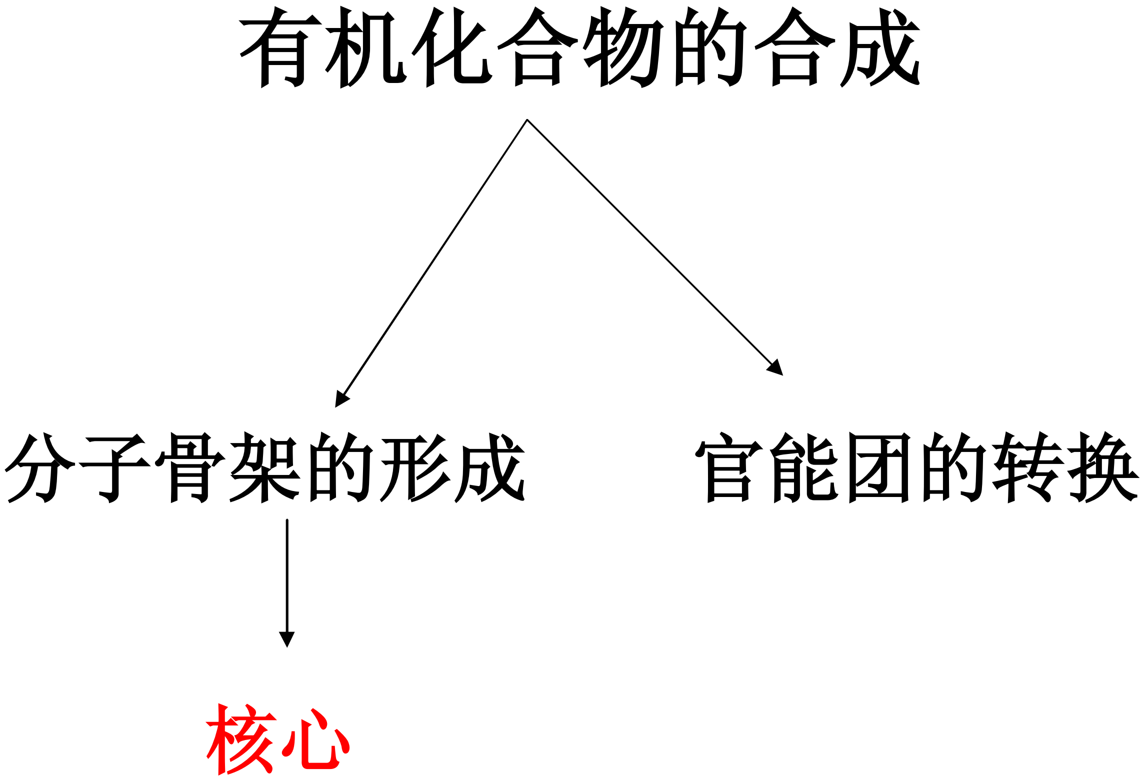
第六章 碳碳键的形成



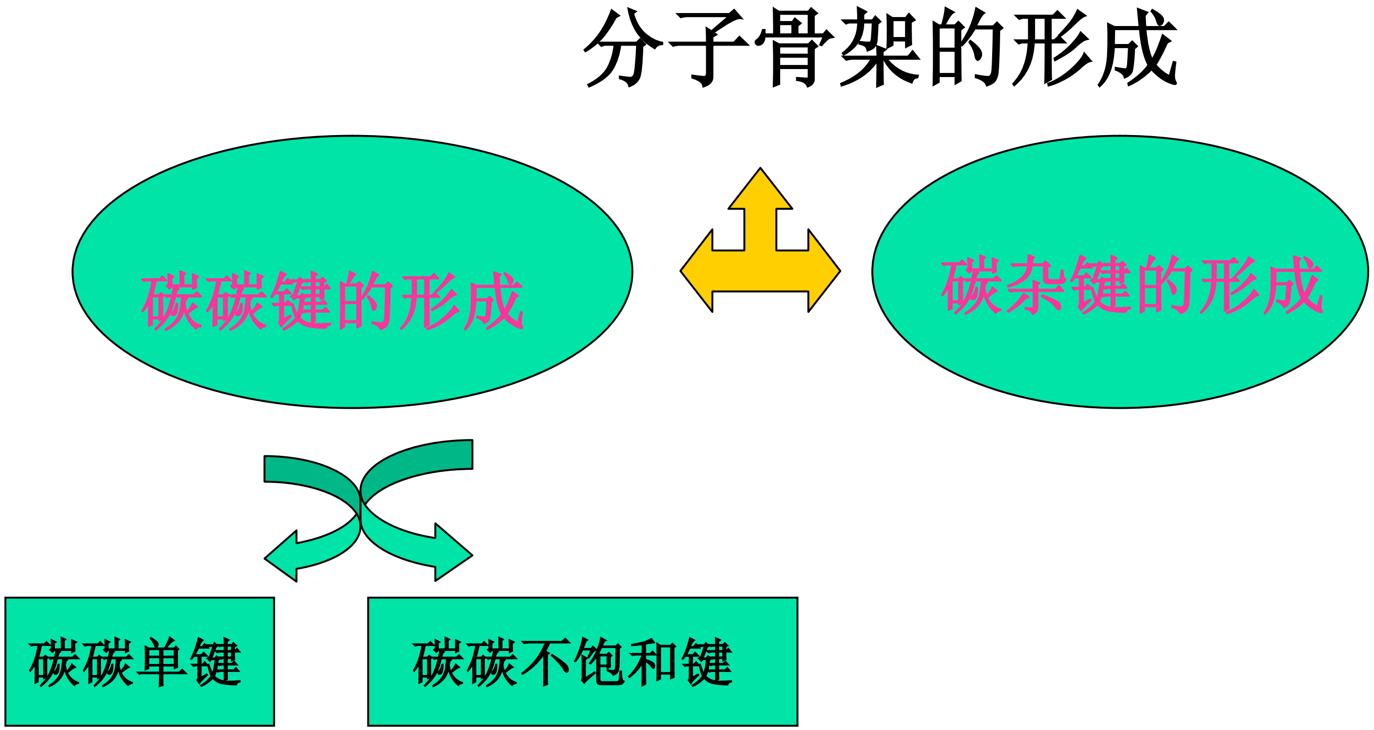
有机化合物的合成

分子骨架的形成

官能团的转换

核心

分子骨架的形成



分子骨架的形成

碳碳键的形成

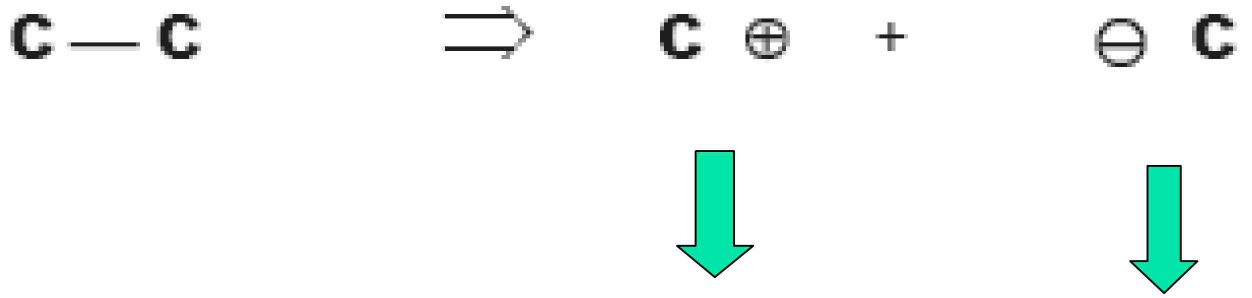
碳杂键的形成

碳碳单键

碳碳不饱和键

C-C bond formation

1. Enolate Alkylations

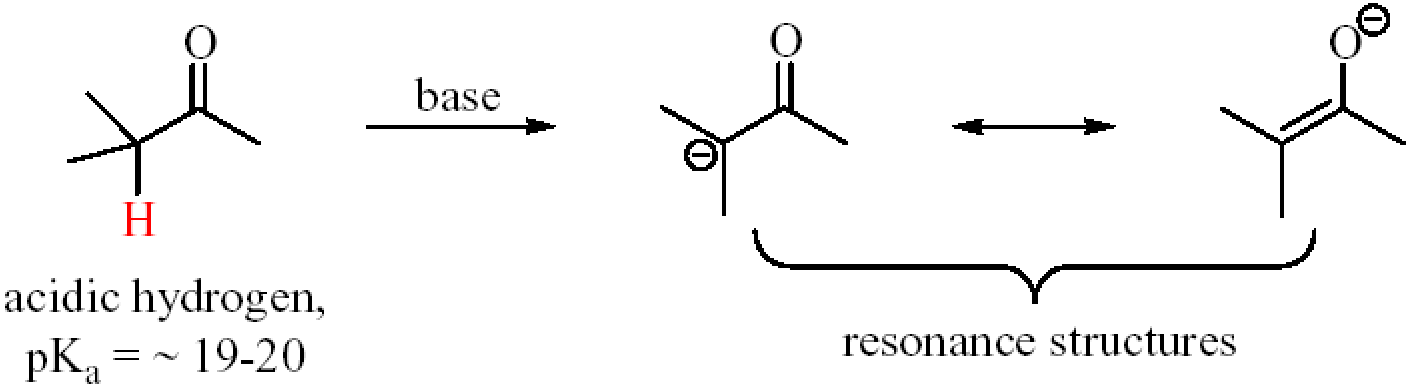


$$C-C \Rightarrow C^{\oplus} + {}^{\ominus}C$$

carbocation　　carbanion

Basic Information

- **The carbonyl group of an aldehyde or a ketone is an electron-withdrawing group by both induction and resonance. So α-hydrogens to the group possess increased acidity simply due to their proximity and the incipient anion can be stabilized through π - resonance with the carbonyl group.**

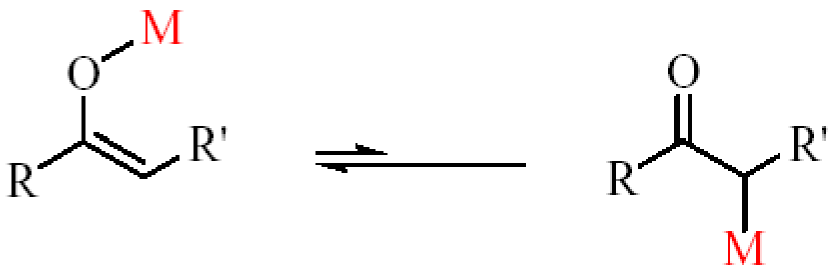


acidic hydrogen, $pK_a = \sim 19\text{-}20$

resonance structures

Basic Information

Metal Tautomerism



For alkali metal enolates (M = Li, Na, K, etc.) alkaline earth enolates (Mg^{2+}etc.), the O-metal tautormer is strongly favored. These are the generally useful enolate nucleophiles.

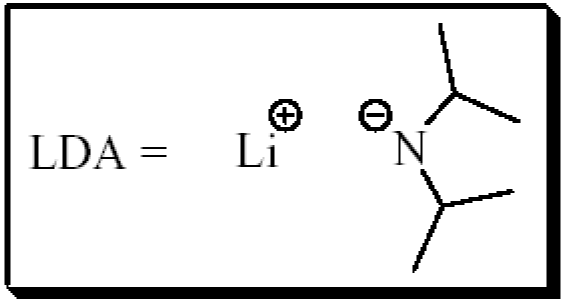
For certain metal enolates from heavy metals, such as M= Hg^{2+}, the C-metal tautomer is sometimes favored.

Basic Information

Bases suitable for deprotonation of an aldehyde or ketone must meet two principal requirements:

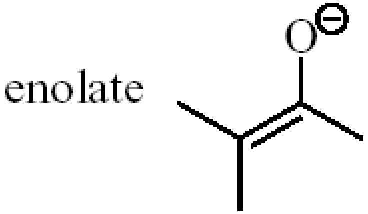
(a) Any base whose conjugate acid has a pK_a greater than 20 will be suitable. Sometimes a weaker base will work, but the reaction must proceed under equilibrium deprotonation conditions.

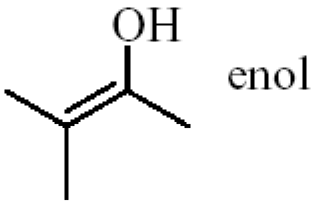
(b) Best using non-nucleophilic and sterically hindered base. LDA, lithium diisopropylamide is often the base of choice.



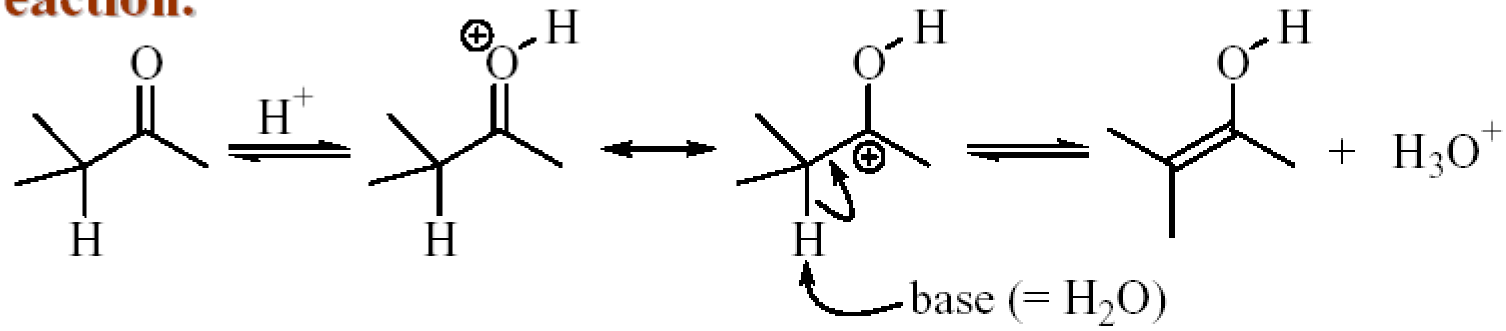
Basic Information

- The resonance-stabilized anion that results from these deprotonation reactions is called an enolate, which means that it is the anion of an acid called an enol.





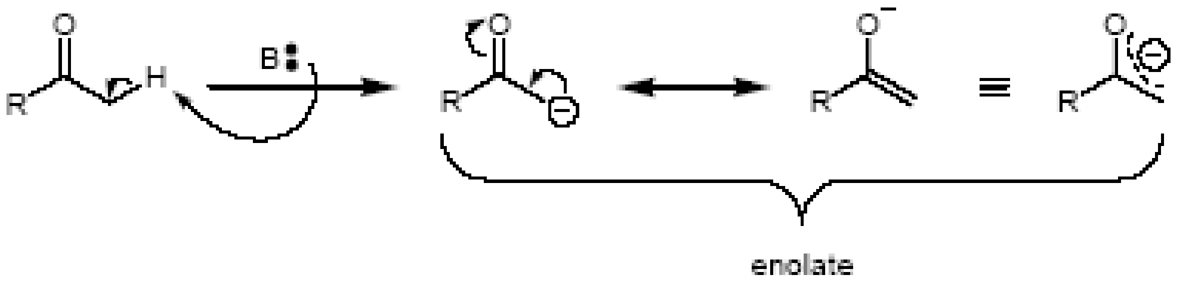
Enols can be generated through a reversible acid catalyzed reaction.



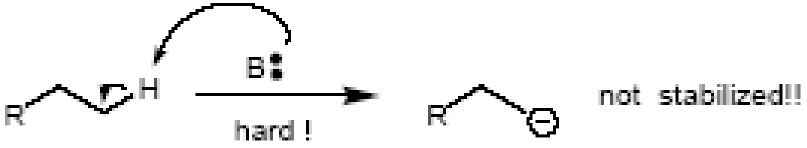
H is much more acidic since the protonated carbonyl is much better electron sink

What is carbanion?

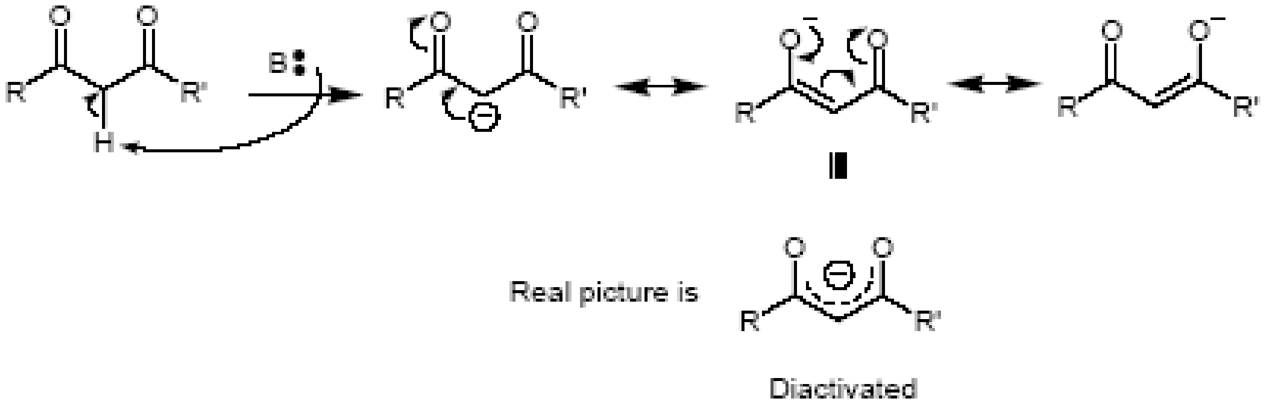
Enolate: stabilized



Compared to



If one C=O group helps to stabilize a carbanion, then 2 C=O help to stabilize even more:



> 2 electron-withdrawing sites where minus charge can be distributed.

> more resonance structures for the carbanion can be drawn.

The *pKa* of the carban acid

Compounds	*pKa*	Compounds	*pKa*
Cyclohexane	**45**	**Ethanol**	**17**
Ethane	**42**	**Cyclohexanone**	**17**
Benzene	**37**	H_2O	**16**
Sodium hydride(NaH)	**37**	$EtO_2CCH_2CO_2Et$	**13**
Ethylene (ethane)	**36**	$EtO_2SCH_2SO_2Et$	**12**
Et_2NH	**36**	$CH_3COCH_2CO_2Et$	**11**
Toluene	**35**	$R_3NH^+Cl^-$	**10**
Ph_3CH	**28**	$CH_3COCH_2COCH_3$	**9**
Ethyne	**25**	CH_3NO_2	**8.6**
CH_3CN, CH_3CO_2Et	**25**	CH_3CO_2H	**5**
Acetone	**20**	**Py.HCl**	**5**
$(CH_3)_3COH$	**19**		

$pKa = -\log Ka = -\log [H^+]$

Decrease in *pKa* means increase in $[H^+]$ and acidity

Increase in *pKa* means decrease in $[H^+]$ and acidity

1. **Note which functional groups are carbanion stabilizing groups (electron-withdrawing groups EWG): $-CN$, $-CO_2R$, $-COR$, $-NO_2$, $-SO_2R$;**
2. **Note the additivity of stabilizing effects, eg. Ph3CH is more acidic than $PhCH_3$;**
3. **Note their strengths of activation:**

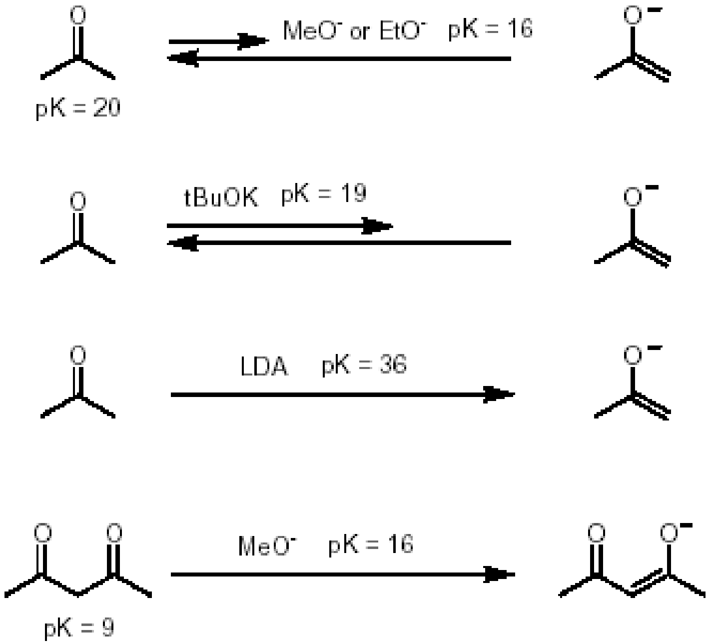
$-NO_2 > -COR > -COOR > -SO_2Ph > -CN > -CONH_2 > -Ph \sim -X > -H > -R$

4. **Note which bases are strong or weak, and which are necessary for deprotonations.**

n-BuLi > LDA > $NaNH_2$ > NaH > t-BuOK > EtONa > NaOH ~ NaOMe > Et_3N

**Note that deprotonation reactions are EQUILIBRIA:

ie.



Weak bases mean that both the protonated (ketone) and deprotonated (enolate) coexist in the reaction.

Strong bases mean that the equilibrium is very far to the right, hence the reaction contains essentially all enolate.

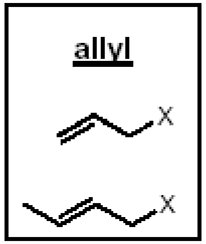
What is carbocation?

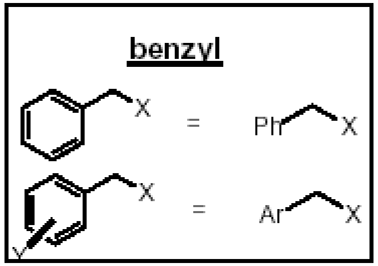
>> $C^{\oplus} \approx R-X$, where X is a halide, ie. the class of alkyl halides .

Attack of enolate C^- on R-X is an S_N2 substitution.

For good S_N2 substitutions , R= methyl, primary > secondary >>tertiary

R= primary,





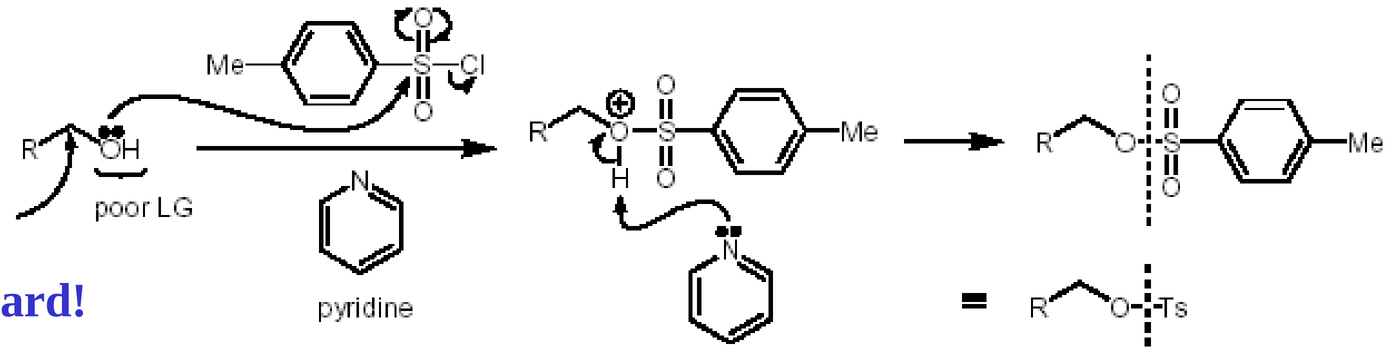
are particularly reactive

For good S_N2 substitutions, good leaving group ability is where X= $I^- > Br^- > Cl^-$

2. Similar to R-X is the class of ROH where the hydroxyl group is activated:

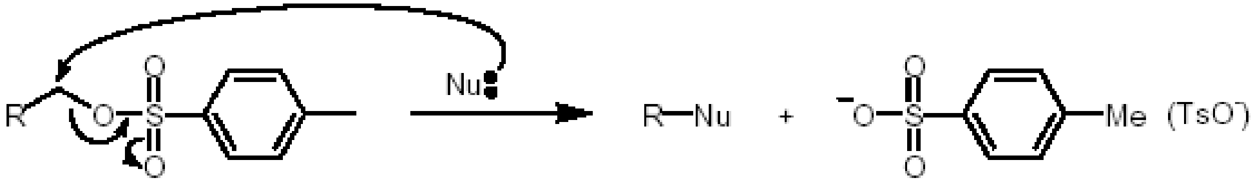
OH^- is not really a good LG. But:

ACTIVATION:

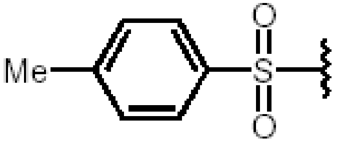


S_N2 is hard!

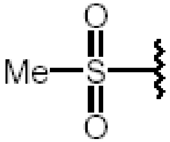
SUBSTITUTION:



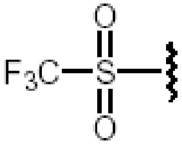
- Now, the substitution proceeds well.



≡ p-toluenesulfonyl or "tosyl" Ts; TsO$^-$ ≡ tosylate

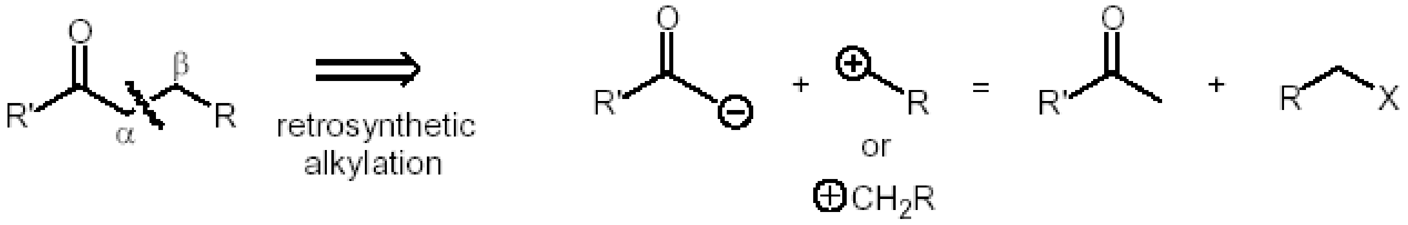


≡ methanesulfonyl or "mesyl" Ms; MsO$^-$ ≡ mesylate



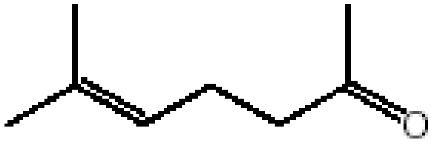
≡ trifluoromethanesulfonyl or "triflic" Tf; TfO$^-$ ≡ triflate

ℜ! An α–R group (especially when R is a good alkylating group such as allyl, benzyl, methyl…) is a synthon for an alkylation. Disconnection is at the α–β bond.

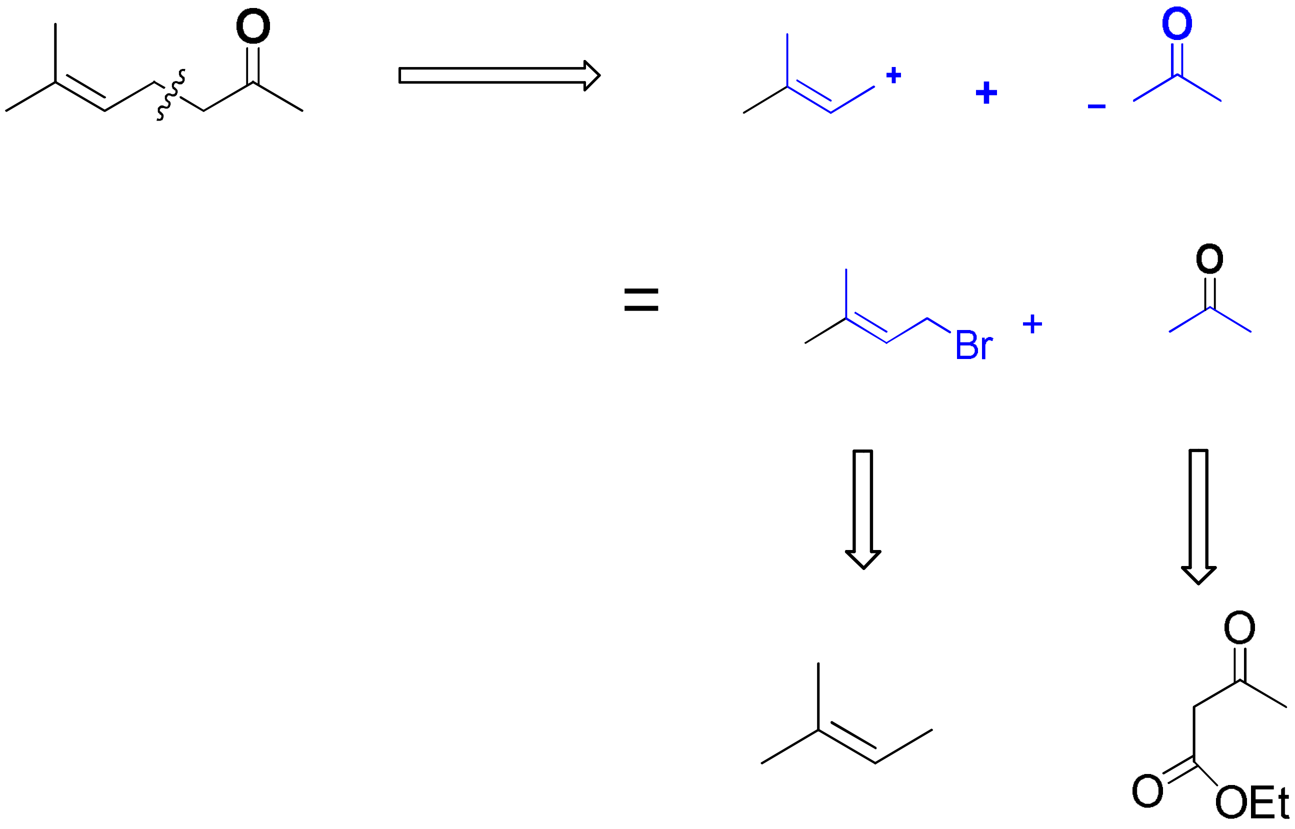


i.e. you can make more complex ketones from simple ketones

Example: Synthesize the following target molecule, showing your retroanalysis and detailed forward synthesis:



Retroanalysis:

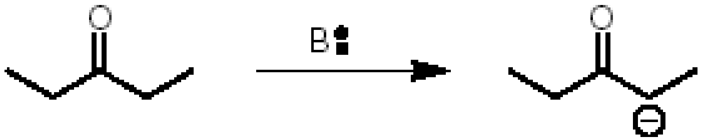


B: A More In-Depth Look at Enolate alkylation:

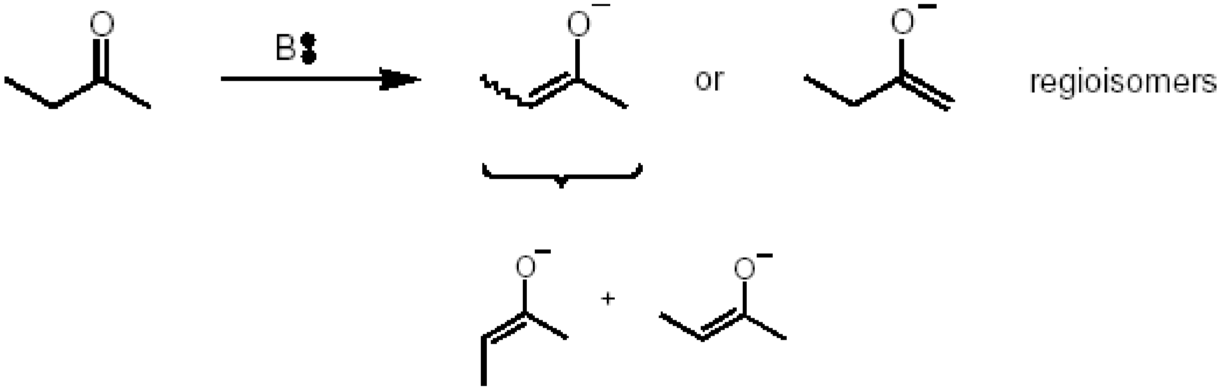
Regiochemistry in Enolate Formation:

Enolate regioisomers: when is this an issue??

Symmetrical Ketones: no regioisomer issue:



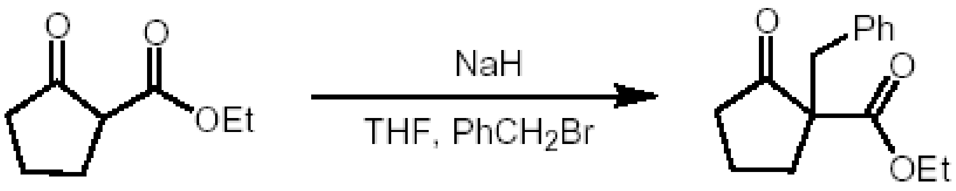
Unsymmetrical Ketones:2 regioisomers--How can you control which one is formed???



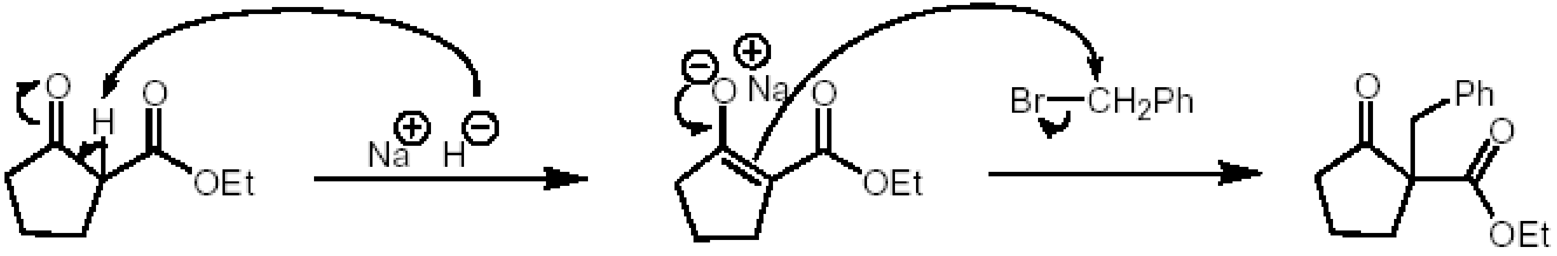
C. Other Enolates and Enolate derivatives

1. Stabilized enolates or Diactivated nucleophiles

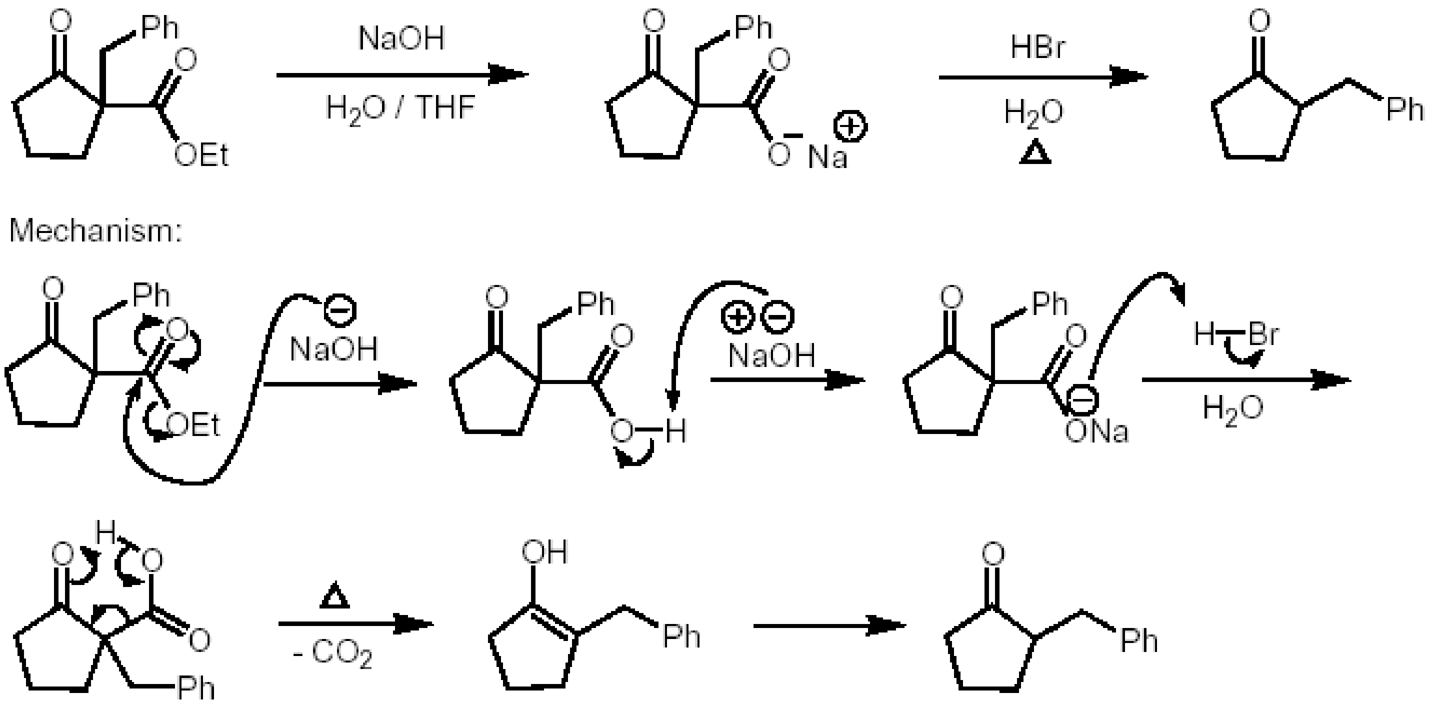
Deprotonation only requires relatively weak bases, therefore very convenient experimentally.



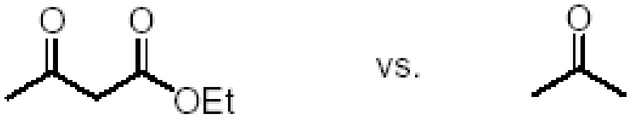
Mechanism:



The ketoester can then be hydrolyzed, and the β -ketoacids subsequently **decarboxylated** to yield the simple alkylation products



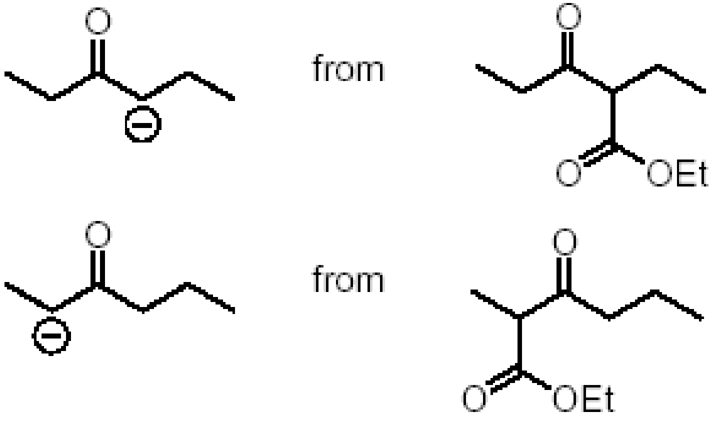
Q.: Why use enolates of β-ketoesters, rather than the ketone enolates themselves?



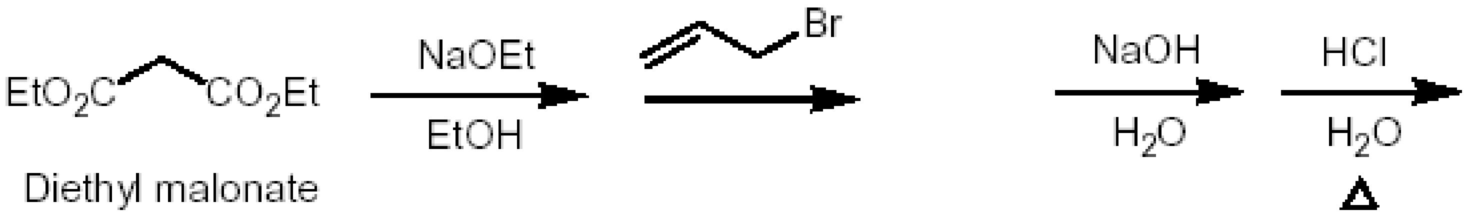
A. 1. The β-ketoesters are easier to deprotonate, so the use of strong bases are not necessary.

