Lecture Notes

Modern Organic Synthesis

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The CD versions of the Lecture Notes (Versions 1.01 and 1.02) contain corrections and updates to the science and will differ slightly from the printed text (First Edition, 1999). We anticipate that this will continue on an annual basis, as with any set of classroom lecture notes. Consequently, we would like to encourage you to inform us of mistakes you might find and we welcome suggestions for additions to the content. In fact, if we are provided ChemDraw files of science you would like to see included, the barriers to its incorporation are minimized.
The text of the CD may be searched by Adobe Acrobat Reader and this may be used in lieu of an index.

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Preface

The notes have been used as the introductory section of a course on Modern Organic Synthesis that composes 6 weeks or a little more than one-half of a quarter course at The Scripps Research Institute, Department of Chemistry. Consequently, an exhaustive treatment of the individual topics is beyond the scope of this portion of the course. The remaining 4 weeks of the quarter delve into more detail on various topics and introduce concepts in multistep organic synthesis (E. Sorensen). For our students, this is accompanied by a full quarter course in physical organic chemistry and is followed by a full quarter course on state of the art natural products total synthesis (K. C. Nicolaou, E. Sorensen) and a quarter elective course on transition metal chemistry. Complementary to these synthetic and mechanistic courses, two quarter courses on bioorganic chemsitry and an elective course on the principles of molecular biology and immunology are available to our students. Efforts have been made to not duplicate the content of these courses. For those who might examine or use the notes, I apologize for the inevitable oversight of seminal work, the misattribution of credit, and the missing citations to work presented. The original notes were not assembled with special attention to this detail, but rather for the basic content and the 'nuts and bolts' laboratory elements of organic synthesis. In addition, some efforts were made to highlight the chemistry and contributions of my group and those of my colleagues for the intrinsic interest and general appreciation of our students. I hope this is not mistaken for an effort to unduly attribute credit where this was not intended. We welcome any suggestions for content additions or corrections and we would be especially pleased to receive even minor corrections that you might find. – Dale L. Boger

Heinrich Friedrich von Delius (1720–1791) is credited with introducing chemistry into the academic curriculum.

Acknowledgments

Significant elements of the material in the notes were obtained from the graduate level organic synthesis course notes of P. Fuchs (Purdue University) and were influenced by my own graduate level course taught by E. J. Corey (Harvard). They represent a set of course notes that continue to evolve as a consequence of the pleasure of introducing young colleagues to the essence and breadth of modern organic synthesis and I thank them for the opportunity, incentive, and stimulation that led to the assemblage of the notes. Those familiar with ChemDraw know the efforts that went into reducing my hand drafted notes and those maintained by Robert J. Mathvink (Purdue University) and Jiacheng Zhou (The Scripps Research Institute) to a ChemDraw representation. For this, I would like to thank Robert M. Garbaccio for initiating, coordinating, proofing and driving the efforts, and Steve, Richard, Chris, Bryan, Clark, Marc, Jason, Rob, Wenge, Jiyong, Brian, Mark, Gordon, Robert and Joel for reducing the painful task to a reality. Subsequent updates have been made by Steven L. Castle (Version 1.01) and Jiyong Hong (Version 1.02).

It is a pleasure to dedicate this book and set of notes to Richard Lerner who is responsible for their appearance. His vision to create a chemistry program within Scripps, his energy and enthusiasm that brought it to fruition, his support for the graduate program and committment to its excellence, and his personal encouragement to this particular endeavour of developing a graduate level teaching tool for organic synthesis, which dates back to 1991, made this a reality.

Antoine L. Lavoisier, universally regarded as the founder of modern chemistry, published in 1789 his *Elementary Treatise on Chemistry* that distinguished between elements and compounds, initiated the modern system of nomenclature, and established the oxygen theory of combustion. He and his colleagues founded *Annales de Chemie* in 1789, he earned his living as a tax official and his "chemical revolution" of 1789 coincided with the start of the violent French Revolution (1789–1799). He was executed by guillotine in 1794.

Jons Jacob Berzelius (1779–1848), a Swedish chemist, discovered cerium, produced a precise table of experimentally determined atomic masses, introduced such laboratory equipment as test tubes, beakers, and wash bottles, and introduced (1813) a new set of elemental symbols based on the first letters of the element names as a substitute for the traditional graphic symbols. He also coined the term "organic compound" (1807) to define substances made by and isolated from living organisms which gave rise to the field of organic chemistry.

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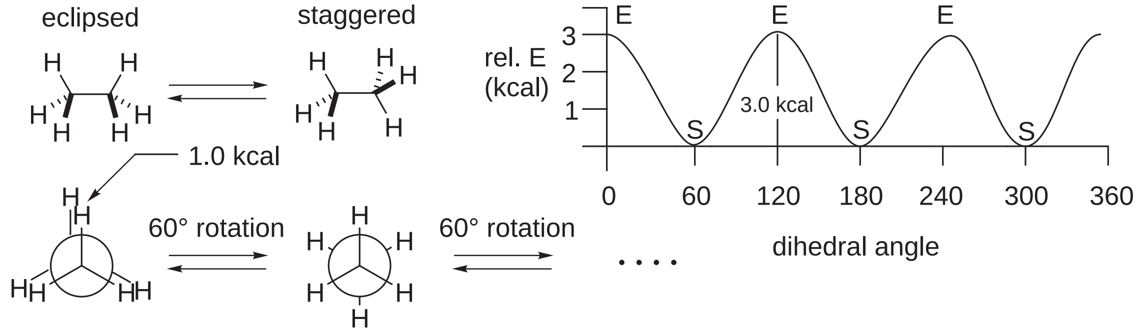
I. Conformational Analysis

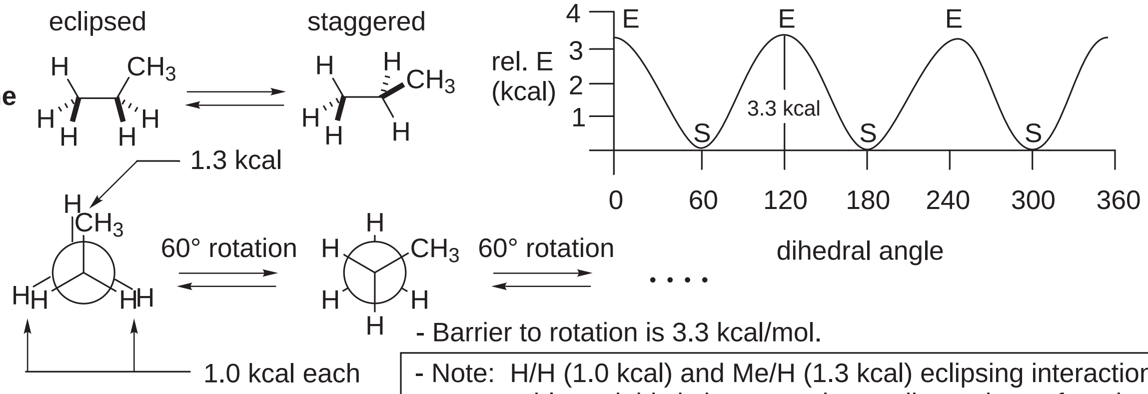
A. Acyclic sp^3–sp^3 Systems: Ethane, Propane, Butane

1. Ethane



- Two extreme conformations, barrier to rotation is 3.0 kcal/mol.

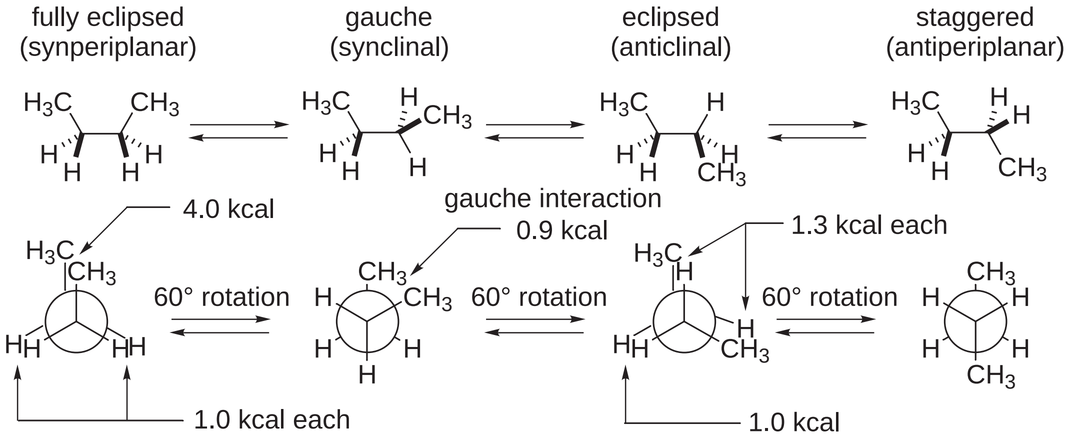
2. Propane

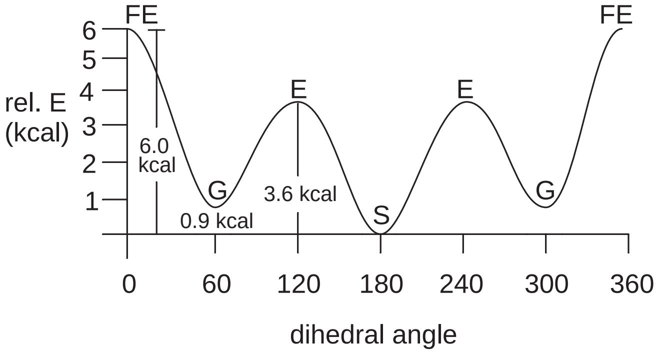


- Barrier to rotation is 3.3 kcal/mol.

- Note: H/H (1.0 kcal) and Me/H (1.3 kcal) eclipsing interactions are comparable and this is important in our discussions of torsional strain.

3. Butane

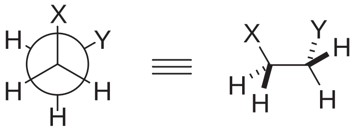




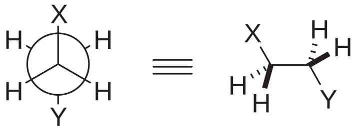
- Note: the gauche butane interaction and its magnitude (0.9 kcal) are very important and we will discuss it frequently.

4. Substituted Ethanes

- There are some exceptions to the lowest energy conformation. Sometimes, a gauche conformation is preferred over staggered if X,Y are electronegative substituents. cf: Kingsbury *J. Chem. Ed.* **1979**, *56*, 431.



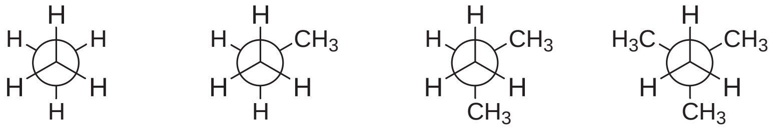
gauche



staggered

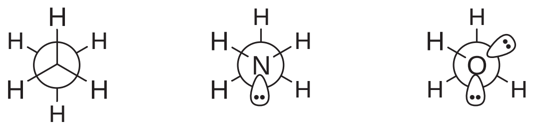
$E_{gauche} < E_{staggered}$ if X = OH, OAc and Y = Cl, F

5. Rotational Barriers



2.88 kcal/mol	3.40 kcal/mol	3.90 kcal/mol	4.70 kcal/mol	- Experimental
(3.0 kcal/mol	3.3 kcal/mol	3.6 kcal/mol	3.9 kcal/mol)	- Simple prediction

- The rotational barrier increases with the number of CH_3/H eclipsing interactions.

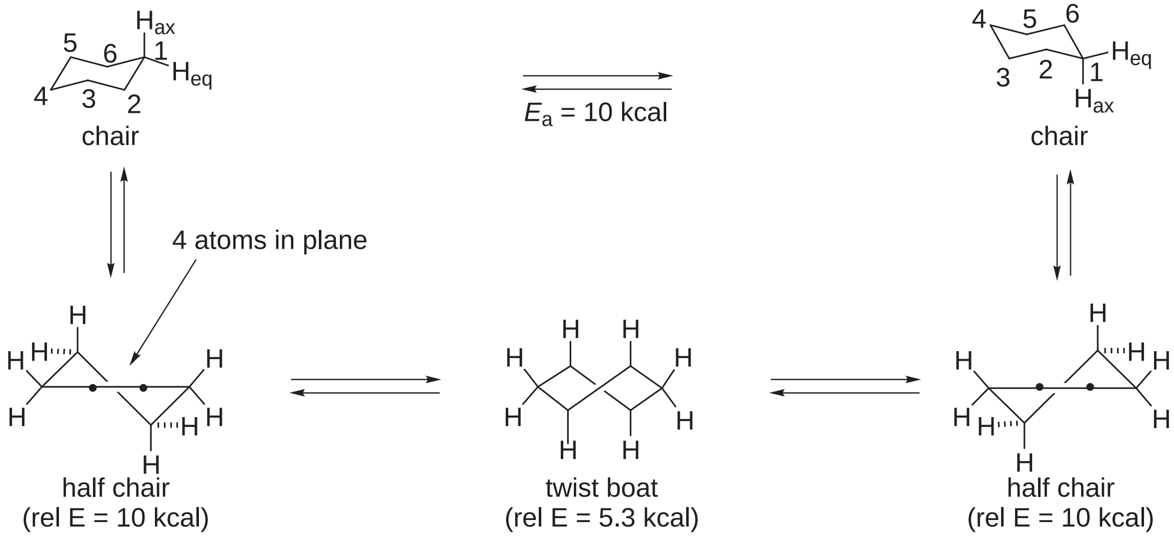


2.88 kcal/mol	1.98 kcal/mol	1.07 kcal/mol	- Experimental
(3.0 kcal/mol	2.0 kcal/mol	1.0 kcal/mol)	- Simple prediction

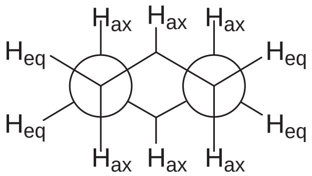
- The rotational barrier increases with the number of H/H eclipsing interactions.

B. Cyclohexane and Substituted Cyclohexanes, A Values (Δ*G*°)

1. Cyclohexane

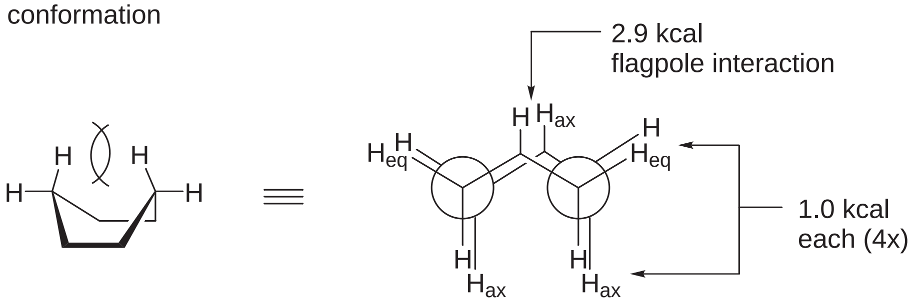


- Chair conformation (all bonds staggered)

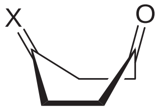


- Rapid interconversion at 25 °C (E_a = 10 kcal/mol, 20 kcal/mol available at 25 °C).
- H_{ax} and H_{eq} are indistinguishable by ^{1}H NMR at 25 °C.
- At temperatures < –70 °C, H_{eq} and H_{ax} become distinct in ^{1}H NMR.

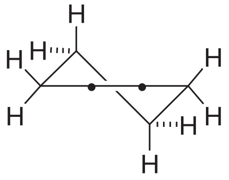
- Boat conformation



- Rel E = 6.9 kcal, not local minimum on energy surface.
- More stable boat can be obtained by twisting (relieves flagpole interaction somewhat).
- Twist boat conformation (rel E = 5.3 kcal) does represent an energy minimum.
- The boat conformation becomes realistic if flagpole interactions are removed, i.e.

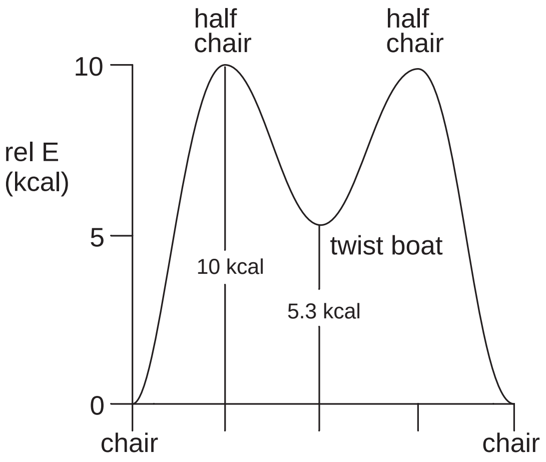


- Half chair conformation



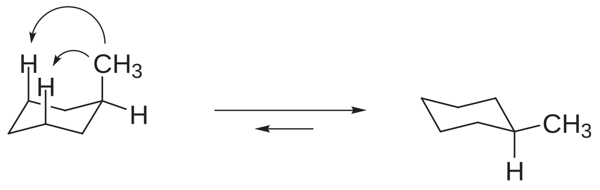
D.H.R. Barton received the 1969 Nobel Prize in Chemistry for his contributions to conformational analysis, especially as it relates to steroids and six-membered rings. Barton *Experientia* **1950**, *6*, 316.

- Energy maximum (rel E = 10.0 kcal)



2. Substituted Cyclohexanes

- Methylcyclohexane



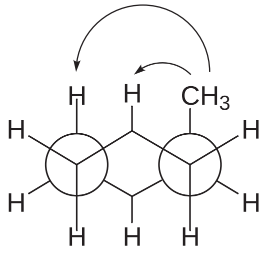
1.8 kcal more stable

$\Delta G° = -RT(\ln K)$

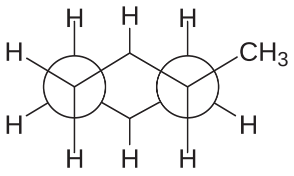
$\dfrac{-1.8 \times 1000}{1.99 \times 298} = -\ln K$

$K = 21$

- The gauche butane interaction is most often identifiable as 1,3-diaxial interactions.



2 gauche butane interactions
2 × 0.9 kcal = 1.8 kcal
(experimental 1.8 kcal)



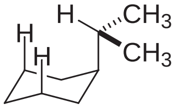
0 gauche butane interactions

- A Value ($-\Delta G°$) = Free energy difference between equatorial and axial substituent on a cyclohexane ring.

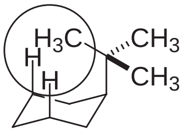
Typical A Values

R	A Value (kcal/mol)		R	A Value (kcal/mol)	
F	0.25		CN	0.2	Small, linear groups
Cl	0.52	ca. 0.5 kcal	C≡CH	0.41	
Br	0.5–0.6		NO_2	1.1	
I	0.46		CH=CH_2	1.7	
OH	0.7 (0.9)	ca. 0.7 kcal (2nd atom effect very small)	CH_3	1.8	2nd atom effect very small
OCH_3	0.75		CH_2CH_3	1.9 (1.8)	
$OCOCH_3$	0.71		${}^{n}C_3H_7$	2.1	
NH_2	1.8 (1.4)		${}^{n}C_4H_9$	2.1	
NR_2	2.1		$CH(CH_3)_2$	2.1	
CO_2H	1.2 (1.4)		$C(CH_3)_3$	>4.5 (ca. 5.4)	
CO_2Na	2.3		C_6H_5	3.1 (2.9)	
CO_2Et	1.1				
SO_2Ph	2.5				

- Note on difference between ^{i}Pr and ^{t}Bu A values.

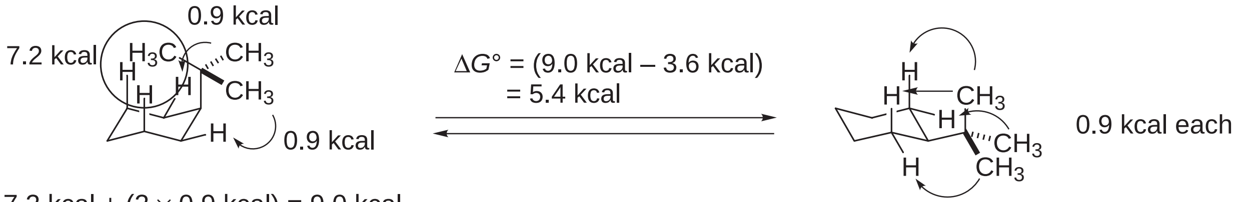


^{i}Pr group can position H toward "inside,"



but ^{t}Bu group cannot.
Very serious interaction, 7.2 kcal.

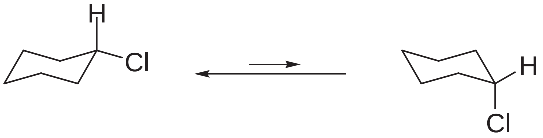
- Determination of A value for ^{t}Bu group.



7.2 kcal + (2 × 0.9 kcal) = 9.0 kcal

4 × 0.9 kcal = 3.6 kcal

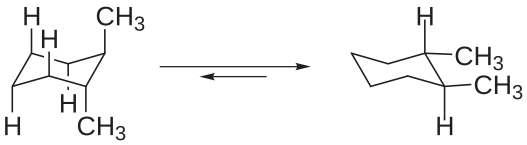
- Note on interconversion between axial and equatorial positions.



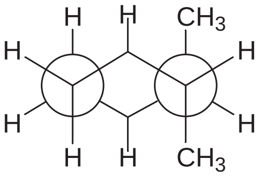
$t_{1/2}$ = 22 years at –160 °C

Even though Cl has a small A value (i.e., small $\Delta G°$ between rings with equatorial and axial Cl group), the E_a (energy of activation) is high (it must go through half chair conformation).

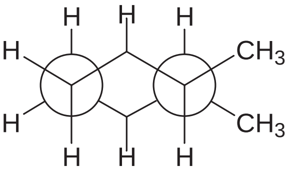
trans-1,2-dimethylcyclohexane



2.7 kcal/mol more stable

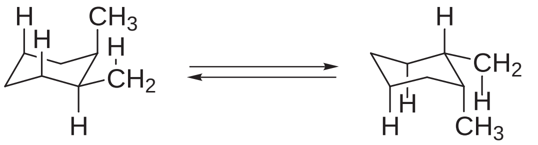


4 × (gauche interaction)
4 × (0.9 kcal) = 3.6 kcal

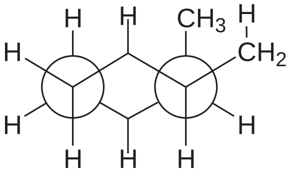


1 × (gauche interaction)
1 × (0.9 kcal) = 0.9 kcal

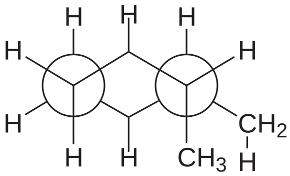
cis-1,2-dimethylcyclohexane



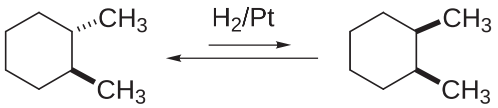
ΔE = 0 kcal/mol



3 × (gauche interaction)
3 × (0.9 kcal) = 2.7 kcal

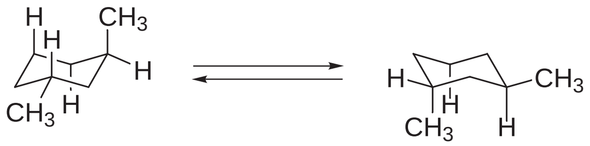


3 × (gauche interaction)
3 × (0.9 kcal) = 2.7 kcal

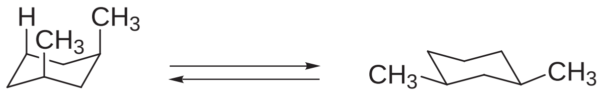


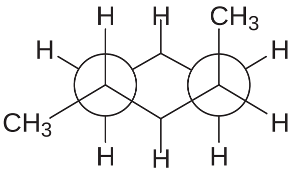
ΔG = 1.87 kcal/mol (exp)
ΔG = 1.80 kcal/mol (calcd)

trans-1,3-dimethylcyclohexane

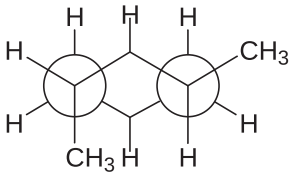


cis-1,3-dimethylcyclohexane

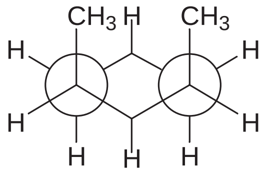




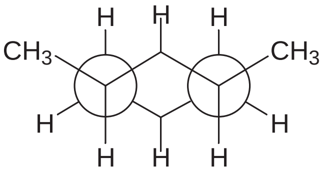
2 × (gauche interaction)
2 × (0.9 kcal) = 1.8 kcal



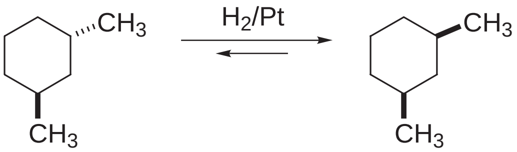
2 × (gauche interaction)
2 × (0.9 kcal) = 1.8 kcal



2 × (gauche interaction) +
1 × (Me–Me 1,3 diaxial int)
2 × (0.9 kcal) + 3.7 kcal
= 5.5 kcal

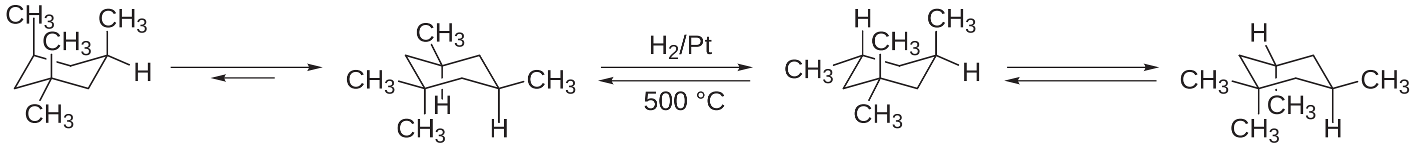


0 × (gauche interaction)
0 × (0.9 kcal) = 0 kcal



Δ*G* = 1.80 kcal/mol (exp and calcd)

- Determination of energy value of Me–Me 1,3-diaxial interaction.



3 × Me–Me 1,3-diaxial interaction

2 × (gauche interaction)
2 × (0.9 kcal) = 1.8 kcal

2 × (gauche interaction) +
1 × (Me–Me 1,3 diaxial int) =
2 × (0.9 kcal) + ?

2 × (gauche interaction) +
1 × (Me–Me 1,3 diaxial int) =
2 x (0.9 kcal) + ?

Δ*G* = 3.7 kcal/mol (exp)
So, Me–Me 1,3-diaxial interaction = 3.7 kcal/mol.

1,3-diaxial interactions

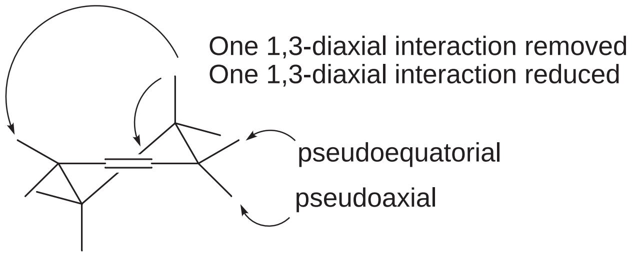
R/R	Δ*G*°
OH/OH	1.9 kcal
OAc/OAc	2.0 kcal
OH/CH_3	2.4 (1.6) kcal
CH_3/CH_3	3.7 kcal

Δ*G*° of common interactions

	ax OH	ax CH_3	eq OH
ax H	0.45*	0.9	0.0
ax OH	1.9	1.6	0.35
eq OH	0.35	0.35	0.35
eq CH_3	0.35	0.9	0.35

*1/2 of A value

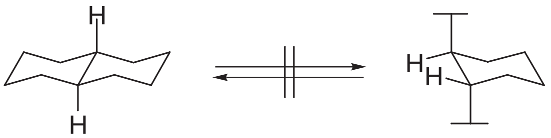
C. Cyclohexene



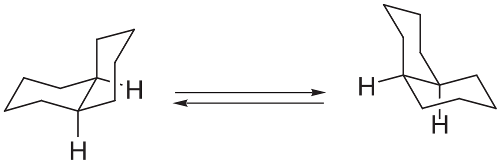
- half-chair
- E_a for ring interconversion = 5.3 kcal/mol
- the preference for equatorial orientation of a methyl group in cyclohexene is less than in cyclohexane because of the ring distortion and the removal of one 1,3-diaxial interaction (1 kcal/mol)

D. Decalins

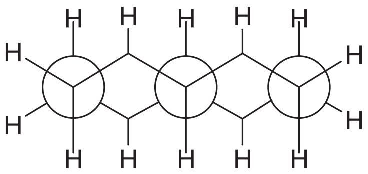
trans-decalin



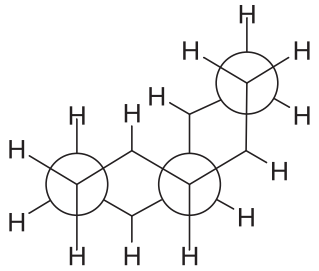
cis-decalin



two conformations equivalent



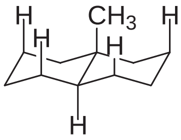
0.0 kcal



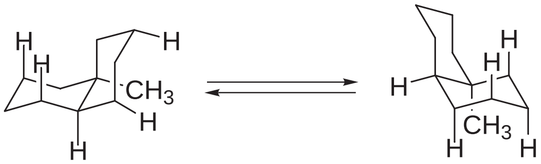
3 gauche interactions
3 × 0.9 kcal = 2.7 kcal

ΔE between *cis*- and *trans*-decalin = 2.7 kcal/mol

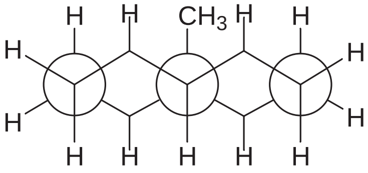
trans-9-methyldecalin



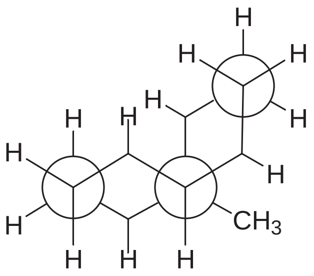
cis-9-methyldecalin



two conformations equivalent



4 gauche interactions
4 × 0.9 = 3.6 kcal



5 gauche interactions
5 × 0.9 = 4.5 kcal

ΔE between *cis*- and *trans*-9-methyldecalin = 0.9 kcal/mol

E. Acyclic sp^3–sp^2 Systems

- Key references

- Origin of destabilization for eclipsed conformations:

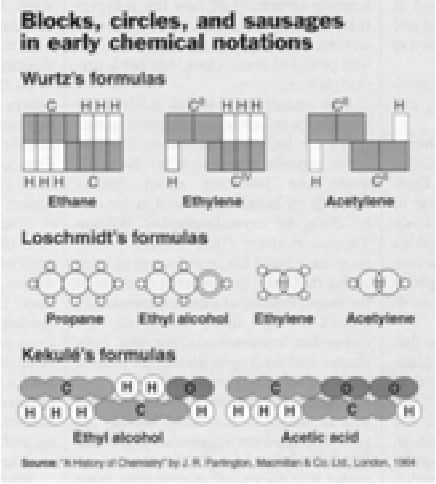
Lowe	*Prog. Phys. Org. Chem.* **1968**, *6*, 1.
Oosterhoff	*Pure Appl. Chem.* **1971**, *25*, 563.
Wyn-Jones, Pethrick	*Top. Stereochem.* **1970**, *5,* 205. *Quat. Rev., Chem. Soc.* **1969**, *23*, 301.
Brier	*J. Mol. Struct.* **1970**, *6*, 23.
Lowe	*Science* **1973**, *179*, 527.

- Molecular orbital calculations: Repulsion of overlapping filled orbitals:

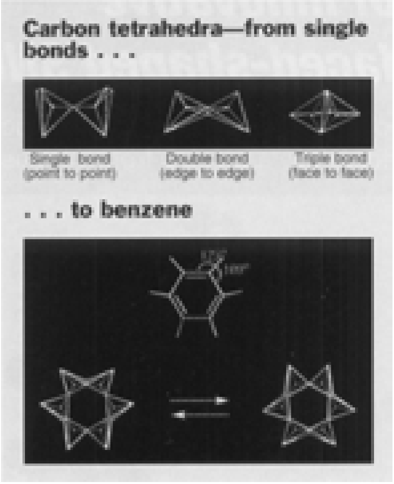
Pitzer	*Acc. Chem. Res.* **1983**, *16*, 207.

- Propionaldehyde:	Butcher, Wilson	*J. Chem. Phys.* **1964**, *40*, 1671.
	Allinger, Hickey	*J. Mol. Struct.* **1973**, *17*, 233.
	Allinger	*J. Am. Chem. Soc.* **1969**, *91*, 337.
- Propene:	Allinger	*J. Am. Chem. Soc.* **1968**, *90*, 5773.
	Herschbach	*J. Chem. Phys.* **1958**, *28*, 728.
- 1-Butene:	Geise	*J. Am. Chem. Soc.* **1980**, *102*, 2189.
- Allylic 1,3-strain:	Houk, Hoffmann	*J. Am. Chem. Soc.* **1991**, *113*, 5006.
	Hoffmann	*Chem. Rev.* **1989**, *89*, 1841.

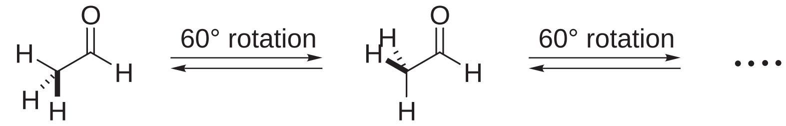
Jacobus van't Hoff studied with both Kekule and Wurtz and received the first Nobel Prize in Chemistry (1901) in recognition of his discovery of the laws of chemical kinetics and the laws governing the osmotic pressure of solutions. More than any other person, he created the formal structure of physical chemistry and he developed chemical stereochemistry which led chemists to picture molecules as objects with three dimensional shapes. He published his revolutionary ideas about chemistry in three dimensions just after his 22nd birthday in 1874, before he completed his Ph.D, in a 15 page pamphlet which included the models of organic molecules with atoms surrounding a carbon atom situated at the apexes of a tetrahedron. Independently and two months later, Joseph A. Le Bel, who also studied with Kekule at the same time as van't Hoff, described a similar theory to the Paris Chem. Soc. Kekule himself had tetrahedral models in the lab and historians concur that they must have influenced van't Hoff and Le Bel. Interestingly, these proposals which serve as the very basis of stereochemistry today were met with bitter criticism.



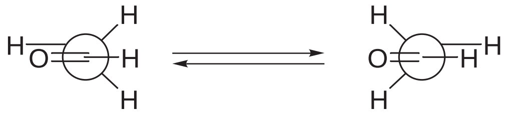
Source: "A History of Chemistry" by J. R. Partington, Macmillan & Co. Ltd., London, 1964

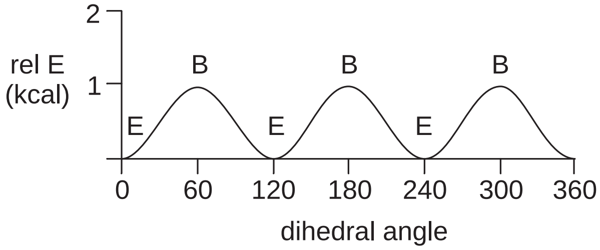


1. Acetaldehyde



eclipsed bisected



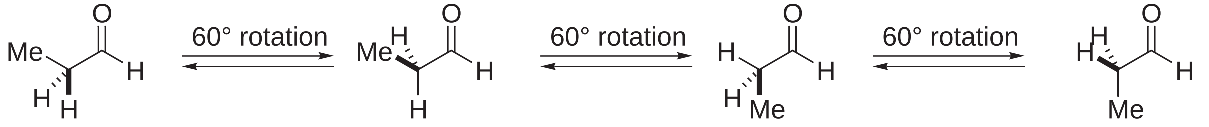


relative energies (kcal)

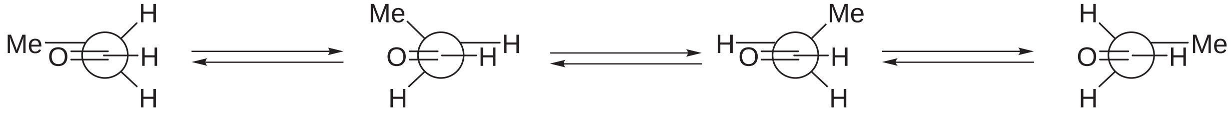
Exp	0.0	1.0
MM2	0.0	1.1–1.2

- Two extreme conformations.
- Barrier to rotation is 1.0 kcal/mol.
- H-eclipsed conformation more stable.

2. Propionaldehyde

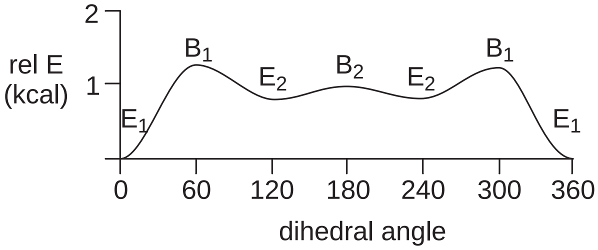


eclipsed bisected eclipsed bisected

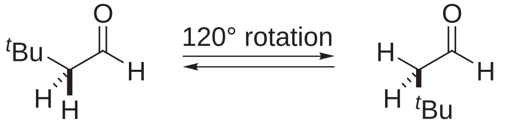


relative energies (kcal)

Exp	0.0	1.25, 2.28	0.8, 0.9, 1.0	unknown
MM2	0.0	2.1	0.8, 0.9	1.0, 2.3–1.7, 1.5
Ab initio	0.0	1.7	0.4	0.7



- *J. Chem. Phys.* **1964**, *40*, 1671.
- *J. Mol. Struct.* **1973**, *17*, 233.
- *J. Am. Chem. Soc.* **1969**, *91*, 337.



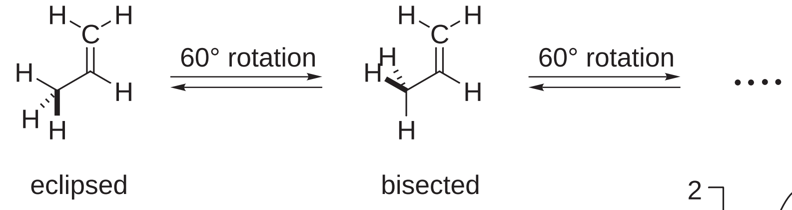
alkyl eclipsed H-eclipsed

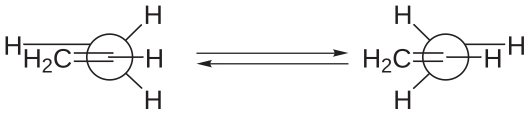
relative energies (kcal)

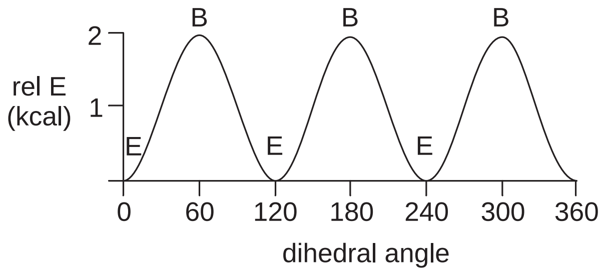
Exp	2.5	0.0

- Alkyl eclipsed conformation more stable than H-eclipsed and exceptions occur only if alkyl group is very bulky (i.e., ^{t}Bu).
- Because E differences are quite low, it is difficult to relate ground state conformation to experimental results. All will be populated at room temperature.

3. Propene





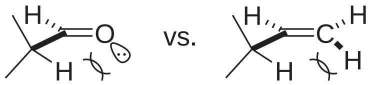


relative energies (kcal)

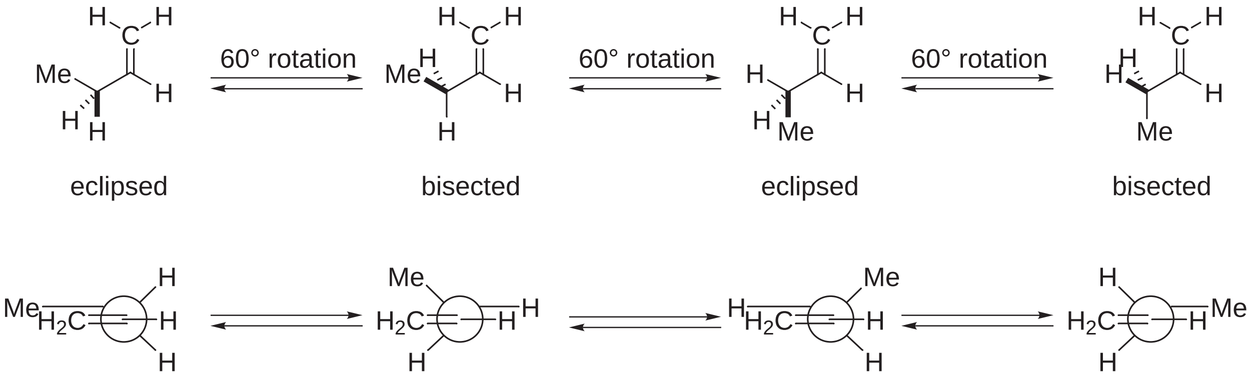
Exp	0.0	2.0
MM2	0.0	2.1–2.2

- Two extreme conformations
- Barrier to rotation is 2.0 kcal/mol

Note:

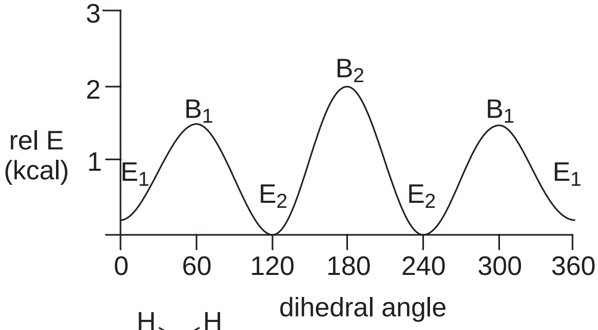


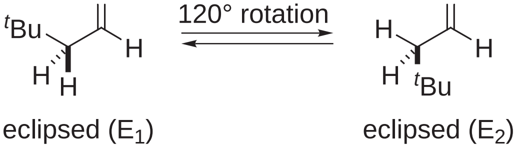
4. 1-Butene



relative energies (kcal)

Exp	0.0, 0.2, 0.4, 0.5	-	0.0	-
MM2	0.5, 0.7	1.4–1.7 (2.6)	0.0	1.4–1.8 (2.6)
Ab initio	0.6	-	0.0	2.0



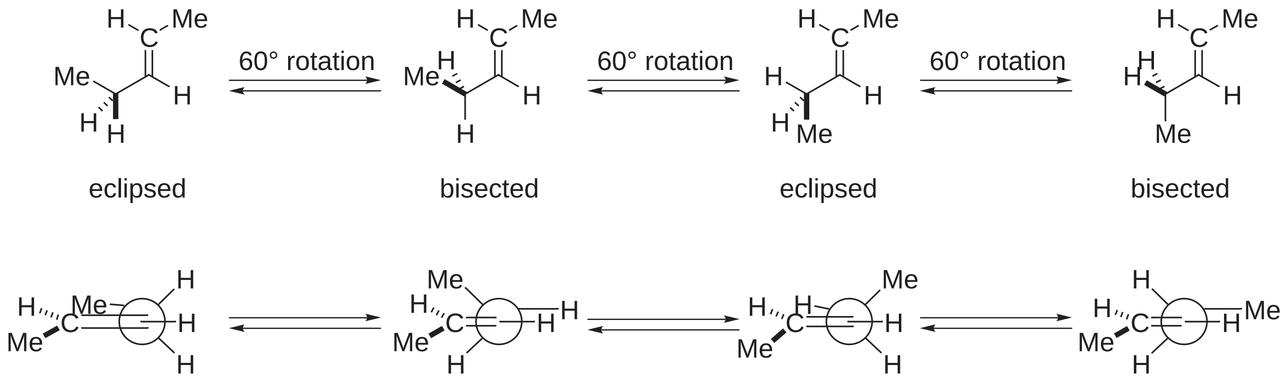


relative energies (kcal)

Exp	B_1, B_2 > E_1 >> E_2

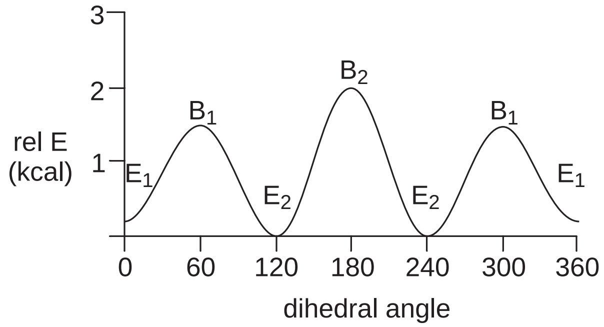
- There is an additional destabilization of placing the alkyl group eclipsed with C=C. This is due to the larger steric size of olefinic CH compared to carbonyl C=O.
- The eclipsed conformations (even with an α-^{t}Bu) are both more stable than the bisected conformations.

5. *E*-2-Pentene



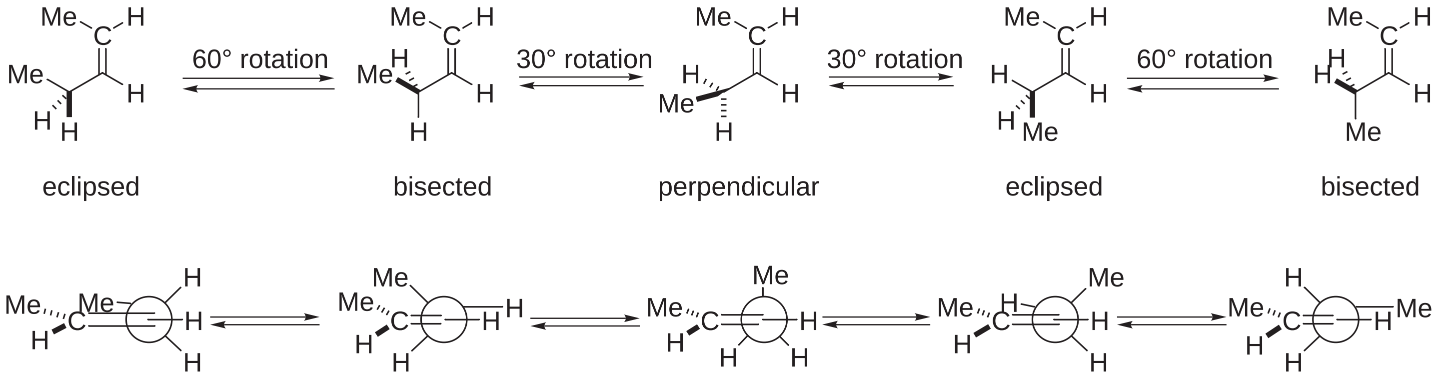
relative energies (kcal)

Exp	0.0 (0.0–0.4)	-	0.0	-
MM2	0.6	1.4–1.7 (2.6)	0.0	1.5–1.8 (2.6)



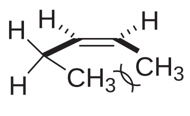
- Analogous to 1-butene.

6. *Z*-2-Pentene

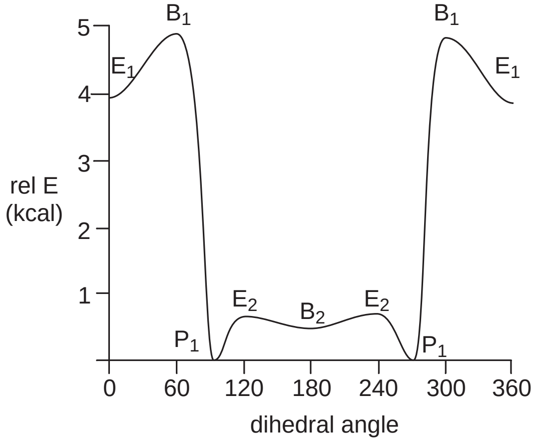


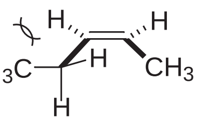
relative energies (kcal)

MM2	3.9	4.9	0.0	0.6	0.5



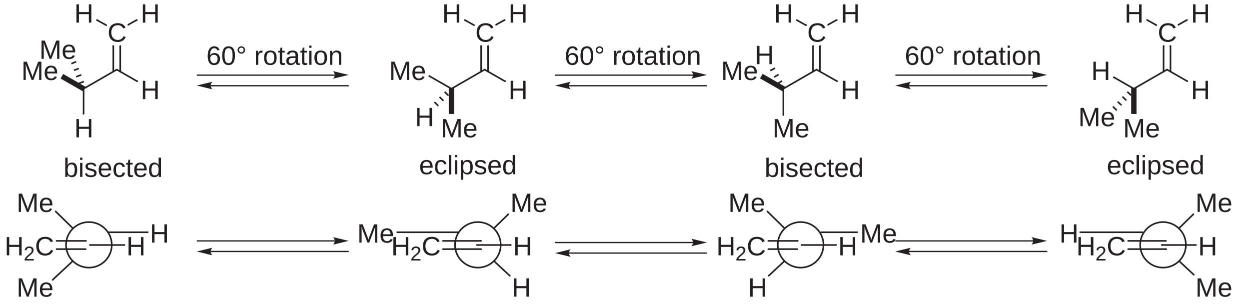
- Serious destabilizing interaction, often referred to as allylic 1,3-strain (A 1,3-strain).





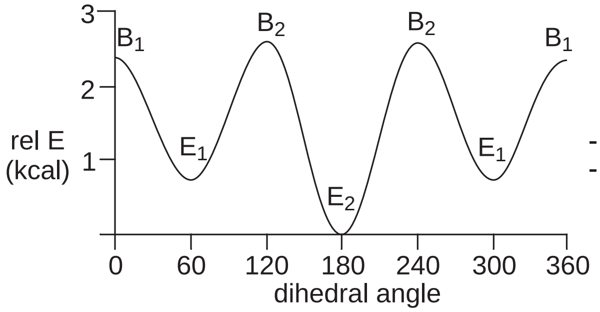
- The analogous H/CH_3 eclipsing interaction in the bisected conformation is often referred to as allylic 1,2-strain (A 1,2-strain).

7. 3-Methyl-1-butene



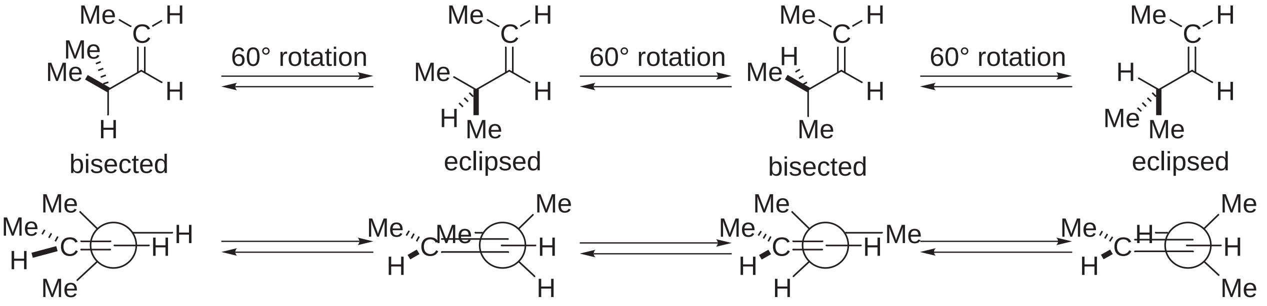
relative energies (kcal)

Ab initio	2.4–3.0	0.73–1.19	2.60–2.94	0.0



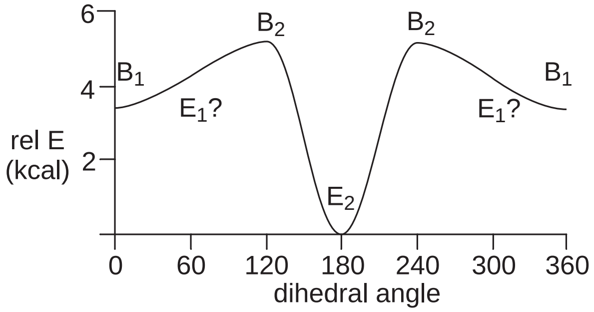
- *J. Am. Chem. Soc.* **1991**, *113*, 5006.
- *Chem. Rev.* **1989**, *89*, 1841.

8. 4-Methyl-2-pentene



relative energies (kcal)

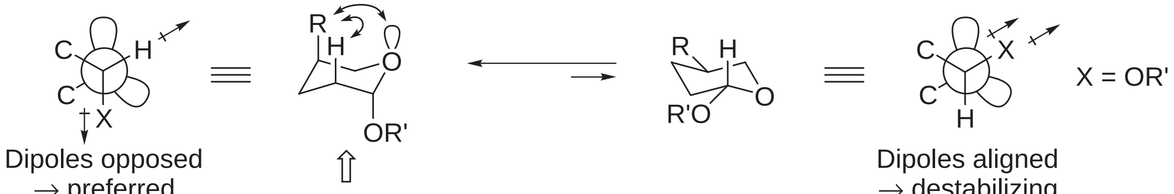
Ab initio	3.4–4.3	-	4.9–5.9	0.0



- Only H-eclipsed conformation is reasonable.

F. Anomeric Effect

1. Tetrahydropyrans (e.g., Carbohydrates)



Dipoles opposed
→ preferred

Dipoles aligned
→ destabilizing

R = H, preferred conformation. $\Delta G° = 0.85$ kcal/mol

- generally 0–2 kcal/mol, depends on C2/C3 substituents
- effect greater in non-polar solvent

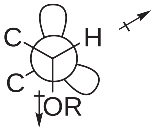
Comprehensive Org. Chem. Vol. 5, 693.
Comprehensive Het. Chem. Vol. 3, 629.
Review: *Tetrahedron* **1992**, *48*, 5019.

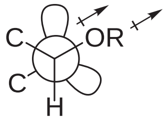
1. A value for R group will be smaller, less preference for equatorial vs axial C3 or C5 substituent since one 1,3-diaxial interaction is with a lone pair versus C–H bond.
2. Polar, electronegative group (e.g., OR and Cl) adjacent to oxygen prefers axial position.
3. Alkyl group adjacent to oxygen prefers equatorial position.
4. Electropositive group (such as $^+NR_3$, NO_2, $SOCH_3$) adjacent to oxygen strongly prefers equatorial position. ⇒ Reverse Anomeric Effect

- Explanations Advanced:

1. Dipole stabilization

opposing dipoles, stabilizing

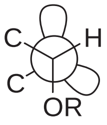


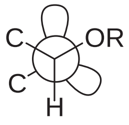


dipoles aligned, destabilizing

2. Electrostatic repulsion

minimizes electrostatic repulsion between lone pairs and the electronegative substituent



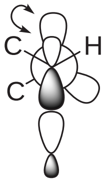


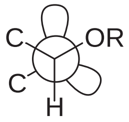
maximizes destabilizing electrostatic interaction between electronegative centers (charge repulsion)

3. Electronic stabilization

n–σ* orbital stabilizing interaction

n electron delocalization into σ* orbital

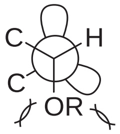


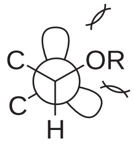


no stabilization possible

4. Gauche interaction involving lone pairs is large (i.e., steric)

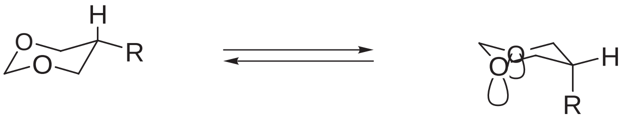
1 lone pair / OR gauche interaction + 1 C/OR gauche interaction (0.35 kcal/mol)





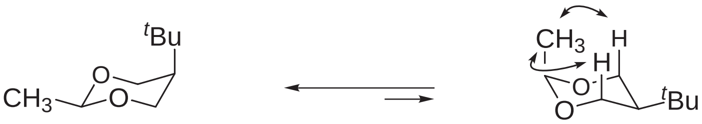
2 lone pair / OR gauche interactions, but would require that they be ~1.2 kcal/mol

2. Anomeric Effect and 1,3-Dioxanes



lone pair / R interaction

1. Polar, electronegative C2/C4 substituents prefer axial orientation.
2. The lone pair on oxygen has a smaller steric requirement than a C–H bond. Δ*G*° is much lower, lower preference between axial and equatorial C5 substituent
3. Polar electropositive groups C2 equatorial position preferred: C5 axial position may be preferred for F, NO_2, $SOCH_3$, $^+NMe_3$.



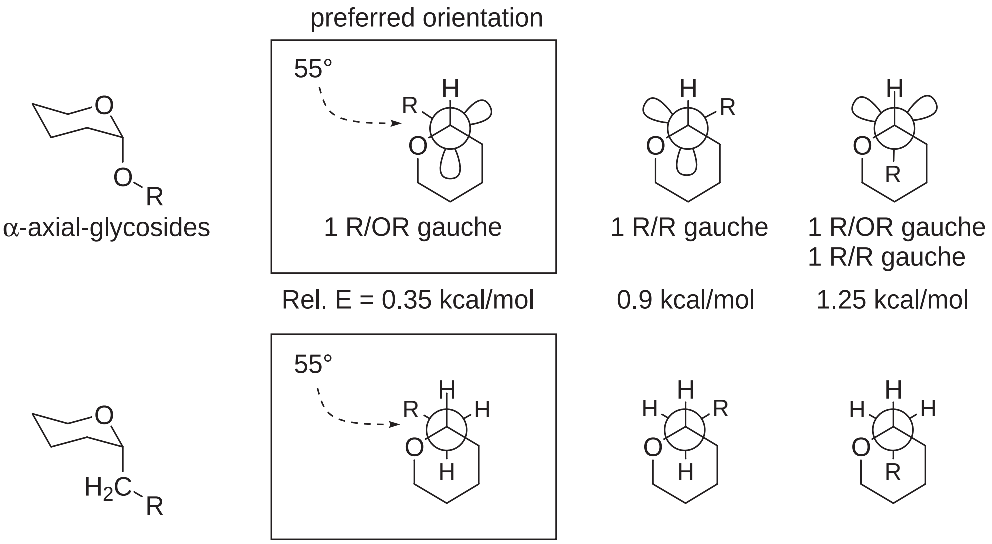
preferred conformation

Eliel *J. Am. Chem. Soc.* **1968**, *90*, 3444.

A Value (kcal/mol) for Substituents on Tetrahydropyran and 1,3-Dioxane versus Cyclohexane

Group	Cyclohexane	Tetrahydropyran C2	1,3-Dioxane C2	1,3-Dioxane C5
CH_3	1.8	2.9	4.0	0.8
Et	1.8		4.0	0.7
^{i}Pr	2.1		4.2	1.0
^{t}Bu	>4.5			1.4

3. Exo Anomeric Effect



Kishi *J. Org. Chem.* **1991**, *56*, 6412.

G. Strain

Cyclic Hydrocarbon, Heats of Combustion/Methylene Group (gas phase)

	Ring Size	$-\Delta H_c$ (kcal/mol)	Ring Size	$-\Delta H_c$ (kcal/mol)	
	3	166.3	10	158.6	
	4	163.9	11	158.4	
	5	158.7	12	157.8	largely strain free
strain free	6	157.4	13	157.7	
	7	158.3	14	157.4	
	8	158.6	15	157.5	
	9	158.8	16	157.5	

1. Small rings (3- and 4-membered rings): small angle strain

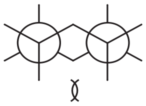
For cyclopropane, reduction of bond angle from ideal 109.5° to 60°
27.5 kcal/mol of strain energy.

For cyclopropene, reduction of bond angle from ideal 120° to 60°
52.6 kcal/mol of strain energy.

To form a small ring in synthetic sequences, must overcome the energy barrier implicated in forming a strained high energy product.

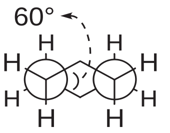
2. Common rings (5-, 6-, and 7-membered rings):
   - largely unstrained and the strain that is present is largely torsional strain (Pitzer strain).

3. Medium rings (8- to 11-membered rings):
   - a. large angle strain
     - bond angles enlarged from ideal 109.5° to 115–120°.
     - bond angles enlarged to reduce transannular interactions.
   - b. steric (transannular) interactions
     - analogous to 1,3-diaxial interactions in cyclohexanes, but can be 1,3-, 1,4-, or 1,5- ...



   - c. torsional strain (Pitzer strain)

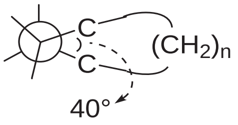
in cyclohexanes



just like gauche butane.

in medium rings

- deviation from ideal ϕ of 60° and approach an eclipsing interaction.



4. Large rings (12-membered and up):
   - little or no strain.

5. Some highly strained molecules:

Buckminsterfullerene (C_{60}) has a strain energy of 480 kcal/mol and is one of the highest strain energies ever computed. However, since there are 60 atoms, this averages to ca. 8 kcal/mol per carbon atom - not particularly unusual.

First isolated in 1990:
Kroto, Heath, O'Brian, Curl, and Smalley
Nature **1985**, *318*, 162.

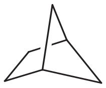
Robert Curl, Harold Kroto, and Richard Smalley shared the 1996 Nobel Prize in Chemistry for the discovery of fullerenes.

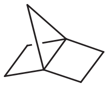
[1.1.1] propellane

Wiberg *J. Am. Chem. Soc.* **1982**, *104*, 5239.

strain energy = 98 kcal/mol

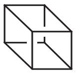
note: the higher homologs are not stable at 25 °C.





Wiberg *J. Am. Chem. Soc.* **1983**, *105*, 1227.

cubane

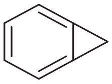


Eaton *J. Am. Chem. Soc.* **1964**, *86*, 3157.

strain energy = 155 kcal/mol

note: kinetically very stable, may be prepared in kg quantities.

cyclopropabenzene



Vogel *Tetrahedron Lett.* **1965**, 3625.

strain energy = 68 kcal/mol

note: even traces of this substance provides an intolerable smell and efforts to establish its properties had to be cancelled at the Univ. of Heidelberg.

H. pK_a of Common Organic Acids

Acid	pK_a
cyclohexane	45
ethane	42
benzene	37
ethylene	36
Et_2NH	36
NH_3 (ammonia)	35
toluene, propene	35
$(C_6H_5)_3CH$	28–33
DMSO ($CH_3S(O)CH_3$)	31
$C_6H_5NH_2$	27
$HC{\equiv}CH$	25
CH_3CN	25
CH_3CO_2Et	25
$CH_3SO_2CH_3$	23–27
CH_3CONMe_2	25
aliphatic ketones	20–23
$(CH_3)_3CCOCH(CH_3)_2$	23
$(CH_3)_3CCOCH_3$	21
CH_3COCH_3	20
$CH_3COC_6H_5$	19
$(CH_3)_3COH$	19
$C_6H_5C{\equiv}CH$	19

Acid	pK_a
$(CH_3)_2CHOH$	18
CH_3CH_2OH	17
cyclic ketones	17
e.g. cyclohexanone	17
CH_3OH	16 (16–18)
$CH_3CONHCH_3$	16–17
$PhCH_2COPh$	16
H_2O	16
cyclopentadiene	15
$CH_2(CO_2Et)_2$	13
$CH_2(CN)_2$	11
$CH_3COCH_2CO_2Et$	11
CH_3NO_2	10
phenol	10
$R_3NH^+Cl^-$	10
HCN	9
$CH_3CH_2NO_2$	9
$CH_3COCH_2COCH_3$	9
$CH_2(CN)CO_2Et$	9
CH_3CO_2H	5
py•HCl	5
$C_6H_5NH_3^+Cl^-$	5

$$XH \rightleftharpoons H^+ + X^- \qquad K_a = \frac{[H^+][X^-]}{[HX]}$$

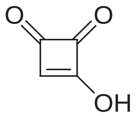
pK_a = $-\log K_a = -\log[H^+]$
Increase in pK_a means decrease in $[H^+]$ and acidity
Decrease in pK_a means increase in $[H^+]$ and acidity

For more extensive lists, see:
The Chemist's Companion, p 58–63.

Familiarity with these pK_a's will allow prediction/estimation of acidities of other compounds. This is important, since many organic reactions have a pK_a basis (i.e., enolate alkylations).

> Alfred Werner, who received the 1913 Nobel Prize in Chemistry for his studies of stereochemistry and inorganic complexes, is also responsible for the redefinition of (acids and) bases as compounds that have varying degrees of ability to attack hydrogen ions in water resulting in an increase in hydroxide ion.

The most acidic natural product is the mycotoxin monliformin also known as semisquaric acid, pK_a = 0.88



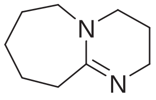
Springer, Clardy *J. Am. Chem. Soc.* **1974**, *96*, 2267.

Compare the strength of the following neutral bases:

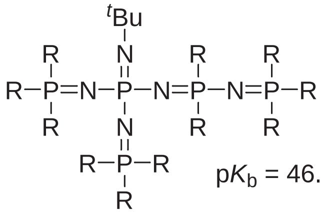
Me_3N

pK_b = 4.1

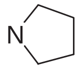
DBU



pK_b = 24.3



pK_b = 46.9

R = 

Schwesinger *Liebigs Ann.* **1996**, 1055.

II. Kinetics and Thermodynamics of Organic Reactions

A. Free Energy Relationships

$$\Delta G = \Delta H - T\Delta S$$

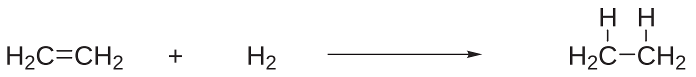
The equilibrium for the reaction can be described by

$$\ln K_{eq} = -\frac{\Delta G}{RT}$$

To achieve a high ratio of two products (desired product and undesired product) in a thermodynamically controlled reaction run under reversible conditions, one needs the following ΔG's:

K (25 °C)		ΔG (kcal/mol)	*K* (0 °C)		ΔG (kcal/mol)	*K* (–78 °C)		ΔG (kcal/mol)
2	(67:33)	0.41	2.1	(68:32)	0.41	2.9	(75:25)	0.41
5	(83:17)	0.95	5.7	(85:15)	0.95	11.6	(92:8)	0.95
9	(90:10)	1.30	10.9	(92:18)	1.30	28.5	(97:3)	1.30
20	(95:5)	1.74	27.5	(96:4)	1.80	103.3	(99:1)	1.80
99	(99:1)	2.73						
999	(99.9:0.1)	4.09						

Hydrogenation reaction:



$$H_2C{=}CH_2 \quad + \quad H_2 \longrightarrow H_2\overset{H}{C}{-}\overset{H}{C}H_2$$

bonds broken		
1	C=C	163 kcal/mol
1	H–H	104 kcal/mol
		267 kcal/mol

bonds formed		
1	C–C	88 kcal/mol
2	C–H	2 × 98 kcal/mol
		284 kcal/mol

-Overall reaction is *exothermic* -> $\Delta G = -17$ kcal/mol, so reaction is *favorable, spontaneous.*

-To calculate equilibrium constant:

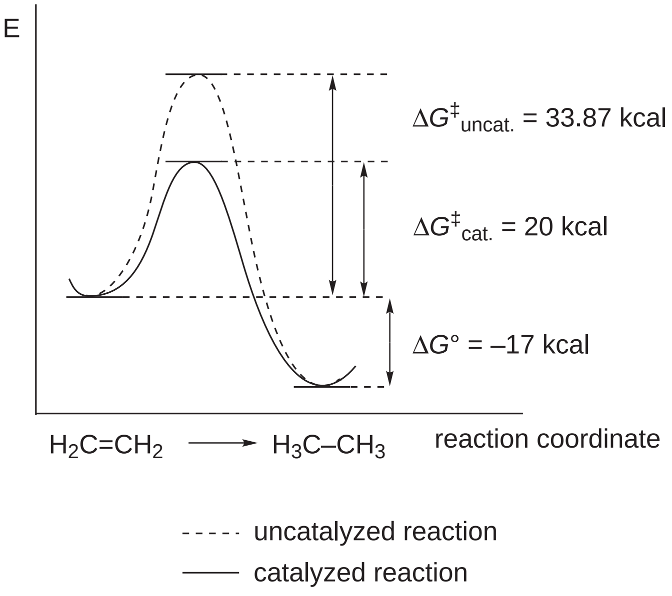
$$\ln K_{eq} = -\frac{\Delta G}{RT}$$

$$\begin{aligned} 2.303 \log K_{eq} &= 17 \text{ kcal} \times 1000 \text{ cal/mol} / (298 \text{ K}) \times 1.99 \\ \log K_{eq} &= 12.45 \\ K_{eq} &= 2.8 \times 10^{12} \end{aligned}$$

- But experimentally this reaction is very slow.
- Molecule rate (experimentally) = 10^{12} molecules/sec

$$\text{mole rate} = \frac{6.023 \times 10^{23} \text{ molecules/mol}}{(10^{12} \text{ molecules/sec}) \times (60 \text{ sec/min}) \times (60 \text{ min/hour}) \times (24 \text{ hour/day}) \times (365 \text{ day/year})} = 2 \times 10^{4} \text{ years}$$

i.e., 2×10^4 years to hydrogenate one mole of ethylene (without catalyst).



Transition State: A transition state (TS) possesses a defined geometry and charge delocalization but has no finite existence. At TS, energy usually higher and although many reactant bonds are broken or partially broken, the product bonds are not yet completely formed.

Svante Arrhenius received the 1903 Nobel Prize in Chemistry in recognition of his theory of electrolytic dissociation where he introduced the idea that many substances dissociate into positive and negative ions ($NaCl \rightleftarrows Na^+ + Cl^-$) in water including the partial dissociation of weak acids like HOAc, where the equilibrium amount depends on the concentration. His qualitative ideas on the exponential increase in the rate of reactions when temperature is increased are retained in modern theories that relate kinetic rate constants to temperature by means of an energy of activation.

B. Transition State Theory

Ahmed Zewail was awarded the 1999 Nobel Prize in Chemistry for his studies of the transition states of chemical reactions using femtosecond spectroscopy.

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$

- Free Energy of Activation ($\Delta G^\ddagger$)
- Enthalpy of Activation ($\Delta H^\ddagger$): Difference in bond energy between reactants and the transition state.
- Entropy of Activation ($-T\Delta S^\ddagger$): $\Delta S^\ddagger$ usually negative, making the change more endothermic.

From $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$, $\Delta G^\ddagger = -RT \ln K^\ddagger$

for uncatalyzed H_2 reaction $\Delta G^\ddagger = 33.9$ kcal/mol

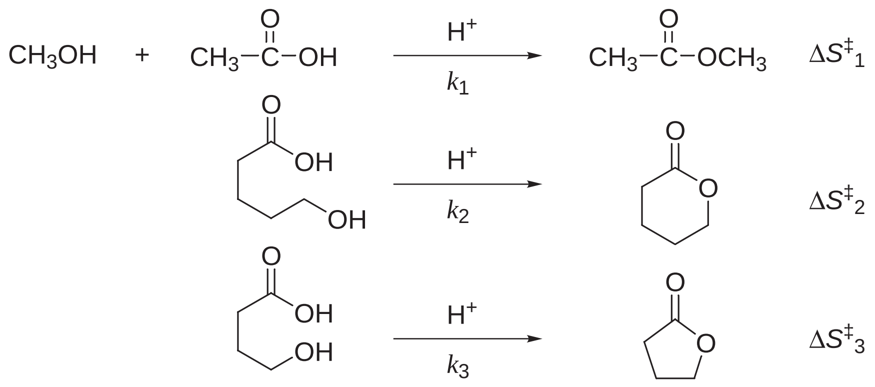
catalyzed H_2 reaction $\Delta G^\ddagger = 20$ kcal/mol

and for the rate

for uncatalyzed H_2 reaction $k = 1.0 \times 10^{12}$ mol/sec

catalyzed H_2 reaction $k = 1.0 \times 10^{22}$ mol/sec

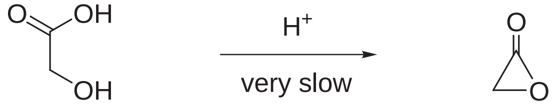
C. Intramolecular Versus Intermolecular Reactions



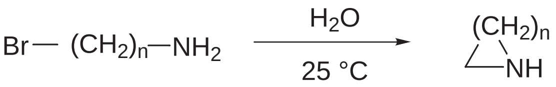
$k_3 > k_2 > k_1$

$$-T\Delta S^\ddagger_1 > -T\Delta S^\ddagger_2 > -T\Delta S^\ddagger_3 > 0$$
$$\Delta S^\ddagger_1 < \Delta S^\ddagger_2 < \Delta S^\ddagger_3 < 0$$
$$\Rightarrow \Delta G^\ddagger_3 < \Delta G^\ddagger_2 < \Delta G^\ddagger_1$$

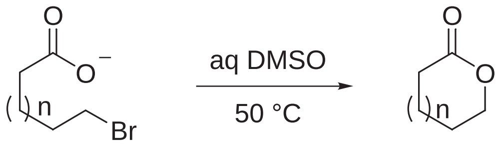
- Intramolecular versus intermolecular reactions benefit from a far more favorable entropy of activation ($\Delta S^{\ddagger}$).
- In forming small rings, ring strain developing in the product decelerates the rate of reaction (large $\Delta H^{\ddagger}$) and that can offset the favorable $\Delta S^{\ddagger}$ rate acceleration.



Examples:

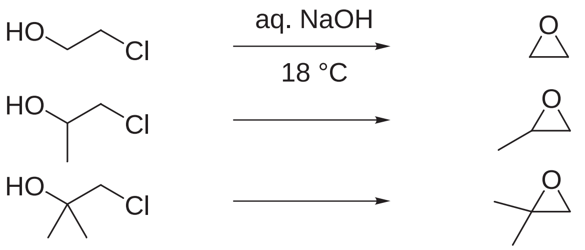


Ring size	Rel. Rate
3	70
4	1.0
5	10000
6	1000
7	2



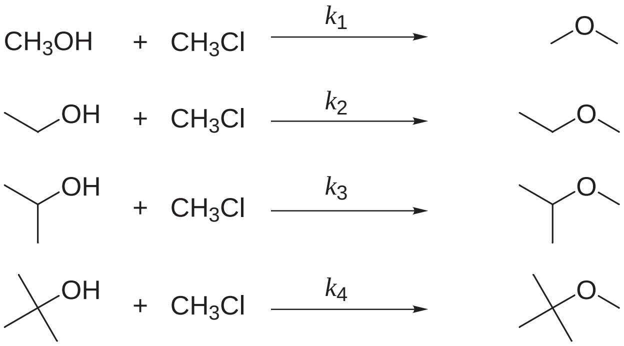
Ring size	Rel. Rate	Ring size	Rel. Rate
3	21.7	11	8.51
4	5.4×10^3	12	10.6
5	1.5×10^6	13	32.2
6	1.7×10^4	14	41.9
7	97.3	15	45.1
8	1.00	16	52.0
9	1.12	17	51.2
10	3.35	18	60.4

- gem dimethyl effect



Rel. Rate
1.0
325
39000

Compare to relative rates of intermolecular S_N2 displacement where the more substituted alkoxide reacts slowest:



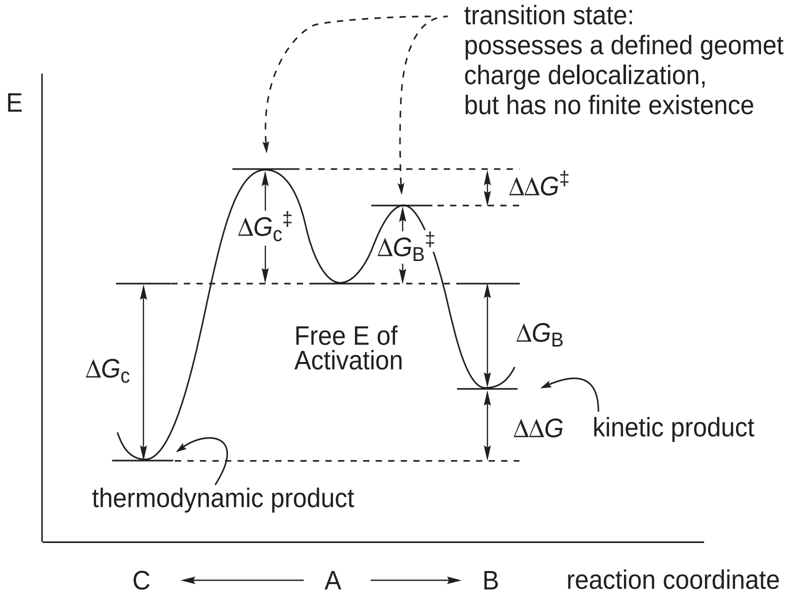
$k_1 > k_2 > k_3 > k_4$

DeTar *J. Am. Chem. Soc.* **1980**, *102*, 4505.
Winnik *Chem. Rev.* **1981**, *81*, 491.
Mandolini *J. Am. Chem. Soc.* **1978**, *100*, 550.
Illuminati *J. Am. Chem. Soc.* **1977**, *99*, 2591.
Mandolini, Illuminati *Acc. Chem. Res.* **1981**, *14*, 95.

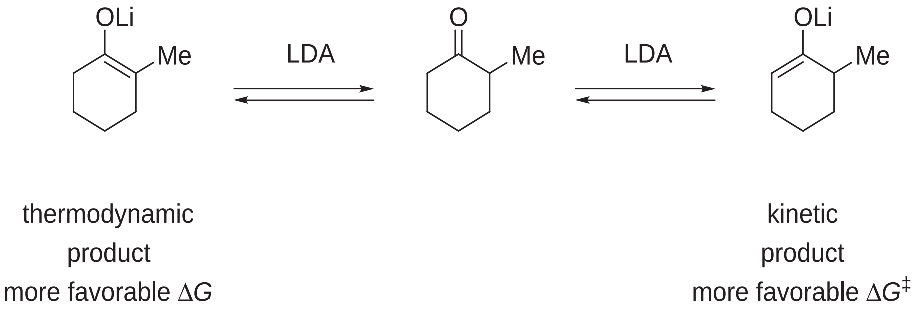
For the intramolecular case:
The reactive conformation is more favorable and populated to a greater extent in the more substituted case
⇒ One must consider both the length of the chain (i.e., ring size being formed) and the nature of the atoms in the chain (i.e., conformation, hybridization).

D. Kinetic and Thermodynamic Control

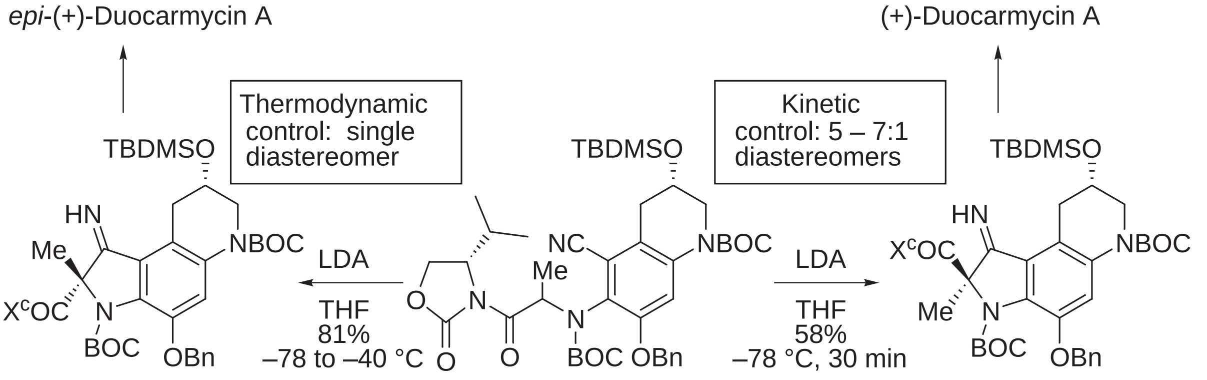
- For competitive reactions:



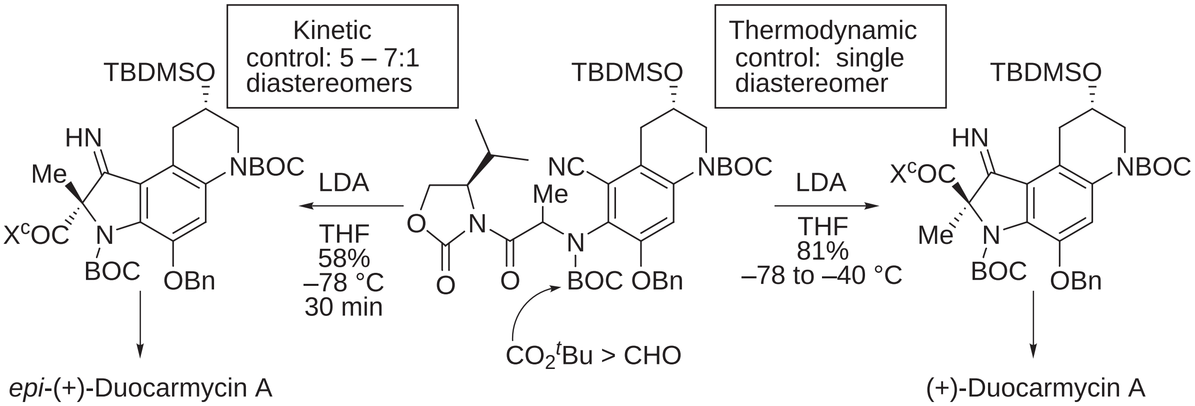
If this is an irreversible reaction, most of the reaction product will be B (kinetic product).
If this is a reversible reaction, most of the product will be C (more stable, thermodynamic product).

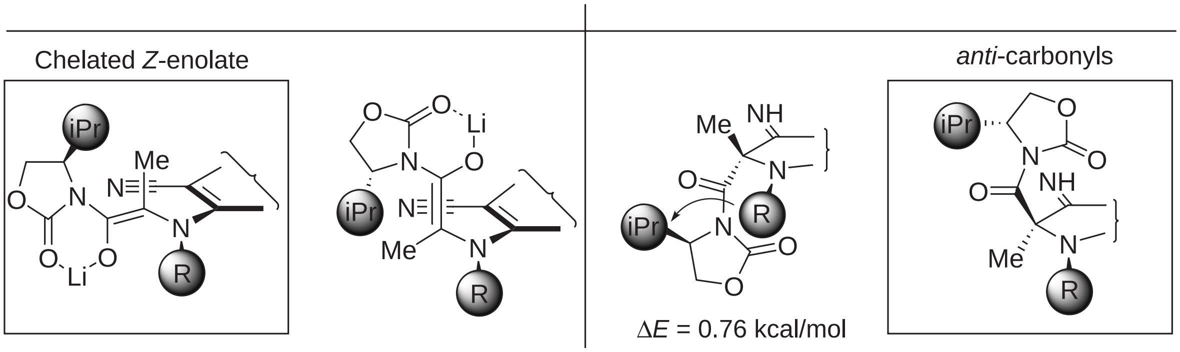


A beautiful example of this was observed in the kinetic versus thermodynamic asymmetric Dieckmann-like condensation illustrated below. The most stable product (lower ΔG) was observed upon conducting the reaction under equilibrating conditions for the reversible reaction while the alternative kinetic product (lower $\Delta G^\ddagger$) was observed when the reaction was conducted under lower temperature and nonequilibrating conditions (kinetic conditions).



Divergent Control of C6-Stereochemistry





Boger *J. Am. Chem. Soc*. **1997**, *119*, 311.

E. Hammond Postulate

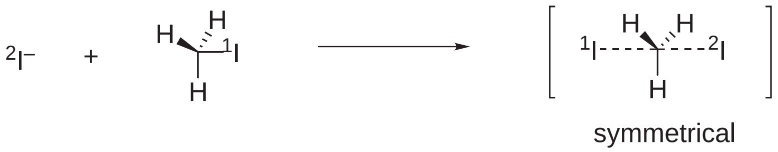
The geometry of the transition state for a step most closely resembles the side (i.e., reactant or product) to which it is closer in energy.

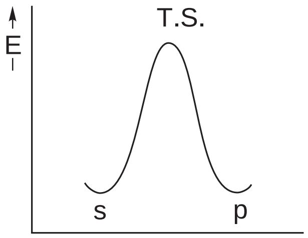
Transition state can not be studied experimentally – has zero lifetime (transient species)
→ information obtained indirectly
⇒ Hammond postulate

Examples:

1) Thermoneutral reactions:

$$CH_3{-}^{1}I \quad + \quad {}^{2}I^{-} \quad \longrightarrow \quad CH_3{-}^{2}I \quad + \quad {}^{1}I^{-}$$



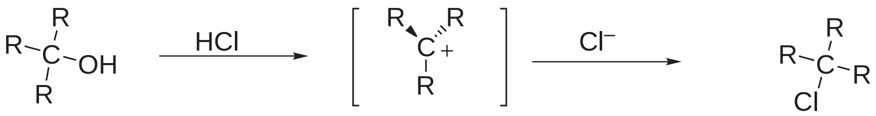


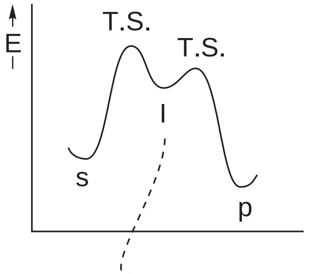
Thermoneutral reaction –
transition state resembles both
starting material and product equally

2) For reactions which proceed through an intermediate: solvolysis of tertiary alcohol

$$A \longrightarrow [X] \longrightarrow B$$

X: discrete intermediate





G. A. Olah received the 1994 Nobel Prize in Chemistry for his contributions to carbocation chemistry.

Resemble the geometry of the carbocation intermediate and not that of the reactant (alcohol) or product (alkyl chloride).

Intermediate (for this reaction it will be C^+ so T.S. ⇒ I)

Notes
a. 20 kcal/mol energy available at 25 °C for free energy of activation.
b. Increase reaction temperature, increase the rate of reaction.
c. Decrease reaction temperature, decrease the rate of reaction, but increase the selectivity of the reaction.

Hammond *J. Am. Chem. Soc.* **1955**, *77*, 334.
Farcasiu *J. Chem*. *Ed*. **1975**, 52, 76.

F. Principle of Microscopic Reversibility

The forward or reverse reactions, run under identical conditions, must proceed by the same mechanism i.e., if forward reaction proceeds via intermediate X

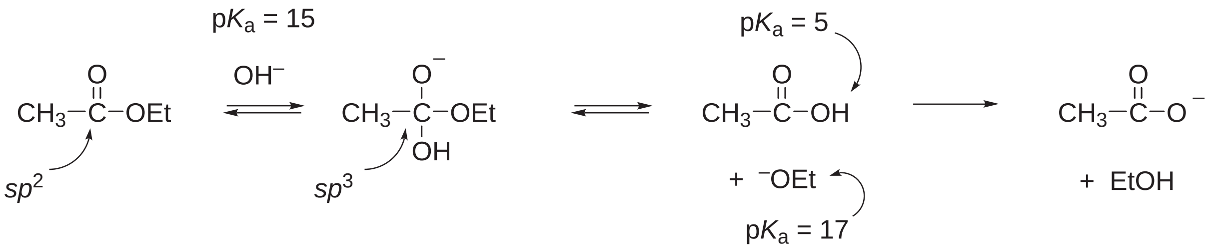
$$A \longrightarrow [X] \longrightarrow B$$

then reverse reaction also goes through X.

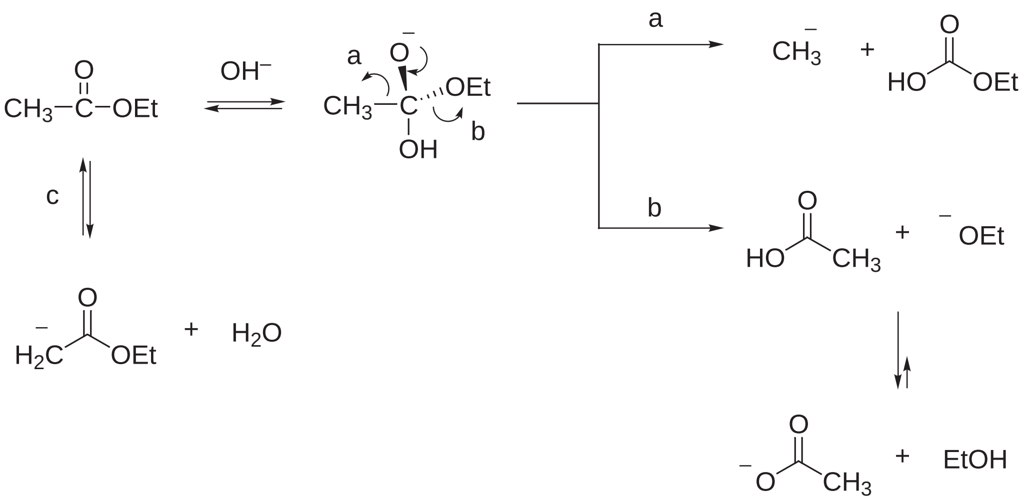
$$B \longrightarrow [X] \longrightarrow A$$

III. Reaction Mechanisms and Conformational Effects on Reactivity

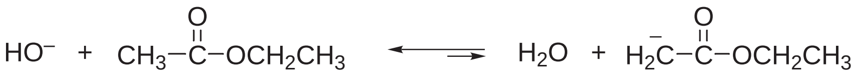
A. Ester Hydrolysis



Reaction driven to completion by final, irreversible step (compare pK_a = 17 to pK_a = 5).

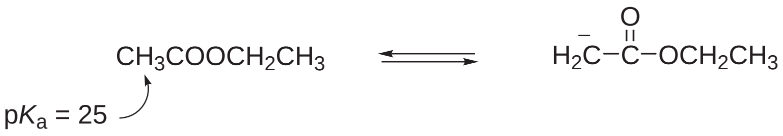


- So, possible competing reaction is α-H removal, but pK_a difference means equilibrium strongly favors ester and OH⁻, i.e.;



$$HO^- + CH_3-\overset{O}{\overset{\|}{C}}-OCH_2CH_3 \rightleftharpoons H_2O + H_2\overset{-}{C}-\overset{O}{\overset{\|}{C}}-OCH_2CH_3$$

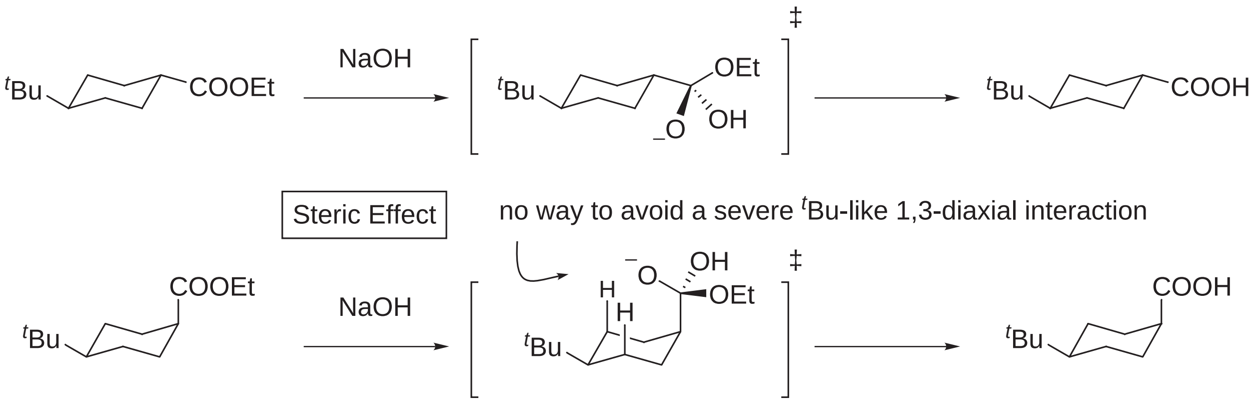
- To deprotonate an ester, must use a strong base which is non-nucleophilic, such as ${}^tBuOK$ or LDA.



$$CH_3COOCH_2CH_3 \rightleftharpoons H_2\overset{-}{C}-\overset{O}{\overset{\|}{C}}-OCH_2CH_3$$

1. ${}^tBuOK$ (pK_a of ${}^tBuOH$ = 19) →	generates low concentration of anion, and a significant amount of ester always present ⇒ self (Claisen) condensation
2. LDA (pK_a of ${}^iPr_2NH$ = 36) →	generates a high concentration of enolate and thus is a good base to carry out stoichiometric alkylation of ester

1. Kinetics of Ester Hydrolysis (Stereochemistry and Rates of Reactions)



A value = 1.2 kcal

A value = 2.3 kcal

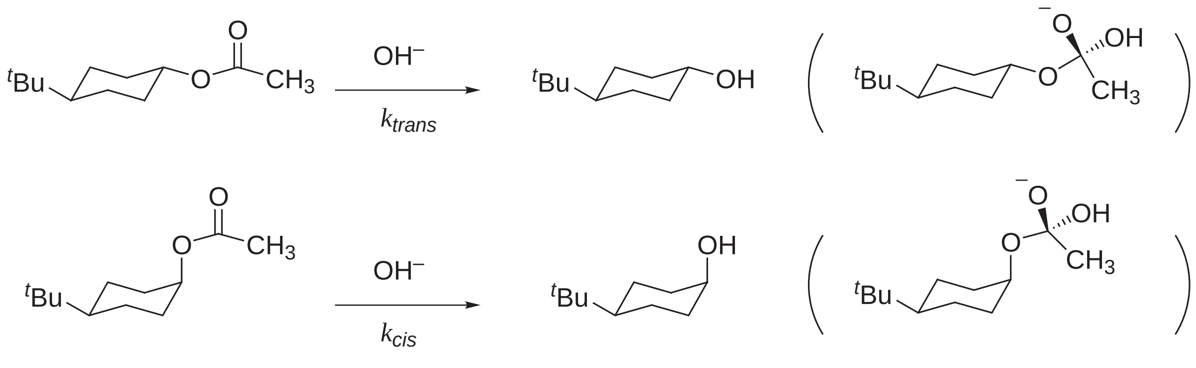
$$\frac{k_{\text{trans}}}{k_{\text{cis}}} = 19.8$$

The rate determining step for ester hydrolysis is the formation of tetrahedral intermediate and the ratio of $k_{\text{trans}}/k_{\text{cis}}$ >> 1.

Eliel *J. Am. Chem. Soc.* **1961**, *83*, 2351.

- Difference in rates much greater than expected if simply considering the difference in either the product or reactant A values.
- Reaction of axial ester decelerated due to more severe developing 1,3-diaxial interactions in transition state (i.e., an axial ^{t}Bu-like group).

2. Same effect is observed, but to a lesser extent with acetate hydrolysis



A value = 0.7 kcal/mol

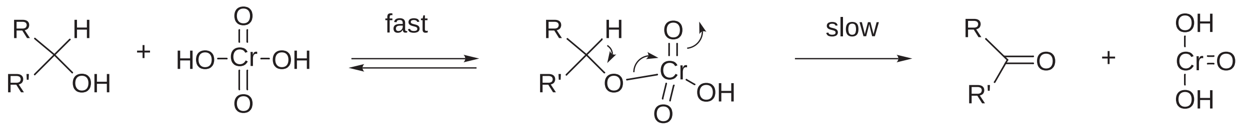
$$\frac{k_{trans}}{k_{cis}} = 6.65$$

effect is smaller because of the more remote distance of the steric interactions

Similarly, the rates of acetylation are $k_{trans} / k_{cis} = 3.7$

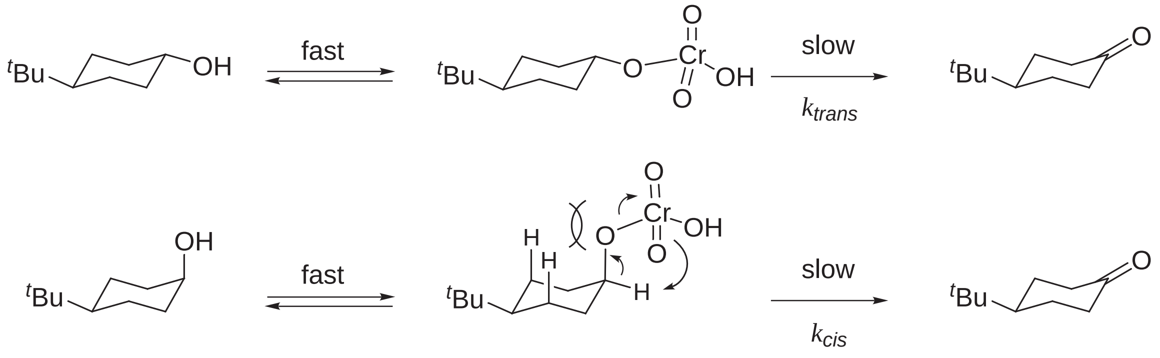
Eliel *J. Am. Chem. Soc.* **1966**, *88*, 3334.

B. Alcohol Oxidations



($CrO_3 + H_2O$)

Westheimer *J. Am. Chem. Soc.* **1951**, *73*, 65.



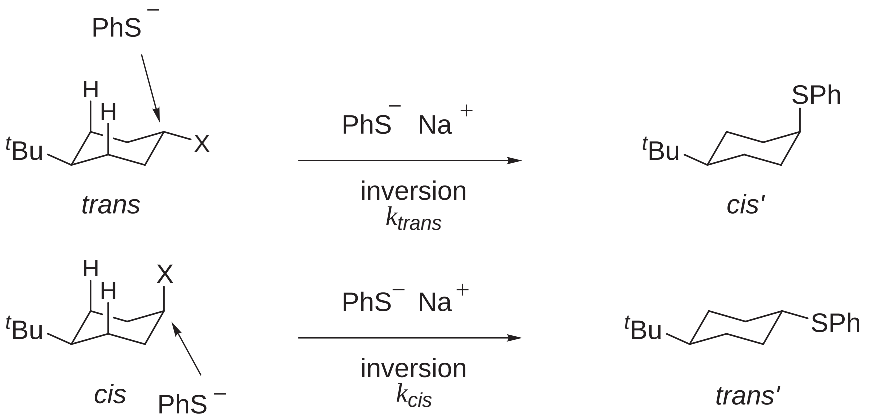
$$\frac{k_{cis}}{k_{trans}} = 4$$

The rate determining step for the alcohol oxidation is break down of the chromate ester with cleavage of C–H bond and O–Cr bond.

Destabilizing 1,3-diaxial interactions in *cis* chromate ester accelerate its breakdown to the ketone (would be slower if the slow step for the reaction were formation of chromate ester).

Eliel *J. Am. Chem. Soc.* **1966**, *88*, 3327.

C. S_N2 Reactions



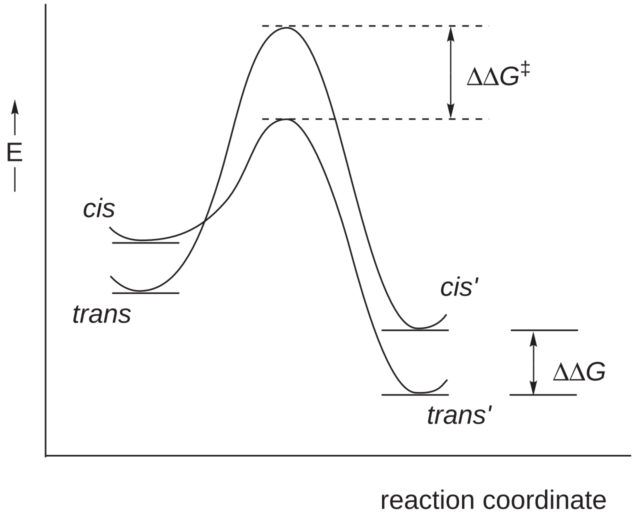
less stable product formed and proceeds through a less stable T.S.

- The free energy of activation (E_a, or $\Delta G^{\ddagger}$) for reaction of the *trans* isomer is higher due to steric interactions felt in the transition state (interactions of incoming nucleophile with axial H's).

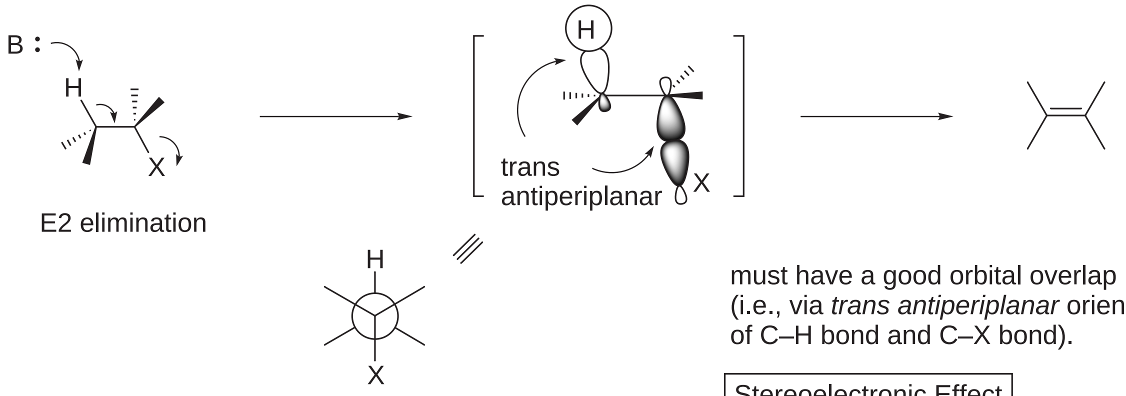
→ $k_{cis} > k_{trans}$

$\Delta\Delta G^{\ddagger}$ greater than $\Delta\Delta G$ of products.

- The reaction of the *trans* isomer is kinetically slower and thermodynamically less favorable.



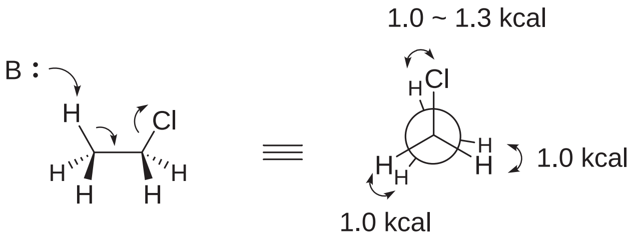
D. Elimination Reactions



must have a good orbital overlap
(i.e., via *trans antiperiplanar* orientation
of C–H bond and C–X bond).

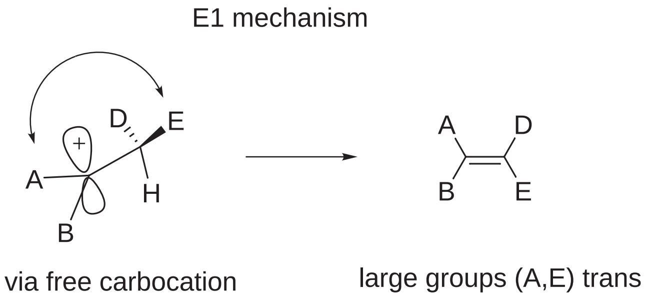
Stereoelectronic Effect

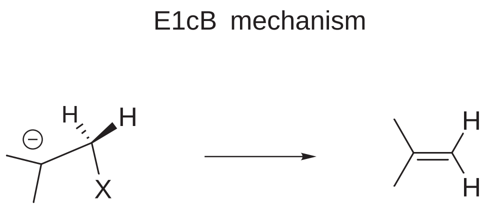
- Alternatively, if dihedral angle = 0° (i.e., eclipsed X and H), elimination can take place (orbital overlap good).



eclipsed conformation is 3.0–3.3 kcal/mol higher in E, so elimination takes place mainly through *trans antiperiplanar* arrangement.

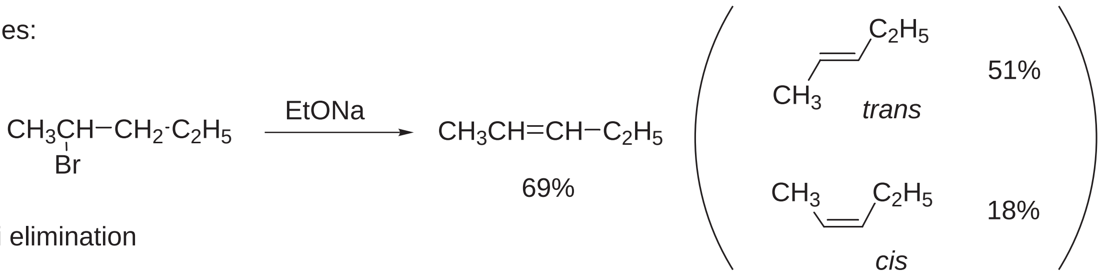
- Alternate mechanisms also possible:





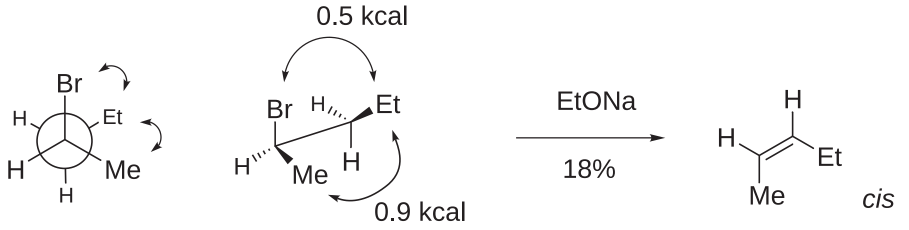
Acyclic Substrate

– Examples:



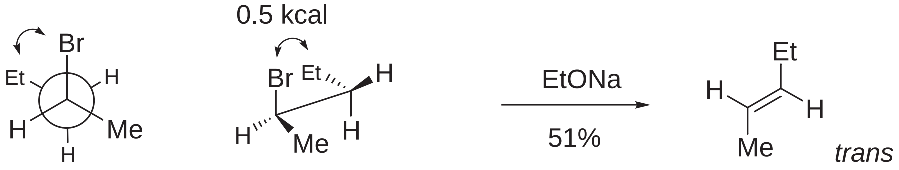
$$CH_3\underset{Br}{C}H-CH_2-C_2H_5 \xrightarrow{EtONa} CH_3CH{=}CH-C_2H_5$$

Anti elimination



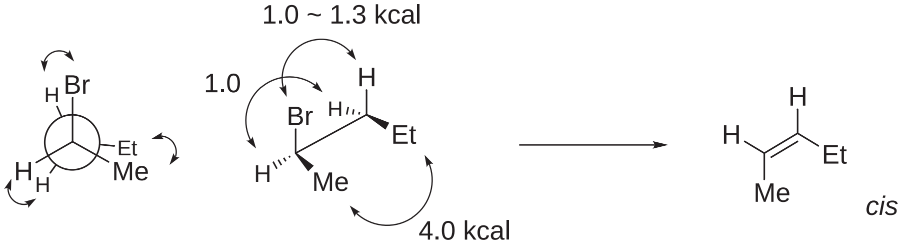
ΔE = 0.9 kcal

trans is more stable than
cis (1.0 kcal/mol)

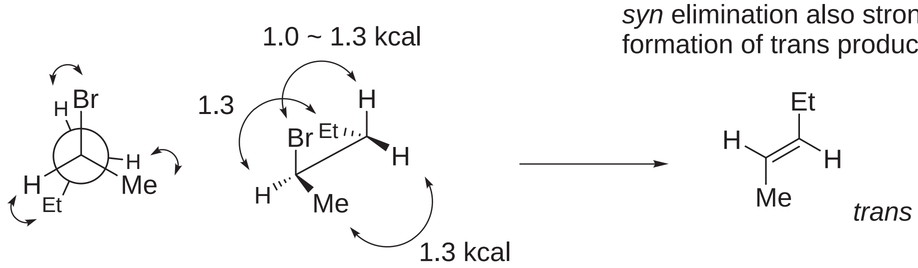


– For other possible mechanisms:

Syn elimination

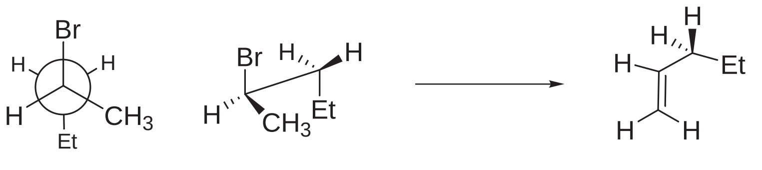


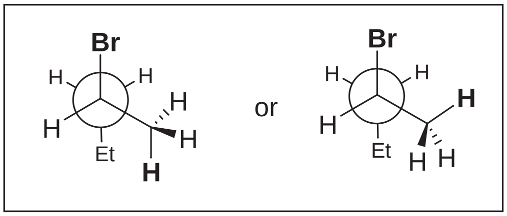
syn elimination also strongly favors
formation of trans product



Both are very much destabilized relative to *anti*-elimination T.S. / conformations.
Neither contribute to ground state conformation of bromide at room temperature.

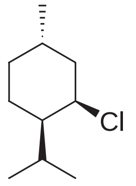
And, there is another product formed:



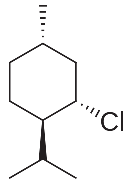


Cyclic Substrate

Consider E2 elimination of

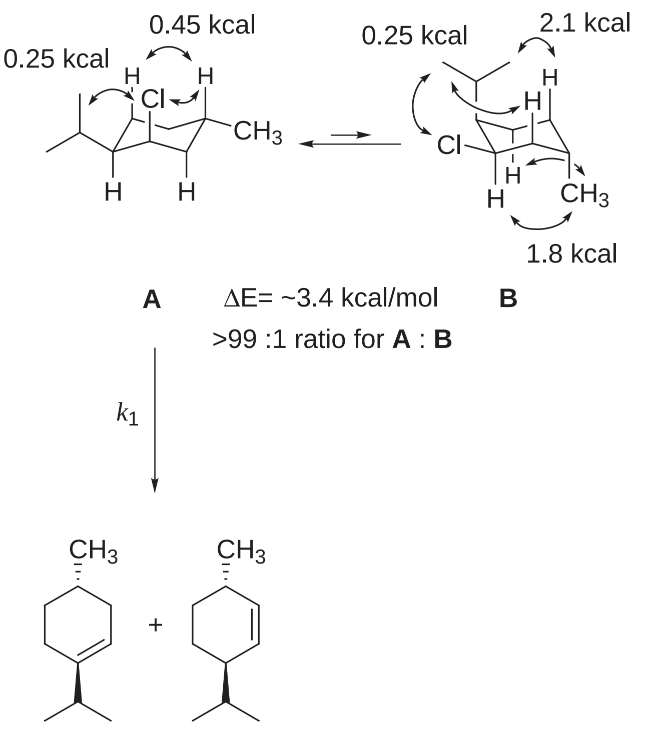


neomenthyl chloride



menthyl chloride

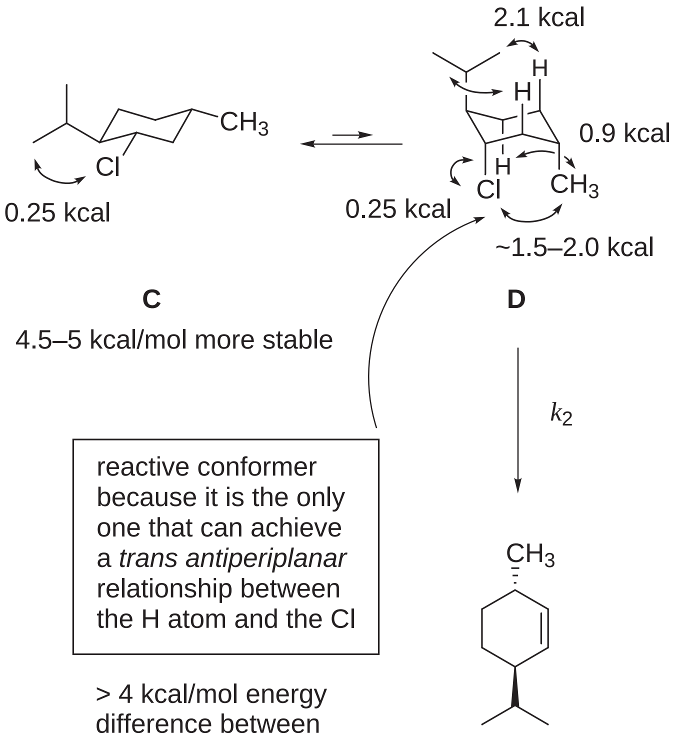
Look at all conformations of each:



A ΔE= ~3.4 kcal/mol **B**

>99 :1 ratio for **A** : **B**

78 : 22



C **D**

4.5–5 kcal/mol more stable

reactive conformer because it is the only one that can achieve a *trans antiperiplanar* relationship between the H atom and the Cl

> 4 kcal/mol energy difference between ground state conformation and the reactive conformation

only product !

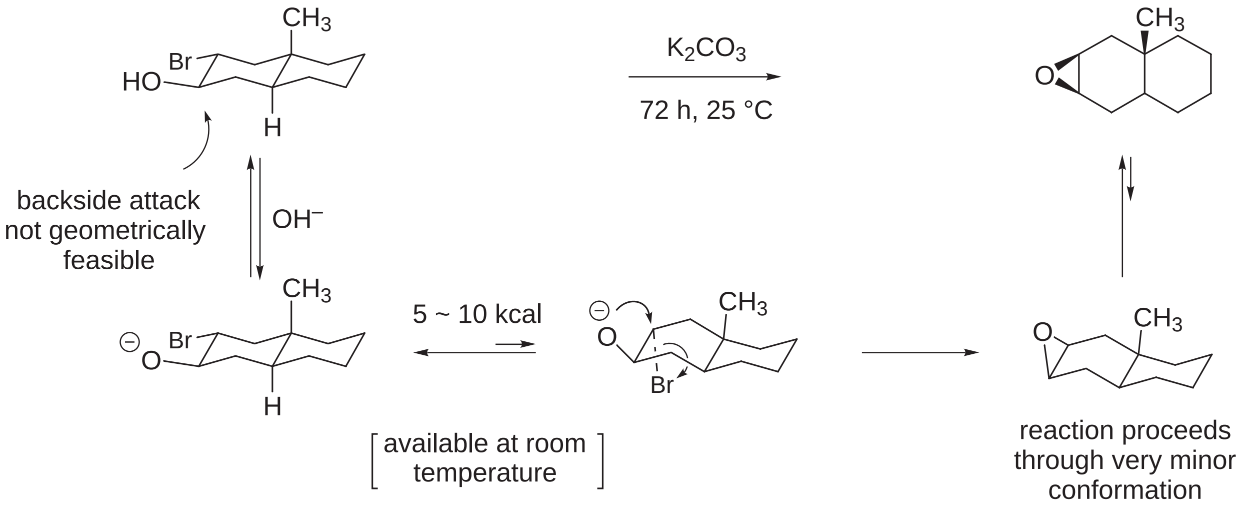
The reaction of the neomenthyl chloride is much faster (k_1/k_2 = 193:1)

From **D** (menthyl chloride) – only one product is possible

Curtin–Hammett principle :	Ground state conformation need not be decisive in determining product of a reaction.

E. Epoxidation by Intramolecular Closure of Halohydrins

– Must involve backside displacement → geomerical constraints !



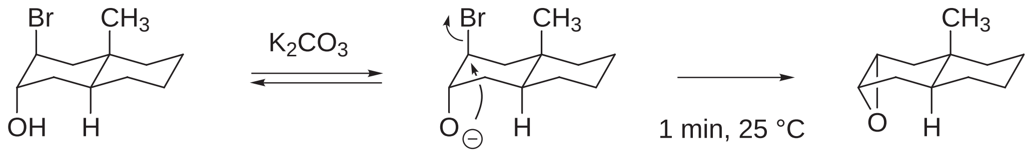
backside attack not geometrically feasible

[available at room temperature]

reaction proceeds through very minor conformation

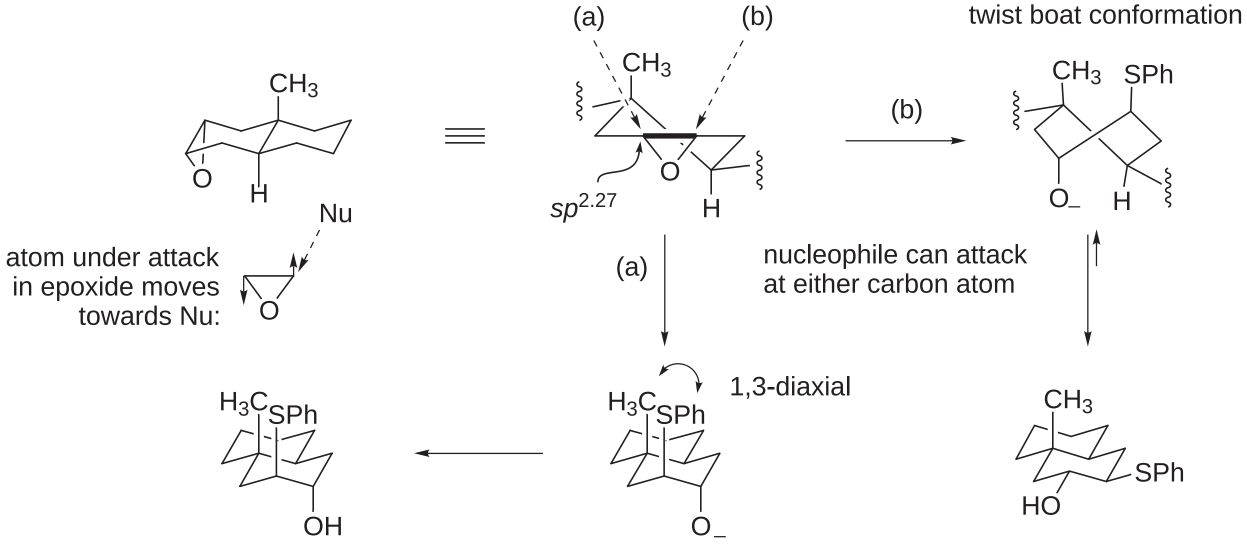
Again, ground state conformation of reactant is not a determinant in reaction product (Curtin–Hammett principle).

– Another example:



reaction much faster and proceeds from a ground state conformation

F. Epoxide Openings (S_N2)



atom under attack in epoxide moves towards Nu:

nucleophile can attack at either carbon atom

less stable product

chair conformation

more stable product

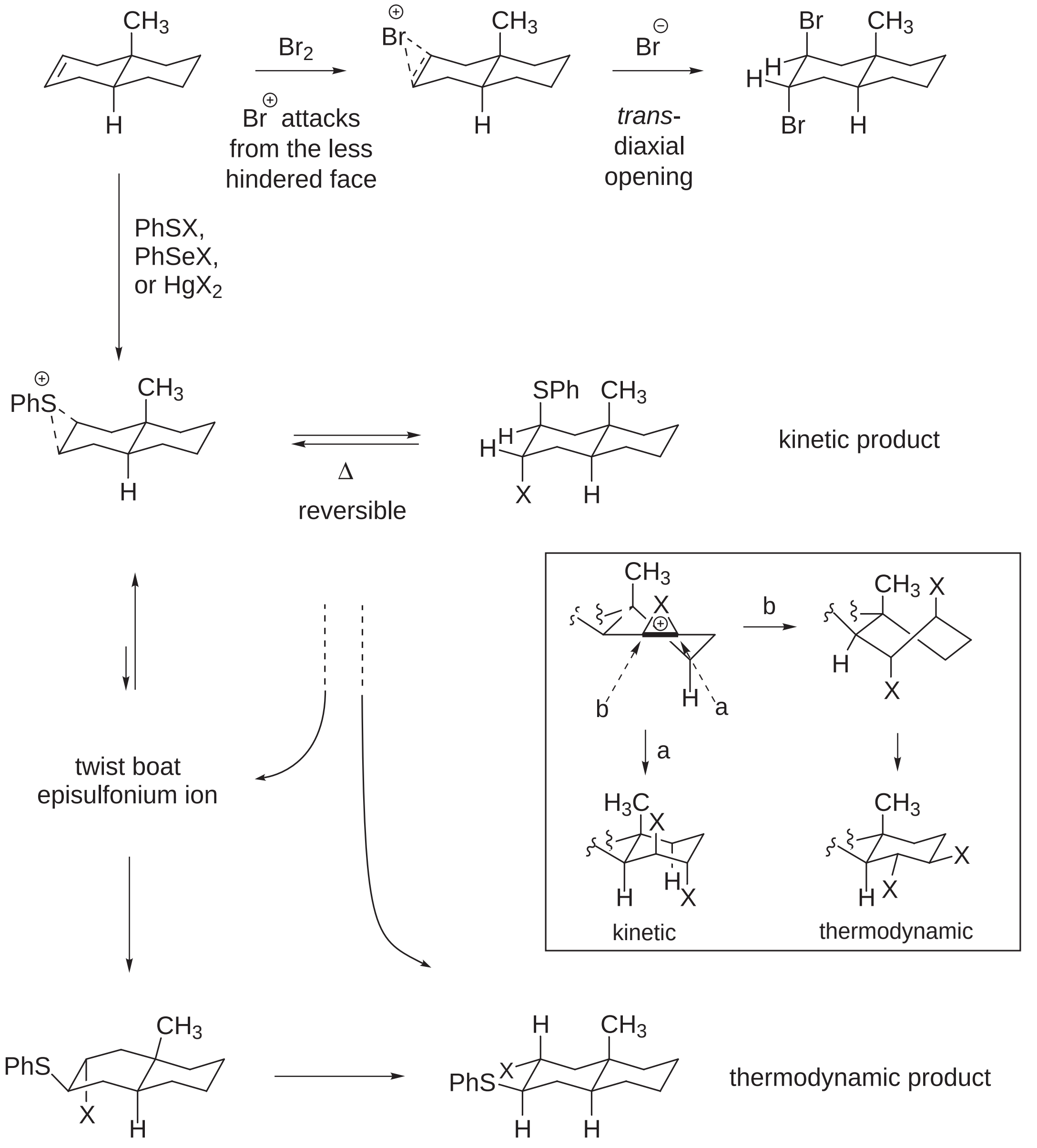
This is the only product formed!

⟹ Product ratio dependent on E_a (i.e., relative energy of two T.S.), route (a) proceeding through chair conformation and destabilizing 1,3-diaxial interaction is of lower energy than route (b) proceeding through twist boat T.S.

- Conformational effects determine regioselectivity

G. Electrophilic Additions to Olefins

Follows same principles

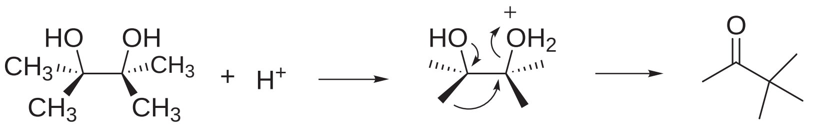


- Conformational effects control regioselectivity and stereochemistry

  But, it is not always possible to obtain the thermodynamic product
  ⇒ must have the 20–30 kcal/mol of energy required and a mechanism to reverse the reaction.

H. Rearrangement Reactions

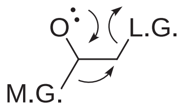
pinacol → pinacolone rearrangement



pinacolone

– Prototype of rearrangement:

heteroatom:



leaving group

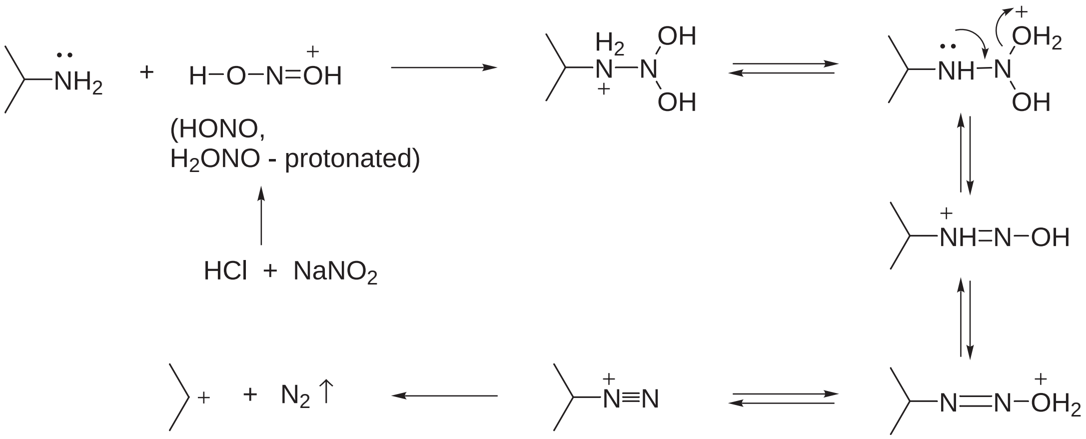
$-OH_2^+$

$-OSO_2R$

$-N_2^+$ diazonium ion

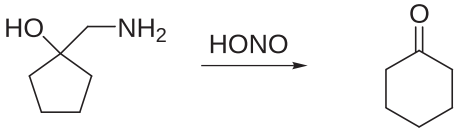
This process is conformationally dependent!

migrating group



Tiffeneau–Demjanov Reaction

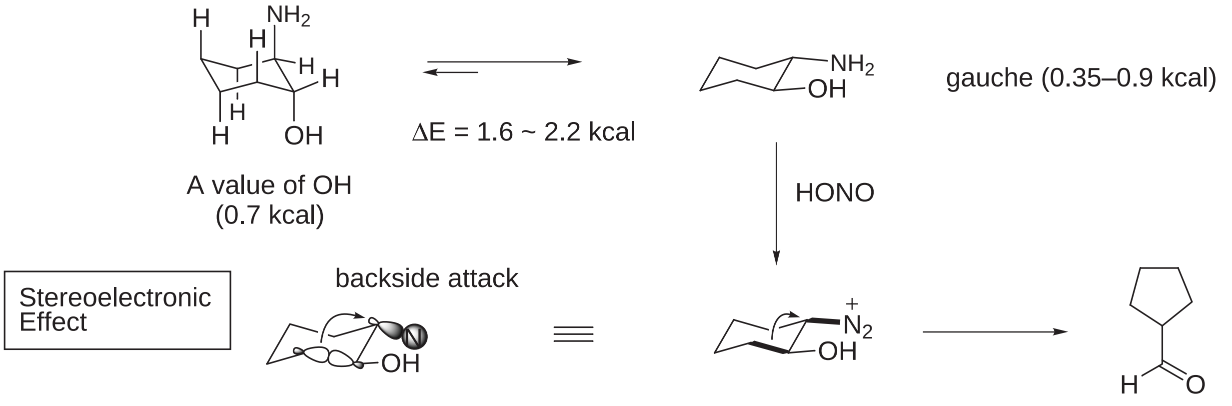
Ring expansion of cyclic β-amino alcohols



Tiffeneau *Compt. rend.* **1937**, *205*, 54.
review: *Org. React.* **1960**, *11*,157.

The course of rearrangement is conformationally dependent:

A value of NH_2/NH_3^+ (1.8–1.4 kcal)



gauche (0.35–0.9 kcal)

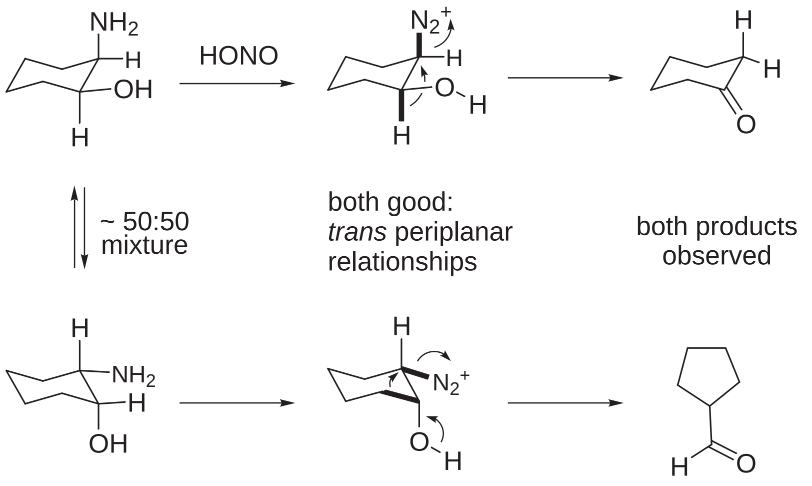
A value of OH
(0.7 kcal)

trans periplanar arrangement

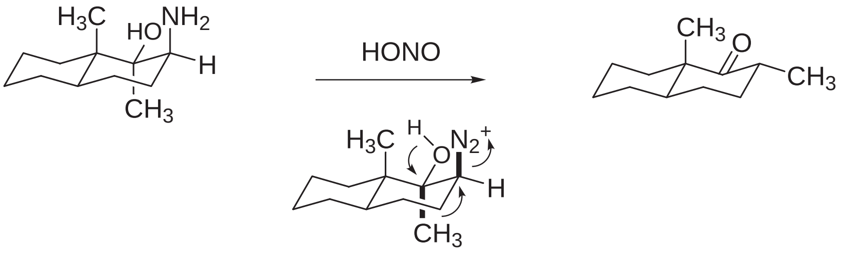
only product observed

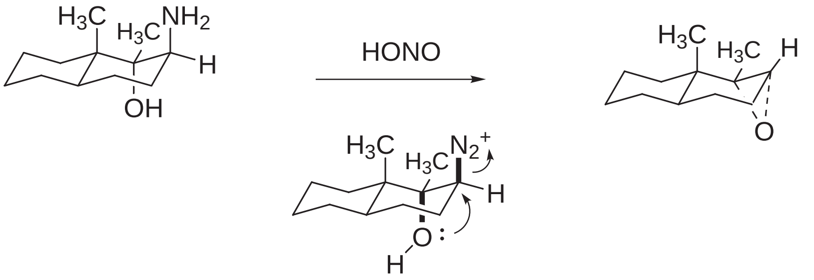
Compare to:

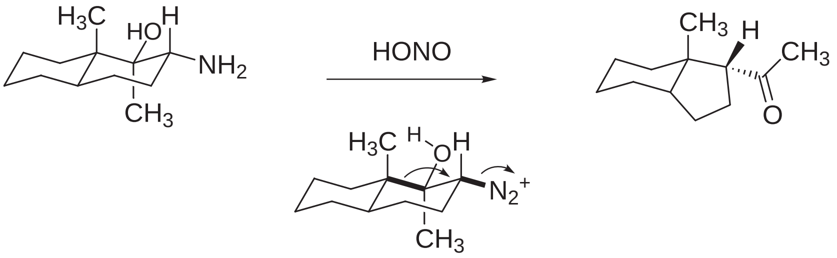
Stereoelectronic effects dominate the control of regioselectivity

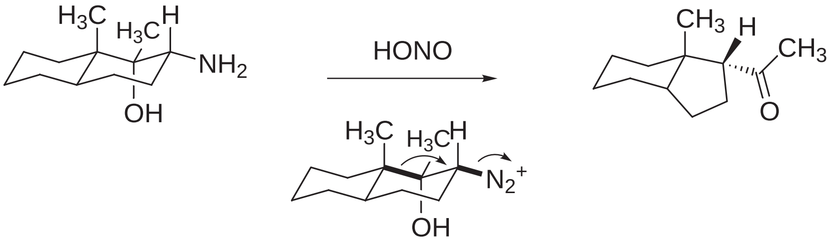


Explain the following results:

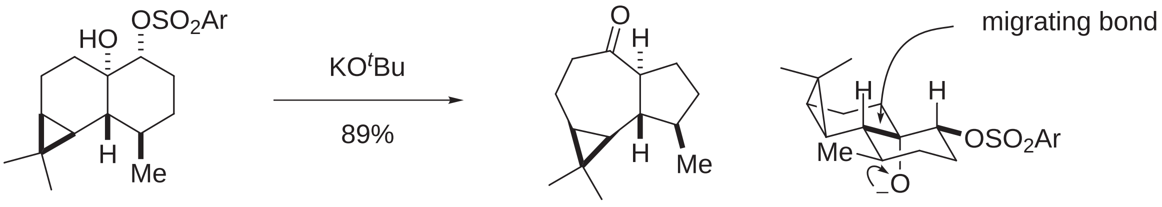




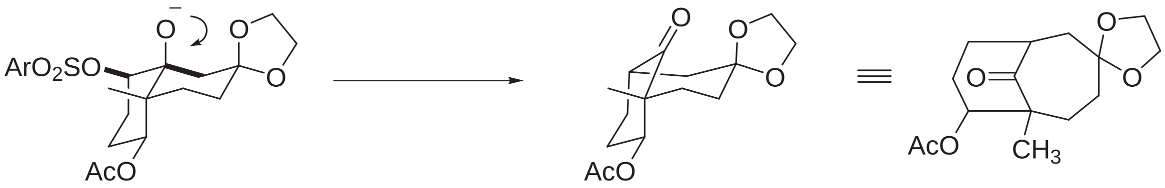




- Additional examples



Büchi *J. Am. Chem. Soc.* **1966**, *88*, 4113.



Heathcock *J. Am. Chem. Soc.* **1982**, *104,* 1907.

I. Pericyclic Reactions

1. Conservation of Orbital Symmetry, FMO Analysis

- Concerted reactions where there is a single transition state and no intermediates proceed through cyclic transition states.
- Cyclic transition state corresponds to an allowed arrangement of participating orbitals that can maintain a bonding interaction between the reaction components throughout the course of the reaction. This dictates features of relative reactivity, regioselectivity, and diastereoselectivity.
- This also established and formalized the viability of utilizing Frontier Molecular Orbitals (FMO) composed of the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) to analyze pericyclic reactions.

Woodward, Hoffmann *The Conservation of Orbital Symmetry,* Academic: New York, 1970.
J. Am. Chem. Soc. **1965**, *87*, 395.

Fukui *Acc. Chem. Res.* **1971**, *4*, 57; *Angew. Chem., Int. Ed. Eng.* **1982**, *21*, 801.

Encouraged by E. J. Corey, Hoffmann began examining mechanistic problems in organic chemistry and, as a junior fellow at Harvard, entered into a collaboration with R. B. Woodward that combined his insights in MO theory with Woodward's knowledge of experimental pericyclic reactions. This led to five papers in 1965 before he was 30 years old, that were the foundation of what we now refer to as the **Woodward–Hoffmann rules**.

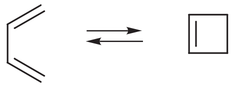
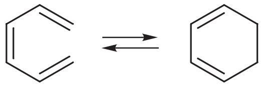
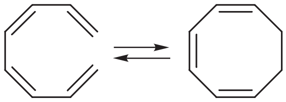
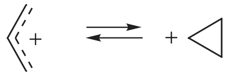
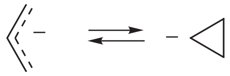
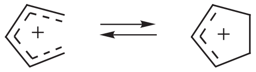
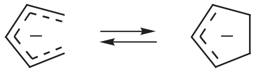
R. Hoffmann received the 1981 Nobel Prize in Chemistry for the launch and development of the concept of orbital symmetry conservation.

K. Fukui received the 1981 Nobel Prize in Chemistry for his Frontier Orbital theory of chemical reactivity.

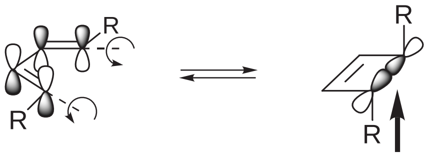
This followed and was not included in the 1965 Nobel Prize in Chemistry awarded to R. B. Woodward for his contributions to the "art of organic synthesis".

2. Electrocyclic Reactions

- This is composed of a series of reactions in which a ring closure occurs with formation of a single bond at the ends of a linear, conjugated system of π electrons and the corresponding reverse reaction with ring opening.

System	π electrons	Thermal Reaction Ground State (HOMO)	hν Reaction Excited State (LUMO)
	$4\ \pi\ e^-$	conrotatory	disrotatory
	$6\ \pi\ e^-$	disrotatory	conrotatory
	$8\ \pi\ e^-$	conrotatory	disrotatory
	$2\ \pi\ e^-$	disrotatory	conrotatory
	$4\ \pi\ e^-$	conrotatory	disrotatory
	$4\ \pi\ e^-$	conrotatory	disrotatory
	$6\ \pi\ e^-$	disrotatory	conrotatory

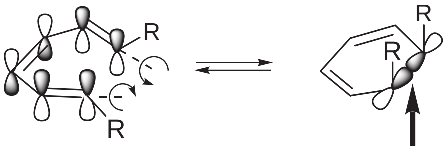
$4\ \pi\ e^-$ thermal reaction (ground state, HOMO)



conrotatory movement ⟶ bonding interaction

- Stereochemistry dictated by orbital symmetry allowed reaction course

$6\ \pi\ e^-$ thermal reaction (ground state, HOMO)



disroratory movement ⟶ bonding interaction

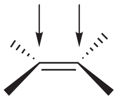
- Generalization:

No. of π electrons	Thermal	hν
4n π electrons (n = 0,1,...)	conrotatory	disrotatory
4n + 2 π electrons (n = 0,1,...)	disrotatory	conrotatory

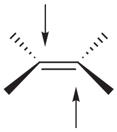
3. Cycloadditions and Cycloreversions

- These are discussed in terms of suprafacial or antarafacial addition to the ends of a π system.

Suprafacial



Antarafacial



- Generalization:

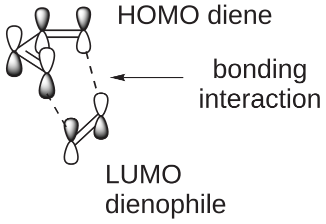
Total π electrons	Allowed in Ground State	Allowed in Excited State
4n	$m_s + n_a$	$m_s + n_s$
	$m_a + n_s$	$m_a + n_a$
4n + 2	$m_s + n_s$	$m_s + n_a$
	$m_a + n_a$	$m_a + n_s$

- Notations

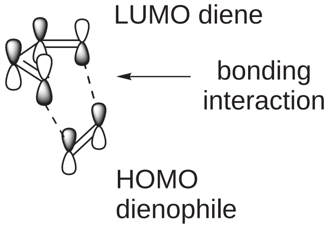
$$\underset{\pi,\ \sigma,\ \omega}{\text{orbital type}} \Rightarrow \underset{\substack{\Uparrow \\ \text{number of } e^-}}{\pi 2_s} \Leftarrow \begin{array}{l}\text{suprafacial (s) or}\\ \text{antarafacial (a)}\end{array}$$

- Diels-Alder Reaction (6π e^-), Ground State Thermal Reaction

Normal Diels–Alder Reaction



Inverse Electron Demand Diels–Alder Reaction

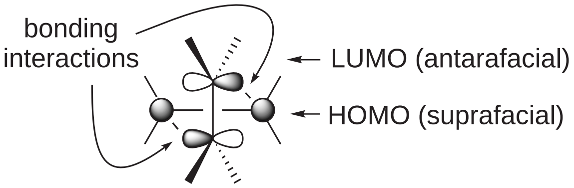


[$\pi 4_s + \pi 2_s$] cycloaddition

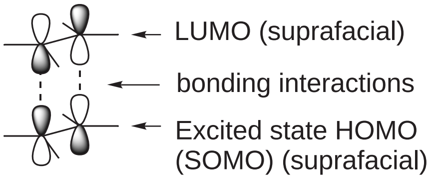
- Suprafacial with respect to both reacting components and this defines the orientatio with which the two reactants approach: boat transition state.
- The FMO analysis may also be used to predict relative rates, regioselectivity, and diastereoselectivity (*endo* effect) and we will discuss this in detail along with the Diels–Alder reaction.

- [2 + 2] Cycloaddition (4π e^-)

Ground State (thermal)



Excited State (hν)



[$\pi 2_a + \pi 2_s$] cycloaddition

- Antarafacial with respect to one olefin and suprafacial with respect to the second, dicates perpendicular approach to permit bonding.

[$\pi 2_s + \pi 2_s$] cycloaddition

- Suprafacial with respect to both olefins.

4. Sigmatropic Rearrangements

- Class of reactions characterized by migration of an allylic group from one end of a π system to the other.
- Generalization:

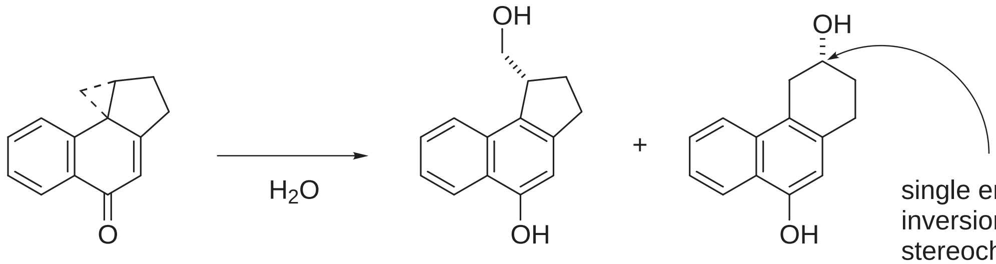
Total π electrons	Ground State	Excited State
4n	antara - supra supra - antara	antara - antara supra - supra
4n + 2	supra - supra antara - antara	antara - supra supra - antara

- These include a wide range of rearrangements including [1,3]-, [1,5]-, [1,7]-, [3,3]-, and [2,3]-sigmatropic reactions which we will discuss in detail.

J. Subtle Conformational and Stereoelectronic Effects on Reactivity and Reaction Regioselectivity

1. Kinetics, Stereochemistry, and Reaction Mechanisms

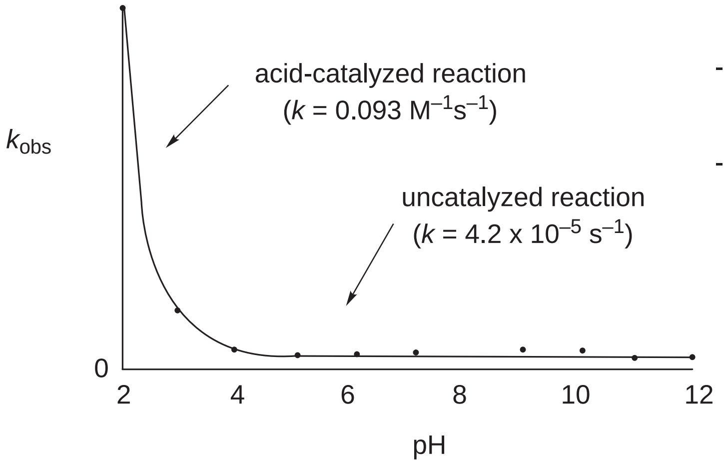
- Two of the cornerstones of defining a mechanism rest with the establishment of the stereochemistry of the reaction in conjunction with kinetic studies of the reaction.
- For example, for a reaction that might entail acid or base catalysis, it is common to examine the pH rate profile.



optically active

1 : 15

single enantiomer with clean inversion of absolute stereochemistry, therefore S_N2, not S_N1, ring opening.



acid-catalyzed reaction ($k = 0.093\ M^{-1}s^{-1}$)

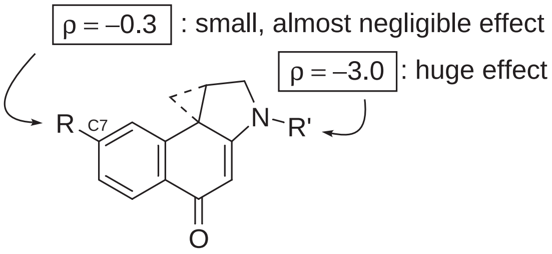
uncatalyzed reaction ($k = 4.2 \times 10^{-5}\ s^{-1}$)

- Below pH 4, H^+ catalyzed reaction dominates.
- Above pH 4 (pH 4–12), the uncatalyzed direct S_N2 addition reaction dominates.

Boger *J. Org. Chem.* **1998**, *63*, 8004; *J. Org. Chem.* **1999**, *64*, 5666.

2. Substituent Effects

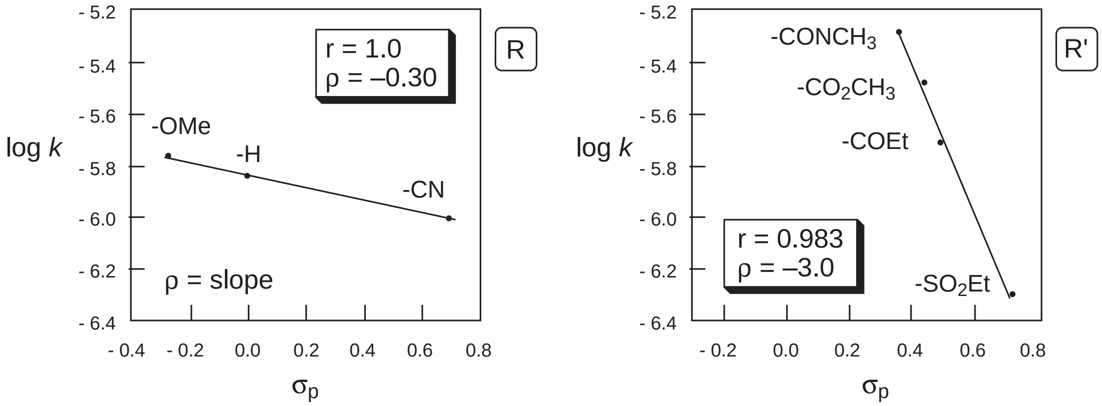
- These can be quantitated using a Hammett treatment and can provide insights into reaction mechanisms.



- C7 substituents (R) have little effect on reactivity
- N substituent (R') has a pronounced effect on reactivity and even subtle perturbations will change reactivity greatly (-$SO_2R \rightarrow$ -CO_2R, 10 ×)

ρ values are characterized in a log scale

- The negative ρ value indicates δ^+ charge buildup in the rate-determining step of the reaction.



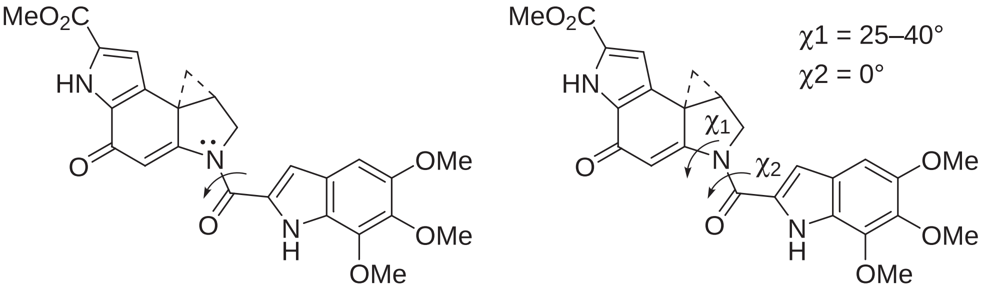
Boger *J. Am. Chem. Soc.* **1994**, *116*, 5523.
J. Org. Chem. **1996**, *61*, 1710 and 4894.

3. Structure versus Reactivity and Reaction Regioselectivity

- Structure can have a pronounced effect on reactivity and reaction regioselectivity.

One nice example of this can be illustrated with a series of analogues related to CC-1065 and the duocarmycins which are potent antitumor antibiotics that derive their biological properties from a sequence-selective DNA alkylation reaction. The reactivity changes that one sees as a consequence of the loss of the vinylogous amide stabilization are related to the source of DNA alkylation catalysis.

Binding-induced conformational change: shape-selective catalysis



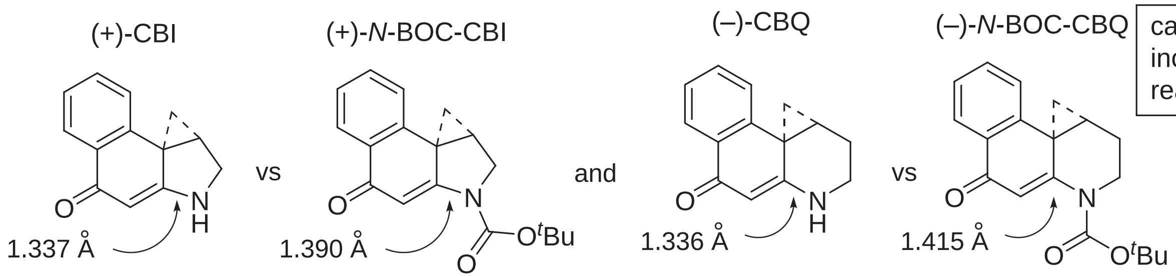
Alexander R. Todd received the 1957 Nobel Prize in Chemistry for his work on the synthesis of nucleotides and nucleotide coenzymes.

Francis Crick and James Watson shared the 1962 Nobel Prize in Physiology and Medicine for their elucidation of the structure of DNA.

- DNA bound agent adopts helical conformation, twist adjusted at linking amide.
  - DNA bound agent maintains full amide. (χ2 = 0°)
  - Vinylogous amide stabilization diminished. (χ1 = 25–40°)
  - Cyclohexadienone structure destabilized.
- **Shape-dependent catalysis**: Preferential activation in AT-rich minor groove. Binding induced twist greatest in the narrower, deeper AT-rich minor groove.
- **Shape-selective recognition**: Preferential binding in AT-rich minor groove.

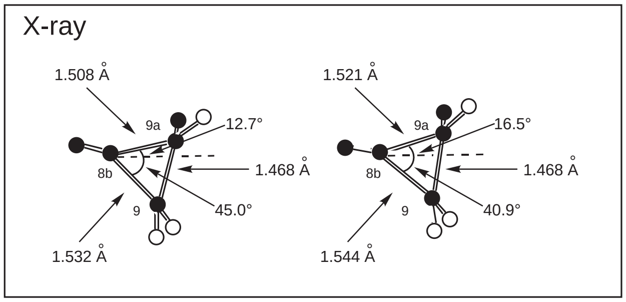
Boger *J. Am. Chem. Soc.* **1997**, *119*, 4977 and 4987.
Boger, Garbaccio *Bioorg. Med. Chem.* **1997**, *5*, 263.
Acc. Chem. Res. **1999**, *32*, 1043.

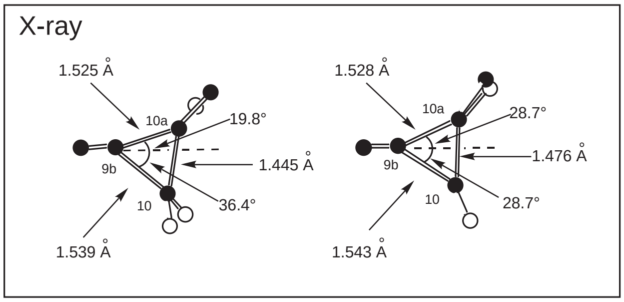
- *N*-Acylation and its effect on vinylogous amide and cyclopropane conjugation.



ca. 10–50 × increase in reactivity

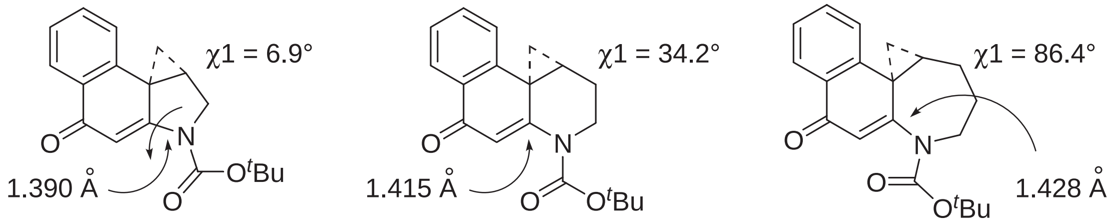
$t_{1/2}$ = 920 h (pH 3)	$t_{1/2}$ = 133 h (pH 3)	$t_{1/2}$ = 91 h (pH 3)	$t_{1/2}$ = 2.1 h (pH 3)
		$t_{1/2}$ = stable (pH 7)	$t_{1/2}$ = 544 h (pH 7)





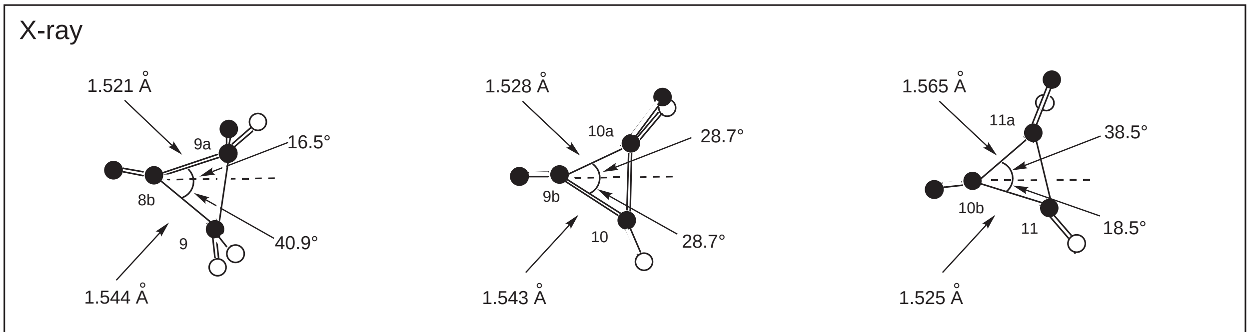
- *N*-acylation decreases the cross-conjugated vinylogous amide conjugation, increases the cyclopropane conjugation and bond lengths, and increases cyclopropane reactiviity. This can be observed in the corresponding X-ray crystal structures.

- Amide twist effect on the vinylogous amide and cyclopropane conjugation.



H$^+$ catalyzed reaction →	$t_{1/2}$ = 133 h (pH 3)	$t_{1/2}$ = 2.1 h (pH 3)	$t_{1/2}$ = 0.03 h (pH 3)
Uncatalyzed → reaction and rates	$t_{1/2}$ = stable (pH 7)	$t_{1/2}$ = 544 h (pH 7)	$t_{1/2}$ = 2.1 h (pH 7)
	- Decreases vinylogous amide cross-conjugation	- Increases cyclopropane conjugation (bond lengths)	- Increases cyclopropane reactivity

10^4 × increase in reactivity



regioselectivity: > 20 : 1 3 : 2 < 1 : 20

- Note the change in solvolysis regioselectivity where the stereoelectronically aligned cyclopropane bond is the bond which is cleaved. The stereoelectronically aligned bond is that which is positioned to best overlap with the developing π-system of the product phenol.

- In each case, the ring expansion occurred with generation of a single enantiomer by a S_N2 mechanism.

complete reversal of reaction regioselectivity

Boger *J. Org. Chem.* **1997**, *62*, 5849; *J. Am. Chem. Soc.* **1997**, *119*, 4977.

K. Methods for the Synthesis of Optically Active Materials

Morrison *Asymmetric Synthesis*, Academic: New York, 1983; Vol. 1–5.

Note: A summary of approaches which will be highlighted throughout the following material.

1. Partial Synthesis

- From readily available, naturally-derived optically active materials, examples include

a. Progesterone from sapogenin diosgenin.

b. Synthetic penicillins from the fermentation product 6-aminopenicillanic acid (6-APA).

c. Vitamin D_3 (1-hydroxycholecalciferol) from cholesterol.

Louis Pasteur (1822–1895) conducted the first separation of a racemate into its enantiomers (by hand!) and by fractional crystallization. Thus, he conducted the first diastereomeric resolution (tartaric acid + quinine). His investigations into the process of fermentation led to the development of microbiology and the important method of preserving foods known as pasteurization. His research into immunity led to preventative vaccinations using weakened strains of bacteria. He developed the first vaccines for rabies.

2. Resolution

a. Diastereomeric salts and selective crystallization.

b. Diastereomeric derivatization and chromatography or selective crystallization.

c. Direct chromatographic resolution of enantiomers on an optically active stationary support.

d. Enzymatic resolution.

e. Kinetic resolution with selective production of desired enantiomer or selective consumption of undesired enantiomer.

Advantage:	Both enantiomers are made available.
Disadvantage:	1/2 of the material is wasted if only one enantiomer is desired. Ambiguous assignment of absolute configuration.

See: Jacques, Collet, Wilen *Enantiomers, Racemates, and Resolutions*, Wiley: New York, 1981.

A. J. P. Martin and B. L. M. Synge shared the 1952 Nobel Prize in Chemistry for developing the technique of liquid–liquid partition chromatography. Their collaboration also led to the invention of gas–liquid partition chromatography (GLC). The use of chromatography can be traced back to a Russian botanist, M. Tswett, who separated plant pigments by such methods in 1906. Martin and Synge pioneered the rapid progress in this area made in the 1940's and early 1950's.

3. Synthesis from Chiral Pool

- Readily available, abundant or naturally occurring starting materials.

a. Carbohydrates

b. Amino acids

c. α-Hydroxy carboxylic acids

d. Terpenes

e. Readily available, abundant natural products

O. Wallach, a colleague and collaborator of A. Kekule, received the 1910 Nobel Prize in Chemistry for his work on essential oils that converted the field of natural products from a disorganized collection of confusing observations into a complete, organized and integrated field. He established the isoprene rule.

4. Asymmetric Synthesis

a. Optically active reagent (Stoichiometric)
b. Optically active auxiliary incorporated into substrate (Stoichiometric)
c. Optically active catalyst (Catalytic)

See: Koskinen *Asymmetric Synthesis of Natural Products*; Wiley: New York, 1993.
Gawley, Aube *Principles of Asymmetric Synthesis*; Elsevier: Amsterdam, 1996.

5. Microbial, Enzymatic, or Catalytic Antibody Transformation

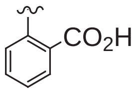
See: Wong, Whitesides *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994.

IV. Oxidation Reactions

A. Epoxidation Reactions: Oxidation of Carbon–Carbon Double Bonds

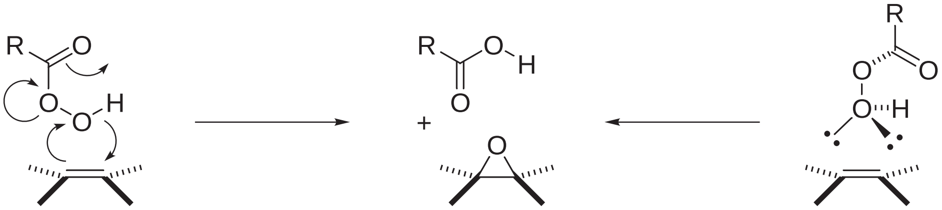
Comprehensive Org. Syn.; Vol. 1, 819; Vol. 7, pp. 357 and 389 (asymmetric).
First report: Prilezhaev *Ber.* **1909**, *42*, 4811.

1. Peracid Reactivity

Rate increases: R =	CH_3	<	C_6H_5	<	*m*-ClC_6H_4	<	H	<	*p*-$NO_2C_6H_4$	<		<	CF_3
pK_a of acid (RCO_2H):	4.8		4.2		3.9		3.8		3.4		2.9		0

The lower the pK_a, the greater the reactivity (i.e., the better the leaving group).

2. Mechanism



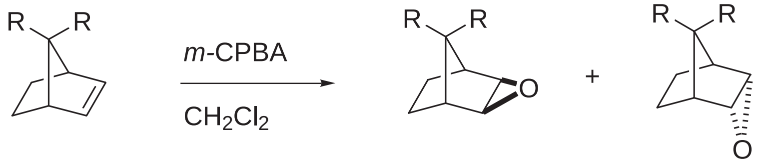
Butterfly mechanism
(usual representation)
Bartlett *Rec. Chem. Prog.* **1950**, *11*, 47.

Refined representation:
trans antiperiplanar arrangement of O–O bond and reacting alkene, n-π^* stabilization by reacting lone pair in plane.

The synchronicity of epoxide C–O bond formation and an overall transition state structure postulated using *ab initio* calculations and experimental kinetic isotope effects.
Singleton, Houk *J. Am. Chem. Soc.* **1997**, *119*, 3385.

3. Stereochemistry

a. Stereochemistry of olefin is maintained: diastereospecific.
b. Reaction rate is insensitive to solvent polarity implying concerted mechanism without intermediacy of ionic intermediates.
c. Less hindered face of olefin is epoxidized.

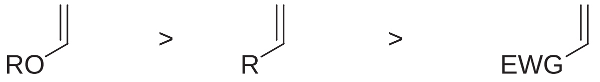


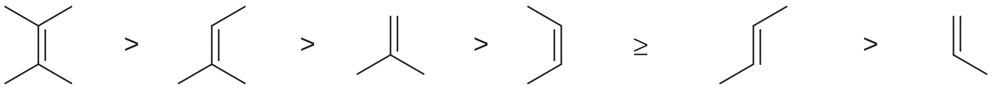
R = H	20 min, 25 °C	99%	1%
R = CH_3	24 h, 25 °C	< 10%	90%

Brown *J. Am. Chem. Soc.* **1970**, *92*, 6914.

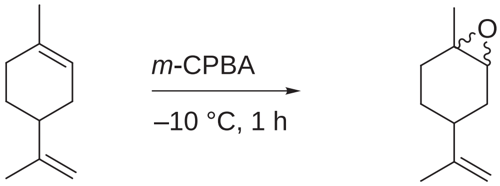
4. Chemoselectivity

– Electrophilic reagent: most nucleophilic C=C reacts fastest.

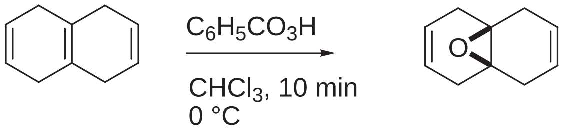




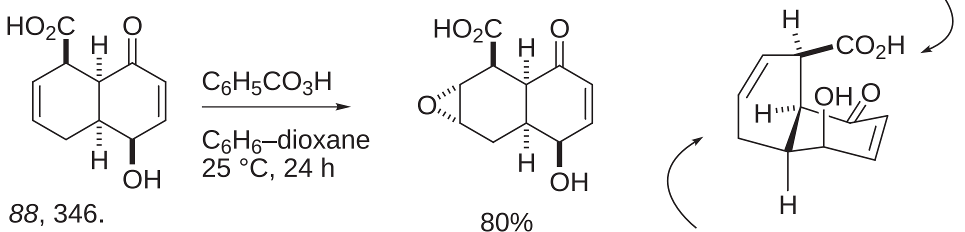
- Examples



cis : *trans* 1 : 1



Concave face hindered toward peracid attack



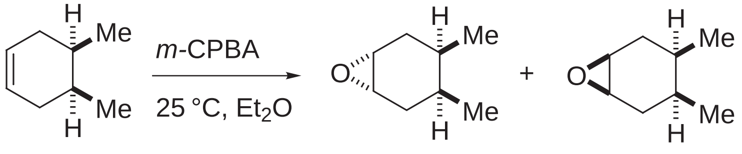
Convex face open to peracid attack

Hückel *Chem. Ber.* **1955**, *88*, 346.
Woodward *Tetrahedron* **1958**, *2*, 1.
Tamm *Helv. Chim. Acta* **1975**, *58*, 1162.

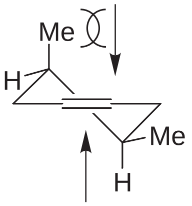
5. Diastereoselectivity

a. Endocyclic Olefins Rickborn *J. Org. Chem.* **1965**, *30*, 2212.

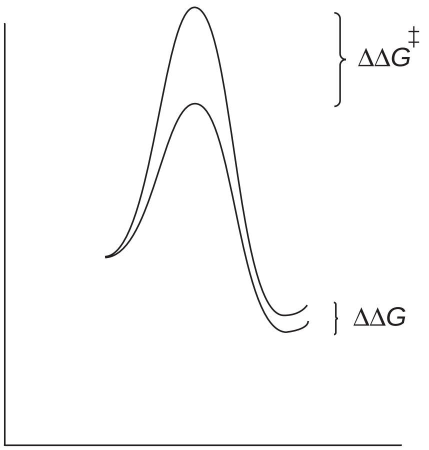
Destabilizing steric interaction between reagent and axial Me

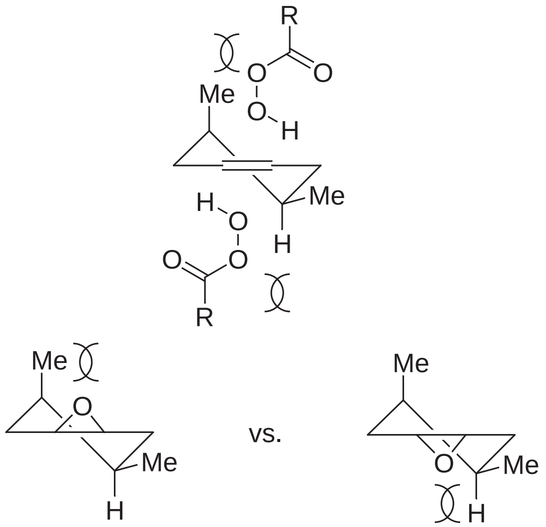


87 : 13



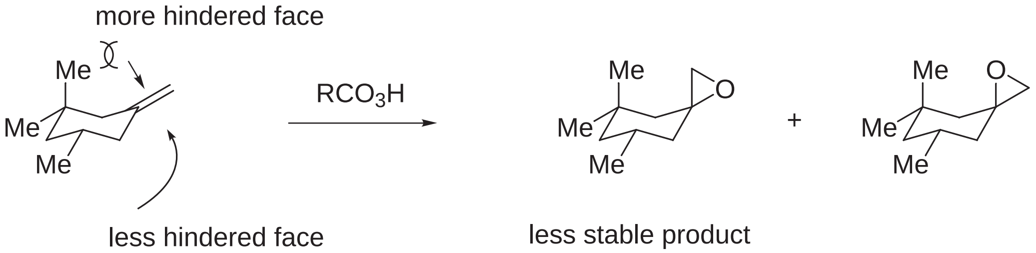
Attack principally from this face





Small difference for products: but larger difference for reagent approach in transition state.

b. Exocyclic Olefins

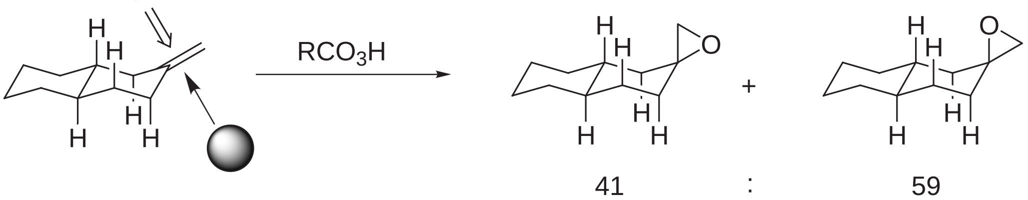


– Solvent dependent			
	CCl_4	75%	25%
	C_6H_6	80%	20%
	CH_2Cl_2 or $CHCl_3$	83%	17%

Henbest *J. Chem. Soc., Chem. Commun.* **1967**, 1085.

– The effective size of the reagent increases with increasing solvent polarity, i.e., the solvation shell of the reagent increases in size.

– Small reagent preference: axial attack and 1,3-diaxial interactions vary with size of the reagent.

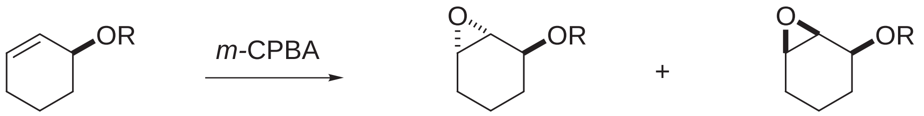


– Large reagent preference: equatorial attack and 1,2-interactions (torsional strain) are relatively invariant with the size of the reagent.

Carlson *J. Org. Chem.* **1967**, *32*, 1363.

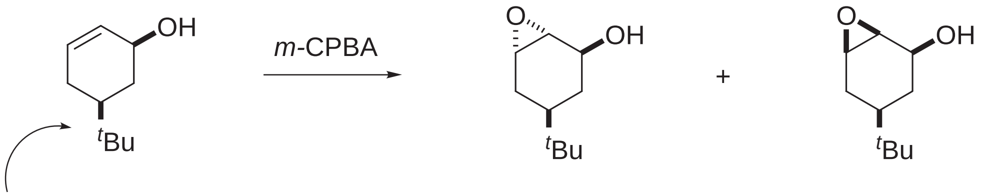
c. Allylic Alcohols (endocyclic)

Henbest *J. Chem. Soc.* **1957**, 1958; *Proc. Chem. Soc.* **1963**, 159.



R = $COCH_3$	20 °C	C_6H_6	43%	57%	38% yield
R = H	5 °C	C_6H_6	9%	91%	86% yield

– Diastereoselectivity and rate (*ca*. 10×) of reaction accelerated by unprotected allylic alcohol.

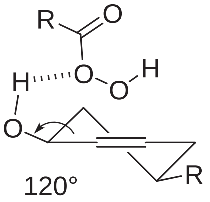


Prefers equatorial position, locking conformation of substrate

4% 96%

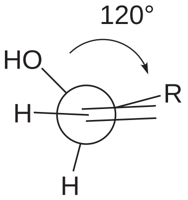
– Original proposal for the origin of selectivity:

H-bonding to proximal peroxide oxygen directs epoxidation to the same face as OH group and accelerates/facilitates the reaction.

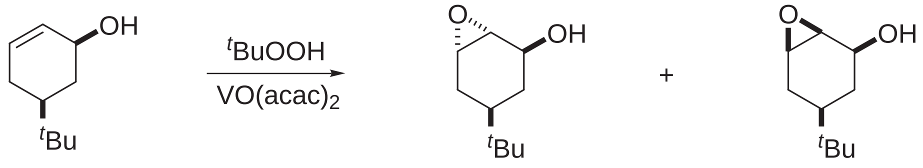


R = H, ^{t}Bu

– Equivalent to the ground state eclipsed conformation of acyclic allylic alcohols:



– Metal-catalyzed epoxidations of allylic alcohols exhibit a more powerful directing effect and rate acceleration (*ca.* 1000×). Metal bound substrate (as an alkoxide) delivers olefin to metal bound peroxide (tighter association than H-bonding).



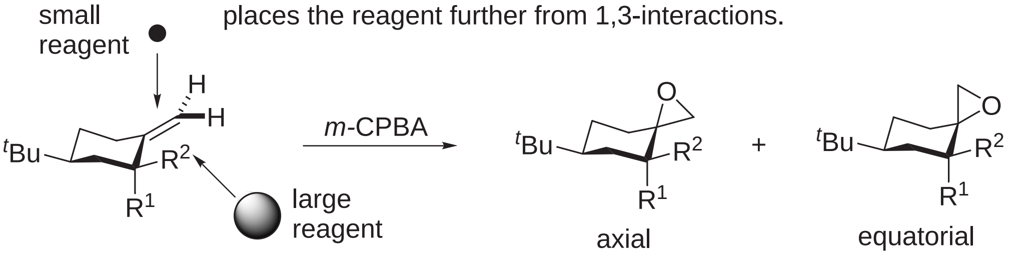
83% 0% 100%

Sharpless *Aldrichimica Acta* **1979**, *12*, 63.

– This may also be utilized to chemoselectively epoxidize an allylic alcohol vs. unactivated olefin.

d. Allylic Alcohols (exocyclic)

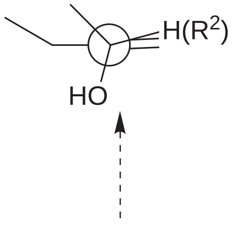
Early transition state and the asynchronous bond formation places the reagent further from 1,3-interactions.



R^1	R^2	axial		equatorial
H	H	69	:	31
H	OH	60	:	40
H	OCH_3	60	:	40
$\boxed{CH_3}$	OCH_3	88	:	12
H	OAc	75	:	25
OH	H	11	:	89
OH	CH_3	13	:	87
OCH_3	H	83	:	17
OCH_3	CH_3	83	:	17

Equatorial substitution

Axial substitution blocks equatorial reagent delivery

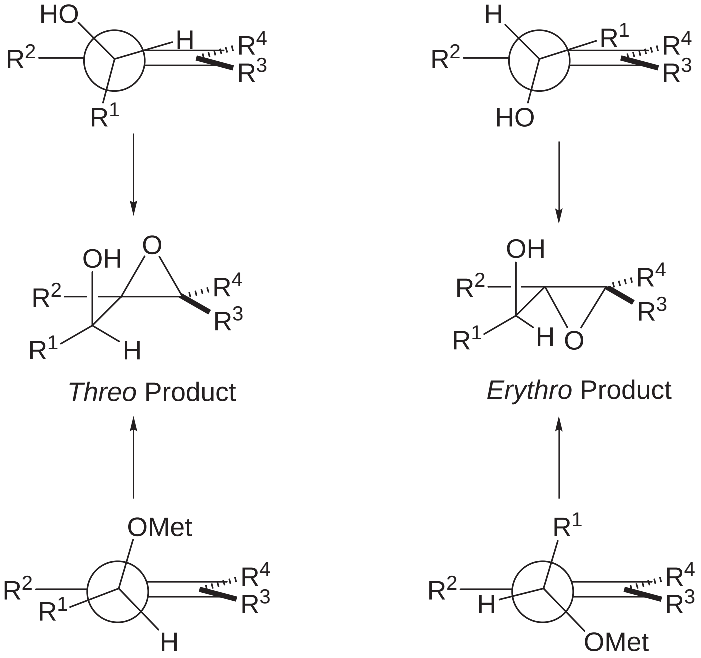


axial OH directs epoxidation to the syn-face of the exocyclic double bond

Vedejs and Dent *J. Am. Chem. Soc.* **1989**, *111*, 6861.

e. Acyclic Allylic Alcohols

Generalizations: Eclipsed Conformations in *m*-CPBA Epoxidation

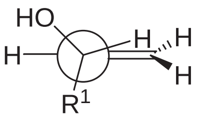


Bisected Conformations in Metal-Catalyzed Epoxidation

–Examples

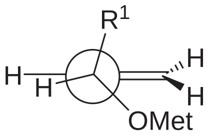
		threo	*erythro*
R^1 = Me	*m*-CPBA	60	40
	$\mathrm{VO(acac)_2}$, ^{t}BuOOH	20	80
= Et	*m*-CPBA	61	39
	$\mathrm{VO(acac)_2}$, ^{t}BuOOH	20	80
= ^{i}Pr	*m*-CPBA	58	42
	$\mathrm{VO(acac)_2}$, ^{t}BuOOH	15	85

H vs. alkyl eclipsing interaction with double bond has little to no effect on selectivity. H eclipsing interaction slightly more stable.

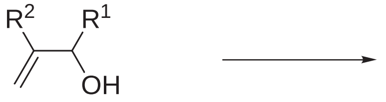


threo

H,H eclipsing in *erythro* T.S. favored over H,alkyl eclipsing in *threo* T.S.

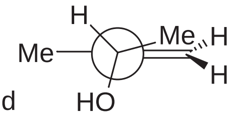


erythro



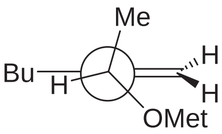
		threo	*erythro*
R^1,R^2 = Me	*m*-CPBA	45	55
	$\mathrm{VO(acac)_2}$, ^{t}BuOOH	5	95
R^1 = Me R^2 = ^{n}Bu	*m*-CPBA	41	59
	$\mathrm{VO(acac)_2}$, ^{t}BuOOH	2	98

Erythro slightly favored due to Me,Me gauche interaction in *threo* T.S.

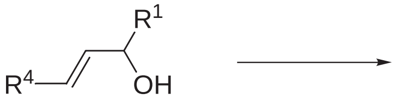


erythro

H,Bu eclipsing in *erythro* T.S. favored over Me,Bu eclipsing in *threo* T.S.

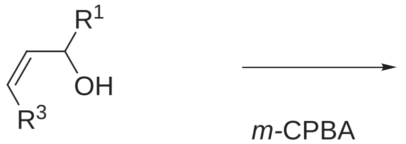


erythro



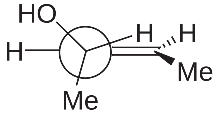
		threo	*erythro*
R^1,R^4 = Me	*m*-CPBA	64	36
	$\mathrm{VO(acac)_2}$, ^{t}BuOOH	29	71

Similar to R^4 = H. R^4 does not sterically influence either T.S. The R^1 steric effect predominates.

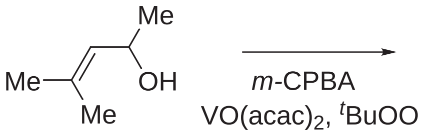


		threo	*erythro*
R^1,R^3 = Me	*m*-CPBA	95	5
	$\mathrm{VO(acac)_2}$, ^{t}BuOOH	71	29

Large 1,3-allylic strain avoided.

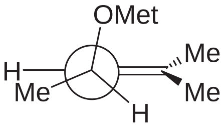


threo



		threo	*erythro*
	m-CPBA	95	5
	$\mathrm{VO(acac)_2}$, ^{t}BuOOH	86	14

Large 1,3-allylic strain avoided.

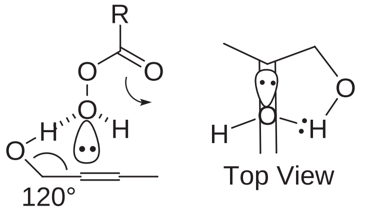


threo

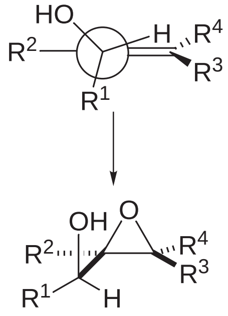
f. Refined Models for Directed Epoxidation of Acyclic Allylic Alcohols

– Peracid Mediated Epoxidation   Sharpless *Tetrahedron Lett*. **1979**, 4733.

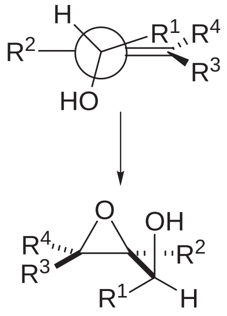
1. *Trans* antiperiplanar arrangement of O–O bond with alkene C=C.
2. H-bonding to distal oxygen of peroxide through the lone pair out of the plane of reaction.
3. Lone pair in plane of reaction provides π^*–lone pair (n-π^*) stabilization.
4. Secondary isotope effect suggests that the formation of the C–O bonds is asynchronous.



– Eclipsed Conformations in *m*-CPBA Epoxidation   Sharpless *Aldrichimica Acta* **1979**, *12*, 63.



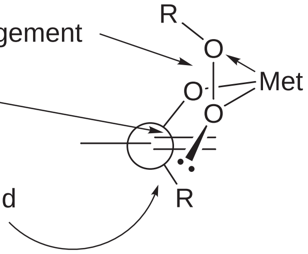
threo product

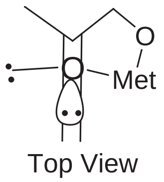


erythro product

– Transition-metal Catalyzed Epoxidation

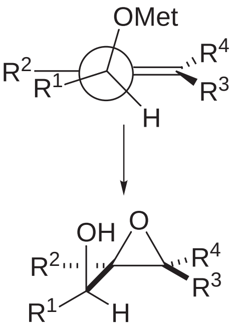
1. *Trans* antiperiplanar arrangement
2. 50° dihedral angle
3. In-plane lone pair
4. Lone pair bisects C=C bond



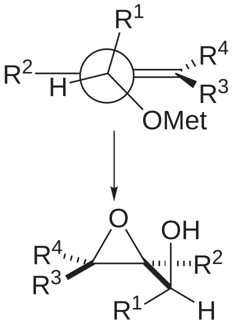


– Curtin-Hammett Principle:
  - The reactive conformation is not necessarily related to the ground state conformation.
  - The substrate is forced into a non-ground state conformation due to the geometrical constraints of the reaction.

– Bisected Conformations in Metal-Catalyzed Epoxidation



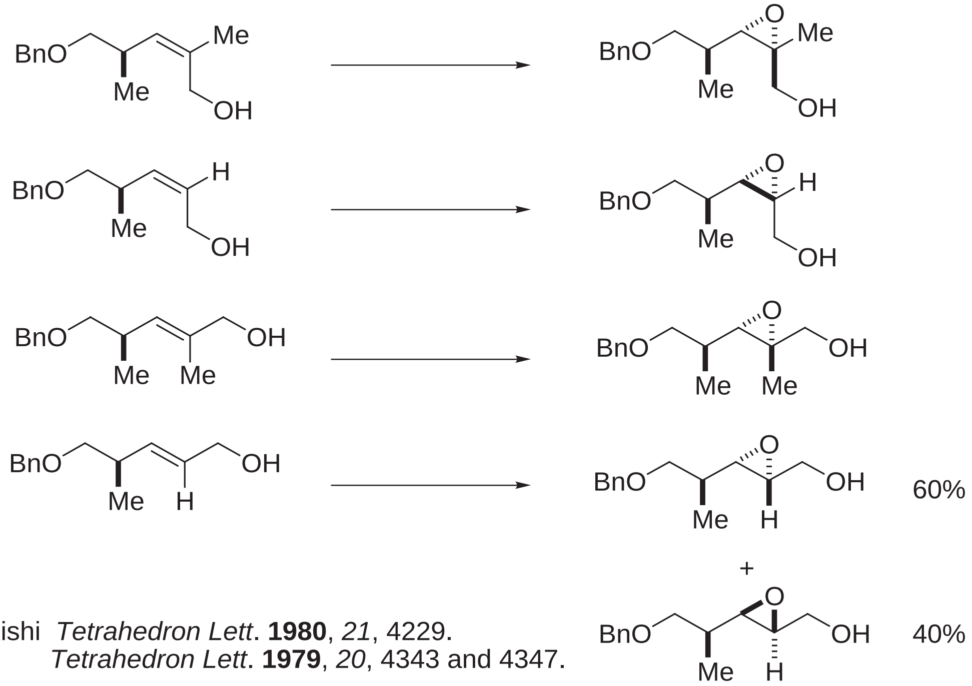
Threo Product



Erythro Product

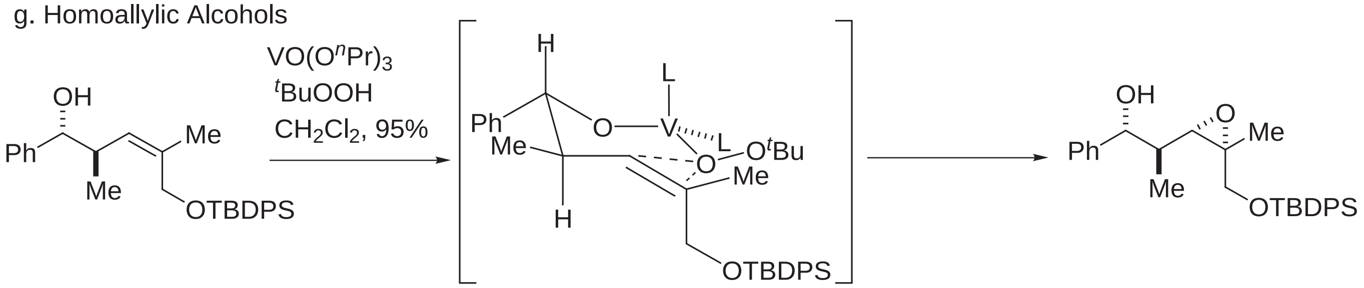
Take Home Problem

Epoxidations of 3 of the 4 olefins below are diastereoselective; the fourth is not. Why?



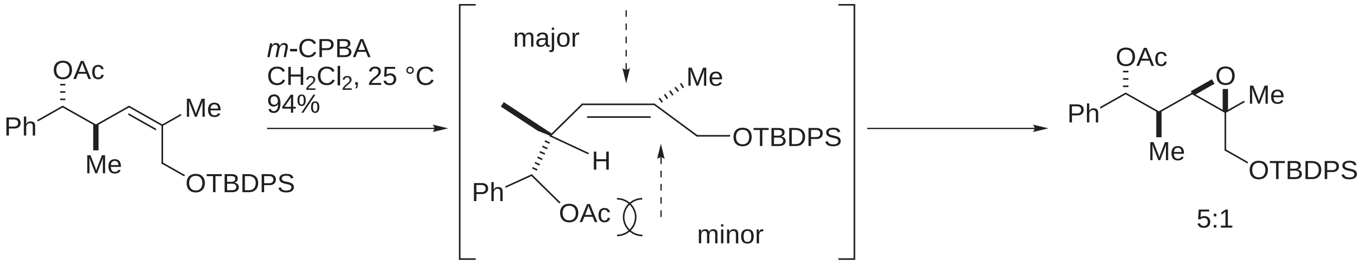
references: Kishi *Tetrahedron Lett*. **1980**, *21*, 4229.
Tetrahedron Lett. **1979**, *20*, 4343 and 4347.

g. Homoallylic Alcohols



- Alternative chair has two axial substituents.
- Intramolecular oxygen delivery occurs through most stable chair-like transition state.

VS.

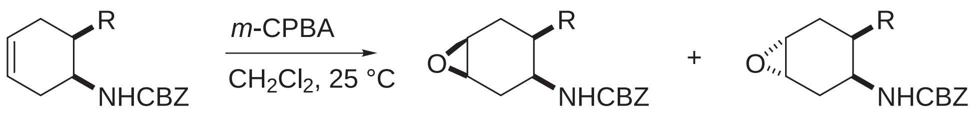


- H-Eclipsed conformation
- Epoxidation from least hindered face
- Not a directed epoxidation!
- Diastereoselectivity still good and through H-eclipsed conformation.

Schreiber *Tetrahedron Lett*. **1990**, *31*, 31.
Hanessian *J. Am. Chem. Soc.* **1990**, *112*, 5276.
Mihelich *J. Am. Chem. Soc.* **1981**, *103*, 7690.

h. Other Directed Epoxidations

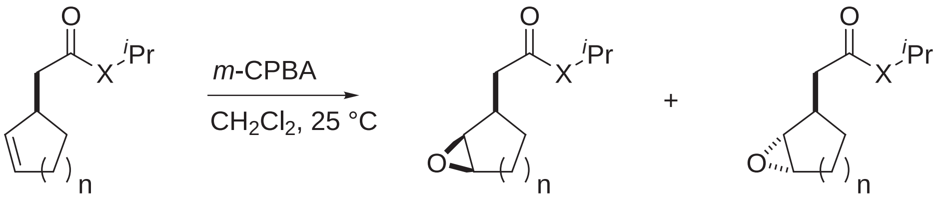
– Studies suggest axial -NHCBZ delivers syn epoxide while equatorial does not.



R = NHCBZ	86%	100	0
= CH_2OH	83%	100	0
= CH_2OAc	72%	100	0
= CO_2Me	59%	100	0
= CH_2NHCBZ	81%	100	0
= $CH_2OTBDMS$	54%	0	100

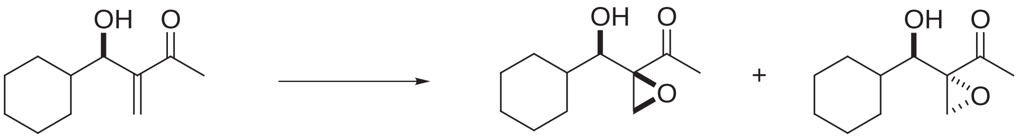
Presence of H-bonding, directing substituent enhances rate and yield of reaction.

Witiak *J. Med. Chem.* **1989**, *32*, 214.
Rotella *Tetrahedron Lett.* **1989**, *30*, 1913.



n = 1, X = NH	80%	20	1
X = O		3	1
n = 2, X = NH		20	1
X = O		3	1

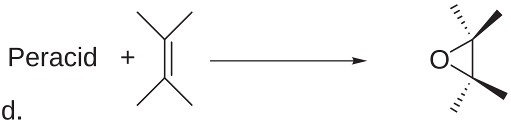
Mohamadi *Tetrahedron Lett*. **1989**, *30*, 1309.



H_2O_2 / NaOH / MeOH / 0 °C	40	:	60
Ti(^{i}PrO)$_4$ / ^{t}BuOOH / CH_2Cl_2 / –15 °C	>99	:	1

Ollis *Tetrahedron Lett*. **1991**, *32*, 2687.

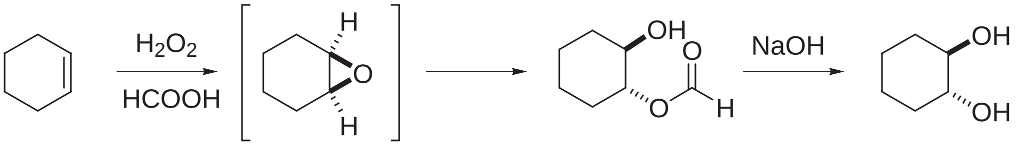
6. Scope and Limitations



a. Olefin geometry is maintained.

b. Reaction is **diastereospecific**: the stereochemistry of the reactant and product bear a definite relationship to one another.

c. Reaction can be buffered to prevent epoxide opening. The pK_a of parent acid is much lower than that of the peracid, and the peracid is not nearly as acidic. Reaction requires the protonated peracid so the buffer must not deprotonate the peracid but should deprotonate the product carboxylic acid.



Na_2CO_3 / $NaHCO_3$
CH_3COOH / NaOAc
CF_3CO_3H / Na_2HPO_4 – NaH_2PO_4

These reagents can be used as a buffer when the peracids are used as epoxidation reagents.

e.g.

HCOOH	pK_a 3.6	CH_3COOH	pK_a 4.8
HCO_3H	pK_a 7.1	CH_3CO_3H	pK_a 8.2

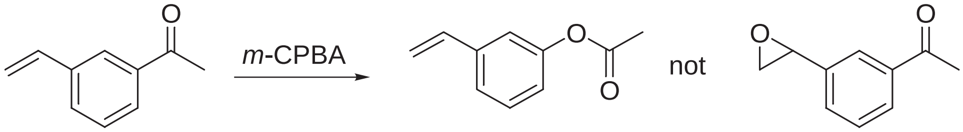
– So, choose bases (Na_2CO_3, $NaHCO_3$, Na_2HPO_4) to deprotonate only the RCOOH formed.

d. Also, at higher temperatures, a free radical scavenger may be used to avoid peracid decomposition.

e. Common side reactions

1. Baeyer–Villiger reactions of ketones and aldehydes

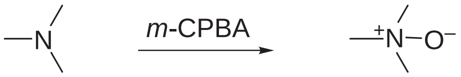
e.g.



– When peracids are used to oxidize olefins to epoxides in the presence of carbonyl functionality (ketones or aldehydes), protection of the carbonyl group may be necessary.

– One may choose to select a reagent which attacks olefins preferentially.

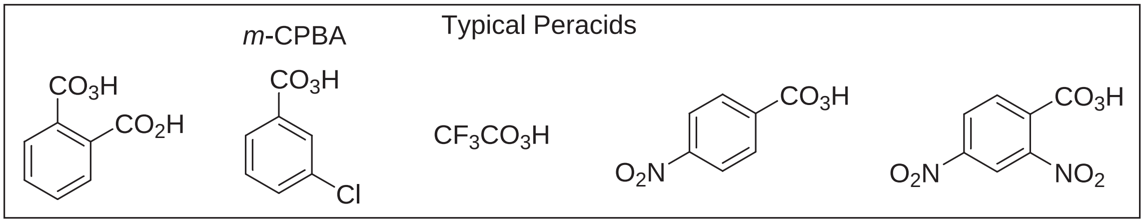
2. Oxidation of amines



– Nitrogen must be protected (e.g., as amide) or another reagent selected.

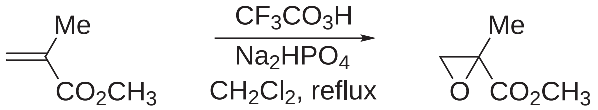
3. Imine oxidation

4. Sulfur oxidation

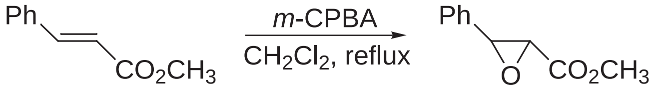


7. Epoxidation of Electron-deficient Olefins

a. α,β-unsaturated esters: can choose a strong peracid or vigorous reaction conditions

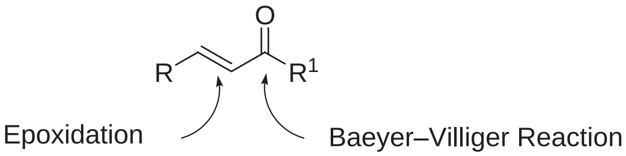


84% Emmons *J. Am. Chem. Soc.* **1955**, *77*, 89.



47% MacPeek *J. Am. Chem. Soc.* **1959**, *81*, 680.

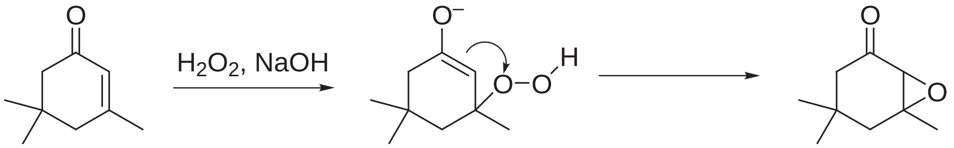
b. α,β-unsaturated ketones: Baeyer–Villiger competes with epoxidation



Solution: different conditions (reagents) are needed

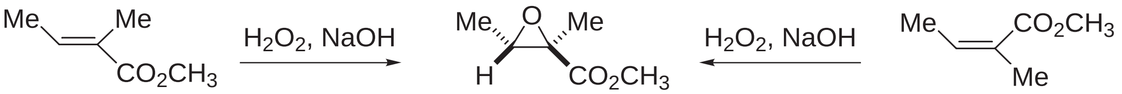
B. Additional Methods for Epoxidation of Olefins

1. H$_2$O$_2$, NaOH

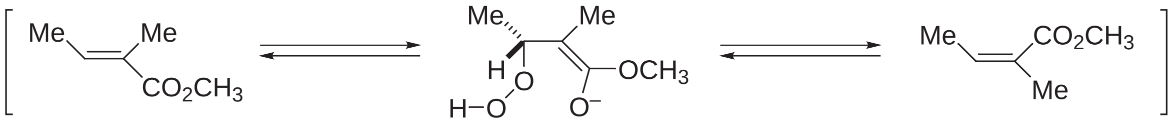


70%

– The following reaction is **diastereoselective** (but not diastereospecific): a single stereoisomer of the product is formed which bears no relationship to the reactant.

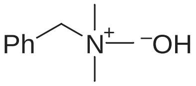


The reaction occurs via a reversible process:

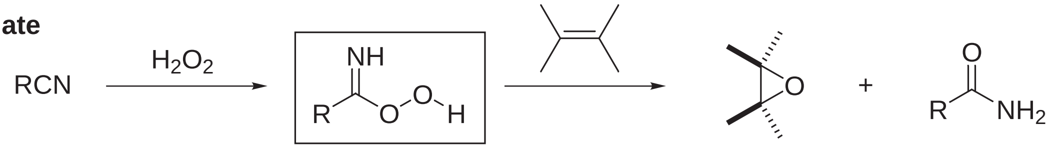


Similarly,

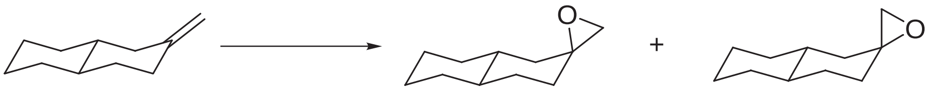
^{t}BuOOH/Triton B	Payne *J. Org. Chem.* **1961**, *26*, 651.
Ph$_3$COOH/R$_4$NOH	Corey *J. Am. Chem. Soc.* **1988**, *110*, 649.
^{t}BuOOH/^{n}BuLi	Jackson *Tetrahedron* **1988**, *29*, 4889.

Triton B =


2. Peroxyimidate



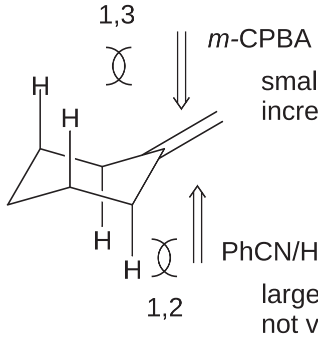
– This reagent permits the use of neutral reaction conditions. Unlike *m*-CPBA, the reagent behaves as a large reagent and thus approaches from the equatorial face of an exocyclic double bond.



small reagent	⟸	*m*-CPBA	59	41
large reagent	⟸	PhCN / H$_2$O$_2$	14	86

Carlson *J. Org. Chem.* **1967**, *32*, 1363.
(*m*-CPBA & PhCN/H_2O_2)

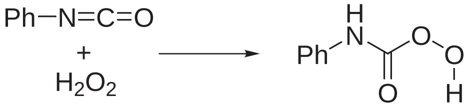
Vedejs *J. Am. Chem. Soc.* **1989**, *111*, 6861.
(*m*-CPBA)



small reagent, but the interaction will increase with the size of the reagent

larger reagent, but the interaction will not vary with size, predominately equatorial attack

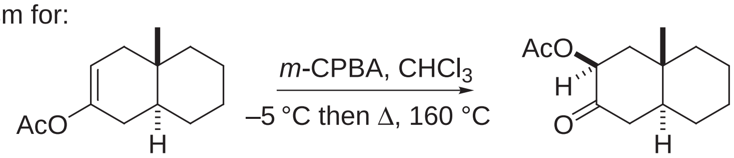
–Analogous reagent:

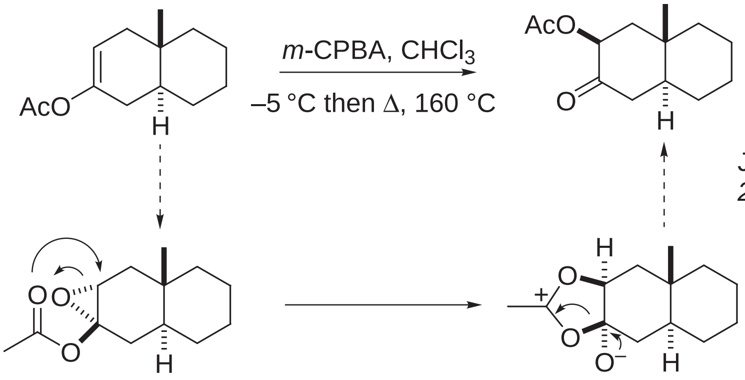


Christl *Angew. Chem., Int. Ed. Eng.* **1980**, *19*, 458.

Mechanism Problem

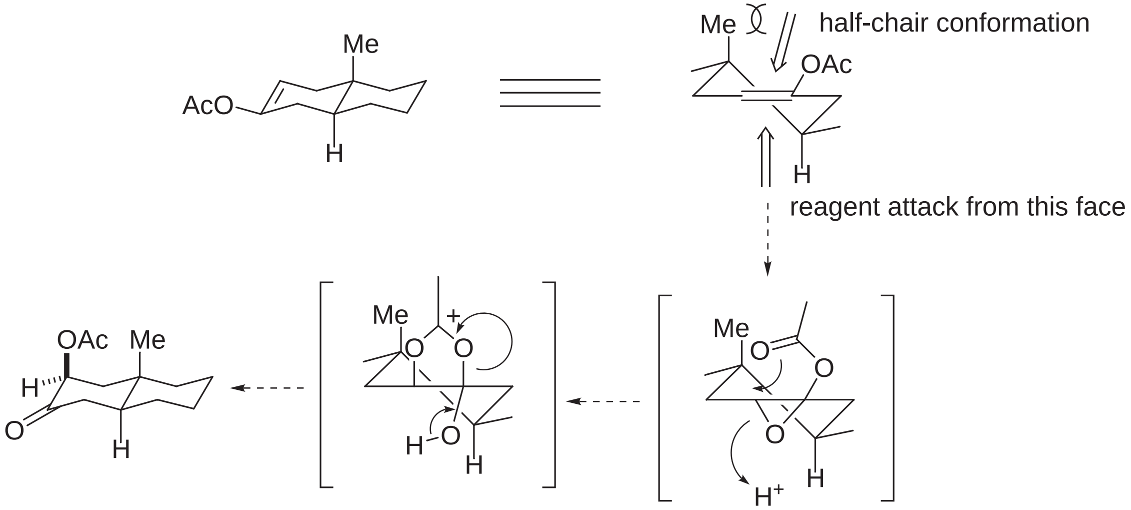
Provide mechanism for:



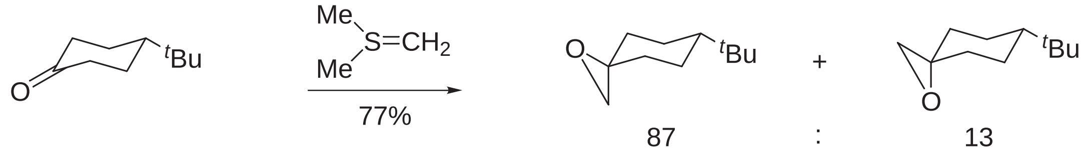


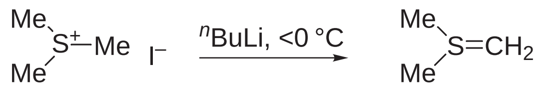
Johnson *J. Org. Chem.* **1961**, *26*, 4563.

Why does this reaction need to be heated to 160 °C?



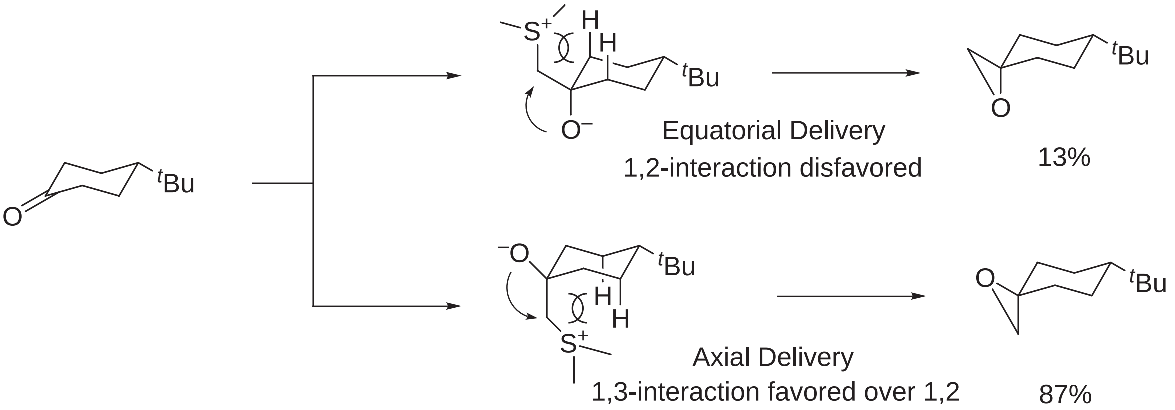
3. Sulfur Ylides

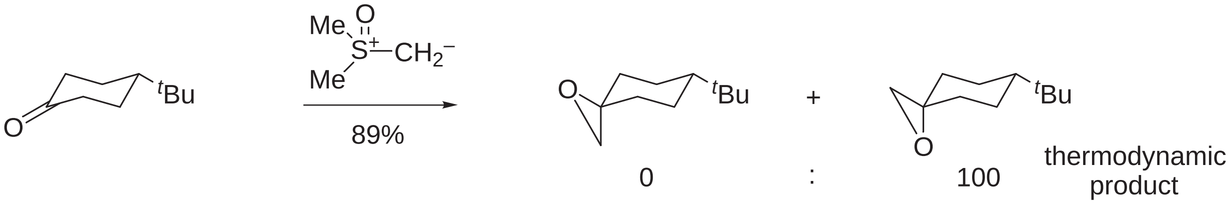


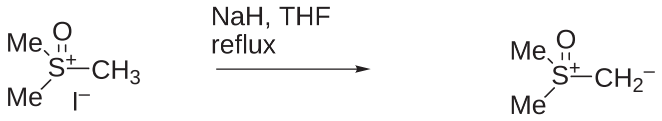


dimethylsulfonium methylide
small reagent that prefers axial delivery

– This is the result of kinetic control: reaction gives the thermodynamically less stable epoxide product.

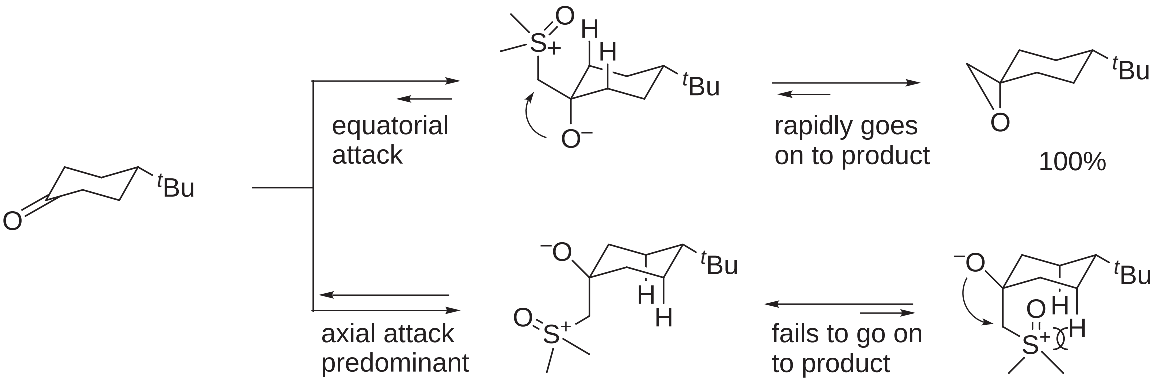






dimethyloxo sulfonium methylide
small reagent that prefers axial attack

Corey, Chaykovsky *J. Am. Chem. Soc.* **1965**, *87*, 1353.

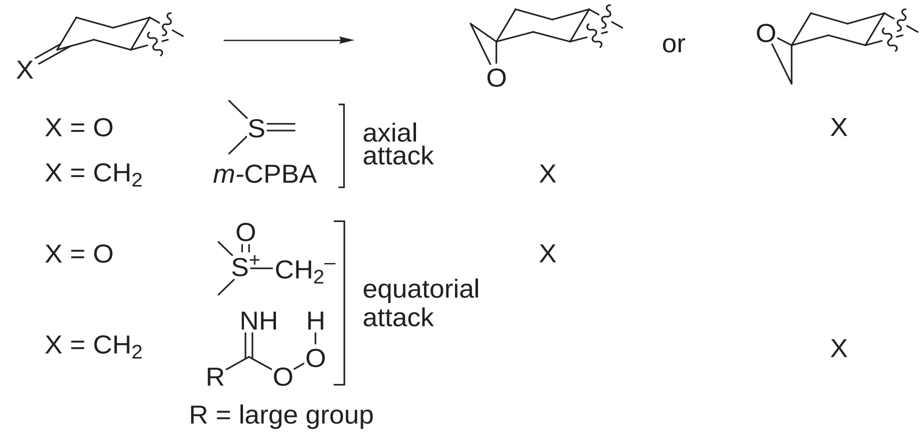


backside attack not possible due
to destabilizing 1,3-interactions

For this reaction: Initial reaction is reversible and is not capable of generating the axial delivery product because of the destabilizing 1,3-interactions in the transition state required for epoxide closure.

Summary of Exocyclic Epoxide Formation

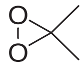
Note: defined conformation of 6-membered ring required for comparisons



Sulfur ylides deliver "CH_2"
Peroxides deliver "O"

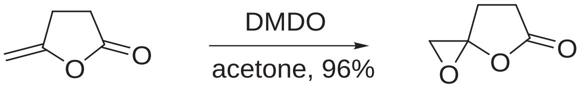
Learn reagents by:
1) Conditions required
2) Advantages and disadvantages
3) Competitive reactions
4) Stereochemistry limitations / highlights

4. Dimethyl Dioxirane (DMDO)



A mild neutral reagent

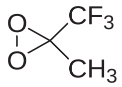
Murray *J. Am. Chem. Soc.* **1986**, *108*, 2470.
Acc. Chem. Res. **1989**, *22*, 205.



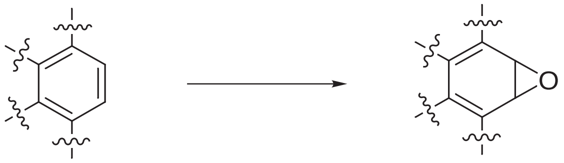
Peracid reaction suffers from H^+ catalyzed epoxide opening

Adam *Tetrahedron Lett.* **1989**, *30*, 4223.

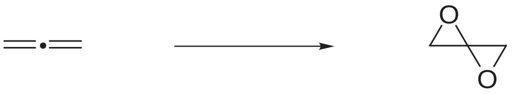
Curci *Tetrahedron Lett.* **1989**, *30*, 257.



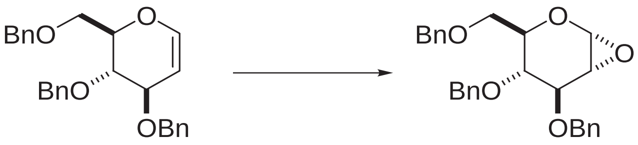
Excellent for oxidation of highly substituted enol ethers



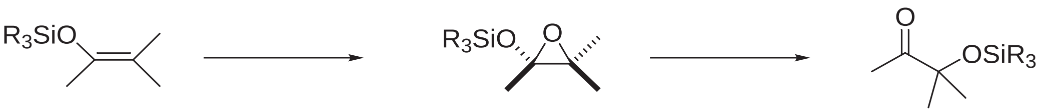
Boyd *Tetrahedron Lett.* **1989**, *30*, 123.



Crandall *J. Org. Chem.* **1988**, *53*, 1338.
Tetrahedron Lett. **1988**, *29*, 4791.



Danishefsky *J. Am. Chem. Soc.* **1989**, *111*, 6661.
Useful for glycosidation reactions.



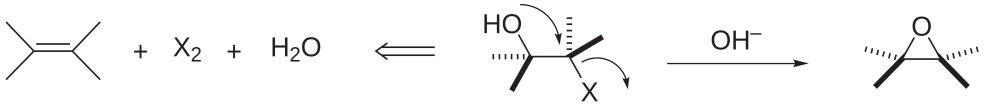
stable and characterizable

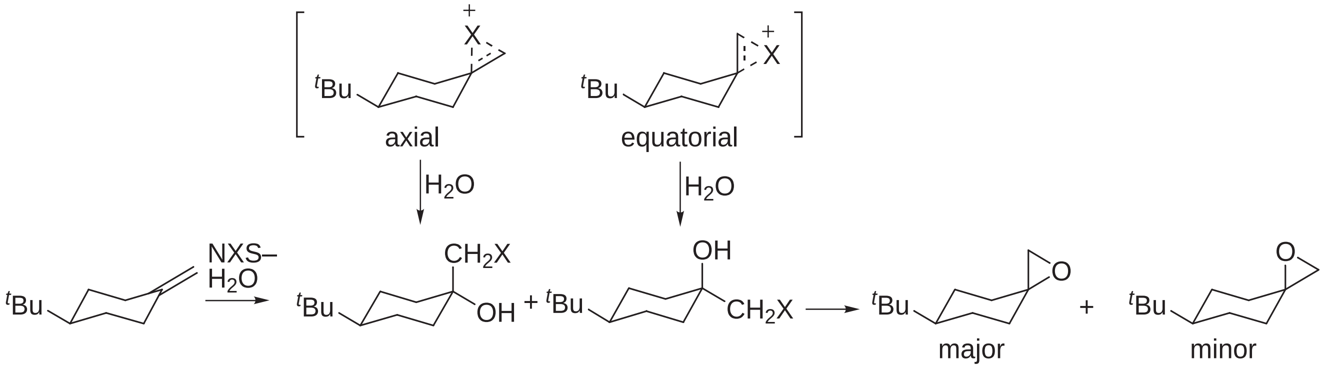
Danishefsky *J. Org. Chem.* **1989**, *54*, 4249.

pH dependence: rate at pH 11 > 7, acetone–oxone Shi *J. Org. Chem.* **1998**, *63*, 6425.

5. Summary of Other Methods of Epoxide Formation

a. Cyclization of Halohydrins





Increased reagent size yields increased equatorial approach

NCS–H_2O	90	:	10
NBS–H_2O	82	:	18
NIS–H_2O	55	:	45

Analogous results observed with:

Br_2, $ClCH_2CH_2Cl$	70	:	30
Br_2, MeOH	90	:	10

90 : 10

vs

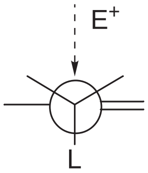
31 : 69

For *m*-CPBA, complementary stereochemistries

-The electrophilic reagents behave as small reagents and approach from the axial direction

Chiappe *J. Org. Chem.* **1995**, *60*, 6214.

-For acyclic systems:

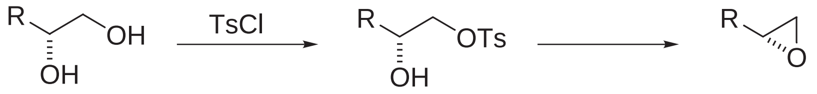


LUMO electrophile
HOMO alkene

Houk *Acc. Chem. Res.* **1990**, *23*, 107.

-Large or electropositive group

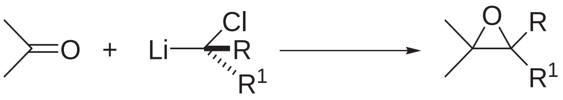
b. Cyclization of 1,2-diols



– primary alcohol > secondary alcohol for tosylation reaction

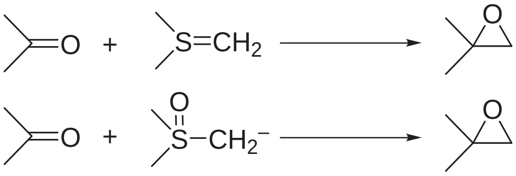
c. Epoxides from carbonyl compounds

d.

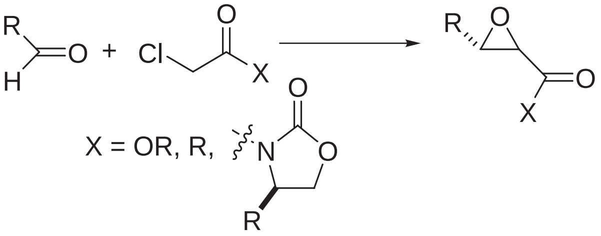


Köbrich *Angew. Chem., Int. Ed. Eng.* **1972**, *11*, 473.

e.



f.



X = OR, R,

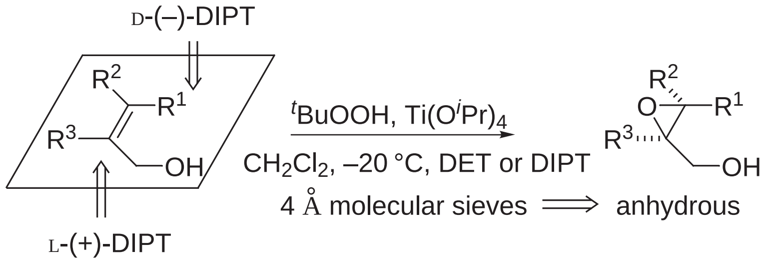
Darzen's Condensation:
First Example: Erlenmeyer *Ann.* **1892**, *271*, 161.
Generalized by Darzen through years 1904–1937
Compt. rend. **1904**, *139*, 1214.
Comprehensive Org. Syn., Vol. 2, p 409.
Newman, Magerlein *Org. React*. **1968**, *5*, 413.
Asymmetric variants:
Lantos *J. Am. Chem. Soc.* **1986**, *108*, 4595.
Shioiri *Tetrahedron* **1999**, *55*, 6375.

C. Catalytic Asymmetric Epoxidation

1. Sharpless Catalytic Asymmetric Epoxidation (AE Reaction)

Key references: *Asymmetric Synthesis*: Vol. 5, Morrison, J.D. Ed., Academic Press, Chapters 7 and 8.
Reviews: Katsuki, Martin *Org. React.* **1996**, *48*, 1.
Comprehensive Org. Syn.; Vol. 7, pp 389–436.
Sharpless *J. Am. Chem. Soc.* **1980**, *102*, 5974; **1987**, *109*, 5765; **1981**, *103*, 6237;
1984, *106*, 6430; **1991**, *113*, 106, 113; **1987**, *109*, 1279.

1. The enantiofacial selectivity of the reaction is general and dependable for assignments.



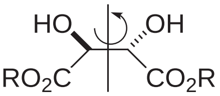
2. Selectivity is catalyst dependent

Ti(O^{i}Pr)$_4$	95% ee	Zr(O^{i}Pr)$_4$	10% ee
Al(O^{t}Bu)$_3$	5% ee	Hf(O^{i}Pr)$_4$	3% ee
MoO$_2$(acac)$_2$	15% ee	Nb(OEt)$_3$	5% ee
VO(O^{i}Pr)$_3$	17% ee	Ta(O^{i}Pr)$_5$	39% ee
Sn(O^{i}Pr)$_4$	NR		

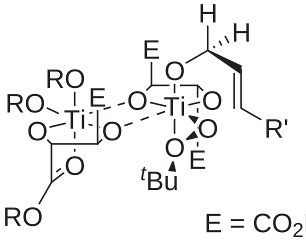
3. Chemical Conversion

			yield
unsubstituted	R^1 = R^2 = R^3 = H	95% ee	15% (isolation problematic)
trans-disubstituted	R^1, R^3 = H	>95% ee	70–90%
cis-disubstituted	R^2, R^3 = H	85–95% ee	70–90%
1,1-disubstituted	R^1 = R^2 = H	85–95% ee	70–90%
trans-1,1,2-trisub.	R^1 = H	>95% ee	70–90%
cis-1,1,2-trisub.	R^2 = H	>90% ee	70–90%
1,2,2-trisubstituted	R^3 = H	>95% ee	70–80%

4. Sharpless asymmetric epoxidation is one of the best known and practical asymmetric reactions utilized in organic synthesis. Discovered in 1980, this catalytic process utilizes an optically active ligand to direct a transition metal catalyzed reaction. Epoxidation from a single face of a prostereogenic allylic alcohol:



C^2 symmetry



R = Et DET
R = ^{i}Pr DIPT

E = CO$_2$R

(Useful in ligand design- predictable and repetitive structural units which reduce number of diastereomeric transition states)

a. Match of Ti / Tartrate such that a single complex dominates the chemistry.

The concentration of each complex in the mixture of complexes is dictated by thermodynamic considerations. However, it could not be predicted that a single species would dominate the Ti–tartrate equilibrium mixture and that this species would be so kinetically active. The tartrate–Ti complex is perfectly matched and slight deviations in the ligand structure or change in the metal alkoxide reduces the effectiveness of the reaction.

b. Ligand acceleration of reaction.

This is not essential but extremely beneficial. It ensures that the enantioselective version of the reaction (the one in which the auxiliary ligand is present) will be the most viable kinetic pathway.

c. Steric and stereoelectronic features of reaction control enantioselectivity.

Stereoelectronic:

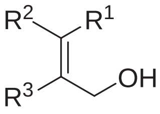
1. Alkyl peroxide is activated by bidentate coordination to the Ti(IV) center.
2. The olefin is constrained to attack the coordinated peroxide along the O–O bond axis. (stereoelectronic effect)
3. The epoxide C–O bonds are formed simultaneously.

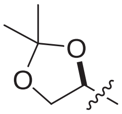
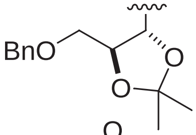
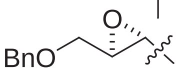
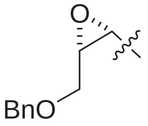
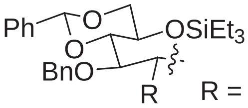
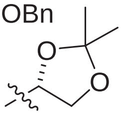
Steric factors:

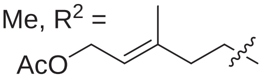
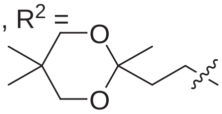
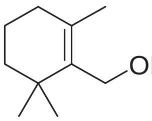
1. Bulky hydroperoxide is forced to adopt a single orientation when bound in a bidentate fashion.
2. The allylic alkoxide is thereby restricted to reaction at a single coordination site on the metal center. Steric interactions of the bound substrate with the catalyst framework provide for the kinetic resolution patterns.
3. Efficient catalytic turnover provided by the labile coordinated ester, permitting rapid alkoxide–alcohol exchange.

Scope

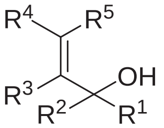
Epoxidation with Titanium–Tartrate Catalysts

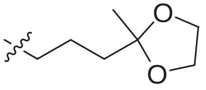
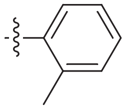


			yield
unsubstituted ($R^1 = R^2 = R^3 = H$)		95% ee	15%
trans-disubstituted ($R^1 = R^3 = H$)	$R^2 = CH_3$	>95% ee	45%
	$R^2 = {}^nC_{10}H_{21}$	>95% ee	79%
	$R^2 = (CH_2)_3CH{=}CH_2$	>95% ee	80%
	$R^2 = Me_3Si$	>95% ee	60%
	$R^2 = {}^tBu$	>95% ee	
	$R^2 = Ar$	≥95% ee	0–90%
	$R^2 = CH_2OBn$	98% ee	85%
	$R^2 =$ 	>95% ee	78–85%
	$R^2 =$ 	>95% ee	70%
	$R^2 =$ 	>99% ee	76%
	$R^2 =$ 	>99% ee	70%
	$R^2 =$  R = OBn, OH	>93% ee	70–88%
cis-disubstituted ($R^2 = R^3 = H$)	$R^1 = {}^nC_{10}H_{21}$	90% ee	82%
	$R^1 = CH_2Ph$	91% ee	83%
	$R^1 = CH_2OBn$	92% ee	84%
	$R^1 =$ 	96% ee	55%

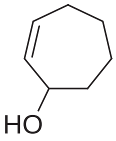
1,1-disubstituted ($R^1 = R^2 = H$)	R^3 = -cyclohexyl	>95% ee	81%
	$R^3 = {}^nC_{14}H_{29}$	>95% ee	51%
	$R^3 = {}^tBu$	85% ee	
trans-1,1,2-trisubstitued (R^1 = H)	$R^3 = R^2$ = Ph	>95% ee	87%
	R^3 = Me, R^2 = Et	>95% ee	79%
	R^3 = Me, R^2 = 	>95% ee	70%
	R^3 = Me, R^2 = 	>95% ee	92%
cis-1,1,2-trisubstituted (R^2 = H)	$R^3 = CH_3$, R^1= Bn	91% ee	90%
1,2,2-trisubstituted (R^3 = H)	$R^2 = (CH_2)_2CH{=}C(CH_3)_2$, $R^1 = CH_3$	>95% ee	77%
	$R^2 = CH_3$, $R^1 = (CH_2)_2CH{=}C(CH_3)_2$	94% ee	79%
tetrasubstituted	$R^3 = CH_3$, R^2 = Ph, R^1 = Bn	94% ee	90%
		94% ee	90%

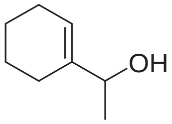
Allylic Alcohols Undergoing Kinetic Resolution with Relative Rates >15 at –20 °C

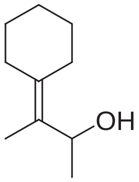


$R^1 = {}^nC_6H_{13}$
$R^1 = (CH_2)_2Ph$
R^1 = 
R^1 = cyclohexyl
R^1 = 

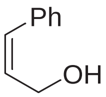
$R^1 = {}^nC_4H_9$, $R^3 = CH_3$
R^1 = cyclohexyl, $R^3 = CH_3$
$R^1 = {}^nC_4H_9$, R^4 = Et or CH_3
R^1 = cyclohexyl, $R^4 = CH_3$
R^1 = Et, R^4 = Ph
$R^1 = CH_2CH(CH_3)_2$, $R^4 = CH_3$
$R^1 = R^5 = CH_3$
R^1 = Et, $R^4 = {}^nC_6H_{13}$

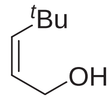


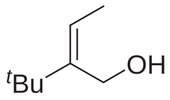


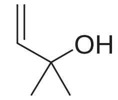


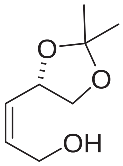
Poor Substrates for Asymmetric Epoxidation or Kinetic Resolution Catalyzed by Titanium–Tartrates

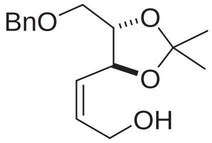


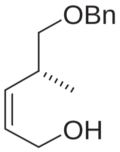


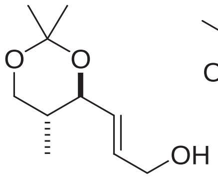


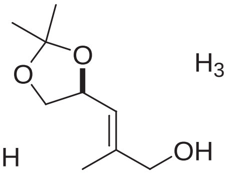


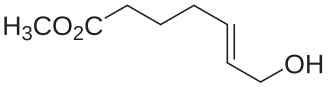


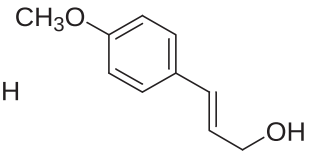


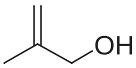


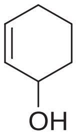


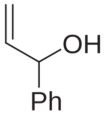


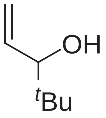


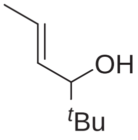


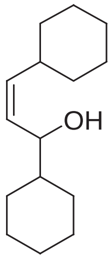


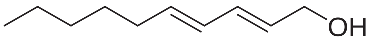








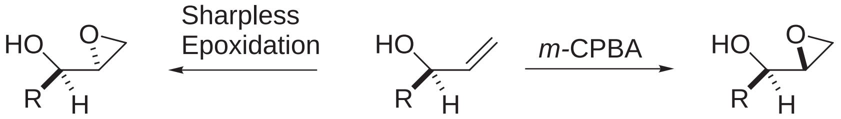


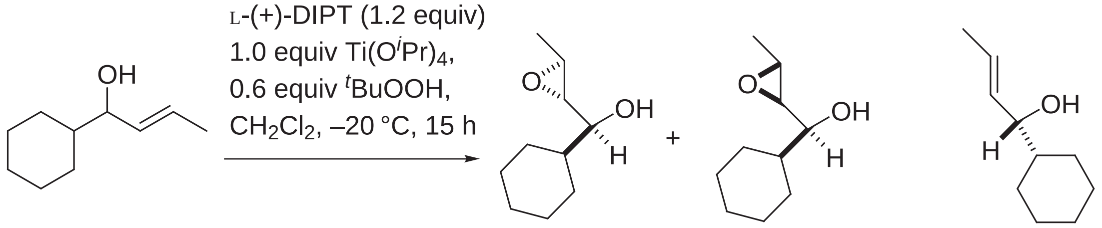


5. Kinetic Resolution

Sharpless *J. Am. Chem. Soc.* **1981**, *103*, 6237.
Pure Appl. Chem. **1983**, *55*, 589.

– Sharpless epoxidation product is different from the directed oxidation of allylic alcohols by peracids (*m*-CPBA).





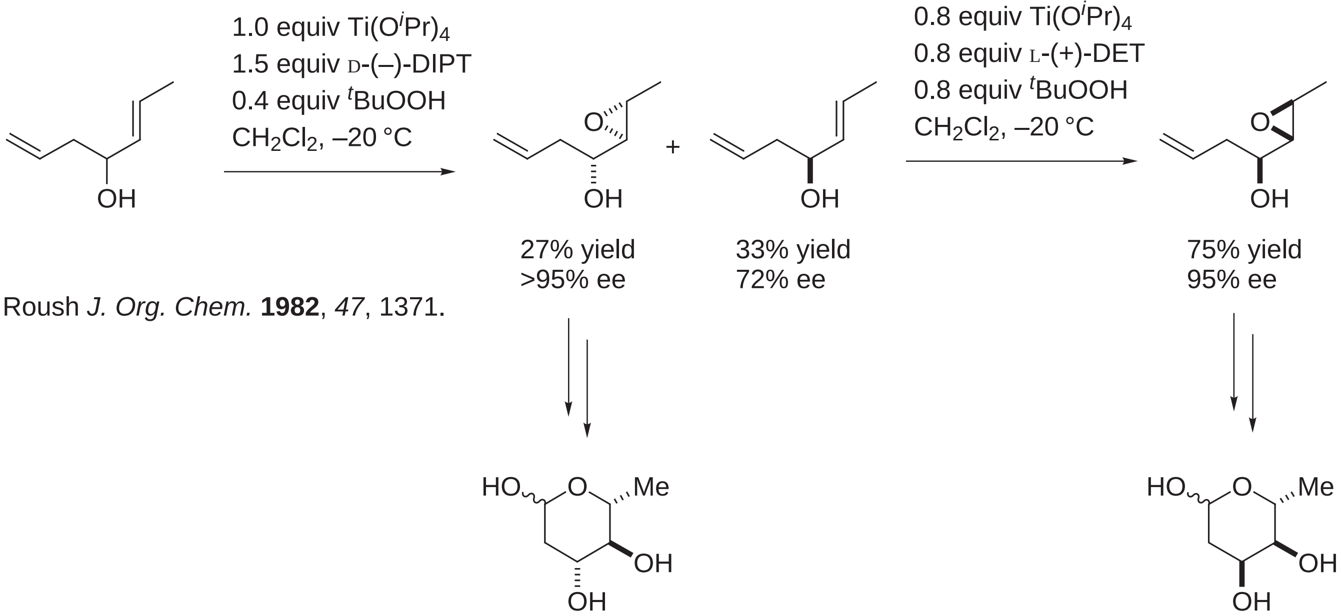
racemic

98

2

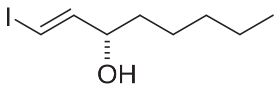
(*R*)-enantiomer recovered

relative rates = k_S / k_R = 104
(*S*)-enantiomer reacts



Roush *J. Org. Chem.* **1982**, *47*, 1371.

Sato *Tetrahedron Lett.* **1987**, *28*, 6351.



Sharpless epoxidation
Kinetic resolution

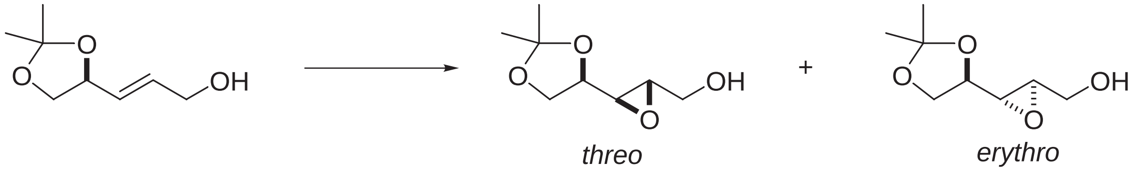
6. Total Synthesis of the L-Hexoses

Sharpless, Masamune *Science* **1983**, *220*, 949.
Tetrahedron **1990**, *46*, 245.

"Reagent-control" Strategy: selection of reagent dictates ultimate absolute stereochemistry of reaction products irrespective of stereofacial bias of substrate.

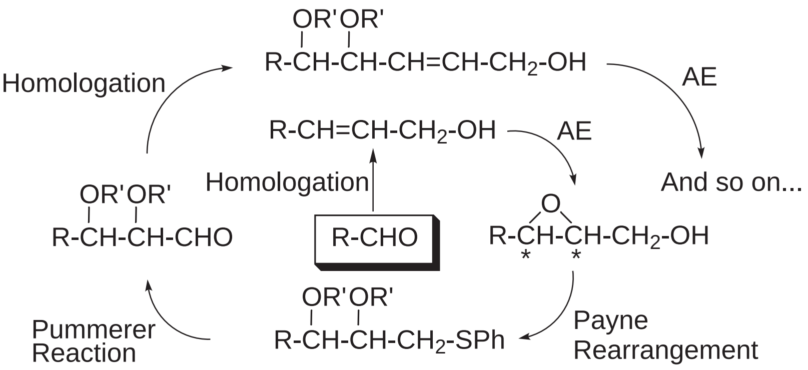
"Substrate-control" Strategy: stereochemistry of reaction products dictated by the inherent stereofacial bias of the substrate.

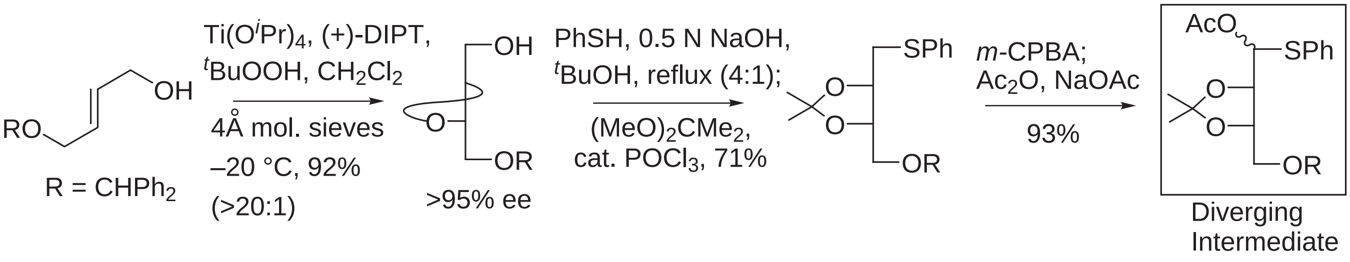
Masamune *Angew. Chem., Int. Ed. Eng.* **1985**, *97*, 1.
Sharpless *Chemica Scripta* **1985**, *25*, 71.

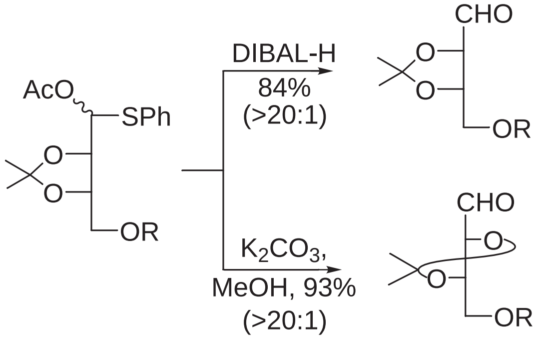


Reagent	Product Ratio (*threo*:*erythro*)	
m-CPBA	1 : 1.4	achiral reagents "substrate control"
$VO(acac)_2$–TBHP	1 : 1.8	
$Ti(O^iPr)_4$–TBHP	1 : 2.3	
$Ti(O^iPr)_4$–(–)-tartrate–TBHP	1 : 90	"matched pair"
$Ti(O^iPr)_4$–(+)-tartrate–TBHP	22 : 1	"mismatched pair" "reagent control"

-Reiterative two-carbon extension cycle employed for the synthesis of all L-hexoses:

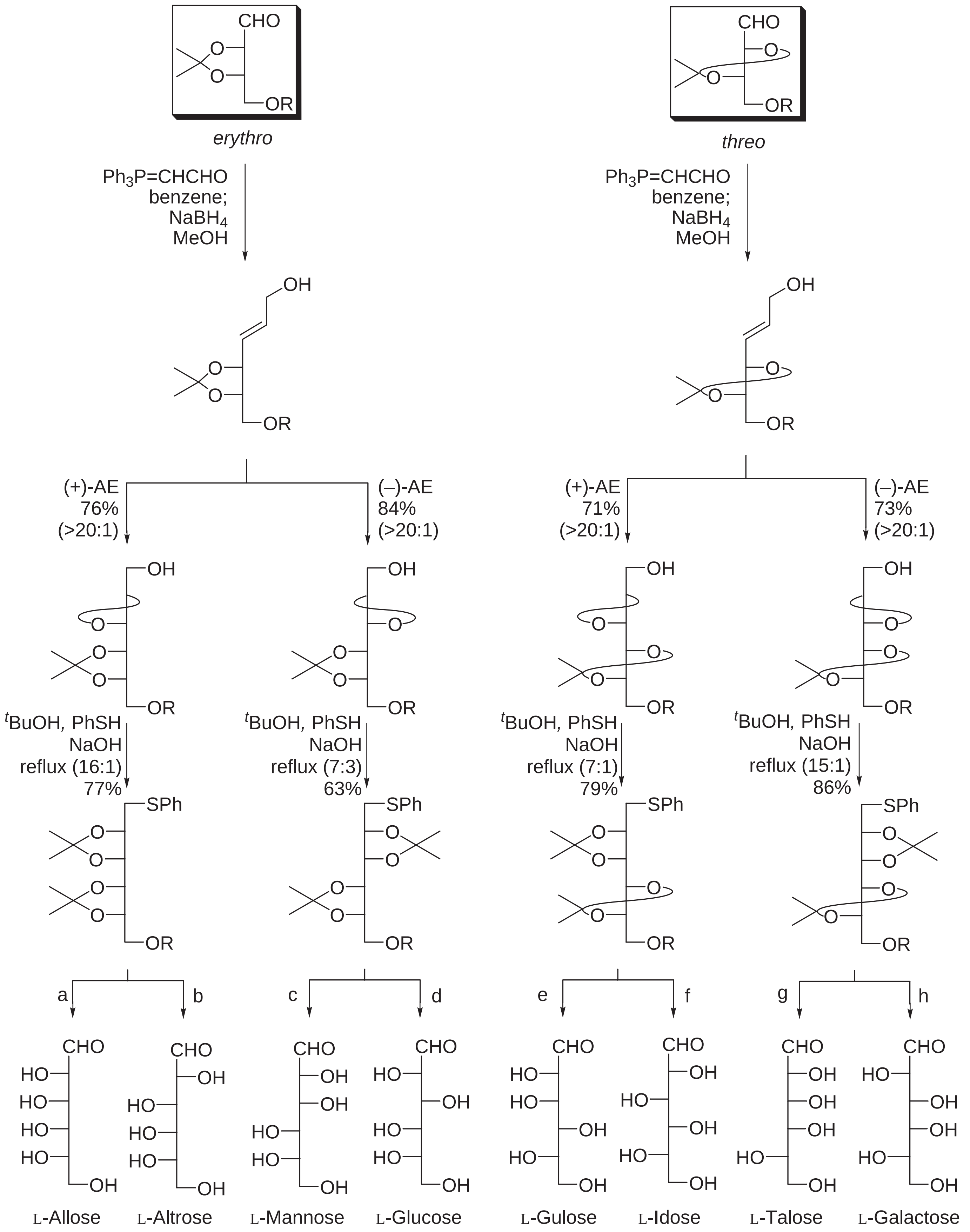






erythro
corresponds to C_4 and C_5 of allose, altrose, mannose, and glucose

threo
corresponds to C_4 and C_5 of gulose, idose, talose, and galactose

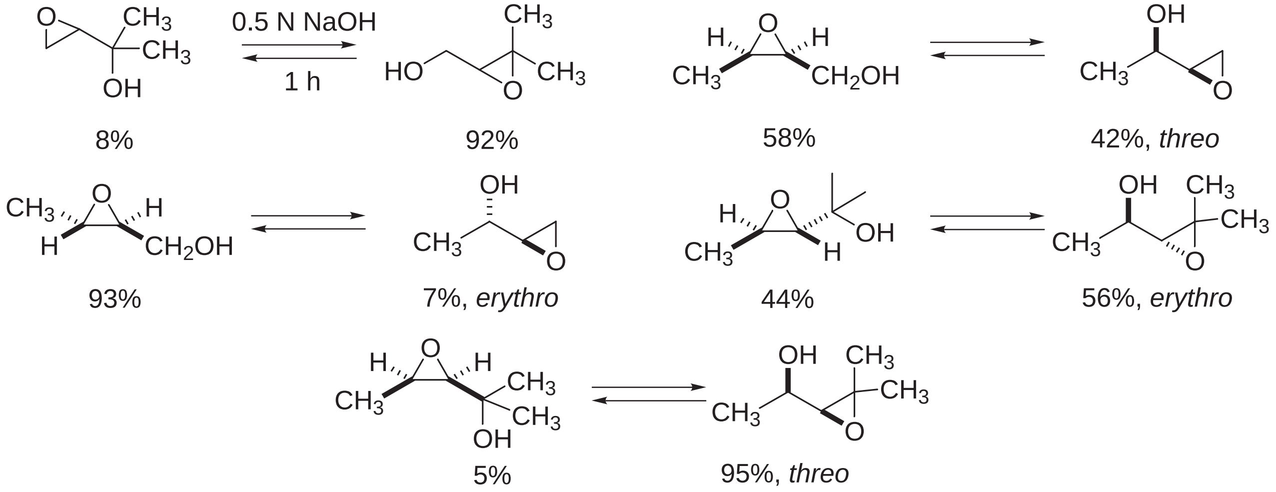


For a, c, e, and g: 1. Pummerer reaction, 2. DIBAL-H, 3. Deprotection.
For b, d, f, and h: 1. Pummerer reaction, 2. K_2CO_3/MeOH, 3. Deprotection.

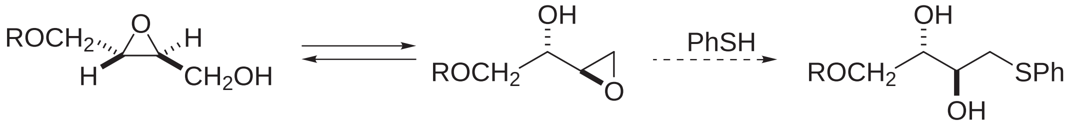
-Payne Rearrangement

Payne *J. Org. Chem.* **1962**, *27*, 3819.

Base-catalyzed (aq. NaOH) migration of α,β-epoxy alcohols:



1. In general, the more substituted epoxide is favored as the reaction product.
2. However, steric factors and relative alcohol acidities (1° > 2° > 3°) are additional factors which determine the ultimate composition of the equilibrium mixture.
3. The more reactive epoxide can be trapped by strong nucleophiles (e.g., PhSH).



Emil Fischer attended the lectures of A. Kekule, worked with A. Baeyer as a student and received the 1902 Nobel Prize in Chemistry for his work on carbohydrate and purine syntheses. Discoverer of the Fischer indole synthesis using arylhydrazones, he utilized phenylhydrazine to derivatize carbohydrates as crystalline solids for characterization that enabled him to elucidate their chemistry and structure. From the work of Le Bel and van't Hoff he knew glucose must have 16 stereoisomers and in the now classic studies synthesized most of them and established the correct configuration of glucose. He introduced the use of Fischer projection formulas. He proposed structures for uric acid, caffeine, theobromide, xanthine, and guanine and later synthesized theophylline and caffeine (1895), uric acid (1897), and coined the term purine. By 1900 he prepared more than 130 derivatives including hypoxanthine, xanthine, theobromide, adenine, and guanine. In 1914, he made glucose derivatives and from them the nucleosides. He is responsible for the "lock and key" analogy for describing enzyme–substrate interactions, prepared the D- and L-amino acids with fractional crystallization resolution and made a peptide of 18 amino acids. Having suffered from the effects phenylhydrazine, he is also among the first to implement safety precautions (ventilation) and designed the first exhaust system put into general use.

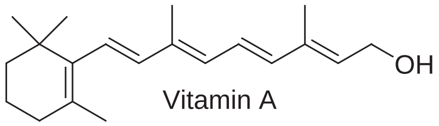
"...the intimate contact between the molecules...is possible only with similar geometrical configurations. To use a picture, I would say that the enzyme and the substrate must fit together like a lock and key." Emil Fischer, 1895

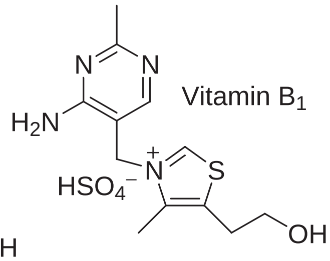
W. Haworth received the 1937 Nobel Prize in Chemistry for his investigations on the structure determination of carbohydrates (cyclic monosaccharides, disaccharides, and polysaccharides) including their derivitization as methyl ethers and vitamin C. The latter was accepted with wide acclaim and Haworth was also one of the first to prepare vitamin C, the first vitamin to be prepared by synthesis. This made vitamin C available to the world population for the treatment of scurvy, eliminating the need for treatment with fresh limes or lemons.

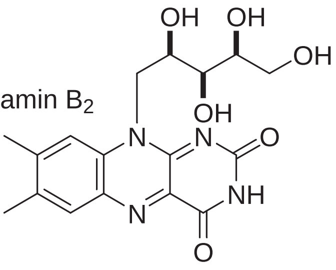
Albert Szent-Gyorgyi von Nagyrapolt received the 1937 Nobel Prize in Medicine. He was responsible for the isolation of vitamin C for the first time, but was recognized for his investigations into biological mechanisms of oxidation.

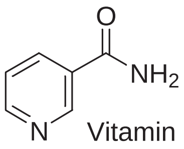
Vitamins represent one of the great success stories of organic synthesis. They are necessary requirements of both animals and humans, but cannot be made by these species. The needs are met by dietary sources or through symbiotic relationships with microorganisms (intestinal bacteria). There are now 13 vitamins. All, except vitamin B_{12} which is produced by fermentation, are made commercially by chemical means.

