Master Course
in Organic Chemistry

2018-19

methods **and design** in organic synthesis

Pere Romea

THE LORD OF THE RINGS
THE FELLOWSHIP OF THE RING

by John R. R. Tolkien









6.3. Making rings (I)

membered rings are excellent benchmarks to test any kind of reactivity

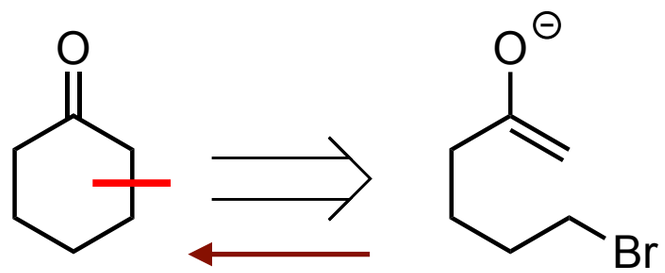
promoted by nucleophiles,
radicals,
electrophiles

pericyclic processes,

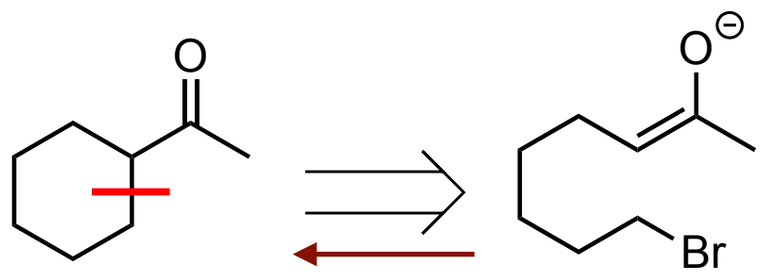
cascade sequences

& others (BIRCH REACTION)

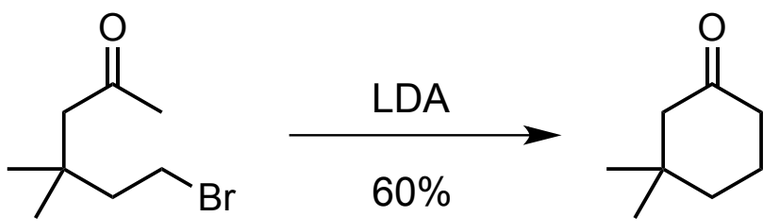
Alkylation Reactions

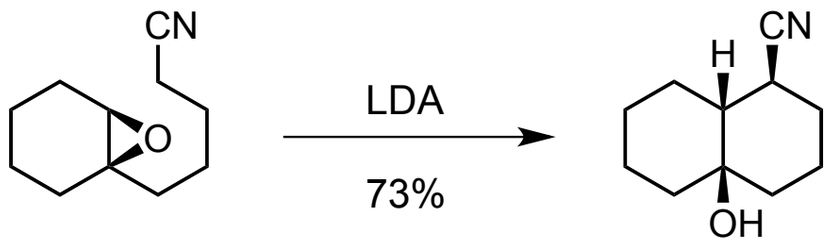


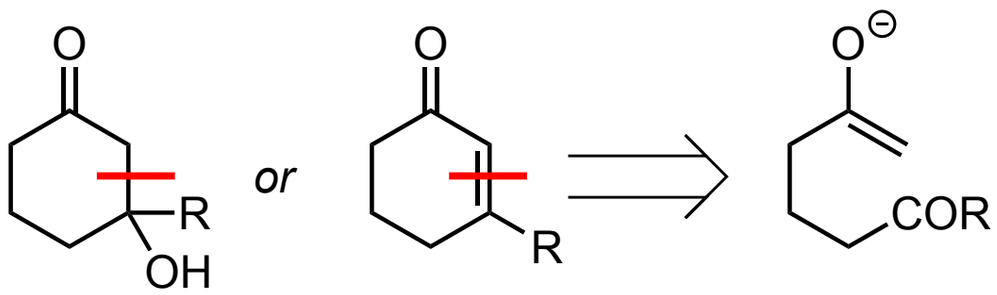
6-enolendo-exotet



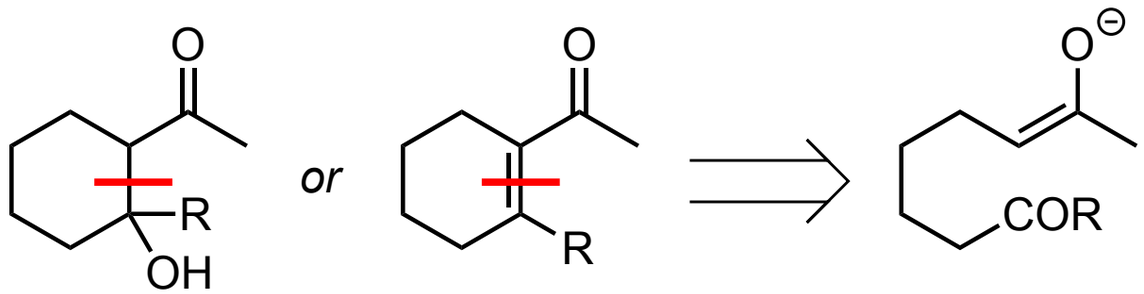
6-enolexo-exotet





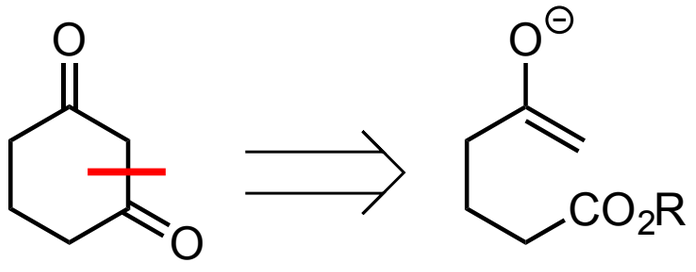


6-enolendo-exotrig



6-enolexo-exotrig

Aldol Reactions



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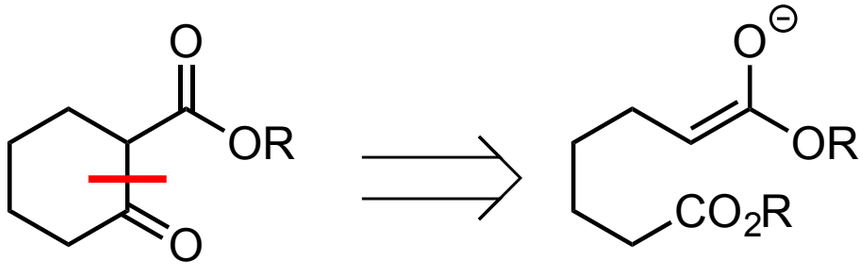
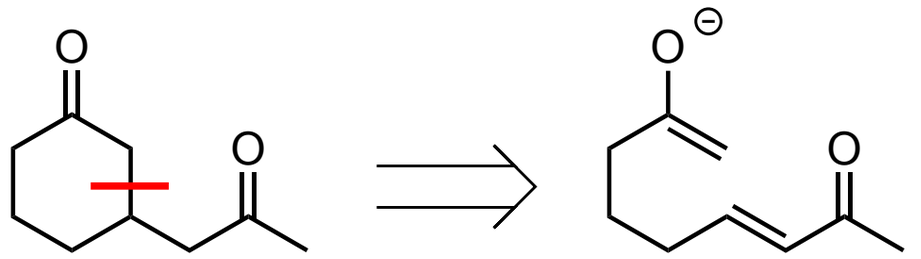


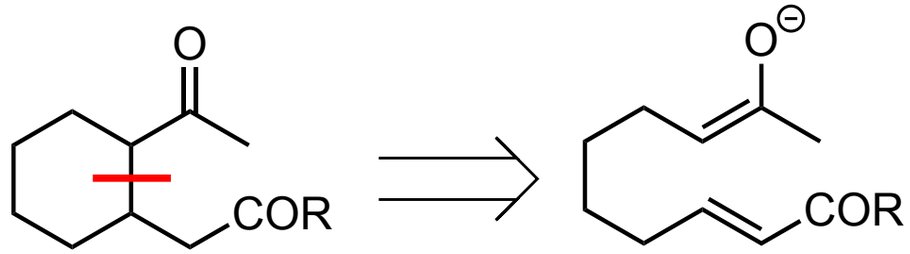
6-enolexo-exotrig

Dieckmann Reactions



6-enolendo-exotrig

✔



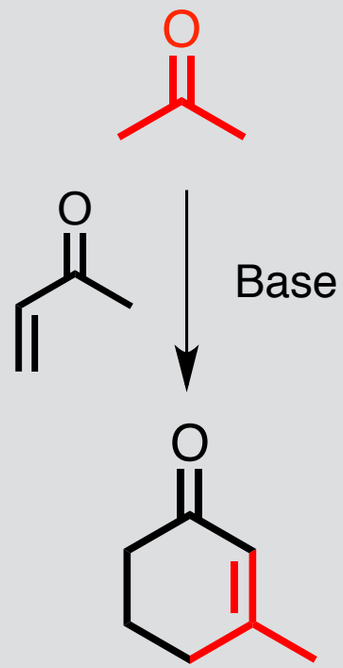
6-enolexo-exotrig

✔

Michael Reactions

Robinson annulation

Michael addition of a carbonyl to an enone followed by an intramolecular aldol condensation

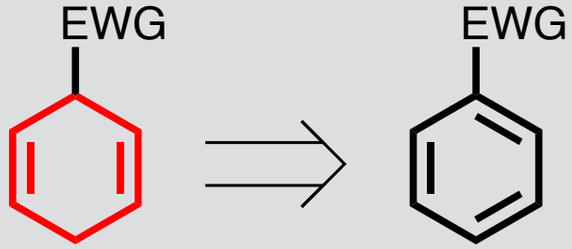


Sir Robert Robinson

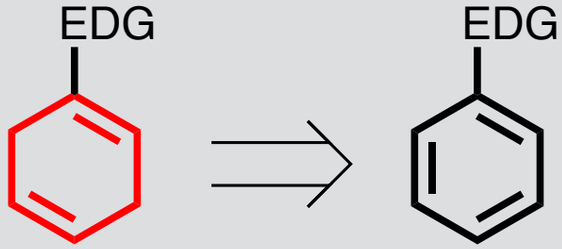
(1886-1975)

NOBEL PRIZE IN CHEMISTRY 1947

for his investigations on plant products of biological importance, especially the alkaloids



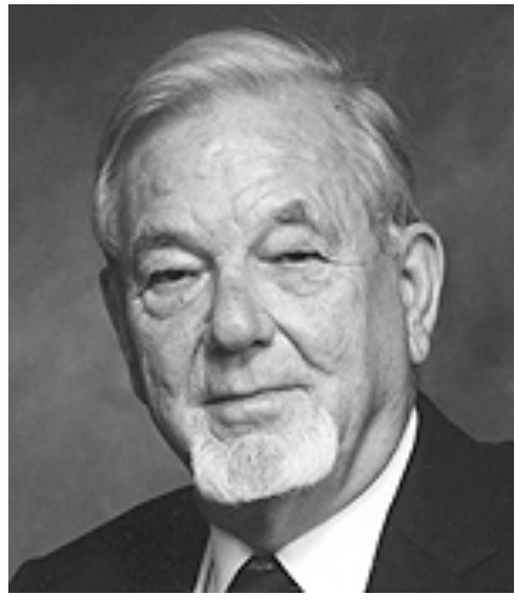
EWG: CO_2H, COR, CN



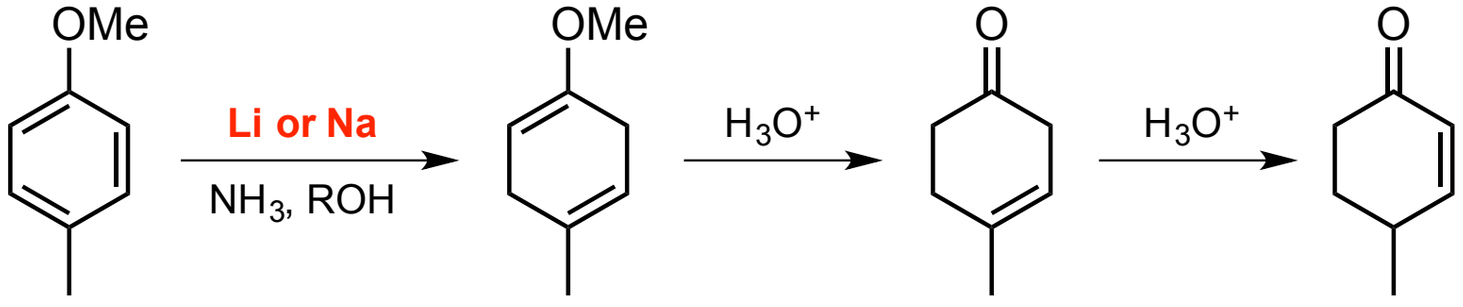
EDG: OR, NR_2, alkyl

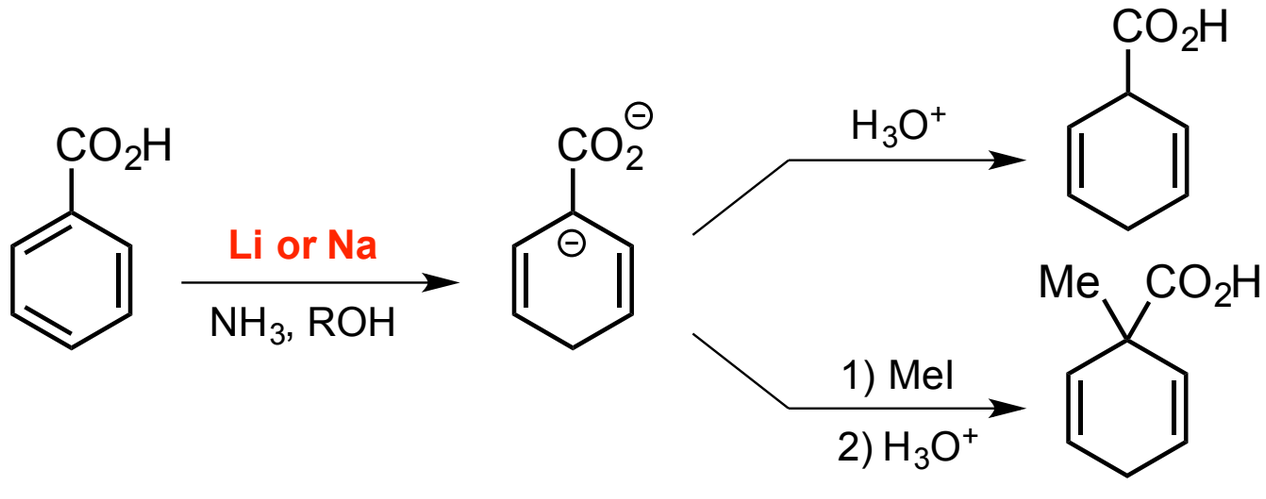
Birch Reduction

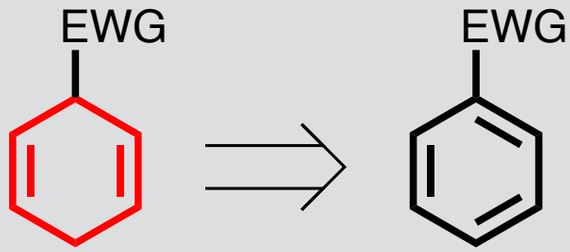
Arthur John Birch
(1915-1995)



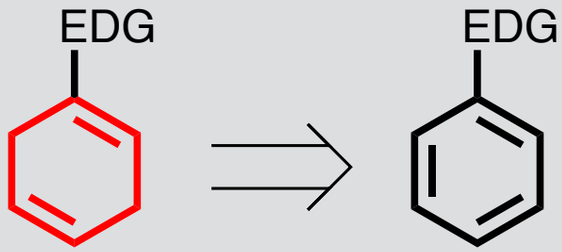
Sir Robert Robinson was his PhD supervisor







EWG: CO_2H, COR, CN



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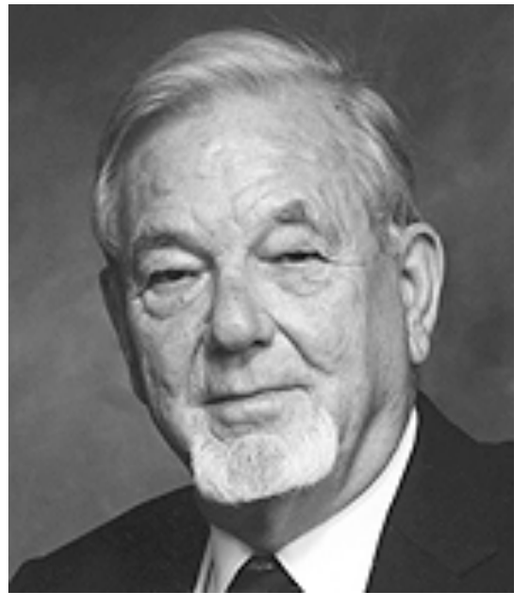
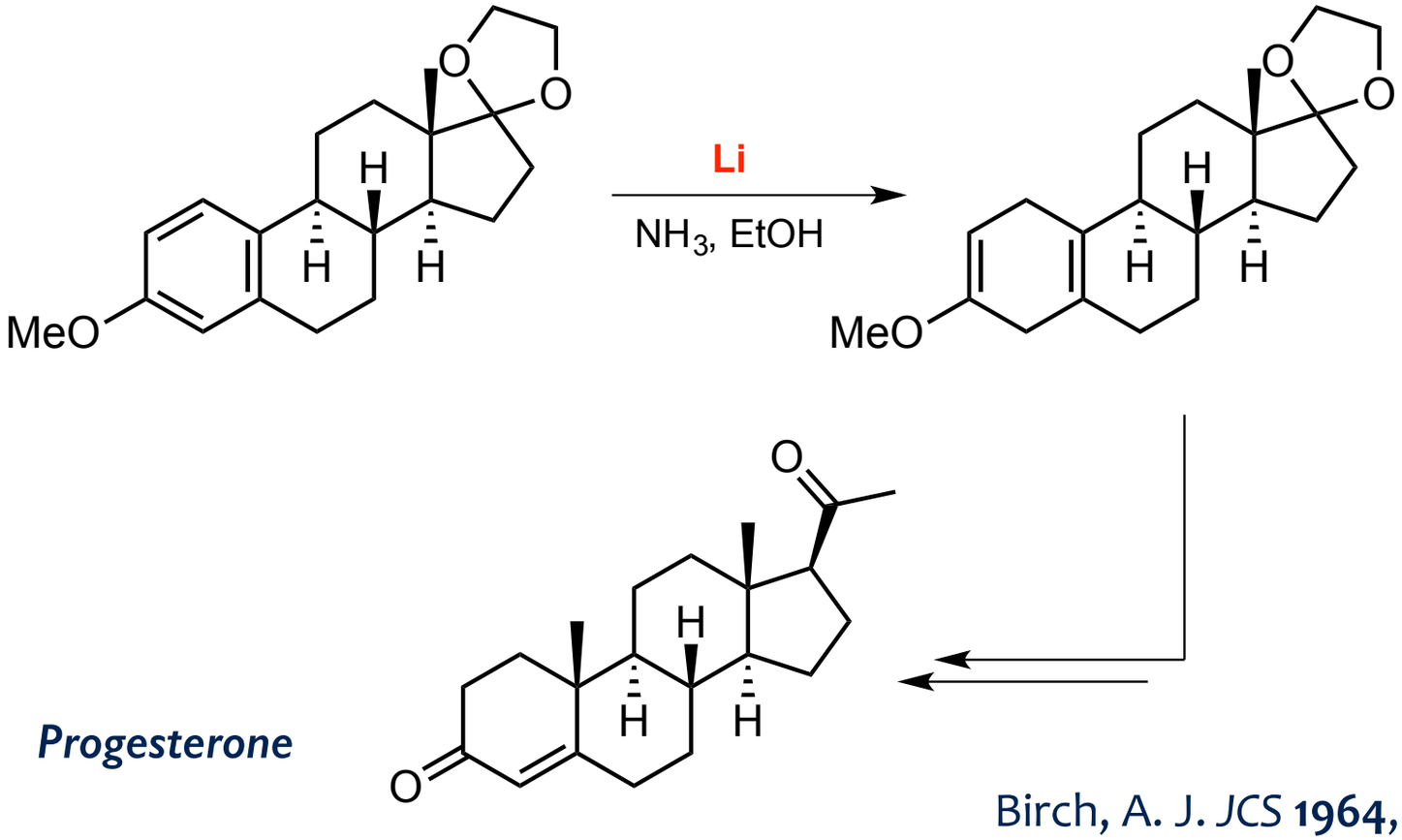
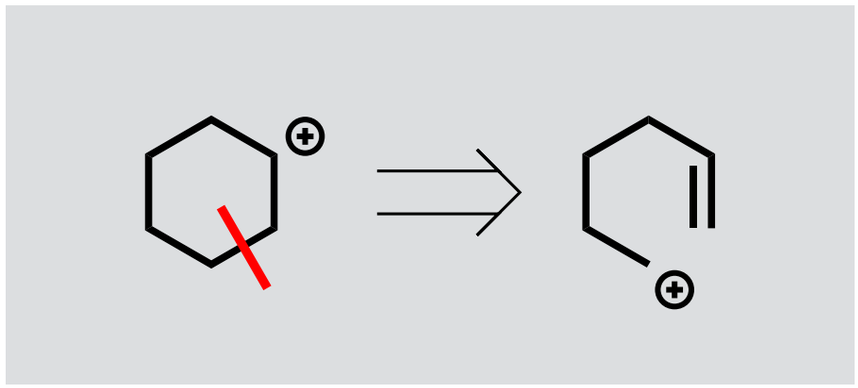


Sir Robert Robinson was his PhD supervisor



Progesterone

Birch, A. J. *JCS* **1964**, 3309



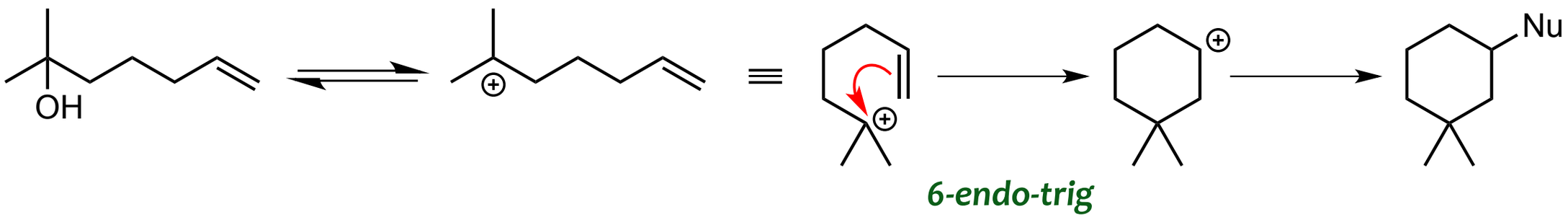
Cationic cyclizations

Initiation *generation of the cationic center*

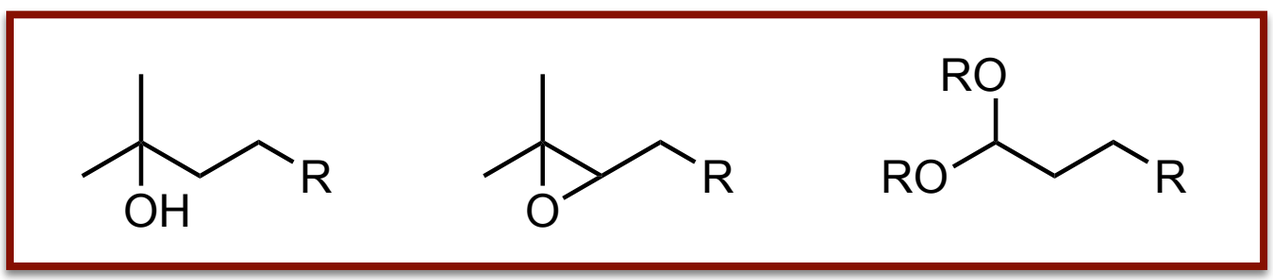
Cyclization *interaction of the cationic center with a π-bond*