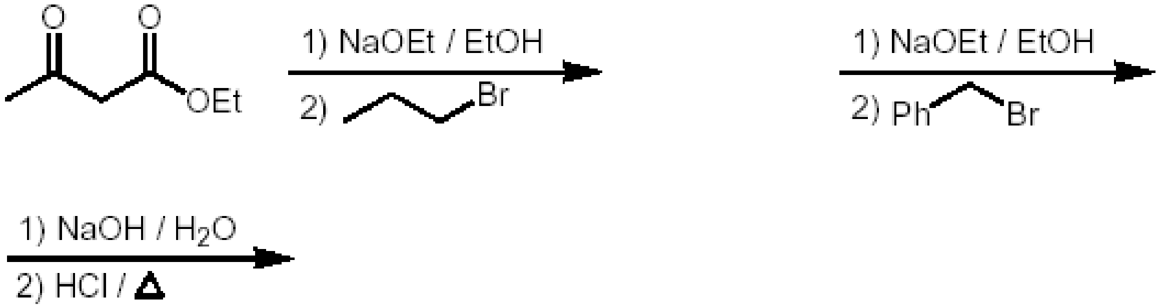
A. 2. Some side reactions (such as the aldol reaction) can be easily avoided.

A. 3. The β-ketoester nucleophiles provide unambiguous sites of reaction.

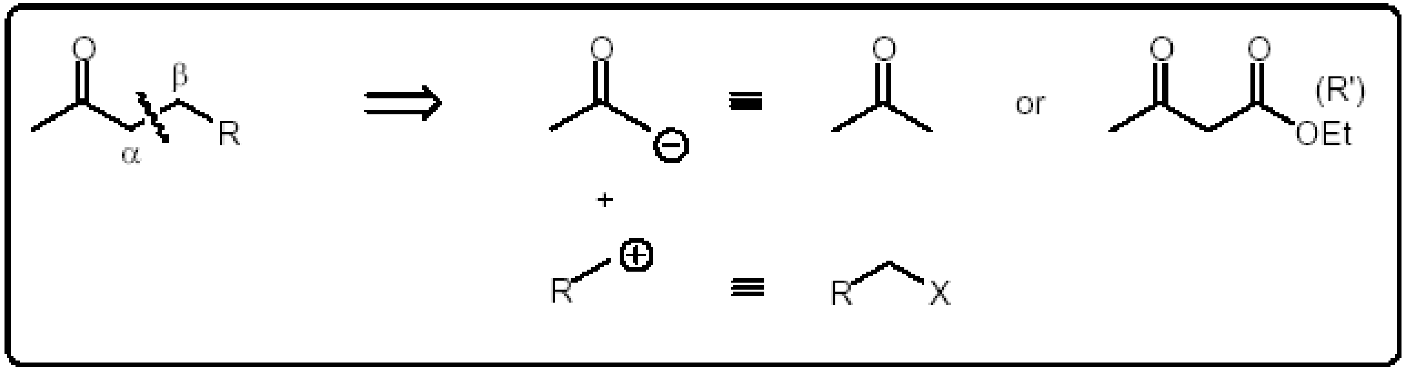


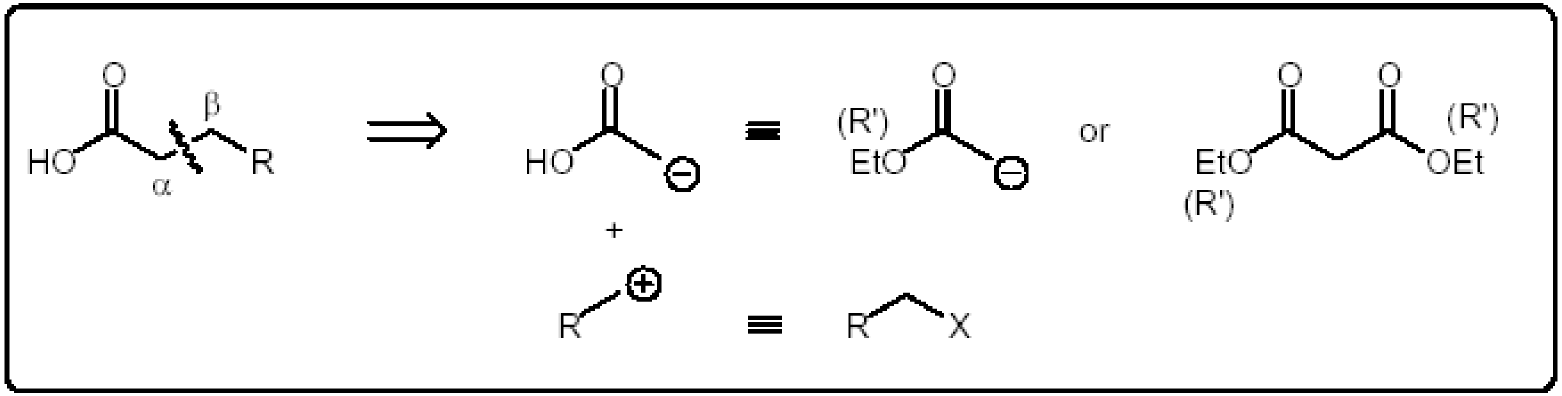
Exercise: Show reaction products and the **mechanisms** of formation in the following sequence.





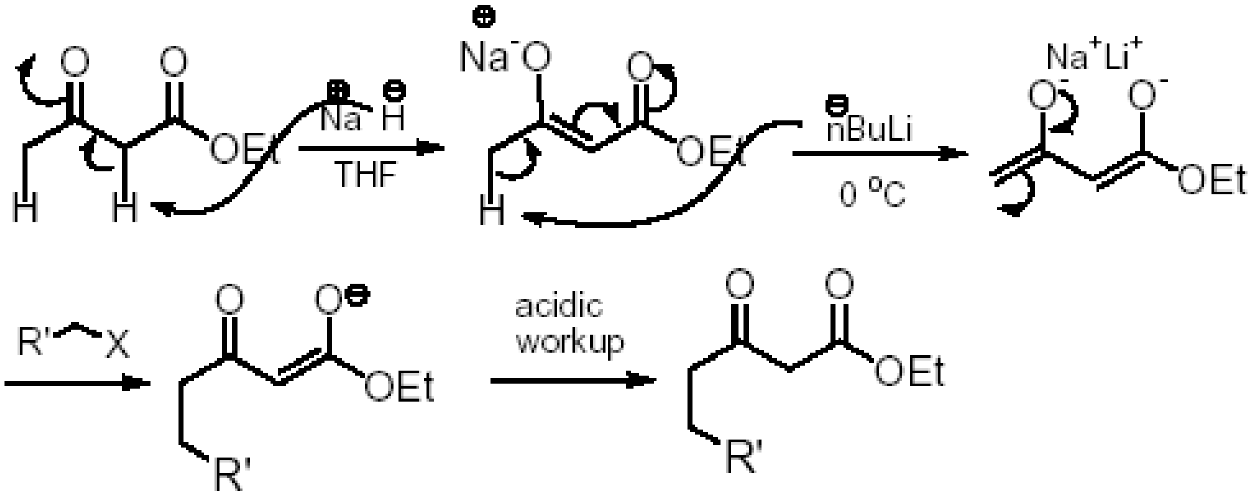
Note that the following are synthons of the enolates of ketones and carboxylic acids.





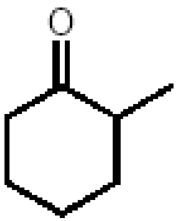
Dianions of β -ketoester, and β -diketones

Example:

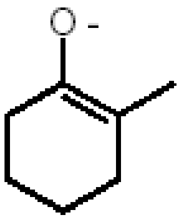


Two equivalents of LDA will also make the dianion of β -ketoester, and β -diketones.

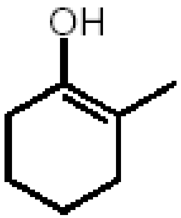
Silyl enol ethers



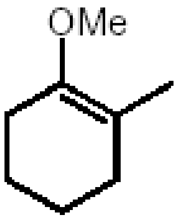
Ketone



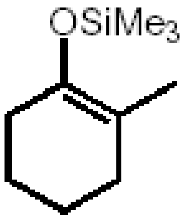
Enolate



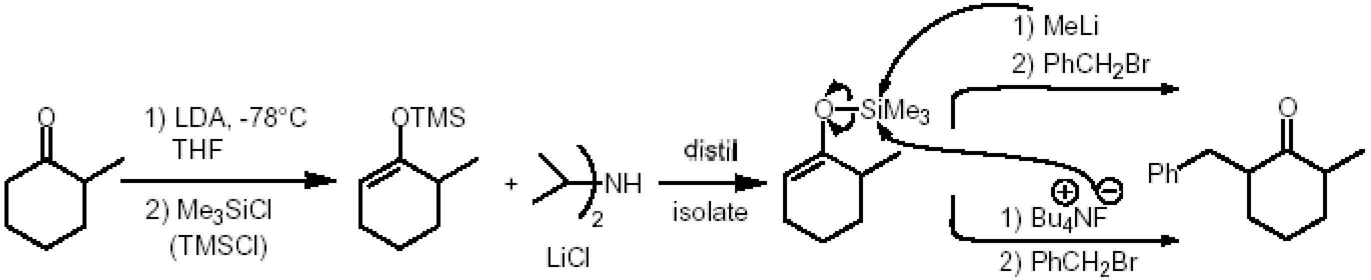
Enol

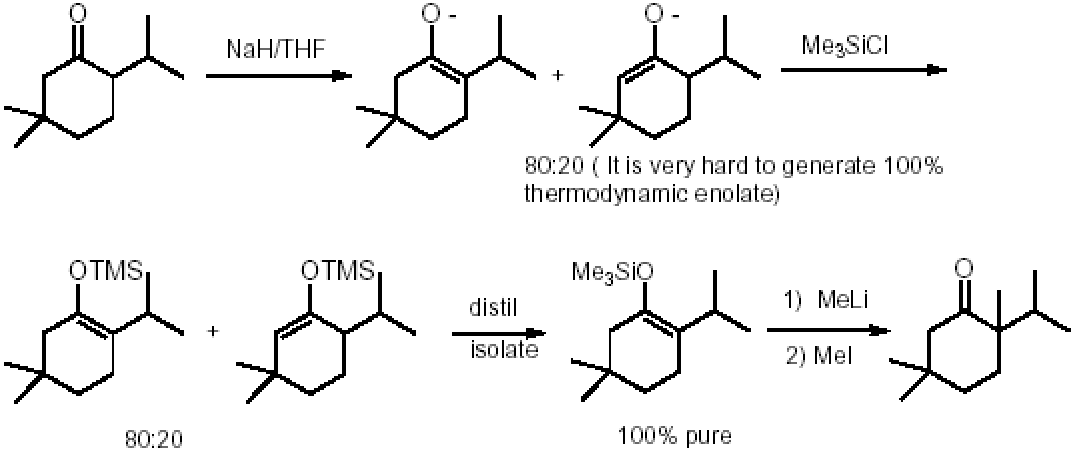


Enol ether



Silyl enol ether





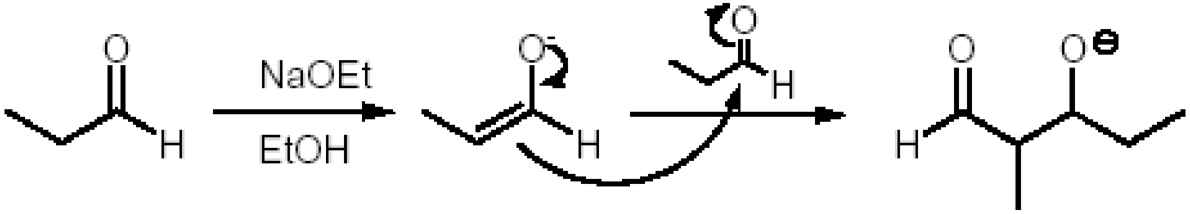
80:20 (It is very hard to generate 100% thermodynamic enolate)

80:20

100% pure

4. Enamines

Enolates of aldehydes are hard to generate pure because unless they are very rapidly and quantitatively formed, they will undergo a self-aldol reaction (more about this reaction later).

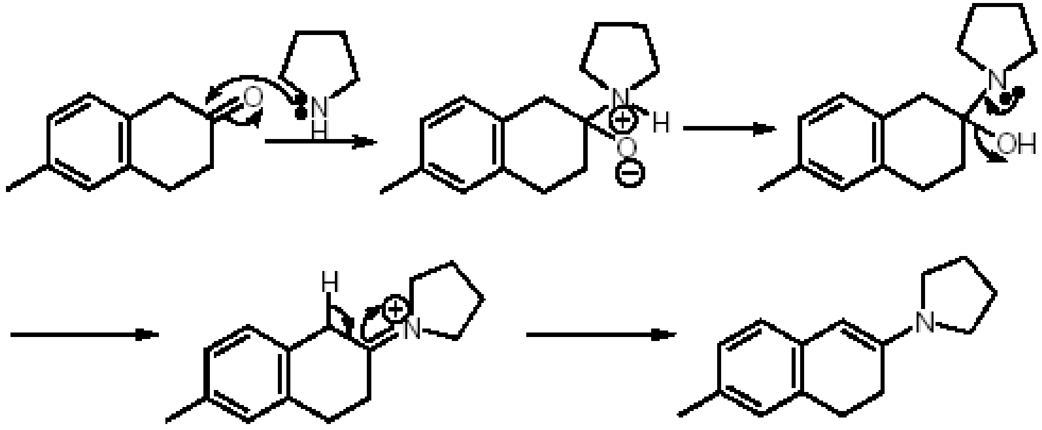


To use aldehydes as a nucleophile, it is much better to first convert the aldehydes into **enamines**.

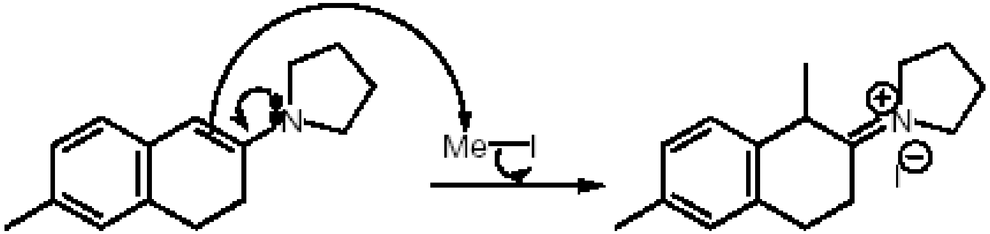
Ketones can also be converted to their enamines for reaction.

A. Generation of Enamines

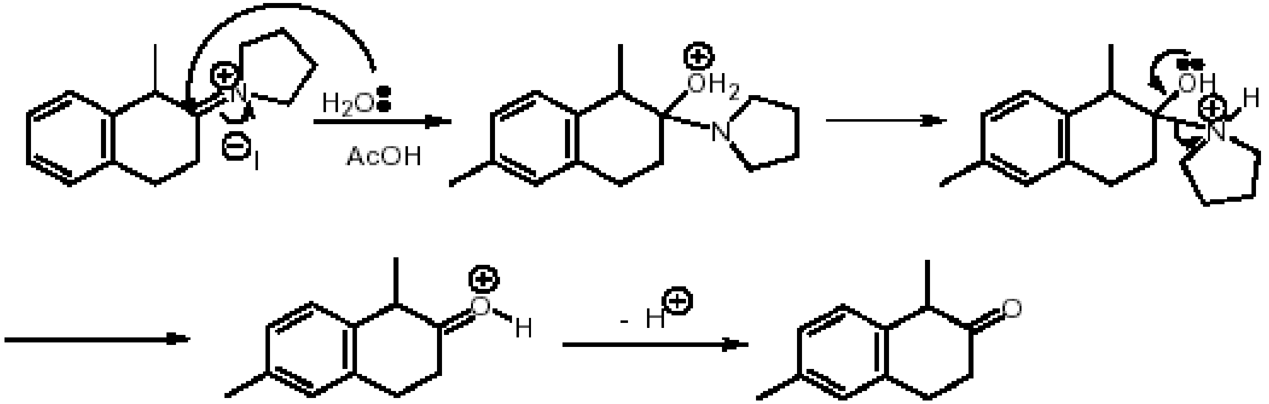
Mechanism:



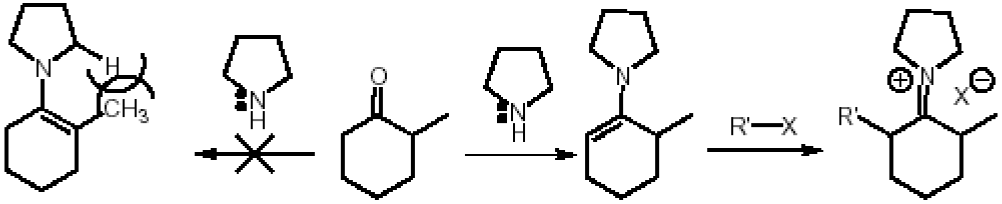
B. Reactivity of Enamines



C. Must regenerate the keto group by hydrolysis of iminium salt.



Notice the very useful regioselectivity of alkylation by the use of enamines of ketones.



C-C bond formation

- 2. 金属有机化合物的反应

  金属有机化合物：金属原子与碳原子直接相连的化合物。

Organometallic

Journal of Organometallic Chemistry

Applied Organometallic Chemistry

金属有机化合物的反应

- 一、有机镁化合物
- 格氏试剂（Grignard Reagents）

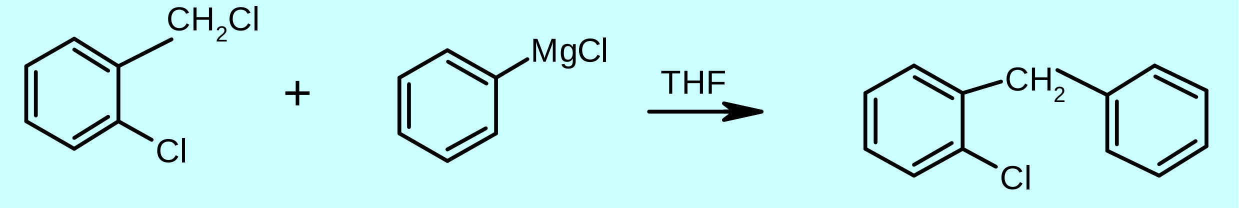
$$\mathrm{RX} + \mathrm{Mg} \xrightarrow[\mathrm{orTHF}]{\text{无水 } \mathrm{Et_2O}} \mathrm{RMgX}$$

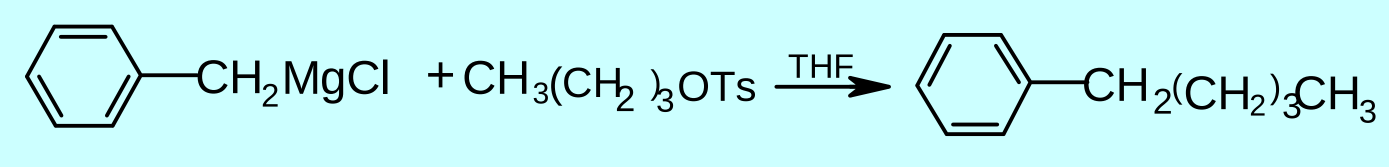
1)、烃化(alkylation)：

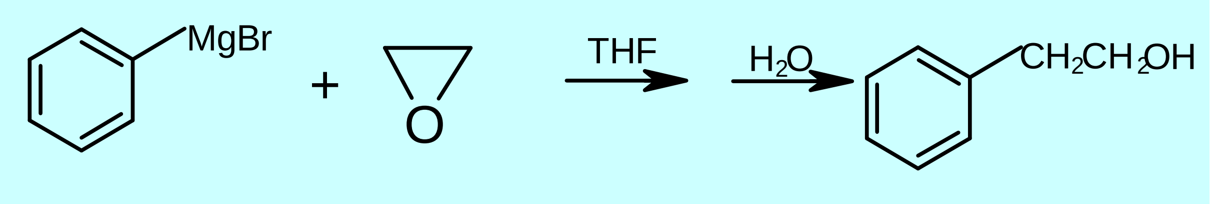
例：

$RMgX + R'X' \rightarrow R\text{-}R' + MgXX'$ (X=Cl,Br,I)

$CH_3(CH_2)_{11}MgI + CH_3(CH_2)_{11} \xrightarrow{THF} CH_3(CH_2)_{22}CH_3$

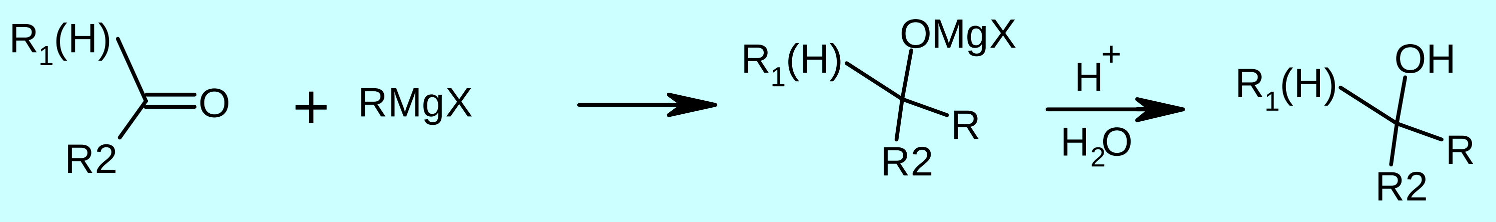




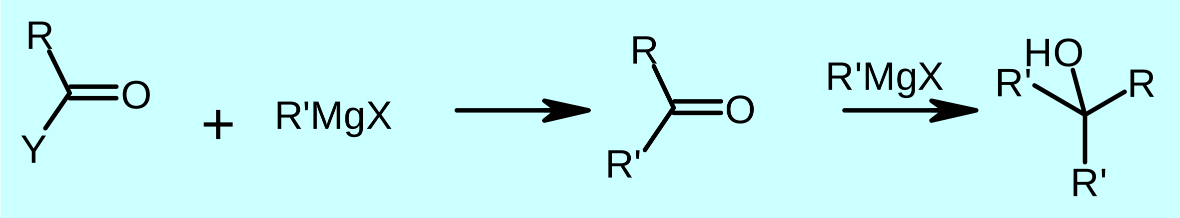


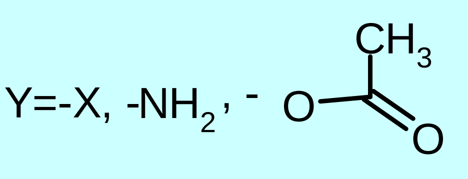
2)、与羰基的反应 (Reaction with Carbonyl Compounds)

- （1）、与醛酮的反应

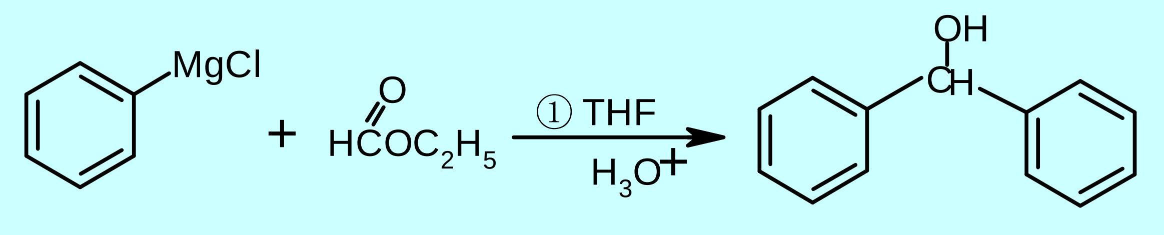


（2）、与羧酸衍生物的反应：

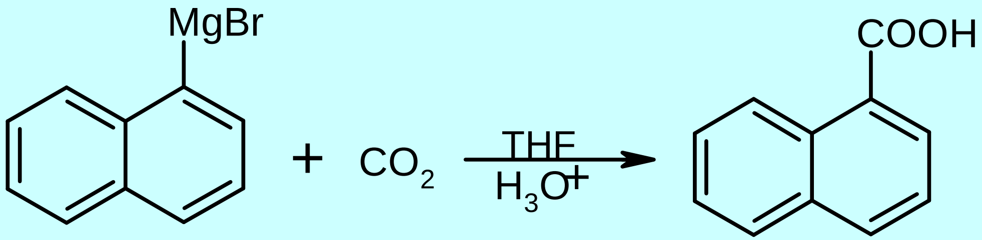




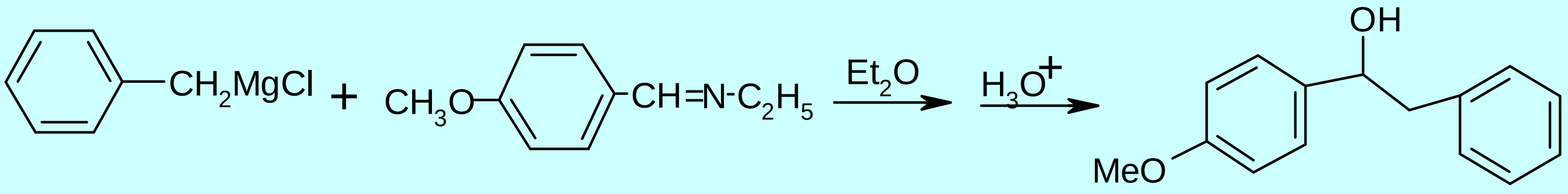
（3）、与酯的反应：

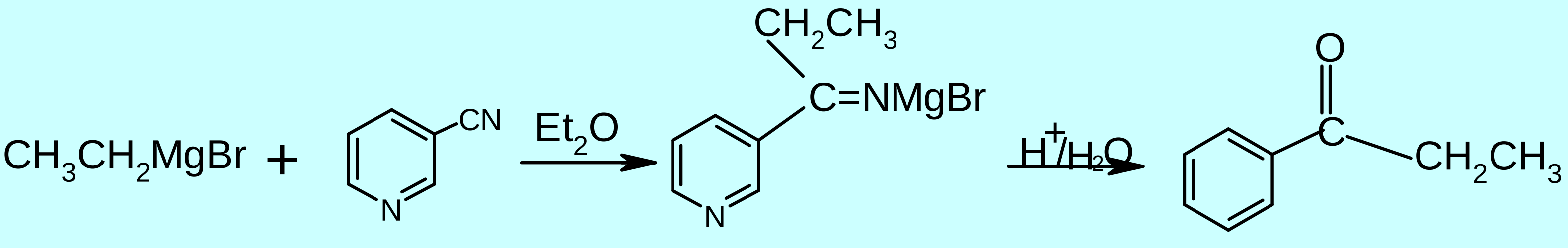


3)、与CO_2的反应(carbon dioxide)：



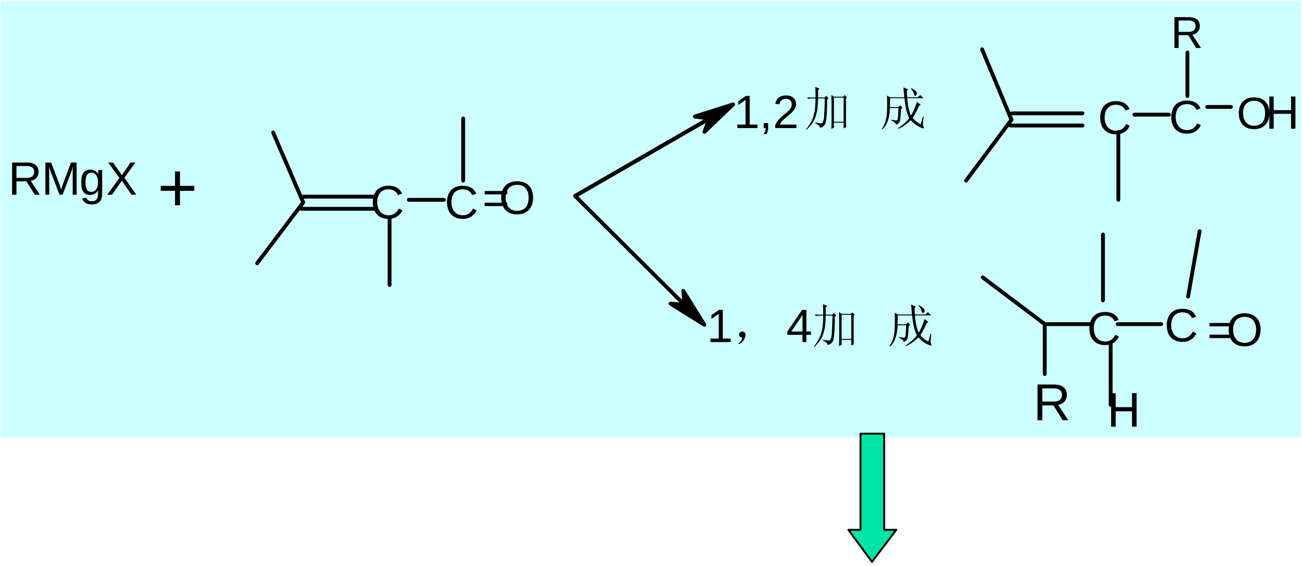
4)、与Schiff碱或碳氮三键的反应





5)、与α，β不饱和醛酮反应

- α，β-unsaturated ketones or aldehydes

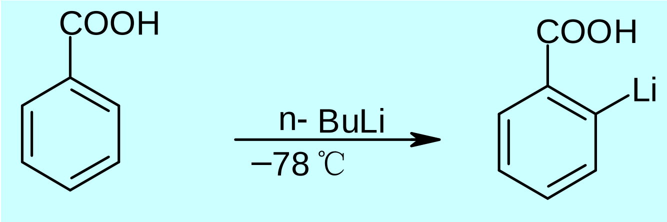


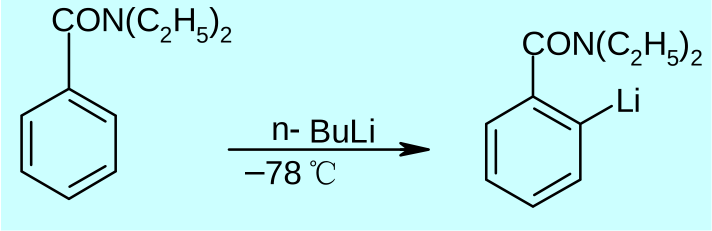
Conjugated Addition

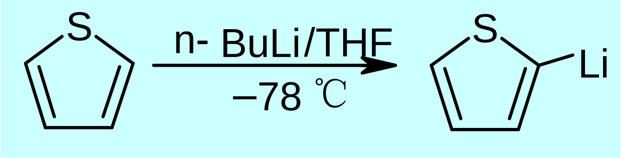
二、有机锂试剂

1、制备(Preparation)：

$$\mathrm{RBr} + 2\mathrm{Li} \xrightarrow{\text{醚}} \mathrm{RLi} + \mathrm{LiBr}$$

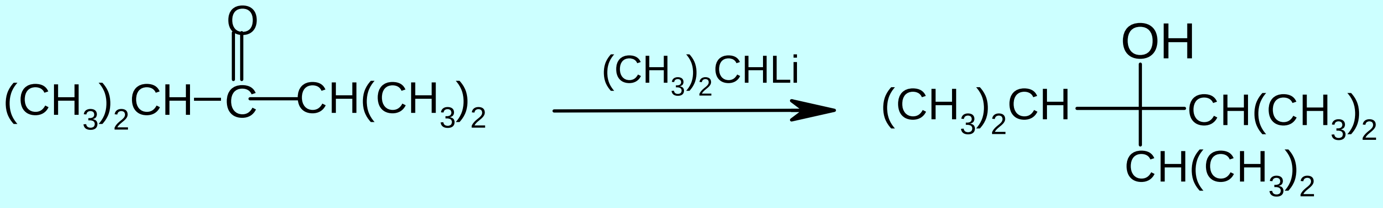




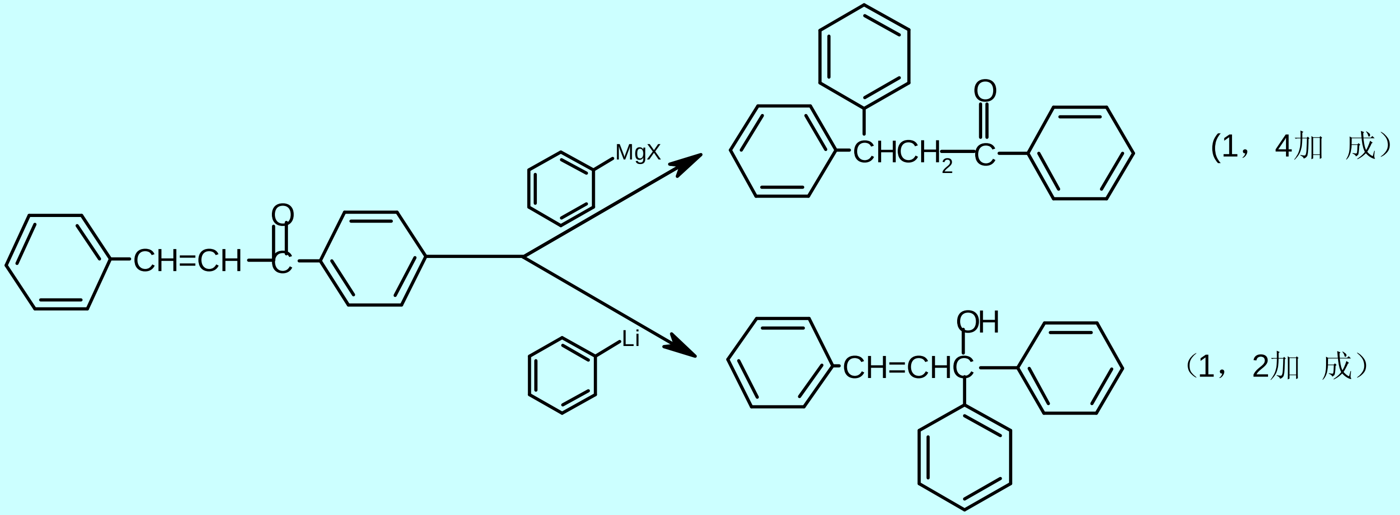


2、有机锂试剂的反应

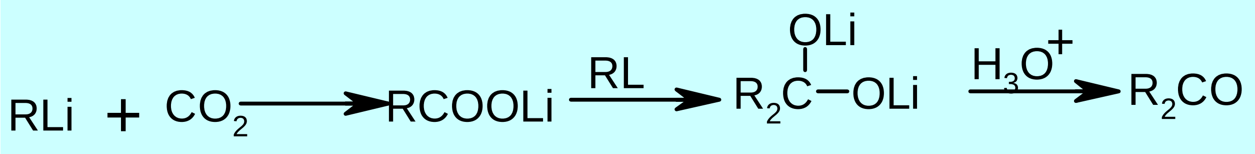
（1）、与酮反应：



（2）、与α，β不饱和羰基化合物反应：



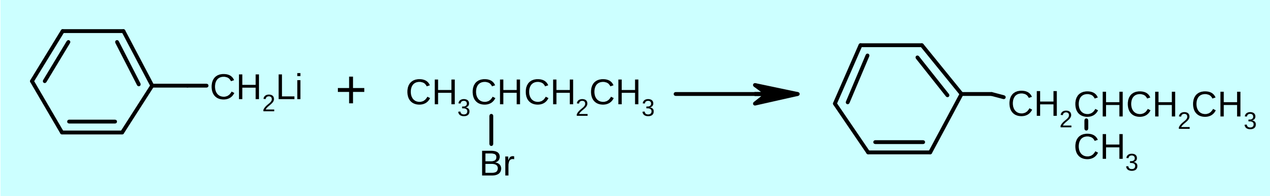
（3）与CO_2 反应



$$RLi + CO_2 \longrightarrow RCOOLi \xrightarrow{RL} R_2\overset{OLi}{\overset{|}{C}}-OLi \xrightarrow{H_3O^+} R_2CO$$

（4）与RX反应：

$$RLi + R'x \longrightarrow R-R' + LiX$$



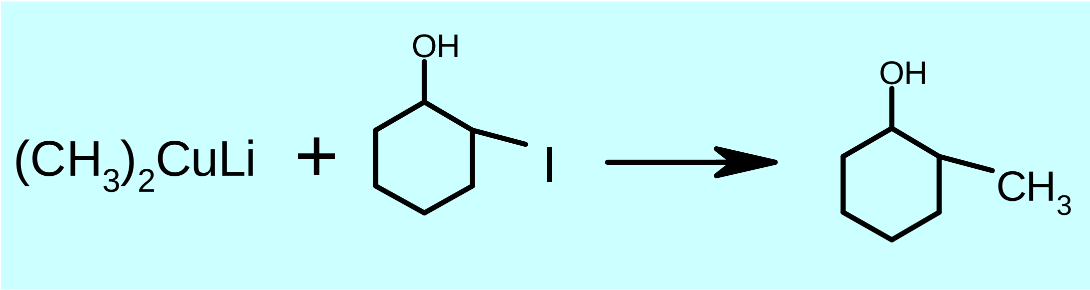
三、有机铜化合物（主要介绍二烃基铜锂试剂）

制备：

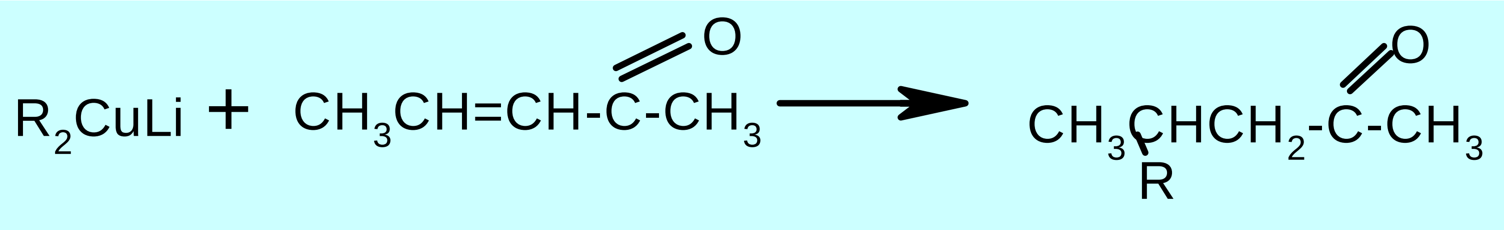
$$2RLi + CuX \longrightarrow R_2CuLI + LiX$$

1、烃基取代反应

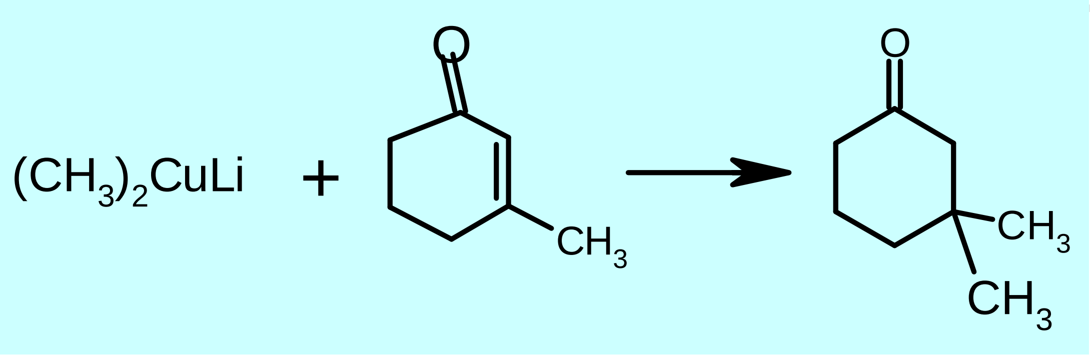
$$R_2CuLi + R'x \longrightarrow R{-}R' + LiX$$



