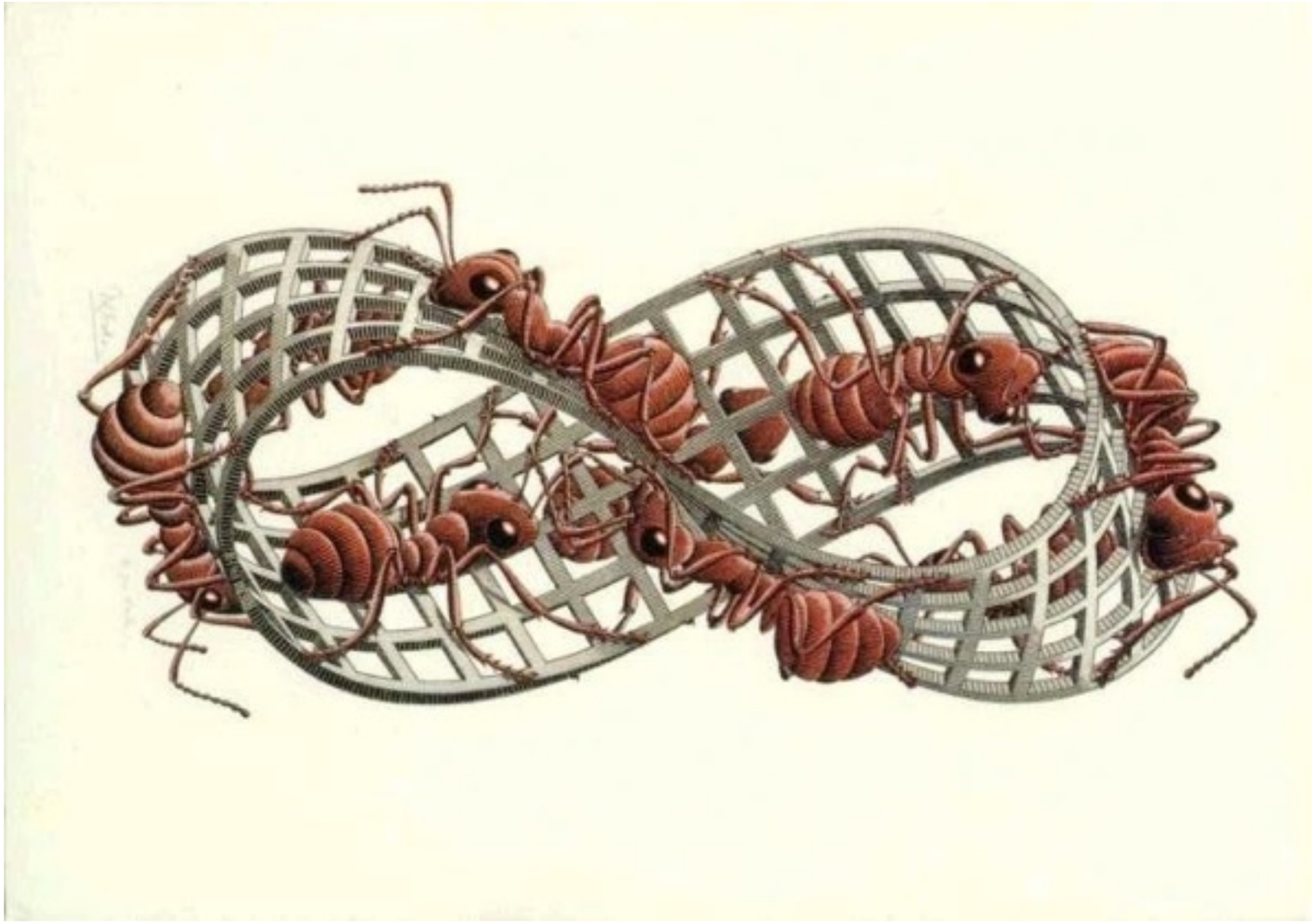


Moebius Strip
M. C. Escher, 1963

Universitat de Barcelona

Dr. Pere Romea
Department of Organic Chemistry

2. Pericyclic Reactions

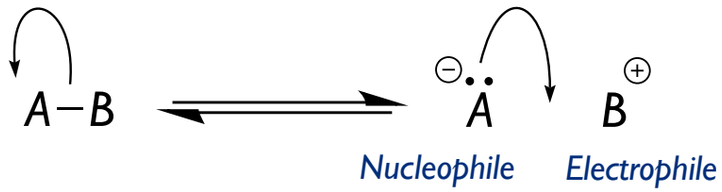
Organic Synthesis 2014-2015 Autumn Term

The organic reactions can be classified according to their mechanism ...

1. Ionic or polar reactions ...

... the bond-forming or -breaking processes

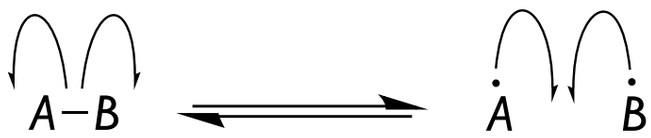
are associated to pair of electrons



2. Radical reactions ...

... the bond-forming or -breaking processes

are associated to single electrons



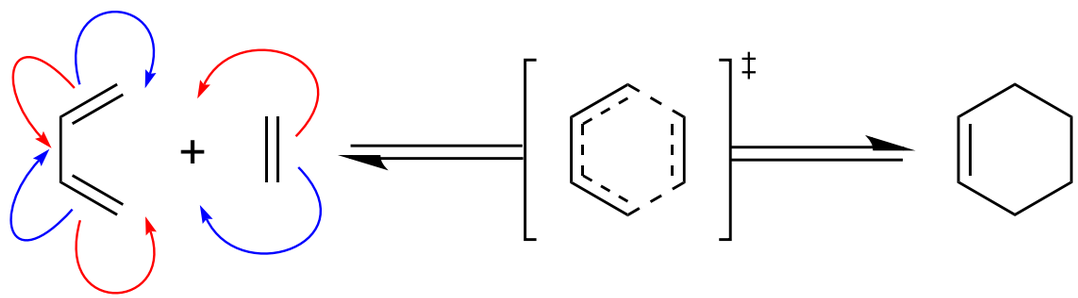
3. Pericyclic reactions ...

... the bond-forming or -breaking processes

take place in a ***concerted way****,*

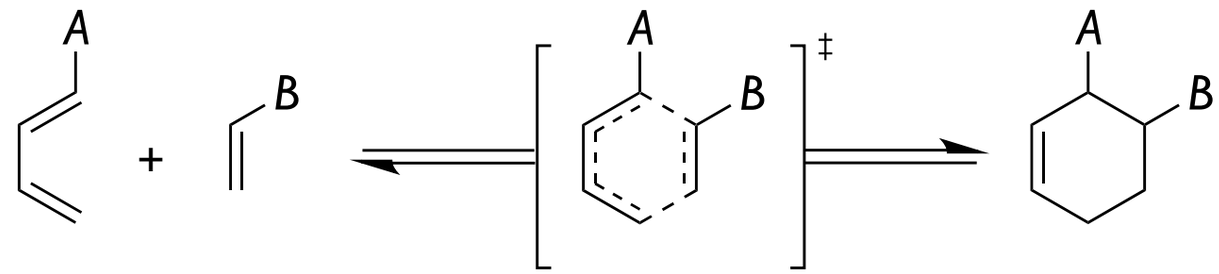
without the formation of any intermediate

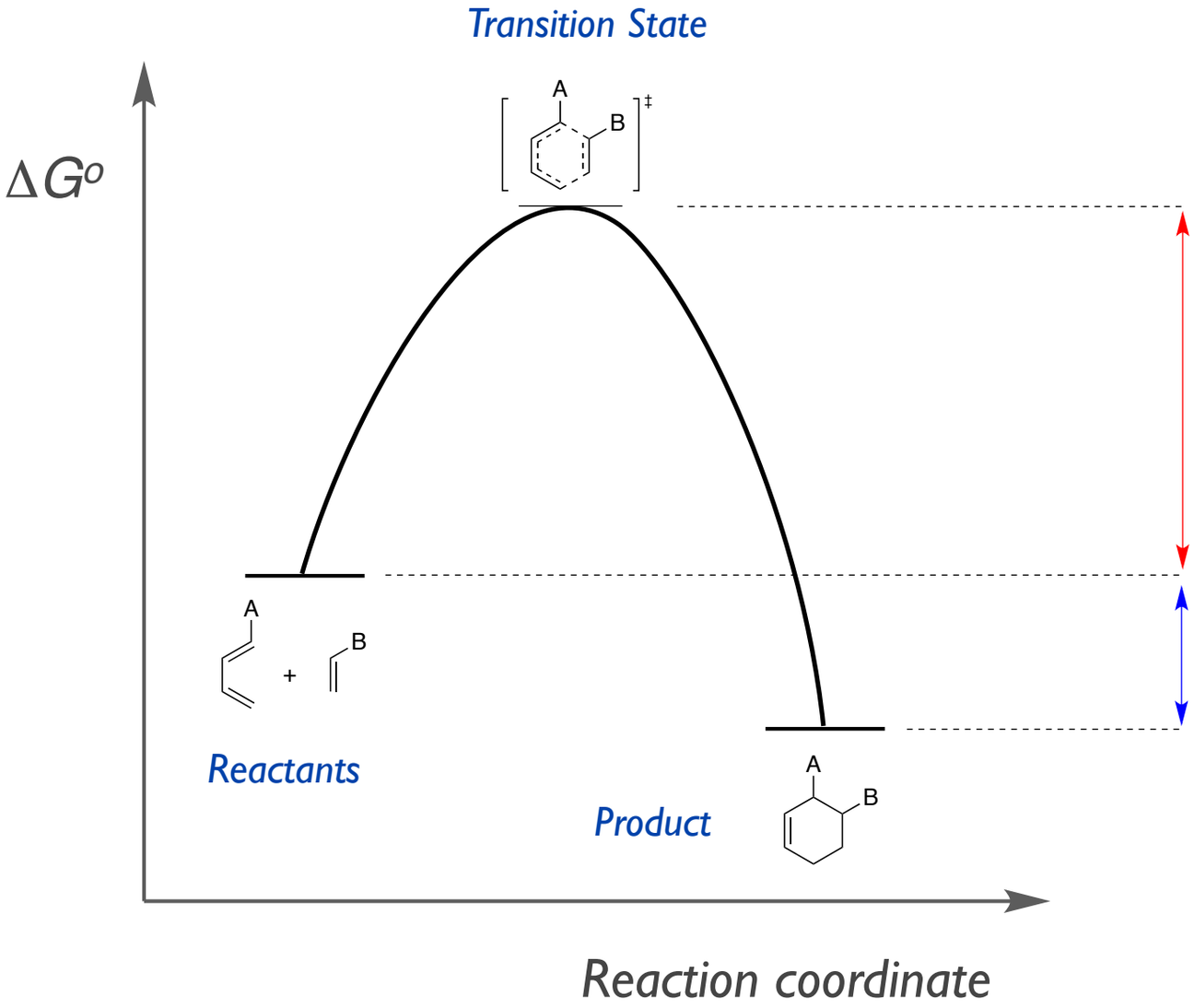
through a ***cyclic transition state***



A cycloaddition as a model

Introduction: Key Concepts





Thermal

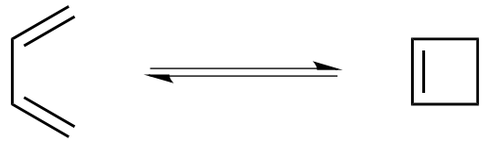
... ground electronic state

Photochemical

... excited electronic state

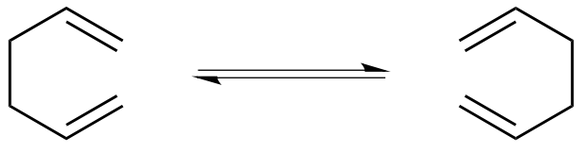
1. Electrocyclic Reactions ...

... ring formation from an open-chain conjugated system



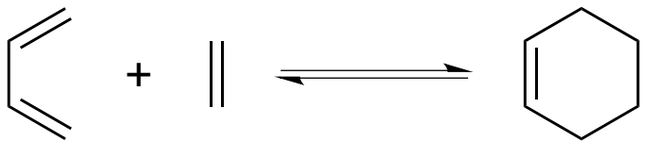
2. Sigmatropic Rearrangements ...

... intramolecular isomerizations that formally involve the migration of a σ bond flanked by one or more π systems

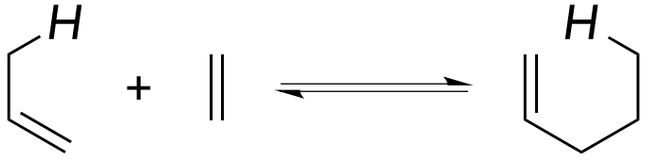


3. Cycloadditions ...

... ring formation from two components, coming together to form two new σ bonds, one at each end of both components



4. Group Transfer Reactions ...



Pericyclic reactions are ...

- *concerted transformations*
- *proceeding through cyclic transition states without reacting intermediates*
- *in a highly selective manner*

Conservation of Orbital Symmetry

A ground-state pericyclic change is symmetry allowed when the total number of $(4q + 2)_s$ and $(4r)_a$ component is odd

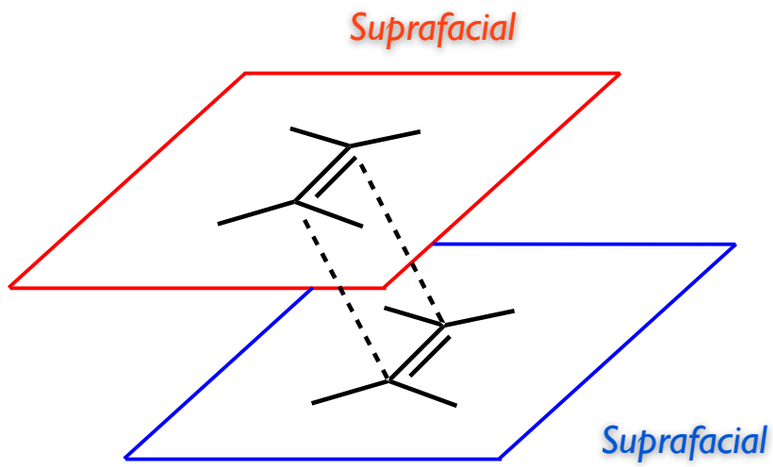
The Conservation of Orbital Symmetry, Woodward, R. B.; Hoffmann, R. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781
Woodward, R. B.; Hoffmann, R. *Acc. Chem. Res* **1968**, *1*, 17

Allowed o *permesa*, *if it proceeds easily according to the conservation of orbital symmetry*

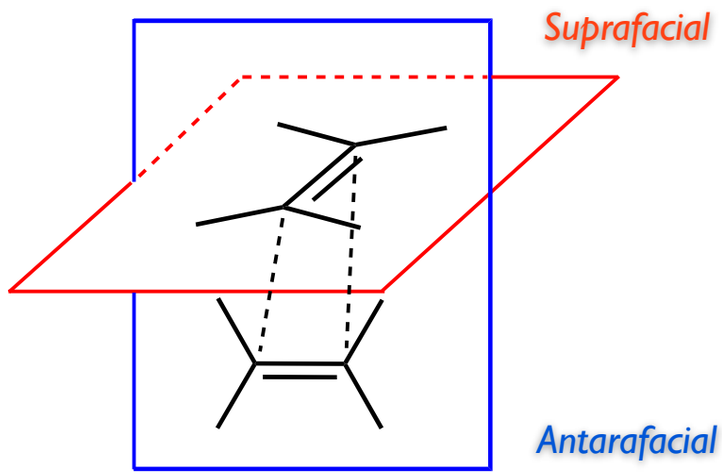
Forbidden o *prohibida*, *if harsh conditions are required because the conservation of orbital symmetry rules are not met*

A ground-state pericyclic change is symmetry allowed when the total number of $(4q + 2)_s$ and $(4r)_a$ component is odd

