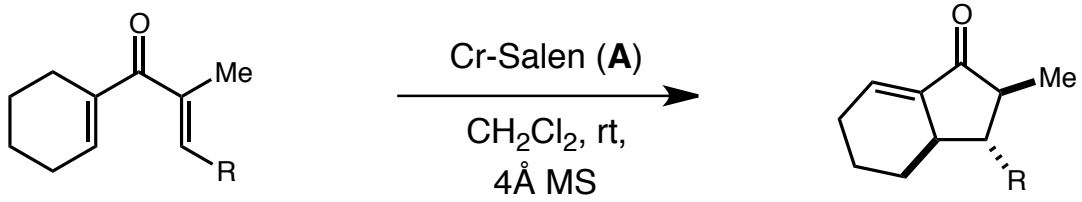

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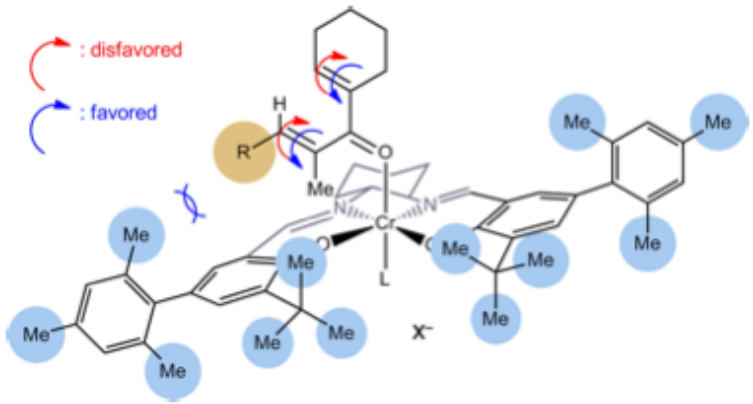

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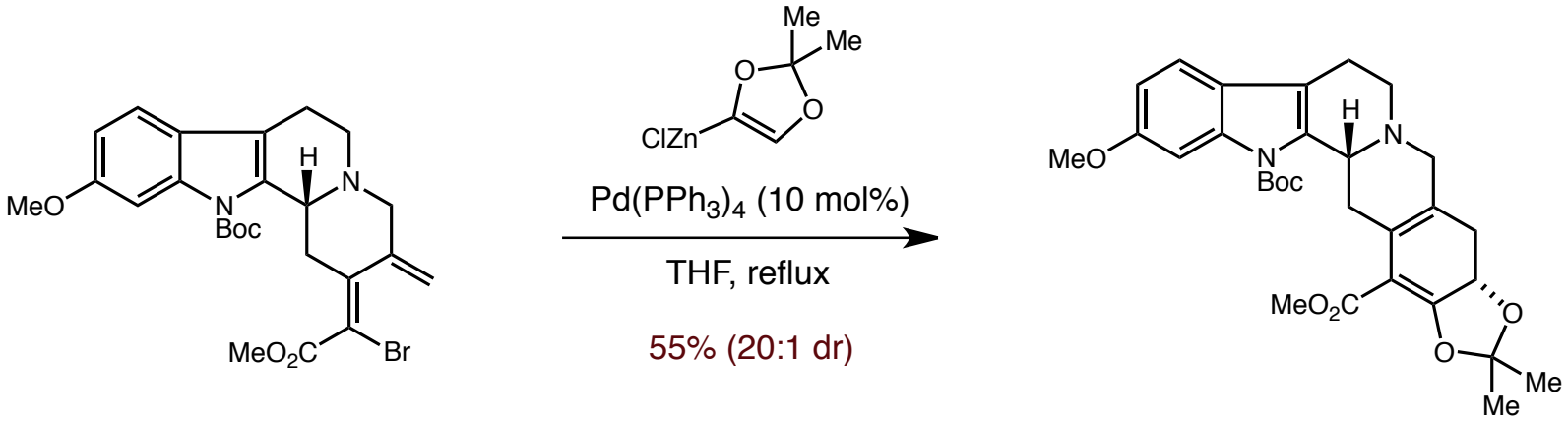

Remote 1,6-stereoinduction
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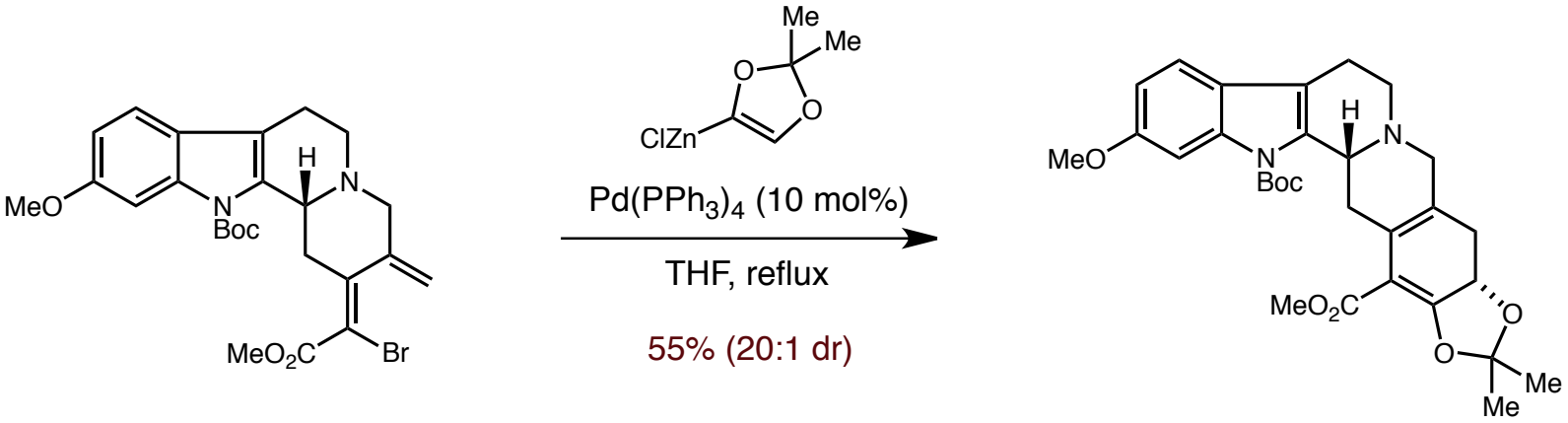
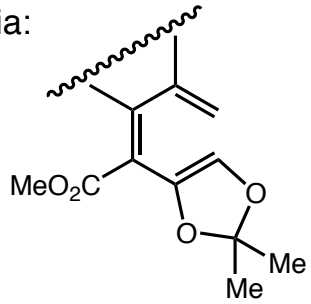