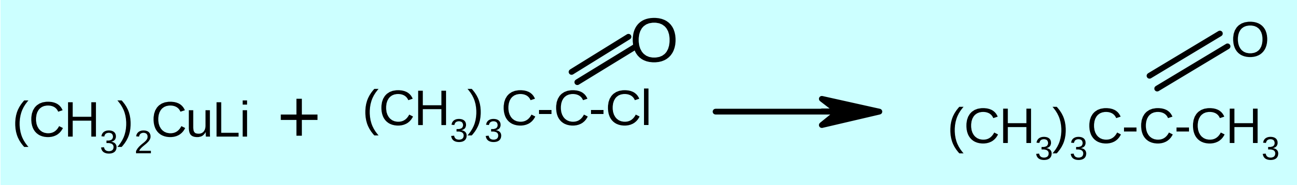
2、与α，β不饱和羰基化合物反应：



$$R_2CuLi + CH_3CH{=}CH\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 \longrightarrow CH_3\underset{R}{CH}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3$$

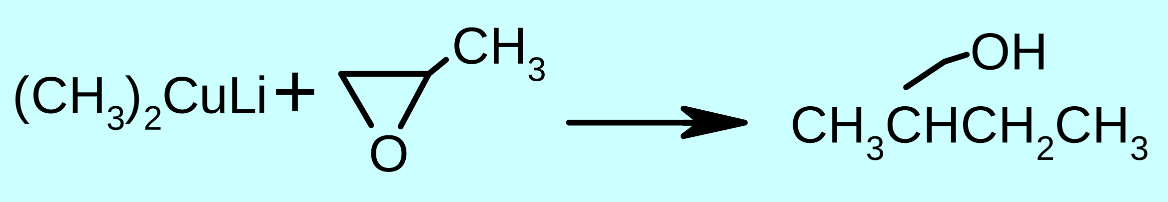


3、与酰氯反应：



$$(CH_3)_2CuLi + (CH_3)_3C\text{-}\overset{O}{\overset{\|}{C}}\text{-}Cl \longrightarrow (CH_3)_3C\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3$$

4、与环氧化合物加成：

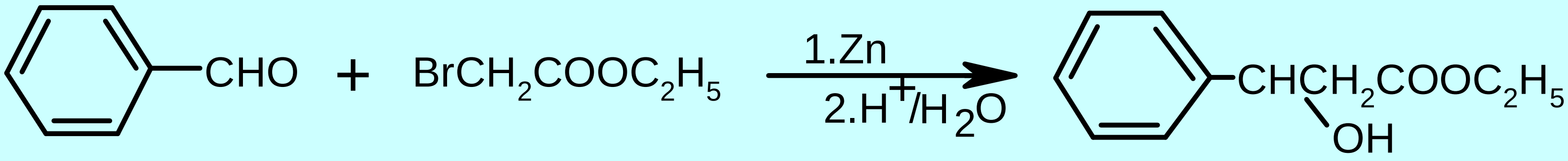


5、偶合反应：

$$Ph_2CuLi \xrightarrow[O_2]{THF\ -78^{\circ}C} Ph\text{-}Ph$$

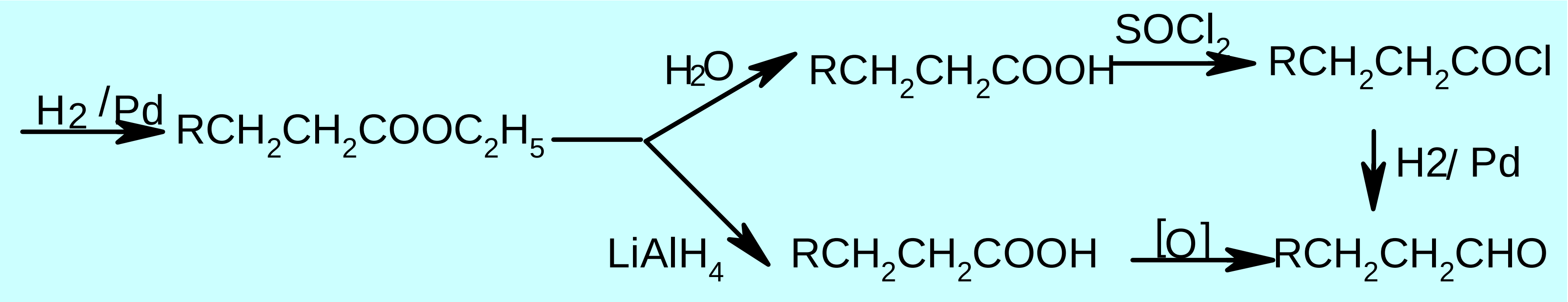
四 、有机锌化合物：

- Reformatsky反应：
- 用α-卤代羧酸酯在锌的作用下与醛或酮反应，生成β-羟基酸酯，或脱水生成α，β不饱和羧酸酯。



Application of Reformatsky Reaction

$$RCHO + BrCH_2COOC_2H_5 \xrightarrow[\text{溶 剂}]{Zn} \underset{\substack{|\\ OH}}{RC}HCH_2COOC_2H_5 \xrightarrow{-H_2O} RCH{=}CHCOOC_2H_5$$



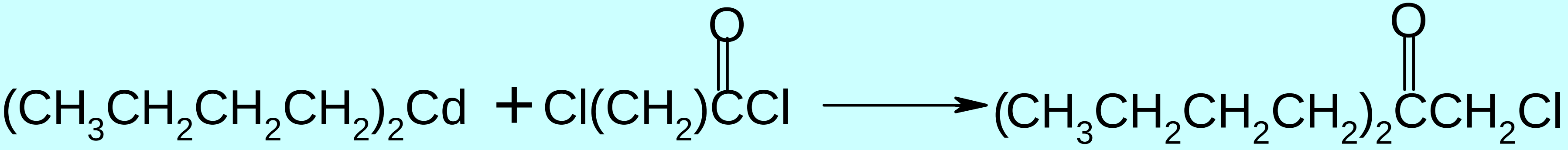
$$\begin{tikzcd}
 & & RCH_2CH_2COOH \arrow[r, "SOCl_2"] & RCH_2CH_2COCl \arrow[dd, "H2/\ Pd"] \\
{} \arrow[r, "H_2\ /Pd"] & RCH_2CH_2COOC_2H_5 \arrow[ur, "H_2O"] \arrow[dr, "LiAlH_4"'] & & \\
 & & RCH_2CH_2COOH \arrow[r, "{[O]}"] & RCH_2CH_2CHO
\end{tikzcd}$$

五、有机镉试剂

制备

$$RMgX + CdCl_2 \longrightarrow R_2Cd$$

与酰卤的反应：



$$(CH_3CH_2CH_2CH_2)_2Cd + Cl(CH_2)\overset{O}{\overset{\|}{C}}Cl \longrightarrow (CH_3CH_2CH_2CH_2)_2\overset{O}{\overset{\|}{C}}CH_2Cl$$

C-C bond formation

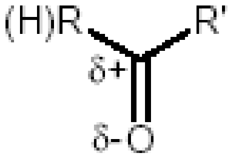
3. Condensation Reaction

A) Aldol Condensation

So far we have seen C ⊕ ≈ R-X

R-OTs

Now C ⊕ ≈



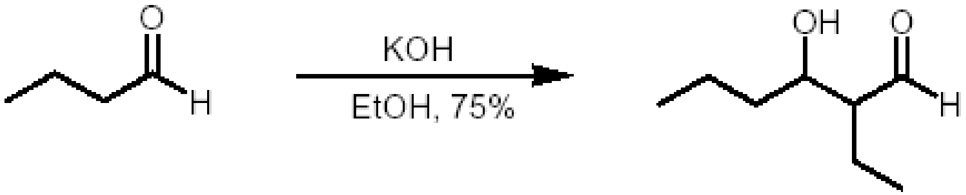
This is the **aldol** reaction.

Self condensation of keto compounds

the enolate of an aldehyde
is hard to generate pure, without
contamination by aldol products

To make the enolate, one must add aldehyde dropwise to base at low T

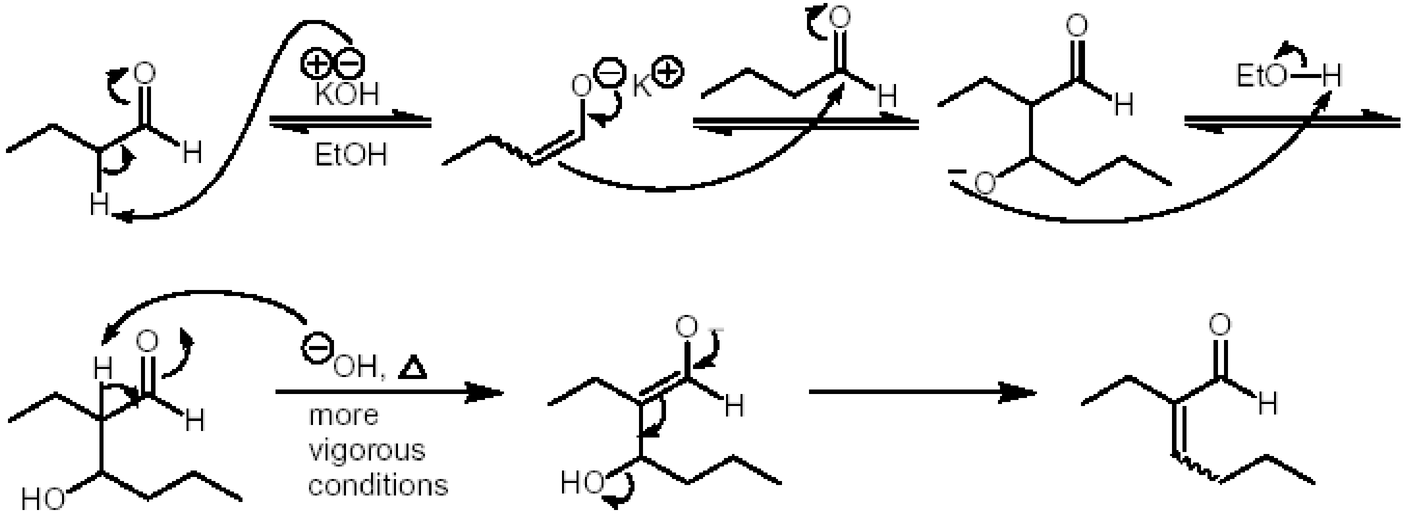
If a weak base is used, self condensation will occur:



Mechanisms of aldol:

- Base-catalyzed aldol:

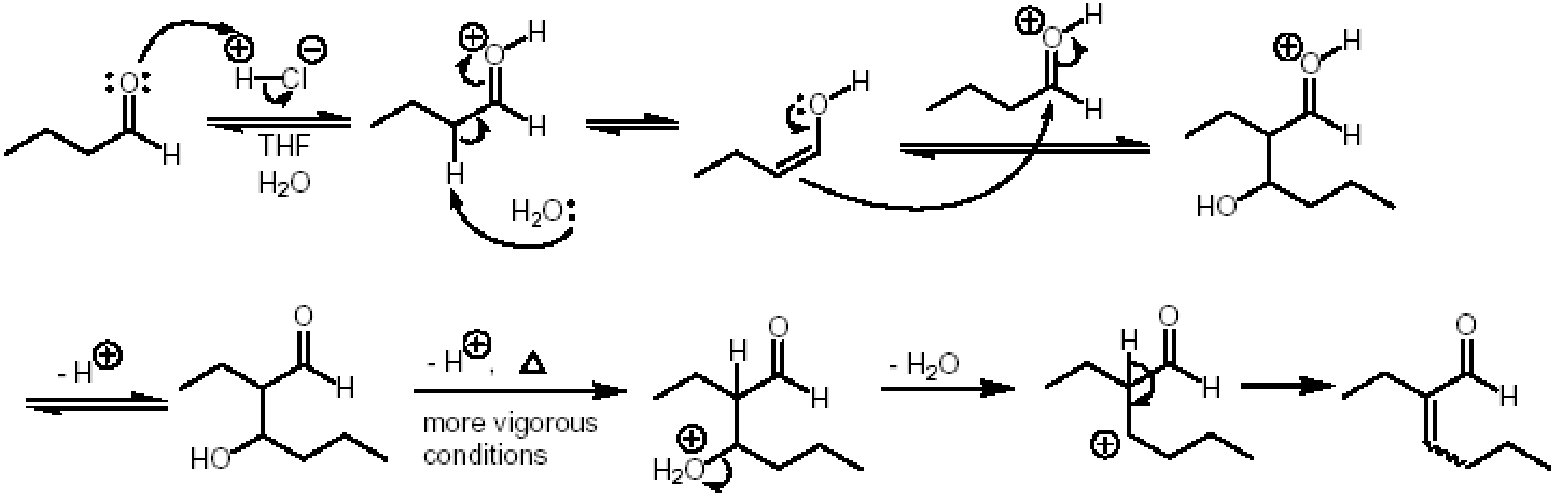
Here the nucleophilic specie C⊖ is the **enolate**.



Mechanisms of aldol:

- Acid-catalyzed adol

Here the nucleophilic specie C⊖ is the **enol**.



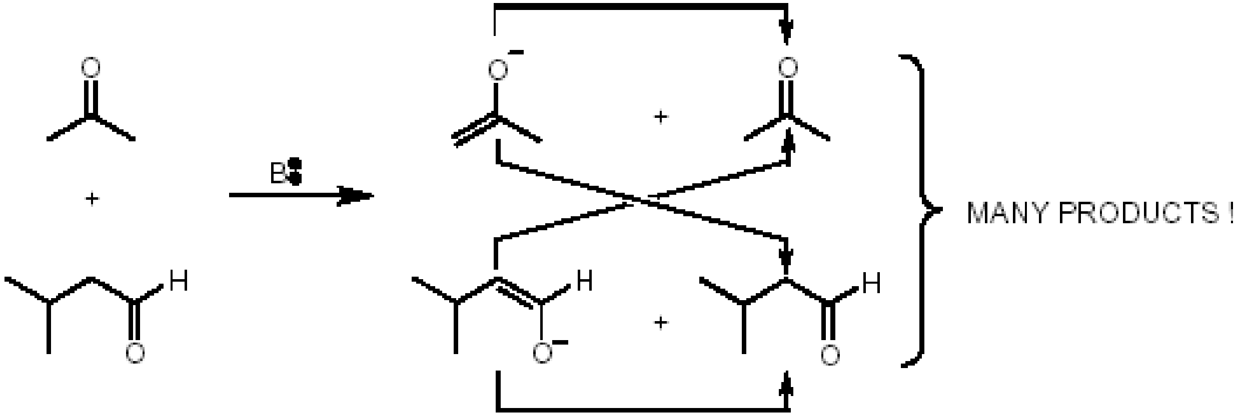
Aldol Condensation

- Mixed or cross adol

$$\mathbf{C{-}C} \quad \Rightarrow \quad C^{\ominus} \quad + \quad C^{\ominus}$$

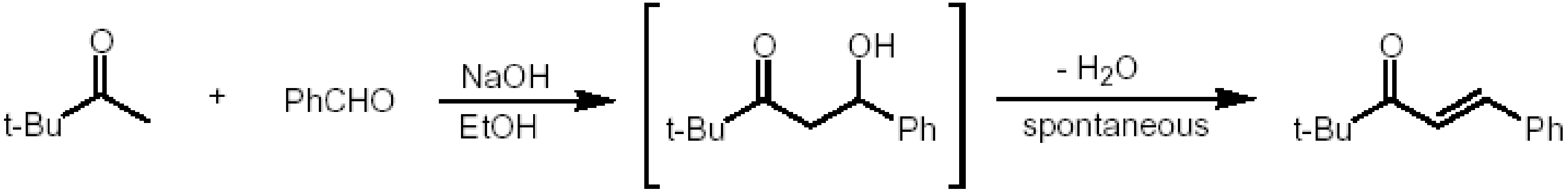
Enolate^{-} + **Electrophile^{+}**

Note the potential problem



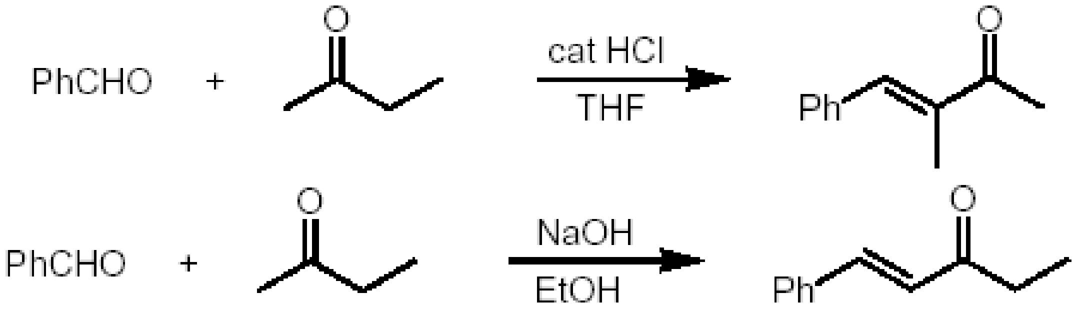
Two solution to this probelm

Solution 1: Claisen-Schmidt aldol reaction



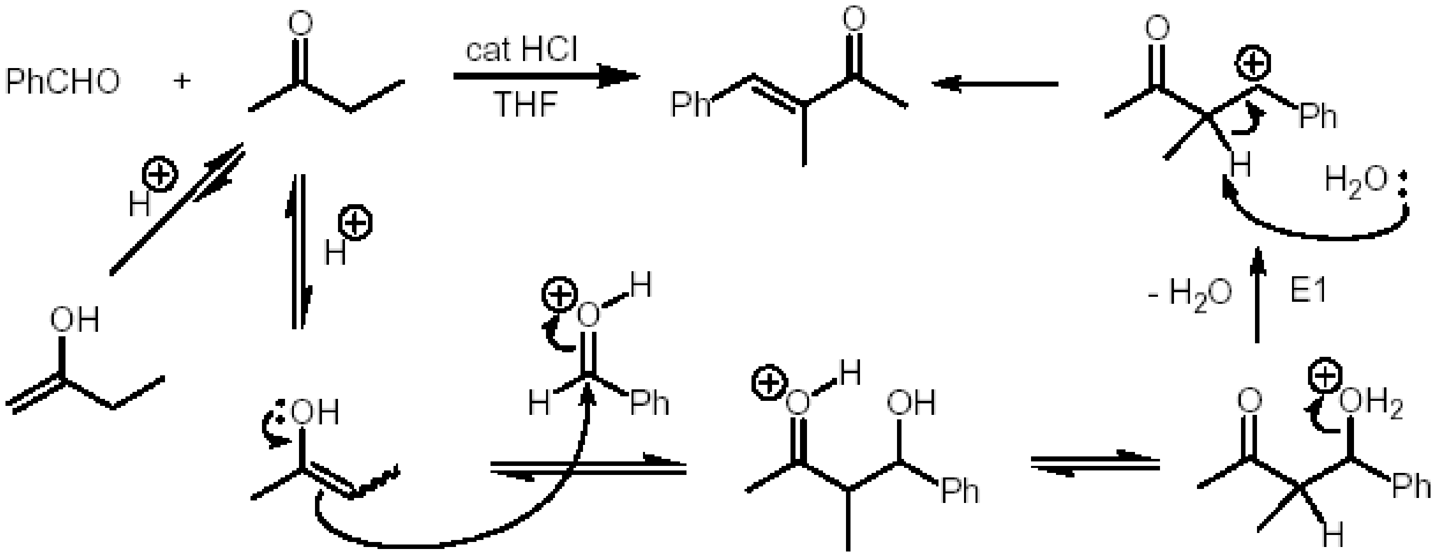
Aldol Condensation

- **Note that the products from acid or base-catalyzed aldols can be different.**

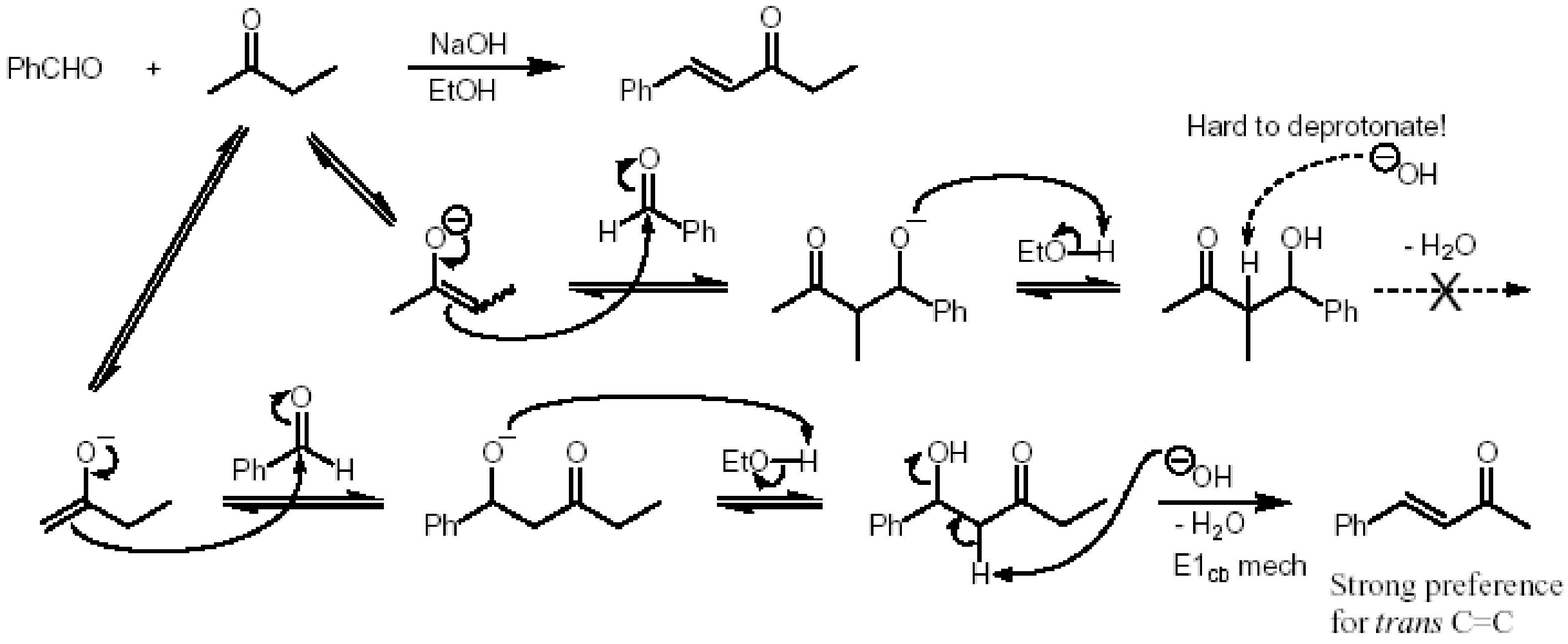


Why?

Mechanism under acidic conditions



Mechanism under basic conditions



Aldol Condensation

- Solution 2: Preform C⊖ and add this to C⊕ .

Preformed C⊖ can be

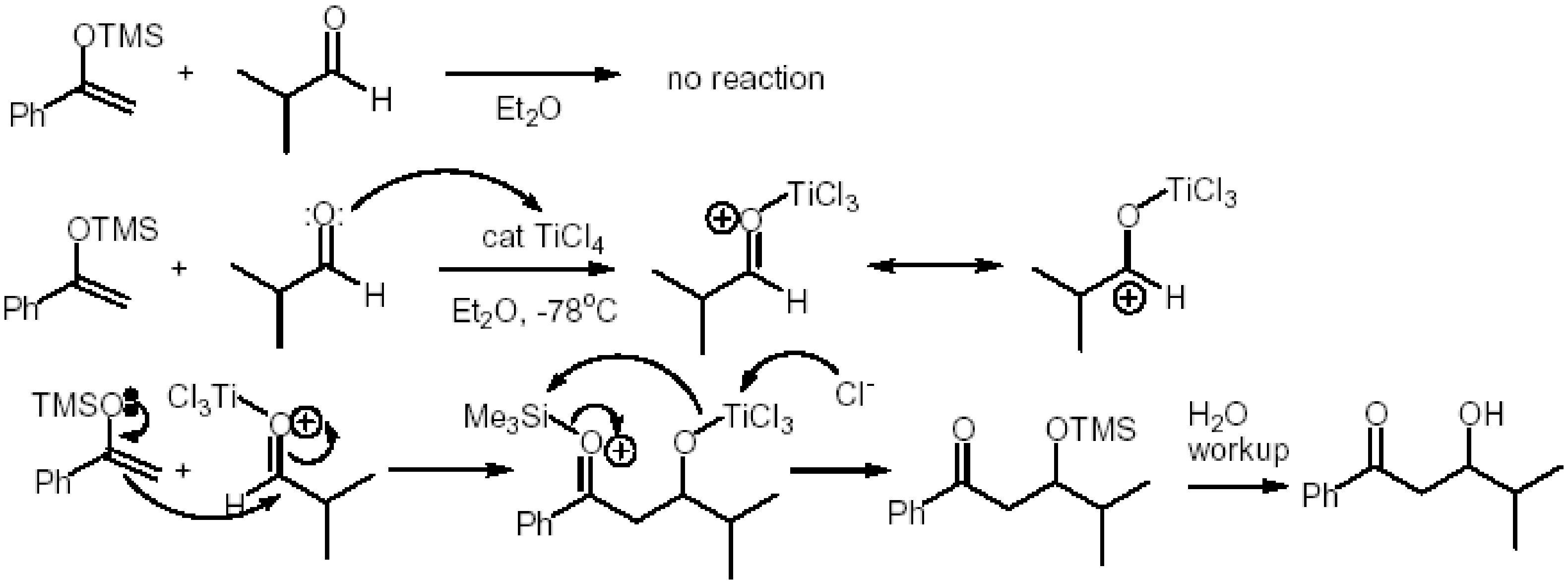
1) enolate which has been fully converted from the ketone/aldehyde by strong base;

2) enamine or metalloenamine;

3) silyl enol ether in the presence of Lewis acids or fluoride. (IN PARTICULAR, THE LEWIS ACID-CATALYSED ALDOL REACTION OF A SILYL ENOL ETHER WITH AN ALDEHYDE IS CALLED A"MUKAIYAMA ALDOL REACTION".)

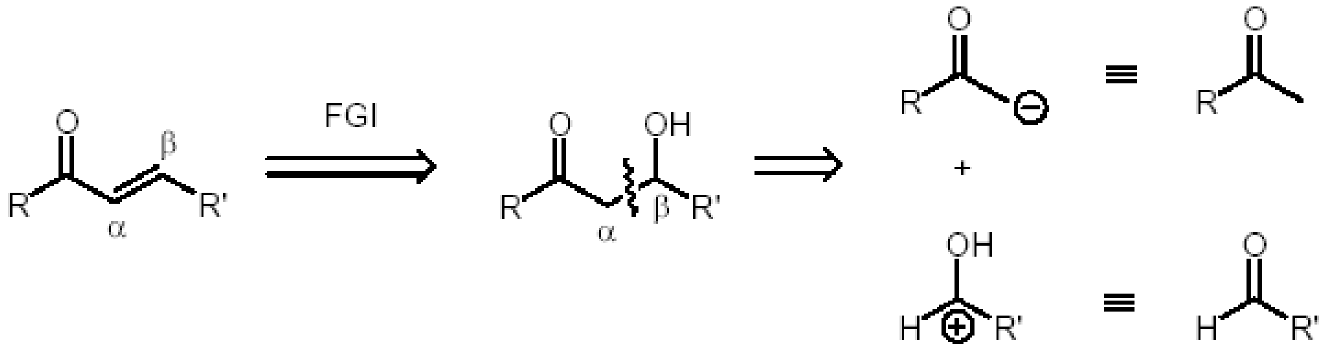
Aldol Condensation

Example of a Mukaiyama Adol

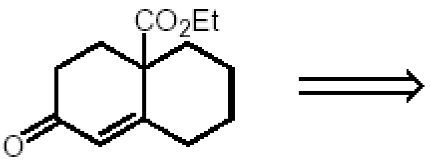


Aldol Condensation

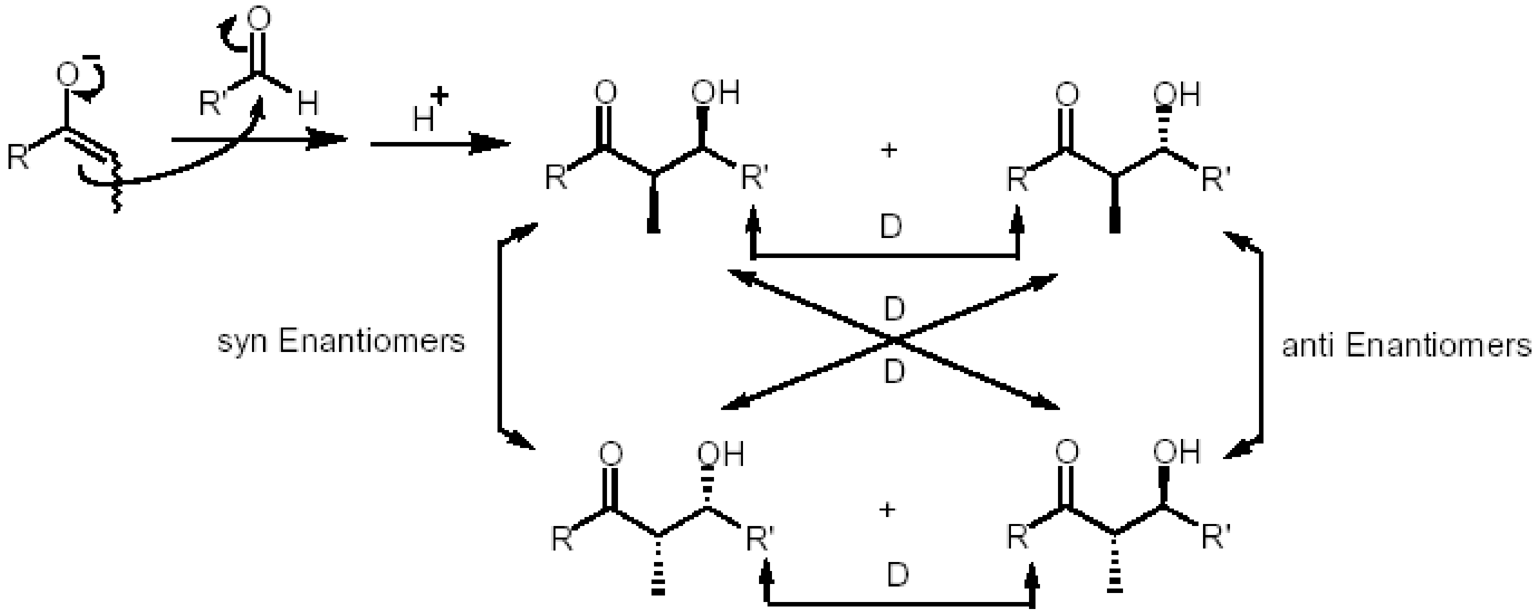
ℜ! The **β-hydroxy-carbonyl**, and the **α,β unsaturated carbonyl** are the synthons of the aldol reaction. Disconnect at the α–β bond.



Exercise in retroanalysis

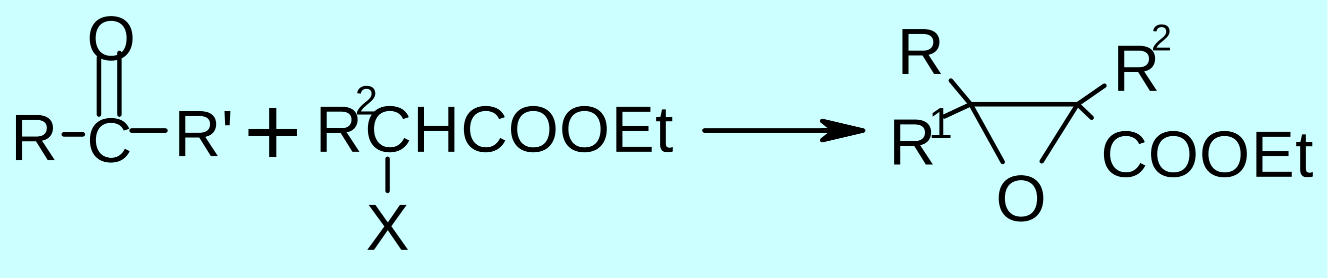


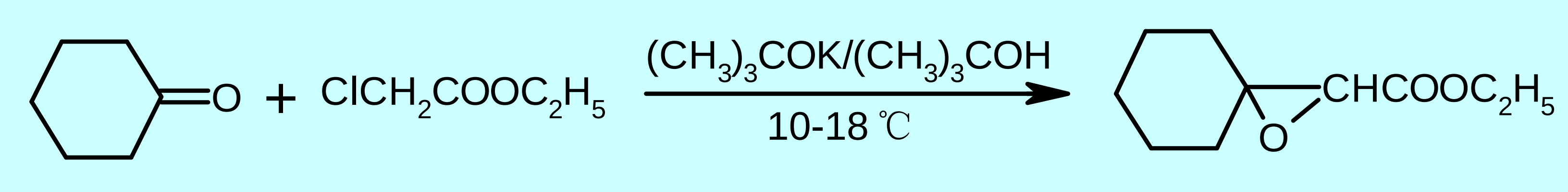
Stereochemistry of the aldol condensation



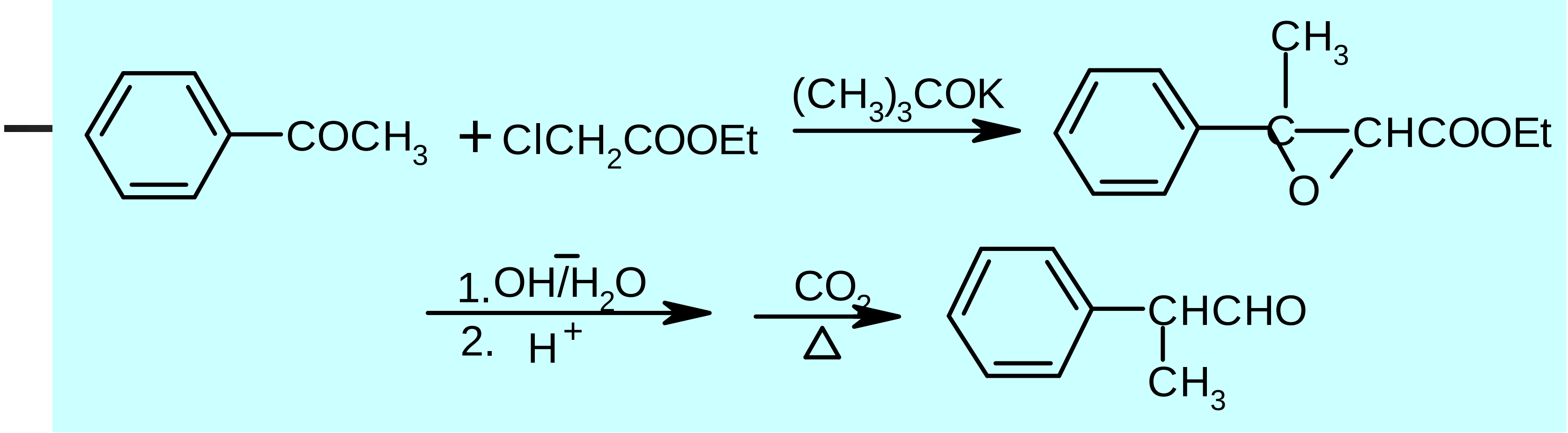
B) Darzen reaction

醛或酮与α-卤代酸酯在碱催化下缩合生成α，β-环氧羧酸酯的反应称为Darzen缩合。

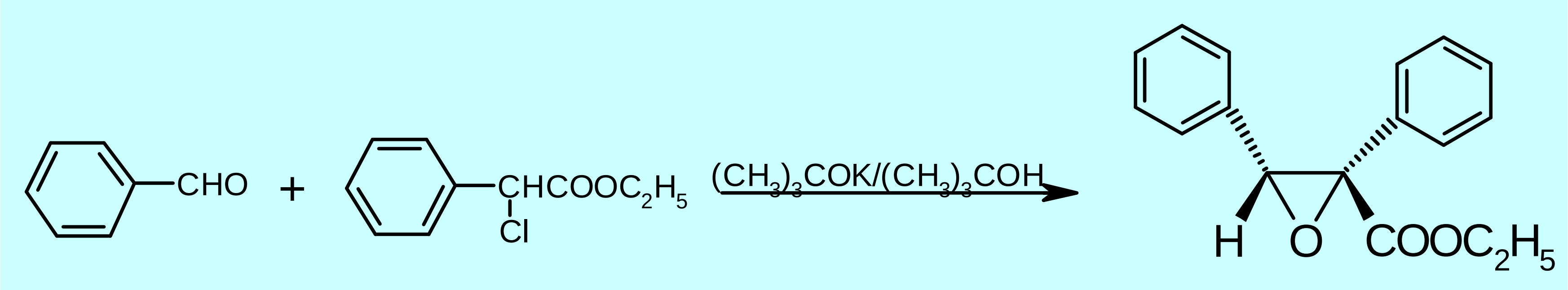




Darzen缩合的产物α，β-环氧羧酸酯经水解、脱羧可以转化成比原有反应物醛、酮增加一个碳原子的醛酮。



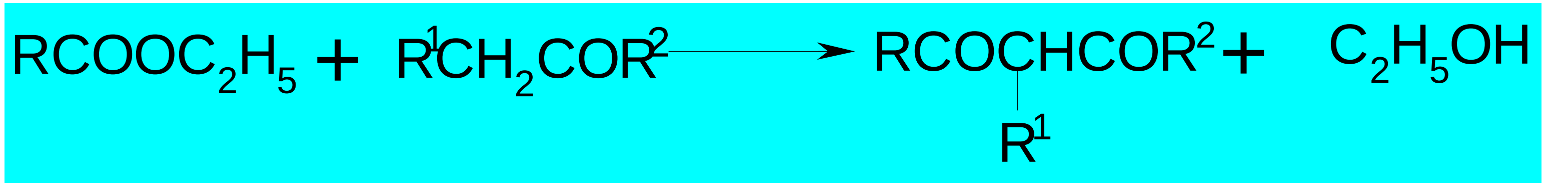
芳香醛或不对称酮与α-羟基取代的卤乙酸酯反应，则优先生成β-碳为较大的取代基与酯基成反式的产物。



（75%）

(C) Claisen Reaction

- 羧酸酯在碱性催化剂作用下与含有活泼亚甲基的羰基化合物缩合生成β－羰基化合物的反应，总称为Claisen缩合反应.



$$RCOOC_2H_5 + R^1CH_2COR^2 \longrightarrow RCO\underset{R^1}{\underset{|}{C}}HCOR^2 + C_2H_5OH$$

其中R可以是氢、烃基、芳基或杂环基，R^1,R^2可为任意有机基团.

反应常用的催化剂有RONa,$NaNH_2$,NaH等。

Claisen缩合是制备β－酮酸酯和β－二酮的重要方法.

