Master Course
in Organic Chemistry

2018-19

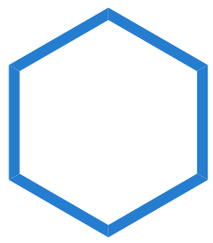
methods **and design** in organic synthesis

Pere Romea

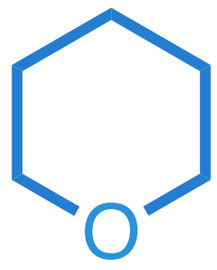
My precious !

Gollum/Sméagol
in
The Lord of the Rings

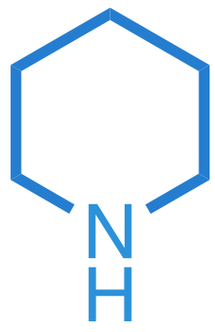
6.1. Rings

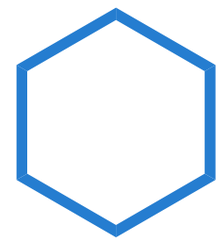


carbocycle

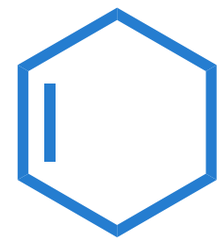


heterocycle

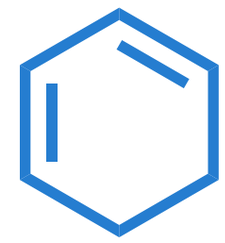


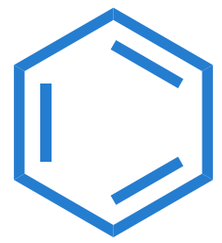


saturated

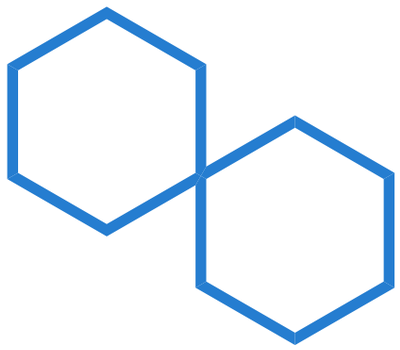


unsaturated



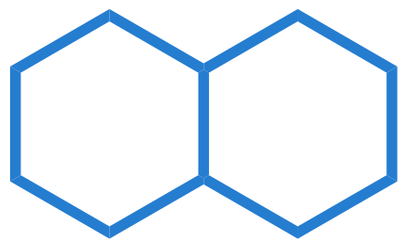


aromatic



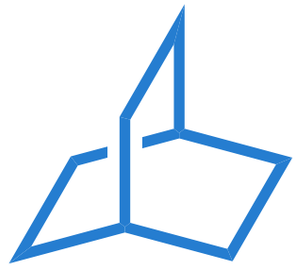
spiro rings

spiro[5.5]undecane



fused rings

decaline



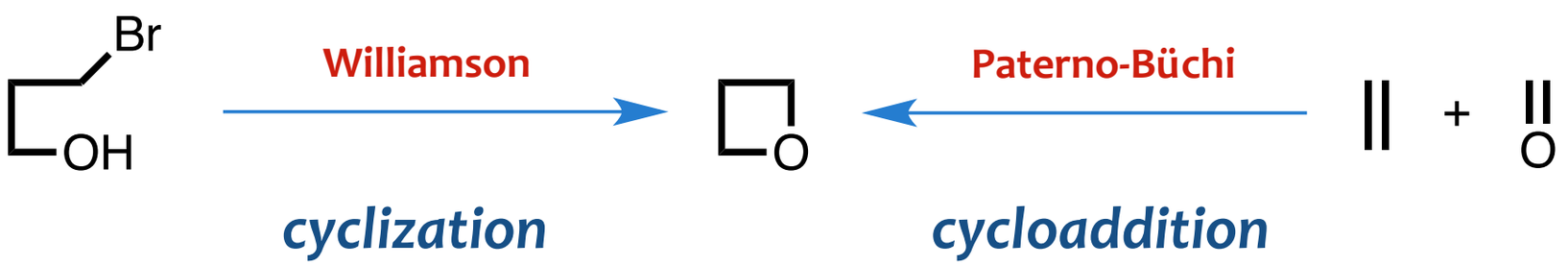
bridged rings

bicyclo[2.2.2]octane

Rings can be prepared by **expansion/contraction** from other rings …

… or by **cyclization** of a chain or acyclic compounds.

A cycloaddition corresponds to a ring closure in which the resultant adduct contains all the atoms of the initial component(s). No losses of atoms or small molecules



STRAIN ENERGY refers to
the excess energy of a given array of atoms an (as yet hypothetical)
molecule over the minimum array that the array would possess
if certain kinds of interactions were "turned off"

$$V = V_s + V_a + V_t + V_{nb} + V_E - V_{sol}$$

- V_s — *bond stretching*
- V_a — *bond angle* **Baeyer strain**
- V_t — *bond torsion* **Pitzer strain**
- V_{nb} — *nonbonding* **van der Waals**
- V_E — *electrostatic*
- V_{sol} — *solvation*

Eliel. E. L. *Stereochemistry of Organic Compounds.* p 33

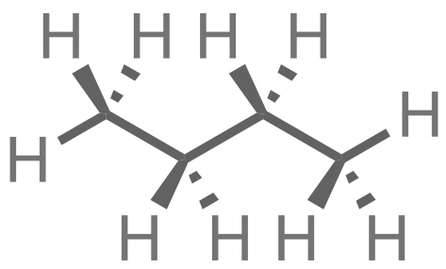
RING STRAIN (ENERGY)
for a cycloalkane refers to the excess energy relative to the parent acyclic alkane

$$V = V_s + V_a + V_t + V_{nb} + V_E - V_{sol}$$

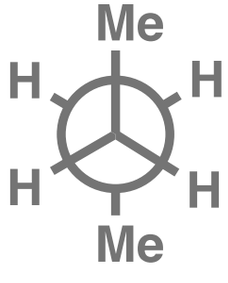
- V_a: *bond angle*
- V_{nb}: *nonbonding*
- V_t: *bond torsion*
- V_s: *bond stretching*
- V_E: *electrostatic*
- V_{sol}: *solvation*

Eliel. E. L. *Stereochemistry of Organic Compounds.* p 33

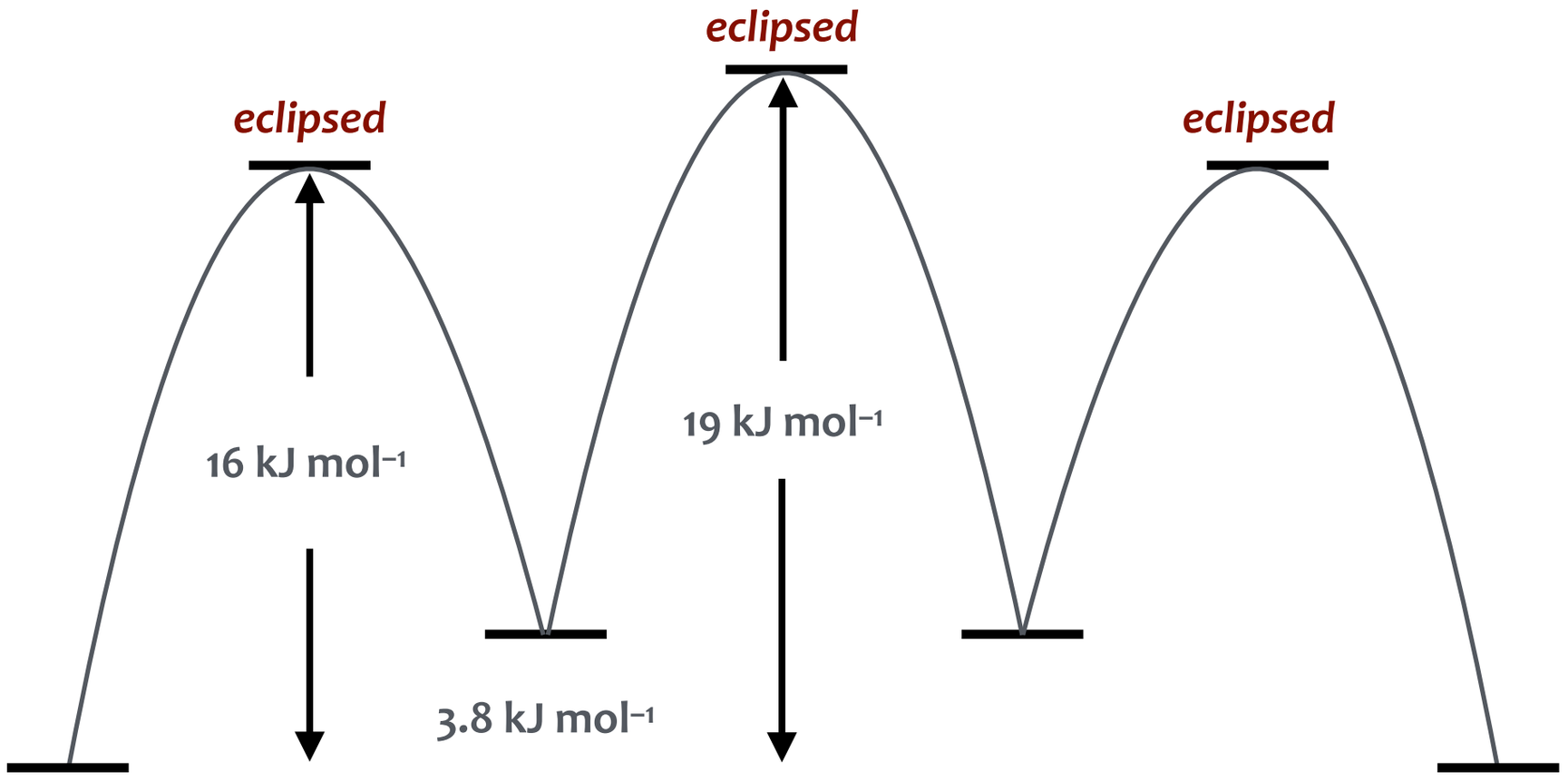
butane



α ~ 109°

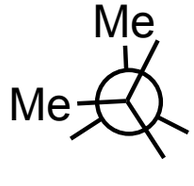


antiperiplanar

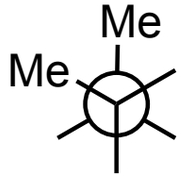


staggered *staggered* *staggered* *staggered*

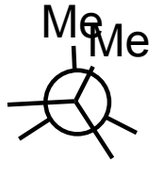
antiperiplanar



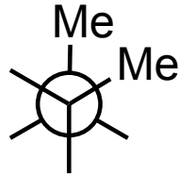
anticlinal



gauche



synperiplanar



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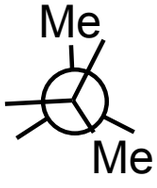
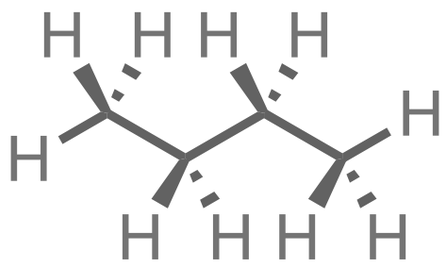