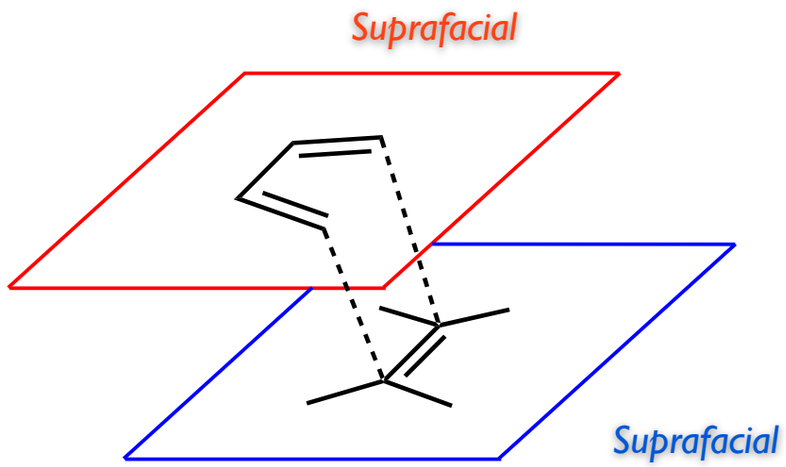
Suprafacial *Antarafacial*



1 $(4q+2)_s$
1 $(4q+2)_s$ ✗



1 $(4q+2)_s$
0 $(4r)_a$ ✓

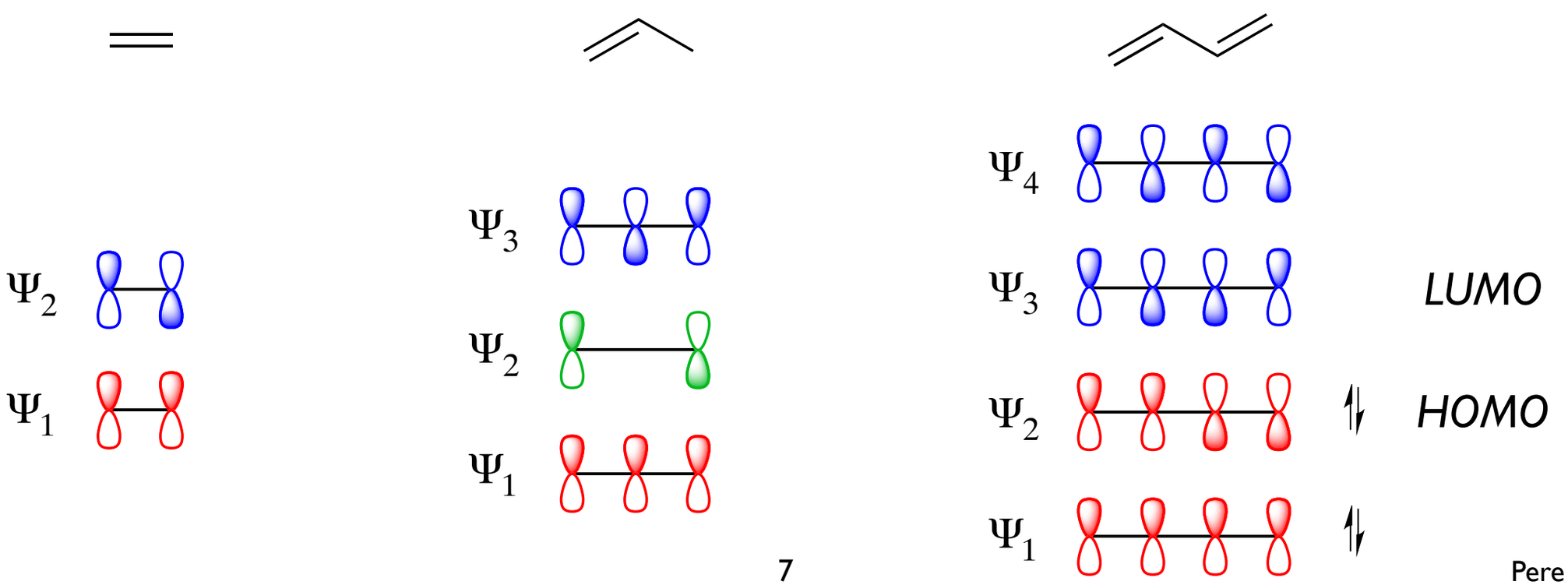


1 $(4q+2)_s$
0 $(4r)_a$ ✓

Differents models are used to apply the ideas of the conservation of orbital symmetry

- *Electronic state correlation diagrams*
- *Frontier Orbitals / HOMO-LUMO (Fukui-Klopman-Salem)*
- *Aromaticity of transition states / Hückel-Moebius (Dewar-Zimmermann)*

... The orbital topology plays a crucial role



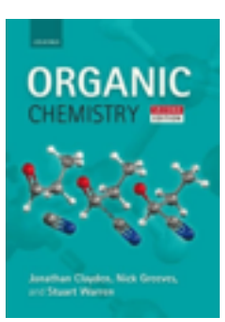
- *Electronic state correlation diagrams*
- ***Frontier Orbitals / HOMO-LUMO (Fukui-Klopman-Salem)***
- *Aromaticity of transition states*

... with the Diels-Alder reaction, the Claisen rearrangement, and the oxy-Cope rearrangement providing the majority of reactions that are used "day to day" in the chemistry lab

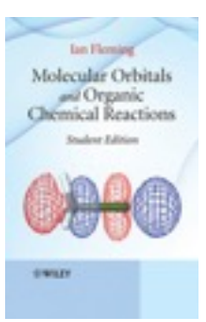
Anslyn & Dougherty. *Modern Physical Organic Chemistry* p 878

Look at Química Orgànica III

Chaps. 7/29



Chaps. 34/35



Chap. 6

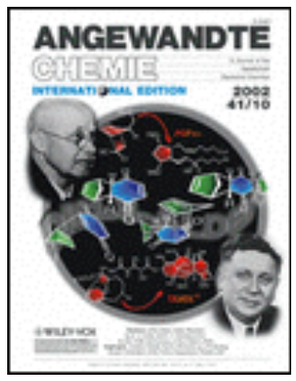
The venerable Diels-Alder reaction: a straightforward route to six-membered rings

The Nobel Prize in Chemistry 1950 ...

Otto Diels

Kurt Alder

... for their discovery and development of the diene synthesis



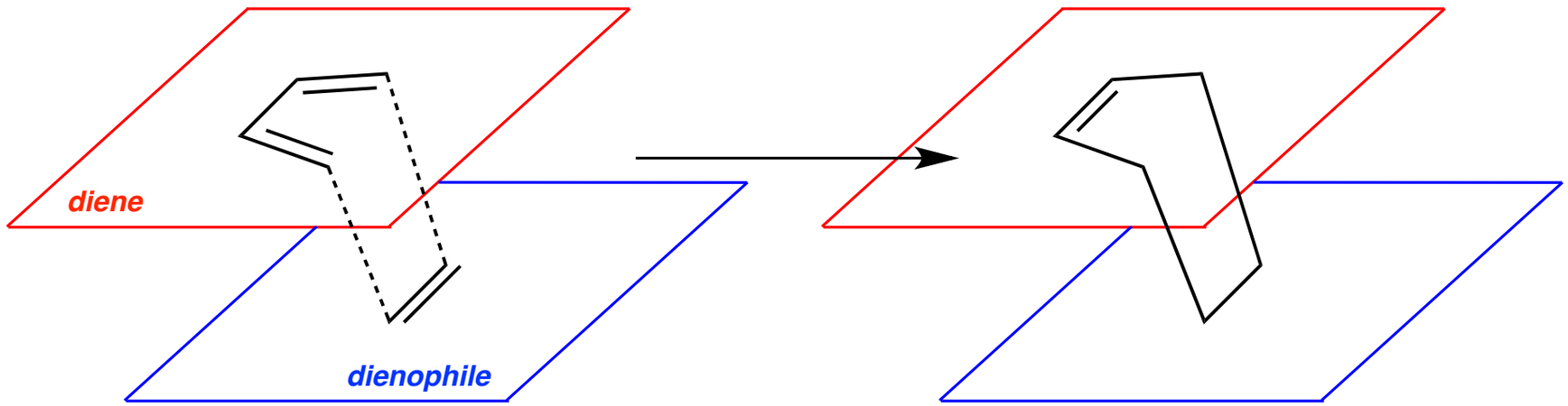
For a review on the Diels-Alder reaction in total synthesis:

Nicolaou, K. C. *ACIE* **2002**, *41*, 1668

For a recent view on industrial applications of the Diels-Alder reaction:

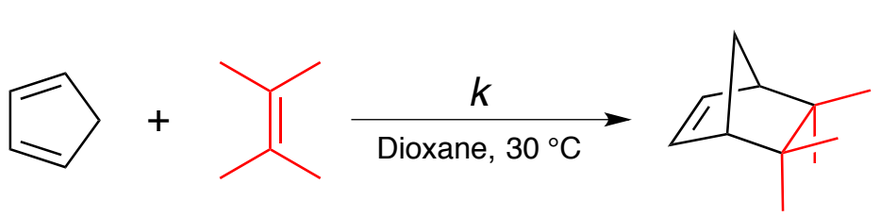
Funel, J.-A. *ACIE* **2013**, *52*, 3822

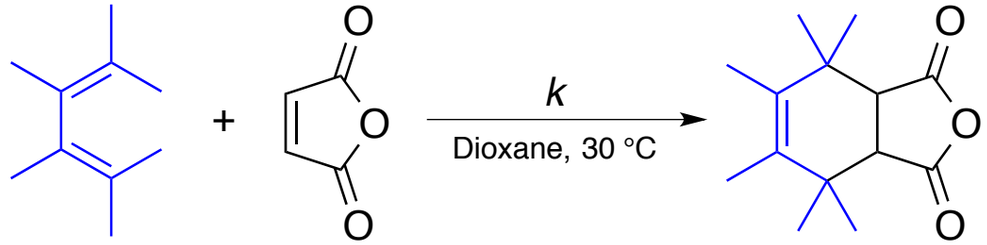
The venerable Diels-Alder reaction is a [4π_s + 2π_s] cycloaddition



Remember that an alkyne can also participate in the process

*The kinetics of the reaction depends on **electronic** … and conformational issues.*





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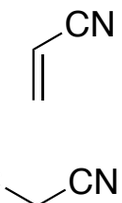

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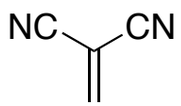
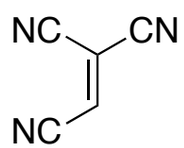
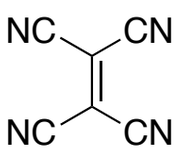


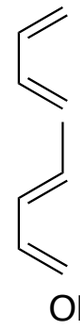
$5 \cdot 10^4$



$5 \cdot 10^5$



$5 \cdot 10^7$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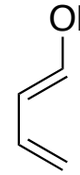
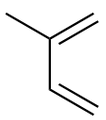
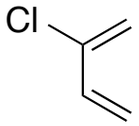


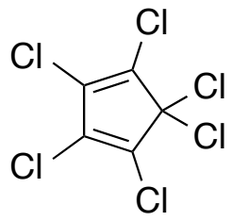
12.3


2.25



0.1


1350



~ 0

Essential:

electronically rich diene & electronically poor dienophile

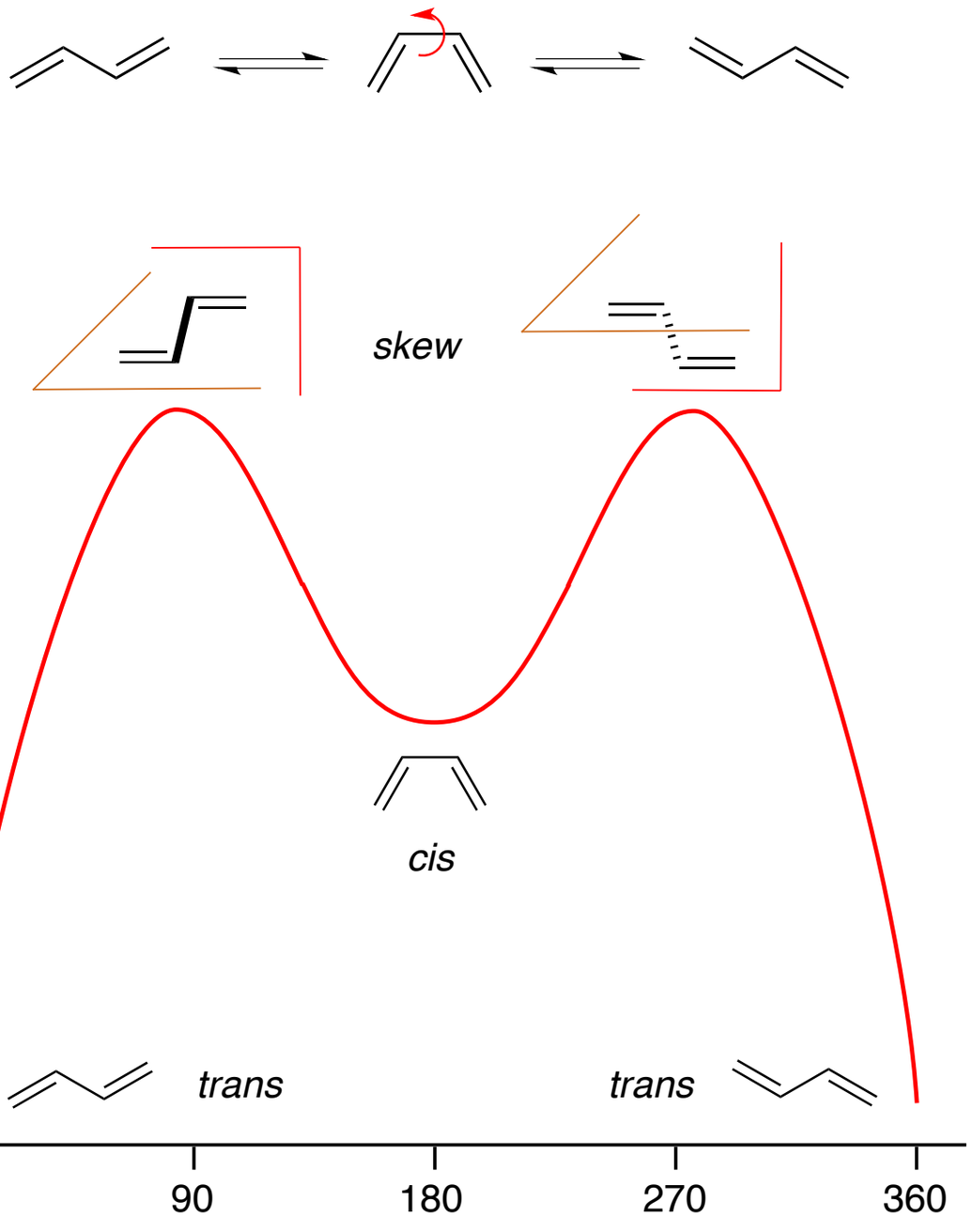
Complementary character.

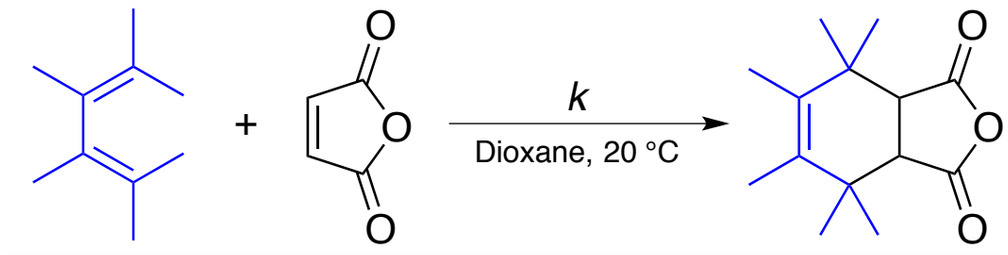
For reviews on mechanistic aspects of the Diels-Alder reaction:

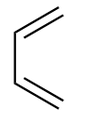
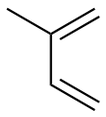
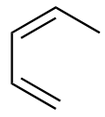
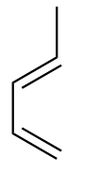
Sauer, *J. ACIEE* **1967**, *6*, 16 ; Sustmann, R. *ACIEE* **1980**, *19*, 779

Diels-Alder Reaction: Kinetics

*The kinetics of the reaction depends on electronic and **conformational** issues.*

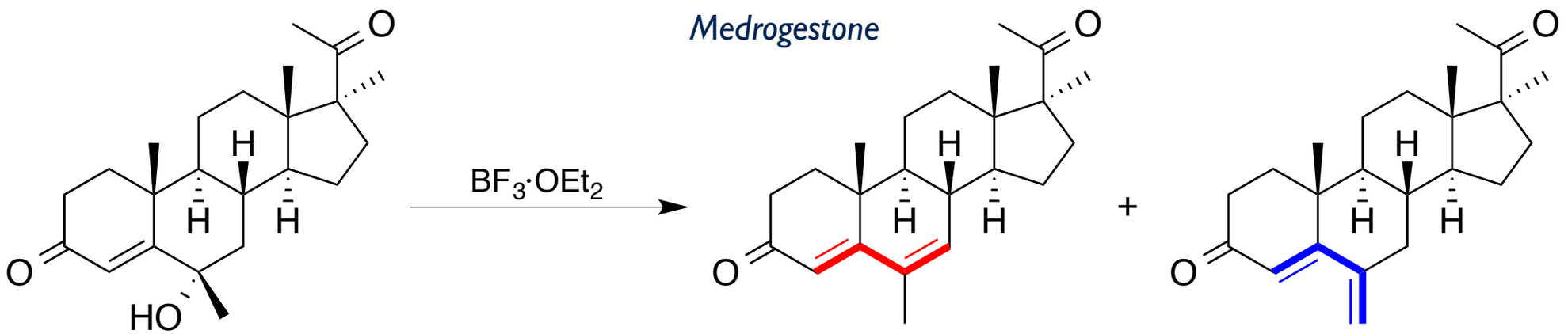




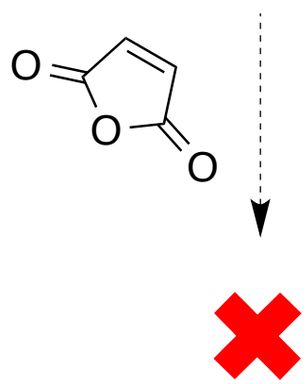
	1
	2.25
	~ 0
	3
	1350

For a conformational analysis on 1,3-butadienes: Squillacote, M. E. *JOC* **2005**, *70*, 6564