Via:



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Electrocyclic Reactions

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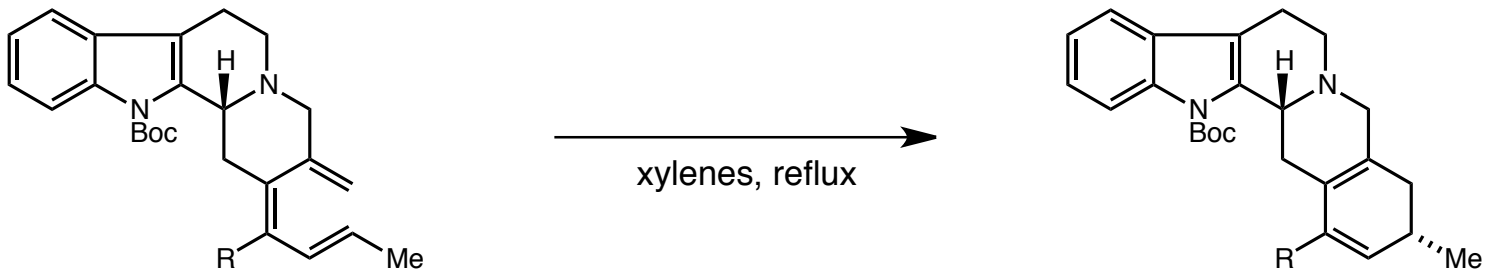

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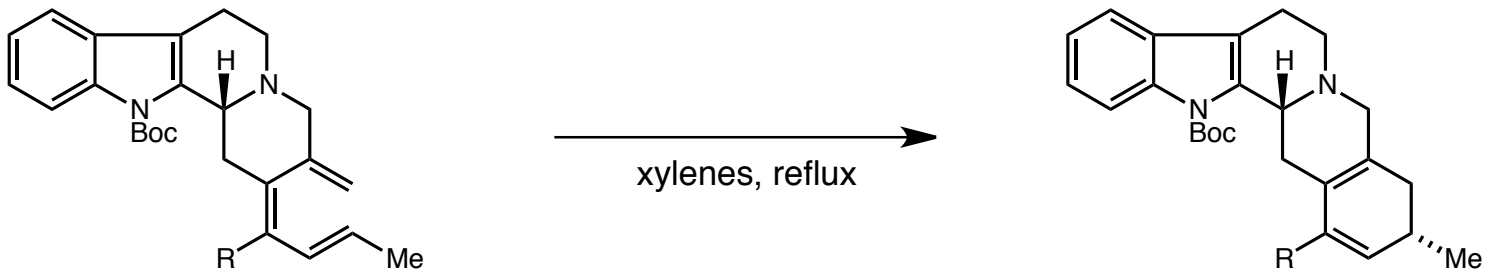

R	A-value	Product dr
H	0	3.5 : 1

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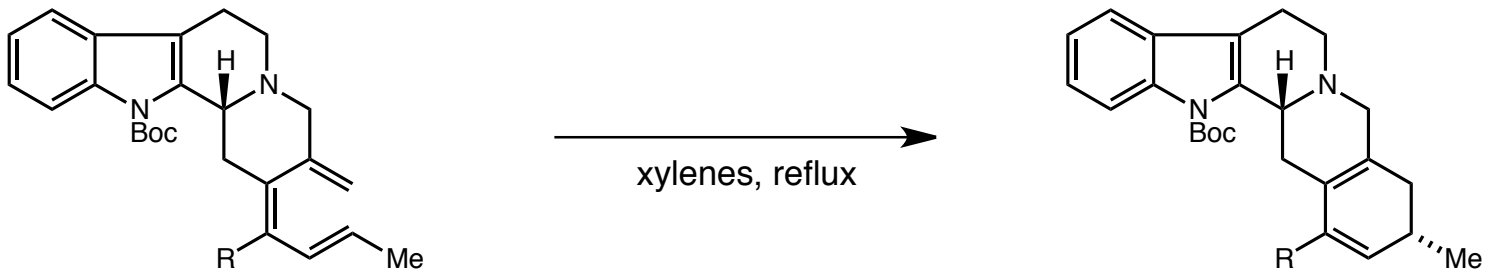