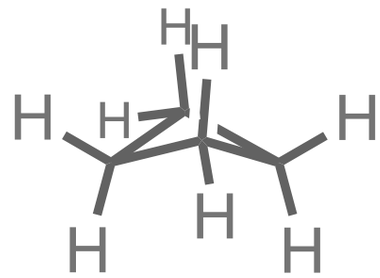
anticlinal

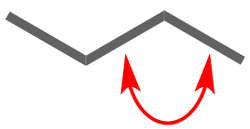
antiperiplanar

butane

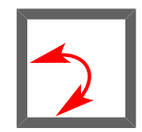
cyclobutane



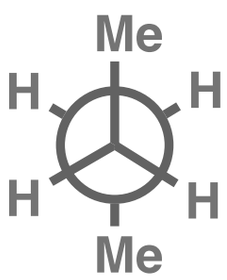




α ~ 109°

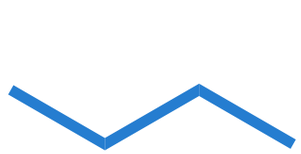


α ~ 88°



antiperiplanar

eclipsed



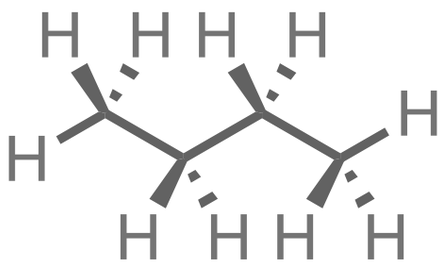
butane

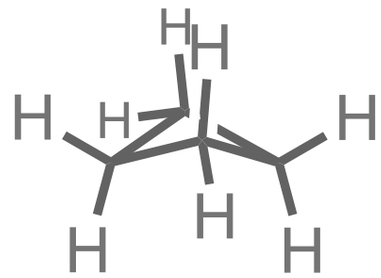
ring strain

$\Delta\Delta G^{o}_{f}$

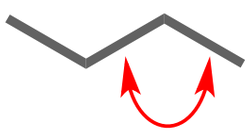
$\Delta\Delta G^{o}_{combustion}$

cyclobutane

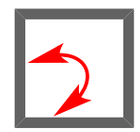




bend angle

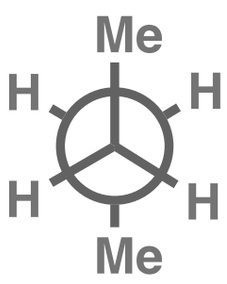


$\alpha \sim 109°$



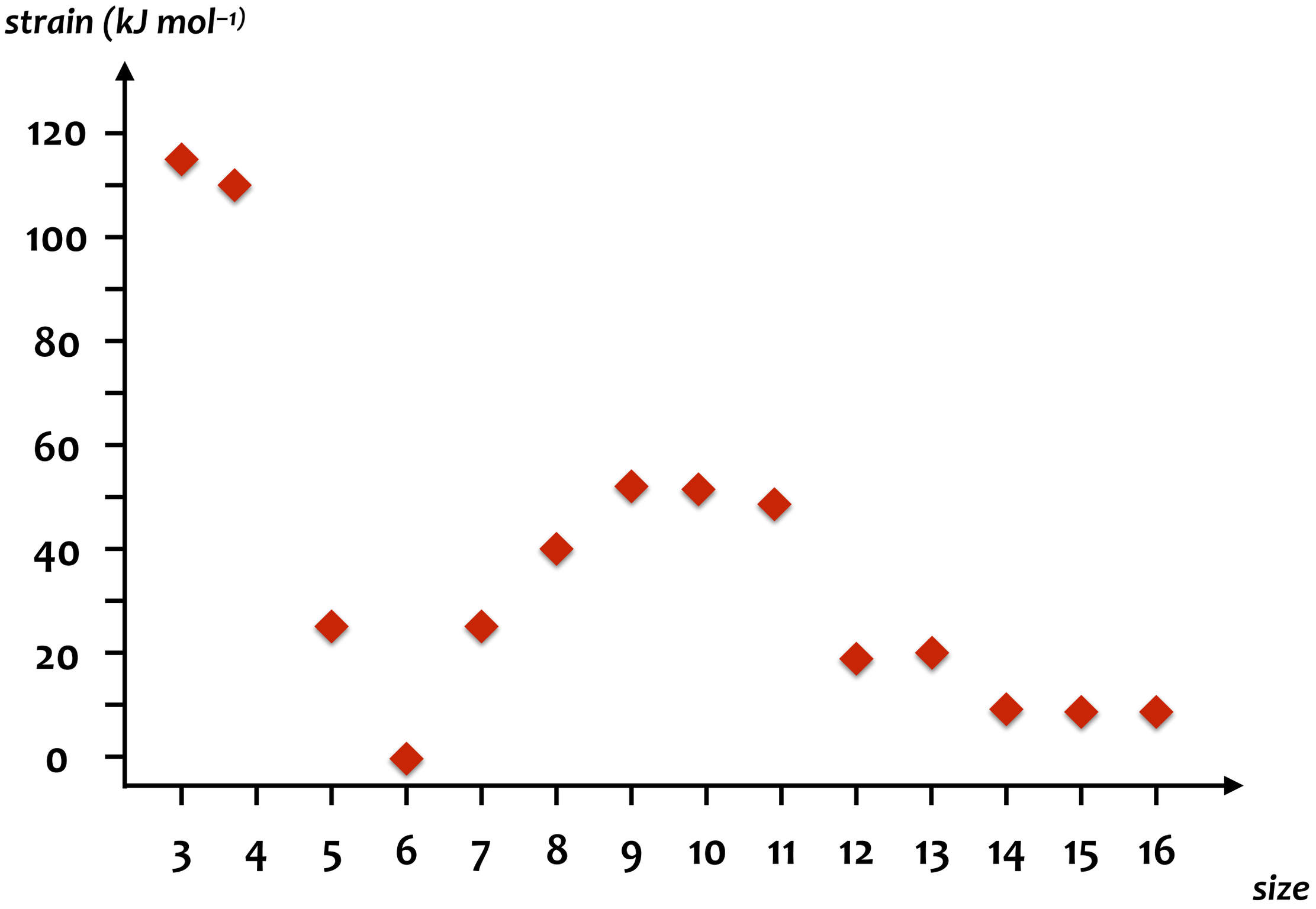
$\alpha \sim 88°$

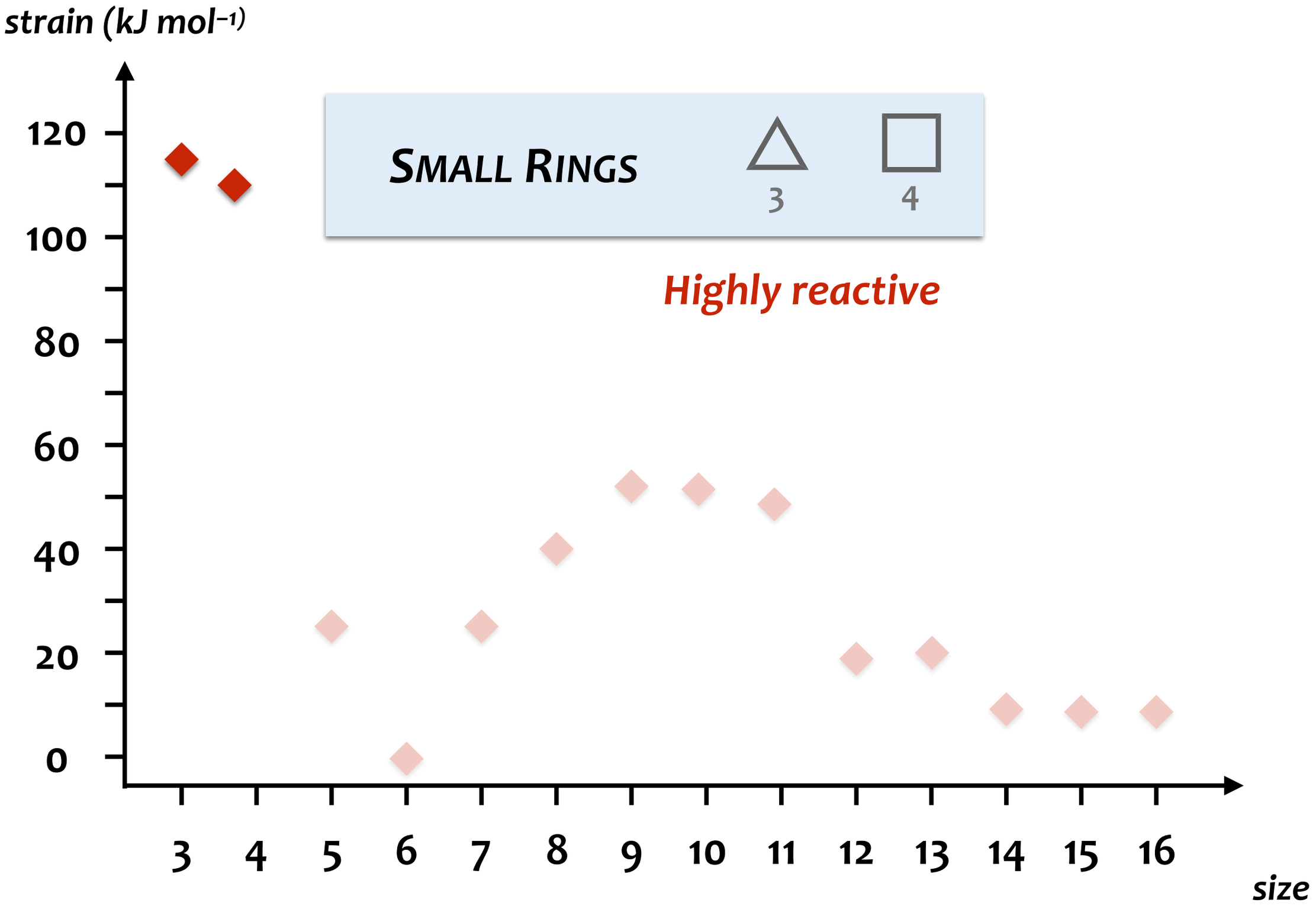
torsion



antiperiplanar

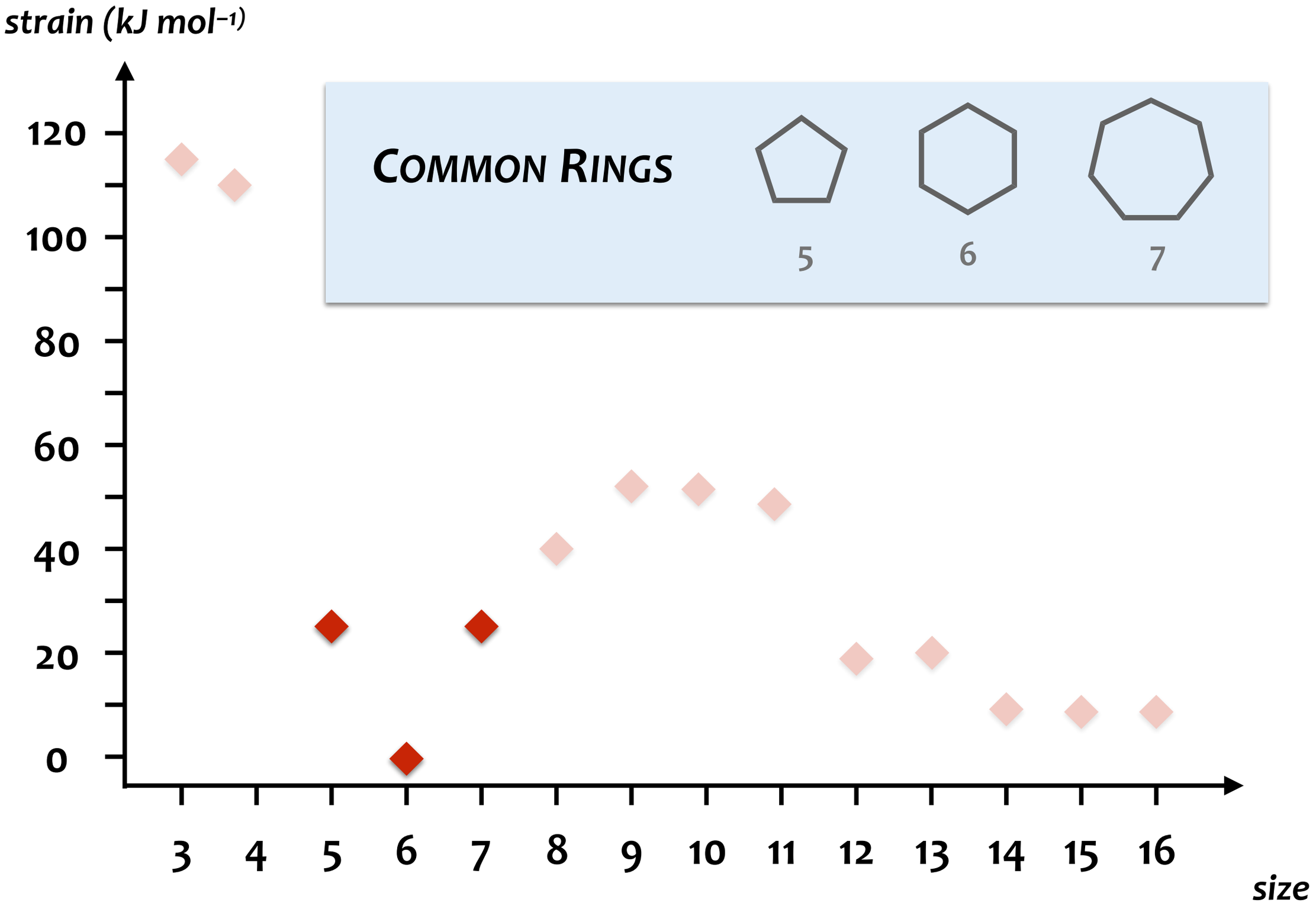
eclipsed


strain (kJ mol⁻¹)
120
100
80
60
40
20
0
3
4
5
6
7
8
9
10
11
12
13
14
15
16
size

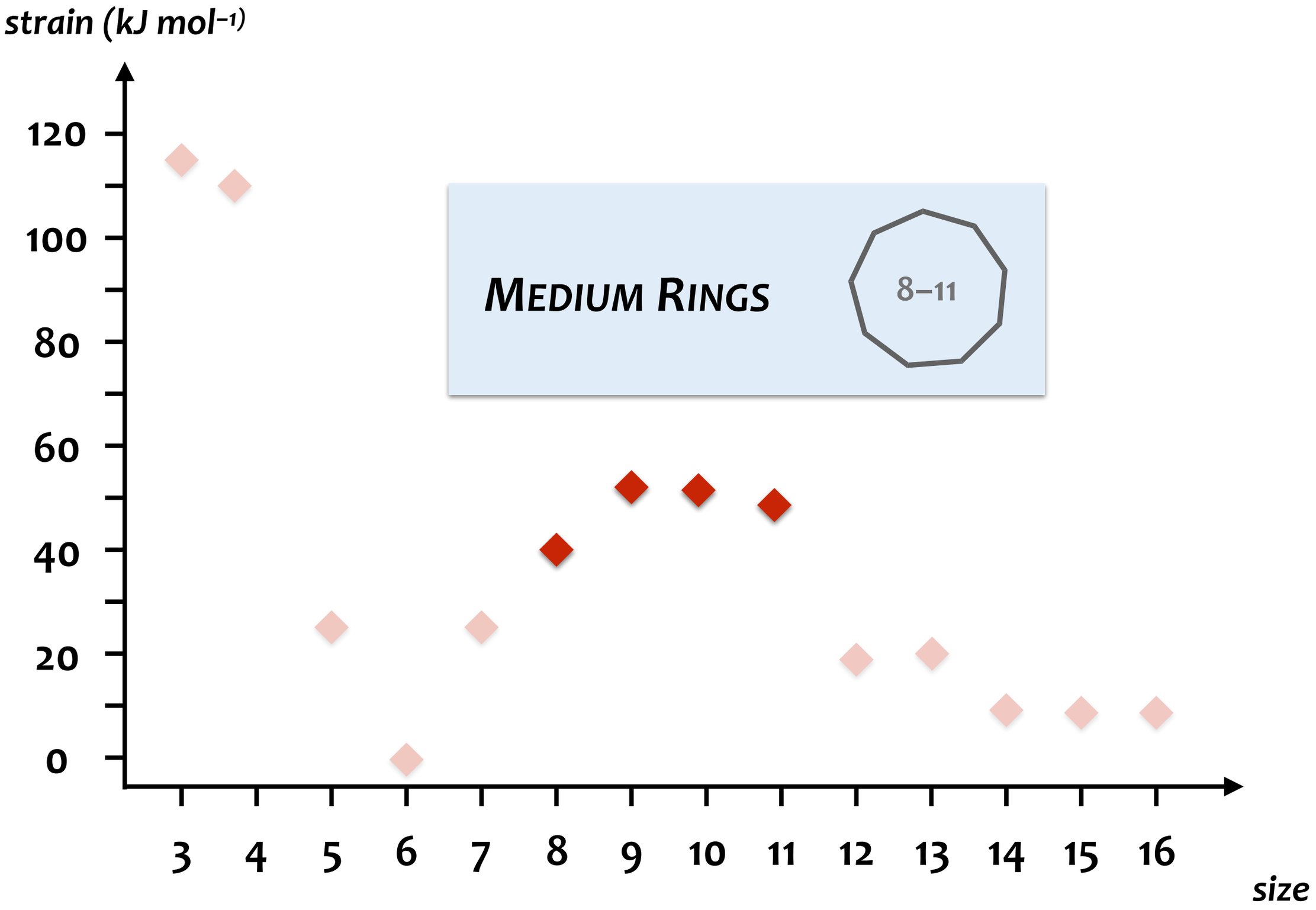


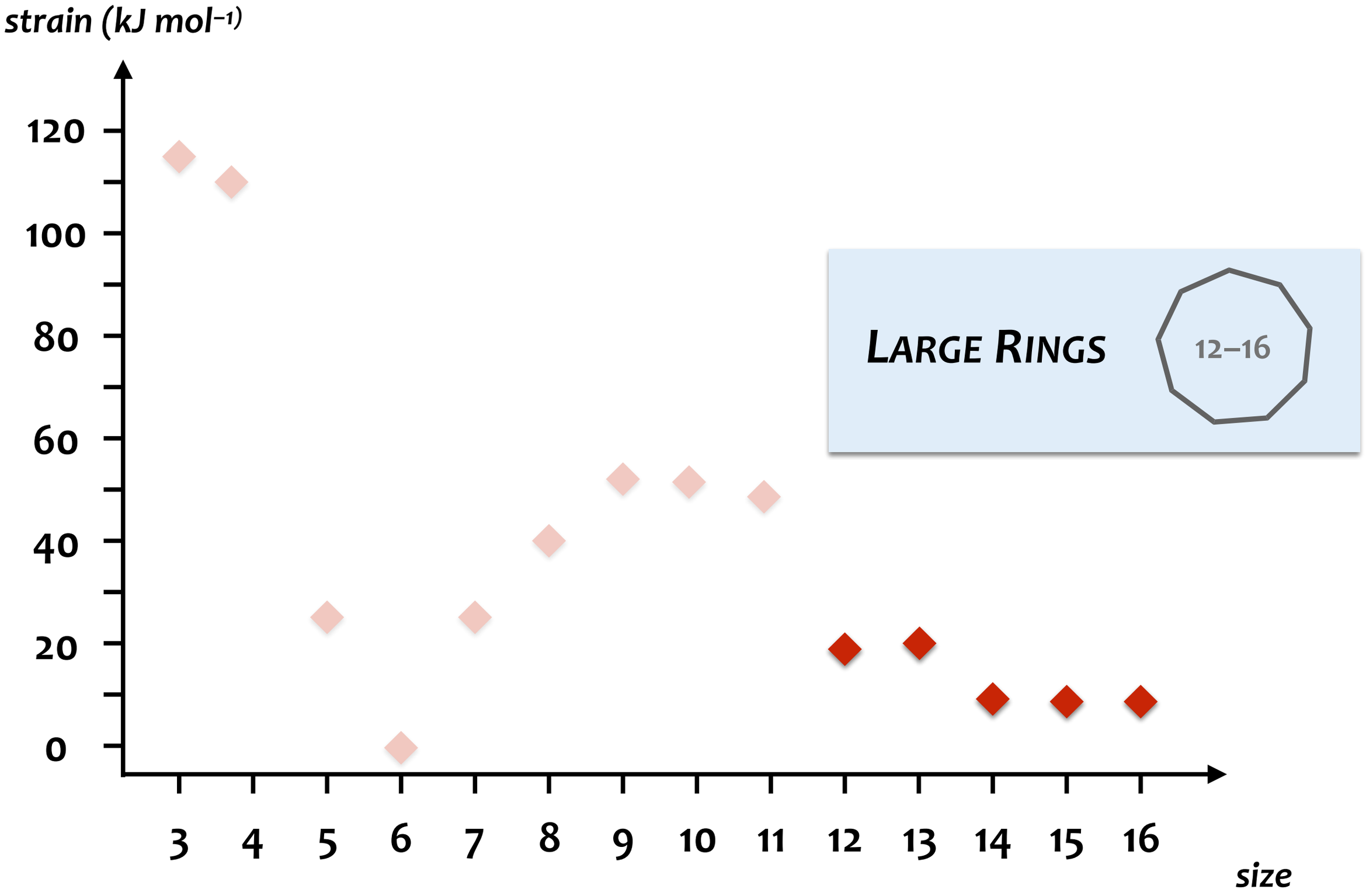
SMALL RINGS

Highly reactive

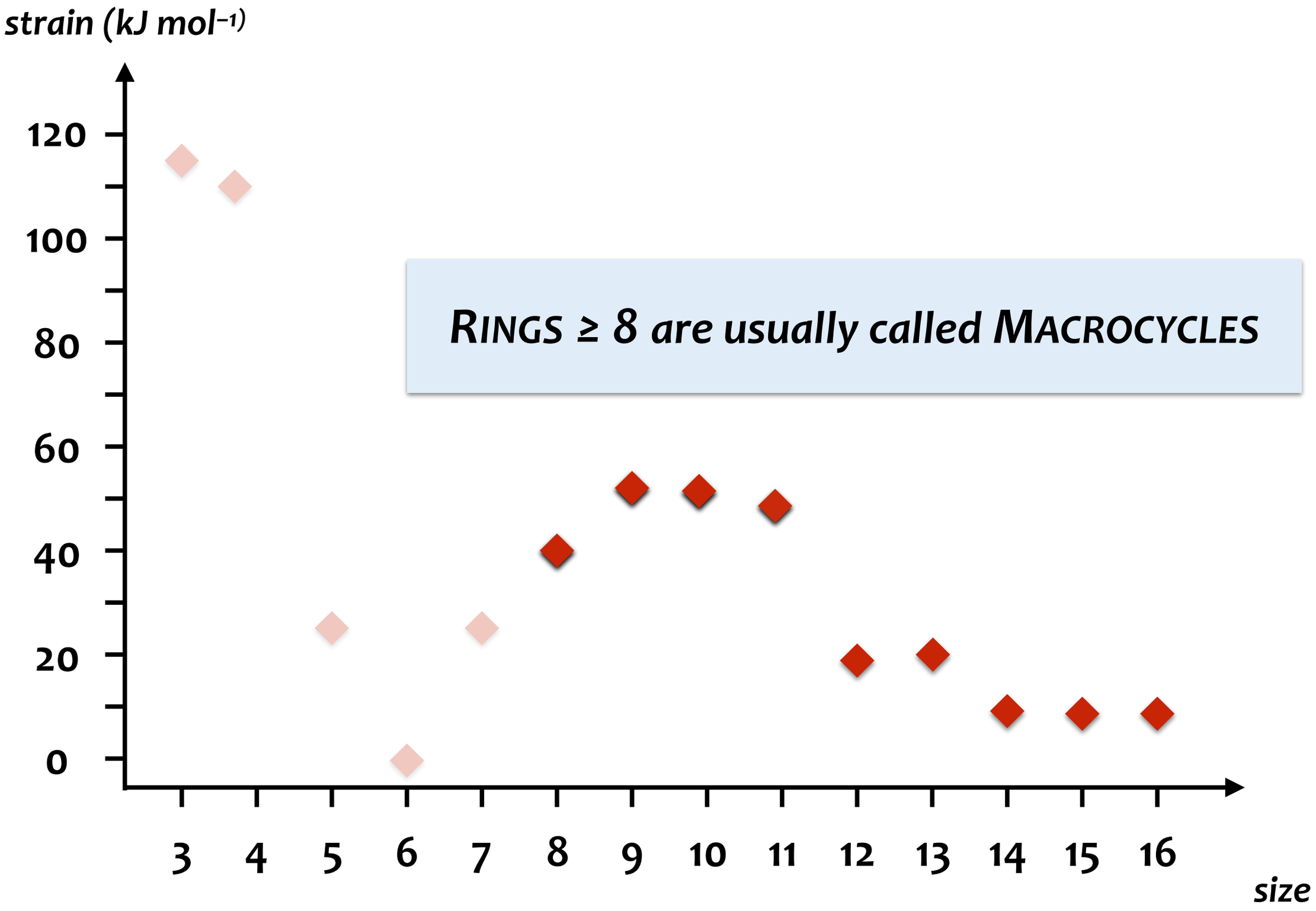


COMMON RINGS

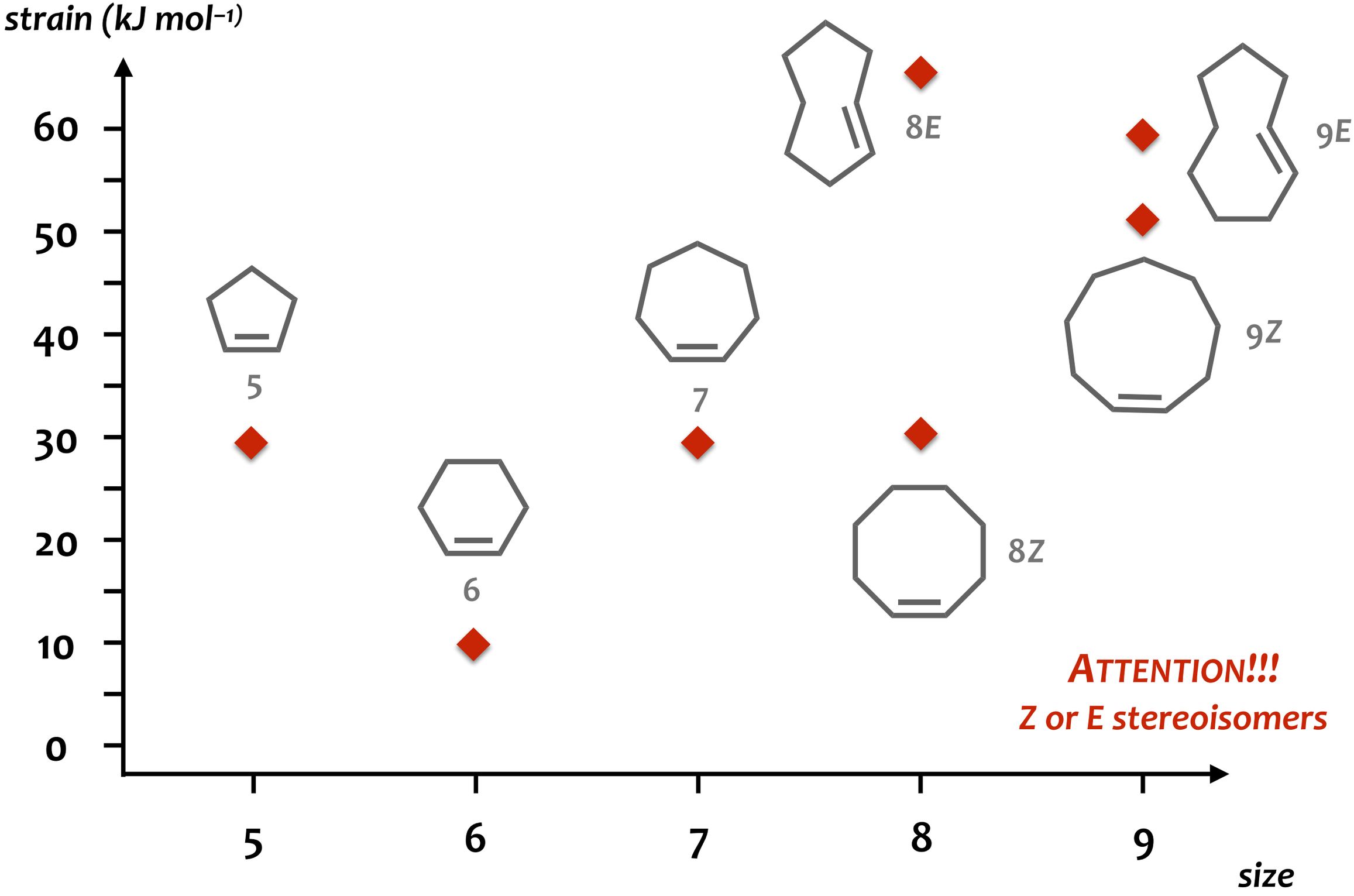

strain (kJ mol⁻¹)
120
100
80
60
40
20
0
3
4
5
6
7
8
9
10
11
12
13
14
15
16
size
MEDIUM RINGS
8–11



LARGE RINGS 12–16

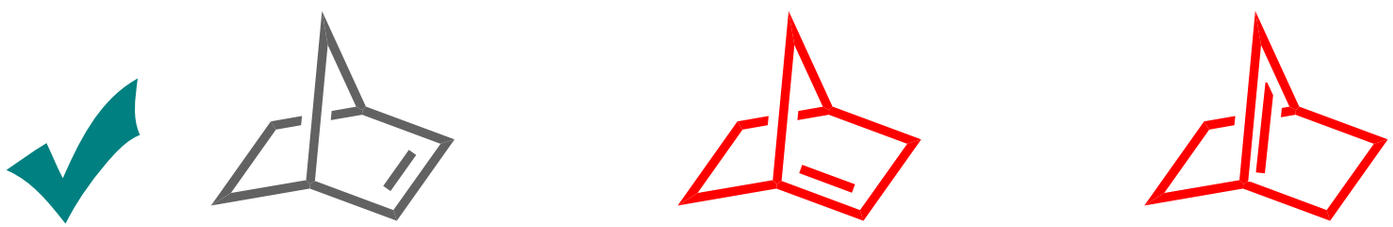


RINGS ≥ 8 are usually called MACROCYCLES


strain (kJ mol⁻¹)
60
50
40
30
20
10
0
5
6
7
8
9
size
5
6
7
8E
8Z
9E
9Z
ATTENTION!!!
Z or E stereoisomers

Bicyclic alkenes require a special attention

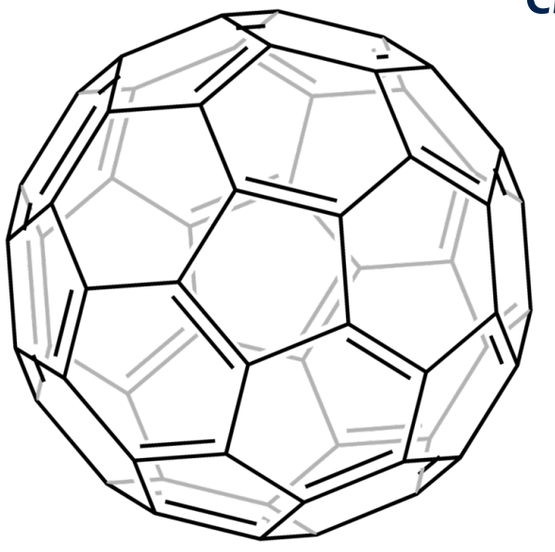
These substrates are subject to strain resulting from distortion of the sp^2 carbon centers. The angle strain is the basis of ***Bredt's rule****, which dictates that bridgehead carbon atoms are not incorporated in alkenes because the strain angle*



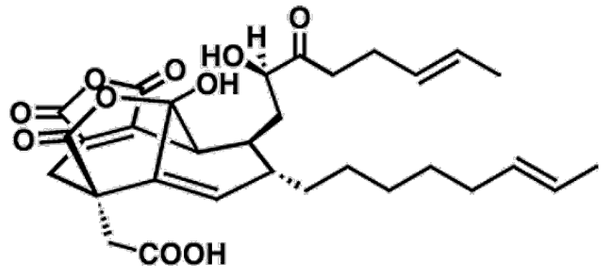
Norbornene *Forbidden norbornenes*

but …

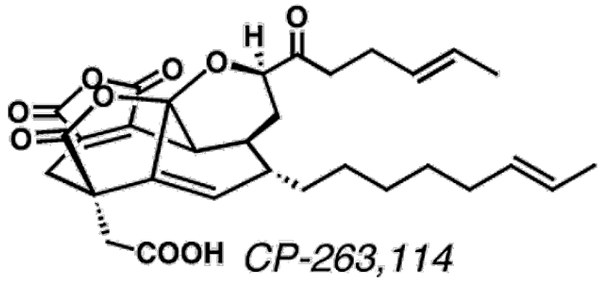
Fullerene



CP-Molecules



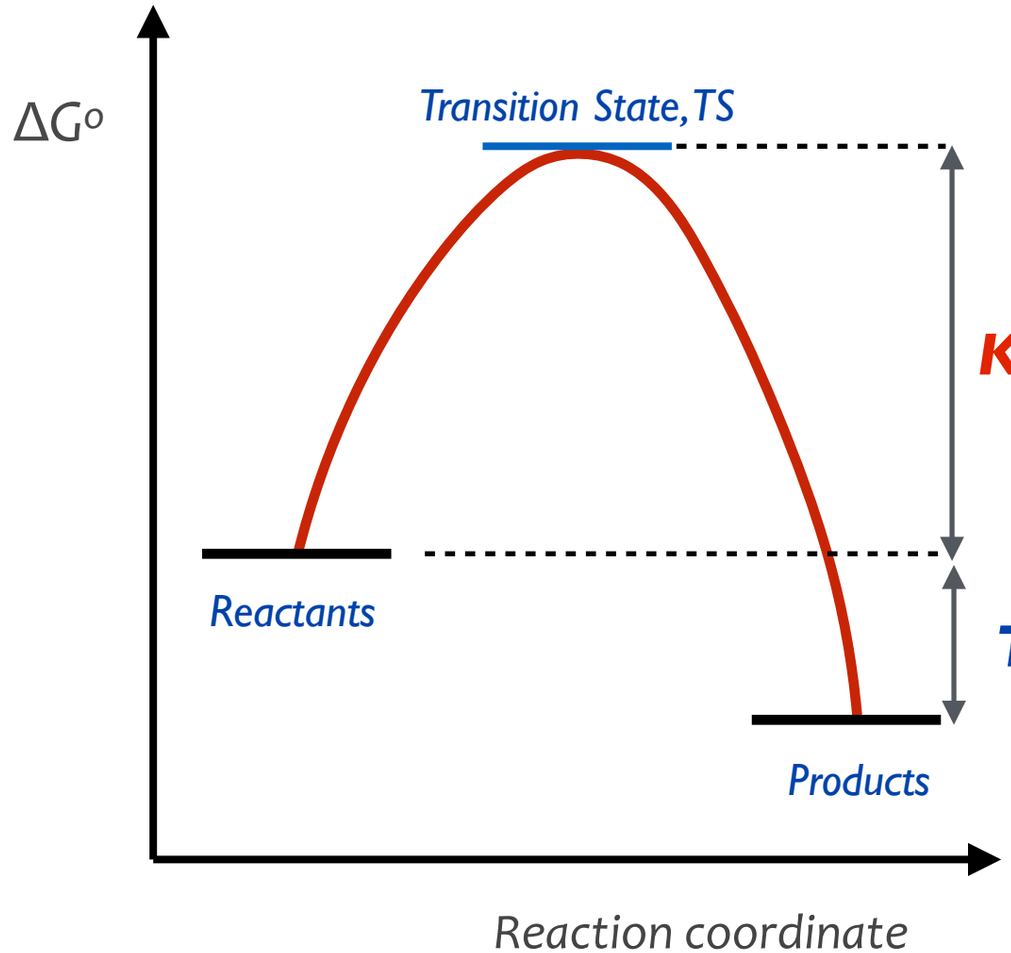
CP-225,917



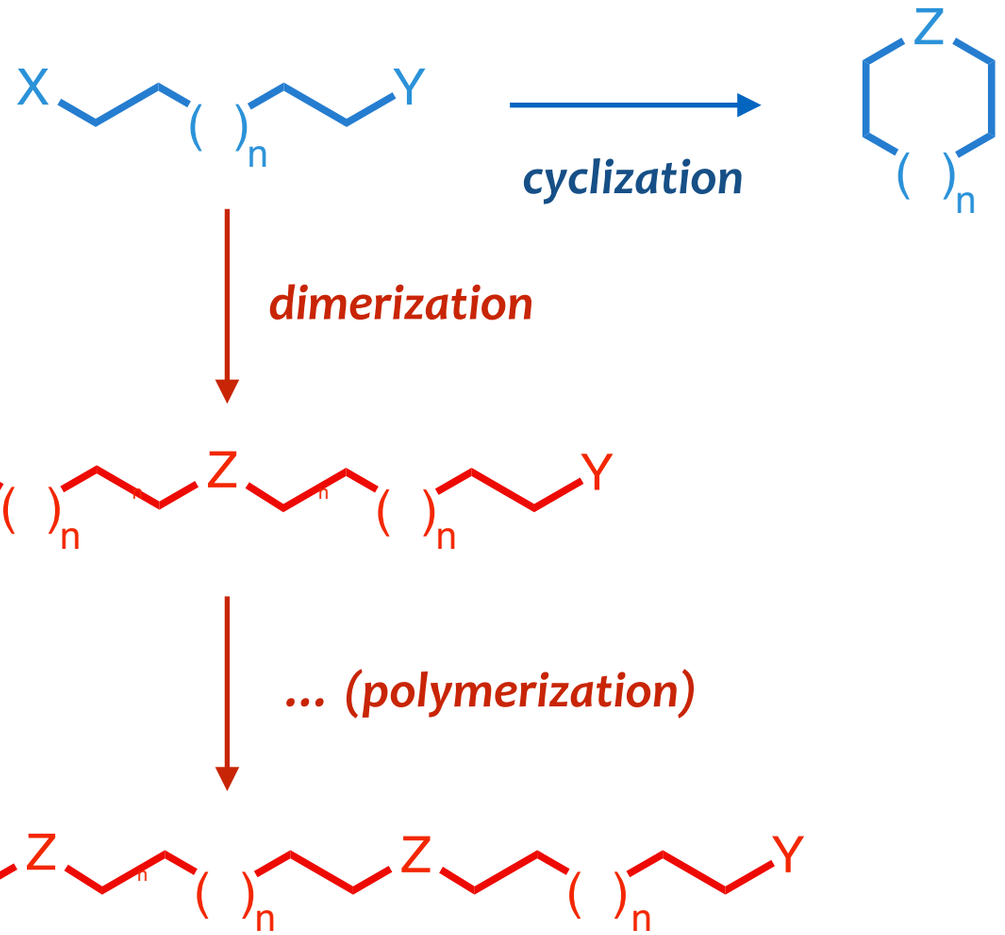
CP-263,114

or Taxol (see Chapter 1)

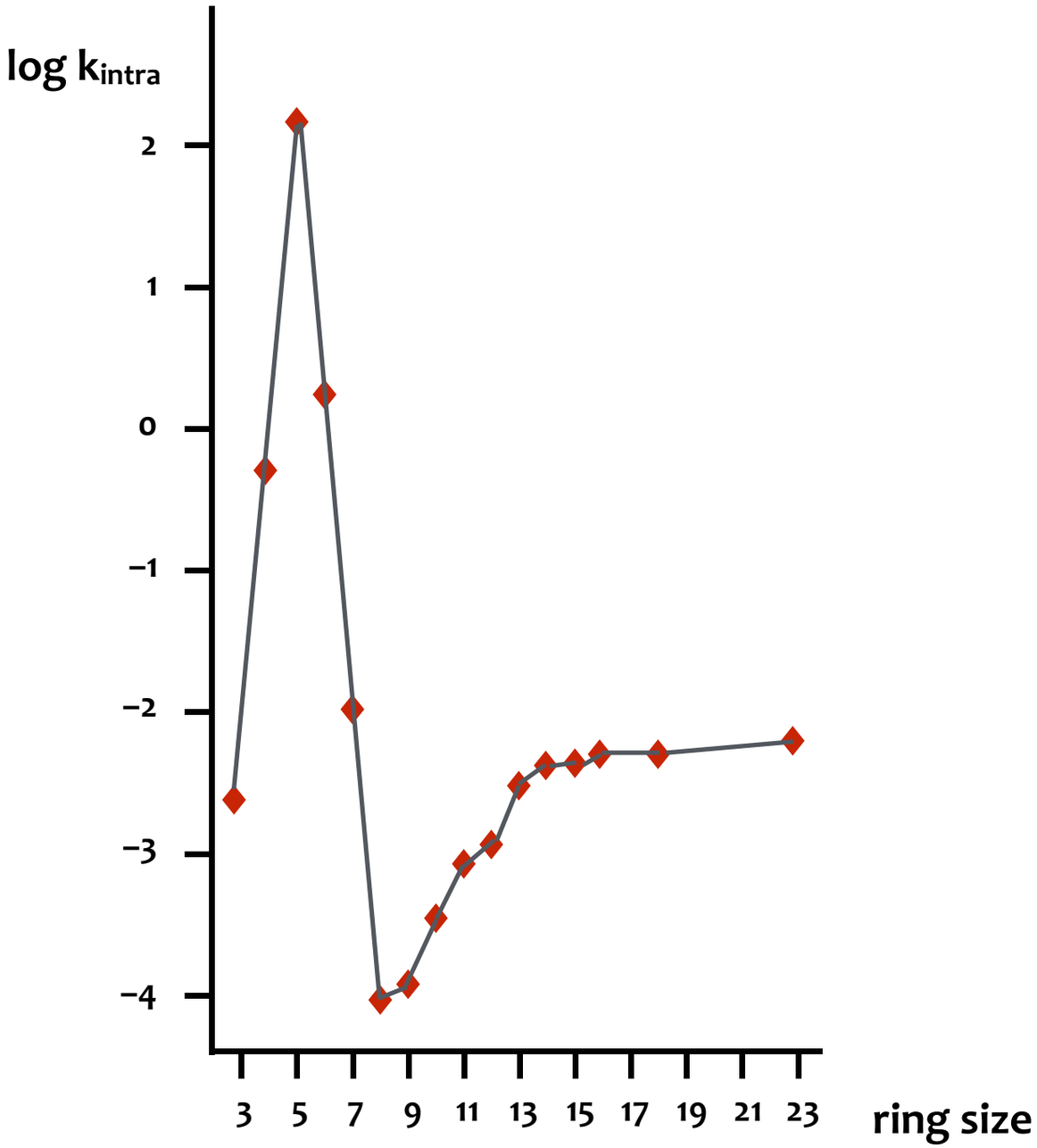
The kinetics of the cyclization is associated with $[\Delta G^\circ]^\ddagger$



$$[\Delta G^\circ]^\ddagger = [\Delta H^\circ]^\ddagger - T\,[\Delta S^\circ]^\ddagger$$