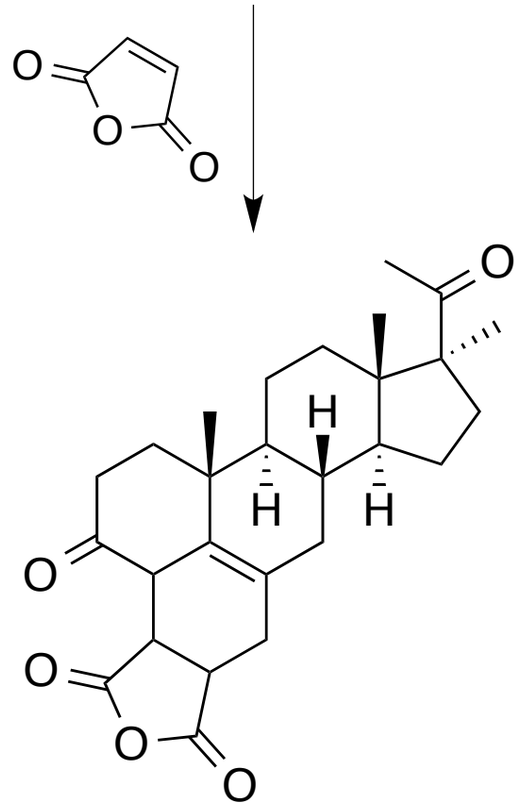
Occasionally, the lack of conformational freedom can be useful …



trans *conformation unreactive*



cis *conformation reactive*

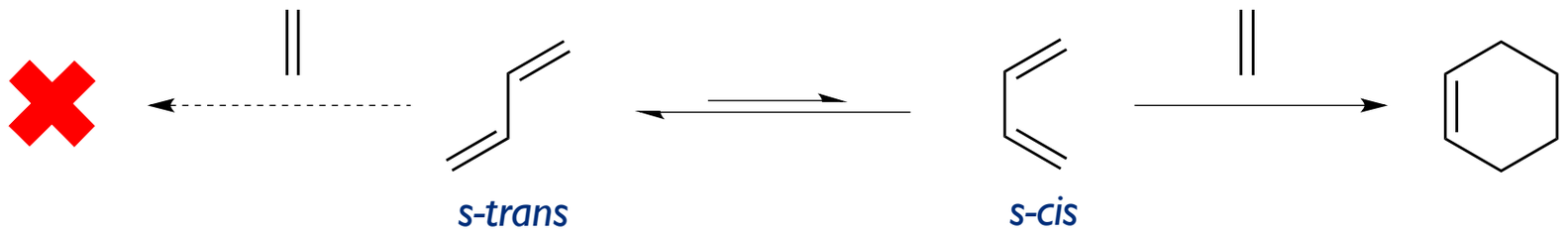


Winkley, M.W.; Mitchell, R. D. (American Home Products)

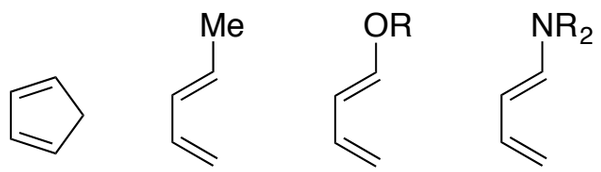
US5428151A, **1995**

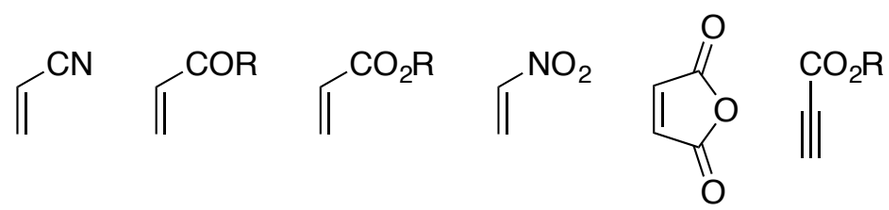
*In Diels-Alder reactions under **Normal electronic demand***

- *diene must be able to achieve the s-cis conformation*

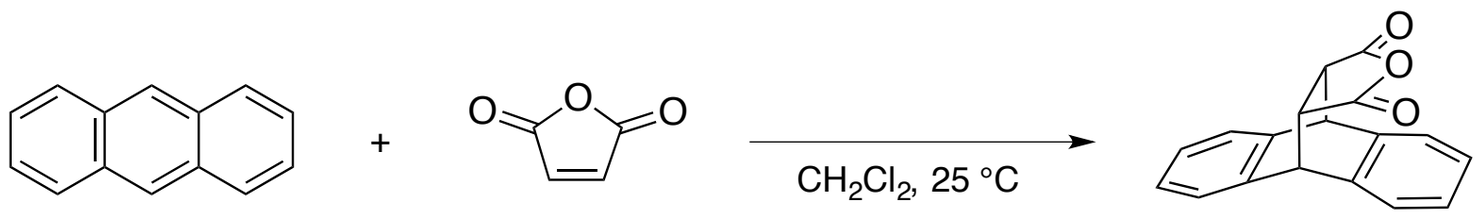


- *diene should contain electrondonating groups (EDG); dienophile, electronwithdrawing groups (EWG)*





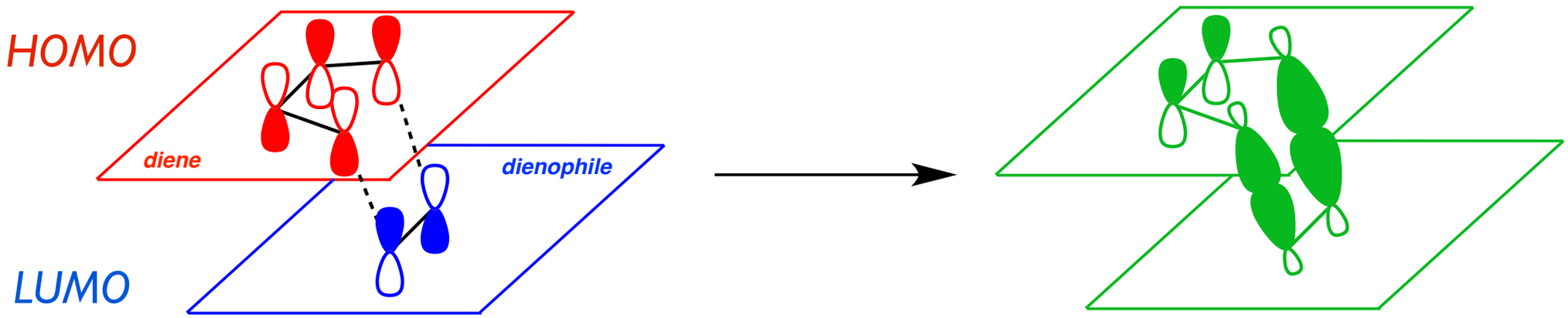
- *Lewis acids catalyze such cycloadditions*



Without $AlCl_3$ $t_{1/2} \sim$ 2400 h

With 1 equiv $AlCl_3$ $t_{1/2} < 1$ min

The mechanistic pathway of the Diels-Alder reaction can be rationalized through FMO analysis

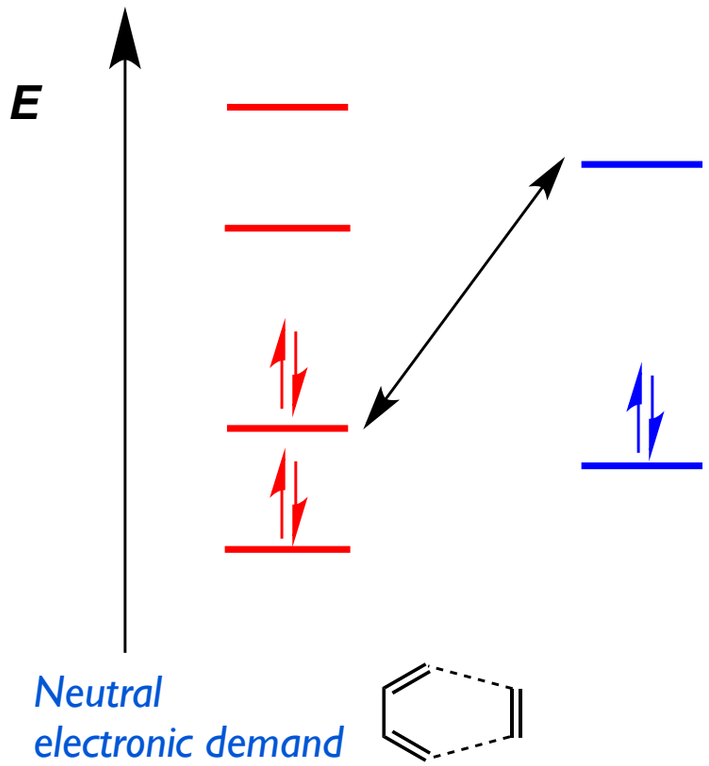


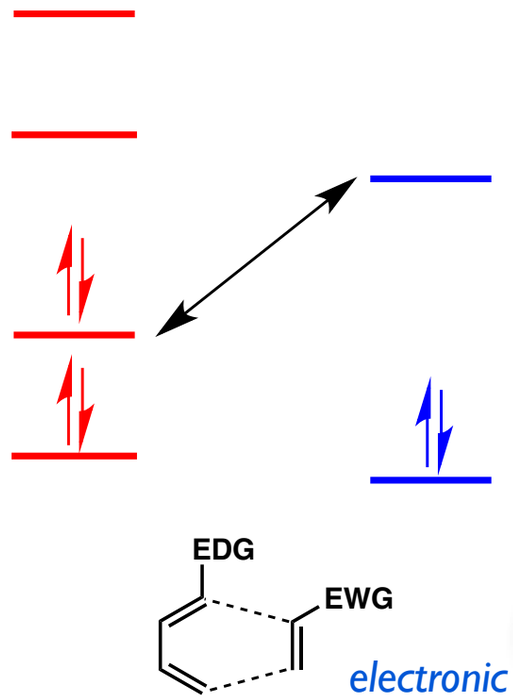
Thermodynamics: *broken bonds, 3 π*
new bonds, 2 σ + 1 π

2 σ – 2 π

The critical energy difference:
E (LUMO) - E (HOMO)
The closer the two orbitals are in energy, the better they interact

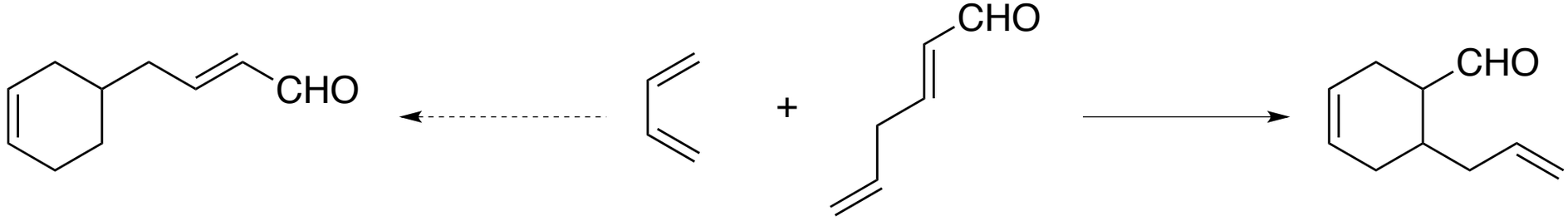
Kinetics: *As ΔE decreases for the relevant ground state FMOs, reaction rate increases*

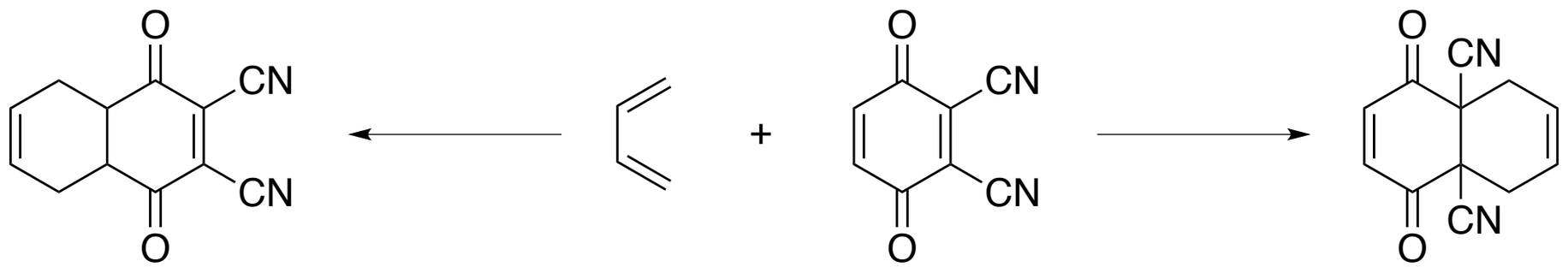




The HOMO-LUMO interaction and the cyclic transition state provide outstanding levels of ***selectivity*** *...*