R	A-value	Product dr
H	0	3.5 : 1
SPh	0.8	6.7 : 1
CO_2Me	1.3	15.7 : 1
Me	1.7	13.3 : 1

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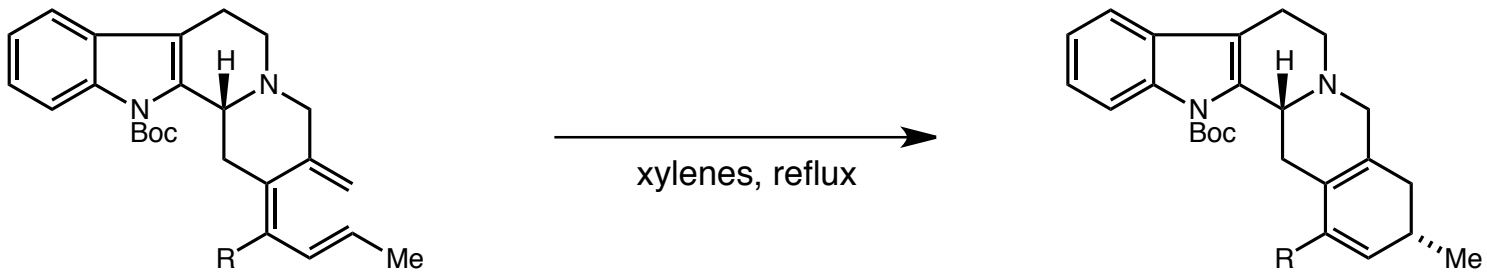

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H	0	3.5 : 1
SPh	0.8	6.7 : 1
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Me	1.7	13.3 : 1
TMS	2.4	4.3 : 1

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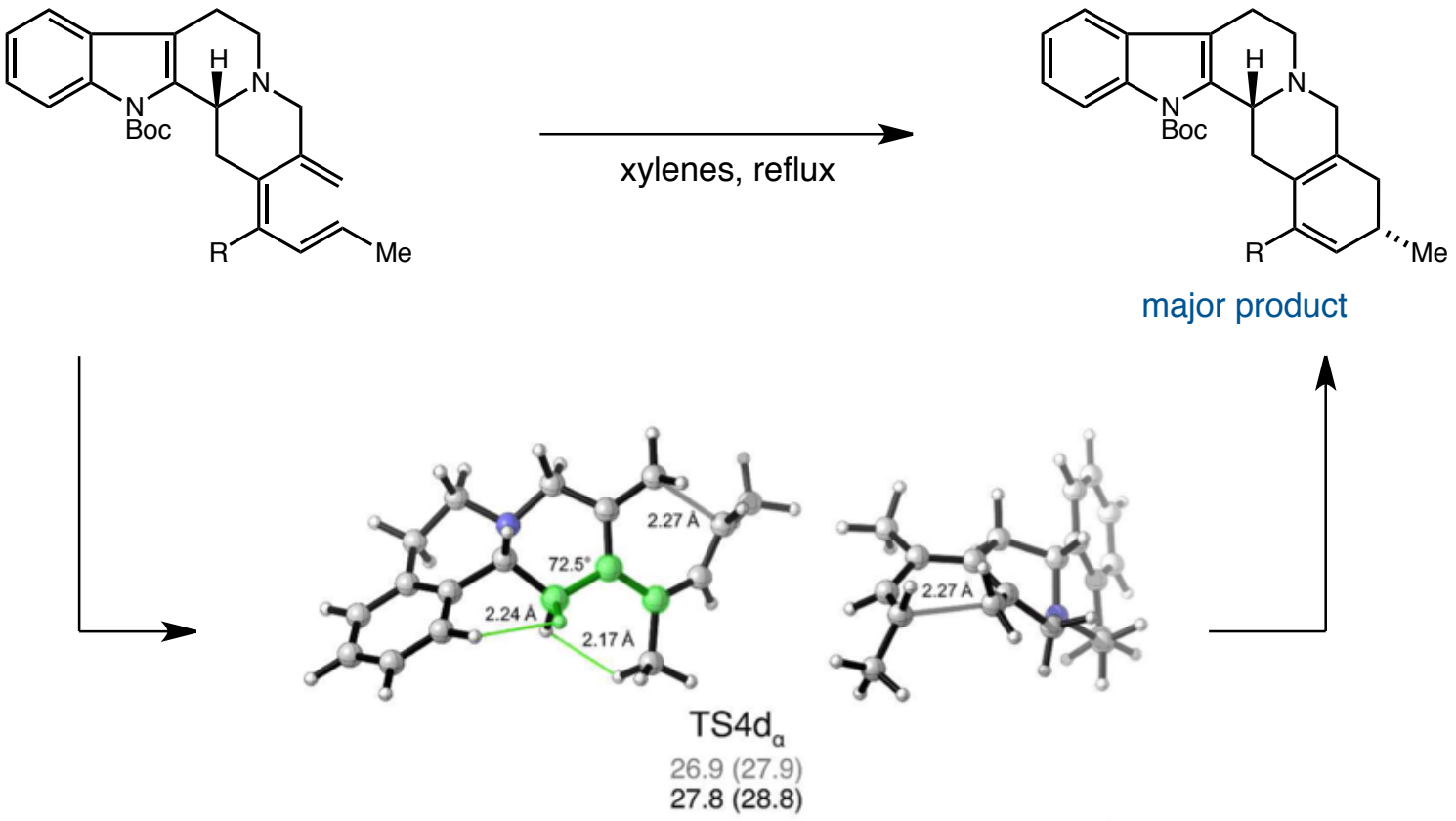