The kinetics of the cyclization is associated with $[\Delta G^\circ]^\ddagger$



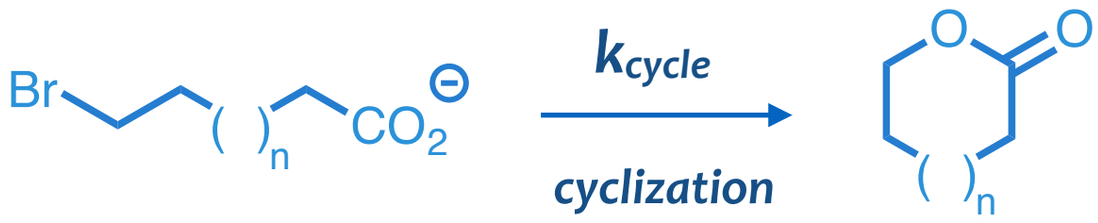
$$[\Delta G^\circ]^\ddagger = [\Delta H^\circ]^\ddagger - T\,[\Delta S^\circ]^\ddagger$$

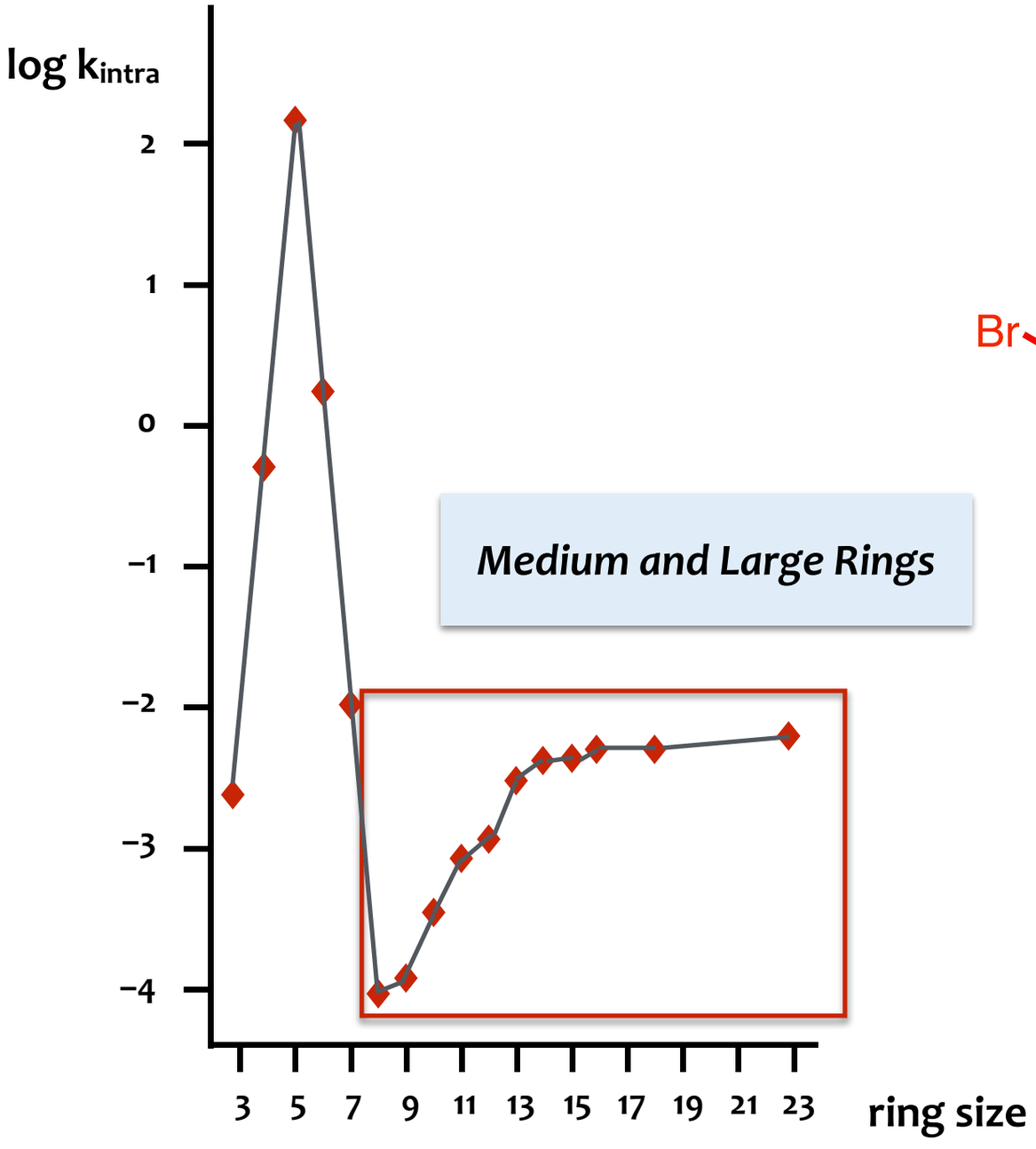
$[\Delta H^\circ]^\ddagger > 0$ *provides a measure of the strain*

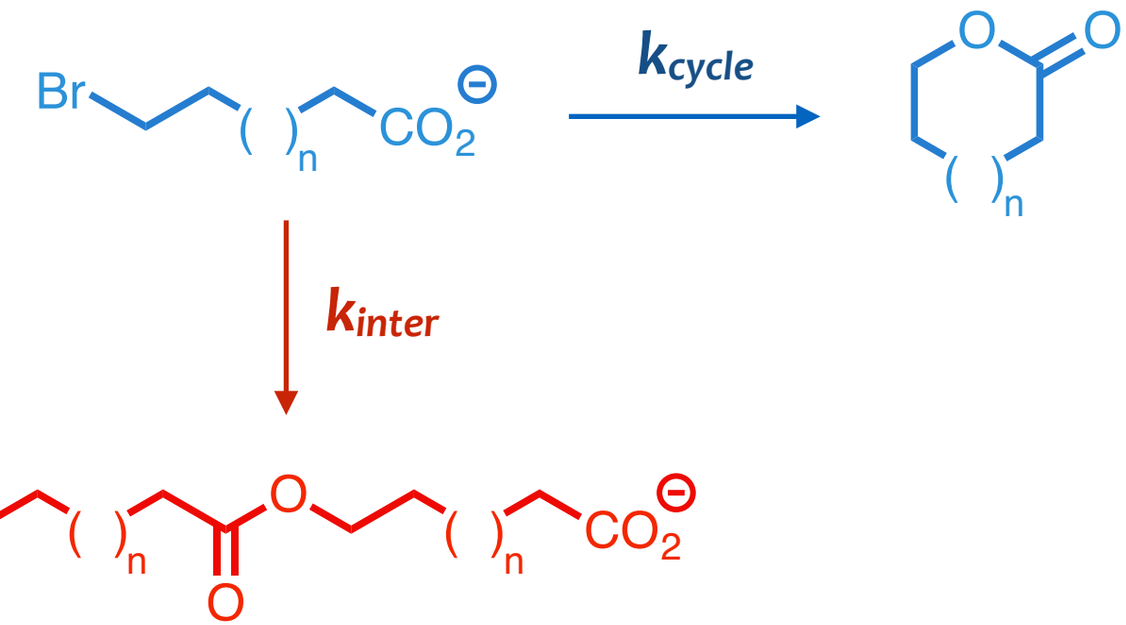
$[\Delta S^\circ]^\ddagger < 0$ *provides a measure of the probability of end-to-end (intramolecular reaction)*

Entropy decreases as the chain length increases

Illluminati, G.; Mandolini, L. *ACR* **1981**,*14*, 95


Br
( )n
CO2
kcycle
cyclization
O
O
( )n





$$\frac{v_{cycle}}{v_{inter}} = \frac{k_{cycle}\,[S]}{k_{inter}\,[S]^2} = \frac{k_{cycle}}{k_{inter}\,[S]}$$

$$\frac{v_{cycle}}{v_{inter}} \uparrow \Longrightarrow [S] \rightarrow 0$$

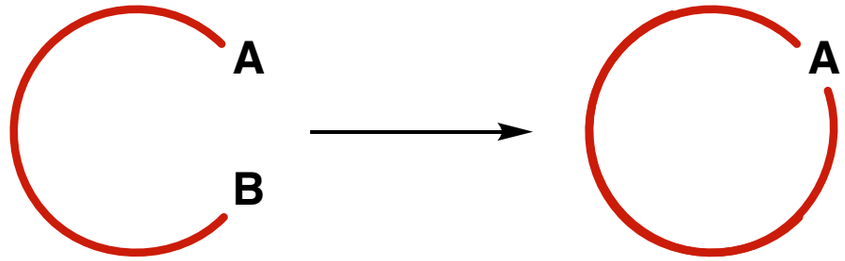
High dilution is required

Illluminati, G.; Mandolini, L. *ACR* **1981**,*14*, 95

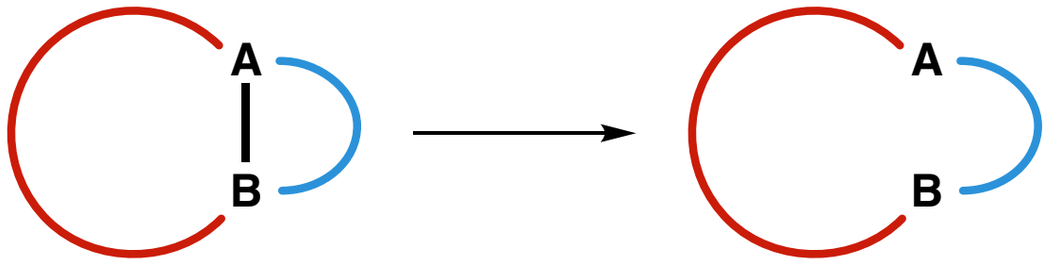
The synthesis of medium- and large-sized cyclic compounds
is a daunting challenge mainly due to unfavorable enthalpies and entropic factors

Three main strategies can be deployed to attempt their synthesis

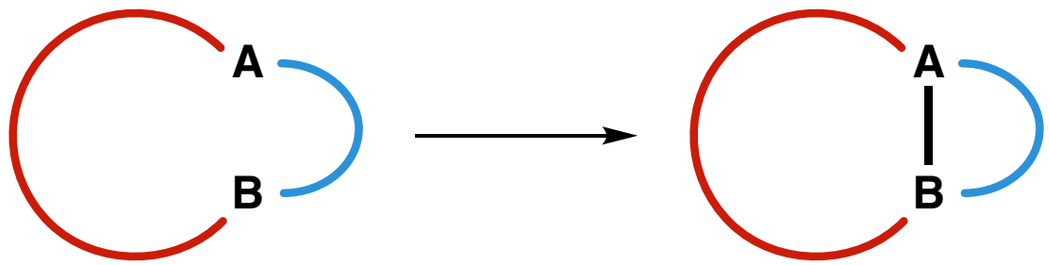
- ***Cyclization***



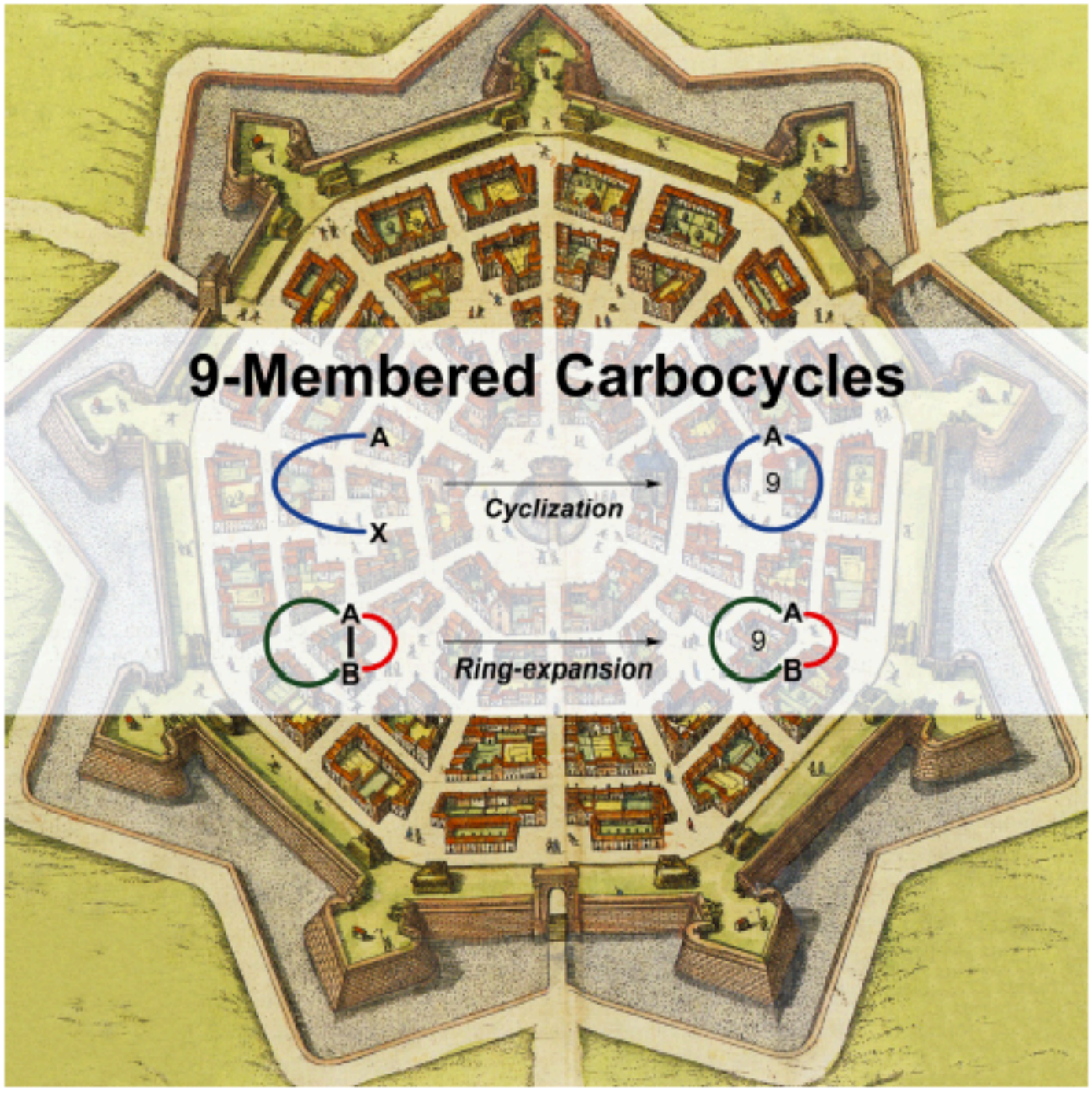
- ***Ring Expansion***



- ***Ring Contraction***

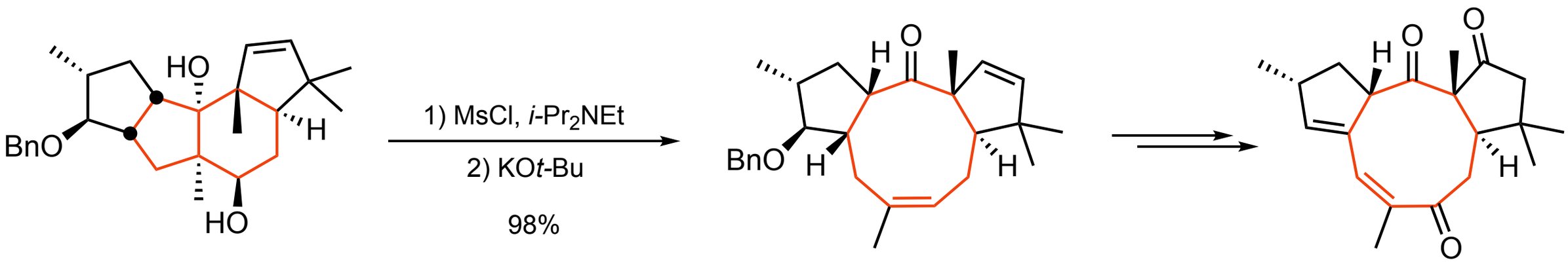


A representative example involves the construction of nine-membered carbocycles



Magauer, T. *CEJ* **2018,** *24,* 12107

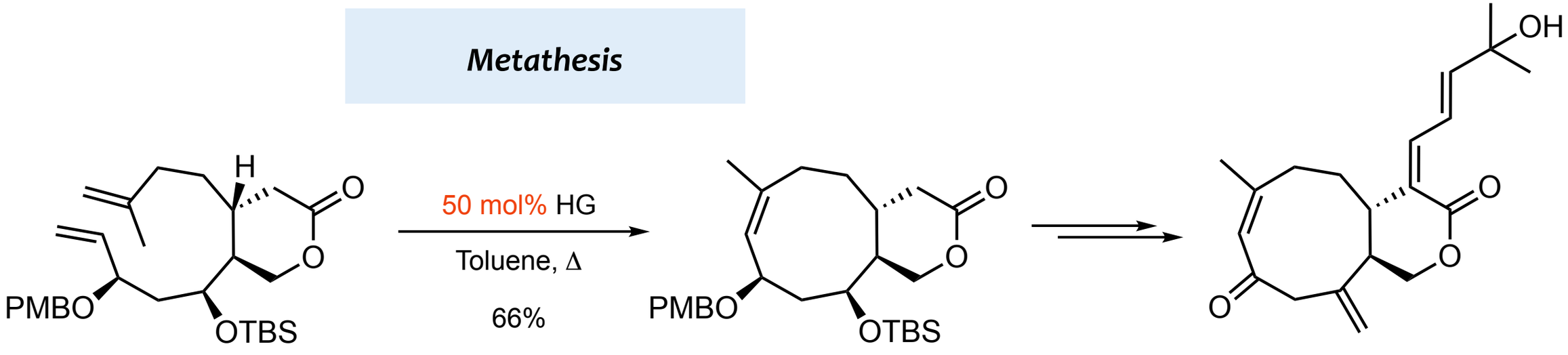
Grob fragmentation



Paquette, L. *JACS* **2003,***125*, 1567

Jatrophatrione

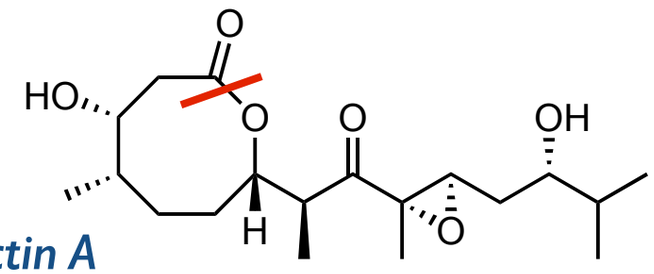
Metathesis



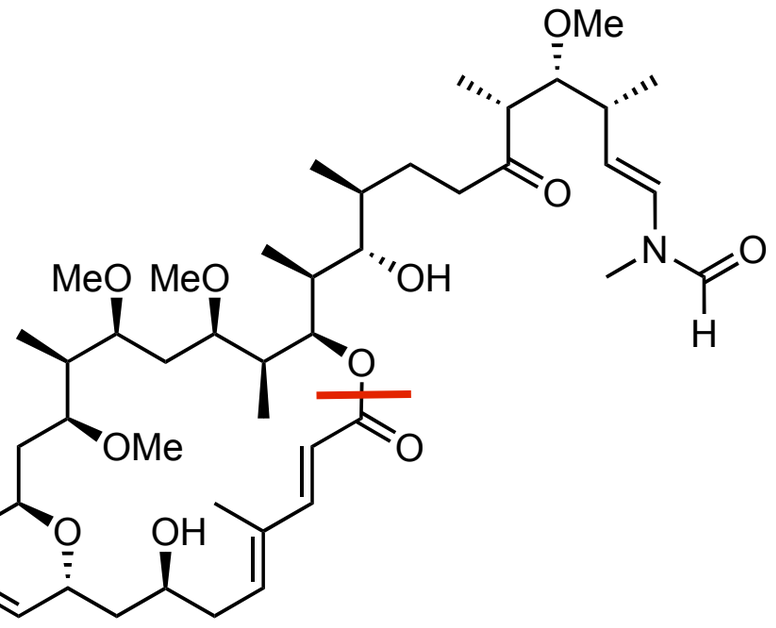
Altman, K. H. *ACIE* **2008**, *47*, 10081

Blumiolide C

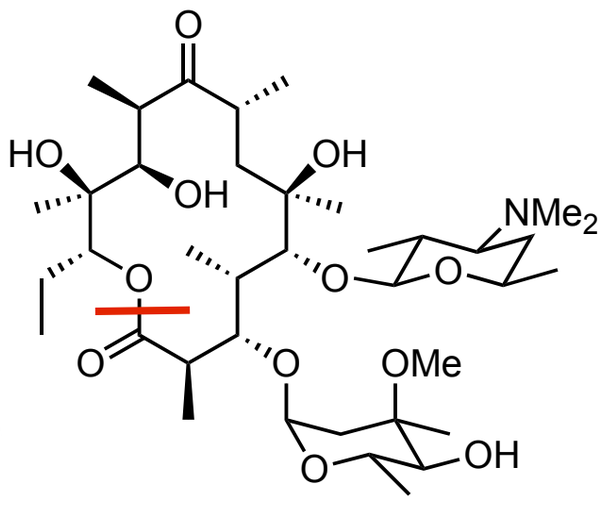
Lactones (cyclic esters) are a common structural motif in natural products



Octalactin A
(8)

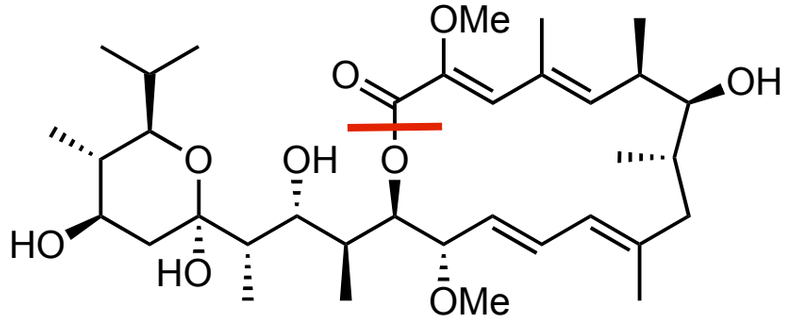


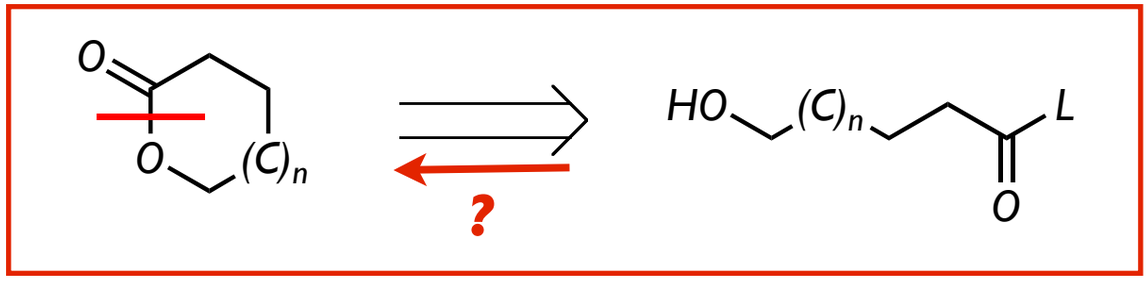
Scytophycin C
(20)



Erythromycin A
(14)

Bafilomycin A
(16)





Campagne, J. -M.
CR **2006**, *106*, 911 & **2013**, *113*, PR1

Synthesis of Medium and Large Rings: Macrolactones

The COOH is not active enough to facilitate the synthesis of an ester

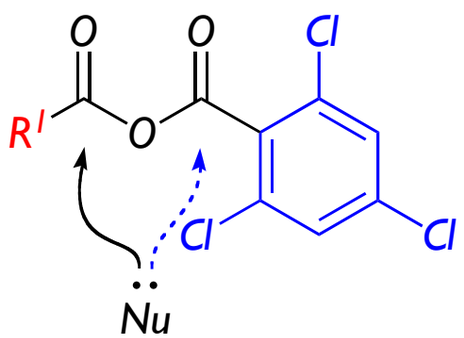
It needs to be activated …

… to provide the macrolactone

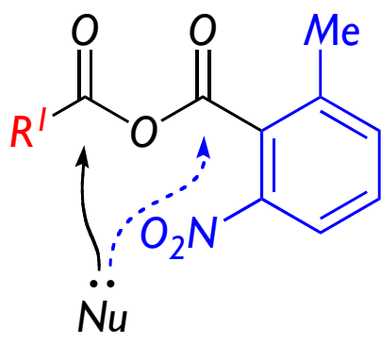
The COOH must be activated chemoselectively to complete the cyclisation under high dilution conditions

Acylation with mixed anhydrides

Mixed anhydrides are usually prepared quantitatively from acid chlorides or other anhydrides.
They are not isolated.