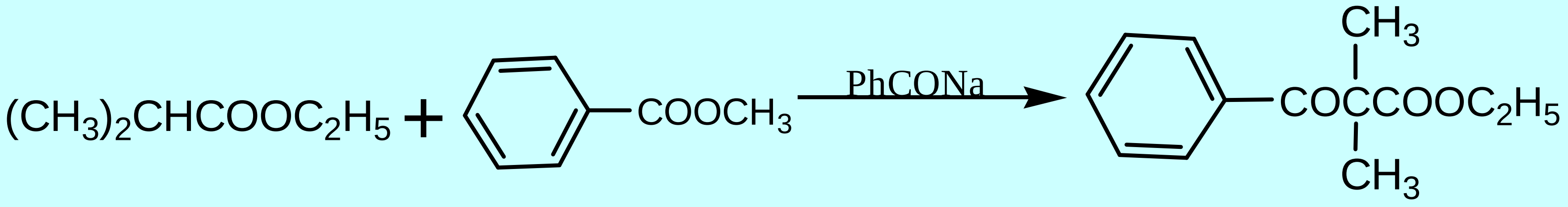
(D)酯-酯缩合

- 分子间缩合反应（Claisen Condesation）

a 酯的自身缩合

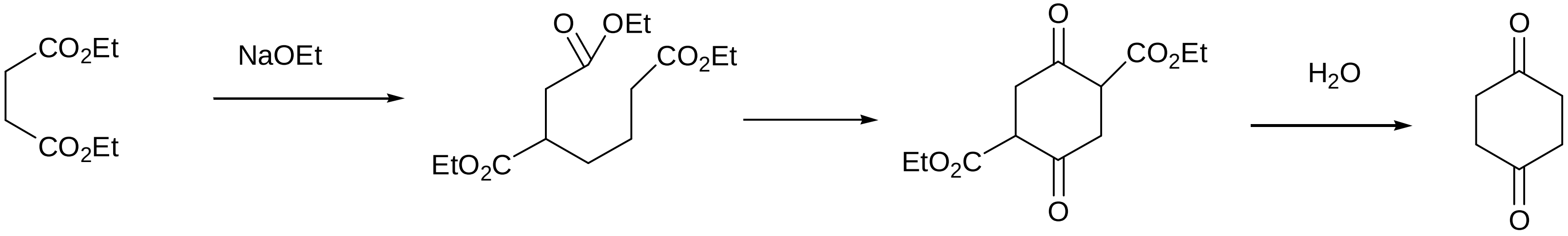
$$CH_3COOC_2H_5 + CH_3COOC_2H_5 \overset{C_2H_5ONa}{\rightleftharpoons} CH_3COCH_2COOC_2H_5 + C_2H_5OH$$

b 酯的交叉缩合

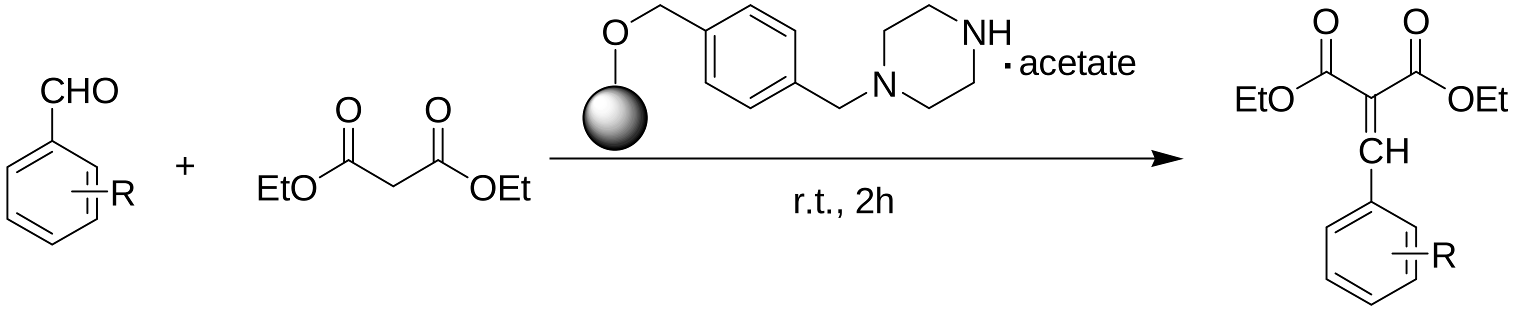


(D)酯-酯缩合

- 分子内酯-酯缩合（Dieckmann Condesation)



(E)、 Knoevenagel **Reaction**



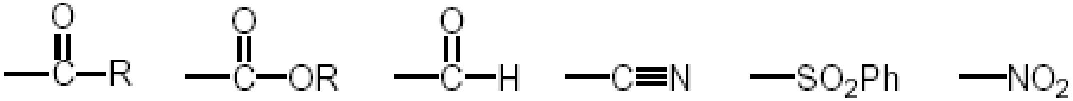
(F) Michael Additions

Review: What have we seen as C ⊖ (*carbon nucleophile*) so far?

C ⊕ (*carbon electrophile*) ?

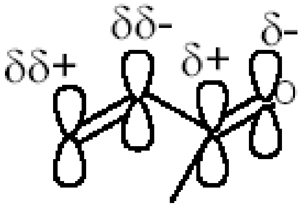
Now, another broad class of C ⊕ :  called "Michael acceptors".

EWG can be :

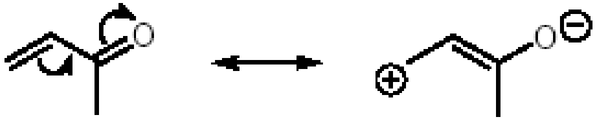


$-\overset{O}{\overset{\|}{C}}-R$ $-\overset{O}{\overset{\|}{C}}-OR$ $-\overset{O}{\overset{\|}{C}}-H$ $-C\equiv N$ $-SO_2Ph$ $-NO_2$

The electrophilicity of the C=O (or EWG) is translated down the π-system:



or as resonance structures:



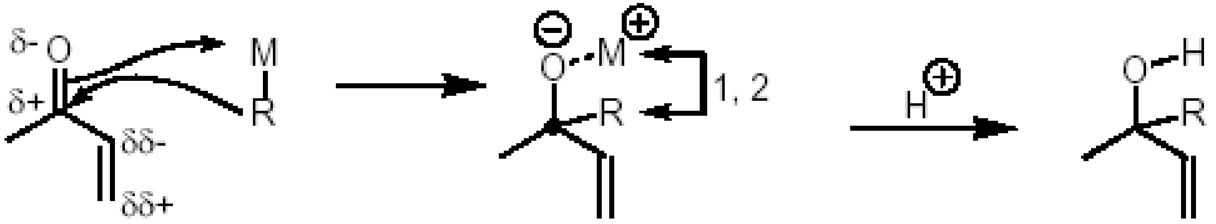
electron deficient C=C

minor contribution

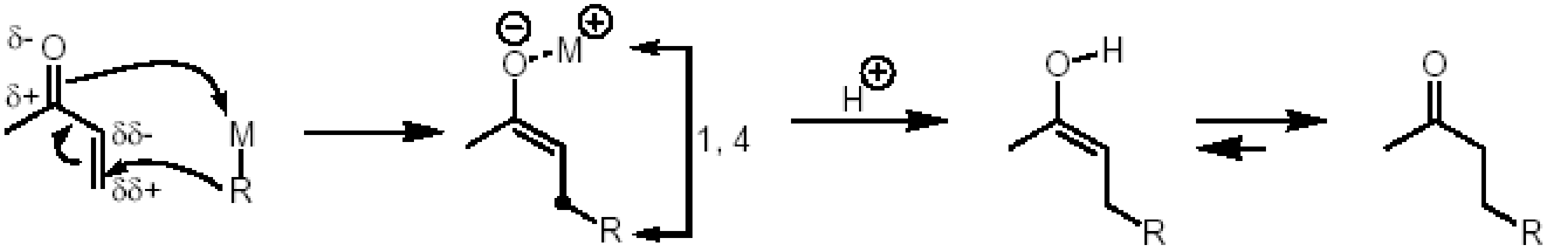
Michael Additions

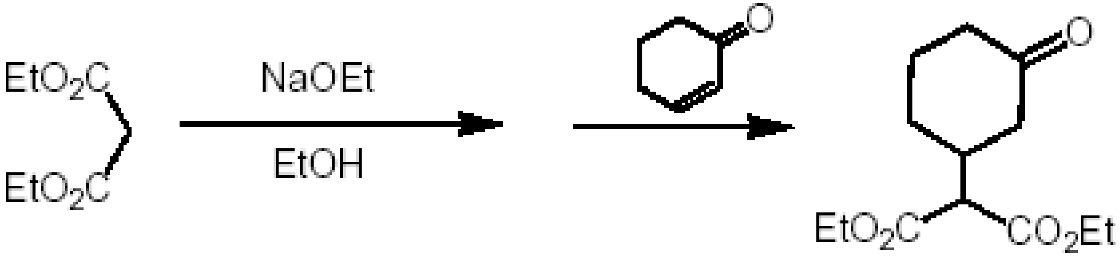
Nucleophiles (R^-M^+)can undergo **1,2- or 1,4-**addition to Michael acceptors:

*****1,2-addition:**

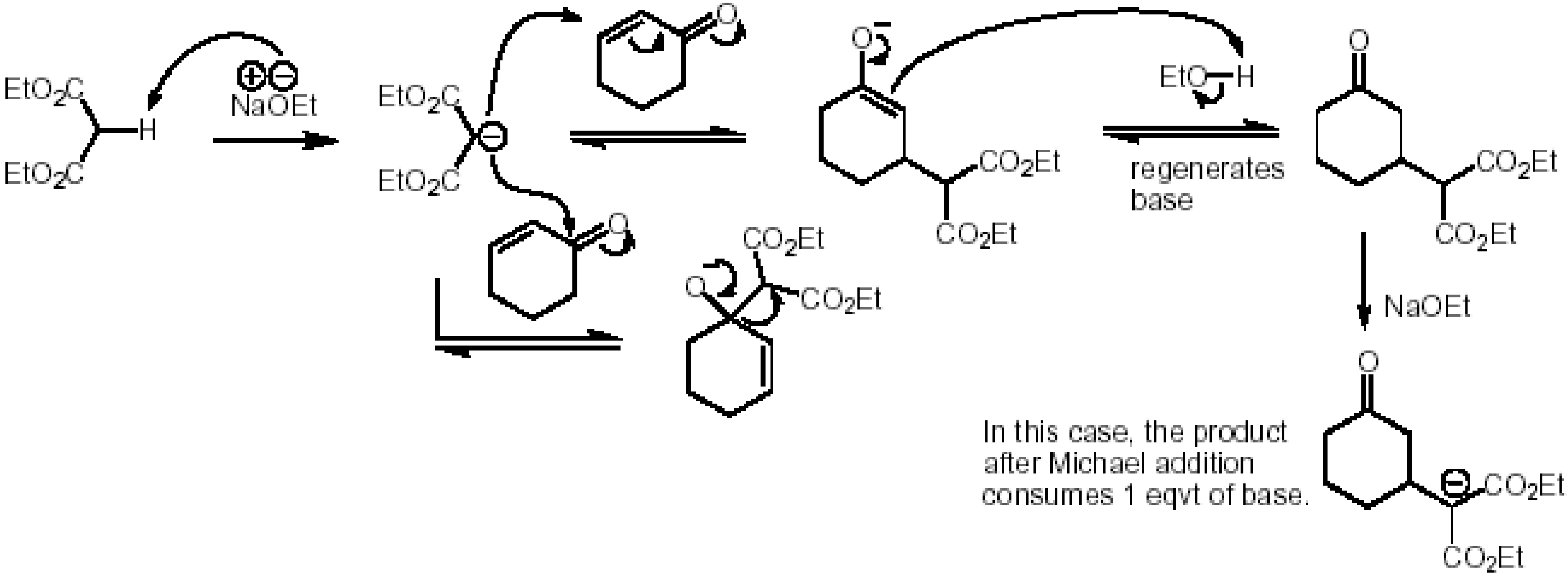


*****1,4-addition, also called Michael addition, or conjugate addition:**



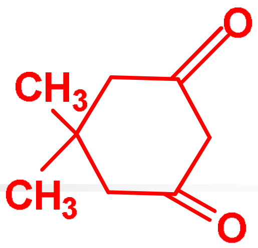


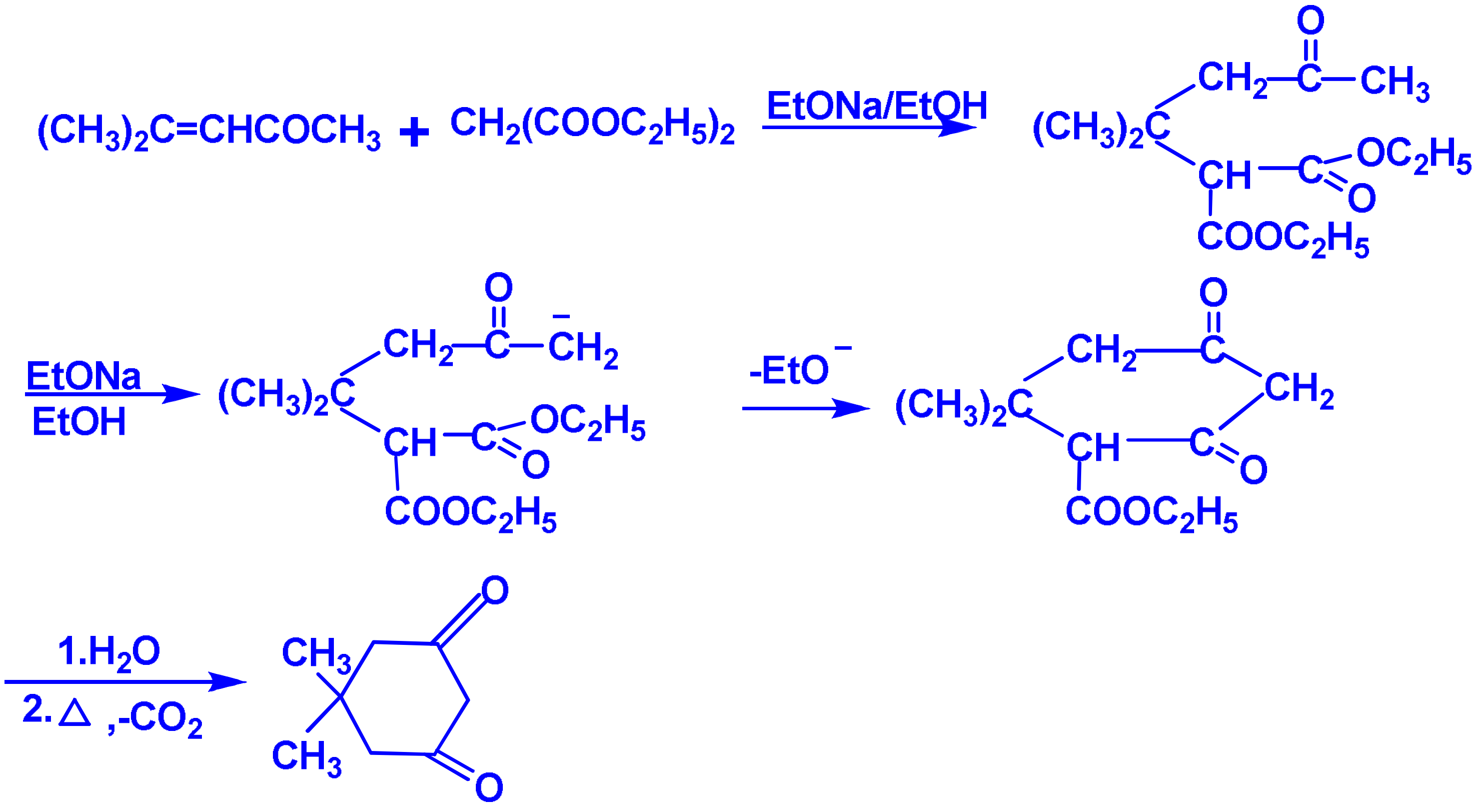
Mechanism



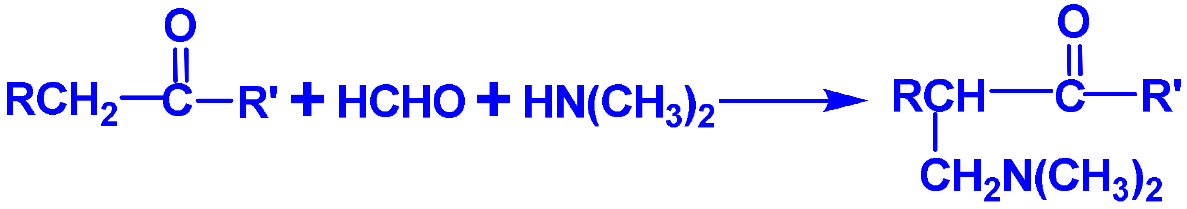
In this case, the product
after Michael addition
consumes 1 eqvt of base.

Give a synthetic route for the following compound





(G)Mannich Reaction



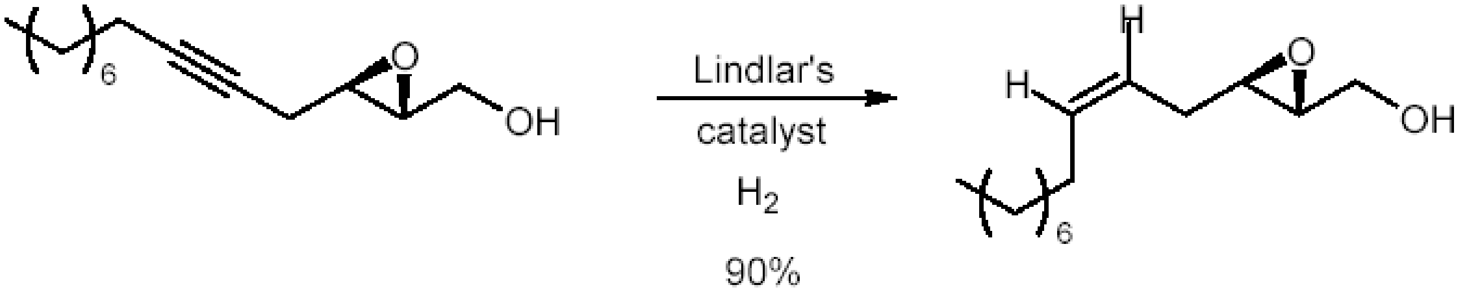
$$RCH_2-\overset{\overset{\displaystyle O}{\|}}{C}-R' + HCHO + HN(CH_3)_2 \longrightarrow \underset{\underset{\displaystyle CH_2N(CH_3)_2}{|}}{RCH}-\overset{\overset{\displaystyle O}{\|}}{C}-R'$$

Olefin Synthesis

I. Reduction of Alkynes

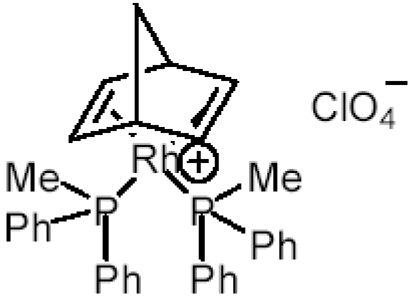
A) Semi-hydrogenation

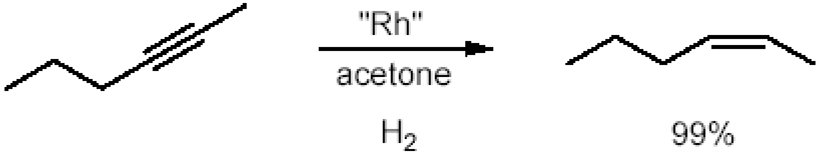
1) Lindlar's catalyst
  - Pd on $CaCO_3$
  - Pd and an amine (usually quinoline) which "poison" or deactivate the Pd catalyst

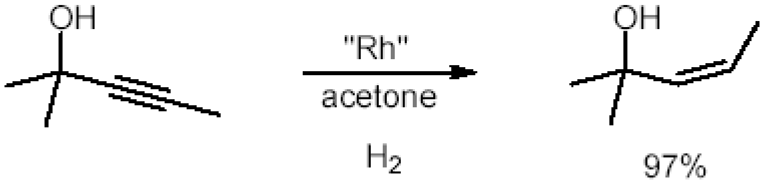


Olefin Synthesis

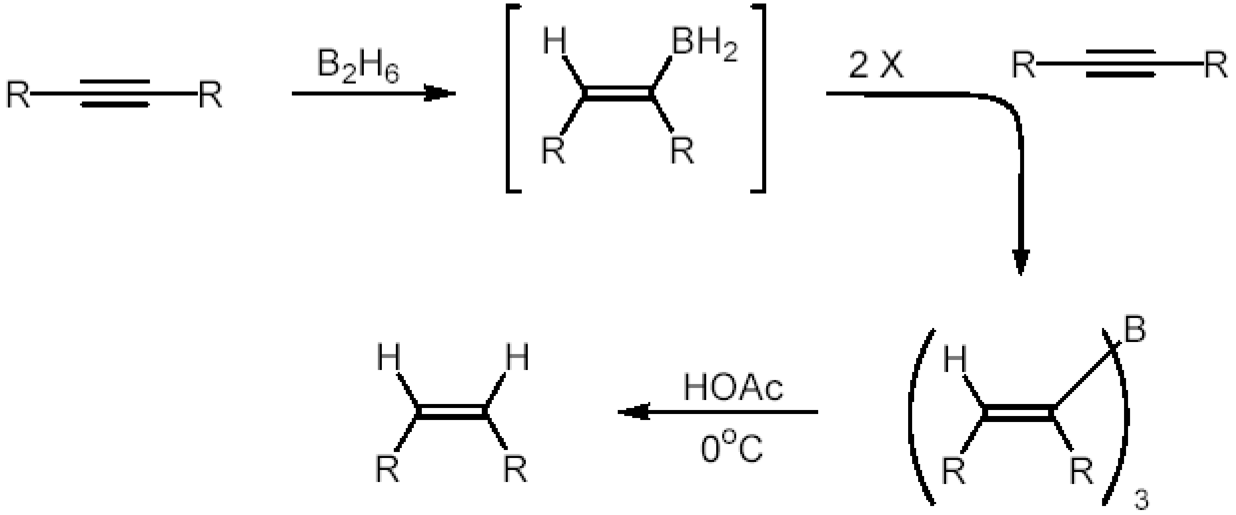
2) Rhodium catalyst (homogeneous)

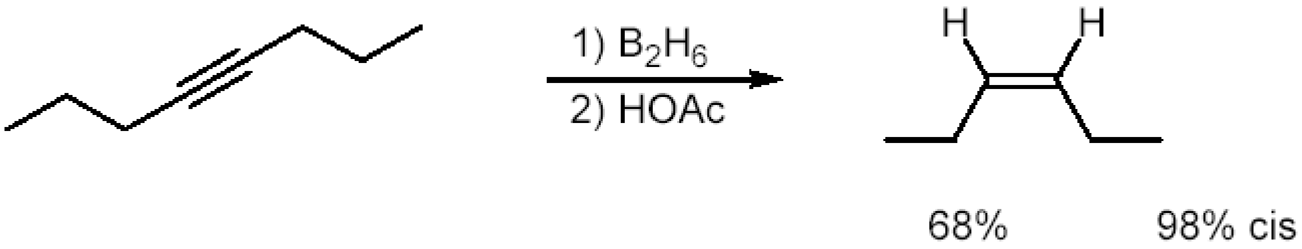




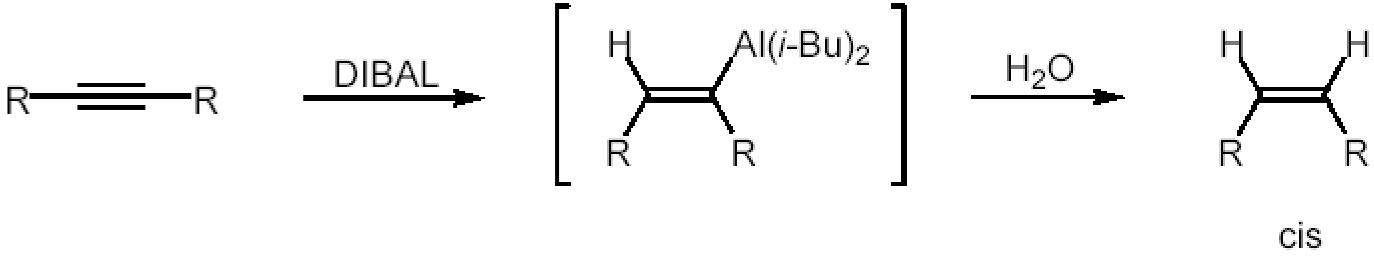


B) Hydroboration

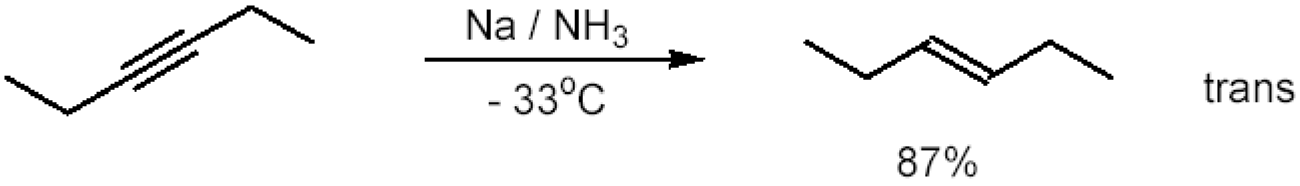




C) Hydroalumination with DIBAL: $(i\text{Bu})_2\text{AlH}$

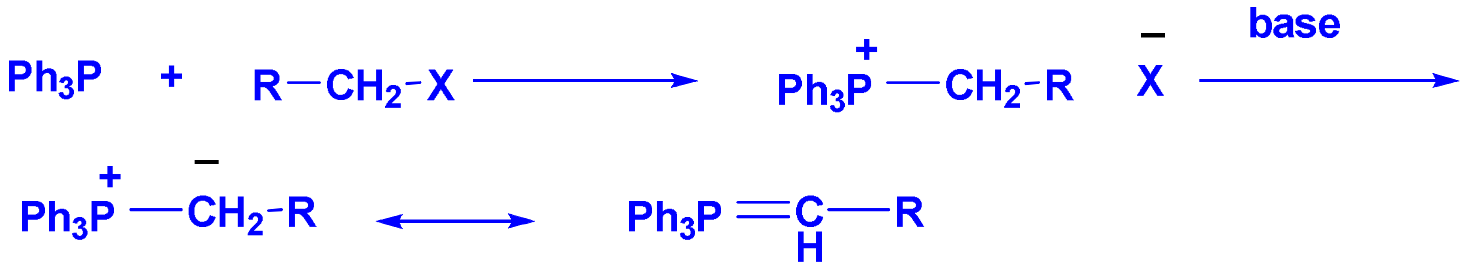


D) Dissolved Metal Reduction

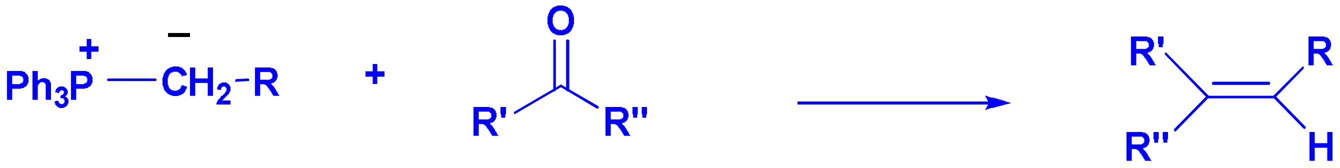


II. Wittig Olefination

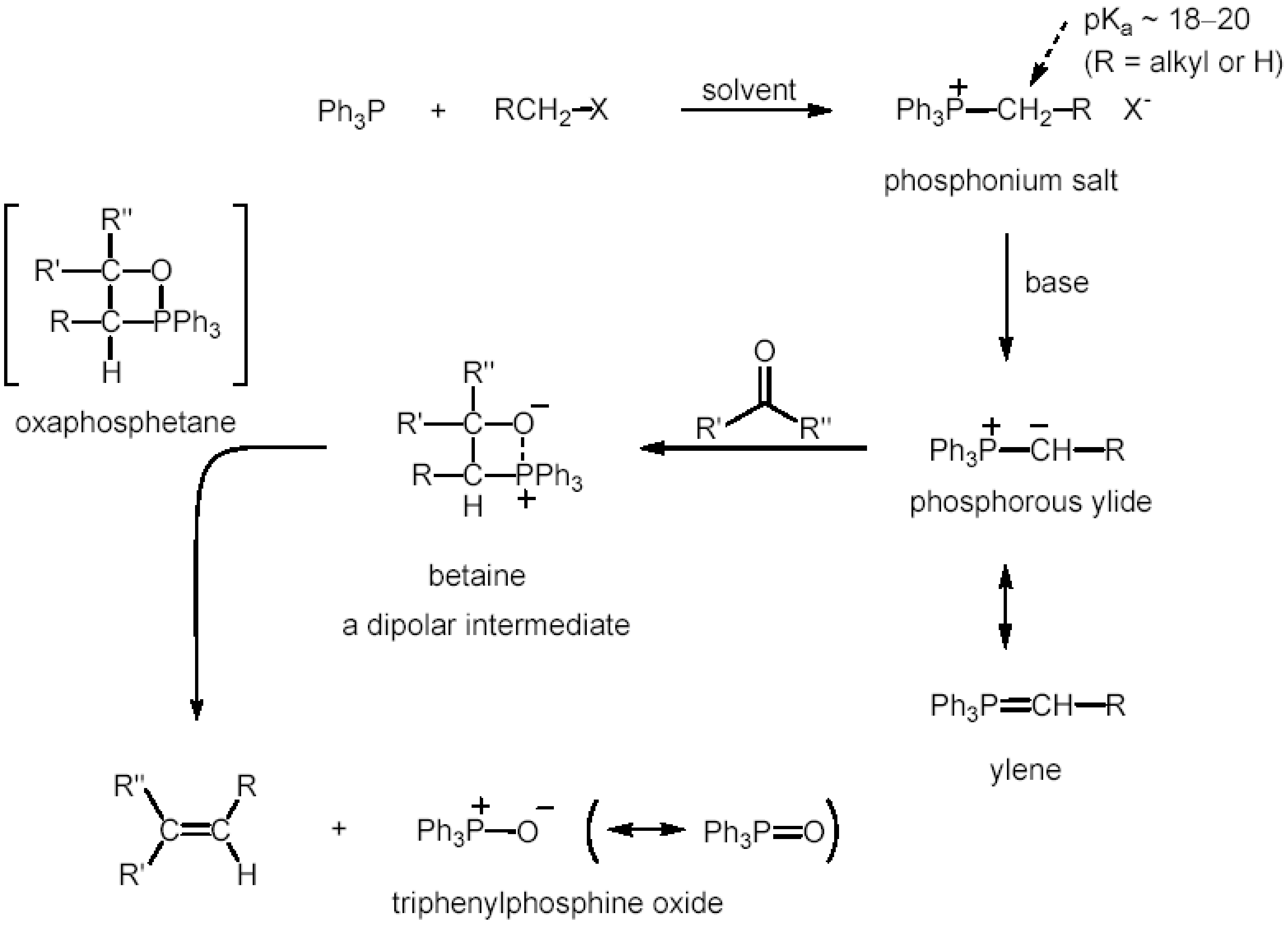
Preparation(Yilde)



Reaction



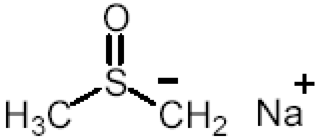
Mechanism


Ph_3P + RCH_2–X
solvent
$Ph_3\overset{+}{P}$–CH_2–R X^-
pKa ~ 18–20
(R = alkyl or H)
phosphonium salt
base
phosphorous ylide
ylene
betaine
a dipolar intermediate
oxaphosphetane
triphenylphosphine oxide

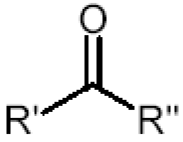
Wittig Olefination

Solvent: Et_2O, THF, DME, DMSO, ROH

Base: PhLi, *n*-BuLi, LDA, RONa, KHMDS



Substrates: ketones or aldehydes

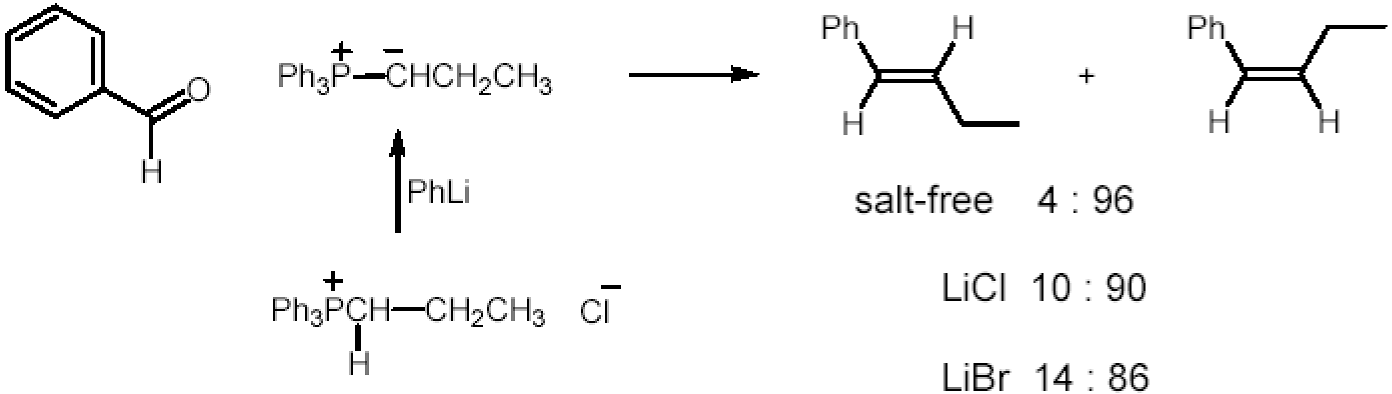


Wittig Olefination

None-stabilized ylides (R = alkyl group or EDG) are sensitive to H_2O and O_2.

- Require strong base to generate ylide from the phosphonium salt.
- Cis-alkene is the predominant product.

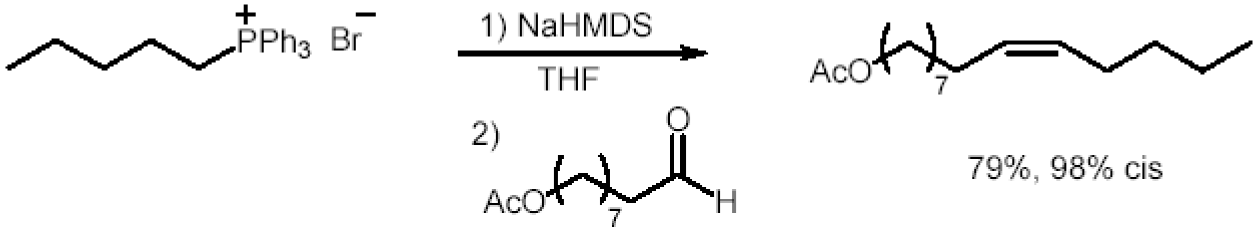
e.g.