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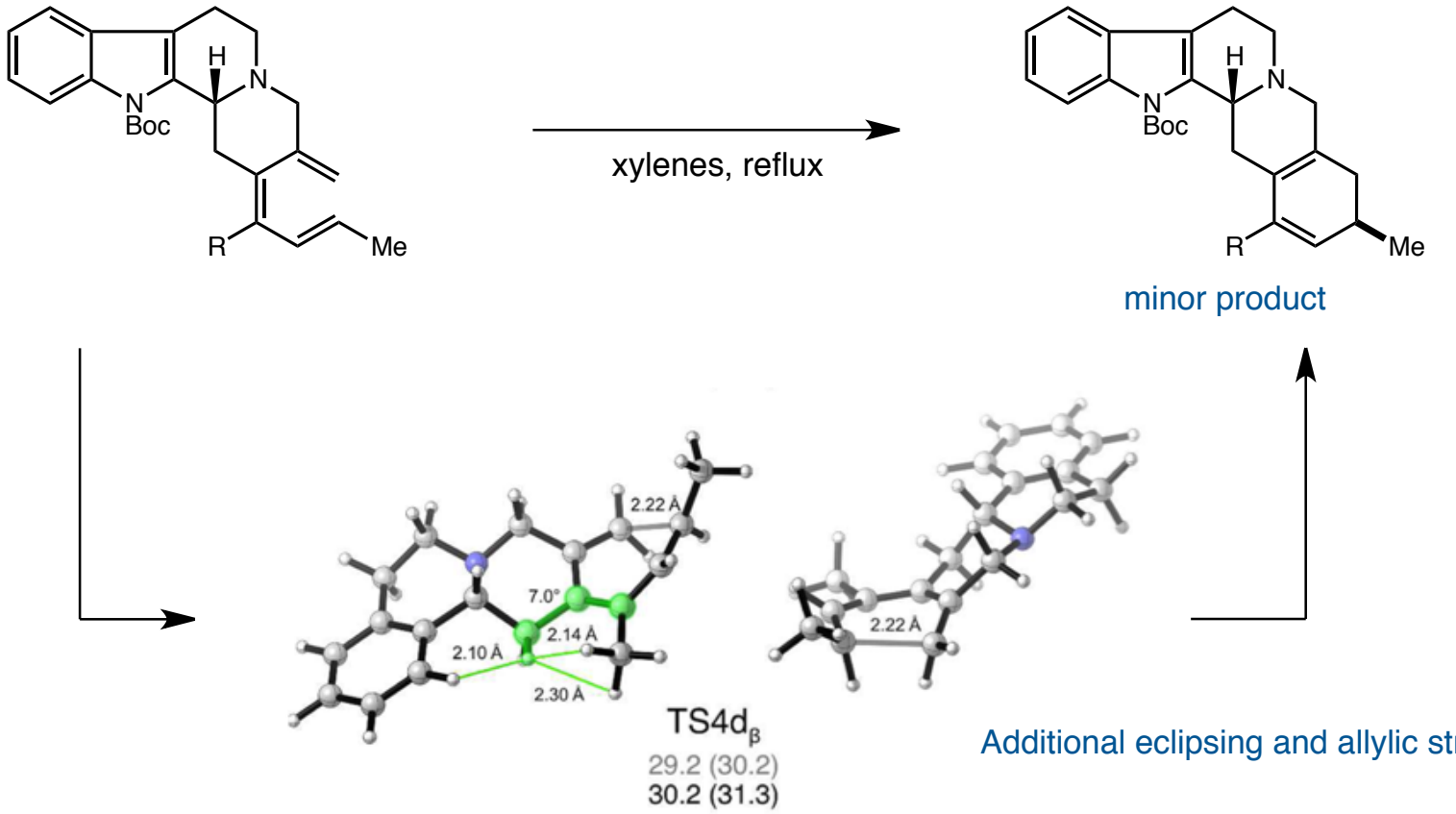

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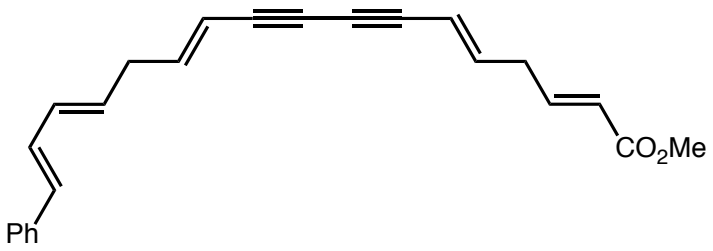
Electrocyclic Reactions in Synthesis