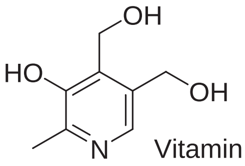
vitamin C	(60,000 metric tons/yr)* - humans	
vitamin E	(22,500 metric tons/yr)* - 75% for animal nutrition	
niacin	(21,600 metric tons/yr)* - 75% for animal nutrition	
vitamin B_{12}	(14 metric tons/yr)* - 55% animal/45% human	* for 1994

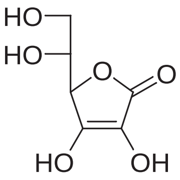

Vitamin A

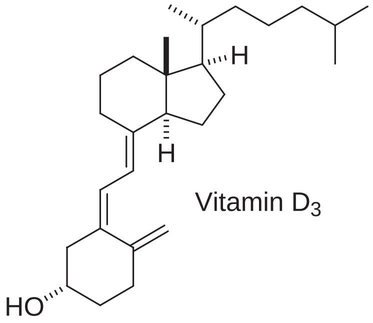

Vitamin B_1

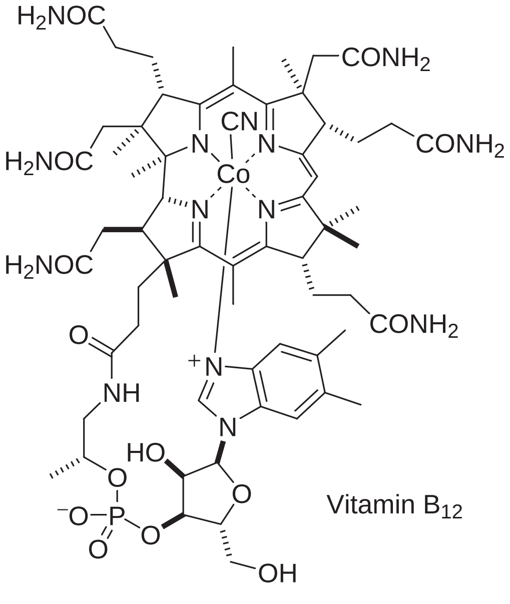

Vitamin B_2

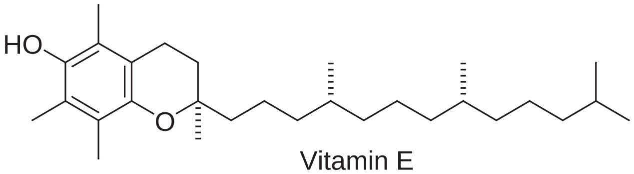

Vitamin B_3

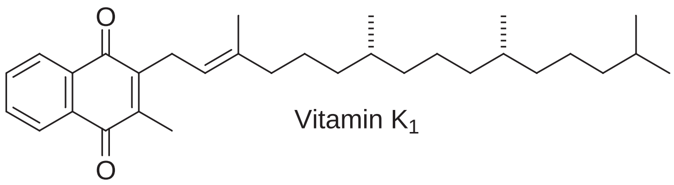

Vitamin B_6

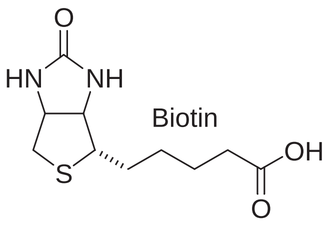

Vitamin C

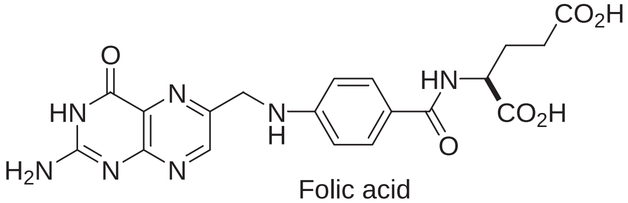

Vitamin D_3

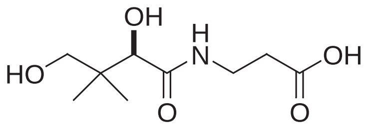

Vitamin B_{12}


Vitamin E


Vitamin K_1


Biotin

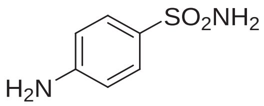

Folic acid


Pantothenic acid

Paul Karrer received the 1937 Nobel Prize in Chemistry for his research on carotenoids, flavins, and vitamin A and B_2. He published over 1000 papers in his career and his textbook on organic chemistry was a classic in the field (13 editions). He along with Hans von Euler-Chelpin (Nobel, 1929) discovered that carotene and vitamin A had the same activity and that the addition of two molecules of H_2O to carotene produces two molecules of vitamin A, elucidating its structure before it had been isolated. It was in Karrer's lab that George Wald (Nobel Prize in Physiology or Medicine, 1967) showed that vitamin A plays an important role in the chemistry of vision. The total synthesis of the carotenoids was accomplished by Karrer in 1950. In 1931, he synthesized squalene, he confirmed the structure of vitamin C, and he completed the total synthesis of riboflavin and vitamin B_2 (in 1934), and he completed the first total synthesis of vitamin E (tocopherols) in 1938. He also isolated vitamin K, at the same time as Henrik Dam (Nobel Prize in Physiology or Medicine, 1943) and Edward Doisy (Nobel Prize in Physiology or Medicine, 1943). He and Warburg (Nobel Prize in Physiology or Medicine, 1931) unraveled the role of NADPH and he prepared other coenzymes including thiamine pyrophosphate and pyridoxal-5-phosphate.

Richard Kuhn received the 1938 Nobel Prize in Chemistry for his work on carotenoids and vitamins. He also put forth the concept of and coined the term atropisomerism. He isolated ca. 1 g of riboflavin, vitamin B_2, from 5300 L of skim milk and carried out structural studies that led to its structure identification and a synthesis that confirmed it. Kuhn proved the structure of riboflavin-5-phosphate which clarified its double role as an enzyme cofactor (coenzyme) and a vitamin. Similar efforts led to the isolation, structure determination, and synthesis of vitamin B_6, pyridoxol.

Sulfonamides

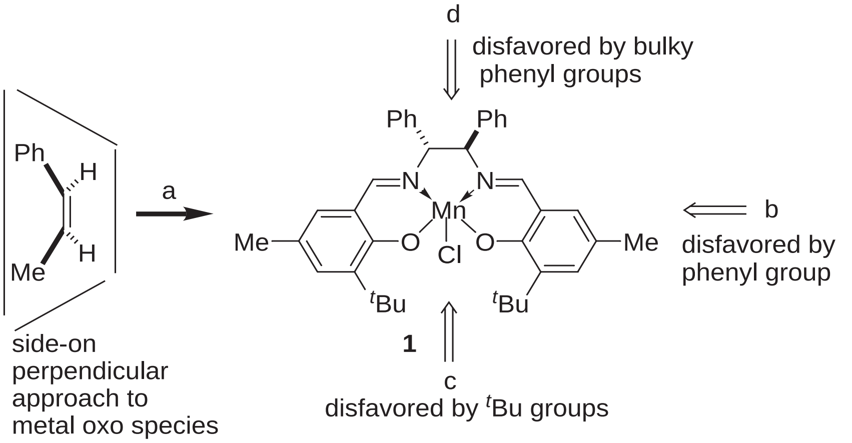


Prontosil-1938

G. Domagk received the 1939 Nobel Prize in Medicine for discovering in 1932 that prontosil protected mice from fatal infections of *Streptococci*. By the end of 1936, sulfa drugs were well on their way to becoming the first antibiotics in wide clinical usage. They are structural analogs of *p*-aminobenzoic acid and inhibit the bacterial formation of folic acid (antimetabolite), which we receive from our diet, selectively preventing bacteria from replicating without exhibiting mammalian toxicity.

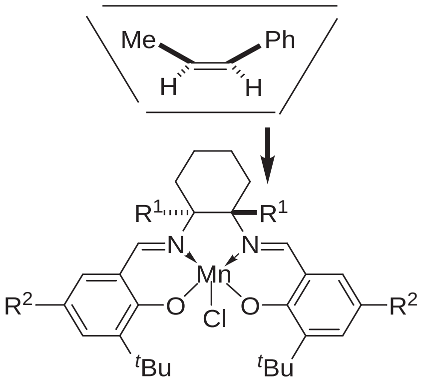
2. Jacobsen Epoxidation

-Unactivated alkenes
Jacobsen *J. Am. Chem. Soc.* **1991**, *113*, 7063.



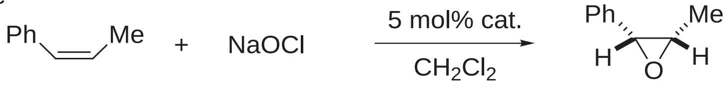
1

side-on
perpendicular
approach to
metal oxo species



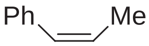
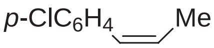
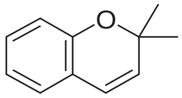
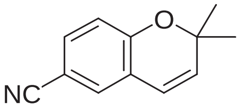
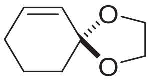
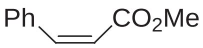
	R^1	R^2
2	Me	Me
3	H	Me
4	Me	^{t}Bu
5	H	^{t}Bu

Styrene still low: 70% ee



R,*R*-**1**	88%	84% ee	1*R*,2*S*
S,*S*-**2**	54%	49% ee	1*S*,2*R*
S,*S*-**3**	87%	80% ee	1*S*,2*R*
S,*S*-**4**	56%	55% ee	1*S*,2*R*
S,*S*-**5**	81%	92% ee	1*S*,2*R*

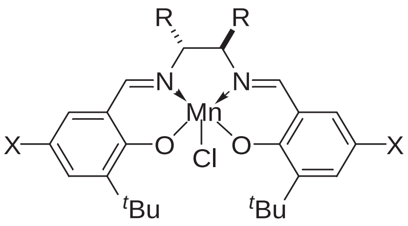
catalyst **5**

	84%	92% ee	cat. 0.04 equiv
	67%	92% ee	0.04 equiv
	72%	98% ee	0.02 equiv
	96%	97% ee	0.03 equiv
	63%	94% ee	0.15 equiv
	65%	89% ee	0.10 equiv

The above studies focused on steric effects of the catalyst.

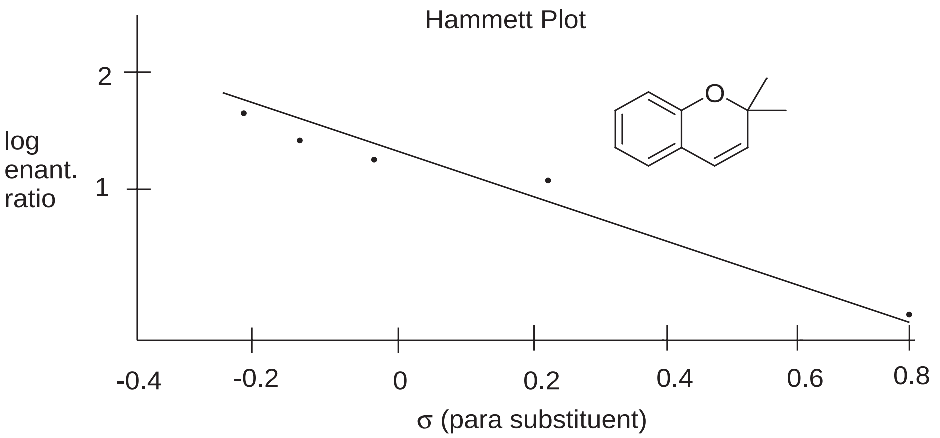
– Electronic effects of the catalyst

Jacobsen *J. Am. Chem. Soc.* **1991**, *113*, 6703.



1 **R** = Ph
2 = $(CH_2)_4$

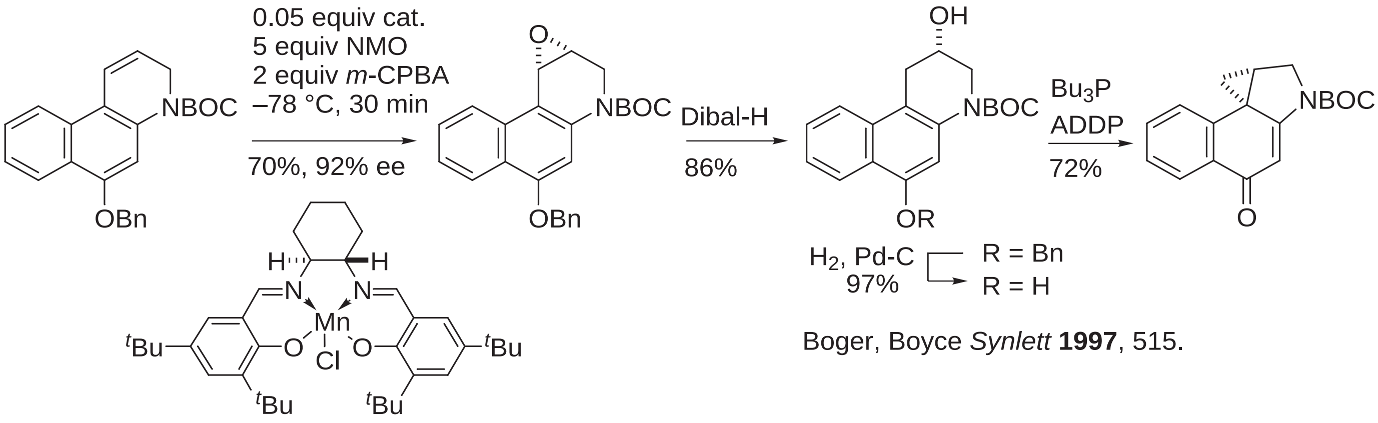
1a X = OMe 96% ee
1b = Me
1c = H
1d = Cl
1e = NO_2 22% ee



1. $\Delta\Delta G^{\ddagger}$ 2.0 kcal/mol
2. **1e** / **1a** $k_{rel} = 4$

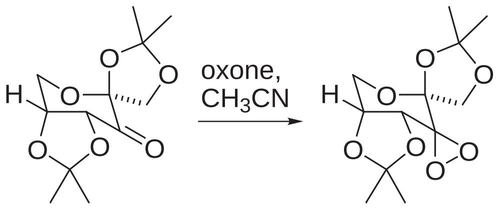
- conformational effects on catalyst?
- provoke changes in Mn–oxo bond length? reactivity vs transition state structure:
- the less reactive catalyst providing a tighter, more product-like T.S.

-Example



Boger, Boyce *Synlett* **1997**, 515.

3. Chiral Dioxiranes

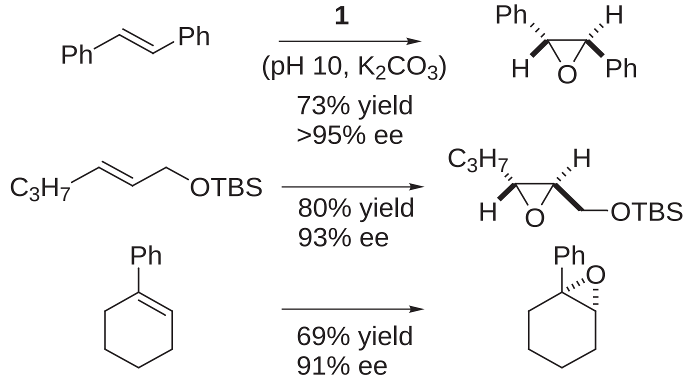


catalytic amounts

1

Shi *J. Am. Chem. Soc.* **1996**, *118*, 9806.
J. Am. Chem. Soc. **1997,** *119***,** 11224**.**
J. Org. Chem. **1997**, *62*, 2328; **1998**, *63*, 8475.
J. Org. Chem. **1998**, *63*, 2948.
(conjugated dienes)

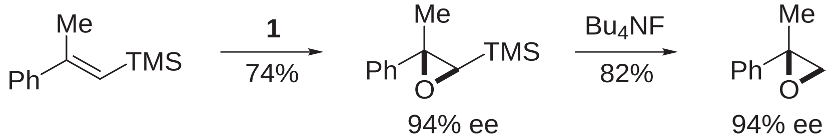
– Examples of *trans* and trisubstituted olefins



- pH 10 (K_2CO_3) suppresses Baeyer–Villiger reaction of ketone precursor.

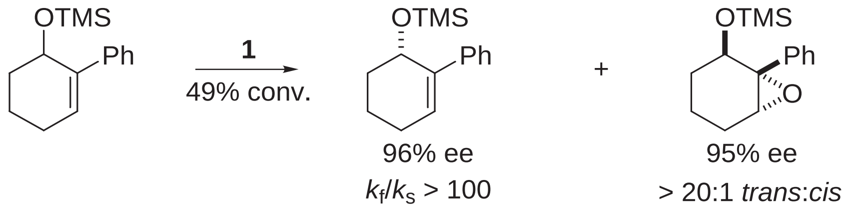
Reagent generation with H_2O_2–CH_3CN via in situ generation of $CH_3C(=NH)O_2H$
Shi *Tetrahedron Lett.* **1999**, *40*, 8721*.*

Terminal, disubstituted alkenes via vinylsilanes



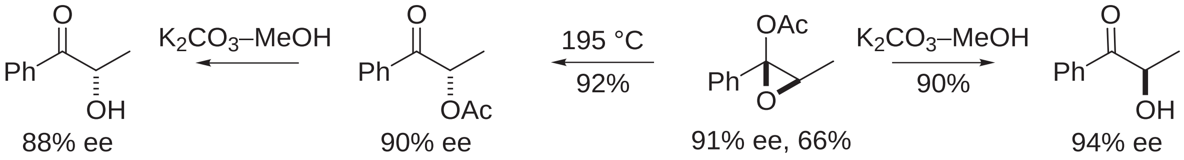
Shi *J. Org. Chem.* **1999**, *64*, 7675*.*

Kinetic resolution

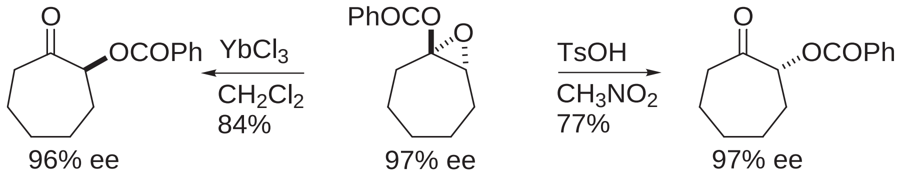


Shi *J. Am. Chem. Soc.* **1999**, *121*, 7718*.*

Enol ethers and esters



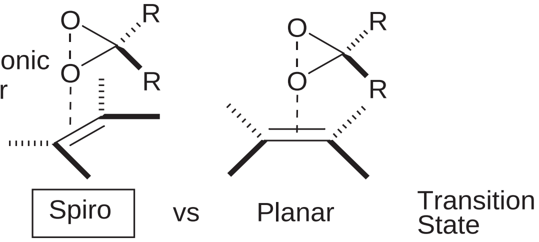
Shi *Tetrahedron Lett.* **1998**, *39*, 7819*.*



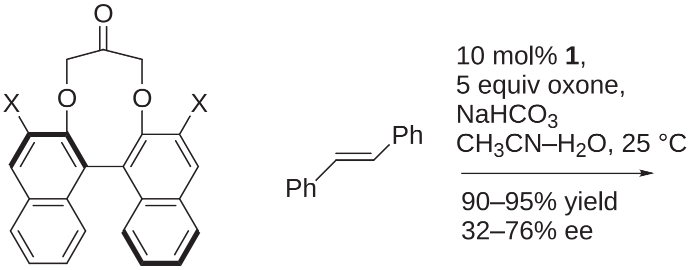
Shi *J. Am. Chem. Soc.* **1999**, *121*, 4080*.*

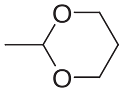
Note the stereoelectronic alignment of lone pair with spiro T.S.

consistent with ⟹



Yang *J. Am. Chem. Soc.* **1996**, *118*, 11311; **1998**, *120*, 5943.

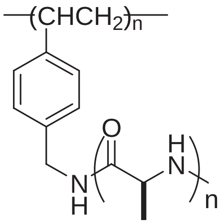


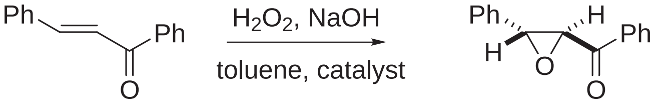
1	X = H	47% ee	**5**	X = Me	56% ee
2	X = Cl	76% ee	**6**	X = CH_2OCH_3	66% ee
3	X = Br	75% ee	**7**	X = 	71% ee
4	X = I	32% ee	**8**	X = $SiMe_3$	44% ee

OXONE® = $2KHSO_5•KHSO_4•K_2SO_4$

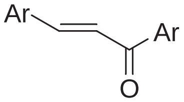
4. Polymer Supported Poly Amino Acids Review: Roberts *Bioorg. Med. Chem.* **1999**, *7*, 2145.

polyleucine:
92% yield, 99% ee





General for

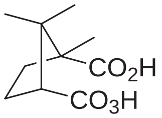


: 83–98%; 87–99% ee

Itsuno *J. Org. Chem.* **1990**, *55*, 6047.
Vega *Angew. Chem., Int. Ed. Eng.* **1980**, *19*, 929.

D. Stoichiometric Asymmetric Epoxidation

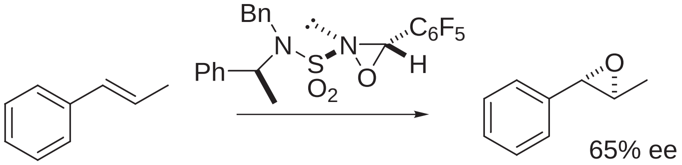
1. Chiral Peracids



- To date, ee's are modest (<10%)
- Not catalytic, but stoichiometric reagent

Ewins *J. Chem. Soc., Chem. Commun.* **1967**, 1085.
Montanari *J. Chem. Soc., Chem. Commun.* **1969**, 135.
Rebek *J. Am. Chem. Soc.* **1980***, 102,* 5602*.*
Curci *J. Chem. Soc., Chem. Commun.* **1984**, 155.

2. Chiral *N*-sulfamyloxaziridines



- Good ee's
- Stoichiometric reagent

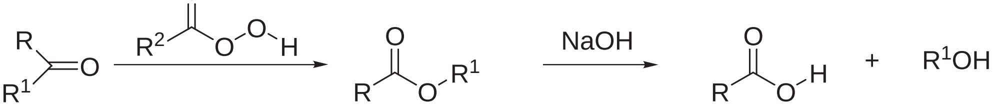
Davis *J. Am. Chem. Soc.* **1983**, *105*, 3123.
Tetrahedron Lett. **1986**, *27*, 5079.
Tetrahedron **1989**, *45*, 5703.

E. Baeyer–Villiger and Related Reactions

Comprehensive Org. Syn. Vol. 7, pp 671–688.
Org. React. **1957**, *9*, 73; **1993**, *43*, 251.

> A. Baeyer received the 1905 Nobel Prize in Chemistry for his work on dyes (indigo). He also discovered barbituric acid and named it after his girlfriend Barbara.

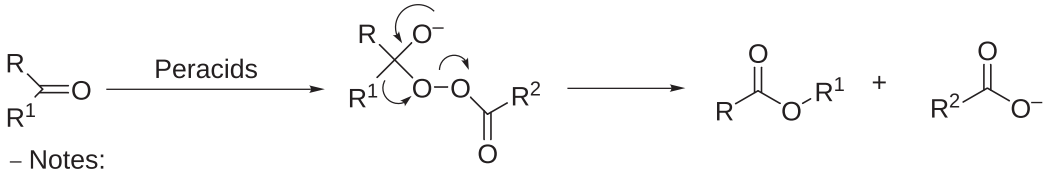
1. Baeyer–Villiger Reaction



Baeyer, Villiger
Ber. **1899**, *32*, 3625.
Ber. **1900**, *33*, 858.

Note: Sometimes the Baeyer–Villiger reaction is used not only for preparing carboxylic acids or esters, but also for ROH.

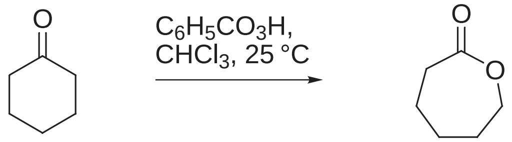
- Mechanism: (Peracid nucleophilic addition reaction)



- Notes:
  1. Alkyl group that migrates does so with retention of configuration.
  2. The more electron-rich (most-substituted) alkyl group migrates in preference (in general).
     ^{t}alkyl > ^{s}alkyl > benzyl > phenyl > ^{n}alkyl > methyl
     Thus, methyl ketones invariably provide acetates.

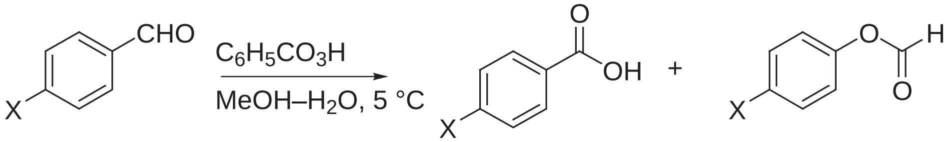
- Examples:

Friess *J. Am. Chem. Soc.* **1949**, *71,* 2571*.*



71%

Ogata *J. Org. Chem.* **1969**, *34*, 3985.

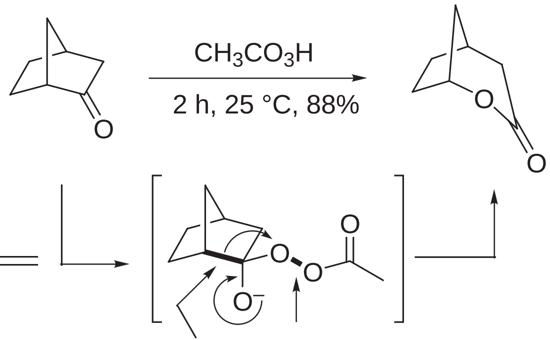


X = H
X = OCH_3

90%
19%

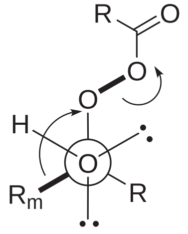
0%
73%

Meinwald *J. Am. Chem. Soc.* **1960**, *82*, 5235.



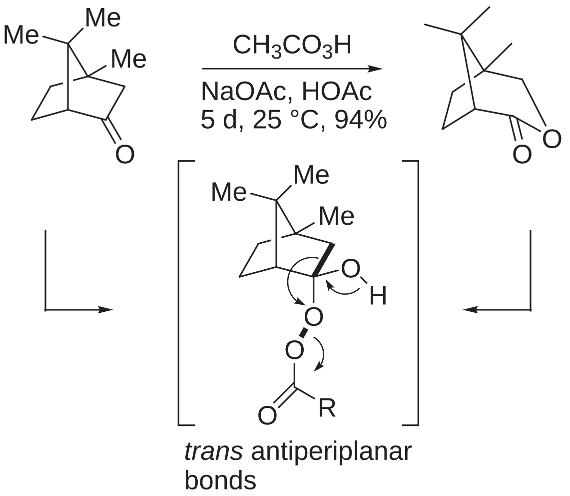
- Nucleophilic attack from least hindered exo face.
- Most substituted (electron-rich) carbon migrates.

Migrating C–C bond and O–O bond must be *trans* antiperiplanar ⟸



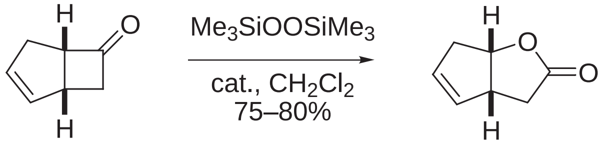
- Antiperiplanar arrangement of C–R_m bond and the breaking O–O bond (stereoelectronic requirement).
- Hydroxyl lone pair or O–H bond antiperiplanar to the migrating C–R_m bond.

Sauers *J. Am. Chem. Soc.* **1961**, *83*, 2759.



- In contrast to simple expectations, the less electron-rich bond migrates due to stereoelectronic considerations.
- Nucleophilic attack from endo face, exo face blocked by Me's.
- Reaction much slower than norbornone.

- Bis(trimethylsilyl) Peroxide $Me_3Si–OO–SiMe_3$



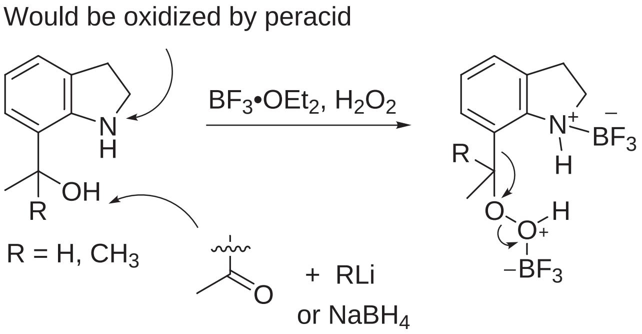
Noyori *J. Org. Chem.* **1982**, *47*, 902.
Nozaki *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2029.

cat. = $Me_3SiSO_3CF_3$, $SnCl_4$, $BF_3•Et_2O$

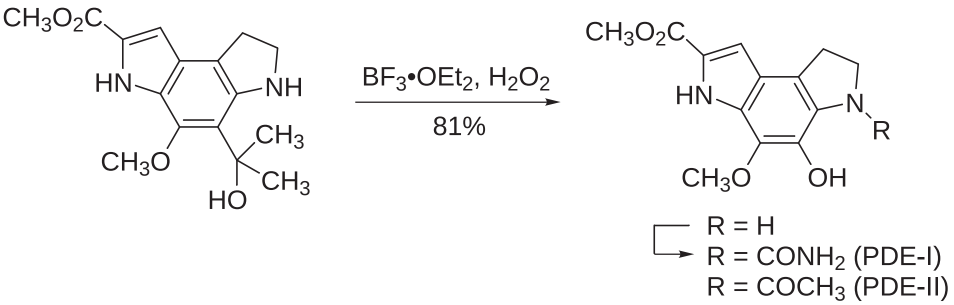
The Baeyer–Villiger oxidation proceeds in a regio- and chemoselective manner and competing epoxidation does not occur.

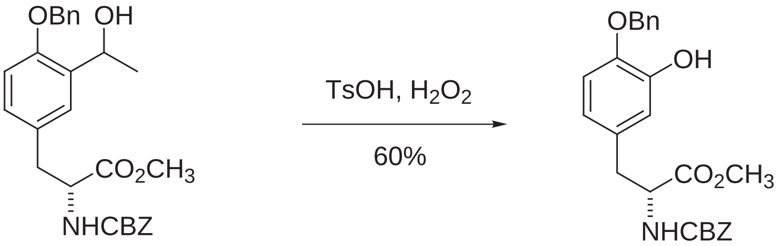
2. Benzylic Hydroperoxide Rearrangement

- Alternative to Baeyer–Villiger Reaction



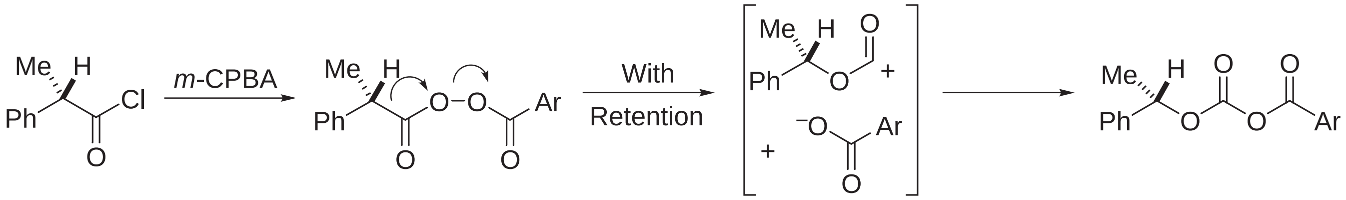
Boger, Coleman
J. Org. Chem. **1986**, *51*, 5436.
J. Am. Chem. Soc. **1987**, *109*, 2717.
Tetrahedron Lett. **1987**, *28*, 1027.





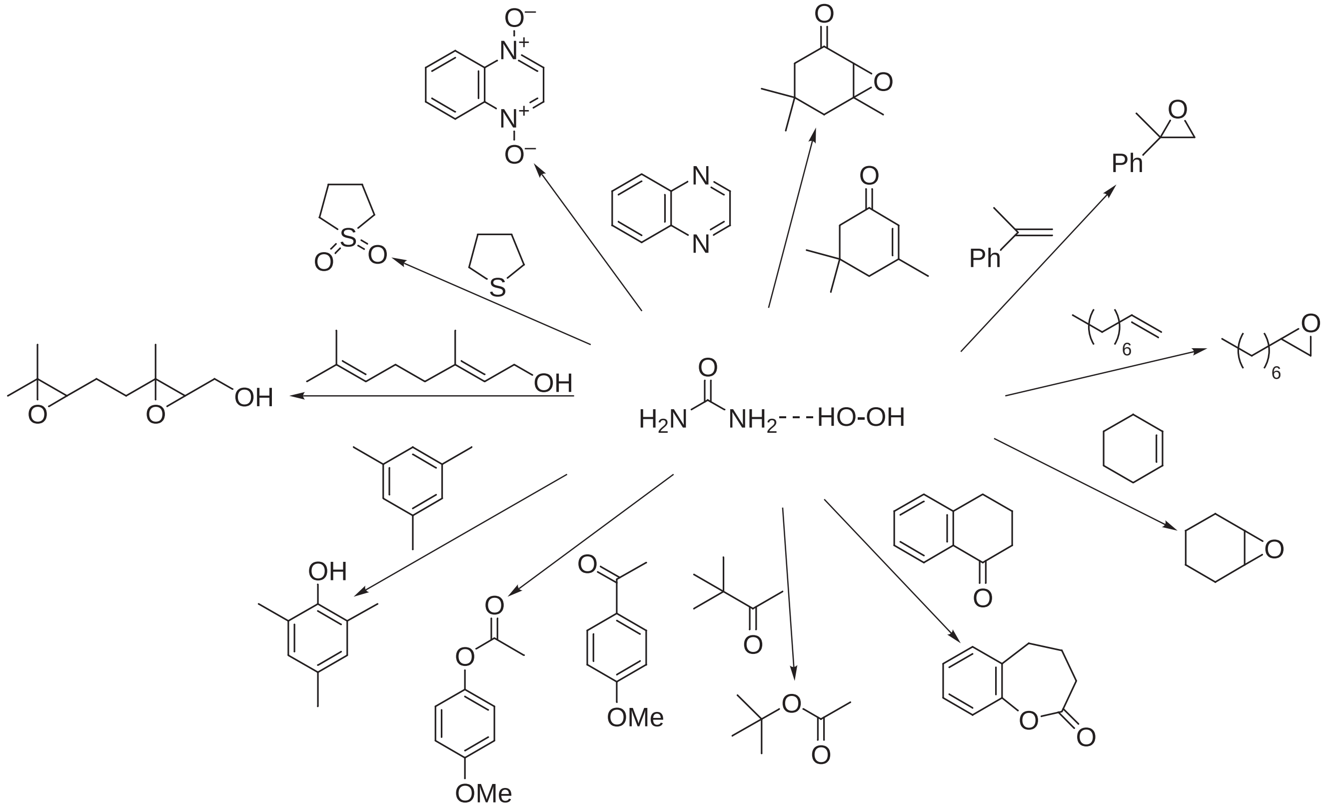
Boger, Yohannes
J. Org. Chem. **1987**, *52*, 5283.

3. Carboxy Inversion Reaction



4. Urea–H_2O_2: a safe alternative to H_2O_2

Heaney *Synlett* **1990**, 533.



- Alternative to 90% H_2O_2 as a source of anhydrous H_2O_2.
- White, crystalline powder.
- Commercially available.
- Dry over $CaCl_2$ in a desiccator.

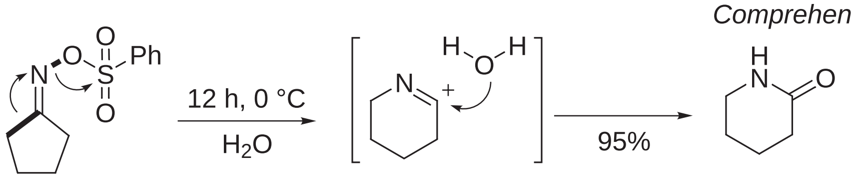
> Friedrich Wohlers' (1800–1882) synthesis of urea, an organic substance, from inorganic materials in 1828 dispelled the belief that biotic powers were needed to produce organic substances and is considered the birth of synthetic organic chemistry. This was first described in a letter to J. J. Berzelius. In a joint paper, the two wrote: "sugar, salicin (the natural product precursor to aspirin), and morphium will be produced artificially. Of course, we do not know the way yet by which the end result may be reached since the prerequisite links are unknown to us from which these materials will develop-however, we will get to know them."

F. Beckmann Rearrangement and Related Reactions

- An analogous rearrangement reaction can be utilized to prepare lactams and amides.

1. Beckmann Rearrangement

Heldt *Org. React.* **1960**, *11*, 1.
Gawley *Org. React*. **1988**, *35*, 1.
Comprehensive Org. Syn., Vol. 7, pp 689–702.

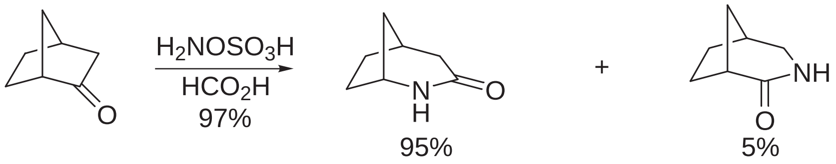


- Prepared from the oxime.

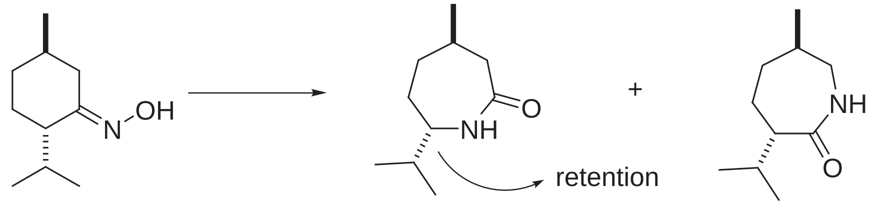
Beckmann *Ber*. **1886**, *19*, 988.

- A wide range of leaving groups and catalysts have been utilized.

1. Group anti to oxime leaving group migrates.
2. The alkyl group migrates with retention of configuration.



Note: Isomerization of oxime or its activated derivative may occur under the reaction conditions and fragmentation to a nitrile may compete when the migrating center is 3°.

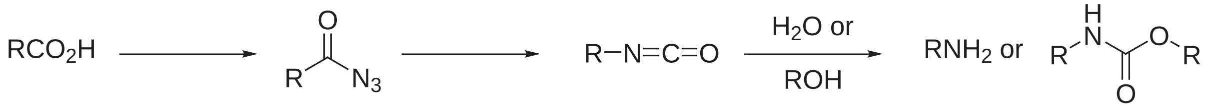


$POCl_3$, pyridine	98%	2%
$SOCl_2$, pyridine	90%	10%
20% aq. H_2SO_4	43%	57%
HCl / Et_2O	5%	95%

2. Curtius Rearrangement

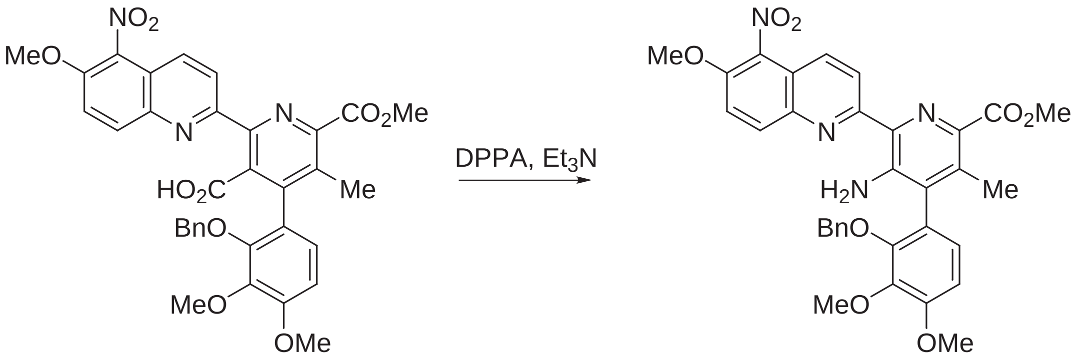
Smith *Org. React.* **1946**, *3*, 337.
Comprehensive Org. Syn., Vol. 6, pp 806–816.

Curtius *Ber.* **1890**, *23*, 3023. (initially not recognized)

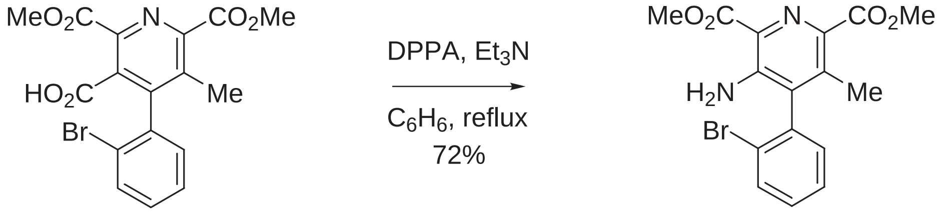


- $(PhO)_2P(O)N_3$ (DPPA) is a useful reagent for the direct conversion of carboxylic acids to acyl azides under *in situ* conditions for the rearrangement. Shiori, Yamada *Tetrahedron* **1974**, *30*, 2151.
- R group migrates with retention of configuration.

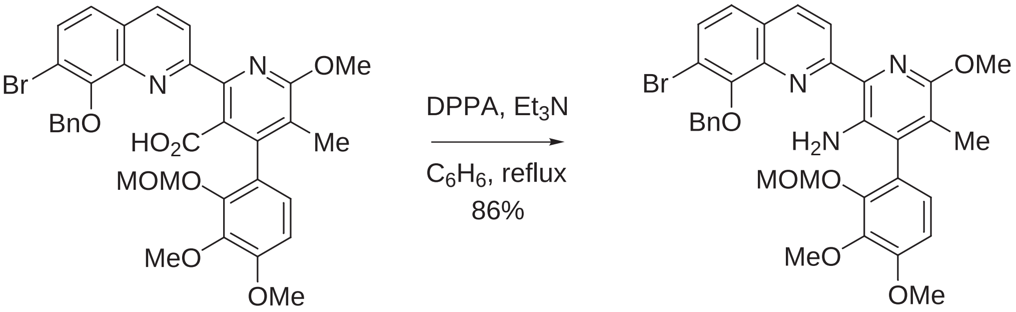
-Examples



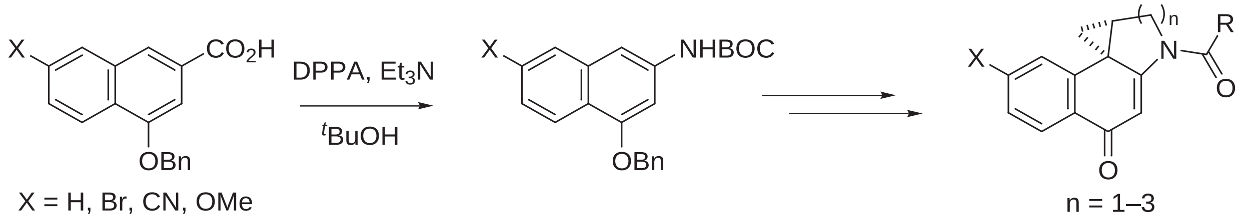
Boger, Panek
(streptonigrin)
J. Am. Chem. Soc.
1985, *107*, 5745.



Boger
(lavendamycin)
J. Org. Chem.
1985, *50*, 5782.



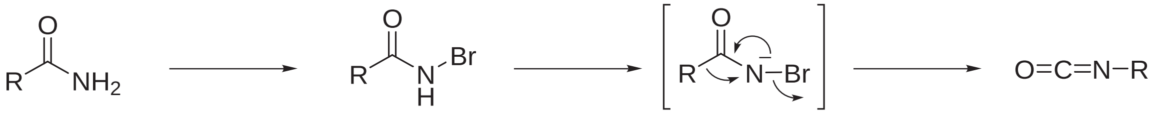
Boger
(streptonigrone)
J. Am. Chem. Soc.
1993, *115*, 10733.



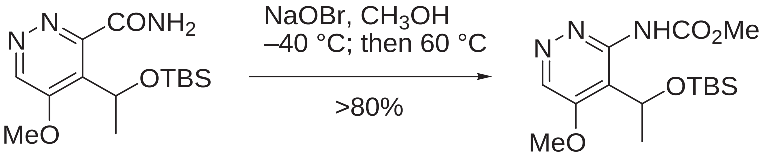
Boger *J. Org. Chem.* **1995**, *60*, 1271;
1996, *61*, 1710 and 4894;
1997, *62*, 5849.
J. Am. Chem. Soc. **1994**, *116*, 11335.
Synlett **1997**, 515.

3. Hofmann Rearrangement

Lane *Org. React.* **1946**, *3*, 267.
Comprehensive Org. Syn., Vol. 6, pp 800–806.



Hofmann *Ber*. **1881**, *14*, 2725.



Boger, Coleman
(PDE-I, PDE-II, CC-1065)
J. Org. Chem. **1986**, *51*, 3250.
J. Am. Chem. Soc. **1987**, *109*, 2717.

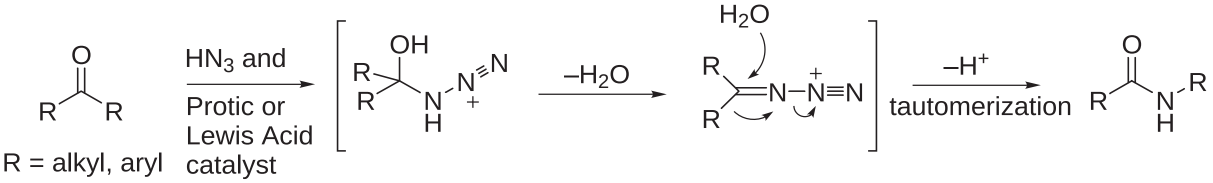
- Reagents employed include basic hypohalides, $Pb(OAc)_4$, $PhI(OCOCF_3)_2$, PhIO.
- R group migrates with retention of configuration.

4. Schmidt Reaction

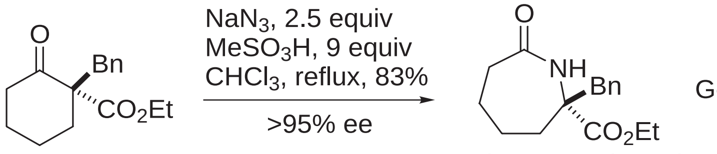
Schmidt *Angew. Chem.* **1923**, *36*, 511.
Wolff *Org. React.* **1946**, *3*, 307.
Comprehensive Org. Syn., Vol. 6, pp 817–821.

The Schmidt Reaction is a general name for what are three individual reactions:

A. Conversion of Ketones to Amides

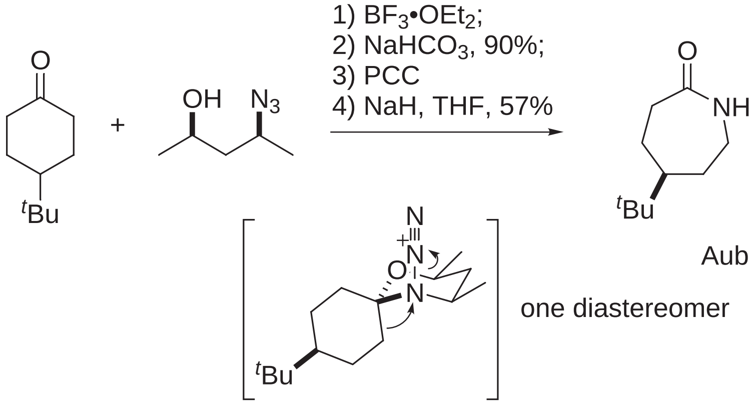


- Most studied of Schmidt variants, similar to Beckmann Rearrangement.
- Asymmetric variant (Aube) utilizes chiral alkyl azide donors which provide products in high diastereoselectivity.
- Bicyclic ketones slightly favor migration of less substituted group, opposite of Beckmann.
- Reactivity: dialkyl ketone > alkyl,aryl ketone > diaryl ketone > carboxylic acid or alcohol.



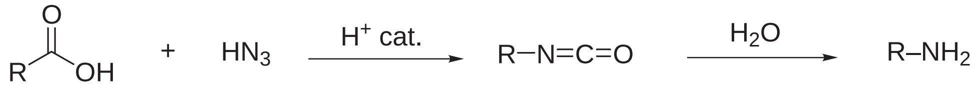
retention of configuration

Georg *Bioorg. Med. Chem. Lett.* **1991**, *1*, 125.



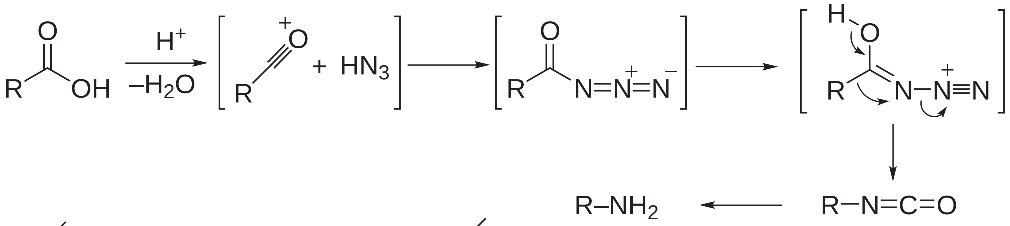
Aube *J. Am. Chem. Soc.* **1995**, *117*, 8047.

B. Conversion of Carboxylic Acids to Amines



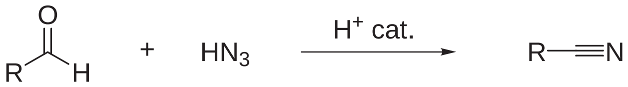
- Acid catalyst usually H_2SO_4, PPA, TFA–TFAA, or sometimes Lewis acid.
- Good results when R = alkyl, hindered alkyl or aryl.
- Advantage in process length over Hofmann and Curtius Rearrangements, but more drastic conditions.
- Mechanism controversy.

Hayes *J. Org. Chem.* **1979**, *44*, 3682.
Koldobskii *Russ. Chem. Rev.* **1978**, *47*, 1084.

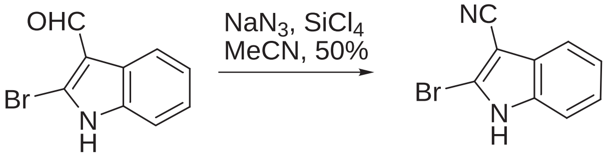


Sato *Tetrahedron: Asymmetry* **1992**, *3*, 5.

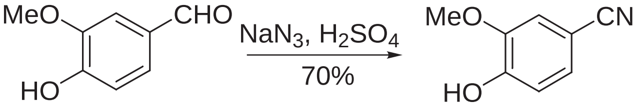
C. Conversion of Aldehydes to Nitriles



- Acid catalyst usually H_2SO_4, can be Lewis acid.
- Schmidt reaction is the usual byproduct under these conditions to provide formamide.
- More common method is to convert aldehyde to oxime with hydroxylamine, followed by dehydration.
- Aromatic aldehydes are good substrates.



Elmorsy *Tetrahedron Lett.* **1995**, *36*, 2639.



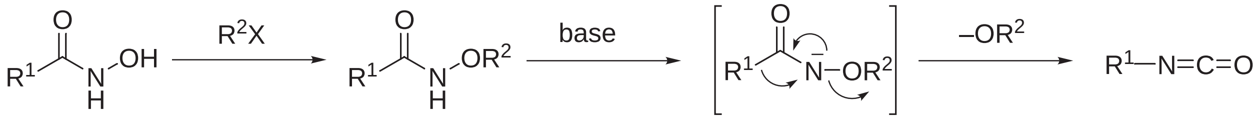
Houff *J. Org. Chem.* **1957**, *22*, 344.

The airbag restraint system in cars is inflated in a fraction of a second by the release of N_2 gas. The nitrogen comes from explosion of a mixture of $NaNO_3$ and amorphous boron initiated by electronic priming with NaN_3.

5. Lossen Rearrangement

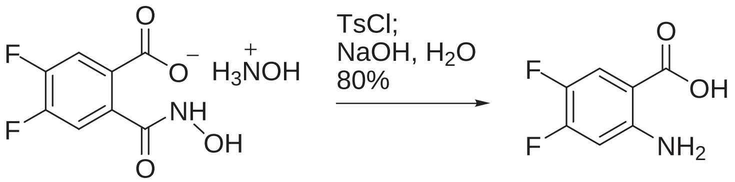
Lane *Org. React.* **1946**, *3*, 269 and 366.
Comprehensive Org. Syn., Vol. 6, pp 821–823 (basic conditions)
pp 824–825 (neutral/acidic)

Lossen *Liebigs Ann. Chem.* **1872**, *161*, 347.

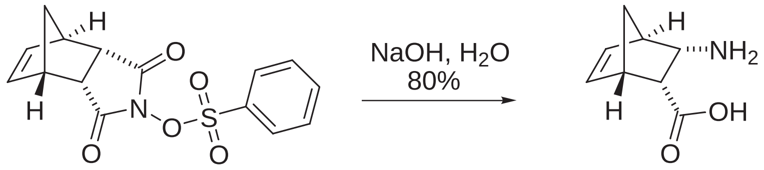


Hydroxamic acid
-prepared readily from carboxylic acids, esters or acyl halides

- R^{2}X usually AcCl, ArSO$_2$Cl, RPO$_2$Cl
- rate of reaction proportional to the acidity of leaving group conjugate acid
- R^1 migrates with retention of configuration

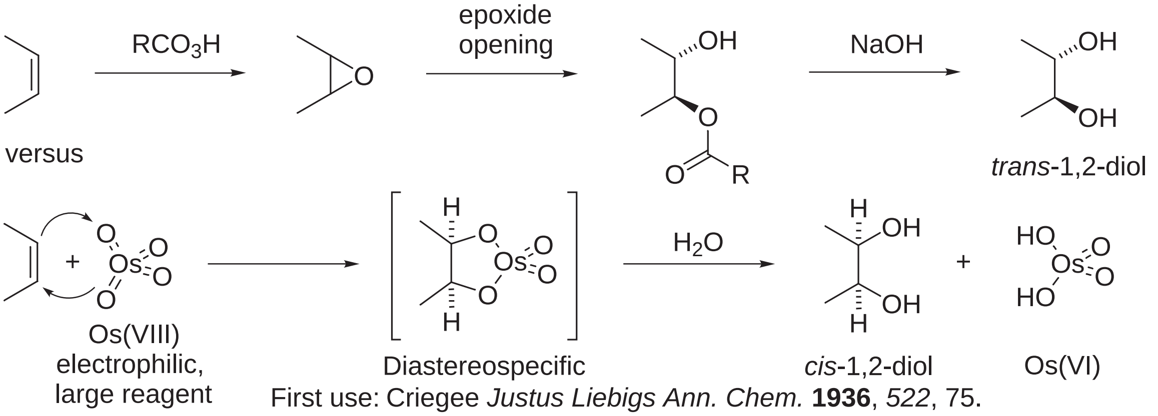


Braish *Syn. Commun.* **1992**, *22*, 3067.



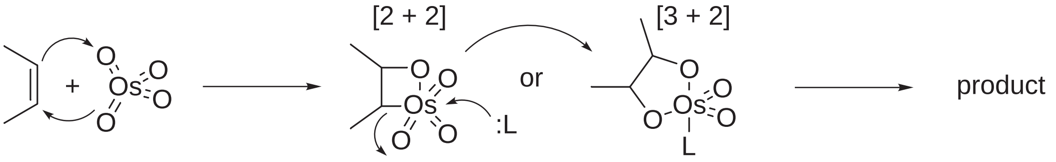
Bauer *J. Org. Chem*. **1959**, *24*, 1293.

G. Olefin Osmylation (Dihydroxylation)



First use: Criegee *Justus Liebigs Ann. Chem.* **1936**, *522*, 75.
Milas *J. Am. Chem. Soc.* **1936**, *58*, 1302.

1. Mechanism



[2 + 2] Mechanism:

Sharpless *J. Am. Chem. Soc.* **1977***, 99*, 3120.
Jorgensen *Chem. Rev.* **1990**, *90*, 1483.
Sharpless *Angew. Chem. Int. Ed. Eng.* **1993**, *32*, 1339.

[3 + 2] Mechanism:

Boeseken *Recl. Trav. Chim.* **1922**, *41*, 199.
Criegee *Angew. Chem.* **1938**, *51*, 519.
Criegee *Justus Liebigs Ann. Chem.* **1942**, *550*, 99.

2. Scope *Comprehensive Org. Syn.,* Vol. 7, pp 437–448. *Chem. Rev.* **1980**, *80*, 187.

1. OsO$_4$ is an electrophilic reagent, and it behaves as a large reagent.
2. Strained, unhindered olefins react faster than unstrained, sterically hindered olefins.
3. Electron-rich olefins react faster than electron-deficient olefins.
4. Diastereospecific, with attack on the C=C from the least hindered face.

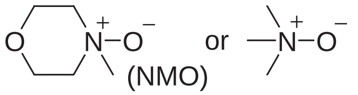
-but OsO_4 is expensive, volatile, and toxic

-various improvements: 1) only catalytic amount of OsO_4 used
2) use of an equivalent osmium salt ($K_2OsO_2(OH)_4$)

Examples:

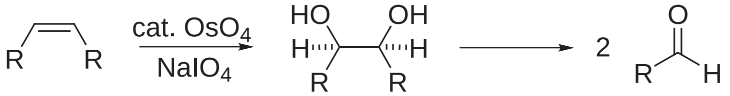
H_2O_2, cat. OsO_4 — *J. Am. Chem. Soc.* **1936**, *58*, 1302; **1937**, *59*, 2345; *Synthesis* **1989**, 295.

${}^tBuOOH$, cat. OsO_4 — Sharpless *J. Org. Chem.* **1978**, *43*, 2063.



Tetrahedron Lett. **1976**, 1973;
Tetrahedron Lett. **1980**, *21*, 449.

Note: Johnson–Lemieux Oxidation ($NaIO_4$ and catalytic OsO_4 cleaves C=C bonds, forms diol and then aldehyde: *J. Org. Chem.* **1956**, *21*, 478).



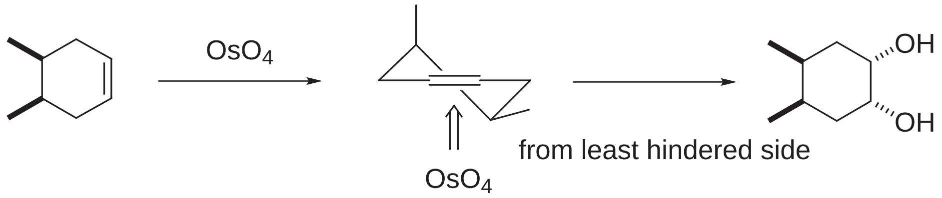
-Alternative reagents to OsO_4:

$KMnO_4$: *Synthesis* **1987**, 85.
Yields rarely as high as OsO_4 but less hazardous and less expensive especially for large scale

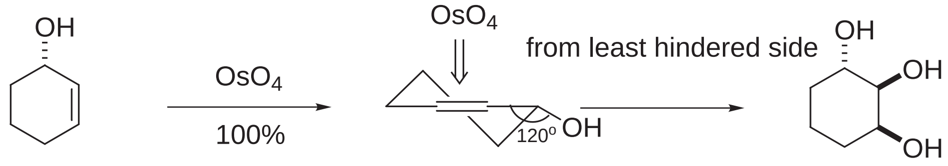
RuO_4 or $RuO_2–2H_2O/RuCl_3–H_2O$ + cooxidant
More vigorous than OsO_4 and olefin cleavage is observed

3. Diastereoselectivity

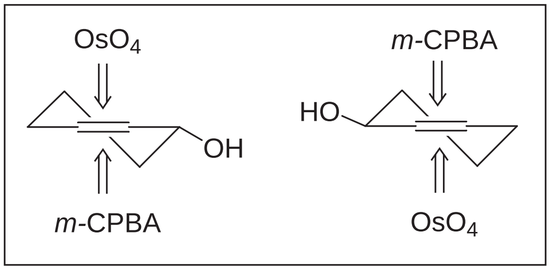
a. Endocyclic Olefins

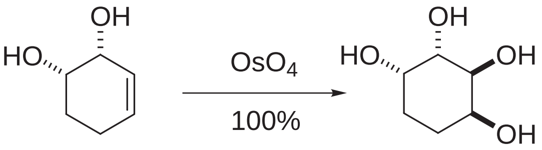


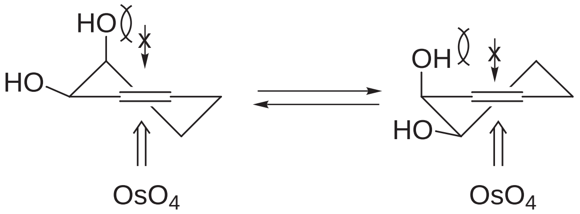
-endocyclic allylic alcohols

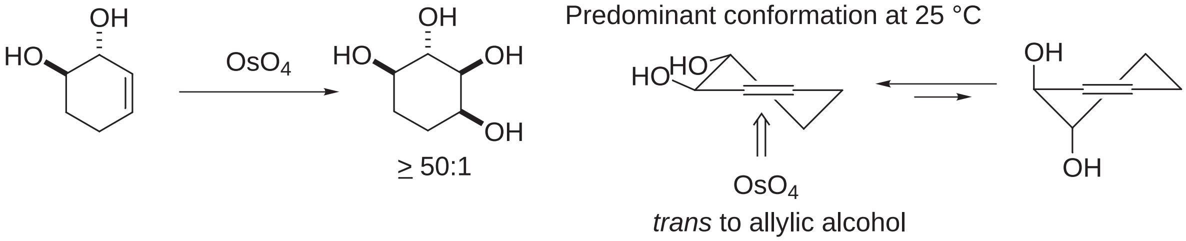


Note: *m*-CPBA comes in *cis* to the allylic -OH, but OsO_4 comes in *trans* to the allylic -OH.
So, we obtain:





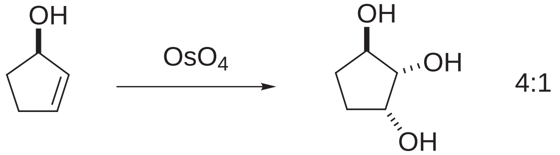




≥ 50:1

Predominant conformation at 25 °C

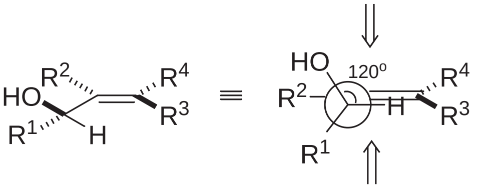
trans to allylic alcohol



b. Acyclic Systems

- OsO_4 is delivered from face opposite the allylic hydroxyl group in the preferred (H-eclipsed) ground state conformation.

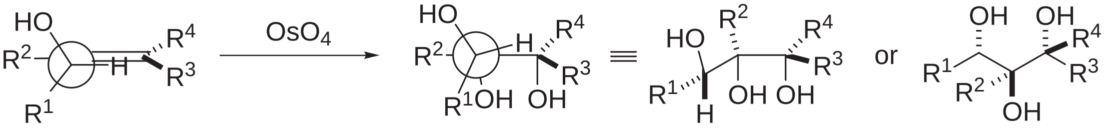
m-CPBA (*cis* to allylic alcohol 120°)



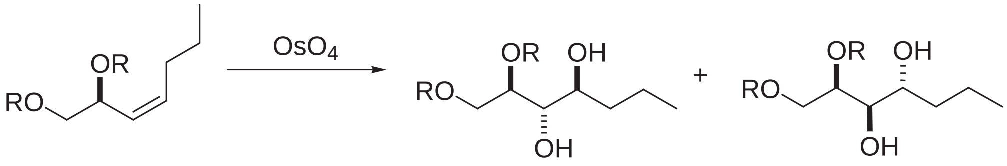
OsO_4 (*trans* to allylic alcohol 120°)

- Kishi model (empirical model).
  So, for the OsO_4 oxidation:

Tetrahedron Lett. **1983**, *24,* 3943, 3947.
Tetrahedron **1984**, *40*, 2247.



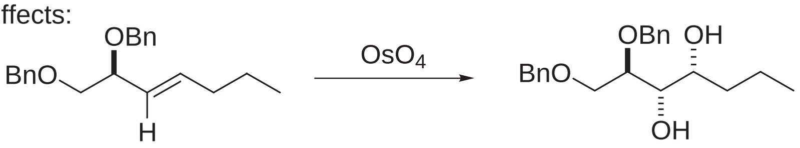
- Preferred ground state conformation (higher diastereoselection when R^3 is not H).
- Also observed with allylic ethers



		erythro		*threo*
1) electronic effects:	R = Bn	8.9	:	1
	R = CO_2CH_3	2	:	1
	R = COC_6H_4-NO_2	1	:	1

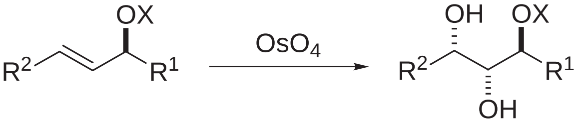
electronic effect of alkoxy substituent directs osmylation to reverse face

2) steric effects:

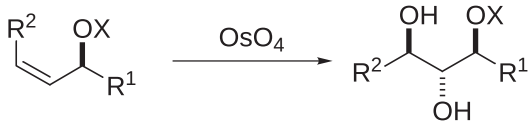


7:1, modest selectivity

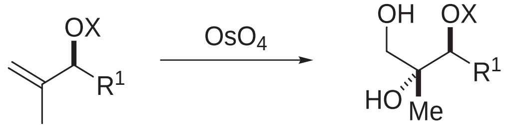
- Higher diastereoselectivity of *Z* vs. *E* isomer implies eclipsed conformation important.



< 8:1, modest selectivity
(anti 1,2-diol relationship)



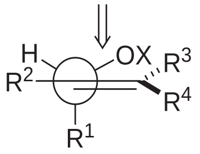
high selectivity



moderate to high selectivity

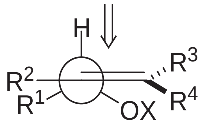
- As R^1 increases in size relative to OX, the selectivity increases.
- X-effect (steric effect): smaller X provides better selectivity.
- There are additional empirical models used to explain the acyclic allylic alcohol induced diastereoselectivity:

1. Houk Model (inside alkoxy model):
Science **1986**, *231*, 1108.



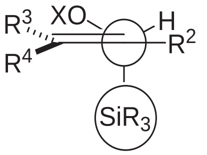
non ground state conformation

2. Vedejs Model:
J. Am. Chem. Soc. **1989**, *111*, 6861.



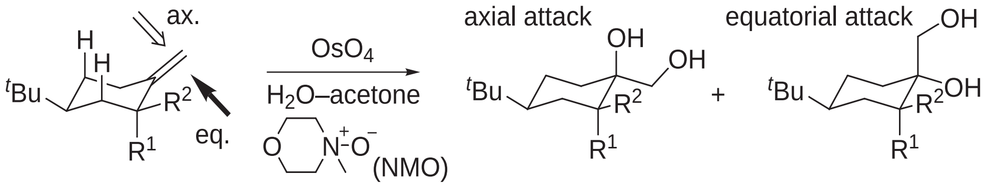
OsO_4 is large reagent; steric effects between reagent & allylic substituent are important factors

3. Panek:
J. Am. Chem. Soc. **1990**, *112*, 4873.



selectivity increases:
a) OH > OR
b) now *E* > *Z*
c) with very large R^1: inside alkoxy or anti Si

c. Exocyclic Olefins: Vedejs *J. Am. Chem. Soc.* **1989**, *111*, 6861.



R^1	R^2	ax.	eq.
H	H	14	86
H	OH	<5	95
H	OCH_3	<5	95
CH_3	OCH_3	20	80
H	OAc	8	92
H	SCH_3	<5	95
OH	H	33	67
OH	CH_3	14	86
OCH_3	H	88	12
OCH_3	CH_3	90	10
OAc	CH_3	67	33
SCH_3	H	92	8

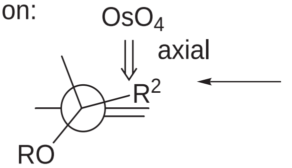
OsO_4 is a large reagent, prefers equatorial attack

Consistent with Kishi empirical model
Inconsistent with Houk model

H-bonding?

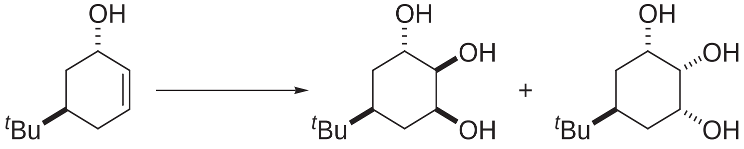
Equatorial attack predominates, except with axial OCH_3, OAc, SMe: In these cases, equatorial attack further retarded and proceeds at even slower rate (kinetic studies)

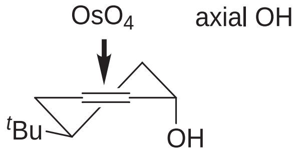
Exception:



d. H-Bonding and Directed Dihydroxylation

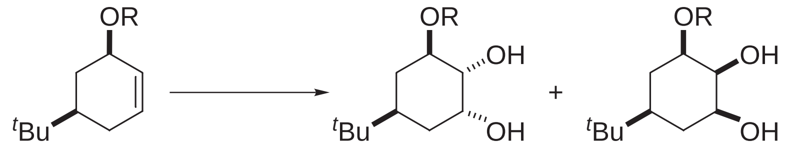
Cyclic allylic alcohols

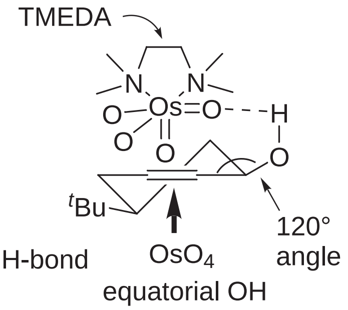




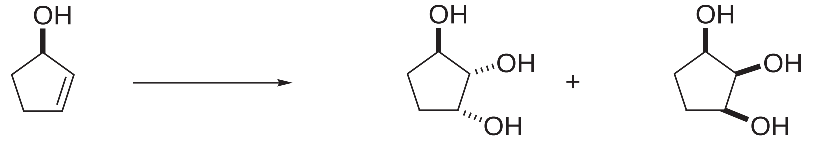
cat. OsO_4, NMO, acetone–H_2O	94:6	(90%)
1 equiv OsO_4, CH_2Cl_2 (anhydrous)	75:25	(97%)

competing H-bonding delivery reduces diastereoselectivity

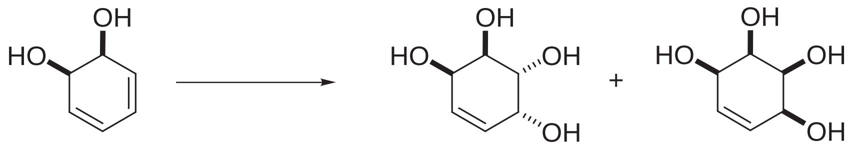




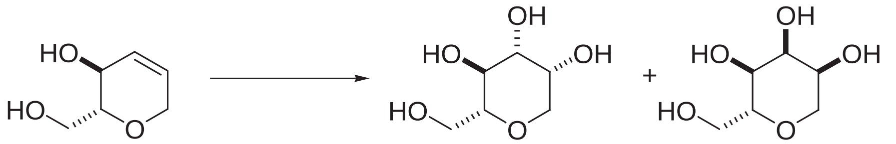
R = H:	cat. OsO_4, NMO, acetone–H_2O	85:15	(91%)	
	1 equiv OsO_4, CH_2Cl_2	63:37	(45%)	competing H-bond delivery
	cat. OsO_4, Me_3NO, CH_2Cl_2	45:55	(55%)	
	1 equiv OsO_4, TMEDA, CH_2Cl_2, –78 °C	4:96	(91%)	← H-bond delivery
R = CH_3:	1 equiv OsO_4, CH_2Cl_2	95:5		← no H-bonding



cat. OsO_4, NMO, acetone–H_2O	80:20		
1 equiv OsO_4, TMEDA, CH_2Cl_2, –78 °C	12:88	(76%)	← H-bond delivery



cat. OsO_4, NMO, acetone–H_2O	75:25		
1 equiv OsO_4, TMEDA, CH_2Cl_2, –78 °C	5:95	(54%)	← H-bond delivery

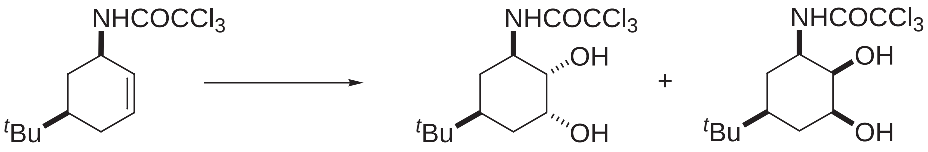


cat. OsO_4, NMO, acetone–H_2O	94:6		
1 equiv OsO_4, TMEDA, CH_2Cl_2, –78 °C	14:86	(63%)	← H-bond delivery

- OsO_4–TMEDA can also be utilized to effect chemoselectivity by preferentially oxidizing allylic alcohols over unactivated (non allylic -OH) double bonds.

  Donohoe *Tetrahedron Lett.* **1996**, *37*, 3407; *Tetrahedron Lett.* **1997**, *38*, 5027.

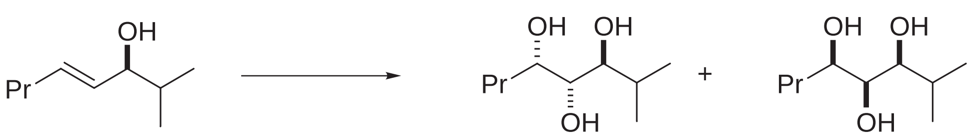
- Catalytic procedures require QNO (quinuclidine *N*-oxide) and a strong H-bond donor (–$NHCOCCl_3$)

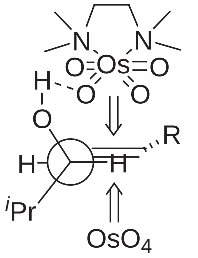


cat. OsO_4, NMO, acetone–H_2O, 25 °C	1.6:1	(96%)	
cat. OsO_4, Me_3NO, CH_2Cl_2, 25 °C	1:6	(81%)	
cat. OsO_4, QNO, CH_2Cl_2, 25 °C	1:13	(77%)	← H-bond delivery

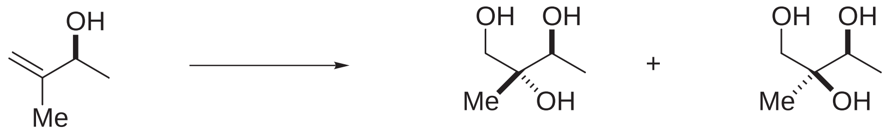
Donohoe *Tetrahedron Lett.* **2000**, *41*, 4701.

Acyclic allylic alcohols

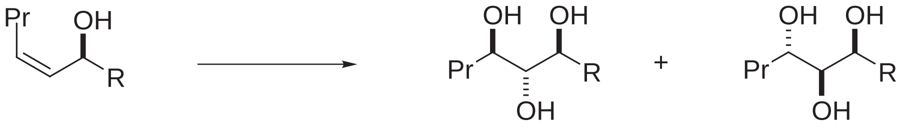


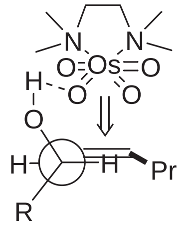


cat. OsO_4, NMO, acetone–H_2O 80:20 (86%)
1 equiv OsO_4, TMEDA, CH_2Cl_2, – 78 °C 25:75 (84%) ← H-bond delivery (empirical model)

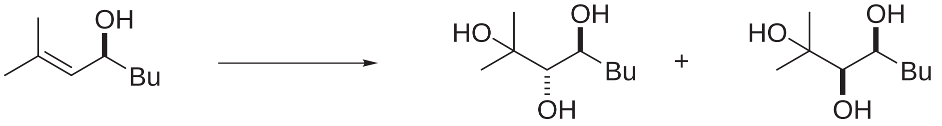


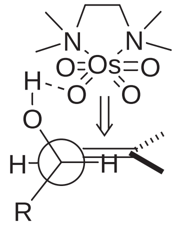
cat. OsO_4, NMO, acetone–H_2O 90:10 (71%)
1 equiv OsO_4, TMEDA, CH_2Cl_2, – 78 °C 67:33 (75%)





R = Pr: cat. OsO_4, NMO, acetone–H_2O 38:62 (76%)
1 equiv OsO_4, TMEDA, CH_2Cl_2, – 78 °C 4:>96 (74%)
R = ^{i}Pr: cat. OsO_4, NMO, acetone–H_2O 20:80 (85%)
1 equiv OsO_4, TMEDA, CH_2Cl_2, – 78 °C 4:>96 (79%)





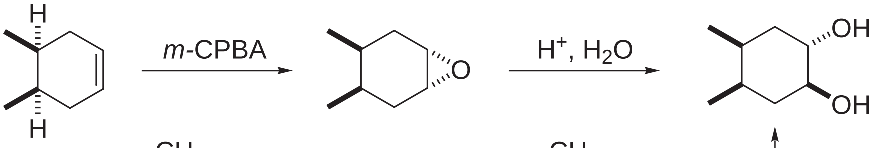
cat. OsO_4, NMO, acetone–H_2O 34:66 (96%)
1 equiv OsO_4, TMEDA, CH_2Cl_2, – 78 °C 4:>96 (78%)

- Results with OsO_4/TMEDA are analogous to the *m*-CPBA epoxidation of acyclic allylic alcohols and are derived from a H-bonded delivery from a H-eclipsed conformation.

Donohoe *Tetrahedron Lett.* **1999**, *40*, 6881.

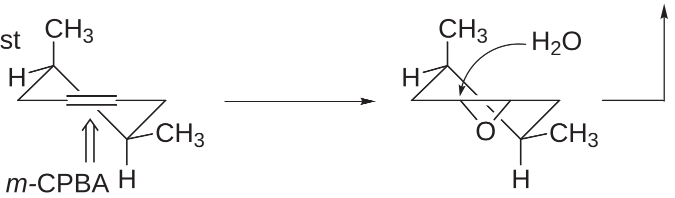
4. Comparison of Diol Stereochemistry Generated by Different Methods

a. *m*-CPBA



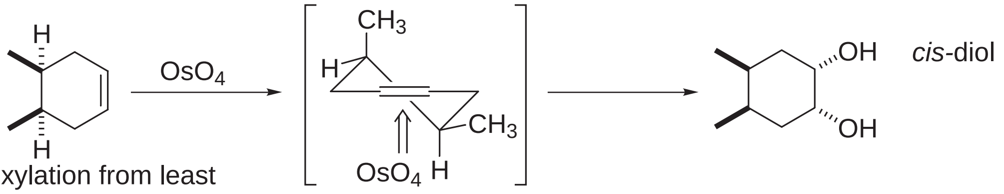
trans-diol

-Epoxidation from least hindered face



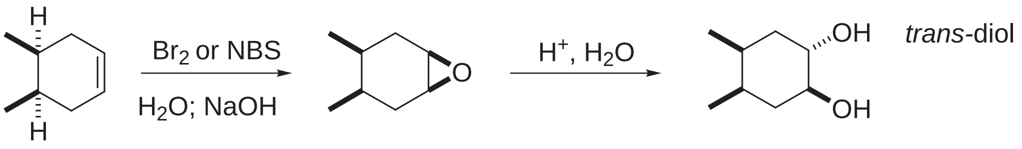
trans diaxial opening of epoxide

b. OsO_4

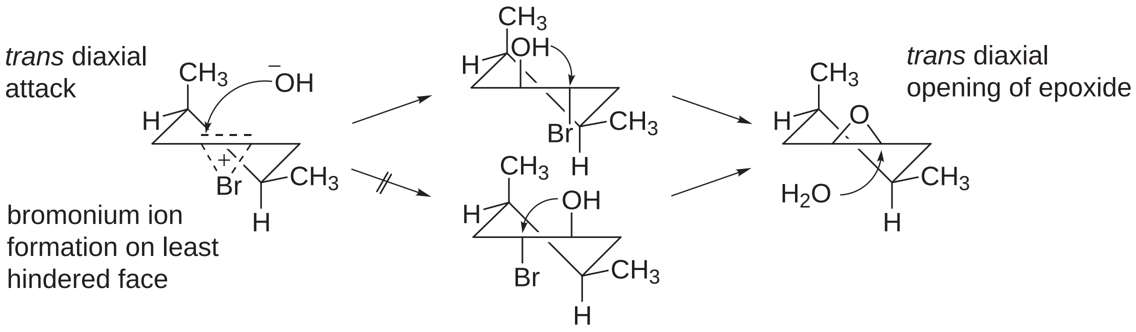


-*cis* dihydroxylation from least hindered face (OsO_4 is a large reagent)

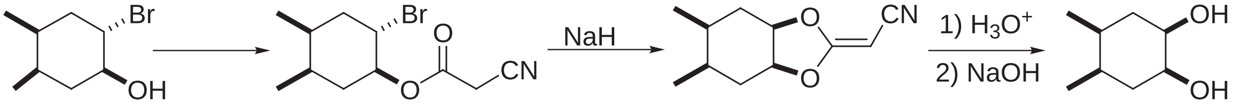
c. Via Bromohydrin



-Epoxidation on most hindered face of olefin (to give different epoxide from *m*-CPBA oxidation), *trans* diaxial ring opening (to give same hydrolysis product as from *m*-CPBA oxidation)

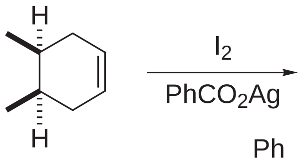


-Corey *Tetrahedron Lett.* **1982**, *23*, 4217: *cis* dihydroxylation from most hindered olefin face.

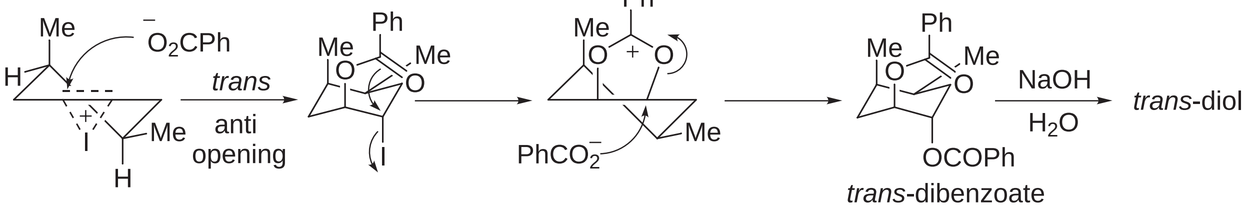


d. Prevost

Compt. rend. **1933**, *196*, 1128.

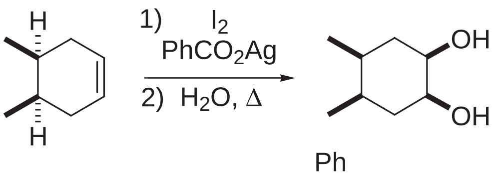


-Neighboring Group Participation

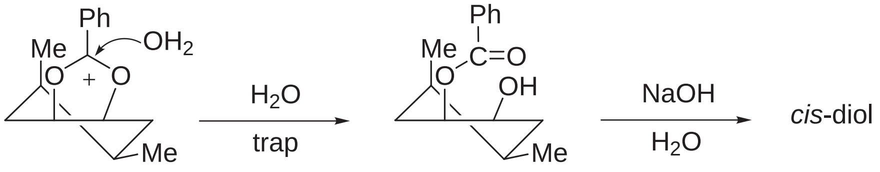


e. Woodward

J. Am. Chem. Soc. **1958**, *80*, 209.



-Complements OsO_4 reaction (i.e. *cis* dihydroxylation from most hindered face)



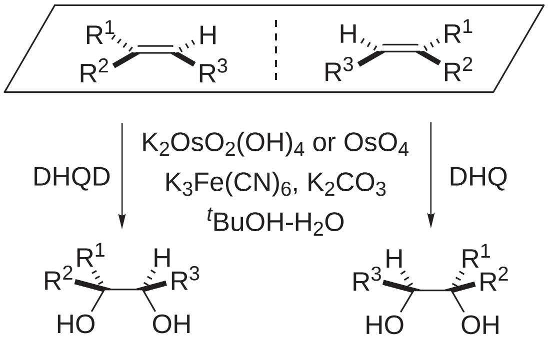
-Same intermediate as Prevost, but different conditions (+ H_2O)

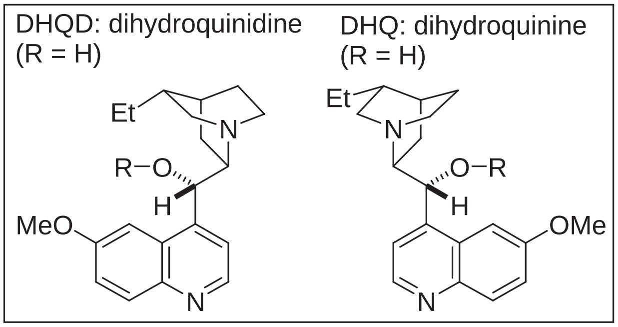
H. Asymmetric Dihydroxylation Reaction Catalyzed by OsO_4 and Related Reagents

1. Catalytic Methods

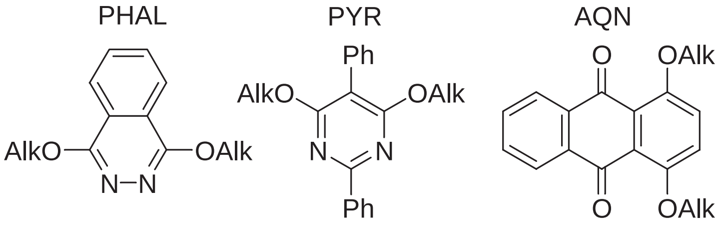
Sharpless Catalytic Asymmetric Dihydroxylation (AD) Reaction, Review: *Chem. Rev.* **1994**, *94*, 2483.

J. Am. Chem. Soc. **1980**, *102*, 4263.
J. Am. Chem. Soc. **1988**, *110*, 1968.
J. Am. Chem. Soc. **1989**, *111*, 1123.
Tetrahedron Lett. **1989**, *30*, 2041.
Tetrahedron Lett. **1990**, *31*, 2999, 3003, 3817.
J. Org. Chem. **1991**, *56*, 4585.
J. Org. Chem. **1992**, *57*, 2768.
J. Am. Chem. Soc. **1992**, *114*, 7568, 7570.
Tetrahedron Lett. **1993**, *34*, 7375.
J. Org. Chem. **1993**, *58*, 3785.
J. Am. Chem. Soc. **1994**, *116*, 1278.
Angew. Chem., Int. Ed. Eng. **1996**, *35*, 448.

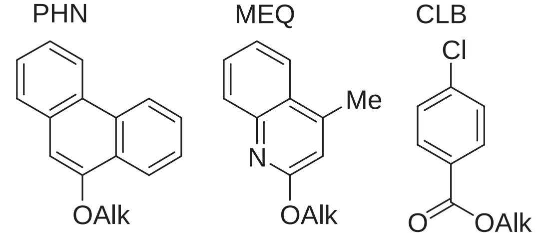




Second Generation Ligands (Alk = DHQ or DHQD)



First Generation Ligands (Alk = DHQ or DHQD)



Catalyst: OsO_4 (1.25 mol%) or $K_2OsO_2(OH)_4$ (0.05 mol%, nonvolatile)
Solvent: ^{t}BuOH or cyclohexane, H_2O, K_2CO_3
Ligands: DHQD or DHQ (0.2 to 0.004 mol%)
Oxidant to recycle OsO_4: $K_3Fe(CN)_6$

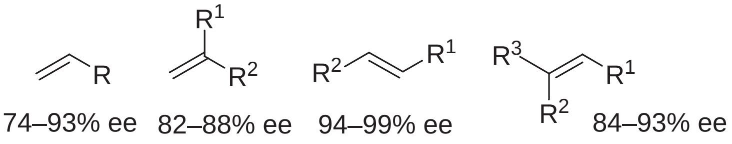
Note: **Ligand accelerated catalysis**, Sharpless *Angew. Chem., Int. Ed. Eng.* **1995**, *34*, 1059.

-Addition of pyr led to marked increase in rate of formation of cyclic osmate ester from alkene and OsO_4. First noted by Criegee *Justus Liebigs Ann. Chem.* **1936**, *522*, 75; **1940**, *550*, 99.

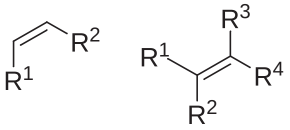
-The "Criegee effect" (or the facilitation of osmylation step by nitrogen donor) has been examined with quinuclidine and cinchona alkaloid ligands: Sharpless *J. Am. Chem. Soc.* **1994**, *116*, 1278, 8470.

-Results:

Good to excellent selectivity (ee%) for:

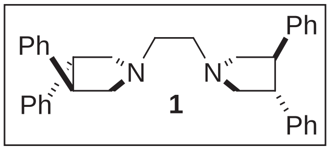


Poor selectivity for:

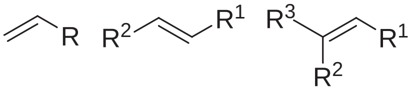


2. Stoichiometric methods

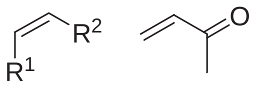
-Tomioka *J. Am. Chem. Soc.* **1987**, *109*, 6213.



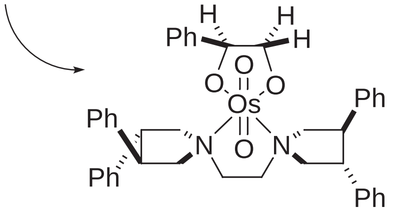
Using **1** as a chiral ligand, good selectivity for:



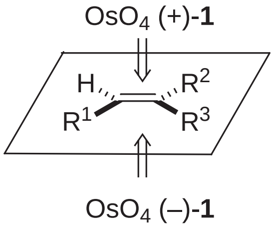
Poor selectivity for:

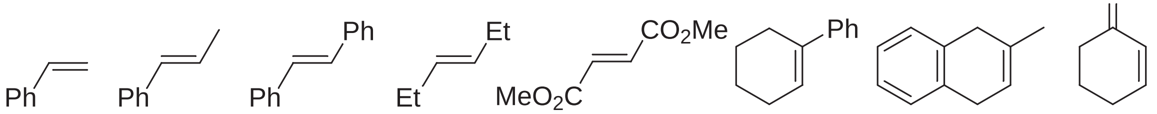


- Product does not seem to reflect most favorable steric approach for [3 + 2] cycloaddition but is more easily rationalized by [2 + 2].



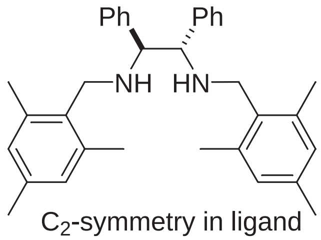
X-ray structure
stoichiometric reagent
(LiAlH$_4$ to reduce off osmate ester)



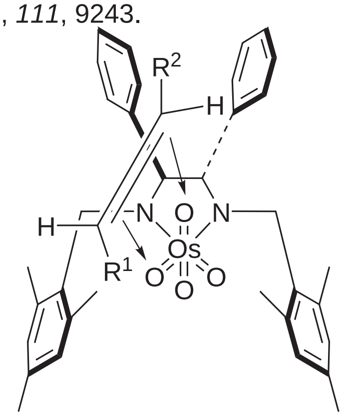


ee: 90% 95% 97% 90% 93% 83% 26% 41%

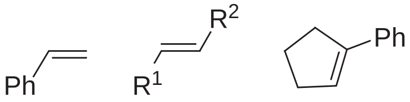
-Corey *J. Am. Chem. Soc.* **1989**, *111*, 9243.



C$_2$-symmetry in ligand
Os (6 coordinate)
nucleophilic equatorial oxygen
electrophilic axial oxygen



Ligand accelerated reaction
OsO$_4$, –90 °C, 2 h

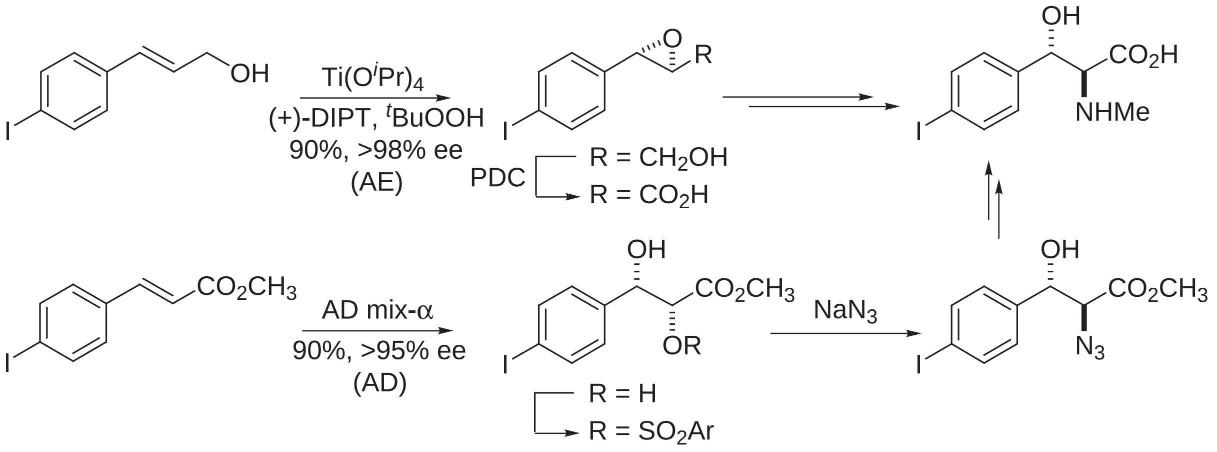


92% ee 82–98% ee 60% ee

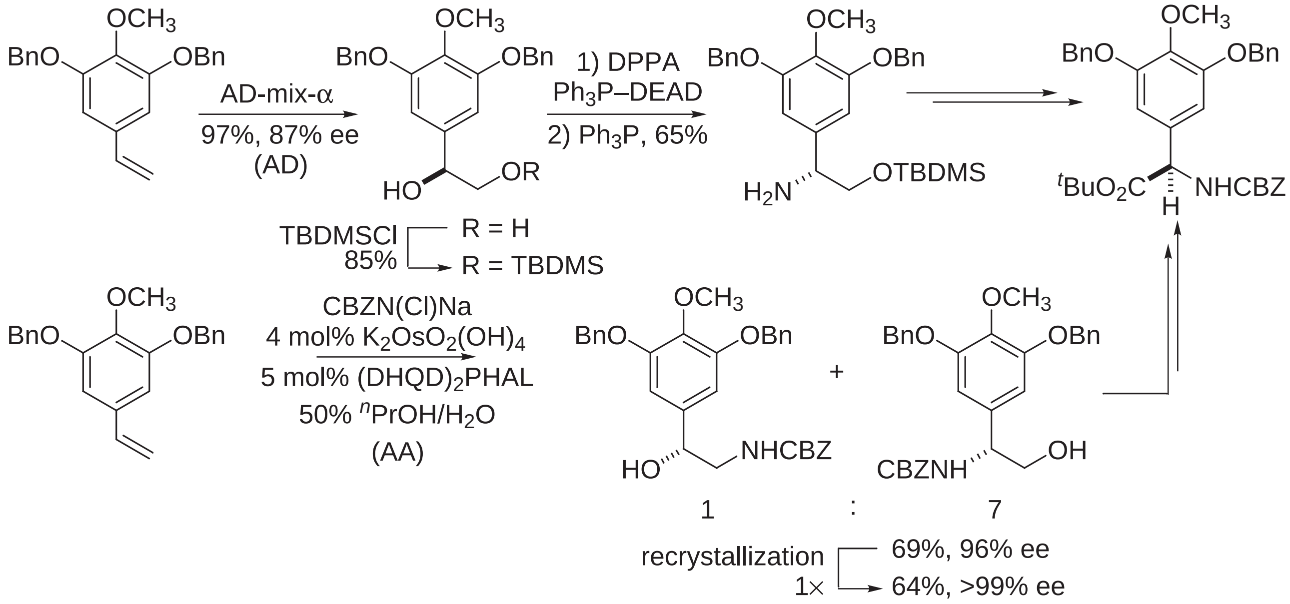
-Other stoichiometric reagents: *Chem. Lett.* **1986**, 131.
Tetrahedron Lett. **1986**, *27*, 3951.
Tetrahedron Lett. **1990**, *31*, 1741.
Chem. Commun. **1989**, 665.
J. Org. Chem. **1989**, *54*, 5834.
Tetrahedron **1993**, *49*, 10793.

3. Examples

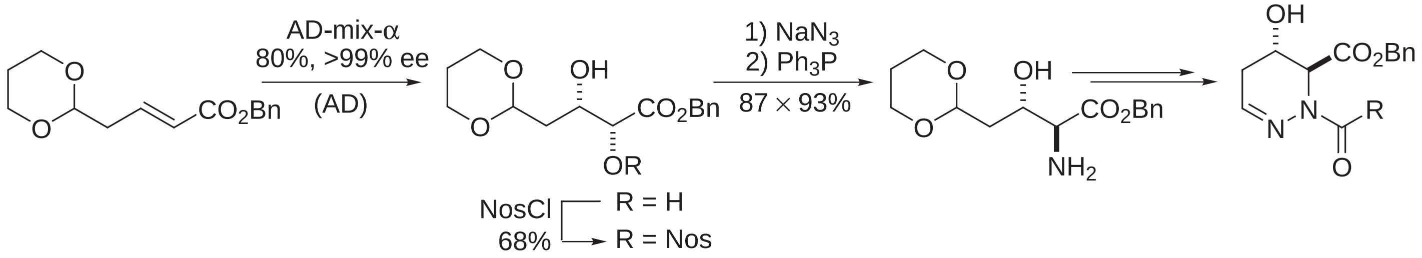
-Total synthesis of Bouvardin and RA-VII: Boger *J. Am. Chem. Soc.* **1994**, *116*, 8544.



-Vancomycin central amino acid: Boger *J. Org. Chem.* **1996**, *61*, 3561; *J. Org. Chem.* **1997**, *62*, 4721.

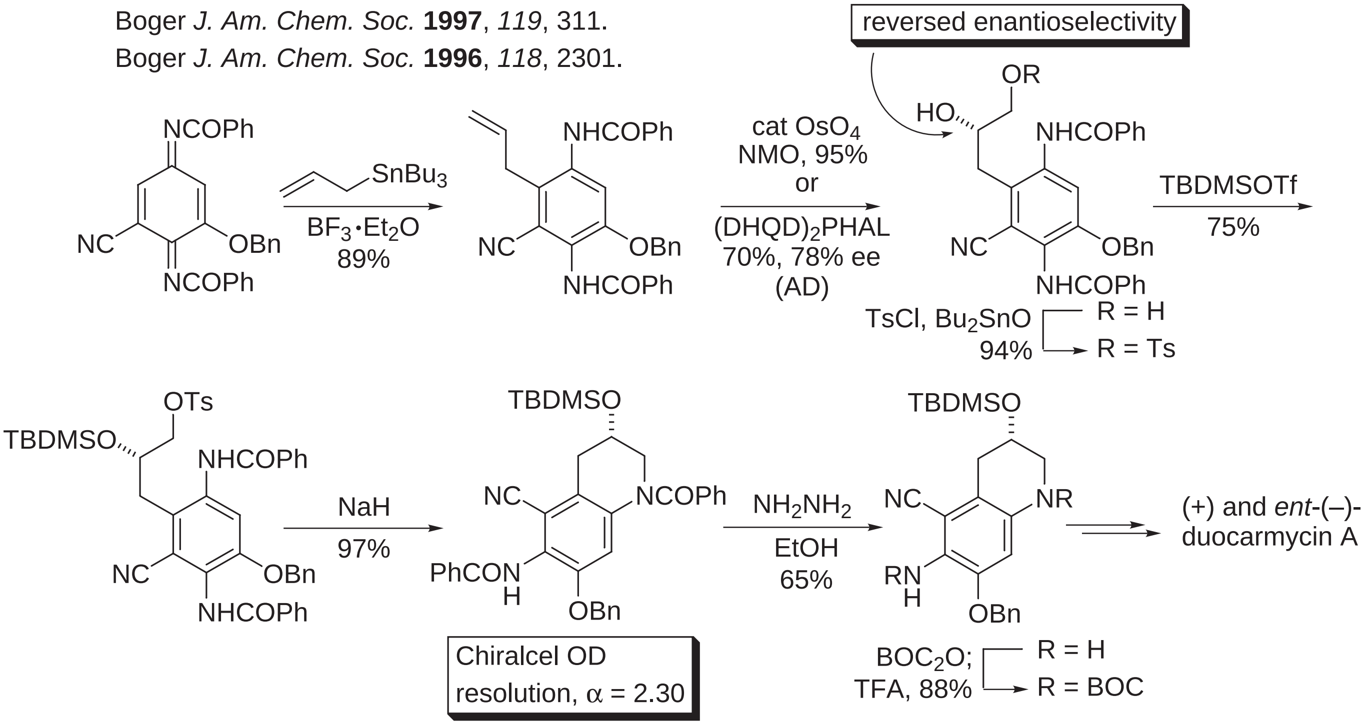


-Luzopeptin Htp amino acid: Boger *J. Org. Chem.* **1998**, *63*, 6421; *J. Am. Chem. Soc.* **1999**, *121*, 1098.



-Prediction of absolute stereochemistry is so firmly documented that it may be used to assign absolute stereochemistry. However, there are a few rare exceptions to be aware of, for example:

Boger *J. Am. Chem. Soc.* **1997**, *119*, 311.
Boger *J. Am. Chem. Soc.* **1996**, *118*, 2301.



-Appears to be general for the class of olefins $ArCH_2CH=CH_2$

I. Sharpless Catalytic Asymmetric Aminohydroxylation (AA)

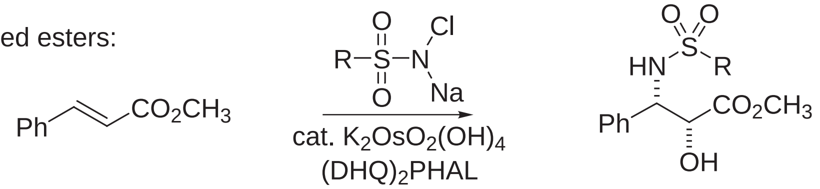
- Reviews: *Transition Metals for Fine Chemicals and Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998.

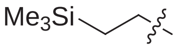
Angew. Chem. Int., Ed. Eng. **1996**, *35*, 451, 2810 and 2813. *J. Am. Chem. Soc.* **1998**, *120*, 1207.
Angew. Chem. Int., Ed. Eng. **1997**, *36*, 1483 and 2637. *Tetrahedron Lett.* **1998**, *39*, 2507 and 3667.

- Development of AA reaction (reactions generally run with 4 mol% catalyst ($K_2OsO_2(OH)_4$) and 5 mol% ligand (($(DHQ)_2$PHAL or $(DHQD)_2$PHAL): *in situ* generation and reactions of RN=OsO_3.

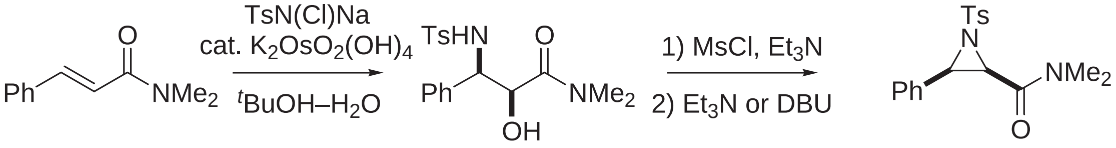
a. Sulfonamide variant

-α,β-unsaturated esters:



R =				
	p-Tol	1:1 $CH_3CN–H_2O$	81% ee (64%)	Reductive cleavage of sulfonamides requires harsh conditions (Birch reduction, Red-Al, or 33% HBr/AcOH).
	Me	1:1 $^nPrOH–H_2O$	95% ee (65%)	
		1:1 $^nPrOH–H_2O$	70% ee (48%) 83:17 regioselectivity	← Sulfonamide cleaved with Bu_4NF in CH_3CN

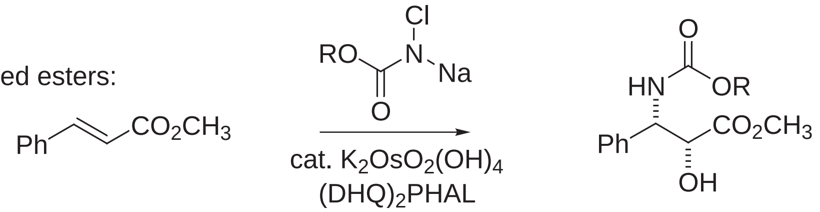
-α,β-unsaturated amides: no enantioselection, AA gives racemic products.
-reaction works well without a ligand.



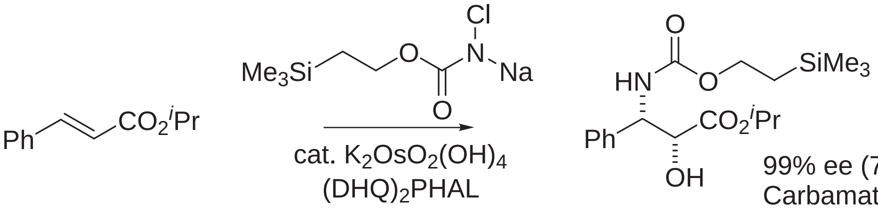
5:1 regioselectivity, racemic (94%)

b. Carbamate variant

-α,β-unsaturated esters:

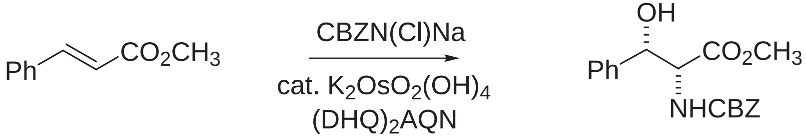


R =				
	Bn	1:1 $^nPrOH-H_2O$	94% ee (65%)	← Amine can be deprotected by hydrogenolysis.
	Et	1:1 $^nPrOH-H_2O$	99% ee (78%)	
	^{t}Bu	2:1 $^nPrOH-H_2O$	78% ee (71%)	← Amine can be deprotected by acid.



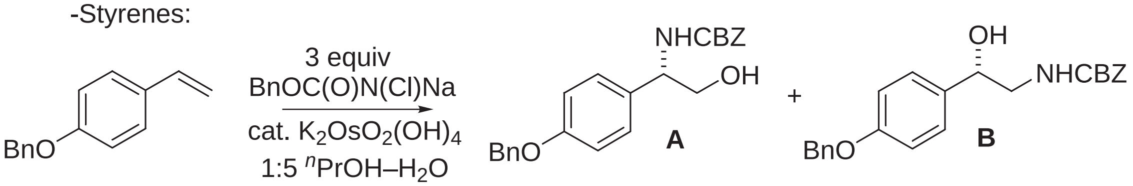
99% ee (70%)
Carbamate cleaved with Bu_4NF in CH_3CN.

-Reversal of regioselectivity using $(DHQ)_2AQN$ ligand



95% ee (58%)
79:21 regioselectivity

-Styrenes:



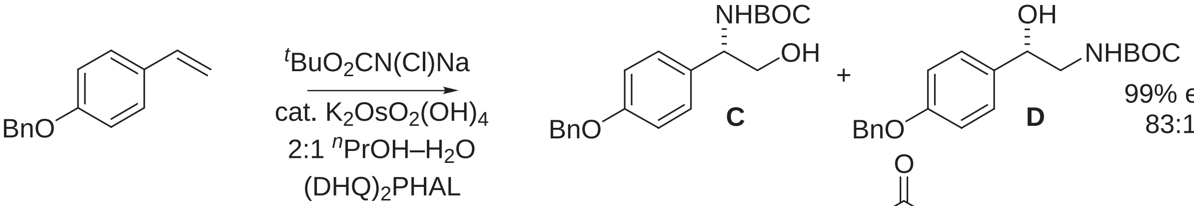
97% ee (76%)
88:12 **A**:**B**

-Influence of ligand and solvent on regioselectivity:

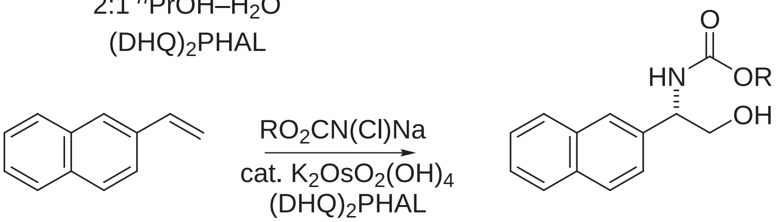
ligand	solvent	**A:B**
$(DHQ)_2PHAL$	^{n}PrOH–H_2O	88:12
$(DHQ)_2AQN$	$CH_3CN–H_2O$	25:75

- However, enantioselectivities for **B** regioisomers are poor (0–80% ee).

- ^{t}Bu carbamate based AA affords slightly poorer regioselectivities and yields compared to benzyl carbamate series, but enantioselectivities approach 100% in both cases:

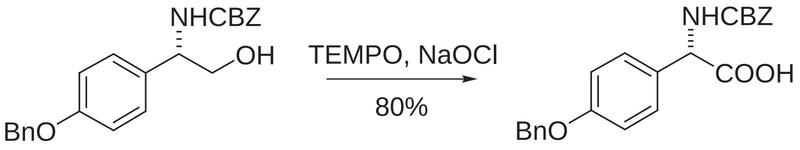


99% ee (68%)
83:17 **C**:**D**



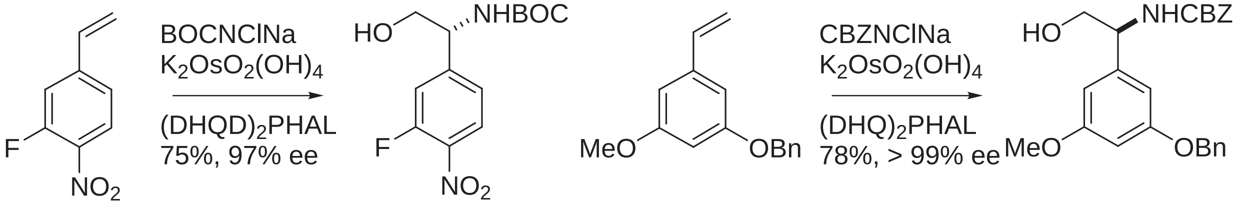
R =		
Bn	99% ee (70%)	>10:1 regioselectivity
^{t}Bu	98% ee (70%)	88:12 regioselectivity
Me_3Si	97% ee (48%)	86:14 regioselectivity

-Oxidation of α-arylglycinols to corresponding α-arylglycines, see: Boger *J. Org. Chem.* **1996**, *61*, 3561.

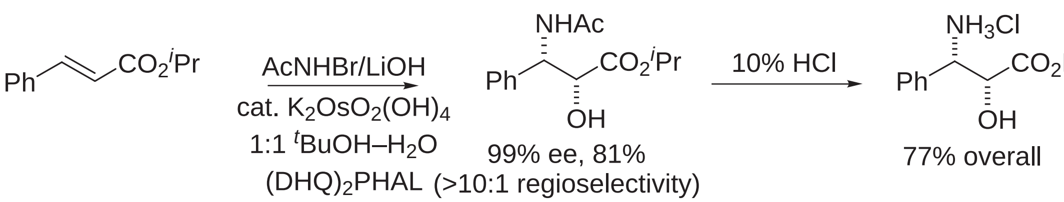


80:20 mixture
of regioisomers

-Teicoplanin α-arylglycines Boger *J. Am. Chem. Soc.* **2000**, *122*, 7416.



c. Amide variant



J. Ozonolysis

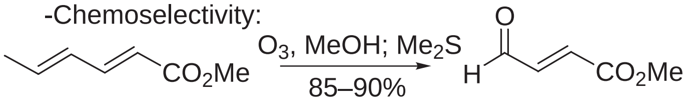
Comprehensive Org. Syn., Vol. 7, pp 541–591.

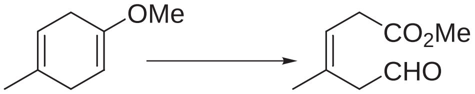
Introduced by Harries *Justus Liebigs Ann. Chem.* **1905**, *343*, 311.

P. Crutzen, M. Molina, and F. S. Rowland shared the 1995 Nobel Prize in Chemistry for their work in atmospheric chemistry, particularly concerning the formation and decomposition of the protective ozone layer.

-Electrophilic reagent, rate: electron-rich > neutral > electron-deficient olefin

-Chemoselectivity:



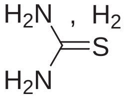


-O_3 exhibits very light blue color, ozonolysis complete when color persists

-Controlled ozonolysis (very reactive agent): KI–starch: characteristic blue color
O_3 sensitive dyes with varying reactivities and detect color disappearance: Mitscher *Synthesis* **1980**, 807.

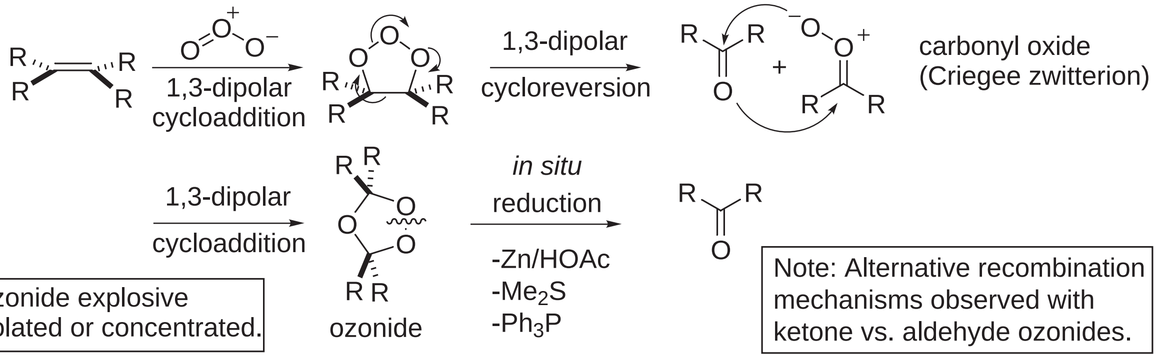
-Oxidative workup: H_2O_2, $KMnO_4$, Cr(VI), RuO_4 -> ketones, carboxylic acids

-Reductive workup: $NaBH_4$, $LiBH_4$ -> alcohols
Me_2S, Ph_3P, Zn/HOAc,



, H_2, Pd/$CaCO_3$ -> aldehydes, ketones

-Mechanism, Review: Criegee *Angew. Chem., Int. Ed. Eng.* **1975**, *14*, 745.



Note: Ozonide explosive when isolated or concentrated.

Note: Alternative recombination mechanisms observed with ketone vs. aldehyde ozonides.

V. Oxidation of Alcohols

Comprehensive Org. Syn., Vol. 7, pp 251–327.

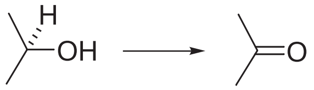
Stoichiometries:

$$3\ R_2CHOH + 2\ CrO_3 + 6\ H^+ \longrightarrow 3\ R_2C{=}O + 2\ Cr^{3+} + 6\ H_2O$$
$$5\ R_2CHOH + 2\ MnO_4^- + 6\ H^+ \longrightarrow 5\ R_2C{=}O + 2\ Mn^{2+} + 8\ H_2O$$
$$3\ R_2CHOH + 2\ MnO_4^- \longrightarrow 3\ R_2C{=}O + 2\ Mn^{2+} + 2\ H_2O$$

A. Chromium-based Oxidation Reagents

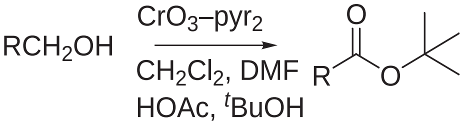
1. Collins Reagent: Collins *Tetrahedron Lett.* **1968**, 3363; *Org. Syn*. **1972**, *52*, 5.

- CrO_3–pyr_2, alkaline oxidant
- Hygroscopic, red crystalline complex
- Can also be isolated and stored, but usually generated *in situ* by CrO_3 + pyr (**Sarett Reagent**) *J. Am. Chem. Soc.* **1953**, *75*, 422. Note: Add CrO_3 to pyr, not pyr to CrO_3 (inflames)
- Good for acid sensitive substrates
- **Ratcliffe modification:** *in situ* preparation and use in CH_2Cl_2, *J. Org. Chem.* **1970**, *35*, 4000.



$$RCH_2OH \longrightarrow RCHO \not\longrightarrow RCOOH$$

no over oxidation



Provide a mechanism for this transformation.

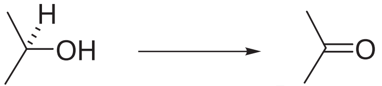
General except for ArCHO Corey, Samuelsson *J. Org. Chem.* **1984**, *49*, 4735.

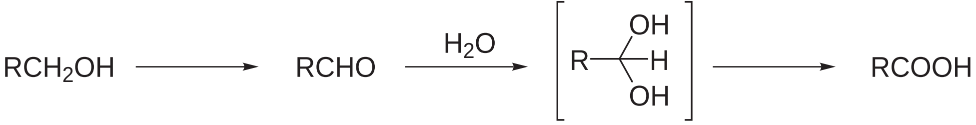
Review of Cr(VI)-amine oxidizing agents: Luzzio *Org. React.* **1998**, *53*, 1.

2. Jones Reagent: Jones *J. Chem. Soc.* **1953**, 2548; *J. Chem. Soc.* **1946**, 39.

$$CrO_3 \text{ in aq. } H_2SO_4\text{/acetone} \longrightarrow H_2Cr_2O_7 \xrightleftharpoons{H_2O} 2\ H_2CrO_4$$

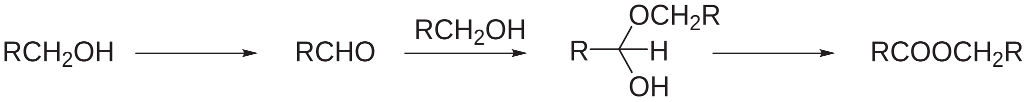
- Acetone solvent serves to protect substrate from over oxidation
- Not good for oxidations of acid sensitive substrates





$$RCH_2OH \longrightarrow RCHO \xrightarrow{H_2O} \left[R-\overset{OH}{\underset{OH}{C}}-H \right] \longrightarrow RCOOH$$

- Acidic oxidation conditions, H^+ catalyzed reactions possible
- Another common side reaction for primary alcohol oxidation:



$$RCH_2OH \longrightarrow RCHO \xrightarrow{RCH_2OH} R-\overset{OCH_2R}{\underset{OH}{C}}-H \longrightarrow RCOOCH_2R$$

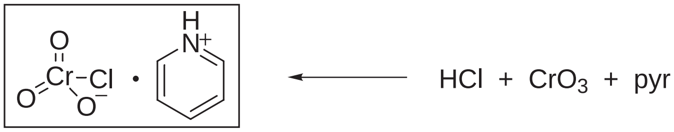
Solution: run under dilute reaction conditions to circumvent esterification

hemiacetal

ester

- **Brown oxidation**: run under two phase reaction conditions, Et_2O–H_2O, *J. Org. Chem.* **1971**, *36*, 387.
- $[R_4N]_2Cr_2O_7$ *Synth. Commun.* **1980**, 75. Oxidation of allylic/benzylic alcohols under neutral conditions.

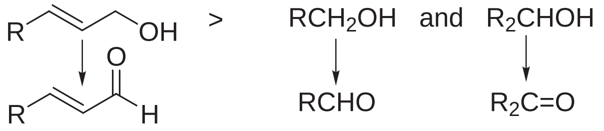
3. Pyridinium Chlorochromate (PCC): Corey and Suggs *Tetrahedron Lett.* **1975**, 2647.



-Chloride facilitates formation of chromate ester (slow step in oxidation reaction)
-Stable, commercially available reagent

-Reaction usually carried out in CH_2Cl_2

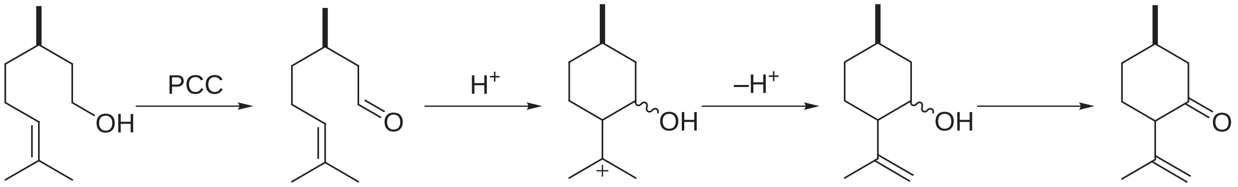
-Rates:



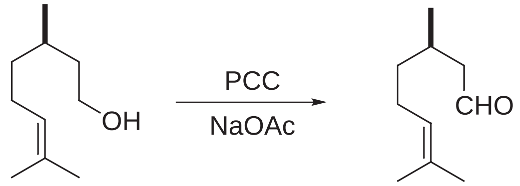
no over oxidation

-Usually only need 1–2 equiv of Cr(VI) reagent (Jones & Collins usually require 6 equiv)

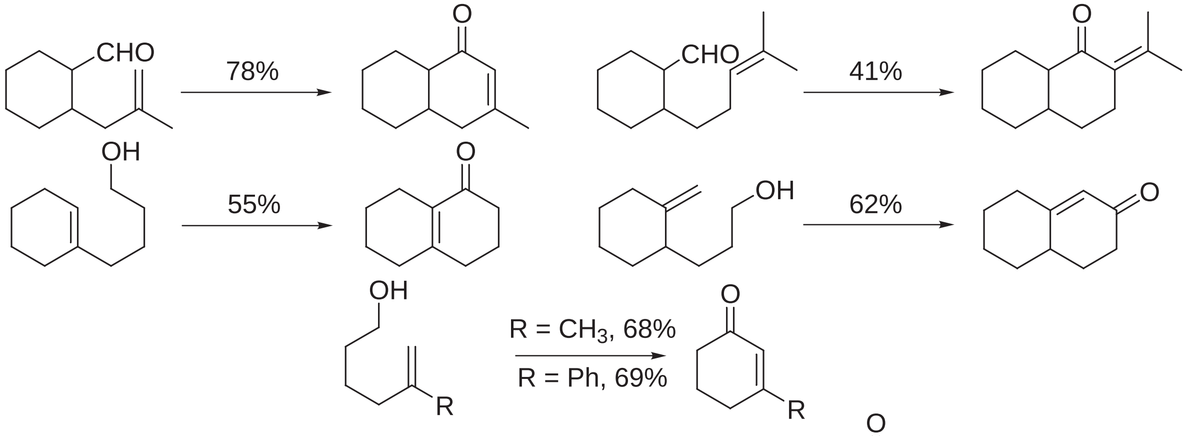
-PCC slightly acidic which can cause side reactions, for example:



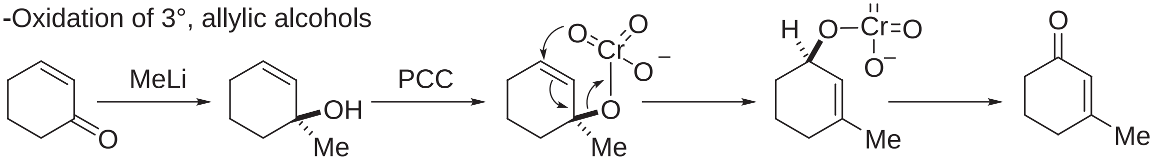
-To avoid H^+ catalyzed side reaction, use sodium acetate buffer:



-Can take advantage of acidity in PCC reaction (Boger and Corey *Tetrahedron Lett.* **1978**, 2461):



-Oxidation of 3°, allylic alcohols



[3,3]-sigmatropic rearrangement, Dauben *J. Org. Chem.* **1977**, *42*, 682.

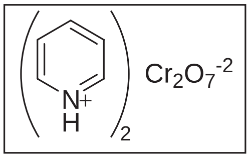
-Aromatic amine effect: dampens reactivity so only selective oxidation of allylic alcohols may be observed

PCC, pyr (2%) in CH_2Cl_2	*Chem. Phys. Lipids* **1980**, *27*, 281.
PCC, 3,5-dimethylpyrazole (2%) in CH_2Cl_2	*J. Org. Chem.* **1983**, *48*, 4766.
PCC, benzotriazole (2%) in CH_2Cl_2	*Synth. Commun.* **1985**, *15*, 393.
-3 Å MS accelerate rate of oxidation (PCC and PDC)	*J. Chem. Soc., Perkin Trans. 1* **1982**, 1967.

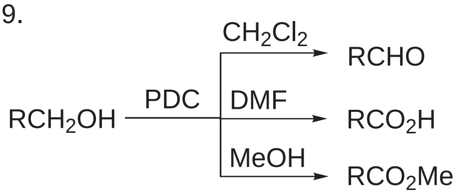
-**Pyridinium fluorochromate**, related stable reagent that is slightly less acidic (Corey and Suggs)

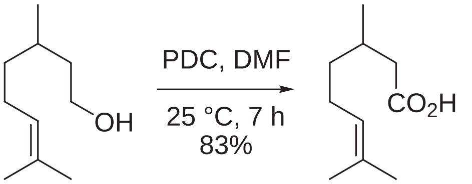
-Other related reagents include bipyridinium chlorochromate (BPCC), DMAP chlorochromate, quinolinium chlorochromate, and pyrazinium chlorochromate.

4. Pyridinium Dichromate (PDC): Corey *Tetrahedron Lett.* **1979**, 399.



$\leftarrow$ CrO_3 + pyr + H_2O

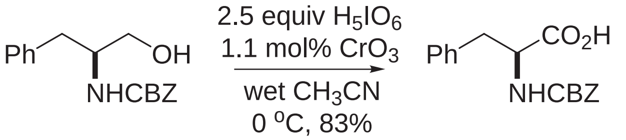


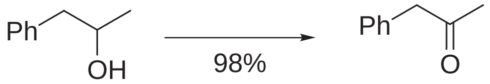


- Stable, commercially available reagent
- Not as acidic as PCC
- Oxidations slower than PCC or other oxidation reagents
- Can selectively oxidize 1° alcohols to aldehyde or carboxylic acid depending on solvent
- 2° alcohols oxidize only slowly and sometimes require an acid catalyst (pyridinium trifluoroacetate or 3 Å MS)
- Note: Original reagent made in search of more acidic reagent, attempted preparation of pyridinium trifluoroacetyl chromate (Boger, Ph.D. dissertation, Harvard Univ., 1980).
- Other related reagents include nicotinium dichromate, quinolinium dichromate, and imidazolium dichromate
- Note: Cr based reagents will oxidize amines and sulfides. Substrates with these functional groups must be oxidized with other reagents (PDC will sometimes leave sulfides unaffected).

5. CrO_3–H_5IO_6: Zhao and Reider *Tetrahedron Lett.* **1998**, *39*, 5323.

- Catalytic in CrO_3 (1–2%, Industrial scale chromium-based oxidations)
- 1° alcohols ⟶ carboxylic acids with no racemization
- 2° alcohols ⟶ ketones

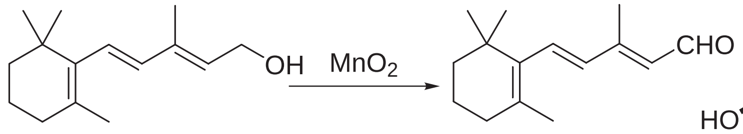


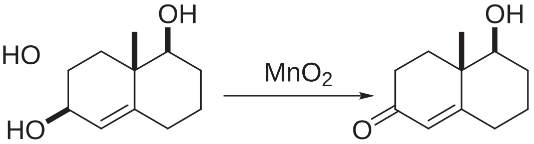


B. Manganese-based Oxidation Reagents

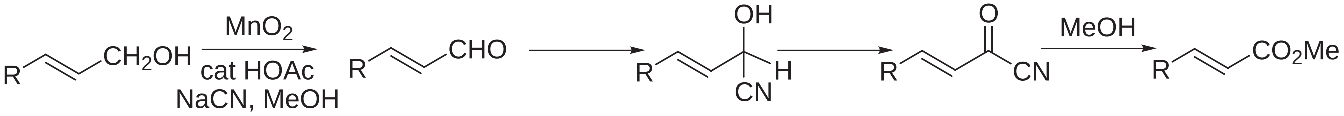
1. Manganese Dioxide (MnO_2)

- Very mild oxidizing reagent, special "activated" MnO_2 preparation required
- Selectively oxidizes allylic and benzylic alcohols to aldehyde or ketone
- Requires nonpolar solvent (CH_2Cl_2, $CHCl_3$, pentane, benzene, etc.)
- Oxidizing reagent : substrate = 10:1 (10 wt. equiv)





- No isomerization of conjugated double bond. Cr-based reagent will cause problem due to H^+ catalysis
- Chemical MnO_2 (CMD), commerically available, also works well
  Shioiri *Synlett* **1998**, 35; *Tetrahedron Lett.* **1992**, *33*, 4187.
- NiO_2: alternative reagent that behaves similar to MnO_2
- Oxidize alcohol to ester, no isomerism of C=C bond (Corey and Ganem *J. Am. Chem. Soc.* **1968**, *90*, 5616)



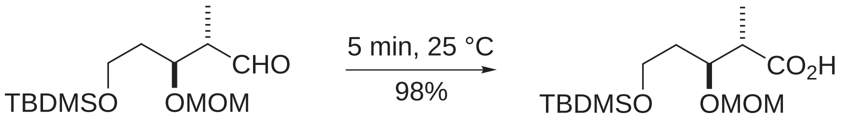
2. $KMnO_4$

a. $KMnO_4/H_2SO_4$

- Good for RCH_2OH ⟶ RCOOH
- Reaction runs in aqueous solution because of the insolubility of $KMnO_4$ in organic solvents

b. $KMnO_4$ in ${}^tBuOH$–5% NaH_2PO_4 aqueous buffer (Masamune *Tetrahedron Lett.* **1986**, *27*, 4537).

- For highly oxygenated systems where multiple side reaction pathways are present with other oxidants



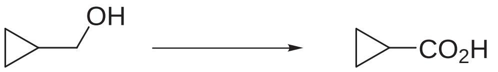
c. Lemieux–von Rudloff oxidation: aqueous KIO_4/cat. $KMnO_4$

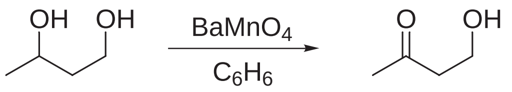
-For cleavage of carbon–carbon double bonds

3. R_4NMnO_4

-Same capabilities as $KMnO_4$ but soluble in organic solvents

4. $Cu(MnO_4)$-$6H_2O$ and $BaMnO_4$





Lee *J. Am. Chem. Soc.* **1983**, *105*, 3188; *J. Org. Chem.* **1982**, *47*, 2790.
Hauser *J. Am. Chem. Soc.* **1984**, *106*, 1862.
Jefford *J. Chem. Soc., Chem. Commun.* **1988**, 634.
Kim *Tetrahedron Lett.* **1989**, *30*, 2559.

C. Other Oxidation Reagents

1. RCH_2OH or R_2CHOH oxidation

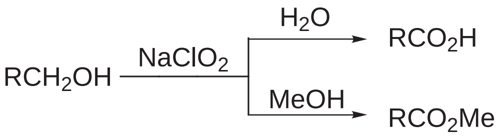
a. Sodium Hypochlorite (NaOCl): Used primarily to oxidize alcohols or aldehydes to carboxylic acids.

$$RCH_2OH \longrightarrow RCHO \longrightarrow RCOOH$$

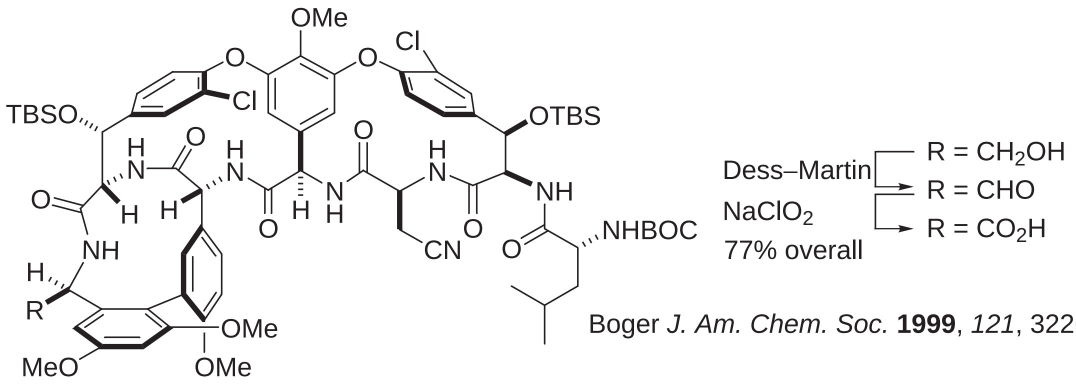
Stevens, Chapman *J. Org. Chem.* **1980**, *45*, 2030;
Tetrahedron Lett. **1982**, *23*, 4647.

b. Sodium Chlorite ($NaClO_2$) Pinnick *Tetrahedron* **1981**, *37*, 2091.

Also Calcium Hypochlorite ($Ca(OCl)_2$):
McDonald *Tetrahedron Lett.* **1993**, *34*, 2741.



- -Good for oxidation of sensitive aldehydes to carboxylic acids
- -Becoming the method of choice for the oxidation of RCHO to RCO_2H.
- -Two-step procedures for RCH_2OH to RCO_2H (i.e., MnO_2, Swern, Dess–Martin for RCH_2OH to RCHO and $NaClO_2$ for RCHO to RCO_2H most often better than single step reagent conversions.
- -Scavengers are often added to trap or eliminate positive Cl species leading to byproducts. Typical scavengers are resorcinol, 2-methyl-2-butene, DMSO, H_2NSO_3H.



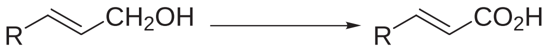
Boger *J. Am. Chem. Soc.* **1999**, *121*, 3226 and 10004.

c. Ag_2O and Ag_2CO_3

$$RCH_2OH \xrightarrow{Ag_2O} RCHO \xrightarrow[\text{or}\ AgO]{Ag_2CO_3\ \text{Celite}} RCOOH$$

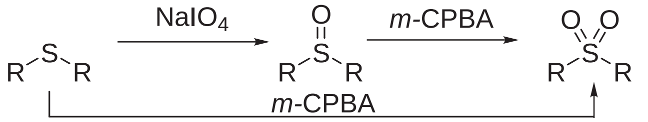
d. AgO

$$RCH_2OH \longrightarrow RCHO \text{ or } RCO_2H$$

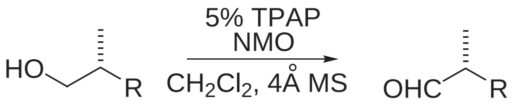


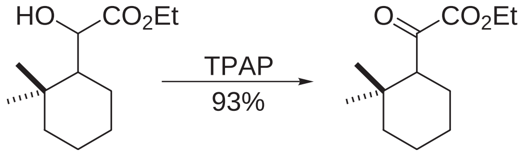
Corey, Ganem *J. Am. Chem. Soc.* **1968**, *90*, 5616.

2. *m*-CPBA and $NaIO_4$ (Amine and sulfide oxidation)



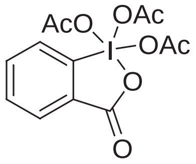
3. TPAP, $[Pr_4NRuO_4]$





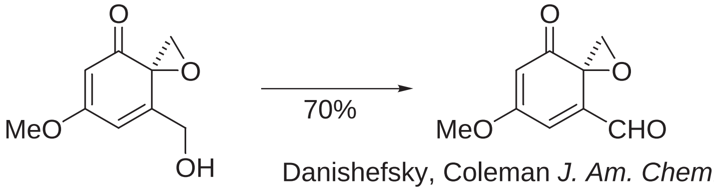
Ley *J. Chem. Soc., Chem. Commun.* **1987**, 1625.
Aldrichim. Acta **1990**, *23*, 13.
Synthesis **1994**, 639.

4. Dess–Martin Oxidation:
Dess and Martin *J. Am. Chem. Soc.* **1978**, *100*, 300; *J. Am. Chem. Soc.* **1979**, *101*, 5294; *J. Org. Chem.* **1983**, *48*, 4155; *J. Am. Chem. Soc.* **1991**, *113*, 7277.

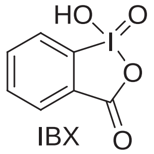


-periodinane
-CH_2Cl_2, 25 °C

$RCH_2OH \longrightarrow RCHO$
$R_2CHOH \longrightarrow R_2C{=}O$

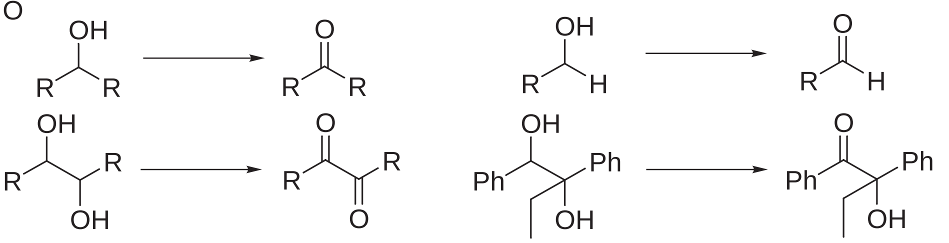


Danishefsky, Coleman *J. Am. Chem. Soc.* **1991**, *113*, 3850.

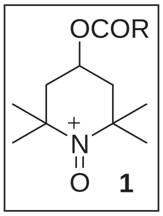


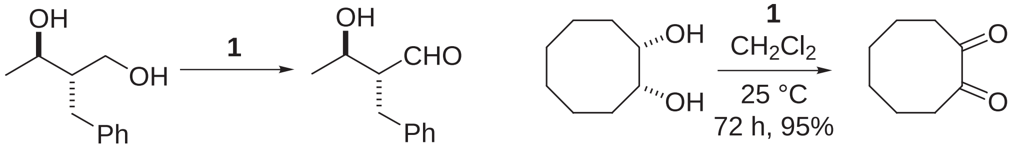
IBX

- Precursor to Dess–Martin reagent
- Insoluble in almost all organic solvents but is soluble in DMSO and oxidations in this solvent work effectively (25 °C): Frigerio *Tetrahedron Lett.* **1994**, *35*, 8019.

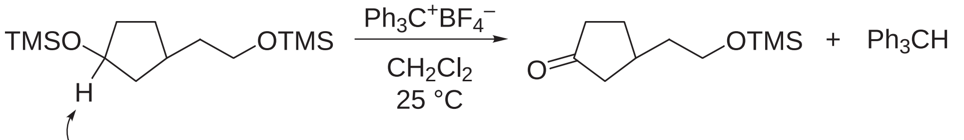


5. Oxoammonium Salt:
Torii *J. Org. Chem.* **1990**, *55*, 462; Skarzewski *Tetrahedron Lett.* **1990**, *31*, 2177.
Bobbitt *J. Org.Chem.* **1998**, *63*, 9367.





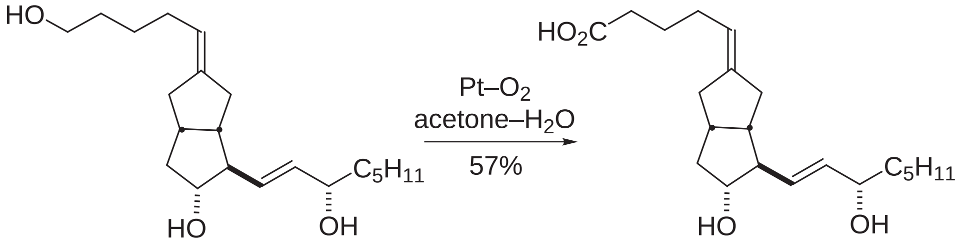
6. Trityl Cation:
Jung *J. Am. Chem. Soc.* **1976**, *98*, 7882.



3° carbon H abstracted faster

7. Pt–O_2:
Fuchs and Hutchinson *J. Am. Chem. Soc.* **1987**, *109*, 4755.
-Good for oxidation of 1° alcohols directly to carboxylic acids

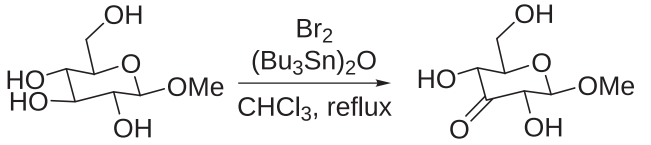
1° alcohols > 2° alcohols
2° axial alcohols > 2° equatorial alcohols



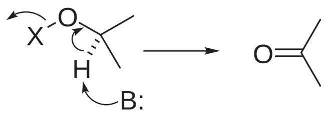
8. Via Hypohalite

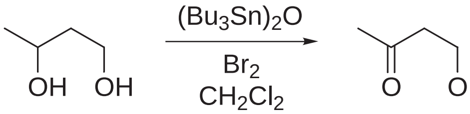
Just *Tetrahedron Lett.* **1980**, *21*, 3219.
Doyle *Tetrahedron Lett.* **1980**, *21*, 2795.
Oshima, Nozaki *Tetrahedron Lett.* **1982**, *23*, 539.
Hanessian *Synthesis* **1981**, 394.
Kanemitsu *Chem. Pharm. Bull.* **1989**, *37*, 2394.
Stevens *Tetrahedron Lett.* **1982**, *23*, 4647.

-For example: $(Bu_3Sn)_2O$, Br_2 $NiBr_2$, $(PhCO_2)_2$ NIS, Bu_4NI $NaBrO_3$, CAN NaOCl, HOAc

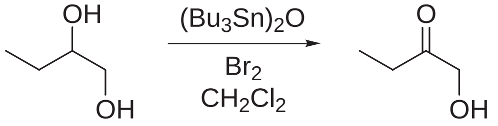


Mechanism:





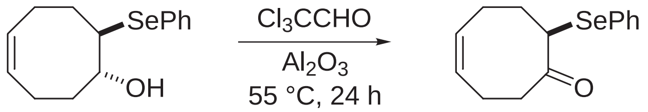
Tetrahedron Lett. **1976**, 4597.



2° alcohol > 1° alcohol

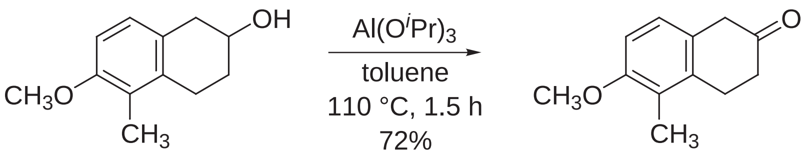
9. Oppenauer Oxidation:

see Meerwein–Pondorff–Verley reduction, Review: *Org. React.* **1951**, *6*, 207.
Oppenauer *Rec. Trav. Chim.* **1937**, *56*, 137.



- Suitable for oxidation of 2° alcohol in the presence of 1° alcohol which do not react
- Good for oxidation of substrates containing easily oxidized functional groups

Posner *Angew. Chem., Int. Ed. Eng.* **1978**, *17*, 487; *Tetrahedron Lett.* **1977**, 3227; **1976**, 3499.



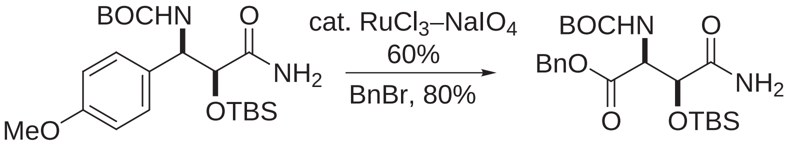
Boger *J. Org. Chem.* **1984**, *49*, 4045.

10. Ruthenium Tetroxide (RuO_4)

$RCH_2OH \longrightarrow RCO_2H$ $R_2CHOH \longrightarrow R_2C{=}O$

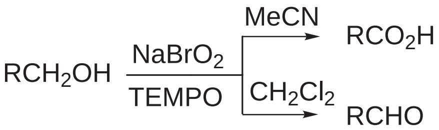
-*in situ* generation from RuO_2–$NaIO_4$ or RuO_2–NaOCl: *Tetrahedron Lett.* **1970**, 4003.
J. Org. Chem. **1987**, *52*, 1149.
from $RuCl_3$–H_5IO_6: Sharpless *J. Org. Chem.* **1988**, *53*, 5185.
J. Org. Chem. **1981**, *46*, 3936.

-Note: RuO_4 attacks C=C bonds and will cleave 1,2-diols.
Often used to cleave aromatic rings:



Boger *J. Org. Chem.* **2000**, *65*, 6770.
(total synthesis of ramoplanin)

11. TEMPO



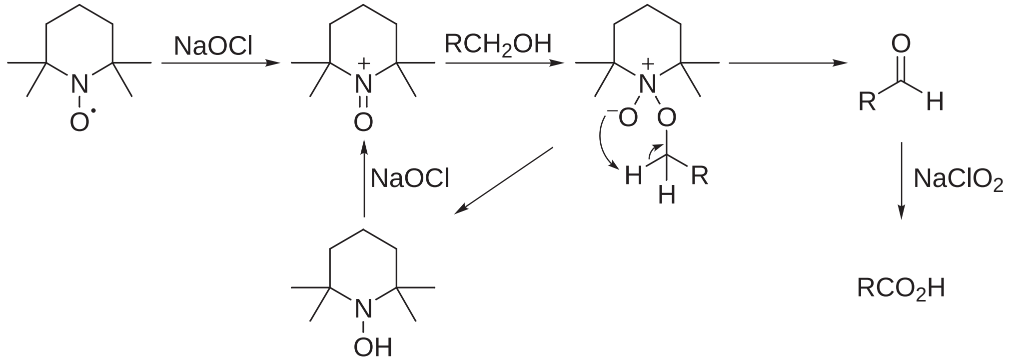
-with cat. NaOCl or $NaBrO_2$: *J. Org. Chem.* **1985**, *50*, 1332.
J. Org. Chem. **1987**, *52*, 2559.
J. Org. Chem. **1990**, *55*, 462.

-with cat. $Ca(OCl)_2$: Dess and Martin *J. Org. Chem.* **1983**, *48*, 4155.
Corey *J. Am. Chem. Soc.* **1996**, *118*, 1229.
Smith *J. Am. Chem. Soc.* **1989**, *111*, 5761.

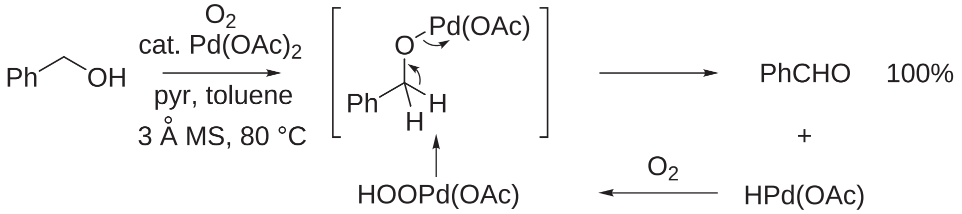
Vancomycin central amino acid
J. Org. Chem. **1996**, *61*, 3561.

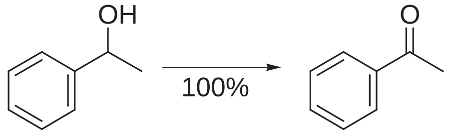
-With $NaClO_2$, NaOCl

Zhao, Reider *J. Org. Chem.* **1999**, *64*, 2564.



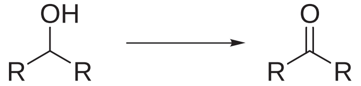
12. Pd–O_2: *J. Org. Chem.* **1976**, *41*, 957 and 3329.





$RCH_2OH \longrightarrow RCHO$

3 Å MS absorbs or decomposes H_2O_2 (O_2 + H_2O)

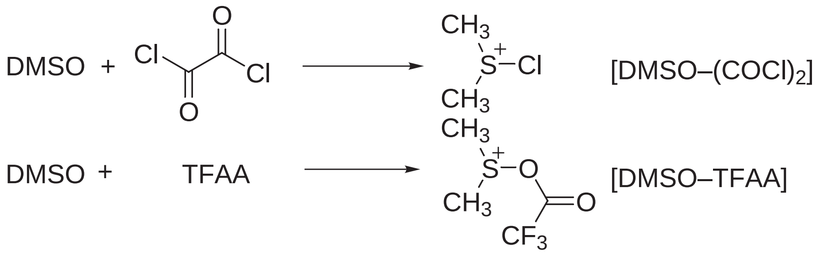


Uemura *J. Org. Chem.* **1999**, *64*, 6750.

D. Swern Oxidation and Related Oxidation Procedures

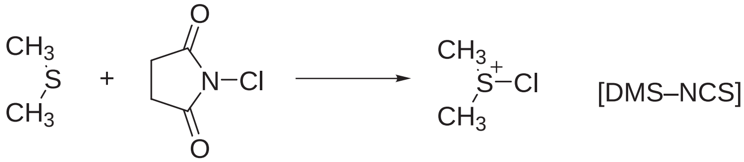
1. Swern Oxidation: *J. Org. Chem.* **1976**, *41*, 957 and 3329.

Reviews: *Chem. Rev.* **1967**, *67*, 247.
Tetrahedron **1978**, *34*, 1651.
Synthesis **1981**, 165.
Org. React. **1990**, *39*, 297.

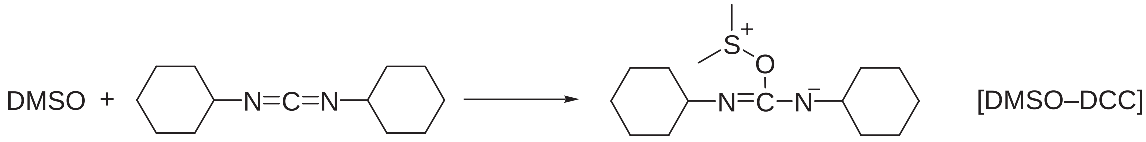


-Also DMSO–Ac_2O, DMSO–SO_3/pyr, DMSO–$SOCl_2$, DMSO–Cl_2
DMSO–Ac_2O is often referred to as the Albright–Goldman reagent
Albright, Goldman *J. Am. Chem. Soc.* **1965**, *87*, 4214, **1967**, *89*, 2416.

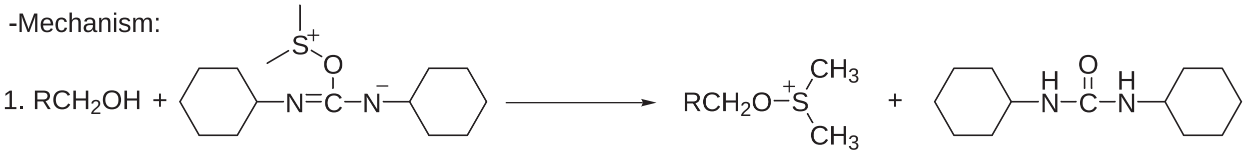
2. Corey–Kim Oxidation: *Tetrahedron Lett.* **1974**, 287; *J. Am. Chem. Soc.* **1972**, *94*, 7586.

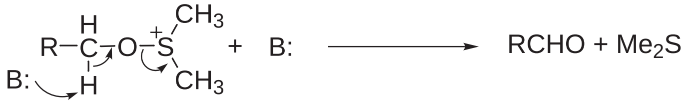


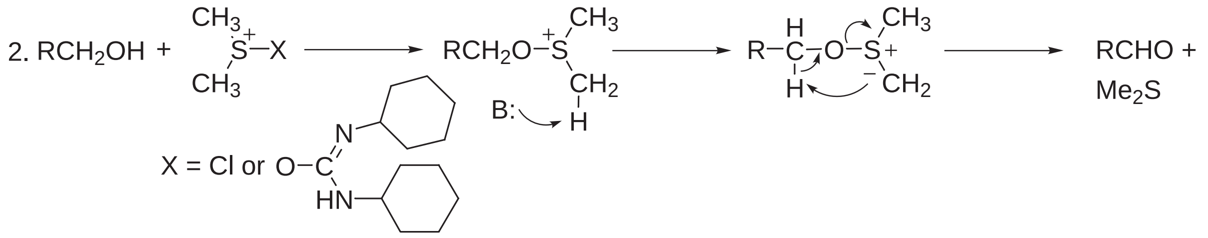
3. Moffatt–Pfitzner Oxidation (DCC–DMSO): *J. Am. Chem. Soc.* **1963**, *85*, 3027; *J. Am. Chem. Soc.* **1965**, *87*, 5670.



-Mechanism:





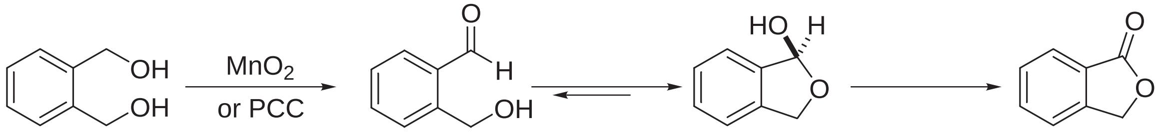


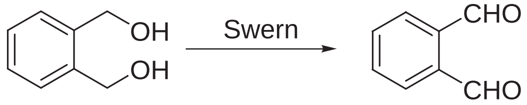
-All Swern type complexes react with alcohols, in presence of base, to give "activated alcohol complexes".

-Examples:

-Other oxidants cleave diol C–C bond

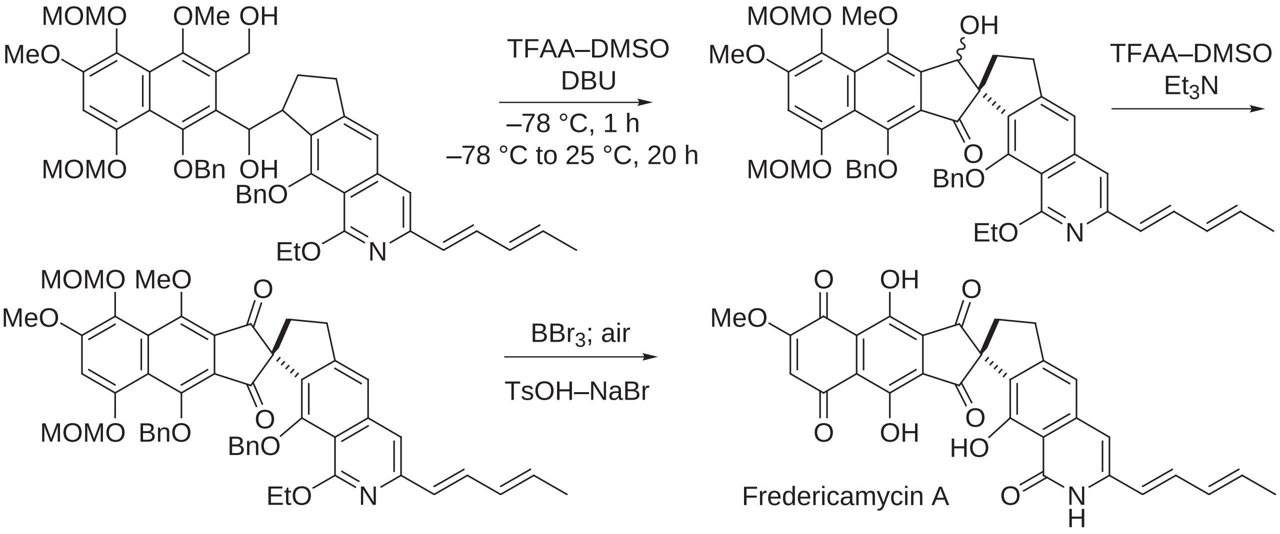
-Swern oxidation run under very mild conditions (usually –78 °C to –50 °C)





Boger *J. Org. Chem.* **1990**, *55*, 1919.
Boger *J. Org. Chem.* **1991**, *56*, 2115.
Boger *Tetrahedron Lett.* **1989**, *30*, 2037.

-Fredericamycin A: Boger *J. Am. Chem. Soc.* **1995**, *117*, 11839.

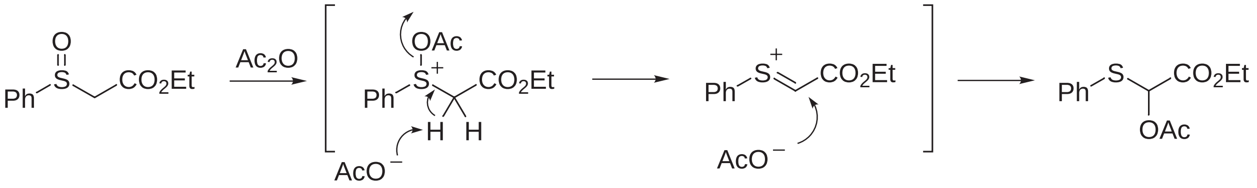


Note: **Kornblum oxidation**, *J. Am. Chem. Soc.* **1957**, *79*, 6562 via DMSO oxygen based displacement of halide (usually activated: benzylic or α-keto halide) to provide aldehyde or ketone.

Common byproducts of Swern oxidations are (methylthio)methyl ethers and the amount varies with DMSO coactivator and reaction temperature. It is derived from alcohol trap of a Pummerer rearrangement intermediate: $CH_2{=}^{+}SCH_3$.

Note: **Pummerer rearrangement** is also a formal oxidation reaction

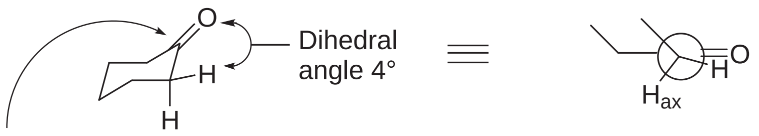
Pummerer *Chem Ber.* **1909**, *42*, 2282; *Chem Ber.* **1910**, *43*, 1401.



Reviews: *Org. React.* **1991**, *40*, 157. *Comprehensive Org. Syn.*, Vol. 7, pp 194–206.

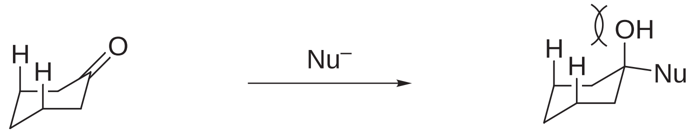
VI. Reduction Reactions

A. Conformational Effects on Carbonyl Reactivity



Eclipsed conformation
of carbonyl

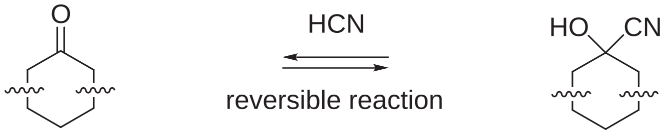
sp^2 ← sp^3
120° ← 109.5°
introduces
torsional strain → This torsional strain accounts for the increased reactivity of six-membered ring cyclic ketones over acyclic ketones.



Overall, the addition to cyclohexanones is favorable:
1. gain 1,3-diaxial interactions (A value = 0.7 kcal/mol for OH)
2. lose the torsional strain (~3–5 kcal/mol)

- So, additions to cyclic ketones are thermodynamically and kinetically favorable.

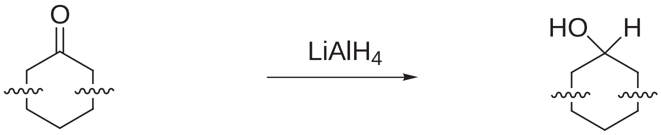
1. Reversible Reactions



$$K_{eq} \text{ for } \frac{\text{cyclohexanone}}{\text{acyclic ketone}} \simeq 70$$

- Thermodynamically more favorable for cyclohexanone due to the loss of torsional strain.
- Thermodynamic effect of sp^2 hybridization: the strain free acyclic system does not suffer the strain destabilization of the ground state, so little gain going from sp^2-> sp^3.

2. Irreversible Reactions (kinetic effect is pertinent)

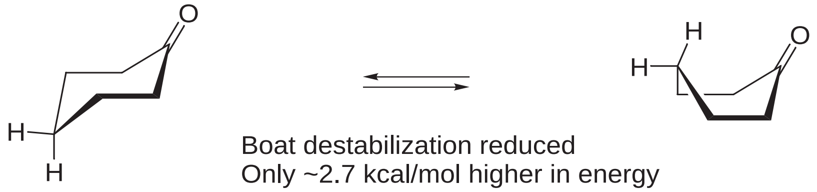


$$\text{Rate } (k) \text{ for } \frac{\text{cyclohexanone}}{\text{acyclic ketone}} \simeq 335$$

*Implication: One can selectively reduce a cyclic carbonyl in the presence of an acyclic carbonyl: under kinetic or thermodynamic conditions.

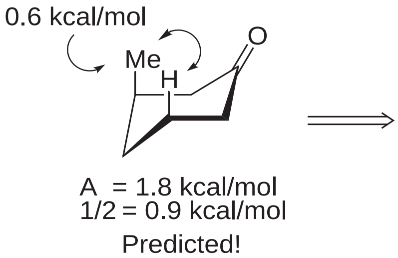
- Synthetic consideration: may not have to protect acyclic ketone.

3. Additional Conformational Effects



Boat destabilization reduced
Only ~2.7 kcal/mol higher in energy

-Cyclohexanones potentially have more accessible conformations available.



Theoretical prediction (0.9 kcal/mol), actually this 1,3-diaxial Me–H interaction is only about 0.6 kcal/mol. This difference (0.3 kcal/mol) in energies observed between theoretical and experimental results is due to the fact that the sp^2 carbonyl carbon moves these groups (Me and H) further away from each other: bond angle of 120° vs. 109.5°.

- Substituents on the ring benefit from a reduced A value since one axial substituent is removed and the opened bond angle of the carbonyl further reduces the remaining 1,3-diaxial interaction (greater distance).

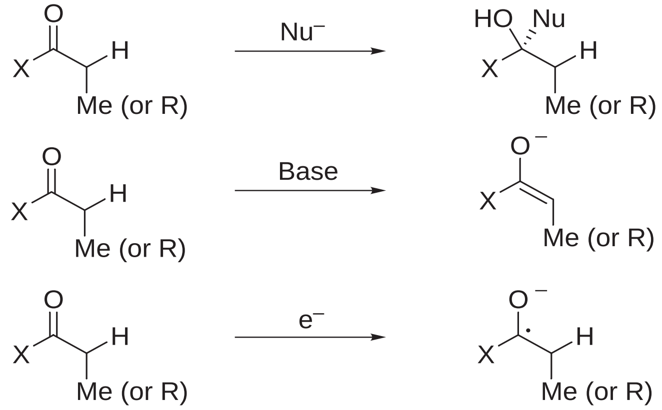
B. Reactions of Carbonyl Groups

- Three primary reactions which we will discuss relative to nucleophilic addition:

Nucleophilic addition:

α-Deprotonation:
(enolate formation)

Addition of e^-, formation of radical anion:

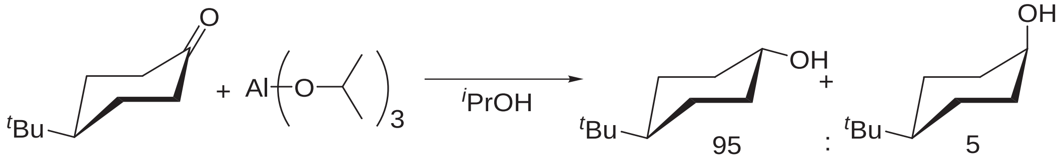


- Each reagent will display competitive reactions among the three primary pathways. Nature of each reagent and the nature of X will determine the course.

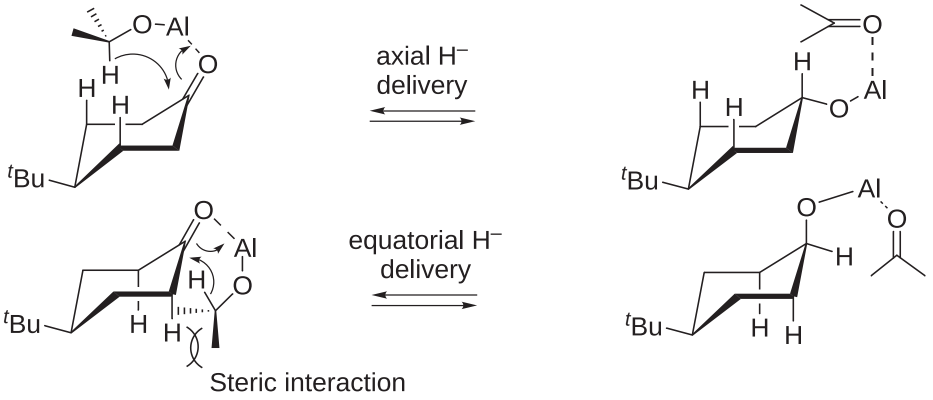
C. Reversible Reduction Reactions: Stereochemistry

- Meerwein–Ponndorf–Verley Reduction (the reverse reaction is the Oppenauer Oxidation). ⟹ Reversible Reduction

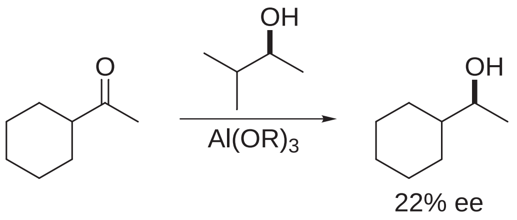
Review: Djerassi *Org. React.* **1951**, *6*, 207.
Meerwein *Justus Liebigs Ann. Chem.* **1925**, *444*, 221.
Ponndorf *Angew. Chem.* **1926**, *39*, 138.
Verley *Bull. Soc. Chim., Fr.* **1925**, *37*, 537.

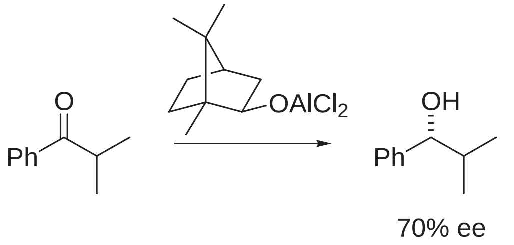


- Mechanism: Reversible Intramolecular Hydride Transfer.



- Since it is freely reversible, one obtains the most stable alcohol from the reduction. The reaction is driven to completion by use of excess reagent and by distilling off the acetone formed in the reaction.
- But, the A value of OH = 0.7 kcal/mol and $K = e^{-\Delta G/RT}$ would predict a 72:28 ratio. Why does the experimental result give better selectivity than the prediction (95:5 > 72:28)?
- We must not only consider the A value, but the larger 1,2-destabilizing steric interactions of the isopropoxy group in the transition state for the equatorial delivery of the hydride: that is, the larger ΔE in the transition state.



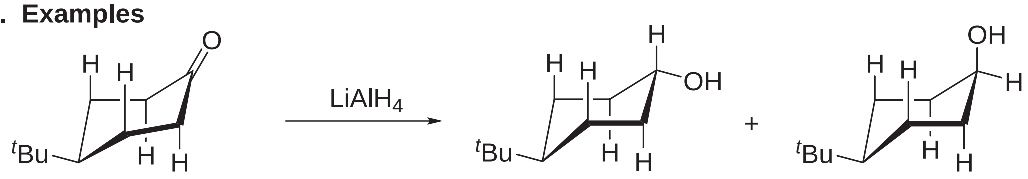


Doering *J. Am. Chem. Soc.* **1950**, *72*, 631.   Nasipuri *J. Indian Chem. Soc.* **1967**, *44*, 165.

D. Irreversible Reduction Reactions: Stereochemistry of Hydride Reduction Reactions and Other Nucleophilic Additions to Carbonyl Compounds

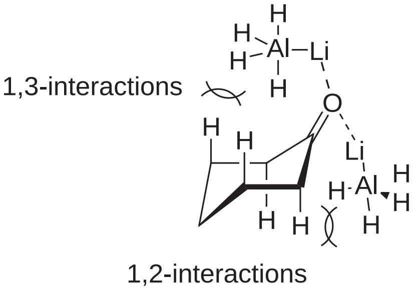
1. Cyclic Ketones

a. Examples



90 : 10

Nearly the same ratio obtained under these kinetic and the above thermodynamic conditions.

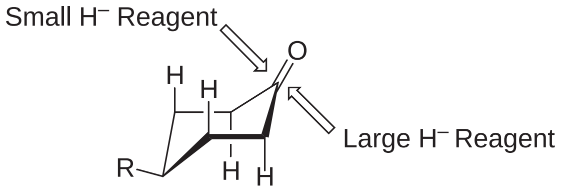


Why?

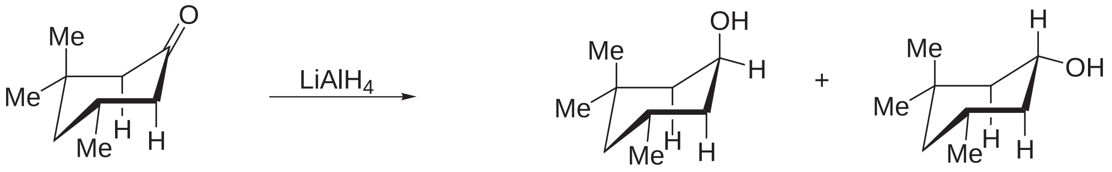
- Difference in the relative rates: 1,2-interactions slow the equatorial addition by a factor of ~ 10
- LiAlH$_4$ = small reagent $\Longrightarrow$ favor axial hydride delivery

- 1,3-interactions are more remote (i.e., smaller), when compared to the 1,2-interactions (larger).
- The destabilizing 1,3-interactions increase as the size of the reagent increases or with the size of the 1,3-diaxial substituents while the 1,2-interactions are not nearly so sensitive to the size of reagents or the size of the substituents.

- For the reduction of cyclohexanone and derivatives, we see the following generalizations:



Examples:

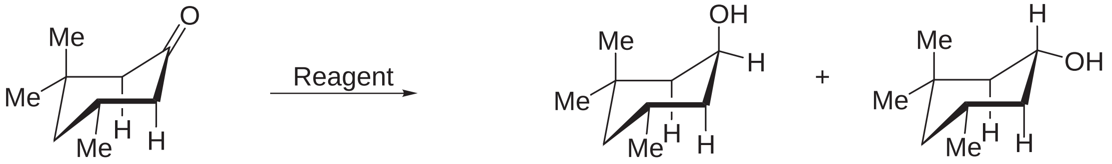


45 : 55

Increased steric hinderance of the 1,3-diaxial interactions (Me/reagent) make axial hydride delivery more difficult.

100 : 0

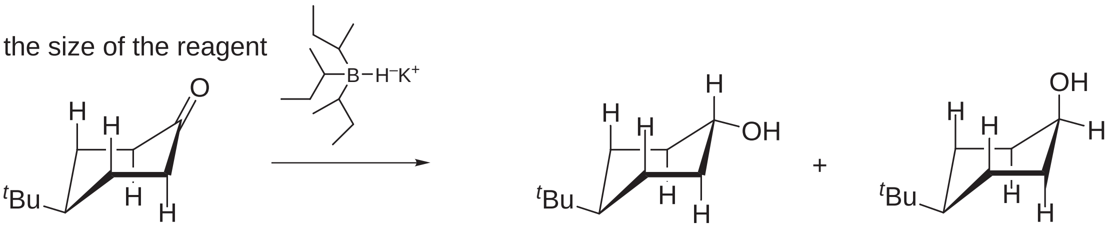
Serious 1,3-interactions preclude axial delivery of the hydride, but the axial Me's have no effect on the 1,2-interactions.



$LiAlH_4$	52–63	:	37–48
$NaBH_4$	55–64	:	36–45
$LiAl(OMe)_3H$	92–98	:	2–8

Larger reagent: greater selectivity for equatorial H⁻ delivery.

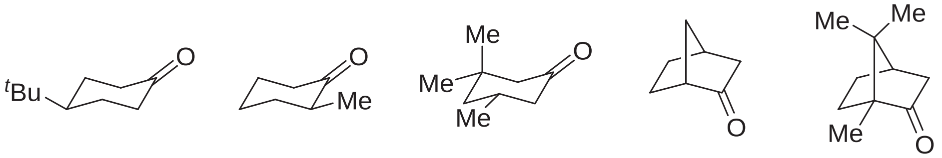
Effect of the size of the reagent



3.5 : 96.5

Much larger reagent! Now, even the 1,3-H/reagent interactions are large while the 1,2-torsional interactions are not affected. Brown *J. Am. Chem Soc.* **1972**, *94*, 7159.

- Comparison of Diastereoselectivity of Hydride Reducing Reagents.



Reagent	% axial OH	% axial OH	% axial OH	% endo OH	% endo OH
$NaBH_4$	20	25	58	86	14
$LiAlH_4$	8	24	63	89	8
$LiAl(OMe)_3H$	9	69	92–98	98	1
$LiAl(O^tBu)_3H$	9	36	95	94	6
$(^sBu)_3BHLi$	93	98	99.8	99.6	0.4
$(Me_2CHCHMe)_3BHLi$	>99	>99	-	>99	no reaction
$LiMeBH_3$	2	13	66	-	-

Brown *J. Am. Chem. Soc.* **1970**, *92*, 709; **1972**, *94*, 7159; **1976**, *98*, 3383.

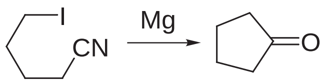
- Stereochemistry of Other Representative Nucleophilic Additions to Cyclohexanones.

Reagent	% axial OH	% axial OH	% axial OH
$MeLi/Et_2O$	65	85	100
$MeMgI/Et_2O$	53	84	100
$EtMgBr/Et_2O$	71	95	100
$PhMgBr/Et_2O$	49	91	100
PhLi	58	88	-

Note: Typically alkyllithium reagents behave as large nucleophiles and approach from the equatorial direction

Ashby *Chem. Rev.* **1975**, *75*, 521.

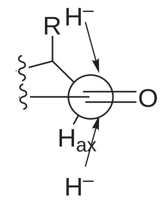
V. Grignard received the 1912 Nobel prize in Chemistry for his discovery of the role of organomagnesium halides in organic synthesis which he made as a graduate student working with P. A. Barbier.



Barbier *Compt. rend.* **1899**, *128*, 110.
Grignard *Comp. rend.* **1900**, *130*, 1322.

b. Origin of Diastereoselectivity

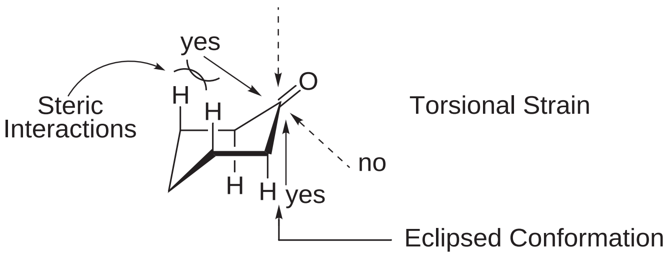
Axial attack



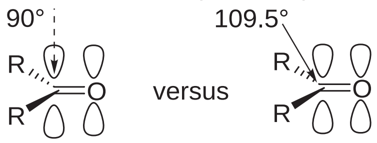
versus

Felkin - equatorial attack (largely torsional strain - when R = H, worse than axial attack mode)

Note: The direction of attack is not from the axial or equatorial vector, but with a 109.5° approach of the nucleophile.

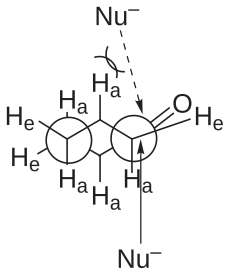


- Stereoelectronic effects



Dunitz angle: *Tetrahedron* **1974**, *30*, 1563.
Good overlap and ~ approaches bond angle required of sp^3 hybridization. Better $\sigma - \pi^*$ overlap (FMO) for nucleophilic addition.

- Cyclic Ketones: Steric vs. Torsional Interactions.



- As the nucleophile gets larger, this steric interaction with the C_3-axial H gets worse and equatorial approach becomes the preferred line of attack.
- For C_3 and C_5-H substituents, this torsional interaction is worse than the steric interaction of Nu^- / C_3 and C_5-H's (for small, unhindered Nu^-).

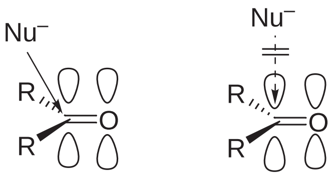
- All H^- reductions have transition states that resemble reactant geometry.
- Diastereoselectivity is influenced by:
  1) Steric interactions (1,3-diaxial interactions)
  2) Torsional strain (1,2-interactions)
  3) Remote electronic effects (electrostatic interactions)
- In contrast to early theories of "product development control" / late transition state vs "steric approach control" / early transition state.

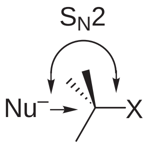
c. Baldwin's Rules and Burgi–Dunitz Angle of Attack

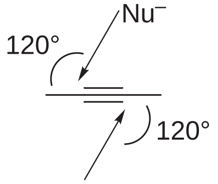
Recent review: *Acc. Chem. Res.* **1993**, *26*, 476.
Dunitz angle of attack: Burgi, Dunitz *Tetrahedron* **1974**, *30*, 1563; *J. Am. Chem. Soc.* **1973**, *95*, 5065.

- Nucleophile addition to carbonyl compound takes place not at 90° (perpendicular) to the C=O, but at an angle of ~105° ± 5°

sp^2 = 105° ± 5° sp^3 = 180° sp = 120°

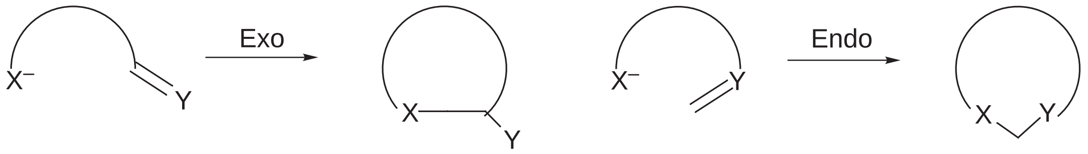






Ring closure reactions

- Importance of approach trajectory first detailed by Eschenmoser *Helv. Chem. Acta* **1970**, *53*, 2059.
- Expanded and elaborated to: Baldwin's Rules for Ring Closure *J. Chem. Soc., Chem. Commun.* **1976**, 734, 736.
- Vector analysis and approach trajectory on sp^2, sp, and sp^3 systems.
- For intramolecular reactions the favored pathways are those where the length and nature of the linking chain enables the terminal atoms to achieve proper geometry for reaction.



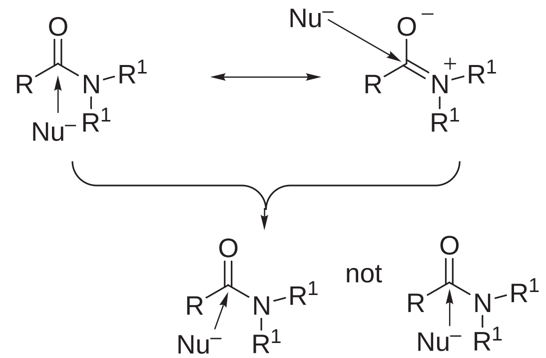
sp^3 = *tet*
sp^2 = *trig*
sp = *dig*

Baldwin's Rules

Rule 1: tetrahedral (sp^3) systems	**Rule 2**: trigonal (sp^2) systems	**Rule 3**: digonal (sp) systems
(a) 3 to 7-*exo-tet* are favored	(a) 3 to 7-*exo-trig* are favored	(a) 3 to 4-*exo-dig* are disfavored
(b) 5 to 6-*endo-tet* are disfavored	(b) 3 to 5-*endo-trig* are disfavored	(b) 5 to 7-*exo-dig* are favored
	(c) 6 to 7-*endo-trig* are favored	(c) 3 to 7-*endo-dig* are favored

-Baldwin: Approach Vector Analysis (Vector Sum establishes the approach of reagent).

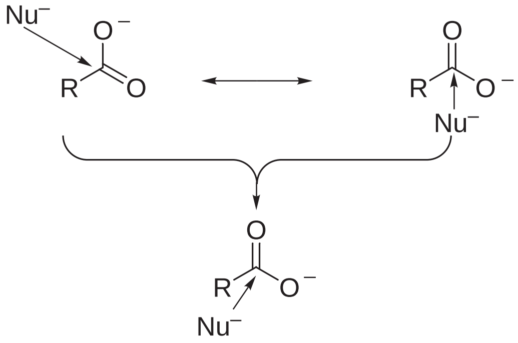
1. Amides



nonequivalent contributions of each resonance form

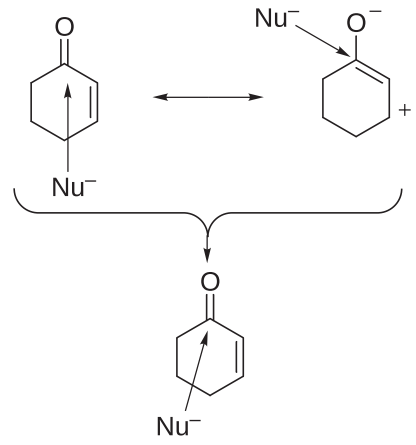
line of attack is weighted average of the two contributing resonance forms

2. Carboxylate



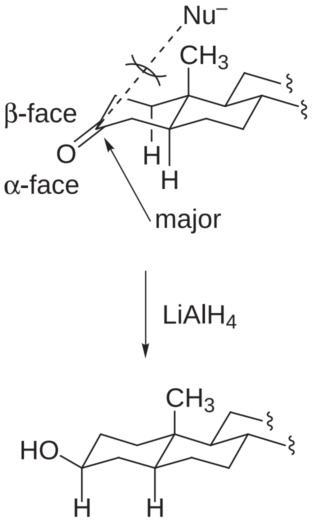
equivalent and Nu^- approaches over (eclipsing) the R group

3. Cyclohexenones



substituents in the C_5 and C_6 position will have a more significant effect on the rate and the stereochemical outcome

Examples:

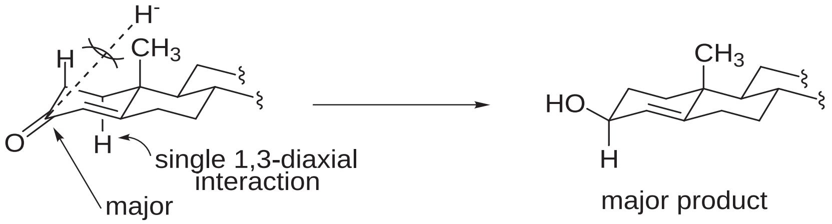


- locked *trans* diaxial ring fusion
- preferential axial delivery of reagent
- equatorial OH is major product
- addition of Nu^- from β-face (equatorial delivery) suffers from repulsive interaction with axial Me

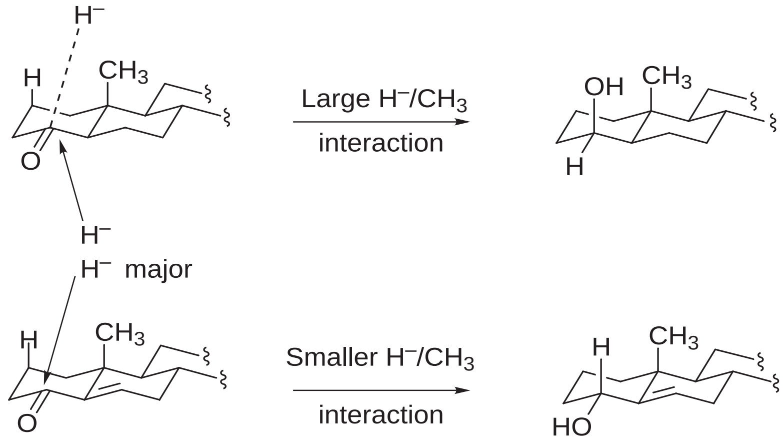
Houk and Trost *J. Org. Chem.* **1991**, *56*, 3656.

70–90%

- vs.



- but



- With enones, the substituents in the 5,6-positions play a more dominant role in determining stereochemical outcome of nucleophilic addition to the carbonyl.

2. Acyclic Carbonyl Groups

Review: *Comprehensive Org. Syn.*, Vol. 1, pp 49-75.

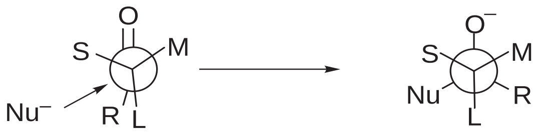
- Cram's Rule	*J. Am. Chem Soc.* **1952**, *74*, 5828. Empirical and no mechanistic interpretation is imposed on model *J. Am. Chem Soc.* **1959**, *81*, 2748. (chelation-controlled addition)
- Prelog	*Helv. Chim. Acta* **1953**, *36*, 308. (1,3-induction)
- Felkin model: (or Felkin–Anh)	*Tetrahedron Lett.* **1968**, 2199, 2205. *Tetrahedron Lett.* **1976**, 155, 159. *Nouv. J. Chim.* **1977**, *1*, 61.

V. Prelog received the 1975 Nobel prize in Chemistry for his research into stereochemistry of organic molecules and reactions.

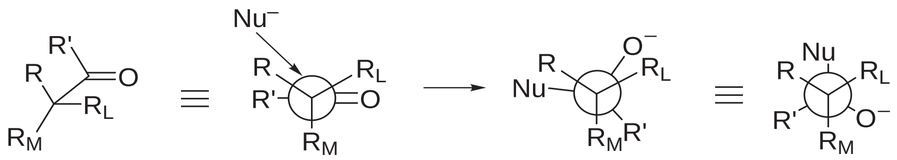
a. Cram's Rule

D. J. Cram was awarded the 1987 Nobel prize in Chemistry for his "host – guest" complex studies.

- Empirical Model



- Large group L eclipsed with R and not the carbonyl, Nu⁻ approach from side of small (S) group.
- Stereoselectivity observed usually modest.
- But, most populated (most stable) conformation of acyclic ketone would be the eclipsed carbonyl conformation.



This is not the observed stereochemistry!

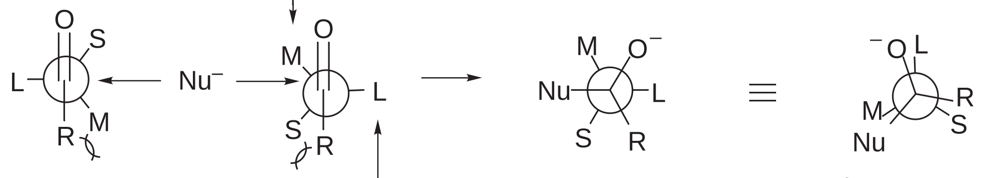
Note: Reaction is not from the ground state carbonyl eclipsed R_L conformation, i.e., the ground state conformation is not the reactive conformation (Curtin–Hammett Principle).

b. Felkin (–Anh) Model

- Large group (L) *trans* antiperiplanar to forming bond

versus

the sterically next most demanding substituent is gauche to carbonyl



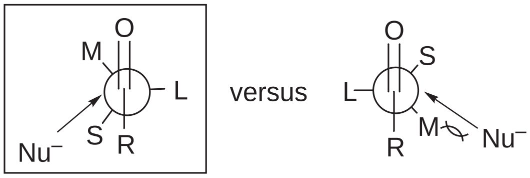
minimizes torsional strain (Pitzer strain) in transition state (**Felkin Model**)

Same as Cram Product:

sterically most demanding group is perpendicular to the plane of the carbonyl, anti to incoming nucleophile

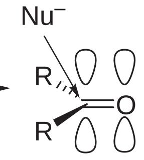
- Here, L is either the largest group (sterically) or the group whose bond to the α-carbon provides the greatest σ–π* overlap (e.g. halide, alkoxy groups).
- Computational studies of Anh confirmed this is the most stable transition state and extended it to α-chloroketones. In the latter case, this minimizes destabilizing electrostatic interactions between the halogen (electronegative group) and the incoming nucleophile.

Anh further refined the Felkin Model, i.e.,
Felkin–Anh Model, as shown below

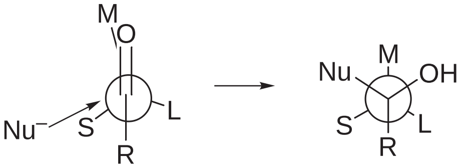


Preferred

Nucleophile prefers approach that minimizes torsional strain and incorporates Burgi–Dunitz trajectory. Primary interaction is now between the Nu⁻ and the small or medium substituent.

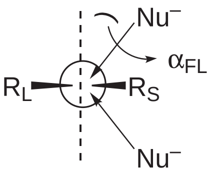


Note: Karabatose proposed a similar model as an alternative to the original Cram empirical rationalization based on computational studies that suggested the most favored conformation would have the medium-sized group eclipsing the carbonyl and addition of H⁻ occurs from the side of the small substituent.



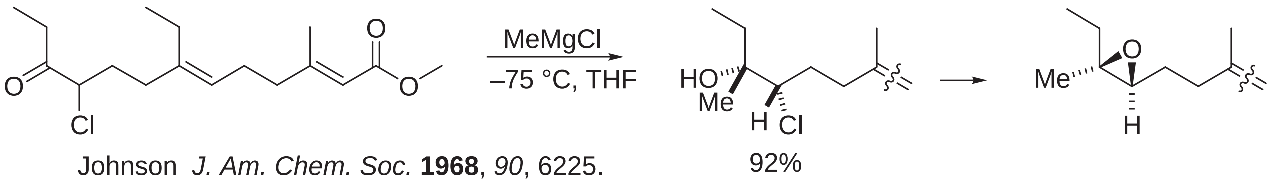
Karabatose *J. Am. Chem. Soc.* **1967**, *89*, 1367.

The model incorporating the Burgi–Dunitz angle has been even further refined to reflect the impact of substantially different sized R groups on the carbonyl. As the size difference between the two substituents increases, the incoming nucleophile would try to avoid the larger one and the approach vector would be tilted away from the normal plane by an angle referred to as the Flippin–Lodge angle (α_{FL}).

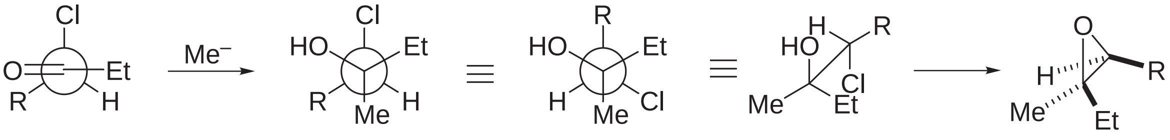


Heathcock *Aldrichchim. Acta* **1990**, *23*, 99.

Examples:



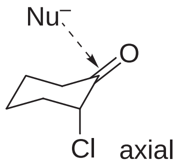
Johnson *J. Am. Chem. Soc.* **1968**, *90*, 6225.



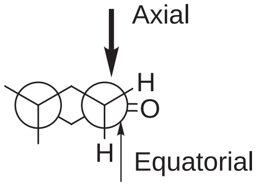
-First observed in cyclic systems: Cornforth

J. Chem. Soc. **1959**, 112 and 2539.
J. Chem. Soc. **1957**, 158.

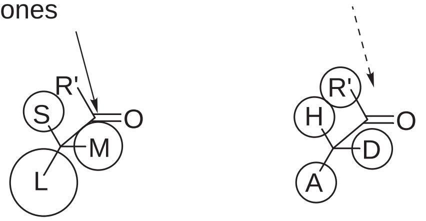
J. W. Cornforth received the 1975 Nobel prize in Chemistry jointly with V. Prelog for outstanding intellectual achievement on the stereochemistry of reactions catalyzed by enzymes.



-For cyclic ketones

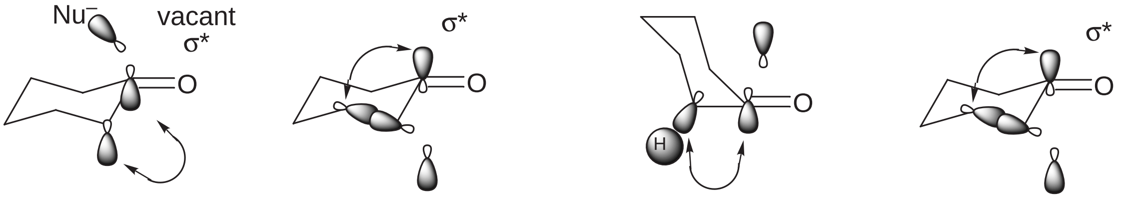


-For acyclic ketones



Allylic bonds prefer to be staggered (axial attack) with respect to the incoming nucleophile rather than eclipsing (equatorial attack).

c. Cieplak Model *J. Am. Chem. Soc.* **1981**, *103*, 4540.



adjacent σ bonds considered

axial attack stabilization

equatorial attack stabilization

1. C–H bond is more electron-rich, better σ e-donation in stabilization of the developing σ* of bond formation than C–C bond, therefore axial approach preferred.
2. σ C–O > σ C–H > σ C–C > σ C–S.
3. Nucleophile can affect intensity of effect, σ* (LUMO of developing bond).

   ↑ LUMO, ↓ effect, ↓ overlap/stabilization

   (a) Electron donation of solvent (polarity) will increase σ*, ↑ LUMO, ↓ overlap,
   ↑ equatorial attack, i.e. preferentially ↓ axial attack

   (b) Counterion effect: its ability to complex/stabilize σ*, lower σ* ↑ effect, ↑ axial attack.

   (c) Electron-rich Nu⁻: ↑ σ* nucleophile, ↓ overlap/effect, ↓ axial attack ↑ equatorial attack.
4. Heteroatom at 4-position exhibits preference for axial attack: n–σ* stabilization.
   Review: Cieplak *Chem. Rev.* **1999**, *99*, 1265.

d. Additional Models

- Product development/steric approach control

Dauben: *J. Am. Chem. Soc.* **1956**, *78*, 2579.

- Torsional strain (preference for staggered conformation in the transition state)

Felkin: *Tetrahedron Lett.* **1968**, 2199, 2205.
Houk: *J. Am. Chem. Soc.* **1987**, *109*, 906.
J. Am. Chem. Soc. **1988**, *110*, 3228.
Science **1986**, *231*, 1108.
J. Am. Chem. Soc. **1991**, *113*, 5018.
J. Am. Chem. Soc. **1993**, *115*, 10992.
Angew. Chem., Int. Ed. Eng. **1992**, *31*, 1019.
cf. *Chemtracts: Org. Chem.* **1988**, *1*, 65.
Houk–Trost: *J. Am. Chem. Soc.* **1987**, *109*, 5560.

higher level calculations than Anh or Cieplak: C–C > C–H electron donation.

remote-through space electrostatics and torsional effects account for Cieplak observations.

- Principles of least motion

Yates: *J. Am. Chem. Soc.* **1974**, *96*, 3141.

- Stereoelectronic control and smallest change in conformation

Toromanoff: *Tetrahedron* **1980**, *36*, 2809.

- Electrostatic model

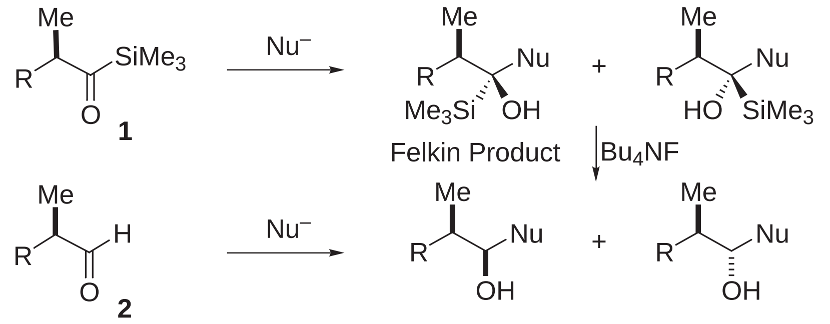
Kahn, Hehre, Chamberlin: *J. Am. Chem. Soc.* **1987**, *109*, 650, 663, 666.
J. Am. Chem. Soc. **1986**, *108*, 7396, 7399.

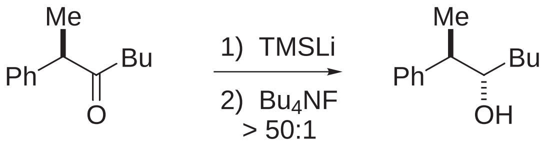
- Electronic nonequivalence of carbonyl faces
  Klein: *Tetrahedron Lett.* **1973**, 4307; **1974**, *30*, 3349.
- Dissymmetric π-electron clouds
  Fukui: *J. Am. Chem. Soc.* **1976**, *98*, 4054.
  Burgess, Liotta: *J. Am. Chem. Soc.* **1984**, *106*, 4849.
- Antiperiplanar approach of Nu⁻ to other bonds
  - Preferential attack antiperiplanar to the best electronic acceptor
    Anh: *Tetrahedron Lett.* **1976**, 155, 159.
    Nouv. J. Chim. **1977**, *1*, 61.
    Top. Curr. Chem. **1980**, *88*, 145.
    Dunitz, Eschenmoser: *Helv. Chim. Acta* **1980**, *63*, 1158.
  - Preferential attack antiperiplanar to the best electronic donor
    Cieplak Model: *J. Am. Chem. Soc.* **1981**, *103*, 4540.
    J. Chem. Soc., Perkin Trans. 1 **1997**, 530.
    Chem. Rev. **1999**, *99*, 1265.
- Others
  Ashby: *J. Org. Chem.* **1976**, *41*, 2890.
  Wigfield: *J. Org. Chem.* **1976**, *41*, 2396; **1977**, *42*, 1108.
- Bent bond or Tau-bond model
  Vogel, Eschenmoser: *Chem. Lett.* **1987**, 219.
  Winter: *J. Chem. Educ.* **1987**, *64*, 587.
- Hyperconjugation
  Coxon, Luibrand: *Tetrahedron Lett.* **1993**, *34*, 7097.
- Recent reviews of the various models: *Chem Rev.* **1999**, *99*, 1225–1467.

e. Comparative Examples of Diastereoselection

- Diastereoselection depends on the size of the ketone substituent.

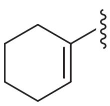
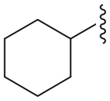
Kobayashi, Ohno *J. Am. Chem. Soc.* **1988**, *110*, 4826.





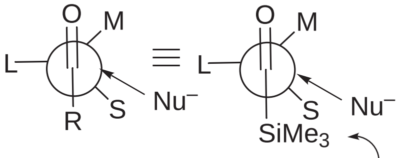
Complementary stereochemistry to that illustrated with acylsilanes.

Note: Desilylation proceeds with complete retention (>99:1): Hudrlik *J. Am. Chem. Soc.* **1982**, *104*, 6809.

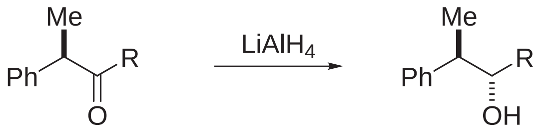
		From **1**	From **2**
R = Ph	^{n}BuLi	> 100:1	5:1
R = Ph	MeLi	> 40:1	4:1
R = Ph	 SiMe3	> 100:1	2:1
R = Ph	 MgBr	11:1	1.7:1
R = 	^{n}BuLi	> 30:1	1.6:1
	MeLi	> 100:1	1.9:1
	 SiMe3	> 30:1	1:1
	 MgBr	11:1	2.5:1
R = 	^{n}BuLi	15:1	3.5:1
	MeLi	21:1	2:1
	 SiMe3	> 100:1	1.5:1
	 MgBr	3.5:1	2:1

Note: Typical Felkin diastereoselection is modest.

Note: Diastereoselection is increased dramatically with very large ketone substituent.



Increase size, increase diastereoselectivity

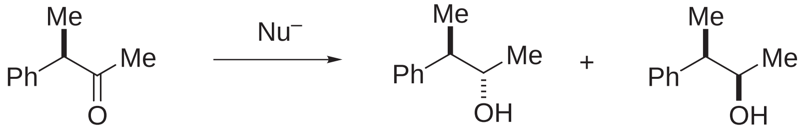


R	ratio
Me	74 : 26
Et	76 : 24
^{i}Pr	83 : 17
^{t}Bu	98 : 2

- Diastereoselectivity depends on size of nucleophile.

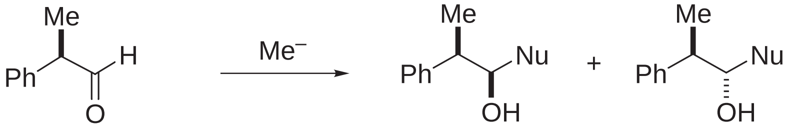
Felkin *Tetrahedron Lett.* **1968**, 2199 and 2205.
Diastereoselectivity for reduction with LiAlH$_4$

R = ^{t}Bu > ^{i}Pr > Et > Me



LiAlH$_4$	74	26
(^{s}Bu)$_3$BHLi	>99	<1

Yamamoto *J. Am. Chem. Soc.* **1988,** *110*, 4475.

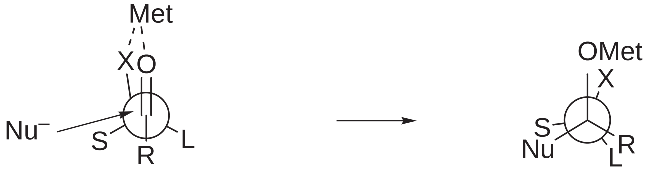


MeLi	65	35
MeMgBr	66	34
MeTi(O^{i}Pr)$_3$	88	12
MeTi(OPh)$_3$	93	7
MeMgOTs	92	8
MeMgOPiv	94	6
	Felkin Product	

Reetz *Top. Curr. Chem.* **1982**, *106*, 1.
Reetz *Angew. Chem., Int. Ed. Eng.* **1992**, *31*, 342.

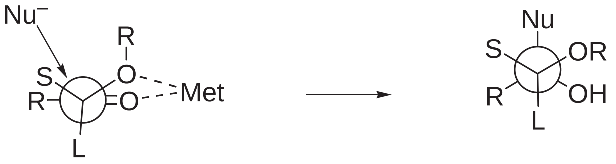
f. Chelation-controlled Addition

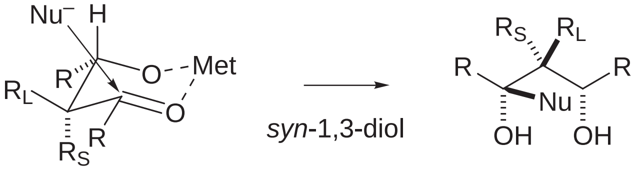
- Review: *Acc. Chem. Res.* **1993**, *26*, 462.
- 1,2-chelation-controlled additions (α-chelation-controlled additions)
  also formulated by Cram: *J. Am. Chem. Soc.* **1959**, *81*, 2748.
  So please do not refer to as anti-Cram addition as many have!



1,2-chelation X = OH, OR

Can usually provide excellent diastereoselectivity



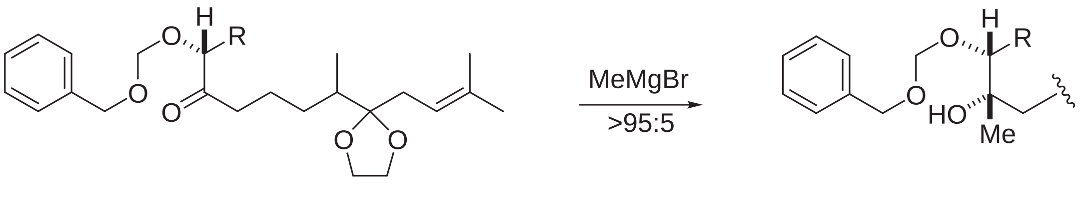


1,3-chelation

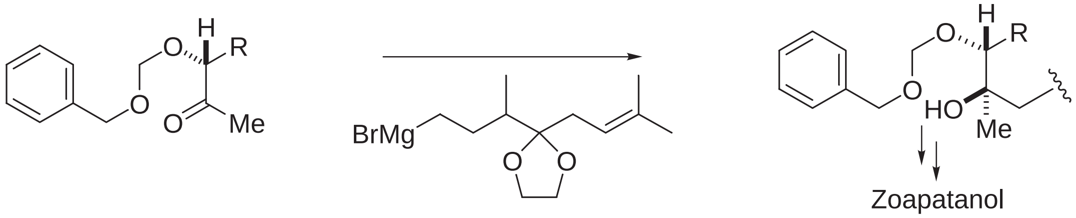
Axial delivery on most stable chair-like transition state

Asymm. Syn. Vol. 2, 125.

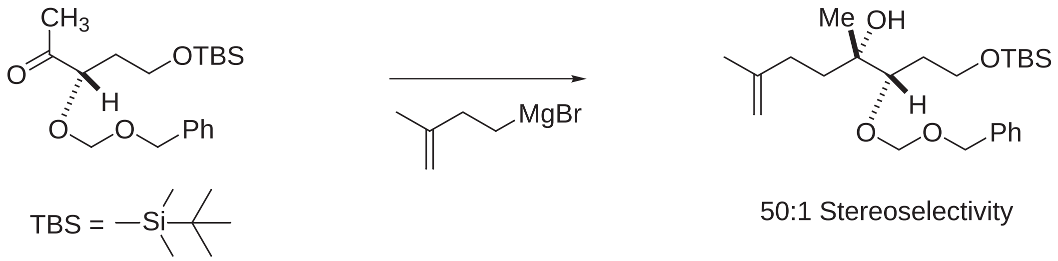
- Examples of 1,2-chelation-control
  - Nicolaou *J. Am. Chem. Soc.* **1980**, *102*, 6611. ⟹ Zoapatanol synthesis



-But to invert the stereochemistry

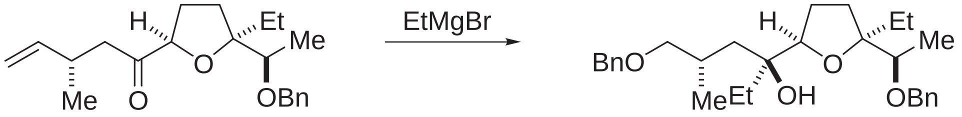


- Still *J. Am. Chem. Soc.* **1980**, *102*, 2117, 2118 and 2120. ⟹ Monensin synthesis

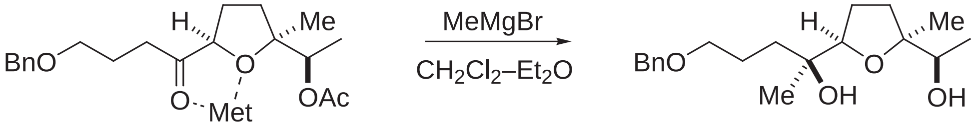


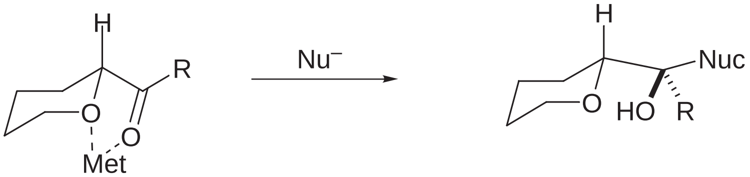
- Note that non chelation-controlled additions exhibit relatively modest stereoselectivities, but chelation-controlled additions can exhibit very good stereocontrol.

- Kishi *Tetrahedron Lett.* **1978**, 2745.
J. Am. Chem. Soc. **1979**, *101*, 260.



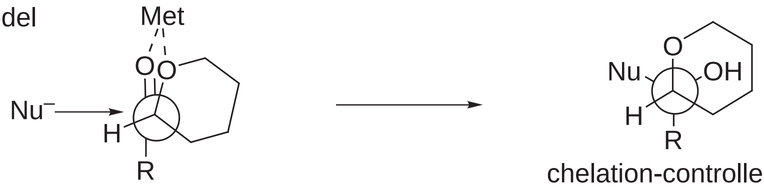
- Evans *J. Am. Chem. Soc.* **1990**, *112*, 5290.





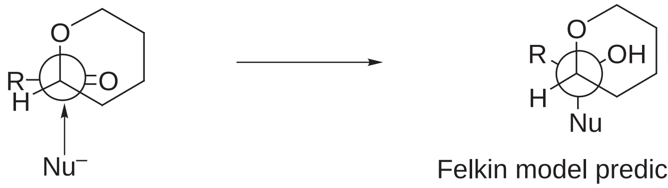
R = CH_3	Nu^- = PhMgI	100:0
Ph	MeMgBr or MeLi	100:0
Ph	$LiAlH_4$	84:16
Ph	$(^{s}Bu)_3BHLi$	100:0
CH_3	$(^{s}Bu)_3BHLi$	78:22

- Chelation Model



chelation-controlled product

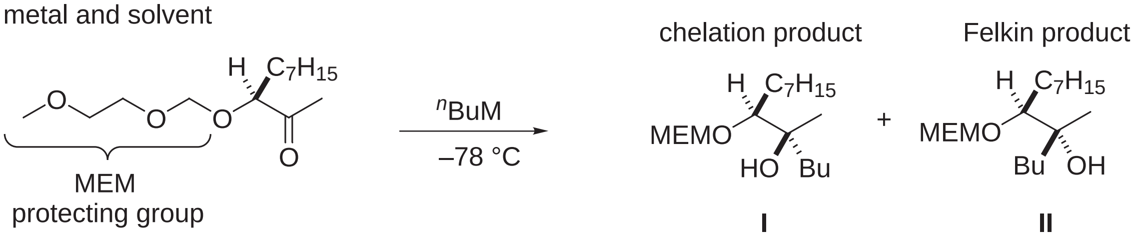
- Felkin Model



Note: here Felkin model will predict wrong product

Felkin model predicted product

- Effect of metal and solvent



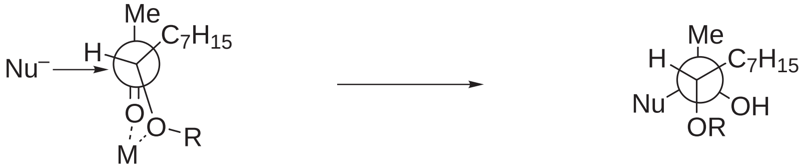
I II

	solvent	I	II
M = MgBr	pentane	90	10
"	CH_2Cl_2	93.5	6.5
"	Et_2O	90	10
"	THF	100	0

	solvent	I	II
M = Li	pentane	67	33
"	CH_2Cl_2	75	25
"	Et_2O	50	50
"	THF	41	59

Still *Tetrahedron Lett.* **1980**, *21*, 1031.

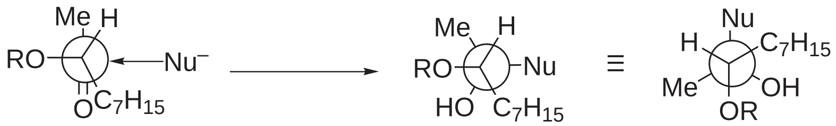
Note: Li is less able to coordinate to two O atoms and THF has good solvation capabilities (ie., removes Li^+; no α-chelation control)



chelation model

chelation-controlled product

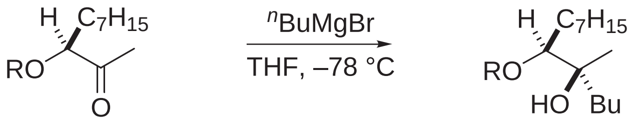
Two models provide different products



Felkin model

Felkin model predicted product

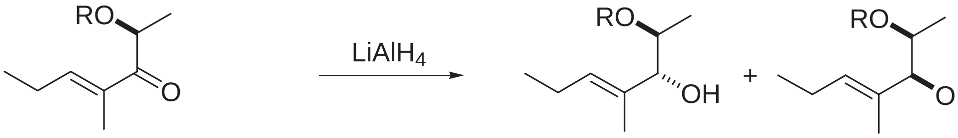
- Effect of protecting group



R = MEM	> 99:1
= MOM	> 99:1
= MTM	> 99:1
= CH_2Ph	99.5:0.5
= CH_2OCH_2Ph	99:1
= THP	75:25

Note: THP poor for chelation-control.

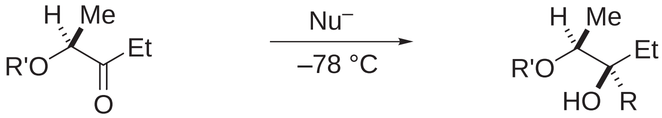
Still *Tetrahedron Lett.* **1980**, *21*, 1035.



Note: OTBS does not chelate

R = Bn	Et_2O, –10 °C	98	:	2	← chelation-controlled
R = TBS	THF, –20 °C	5	:	95	← Felkin addition

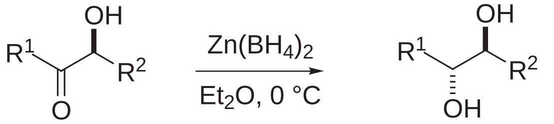
Overman *Tetrahedron Lett.* **1982**, *23*, 2355.



R' = CH_2Ph	MeMgCl	Et_2O	> 99:1	← chelation-controlled
	MeLi	THF	60:40	
R' = TBS	MeMgCl	Et_2O	60:40	
	⁄⁄⁄MgCl	THF	10:90	← Felkin addition

Note: Silyl ether poor for chelation-control.

Reetz *J. Chem. Soc., Chem. Commun.* **1986**, 1600.

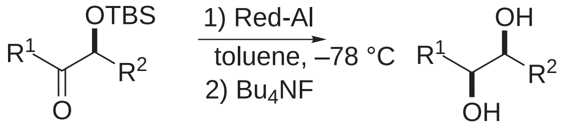


anti-1,2-diol
chelation-controlled addition

77–99 : 23–1

versus

Note: TBS very good at suppressing chelation.

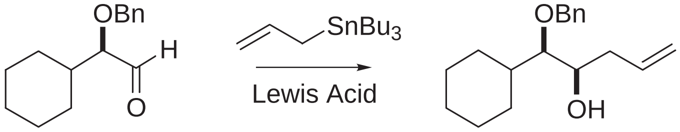


syn-1,2-diol
Felkin addition

76–98 : 24–2

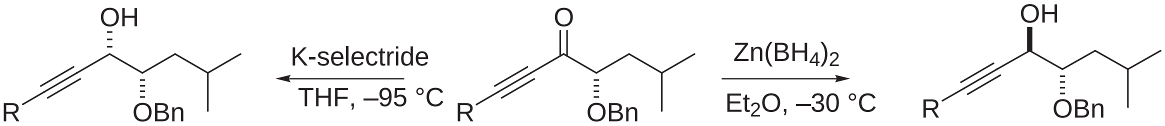
Nakata *Tetrahedron Lett.* **1983**, *24*, 2653 and 2661.

- Effect of metal



BF_3•OEt_2	2:3
$ZnBr_2$	3:1
$MgBr_2$	> 250:1
$TiCl_4$	> 250:1

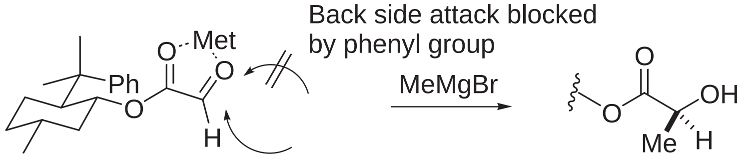
Keck *Tetrahedron Lett.* **1984**, *25*, 265.



90:10
Felkin addition

95:5
chelation-controlled

Note: Red-Al was *anti* selective due to coordination of OBn
Tsuji *Tetrahedron Lett.* **1985**, *26*, 5139.



Back side attack blocked by phenyl group

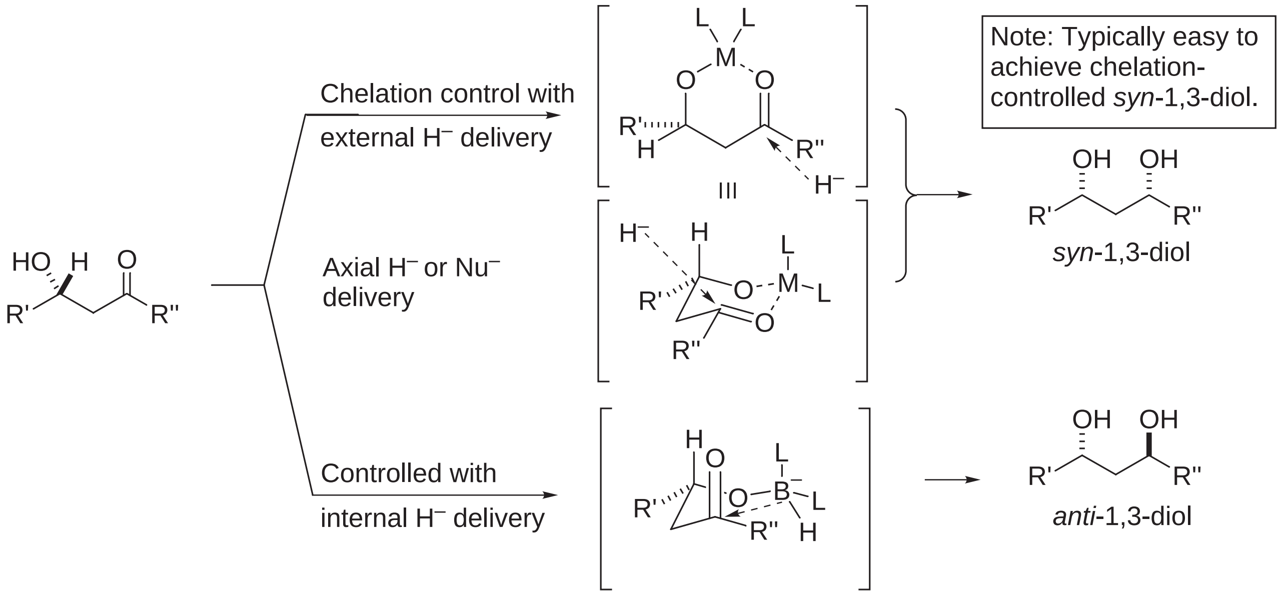
98% de

Metal chelate and preference for H-eclipsed carbonyl conformation provides a dominant conformation.

Whitesell *Acc. Chem. Res.* **1985**, *18*, 280.
J. Org. Chem. **1986**, *51*, 5443.

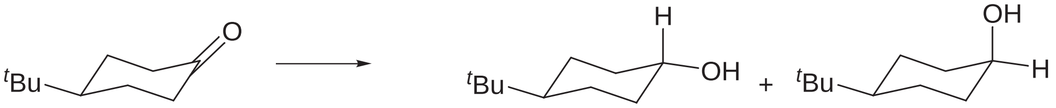
-1,3-Chelation-Controlled Additions (β-chelation-controlled additions):

- First highly selective method was developed with $R_3B/NaBH_4$ and later with Et_2BOCH_3–$NaBH_4$ in THF–MeOH:
  Pai *Tetrahedron* **1984**, *40*, 2233.
  Shapiro *Tetrahedron Lett.* **1987**, *28*, 155. (*syn:anti* 98:2)
- Dibal-H (> 92:8 *syn:anti*) Kiyooka *Tetrahedron Lett.* **1986**, *27*, 3009.

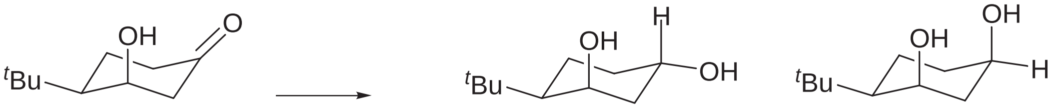


- Examples of *anti*-1,3-diol preparation:

Evans, Carreira, Chapman *J. Am. Chem. Soc.* **1988**, *110*, 3560.



$NaBH_4$	90	:	10
$Me_4NBH(OAc)_3$	no reaction		



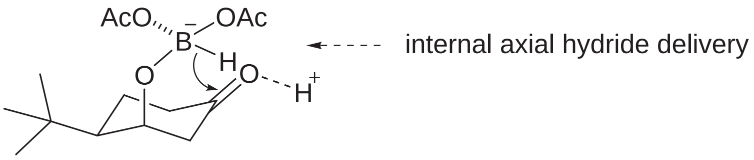
$NaBH_4$	1	:	1
$Me_4NBH(OAc)_3$	300	:	1

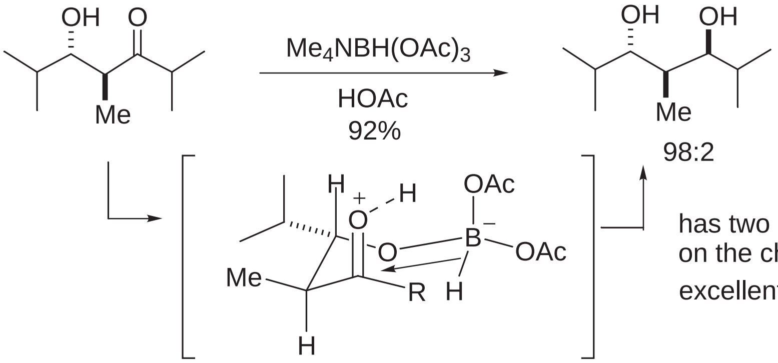
HOAc, low temperature protonates carbonyl,
activation for reduction, no reduction without HOAc

- Note that $Me_4NBH(OAc)_3$ is unreactive toward carbonyl unless carbonyl oxygen is protonated.
- The key to success is the lack of reactivity of the reagent in the intermolecular reaction, which permits formation of complex:

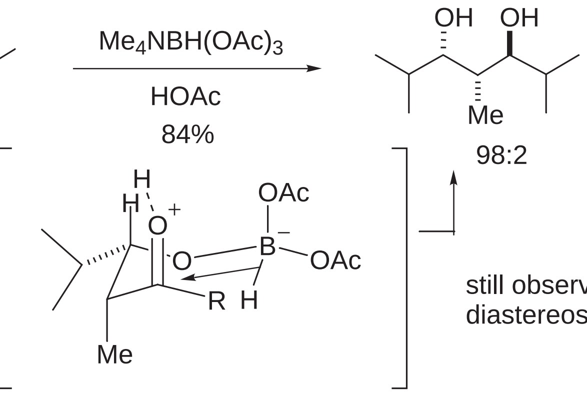
First example of $NaBH(OAc)_3$/HOAc intramolecular reduction of a ketone, see:
Saksena, Mangiaracina *Tetrahedron Lett.* **1983**, *24*, 273.

For the reduction of aldehydes in the presence of ketones which are not reduced, see:
Gribble *J. Chem. Soc., Chem. Commun.* **1975**, 535.





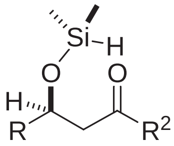
has two equatorial substituents,
on the chair-like transition state
excellent diastereoselectivity



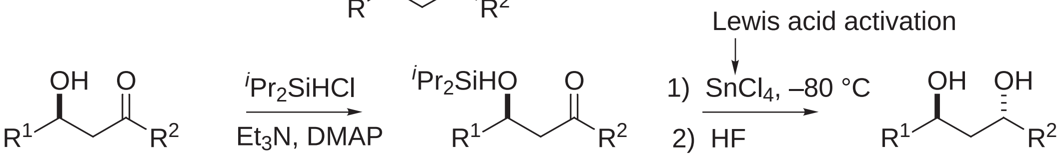
axial alkyl group, but no
destabilizing 1,3-diaxial
interactions

still observe excellent
diastereoselectivity

-Also, works with



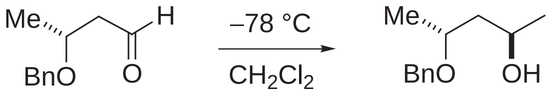
\+ Lewis acid (to activate carbonyl)



Davis *Tetrahedron* **1988**, *44*, 3761.

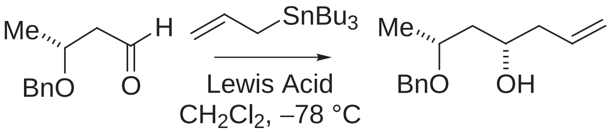
internal H$^-$ delivery *anti*-1,3-diol

- Nucleophiles other than H$^-$



MeMgCl, THF	40:60
$MeTiCl_3$	90:10

Reetz *J. Am. Chem. Soc.* **1983**, *105*, 4833.

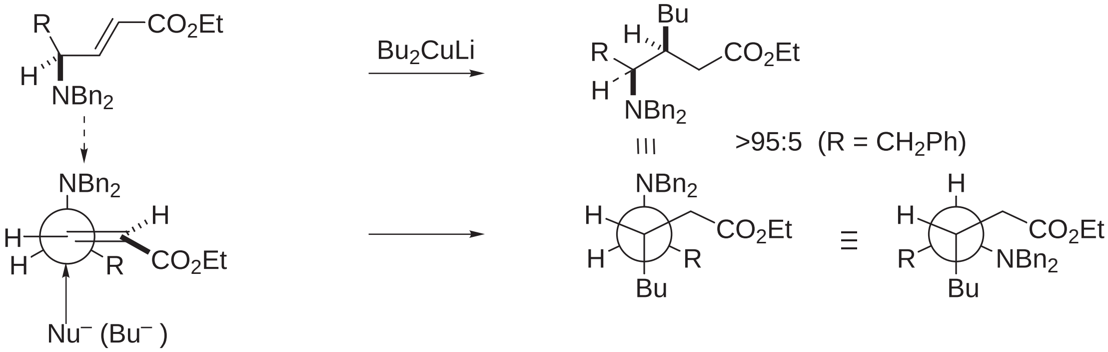


$TiCl_4$	95:5
$SnCl_4$	95:5
BF_3•OEt_2	85:15

Reetz *Tetrahedron Lett.* **1984**, *25*, 729.

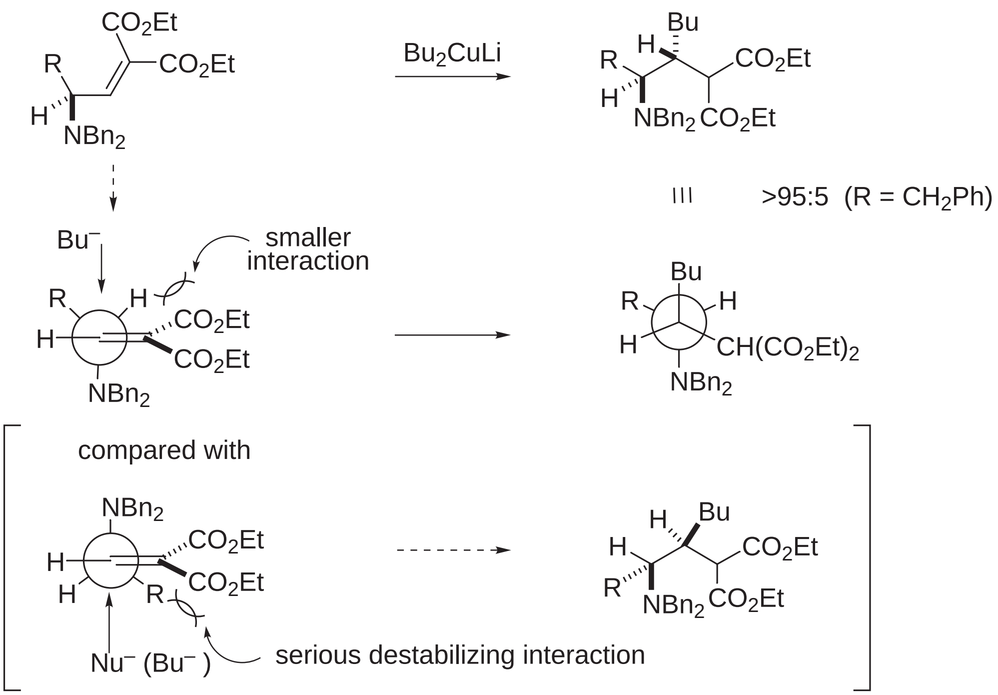
g. Felkin Addition to Other π-Systems

- Reetz *Angew. Chem., Int. Ed. Eng.* **1989**, *28*, 1706.

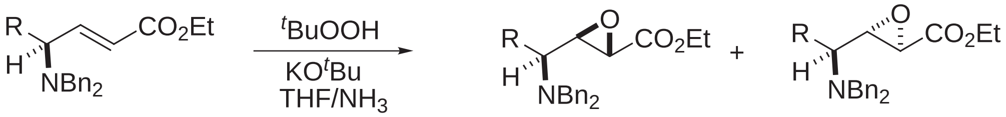


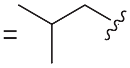
- Felkin Model

But,



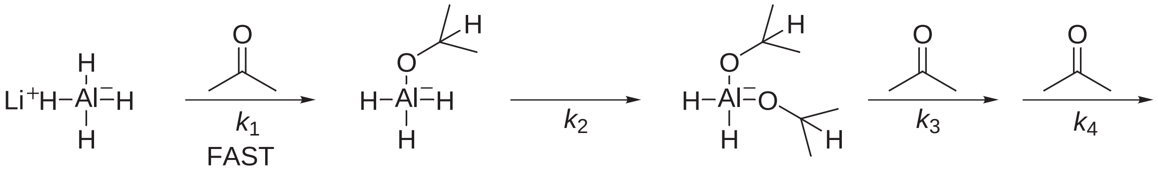
- Rationalize the following results:



R = CH_3	46%	> 96	:	4
R = $PhCH_2$	60%			
R = 	68%			
R = TBDMSOCH$_2$	80%			

E. Aluminum Hydride Reducing Agents

- $LiAlH_4$ coordinates with carbonyl oxygen and activates it towards reduction.



- Rate of addition decreases as additional alkoxy groups are placed on Al: $k_1 > k_2 > k_3 > k_4$, especially for hindered ketones.

- The aluminum alkoxide hydrides are stable in that they do not disproportionate.

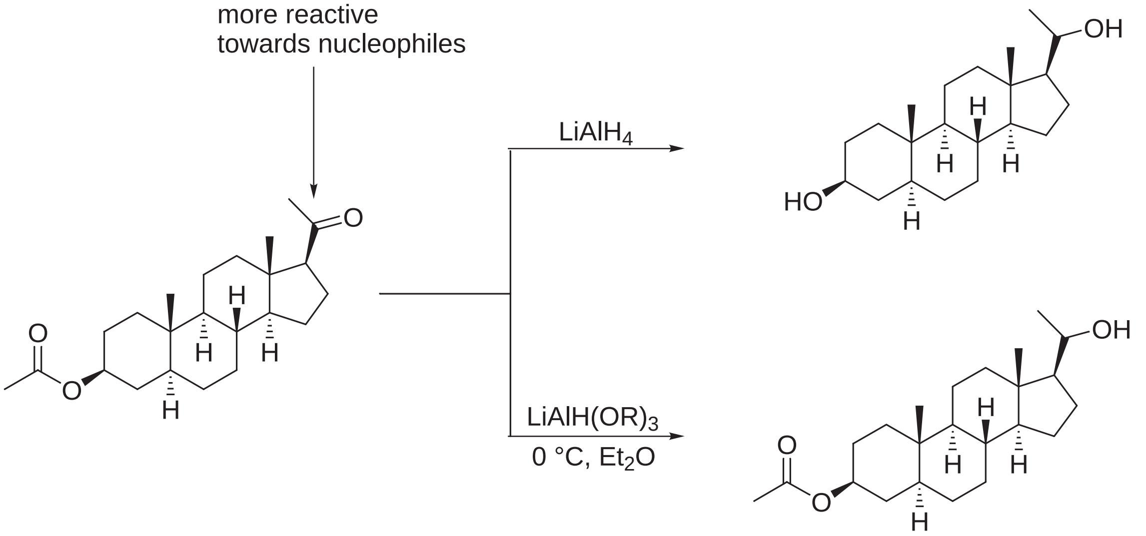
- Reagents have been designed which are less reactive, thus more selective:

  - Reactivity: $LiAlH_4 > LiAl(OR)H_3 > LiAl(OR)_2H_2 > LiAl(OR)_3H$

$$LiAlH_4 \xrightarrow{3\ ROH} LiAlH(OR)_3$$

  - Most common are $LiAlH(OCH_3)_3$ and $LiAlH(O^tBu)_3$

- Examples:

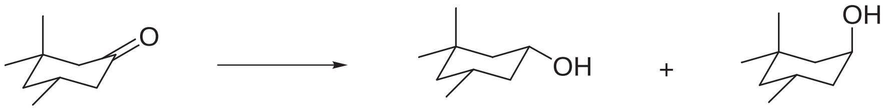


Chemoselectivity: differentiation between competitive functional groups

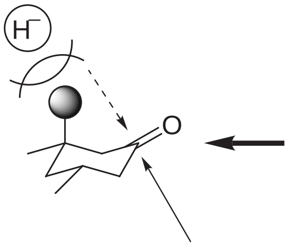
vs.

Regioselectivity: differentiate between orientations.

- Lithium trialkoxyaluminumhydrides can be chemoselective.



NaBH$_4$	36–45	:	55–64
LiAlH$_4$	37–48	:	52–63
LiAlH(OCH$_3$)$_3$	2–8	:	92–98
LiAlH(O^{t}Bu)$_3$	4–12	:	88–96



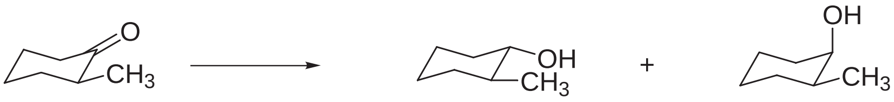
- this is actually dimeric in solution, so effective bulk greater than LiAlH(O^{t}Bu)$_3$
- degree of stereocontrol is concentration dependent with LiAlH(OCH$_3$)$_3$ (dimer and higher aggregates) but not LiAlH(O^{t}Bu)$_3$ (monomeric)

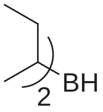
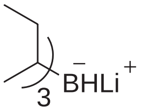
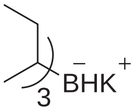
F. Borohydride Reducing Agents

- Borohydrides (Na$^+$, Li$^+$, K$^+$, Zn^{2+}) are nucleophilic H$^-$ sources.
- Alkoxyborohydrides (RO)$_3$B$^-$H tend to disproportionate.

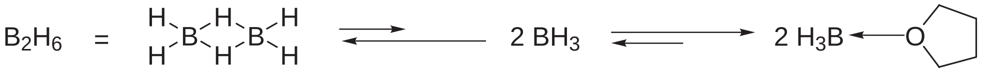
$$\text{Na (RO)}_3\text{BH} \rightleftarrows \text{NaBH}_4$$

  - Therefore, $k_1 \sim k_2 \sim k_3 \sim k_4$ for the stepwise reactions and you can't typically moderate the reactivity (electronically) by introducing alkoxy substituents.
  - However, substitution with bulky alkyl groups on boron will moderate reactivity and diastereoselectivity.



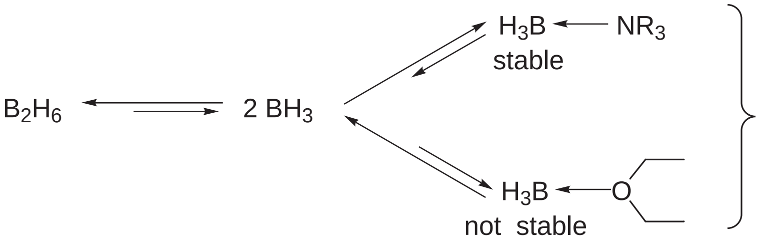
	$LiAlH_4$	75	:	25
	BH_3•THF	74	:	26
		21	:	79
Li-Selectride		<1	:	>99
K-Selectride		<1	:	>99

- NOTE: on diborane



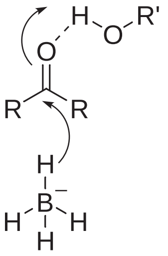
- THF optimally provides uncomplexed, monomeric BH_3 available for reduction (or other reactions).
- In ether (B_2H_6), or in the presence of amines (BH_3•NR_3), less reactive borane-complexes are formed.

B_2H_6
BH_3•THF
BH_3•OEt_2
BH_3•SMe_2
BH_3•NR_3



reactions of B_2H_6 in Et_2O or in the presence of 3° amines will be slower than reactions run in THF

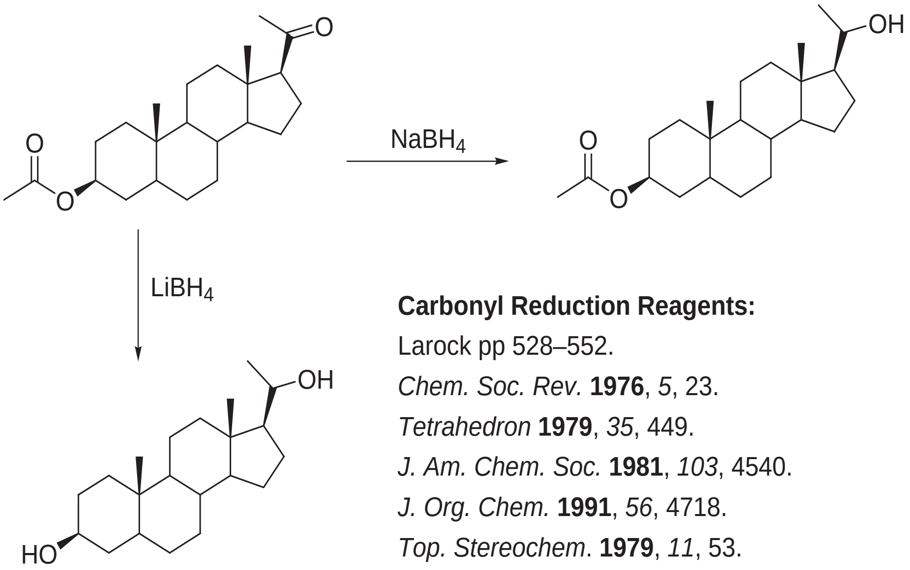
- $NaBH_4$ requires activation of the carbonyl by hydrogen-bonding with alcoholic solvent for reductions. Therefore the reactions are run in alcoholic solvents. The reagent slowly reacts with solvent: MeOH (30 min) > EtOH (slow) > ^{i}PrOH (stable) > ^{t}BuOH (stable).



- But trialkylborohydrides ($R_3B^{-}HM^{+}$) are reactive enough to use in ethereal solvents (e.g., THF) and don't require this activation of C=O by solvent.

- $LiBH_4$ is also more reactive than $NaBH_4$ (Li^+ coordinates better to carbonyl oxygen, activating the carbonyl toward attack by H^-).

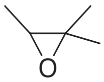
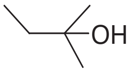
- Differences in reactivity can give rise to Chemoselectivity:

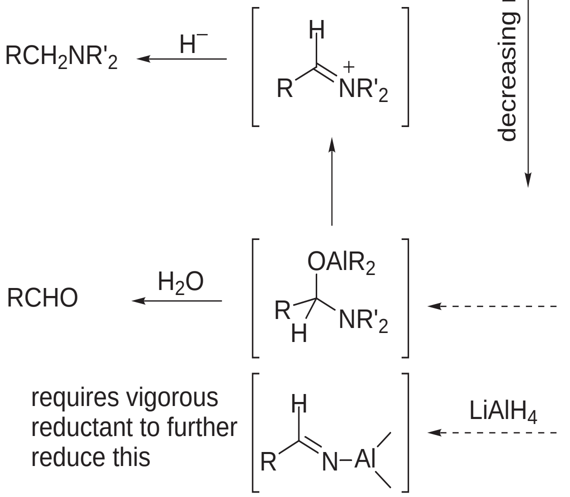


Carbonyl Reduction Reagents:
Larock pp 528–552.
Chem. Soc. Rev. **1976**, *5*, 23.
Tetrahedron **1979**, *35*, 449.
J. Am. Chem. Soc. **1981**, *103*, 4540.
J. Org. Chem. **1991**, *56*, 4718.
Top. Stereochem. **1979**, *11*, 53.

G. Hydride Reductions of Functional Groups

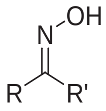
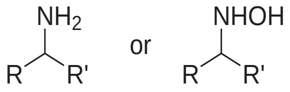
decreasing reactivity

Substrate	$\xrightarrow{LiAlH_4}$	Product
RCOCl		RCH_2OH
RCHO		RCH_2OH
RCOR'		RCH(OH)R'
		 OH
RCOOR'		RCH_2OH + R'–OH
$RCOO^-$ (slow)		RCH_2OH
$RCONR'_2$		RCH_2NH_2 or RCHO
RC≡N		RCH_2NH_2 or RCHO



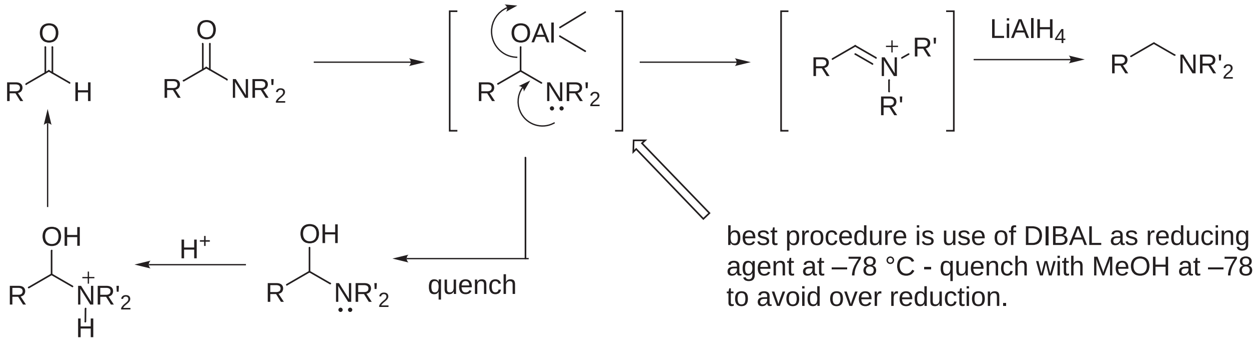
requires vigorous reductant to further reduce this

- DIBAL-H + RC≡N (at 0 °C) gives good yields of RCHO

Substrate	Product
	
RNO_2	RNH_2
RCH_2X	RCH_3
$R\underset{R'}{C}HX$	RCH_2R'

X = Br, Cl, I, OSO_2R

- Reductions of

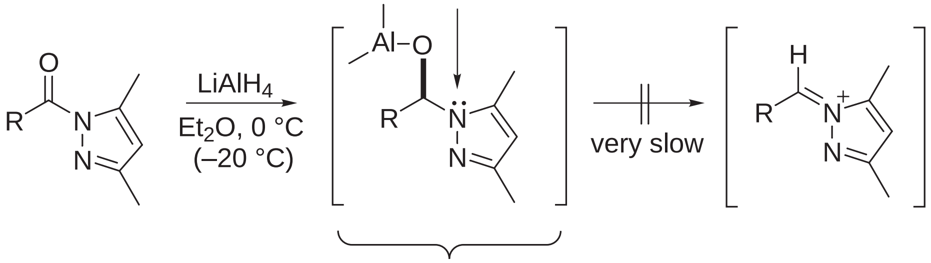


best procedure is use of DIBAL as reducing agent at –78 °C - quench with MeOH at –78 °C to avoid over reduction.

- or other specially selected amides will cleanly give aldehyde:

enlisting these electrons disrupt the aromaticity of pyrazole

1.

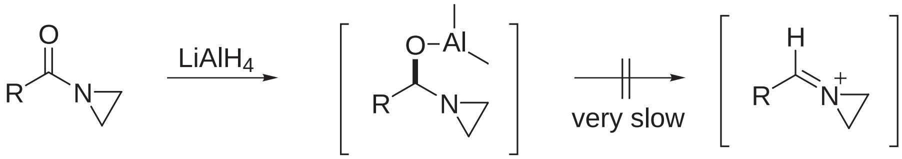


breakdown to iminium ion intermediate very slow

no longer aromatic

Ried *Angew. Chem.* **1958**, *70*, 165.

2.

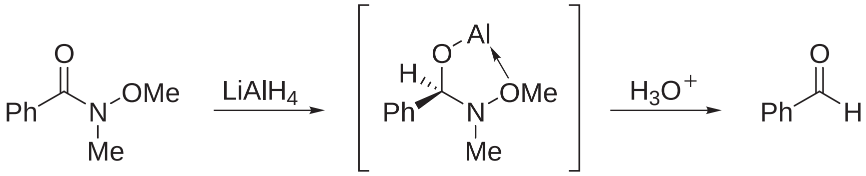


too strained

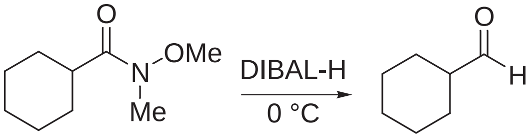
Brown *J. Am. Chem. Soc.* **1961**, *83*, 2016 and 4549.

3. Weinreb amide

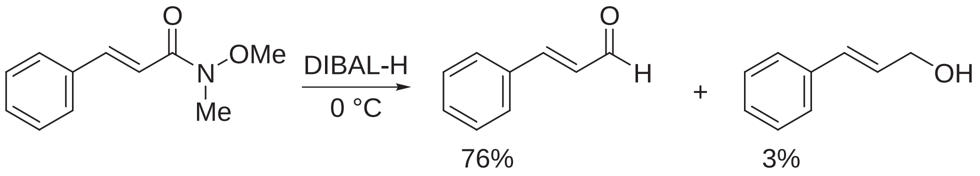
- A more recent and now widely employed method for controlled reduction and nucleophilic addition (i.e. RLi) to carboxamides was introduced by Weinreb (*Tetrahedron Lett*. **1981**, *22*, 3815).

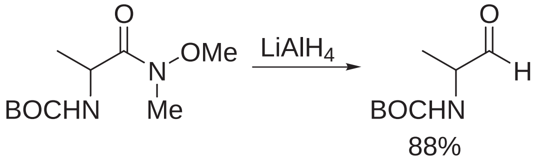


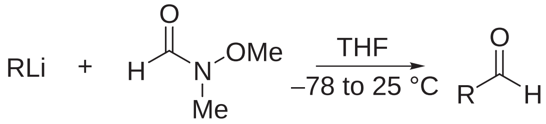
Chelation stabilizes intermediate which does not breakdown during the reaction, but only upon workup.



74%







Castro *Synthesis* **1983**, 676. Lipshutz *Tetrahedron Lett.* **1999**, *40*, 7889.

4. The Rosenmund reduction is a much older method that may be utilized to convert carboxylic acids to aldehydes via the acid chloride.

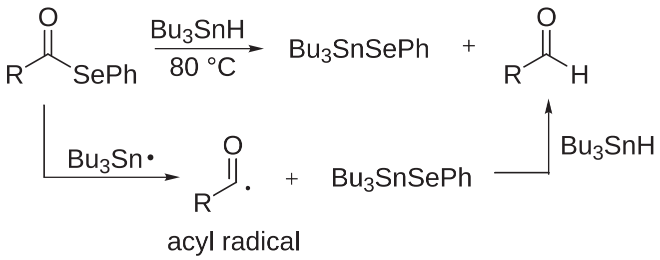
$$RCO_2H \longrightarrow RCOCl \xrightarrow[Pd/BaSO_4]{H_2} RCHO$$

Rosenmund *Ber.* **1921**, *54*, 425; *Ber.* **1918**, *51*, 585.

Review: *Org. React.* **1948**, *4*, 362.

Burgstahler *Synthesis* **1976**, 767.

5. Bu_3SnH will selectively reduce selenoesters to aldehydes without further reduction by a free radical mechanism.



- Also possible to promote decarbonylation prior to reduction to achieve conversion to the corresponding hydrocarbon.

Pfenninger *Helv. Chim. Acta* **1980**, *63*, 2328.

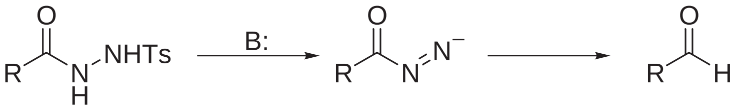
- Review of RCOX ⟶ RCHO: *Comprehensive Org. Syn.,* Vol. 8, pp 259 and 283.