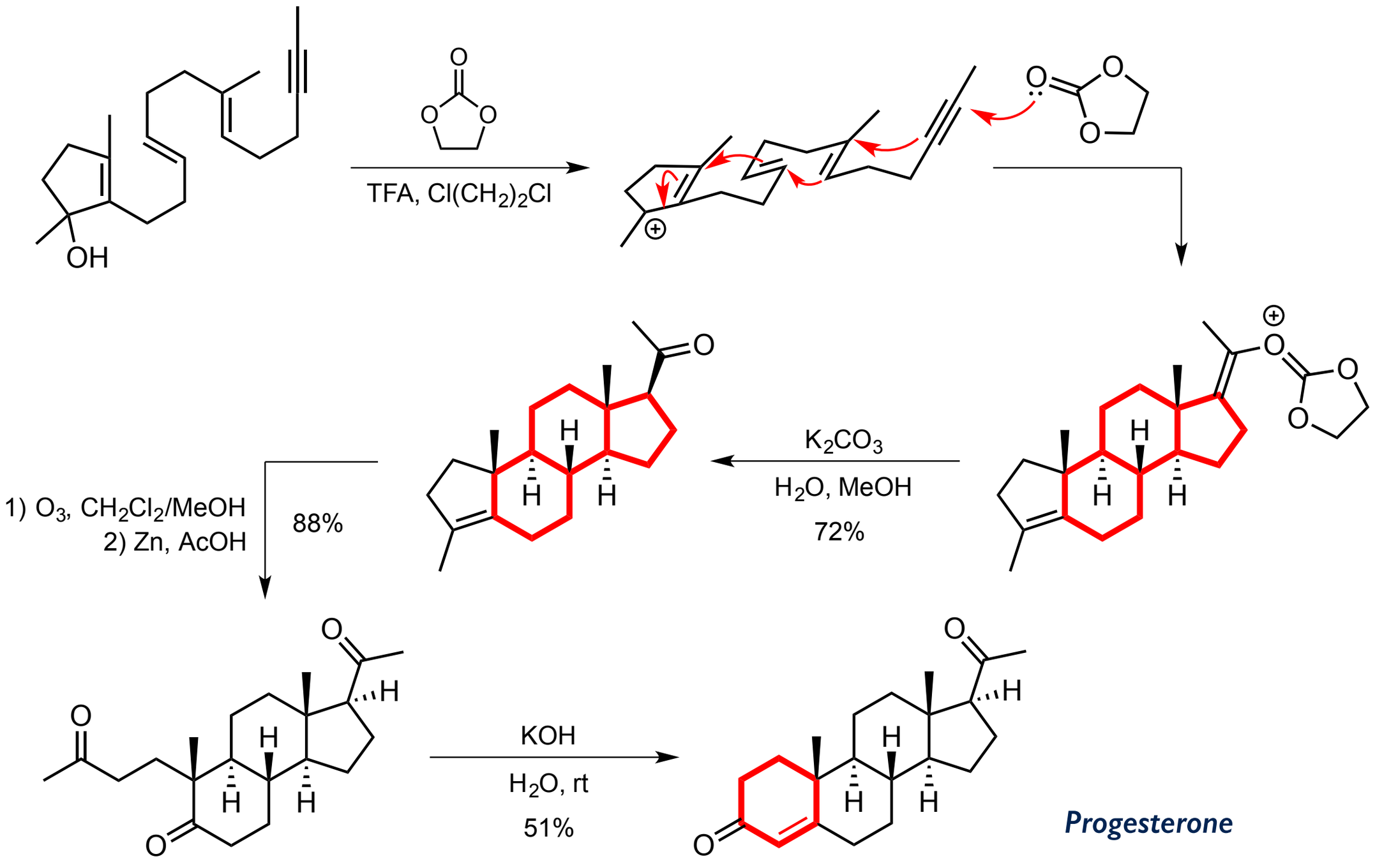
Termination *fate of the resultant cation*

initiation ***cyclization*** ***termination***



6-endo-trig

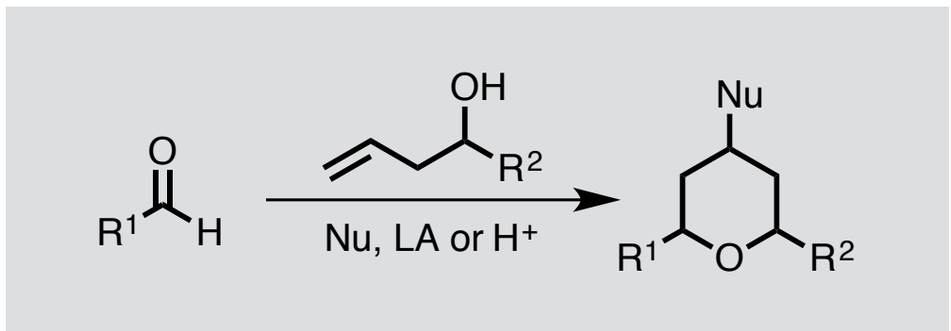




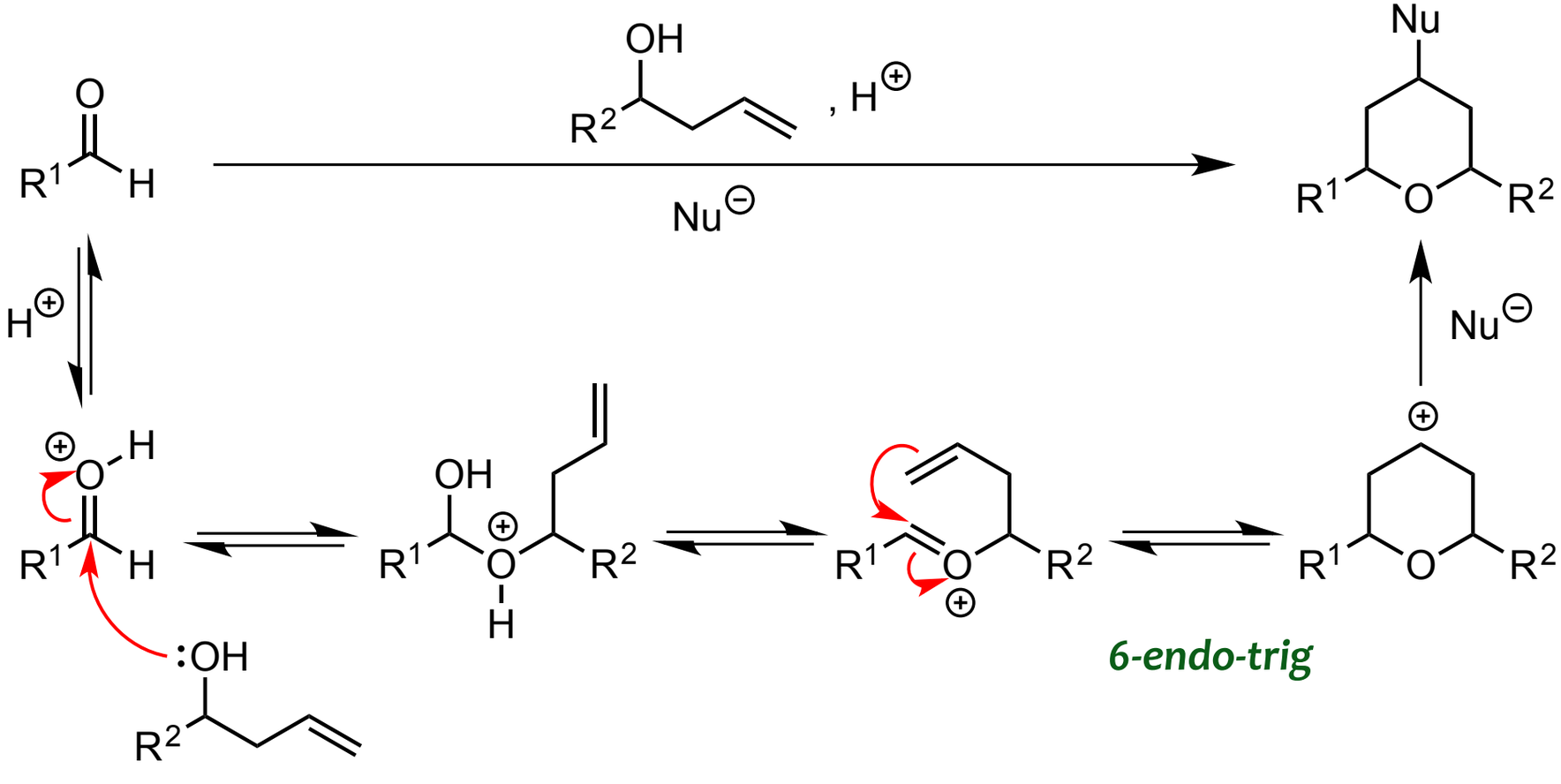
Progesterone

Johnson, W. S. *JACS* **1971,** *93*, 4332; **1978,** *100*, 4274

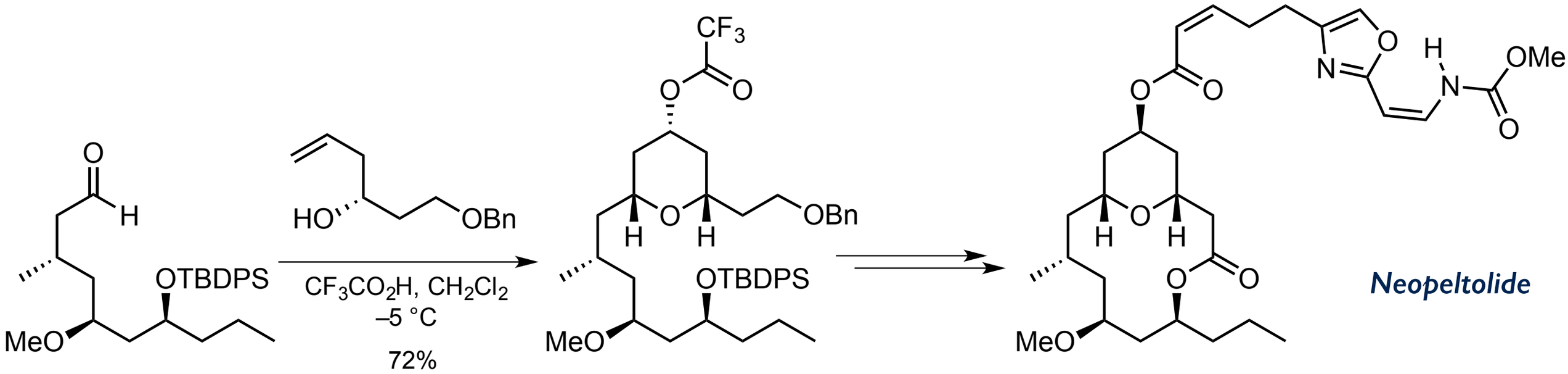
*The **Prins reaction** refers to the acid mediated attack of an alkene to a carbonyl*



Prins cyclization

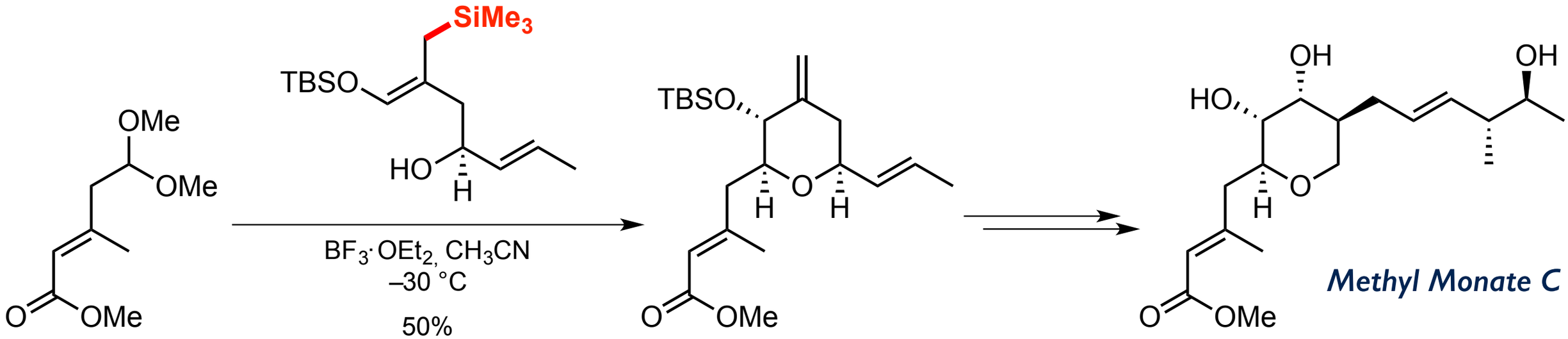


For a microreview, see: Floreancig, P. E. *EJOC* **2013,** 1193



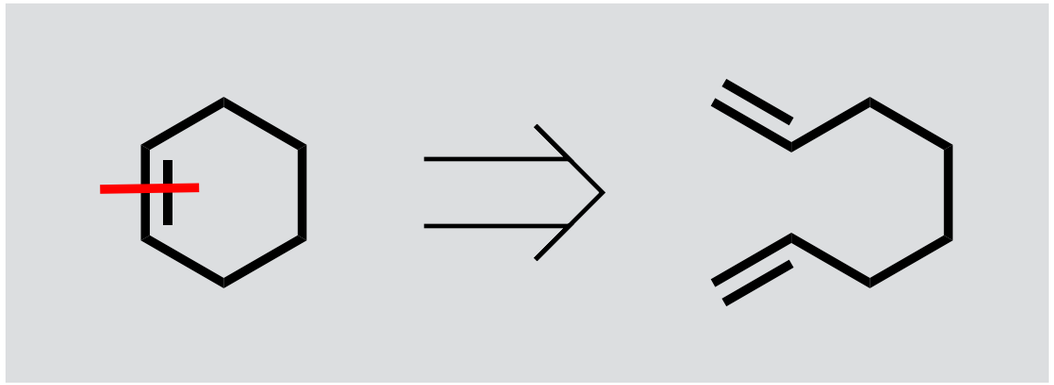
Neopeltolide

Maier, M. E. *CEJ* **2008**, *14*, 11132

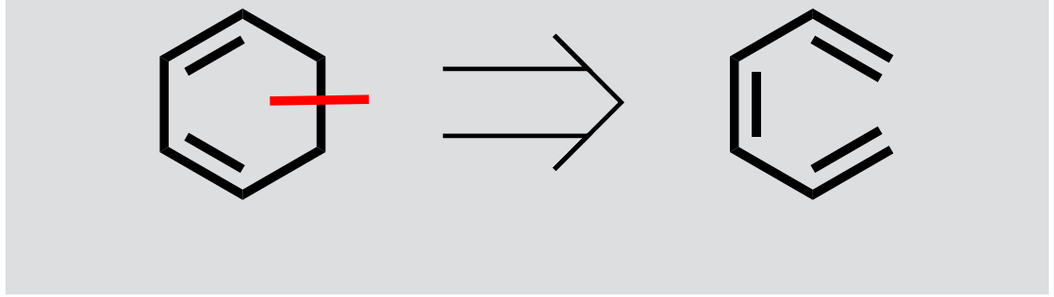


Methyl Monate C

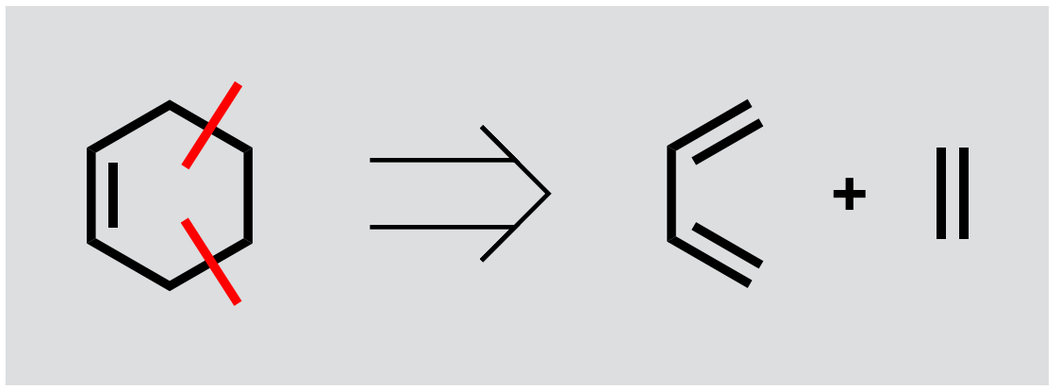
Markó, I. E. *CEJ* **2006**, *8*, 6111



Ring Closing Metathesis (RCM)



Electrocyclic Rearrangement



Diels Alder Cycloaddition

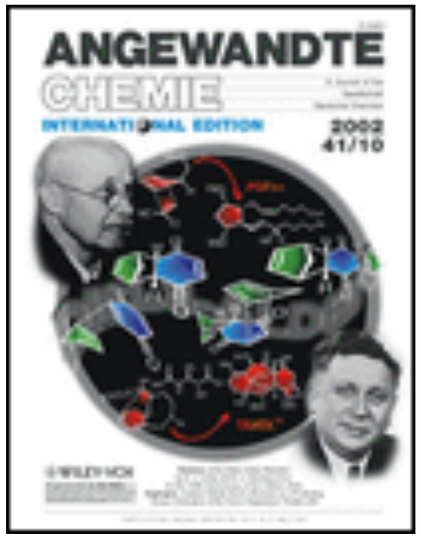
The venerable Diels-Alder reaction: a straightforward route to six-membered rings

The Nobel Prize in Chemistry 1950 ...

Otto Diels

Kurt Alder

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



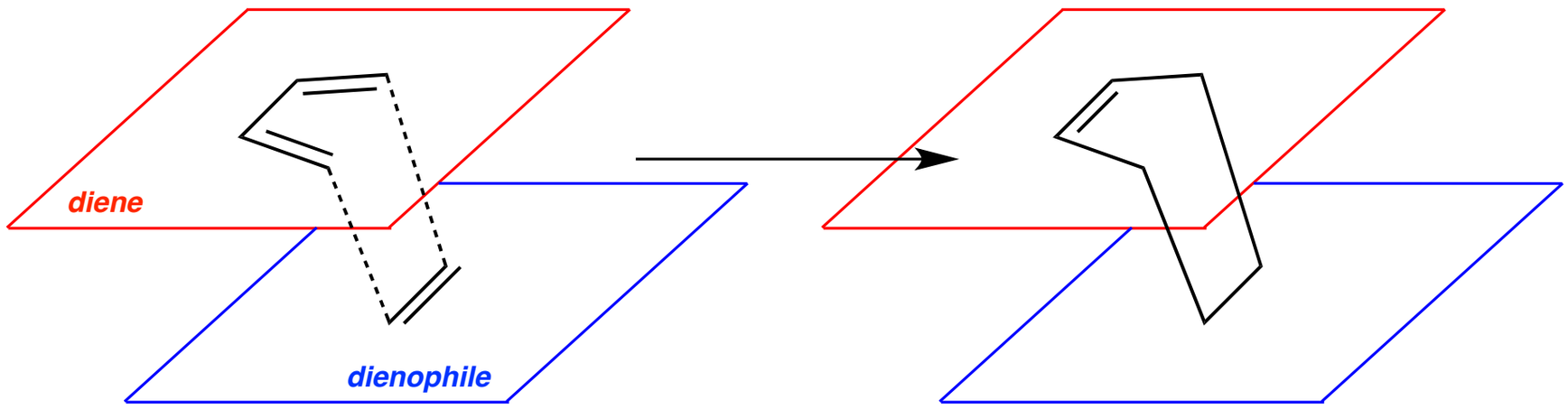
For a review on the Diels-Alder reaction in total synthesis:

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

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

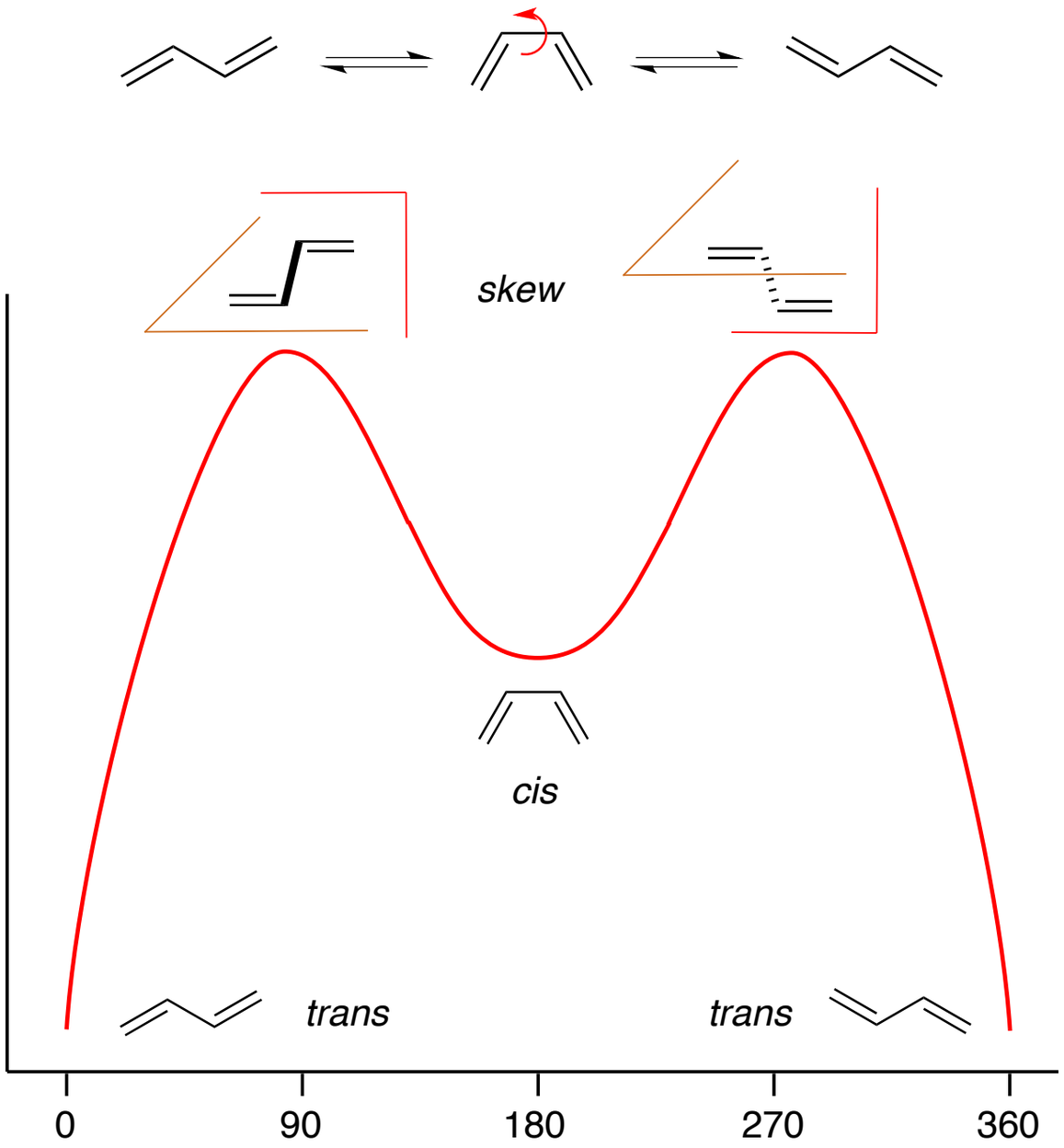
Funel, J.-A. *ACIE* **2013**, 52, 3822

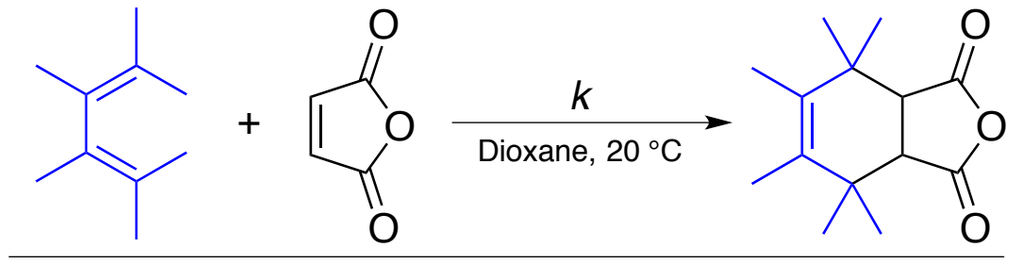
*The venerable **Diels-Alder** reaction is a [$4\pi_s + 2\pi_s$] cycloaddition*