- Nicolaou's key cascade towards endiandric acids B, C, F and G



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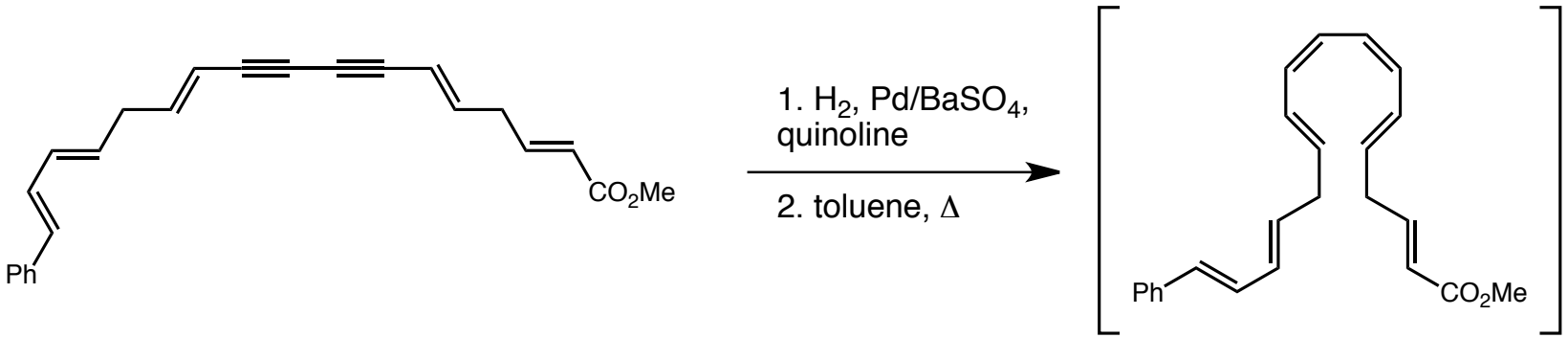

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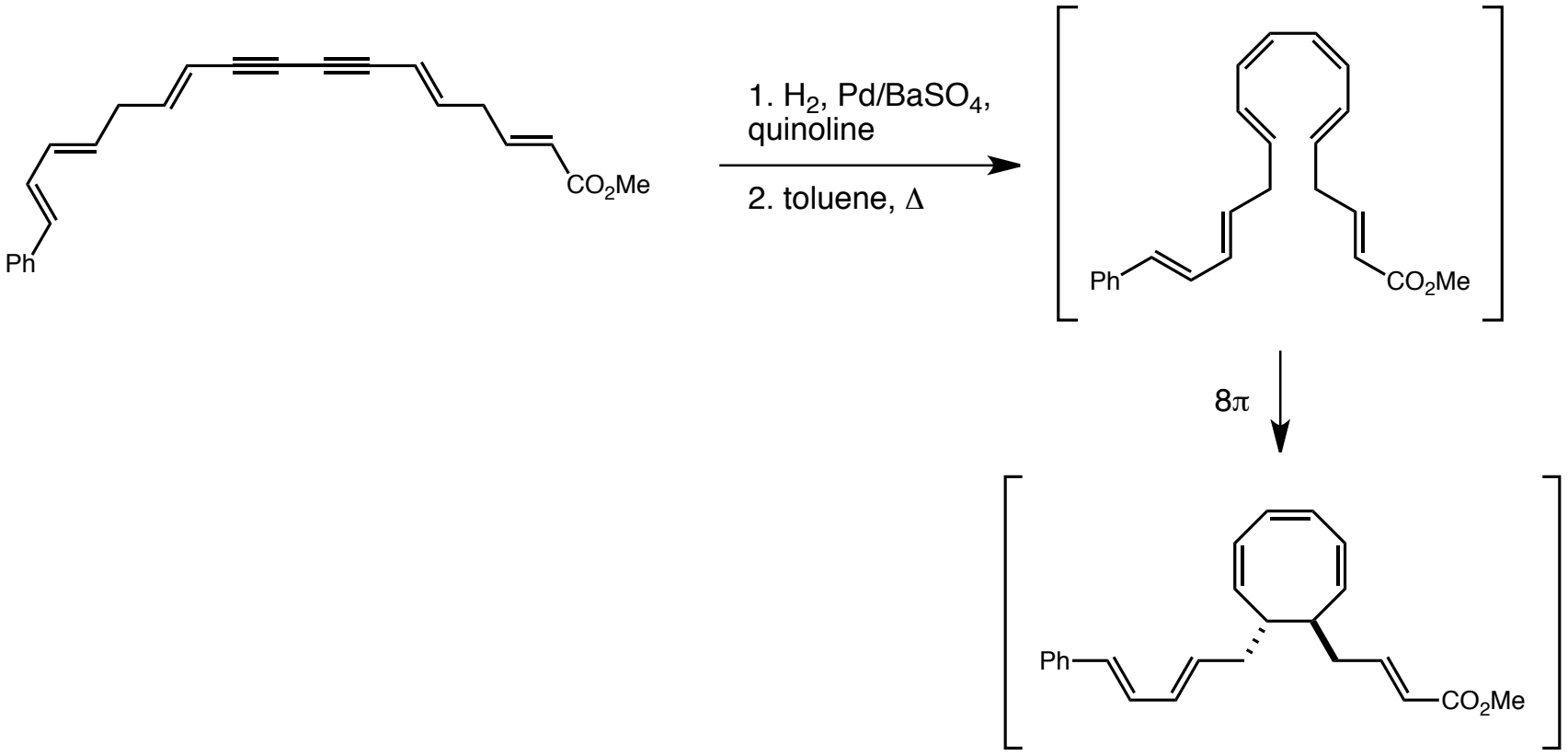