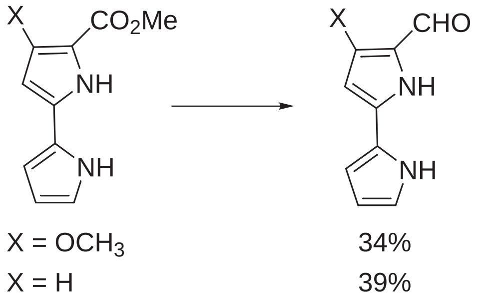
6. $Bu_3SnH–InCl_3$

$$RCOCl \xrightarrow[\substack{0.2\ \text{equiv}\ Ph_3P \\ >80\%}]{\substack{Bu_3SnH \\ 0.1\ \text{equiv}\ InCl_3}} RCHO$$

Baba *Tetrahedron Lett.* **2000**, *41*, 113.

7. McFadyen–Stevens reduction: *J. Chem. Soc.* **1936**, 584.





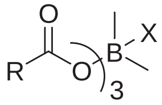
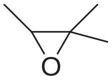
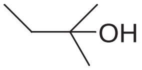
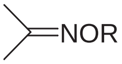
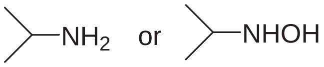
Boger *J. Org. Chem.* **1988**, *53*, 1405. (Prodigiosin)

- Reactions of Borane (BH_3) - - - - → an electrophilic reagent

Carboxylic acids may be selectively reduced in the presence of a wide range of functional groups.

Amides may be reduced selectively in the presence of esters.

decreasing reactivity

Substrate	→	Product
RCOOH	→ 	RCH_2OH
RHC=CHR'		$RCH_2CH(B)R'$
$RCONR'_2$		$RCH_2NR'_2$
RCHO, RCOR'		RCH_2OH, RCH(OH)R'
RC≡N (slow)		RCH_2NH_2
 (very slow, Lewis acid activation required)		
RCOOR'		RCH_2OH
		
RCOCl		RCH_2OH
$RCOO^-$, RNO_2		no reaction

But: see *Tetrahedron Lett*. **1982**, *23*, 2475.

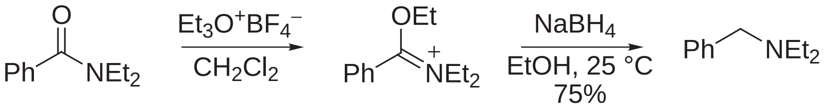
H. Characteristics of Hydride Reducing Agents

Borohydrides

1. $NaBH_4$

- Review: *Aldrichim. Acta* **1979**, *12*, 3.
- Mild reducing agent used primarily for the reduction of aldehydes and ketones.
- Also available as $NaBD_4$, $NaBT_4$ (although somewhat less reactive) for labelling.
- H^+ workup of $NaBH_4$ reductions may form BH_3 (if excess $NaBH_4$ used)
  - - - - → might react with other functional groups (this is the origin of the discovery of BH_3 and its hydroboration of alkenes).
- $NaBH_4$ reacts with H_2O, CH_3OH at 25 °C → ca. 30 min
  reacts only slowly with EtOH (good solvent), is stable in ^{i}PrOH or ^{t}BuOH and can also be used in diglyme but the latter reduction is very slow.

Although amides are not reduced by $NaBH_4$, the corresponding imino ester salts can be

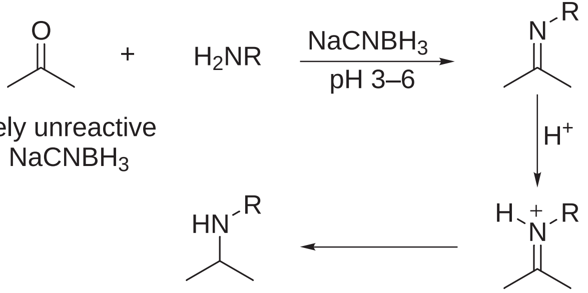


Borch *Tetrahedron Lett.* **1968**, 61.

2. $NaCNBH_3$

- Less reactive than $NaBH_4$.
- Stable in aqueous solutions even at pH > 3 (permits activation of C=O by protonation).
- Can be used in CH_3OH.
- Can be used in THF but reduction very slow.

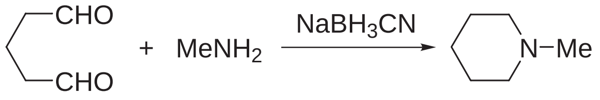
- Reductive amination (Borch reduction):



relatively unreactive
toward $NaCNBH_3$

Under acidic conditions the protonated imine is more reactive than starting ketone or aldehyde.

very good way to make 2° amines

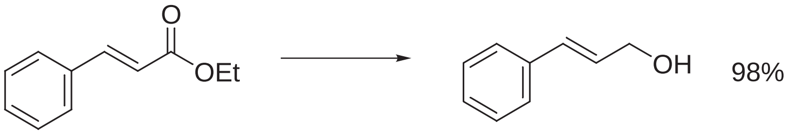


Borch *J. Am. Chem. Soc.* **1969**, *91*, 3996; **1971**, *93*, 2897.
J. Chem. Soc., Perkin 1 **1984**, 717.

- Review: *Comprehensive Org. Syn*., Vol. 8, pp 25–78. This review also discusses the diastereoselectivity of cyclic/acyclic imine/iminium reductions with comparisons to the corresponding ketone. Many similarities but also many important distinctions.

3. $LiBH_4$

- More reactive than $NaBH_4$ (Li_+ activates C=O by coordination).
- Can be used in THF, diglyme and non protic solvents. Reactivity: Et_2O > THF = diglyme > ^{i}PrOH
- Excellent reagent for mild reductions.



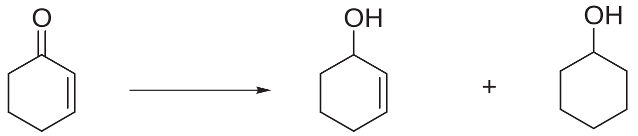
- clean 1,2-reduction!
- $NaBH_4$ does not typically reduce esters

4. Me_4NBH_4, Et_4NBH_4

- Soluble in nonpolar aprotic solvents (e.g., THF, benzene).

5. $Zn(BH_4)_2$

- Good in instances of potential competing 1,4-reduction.
- Zn^{+2} coordinates to and activates carbonyl.
- Good for chelation-controlled reductions.

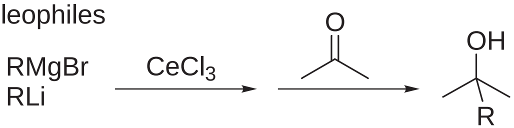


$Zn(BH_4)_2$	96%	4%
$NaBH_4$	59%	41%

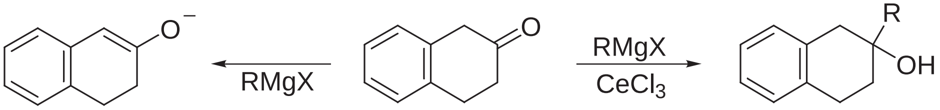
- Review: Narasimhan *Aldrichim. Acta* **1998**, *31*, 19.

6. $NaBH_4/CeCl_3$ (catalytic amount (0.1 equiv))

- Luche *J. Am. Chem. Soc.* **1981**, *103*, 5454; **1978**, *100*, 2226.
- Readily enolizable carbonyl can be reduced.
  - also true of other nucleophiles

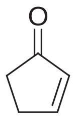


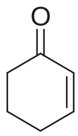
- clean addition, no enolization



Imamoto *J. Am. Chem. Soc.* **1989**, *111*, 4392.
Review: Liu *Tetrahedron* **1999**, *55*, 3803.

- No conjugate reduction: clean 1,2-reduction.
    - Reagent comparisions for 1,2- vs. 1,4-reduction





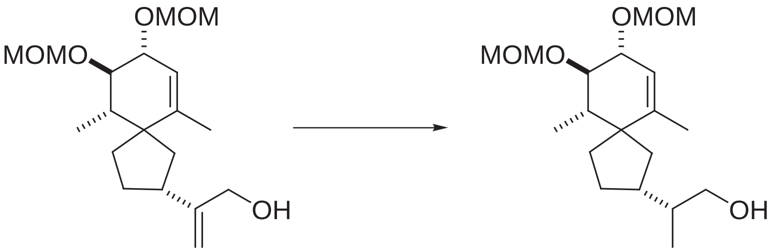
Reagent	1,2 : 1,4		1,2 : 1,4		
$LiAlH_4$	85 : 15	(100%)	94 : 6	(97%)	
$NaBH_4$	0 : 100	(100%)	59 : 41	(90%)	
$NaBH_4/CeCl_3$	97 : 3	(100%)	>99 : 1	(100%)	← !!!
$LiAlH_4/CeCl_3$	64 : 36	(99%)	98 : 2	(100%)	
DIBAL-H	98 : 2	(81%)	98 : 2	(100%)	← Masamune *J. Chem. Soc.*, *Chem Commun.* **1970**, 213.
DIBAL-H/^{n}BuLi	99 : 1	(83%)	94 : 6	(96%)	
9-BBN	>99 : 1	(85%)	>99 : 1	(85%)	← Brown *J. Org Chem.* **1977**, *42*, 1197.
$LiAlH(OMe)_3$	90 : 10		95 : 5		
$LiAlH(O^tBu)_3$	0 : 100		22 : 78		

7. $NaBH_4$–$CoCl_2$

- Selective reduction of nitriles.

Ganem *J. Am. Chem. Soc.* **1982**, *104*, 6801

- But will also reduce olefins, allylic alcohols, and ketones.



Iwata *Chem. Pharm. Bull.* **1990**, *33*, 361.

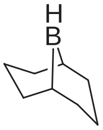
8. $Me_4NBH(OAc)_3$ and $NaBH(OAc)_3$

- Unreactive, no intermolecular ketone reductions.
- OAc can exchange with substrate alcohol and provides opportunity for intramolecular reductions (CH_3CN–HOAc). Used to form *anti*-1,3-diols from acyclic β-hydroxyketones.

9. $KBH(O^iPr)_3$

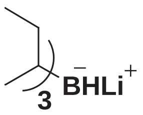
- Stable (does not undergo disproportionation reaction as with other alkoxy BH), mild reagent.
- Used in THF and only reduces aldehydes and ketones; bulky reagent so it gives equatorial attack on cyclohexanones.

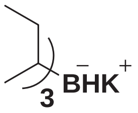
10. 9-BBN



- Stable solid; more stable and less reactive/more selective.
- Gives good 1,2- vs. 1,4-reduction selectivity.
- Very selective reagent.

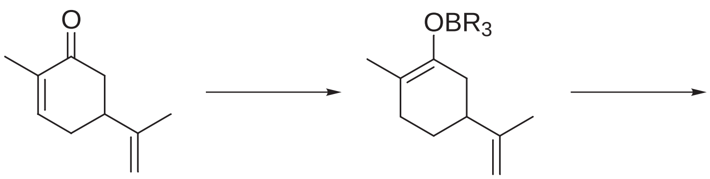
11. Li-Selectride K-Selectride





- Large reagents, near exclusive cyclohexanone equatorial H^- delivery.
- Very bulky.

- Very reactive and give preferential 1,4-reduction.



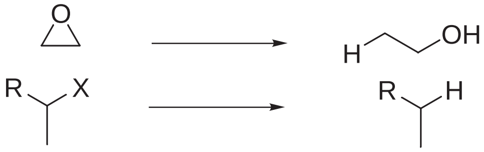
- Reductive alkylation with regiospecific enolate generation.

can alkylate these enolates

Ganem *J. Org. Chem.* **1976**, *41*, 2194.

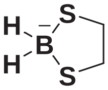
12. $LiBHEt_3$ (Super Hydride)

- Very powerful (stronger than $LiAlH_4$), so good for reductions which are otherwise slow.



Relative reactivity: Et_3BH^- (10,000), AlH_4^- (240), BH_4^- (1).
Brown *J. Org. Chem.* **1983**, *48*, 3085.

13. $NaBH_4–HSCH_2CH_2SH$



- Used in THF.
- Guida *J. Org. Chem.* **1984**, *49*, 3024.

$RCO_2Et \xrightarrow[\text{THF}]{} RCH_2OH$

$PhCO_2{}^iPr \xrightarrow[83\%]{} PhCH_2OH$

} Note the selectivity available

$PhCO_2{}^tBu \not\longrightarrow$

$PhCN \not\longrightarrow$

$PhCONH_2 \longrightarrow PhCH_2NH_2$ } Yet powerful enough to reduce amides

Aluminum Hydrides

1. $LiAlH_4$

- $LiAlD_4$ and $LiAlT_4$ are also available for labelling.
- Reductions can be conducted in ether, THF, DME, diglyme.
- Workup best conducted by 1,2,3 method:

for 1.0 g $LiAlH_4$ used, add 1 mL H_2O (slowly)
then 2 mL of 10% aqueous NaOH, then 3 mL
H_2O ⟶ Al salts are now easily filtered

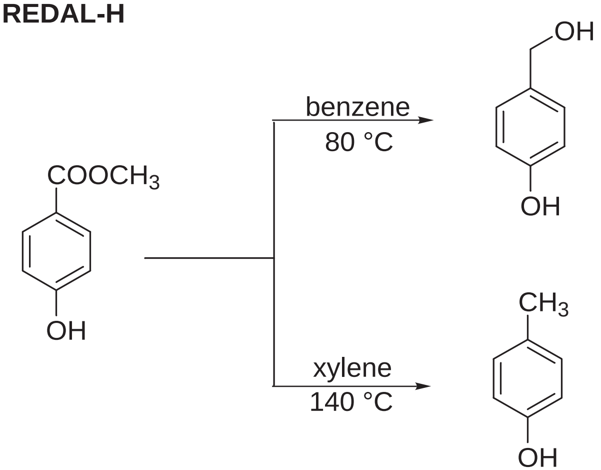
2. $NaAlH_4$

- Not quite as reactive as $LiAlH_4$, but still quite strong reducing agent.
- THF, DME, diglyme solvents.

3. $LiAlH(O^tBu)_3$
$LiAlH(OEt)_3$
$LiAlH(OMe)_3$ ⟶ this is the largest reagent (due to aggregation) of the three

- Use in THF, diglyme.
- Review on alkoxyaluminum hydrides: *Org. React.* **1985**, *34*, 1; **1988**, *36*, 249.

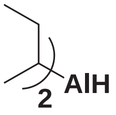
4. $NaAlH_2(OCH_2CH_2OMe)_2$ = REDAL-H

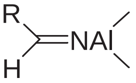


powerful reducing agent

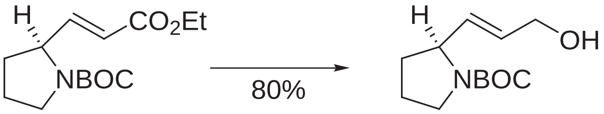
Cerny, Malek *Tetrahedron Lett.* **1969**, 1739.

- Xylene, benzene, toluene good solvents.
- Good for epoxide openings (especially if able to be directed by proximal OH), halide and sulfonate reduction.

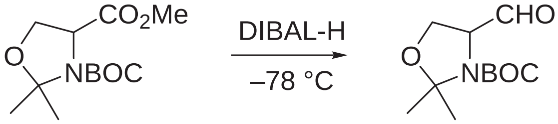
5.  = DIBAL-H

- Good for RC≡N → RCHO via 

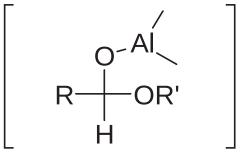
- Because there is no metal cation (Li^+, K^+, etc.) in the reagent, very good for directed reductions (i.e., chelation-controlled reductions).
- Good for 1,2- vs. 1,4-reduction.



- Also good for RCOOR' → RCHO



Garner *Org. Syn.* **1992**, *70*, 18.

via 

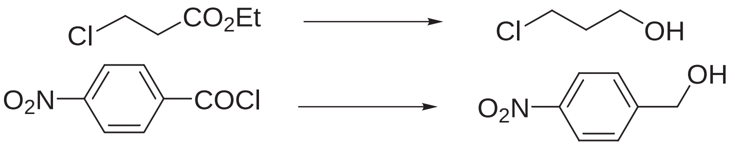
stable at –78 °C but breaks down at higher temperatures to give alcohol (upon further reduction) → to get RCHO, quench must be conducted at –78 °C (use MeOH or HOAc as proton source, H_2O freezes into a solid) then warmed to 25 °C

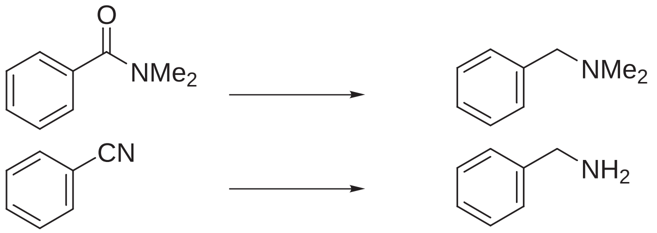
- Also, use of noncoordinating hydrocarbon solvent (toluene) provides better control than THF for reductions to RCHO.

6. AlH_3
$AlH_3–NR_3$

- Park *J. Org. Chem.* **1990**, *55*, 2968.

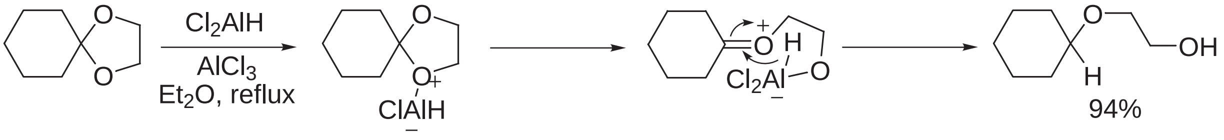
$$RCO_2H \longrightarrow RCH_2OH$$





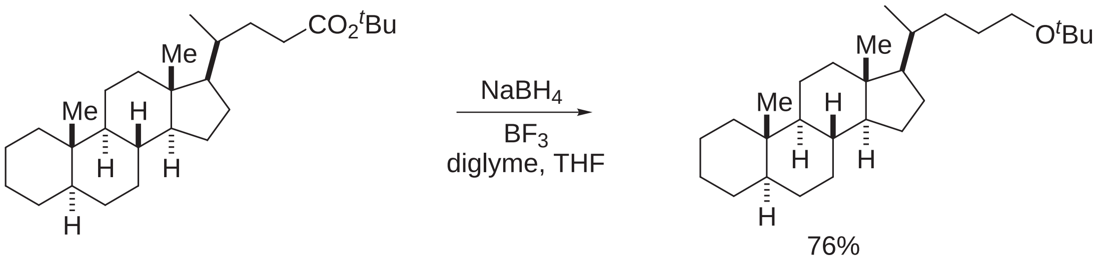
7. Cl_2AlH

Strong electrophilic reducing agent



Eliel *Org. Syn.* **1967**, *47*, 37.

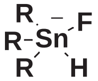
A related and often overlooked alternative enlists $NaBH_4$ + Lewis acid



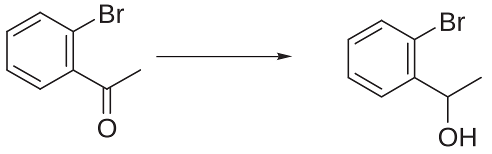
Pettit *J. Org. Chem.* **1962**, *27*, 2127.
Eliel *J. Org. Chem.* **1964**, *29*, 1630. (thiol ester ⟶ dialkylsulfide)

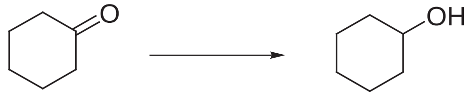
Other Representative Reagents

1. $Bu_3SnH–Bu_4NX$, X = Cl, F

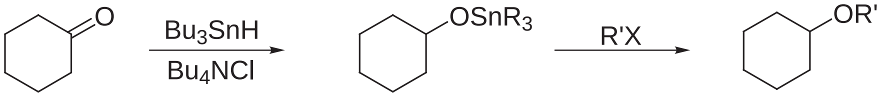


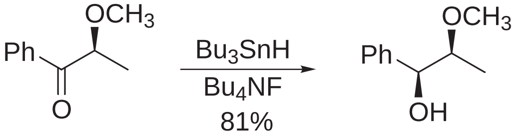
- Shibata *Chem. Lett.* **1991**, 307.





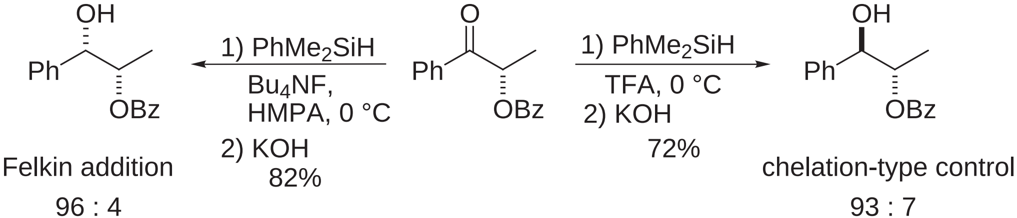
- Can alkylate intermediate directly:





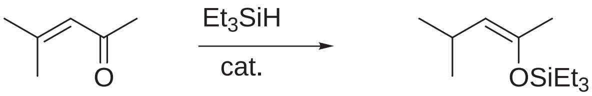
100%
Felkin addition

2. $PhMe_2SiH$



Hiyama *J. Org. Chem.* **1988**, *53*, 5405 and 5415.
J. Am. Chem. Soc. **1984**, *106*, 4629.

3. Et_3SiH



- Regioselective enolate trap, conjugate reduction.

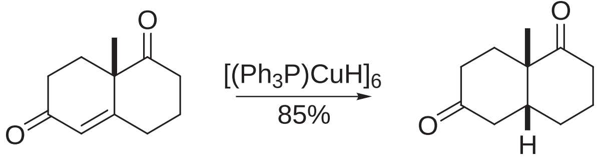
4. $(EtO)_3SiH$/catalytic $Ti(O^iPr)_4$

- No solvent, stable to air.
- Reduces esters to alcohols in the presence of a wide variety of functional groups.

$$RCO_2Et \longrightarrow RCH_2OH$$

- Buchwald *J. Org. Chem.* **1992**, *57*, 3751.

5. $[(Ph_3P)CuH]_6$



94:6 *cis*:*trans*

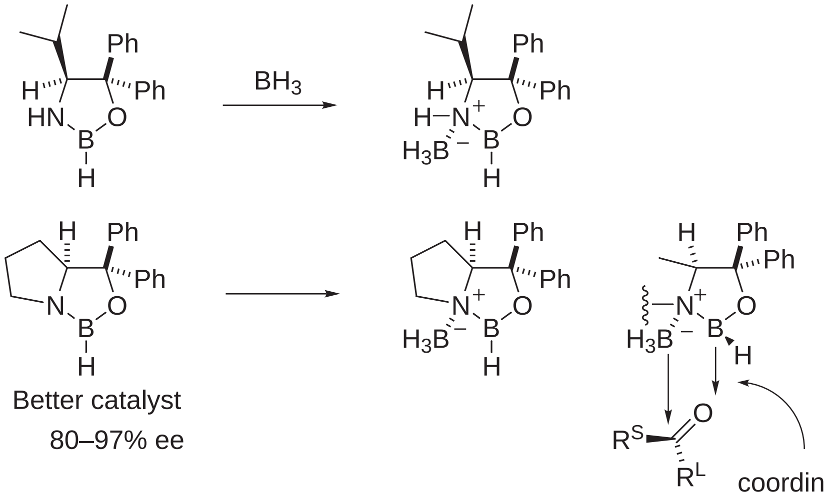
Stryker *Tetrahedron Lett.* **1988**, *29*, 3749; **1989**, *30*, 5677; **1990**, *31*, 3237.
J. Am. Chem. Soc. **1988**, *110*, 291.
Tetrahedron **2000**, *56*, 2153.

I. Asymmetric Carbonyl Reductions

- Review: *Comprehensive Org. Syn.*, Vol. 8, pp 159.
- Itsuno *Org. React.* **1998**, *52*, 395.

1. Catalytic Asymmetric Reduction

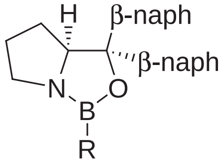
- Corey *J. Am. Chem. Soc.* **1987**, *109*, 5551.



Better catalyst
80–97% ee

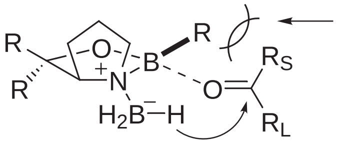
coordinates anti
to large substituent
(in plane)

- Corey *J. Am. Chem. Soc.* **1987**, *109*, 7925. (catalytic)



>90% ee

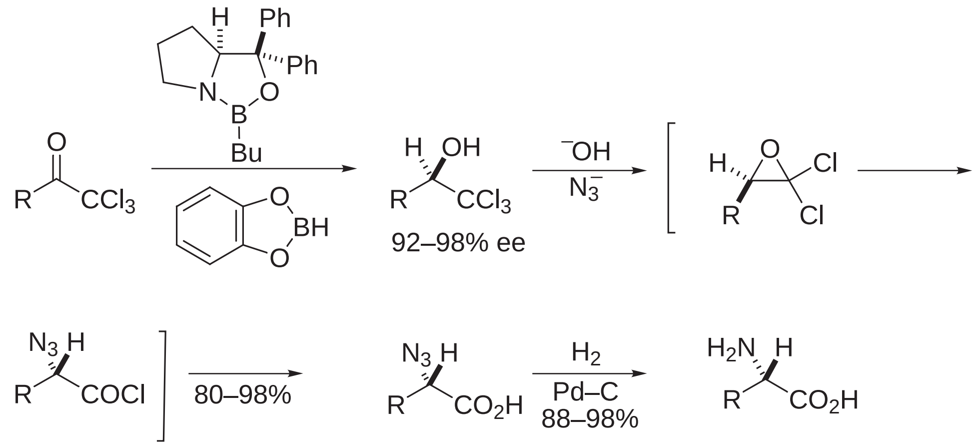
R = H, Bn, CH_3, Bu



R_S vs. R_L
in plane carbonyl
lone pair
complexes
boron

intramolecular
H^- delivery through
boat-like T. S.

- Corey *Tetrahedron Lett.* **1989**, *30*, 6275.

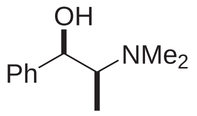


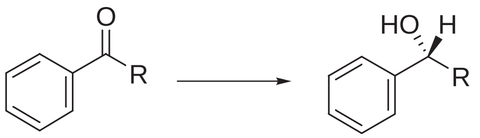
- General, catalytic, enantioselective synthesis of α-amino acids.
- Corey *J. Am. Chem. Soc.* **1992**, *114*, 1906; *Tetrahedron Lett*. **1992**, *33*, 3431, 3435.
- Review: Corey *Angew. Chem., Int. Ed. Eng.* **1998**, *37*, 1986.

2. Stoichiometric Reagents for Asymmetric Carbonyl Reductions

- Bothner-By *J. Am. Chem. Soc.* **1951**, *73*, 846 (camphor ligand and first report of an asymmetric reduction with optically active reagent). Most subsequent efforts have used chirally modified $LiAlH_4$.

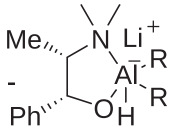
- $LiAlH_4$/N-methylephedrine

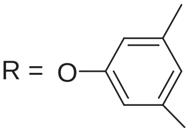


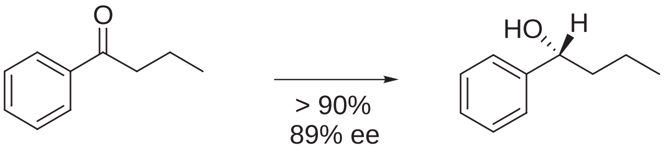


R = Me 75% ee
R = Et 62% ee
R = ^{i}Pr 30% ee
R = ^{t}Bu 36% ee

Mosher *J. Am. Chem. Soc.* **1972**, *94*, 9254; *J. Org. Chem.* **1973**, *38*, 1870.

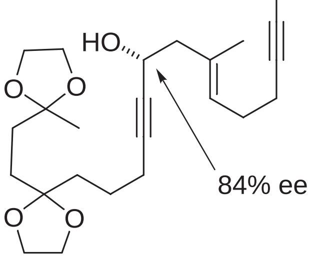






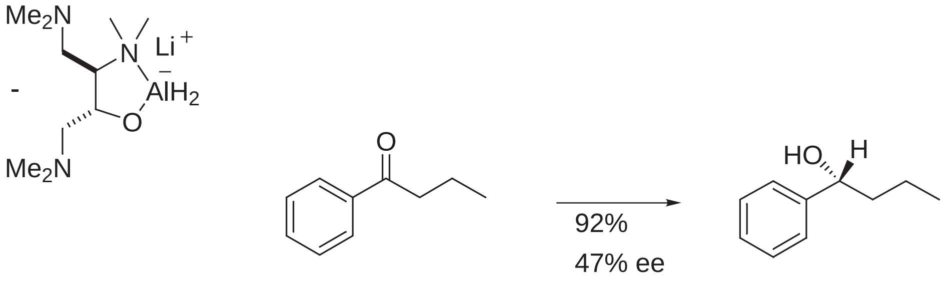
R-alcohol

- Vigneron *Tetrahedron Lett.* **1974**, 2065; **1979**, 2683; *Tetrahedron* **1976**, *32*, 939; used in cationic cyclization approach to steroids.
- Early work with acetylenic ketones, W. S. Johnson



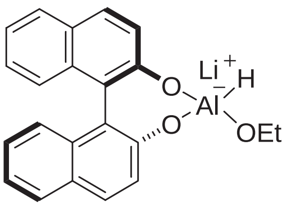
asymmetric total synthesis of steroids via cation–olefin cyclizations

Brinkmeyer *J. Am. Chem. Soc.* **1977**, *99*, 8339.
Johnson *J. Am. Chem. Soc.* **1977**, *99*, 8341.

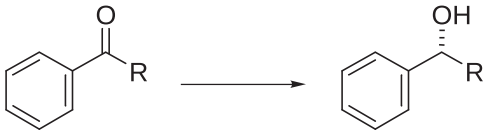
- 

Seebach *Chem. Ber.* **1974**, *107*, 1748.

- LiAlH$_4$/*N*-methylephedrine/*N*-ethylaniline or *N*-ethyl 2-pyridylamine (high ee's for enones: >90% ee)
  - Koga, Terashima *Tetrahedron Lett.* **1980**, *21*, 2753.

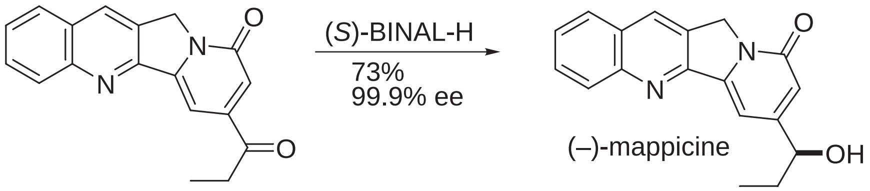
- BINAL-H 

(*R*)-BINAL-H

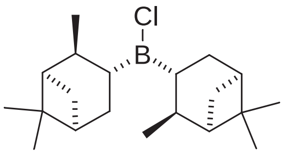


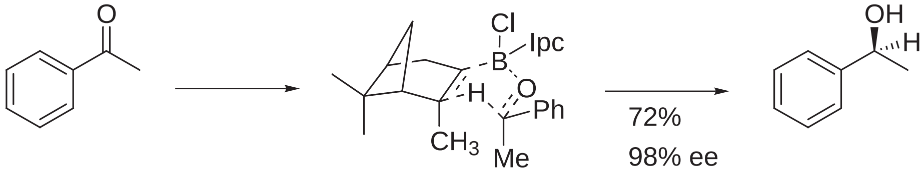
R = Me	95% ee	R = ^{n}Bu	100% ee
R = Et	98% ee	R = ^{i}Pr	71% ee
R = ^{n}Pr	100% ee	R = ^{t}Bu	44% ee

Noyori *J. Am. Chem. Soc.* **1984,** *106***,** 6709**.**



Boger *J. Am. Chem. Soc.* **1998**, *120*, 1218.

- Ipc$_2$BCl 

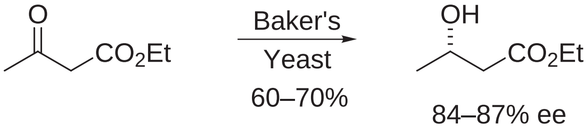


Midland *J. Org. Chem.* **1989**, *54*, 159.
Brown *J. Org. Chem.* **1989**, *54*, 4504.

3. Enzyme-catalyzed Ketone Reductions have been extensively used in organic synthesis

- Review: *Comprehensive Org. Syn.*, Vol. 8, pp 183.

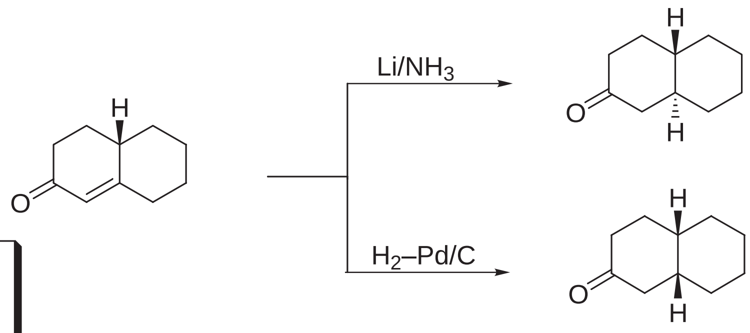
4. Baker's Yeast



Seebach *Org. Syn.* **1985**, *63*, 1

J. Catalytic Hydrogenation

- Amine and sulfur-containing groups will tend to poison catalysts (especially Pd/C).



- *Comprehensive Org. Syn.* Vol. 8, 479.
- *Comprehensive Org. Syn.* Vol. 8, 524.

Solvent	*cis* : *trans*
EtOH–HCl	93 : 7
EtOH	53 : 47
DMF	79 : 21
EtOAc	57 : 43
Et_2O	58 : 42
hexane	48 : 52
MeOH	41 : 59
^{n}PrOH	68 : 32
^{t}BuOH	91 : 9

P. Sabatier received the 1912 Nobel Prize in Chemistry for his contributions to catalysis, especially the hydrogenation of unsaturated organic compounds.

- *Comprehensive Org. Syn.,* Vol. 8, pp 417 and 533.
- *Comprehensive Org. Syn.,* Vol. 8, pp 471.

1. H_2 delivery from least hindered face of double bond.

2. Cis H_2 delivery

   - activity of catalysts toward C=C: Pd > Rh > Pt > Ni > Ru

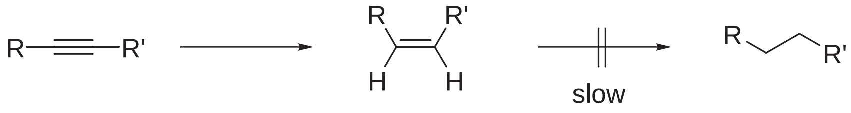
3. Increasing substitution on olefin decreases reactivity.

   - note potential isomerization of olefin and H-migration/allylic exchange in D_2/T_2 hydrogenations
   - propensity for olefin isomerization: Pd >> Rh/Ru/Pt > Ir

4. Alkynes are more reactive than alkenes. Reagents have been developed to selectively prepare olefins from alkynes without over reduction:

   - Lindlar catalyst: Pd($CaCO_3$)/Pb, poisoned or deactivated catalyst

     - will only reduce an alkyne to an alkene (*cis*) Lindlar *Helv. Chim. Acta* **1952**, *35*, 446.



5. Many kinds of catalyst, but most common are 5–10% Pd/C or PtO_2

   - Pd($BaSO_4$): Rosenmund catalyst ($RCOCl \rightarrow RCHO$)

     Rosenmund *Chem. Ber.* **1918**, *51*, 585.

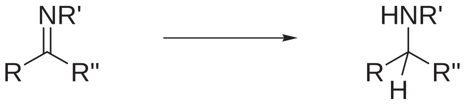
   - $Pd(OH)_2$: Pearlman catalyst, often used for difficult debenzylations where other, more typical, Pd catalysts fail.

     Pearlman *Tetrahedron Lett.* **1967**, *17*, 1663.

   - $PtO_2 \xrightarrow{H_2} Pt^o$ (Adam's catalyst)

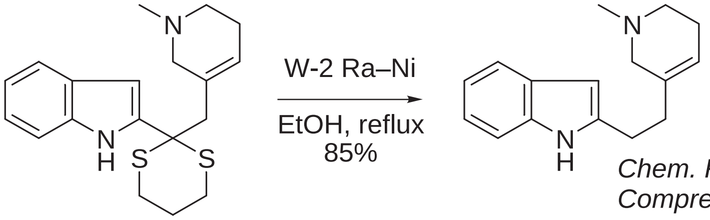
Roger Adams (Ph.D. 1912, Harvard Univ.; postdoctoral with Diels and Willstatter) was the central figure in US organic chemistry in the 1930–40's. He established the structures of tetrahydrocannabinol, gossypol, chaulmoogric acid, and the Senecio alkaloids, and contributed to the development of many fundamental organic reactions.

- PtO_2 is particularly good for imine reduction to amines.
- Amines will poison Pd/C catalyst, but not Pt(0).



- Raney-Ni (Ra–Ni) also useful (especially for removing sulfide groups).

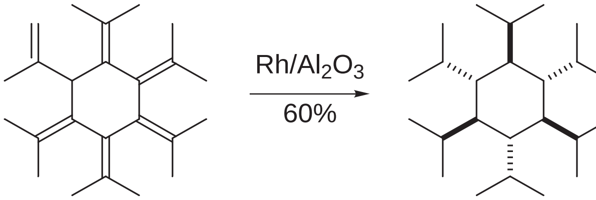
Generally stored in alcoholic solvent, ignites upon contact with air. It loses its activity over ca. 6 months. Various reactivities depending upon the preparation (*i.e.* W-1 through W-7 Ra–Ni).



Husson *Heterocycles* **1991**, *32*, 663.

Chem. Rev. **1962**, *62*, 347.
Comprehensive Org. Syn. Vol. 8, p 835.

- Rh/Al_2O_3, the high activity of rhodium often permits the use of room temperature and atmospheric pressure even for difficult reductions.

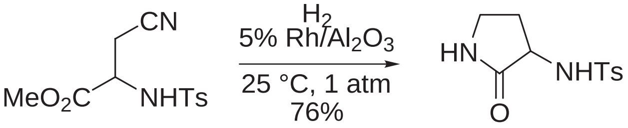


1

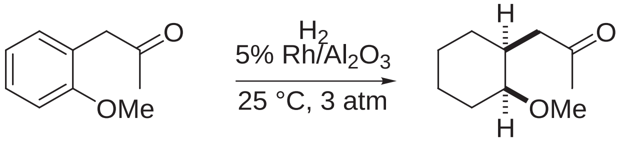
Biali *J. Am. Chem. Soc.* **1990**, *112*, 9300.

note: what would you expect the ground state conformation of **1** to be?

Good for the reduction of nitriles and aromatic rings:



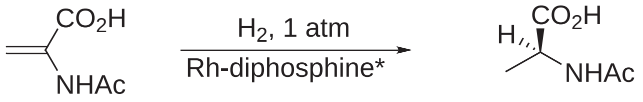
Mendoza *J. Org. Chem.* **1991**, *56*, 452.



Tarbell *J. Am. Chem. Soc.* **1964**, *86*, 2902.

- $(Ph_3P)_3RhCl$ Wilkinson's catalyst (homogeneous).
  - a homogeneous catalyst (e.g., dissolve in organic solvent for reaction).
  - Review: *Org. React.* **1976**, *24*, 1.
- One of the earliest, successful examples of catalytic asymmetric synthesis entailed the homogeneous hydrogenation of enamides to provide amino acid derivatives

G. Wilkinson received the Nobel Prize in Chemistry in 1973 for deducing the structure of metallocenes.



DIOP	DIPAMP	NORPHOS	BPPM	BINAP	BPPFA
73% ee	34% ee	90% ee	99% ee	98% ee	93% ee

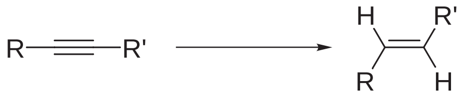
Kagan *J. Chem. Soc., Chem. Commun.* **1971**, 481.

Knowles (Monsanto) *J. Chem. Soc., Chem. Commun.* **1972**, 10;
J. Am. Chem. Soc. **1977**, *99*, 5946.

K. Dissolving Metal Reductions

1. Birch Reduction

- Reviews: *Comprehensive Org. Syn.*, Vol. 8, 489.
  Org. React. **1992**, *42*, 1 (aromatic ring reduction).
  Org. React. **1976**, *23,* 1 (carbonyl and enone reductions).



trans alkene
- most stable product

- First reported by Wooster *J. Am. Chem. Soc.* **1937**, *59*, 596.
- Extensively developed by Birch *Quart. Rev., Chem. Soc.* **1950**, *4*, 69.

a. Reduction potential and solubility

Metal	Solubility (g/100 g NH_3)	Reduction Potential
Li	10.9	–2.99
Na	24.5	–2.59
K	47.8	–2.73

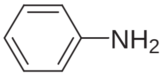
Arthur Birch, along with Robert Robinson, was one of the earliest chemists to perform biosynthetic studies using radiolabels although he is best known for the Birch reduction of aromatic rings.

b. Solvent system

- Typical solvent system

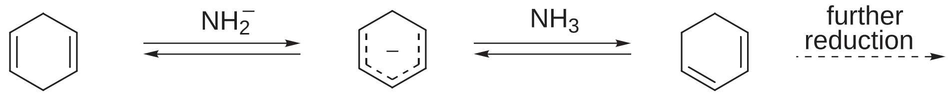
NH_3	:	THF	:	^tBuOH
2	:	1	:	1

Charles A. Kraus (1875–1967) demonstrated that the blue color arising from dissolving sodium in liquid ammonia is a consequence of solvated electrons in the course of research on ammonia.

- Liquid NH_3 (bp –33 ^oC) is used to dissolve metal, ether cosolvent (Et_2O or THF) is used to dissolve substrate, and a proton source ^tBuOH; EtOH; MeOH;  is used to quench the reaction.

- If proton source is absent:

$$NH_3 \longrightarrow NH_2^- \quad \text{isomerization of diene and overreduction}$$



- Be sure to use an argon atmosphere, **not N_2** which forms lithium nitrides.

William Ramsay received the 1904 Nobel Prize in Chemistry for his experimental work that included the discovery and isolation of the noble gas family.

Hamilton P. Cady (1843–1943) and D. McFarland (1978–1955) discovered He in natural gas in 1905 in Bailey Hall, University of Kansas, an element that had been previously detected only on the sun. "It assures the fact that He is no longer a rare element but a very common element existing in goodly quantities for the uses that are yet to be found for it." A drilling company in Dexter, Kansas thought they hit paydirt with a well that released 9 million cubic feet of gas each day. At a celebration to culminate the discovery, and stock issuance, a burning bale of hay expected to produce a great pillar of flame was extinghuished when pushed into contact. E. Haworth (Univ. of Kansas) collected a sample of the gas which McFarland analyzed as 15% CH_4, 72% N_2, O_2 (0.2 %), H_2 (0.8%), and 12 % unknown. H. Cady helped indentify the remainder. Using a method described by Sir James Dewar, all atmospheric gases except H_2, Ne (and He) were completely removed (adsorbed) by coconut charcoal at the temperature of boiling liquid air (–310 °F). What remained exhibited spectroscopic properties identical with He detected only on the sun. One of the first secret uses was to inflate blimps and the Allies dirigibles filled with "Gas X" did not explode like the Axis powers zeppelines which were filled with flammable H_2. Today, 60% of the He isolated is used for cryogenic applications including NMR and MRI.

Commercial NH_3 production is second in size only behind H_2SO_4 and is used extensively in the production of fertilizers (>102 $\times$ 10^6 tons/yr, 1998).

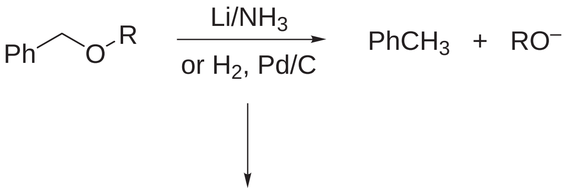
Benzene production through the refinement of crude oil reached 37 $\times$ 10^6 metric tons in 1997 and serves as the starting material for a host of derivatives including styrene/EtC_6H_5.

W = COOH $\curvearrowright$ COO^-

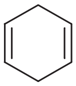
$CONR_2$, $SiMe_3$, Ar (electron-withdrawing groups)

\- but CO_2R, COR, CHO $\xrightarrow{Li/NH_3}$ $—CH_2O^-$, so they are part of donor (D) grouping.

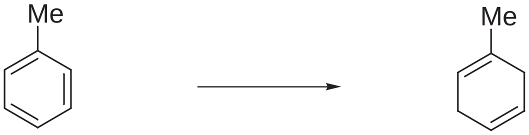
e. Common application: hydrogenolysis



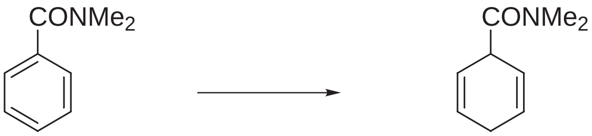
5–10% Pd on C as catalyst

H_2 can be replaced by $HCOONH_4$ or  as the source of H_2 and this type of reduction is a transfer hydrogenation: *Comprehensive Org. Syn.,* Vol. 8, 955.

f. Examples

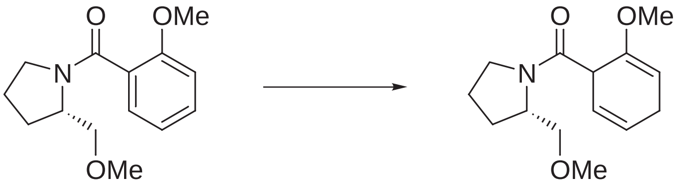


\- Krapcho *J. Am. Chem. Soc.* **1959**, *81*, 3658.



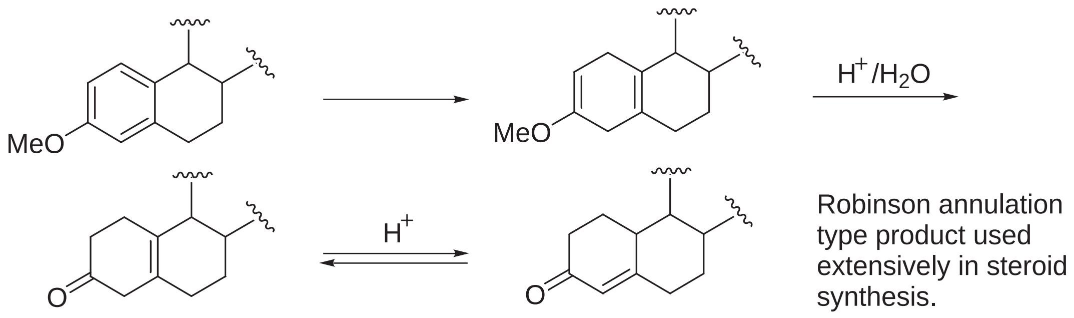
\- Schultz *J. Org. Chem.* **1986**, *51*, 4983.

\- Dryden *J. Org. Chem.* **1961**, *26*, 3237.

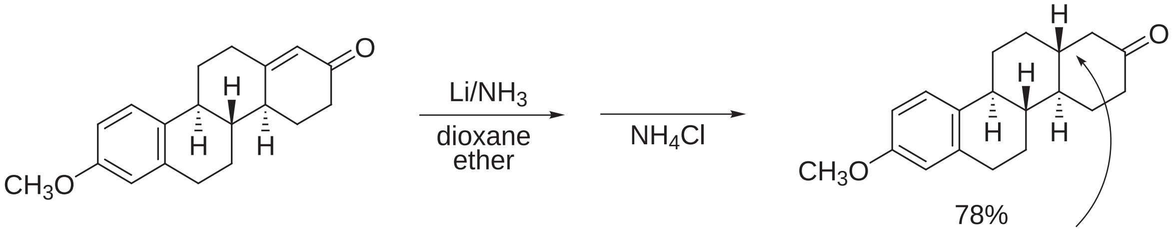


\- Magnus *Tetrahedron Lett.* **1997**, *38*, 1341.

- can also be used for enone reduction and/or reductive alkylation with alkylative trap of the final enolate



Robinson annulation type product used extensively in steroid synthesis.



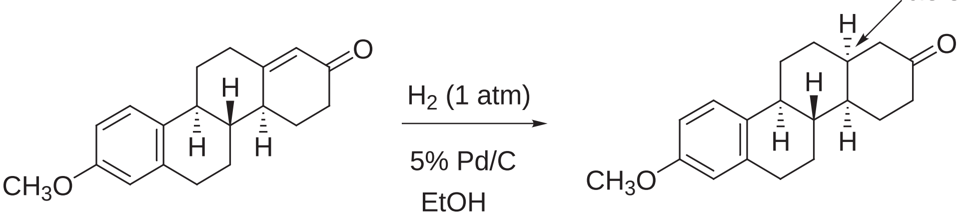
Johns *J. Org. Chem.* **1963**, *28*, 1856.

Dryden *J. Org. Chem.* **1961**, *26*, 3237.

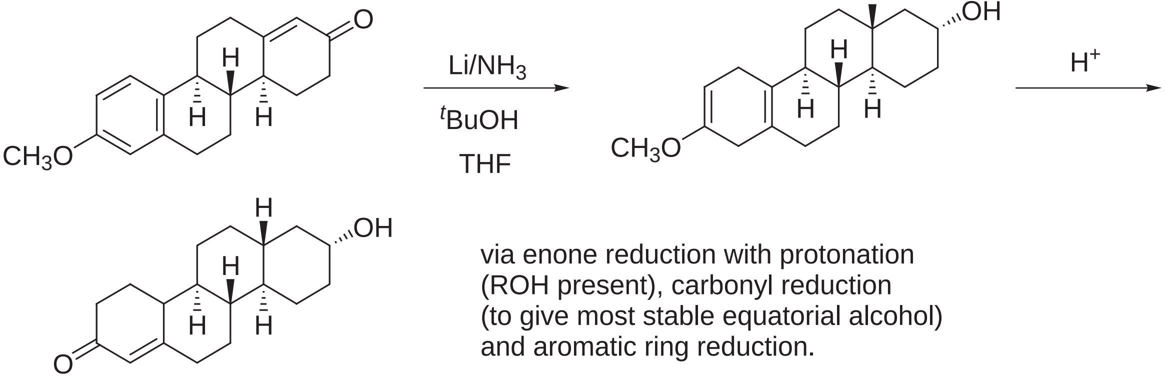
more stable product - *trans* ring fusion

- As opposed to

cis stereochemistry



- or more vigorous Birch conditions:



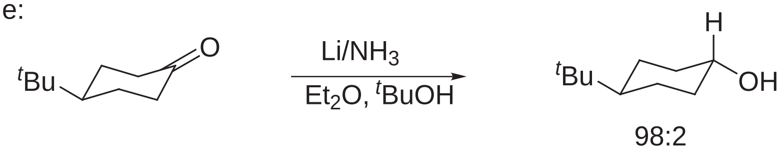
via enone reduction with protonation (ROH present), carbonyl reduction (to give most stable equatorial alcohol) and aromatic ring reduction.

2. Dissolving Metal Carbonyl Reduction

a. Ketone Reduction

- Review: *Comprehensive Org. Syn.*, Vol. 8, 107.

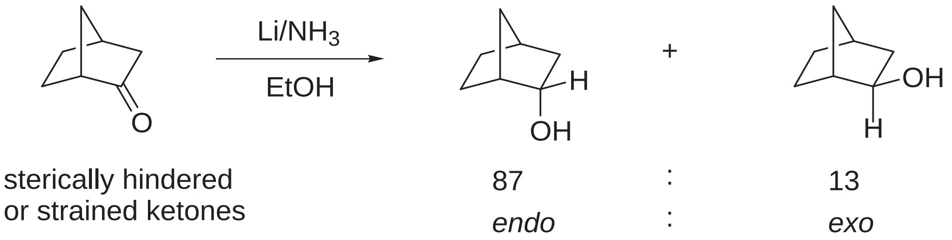
- Rule:



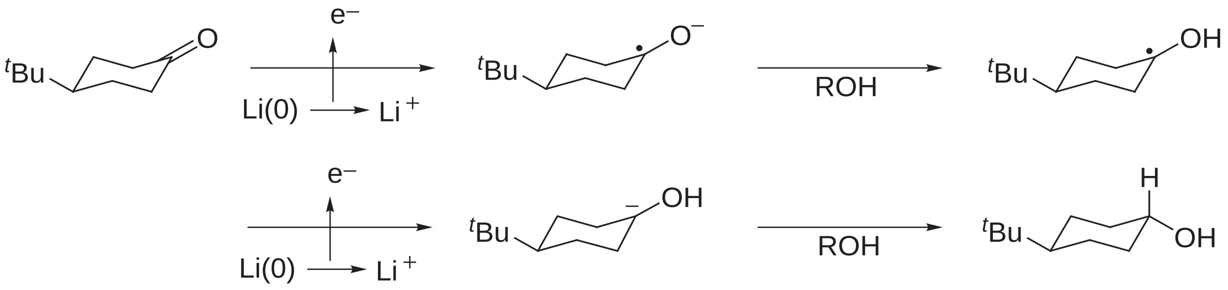
98:2

Birch reduction forms the most stable product.

- Exception:



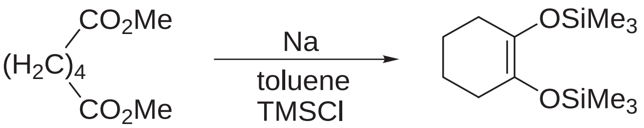
- Mechanism:



Special variants of this reaction include the:

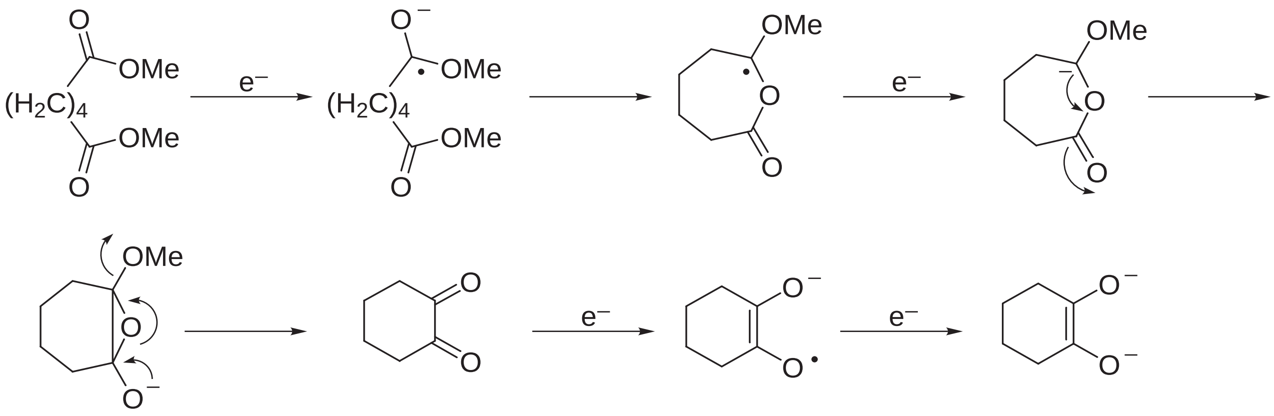
b. Acyloin Condensation

First report: Freund *Justus Liebigs Ann. Chem.* **1861**, *118*, 33.



Comprehensive Org. Syn.,
Vol. 3, 613.
Org. React. **1976**, *23*, 259.
Org. React. **1948**, *4*, 256.

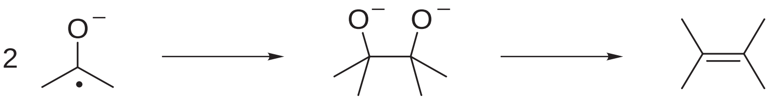
- Ruhlmann modification: *Synthesis* **1971**, 236.
- Mechanism: diketyl generation and diradical coupling or:



- Sheehan *J. Am. Chem. Chem.* **1950**, *72*, 3376.
- Bloomfield *J. Org. Chem.* **1975**, *40*, 393.
- Bloomfield *Tetrahedron Lett.* **1968**, 591.
- Macrocyclization: Finley *Chem. Rev.* **1964**, *64*, 573.

c. Pinacol Coupling

- Review: *Comprehensive Org. Syn.,* Vol. 3, 563.



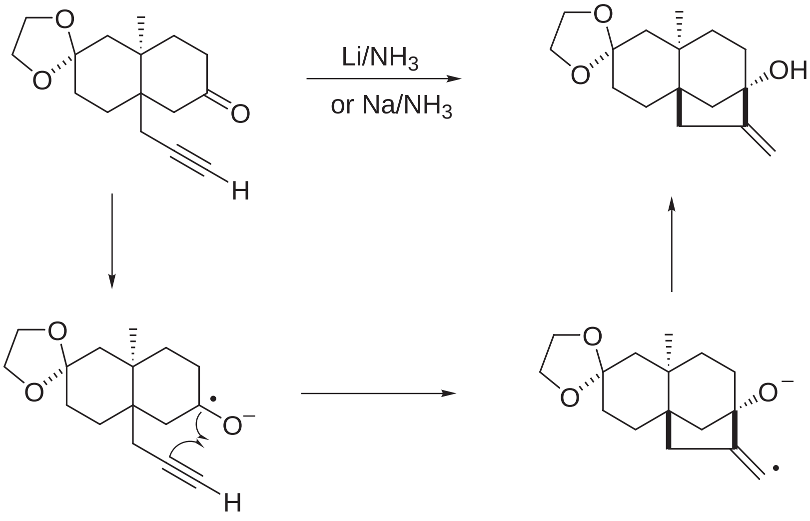
d. McMurry Coupling

- Review: McMurry *Chem. Rev.* **1989**, *89*, 1513.

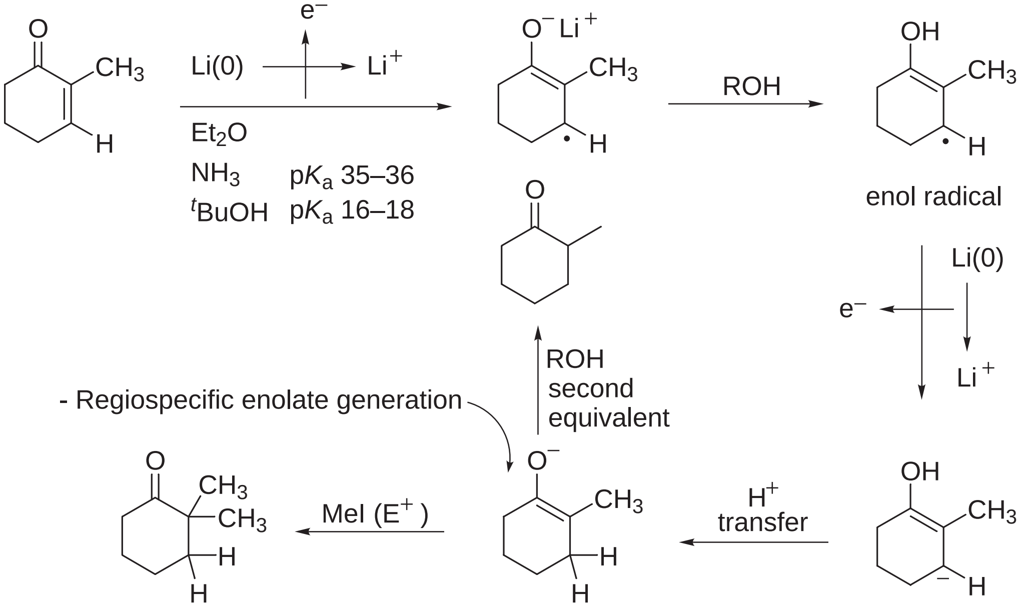
Zn–Cu/$TiCl_3$	McMurry *J. Org. Chem.* **1977**, *42*, 2655.	olefin product
$LiAlH_4$/$TiCl_3$	McMurry *J. Am. Chem. Soc.* **1983**, *105*, 1660.	
Mg–Hg/$TiCl_4$ - diol product	Corey *J. Org. Chem.* **1976**, *41*, 260.	

e. Radical-Alkyne/Alkene Addition

- The ketyl (radical anion) can be trapped in intramolecular reactions:
  - Stork *J. Am. Chem. Soc.* **1979**, *101*, 7107.



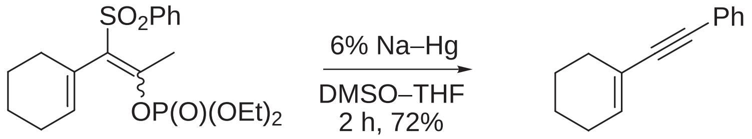
f. Reductive Alkylation



L. Amalgam-derived Reducing Agents

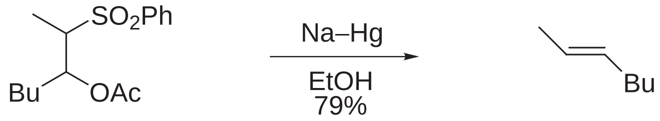
1. Na–Hg

Sodium amalgam is used for the reduction of a variety of functional groups including those leading to the preparation of alkenes and alkynes and for the reductive cleavage of C–S and N–O bonds.

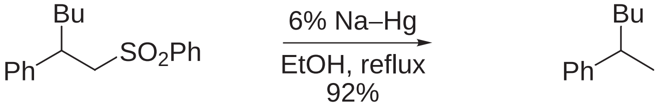


Lythgoe *J. Chem. Soc., Perkin 1* **1979**, 2429.

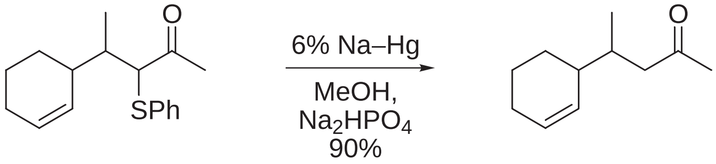
Julia Olefin Synthesis:



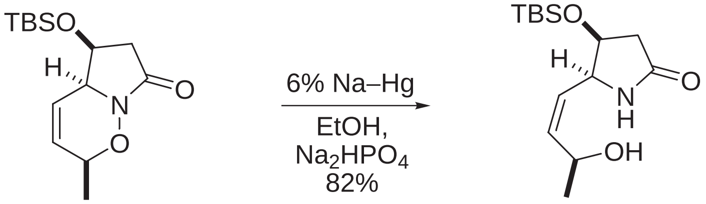
Julia *Tetrahedron Lett.* **1973**, 4833.



Posner *Tetrahedron Lett.* **1973**, 935.



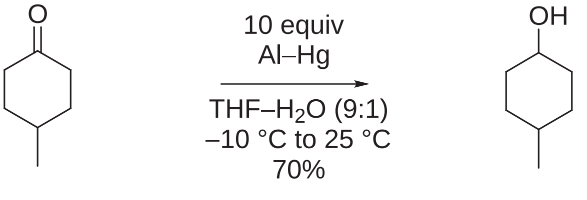
Trost *Tetrahedron Lett.* **1976**, 3477.



Keck *Tetrahedron Lett.* **1978**, 4763, 4767.

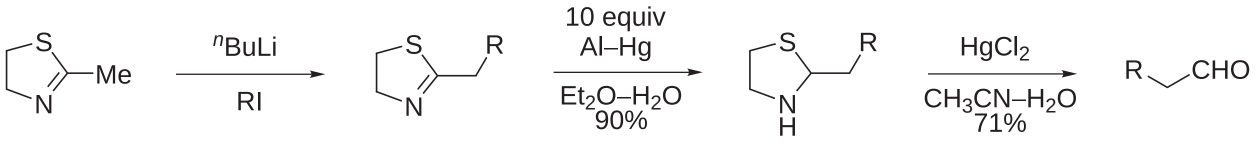
2. Al–Hg

Aluminum amalgam is another metal-based reducing agent.
It is quite mild and used effectively in a number of reductions.

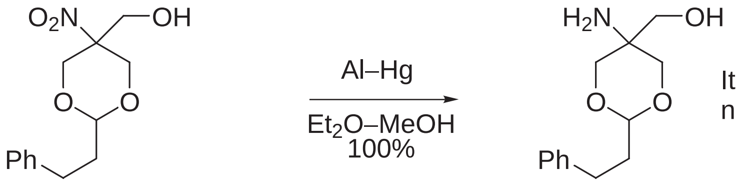


Cyclic ketones and aldehydes are reduced
Acyclic ketones are inert.

Hulce *Tetrahedron Lett.* **1988**, *29*, 525.

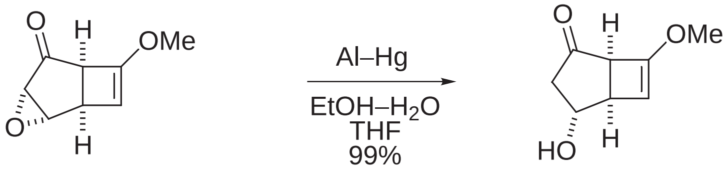


Meyers *J. Org. Chem.* **1975**, *40*, 2021, 2025.

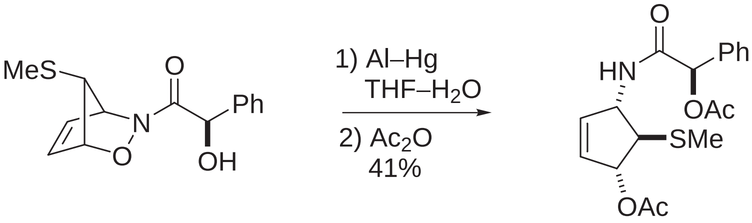


It is an excellent reagent for reducing nitro groups and azides to amines.

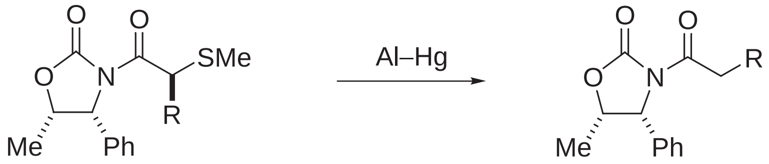
Corey *J. Am. Chem. Soc.* **1968**, *90*, 3247.
Trost *J. Am. Chem. Soc.* **1989**, *111*, 5902.
Shin *Chem. Lett.* **1976**, 1095.

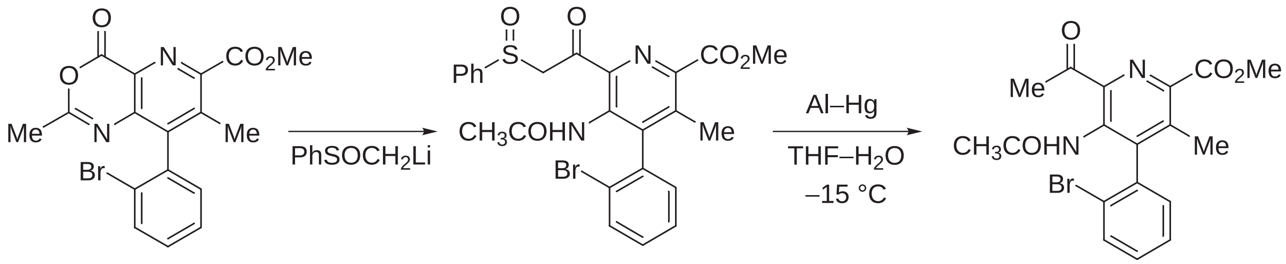


Green, Crabbe *J. Org. Chem.* **1982**, *47*, 2553.



Keck *Synth. Commun.* **1979**, *9*, 281.

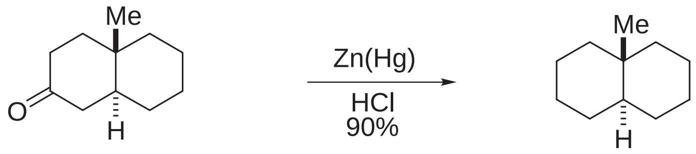




Boger, Panek *J. Org. Chem.* **1985**, *50*, 5790. (total synthesis of lavendamycin)

3. Zn(Hg)

Clemmensen reduction
Clemmensen *Chem. Ber.* **1913**, *46*, 1838.



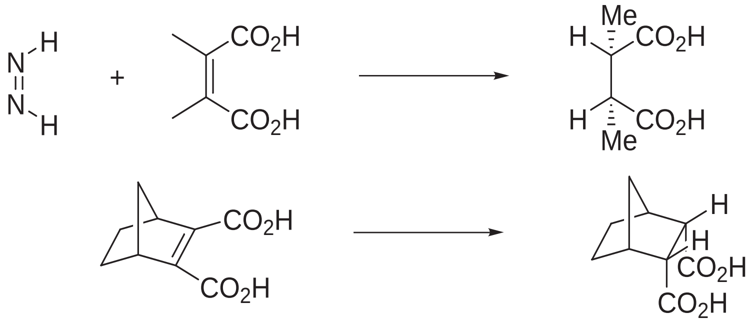
Dauben *J. Am. Chem. Soc.* **1954**, *76*, 3864.

Reviews: Martin *Org. React.* **1942**, *1*, 155.
Vedejs *Org. React.* **1975**, *22*, 401.

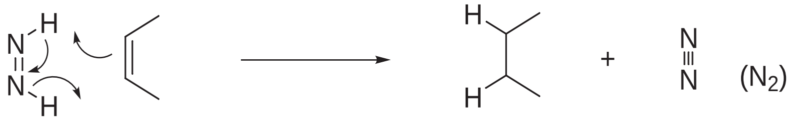
M. Other Reduction Methods

1. Diimide Reduction

- Review: *Org. React.* **1991**, *40*, 91.

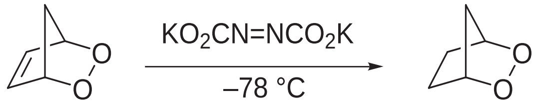


- Mechanism:



- *Cis* delivery of H_2
- From least hindered face of olefin
- *trans* > *cis* olefin (rate)
- Rate decreases with substitution of olefin
- C=O, NO_2, CN, S=O , —S—S— stable

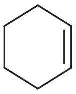
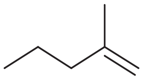
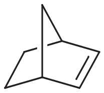
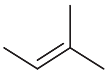
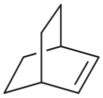
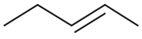
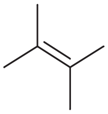
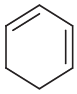
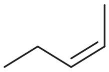
complements H_2/cat.
same results but:
many functional groups are
stable to conditions/reagent



no reduction of
endoperoxide

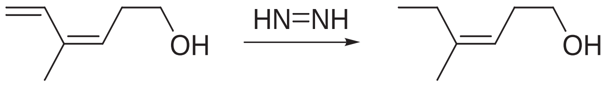
Adam *J. Org. Chem.* **1977**, *42*, 3987.

Relative reactivities toward diimide reduction

	k_{rel}		k_{rel}		k_{rel}
	1.0		2.04		450.0
	20.2		0.28		29.0
	2.59		0.50		47.0
	2.65				

- Decreases with alkyl substitution
- Increases with strain

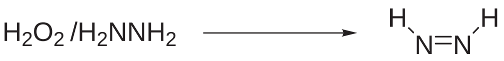
Garbisch *J. Am. Chem. Soc.* **1965**, *87*, 2932.



Mori *Tetrahedron* **1972**, *28*, 3739.

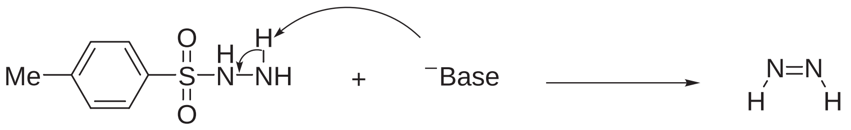
- Formation (generation) of reagents (diimide)

i.



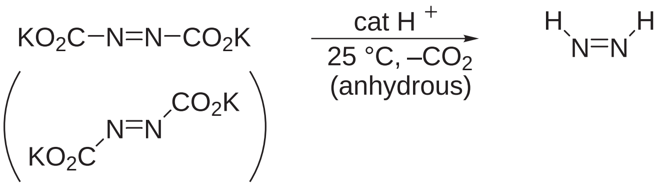
old method

ii. recent method

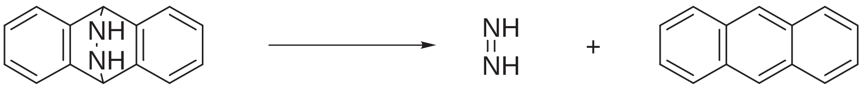


- related to McFadyen–Stevens Reduction.

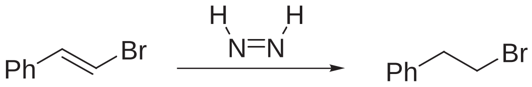
iii.



iv. retro Diels–Alder reaction



- Example of use:



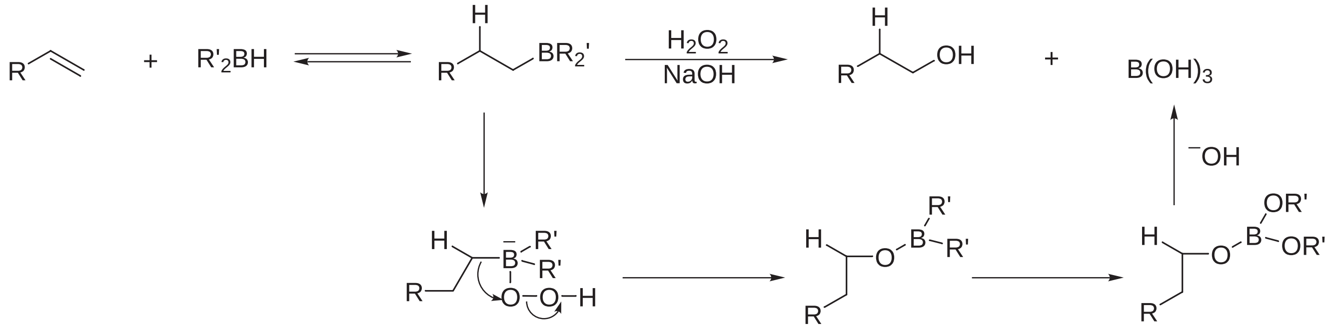
- Other reduction methods would give substantial debromination.

VII. Hydroboration–Oxidation (Reduction–Oxidation)

- Review: *Comprehensive Org. Syn.*, Vol. 8, pp 703–732.
  Brown *Organic Synthesis via Boranes*, Wiley: New York, 1975.
  Brown *Boranes in Organic Chemistry*, Cornell Univ. Press: New York, 1972.

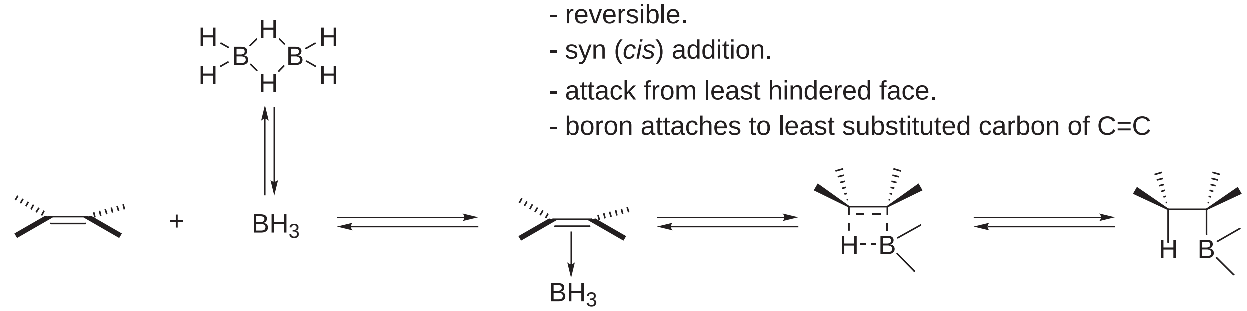
A. Mechanism

Brown *J. Am. Chem. Soc.* **1956**, *78*, 2583; *Org. React.* **1963**, *13*, 1.



- anti-Markovnikov addition of H_2O to C=C

- reversible.
- syn (*cis*) addition.
- attack from least hindered face.
- boron attaches to least substituted carbon of C=C

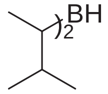


- rate
  - Increased by electron-donating substituents on olefins.
  - Increased by strain of olefins.
  - Increased by decreased steric hinderance of olefins.

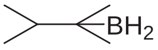
> The discovery of the unusual bridged structure of diborane vs a once more conventional ethane-like structure $H_3B–BH_3$ (G. N. Lewis, S. H. Bauer) occupied the efforts of many of the very best chemists, enlisting newly emerging experimental and theoretical tools, including H. I. Schlesinger, C. Longuet-Higgins, F. Stitt and W. C. Price (IR), J. N. Shoolery (NMR), R. S. Mulliken, K. S. Pitzer, A. D. Walsh (MO and valence bond descriptions), K. Hedberg and V. Schomaker (electron diffraction). Essay: Laszlo *Angew. Chem. Int. Ed.* **2000**, *39*, 2071.

The reaction is characterized by a slight tendency for H (H^-) to add to carbon most capable of stabilizing a δ^+ charge or, in other words, for the nucleophilic carbon to attack the electrophilic B. However, it is also characterized by a nonpolar transition state where the rate of reaction and regioselectivity are determined principally by steric factors with unsymmetrical olefins.

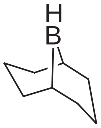
$BH_3 \rightleftharpoons B_2H_6$



disiamylborane (Sia_2BH)



thexylborane ($ThxBH_2$)

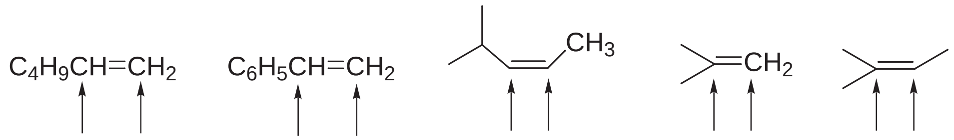


9-BBN

> H. C. Brown (Purdue University) received the Nobel Prize in Chemistry (1979) for the discovery and development of the hydroboration reaction. He is also responsible for the discovery and development of $NaBH_4$ and most of the many, subsequent boron and aluminum hydrides used widely in organic synthesis today.

B. Regioselectivity

1. Steric Effects

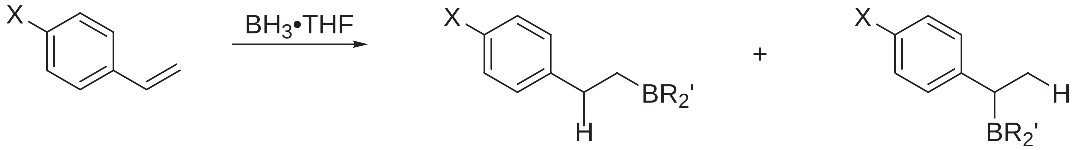


	$C_4H_9CH=CH_2$	$C_6H_5CH=CH_2$			
BH_3•THF	6 : 94	19 : 81	43 : 57	<1 : >99	2 : 98
$ThxBH_2$	6 : 94	6 : 94	34 : 66		
Sia_2BH	1 : 99	2 : 98	3 : 97		
9-BBN	0.1 : 99.9	1.5 : 98.5	0.2 : 99.8		

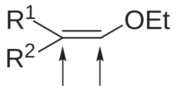
- diisoamylborane ⟹ larger than BH_3•THF and more selective.

2. Electronic Effects

Brown *J. Am. Chem. Soc.* **1966**, *88*, 5851.

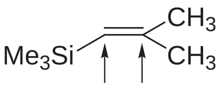


X = H	81	:	19
OCH_3	93	:	7
Cl	73	:	27
CF_3	66	:	34

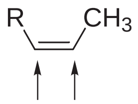


100 : 0

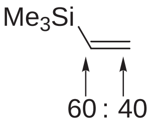
$R^1 = R^2 = Me$
$R^1 = R^2 = Et$



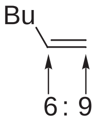
95 : 5



R = ^{i}Pr	43 : 57	BH_3
	3 : 97	Sia_2BH
R = $SiMe_3$	95 : 5	BH_3



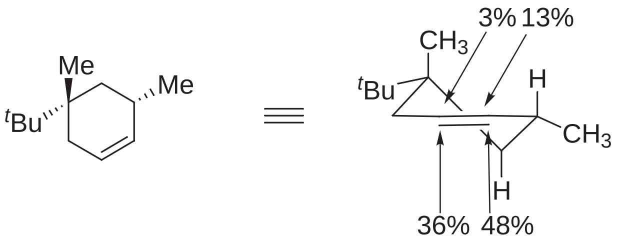
vs



60 : 40	(BH_3)	6 : 94
5 : 95	(Sia_2BH)	1 : 99
0 : 100	(9-BBN)	0.1 : 99.9

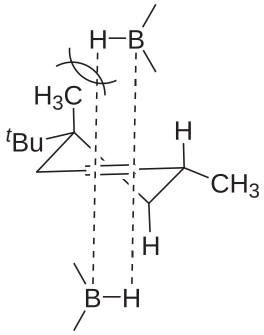
C. Diastereoselectivity

1. Endocyclic Olefins

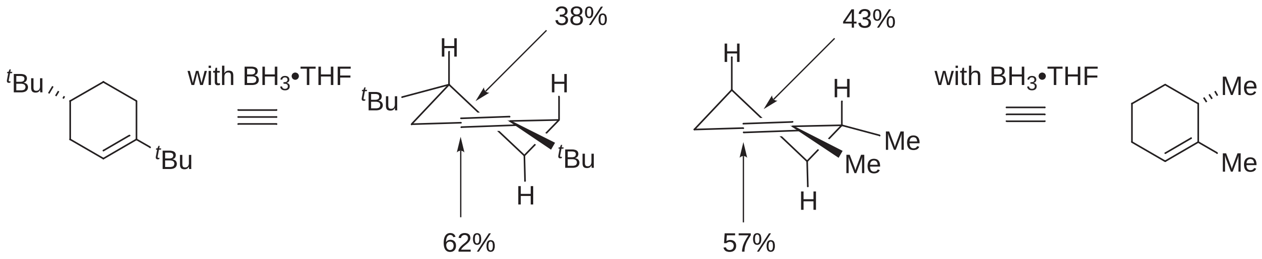


- predominant attack from least hindered face.

- *cis* addition
- from least hindered side
- least substituted position

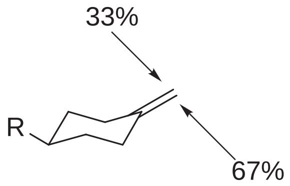


Pasto, Klein *J. Org. Chem.* **1968**, *33*, 1468.

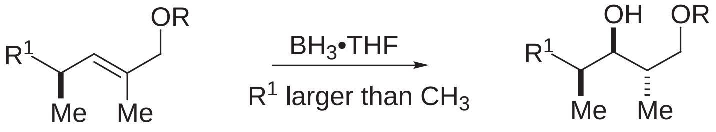


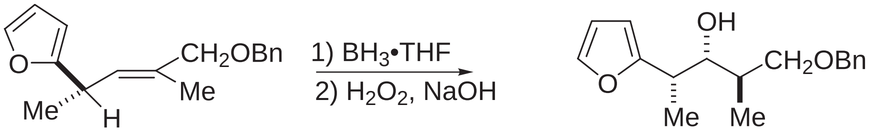
with BH_3•THF ⟹ Better with bulkier boranes

2. Exocyclic Olefins



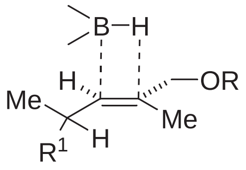
3. Acyclic Olefins





89% de

Kishi *J. Am. Chem. Soc.* **1979**, *101*, 259. (Monensin)



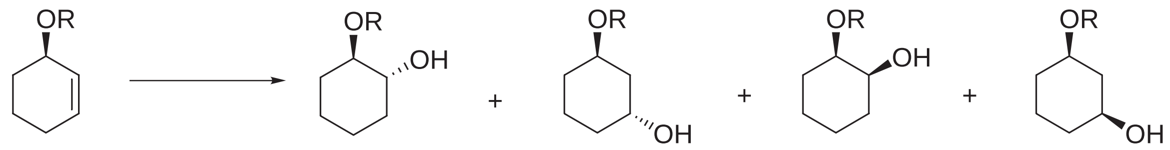
Considering the top case:
attack on least hindered
face of H-eclipsed conformation

R^1/BH_2 interactions are worse
than Me/BH_2 interactions

Kishi *Aldrichim. Acta* **1980**, *13*, 23.

4. Allylic Alcohols and Ethers

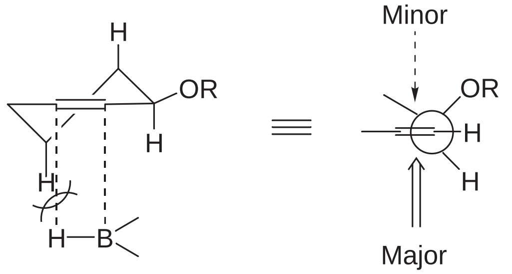
- Cyclic allylic alcohols and ethers.



R = H	83	18	5	72	2	1	10	9
R = Bn	68	7	13	72	0	8	19	13
R = TBDMS	74	2	13	86	0	1	13	11

9-BBN — catechol borane/Rh(I)

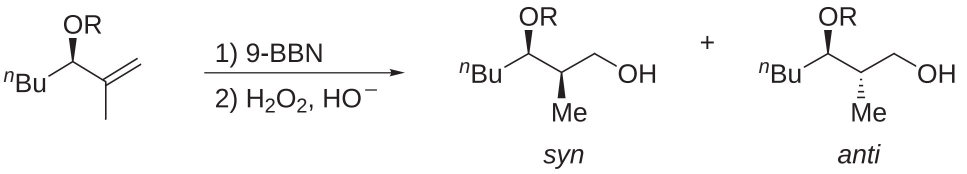
Evans *J. Am. Chem. Soc.* **1988**, *110*, 6917.



9-BBN reaction:

- Least hindered face opposite alkoxy group.
- Regioselectivity avoids a R_2B/H 1,3-diaxial interaction.

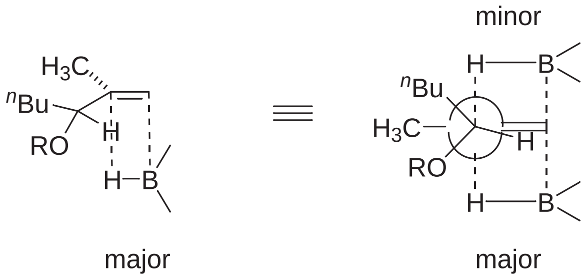
- Acyclic allylic alcohols and ethers



	syn	anti
R = H	8	92
R = TBDMS	11	89

- Reaction takes place from H-eclipsed conformation and *cis* to the smaller OR group.

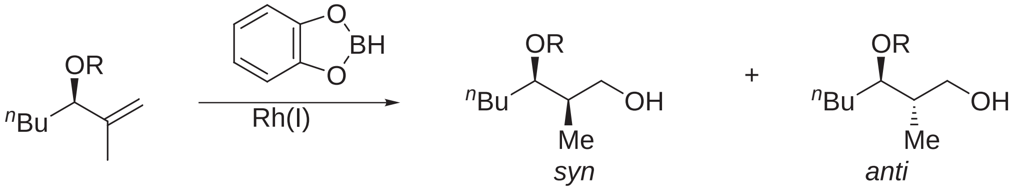
Still *J. Am. Chem. Soc.* **1983**, *105*, 2487.



attack on face *syn* to smaller alkoxy substituent in the H-eclipsed conformation.

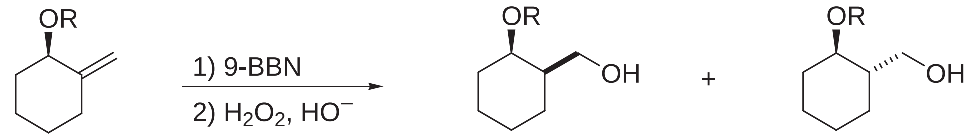
D. Metal-Catalyzed Hydroboration

- Diastereoselectivity (below) and regioselectivity (prior page) can be altered or even reversed with catecholborane and Rh(I) catalyst (i.e., Wilkinson's catalyst).



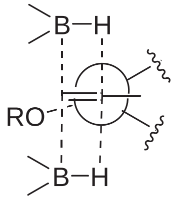
	syn	anti
R = H	75	25
R = TBDMS	96	4

- Exocyclic allylic alcohols and ethers



R = H	50	90	50	10
R = TBDMS	39	96	61	4

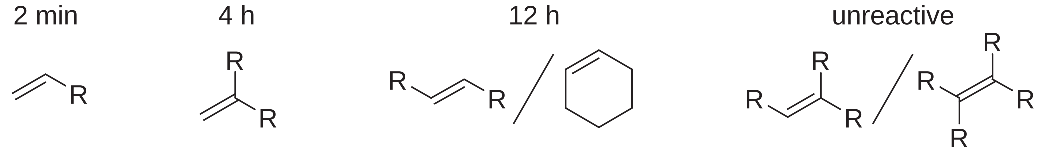
9-BBN catecholborane/catalytic Rh(I)



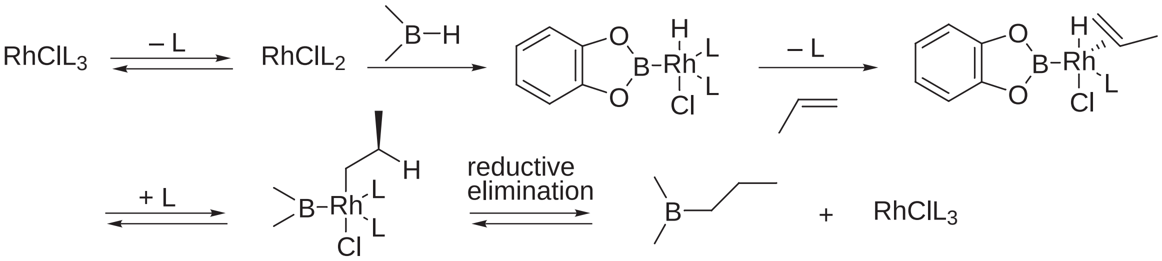
9-BBN
No distinguishing
steric interactions

Evans *J. Am. Chem. Soc.* **1988**, *110*, 6917.

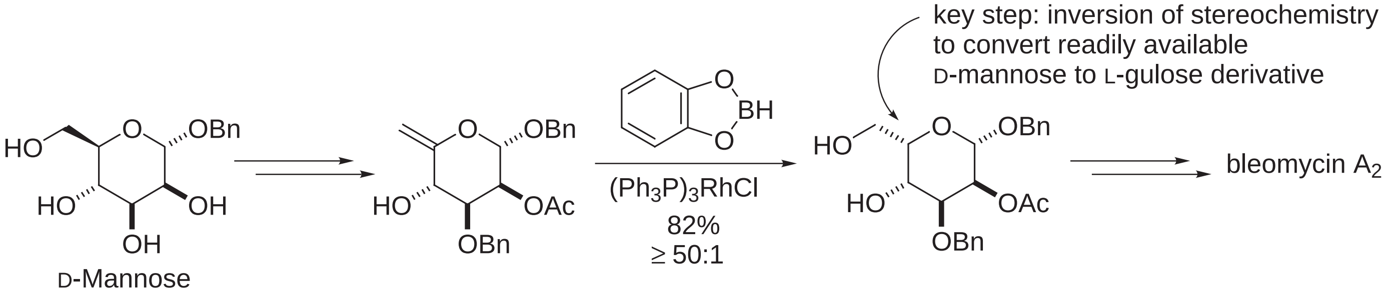
- Olefin reactivity, chemoselectivity
  catecholborane/2% $RhCl(PPh_3)_3$ reaction times



- Review of transition metal-catalyzed hydroboration: Beletskaya and Pelter *Tetrahedron* **1997**, *53*, 4957.



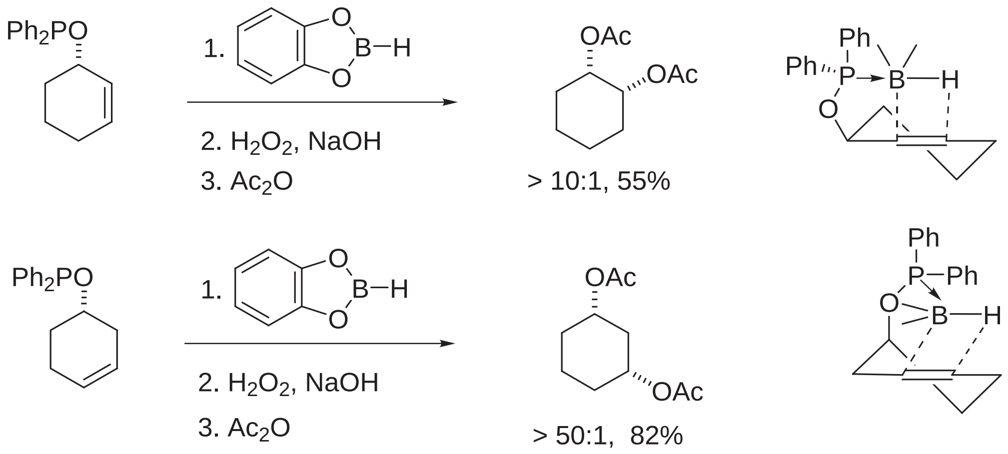
- This was utilized in the synthesis of the unusual L-gulose sugar found in the disaccharide of bleomycin A_2



key step: inversion of stereochemistry
to convert readily available
D-mannose to L-gulose derivative

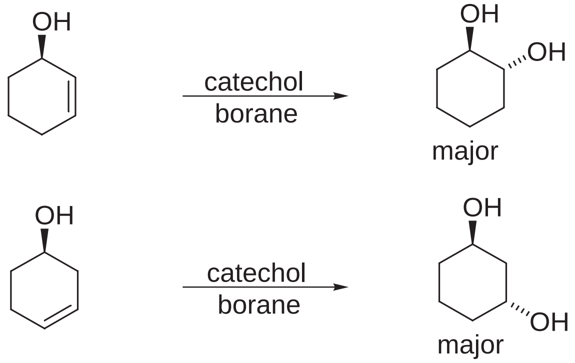
Boger *J. Am. Chem. Soc.* **1994**, *116*, 5647.

E. Directed Hydroboration



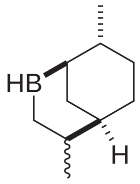
Evans *J. Am. Chem. Soc.* **1988**, *110*, 6917.

versus

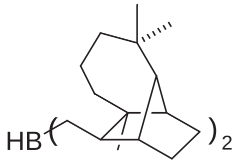


F. Asymmetric Hydroboration

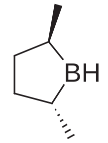
Review: Brown *J. Organometal. Chem.* **1995**, *500*, 1.



LimBH

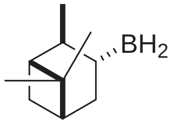


Dilongifolyborane
(Lgf$_2$BH)

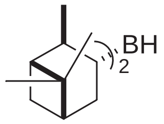


Masamune *J. Am. Chem. Soc.* **1985**, *107*, 4549.

trans-2,5-dimethyl-
borolane



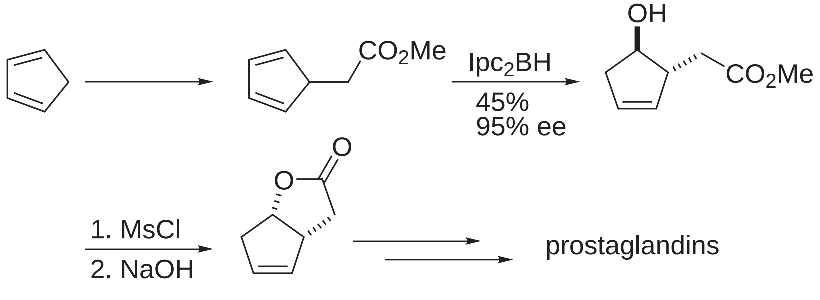
IpcBH$_2$



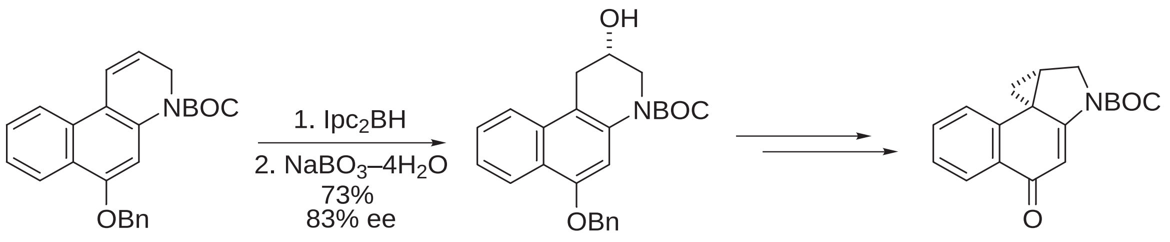
Ipc$_2$BH

monoisopinocamphenylborane

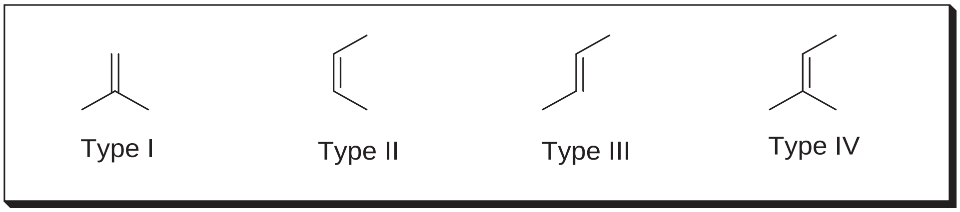
- Brown *Tetrahedron* **1981**, *37*, 3547; *J. Org. Chem.* **1981**, *46*, 2988; **1982**, *47*, 5065.



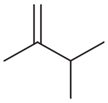
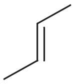
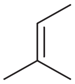
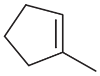
Partridge *J. Am. Chem. Soc.* **1973**, *95*, 7171.



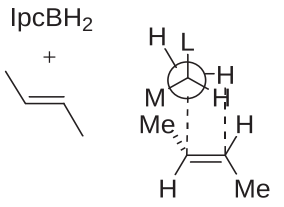
Boger *Synlett* **1997**, 515.

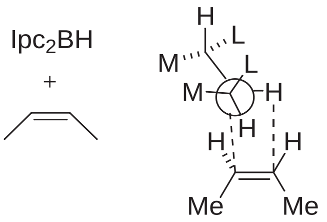


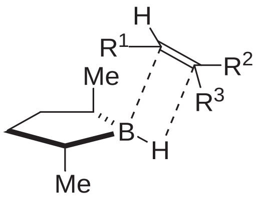
% ee for Asymmetric Hydroboration

	Type	Ipc$_2$BH	IpcBH$_2$	Lgf$_2$BH	LimBH	borolane
	I	30	1.5	–	–	1.4
	II	98	24	78	66	95
	III	13	73	–	59	97
	IV	14	53	70	67	94
	IV	22	66	62	45	97

- Models







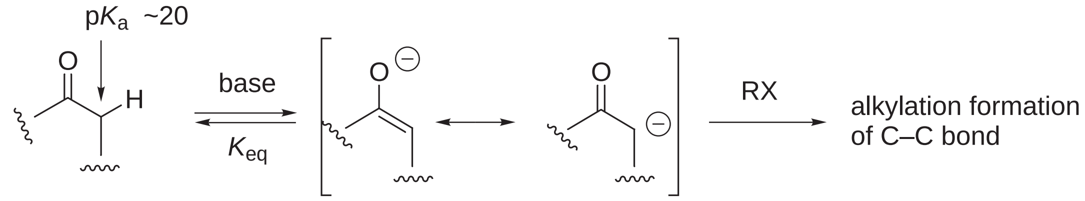
minimize R^1/Me interaction
C2-symmetric

VIII. Enolate Chemistry

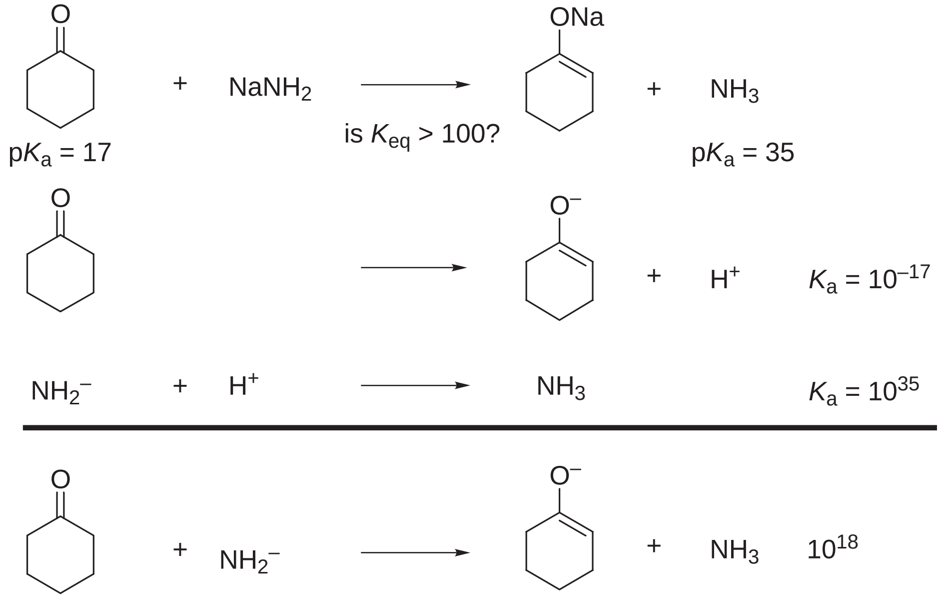
Enolate Alkylations:	*Comprehensive Org. Syn.,* Vol. 3, 1.
Formation of Enolates:	*Comprehensive Org. Syn.,* Vol. 2, 99.
Aldol Condensation:	*Comprehensive Org. Syn.,* Vol. 2, 133, 181 and 239.
Reformatsky Reaction:	*Comprehensive Org. Syn.,* Vol. 2, 277.
Acylation of Enolates:	*Comprehensive Org. Syn.,* Vol. 2, 796.
Enol Ethers:	*Comprehensive Org. Syn.,* Vol. 2, 595 and 629.
Metalloenamines:	*Comprehensive Org. Syn.,* Vol. 2, 475.
Hydrazones:	*Comprehensive Org. Syn.,* Vol. 2, 503.

A. Acidic Methylene Compounds (i.e., Malonates)

- α-Deprotonation

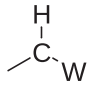


- Use of a base which stoichiometrically deprotonates the ketone completely: (i.e. K_{eq} > 100)



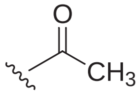
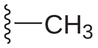
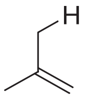
Therefore, a good deprotonation (essentially all ketone deprotonated)
Note: need to have pK_a difference of 2 pK_a units to get K_{eq} = 100.

1. Estimation of pK_a

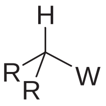


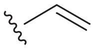
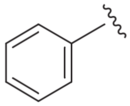
W = Cl inductive stabilization

W =  , NO_2, etc. resonance stabilization

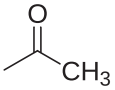
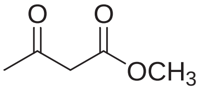
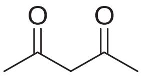
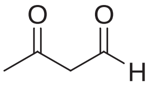
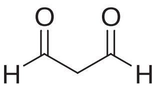
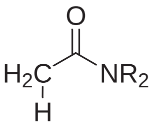
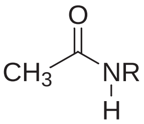
 pK_a = 20;  pK_a = 45;  pK_a = 35–37

- an increase in acidity of H results in a *faster* deprotonation (kinetic effect) as well as a stabilization of anion formed (thermodynamic effect).

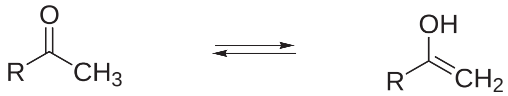


Group (–W)	**pK_a effect (units)**	**Note**
alkyl	~1–2 ↑ (decrease in acidity)	both due to inductive effects
halogen	~1–2 ↓	
	~5–7 ↓	both depend on favorable orbital overlap to allow resonance stabilization
	~5–7 ↓	
RS—	~3–5 ↓	

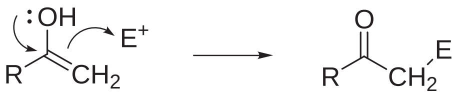
Others: NO_2 > COR >SO_2R > CO_2R, CN > SOR, Ph

Compound	**pK_a**	**Note**
	20	
	13	ketone better enolate stabilizer than ester
	11	
	9	
	5	~same as acetic acid
H_2O	14	
	25	
	15	

2. Ketone–Enol Tautomerism

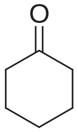
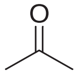
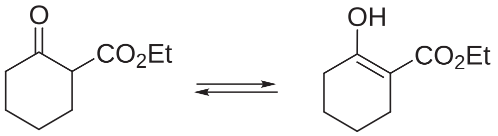
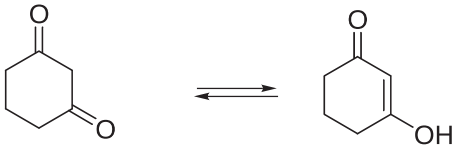
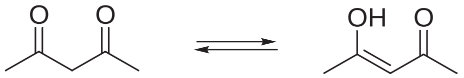
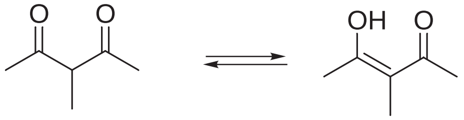


- generally << 1% enol



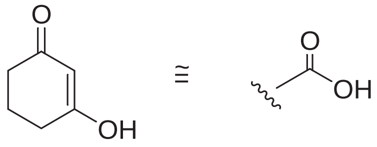
<< 1%

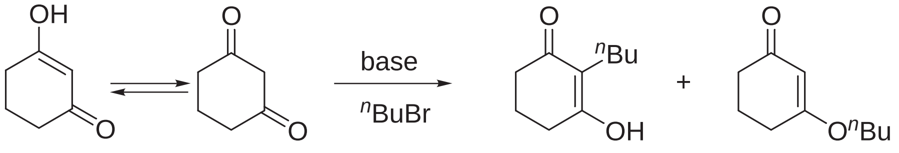
- Usually not likely to form a bond with weak electrophile (e.g., CH_3I) since not present in high concentration
- However, some ketones do exist in high enol concentration and react via enol

Compound	**Enol content**	
	0.0004%	
	< 0.002%	
	40% (neat) 60% (EtOH)	
	100%(neat) 95% (H_2O) 2–14% (cyclohexane)	
	10–13% (EtOH) 50% (cyclohexane) ←	intramolecular H-bond
	16% (H_2O) 63% (EtOH) 92% (cyclohexane) ←	intramolecular H-bond
	3% (H_2O) 31% (EtOH) 55% (cyclohexane) ←	intramolecular H-bond

- If a compound has a vinyl spacer, the reactivity parallels that of the parent compound.

1,3-Cyclohexadione in its enol form is a vinylogous carboxylic acid and it exhibits many properties of a RCOOH, including low pK_a, O-alkylation.



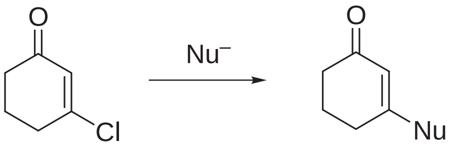


15%

37%

analogous to
RCOOH -> RCOO^{n}Bu

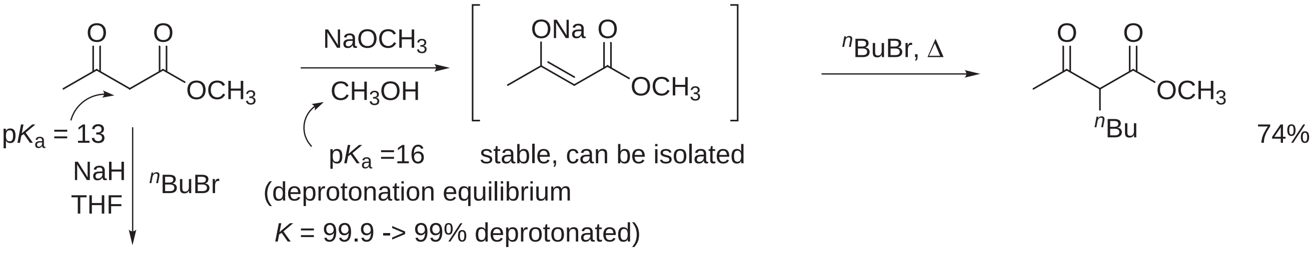
VINYLOGY RULE



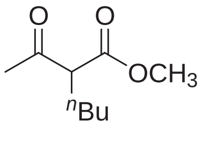
analogous to RCOCl -> RCONu

vinylogous acid chloride

3. Acetoacetic Ester Synthesis



74%

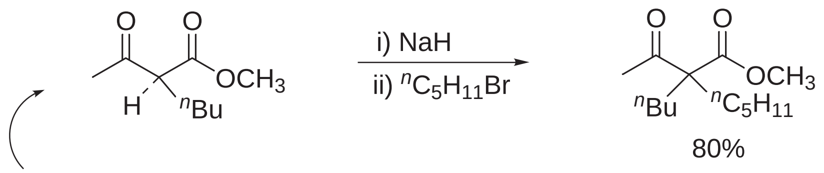


~70%

NaH: strong base, operates in range up to pK_a = 35. Sometimes kinetically slow, sometimes difficult to reproduce. It is insoluble and the reaction is heterogeneous. Thought that trace $^-$OH might be active base. Therefore, deliberately add 0.05–0.1 equiv. CH$_3$OH to obtain reproducible reaction.

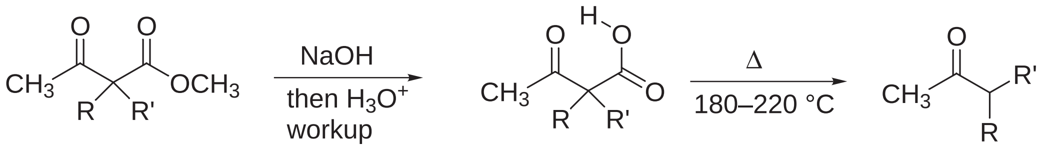
Henri Moissan, who received the 1906 Nobel Prize in Chemistry for his investigation and isolation of the element fluorine and for the high temperature electric furnace named after him, prepared and studied the alkali metal hydrides.

- The product can be further alkylated:

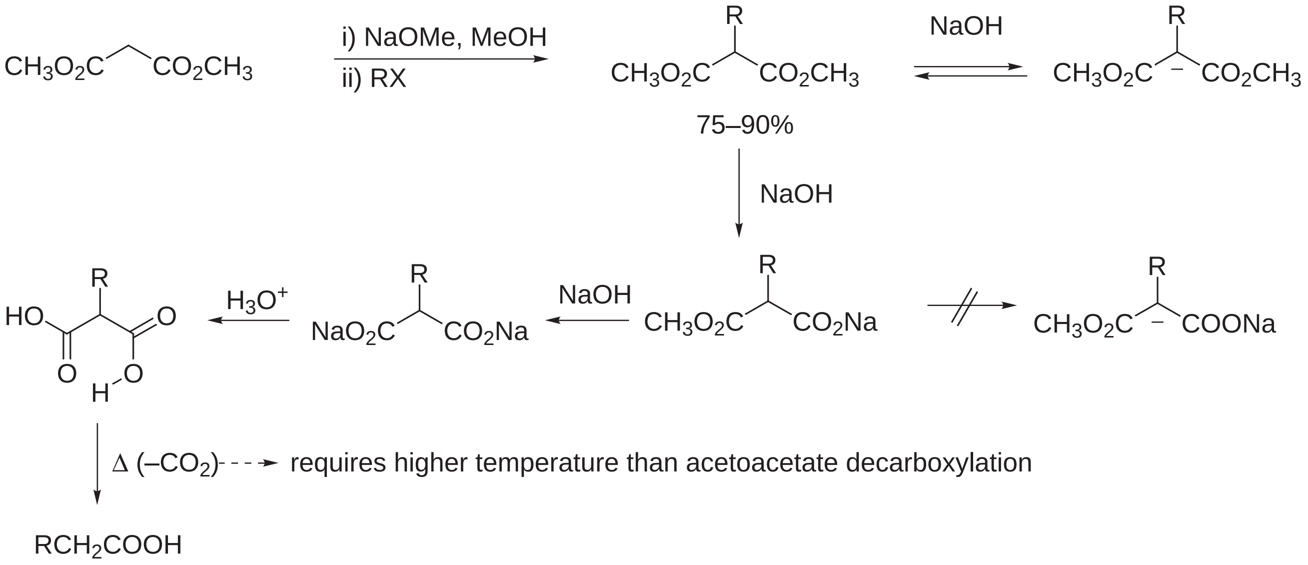


pK_a now 1–2 units higher than parent ⟹ concentration of parent enolate vs. concentration of product enolate in monoalkylation reaction is very high (> 90:10) -> monoalkylation fairly clean.

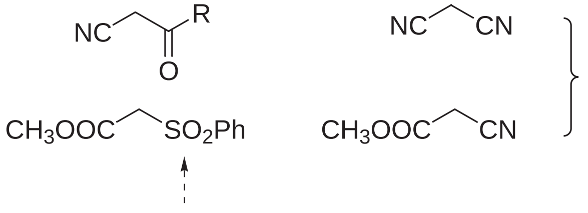
- Hydrolysis and decarboxylation gives α-substituted ketones:



4. Malonic Ester Alkylation

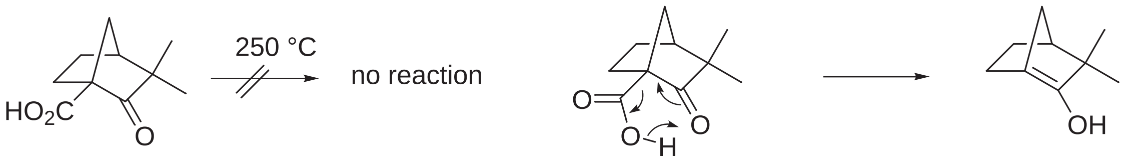


requires higher temperature than acetoacetate decarboxylation



related stabilized enolates

can be removed reductively

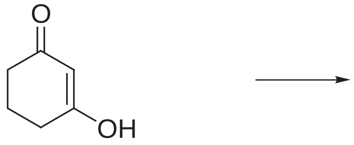


violates Bredts Rule,
bridgehead olefin

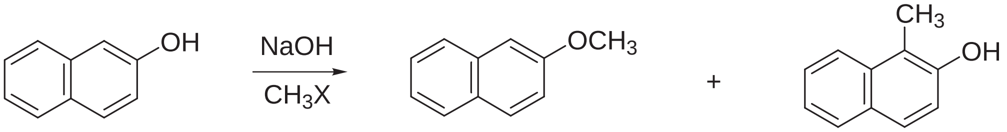
5. Enolates: *C*- vs. *O*-Alkylation

- Ketones which are more acidic tend to give more *O*-alkylation.

e.g.



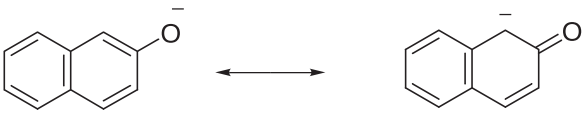
37% *O*-alkylation
15% *C*-alkylation



- The more reactive the alkylating agent, the more *O*-alkylation observed

X = I 66 : 33
X = OTs 100 : 0

- Rarely see *O*-alkylation of ketone enolates often see *O*-alkylation of stabilized enolates e.g., β-diketones and β-keto esters



localized,
harder anion

softer, more
diffuse anion

- tends to react with harder electrophiles (CH$_3$OTs, $\overset{+}{\mathrm{Me}_3}\mathrm{O}\overset{-}{\mathrm{BF}_4}$)

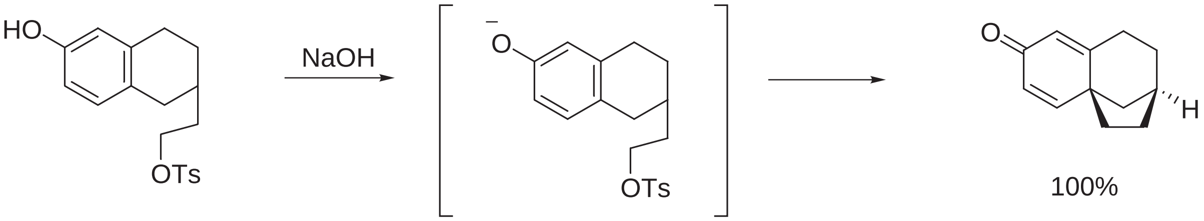
$\uparrow$

Meerwein's salt

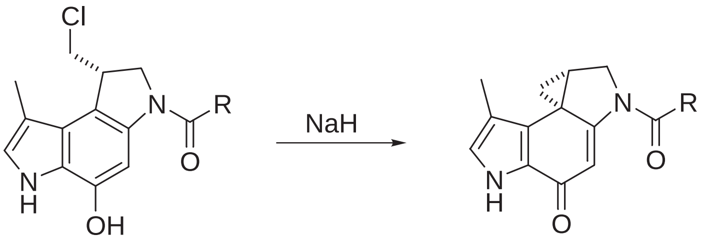
reacts with softer alkylating agents (RI, RBr)

more reactive or more ionized = harder

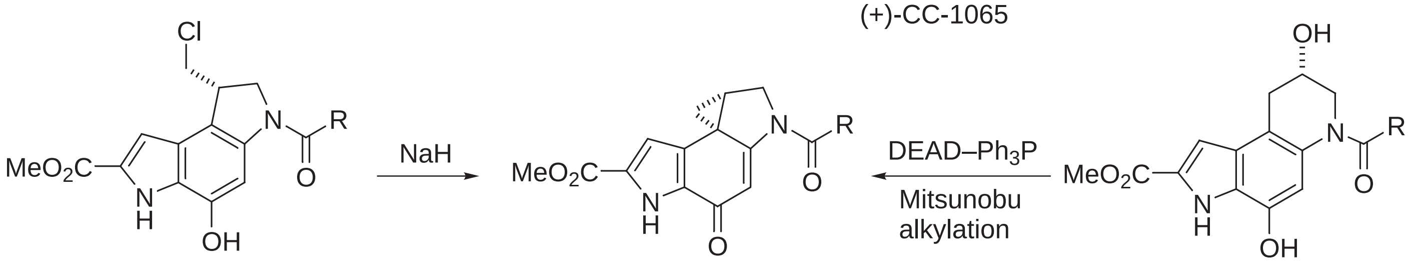
- Intramolecular constraints can affect course of *C*- vs. *O*-alkylation



100%



(+)-CC-1065



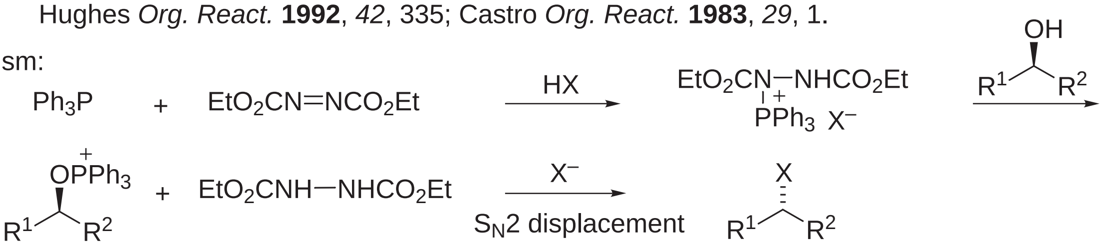
duocarmycin SA

Boger *Chem. Rev.* **1997**, *97*, 787.

- Mitsunobu alkylation

Mitsunobu, Yamada, Mukaiyama *Bull. Chem. Soc., Jpn.* **1967**, *40*, 935.
Mitsunobu *Bull. Chem. Soc., Jpn.* **1967**, *40*, 4235.
Review: Mitsunobu *Synthesis* **1981**, 1.
Hughes *Org. React.* **1992**, *42*, 335; Castro *Org. React.* **1983**, *29*, 1.

- Mechanism:

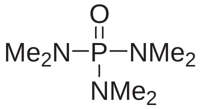


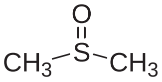
HX: pK_a typically <15 (RCO_2H, phenols, imides, malonates, β-keto esters)

Related reagents including Ph_3P/CCl_4, Ph_3P/NXS are used to convert an alcohol to the corresponding halide with inversion of stereochemistry.

- Factors which favor *O*-alkylation

1. Polar solvent:

HMPA 
$Me_2N{-}\overset{\overset{O}{\|}}{\underset{\underset{NMe_2}{|}}{P}}{-}NMe_2$

DMSO 
$CH_3{-}\overset{\overset{O}{\|}}{S}{-}CH_3$

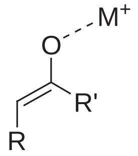
DMF Me_2NCHO

polar, aprotic solvents:

a. separate metal cation from enolate oxygen, making oxygen more free to react
b. coordinate electrophile, activate and increase their reactivity
c. increase rate of reaction

2. Large, noncoordinating metal cation:

- again, frees up oxygen to react



$M^+ = R_4N^+ > K^+ > Na^+ > Li^+$

O-alkylation ⇢ *C*-alkylation
⇠ rate of reaction

ion pair
separation of charge, harder
more reactive anion

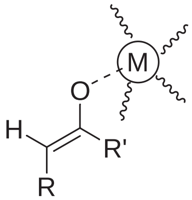
lithium essentially covalently coordinated to O

3. Aggregation/Solubility:

Homogeneous, monomeric enolates → *O*-alkylation

Heterogeneous, aggregate enolates → *C*-alkylation

Li enolates tend to be more aggregated



hard for RX to get to O atom, so reacts at C

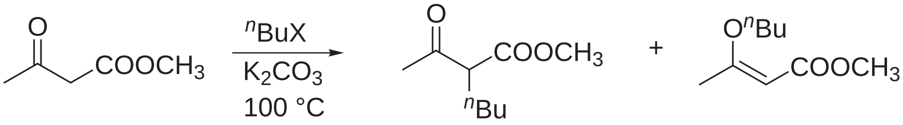
4. Structure of alkylating agent

a. Leaving group:

(hard alkylating agents) (soft alkylating agents)

for RX: X = $Me_3\overset{+}{O}$ > OTs > Cl > Br > I

O-alkylation - - - - - - - → *C*-alkylation

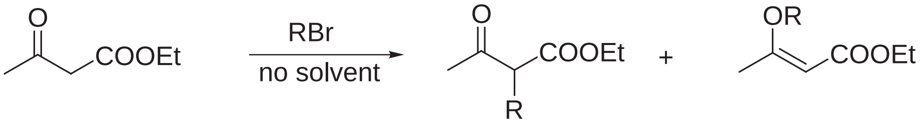


O-alkylation ↓ Polarity of solvent ↓

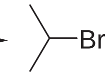
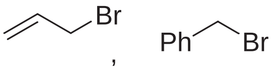
Solvent	X	*C*- : *O*-alkylation rel % products
acetone	Cl	90 : 10
CH_3CN	Cl	81 : 19
DMSO	Cl	53 : 47
DMF	Cl	54 : 46
DMF	Br	67 : 33
DMF	I	>99 : 1

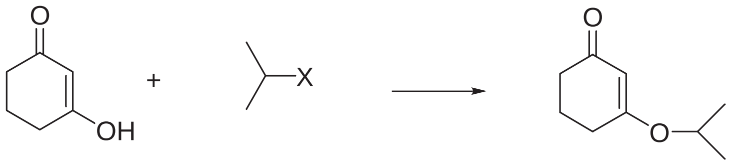
For *C*-alkylation:
I > Br > Cl

b. Degree of substitution of alkylating agent:



more sterically hindered, so "harder" →

$^{n}C_3H_7Br$	97	:	3
	73	:	27
	mainly *C*-alkylation		



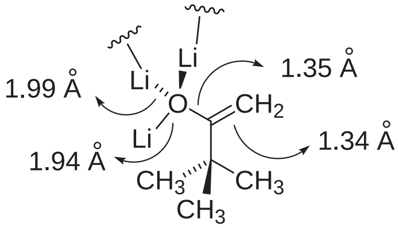
works well in polar, aprotic solvents (ie., HMPA, DMSO),
or even K_2CO_3, acetone will work

B. Enolate Structure

- Actually exist as higher aggregates in solution: dimer–tetramer.
- Originally suggested by House *J. Org. Chem.* **1971**, *36*, 2361 and Brown *J. Organometal. Chem.* **1971**, *26*, 57.
- Supported by NMR studies: Jackman *Tetrahedron* **1977**, *33*, 2737.
- Confirmed by X-ray: Dunitz *Helv. Chim. Acta* **1981**, *64*, 2617.

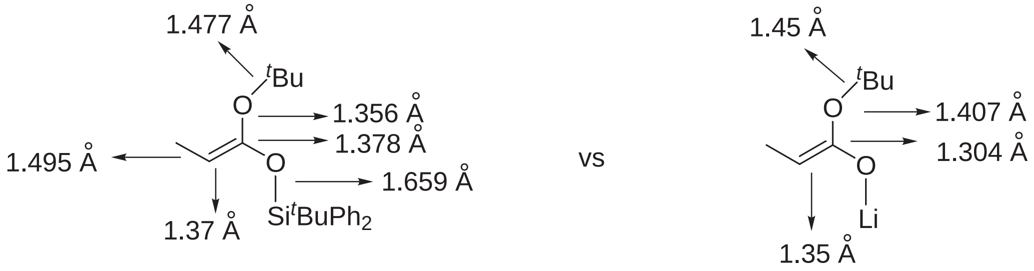
see also:

Seebach *J. Am. Chem. Soc*. **1985**, *107*, 5403.
Angew. Chem., Int. Ed. Eng. **1988**, *27*, 1624.
Lynch *Tetrahadron Lett*. **1989**, *30*, 447.

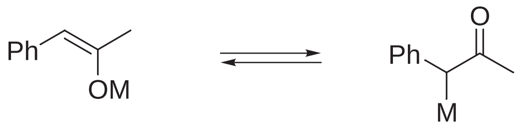


tetramer aggregates

bond lengths, angles much like those of enol ether.



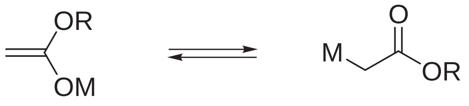
Ketone Enolates:



K_{eq} < 1 for most metals (Li, Na, K, MgX, ZnX) ⟶ negative charge, M^+ on oxygen.

> 1 for M = HgI

Ester Enolates:



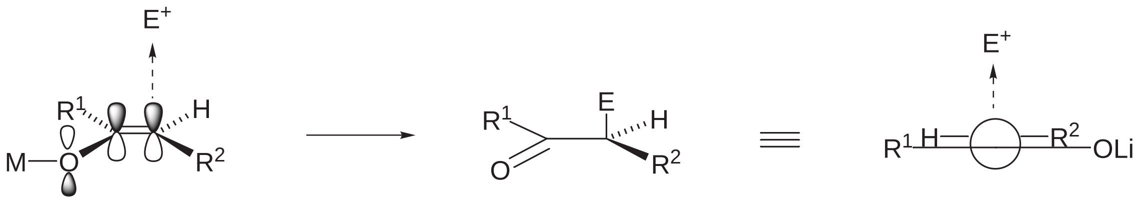
$K_{eq} < 1$ for Li $K_{eq} > 1$ for ZnBr (Reformatsky reagents)

Reformatsky *Ber.* **1887**, *20*, 1210.
Reviews: Shriner *Org. React.* **1946**, *1*, 423.
Rathke *Org. React.* **1975**, *22*, 423.
Furstner *Synthesis* **1989**, 571.

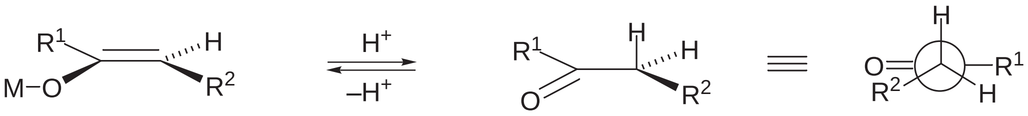
C. Enolate Alkylations: π-Facial Stereoselectivity

1. Stereoelectronic Effects

- The attacking electrophile must obey the principle of maximum overlap of the participating orbitals by perpendicular approach to the plane of atoms which constitute the enolate (enol) function.



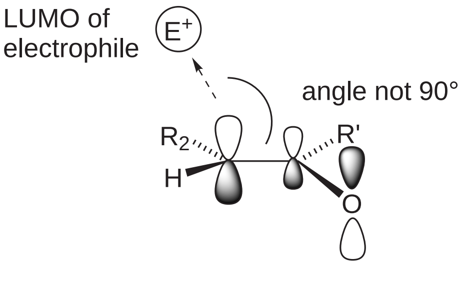
- Also applies to protonation in reprotonation reaction:



- Nucleophilic addition to carbonyl compound takes place not at 90° (perpendicular) but at an angle of 105 ± 5°

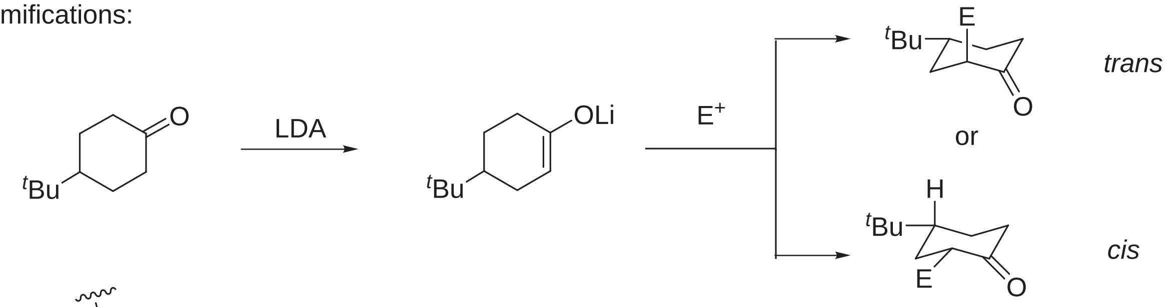
Dunitz *Tetrahedron* **1974**, *30*, 1563.

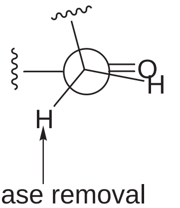
- Same applies to enolate alkylations



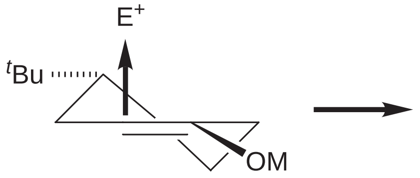
enolate HOMO

- Ramifications:





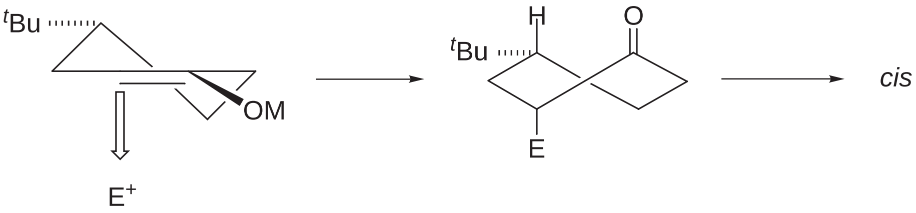
base removal
of axial proton



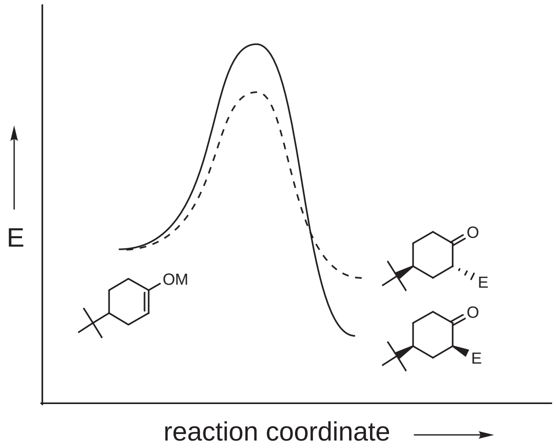
predominant *trans*
product observed

axial attack proceeds
through a chair-like T.S.

- In order to get *cis*, must proceed through a boat-like T.S.!



- Therefore



Energy of activation for formation of the more stable *cis* product is higher because it involves a boat-like T.S.

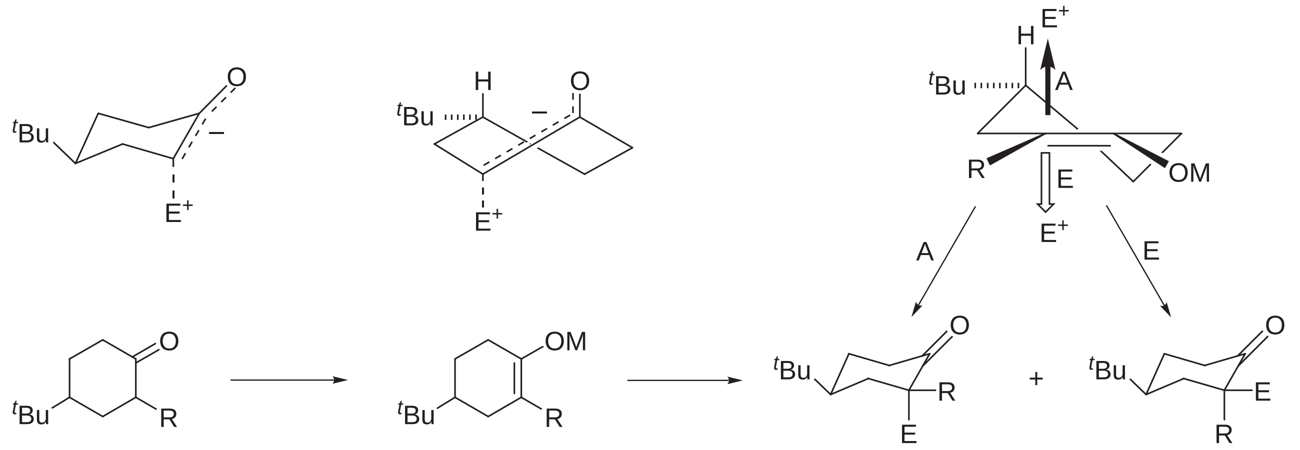
Corey, Sneen *J. Am. Chem. Soc.* **1956**, *78*, 6269 (origin of axial alkylation).
They also introduced the term stereoelectronic effect to describe this behavior.

This was the pioneering work that led to the now widespread predictions about reactions and reaction products based on orbital alignment or overlap and provided the term "stereoelectronic" effect.

- Examples of stereoelectronic control

axial alkylation
chair-like transition state

equatorial alkylation
via twist boat T.S.



House *J. Org. Chem.* **1968**, *33*, 935.
Caine *J. Org. Chem.* **1969**, *34*, 3070.

M	R	E	axial		equatorial
Li	H	$Et_3O^+BF_4^-$	51	:	49
Li	H	EtI	54	:	46
Li	H	MeI	55	:	45
Li	H	DOAc	70	:	30
Li	Et	HOAc	80	:	20
Li	Me	CD_3I	70	:	30
Li	CN	CH_3I	77	:	23
Li	$COOCH_3$	CH_3I	83	:	17

less reactive enolates
(so more selective)

Kuehne *J. Org. Chem.* **1970**, *35*, 161, 171.

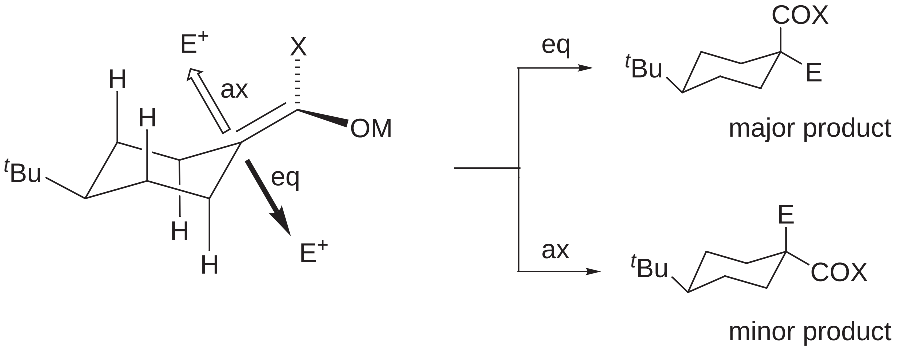
2. Steric Effects

- Stereoelectronic effects equivalent for exocyclic enolates.
- Relatively insensitive to alkylating agent and conditions.

Behavior as a large reagent preferring equatorial delivery.

- Transition states for enolate alkylations are thought to be REACTANT-LIKE.

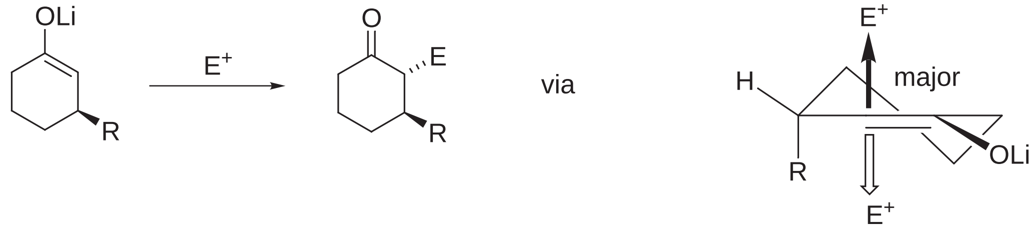
House *J. Org. Chem.* **1968**, *33*, 943.
Krapcho *J. Org. Chem.* **1980**, *45*, 3236.



major product

minor product

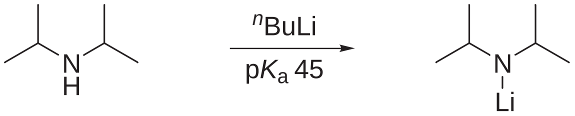
X	E		eq : ax
CH_3	MeI	25 °C	85 : 15
OCH_3	MeI	–78 °C	84 : 16
OCH_3	^{n}BuBr	–78 °C	87 : 13



D. Enolate Generation

1. Soluble Bases

- $NaNH_2$, $LiNH_2$, KNH_2 → strong bases, but insoluble in conventional organic solvents
- Soluble secondary amine derived bases

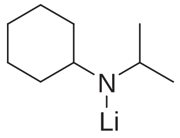


= LDA

pK_a = 35

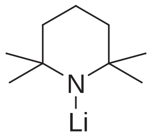
readily available, soluble; amine byproduct is low MWt, volatile, and easily removed. The anion is also nonnucleophilic (relatively hindered)

- Aggregates: Williard *J. Org. Chem.* **1993**, *58*, 1 (X-ray).
- Other widely used bases:



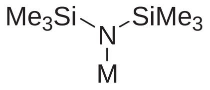
= Lithium isopropylcyclohexylamide (LICA)

very hindered base



= Lithium 2,2,6,6-tetramethylpiperidide ("FAT ALBERT", LTMP)

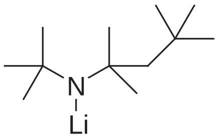
very hindered



M = Li Lithium hexamethyldisilazide (LHMDS or LHDS)

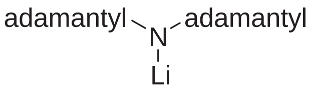
= Na Sodium hexamethyldisilazide (NaHMDS)

= K Potassium hexamethyldisilazide (KHMDS)



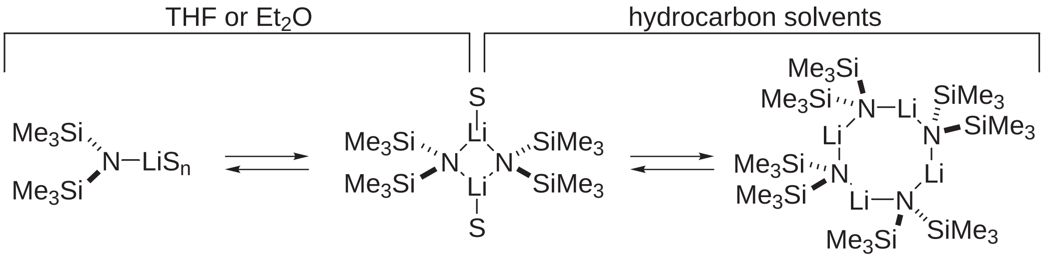
= Lithium ^{t}octyl-^{t}butylamide (LOBA)

Corey *Org. Syn.* **1987**, *65*, 166; *Tetrahedron Lett.* **1984**, *25*, 491 and 495.



= Lithium bis(2-adamantyl)amide (LBAA)

Collum *Tetrahedron Lett.* **1993**, *34*, 5213.



monomer dimer tetramer

Brown *J. Organometal. Chem.* **1971**, *26*, 57.

Collum *Acc. Chem. Res.* **1993**, *26*, 227; **1999**, *32*, 1035 (^{6}Li and ^{15}N NMR).

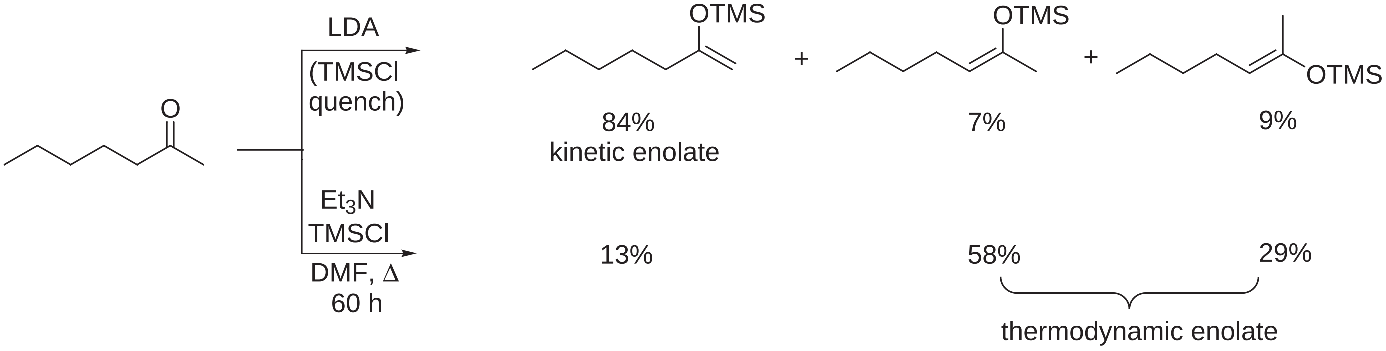
- X-ray structures

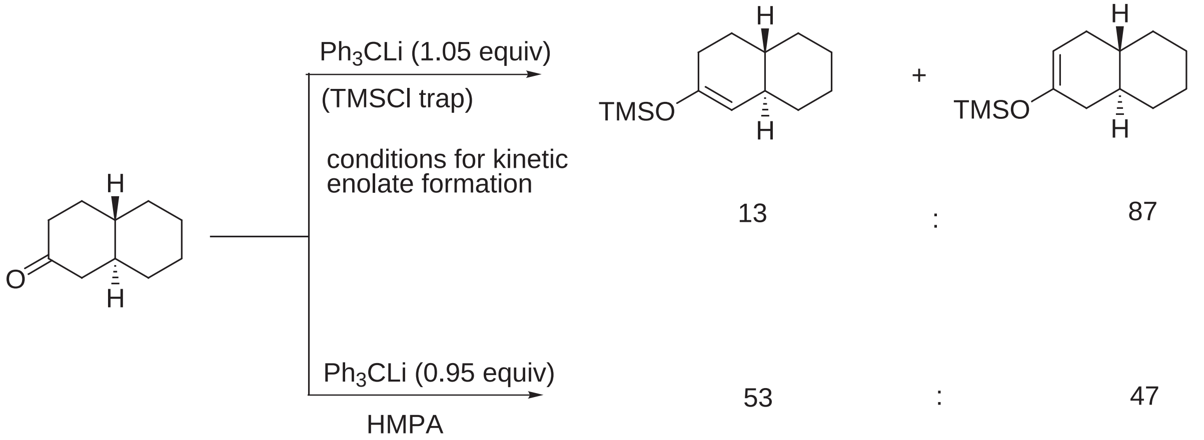
Williard *J. Am. Chem. Soc.* **1997**, *119*, 11855.

Reviews:

Conia	*Rec. Chem. Prog.* **1963**, *24*, 43.
House	*Rec. Chem. Prog.* **1967**, *28*, 98.
Fleming	*Chimica* **1980**, *34*, 265.
Petragnani	*Synthesis* **1982**, 521.
Kaiser	*Synthesis* **1977**, 509.
d'Angelo	*Tetrahedron* **1976**, *32,* 2979 (Methods for regiospecific enolate generation).
Evans	*Asymm. Synthesis*, Morrison, Ed., Vol. 3, 1.
Collum	*Acc. Chem. Res.* **1999**, *32*, 1035.

2. Kinetic and Thermodynamic Enolates

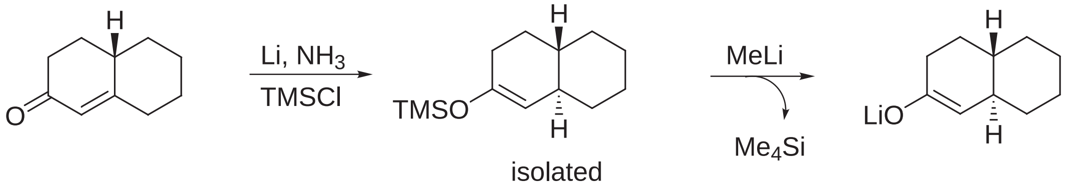




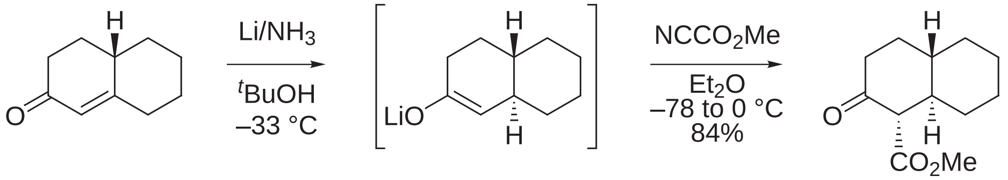
some ketone always present, so deprotonation–reprotonation equilibrium → conditions for thermodynamic enolate formation

3. Regiospecific Enolate Generation

- In the above case, the $\Delta^{2,3}$ enolate cannot be cleanly obtained directly, but other approaches to this have been developed.

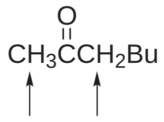


See: Stork *J. Am. Chem. Soc.* **1961**, *83*, 2965; **1965**, *87*, 275.



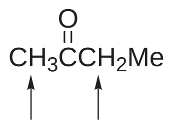
Mander *Org. Syn.* **1992**, *70*, 256.

- Representive enolate selectivities:



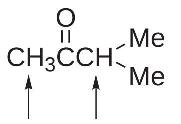
$CH_3\overset{O}{C}CH_2Bu$

100 0 (LDA, –78 °C)



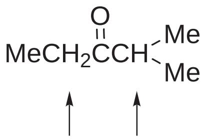
$CH_3\overset{O}{C}CH_2Me$

71 29 (LDA, 0 °C)



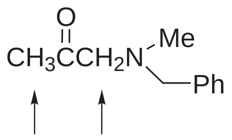
$CH_3\overset{O}{C}CH\begin{smallmatrix}Me\\Me\end{smallmatrix}$

99 1 (KHMDS, –78 °C)

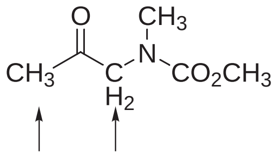


$MeCH_2\overset{O}{C}CH\begin{smallmatrix}Me\\Me\end{smallmatrix}$

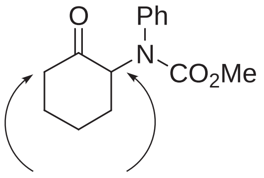
95 5 (LDA, 0 °C)



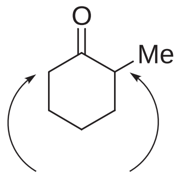
75 25 (LDA, –78 °C)



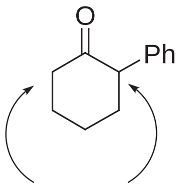
18 82 (LDA, –78 °C)



LDA: 33 : 67 (kinetic)
LHMDS: 2 : 98 (thermodynamic)

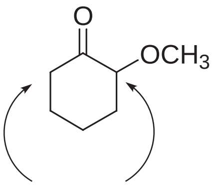


99 : 1 (LDA, 0 °C)

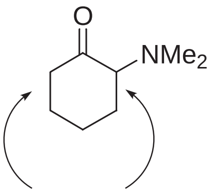


>99 : 1 (LDA, –78 °C)

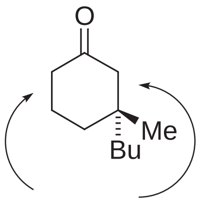
Albizati *J. Am. Chem. Soc.* **1990**, *112*, 6965.



85 : 15 (LDA, –78 °C)

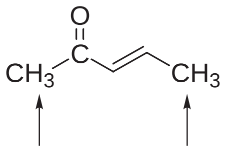


98 : 2 (LDA, –78 °C)
98 : 2 (LHMDS, thermodynamic)

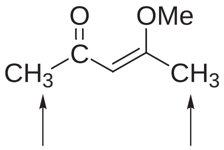


91 : 9 (LDA, 25 °C)

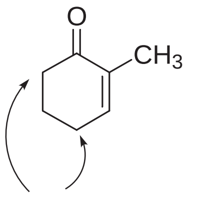
Albizati *J. Am. Chem. Soc.* **1990**, *112*, 6965.



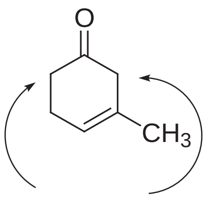
100 : 0 (LDA, –78 °C)



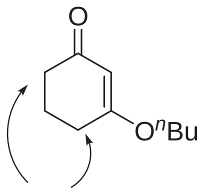
100 : 0 (LDA, –78 °C)



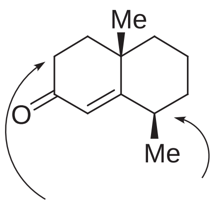
100 : 0 (LDA, –78 °C)



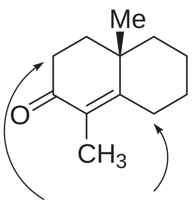
20 : 80 (LDA, –78 °C)



100 : 0 (LHMDS, –78 °C)



100 : 0 (LDA, –78 °C)



0 : 100 (NaH, 100 °C) - - - -→ thermodynamic enolate formation

Taken from: Evans *Asymm. Synthesis*, Morrison, Ed., Vol. 3, 1.

- Enantio- or diastereoselective protonation of ketone enolates

deprotonation:

Majewski *Can. J. Chem.* **1994**, *72*, 1699.

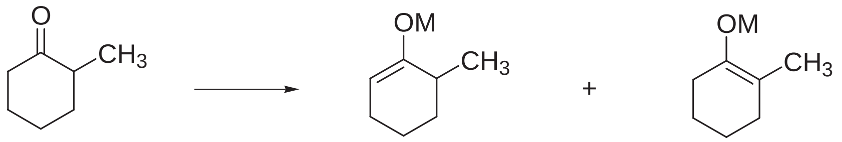
Simpkins *Tetrahedron Lett.* **1992**, *33*, 8141.
1989, *30*, 7241.

protonation:

Fehr *Angew. Chem., Int. Ed. Eng.* **1994**, *33*, 1764.

4. Cyclic Carbonyl Compounds

- site of deprotonation
- enolate geometry fixed

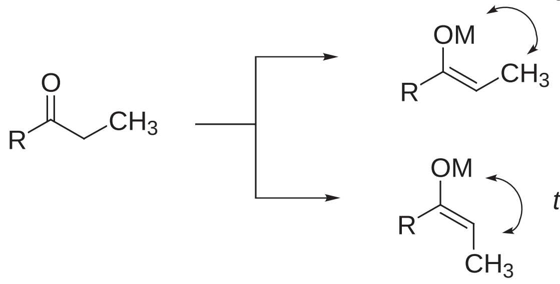


Base	Control	Selectivity
LDA (0 °C, THF)	kinetic	99 : 1
KHMDS (–78 °C)	"	95 : 5
Ph_3CLi (–78 °C)	"	90 : 10
Ph_3CK (–78 °C)	"	67 : 33
Ph_3CLi	thermodynamic	10 : 90
NaH	"	26 : 74
Ph_3CK	"	38 : 62

potassium bases not as effective for kinetic enolate generation. - - - → Ph_3CK (–78 °C)

5. Acyclic Carbonyl Compounds

- Two issues: i. site of deprotonation
  ii. geometry of enolate formed

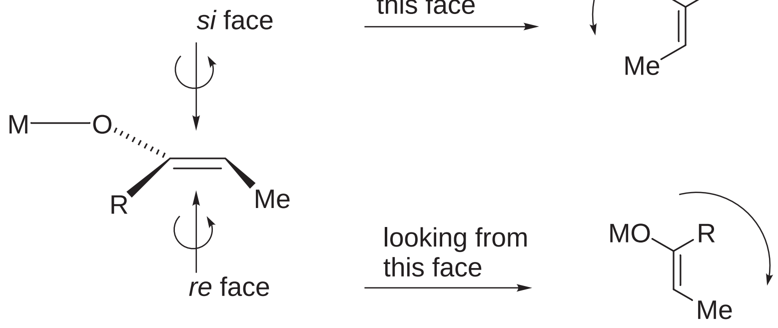


cis *Z*-enolate (Zusammen)

trans *E*-enolate (Entgegen)

- Also: the enolate has two diastereotopic faces:

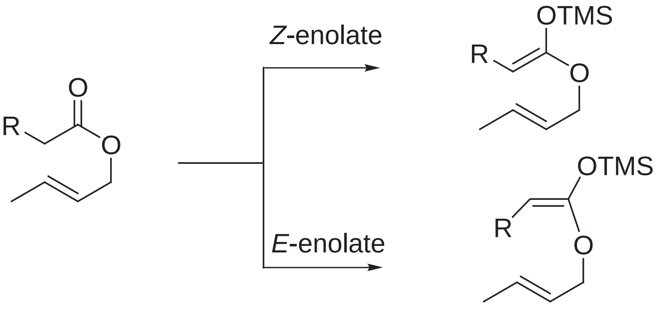
For *E*-enolate



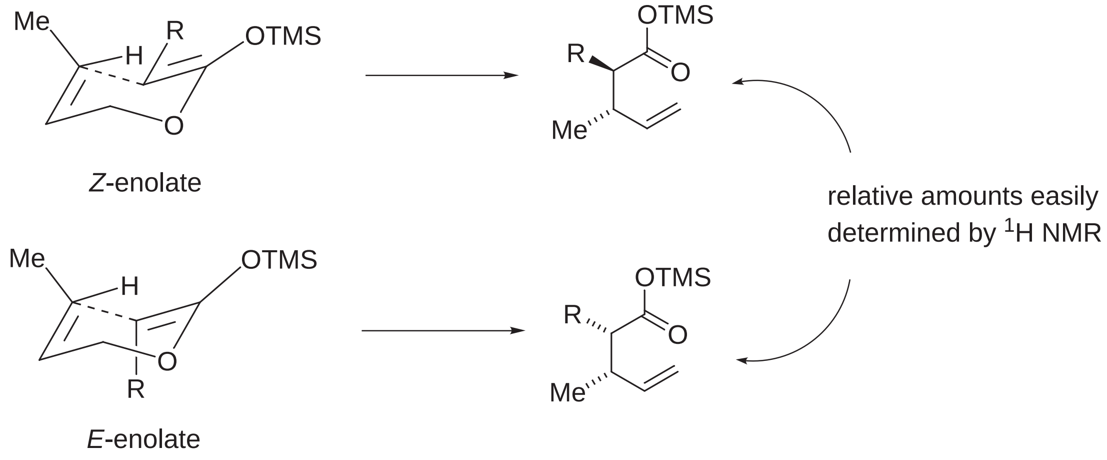
counterclockwise = *si*

clockwise = *re*

- ASIDE: Geometry of enolate can be determined by Claisen rearrangement:

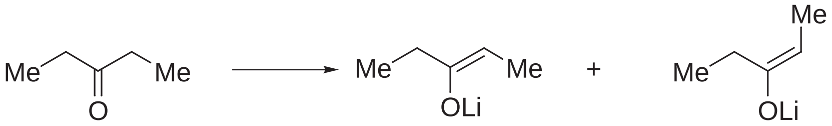


- Claisen rearrangement known to proceed through *chair-like* T.S.:



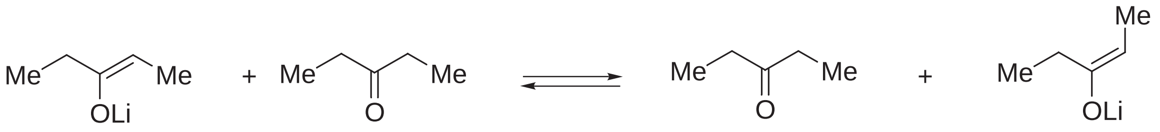
relative amounts easily determined by ^{1}H NMR

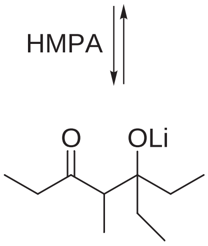
A. Acyclic Ketones



	Base	*Z*		*E*	
very hindered amide base	LTMP (–78 °C)	14	:	86	kinetic enolate
	LTMP/HMPA	92	:	8	thermodynamic enolate
	LDA	23	:	77	
	LICA	35	:	65	
	LHMDS	66	:	34	
	$(PhMe_2Si)_2NLi$	100	:	0	

- Thermodynamic enolate formation

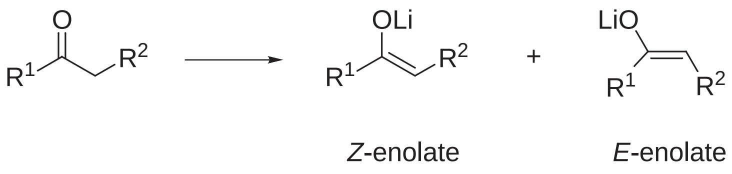




or may take place by reversible aldol addition

Rathke *J. Am. Chem. Soc*. **1980**, *102*, 3959.

For the effect of HMPA on R_2NLi aggregation:
Collum, Romesberg *J. Am. Chem. Soc.* **1994**, *116*, 9198; **1993**, *115*, 3475.



Note: As R^1 becomes sterically more demanding, *Z*-enolate increases or predominates even under kinetic conditions.

R^1	R^2		*Z*	*E*	
Et	Me	LDA	23	77	
Et	Me	LTMP	14	86	
Et	Me	LTMP–LiBr	2	98	← best conditions for *E*-enolate (kinetic)
^{i}Pr	Me	LDA	37	63	
^{i}Pr	Me	LTMP	33	67	
^{i}Pr	Me	LTMP–LiBr	5	95	
^{t}Bu	Me	LDA	98	2	
^{t}Bu	Me	LTMP	95	5	
^{t}Bu	Me	LTMP–LiBr	95	5	← *Z*-enolate only very large R^1
Me	Ph	LDA	7	93	
Me	Ph	LTMP	8	92	
Me	Ph	LTMP–LiBr	3	97	

Note: As R^2 becomes sterically more demanding, *E*-enolate selectivity increases under kinetic conditions: Ph > Me.

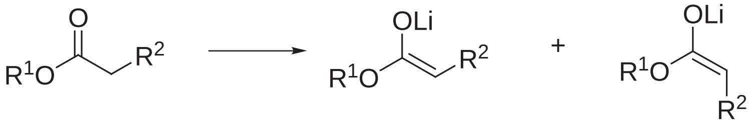
Collum *J. Am. Chem. Soc.* **1991**, *113*, 9571.

Et	Me	LOBA	2	98	← kinetic *E*-enolate

Corey *Tetrahedron Lett.* **1984**, *25*, 491 and 495.

B. Acyclic Esters

- Similar to ketones:



Z — thermodynamic enolate (more stable)

E — kinetic enolate

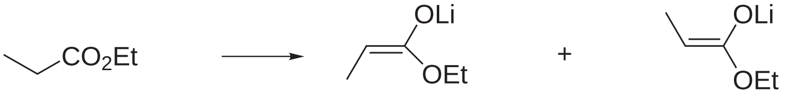
R^1	R^2	base	*Z*	:	*E*	
Me	Me	LDA	5	:	95	
^{t}Bu	Me	LDA	5	:	95	
Me	Et	LDA	9	:	91	← kinetic
Me	Et	LDA/HMPA	84	:	16	← thermodynamic
^{t}Bu	Et	LDA	5	:	95	
^{t}Bu	Et	LDA/HMPA	77	:	23	

Role of HMPA: increase rate of equilibration, break up enolate aggregation

R^1	R^2	base	*Z*	:	*E*
Me	Et	LOBA	5	:	95
Bn	Me	LDA	20	:	80
Bn	Me	LOBA	5	:	95

Corey *Tetrahedron Lett.* **1984**, *25*, 491 and 495.

kinetic *E*-enolate — thermodynamic *Z*-enolate

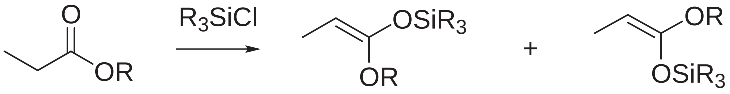


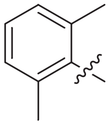
LDA	THF	94	:	6
LDA	THF–45% DMPU	7	:	93
LDA	THF–23% HMPA	15	:	85

Ireland, Wipf *J. Org. Chem*. **1991**, *56*, 650 and 3572.

- Silyl Ketene Acetals

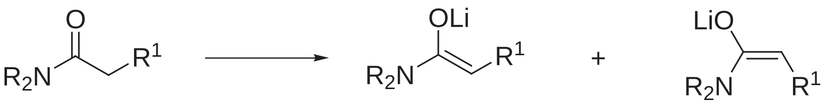
Otera *Synlett* **1994**, 213.



R = ^{t}Bu	LDA	>99	:	1
$EtMe_2C$	LDA	97	:	3
Ph_3C	LDA	>99	:	1
	LDA	99	:	1
^{i}Pr	LDA	83	:	17
bornyl	LDA	83	:	17
Et	LDA	84	:	16
Me	LDA	87	:	13
Me	LDA–HMPA or DMPU	4	:	96
Et	"	3	:	97
bornyl	"	13	:	87
^{i}Pr	"	13	:	87
$EtMe_2C$	"	26	:	74
^{t}Bu	"	28	:	72

C. Acyclic Amides

give only *Z*-enolate



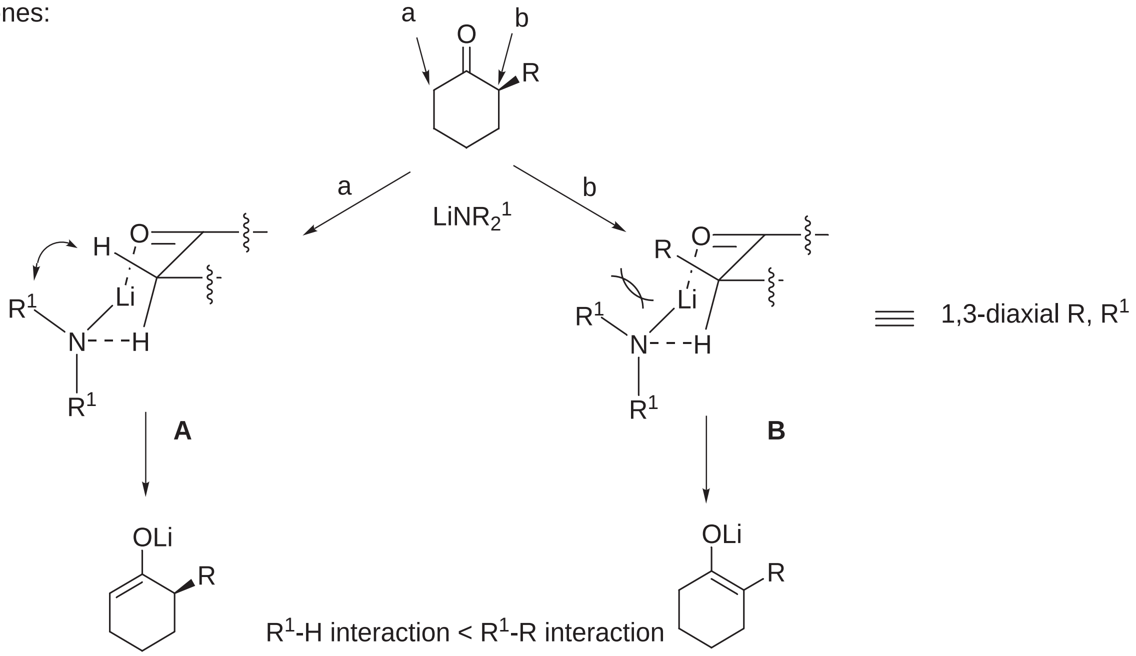
Z-enolate *E*-enolate

R	R^1	base	*Z*		*E*
Et	CH_3	LDA	>97	:	3
$(CH_2)_4$	CH_3	LDA	>97	:	3

6. Ireland Transition State Model for Deprotonation

J. Am. Chem. Soc. **1976**, *98*, 2868.
Tetrahedron Lett. **1975**, 3975.

- For Cyclic Ketones:

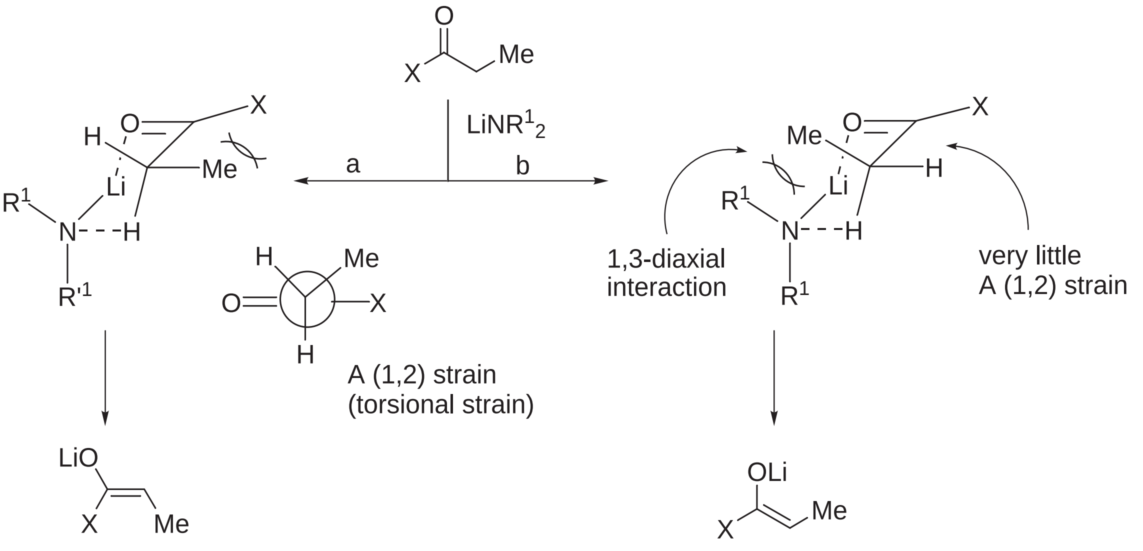


R^1-H interaction < R^1-R interaction

ketone	base	**A** vs. **B**	1,3-diaxial interaction
R = CH_3	LDA	99 : 1	^{i}Pr, CH_3
Ph	LDA	>99 : 1	^{i}Pr, Ph
OCH_3	LDA	85 : 15	^{i}Pr, OCH_3
NMe_2	LDA	98 : 2	^{i}Pr, NMe_2

- More hindered bases (^{t}Bu$_2$NLi, LiHMDS, LTMP) would increase selectivity for kinetic enolate formation (1,3-diaxial interactions even larger in T.S. for thermodynamic enolate formation)

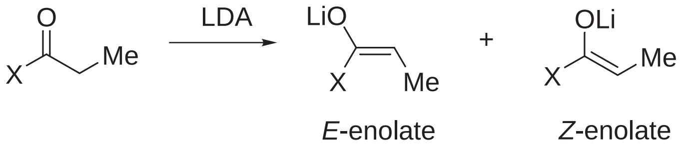
- For Acyclic Ketones, Esters, and Amides:



E-enolate ◂- - - - - in most instances, kinetically favored

Z-enolate thermodynamically more stable enolate

- Example:



X	LDA	*E* : *Z*
OCH_3		95 : 5
O^tBu		95 : 5
Et		77 : 23
^iPr		40 : 60
^tBu		0 : 100
Ph		0 : 100
NEt_2		0 : 100

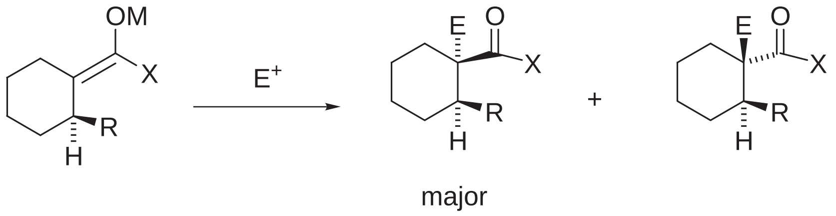
Me/R^1 1,3-diaxial interaction worse than Me/X A (1,2)-interaction

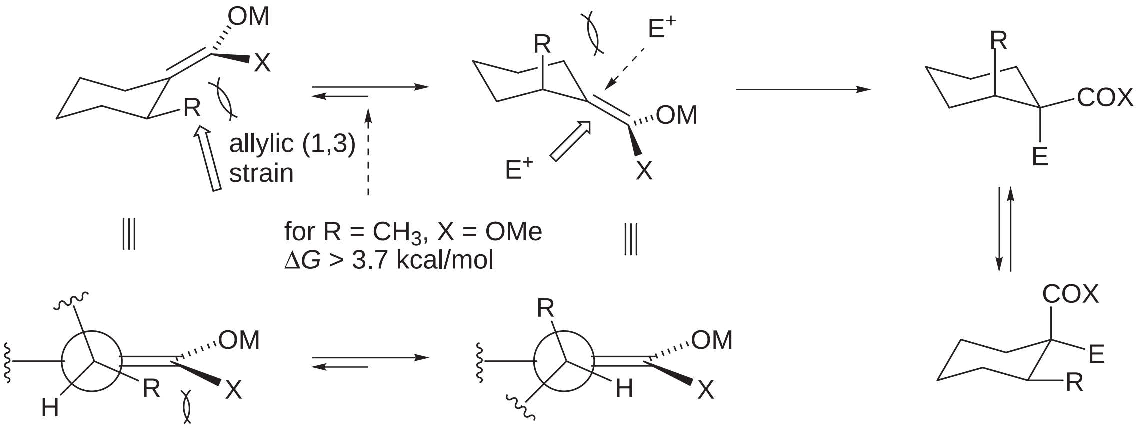
X getting larger, so A (1,2) steric interaction outweighs the Me/R^1 1,3-diaxial interaction

E. Alkylation Reactions: Stereochemistry

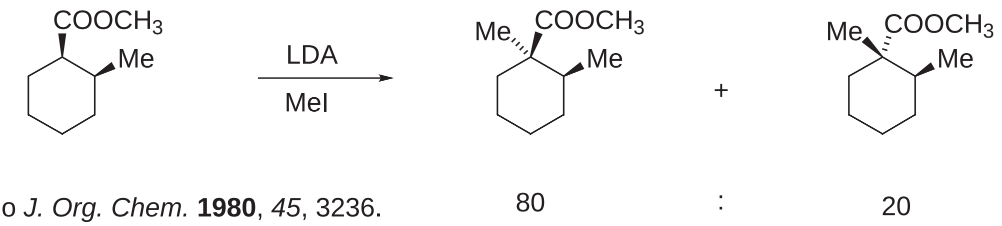
1. Exocyclic Enolates

i. 1,2-Stereocontrol in Exocyclic Enolates

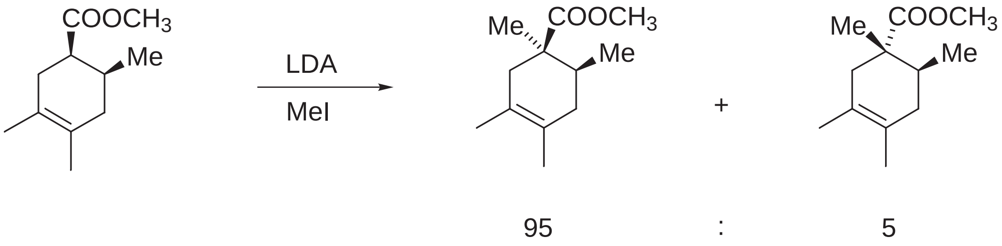


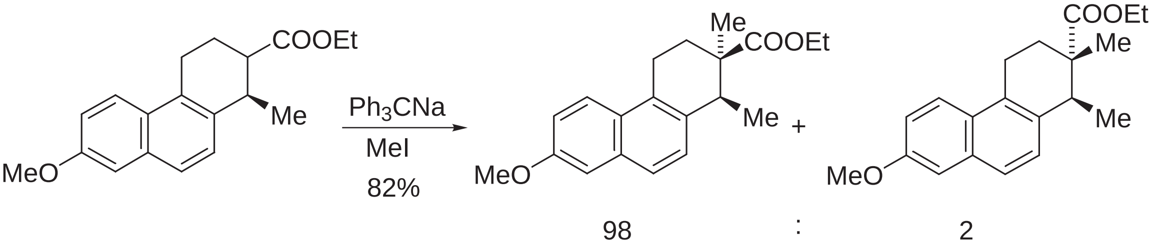


H-eclipsed conformation



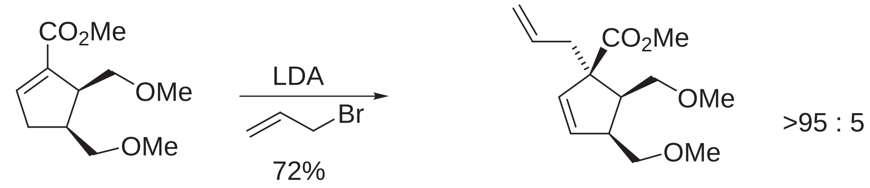
Krapcho *J. Org. Chem.* **1980**, *45*, 3236.



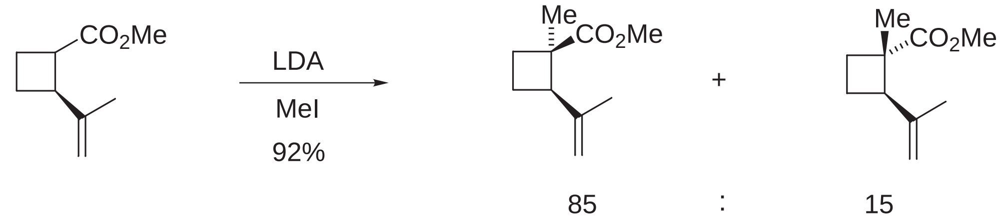


Hogg *J. Am. Chem. Soc.* **1948**, *70*, 161.

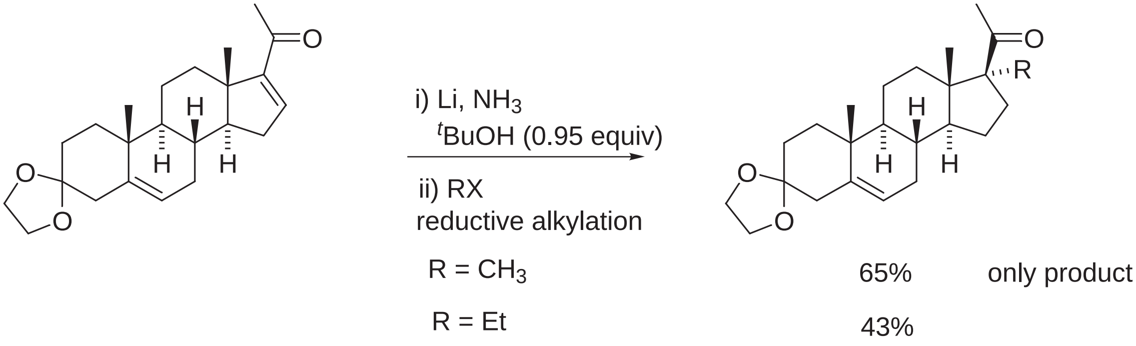
- Also true for other common ring sizes:



Heathcock *Tetrahedron Lett.* **1979**, 2115.

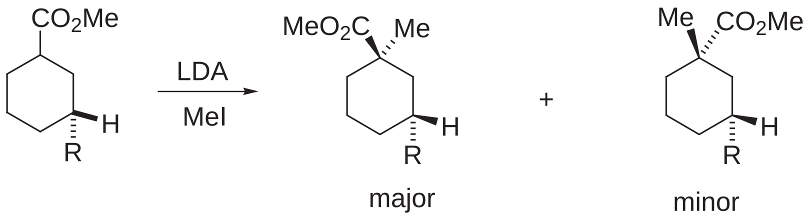


Clark *Syn. Commun.* **1979**, 325.



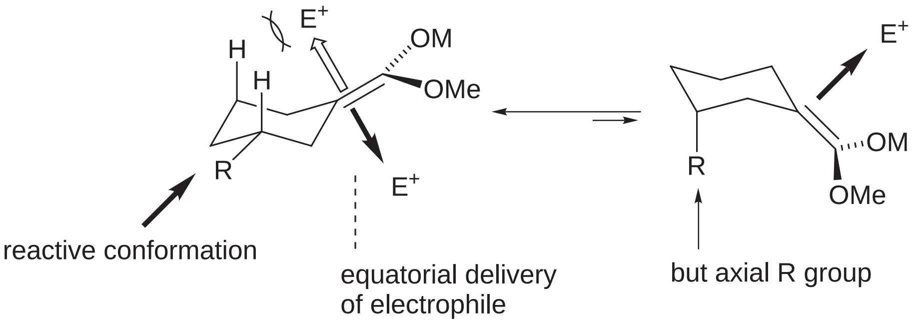
Weiss, Coscia *Tetrahedron* **1964**, *20*, 357.

ii. 1,3-Stereocontrol

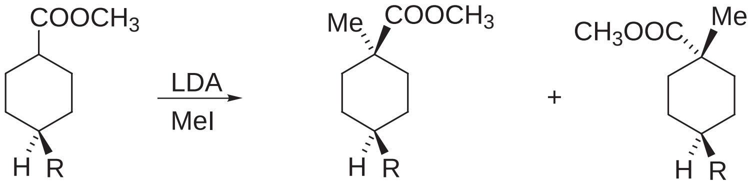


R = CH_3	90	:	10
R = OCH_3	78	:	22

Krapcho *J. Org. Chem.* **1980**, *45*, 3236.

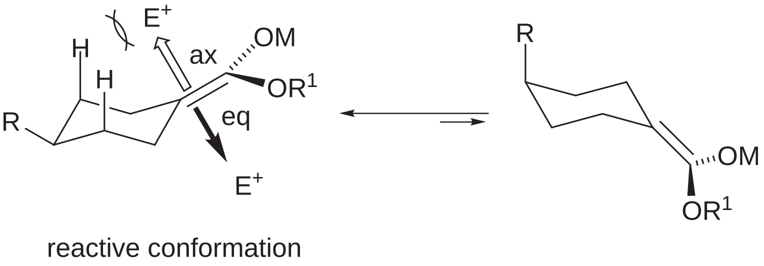


iii. 1,4-Stereocontrol



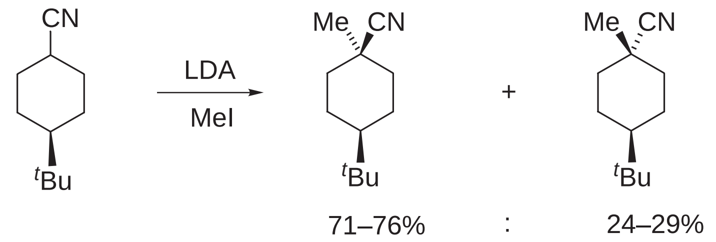
R = ^{t}Bu	84	:	16
OCH_3	84	:	16

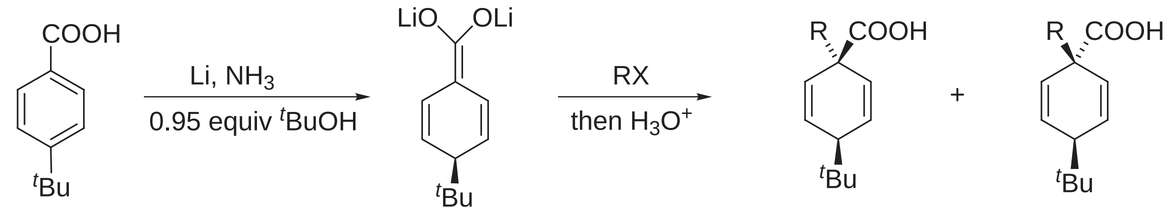
Krapcho *J. Org. Chem.* **1980**, *45*, 3236.



Again, equatorial attack predominates due to destabilizing steric interactions for axial approach of electrophile.

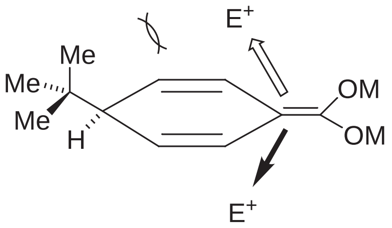
House *J. Org. Chem.* **1968**, *33*, 943.
Ziegler, Wender *J. Am. Chem. Soc.* **1971**, *93*, 4318.





Van Bekkum *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 137.

RX			
MeI	45	:	55
EtBr	88	:	12
^{i}PrBr	93	:	7

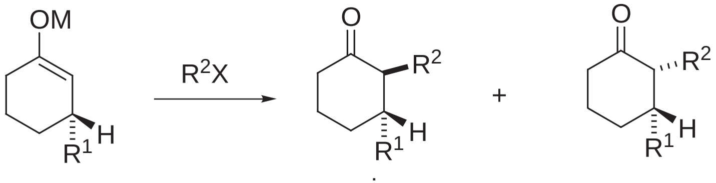


Surprising given the distance, but Schöllkopf subsequently put such observations to effective use.

Steric Effects? ← pronounced effect of size of alkylating agent on stereoselectivity.

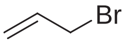
2. Endocyclic Enolates

a. 1,2-Stereocontrol

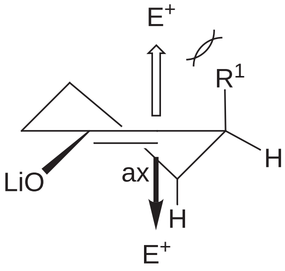


major

vinyl group sterically smaller, so stereoselectivity lower

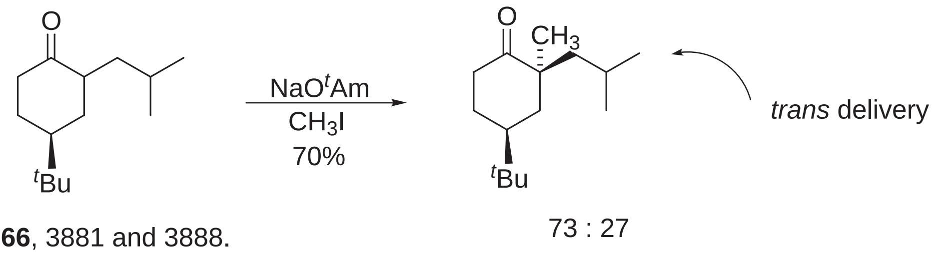
R^1	R^2X			
^{n}Bu	MeI	88	:	12
$CH=CH_2$	MeI	75	:	25
Me	 Br	89	:	11

Posner *J. Am. Chem. Soc.* **1975**, *97*, 107.
Coates *J. Org. Chem.* **1974**, *39*, 275.

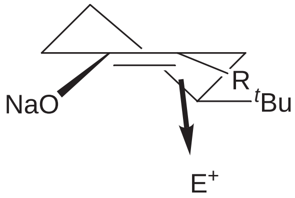


axial attack preferred on stereoelectronic and steric grounds

b. 1,3-Stereocontrol



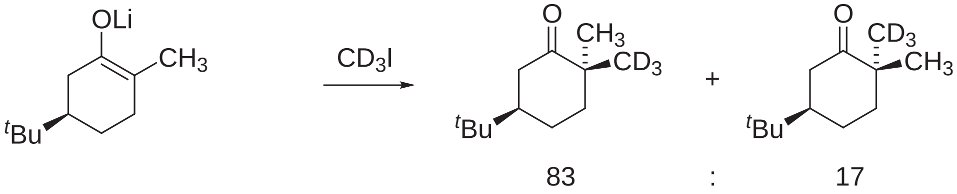
Conia *Bull. Soc. Chim., Fr.* **1966**, 3881 and 3888.



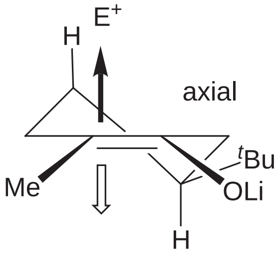
- ^{t}Bu group in preferred equatorial position

- axial attack favored on stereoelectronic basis
no steric bias for either face

c. 1,4-Stereocontrol

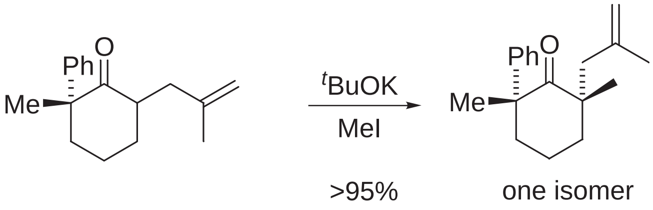


House *J. Org. Chem.* **1973**, *38*, 1000.

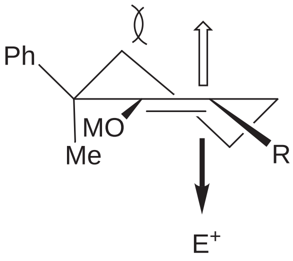


preferred stereoelectronic approach from most
stable conformation with ^{t}Bu equatorial

d. 1,5-Stereocontrol



Ireland *J. Org. Chem.* **1970**, *35*, 570.

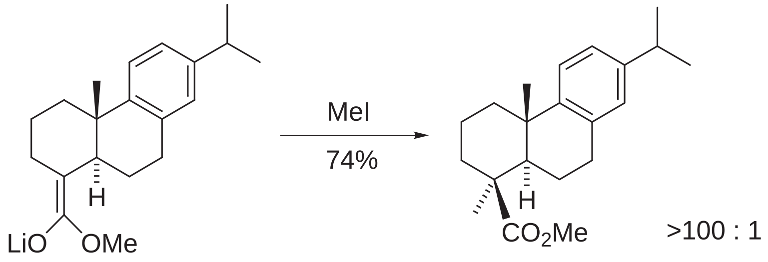


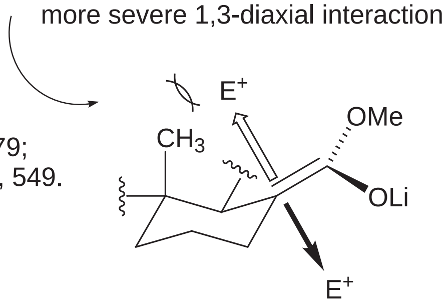
reaction from preferred conformation where
Me group vs Ph adopts pseudo axial position

preferred stereoelectronic approach

3. Other Conformationally Inflexible Systems

- Exocyclic Enolates of a Fixed Conformation

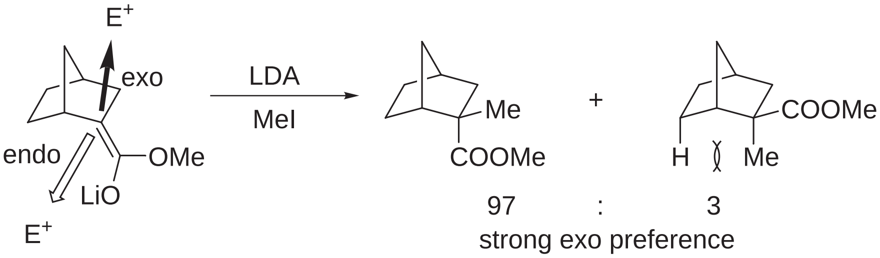




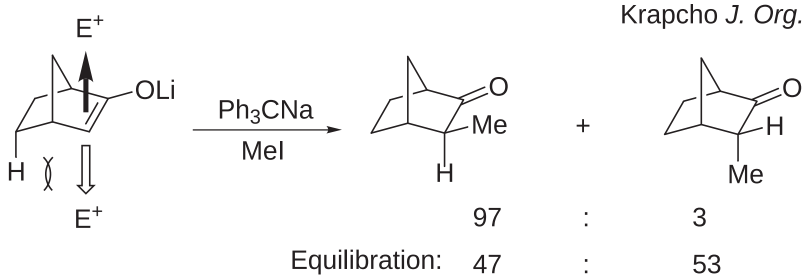
Welsch *J. Org. Chem.* **1977**, *42*, 2879;
J. Am. Chem. Soc. **1977**, *99*, 549.

This leads to a further enhancement of the preferred equatorial delivery of electrophile.

- Exocyclic Norbornanes

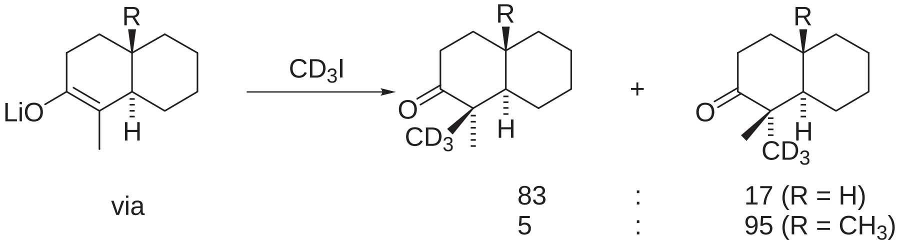


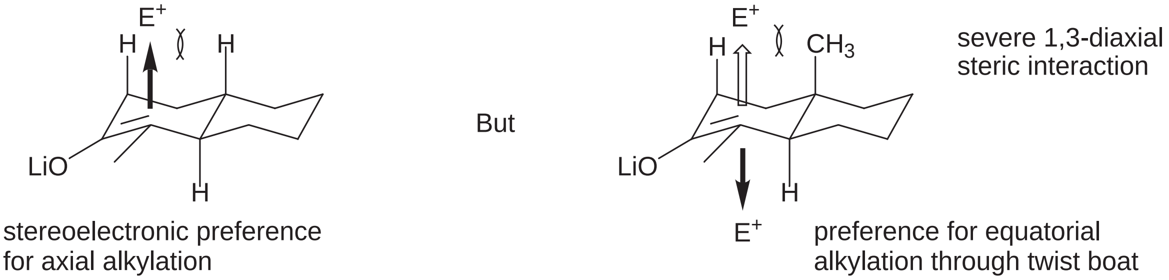
Krapcho *J. Org. Chem.* **1980**, *45*, 3236.



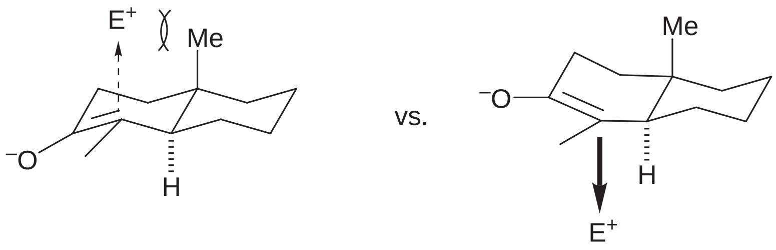
Corey *J. Am. Chem. Soc.* **1962**, *84*, 2611.

- Confined Endocyclic Enolates

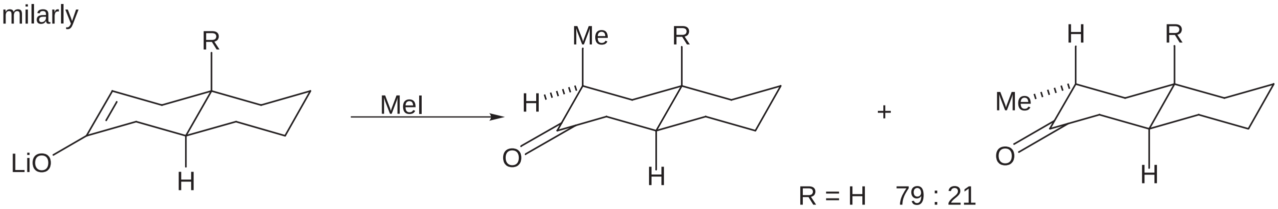




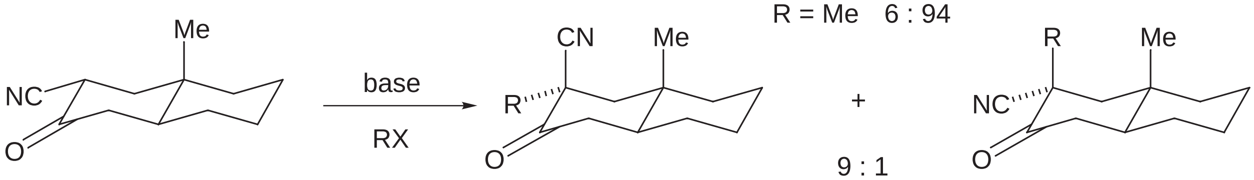
Matthews *J. Chem. Soc., Chem. Commun.* **1970**, 38 and 708.



- Similarly

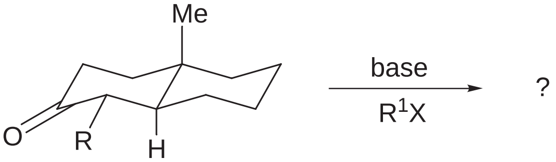


R = H 79 : 21
R = Me 6 : 94



Kuehne *J. Org. Chem.* **1970**, *35*, 161.

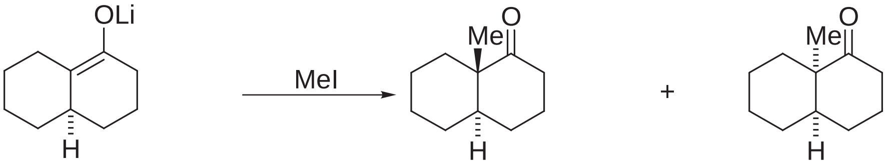
- Predict the major product for



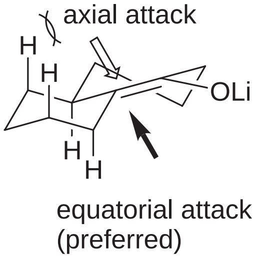
R = CN, CO_2Me

Kuehne *J. Org. Chem.* **1970**, *35*, 171.
Morris *J. Org. Chem.* **1972**, *37*, 789.

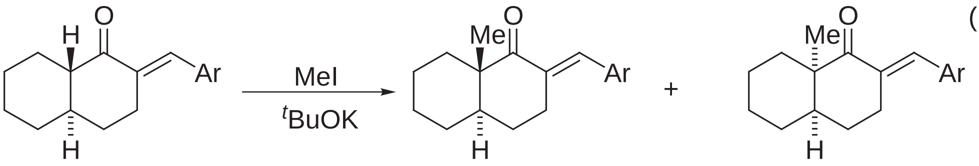
Stork *J. Am. Chem. Soc.* **1961**, *83*, 2965; **1965**, *87*, 275.



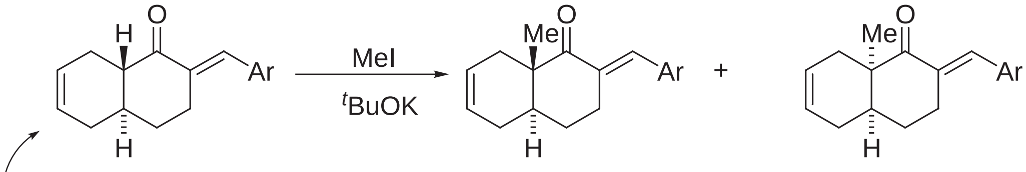
20 : 80



House, Trost *J. Org. Chem.* **1965**, *30*, 2502.



32 : 68

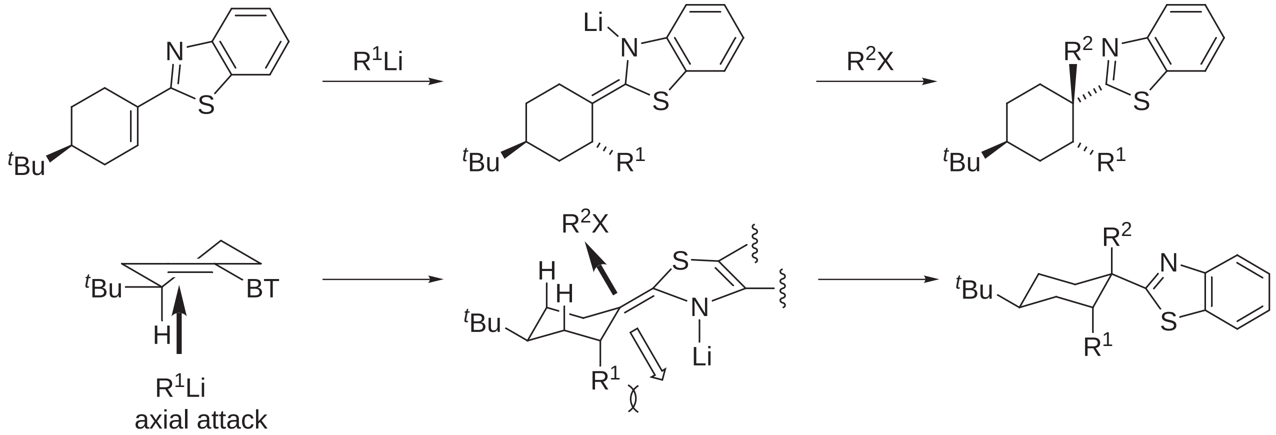


removes one 1,3-diaxial interaction for
axial alkylation through chair-like T.S.

90 : 10

4. Conjugate Addition/Alkylation: Stereochemistry

- There are also many examples of tandem conjugate addition/alkylation reactions and conjugate reduction/alkylation reactions that combine elements of both the conjugate addition or reduction with the subsequent alkylation.

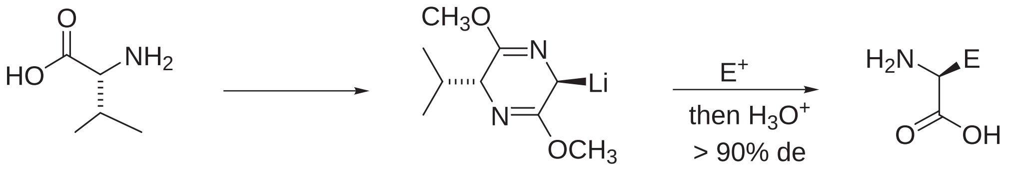


Corey and Boger *Tetrahedron Lett*. **1978**, 5, 9, and 13.

F. Asymmetric Alkylations

Conformational or Intraannular Chirality Transfer

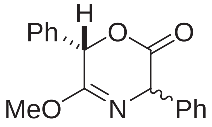
1. Schöllkopf asymmetric amino acid synthesis:



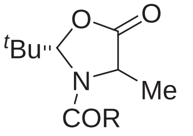
(*S*)-valine alkylation on face opposite ^{i}Pr group (1,4-stereocontrol)

Angew. Chem., Int. Ed. Eng. **1979**, *18*, 863; **1981**, *20*, 798 and 977.
Liebigs Ann. Chem. **1981**, 696 and 2407.
Synthesis **1981**, 966 and 969.

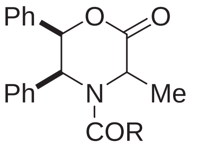
- Representative recent templates for asymmetric amino acid synthesis



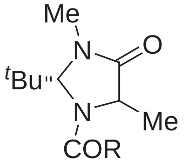
Schollkopf *Ann.* **1982**, 1952.



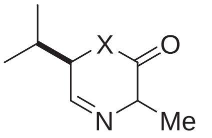
Spanton *J. Org. Chem.* **1990**, *55*, 5437.



Williams *J. Am. Chem. Soc.* **1991**, *113*, 9276.



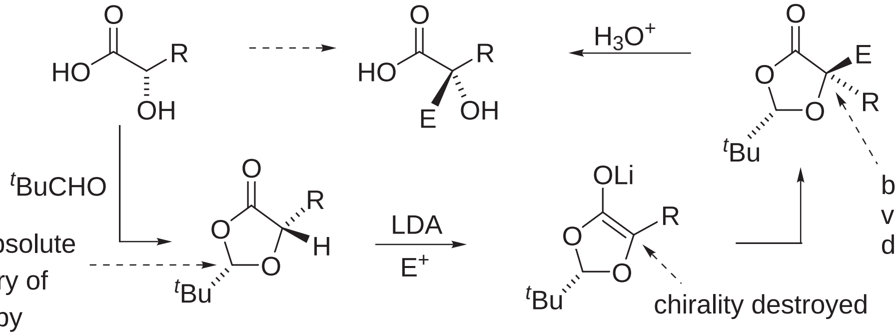
Seebach *Liebigs Ann.* **1995**, 217.



X = NBOC, O

Najera *J. Heterocyclic Chem.* **2000**, *37*, 467.

2. Seebach:



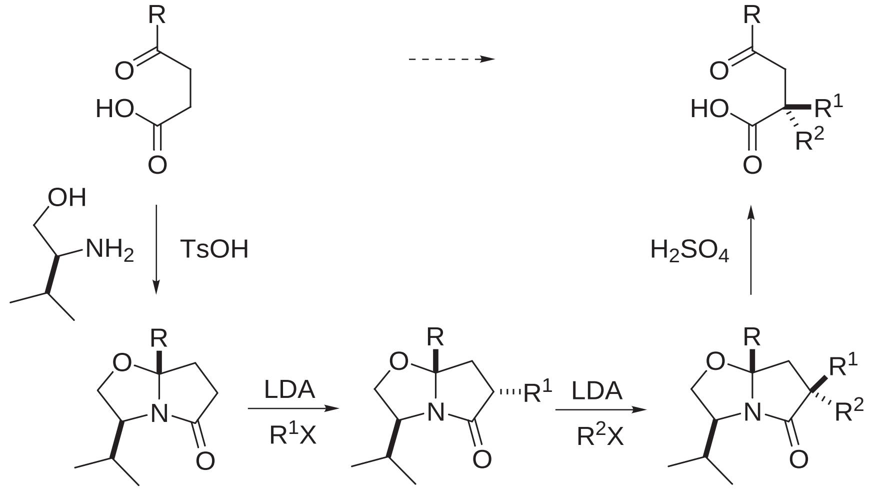
relative and absolute stereochemistry of ^{t}Bu group set by substrate and incorporation into 5-membered ring

chirality destroyed

but restored by virtue of alkylation diastereoselectively

Seebach *J. Am. Chem. Soc.* **1983**, *105*, 5390.
Fráter *Tetrahedron Lett.* **1981**, *22*, 4221.

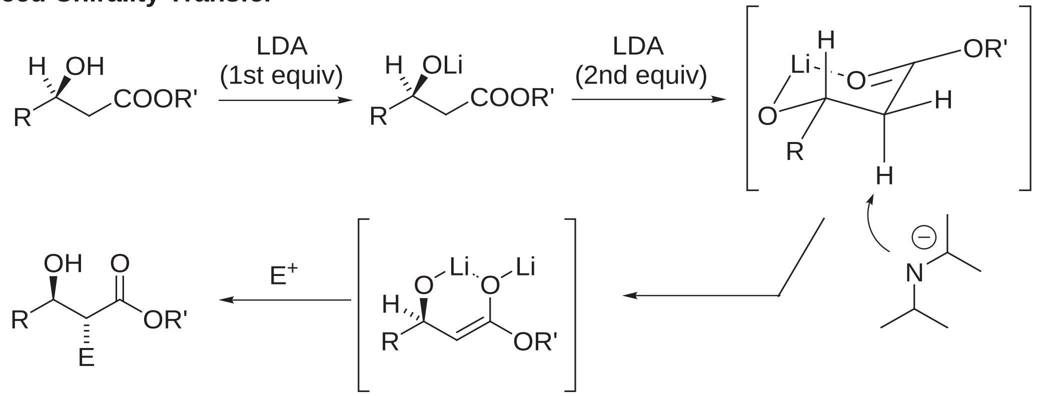
3. Meyers:

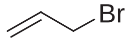


Meyers *J. Am. Chem. Soc.* **1984**, *106*, 1146; *J. Org. Chem.* **1989**, *54*, 2509.

Chelation Enforced Chirality Transfer

4.



E+ =  Br 96 : 4

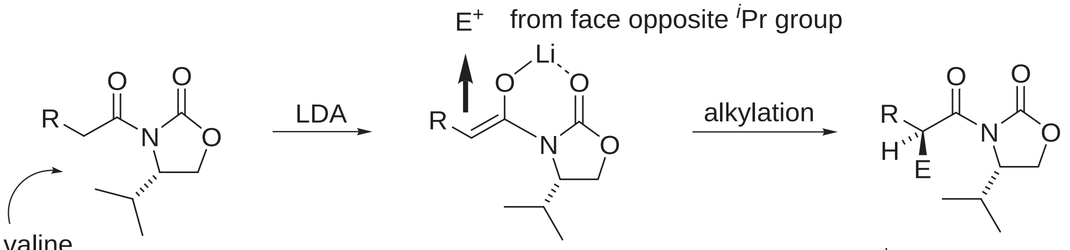
= ^{n}BuBr 97 : 3

Z-enolate (note that normally get *E*-enolate from esters) ← removal of axial proton (much more sterically accessible)

Seebach *Angew. Chem., Int. Ed. Eng.* **1981**, *20*, 971.
Helv. Chim. Acta **1980**, *63*, 197, 2005.
Fráter *Tetrahedron Lett.* **1981**, *22*, 425.
Helv. Chim. Acta **1979**, *62*, 2825 and 2829; **1980**, *63*, 1383.
Kraus *Tetrahedron Lett.* **1977**, *18*, 4575.

5. Evans' chiral imide auxiliaries: *J. Am. Chem. Soc.* **1982**, *104*, 1737.

N-acyl oxazolidinones

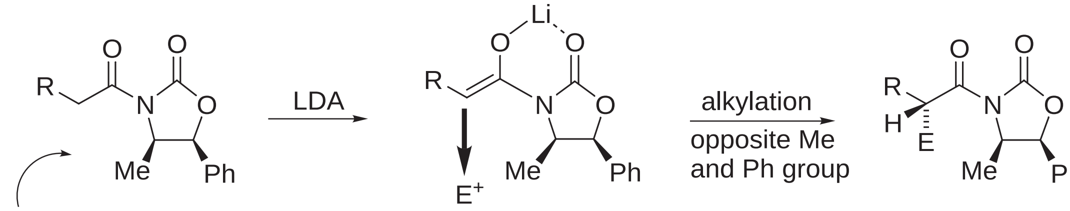


from valine

Z-enolate

E+ = BnBr, 120 : 1

- and



from norephedrine

Z-enolate

Access to either enantiomer ⟸ new chiral centers created which have opposite absolute configuration.

- Factors responsible for high diastereoselectivity:
  - a. exclusive formation of *Z*-enolate.
  - b. chelation results in formation of rigid template, single conformation.
  - c. π-facial selectivity results from sterics of alkylation.

Other electrophiles beyond RX may be employed

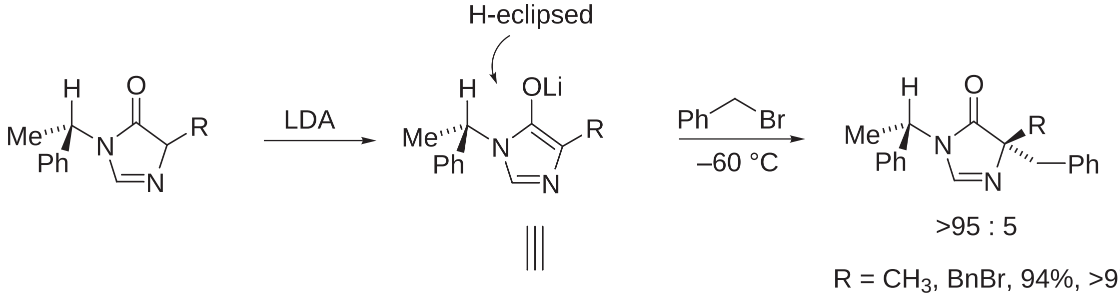
alcohols

$ArSO_2N_3$ → azides

NBS → bromides

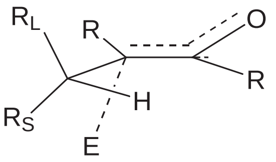
Extraannular Chirality Transfer

6. Schöllkopf *Liebigs Ann. Chem.* **1981**, 439.



R = CH_3, BnBr, 94%, >97 : 3
R = Et, BnBr, 85%, 97.5 : 2.5

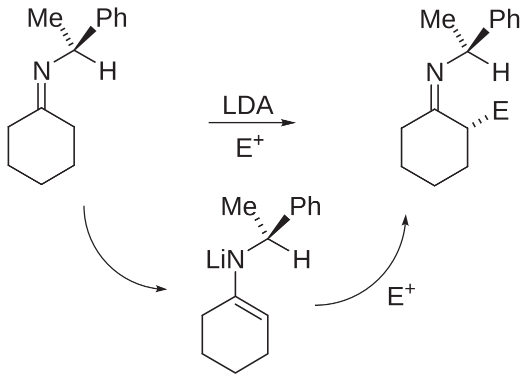
	R_S	R_L	(E^+ = D_2O)
	Me	OEt	10 : 1
Stereoelectronic →	Me	OPh	10 : 1
Steric →	Me	^{t}Bu	9 : 1
	Me	O^{t}Bu	8 : 1
	Me	S^{t}Bu	7.5 : 1
	Me	OMe	7 : 1
	Me	CF_3	5 : 1
	Me	Ph	3 : 1
	Me	^{i}Pr	2.3 : 1
	Me	Et	1.4 : 1



with control of enolate geometry available, reaction via H-eclipsed conformation might be facially selective. To date, this has not been extensively examined with acyclic systems.

See: Mohrig *J. Am. Chem. Soc.* **1997**, *119*, 479.

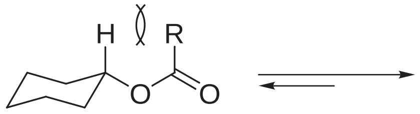
7. Fraser *Tetrahedron Lett.* **1979**, *20*, 3929.



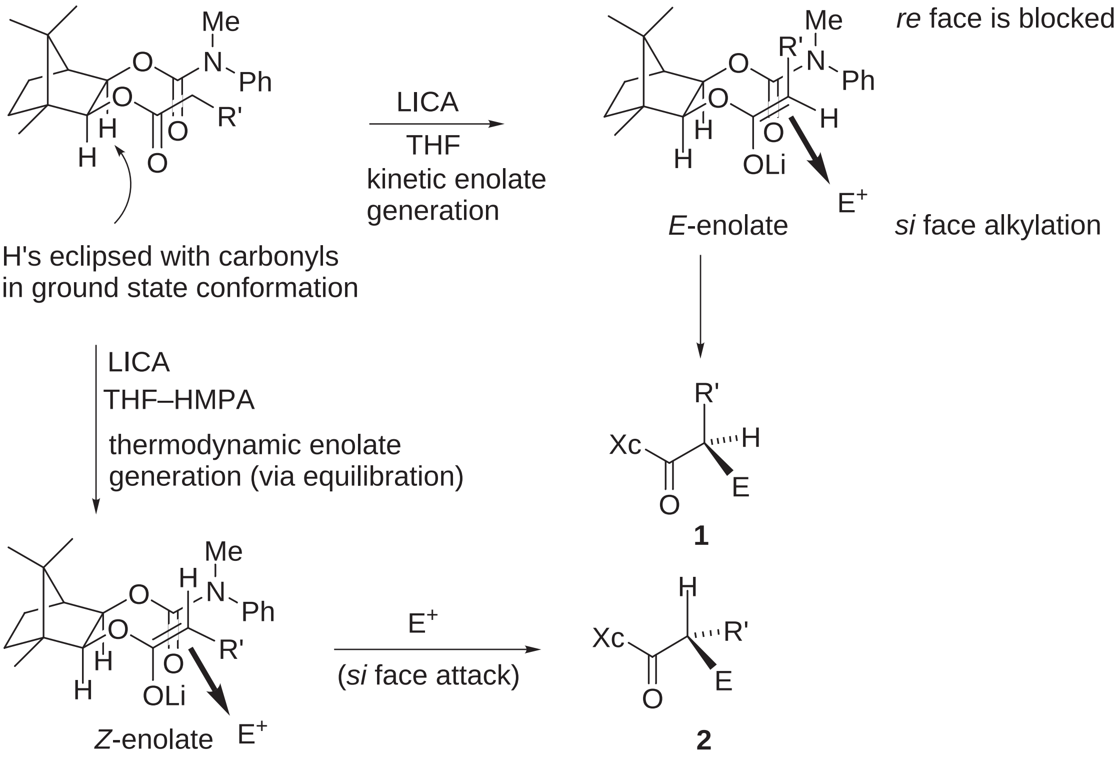
E^+ = MeI, 3.2 : 1

Through Space Interactions/Blocking Groups

8.



with certain esters of chiral alcohols, could see enantioselectivity via conformational control ⇐ H and carbonyl are eclipsed in much preferred conformation



H's eclipsed with carbonyls in ground state conformation

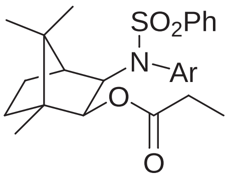
1

2

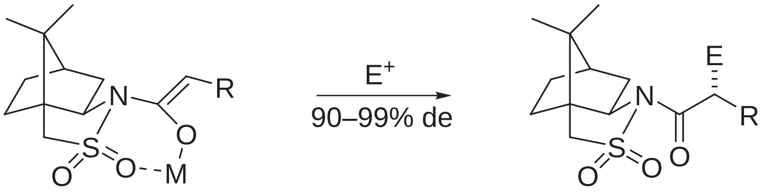
R'	solvent	E^+	**1** : **2**	yield
CH_2Ph	THF	MeI	95 : 5	95%
Me	THF	BnBr	94 : 6	96%
Me	THF–HMPA	BnBr	30 : 70	96%

lower diastereoselectivity due to inability to generate exclusively the *Z*-enolate (70:30 = *Z* : *E* formed)

Helmchen *Angew. Chem., Int. Ed. Eng.* **1981**, *20*, 207.
Tetrahedron Lett. **1980**, *21*, 1137; **1983**, *24*, 3213.

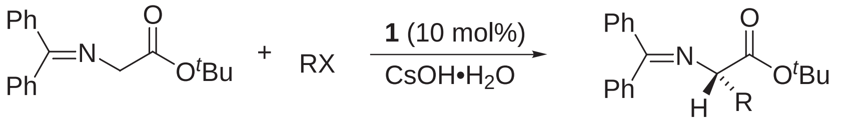


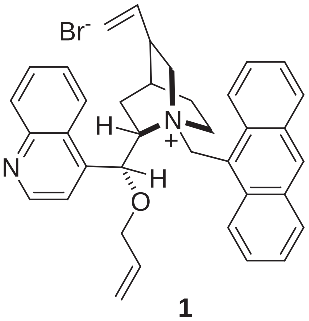
Helmchen



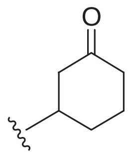
Oppolzer *Tetrahedron Lett.* **1989**, *30*, 5603 and 6009.

9. Catalytic asymmetric alkylation: Corey *Tetrahedron Lett.* **1998**, *39*, 5347.



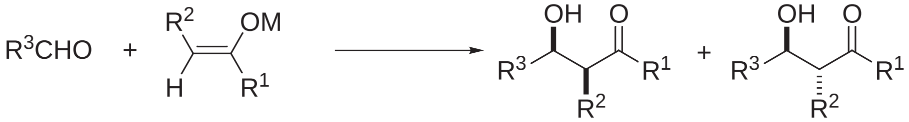


1

R =	-$(CH_2)_4Cl$	-$(CH_2)_2CO_2CH_3$		-$(CH_2)_2COEt$
ee (%)	99	95	99	91

Additional examples of asymmetric alkylations may be found in the sections discussing enolate equivalents.

G. Aldol Addition (Condensation)



First report: Wurtz *Bull. Soc. Chim. Fr.* **1872**, *17*, 436.

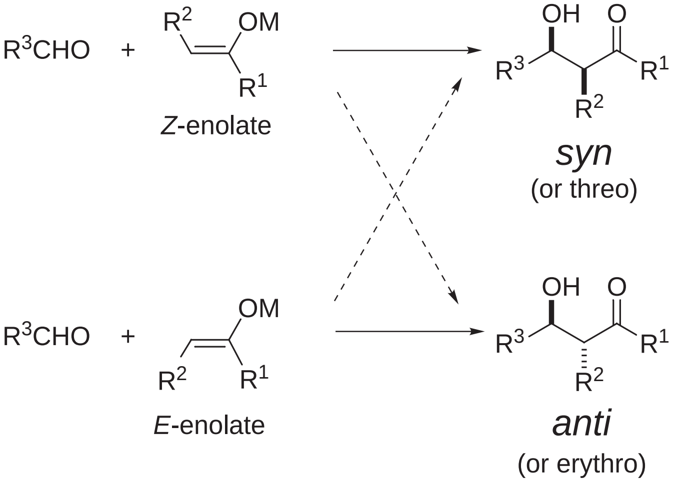
syn
(or threo)

anti
(or erythro)

1. Nomenclature

syn/*anti*	*J. Am. Chem. Soc.* **1981**, *103*, 2106. (supercedes erythro/threo nomenclature)
erythro/threo	*Angew. Chem., Int. Ed. Eng.* **1980**, *19*, 557.
Summary	*Asymm. Synth*. Vol. 3, pp 111–212. (Review of aldol diastereoselection)
IUPAC	*Pure Appl. Chem.* **1976**, *45*, 11.
Others	*Angew. Chem., Int. Ed. Eng.* **1966**, *5*, 385. (Cahn, Ingold, Prelog)
	Angew. Chem., Int. Ed. Eng. **1982**, *21*, 654. (Seebach, Prelog)
	J. Org. Chem. **1982**, *47*, 3811. (Carey, Kuehne)

2. Generalizations



1. *Z*-enolates give predominantly *syn* (or threo) aldol products (thermodynamic enolates).
2. *E*-enolates give predominantly *anti* (or erythro) aldol products (kinetic enolates).

and

3. Diastereoselectivity (for *syn* aldol) of *Z*-enolates is greater than that of *E*-enolates (for *anti*).
4. Correlation for *E* or *Z*-enolate is greater when R^1 is sterically demanding.
5. Correlation is stronger when R^3 is large (most important for boron enolates).
6. Correlation is reversed when R^2 is sterically demanding (very large).

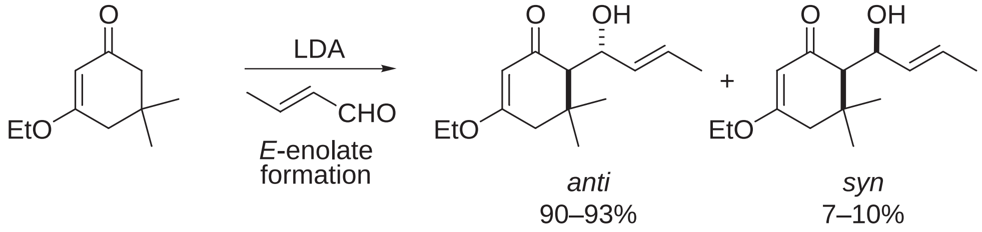
- Advances in ^{1}H NMR, ^{13}C NMR permitted detection, quantification and identification.
- Issue of equilibration addressed.

Francis W. Aston was awarded the 1922 Nobel Prize in Chemistry for his contributions to analytical chemistry and the study of atomic structure. He is primarily associated with the design and use of the mass spectrometer.

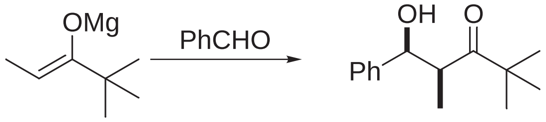
Fritz Pregl received the 1923 Nobel Prize in Chemistry for his development of microanalytical techniques (accurate microbalance weighing of 1 μg–20 g) and for refinements in characterizing organic compounds (CHNSX analysis).

R. R. Ernst received the 1991 Nobel Prize in Chemistry for the development of the methodology of high resolution NMR spectroscopy.

3. Examples



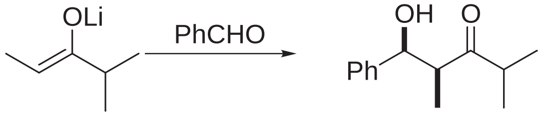
- Steric size of R^1 affects diastereoselectivity



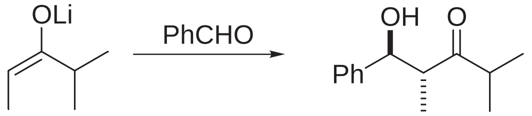
syn:*anti* >98:2

note: R^1 = ^{t}Bu > ^{i}Pr

- *Z*-enolate

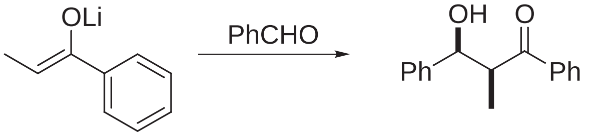


syn:*anti* 90:10



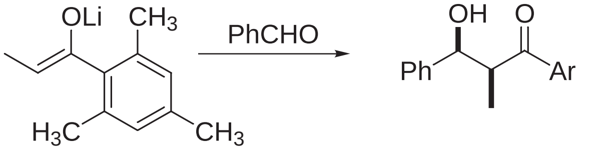
syn:*anti* 45:55

note: *Z* > *E*, stereoselectivity much lower with *E*-enolate



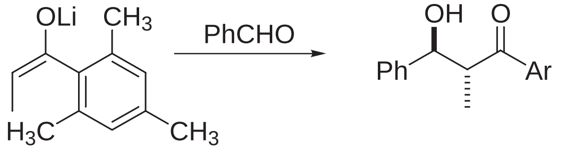
> 98:2 *Z*:*E*

syn:*anti* 88:12



87:13 *Z*:*E*

syn:*anti* 88:12



92:8 *E*:*Z*

anti:syn 92:8

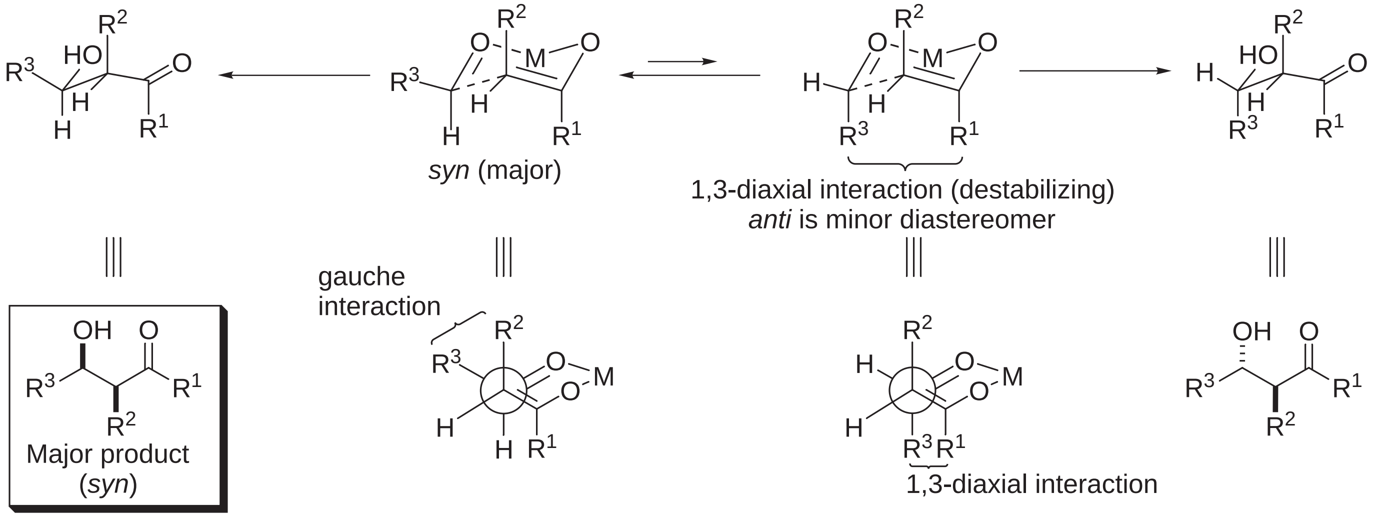
note: larger R^1 helps maintain high selectivity dictated by enolate geometry and substantially enhances *E*-enolate diastereoselectivity

Heathcock *J. Org. Chem.* **1980**, *45*, 1066.

4. Origin of Diastereoselectivity

- Zimmerman–Traxler Model (*J. Am. Chem. Soc*. **1957**, *79*, 1920)
- Chair-like, closed transition state: metal coordination to both carbonyls

a. *Z*-enolates



1. Diastereoselectivity for Z-enolate (giving *syn* aldol product) is maximized when R^1 and R^3 are sterically demanding (R^1/R^3 interaction is maximized).
2. Diastereoselectivity also increases as metal is changed to boron. This is attritubted to a tighter T.S. (B–O bond shorter, so R^1/R^3 steric interactions are magnified in T.S. for *anti* product).
3. When R^2 is very large the R^3/R^2 gauche interaction > R^1/R^3 1,3-diaxial interaction (Why?).

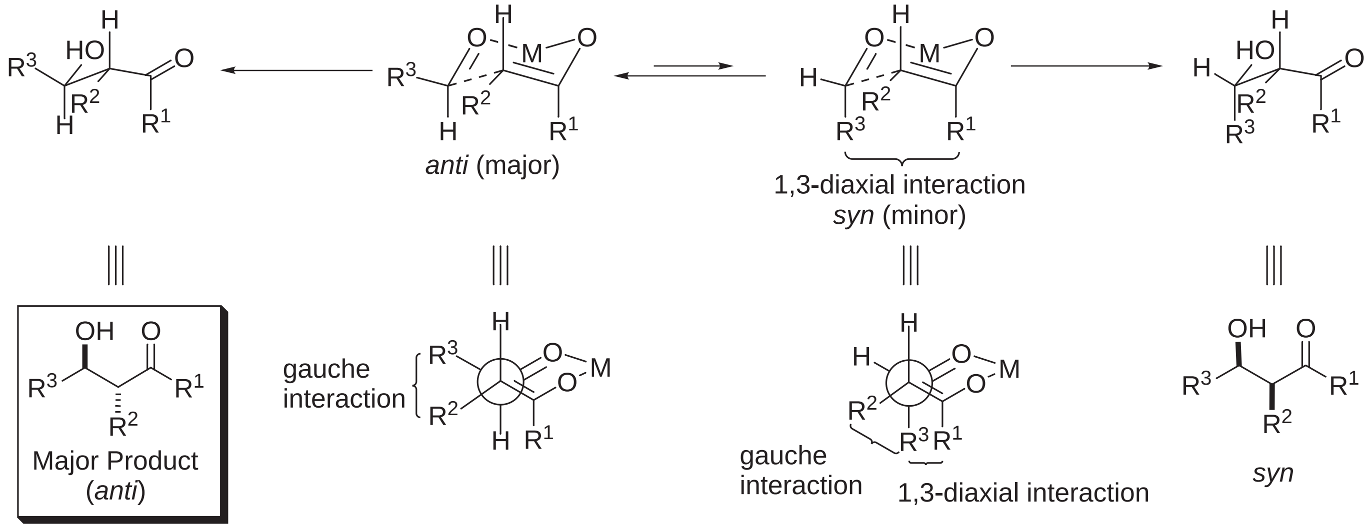
Li–O	1.92–2.00 Å
Mg–O	2.01–2.03 Å
Zn–O	1.92–2.16 Å
Al–O	1.92 Å
B–O	**1.36–1.47 Å**
Ti–O	1.62–1.73 Å
Zr–O	2.15 Å

⇐

Diastereoselection:

B > Li > Na > K

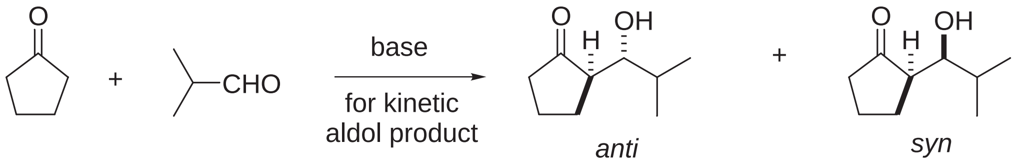
b. *E*-enolates



1. Diastereoselectivity increases as R^1 and R^3 become sterically large, and a switch to the boron enolate will increase selectivity.
2. Diastereoselectivity may switch when R^2 is very large (Why?).

5. Cyclic Ketones

- Only *E*-enolate and therefore *anti* aldol.
- Aldol addition is reversible, can get very different selectivity by allowing reaction products to equilibrate (and equilibration can be very fast).

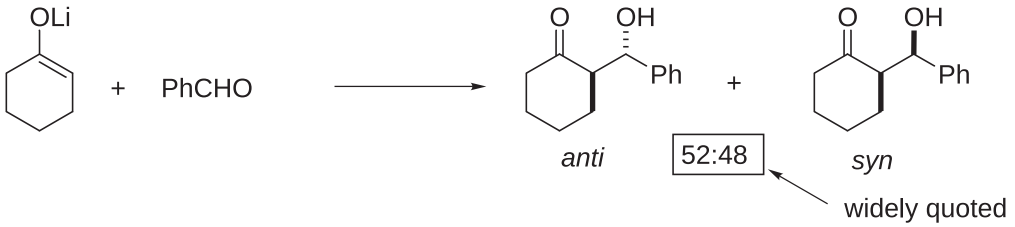


(stabilization of adduct via coordinating countercation)

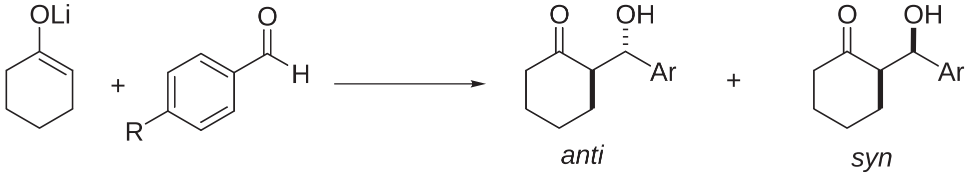
Dubois:

base	*anti*:*syn*	
LiOH	>95:5	
KOH	>95:5	
$Me_4N^+OH^-$	30:70	← thermodynamic ratio

- Instructive examples:
  Majewski *Tetrahedron Lett.* **1989**, *30*, 5681.
  House *J. Am. Chem. Soc.* **1973**, *95*, 3310.
  Heathcock *J. Org. Chem.* **1980**, *45*, 1066.

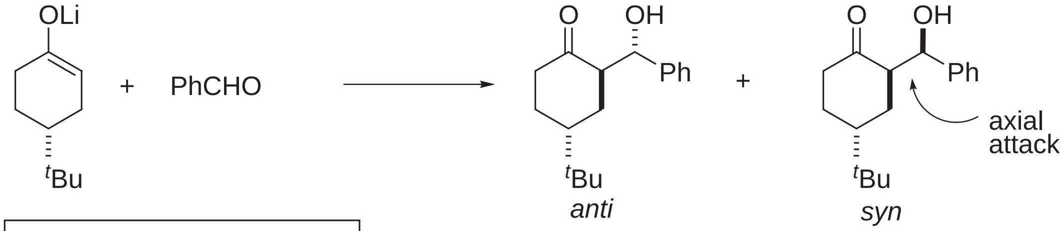


- but really is the result of equilibration: *Tetrahedron Lett.* **1989**, *30*, 5681.



THF > DME

R	solvent	*anti*	:	*syn*	yield
R = H	THF	84	:	16	75%
	DME	72	:	28	50%
	Et_2O	76	:	24	84%
R = NMe_2	THF	73	:	27	68%
R = OCH_3	THF	78	:	28	68%
R = Ph	THF	94	:	6	67%
R = CF_3	THF	74	:	26	80%

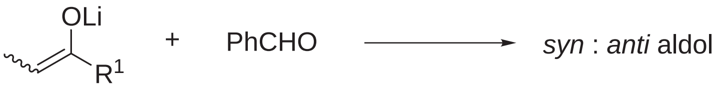


1. *E*-enolate -> *anti* aldol.
2. Axial attack of enolate (stereoelectronic control).

solvent	*anti*	:	*syn*	yield
THF	81	:	19	63%
Et_2O	75	:	25	61%
Et_2O–HMPA	68	:	32	68%

6. Acyclic Enolates

- Effect of R^1



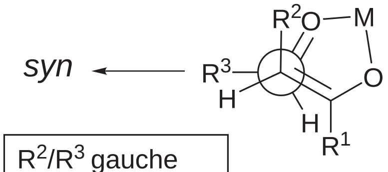
	***syn* : *anti* ratio**	
R^1	*Z*-enolate	*E*-enolate
OMe	–	1.5
O^{t}Bu	–	1.0
H	1.0	1.5
Et	9.0	1.5
^{i}Pr	9.0	1.0
Ph	7	–
^{t}Bu	70	–
mesityl	>50	<0.02

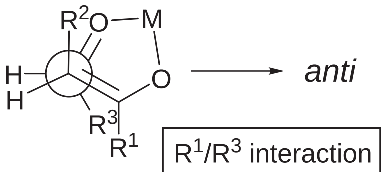
typically:
Z > *E* diastereoselection

diastereoselection increases as size of R^1 increases

7. Refined and Alternative Models

- Idealized closed, chair transition state does not account for *Z* > *E* diastereoselectivity nor does it explain the switch in diastereoselectivity when R^2 is sterically demanding.
- It has been suggested that the transition state for addition more closely resembles an eclipsed conformation.
- Dubois, Fellmann *Tetrahedron Lett.* **1975**, 1225; *Tetrahedron* **1978**, *34*, 1349.
- Heathcock *J. Org. Chem.* **1980**, *45*, 1066.
- For *Z*-enolate

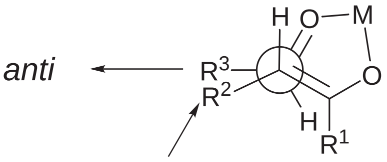


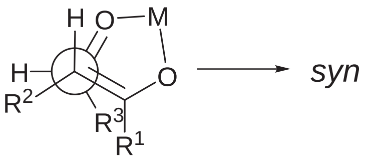


R^2/R^3 gauche interaction is further minimized

R^1/R^3 interaction even worse than in staggered ⇒ *Z* > *E* diastereoselectivity

- For *E*-enolate

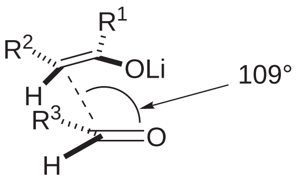




nearly eclipsed
much worse than gauche interaction
As R^2 increases in size, R^2/R^3 interaction competes with or surpasses R^1/R^3 interaction

⟹ *E* < *Z* diastereoselectivity
diastereoselectivity reverses when R^2 becomes sterically demanding

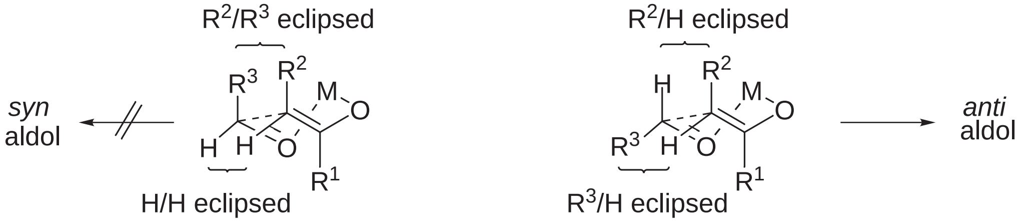
- Burgi–Dunitz approach angle -skewed approach where R^2/R^3 come closer together than R^1/R^3



- An additional alternative explanation considers the boat transition states Evans *Top. Stereochem.* **1982**, *13*, 1.

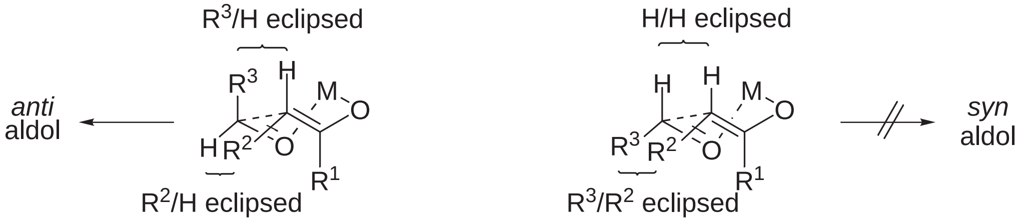
- In addition to the four idealized closed chair transition states, four closed boat transition states must be considered as well.

- *Z*-enolate



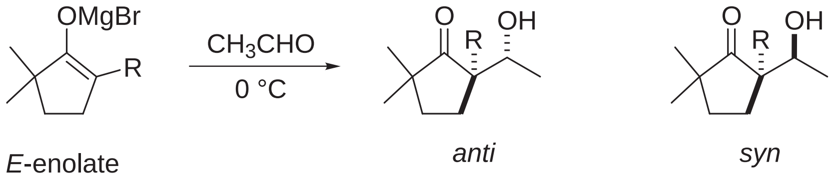
- when the R^2/R^3 gauche interaction is large in chair TS, *Z*-enolate boat TS might become competitive leading to the *anti* aldol

- *E*-enolate



- However, the boat transition state alternative does not explain the *E*-enolate switch from *anti* to *syn* aldol when R^2 becomes sterically more demanding.

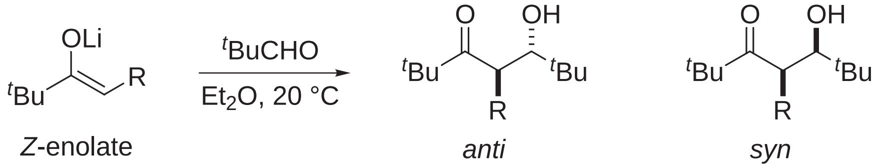
- Examples



Dubois, Fellmann *C. R. Hebd. Seances Acad. Sci. Ser. C.* **1972**, *274*, 1307.

R	anti		syn
= Me	93.5	:	6.5
= Et	87.5	:	12.5
= ^{i}Bu	80	:	20
= ^{i}Pr	46	:	54
= ^{t}Bu	29	:	71

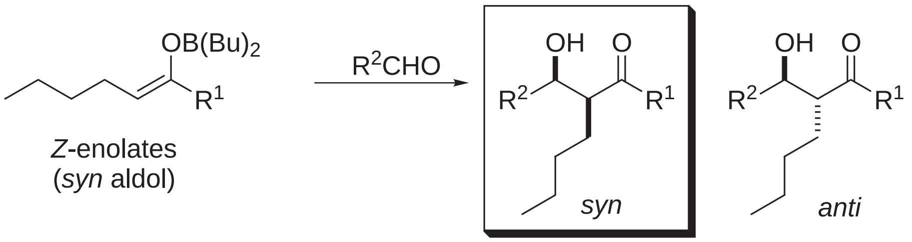
anti:syn ratio decreases smoothly as R becomes larger (R^2 in models above)



R	anti		syn
= Me	0	:	100
= Et	0	:	100
= ^{n}Pr	2	:	98
= ^{i}Bu	3	:	97
= ^{i}Pr	71	:	29
= ^{t}Bu	100	:	0

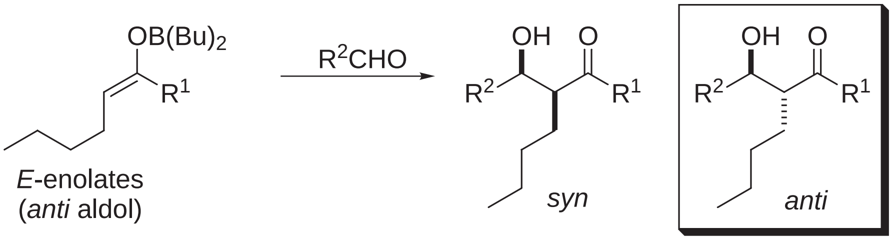
8. Boron Enolates

- Often much more diastereoselective in their aldol addition reactions
- This results from a shorter B–O bond length, tighter transition state



R^1 = Me R^2 = Ph
R^1 = PhCH$_2$ R^2 = Ph
R^1 = Ph R^2 = Ph
R^1 = Ph R^2 = Et
R^1 = Ph R^2 = ^{i}Pr

>95:5 for all cases



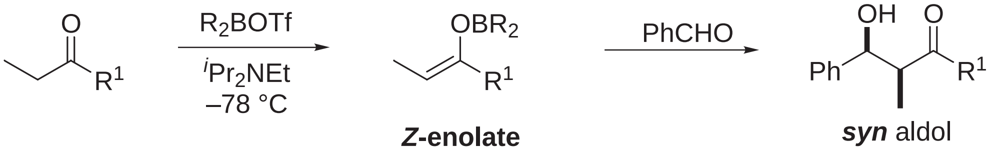
R^1 = Me	R^2 = Ph	25:75
R^1 = PhCH$_2$	R^2 = Ph	20:80
R^1 = Ph	R^2 = Ph	25:75

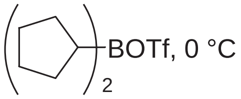
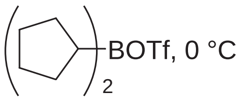
Z > *E* diastereoselection

E-enolates give
lower diastereoselectivity

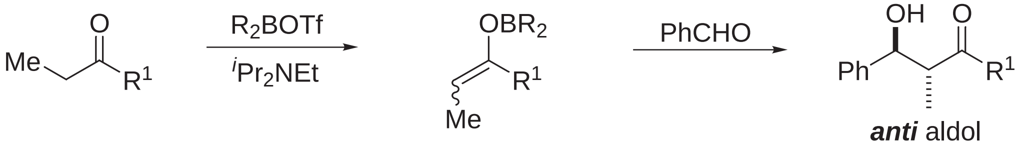
Masamune *Tetrahedron Lett.* **1979**, 1665.

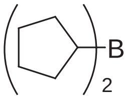
a. *Z*-enolate Preparation and Reactions



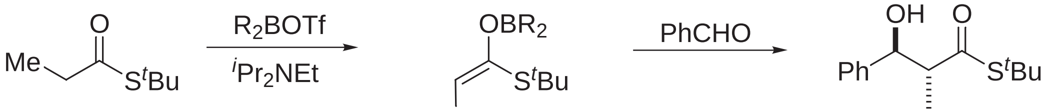
R^1 = Et	Bu$_2$BOTf, –78 °C	>97:3	>97:3 *syn*/*anti*
R^1 = Et		82:18	84:16 *syn*/*anti*
R^1 = Ph	9-BBNOTf, 0 °C	>95:5	>97:3 *syn*/*anti*
R^1 = Ph		>99:1	>95:5 *syn*/*anti*

b. *E*-enolate Preparation and Reactions

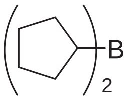


$R^1 = {}^iPr$	Bu_2BOTf, –78 °C	45:55 *Z*:*E*	44:56 *syn*/*anti*
$R^1 = {}^iPr$	 BOTf, 0 °C	19:81 *Z*:*E*	18:82 *syn*/*anti*

- originally difficult to control but:

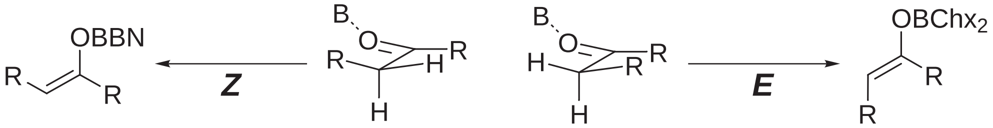


Masamune *Tetrahedron Lett.* **1979**, 2225.

Bu_2BOTf, 0 °C	>95:5	10:90 *syn*/*anti*
 BOTf, 0 °C	>95:5	5:95 *syn*/*anti*

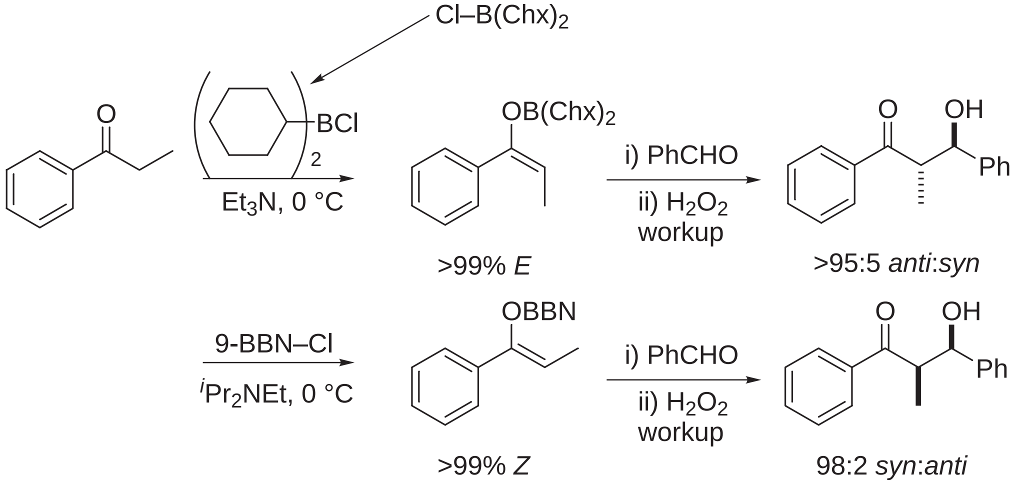
E-enolates very accessible using ^{t}butylthiol esters

c. Examples of more recent methods to control boron enolate geometry



9-BBN–Cl/ ^{i}Pr_2NEt (hindered base)
Z-enolate
thermodynamic enolate
E1 elimination mechanism

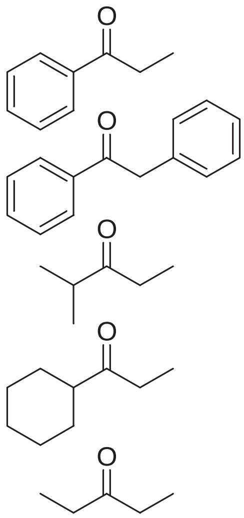
$Cl–B(Chx)_2/Et_3N$
E-enolate
kinetic enolate
E2 elimination mechanism

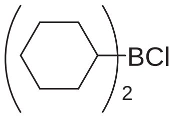


-These results are difficult to achieve with boron triflates

Brown *J. Am. Chem. Soc.* **1989**, *111*, 3441.