Remember that an alkyne can also participate in the process

The kinetics of the reaction depends on ***conformational*** *…*

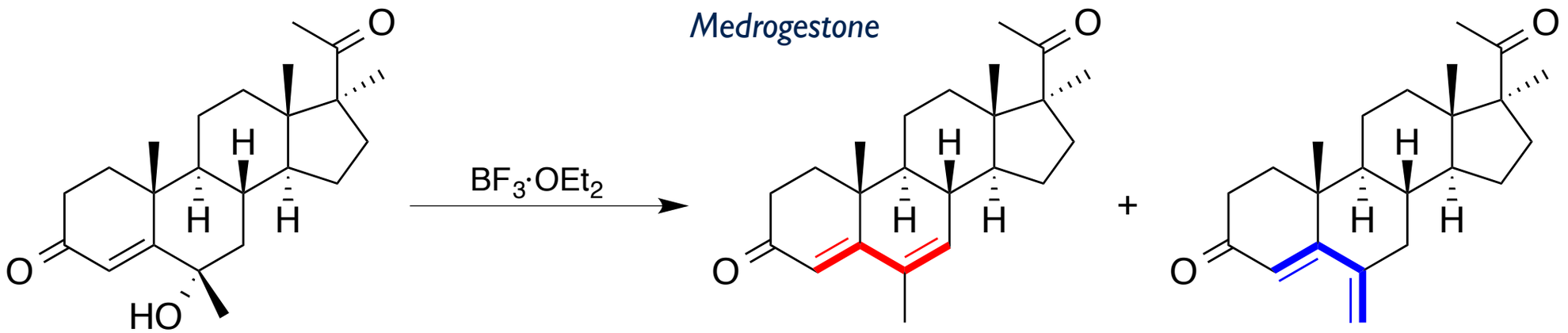




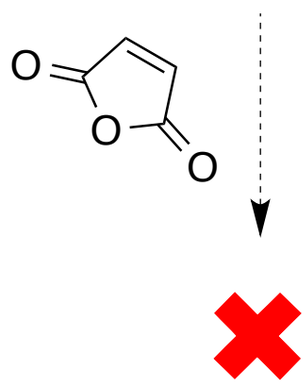
	1
	2.25
	~ 0
	3
	1350

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

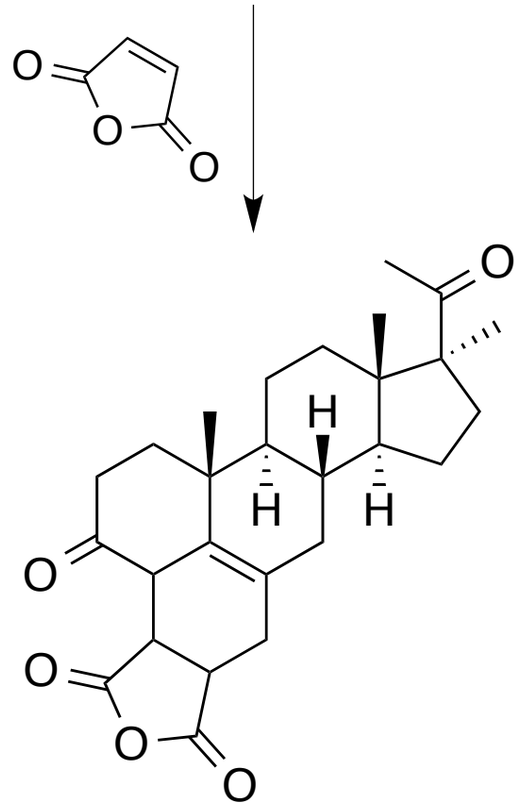
Occasionally, the lack of conformational freedom can be useful …



trans *conformation unreactive*



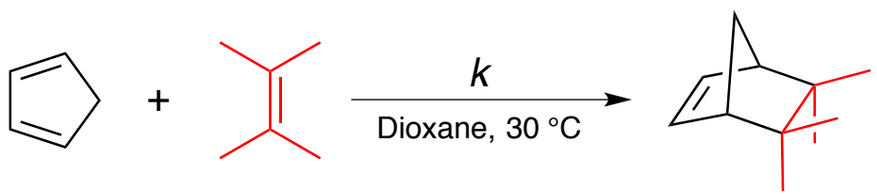
cis *conformation reactive*

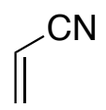
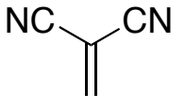
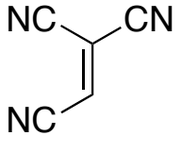
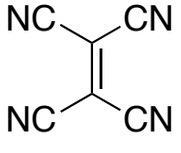


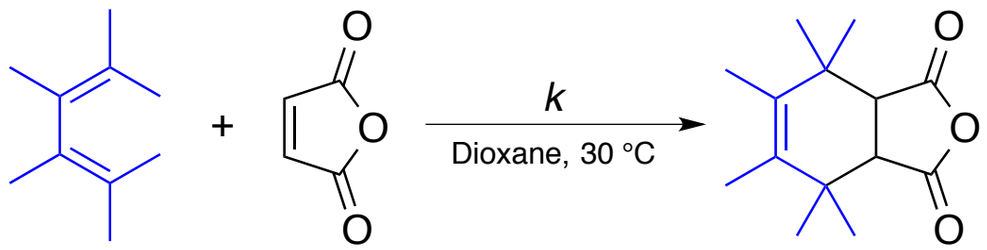
Winkley, M. W.; Mitchell, R. D. (American Home Products)
US5428151A, **1995**

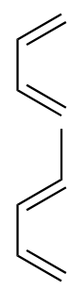
Diels-Alder Reaction: Kinetics

*… and **electronic** issues.*



	1
	$5 \cdot 10^4$
	$5 \cdot 10^5$
	$5 \cdot 10^7$



	1
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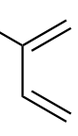
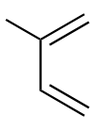
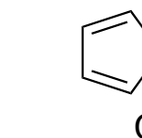
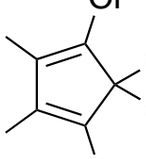
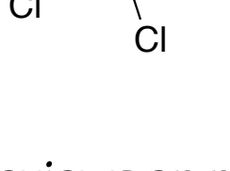
	12.3
	2.25
	0.1
	1350
	~ 0

Essential:

electronically rich diene & electronically poor dienophile

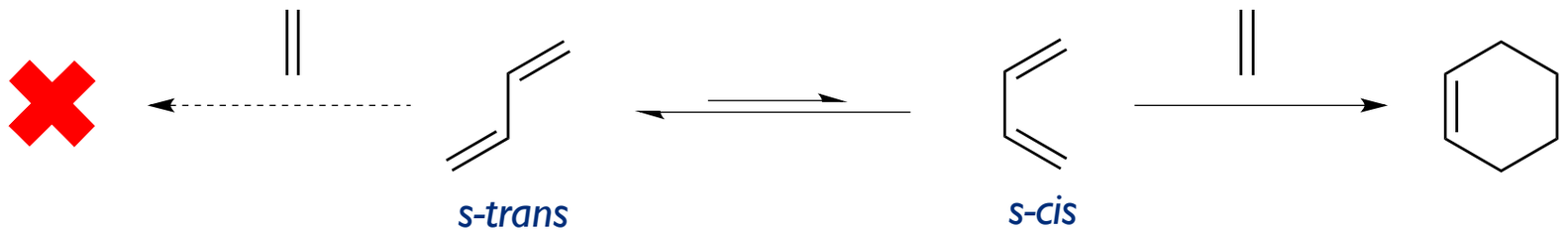
Complementary character.

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

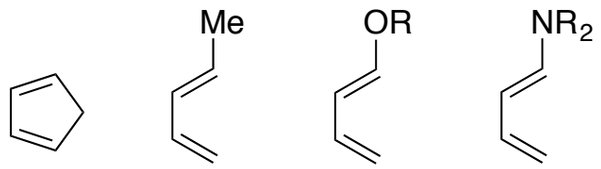
Sauer, *J. ACIEE* **1967**, *6*, 16 ; Sustmann, R. *ACIEE* **1980**, *19*, 779

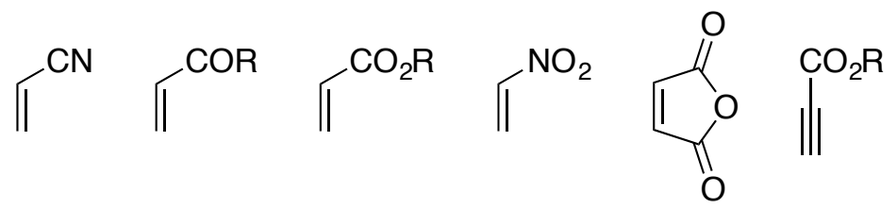
In Diels-Alder reactions under ***Normal electronic demand***

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

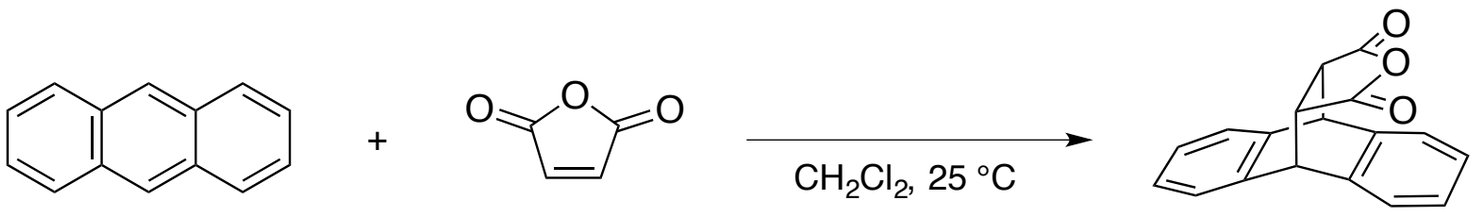


- *diene should contain electrondonating groups (EDG); dienophile, electronwithdrawing groups (EWG)*





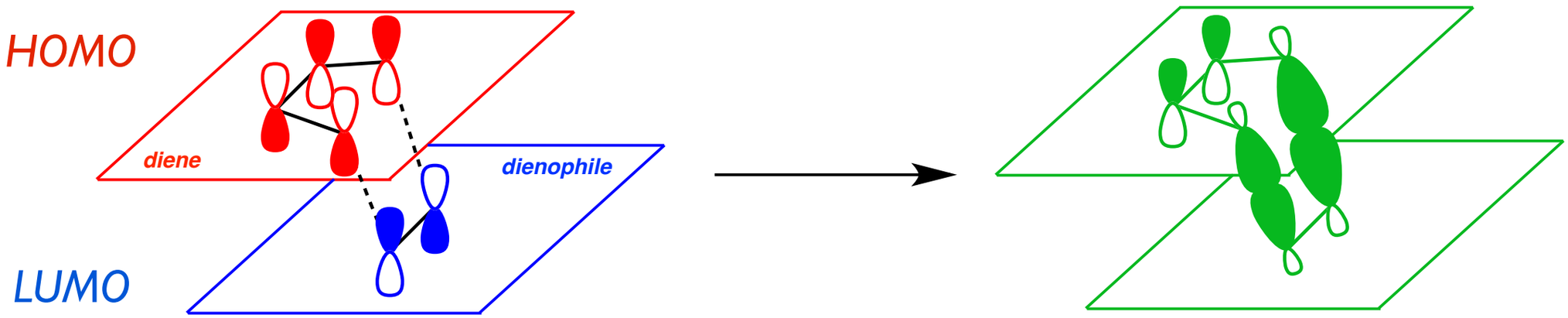
- *Lewis acids catalyze such cycloadditions*



Without $AlCl_3$ $t_{1/2}$ ~ 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

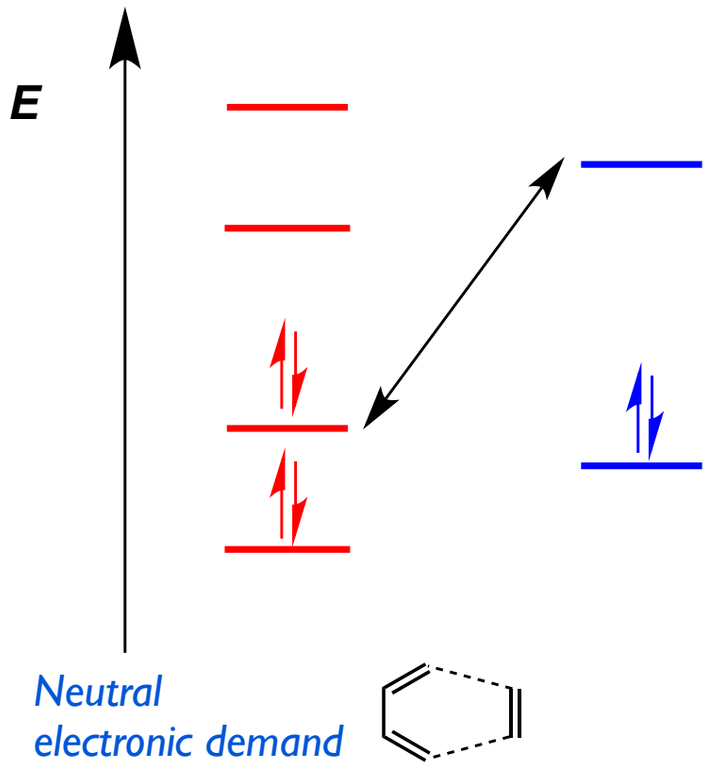


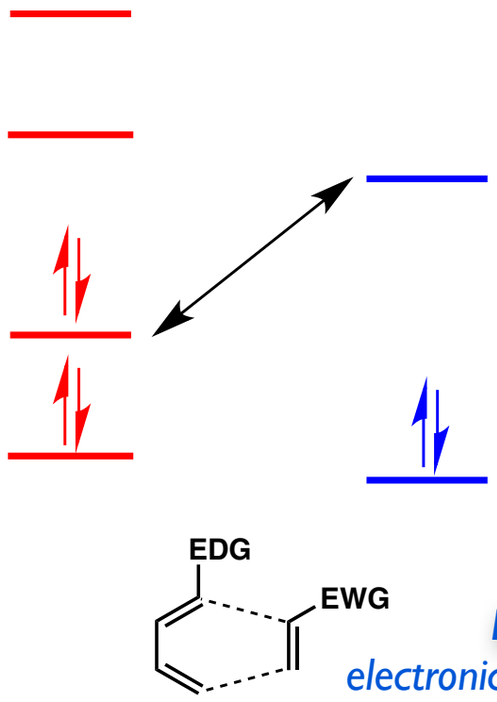
Thermodynamics: broken bonds, 3 π
new bonds, 2 σ + 1 π

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

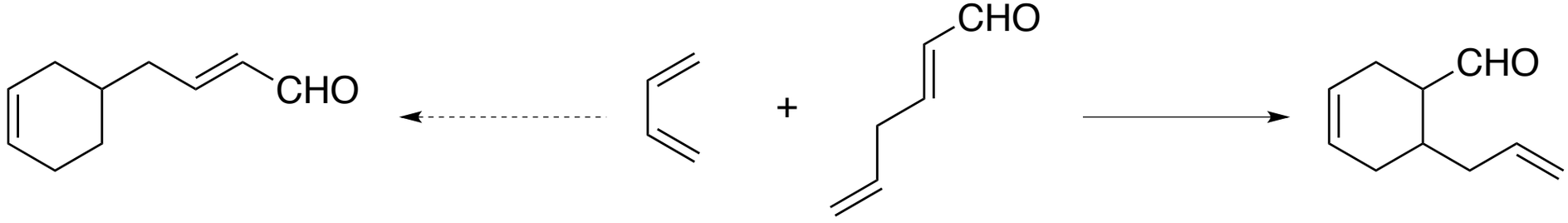


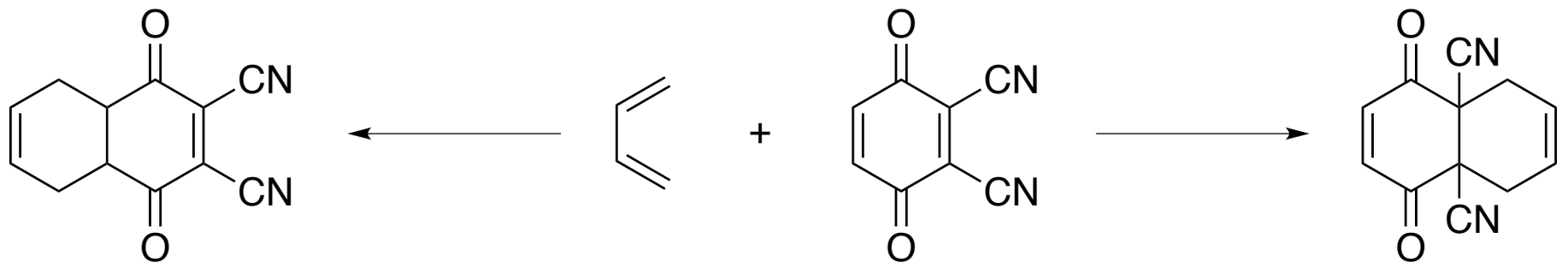


The HOMO-LUMO interaction and the cyclic transition state

*provide outstanding levels of **selectivity** ...*

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

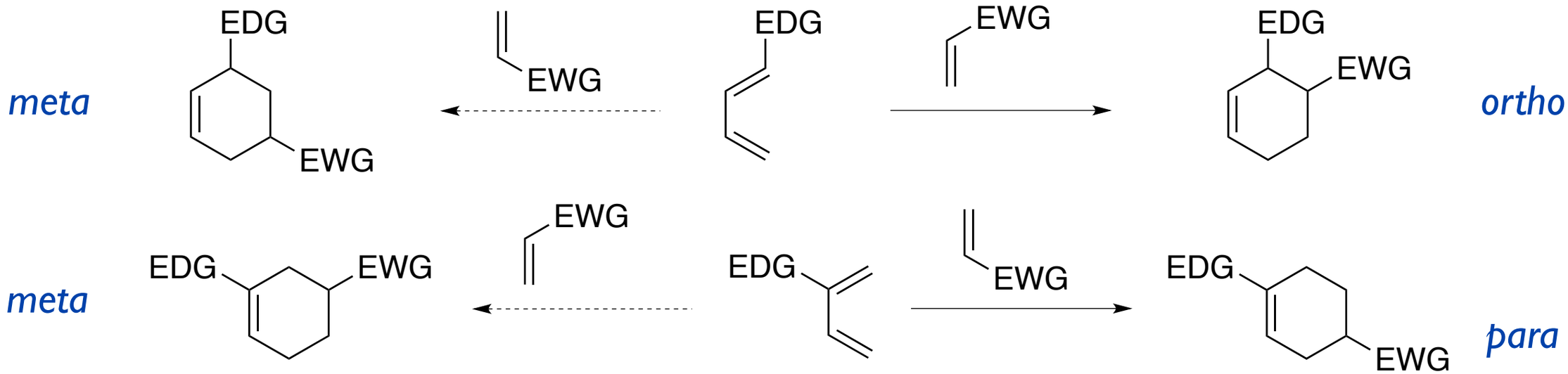


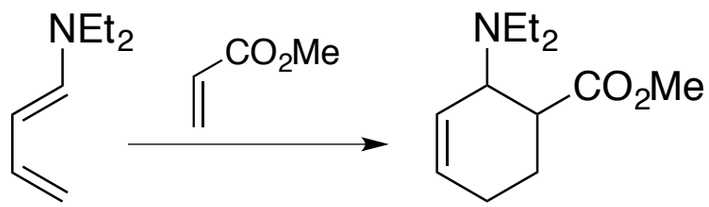


16%

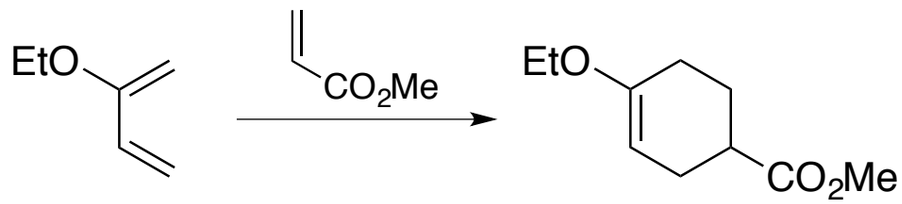
62%

Regioselectivity: *ortho-para rule*



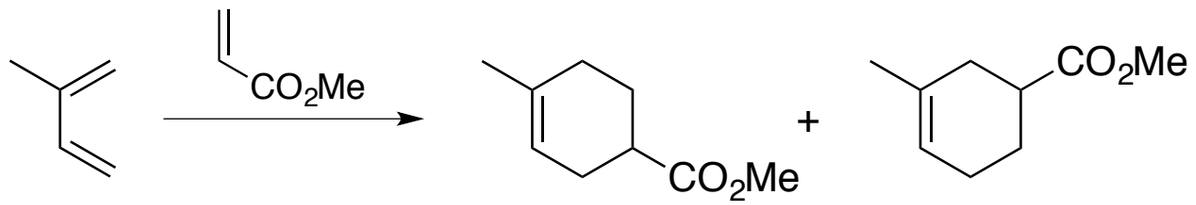


Single product



Single product

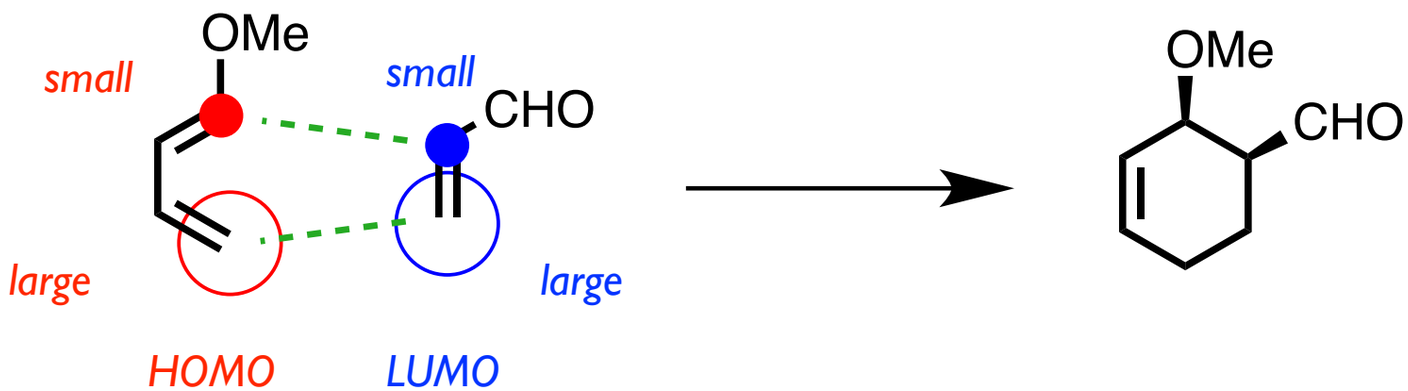
Lewis acids improve the regioselectivity

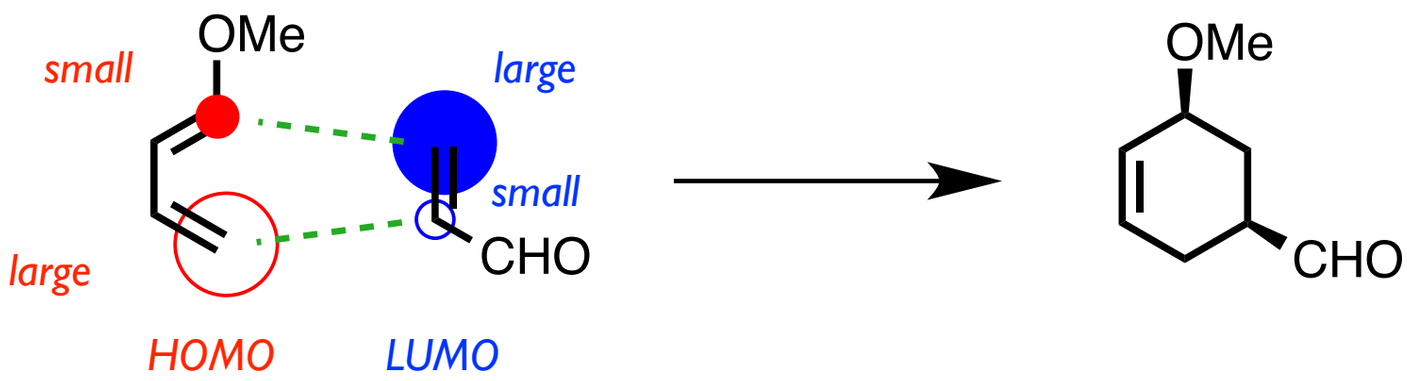


para *meta*

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

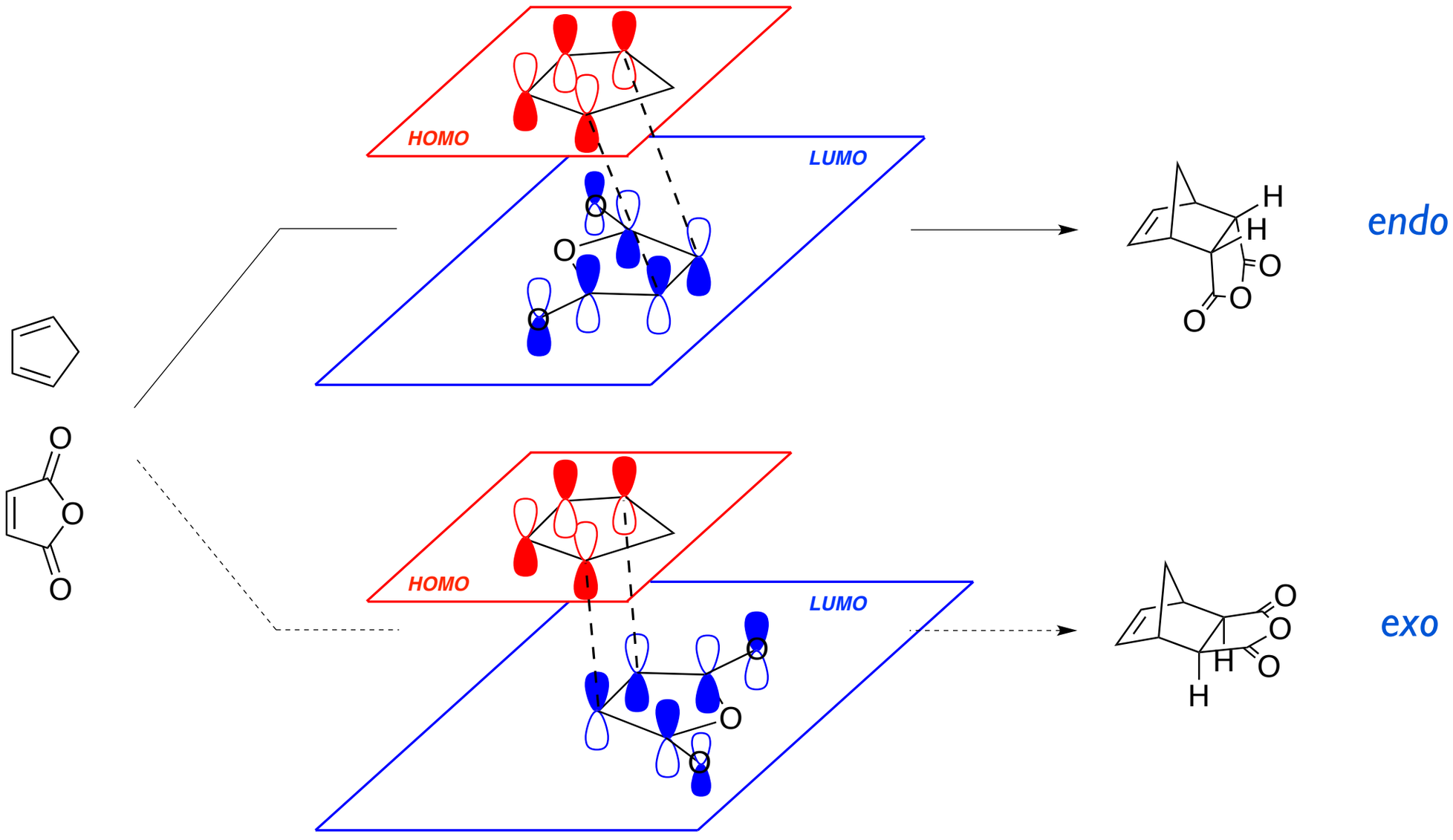
*The **ortho-para** rule can be understood through analysis of FMO orbitals*