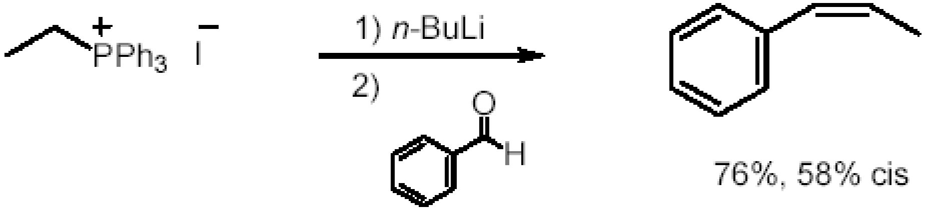


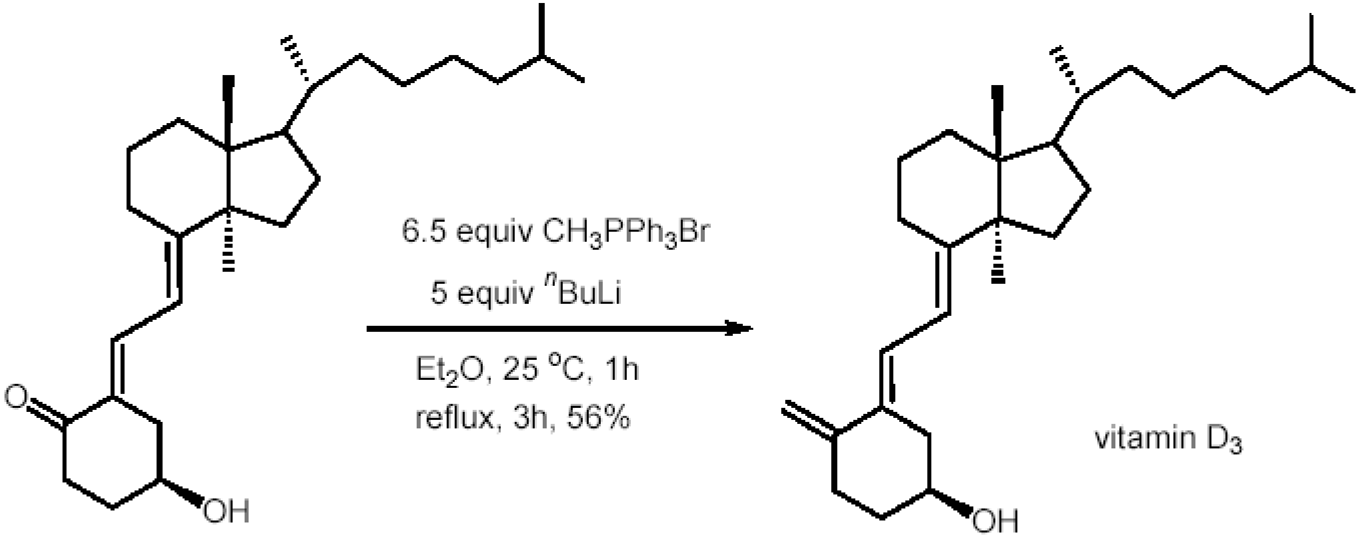
salt-free 4 : 96

LiCl 10 : 90

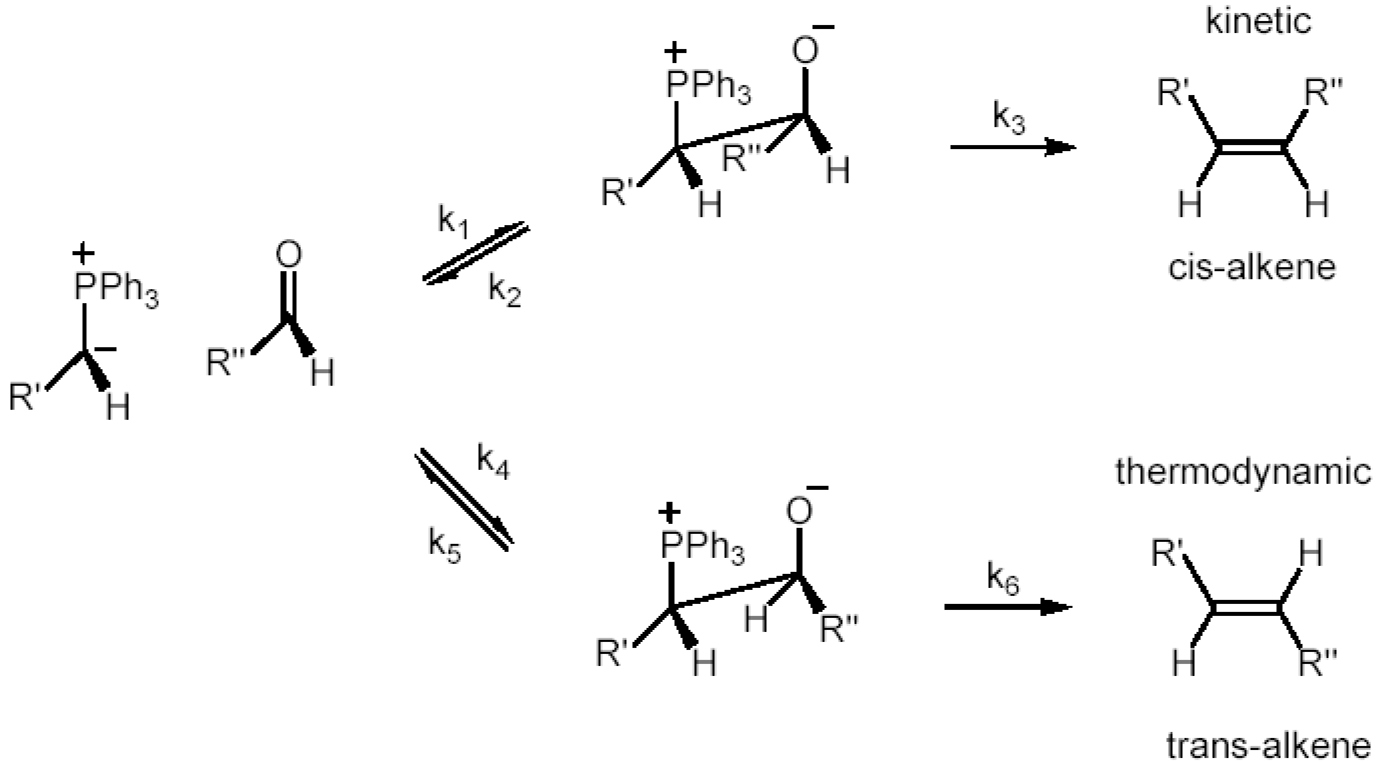
LiBr 14 : 86


$^{+}$PPh$_3$ Br^{-}
1) NaHMDS
THF
2)
AcO
7
O
H
AcO
7
79%, 98% cis


$^{+}$PPh$_3$ I^{-}
1) *n*-BuLi
2)
O
H
76%, 58% cis

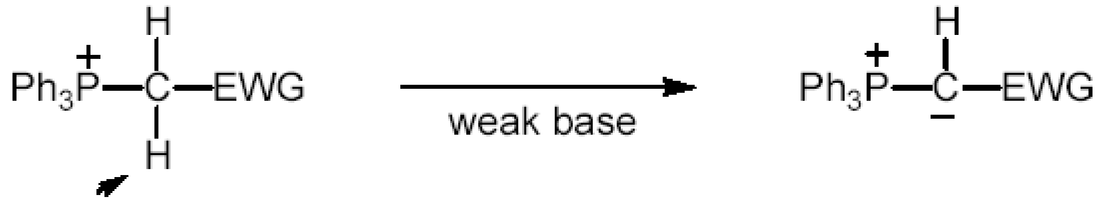

O
OH
6.5 equiv CH_3PPh_3Br
5 equiv ^nBuLi
Et_2O, 25 ^oC, 1h
reflux, 3h, 56%
OH
vitamin D_3

Stereochemistry of Wittig reaction



- $k_1 >> k_4$ => the cis-alkene is the kinetic product.
- The trans-alkene is more stable (thermodynamic product)

Stabilized yildes

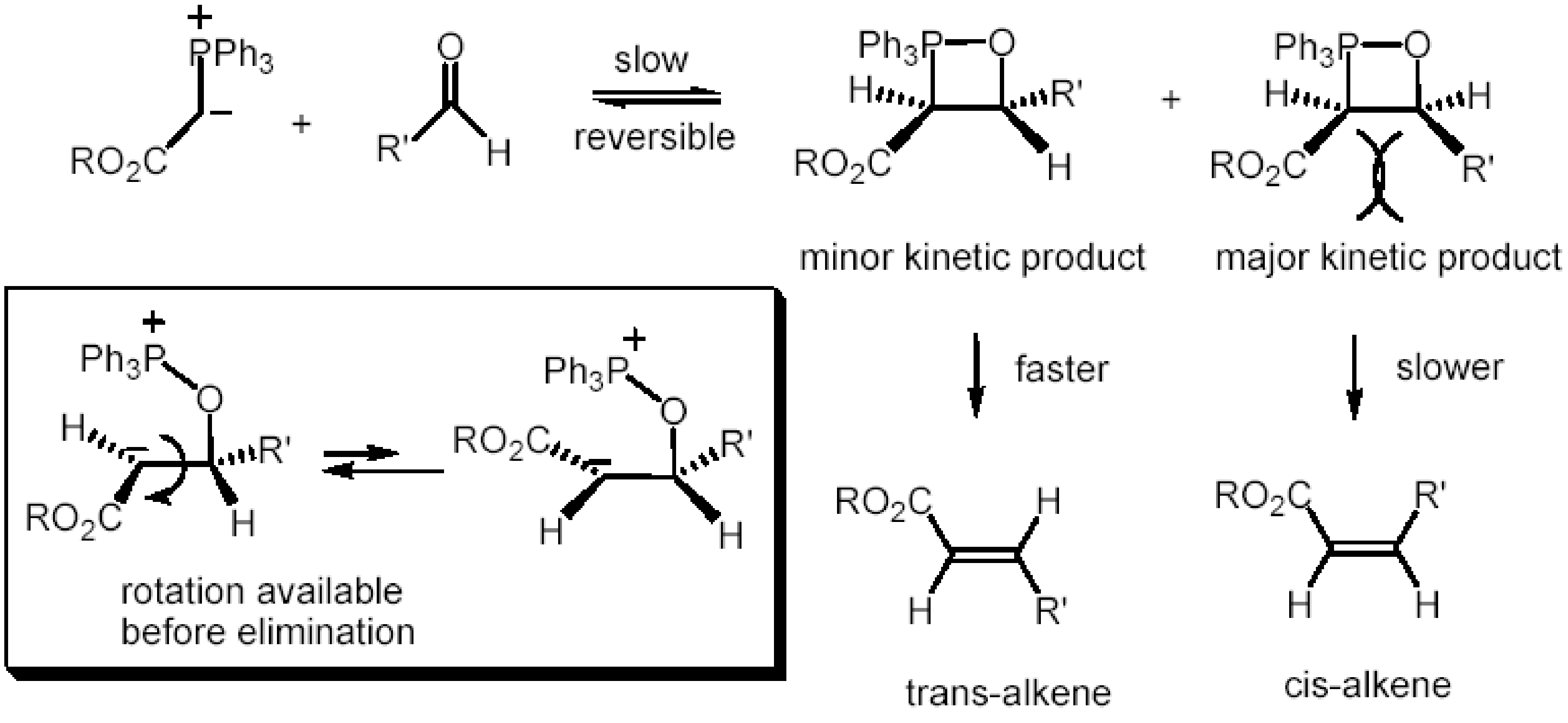


$Ph_3\overset{+}{P}-CH_2-EWG \xrightarrow[\text{weak base}]{} Ph_3\overset{+}{P}-\overset{-}{C}H-EWG$

Has two EWGs
so the pK_a is very low

- EWG: -COOR’, -COPh, -CN, -Aryl
- Weak base: OR^-, OH^-, CO_3^{2-}
- Stabilized ylides are solid; stable to storage, not particularly sensitive to moisture
- More easy to form, but less reactive (react with aldehydes and activated ketones).
- Generally gives *trans*-alkenes as the major product.

Mechanism



slow

reversible

minor kinetic product

major kinetic product

faster

slower

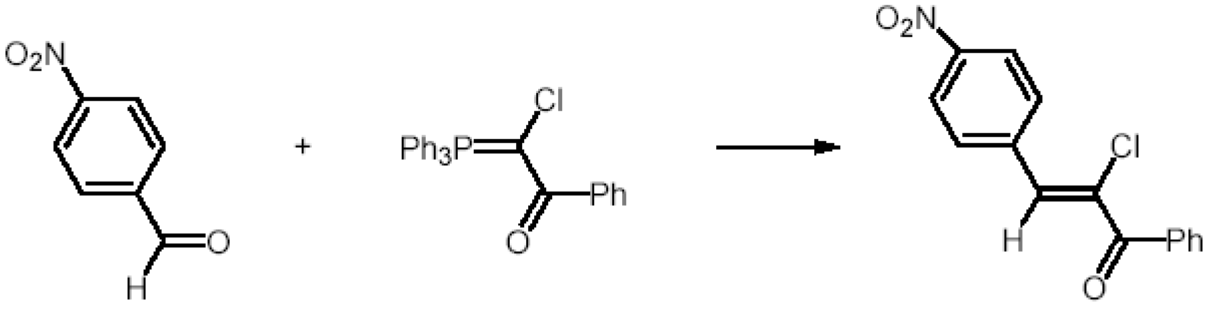
trans-alkene

cis-alkene

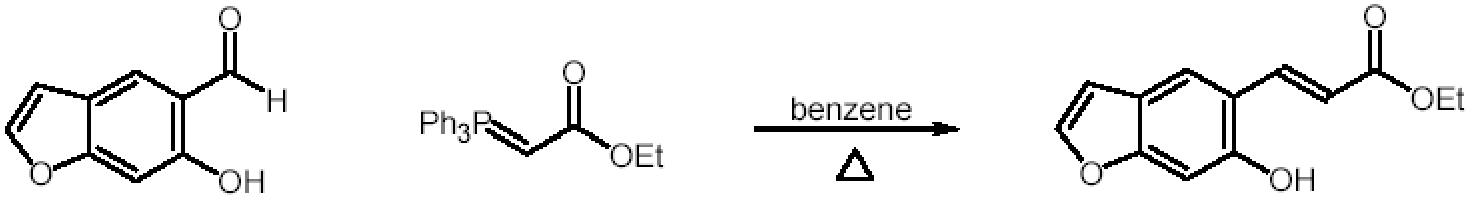
rotation available
before elimination

thermodynamically more stable
prodominant or exclusive product

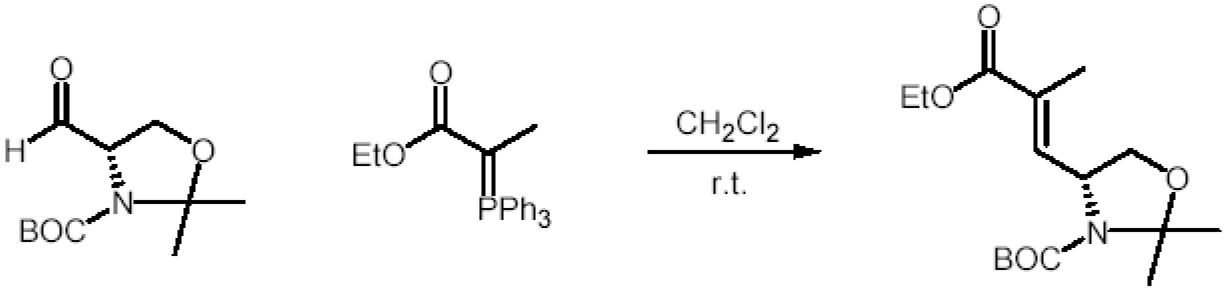
e. g.



major



(86%)



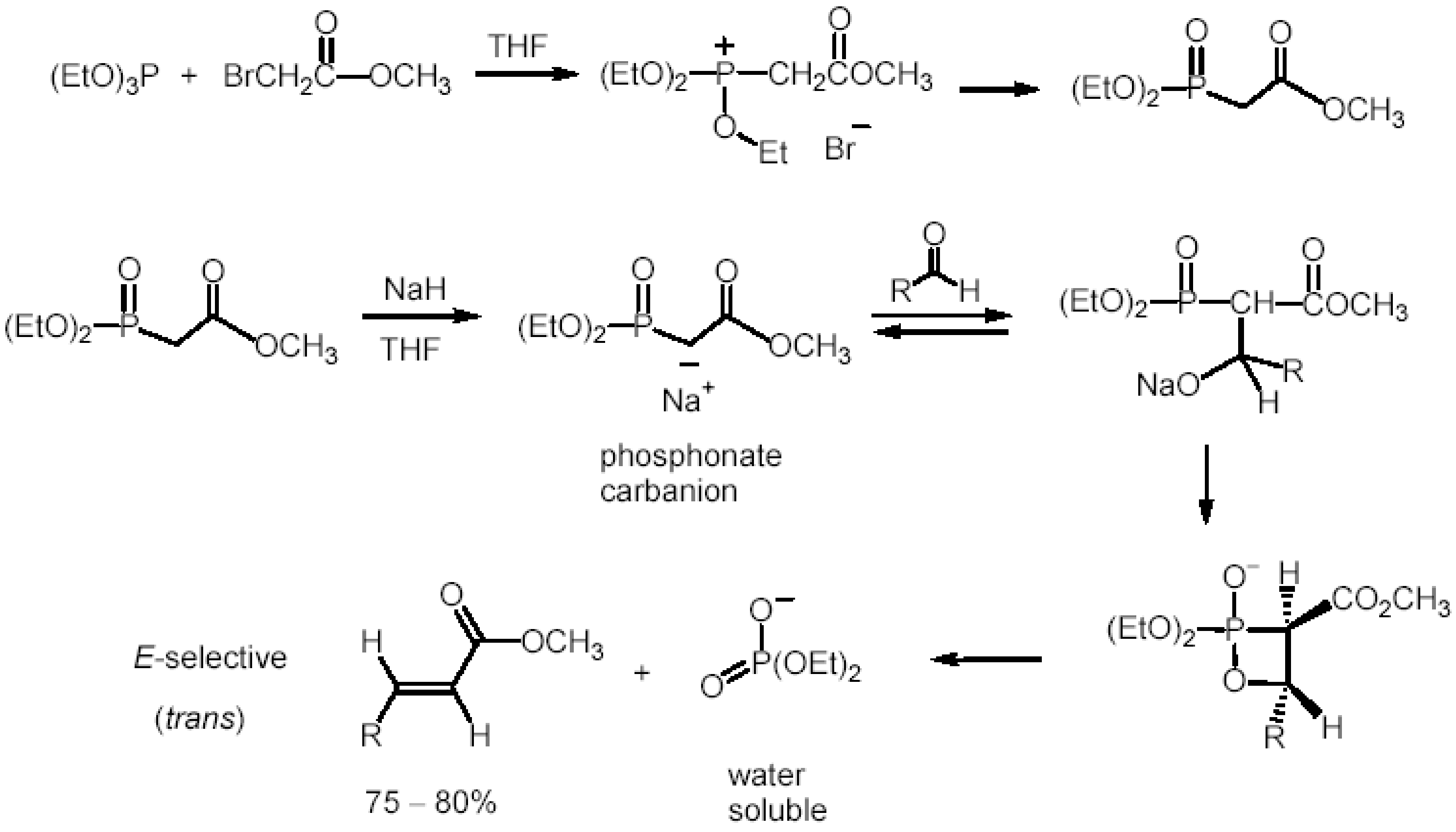
66% (*E* : *Z* = 20 : 1)

III. Horner-Wadsworth-Emmons Olefination

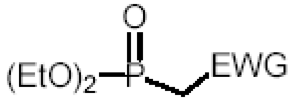
- Horner reaction

HWE reaction

Wadsworth and Emmons modified the Horner reaction to use phosphonate esters (prepared by Arbuzov reaction).

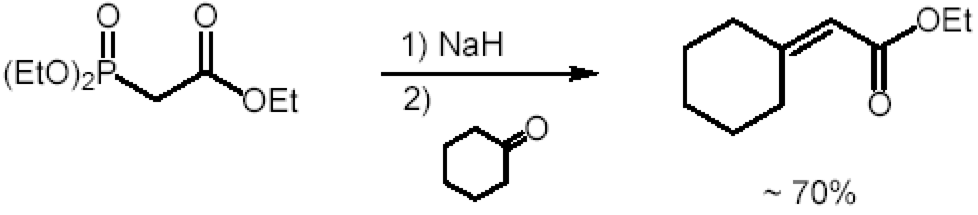


Good reactions for:

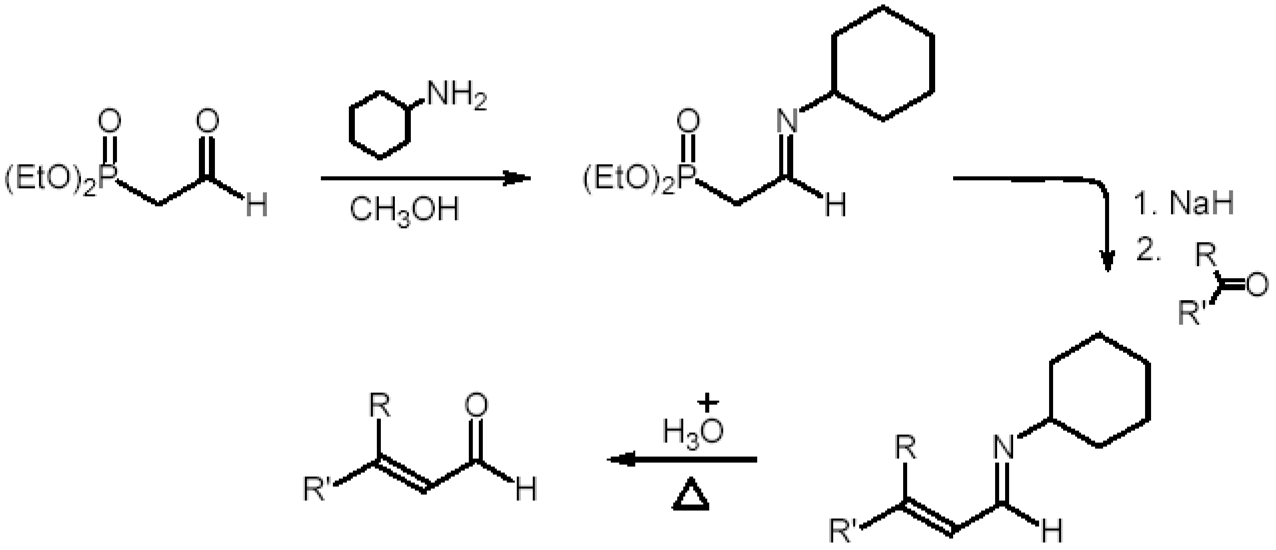


EWG = CN, CO_2R, COR, CHO, SO_2Ph, Ph

e. g.

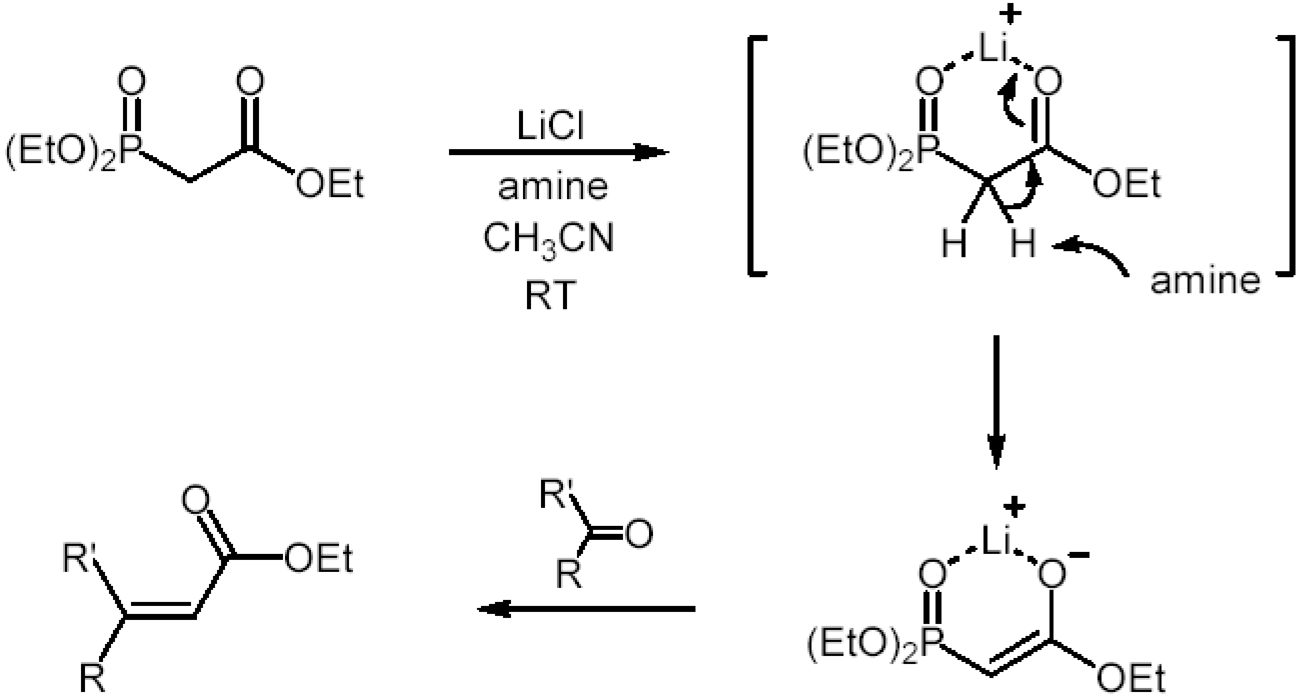


(EtO)$_2$P
O
O
OEt
1) NaH
2)
O
OEt
O
~ 70%



(EtO)$_2$P
O
O
H
NH$_2$
CH$_3$OH
(EtO)$_2$P
O
N
H
1. NaH
2.
R
R'
O
R
N
R'
H
$H_3\overset{+}{O}$
Δ
R
O
R'
H

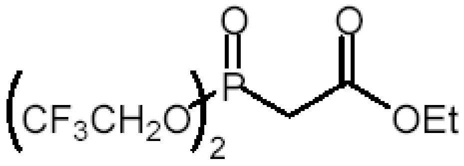
Masamune-Roush modification:



- Very mild conditions: can be done at RT with a mild base (DBU or DIPEA).
- The *trans*-alkene is the major product.

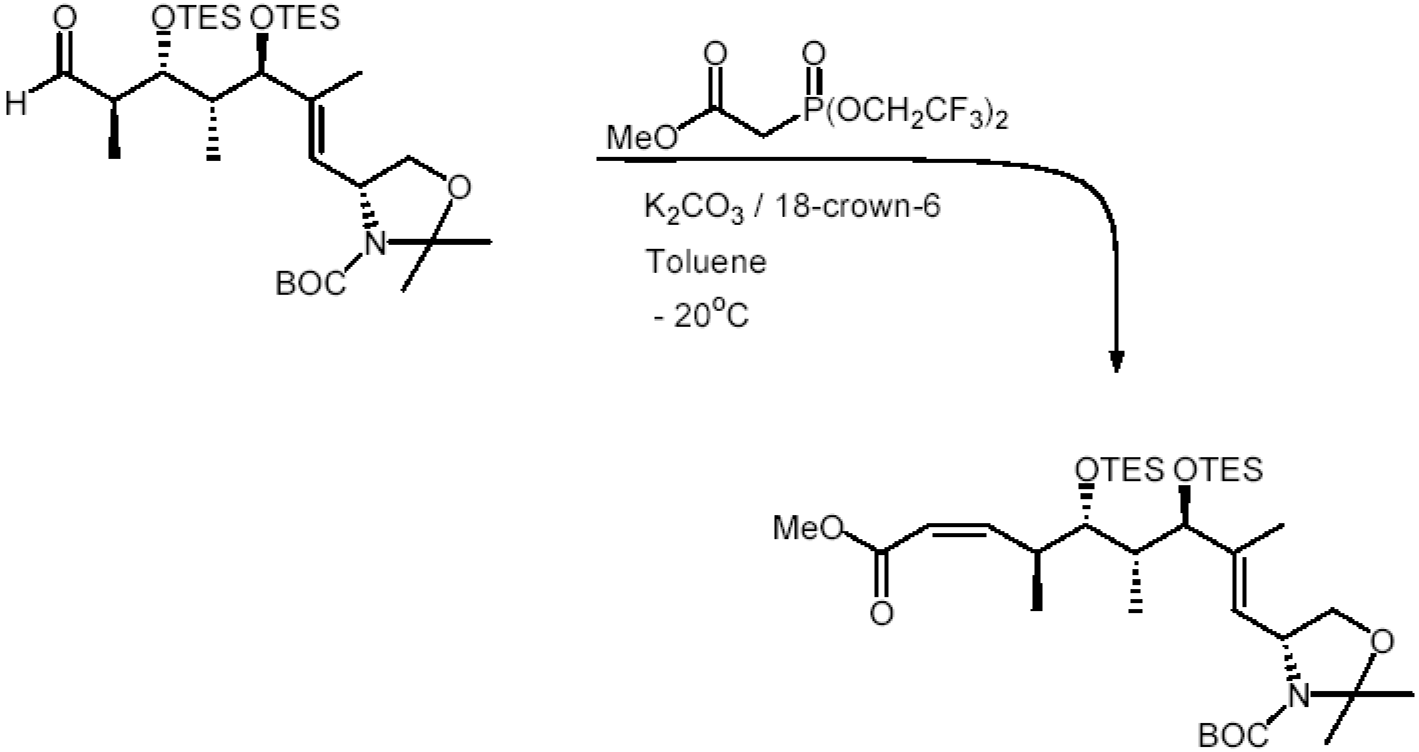
Still modification:

Still's phosphonate



Due to the electron withdrawing group (CF_3CH_2O) of the phosphonate, the elimination step is fast and formation of the kinetic product (cis- or Z-alkene) become predominant.

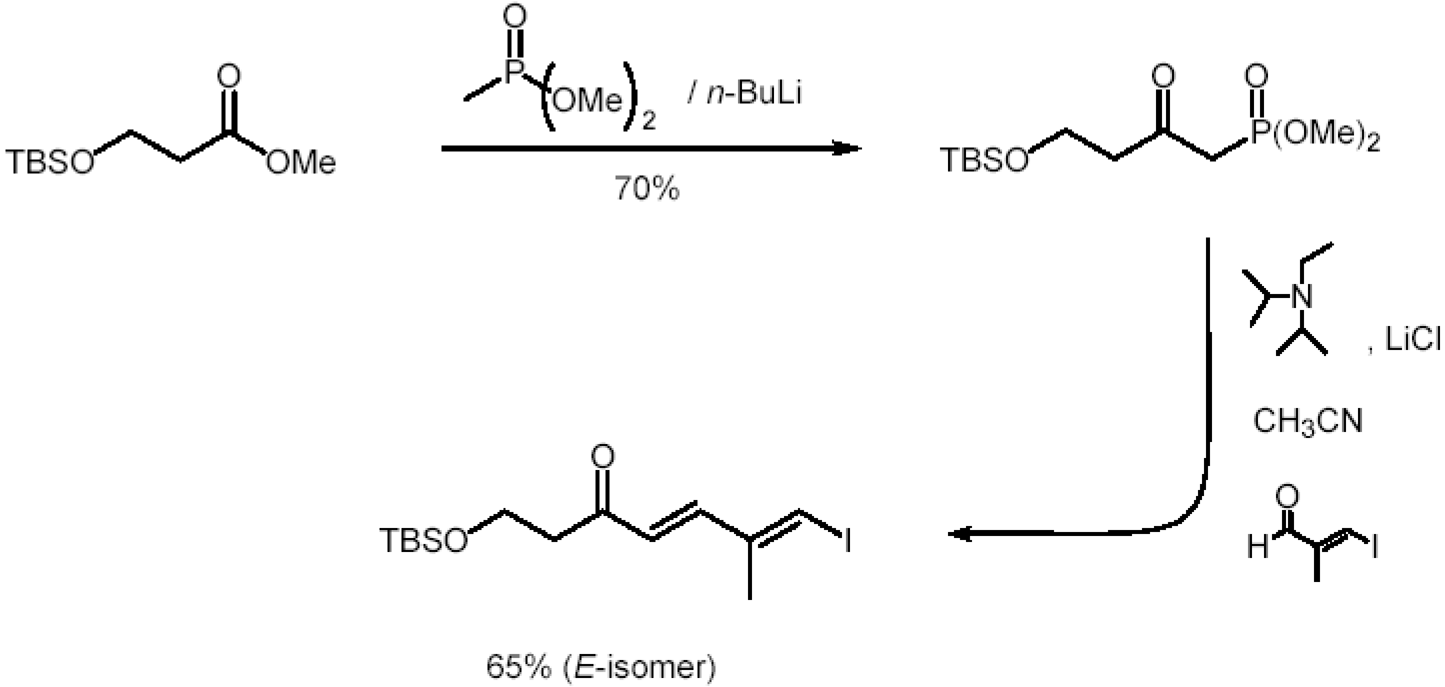
Typical conditions: K_2CO_3, toluene, 18-crown-6, -40 – 0°C


O
OTES OTES
H
O
N
BOC
O
O
MeO
P(OCH2CF3)2
K2CO3 / 18-crown-6
Toluene
- 20oC
OTES OTES
MeO
O
O
N
BOC

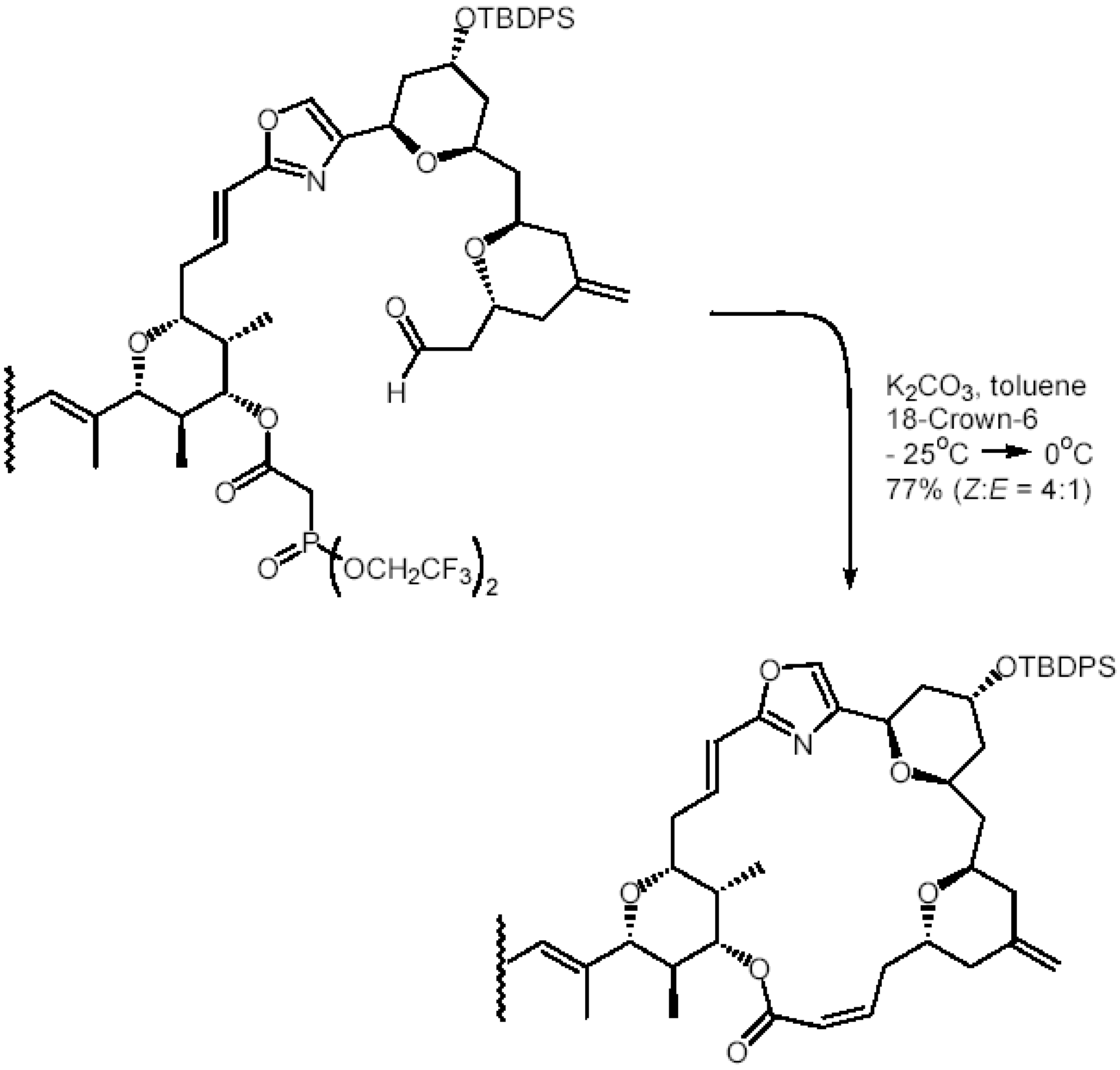
75% cis-only

Applications in natural product synthesis:

Example 1.



Example 2.



K_2CO_3, toluene
18-Crown-6
- 25°C → 0°C
77% (*Z*:*E* = 4:1)

IV. Olefin Metathesis

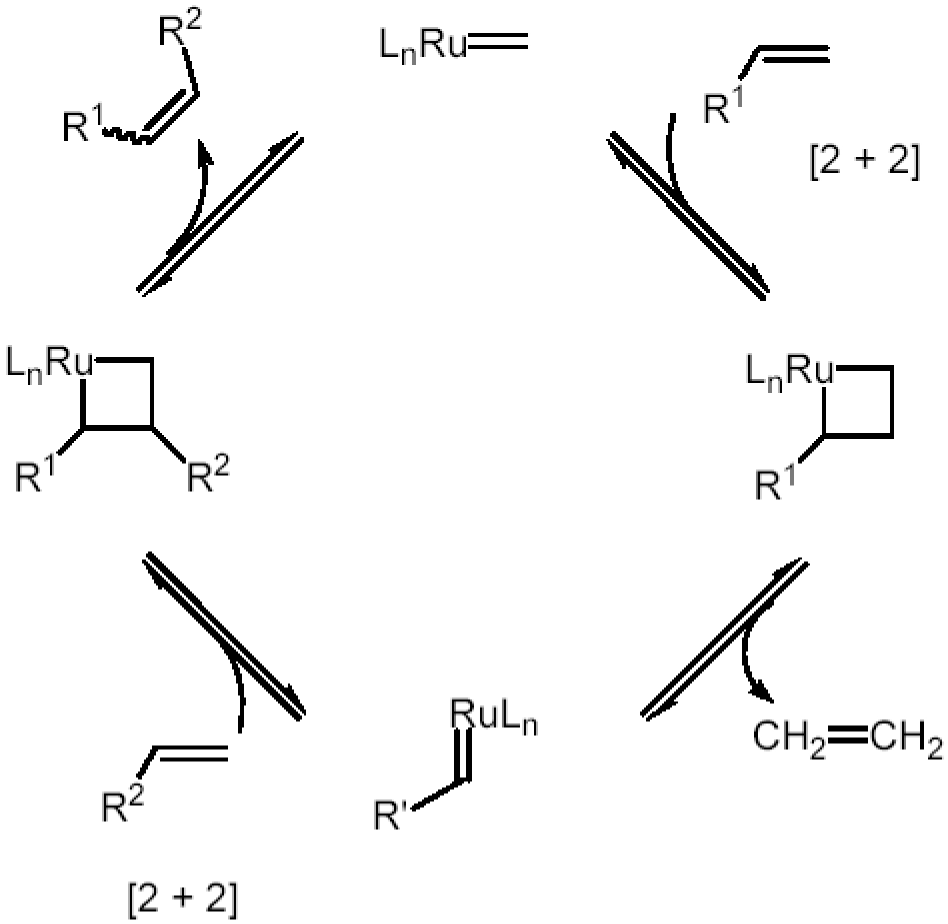
Mechanism

- The olefin metathesis reaction was reported as early as 1955 in a Ti(II)-catalyzed polymerization of norbornene: Anderson, A. W.; Merckling, M. G. *Chem. Abstr.* **1955**, *50*, 3008i.

- • 15 years later, Chauvin first proposed that olefin metathesis proceeds via metallacyclobutanes: Herisson, P. J.-L.; Chauvin, Y. *Makromol. Chem.* **1970**, *141*, 161-176.

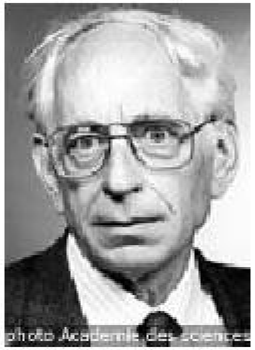
- • It is now generally accepted that both cyclic and acyclic olefin metathesis reactions proceed via metallacyclobutane and metal-carbene intermediates: Grubbs, R. H.; Burk, P. L.; Carr, D. D. *J. Am. Chem. Soc.* **1975**, *97*, 3265-3266.