- Examples

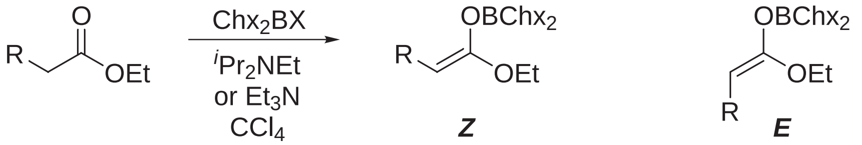


9-BBN–Cl	
99:1 (*Z*:*E*)	<1:99 (*Z*:*E*)
>99:1	15:85
98:2 (via equilibration)	<1:99
96:4 (via equilibration)	<1:99
99:1 (via equilibration)	21:79

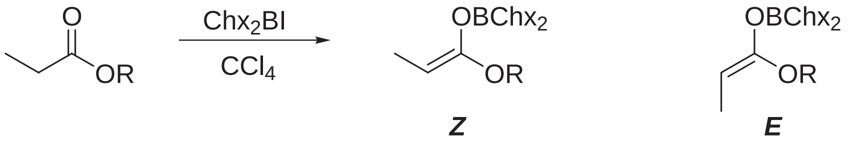
> *Z*-enolate is easy to access: thermodynamic enolate
> *E*-enolate is less stable, more difficult to generate without equilibration (also still difficult to prepare unless alkyl groups are bulky).

- see also Brown *J. Org. Chem.* **1992**, *57*, 499 and 2716.

Brown *J. Org. Chem.* **1994**, *59*, 2336.



R = CH_3	X = I	>97	:	3
R = CH_3	X = Br	84	:	17
R = Et	X = I	95	:	5
R = ^{i}Pr	X = I	<3	:	>97
R = ^{t}Bu	X = I	<3	:	>97
R = Ph	X = I	<3	:	>97

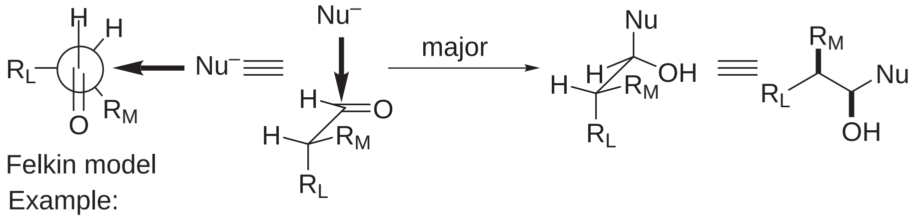


R = CH_3	Et_3N	>97	:	<3
	${}^iPr_2NEt$	>97	:	<3
R = Et	Et_3N	>97	:	<3
	${}^iPr_2NEt$	>97	:	<3
R = ^{i}Pr	Et_3N	86	:	14
	${}^iPr_2NEt$	64	:	36
R = ^{t}Bu	Et_3N	59	:	41
	${}^iPr_2NEt$	3	:	97

9. Aldol Condensation with Chiral Aldehydes

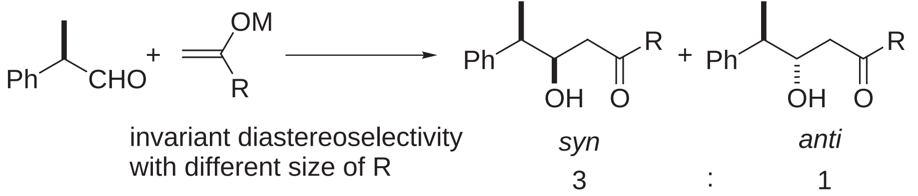
a. Felkin Addition

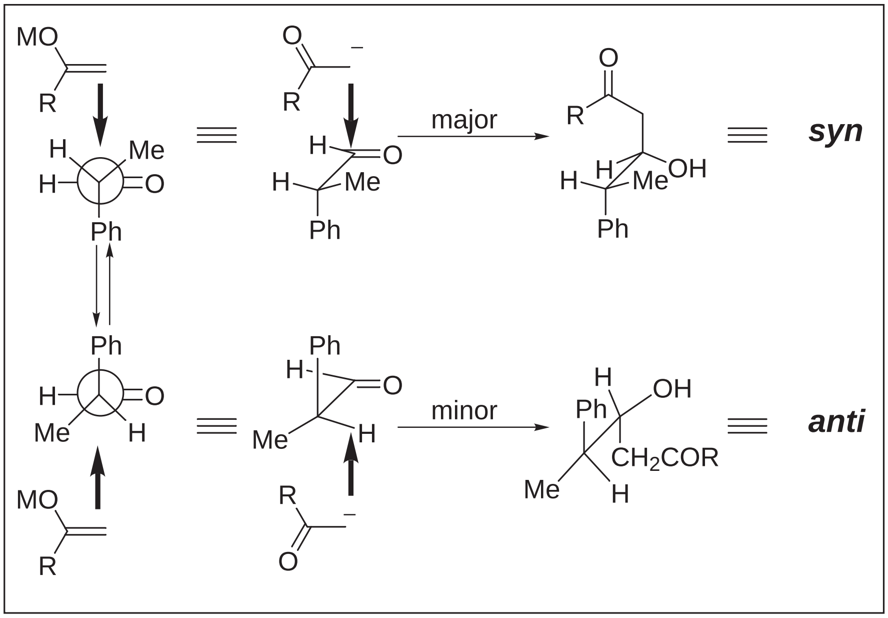
- Two faces of aldehyde are diastereotopic.
- Nucleophilic addition of enolate follows Cram's empirical generalization (Felkin–Anh addition).



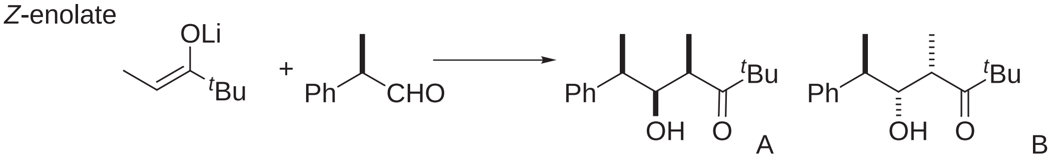
Felkin model

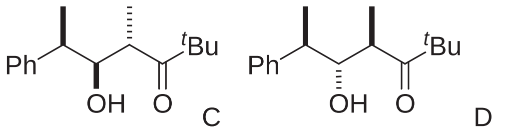
- Example:





- Can combine all selectivities to give 3 contiguous chiral centers, if the chiral aldehyde and enolate partners are both highly diastereoselective.





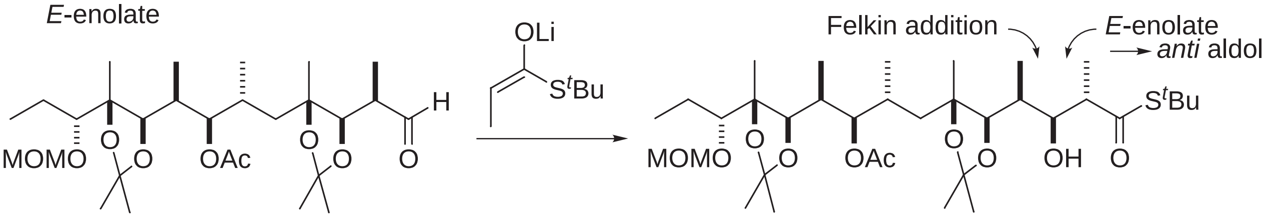
- A & B represent 2,3 *syn* products
  (from *Z*-enolate with large R group)

- A & C represent 3,4 *syn* products
  (from Cram/Felkin–Anh addition to aldehyde)

experimental: A:B:C:D = 86:14:0:0

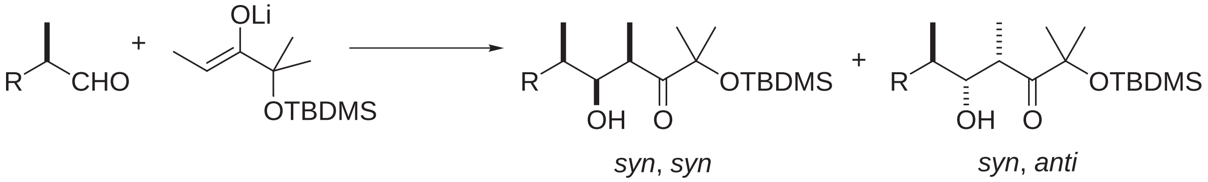
Heathcock *J. Org. Chem.* **1980**, *45*, 1066.

- *syn* aldol reaction proceeds with >98% *syn* selectivity
- Cram/Felkin–Anh addition proceeds with 86:14 *syn* selectivity



Woodward *J. Am. Chem. Soc.* **1981**, *103*, 3210, 3213, 3215. ⟹ erythromycin

b. Chelation Control



R = Ph 81 : 19

Z-enolate (with large R group) gives clean *syn* aldol product for both.

>98% *syn* aldol, 81:19 Cram addition

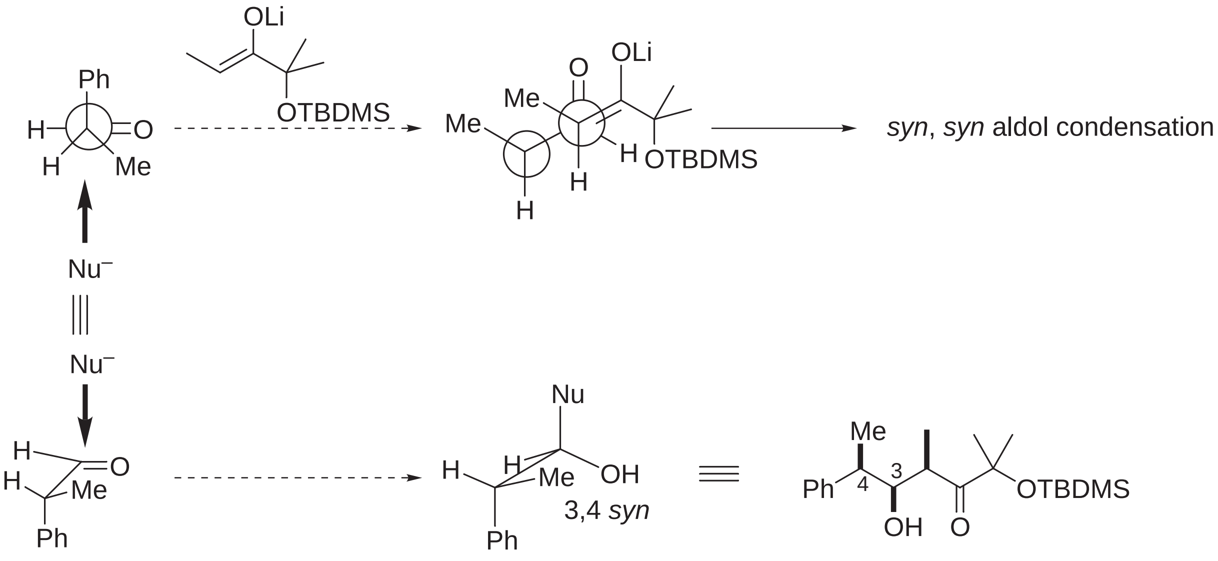
R = $CH_2OTBDMS$ 21 : 79

>98% *syn* aldol, 79:21 chelation-controlled addition to RCHO

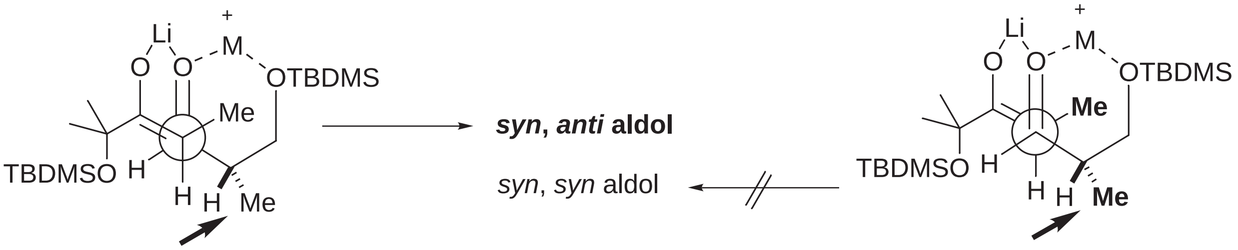
Heathcock *J. Org. Chem.* **1980**, *45*, 1066.

Explanation of Chelation Control

1. without chelation control



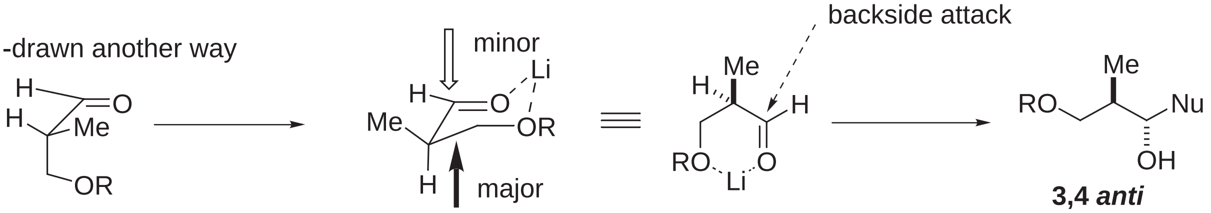
2. with chelation control



nucleophilic addition opposite to larger (Me) substituent

severe Me/Me interaction

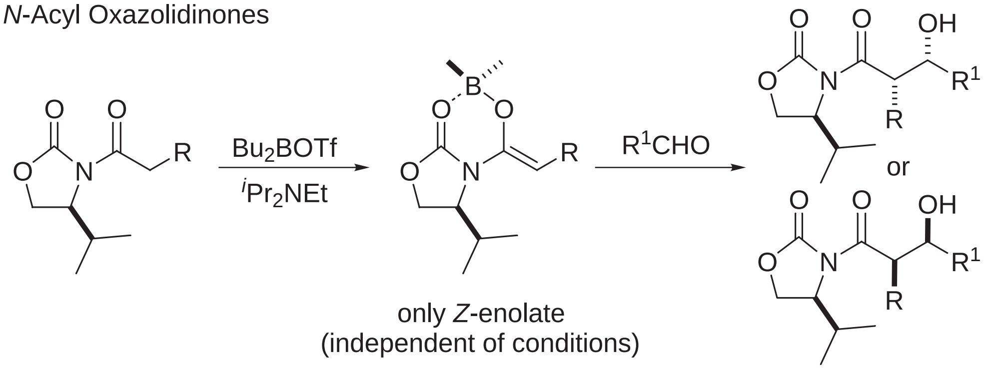
-drawn another way



3,4 *anti*

10. Aldol Condensation with Chiral Enolates

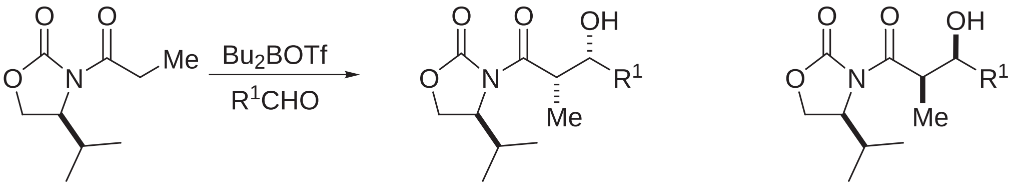
Evans' Chiral *N*-Acyl Oxazolidinones



only *Z*-enolate
(independent of conditions)

two possible *syn* aldol products
(relative to chiral center on aux.)

1. Experimental results



R^1 = ^{n}Bu	99.3	:	0.7
R^1 = ^{i}Pr	99.8	:	0.2
R^1 = Ph	>99.8	:	<0.2

* no *anti* adducts

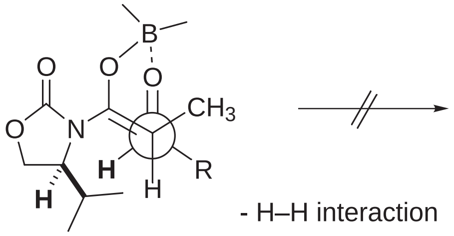
Evans *J. Am. Chem. Soc.* **1981**, *103*, 2127, 2876, and 3099.

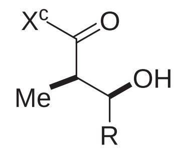
2. Origin of diastereoselectivity

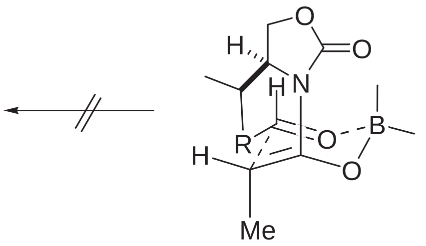
- *Z*-enolate (boron enolate/amide) gives *syn* aldol

Chair transition state
non-chelated *Z*-enolate

(minor *syn* aldol product)



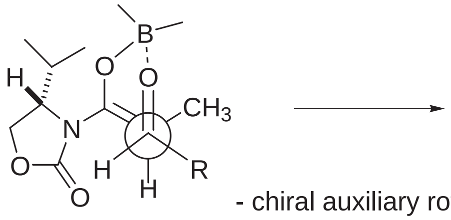


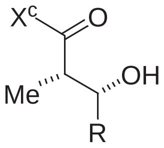


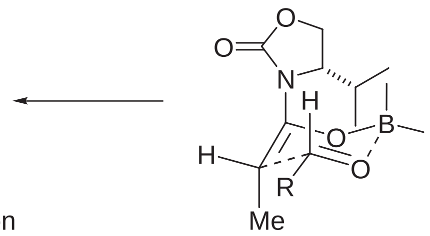
- H–H interaction
- steric interaction with ^{i}Pr (facial selectivity)
- aligned dipoles less favorable

Aldehyde R group equatorial
(axial would give *anti* aldol)

observed *syn* aldol product



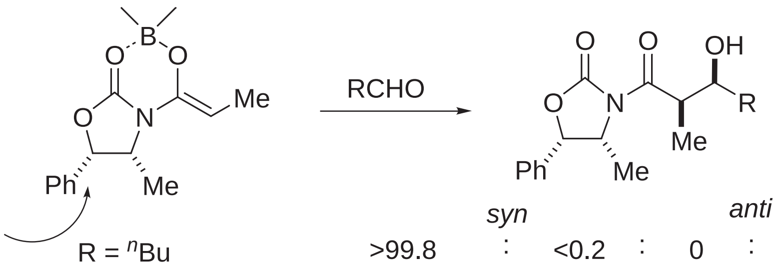




- chiral auxiliary rotates
- non-chelated enolate: opens coordination site on boron required to complex and activate aldehyde
- dipoles non-aligned, more favorable

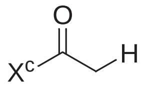
3. For the alternative enantiomer

Auxiliary with the
opposite absolute
configuration
or
the more accessible

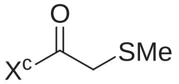


	syn		anti	
R = ^{n}Bu	>99.8 :	<0.2 :	0 :	0
R = ^{i}Pr	>99.8 :	<0.2 :	0 :	0
R = Ph	>99.8 :	<0.2 :	0 :	0

- Note: selectivity not good for

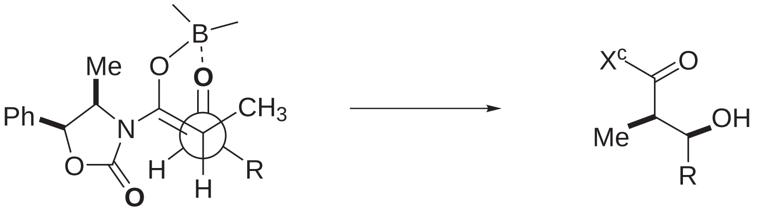


- Solution: use removable substituent



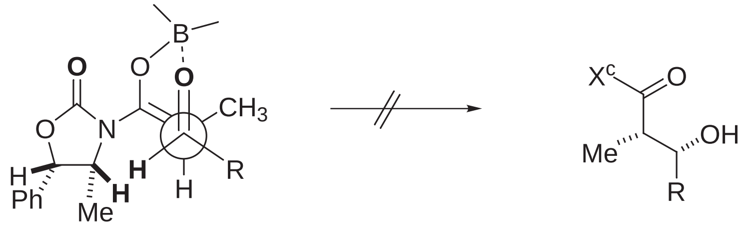
Evans aldol overrides any chiral aldehyde directing preference:
i.e. Felkin–Anh preference.

As before - two possible transition states for *syn* aldol product formation



- *anti* carbonyl conformation

observed *syn* aldol product

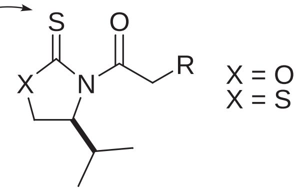


- *syn* carbonyl conformation
- steric interactions between H's

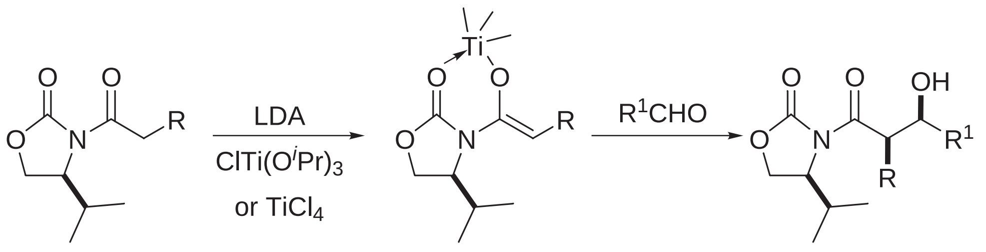
(minor *syn* aldol product)

Note: Availability of oxazolidinone alternatives
Fujita *J. Org. Chem.* **1986**, *51*, 2391.
Crimmins *J. Am. Chem. Soc.* **1997**, *119*, 7883.

Advantages: S > O for chelation and more readily cleaved



4. Ti enolate promoted Evans aldol (non-Evans *syn* aldol)



Et$_2$O vs. THF
as solvent

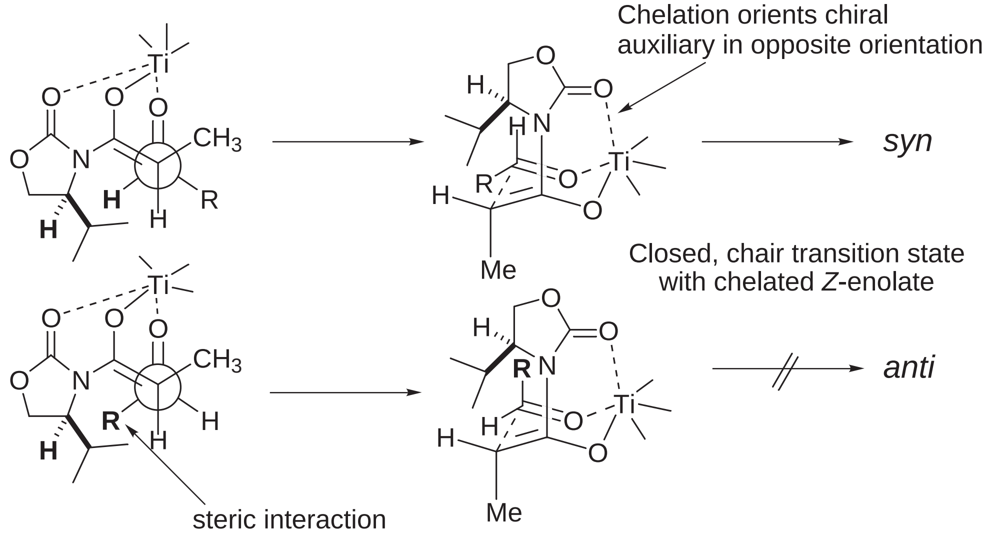
Z-enolate and chelated enolate
higher coordination sphere of Ti

syn		anti	
8 :	87 :	5 :	0

Thornton *J. Am. Chem. Soc.* **1989**, *111*, 5722; **1991**, *113*, 1299.
Evans *J. Am. Chem. Soc.* **1991**, *113*, 1047.
Thornton *J. Org. Chem*. **1991**, *56*, 2489.
Heathcock *J. Org. Chem.* **1991**, *56*, 5747.

syn aldol product but opposite absolute stereochemistry (non-Evans *syn* aldol).

5. Origin of diastereoselectivity - chelated *Z*-enolate

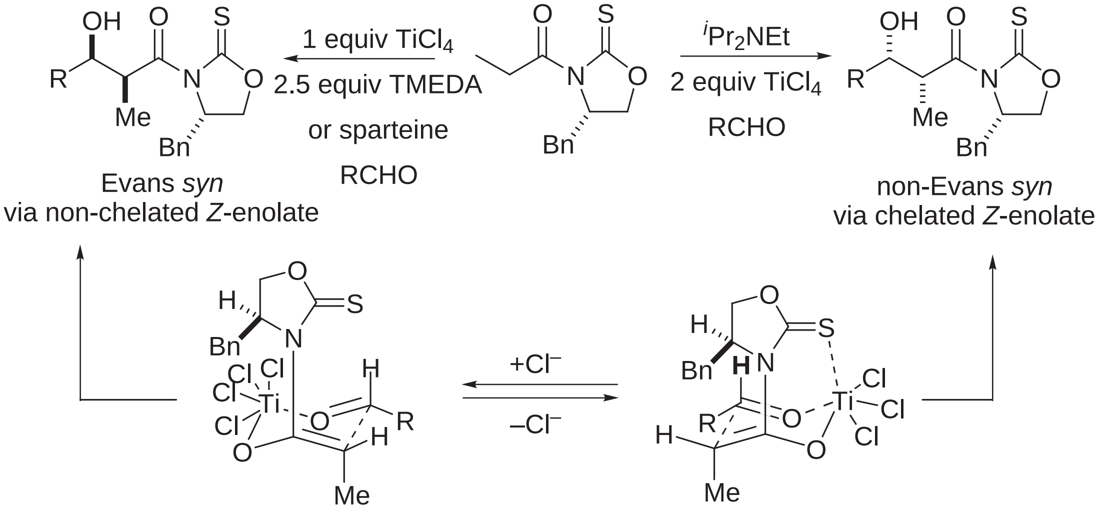


Chelation orients chiral auxiliary in opposite orientation

Closed, chair transition state with chelated *Z*-enolate

steric interaction

6. Chelated and non-chelated Ti enolates

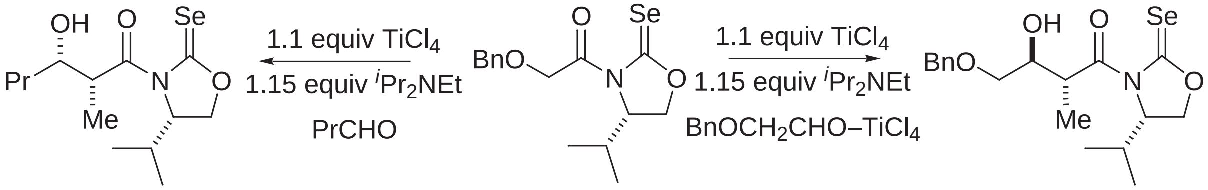


Evans *syn*
via non-chelated *Z*-enolate

non-Evans *syn*
via chelated *Z*-enolate

Crimmins *J. Am. Chem. Soc.* **1997**, *119*, 7883.

7. *Anti*-selective additions
- see also Heathcock *Aldrichimica Acta* **1990**, *23*, 99; *J. Org. Chem.* **1991**, *56*, 5747.



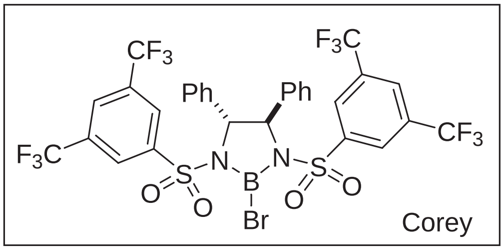
90%, > 98% *syn*
non-Evans *syn*

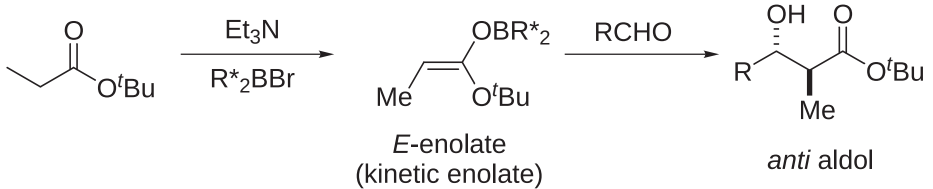
Silks *J. Am. Chem. Soc.* **2000**, *122*, 386.

90%, > 99.9% *anti*
via chelated *Z*-enolate

11. Asymmetric Aldol Reactions

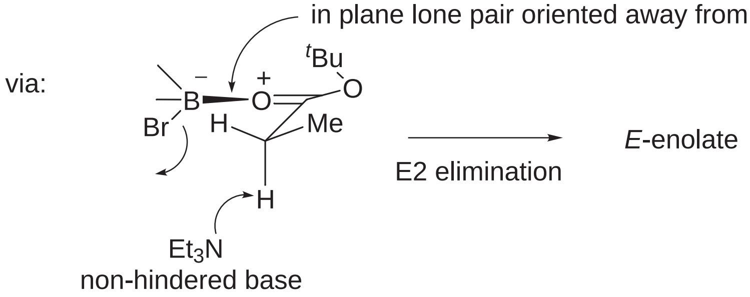
- Review: Paterson *Org. React.* **1997**, *51*, 1.
Corey *J. Am. Chem. Soc.* **1990**, *112*, 4976.
Corey *J. Am. Chem. Soc*. **1989**, *111*, 5493.

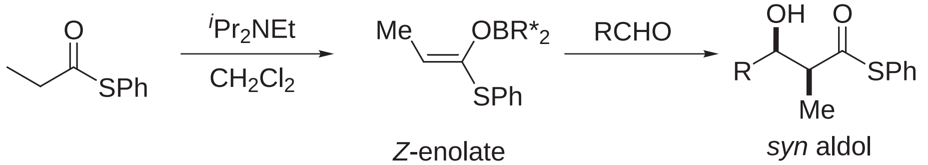




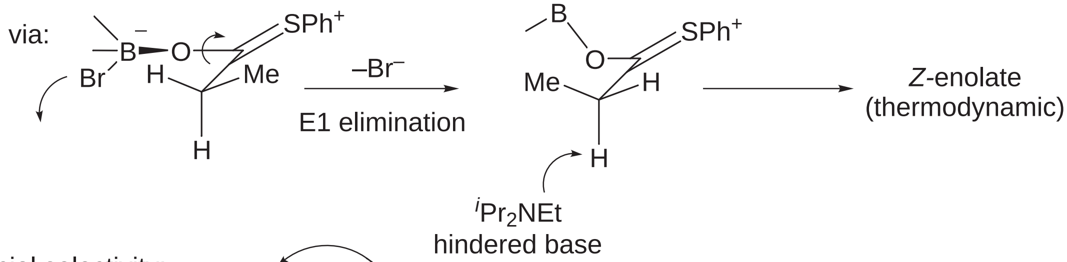
			anti:*syn*	
toluene–hexane	R = Ph	93%	98:2	94% ee
CH_2Cl_2	R = Ph	90%	96:4	89% ee

in plane lone pair oriented away from ester

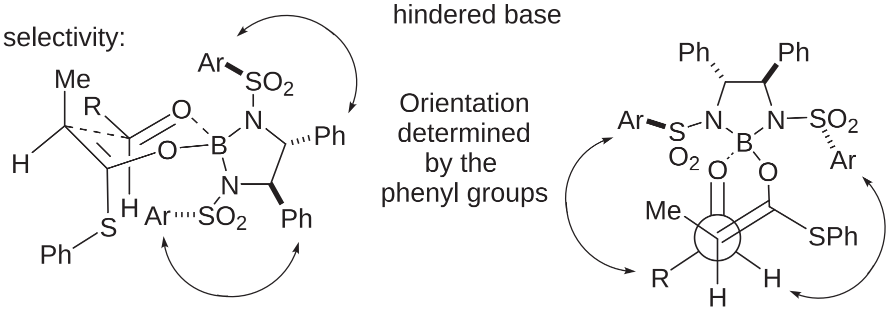




		anti:*syn*	
R = Ph	93%	1:99	97% ee



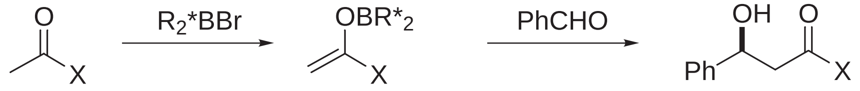
Facial selectivity:



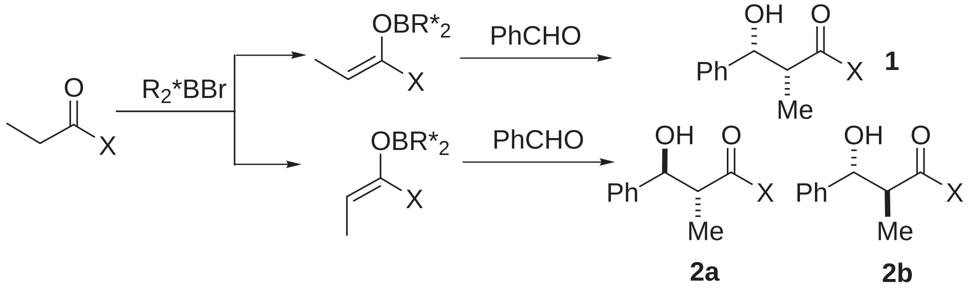
- Chair transition state
- Boron enolate
- *Z*-enolate

Examples

Corey *Tetrahedron Lett.* **1993**, *34*, 1737.



X	Conditions	Yield	Config.	ee
X = SPh	CH_2Cl_2, $^iPr_2NEt$	82%	*S*	64%
X = O^{t}Bu	CH_2Cl_2, $^iPr_2NEt$	78%	*S*	80%
X = S^{t}Bu	CH_2Cl_2, $^iPr_2NEt$	82%	*S*	73%
X = S^{t}Bu	toluene, Et_3N	94%	*S*	52%

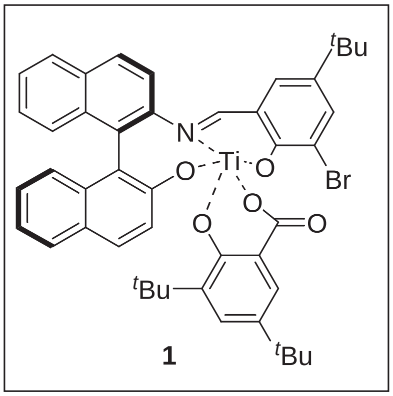


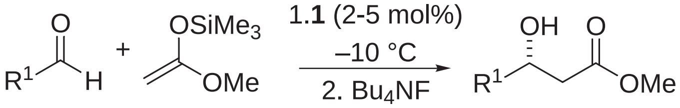
Note: *Z*-enolate → X = OBn (CH_2Cl_2, $^iPr_2NEt$); *E*-enolate → X = OBn (toluene, Et_3N)

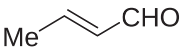
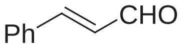
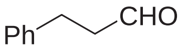
X	Conditions	Yield	*syn*:*anti*	Major Prod.	ee
X = SPh	CH_2Cl_2, $^iPr_2NEt$	90%	99:1	**1**	97%
X = SPh	toluene, Et_3N	78%	94:6	**1**	95%
X = O^{t}Bu	CH_2Cl_2, $^iPr_2NEt$	89%	4:96	**2a**	94%
X = O^{t}Bu	toluene, Et_3N	64%	2:98	**2a**	94%
X = OBn	CH_2Cl_2, $^iPr_2NEt$	73%	84:16	**1**	97%
X = OBn	toluene, Et_3N	78%	15:85	**2a**	97%
X = SBn	CH_2Cl_2, $^iPr_2NEt$	79%	70:30	**1**	81%
X = SBn	toluene, Et_3N	84%	9:91	**2a**	94%
X = S^{t}Bu	CH_2Cl_2, $^iPr_2NEt$	73%	71:29	**1**	50%
X = S^{t}Bu	toluene, Et_3N	86%	6:94	**2b (+ 2a)**	46%

see also: Corey *Tetrahedron Lett.* **1992**, *33*, 6735.

- Mukaiyama *Chem. Lett.* **1973**, 1011; review *Org. React.* **1982**, *28*, 203.
- Carreira's catalytic asymmetric aldol

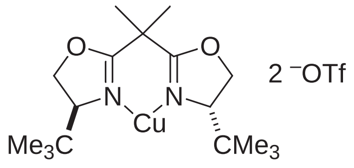




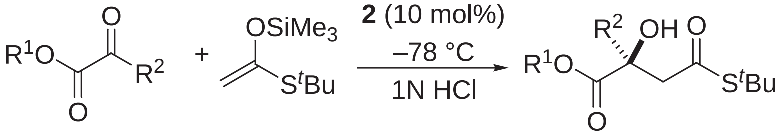
Aldehyde	ee:
	97%
	95%
	97%
	94%
$C_6H_{11}CHO$	95%
PhCHO	96%

Carreira *J. Am. Chem. Soc.* **1994**, *116*, 8837.

- Evans C2-symmetric bisoxazoline catalysts

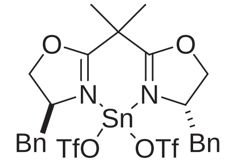


2

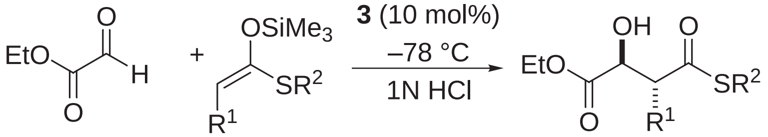


R^1	R^2	ee:
Me	Me	99%
Bn	Me	99%
^{t}Bu	Me	99%
Me	Et	94%
Me	^{i}Bu	94%
Et	^{i}Bu	36%

Evans *J. Am. Chem. Soc.* **1997**, *119*, 7893.



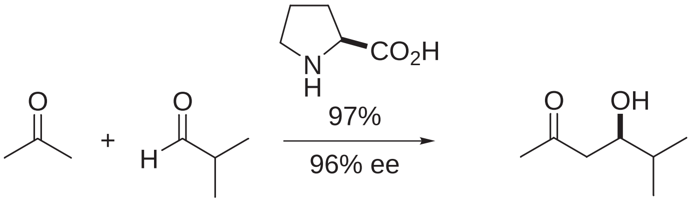
3



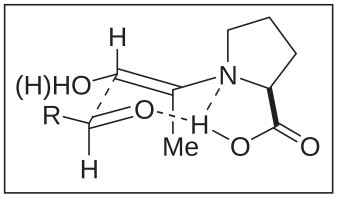
R^1	R^2	*anti*:*syn*	ee
H	Ph	–	98%
Me	Ph	90:10	95%
Et	Ph	92:8	95%
^{i}Pr	Ph	93:7	95%
^{i}Bu	Ph	92:8	98%
^{i}Bu	^{t}Bu	96:4	96%
^{i}Bu	Et	92:8	92%

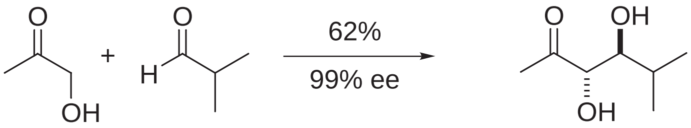
- review of catalyzed enantioselective aldol reaction *Tetrahedron Asymm.* **1998**, *9*, 357.

Evans *J. Am. Chem. Soc.* **1997**, *119*, 10859.



List, Lerner, and Barbas *J. Am. Chem. Soc.* **2000**, *122*, 2395.



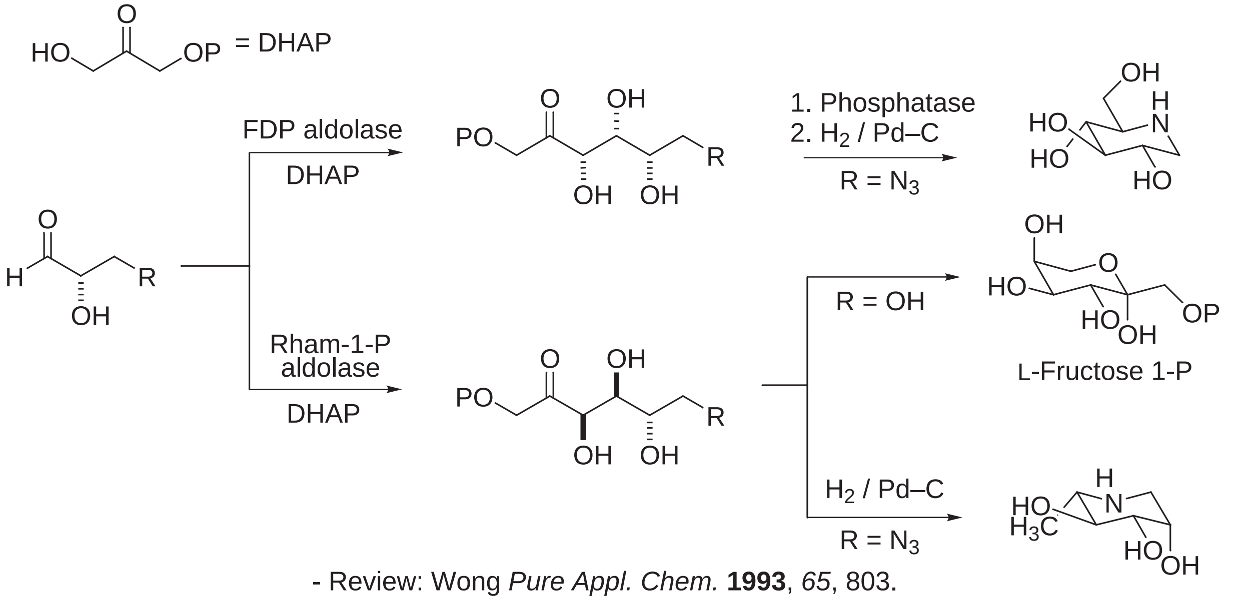


regioselectivity	> 20:1
diastereoselectivity	> 20:1
enantioselectivity	> 100:1

List *J. Am. Chem. Soc.* **2000**, *122*, 7386.

12. Enzyme-Catalyzed Aldol

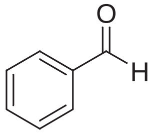
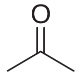
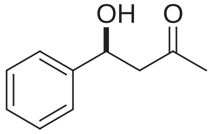
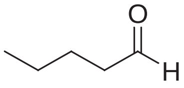
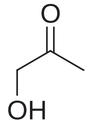
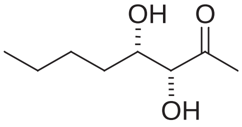
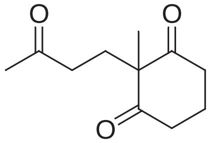
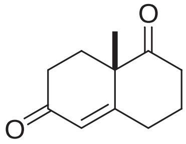
- Wong aldolase based synthesis of carbohydrates and aza-sugars



- Review: Wong *Pure Appl. Chem.* **1993**, *65*, 803.

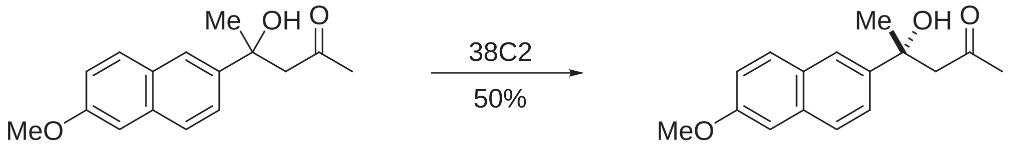
Niels K. Jerne, Georges F. Kohler, and Cesar Milstein shared the 1984 Nobel Prize in Medicine for the preparation of monoclonal antibodies.

- Lerner catalytic antibodies
  - wide range of donors and acceptors utilized
  - commercially available

Acceptor	Donor	Product	38C2 ee	33F12 ee
			>99%	>99%
			>98%	89%
			>95%	>95%

Lerner, Barbas *J. Am. Chem. Soc.* **1998**, *120*, 2768.
Org. Lett. **1999**, *1*, 59.

Kinetic resolution



> 99% ee

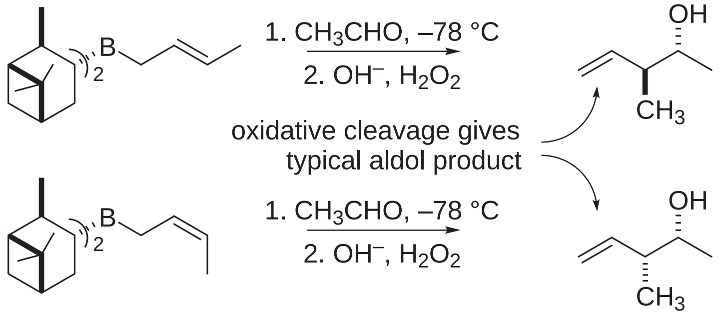
catalyzes retro aldol of only one enantiomer

Lerner, Barbas *J. Am. Chem. Soc.* **1999**, *121*, 7283.

H. Aldol Equivalents

1. Chiral Organoboranes

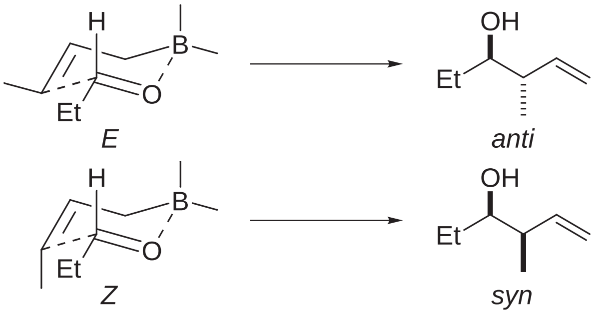
Brown:

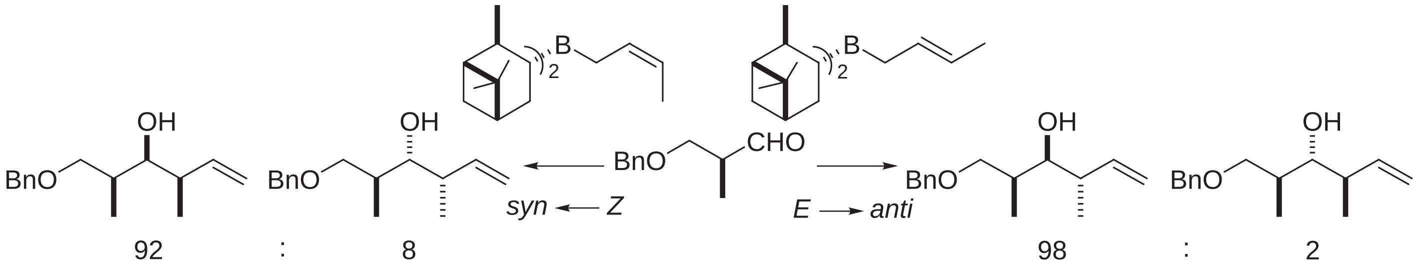


de%	ee%	yield%
99	95	78
99	95	75

Brown *J. Am. Chem. Soc.* **1986**, *108*, 293 and 5919.
J. Org. Chem. **1989**, *54*, 1570.

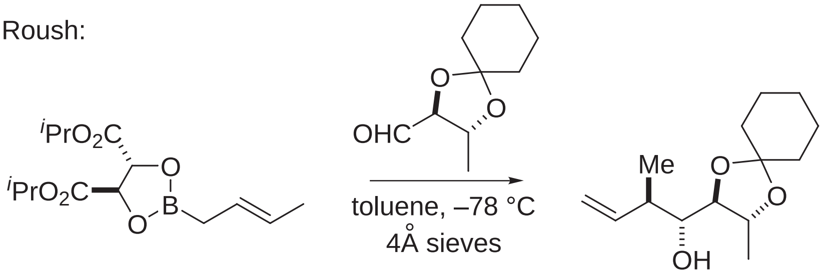
The relative configuration, *syn* or *anti*, of the product is determined by the configuration of the olefin.





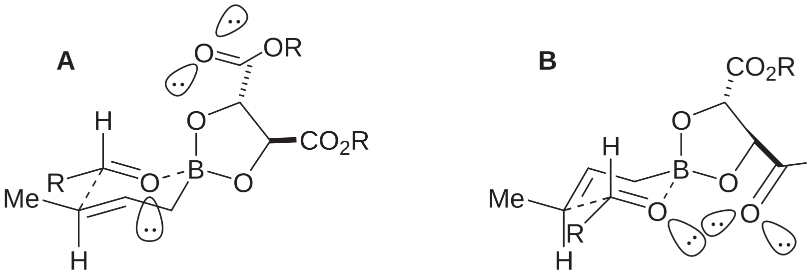
The reagent controls facial selectivity of addition and determines the absolute configuration of product.

Roush:



de%	ee%	yield%
80	84	80

Roush and Halterman *J. Am. Chem. Soc.* **1986**, *108*, 294.

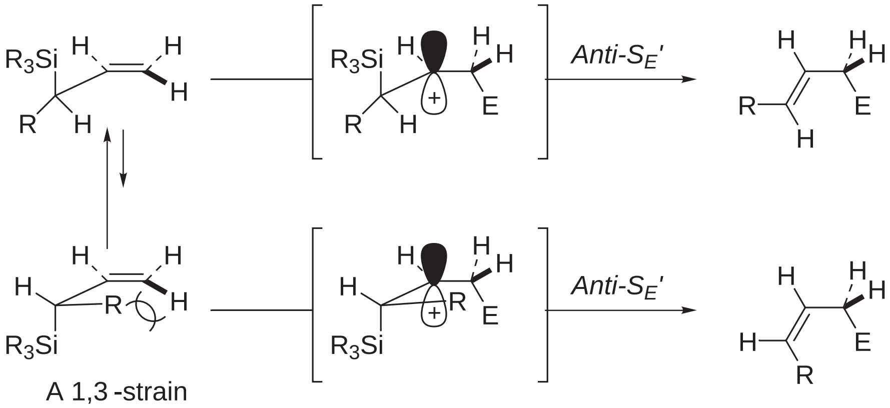


- asymmetric induction is a consequence of n/n electronic repulsive interactions disfavoring transition state B relative to transition state A

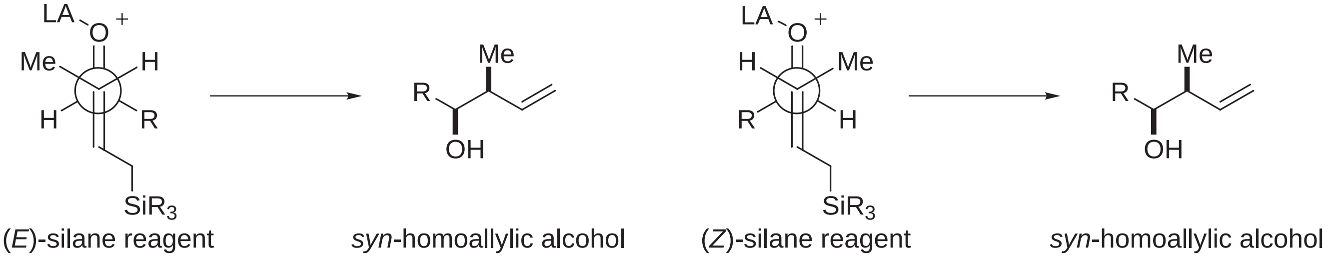
2. Allylsilanes

Reviews: Fleming *Org. React.* **1989**, *37*, 57.
Panek *Chem. Rev.* **1995**, *95*, 1293.

A. Chiral allylsilanes yield *E*-olefins selectively

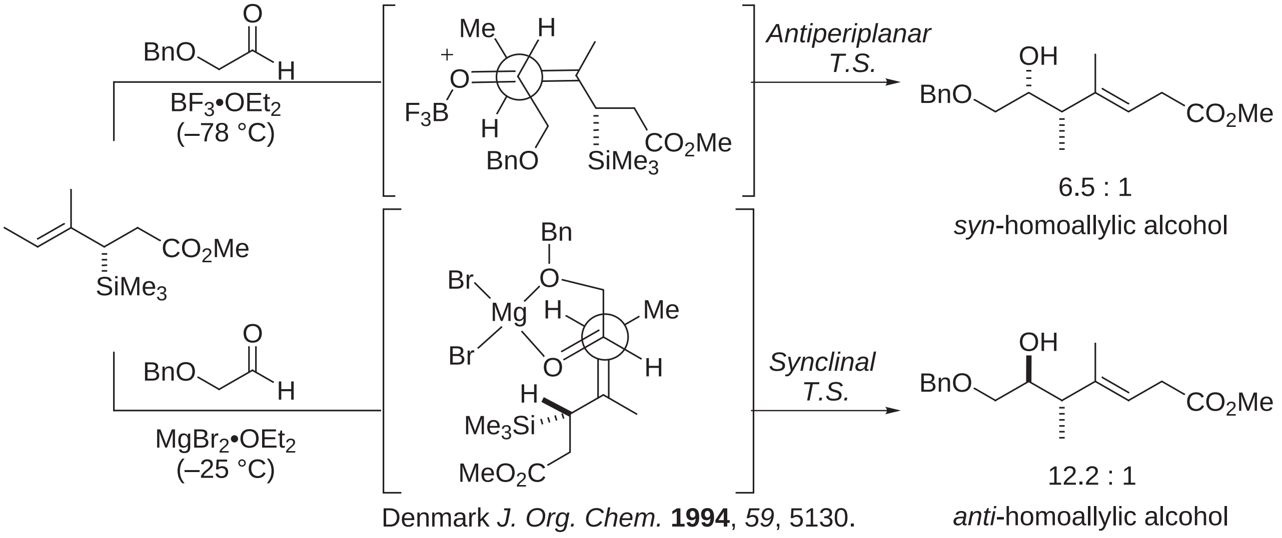


- Chiral allylsilanes add to carbonyls in *syn* fashion (either synclinal or antiperiplanar T.S.)
(Unless chelation control is utilized)



(*E*)-silane reagent *syn*-homoallylic alcohol (*Z*)-silane reagent *syn*-homoallylic alcohol

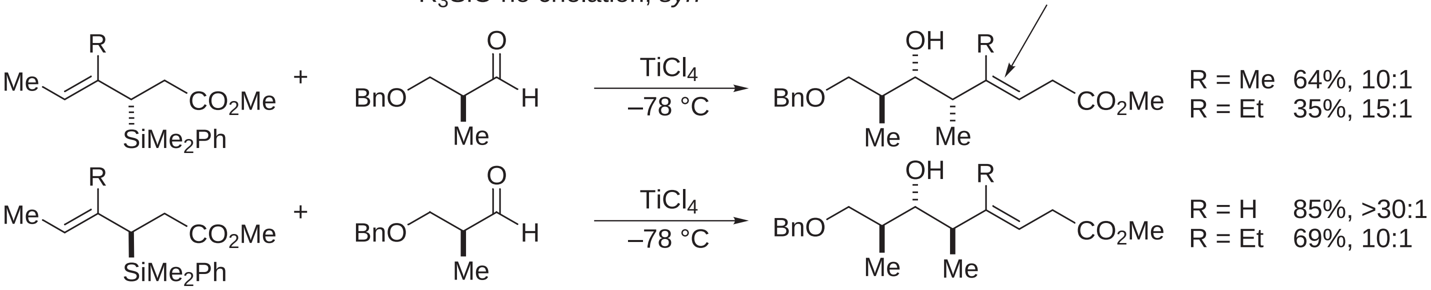
B. Additions to Aldehydes (Opposite face of silane)

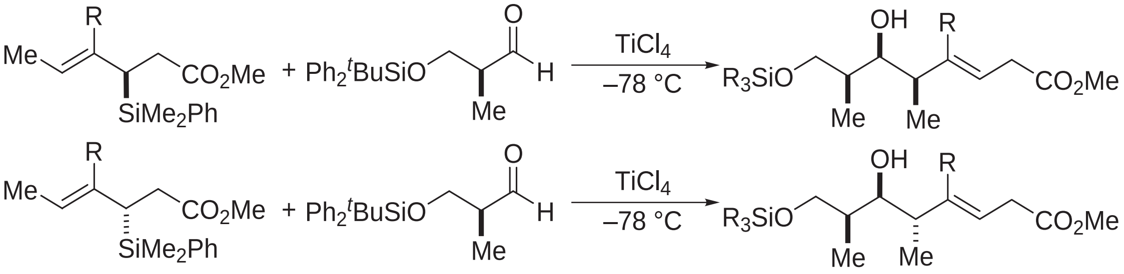


Denmark *J. Org. Chem.* **1994**, *59*, 5130.

C. Additions to Chiral Aldehydes - BnO chelation, *anti*
R_3SiO no chelation, *syn*

oxidative cleavage provides aldehyde, carboxylic acid (R = H) or ketone (R = Me, Et) aldol addition products





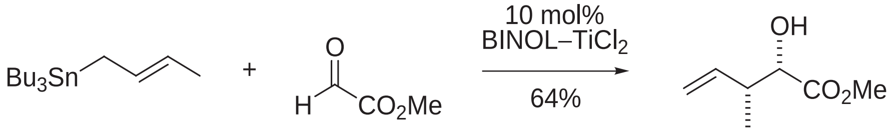
R = H 90%, >30:1
R = Me 79%, >30:1
R = Et 74%, 15:1

R = Me 98%, 8:1
R = Et 79%, 10:1

Jain and Panek *J. Am. Chem. Soc.* **1996**, *118*, 12475.

3. Allylstannanes

A. Asymmetric addition via optically active catalyst



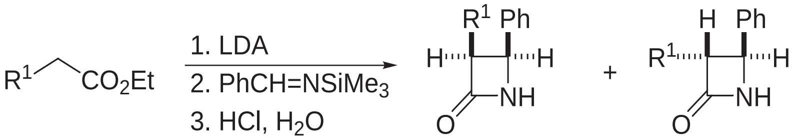
84% *syn*, 86% ee

Aoki *Tetrahedron* **1993**, *49*, 1783.
Keck *J. Am. Chem. Soc.* **1993**, *115*, 8467; *J. Org. Chem.* **1993**, *58*, 6543.

- Also applicable to allylsilanes.

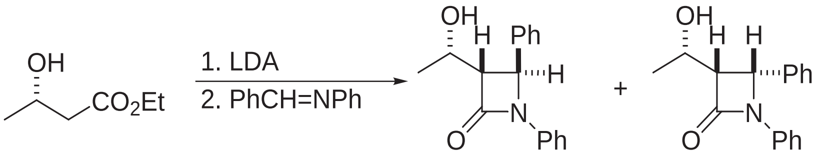
I. Enolate-imine Addition Reactions

- Review: Hart *Chem. Rev.* **1989**, *89*, 1447.



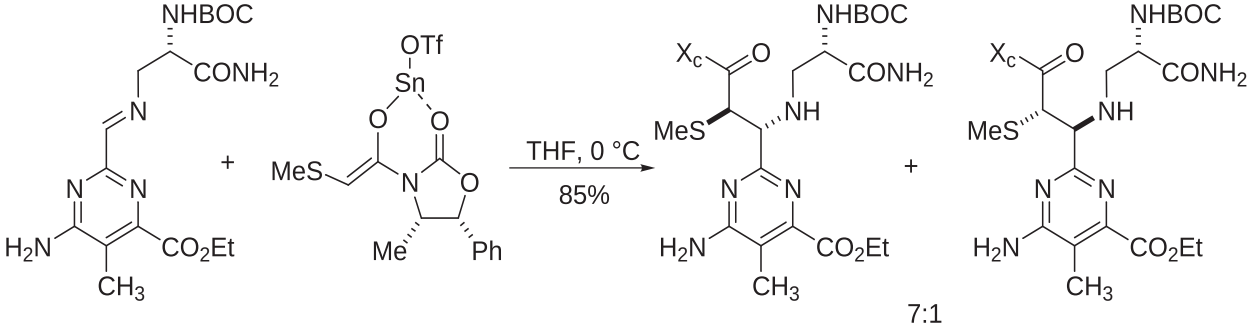
R^1	yield	yield
H	14%	0%
Me	41%	3%
Et	72%	0%
^{i}Pr	80%	1%
^{t}Bu	40%	0%

Hart *J. Am. Chem. Soc.* **1984**, *106*, 4819.



25% 16%

Georg *Tetrahedron Lett.* **1985**, *26*, 3903.

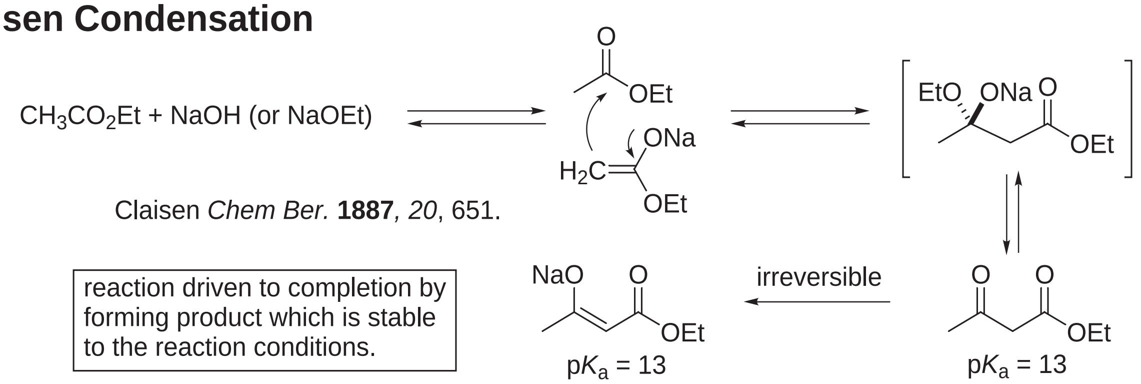


7:1

Boger *J. Am. Chem. Soc.* **1994**, *116*, 5619.

anti:*syn* (>16:1)

J. Claisen Condensation

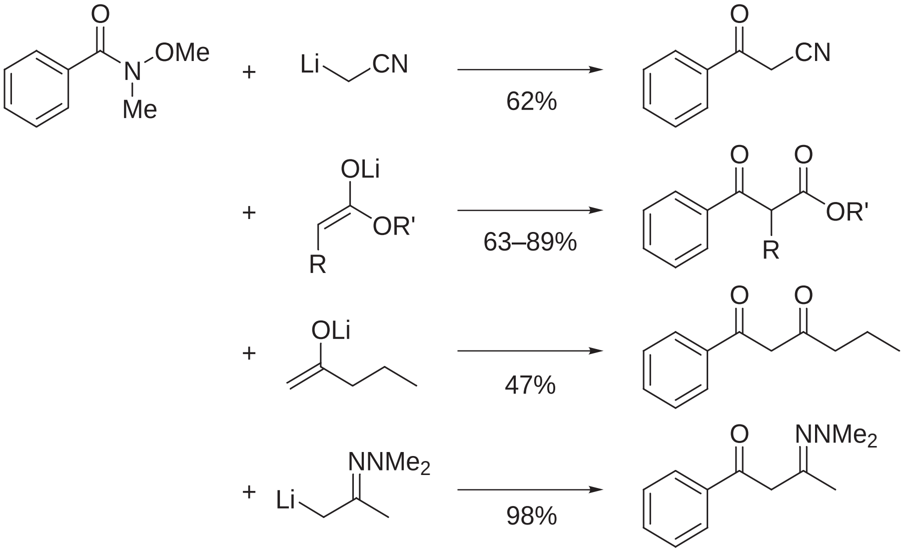


Claisen *Chem Ber.* **1887**, *20*, 651.

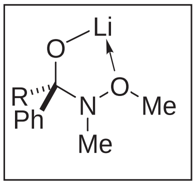
reaction driven to completion by forming product which is stable to the reaction conditions.

- Weinreb Amide

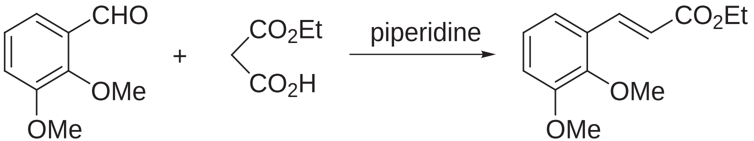
Turner *J. Org. Chem.* **1989**, *54*, 4229.



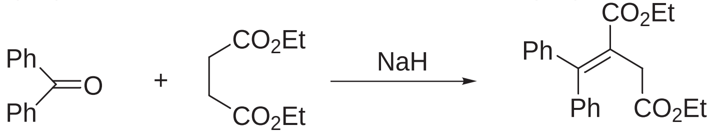
- Tetrahedral intermediate is stabilized
- Breaks down upon workup, not in reaction
- Generality of Weinreb amide
- Weinreb *Tetrahedron Lett.* **1981**, *22*, 3815.



- Knoevenagel–Doebner and Stobbe Condensation

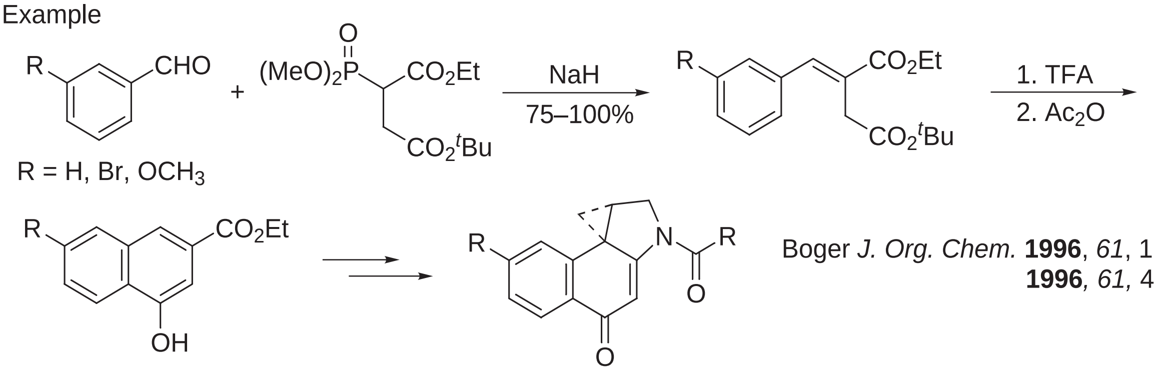


Knoevenagel–Doebner condensation
Knoevenagel *Chem. Ber.* **1896**, *29*, 172.
Doebner *Chem. Ber.* **1900**, *33*, 2140.
Review: *Org. React.* **1967**, *15*, 204.



Stobbe condensation
Stobbe *Chem. Ber.* **1893**, *26*, 2312.
Review: *Org. React.* **1951**, *6*, 1.

- Example

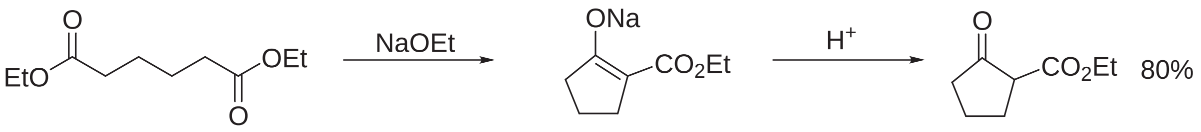


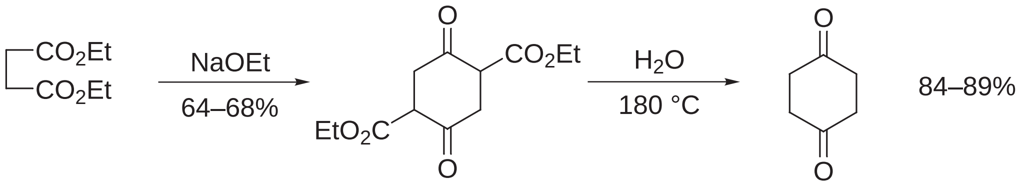
Boger *J. Org. Chem.* **1996**, *61*, 1710.
1996, *61,* 4894.

K. Dieckmann Condensation

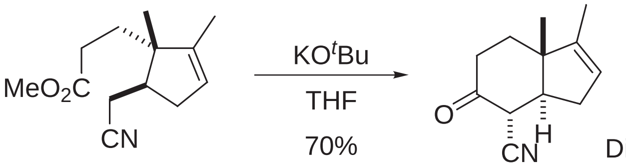
- *Org. React.* **1967**, *15,* 1.

- Examples





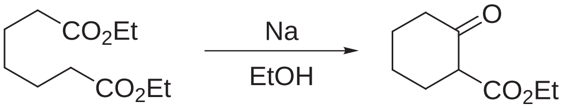
- *Org. Syn.* Coll. Vol. 2, 288.



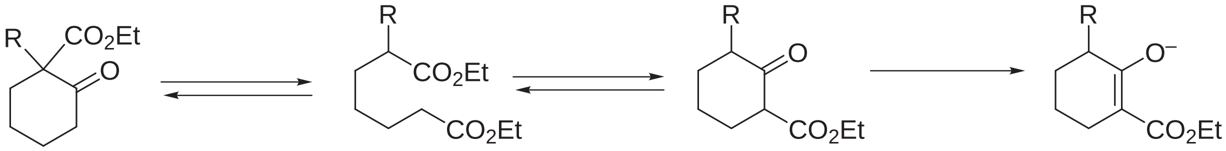
Thorpe–Ziegler condensation

Dinitrile is Ziegler condensation
Ziegler *Chem. Ber.* **1934**, *67*, 139.

Stevens *J. Am. Chem. Soc.* **1977**, *99*, 6105.



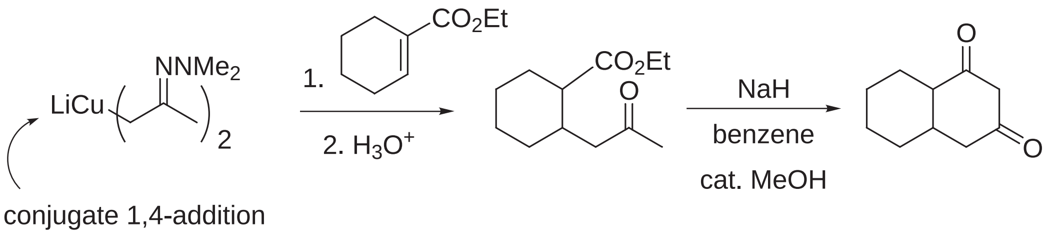
Dieckmann *Ber*. **1894**, *27*, 965.
Fehling *Ann.* **1844**, *49*, 192.
(1st example - product not identified)



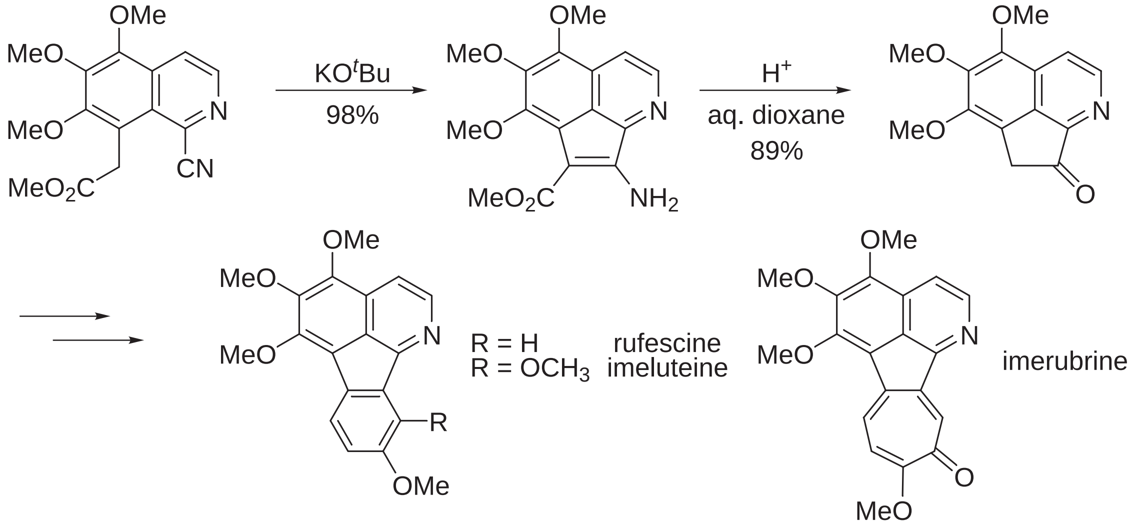
2 **1**

- products interconvert under reaction conditions equilibration driven to **1** by formation of enolate.

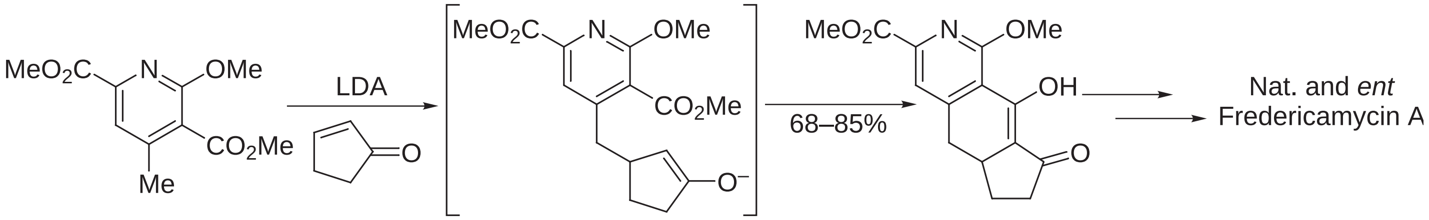
The analogous intramolecular keto ester condensation may be described as "occurring under Dieckmann conditions see: *Org. React.* **1959**, *8*, 79.



Boger and Corey *Tetrahedron Lett.* **1978**, 4597.

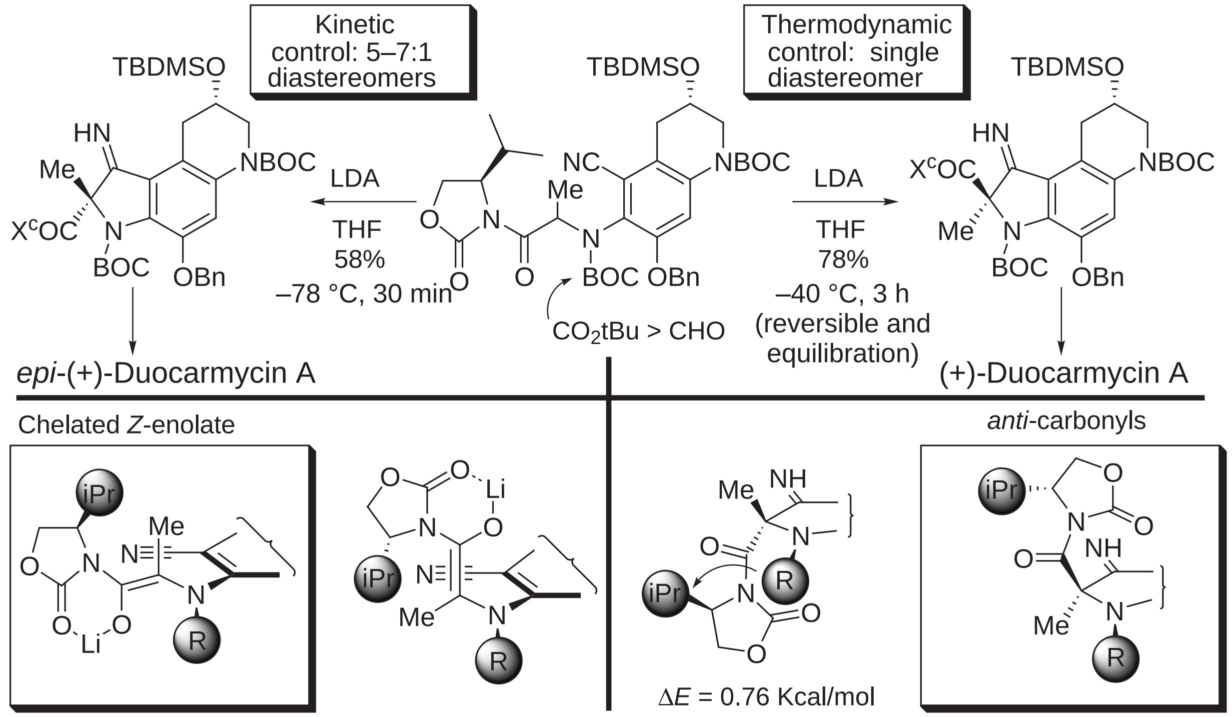


Boger and Brotherton *J. Org. Chem.* **1984**, *49*, 4050.
Boger and Takahashi *J. Am. Chem. Soc.* **1995,** *117*, 12452.



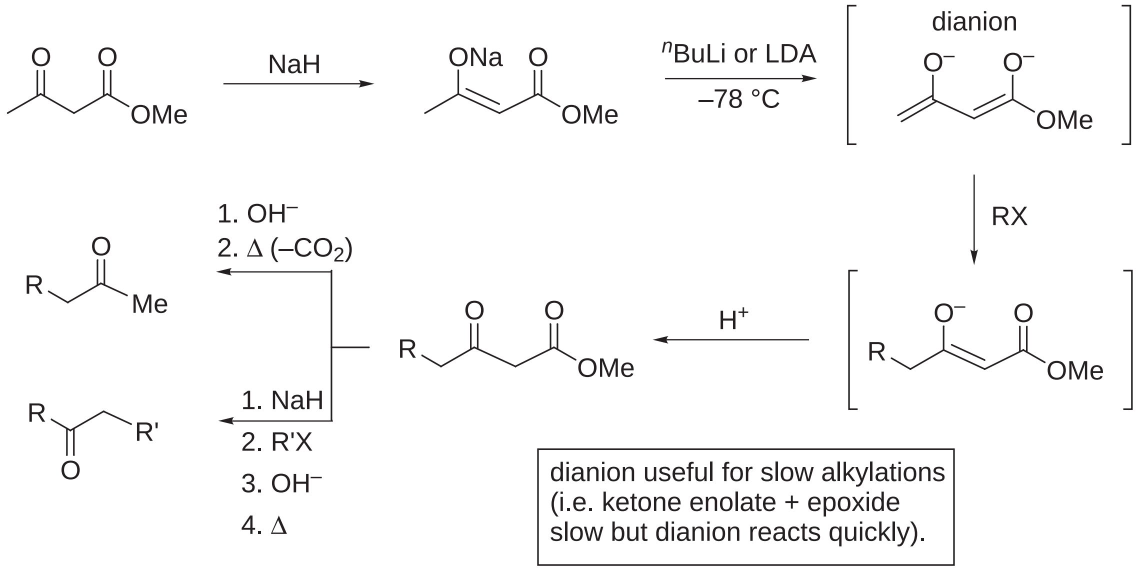
Boger *J. Org. Chem.* **1992**, *57*, 3974.
Boger *J. Am. Chem. Soc.* **1995**, *117*, 11839.

- Asymmetric Dieckmann-like condensation



Boger *J. Am. Chem. Soc.* **1997**, *119*, 311.

L. Enolate Dianions



dianion useful for slow alkylations (i.e. ketone enolate + epoxide slow but dianion reacts quickly).

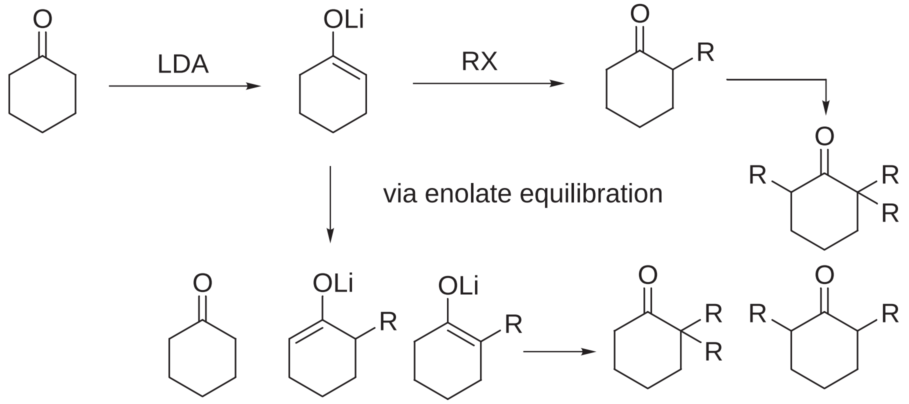
Weiler *J. Am. Chem. Soc.* **1974**, *96*, 1082.
Weiler *Tetrahedron Lett.* **1983**, *24*, 253.
Harris *Org. React.* **1969**, *17*, 155–212.
(review)

M. Metalloimines, Enamines and Related Enolate Equivalents

Metalloimines: Stork *J. Am. Chem. Soc.* **1963**, *85*, 2178.

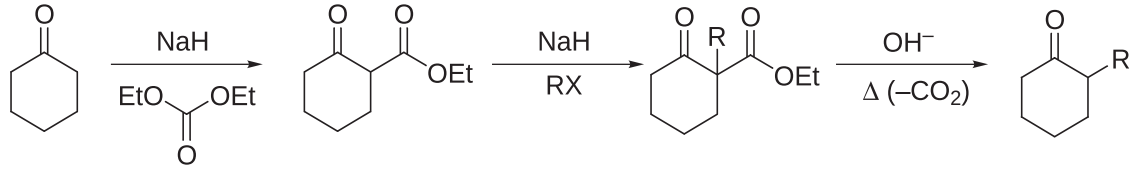
- Stork *J. Am. Chem. Soc.* **1971**, *93*, 5938.
  (Metalloimines, dimethylhydrazones)

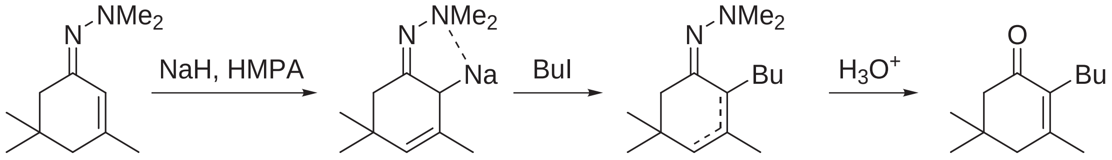
- Corey, Enders *Tetrahedron Lett.* **1976**, 3 and 11.
  Chem. Ber. **1978**, *111*, 1337 and 1362.
  (Dimethylhydrazones)



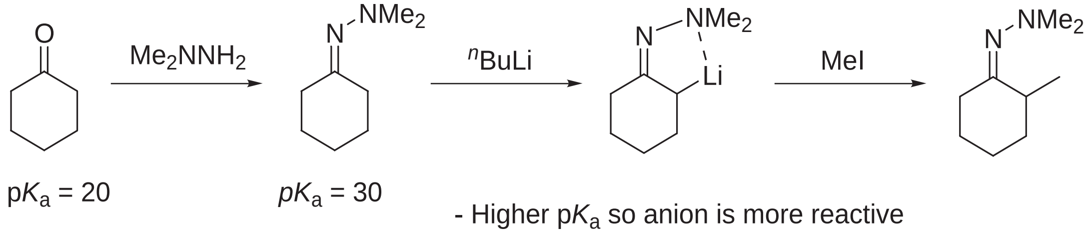
- Simple alkylation of enolates not always straightforward.
- Can get polyalkylation mixtures.

- Solutions

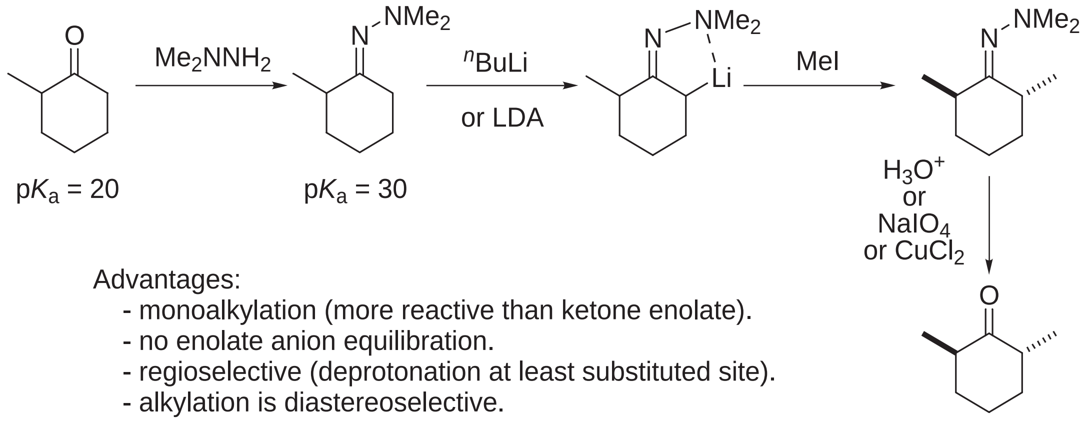




Stork *J. Am. Chem. Soc.* **1971**, *93*, 5938.



- Higher pK_a so anion is more reactive
- Alkylation much faster and polyalkylation is not a problem

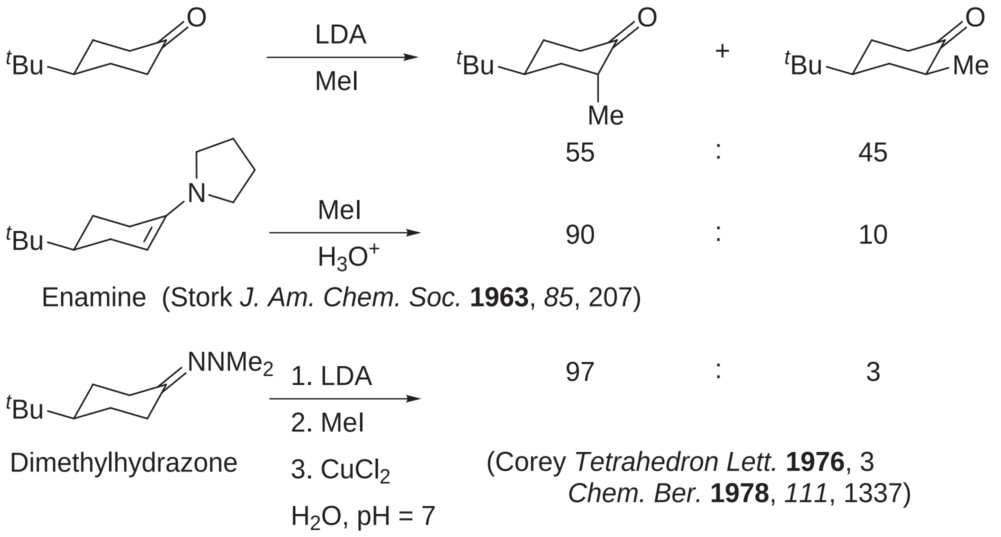


Advantages:
- monoalkylation (more reactive than ketone enolate).
- no enolate anion equilibration.
- regioselective (deprotonation at least substituted site).
- alkylation is diastereoselective.

Corey *Tetrahedron Lett.* **1976**, 3

Note: preference for *trans* product is thermodynamic in origin. *Cis* (kinetic) product can also be obtained selectively (Collum *J. Am. Chem. Soc.* **1984**, *106*, 4865).

- Examples:

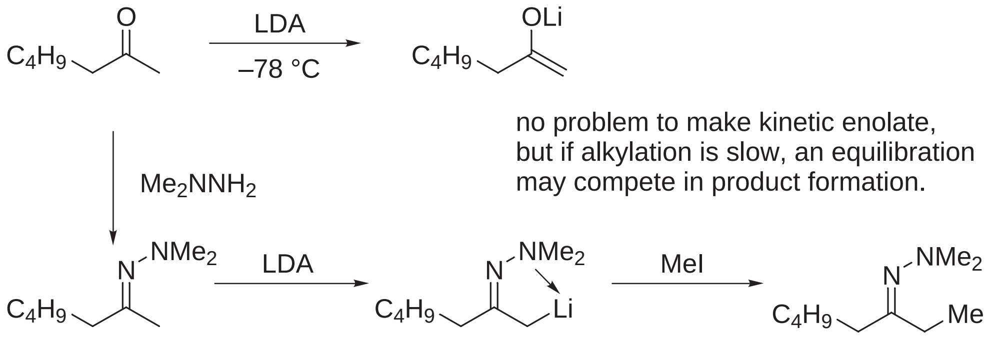


Enamine (Stork *J. Am. Chem. Soc.* **1963**, *85*, 207)

Dimethylhydrazone

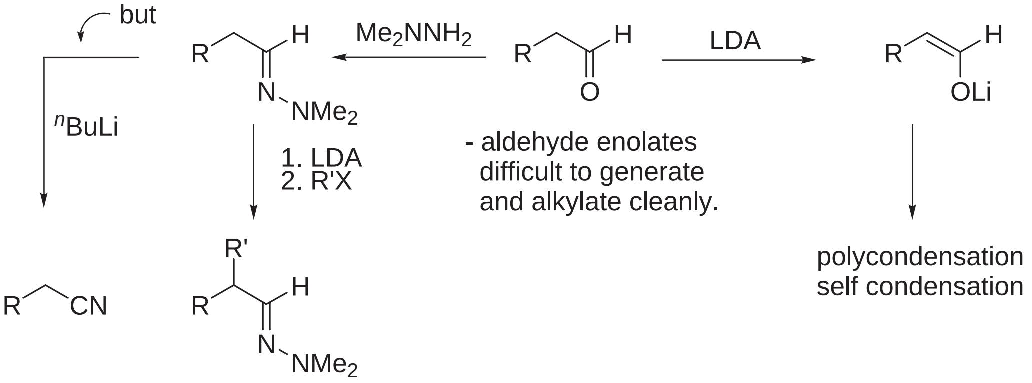
(Corey *Tetrahedron Lett.* **1976**, 3
Chem. Ber. **1978**, *111*, 1337)

-also useful in acyclic cases



no problem to make kinetic enolate,
but if alkylation is slow, an equilibration
may compete in product formation.

- very good as aldehyde enolate equivalents



- aldehyde enolates
difficult to generate
and alkylate cleanly.

polycondensation
self condensation

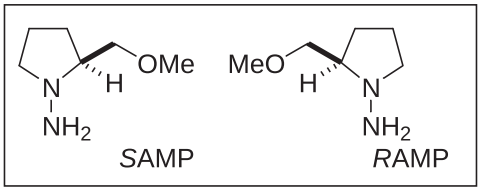
Review of methods for dimethylhydrazone cleavage: Enders *Acc. Chem. Res.* **2000**, *33*, 157.

Oxidative methods: O_3, $^1O_2$, $NaIO_4$, $NaBO_3$, $(Bu_4N)_2S_2O_8$, HTIB/BTI, MMPP, *m*-CPBA, CH_3CO_3H, H_2O_2/SeO_2, H_2O_2, $MeReO_3/H_2O_2$, DMDO. Note: aldehyde dimethylhydrazones provide the nitrile upon oxidative cleavage.

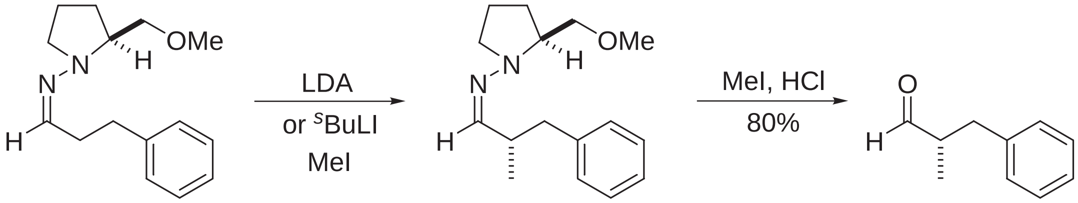
Hydrolytic methods: $CuCl_2$, $Cu(OAc)_2$, $(CO_2H)_2$, $(NH_4)H_2PO_4$, MeI–HCl, HCl, SiO_2–H_2O, $BiCl_3$/µW, $Pd(OAc)_2/SnCl_2$, BF_3•OEt_2

Reductive methods: $=NNMe_2 \rightarrow =NH \rightarrow =O$, $TiCl_3$, $SnCl_2$, $Cr(OAc)_2$, VCl_2

- Enders chiral hydrazones (*S*AMP and *R*AMP)



- alkylation from the
least hindered face
of chelated anion.

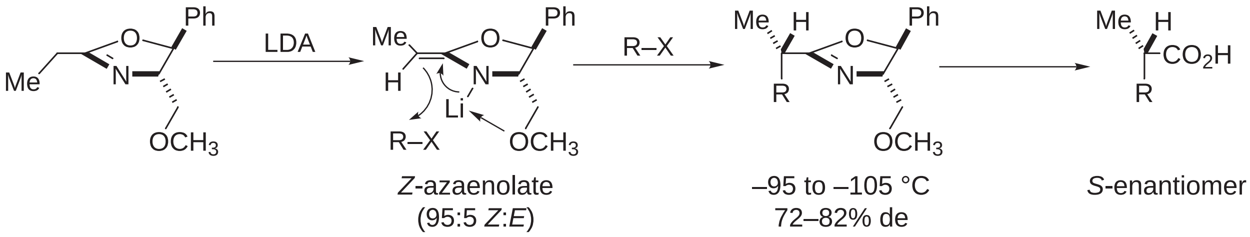


90% de

Review: *Asymm. Synth.* Vol. 3, 275.

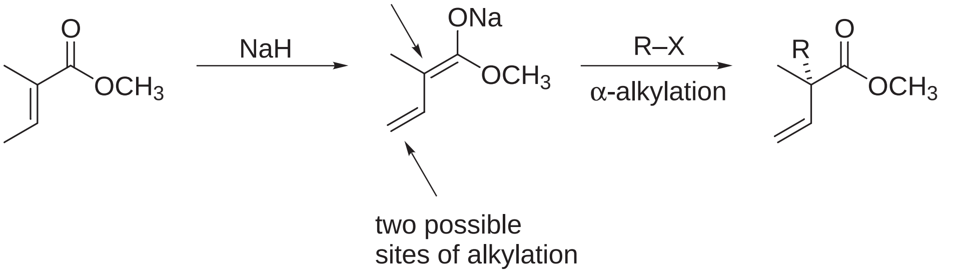
- Meyers chiral oxazolines

- Phenyl group shields top face to E^+ attack

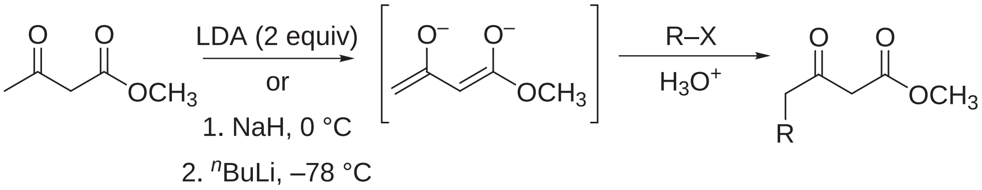


Review: *Asymm. Synth.* Vol. 3, 213.

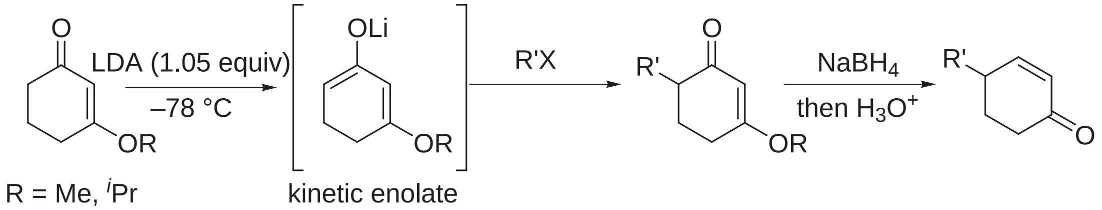
N. Alkylation of Extended Enolates



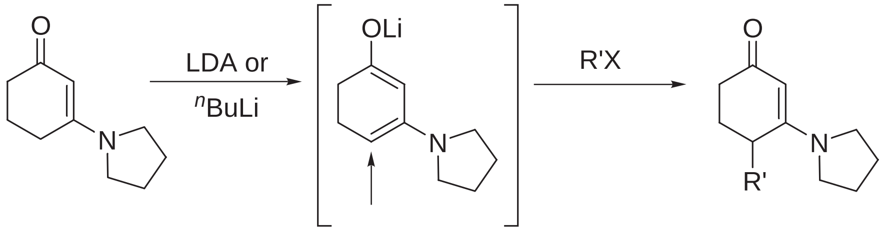
- For alkylation in the γ position - can use a dianion



- In cyclic systems



Danheiser, Stork *J. Org. Chem.* **1973**, *38*, 1775.
Cargill *J. Org. Chem.* **1973**, *38*, 2125.



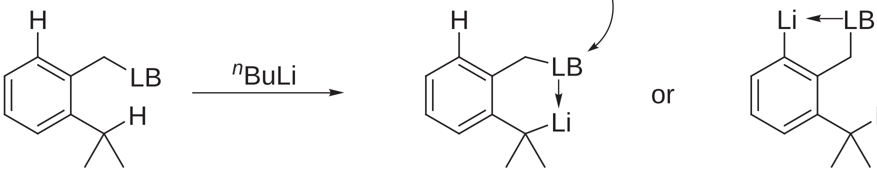
Yoshimoto, Ishida, Hiraoka *Tetrahedron Lett.* **1973**, 39.
Bryson, Gammill *Tetrahedron Lett.* **1974**, 3963.

IX. Metalation Reactions

A. Directed Metalation

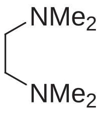
- Kinetic acceleration of deprotonation of a relatively non-acidic site.
- *Synthesis* **1983**, 95.
- *Acc. Chem. Res*. **1982**, *15*, 306.
- *Org. React.* **1979**, *26*, 1.

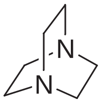
lateral lithiation: *Org. React.* **1995**, *47*, 1.



- Usually requires very strong base (^{n}BuLi, ^{s}BuLi or ^{t}BuLi, sometimes LDA).
- Sometimes requires additives (TMEDA, DABCO) to break up Li aggregates (make bases more reactive).

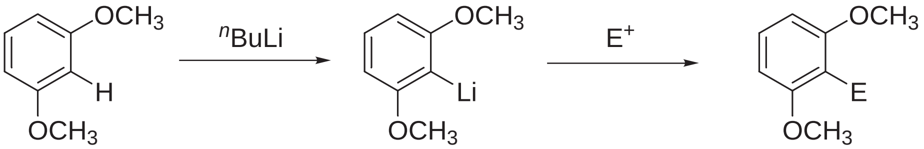
TMEDA



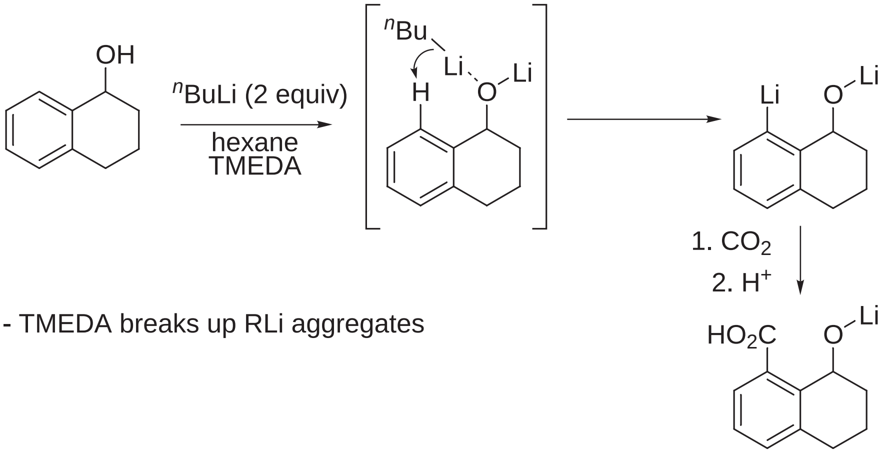


DABCO

- Examples:

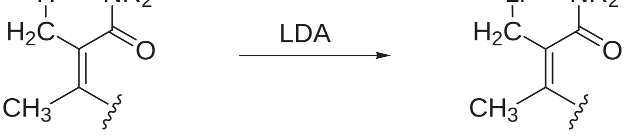


- All aromatic H's have approximately the same pK_a



- TMEDA breaks up RLi aggregates

- Not limited to aromatic substrates



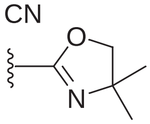
- Kinetic acceleration of deprotonation even in the presence of a more acidic proton.

- Directed Metalation Groups

carbon based

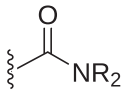
Strong:

$CON^{-}R$
$CSN^{-}R$
$CONR_2$
$CON(R)CH(Z)TMS$, Z = H,TMS
$CH{=}NR$
$(CH_2)_nNR_2$, n = 1,2
$CH(OH)CH_2NR_2$
CN



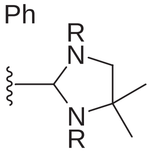
Moderate:

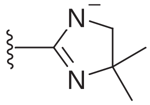
CF_3



Weak:

$C(OTMS){=}CH_2$
$CH(OR)_2$
$C{\equiv}C^{-}$
Ph





heteroatom based

Strong:

$N^{-}COR$
$N^{-}CO_2R$
$OCONR_2$
$OPO(NR)_2$
OCH_2OMe
OTHP
OPh
SO_3R
$SO_2N^{-}R$
SO_2NR
SO_3^{-}
$SO_2{}^{t}Bu$
$SO^{t}Bu$

Moderate:

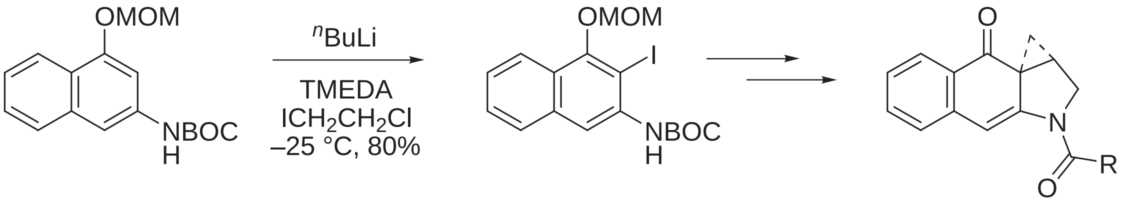
NR_2
$N{\equiv}C$
OMe
$OCH{=}CH_2$
$OPO(OR)_2$
$O(CH_2)_2X$, X = OMe, NR_2
F
Cl
$PO(NR)_2$
$PS(Ph)NR_2$

Weak:

O^{-}
S^{-}

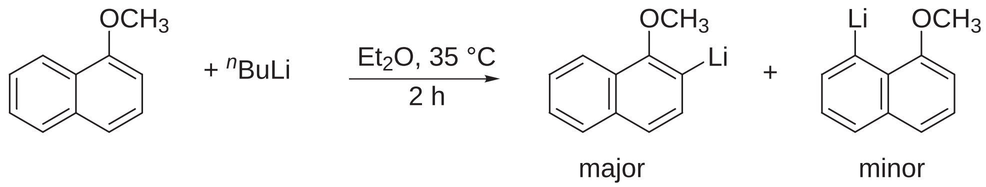
Snieckus *Chem. Rev.* **1990**, *90*, 879.

- Examples (cooperative effect)

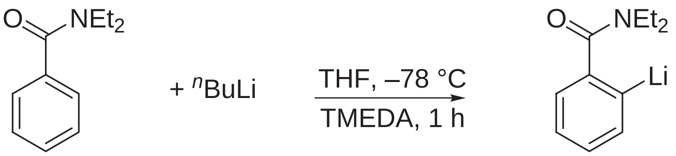


Boger and Garbaccio, *J. Org. Chem.* **1997**, *62*, 8875.

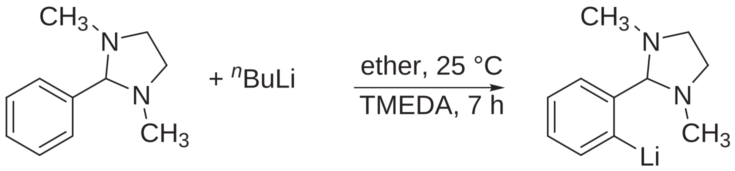
- Representative Organolithium Compounds by Directed Metalation



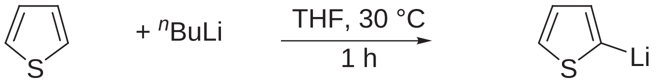
Shirley *J. Org. Chem.* **1966**, *31*, 1221.



Beak *J. Org. Chem.* **1977**, *42*, 1823.
Beak *J. Org. Chem.* **1979**, *44*, 4463.

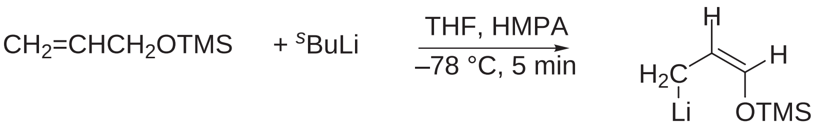


Harris *J. Org. Chem.* **1979**, *44*, 2004.



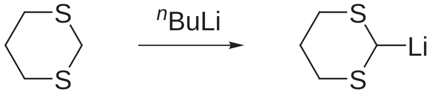
Jones and Moodie *Org. Synth.* **1988**, *6*, 979.

Baldwin *J. Am. Chem. Soc.* **1974**, *96*, 7125.



Still *J. Org. Chem.* **1976**, *41*, 3620.

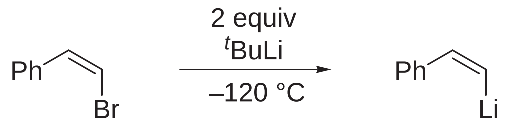
Eisch *J. Am. Chem. Soc.* **1976**, *98*, 4646.



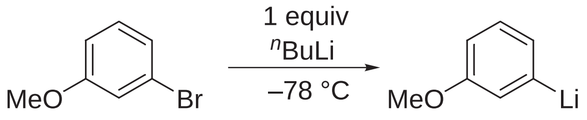
Corey, Seebach *J. Org. Chem.* **1975**, *40*, 231.

B. Organolithium Compounds by Metal–Halogen Exchange

Jones and Gilman *Org. React.* **1951**, *6*, 339.

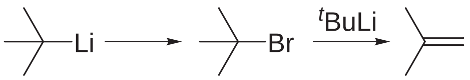


- configurationally stable
- retention of configuration



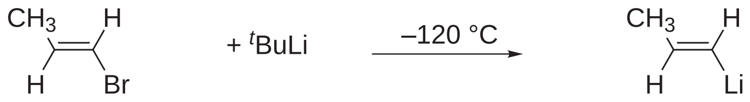
Seebach *Tetrahedron Lett.* **1976**, 4839.
Hoye *J. Org. Chem.* **1982**, *47*, 331.

Note: 2 equiv of reagent are required

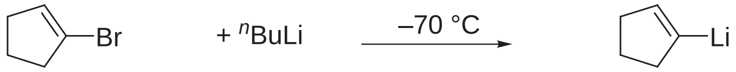


^{n}BuLi -> ^{n}BuBr - slower elimination but such products may still compete with desired electrophile for reaction with the generated organolithium reagent.

- Additional examples

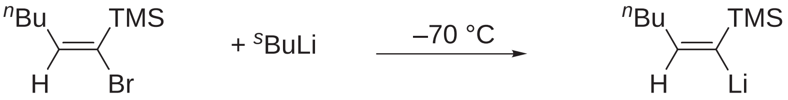


Seebach *Tetrahedron Lett.* **1976**, 4839.

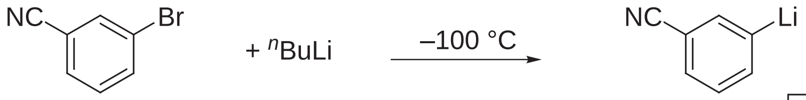


Linstrumelle *Synthesis* **1975**, 434.

Corey *Tetrahedron Lett.* **1975**, 3685.

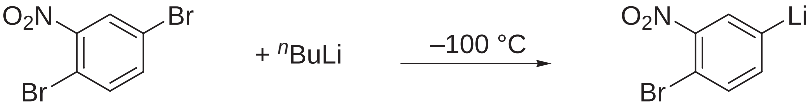


Miller *J. Org. Chem.* **1979**, *44*, 4623.



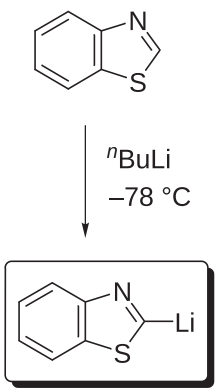
Parham *J. Org. Chem.* **1976**, *41*, 1187.

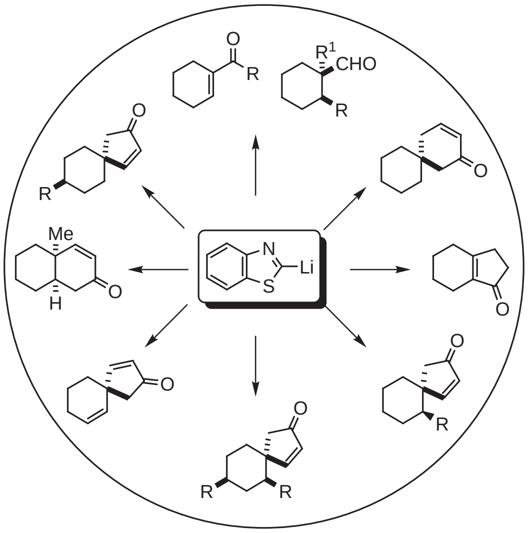
note: metalation in presence of reactive groups.

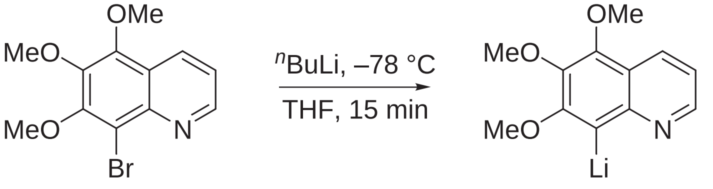


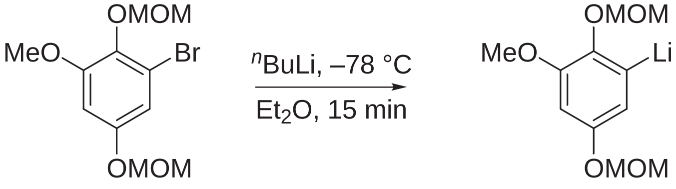
Parham *J. Org. Chem.* **1977**, *42*, 257.

Corey and Boger *Tetrahedron Lett.* **1978**, 5, 9, and 13.







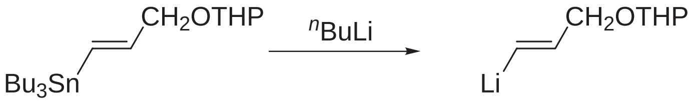


Boger *J. Org. Chem.* **1984**, *49*, 4050.
J. Am. Chem. Soc. **1995**, *117*, 12452.

Boger *J. Org. Chem.* **1991**, *56*, 2115.
J. Am. Chem. Soc. **1995**, *117*, 11839.

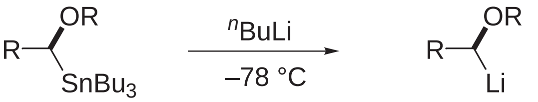
C. Organolithium Compounds by Metal–Metal Exchange

- Reactions of organotin reagents with alkyllithium reagents are particularly significant.



Proceeds in direction of placing the more electropositive metal on the more electronegative (acidic) carbon.

Corey *J. Org. Chem.* **1975**, *40*, 2265.



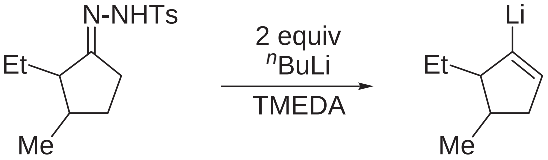
$$R_2NCH_2SnBu_3 \xrightarrow[0\ °C]{^{n}BuLi} R_2NCH_2Li$$

Still *J. Am. Chem. Soc.* **1978**, *100*, 1481.
J. Am. Chem. Soc. **1980**, *102*, 1201.
McGarvey Macdonald *J. Am. Chem. Soc.* **1988**, *110*, 842.

- transmetalation with retention and maintenance of configuration

Peterson *J. Am. Chem. Soc.* **1971**, *93*, 4027.

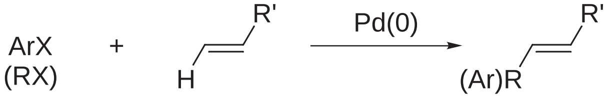
D. Organolithium Compounds from the Shapiro Reaction



Bamford, Stevens *J. Chem. Soc.* **1952**, 4735.
Shapiro *Org. React.* **1976**, *23*, 405.
Bond *J. Org. Chem.* **1981**, *46*, 1315.
Chamberlin *Org. React.* **1990**, *39*, 1.

E. Key Organometallic Reactions Enlisting Metalation and Transmetalation Reactions

Heck Reaction



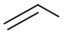
Heck *J. Am. Chem. Soc.* **1974**, *96*, 1133.
Org. React. **1982**, *27*, 345.
Acc. Chem. Res. **1979**, *12*, 146.

Stille Coupling Reaction

$$RX + R'SnR_3 \xrightarrow{Pd(0)} R{-}R'$$

Stille *J. Am. Chem. Soc.* **1978**, *100*, 3636.
Farina *Org. React.* **1997**, *50*, 1.
Stille *Angew. Chem., Int. Ed. Eng.* **1986**, *25*, 508.

↓

RCOCl, X, ArX, XCH_2CO_2R

1) oxidative addition (R–Pd–X), generally rate determining step
2) transmetalation (R–Pd–R' + $XSnR_3$ or $XB(OH)_2$)
3) reductive elimination (R–R' + Pd(0))

Suzuki Reaction

$$RX + R'B(OH)_2 \xrightarrow{Pd(0)} R{-}R'$$

↓

I > OTf > Br >> Cl: generally the initial oxidative addition is the rate determining step.

Suzuki *J. Chem. Soc., Chem. Commun.* **1979**, 866.
Suzuki *Chem. Rev.* **1995**, *95*, 8457.

X. Key Ring Forming Reactions

A. Diels–Alder Reaction

1. Reviews

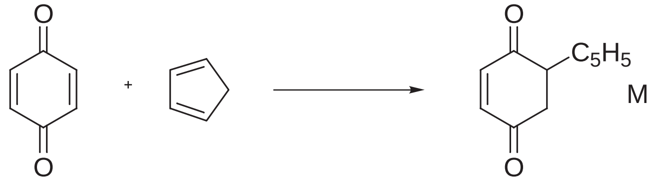
1. General reference: Onishchenko, A. S. *Diene Synthesis*; Daniel Davy: New York, 1964.
2. General reference: Wasserman, A. *Diels–Alder Reactions*; Elsevier: New York, 1965.
3. General review: Alder, K. *Newer Methods of Preparative Organic Chemistry*, Vol. 1, Wiley: New York, 1948, pp 381–511.
4. General review: Huisgen, R.; Grashey, R.; Sauer, J. in *Chemistry of Alkenes*; S. Patai, Ed.; Wiley: New York, 1964, pp 878–953.
5. General review: Wollweber, H. in Houben–Weyl, *Methoden der Organischen Chemie*; E. Muller, Ed.; Georg Thieme: Stuttgart, 1970, pp 977–1210.
6. General reference: Wollweber, H. *Diels–Alder Reaction*; Georg Thieme: Stuttgart, 1972.
7. General reference: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions;* Wiley: New York, 1977.
8. Diels–Alder reactions with maleic anhydride: Kloetzel, M. C. *Org. React.* **1948**, *4*, 1.
9. Diels–Alder reactions with ethylenic and acetylenic dienophiles: Holmes, H. L. *Org. React*. **1948**, *4*, 60.
10. Diels–Alder reactions with quinones: Butz, L. W.; Rytina, A. W. *Org. React*. **1949**, *5*, 136.
11. Diels–Alder reaction: preparative aspects: Sauer, J. *Angew. Chem., Int. Ed. Eng.* **1966**, *5*, 211.
12. Diels–Alder reaction: mechanism: Sauer, J. *Angew. Chem., Int. Ed. Eng*. **1967**, *6*, 16.
13. Stereochemistry of the Diels–Alder reaction: Martin, J. G.; Hill, R. K. *Chem. Rev*. **1961**, *61*, 537.
14. Regiochemistry of the Diels–Alder reaction: Titov, Y. A. *Russ. Chem. Rev*. **1962**, *31*, 267.
15. Mechanism of the Diels–Alder reaction: Seltzer, S. *Adv. Alicycl. Chem*. **1968**, *2*, 1.
16. Diels–Alder reaction of heteroatom-substituted dienes: Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753.
17. Preparation and Synthetic Aspects: Wagner-Jauregg, T. *Synthesis* **1976**, 349; *Synthesis* **1980**, 165, 769.
18. Diels–Alder reaction of azadienes: Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.
19. Review on "Danishefsky's diene" and related dienes: Danishefsky, S. *Acc. Chem. Res*. **1981**, *14*, 400.
20. Intramolecular Diels–Alder reaction: Carlson, R. G. *Ann. Rep. Med. Chem*. **1974**, *9*, 270.
21. Intramolecular Diels–Alder reaction: Oppolzer, W. *Angew. Chem.* **1977**, *16*, 10.
22. Intramolecular Diels–Alder reaction of *o*-quinodimethanes: Oppolzer, W. *Synthesis* **1978**, 793.
23. Intramolecular Diels–Alder reaction: Brieger, G.; Bennett, J. N. *Chem. Rev*. **1980**, *80*, 63.
24. Intramolecular Diels–Alder reaction: Ciganek, E. *Org. React*. **1984**, *32*, 1.
25. Intramolecular Diels–Alder reaction: Fallis, A. G. *Can. J. Chem*. **1984**, *62*, 183.
26. Intermolecular Diels–Alder reaction: Oppolzer, W. in *Comprehensive Organic Synthesis*, Vol. 5; pp 315–399.
27. Intramolecular Diels–Alder reaction: Roush, W. R. in *Comprehensive Organic Synthesis*, Vol. 5; pp 513–550.
28. Retrograde Diels–Alder reactions: Sweger, R. W. in *Comprehensive Organic Synthesis*, Vol. 5; pp 551–592.
29. The Retro Diels–Alder reaction: Rickborn, B. *Org. React*. **1998**, *52*, 1.
30. Heterodienophile Diels–Alder reactions: Weinreb, S. M. in *Comprehensive Organic Synthesis*, Vol. 5; pp 401–449.
31. Heterodiene Diels–Alder reactions: Boger, D. L. in *Comprehensive Organic Synthesis*, Vol. 5; pp 451–512.
32. Hetero Diels–Alder reaction: Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: San Diego, 1987.
33. Catalytic Asymmetric Diels–Alder reactions: Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.
34. Asymmetric Hetero Diels–Alder reaction: Waldermann, H. *Synthesis* **1994**, 535.

2. Discovery

Wieland (*Ber*. **1906**, *39*, 1492) described the 1:1 dimerization of conjugated dienes in what was probably the first report of a Diels–Alder reaction.

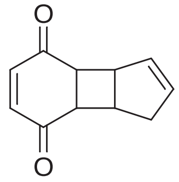
Wieland received the 1927 Nobel Prize in Chemistry for his steroid work unrelated to these observations.

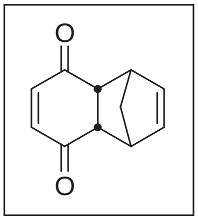
Albrecht (Thiele) Reaction:
Ann. **1906**, *348*, 31.



Misassigned structure

Staudinger Structure:
Die Ketene, Stuttgart
1912, 59.

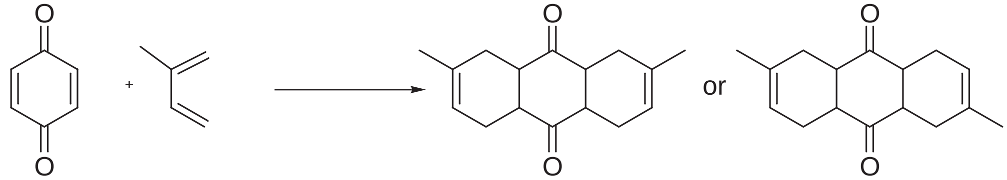




Structure established by Diels and Alder, and they went on to define scope and mechanism of the reaction. For this, they received the 1950 Nobel Prize in Chemistry.

Diels and Alder *Ann*. **1928**, *460*, 98.

In fact, von Euler had correctly, but tentatively, identified the 2:1 adduct of isoprene with *p*-benzoquinone before Diels and Alder's work. von Euler, Josephson *Ber*. **1920**, *53*, 822.



von Euler received the 1929 Nobel Prize in Chemistry for his investigations on fermentations of sugars and the fermentative enzymes. He had trained with Landolt, Nernst, van't Hoff, Arrhenius, Hantzsch, and Thiele and was remarkable in his scientific pursuits. By 1910, he had already initiated his monumental studies of enzyme structure, kinetics, and mechanism and his occasional forays into pure organic chemistry were just as remarkable.

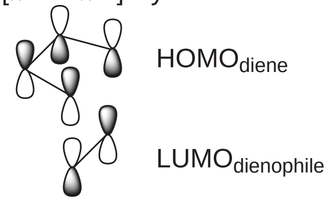
For an engaging description of the discovery of the Diels–Alder reaction, the competition for its exploration and applications, and the missed opportunities, see: Berson *Tetrahedron* **1992**, *48*, 3.

Even in their first disclosure, Diels and Alder recognized the potential the reaction might hold for synthesis: "Thus, it appears to us that the possibility of synthesis of complex compounds related to or identical with natural products such as terpenes, sesquiterpenes, perhaps also alkaloids, has moved to a near prospect." They also felt this could be reserved: "We explicitly reserve for ourselves the application of the reaction discovered by us to the solution of such problems." Fortunately, this was not the case and an extraordinary group of investigators helped define the scope and mechanism of the Diels–Alder reaction.

The first applications in total synthesis include: Cortisone by Woodward, Sondheimer *J. Am. Chem. Soc.* **1951**, *73*, 2403; Sarett (Merck) *J. Am. Chem. Soc.* **1952**, *74*, 4974. Cantharidin by Stork, Burgstahler, van Tamelen *J. Am. Chem. Soc.* **1951**, *73*, 4501.

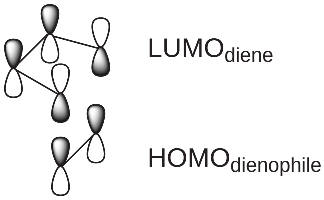
3. Mechanism, FMO Treatment

[$\pi^2s + \pi^4s$] Cycloaddition



This is the dominant interaction in a normal Diels–Alder reaction.

Alternatively:



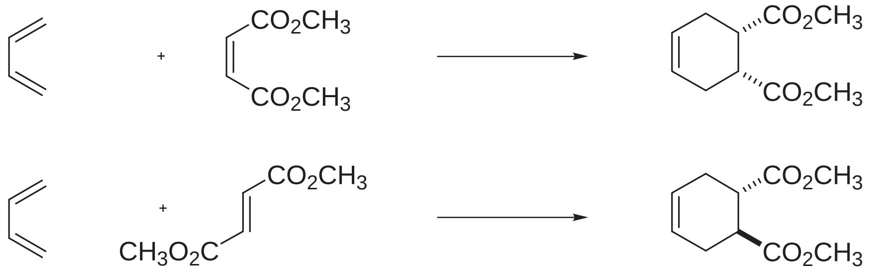
Dominant interaction in an inverse electron demand Diels–Alder reaction.

1. Large E_a for the reactions.
2. Driving force is formation of two new σ bonds accompanying the loss of two π bonds.

4. Diastereoselectivity

a. *cis* Principle: Geometry of dienophile and diene are maintained in the [4 + 2] cycloadduct.

e.g.

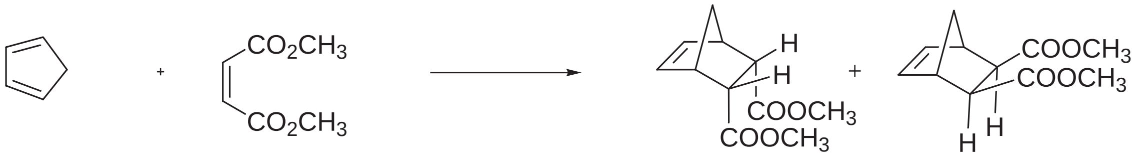


Stereospecific

b. Alder's Endo Rule:

Stereoselective ← *Endo* product and *endo* transition state predominate even though *exo* products are usually more stable; *endo* is the kinetic product.

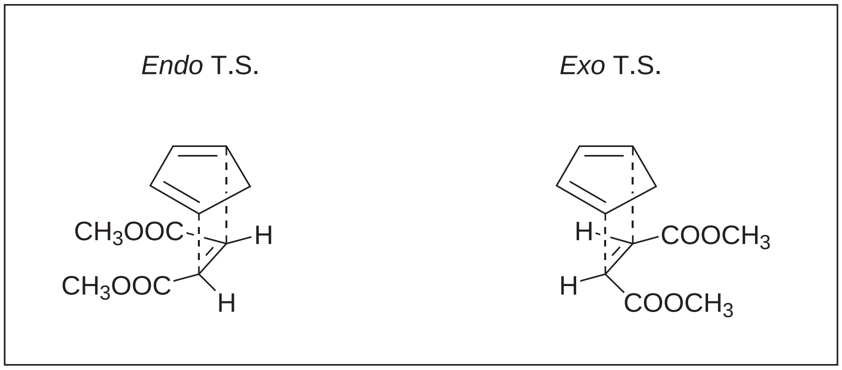
e.g.



endo Major

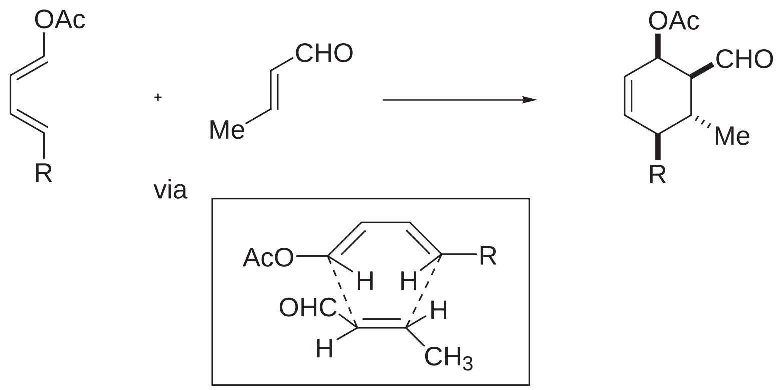
exo Minor

Endo, boat transition state



Result: Both *cis* rule and *endo* rule $\Longrightarrow$ Diels–Alder reaction very useful, diastereoselective

c. Factors influencing *endo* selectivity of the Diels–Alder reaction



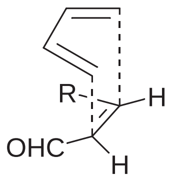
i. *Endo* transition state is favored by stabilizing secondary orbital interactions.

ii. *Endo* selectivity often increases with the use of Lewis acid catalysis.

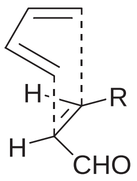
iii. *Endo* selectivity often increases with increase in pressure of reaction.

Endo selectivity ↑ , pressure ↑

$\Delta\Delta V^{\ddagger}$ = –4 to –8 cm^3/mol
(*endo*/*exo*)



endo T.S.



exo T.S.

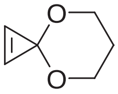
Raistrick *J. Chem. Soc.* **1939**. 1761, 1770.
Jones *Tetrahedron* **1962**, *18*, 267.
Dauben demonstrated pressure-promoted reactions are viable:
J. Am. Chem. Soc. **1974**, *96*, 3664.
J. Am. Chem. Soc. **1976**, *98*, 1992.
J. Org. Chem. **1977**, *42*, 282.

-$\Delta V^{\ddagger}$ is negative (–25 to –38 cm^3/mol). So increase pressure, increase rate of reaction.

↓

-And *endo* T.S. is more compact, so $\Delta\Delta V^{\ddagger}$ for *endo*:*exo* also negative.
(i.e., diastereoselectivity increases)

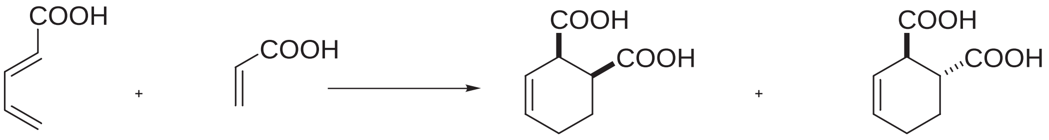
Example of



Boger *J. Am. Chem. Soc.* **1988**, *108*, 6695 and 6713.

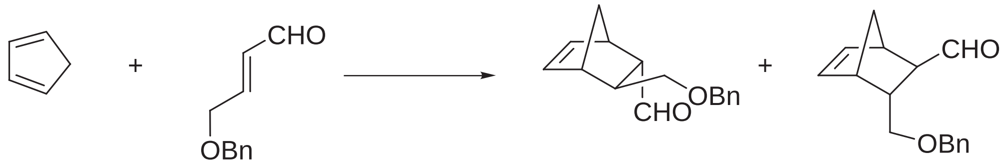
iv. *Endo* selectivity also increases with decreases in temperature at which the reaction is conducted

e.g.



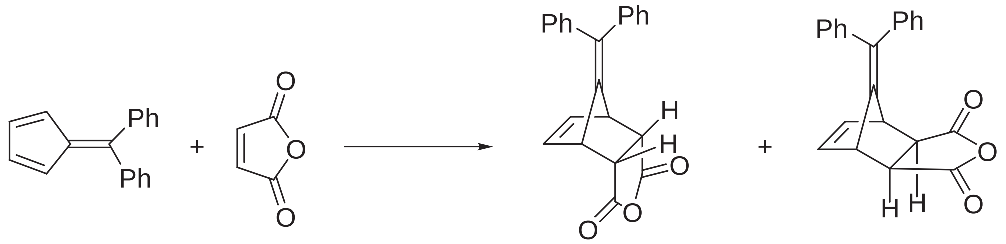
Endo selectivity ↑ , temperature ↓

temp.	*endo*		*exo*
75 °C	only *endo*		
90 °C	7	:	1
100 °C	4.5	:	1
110 °C	2	:	1
130 °C	1	:	1



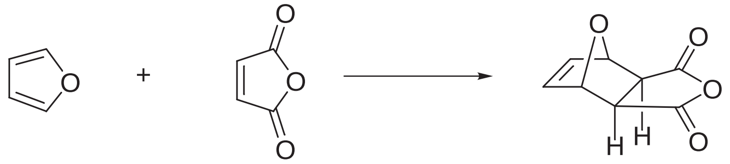
conditions	*endo*		*exo*
10 days, 0 °C	66	:	34
6 h, 200 °C	34	:	66
Lewis acid-catalyzed → BF$_3$•OEt$_2$, 5 min, –20 °C	90	:	10

Furukawa *J. Am. Chem. Soc.* **1970**, *92*, 6548.



temp.	*endo*		*exo*
25 °C	100	:	0
140 °C	29	:	71

Some Diels–Alder adducts are thermally unstable (reversible) and subject to equilibration via retro Diels–Alder reaction to provide the most stable product: Ripoll *Tetrahedron* **1978**, *34*, 19.

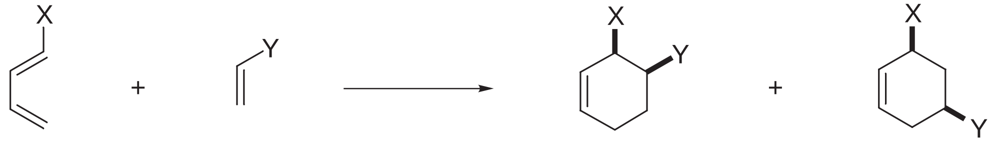


100% *exo*

see also: Rickborn *Org. React.* **1998**, *52*, 1.

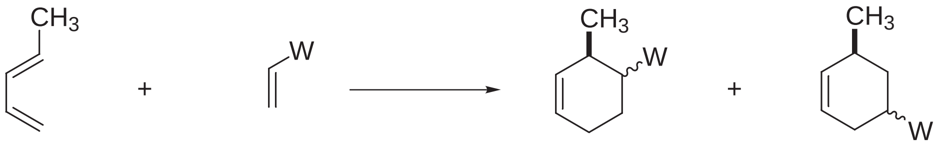
5. Regioselectivity

a. 1-Substituted dienes react with substituted dienophiles to give the *ortho* product:



usually around 9:1

For example:

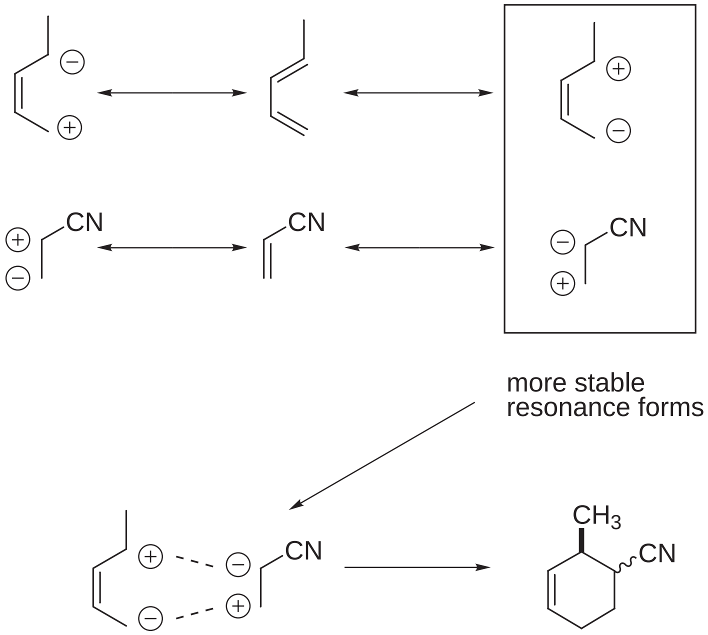


W = CN	100 °C, 12 h, 30%	9	:	1
= COOR	200 °C, 2 h, 85%	6.8	:	1

higher temperature decreases regioselectivity

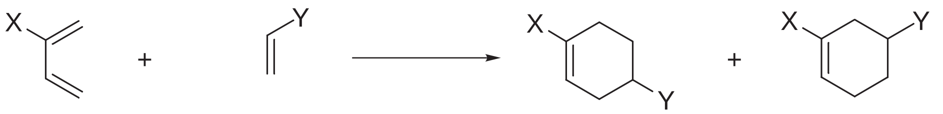
regioselectivity lower, because COOR not as strongly electron-withdrawing as CN

-Device for predicting regioselectivity: draw out "zwitterionic" representations (resonance structures) for the reactants.



Reaction: 100 °C, 12 h
30%, 9:1 regioselectivity

b. 2-Substituted dienes give predominantly the *para* product:



X = CH_3	Y = $COOCH_3$	6	:	1
= OCH_3	= $COOCH_3$	10	:	1
= CN	= $COOCH_3$	10	:	1

higher regioselectivity because OCH_3 better donating group than CH_3.

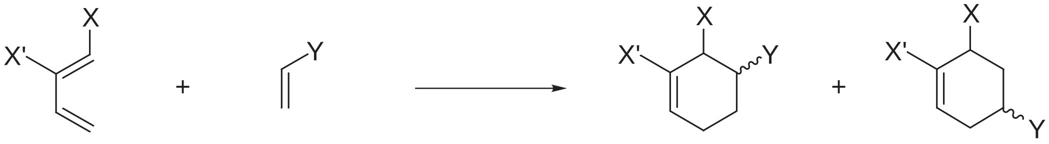
c. Complementary substitution usually provides even greater regioselectivity

-1,3-Disubstituted Dienes

ortho to X group
para to X' group

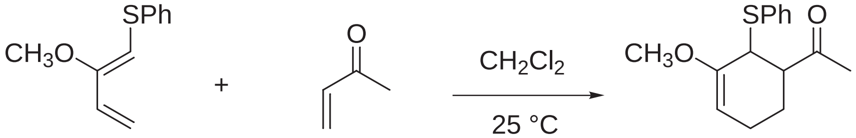
But noncomplementary substitution may cause problems (lower regioselectivity)

-1,2-Substituted Dienes



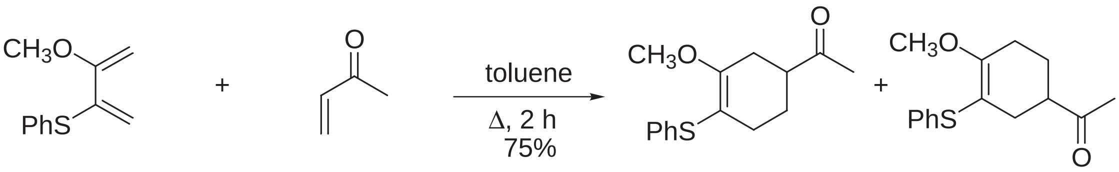
relative amounts of each depend on electron donating strength of substituents X and X'

$NHCO_2R$ > SR > OR > alkyl > H



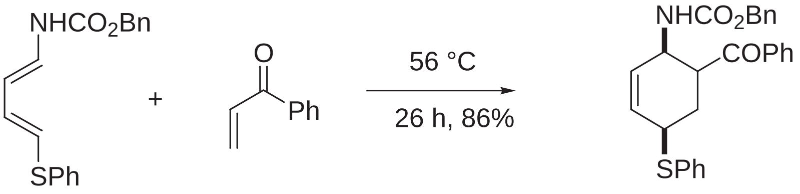
85% 100:0

Cohen *J. Org Chem*. **1982**, *47*, 4005.



> 5 : 1

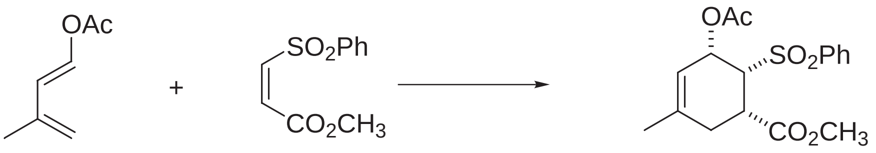
Trost *J. Am. Chem. Soc*. **1980**, *102*, 3548.



Overman *J. Am. Chem. Soc*. **1983**, *105*, 6335.

d. Apparent regioselectivity can be altered by adding a controlling group that is subsequently removed

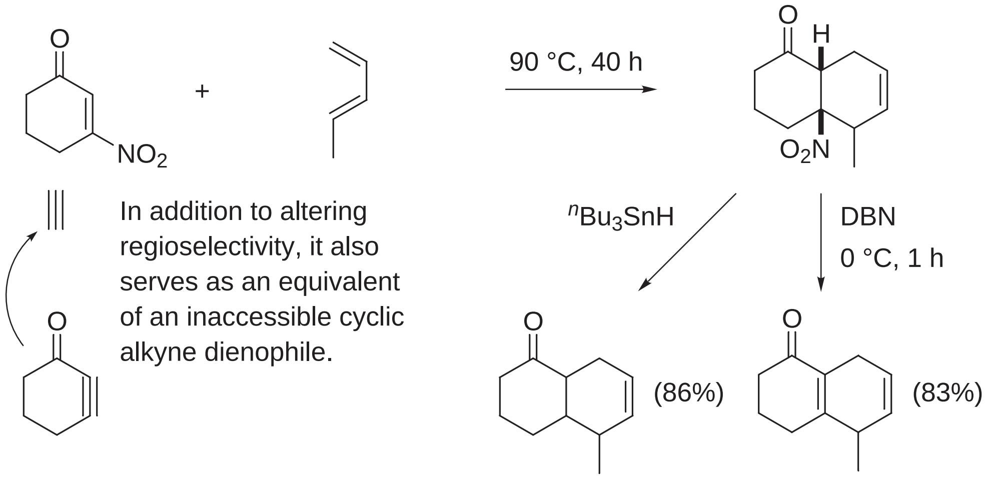
-Dienophile



-*endo* addition
-CO_2CH_3 is in *meta* position
-SO_2Ph > CO_2CH_3 in controlling regioselectivity

Parsons *J. Chem. Soc., Chem. Commun.* **1987**, 1836.

- Diene

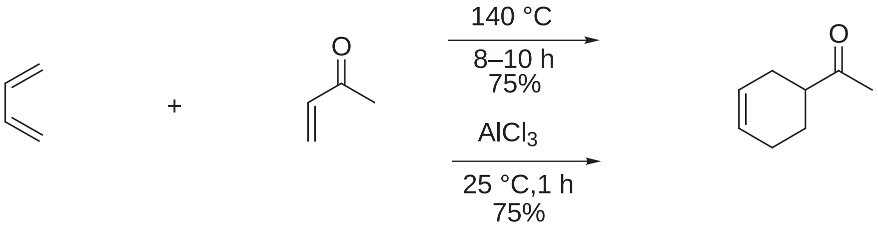


In addition to altering regioselectivity, it also serves as an equivalent of an inaccessible cyclic alkyne dienophile.

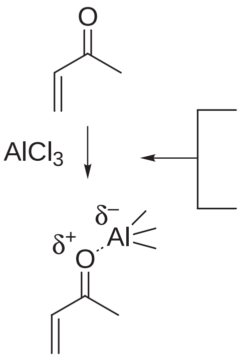
Corey *Tetrahedron Lett.* **1981**, *22*, 603.
Ono *J. Chem. Soc., Perkin Trans. 1* **1987**, 1929.
Tanis *Syn. Commun.* **1986**, *16*, 251.

Rate of reaction generally insensitive to solvent polarity, but...

6. Lewis Acid Catalysis



Addition of Lewis Acid Catalysts:



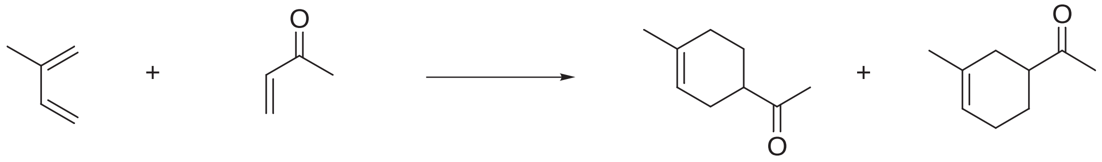
i. Lowers LUMO of dienophile, so increases rate of reaction.

ii. Increases the difference in magnitude of coefficients of dienophile
-----so increases regioselectivity.

iii. Changes coefficient at dienophile substituent, so increases opportunity of secondary orbital interactions
.....often increases *endo* stereoselectivity.

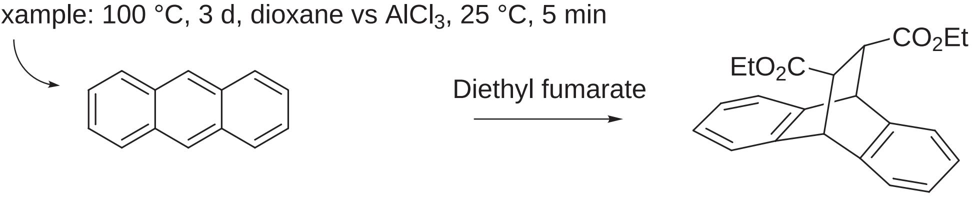
Increases:
1. Reaction Rate
2. Reaction Regioselectivity
3. Reaction *Endo* Diastereoselectivity

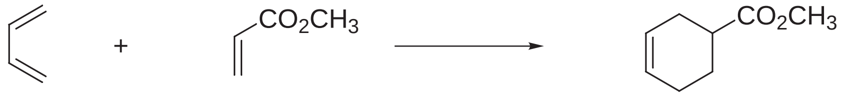
-Examples



Lutz *J. Am. Chem. Soc*. **1964**, *86*, 3899.	toluene, 120 °C, 24 h	71	:	29
Yates *J. Am. Chem. Soc*. **1960**, *82*, 4436.	$SnCl_4$, benzene, 25 °C, 1 h	93	:	7

1st example: 100 °C, 3 d, dioxane vs $AlCl_3$, 25 °C, 5 min

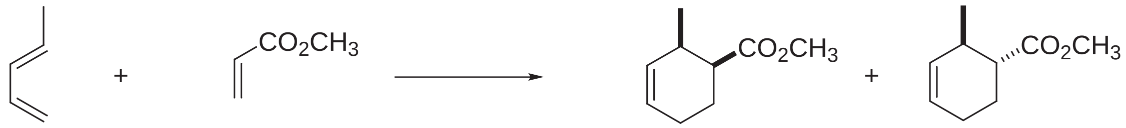




$AlCl_3$: $\Delta G^{\ddagger}$ 9.3 kcal/mol lower than uncatalyzed reaction

Inukai, Kojima *J. Org. Chem*. **1967**, *32*, 872.

ΔE *endo/exo*:

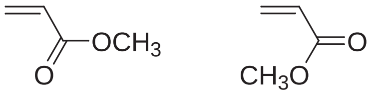


uncat. reaction: 0.2 kcal/mol; $AlCl_3$ cat. reaction: 1.8 kcal/mol

Spellmeyer , Houk *J. Am. Chem. Soc*. **1988**, *110*, 3412.
Jensen, Houk *J. Am. Chem. Soc*. **1987**, *109*, 3139.

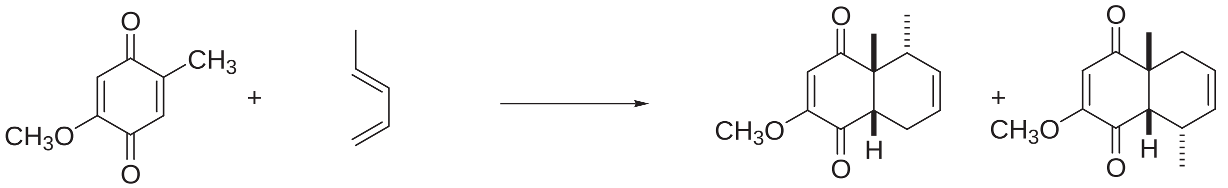
Calculations: s-*cis* > s-*trans*

ΔE for:	catalyzed reaction:	uncatalyzed reaction:
	1.9 kcal/mol for *endo*	0.6 kcal/mol for *endo*
	2.7 kcal/mol for *exo*	1.7 kcal/mol for *exo*



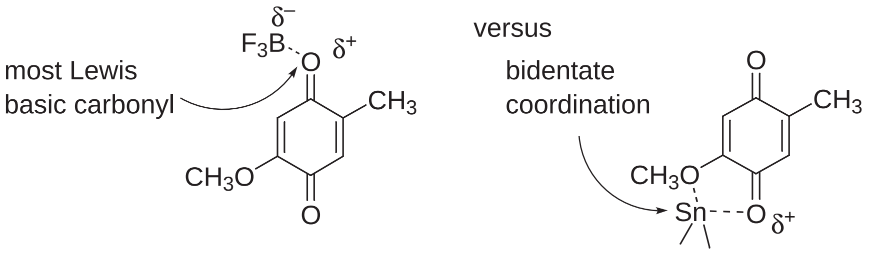
Birney, Houk *J. Am. Chem. Soc*. **1990**, *112*, 4127.

-Lewis Acid catalysis can also alter regioselectivity



100 °C	1	:	1	80%
BF_3•OEt_2, –16 °C	4	:	1	>85%
cat. $SnCl_4$, –16 °C	1	:	20	>85%

Rationalization: monodentate vs. bidentate coordination



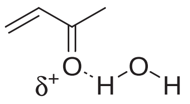
-Hydrophobic effect: H_2O solvent acceleration:

Breslow *J. Am. Chem. Soc*. **1980**, *102*, 7816.
Breslow, Rideout *Tetrahedron Lett*. **1983**, *24*, 1901.

also:

Sternbach *J. Am. Chem. Soc*. **1982**, *104*, 5853.
Grieco *Tetrahedron Lett*. **1983**, *24*, 1897.

Jorgensen - Hydrogen-bonding of H_2O serves in the same capacity as a mild Lewis acid.



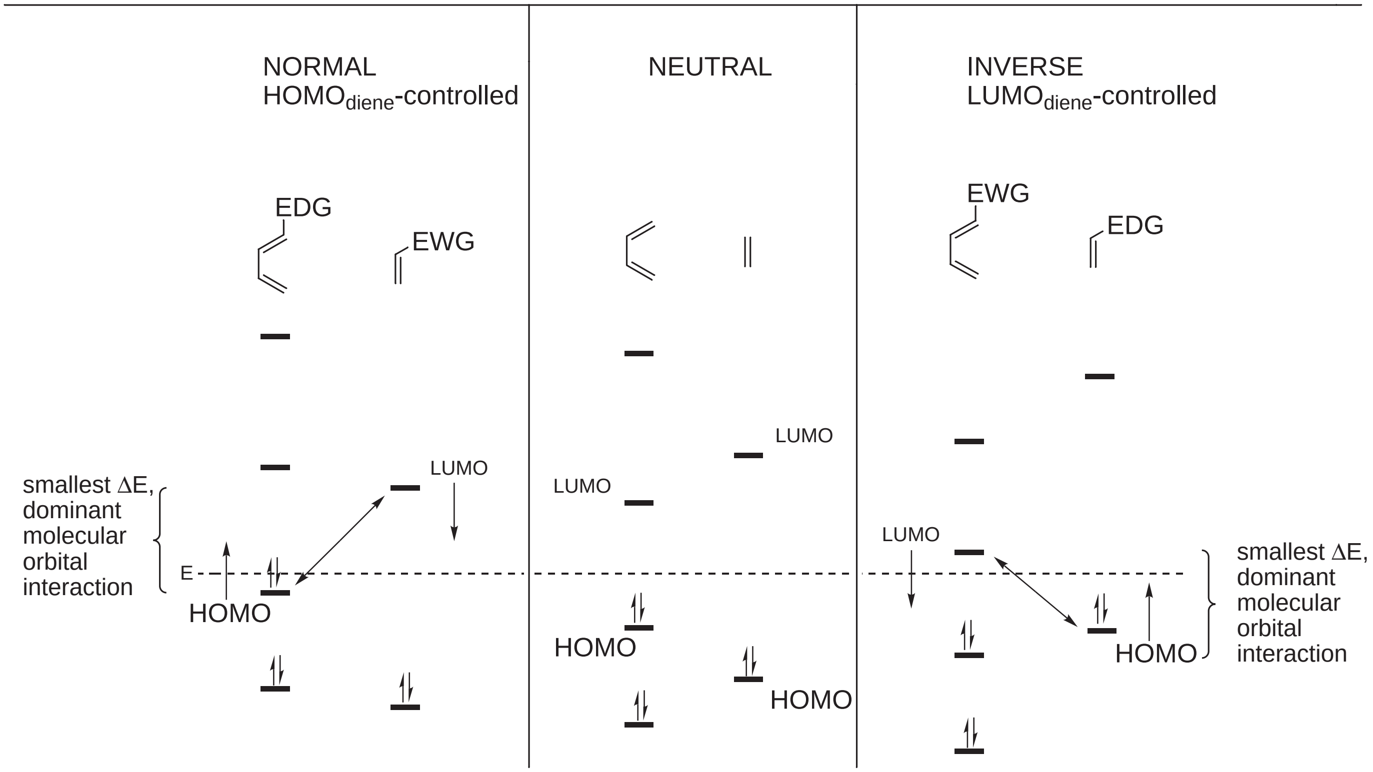
requires H-bonding carbonyl
requires H-bonding solvent

Jorgensen *J. Am. Chem. Soc*. **1991**, *113*, 7430.
J. Org. Chem. **1994**, *59*, 803.

7. Detailed FMO Analysis

-Using simple computational tools now available, one can quickly and easily predict regioselectivity and comparatively assess rate and diastereoselectivity of a Diels–Alder reaction by examining the frontier molecular orbitals (FMO). Each of the calculations that follow took < 1 min to run.

Classification of Diels–Alder Reactions.



J. A. Pople (computational methods in quantum chemistry) and W. Kohn (density-functional theory) received the 1998 Nobel Prize in Chemistry for their pioneering contributions to theoretical and computational methods for defining properties and chemical behavior.

Common Computational Tools:

Semiempirical

MNDO: Dewar *J. Am. Chem. Soc.* **1977**, *99*, 4899.

AM1: Dewar *J. Am. Chem. Soc.* **1985**, *107*, 3902.

Ab Initio

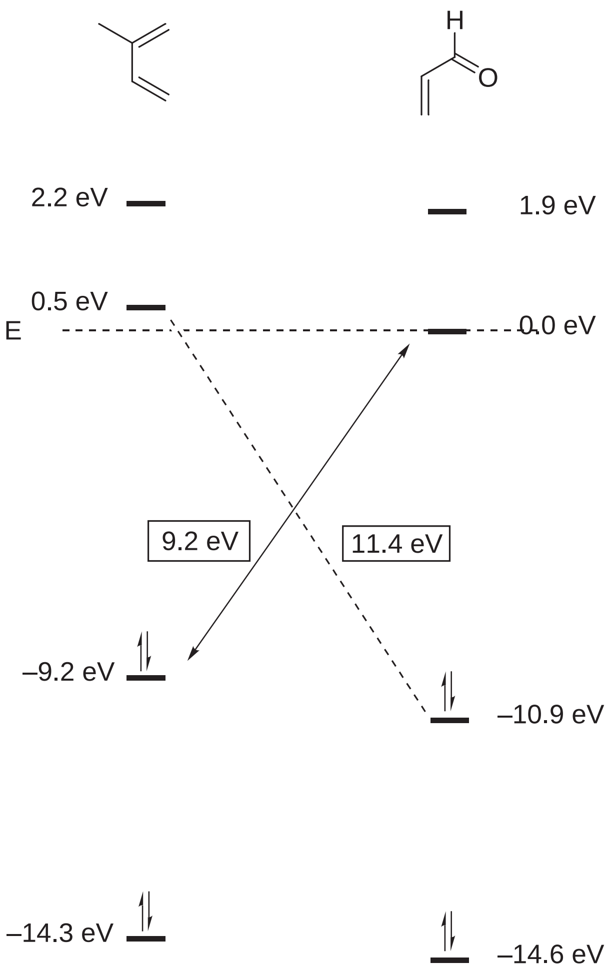
Gaussian: Pople, Carnegie-Mellon Quantum Chem. Pub. Unit, Pittsburgh, PA.

AM1 Theoretical Highest Occupied π Orbital (HOMO) and Lowest Unoccupied π Orbital (LUMO)

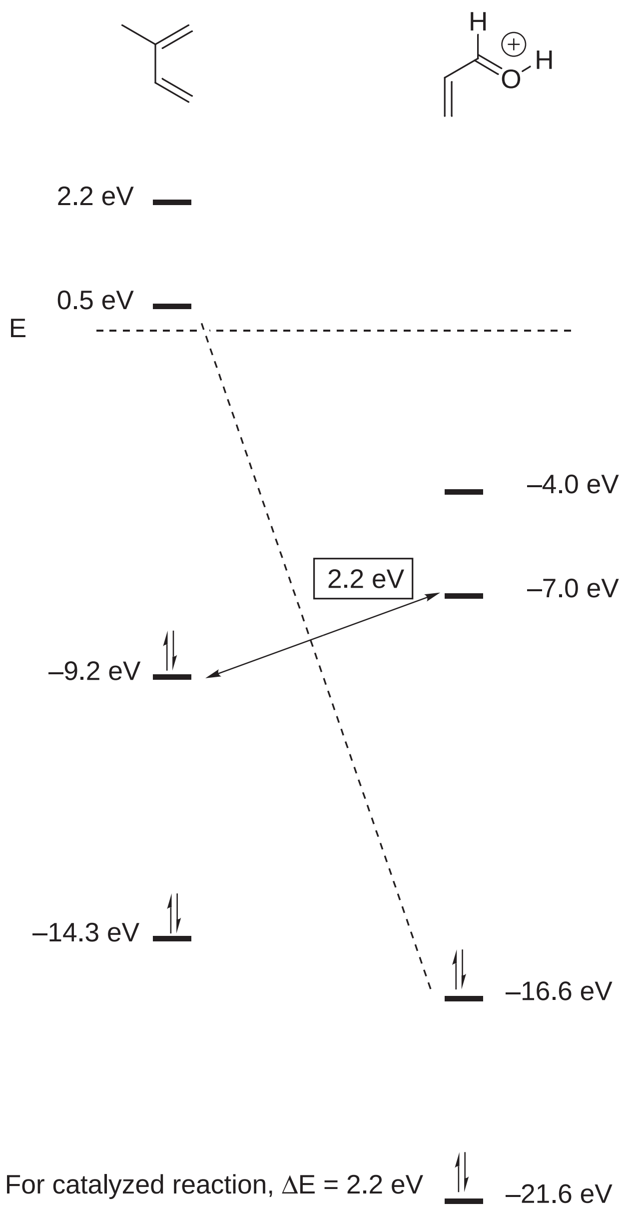
π system	E	Coefficients				
$H_2C{=}CH{-}CH{=}O$			O-1	C-2	C-3	C-4
E LUMO	0.0 eV	LUMO:	0.42	–0.50	–0.43	0.63
E HOMO	–10.9 eV	HOMO:	0.35	0.05	–0.68	–0.65
$H_2C{=}CH{-}CH{=}OH^+$						
E LUMO	–7.0 eV	LUMO:	0.36	–0.73	–0.03	0.58
E HOMO	–16.6 eV	HOMO:	0.36	0.23	–0.73	–0.53
$H_2C^4{=}CH{-}C(CH_3){=}C^1H_2$			C-1	C-2	C-3	C-4
E LUMO	0.5 eV	LUMO:	0.57	–0.43	–0.37	0.51
E HOMO	–9.2 eV	HOMO:	0.60	0.45	–0.41	–0.55
$H_2C^4{=}CH{-}C(OCH_3){=}C^1H_2$						
E LUMO	0.4 eV	LUMO:	0.51	–0.41	–0.44	0.58
E HOMO	–9.1 eV	HOMO:	0.67	0.42	–0.28	–0.41
$H_2C^2{=}CH{-}OCH_3$			C-1	C-2	**O**CH_3	
E LUMO	1.4 eV	LUMO:	0.72	–0.66	0.21	
E HOMO	–9.5 eV	HOMO:	0.48	0.69	–0.51	

AM1 π-MO's

Thermal reaction



Model for Lewis acid-catalyzed reaction



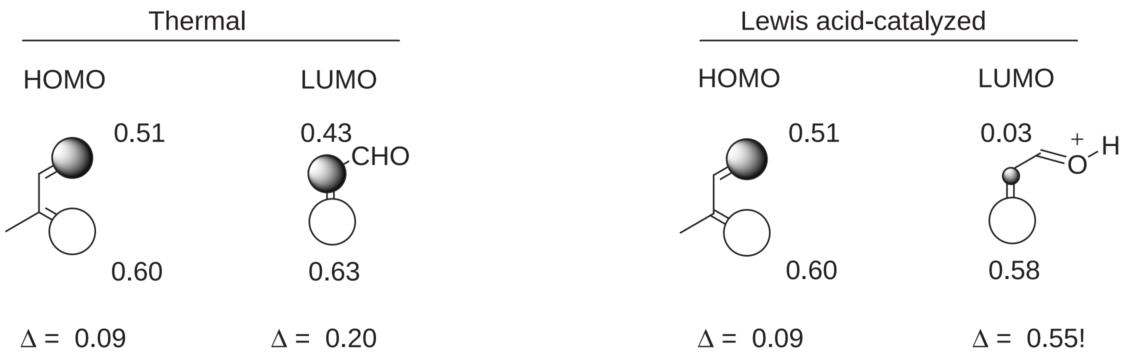
HOMO$_{\text{diene}}$ – LUMO$_{\text{dienophile}}$ energy difference is controlling factor for normal Diels-Alder reaction - making this E difference smaller will increase rate of reaction. For uncatalyzed reaction, ΔE = 9.2 eV

For catalyzed reaction, ΔE = 2.2 eV

Rate:
-Lewis acids catalyze reaction by lowering energy of π MO's of dienophile.
-Importantly, the LUMO of the dienophile becomes much lower in energy.

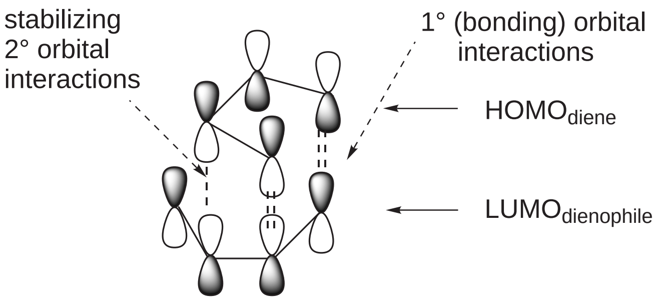
Rate increase by Lewis acid catalysis due to lowering of E of LUMO$_{\text{dieneophile}}$.

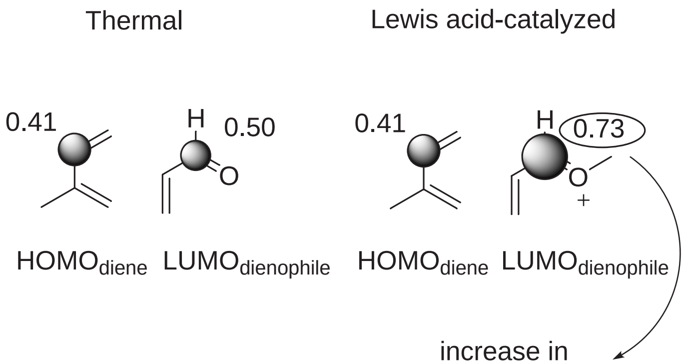
Regioselectivity:



Enhanced polarization of dienophile leads to enhanced regioselectivity.

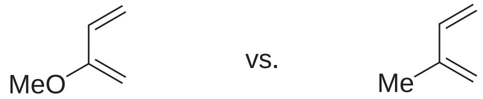
Diastereoselectivity (*endo* cycloaddition):

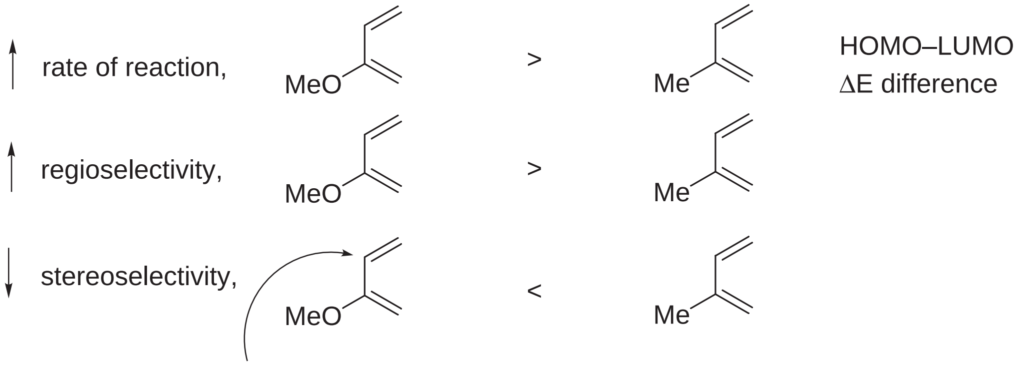




greater *endo* stereoselectivity ← gives rise to ← increase in coefficient at complexed carbonyl carbon

NOTE comparison of

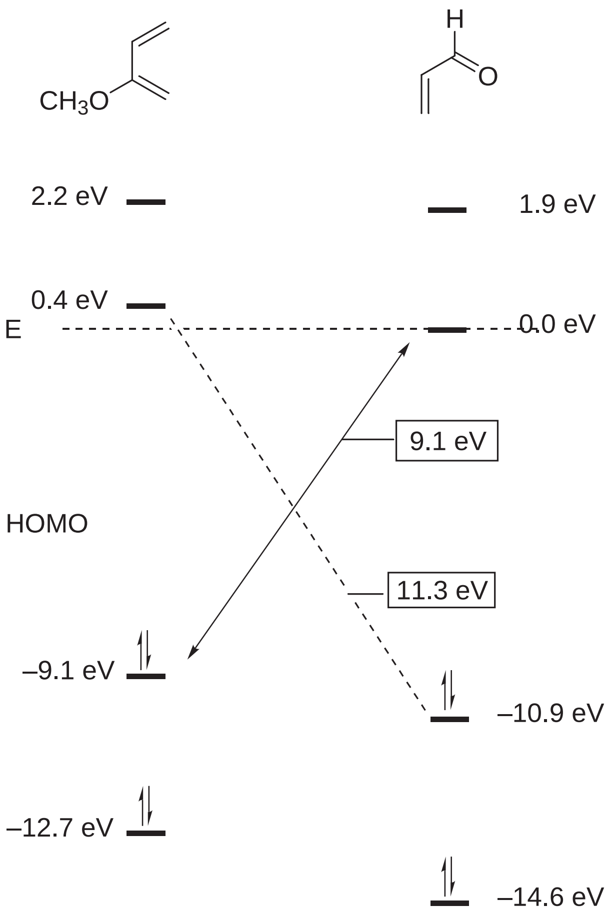




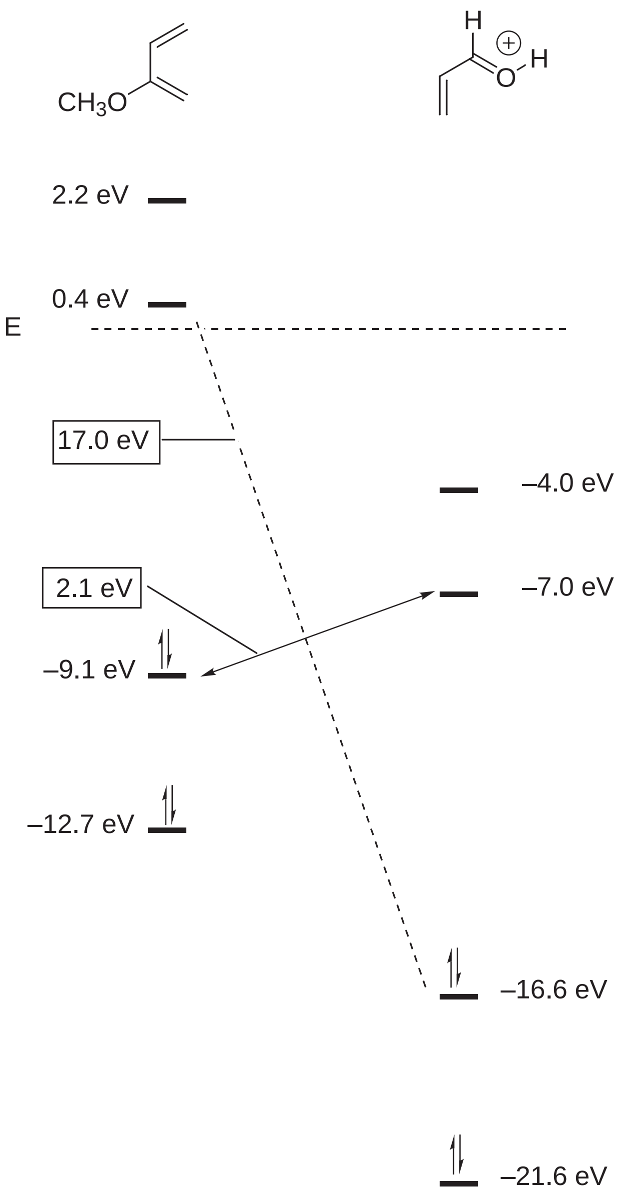
due to smaller (relative) coefficient at C3 of diene.

AM1 Results

HOMO$_{\text{diene}}$-controlled
Diels–Alder reaction



Lewis acid-catalyzed
HOMO$_{\text{diene}}$-controlled
Diels–Alder reaction

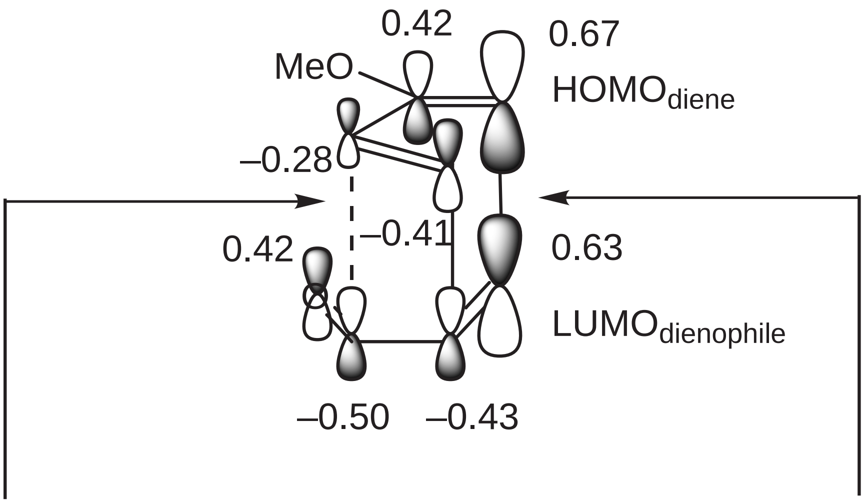


Note: 1 eV = 23.06 kcal/mol, so difference of 0.1 eV is 2.3 kcal/mol and is significant in $\Delta\Delta G^{\ddagger}$.

Rate: ΔE (E LUMO$_{\text{dienophile}}$ – E HOMO$_{\text{diene}}$) = 9.1 eV

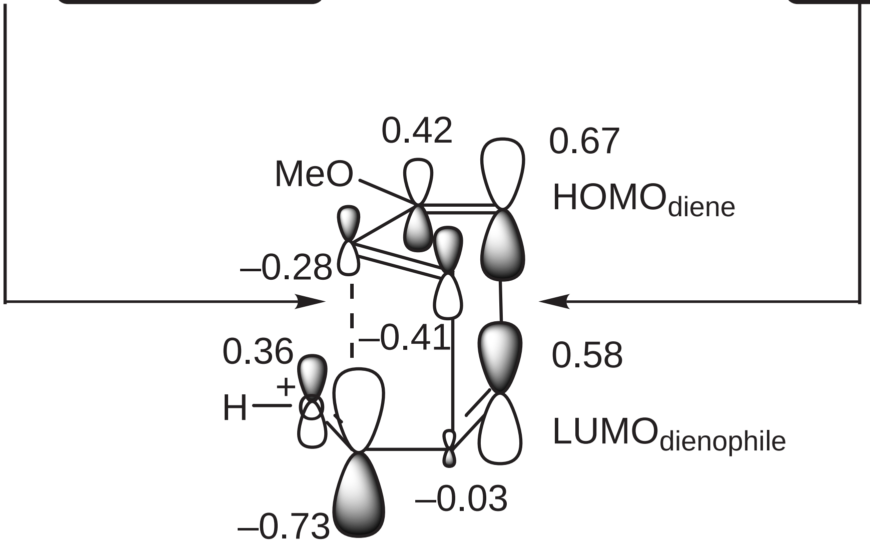
versus

ΔE (E LUMO$_{\text{diene}}$ – E HOMO$_{\text{dienophile}}$) = 11.3 eV



stabilizing secondary orbital interaction: *endo* selectivity

dominant HOMO$_{\text{diene}}$–LUMO$_{\text{dienophile}}$ orbital interaction: regioselectivity



Rate: ΔE (E LUMO$_{\text{dienophile}}$ – E HOMO$_{\text{diene}}$) = 2.1 eV

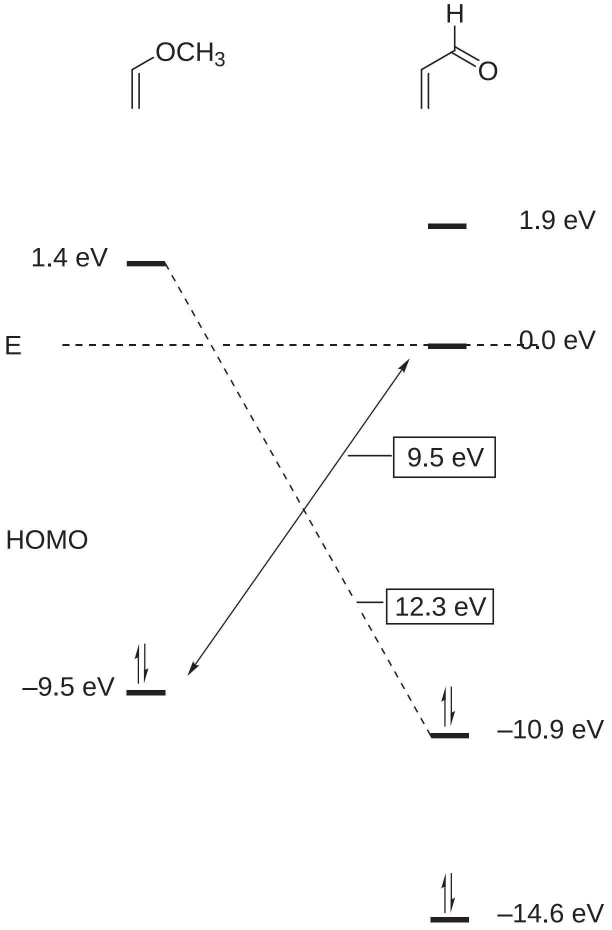
versus

ΔE (E LUMO$_{\text{diene}}$ – E HOMO$_{\text{dienophile}}$) = 17.0 eV

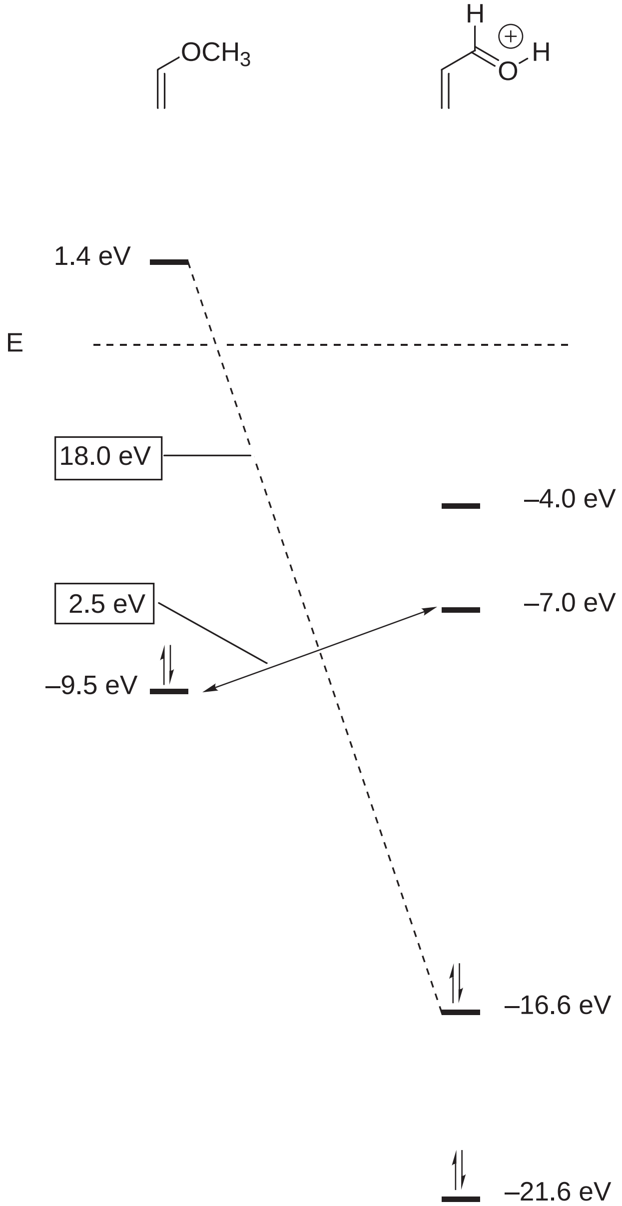
Thermal and (Lewis) acid-catalyzed HOMO$_{\text{diene}}$-controlled
Diels–Alder reaction of acrolein and 2-methoxybutadiene, AM1 results

AM1 Results

LUMO$_{\text{diene}}$-controlled
Diels–Alder reaction

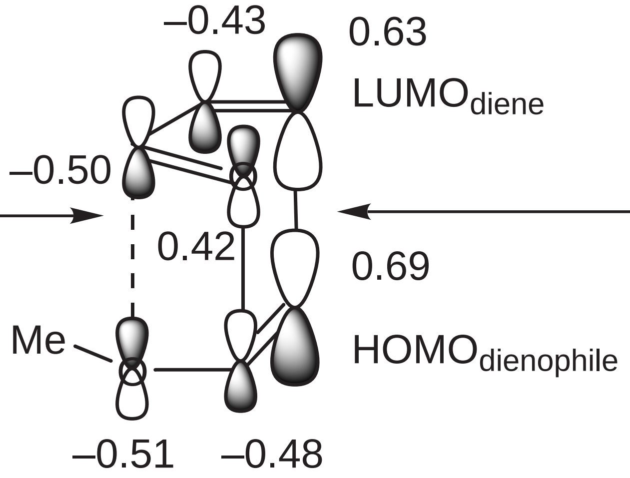


Lewis acid-catalyzed
LUMO$_{\text{diene}}$-controlled
Diels–Alder reaction



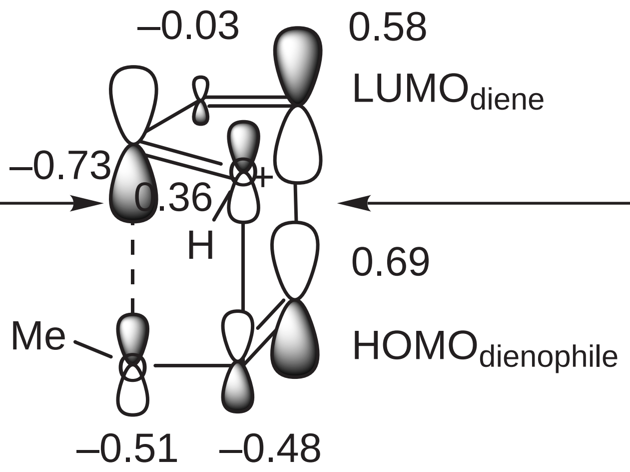
Rate:

ΔE (E LUMO$_{\text{dienophile}}$ – E HOMO$_{\text{diene}}$) = 12.3 eV
versus
ΔE (E LUMO$_{\text{diene}}$ – E HOMO$_{\text{dienophile}}$) = 9.5 eV



stabilizing secondary orbital interaction: *endo* selectivity

dominant LUMO$_{\text{diene}}$–HOMO$_{\text{dienophile}}$ orbital interaction: regioselectivity

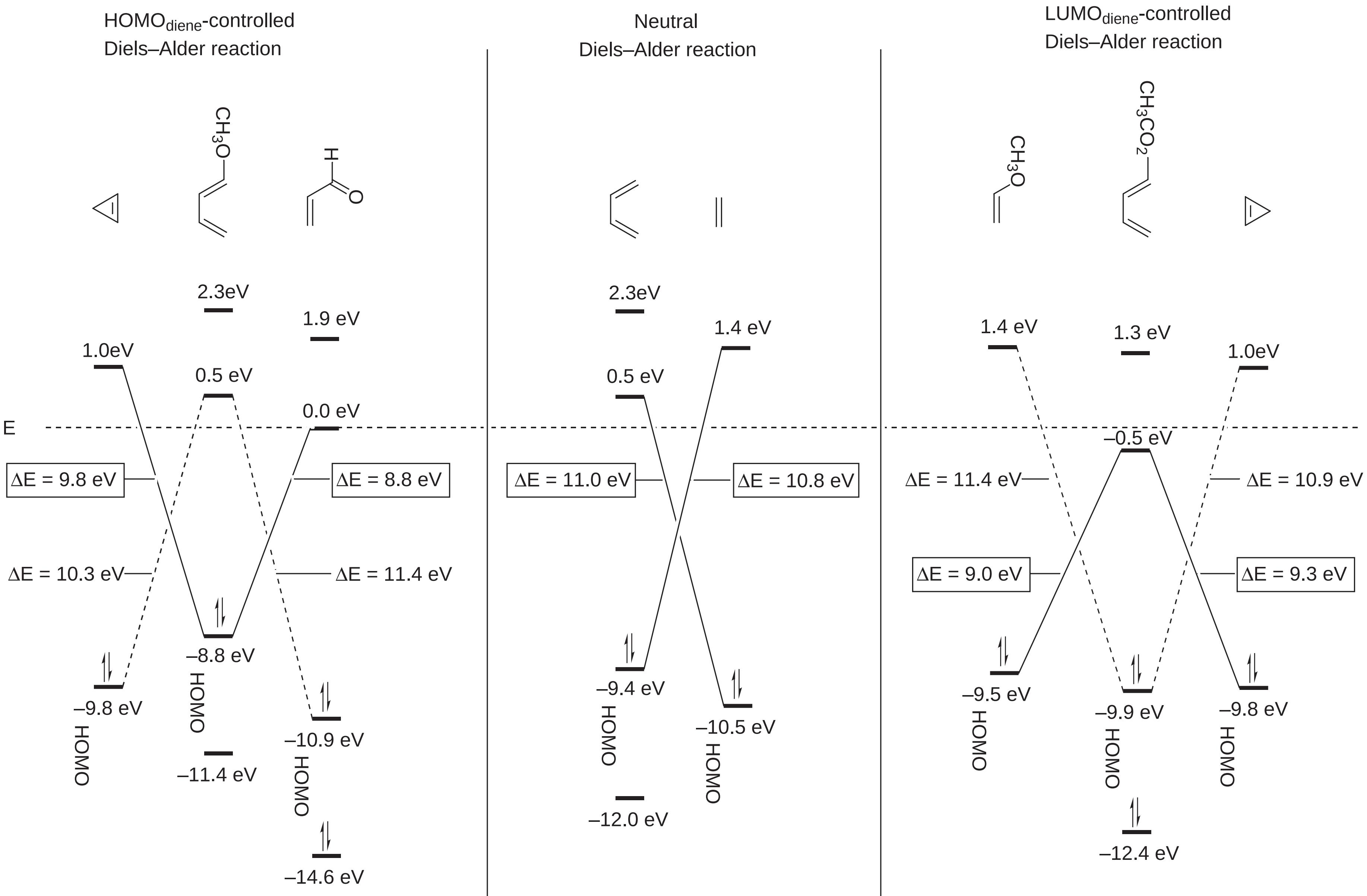


Rate:

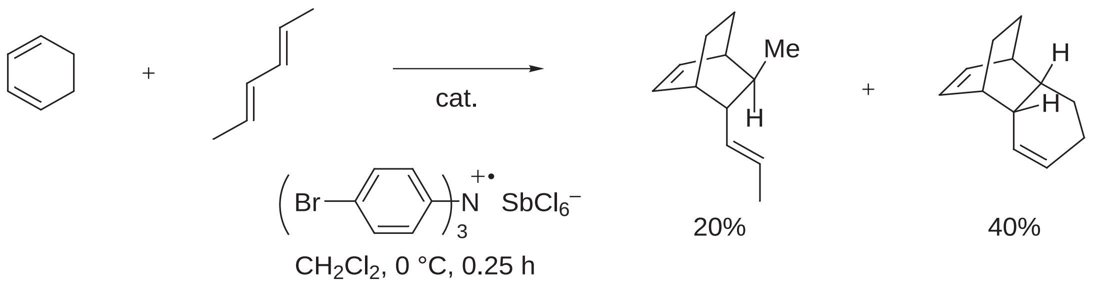
ΔE (E LUMO$_{\text{dienophile}}$ – E HOMO$_{\text{diene}}$) = 18.0 eV
versus
ΔE (E LUMO$_{\text{diene}}$ – E HOMO$_{\text{dienophile}}$) = 2.5 eV

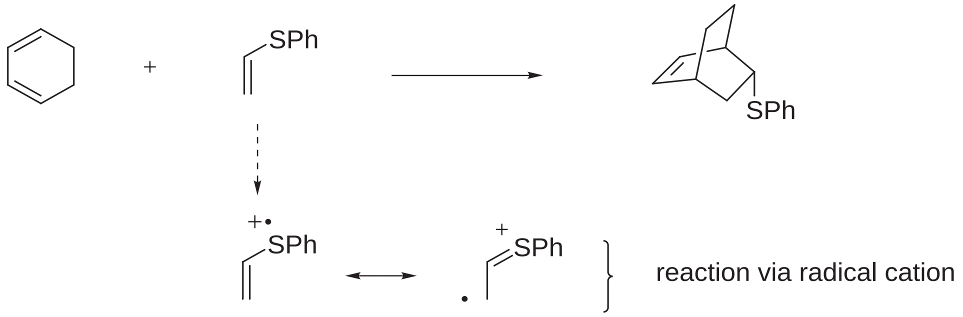
Thermal and (Lewis) acid-catalyzed LUMO$_{\text{diene}}$-controlled Diels–Alder reaction of acrolein and methyl vinyl ether, AM1 results

Strained Olefins Participate in Accelerated Normal or Inverse Electron Demand Diels–Alder Reactions: FMO Basis



8. Cation–Radical Diels–Alder Reaction

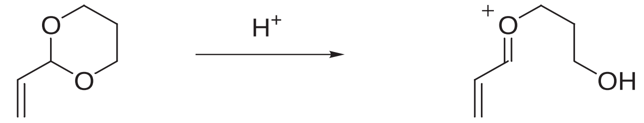




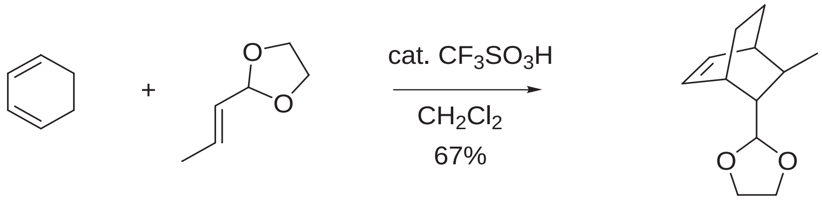
reaction via radical cation

Bauld *J. Am. Chem. Soc*. **1981**, *103*, 718; **1982**, *104*, 2665; **1983**, *105*, 2378.

9. Ionic Diels–Alder Reaction



much more reactive,
much more electron
deficient



Gassman *J. Am. Chem. Soc*. **1987**, *109*, 2182.
J. Chem. Soc., *Chem. Commun.* **1989**, 837.

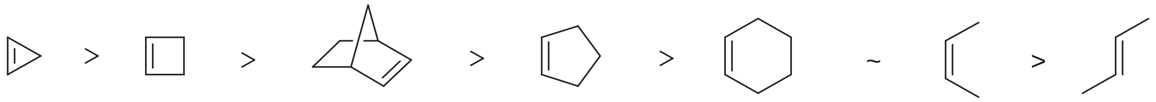
10. Dienophiles

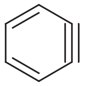
a. Effect of electron-withdrawing group

X =	COCl	> $PhSO_2$	> PhCO	> $COCH_3$	> CN ~	$COOCH_3$
relative rates:	6700	155	18	4	1.1	1.0

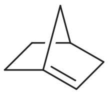
b. Alkyl groups on dienophile can slow Diels-Alder reaction (steric effect)

c. Strain in dienophile



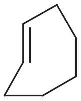


benzyne

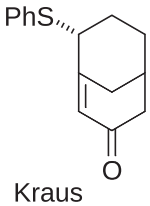


bridgehead olefins
Keese, Krebs *Angew. Chem., Int. Ed. Eng*. **1972**, *11*, 518.

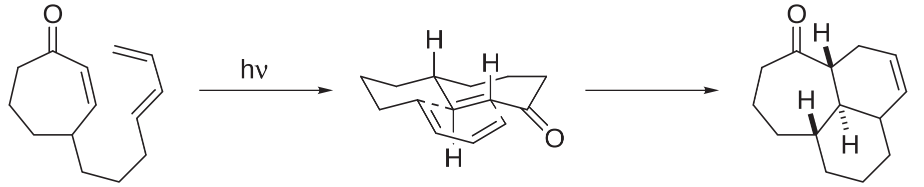
Wiberg
J. Am. Chem. Soc. **1960**, *82*, 6375.



Corey
J. Am. Chem. Soc. **1965**, *87*, 934.



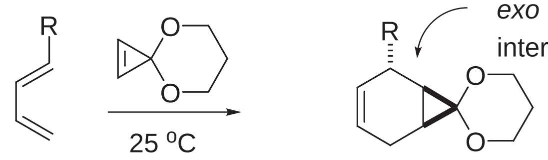
Kraus
J. Org. Chem. **1988**, *53*, 1397.



Photochemical isomerization to strained trans enone (7-membered: Corey *J. Am. Chem. Soc.* **1965**, *87*, 2051. 8-membered rings: Eaton *J. Am. Chem. Soc.* **1965**, *87*, 2052) followed by inter- or intramolecular Diels–Alder reaction.

intermolecular: Eaton *Acc. Chem. Res.* **1968**, *1*, 50.
intramolecular: Rawal *J. Am. Chem. Soc.* **1999**, *121*, 10229.

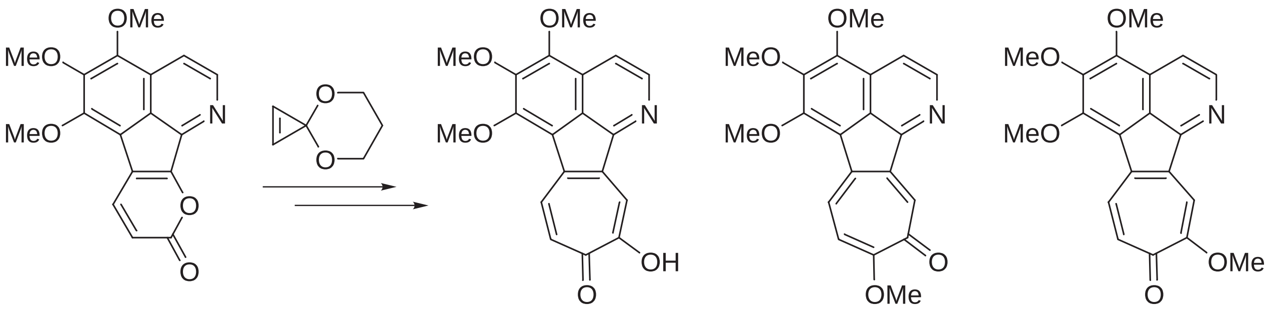
-Normal and inverse electron demand Diels–Alder reactions of cyclopropenone ketals



exo adduct due to destabilizing steric interactions in preferred *endo* T.S.

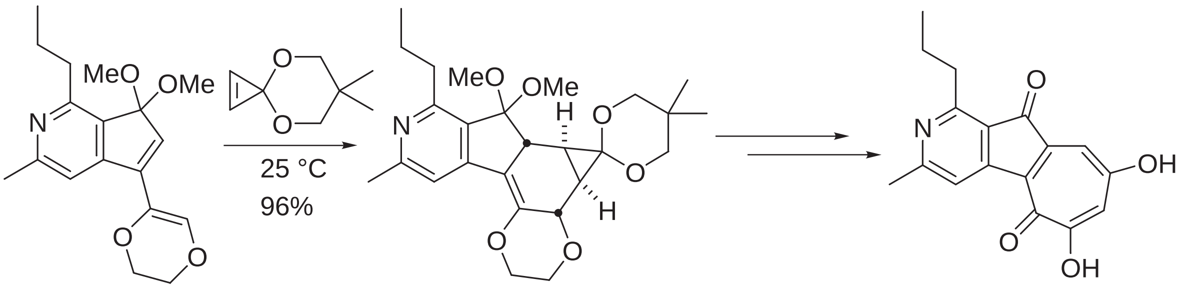
72% R = OMe
69% R = H
65% R = CO_2Me

Boger *Tetrahedron* **1986**, *42*, 2777.
Boger *J. Am. Chem. Soc.* **1986**, *108*, 6695.



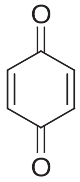
Grandirubrine Imerubrine Isoimerubrine

Boger *J. Am. Chem. Soc.* **1995**, *117*, 12452.

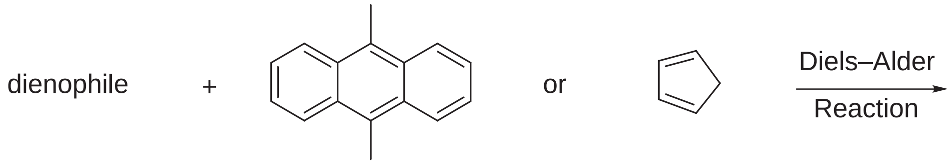


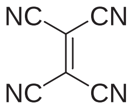
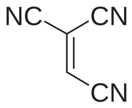
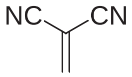
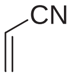
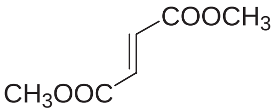
Boger *J. Am. Chem. Soc.* **2000**, *122*, 12169. Rubrolone aglycon

d. Quinones are outstanding dienophiles



e. Number and position of electron-withdrawing groups



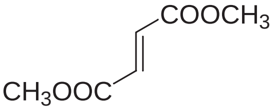
Dienophile	Relative Rates	
	1.3 x 10^9	4.3 x 10^7
	5.9 x 10^5	4.8 x 10^5
	1.3 x 10^4	4.5 x 10^4
	0.09	1
	215	74
$CH_3OOC-C\equiv C-COOCH_3$	140	31

NOTE: large increase in rate by addition of one more complementary EWG

NOT as large an increase upon addition of one more noncomplementary EWG

f. *cis* vs. *trans* Dienophiles

-In polar (or radical) processes, *cis* isomer reacts faster than *trans*, but in Diels–Alder reaction:



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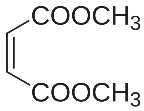
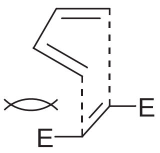
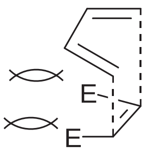


Due to





one additional destabilizing steric interaction

-The relative rates of such *cis* vs. *trans* reactions are sometimes used to distinguish between concerted cycloadditions vs. nonconcerted stepwise reactions.

g. Heterodienophiles: typically electron-deficient

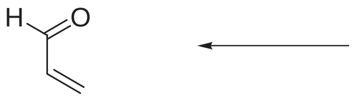
e.g.

2π component

HOMO$_{\text{diene}}$-controlled Diels–Alder reaction.

h. Heterodienes: typically electron-deficient

e.g.



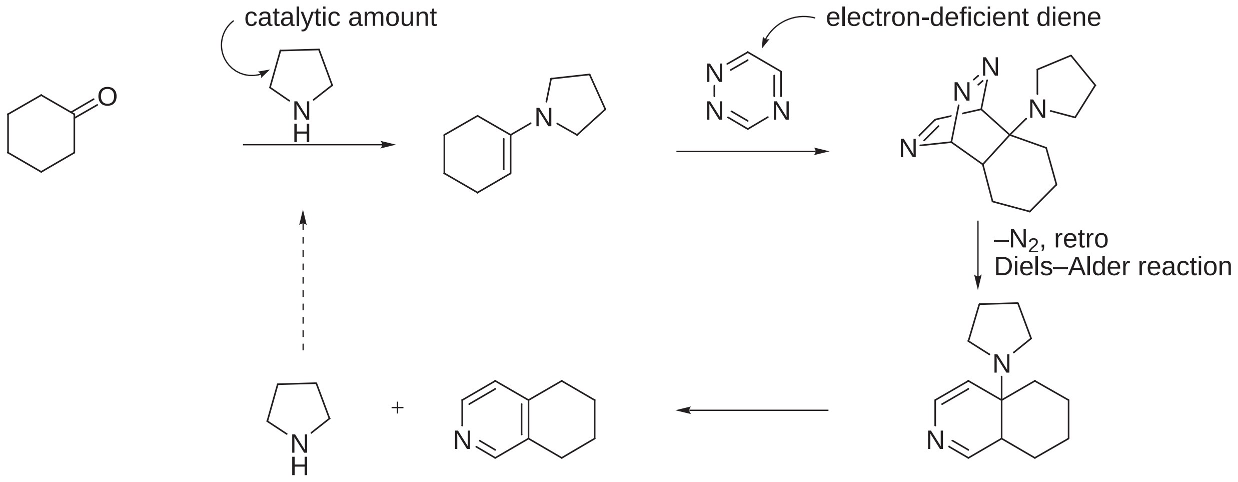
4π component

LUMO$_{\text{diene}}$-controlled Diels–Alder reaction.

introduction of heteroatom makes diene electron-deficient.

Note: Dienophiles can also be generated *in situ*:

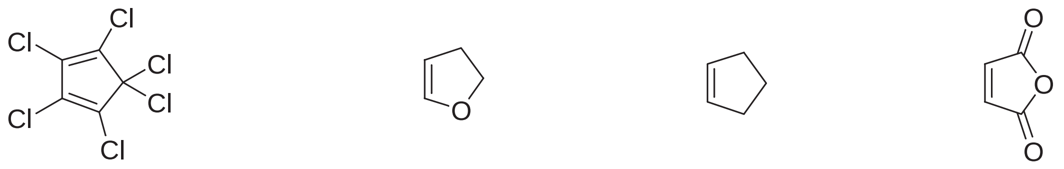
Boger *J. Org. Chem*. **1984**, *49*, 4050.



Catalytic Diels–Alder reaction
Boger *J. Org. Chem*. **1982**, *47*, 895.

i. Dienophiles which are not electron-deficient

(1) Participate in inverse electron demand Diels–Alder reactions:



k_{rel} = 12 2 1

McBee *J. Am. Chem. Soc.* **1954**, *77*, 385.
Jung *J. Am. Chem. Soc.* **1977**, *99*, 5508.

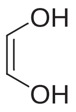
(2) Can be used in cation–radical Diels–Alder reactions.

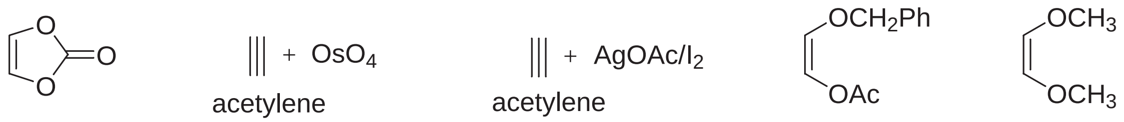
(3) Also include the behavior of strained olefins.

j. Dienophile equivalents

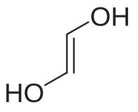
-Many specialized dienophiles have been developed which react well in the Diels–Alder reaction and which serve to indirectly introduce functionality not otherwise directly achievable.

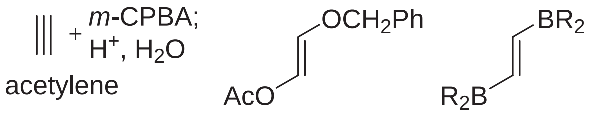
inaccessible dienophile | equivalent dienophile



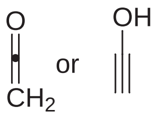


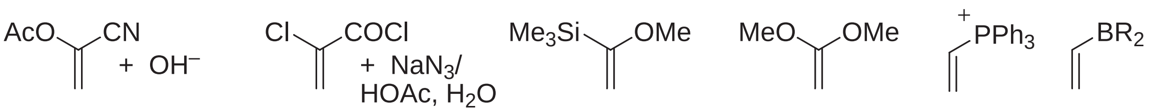
J. Am. Chem. Soc. **1958**, *80*, 209.
J. Org. Chem. **1988**, *53*, 5793.
J. Org. Chem. **1984**, *49*, 4033.



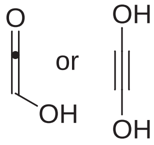


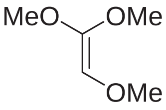
Chem. Ber. **1964**, *97*, 443.
J. Org. Chem. **1988**, *53*, 5793, 3373.
Tetrahedron Lett. **1994**, *35*, 509.



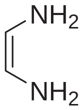


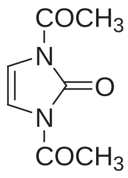
J. Am. Chem. Soc. **1956**, *78*, 2473.
J. Am. Chem. Soc. **1971**, *93*, 4326.
J. Org. Chem. **1977**, *42*, 4095.
Review: *Synthesis* **1977**, 289.
Review: *Tetrahedron* **1999**, *55*, 293.



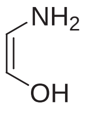


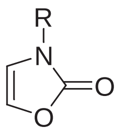
J. Org. Chem. **1984**, *49*, 4033.





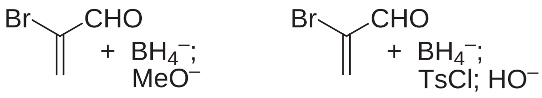
Tetrahedron Lett. **1981**, 2063.



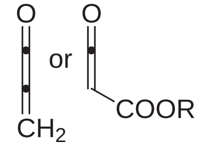
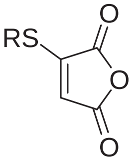
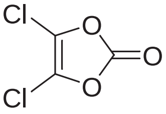
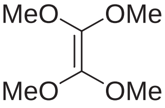
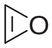
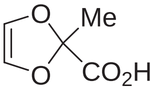
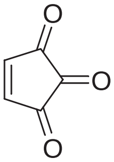
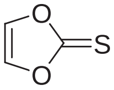
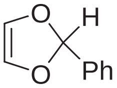
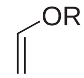
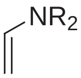
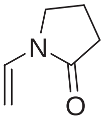
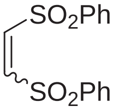
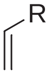
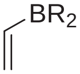
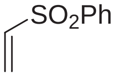
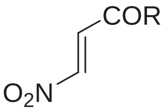
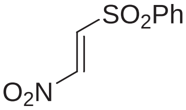
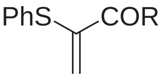
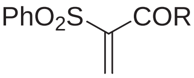
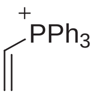
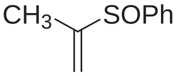
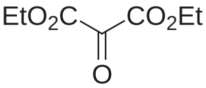


R = H, COCH$_3$

Tetrahedron Lett. **1977**, 3115.
Ann. **1976**, 1319.

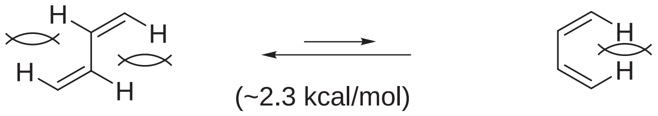


J. Am. Chem. Soc. **1972**, *94*, 2549.

inaccessible dienophile	equivalent dienophile	
		*J. Am. Chem. Soc*. **1977**, *99*, 7079.
	 	*J. Am. Chem. Soc*. **1977**, *99*, 7079.
	 + *m*-CPBA  + PCl_5; HO^-	*Chem. Ber*. **1964**, *97*, 443. *J. Org. Chem*. **1973**, *38*, 1173.
	 + H_2O; $Pb(OAc)_4$  + $(RO)_3P$  + ^nBuLi	
	 R = Et, Ac  enamines   	*J. Am. Chem. Soc*. **1973**, *95*, 7161. *J. Org. Chem*. **1984**, *49*, 4033.
 R = H, R	 	*J. Am. Chem. Soc*. **1980**, *102*, 853. *J. Am. Chem. Soc*. **1990**, *112*, 7423.
	  reversed regioselectivity	*J. Am. Chem. Soc*. **1978**, *100*, 2918. *Tetrahedron Lett*. **1981**, *22*, 603. *J. Org. Chem*. **1979**, *44*, 1180. *J. Org. Chem*. **1977**, *42*, 2179. *J. Am. Chem. Soc*. **1978**, *100*, 1597.
	 	*J. Org. Chem*. **1981**, *46*, 624. *J. Am. Chem. Soc*. **1978**, *100*, 1597.
	 	*J. Org. Chem*. **1977**, *42*, 4095. *J. Chem. Soc., Chem. Commun.* **1991**, 1672.
		*J. Org. Chem*. **1977**, *42*, 4095.

11. Diene

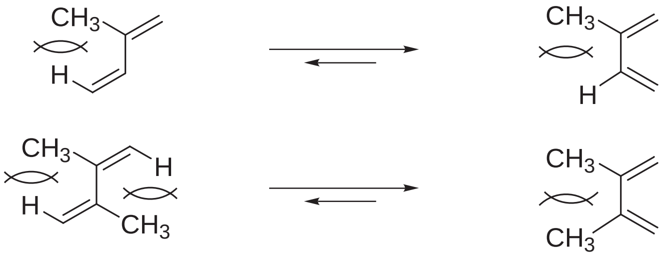
-Dienes must adopt an s-cisoid (s-*Z*) conformation to react.



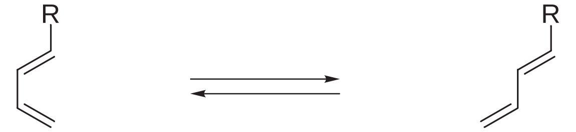
s-*E* (transoid) s-*Z* (cisoid)

Cisoid conformation of diene is favored with:

(a) 2- and/or 3-substitution

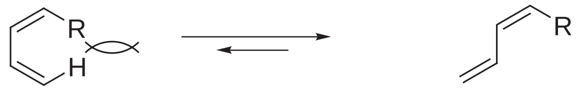


(b) 1-Substituted dienes



E-diene

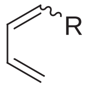
But



not very reactive

Z-diene

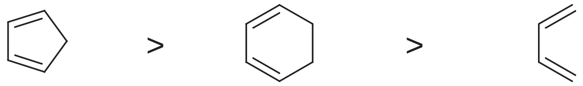
10^5 rate difference for *cis* and *trans*



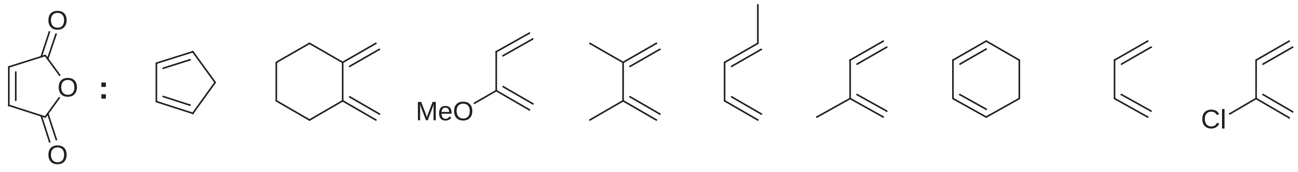
↓

can be used to separate *cis* and *trans* isomers of dienes

(c) And, by locking the diene into cisoid conformation



reaction rates for cyclic dienes are faster

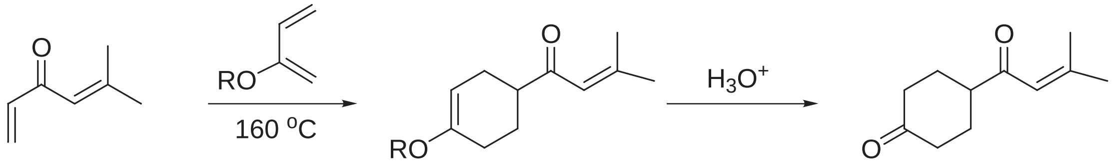


k_{rel} = 1348 110 12 5 3.3 2.2 2 1 0.1

12. Functionalized Dienes

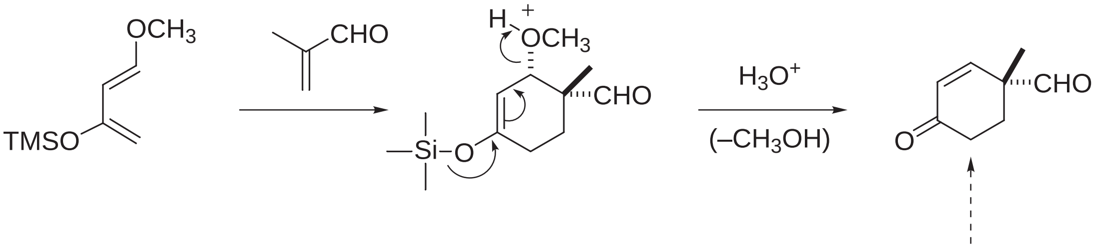
Review: Petrzilka, Grayson *Synthesis* **1981**, 753.

-Diels–Alder reaction with introduction of useful functionality



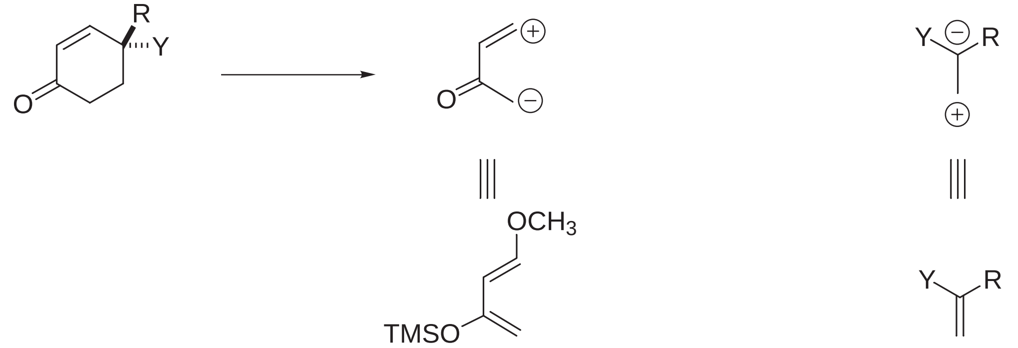
Danishefsky *J. Am. Chem. Soc*. **1979**, *101*, 6996.

-Danishefsky:

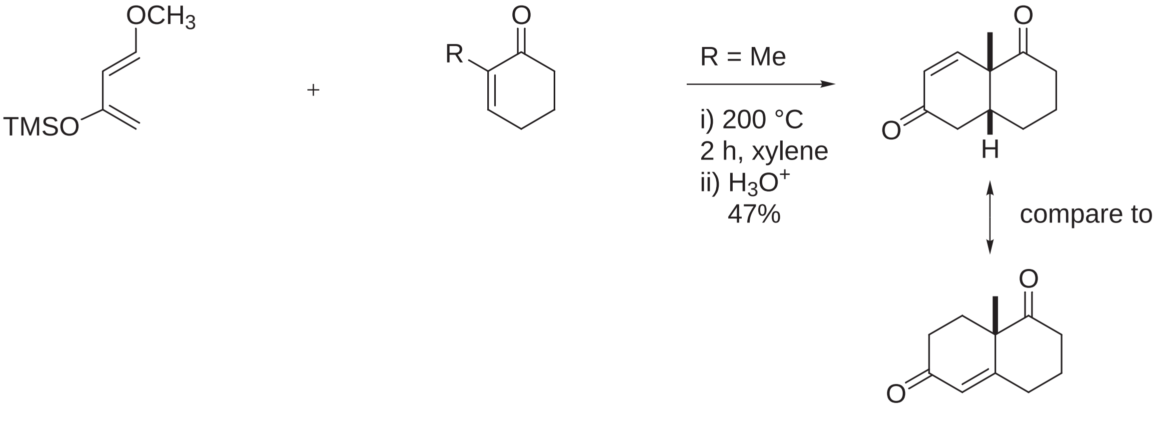


So an alternative disconnection for α,β-unsaturated enones

looks like a Robinson annulation product



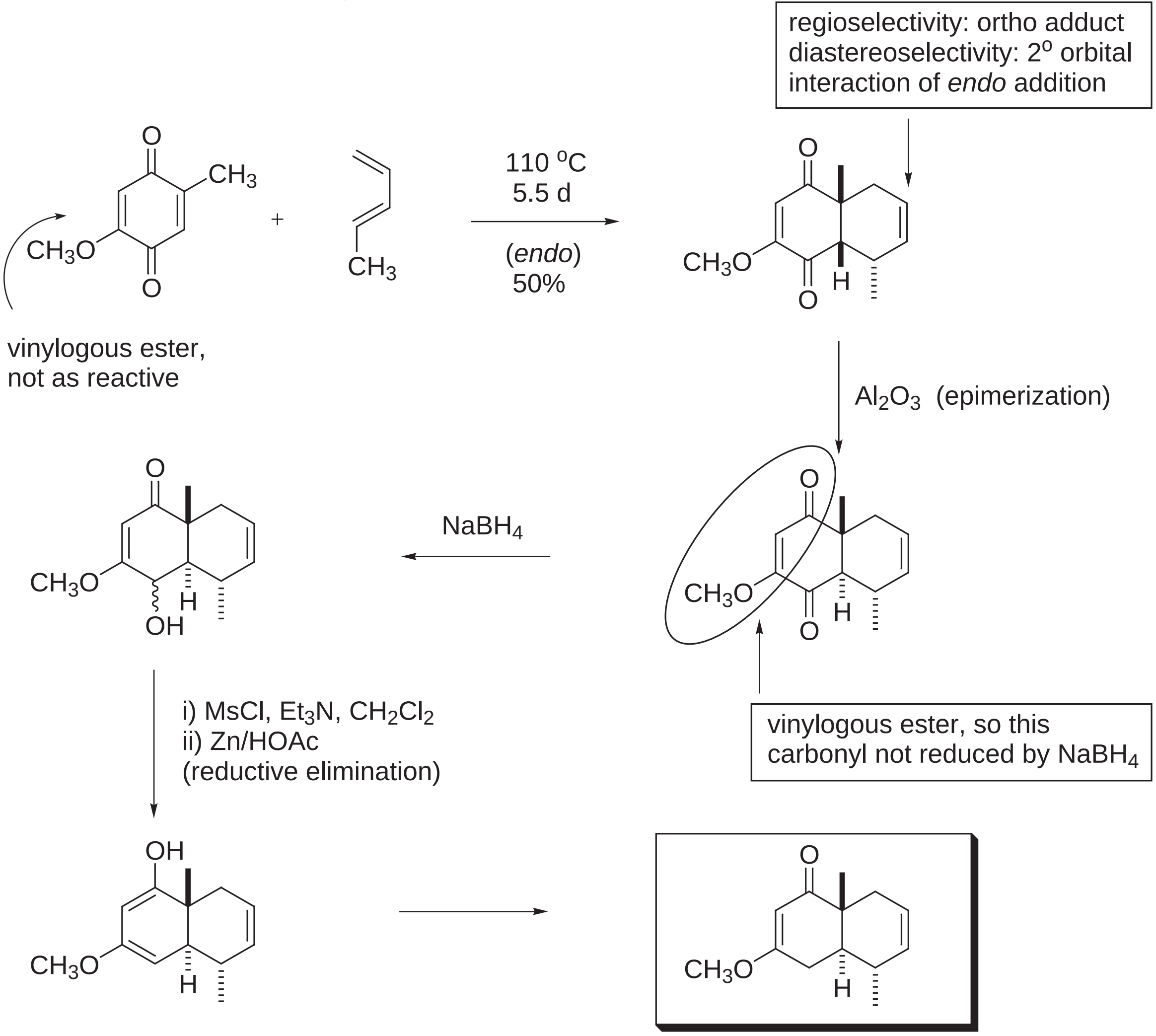
Example:



Wieland–Miescher Ketone

see also: Danishefsky *J. Am. Chem. Soc*. **1979**, *101*, 6996, 7001, 7008, 7013.

Companion Strategy: Woodward *J. Am. Chem. Soc*. **1952**, *74*, 4223;
Bloom *J. Org. Chem*. **1959**, *24*, 278.



regioselectivity: ortho adduct
diastereoselectivity: 2^o orbital interaction of *endo* addition

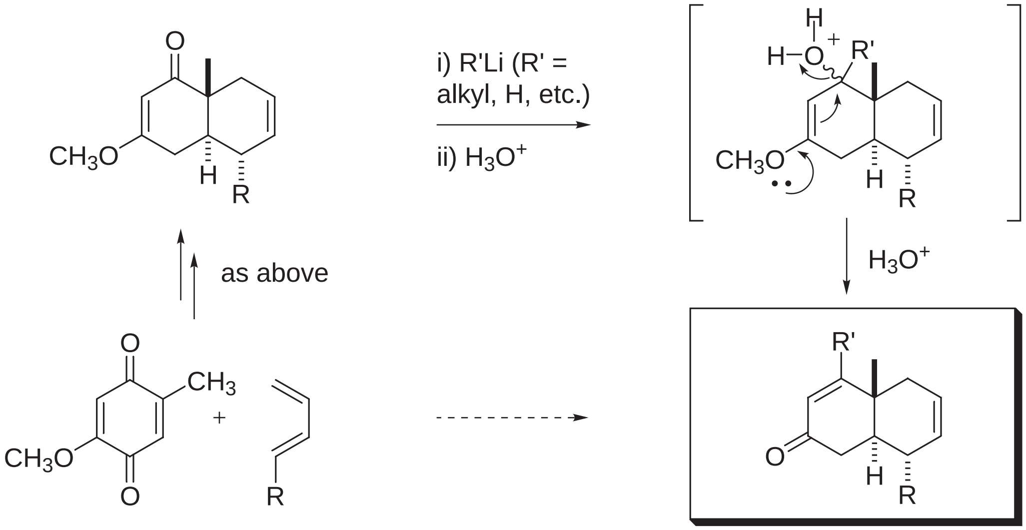
vinylogous ester,
not as reactive

vinylogous ester, so this carbonyl not reduced by $NaBH_4$

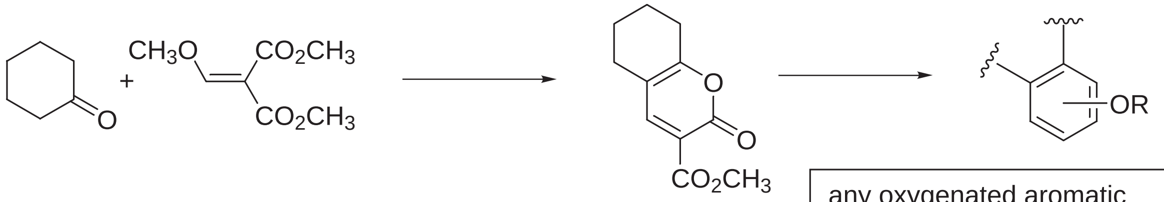
very useful

See also:
Robinson *J. Am. Chem. Soc*. **1961**, *83*, 249.
Orchin, Butz *J. Org. Chem*. **1943**, *8*, 509.
Kishi *Tetrahedron Lett*. **1970**, 5127.
Kakushima *Can. J. Chem*. **1976**, *54*, 3304.

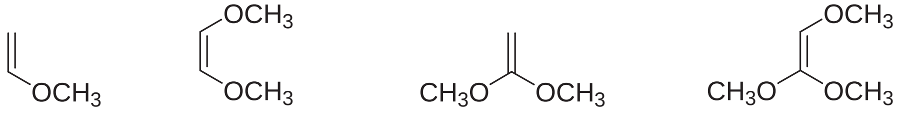
Can also add nucleophiles (RLi, H^-) to the "vinylogous ester" carbonyl:



-Aromatic Annulation

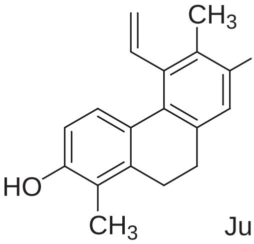


any oxygenated aromatic substitution pattern using different electron-rich olefins.

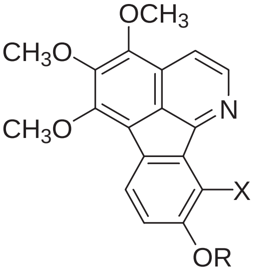


Boger *J. Org. Chem*. **1984**, *49*, 4033, 4045 and 4050.

Use of aromatic annulation in total synthesis:

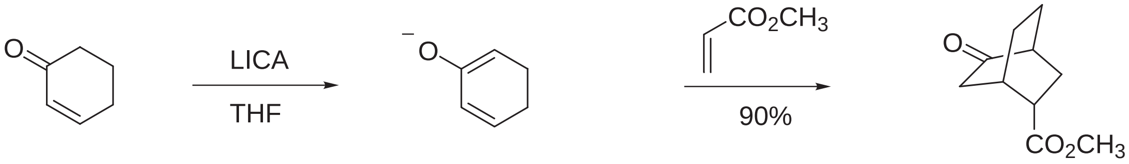


Juncusol

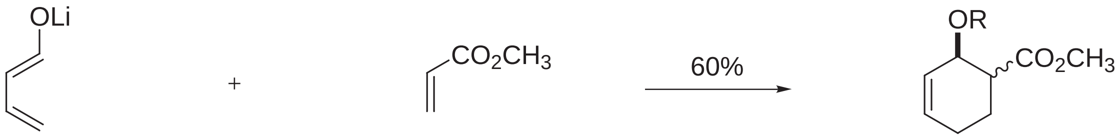


Rufuscine, Imelutine
Norrufuscine
X = H, OR

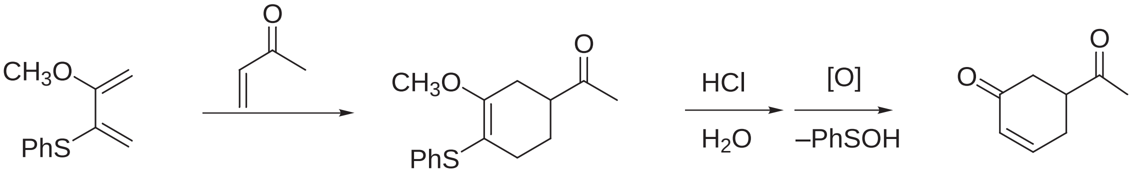
Heteroatom Substituted Dienes:



Diels–Alder or Michael–Michael Reaction
Lee *Tetrahedron Lett*. **1973**, 3333.



Kraus *Tetrahedron Lett*. **1977**, 3929.

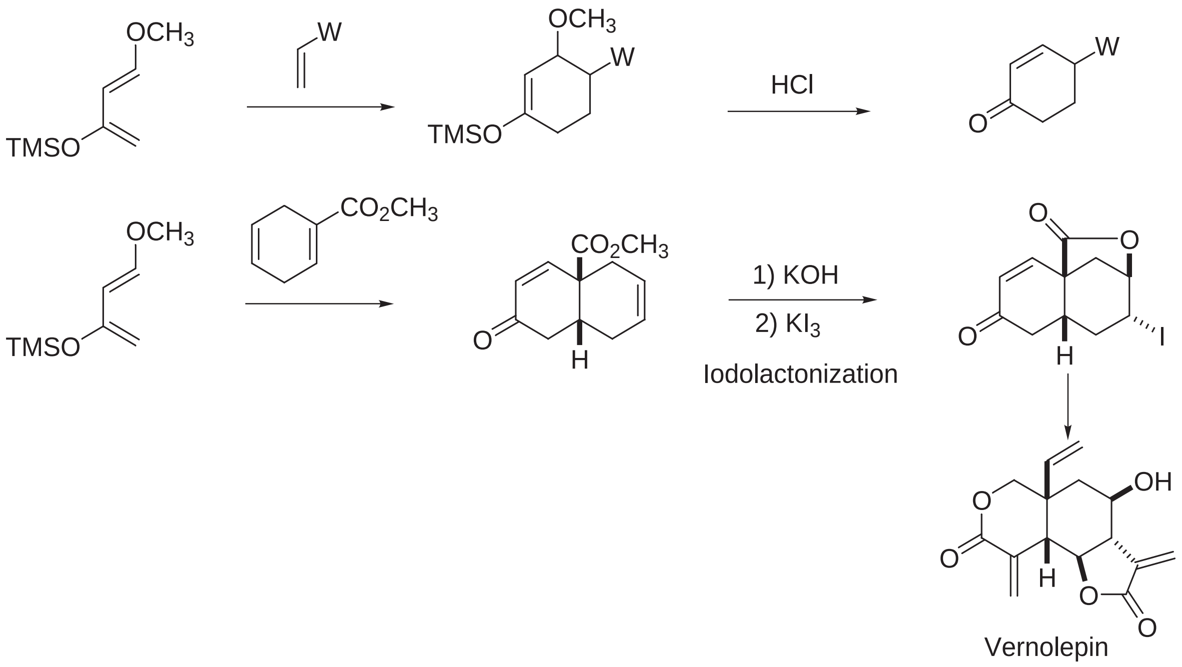


5:1
RS > OR

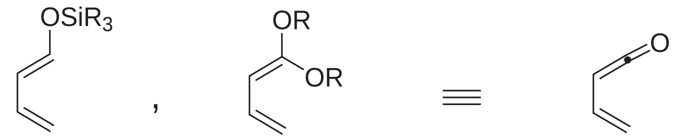
complement to
Danishefsky diene
Diels–Alder product.

Trost *J. Am. Chem. Soc*. **1980**, *102*, 3554.

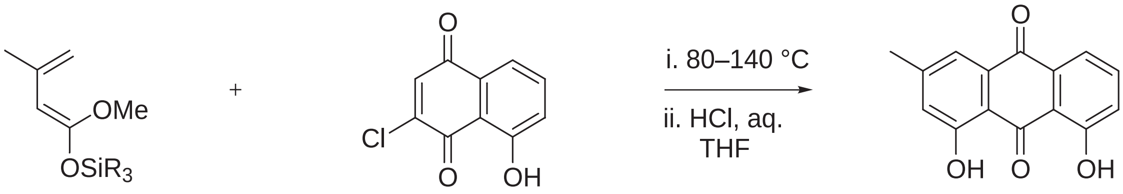
Danishefsky Diene: (see summary list)



Danishefsky *J. Am. Chem. Soc*. **1977**, *99*, 6066.



Note the dienophile and diene equivalency list



Brassard *Tetrahedron Lett*. **1979**, 4911.

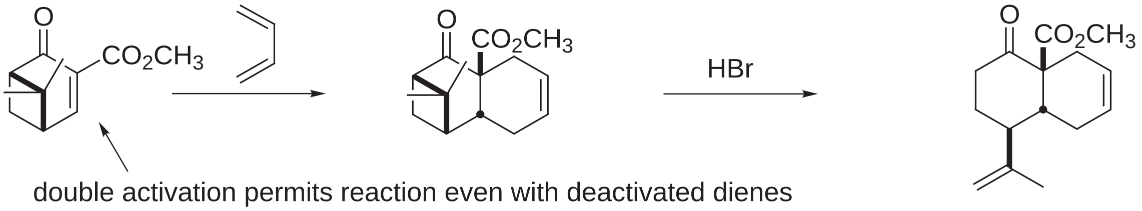
Danishefsky Applications

Reviews: Danishefsky *Chemtracts: Org. Chem.* **1989**, *2*, 273.
Danishefsky *Acc. Chem. Res.* **1981**, *14*, 400.

dienes	*J. Am. Chem. Soc*. **1979**, *101*, 6996, 7001 and 7008.
tatettine	*J. Am. Chem. Soc*. **1980**, *102*, 2838.
coriolin	*J. Am. Chem. Soc*. **1980**, *102*, 2097.
prephenate	*J. Am. Chem. Soc*. **1979**, *101*, 7013.
griseofulvin	*J. Am. Chem. Soc*. **1979**, *101*, 7018.
pentalenolactone	*J. Am. Chem. Soc*. **1979**, *101*, 7020.
vernolepin	*J. Am. Chem. Soc*. **1977**, *99*, 6066.
lasiodiplodin	*J. Org. Chem.* **1979**, *44*, 4716.
papulacandin aglycon	*Carbohydr. Res*. **1987**, *171*, 317.
vineomycinone	*J. Am. Chem. Soc*. **1985**, *107*, 1285.

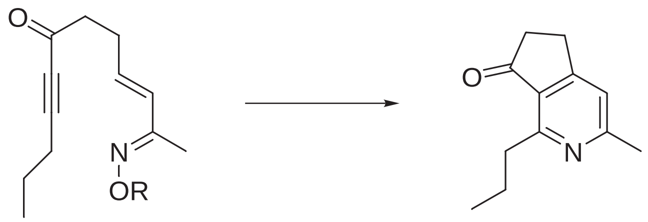
methyllincosaminide	*J. Am. Chem. Soc*. **1985**, *107*, 1274.
KDO and *N*-acetylneuraminic acid	*J. Am. Chem. Soc*. **1988**, *110*, 3929.
tunicaminyluracil	*J. Am. Chem. Soc*. **1985**, *107*, 7761.
mevinolin	*J. Am. Chem. Soc*. **1989**, *111*, 2596.
	Pure App. Chem. **1988**, *60*, 1555.
compactin	*J. Am. Chem. Soc*. **1989**, *111*, 2599.
avermectin A_{1a}	*J. Am. Chem. Soc*. **1987**, *109*, 8119.
	J. Am. Chem. Soc. **1987**, *109*, 8117.
	J. Am. Chem. Soc. **1989**, *111*, 2967.
octosyl acid	*J. Am. Chem. Soc*. **1988**, *110*, 7434.
methyl-α-peracetylhikosanamide	*J. Am. Chem. Soc*. **1989**, *111*, 2193.
zincophorin	*J. Am. Chem. Soc*. **1988**, *110*, 4368.
6a-deoxyerythronolide	*Silicon Chem.* **1988**, 25 (Ellis Horwood Ltd.)

-Unactivated dienes



double activation permits reaction even with deactivated dienes

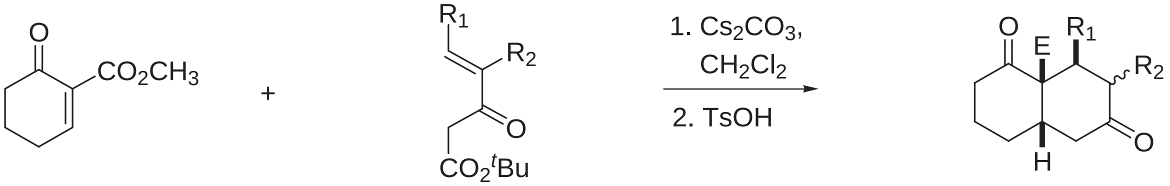
Boger *J. Org. Chem*. **1985**, *50*, 1904.



intramolecular reaction permits use of unactivated diene or dienophile

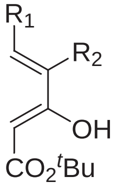
Boger *Tetrahedron Lett*. **1991**, *32*, 7643.

-Deslongchamps: *Tetrahedron Lett*. **1990**, *31*, 3969; *Synlett* **1990**, 516.



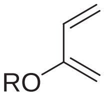
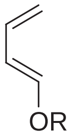
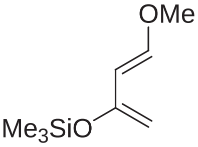
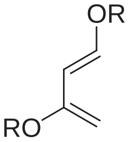
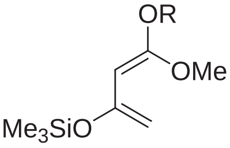
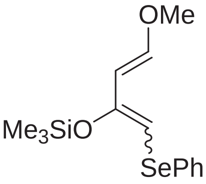
E = CO_2CH_3

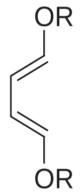
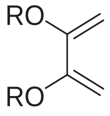
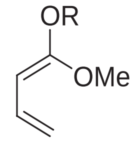
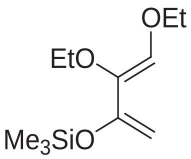
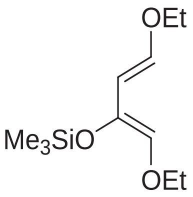
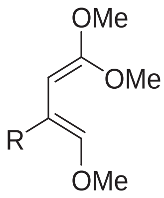
via [4 + 2] Diels–Alder reaction

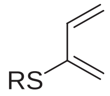
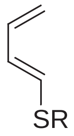
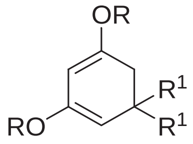
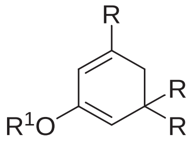
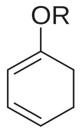
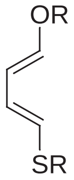
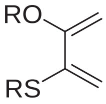
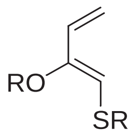
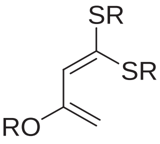
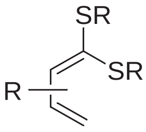


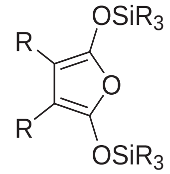
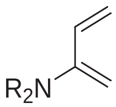
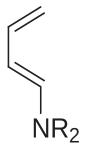
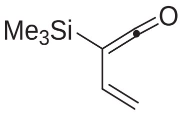
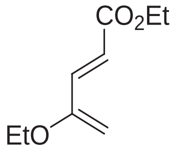
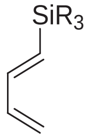
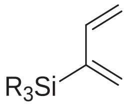
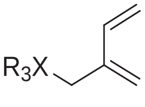
-Compilation of Representative Functionalized Dienes

Review: Petrzilka, Grayson *Synthesis* **1981**, 753.

diene		reference
	R = $SiMe_3$	*Tetrahedron Lett*. **1976**, 2935. *J. Chem. Soc*., *Chem. Commun.* **1974**, 956.
	R = Et	*J. Chem. Soc*., *Chem. Commun.* **1966**, 1152. *J. Am. Chem. Soc*. **1980**, *102*, 3270.
	R = Ac	*J. Am. Chem. Soc*. **1976**, *98*, 1967.
	R = $P(O)(OEt)_2$	*Helv. Chim. Acta* **1979**, *62*, 442; *Synthesis* **1981**, 753.
	R = CH_3, Ac	*Tetrahedron Lett*. **1976**, 3869, 3873.
	R = Ac	*J. Am. Chem. Soc*. **1977**, *99*, 8116.
	R = CH_3, 3-Me	*Tetrahedron Lett*. **1978**, 1387.
	R = CH_3, 4-Me	*Tetrahedron Lett*. **1978**, 3869.
	R = Ac, 3-Me	*J. Chem. Soc*., *Chem. Commun.* **1980**, 197.
		Syn. Commun. **1980**, 233.
		J. Org. Chem. **1980**, *45*, 4825.
	Danishefsky's diene	*J. Am. Chem. Soc*. **1974**, *96*, 7807. *J. Org. Chem*. **1975**, *40*, 538. *J. Am. Chem. Soc*. **1977**, *99*, 5810. *J. Am. Chem. Soc*. **1979**, *101*, 6996, 7001. See Danishefsky reference list. see also: *J. Chem. Soc*., *Perkin Trans. 1* **1979**, 3132.
	R = Me	*J. Org. Chem*. **1982**, *47*, 4774.
	R = Et	*J. Am. Chem. Soc*. **1978**, *100*, 7098.
	R = $SiMe_3$	*Syn. Commun*. **1977**, *7*, 131.
		Chem. Lett. **1978**, 649.
		Tetrahedron Lett. **1976**, 3169.
		Chem. Pharm. Bull. **1978**, *26*, 2442.
		Synthesis **1981**, 30.
		Tetrahedron Lett. **1979**, 159.
		Tetrahedron Lett. **1980**, *21*, 3557.
	R = $SiMe_3$	*Tetrahedron Lett*. **1979**, 4437. *Chem. Lett*. **1978**, 649.
	R = Me	*J. Chem. Soc*., *Perkin Trans. 1* **1976**, 1852. *J. Org. Chem*. **1978**, *43*, 379. *J. Am. Chem. Soc*. **1979**, *101*, 7001. See Danishefsky reference list.
		*J. Org. Chem*. **1977**, *42*, 1819.

diene		reference
	R = CH_3	*J. Am. Chem. Soc*. **1978**, *100*, 7098.
	R = Ac, 2-Me	*J. Org. Chem*. **1976**, *41*, 2625.
	R = $SiMe_3$	*J. Org. Chem*. **1976**, *41*, 1799.
		Tetrahedron Lett. **1980**, *21*, 3413.
	R = Ac	*J. Org. Chem*. **1965**, *30*, 2414.
		Org. Syn. **1970**, *50*, 24.
		Angew. Chem., *Int. Ed. Eng*. **1979**, *18*, 304.
		J. Chem. Soc., *Dalton Trans.* **1974**, 956.
		Chem. Ber. **1957**, *90*, 187.
		J. Org. Chem. **1976**, *41*, 1655, 2625.
		J. Org. Chem. **1978**, *43*, 4559.
		J. Chem. Soc., *Chem. Commun.* **1974**, 956.
	R = $SiMe_3$	*J. Org. Chem*. **1978**, *43*, 2726.
		Chem. Lett. **1977**, 1219; **1978**, 649.
		Synthesis **1971,** 236.
		Synthesis **1976,** 259.
		Tetrahedron Lett. **1972**, 4593.
	Others	*J. Org. Chem*. **1960**, *25*, 1279.
		J. Am. Chem. Soc. **1957**, *79*, 3878.
		J. Am. Chem. Soc. **1941**, *63*, 131.
		J. Chem. Soc., *Perkin Trans. 1* **1979**, 1893.
	R = CH_3	*Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 196.
	R = $SiMe_3$	*Tetrahedron Lett*. **1979**, 4911.
	R = CH_3, 3-Me	*Tetrahedron Lett*. **1979**, 4912.
		J. Org. Chem. **1976**, *41*, 3018.
		Can. J. Chem. **1974**, *52*, 80.
		J. Org. Chem. **1978**, *43*, 1435.
		*J. Chem. Soc*., *Perkin Trans. 1* **1979**, 3132.
		*J. Chem. Soc*., *Perkin Trans. 1* **1979**, 3132.
	R = H, $OSiMe_3$	*J. Chem. Soc*., *Perkin Trans. 1* **1979**, 3132.
		J. Org. Chem. **1978**, *43*, 1435.

diene		reference
		*J. Org. Chem.* **1976**, *41*, 3218. *J. Org. Chem.* **1978**, *43*, 1208. *Angew. Chem.*, *Int. Ed. Eng*. **1966**, *5*, 668. *J. Chem. Soc.*, *Chem. Commun.* **1978**, 657.
		*J. Org. Chem.* **1976**, *41*, 3218. *J. Am. Chem. Soc.* **1972**, *94*, 2891. (also reports corresponding sulfoxides). *J. Org. Chem.* **1978**, *43*, 1208.
	R = CH_3, R^1 = H	*J. Chem. Soc*. **1964**, 2932, 2941.
	R = $SiMe_3$, R^1 = H, Me	*Tetrahedron Lett*. **1976**, 3169.
	R = H, R^1 = Me	*Tetrahedron Lett*. **1970**, 4427.
	R = H, R^1 = Ac	*J. Am. Chem. Soc.* **1968**, *90*, 113.
	R = Me, R^1 = $SiMe_3$	*Tetrahedron Lett*. **1977**, 611.
	R = $SiMe_3$	*Tetrahedron Lett*. **1981**, *22*, 645. *J. Am. Chem. Soc*. **1980**, *102*, 3654 and 5983.
	R = CH_3	*J. Chem. Soc*. **1964**, 2932 and 2941. *J. Chem. Soc*., *Perkin Trans. 1* **1973**, 3132; **1976**, 2057. *Tetrahedron Lett*. **1970**, 3467 and 4427. *Tetrahedron* **1967**, *23*, 87.
		*J. Org. Chem.* **1978**, *43*, 4559. *J. Am. Chem. Soc.* **1977**, *99*, 8116.
		*J. Am. Chem. Soc.* **1976**, *98*, 5017. *J. Am. Chem. Soc.* **1977**, *99*, 8116. *J. Am. Chem. Soc.* **1980**, *102*, 3548 and 3554.
		*J. Org. Chem.* **1982**, *47*, 4005. *J. Org. Chem.* **1978**, *43*, 4052. *J. Org. Chem.* **1976**, *41*, 3218. *Org. Syn.* **1979**, *59,* 202.
		*J. Org. Chem.* **1976**, *41*, 2934.
		*J. Org. Chem.* **1972**, *37*, 4474.

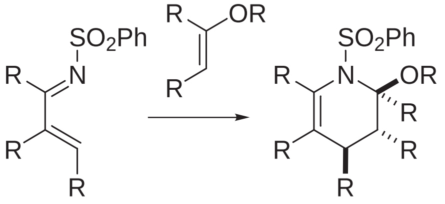
diene		reference
		*Tetrahedron Lett*. **1980**, *21*, 3423. *J. Chem. Soc*., *Chem. Commun.* **1981**, 211.
	NR_2 = NEt_2	*J. Org. Chem.* **1966**, *31*, 2885.
	NR_2 = NHCOX	*J. Am. Chem. Soc.* **1976**, *98*, 2352 and 8295.
	NR_2 = NHCOX	*Tetrahedron Lett*. **1976**, 3089.
	NR_2 = $NHCO_2R$	*J. Org. Chem.* **1979**, *44*, 4183.
		Tetrahedron Lett. **1980**, *21*, 3323.
		J. Am. Chem. Soc. **1976**, *98*, 2352.
		J. Org. Chem. **1978**, *43*, 2164.
		Helv. Chim. Acta **1975**, *58*, 587.
		Tetrahedron Lett. **1979**, 981.
	NR_2 = NEt_2	*Chem. Ber*. **1957**, *90*, 238.
		Chem. Ber. **1942**, *75*, 232.
	NR_2 (comparison)	*J. Liebigs Ann. Chem*. **1969**, *728*, 64.
		*J. Org. Chem.* **1980**, *45*, 4810.
		*J. Org. Chem.* **1970**, *35*, 3851.
		*Tetrahedron* **1979**, *35*, 621.
		*J. Chem. Soc*., *Chem. Commun.* **1976**, 679, 681.
 X = Si, Sn		*Tetrahedron Lett.* **1980**, *21*, 355.

13. Heterodienes

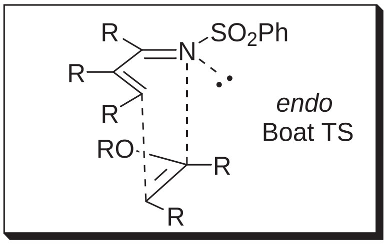
-Typically, heterodienes are electron-deficient and participate in inverse electron demand Diels–Alder reactions

Reviews: Boger *Tetrahedron* **1983**, *34*, 2869.
Comprehensive Org. Syn., Vol. 5, 451.
Behforouz *Tetrahedron* **2000**, *56*, 5259.

-Acyclic azadienes, *N*-sulfonyl-1-azadienes:



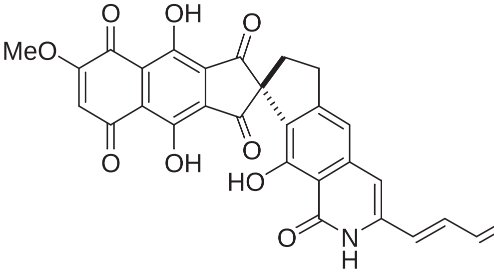
- Regiospecific and Diastereospecific



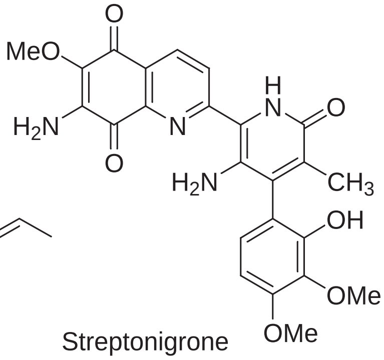
- Secondary orbital interaction (C-2 diene/OR)
- n–σ^* stabilization (T.S. anomeric effect)
- Solvent independent rate
- Dienophile geometry conserved

- Pressure-induced *endo* diastereoselectivity
- *k* (*trans*) > *k* (*cis*)
- C-3 EWG accelerates reaction (25 °C)
- And C-2 or C-4 EWG accelerate reaction
- C-3 > C-2 or C-4 (25 °C)

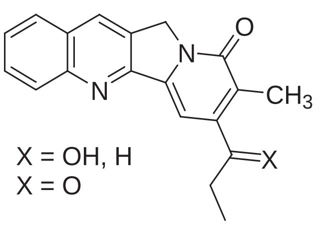
Boger *J. Am. Chem. Soc.* **1991**, *113*, 1713.



Fredericamycin A
Boger *J. Am. Chem. Soc.*
1995, *117*, 11839.

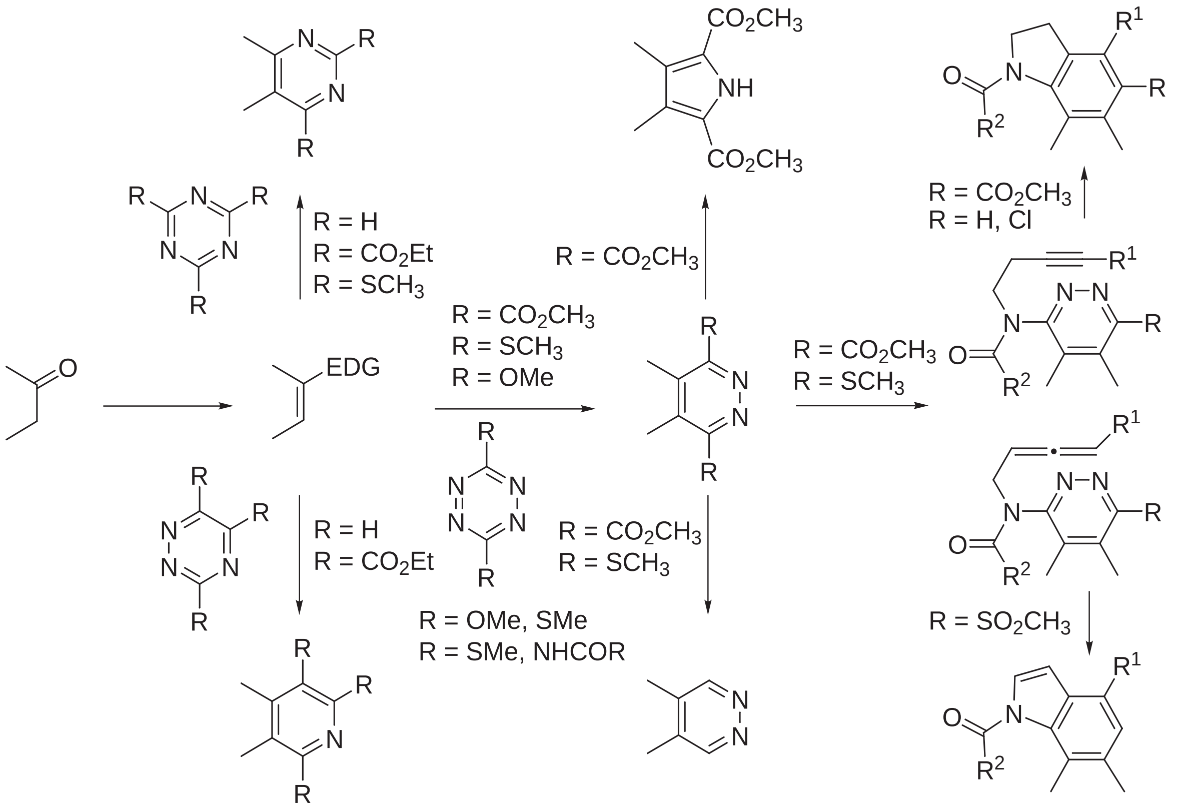


Streptonigrone
Boger *J. Am. Chem. Soc.*
1993, *115*, 10733.