- ***Chemoselectivity (Siteselectivity):*** *rich diene / poor dienophile*

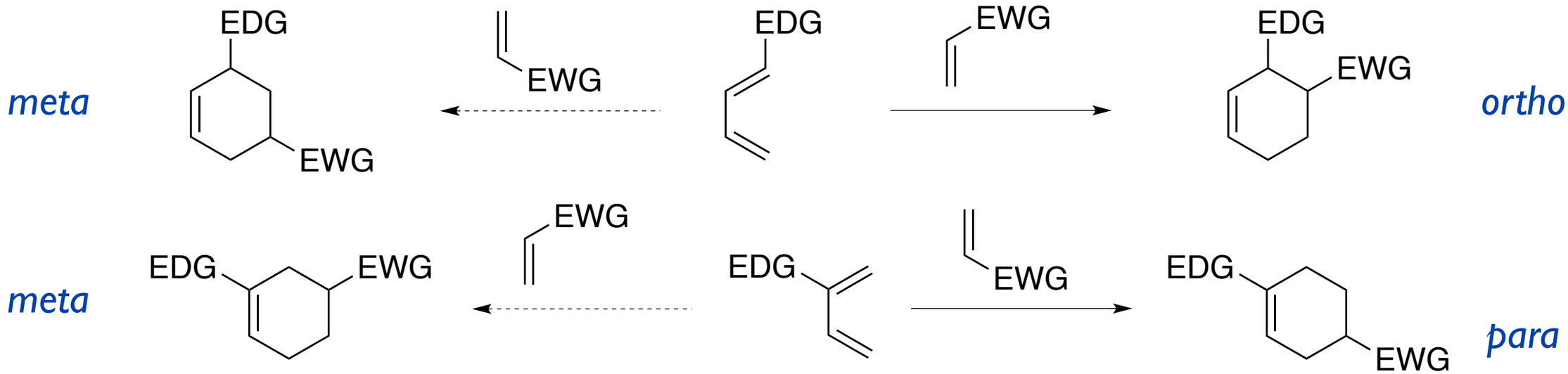


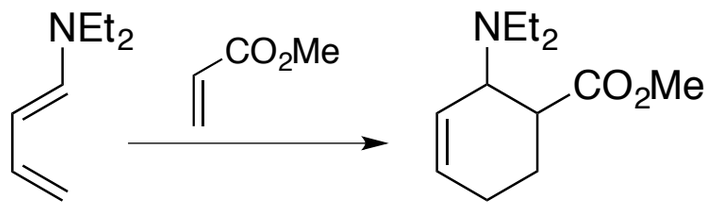


16%

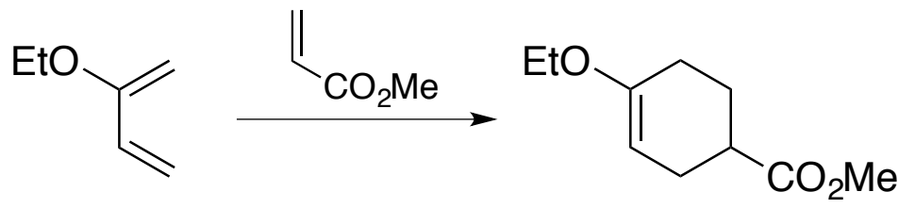
62%

Regioselectivity: ortho-para rule



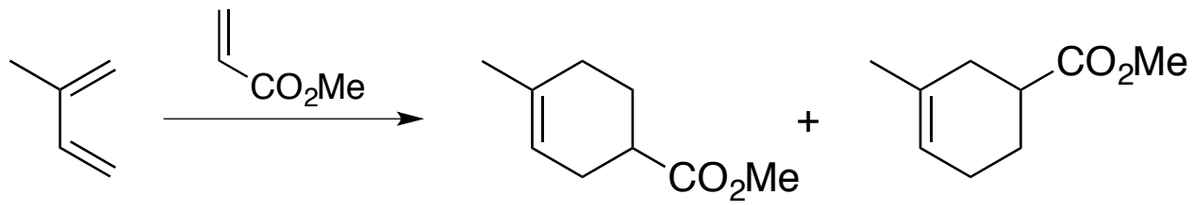


Single product



Single product

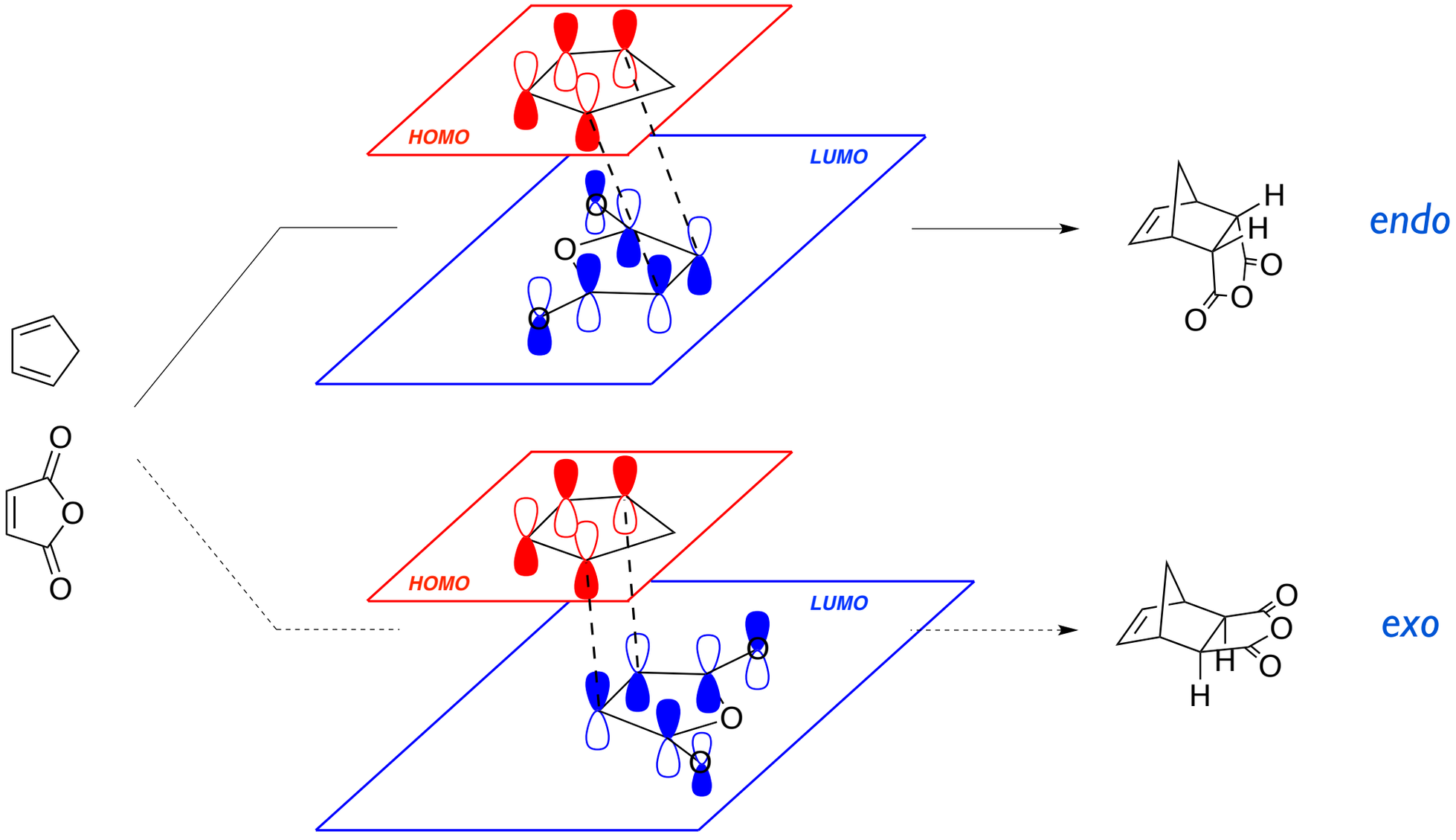
Lewis acids improve the regioselectivity



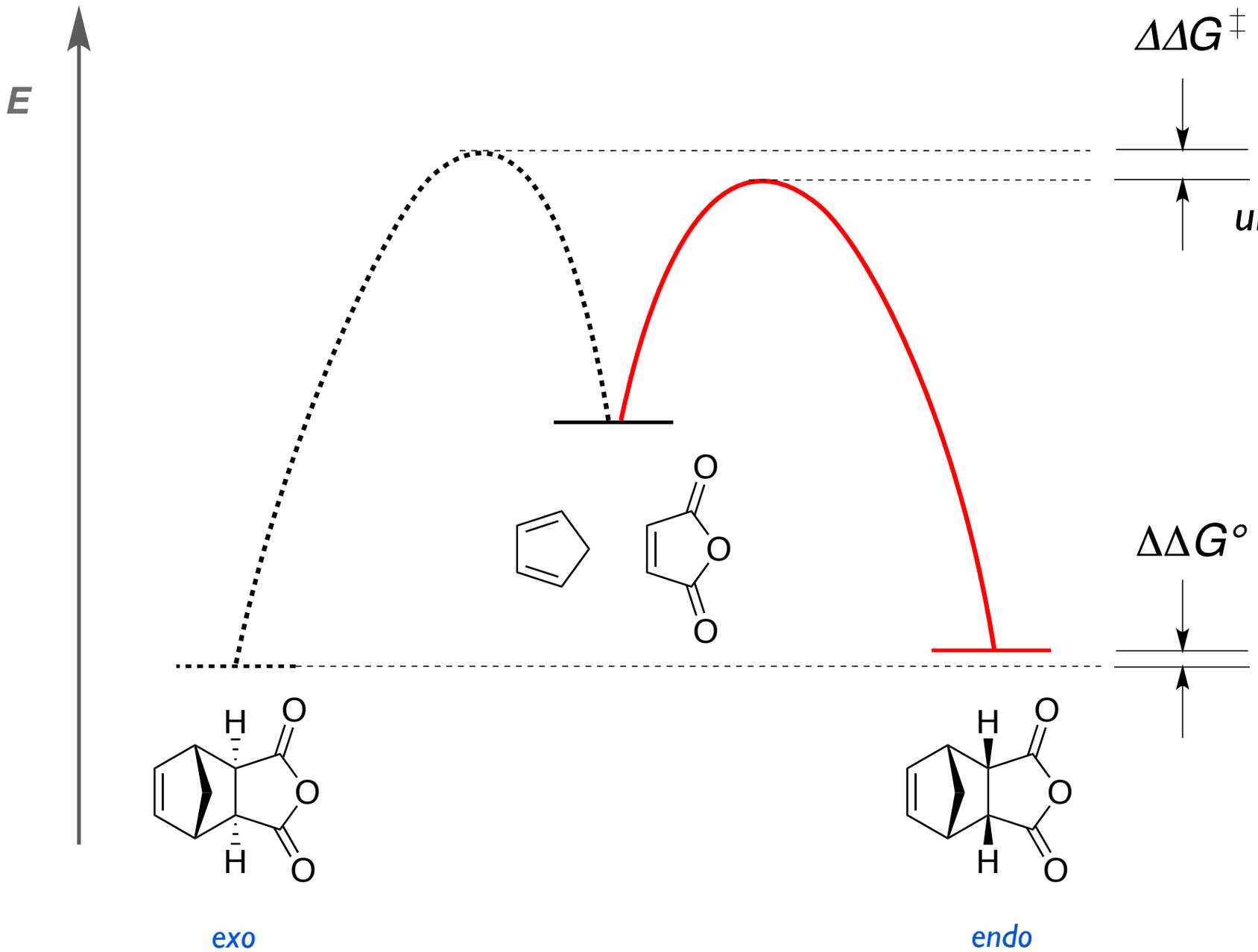
para *meta*

Without Lewis acid, 120 °C, 6 h	*70*	*30*
1 eq $AlCl_3$, 20 °C, 3 h	*95*	*5*

Stereoselectivity: endo rule



Kinetic vs Thermodynamic Control



exo

endo

*If equilibrium cannot be reached under the experimental conditions, the **endo** isomer predominates*

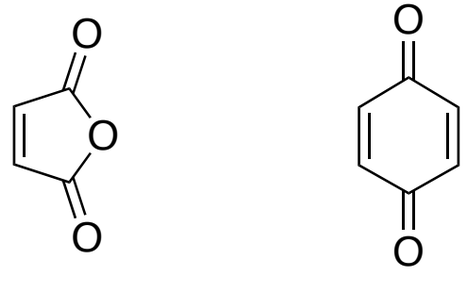
Kinetic Control

*Instead, the **exo** isomer predominates at equilibrium*

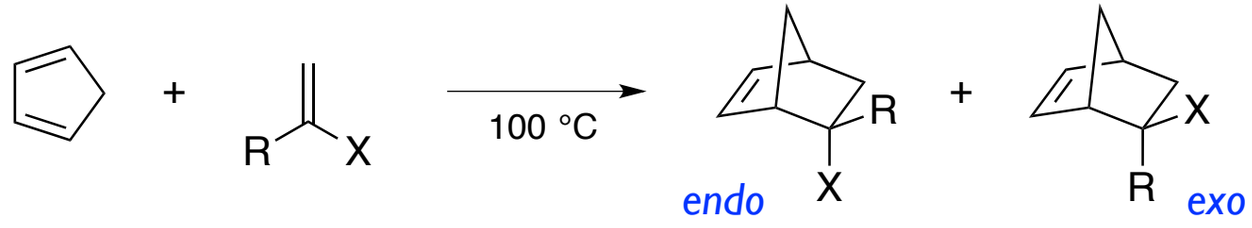
Thermodynamic Control

Diels-Alder Reaction: Stereoselectivity

- *Endo stereoselectivity is excellent with planar dienophiles*

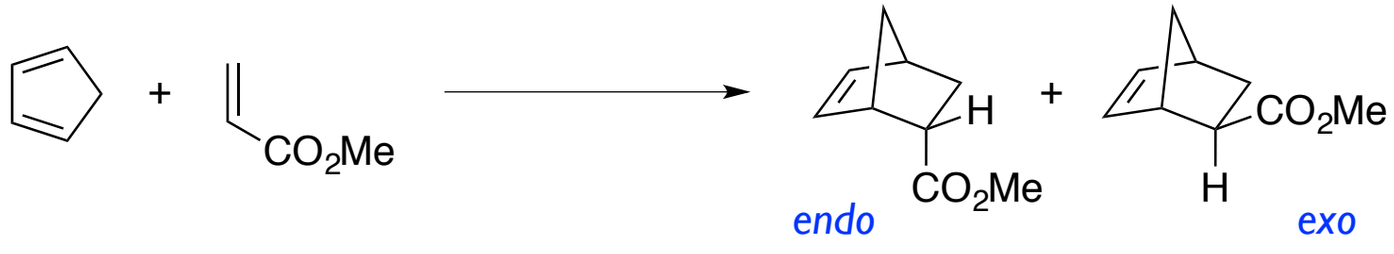


- *Exo diastereomers are preferred with α substituted dienophiles*



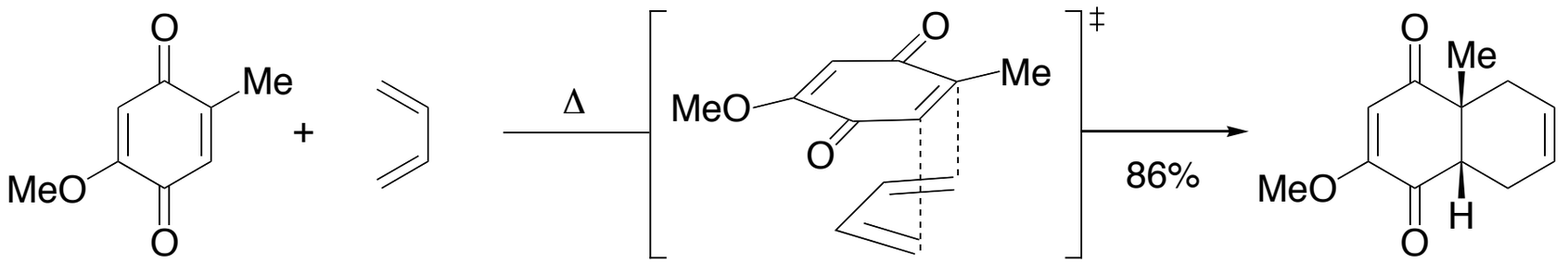
R	X	*endo* : *exo*
H	CN	55 : 45
H	COOMe	71 : 29
H	CHO	71 : 29
Me	CN	16 : 84
Me	COOMe	32 : 68
Me	CHO	24 : 76

- *Lewis acids improve endo stereoselectivity*

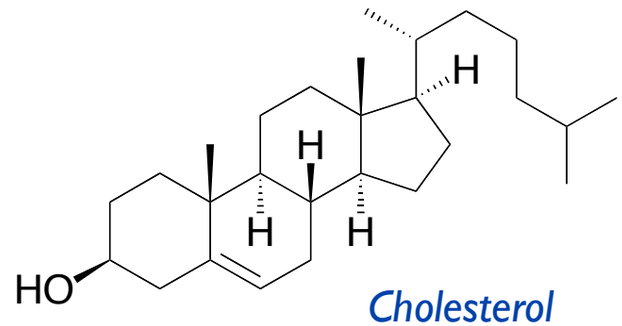


	endo : *exo*
CH_2Cl_2, 0 °C	80 : 20
C_6H_6, $SnCl_4$, 25 °C	95 : 5

Classical syntheses by Woodward took advantage of Diels-Alder reaction ...



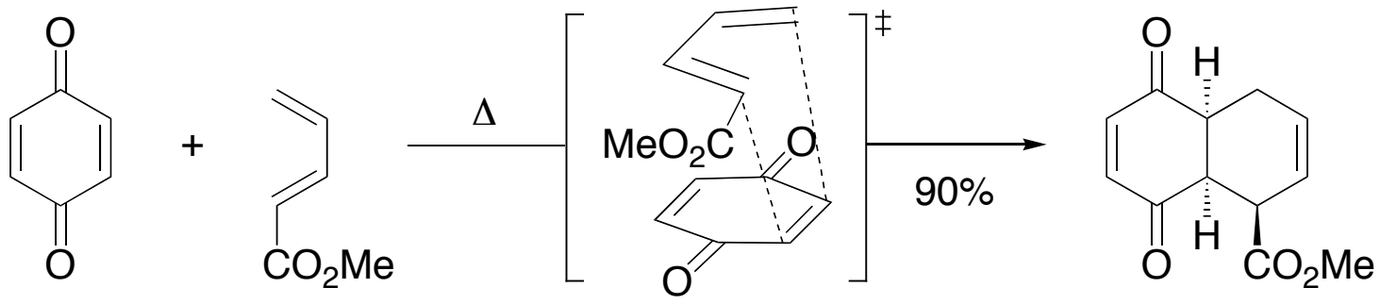
endo TS



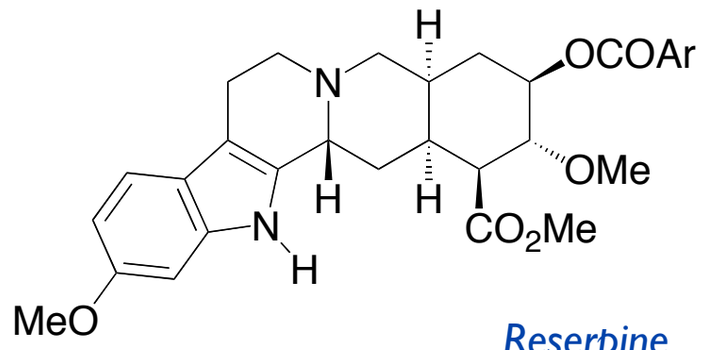
Cholesterol

Woodward, R. B. *JACS* **1952**, *74*, 4223

... even with dienes containing EWG groups ...



endo TS



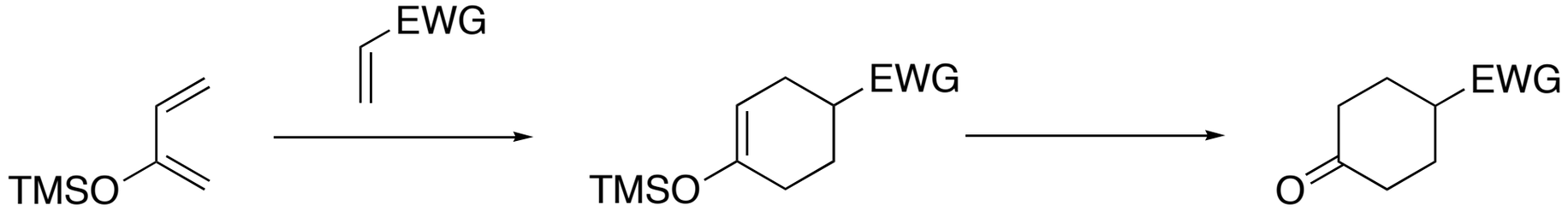
Reserpine

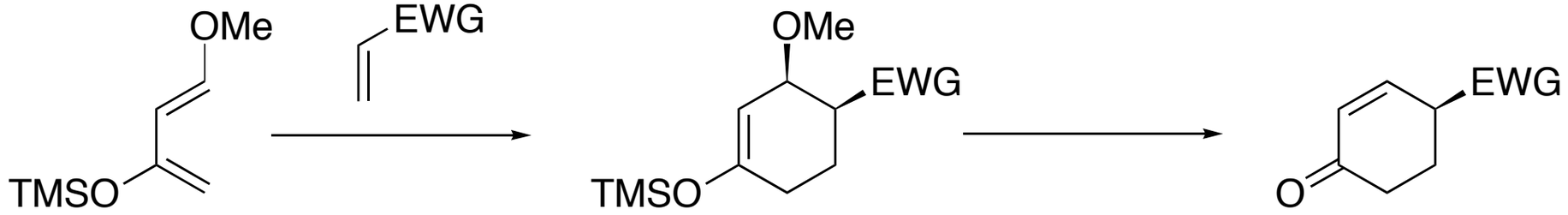
Woodward, R. B. *JACS* **1956**, *78*, 2023, 2657