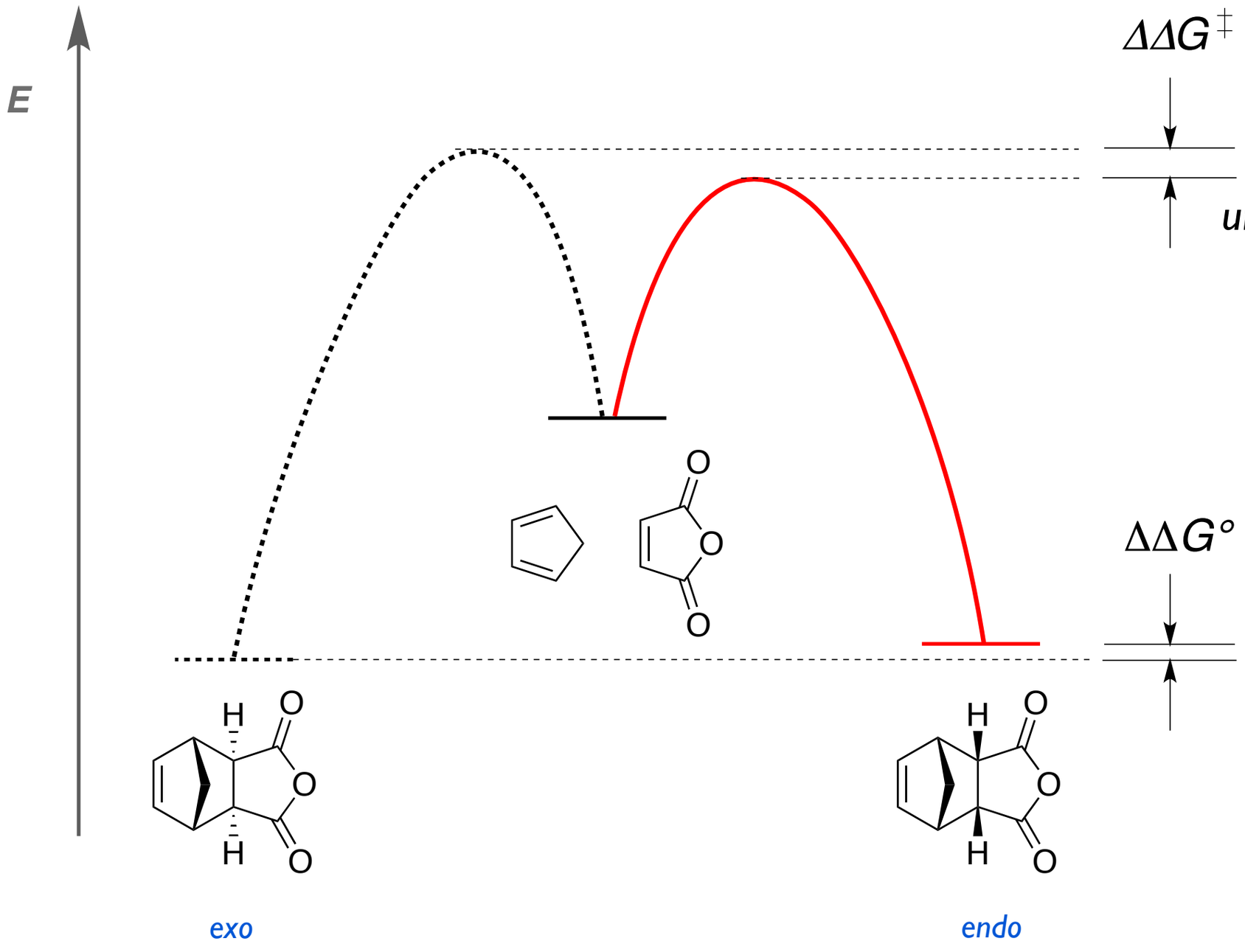


Large/Large & Small/Small interactions are better than Large/Small & Small/Large interactions

Stereoselectivity: *endo rule*



Kinetic vs Thermodynamic Control



exo

endo

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

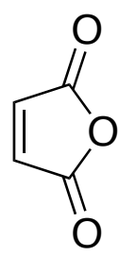
Kinetic Control

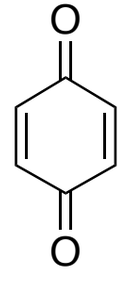
*Instead, the **exo** isomer predominates at equilibrium*

Thermodynamic Control

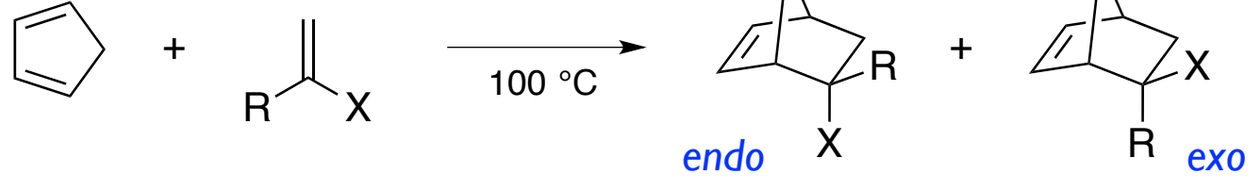
Diels-Alder Reaction: Stereoselectivity

- ***Endo*** *stereoselectivity is excellent with planar dienophiles*



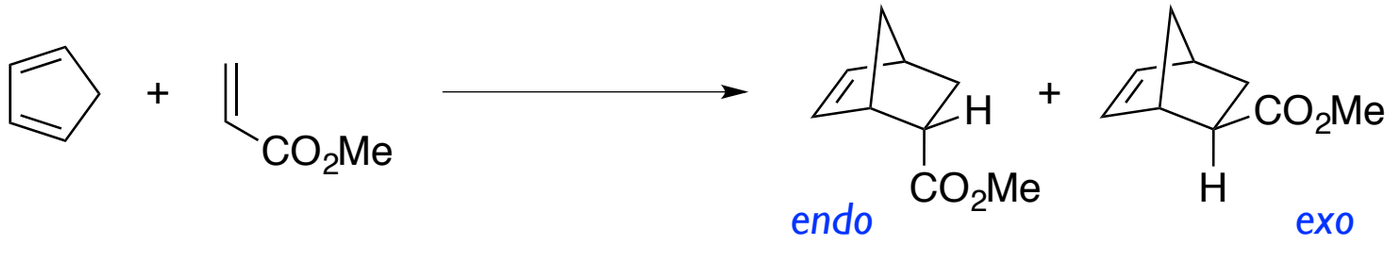


- ***Exo*** *diastereomers are preferred with α substituted dienophiles*



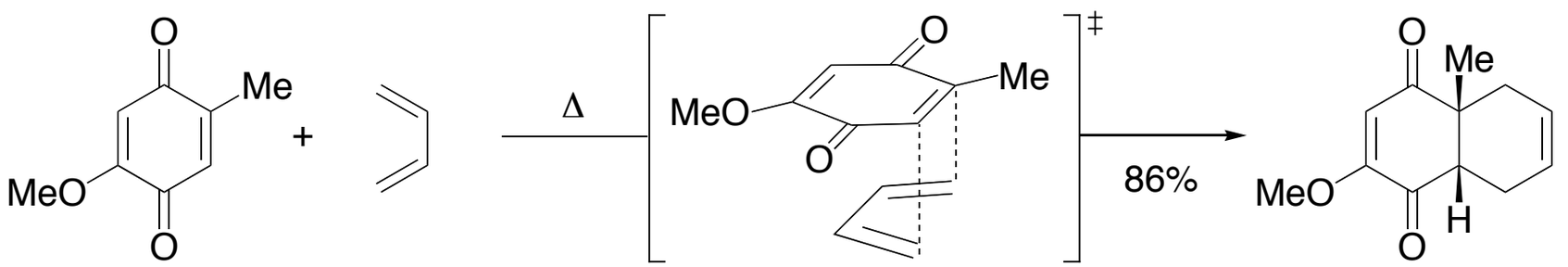
R	X	*endo* : *exo*
H	CN	55 : 45
H	COOMe	71 : 29
H	CHO	71 : 29
Me	CN	16 : 84
Me	COOMe	32 : 68
Me	CHO	24 : 76

- *Lewis acids improve* ***endo*** *stereoselectivity*

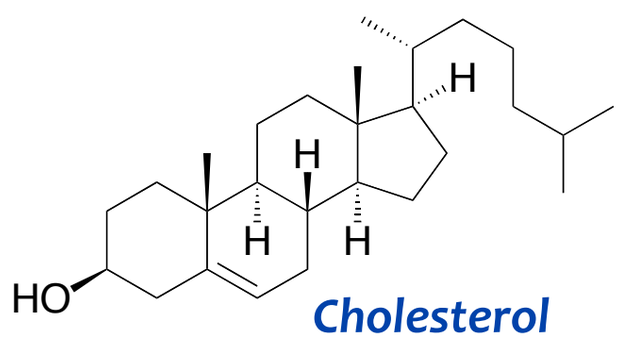


	endo : *exo*
CH_2Cl_2, 0 °C	80 : 20
C_6H_6, $SnCl_4$, 25 °C	95 : 5

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



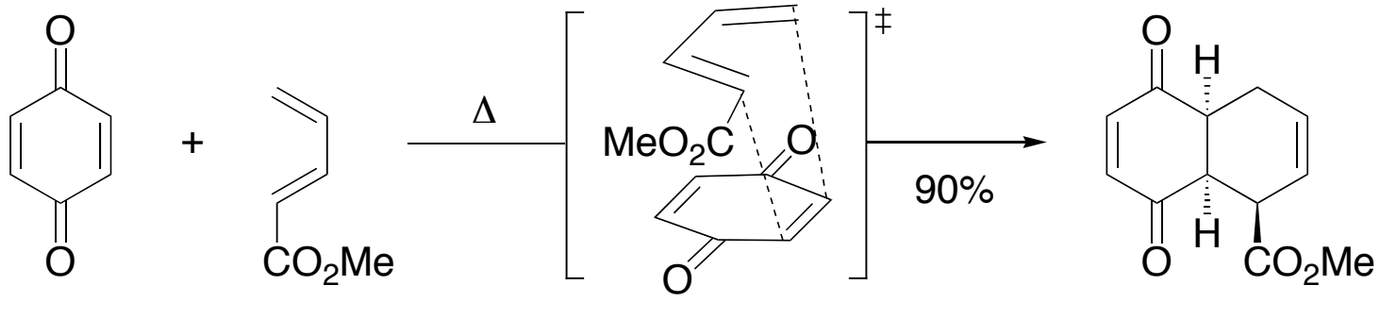
endo TS



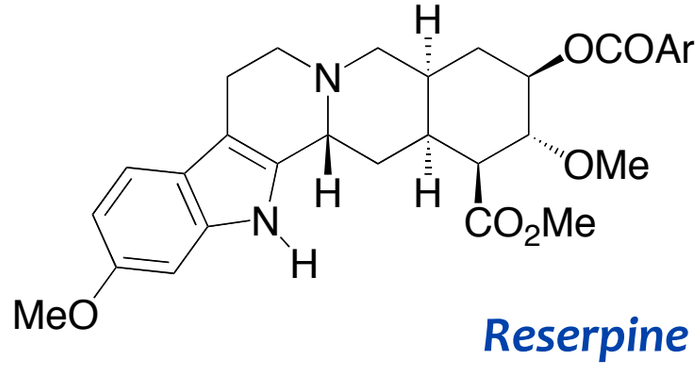
Cholesterol

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

… even with dienes containing EWG groups …



endo TS



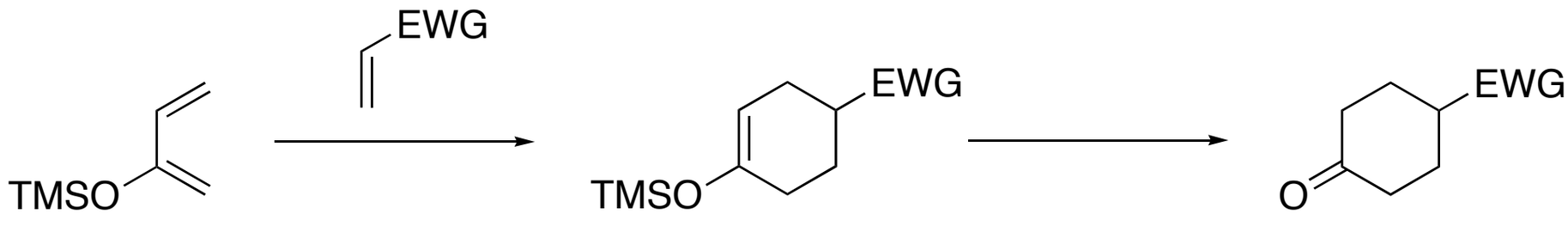
Reserpine

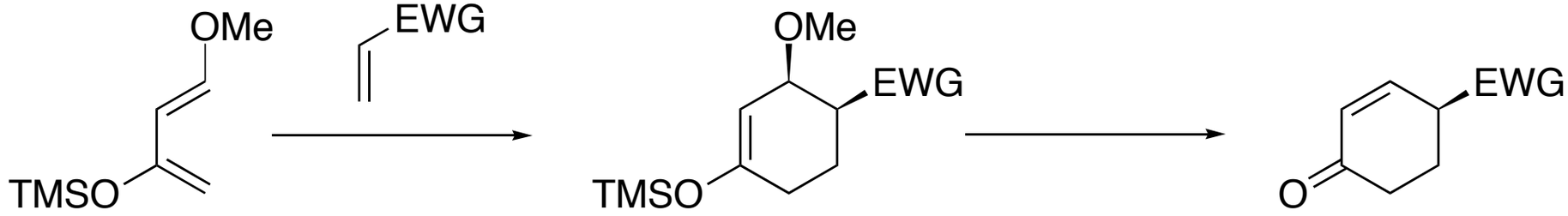
Woodward, R. B. *JACS* **1956**, *78*, 2023, 2657

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

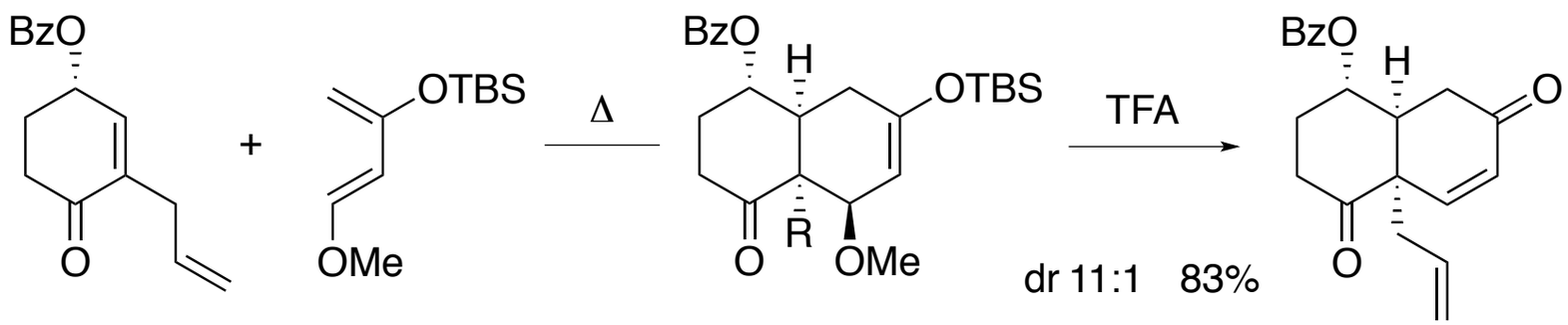
Moody, C. J. *ACIE* **2014**, *53*, 2056

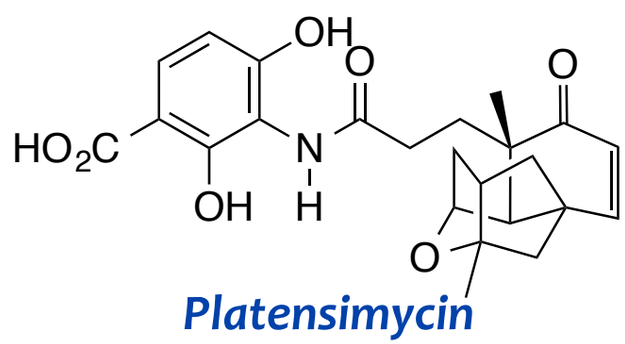
In fact, electronrich dienes containing R_3SiO substituents are very useful …





Danishefsky's diene

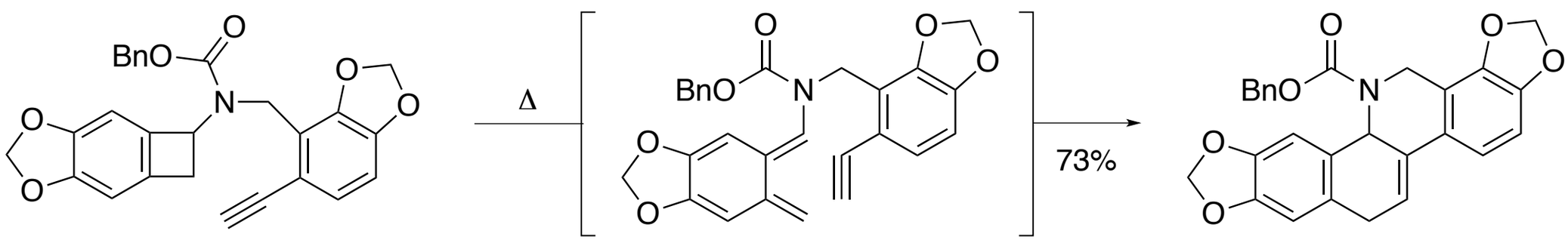




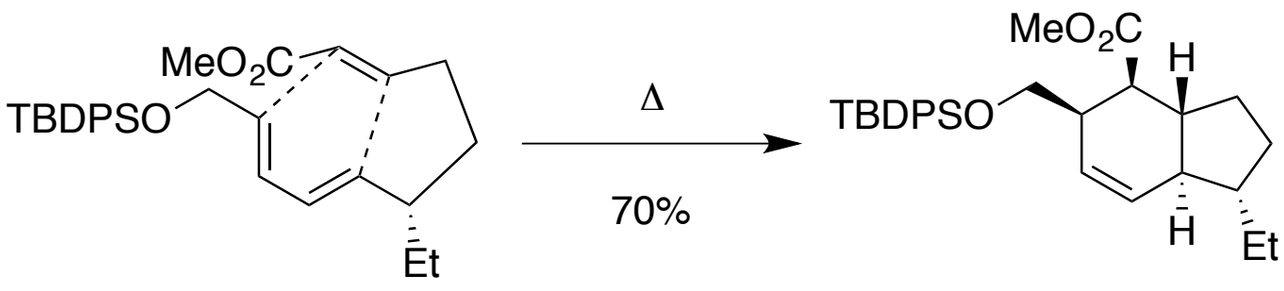
Platensimycin

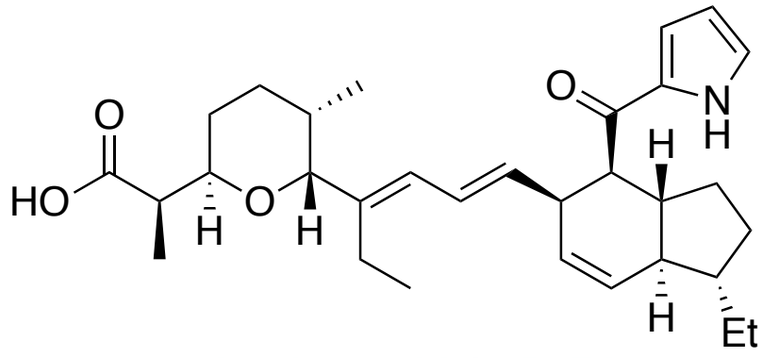
Matsuo, J.-i. *OL* **2010**, *10*, 4049

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



Conrotatory ring opening

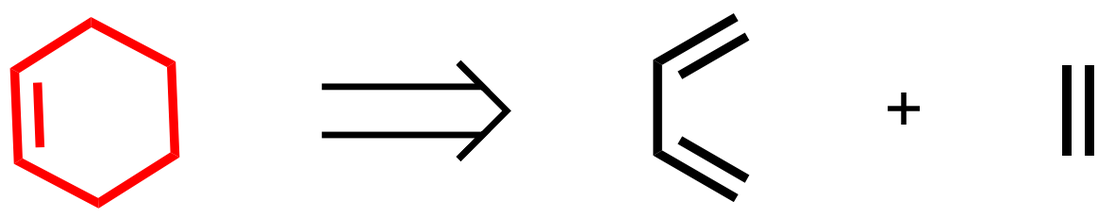




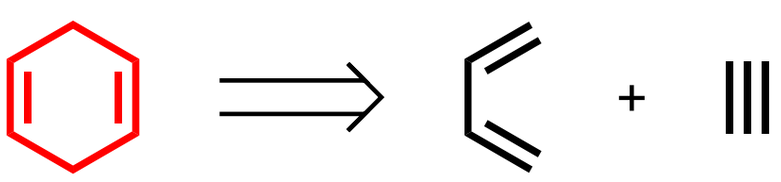
Antibiotic X-14547A

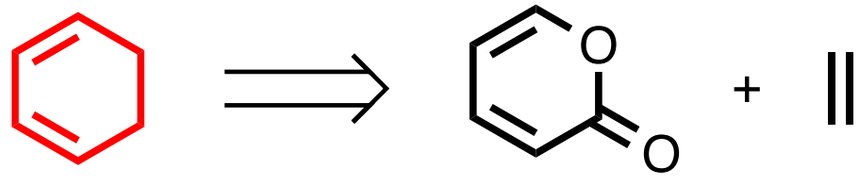
Nicolaou, K. C. *JOC* **1985**, *50*, 1440