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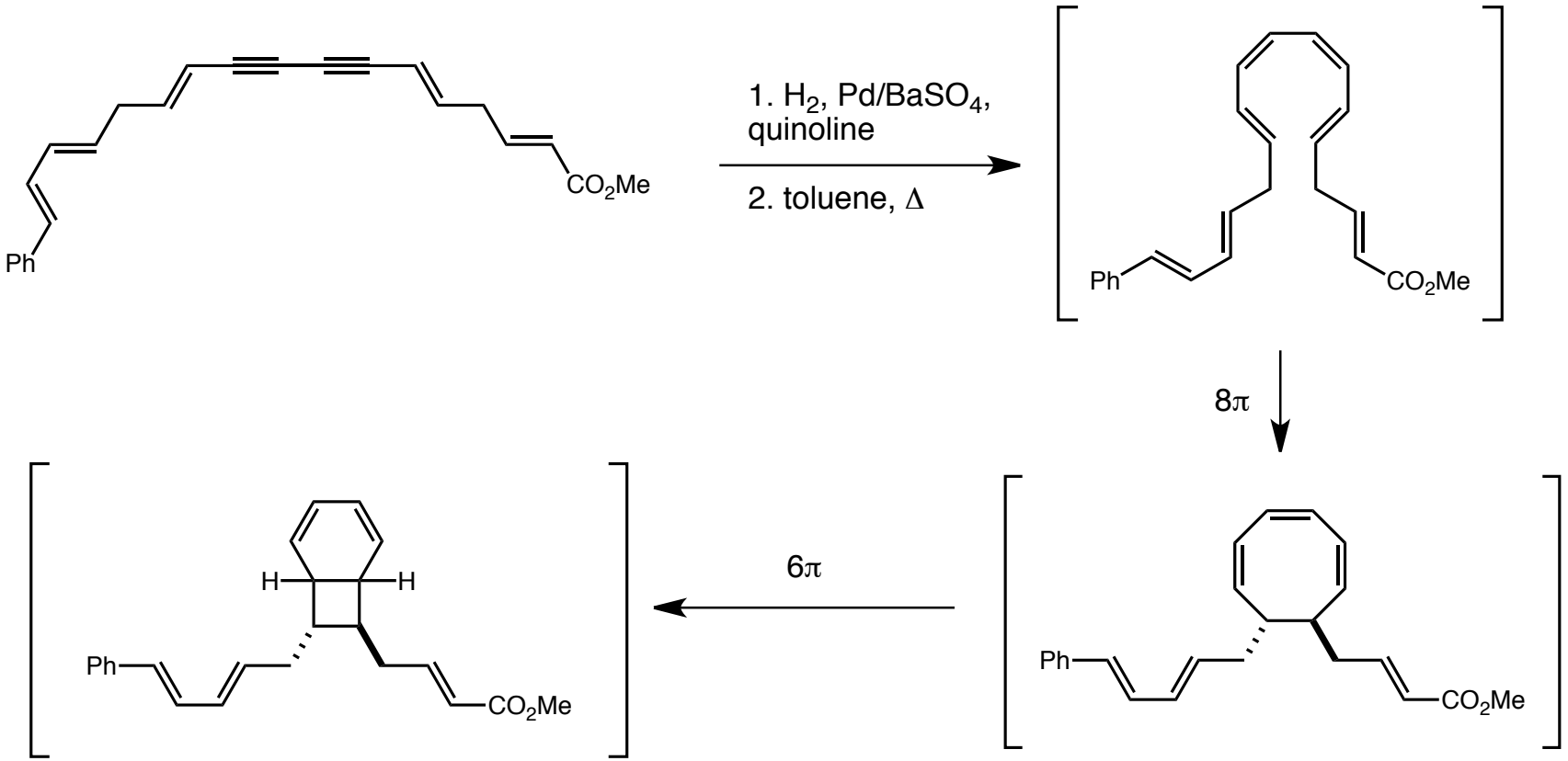