For a review on quinones as dienophiles in Diels-Alder reaction:

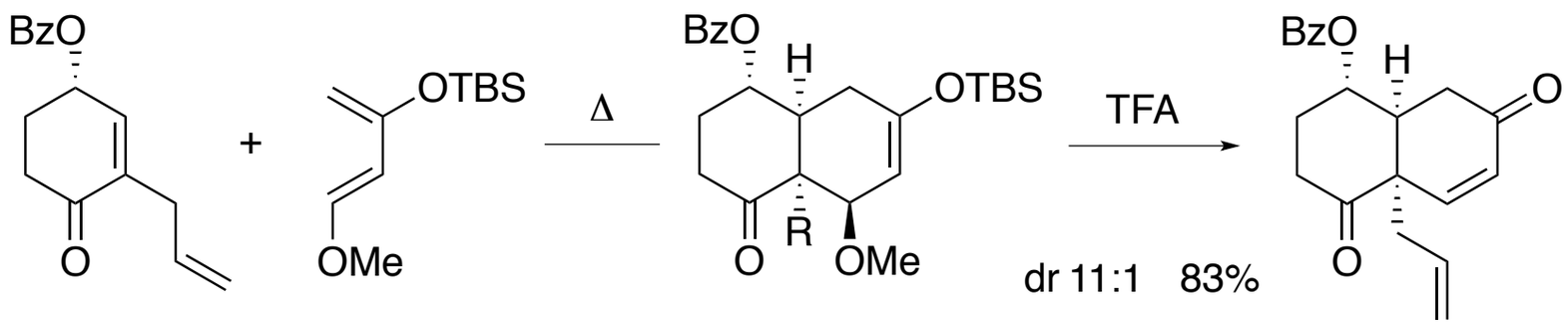
Moody, C. J. *ACIE* **2014**, *53*, 2056

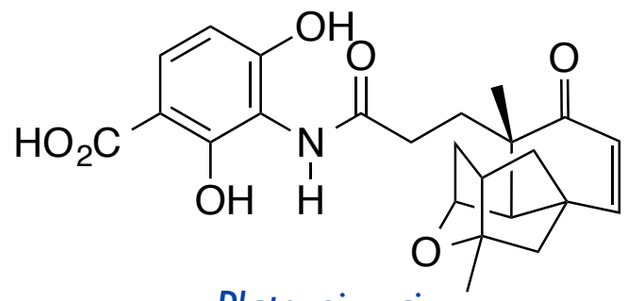
In fact, electronrich dienes containing R_3SiO substituents are very useful ...





Danishefsky's diene

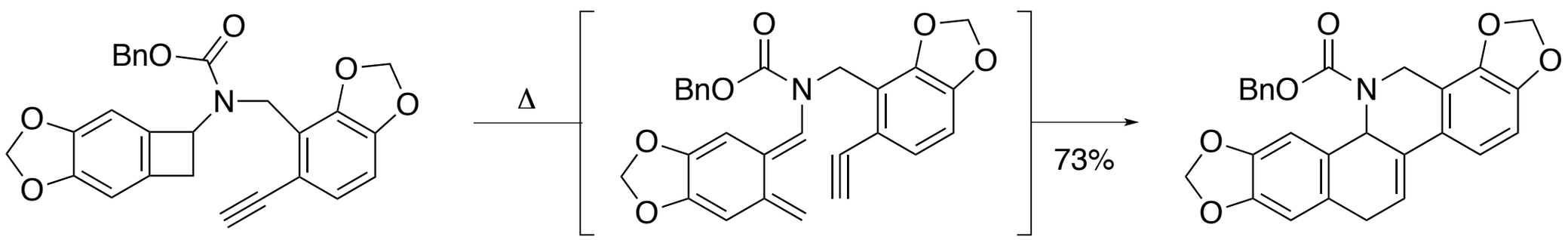




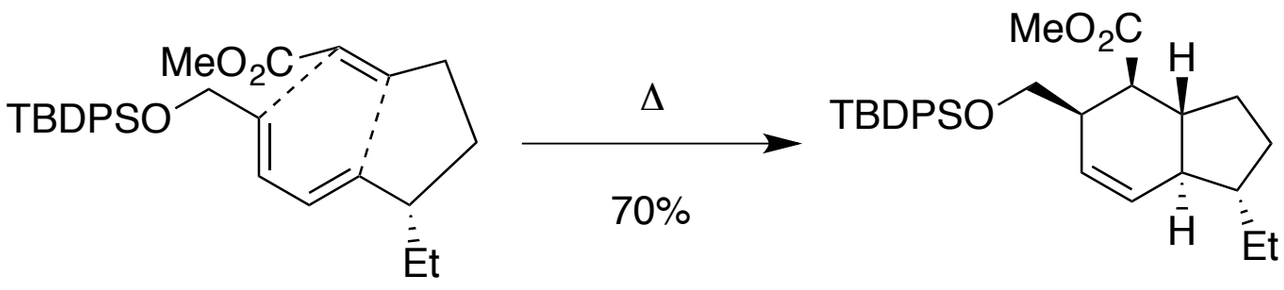
Platensimycin

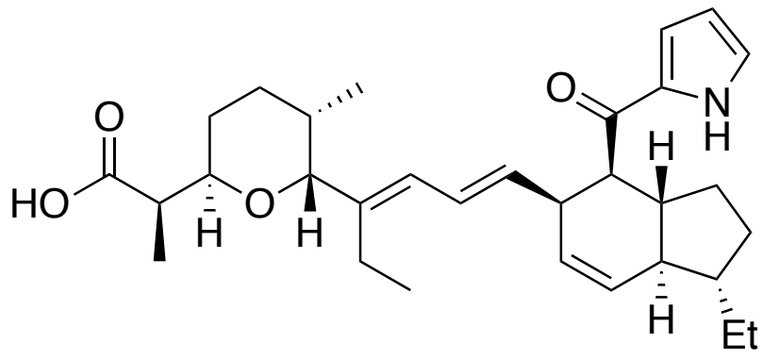
Matsuo, J.-i. *OL* **2010**, *10*, 4049

Intramolecular Diels-Alder (IMDA) reactions are very efficient ...



Conrotatory ring opening



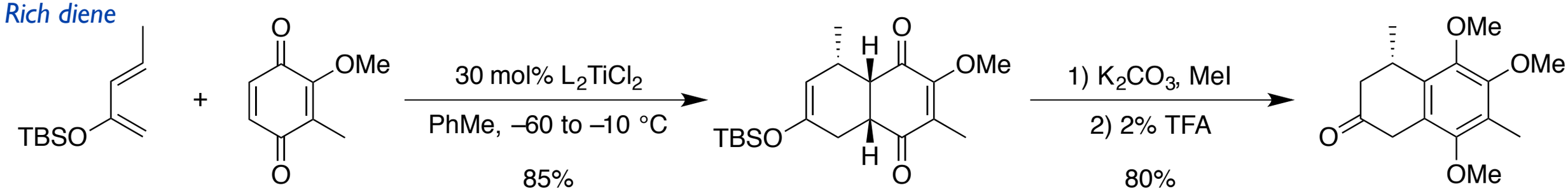


Antibiotic X-14547A

Nicolaou, K. C. *JOC* **1985**, *50*, 1440

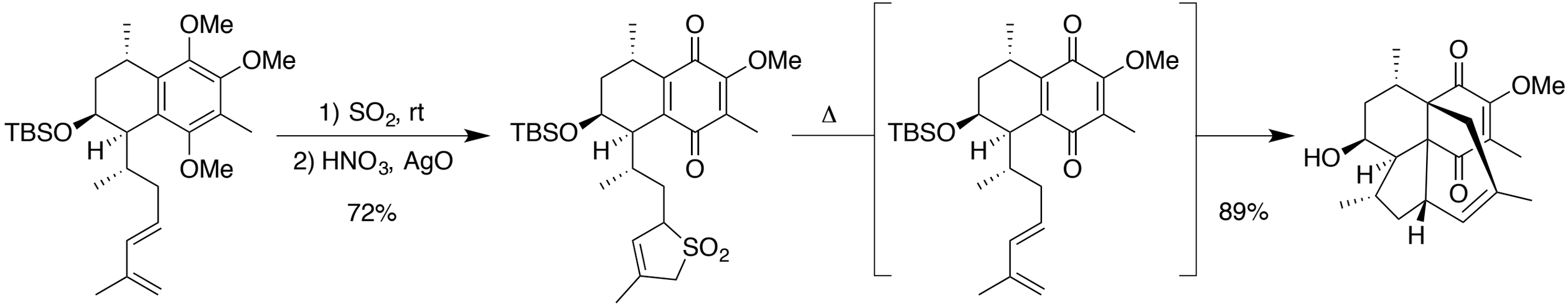
TOTAL SYNTHESIS of COLOMBIASIN A

Rich diene — *Poor dienophile*



Lewis acids catalyze DA

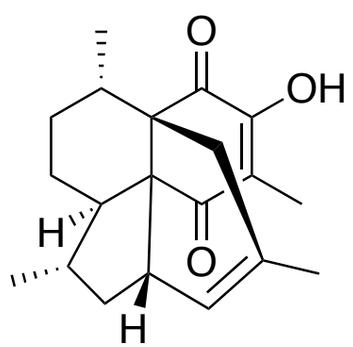
Excellent site-, regio- and endo-selectivity



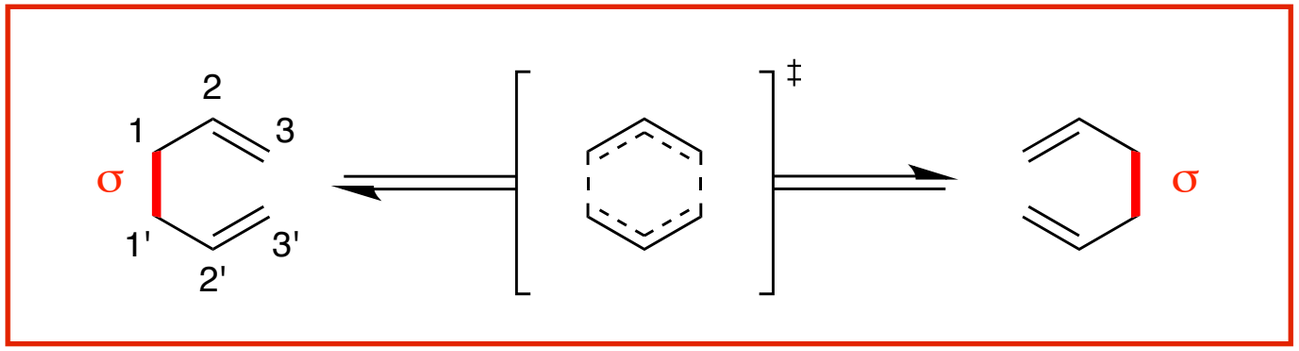
Chelotropic reaction

IMDA

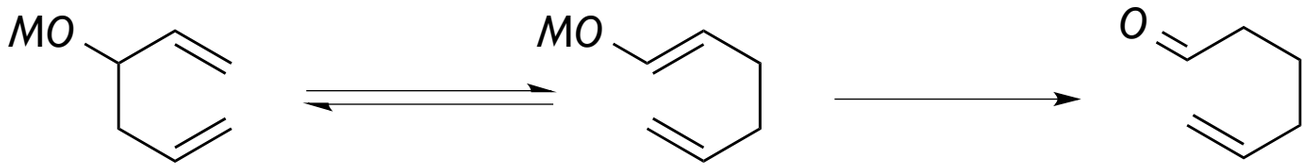
100% endo-selectivity



Nicolaou, K. C. *CEJ* **2001**, *7*, 5359

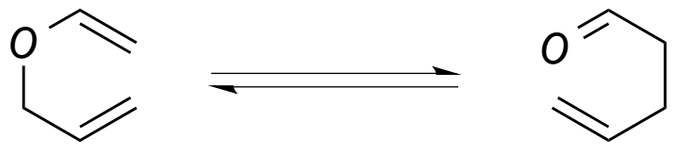


Cope

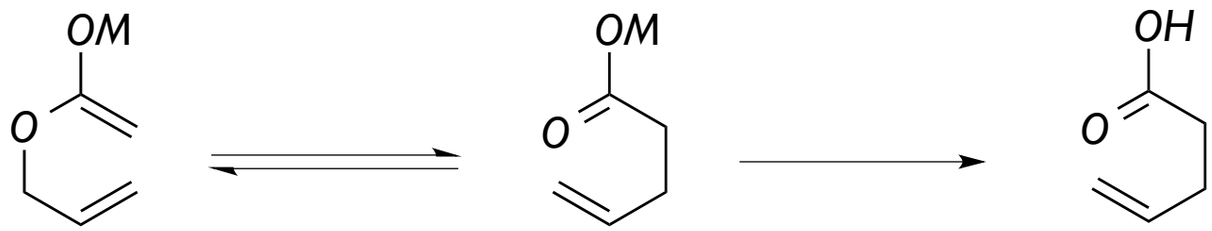


M: H, Na, K, SiR_3

Oxy-Cope



Claisen

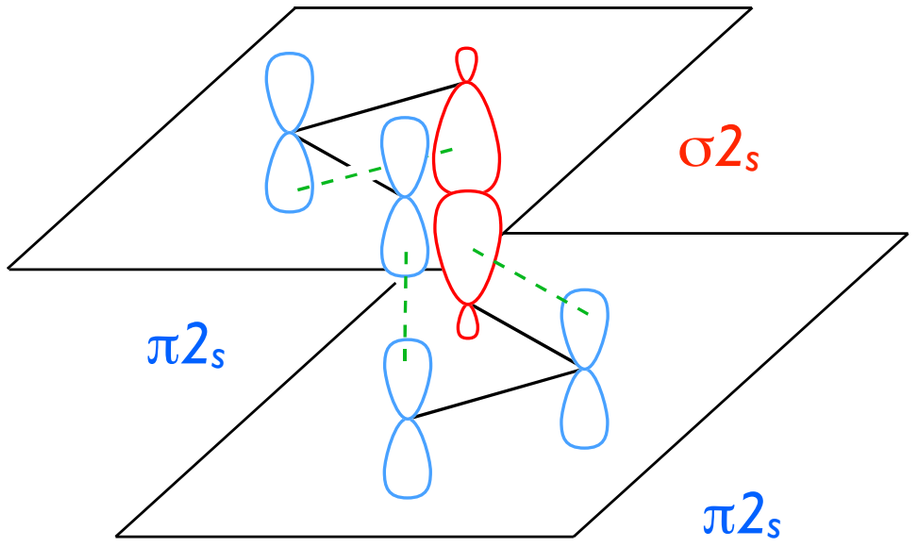


M: H, Na, K, SiR_3

Ireland-Claisen

For a review on Claisen rearrangement and variants, see Martín Castro, A. M. *Chem. Rev.* **2004**, *104,* 2939
For a review on sigmatropic rearrangements, see Jones, A. C.; Stoltz, B. M. *ACIE.* **2014**, *53,* 2556

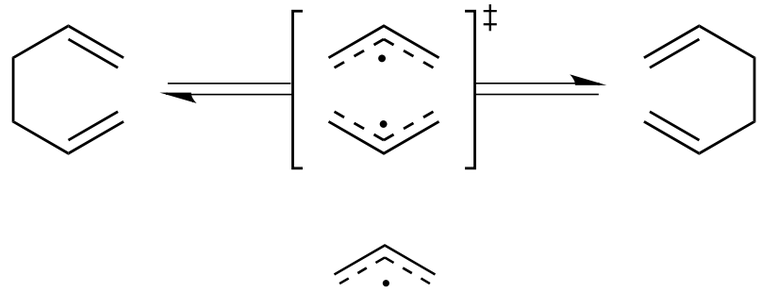
This is symmetry allowed ...