Retron: molecular substructure that enables certain transformations

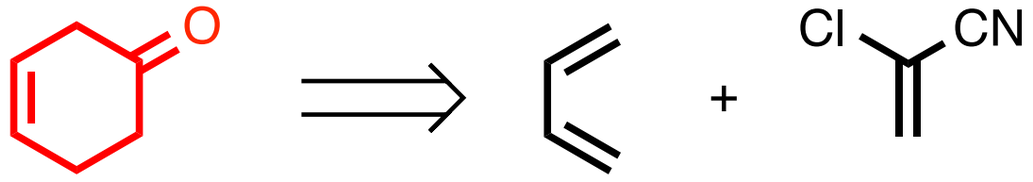


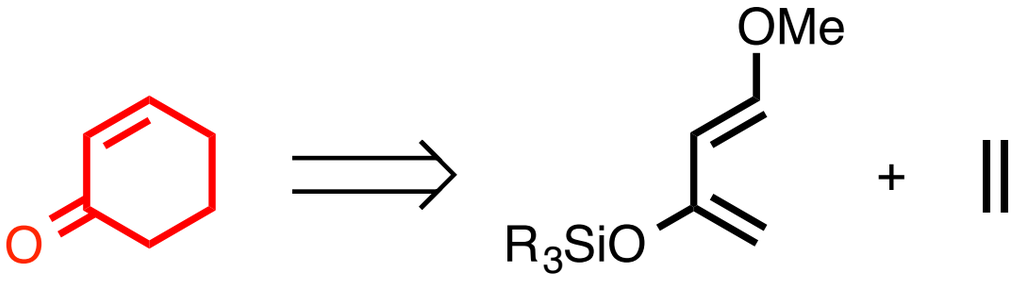
Supra Retron: molecular substructure that can be associated with a variant of a general transform





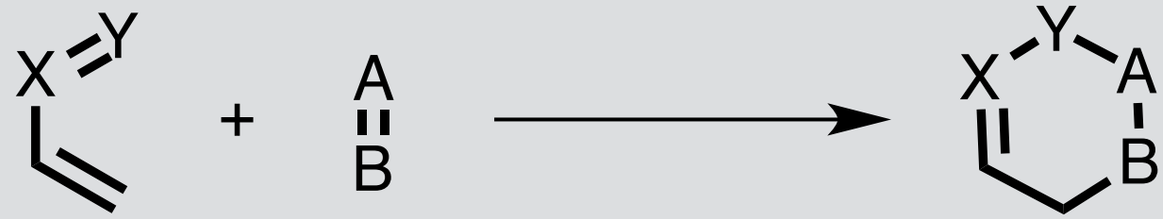
α-pyrone





Danishefsky's diene

The substitution of a C atom of one of the reagents involved in the former ***carbo*** *Diels-Alder gives rise to a new* $[4\pi_s + 2\pi_s]$ *cycloaddition named* ***hetero Diels-Alder***



X, Y, A, or B: **N** or **O**

diene ***dienophile***

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

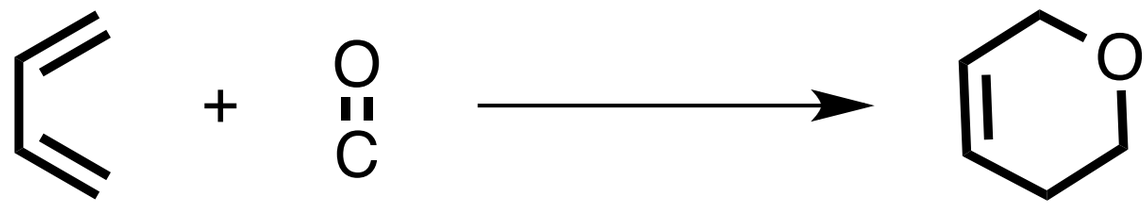
2 σ **– 2** π

KEEP ALSO IN MIND THE ENTROPIC FACTOR

*The **hetero Diels-Alder** reactions are mechanistically much more complex*
*than the related **carbo Diels-Alder** reactions,*
*but one can also differentiate **normal** and **inverse HDA***

Normal HDA

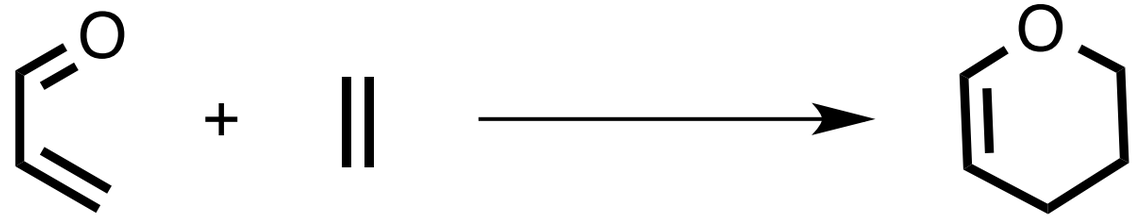
$HOMO_{diene} - LUMO_{dienophile}$



diene ***dienophile***

Inverse HDA

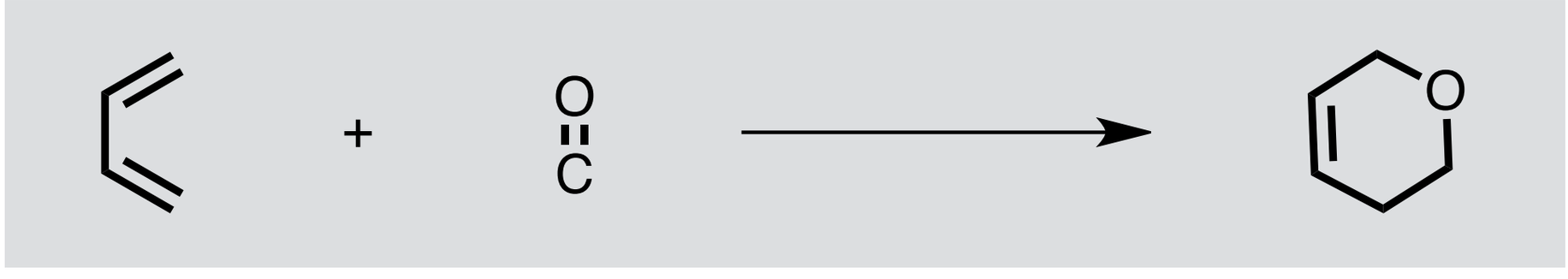
$HOMO_{dienophile} - LUMO_{diene}$



diene ***dienophile***

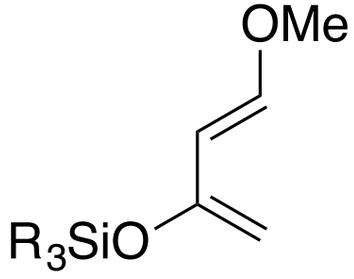
For reviews on HDA reactions see, Jorgensen, K. A. *ACIE* **2000**, 39, 3558; *EJOC* **2004**, 2093
Feng, X. *Synlett* 2007, 2147; Pellissier, H. *Tet* **2009**, 65, 2839
Miller, M. J. *ACIE* **2011**, *50*, 5630; Kumar, K.; Waldmann, H. *ACIE* **2014**, *53*, 11146

Normal HDA

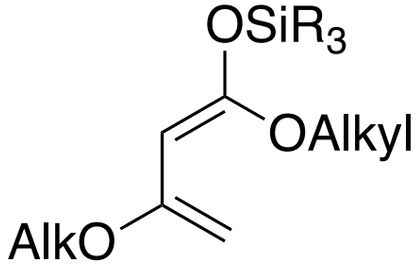


electron-rich diene

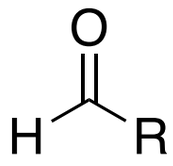
electron-poor dienophile



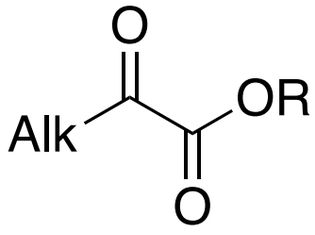
Danishefsky dienes



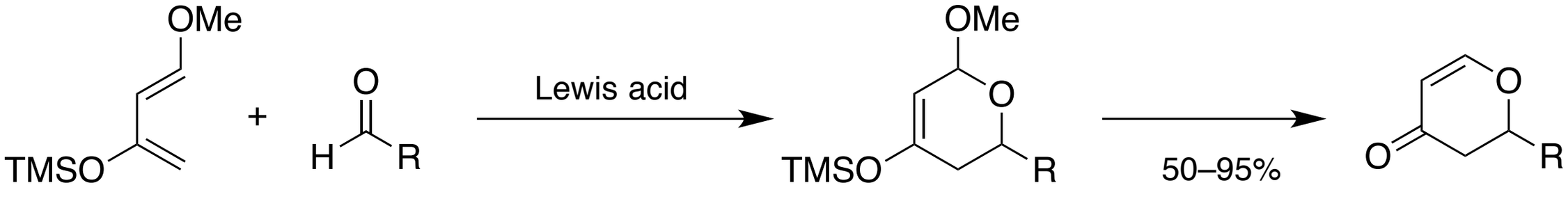
Brassard dienes



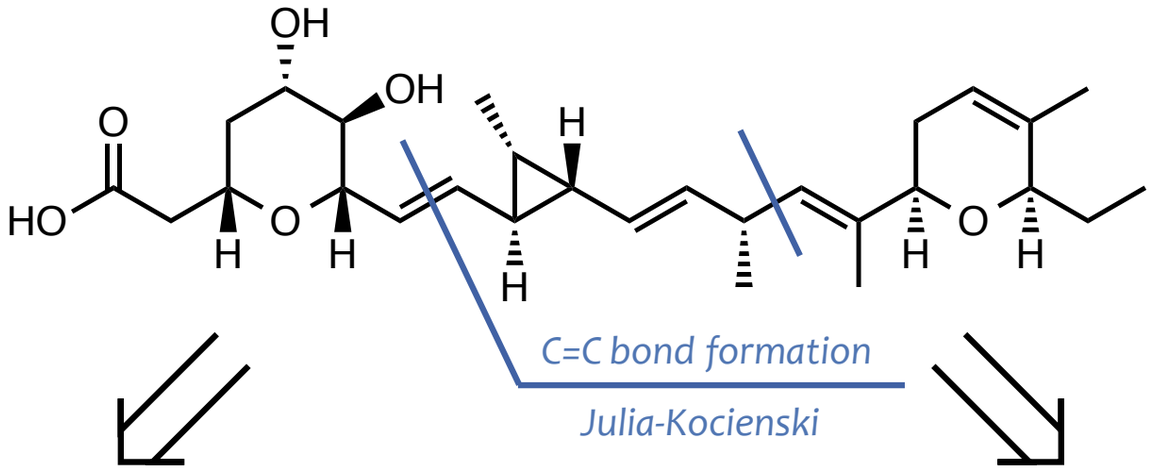
Aldehydes



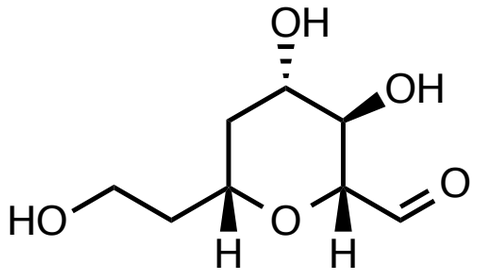
a-Oxoesters

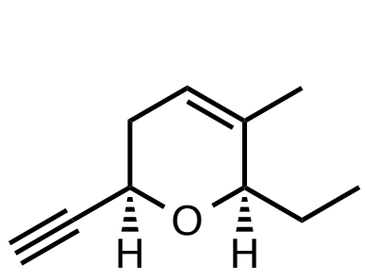


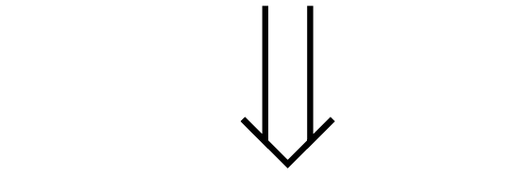
Stereoselective Synthesis of (+) Ambruticin

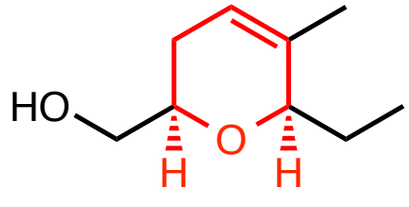


(+) Ambruticin





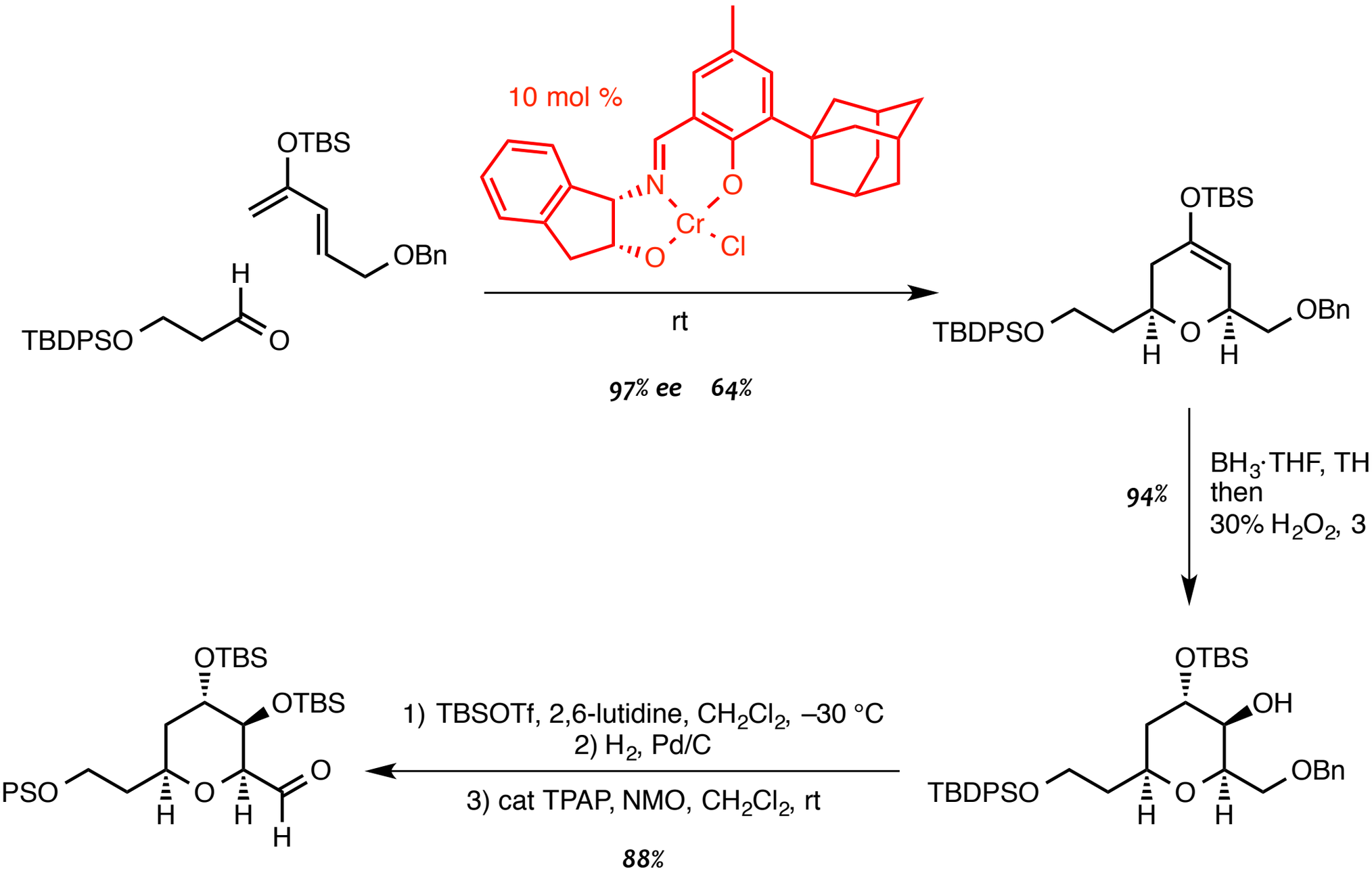




Asymmetric HDA provides a quick access to both pyran heterocycles

Jacobsen, E. N.
JACS **2001**, *123*, 10772

Stereoselective Synthesis of (+) Ambruticin

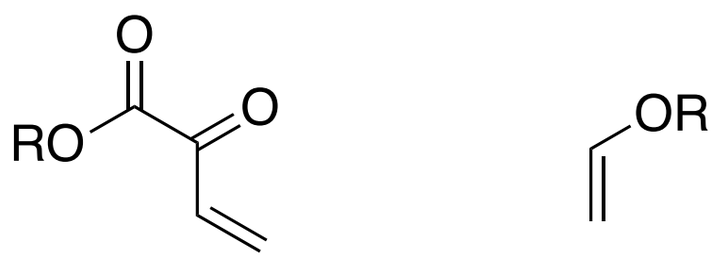


Jacobsen, E. N.
JACS **2001,** *123,* 10772

Inverse HDA

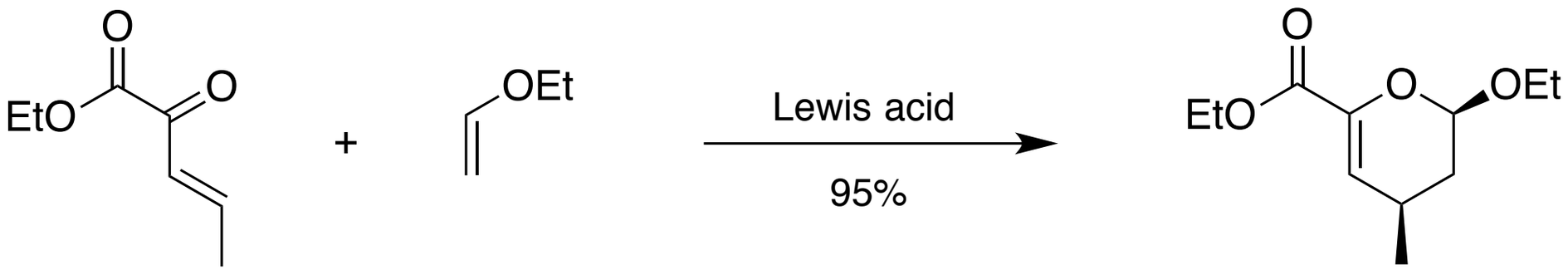
electron-poor diene

electron-rich dienophile

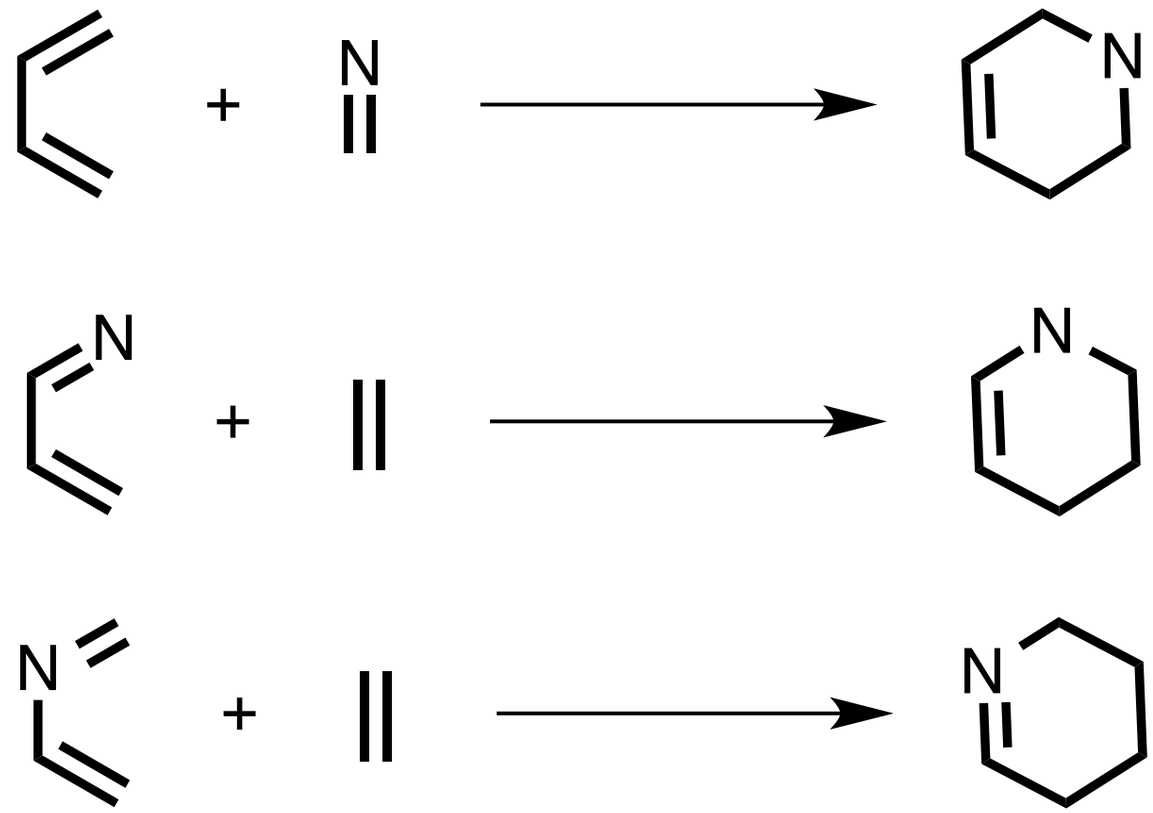


Deactivated enones

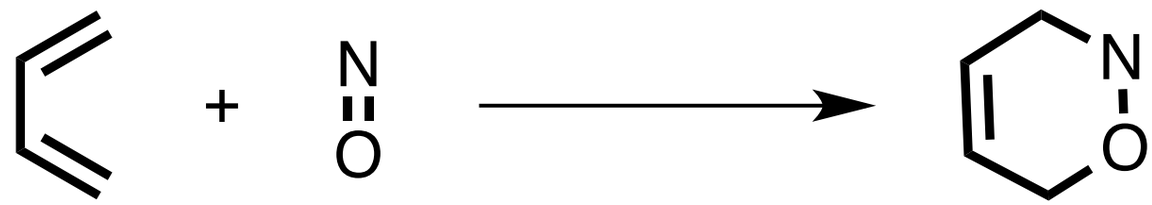
Vinyl ethers



Aza Diels Alder



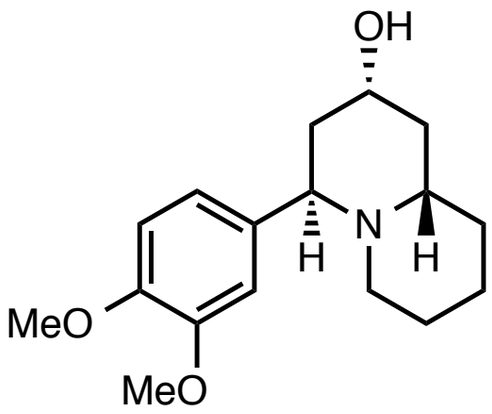
Nitroso Diels Alder



For reviews on as HDA reactions see, Oh, T. *Tet* **2001**, *57*, 6099

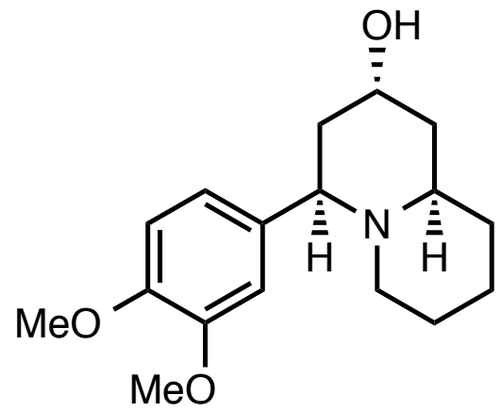
Masson, G. *CSR* **2013**, *42*, 902

Stereoselective Syntheses of (+) Lasubines

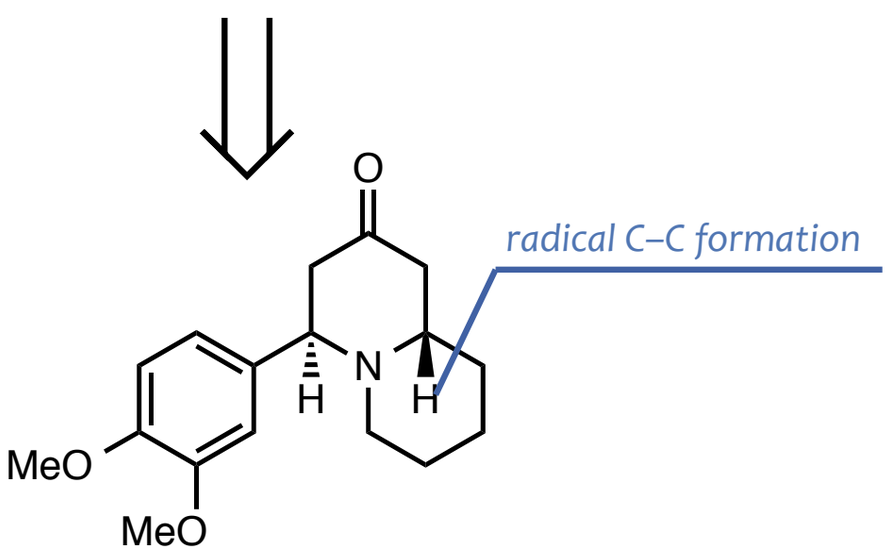


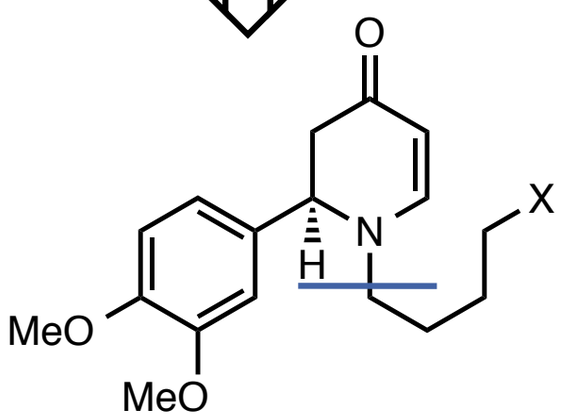
(+) Lasubine I

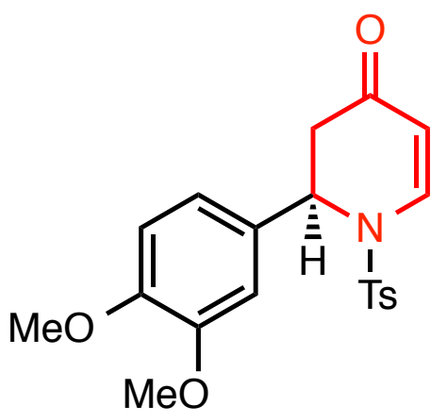
(+) Lasubine II

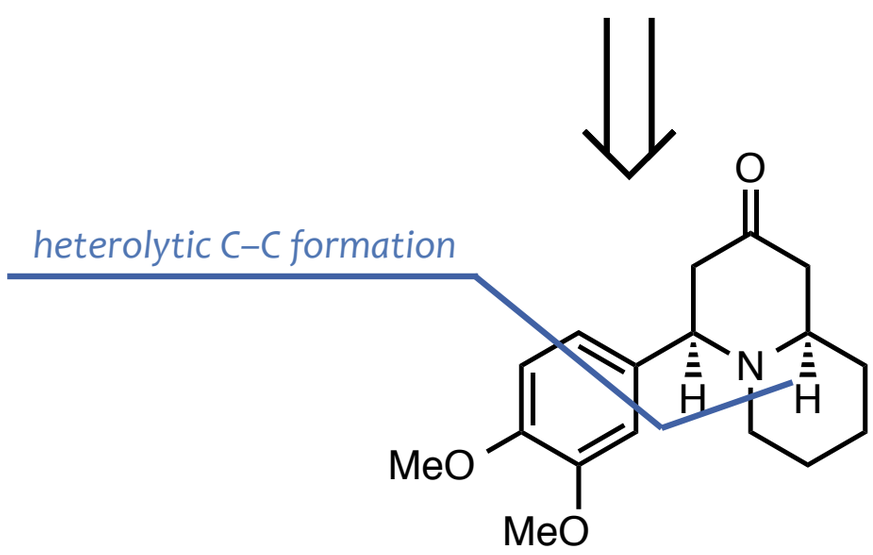


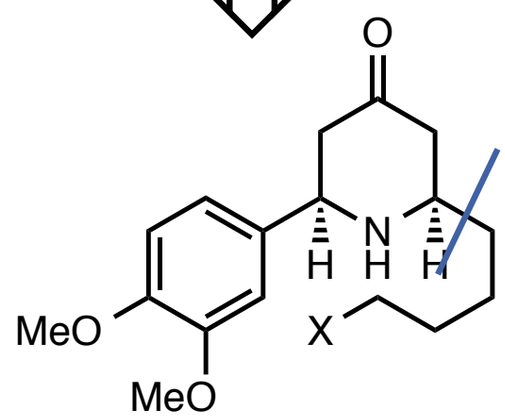
Carretero, J. C. *JOC* **2007**, *72*, 10294