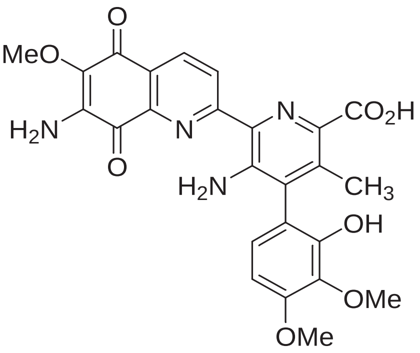
(–)-Mappicine
Nothapodytine B
Boger *J. Am. Chem. Soc.*
1998, *120*, 1218.

-Representative heteroaromatic azadiene Diels–Alder reactions taken from the work of Boger

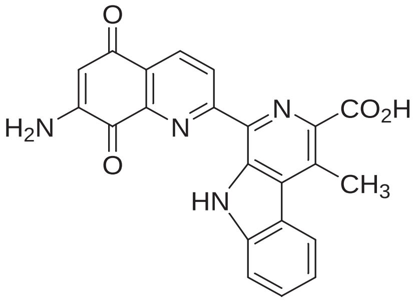


Reviews: Boger *Tetrahedron* **1983**, *34*, 2869.
Chem. Rev. **1986**, *86*, 781.
Chemtracts: Org. Chem. **1996**, *9*, 149.
Prog. Heterocycl. Chem. **1989**, *1*, 30.
Bull. Chim. Soc. Belg. **1990**, *99*, 599.

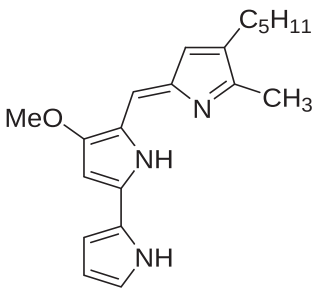
-Heterocyclic azadiene Diels–Alder reaction total synthesis applications taken from the work of Boger



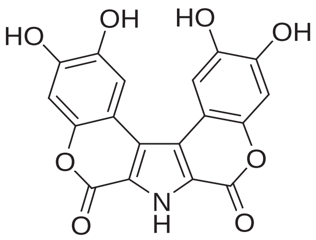
Streptonigrin
J. Am. Chem. Soc. **1985**, *107*, 5745.

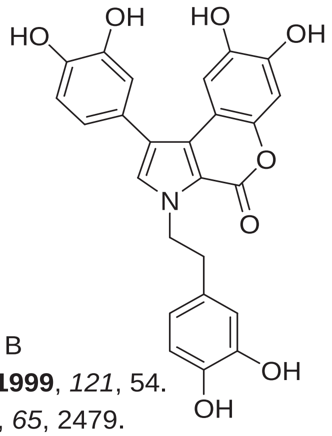


Lavendamycin
J. Org. Chem. **1985**, *50*, 5782 and 5790.

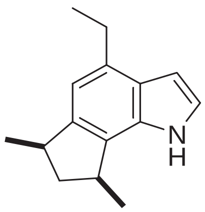


Prodigiosin
J. Org. Chem. **1988**, *53*, 1405.

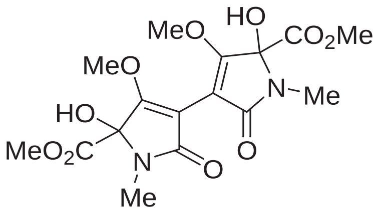




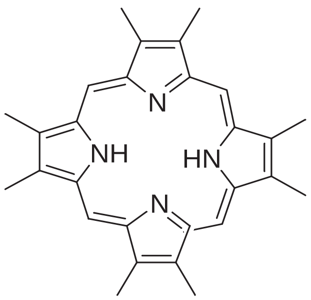
Ningalin A   Nigalin B
J. Am. Chem. Soc. **1999**, *121*, 54.
J. Org. Chem. **2000**, *65*, 2479.



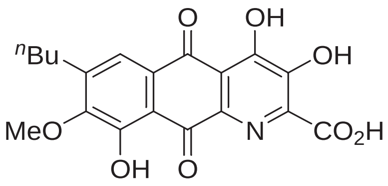
cis-Trikentrin A
J. Am. Chem. Soc. **1991**, *113*, 4230.



Isochrysohermidin
J. Am. Chem. Soc. **1993**, *115*, 11418.



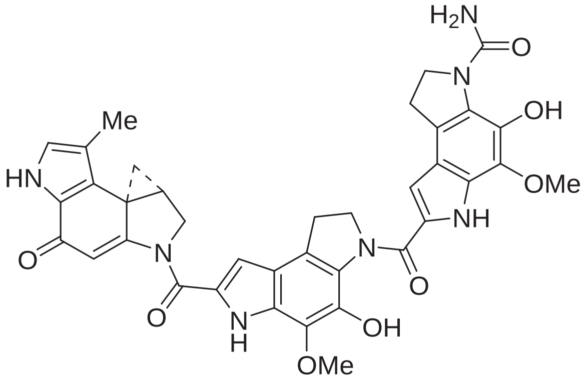
OMP
J. Org. Chem. **1984**, *49*, 4405.



Phomazarin
J. Am. Chem. Soc. **1999**, *121*, 2471.

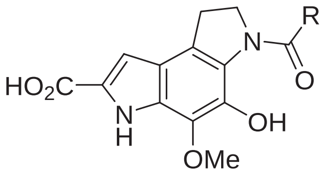
H. Fischer received the 1930 Nobel Prize in Chemistry on the structure of haemin and chlorophyll and the subsequent synthesis of haemin. By many, this is regarded as a milestone accomplishment for the field of organic synthesis.

Richard M. Willstatter received the 1915 Nobel Prize in Chemistry for his investigations of plant pigments, particularly chlorophyll. His use of chromatography to isolate natural products first popularized the technique introduced in 1906 by M. Tswett and his synthesis of cocaine is considered by many as the launch of modern day natural products total synthesis.



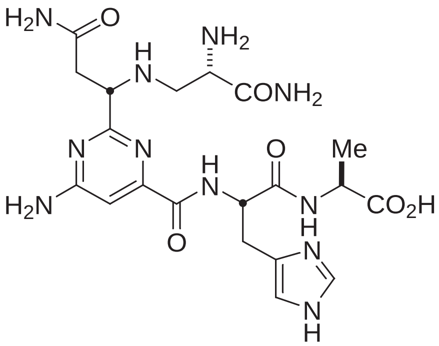
(+)-CC-1065

J. Am. Chem. Soc. **1988**, *110*, 4796.



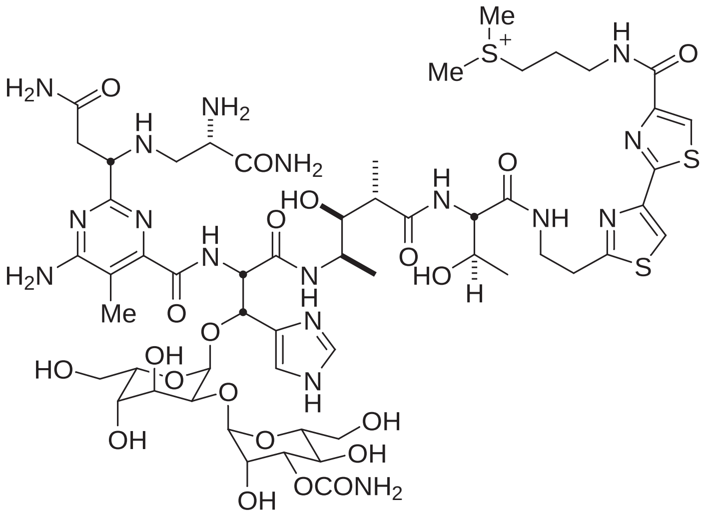
PDE-I R = NH_2
PDE-II R = CH_3

J. Am. Chem. Soc. **1987**, *109*, 2717.



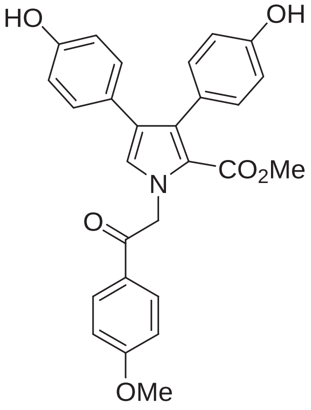
(+)-P-3A

J. Am. Chem. Soc. **1994**, *116*, 82.

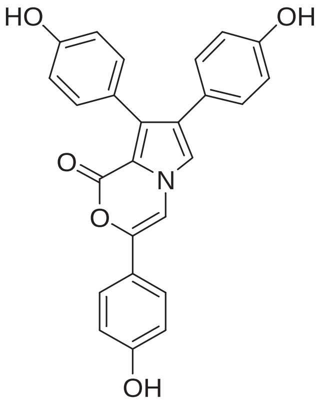


Bleomycin A_2

J. Am. Chem. Soc. **1994**, *116*,
5607, 5619, 5631, 5647.

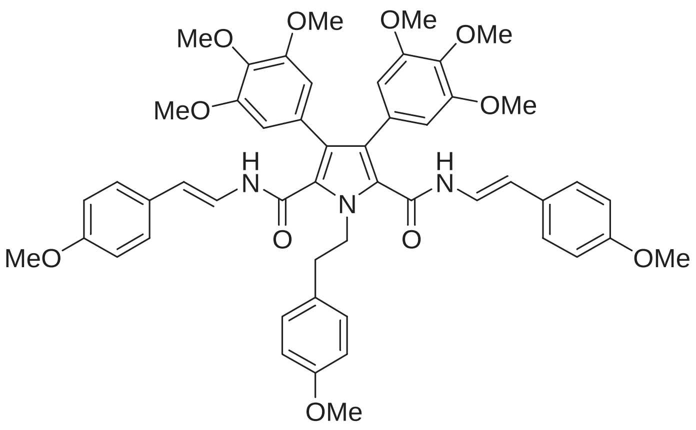


Lamellarin O



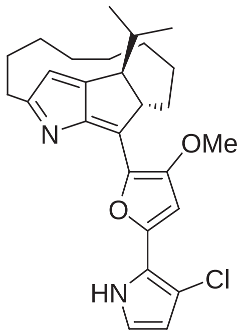
Lukianol A

J. Am. Chem. Soc. **1999**, *121*, 54.

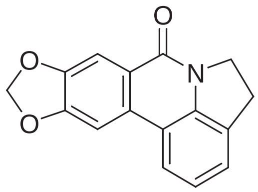


Permethyl Storniamide A

J. Am. Chem. Soc. **1999**, *121*, 54.



ent-(–)-Roseophilin
J. Am. Chem. Soc. **2001**, *123*, 8515.



Anhydrolycorinone
J. Org. Chem. **2000**, *65*, 9120.

14. Intramolecular Diels–Alder Reactions

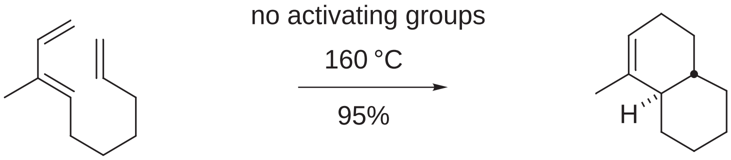
Review: Ciganek *Org. React*. **1984**, *32*, 1.
Jung *Synlett* **1990**, 186.
Thomas *Acc. Chem. Res*. **1991**, *24*, 229.
Weinreb *Acc. Chem. Res*. **1985**, *18*, 16.
Oppolzer *Comprehensive Org. Syn.*, Vol. 5; pp 315.

A. General Considerations:

-less negative $\Delta S^{\ddagger}$, which accelerates reaction and results in milder reaction conditions.

-naturally affects regioselectivity and diastereoselectivity.

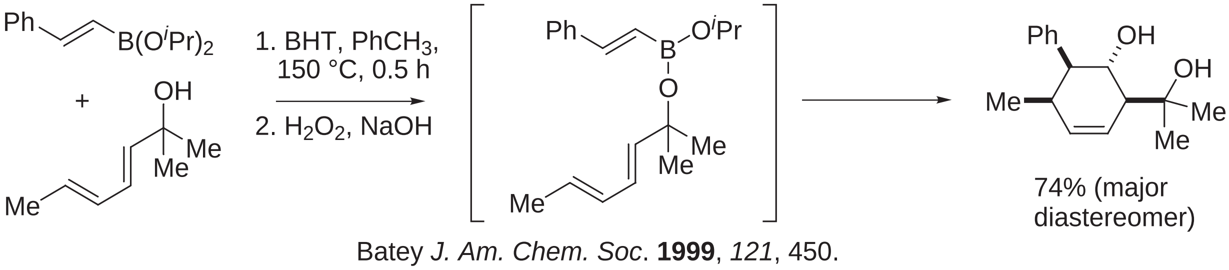
-extends Diels–Alder reaction to include systems which are normally unreactive.



Wilson *J. Am. Chem. Soc*. **1978**, *100*, 6289.

B. Notable applications in synthesis:

-tethered intramolecular Diels–Alder reactions

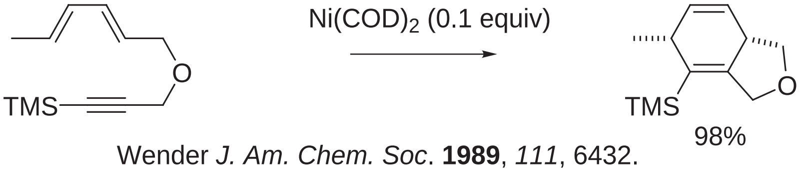


Batey *J. Am. Chem. Soc*. **1999**, *121*, 450.

-metal-catalyzed intramolecular Diels–Alder reactions

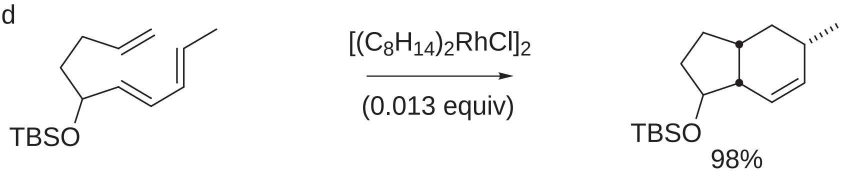
An emerging group of transition-metal mediated [4 + 2] cycloadditions are under development.

Ni-catalyzed



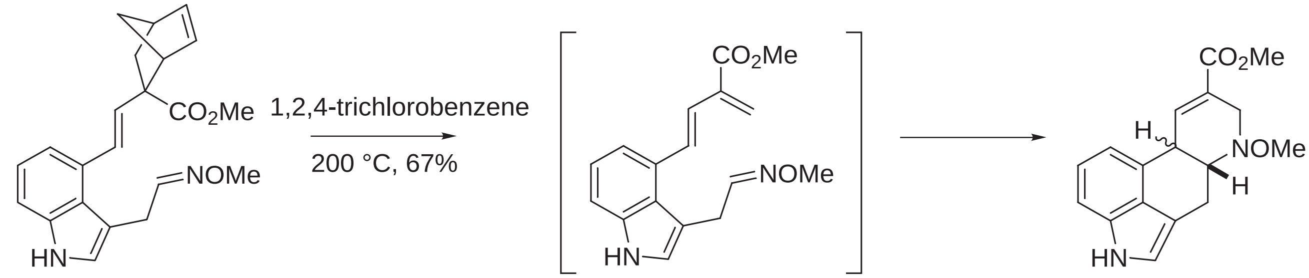
Wender *J. Am. Chem. Soc*. **1989**, *111*, 6432.

Rh-catalyzed

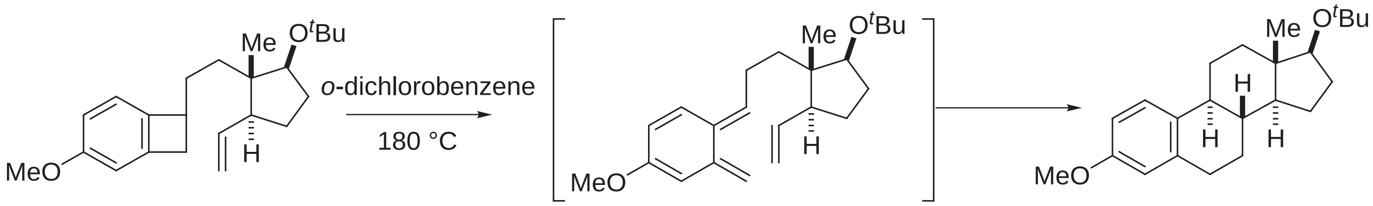


Livinghouse *J. Am. Chem. Soc*. **1990**, *112*, 4965.

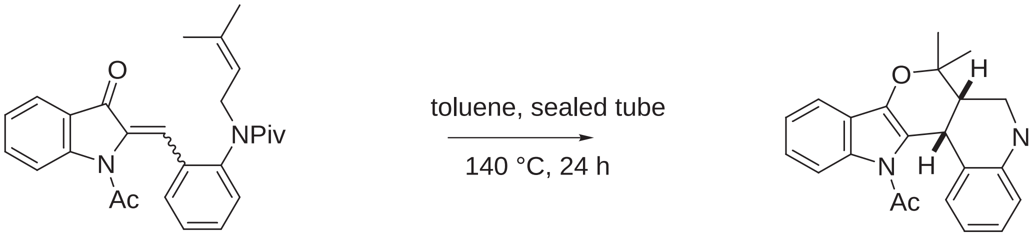
-applications in total synthesis



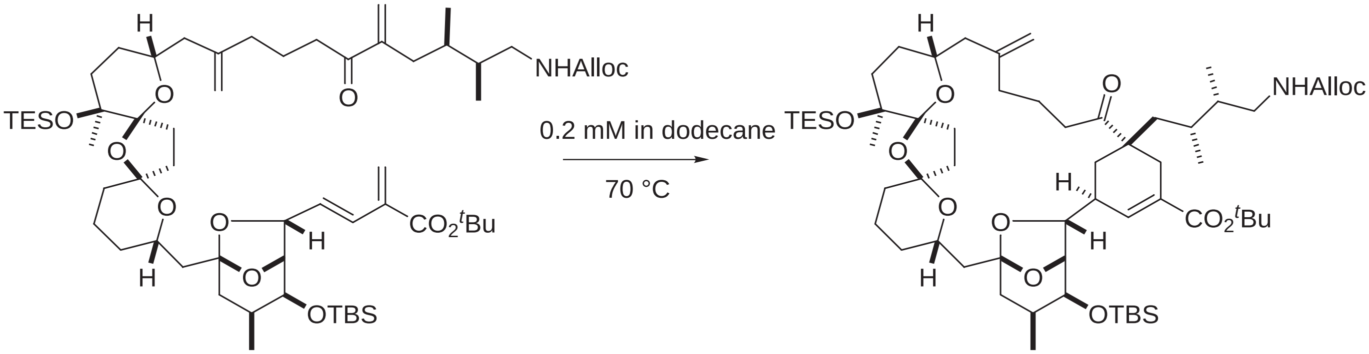
Oppolzer *Helv. Chim. Acta* **1981**, *64*, 478. for lysergic acid



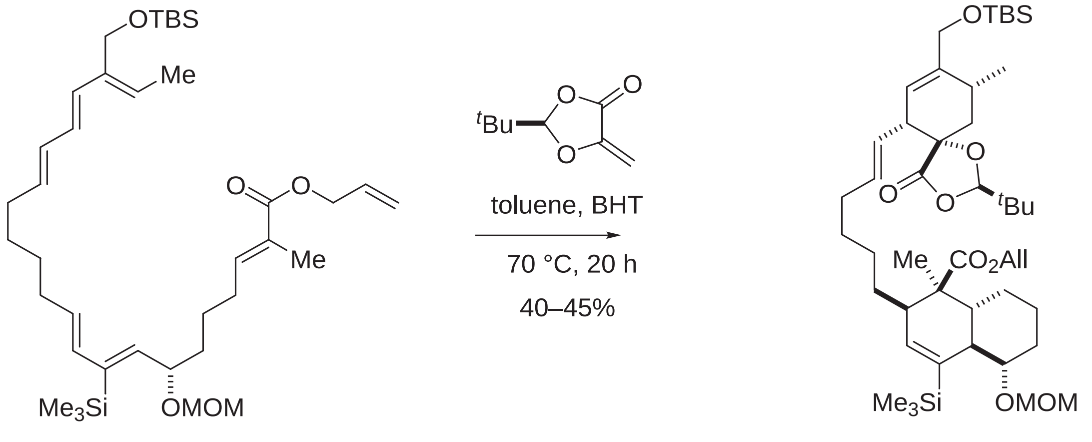
Kametani *J. Am. Chem. Soc.* **1978**, *100*, 6218. for estrone



Merour *Synlett* **1998**, 1051.



Kishi *J. Am. Chem. Soc.* **1998**, *120*, 7647. for pinnatoxin A



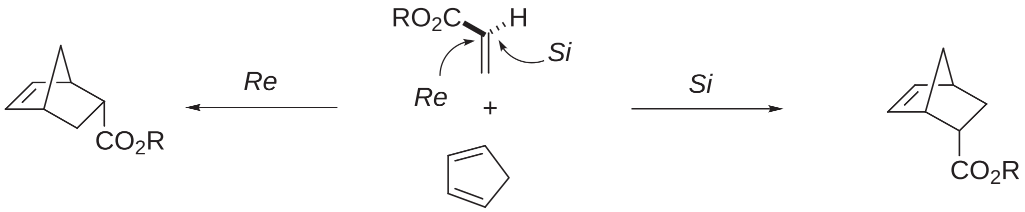
Roush *J. Am. Chem. Soc.* **1998**, *120*, 7411. for chlorothricolide

15. Asymmetric Diels–Alder Reaction

Catalytic Asymmetric Diels–Alder Reactions: Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.
Asymmetric Hetero Diels–Alder Reaction: Waldermann, H. *Synthesis* **1994**, 535.

A. General considerations

-Unsymmetrically substituted dienes or dienophiles have enantiotopic faces. Even with exclusive *cis-endo* addition and regioselectivity, products occur as a pair of enantiomers.

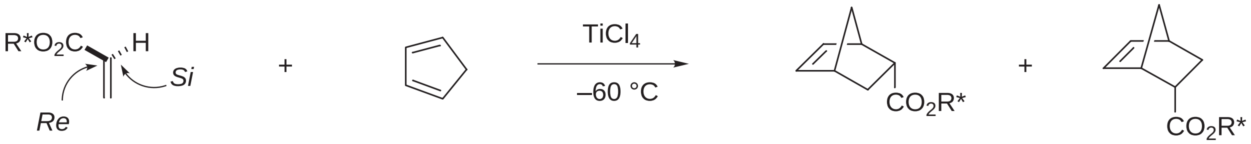


-There are three possible ways to obtain one of the enantiomers in excess:

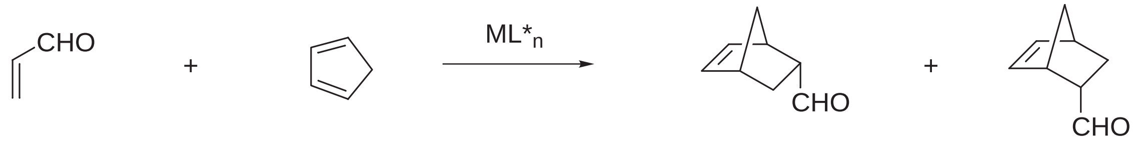
a) using chiral dienes.
b) using chiral dienophiles.
c) using chiral Lewis acid catalysts.
In addition, double stereoselection can be realized in many situations.

-Comparison of chiral substrate vs. chiral catalyst

use of a chiral substrate (chiral diene or dienophile): a stoichiometric amount of chiral auxiliary R* is needed and its introduction before and removal after the Diels–Alder reaction are neccessary.



use of a chiral catalyst: usually 0.1 equiv. is enough to introduce chirality and the catalyst can be recovered from the reaction mixture and reused.

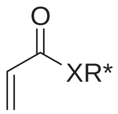


B. Chiral dienophiles

Review: Oppolzer *Angew. Chem., Int. Ed. Eng*. **1984**, *23*, 876.
Ager and East *Asymmetric Synthetic Methodology*; CRC Press: New York, 1996.

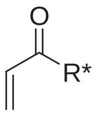
-Chiral dienophiles provide the vast majority of the examples of asymmetric Diels–Alder reactions.

Type I



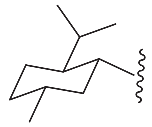
X = O, NR*

Type II

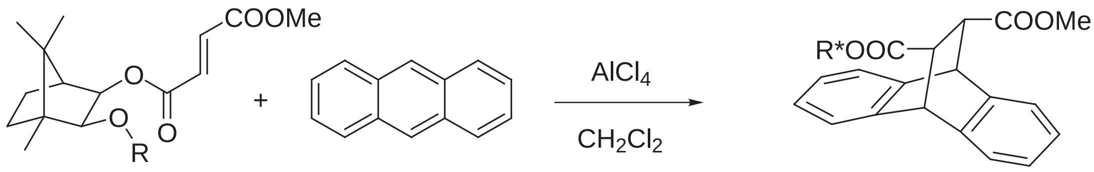


First example:

78% *de* 80% yield



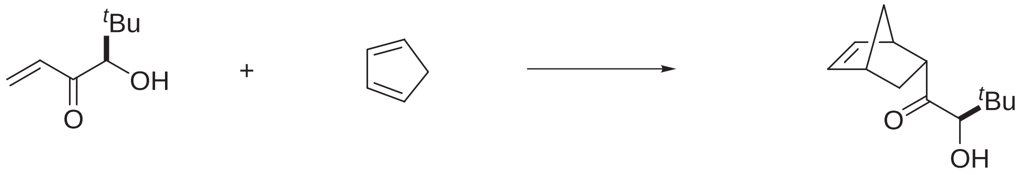
Walborsky *Tetrahedron* **1963**, *19*, 2333.



R = CH$_2$Ph, CONHPh

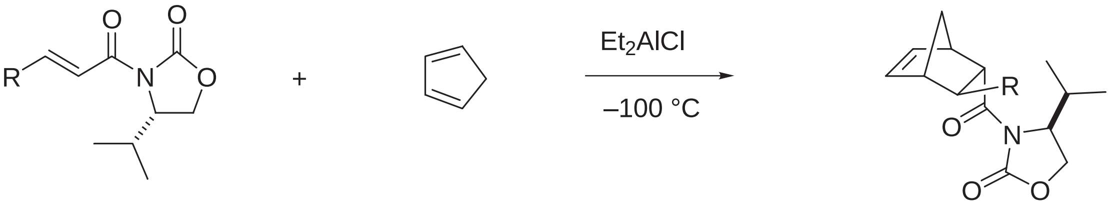
99% *de*

Helmchen *Angew. Chem., Int. Ed. Eng*. **1981**, *20*, 205.

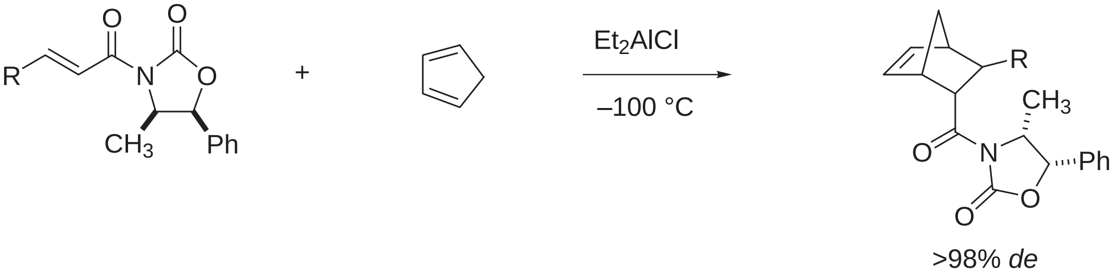


conditions	*endo*	*de*	yield
–20 °C, 24 h	89%	99%	90%
ZnCl$_2$, –43 °C, 1 h	94%	>99%	95%

Masamune *J. Org. Chem.* **1983**, *48*, 1137, 4441.



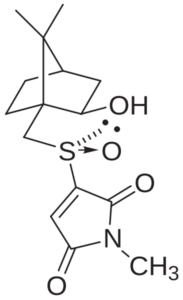
>86% *de*



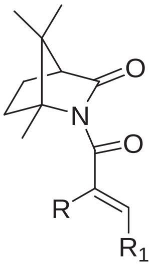
>98% *de*

Evans *J. Am. Chem. Soc.* **1984**, *106*, 4261; **1988**, *110*, 1238.

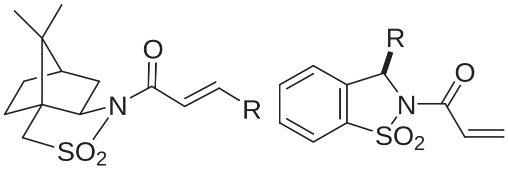
other notable chiral dienophiles:



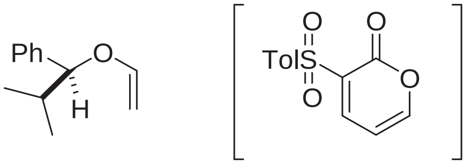
Arai *J. Org. Chem*. **1991**, *56*, 1983.



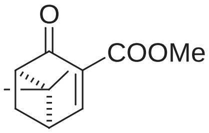
Boeckman *J. Am. Chem. Soc*. **1992**, *114*, 2258.



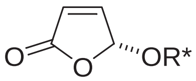
Oppolzer *Helv. Chim. Acta* **1989**, *72*, 123.
Oppolzer *Tetrahedron Lett*. **1990**, *31*, 5015.



Inverse electron demand Diels–Alder reaction
Posner *J. Am. Chem. Soc*. **1986**, *108*, 7373.

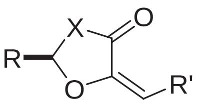


Liu *Tetrahedron Lett*. **1991**, *32*, 2005.
Boger *J. Org. Chem.* **1985**, *50*, 1904.



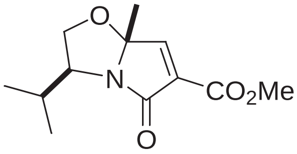
R* = *l*-menthyl

Feringa *Tetrahedron: Asymmetry* **1991**, *2*, 1247.

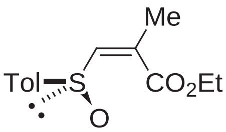


X = O, NAc

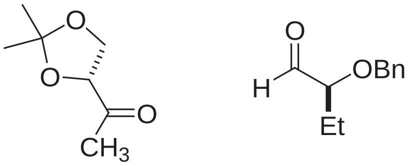
Roush *Tetrahedron Lett*. **1989**, *30*, 7305 and 7309.
Kneer *Synthesis* **1990**, 599.



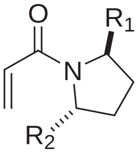
Meyers *Tetrahedron Lett*. **1989**, *30*, 6977.



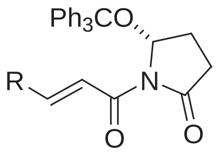
Koizumi *Tetrahedron Lett*. **1984**, *25*, 87.



Danishefsky *J. Am. Chem. Soc*. **1982**, *104*, 6457.
Danishefsky *J. Am. Chem. Soc*. **1984**, *106*, 2455.



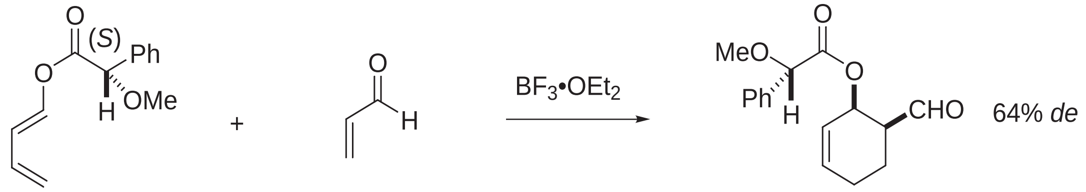
Ghosez *Tetrahedron Lett*. **1989**, *30*, 5891.



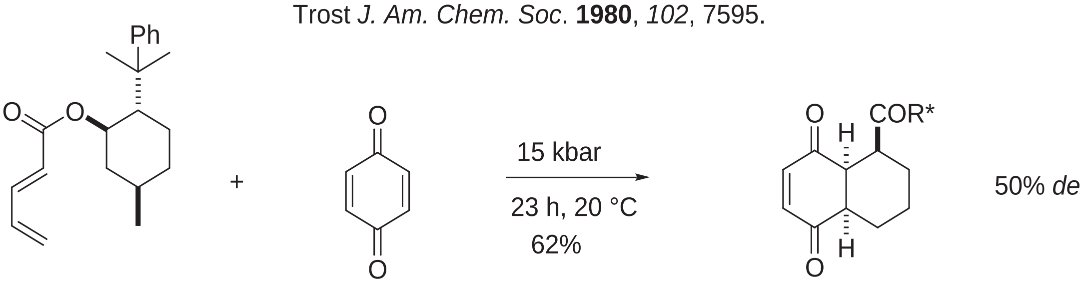
Koga *J. Chem. Soc., Perkin Trans. 1* **1990**, 426.

C. Chiral dienes

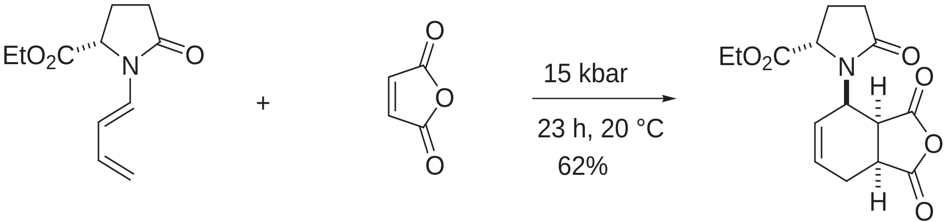
-These have been much less extensively studied.



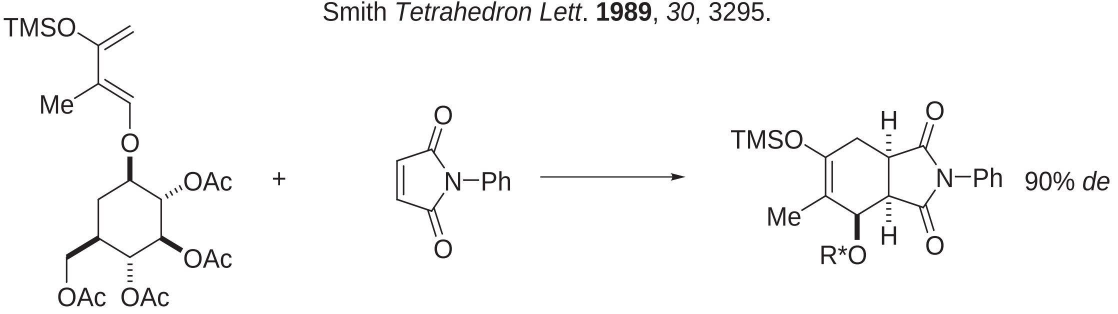
Trost *J. Am. Chem. Soc*. **1980**, *102*, 7595.



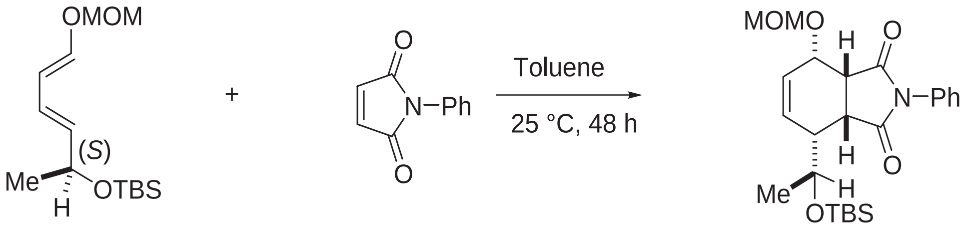
Dauben *Tetrahedron Lett*. **1982**, *23*, 4875.

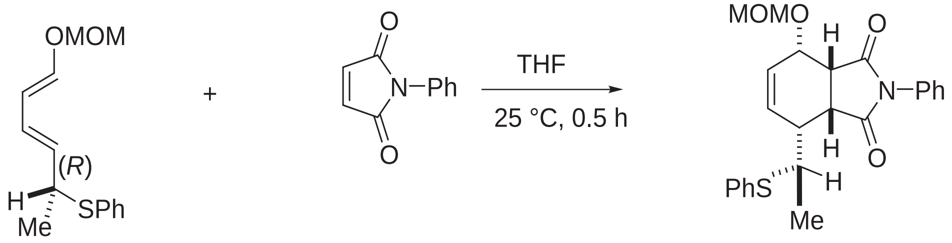


Smith *Tetrahedron Lett*. **1989**, *30*, 3295.

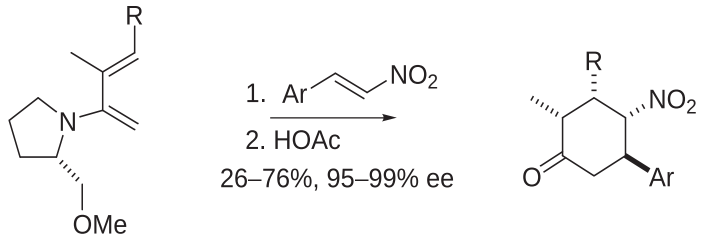


Stoodley *J. Chem. Soc*., *Perkin Trans. 1* **1990**, 1339.

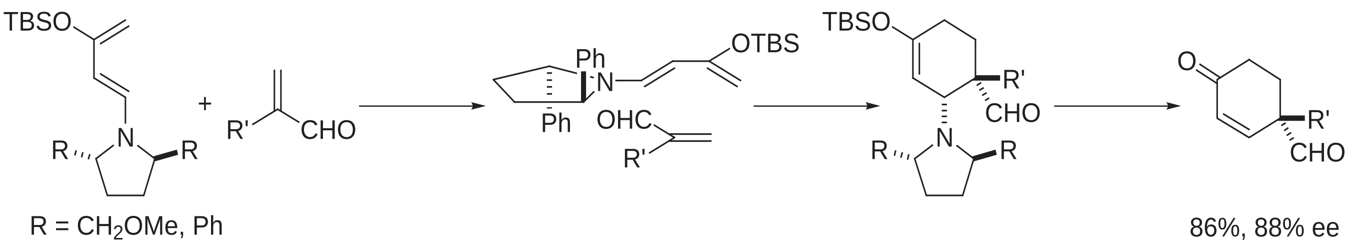




McDougal *Tetrahedron Lett*. **1989**, *30*, 3897.



Enders *Synthesis* **1992**, 1242; **1994**, 66.
Barluenga *J. Am. Chem. Soc.* **1993**, *115*, 4403; **1998**, *120*, 2514.

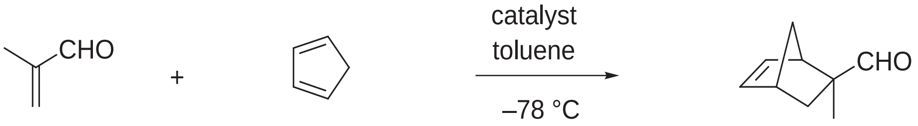


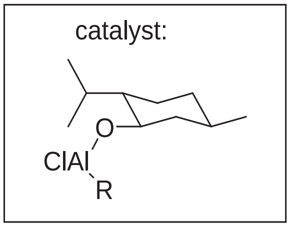
Rawal *J. Am. Chem. Soc.* **1999**, *121*, 9562.

D. Chiral Lewis acid catalysts

Review: Oh *Org. Prep. Proced. Int*. **1994**, *26*, 129.
Age and East *Asymmetric Synthetic Methodology*; CRC Press: New York, 1996.

-Pioneer work

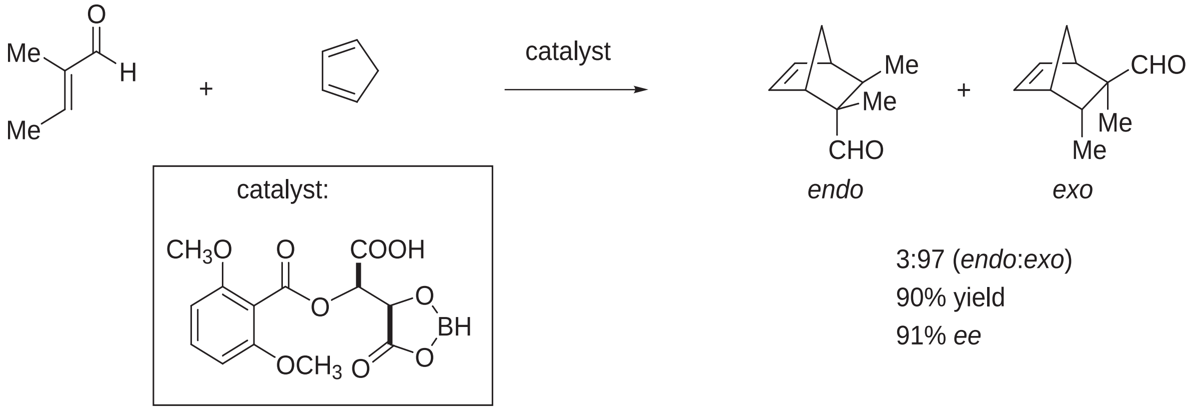




R	yield	*ee*
Cl	56%	57%
Et	57%	35%
^{i}Bu	67%	23%

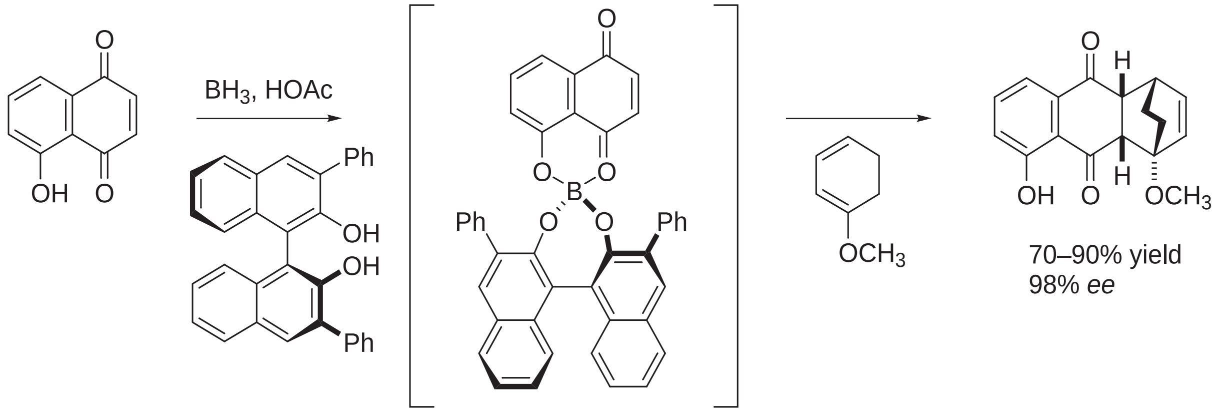
Koga *J. Chem. Soc., Chem. Commun*. **1979**, 437.
Tetrahedron Lett. **1987**, *28*, 5687.

a. Boron-based Lewis acids

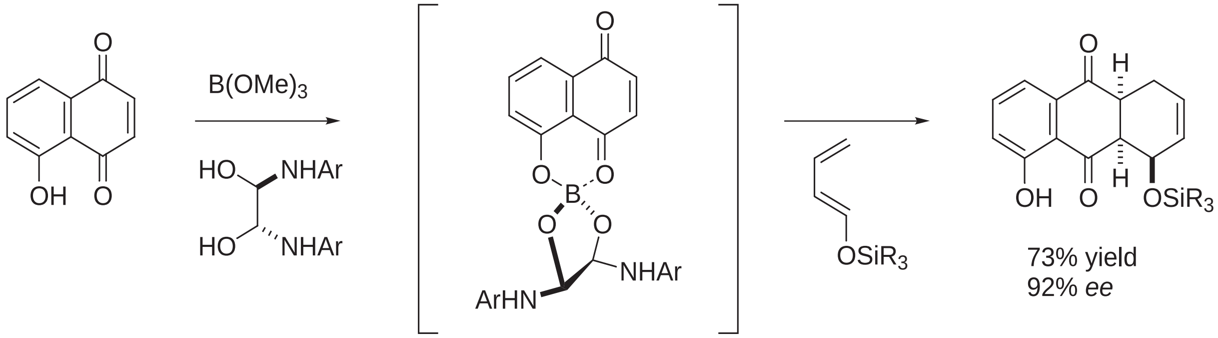


3:97 (*endo*:*exo*)
90% yield
91% *ee*

Yamamoto *J. Org. Chem*. **1989**, *54*, 1481.

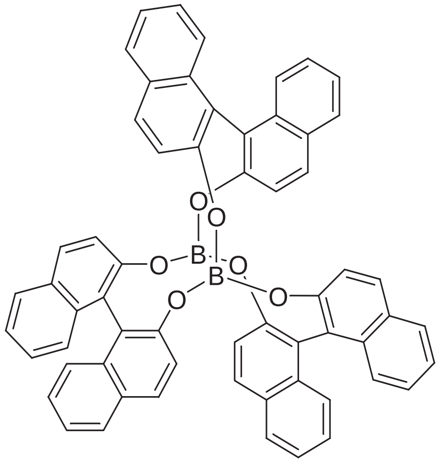


Kelly *J. Am. Chem. Soc*. **1986**, *108*, 3510.



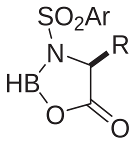
Yamamoto *Tetrahedron Lett*. **1986**, *27*, 4895.

other boron-based catalysts



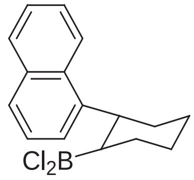
C_3-symmetric

Kaufmann *Angew. Chem., Int. Ed. Eng*. **1990**, *29*, 545.
See also: Yamamoto *J. Am. Chem. Soc*. **1998**, *120*, 6920.

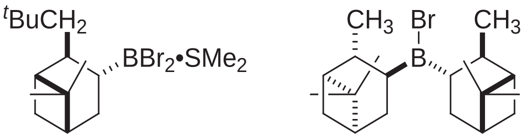


R = Et
R = ^{i}Pr
R = 3-indole

Yamamoto *Synlett* **1990**, 194.
Helmchen *Synlett* **1990**, 197.
Mukaiyama *Chem. Lett*. **1991**, 1341.
Corey *J. Am. Chem. Soc*. **1991**, *113*, 8966.

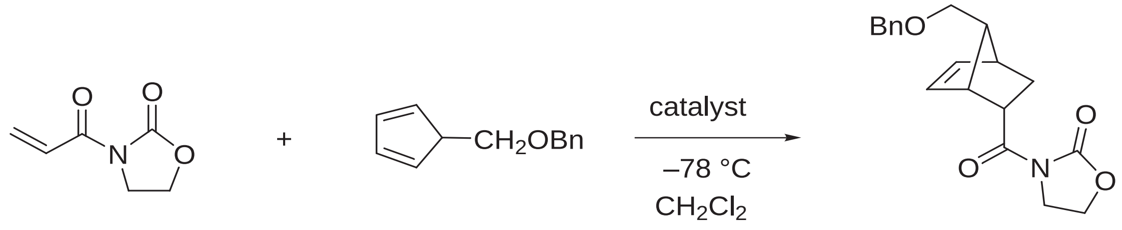


Hawkins *J. Am. Chem. Soc*. **1991**, *113*, 7794.

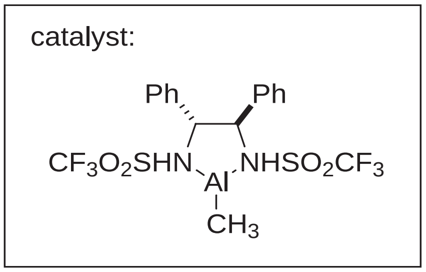


Kaufmann *Tetrahedron Lett*. **1987**, *28*, 777.
Kaufmann *J. Organomet. Chem*. **1990**, *390*, 1.

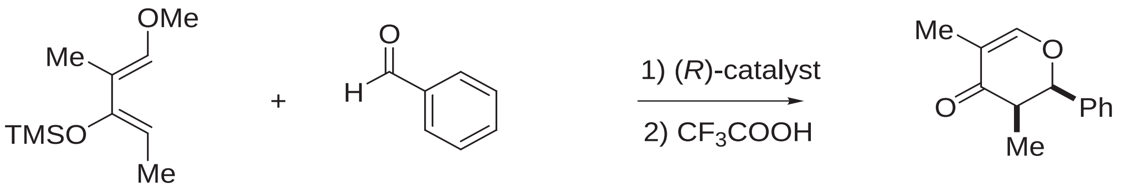
b. Aluminum-based Lewis acids



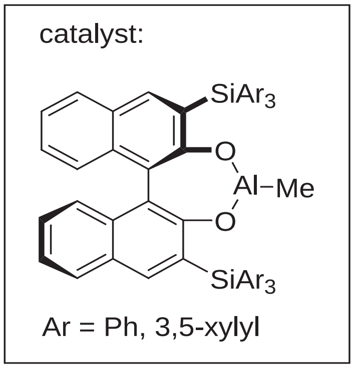
94% yield
95% *ee*



Corey *J. Am. Chem. Soc*. **1989**, *111*, 5493.
Corey *J. Am. Chem. Soc*. **1992**, *114*, 7938.

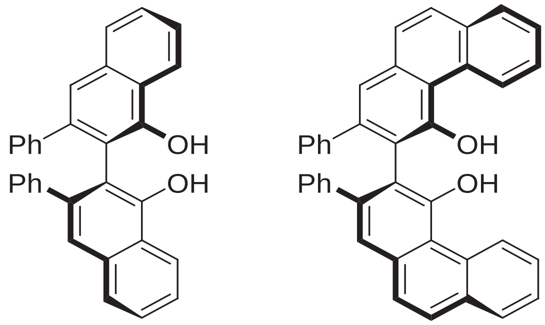


95–97% *ee*

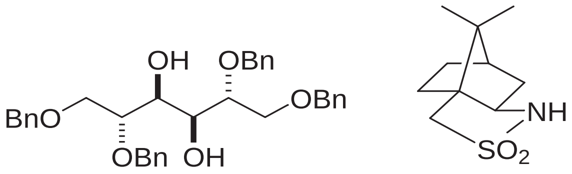


Yamamoto *J. Am. Chem. Soc*. **1988**, *110*, 310.

other chiral ligands used for chiral aluminum-based Lewis acids:



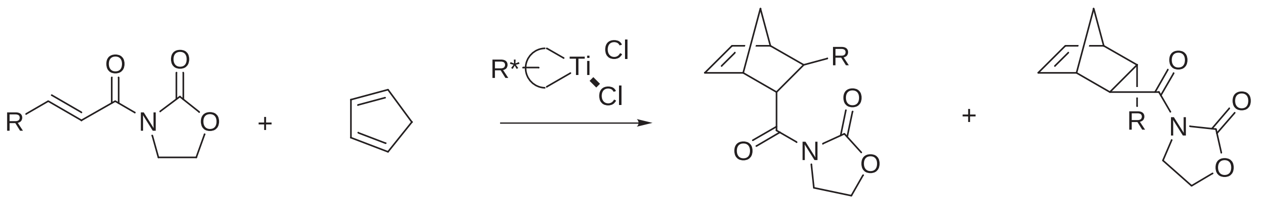
Kagan *Tetrahedron: Asymmetry* **1990**, *1*, 199.



Wulff, Rheingold *J. Am. Chem. Soc*. **1993**, *115*, 3814.

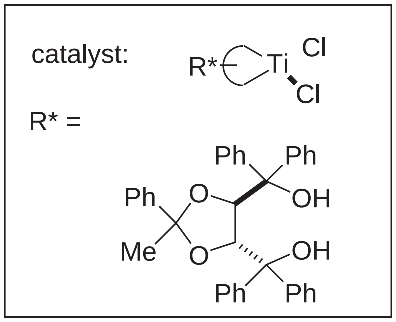
Chapuis *Helv. Chim. Acta* **1987**, *70*, 436.

c. Titanium-based Lewis acids



endo

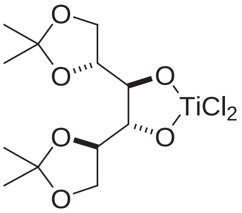
exo



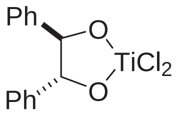
endo:exo (90:10)
endo 92% *ee*

Narasaka *J. Am. Chem. Soc*. **1989**, *111*, 5340.
Seebach *Helv. Chim. Acta* **1987**, *70*, 954.

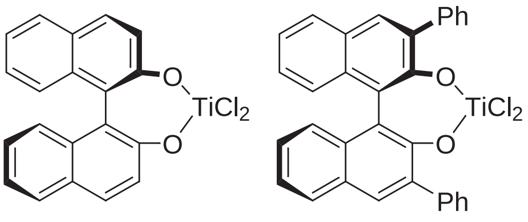
Other Titanium catalysts:



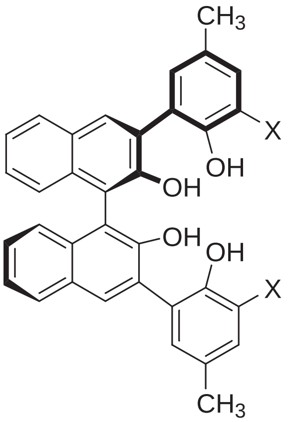
Chapuis *Helv. Chim. Acta* **1987**, *70*, 436.



Oh *J. Org. Chem*. **1992**, *57*, 396.



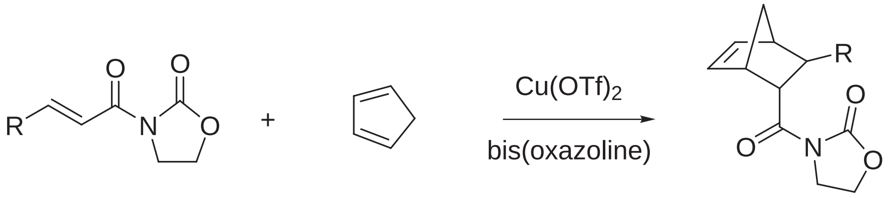
Mikami *Tetrahedron: Asymmetry* **1991**, *2*, 643.
Chapuis *Helv. Chim. Acta* **1987**, *70*, 436.



X = Ph, SiPh$_3$,
Si^{t}BuPh$_2$,
Si^{i}Pr$_3$,
Si(*o*-tolyl)$_3$

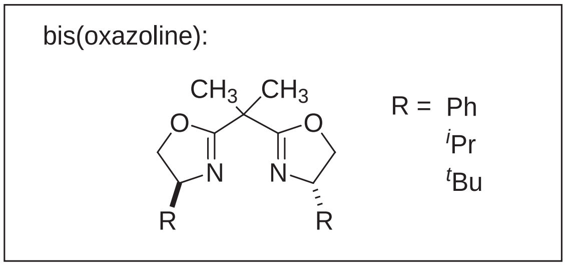
Yamamoto *J. Org. Chem*. **1993**, *58*, 2938.

d. Copper-based Lewis acids

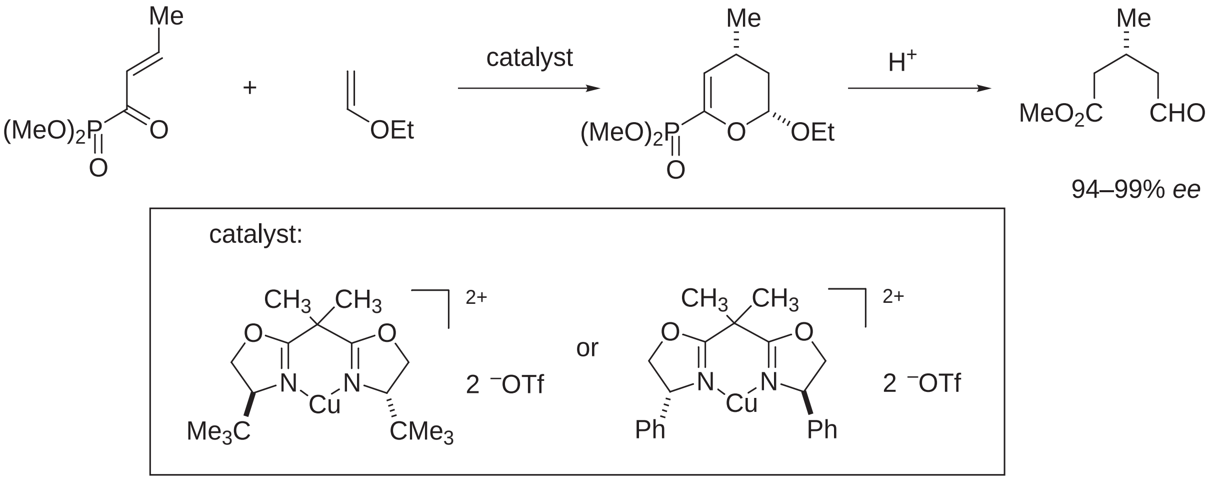


R = H, CH$_3$, Ph, CO$_2$Me

90–97% *ee*
85–92% yield

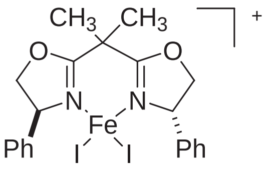


Evans *J. Am. Chem. Soc*. **1993**, *115*, 6460.
Evans *Tetrahedron Lett*. **1993**, *34*, 7027.
Review: Evans *Acc. Chem. Res.* **2000**, *33*, 325.

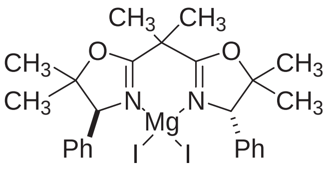


Evans *J. Am. Chem. Soc*. **1998**, *120*, 4895; **1999**, *121*, 7559 and 7582.

e. Iron, Magnesium-based Lewis Acids

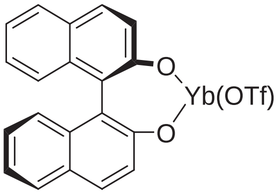


Corey *J. Am. Chem. Soc*. **1991**, *113*, 728.

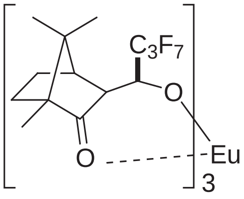


Corey *Tetrahedron Lett*. **1992**, *33*, 6807.

f. Miscellaneous chiral Lewis acids



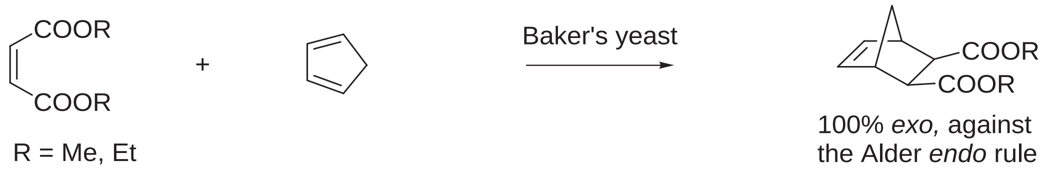
Kobayashi *Tetrahedron Lett*. **1993**, *34*, 4535.



Eu(hfc)$_3$

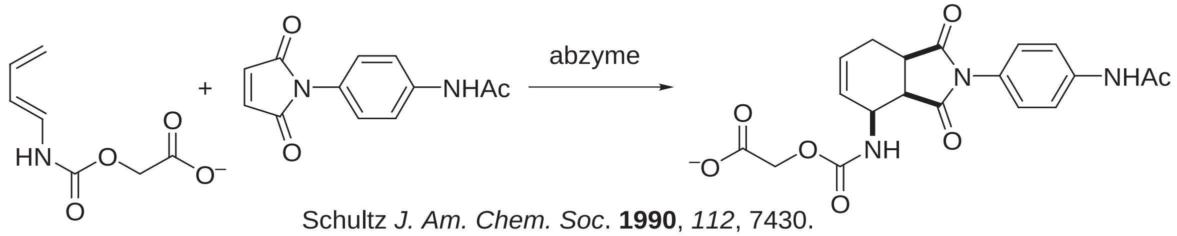
Danishefsky *J. Am. Chem. Soc*. **1986**, *108*, 7060.

E. Biological catalysts

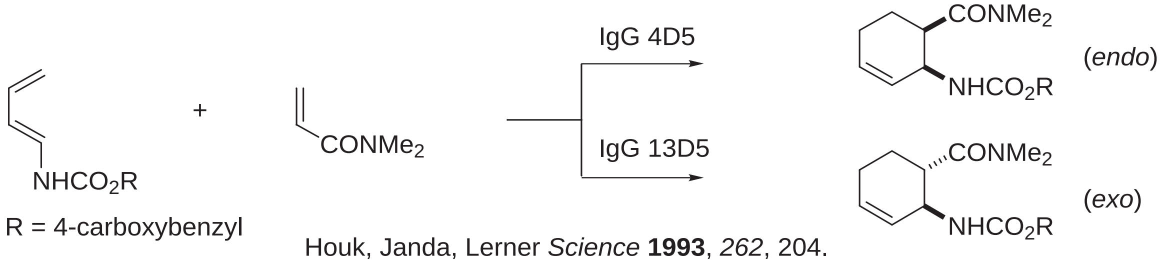


Rao *Tetrahedron Lett*. **1990**, *31*, 5959.

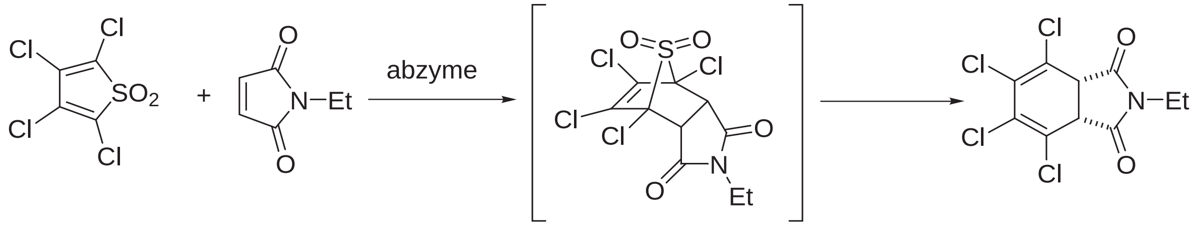
Catalytic antibodies (abzymes):



Schultz *J. Am. Chem. Soc*. **1990**, *112*, 7430.
Schultz *Science* **1998**, *279*, 1929.
Review: Schultz, Lerner *Science* **1995**, *269*, 1835.

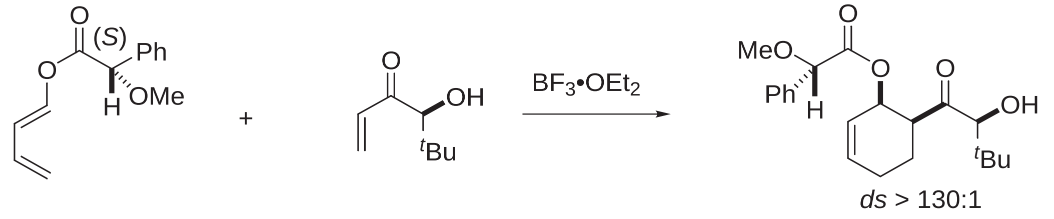


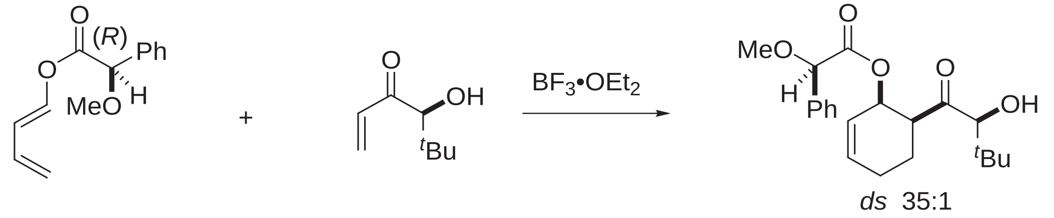
Houk, Janda, Lerner *Science* **1993**, *262*, 204.
Janda *J. Am. Chem. Soc*. **1995**, *117*, 7041.
Houk, Janda, Wilson *Science* **1998**, *279*, 1934.



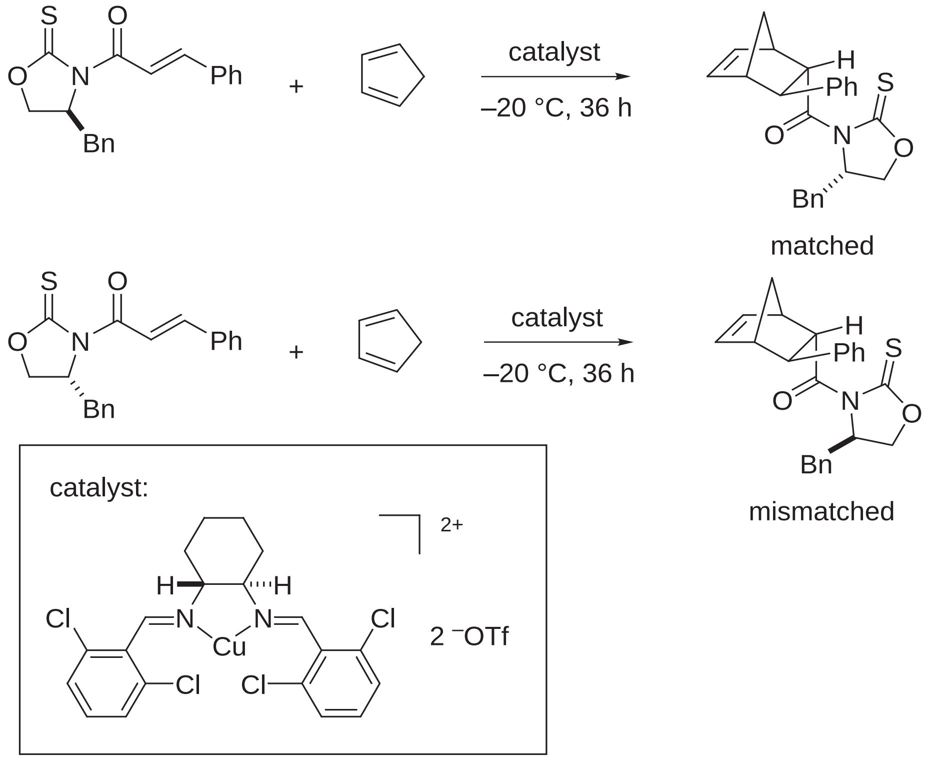
Hilvert *J. Am. Chem. Soc*. **1989**, *111*, 9261.

F. Double asymmetric induction





Masamune *J. Org. Chem*. **1983**, *48*, 4441.

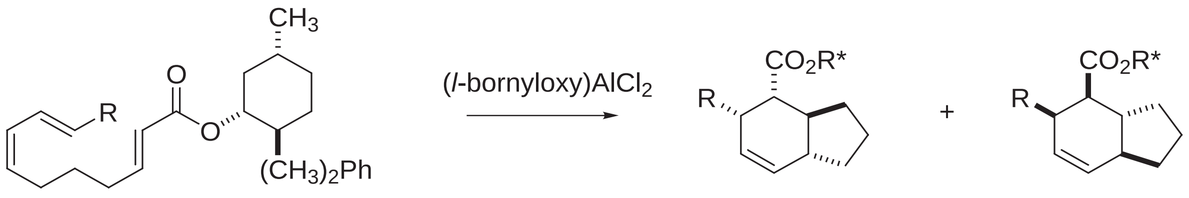


conversion 72%
endo:exo > 97:3
endo$_1$:*endo*$_2$ 97:3

conversion 7%
endo:exo 97:3
endo$_1$:*endo*$_2$ 57:43

Evans *Tetrahedron Lett*. **1993**, *34*, 7027.

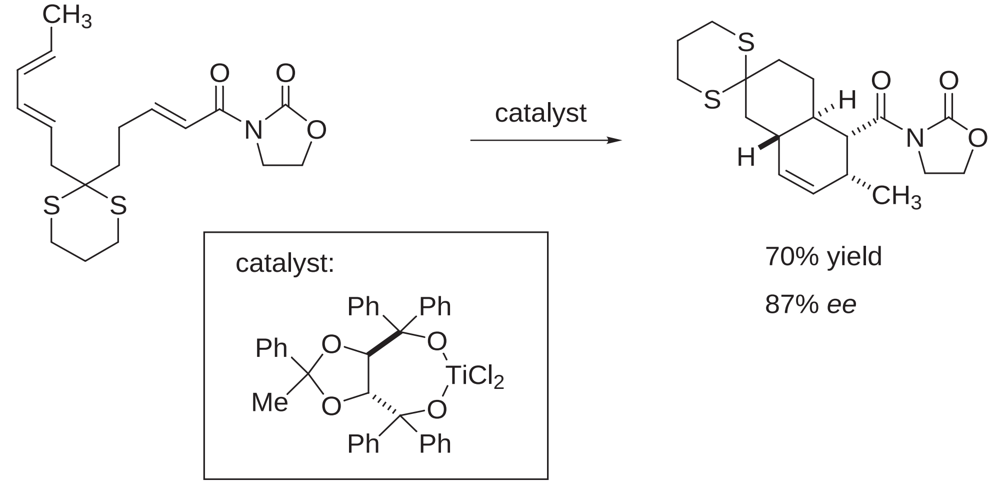
G. Intramolecular Diels–Alder reactions



82 : 18

64% *ee*

Roush *J. Am. Chem. Soc*. **1982**, *104*, 2269.

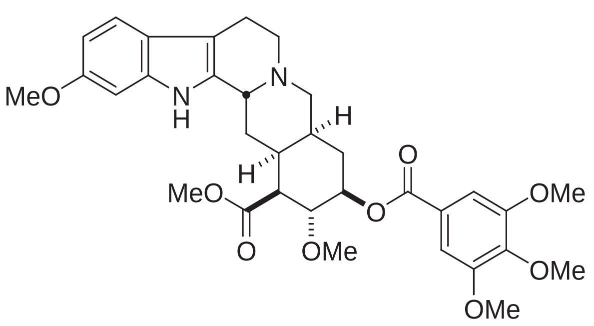


70% yield

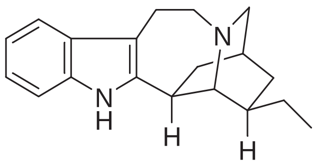
87% *ee*

Narasaka *Chem. Lett*. **1989**, 1947.

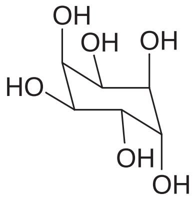
16. Some Classic and Favorite Total Synthesis Applications



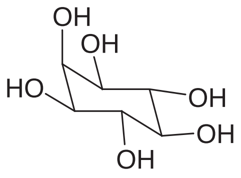
Reserpine
Woodward *Tetrahedron* **1958**, *2*, 1.
Wender *J. Am. Chem. Soc.* **1980**, *102*, 6157.



Ibogamine
Sallay *J. Am. Chem. Soc*. **1967**, *89*, 6762.
Trost *J. Am. Chem. Soc*. **1978**, *100*, 3930.

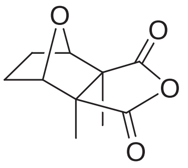


allo-Inositol

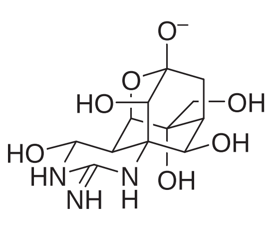


myo-Inositol

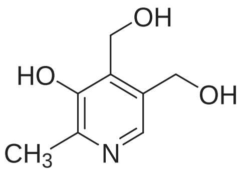
Kowarski *J. Org. Chem.* **1973**, *38*, 117.



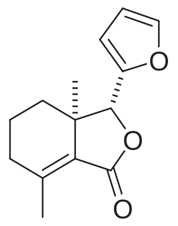
Cantharidin
Stork, Burgstahler *J. Am. Chem. Soc*. **1953**, *75*, 384.
Dauben *J. Am. Chem. Soc*. **1980**, *102*, 6893.
Grieco *J. Am. Chem. Soc.* **1990**, *112*, 4595.



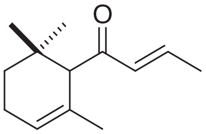
Tetrodotoxin
Kishi *J. Am. Chem. Soc*. **1972**, *94*, 9217.



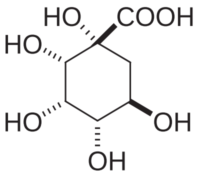
Pyridoxol
Harris *J. Org. Chem.* **1962**, *27*, 2705.
Doktorova *Tetrahedron* **1969**, *25*, 3527.



Fraxinellone
Fukuyama *Tetrahedron Lett.* **1972**, 3401.



α-Damascone
Cookson *J. Chem. Soc*., *Chem. Commun.* **1973**, 161, 742.



Quinic acid

Raphael *J. Chem. Soc*. **1960**, 1560.

Smissman *J. Am. Chem. Soc*. **1963**, *85*, 2184.

Wolinsky *J. Org. Chem.* **1964**, *29*, 3596.

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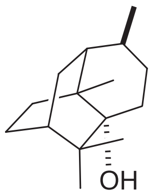
Newkome *Tetrahedron Lett*. **1968**, 1851.



Patchouli alcohol
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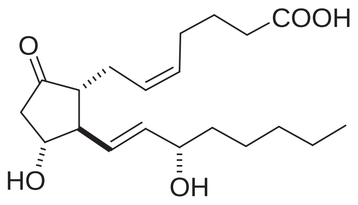

Prostaglandins
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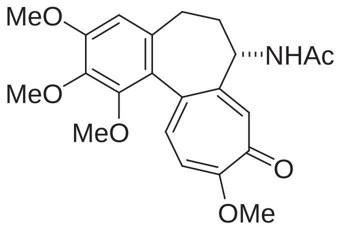

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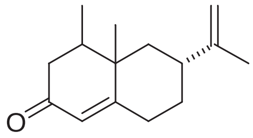

Nootkatone
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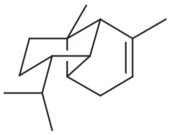

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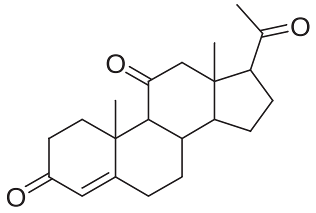

Steroids
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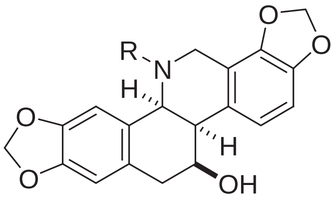

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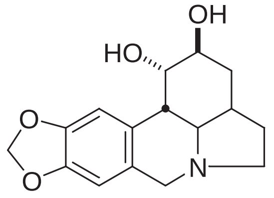

Lycorine
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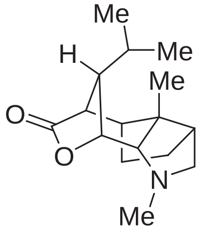

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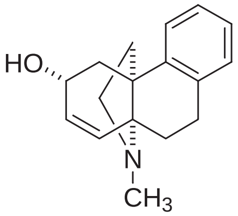

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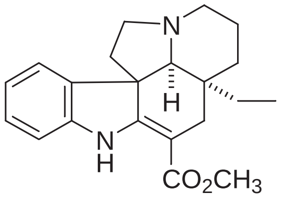

Minovine
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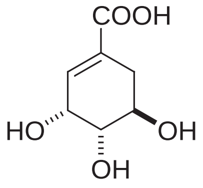

Shikimic acid
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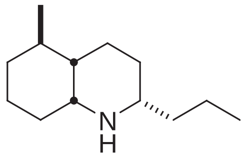

Pumilotoxin
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Inubushi *Chem. Pharm. Bull.* **1978**, *26*, 2442.
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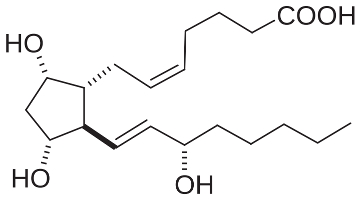

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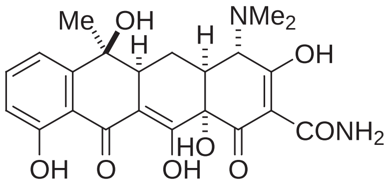

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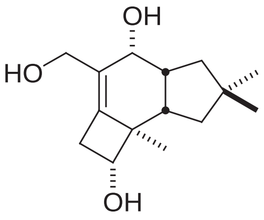

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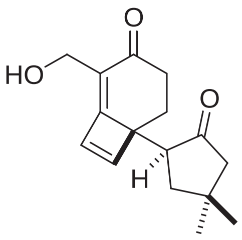

Fomannosin
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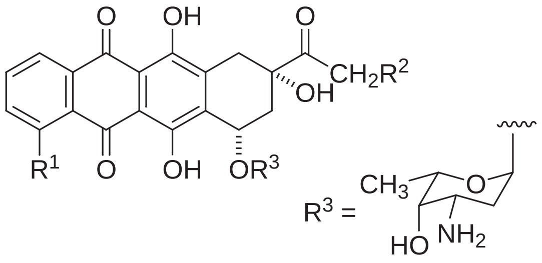

Anthraquinone antibiotics (aglycon)
Kelly *J. Am. Chem. Soc*. **1980**, *102*, 5983.
Cava *J. Am. Chem. Soc*. **1981**, *103*, 1992.
Vogel *Tetrahedron Lett.* **1979**, 4533.
Brassard *Tetrahedron Lett.* **1979**, 4911.
Gesson *Tetrahedron Lett.* **1981**, *22*, 1337.
Rapoport *Tetrahedron Lett.* **1980**, *21*, 4777.
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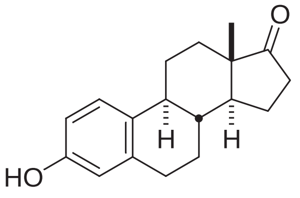

Estrone (orthoquinodimethide)
Grieco *J. Org. Chem*. **1980**, *45*, 2247.
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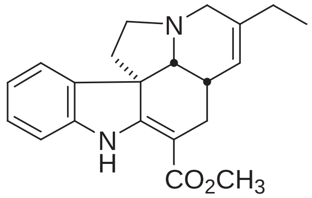

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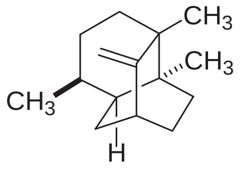

Seychellene
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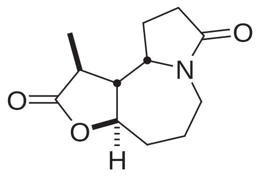

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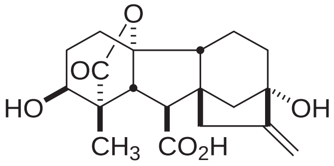

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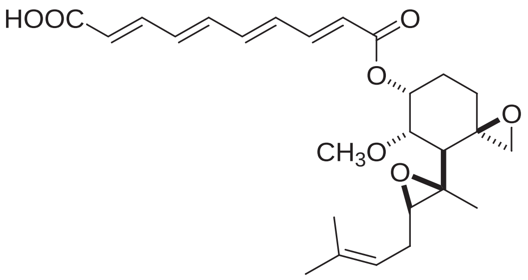

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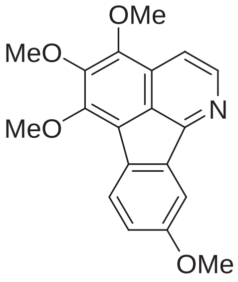

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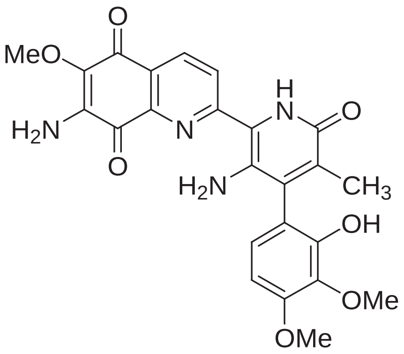

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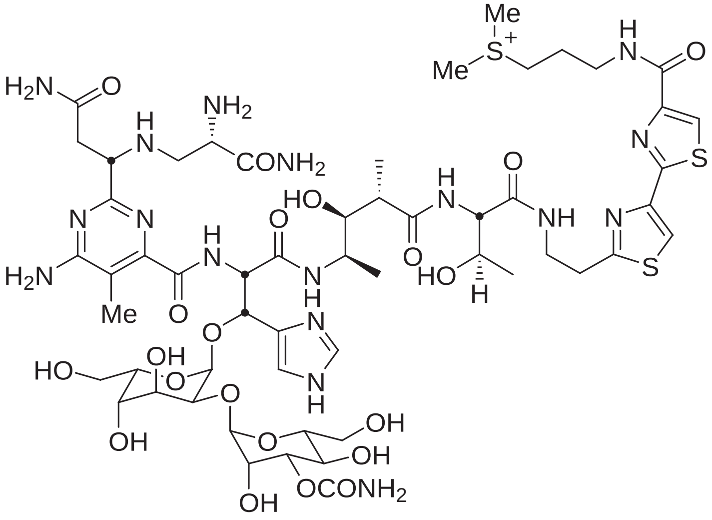

Bleomycin A$_2$
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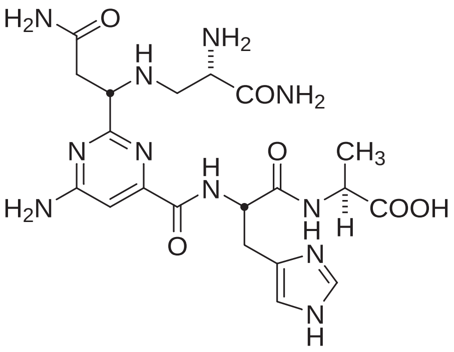

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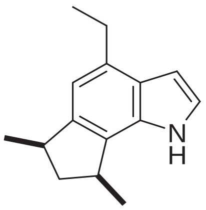

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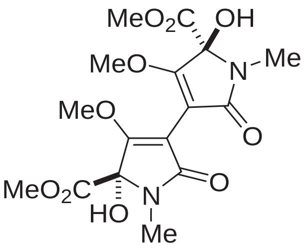

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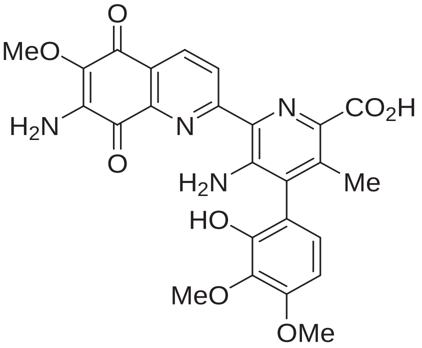

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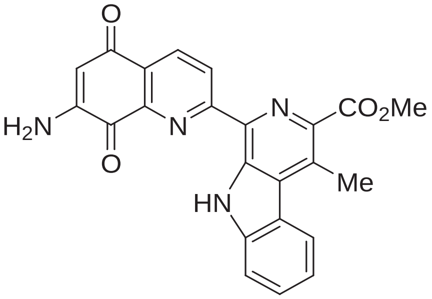

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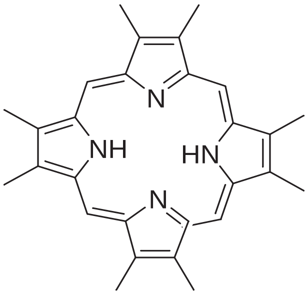

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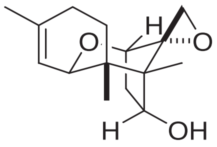

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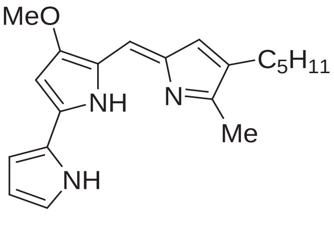

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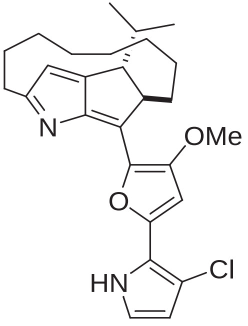

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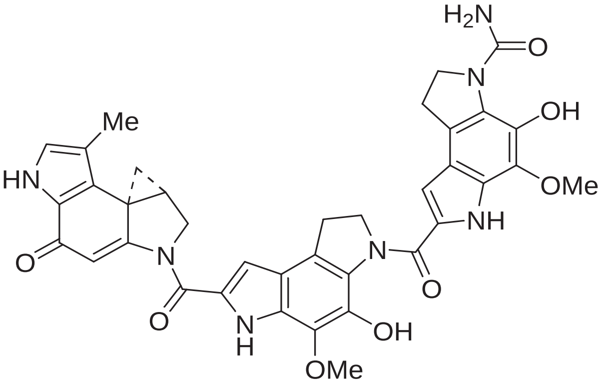

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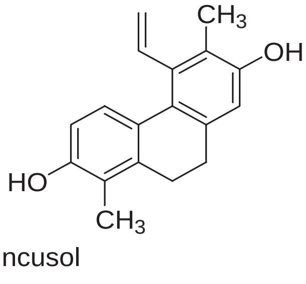

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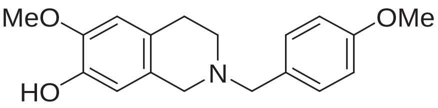

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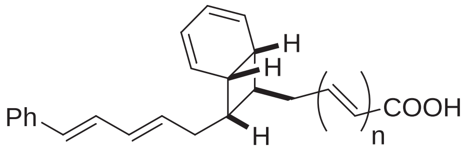

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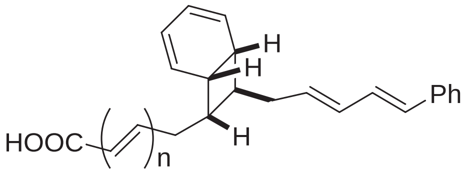

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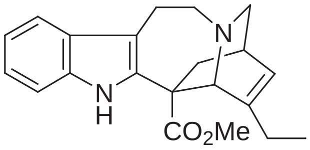

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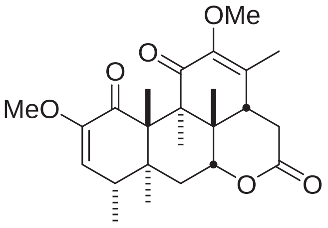

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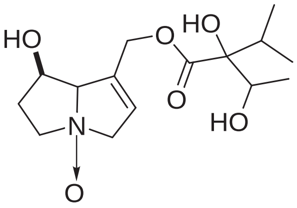

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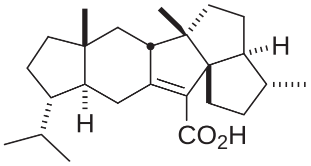

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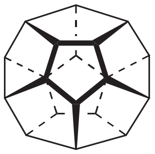

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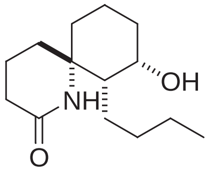

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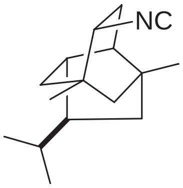

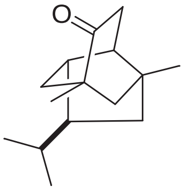

9-Isocyanopupukeanone 9-Pupukeanone
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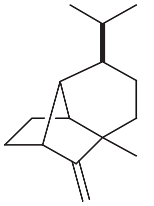

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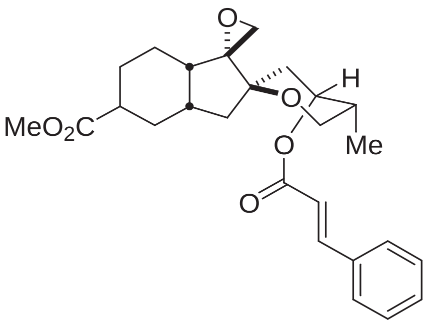

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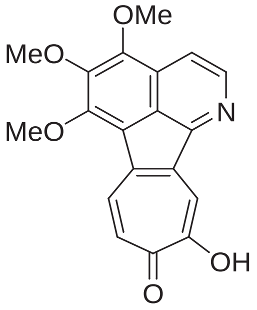
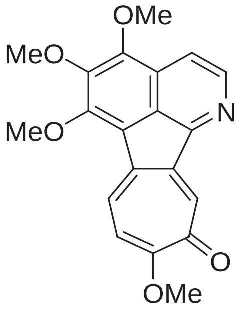
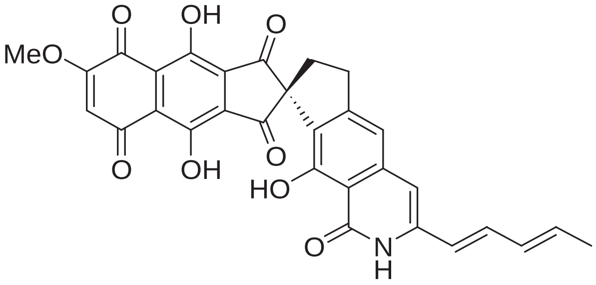
Burke *Tetrahedron Lett.* **1986**, *27*, 4237.

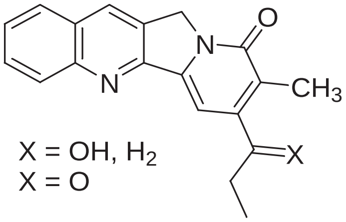




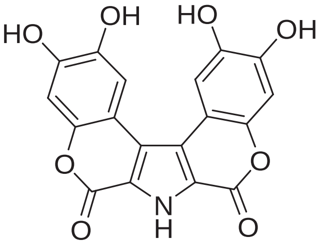
Grandirubrine Imerubrine
Boger *J. Am. Chem. Soc.* **1995**, *117*, 12452.



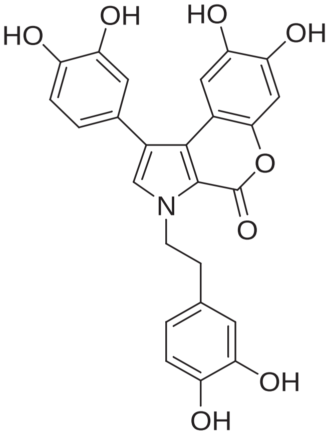
Fredericamycin A
Boger *J. Am. Chem. Soc.* **1995**, *117*, 11839.



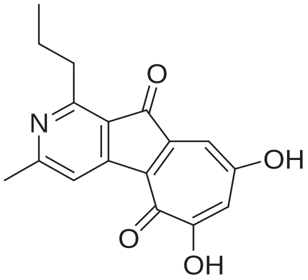
(–)-Mappicine and Nothapodytine B
Boger *J. Am. Chem. Soc.* **1998**, *120*, 1218.



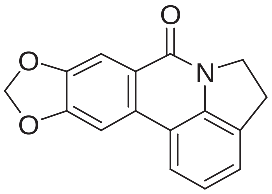
Ningalin A
J. Am. Chem. Soc. **1999**, *121*, 54.



Nigalin B
J. Org. Chem. **2000**, *65*, 2479



Rubrolone
J. Am. Chem. Soc. **2000**, *122*, 12169.



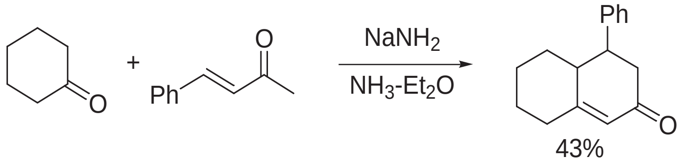
Anhydrolycorinone
J. Org. Chem. **2000**, *65*, 9120.

B. Robinson Annulation

Reviews
M. Jung, *Tetrahedron* **1976**, *32*, 3.
Org. React. **1959**, *10*, 179.
Org. React. **1968**, *16*, 3.
Synthesis **1976**, 777.
Synthesis **1969**, 49.

R. Robinson was awarded the 1947 Nobel Prize in Chemistry for his work on the synthesis of natural products, especially steroids and alkaloids. Notably, he was also the first to address the issue of reaction mechanisms with applications of valence theory to reaction mechanisms, and is credited with the first use of the curved arrow to indicate electron movement. His synthesis of tropinone (1917) is viewed by many to represent the first natural product total synthesis from simple precursors (succindialdehyde, acetone, and methylamine).

Robinson *J. Chem. Soc.* **1917**, 762. (tropinone)

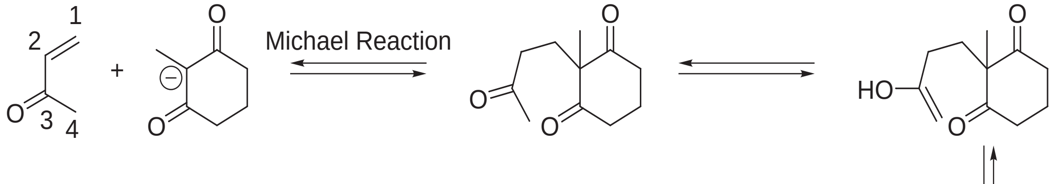


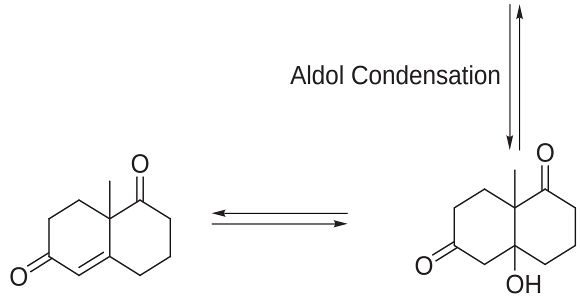
Robinson *J. Chem. Soc.* **1935**, 1285.

Generated a great deal of interest and subsequent work because of relationship to steroid synthesis.

1. Scope

- Formally, a [4 + 2] condensation approach





Wieland–Miescher ketone

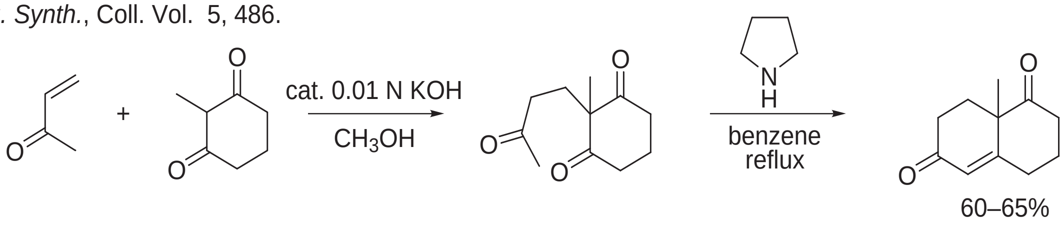
H. Wieland received the 1927 Nobel Prize in Chemistry for his work in isolating and deducing the structures of bile acids/steroids including cholic acid. He concluded his Nobel Lecture with the statement that he had a "duty" to synthesize the bile acids even though the task was insurmountable at the time.

Wieland and Miescher *Helv. Chim. Acta* **1950**, *33*, 2215.

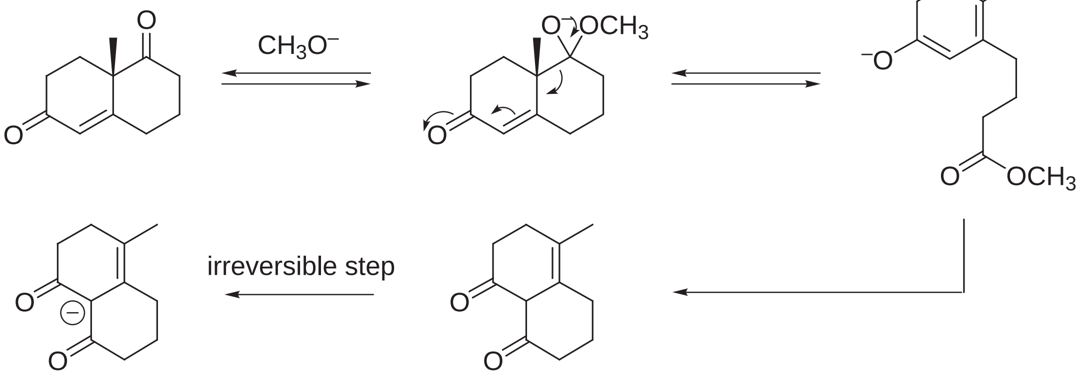
- Alternative "[3 + 3] Robinson Annulation"

Both the [4 + 2] and [3 + 3] approaches were first generalized by Robinson *J. Chem. Soc.* **1937**, 53.

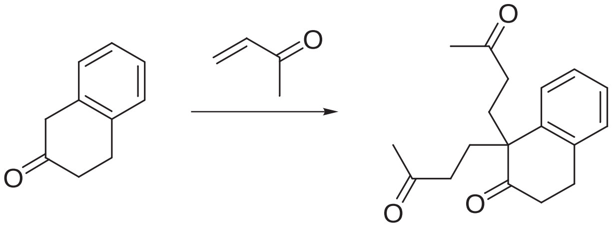
- *Org. Synth.*, Coll. Vol. 5, 486.



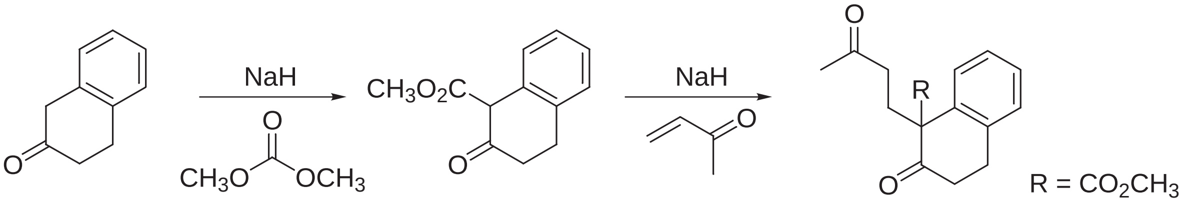
- With stronger base, other reactions are observed:



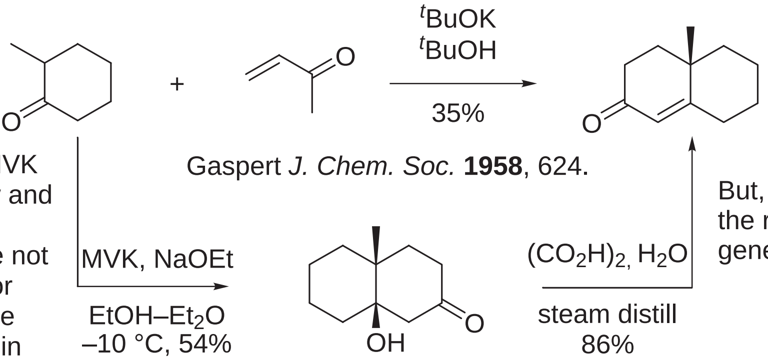
- Double addition of methyl vinyl ketone (MVK) sometimes a problem, especially at more acidic sites.



-Solutions



- For the preparation of the useful starting octalone derivatives, the low yield has been considered acceptable since it is prepared from readily available materials.



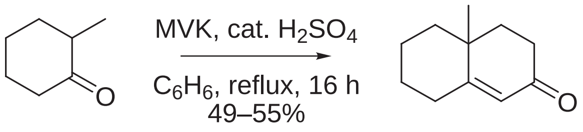
Gaspert *J. Chem. Soc.* **1958**, 624.

At low temperature, MVK polymerization is slow and Michael reaction OK, but, the conditions are not sufficiently vigorous for H_2O elimination, so the reaction is conducted in two steps.

But, many variations on the reaction have provided general improvements.

Marshall *J. Org. Chem.* **1964**, *25*, 2501.

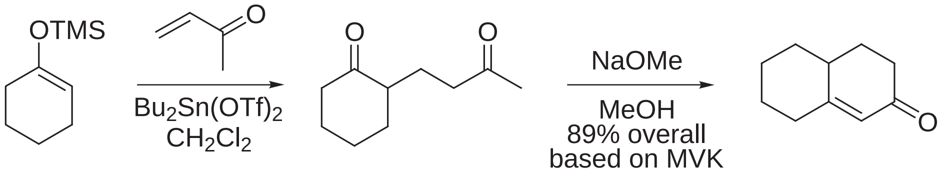
Acid-catalyzed variant of reaction.



Reaction simple to set up, but, conversion still modest.

Heathcock and McMurry *Tetrahedron Lett.* **1971**, 4995.

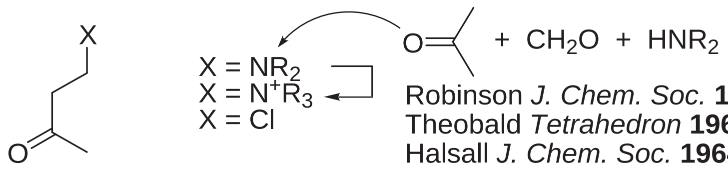
Lewis acid catalyzed variant of reaction.



Superb conversions possible.

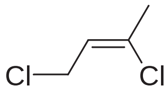
Nozaki *Tetrahedron* **1991**, *47*, 9773.
J. Am. Chem. Soc. **1992**, *113*, 4028.

- Alternatives to methyl vinyl ketone: MVK difficult to employ due to tendency to polymerize

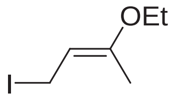


Robinson *J. Chem. Soc.* **1937**, 53.
Theobald *Tetrahedron* **1966**, *22*, 2869.
Halsall *J. Chem. Soc.* **1964**, 1029.

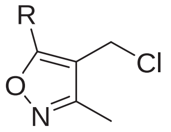
- Other equivalents



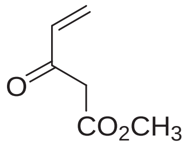
Julia *Bull. Soc. Chim., Fr.* **1954**, *5*, 780.



Stork *J. Am. Chem. Soc.* **1956**, *78*, 501.

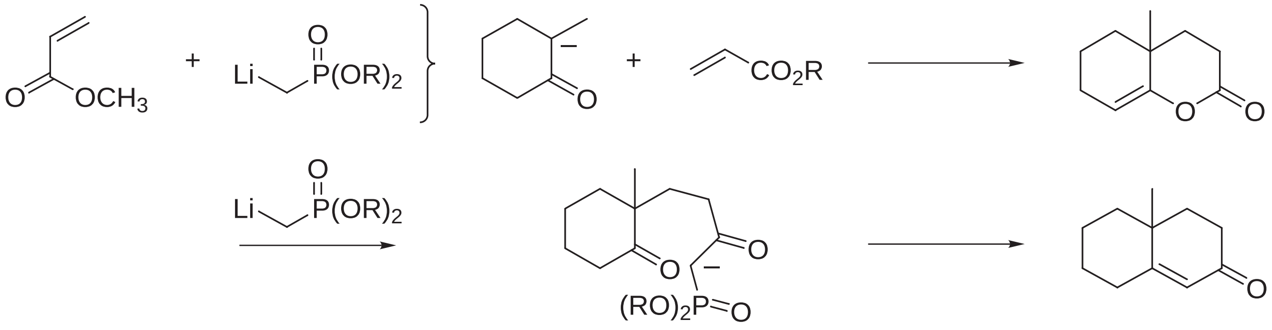


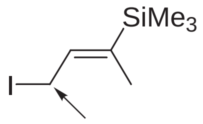
Stork *J. Am. Chem. Soc.* **1967**, *89*, 5461 and 5463.



Stork *Tetrahedron Lett.* **1972**, 2755.
Wenkert *J. Am. Chem. Soc.* **1964**, *86*, 2038.

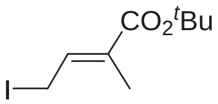
Fried *J. Am. Chem. Soc.* **1968**, *90*, 5926.



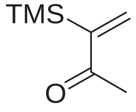


Stork *J. Am. Chem. Soc.* **1974**, *96*, 3682.

(allylic alkylation reaction is rapid and yield is high)

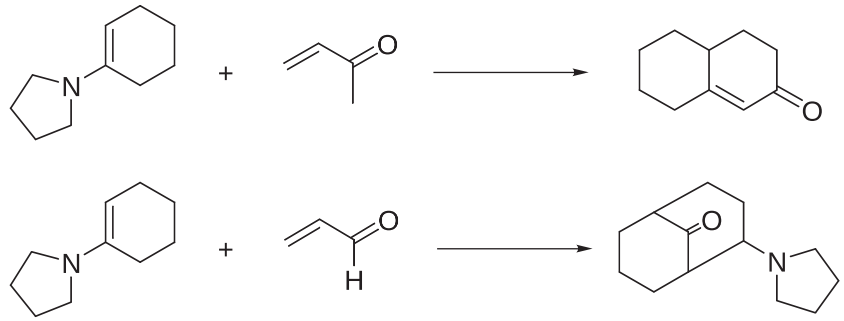


Stotter *J. Am. Chem. Soc.* **1974**, *96*, 6524.

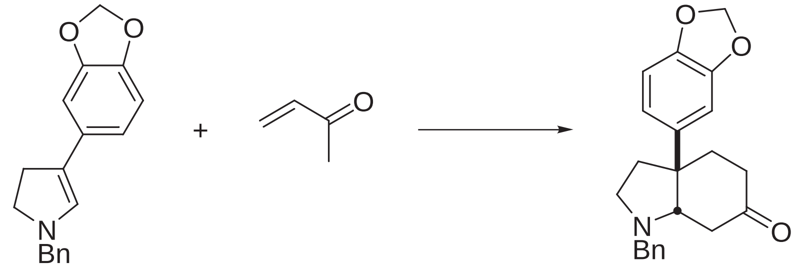


Stork *J. Am. Chem. Soc.* **1973**, *95*, 6152.
Boeckman *J. Am. Chem. Soc.* **1973**, *95*, 6867.

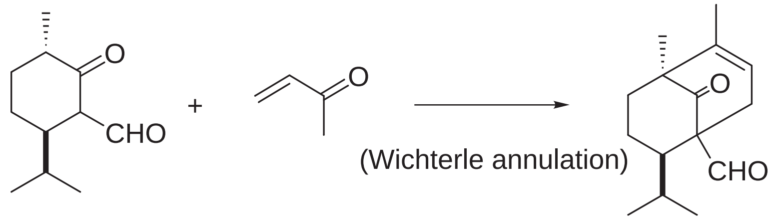
Enamine Annulations



Stork *J. Am. Chem. Soc.* **1956**, *78*, 5129.
J. Am. Chem. Soc. **1963**, *85*, 207.
Henderickson *J. Am. Chem. Soc.* **1971**, *93*, 1307.

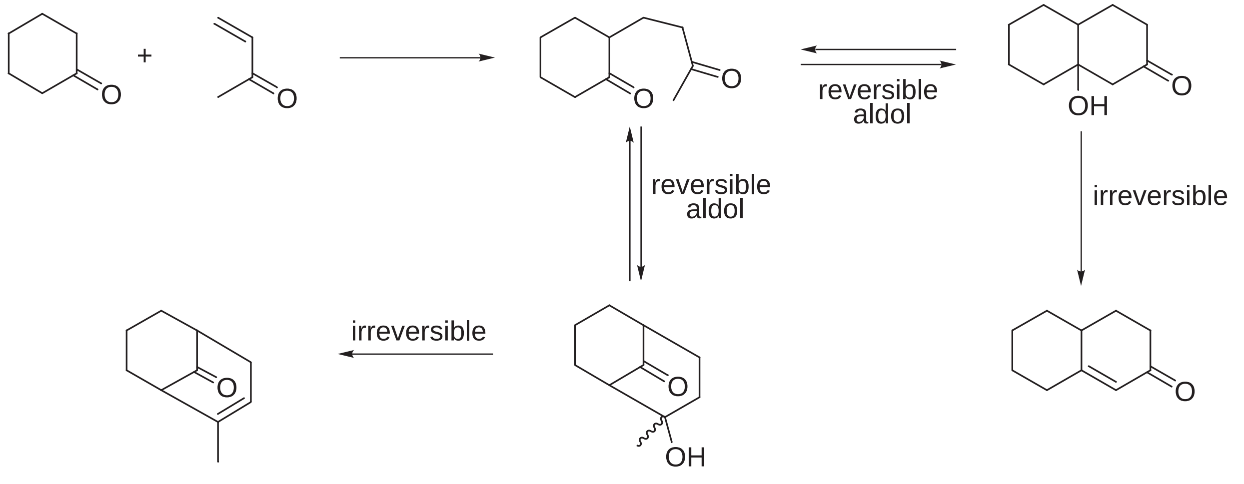


Stevens *J. Chem. Soc., Chem. Commun.* **1970**, 1585.
Evans *Tetrahedron Lett.* **1969**, 1573.
Evans *J. Org. Chem.* **1970**, *35*, 4122.



Corey *J. Am. Chem. Soc.* **1963**, *85*, 3527.

- The bridged annulation

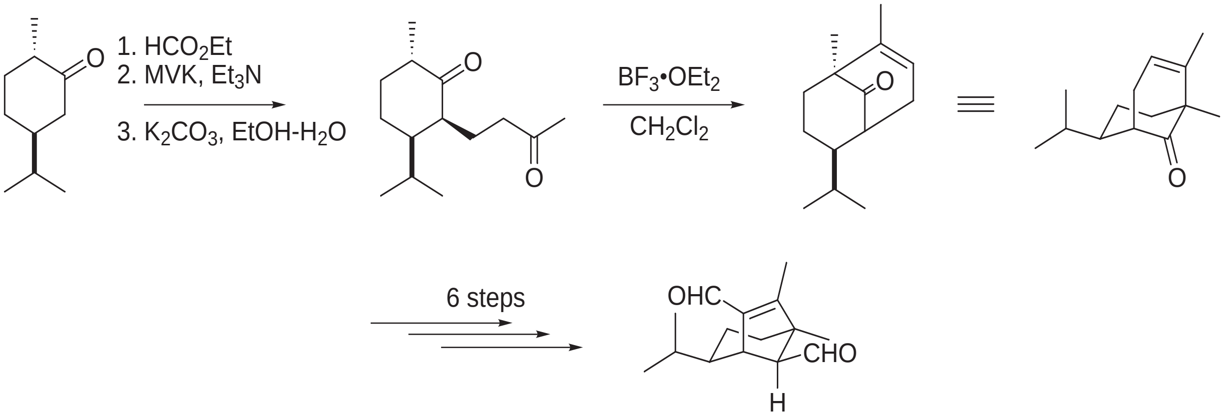


slow, difficult –H_2O: requires vigorous H^+conditions

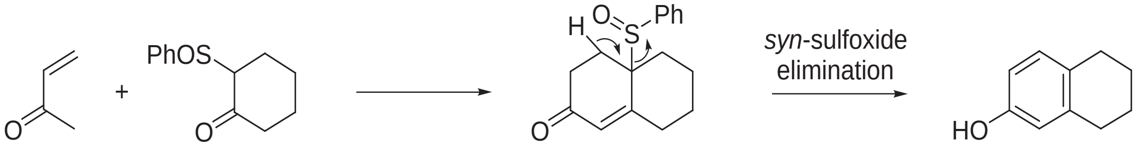
usually kinetic aldol product but formed reversibly

elimination especially effective under basic conditions

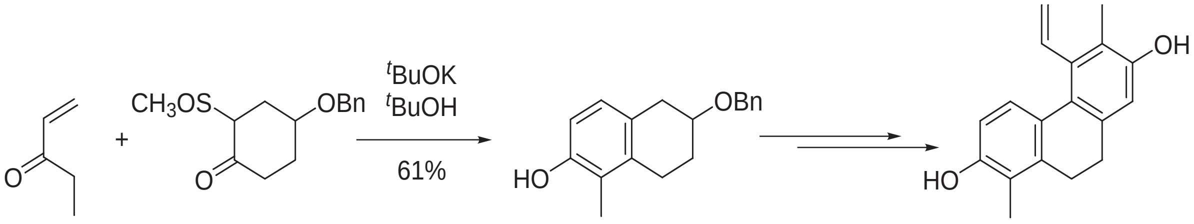
- Helminthosporal synthesis, Corey *J. Am. Chem. Soc.* **1963**, *85*, 3527.



Aromatic Annulation



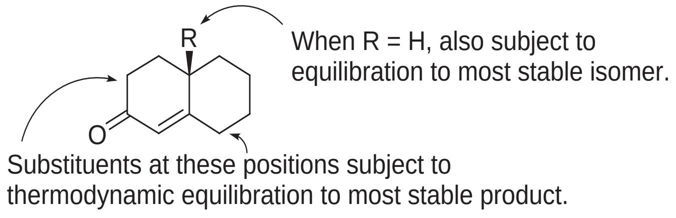
Boger *J. Org. Chem.* **1980**, *45*, 5002.



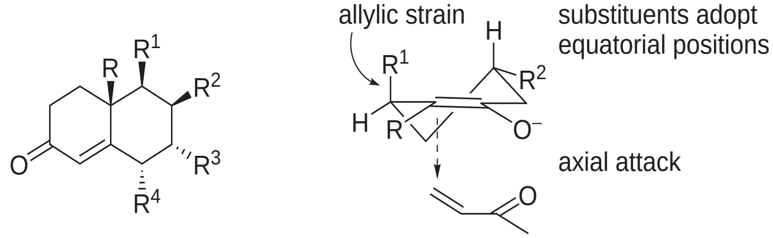
Boger *J. Org. Chem.* **1984**, *49*, 4045.

Juncusol

2. Diastereoselectivity



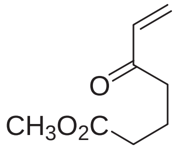
General Observations:



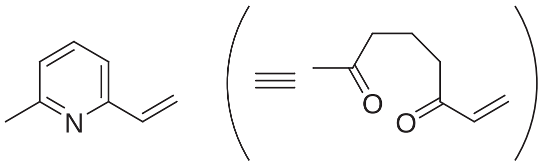
3. Tandem Robinson Annulation

(Incorporation of more than four carbons from MVK for more convergent syntheses)

- Examples



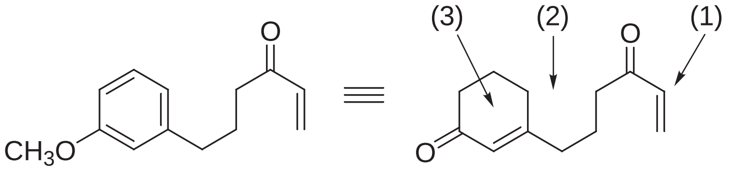
Karady *Tetrahedron Lett.* **1976**, 2401.
Velluz *Angew. Chem., Int. Ed. Eng.* **1965**, *4*, 181.



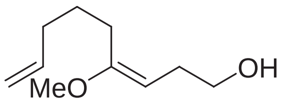
via Michael addition to vinyl pyridine
Birch reduction to dihydropyridine, and hydrolysis to diketone

Danishefsky *J. Am. Chem. Soc.* **1968**, *90*, 520.
Danishefsky *J. Am. Chem. Soc.* **1975**, *97*, 380.

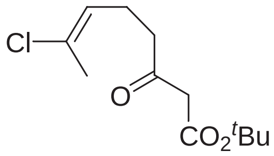
Elements of three sequential Robinson annulations



via Birch reduction of aromatic ring, followed by hydrolysis

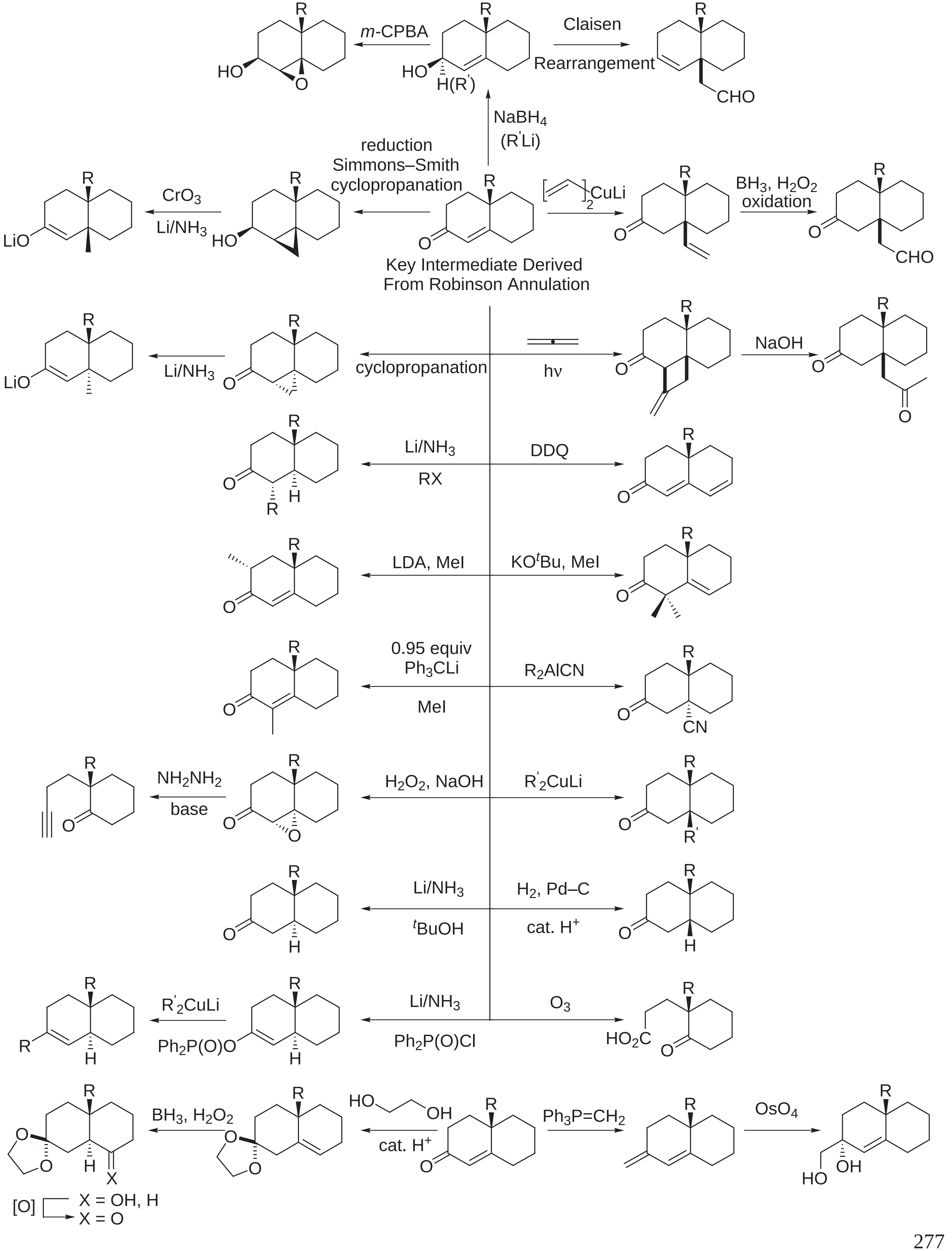


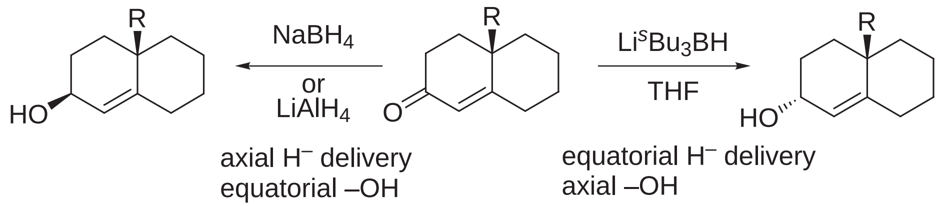
Poirier *Tetrahedron* **1989**, *45*, 4191.



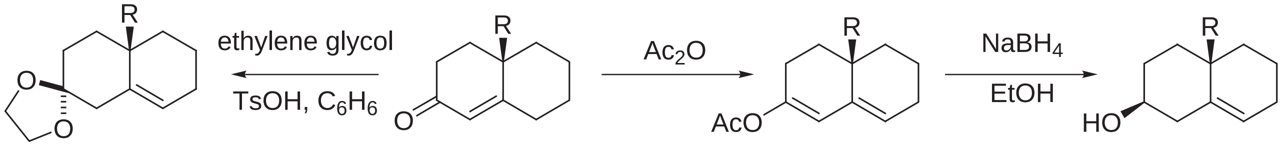
Danishefsky *J. Am. Chem. Soc.* **1971**, *93*, 2356.

4. Robinson Annulation: Key Synthetic Transformations of the Robinson Annulation Product



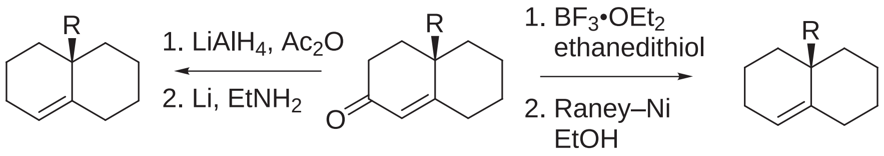


- Deconjugation with ketalization or reduction

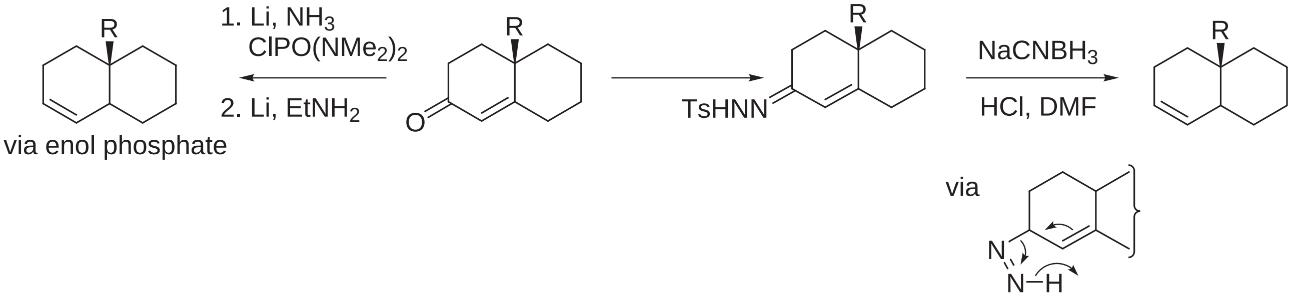


Marshall *J. Org. Chem.* **1972**, *37*, 982.

- Reductive deoxygenation:
  - without double bond migration

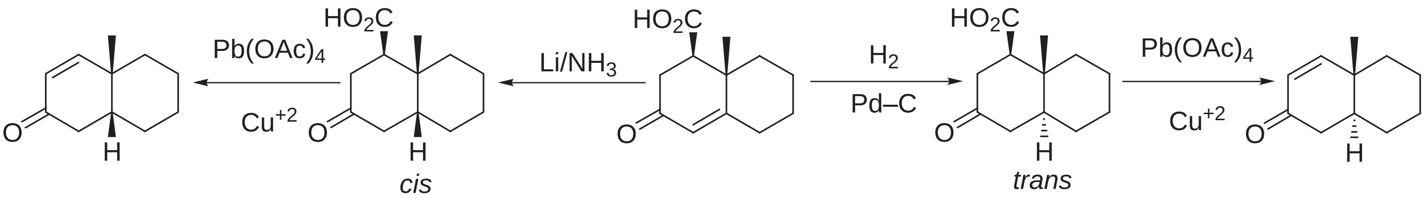


  - with double bond migration



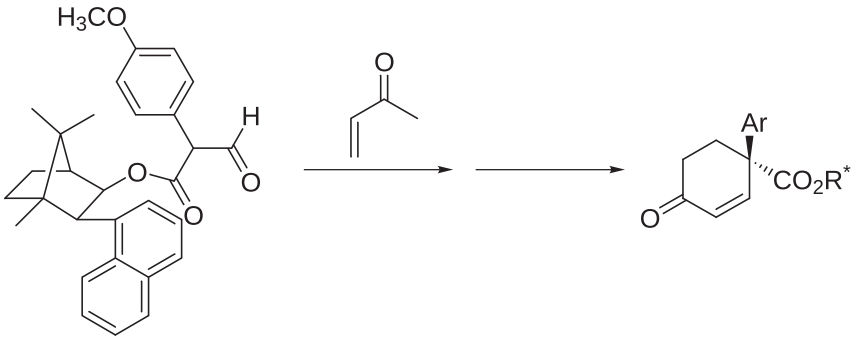
Hydrogenation: McMurry *J. Am. Chem. Soc.* **1968**, *90*, 6821; *Can. J. Chem.* **1972**, *50*, 336.

Birch reduction: For exceptions to generalizations which can exist, see: Boger *Tetrahedron Lett.* **1978**, 17.



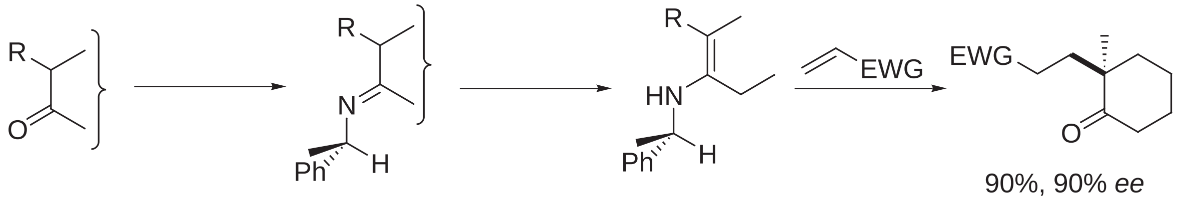
5. Asymmetric Robinson Annulation and Related Reactions

Taber *J. Org. Chem.* **1989**, *54*, 3831.

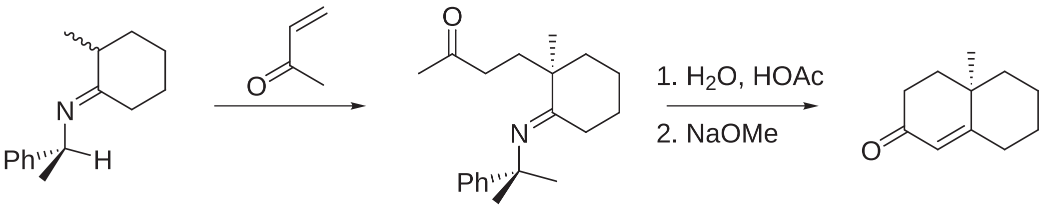


Asymmetric Michael

Revial *Tetrahedron Lett.* **1989**, *30*, 4121.
d'Angelo *J. Am. Chem. Soc.* **1985**, *107*, 273.
Guingant *Tetrahedron: Asymmetry* **1993**, *4*, 25.

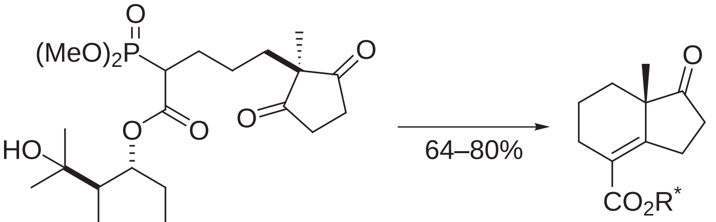


90%, 90% *ee*



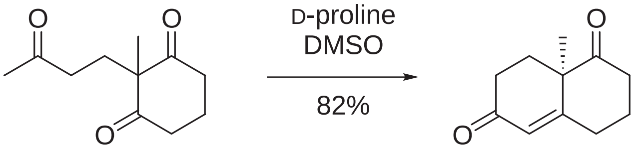
Revial *Org. Syn.* **1992**, *70*, 35.
Review: d'Angelo *Tetrahedron: Asymmetry* **1992**, *3*, 456.

Asymmetric Aldol



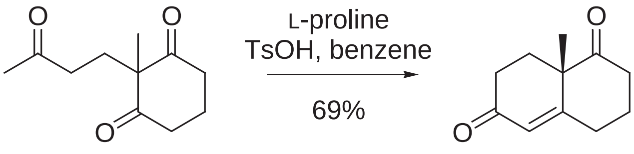
91–98% *de*

Mandai *J. Org. Chem.* **1994**, *59*, 5847.



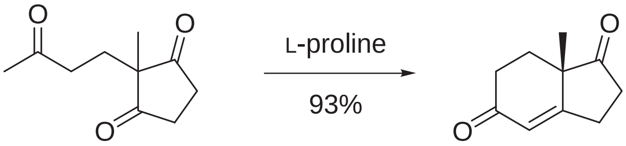
69% *ee*

Harada *Synthesis* **1990**, *53*.



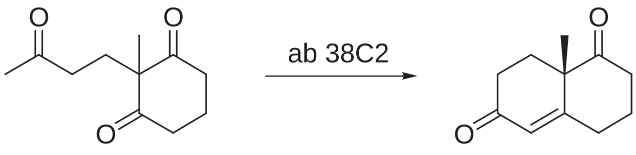
63% *ee*

Swaminathan *Tetrahedron: Asymm.* **1996**, *7*, 2189.



88% *ee*

Hajos *J. Org. Chem.* **1974**, *39*, 1615.



>95% *ee*

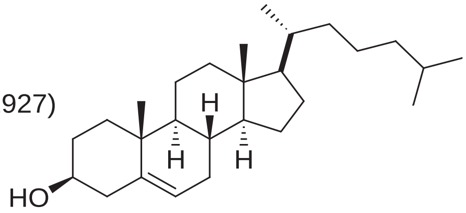
Lerner *J. Am. Chem. Soc.* **1998**, *120*, 2768.

6. Steroid Synthesis

Steroid synthesis: Woodward (Nobel 1965), Robinson (Nobel 1947)
Isolation methods: Chromatography
Conformational analysis: Barton (Nobel 1969)
UV spectroscopy: Woodward, Fieser
ORD: Djerassi
Biosynthesis theory: Bloch and Lynen (Nobel in Medicine 1964),
Cornforth (Nobel 1975)

Adolf Windaus received the 1928 Nobel prize in Chemistry for his work in the sterol area contributing to the structure determination of cholesterol, ergosterol, vitamin D, and vitamin B_1.

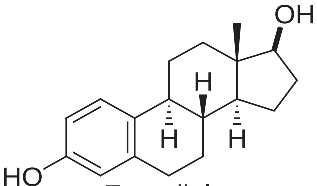
1. Cholesterol



Isolation: 1812
Structure, wrong!, Windaus (Nobel 1928) and Wieland (Nobel 1927)
1932, correct planar connectivity (Wieland)
1947, stereochemistry (Hodgkin, X-ray, Nobel 1964)
1952, absolute stereochemistry (Ruzicka, Nobel 1939)

Leopold Ruzicka received the 1939 Nobel Prize in Chemistry that recognized his contribution in three areas: macrocyclic compounds, higher terpenes, and steroids including the male sex hormones. He was the first to use Wallach's isoprene rule (1887) and defined monoterpenes as naturally occurring compounds composed of two isoprene units, sesquiterpenes (three), and diterpenes (four). His biogenetic isoprene rule and the complete structure elucidation of cholesterol are among his greatest achievements.

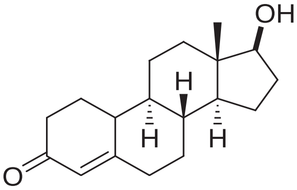
2. Sex Hormones



Estradiol

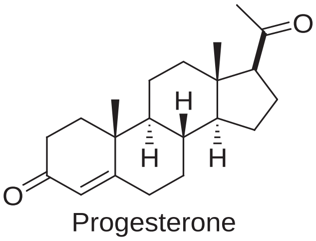
The hormone responsible for female development and maintenance of reproductive organs and secondary sex characteristics.
Pure material isolated 1929, E. Doisy (St. Louis Univ. Medicine Nobel 1943) and A. Butenandt (Gottingen, Nobel 1939)
4 tons of sow ovaries: 25 mg

Adolf Butenandt, a student of A. Windaus, received the 1939 Nobel Prize in Chemistry for his work on the isolation and structure elucidation of sex hormones. In 1929, he isolated estrone simultaneously with E. Doisy, the hormone that determines sexual development in females in pure crystalline form. Within a few years, he isolated androsterone (1931), a male sex hormone, and progesterone (1934), a hormone involved in pregnancy.



Testosterone

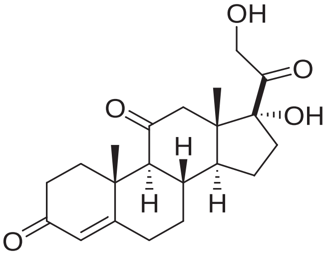
The male sex hormone
1931, Butenandt isolated androsterone (metabolite of testosterone)
15,000 L of men's urine: 15 mg
1935, testosterone isolated from 100 kg bull testicles: 10 mg, E. Laquer
1939, planar structure elucidated by Butenandt, Ruzicka (Nobel 1939)



Progesterone

The pregnancy hormone: maintains proper uterine environment for development of fetus, inhibits further ovulation, nature's contraceptive.
1934, isolation and planar structure, Butenandt
50,000 sows to provide 625 kg ovaries: 20 mg

3. Cortisone

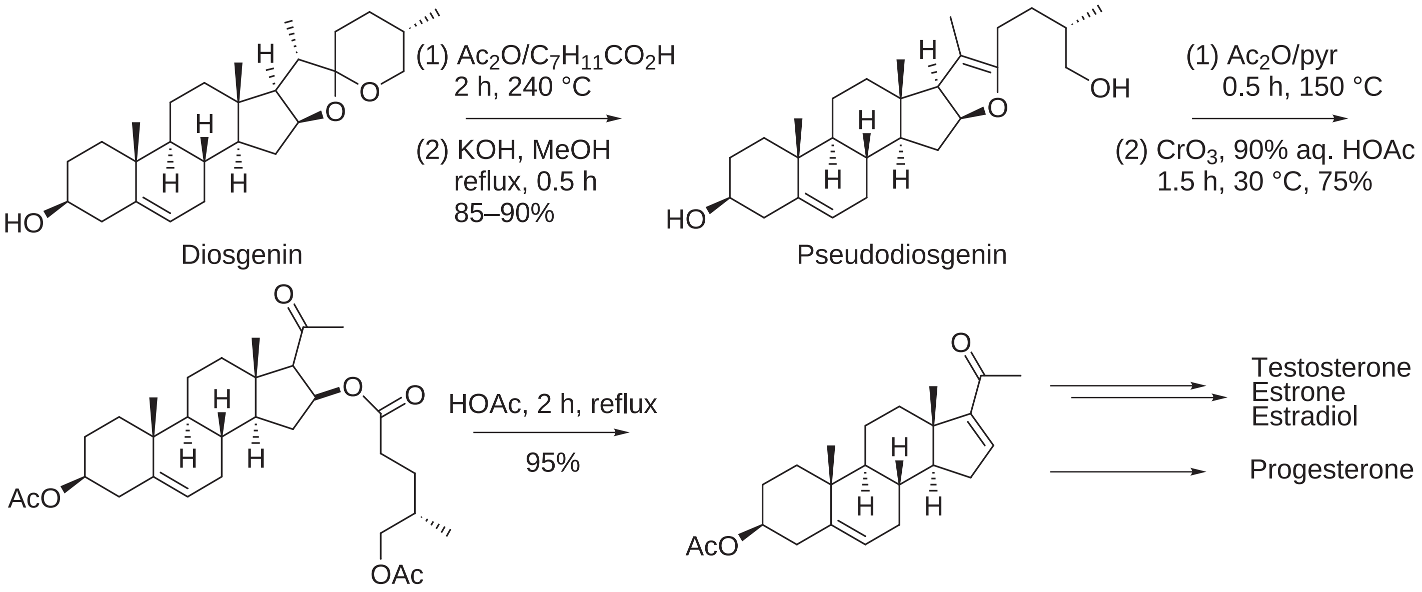


Structure: 1935–38, Kendall, Reichstein, Wintersteiner
from adrenal cortex of 1.25 million cattle
1952, 36 step synthesis via degradation of bile acids (Sarett, Merck)
1949, Hench and Kendall (Mayo Clinic), 1950 Nobel with Reichstein for anti-arthritic activity
1951, Djerassi (Syntex), synthesis from Mexican yam steroid
1951, Upjohn microbial process for C11 oxidation of progesterone

Tadeus Reichstein received the 1950 Nobel Prize in Medicine for the isolation and structural characterization of pituitary hormones, including cortisone.

Natural steroid hormones are present in such trace amounts in mammals that it is not a practical source. Synthetic steroids, e.g. 19-nor steroids, became commercially important.

Russell E. Marker (Syntex, Penn. State)
Degradation of sapogenins and other plant products
J. Am. Chem. Soc. **1947**, *69*, 2167.
Diosgenin is obtained from the Mexican diocorea plant (Mexican yams).



Diosgenin

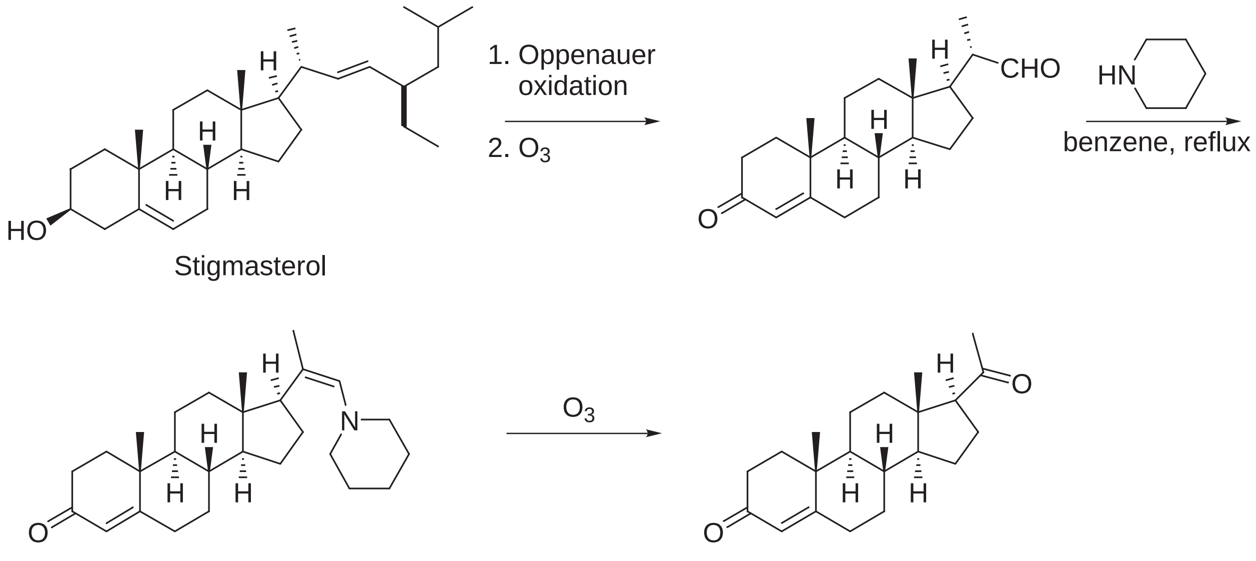
Pseudodiosgenin

Diosone

16-Dehydropregnen-3(β)-ol-20-one acetate
(> 60% overall)

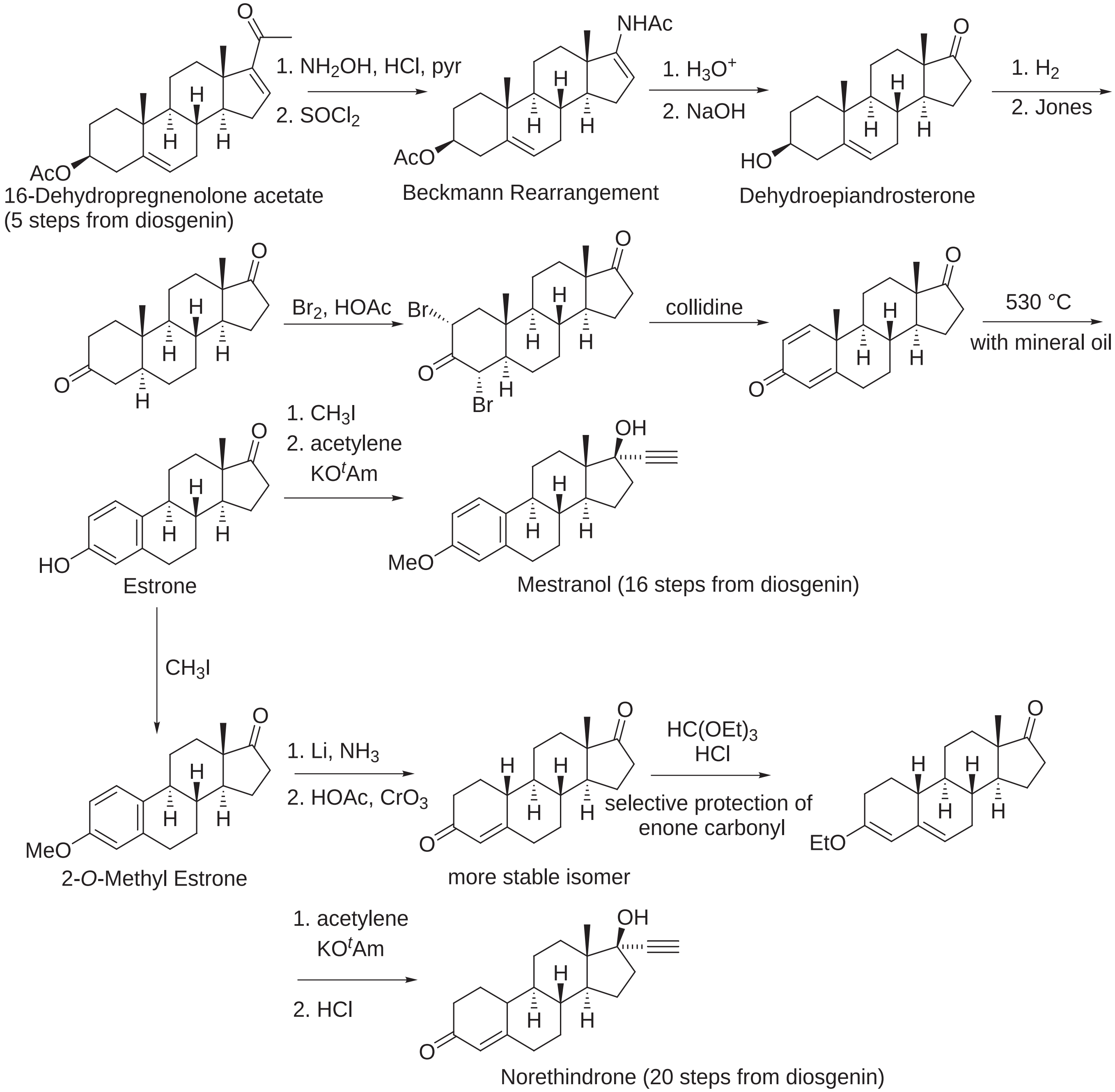
Dehydropregnenolone is easily transformed to progesterone in 3 steps:
(1) H_2, Pd–C (2) hydrolysis (3) Oppenauer oxidation: cyclohexanone, $Al(O^iPr)_3$

Upjohn avoided attempted monopoly by use of stigmasterol obtained from soybeans:



Stigmasterol

Progesterone



There are more stories told about Russell Marker (1902–1995) than perhaps any other chemist. Marker achieved the first practical synthesis of progesterone which led to the creation of Syntex S.A. in Mexico. Marker received not only his B.Sc. (1923), but also a M.S. degree in physical chemistry from the Univ. of Maryland (1924) and subsequently completed enough work in 1 year for his doctoral degree with M. Kharasch at Maryland. However, he did not receive his Ph.D. because he refused to complete his physical chemistry coursework, which he considered a waste of time. In 1925, he joined Ethyl Corp. where he invented the gasoline "octane number" rating system. Following a subsequent position at Rockefeller Univ. with P. A. Levene, he joined Penn State College in a position funded by Parke–Davis. After discovering an economical source of a steroid starting material (diosgenin) in a Mexican yam, Marker developed a degradation synthesis of progesterone producing 3 kg at a time it was selling for $80/g. Marker commercialized his process in 1944 at Syntex in Mexico which he cofounded. After a dispute in 1945, Marker left Syntex and took with him the details of the synthesis, the key operations which only he had conducted. He founded another company Botanica-Mex which became Hormonosynth and subsequently Diosynth.

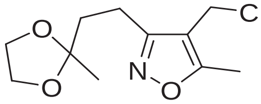
Syntex did not fade into the background. After a few months, it was back up a running recruiting C. Djerassi and entrepreneur A. Zaffaroni. Using Syntex progesterone, Djerassi focused on the discovery of a mimic that would not only prevent ovulation like progesterone, but would also be orally active. His group prepared norethindrone, the active ingredient of the first birth control pill.

The Total Synthesis Of Steroids

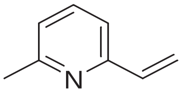
Representative strategies employing the Robinson and related annulations

The Velluz Approach (Roussel–Uclaf, Paris)
Compt. rend. **1960**, *250*, 1084, 1511.
Angew. Chem., Int. Ed. Eng. **1965**, *4*, 181.

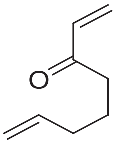
Stork isoxazoles, *J. Am. Chem. Soc.* **1967**, *89*, 5464.



S. Danishefsky vinyl pyridines, *J. Am. Chem. Soc.* **1975**, *97*, 380.



J. Tsuji via Wacker oxidation of terminal double bonds, *J. Am. Chem. Soc.* **1979**, *101*, 5070.

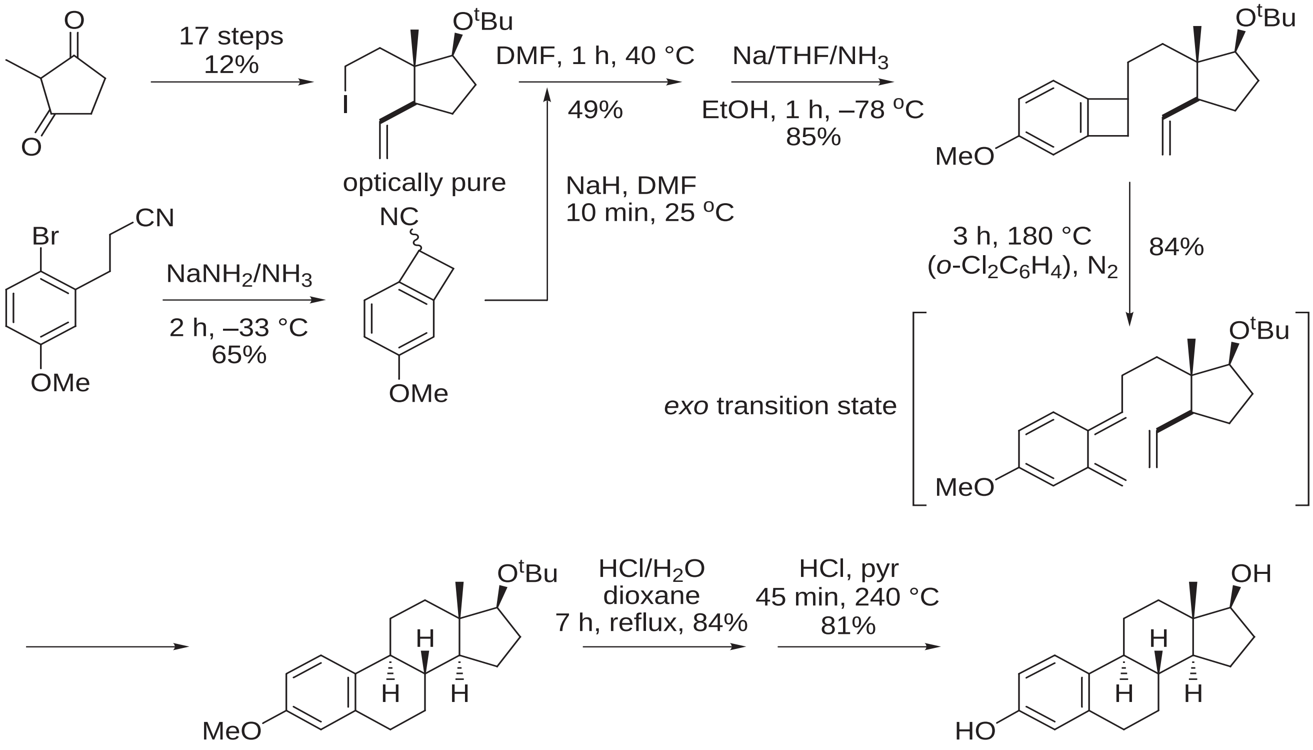


Comparison of strategies employing the intramolecular Diels–Alder reaction:

First applications of this strategy were developed independently in laboratories of
T. Kametani and W. Oppolzer.

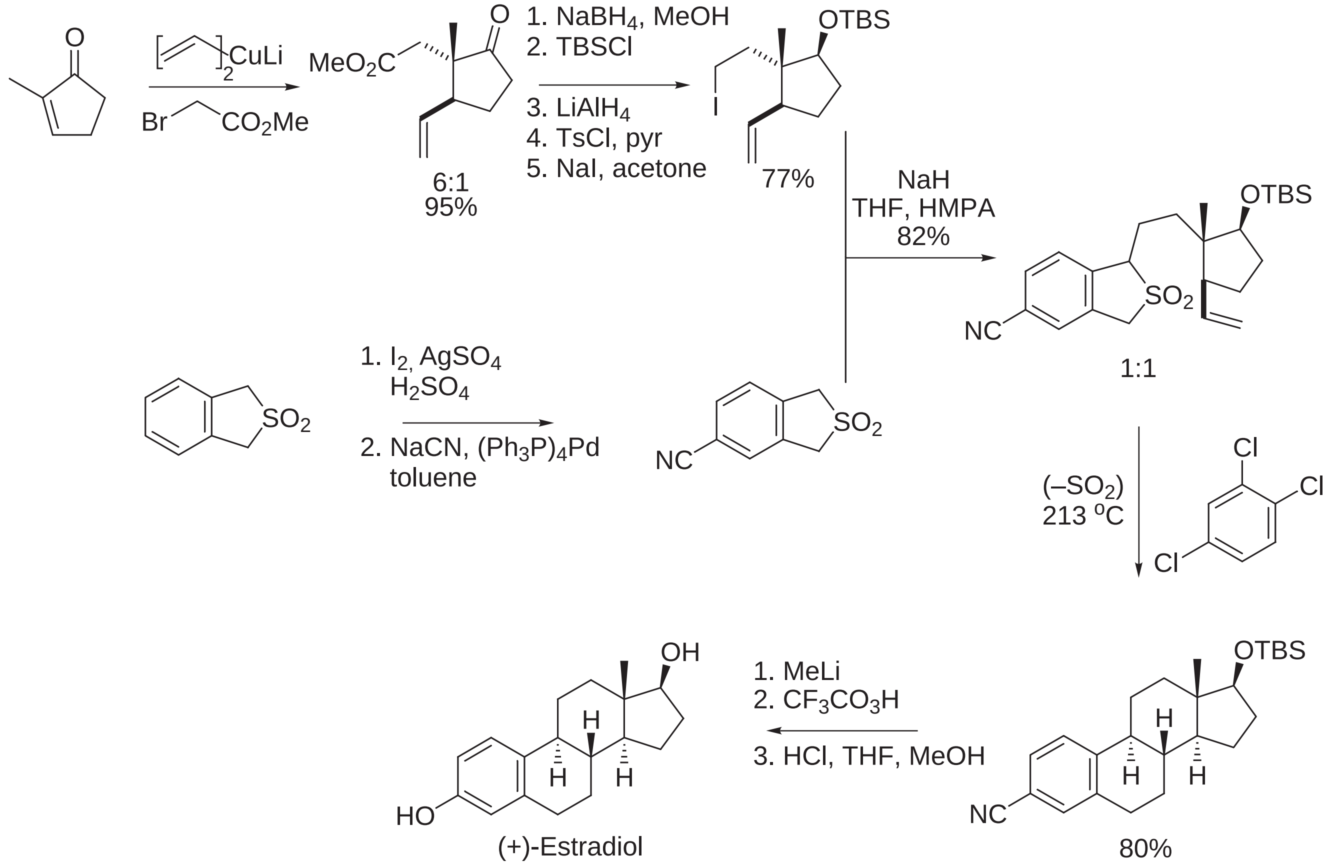
Examples

T. Kametani, *Tetrahedron Lett.* **1978**, 2425.
J. Am. Chem. Soc. **1976**, *98*, 3378.
J. Am. Chem. Soc. **1977**, *99*, 3461.
J. Am. Chem. Soc. **1978**, *100*, 6218.



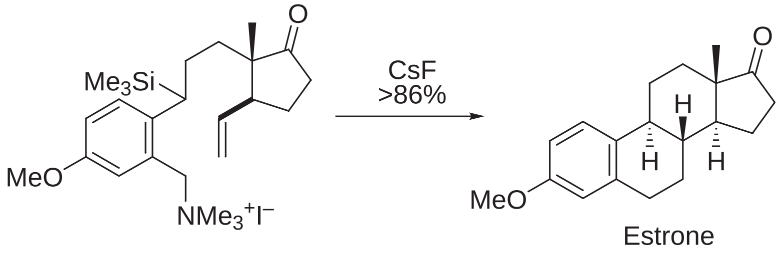
(+)-Estradiol

Oppolzer *Helv. Chim. Acta* **1977**, *60*, 2964.
Oppolzer *Angew. Chem., Int. Ed. Eng.* **1977**, *16*, 10.
Oppolzer *Helv. Chim. Acta* **1980**, *63*, 1703.

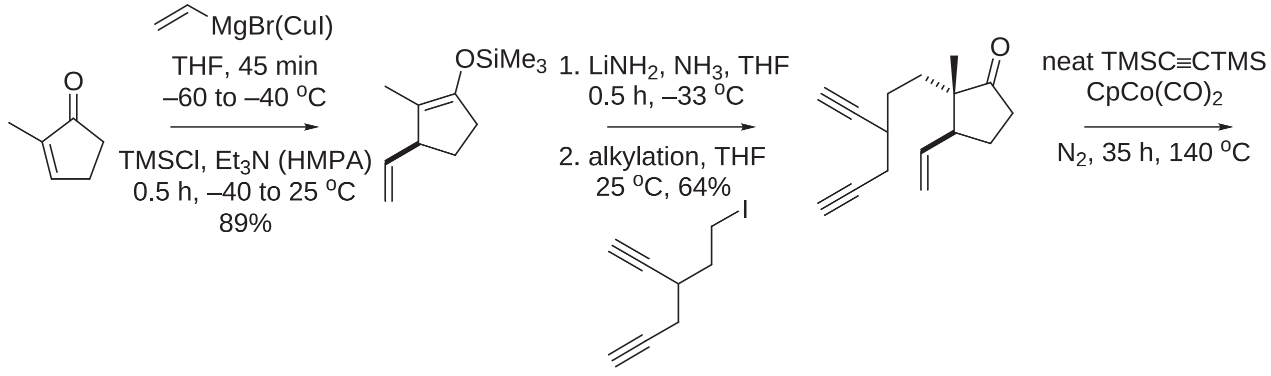


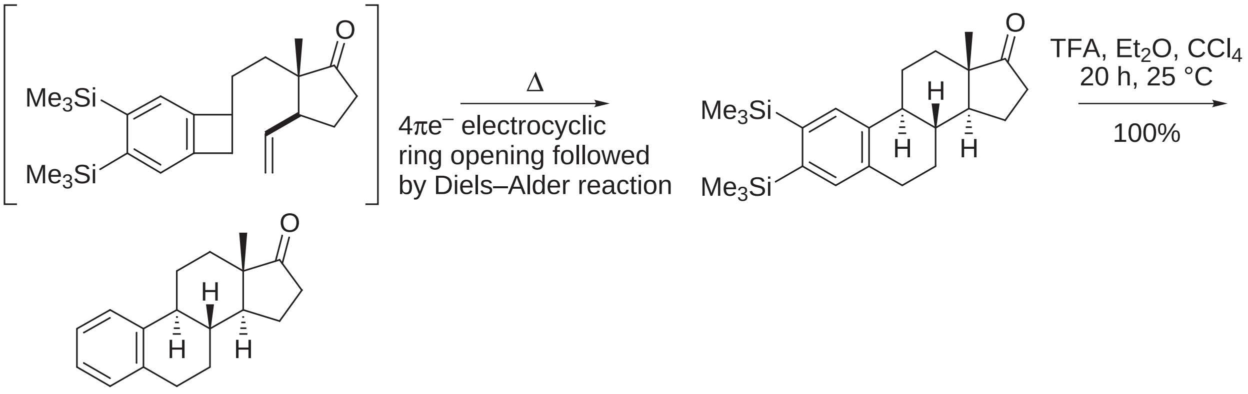
retro-cheletropic cycloaddition
followed by Diels–Alder reaction

T. Saegusa *J. Am. Chem. Soc.* **1981**, *103*, 476.



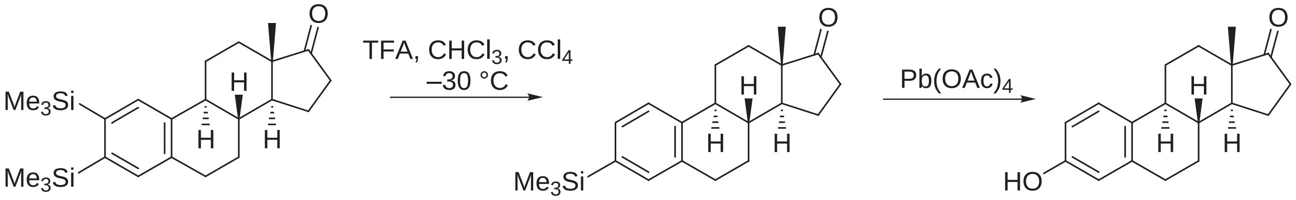
K. P. C. Vollhardt and R. Funk *J. Am. Chem. Soc.* **1977**, *99*, 5483.





(±)-Estra-1,3,5(10)-trien-17-one

K. Vollhardt *J. Am. Chem. Soc.* **1979**, *101*, 215.



90%, 9:1 regioselectivity

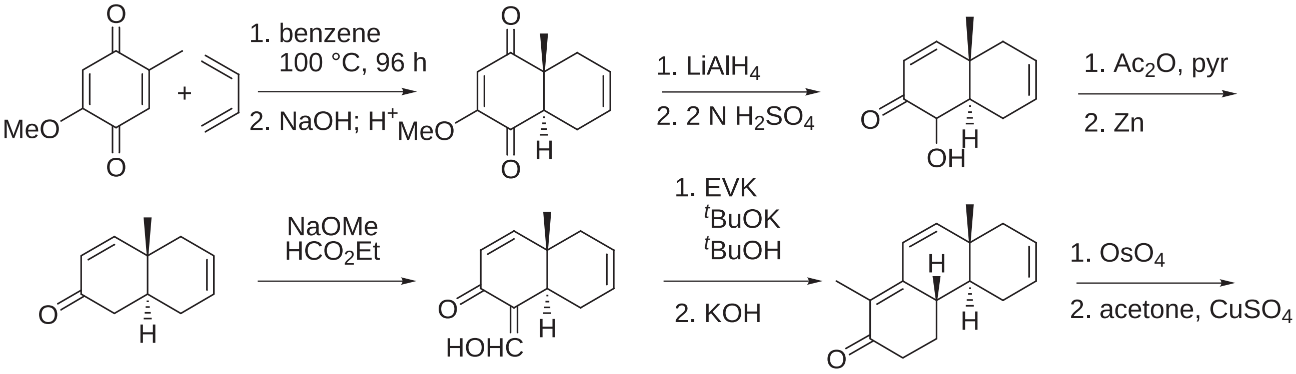
Estrone

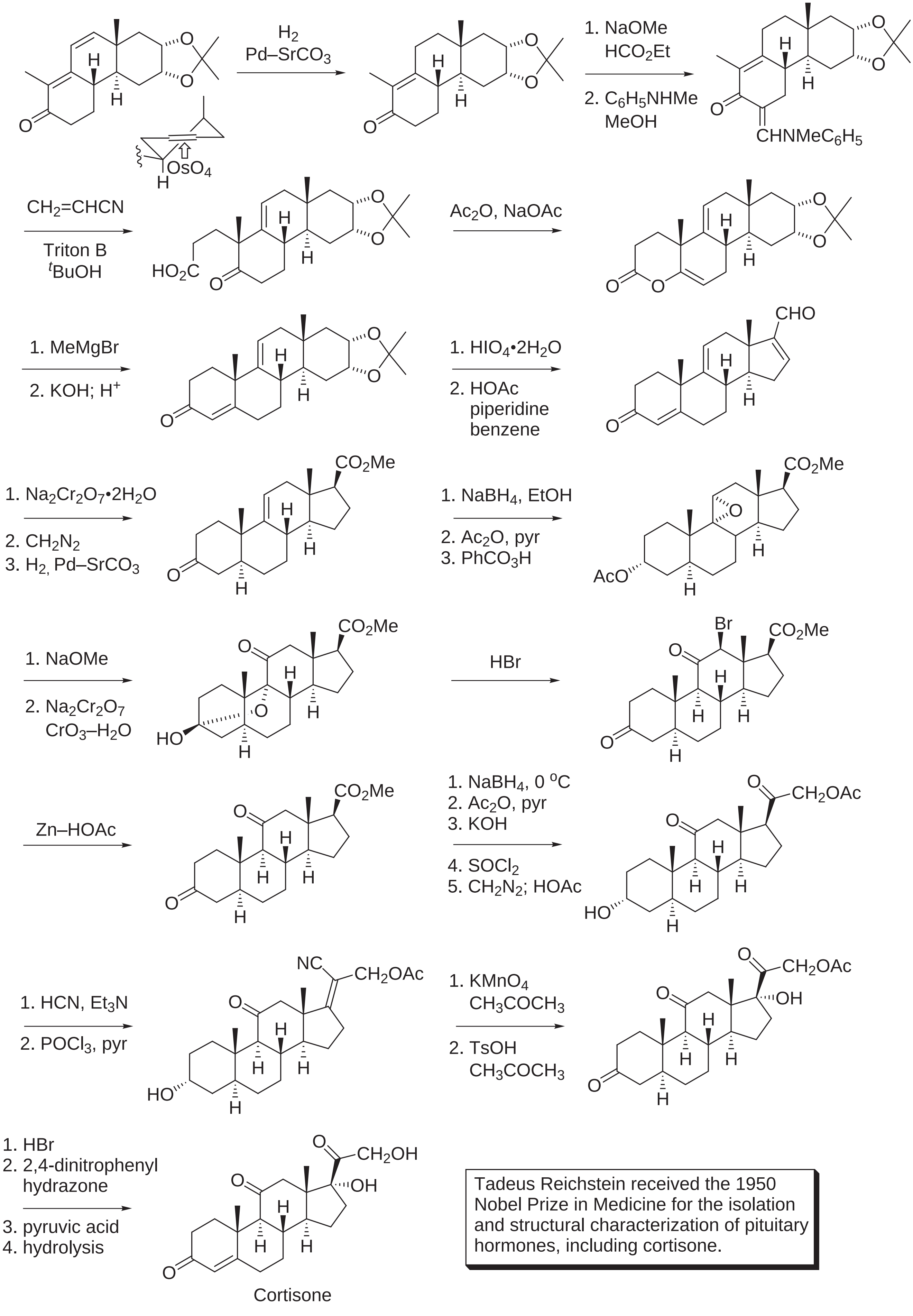
Total Synthesis of Cortisone

> R. B. Woodward received the 1965 Nobel Prize in Chemistry for "Contributions to the Art of Organic Synthesis" and the award preceded the total synthesis of vitamin B_{12} carried out in collaboration with A. Eschenmoser, the principles of orbital symmetry conservation (Hoffmann Nobel Prize in 1981), the Wilkinson structure determination of ferrocene (Nobel 1973) carried out with Woodward, and the collaborative delineation of the steroidal biosynthesis involving stereoselective cation–olefin cyclizations in collaboration with Bloch (Nobel 1964). Woodward changed synthesis from the application of empirical reactions to a mechanistic foundation for predicting reactions and substrate reactivity (rates, stereoselectivity) and designed this rationale into the preplanned synthesis. The results were stunning with unattainable objectives falling one after another: quinine (1944), patulin (1950), cholesterol (1951), cortisone (1951), lanosterol (1954), lysergic acid (1954), strychnine (1954), reserpine (1956), chlorophyll (1960), tetracyclines (1962), colchicine (1963), cephalosporin C (1966), most before the wide spread usage of ^{1}H NMR. Breathtaking natural product structure determinations: penicillin (1945), strychnine (1948), patulin (1949), terramycin (1952), aureomycin (1952), cervine (1954), magnamycin (1956), gliotoxin (1958), oleandomycin (1960), streptonigrin (1963), and tetrodotoxin (1964) also preceded the reliance on ^{1}H NMR. The formal total synthesis of vitamin B_{12} was completed in 1972 in collaboration with A. Eschenmoser (>100 postdoctoral fellows) and synthetic cobyric acid was converted to vitamin B_{12} in 1976.

R. B. Woodward
J. Am. Chem. Soc. **1951**, *73*, 2403, 3547, 4057.
J. Am. Chem. Soc. **1952**, *74*, 4223.

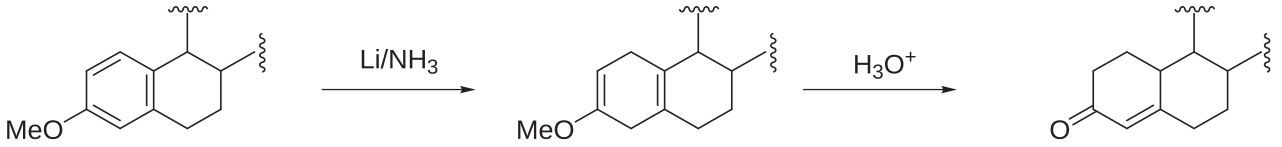
> The chemical publication with the most coauthors (49) is the posthumous account of the total synthesis of erythromycin by Woodward (*J. Am. Chem. Soc.* **1981**, *103*, 3210). Physics holds the record with 406 coauthors: *Phys. Rev. Lett.* **1993**, *70*, 2515.





Tadeus Reichstein received the 1950 Nobel Prize in Medicine for the isolation and structural characterization of pituitary hormones, including cortisone.

C. Birch Reduction

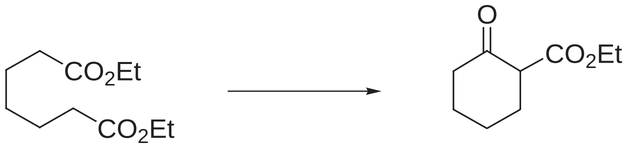


Robinson annulation-type product

- See the discussion in the sections on the Birch reduction and the Robinson annulation.
- Allows an aromatic ring to be incorporated into a synthesis and converted into a useful, nonaromatic ring system.

D. Dieckmann Condensation

- An intramolecular Claisen condensation, see enolate section for a more detailed discussion.



E. Intramolecular Nucleophilic Alkylation

- Powerful approach to closure of rings

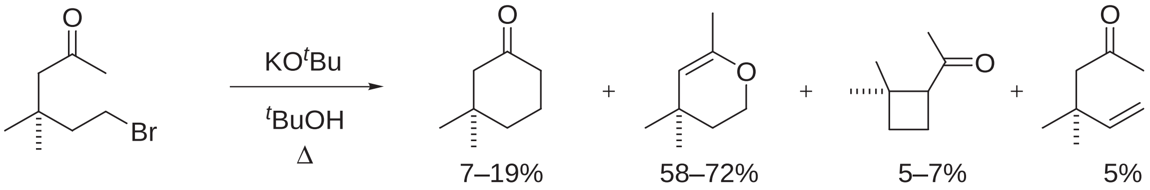
Examples:

- Kinetic enolate generation (Note: *O*-alkylation may compete).

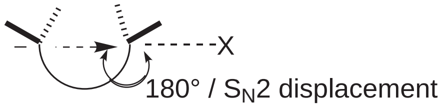
- Gem dimethyl effect facilitates cyclization

House *J. Org. Chem*. **1978**, *43*, 700.

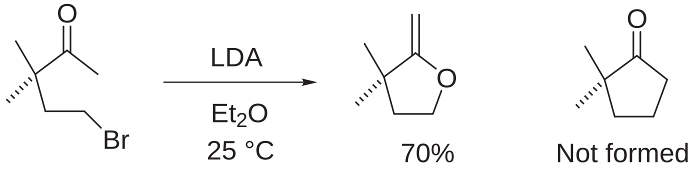
- Versus thermodynamic enolate generation (Note: *O*-alkylation may compete).

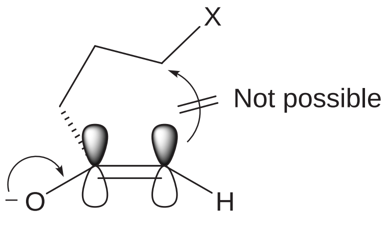


- Closure subject to stereoelectronic control.

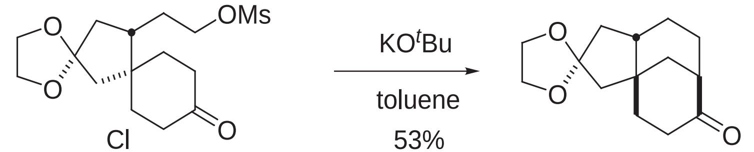


- Note Baldwins Rules
  Preceded by Eschenmoser
  Helv. Chim. Acta **1970**, *53*, 2059.

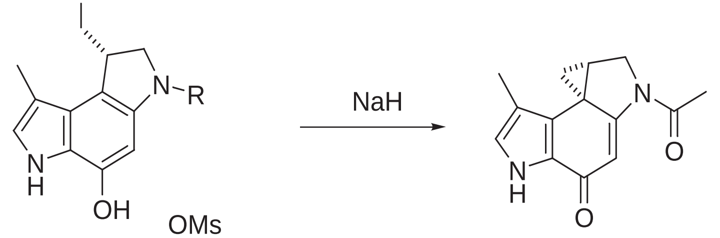




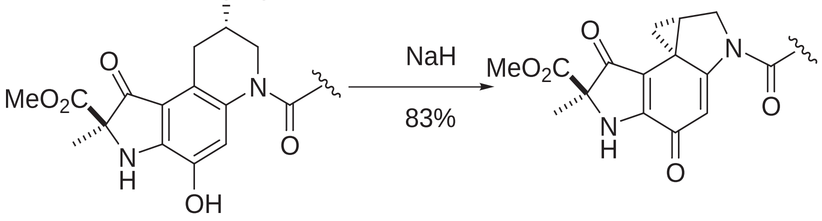
- Examples



Gibberelic Acid, Corey
J. Am. Chem. Soc. **1979**, *101*, 1038.



CC-1065, Boger
J. Am. Chem. Soc. **1988**, *110*, 4796.



Duocarmycin SA, Boger
J. Am. Chem. Soc. **1992**, *114*, 10056.
J. Am. Chem. Soc. **1993**, *115*, 9025.

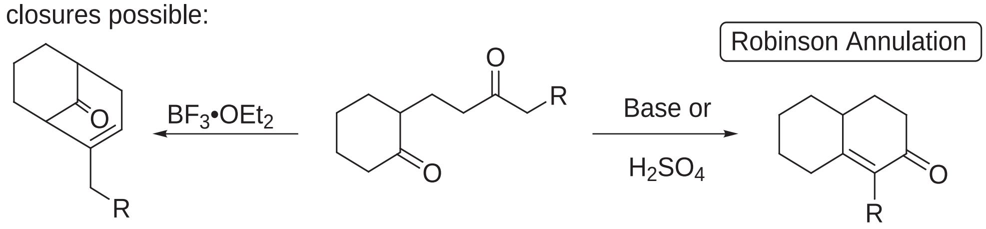
Duocarmycin A, Boger
J. Am. Chem. Soc. **1996**, *118*, 2301.
J. Am. Chem. Soc. **1997**, *119*, 311.

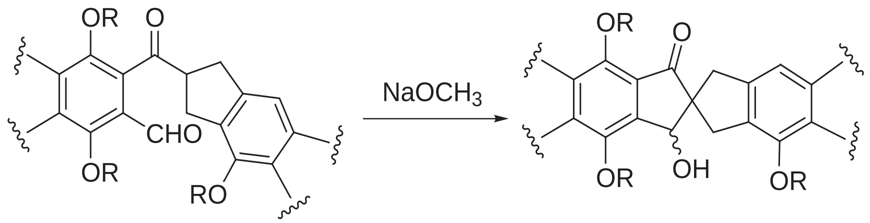
F. Intramolecular Aldol Condensation

- The intramolecular aldol condensation has been used extensively to close or form rings.

Representative Examples:

- Two aldol closures possible:

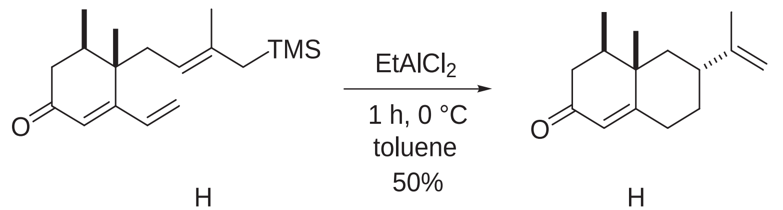




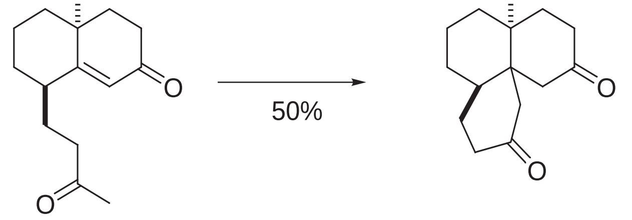
Fredericamycin A
Boger *J. Org. Chem.* **1991**, *56*, 2115.
J. Am. Chem. Soc. **1995**, *117*, 11839.

G. Intramolecular Michael Reaction

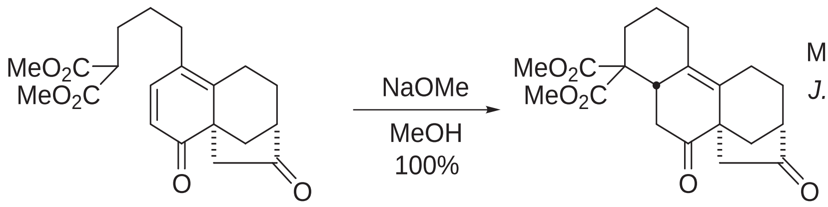
Michael *J. Prakt. Chem.* **1887**, *36*, 113.



Majetich
J. Org. Chem. **1985**, *50*, 3615.
Tetrahedron Lett. **1988**, *29*, 2773.



House
J. Org. Chem. **1965**, *30*, 2513.



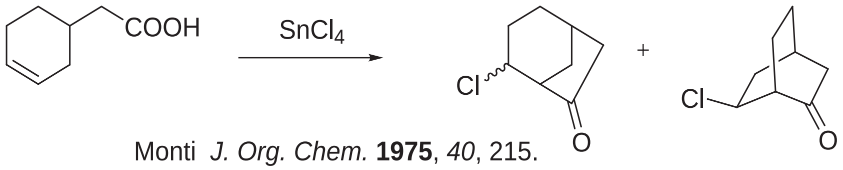
Mander
J. Am. Chem. Soc. **1979**, *101*, 3373.

H. Cation–Olefin Cyclization

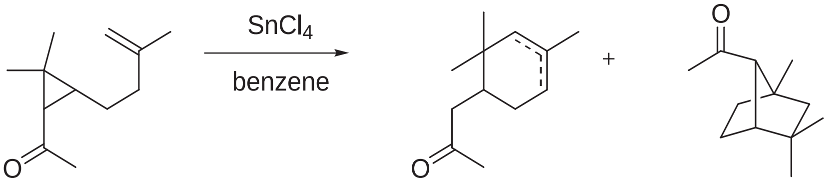
1. Reviews

Johnson	*Acc. Chem. Res.* **1968**, *1*, 1. *Angew. Chem., Int. Ed. Eng.* **1976**, *15*, 9. *Bioorg. Chem.* **1976**, *5*, 51.
van Tamelen	*Acc. Chem. Res.* **1968**, *1*, 111.
Harding	*Bioorg. Chem.* **1973**, *2*, 248.
Goldsmith	*Fortschr. Chem. Org. Nat.* **1972**, *29*, 363.
Lansbury	*Acc. Chem. Res.* **1972**, *5*, 311.
Speckamp	*Recl. Trav. Chim. Pays-Bas.* **1981**, *100*, 345.
Sutherland	*Comprehensive Org. Syn.* Vol 3, pp 341–377.

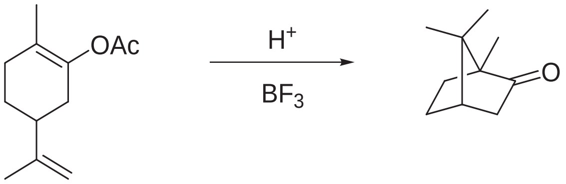
2. Representative Cation–Olefin Cyclizations



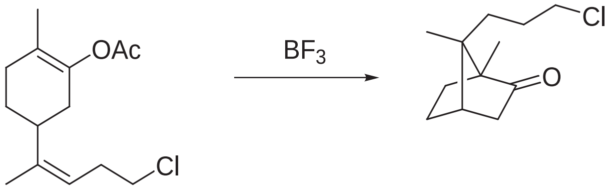
Monti *J. Org. Chem.* **1975**, *40*, 215.



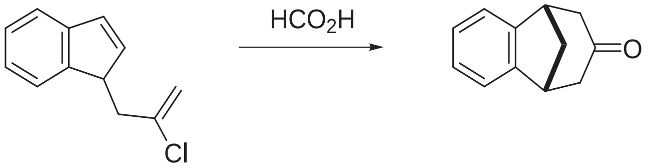
Grieco *Tetrahedron Lett.* **1974**, 527.



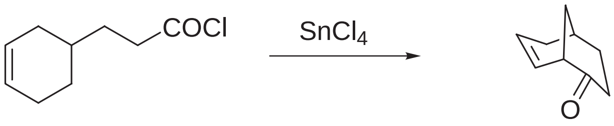
Money *J. Chem. Soc., Chem. Commun.* **1969**, 1196.
Goldsmith *J. Org. Chem.* **1970**, *35*, 3573.



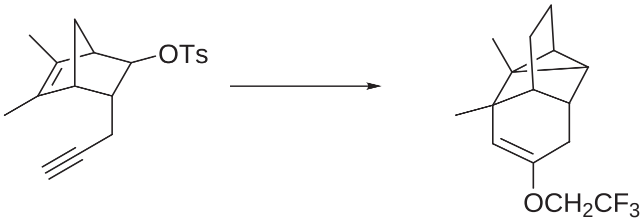
Money *J. Chem. Soc., Chem. Commun.* **1971**, 766.



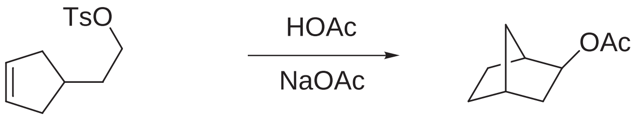
Lansbury *J. Am. Chem. Soc.* **1966**, *88*, 4290.
J. Am. Chem. Soc. **1970**, *92*, 5649.



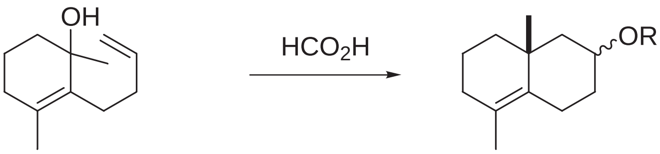
Marvell *J. Org. Chem.* **1970**, *35*, 391.



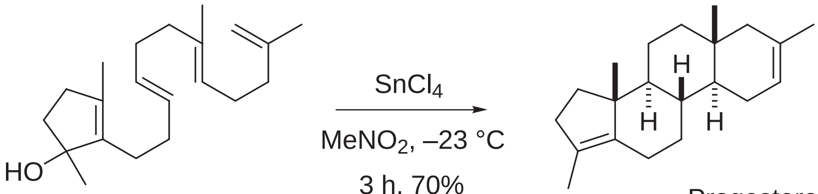
Baldwin *Tetrahedron Lett.* **1975**, 1055.



Bartlett *J. Am. Chem. Soc.* **1965**, *87*, 1288.
Johnson *J. Am. Chem. Soc.* **1964**, *86*, 5593.

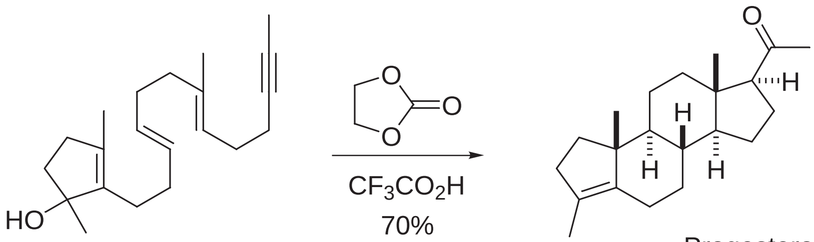


Marshall *J. Am. Chem. Soc.* **1965**, *87*, 2773.
J. Am. Chem. Soc. **1966**, *88*, 3408.



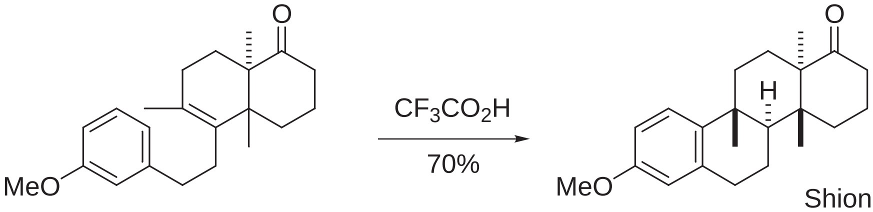
Progesterone total synthesis

Johnson *J. Am. Chem. Soc.* **1968**, *90*, 2994.



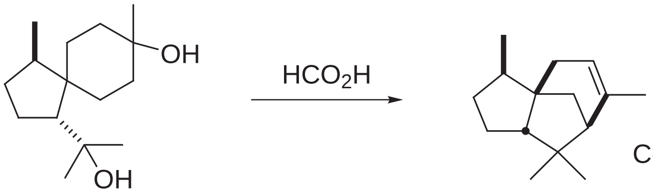
Progesterone total synthesis

Johnson *J. Am. Chem. Soc.* **1970**, *92*, 4461.
J. Am. Chem. Soc. **1980**, *102*, 7800.



Shionone total synthesis

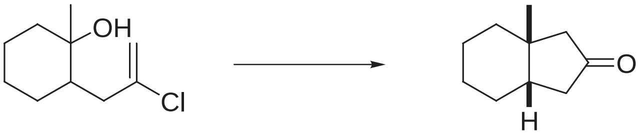
Ireland *J. Am. Chem. Soc.* **1974**, *96*, 3333.
J. Org. Chem. **1975**, *40*, 973.
J. Am. Chem. Soc. **1970**, *92*, 2568.



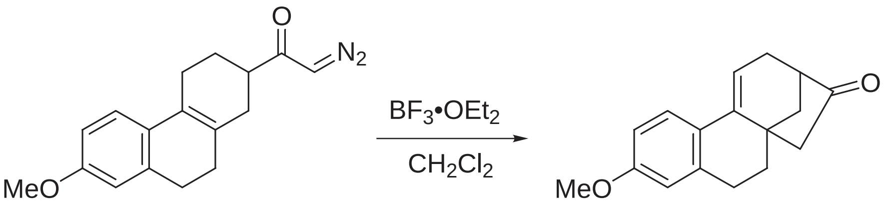
Cedrene

Corey *J. Am. Chem. Soc.* **1969**, *91*, 1557.
Tetrahedron Lett. **1973**, 3153.

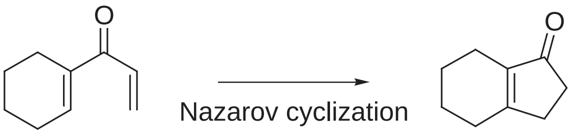
Stork *J. Am. Chem. Soc.* **1955**, *77*, 1072.
J. Am. Chem. Soc. **1961**, *83*, 3114.



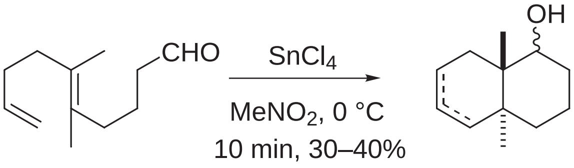
Lansbury *J. Am. Chem. Soc.* **1966**, *88*, 4290.
J. Chem. Soc., Chem. Commun. **1971**, 1107.
Tetrahedron Lett. **1973**, 5017.



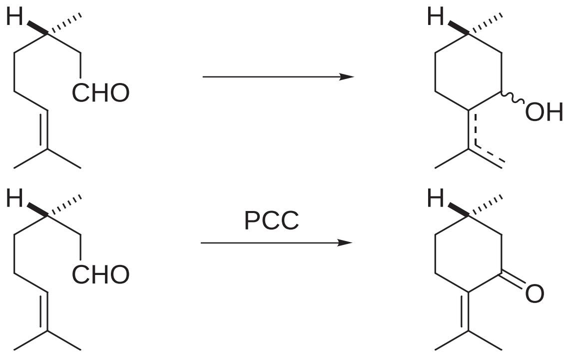
Mander *J. Chem. Soc., Chem. Commun.* **1971**, 773.
Erman *J. Am. Chem. Soc.* **1971**, *93*, 2821.



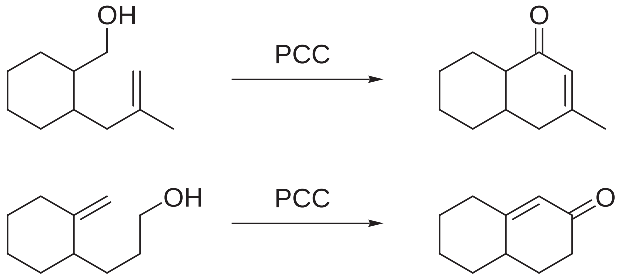
Hiyama *J. Am. Chem. Soc.* **1974**, *96*, 3713.



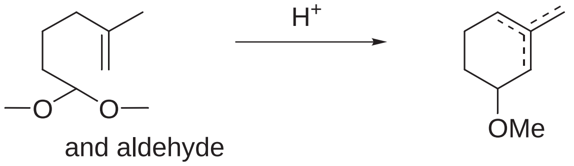
Ireland *J. Am. Chem. Soc.* **1974**, *96*, 3333.
J. Org. Chem. **1975**, *40*, 973.
J. Am. Chem. Soc. **1970**, *92*, 2568.



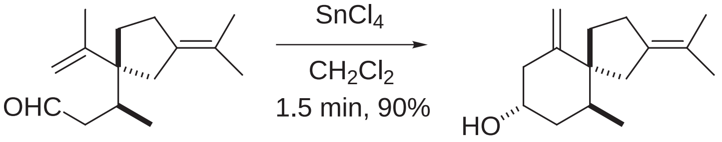
Naves *Helv. Chim. Acta* **1964**, *47*, 51.
Corey *J. Org. Chem.* **1976**, *41*, 380.



Corey, Boger *Tetrahedron Lett.* **1978**, 2461.

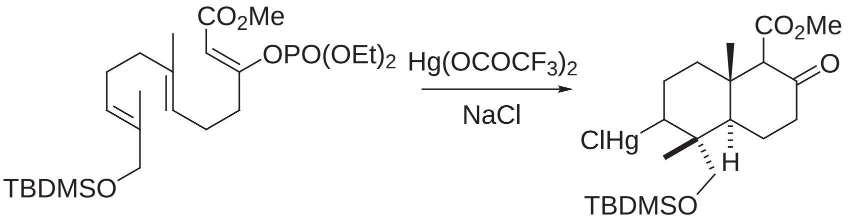


Johnson *J. Am. Chem. Soc.* **1967**, *89*, 170.
J. Am. Chem. Soc. **1973**, *95*, 2656.



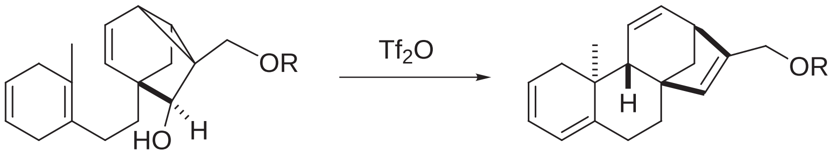
β-Vetivone and
Vetispirene
total syntheses

McCurry, Jr. *Tetrahedron Lett.* **1973**, 3325.



Aphidicolin
total syntheses

Corey, Tius *J. Am. Chem. Soc.* **1980**, *102*, 1742. (Aphidicolin)
J. Am. Chem. Soc. **1980**, *102*, 7612. (Stemodinone)
J. Am. Chem. Soc. **1982**, *104*, 5551. (K-76)



Corey *J. Am. Chem. Soc.* **1987**, *109*, 6187. (Atractyligenin)
J. Am. Chem. Soc. **1987**, *109*, 4717. (Cafestol)

3. Background

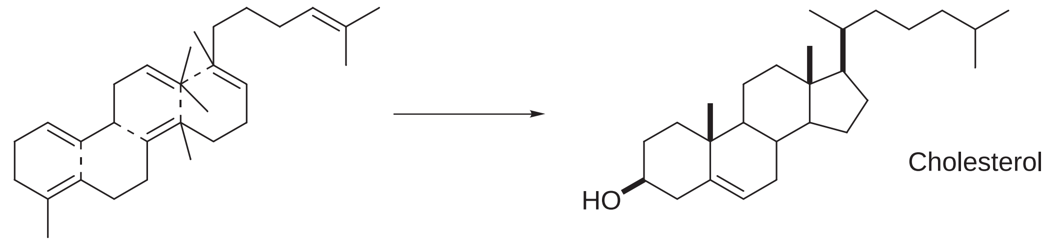
Squalene cyclization first suggested as a biosynthetic precursor to cholesterol

Heilbron, Kamm, and Owens *J. Chem. Soc.* **1926**, 1630.

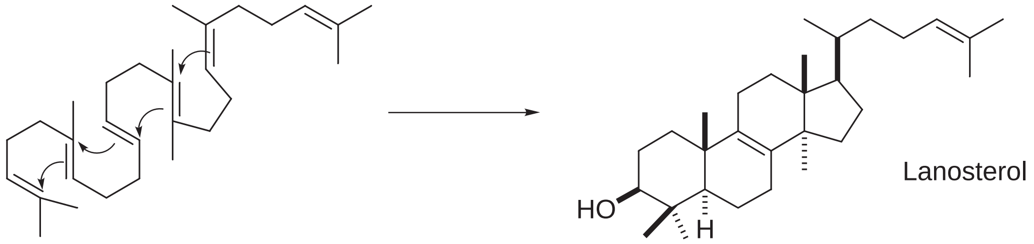
Robinson *Chem. Ind.* **1934**, *53*, 1062.

J. L. Goldstein and M. S. Brown received the 1985 Nobel Prize in Medicine for their discoveries concerning the regulation of cholesterol metabolism.

- Robinson's proposal



- Correct cyclization scheme



- Lanosterol was proposed in 1953 by Woodward and Bloch.

- Experimental verification that cholesterol is biosynthesized from squalene was developed independently by

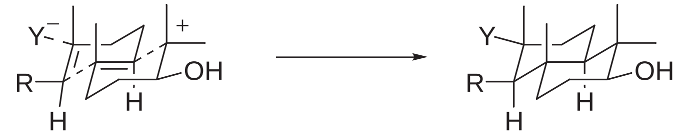
Bloch	*J. Biol. Chem.* **1953**, *200*, 129.
Cornforth	*Biochem. J.* **1954**, *58*, 403. *Biochem. J.* **1957**, *65*, 94.

K. Bloch received the 1964 Nobel Prize in Medicine for his discoveries concerning the mechanism and regulation of the cholesterol and fatty acid metabolism.

J. W. Cornforth received the 1975 Nobel Prize in Chemistry jointly with V. Prelog for outstanding intellectual achievement on the stereochemistry of reactions catalyzed by enzymes.

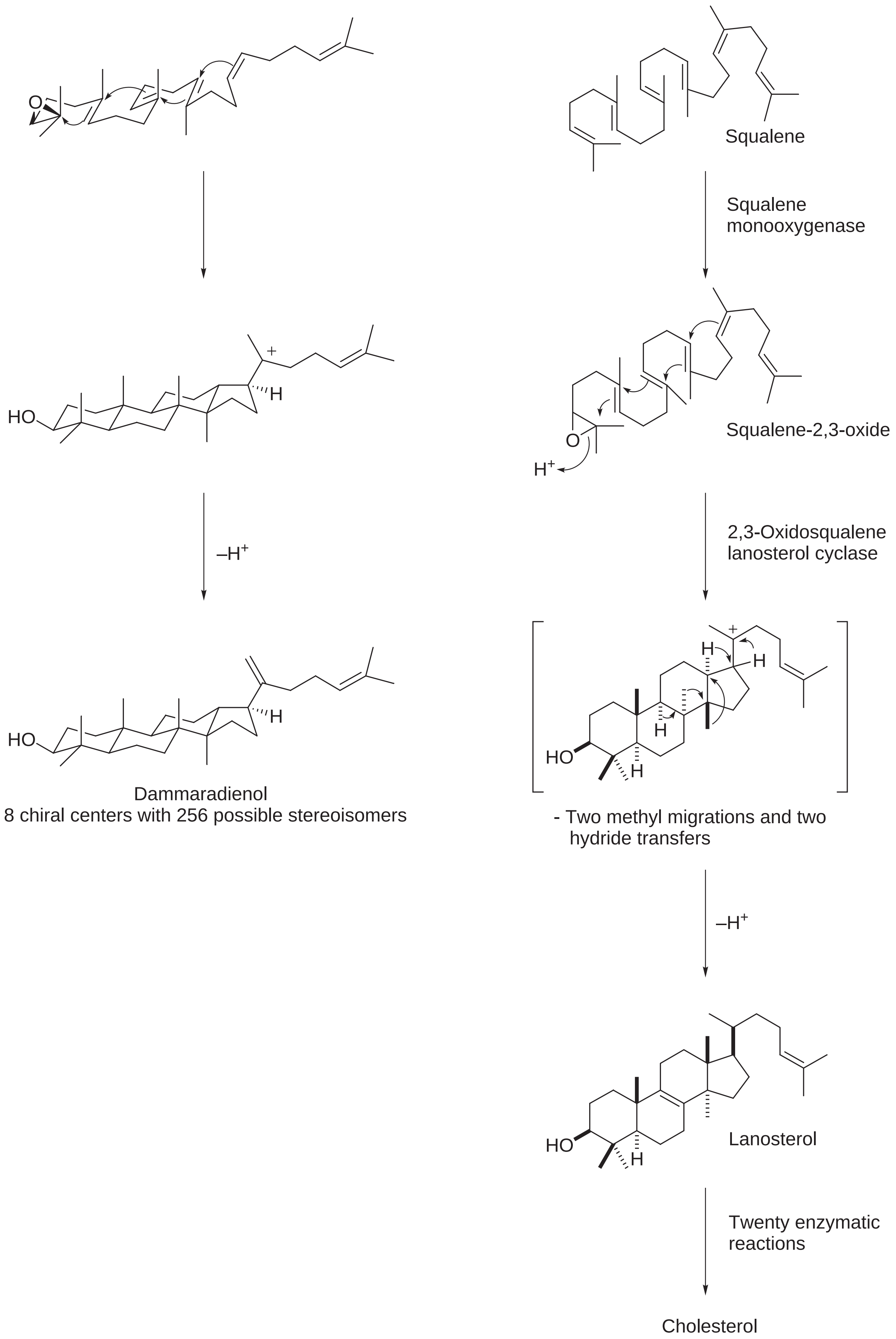
- Stork–Eschenmoser hypothesis: the *trans-anti-trans* stereochemistry of the steroids and many terpenoids is a consequence of a concerted polyene cyclization.

Cyclization about a *trans* olefin



Cyclization about a *cis* olefin

- Anti addition of a carbocation and nucleophilic olefin on opposite faces of a π-bond analogous to *trans* electrophilic addition to alkenes. Therefore, cyclization of a *trans* olefin leads to a *trans* ring fusion and cyclization of a *cis* olefin leads to a *cis* ring fusion.



Dammaradienol
8 chiral centers with 256 possible stereoisomers

- Two methyl migrations and two hydride transfers

4. Key Publications

- Initial experimental demonstrations of multiple cascade cyclizations and the Stork-Eschenmosher steroid-type cyclizations:

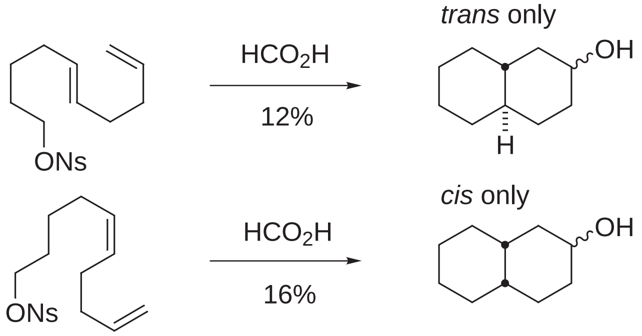
Stork and Burgstahler *J. Am. Chem. Soc.* **1955**, *77*, 5068.

Eschenmoser, Ruzicka, Jeger, and Arigoni *Helv. Chim. Acta* **1955**, *38*, 1890.

First disclosed in lectures and proposals as early as 1950, but experimental verification was difficult.

- A clear verification of Stork–Eschenmoser hypothesis:

Johnson *J. Am. Chem. Soc.* **1964**, *86*, 1959.
J. Am. Chem. Soc. **1964**, *86*, 2085.



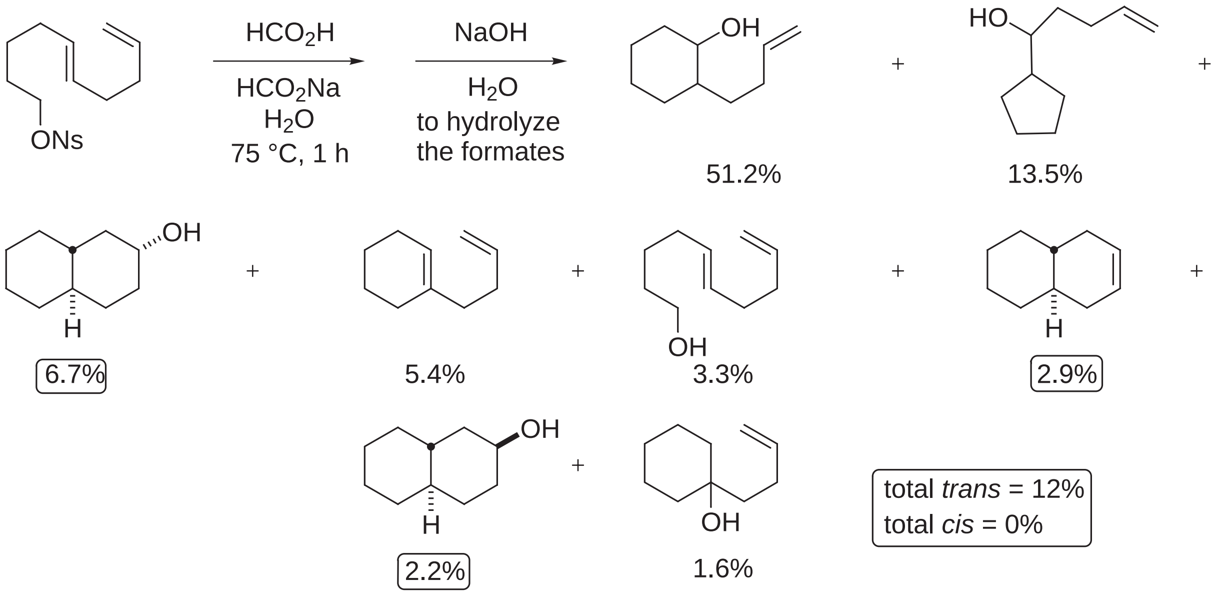
Only bicyclic products isolated or generated

5. Three Stages of Reaction

- Initiation
- Cyclization and Propagation
- Termination

- Mechanistically all three may take place simultaneously or stepwise paths may be involved.
- Depends on the nature of the substrate and the reaction medium.
- Without careful control, the formation of many products will result in a complex mixture.

- For example: Johnson verification of Stork–Eschenmoser hypothesis.

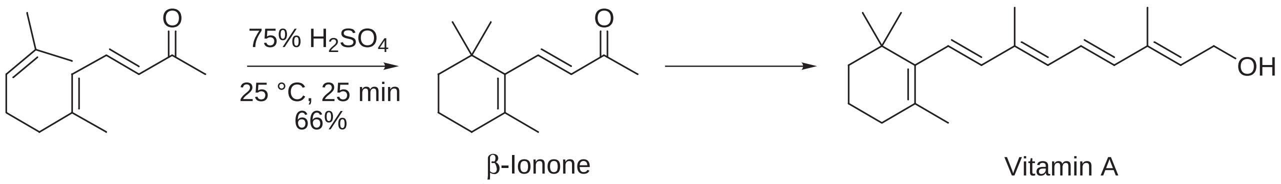


total *trans* = 12%
total *cis* = 0%

- Much effort expended to control the reaction through mild, selective and efficient initiation and termination.

A. Initiation

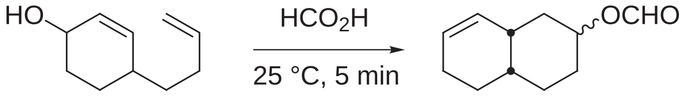
- Alkenes



used in perfumes

Isler *Helv. Chim. Acta* **1949**, *32*, 489.

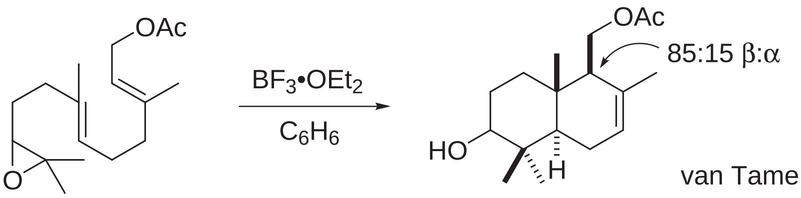
- Alcohols and Derivatives



tertiary allylic alcohols have been extensively used

Johnson *J. Am. Chem. Soc.* **1964**, *86*, 1972.

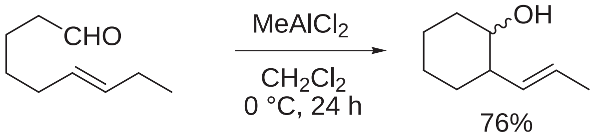
- Epoxides



85:15 β:α

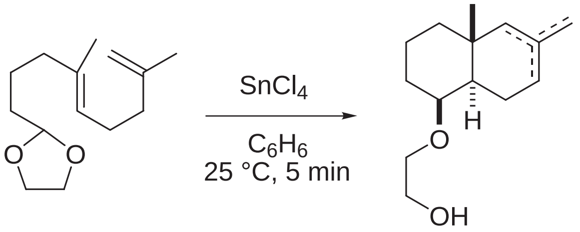
van Tamelen *J. Am. Chem. Soc.* **1963**, *85*, 3295.

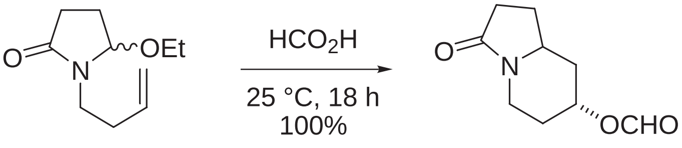
- Aldehydes and Ketones



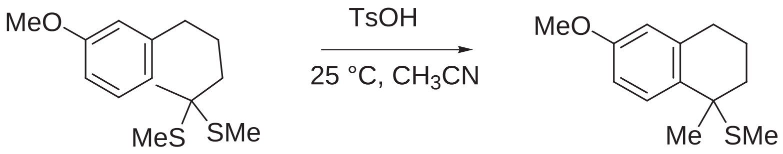
Snider *J. Am. Chem. Soc.* **1980**, *102*, 7951.

- Aldehyde or Ketone Derivatives



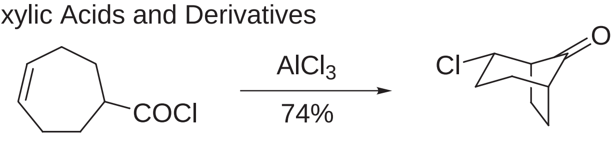


Johnson *J. Am. Chem. Soc.* **1968**, *90*, 5277; **1974**, *96*, 3979. Speckamp *Tetrahedron Lett.* **1975**, 4047.

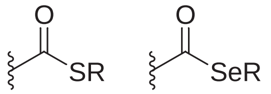


Trost *J. Am. Chem. Soc.* **1979**, *101*, 257.

- Carboxylic Acids and Derivatives

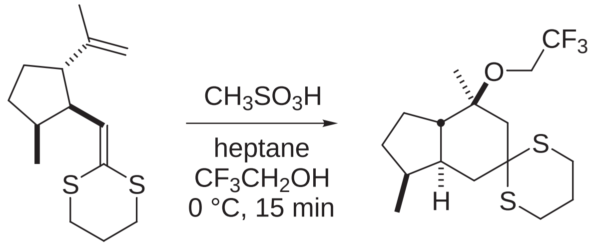


Kemp *J. Chem. Soc., Chem. Commun.* **1973**, 84.



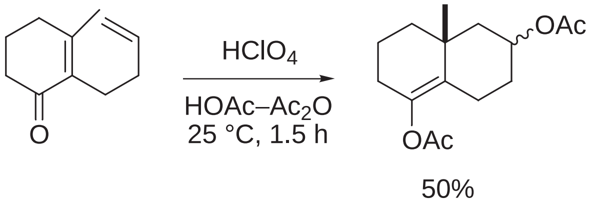
also extensively studied

- Ketene Acetals and Thioacetals



Andersen, Yamamoto *Tetrahedron Lett.* **1975**, 4547.

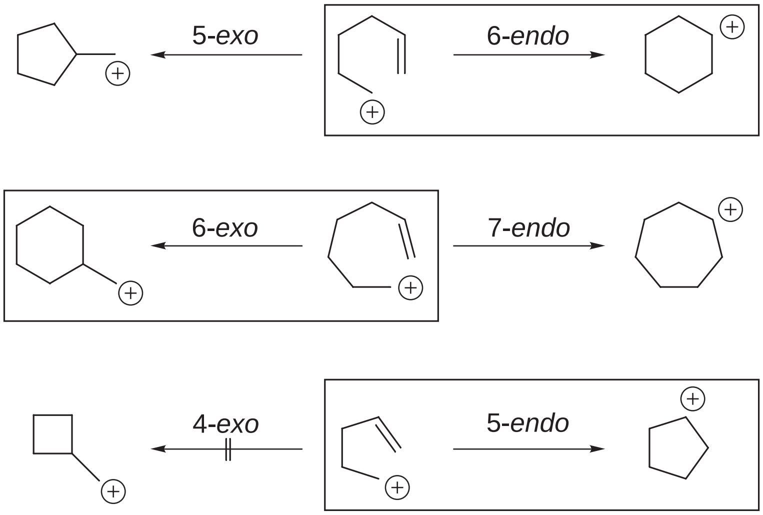
- α,β-Unsaturated Ketones, Esters,......



Harding *Tetrahedron Lett.* **1977**, 3321.

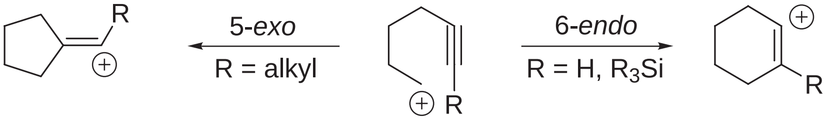
B. Cyclization and Propagation

a. Alkenes

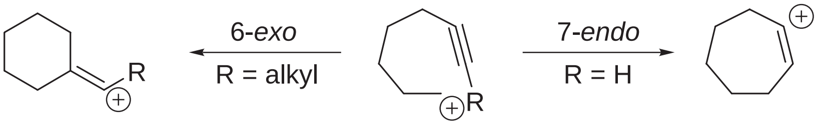


In the absence of olefin substituent directing effects:
- 5-*endo* >> 4-*exo*, the latter violates Baldwin's rules
- 6-*endo* > 5-*exo*
- 6-*exo* > 7-*endo*

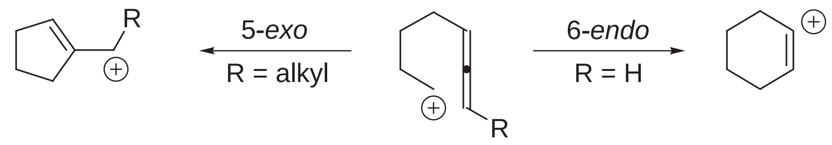
b. Alkynes



but can further rearrange to 6-*endo* product



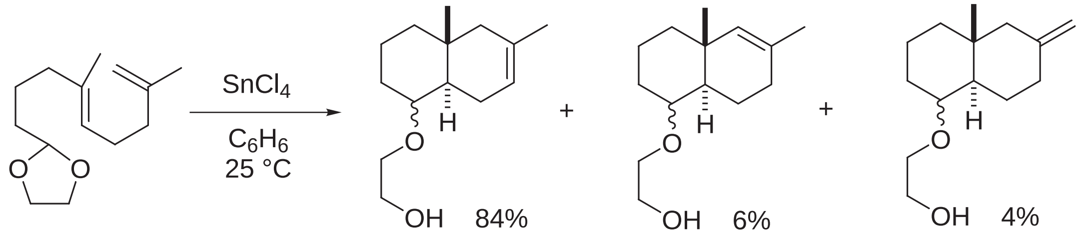
c. Allenes



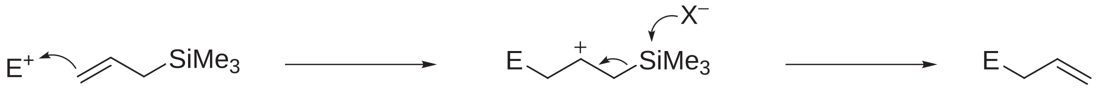
C. Termination

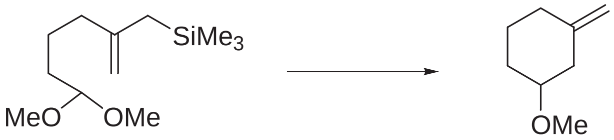
- Alkenes and Arenes

Elimination of H^+ reintroduces double bond or aromatic system.
Can result in complex mixture of products.

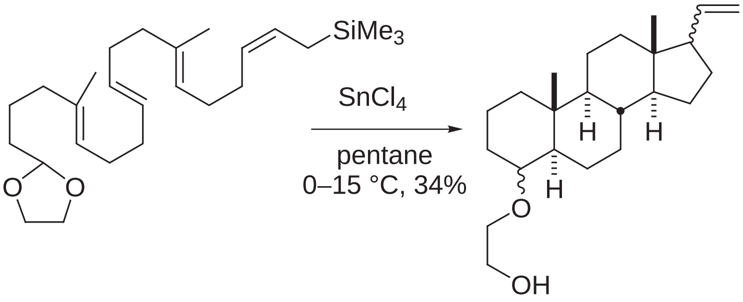


Allylsilanes can be enlisted to direct the termination.





Fleming *J. Chem. Soc., Chem. Commun.* **1976**, 182.



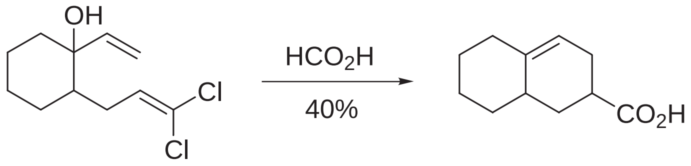
Johnson *J. Am. Chem. Soc.* **1983**, *105*, 6653.

Substitution on alkene can also alter regioselectivity (5-*exo* vs 6-*endo*)

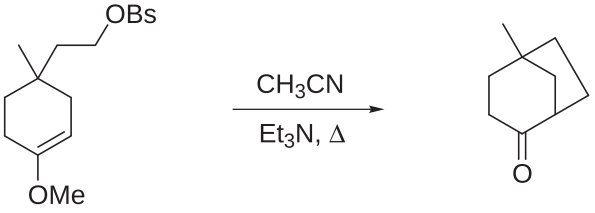
- Substituted Alkenes

Allows regiocontrol, but need to select substituents that avoid complications with initiation.

Vinyl chlorides and fluorides

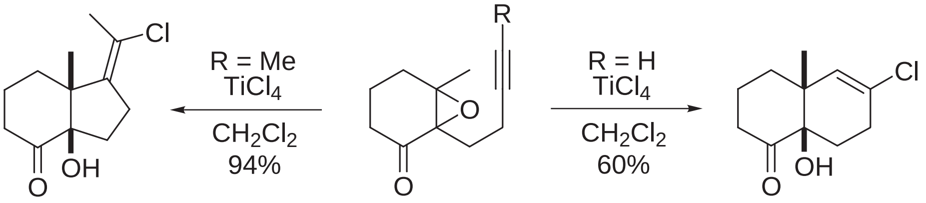


Landsbury *Acc. Chem. Res.* **1972**, *5*, 311.



Felkin *J. Chem. Soc., Chem. Commun.* **1968**, 60.

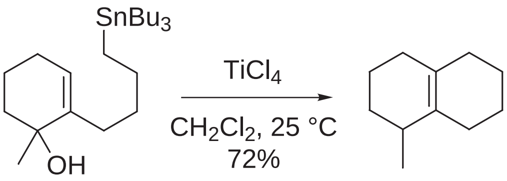
- Acetylenes

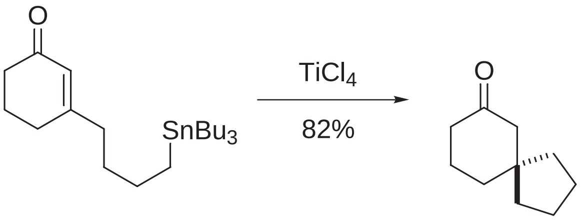


Sutherland *J. Chem. Soc., Chem. Commun.* **1978**, 526.

- Allenes see: Harding *J. Am. Chem. Soc.* **1978**, *100,* 993.

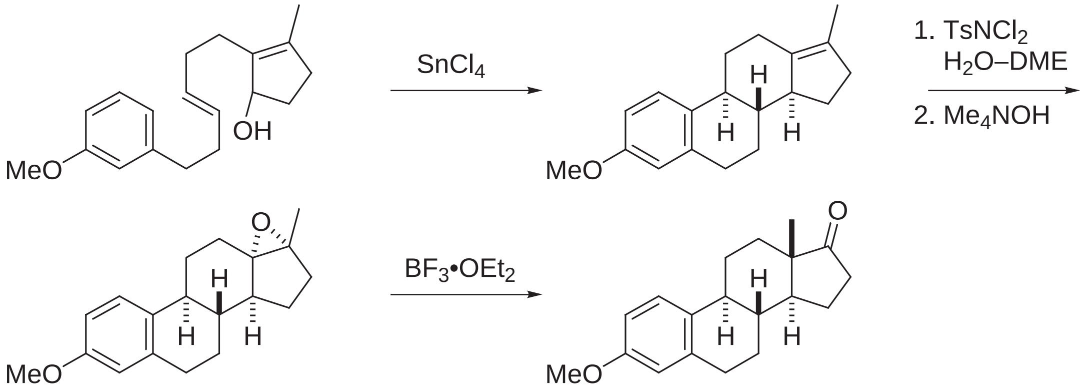
- Organostannanes





Macdonald *J. Am. Chem. Soc.* **1980**, *102,* 2113; **1981**, *103*, 6767.

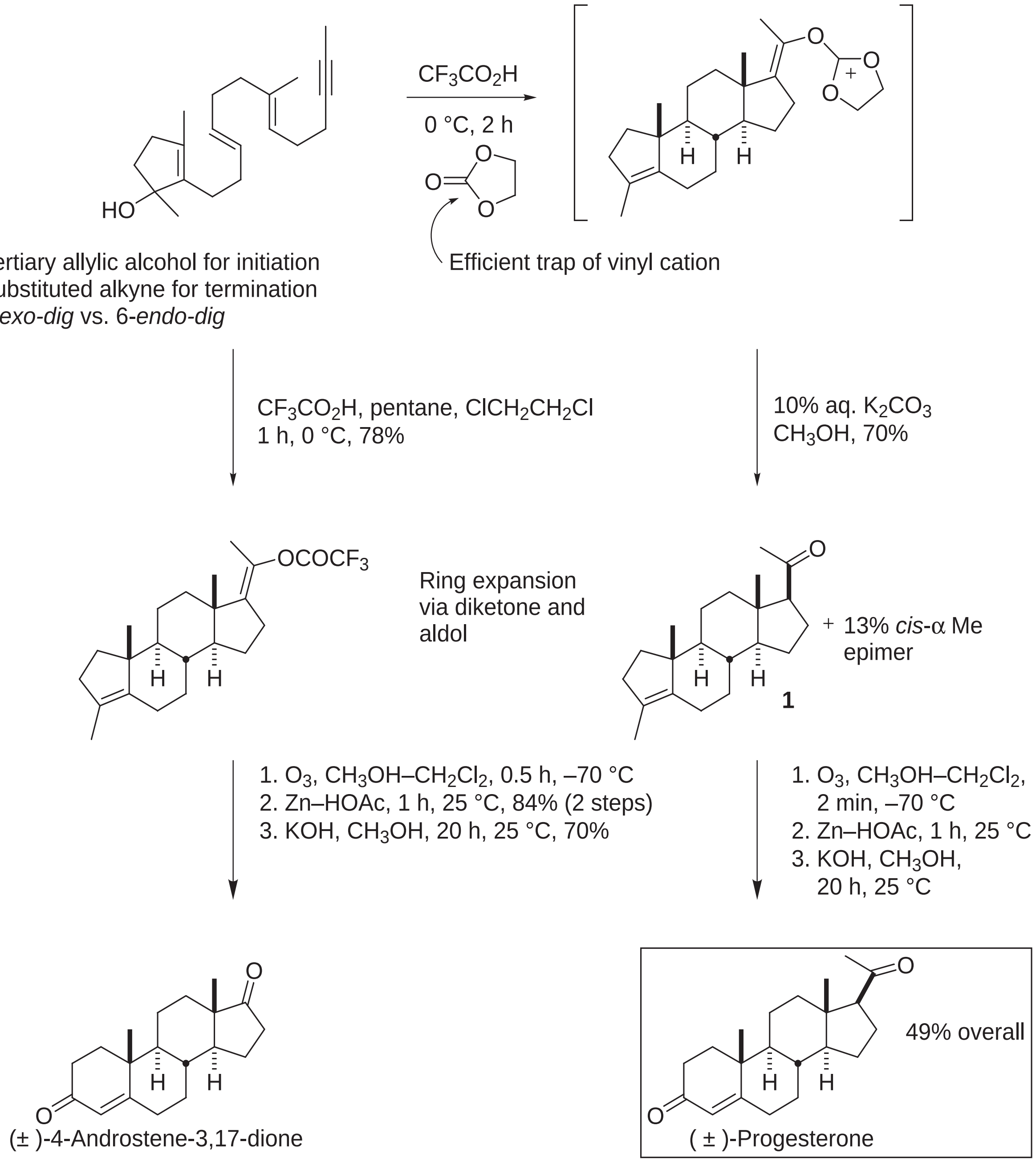
6. Synthesis of Estrone



Bartlett and Johnson *J. Am. Chem. Soc.* **1973**, *95*, 7501.

7. Synthesis of Progesterone

Johnson
J. Am. Chem. Soc. **1971**, *93*, 4332.
J. Am. Chem. Soc. **1978**, *100*, 4274.



CF_3CO_2H
0 °C, 2 h

- Tertiary allylic alcohol for initiation
- Substituted alkyne for termination
- 5-*exo-dig* vs. 6-*endo-dig*

Efficient trap of vinyl cation

CF_3CO_2H, pentane, $ClCH_2CH_2Cl$
1 h, 0 °C, 78%

10% aq. K_2CO_3
CH_3OH, 70%

Ring expansion
via diketone and
aldol

+ 13% *cis*-α Me
epimer

1

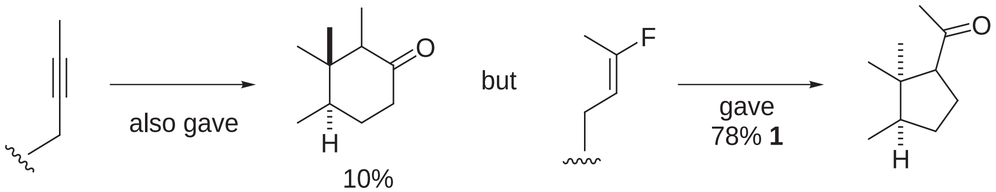
1. O_3, $CH_3OH–CH_2Cl_2$, 0.5 h, –70 °C
2. Zn–HOAc, 1 h, 25 °C, 84% (2 steps)
3. KOH, CH_3OH, 20 h, 25 °C, 70%

1. O_3, $CH_3OH–CH_2Cl_2$,
   2 min, –70 °C
2. Zn–HOAc, 1 h, 25 °C
3. KOH, CH_3OH,
   20 h, 25 °C

(±)-4-Androstene-3,17-dione

49% overall

(±)-Progesterone



also gave

10%

but

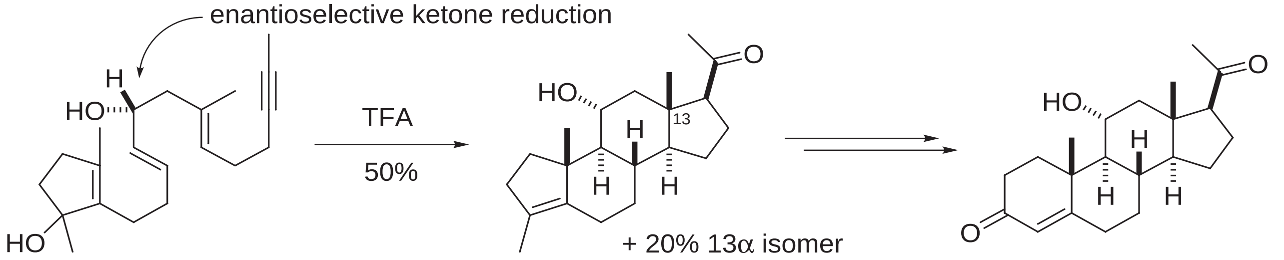
gave
78% **1**

Johnson *J. Am. Chem. Soc.* **1980**, *102*, 7800.

and only 3.5% *cis*-α Me epimer

- More recent efforts have reduced this to the synthesis of optically active agents.
- How would you imagine doing this?
- Remember chair-like transition states for the cyclization.

8. Enantioselective Synthesis of 11-Hydroxyprogesterone



Johnson *J. Am. Chem. Soc.* **1977**, *99*, 8341.

I. Free Radical Cyclizations

1. Reviews

Acyloin Condensation: Bloomfield, J. J.; Owsley, D. C.; Nelke, J. M. *Org. React.* **1976,** *23*, 259.

McMurry Coupling: McMurry, J. E. *Acc. Chem. Res.* **1983,** *16*, 405.

Julia Free Radical Cyclization: Julia, M. *Acc. Chem. Res.* **1971,** *4*, 386.
Pure App. Chem. **1967,** *15*, 167.

- General Reviews

Beckwith, A. L. J.; Ingold, K. U. *Rearrangements in Ground State and Excited States*, Vol. 1; de Mayo, P., Ed.; Academic: NY, 1980, pp 182–220.

Beckwith, A. L. J. *Tetrahedron* **1981,** *37*, 3073. (Regioselectivity of ring cyclization)

Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon: Oxford, 1986.

Symposium-in-print: *Tetrahedron* **1985,** *41*, no. 19.

Curran, D. P. *Synthesis* **1988,** 417 and 489.

Hart, D. J. *Science* **1984**, *223*, 883.

Ramaiah, M. *Tetrahedron* **1987,** *43*, 3541.

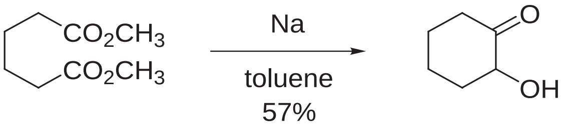
Comprehensive Org. Syn., Vol. 4, Chapter 4.1 and 4.2, pp 715–831.

Laird, E. R.; Jorgensen, W. L. *J. Org. Chem.* **1990**, *55*, 9.

Giese, B. *Org. React.* **1996,** *48***,** pp 301–856.

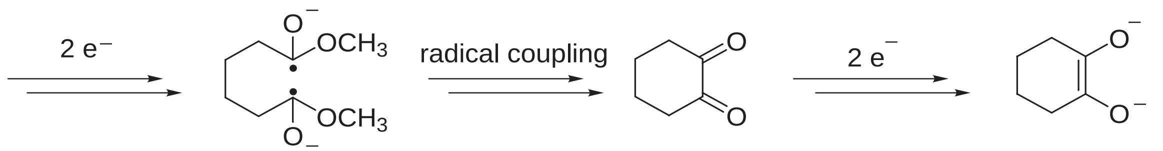
2. Reductive Coupling of Carbonyl Compounds

a. Acyloin Condensation

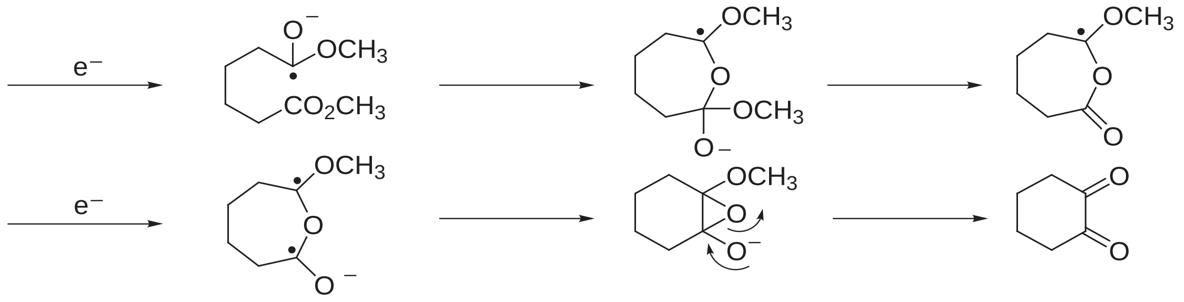


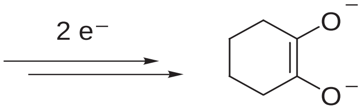
Sheehan *J. Am. Chem. Soc.* **1950**, *72*, 3376.

- Mechanism



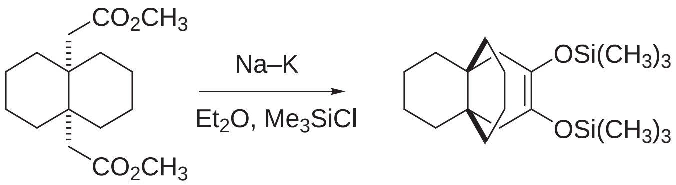
- Alternative





First report: Freund *Justus Liebigs Ann. Chem.* **1861**, *118*, 33.
Macrocyclization: Finley *Chem. Rev.* **1964**, *64*, 573.
Review: *Comprehensive Org. Syn.* Vol. 3, 613.

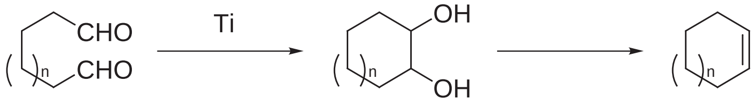
b. Rühlmann Modification with Me_3SiCl

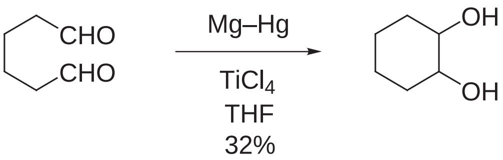


Bloomfield *Tetrahedron Lett*. **1968**, 591.
Ruhlmann *Synthesis* **1971**, 236.

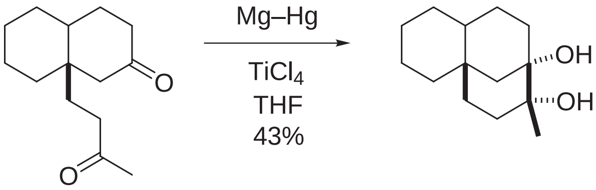
3. Reductive Coupling of Ketones and Aldehydes (Pinacol Coupling and McMurry Reaction)

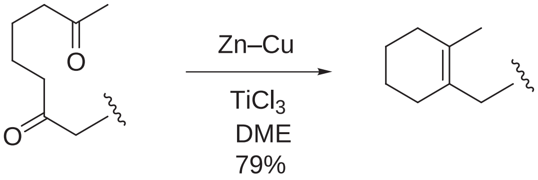
- Low valent Ti reagents used to generate ketyl radicals and chosen to permit generation of either the pinacol or olefin product.



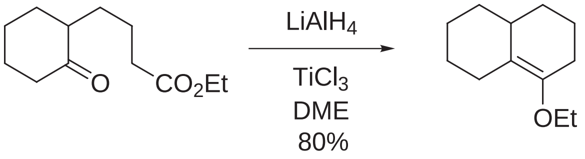


Corey, Danheiser *J. Org. Chem.* **1976**, *41*, 260.

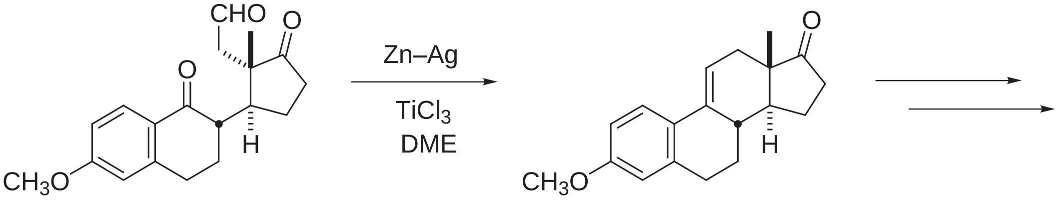




McMurry *J. Org. Chem.* **1977**, *42*, 2655.

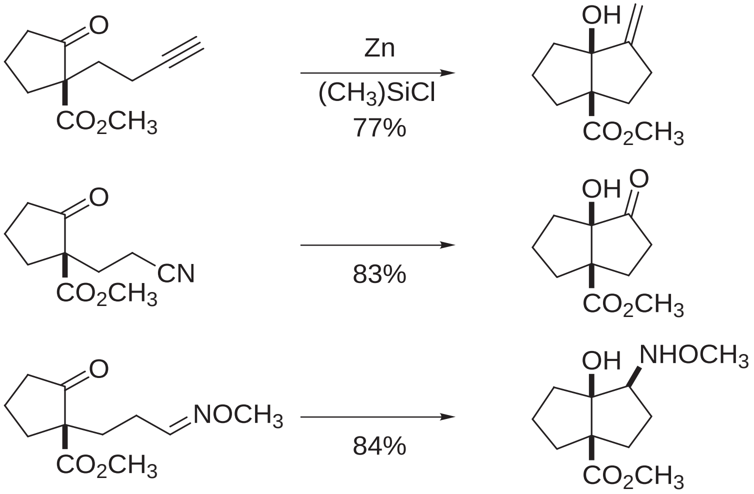


McMurry *J. Am. Chem. Soc.* **1983**, *105*, 1660.



Estrone Synthesis: Ziegler *J. Org. Chem.* **1982**, *47*, 5229.

- Other Functional Groups: Corey *Tetrahedron Lett.* **1983**, *24*, 2821.



4. SmI_2 Promoted Reductive Coupling Reactions (Radical Mechanisms)

- Lanthanide chemistry reviews

Molander *Chem. Rev.* **1992**, *92*, 29.

Molander in *Chemistry of the Carbon Metal Bond*, Hartley, F. R.; Patai, S., Eds.; Wiley: NY, 1989, Vol. 5

Molander in *Comprehensive Org. Syn.*, Vol. 1, 262.

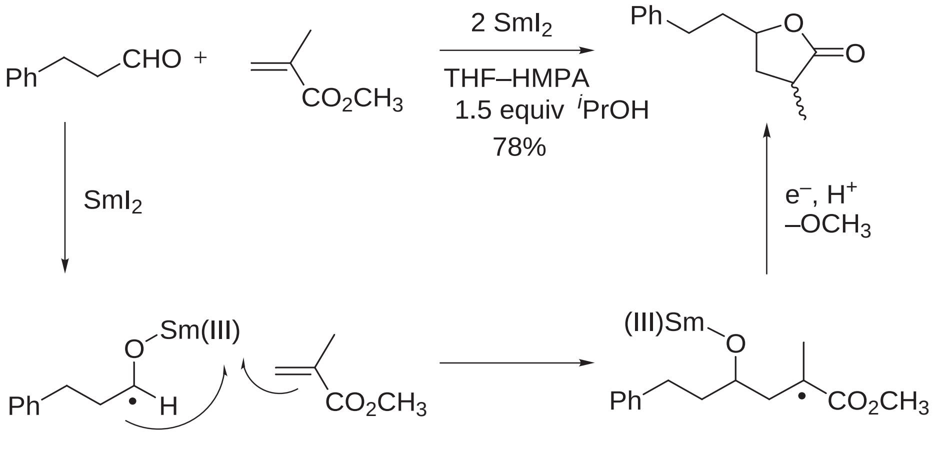
Kagan *New. J. Chem.* **1990**, *14*, 453.

Kagan *Tetrahedron* **1986**, *42*, 6573.

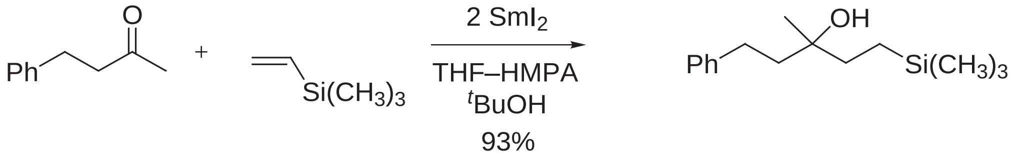
Soderquist *Aldrichim. Acta* **1991**, *24*, 15.

a. Ketyl–Olefin Coupling Reactions

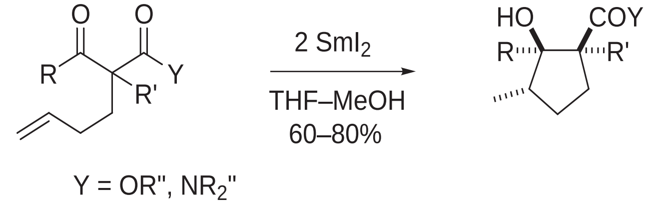
- Intermolecular (Only effective for activated olefins)

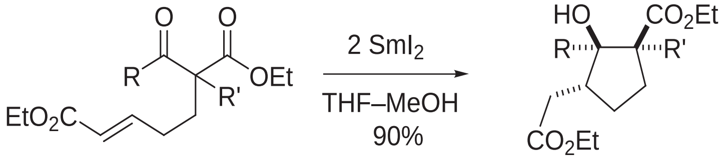


Inanaga *Tetrahedron Lett.* **1986**, *27*, 5763.
Tetrahedron Lett. **1989**, *30*, 2837.



- Intramolecular





Molander

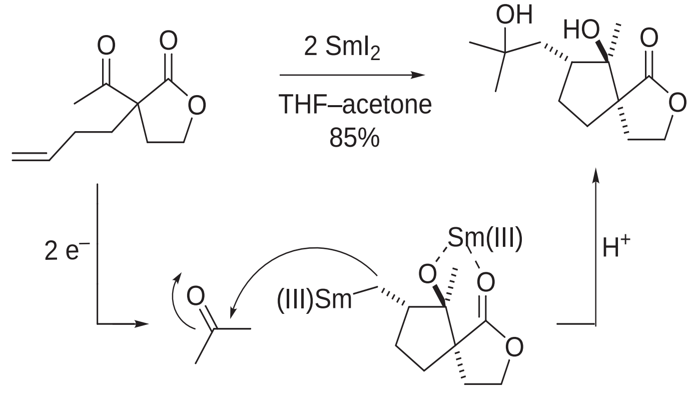
Tetrahedron Lett. **1987**, *28*, 4367.

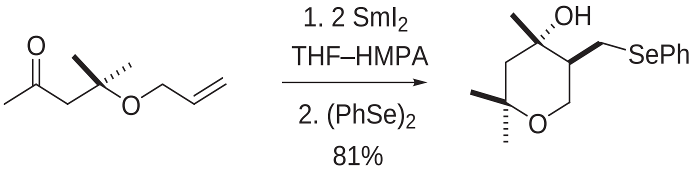
J. Am. Chem. Soc. **1989**, *111*, 8236.

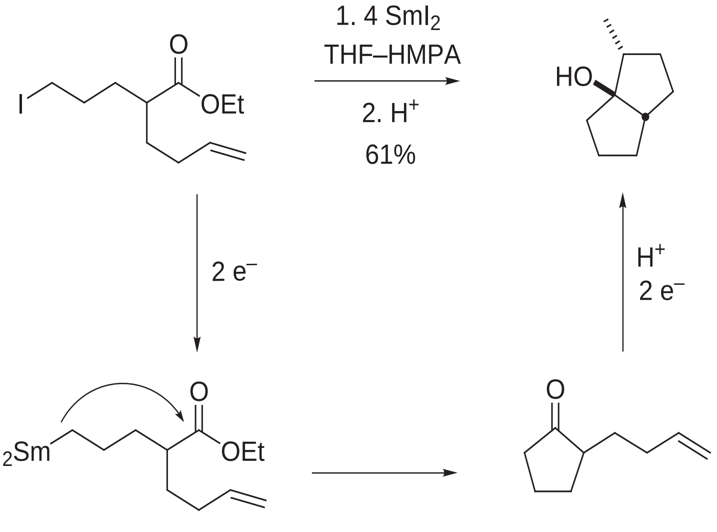
J. Org. Chem. **1991**, *56*, 1439.

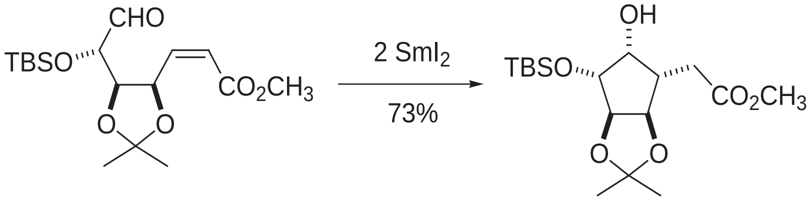
J. Org. Chem. **1993**, *58*, 7216.

J. Org. Chem. **1994**, *59*, 3186.

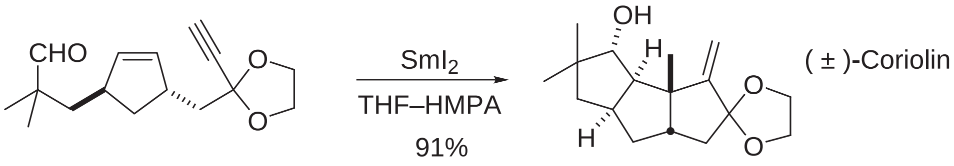




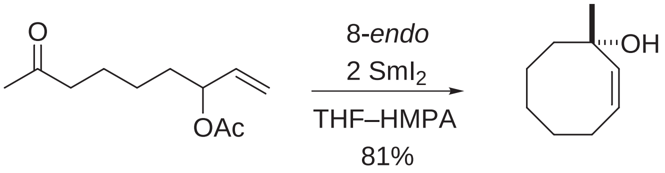




Enholm *J. Am. Chem. Soc.* **1989**, *111*, 6463.

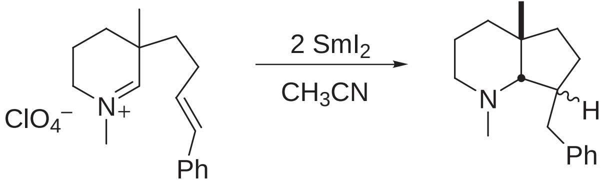


Curran *J. Am. Chem. Soc.* **1988**, *110,* 5064.



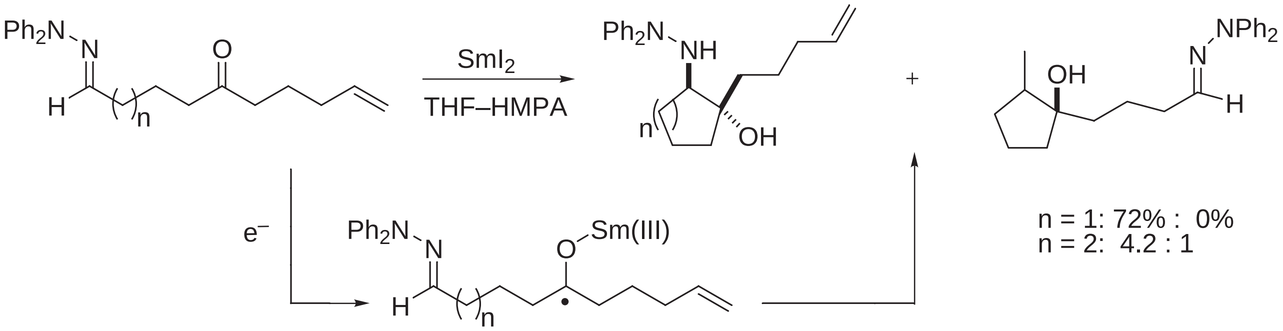
Molander *J. Org. Chem.* **1994**, *59*, 3186.

- Imminium ion generated *in situ*



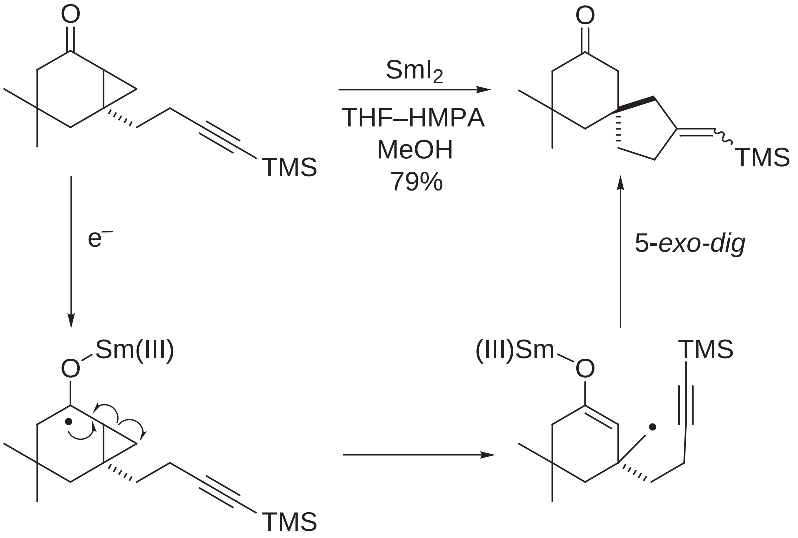
Martin *Tetrahedron Lett.* **1988**, *29*, 6685.

- Hydrazone (5-*exo* hydrazone >> 5-*exo* alkene; 6-*exo* hydrazone > 5-*exo* alkene)



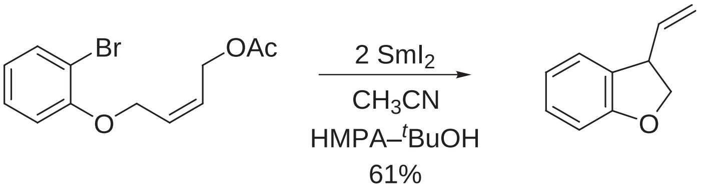
Fallis *J. Am. Chem. Soc.* **1994**, *116*, 7447.
J. Org. Chem. **1994**, *59*, 6514.

- Fragmentation–cyclization

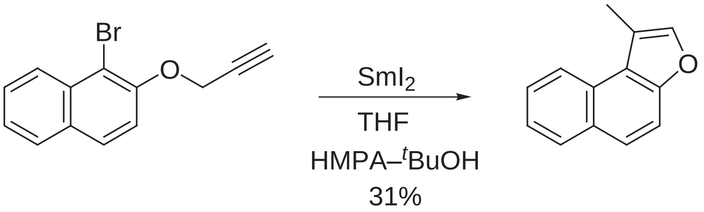


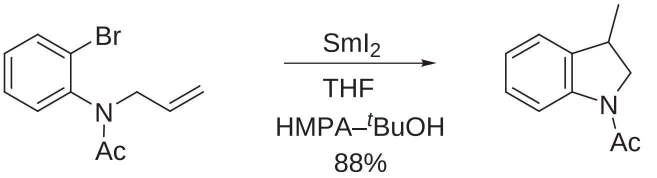
Motherwall *Tetrahedron Lett.* **1991**, *32*, 6649.