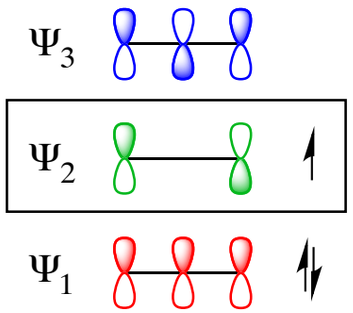


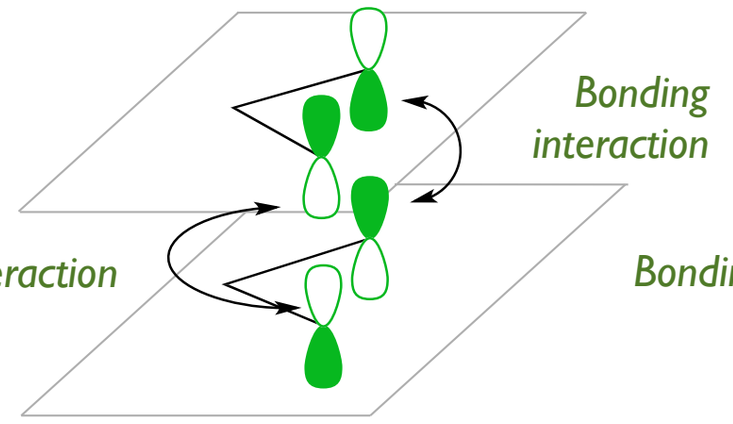
3 (4q+2)s

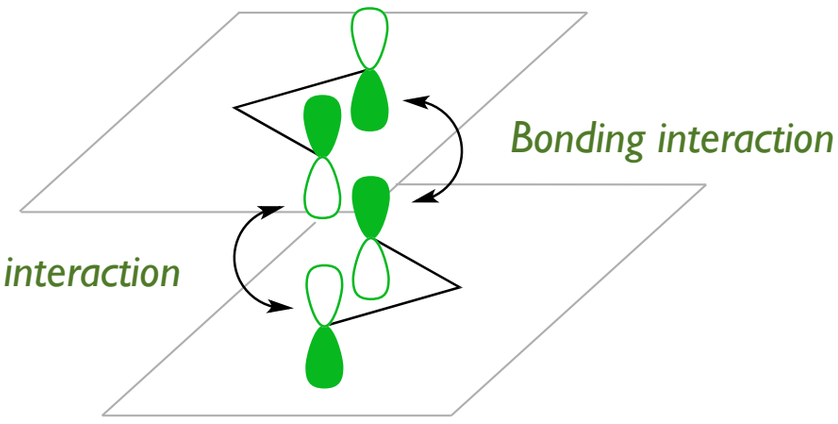
0 (4r)a

... the FMO approach takes into account two allyl radicals in the TS

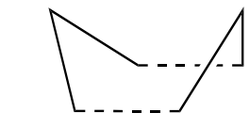




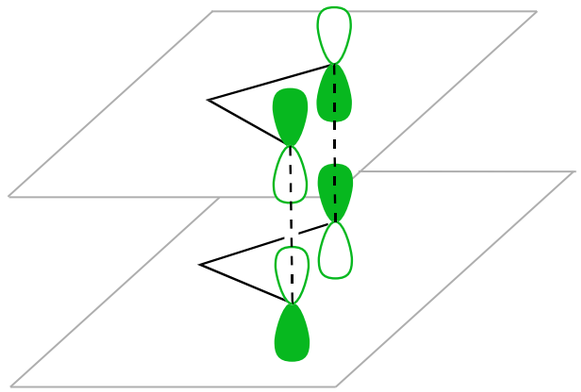


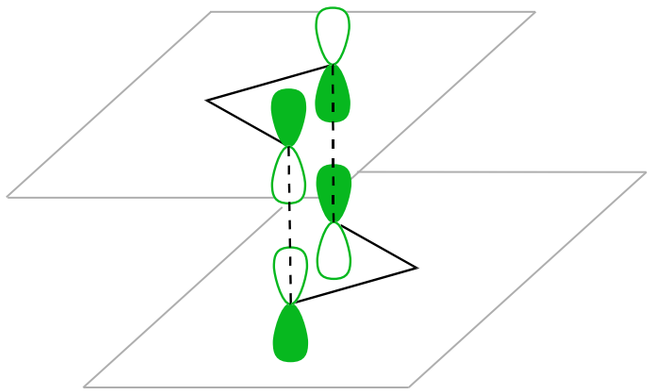


[3,3] Sigmatropic Rearrangements: Boat- versus Chair-like Transition States

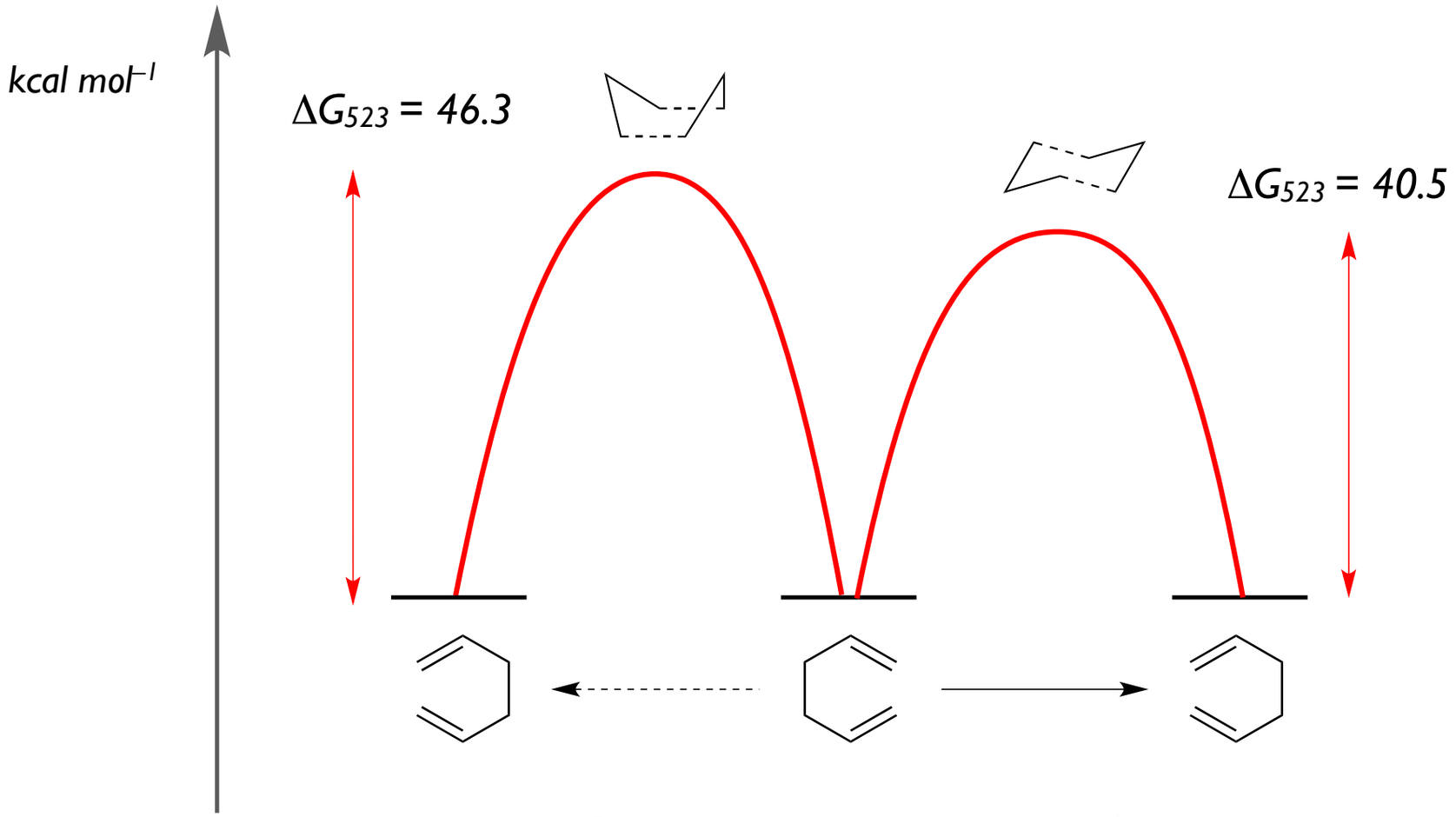


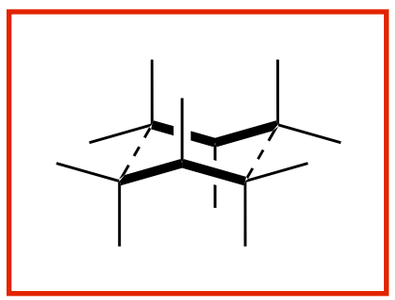
Boat-like TS





Chair-like TS

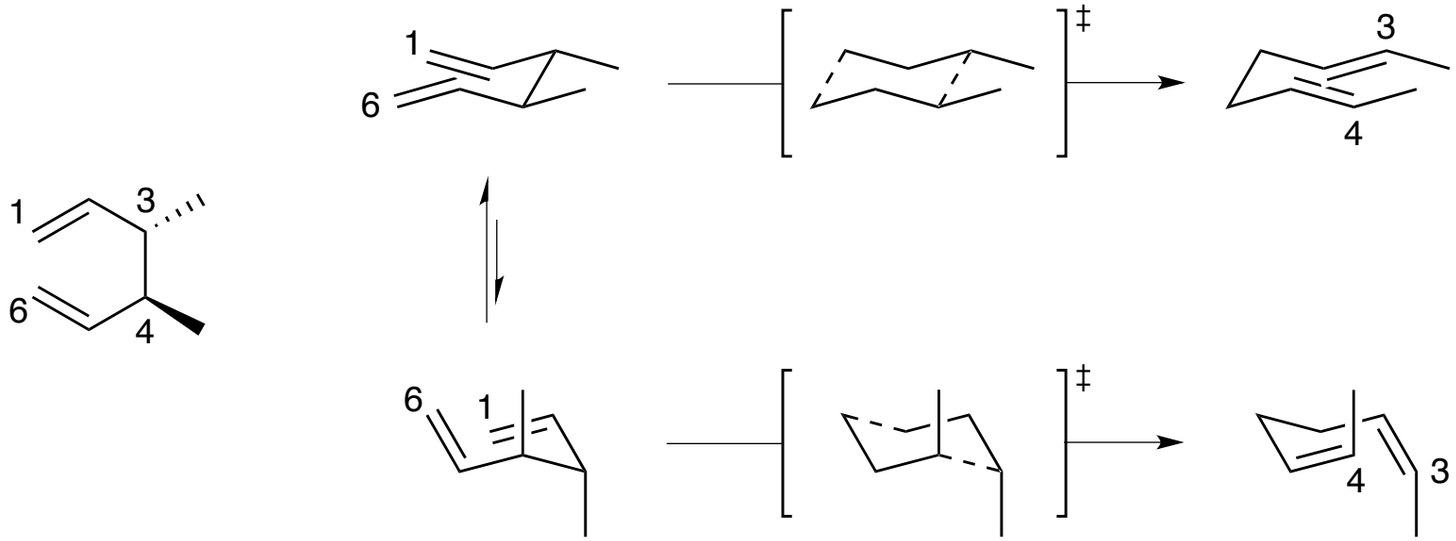


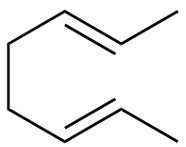


Stereoselectivity?

Goldstein, M. J. *JACS* **1972**, *94*, 7147

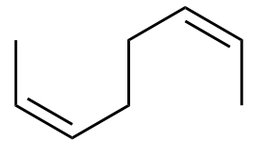
The C3–C4 relative configuration determines the geometry of the resultant alkenes ...



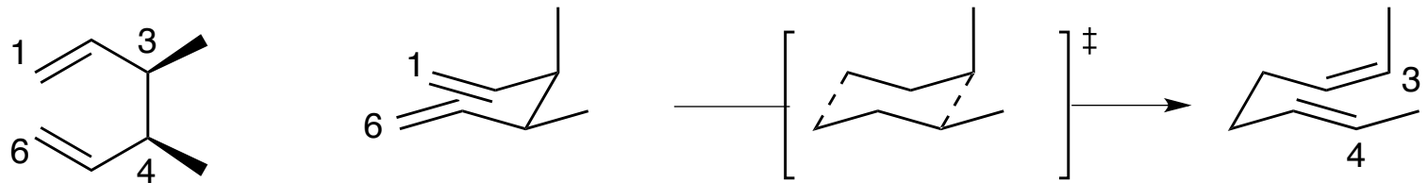


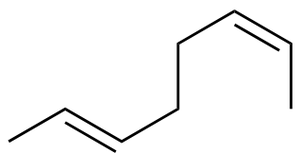
(E,E)

(E,E) / (Z,Z) 9:1



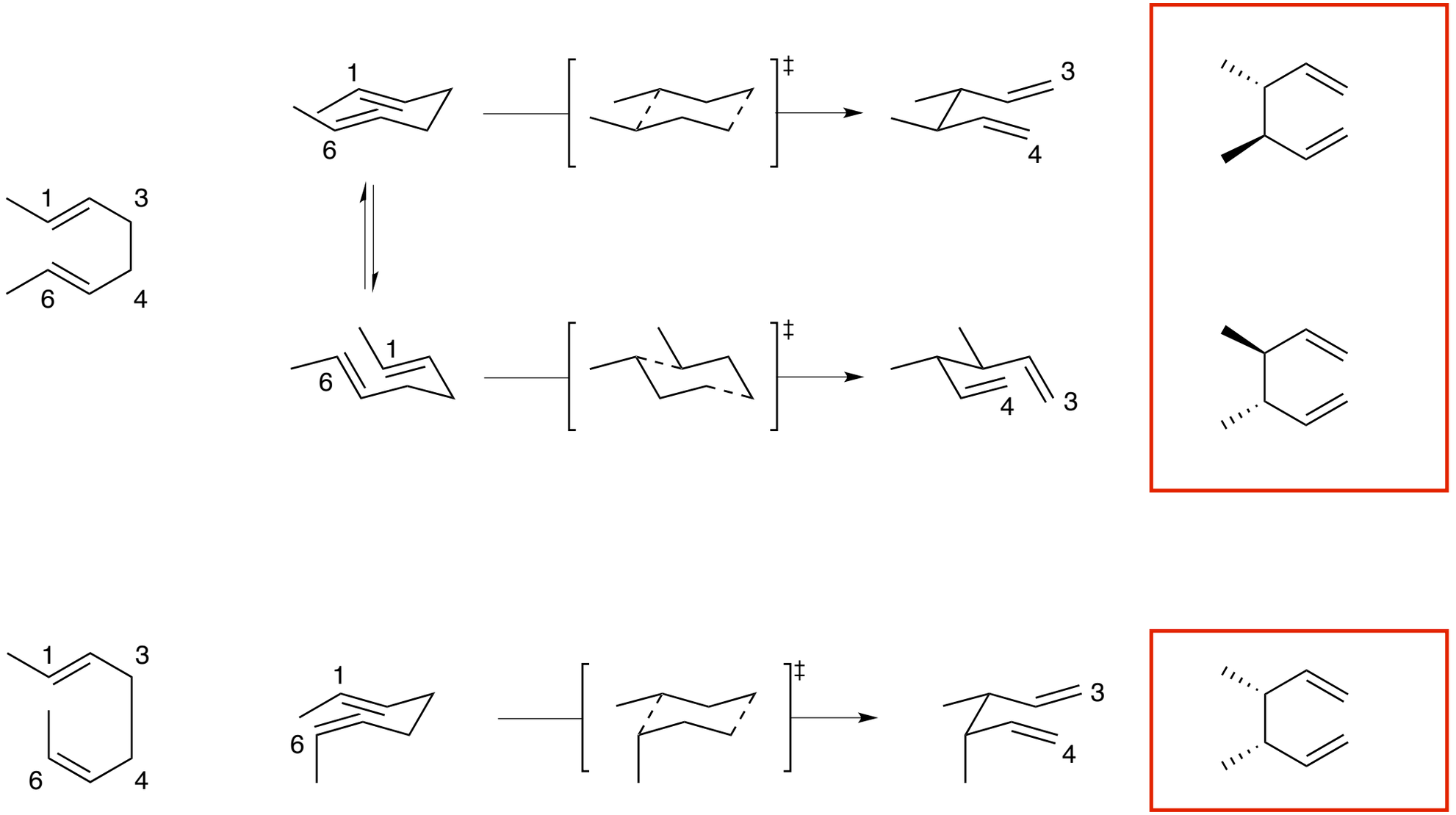
(Z,Z)





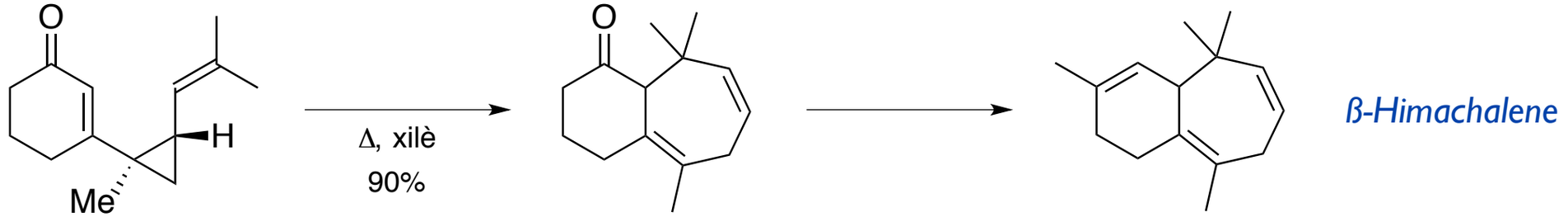
(E,Z)

The geometry of the alkenes determines the C3–C4 relative configuration ...