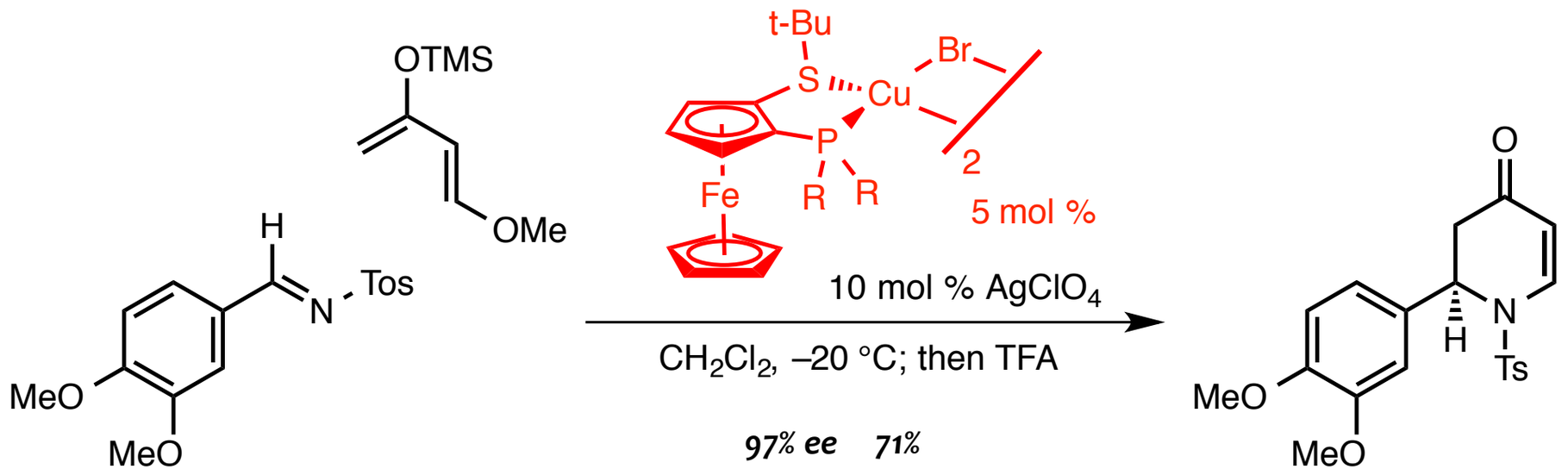


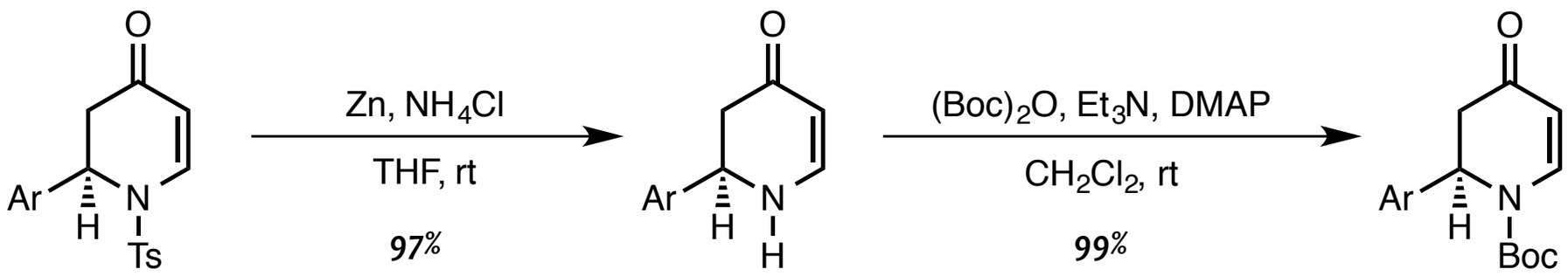






Stereoselective Syntheses of (+) Lasubines



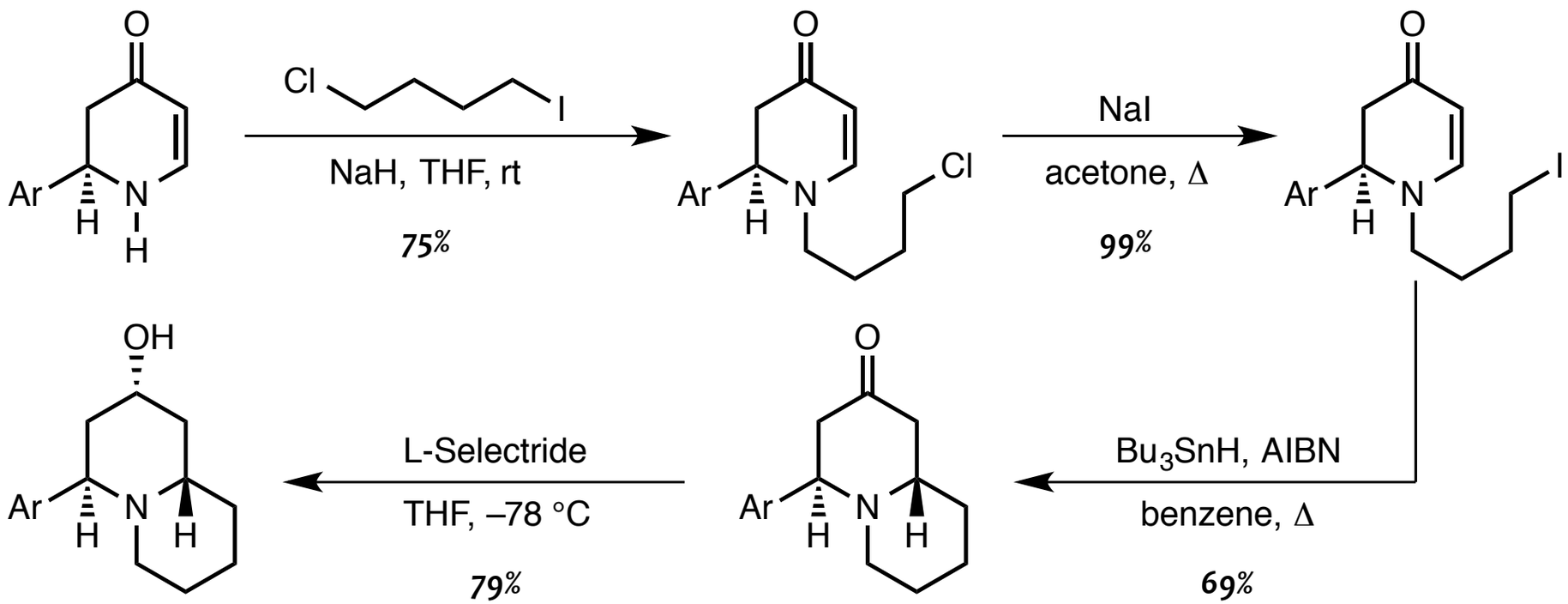


(+) Lasubine I ***(+) Lasubine II***

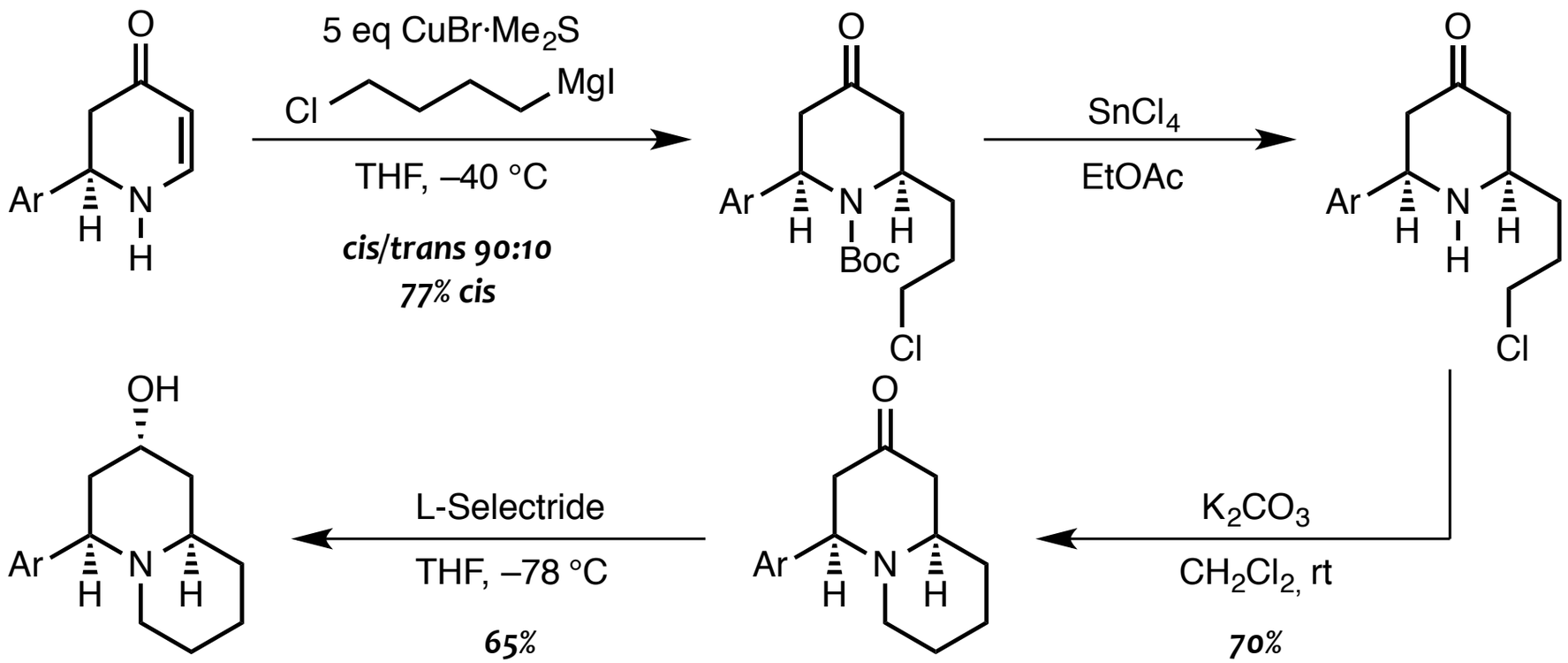
Carretero, J. C. *JOC* **2007,** *72,* 10294

Stereoselective Syntheses of (+) Lasubines

(+) Lasubine I



(+) Lasubine II



What do I wear in bed?

Marilyn Monroe

5-Membered Rings

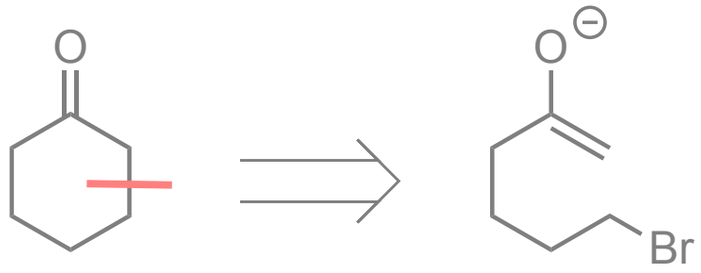
Five membered rings are highly valuable substrates and a huge variety of approaches have been devised

The synthetic methods for the 5-membered-rings are similar but not identical to those for 6-membered-rings

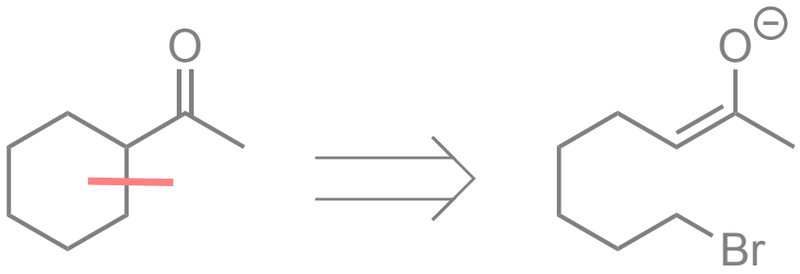
Radical cascades Nazarov 1,3-Dipolar cycloadditions Pauson-Khand

	Exo			*Endo*		
	Tet	*Trig*	*Dig*	*Tet*	*Trig*	*Dig*
3	✓	✓	≈	✗	✗	✗
4	✓	✓	≈	✗	✗	✗
5	✓	✓	✓	✗	✗	≈
6	✓	✓	✓	✗	✓	✓
7	✓	✓	✓	✗	✓	✓

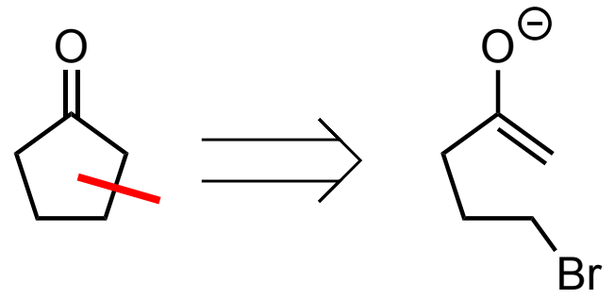
	Enolendo-Exo		*Enolexo-Exo*	
	Tet	*Trig*	*Tet*	*Trig*
3	✗	✗	✓	✓
4	✗	✗	✓	✓
5	✗	✗	✓	✓
6	✓	✓	✓	✓
7	✓	✓	✓	✓



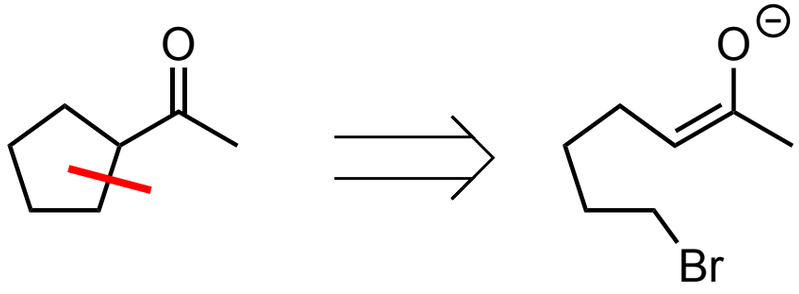
6-enolendo-exotet



6-enolexo-exotet

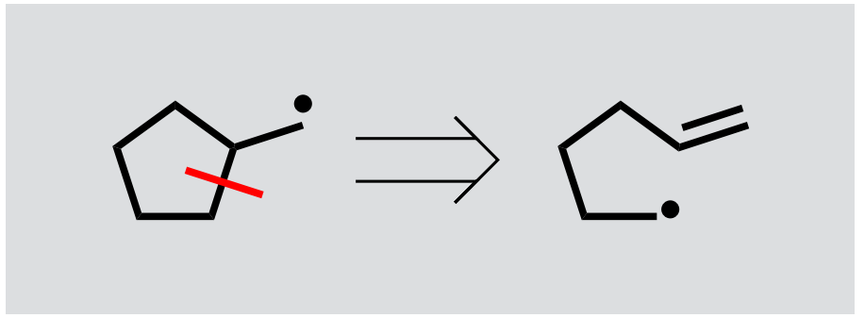


5-enolendo-exotet



5-enolexo-exotet

Alkylation reactions



Radical cyclizations

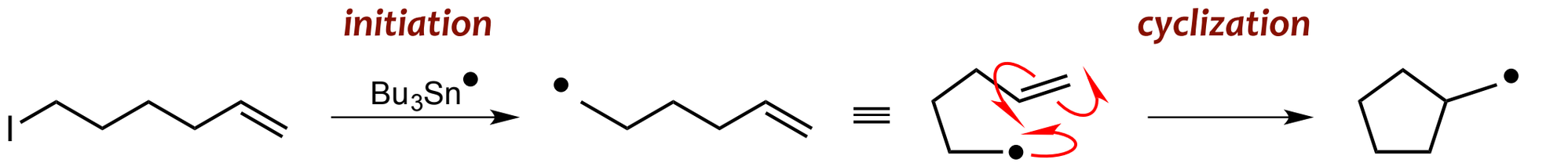
Initiation *generation of the radical center*

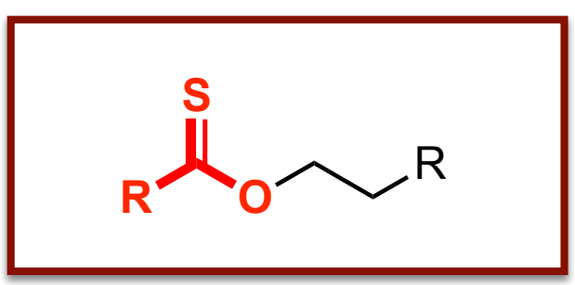
Cyclization *interaction of the radical center with a π-bond*

Termination *fate of the resultant radical*

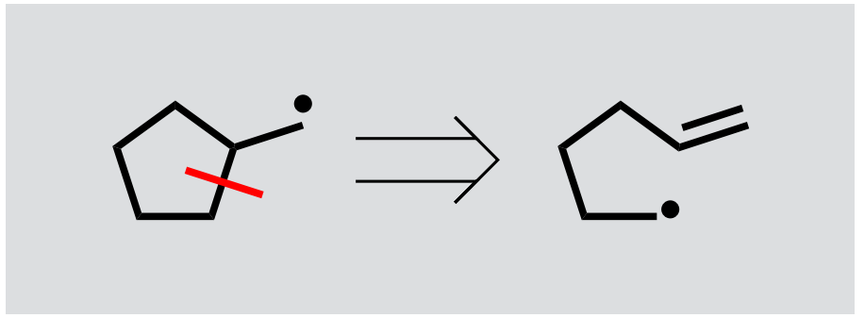
Radical cyclizations tolerate a large variety of FG

initiation ***cyclization***

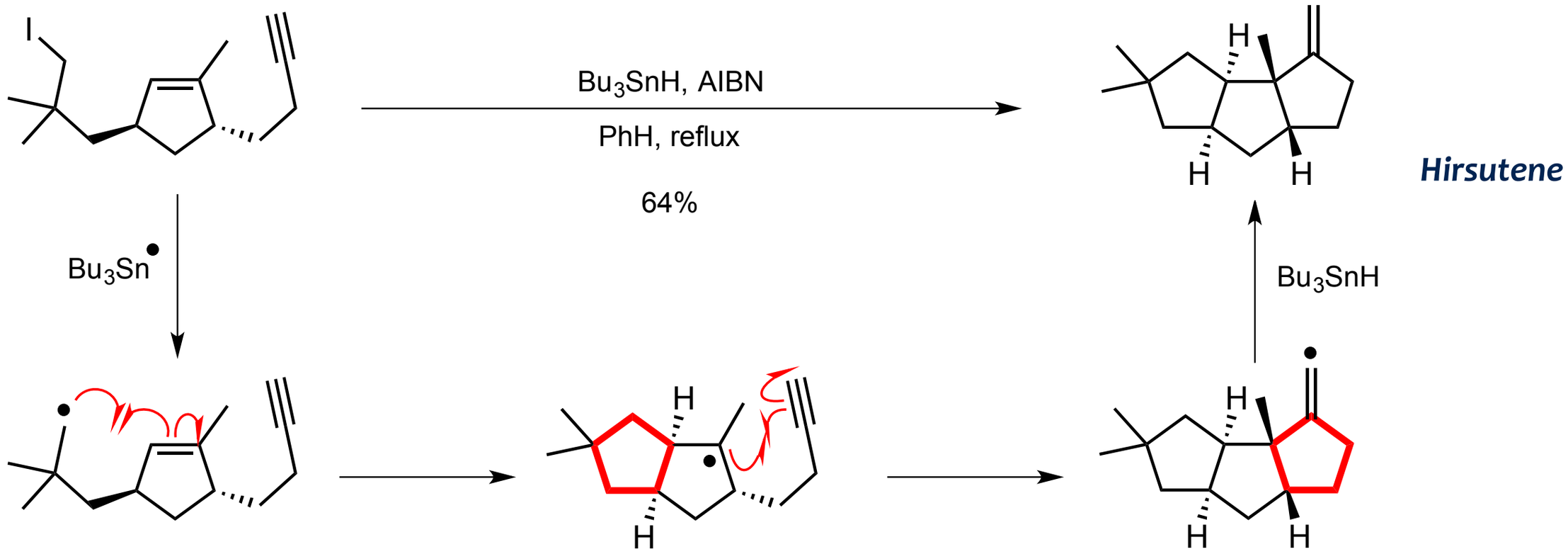




termination

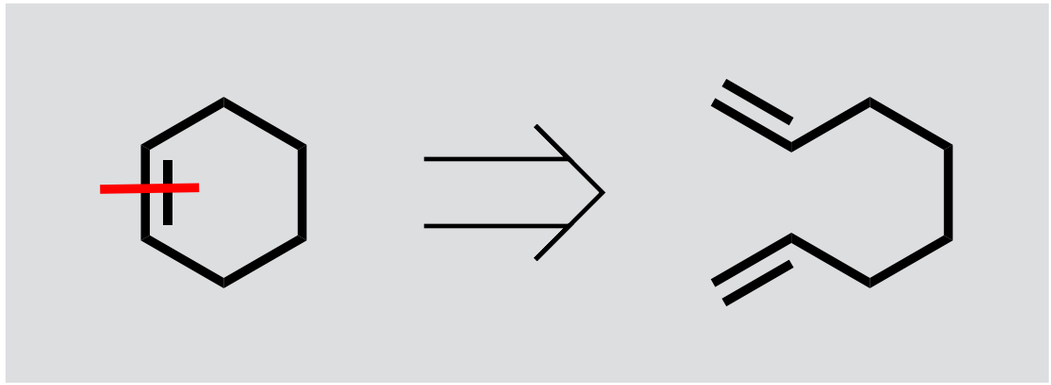


Radical cyclizations

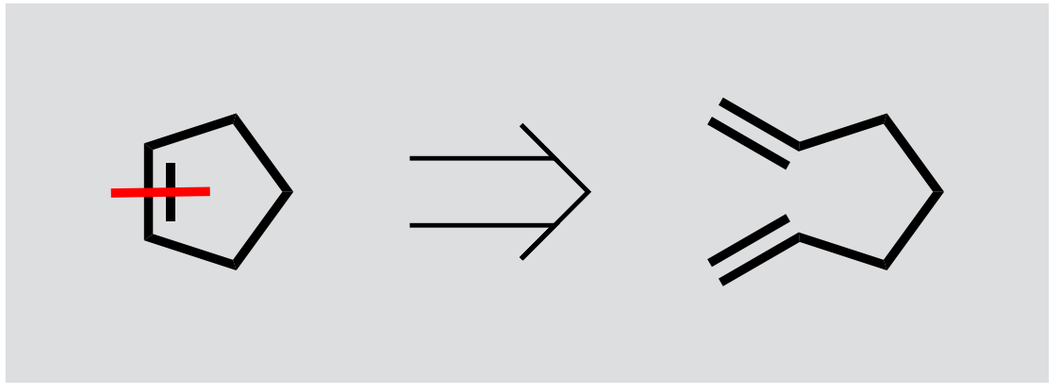


Hirsutene

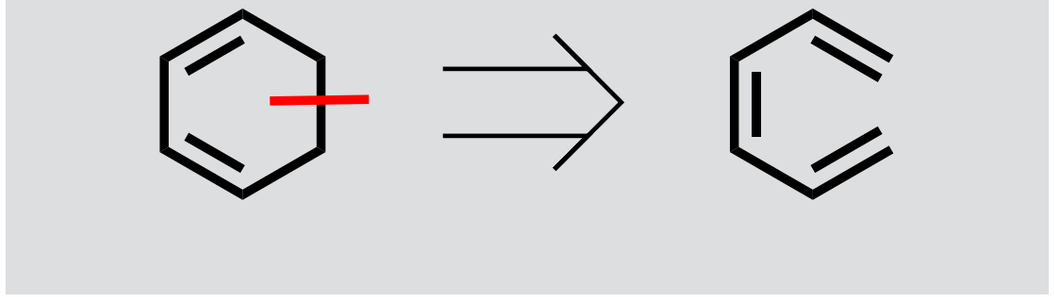
Curran, D. P. *JACS* **1985,** *107,* 1445