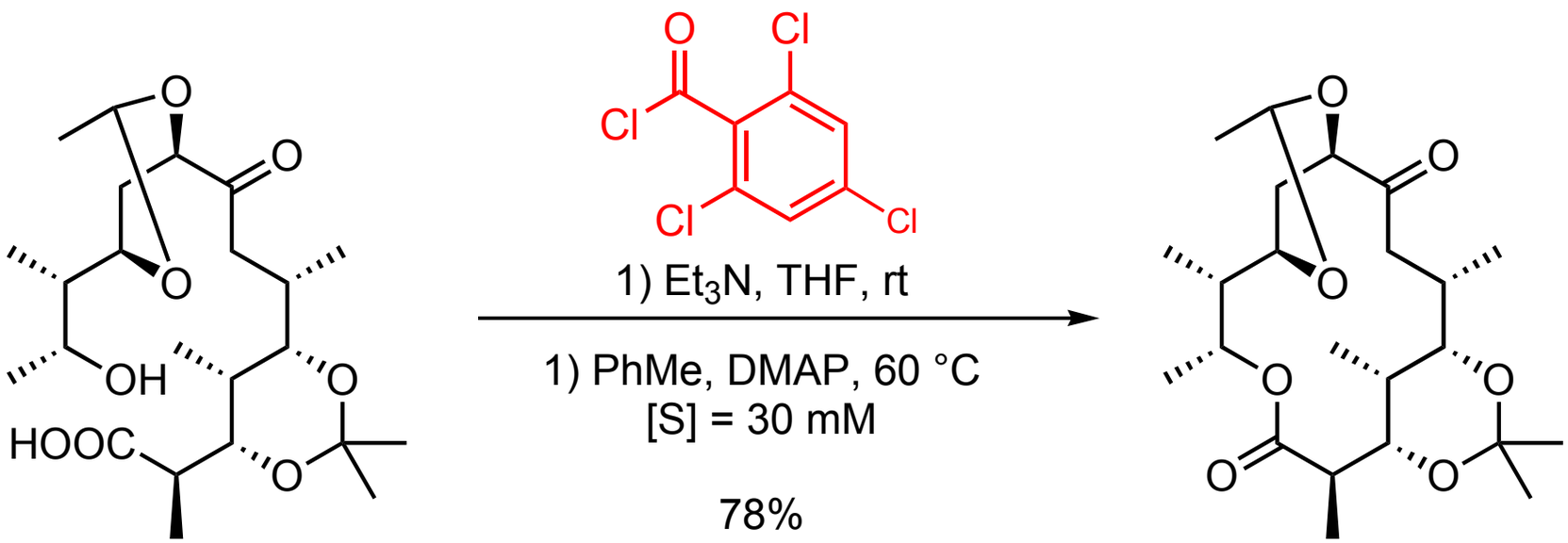


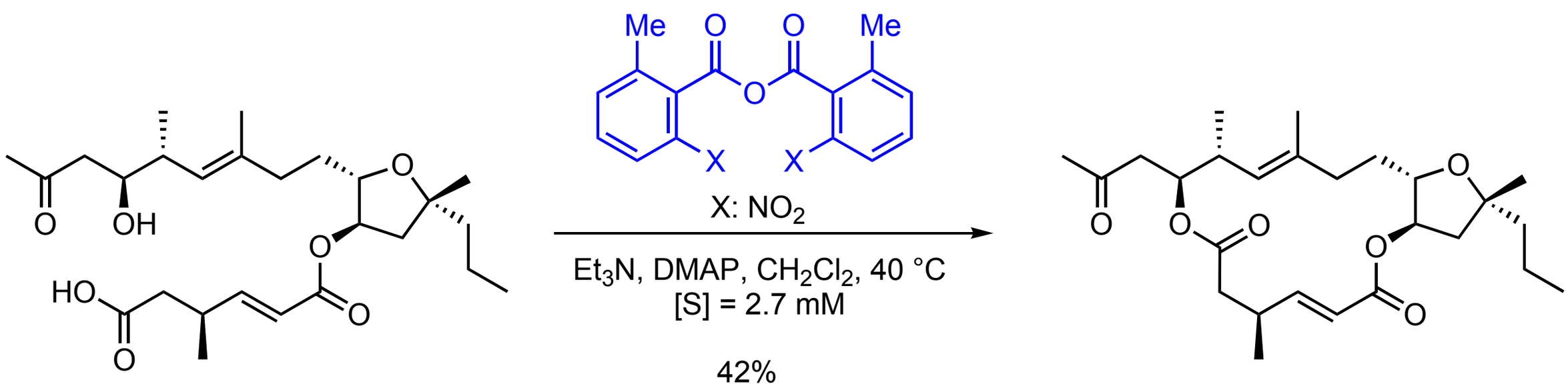
Yamaguchi Method



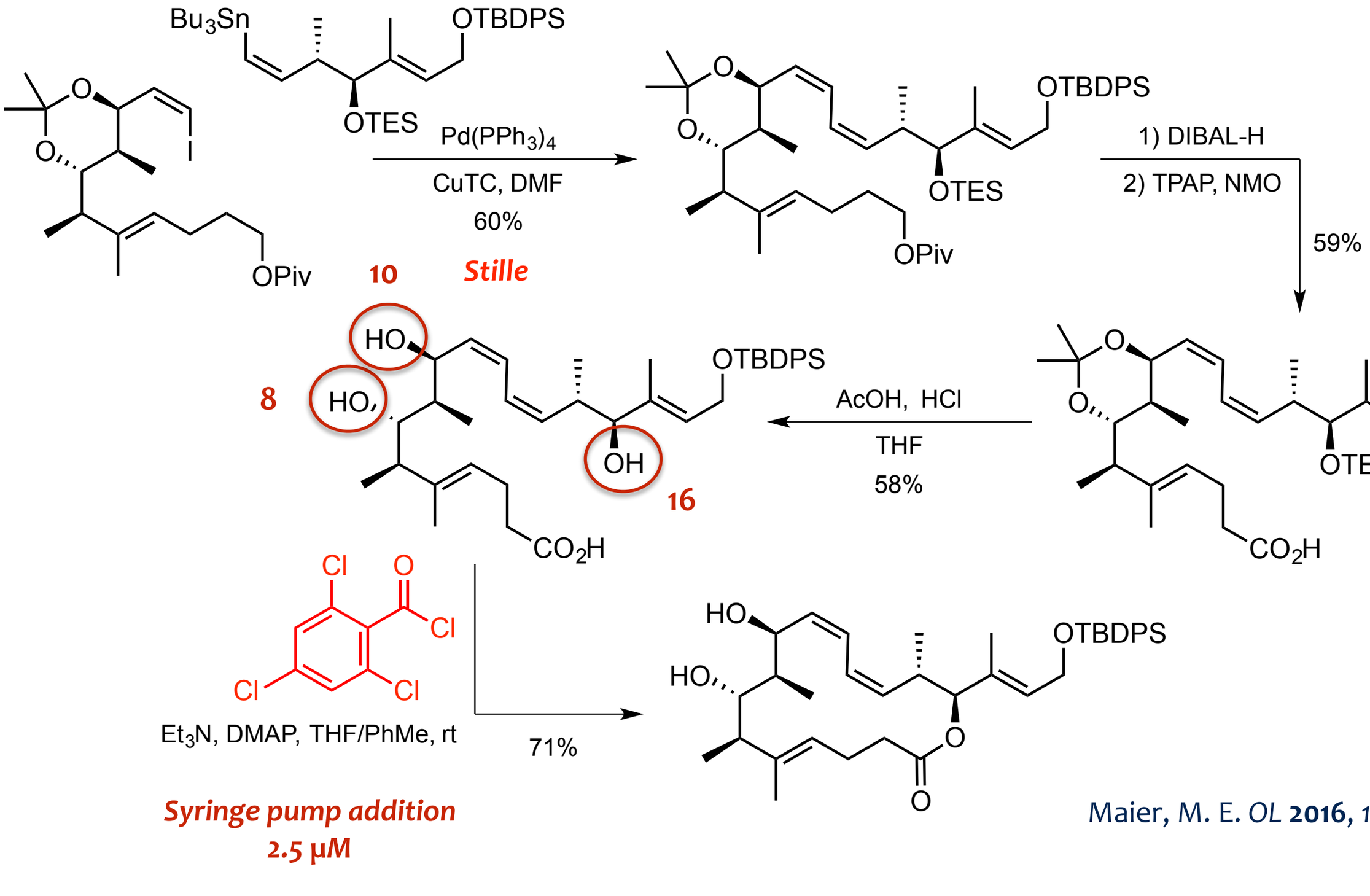
Shiina Method

JOC **2004**, 69, 1822


O
Cl
Cl
Cl
Cl
1) Et3N, THF, rt
1) PhMe, DMAP, 60 °C
[S] = 30 mM
78%
OH
HOOC


Me
O
O
Me
X
X
X: NO2
Et3N, DMAP, CH2Cl2, 40 °C
[S] = 2.7 mM
42%
OH
HO

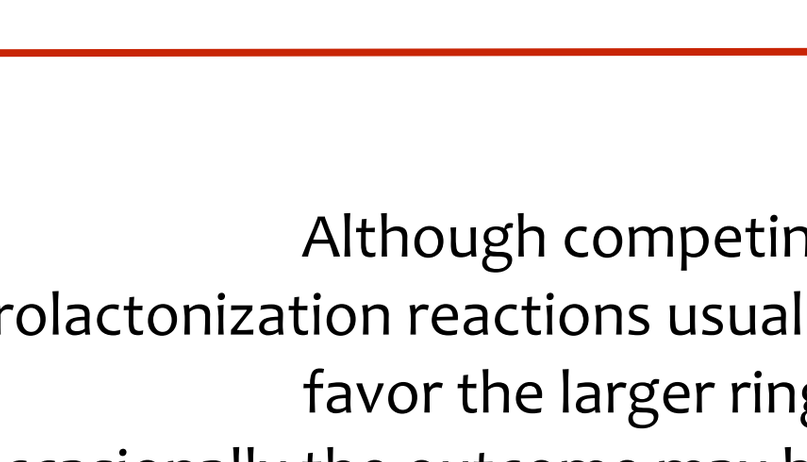
This kind of macrolactonization can be very siteselective



Syringe pump addition
2.5 µM

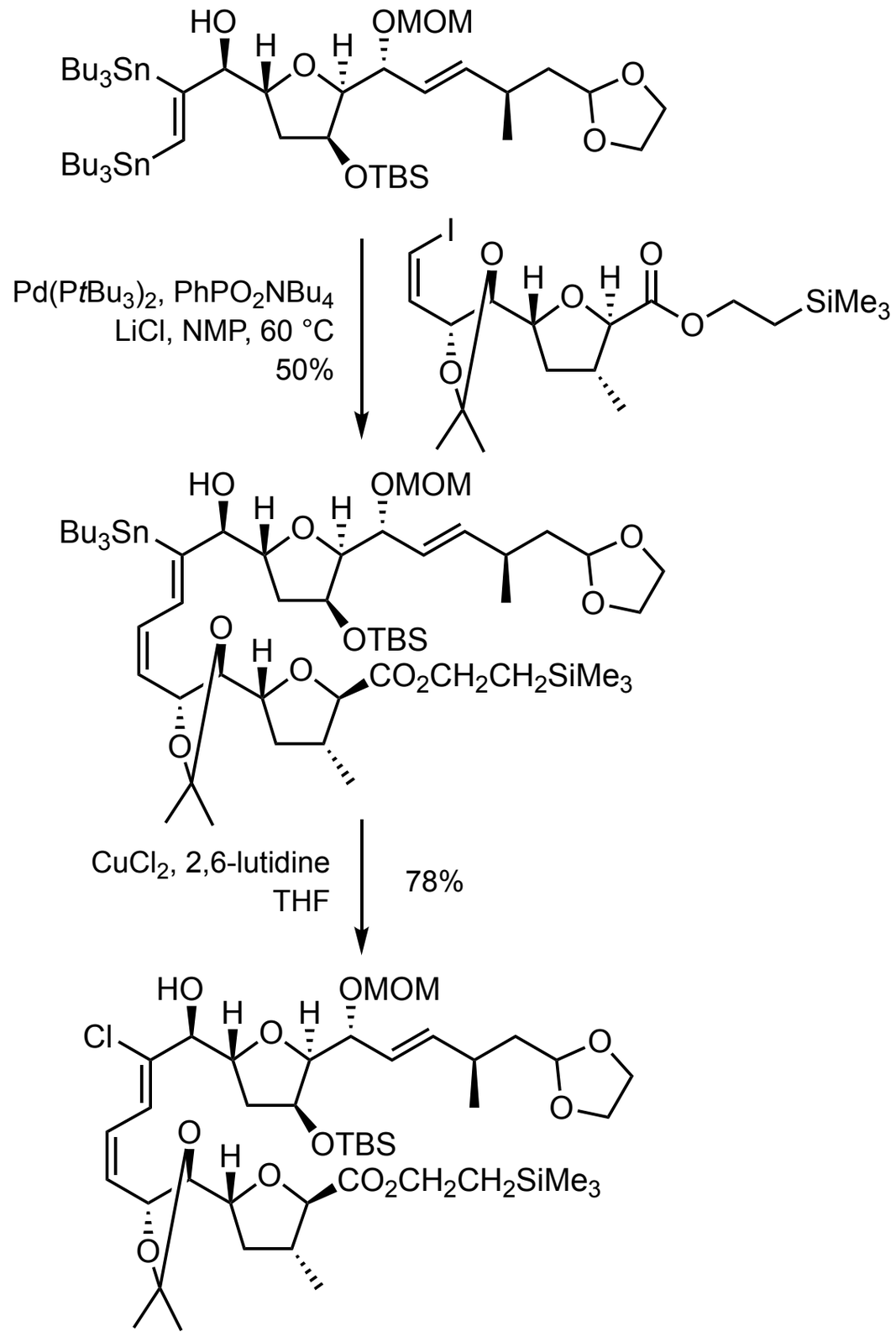
Maier, M. E. *OL* **2016**, *18*, 3146

Although competing macrolactonization reactions usually favor the larger ring, occasionally the outcome may be different depending on structural features

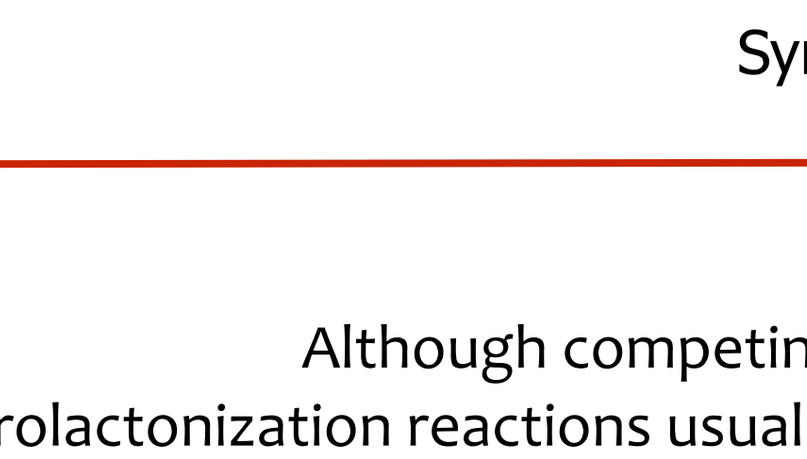


Chagosensine

Fürstner, A. *ACIE* **2018**, *57*, 13575

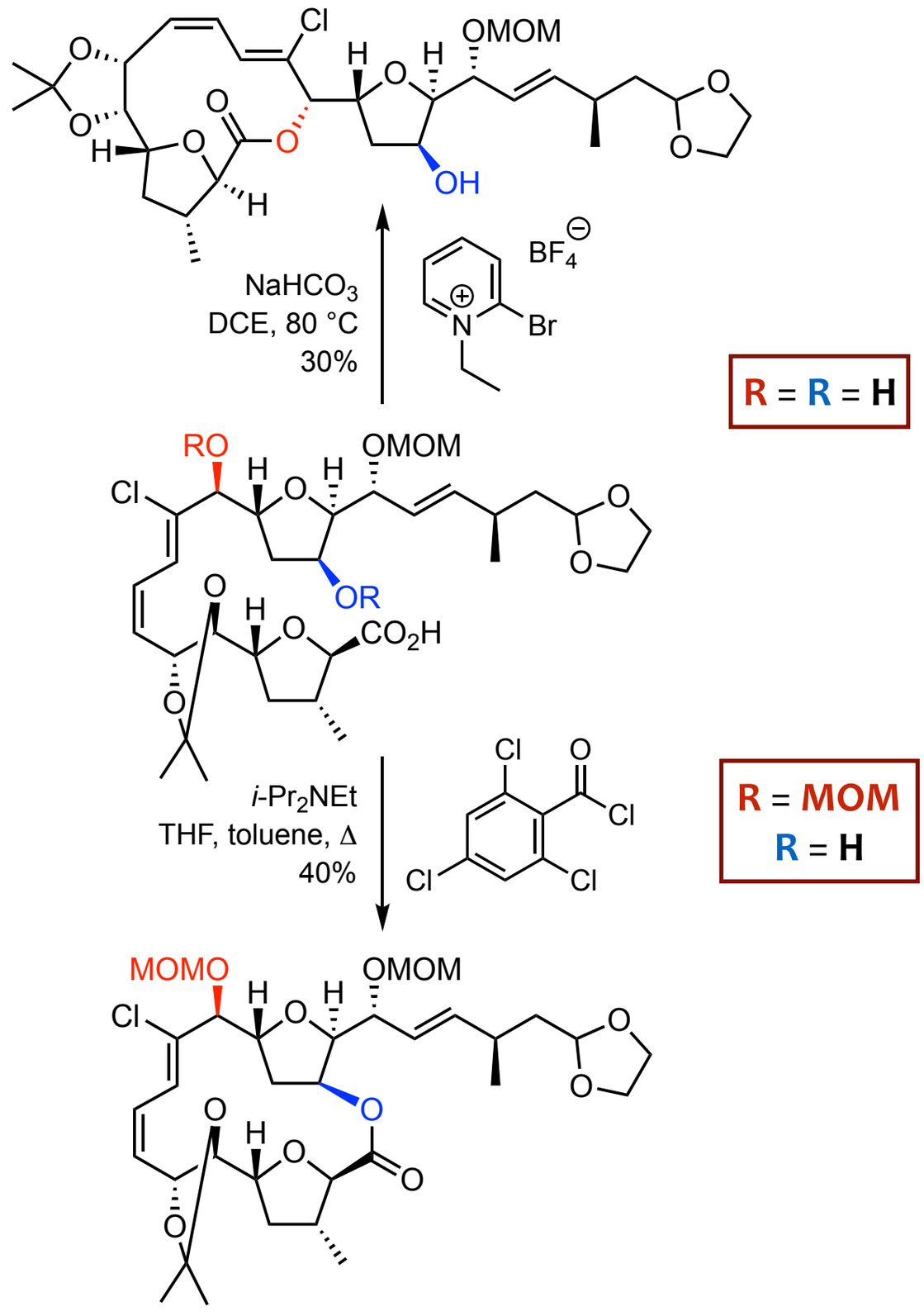


Although competing macrolactonization reactions usually favor the larger ring, occasionally the outcome may be different depending on structural features



Chagosensine

Fürstner, A. *ACIE* **2018**, *57*, 13575

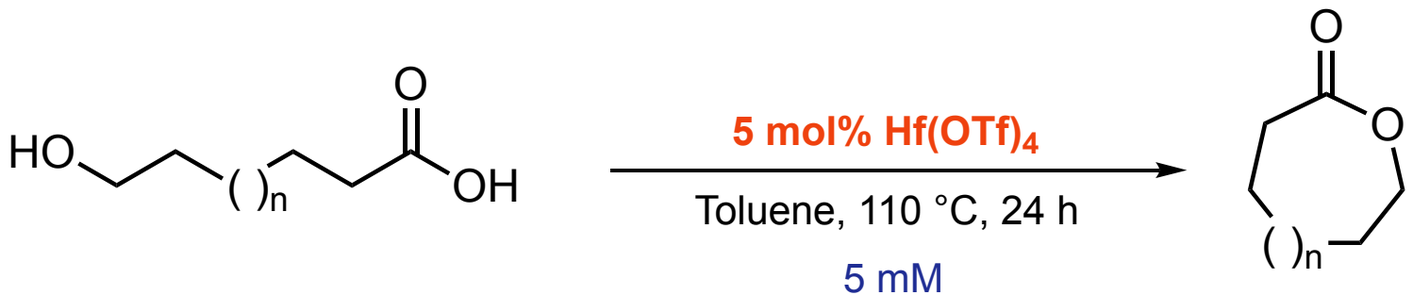


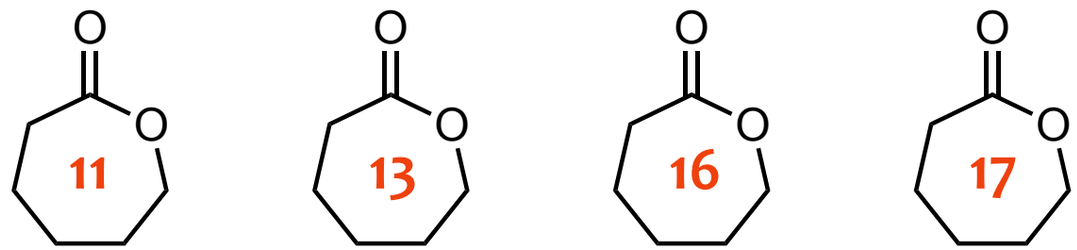
Current macrolactonization reactions from seco acids involve **stoichiometric** activation of the carboxylic acid and cyclization conducted at high dilution conditions

Is it possible to run a direct macrolactonization under catalytic conditions …?

Two **main problems:** equilibrium open/cyclic & polimerization

so efficient catalytic direct macrolactonization of seco acids are rare

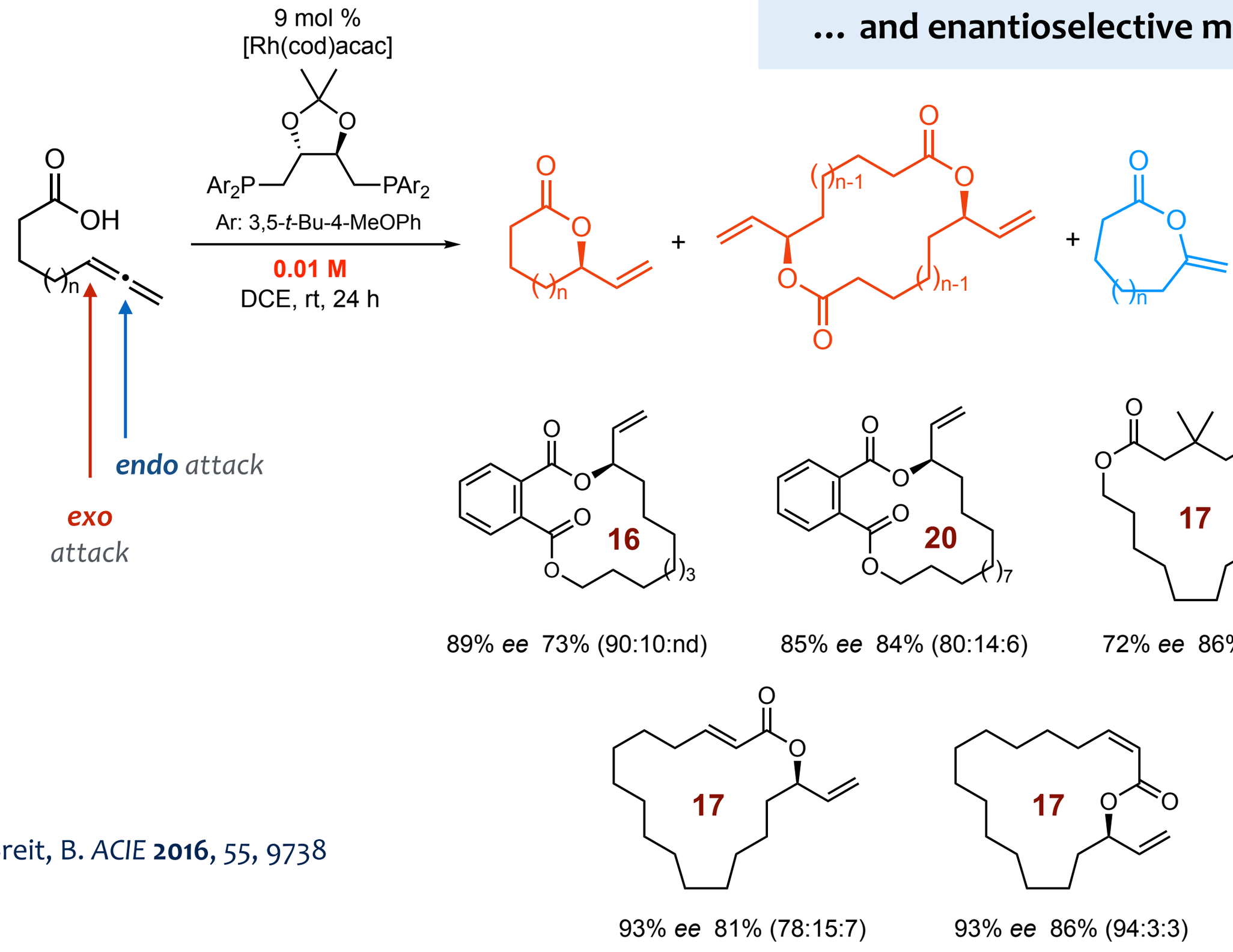




Collins, S. K.
ACS Catalysis **2015,** 5, 1462

Synthesis of Medium and Large Rings: Macrolactones

… and enantioselective manner?