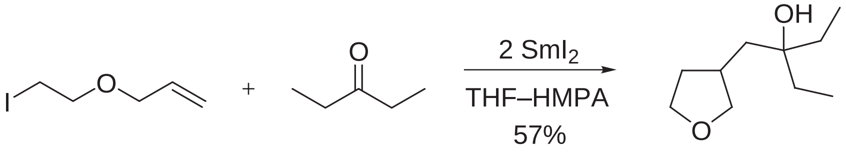
b. Alkyl/Aryl Radical Cyclizations



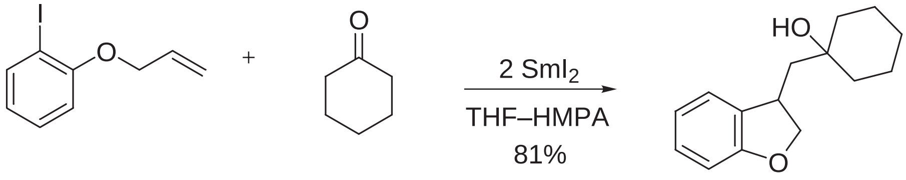
Inanaga *Tetrahedron Lett.* **1991**, *32*, 1737.







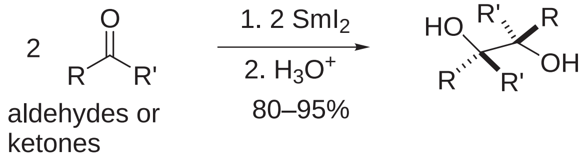
Molander *J. Org. Chem.* **1990**, *55*, 6171.



Curran *Synlett* **1990**, 773.

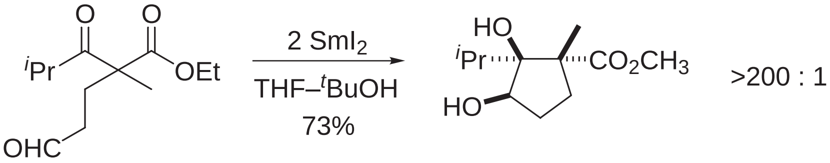
c. Pinacol-type Coupling Reactions

- Intermolecular

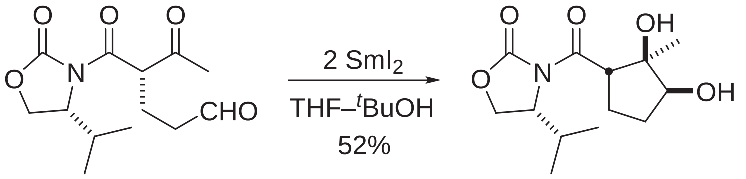


Kagan *Tetrahedron Lett.* **1983**, *24*, 765.

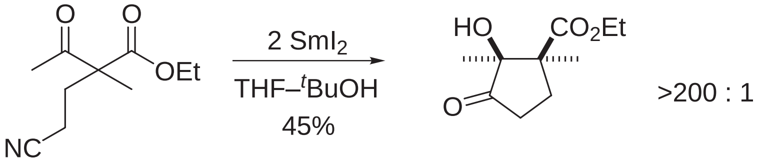
- Intramolecular



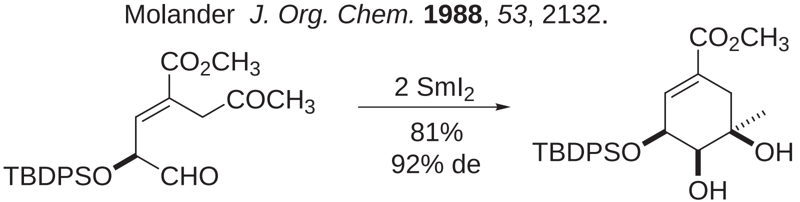
Molander *J. Org. Chem.* **1988**, *53*, 2132.



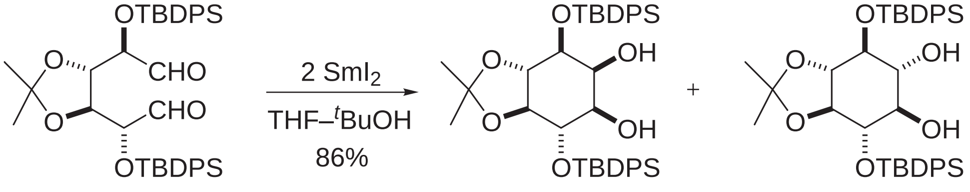
Molander *J. Org. Chem.* **1988**, *53*, 2132.



Molander *J. Org. Chem.* **1988**, *53*, 2132.

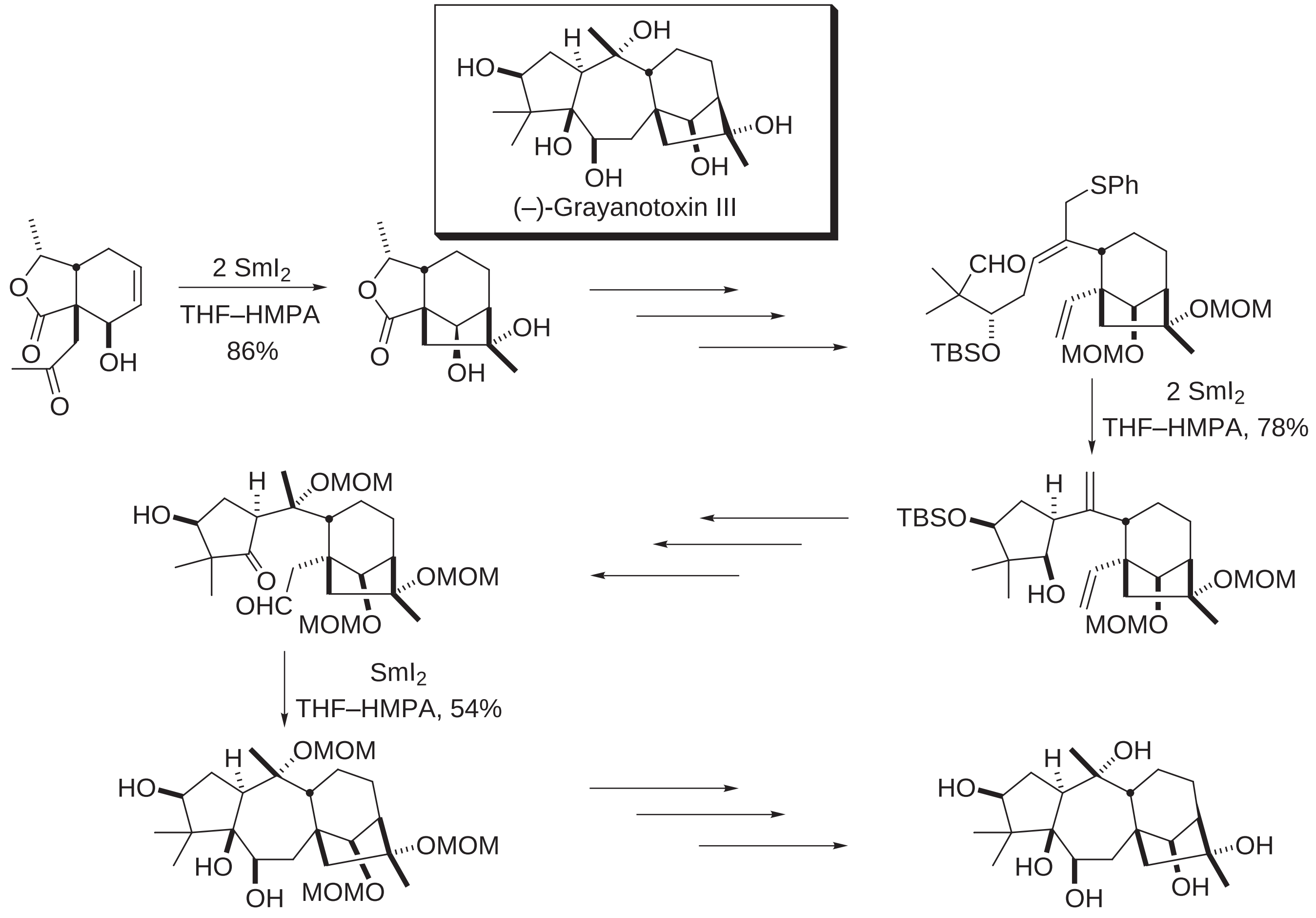


Hanessian *Tetrahedron Lett.* **1991**, *32*, 1125.



Chiara *Tetrahedron Lett.* **1994**, *35*, 2969.

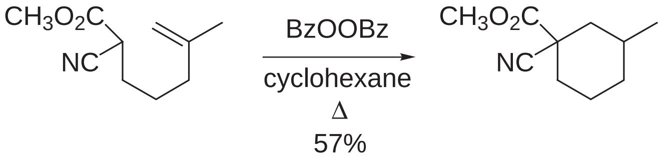
- A recent total synthesis of (–)-Grayanotoxin III incorporated two ketyl–olefin cyclization reactions and a pinacol coupling reaction (SmI_2-promoted).
- Shirahama *J. Org. Chem.* **1994**, *59*, 5532.



5. Radical–Olefin Cyclizations

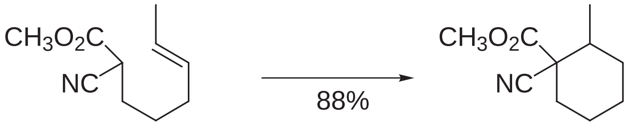
a. Representative Examples

- Concurrent with Johnson's investigation of cation–olefin cyclizations, Julia initiated radical–olefin cyclization studies.



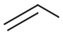
Julia *Compt. rend.* **1960**, *251*, 1030.

Reversible, thermodynamically controlled reactions.



6-*endo-trig*

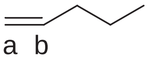
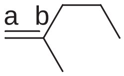
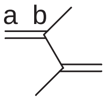
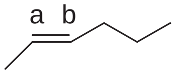
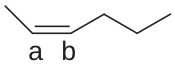
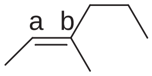
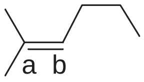
b. Reactivity and Regioselectivity

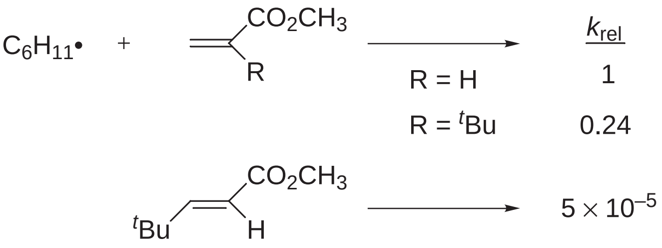
- Relative rates of addition to  $PO(OEt)_2$: typical electron-deficient olefin.

	$CH_3\bullet$	$CH_3CH_2\bullet$	$CH_3OCH_2\bullet$	$(CH_3)_2CH\bullet$	$(CH_3)_3C\bullet$
k_{rel} =	1	1	2.7	4.8	24

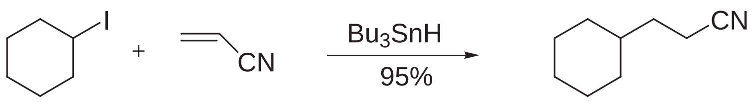
- Alkyl radicals are regarded as nucleophilic.

Steric Effects on Addition Regioselectivity

olefin	% addition to: Ca	Cb	k_{rel}
	>95	<5	1.16
	>95	<5	18.4
	>95	<5	2 × 136
	50	50	2 × 0.50
	50	50	2 × 0.63
	>95	5	15
	<5	>95	13.9

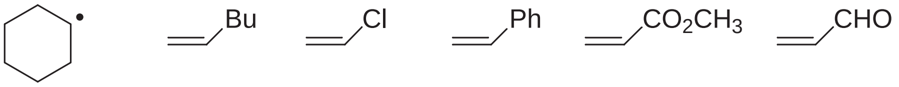


β-substitution strongly decelerates intermolecular addition with activated acceptors



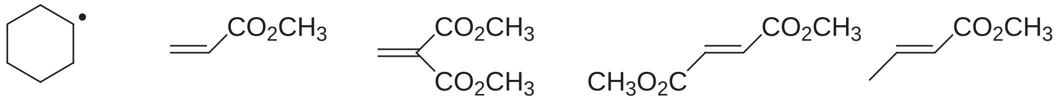
Nucleophilic radical

Electrophilic acceptor alkene



k_{rel}	1.0	8.4	84	3000	8500

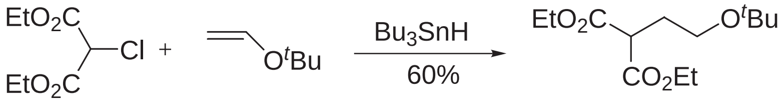
Note the substantial effect of two geminal vs vicinal electron-withdrawing groups



k_{rel}	1.0 (3000)	150 (450000)	5 (15000)	0.01 (30)

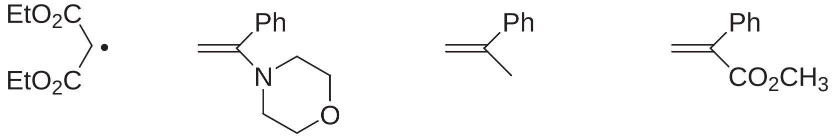
( ), relative to 

Note the substantial deceleration of the reaction rate by β-substitution (100×)



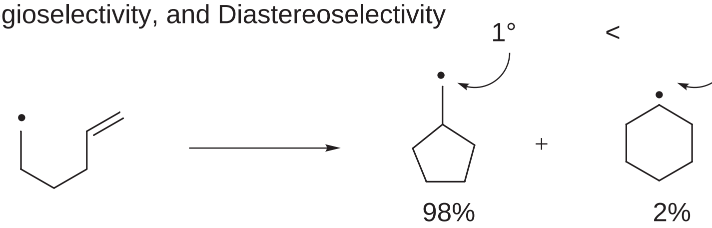
Electrophilic radical

Nucleophilic acceptor alkene



k_{rel}	23	3.5	1

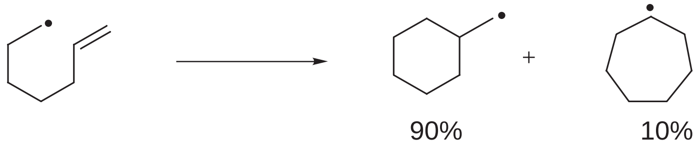
c. Cyclization Rates, Regioselectivity, and Diastereoselectivity



Stability

but
5-*exo* > 6-*endo*

Beckwith *J. Chem. Soc., Chem. Commun.* **1974**, 472.
Beckwith *J. Chem. Soc., Chem. Commun.* **1980**, 484.

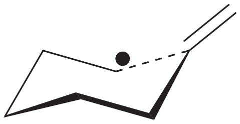


6-*exo* > 7-*endo*

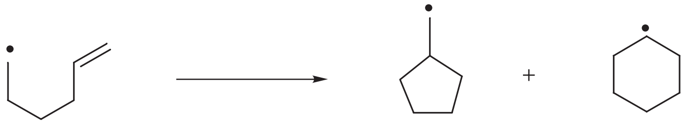
- Chair-like transition state subject to stereoelectronic and kinetic control rather than thermodynamic control.

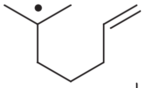
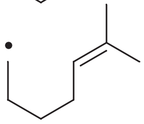
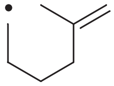
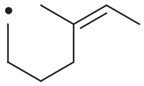
≡ 5-*exo*

Stereochemical features of substitution can be rationalized and predicted based on these models.

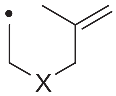


≡ 6-*exo*

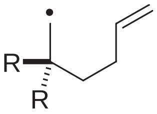


	k_{rel} *exo*	k_{rel} *endo*	Product ratio
	1.0	0.02	(98 : 2)
	1.4	0.02	(99 : 1)
	2.4	<0.01	(>200:1)
	0.022	0.04	(36 : 64) *endo* predominates
	0.16	<0.002	*exo* >> *endo* (>80:1)

- Linker chain effects

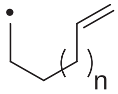


	k_{exo}/k_{endo}	
X = CH_2	0.55	*endo* > *exo*
X = O	38.6	*exo* >> *endo*



	k_{rel}
R = H	1
R = CH_3	10

} gem dimethyl effect

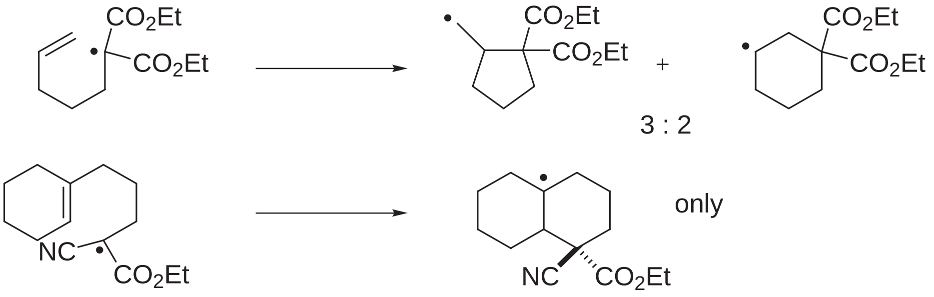


	ring size	k	k_{rel}
n = 1	5	~10^5 s^{-1}	1
n = 2	6	~10^4 s^{-1}	0.1
n = 3	7	~10^2 s^{-1}	0.001 ←

exo >> *endo*

7-membered ring closure so slow that reduction competes.

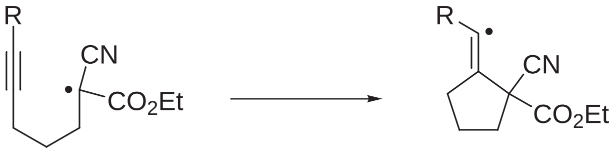
- Stabilized radicals participate in reversible cyclizations and the thermodynamic product is observed.



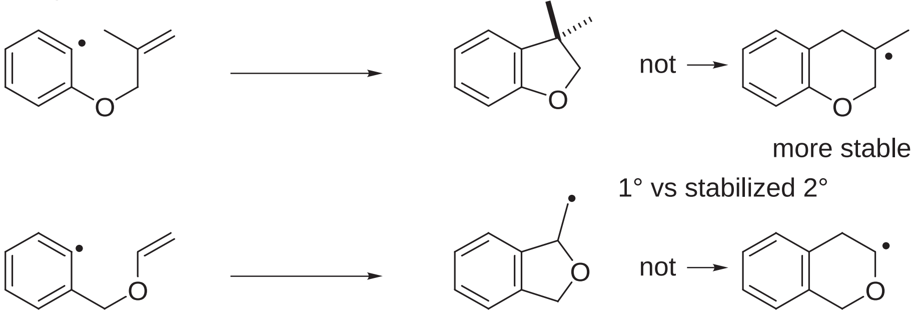
3 : 2

only

- Alkynyl radicals give 5-*exo* closure (stereoelectronic) even with stabilized radicals.



- Note effect of additional sp^2 centers in the linking chain: 5-*exo* closure takes precedence over the overall stability of the resulting free radical.



1° vs 3°

not →

more stable

1° vs stabilized 2°

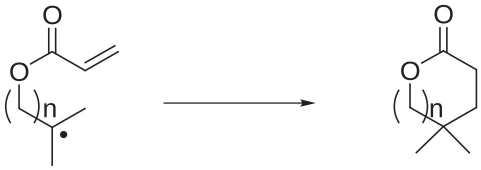
not →

more stable

- Closure onto carbonyls possible

6-*exo* HCO > 5-*exo* C=C

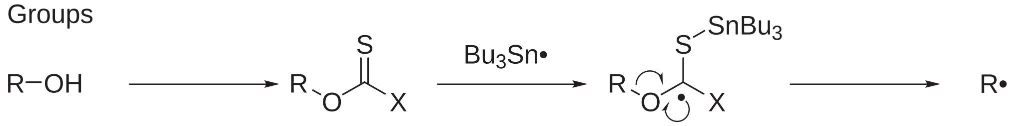
- Macrocyclizations are very facile



- Requires unsubstituted and activated acceptor alkene to compete with reduction.

Porter *J. Am. Chem. Soc.* **1987**, *109*, 4976.

d. Initiator Groups

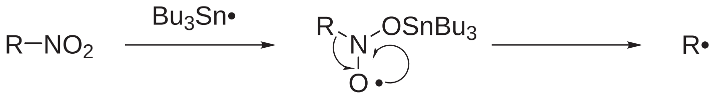


X = SR, OR, SeR

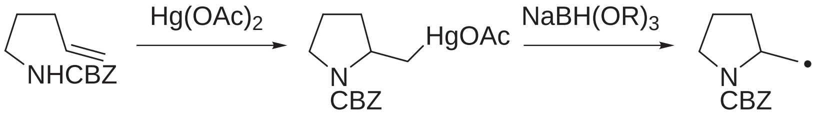
Barton deoxygenation reaction

$R{-}X \xrightarrow{Bu_3Sn\bullet} R\bullet + Bu_3SnX$ X = Br, I

$R{-}SePh \xrightarrow{Bu_3Sn\bullet} R\bullet + Bu_3SnSePh$



$R{-}SO_2R \xrightarrow{Bu_3Sn\bullet} R\bullet$



- Different Initiators

Special reagent that increases reactivity of Si–H so it may be used effectively in synthesis.

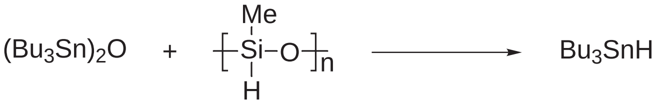
M–H Bond strength (kcal/mol)	74	79	84	90
	$^{n}Bu_3Sn{-}H$	$(Me_3Si)_3Si{-}H$	$^{n}Bu_3Ge{-}H$	$Et_3Si{-}H$
weakest	Sn-H	<	Ge-H <	Si-H

More competitive reduction by H• abstraction from reagent

Giese *Tetrahedron Lett.* **1989**, *30*, 681.
Ingold *Int. J. Chem. Kinet.* **1969**, *7*, 315.

- Initiation Conditions

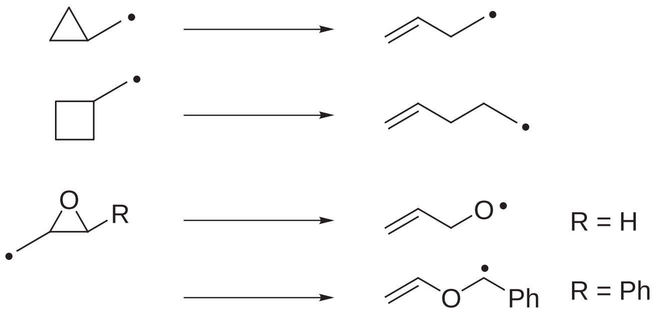
In situ generation of Bu_3SnH (catalytic amount of Sn)



$$(Bu_3Sn)_2O + \left[\overset{Me}{\underset{H}{Si}}{-}O\right]_n \longrightarrow Bu_3SnH$$

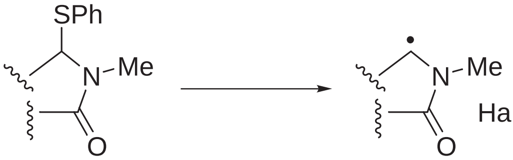
PMSH (polymethylsiloxane), readily avaible
Green *J. Org. Chem.* **1967**, *32*, 882.

e. Rearrangements are possible



f. Functionalized Free Radicals

Stork, vinyl radicals



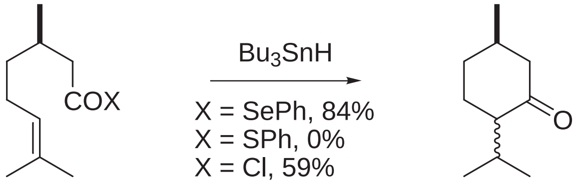
Hart *J. Am. Chem. Soc.* **1997**, *119*, 6226.

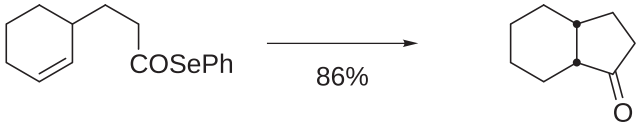
review: Chatgilialoglu, Crich, Ryu *Chem. Rev.* **1999**, *99*, 1991.

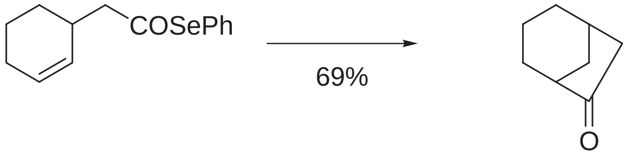
Keck *Synlett* **1999**, 1657.

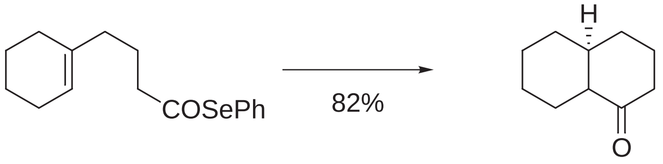
Boger, acyl radicals
J. Org. Chem. **1988**, *53*, 3377. Intramolecular
J. Org. Chem. **1989**, *54*, 1777. Intermolecular
J. Am. Chem. Soc. **1990**, *112*, 4003. Tandem cyclization
J. Am. Chem. Soc. **1990**, *112*, 4008. Macrocyclization
J. Org. Chem. **1990**, *55*, 5442. Ring expansion
J. Org. Chem. **1992**, *57*, 1429. Full description
Israel J. Chem. **1997**, *37*, 119. Review

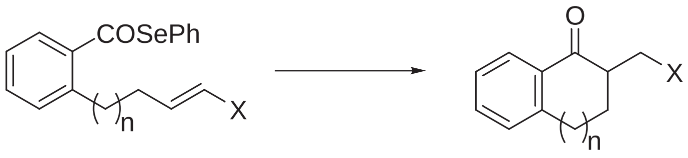
- Examples





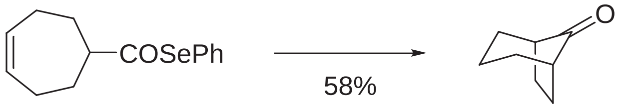






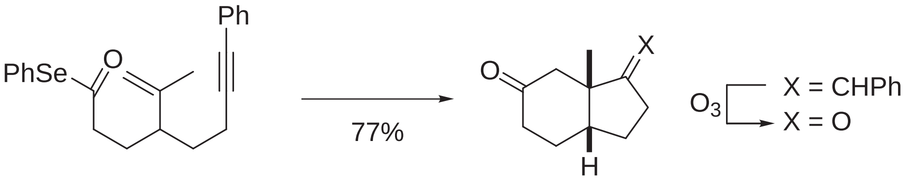
			ring size
X = H	n = 0	81%	5
	n = 1	76%	6
	n = 2	74%	7
X = CO_2CH_3	n = 0	88%	5
	n = 1	84%	6
	n = 2	92%	7

		ring size
n = 0	83%	6
n = 1	71%	7

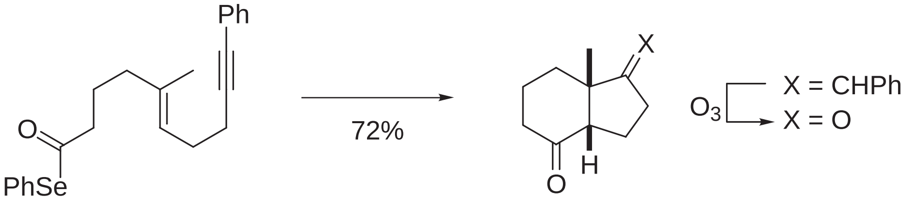


Note: Alkyl and vinyl radicals are subject to faster reduction. Cyclizations such as the above example or those for the formation of 7-membered rings are not very successful, but acyl radicals are much more stable and not subject to competitive reduction.

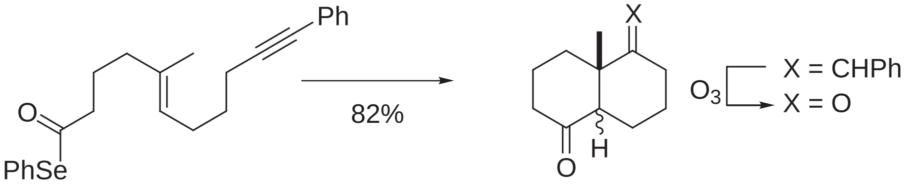
- Tandem Cyclizations



> 98% *cis*

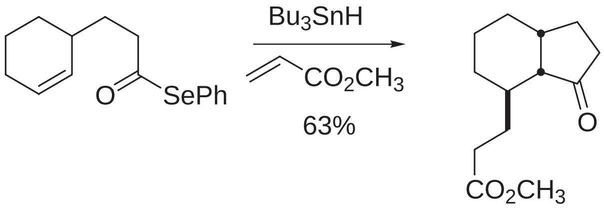


> 97% *cis*

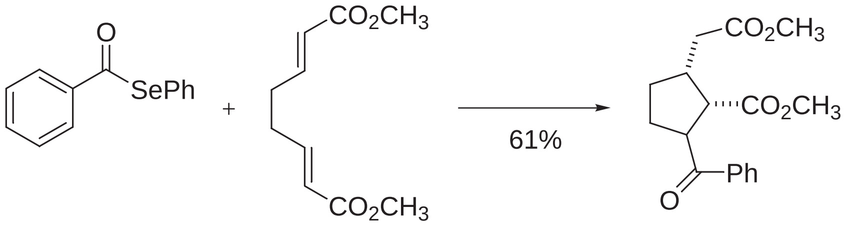


6 : 4 *cis* : *trans*

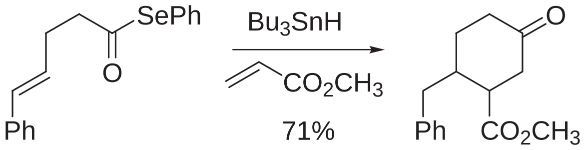
- Cyclization–Addition Reactions



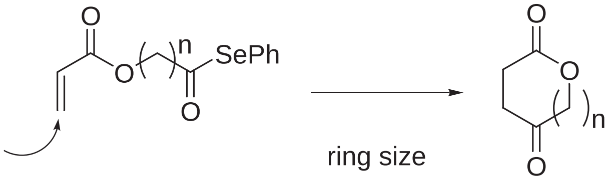
- Addition–Cyclization Reactions



2.4 : 1 diastereomers



- Macrocyclization Reactions

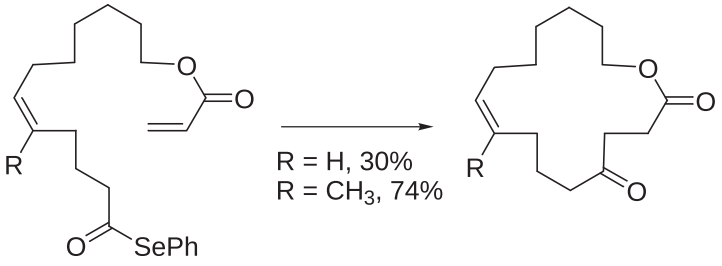


activated, unsubstituted acceptor alkene

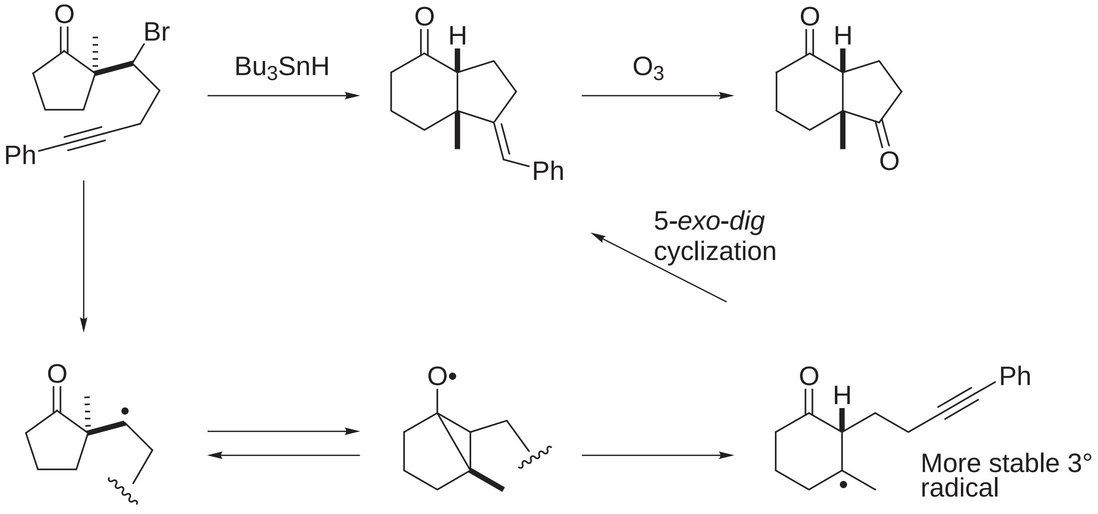
- decarbonylation very slow
- reduction very slow
- macrocyclization proceeds exceptionally well

	ring size	
n = 15	20	57%
n = 11	16	68%
n = 9	14	55%
n = 7	12	46%
n = 6	11	47%

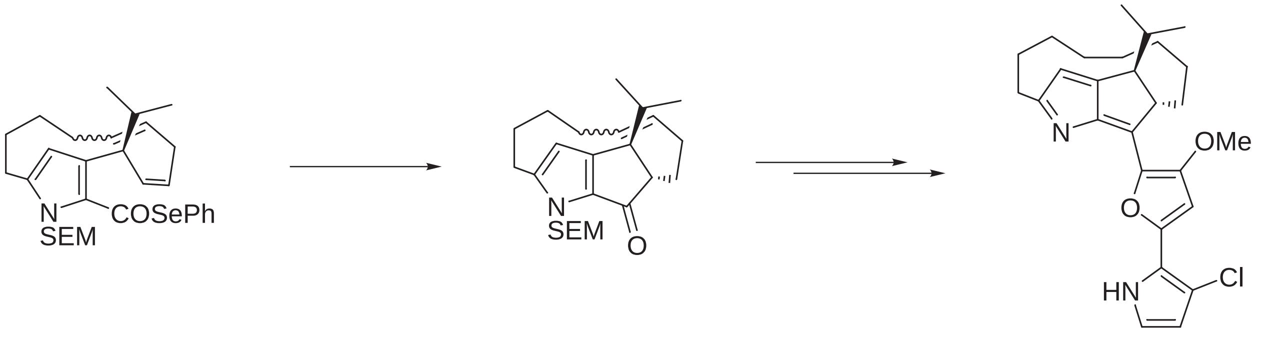
- Macrocyclization onto activated acceptor is faster than 6-*exo*, 7-*exo* or 6-*endo* closure.
- Competitive with 5-*exo* closure.



- Rearrangement/Ring Enlargement Cyclization



- Applications



Hong, Boger *J. Am. Chem. Soc.* **2001**, *123*, 8515.

ent-(–)-Roseophilin

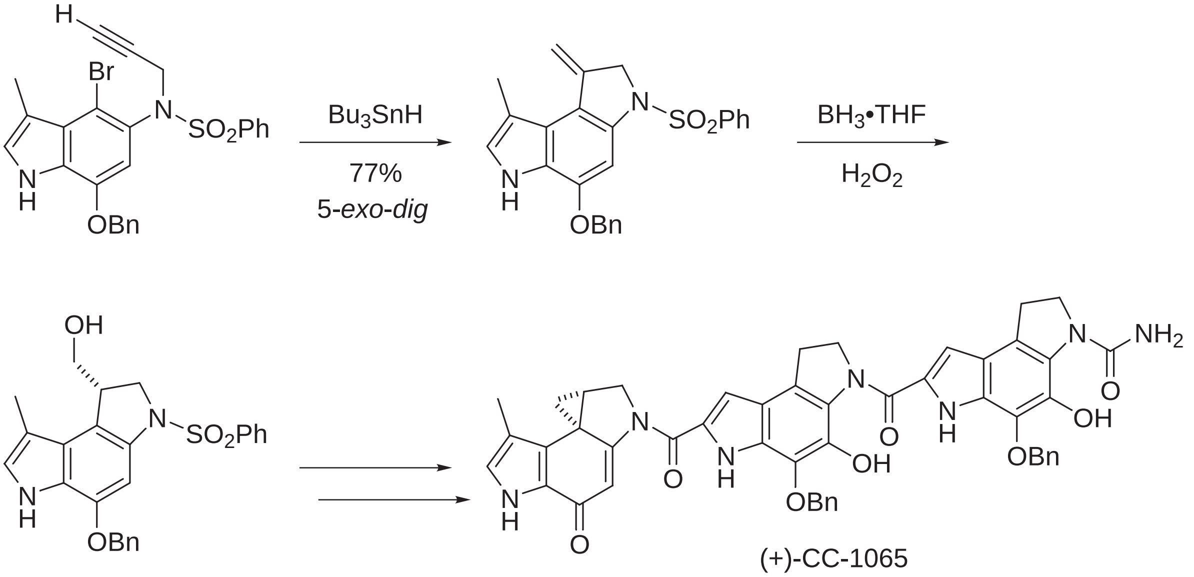
Remarkabley, *ent*-(–)-roseophilin was found to be 10-fold *more* potent than the natural enantiomer in cytotoxic assays. To our knowledge, this is the first example of an unnatural enantiomer of a naturally occurring antitumor agent diaplaying more potent activity although several instances of comparable activity have been disclosed.

(+)- and *ent*-(–)-CC-1065:
    Kelly *J. Am. Chem. Soc.* **1987**, *109*, 6837.
    Boger and Coleman *J. Am. Chem. Soc.* **1988**, *110*, 4796.
Natural and *ent*-fredericamycin A
    Boger *J. Am. Chem. Soc.* **1995**, *117*, 11839.
Natural and *ent*-mitomycin C
    Fukuyama and Tomasz *J. Am. Chem. Soc.* **1995**, *117*, 9388.

Table. In vitro cytotoxic activity

compound	IC_{50} (μM)	
	L1210	CCRF-CEM
ent-(–)-roseophilin	0.02	0.1
nat-(+)-roseophilin	0.2	1.5

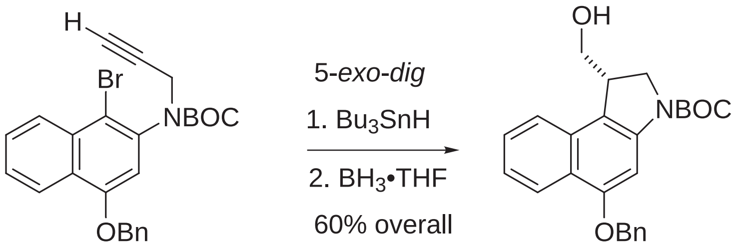
g. A case study comparison of cyclization approaches



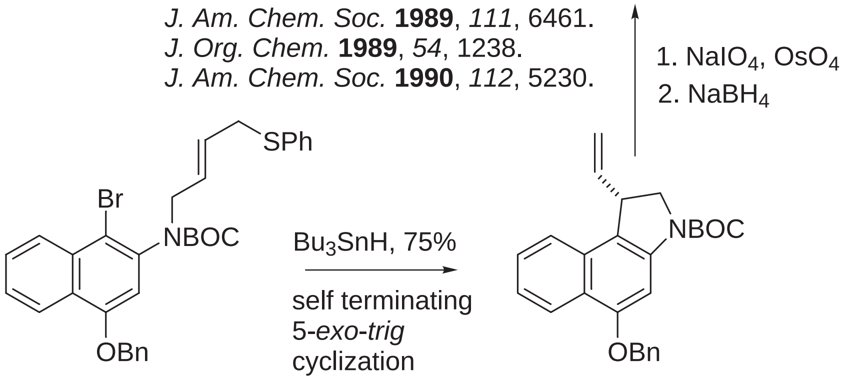
(+)-CC-1065

Boger and Coleman *J. Am. Chem. Soc.* **1988**, *110*, 1321.
J. Am. Chem. Soc. **1988**, *110*, 4796.

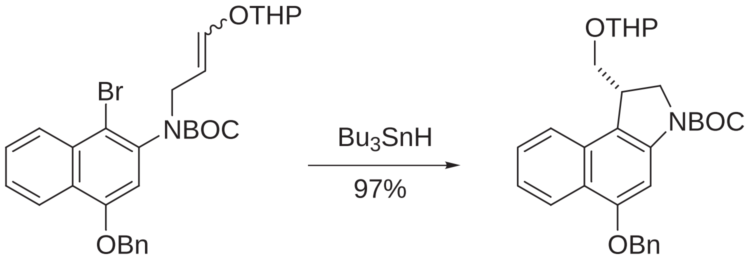
- A useful comparison series employed in the preparation of analogs of CC-1065 and the duocarmycins (Boger)



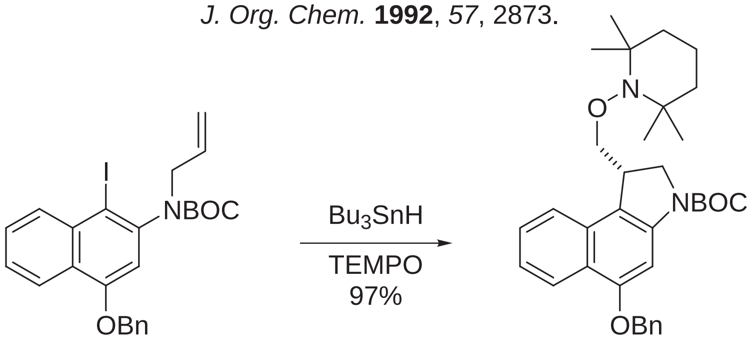
J. Am. Chem. Soc. **1989**, *111*, 6461.
J. Org. Chem. **1989**, *54*, 1238.
J. Am. Chem. Soc. **1990**, *112*, 5230.



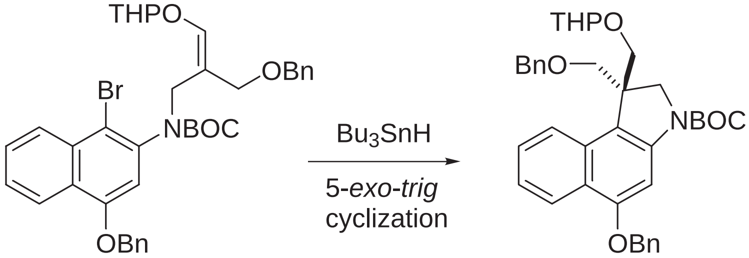
J. Org. Chem. **1990**, *55*, 5823.



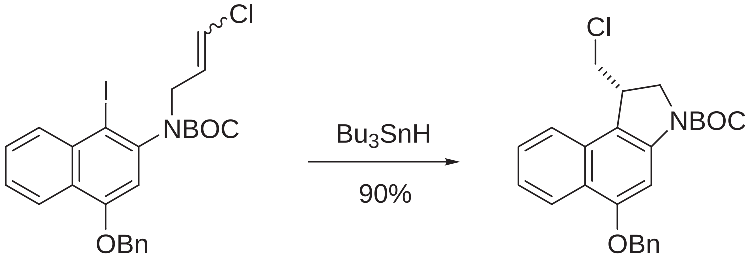
J. Org. Chem. **1992**, *57*, 2873.



J. Org. Chem. **1995**, *60*, 1271.

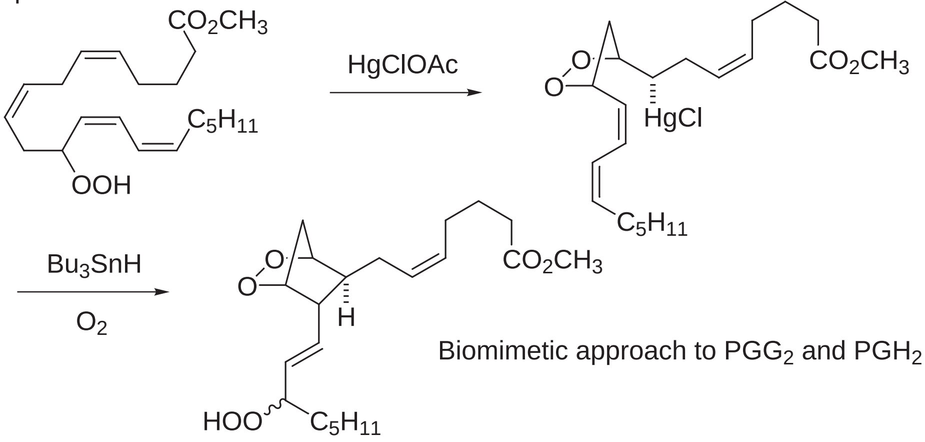


J. Am. Chem. Soc. **1992**, *114*, 9318.



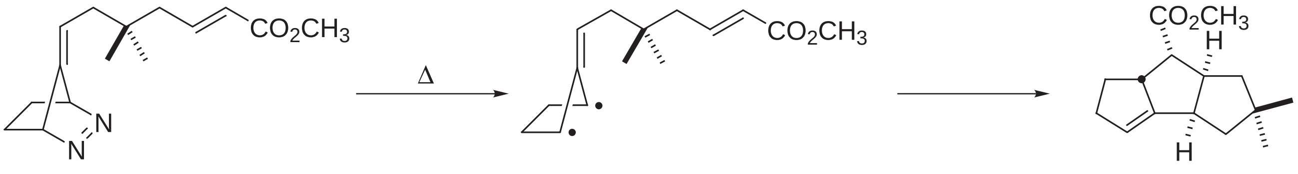
Tetrahedron Lett. **1998**, *39*, 2227.

h. Further Notable Examples



Biomimetic approach to PGG_2 and PGH_2

Corey *Tetrahedron Lett.* **1984**, *25*, 5013.
For a more successful alternative see
Corey *Tetrahedron Lett.* **1994**, *35*, 539.



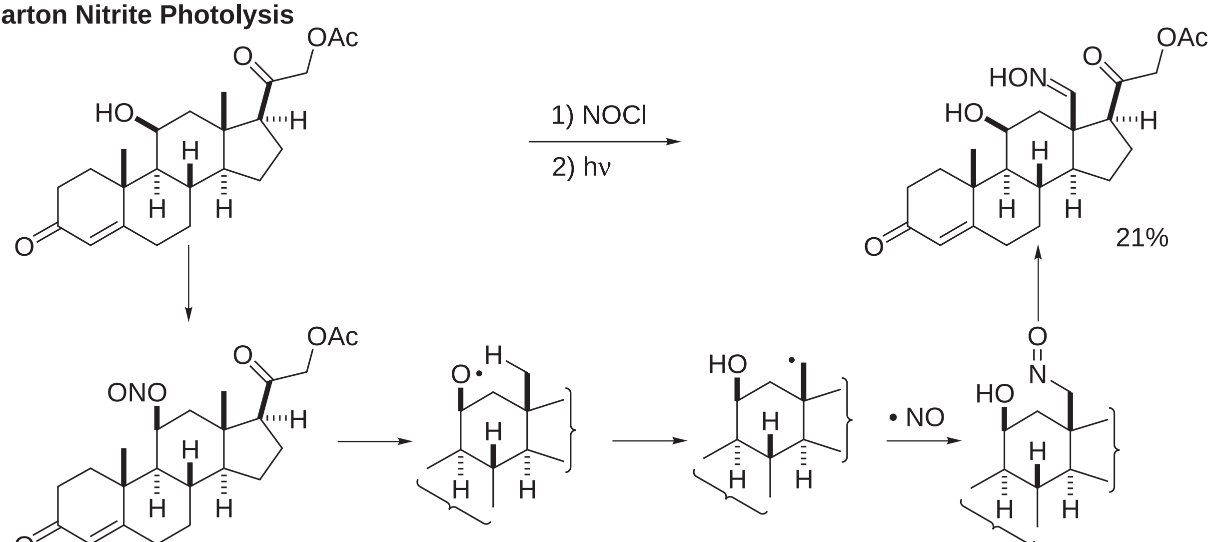
Hirsutene synthesis

diyl

Little *J. Am. Chem. Soc.* **1981**, *103*, 2744.

i. Selected Notable Free Radical Reactions

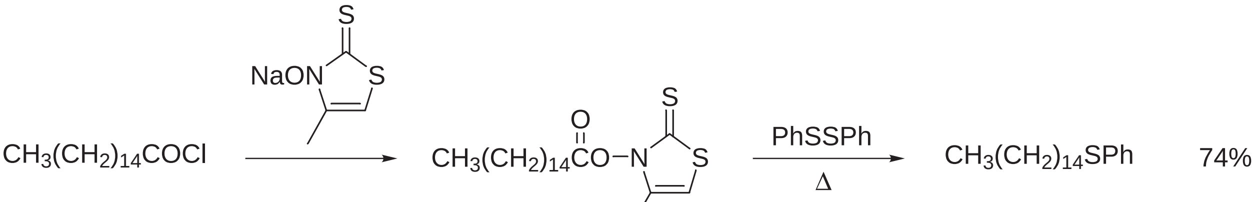
Barton Nitrite Photolysis



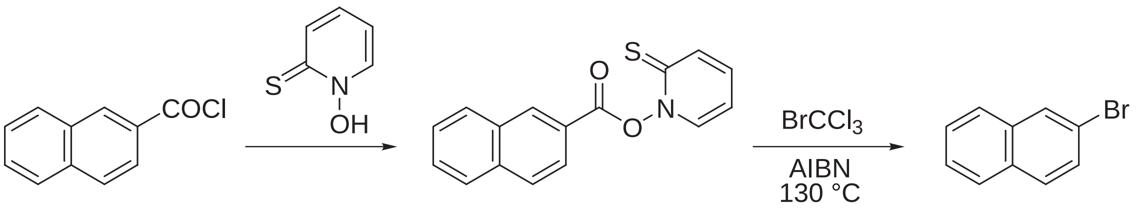
Barton *J. Am. Chem. Soc.* **1960**, *82*, 2640.

This process was used to produce 60 g of aldosterone at a time the world supply was in mg quantities. The aldosterone synthesis ("a good problem") was achieved in 1961 by J. M. Beaton ("a good experimentalist") through a nitrite photolysis ("a good idea"), quotes from D. H. R. Barton, 1991 ACS autobiography.

Barton Decarboxylation Barton *J. Chem. Soc., Chem. Commun.* **1983**, 939.



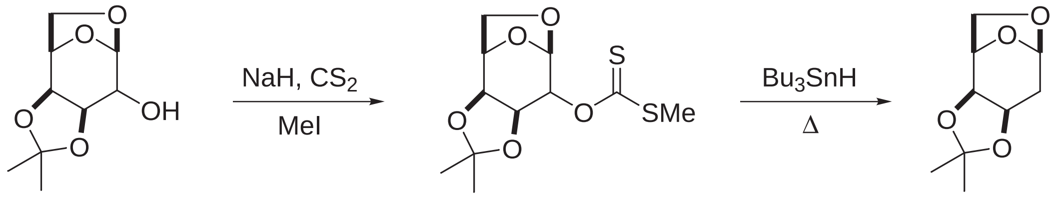
Barton *Tetrahedron Lett.* **1984**, *25*, 5777.



75%

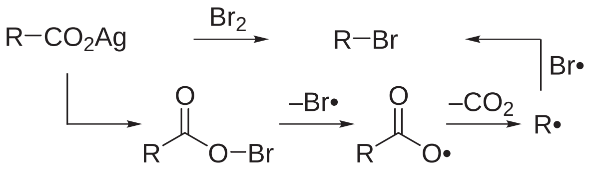
Barton *Tetrahedron Lett.* **1985**, *26*, 5939.

Barton–McCombie Deoxygenation



Barton, McCombie *J. Chem. Soc., Perkin 1* **1975**, 1574.

Hunsdiecker Reaction



Hunsdiecker, H.; Hunsdiecker, C. *Ber.* **1942**, *75*, 291.

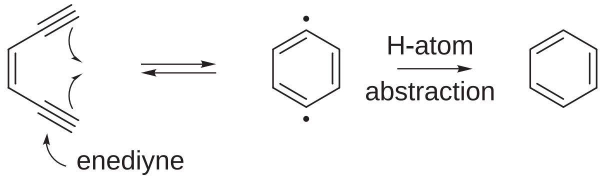
Wiberg *Acc. Chem. Res.* **1984**, *17*, 379.

Kochi Reaction

$$RCO_2H \xrightarrow[\text{LiCl}]{\text{Pb(OAc)}_4} RCl$$

Kochi *J. Org. Chem.* **1965**, *30*, 3265.
Org. React. **1972**, *19*, 279.

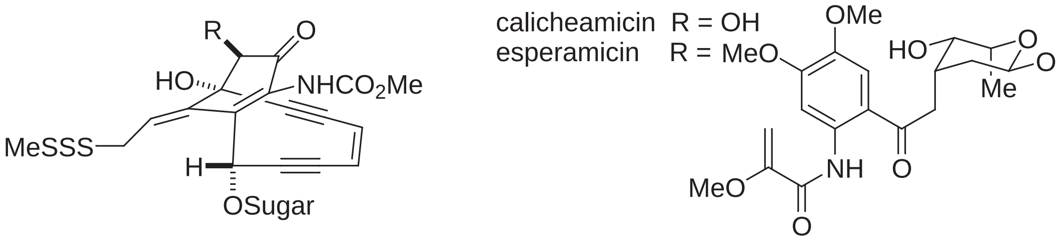
Bergman Cyclization

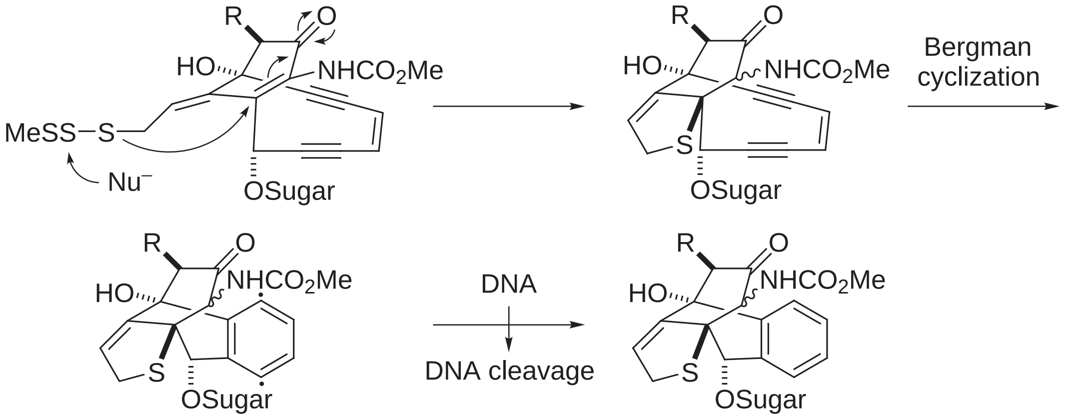


Bergman *J. Am. Chem. Soc.* **1972**, *94*, 660.
Acc. Chem. Res. **1973**, *6*, 25.

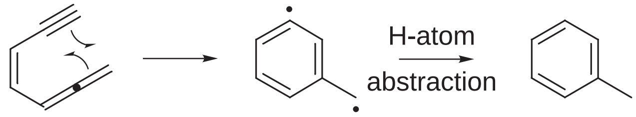
Calicheamicin and esperamicin derive their biological properties through DNA binding and trisulfide cleavage which initiates a reaction cascade which culminates in a Bergman cyclization which results in DNA H-atom abstraction and DNA cleavage.

Ellestad *J. Am. Chem. Soc.* **1987**, *109*, 3466.
Nicolaou *Angew. Chem., Int. Ed. Eng.* **1991**, *30*, 1387.



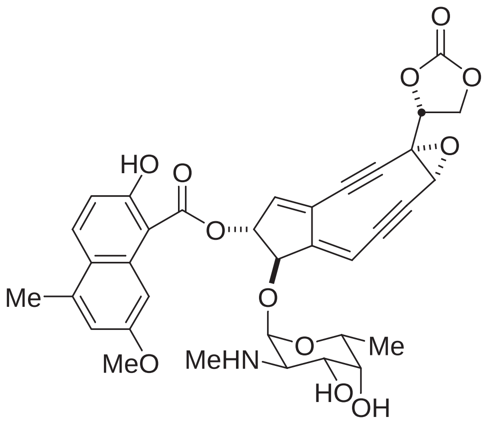


Myers Cyclization

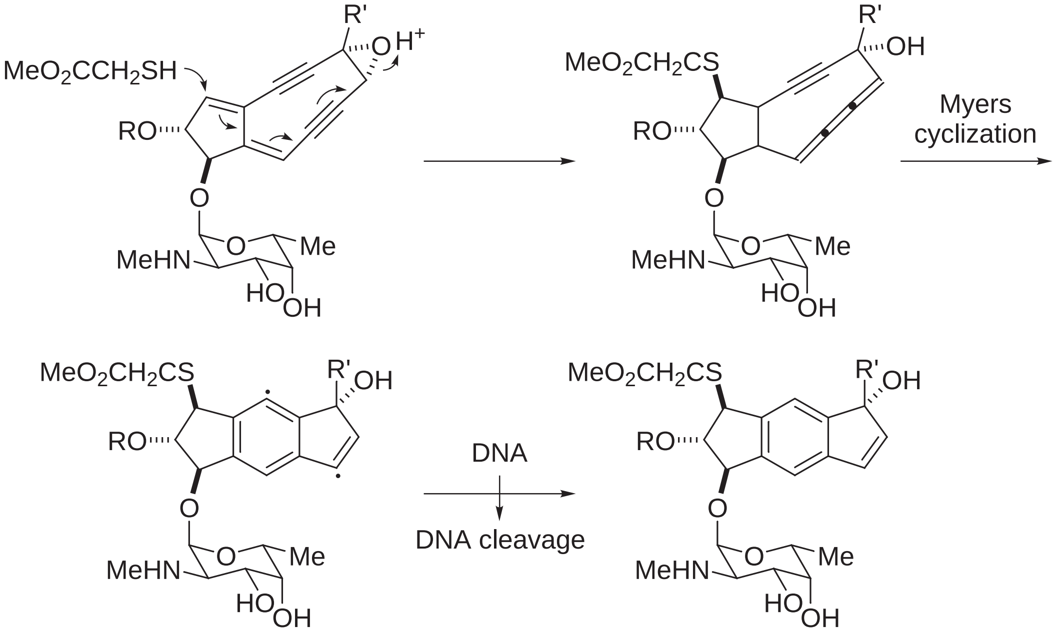


Myers *J. Am. Chem. Soc.* **1988**, *110*, 7212; **1992**, *114*, 9369.

Neocarzinostatin is activated for DNA cleavage by thiol addition generating the reactive enyne allene.



neocarzinostatin chromophore

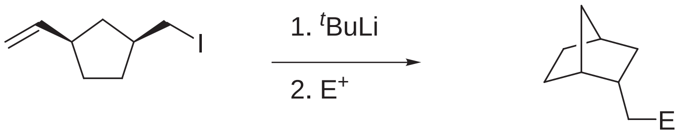


J. Anionic Cyclizations

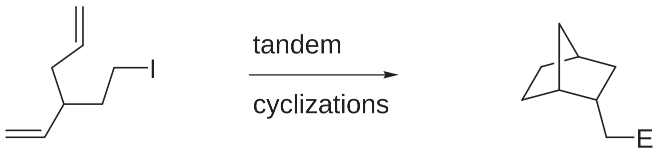
stable at –78 °C
$t_{1/2}$ = 5.5 min at 25 °C

Bailey *J. Am. Chem. Soc.* **1992**, *114*, 8053.
J. Am. Chem. Soc. **1991**, *113,* 5720.
J. Am. Chem. Soc. **1987**, *109*, 2442.

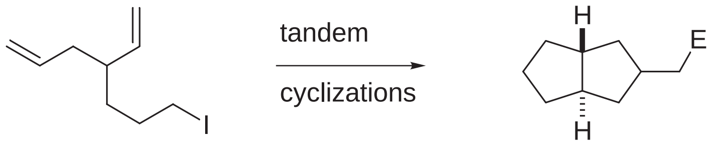
Intramolecular carbometalation, review:
Comprehensive Org. Syn., Vol. 4, 871.



63–91%

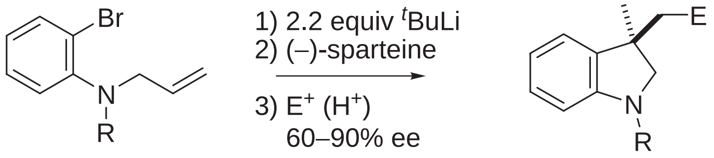


65–90%



65–87%

Stereochemistry and comparison with radical cyclizations: Cooke *J. Org. Chem.* **1992**, *57*, 1495.

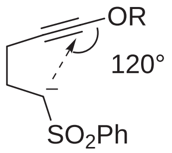


R = $CH_2CH{=}CH_2$
R = CH_3
R = Bn

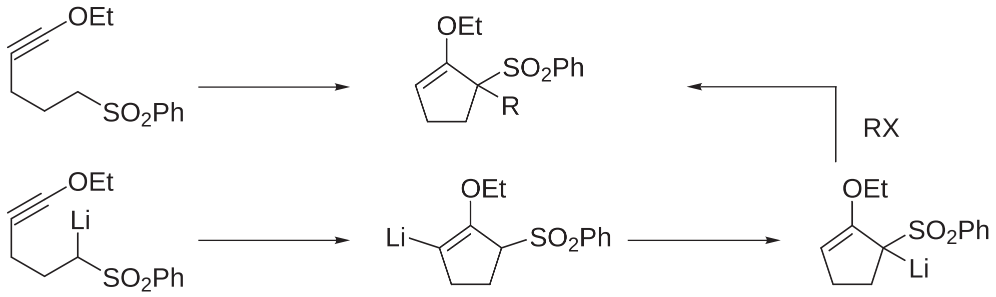
Bailey *J. Am. Chem. Soc.* **2000**, *122*, 6787.
Groth *J. Am. Chem. Soc.* **2000**, *122*, 6789.

Funk *J. Am. Chem. Soc.* **1993**, *115*, 7023.

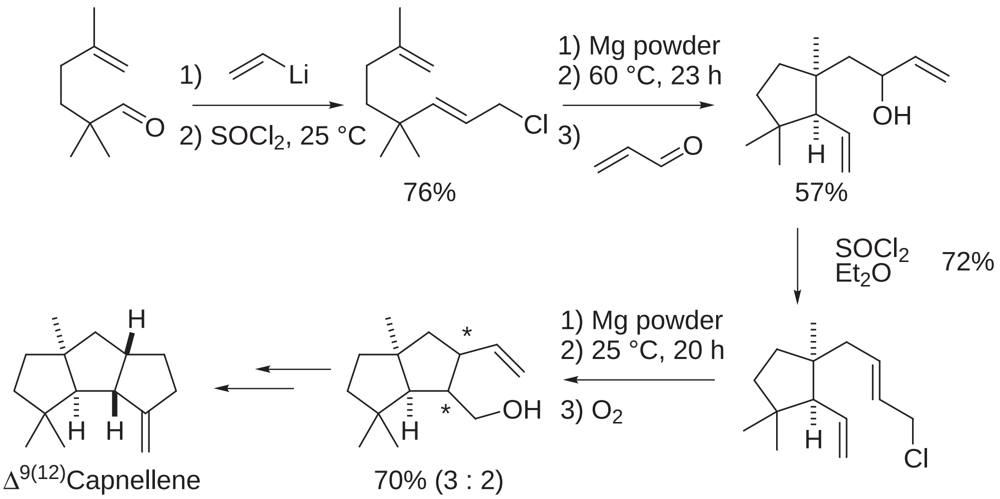
5-*endo-dig* cyclization



line of attack



Synthetic aspects of magnesium (Grignard) carbometalation have been studied in detail.
For a review see: Oppolzer *Angew. Chem., Int. Ed. Eng.* **1989**, *28*, 38.



Oppolzer *Tetrahedron Lett.* **1982**, *23*, 4669.

K. 1,3-Dipolar Cycloadditions

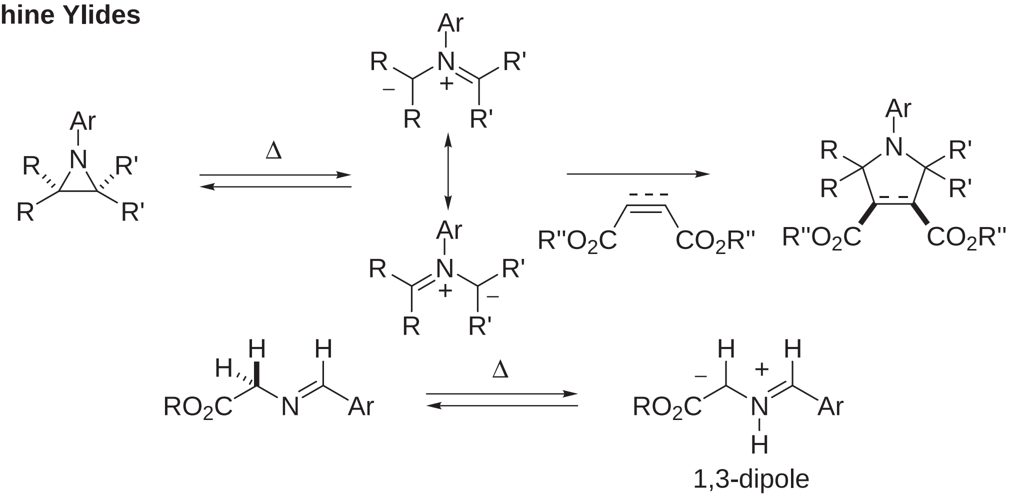
Review: *1,3-Dipolar Cycloaddition Chemistry*, Padwa, A., Ed., Wiley: New York, 1984.

- $2\pi^s + 4\pi^s$ Cycloaddition
- Subject to FMO control: can predict regioselectivity and reactivity.

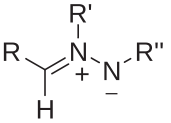
- FMO Control:

(a) Reactivity: ΔE (HOMO/LUMO) and the reactivity of the system is related to the magnitude of the smallest energy gap of the pair of HOMO–LUMO combinations.
(b) Regioselectivity: depends on the magnitude of the orbital coefficients and is determined by the orbital coefficients on the predominant HOMO–LUMO interaction. The largest coefficient on the 1,3-dipole binds to the largest coefficient on the dipolarophile.
(c) Diastereoselectivity: influenced by stabilizing secondary orbital interactions and subject to an *endo* effect.
(d) Olefin geometry is maintained in the course of the cycloaddition reaction, they are concerted reactions.
(e) No solvent effect on the reaction rate: concerted reactions.
(f) No rearrangement products from postulated zwitterion or biradical.
(g) *Trans*-1,2-disubstituted olefins react faster than *cis*-1,2-disubstituted olefins. *Cis* olefins are generally more reactive than *trans* olefins in ionic or radical addition reactions.

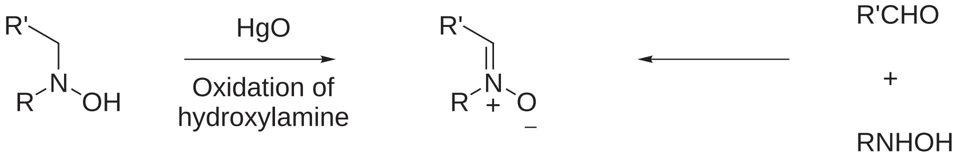
1. Azomethine Ylides



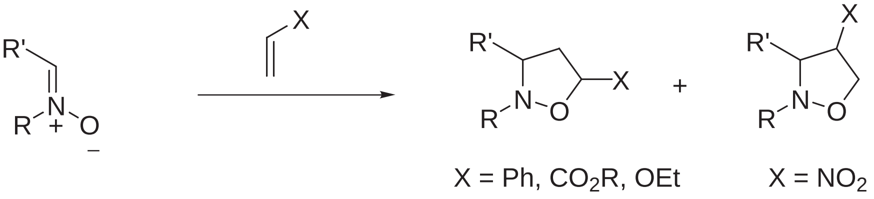
2. Azomethine Imines



3. Nitrones

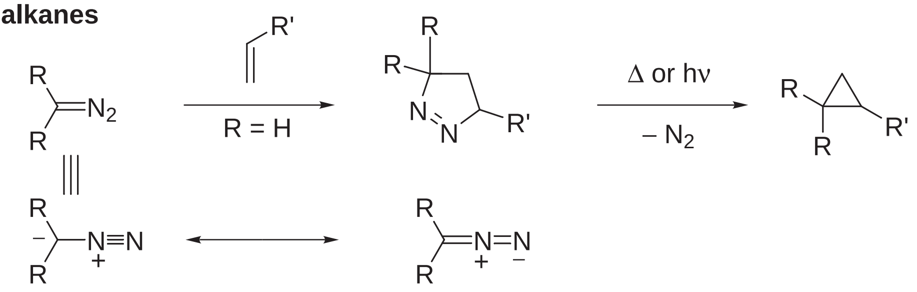


- Symmetrical precursor or a precusor with one adjacent oxidizable center.

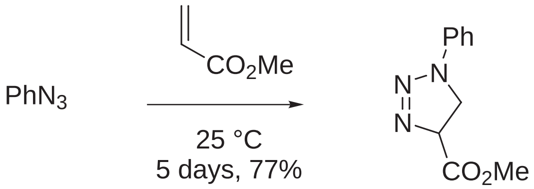


- The regioselectivity depends on X and the substitution pattern of the nitrone.
- Review: Confalone *Org. React.* **1988**, *36*, 1.

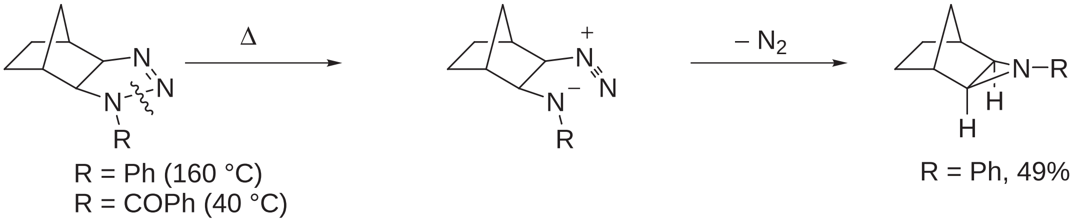
4. Diazoalkanes

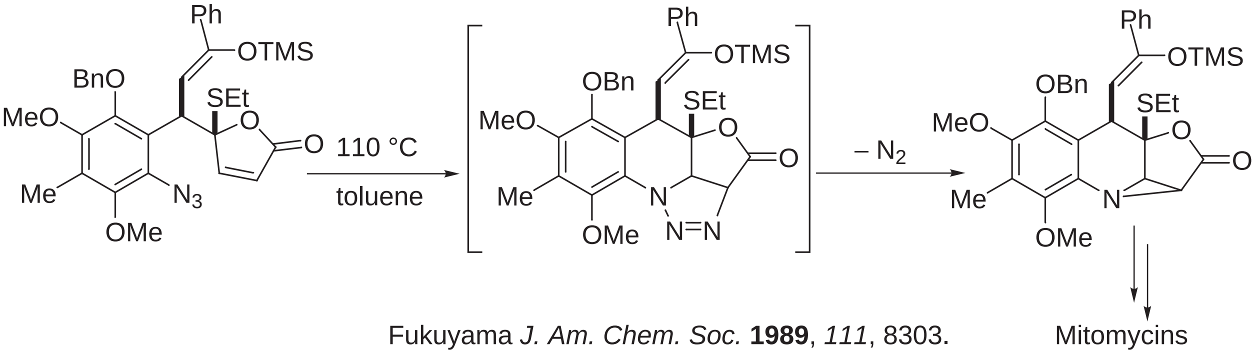


5. Azides



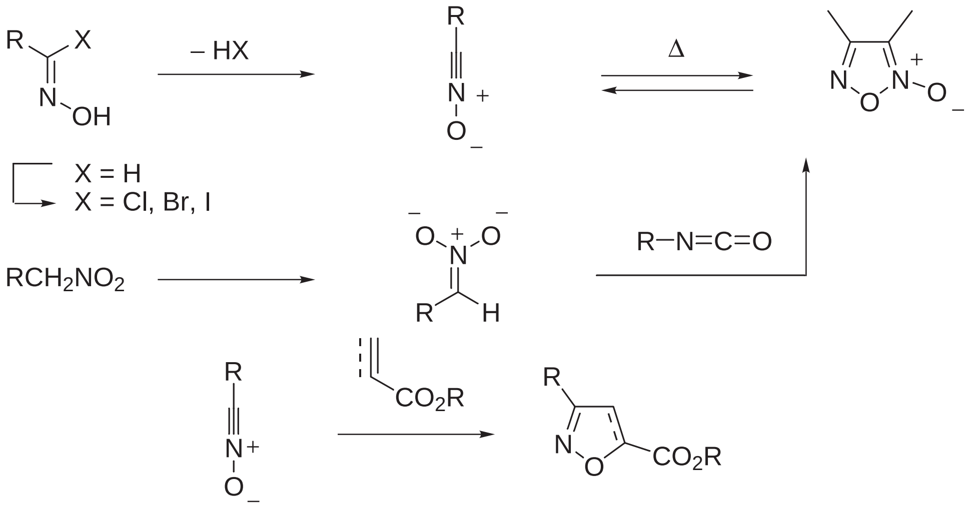
$$PhN_3 \equiv Ph-\overset{-}{N}-\overset{+}{N}\equiv N \longleftrightarrow Ph-N=\overset{+}{N}=\overset{-}{N}$$



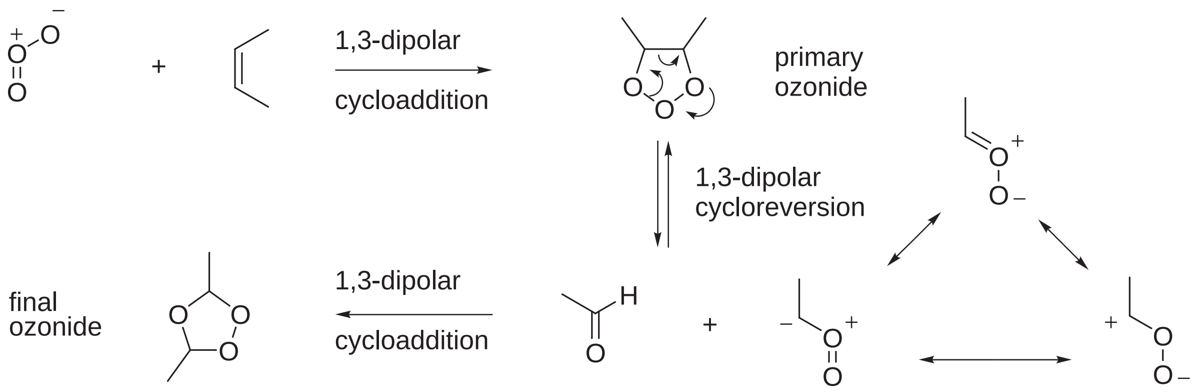


Fukuyama *J. Am. Chem. Soc.* **1989**, *111*, 8303.

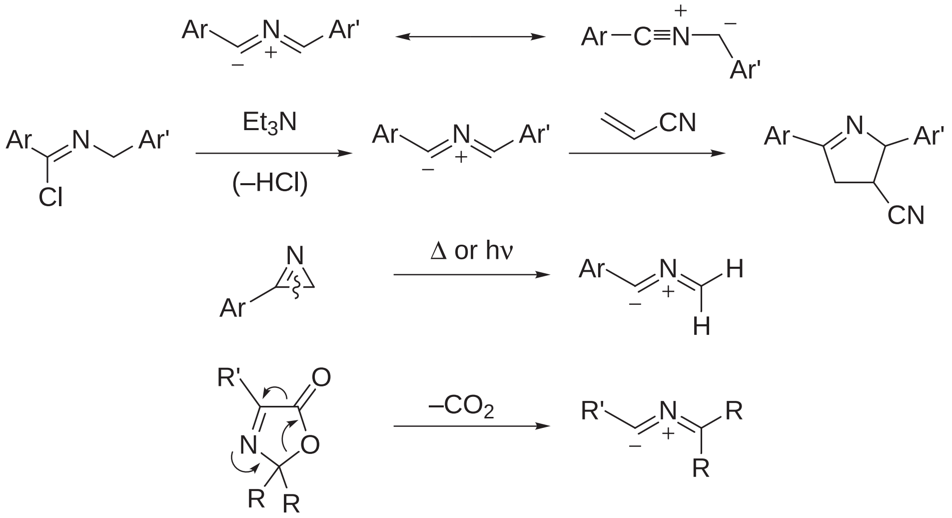
6. Nitrile Oxides



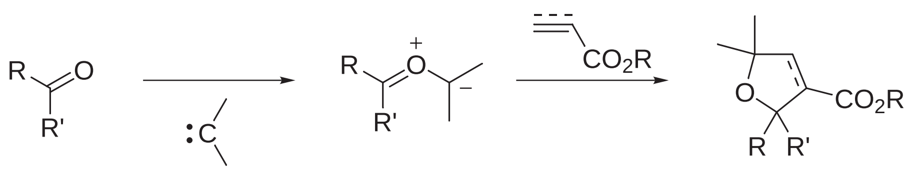
7. O_3 / Carbonyl Oxides



8. Nitrile Ylides

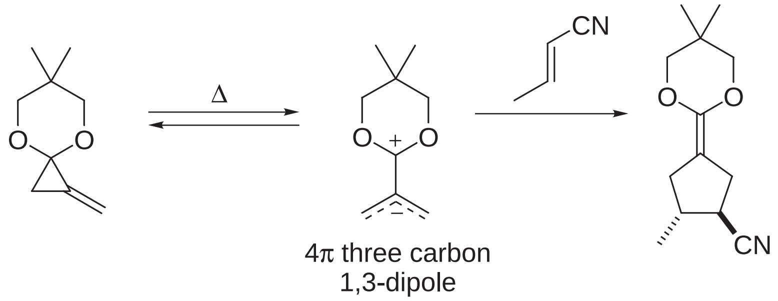


9. Carbonyl Ylides



- problem: collapse of the carbonyl ylide to the epoxide

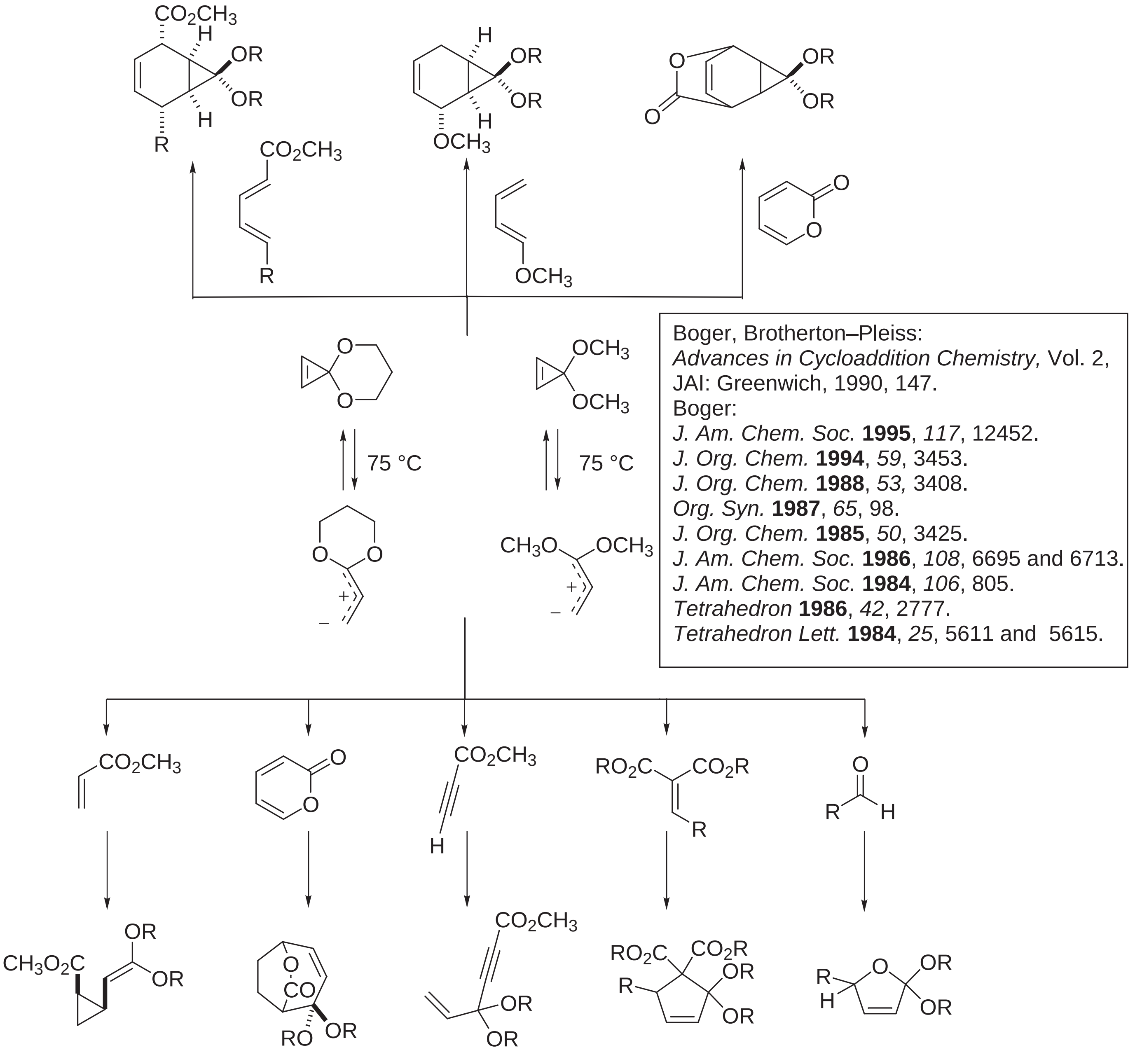
10. Methylene Cyclopropanone Ketals



Nakamura *J. Am. Chem. Soc.* **1989**, *111*, 7285.
J. Am. Chem. Soc. **1991**, *113*, 3183.

Key: reversible ring opening generation of the 4π component

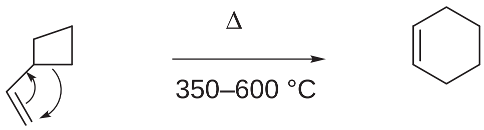
11. Cyclopropenone Ketal (CPK) Diels–Alder/Dipolar Cycloadditions



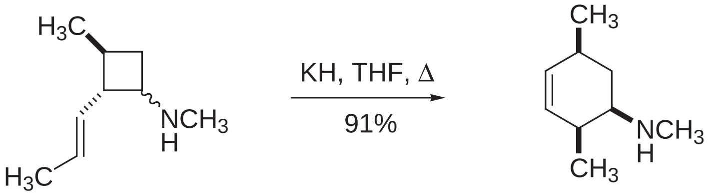
Boger, Brotherton–Pleiss:
Advances in Cycloaddition Chemistry, Vol. 2, JAI: Greenwich, 1990, 147.
Boger:
J. Am. Chem. Soc. **1995**, *117*, 12452.
J. Org. Chem. **1994**, *59*, 3453.
J. Org. Chem. **1988**, *53,* 3408.
Org. Syn. **1987**, *65*, 98.
J. Org. Chem. **1985**, *50*, 3425.
J. Am. Chem. Soc. **1986**, *108*, 6695 and 6713.
J. Am. Chem. Soc. **1984**, *106*, 805.
Tetrahedron **1986**, *42*, 2777.
Tetrahedron Lett. **1984**, *25*, 5611 and 5615.

L. 1,3-Sigmatropic Rearrangement

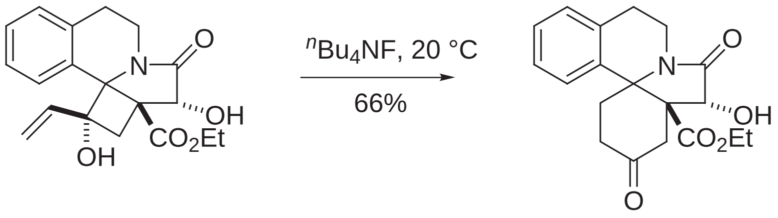
1. Vinylcyclobutane rearrangement



Overberger *J. Am. Chem. Soc* **1960**, *82*, 1007.



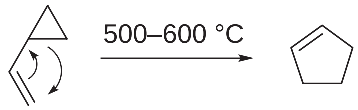
Bauld *J. Am. Chem. Soc.* **1988**, *110*, 8111.



Sano *Chem. Pharm. Bull.* **1992**, *40*, 873.

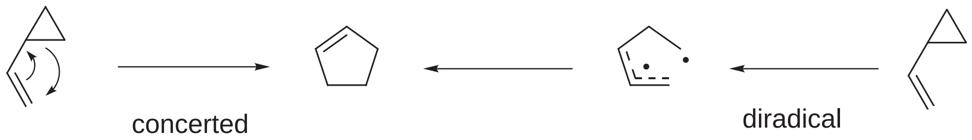
2. Vinylcyclopropane rearrangement

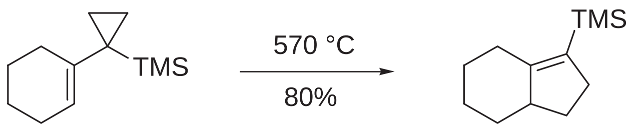
First report: Neureiter *J. Org. Chem.* **1959**, *24*, 2044.
Review: Hudlicky *Chem. Rev.* **1989**, *89*, 165.



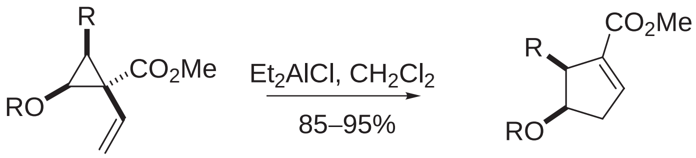
Org. React. **1985** *33*, 247.

Mechanism:

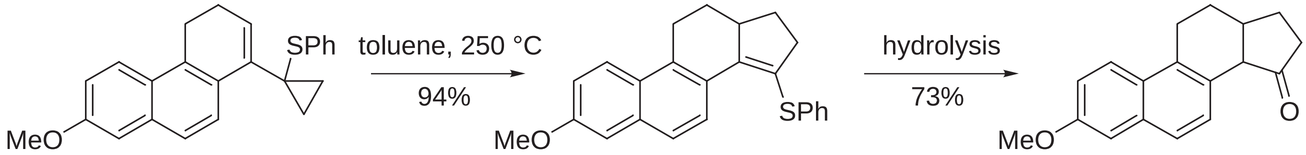




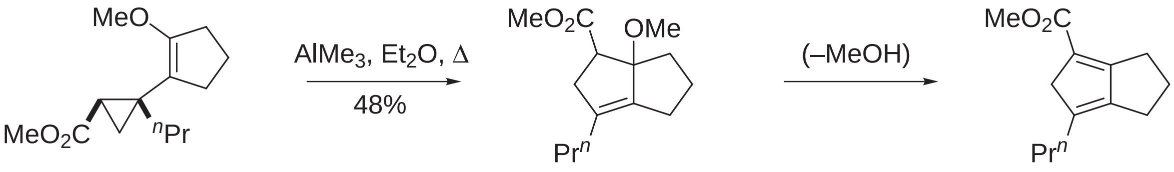
Paquette *Tetrahedron Lett.* **1982**, *23*, 263.



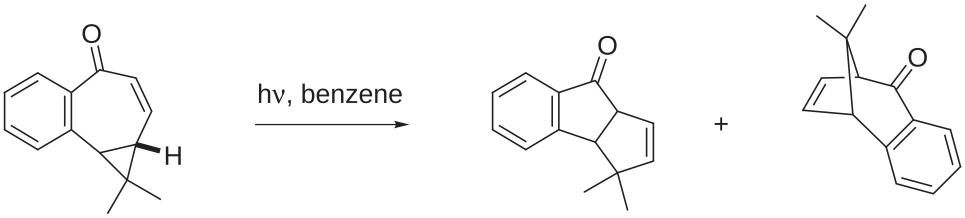
Davies *Tetrahedron Lett.* **1992**, *33*, 453.



Trost *J. Am. Chem. Soc.* **1976**, *98*, 248.

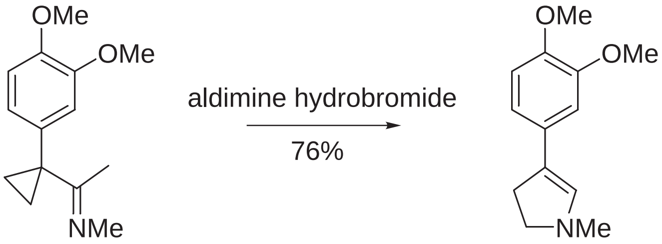


Harvey *Tetrahedron Lett.* **1991**, *32*, 2871.

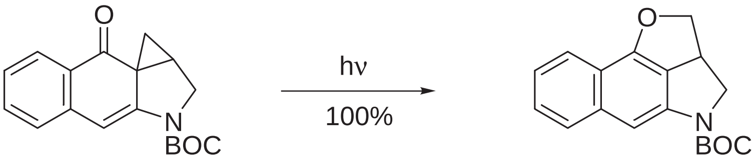


Wood, Smith *J. Am. Chem. Soc.* **1992**, *114*, 10075.

3. Carbonyl/Imine cyclopropane rearrangement

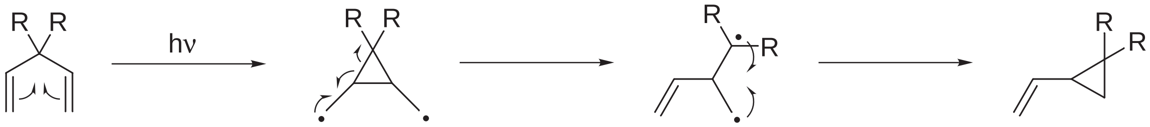


Stevens *J. Am. Chem. Soc.* **1968**, *90*, 5580.



Boger, Garbaccio *J. Org. Chem.* **1997**, *62*, 8875.

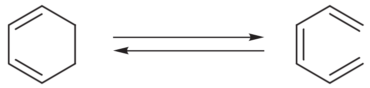
Note: The di-π-methane rearrangement produces substrates that may be used in the vinylcyclopropane rearrangement.

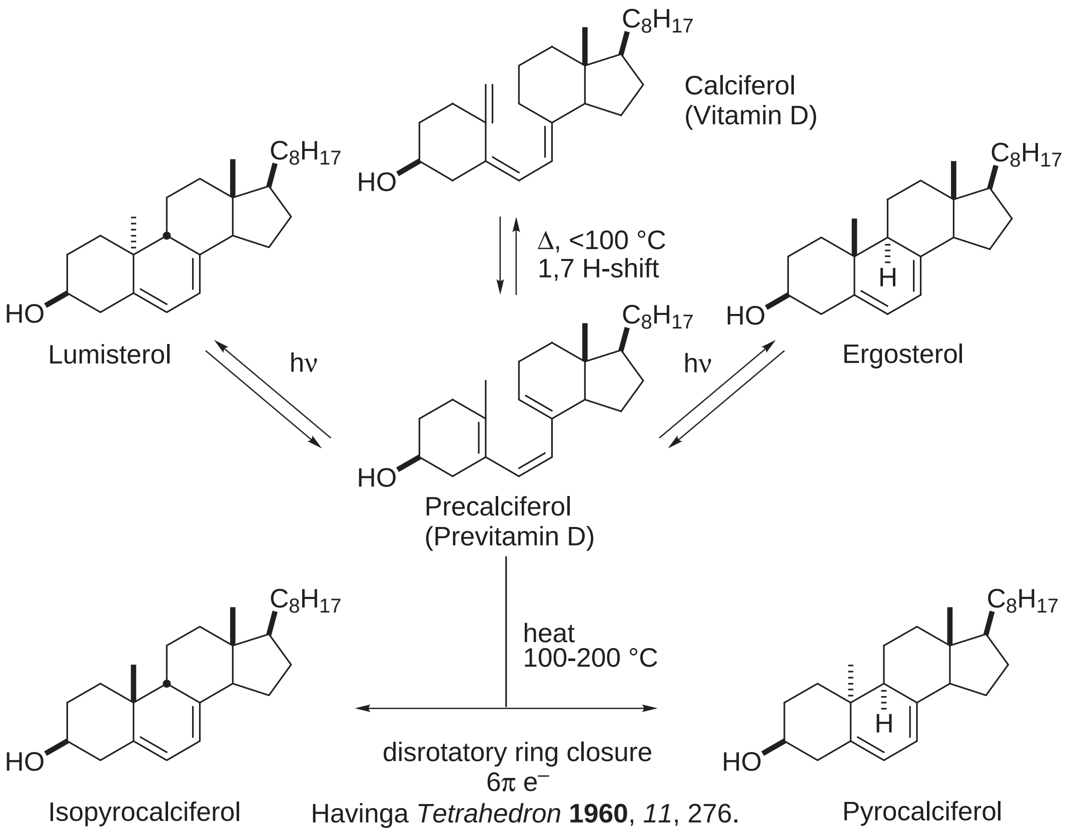


Zimmerman, Grunewald *J. Am. Chem. Soc.* **1966**, *88*, 183.
Zimmerman *Chem. Rev.* **1973**, *73*, 531; **1996**, *96*, 3065.

M. Electrocyclic Reactions

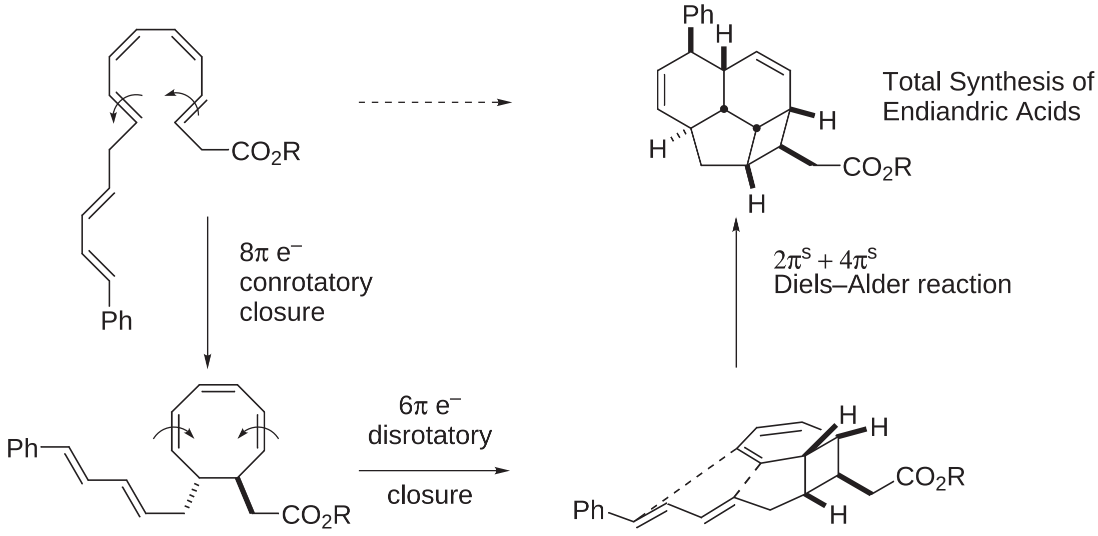
Comprehensive Org. Syn., Vol. 5, 699.





Havinga *Tetrahedron* **1960**, *11*, 276.
Tetrahedron **1961**, *12*, 146.

Provided the impetus for the Woodward–Hoffmann rules

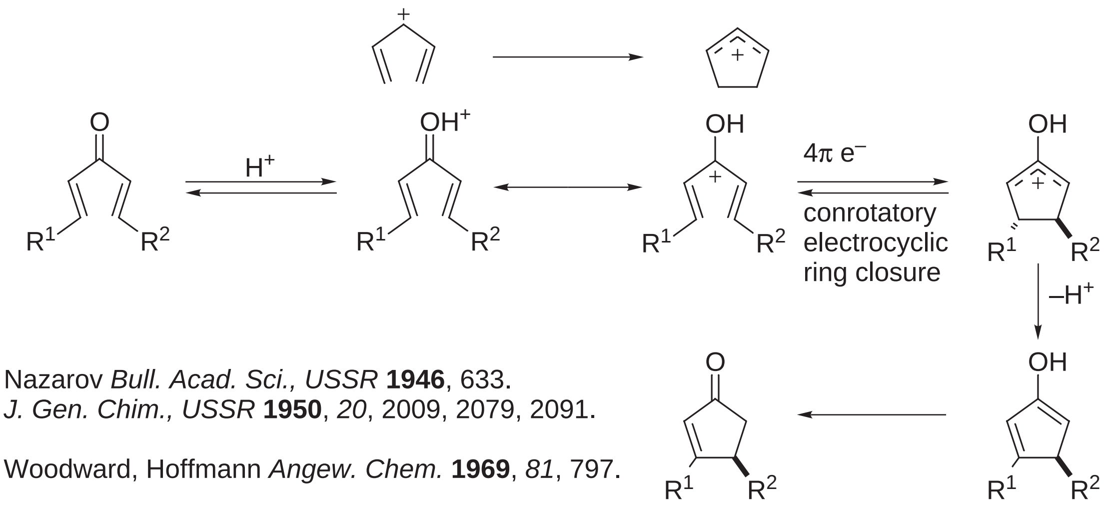


Nicolaou *J. Am. Chem. Soc.* **1982**, *104*, 5555, 5557, 5558 and 5560.

N. Nazarov Cyclization

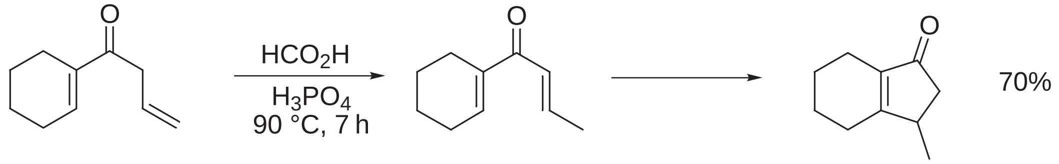
4π e⁻ Conrotatory electrocyclic ring closure

Review: Santelli–Rouvier, C.; Santelli, M. *Synthesis* **1983**, 4295.
Nazarov *Usp. Khim.* **1949**, *18*, 377.; *Usp. Khim.* **1951**, *20*, 71.
Denmark *Org. React.* **1994**, *45*, 1–158.
Denmark *Comprehensive Org. Syn.,* Vol. 5, pp 751–784.

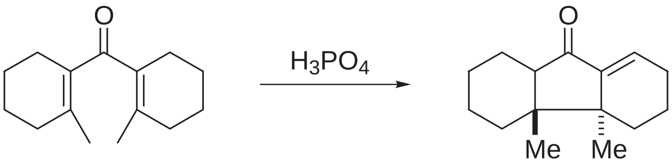


Nazarov *Bull. Acad. Sci., USSR* **1946**, 633.
J. Gen. Chim., USSR **1950**, *20*, 2009, 2079, 2091.

Woodward, Hoffmann *Angew. Chem.* **1969**, *81*, 797.

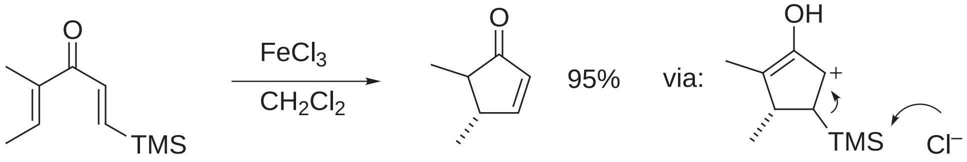


Nazarov *Chem. Abstr.* **1948**, *42*, 7731a, 7731h, 7732g, 7733e, 7734a, 7734.



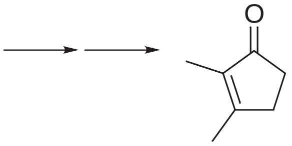
Braude *J. Chem. Soc.* **1953**, 2202.

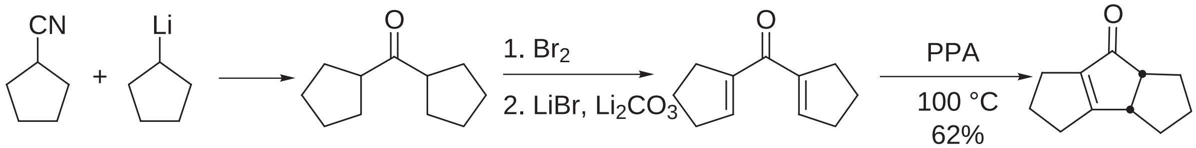
- Silicon-directed Nazarov cyclization.



Denmark *J. Am. Chem. Soc.* **1982**, *104*, 2642.

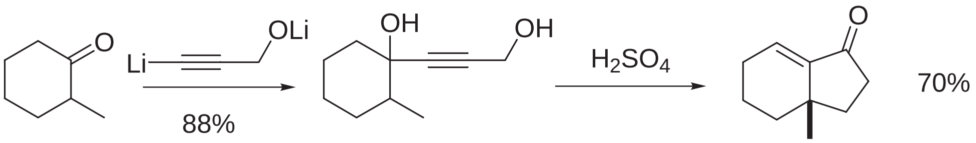
under usual Nazarov conditions: isomerization to





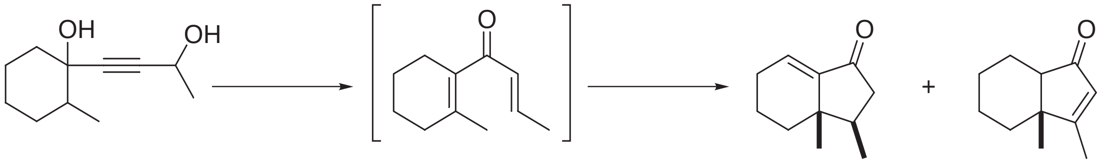
Eaton *J. Org. Chem.* **1976**, *41*, 2238.

- Extensions to annulation procedures.



Raphael *J. Chem. Soc.* **1953**, 2247.
J. Chem. Soc., Perkin Trans. 1 **1976**, 410.

- Stereochemical course of the reaction: via Nazarov cyclization.



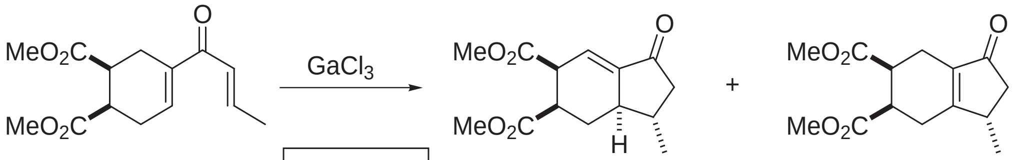
conrotatory 4π e⁻ electrocyclization

67%

10%

Hiyama *J. Am. Chem. Soc.* **1979**, *101*, 1599.
Bull. Chem. Soc. Jpn. **1981**, *54*, 2747.

- Lewis acid-catalyzed reactions.



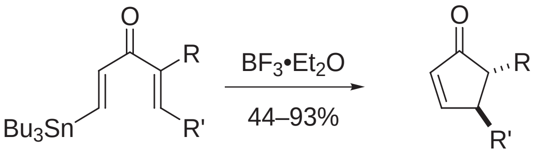
Also: $FeCl_3$
BF_3•Et_2O

49%

40%

Tsuge *Bull. Chem. Soc. Jpn.* **1987**, *60*, 325.

- Tin-directed Nazarov cyclization.



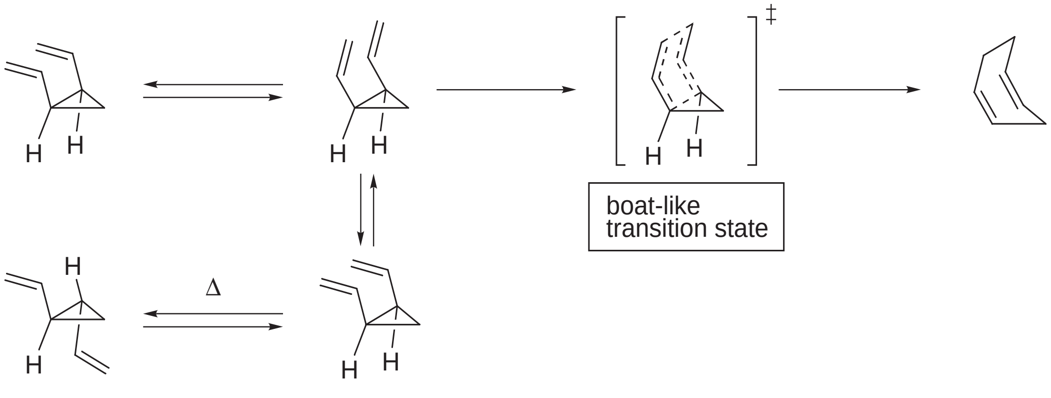
Johnson *Tetrahedron Lett.* **1986**, *27*, 5947.

O. Divinylcyclopropane Rearrangement

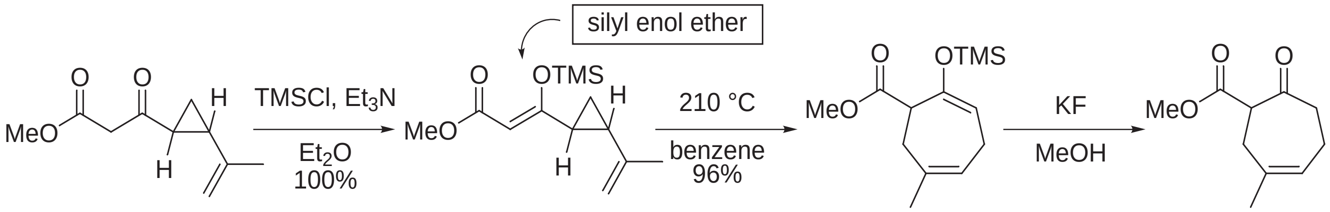
Comprehensive Org. Syn., Vol. 5, 971.
Org. React. **1992**, *41*, 1.

$(2\sigma^s + 2\pi^s + 2\pi^s)$

- Mechanism:

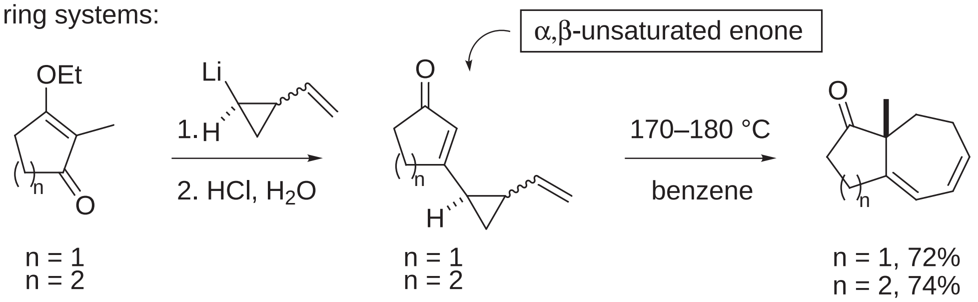


- Synthesis of functionalized 7-membered rings:



Marino *J. Org. Chem.* **1981**, *46*, 1912.

- Fused ring systems:

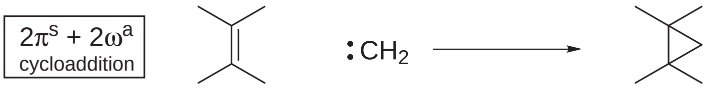


Wender *J. Org. Chem.* **1976**, *41,* 3490.

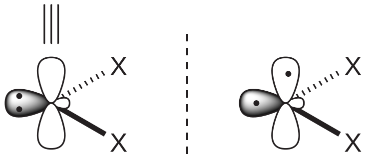
P. Carbene Cycloaddition to Alkenes

1. Halocabenes

Parman, Schweizer *Org. React.* **1963**, *13*, 55.
Moss *Acc. Chem. Res.* **1989**, *22*, 15.
Acc. Chem. Res. **1980**, *13,* 58.
Kostikov, Molchanov, Khlebnikov *Russ. Chem. Rev.* **1989**, *58*, 654.



Addition of a singlet carbene proceeds by a concerted process in a *syn* fashion.



Triplet carbene behaves as a diradical.

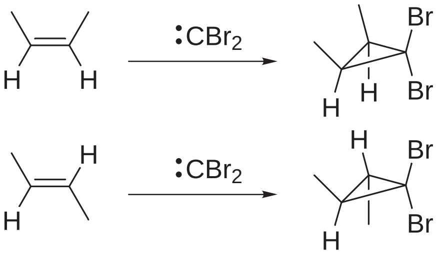
- Methods for generating halocarbenes:

For a comprehensive list see: Kirmse *Carbene Chemistry,* 1971, 313.

$$\mathrm{CHCl_3 + KO^{\mathit{t}}Bu \longrightarrow :CCl_2}$$
$$\mathrm{BrCCl_3 + {}^{\mathit{n}}BuLi \longrightarrow :CCl_2}$$
$$\mathrm{CH_2Cl_2 + RLi \longrightarrow :CHCl}$$
$$\mathrm{N_2CHBr \longrightarrow :CHBr}$$
$$\mathrm{Cl_3CO_2R + RO^- \longrightarrow :CCl_2}$$
$$\mathrm{PhHgCCl_2Br \xrightarrow{\Delta} :CCl_2}$$

reactivity of carbenes
$CH_2 > CHCl > CCl_2 > CBr_2 > CF_2$

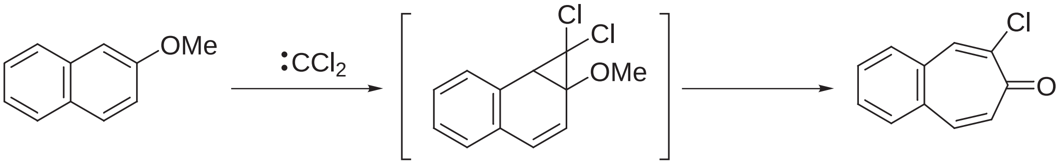
- Reaction with alkenes:



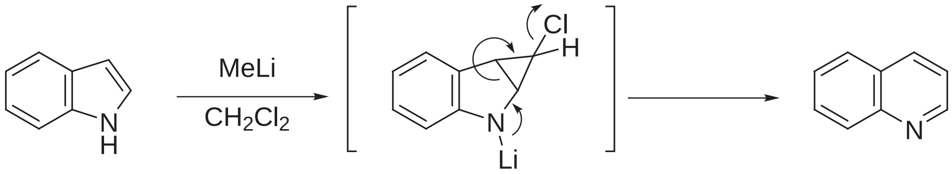
Stereospecific

Doering *J. Am. Chem. Soc.* **1956**, *78*, 5447.

- Reaction with aromatic C=C bonds (cyclopropanation followed by rearrangement):



Parman, Schweizer *J. Am. Chem. Soc.* **1961**, *83*, 603.

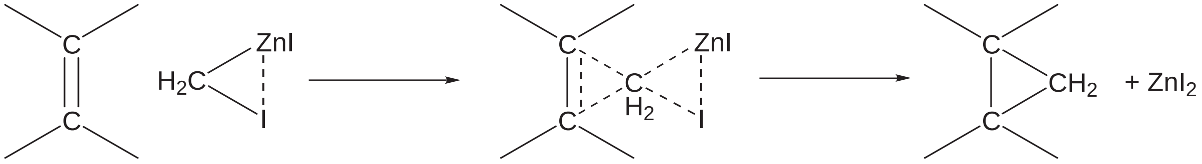


Closs, Schwartz *J. Org. Chem.* **1961**, *26*, 2609.

2. Simmons–Smith Reaction

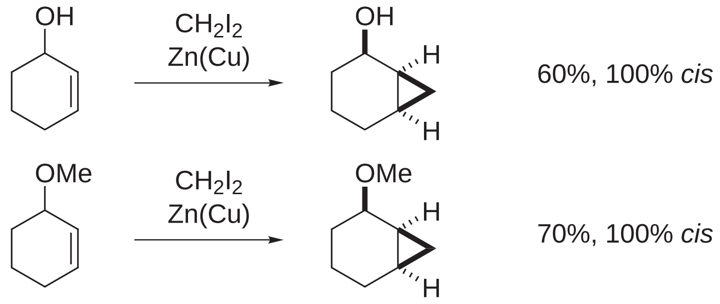
Simmons *Org. React.* **1973**, *20*, 1.
Simmons, Smith *J. Am. Chem. Soc.* **1958**, *80,* 5323; **1959**, *81*, 4256.

- Mechanism:



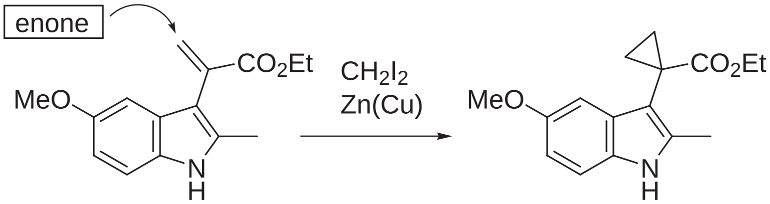
1) concerted mechanism likely (above)
2) reaction is stereospecifically *syn*
3) alkenes with higher alkyl substitution react faster
4) electron donating substituents accelerate reaction
i.e., enol ethers, enamines...

- Addition can be directed by a hydroxyl group or ether functionality:

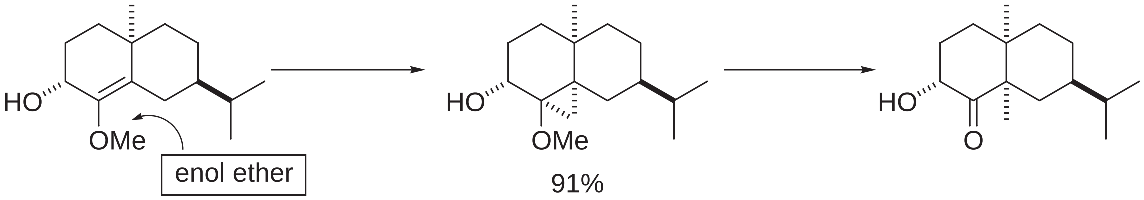


Rickborn *J. Am. Chem. Soc.* **1968**, *90*, 6406.
J. Org. Chem. **1972**, *37*, 738.

- Examples:



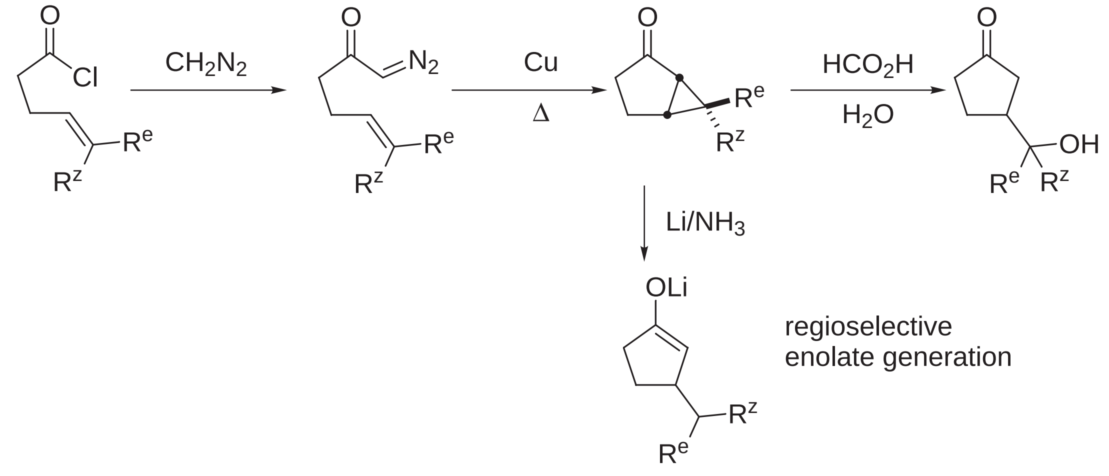
Shen *Chem. Abstr.* **1967**, *67*, 108559m.

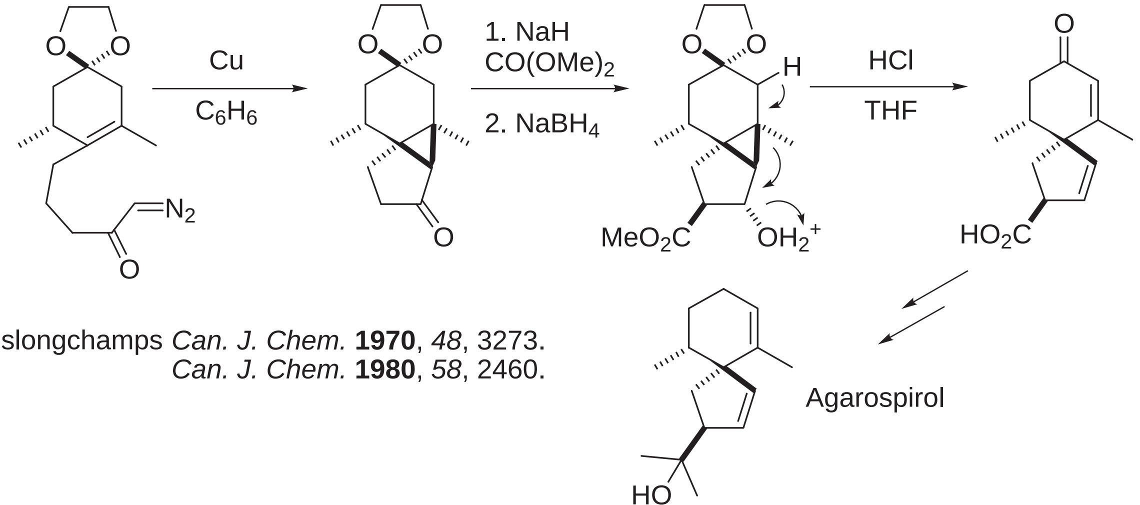


Wenkert, Berges *J. Am. Chem. Soc.* **1967**, *89*, 2507.

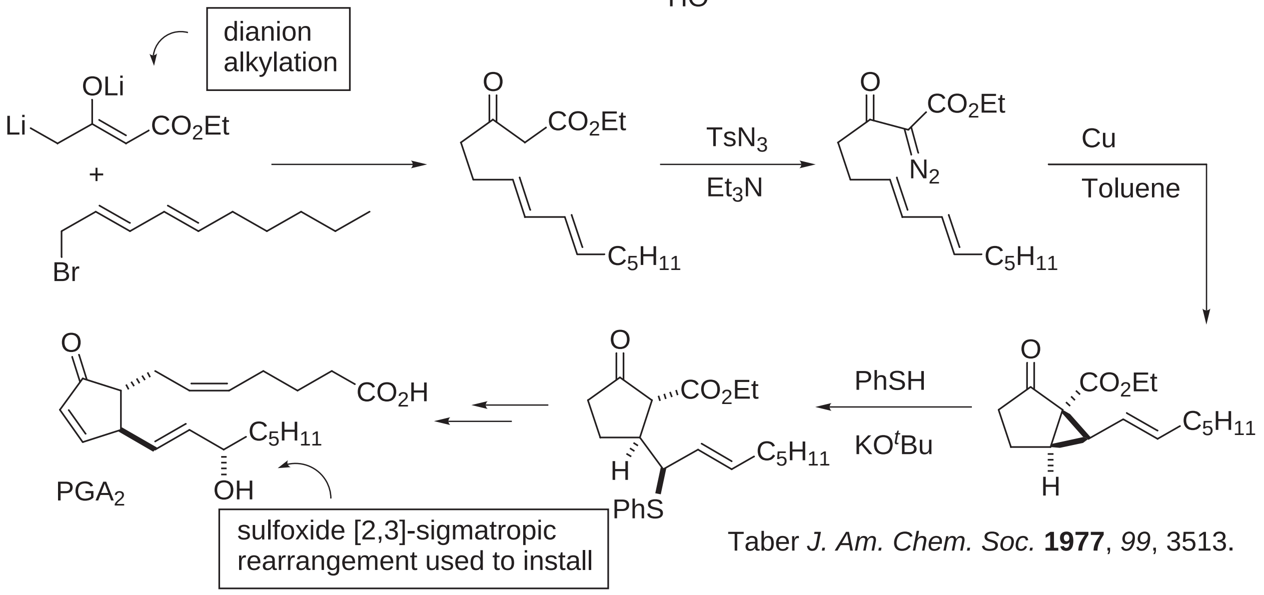
3. Diazocarbene Addition and Rearrangement

Review: Burke and Grieco *Org. React.* **1979**, *26*, 361.





Deslongchamps *Can. J. Chem.* **1970**, *48*, 3273.
Can. J. Chem. **1980**, *58*, 2460.



Taber *J. Am. Chem. Soc.* **1977**, *99*, 3513.

4. Metal Carbene Cycloaddition Reactions

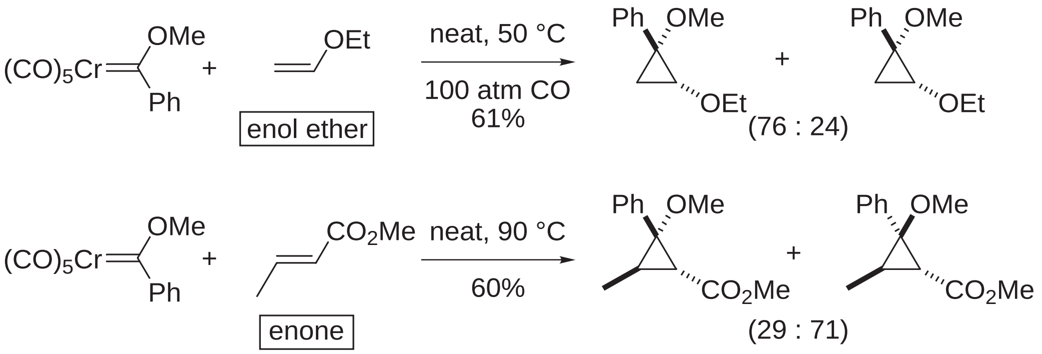
Comprehensive Org. Syn., Vol. 5, 1065.

E. O. Fischer received the 1973 Nobel Prize in Chemistry for his work in organometallic chemistry with transition metal complexes including metallocenes and his stabilized carbene complexes.

- Three-membered ring [2 + 1]

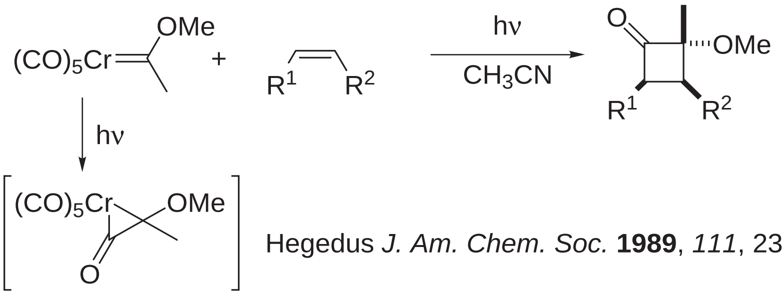
Bookhart, Studabaker *Chem. Rev.* **1987**, *87*, 411.
Doyle *Chem. Rev.* **1986**, *86*, 919.

Reaction works well for electron-rich, electron-poor and unactivated C=C bonds.



Fischer, Dötz *Chem. Ber.* **1972**, *105*, 3966.
Chem. Ber. **1972**, *105*, 1356.

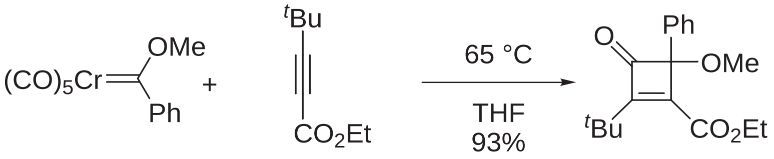
- Four-membered rings [2 + 1 + 1]



R^1 = H, R^2 = OEt, 85%
R^1 = R^2 = Me, 61%
R^1 = H, R^2 = Ph, 30%

Hegedus *J. Am. Chem. Soc.* **1989**, *111*, 2335.

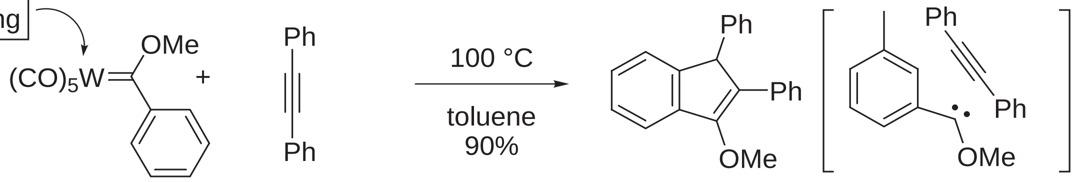
- Fischer carbene addition to alkynes typically leads to 6-membered ring , 4- and 5-membered rings form only under special circumstances.



4-membered ring formation is a result of the large ^{t}butyl group.

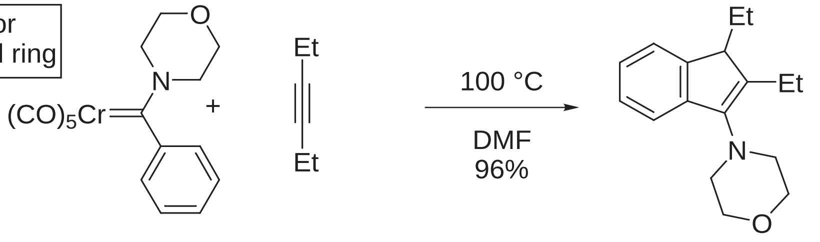
Yamashita *Tetrahedron Lett.* **1986**, *27*, 3471.

Cr leads to 6-membered ring



Foly *J. Am. Chem. Soc.* **1983**, *105*, 3064.

N required for 5-membered ring

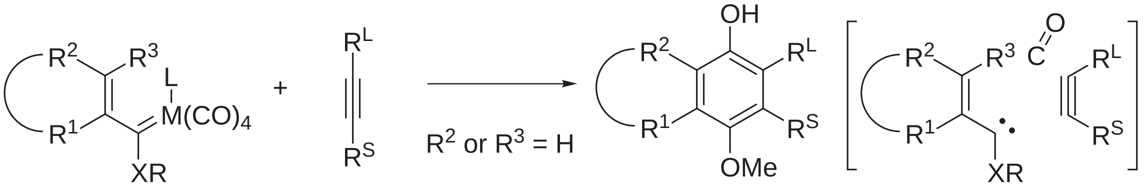


Yamashita *Tetrahedron Lett.* **1986**, *27*, 5915.

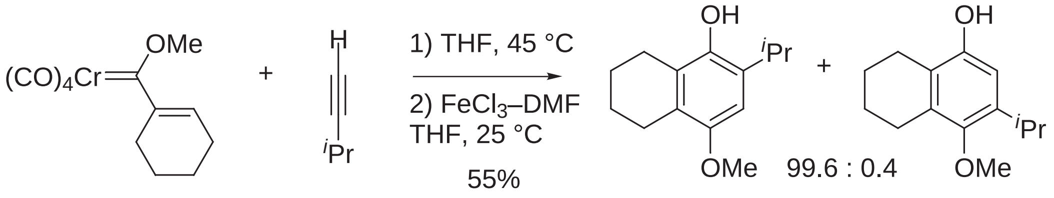
- Six-membered rings [3 + 2 + 1] (Fischer carbene addition to alkynes)

  Dötz, Fischer *Transition Metal Carbene Complexes*, VCH: Deerfield Beach, FL, 1983.
  Dötz *Angew. Chem., Int. Ed. Eng.* **1984**, *23*, 587.
  Casey in *Transition Metal Organometallics in Organic Synthesis*, Academic Press: New York, 1976, Vol. 1.
  Dötz *Pure Appl. Chem.* **1983**, *55*, 1689.
  Casey in *Reactive Intermediates*, Wiley Interscience: New York, 1982, Vol. 2, and 1985, Vol. 3.
  Hegedus *Principles and Applications of Organotransition Metal Chemistry*, University Science Books: Mill Valley, CA, 1987, 783.
  Brown *Prog. Inorg. Chem.* **1980**, *27*, 1.
  Wulff in *Advances in Metal-Organic Chemistry*, JAI Press: Greenwich, CT, 1989, Vol. 1.

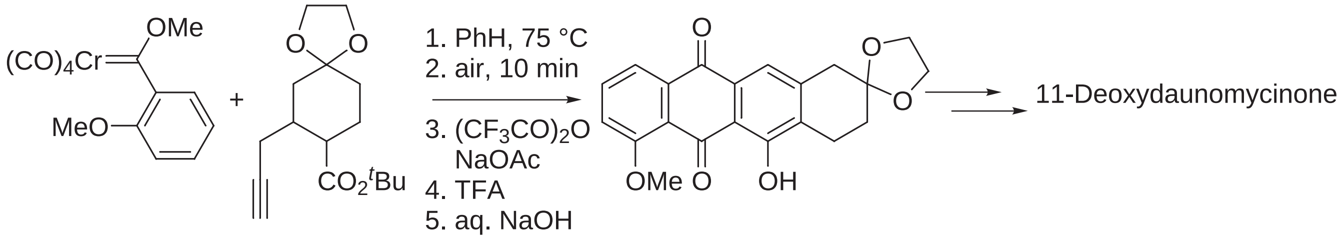
- General scheme



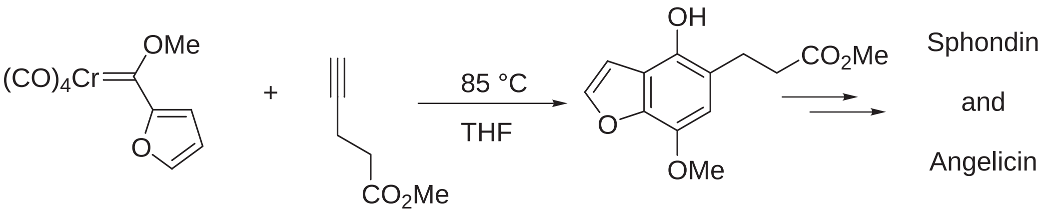
- Most widely studied after cyclopropanation of Fischer carbenes. Extensively applied in natural product synthesis. Examples:



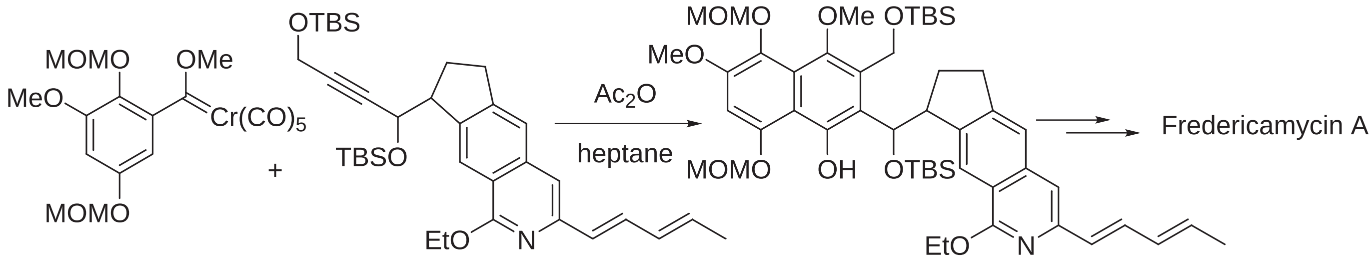
Wulff in *Advances in Metal-Organic Chemistry*, JAI Press: Greenwich, CT, 1989, Vol. 1.



Wulff *Tetrahedron* **1985**, *41*, 5797.



Wulff *J. Am. Chem. Soc.* **1988**, *110*, 7419.



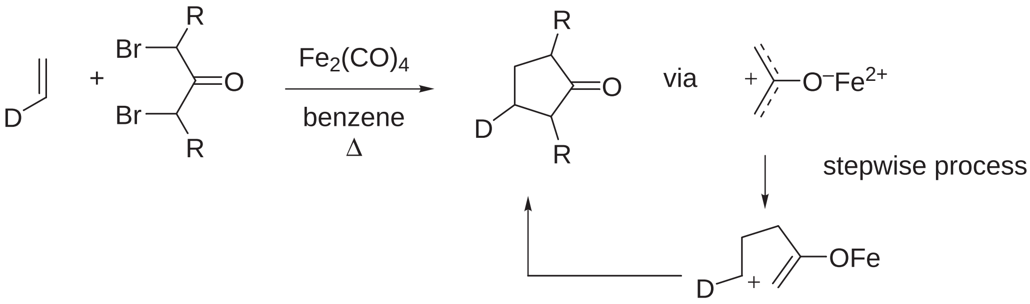
Boger *J. Am. Chem. Soc.* **1995**, *117*, 11839.
J. Org. Chem. **1991**, *56*, 2115.
J. Org. Chem. **1990**, *55*, 1919.

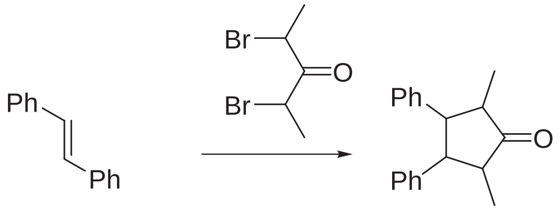
Q. [2 + 3] Cycloadditions for 5-Membered Ring Formation

Review: *Comprehensive Org. Syn.,* Vol. 5, 239.

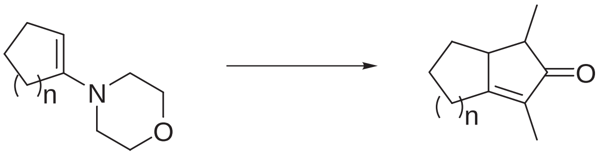
1. (2π + 2π)

- Noyori reaction: *J. Am. Chem. Soc.* **1972**, *94*, 1772.
  J. Am. Chem. Soc. **1973**, *95*, 2722.
  J. Am. Chem. Soc. **1977**, *99*, 5196.
  J. Am. Chem. Soc. **1978**, *100*, 1793.

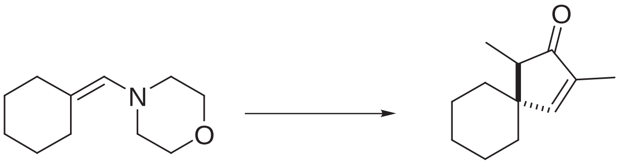




70%



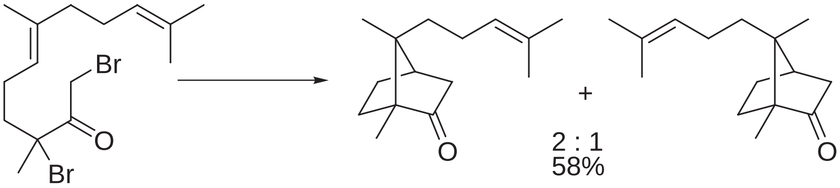
n = 5, 75%
n = 6, 100%



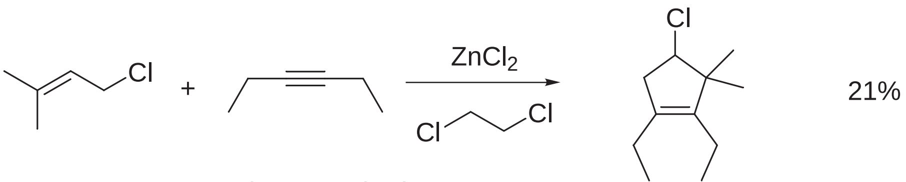
70%

Cuparenone
Noyori *Tetrahedron Lett.* **1978**, 493.

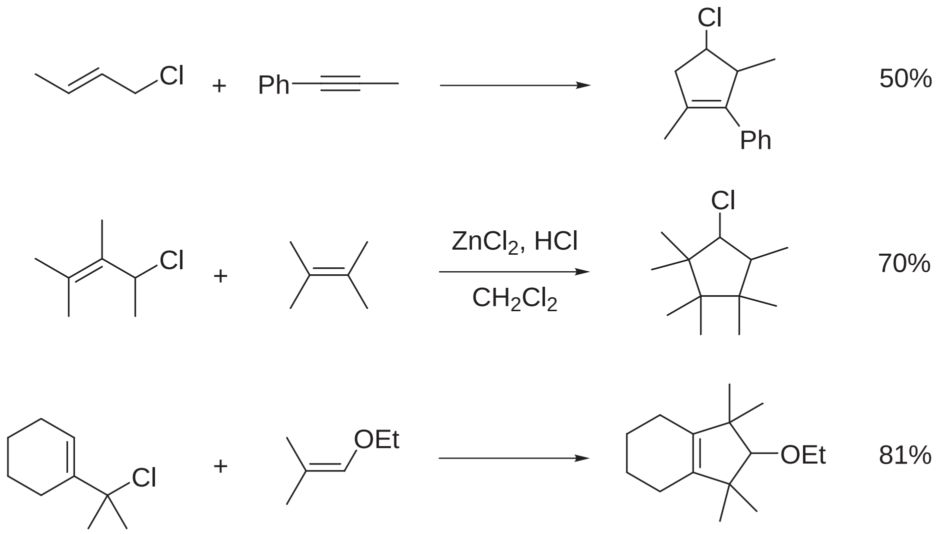
- Intramolecular version: Yamamoto *J. Am. Chem. Soc.* **1979**, *101*, 220.



- Reviews: *Acc. Chem. Res.* **1979**, *12*, 61.
  Org. React. **1983**, *29*, 163.

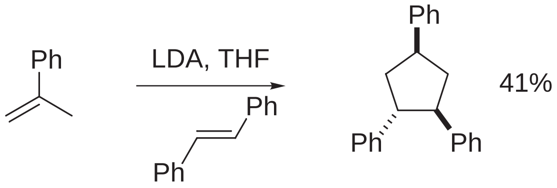


Miller *Tetrahedron Lett.* **1980**, 577.

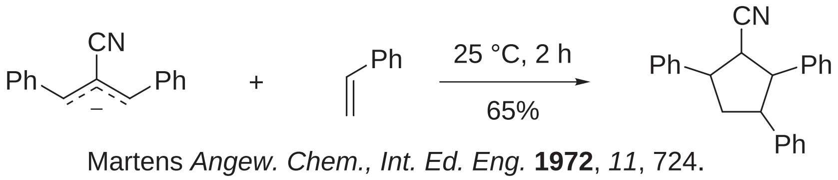


Mayr *Angew. Chem., Int. Ed. Eng.* **1981**, *20*, 1027.

2. (2π + 4π)



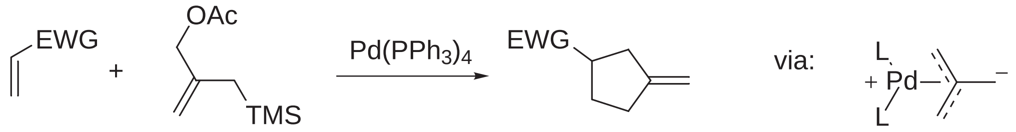
Kauffman *Angew. Chem., Int. Ed. Eng.* **1972**, *11*, 292.



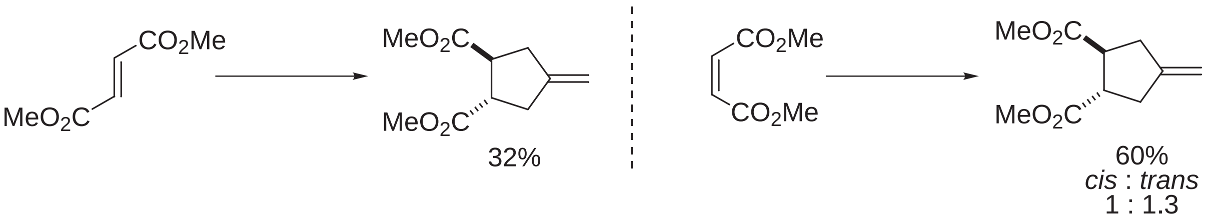
Martens *Angew. Chem., Int. Ed. Eng.* **1972**, *11*, 724.

- Trost trimethylenemethane equivalent:

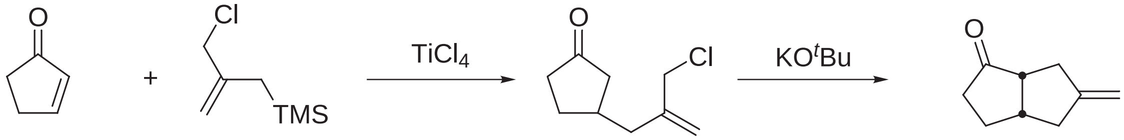
J. Am. Chem. Soc. **1979**, *101*, 6429.
J. Am. Chem. Soc. **1983**, *105*, 2315.



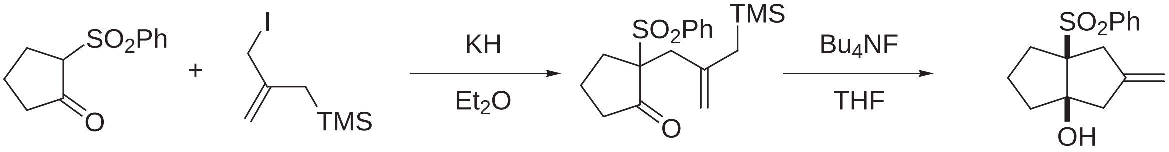
Stepwise mechanism:



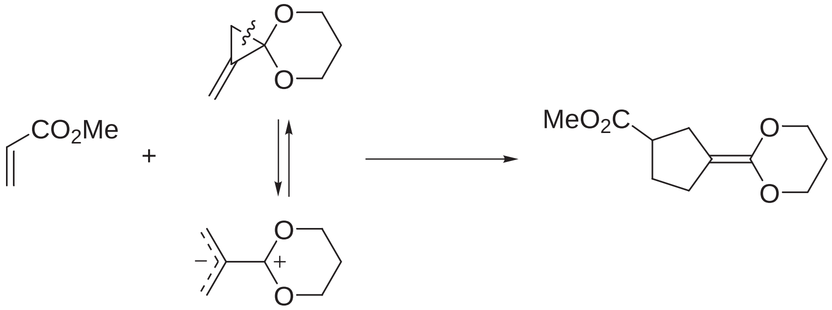
Related equivalents:



1,4-addition of allylsilane: Knapp *Tetrahedron Lett.* **1980**, 4557.



Trost *J. Am. Chem. Soc.* **1980**, *102*, 5680.

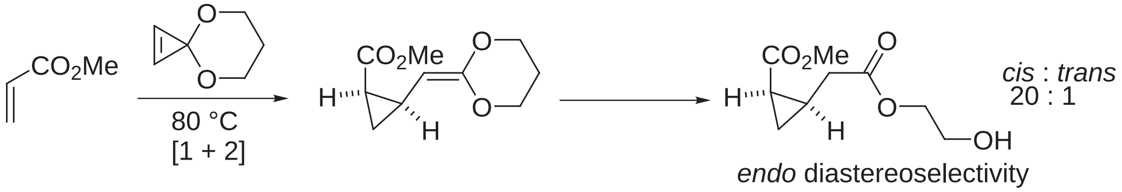


Nakamura *J. Am. Chem. Soc.* **1989**, *111*, 7285.
J. Am. Chem. Soc. **1991**, *113*, 3183.

R. Cyclopropenone Ketal Cycloadditions

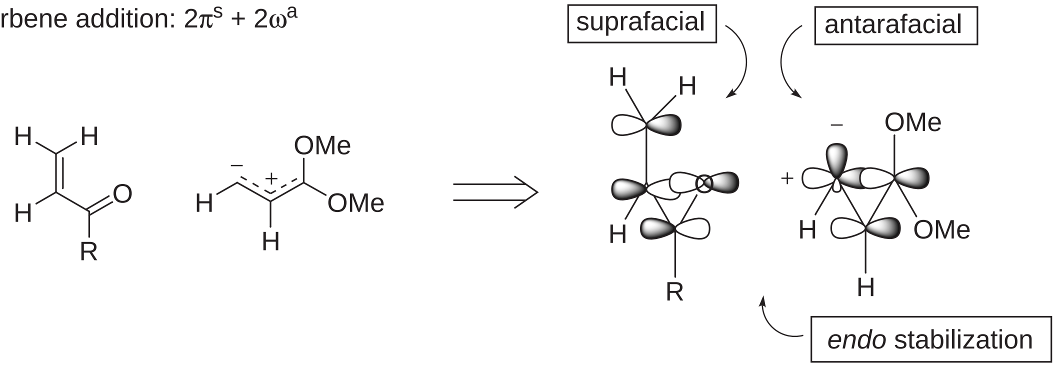
Review: Boger *Adv. Cycloaddition Chem.*, JAI Press: Greenwich, CT, Vol. 2, 1990, pp 147–219.

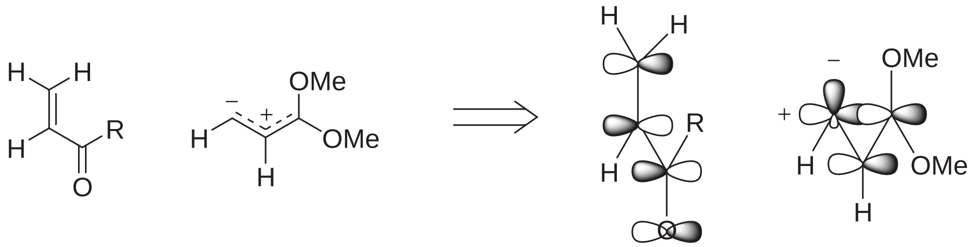
1. [2 + 1] Cycloaddition



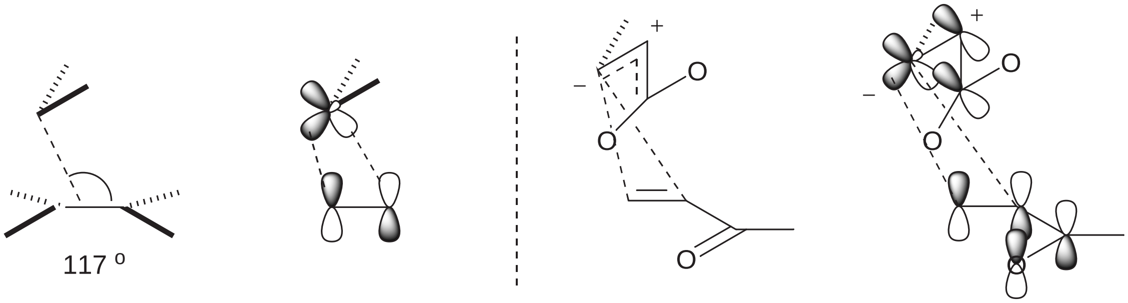
Boger *J. Am. Chem. Soc.* **1986**, *108*, 6695.

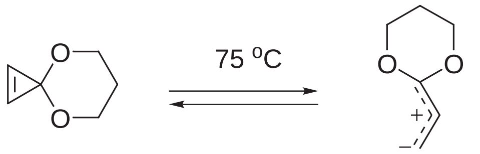
- Carbene addition: $2\pi^s + 2\omega^a$

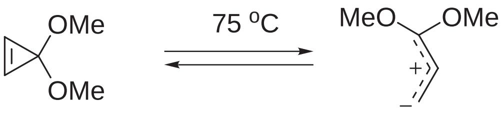




- Carbene angle of attack: Jorgensen *J. Am. Chem. Soc.* **1989**, *111*, 1919.

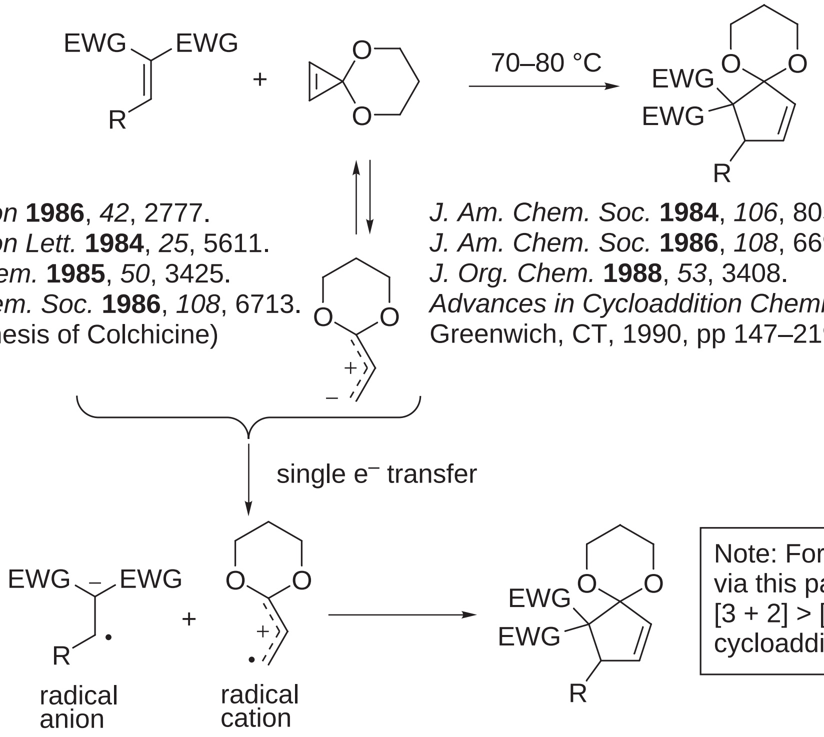






2. [3 + 2] Cycloaddition

- Substrates that contain two geminal electron-withdrawing groups.

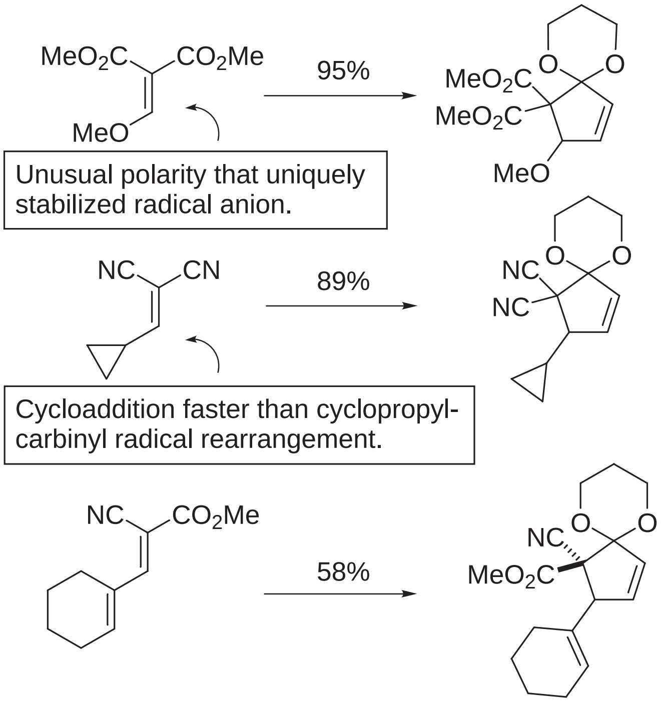


[4 + 2] *Tetrahedron* **1986**, *42*, 2777.
[1 + 2] *Tetrahedron Lett.* **1984**, *25*, 5611.
[3 + 4] *J. Org. Chem.* **1985**, *50*, 3425.
J. Am. Chem. Soc. **1986**, *108*, 6713.
(total synthesis of Colchicine)

J. Am. Chem. Soc. **1984**, *106*, 805.
J. Am. Chem. Soc. **1986**, *108*, 6695.
J. Org. Chem. **1988**, *53*, 3408.
Advances in Cycloaddition Chemistry Vol. 2, JAI: Greenwich, CT, 1990, pp 147–219.

Note: For substrates that may react via this pathway (e⁻ transfer), [3 + 2] > [1 + 2], [4 + 2], or [3 + 4] cycloadditions

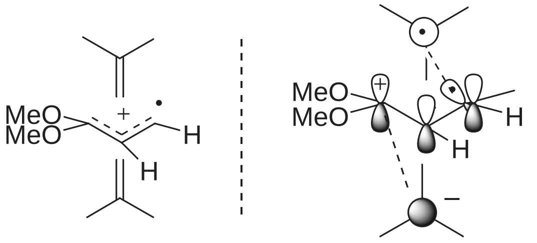
1. Solvent independent rate.
2. No addition–elimination or addition–rearrangement products.
3. No inhibition by free radical traps.
4. Putative carbene addition product (a cyclopropane ketene acetal) does not undergo vinylcyclopropane rearrangement to the product.
5. Little or no loss of olefin stereochemistry and this diastereospecific nature of the reaction increases, not decreases, in polar solvents.

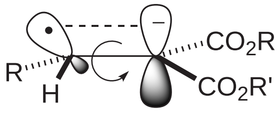


Unusual polarity that uniquely stabilized radical anion.

Cycloaddition faster than cyclopropylcarbinyl radical rearrangement.

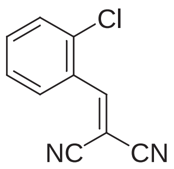
- ($2\pi^s + 2\pi^a$) Cycloaddition





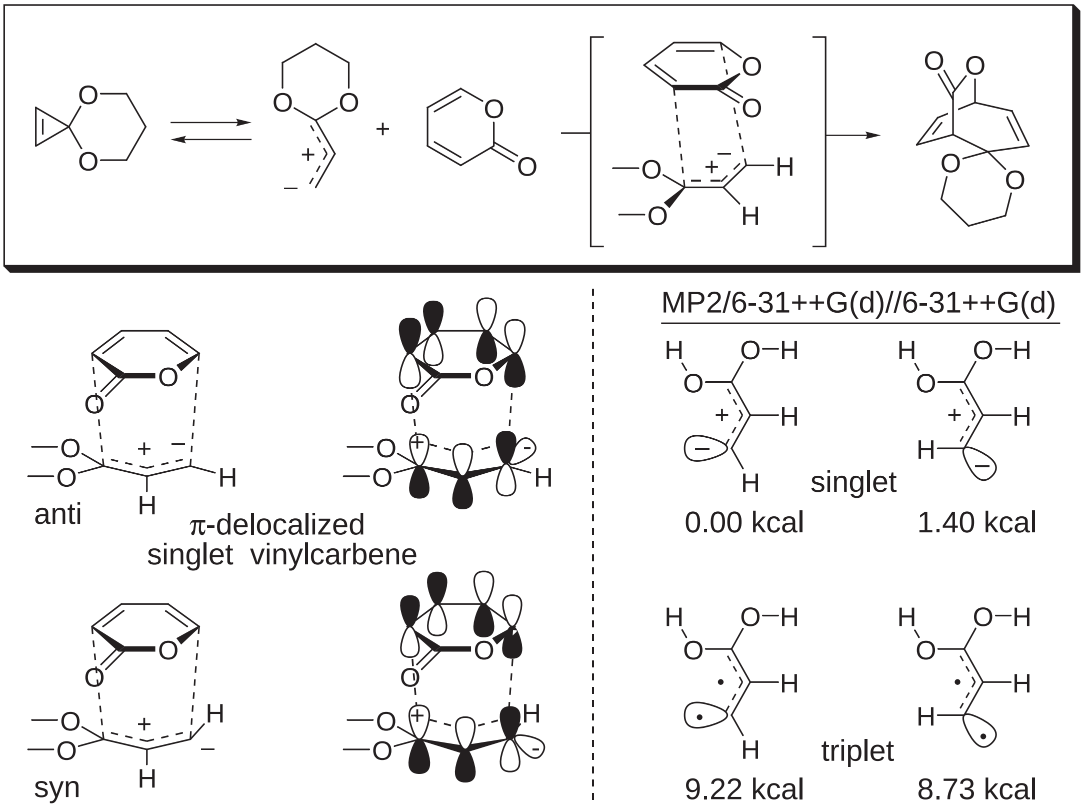
3π e⁻ bond, little loss of stereochemistry due to bond rotation

Tear Gas, CS



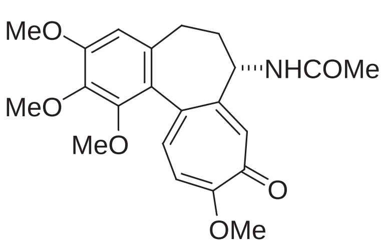
Used as an antiriot agent, the tear gas CS, named after its two developers B. Corson and R. Stoughton who introduced it in 1928, causes pain and burning in the eyes and skin within seconds. It acts as a sulfhydryl alkylating agent resulting in a copious flow of tears, coughing, sneezing, chest tightening, and dizziness which subside within 30 min. No carcinogenic activity was found in mice exposed to CS for up to 2 years.

3. [4 + 3] Cycloaddition

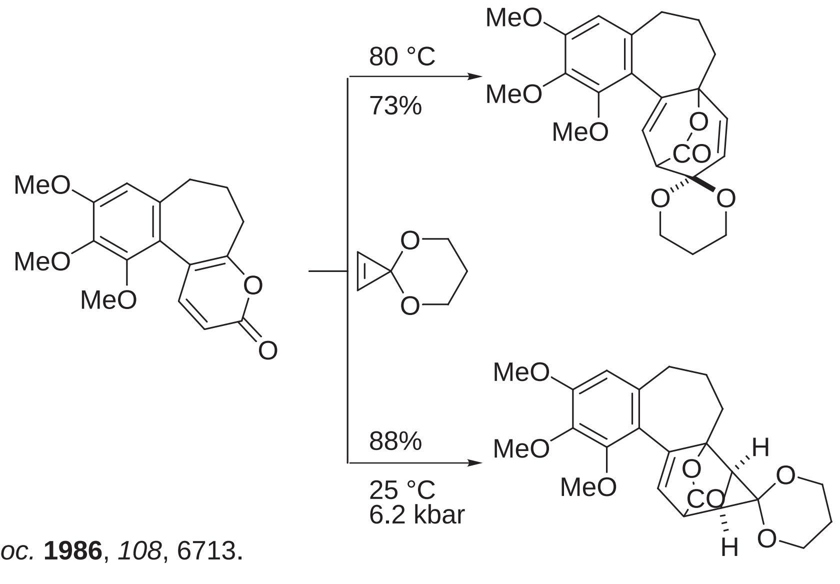


Singlet carbene stabilized by two alkoxy electron-donating substituents

- $2\pi^s + 4\pi^s$ Cycloaddition or Diels–Alder reaction but via a 2π three carbon dienophile.

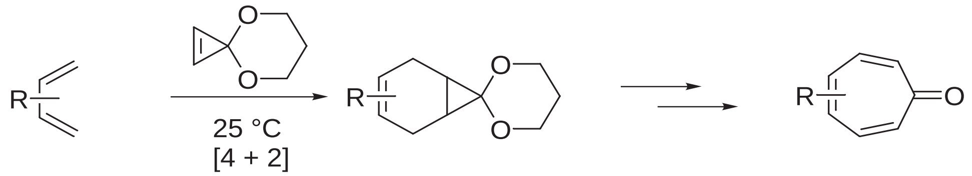


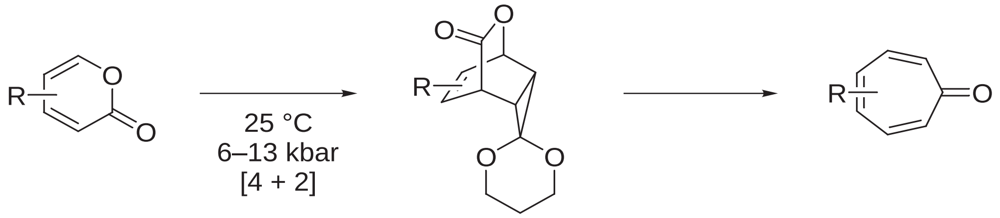
Colchicine



Boger *J. Am. Chem. Soc.* **1986**, *108*, 6713.

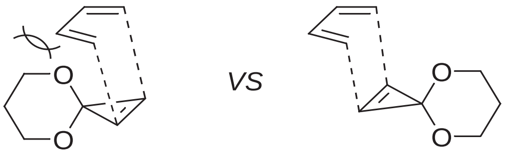
4. [4 + 2] Cycloaddition (standard Diels–Alder reaction)



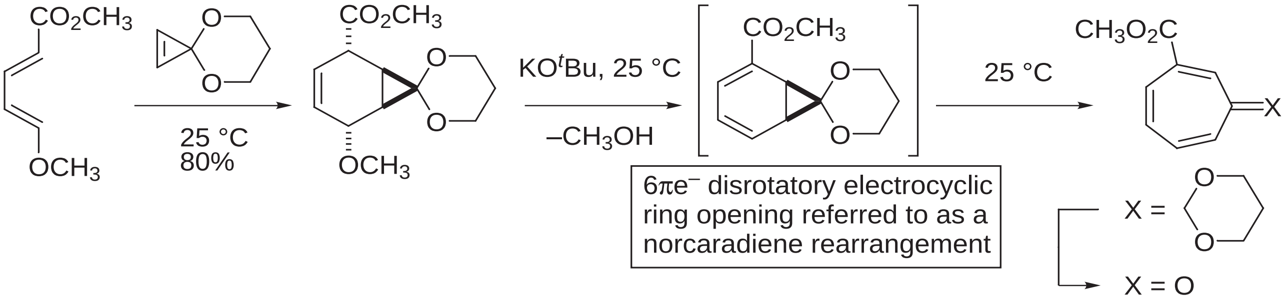


R = CO_2CH_3, 56–65%
R = H, 69%
R = OCH_3, 56–72%

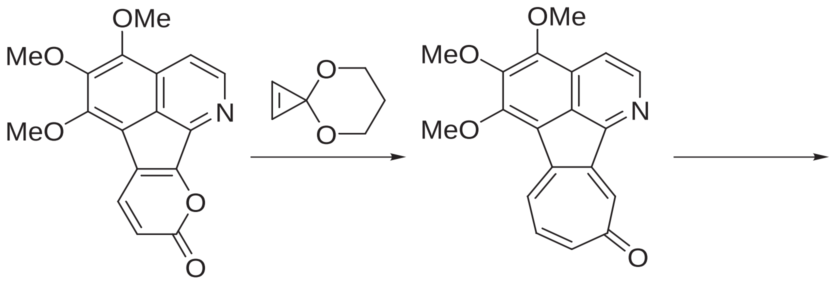
Participates in normal, neutral, or inverse electron demand Diels–Alder reactions, high lying HOMO and low lying LUMO.



Exclusive *exo* addition
Note: cyclopropene itself
is *endo* selective.



6πe$^-$ disrotatory electrocyclic
ring opening referred to as a
norcaradiene rearrangement



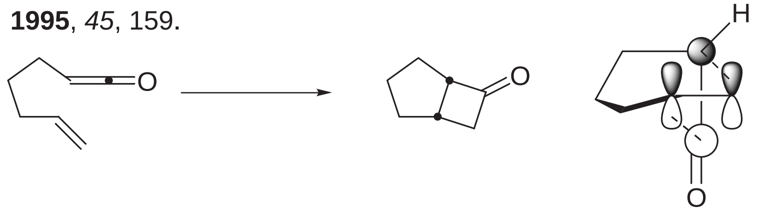
Grandirubrine
Imerubrine
Granditropone

Boger *J. Am. Chem. Soc.* **1995**, *117*, 12452.

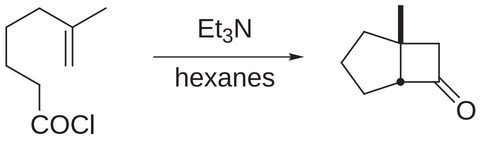
S. [2 + 2] Cycloadditions

1. Ketene [2 + 2] cycloadditions

Org. React. **1995**, *45*, 159.



$2\pi^s + 2\pi^a$ Cycloaddition



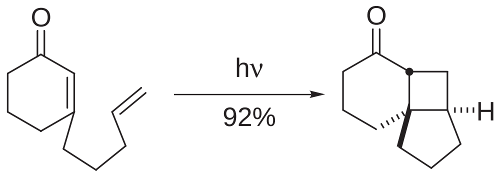
Baldwin *J. Chem. Soc., Chem. Commun.* **1972**, 1337.

Hermann Staudinger, noted for his pioneering studies of ketenes, received the 1953 Nobel Prize in Chemistry for his pioneering work in macromolecular chemistry.

2. Photochemical [2 + 2] cycloaddition

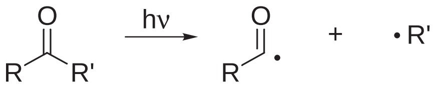
Comprehensive Org. Syn., Vol. 5, 123.
Org. React. **1993**, *44*, 297.

Ronald Norrish received the 1967 Nobel Prize in Chemistry for his work on photochemistry and flash photolysis. The latter was developed with George Porter with whom he shared the 1967 Nobel Prize and is used for the production and spectroscopic determination of short-lived reaction intermediates.

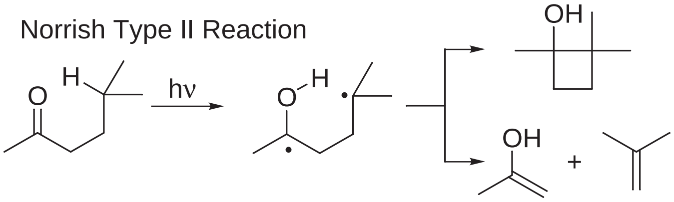


Cargill *Tetrahedron Lett.* **1978**, 4465.

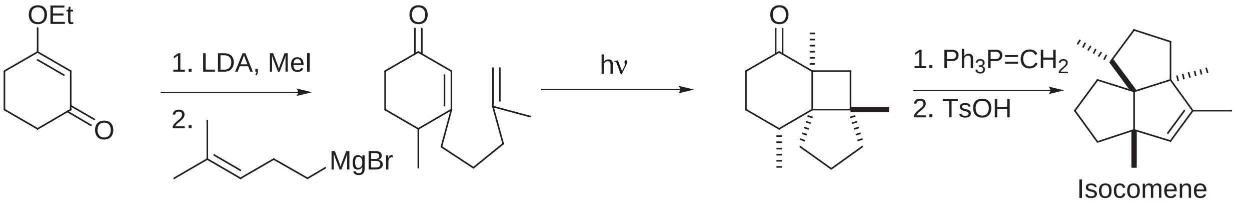
Norrish Type I Fragmentation Reaction



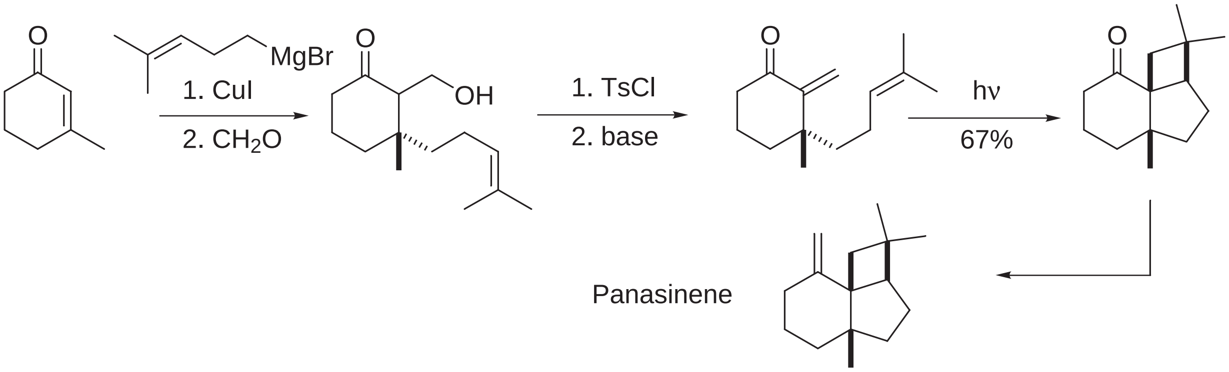
Norrish Type II Reaction



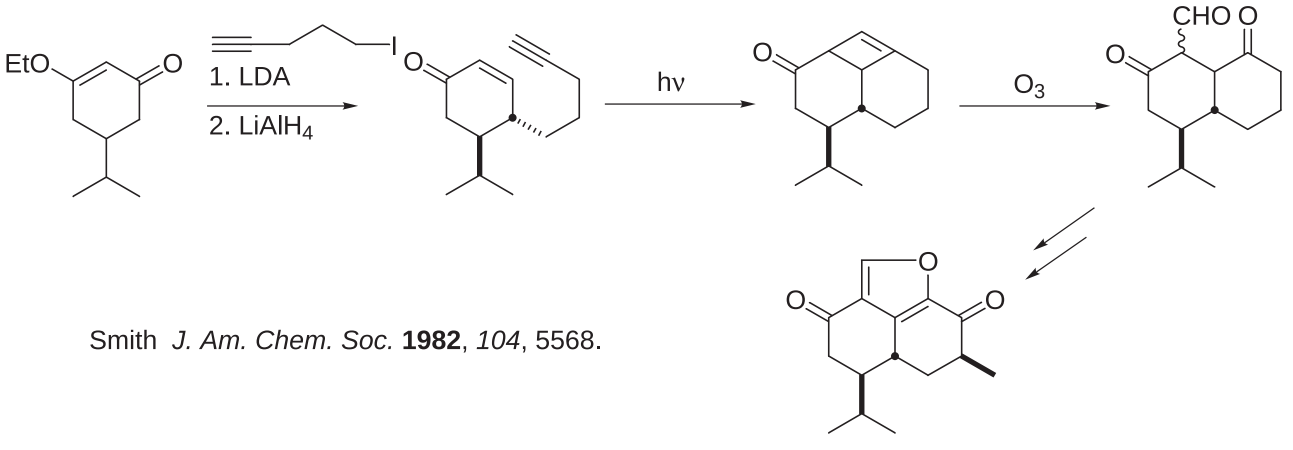
Norrish *Trans. Faraday Soc.* **1937**, *33*, 1521.



Pirrung *J. Am. Chem. Soc.* **1979**, *101*, 7130.
J. Am. Chem. Soc. **1981**, *103*, 82.

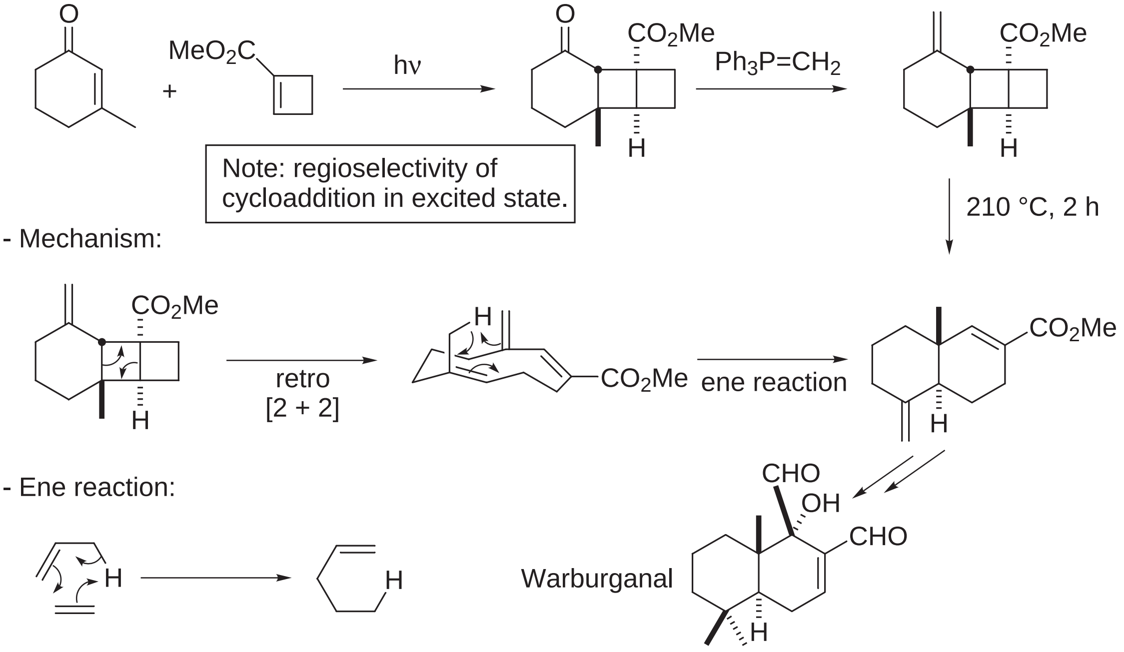


C. R. Johnson *J. Am. Chem. Soc.* **1981**, *103*, 7667.



Smith *J. Am. Chem. Soc.* **1982**, *104*, 5568.

Hibiscone C



Note: regioselectivity of cycloaddition in excited state.

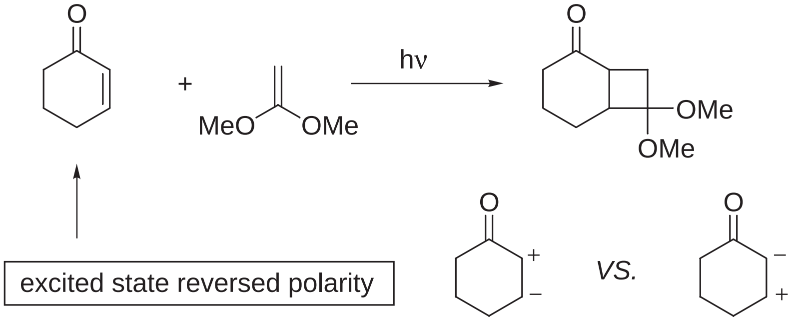
- Mechanism:

- Ene reaction:

Warburganal

Wender *Tetrahedron Lett.* **1982**, *23*, 1871.

- Note regioselectivity:

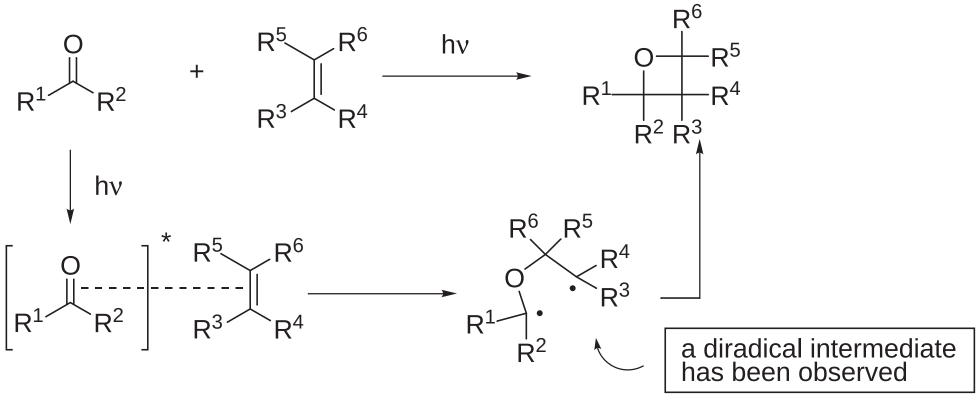


excited state reversed polarity

Corey *J. Am. Chem. Soc*. **1964**, *86*, 5570.

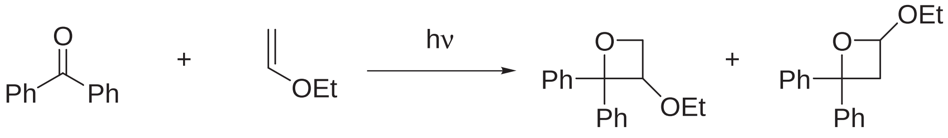
3. Paterno–Buchi Reaction

Comprehensive Org. Syn., Vol. 5, 151.
Dermuth *Synthesis* **1989**, 152.
First studied in detail by Buchi *J. Am. Chem. Soc.* **1954**, *76*, 4327.



a diradical intermediate has been observed

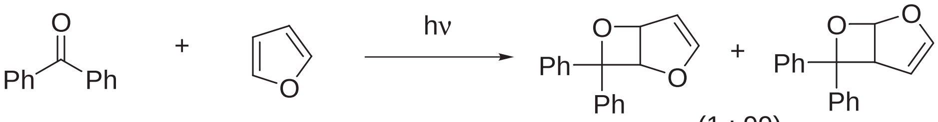
-Addition to enol ether occurs with only moderate selectivity ...



(75 : 25)

Schroeten *J. Org. Chem.* **1969**, *34*, 1181.

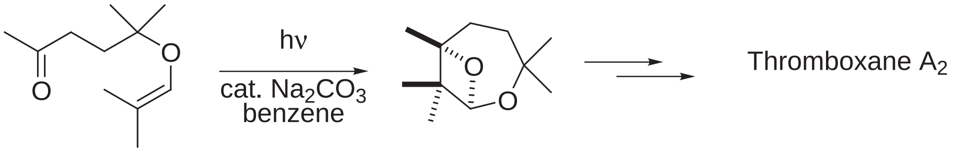
... while addition of the carbonyl to a furan occurs with high selectivity.



(1 : 99)

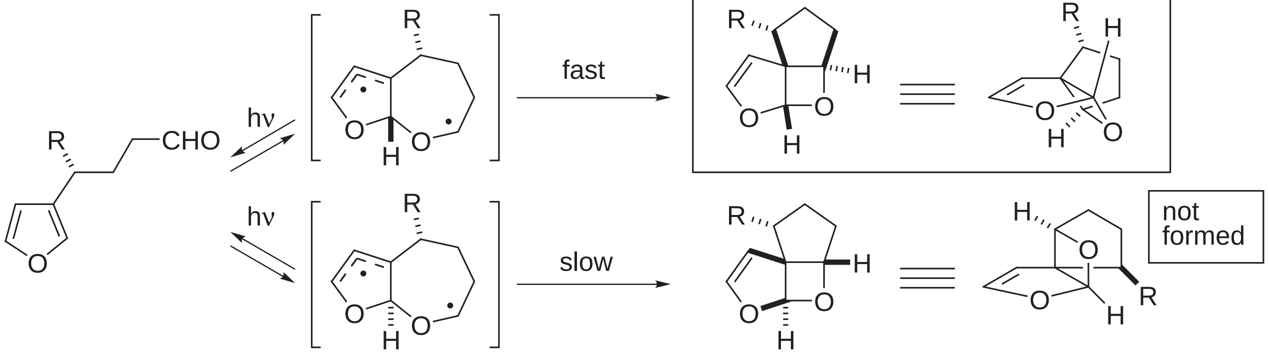
Schenk *Chem. Ber.* **1963**, *96*, 498.

- Intramolecular variant:



Carless *J. Chem. Soc., Chem. Commun.* **1984**, 667.

- Diastereoselectivity:

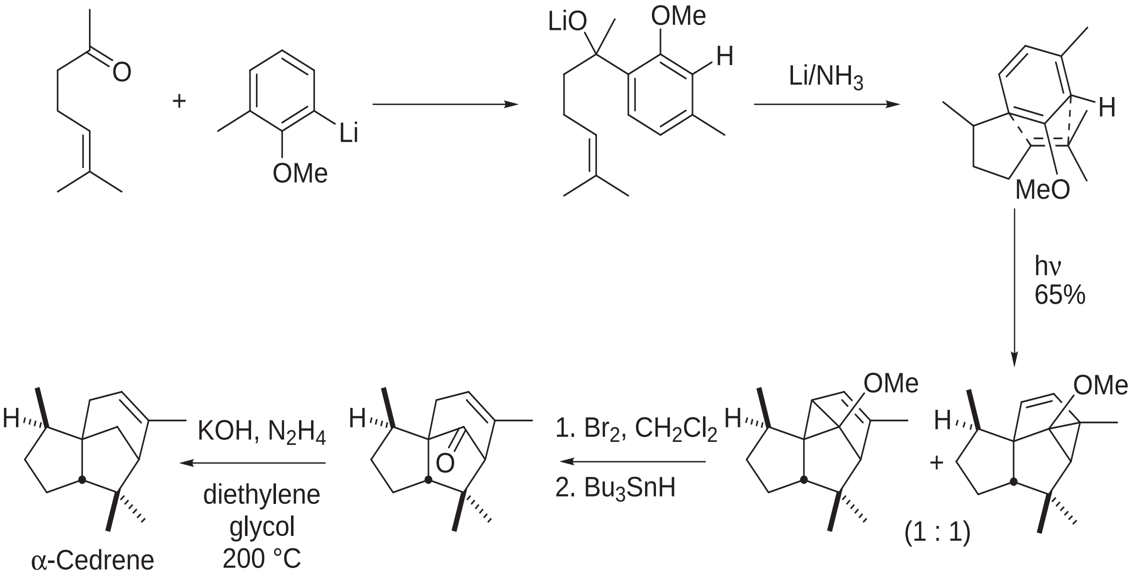


Aoyoma *J. Org. Chem.* **1984**, *49*, 396.
Pattenden *J. Chem. Soc., Chem Commun.* **1980**, 1195.
J. Chem. Soc., Chem Commun. **1979**, 235.

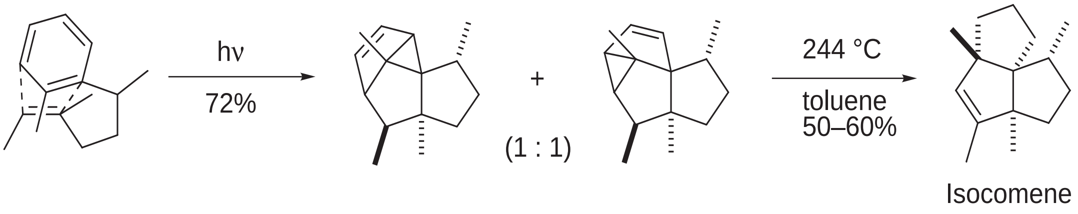
T. Arene–Olefin Photoadditions

- Discovery in 1966: Wilzbach *J. Am. Chem. Soc.* **1966**, *88*, 2066.
  Bryce–Smith *J. Chem. Soc., Chem. Commun.* **1966**, 512.

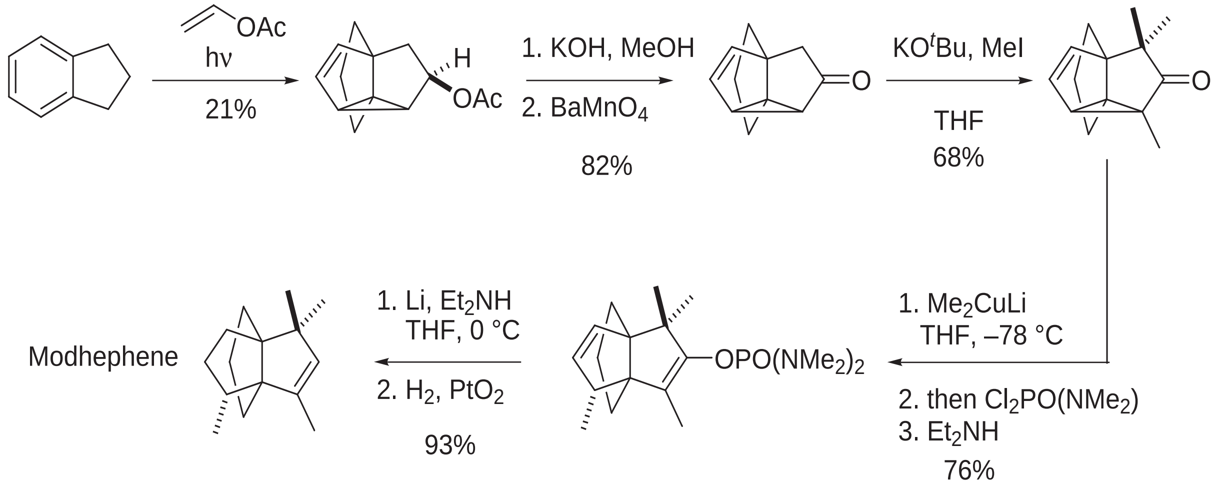
Comprehensive Org. Syn., Vol. 5, 645.



Wender *J. Am. Chem. Soc.* **1981**, *103*, 688.



Wender *Tetrahedron* **1981**, *37*, 4445.



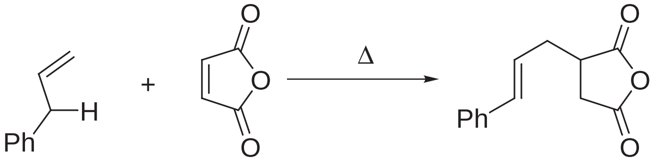
Wender *J. Am. Chem. Soc.* **1982**, *104*, 5805.

U. Intramolecular Ene Reaction

Review: H. M. R. Hoffmann *Angew. Chem., Int. Ed. Eng.* **1969**, *8*, 556.
Comprehensive Org. Syn., Vol. 5, 9.

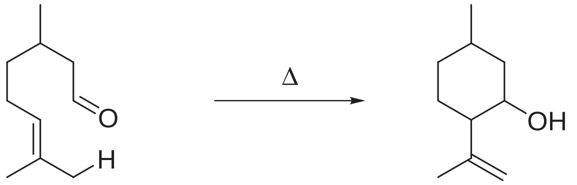
concerted thermal
[4 + 2] cycloaddition

- First systematic study by Alder:

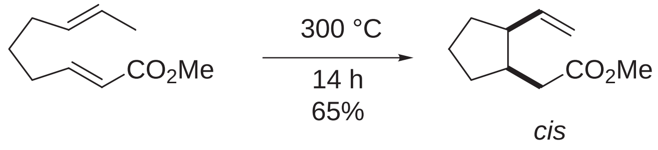


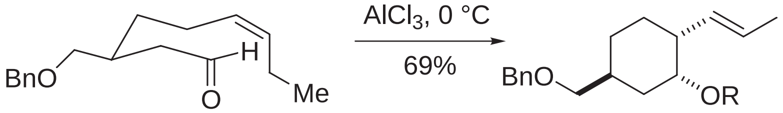
Alder *Chem. Ber.* **1943**, *76*, 27.

- First intramolecular versions: review: Oppolzer *Angew. Chem., Int. Ed. Eng.* **1978**, *17*, 476.

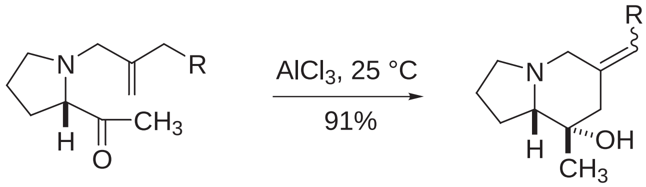


Treibs, Schmidt *Chem. Ber.* **1927**, *60*, 2335.



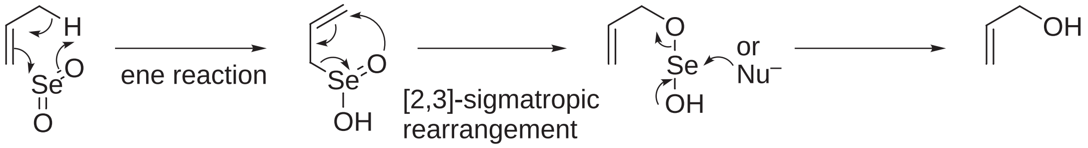


Smith *J. Am. Chem. Soc.* **1991**, *113*, 2071.



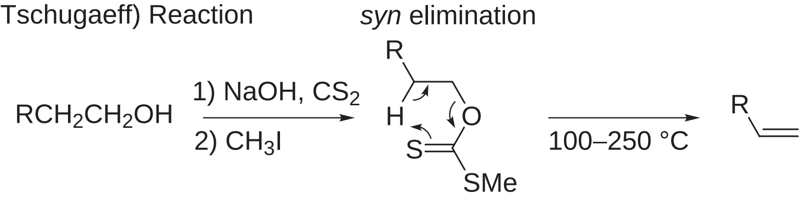
Overman *Tetrahedron Lett.* **1985**, *35*, 4167.

Note the Sharpless mechanism for SeO_2 oxidation of olefins: allylic oxidation involves an ene reaction.



Sharpless *J. Am. Chem. Soc.* **1972**, *94*, 7154.
J. Am. Chem. Soc. **1973**, *95*, 7917.

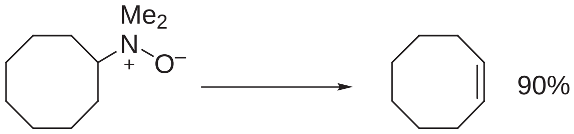
Chugaev (Tschugaeff) Reaction



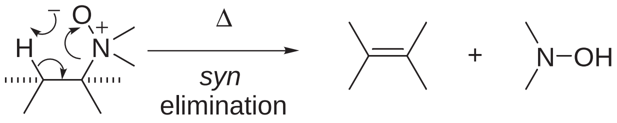
Tschugaeff *Ber.* **1899**, *32*, 3332.
Review: Nace *Org. React.* **1962**, *12*, 57.
DePuy *Chem. Rev.* **1960**, *60*, 431.

Amine Oxide Elimination (Cope Elimination)

Org. React. **1960**, *11*, 361.
Org. Syn. **1963**, *4.* 612.
Cope *J. Am. Chem. Soc.* **1954**, *81*, 2799.
Zutter *J. Am. Chem. Soc.* **1986**, *108*, 1039.



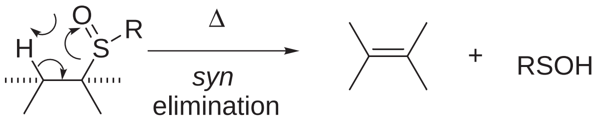
Cope *J. Am. Chem. Soc.* **1949**, *71*, 3929.

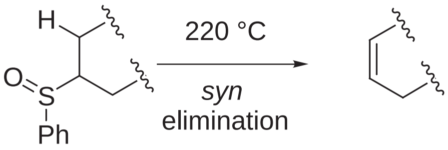


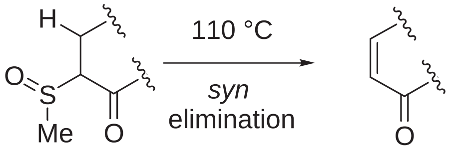
Sulfoxide Elimination

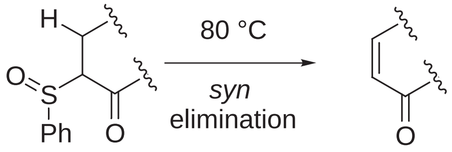
Trost *Chem. Rev.* **1978**, *78*, 363.
Acc. Chem. Res. **1977**, *11*, 453.
J. Am. Chem. Soc. **1973**, *95*, 6840.
J. Am. Chem. Soc. **1976**, *98*, 4887.

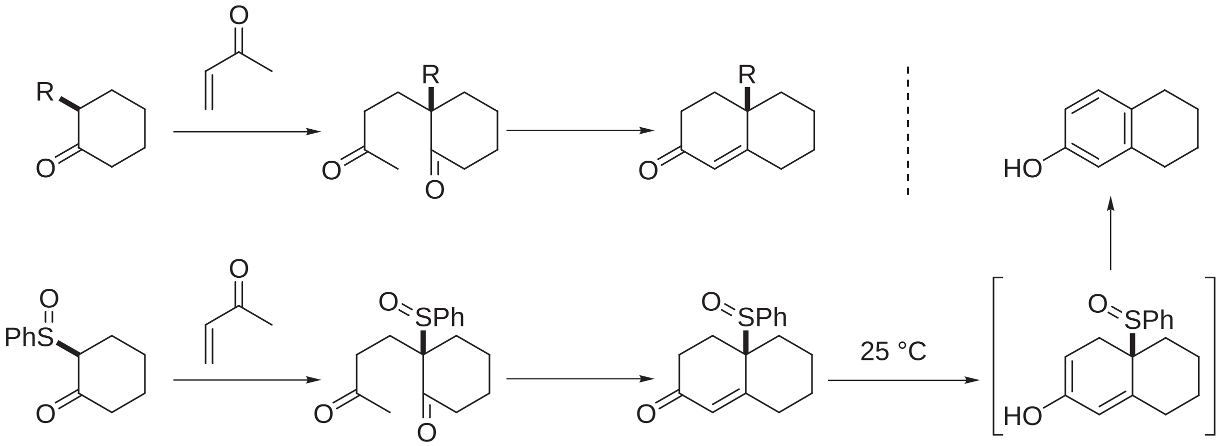
Ziegler *J. Am. Chem. Soc.* **1984**, *106*, 721.
Schreiber *J. Am. Chem. Soc.* **1984**, *106*, 4038.
Agosta *J. Am. Chem. Soc.* **1986**, *108*, 3385.







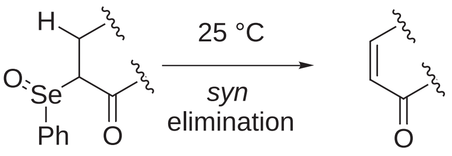




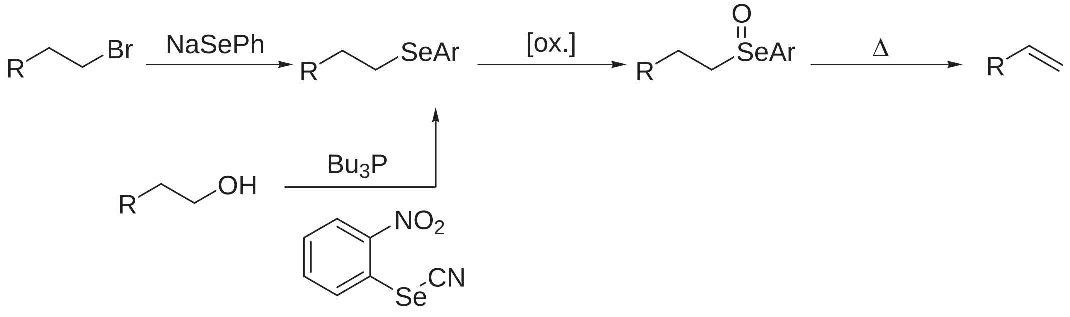
Boger, Mullican *J. Org. Chem.* **1980**, *45*, 5002.
J. Org. Chem. **1984**, *49*, 4045.

- Selenoxide Elimination

Clive *Tetrahedron* **1978**, *34*, 1049.
Reich *Acc. Chem. Res.* **1979**, *12*, 22.

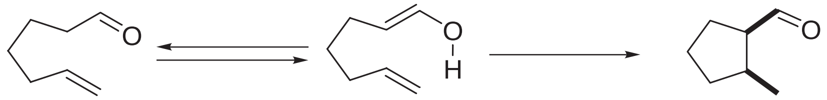


Selenoxide elimination occurs at lower temperature.

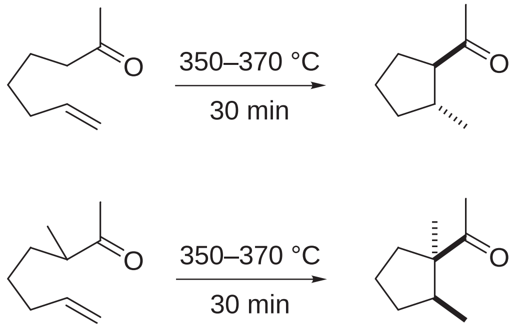


V. Oxy–Ene Reaction: Conia Reaction

Comprehensive Org. Syn., Vol. 5, 20.
Review: J. M. Conia *Synthesis* **1975**, 1.



Conia *Tetrahedron Lett.* **1965**, 3305, 3319.

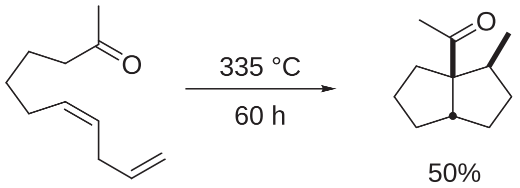


85%

Epimerized to more stable *trans* isomer.

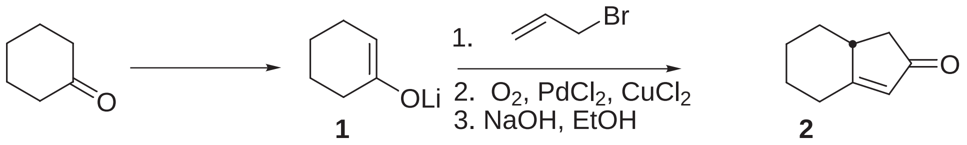
cis

Conia *Bull. Chim. Soc., Fr.* **1969**, 818.

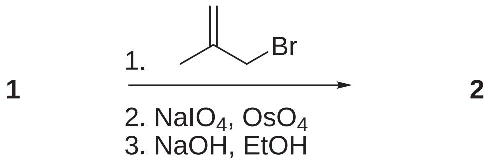


tandem Conia reactions: Conia *Tetrahedron Lett.* **1974**, 2931.

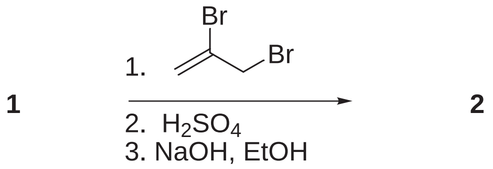
W. Cyclopentenone Annulation Methodology

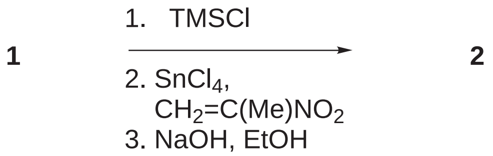


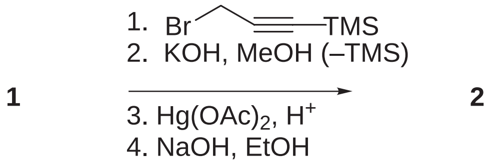
Wacker oxidation, review: Tsuji *Synthesis* **1984**, 369.
Wayner *J. Org. Chem.* **1990**, *55*, 2924.

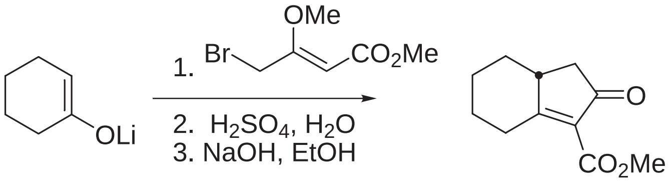


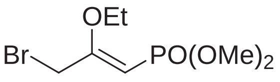
McMurry *J. Am. Chem. Soc.* **1979**, *101*, 1330.

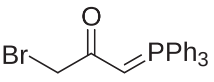










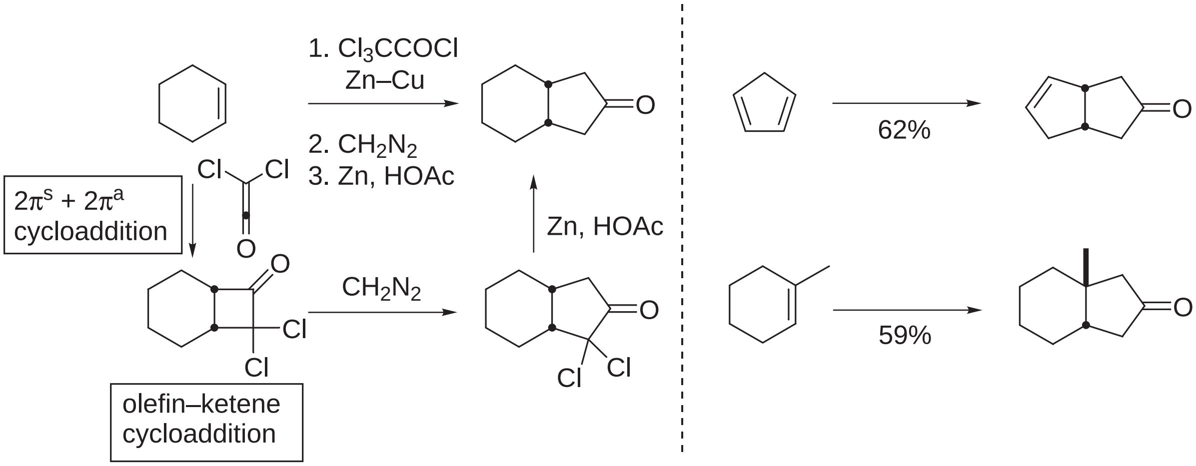


Used in Quadrone total synthesis:
Helquist *J. Am. Chem. Soc.* **1981**, *103*, 4647.

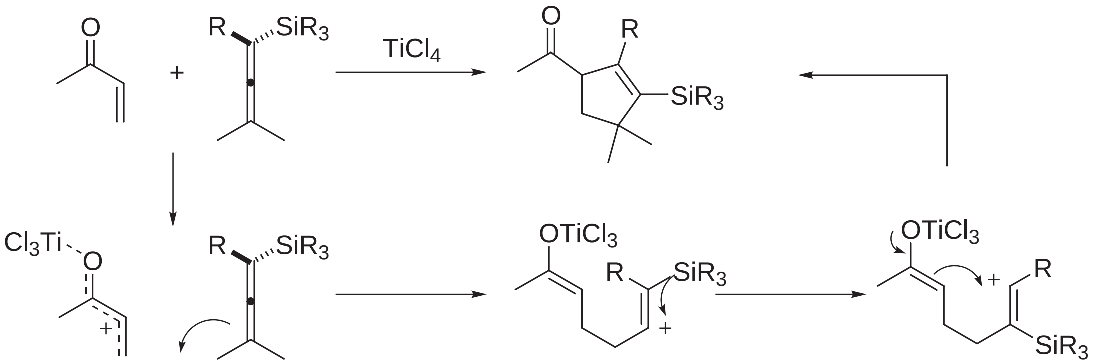
Piers *Tetrahedron Lett.* **1979**, 3279.

Altenbach *Angew. Chem., Int. Ed. Eng.* **1979**, *18*, 940.

- Flemming–Greene Annulation:

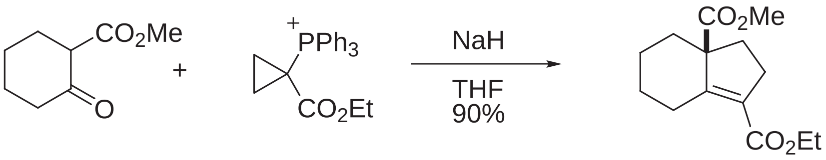


Loganin: Flemming *J. Chem. Soc., Chem. Commun.* **1977**, 81.
Hirsutene: Greene *Tetrahedron Lett.* **1980**, 3059.
Hirsutic Acid: Greene *J. Am. Chem. Soc.* **1983**,*105*, 2435.

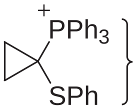


Danheiser *J. Am. Chem. Soc.* **1981**, *103*, 1604.
Tetrahedron **1983**, *39*, 935.

- Cyclopropylphosphonium salts:

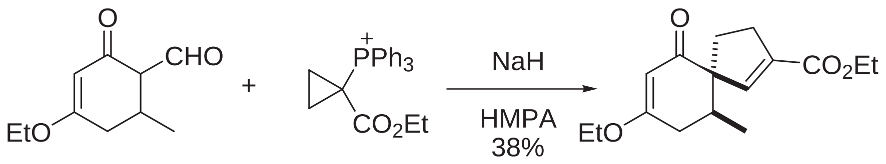


Fuchs *J. Am. Chem. Soc.* **1974**, *96*, 1607.

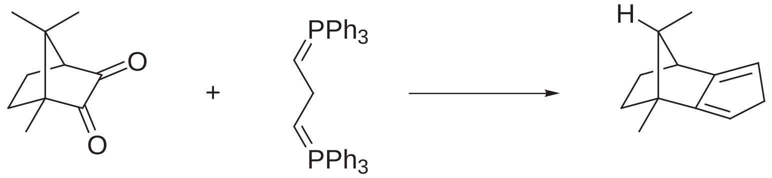


Marino *Tetrahedron Lett.* **1975**, 4531.

- β-Vetivone synthesis:

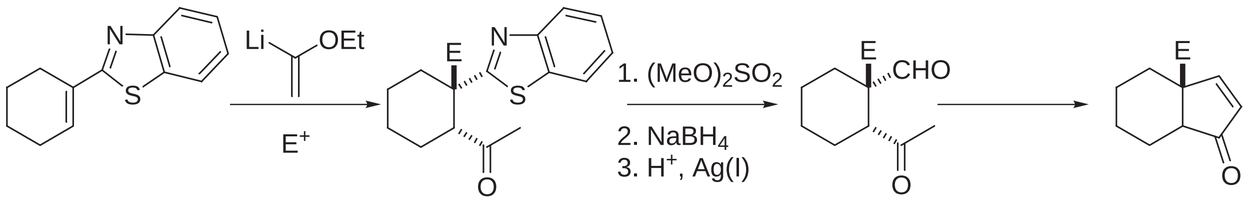


Dauben *J. Am. Chem. Soc.* **1975**, *97*, 1622.

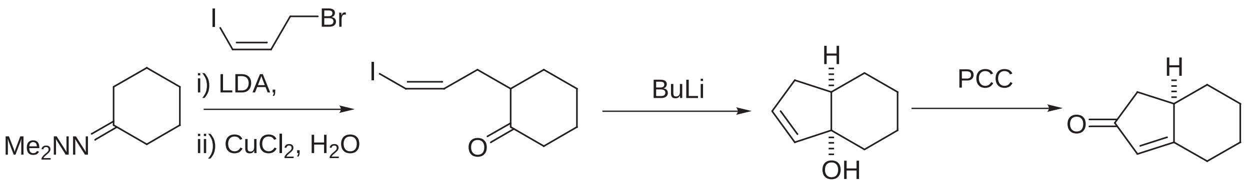


Burgstahler, Boger *Tetrahedron* **1976**, *32*, 309.

- Benzothiazoles as carbonyl equivalents:



Corey, Boger *Tetrahedron Lett.* **1978**, 5, 9, 13 and 4597.

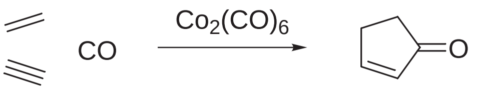


Piers *Tetrahedron Lett.* **1993**, *35*, 8573.

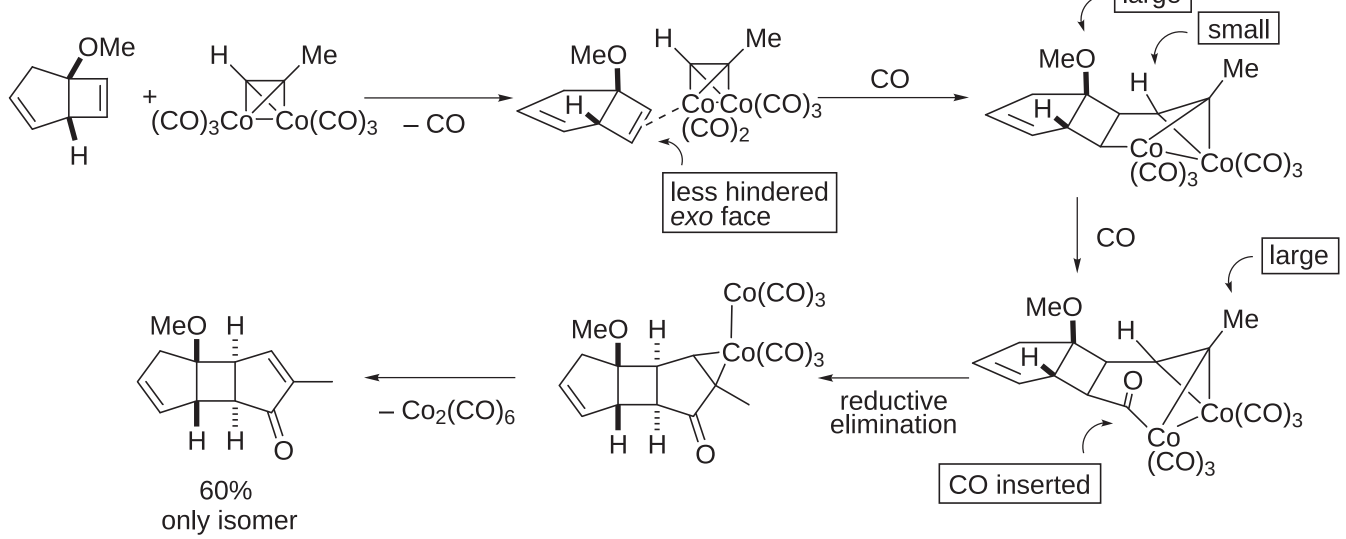
- Additional reviews: Denmark *Org. React.* **1994**, *45*, 1.
  Hudlicky *Chem. Rev.* **1989**, *89*, 1467.
  Sehore *Chem. Rev.* **1988**, *88*, 1085.
  Ramarah *Synthesis* **1984**, 529.

X. Pauson–Khand Reaction

[2 + 2 + 1]
Comprehensive Org. Syn., Vol. 5, pp 1037–1064.
Org. React. **1991**, *40*, 1.
Pauson *Tetrahedron* **1978**, *41*, 5855.
Schore *Chem. Rev.* **1988**, *88*, 1081.
Brummond *Tetrahedron* **2000**, *56*, 3263.
First detailed study: Khand *J. Chem. Soc., Perkin Trans. 1* **1973**, 977.

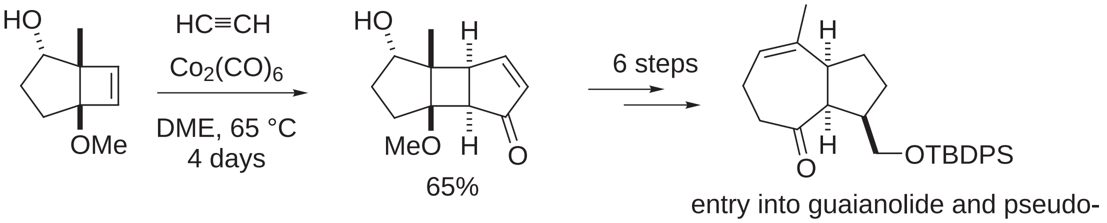


- Mechanism:



1. Regio- and stereochemistry are controlled by steric factors.
2. Complexation of alkene and insertion into Co–C bond occurs from less hindered face.
3. Insertion of the alkene carbon bearing the largest allylic substituent to form the first C–C bond occurs at the alkyne carbon bearing the smallest substituent.
4. Subsequent CO insertion occurs next to the largest alkyne substituent.
5. Reductive elimination followed by decomplexation gives the final product.

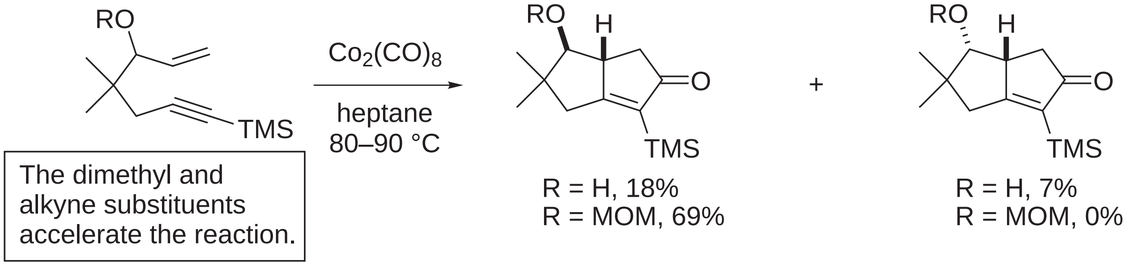
- Intermolecular:



entry into guaianolide and pseudo-guaianolide natural products

Schore *J. Org. Chem.* **1987**, *52*, 3595.

- Intramolecular

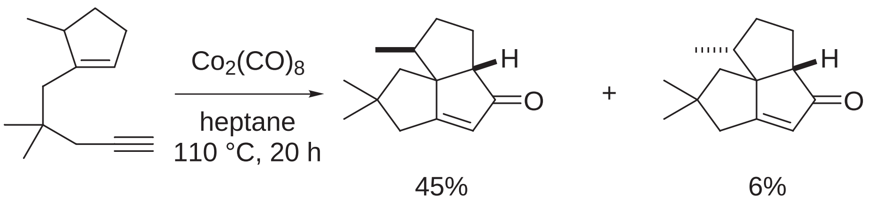


The dimethyl and alkyne substituents accelerate the reaction.

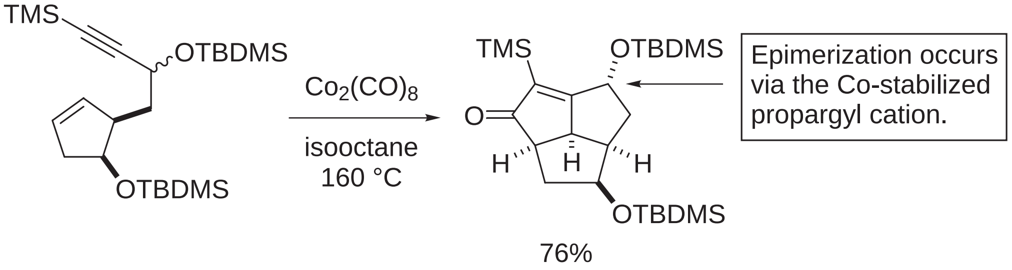
R = H, 18%
R = MOM, 69%

R = H, 7%
R = MOM, 0%

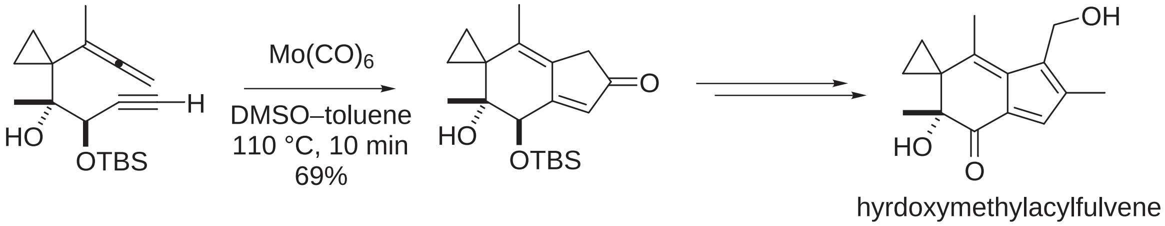
Magnus *J. Am. Chem. Soc.* **1983**, *105*, 2477.



Schore *J. Am. Chem. Soc.* **1988**, *110*, 5224.

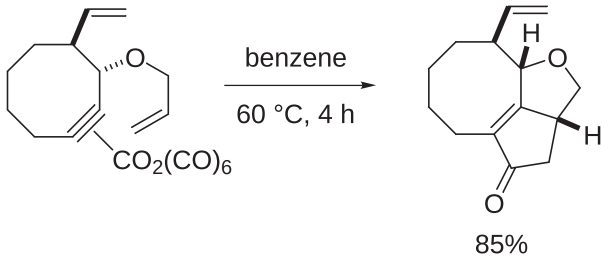


Serratosa *Tetrahedron Lett.* **1985**, *26*, 2475.
Tetrahedron **1986**, *42*, 1831.

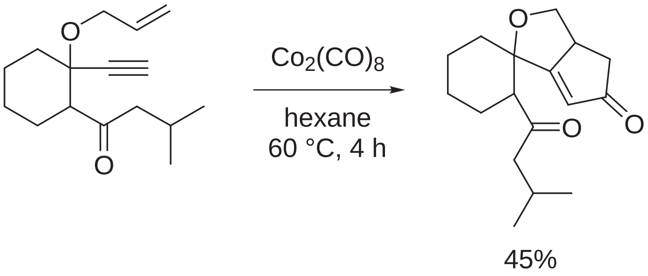


Brummond *J. Am. Chem. Soc.* **2000**, *122*, 4915.

-Heterosubstituted systems:



Schreiber *J. Am. Chem. Soc.* **1986**, *108*, 3128.

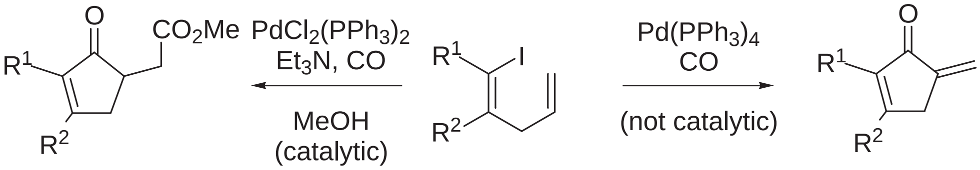


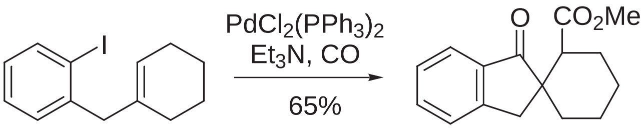
Smith *Tetrahedron Lett.* **1986**, *27*, 1241.

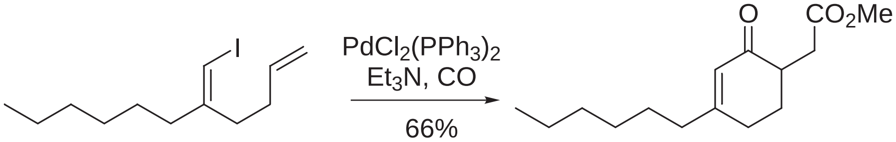
Y. Carbonylation Cyclizations

Comprehensive Org. Syn., Vol. 4, 1015.
Alper *Acc. Chem. Res.* **1995**, *28*, 414.

- Pd mediated carbonylation

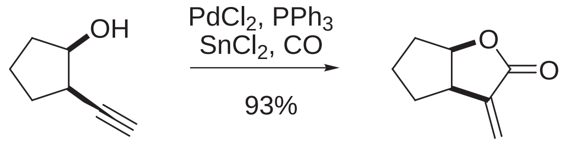






Negishi *J. Am. Chem. Soc.* **1985**, *107*, 8289.

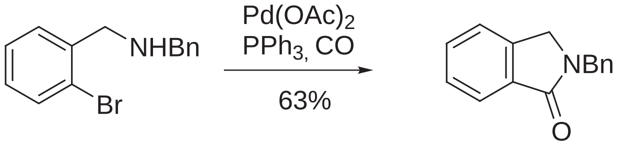
- Formation of lactones



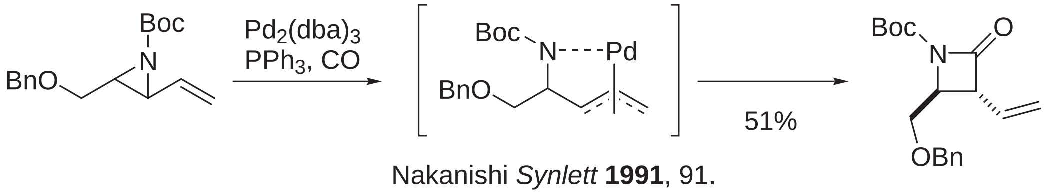
Norton *J. Am. Chem. Soc.* **1981**, *103*, 7520.

- Formation of amides

Heck *J. Org. Chem.* **1975**, *40*, 2667.

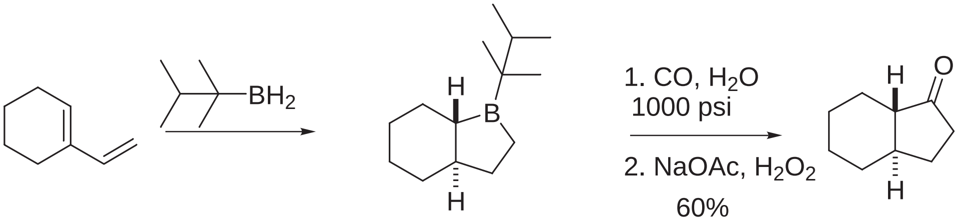


Mori *J. Org. Chem.* **1978**, *43*, 1684.



Nakanishi *Synlett* **1991**, 91.

- Alternative carbonylation method: Hydroboration/Carbonylation



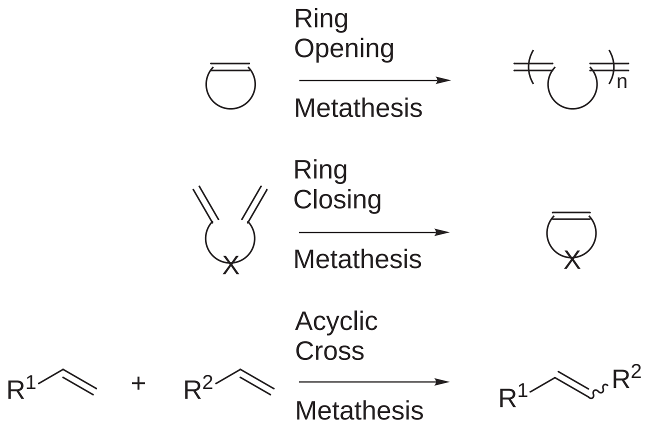
Brown, Negishi *J. Chem. Soc., Chem. Commun.* **1967**, 594.
J. Am. Chem. Soc. **1967**, *89*, 5477.

Z. Olefin Ring Closing Metathesis

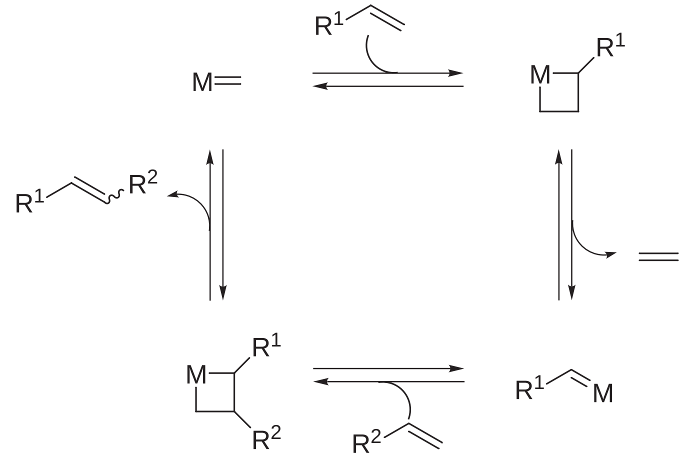
Grubbs *Comprehensive Org. Syn.,* Vol. 5, 1115.
Acc. Chem. Res. **1995**, *28*, 446.
Tetrahedron **1998**, *54*, 4413.
Schrock *J. Am. Chem. Soc.* **1990**, *112*, 3875 and 8378.
J. Am. Chem. Soc. **1991**, *113*, 6899.

K. Ziegler and G. Natta shared the 1963 Nobel Prize in Chemistry for their discovery and development of transition metal catalyzed preparation of polyethylene and stereoregular polymers including polypropylene.

-General concept:



- Mechanism:

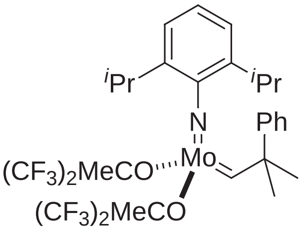


The mechanism appears to be the same regardless of transition metal used.

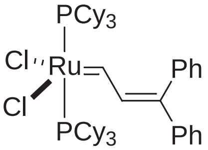
Grubbs *Comprehensive Organometallic Chem.,* Vol. 8, 1982, 499.
Sehrer *J. Sci. Ind. Res.* **1983**, *42*, 250.

- Defined Catalysts

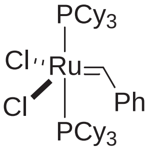
1. Early catalysts were poorly defined and incompatible with basic functionality.
2. Development of well-defined catalysts lead to high catalytic activity and compatibility with a wide variety of funtionalities.
3. Catalysts are based on variety of transition metals including: Mo, Ru, W, Re, Ti and Ta.
4. The mechanism appears the same for all transition metals.
5. The most widely used catalysts are:



1
Schrock



2
Grubbs



3
Grubbs

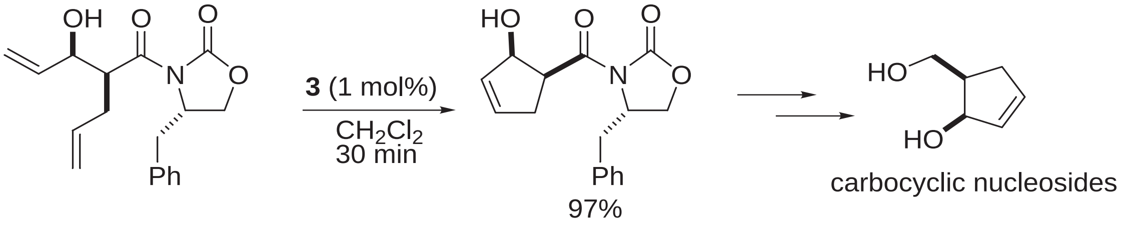
- Applications to organic synthesis — Review: Phillips, Abell *Aldrichim. Acta* **1999**, *32*, 75.

Ring closing metathesis is rapidly becoming one of the more powerful methods for preparing medium and large rings.
Modern use of ring closing metathesis traced back to:

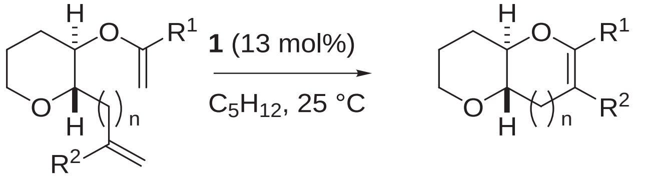
X = O, NR, CHR
n = 1, 2, 3

Grubbs, R. H.; Fu, G. C. *J. Am. Chem. Soc.* **1992**, *114*, 5426, 7324.
J. Am. Chem. Soc. **1993**, *115*, 3800.

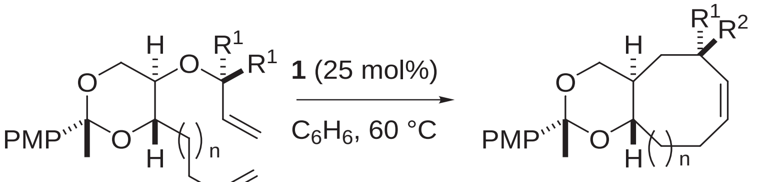
Recent examples:



Crimmins *J. Org. Chem.* **1996**, *61*, 4192.
Jacobsen *J. Org. Chem.* **1996**, *61*, 7963.



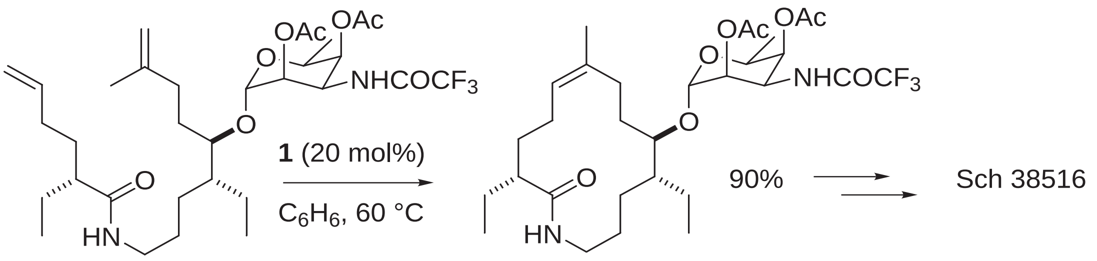
R^1 = H, n = 1, 2 >90%
R^1 = Et, n = 1, 2 42-73%



n	R^1	R^2	conc (M)	Yield
1	H	Et	0.008	97%
2	H	Et	0.003	86%
2	Et	H	0.003	14%
2	H	H	0.003	58%

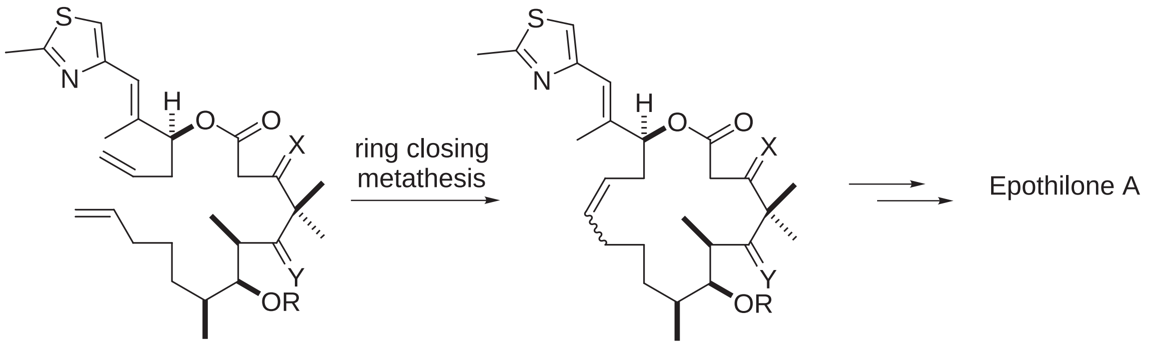
note dependence on conformation
between two diastereomers.

Clark, Kettle *Tetrahedron Lett.* **1997**, *38*, 123 and 127.



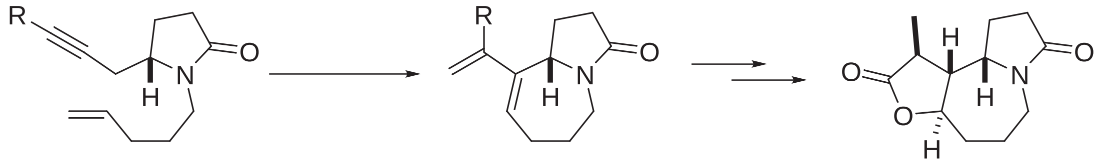
Hoveyda *J. Am. Chem. Soc.* **1995**, *117*, 2943.
J. Am. Chem. Soc. **1996**, *118*, 10926.

- Danishefsky, Nicolaou and Schinzer have all prepared Epothilone A using ring closing metathesis as the key cyclization step.



Danishefsky *J. Am. Chem. Soc.* **1997**, *119*, 2733.
Nicolaou *Angew. Chem., Int. Ed. Eng.* **1997**, *36*, 166.
Schinzer *Angew. Chem., Int. Ed. Eng.* **1997**, *36*, 523.

- Application to ring closing metathesis of enynes:

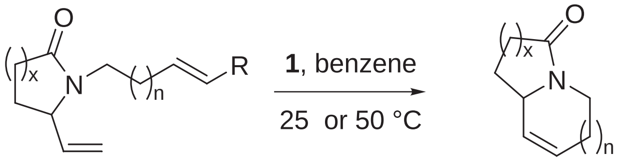


R = Me: **2** (5 mol%), C_6H_6, 50 °C, 73%
R = CO_2Me: **3** (4 mol%), CH_2Cl_2, 25 °C, 87%

(–)-Stemoamide

Kinoshita, Mori *J. Org. Chem.* **1996**, *61*, 8356.

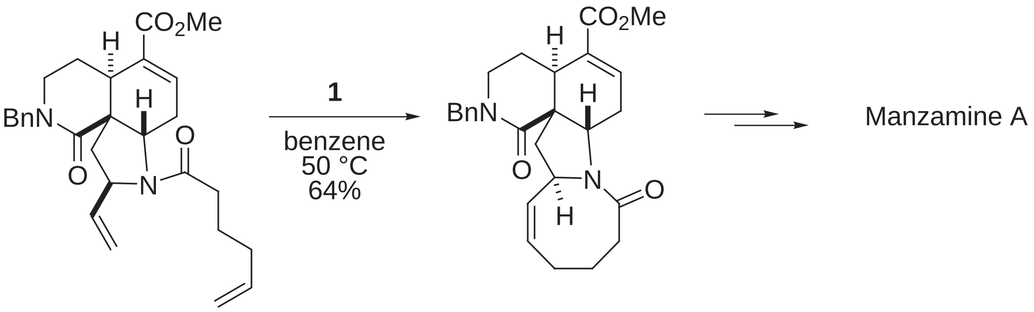
- Application to the synthesis of fused nitrogen heterocycles:



a) x = 1
b) x = 2

a) x = 1
b) x = 2

n = 0, R = Me a (68%)
n = 1, R = H a (92%); b (91%)
n = 2, R = H a (81%); b (84%)
n = 3, R = H a (47%); b (50%)



Martin *Tetrahedron* **1996**, *52,* 7251.

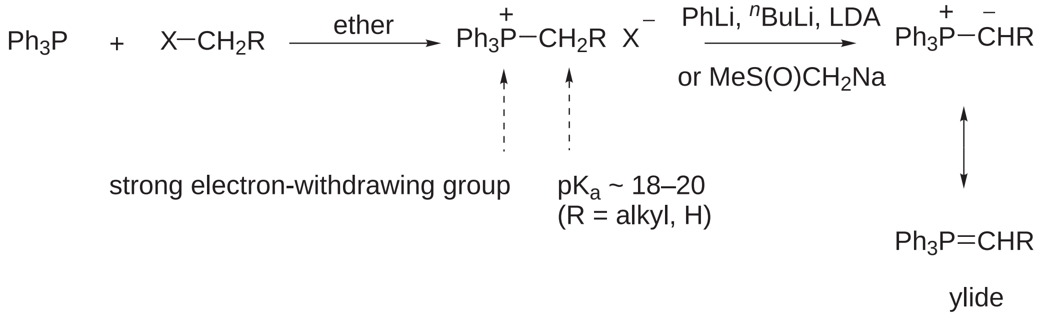
XI. Olefin Synthesis

A. Wittig Reaction

> G. Wittig received the 1979 Nobel Prize in Chemistry for "many significant contributions to Organic Chemistry" which included not only the Wittig reaction, but also PhLi prepared by metal–halogen exchange, benzyne, and the Wittig rearrangement.

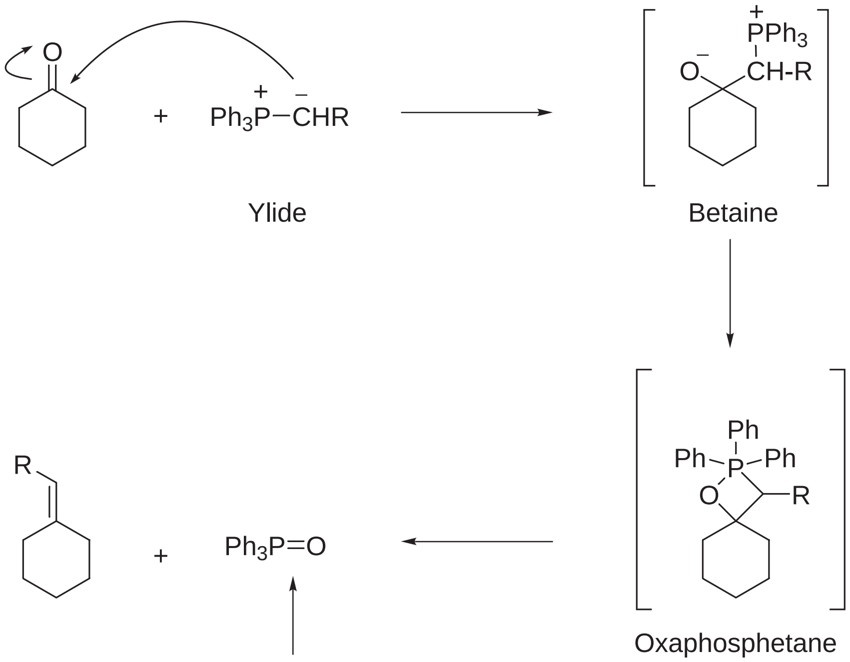
Reviews:	*Comprehensive Org. Syn.,* Vol. 1, 755.
	Org. React. **1965**, *14*, 270.
	Angew. Chem., Int. Ed. Eng. **1964**, *3*, 250.
	Top. Stereochem. **1970**, *5*, 1.
	Pure. Appl. Chem. **1979**, *51*, 515.
	Chem. Rev. **1989**, *89*, 863.

1. Formation of Ylides



- Unstabilized ylides are sensitive to H_2O, O_2

2. Reaction of Ylides with Ketones



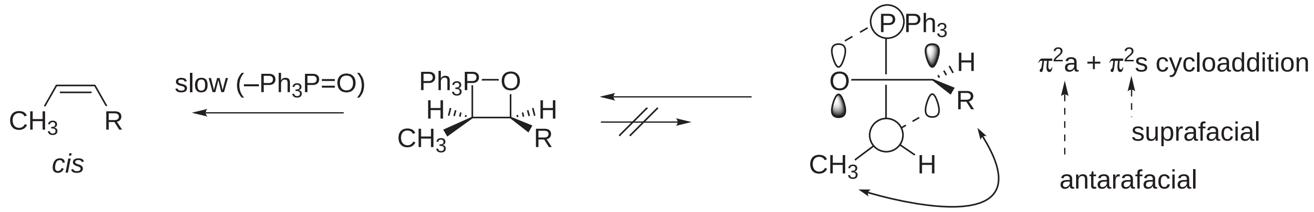
Strong bond formation is part of the driving force for the collapse of the oxaphosphetane.

Wittig and Schöllkopf *Chem. Ber*. **1954**, *87*, 1318.

3. Mechanism and Stereoselectivity of the Wittig Reaction

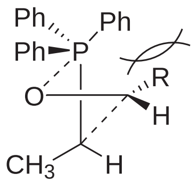
cis olefin from nonstabilized ylides

- Stereoselectivity increases as the size of the R group increases.
- Accepted mechanism today: irreversible and concerted [2 + 2] cycloaddition.

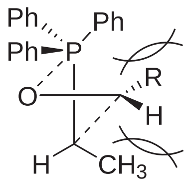


Orientation such that the R groups on the aldehyde and on the ylide are as far apart as possible.

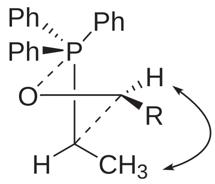
- The three alternative [2 + 2] cycloaddition transition states suffer destabilizing steric interactions:



trans



cis



trans

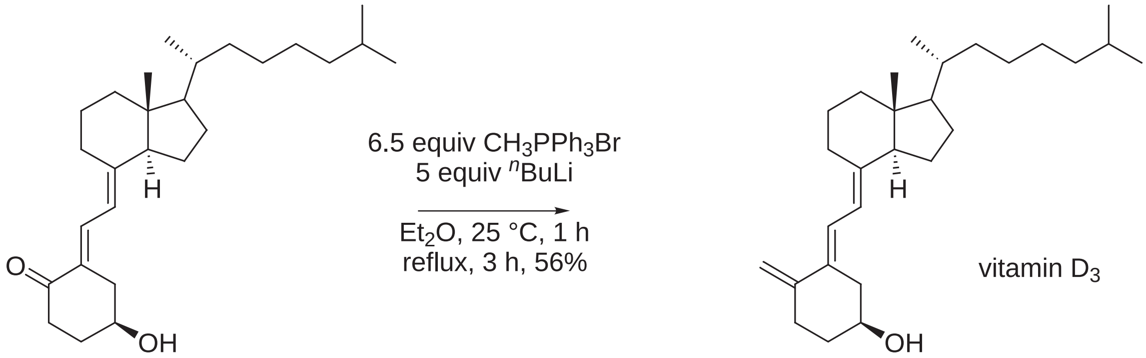
Not bad, probably gives rise to *trans* product

- So, the mechanism involves fast, irreversible [2 + 2] cycloaddition (at –78 °C) followed by slow decomposition of oxaphosphetane (frequently requires warming to 0–25 °C).
- Nonpolar solvents facilitate the initial addition.
- Polar solvents facilitate the final elimination reaction.

4. Representative Examples

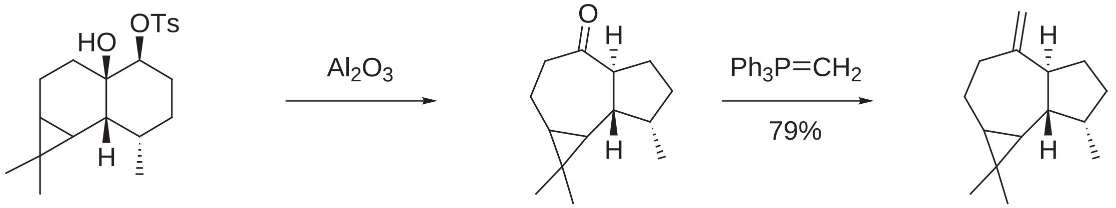
80%, >98% *cis*

Besterman *Chem. Ber*. **1976**, *109*, 1694.

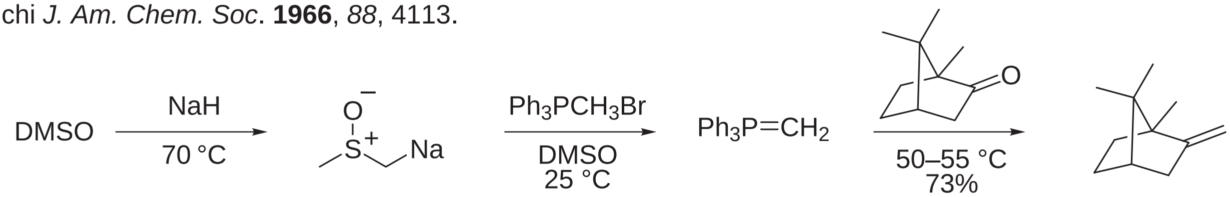


vitamin D_3

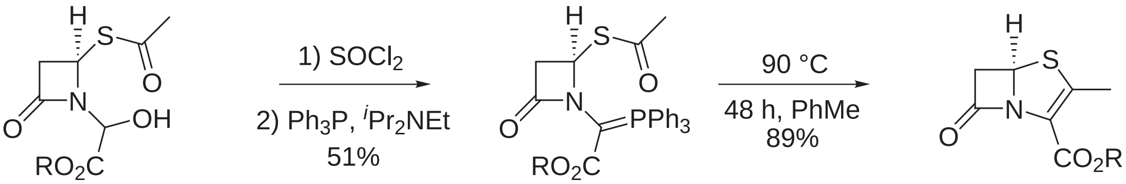
Inhoffen *Chem. Ber*. **1958**, *91*, 2309.



Büchi *J. Am. Chem. Soc*. **1966**, *88*, 4113.

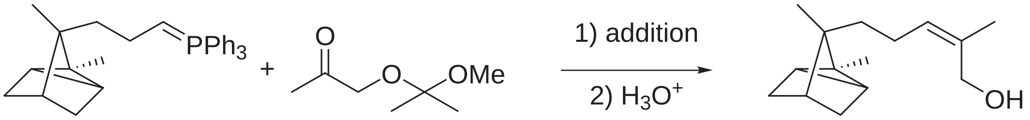


Corey *J. Org. Chem*. **1963**, *28*, 1128.



Woodward *J. Am. Chem. Soc*. **1979**, *101*, 6301.

- α-oxygenated substrates

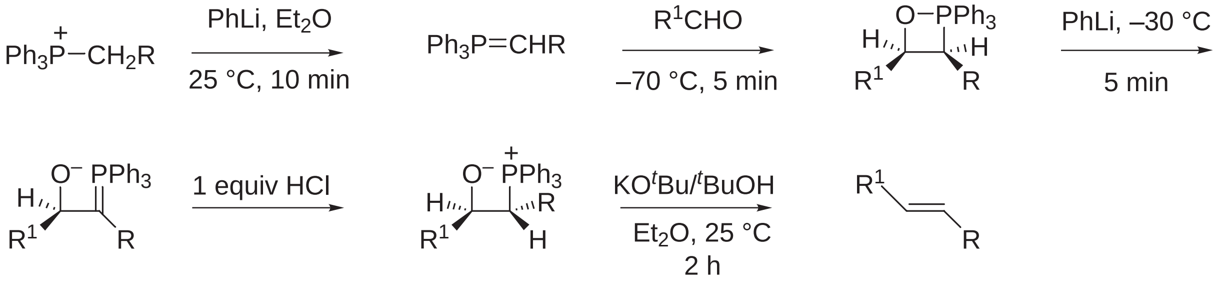


- trisubstituted
  Z-alkene

85%, >99% *Z*

Still *J. Org. Chem*. **1980**, *45*, 4260.

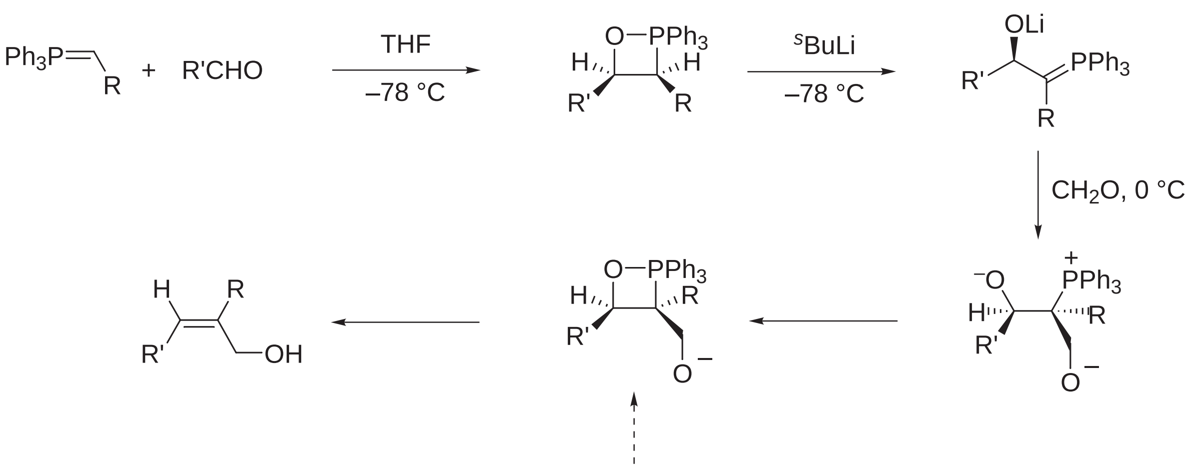
- Schlösser modification: allows the preparation of *trans* vs. *cis* olefins.



R	R^1	% yield	*trans:cis*
CH_3	C_5H_{11}	70	99:1
C_5H_{11}	CH_3	60	96:4
C_3H_7	C_3H_7	72	98:2
CH_3	Ph	69	99:1
C_2H_5	Ph	72	97:3

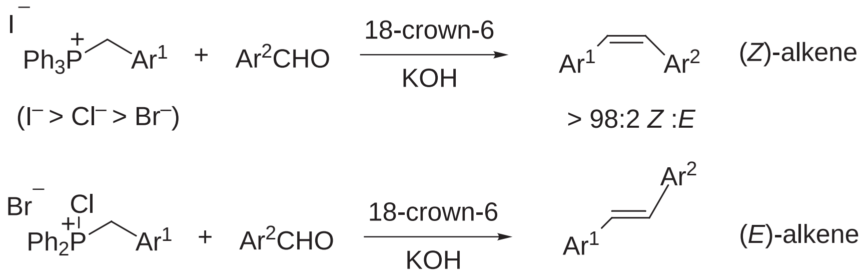
Schlösser *Angew. Chem., Int. Ed. Eng*. **1966**, *5*, 126.

- β-Oxido Phosphonium Ylide Reaction: adaptation of the Schlösser modification for the stereoselective preparation of trisubstituted allylic alcohols.



Only 2° alkoxide forms oxaphosphetane that eliminates to form the olefin.

Corey, Katzenellenbogen and Posner *J. Am. Chem. Soc*. **1967**, *89*, 4245.
Corey and Yamamoto *J. Am. Chem. Soc*. **1970**, *92*, 226.
Corey and Yamamoto *J. Am. Chem. Soc*. **1970**, *92*, 6636.
Corey and Yamamoto *J. Am. Chem. Soc*. **1970**, *92*, 6637.