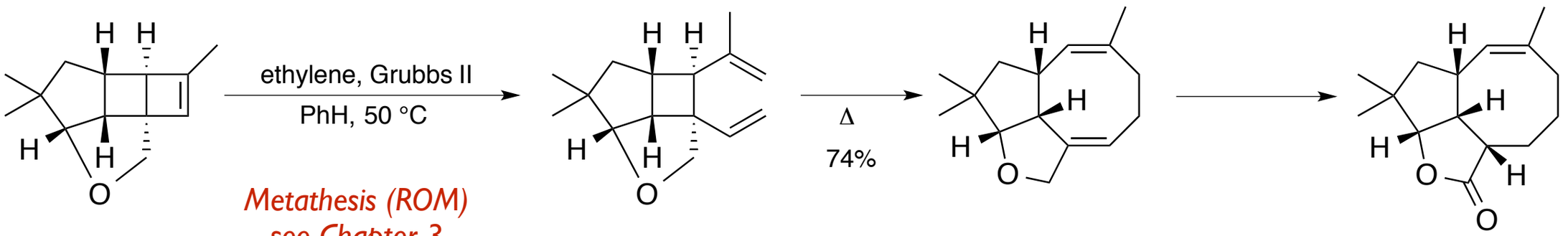
The application of the Cope rearrangement in synthesis is restricted to those situations in which the equilibrium is ruled by the stability of the resultant products, as …

Strain-Release Cope rearrangements



ß-Himachalene

Piers, J. *CAJ* **1983**, *61*, 1226, 1239

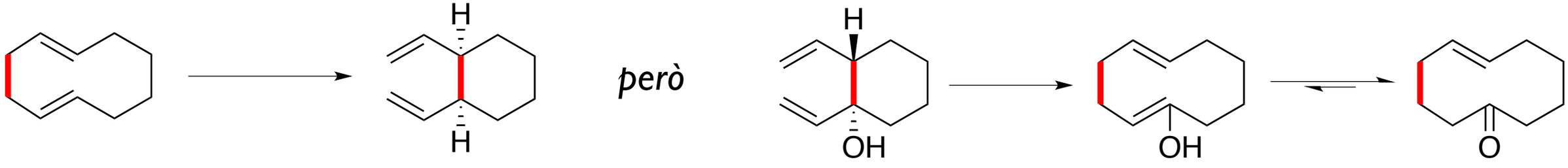


Metathesis (ROM)
see Chapter 3

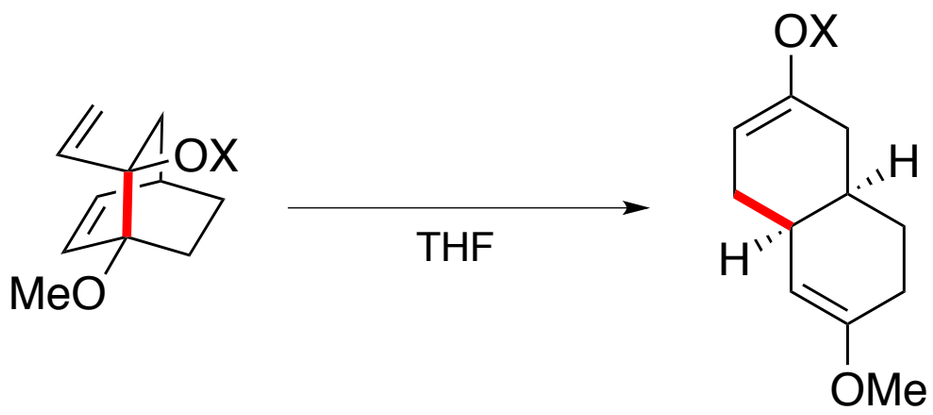
Snapper, M. L. *JACS* **2000**, *122*, 8071

(–) Asteriscanolide

… but it is the origin of a wide array of variants, as the Oxy-Cope rearrangement…



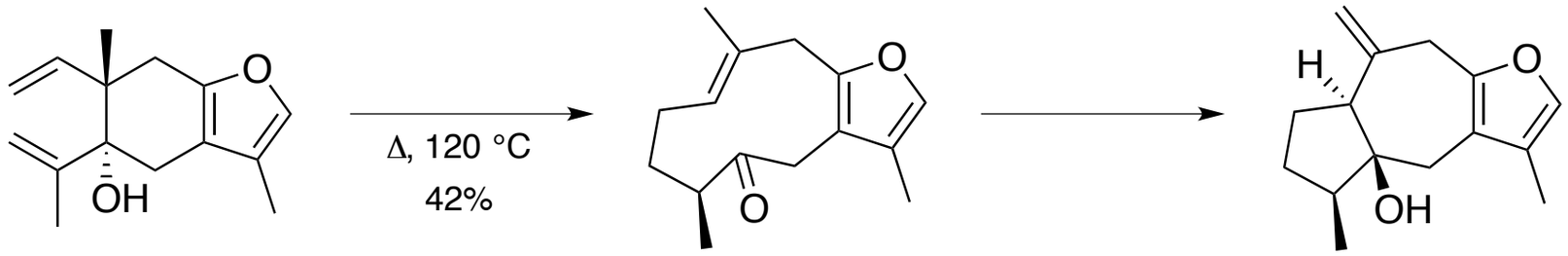
… in which the use of alkoxides increases the reaction rate



X	T	$t_{1/2}$
H	66 °C	–
Li	66 °C	–
Na	66 °C	1.2 h
K	66 °C	1.4 min
K	10 °C	11 h

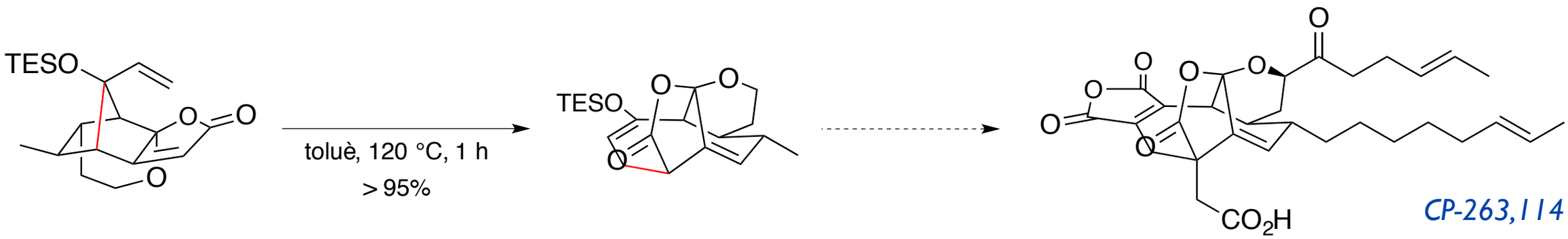
For a review on oxy-Cope rearrangement, Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971

Oxy-Cope Rearrangement in Synthesis



Guaiane

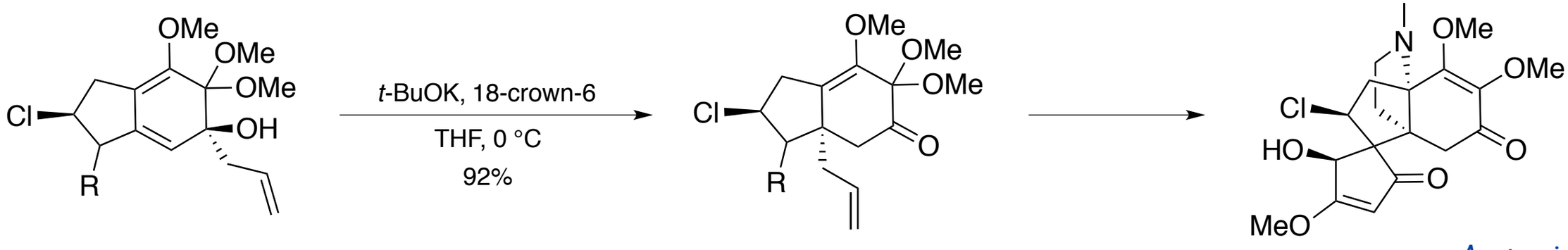
Zografos, A. L. *OL* **2013**, *15*, 152



CP-263,114

... we may thus conclude that qualitatively the strain we have built into lactone spiroketal results in a similar acceleration than the anion effect. In addition, this reaction is in principle an equilibrium process and it is noteworthy that the equilibrium overwhelmingly favors the desired bridged-head double bond.

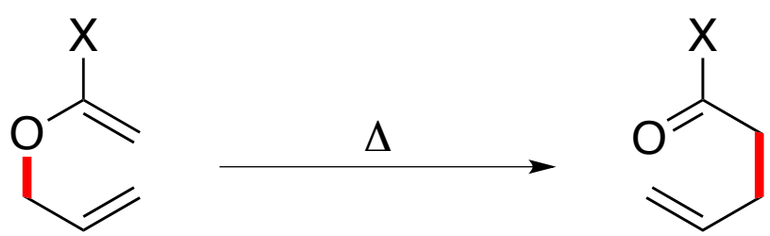
Leighton, J. L. *JACS* **1999**, *121*, 890



Acutumine

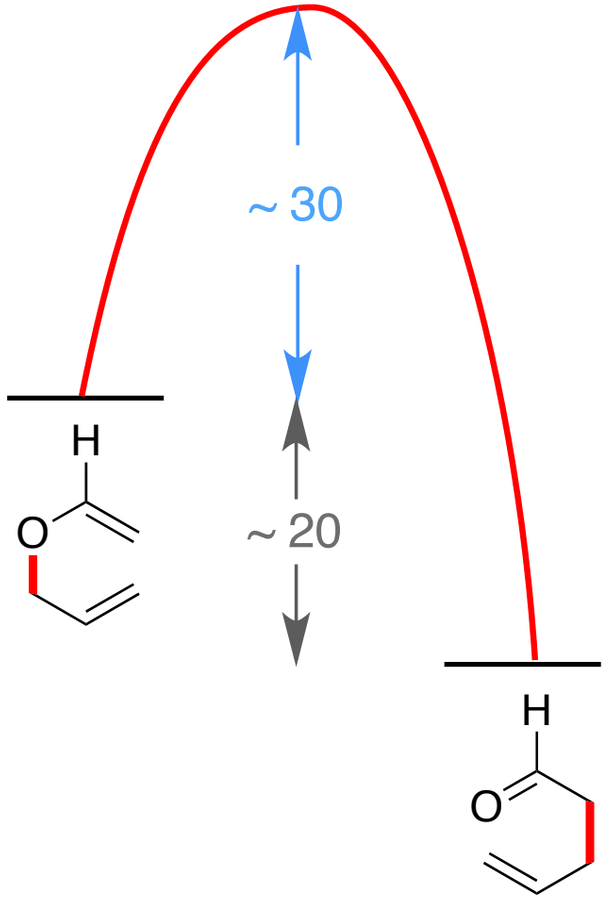
Castle, S. L. *JOC* **2009**, *74*, 9082