89% *ee* 73% (90:10:nd)

85% *ee* 84% (80:14:6)

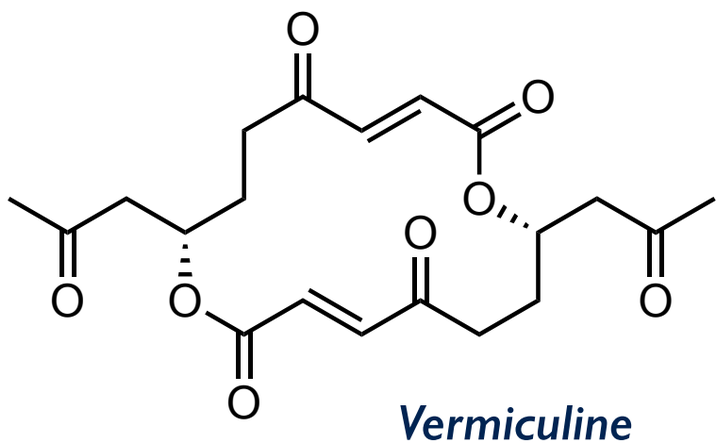
72% *ee* 86% (83:14:3)

93% *ee* 81% (78:15:7)

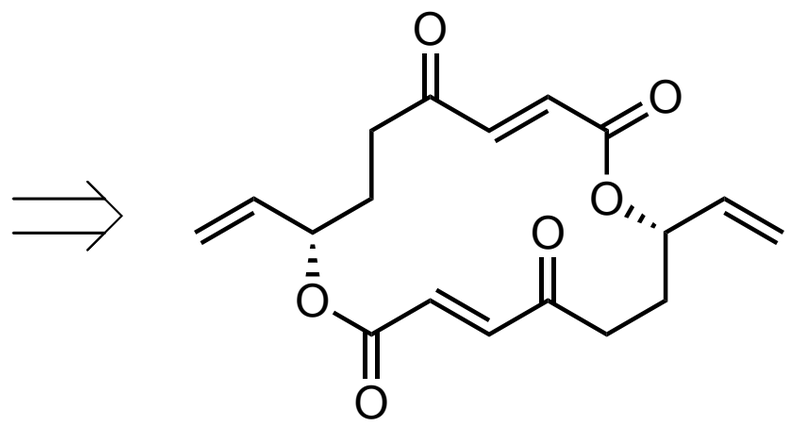
93% *ee* 86% (94:3:3)

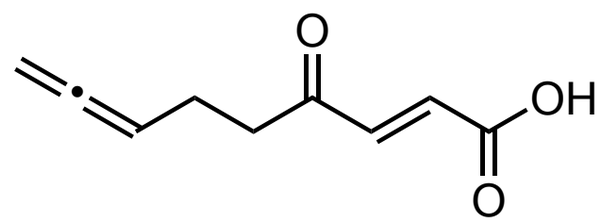
Breit, B. *ACIE* **2016**, 55, 9738

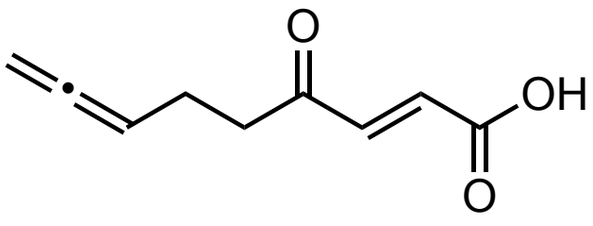
Synthesis of Medium and Large Rings: Macrolactones



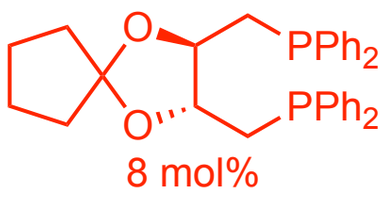
Vermiculine







4 mol% $Rh(cod)Cl_2$

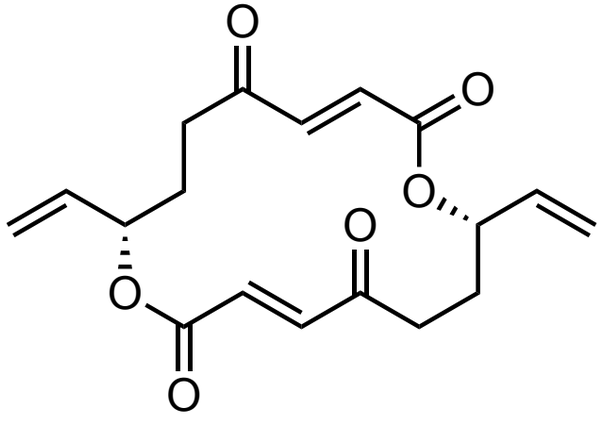


8 mol%

DCE, 10 °C, 48 h

syringe pump addition

dr 81:19 *ee* 99% 73%

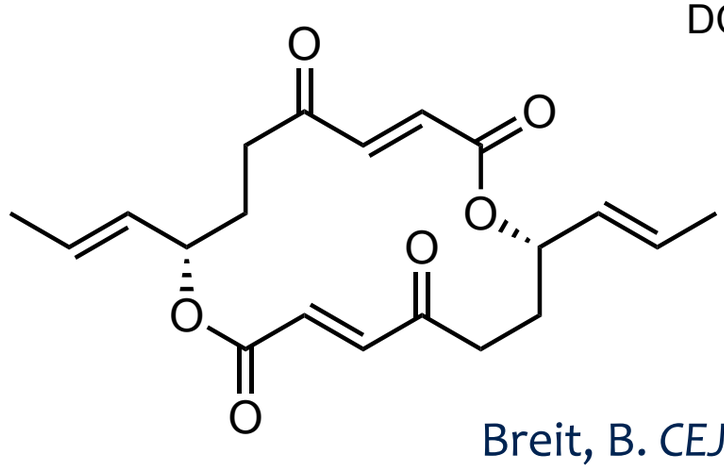


2-butene

10 mol% Grubbs II

DCE, 40 °C

90%



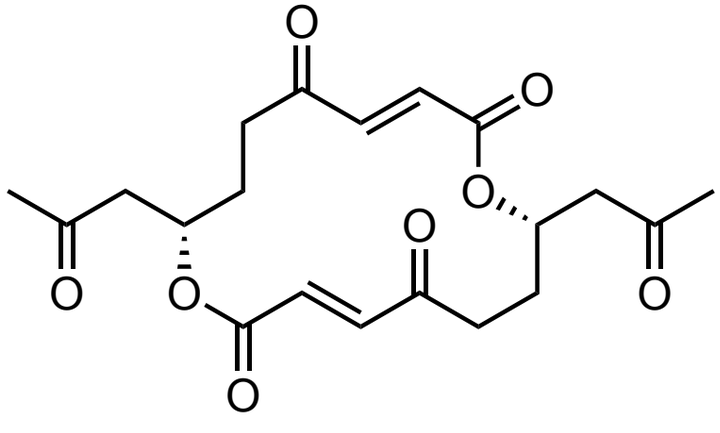
TBHP

20 mol% $Pd(quinox)Cl_2$

50 mol% $AgSbF_6$

DCE, rt

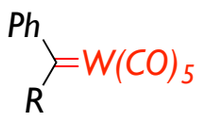
60%



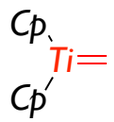
Breit, B. *CEJ* **2019**, 25, 3532

Ring Closing Metathesis (RCM) is a powerful reaction to obtain macrocycles

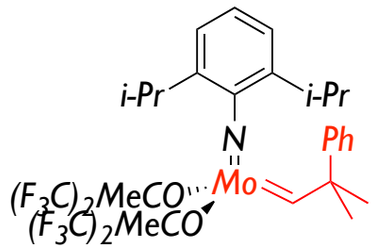
For instance, it can be used to prepare macrolactones



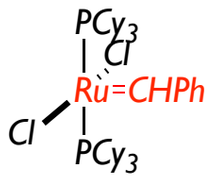
Katz 1976



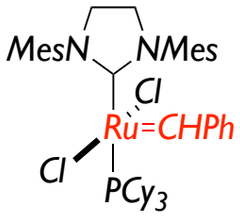
Tebbe 1978



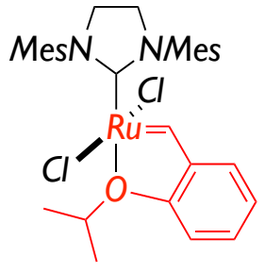
Schrock 1990



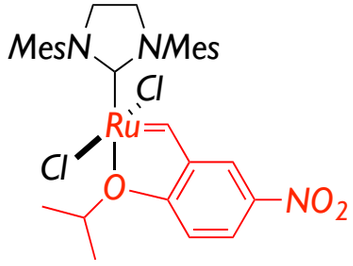
Grubbs I 1995



Grubbs II 1999

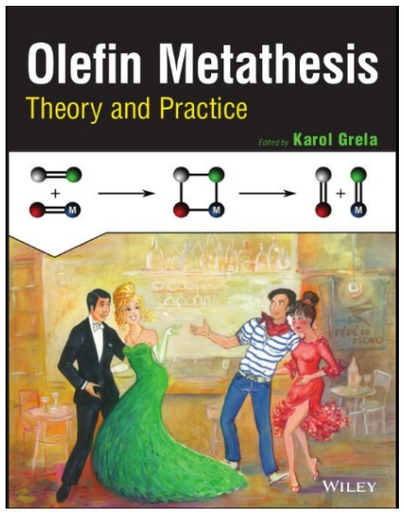


Hoveyda 2000

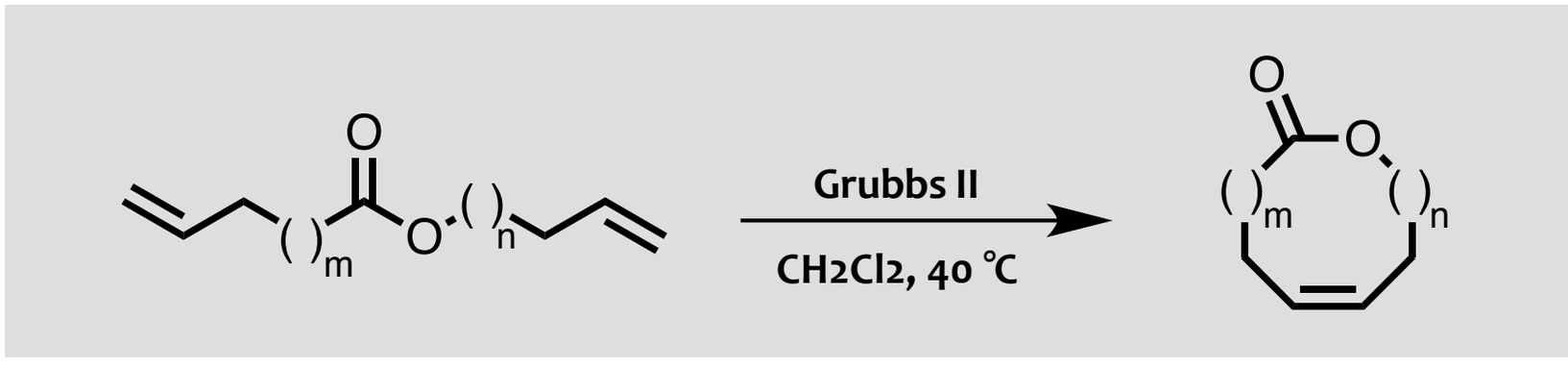


Grela 2002

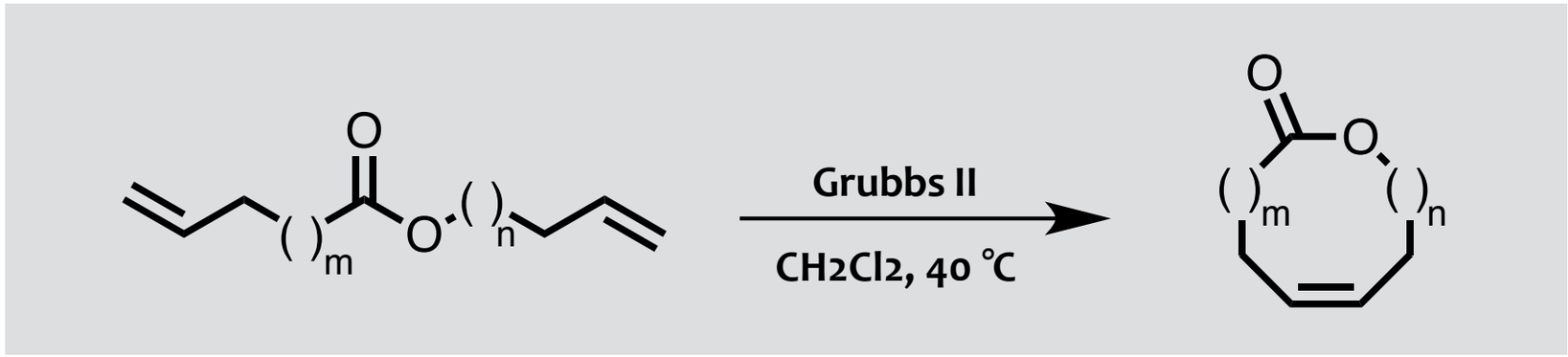
Grela K.
Olefin Metathesis.Theory and Practice.
Wiley



Synthesis of Medium and Large Rings: Ring Closing Metathesis

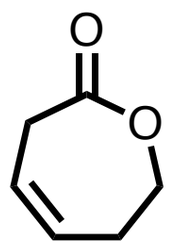


Synthesis of Medium and Large Rings: Ring Closing Metathesis



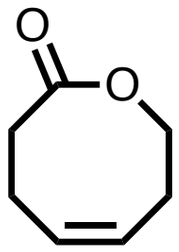
High dilution conditions are often required

PROBLEM: CONTROL OF THE Z/E CONFIGURATION

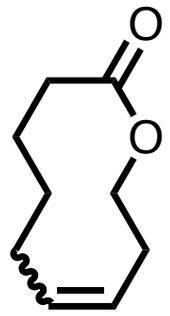


7

5 mM 29%
0.5 mM 70%



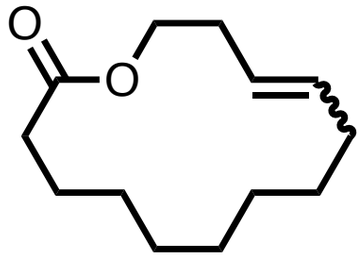
8



10

5 mM 41%
0.5 mM 95%

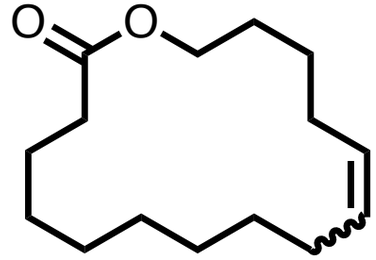
E/Z 41:59



14

5 mM 94%

E/Z 89:11



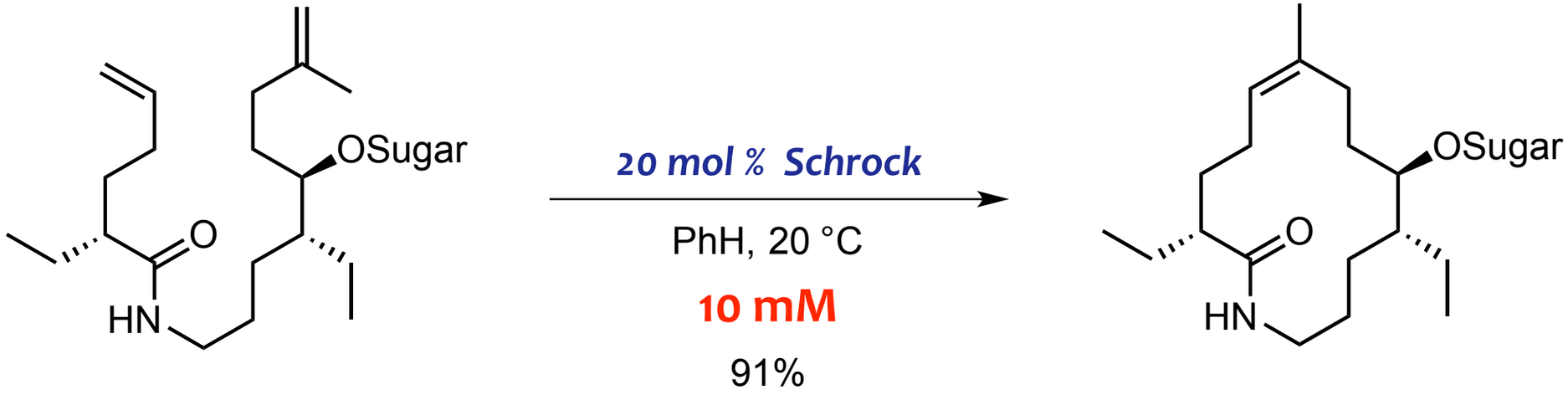
16

5 mM 99%

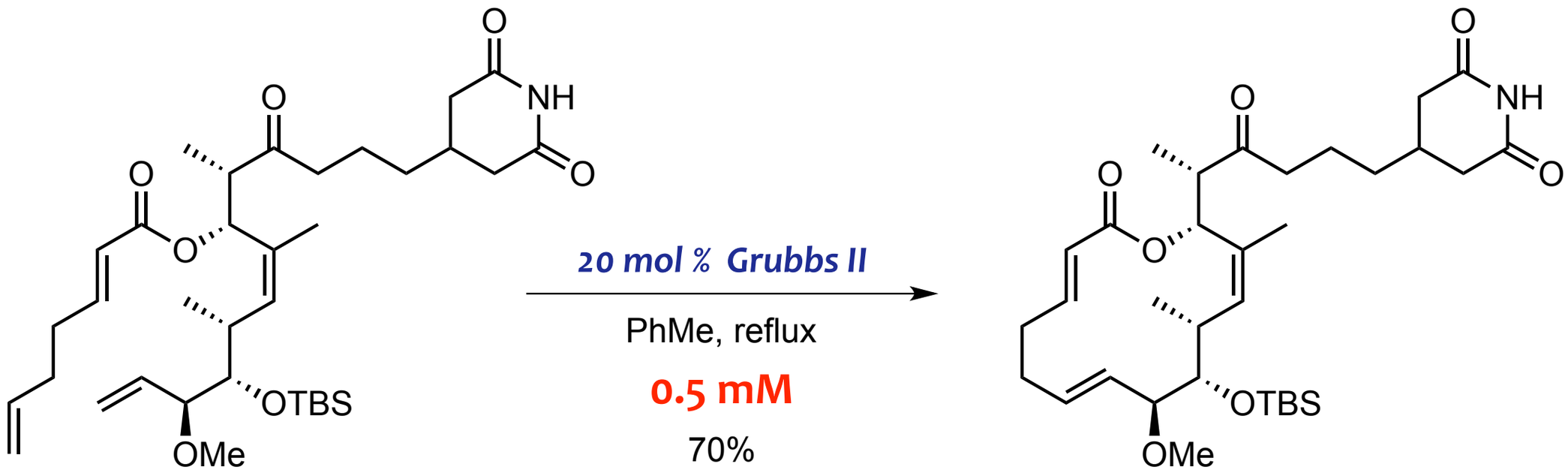
E/Z 72:28

Fogg, D. E. *JACS* **2007**,129, 1024

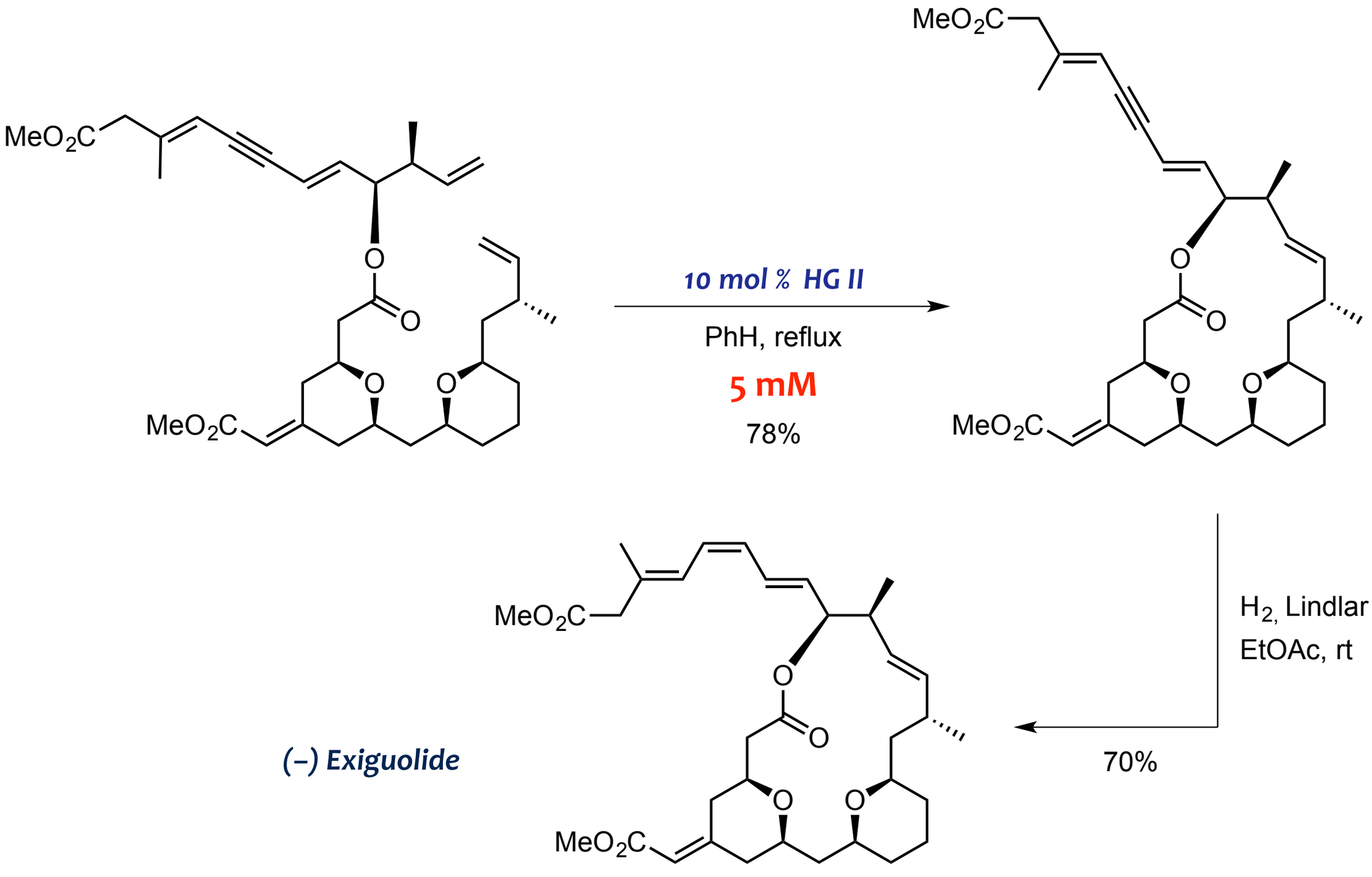
Synthesis of Medium and Large Rings: Ring Closing Metathesis



Hoveyda, A. H. *JACS* **1997**,*119*, 10302



Danishefsky, S. *JACS* **2003**,*125*, 6042

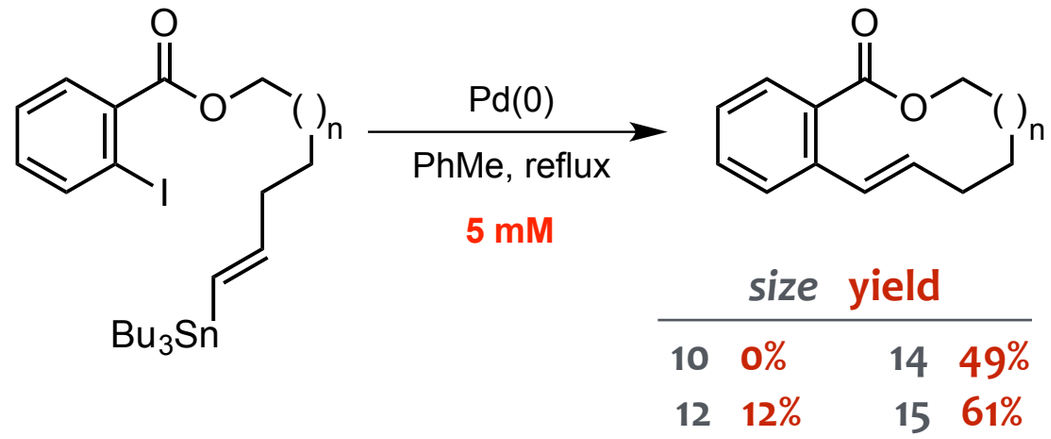


(–) Exiguolide

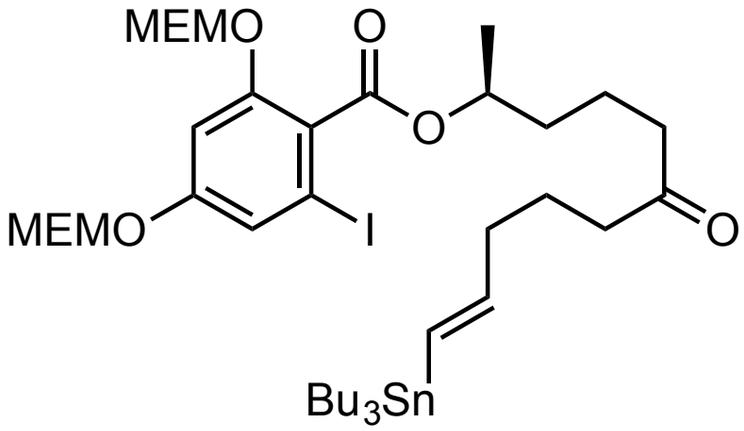
Song, Z. *OL* **2015,** *17,* 4706

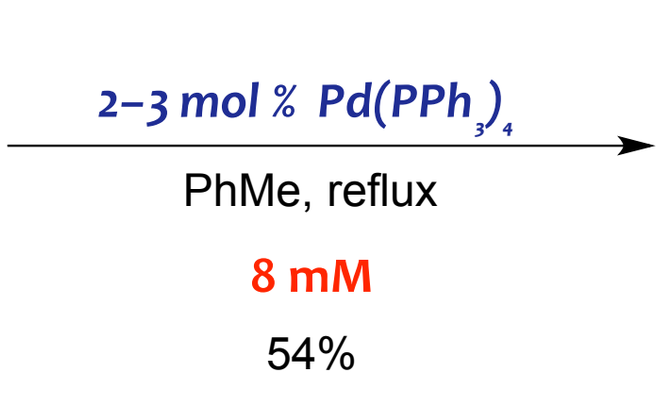
For instance, the STILLE REACTION

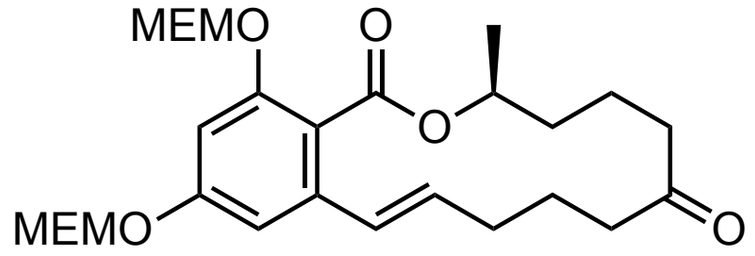
has been used for the synthesis of macrocycles

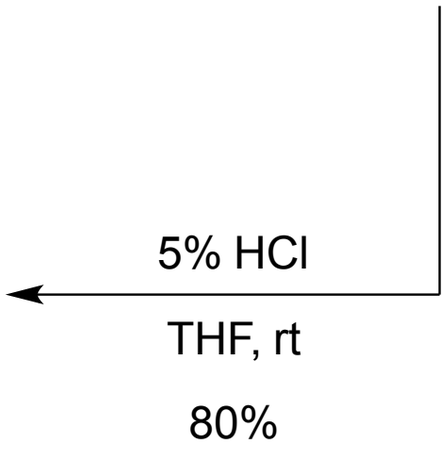


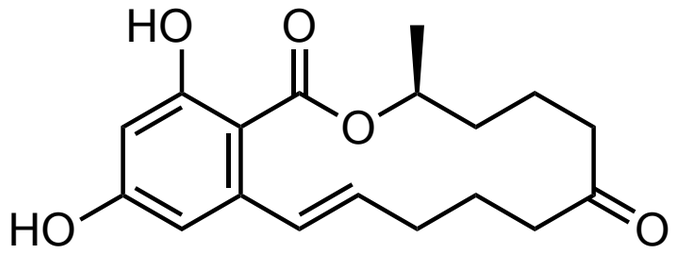
size	yield	size	yield
10	0%	14	49%
12	12%	15	61%