($I^- > Cl^- > Br^-$)

> 98:2 *Z* :*E*

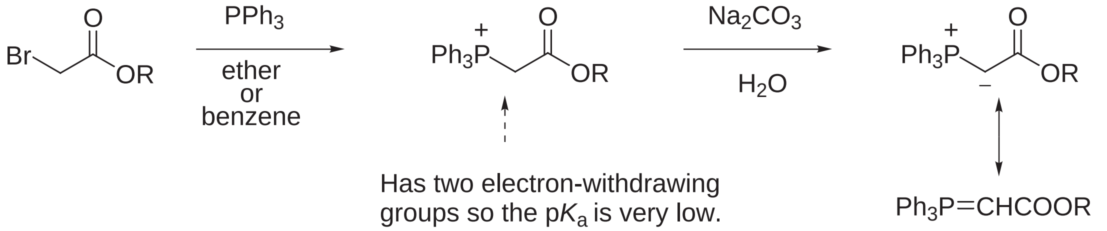
> 96:4 *E* : *Z*

C. J. Pedersen (DuPont) received the 1987 Nobel Prize in Chemistry for his discovery and development of crown ethers.

Jean-Marie Lehn received the 1987 Nobel Prize in Chemistry along with D. J. Cram and C. J. Pedersen for their development and use of molecules with structure-specific interactions of high selectivity.

Chiappe *Tetrahedron Lett*. **1996**, *37*, 4225.

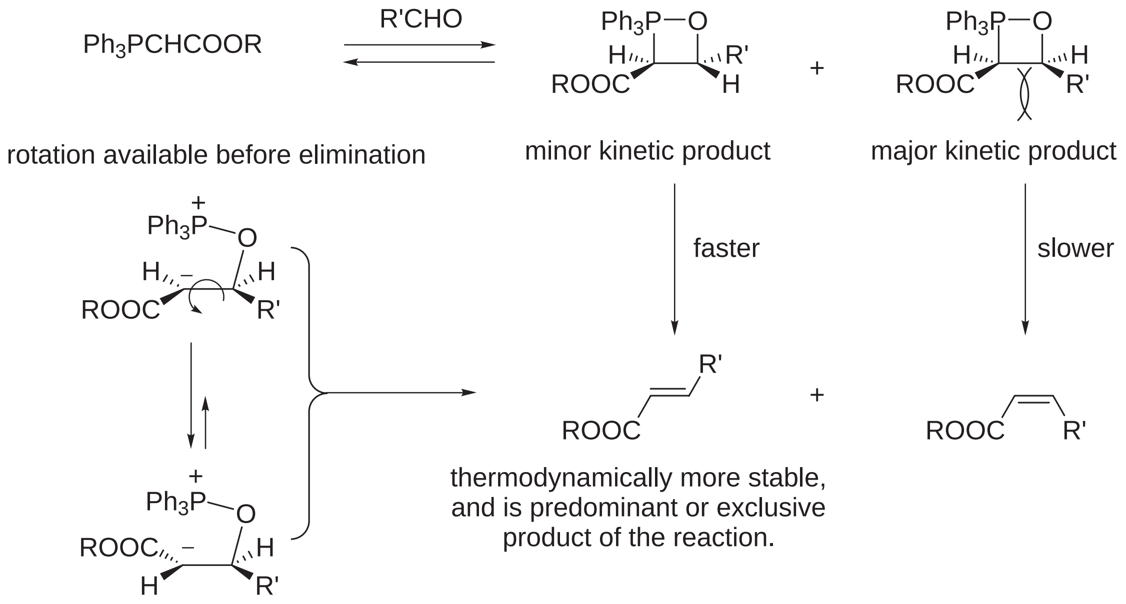
5. Stabilized Ylides



Has two electron-withdrawing groups so the pK_a is very low.

$Ph_3P{=}CHCOOR$

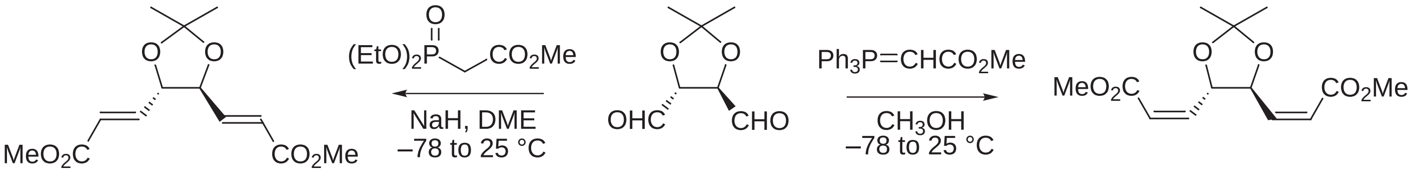
- Stabilized ylides are solid; stable to storage, not particularly sensitive to moisture, and can even be purified by chromatography.
- Because they are stabilized, they are much less reactive than alkyl ylides. They react well with aldehydes, but only slowly with ketones.
- The first step, involving the addition to the aldehyde, is slow and reversible with stabilized ylides.



thermodynamically more stable, and is predominant or exclusive product of the reaction.

- It is also possible that elimination occurs in a stepwise manner via stabilized zwitterionic intermediate that may simply afford the more stable product.

- α-Oxygenated substrates
  - The exception to the generation of *E*-alkenes with stabilized ylides is their reaction with α-alkoxy aldehydes.

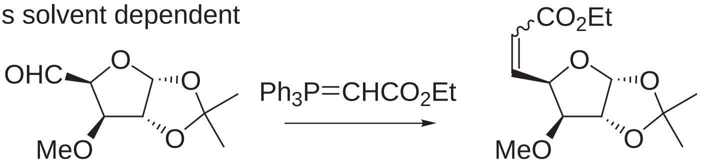


trans (*E*)-olefin

cis (*Z*)-olefin!

Krief *Tetrahedron Lett*. **1988**, *29*, 1083.

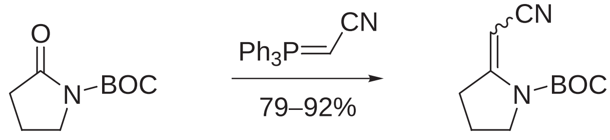
- And, this departure is solvent dependent

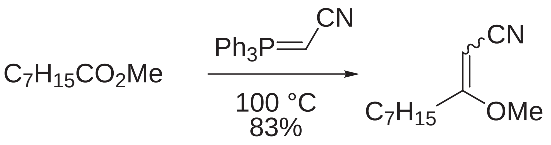


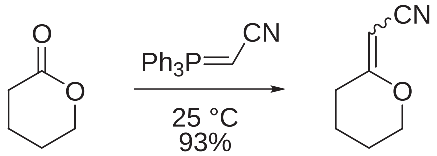
DMF	14 : 86	*Z* : *E*	← *trans*
$CHCl_3$	60 : 40	*Z* : *E*	
MeOH	92 : 9	*Z* : *E*	← *cis*

Tronchet, Gentile *Helv. Chim. Acta* **1979**, *62*, 2091.

- Reaction with esters, lactones, and activated lactams

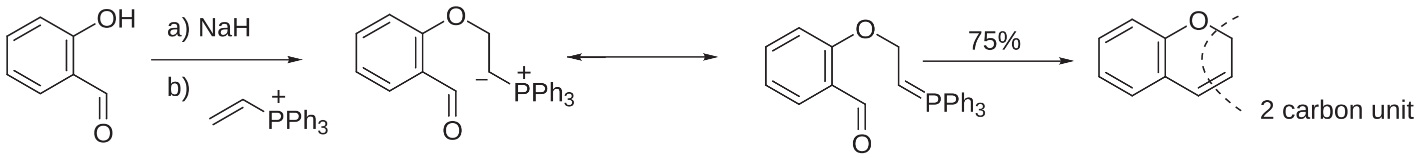


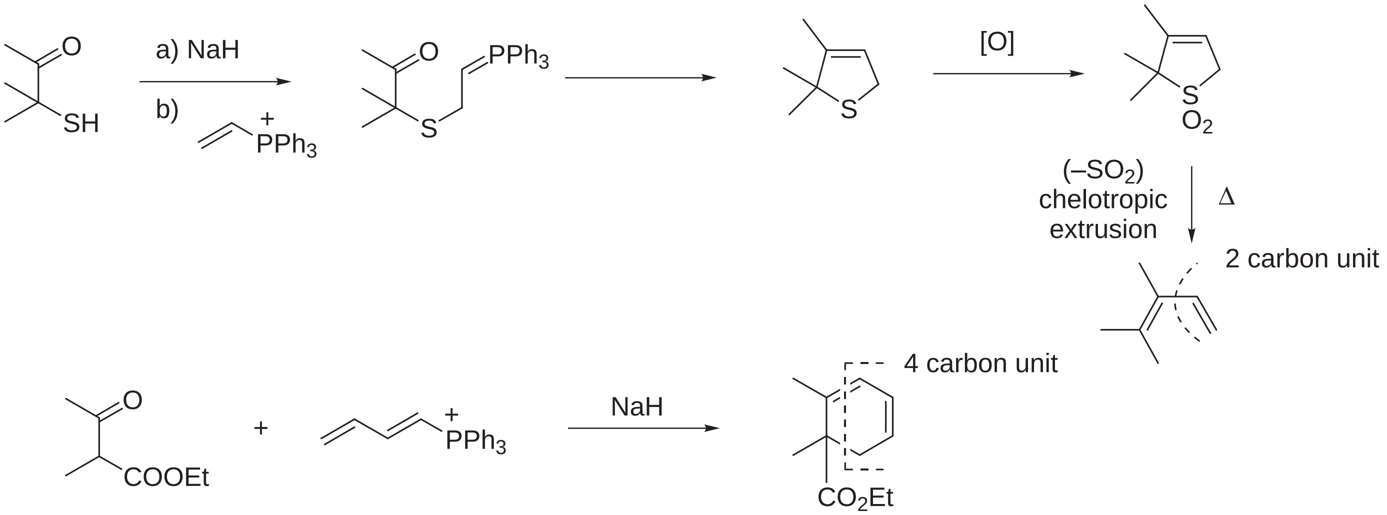




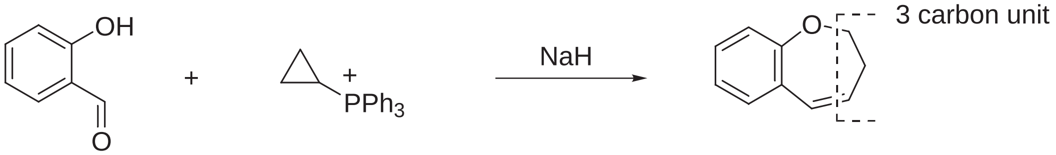
Tsunoda *Tetrahedron Lett.* **2000**, *41*, 235.

6. Annulation Applications of the Wittig Reaction



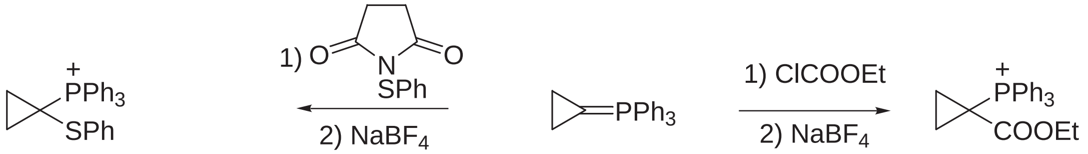


- Homoconjugate addition:



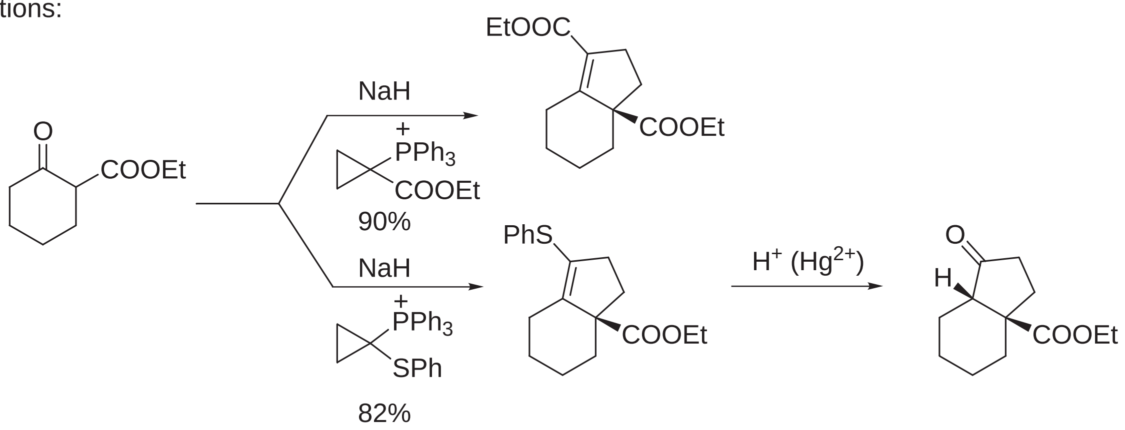
- Modest yields because one electron-withdrawing group is not sufficient to activate the cyclopropane ring to nucleophilic ring opening.

So:



Dauben *J. Am. Chem. Soc*. **1975**, *97*, 1622.

- Applications:



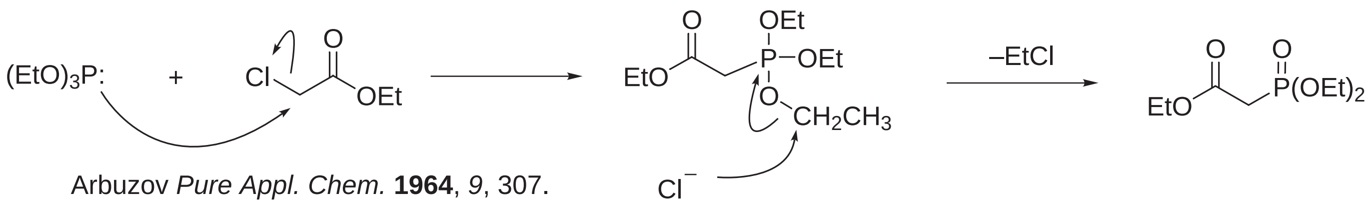
B. Wadsworth–Horner–Emmons Reaction

Horner *Chem. Ber*. **1958**, *91*, 61; **1959**, *92*, 2499.
Wadsworth, Emmons *J. Am. Chem. Soc.* **1961**, *83,* 1733.

Reviews: *Org. React*. **1977**, *25*, 73–253.
Comprehensive Org. Syn., Vol. 1, 761.

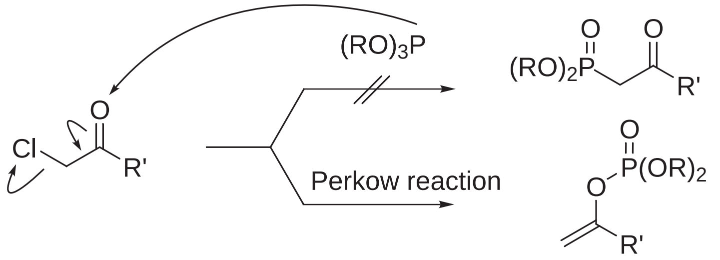
1. Arbuzov (Michaelis–Arbuzov) Reaction: Preparation of Phosphonate Esters

Arbuzov *J. Russ. Phys. Chem. Soc.* **1906**, *38*, 687. Michaelis *Ber.* **1898**, *31*, 1048.

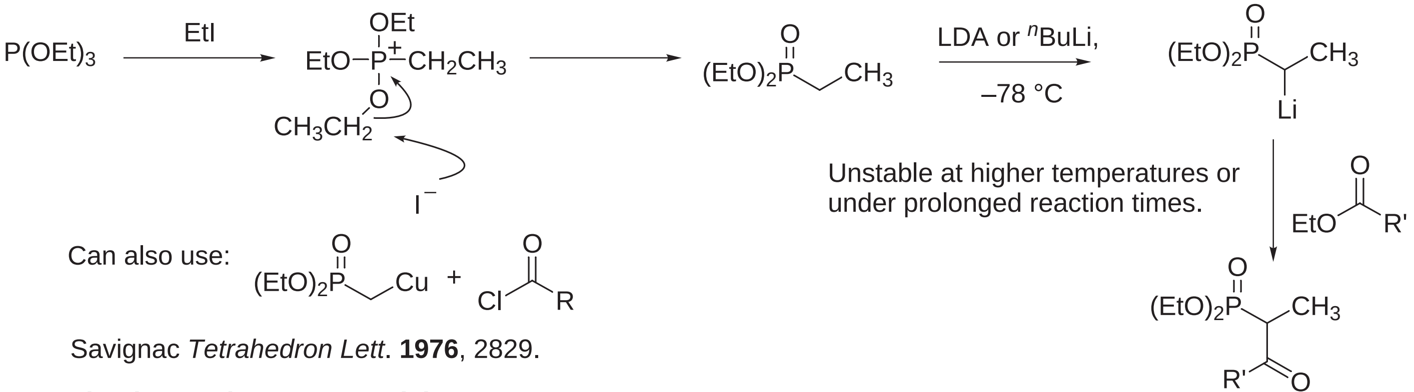


Arbuzov *Pure Appl. Chem.* **1964**, *9*, 307.

- The same approach to the preparation of β-ketophosphonates is not successful:



- But can use variation on Claisen conditions:

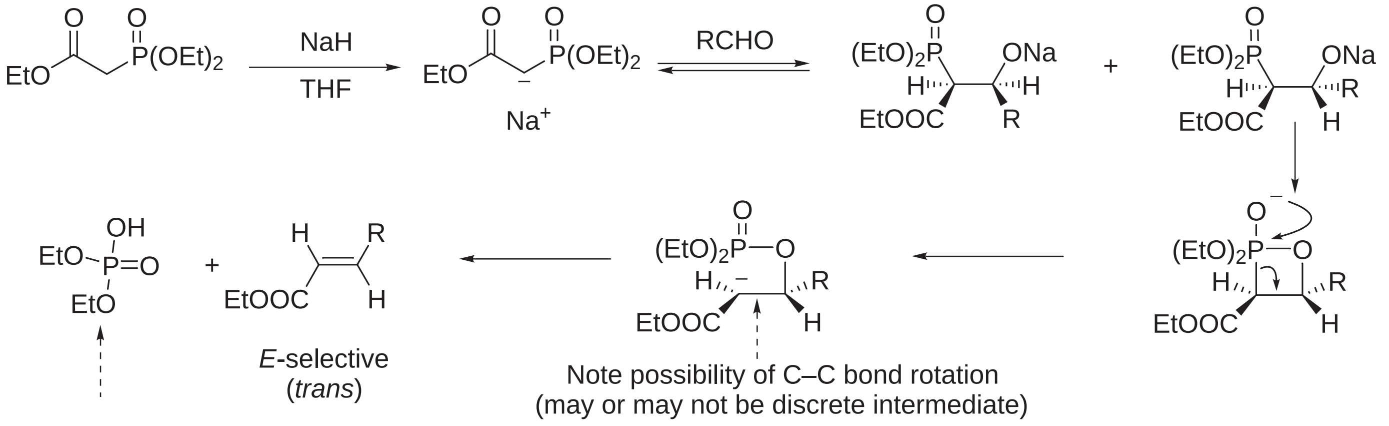


Unstable at higher temperatures or under prolonged reaction times.

Can also use:

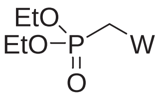
Savignac *Tetrahedron Lett*. **1976**, 2829.

2. Mechanism and Stereoselectivity



Water soluble (easily removed through aqueous workup)

Good reactions for:

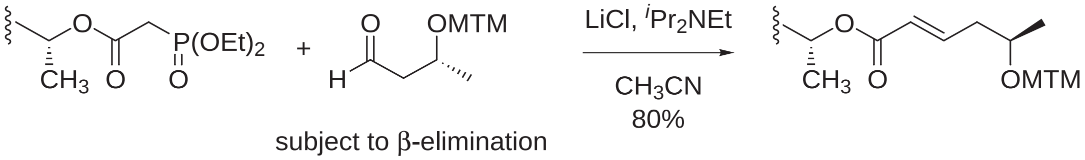


W = CN, COOR, C(O)R, CHO, SO_2Ph, Ph
But not W = alkyl, H

3. Modifications and Scope

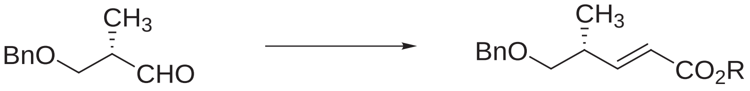
- LiCl/tertiary amines (DBU, ^{i}Pr$_2$NEt, Et$_3$N)

Masamune, Roush *Tetrahedron Lett*. **1984**, *25*, 2183.
Can substitute for conventional conditions and is especially good for base sensitive substrates (epimerization, elimination).



Keck *J. Org. Chem*. **1989**, *54*, 896. (thioester was also stable to these conditions)

-Hindered phosphonates and hindered aldehydes increase *E*-selectivity (*trans*).

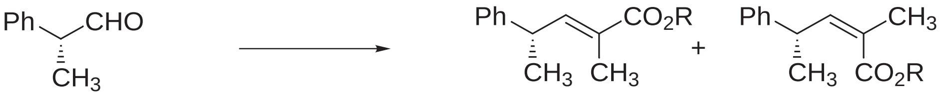


Ph$_3$P=CHCO$_2$Et, CH$_2$Cl$_2$, 0 °C	7 : 1	*E* : *Z*
(^{i}PrO)$_2$POCH$_2$CO$_2$Et, KO^{t}Bu, THF, –78 °C	95 : 5	*E* : *Z*
(MeO)$_2$POCH$_2$CO$_2$Me, KO^{t}Bu, THF, –78 °C	1 : 3	*E* : *Z*

Kishi *Tetrahedron* **1981**, *37*, 3873.

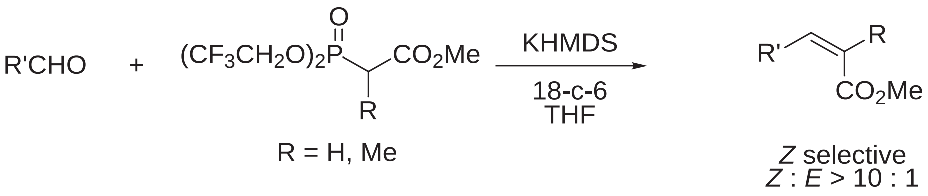
- The use of a nonhindered phosphonate, low temperatures, and a strongly dissociating base (KO^{t}Bu) can give increased or high *Z*-selectivity (*cis*).

- Coordinating countercations slow the rate of elimination relative to equilibration.



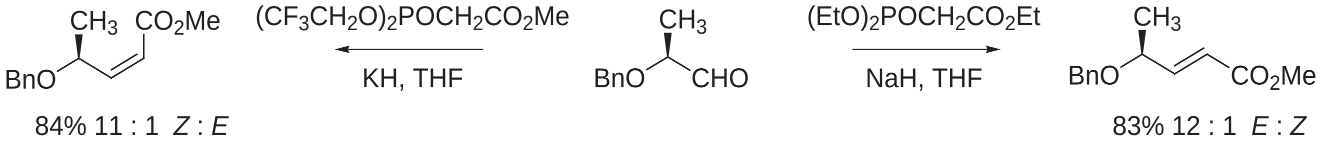
Stabilized Wittig reagent	Ph$_3$P=C(Me)CO$_2$Et, CH$_2$Cl$_2$, 25 °C	95	:	5
	Ph$_3$P=C(Me)CO$_2$Et, MeOH, 25 °C	85	:	15
Wadsworth–Horner–Emmons reagent	(MeO)$_2$POCH(Me)CO$_2$Me, KO^{t}Bu, THF, –78 °C	5	:	95
	(MeO)$_2$POCH(Me)CO$_2$Et, KO^{t}Bu, THF, –78 °C	10	:	90
	(EtO)$_2$POCH(Me)CO$_2$Et, KO^{t}Bu, THF, –78 °C	40	:	60
	(^{i}PrO)$_2$POCH(Me)CO$_2$Et, KO^{t}Bu, THF, –78 °C	90	:	10
	(^{i}PrO)$_2$POCH(Me)CO$_2$^{i}Pr, KO^{t}Bu, THF, –78 °C	95	:	5

- Still–Gennari modification selective for *Z*-alkenes (*cis*):

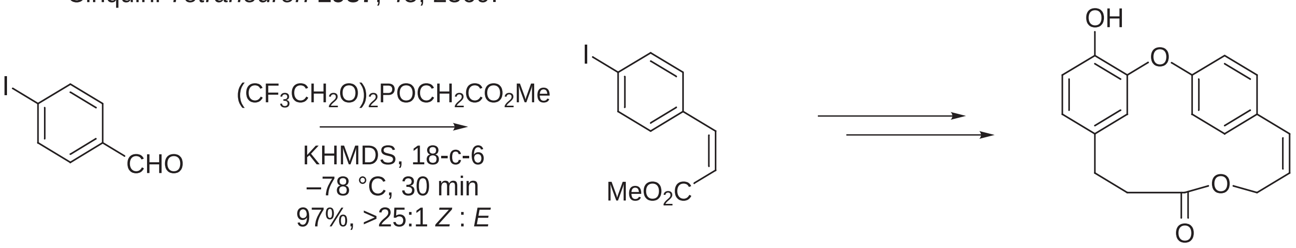


Still *Tetrahedron Lett*. **1983**, *24*, 4405.

R = Br, Kogen *Org. Lett.* **2000**, *2*, 1975. (Trisubstituted olefins via Suzuki or Stille coupling)



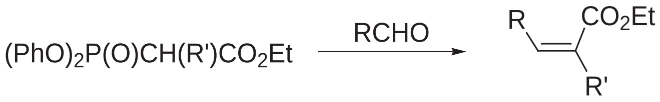
Cinquini *Tetrahedron* **1987**, *43*, 2369.



Boger *J. Org. Chem*. **1991**, *56*, 4204.

Combretastatin D-2

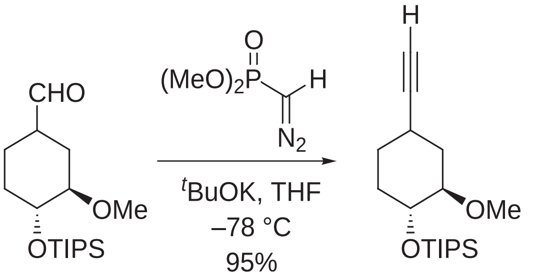
- Additional *Z*-selective stabilized phosphonates.



Ando *J. Org. Chem*. **1997**, *62*, 1934.
Ando *J. Org. Chem*. **2000**, *65*, 4745. (NaI/DBU vs NaH)

Selected diarylphosphonates provide high *Z*-selectivity
Ando *J. Org. Chem*. **1998**, *63*, 8411.

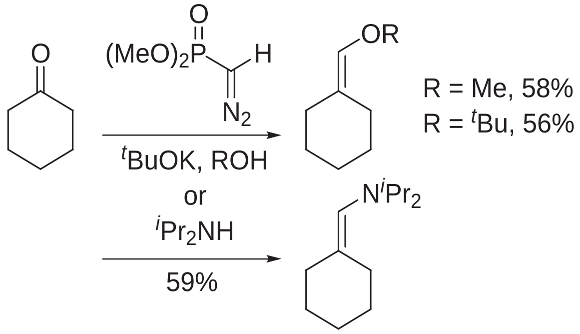
- Other useful reactions of functionalized phosphonates.



- Direct production of alkynes.

Provide a mechanism
for this transformation

Schreiber *J. Am. Chem. Soc.* **1990**, *112*, 5583.



- Synthesis of enol ethers
and enamines.

Gilbert *Tetrahedron Lett.* **1980**, *21*, 2041, 5003; **1984**, *25*, 2303.
J. Org. Chem. **1983**, *48*, 448.

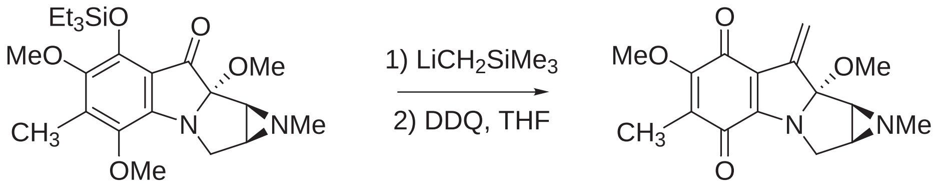
C. Peterson Olefination

Peterson *J. Org. Chem*. **1968**, *33*, 780.
J. Org. Chem. **1967**, *32*, 1717.
J. Am. Chem. Soc. **1975**, *97*, 1464.
Reviews: *Org. React*. **1990**, *38*, 1.

1. Nonstabilized Peterson Reagents

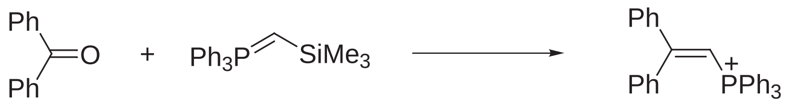
- Me_3SiCH_2Met, Met = Li, Mg, offer an alternative to Wittig or Tebbe procedures. They are more reactive and sterically less demanding than a Wittig reagent and the volatile byproduct (Me_3SiOH/ $Me_3SiOSiMe_3$) is simpler to remove than Ph_3PO. It does, however, require a second step to promote elimination of the β-hydroxysilane.

- Example



Danishefsky *J. Org. Chem*. **1988**, *53*, 3391.

- TMS eliminates in preference to Ph_3P or $P(O)(OR)_2$:

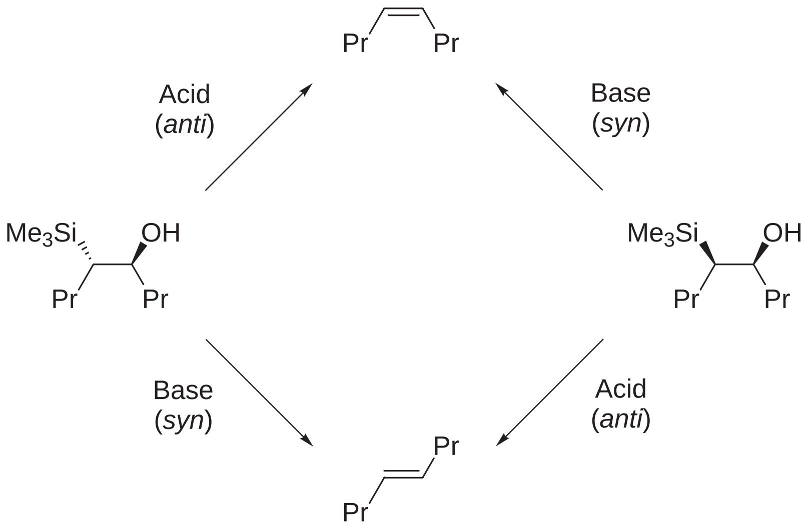


Peterson. *J. Org. Chem*. **1968**, *33*, 780.

Note: this is the origin of its discovery

- Modifications include: Me_3SiCH_2MgBr/ $TiCl_4$ (direct production of olefin), and Me_3SiCH_2Li/ $CeCl_3$ (enolizable ketones and aldehydes, while esters and acid chlorides give allylsilanes via addition 2x).

- The elimination is stereospecific: acid-promoted being *anti* and base-promoted being *syn*.

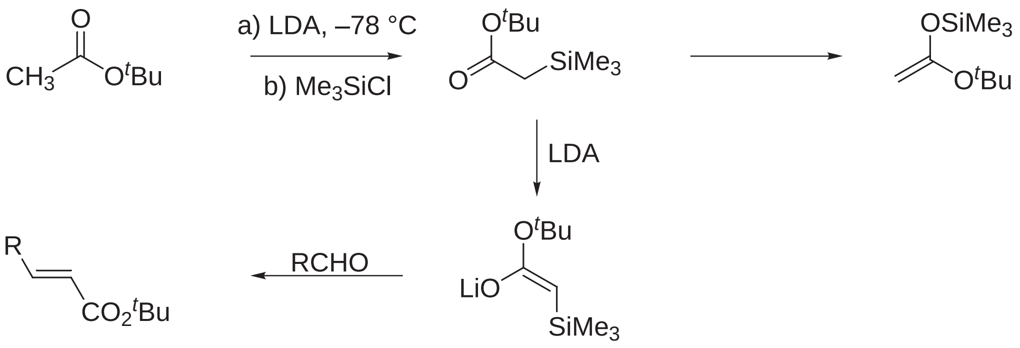


Hudrlik, Peterson *J. Am. Chem. Soc*. **1975**, *97*, 1464.

- Unstabilized Peterson reagents add to ketones and aldehydes irreversibly with little diastereoselectivity. Therefore, mixtures of *cis* and *trans* olefins are obtained and the reactions are not yet as useful as the Wittig reaction.

2. Stabilized Peterson Reagents

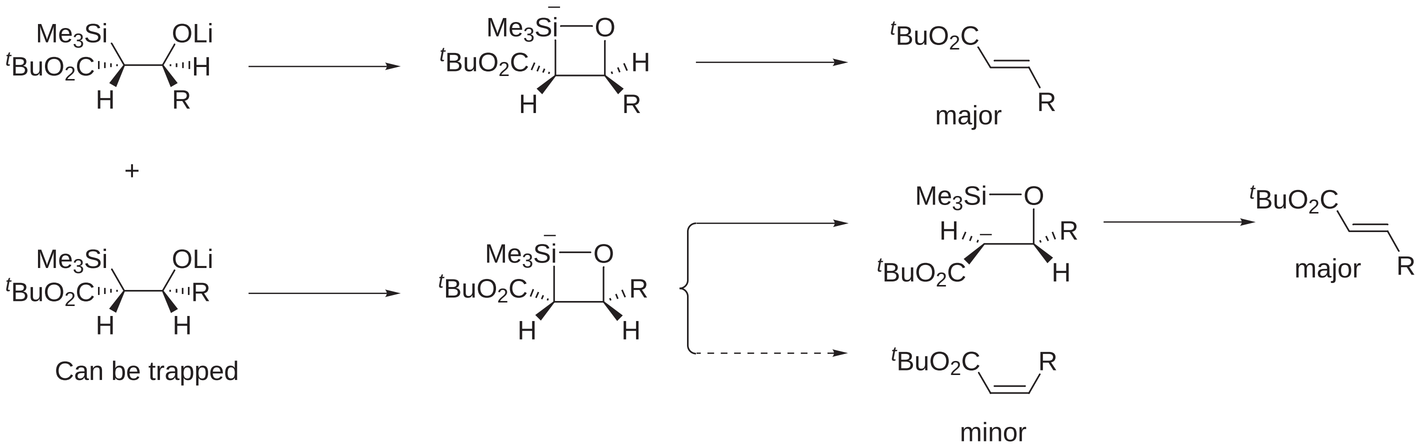
- The stabilized Peterson reagents give predominantly the most stable *trans* olefins (*E*) although this has been studied far less than the Wittig or Wadsworth–Horner–Emmons reactions. The origin of this diastereoselection has not been extensively explored with regard to enolate geometry, reversible/ irreversible addition, or mechanism of elimination. In this case, the elimination takes place under the reaction conditions.



trans predominates

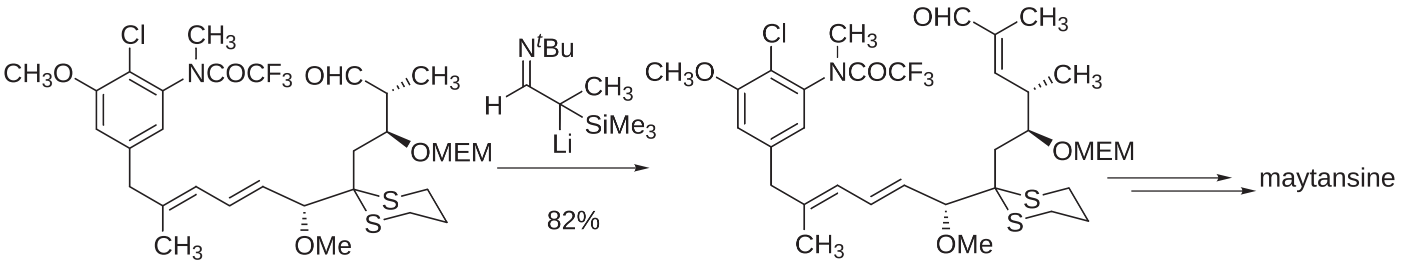
Rathke *Tetrahedron Lett*. **1974**, 1403.
Yamamota *J. Am. Chem. Soc*. **1974**, *96*, 1620.

- via:

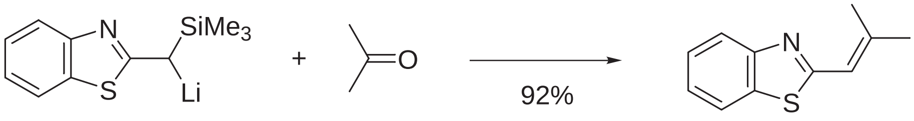


- Both single step and two-step elimination via an equilibration have been proposed.

- Additional examples:



Corey, Weigel, Chamberlin, Lipshutz *J. Am. Chem. Soc*. **1980**, *102*, 1439.
Corey, Enders, Bock *Tetrahedron Lett*. **1976**, 3 and 7.



Corey and Boger *Tetrahedron Lett*. **1978**, 5.

D. The Tebbe Reaction and Related Titanium-stabilized Methylenations

reviews: *Org. React*. **1993**, *43*, 1.
Comprehensive Org. Syn., Vol. 1, 743.

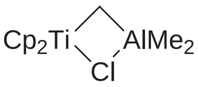
- The Wittig, Wadsworth–Horner–Emmons, and Peterson olefination do not convert esters or amides to the corresponding olefin, but rather fail to react or result in the cleavage of the ester or amide bond.

- Schrock discovered that Ta and Nb *tert*-butyl alkylidene complexes behave analogous to phosphorous ylides and, notably, react with esters and amides to provide the corresponding ^{t}butylalkenes.

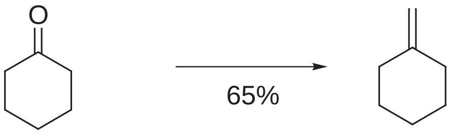
Schrock *J. Am. Chem. Soc*. **1976**, *98*, 5399.

- The Tebbe reagent was introduced in 1978 and was shown to react with aldehydes, ketones, esters, and lactones to produce the methylene derivatives.

X = H, R, OR, NR$_2$



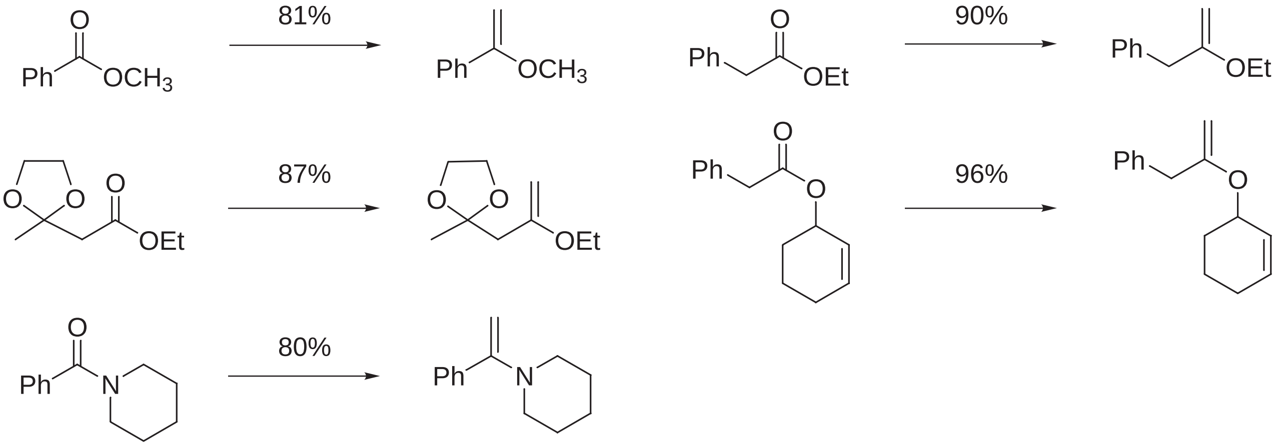
Tebbe reagent



Tebbe *J. Am. Chem. Soc*. **1978**, *100*, 3611.

- Tolerates ketal and alkene derivatives.

Scope defined by Evans and Grubbs *J. Am. Chem. Soc*. **1980**, *102*, 3270.
Extended to tertiary amides by Pine *J. Org. Chem*. **1985**, *50*, 1212.



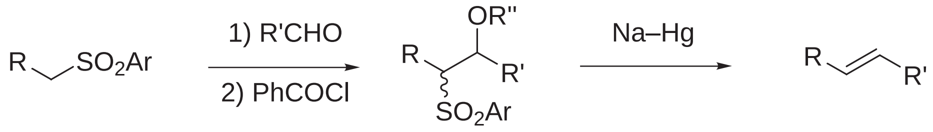
For an analogous use of Cp$_2$TiMe$_2$: Petasis *J. Am. Chem. Soc*. **1990**, *112*, 6392.

E. Representative Other Methods for Terminal Methylene Formation

Reagents	References
R_2CO, CH_2Cl_2, Mg	Cainelli *Tetrahedron Lett*. **1967**, 5153.
R_2CO, $LiCH_2PO(NMe_2)_2$	Corey *J. Am. Chem. Soc*. **1966**, *88*, 5653.
R_2CO, $LiCH_2SPh$; CH_3SO_2Cl; Li/NH_3	Coates *J. Am. Chem. Soc*. **1972**, *94*, 4758.
R_2CO, $LiCH_2SPh$; $(RO)_2PCl$; heat	Kuwajima *Tetrahedron Lett*. **1972**, 737.
R_2CO, $LiCH_2S(O)Ph$	Kuwajima *Tetrahedron Lett*. **1972**, 649.

- Julia Olefination

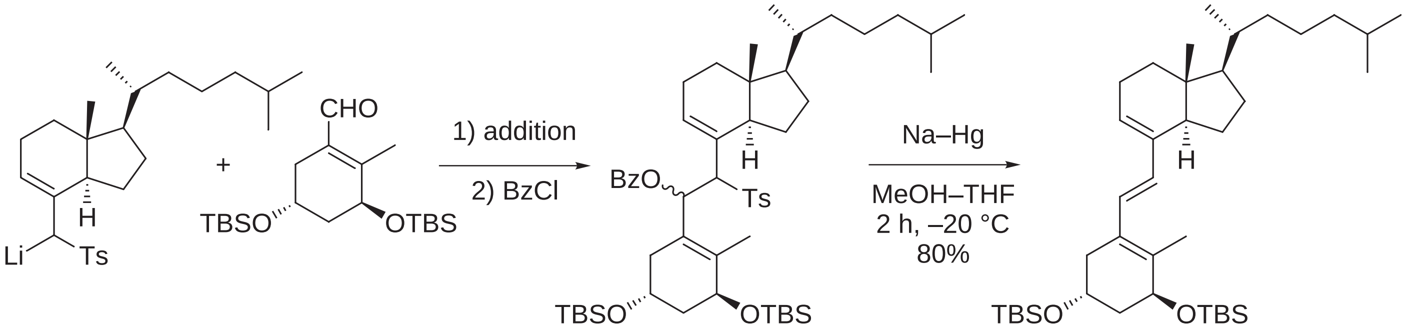
Review: *Comprehensive Org. Syn*., Vol. 1, 792.



R'' = Ms, Ts, Ac, COPh

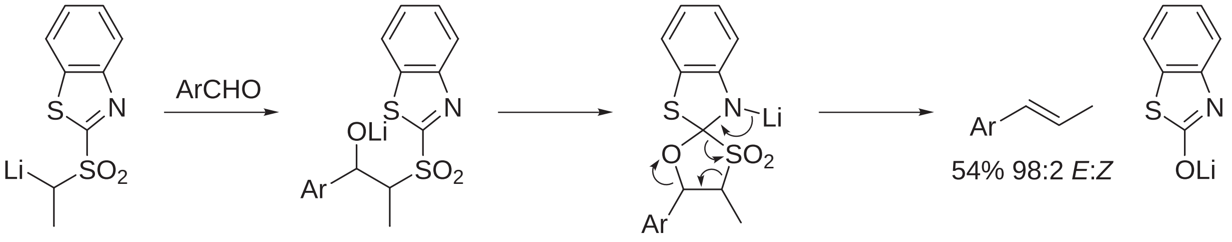
exclusively or predominantly the more stable *trans* isomer

- Example:



Julia *Tetrahedron Lett*. **1973**, 4833.

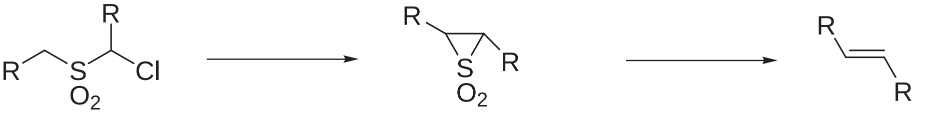
Julia developed a more recent, single-step variant that avoids the reductive elimination



Julia *Bull. Soc. Chim., Fr.* **1993**, *130*, 336.

R_2CO, $LiCH_2S(O)^tBu$; $SOCl_2–CH_2Cl_2$	Durst *J. Am. Chem. Soc*. **1973**, *95*, 3420.
$–CH(OH)CH_2CO_2H$, $HC(OMe)_2NMe_2$, heat	Hara *Tetrahedron Lett*. **1975**, 1545.
$RC{\equiv}CH$, $RCu \longrightarrow R_2C{=}CH_2$	Normant *Tetrahedron Lett*. **1971**, 2583.
RCO_2CH_3, $Ph_3P{=}CH_2 \longrightarrow R(CH_3)C{=}CH_2$	van der Gen *Tetrahedron Lett*. **1975**, 1439.
R_2CO, $PhS(O)(NCH_3)CH_2Li$	Johnson *J. Am. Chem. Soc*. **1973**, *95*, 6462.
$RCH_2SO_2CH_2Cl$, $HO^–$	Doomes and Corfield *J. Am. Chem. Soc*. **1970**, *92*, 2581.

- Ramberg–Backlund reaction



Org. React. **1977**, *25*, 1.

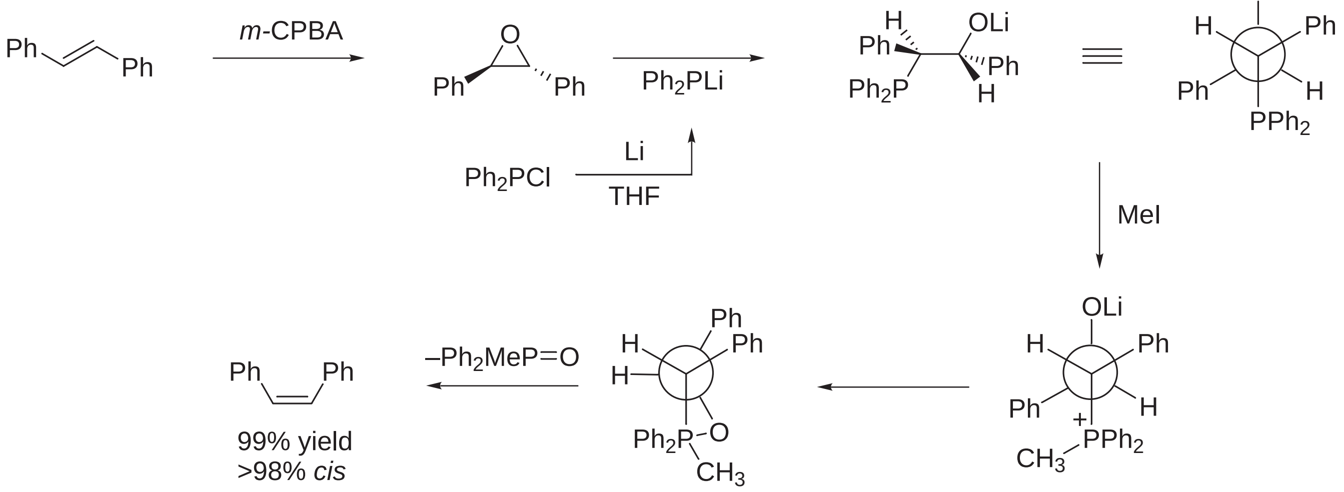
Reagents	References
RC≡CH, H_2/ Lindlar catalyst	*Org. Syn*. **1969**, *46*, 89.
R_2CHCH_2OAc, Δ (pyrolysis)	*Org. React*. **1961**, *12*, 57.
Also: xanthates	*Chem Rev*. **1960**, *60*, 431.
$R_2CHCH_2NMe_2$, H_2O_2, Δ	*Org. React*. **1960**, *11*, 317.

- Cope Elimination
  - it is related to the Hofmann elimination reaction (–$\overset{+}{\mathrm{N}}\mathrm{Me}_3$)
  - Both the acetate pyrolysis and the Cope elimination have been superceeded by the related *syn* elimination reactions of sulfoxides and selenoxides.

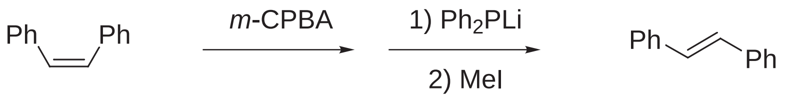
$R_2C(Hal)CH_3$, ^{t}BuOK	*J. Chem. Soc., Chem. Commun*. **1968**, 305.

F. Olefin Inversion Reactions

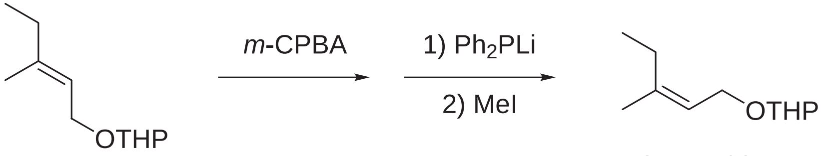
Vedejs *J. Am. Chem. Soc*. **1971**, *93*, 4070.



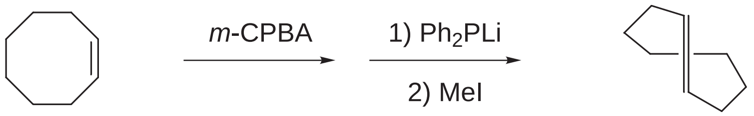
-Other examples:



95%; > 99% *trans*

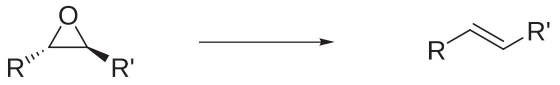


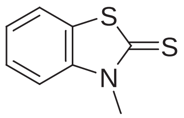
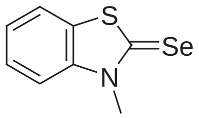
85%; >98% *Z*



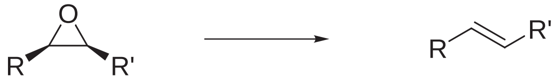
90%; >99% *trans*

-Deoxygenation of epoxides (with retention of geometry)



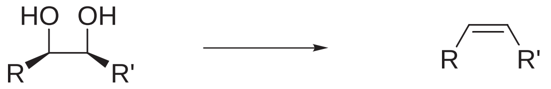
–SCN	van Tamelen *J. Am. Chem. Soc*. **1951**, *73*, 3444.
$Ph_3P{=}S$, H^+	Chan *J. Am. Chem. Soc*. **1972**, *94*, 2880.
	Stojnac *Can. J. Chem*. **1975**, 621.
–SeCN	Johnstone *J. Chem. Soc., Perkin Trans. 1* **1975**, 1216.
$Ph_3P{=}Se$	Clive *J. Chem. Soc., Chem. Commun*. **1973**, 253.
	Chan *Tetrahedron Lett*. **1974**, 2091.
	Calo *Synthesis* **1976**, 200.

-Deoxygenation of epoxides (with inversion of geometry)

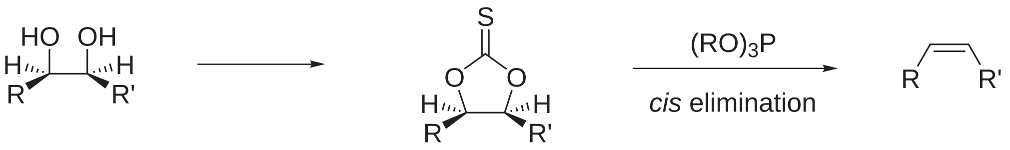


Me_3SiK	Dervan *J. Am. Chem. Soc*. **1976**, *98*, 1265.
$PhMe_2SiLi$	Reetz *Synthesis* **1976**, 199.

-Diol → Alkene

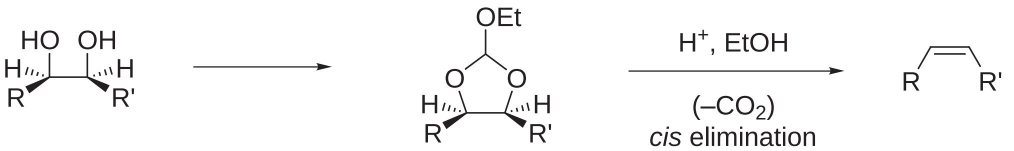


Review: *Org. React*. **1984**, *30*, 457.

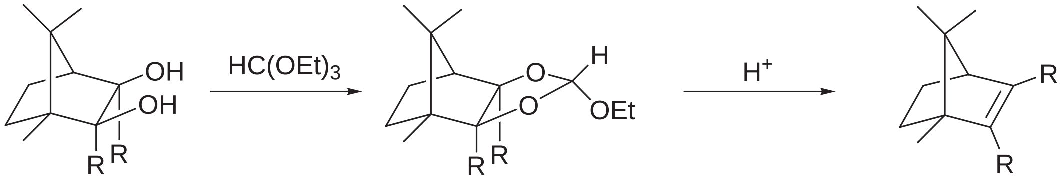


Corey–Winter Olefin Synthesis

Corey *J. Am. Chem. Soc*. **1963**, *85*, 2677.
Corey *J. Am. Chem. Soc*. **1965**, *87*, 934.



Eastwood *Aust. J. Chem*. **1964**, *17*, 1392.
Eastwood *Tetrahedron Lett*. **1970**, 5223.

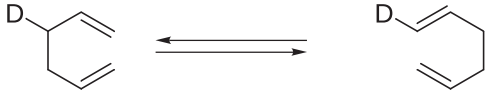


Burgstahler, Boger *Tetrahedron* **1976**, *32*, 309.

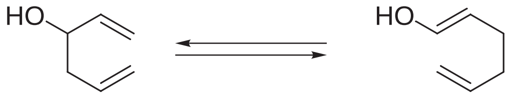
G. [3,3]-Sigmatropic Rearrangements

1. Claisen and Cope Rearrangement

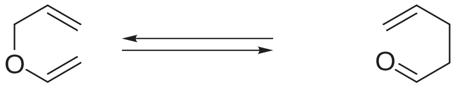
Org. React. **1975**, *22*, 1.
Synthesis **1977**, 589.
Acc. Chem. Res. **1977**, *10*, 227.
Comprehensive Org. Syn., Vol. 5, 785.



Cope Rearrangement



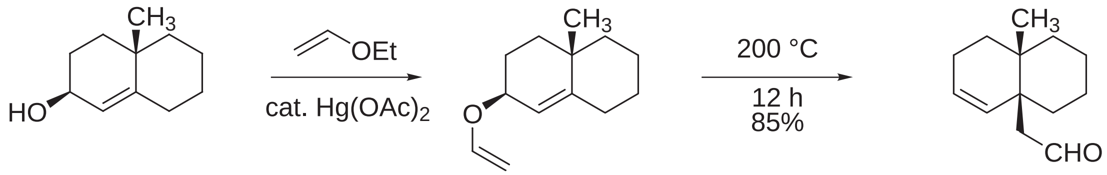
Oxy-Cope Rearrangement



Claisen Rearrangement

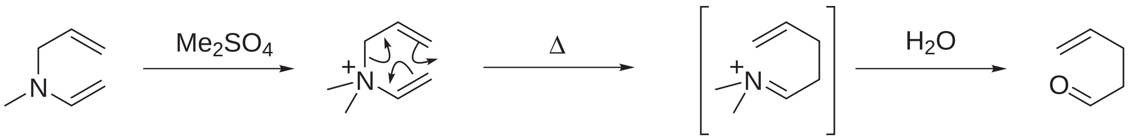
Introduction of C=O is the driving force of the reactio

- Originally conducted on aryl allyl ethers.
- Most useful variant established when extended to nonaromatic substrates.
- First example of an acyclic Claisen rearrangement:



Burgstahler *J. Am. Chem. Soc*. **1961**, *83*, 198.

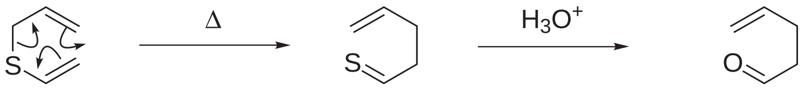
2. Amino-Claisen Rearrangement



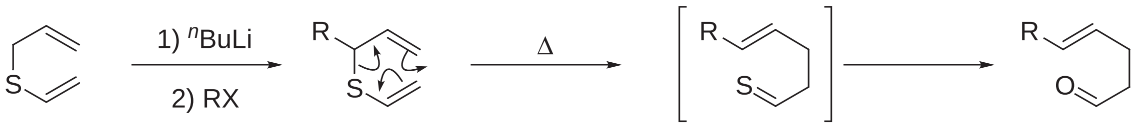
- This reaction occurs best when nitrogen is converted to the ammonium salt.

Gilbert *Tetrahedron Lett*. **1984**, *25*, 2303.
Stille *J. Org. Chem*. **1991**, *56*, 5578.

3. Thio-Claisen Rearrangement



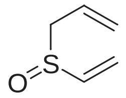
- This reaction is often run with a reagent that will convert sulfur to oxygen following the reaction.
- An advantage of the thio-Claisen rearrangement is that the precursor can be deprotonated and alkylated.



trans C=C bond

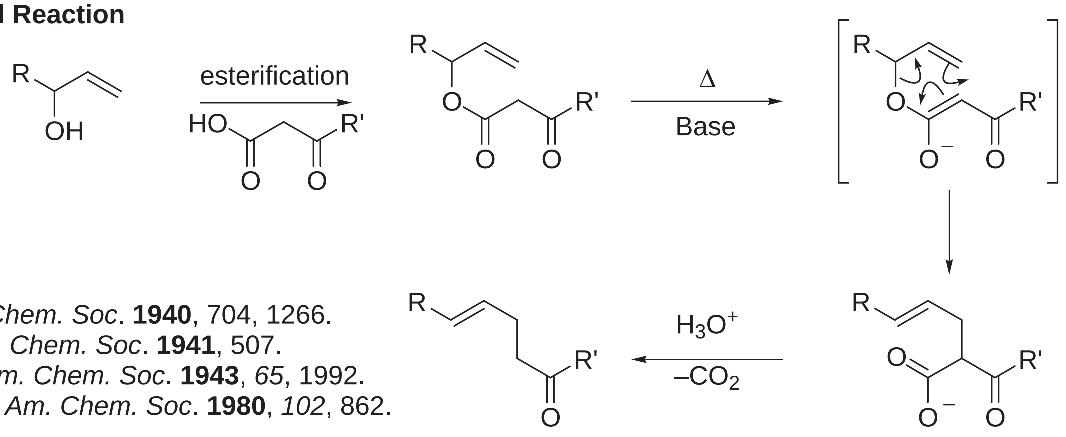
Corey *J. Am. Chem. Soc*. **1970**, *92*, 5522.
Yamamoto *J. Am. Chem. Soc*. **1973**, *95*, 2693 and 4446.

- Also can be conducted with the corresponding sulfoxide.



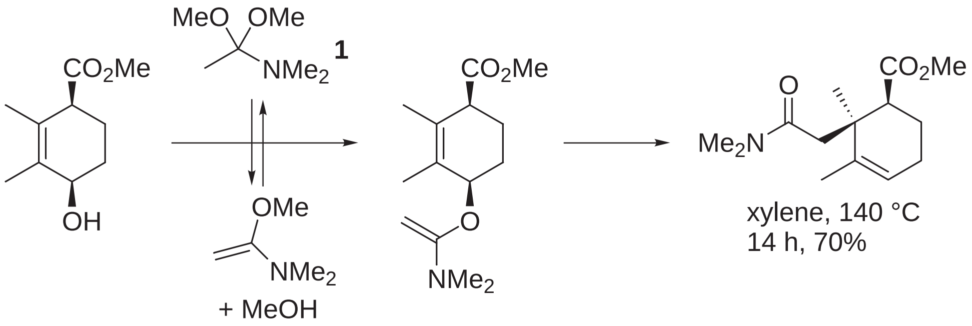
Block *J. Am. Chem. Soc*. **1985**, *107*, 6731.

4. The Carroll Reaction



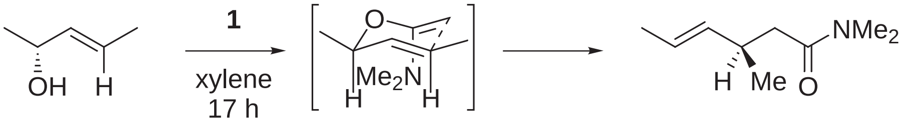
Carroll *J. Chem. Soc*. **1940**, 704, 1266.
Hartung *J. Chem. Soc*. **1941**, 507.
Cope *J. Am. Chem. Soc*. **1943**, *65*, 1992.
Tanabe *J. Am. Chem. Soc*. **1980**, *102*, 862.

5. Eschenmoser–Claisen Rearrangement



xylene, 140 °C
14 h, 70%

Eschenmoser *Helv. Chim. Acta* **1964**, *47*, 2425; **1969**, *52*, 1030.

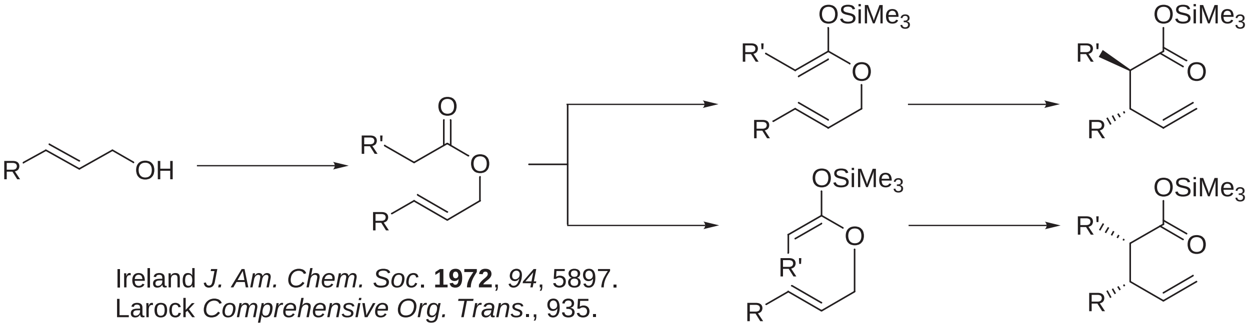


- Chair-like transition state, substituents in equatorial positions lead to *trans* double bond with transfer of chirality.

Hill *J. Org. Chem.* **1972**, *37*, 3737.

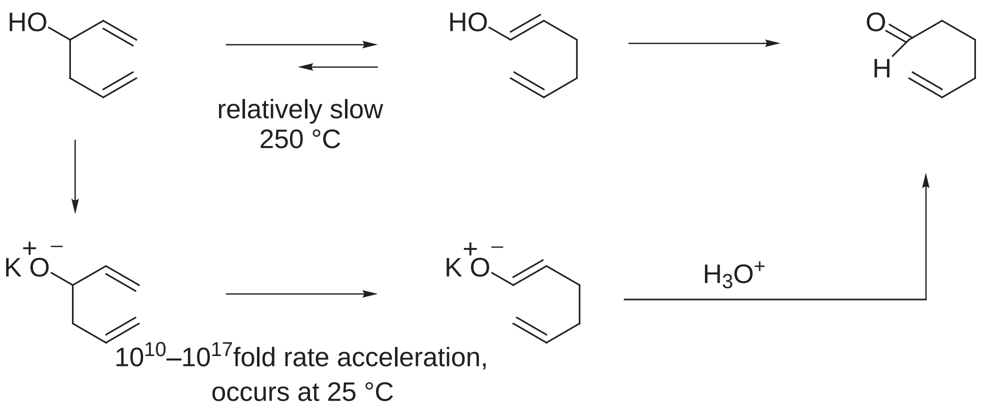
6. Ireland Ester Enolate Claisen Rearrangement

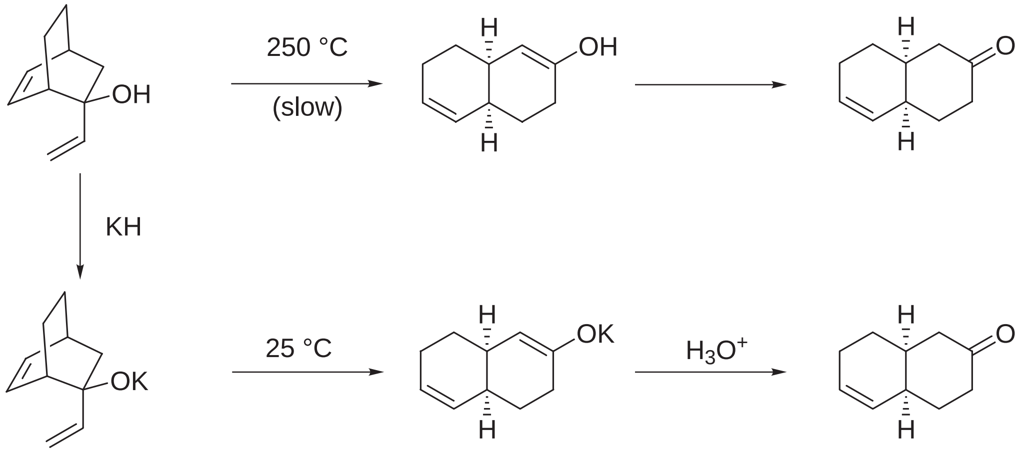
- The most useful of all Claisen rearrangements. The enolate may be trapped with TMSCl or the enolate may be used directly.
- The reaction works well with the free enolate and actually allows for a faster rearrangement that will occur at 25 °C (anion accelerated).



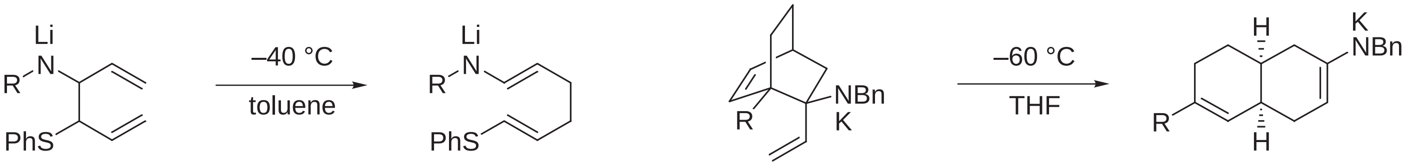
Ireland *J. Am. Chem. Soc*. **1972**, *94*, 5897.
Larock *Comprehensive Org. Trans*., 935.

7. Oxy-Cope Rearrangement





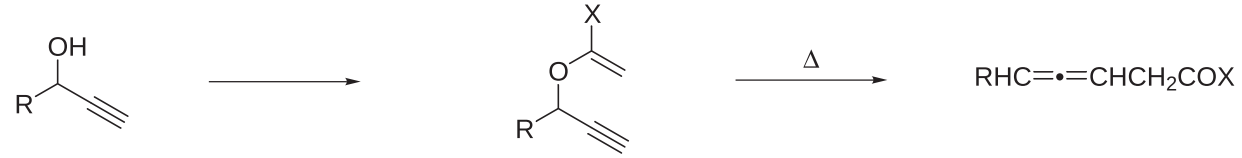
Evans *J. Am. Chem. Soc*. **1975**, *97*, 4765.



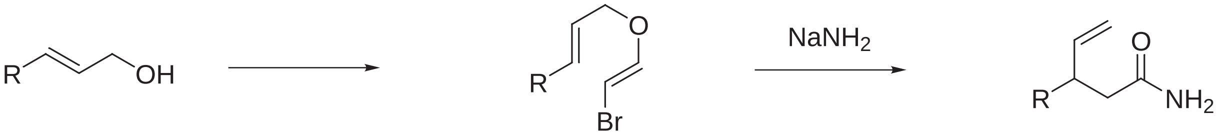
Macdonald *Tetrahedron Lett*. **1993**, *34*, 247.

- For a review of anion accelerated sigmatropic rearrangements: *Org. React*. **1993**, *43*, 93.

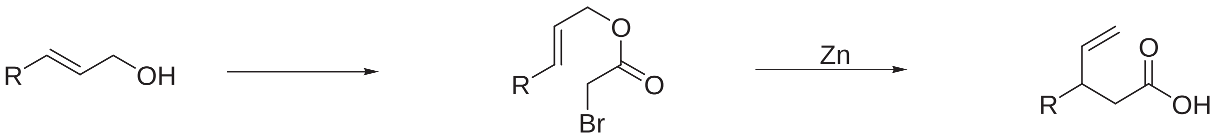
8. Representative [3,3]-Sigmatropic Rearrangement Routes to Olefins



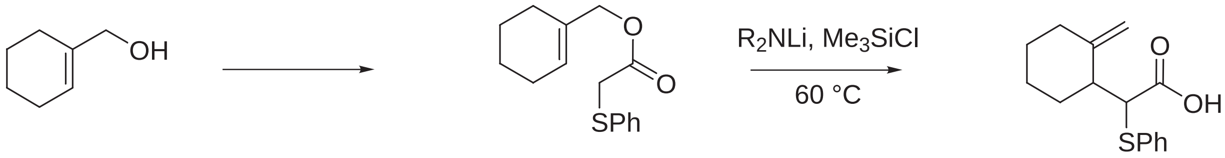
Lumbroso–Bader *Tetrahedron Lett*. **1968**, 4139; **1966**, 3203.



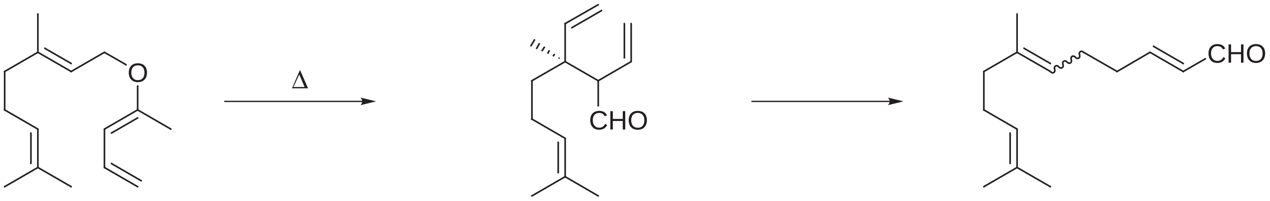
Katzenellenbogen *Tetrahedron Lett*. **1975**, 3275.



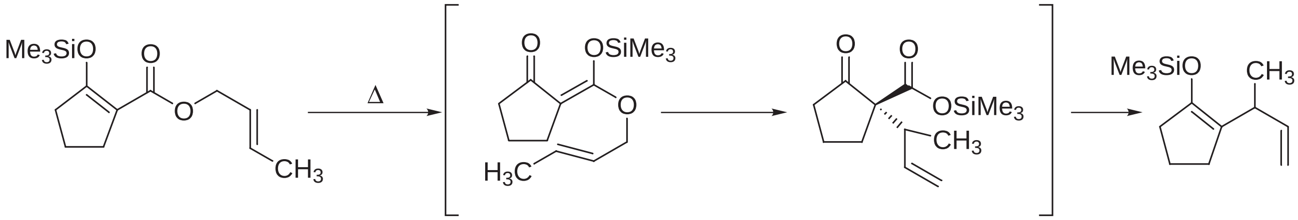
Baldwin *J. Chem. Soc., Chem. Commun*. **1973**, 117.



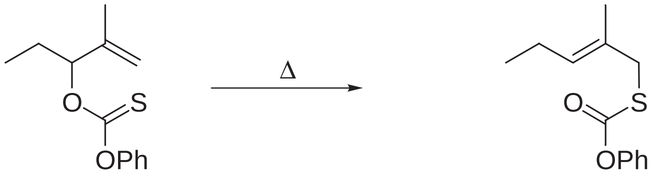
Lythgoe *Tetrahedron Lett*. **1975**, 2593.



Carnduff *J. Chem. Soc., Chem. Commun*. **1967**, 606.



Coates *J. Am. Chem. Soc*. **1975**, *97*, 1619.

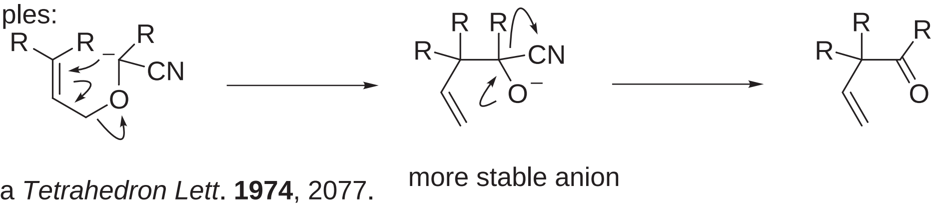


Faulkner *J. Am. Chem. Soc*. **1973**, *95*, 553.

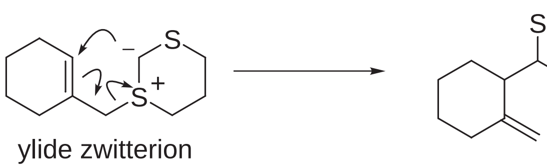
H. [2,3]-Sigmatropic Rearrangements

Review: *Comprehensive Org. Syn*., Vol. 6, pp 834, 873–908.
Org. React. **1994**, *46*, 105–209.

- Analogous to [3,3]-sigmatropic rearrangement except it enlists a localized charge (anion) in place of a double bond.
- Often times the reaction is referred to as a Wittig [2,3]-rearrangement in honor of Wittig's discovery of the related 1,2-alkyl shift of oxycarbanions (Wittig Rearrangement). The reacton is simply a [2,3]-sigmatropic version of the Wittig rearrangement.
- Examples:

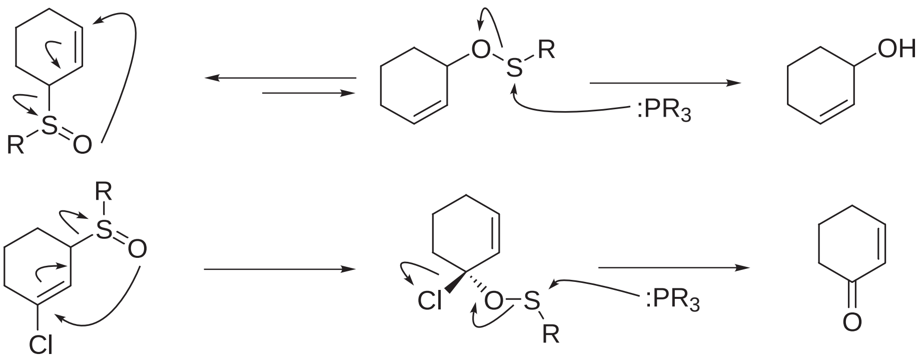


Julia *Tetrahedron Lett*. **1974**, 2077.



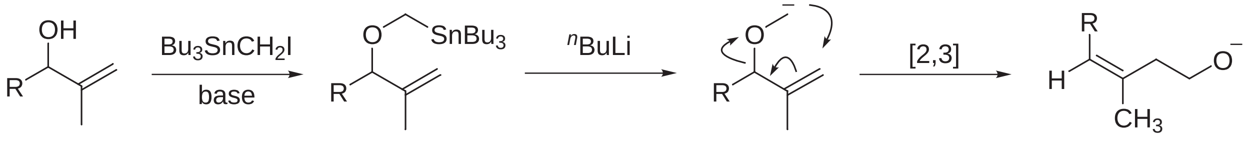
- reaction facilitated by loss of positive charge on sulfur

Lythgoe *J. Chem. Soc., Chem. Commun*. **1972**, 757.

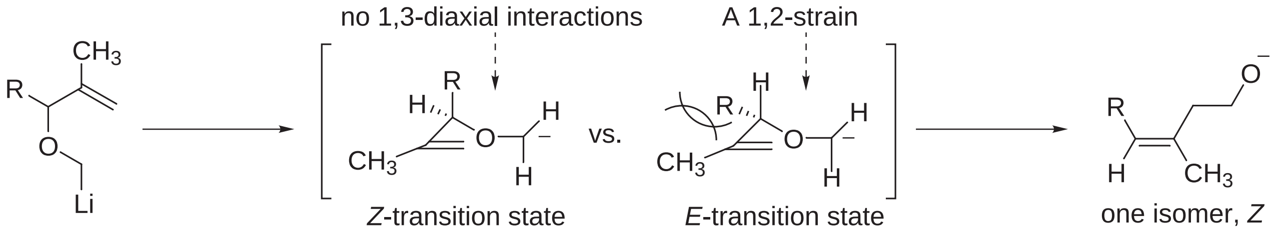


Evans *Acc. Chem. Res*. **1974**, *7*, 147.

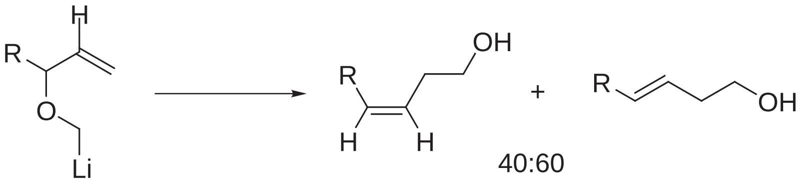
- Still's use of the [2,3]-sigmatropic rearrangement:

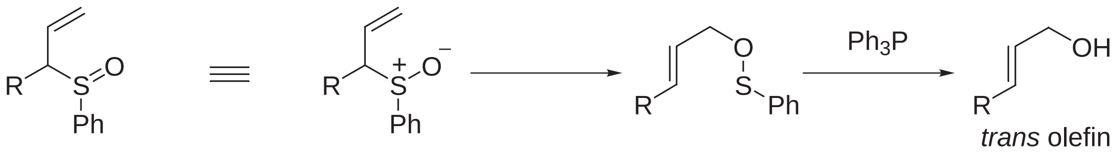


Still *J. Am. Chem. Soc*. **1978**, *100*, 1927.

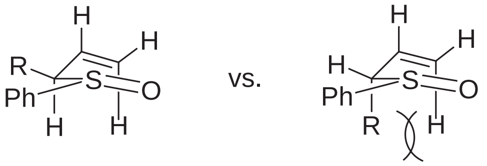


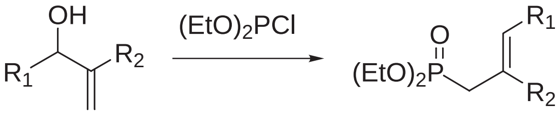
- R prefers the axial versus equatorial position:
- Selectivity is lost when A 1,2-strain is removed





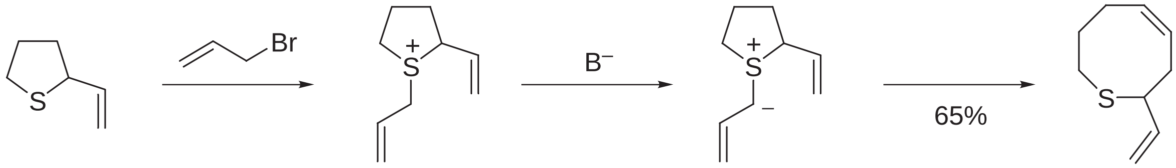
via the transition state:



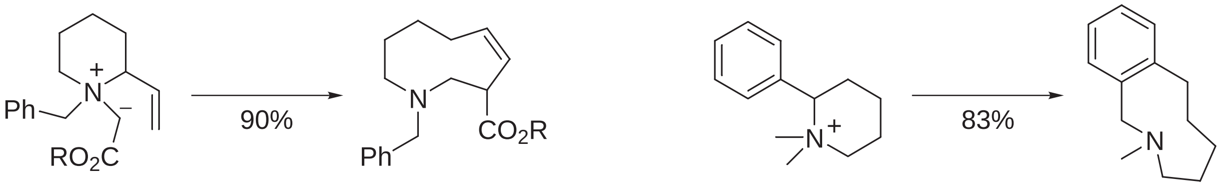


Bodalski *Synthesis* **1990**, 799.

- Ring expansion:

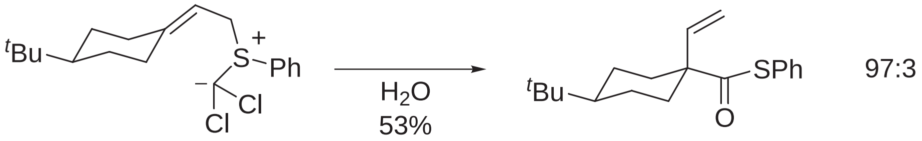


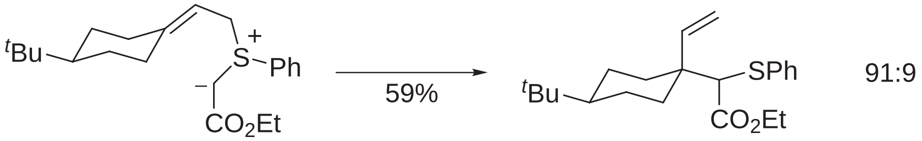
Vedejs *J. Am. Chem. Soc*. **1975**, *97*, 6878.
Vedejs *J. Org. Chem*. **1978**, *43*, 1185.
Vedejs *Tetrahedron Lett*. **1978**, 523, 519.



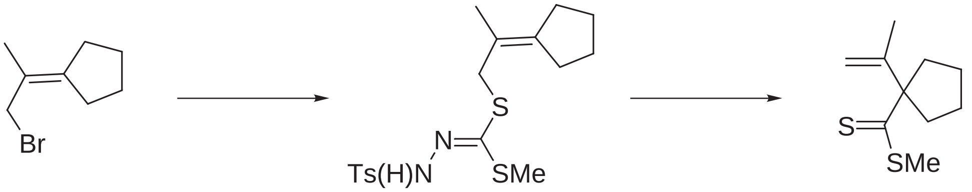
Jones *J. Org. Chem*. **1962**, *27*, 3572.

- Diastereoselectivity:

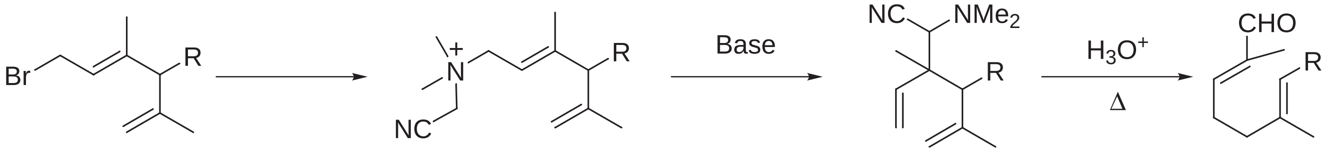




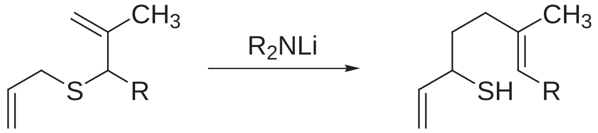
Evans *Tetrahedron Lett*. **1972**, 5121.



Evans *Tetrahedron Lett*. **1973**, 4691.



Mander *J. Org. Chem*. **1973**, *38*, 2915.
Büchi *J. Am. Chem. Soc*. **1974**, *92*, 7573.

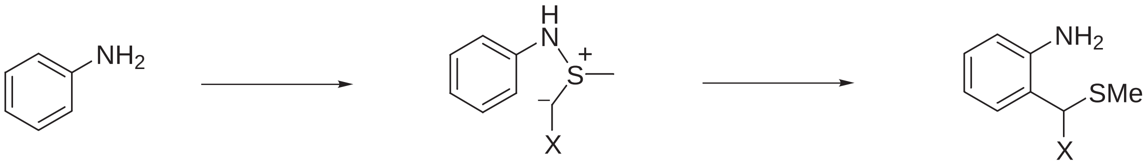


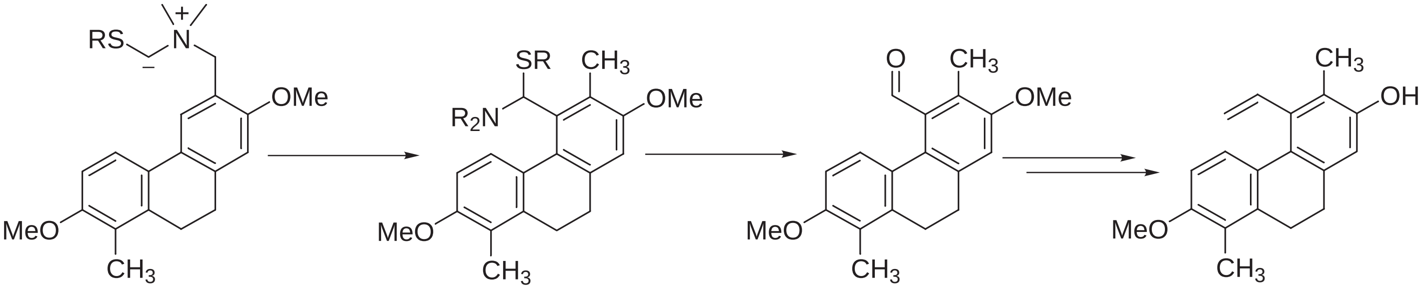
Kreiser *Tetrahedron Lett*. **1975**, 1669.

Stork *J. Am. Chem. Soc*. **1974**, *96*, 6774.

Prostaglandin synthesis; sulfenate/sulfoxide rearrangement.
note olefin inversion.

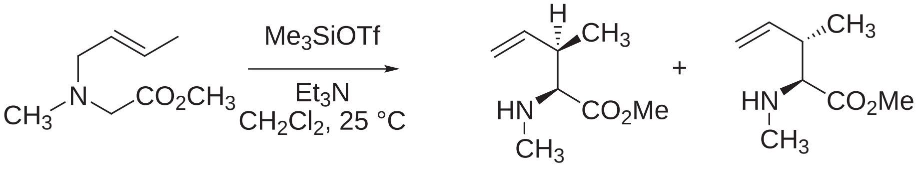
o-formylation of anilines:



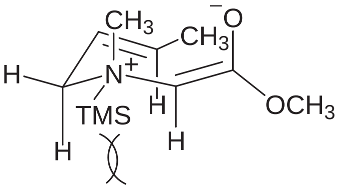


Juncusol

Boger *J. Org. Chem*. **1984**, *49*, 4045.

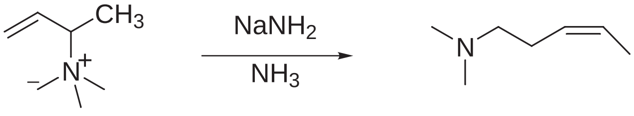


Nakai *Chem. Lett*. **1990**, 2069.



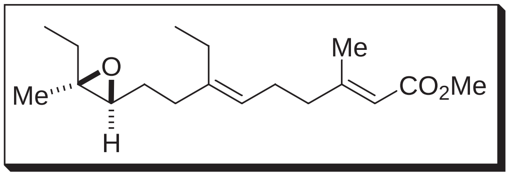
See Also:

Sato *J. Am. Chem. Soc*. **1990**, *112*, 1999.



di- and trisubstituted olefins

I. Olefin Synthesis Exemplified with Juvenile Hormone



1. Trost Synthesis: *J. Am. Chem. Soc.* **1967**, *89*, 5292.

Wadsworth–Horner–Emmons Reaction

2. Syntex Synthesis: *J. Am. Chem. Soc.* **1968**, *90*, 6224.

Robinson Annulation
Alkylation Diastereoselectivity
Fragmentation Reaction
Directed Epoxidation Reaction

3. Corey Synthesis: *J. Am. Chem. Soc.* **1968**, *90*, 5618.

Dissolving Metal Reductions: Cyclic Precursors to Trisubstituted Olefins
Oxidative Cleavage of Enol Ethers
$LiAlH_4$ Reduction of Propargyl Alcohols
Cuprate Coupling Reactions
Allylic Alcohol Oxidation

4. Johnson Synthesis: *J. Am. Chem. Soc.* **1968**, *90*, 6225.

Julia Olefin Synthesis
Cornforth Nucleophilic Addition

5. Corey Synthesis: *J. Am. Chem. Soc.* **1970**, *92*, 6635, 6636, 6637.

Lindlar Catalyst Alkyne Reduction
1,5-Hydrogen Migration
β-Oxido Ylide Reaction
Diimide Reduction

6. Johnson Synthesis: *J. Am. Chem. Soc.* **1970**, *92*, 4463.

[3,3]-Sigmatropic Rearrangements
    Claisen Reaction
    Cope Reaction
    Oxy-Cope Reaction

7. Stotter–Kondo Synthesis: *J. Am. Chem. Soc.* **1973**, *95*, 4444.
J. Chem. Soc., Chem. Commun. **1972**, 1311.

Dihydrothiopyran Strategy: Cyclic Precursors to Trisubstituted Olefins
    Stabilized Allylic Anions, Desulfurization (Benkeser Dissolving Metal Reduction)
Sulfur Ylides
    Cyclopropane Synthesis
    Epoxide Synthesis

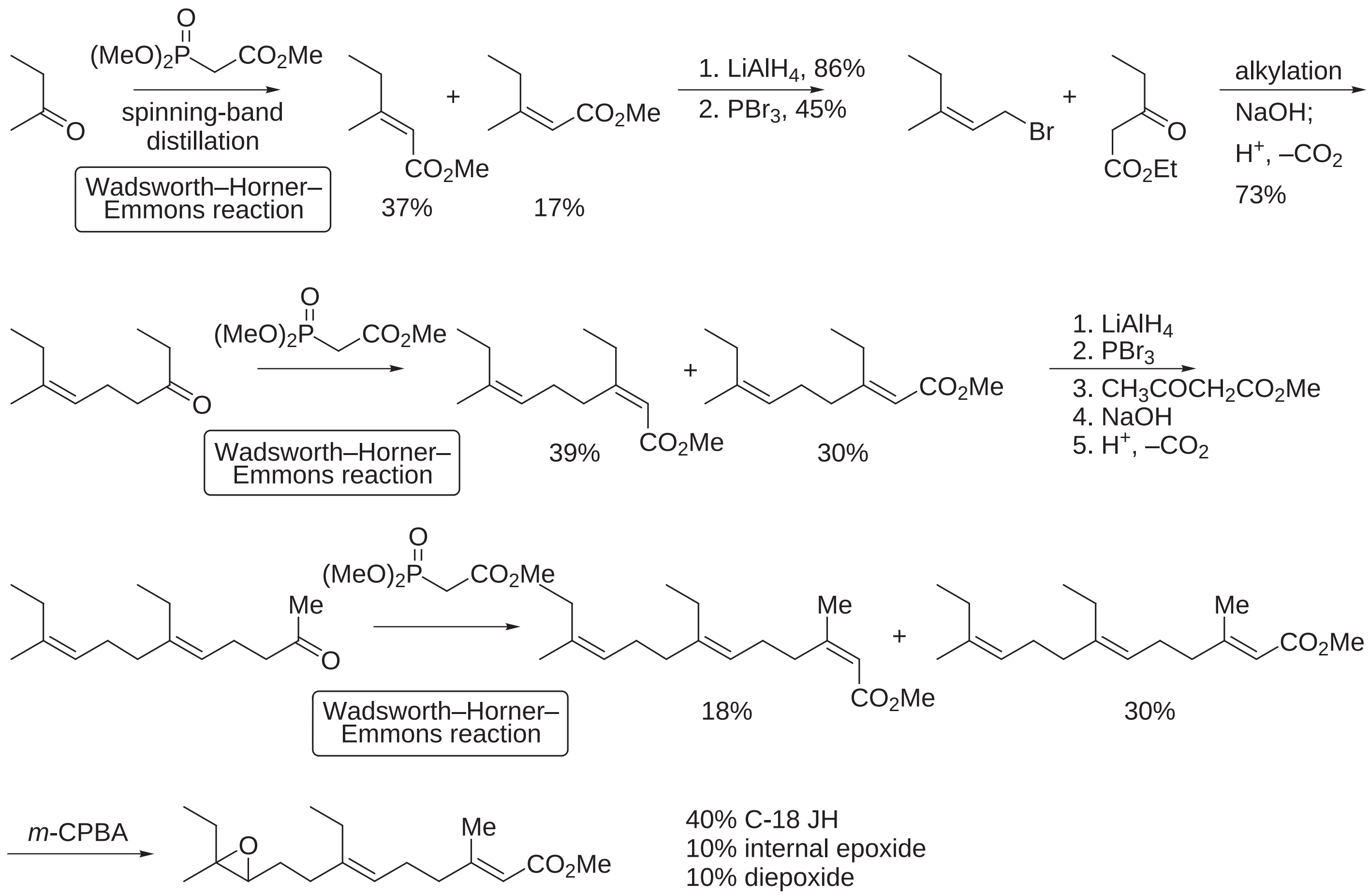
8. Still Synthesis: *Tetrahedron Lett.* **1979**, 593.

[2,3]-Sigmatropic Rearrangement

9. Other Syntheses:

Beltsville Synthesis:	*J. Econ. Entomol.* **1968**, *61*, 866.
Mori Synthesis:	*Tetrahedron* **1969**, *25*, 1667.
MacKay Synthesis:	*J. Chem. Soc., Chem. Commun.* **1969**, 733.
Schering Synthesis:	*Angew. Chem., Int. Ed. Eng.* **1969**, *8*, 271. (Farnesol -> C-18 JH)
Zoecon Synthesis:	*J. Am. Chem. Soc.* **1970**, *92*, 735.
van Tamelen Synthesis:	*J. Am. Chem. Soc.* **1970**, *92*, 737.

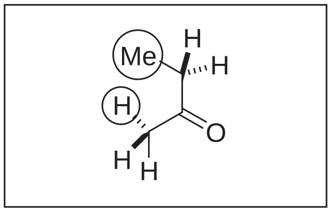
1. Trost Synthesis: *J. Am. Chem. Soc.* **1967**, *89*, 5292. Wadsworth–Horner–Emmons Reaction



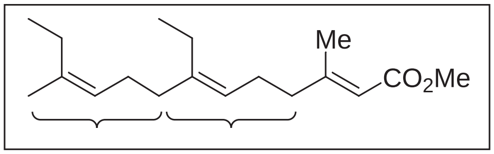
40% C-18 JH
10% internal epoxide
10% diepoxide

Relative Activity	
nat. C-18 JH	1
syn. C-18 JH	1
t-t-t (epoxide)	0.4
c-t-t (triene)	0.1
t-t-t (triene)	0.04
c-t-t (epoxide) ethyl ester	8

Synthesis was relatively non-stereoselective
- structural assignment
- structure–activity studies
- prevents adult development from pupa
- more potent analog found



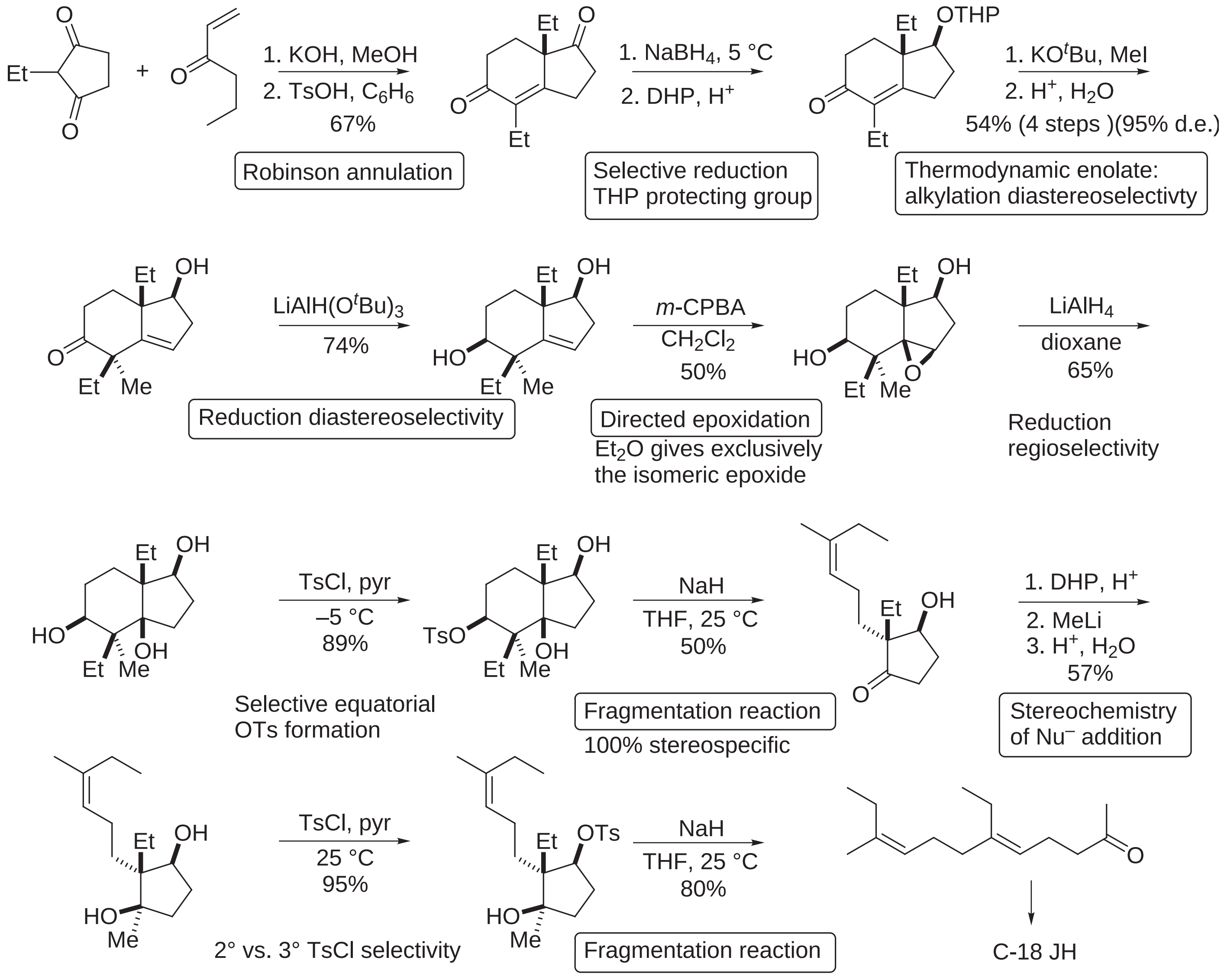
Stereoselectivity
- not much difference between Me and H (second atom steric effect)
- both isomers obtained from the Wadsworth–Horner–Emmons reaction (Modern improvements now available)

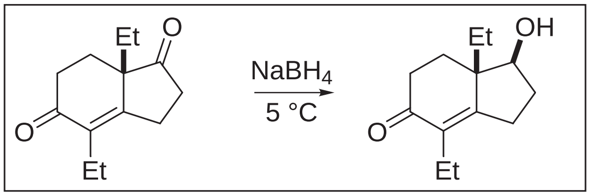


Retrosynthetic Analysis
- repeating subunits recognized
- repeating reactions utilized

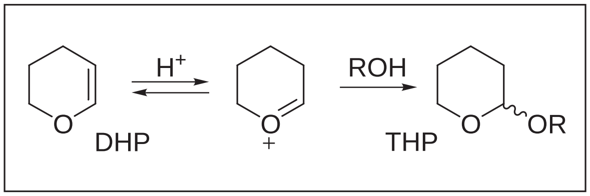
2. Syntex Synthesis: *J. Am. Chem. Soc.* **1968**, *90*, 6224.

Robinson Annulation
Alkylation Diastereoselectivity
Fragmentation Reaction
Directed Epoxidation Reaction

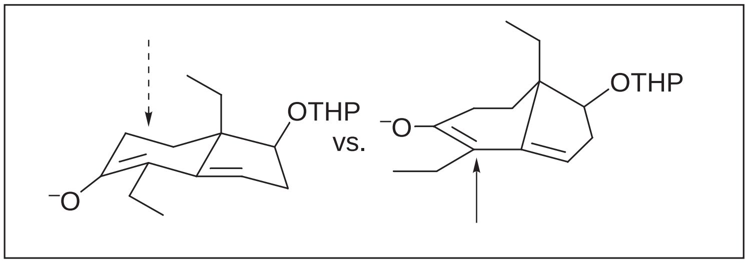




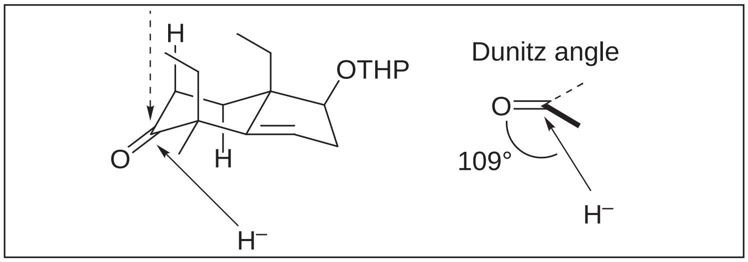
Selective Reduction
- saturated vs. α,β-unsaturated carbonyl
- ring strain associated with 5-membered ring carbonyl released on reduction
- attack from least hindered face



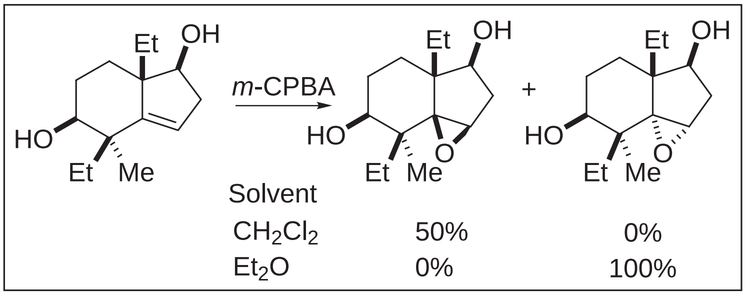
THP Protecting Group
- if R group contains chiral centers, diastereomers result
- removed by mild acid



Thermodynamic Enolate
- severe 1,3-diaxial interaction in chair-like T.S. axial alkylation
- no steric incumberance to axial alkylation on least hindered face of twist boat T.S.

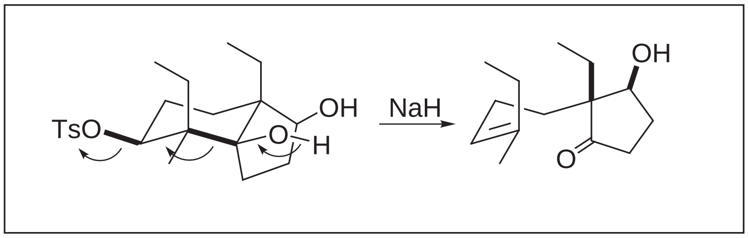


LiAlH(O^{t}Bu)$_3$ Reduction
- large reagent, usually equatorial H^{-} delivery
- 1,2-interaction (torsional strain) relatively invariant to Nu^{-} size
- 1,3-steric interaction highly dependent on Nu^{-} size
- due to absence of axial C(3)–H, large reagent now gives axial delivery

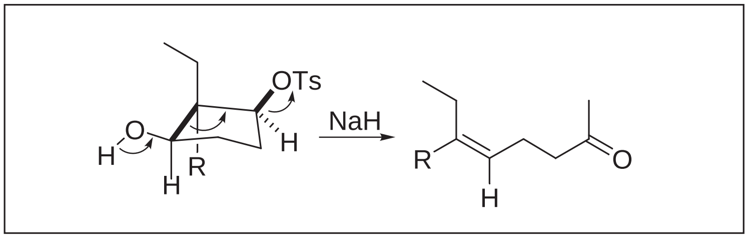


Solvent		
CH_2Cl_2	50%	0%
Et_2O	0%	100%

Epoxidation
- in Et_2O, coordination of peracid to solvent gives delivery from the least hindered α-face
- in CH_2Cl_2, H-bonding of OH to peracid provides delivery to the less accessible β-face
- Teranishi *J. Am. Chem. Soc.* **1979**, *101*, 159.



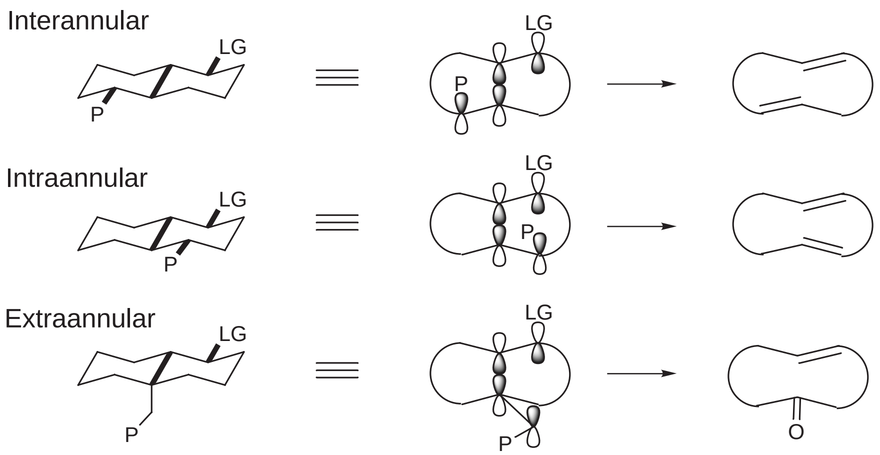
1st Fragmentation
- utilized to control C=C bond stereochemistry
- *trans* periplanar orientation of breaking bonds
- dictates *Z* olefin geometry in product



2nd Fragmentation
- utilized to control C=C bond stereochemistry
- *trans* periplanar orientation of breaking bonds
- dictates *E* olefin geometry in product

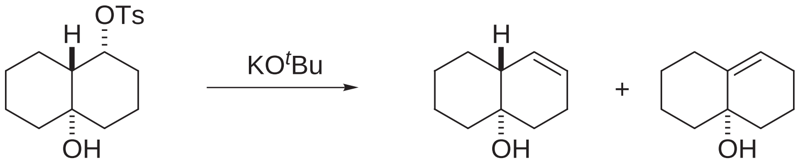
Fragmentation Reactions Grob *Angew. Chem., Int. Ed. Eng.* **1969**, *8*, 535.
Angew. Chem., Int. Ed. Eng. **1967**, *6*, 1.

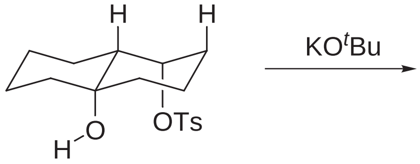
-*Trans* periplanar arrangement of participating bond orbital and departing bond orbital



- Wharton *J. Org. Chem.* **1965**, *30*, 3254.
- Fuchs *J. Am. Chem. Soc.* **1979**, *101*, 3567.

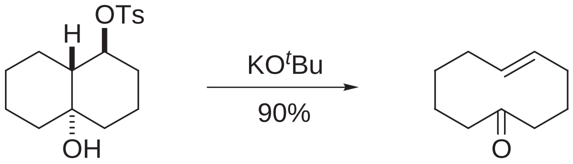
- Case A



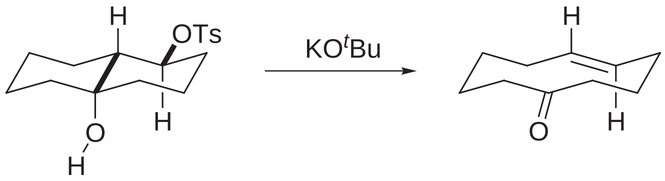


E2 elimination, no fragmentation

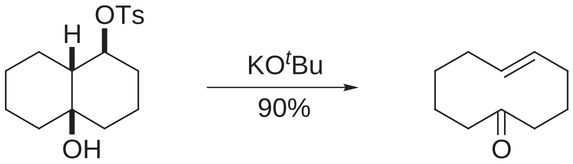
- Case B



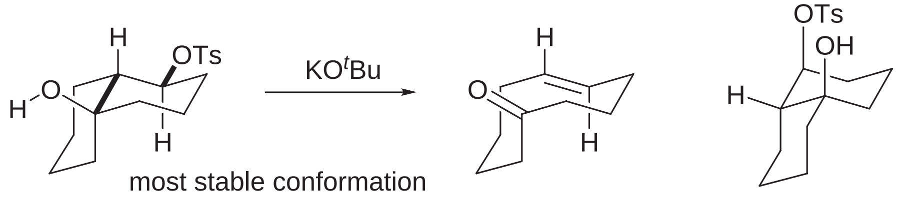
trans olefin only



- Case C

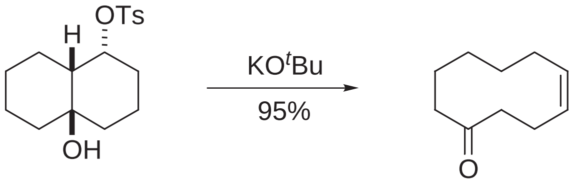


trans olefin only

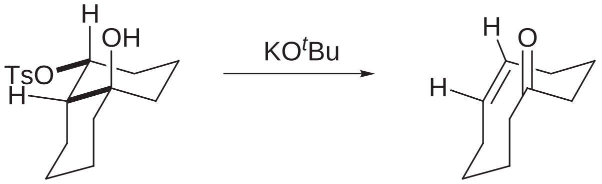


less stable conformation
and not set up for
fragmentation

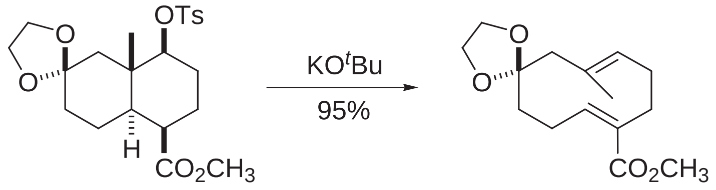
- Case D

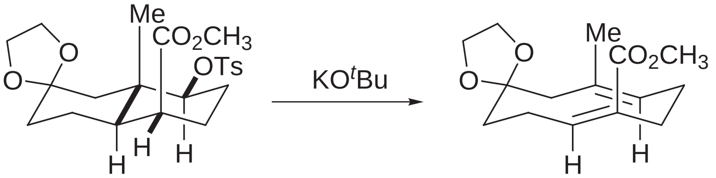


cis olefin only

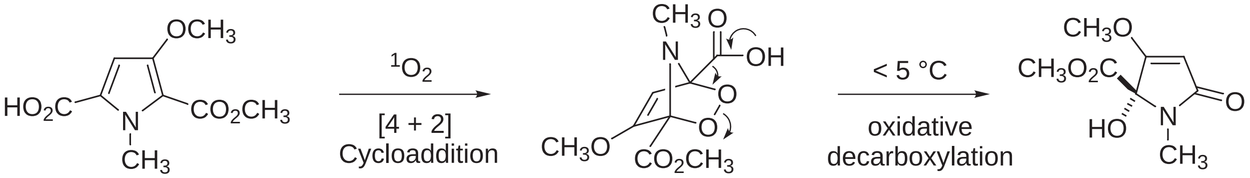


- Other groups at "promoter" site can be used

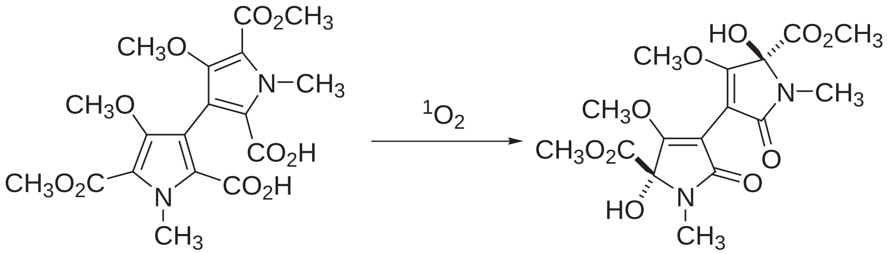




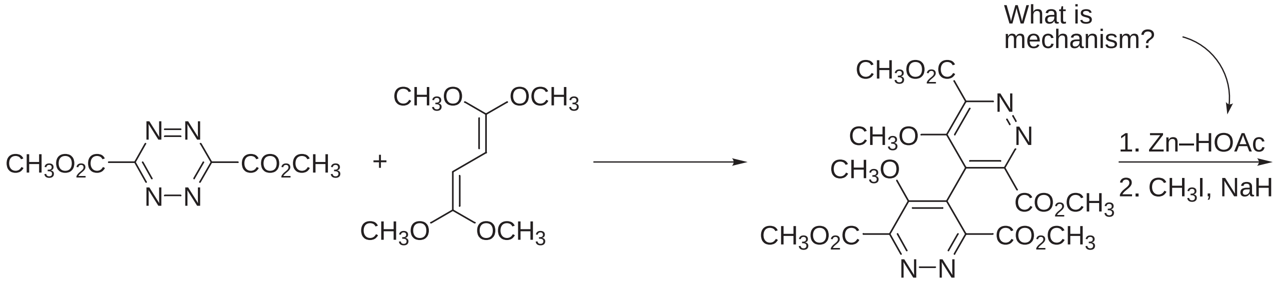
- Many other types of fragmentation reactions

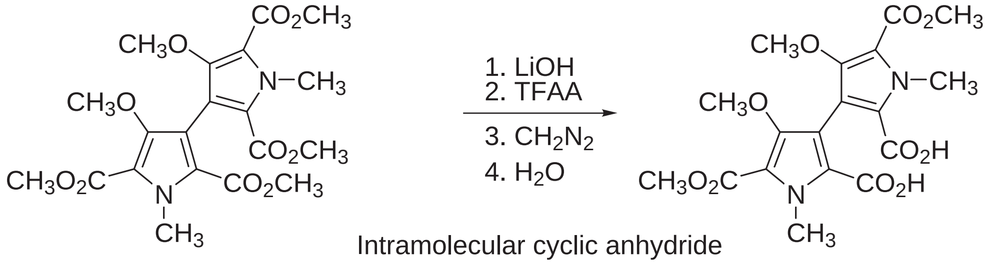


Boger *J. Org. Chem.* **1991**, *96*, 6942.
J. Am. Chem. Soc. **1993**, *115*, 11418.



Isochrysohermidin


What is mechanism?



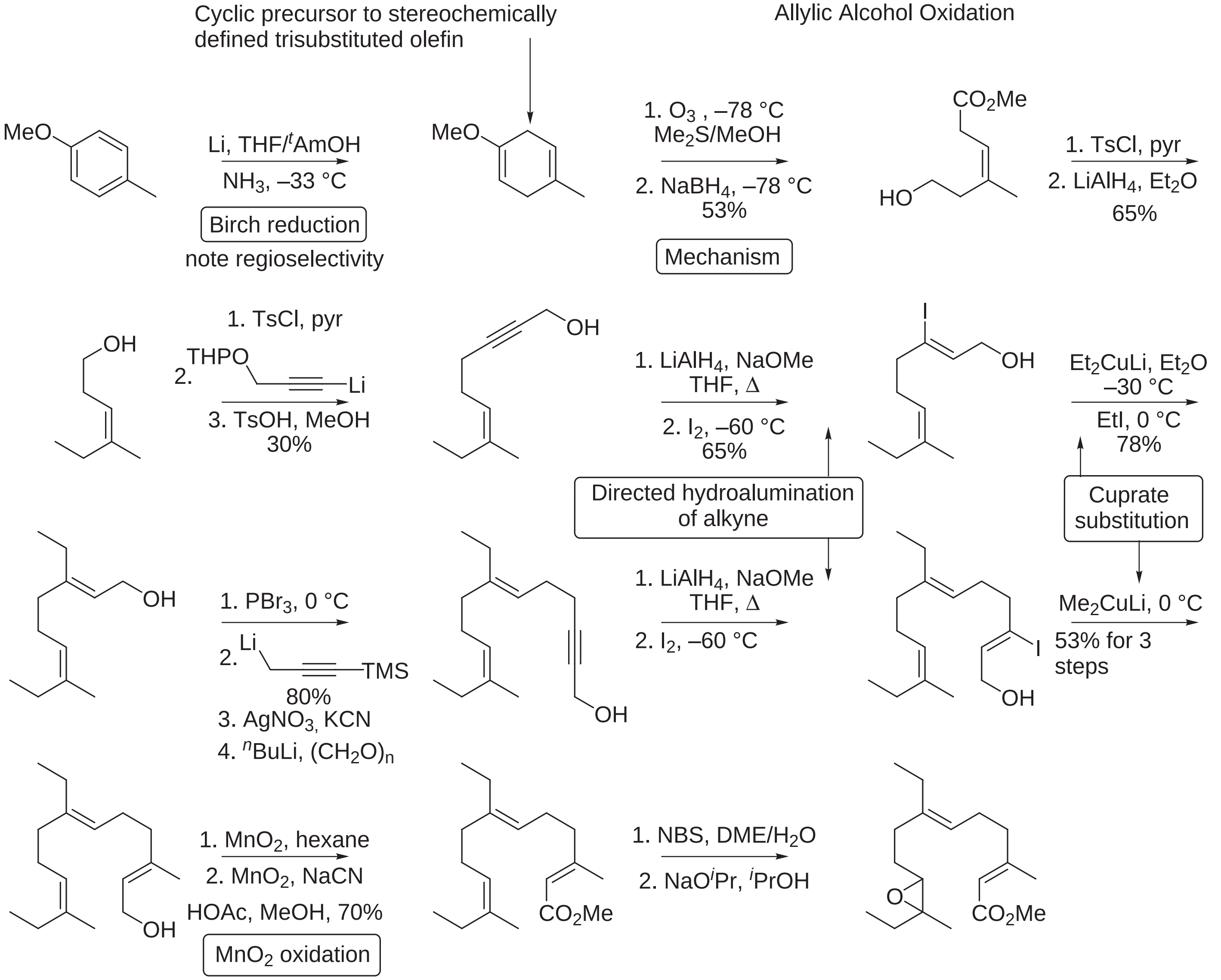
Intramolecular cyclic anhydride
formation utilized to differentiate
internal acids of tetraacid.

3. Corey Synthesis:

J. Am. Chem. Soc. **1968**, *90*, 5618.

Dissolving Metal Reductions
  Cyclic Precursors to Trisubstituted Olefins
Oxidative Cleavage of Enol Ethers
$LiAlH_4$ Reduction of Propargyl Alcohols
Cuprate Coupling Reactions
Allylic Alcohol Oxidation

Cyclic precursor to stereochemically defined trisubstituted olefin



Birch reduction

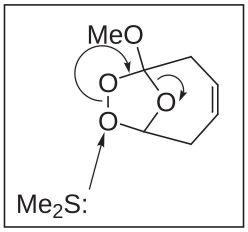
note regioselectivity

Mechanism

Directed hydroalumination of alkyne

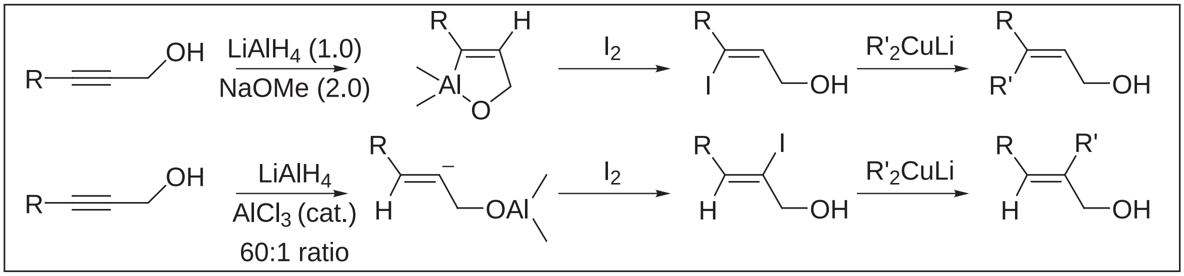
Cuprate substitution

MnO_2 oxidation

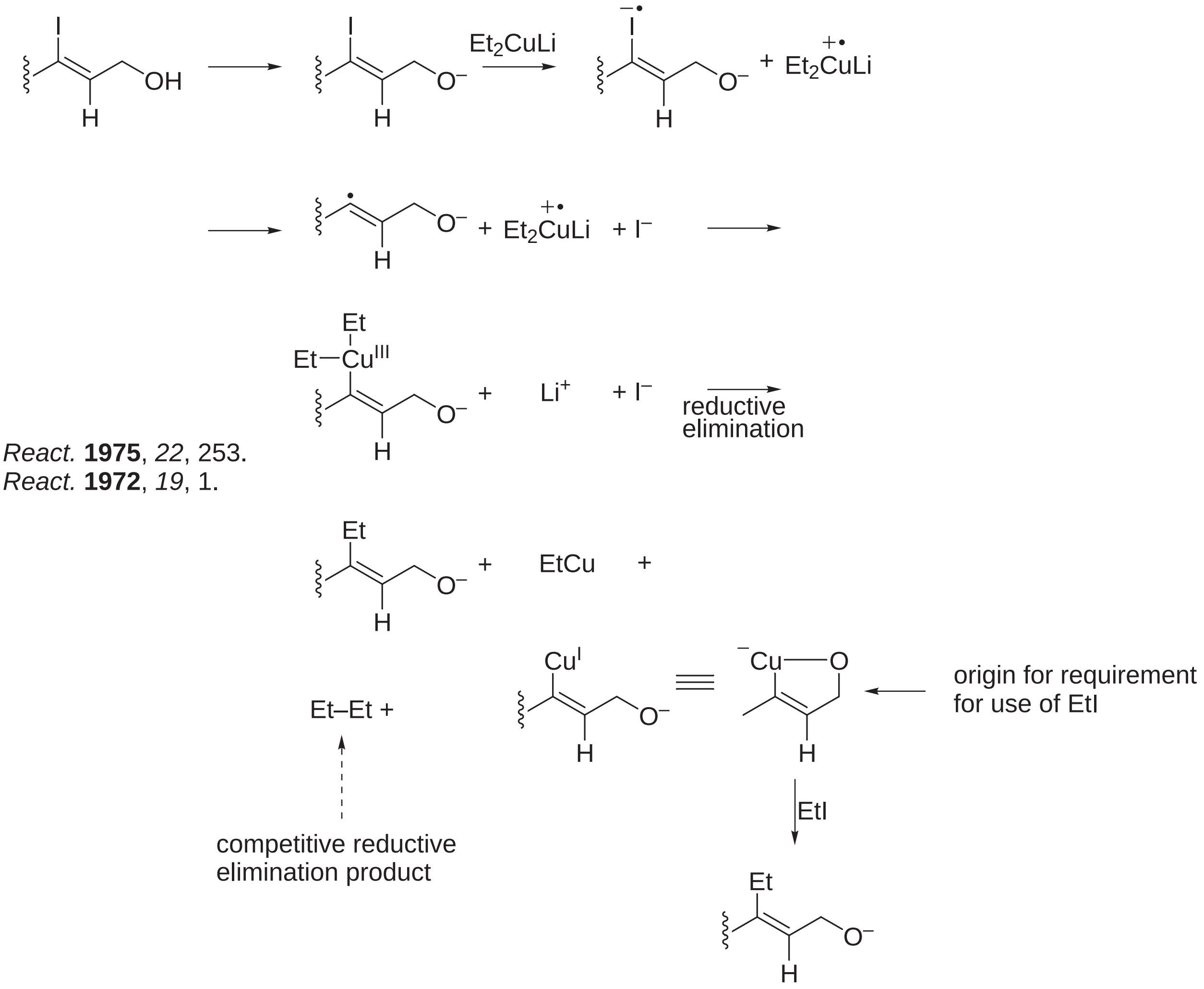


Ozonolysis
- reacts preferentially with more electron-rich C=C
- ring (cleavage) enlisted to control olefin stereochemistry
- addition of MeOH gives methyl ester

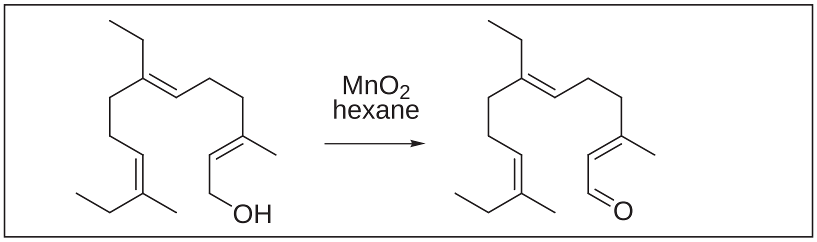
Stereospecific Synthesis of Trisubstituted Olefins
- propargylic alcohols can be reduced with $LiAlH_4$ to give an allylic alcohol

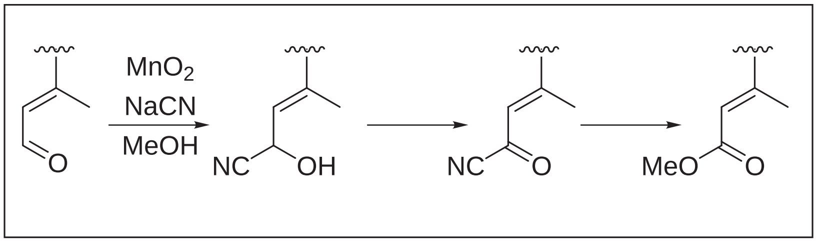


- Cuprate Mechanism

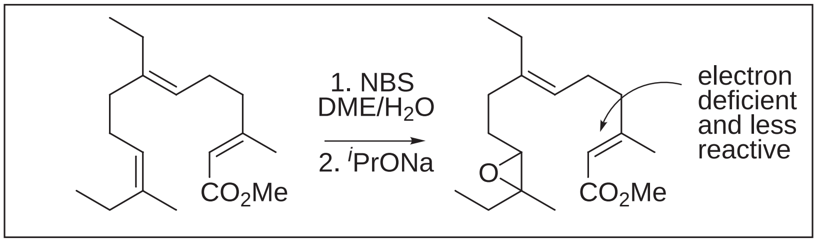


- Posner *Org. React.* **1975**, *22*, 253.
  Org. React. **1972**, *19*, 1.





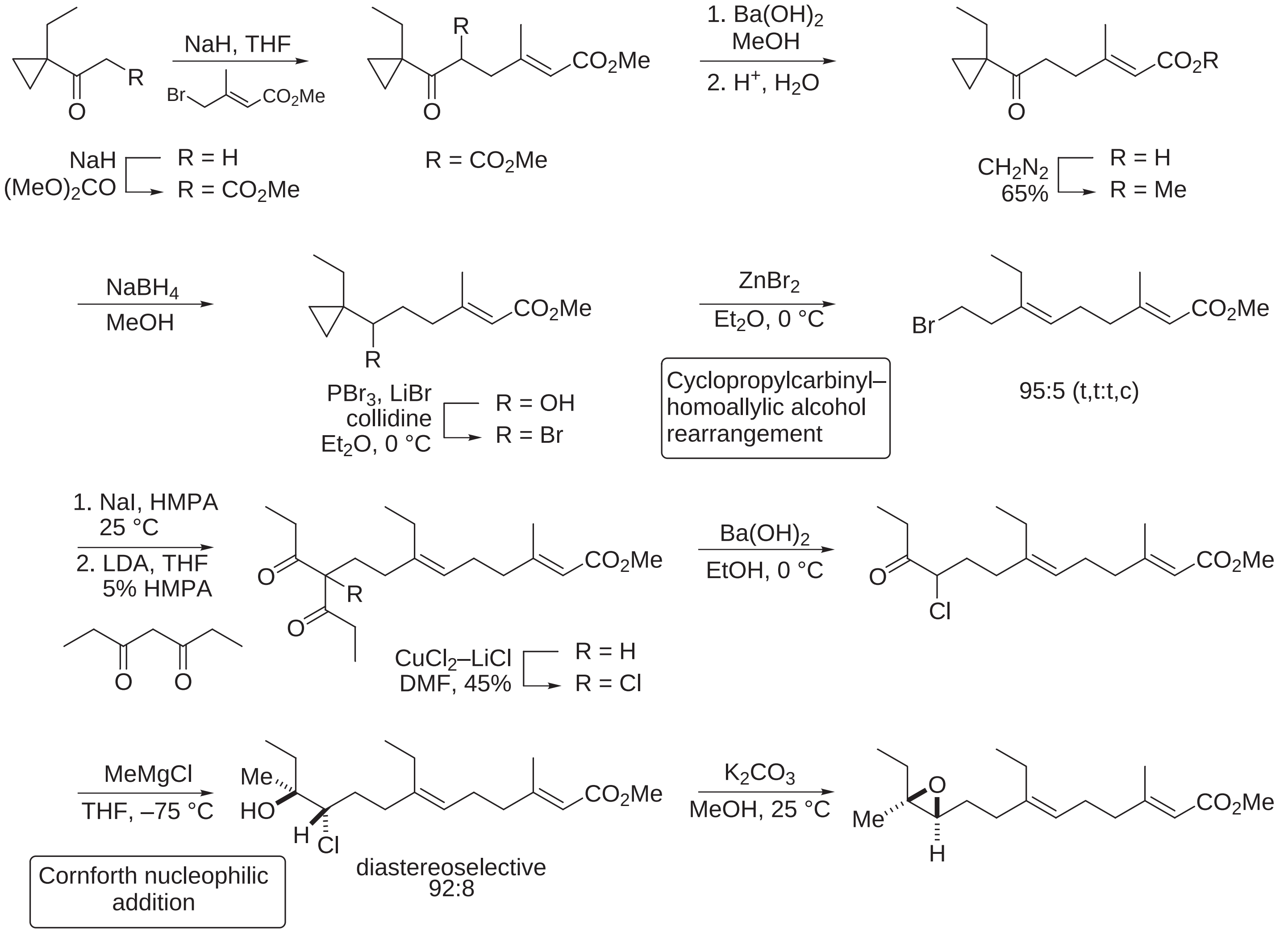
MnO$_2$ Oxidation
- mild oxidation of allylic alcohols
- direct, mild method for oxidation to a methyl ester

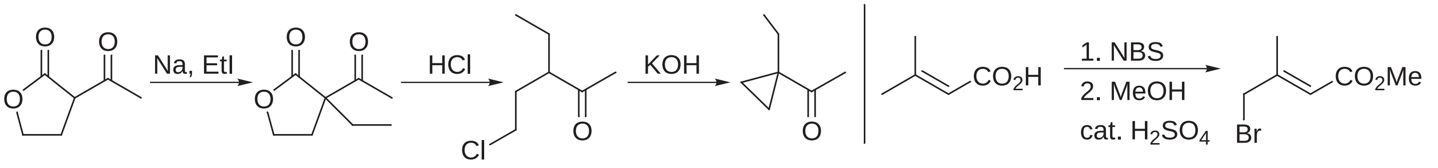


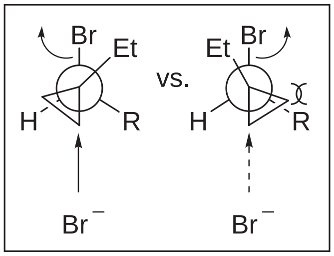
Epoxidation
- selective
- in polar solvent the molecule folds up such that the terminal C=C is more accessible

4. Johnson Synthesis: *J. Am. Chem. Soc.* **1968**, *90*, 6225.

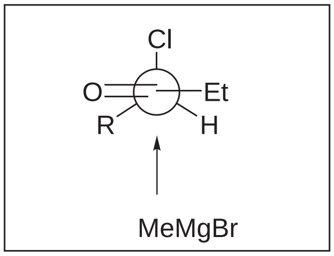
Julia Olefin Synthesis
Cornforth Nucleophilic Addition







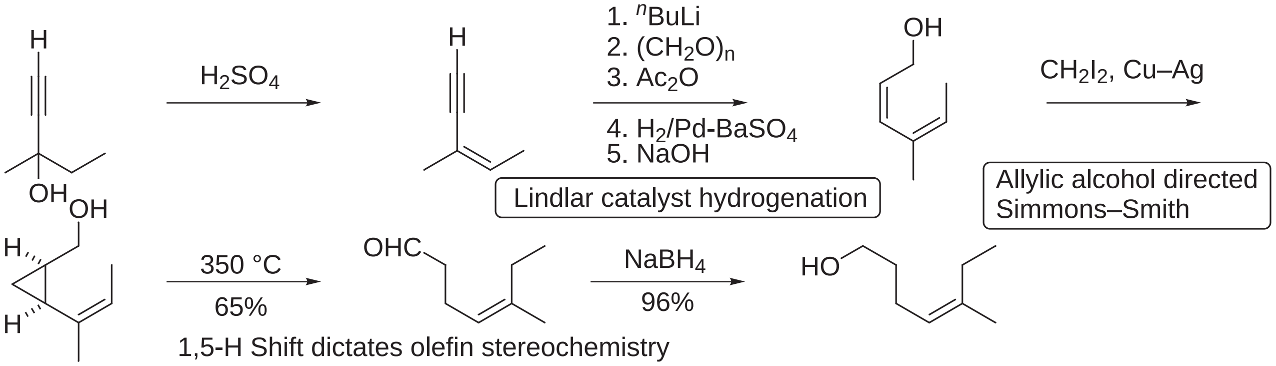
Cyclopropylcarbinyl Bromide Rearrangement
- highly stereoselective modification of Julia olefin synthesis
- Johnson *J. Am. Chem. Soc.* **1968**, *90*, 2882
- Julia *Bull. Soc. Chim., Fr.* **1960**, 1072.
- ring opening concomitant with ionization
- antiperiplanar arrangement of the C–Br and cleaved cyclopropane bond is necessary



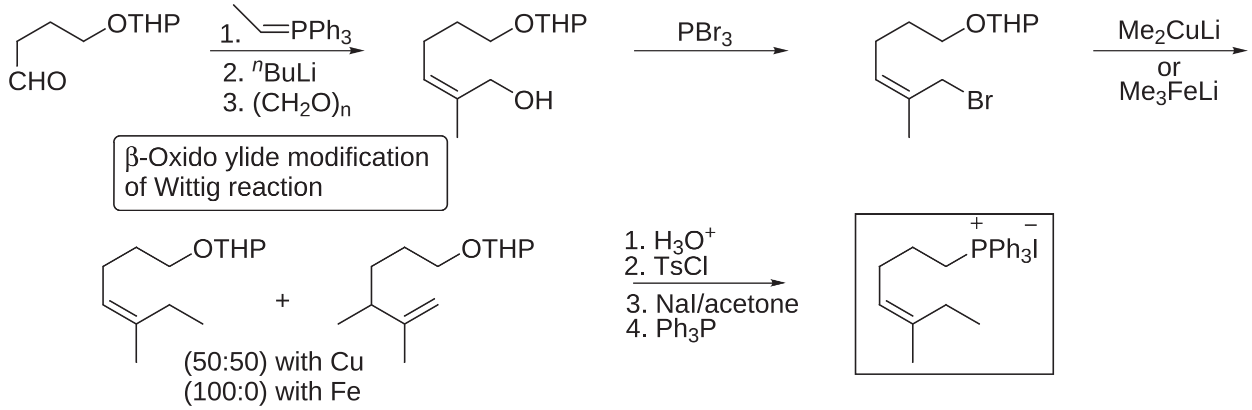
Cornforth Nucleophilic Addition
- *J. Chem. Soc.* **1959**, *112*, 2539.
- earliest generalization of the Felkin model of nucleophilic addition to a carbonyl group in acyclic systems

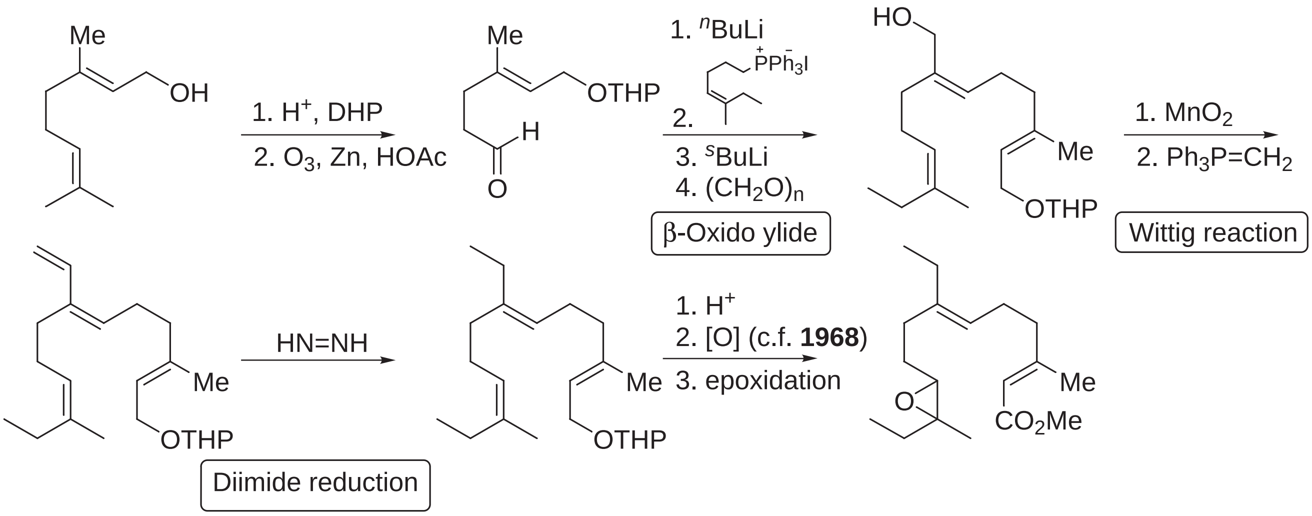
5. Corey Synthesis: *J. Am. Chem. Soc.* **1970**, *92*, 6635, 6636.

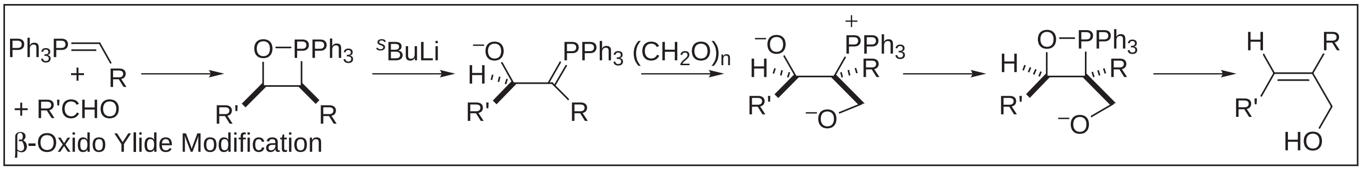
Lindlar Catalyst Alkyne Reduction
1,5-Hydrogen Migration
β-Oxido Ylide Reaction
Diimide Reduction

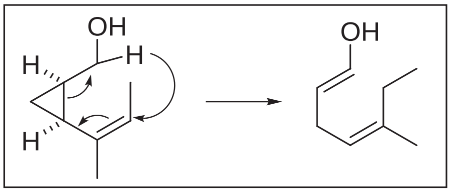


- Alternatively



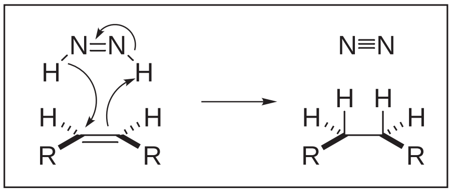






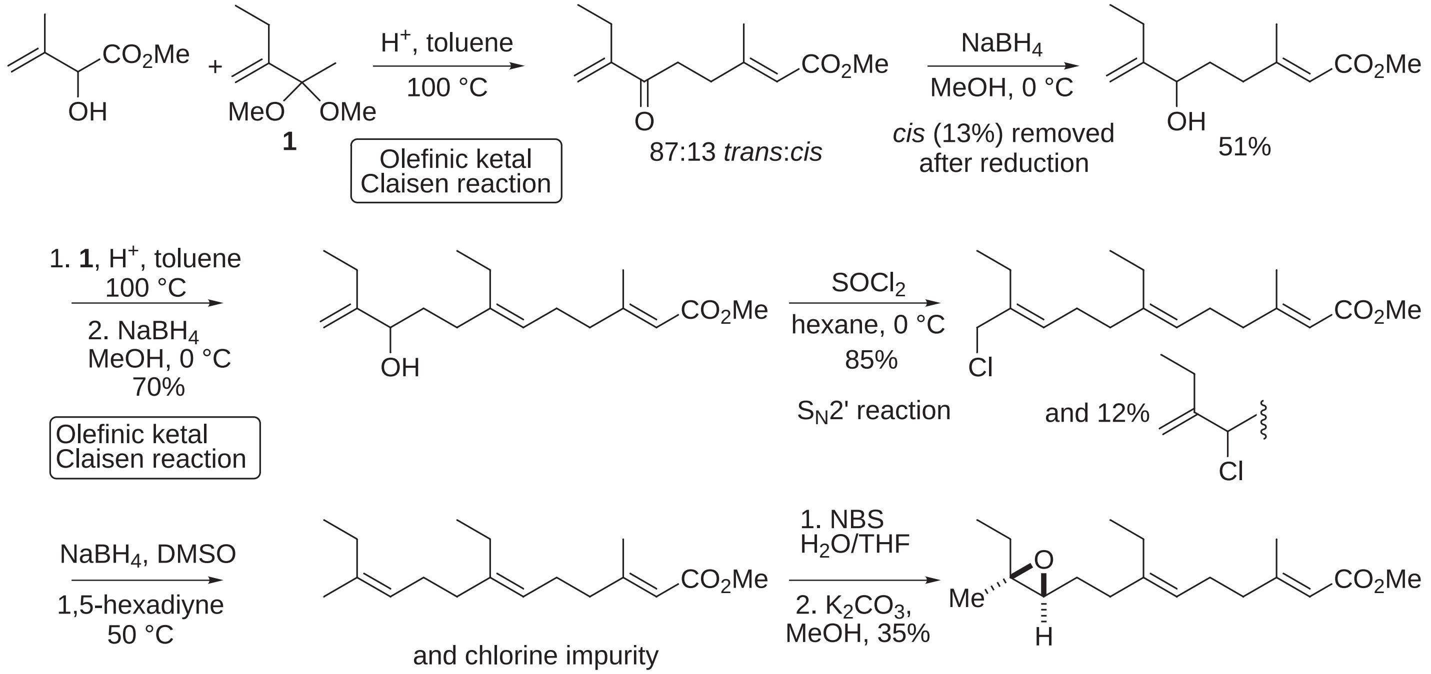
1,5-H Shift

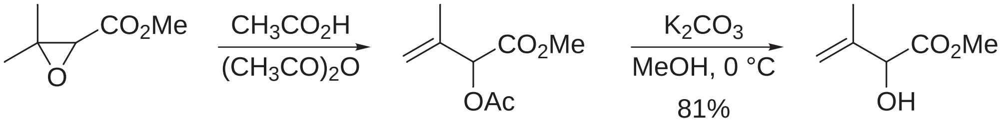
Diimide Reduction
- less substituted C=C reduced more rapidly
- generated *in-situ*

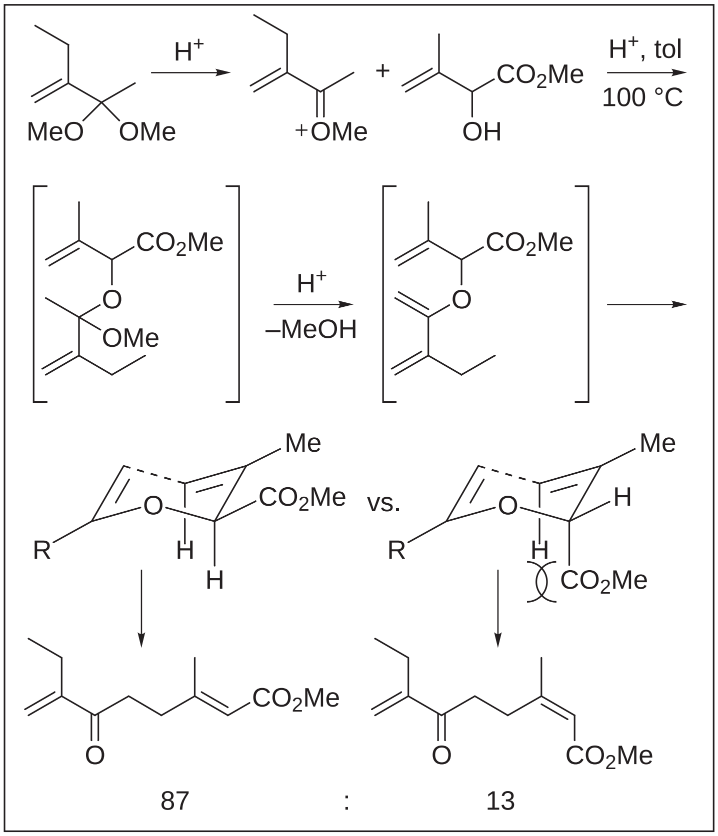


6. Johnson Synthesis: *J. Am. Chem. Soc.* **1970**, *92*, 4463.

[3,3]-Sigmatropic Rearrangements
Claisen Reaction
Cope Reaction
Oxy-Cope Reaction





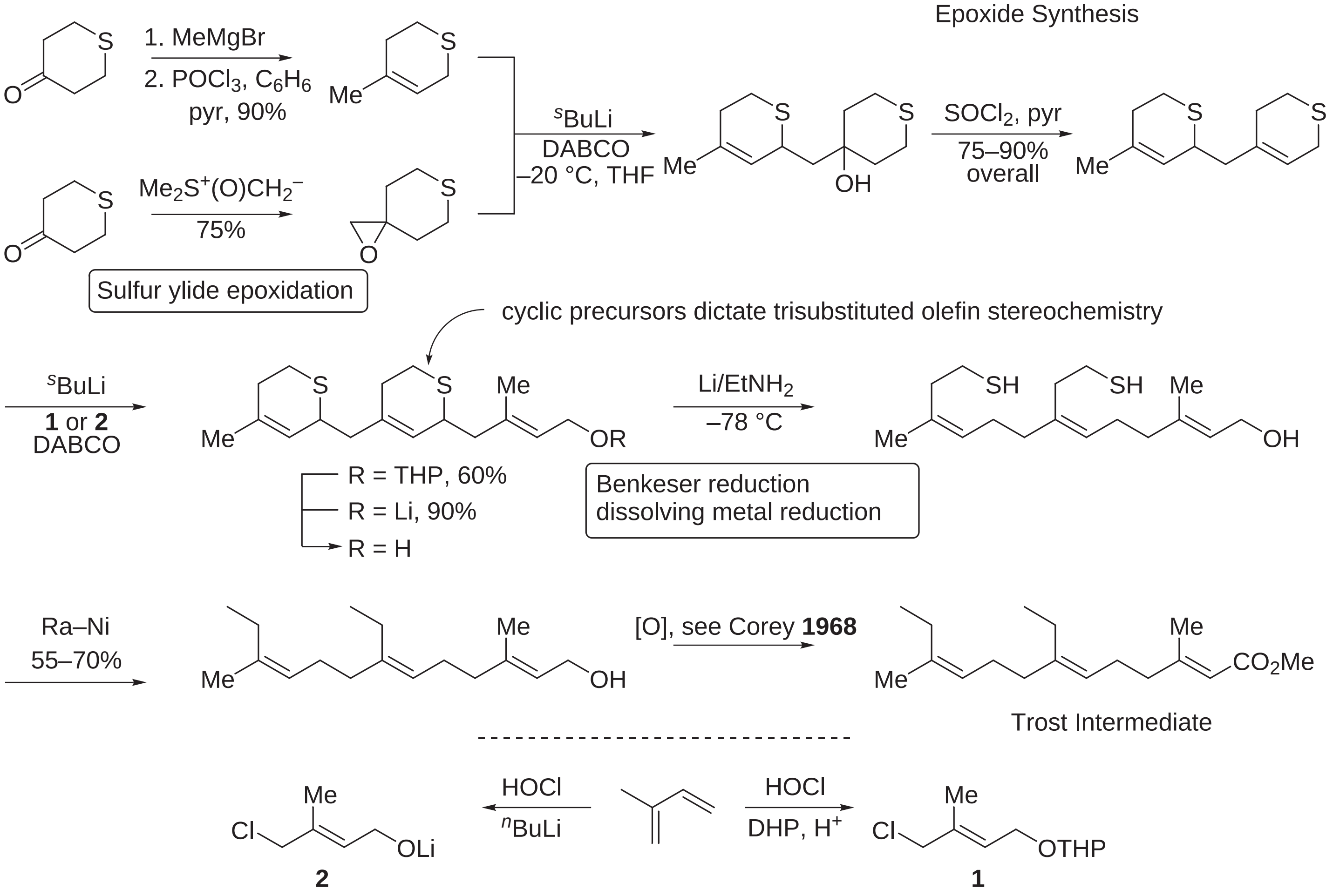


Olefinic Ketal Claisen Reaction
- selectivity dependent on 1,3-interaction in chair-like T.S.
- second Claisen more selective due to larger R group vs. CO_2Me

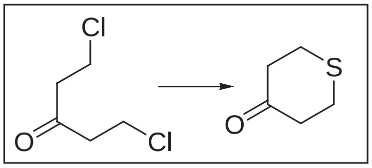
7. Stotter–Kondo Synthesis: *J. Am. Chem. Soc.* **1973**, *95*, 4444.
J. Chem. Soc., Chem. Commun. **1972**, 1311.

Dihydrothiopyran Strategy:
  - Cyclic Precursors to Trisub. Olefins
  - Stabilized Allylic Anions
  - Desulfurization, Benkeser Red.

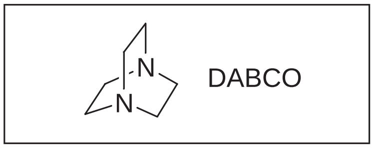
Sulfur Ylides
  - Cyclopropane Synthesis
  - Epoxide Synthesis



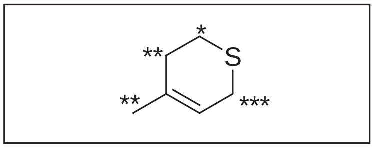
thermodynamic *E* product



Convergent Route
  - symmetrical intermediate



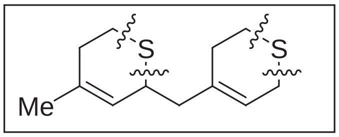
DABCO
  - accelerates slow deprotonation
  - breaks up Li aggregates



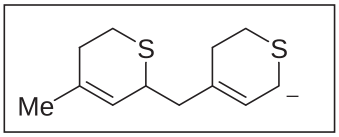
Site of Deprotonation
  - at carbon activated by both S and vinyl

Sulfur Ylides: Trost, Melvin *Sulfur Ylides: Emerging Synthetic Intermediates*, Academic Press, 1975.

Benkeser Reduction *Synthesis* **1972**, 391.

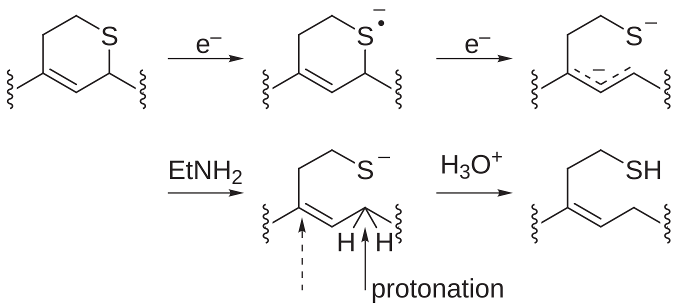


Use of Cyclic Precursors
- control olefin geometry
- insert S, remove with Ra–Ni



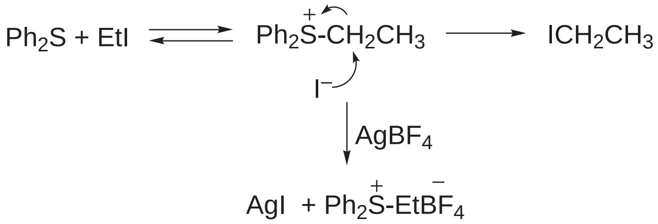
Specific Deprotonation Site
- kinetically preferred site due to sterics
- the thermodynamic and kinetic product
- alkylation occurs cleanly α, not γ, to heteroatom (a well established trend)

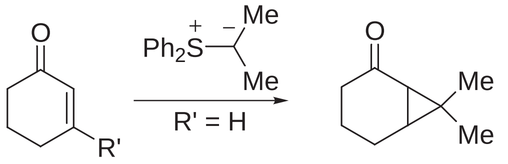
- Li/NH_3 Birch Reduction (blue solution), –33 °C at refluxing NH_3 temperatures
- Li/$EtNH_2$ or $MeNH_2$ Benkeser Reduction, more strongly reducing because of higher reaction temperature



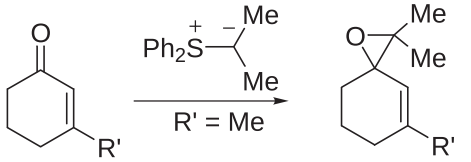
no protonation,
more hindered,
olefin geometry maintained
restricted rotation of allyl
anion π-system

- 1,4-Addition of sulfur ylides -> cyclopropanes





- This reaction is sensitive to substitution pattern on the α,β-unsaturated carbonyl

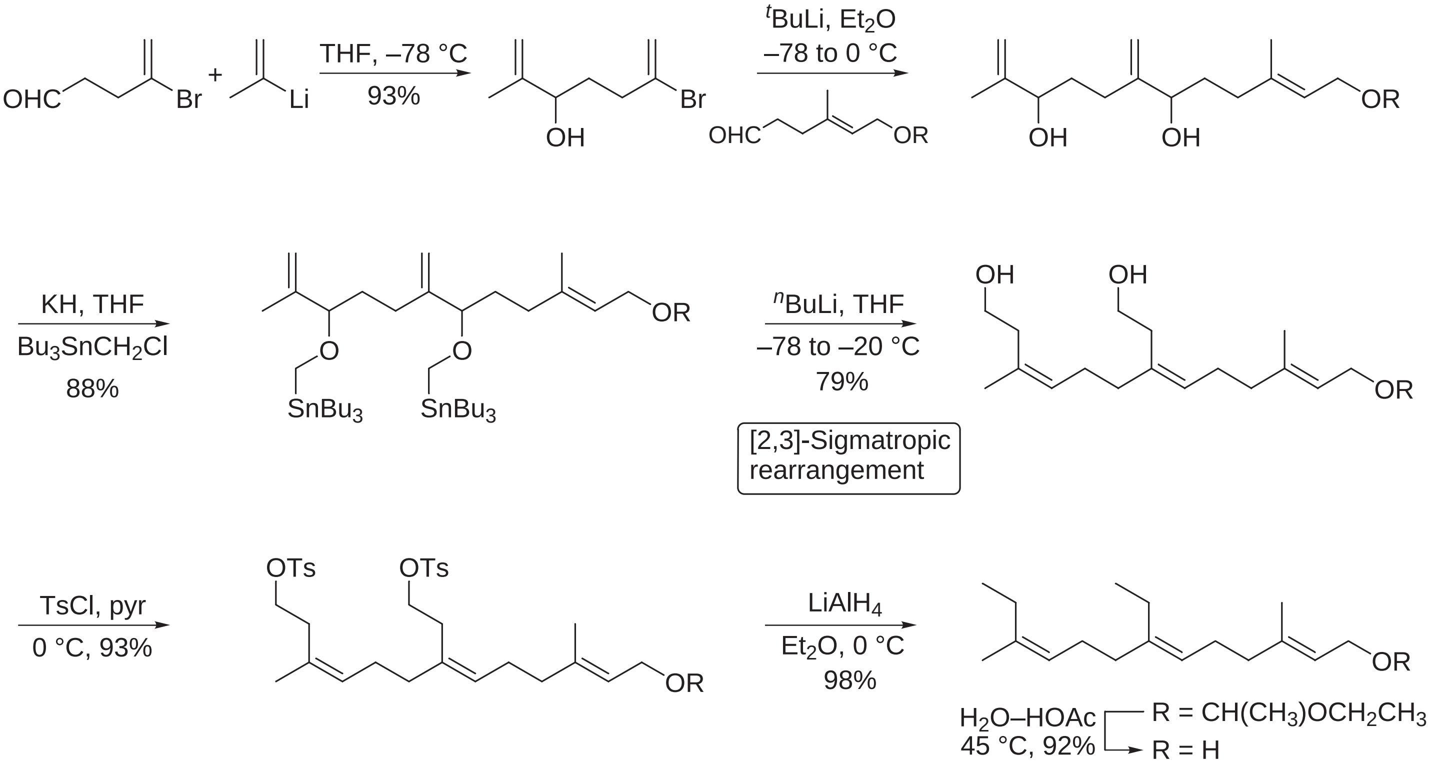


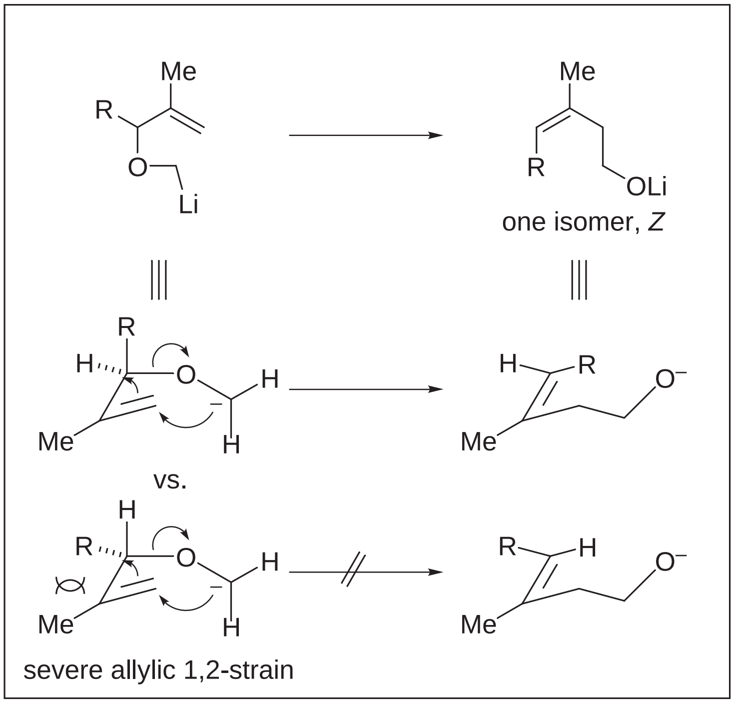
- In addition, a substituted sulfur ylide increases propensity for epoxide formation over cyclopropane formation

8. Still Synthesis:

Tetrahedron Lett. **1979**, 593.

[2,3]-Sigmatropic Rearrangement





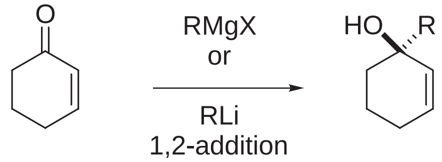
J. Am. Chem. Soc. **1978**, *100*, 1927.

Note: Me substitution on olefin provides *Z* selectivity.

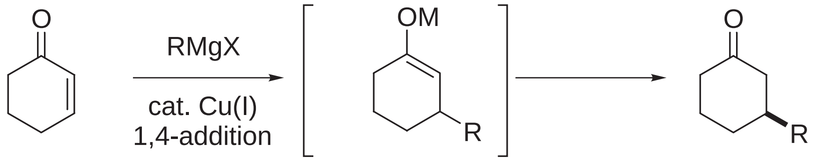
XII. Conjugate Additions: Organocuprate 1,4-Additions

Reviews: House *Acc Chem Res.*, **1976**, *9*, 59.
Ashby *Chem Rev.*, **1975**, *75*, 521.
Comprehensive Org. Syn., Vol. 4, 169.

Review: Lipshutz *Org. React.* **1992**, *41*,135.
Posner *Org. React.* **1975**, *22*, 253.
Posner *Org. React.* **1972**, *19*, 1.



- But Kharasch observed 1,4-addition with added Cu(I) salt:



Kharasch *J. Am. Chem. Soc.* **1941**, *63*, 2308.

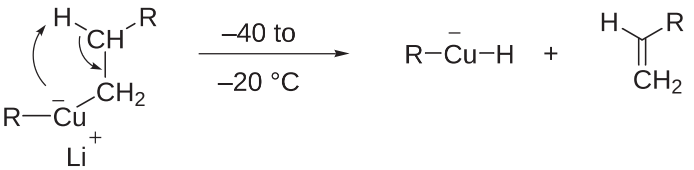
- This led to the development of stoichiometric organocuprate reagents:

$$\underset{(1\ \text{equiv})}{\text{MeLi} + \text{CuI}} \xrightarrow[\text{THF}]{\text{ether or}} \underset{\substack{\text{insoluble,}\\ \text{bright yellow}\\ \text{organocopper}\\ \text{reagent}}}{\text{Me-Cu}} + \text{LiI} \xrightarrow{\text{MeLi (1.0 equiv)}} \underset{\substack{\text{"ate" complex}\\ \text{colorless, soluble,}\\ \text{stable even at 25 °C}}}{\text{Me-}\overset{-}{\text{Cu}}\text{-Me}\ \ \text{Li}^{+}}$$

House, Whitesides *J. Org. Chem.* **1966**, *31*, 3128.

- "ate" complexes incorporating Li^+ were first described by Gilman (*J. Org. Chem.* **1952**, *17*, 1630) and consequently such reagents are often referred to as "Gilman reagents".

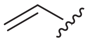
- Most organometallics, including organocuprates, are susceptible to β-elimination:



- So most organocuprates are best handled at temperatures lower than ca. –40 °C.

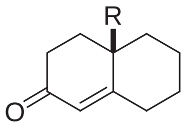
1. Scope

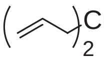
- Relative ease of ligand transfer from Cu follows the order:

 , Ph > Me > Et > ^{i}Pr > ^{t}Bu >> $\boxed{\text{PhS, R}_2\text{N, RC≡C}}$

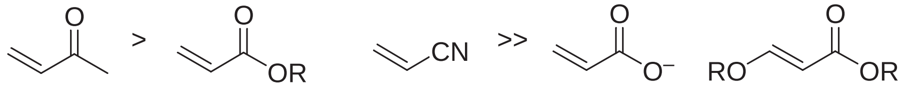
Dummy ligands for mixed cuprates

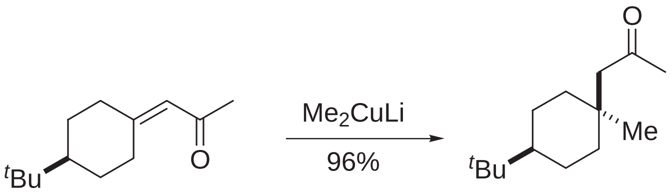
- In addition, the size of the migrating group also affects the conversion:



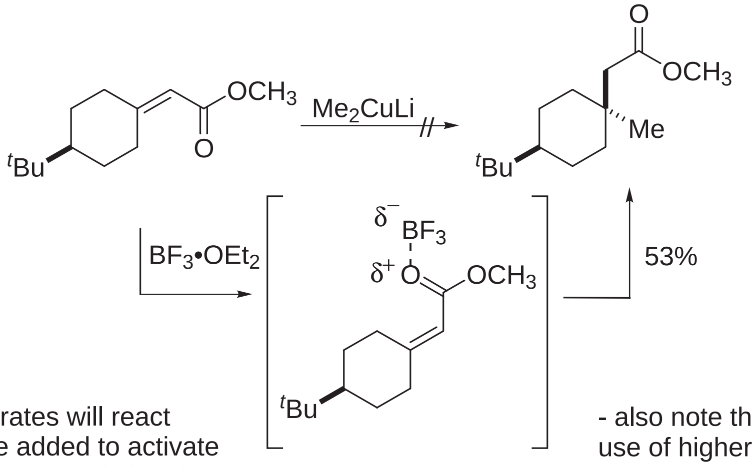
R = H	Me_2CuLi	60–80%	
R = H	Ph_2CuLi	25%	
R = CH_3	Et_2CuLi	55–65%	
R = CH_3	$^iPr_2CuLi$	58%	
R = CH_3	$^tBu_2CuLi$	40%	
R = CH_3	Ph_2CuLi	0%	
R = CH_3	 CuLi	0%	1,2-addition observed

- Effect of substrates:





- Unsaturated esters are less reactive than enones.
- β,β-Disubstitution slows reaction.

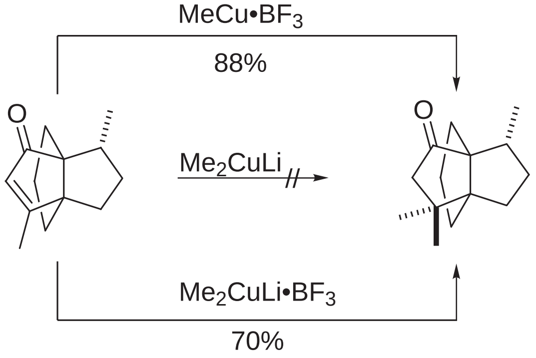


- unreactive substrates will react if Lewis acids are added to activate substrate toward nucleophilic addition.

- also note the alternative use of higher order cuprates $[R_2CuCN]Li_2$.

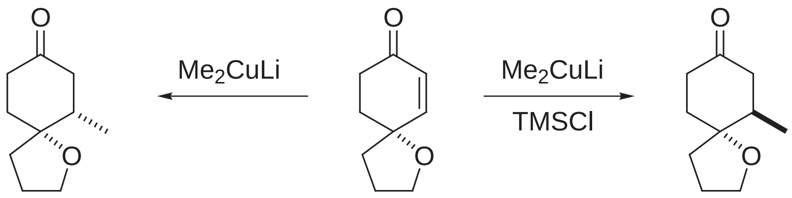
Maruyama *J. Am. Chem. Soc.* **1977**, *99*, 5652.
Yamamoto *J. Am. Chem. Soc.* **1978**, *100*, 3240.

$RCu•BF_3$
Yamamoto *J. Am. Chem. Soc.* **1980**, *102*, 2318.
Yamamoto *J. Org. Chem.* **1979**, *44*, 1745.

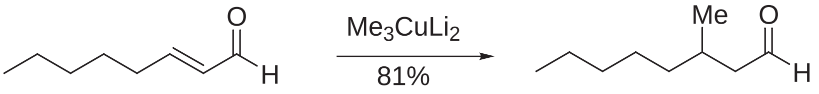


Review: Yamamoto *Angew. Chem., Int. Ed. Eng.* **1986**, *25*, 947.

$Me_2CuLi–TMSCl$
Corey *Tetrahedron Lett.* **1985**, *26*, 6015.



- Conjugate addition to α,β-unsaturated aldehydes is typically problematic but successful examples have been reported.

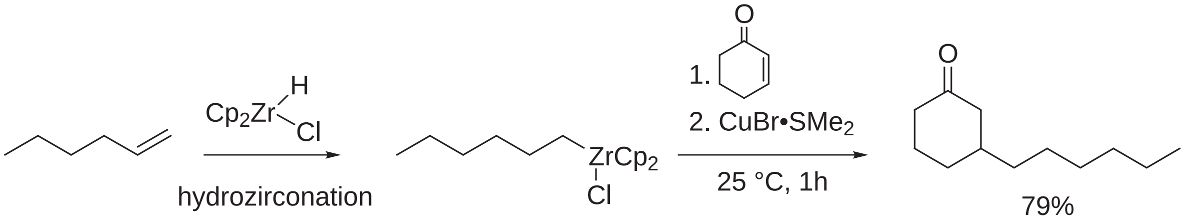


Still *Tetrahedron Lett.* **1976**, 2659.
Meyer *Org. Prep. Proceed.* **1979**, *11*, 97.
Clive *J. Chem. Soc., Chem. Commun.* **1981**, 643. ($Me_5Cu_3Li_2$)
Clive *J. Org. Chem.* **1982**, *47*, 2572.

Conjugate Addition/Alkylation (stereochemistry)
Posner *J. Org. Chem.* **1979**, *44*, 3661.
Review: *Comprehensive Org. Syn.,* Vol. 4, pp 237–268.

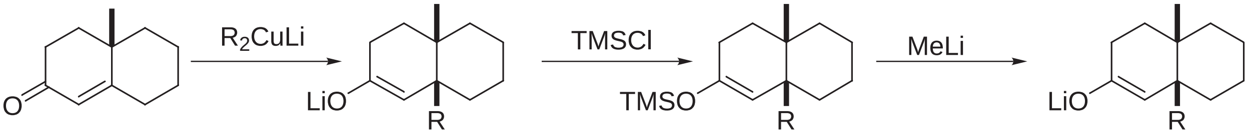
Conjugate Addition/Aldol
Heng *Tetrahedron* **1979**, *35*, 425.

- Cuprates can also be prepared from other organometallic reagents which have greater compatibility with reactive groups: e.g. activated $Cu^{(o)}$/RBr, RZnI, $RSnBu_3/Me_2Cu(CN)Li_2$, $RCH=CH_2$/ $Cp_2Zr(H)Cl$ then $CuBr•SMe_2$



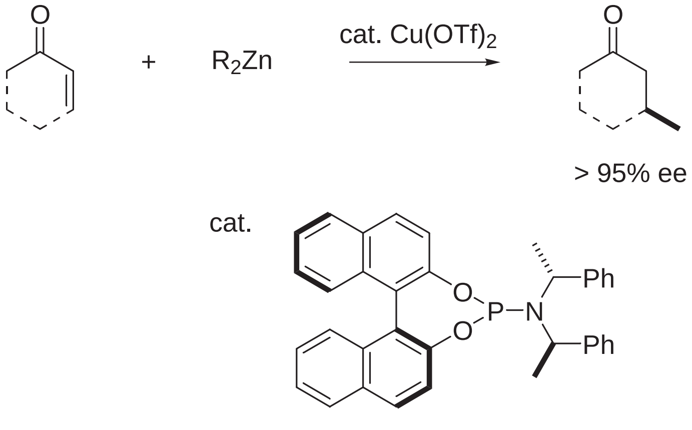
Lipshutz *Tetrahedron Lett.* **1992**, *33*, 5857.

- Useful in the regiospecific trap and subsequent generation of enolates.



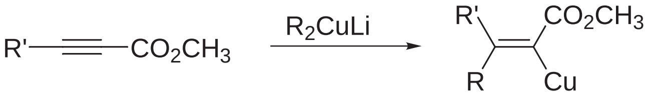
Stork *J. Am. Chem. Soc.* **1974**, *96*, 7114.
Stork *J. Am. Chem. Soc.* **1961**, *83*, 2965.
Horiguchi *Tetrahedron Lett.* **1989**, *30*, 7087.

- Asymmetric 1,4-addition



Feringa *Acc. Chem. Res.* **2000**, *33*, 346.

- Additions to acetylenes

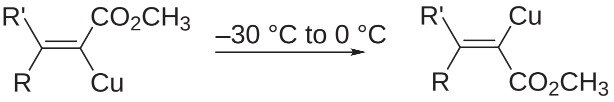


cis addition of "RCu"

R' = Et R = CH_3

THF at –100 °C	97:3	*cis*:*trans*
THF at –78 °C	92:8	lower stereoselectivity due to configurational instability of alkenyl copper reagent
toluene (3 h)	92.5:7.5	
ether (3 h)	24:76	

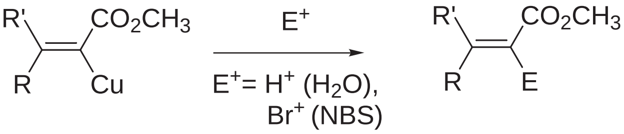
see also: Alexakis *Bull. Chim. Soc., Fr.* **1977**, 693.
Cahiez *Synthesis* **1976**, 245.
Alexakis *Tetrahedron Lett.* **1976**, 2313.
Truce *J. Org. Chem.* **1978**, *43*, 2252.
Marfat *J. Am. Chem. Soc.* **1977**, *99*, 253.



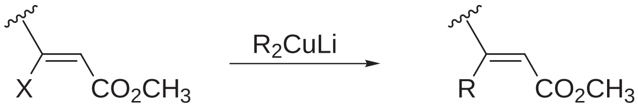
25 °C rapid
0 °C slow
–30 °C observable

Corey, Katzenellenbogen *J. Am. Chem. Soc.* **1969**, *91*, 1851.
Fried *J. Am. Chem. Soc.* **1969**, *91*, 1853.
Klein *J. Chem. Soc., Perkin Trans. 2* **1973**, 1971.

- Alkenyl copper intermediates can be subsequently trapped:

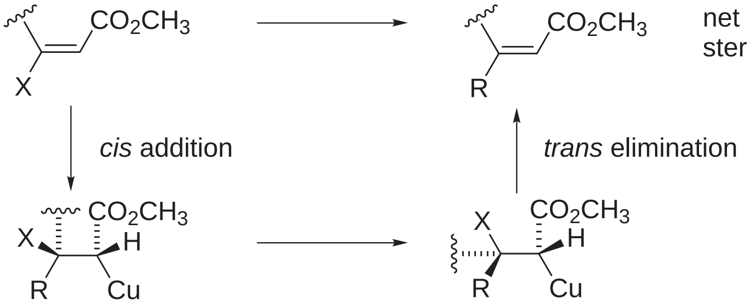


- Also, used in displacement of leaving groups (addition/elimination reactions).



via β-elimination
from intermediate enolate

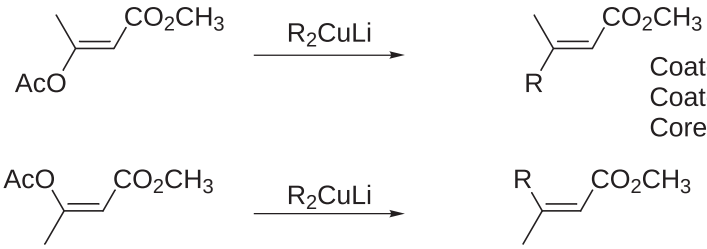
X = SPh, Br, OAc (good leaving group)



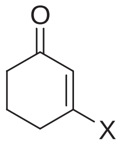
net retention of
stereochemistry

X = SPh
Corey *J. Am. Chem. Soc.* **1969**, *91*, 1851.
Casey *Tetrahedron Lett.* **1974**, 925.
Mukaiyama *Chem Lett*. **1974**, 705.

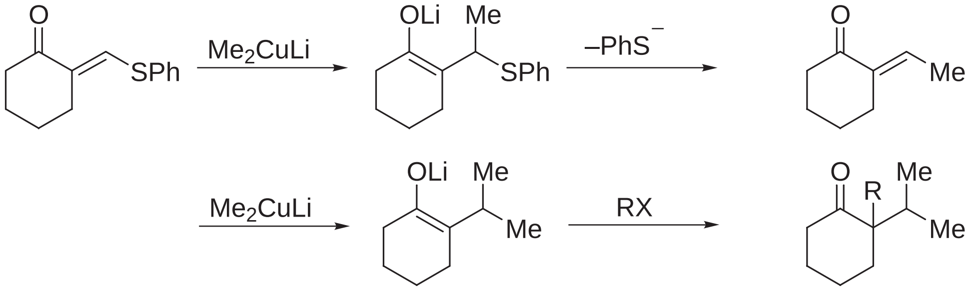
- Examples:

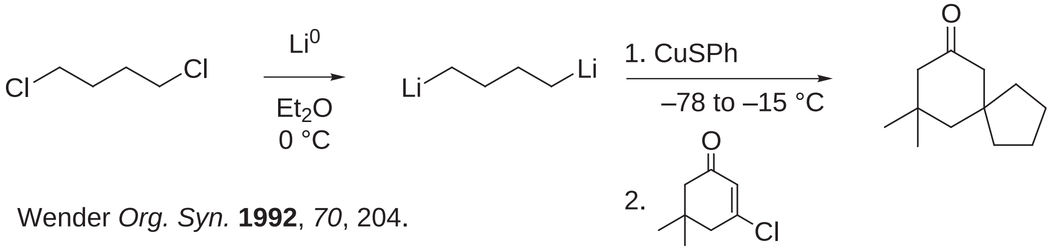


Coates *J. Org. Chem*. **1974**, *39*, 275.
Coates *J. Am. Chem. Soc.* **1971**, *93*, 1027.
Corey *Tetrahedron Lett.* **1973**, 3817.



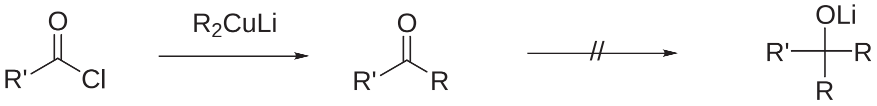
X = SPh, Cl, Br, OAc
(but not for OCH_3)



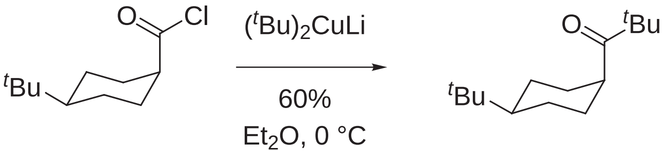


Wender *Org. Syn.* **1992**, *70*, 204.

- Selective preparation of ketones from carboxylic acid derivatives.

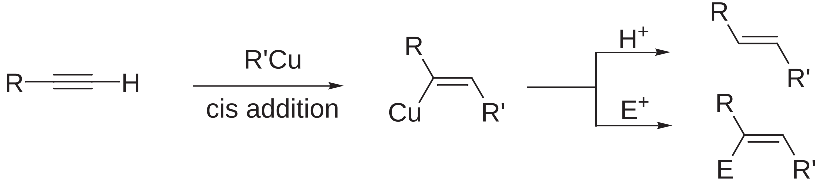


no overaddition
to give 3° alcohol

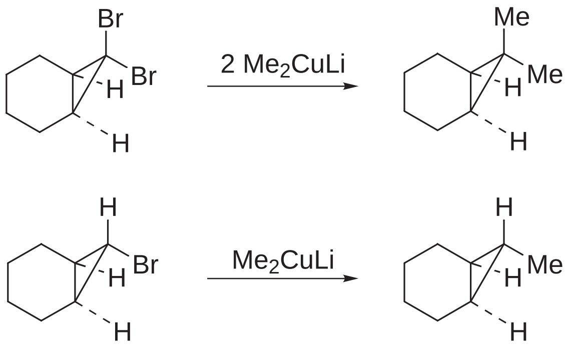


no epimerization of axial
carbonyl group

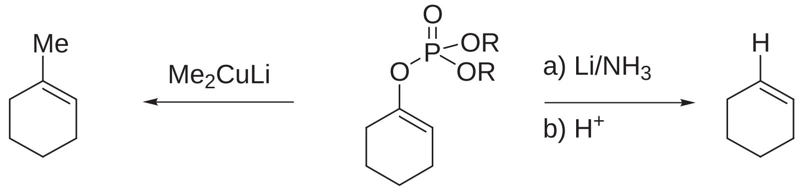
- Additions to terminal alkynes.



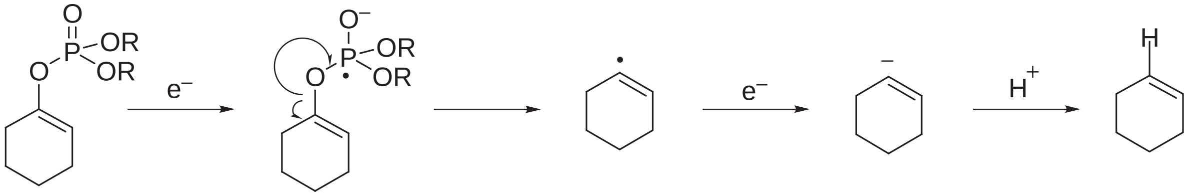
- Alkylation reactions



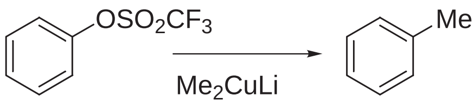
substitution reactions proceed
with retention of configuration



- Mechanism:

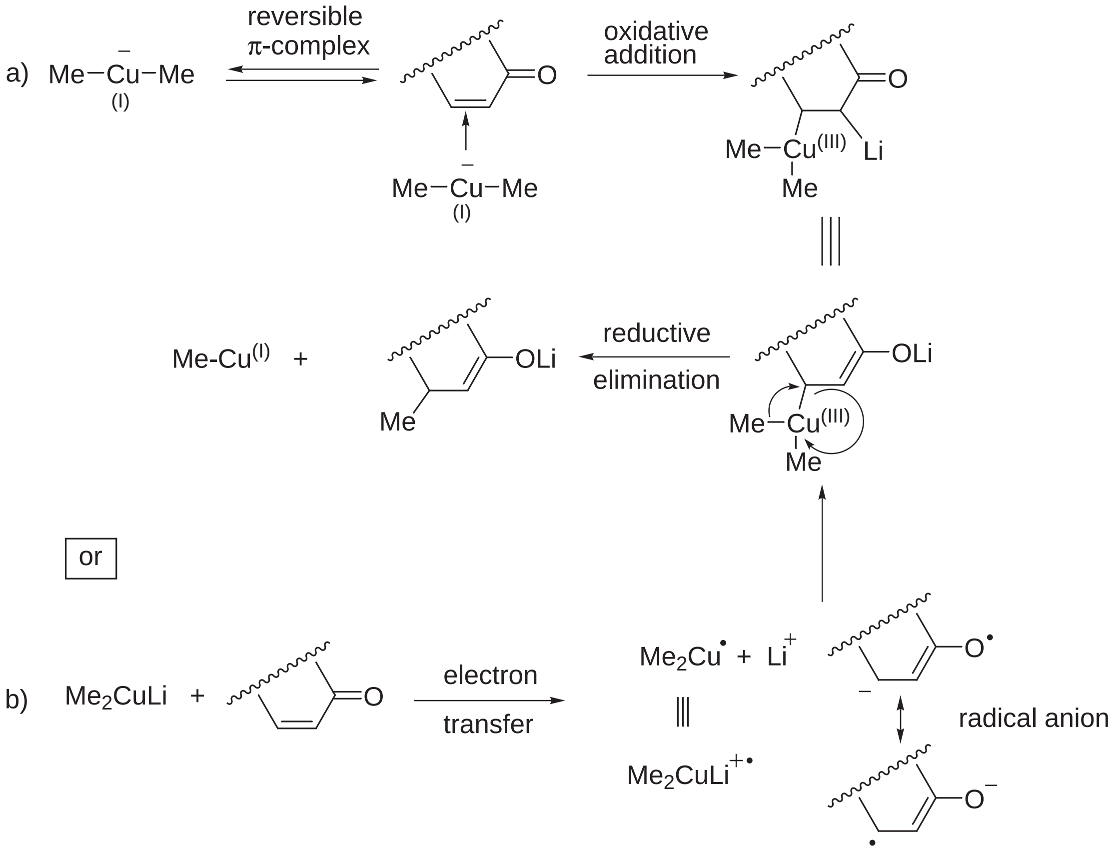


- Also can be conducted with aryl and enol triflates



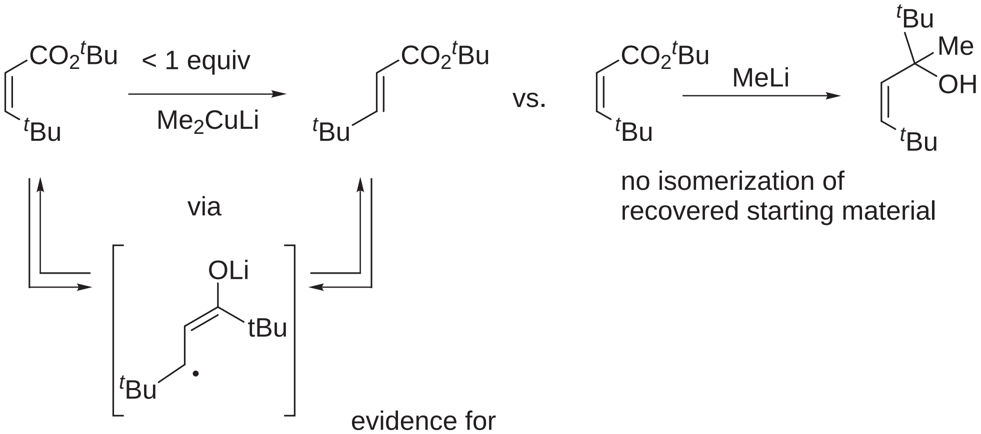
functional group reactivity~ RCOCl > CHO > tosylates > epoxides > bromides > ketones > esters > nitriles

2. Mechanism



-Evidence for mechanism b)

i. Isomerization and recovery of substrates without 1,4-addition



no isomerization of
recovered starting material

evidence for
electron transfer
mechanism

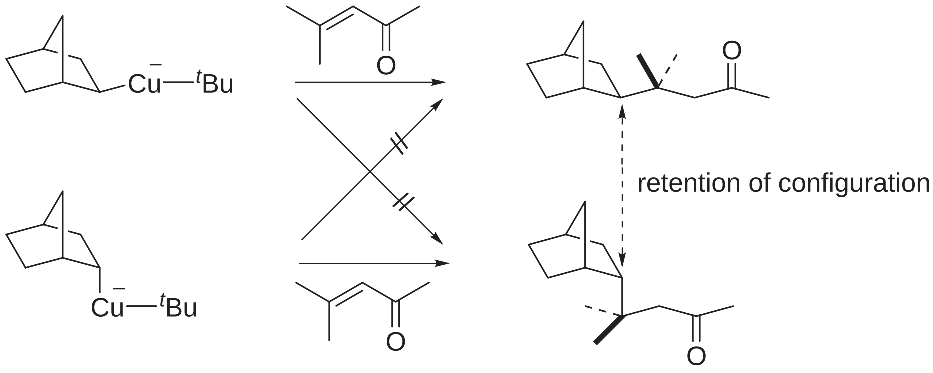
ii. Cation is essential for the reaction $Me_2Cu\textcircled{Li}$

- if crown ethers are added to reaction mixture, reaction is slowed or prevented

- Li^+ complexes with carbonyl oxygen and activates substrate to conjugate addition (Ouannes *Tetrahedron Lett*. **1977**, 815.)

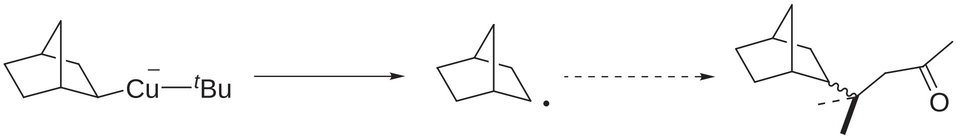
iii. Retention of stereochemistry of cuprate alkyl group that is transferred

e.g.



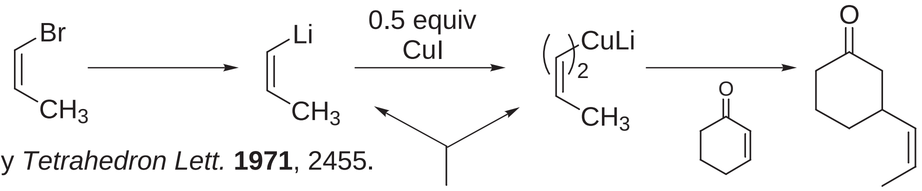
Whitesides *J. Org. Chem.* **1972**, *37*, 3718.
Whitesides *J. Am. Chem. Soc.* **1969**, *91*, 6542.

- So reaction cannot be proceeding through a free-radical



would get mixture

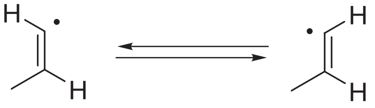
- Retention also observed for alkenyl cuprates:



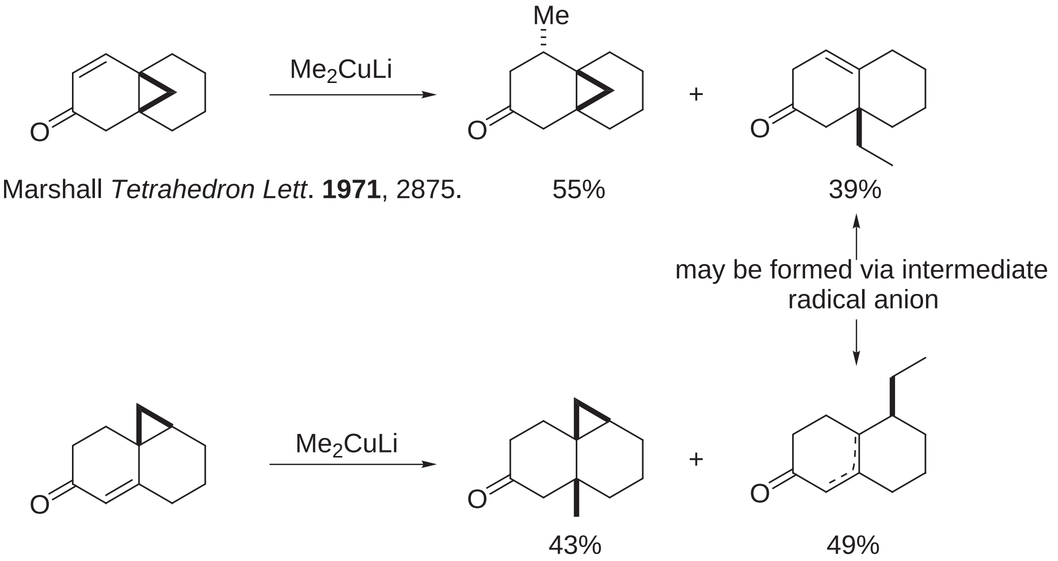
Casey *Tetrahedron Lett.* **1971**, 2455.

Configurationally stable

- Not true for free radical

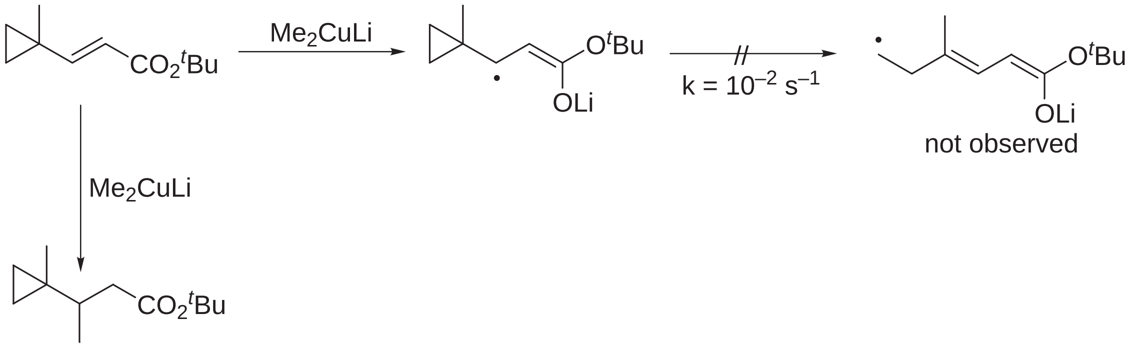


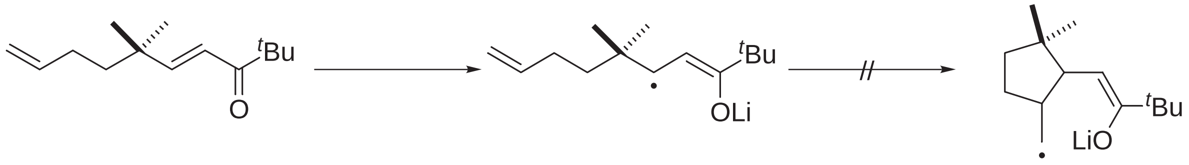
- Additional evidence for radical anion mechanism:



Marshall *Tetrahedron Lett*. **1971**, 2875.

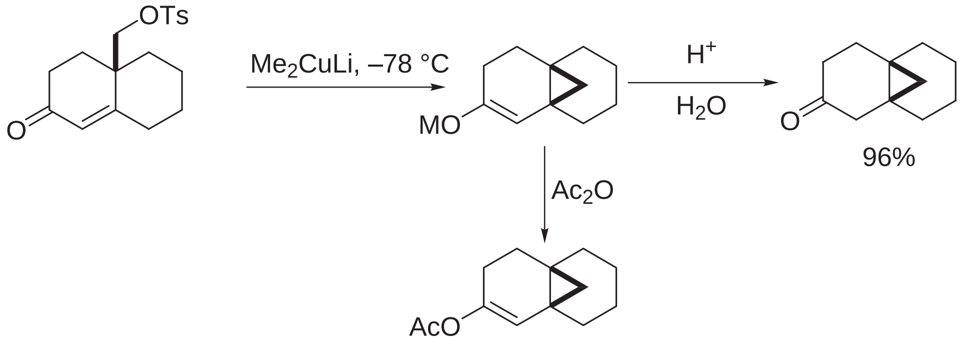
- but





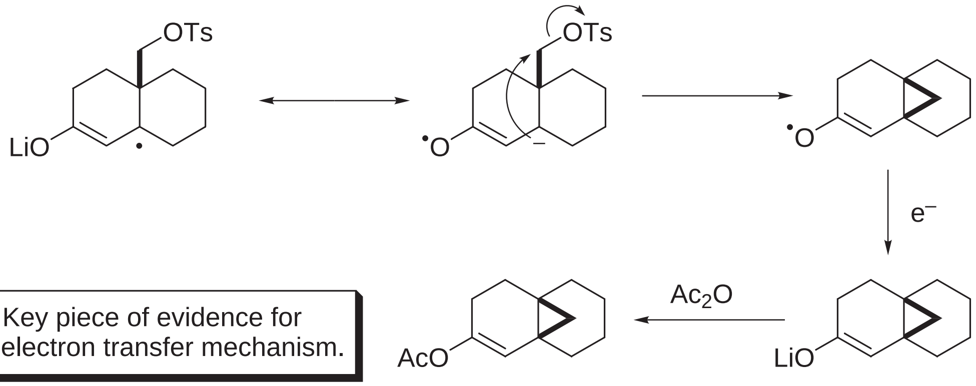
- So half-life of intermediate radical anion is very short.
- Subsequent coupling with cuprate reagent (after e$^-$ transfer) is faster than other radical reactions in some cases.
- However, competitive single electron reductions with cuprates have been observed and they may be used to effect reductive elimination reactions in manner analogous to dissolving metal or Zn reductions.

iv. Trap of intermediate radical anion



- no conjugate or homo-conjugate addition observed, only intramolecular trap of intermediate radical anion

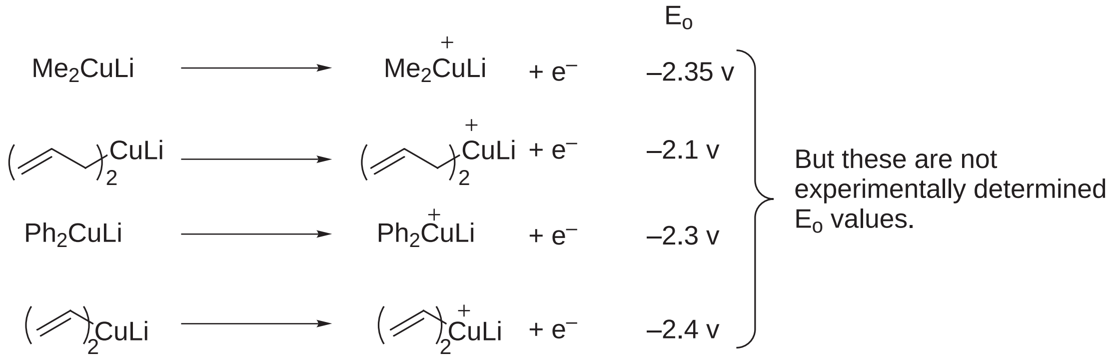
Hannah *Tetrahedron Lett*. **1975**, 187.



- Key piece of evidence for electron transfer mechanism.

v. House *J. Am. Chem. Soc.* **1972**, *94*, 5495.

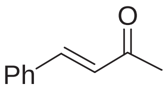
- Rate and ease of conjugate addition to the substrate correlate with the polarographic reduction potential while they do not always correlate with propensities for Michael addition.



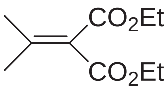
But these are not experimentally determined E$_o$ values.

- And for conjugate addition with Me_2CuLi

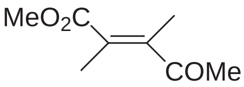
E_{red}



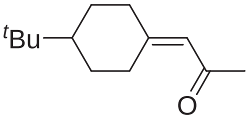
–1.63 v



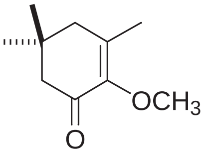
–2.13 v



–2.14 v

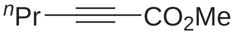


–2.12 v

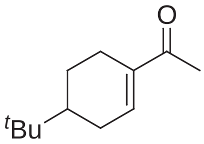


–2.20 v

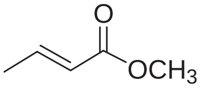
E_{red}



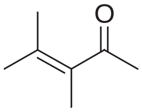
–2.26 v



–2.25 v



–2.33 v

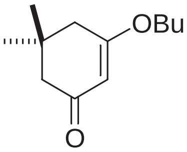


–2.35 v

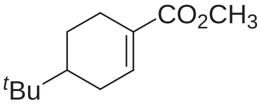
All can accept an e$^-$
(undergo reduction)
by Me_2CuLi.

E_o = –2.35 v

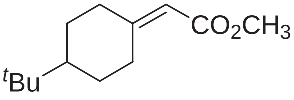
- But these substrates do not react with Me_2CuLi:



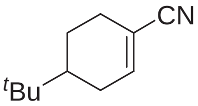
–2.43 v



–2.50 v

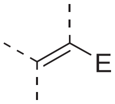


–2.54 v



–2.55 v

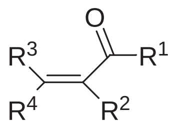
Note that for



the ease of organocuprate conjugate addition decreases in the order:

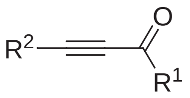
E = COR > CO_2R > CN House *Acc. Chem. Res.* **1976**, *9*, 59.

-House estimation of



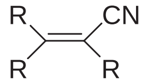
base value = –1.9 v

substituent	R^1	R^2	R^3/R^4
alkyl	–0.1	–0.1	–0.1
alkoxy	–0.3	0	–0.3
phenyl	+0.4	+0.1	+0.4



base value = –1.8 v

substituent	R^1	R^2
alkyl	–0.1	–0.1
alkoxy	–0.3	---

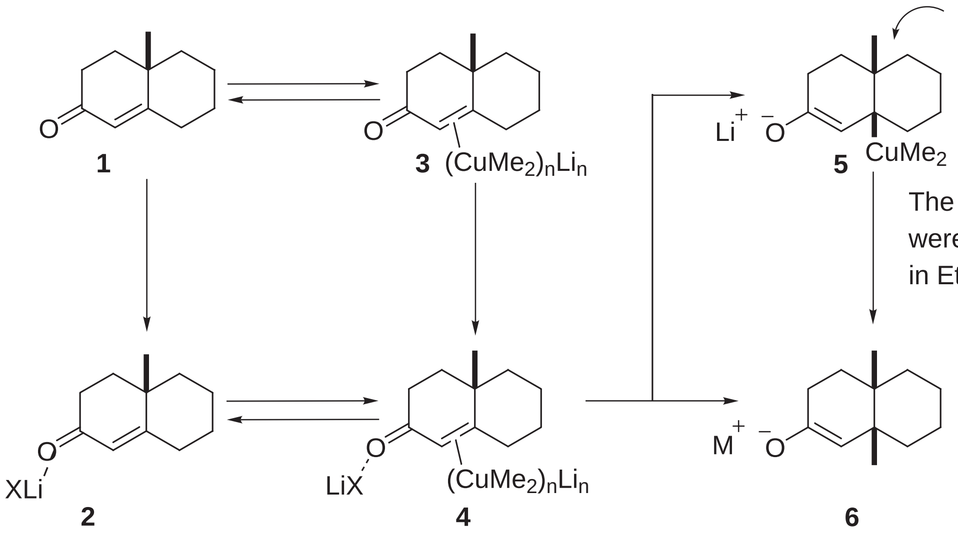


base value = –2.3 v

vi. Kinetic preference for 1,2-addition for standard organometallic (and other) nucleophiles suggests something unique about 1,4-addition of organocuprates

vii. ^{13}C NMR detection of reaction intermediates

- Mechanism of organocuprate conjugate addition: observation of cuprate–olefin complexes and Li-coordinated intermediates in the reaction of lithium dimethyl cuprate with 10-methyl-$\Delta^{1,9}$-2-octalone. Robin and Smith *J. Am. Chem. Soc*, **1989**, *111*, 8276.



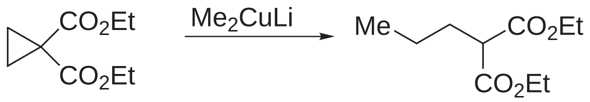
Cu$^{(III)}$ intermediate observed directly

The intermediates **1**–**5** were observed at –78 °C in Et$_2$O-d_6 by ^{13}C NMR

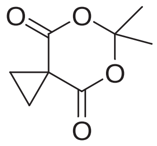
See also: Corey *Tetrahedron Lett.* **1990**, *31*, 1393.

viii. Isolation of the π-complex and conversion on to product
Corey *Tetrahedron Lett.* **1985**, *26*, 6015.

3. Homoconjugate Addition

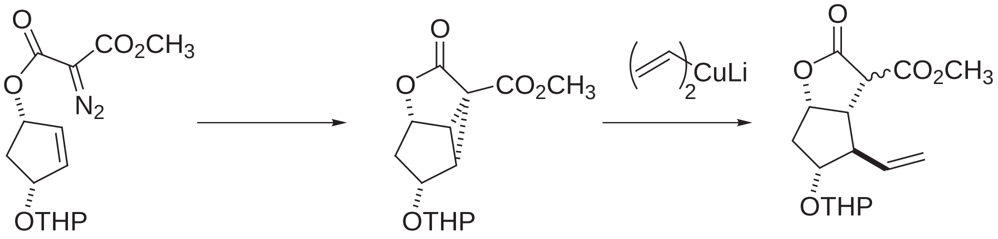


- Can also use



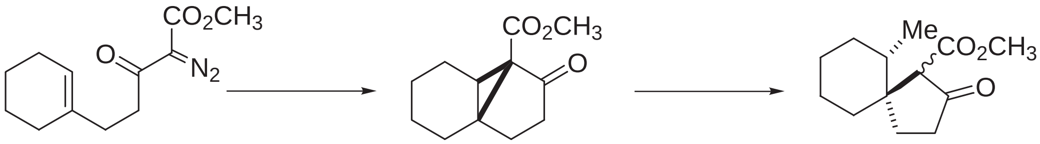
-These reactions work well with Me_2CuLi, and probably vinyl cuprates and aryl cuprates (no problem with β elimination) but not as well for simple alkyl cuprates (less stable, must keep < –30 °C)

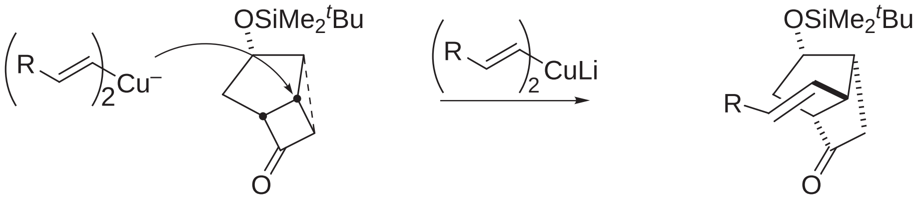
- Application to prostaglandin synthesis:



Corey *J. Am Chem. Soc.* **1972**, *94*, 4013.

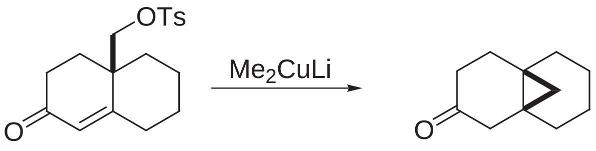
and



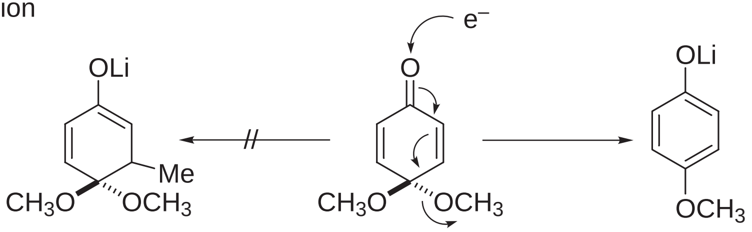


4. Competitive Reduction and Rearrangement

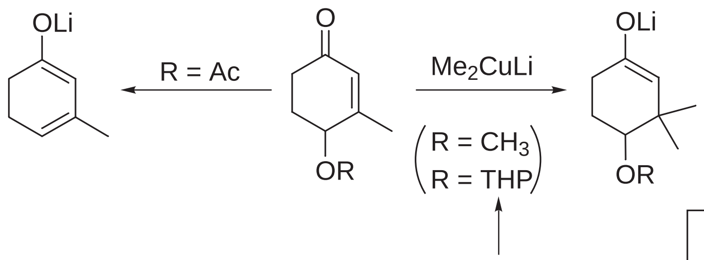
a) Interception of radical–anion intermediate



b) Reduction



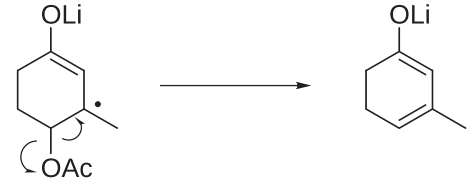
Also observed with γ-acyloxy enones:

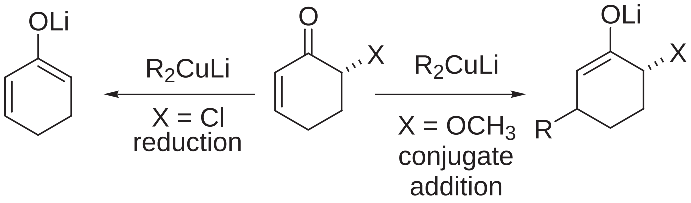


Ruden *Tetrahedron Lett.* **1975**, 2043.

Note: This is cited as further support of the electron transfer mechanism.

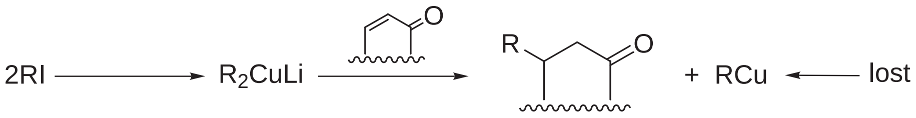
via



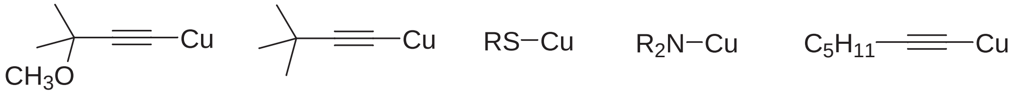


5. Mixed Organocuprates

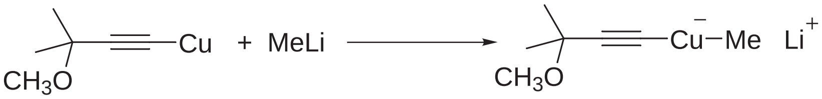
- For dialkylcuprates, one alkyl substituent (ligand) is lost:



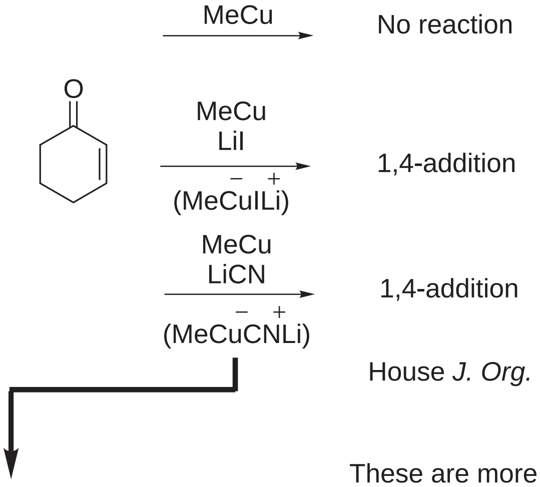
- Mixed cuprates have been developed in which one ligand will not transfer:
  Corey *J. Org. Chem.* **1978**, *43*, 3418.



- With these reagents, only the non-transferable reagent is lost



- Also: addition of Li salts forms cuprate reagents from alkyl copper reagents ("ate" complexes)



House *J. Org. Chem.* **1966**, *31*, 3128.

Higher Order Cuprates - - - - - - - - → These are more reactive and also
very good for sluggish reactions
e.g., epoxide openings, alkylations.

$R_2CuLi \xrightarrow{LiCN} R_2Cu(CN)Li_2$

$2RLi + CuCN \longrightarrow R_2Cu(CN)Li_2$

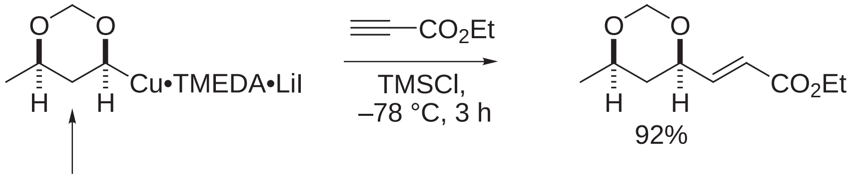
See: Lipshutz *Org. React.* **1992**, *41*, 135.
Lipshutz *Synthesis* **1987**, 325.
Lipshutz *Tetrahedron* **1984**, *40*, 5005.

- Representative Mixed Cuprates

RLi, CuI, R_3P (1:1:2)	Suzuki *Tetrahedron Lett.* **1980**, 1247.
(COD)RCuMgX	Leyendecker *Tetrahedron Lett.* **1980**, 1311.
RCu(SPh)Li, RCu(O^tBu)Li, RCu(NMe_2)Li	Posner *J. Am. Chem. Soc.* **1973**, *95*, 7788.
RCu(SPh)Li	Alexakis *Tetrahedron Lett.* **1976**, 3461. *Org. Prep. Proc. Int.* **1976**, *8*, 13
RCu($C\equiv C^tBu$)Li and RCu(CN)Li	Boeckman *J. Org. Chem.* **1977**, *42*, 1581. Marino *J. Org. Chem.* **1976**, *41*, 3213.
RCu(CN)Li	Acker *Tetrahedron Lett.* **1977**, 3407. Miyaura *Tetrahedron Lett.* **1977**, 3369.
RCu($C\equiv CPr$)Li	Corey *J. Am. Chem. Soc.* **1972**, *94*, 7210.
RCu($C\equiv CC(OMe)Me_2$)Li	Corey *J. Org. Chem.* **1978**, *43*, 3418.

6. Functionalized Organocuprate Reagents

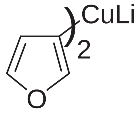
- Examples



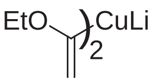
Configurationally stable (better than higher order cyano cuprate):
prepared from the corresponding Bu_3Sn reagent/^{n}BuLi then CuI/TMEDA.

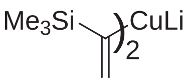
Linderman *J. Org. Chem.* **1991**, *56*, 5491.

- Other representative functionalized organocuprate reagents



Kojima, Wakita and Kato *Tetrahedron Lett.* **1979**, 4577.

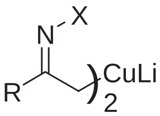


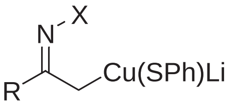


Doyle and West *J. Org. Chem.* **1975**, *40*, 3821.
Nordlander and Haky *J. Org. Chem.* **1979**, *45*, 4780.
Schollkopf and Haenssle *Justus Liebigs Ann. Chem.* **1972**, *763*, 208.
Baldwin, Hoefle and Lever *J. Am. Chem. Soc.* **1974**, *96*, 7125.
Huynh and Linstrumelle*Tetrahedron Lett.* **1979**, 1073.

R_2CuLi
$R = {}^{n}Bu, Ph, CH_2{=}CH, {}^{s}Bu$
$R = {}^{t}Bu, Me, CH_2{=}CHCH_2$

House and Wilkins *J. Org. Chem.* **1978**, *43*, 2443.



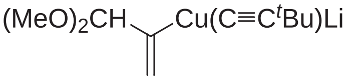


$X = NMe_2, OCH_3$

Corey and Enders *Tetrahedron Lett.* **1976**, 11.
Corey and Boger *Tetrahedron Lett.* **1978**, 4597.
Gawley, Termine, and Aube *Tetrahedron Lett.* **1980**, *21*, 3115.

$(RCH{=}CHCH_2)_2CuLi$

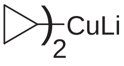
Miginiac, Daviaud and Gerard *Tetrahedron Lett.* **1979**, 1811.

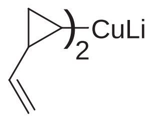


Depezay and Le Merrer *Tetrahedron Lett.* **1974**, 2751.
Boeckman and Rammaiah *J. Org. Chem.* **1977**, *42*, 1581.
Cyano cuprate: Marino and Farina *J. Org. Chem.* **1976**, *41*, 3213.
Thiophenyl cuprate: Grieco, Wang, and Majetich
J. Org. Chem. **1976**, *41*, 726.

$[(EtO)_2P(O)CH_2]_2CuLi$

Savignac and Mathey *Tetrahedron Lett.* **1976**, 2829.
Mathey and Savignac *Synthesis* **1976**, 766.

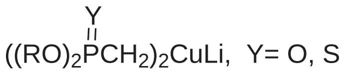




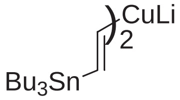
Wender and Filosa *J. Org. Chem.* **1976**, 3490.
Marino and Browne *J. Org. Chem.* **1976**, 3629.
Piers, Lau and Nagakura *Tetrahedron Lett.* **1976**, 3233.
Piers and Nagakura *Tetrahedron Lett.* **1976**, 3237.
Marino and Browne *Tetrahedron Lett.* **1976**, 3241.
Marino and Browne *Tetrahedron Lett.* **1976**, 3245.

$PhSCu(Li)CH_2(CH_2)_nCH_2Cu(Li)SPh$

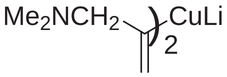
Wender and Eck *Tetrahedron Lett.* **1977**, 1245.


$((RO)_2\overset{\overset{\displaystyle Y}{\|}}{P}CH_2)_2CuLi$, Y= O, S

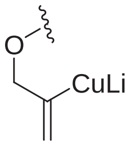
Savignac and Mathey *Tetrahedron Lett.* **1976**, 2829.



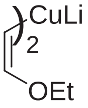
Fargeas *Tetrahedron* **1996**, *52*, 6613; **1994**, *35*, 7767.



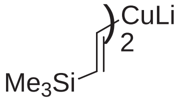
Corey, Cane and Libit *J. Am. Chem. Soc.* **1971**, *93*, 7016.



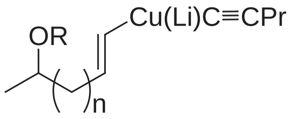
Ireland *J. Org. Chem.* **1975**, *40*, 973.



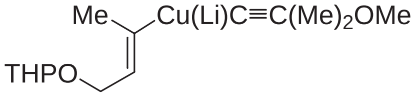
Wollenberg *J. Am. Chem. Soc.* **1977**, *99*, 7365
Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595.



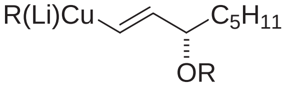
Linstrumelle *Tetrahedron Lett.* **1979**, 1073.



(n = 1, R = THP) Corey *J. Am. Chem. Soc.* **1976**, *98*, 222.
(n = 3, R = TBDMS) Corey *Tetrahedron Lett.* **1976**, 4701 and 4705 .



Corey *Tetrahedron Lett.* **1978**, 1051.
Corey *J. Am. Chem. Soc.* **1978**, *100*, 2916.



Corey *J. Am. Chem. Soc.* **1972**, *94*, 7210.
Corey *Tetrahedron Lett.* **1983**, *24*, 5571.
Corey *Tetrahedron Lett.* **1986**, *27*, 2199 and 3585.

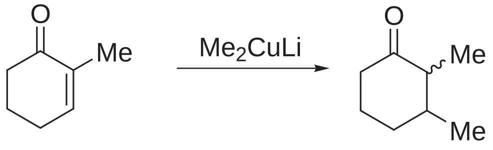
7. Stereochemistry of Organocuprate Conjugate Addition Reactions

A. Cyclic Substrates

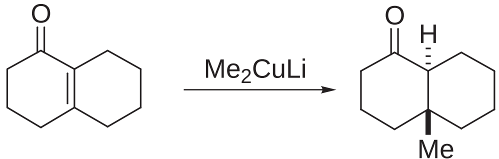
Cyclic enones: intraannular diastereoselectivity

Ref. 2,3-diastereoselectivity

1

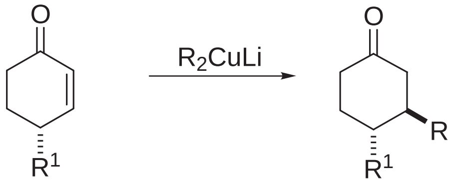


condition dependent:
cis preferred, but isomerization
to *trans* is facile.



3,4-diastereoselectivity

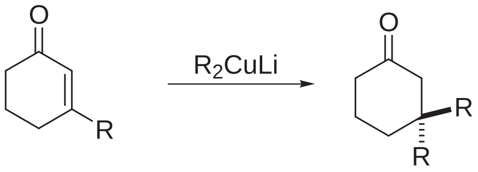
2



R^1	R	*trans*:*cis*	R^1	R	*trans*:*cis*
Me	Me	72:28	Et	Me	77:23
	Et	78:22		Ph	89:11
	^{i}Pr	88:12	^{i}Pr	Me	89:11
	Ph	96:4 (87:13)		Et	92:8

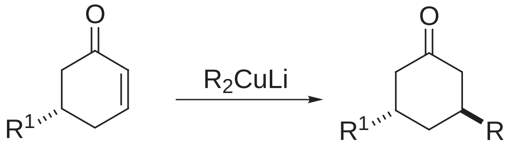
3-substituted enones

3



3,5-diastereoselectivity

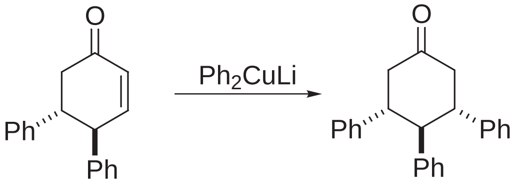
4



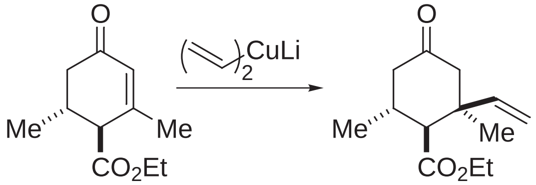
R^1	R	*trans*:*cis*
Me	Me	98:2 (99:1) (93:7)
Me	CH_2Ph	*trans* only

3,4-diastereoselectivity vs 3,5-diastereoselectivity

4



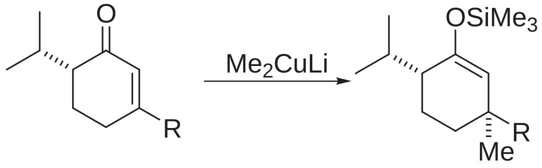
This will be dependent on the relative size of the C-3 and C-4 substituents.



80 : 20

3,6-diastereoselectivity

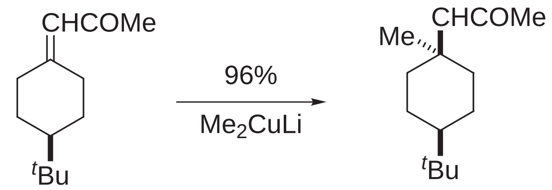
5



Exocyclic enones and esters

Ref.

6



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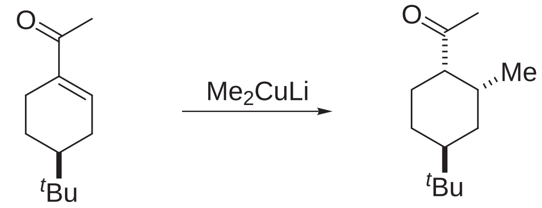
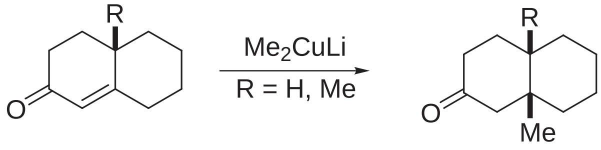


Bicyclic enones and related substrates

8



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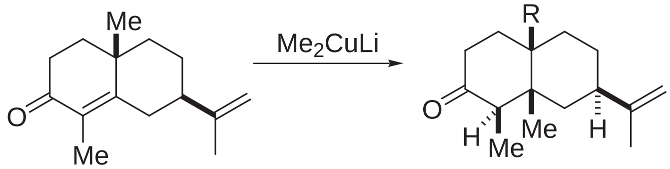

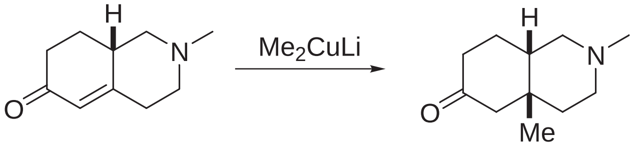

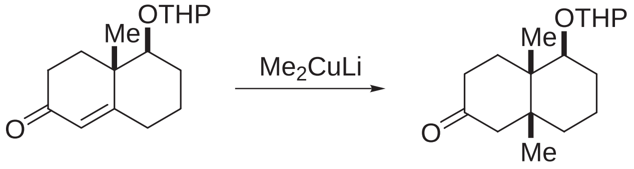

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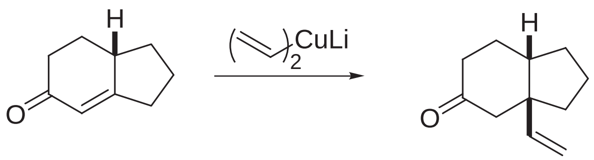

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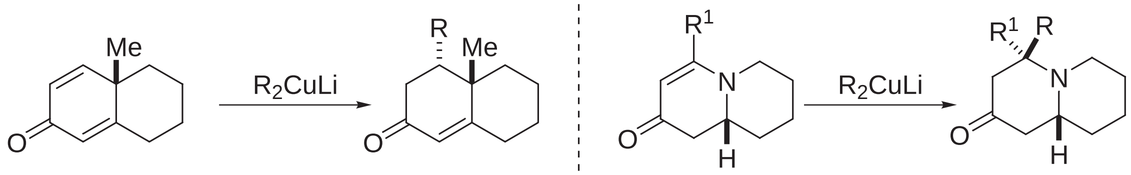
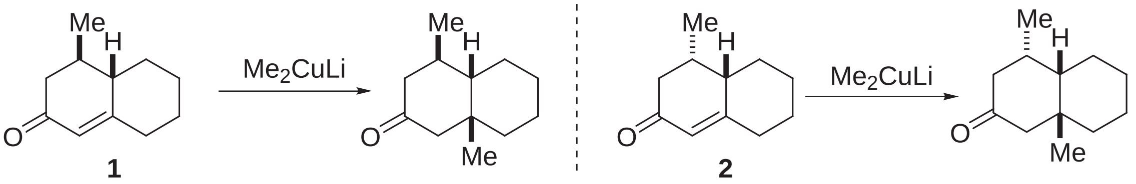


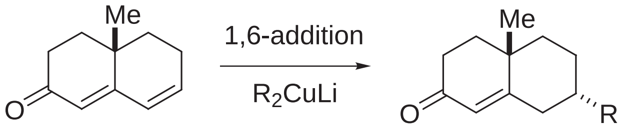
ref.

12



rate: **2** > **1** (>20:1)

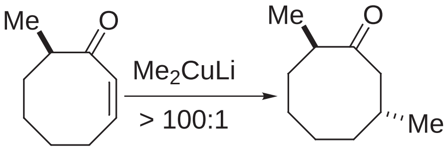
13



R	*trans*:*cis*
Me	93:7
Et	98:2
^{i}Pr	100:0
^{t}Bu	100:0

Medium-sized rings

14



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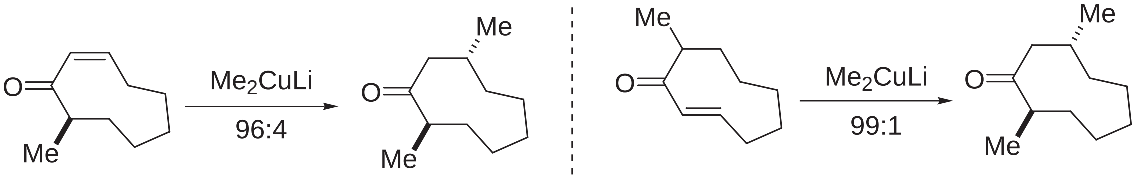
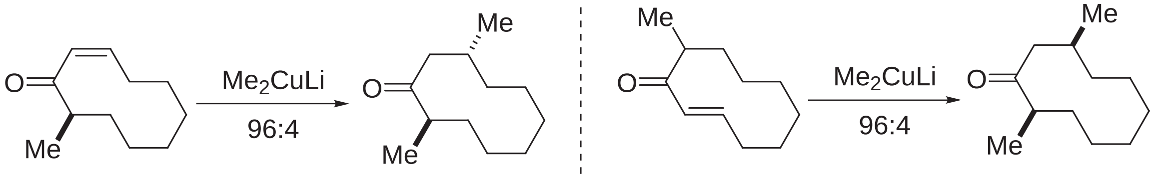


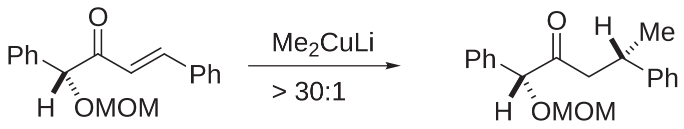
BUT

14



B. Acyclic Substrates

12



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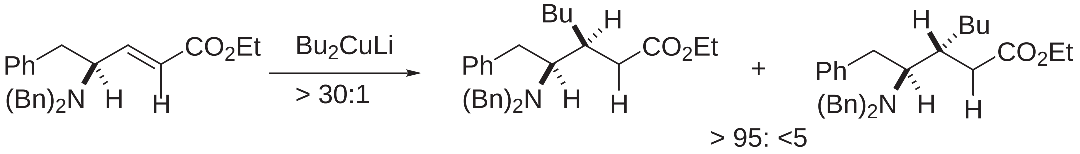

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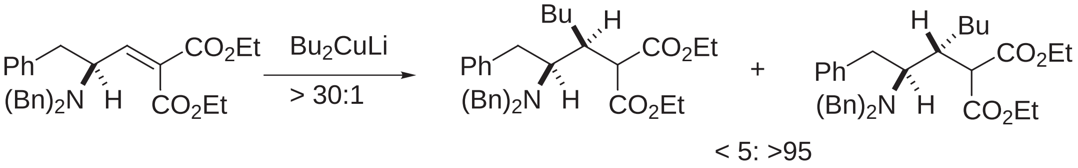

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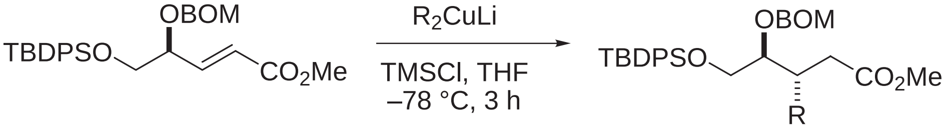
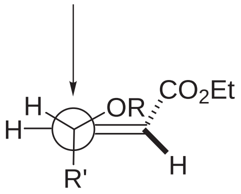
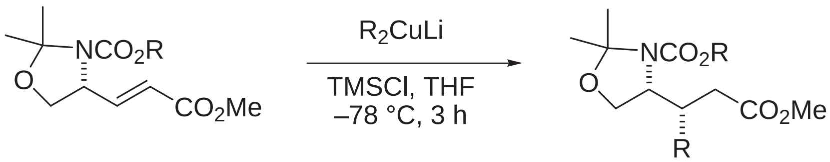


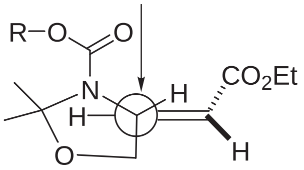
73–93%
> 50:1
R = Me
R = Et
R = Bu



- favorable interaction between alkoxy and π system.
- free of 1,2-allylic strain.
- increased stabilization of the α,β-unsaturated system via interaction between low-level π* orbital and high-level σR'–C orbital.



70–90% yield
> 50:1
R = Me
R = Et
R = Bu



- favorable interaction between parallel σC–R and σ*C–Cu orbitals.
- possibility of chelation between carbamate and ester may overide 1,2-allylic strain as well as bulk of γ-substituent.

Stereochemistry of Organocuprate Conjugate Addition Reactions (References)

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Medium-sized Rings

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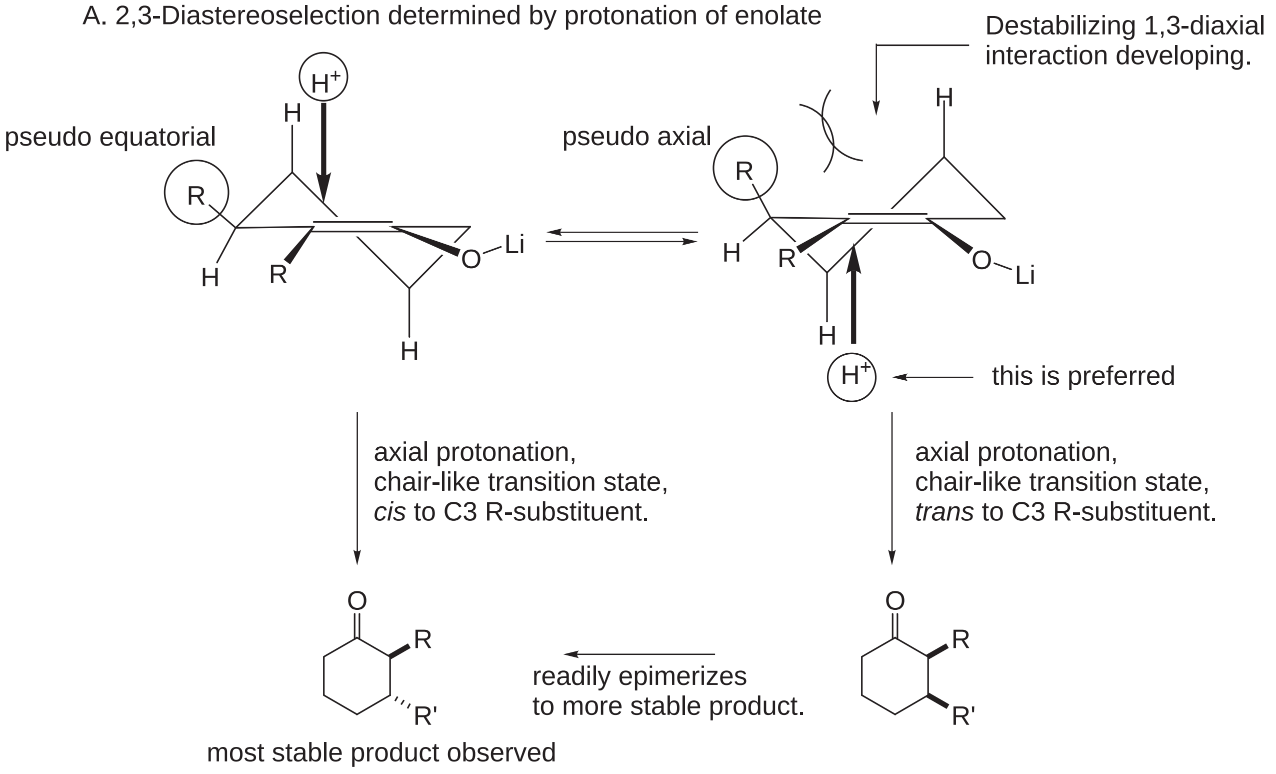
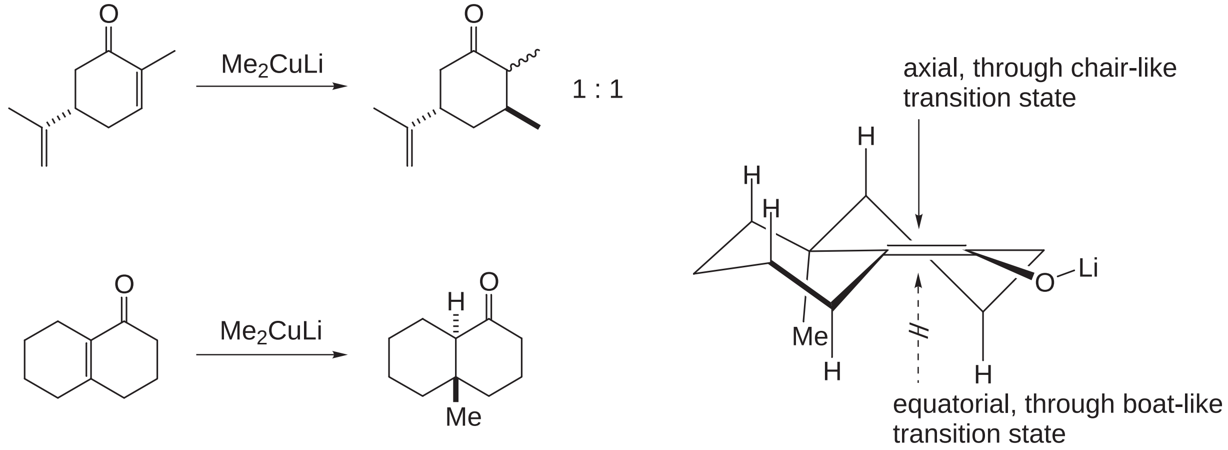
8. Origin of Diastereoselectivity

A. 2,3-Diastereoselection determined by protonation of enolate

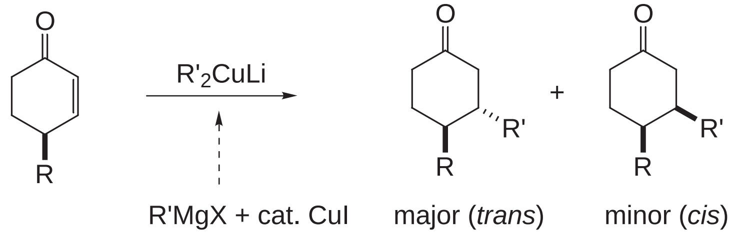


- Examples:



Posner *J. Org. Chem.* **1973**, *38*, 4459.

B. 3,4-Diastereoselection



R = Me

R'	Ratio	
Me	72:28	
Et	78:22	
^{i}Pr	88:12	
Ph	87:13	(75%)
	96:4	(PhCu)

increasing size of R'
increasing amount of *trans*

R = Et

R'	Ratio
Me	77:23
Et	89:11

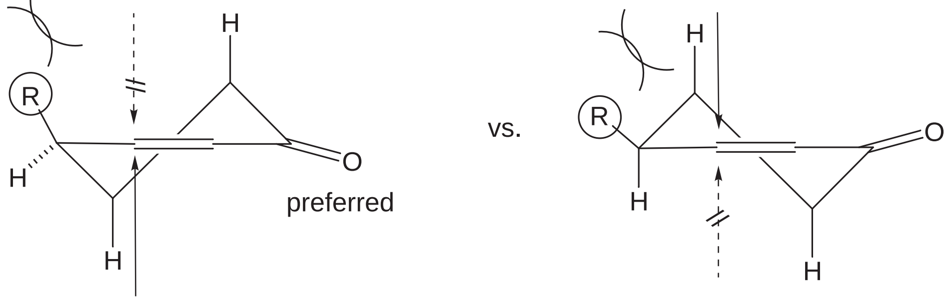
increasing size of R
increasing amount of *trans*

R = ^{i}Pr

R'	Ratio
Me	89:11
Et	92:8

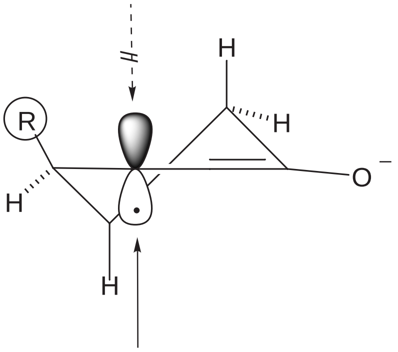
equatorial delivery, boat-like transition state; *cis* to C4 R-substituent

axial delivery, chair-like transition state; *cis* to C4 R-substituent

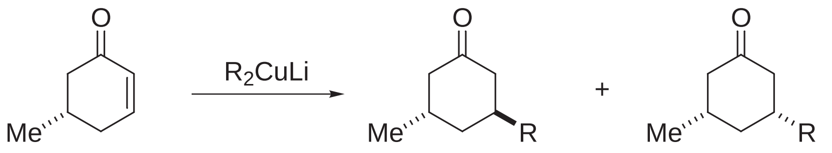


axial delivery, chair-like transition state; *trans* to C4 R-substituent

but remember: reactive intermediate may be radical anion



C. 3,5-Diastereoselectivity



trans (major) *cis* (minor)

House *J. Org. Chem*. **1968**, *33*, 949.

R = Me	93	:	7	(MeMgI, cat, CuI) >90%
	98	:	2	(Me_2CuLi)
	99	:	1	(Me_2CuLi + LiI)

Posner *J. Am. Chem. Soc*. **1975**, *97*, 107.

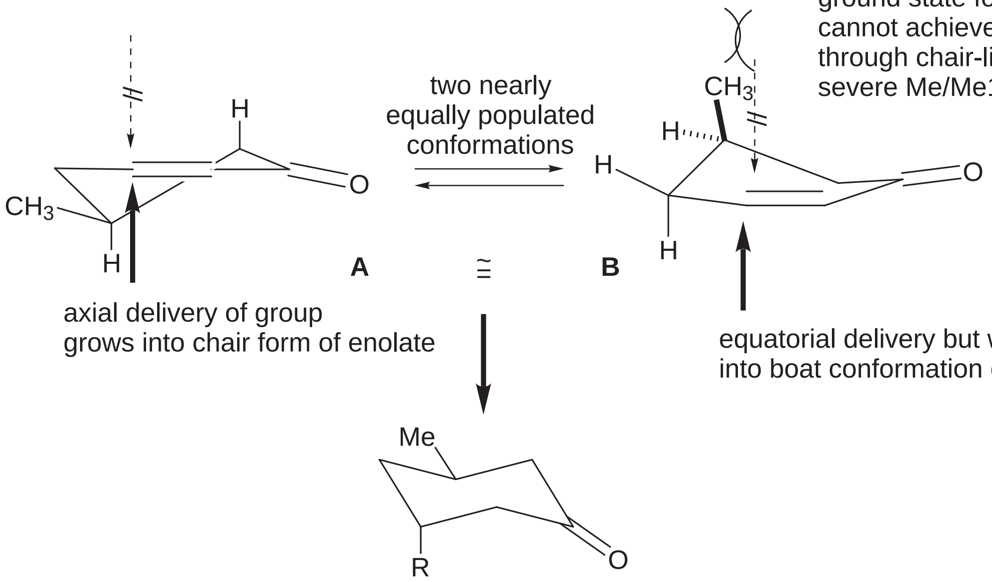
R = CH_2Ar *trans* only

unaffected by C3 substitution

Posner *J. Am. Chem. Soc*. **1975**, 97, 107.

- equatorial delivery of group,
  grows into boat conformation of enolate.

no destabilizing interactions in the ground state for axial Me group but cannot achieve axial delivery of Nu$^-$ through chair-like transition state: severe Me/Me1,3-diaxial interaction.



two nearly equally populated conformations

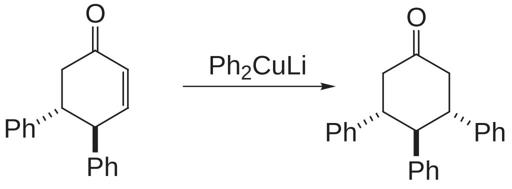
axial delivery of group
grows into chair form of enolate

equatorial delivery but would grow
into boat conformation of enolate

enone with alkyl substituent in the equatorial position is the reactive conformation.

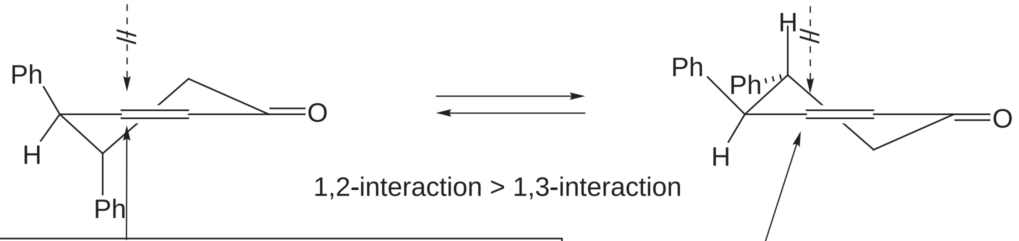
D. 3,4- vs 3,5-Diastereoselectivity

3,4 > 3,5



equatorial delivery
boat-like transition state

axial delivery, chair-like transition state
but destabilizing 1,2-steric interaction



1,2-interaction > 1,3-interaction

axial delivery, 1,3-destabilizing steric interactions
but chair-like transition state.

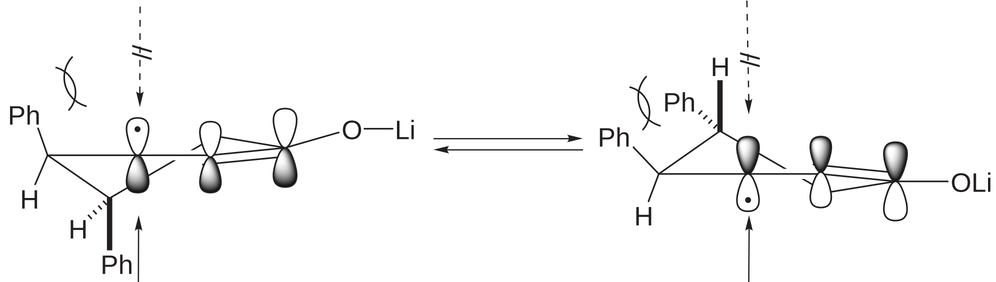
preferred

equatorial delivery requires
boat-like transition state

again, it may be viewed as a radical anion intermediate

equatorial

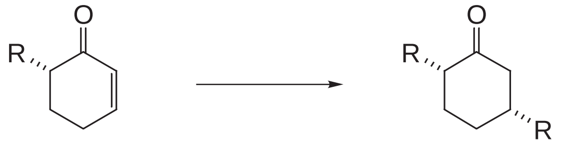
axial



axial

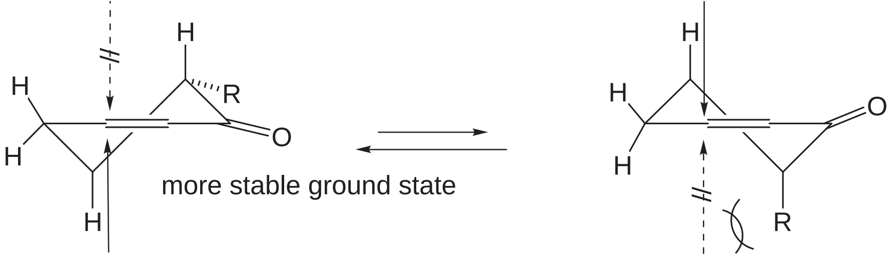
equatorial

E. 3,6-Diastereoselectivity



equatorial delivery, boat-like transition state

axial delivery, chair-like transition state

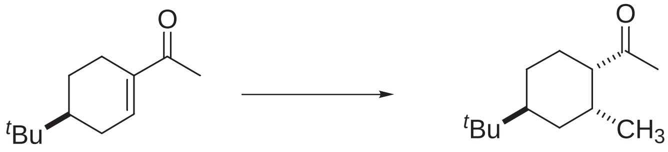


more stable ground state

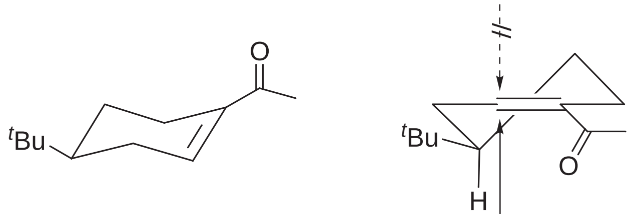
axial delivery, chair-like transition state
cis product predominates

equatorial delivery, boat-like transition state

F. Exocyclic enones



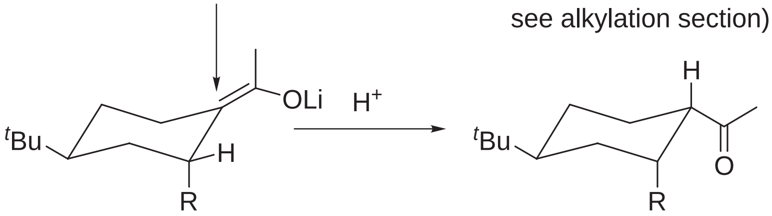
equatorial attack would require boat-like transition state



axial attack proceeds through chair-like transition state

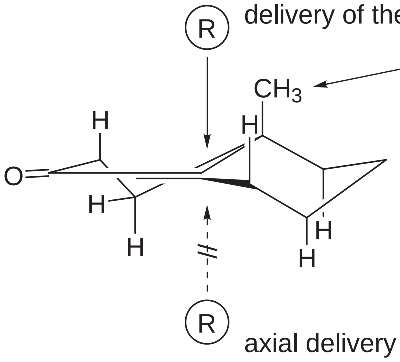
axial protonation

(observed even when ^{t}Bu replaced with H, see alkylation section).



G. Fused enones

relative to B ring this is equatorial delivery of the nucleophile.