Nicolaou, K. C., Petasis, N. A., Zipkin, R. E., Uenishi, J. *J. Am. Chem. Soc.*, **1982**, *104*, 5555.
Nicolaou, K. C., Petasis, N. A., Uenishi, J., Zipkin, R. E. *J. Am. Chem. Soc.*, **1982**, *104*, 5557.
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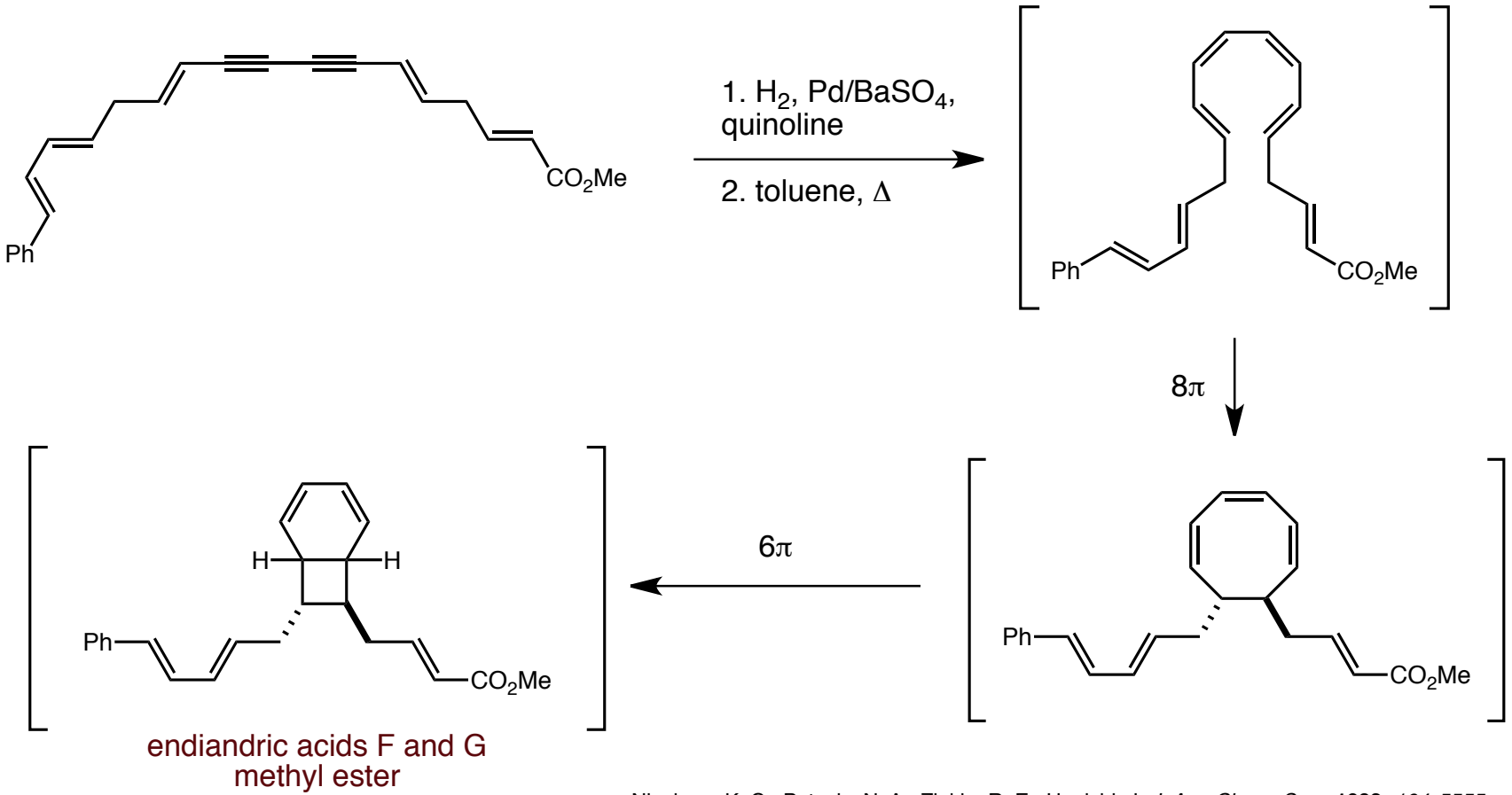
Nicolaou, K. C., Petasis, N. A., Zipkin, R. E. *J. Am. Chem. Soc.*, **1982**, *104*, 5560.

Electrocyclic Reactions in Synthesis

- Nicolaou's key cascade towards endiandric acids B, C, F and G



endiandric acids F and G methyl ester

Nicolaou, K. C., Petasis, N. A., Zipkin, R. E., Uenishi, J. *J. Am. Chem. Soc.*, **1982**, *104*, 5555.
Nicolaou, K. C., Petasis, N. A., Uenishi, J., Zipkin, R. E. *J. Am. Chem. Soc.*, **1982**, *104*, 5557.
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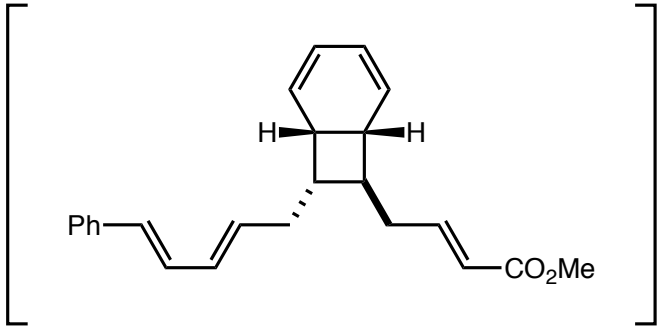
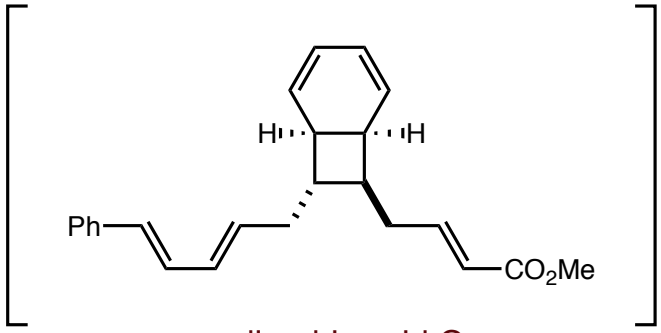
Electrocyclic Reactions in Synthesis