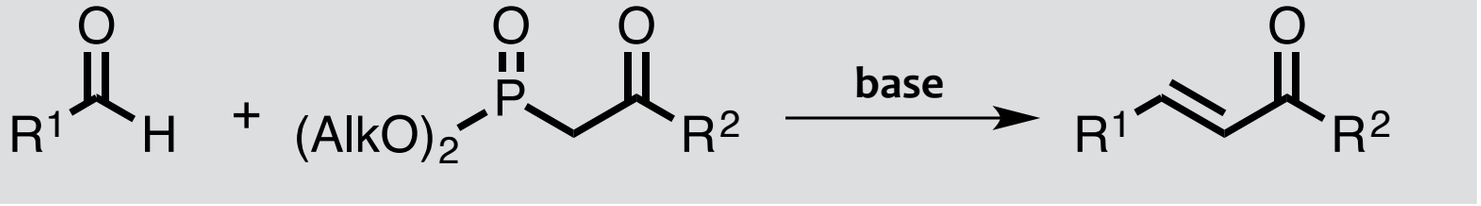


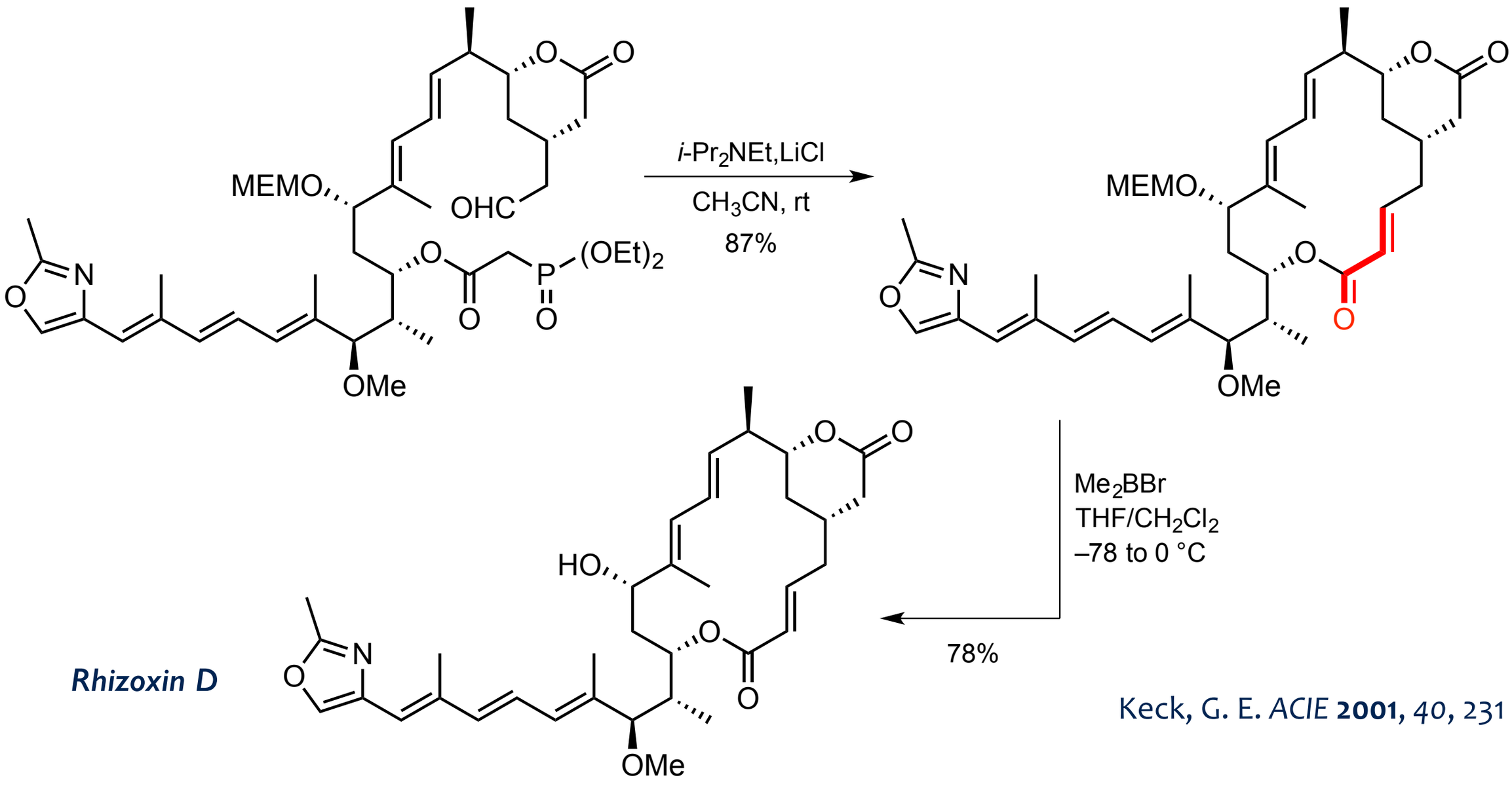


(S) Zearalenone

Hegedus, L. S. *JOC* **1991**, 56, 2883
Nicolaou, K. C. *ACIE* **1998**, 37, 2534

The HORNER-WADSWORTH-EMMONS has also been used for the synthesis of macrocycles

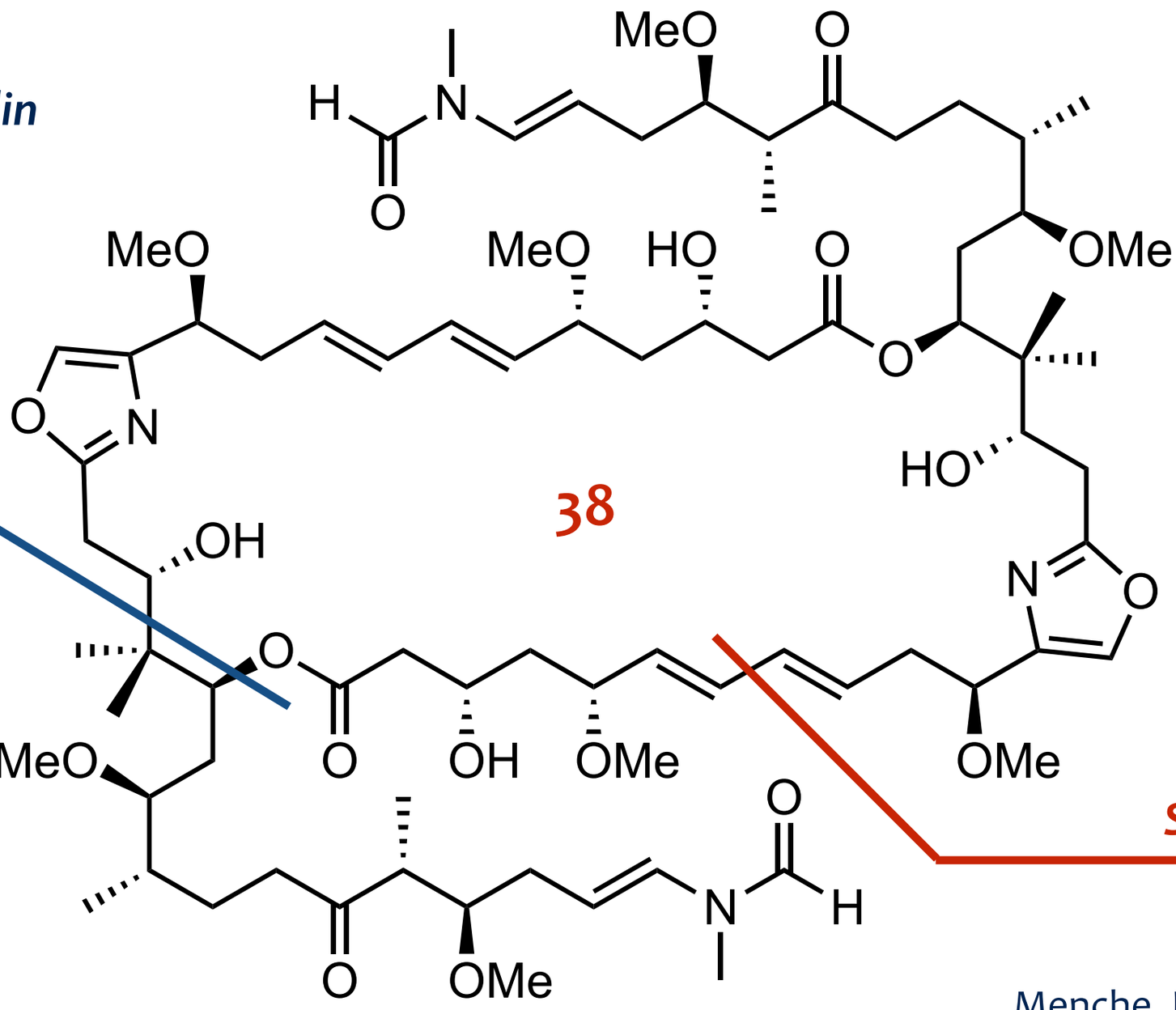




Rhizoxin D

Keck, G. E. *ACIE* **2001**, *40*, 231

(–)-Rhizopodin



38

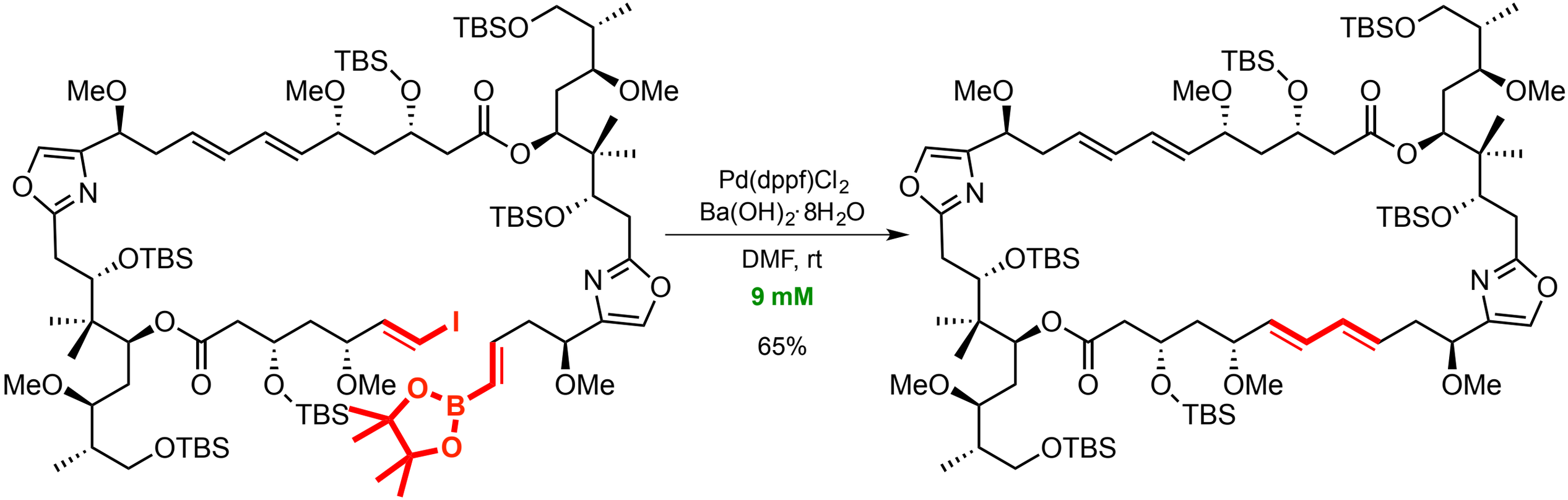
Yamaguchi

(Paterson)

Suzuki, Heck

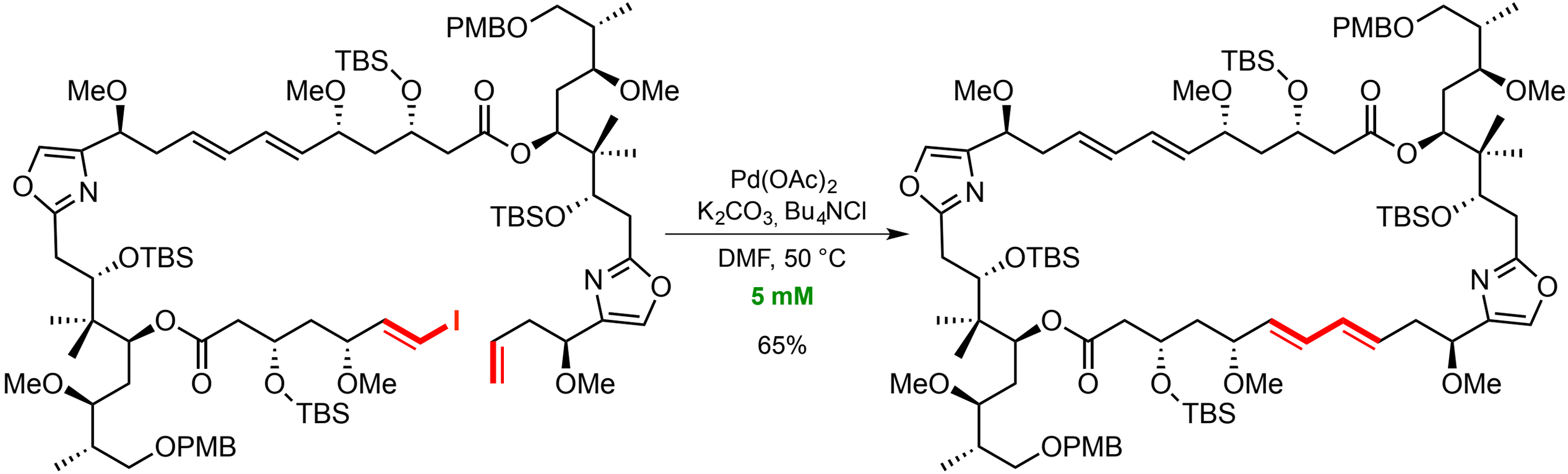
(Menche)

Menche, D. *ACIE* **2012**, *51* 5667
Menche, D. *JOC* **2012**, *77*, 10782
Paterson, I. *ACIE* **2013**, 52, 6517



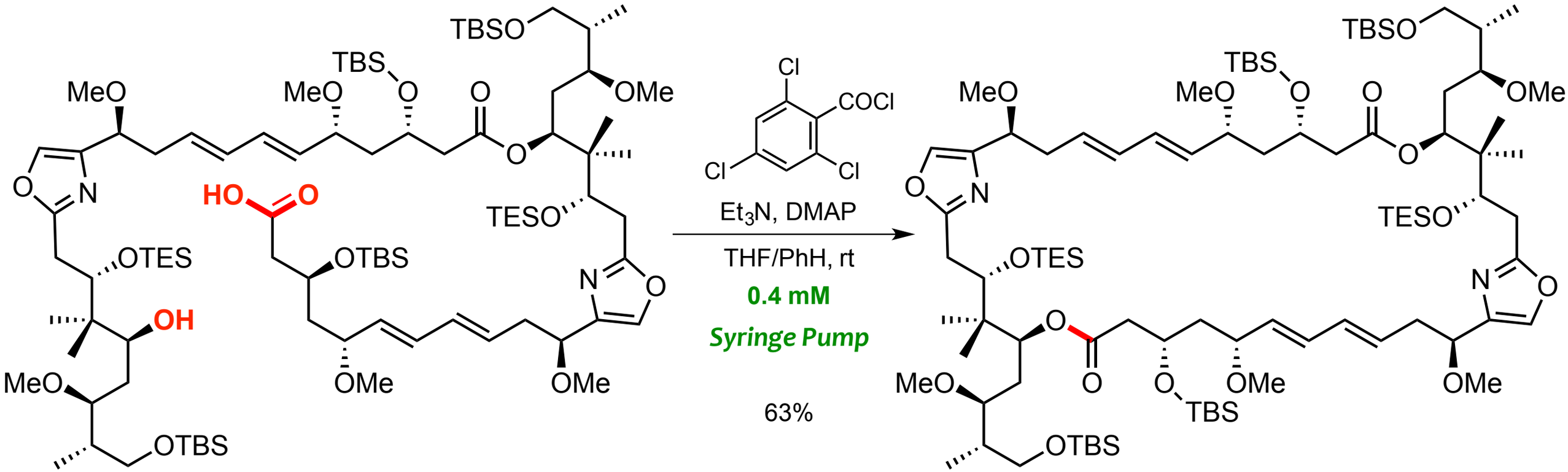
Cyclization through a Suzuki reaction

Menche, D. *ACIE* **2012,** *51* 5667



Cyclization through a Heck reaction

Menche, D. *JOC* **2012**, *77*, 10782



Cyclization through a Yamaguchi reaction

Paterson, I. *ACIE* **2013**, 52, 6517

Three Rings for the Elven-kings under the sky, Seven for the Dwarf-lords in their halls of stone,Nine for Mortal Men doomed to die,
One for the Dark Lord on his dark throneIn the Land of Mordor where the Shadows lie.
One Ring to rule them all, One Ring to find them, One Ring to bring them all and in the darkness bind them
In the Land of Mordor where the Shadows lie.
The Lord of the Rings

6.2. Baldwin Rules

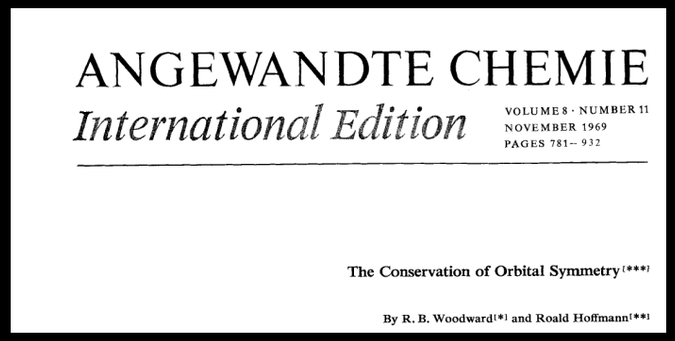
1970

Nobel Prize 1969

Derek H. Barton

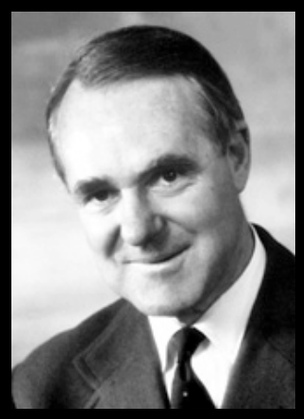
Odd Hassel

For their contribution to the development of the concept of conformation and its application in chemistry

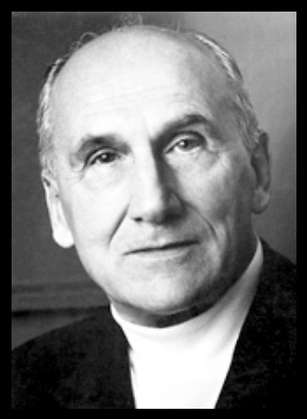


The Conservation of Orbital Symmetry
Woodward, R. B.; Hoffmann, R.
ACIEE **1969**, *8*, 781

Nobel Prize 1975



John W. Cornforth



Vladimir Prelog

For their research into the stereochemistry of organic molecules and reactions

Stereochemistry of Reaction Paths at Carbonyl Centres
Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G
Tetrahedron **1974**, *30*, 1563

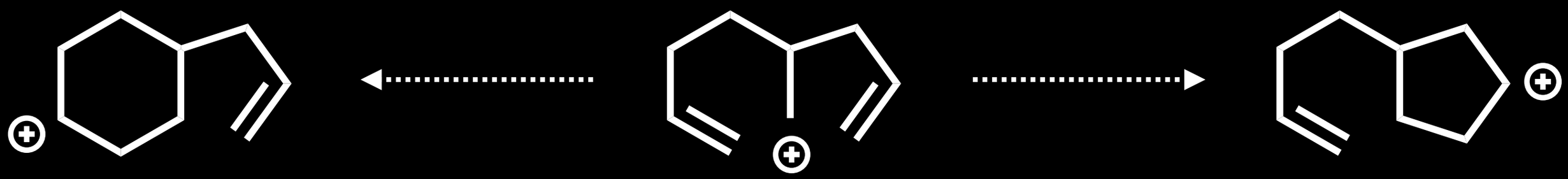
1980

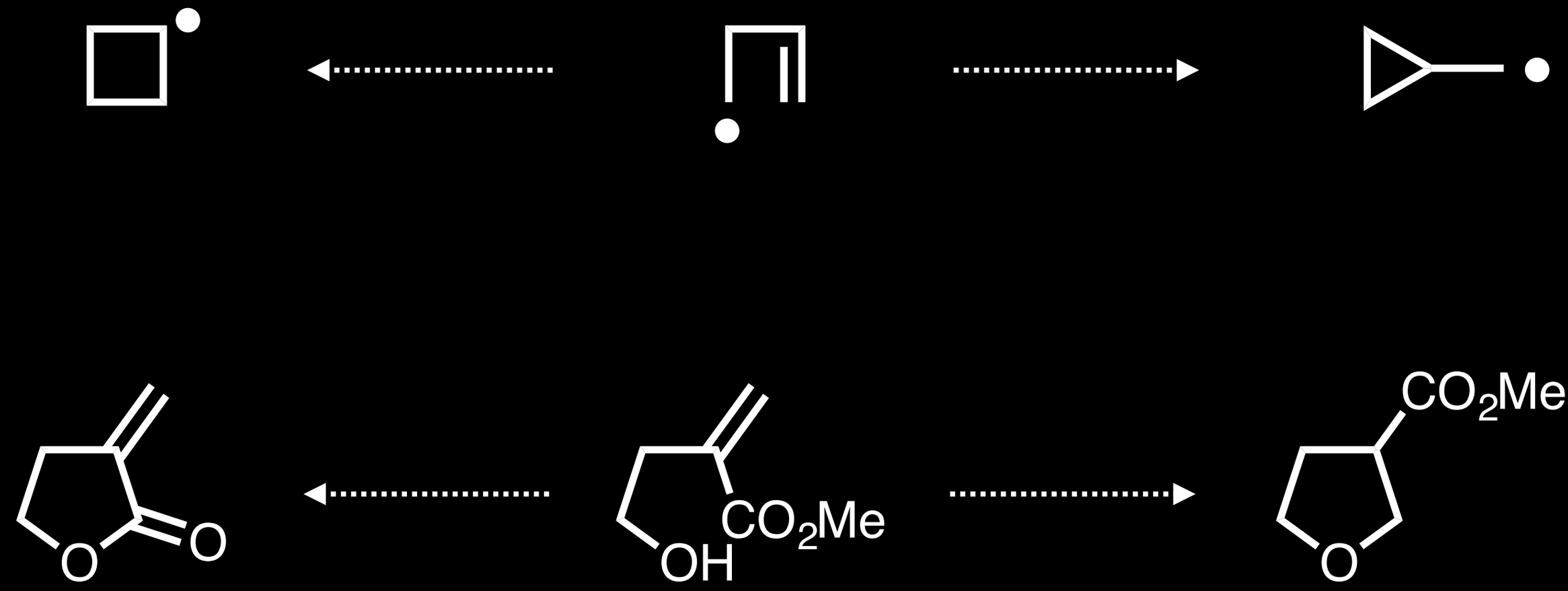
Nobel Prize 1981

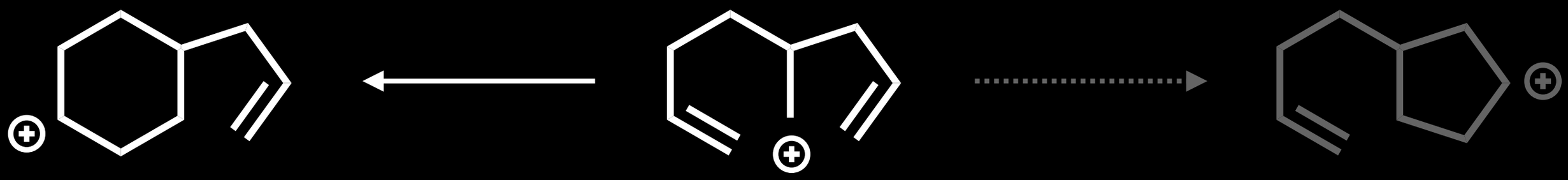
Kenichi Fukui

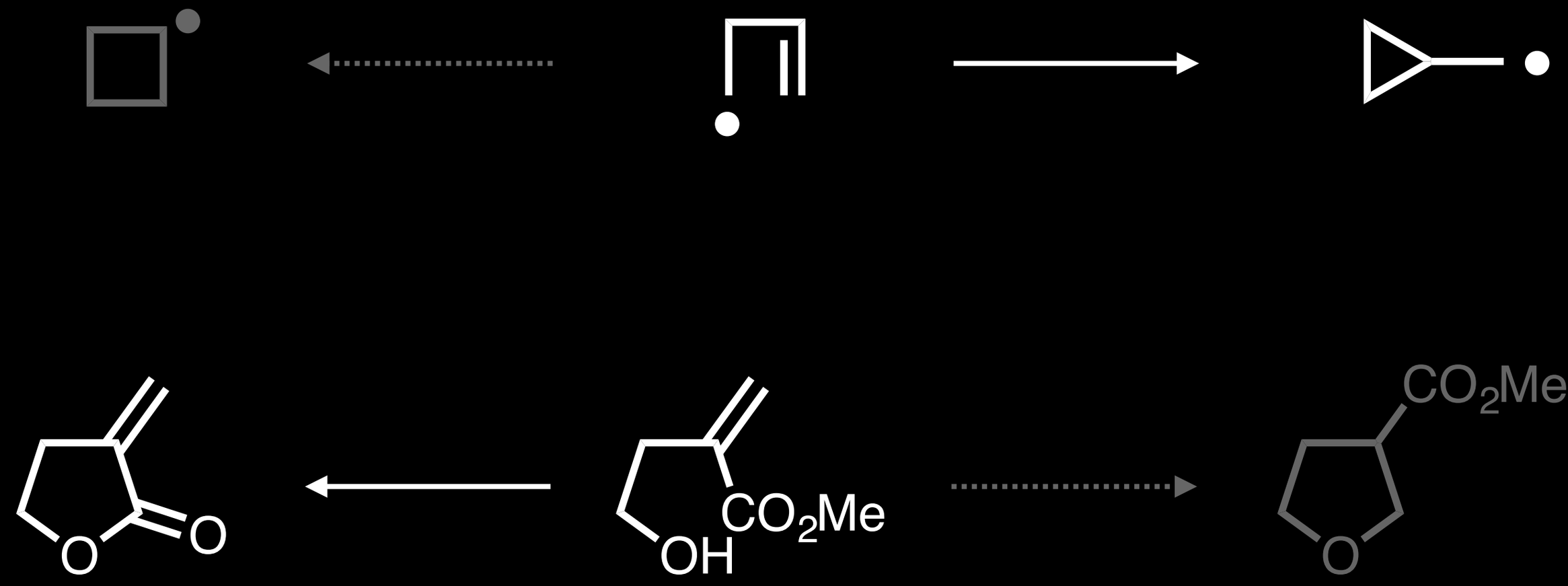
Roald Hoffmann

For their theories concerning the course of chemical reactions




O
O
OH
CO2Me
CO2Me
O




O
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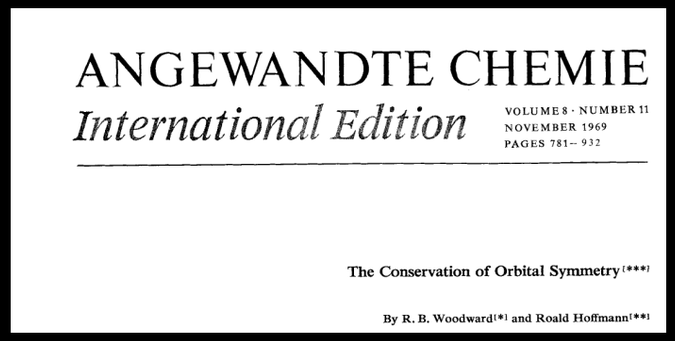
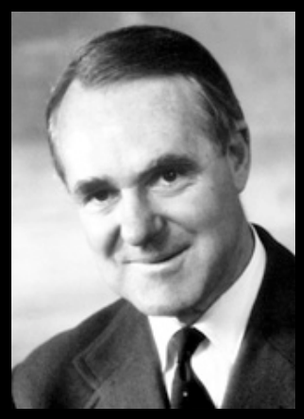
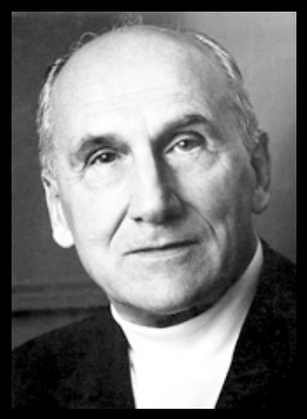


The Conservation of Orbital Symmetry
Woodward, R. B.; Hoffmann, R.
ACIEE **1969**, *8*, 781

Nobel Prize 1975



John W. Cornforth



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Tetrahedron **1974**, *30*, 1563

1980

Nobel Prize 1981

Kenichi Fukui

Roald Hoffmann

For their theories concerning the course of chemical reactions

1976
Baldwin Rules

Baldwin Rules

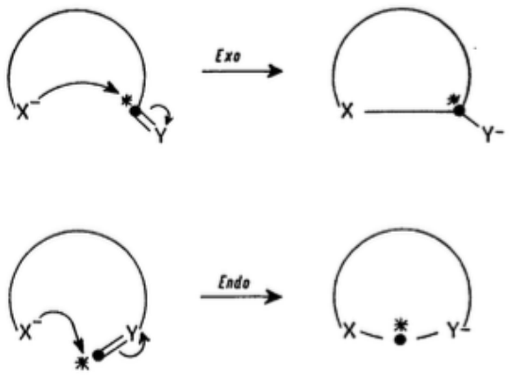
Rules for Ring Closure

By Jack E. Baldwin

(*Chemistry Department, Massachusetts Institute of Technology, Cambridge, Massachusetts* 02139)

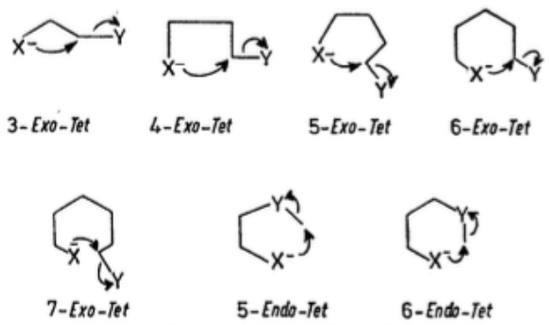
Summary Three rules which have been found useful, on an empirical basis, to predict the *relative facility* of ring forming reactions are presented; the physical bases of such rules are described.