... and finally the Claisen and Ireland-Claisen rearrangements are favored

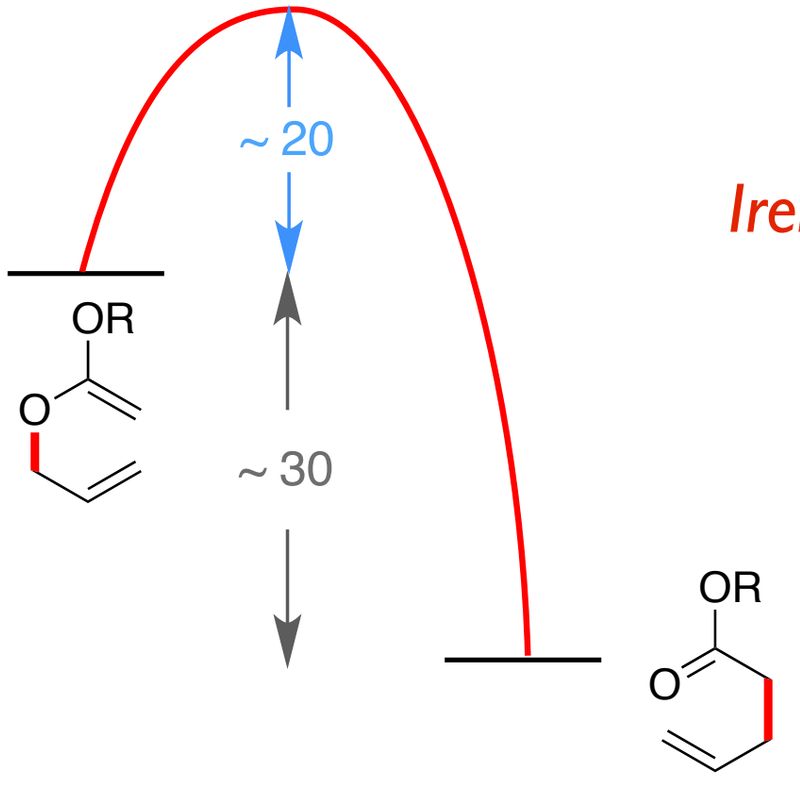


X	ΔH (kcal mol^{-1})
H	–16
OH	–31

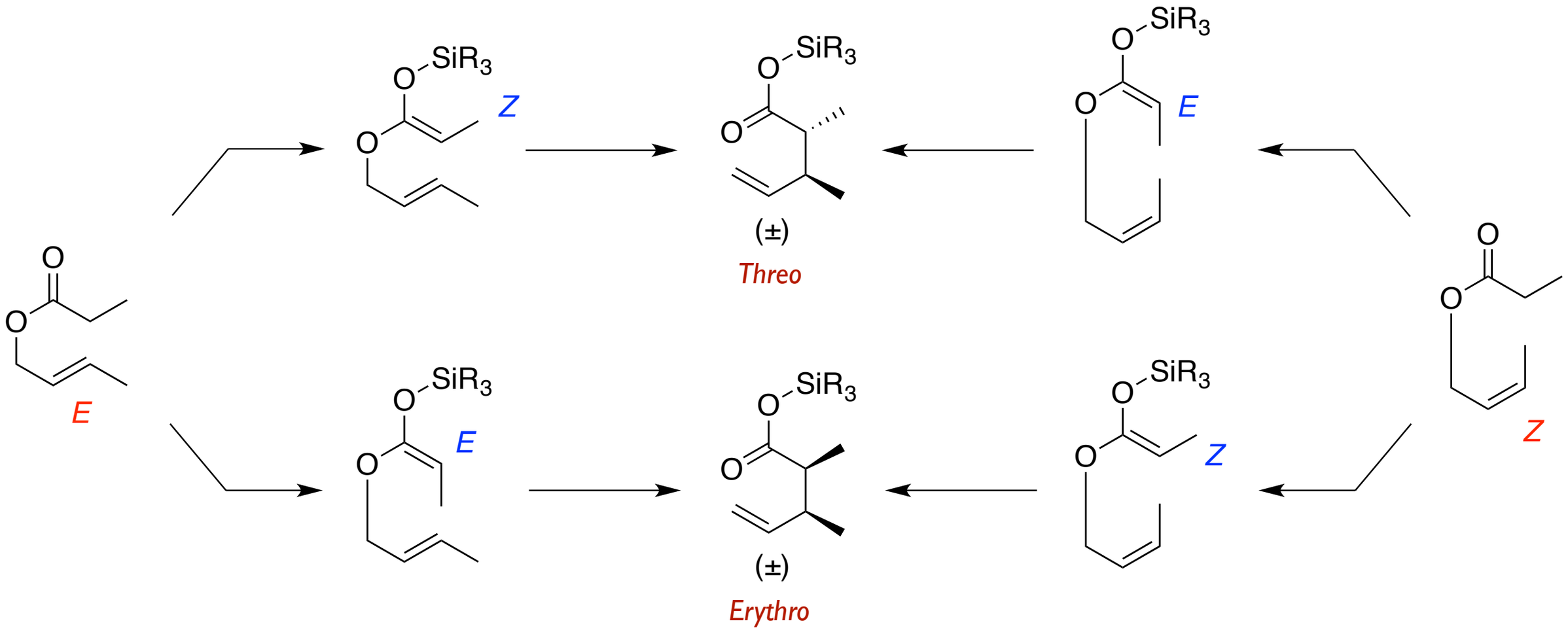
Claisen



Ireland - Claisen



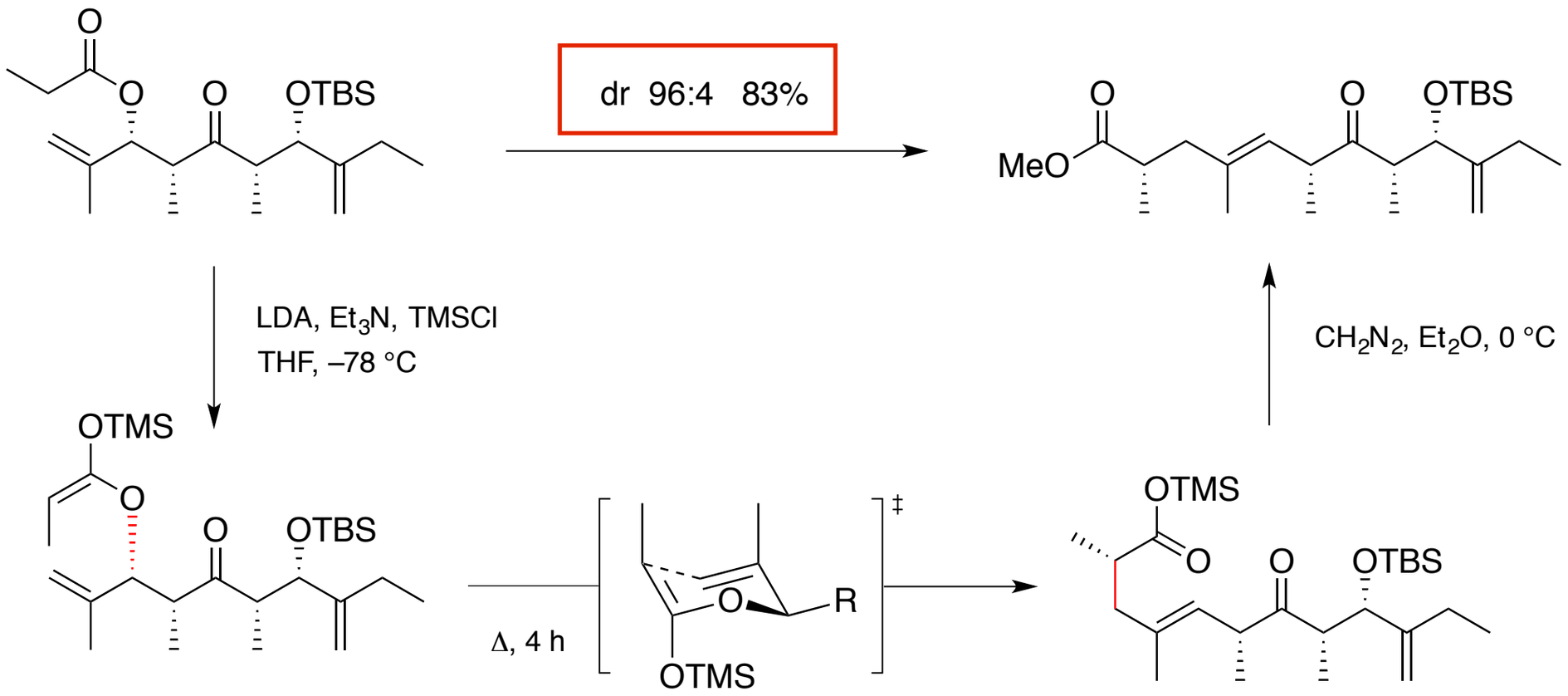
Assuming that both Z- and E-enolates can be prepared stereoselectively and that the Ireland-Claisen proceeds through a chair-like transition state, three and erythro relative configurations are accessible ...



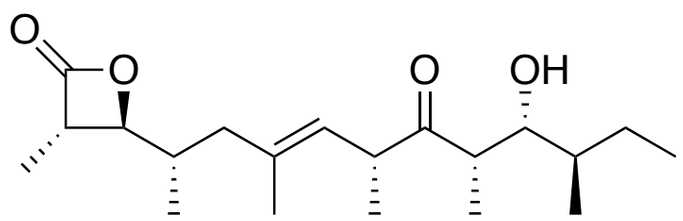
... and the absolute configuration can also be controlled by the introduction of stereocenters

McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905, and refs therein

Ireland-Claisen Rearrangement in Synthesis



Ebelactone A



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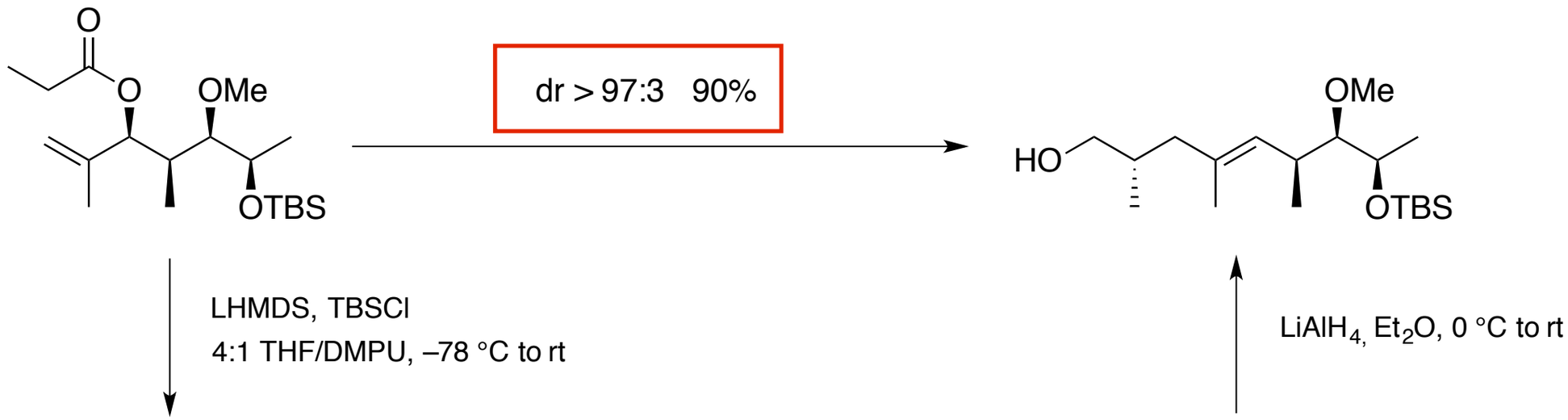
Ireland-Claisen Rearrangement in Synthesis



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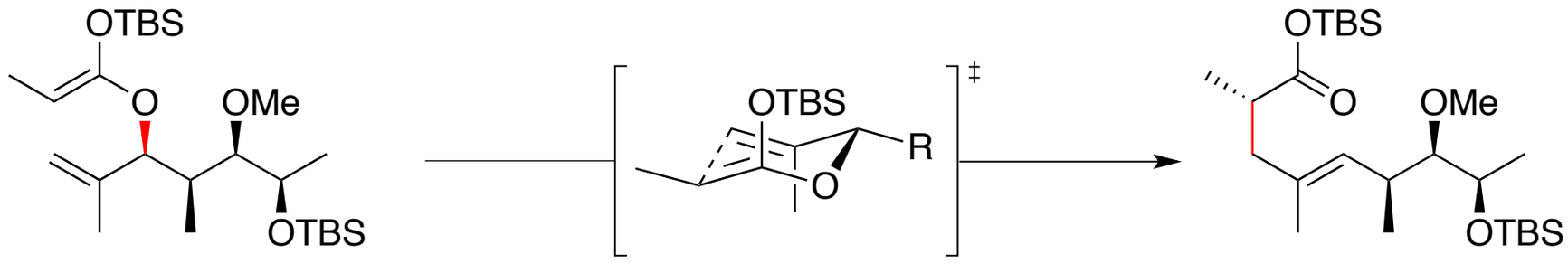

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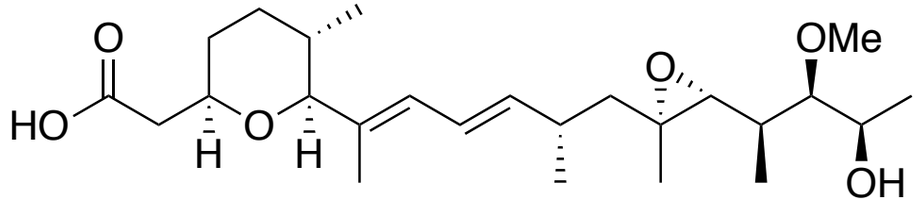

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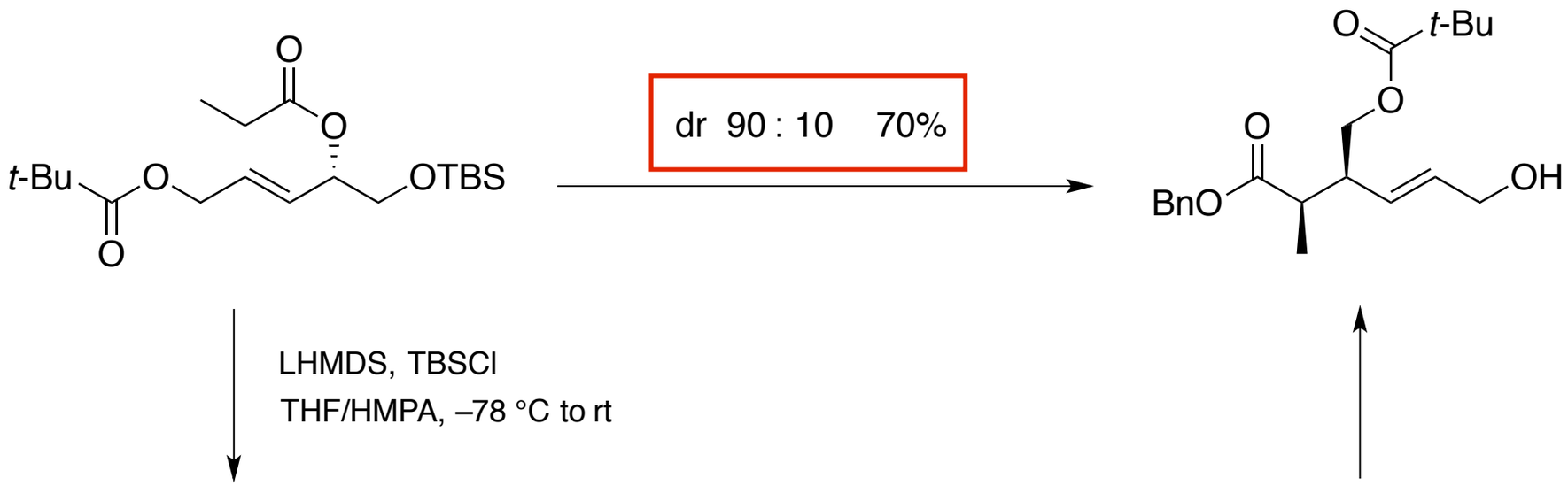

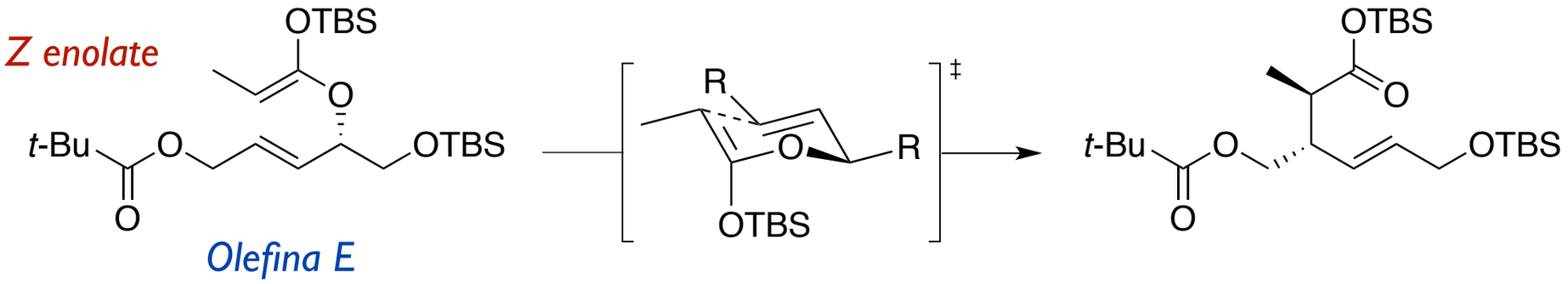

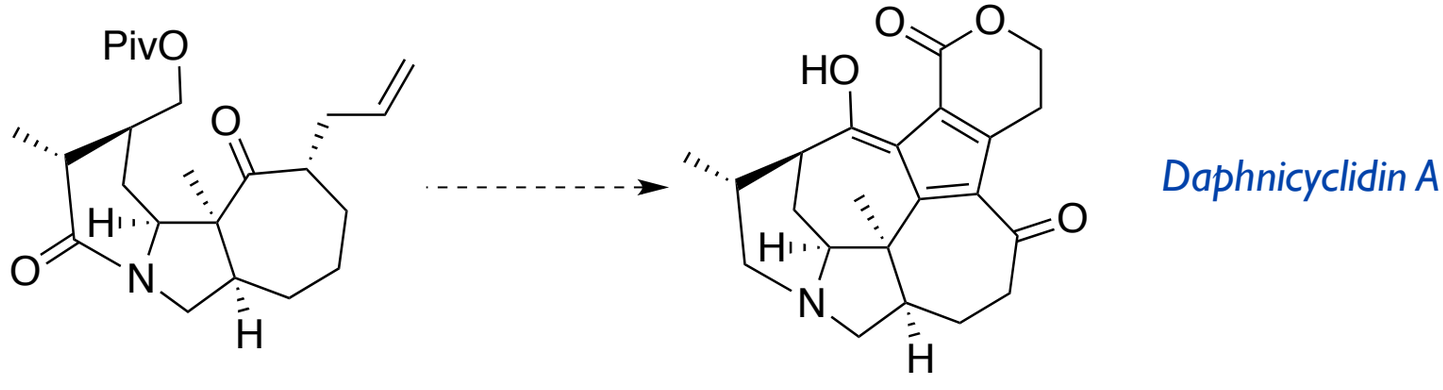

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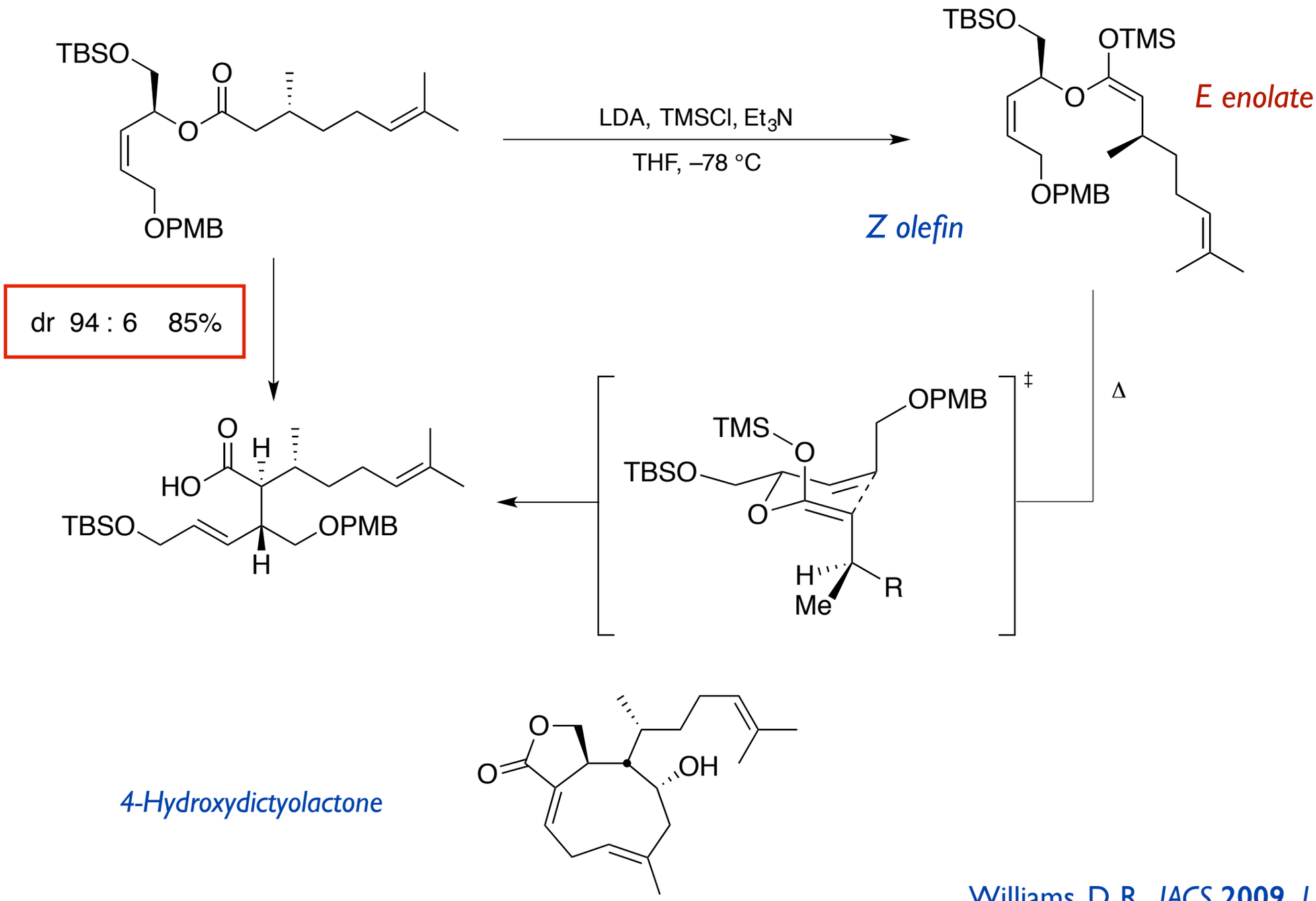

4-Hydroxydictyolactone

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