- Nicolaou's key cascade towards endiandric acids B, C, F and G



endiandric acid F
methyl ester



endiandric acid G
methyl ester

Nicolaou, K. C., Petasis, N. A., Zipkin, R. E., Uenishi, J. *J. Am. Chem. Soc.*, **1982**, *104*, 5555.
Nicolaou, K. C., Petasis, N. A., Uenishi, J., Zipkin, R. E. *J. Am. Chem. Soc.*, **1982**, *104*, 5557.
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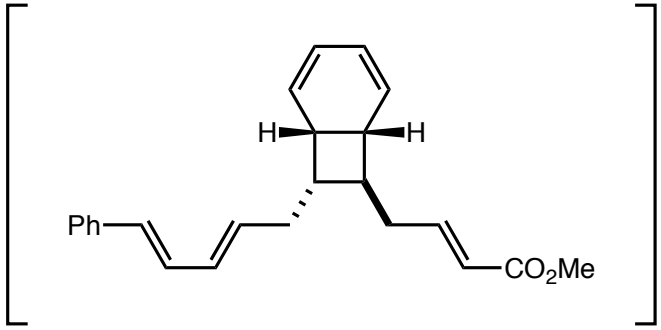
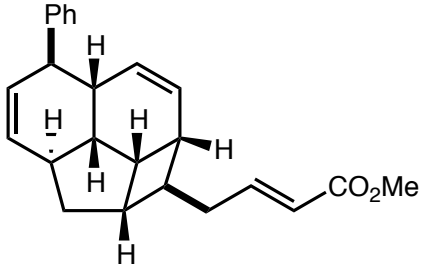
Electrocyclic Reactions in Synthesis

- Nicolaou's key cascade towards endiandric acids B, C, F and G

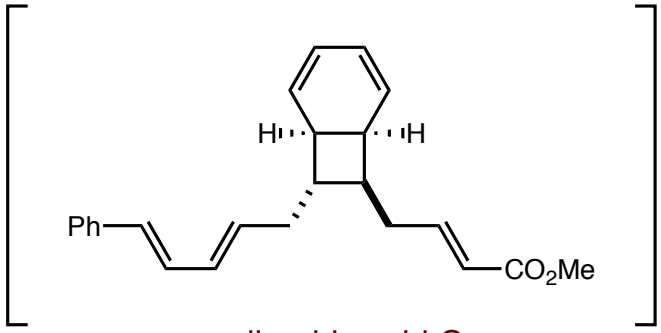


endiandric acid F
methyl ester

[4+2]



endiandric acid B
methyl ester



endiandric acid G
methyl ester

Nicolaou, K. C., Petasis, N. A., Zipkin, R. E., Uenishi, J. *J. Am. Chem. Soc.*, **1982**, *104*, 5555.
Nicolaou, K. C., Petasis, N. A., Uenishi, J., Zipkin, R. E. *J. Am. Chem. Soc.*, **1982**, *104*, 5557.
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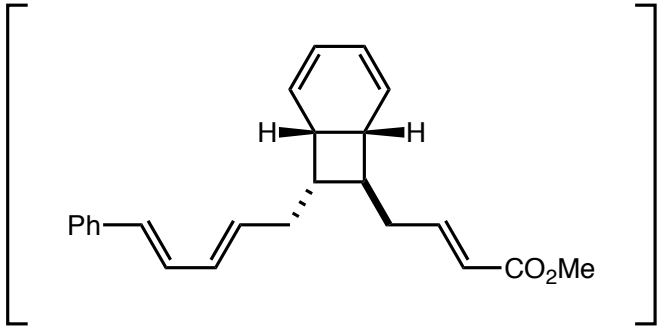
Nicolaou, K. C., Petasis, N. A., Zipkin, R. E. *J. Am. Chem. Soc.*, **1982**, *104*, 5560.

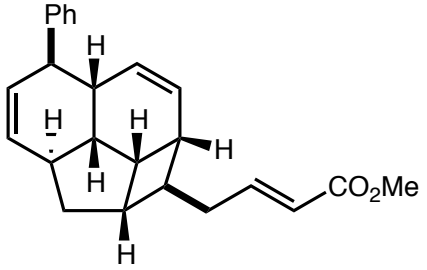
Electrocyclic Reactions in Synthesis

- Nicolaou's key cascade towards endiandric acids B, C, F and G

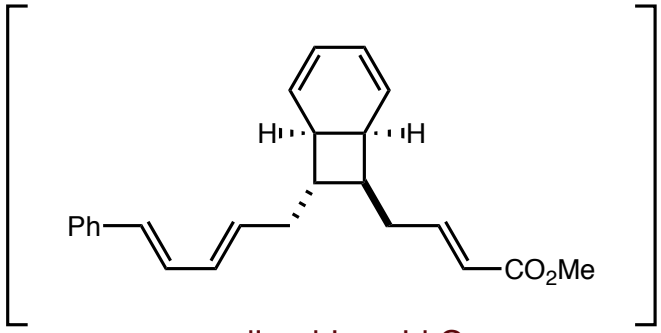


endiandric acid F
methyl ester

[4+2]

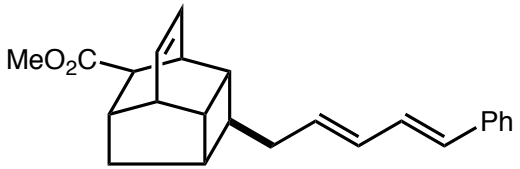


endiandric acid B
methyl ester



endiandric acid G
methyl ester

[4+2]



endiandric acid C
methyl ester

Nicolaou, K. C., Petasis, N. A., Zipkin, R. E., Uenishi, J. *J. Am. Chem. Soc.*, **1982**, *104*, 5555.
Nicolaou, K. C., Petasis, N. A., Uenishi, J., Zipkin, R. E. *J. Am. Chem. Soc.*, **1982**, *104*, 5557.
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Nicolaou, K. C., Petasis, N. A., Zipkin, R. E. *J. Am. Chem. Soc.*, **1982**, *104*, 5560.