Ring-forming reactions are important and common processes in organic chemistry. I now adumbrate a set of simple rules which I have found useful in predicting the relative facility of different ring closures. I believe these



Scheme 1

will be useful to organic chemists, especially in planning syntheses. Also these rules indicate certain experiments which may be helpful to define more precisely their limits. The rules are of a stereochemical nature and it is likely that unambiguous cases of all the possibilities I will discuss are as yet unknown.



Scheme 2: Tetrahedral

I will describe a ring-forming process with the prefix *Exo*, when the breaking bond is exocyclic to the *smallest so formed ring* and *Endo* correspondingly, as in Scheme 1.

Further, I shall use a numerical prefix to describe the ring size, being the number of atoms constituting the skeleton of the cycle, and finally, the suffixes *Tet*, *Trig*, and *Dig*, to indicate the geometry of the carbon atom undergoing the ring-closure reaction (asterisk, Scheme 1). The suffixes refer to tetrahedral, trigonal, and digonal carbon atoms respectively. The various possibilities are shown in Schemes 2—4.

The Rules are as follows:—

Rule 1: *Tetrahedral Systems*: Scheme 2.
(a) 3 to 7-*Exo-Tet* are all favoured[1] processes with many literature precedents;[2]
(b) 5 to 6-*Endo-Tet* are disfavoured.[3]

Rule 2: *Trigonal Systems*: Scheme 3.
(a) 3 to 7-*Exo-Trig* are all favoured processes with many literature precedents;[4]
(b) 3 to 5-*Endo-Trig* are disfavoured;[5] 6 to 7-*Endo-Trig* are favoured.

Rule 3: *Digonal Systems*: Scheme 4.
(a) 3 to 4-*Exo-Dig* are disfavoured processes; 5 to 7-*Exo-Dig* are favoured;[6]
(b) 3 to 7-*Endo-Dig* are favoured.[7]

As a consequence of the larger atomic radii and bond distances in atoms of the second Periodic row the geometric restraints on disfavoured ring closures may be bypassed.[5] Therefore a condition to the application of these rules is that X *must be a first row element* (Scheme 1—4).

The physical bases of the rules lie in the stereochemical requirements of the transition states for the various tetrahedral, trigonal, and digonal ring closure processes. Since the linking chain restricts the relative motion of the terminal groups X and Y (Scheme 1) then the nature and length of this chain, and hence the ring size, will determine whether X and Y can attain the required transition-state geometry and hence the facility, or otherwise, of ring closure. For closures to a carbon atom (asterisk, Scheme 1) the favoured paths to the transition states are represented

Sir Jack E. Baldwin

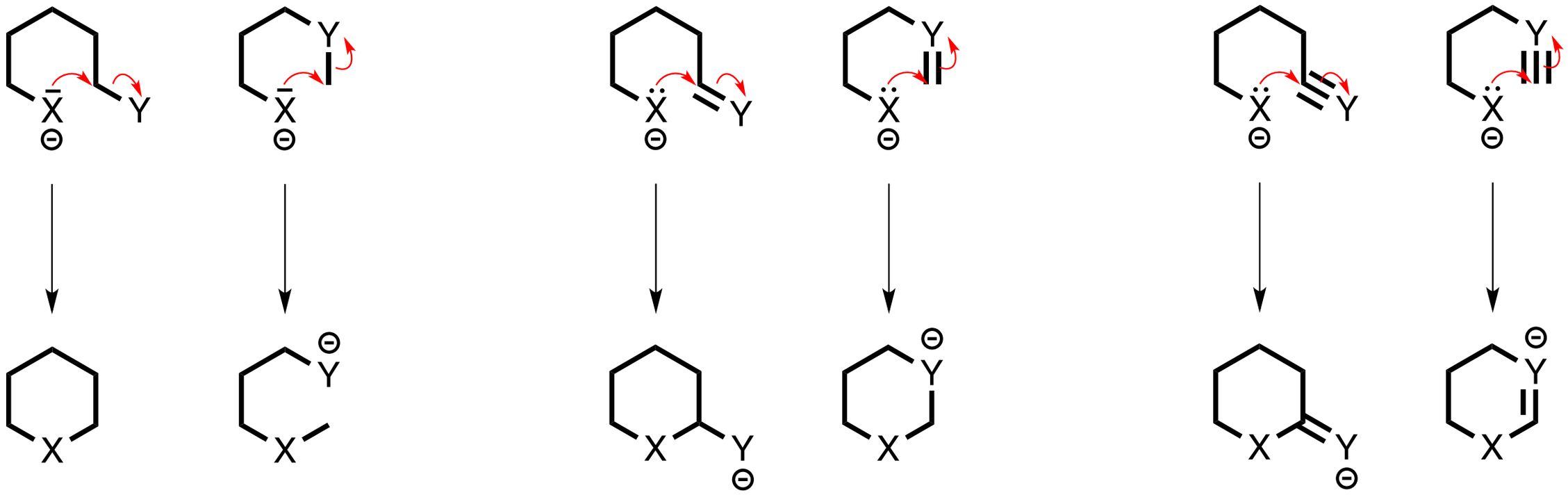
I now adumbrate a set of simple rules which I have found useful in predicting the relative facility of different ring closures

More than 1300 cites

JCS Chem. Commun. **1976,** 734

Ring Forming Processes

*A nucleophilic ring-forming process can be described with the prefix **Exo** when the breaking bond is exocyclic to the smallest so formed ring and **Endo** correspondingly. A numerical prefix is used to describe the ring size and a suffix indicate the hybridization of the electrophilic carbon atom undergoing the ring-closure reaction (tetrahedral or sp3: **Tet**, trigonal or sp2: **Trig**, and digonal or sp: **Dig**)*



6-exo-tet **6-endo-tet** **6-exo-trig** **6-endo-trig** **6-exo-dig** **6-endo-dig**

These rules also apply to homolitic and cationic processes

Baldwin, J. E. *JCS Chem. Commun.* **1976,** 734, 736; *JOC* **1977,** *42*, 3846.

Johnson, C. D. *ACR* **1993,** 26, 476

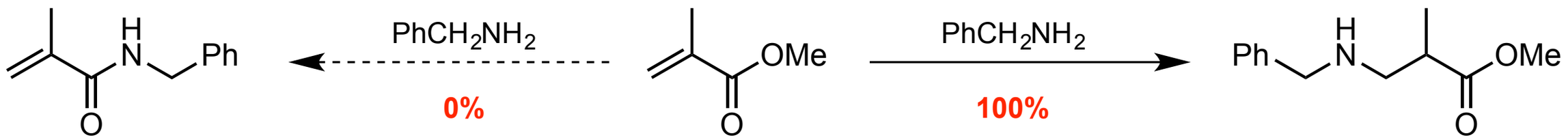
✓ *easy*

✗ *difficult*

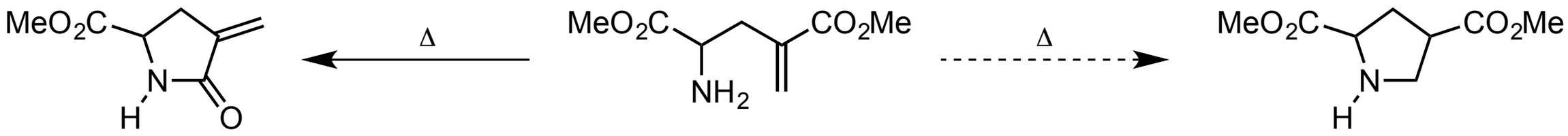
	Exo			Endo		
	Tet	*Trig*	*Dig*	*Tet*	*Trig*	*Dig*
3	✓	✓	✗	✗	✗	✓
4	✓	✓	✗	✗	✗	✓
5	✓	✓	✓	✗	✗	✓
6	✓	✓	✓	✗	✓	✓
7	✓	✓	✓	✗	✓	✓

Baldwin, J. E. *JCS Chem. Commun.* **1976,** 734, 736; *JOC* **1977**, *42*, 3846.
Johnson, C. D. *ACR* **1993**, 26, 476

Baldwin Rules



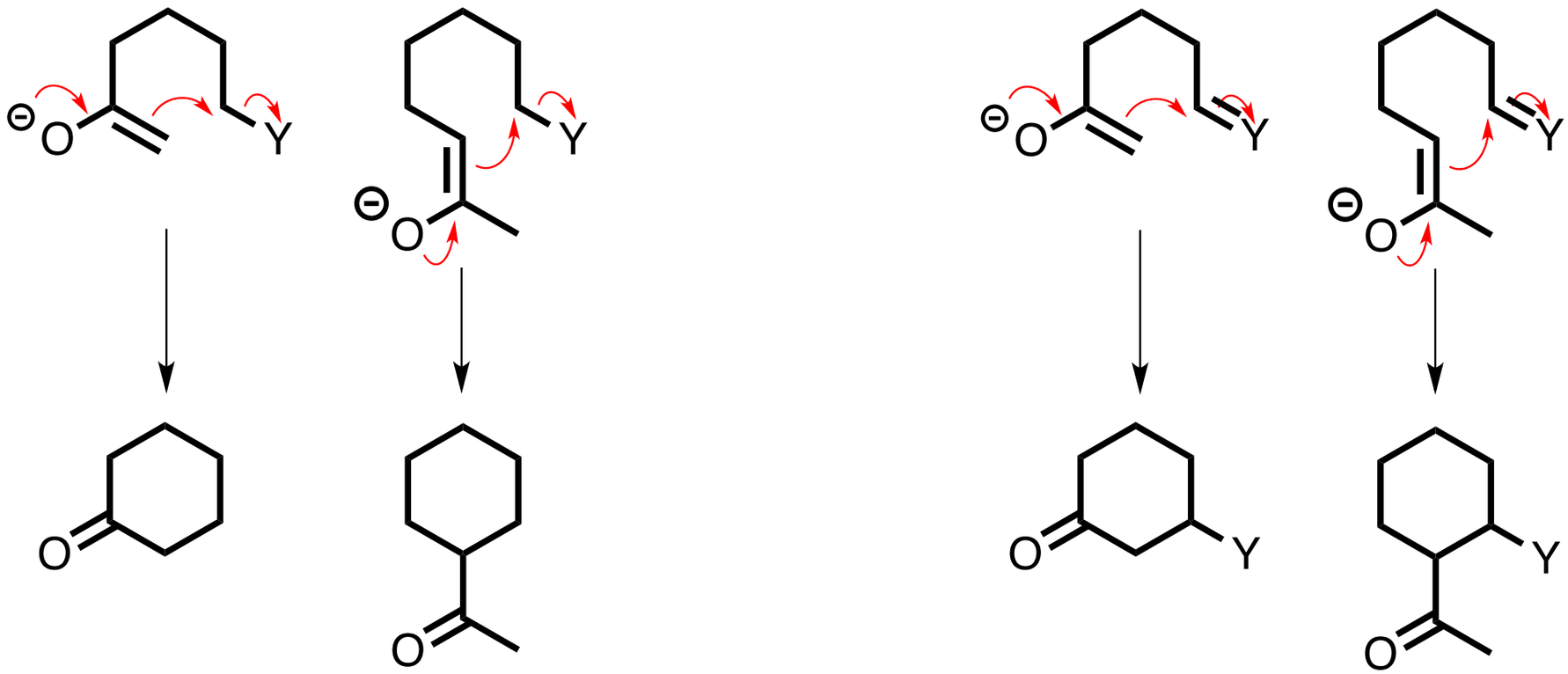
However



5-exo-trig

5-endo-trig

For cyclization involving a trigonal carbon, a bit more complicated analysis has been proposed



6-enolendo-exo-tet **6-enolexo-exo-tet** **6-enolendo-exo-trig** **6-enolexo-exo-trig**

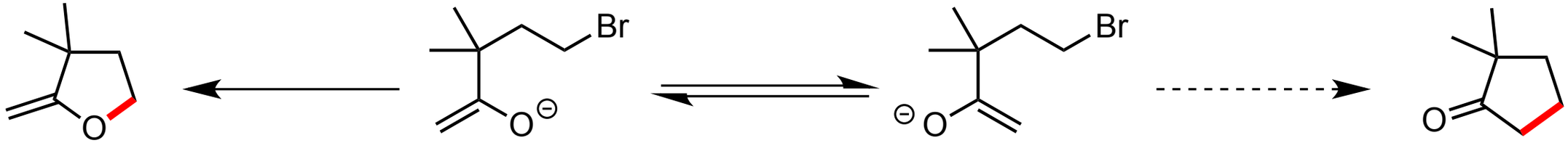
*Such a model can be applicable to **enamines** and other allylic and heteroallylic systems,*
as well as electrophilic cyclization where a cationic center is stabilized by the overlap with an adjacent lone pair,
for example, oxycarbenium or iminium ions.

✓ *easy*

✗ *difficult*

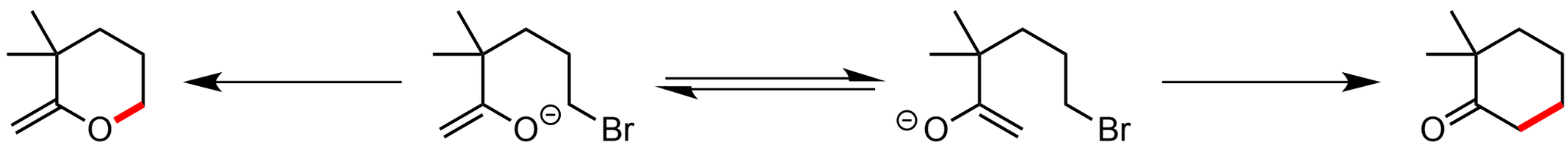
	Enolendo-Exo		*Enolexo-Exo*	
	Tet	*Trig*	*Tet*	*Trig*
3	✗	✗	✓	✓
4	✗	✗	✓	✓
5	✗	✗	✓	✓
6	✓	✓	✓	✓
7	✓	✓	✓	✓

Baldwin, J. E. *JCS Chem. Commun.* **1977**, 323. *Tet* **1982**, *38*, 2939



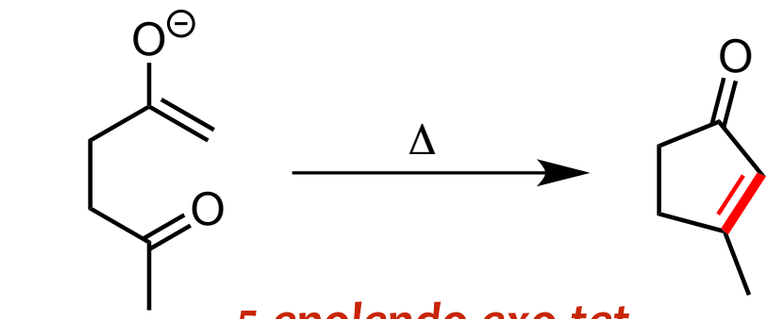
5-exo-tet

5-enolendo-exo-tet

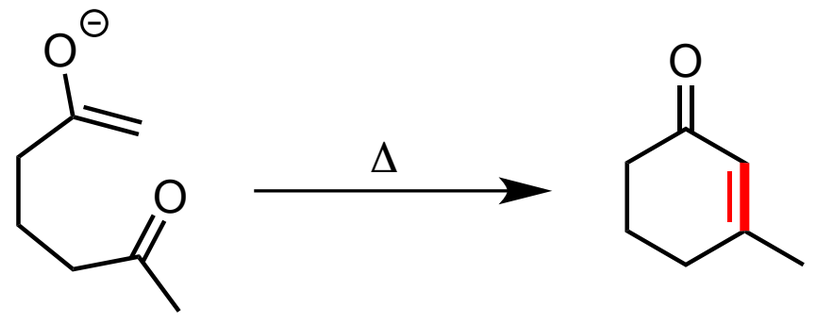


6-exo-tet

6-enolendo-exo-tet

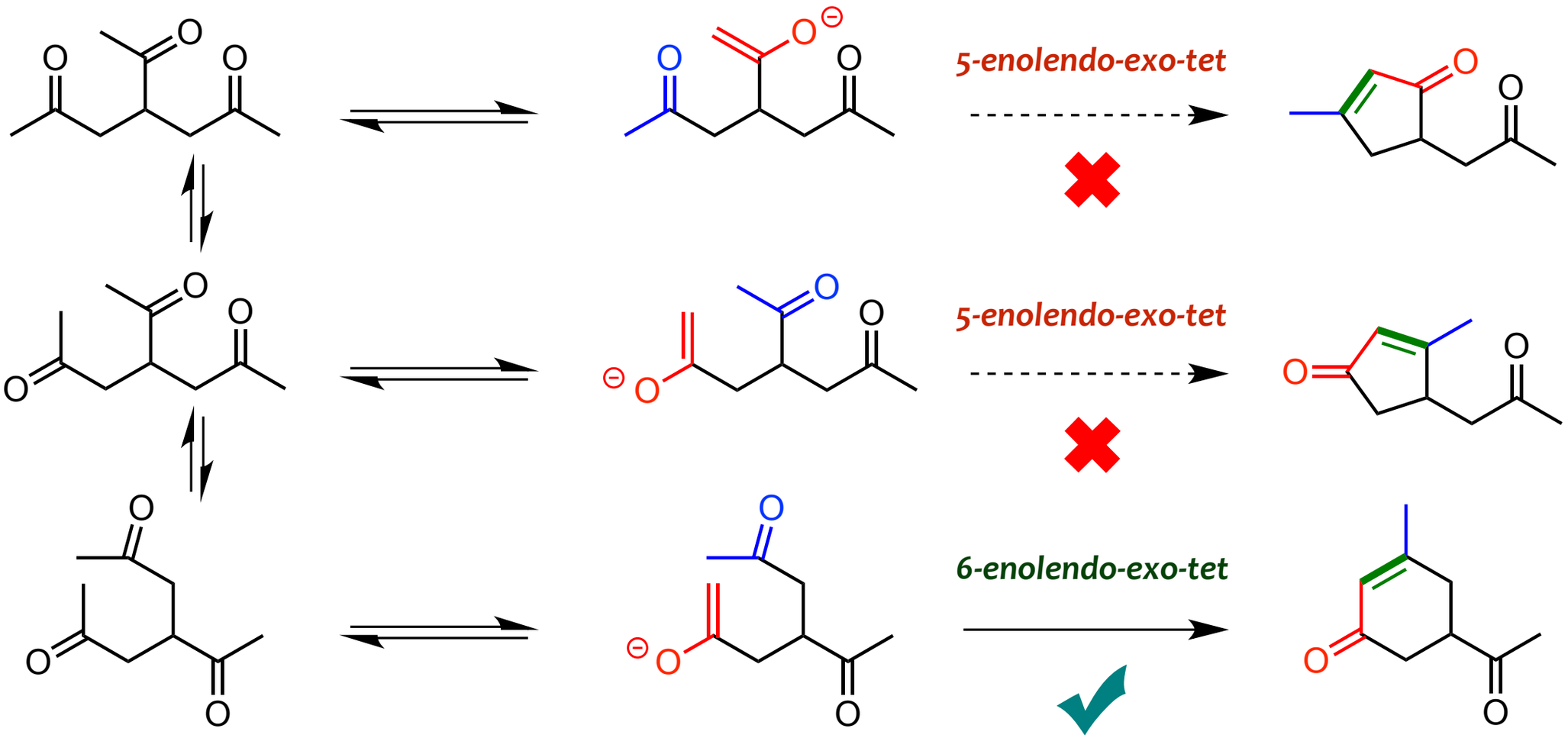


5-enolendo-exo-tet



6-enolendo-exo-tet

…but



***Caution**: the ring forming is not the RDS*

the synthesis of the six-membered ring is favored

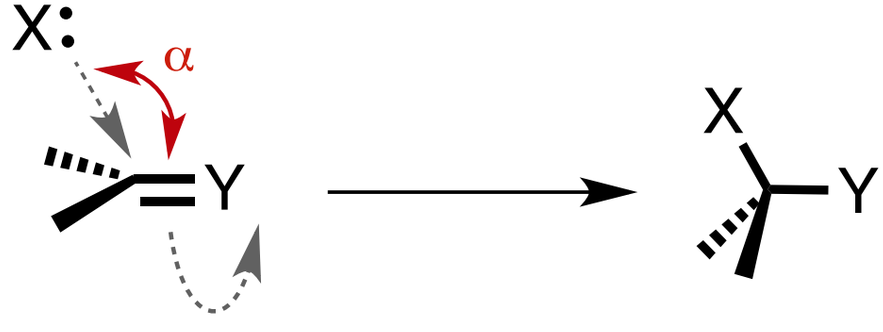
Baldwin Rules

*The **favored** ring-closing reactions are those in which the length and the nature of the linking chain enable the terminal atoms to achieve the **proper geometry** for the reactions.*
*The **disfavored** ring closing processes require distortions of bond angles rendering these reactions pathways higher in energy.*

The physical bases of the rules lie in the stereochemical requirements of the transition states for the various tetrahedral, trigonal, and digonal ring closure processes.
In each case, the subtended angle is maintained during the reaction pathway

Tet

Trig



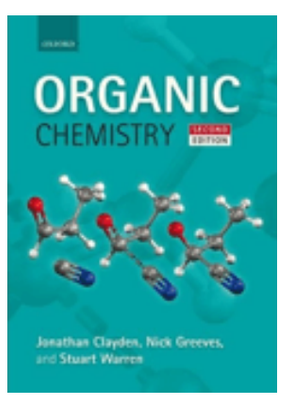
These ideas are rooted on stereoelectronic grounds …

- **For a reaction to take place, molecules must:**

  – overcome their electronic repulsion by charge attraction and/or orbital overlap

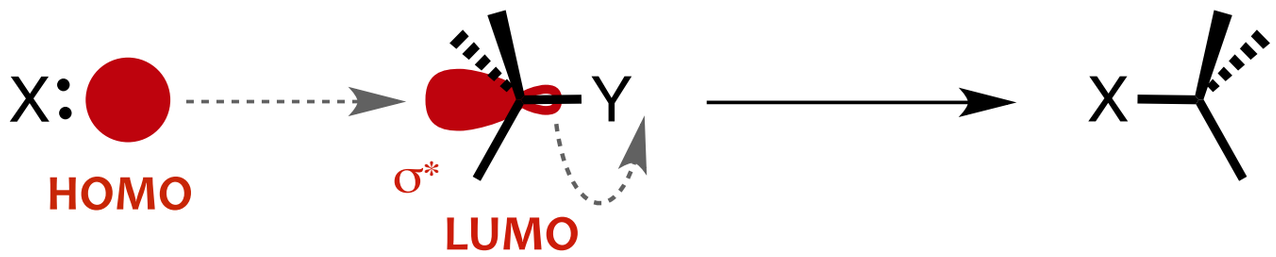
  – have orbitals of appropriate energy to interact:
  a filled orbital on the nucleophile and
  an empty orbital on the electrophile

  – approach each other such that these orbitals can overlap to form a bonding interaction

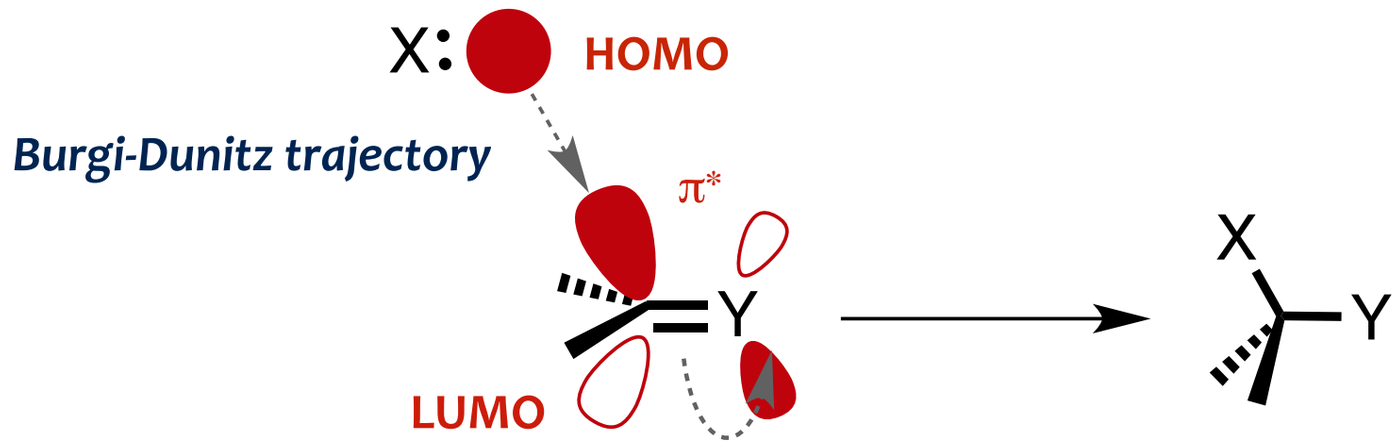


For instance, they are associated with the S_N2 and the ionic additions to carbonyls