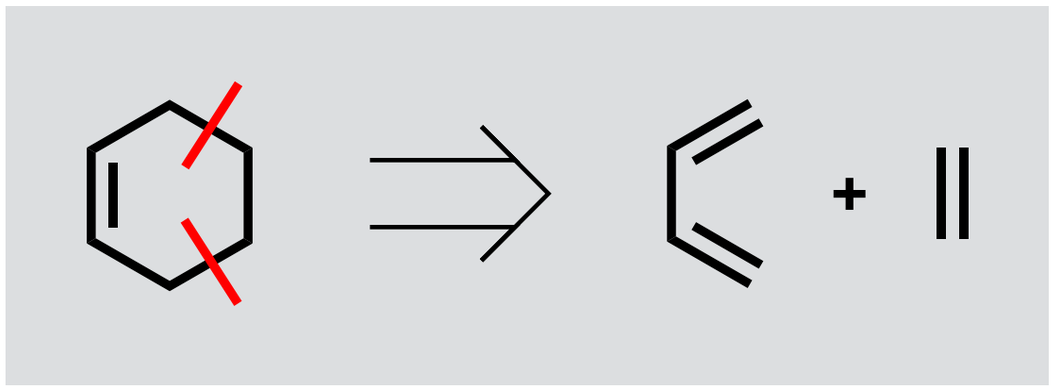
Ring Closing Metathesis (RCM)



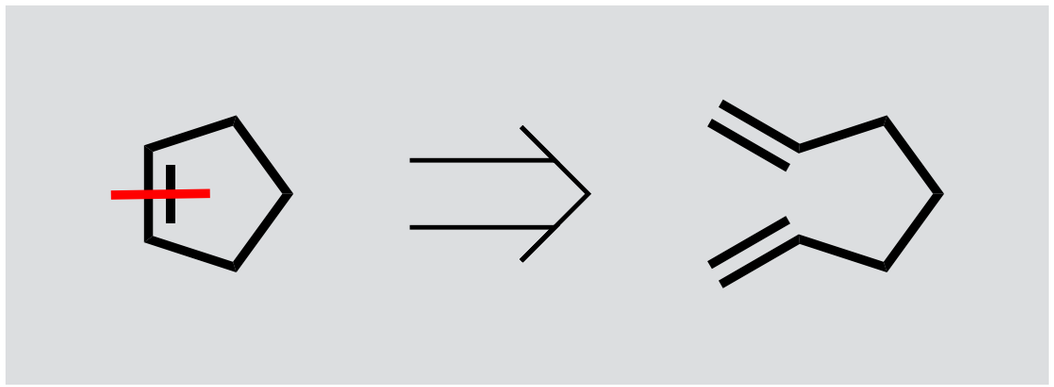
Ring Closing Metathesis (RCM)



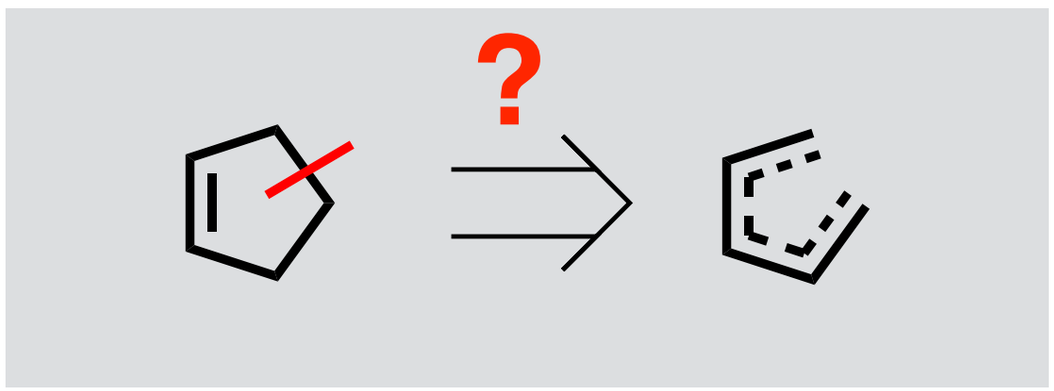
Electrocyclic Rearrangement



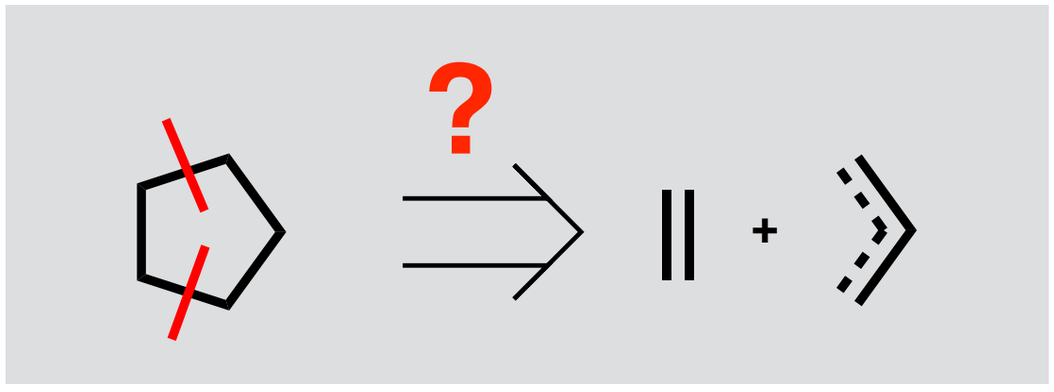
Diels Alder Cycloaddition



Ring Closing Metathesis (RCM)

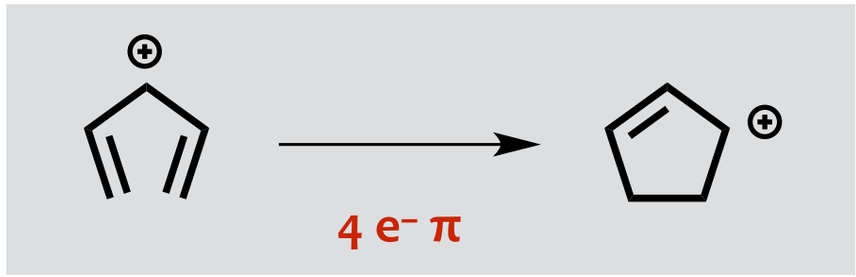


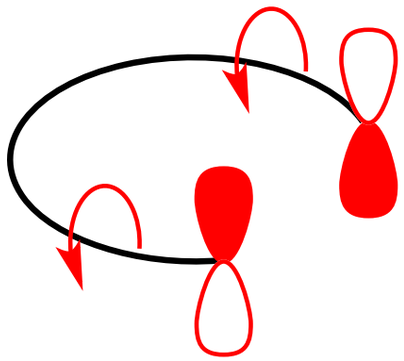
Electrocyclic Rearrangement



Cycloaddition

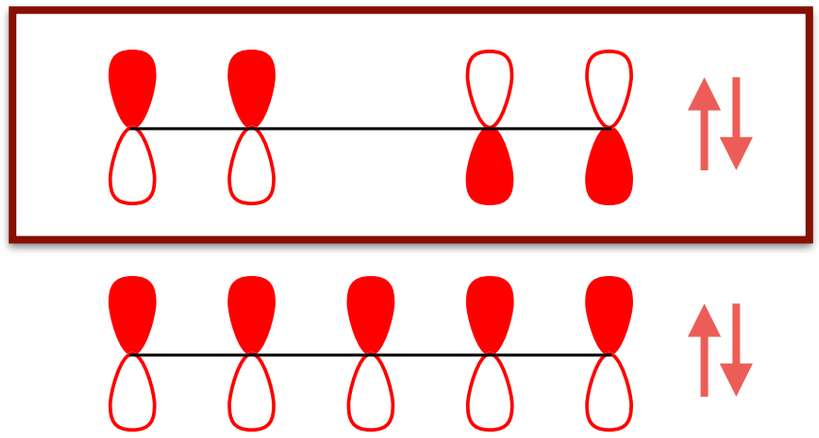
Nazarov: an electrocyclic reaction

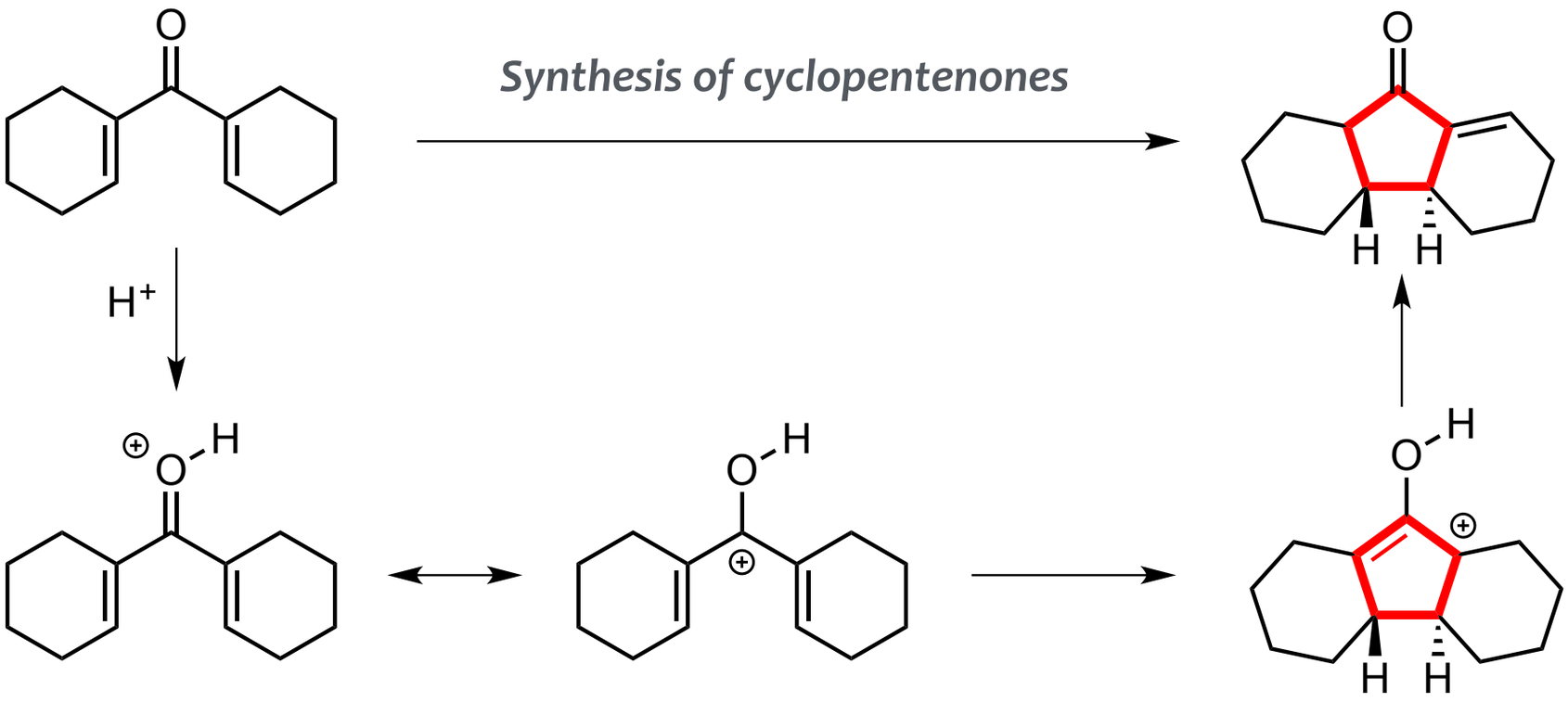




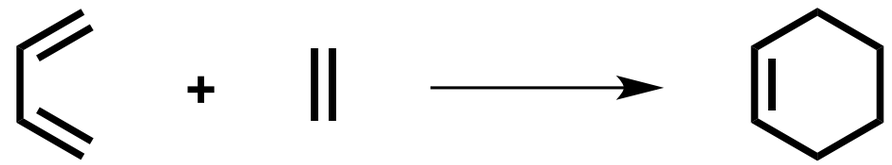
conrotatory under thermical conditions

HOMO





Diels-Alder cycloaddition



diene *dienophile*

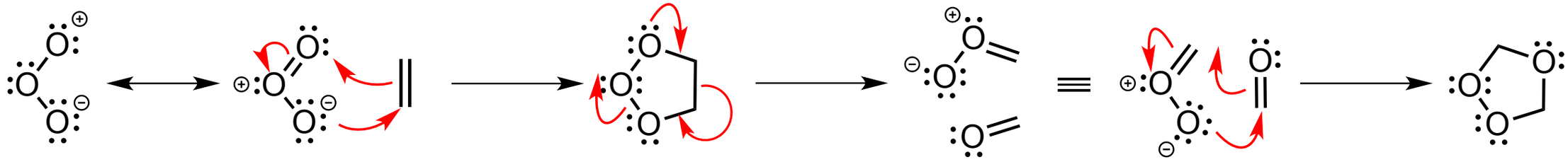
4 e⁻ π **2 e⁻ π**

4 atoms **2 atoms**

Is it possible to find a diene with 4 e⁻ π and just 3 atoms?

1,3-dipolar cycloaddition

1,3-dipolar cycloaddition



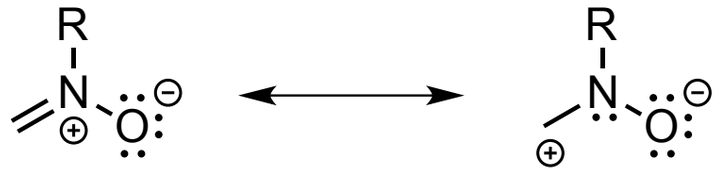
Ozone
an example of 1,3-dipole

retro cycloaddition

1,3-dipole

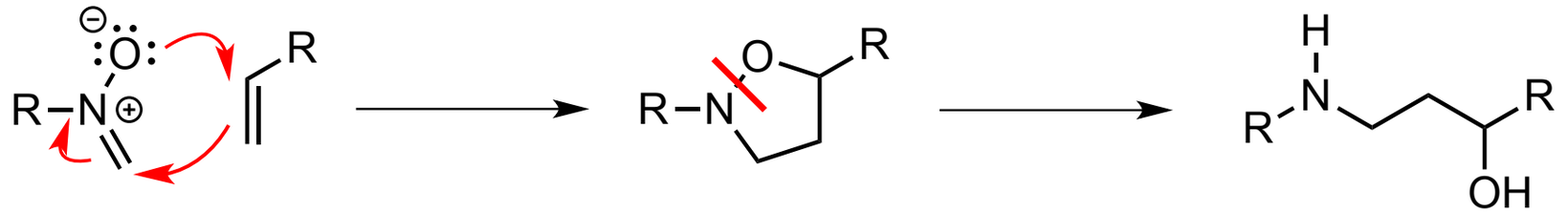
Any other dipoles? Other 1,3-dipolar cycloadditions?