Ruthenium Carbene



The Nobel Prize in Chemistry 2005

"for the development of the metathesis method in organic synthesis"



Yves Chauvin

France

Institut Français du
Pétrole
Rueil-Malmaison, France

b. 1930

Robert H. Grubbs

USA

California Institute of
Technology (Caltech)
Pasadena, CA, USA

b. 1942

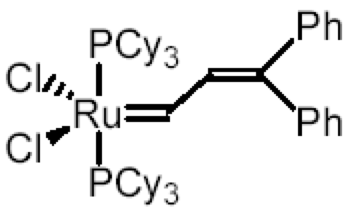
Richard R. Schrock

USA

Massachusetts Institute
of Technology (MIT)
Cambridge, MA, USA

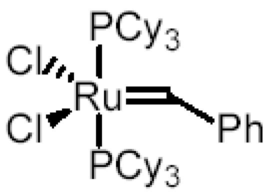
b. 1945

b) Catalysts



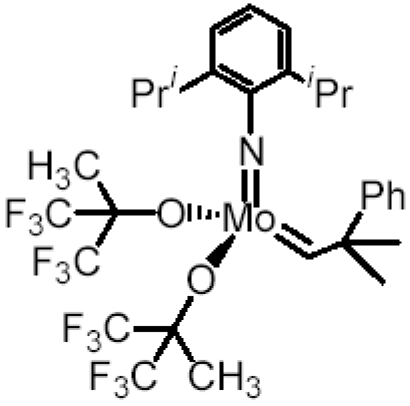
(A)

Grubbs



(B)

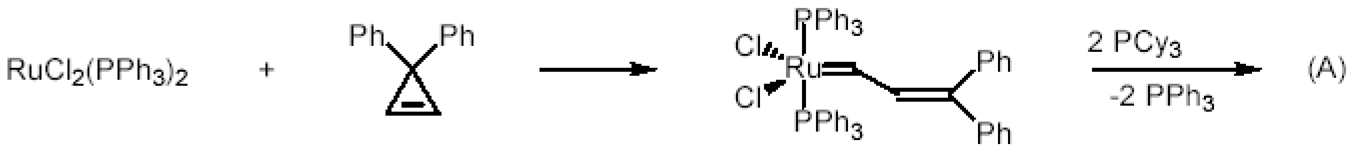
Grubbs

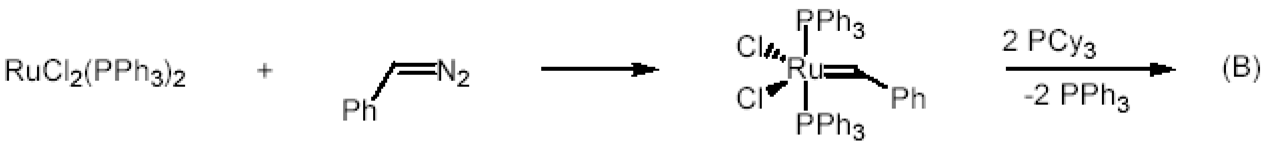


(C)

Schrock

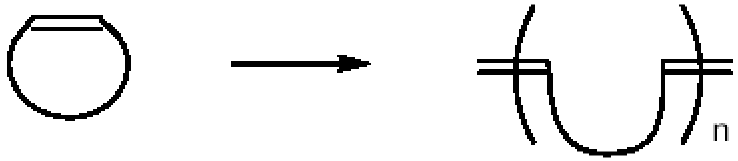
Preparation:



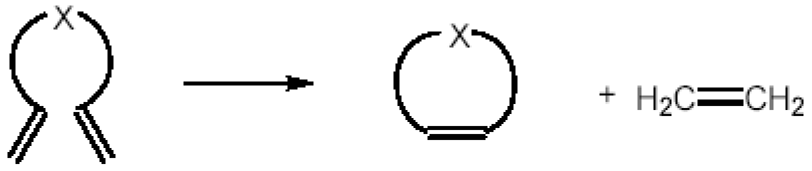


Applications of olefin metathesis:

a) Ring opening metathesis polymerization (ROMP)



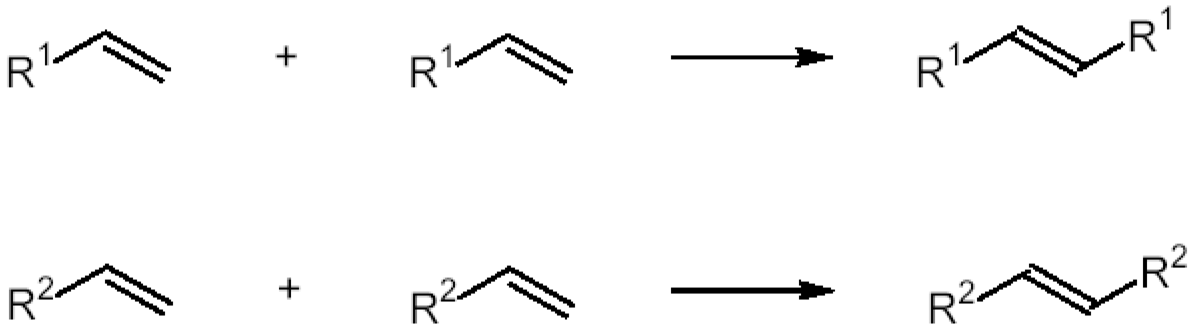
b) Ring-closing metathesis (RCM)



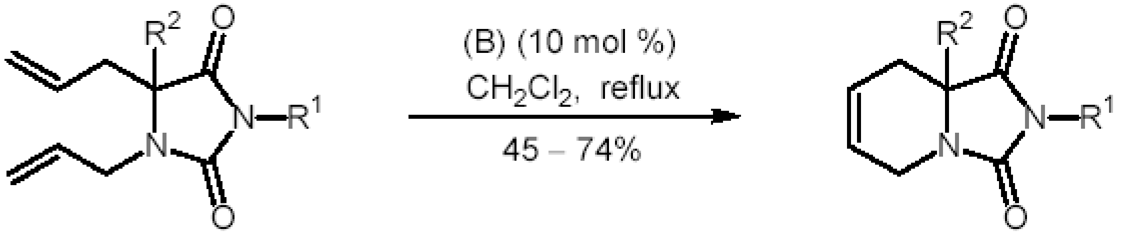
Applications of olefin metathesis:

c) Acyclic cross metathesis

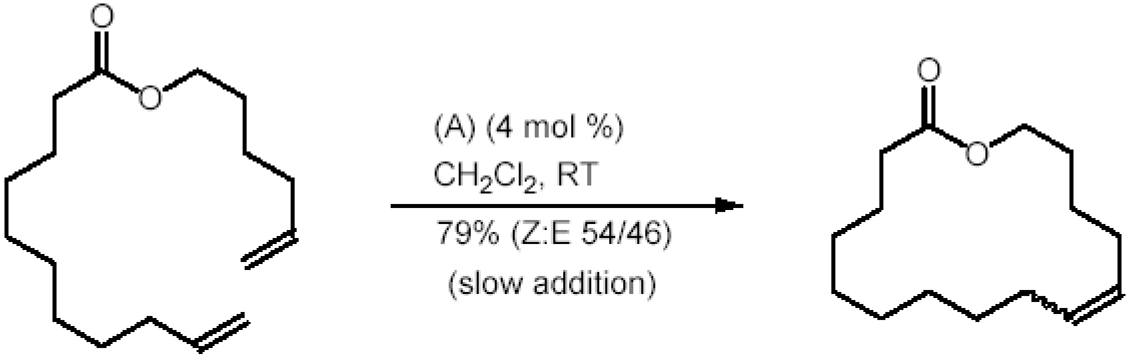
Problem: homocoupling

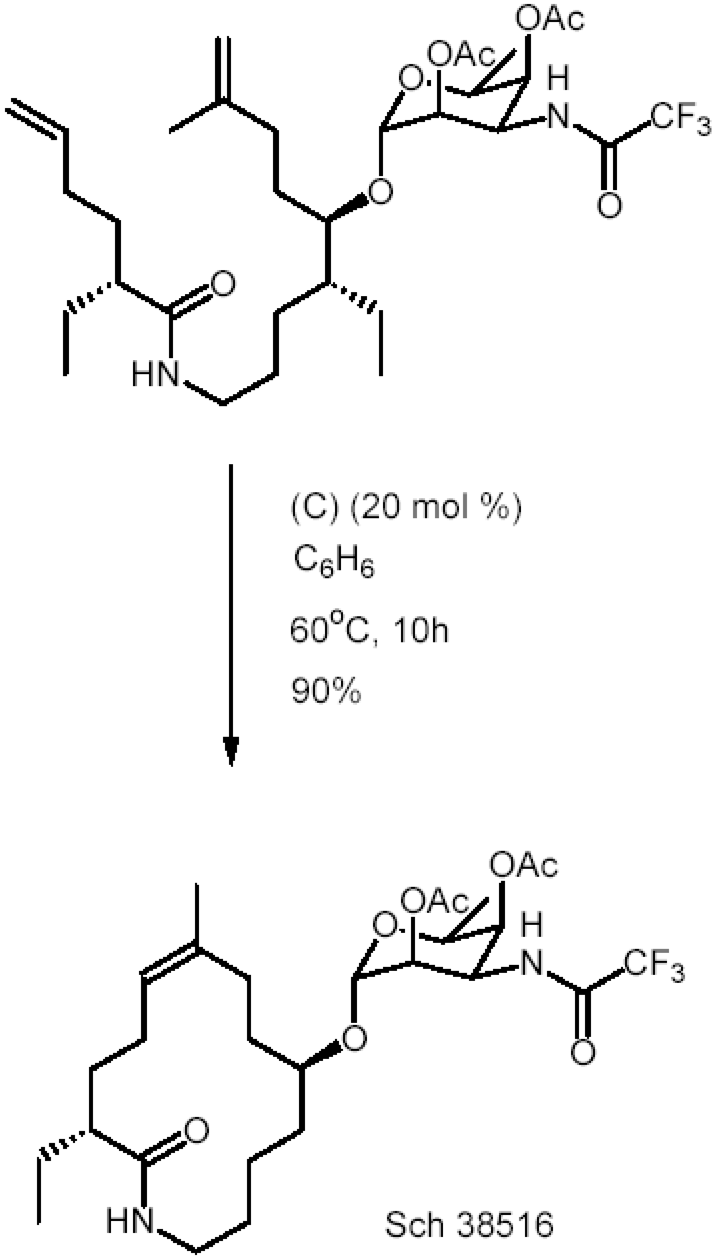


Applications of ring-closing metathesis

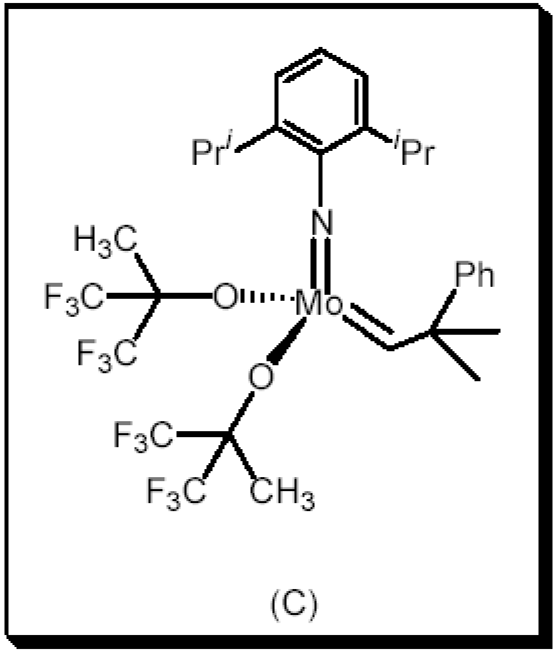


R^1 : alkyl, aryl





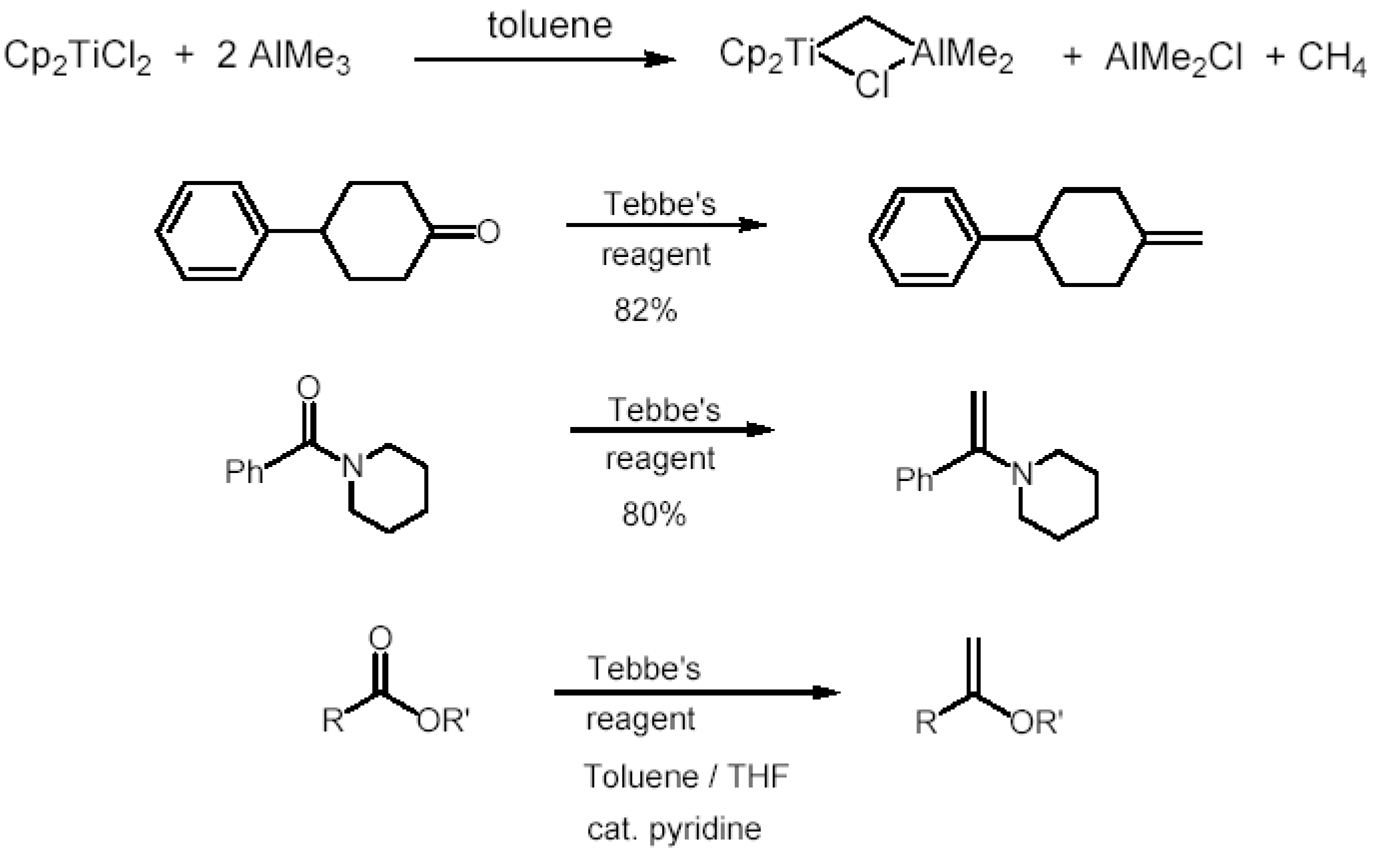
Sch 38516
antifungal agent

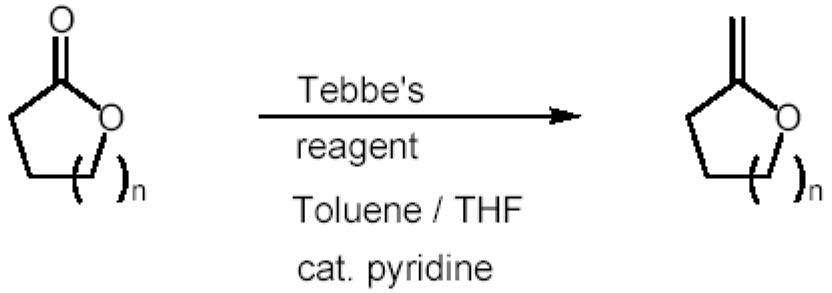


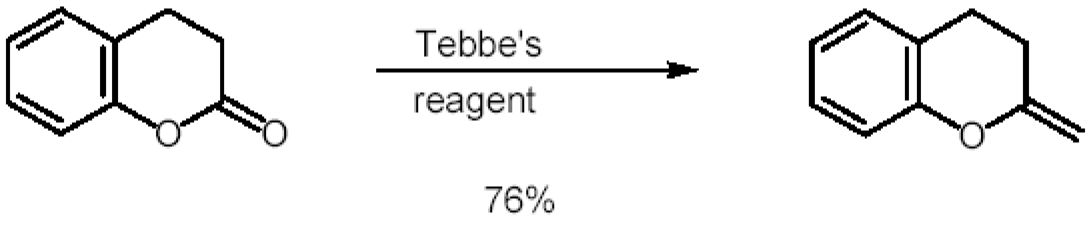
(C)

V. Tebbe’s reagent

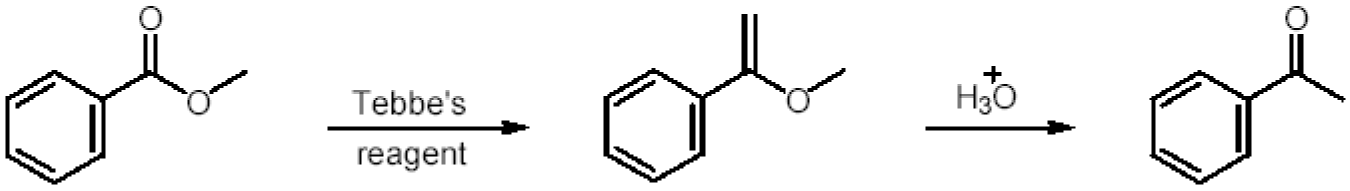
- Preparation:



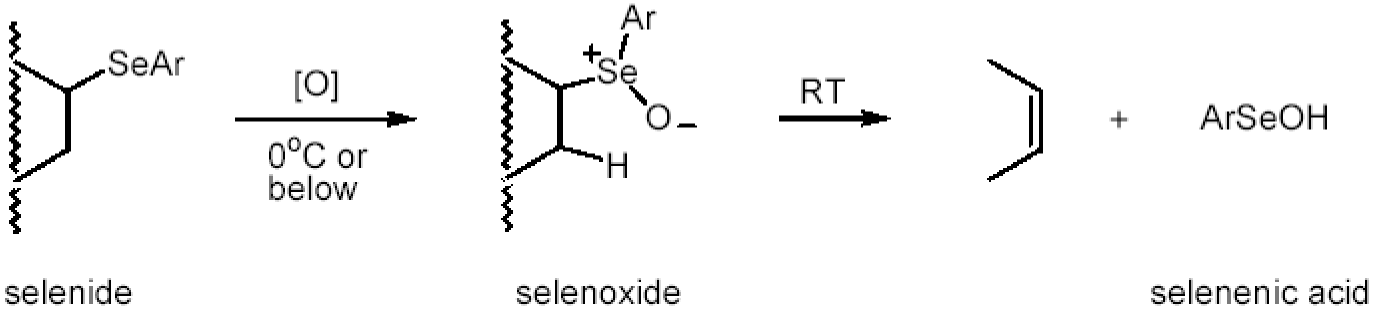




- The resulting enol ether can be hydrolyzed to form a ketone



VI. Selenoxide fragmentation



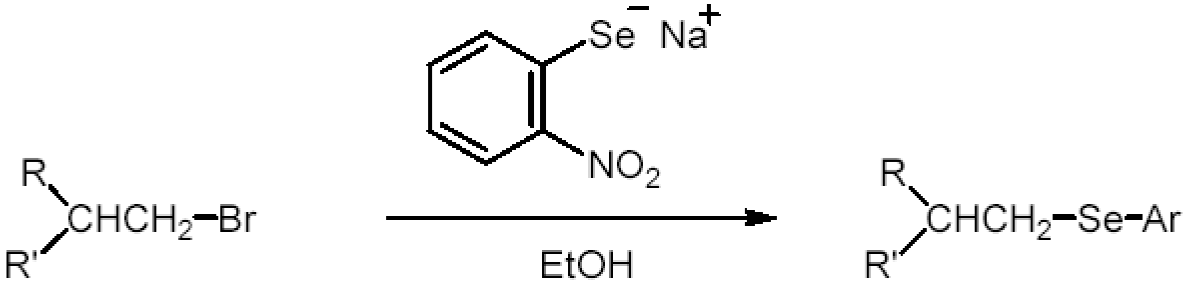
- Alkyl and aryl selenoxide with β-hydrogen undergoes syn-elimination to form alkene under very mild conditions
    - Oxidation conditions:

      a) H_2O_2 / THF / 0°C (most common)
      b) O_3 / CH_2Cl_2 / –78°C
      c) *m*-CPBA / THF
      d) $NaIO_4$ / H_2O / MeOH

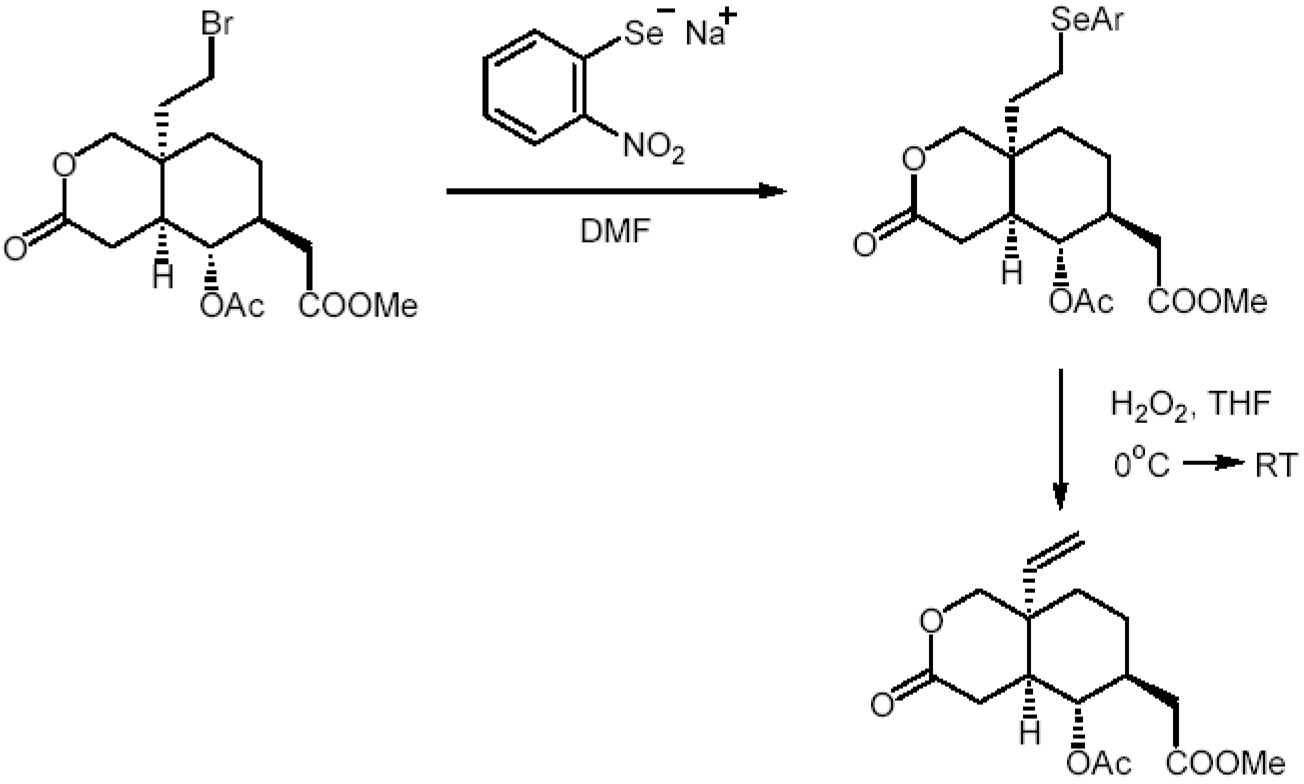
Selenoxide fragmentation

Selenide can be obtained from:

1) Alkyl halide or tosylate

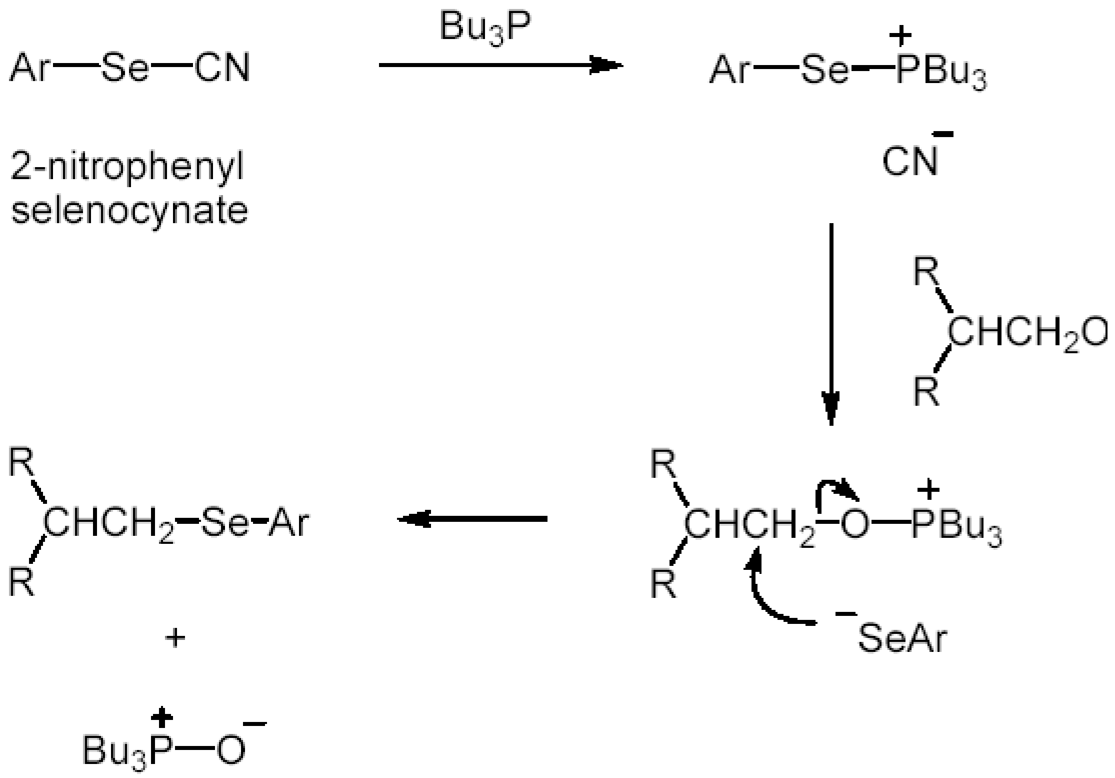


Example 1.

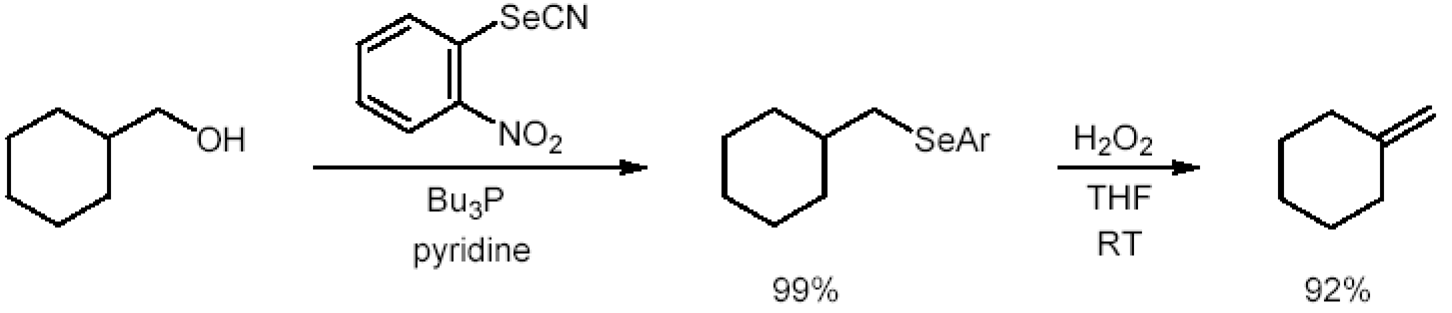

Br
O
O
H
OAc
COOMe
Se⁻ Na⁺
NO2
DMF
SeAr
O
O
H
OAc
COOMe
H2O2, THF
0°C → RT
O
O
H
OAc
COOMe

Selenoxide fragmentation

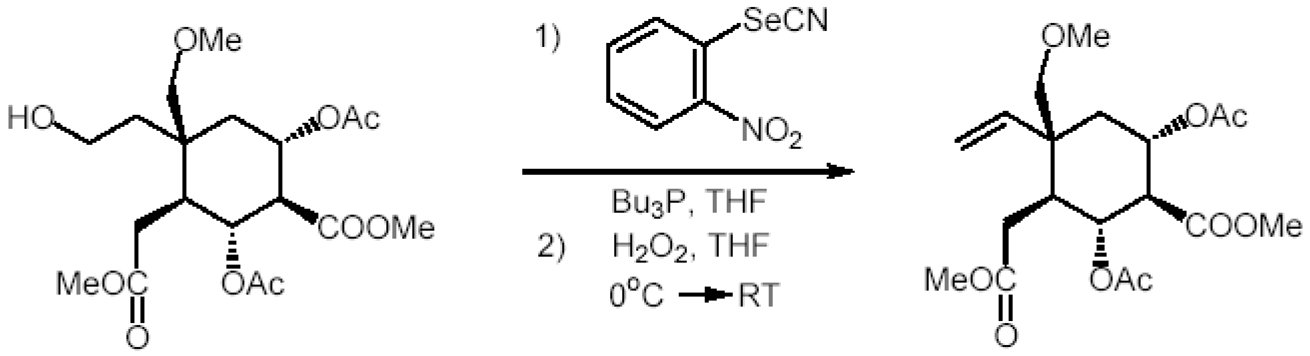
2) Alcohols



Example 1.

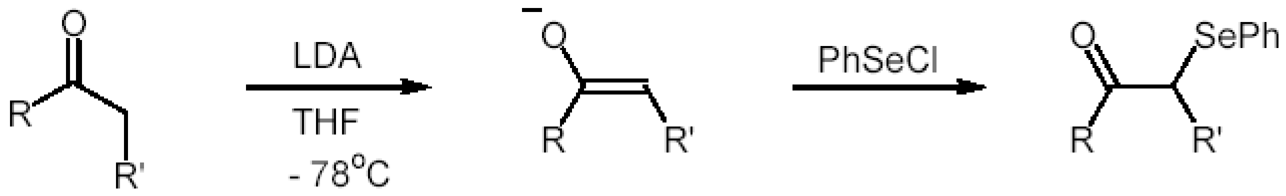


Example 2.

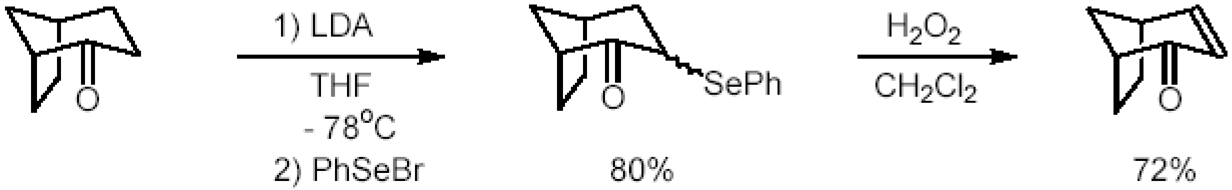


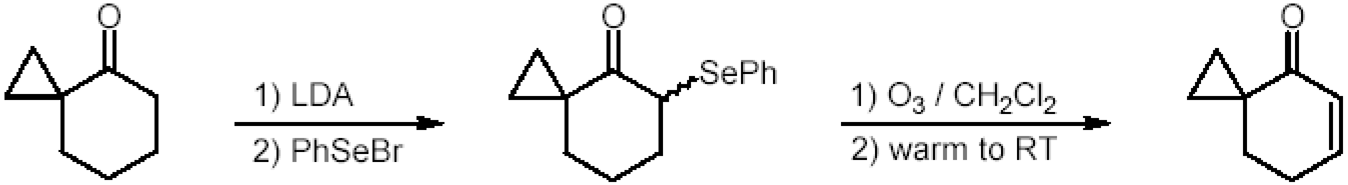
Selenoxide fragmentation

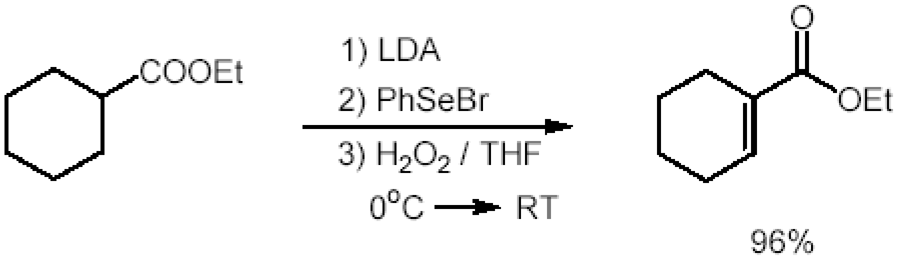
3) Enolate Anions



Examples:


1) LDA
THF
- 78°C
2) PhSeBr
SePh
80%
H2O2
CH2Cl2
72%

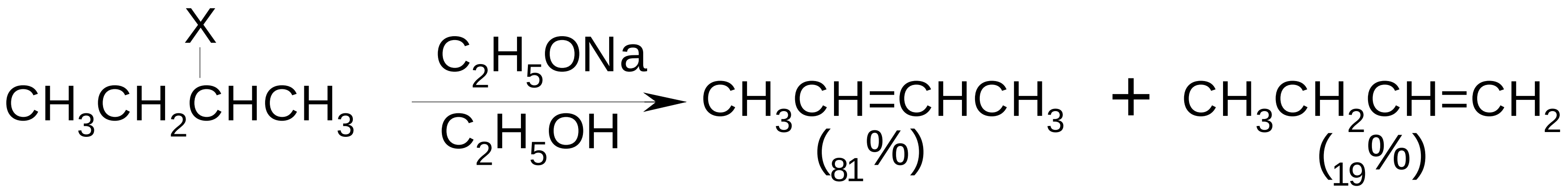

1) LDA
2) PhSeBr
SePh
1) O3 / CH2Cl2
2) warm to RT


COOEt
1) LDA
2) PhSeBr
3) H2O2 / THF
0°C → RT
OEt
96%

Traditional methods

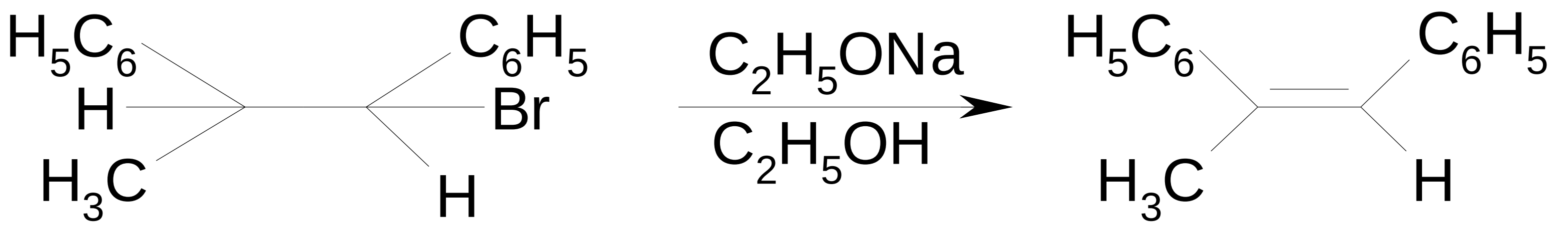
Elimination

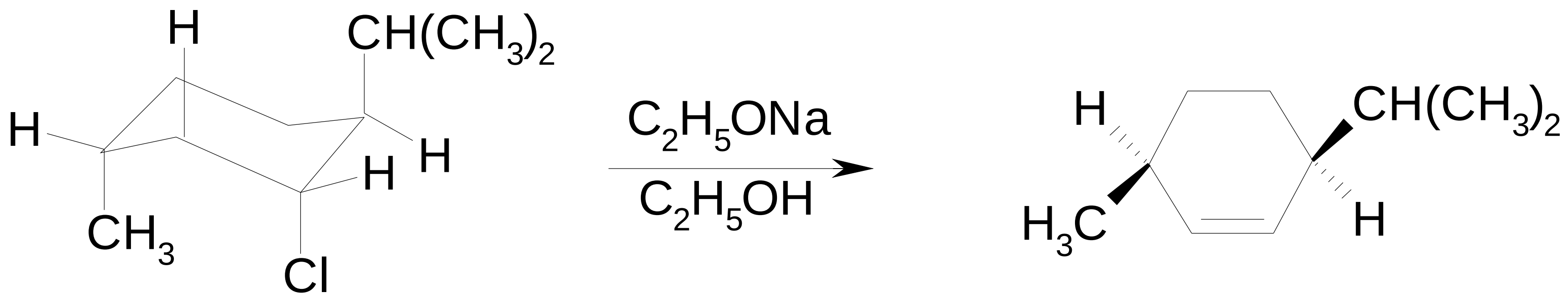
$$\mathrm{RCH_2}\overset{\mathrm{X}}{\mathrm{C}}\mathrm{HR'} \xrightarrow{\text{碱}} \mathrm{RCH{=}CHR'} + \mathrm{HX}$$



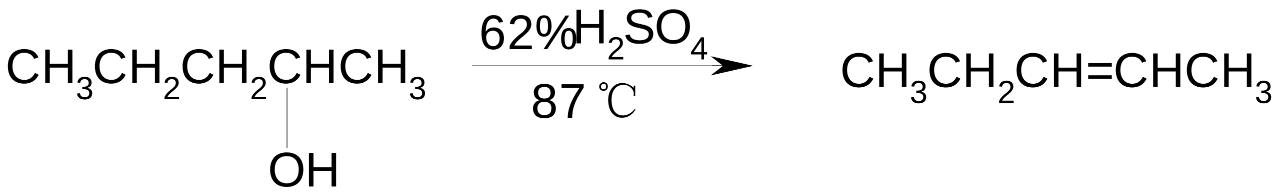
$$\mathrm{CH_3CH_2}\overset{\mathrm{X}}{\mathrm{C}}\mathrm{HCH_3} \xrightarrow[\mathrm{C_2H_5OH}]{\mathrm{C_2H_5ONa}} \underset{(81\%)}{\mathrm{CH_3CH{=}CHCH_3}} + \underset{(19\%)}{\mathrm{CH_3CH_2CH{=}CH_2}}$$

Stereochemistry of β -elimination



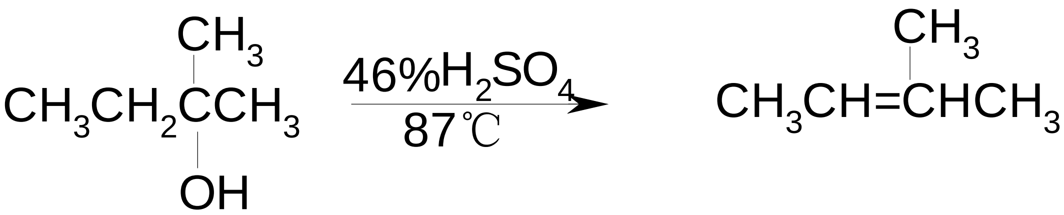


反式消除



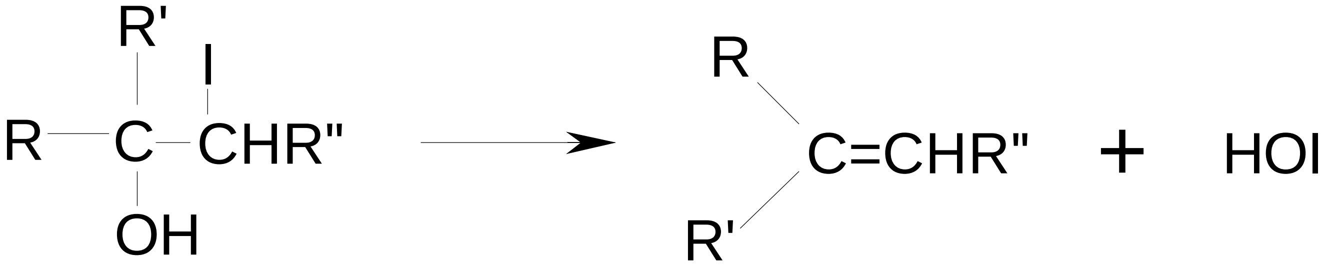
$$CH_3CH_2CH_2\underset{OH}{CH}CH_3 \xrightarrow[87\,℃]{62\%H_2SO_4} CH_3CH_2CH{=}CHCH_3$$

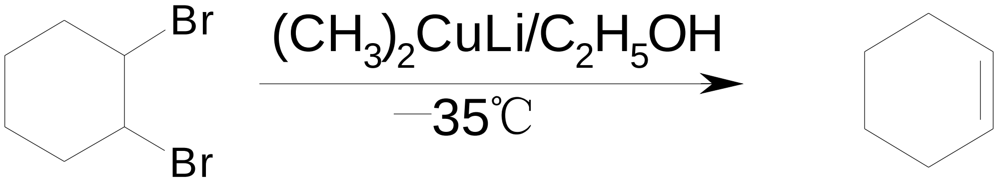
(80%)



$$CH_3CH_2\underset{OH}{\overset{CH_3}{C}}CH_3 \xrightarrow[87℃]{46\%H_2SO_4} CH_3CH{=}\overset{CH_3}{C}HCH_3$$

(87%)





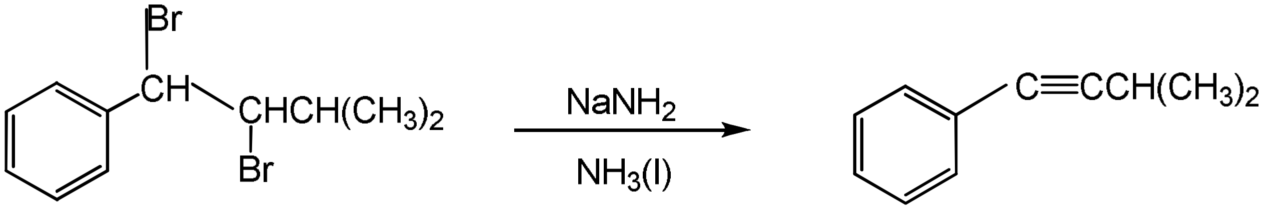
(95%)

C≡C bond formation

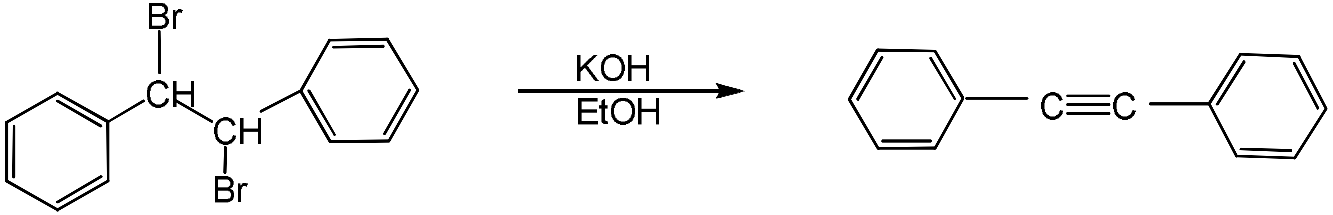
- **1、二卤代烃脱卤化氢:**由二卤化物在碱的作用下脱去卤化氢，在分子中引入碳碳叁键.