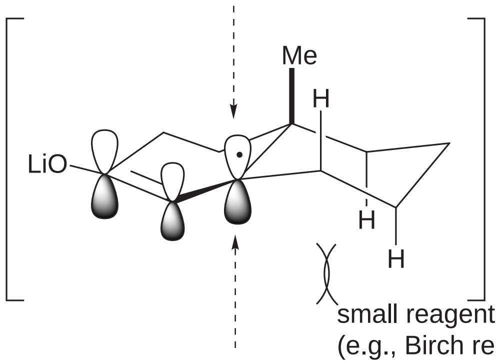
decelerates conjugate addition this steric interaction is a 1,2-interaction or torsional strain (eclipsing interaction)

Cuprate behaves as large nucleophile preferring equatorial attack (1,2-interactions) to axial attack (1,3-interactions) on the exocyclic olefin.

axial delivery of nucleophile suffers severe steric interactions (1,3-diaxial interactions)

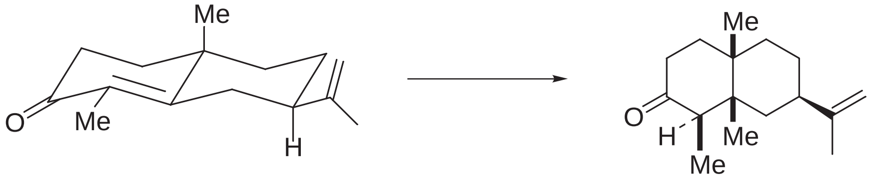
-May really want to consider radical-anion conformation

1,2-torsional interaction large reagent (Cuprate)



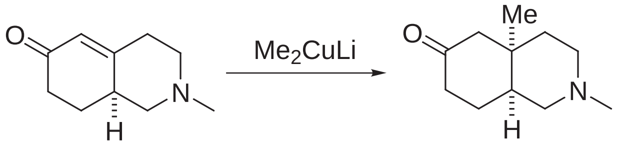
small reagent (H$^+$) (e.g., Birch reduction)

1,3-steric interactions

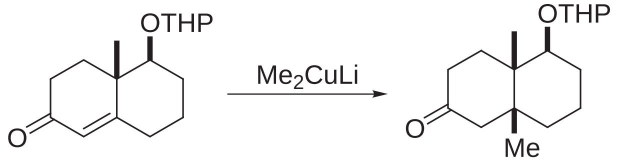


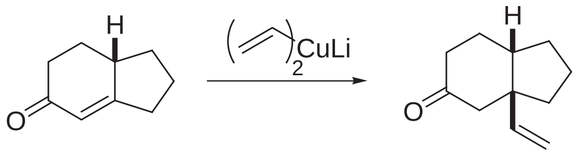
- *cis* ring fusion.
- protonation from least hindered face of enolate, also most stable product.

Piers *Can. J. Chem*. **1969**, *47*, 137.



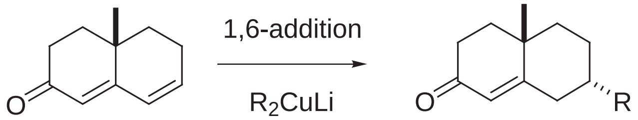
cis fusion



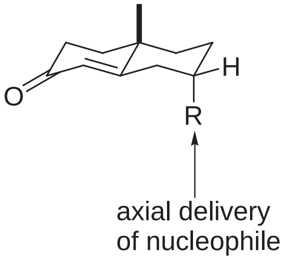


Corey *J. Am Chem. Soc*. **1971**, *93*, 7318.

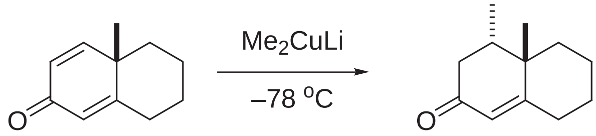
- but

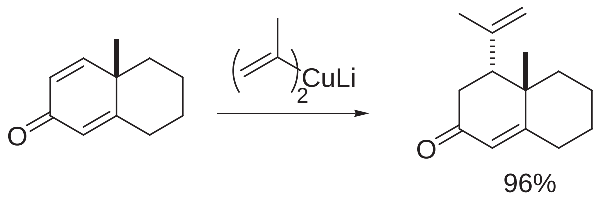


R = Me	93:7
Et	98:2
^{i}Pr	100:0
^{t}Bu	100:0

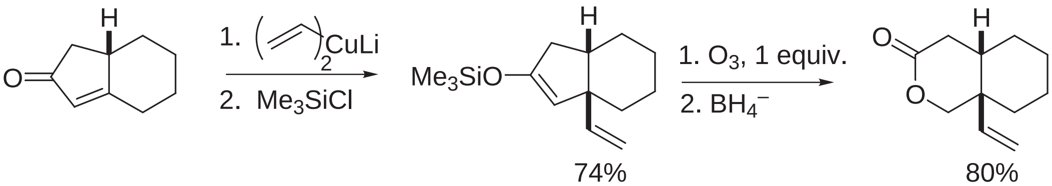


axial delivery of nucleophile



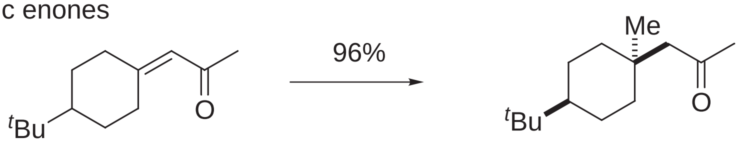


96%

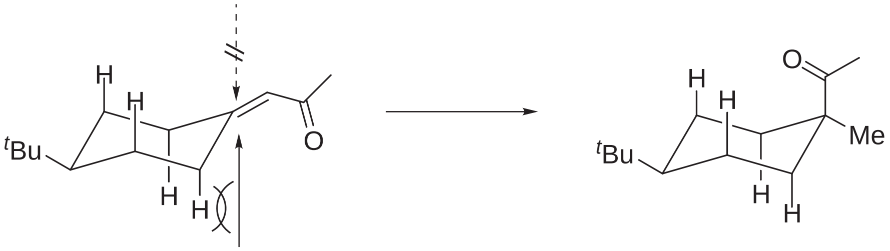


Clark *Tetrahedron Lett*. **1974**, 1713. [for vernolepin]

H. Exocyclic enones



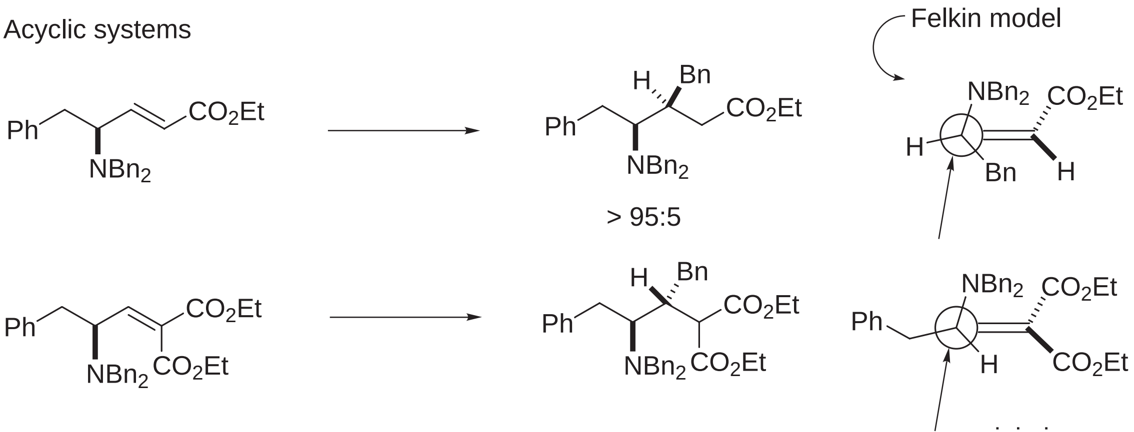
steric 1,3-diaxial interaction



torsional strain
eclipsing 1,2-interaction

Cuprate behaves as a large reagent
preferring equatorial attack

i) Acyclic systems



minimizes
A 1,3-strain

XIII. Synthetic Analysis and Design

Design:

Corey *The Logic of Chemical Synthesis*, Wiley: New York, 1989.
Warren *Organic Synthesis: The Disconnection Approach*, Wiley: New York, 1982.
Fuhrhop, Penzlin *Organic Synthesis: Concepts, Methods, Starting Materials,* VCH: Weinheim, 1994.

Total Synthesis:

Nicolaou, Sorensen *Classics in Total Synthesis*, VCH: Weinheim, 1996.
Hanessian *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon: Oxford, 1983.
Lindberg *Strategies and Tactics in Organic Synthesis*, Vol. 1-3; Academic: San Diego.
ApSimon *The Total Synthesis of Natural Products*, Vol. 1-9; Wiley: New York.
Turner *The Design of Organic Synthesis*, Elsevier: Amsterdam, 1976.
Fleming *Selected Organic Syntheses*, Wiley: New York, 1973.
Bindra *Creativity in Organic Synthesis*, Academic: New York, 1975.
Bindra *Art in Organic Synthesis*, Wiley: New York, 1988.
Lednicer, Mitscher, Georg *The Organic Chemistry of Drug Synthesis*, Vol. 1-4; Wiley: New York.
Nakanishi *Natural Products Chemistry*, Vol. 1-3; Academic: New York.
Koskinen *Asymmetric Synthesis of Natural Products*, Wiley: New York, 1993.
Danishefsky and Danishefsky *Progress in Total Synthesis,* Meredith: New York, 1971.

Key Reviews:

Corey *Science* **1969**, *166*, 178; **1985**, *228*, 408.
Chem. Soc. Rev. **1988,** *17*, 111.
*Pure. App. Chem***.** **1967,** *14*, 19; **1990,** *62*, 1209.
Angew. Chem., Int. Ed. Eng. **1991**, *30*, 455. (Nobel Prize Lecture)

E. J. Corey received the 1990 Nobel Prize in Chemistry for his development of the theory and methodology of organic synthesis. His development and systemization of retrosynthetic analysis transformed organic synthesis from inspired recognition of a route into a precise and logical science. As the modern techniques of structure determination emerged (NMR, IR, X-ray), Corey applied his retrosynthetic analysis to some of the most challenging syntheses of the time. The application of computer analysis with LHASA (Logic and Heuristics Applied to Synthetic Analysis), the development of practical synthetic methodology for individual transformations based on clear mechanistic rationales, and the more than 100 natural product total syntheses that followed transformed modern organic synthesis.

Corey, Cheng *The Logic of Chemical Synthesis*, Wiley: New York, 1989.
Corey, Wipke *Science* **1969**, *166*, 178-192.

Protecting Groups:

Greene, Wuts *Protecting Groups in Organic Synthesis*, 3rd Ed., Wiley: New York, 1999.
Note: The material in this book was first assembled in conjunction with the LHASA project (Corey) and composed the Ph.D. dissertation for T. W. Greene.

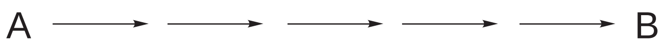
Computer Assisted Analysis:

Corey, Wipke (LHASA: Logic and Heuristics Applied to Synthetic Analysis), *Science* **1969**, *166*, 178.
Corey, Long *J. Org. Chem.* **1978**, *43*, 2208.
Jorgensen (CAMEO: Computer Assisted Mechanistic Evaluation of Organic Reactions):
Pure App. Chem. **1990**, *62*, 1921.
Hendrickson *J. Chem. Inf. Comput. Sci.* **1992**, *32*, 209.
Acc. Chem. Res. **1986**, *19*, 274.

A. Classifications

1. Linear Synthesis

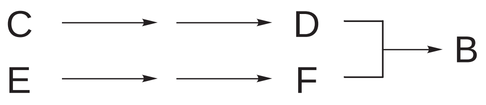
- The target compound is made through a series of linear transformations.



5 steps	overall yield
90%/step	59%
70%/step	17%

2. Convergent Synthesis

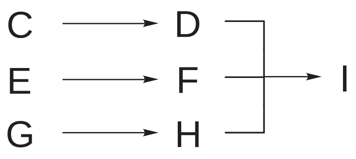
- Individually prepared compounds are convergently brought together to make the target compound.



5 steps	overall yield
90%/step	73%
70%/step	34%

Advantages of a convergent synthesis
- shorter
- simpler to execute
- higher overall yields
- better material balance and supply

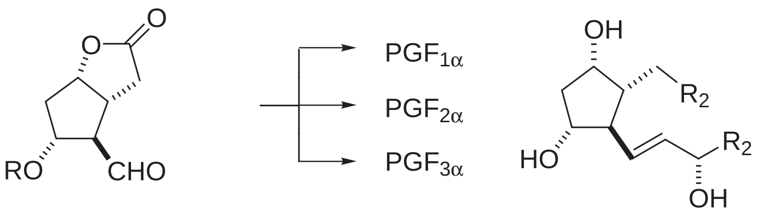
- Triply Convergent Synthesis
  - three major components are brought together in a single step to make the target compound.



3. Divergent Synthesis

- For a class of compounds, it is advantageous to prepare a common intermediate and use this common intermediate to prepare all members of the class of agents.

- Examples: prostaglandins

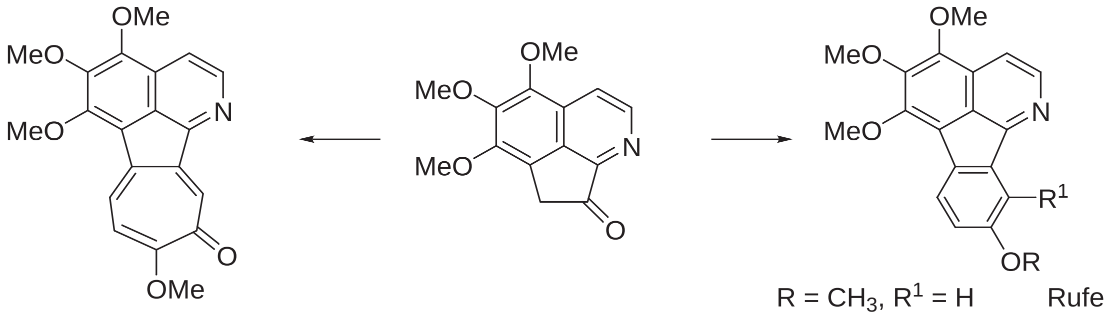


Variations lie only
in the side chains

- Rather than use a linear synthesis for all agents, a divergent synthesis allows the use of a common intermediate to prepare structurally related products.
- The divergent synthesis is a very good strategy if structure–activity studies are the ultimate goal.

Note: Though widely used, the discussion of this strategy was first formally presented in the literature along with a disclosure of a strategy for divergent aromatic annulation in conjunction with the total synthesis of a series of azafluoranthene alkaloids. Today, the divergent introduction of diversity is the basis of most combinatorial chemistry methods.

Boger *J. Org. Chem.* **1984**, *49*, 4050; see also *J. Org. Chem.* **1984**, *49*, 4033 and 4045.



Imerubrine

$R = CH_3$, $R^1 = H$ Rufescine
$R = H$, $R^1 = H$ Norrafescine
$R = CH_3$, $R^1 = OCH_3$ Imeluteine

Boger *J. Am. Chem. Soc.* **1995,** *117*, 12452.

Boger *J. Org. Chem.* **1984,** *49*, 4050.

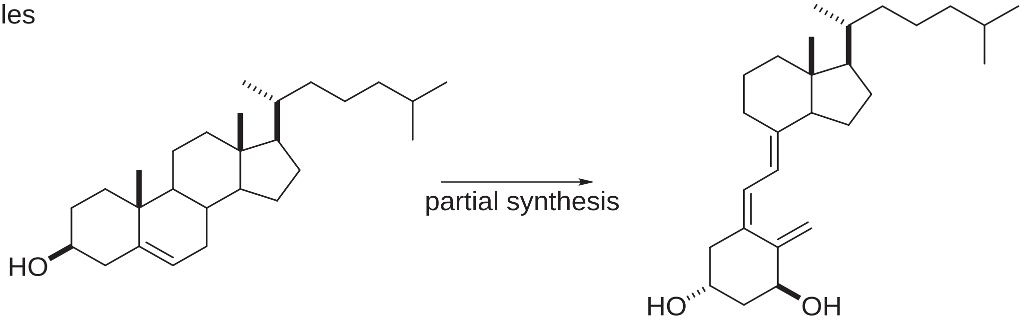
4. Total Synthesis

- Start with readily available materials and build up to the target molecule from simple, common materials.

5. Partial Synthesis

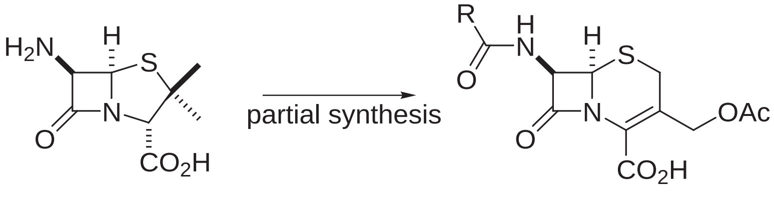
- This is technically not a total synthesis.
- Start with a naturally occurring compound or an advanced intermediate and independently convert that to the target molecule.

- Examples



Previtamin D_3

- For commercialization, it would be hard to match the synthesis starting with cholesterol.



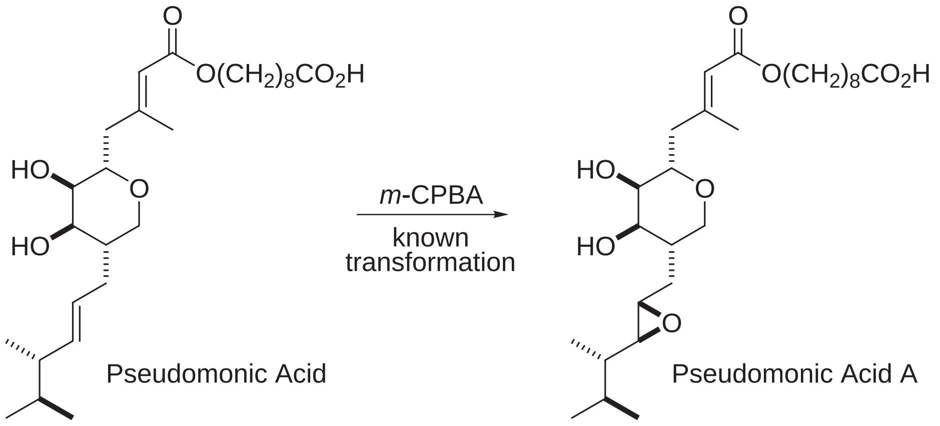
Penicillins, available by fermentation at Lilly, as an inexpensive bulk chemical

Cephalosporins - not as accessible through fermentation

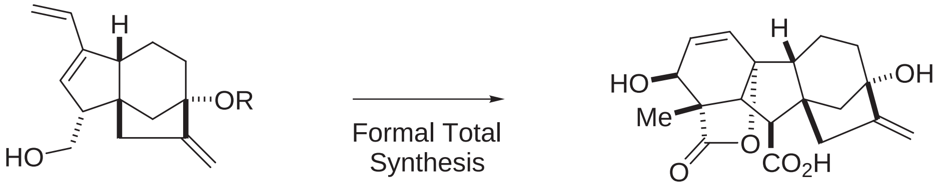
Eduard Buchner, who worked in the laboratories of both E. Erlenmeyer and A. von Baeyer, received the 1907 Nobel Prize in Chemistry for his biochemical research and discovery of cell-free fermentation. Not only did this mark the beginning of the modern era of biochemistry but his greatest legacy might be the development of today's fermentation industry which provides us with not only foods and beverages, but also antibiotics and other important biological products.

Anne S. Miller, the first person to be saved by penicillin in the US (1942) died on May 27, 1999 at the age of 90. Hospitalized, sometimes delirious, with a temperature that spiked at 107 °F, and having not responded to treatment with sulfa drugs, blood transfusions, or surgery, a dose of the experimental drug penicillin provided a quick cure and recovery.

6. Formal Total Synthesis vs. Total Synthesis



Rogers *Tetrahedron Lett.* **1980,** *21*, 881.
Kozikowski *J. Am. Chem. Soc.* **1980**, *102*, 6577.



intermediate

Gibberellic acid

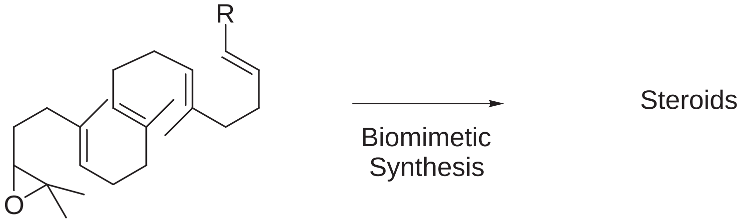
Independent synthesis of this precursor would constitute a formal total synthesis of gibberellic acid since the conversions have been previously accomplished. In this case, the key intermediate is so far from the final target that most would not "claim" such an accomplishment unless the final conversions were also developed within their own laboratories.

7. Biomimetic (Total) Synthesis

- Presumably, nature will not be using a process that is intrinsically difficult or impossible. It is believed that one can effectively mimic the conditions provided by nature, and conduct the same reaction in a flask.

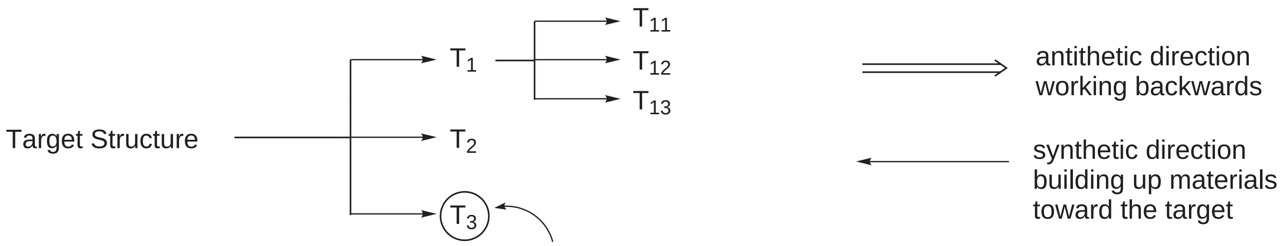
- Two important considerations
  1 - The reaction must be capable of occurring
  2 - The biogenetic process is under a great deal of control (enzymatic) and a similar level of contr in lab may be difficult, but necessary

- Classic example : Steroid synthesis
  Extensively studied and many good chemists failed before the experimental parameters were sufficiently defined to mimic the cation–olefin cyclization.



B. Retrosynthetic Analysis

- Work backwards from the target compound to generate a set of intermediates which can be made from available starting materials.



These less complicated building blocks in organic synthesis were called synthons in the early years. Now they are referred to as retrons.

Objectives:

1. Generate a large number of potential approaches in order to obtain an optimal route.
2. Strive to generate simpler, less complex intermediates which can be obtained from readily available materials.
3. All steps are subject to reevaluation - this allows for design of a better or optimized synthesis.

Steps in Design and Execution of a Synthesis

1. Selection of a problem
2. Selection of goals to be achieved through synthesis
3. Simplification
4. Generation of synthetic pathways
5. Evaluation of synthetic pathways --> assignment of merit
6. Selection of specific reactions and reagents for each step
7. Selection of specific reaction conditions and design of experiments
8. Execution and analysis of results

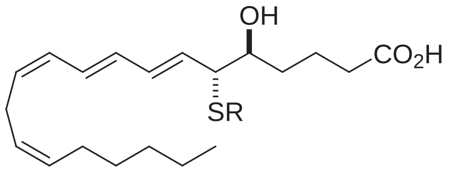
   Because of the amount of time and effort involved in the execution, it is important to be meticulous in evaluating the potential synthetic pathways.

more time is or should be devoted to steps 1 and 2 than most may realize

steps 3 and 4 constitute retrosynthetic analysis

1. Selection of a problem
   - One of the most important considerations.
   - Should be the first consideration, independent of all others. This assures that it is a problem that you want to address.
   - Recognize the time and effort involved in the actual conduct of the synthesis.
   - This will depend on the setting, circumstances and interests of the individual.

2. Selection of goals



SRS-A (Slow Reacting Substance of Anaphylaxis)

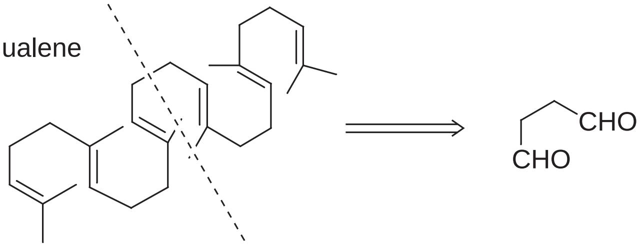
a. Structure determination of SRS-A: the initial intent. The R group on the thiol was not known, so the first synthesis was designed to facilitate the introduction of different R groups permitting a comparison with the endogenous product to confirm the structure.
b. Once the structure was determined, objectives included providing sufficient material for biological testing.
c. Determination of absolute configuration - the chiral centers were unambiguously established through synthesis.
d. Development of a route amenable to analogue preparation: want to inhibit the action of SRS-A (an antagonist development).
e. Biomimetic synthesis (follows the biosynthetic generation of materials) - might constitute a simplification.

f. Development of commercially viable processes.
g. Demonstration of improvements in current methodology.
h. Novel, interesting structures.
i. Common intermediate for a class of structures (divergent synthesis).
j. Mechanism of action of a class of compounds - devise partial structures of the parent compound to define the mechanism of action.
k. Chemistry of a class of compounds.
l. Properties of a class of compounds.

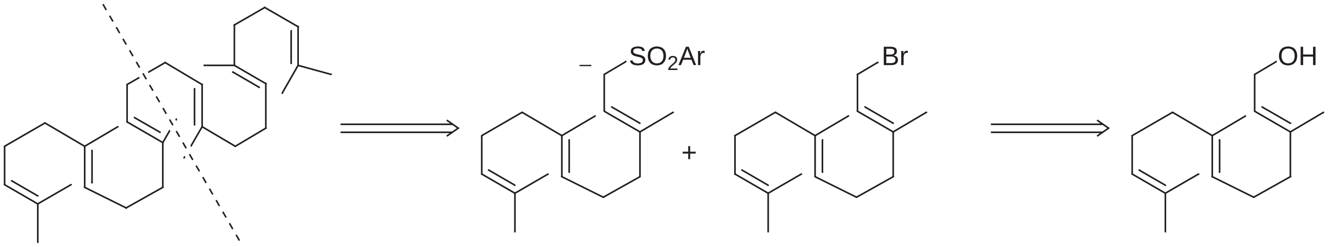
> The specific goals are established prior to the generation of the retrosynthetic pathway. The goals will play an important role in the assignment of relative merit of each potential pathway in the retrosynthetic analysis.

3. Simplification and Background Chemistry
   a. Recognition of symmetry elements present in a structure.

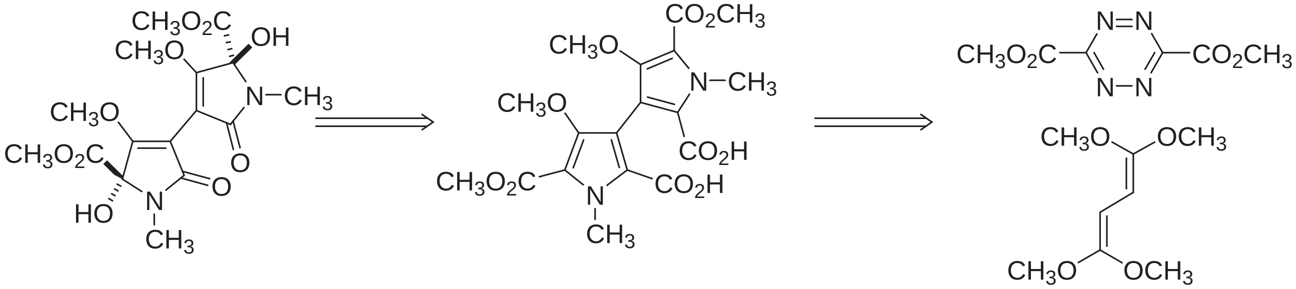
i.e, Squalene



- two identical halves
- build out from a central core by conducting each of the steps twice and simultaneously
- Johnson *J. Am. Chem. Soc.* **1970**, *92*, 741.



- combines two halves prepared from a common intermediate at the end of the synthesis.
- Grieco *J. Org. Chem.* **1974***, 39,* 2135.

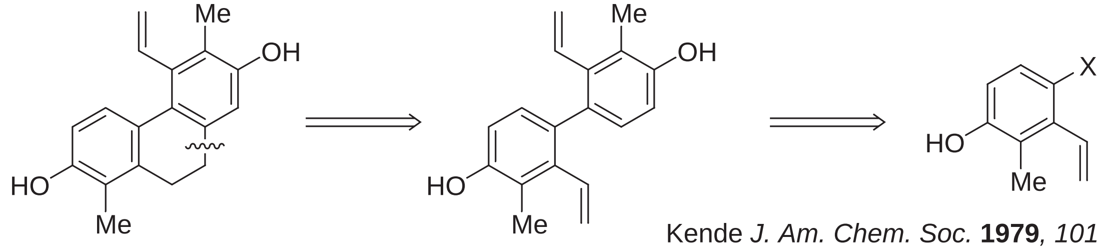


Isochrysohermidin

Boger *J. Am. Chem. Soc.* **1993**, *115*, 11418.

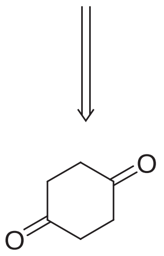
- The recognition of symmetry elements is not always so obvious by initial examination of the agent.

e.g., Juncusol



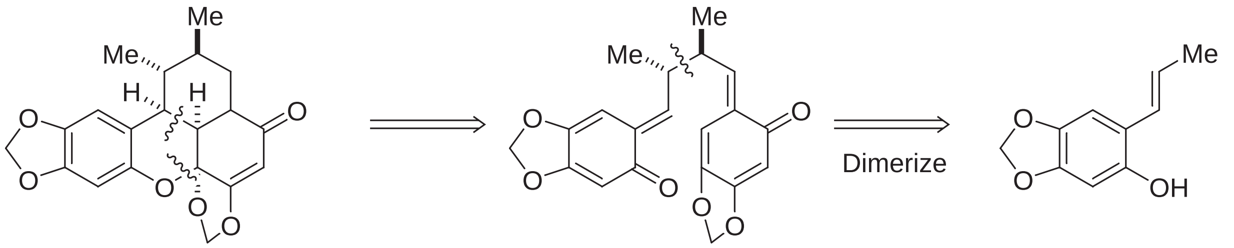
Kende *J. Am. Chem. Soc.* **1979**, *101*, 1857.

now symmetrical - simplification
of the synthetic problem



or start with the central ring and build out in a similar symmetrical fashion
Boger *J. Org. Chem.* **1984**, *49*, 4045.

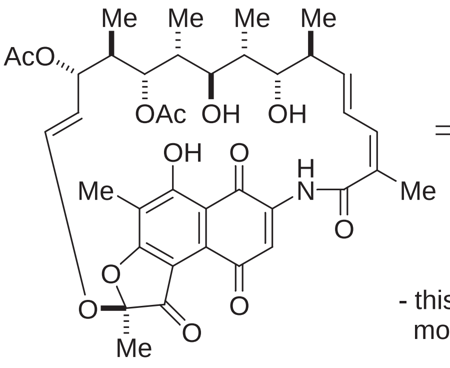
e.g., Carpanone

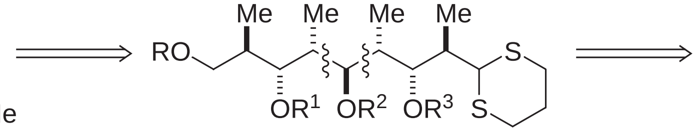


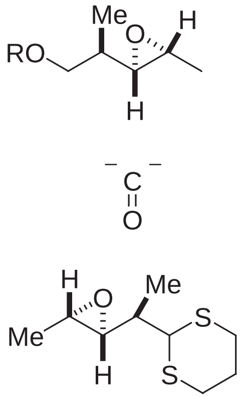
Chapman *J. Am. Chem. Soc.* **1971**, *93*, 6696.

- biomimetic synthesis of this agent allows for simplification.
- this is a very good example where the symmetry elements are not obvious by looking at the agent.

e.g., Rifamycin



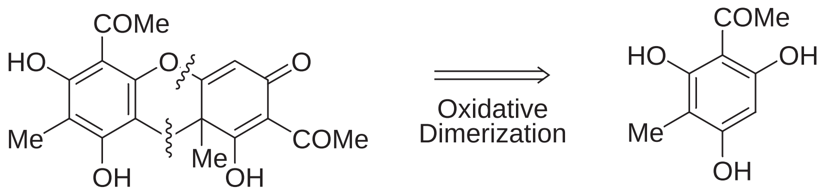




- this agent does not contain symmetry in the entire molecule but a subunit is symmetrical.

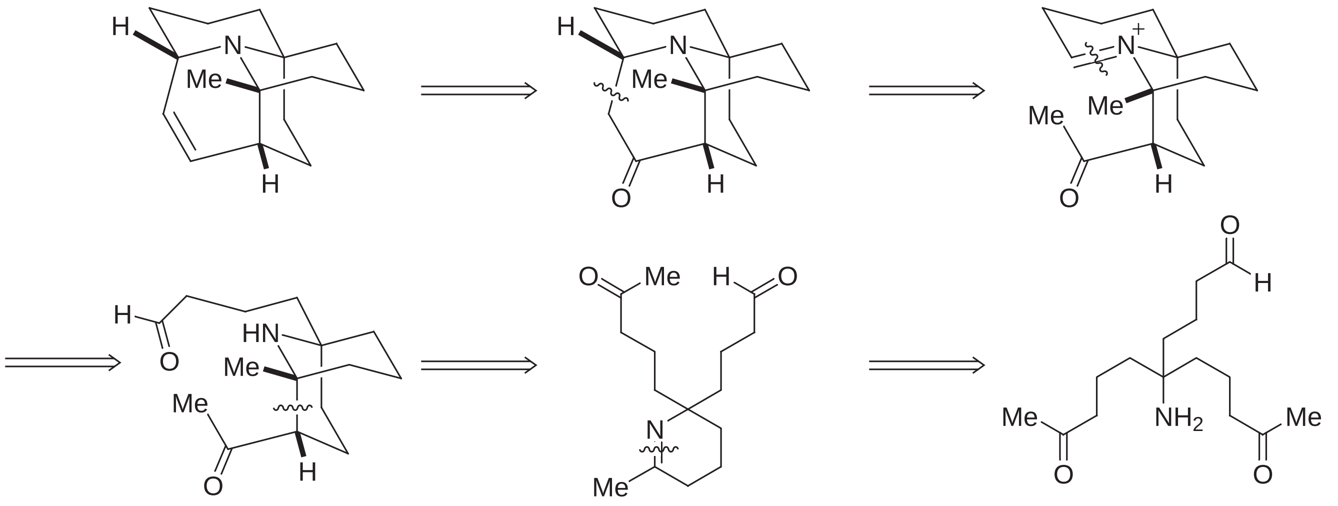
Corey *Tetrahedron Lett.* **1979**, 335.

e.g., Usnic Acid



Barton *J. Chem. Soc.* **1956**, 530.

e.g., Porantherine

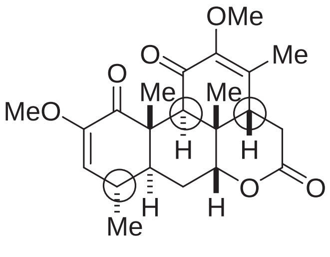


Corey *J. Am. Chem. Soc.* **1974**, *96*, 6516.

- the symmetry elements are tucked more deeply into the structure

b. Background Chemistry
- Information available in the literature will provide very important insights required to effectively design a synthesis.

e.g., Quassin



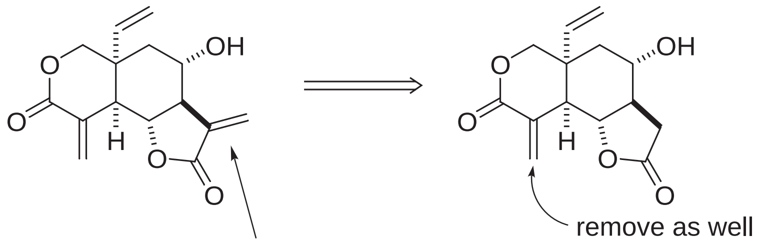
Grieco *J. Am. Chem. Soc.* **1980**, *102*, 7586.

- 7 stereocenters but 3 are epimerizable centers and the natural product possesses the most stable configuration, so a synthesis without stereocontrol of these 3 centers can be used (epimerize later). Need only worry about control of 4 of the 7 stereocenters.

c. Recognize and Remove Reactive Functionality

- Another key to simplification derived from background chemistry

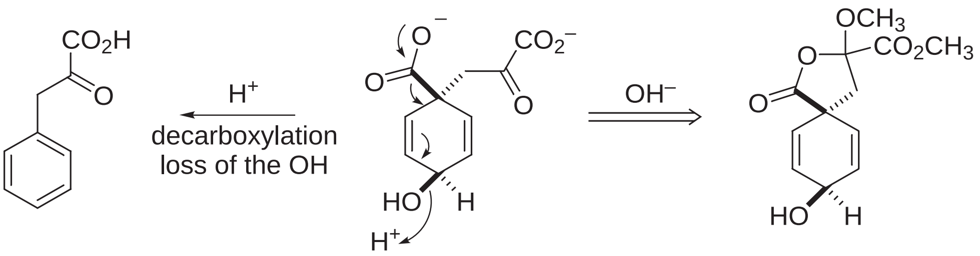
e.g., Vernolepin



- α-Methylene lactone in a *trans* fused 5-membered ring
  This is extraordinarily reactive to nucleophiles (Michael).
  It will not stand up to many synthetic steps/reagents.
- the final step should be introduction of the reactive group.

Danishefsky *J. Am. Chem. Soc.* **1976**, *98*, 3028.
Grieco *J. Am. Chem. Soc.* **1976**, *98*, 1612.
Danishefsky *J. Am. Chem. Soc.* **1977**, *99*, 6066.

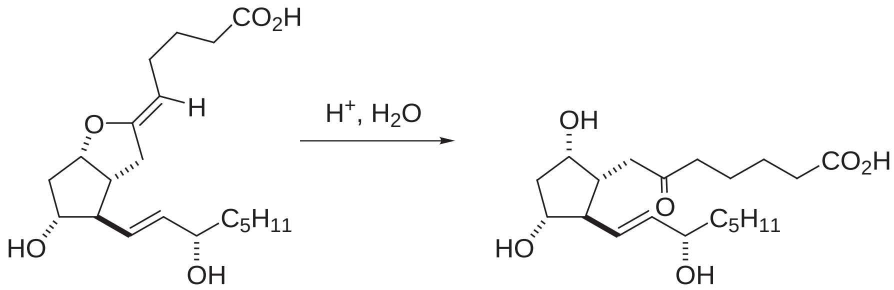
e.g., Precursor to aromatic amino acids



- acid sensitive (derived from background chemistry).
- a successful approach must involve generation under basic conditions.

Danishefsky *J. Am. Chem. Soc.* **1977**, *99*, 7740.

e.g., PGI_2 (prostacyclin)



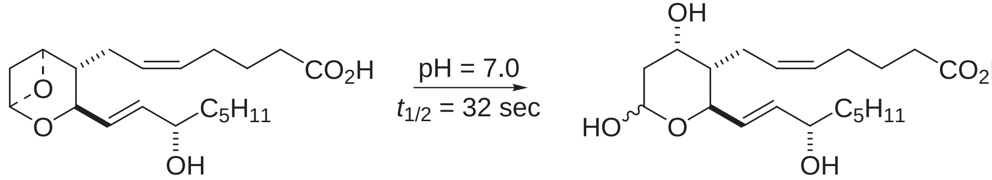
- enol ether sensitive to acid-catalyzed hydrolysis.

Corey *J. Am. Chem. Soc.* **1977**, *99*, 2006.

U. von Euler, B. Katz, and Julius Axelrod received the 1970 Nobel Prize in Medicine for the discovery of hormonal transmitters in the nerve terminals and the mechanism for their storage, release, and inactivation.

S. K. Bergstrom, Bengt I. Samuelsson, and J. R. Vane shared the 1982 Nobel Prize in Medicine for their discovery of the prostaglandins and related biologically active substances.

e.g., Thromboxane A_2 (TXA_2)

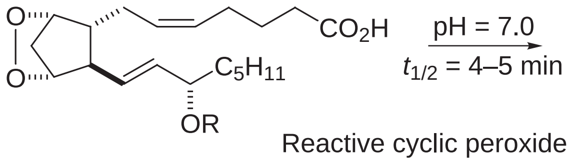


The strained acetal should be introduced late in the synthesis

TXB_2

e.g., PGH_2 (R = H)
PGG_2 (R = OH)

Still *J. Am. Chem. Soc.* **1985**, *107*, 6372.

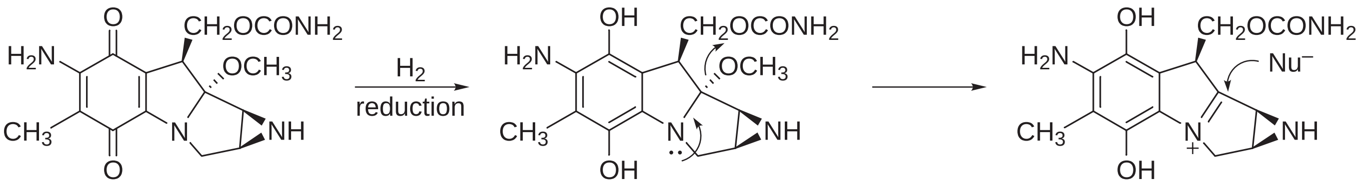


Reduction / Acid-catalyzed Rearrangement

Reactive cyclic peroxide is sensitive to nucleophilic attack - introduce late in the synthesis

Porter *J. Am. Chem. Soc.* **1980**, *102*, 1183.
Salomon *J. Am. Chem. Soc.* **1979**, *101*, 4290.
Porter *J. Am. Chem. Soc.* **1979**, *101,* 4319.

e.g., Mitomycin C - stable as the quinone



note vinylogous amide

hydroquinone - basic, nucleophilic
free amine - intermediate less stable

steer clear of such synthetic intermediates

There are only two total syntheses of mitomycin C to date

Kishi *J. Am. Chem. Soc.* **1977**, *99*, 8115.
Fukuyama *J. Am. Chem. Soc.* **1989**, *111*, 8303.

Absolute configuration established in *J. Am. Chem. Soc.* **1967**, *89*, 2905 by a single crystal X-ray structure (INCORRECT).

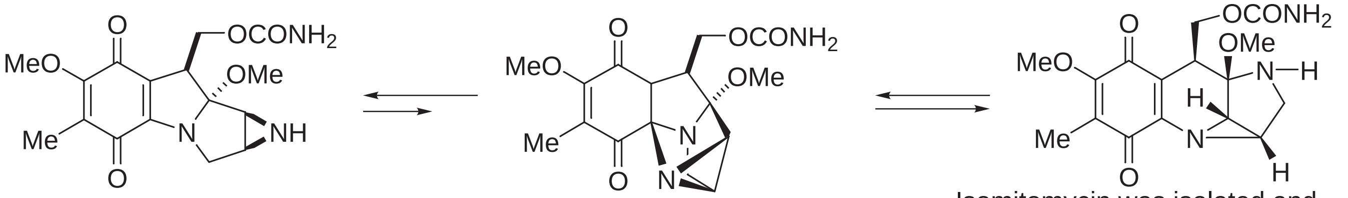
But in the early 1980's, additional X-ray structures on related agents gave the opposite and correct absolute configuration. Take home message: Evaluate the quality of the background chemistry and assess the level of confidence and committment you want to place on it. The earlier X-ray was not on a heavy atom derivative and preceded the advances in direct methods we take for granted today.

Hirayama *J. Am. Chem. Soc.* **1983**, *105*, 7199.

A number of Nobel Prizes have chronicled the achievements of X-ray crystallography including the contributions of:

J. Kendrew and M. Perutz (1962, heavy atoms and structure of hemoglobin).
D Hodgkin (1964, X-ray structure determinations including vitamin B-12, penicillin and insulin).
O. Hassel (1969, chair conformation of cyclohexane reported in 1930).
W. N. Lipscomb (1976, borane structures and chemical bonding, structure of carboxypeptidase A in 1967).
A. Klug (1982, elucidation of nucleic acid–protein complexes).
H. A. Hauptman and J. Karle (1985, direct methods).
J. Deisenhofer, R. Huber, and H. Michel (1988, structure of photosynthetic reaction center (> 10,000 atoms) and first membrane protein structure determination).

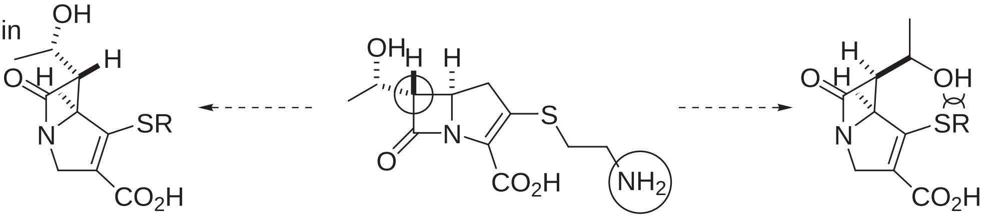
- The background chemistry can provide keys to the design of a synthetic strategy.



Mitomycin Rearrangement

Isomitomycin was isolated and characterized and provided the basis for Fukuyama's total synthesis.

e.g., Thienamycin



trans preferred

cis less favored

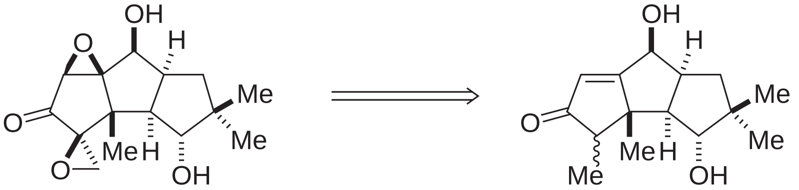
must protect the amine throughout the synthesis.
unusual *trans* H–H relationship - easily epimerizable center and fortunately, *trans* is most stable configuration.

A. Fleming, H. W. Florey, and E. B. Chain received the 1945 Nobel Prize in Medicine for the discovery of penicillin and its curative effects in various infectious diseases.

Grieco *J. Am. Chem. Soc.* **1984**, *106*, 6414.
Georg *J. Am. Chem. Soc.* **1987**, *109*, 1129.

Yet - almost all the early syntheses went to great length to control this relative stereochemistry and it often, unnecessarily, added to their length.

e.g., Coriolin



introduce reactive functionality last

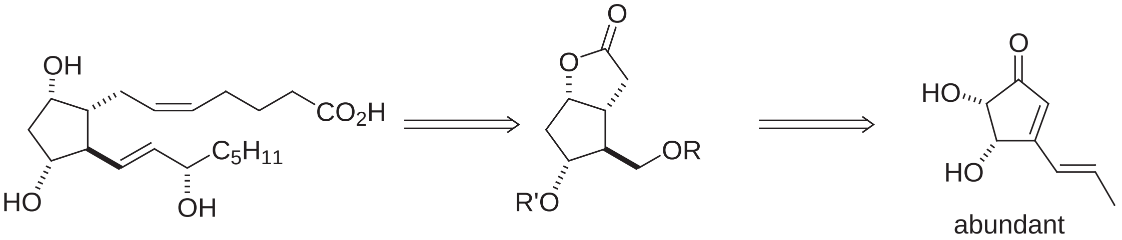
Danishefsky *J. Am. Chem. Soc.* **1981**, *103*, 3460.

4. Generation of Synthetic Pathways (Retrosynthesis) (General strategies employed in working backwards)
Covered in detail in Corey *The Logic of Chemical Synthesis*, Wiley: New York, 1989, pp 1–98.

a. Transform-based strategies
- powerful, simplifying transformation that reduces complexity.
- usually very key reactions in the synthesis that dominate the approach - formation of a key intermediate (i.e., the Diels–Alder transform, the aldol transform).

b. Structure-goal strategies
- oldest approach.
- in working backwards from the target molecule to the various intermediates, an intermediate may actually be located that is already in the literature or commercially available.

e.g., Prostaglandins



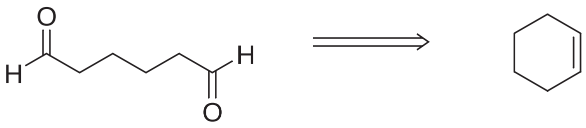
abundant

c. Topological strategies
- strategic bond disconnections (*J. Am. Chem. Soc.* **1975**, *97*, 6116).
- recognize strategic bonds and remove them in the retrosynthetic direction.

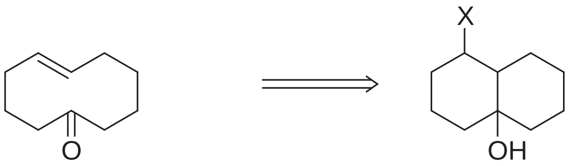
d. Stereochemical strategies
- strategies which remove the stereocenters.
- simplifying the stereochemistry of the product may be related to:
  1. substrate - features of the substrate will permit you to solve the stereochemical problems.
  2. mechanism - reaction mechanism will permit relative or absolute stereocontrol.

e. Functional group strategies
1. Functional group interconversion (FGI)
   - don't gain much but it permits you to get from one point to another.

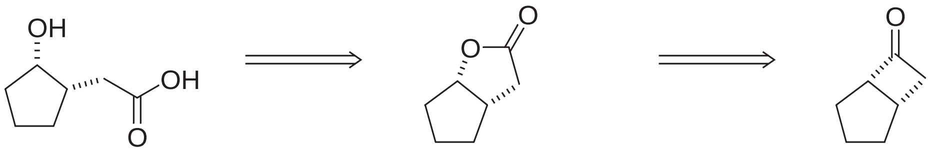
2. Functional group combination (FGC)
   - combine pairs of functional groups.
   - usually a ring forming reaction in the retrosynthetic direction to give you one FG rather than two.



ozonolysis

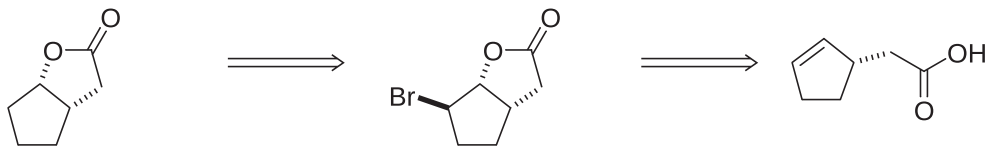


fragmentation

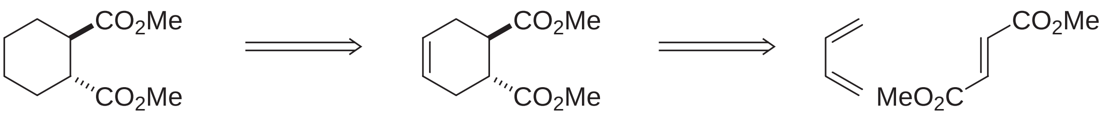


Baeyer–Villiger

3. Functional group addition (FGA)
   - hard to recognize while working in the reverse direction.
   - for example, introduce a double bond which then may key the recognition of a Diels–Alder reaction.

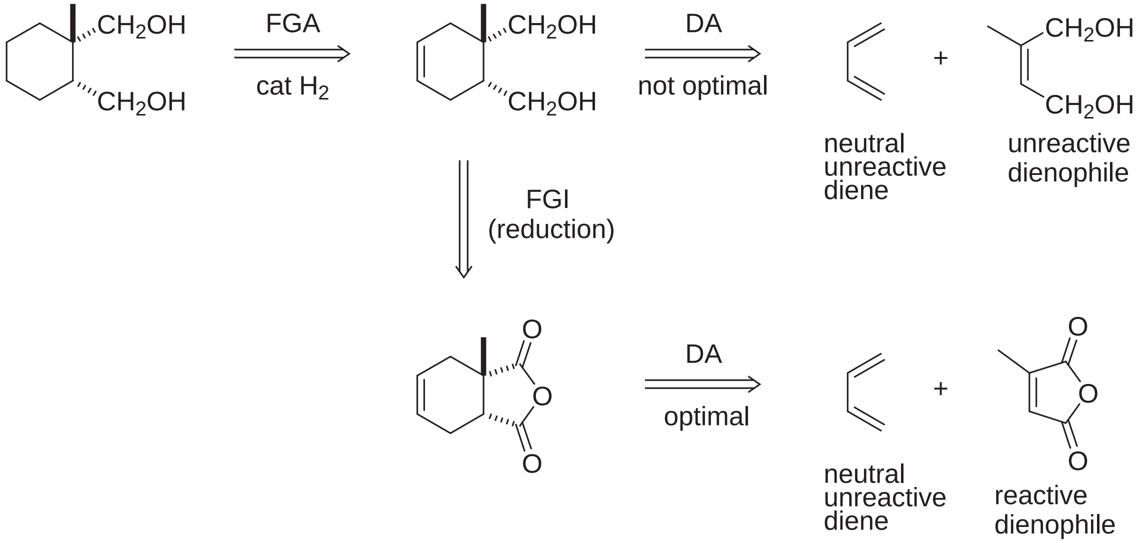


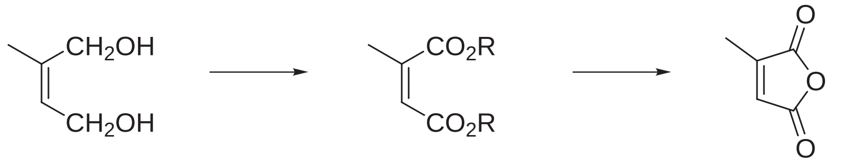
Bromo-lactonization



Diels–Alder

i.e., Diels–Alder reaction



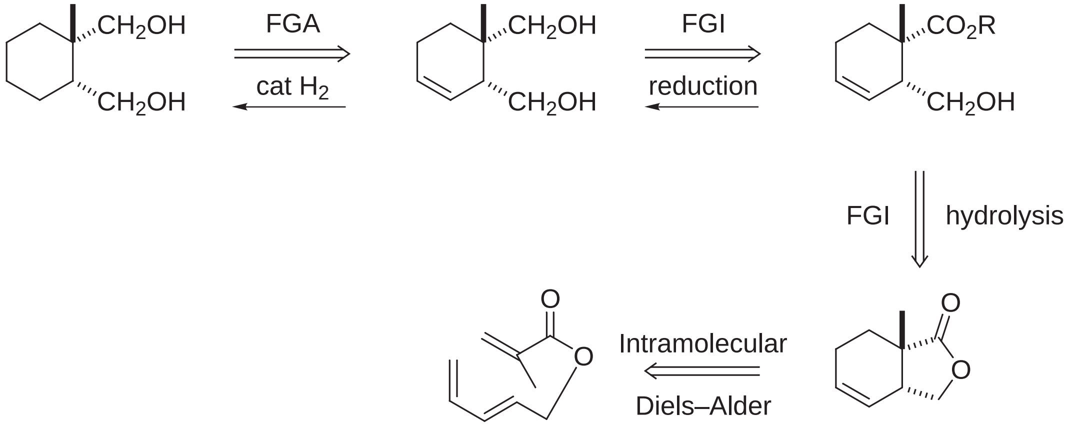


more reactive due to EWG
reevaluation: isomerization
may occur about the C=C.

further enhances reactivity,
assures stereochemistry.

But:

There is an alternative and still better Diels–Alder pathway that most would miss without careful consideration.



5. Evaluation of Pathways and Assignment of Merit
    a. excellent knowledge of organic chemistry
    b. suspect reactions must be recognized - one poor step can ruin the synthesis
    c. control of stereochemistry is clear
    d. want opportunity for alternatives - reactions that look good on paper aren't always successful in lab

6. Selection of Specific Reactions and Reagents
    a. this also requires an excellent knowledge of organic chemistry
    b. check the literature for alternative reagents - it is wiser to change reagents than to change the entire synthesis if problems arise
    c. many reference texts are available

Larock	*Comprehensive Organic Transformations*
Fieser and Fieser	*Reagents for Organic Synthesis* Vol. 1–18
Paquette	*Encyclopedia of Reagents for Organic Synthesis*
	Handbook of Reagents for Organic Synthesis:
Coates, Denmark	*Reagents, Auxiliaries and Catalysts for C–C Bonds*
Burke, Danheiser	*Oxidizing and Reducing Agents*
Reich, Rigby	*Acidic and Basic Reagents*
Pearson, Roush	*Activating Agents and Protecting Groups*
Computer Databases	CLF, Reaccs, Scifinder, Beilstein, Isis

7. Selection of Reaction Conditions
    a. reaction temperature
    b. solvent
    c. knowledge of reaction mechanism
    d. consult current and background literature

8. Execution of the synthesis - most difficult and time consuming element of work
    a. easy: setting up and conducting the reaction
    b. difficult: interpreting the results from the reaction

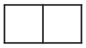
C. Strategic Bond Analysis

- For bridged ring systems Corey *J. Am. Chem. Soc.* **1975**, *97*, 6116.

- Most desirable bond disconnections in the antithetic direction minimize:

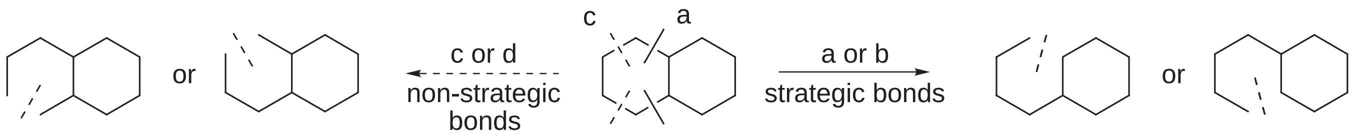
1. appendages
2. appendage chiral centers
3. medium or large size rings
4. bridged rings

Rule 1: Because it is easy to form common size rings, a strategic bond must be in a 4–7 membered primary ring. A primary ring is one which cannot be expressed as an envelope or two or more smaller rings. This is restricted to primary rings because ring forming reactions are strongly affected by the size of the smallest ring containing the newly forming bond.



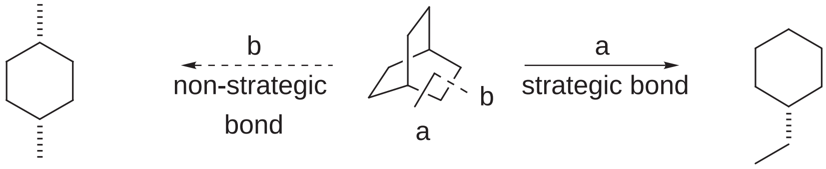
The six membered ring is not primary because it contains two smaller rings.

Rule 2a: A strategic bond must be directly attached to another ring (i.e. exo to another ring). This is because a ring disconnection which produces two functionalized appendages is harder to utilize than one which produces one or no functionalized appendages.

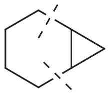


two ring appendages - more complicated

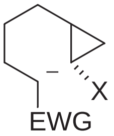
one ring appendage



Rule 2b: A strategic bond may not be exo to a preexisting 3-membered ring.



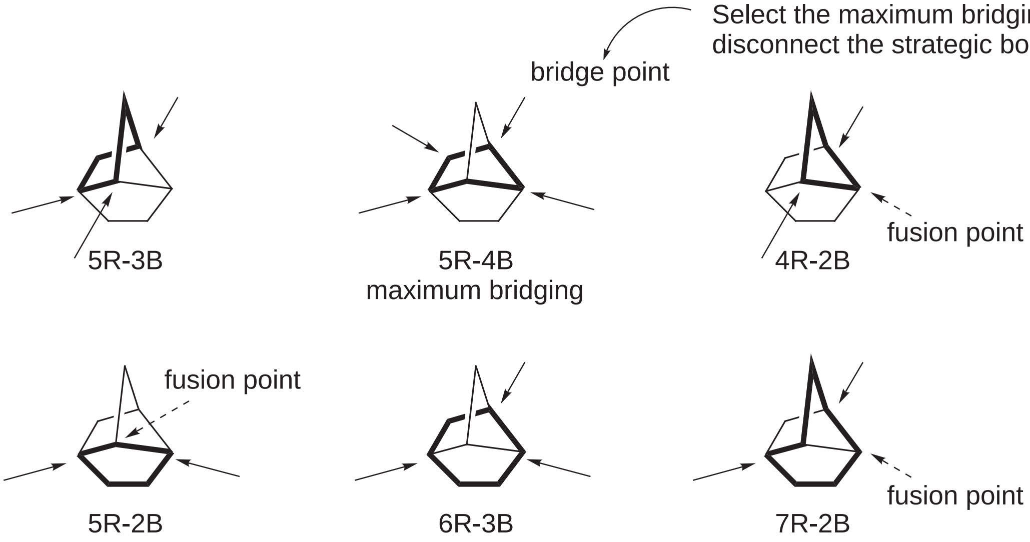
non-strategic even though exo to a ring



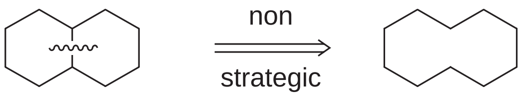
anion displacement reactions don't work well on a three-membered ring

Rule 3: Strategic bonds should be in ring(s) which exhibit the greatest degree of bridging. The maximum bridging ring is selected from the set of synthetically significant rings which is defined as the set of all primary rings plus all secondary rings which are less than 8-membered. The maximum ring is that which is bridged, not fused at the greatest number of sites.

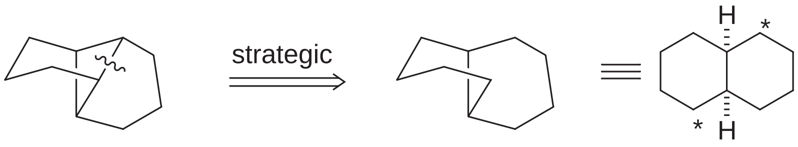
Select the maximum bridging ring and disconnect the strategic bonds within that ring



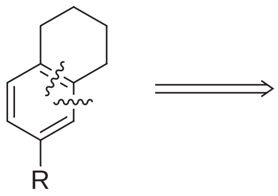
Rule 4: To avoid formation of >7-membered rings during the antithetic bond cleavage, any bond common to a pair of rings whose envelope is >7 is not strategic.



10-membered ring
non-strategic

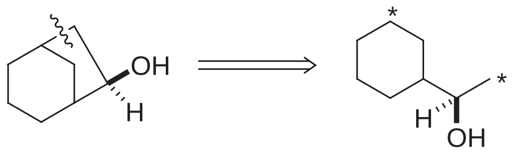


Rule 5: Bonds within aryl rings cannot be strategic.



non-strategic

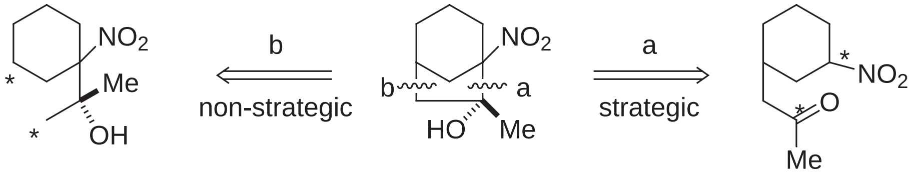
Rule 6a: If a disconnection leaves chiral atoms on the remaining arc then the disconnections cannot be strategic.



non-strategic
increased difficulty

The stereochemistry is much harder to control
on the acyclic precursor than on the cyclic precursor

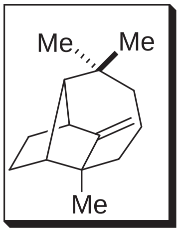
Rule 6b: Chiral atoms may be allowed if they appear directly at the point of attachment.



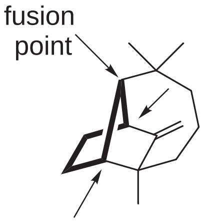
Rule 7: C–X Bonds (X = heteroatom) in rings will be strategic.

C–X bonds are easier to form than C–C

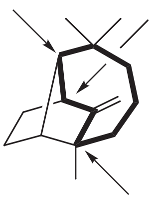
D. Total Synthesis Exemplified with Longifolene



1. Strategic Bond and Retrosynthetic Analysis



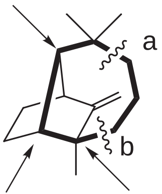
5R, B2



not a fusion point even though it is in a 1,2 relationship

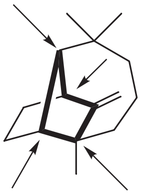
8R, 3B

8 ring - secondary

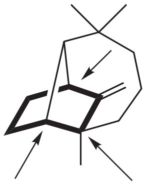


7R, B2

- Ho disconnection (a)
- Kuo disconnection (b)

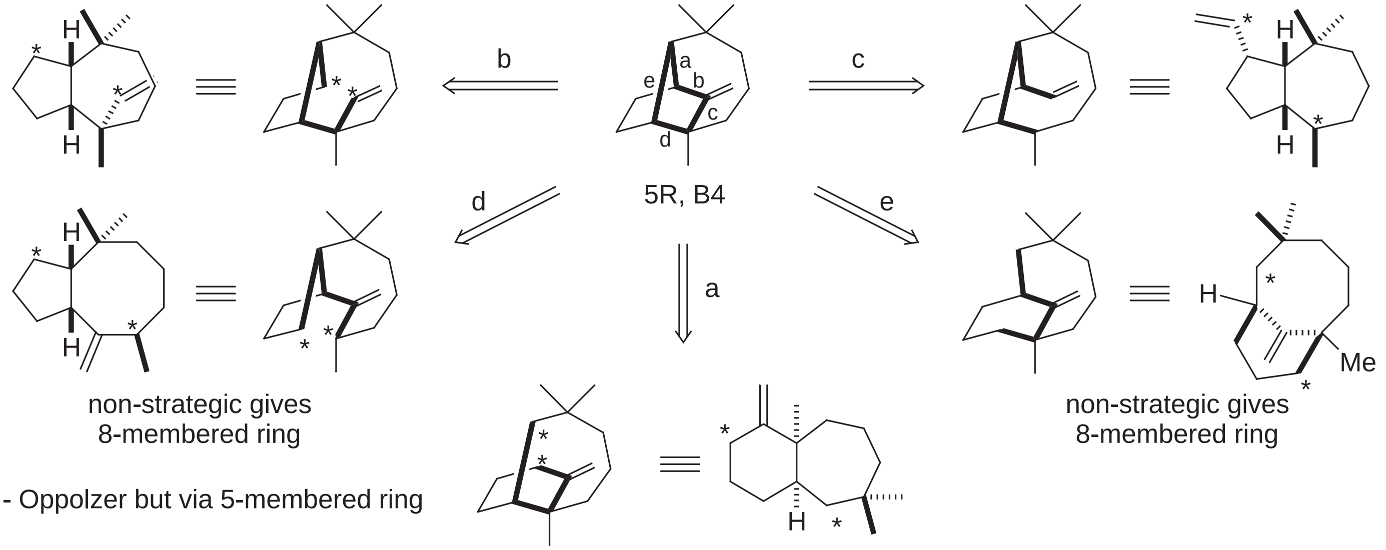


5R, B4



6R, 3B

Fusion vs. bridge points: there must be at least one carbon (not in the ring in question) between the carbon in question and another carbon in the ring for it to be a bridgepoint.



5R, B4

non-strategic gives 8-membered ring

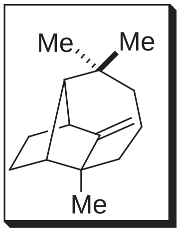
non-strategic gives 8-membered ring

- Oppolzer but via 5-membered ring

much simpler than longifolene!

- Corey and McMurry disconnection
- Schultz disconnection

- Simultaneous or sequential b/d bond disconnection: Brieger, Fallis (Diels–Alder), Johnson (cation–olefin).
- Simultaneous a/e bond disconnection: Schultz (indirect via vinylcyclopropane rearrangement).



2. Corey Synthesis: *J. Am. Chem. Soc.* **1961**, *83*, 1251; **1964**, *86*, 478.

Intramolecular Michael Addition (Santonin–Santonic Acid)
Robinson Annulation
Wittig Reaction
Pinacol Ring Expansion
Dithiane Reduction
Chromatographic Resolution through Diastereomeric Derivatization (Product)

3. McMurry Synthesis: *J. Am. Chem. Soc.* **1972**, *94*, 7132.

Intramolecular Enolate–Epoxide Addition (Alkylation)
Dibromocarbene Addition, Ring Expansion
Ethyl Diazoacetate Ring Expansion
Organocuprate 1,4-Additions
Intramolecular Aldol Reaction, Transannular Reactions
Fragmentation Reaction

4. Brieger Synthesis: (attempted) *J. Am. Chem. Soc.* **1963**, *85*, 3783.

Diels–Alder Reaction
Intramolecular Diels–Alder Reaction
1,5-Hydrogen Migration of Cyclopentadienes

5. Johnson Synthesis: *J. Am. Chem. Soc.* **1975**, *97*, 4777.

Organocuprate 1,4-Addition, Regiospecific Enolate Trap
Cation–Olefin Cyclization

6. Oppolzer Synthesis: *J. Am. Chem. Soc.* **1978**, *100*, 2583.
Helv. Chim. Acta **1984***, 67*, 1154.

Enamine Acylation
Photochemical [2 + 2] Cycloaddition
Retro-Aldol Fragmentation Reaction
Wittig Reaction
Simmons–Smith Cyclopropanation
Hydrogenation of Cyclopropanes
Classical Resolution via Crystallization of Diastereomeric Salts

7. Schultz Synthesis: *J. Org. Chem.* **1985**, *50*, 915.

Birch Reductive Alkylation
Retro Cheletropic Cycloaddition
1,3-Dipolar Cycloaddition
Vinylcyclopropane Rearrangement
Asymmetric Synthesis via Substrate Chiral Auxiliary

8. Fallis Synthesis: *J. Am. Chem. Soc.* **1990**, *112*, 4609.
J. Org. Chem. **1993**, *58*, 2186.

Intramolecular Diels–Alder Reaction
Barton Free Radical Deoxygenation Reaction
Acetate Pyrolysis
Chromatographic Resolution through Diastereomeric Derivatization (Starting Material)

9. Kuo Synthesis: *Can J. Chem.* **1988**, *66*, 1794.

Intramolecular Aldol Addition
Wagner–Meerwein Rearrangement

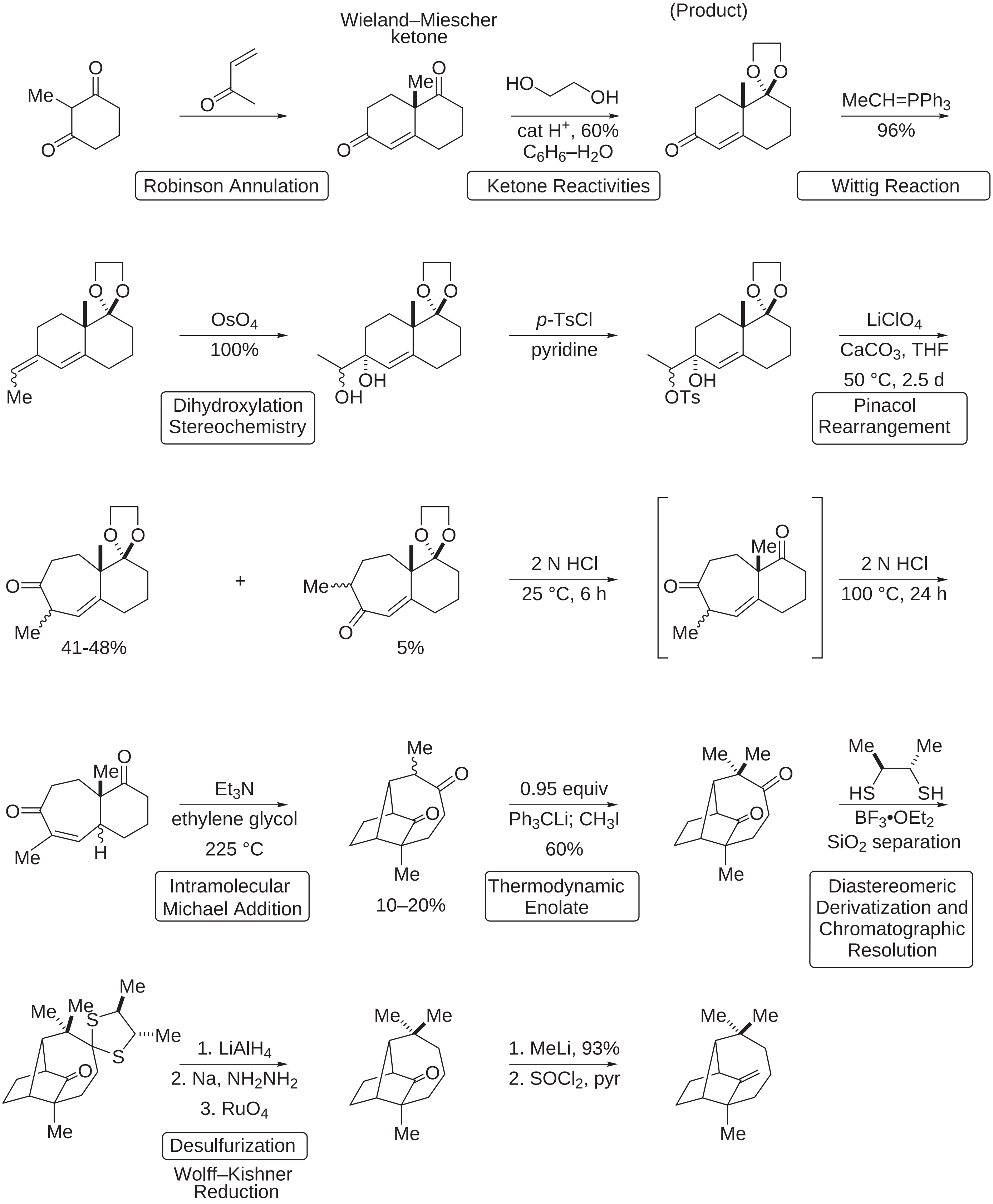
10. Ho Synthesis: *Can J. Chem.* **1992**, *70*, 1375.

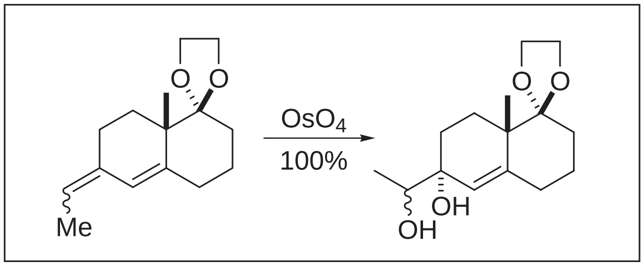
Ethyl Diazoacetate Ring Expansion
Alkylative Esterification

2. Corey Synthesis:

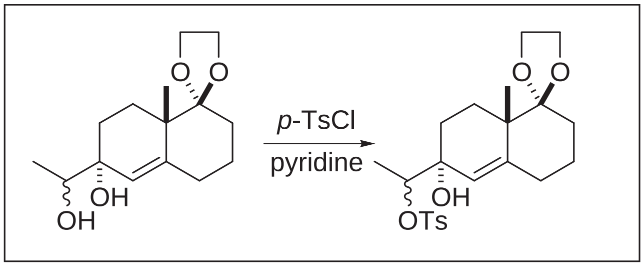
J. Am. Chem. Soc. **1961**, *83*, 1251.
J. Am. Chem. Soc. **1964**, *86*, 478.

Intramolecular Michael Addition
Robinson Annulation
Wittig Reaction
Pinacol Ring Expansion
Dithiane Reduction
Chromatographic Resolution through
Diastereomeric Derivatization
(Product)

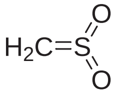




Osmylation
- large reagent reacts preferentially with more accessible double bond and from the least hindered face. Typically, this is from the equatorial direction but one 1,3-diaxial H is removed and axial approach now observed

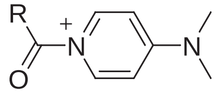


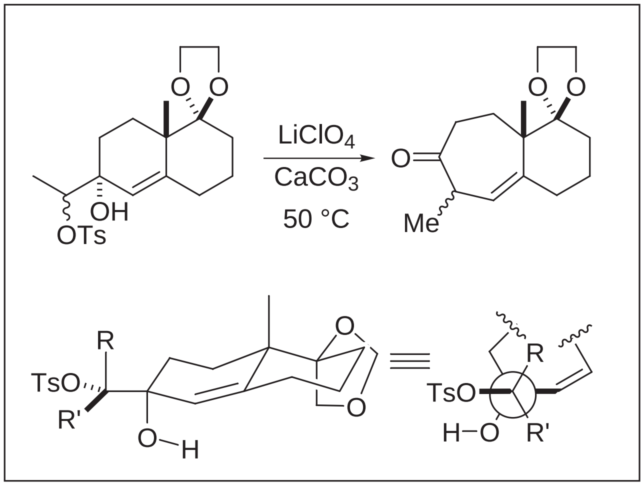
Selective Tosylation
- rates: 1° > 2° > 3°
- 3° alcohols react very slowly
- MsCl and Et_3N generates sulfene which will react with 1°, 2°, 3° OH to give the mesylate



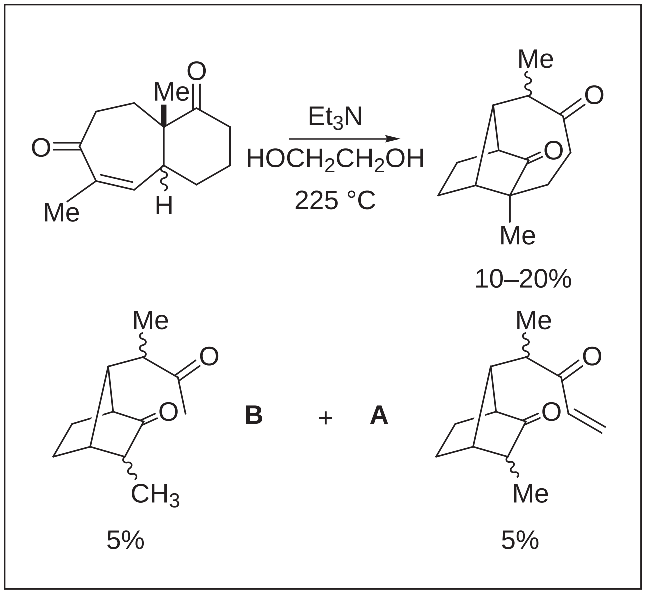
$H_2C{=}SO_2$

- Also note the use of DMAP to acylate 3° alcohols via

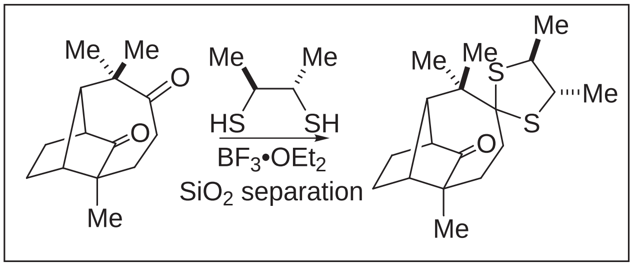




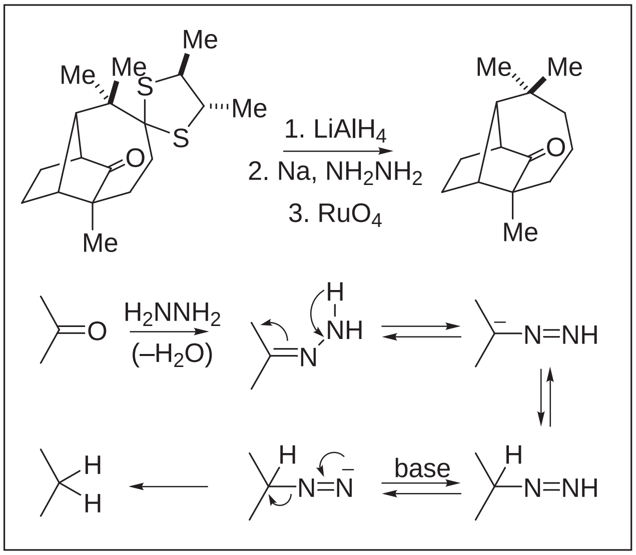
Pinacol Rearrangement
- $LiClO_4$ used as source of free Li^+ ion to accelerate solvolytic loss of TsO group
- migration of unsaturated alkyl group observed preferentially
- *trans* antiperiplanar arrangement



Intramolecular Michael Addition
- only *cis* product undergoes Michael
- side products include the retro-Michael product **A** and the OH^- addition and retro aldol product **B**



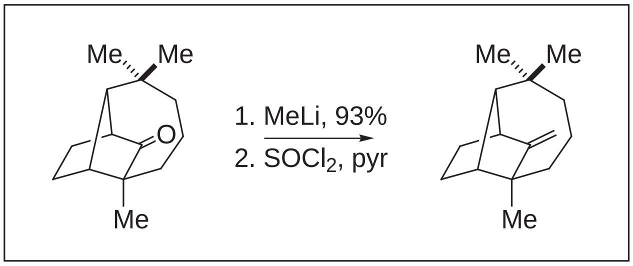
Thio-ketalization (Derivatization)
- other carbonyl much more hindered
- diastereomers arise that are separable by conventional chromatography



Desulfurization
- direct Wolff–Kishner failed
- $LiAlH_4$ protects ketone from reduction
- today: Ra–Ni better for desulfurization and would avoid need to protect ketone
- Wolff–Kishner reduction of dithiane similar to Huang–Minlon protocol of Wolff–Kishner reduction for carbonyl removal (Huang, Minlon *J. Am. Chem. Soc.* **1946**, *68*, 2487; **1949**, *71*, 3301), van Tamelen *J. Am. Chem. Soc.* **1961**, *83*, 4302.

Wolff–Kishner
Wolff *Justus Liebigs Ann. Chem.* **1912**, *394*, 86.

Further improvements
^{t}BuOK, DMSO, 25 °C
Cram *J. Am. Chem. Soc.* **1962**, *84*, 1734.

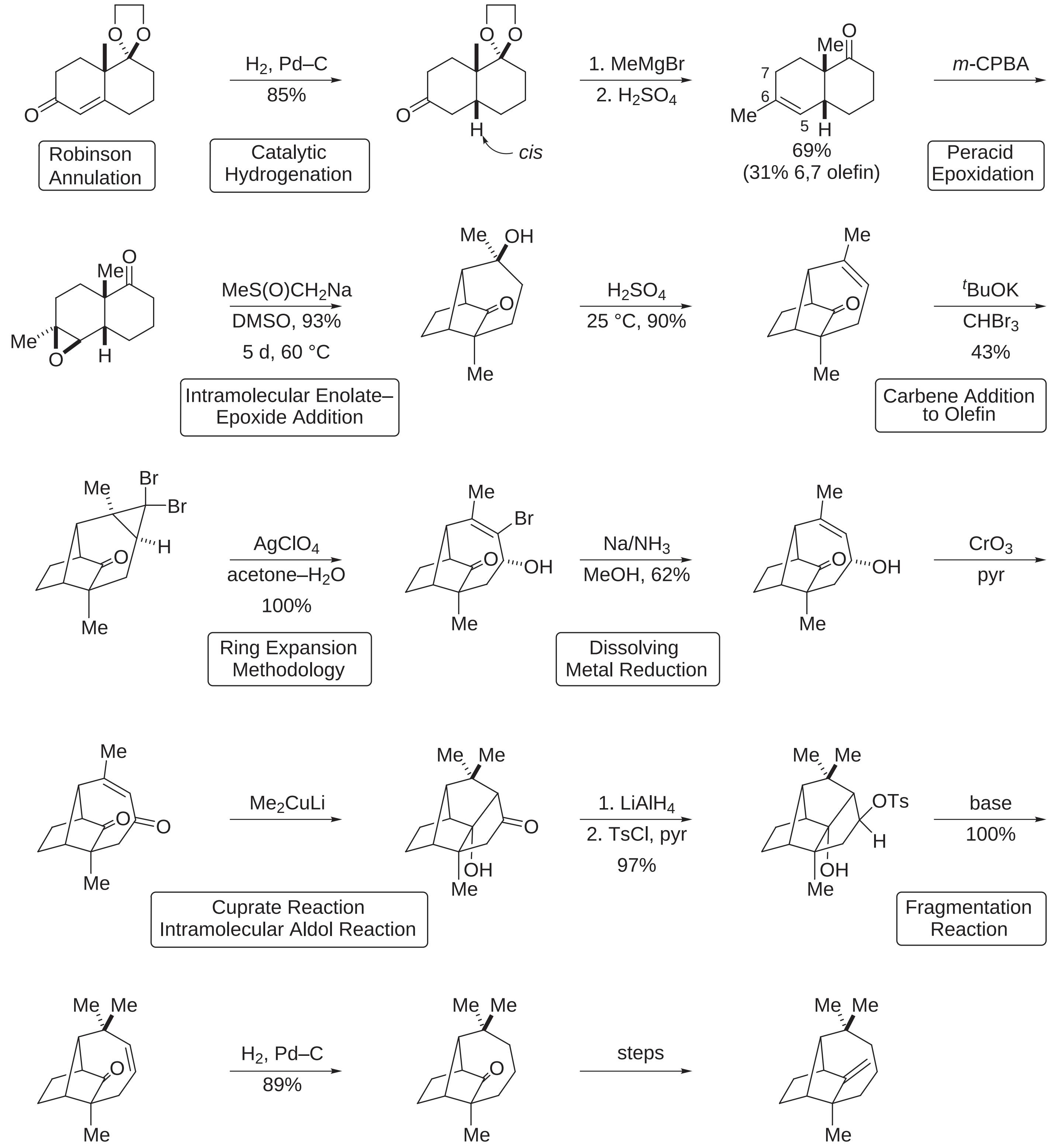


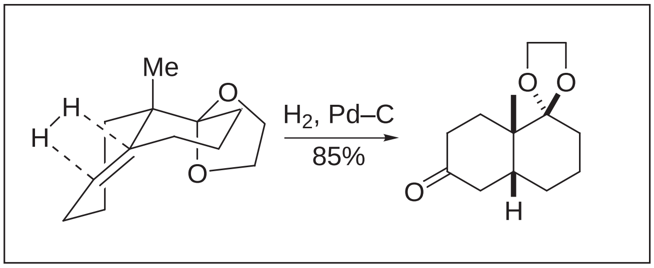
Olefination
- Wittig reaction unsuccessful, ketone too hindered
- two-step procedure adopted

3. McMurry Synthesis:

J. Am. Chem. Soc. **1972**, *94*, 7132.

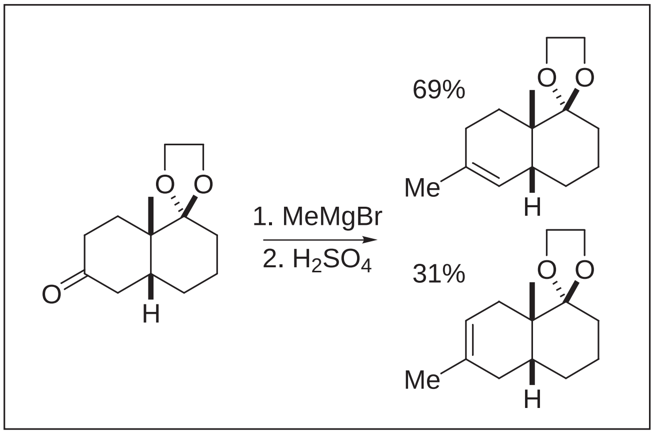
Intramolecular Enolate–Epoxide Addition
Dibromocarbene Addition, Ring Expansion
Ethyl Diazoacetate Ring Expansion
Organocuprate 1,4-Additions
Intramolecular Aldol Reaction
Transannular Reactions
Fragmentation Reaction





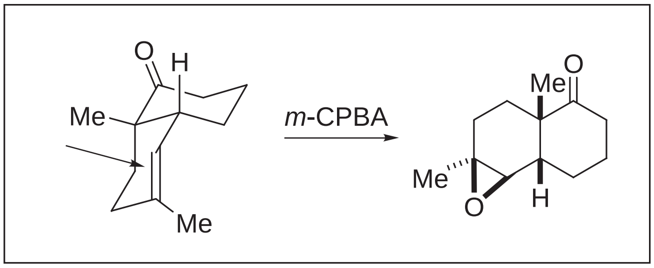
Hydrogenation

- known conditions to give *cis* stereochemistry
- H_2 comes in from less hindered face
- heteroatoms can also direct H_2 to their face



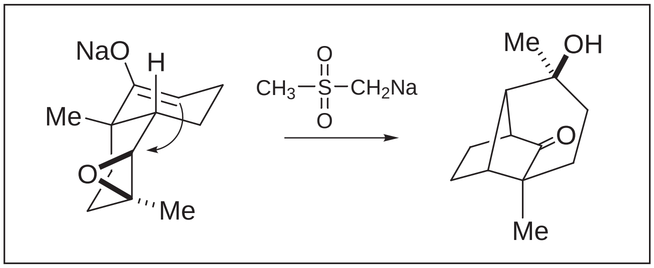
Acid-catalyzed Elimination

- *cis* ring fusion prefers $\Delta^{2,3}$ double bond
- *trans* ring fusion prefers $\Delta^{3,4}$ double bond
- known from steroid chemistry



Epoxidation

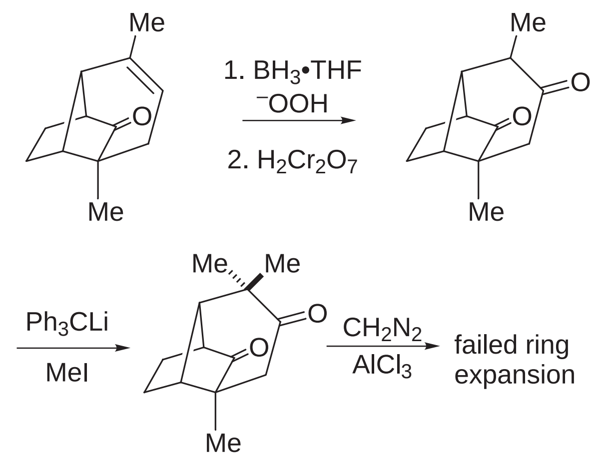
- epoxidation from the least hindered face
- no competitive Baeyer–Villiger at ketone
- trisubstituted olefin more reactive than ketone



Intramolecular Epoxide Addition

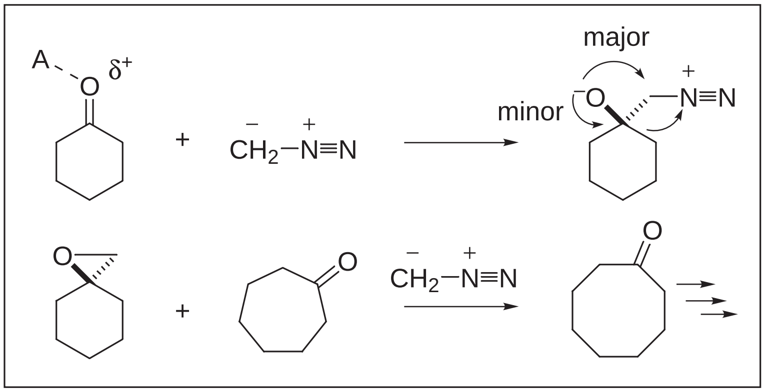
- very slow epoxide opening due to steric encumbrance of Me group
- benefits from irreversible nature of epoxide opening

Alternate route attempted:



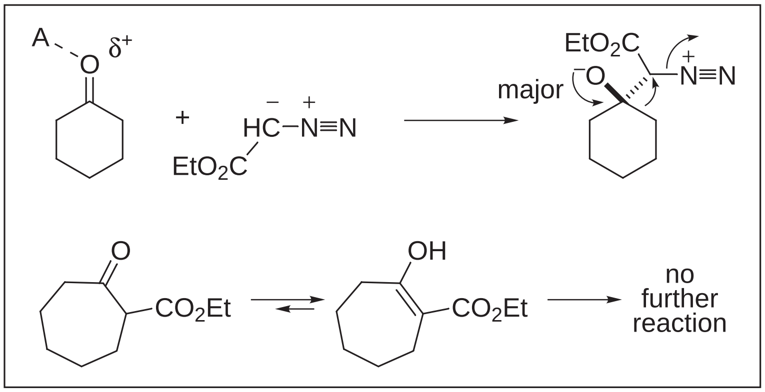
Alternate Route

- hydroboration–oxidation gave ketone
- methylation conditions specifically employed to avoid over-methylation
- ring expansion with CH_2N_2 did not proceed



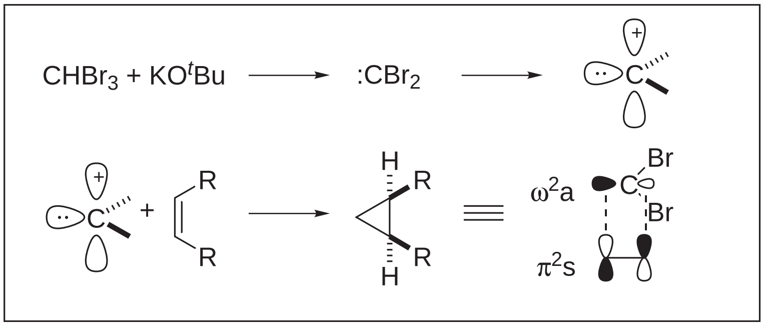
Diazomethane Ring Expansion

- CH_2N_2 poor nucleophile
- $AlCl_3$ added to activate carbonyl
- many side reactions possible
- CH_2N_2 explosive, difficult to use
- products equally reactive toward additional expansions/epoxidations
- $TMSCHN_2$ is a safe alternative to diazomethane CHN_2, a yellow gas, which typically is prepared in situ in special apparatus to diminish the chance of detonation



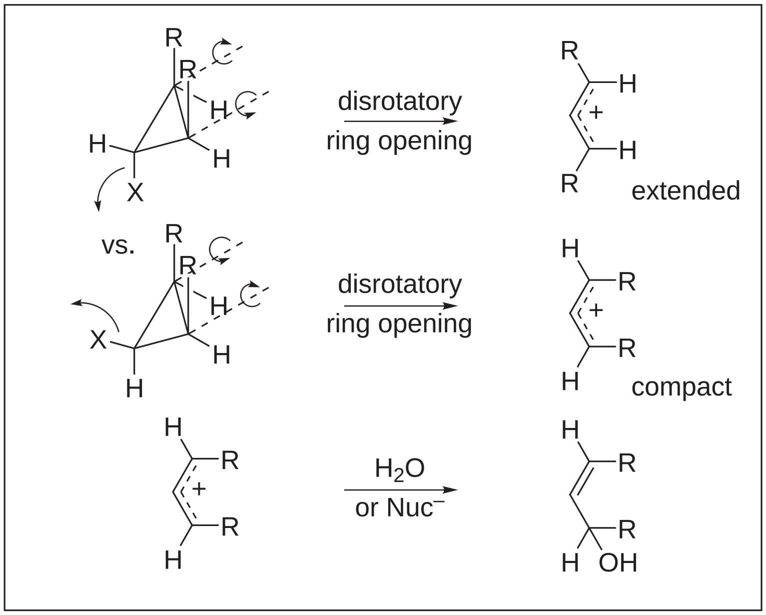
Diazoacetate Ring Expansion

- improvement over diazomethane
- product in enol form and will not further react with reagent
- reagent stable, transportable and readily available
- ultimately employed in the later Ho synthesis



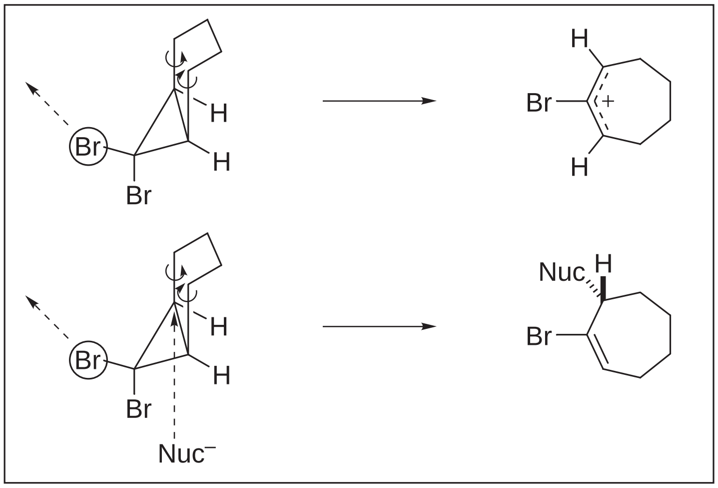
Carbene Addition and Ring Expansion

- singlet carbene has electrophilic character, and undergoes stereospecific reaction with olefins (no scrambling as observed with triplet carbene)
- Br can donate electrons into the empty p-orbital, thus stabilizing the singlet carbene
- cheletropic cycloaddition occurs with olefin geometry maintained via a $\pi^2s + \omega^2a$ cycloaddition



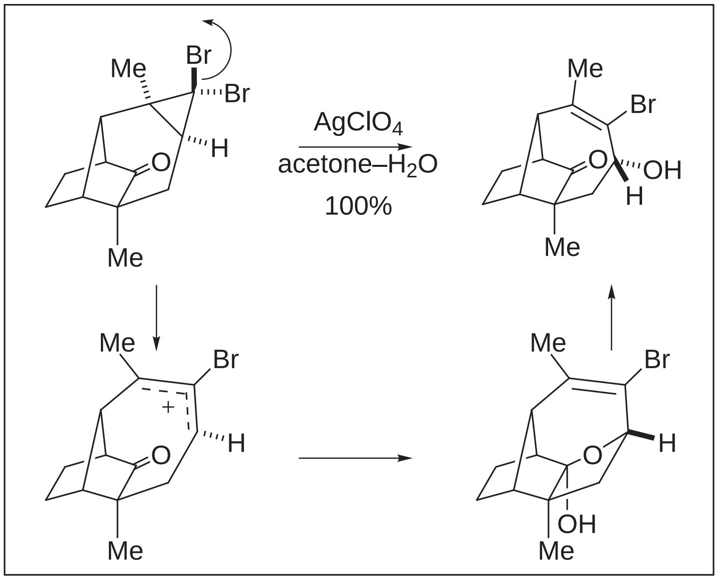
Disrotatory Ring Opening of Halocyclopropanes

- leaving group will influence direction of ring opening
- departure of LG simultaneous with disrotatory ring opening
- substituents *syn* to the departing group will move towards one another while they move away from each other if *anti* leaving group. Since this system is confined to a 7-membered ring, the R groups must move toward each other to give the compact alkyl cation and it is the *syn* bromide that is lost



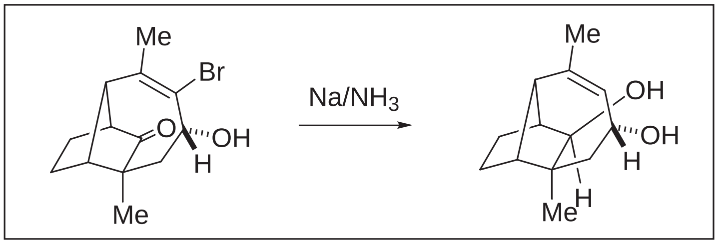
In Fused Bicyclic Systems

- imposed geometry of ring controls opening and directs leaving group
- nucleophile comes in *trans* to departing Br⁻
- exception: bicyclo[5.1.0]octane can give the *trans* double bond via outward rotation
- *Chem. Commun.* **1967**, 294.
- *Chem. Commun.* **1968**, 1593.
- *J. Am. Chem. Soc.* **1970**, *92*, 2566.



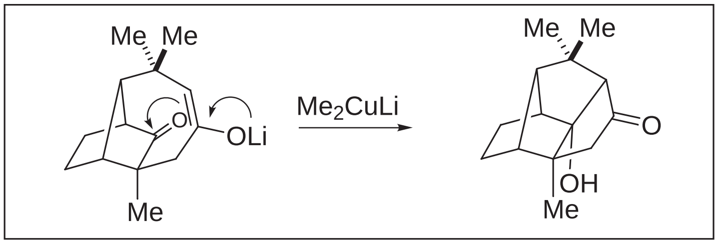
McMurry Application

- ring controls geometry of ring opening, thus only one bromine departs
- nucleophile (OH_2) enters *trans* to leaving Br
- no trap at other end of allyl cation - possible assistance of C=O



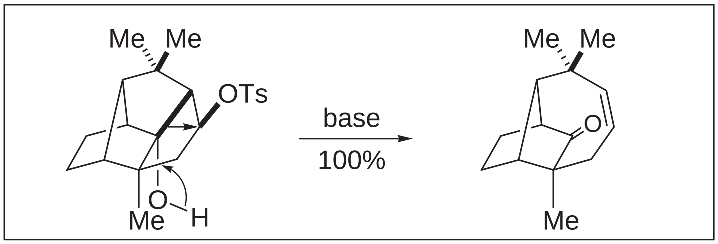
Dissolving Metal Reduction

- stereochemistry of reduced OH - most stable product
- reduction of the vinyl halide



Cuprate Addition - Intramolecular Aldol Reaction

- cuprate adds in Michael fashion to generate enolate
- enolate then attacks carbonyl in intramolecular fashion



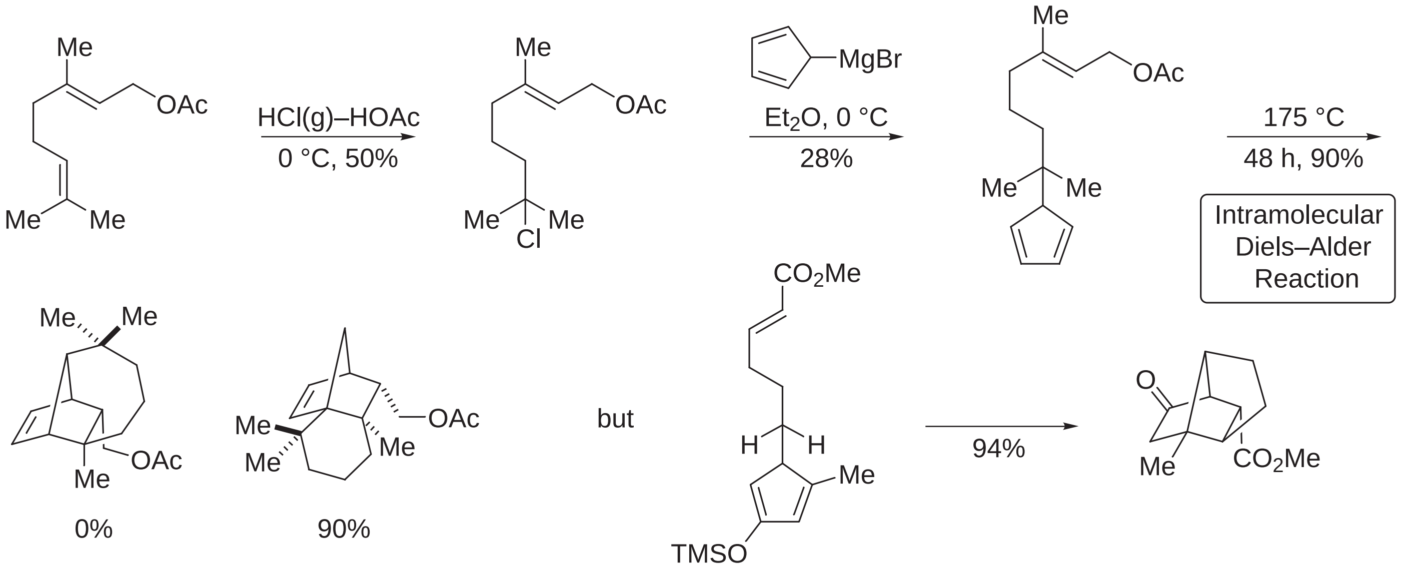
Fragmentation

- reduction occurs from least hindered face
- tosylation selective for 2° > 3°

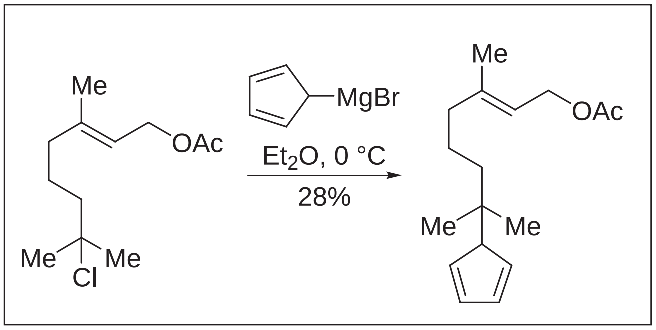
4. Brieger Synthesis: (attempted)

J. Am. Chem. Soc. **1963**, *85*, 3783.

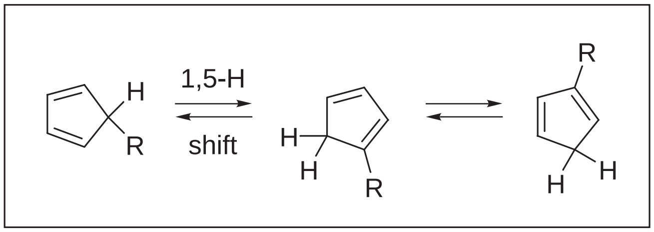
Diels–Alder Reaction
Intramolecular Diels–Alder Reaction
1,5-Hydrogen Migration of Cyclopentadienes



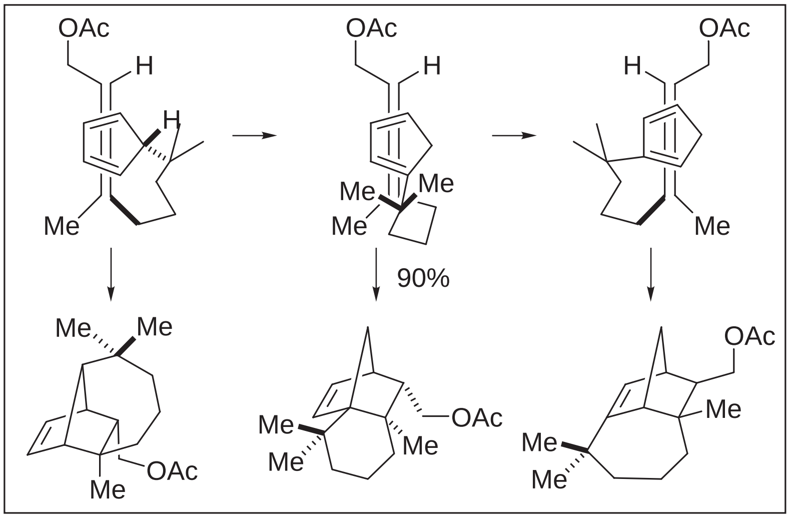
Snowden *Tetrahedron Lett.* **1981**, *22*, 97 and 101.



Grignard Addition
- alkylation at 3° center!
- nonbasic reagent, E2/E1 elimination not observed



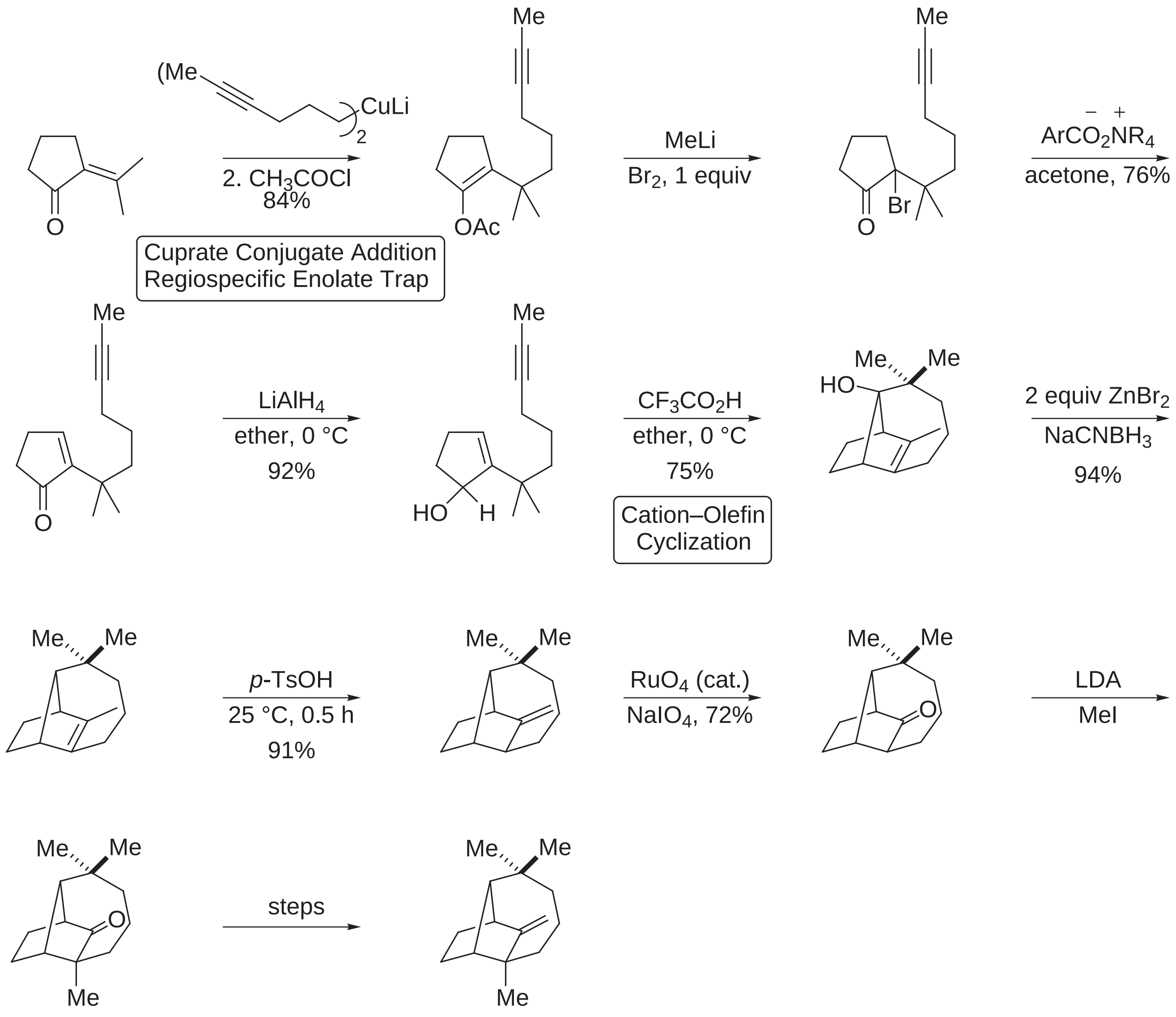
1,5 H-Shift
- proceeds at 0 °C
- causes failure of desired [4 + 2] cycloaddition for longifolene above



Intramolecular Diels–Alder
- at 175 °C, all three 1,5-H shift products present
- provide three different possible products
- only one product observed

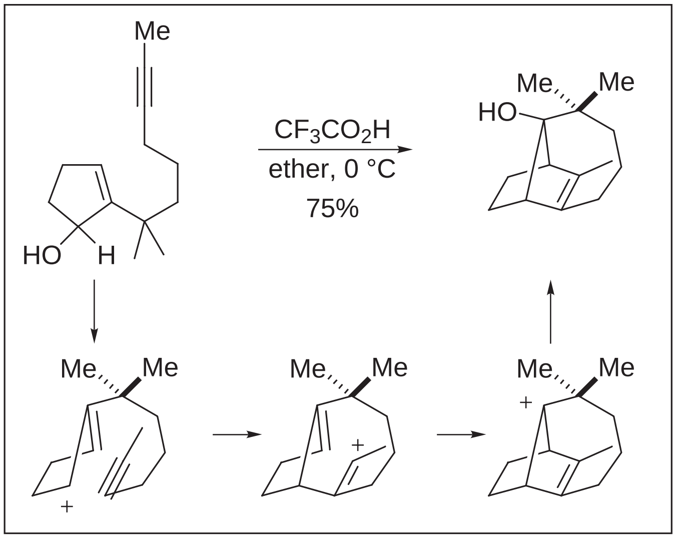
5. Johnson Synthesis: *J. Am. Chem. Soc.* **1975**, *97*, 4777.

Organocuprate 1,4-Addition
Regiospecific Enolate Trap
Cation–Olefin Cyclization



Cuprate Conjugate Addition
Regiospecific Enolate Trap

Cation–Olefin
Cyclization

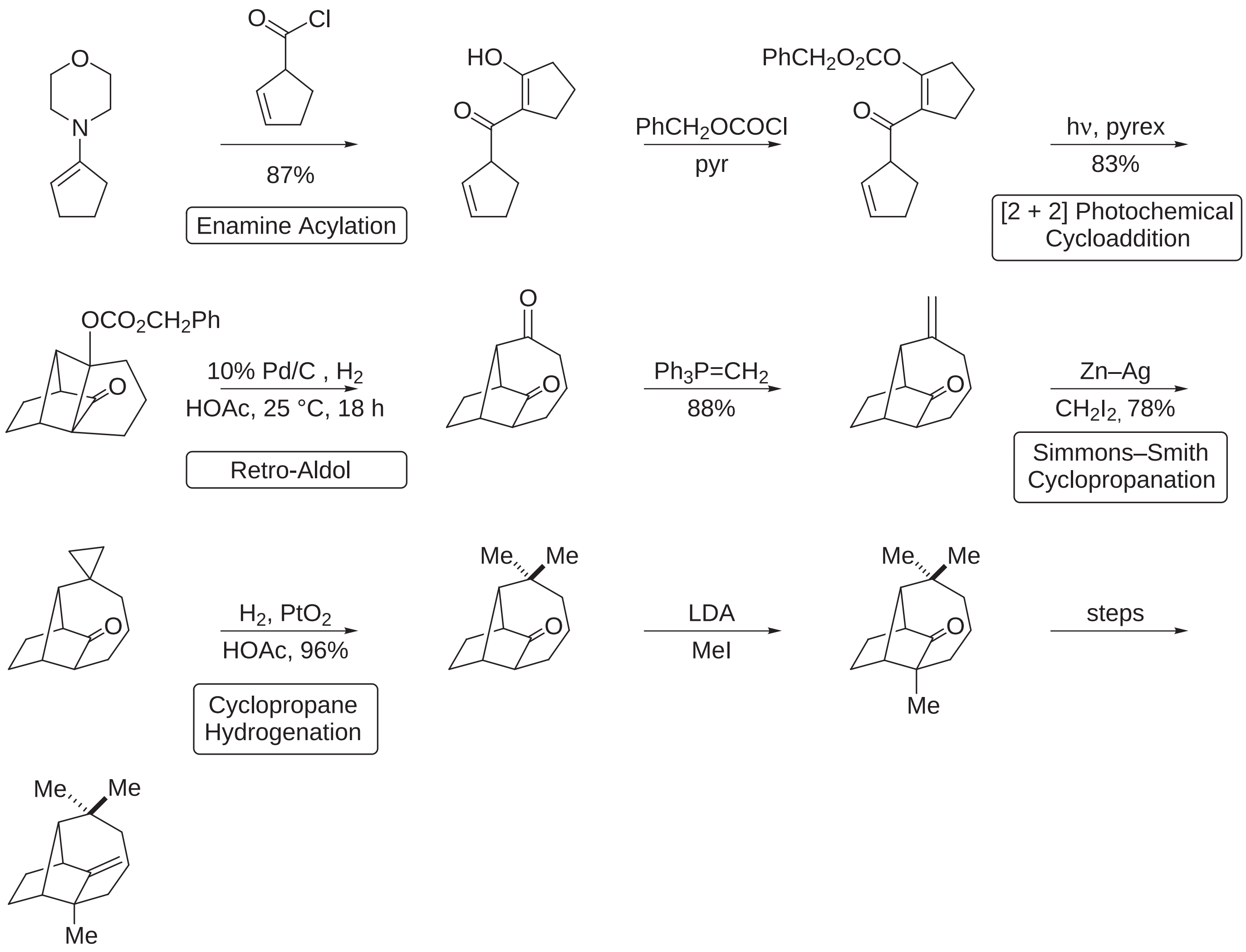


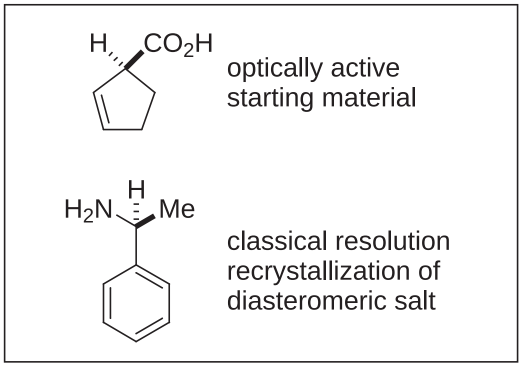
Cation–Olefin Cyclization
- 2° allylic alcohol for initiation site

6. Oppolzer Synthesis:

J. Am. Chem. Soc. **1978**, *100*, 2583.
Helv. Chim. Acta **1984**, *67*, 1154.

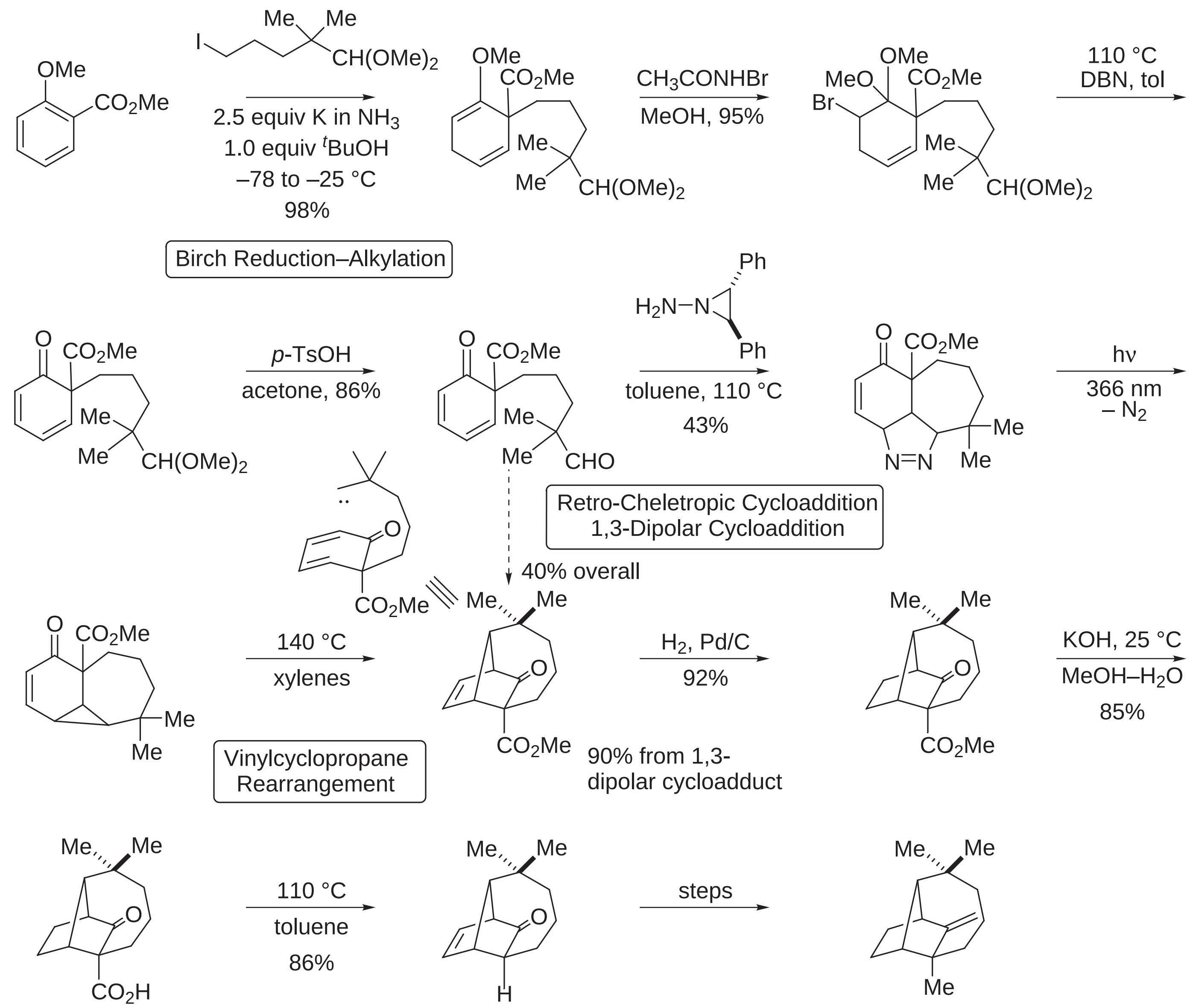
Enamine Acylation
Photochemical [2 + 2] Cycloaddition
Retro-Aldol Reaction
Wittig Reaction
Simmons–Smith Cyclopropanation
Hydrogenation of Cyclopropanes
Classical Resolution via Crystallization of Diastereomeric Salts

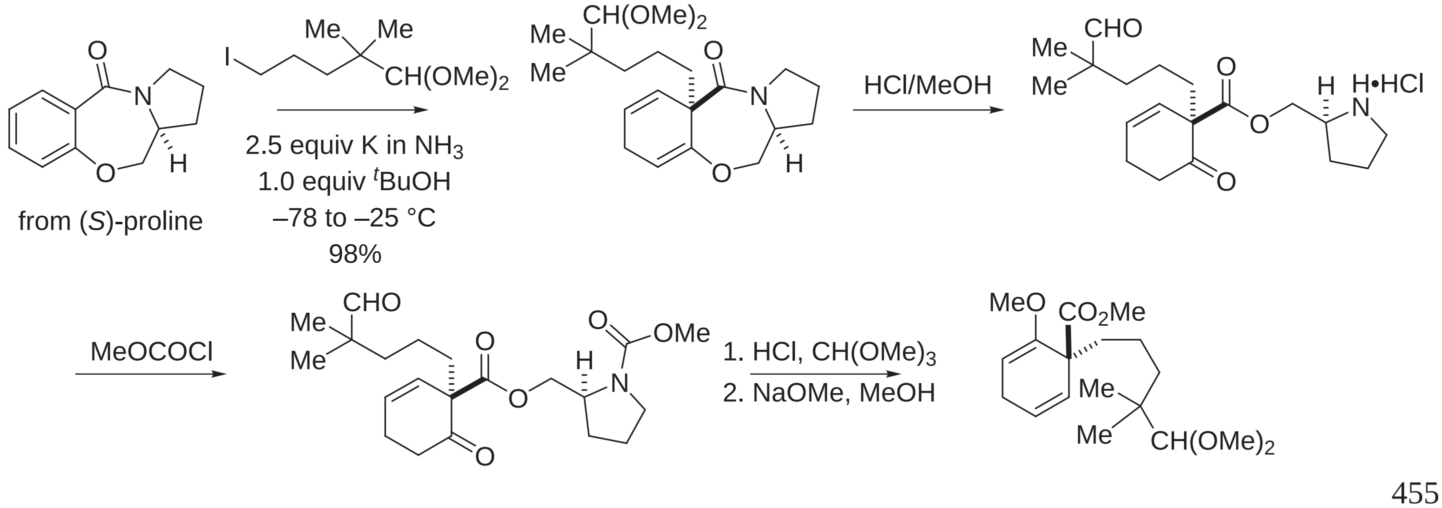


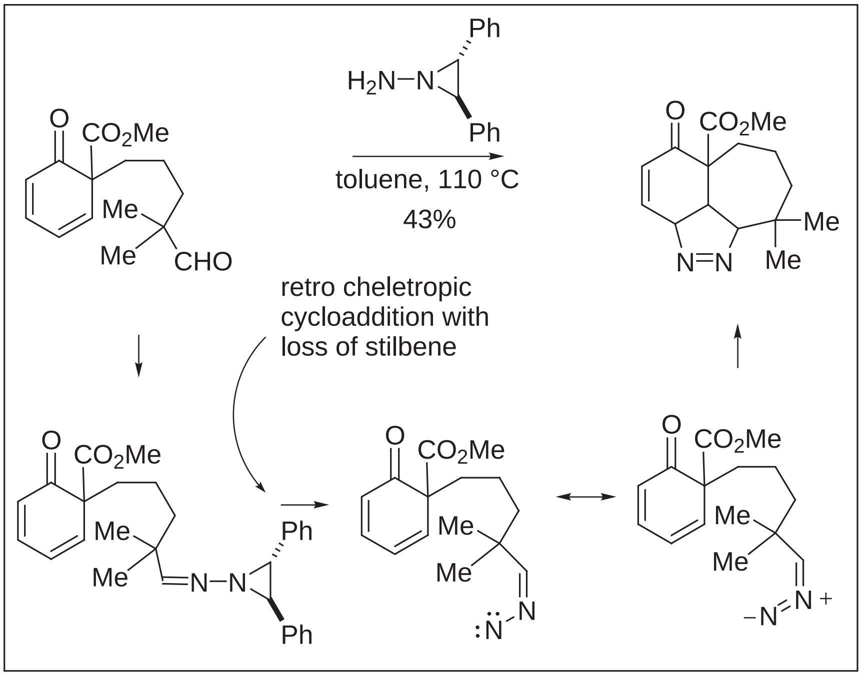


7. Schultz Synthesis: *J. Org. Chem.* **1985**, *50*, 915.

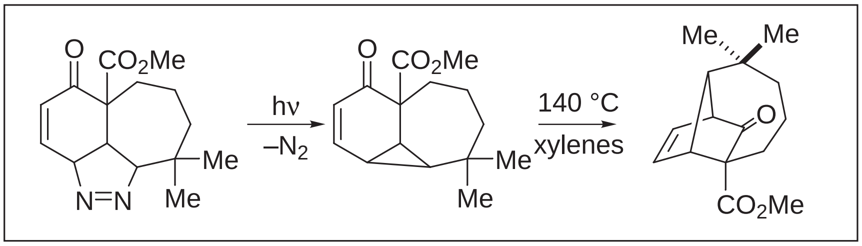
Birch Reductive Alkylation
Retro Cheletropic Cycloaddition
1,3-Dipolar Cycloaddition
Vinylcyclopropane Rearrangement
Asymmetric Synthesis
via Substrate Chiral Auxiliary





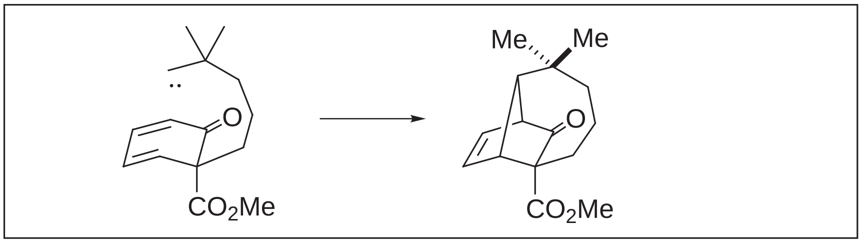


Retro Cheletropic Cycloaddition and Subsequent 1,3-Dipolar Cycloaddition



Vinylcyclopropane Rearrangement

- [1,3]-sigmatropic rearrangement

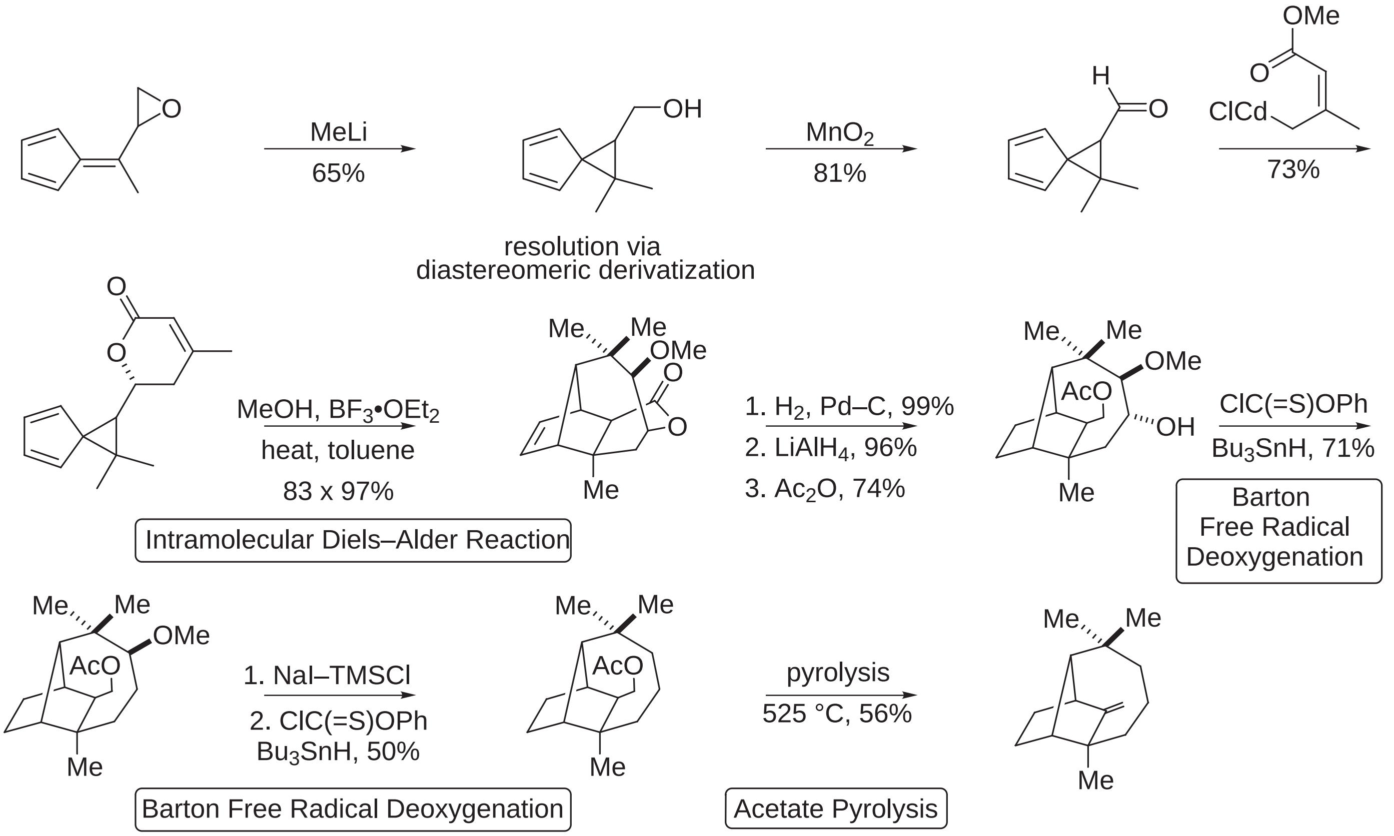


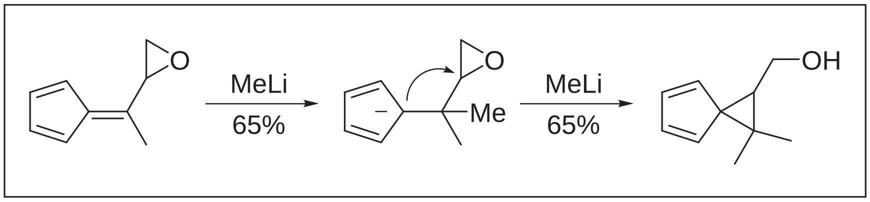
- This sequence is equivalent to adding the elements of a carbene 1,4 across a diene
- Is this $4e^-$ + $2e^-$ cycloaddition possible? Consider the Woodward–Hoffmann rules.

8. Fallis Synthesis:

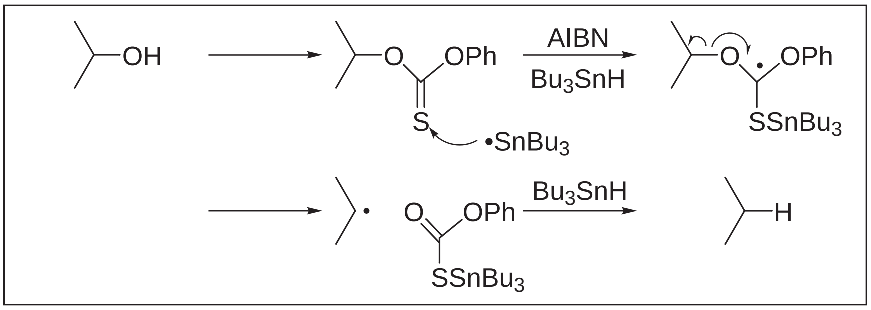
J. Am. Chem. Soc. **1990**, *112*, 4609.
J. Org. Chem. **1993**, *58*, 2186.

Intramolecular Diels–Alder Reaction
Barton Free Radical Deoxygenation Reaction
Acetate Pyrolysis
Chromatographic Resolution through
Diastereomeric Derivatization (Starting Material)

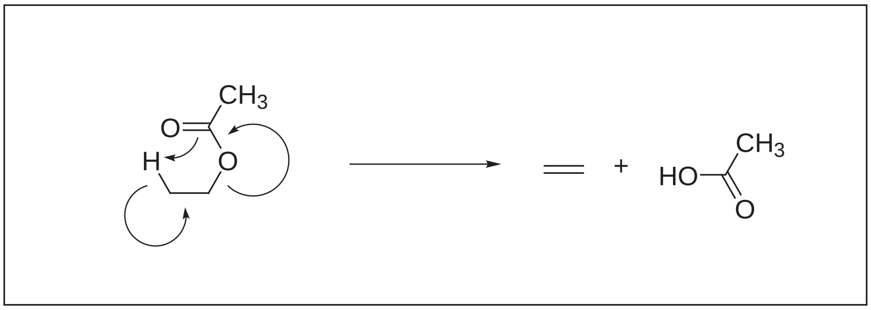




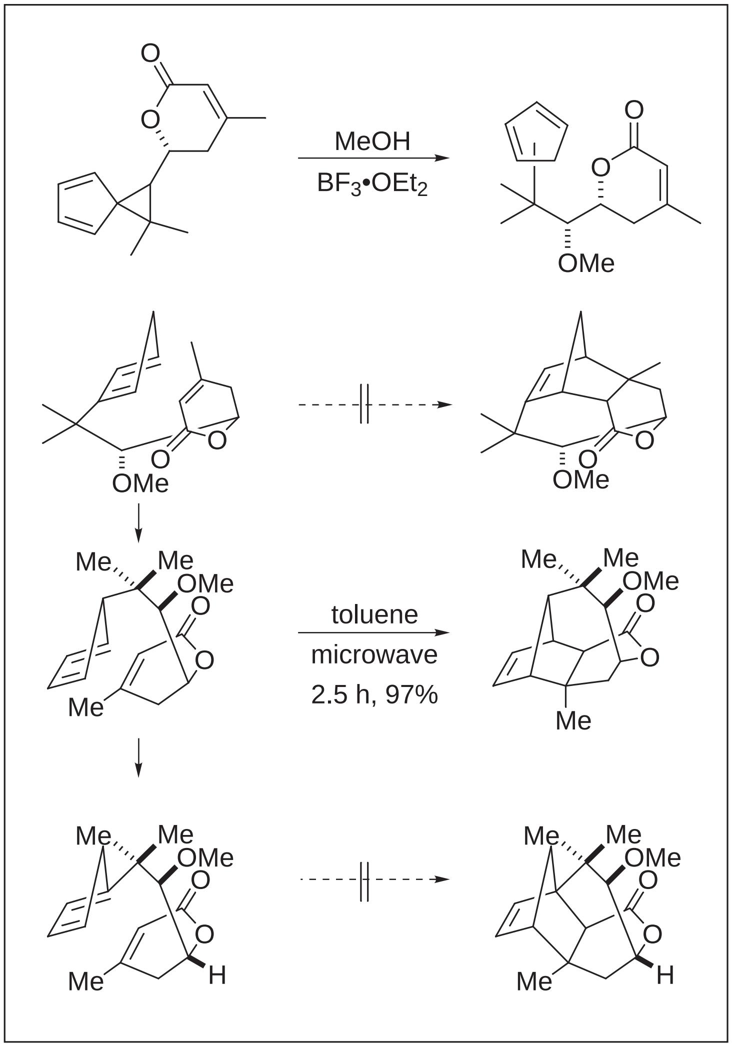
3-*exo-tet* cyclization



Barton Free Radical Deoxygenation
- mild method for removal of alcohols

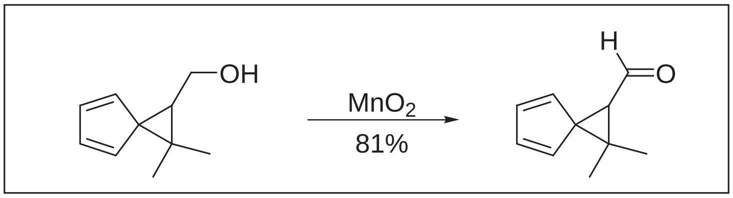


Acetate Pyrolysis
- a retro ene reaction
- comparable to the sulfoxide *syn* elimination (Trost) which is activated by an adjacent EWG
- comparable to the selenoxide *syn* elimination (Reich) which is milder, faster and proceeds at lower temperature

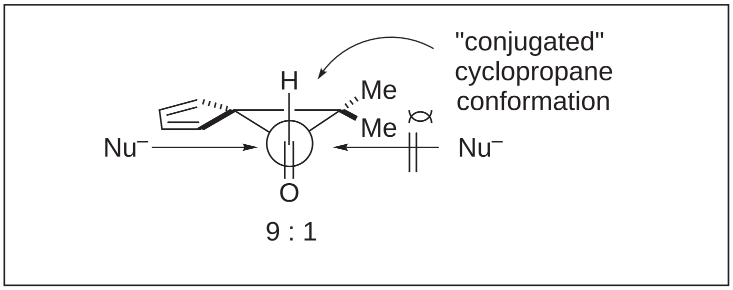


Intramolecular Diels–Alder Reaction

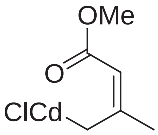
- constraints of the 6-membered ring precludes reaction from the other cyclopentadiene isomers and lactone stereochemistry dictates π-facial selectivity

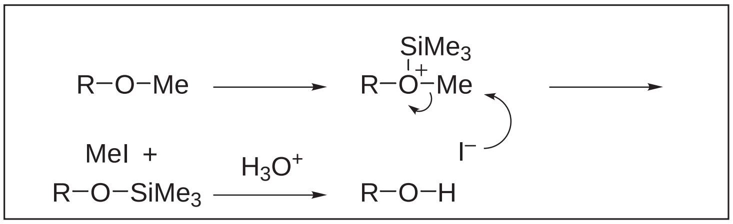


- MnO$_2$ serves to oxidize cyclopropyl alcohol analogous to allylic alcohol oxidation



- Cadmium reagent for α-versus γ-enolate reaction
- Diastereoselective addition



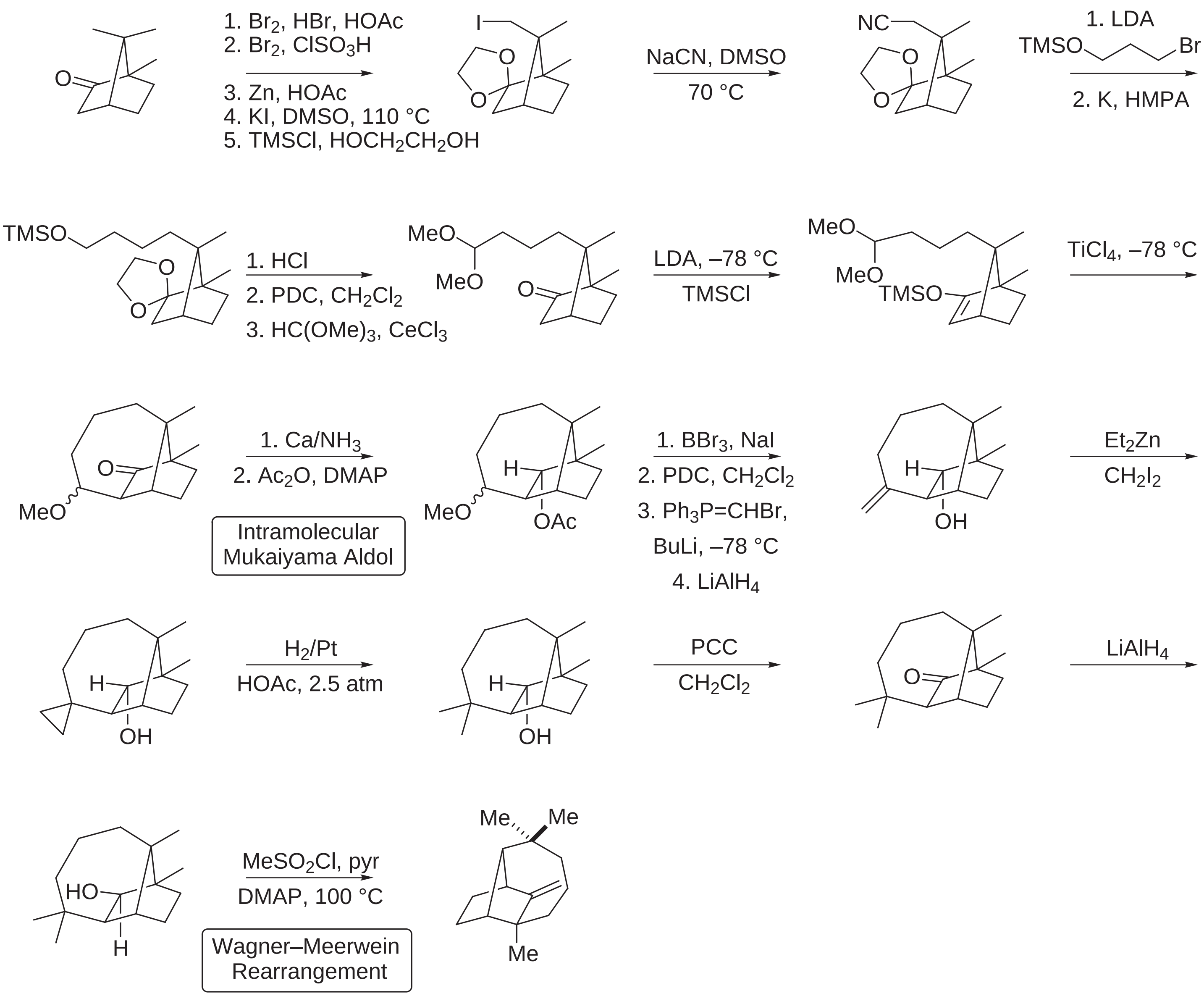


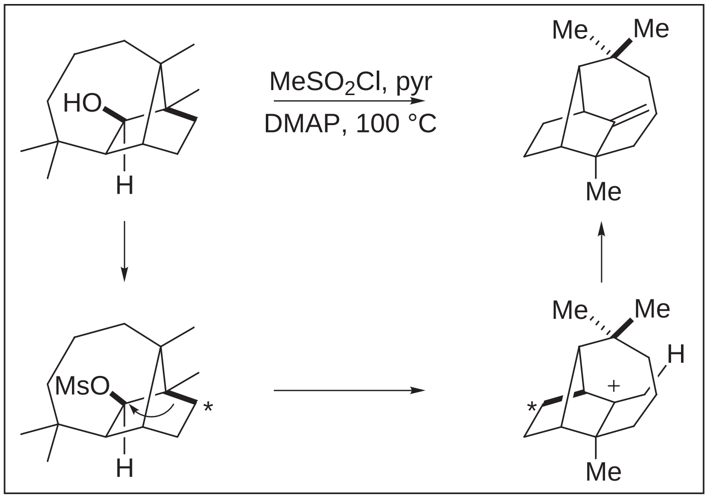
NaI–TMSCl deprotection

- dealkylative S$_N$2 methyl ether deprotection

9. Kuo Synthesis: *Can J. Chem.* **1988**, *66*, 1794.

Intramolecular Aldol Addition
Wagner–Meerwein Rearrangement



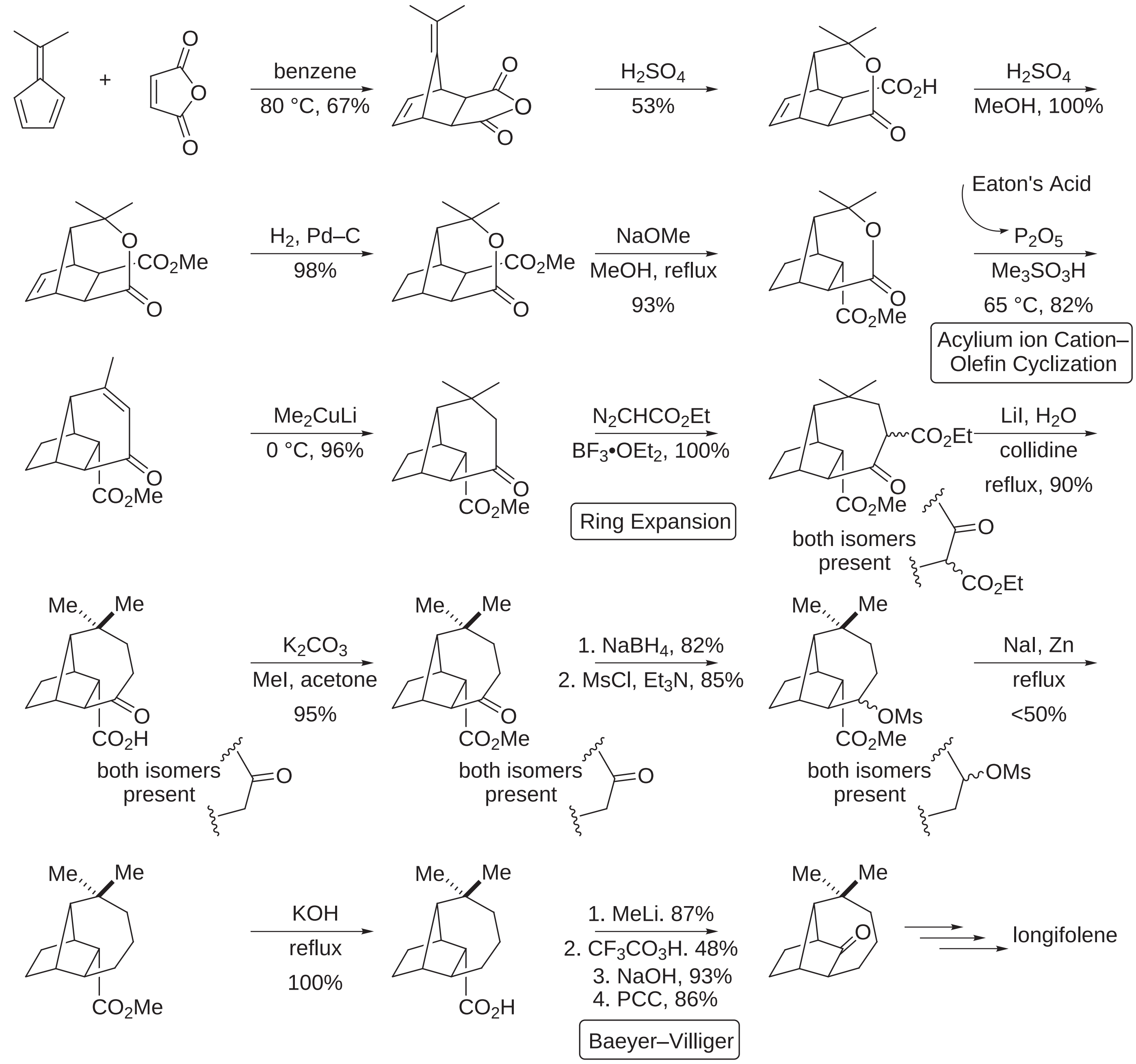


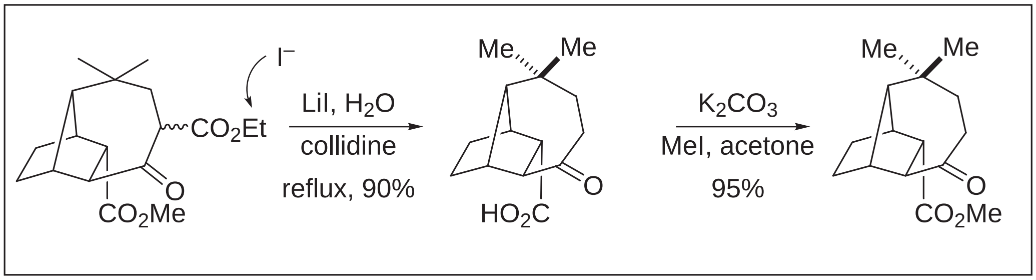
Wagner–Meerwein Rearrangement

10. Ho Synthesis:

Can J. Chem. **1992**, *70*, 1375.

Ethyl Diazoacetate Ring Expansion
Alkylative Esterification





- S_N2 Dealkylative Deesterification followed by decarboxylation of the β-keto acid
- Alkylative Esterification

XIV. Combinatorial Chemistry

Combinatorial Chemistry Reviews

- **A Practical Guide to Combinatorial Chemistry;** Czarnik, A. W. and DeWitt, S. H., Eds.; ACS: Washington, D. C., 1997.

- **Molecular Diversity and Combinatorial Chemistry: Libraries and Drug Discovery;** Chaiken, I. N.; Janda, K. D., Eds.; ACS: Washington, D. C., 1996.

- Balkenhohl, F. *et al.* **Combinatorial Synthesis of Small Organic Molecules,** *Angew. Chem. Int. Ed. Eng*. **1996**, *35*, 2288.

- Ellman, J. A. *et al.* **Synthesis and Applications of Small Molecule Libraries,** *Chem. Rev*. **1996**, *96*, 555.

- Gordon, E. M. *et al.* **Applications of Combinatorial Technologies to Drug Discovery. 1. Background and Peptide Combinatorial Libraries,** *J. Med. Chem*. **1994**, *37*, 1233.

- Gordon, E. M. *et al.* **Applications of Combinatorial Technologies to Drug Discovery. 2. Combinatorial Organic Synthesis, Library Screening Strategies, and Future Directions,** *J. Med. Chem*. **1994**, *37*, 1385.

- Pavia, M. R., Sawyer, T. K. and Moos, W. H., Eds.*;* **The Generation of Molecular Diversity,** *Bioorg. Med. Chem. Lett. Symposia-in-print no. 4.* **1993**, *3,* 381. (First Review Treatment of Field).

- **Combinatorial Peptide and Nonpeptide Libraries: a Handbook;** Jung, G., Ed.; VCH: Weinheim, 1996.

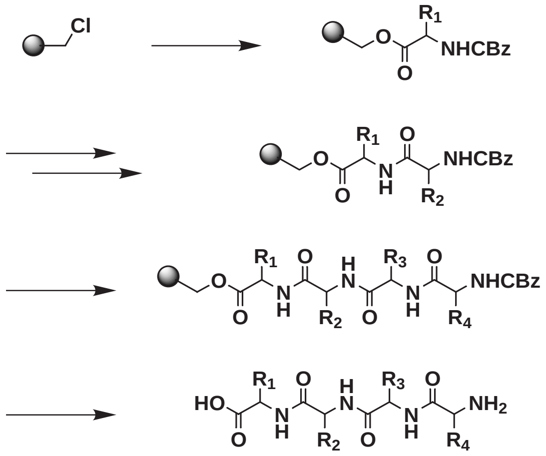
- **Combinatorial Chemistry;** Terrett, N. K.; Oxford Univ. Press: Oxford, UK, 1998.

- Obrecht, D.; Villalgordo, J. M.; **Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries;** Pergamon/ Elsevier, 1998.

- Boger, D. L., Ed*.;* **Combinatorial Chemistry,** *Bioorg. Med. Chem. Lett. Symposia-in-print no. 14.* **1998**, *8,* 2273.

- **An Information Revolution,** *Science* **2000**, *287*, 1951–1981.

Solid Phase Peptide Synthesis



- Attach first amino acid to (chloromethylated) polymer bead
- Deprotect (HBr), Couple (DCC), Cap (acetic anhydride)
- Repeat coupling cycle
- Deprotect, Saponify, Purify

- Allows excess use of reagents and reactants to force reaction to completion
- Removal of reagents, reactants and byproducts by filtration

Merrifield, R. B. *J. Am. Chem. Soc.* **1963,** *85,* 2149.
Nobel Prize, 1984 *"for his development of methodology for chemical synthesis on a solid matrix"*

Additional Highlights in Solid Phase Synthesis

- **1965**: Letsinger and Khorana, the application of solid supports for the synthesis of oligonucleosides (*J. Am. Chem. Soc.* **1965**, *87*, 3526 and **1966**, *88*, 3182)

- **1967**: J. Frechet, a highly loaded trityl resin (2.0 mmol/g)

- **1967**: Wilkinson *et al.*, polymer-bound tris(triphenylphosphine)chlororhodium as hydrogenation catalyst (*J. Chem. Soc. A* **1967**, 1574)

- **1969**: Solid-phase synthesis of Ribonuclease (*J. Am. Chem. Soc.* **1969**, *91*, 501)

- **1971**: Frechet and Schuerch pioneered solid-phase chemistry in the field of carbohydrate research (*J. Am. Chem. Soc.* **1971**, *93*, 492)

- **1973**: Leznoff *et al.*, the use of polymer supports for the mono-deprotection of symmetrical dialdehydes, describing oxime formation, Wittig reaction, crossed aldol condensation, benzoin condensation, and Grignard reaction on solid support (*Can. J. Chem.* **1973**, *51*, 3756)

- **1974**: F. Camps *et al.*, the first synthesis of benzodiazepines on solid support (*An. Quim.* **1974**, *70*, 848)

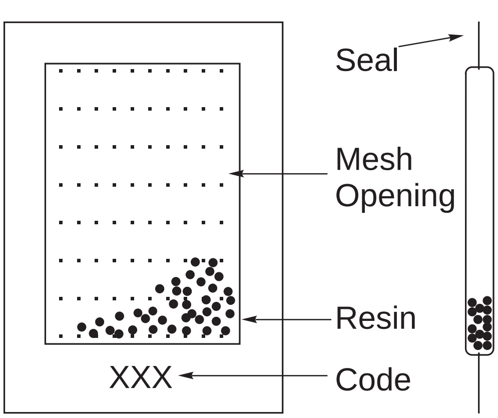
- **1976**: Rapoport and Crowley, published a review and raised three important questions
    - degree of separation of resin-bound functionalities
    - analytical methods to follow reactions on solid support
    - nature and kinetics of competing side reactions

  (*Acc. Chem. Res.* **1976**, *9*, 135)

- **1976–1978**: Leznoff *et al.*, the synthesis of insect sex attractants (*Can. J. Chem.* **1977**, *55*, 1143)

- **1979**: Leznoff *et al.*, a chiral linker for the asymmetric synthesis of (*S*)-2-methylcyclohexanone in 95% *ee* (*Angew. Chem.* **1979**, *91*, 255)

Tea-Bag Method



- 10 to 20 mg of 248 different 13-residue peptides

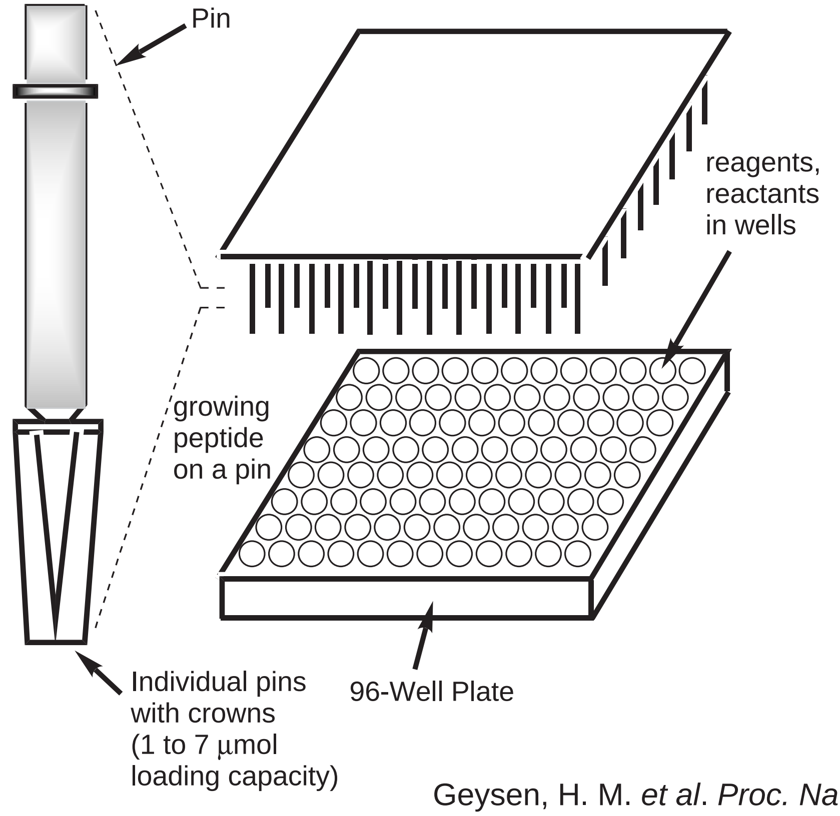
- Sequence

1. Deprotection
2. Wash
3. Coupling
4. Wash
5. HF Cleavage

Repeat

Houghten, R. A. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 5131.

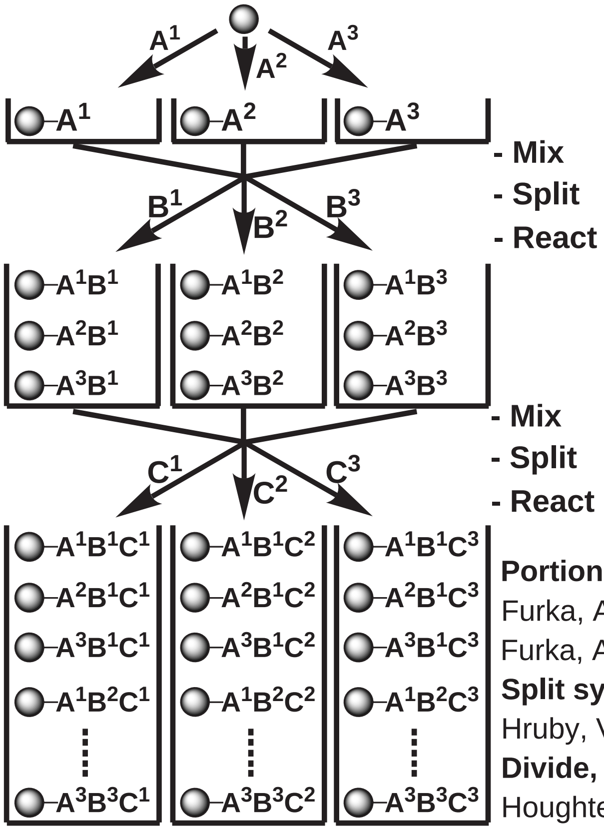
Multipin Peptide Synthesis



- Synthesize on polyacrylate-grafted polyethylene rods
- Utilize conventional solid phase synthesis methods
- Preparation of up to 10,000 spatially separate compounds using inexpensive equipment and readily available automation

Geysen, H. M. *et al*. *Proc. Natl. Acad. Sci. USA* **1984**, *81,* 3998.
Zuckermann, R. N. *et al*. *Bioorg. Med. Chem. Lett.* **1993**, *3,* 463.

Split and Mix Solid Phase Synthesis (Split-Method, Portioning-Mixing Method)



- Solid support is divided before each coupling cycle
- Equimolar mixtures of peptides
- Cannot conduct direct mixture synthesis on solid phase due to differential reaction rates
- One unique peptide on each bead

$$N = n_1 \times n_2 \times n_3 \times \ldots\ldots n_m$$

N = number of products after each cycle

n = number of reactants in each cycle

Portion-mixing

Furka, A. *et al. Bioorg. Med. Chem. Lett.* **1993**, *3,* 413.

Furka, A. *et al*. *Int. J. Peptide Prot. Res.* **1991**, *37*, 487.

Split synthesis

Hruby, V. J. *et al. Nature* **1991***, 354,* 82.

Divide, couple, and recombine

Houghten, R. A. *et al. Nature* **1991**, *354*, 84.

Generation of Combinatorial Antibody Libraries

Use of bacteriophage lambda vector to express in *E. coli* a combinatorial library of Fab fragments

Sequence:

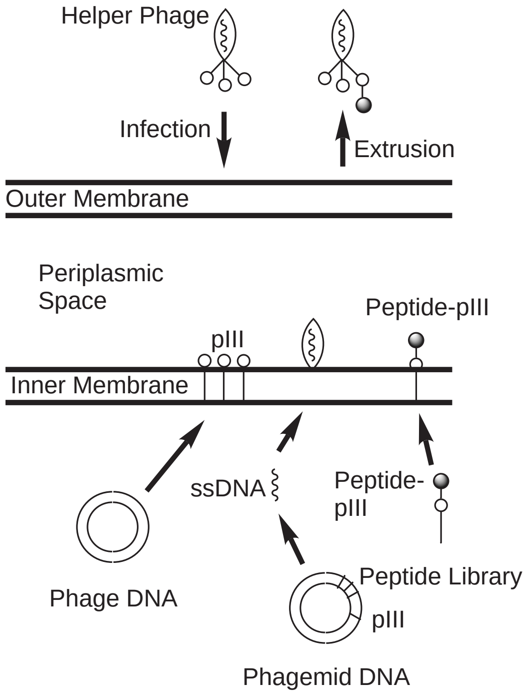
First step: Separation of heavy and light chain libraries which are constructed in λHc2 and λLc1

Second Step: Combination of two libraries are combined at the antisymmetric *Eco R* sites present in each vector

This results in a library of clones each of which potentially coexpresses a heavy and a light chain

Lerner, R. A. *et al*. *Science* **1989**, *246,* 1275.

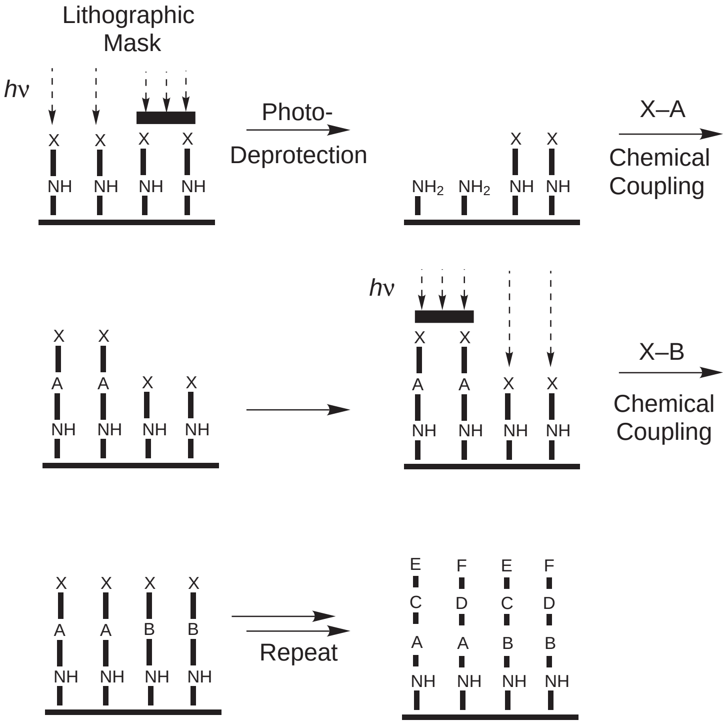
Phage Display



- The general concept is one in which a library of peptides is presented on the surface of a bacteriophage such that each phage displays a unique peptide and contains within each genome the corresponding DNA sequence
- Introduction of randomized DNA into gene III of filamentous phage ⟶ Expression of the corresponding peptides at the *N* terminus of the absorption peptide (pIII)
- Very quick and efficient generation of large combinatorial libraries of peptide fragments
- Screen by panning and enrichment
- Identify by DNA sequence

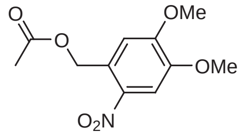
Smith, G. P. *et al*. *Science* **1990**, *249*, 386.

Very Large Scale Immobilized Polymer Synthesis (VLSIPS)



- Light-directed spatially addressable parallel chemical synthesis
- Nitroveratryloxycarbonyl (NVOC) as a photolabile protecting group

X =

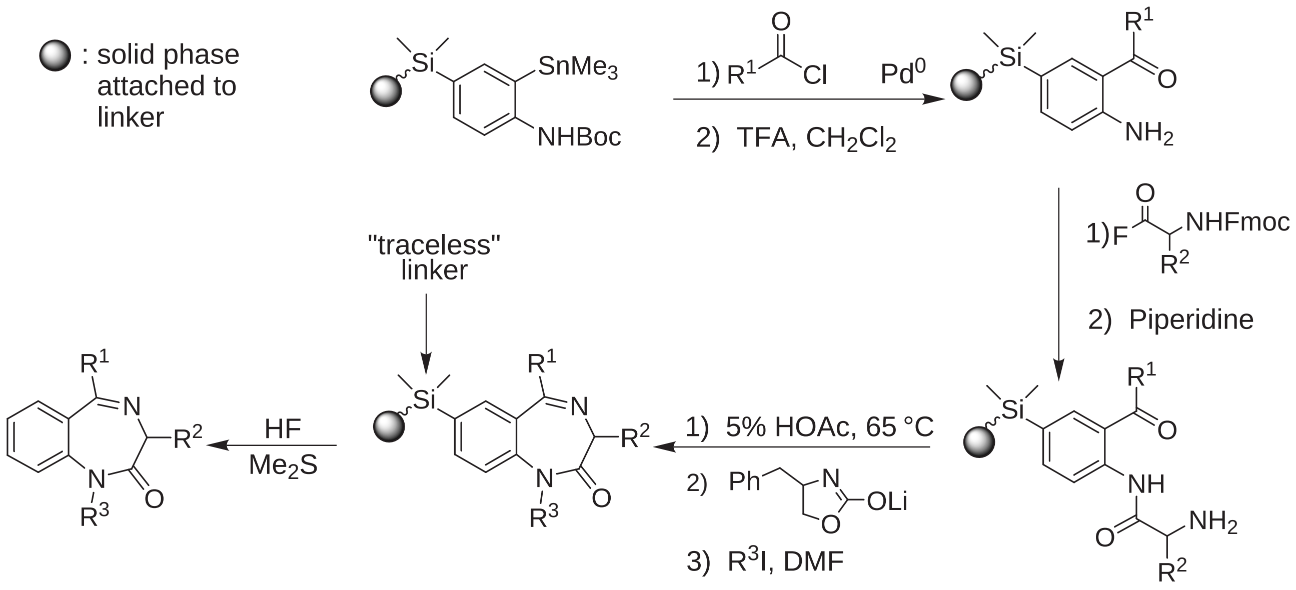


- Binary masking yields 2^n compounds in *n* chemical steps

Fodor, S. P. A.; Pirrung, M. C. *et al*. *Science* **1991**, *251*, 767.

Solid Phase Synthesis of 1,4-Benzodiazepines

- Application of solid-phase combinatorial synthesis to non-oligomeric compounds

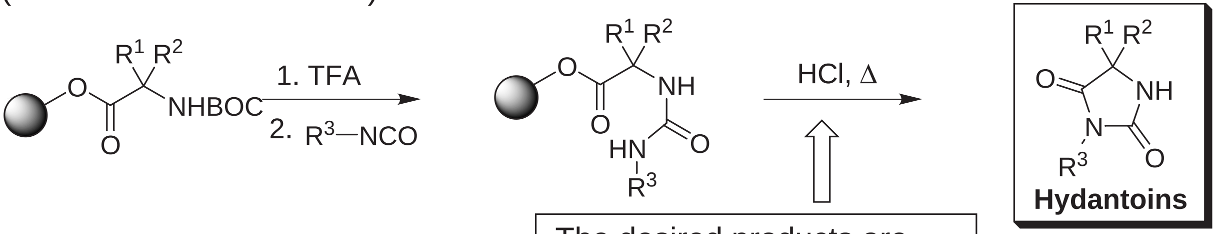


Ellman, J. A. *et al. J. Am. Chem. Soc.* **1992,** *114,* 10997.

DeWitt, S. H. *et al. Proc. Natl. Acad. Sci. USA* **1993,** *90,* 6909.

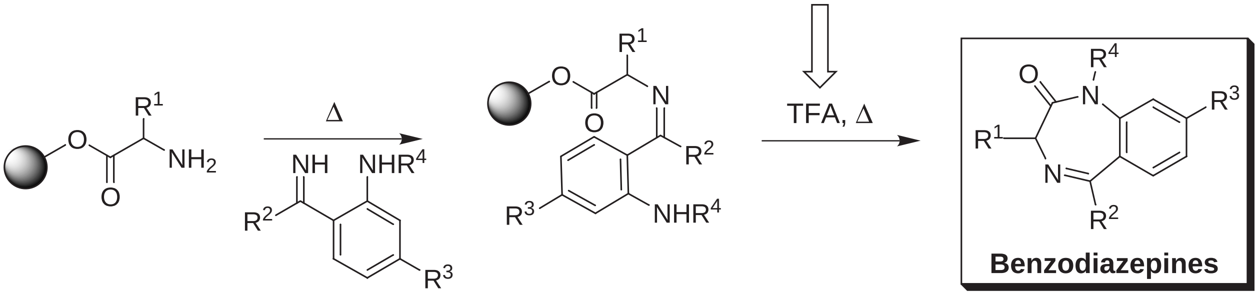
Resin Release Only of Product

First Example: Rapoport, H.; Crowley, J. I. *J. Am. Chem. Soc.* **1970**, *92*, 6363.
(Dieckmann condensation)



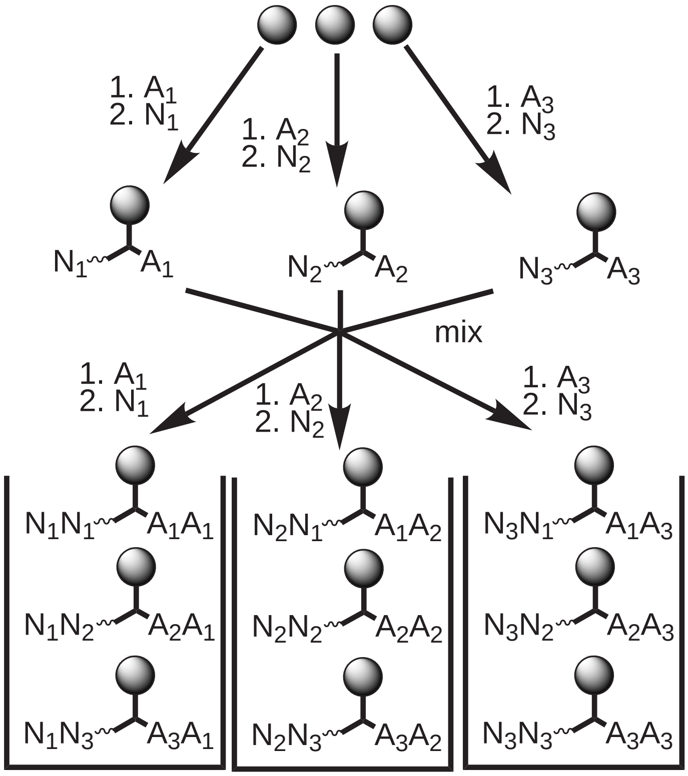
- Insures product purity without deliberate purification and independent of overall conversion

The desired products are formed by acid-catalyzed cyclization and only with cleavage off the solid support



DeWitt, S. H. *et al. Proc. Natl. Acad. Sci. USA* **1993,** *90,* 6909.

Nucleotide Encoding

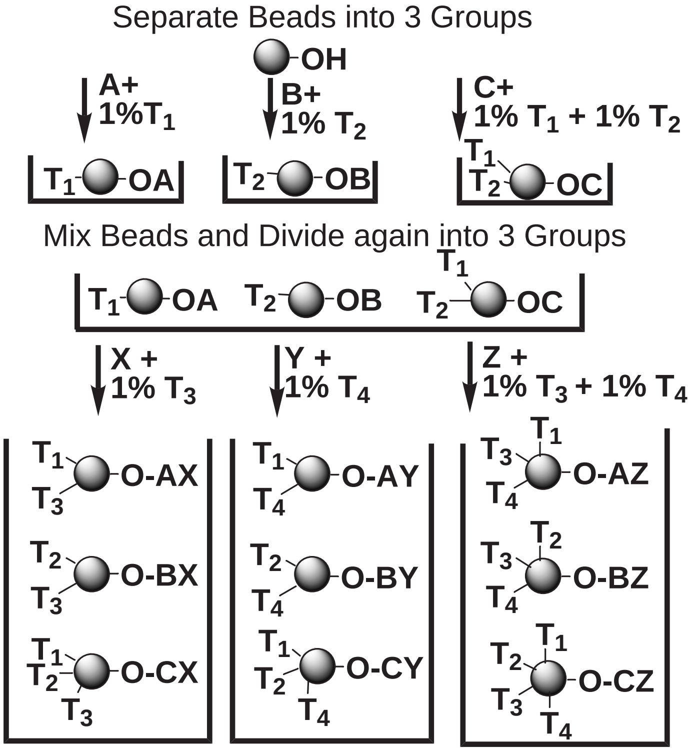


● CPG beads
⅄ Linker Unit
∼ PCR Primer
A_1, A_2, A_3: Amino Acids
N_1, N_2, N_3: Encoding Nucleotides

- Tag attached to molecule, not bead
- PCR enrichment: sensitivity and screening by panning and enrichment
- Bonus: nucleotide tagging could be used for identification as well

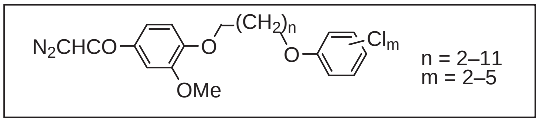
Janda, K. D. *et al. J. Am. Chem. Soc.* **1993**, *115*, 9812.
Brenner, S.; Lerner, R. A. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 5381.

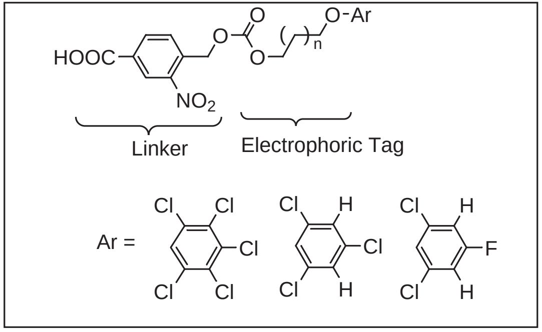
Split Synthesis ENCODED with Tagging Molecules (T_1–T_4)



Tagging Molecules

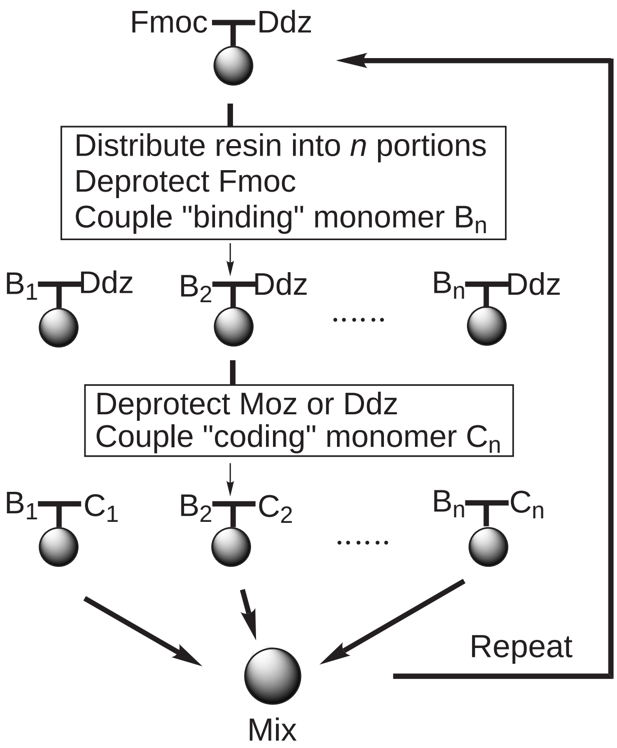
1. Chemically inert
2. Encoding by attachment to the beads
3. After release, analyzed by Capillary Gas Chromatography using Electron Capture Detection (ECGC) on femtomolar scales from single beads
4. Identity only





Still, W. C. *et al. Proc. Natl. Acad. Sci. USA* **1993**, *90*, 10922; *Acc. Chem. Res.* **1996**, *29*, 155.

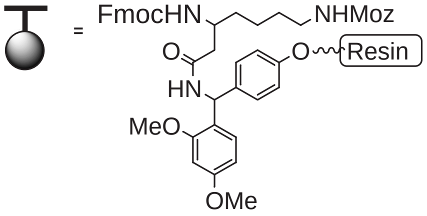
Peptide Encoding



Distribute resin into *n* portions
Deprotect Fmoc
Couple "binding" monomer B_n

Deprotect Moz or Ddz
Couple "coding" monomer C_n

B: Fmoc protected, base-labile monomers
C: Ddz-protected, acid-labile monomers, which give reproducibly strong signals upon Edman sequencing

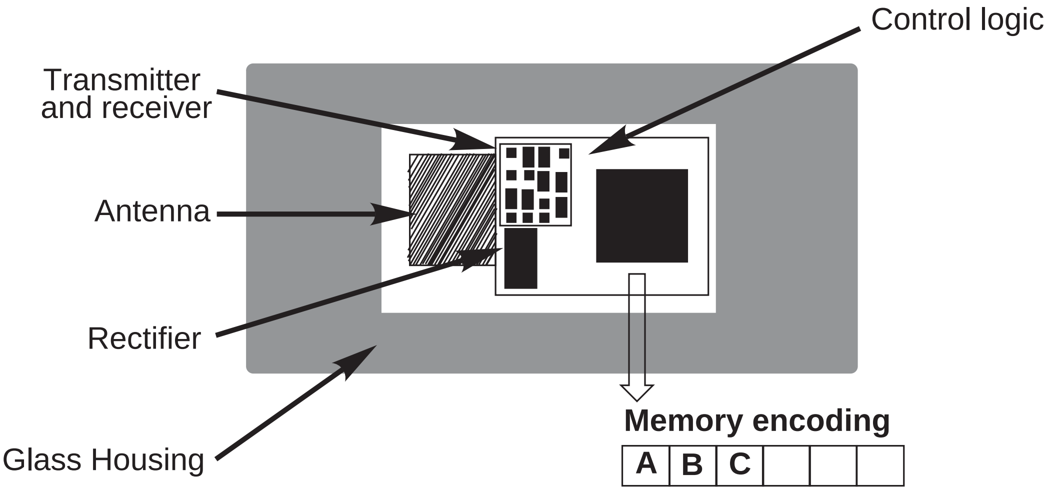


- Identity only

Zuckermann, R. N. *et al. J. Am. Chem. Soc.* **1993**, *115*, 2529.

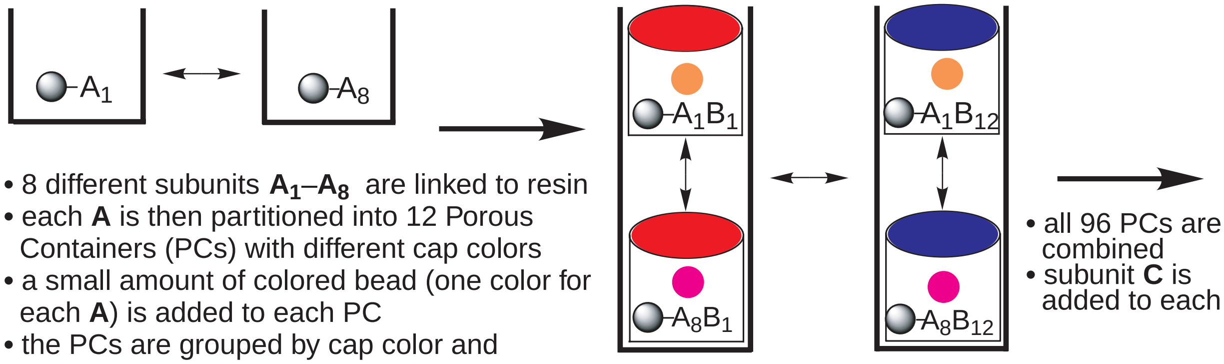
Electronic Encoding

- Radiofrequency memory chips allow libraries to be tagged in a machine-readable form
- The chips (8 x 1 mm) can be incorporated into various reaction platforms (e.g. beads, tubes, bags, pins or cans)



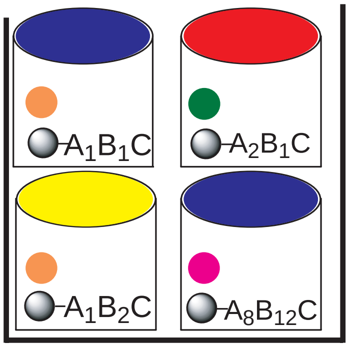
Nova, M. P.; Nicoloau, K. C. *et al. Angew. Chem. Int. Ed. Eng*. **1995**, *34*, 2289.
Armstrong, R. W. *et al*. *J. Am. Chem Soc.* **1995,** *117*, 10787.

Noncovalent Color-Coding Strategy



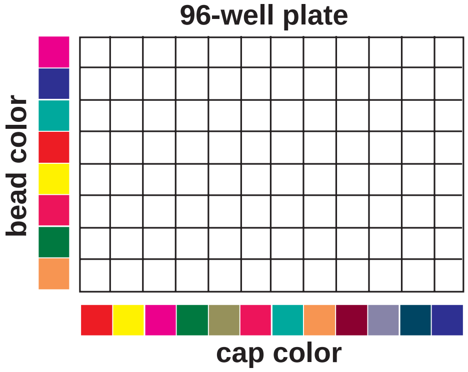
- 8 different subunits $\mathbf{A_1}$–$\mathbf{A_8}$ are linked to resin
- each **A** is then partitioned into 12 Porous Containers (PCs) with different cap colors
- a small amount of colored bead (one color for each **A**) is added to each PC
- the PCs are grouped by cap color and subunit **B** is attached

- all 96 PCs are combined
- subunit **C** is added to each



- compounds are sorted individually by cap and bead color

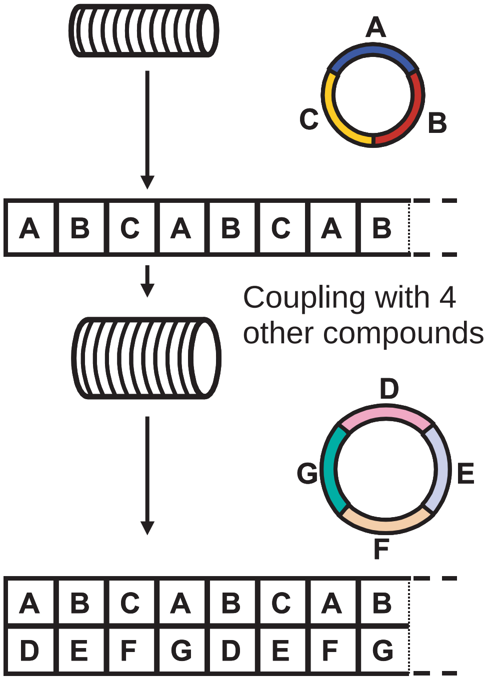
- resin is cleaved
- products are filtered into a separate 96-well plate



Guiles, J. W. *et al. Angew. Chem., Int. Ed.* **1998**, *37*, 926.

Fourier Transform Combinatorial Chemistry

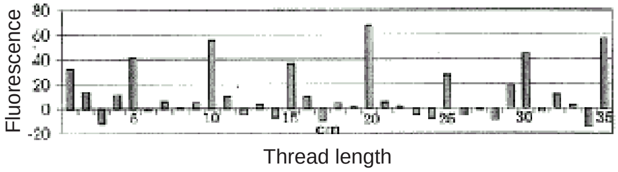
- Cotton thread wrapped around a cylinder
- 3 sectors exposed to 3 different reagents



Coupling with 4 other compounds

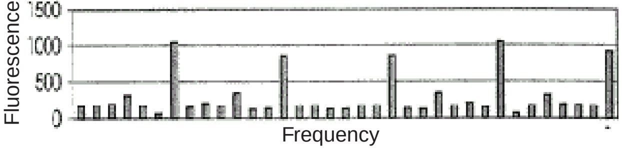
Screening and Evaluation

Thread library evaluation



Fourier Transform

FT Library Spectrum

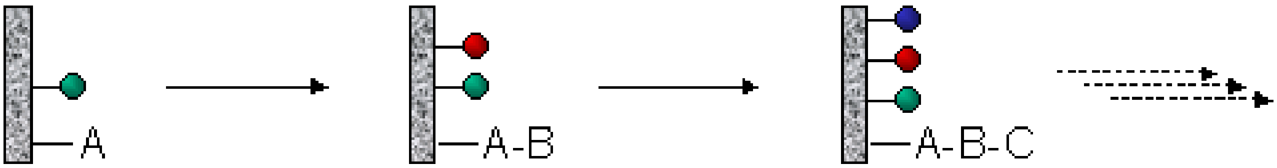


Reverse F.T. at a given frequency

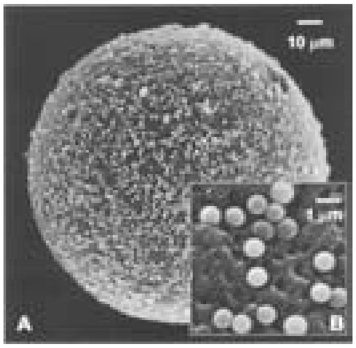
"Fitness Profile" of a sub-molecular unit

Schwabacher, A. W. *et al. J. Am. Chem. Soc.* **1999**, *121*, 8669.

Toward Larger Chemical Libraries: Encoding Fluorescent Colloids



Solid support bead
with numerous silica
particles ("reporter")



- The fluorescent "reporter" is introduced during the Split & Pool synthesis
- Each particle contains a fluorescent dye (or a combination) coding for a single monomer
- "Decoding" the bead (by fluorescence microscopy) allows identification of the compound

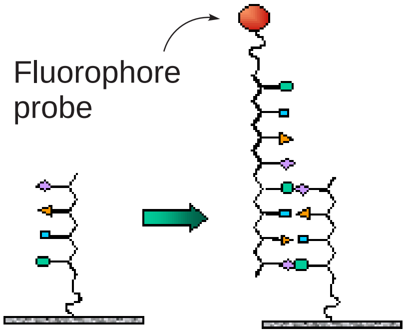
Trau, M. *et al*. *J. Am. Chem. Soc.* **2000**, *122*, 2138.

Microarray Screening: Immobilized Target or Compound

Membrane Printing: the SPOT technique[1]

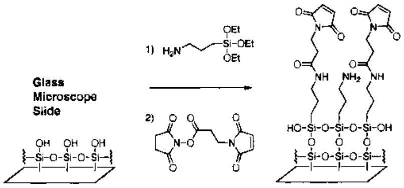
- Peptide synthesis on paper using "Fmoc/^{t}Bu" scheme
- The molecule or synthesis is arrayed by dispensing small droplets in pre-defined areas
- Automation of the technique allows miniaturization of the process and creates high-through put systems

DNA Microarray: Printing oligonucleotide[2]

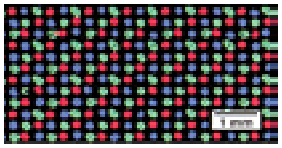


- Covalent immobilization of oligonucleotides on support with high-density arrays
- Detection of DNA/DNA or DNA/RNA interactions for expression analysis, genomics, and cellular response to small molecules

Printing small molecules on a glass surface[3]



- Covalent immobilization of the compound on the glass surface support
- Incubation with the target
- Detection by fluorescence



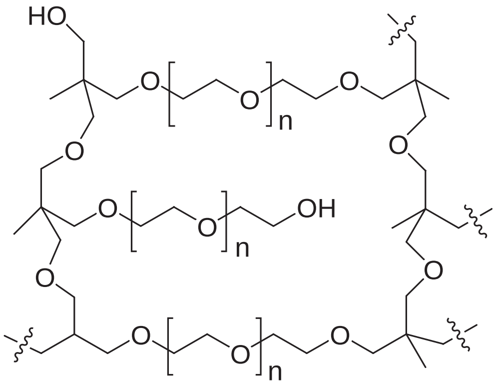
> 1000 spots per cm^2

[1] Frank, R. *et al*. in *Peptide and Nonpeptide Libraries*, Jung, G., Ed., 1996, 363.

[2] Niemeyer, C. M. *et. al. Angew. Chem. Int. Ed.* **1999**, *38*, 2865.

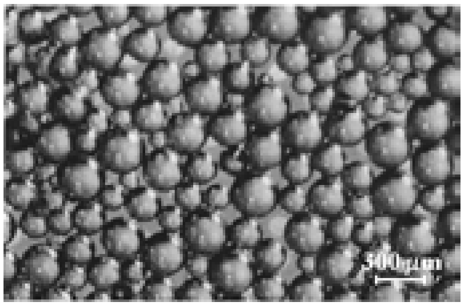
[3] Schreiber, S. L. *et. al. J. Am. Chem. Soc.* **1999**, *121*, 7967.

Screening Mixtures of Beads (Compounds)



- Super permeable resin for organic combinatorial chemistry (SPOCC) fully compatible with organic chemistry and enzyme assays (polyether polymer)

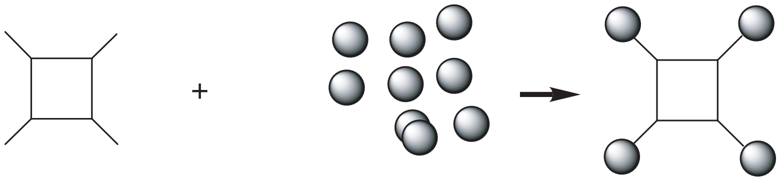
Meldal, M. *et al. J. Am. Chem. Soc.* **1999**, *121*, 5459.



- Peptide substrates contain a fluorescent dye and a quencher for use in fluorescent resonance energy transfer (FRET) assay
- Cleavage of the resin bound substrates leads to formation of strongly fluorescent beads
- Identification of active compounds by MALDI-MS of fluorescent beads

Meldal, M. *Tetrahedron Lett.* **1992**, *33*, 3077.
Meldal, M. *et al. Proc. Natl. Acad. Sci. USA* **1994**, *91*, 3314.
Meldal, M. *et al. Biochem. J.* **1997**, *323*, 427.

One-Step Mixture Synthesis and Deconvolution "Activated Core Approach"



Core molecules:
3 Tetraacid chlorides

Building blocks:
19 amino acids

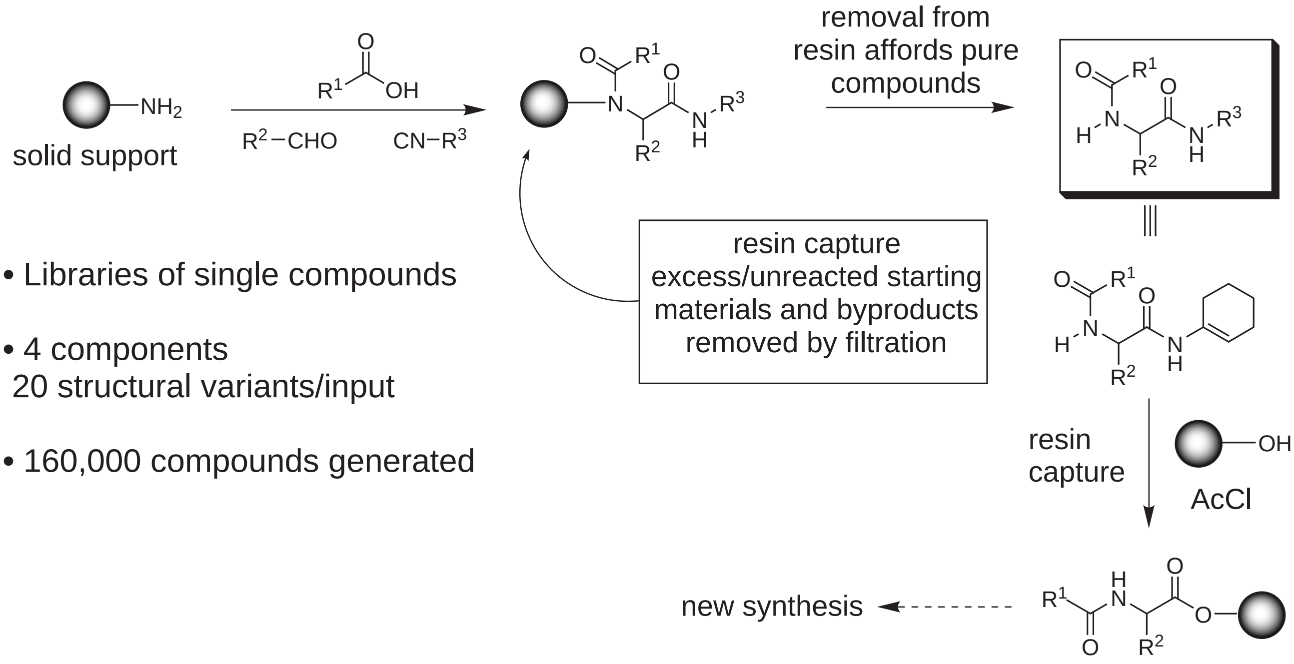
Library size:
A1: 11,191
A2: 65,341
A3: 1,330

Deconvolution by Omission Resynthesis

1. Libraries A1–A3 to find best core molecule
2. Sublibraries B1–B6 to find best 9 building block amino acids (AA)
3. Sublibraries C1–C7 to check if the selected 9 AA are the best combination
4. Sublibraries D1–D9 to find the best 5 AA
5. Sublibraries E1–E7 to find the best 3 or 4 groupings of the 5 AA
6. Sublibraries F1–F6 to find the best relative position of the 4 AA on the core
7. Single compounds G1–G3 synthesized and the best inhibitor of trypsin determined

Rebek, J. Jr., *et al. Chem. Biol*. **1995**, *2*, 171.

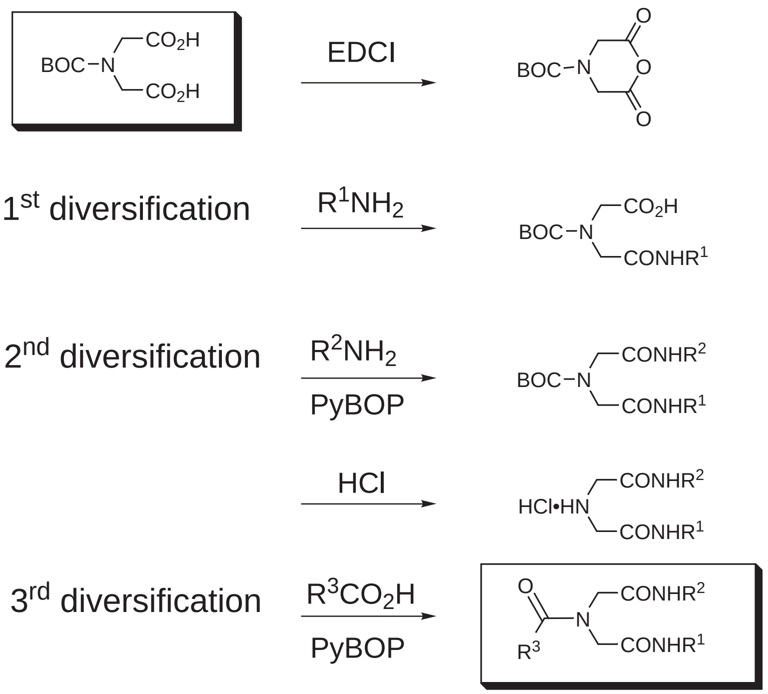
Multicomponent One-Step Mixture Synthesis



- Libraries of single compounds
- 4 components
  20 structural variants/input
- 160,000 compounds generated

Armstrong, R.W. *et al*. *Acc. Chem. Res.* **1996**, *29*, 123.
Ugi, I. *et al. Endeavour* **1994**, *18*, 115.

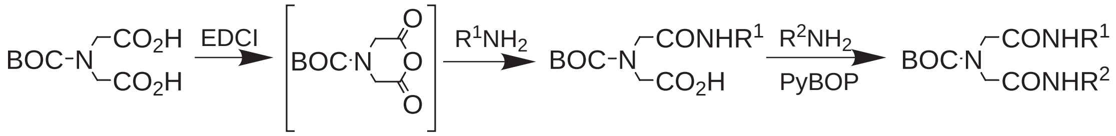
Multistep Solution Phase Synthesis of Combinatorial Libraries Purification via Liquid/Liquid or Liquid/Solid Extraction

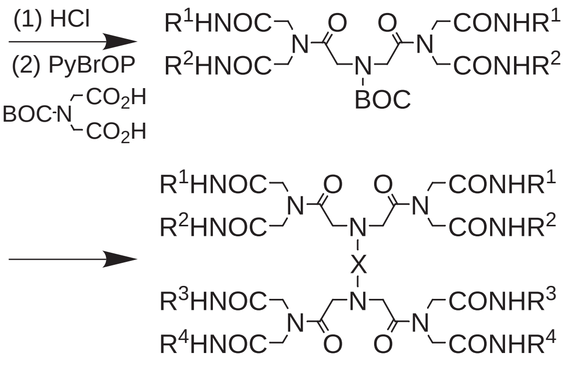


- Solvent, reagent byproducts, excess reagents and reactants removed through extraction with acid and/or base
- Liquid/solid extraction using ion exchange resins
- Products pure irrespective of yield
- 25–50 mg of products
- Multistep synthesis in format of:
  - individual compounds
  - small mixtures
  - large mixture synthesis

Boger, D. L. *et al. J. Am. Chem. Soc.* **1996**, *118*, 2567.

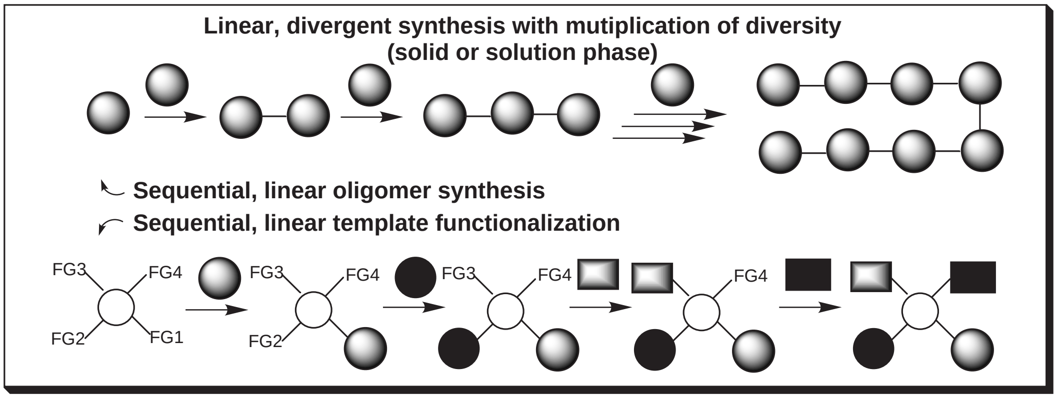
Multistep Convergent Solution Phase Combinatorial Synthesis

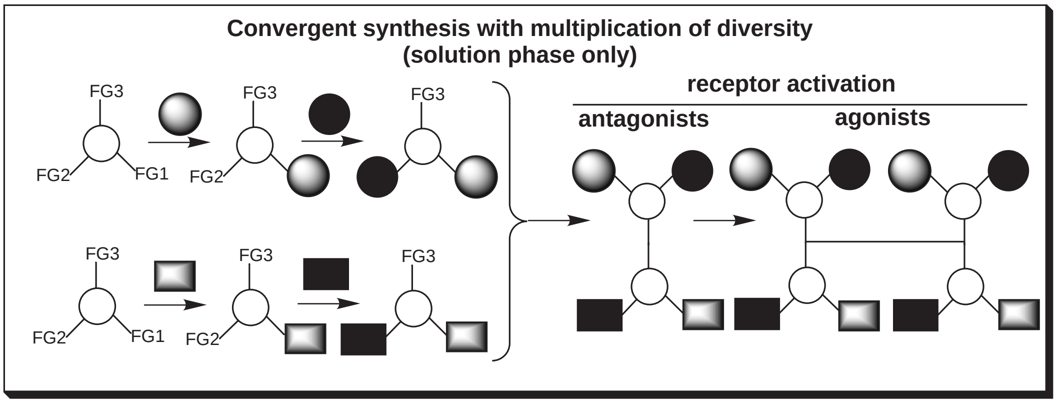




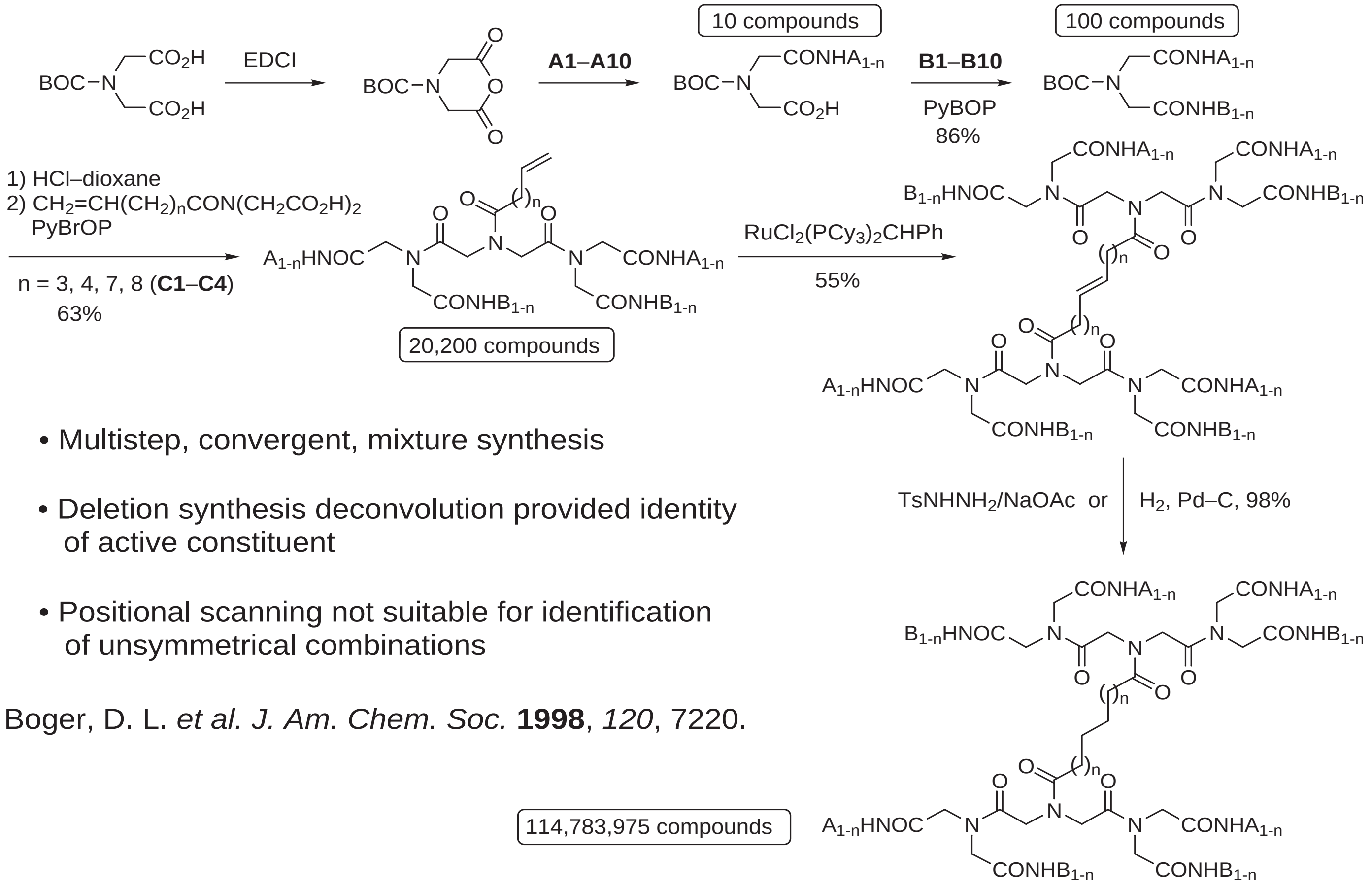
- The synthesis of large molecules is possible in only a few steps
- Purification at each step by acid/base extractions or solid/liquid extractions
- Solution phase only
- Multiplication of diversity
- Final dimerization has been achieved via peptide coupling with diacids or olefin metathesis

Boger, D. L. *et al. Tetrahedron* **1998**, *54*, 3955.
Boger, D. L. *et al. Bioorg. Med. Chem.* **1998**, *6*, 1347.





Boger, D. L. *et al. Tetrahedron* **1998,** *54*, 3955; *J. Am. Chem. Soc.* **1998**, *120*, 7220.

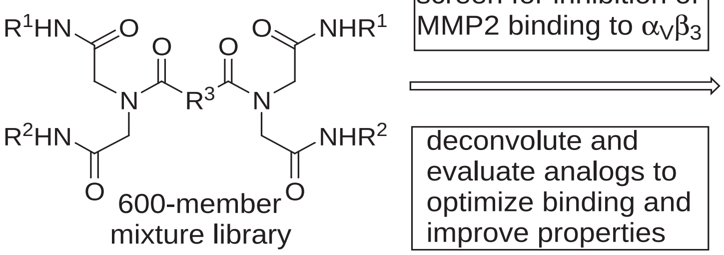


- Multistep, convergent, mixture synthesis
- Deletion synthesis deconvolution provided identity of active constituent
- Positional scanning not suitable for identification of unsymmetrical combinations

Boger, D. L. *et al. J. Am. Chem. Soc.* **1998**, *120*, 7220.

Identification of Potent Inhibitors of Angiogenesis via Inhibition of MMP2 Binding to Integrin $\alpha_V\beta_3$

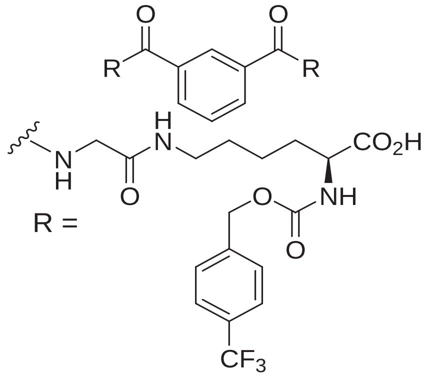
60 mixtures of 10 compounds

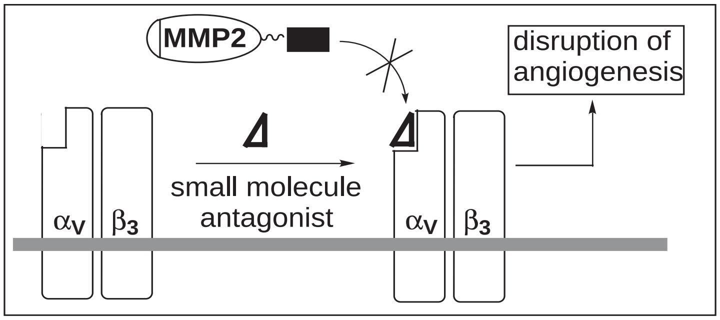


600-member mixture library

screen for inhibition of MMP2 binding to $\alpha_V\beta_3$

deconvolute and evaluate analogs to optimize binding and improve properties



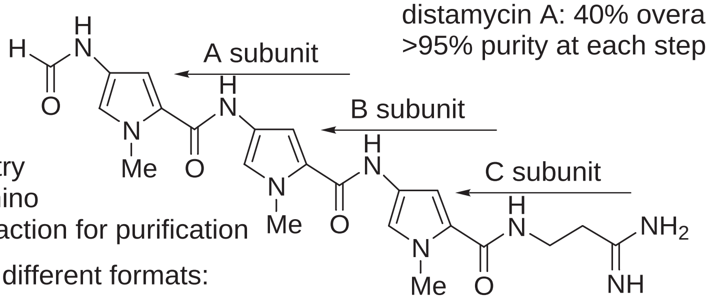


- Blocks angiogenesis and tumor growth on the chick chorioallantoic membrane (CAM) without directly inhibiting $\alpha_V\beta_3$ or MMP2

Boger, D. L. *et al*. *J. Am. Chem. Soc.* **2001**, *123*, 1280.

Application of Multistep Solution Phase Synthesis of Libraries via Liquid–Liquid and Liquid–Solid Extraction

Distamycin A: Naturally occurring polyamide composed of repeating heterocyclic amino acids and a basic side chain



8 step total synthesis of distamycin A: 40% overall
>95% purity at each step

Solution phase combinatorial chemistry using 10–12 different heterocyclic amino acids and liquid–liquid acid/base extraction for purification

Comparison of results from testing in different formats:

Small mixture libraries

1320 compounds (10 x 11 x 12)
(132 mixtures of 10 compounds each)

Large mixture scanning libraries

1000 compounds (10 x 10 x 10)
(30 scanning library mixtures of 100 compounds each)

⟹ First generation libraries of potential DNA binding agents

Derivatization of mixture libraries with a basic side-chain

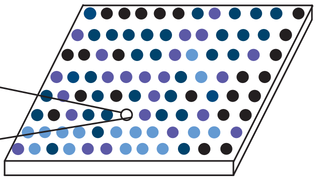
} 2640 analogs in prototype library

⟹ Second generation libraries of potential DNA binding agents with increased affinity

Boger, D. L.; Fink, B. E.; Hedrick, M. P. *J. Am. Chem. Soc.* **2000**, *122*, 6382.

Rapid, High Throughput Screen for DNA Binding Affinity and Establishment of DNA Binding Selectivity

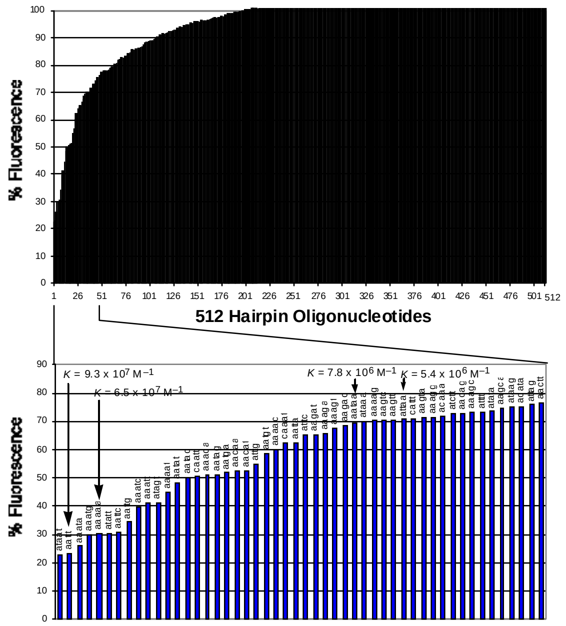
Identify compounds with affinity for single sequence of interest **or** define sequence selectivity of a compound against library of all sequences

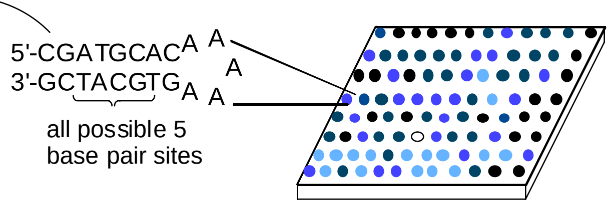


- DNA affinity is measured as a decrease in relative fluorescence indicating binding and displacement of prebound ethidium bromide
- Establish relative or absolute binding constants
- Libraries used at a single concentration during first round of testing or at several concentrations to determine binding constant
- Use of a 96-well fluorescence plate reader allows screening of 100s of libraries in a matter of minutes
- Library of compounds against a single sequence in form of hairpin oligonucleotide
- Single compound assayed against a full library of hairpin oligonucleotide sequences to establish DNA binding selectivity (Profiling DNA binding selectivity)
- Library of compounds assayed against a library of DNA sequences

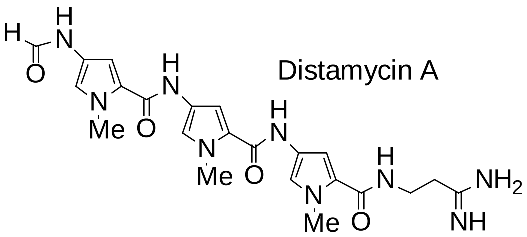
Boger, D. L.; Fink, B. E.; Hedrick, M. P. *J. Am. Chem. Soc.* **2000**, *122*, 6382.
Boger, D. L.; Fink, B. E.; Tse, W.; Hedrick, M. P. *J. Am. Chem. Soc.* **2001**, *123*, 5878.

Rapid, High Throughput Screen for DNA Binding Affinity and Establishment of DNA Binding Selectivity





- DNA affinity is measured as a decrease in relative fluorescence indicating binding and displacement of prebound ethidium bromide
- Use of a 96-well fluorescence plate reader allows screening of 100s of libraries in a matter of minutes

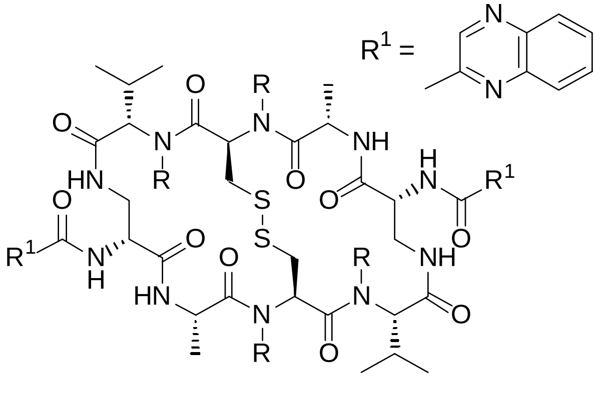


Distamycin A

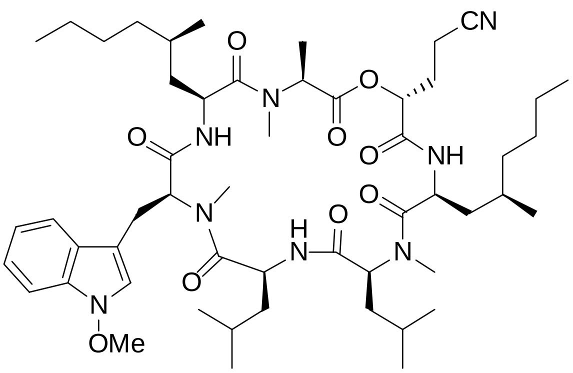
Boger, D. L.; Fink, B. E.; Hedrick, M. P. *J. Am. Chem. Soc.* **2000**, *122*, 6382.
Boger, D. L.; Fink, B. E.; Tse, W.; Hedrick, M. P. *J. Am. Chem. Soc.* **2001**, *123*, 5878.

Application of Multistep Solution Phase Synthesis of Libraries via Liquid–Liquid and Liquid–Solid Extraction

Azatriostin A: cyclic octapeptide, close analogue of the natural occurring depsipeptide Triostin A, an antitumor antibiotic which binds to DNA by bisintercalation

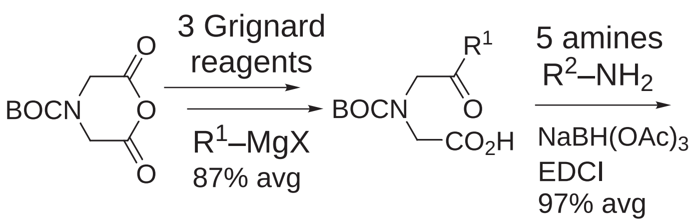


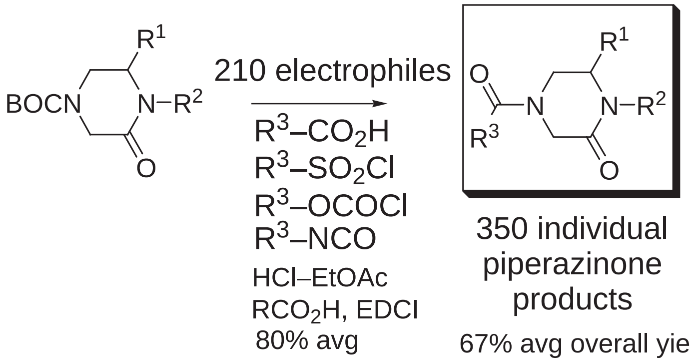
HUN-7293: cyclic heptadepsipeptide potent inhibitor of cell adhesion molecule expression exhibiting anti-inflammatory properties



Azatriostin A: Boger, D. L.; Lee, J. K. *J. Org. Chem.* **2000**, *65*, 5996.
HUN-7293: Boger, D. L.; Chen, Y. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1741.

Multistep Solution Phase Synthesis of Nonamide-Based Libraries with Purification by Liquid–Liquid Extractions

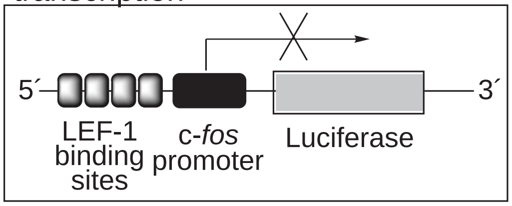




350 individual piperazinone products

67% avg overall yield, >95% pure

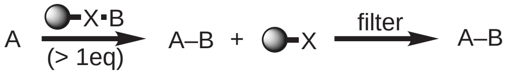
- Isolation and purification by liquid–liquid acid/base extractions
- 25–50 mg of final products
- >95% purity, irrespective of yield
- Potent inhibitors of LEF-1/β-catenin mediated gene transcription



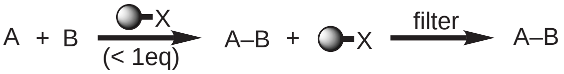
Boger, D. L. *et al. Helv. Chim. Acta*, **2000**, *83*, 1825.

Polymer-supported Scavenging Reagents

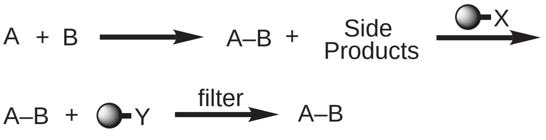
I. polymer-supported reagent



II. polymer-supported catalyst



III. polymer-supported scavenging reagent
(excess reagents, starting materials)



Reviews:
Booth, R. J.; Hodges, J. C.
Acc. Chem. Res. **1999**, *32*, 18.
Flynn, D. L.; Parlow, J. J.
Curr. Opin. Drug Discovery Dev. **1998**, *1*, 41.

- Addresses the purification problem in solution phase synthesis
- Entrain impurities upon completion of solution-phase reactions, either covalently or ionically
- Covalent scavengers: nucleophile–electrophile
- Ionic scavengers: a series of anion and cation exchange resins (liquid–solid extraction)

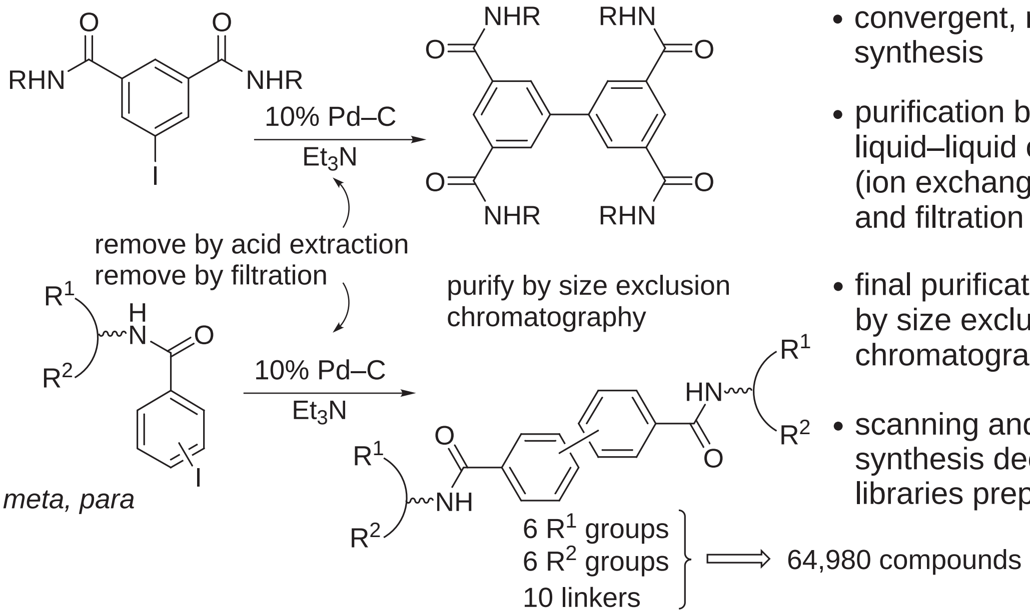
Boger, D. L. *et al*. *J. Am. Chem. Soc*. **1996,** *118*, 2567.

Flynn, D. L. *et al. J. Am. Chem. Soc.* **1997,** *119,* 4874.

Hodges, J. C. *et al*. *J. Am. Chem. Soc*. **1997**, *119*, 4882.

Kaldor, S. W. *et al*. *Tetrahedron Lett*. **1996**, *37*, 7193.

Solution Phase Combinatorial Synthesis of Biaryl Libraries Employing Heterogeneous Conditions for Catalysis and Isolation

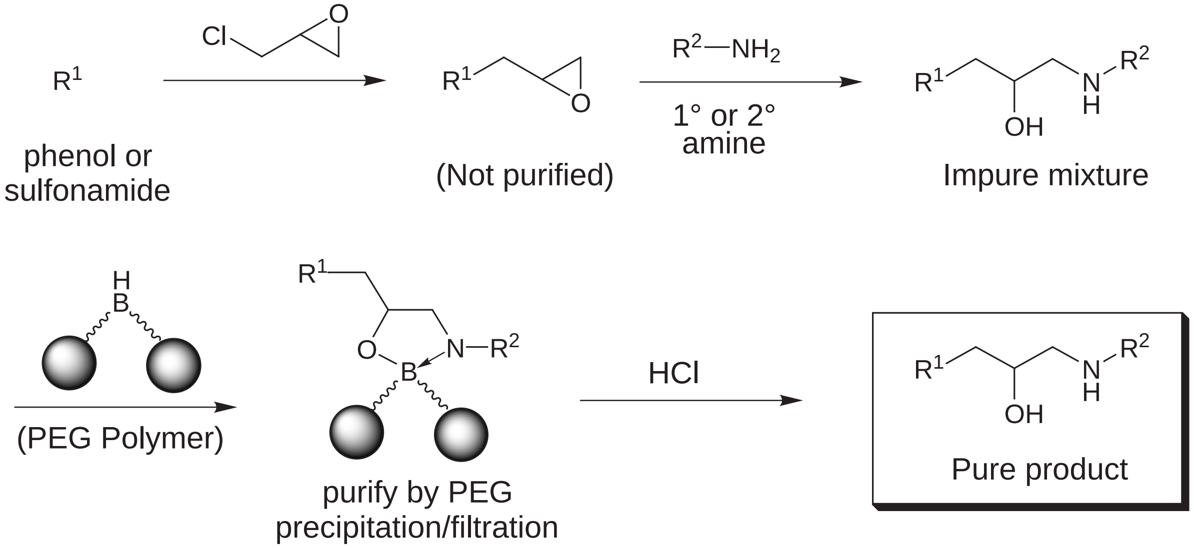


- convergent, mixture synthesis
- purification by acid/base liquid–liquid or liquid–solid (ion exchange) extractions and filtration of catalyst
- final purification possible by size exclusion chromatography
- scanning and deletion synthesis deconvolution libraries prepared

Boger, D. L.; Jiang, W.; Goldberg, J. *J. Org. Chem.* **1999**, *64*, 7094.
Boger, D. L.; Goldberg, J.; Andersson, C.-M. *J. Org. Chem.* **1999**, *64*, 2422.

Resin Capture of Product ("Fishing Out" Principle)

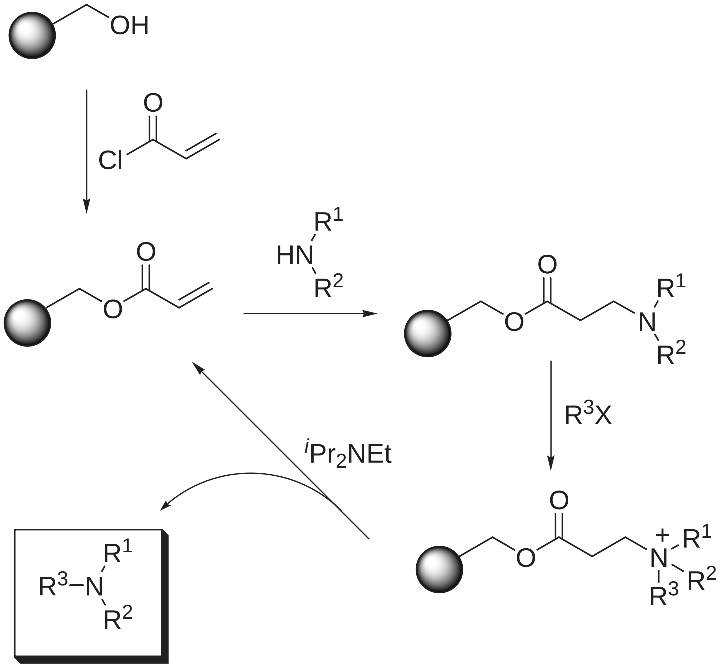
- Libraries of β-amino alcohols are synthesized by parallel synthesis in solution
- Purification is achieved by "fishing out" the desired products with a PEG-bound dialkylborane
- Precipitation of the polymer-bound product allows the removal of unreacted starting materials and any byproducts
- Treatment with HCl releases the product from the polymer support in high purity



Janda, K. D. *et al. J. Org. Chem.* **1998**, *63*, 889.

Ugi reaction with polymer bound carboxylic acid: Armstrong, R. W. *Tetrahedron Lett.* **1996**, *37,* 1149.

Resin Release Only of Product



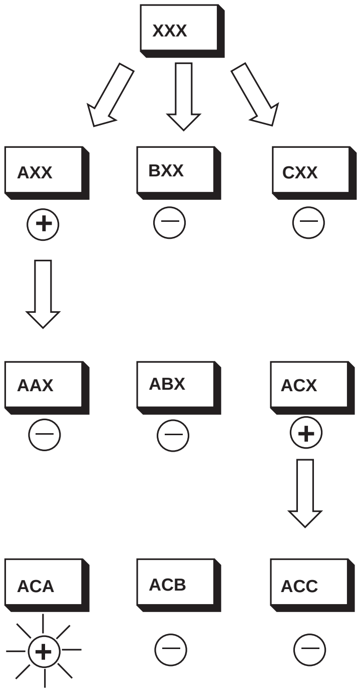
- A wide range of 3° amines can be synthesized on solid support
- The product is released via β-elimination
- Only the activated (quaternary) product is released, ensuring purities >95%
- After cleavage of product, the resin is regenerated and can be reused

Morphy, J. R. *et al. J. Am. Chem. Soc.* **1997**, *119*, 3288.

Iterative Deconvolution

SURF Deconvolution

(Synthetic Unrandomization of Randomized Fragments)

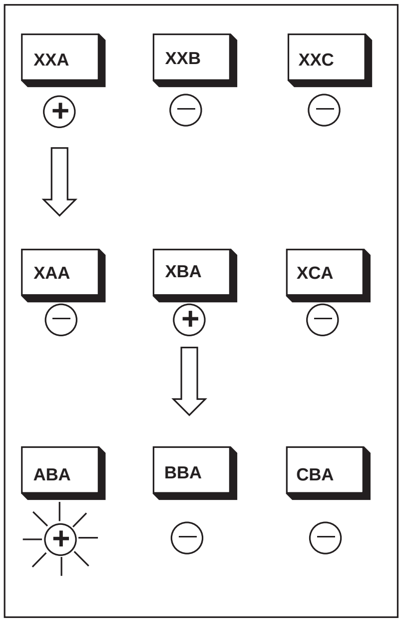


- Iterative deconvolution was first applied to peptide libraries
- The SURF procedure was described for nucleotide libraries
- Libraries are synthesized on solid phase by split synthesis
- Repetitive synthesis and screening of increasingly simplified sets
- At each step of the deconvolution an additional position is known
- Activity increases at each step, enhancing the accuracy of identification
- Most potent library member guaranteed to be found and multiple hits lead to multiple parallel deconvolutions
- Time between synthesis of libraries and hit identity long and cumbersome

Houghten, R. A. *et al. Nature* **1991**, *354*, 84.
Ecker, D. J. *et al. Nucleic Acids Res.* **1993, *21*,** 1853.

Recursive Deconvolution

- The library (XXX) is synthesized by split synthesis
- At each stage 1/3 of the material is stored and labeled as a partial library
- These stored partial libraries are used to deconvolute the full library



Test 3 pools for activity

Couple **A** to saved and catalogued **XA**, **XB**, and **XC**

Test 3 pools for activity

Couple **BA** to saved and catalogued **A**, **B** and **C**

Test 3 pools for activity

Janda, K. D. *et al*. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 11422.

Positional Scanning of Synthetic Peptide Combinatorial Libraries

- Deconvolution libraries produced upfront for testing
- Identifies most active residue at each position in one round of testing
- Screen looking for increases in activity
- This combination is not always the most potent (ca. 20–40% of time)
- Best for identifying multiple hits in a library including weak activities
- Requires mixture synthesis, not suited for solid phase

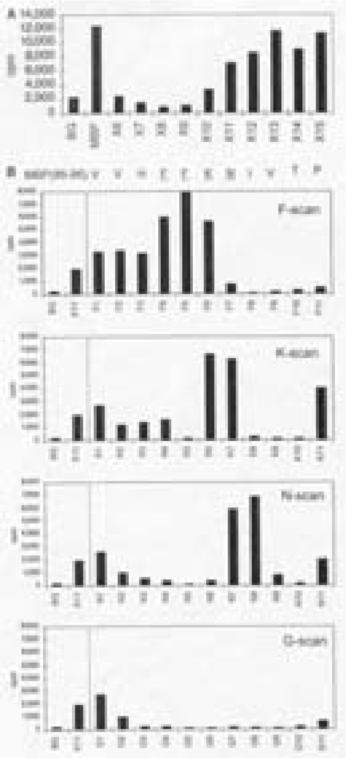
O1	**X**	**X**	**X**	**X**	**X-NH$_2$**
X	**O2**	**X**	**X**	**X**	**X-NH$_2$**
X	**X**	**O3**	**X**	**X**	**X-NH$_2$**
X	**X**	**X**	**O4**	**X**	**X-NH$_2$**
X	**X**	**X**	**X**	**O5**	**X-NH$_2$**
X	**X**	**X**	**X**	**X**	**O6-NH$_2$**

O = individual component

X = mixture

Houghten, R. A. *et al*. *Nature* **1991,** *354,* 84.

Scanning Deconvolution Applications



Proliferative response of TL 5G7 to
MBP and scanning peptide libraries

A: the response to a sizing scan with completely randomized libraries ranging in length from 6 to 15 amino acids

B: the response to peptide sublibraries with fixed amino acid in position 1 to 11 phenylalanine (*F*), lysine (*K*), asparagine (*N*), or glycine (*G*)

- Mixture analysis so the number of compounds assayed can be very large
- Identified single peptides 10^4–10^5x more active than well known natural autoantigen

Hemmer, B. *et al. J. Exp. Med.* **1997**, *185*, 1651. (Multiple sclerosis)
Hemmer, B. *et al. Nature Med.* **1999**, *5*, 1375. (Lyme disease)

Deletion Synthesis Deconvolution

- Deconvolution libraries produced upfront for testing
- Identifies most active residues at each position in one round of testing
- Screen library for loss of activity versus full mixture
- Best at identifying potent hits in a library, poor at identifying weak or multiple hits
- Requires mixture synthesis, not suited for solid phase
- Also suited for symmetrical libraries not capable of being addressed by scanning deconvolution

dA1	**X**	**X**	**X**
dA2	**X**	**X**	**X**
dA3	**X**	**X**	**X**
dA4	**X**	**X**	**X**

X	**X**	**dC1**	**X**
X	**X**	**dC2**	**X**
X	**X**	**dC3**	**X**
X	**X**	**dC4**	**X**

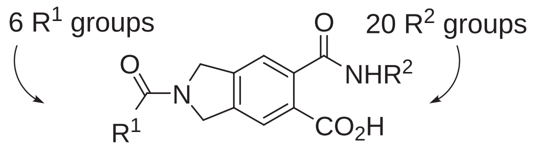
X	**dB1**	**X**	**X**
X	**dB2**	**X**	**X**
X	**dB3**	**X**	**X**
X	**dB4**	**X**	**X**

X	**X**	**X**	**dD1**
X	**X**	**X**	**dD2**
X	**X**	**X**	**dD3**
X	**X**	**X**	**dD4**

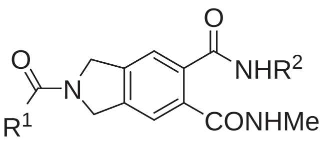
dA1 = mixture minus A1 (delete A1)
X = mixture

Boger, D. L. *et al*. *J. Am. Chem. Soc.* **1998**, *120,* 7220.

Test Case Comparisons of Scanning and Deletion Synthesis Deconvolution



Library 1 (120 compounds)



Library 2 (120 compounds)

- Each individual compound and the scanning and deletion deconvolution sublibraries were prepared and tested side by side to establish which would identify the newly discovered leads

Cytotoxic Activity (L-1210 IC_{50}) of Mixture, Scanning, and Deletion Deconvolution Sublibraries

scanning deconvolution	deletion deconvolution	scanning deconvolution	deletion deconvolution
A5 — **B7** B13 B17	**A4** — **B7** B13	**A5** **B17**	**A5** — B6 B14 **B17**
6 and 20 compd mix gain in activity			100 and 114 compd mix loss in activity

Cytotoxic Activity (IC_{50}, μM) for Individual Compounds

	B7	B13	B17
A4	**5**	26	25
A5	>100	19	28

	B6	B14	**B17**
A5	44	71	**5**

- Deletion synthesis more effective at identifying most potent compound in library
- Scanning deconvolution more sensitive and capable of identifying weak activities
- Combination more powerful than either technique alone

Boger, D. L.; Lee, J. K.; Goldberg, J.; Jin, Q. *J. Org. Chem.* **2000**, *65*, 1467.

Assay and Deconvolution by Mass Spectrometry

Target-assisted isolation of mixture components

Separation of target–ligand complex by:
- size exclusion chromatography
- ultrafiltration
- capillary electrophoresis
- affinity chromatography

Identification of the bound ligand after dissociation of the complex by:
- ESI-MS: exceptional ability to detect ions present in solution with little fragmentation
- MALDI-MS: advantages over ESI-MS are its tolerance against impurities, buffer salts and formation of primarily singly charged ions

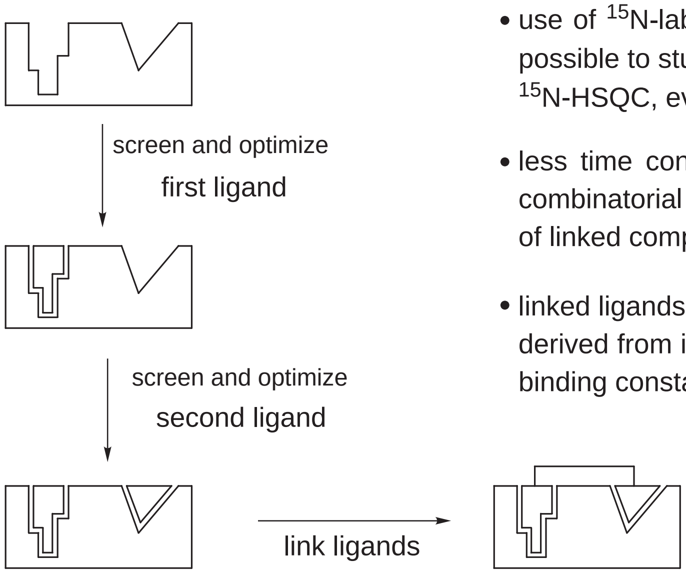
- Analysis of mixtures, so numbers of compounds evaluated can be large

Direct detection and identification of target–ligand complexes

Study of intact non-covalent complexes is possible by FTICR-MS (FTICR: Fourier Transform Ion Cyclotron Resonance). Advantages of FTICR-MS are its high sensitivity due to the accumulation of certain ions in the trap that allows the study of minor mixture components

Review: Eliseev, A. V. *Curr. Opin. Drug Discovery Dev.* **1998**, *1*, 106.

Active Protein-Binding Compounds Through SAR by NMR



- use of ^{15}N-labeled target proteins makes it possible to study the ligand–protein complex by ^{15}N-HSQC, even at high ligand concentrations
- less time consuming compared to the combinatorial approach where a large number of linked compounds have to be synthesized.
- linked ligands with nano molar binding constants derived from individual ligands with micro molar binding constants

Shuker, S. B.; Hajduk, P. J.; Meadows, R. P.; Fesik, S. W. *Science* **1996**, *274*, 1531.

Assay and Deconvolution by NMR

Direct detection and identification of target– ligand complexes (detect bound ligand)

Diffusion encoded spectroscopy (DECODES): combination of pulse field gradient (PFG) NMR and total correlation spectroscopy (TOCSY).
Under PFG conditions, all resonances of low molecular weight ligands disappear from spectrum while signals of target-bound ligand remain. Approach is only applicable for low molecular weight molecules (200–400 Da) as targets and ligands.

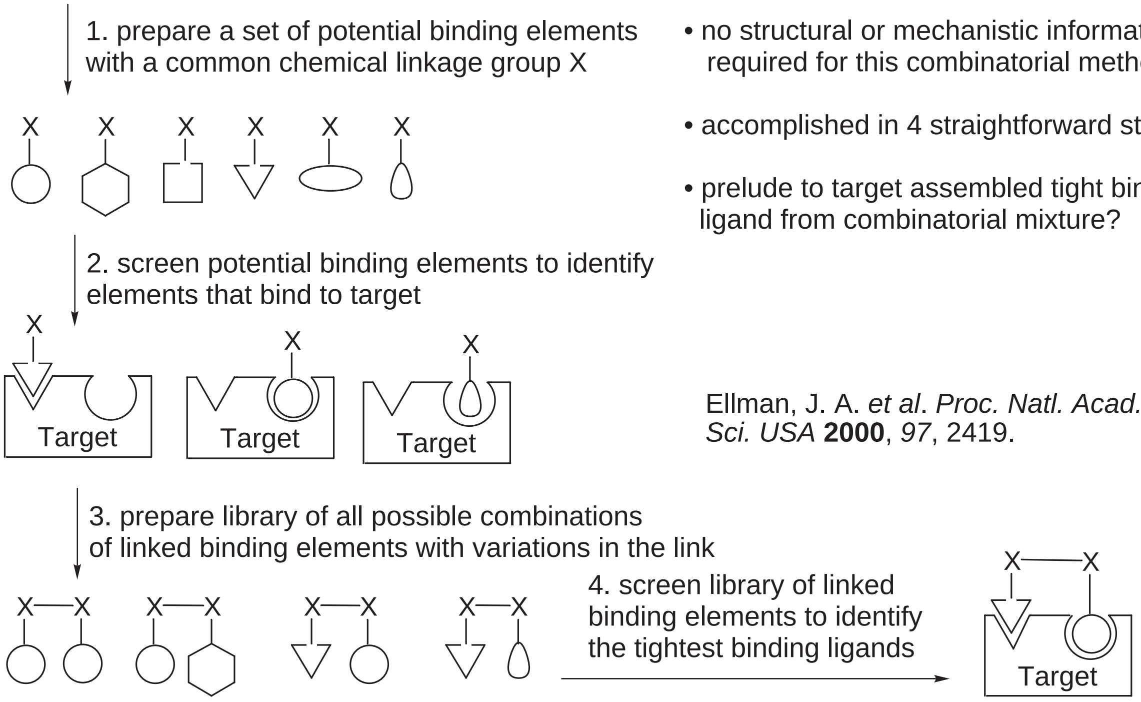
Lin, M.; Shapiro, M. J.; Wareing, J. R. *J. Am. Chem. Soc.* **1997**, *119*, 5249.

Indirect detection and identification of target– ligand complexes (detect unbound ligands)

1D relaxation edited NMR and 1D difusion edited NMR:
Difference spectrum of the 1D edited library-, protein- and mixture of protein with library-spectrum contains only signals from the bound ligand.
There is no need for deconvolution of the library to identify active compounds.
By removing the signals of the biomolecule there is no broadening or obscuring of the ligand's signals by the macromolecule.

Hajduk, P. J.; Olejniczak, E. T.; Fesik, S. W. *J. Am. Chem. Soc.* **1997**, *119*, 12257.

Combinatorial Target-Guided Ligand Assembly



1. prepare a set of potential binding elements with a common chemical linkage group X

2. screen potential binding elements to identify elements that bind to target

3. prepare library of all possible combinations of linked binding elements with variations in the link

4. screen library of linked binding elements to identify the tightest binding ligands

- no structural or mechanistic information required for this combinatorial method
- accomplished in 4 straightforward steps
- prelude to target assembled tight binding ligand from combinatorial mixture?

Ellman, J. A. *et al*. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 2419.

Solid Phase or Solution Phase Combinatorial Synthesis?

Solid Phase

+ Simple removal of excess reagents and reactants
+ Automation straightforward
+ Split and mix synthesis
+ Pseudo-dilution effects

– Adapt chemistry to solid phase and develop linking/cleaving strategies
– Reaction monitoring difficult
– No purification possible
– Linear, cannot conduct convergent synthesis
– Limited scale
– Cannot conduct mixture synthesis

Solution Phase

+ Chemistry not limited by support or linker
+ Monitor by traditional techniques
+ Purification possible after each step
+ Unlimited amounts (scales) available
+ Avoids extra steps for linking, etc
+ Automation by liquid–liquid techniques
+ Mixture or parallel synthesis
+ Convergent or linear synthesis

– Removal of excess reagents and reactants limits scope

Combinatorial Synthesis Using Soluble Polymers

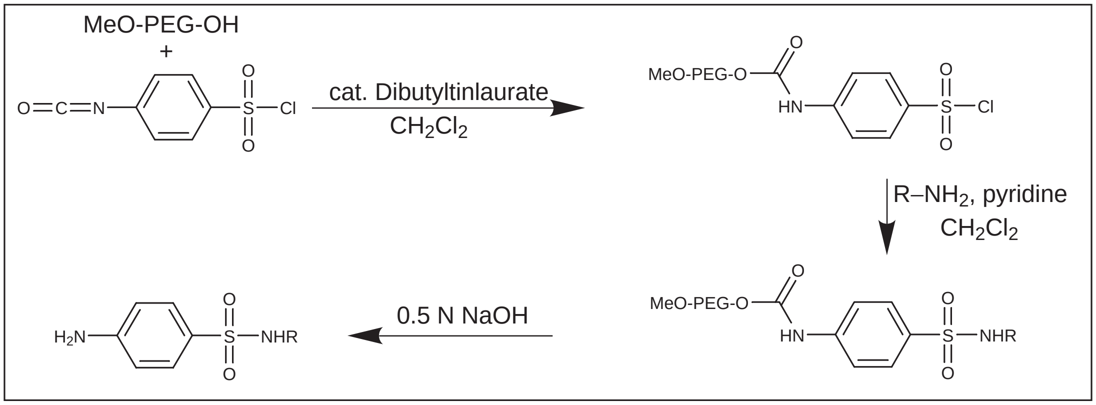
- Reactions were performed in the homogeneous liquid-phase solution using a soluble polymer (MeO-PEG: polyethylene glycol monomethyl ether)

- Homogeneous reaction conditions overcome the difficulties of solid-phase combinatorial synthesis

- Isolation can be accomplished by precipitation of PEG polymer at each stage

- Intermediates can also be purified by conventional means (*e.g.* chromatography)

- Analysis of intermediates is possible by conventional means (*e.g.* NMR)



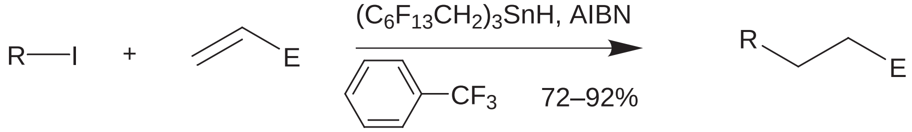
Janda, K. D. *et al. Proc. Natl. Acad. Sci. USA* **1995,** *92,* 6419.
Review: Janda, K. D. *et al. Chem. Rev.* **1997,** *97,* 489.

Fluorous-phase Combinatorial Synthesis

- Fluorous liquids: Immiscible in both water and organic solvents
- Simple purification of products by three-phase liquid–liquid extraction
- Accomplishment of a series of radical additions by homogeneous fluorous-phase combinatorial synthesis

Early applications of fluorous bound substrate included
- Ugi reaction • Biginelli reaction • Stille coupling
- Solid-phase extraction with fluorous reverse-phase silica gel
  Curran, D. P.; Luo, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9069.

Reagents on fluorous phase or
Substrates on fluorous phase



$$PhCO_2C_3H_7 + PhCH_2OH \xrightarrow{\text{Fluorinert Fluid F-77}} PhCO_2CH_2Ph + C_3H_7OH$$

$$C_8H_{17}CH{=}CH_2 + CO \xrightarrow[\substack{C_6H_{13}CH_2CH_2CF_3)_3P \\ Rh(CO)_2(acac)}]{tol/c\text{-}C_6H_{11}CF_3} C_8H_{17}CH(CHO)CH_3 + C_{10}H_{21}CHO$$

Curran, D. P. *et al. J. Am. Chem. Soc.* **1996,** *118*, 2531; *Chemtracts, Org. Chem.* **1996,** *9,* 75.
Science **1997**, *275*, 823; *Angew. Chem. Int. Ed.* **1998**, *37*, 1174.

A Combinatorial Approach to Materials Discovery

Application of the combinatorial approach to the discovery of new solid-state materials with novel physical or chemical properties such as magnetoresistance or high-temperature superconductance.

Substrates: polished MgO or $LaAlO_3$ single crystals

Sputtering Targets: CuO, Bi_2O_3, CaO_3, PbO, $SrCO_3$, Y_2O_3, and $BaCO_3$

Generation of a 128-member binary library using 7 deposition-masking steps

Superconducting materials: $BiSrCaCuO_x$ and $YBa_2Cu_3O_x$

(Binary masks used for library synthesis)

Schultz, P. G. *et al*. *Science* **1995**, *268*, 1738.

Comparison of Combinatorial Chemistry Techniques

Technique	Single compound /mixture	Speed of synthesis	SAR retrieval	Utility
parallel synthesis	single	slow	fast	lead optimization
mixture synthesis (scanning/deletion deconvolution)	mixture	fast	slow (fast)	lead identification
parallel arrayed mixture	mixture	moderate	moderate	lead identification
split and mix	mixture (one compound per bead)	moderate	slow	lead identification lead optimization
chemically encoded mix and split	mixture (one compound per bead)	moderate	moderate	lead identification lead optimization
mix and sort (microreactors)	single	moderate	fast	lead optimization lead identification

Guiles, J. W. *et al. Angew. Chem. Int. Ed.* **1998**, *37,* 926.