1,3-Dipolar cycloadditions



Nitrones

1,3-dipolar cycloaddition

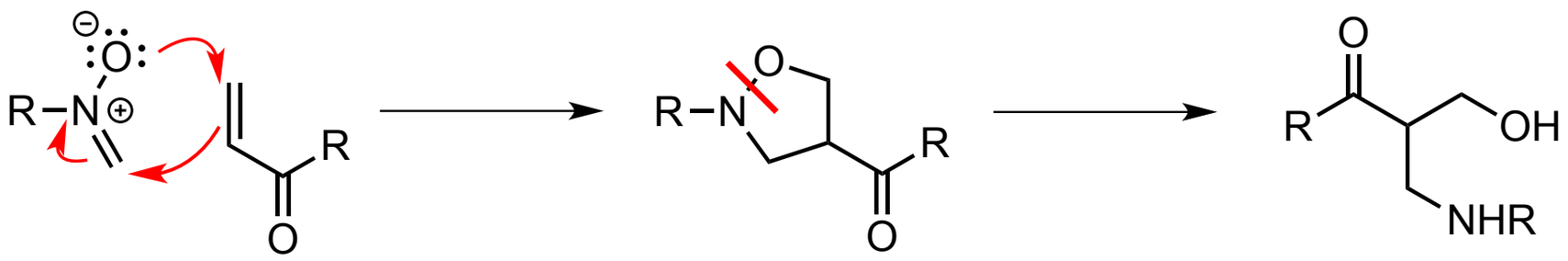


LUMO ***HOMO***

electron-rich alkene

reduction N–O bond

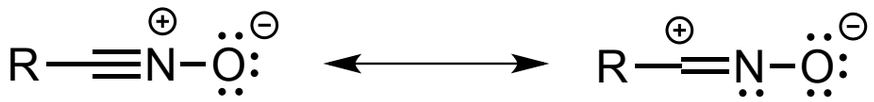
1,3-dipolar cycloaddition



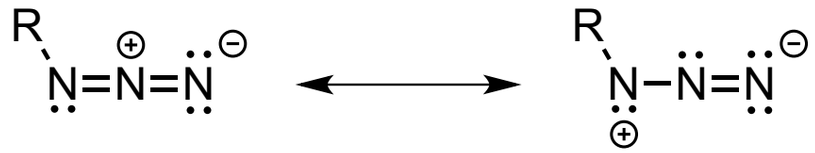
HOMO ***LUMO***

electron-poor alkene

reduction N–O bond



Nitrile oxides

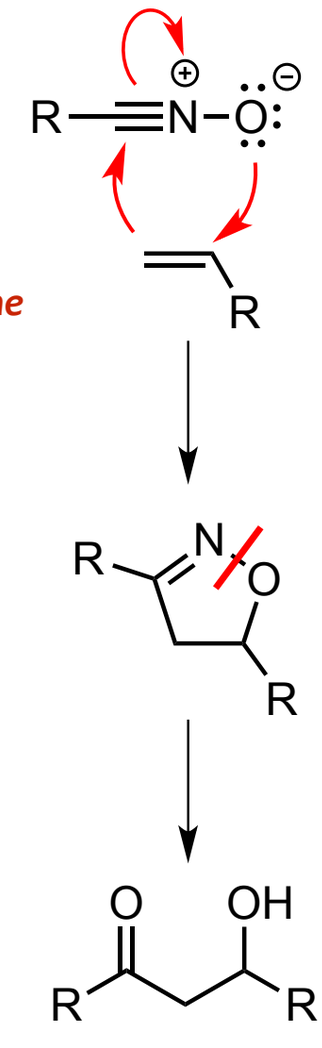


Azides

LUMO

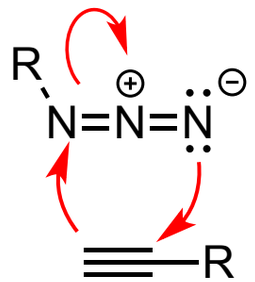
HOMO

electron-rich alkene

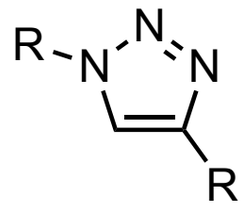


1,3-dipolar cycloaddition

reduction N–O bond

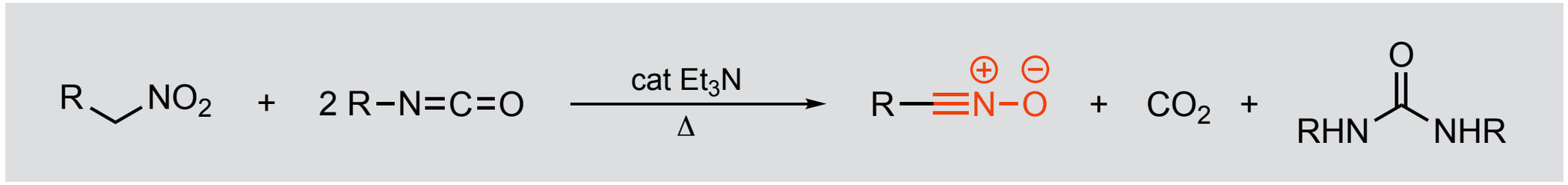


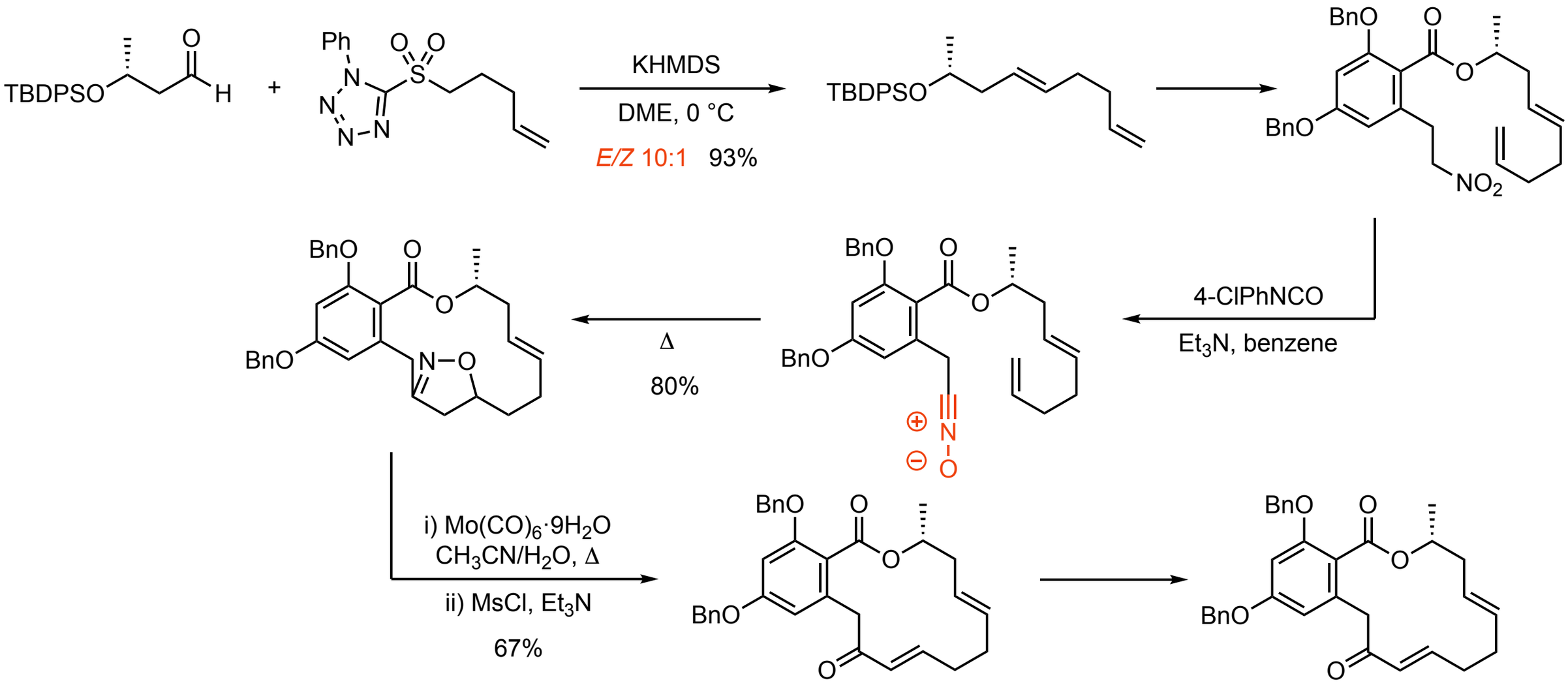
Cu(I) catalyst



Click Chemistry

Sharpless, B. K. *ACIE* **2001**, *40*, 2004

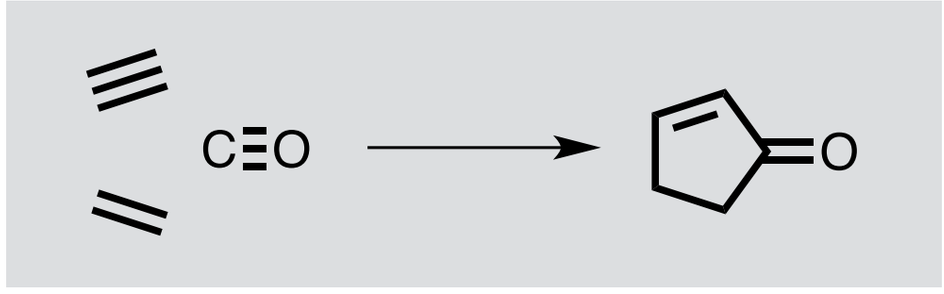




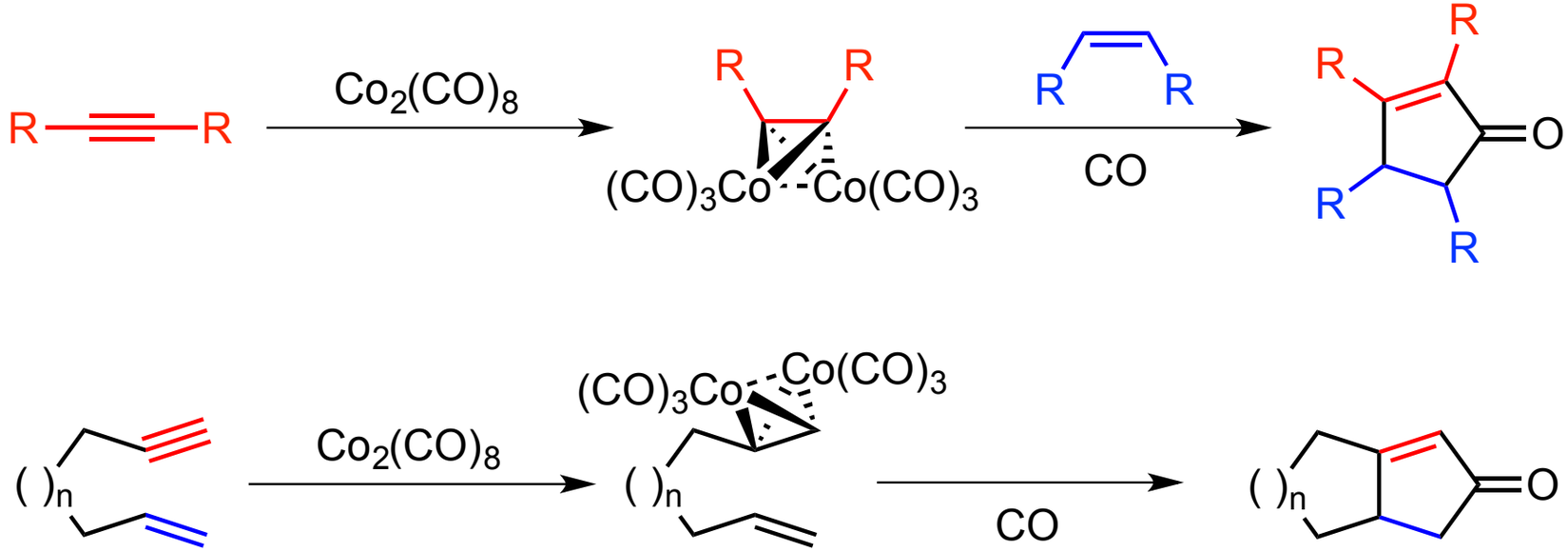
Lee, J. *OL* **2017**, *19*, 6004

(+)-Sieboldine A

Pauson-Khand reaction (PKR)



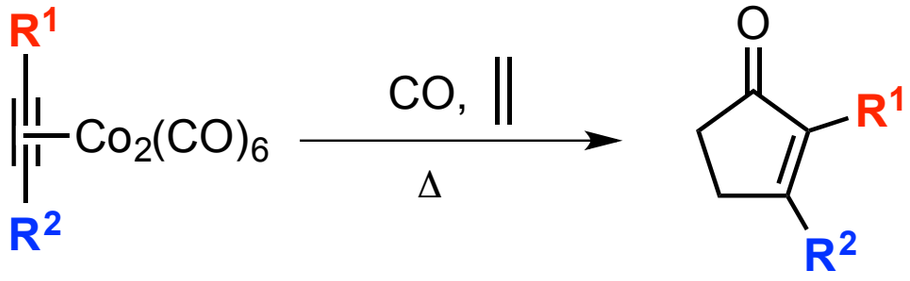
A formal [2+2+1] cycloaddition of an alkyne, an alkene and CO



leading to the inter or intramolecular synthesis of cyclopentenones

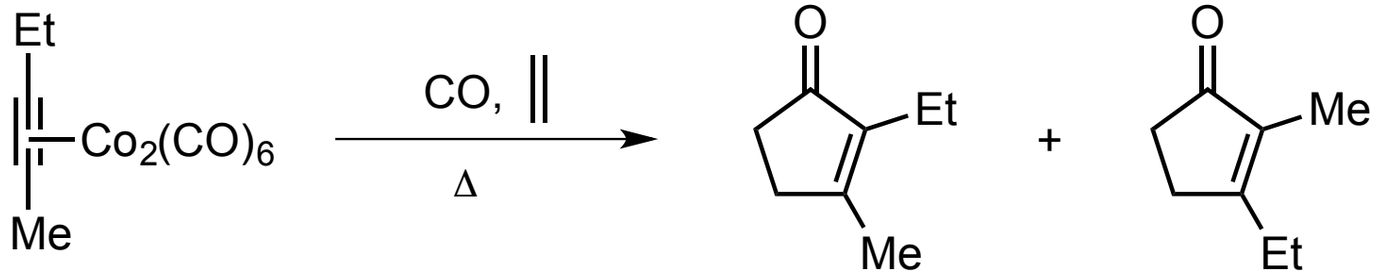
Pérez-Castells, J. *CSR* **2004**, *33*, 32; Afonso, C. A. M. *CR* **2016**, *116*, 5744

PKR can be highly regioselective …

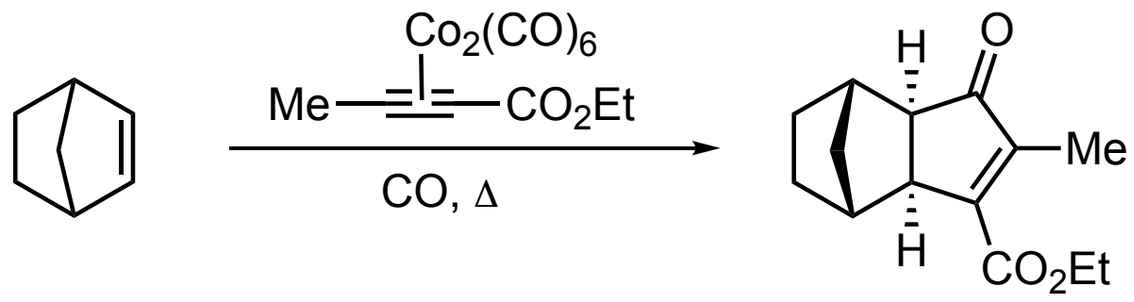


Large and EDG groups

Small and EWG groups

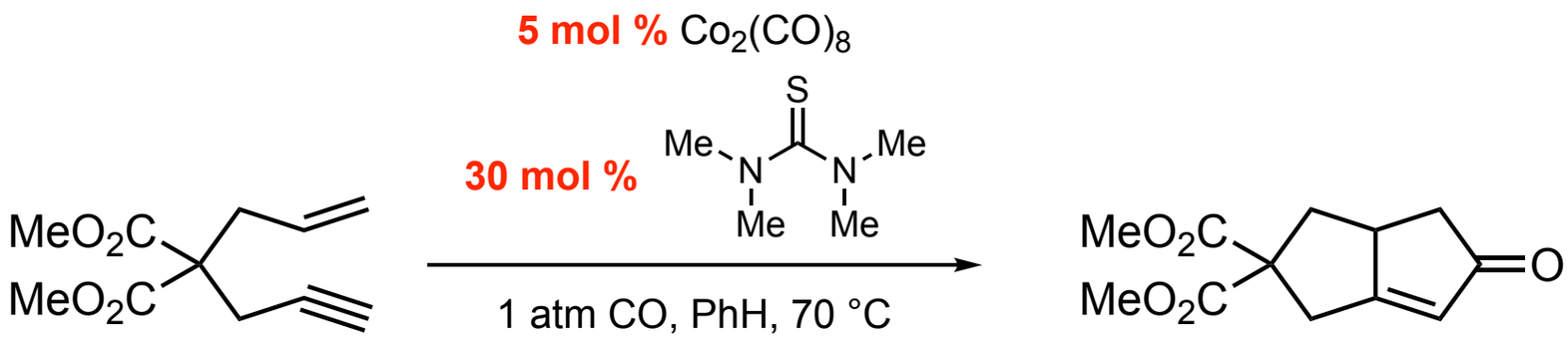


8 : 1



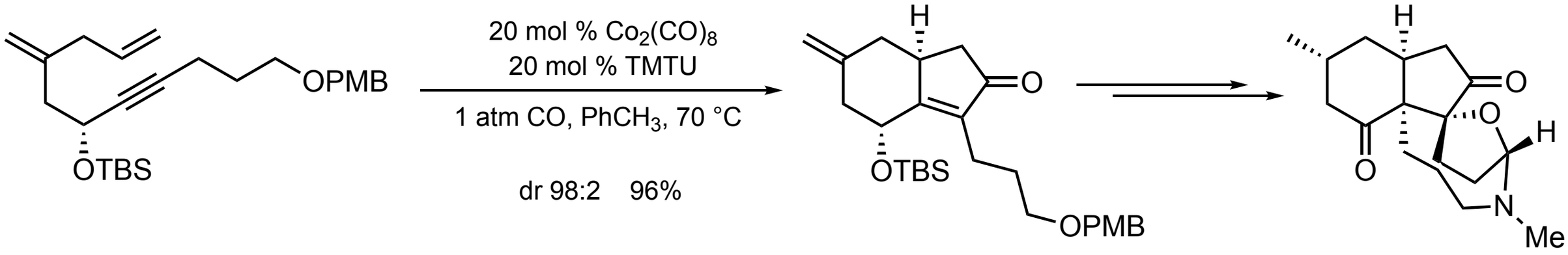
Laschat, S. *Synlett* **2005,** 2547; Riera, A. *JOC* **2014,** *79,* 10999

can be carried out under catalytic conditions…



96%

Chen, J. *S OL* **2005,** *7,* 593



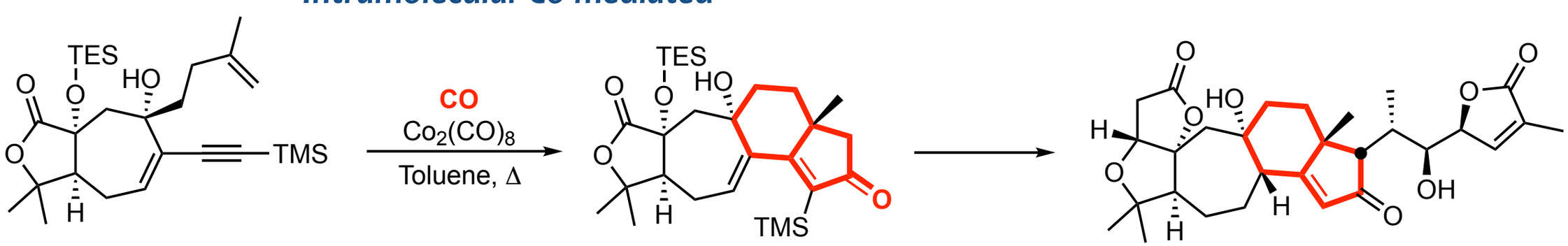
Mukai, C. S *OL* **2017,** *19,* 320

(+)-Sieboldine A

… and become high enantioselective

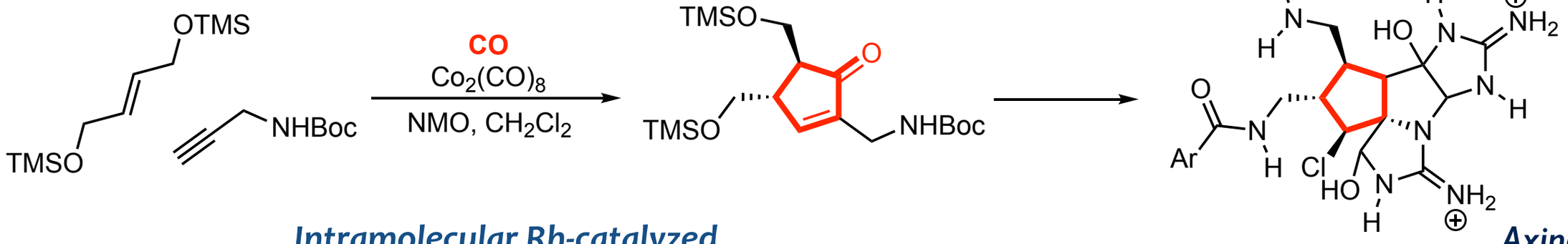
Therefore, the PK reaction is an intra or intermolecular cycloaddition between an alkyne, an alkene, and CO promoted or catalysed by Co, but also Rh, Ir, …

Intramolecular Co-mediated



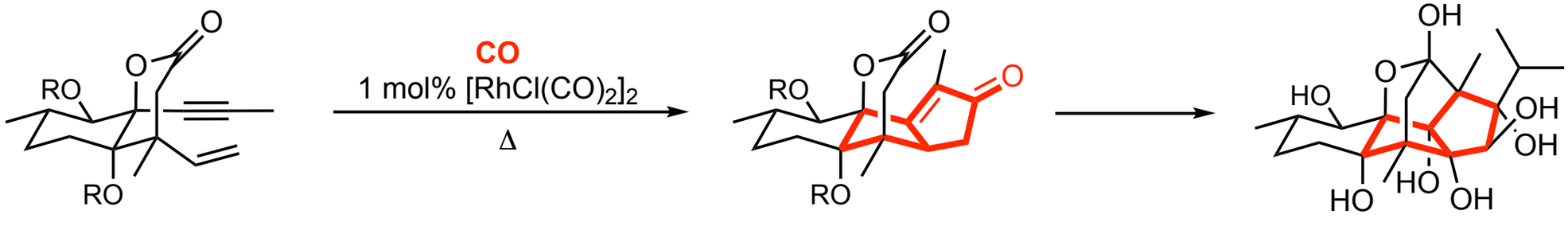
(+)-Propindilactone G

Intermolecular Co-mediated



Axinellamines

Intramolecular Rh-catalyzed



(+)-Ryanodol

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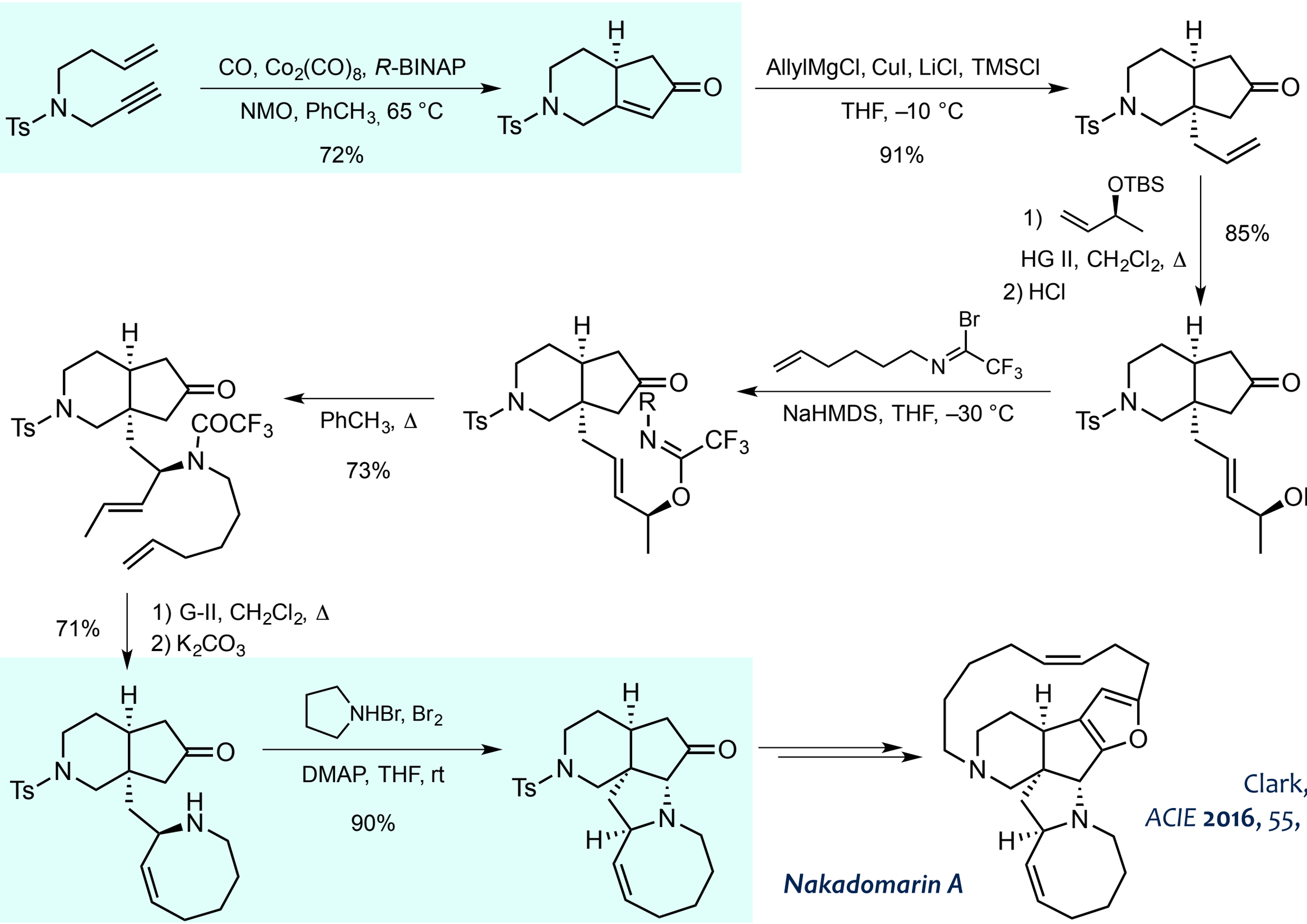
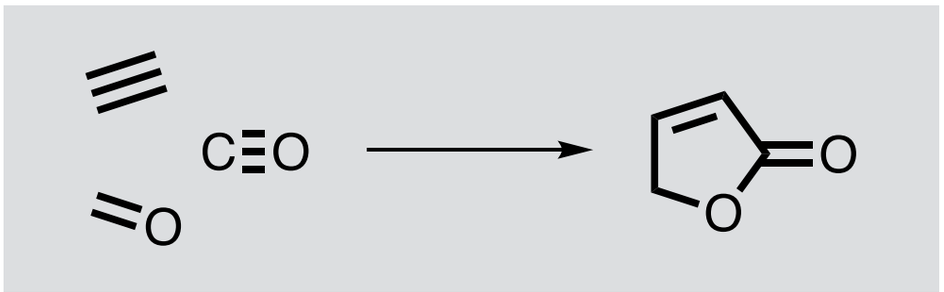
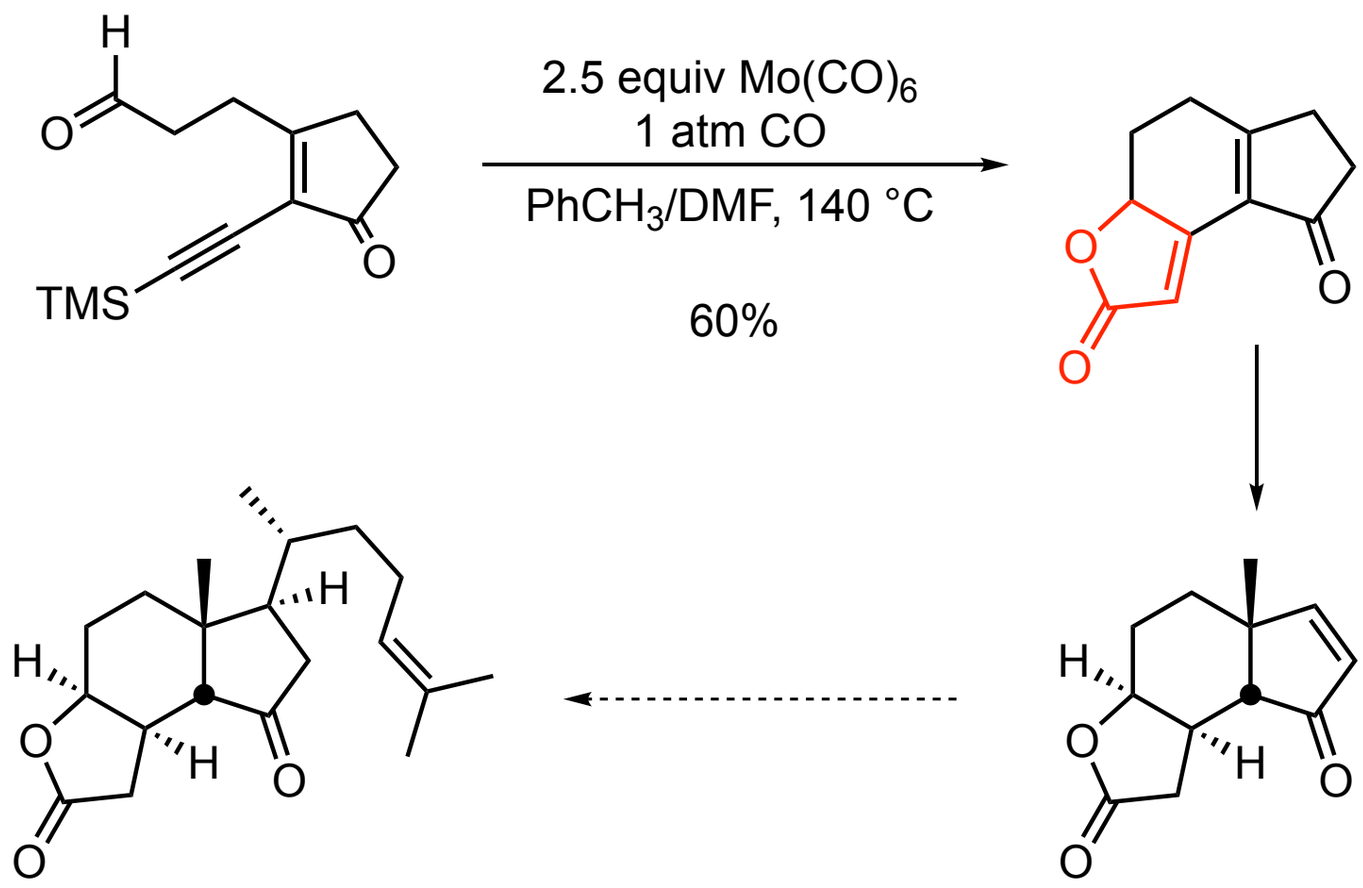


Clark, J. S.
ACIE **2016**, 55, 4332

Occasionally, the alkene (C=C bond) may be replaced by a carbonyl (C=O bond) to produce a conjugated butyrolactone through a formal [2+2+1] cycloaddition

hetero Pauson-Khand reaction (h-PKR)





(±) Aplykurodione

Zhai, H.
OL **2017**, *19*, 1056