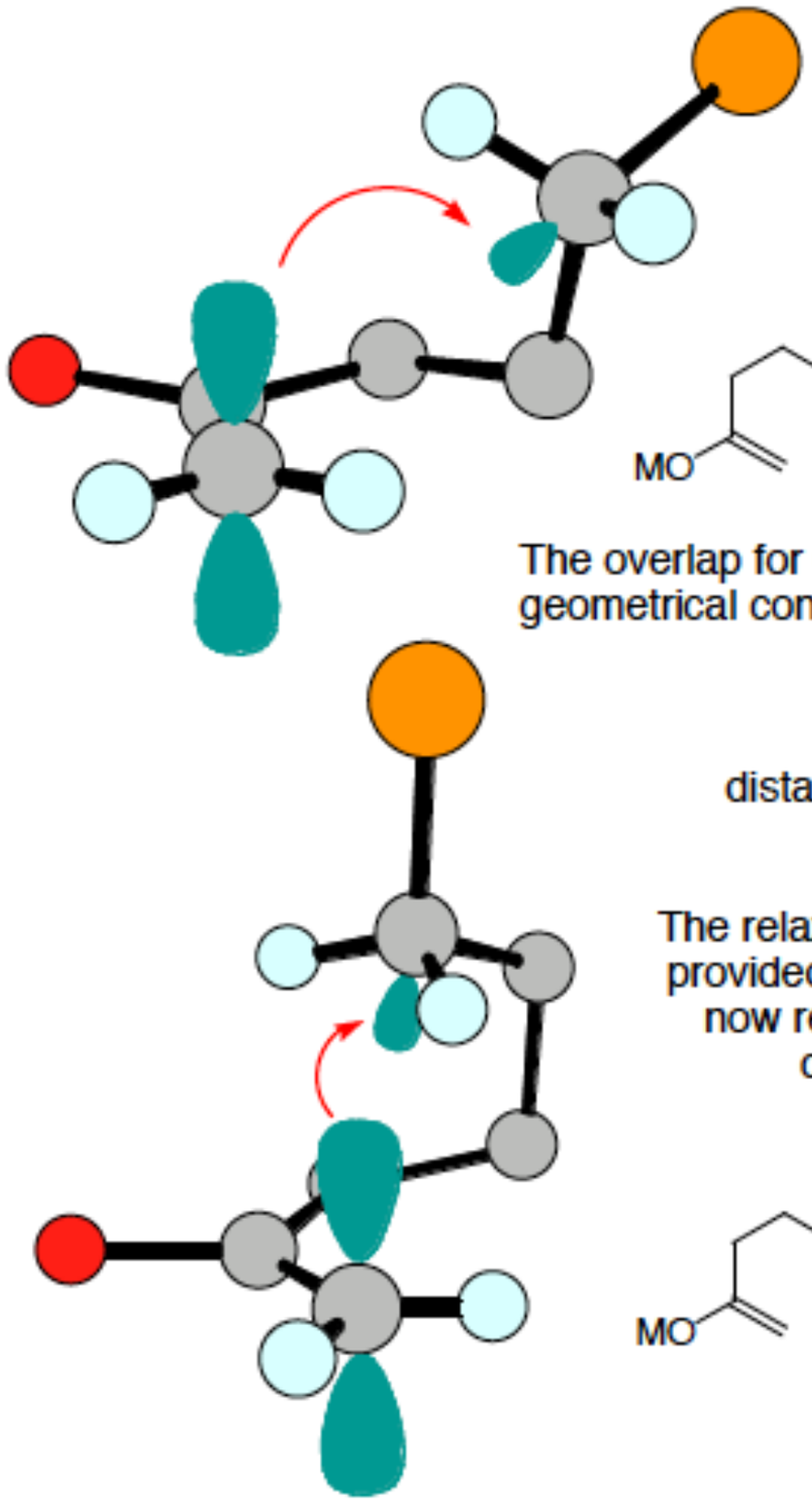
Tet



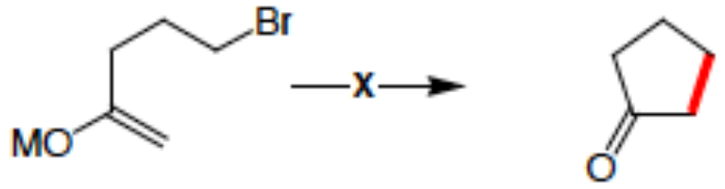
Trig



… or the alkylation of enolates …



distance between reacting centers: 3.37Å



The overlap for C-alkylation is poor due to geometrical constraints of 5-membered ring

distance between reacting centers: 3.04Å

The relaxed geometrical constraint provided by the added CH_2 group now renders the 6-membered cyclization possible

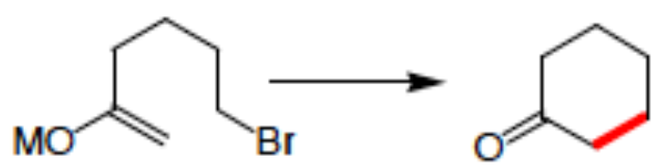


Image from David A. Evans handouts

PROS	CONS
Simple	*Some caveats and "violations"*
First line of analysis	*should be considered*
Useful for the study of mechanisms	*to avoid wrong predictions*
Synthetic language	

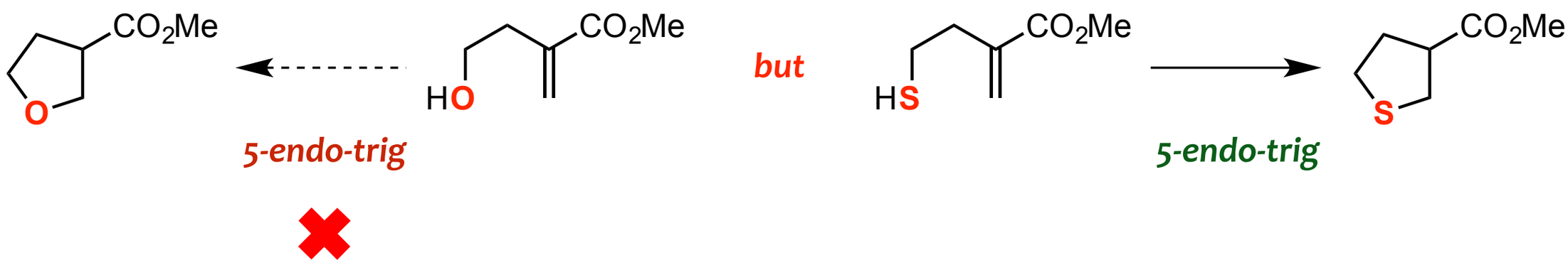
Don't forget that Baldwin rules only predict the relative facility of different ring closures

Caveats to be considered:

1. Do not apply to equilibrium processes: the RDS should be the ring forming step

2. Pericyclic reactions are not affected

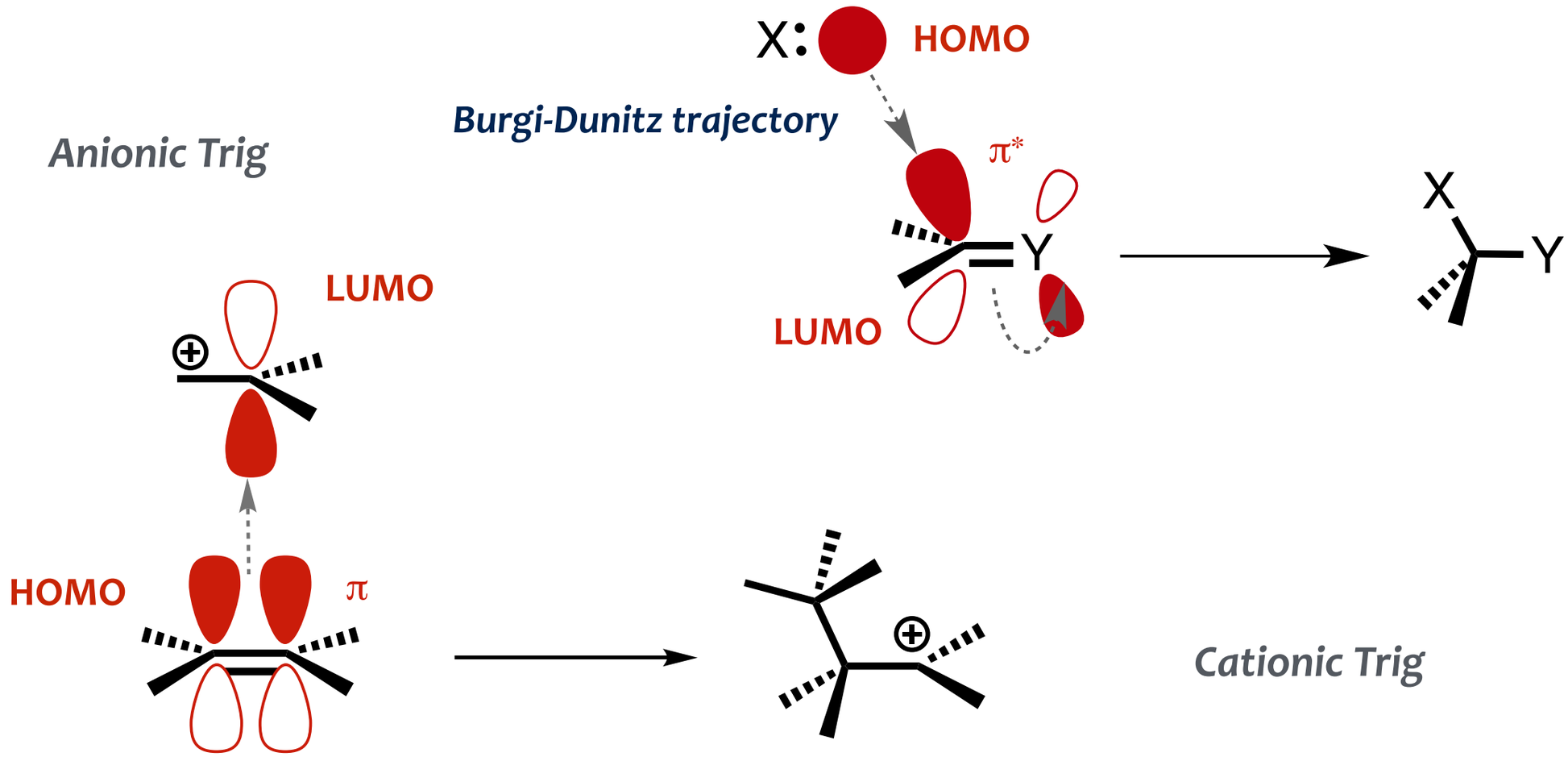
3. Atoms involved must be in the first row: C, N, O. Sulfur and hydrogen, for instance, NO



Alabugin, I. V. *Chem. Commun.* **2013**, *49*, 11246

Caveats to be considered:

4. Anionic, radical, and cationic processes are not ruled by the same stereoelectronic patterns

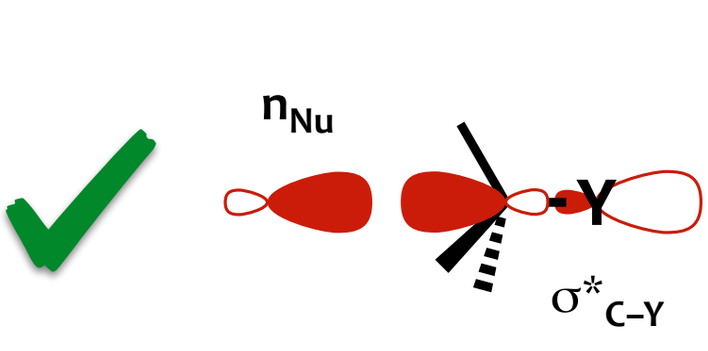


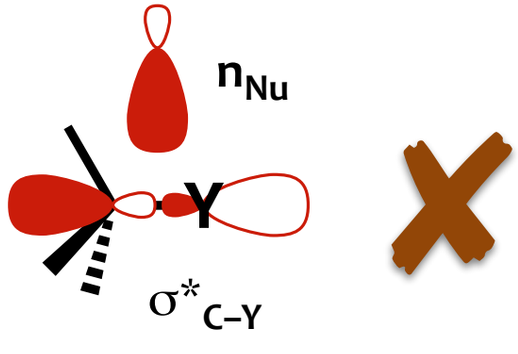
Attack trajectories for electrophilic reagents are quite different from the nucleophilic trajectories

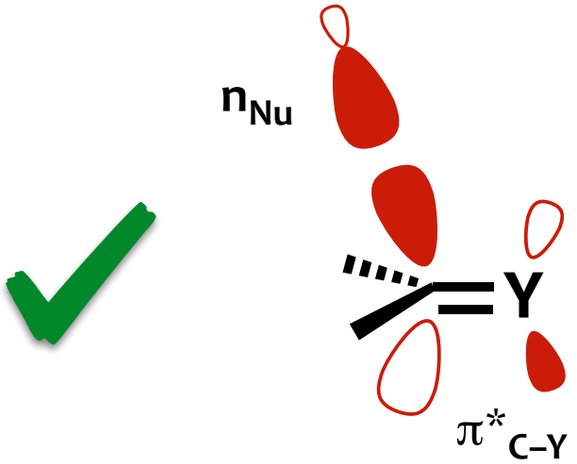
Alabugin, I. V. *Chem. Commun.* **2013**, *49*, 11246

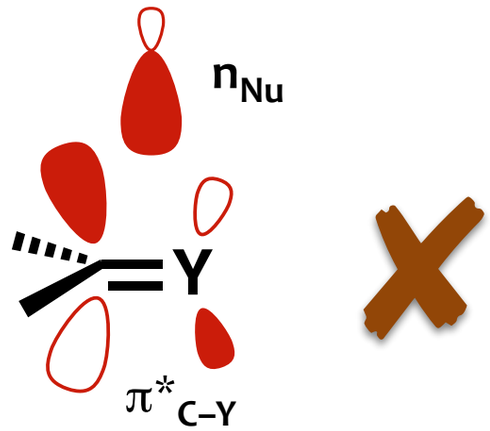
Nucleophilic

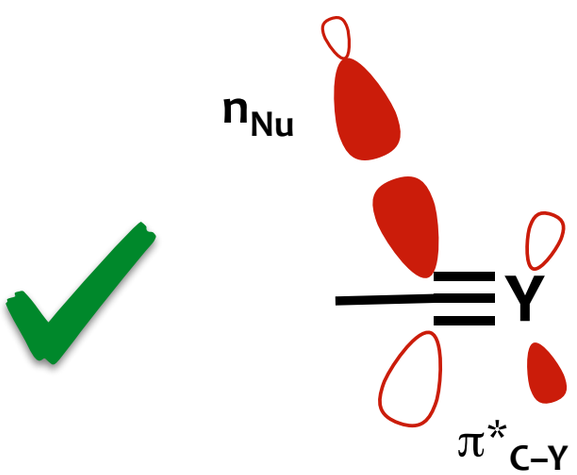
Target: LUMO

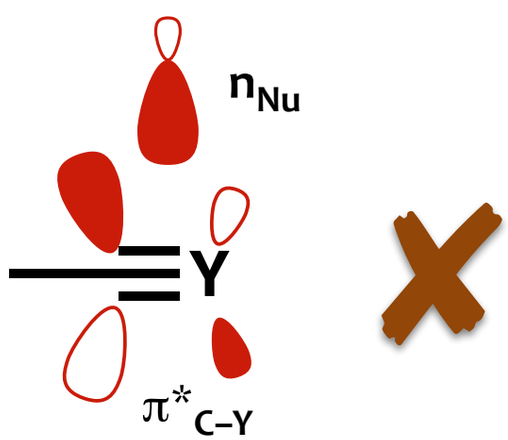






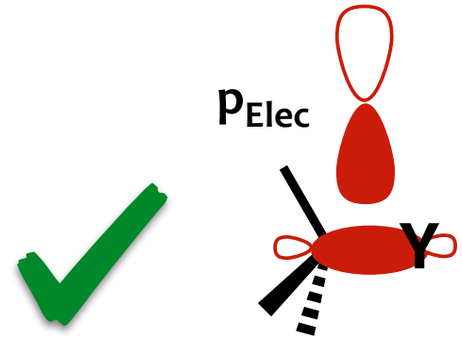


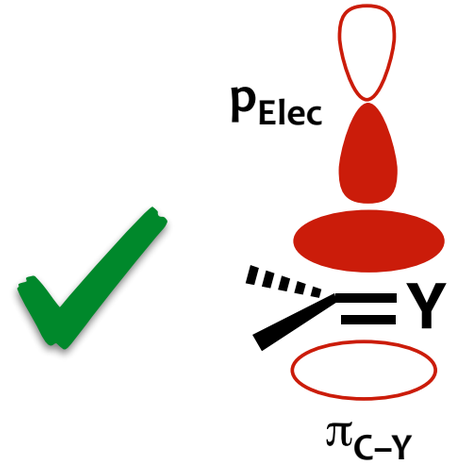


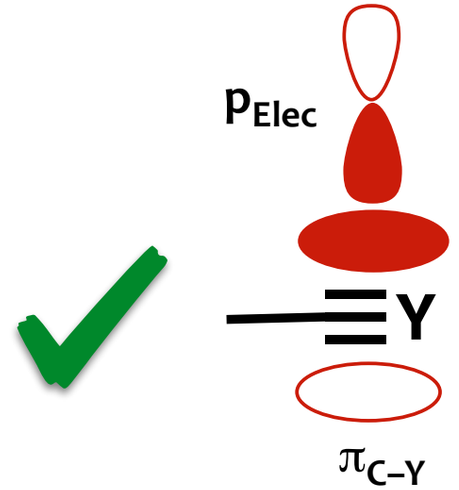


Electrophilic

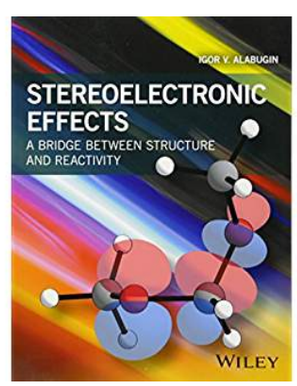
Target: HOMO







Alabugin, I. V.



Caveats to be considered:

4. Anionic, radical, and cationic processes are not ruled by the same stereoelectronic patterns

Some trends in radical cyclization were summarized by Beckwith as follows:

1. Intramolecular additions under kinetic control in lower alkenyl and alkynyl radicals occur preferentially in the exo mode

2. Substituents on an olefinic bond disfavor radical addition to the substituted position

3. Homolytic cleavage is favored when the bond concerned lies close to the plane of an adjacent semi-occupied orbital, or an adjacent filled non-bonding orbital, or π-orbital

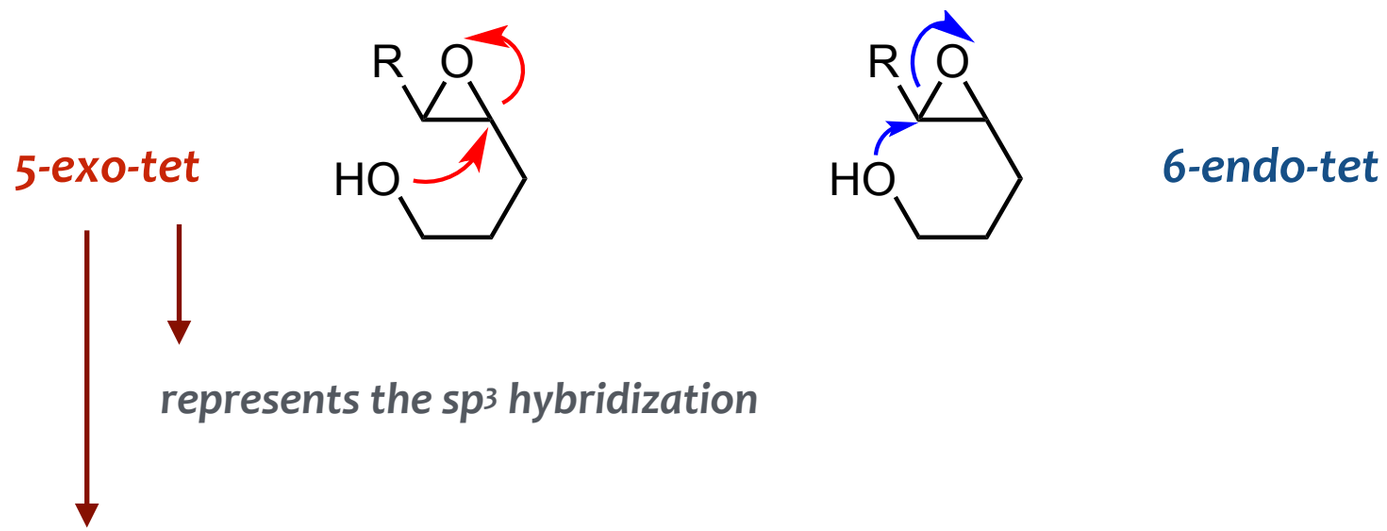
Beckwith, A. L. J. *JCS Chem. Commun.* **1980**, 482. See also Alabugin, I. V. *JACS* **2011**, *133*, 12608

Cationic and radical 5-endo cyclization are often observed

For recent examples, see Smith, M. D. *Nature Chemistry* **2015**, *7*, 171; Bonjoch, J. *OL* **2017**, *19*, 878

Caveats to be considered:

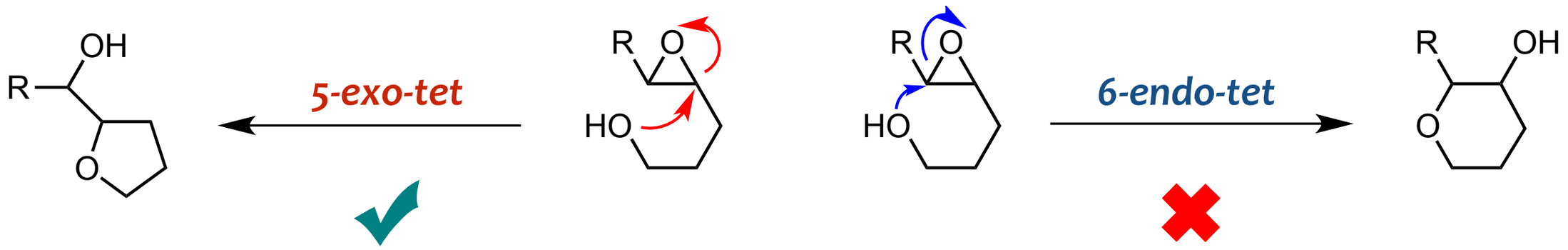
5. Intramolecular epoxide openings tend to follow rules that lie between those for ten and trig

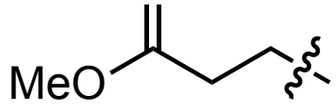
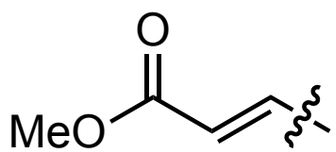


Jamison, T. F.

Mar. Drugs **2010**, *8*, 763

Normally, exo processes are favored



R	exo / endo
	100 / 0
	40 / 60
	0 / 100

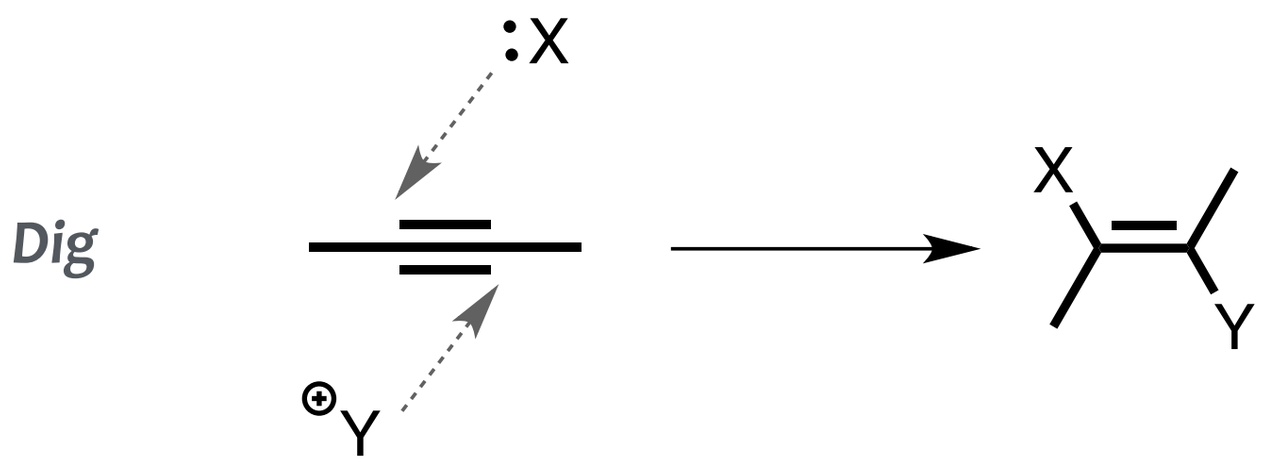
Nicolaou, K. C.
JACS **1989**, *111*, 5330

An anti-Baldwin pathway may become competitive when it is possible to lower the ΔΔG≠

See Alabugin, I. V. *Chem. Commun.* **2013**, 49, 11246

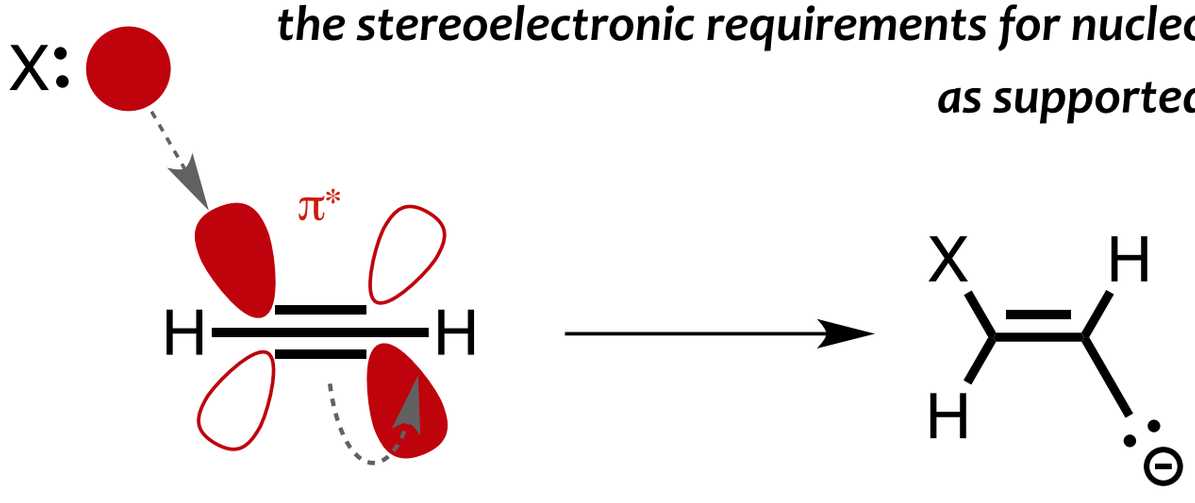
Caveats to be considered:

6. Alkynes require a new set of rules



The original Baldwin's proposal is not supported by theoretical calculations

The proposed digonal trajectory does not satisfy the stereoelectronic requirements for nucleophilic attack to a π-bond, as supported by high level calculations



Alabugin, I. V. *CR* **2011,** *111*, 6513

Actually, the preferred trajectory depends on the type of cyclization …

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

✓ *easy* ≈ *borderline* ✗ *difficult*

Rules adapted from: Alabugin, I. V. *CR* **2011**, *111*, 6513; *JACS* **2011**, *133*, 12608; *JACS* **2012**, *134*, 10584