$$\mathrm{RCHXCHXR'} \xrightarrow{\text{碱}} \mathrm{RC{\equiv}CR'} + 2\,\mathrm{HX}$$

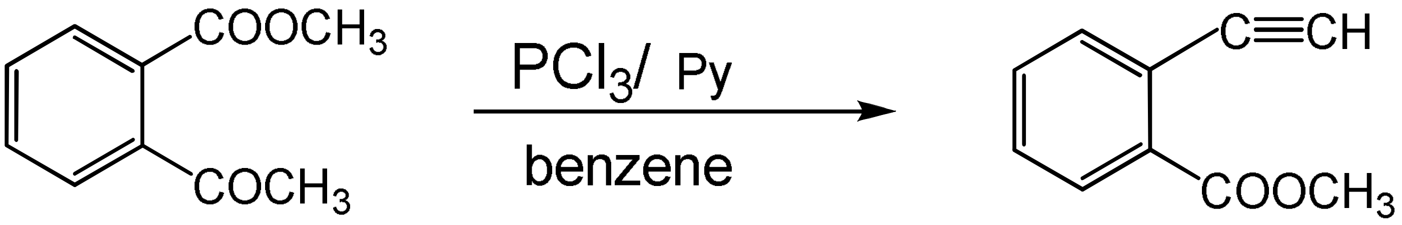
Base: KOH、RONa、NaH、$NaNH_2$


Br
CH
CHCH(CH3)2
Br
NaNH2
NH3(l)
C≡CCH(CH3)2

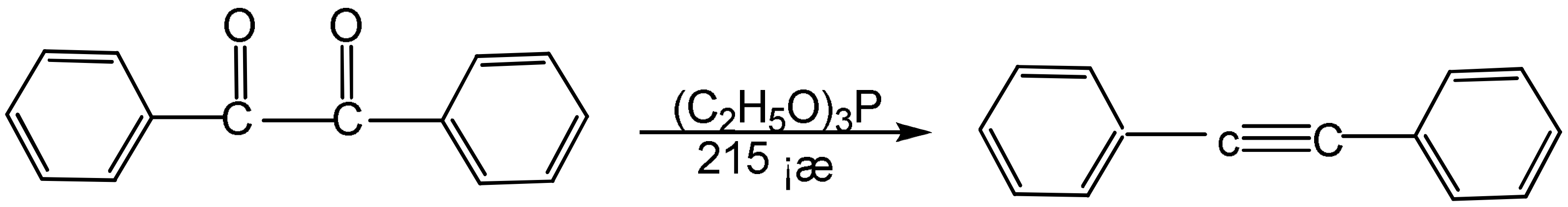
(78%)

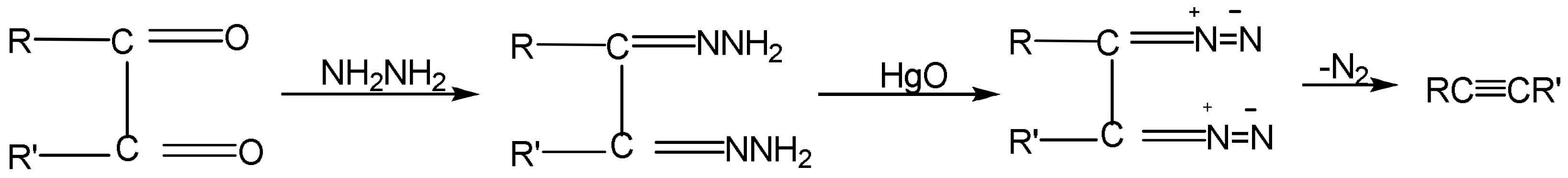

Br
CH
CH
Br
KOH
EtOH
C≡C

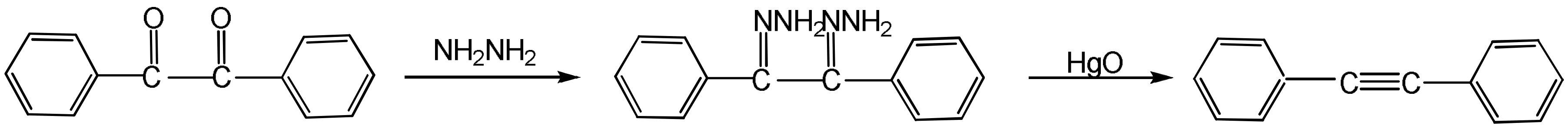
(66%-69%)


COOCH3
COCH3
PCl3/ Py
benzene
C≡CH
COOCH3

2、α 一二酮脱氧







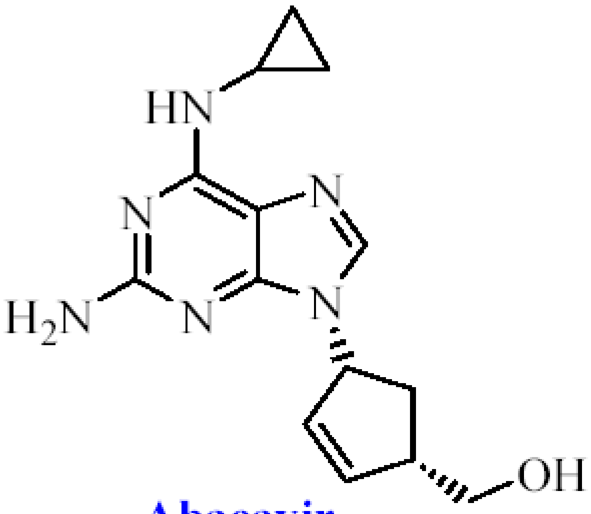
Traditional methods

$$R\equiv CH \xrightarrow{NaNH_2} R\equiv C^{-} \quad Na^{+} \xrightarrow{R'X} R\equiv CR'$$

Cycloaddition Reactions

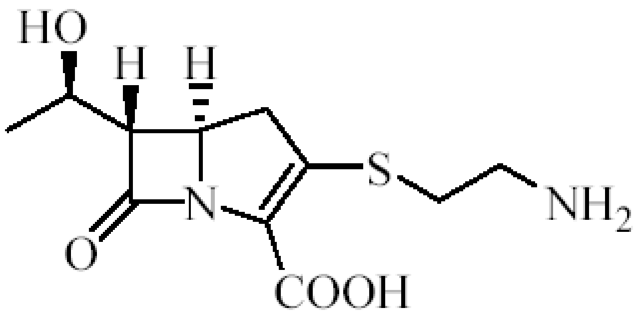
Importance of Ring Structures

- According to the 1995 U.S. Clinical Report, over 80% of the pharmaceutical drugs on the market in the United States contained at least one ring.



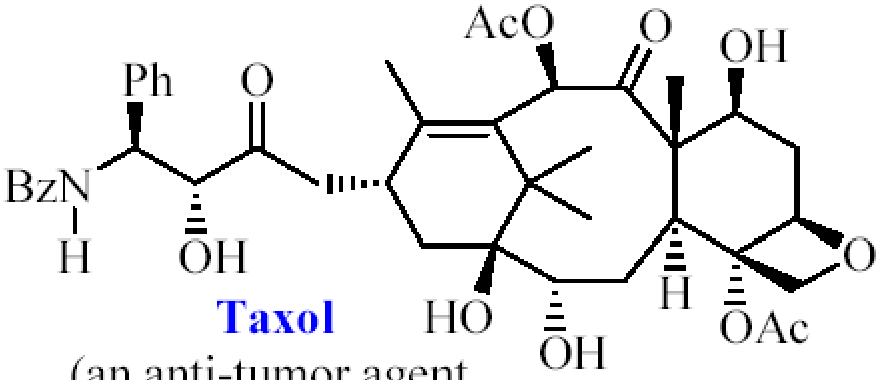
Abacavir

(an antiviral agent)



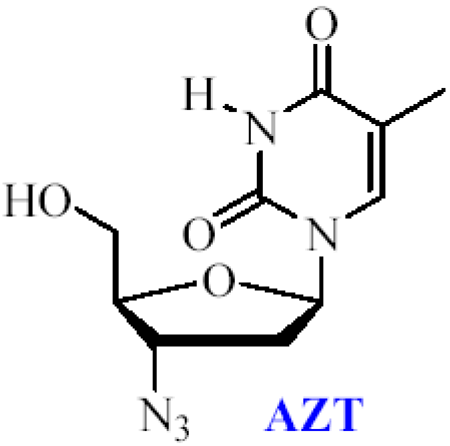
Thienamycin

(treatment of bacterial infections)



Taxol

(an anti-tumor agent,
for treatment of cancer)



AZT

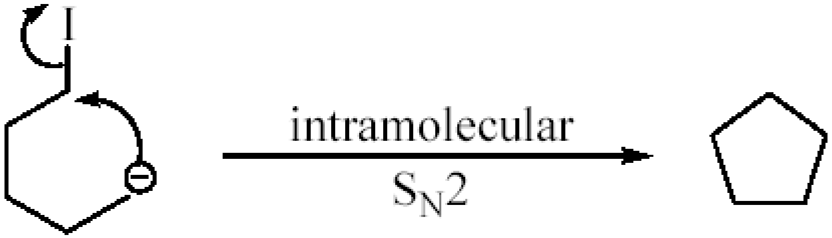
(an antiviral agent,
for treatment of AIDS)

Different Ways to Make Rings

➢ Cyclization reactions

- Intramolecular reaction of an open chain structure

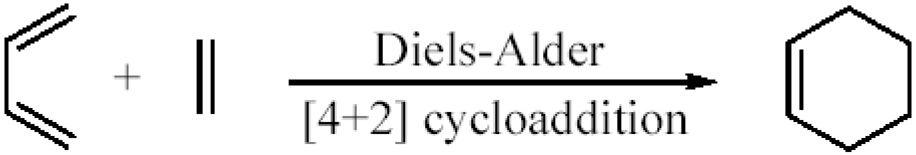
e.g.



➢ Cycloaddition reactions

- Two or more (unsaturated) compounds form a ring through the reorganization of electrons

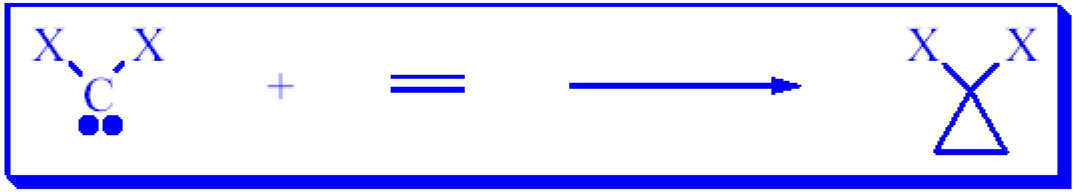
e.g.



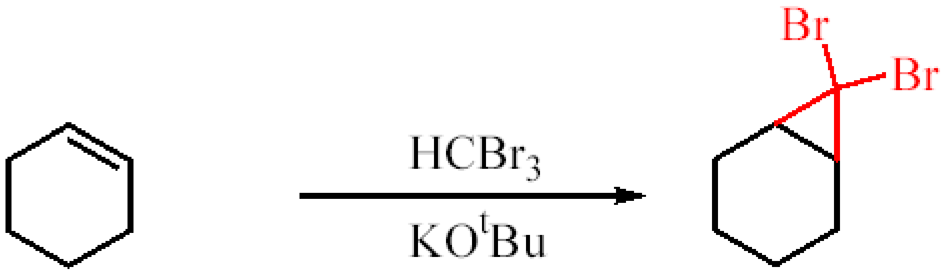
Formation of 3-Membered Ring

[2+1] Cyclopropanation

Halo-carbenes Cyclopropanation

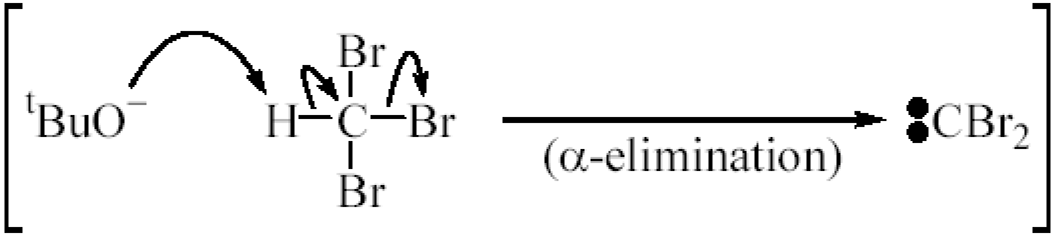


e.g.

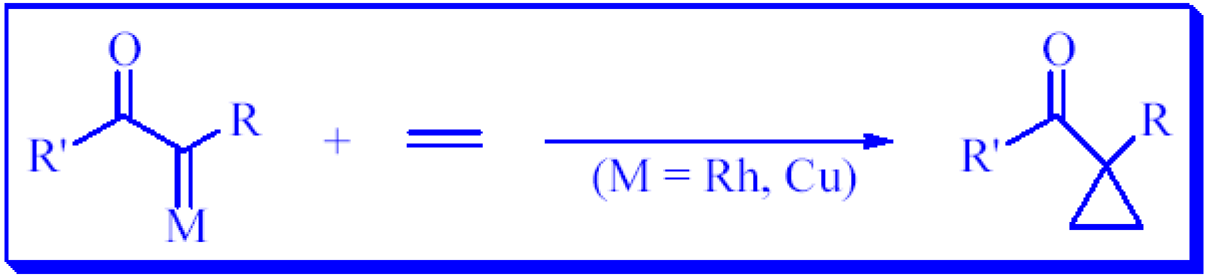


❖ [2+1] Cyclopropanation

Mechanism

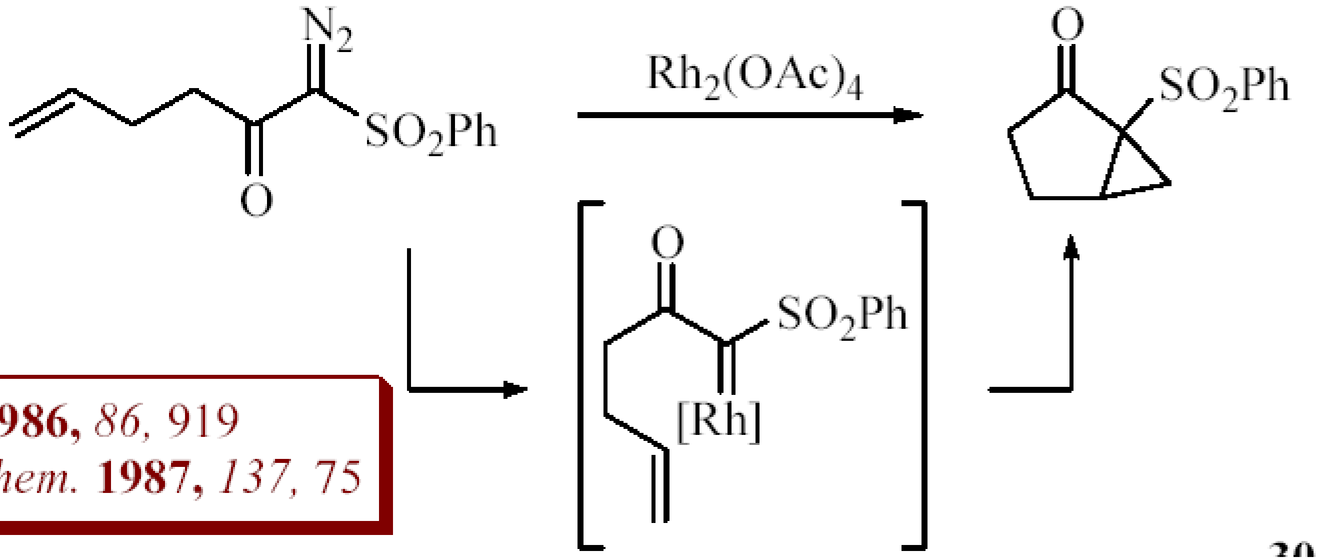


➢ Metal-carbenoids Cyclopropanation



❖ [2+1] Cyclopropanation

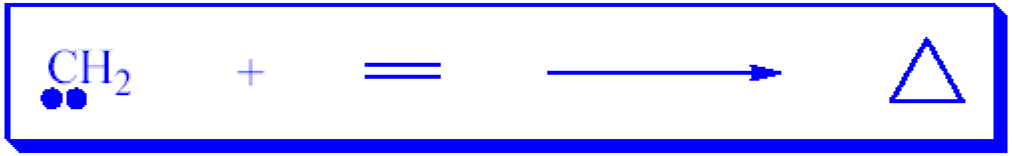
e.g.



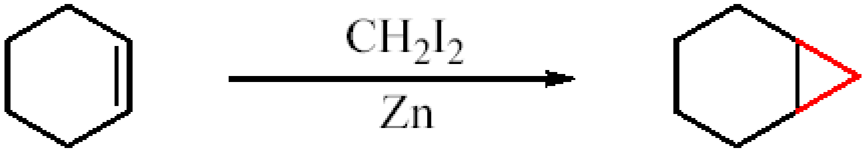
- *Chem. Rev.* **1986,** *86*, 919
- *Top. Curr. Chem.* **1987,** *137*, 75

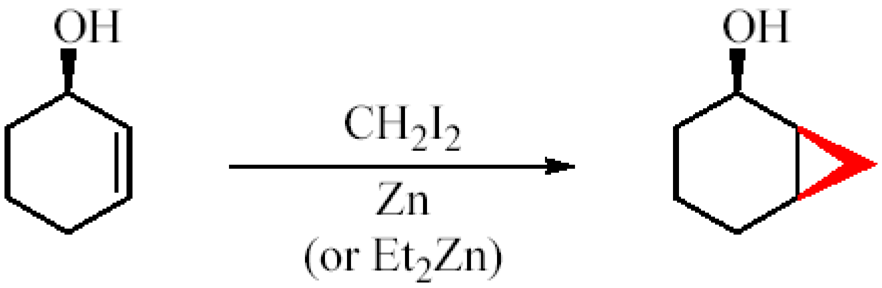
❖ [2+1] Cyclopropanation

➢ Simmons-Smith Cyclopropanation

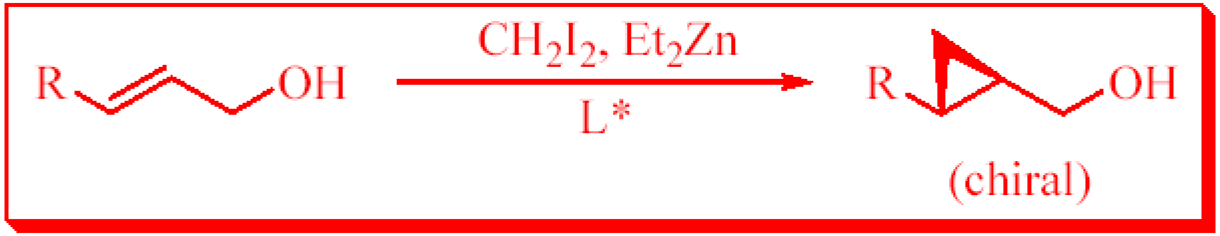


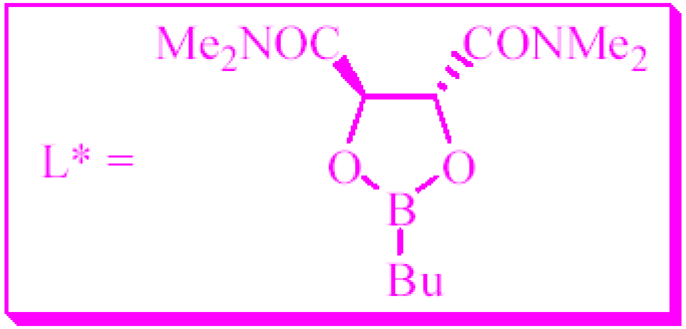
e.g.



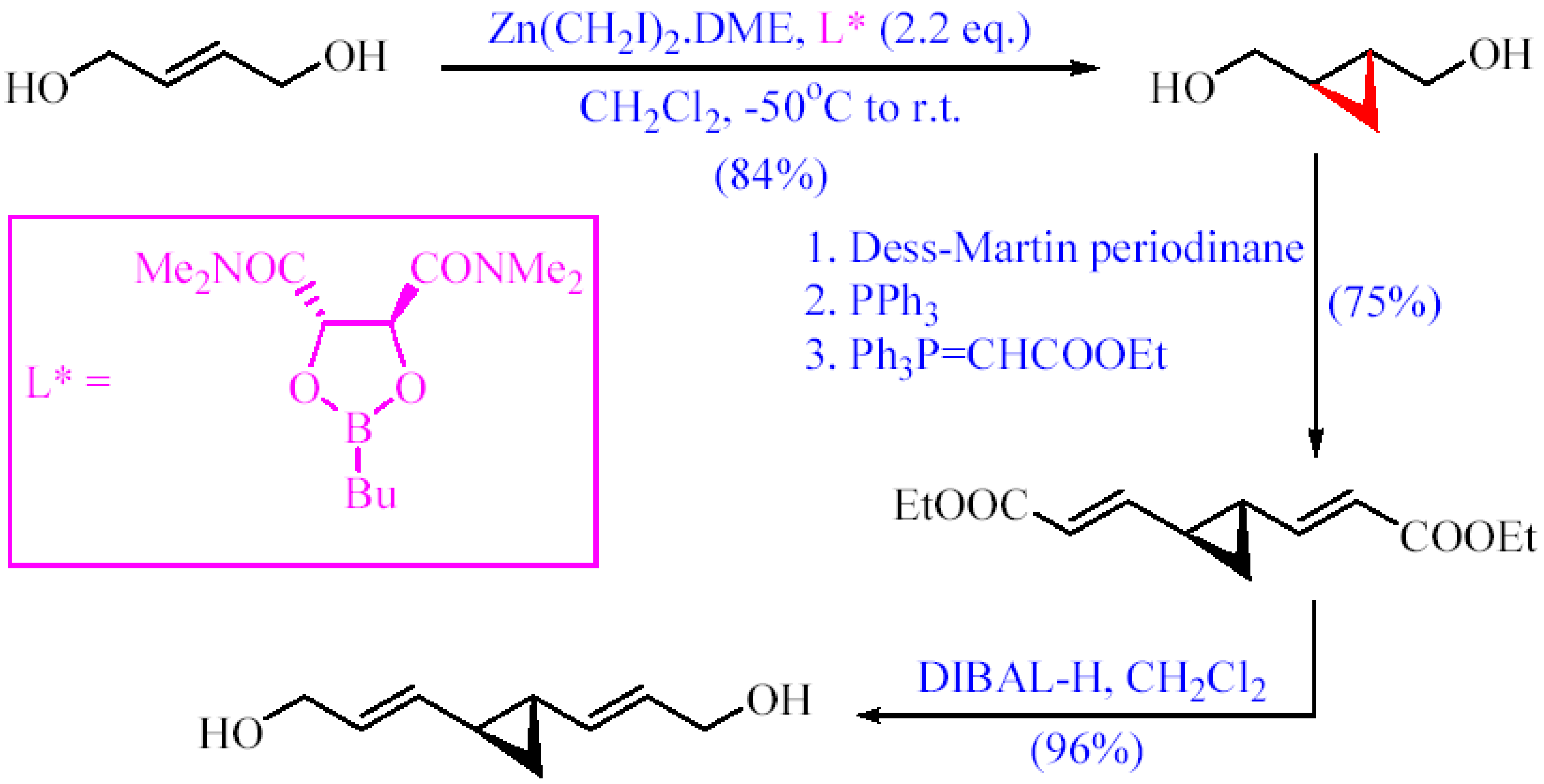


Charette's Asymmetric [2+1]





Application of Charette's Asymmetric Cyclopropanation in Natural Product Synthesis

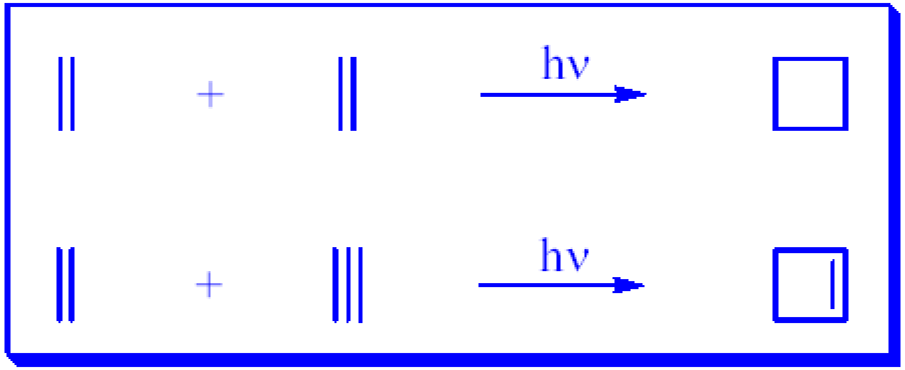


Formation of 4-Membered Ring

❖ [2+2] Cycloaddition

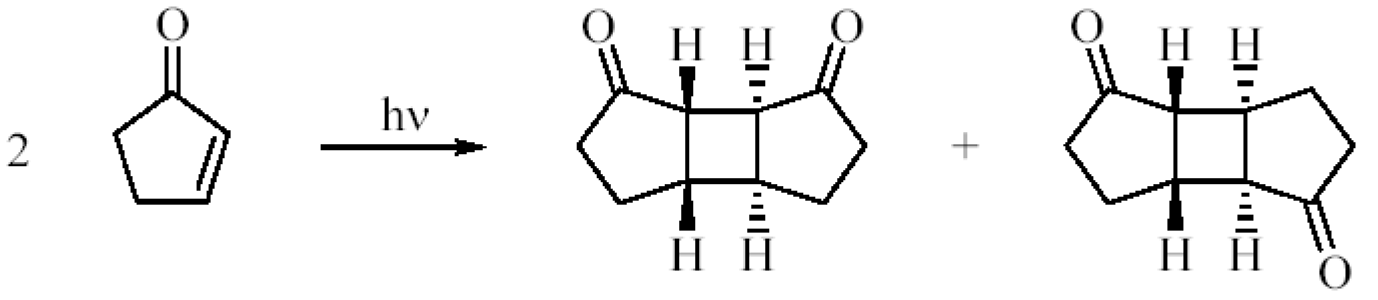
➢ Photochemical [2+2] Cycloaddition

- Photochemical [2+2] Cycloaddition (and other 4n cycloadditions) is a symmetry-allowed process



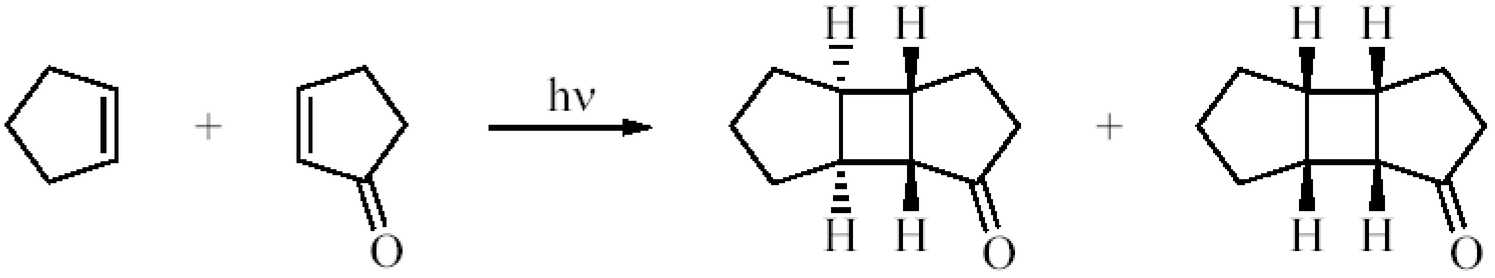
Photochemical [2+2] Cycloaddition

❖ Dimerization of α,β-Unsaturated Ketones



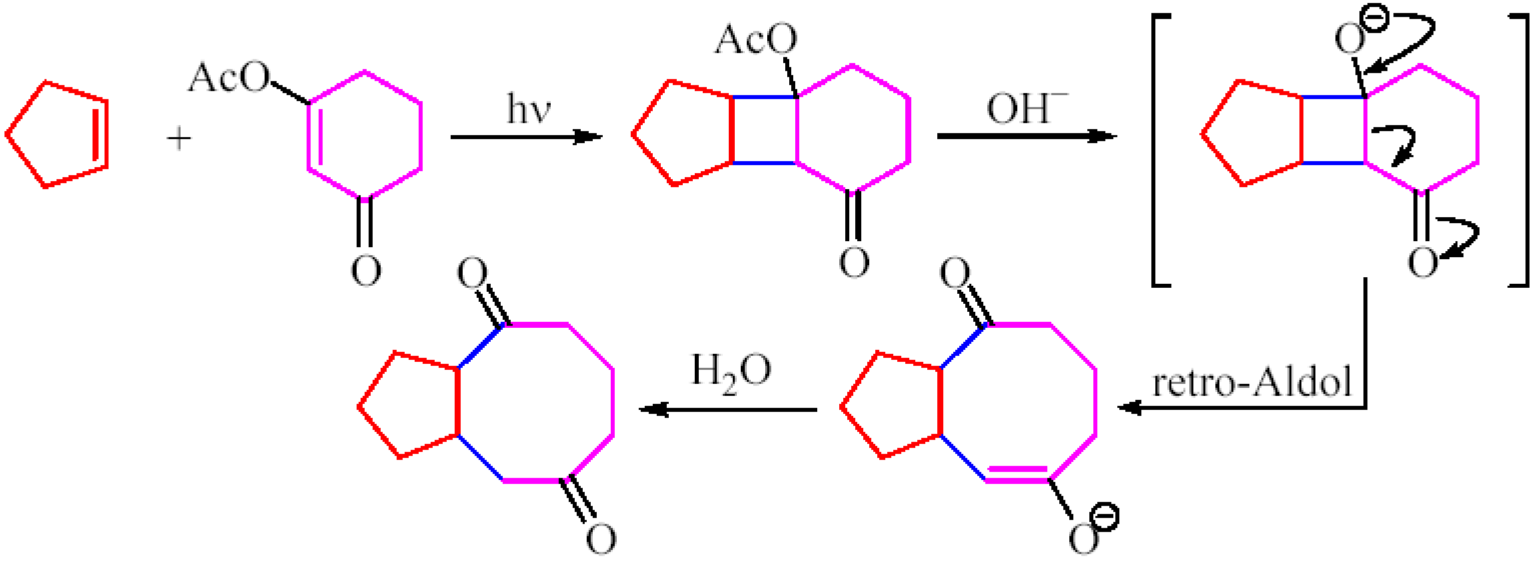
head-to-head head-to-tail

❖ Mixed Cycloaddition between an Alkene & an α,β-Unsaturated Ketone

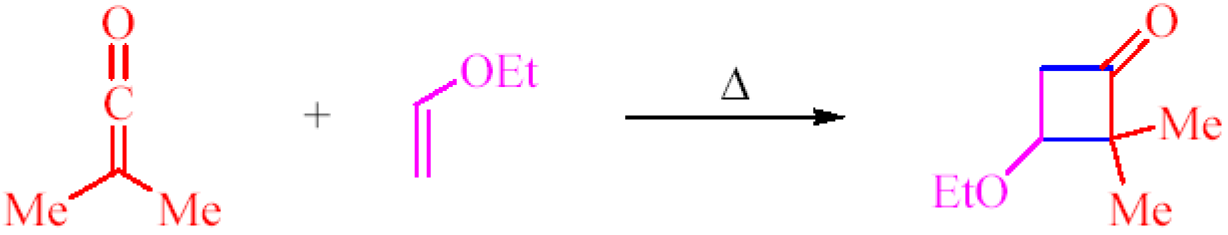


Photochemical [2+2] Cycloaddition

De Mayo Reaction

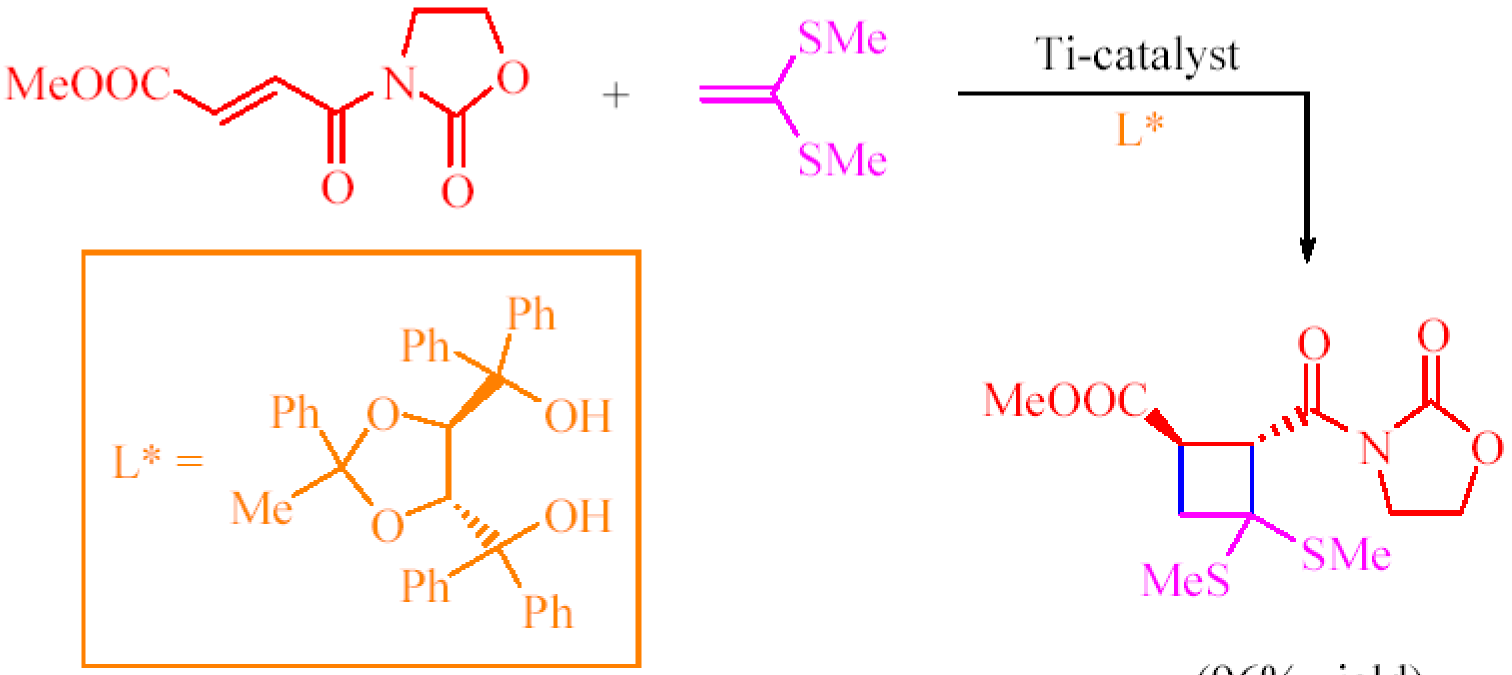


Thermal [2+2] Cycloaddition of Ketene



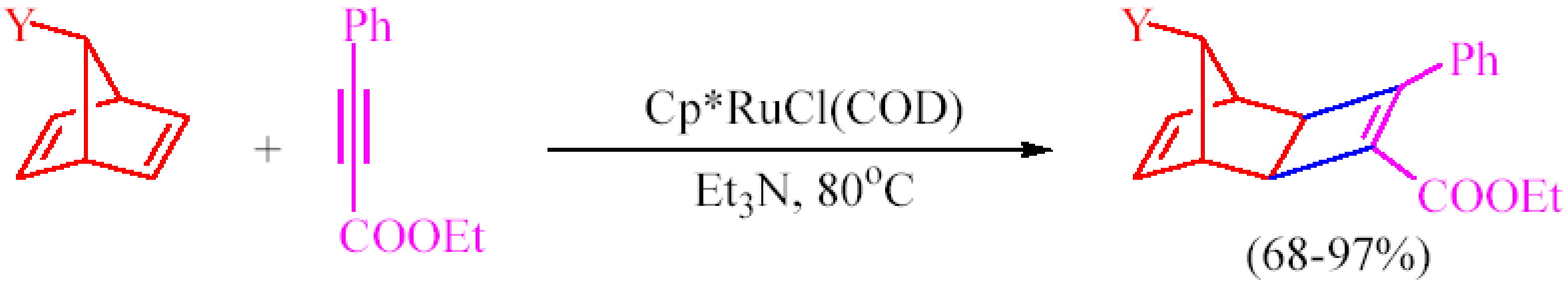
- Normally thermal [2+2] cycloaddition is a symmetry-forbidden process. But in ketene, the two π bonds are orthogonal to each other and can undergo non-concerted thermal [2+2] cycloaddition

Lewis Acid Catalyzed [2+2] Cycloaddition

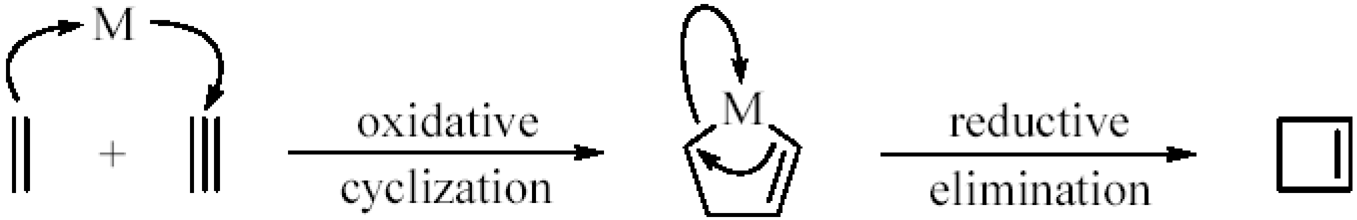


(96% yield)
(98% ee)

Transition Metal Catalyzed [2+2] Cycloaddition

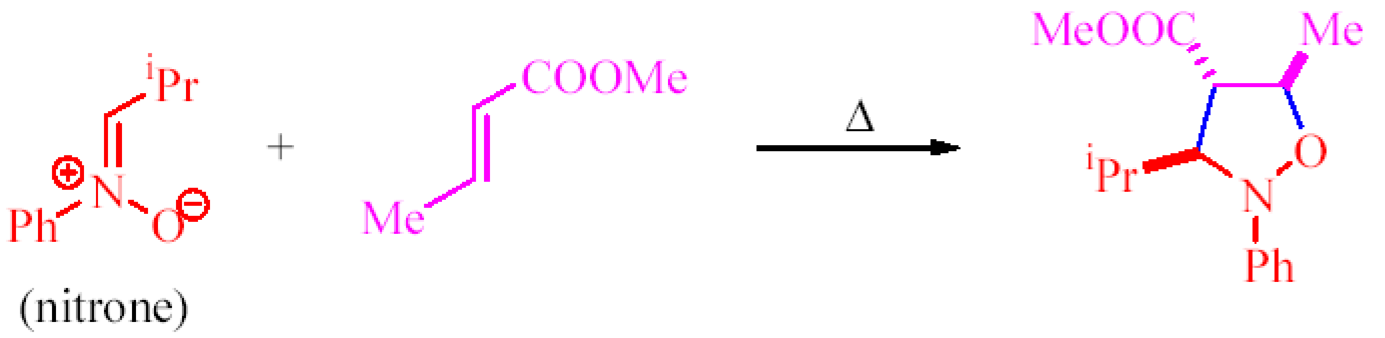


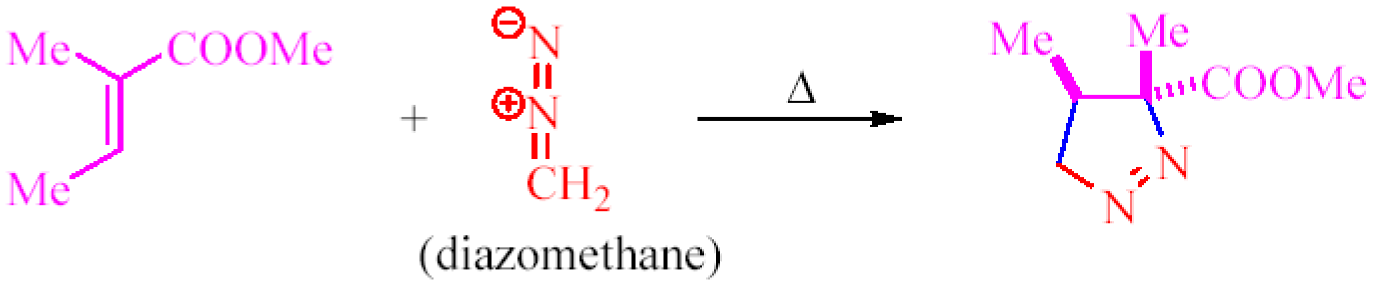
General Mechanism:



Formation of 5-Membered Ring

1,3-Dipolar Cycloadditions

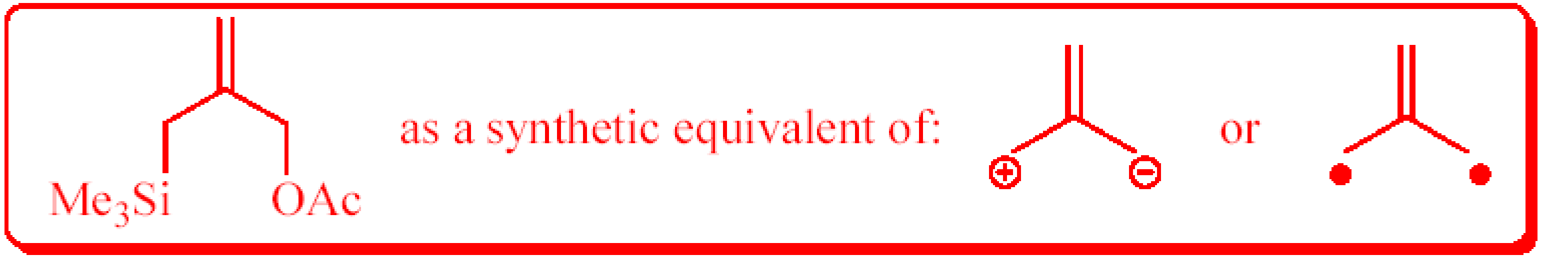


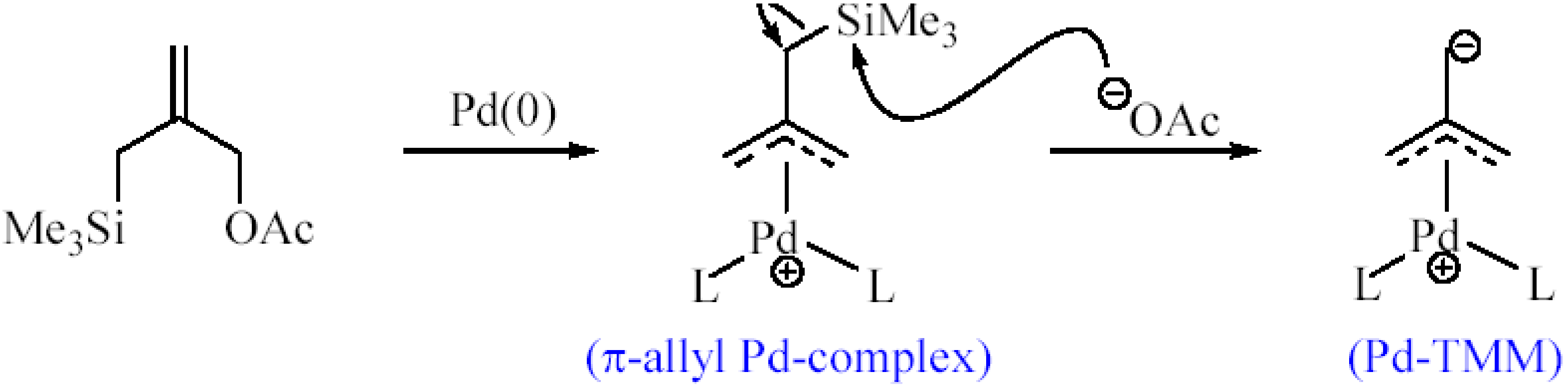


- Other common dipolarophile: azide, nitrile oxide, azomethine ylide

Trost's [3+2] Cycloaddition

❖ Trimethylene Methane Equivalent (TMM)





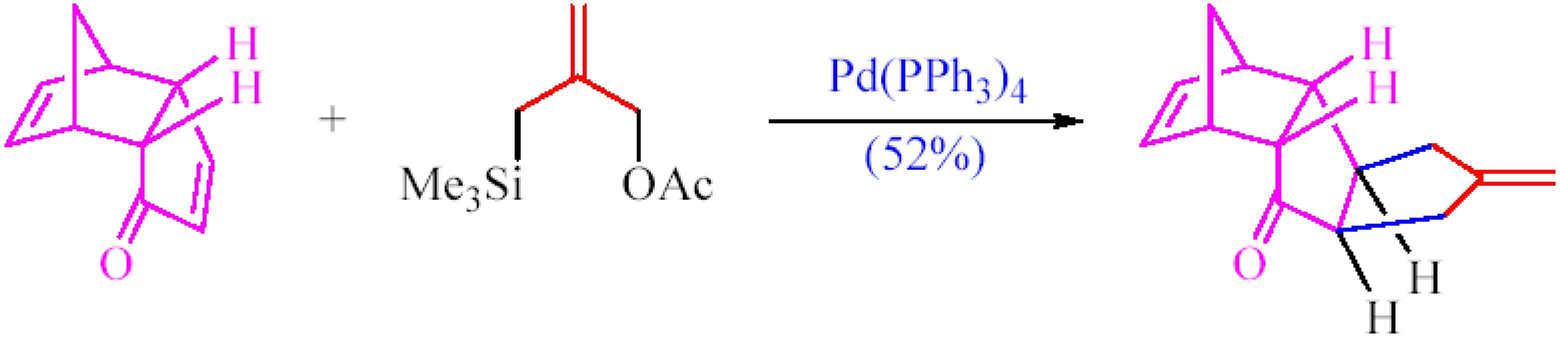
(π-allyl Pd-complex)

(Pd-TMM)

Trost's [3+2] Cycloaddition

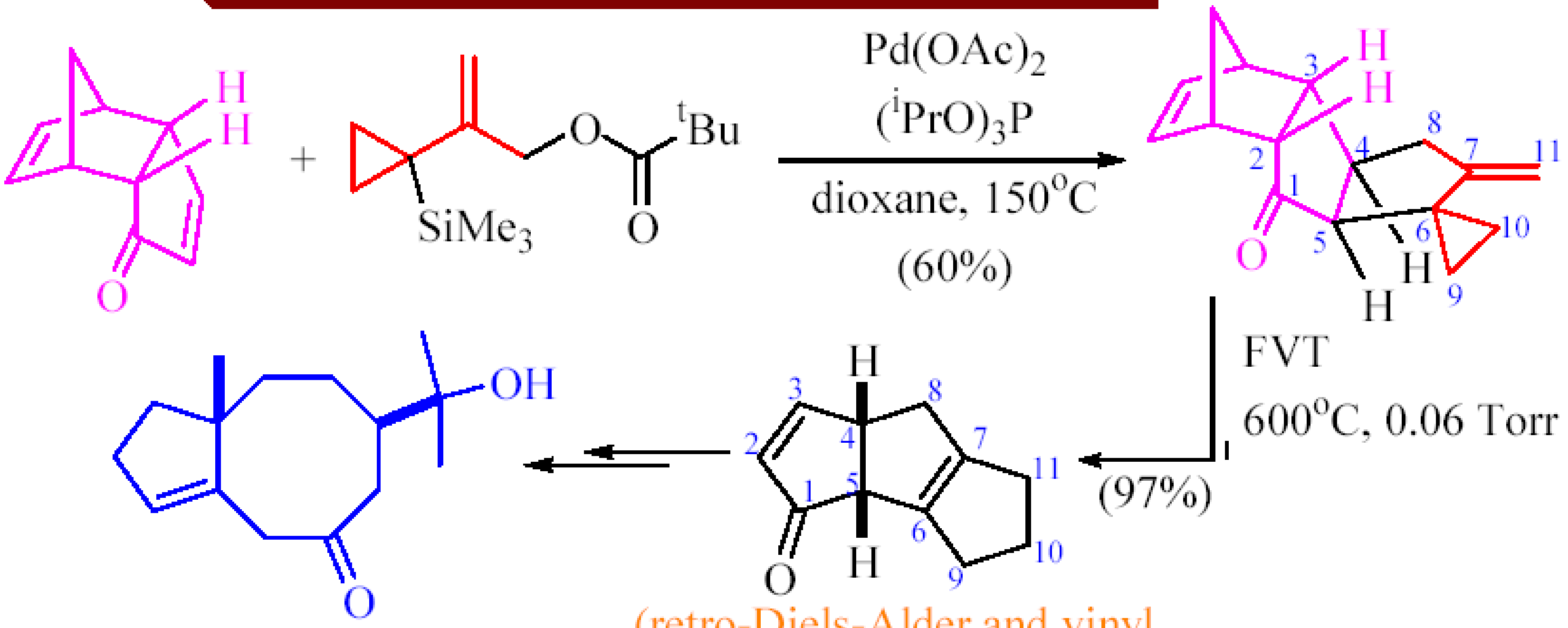
❖ Cycloaddition with Pd-TMM

- Good for electron-deficient double bonds



❖ Application: Total Synthesis of 11-Hydroxyjasionone

Trost, B. M. et. al. *J. Org. Chem.* **1994,** *59,* 7568



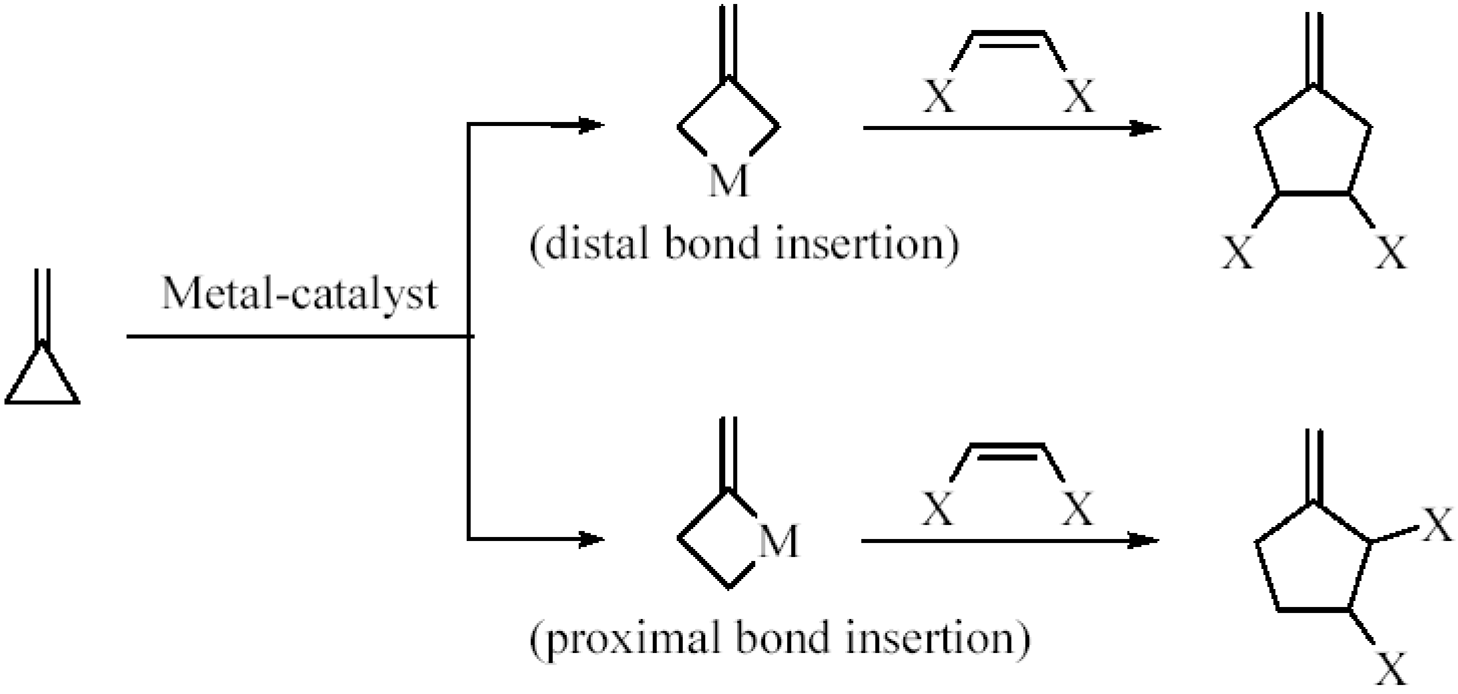
11-Hydroxyjasionone
(antibacterial,
antifungal agent)

(retro-Diels-Alder and vinyl cyclopropane rearrangement)

Review on vinylcyclopropane rearrangement:
Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197.

Binger's [3+2] Cycloaddition

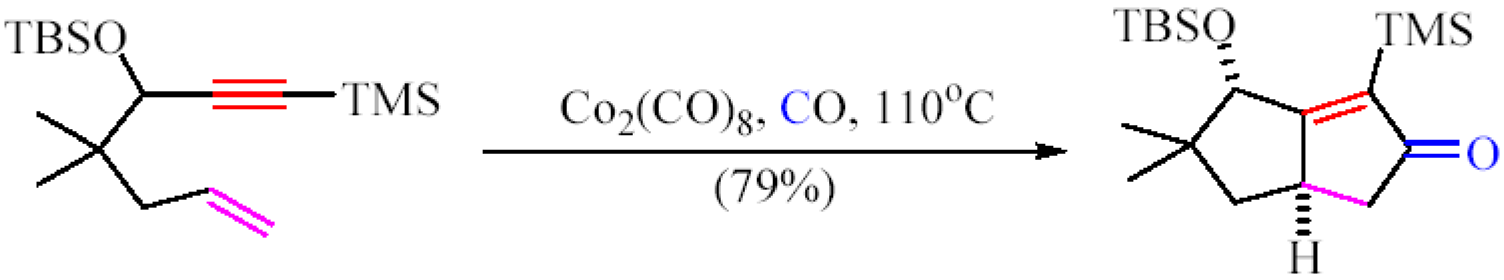
❖ Methylene Cyclopropane



Formation of 5-Membered Ring

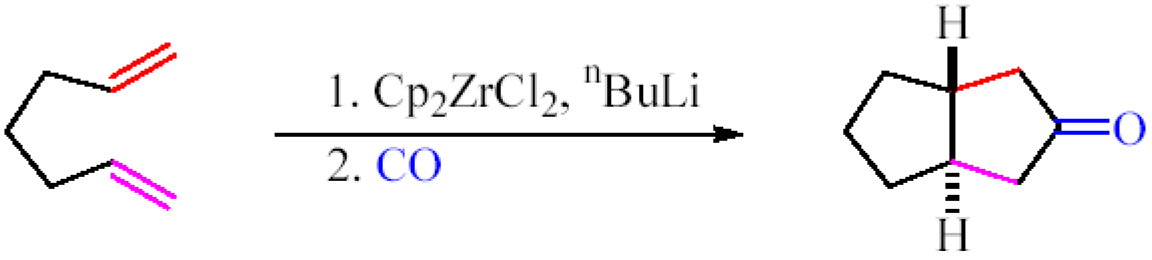
❖ [2+2+1] Cycloadditions

➢ Pauson-Khand Reaction

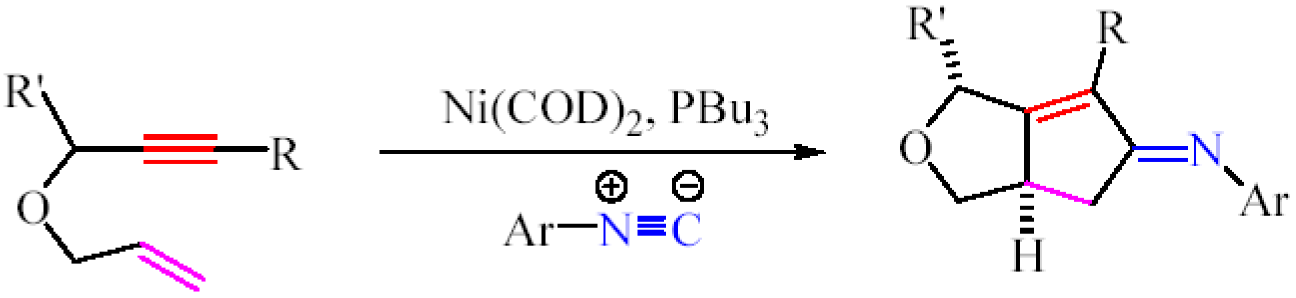


❖ [2+2+1] Cycloadditions

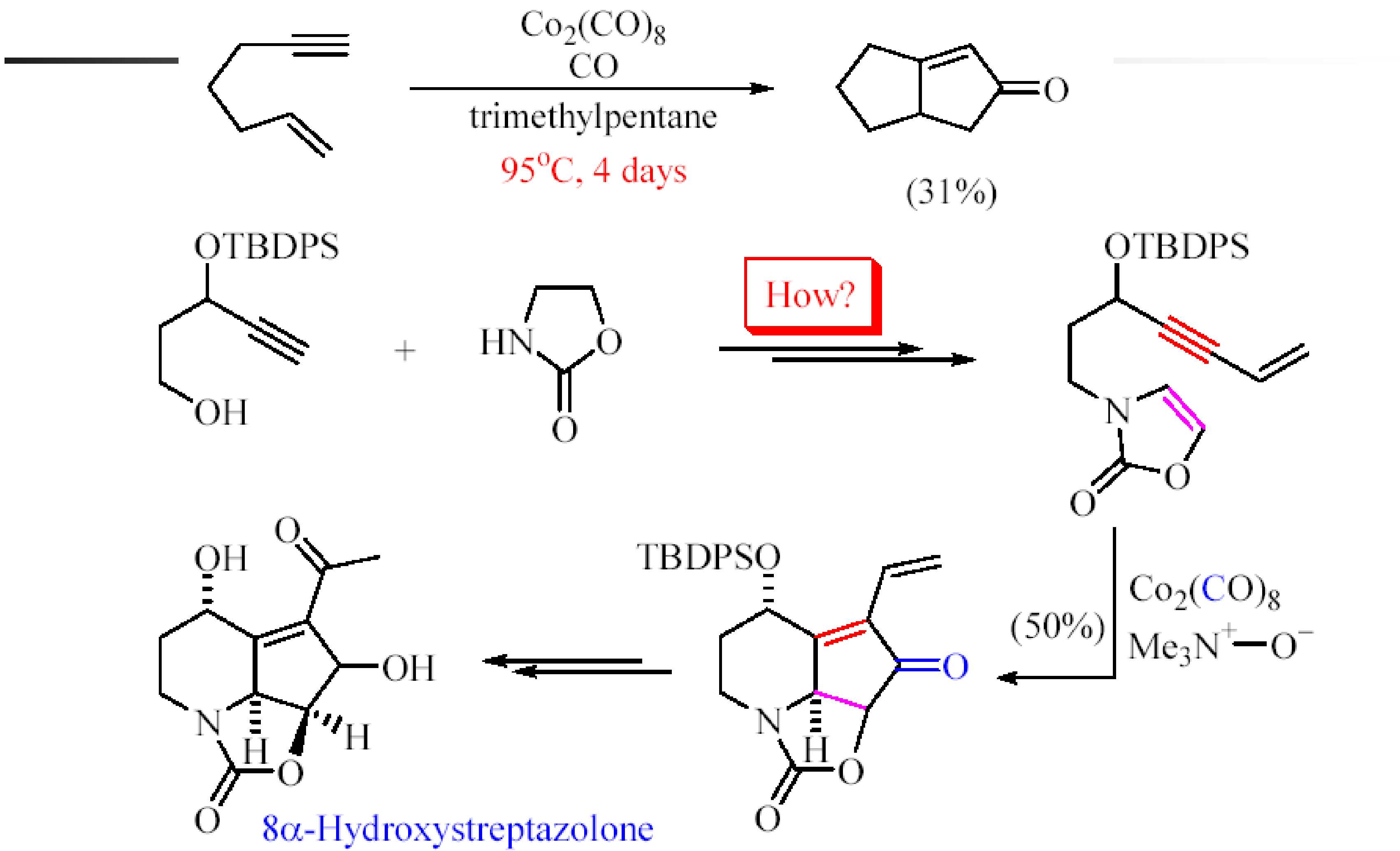
➢ Negishi-Buchwald [2+2+1] Cycloaddition



➢ Other Metal-catalyzed [2+2+1] Cycloaddition



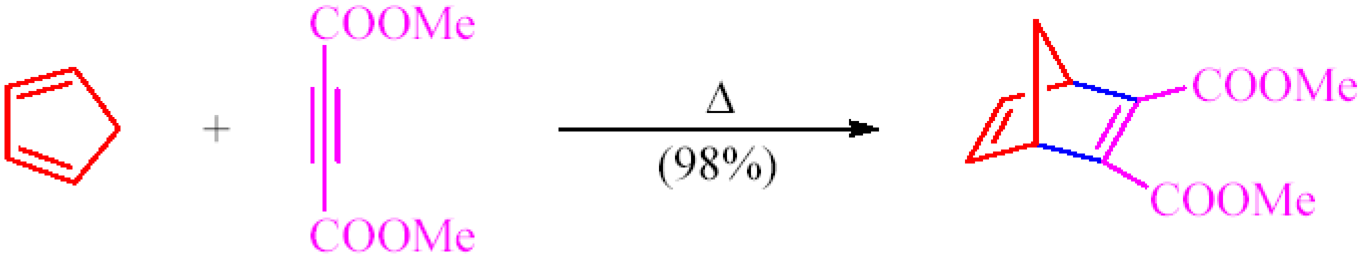
Pauson-Khand [2+2+1] Cycloadditions

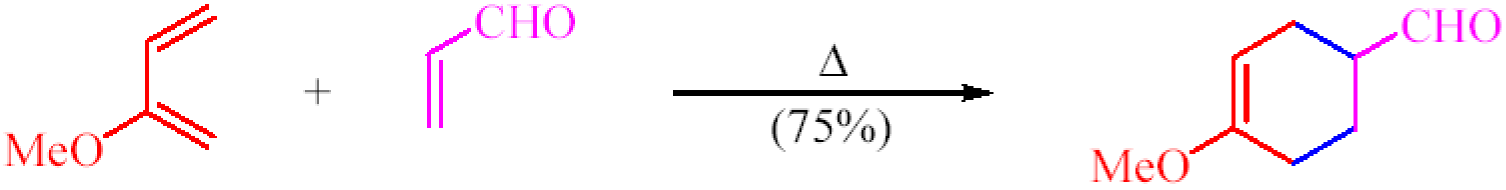


8α-Hydroxystreptazolone
(anti-fungal agent)

Formation of 6-Membered Ring

❖ Diels-Alder [4+2] Cycloadditions

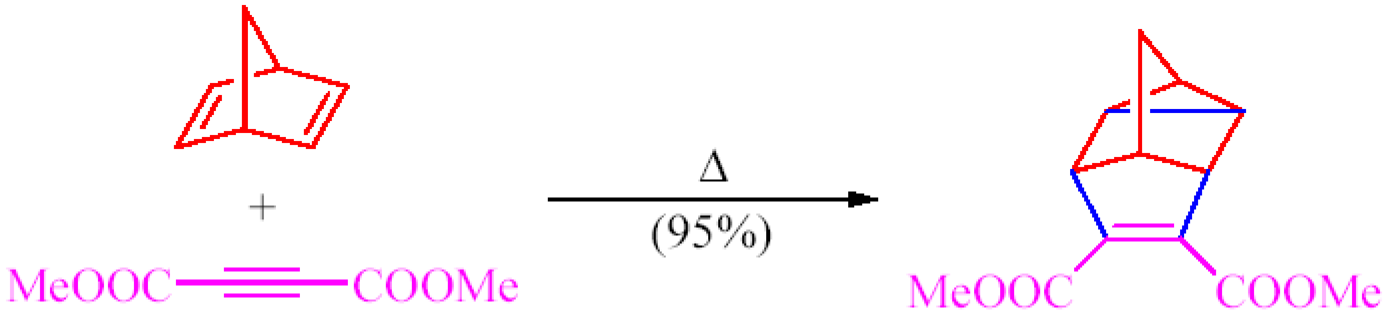




Formation of 6-Membered Ring

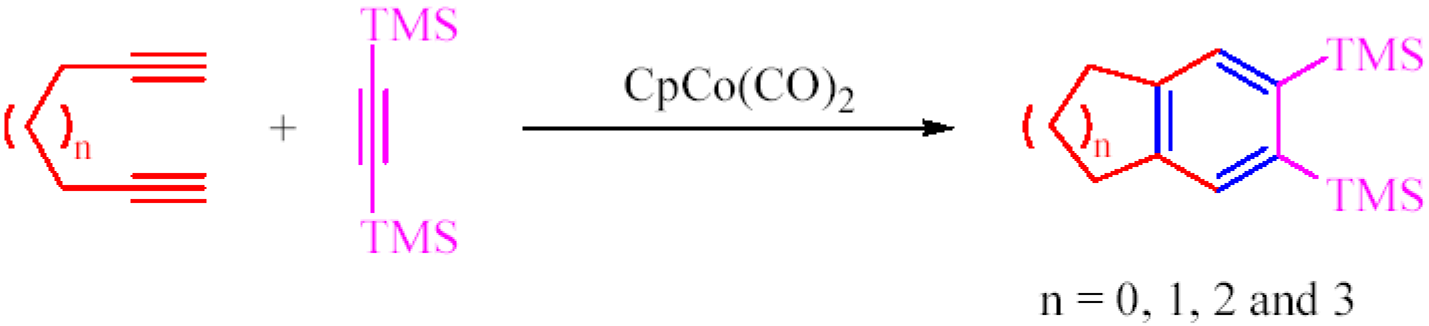
[2+2+2] Cycloadditions

Homo-Diels-Alder Reaction

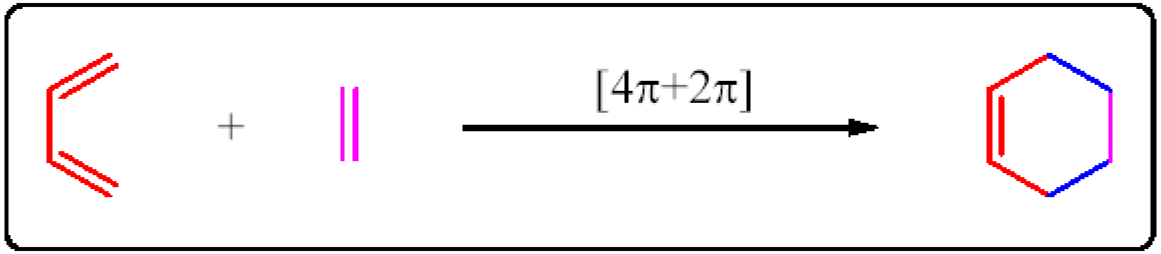


❖ [2+2+2] Cycloadditions

➢Vollhardt [2+2+2] Acetylene Cyclotrimerization



Diels-Alder Reaction



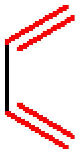
- Promoted by heat, Lewis-acid or metal-catalyst
- Diels-Alder [4+2] cycloaddition is probably the most common and useful reaction in making 6-membered rings
- Diels and Alder: Nobel Prize in 1950

Diels-Alder Reaction

❖ Reactivity Trends

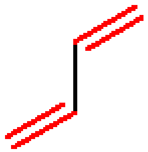
➢ Diene

- Must be *s-cis* in transition state and planar



s-cis

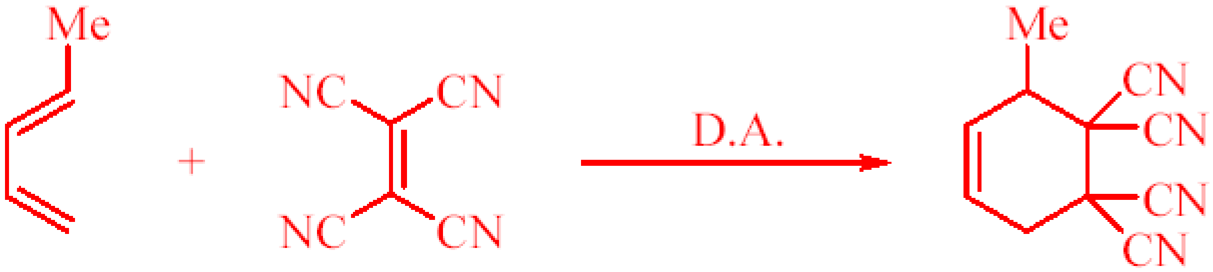
vs



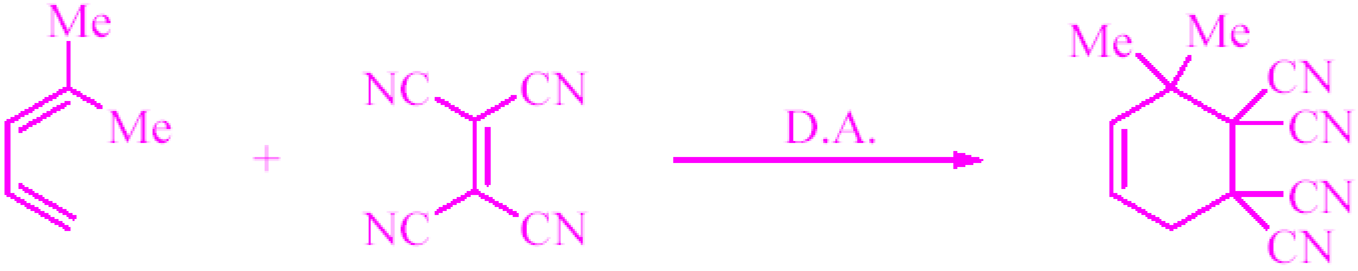
s-trans

❖ Example 1

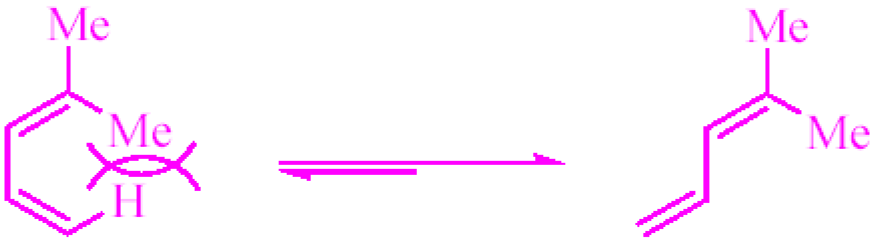
(i)



(ii)

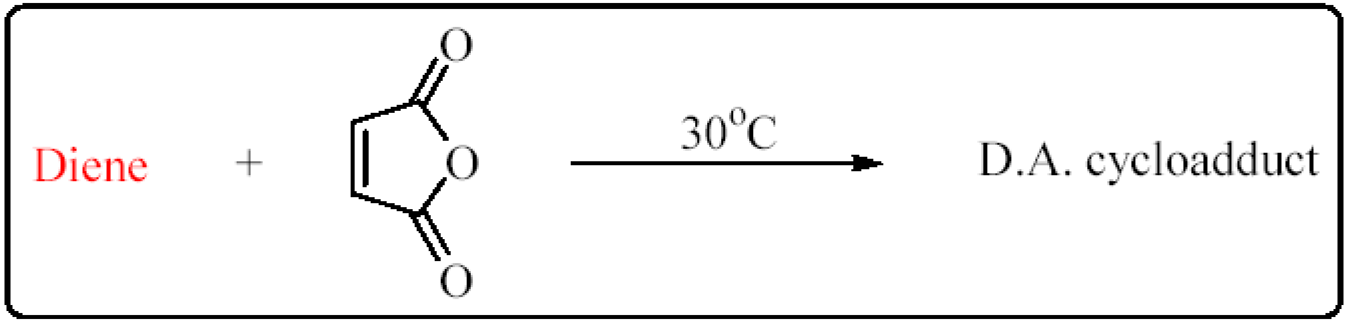


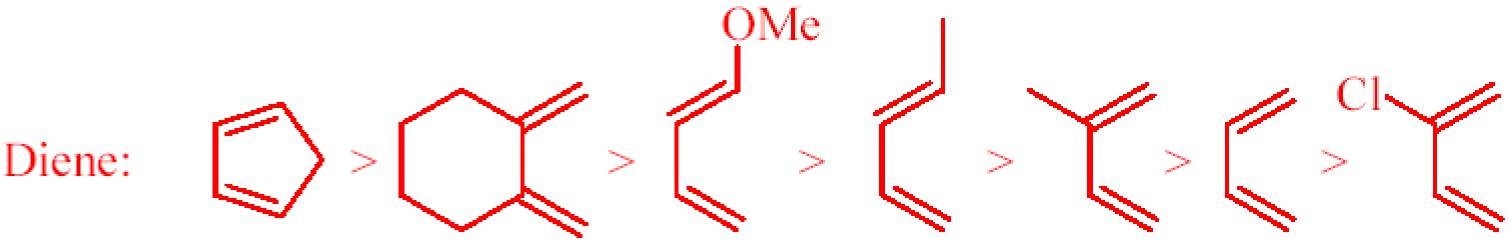
Rate of (i) is 10^3 times faster than (ii) due to:



Diels-Alder Reaction

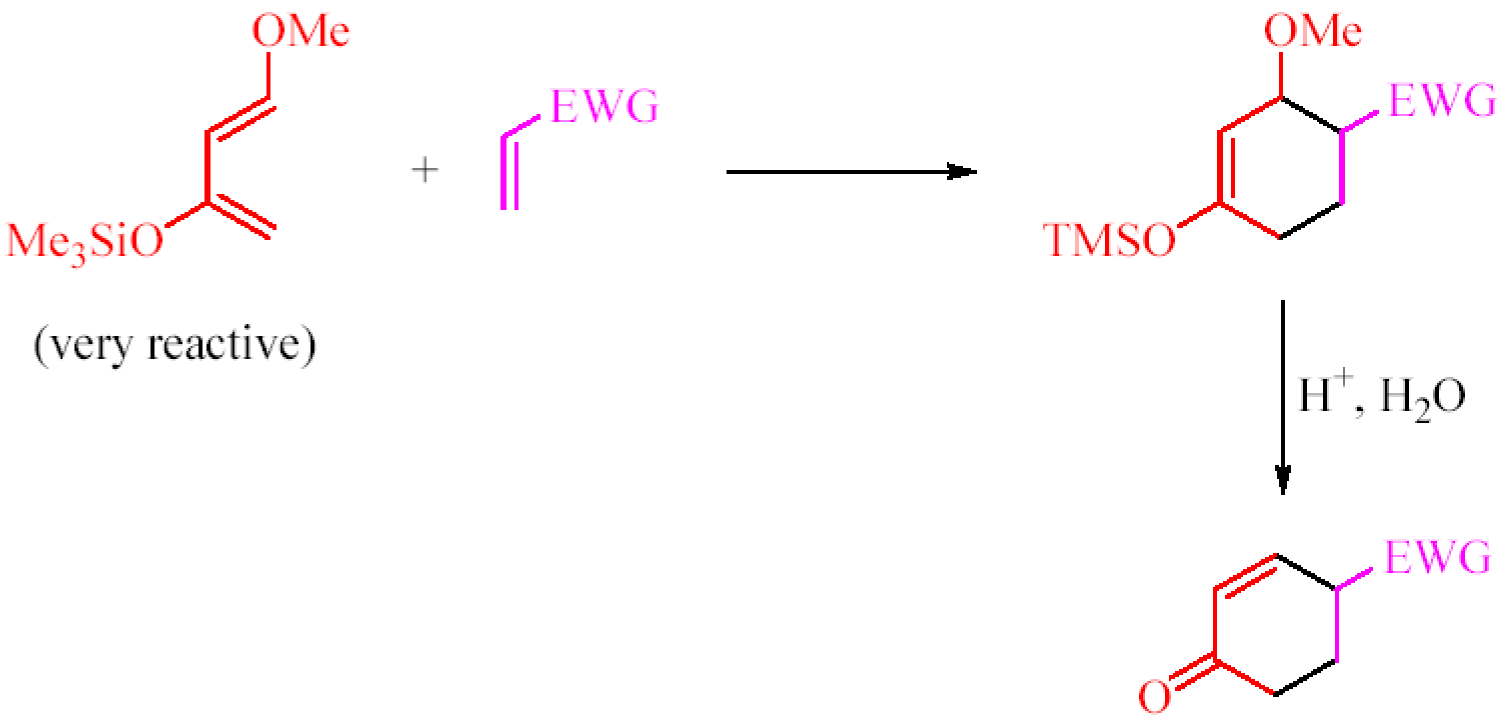
❖ Relative Rate





$t_{1/2}$ 11 sec. 130 s 20 mins. 70 mins. 2 h 4 h 40 h

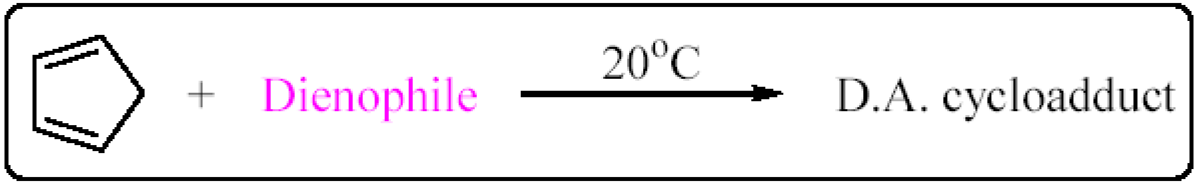
❖ Danishefsky's Diene



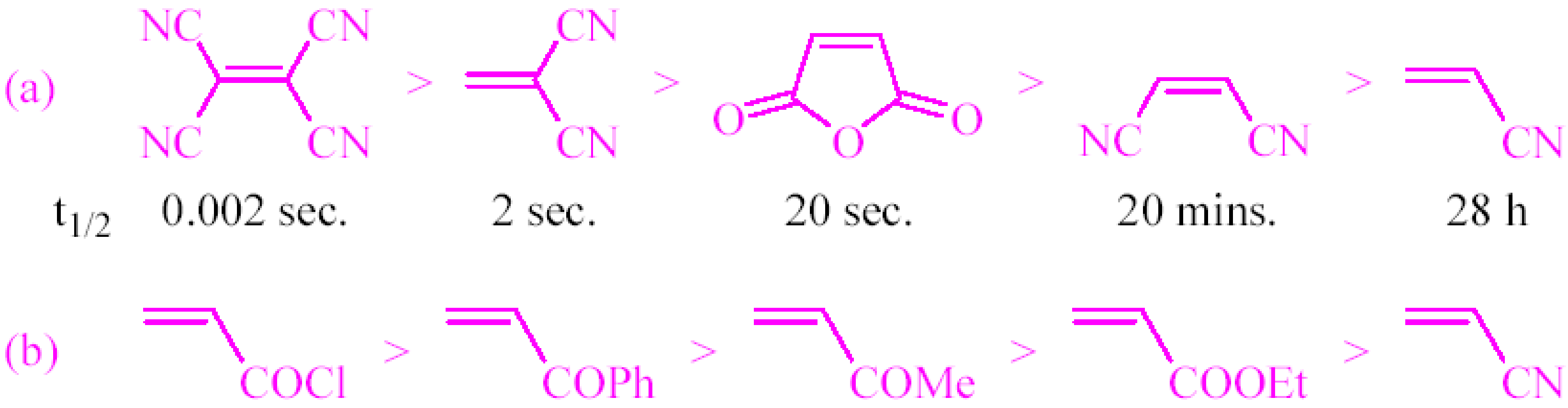
❖ Reactivity Trends

➢ Dienophile

- **Best with electron withdrawing substituents**
- **Relative rate:**

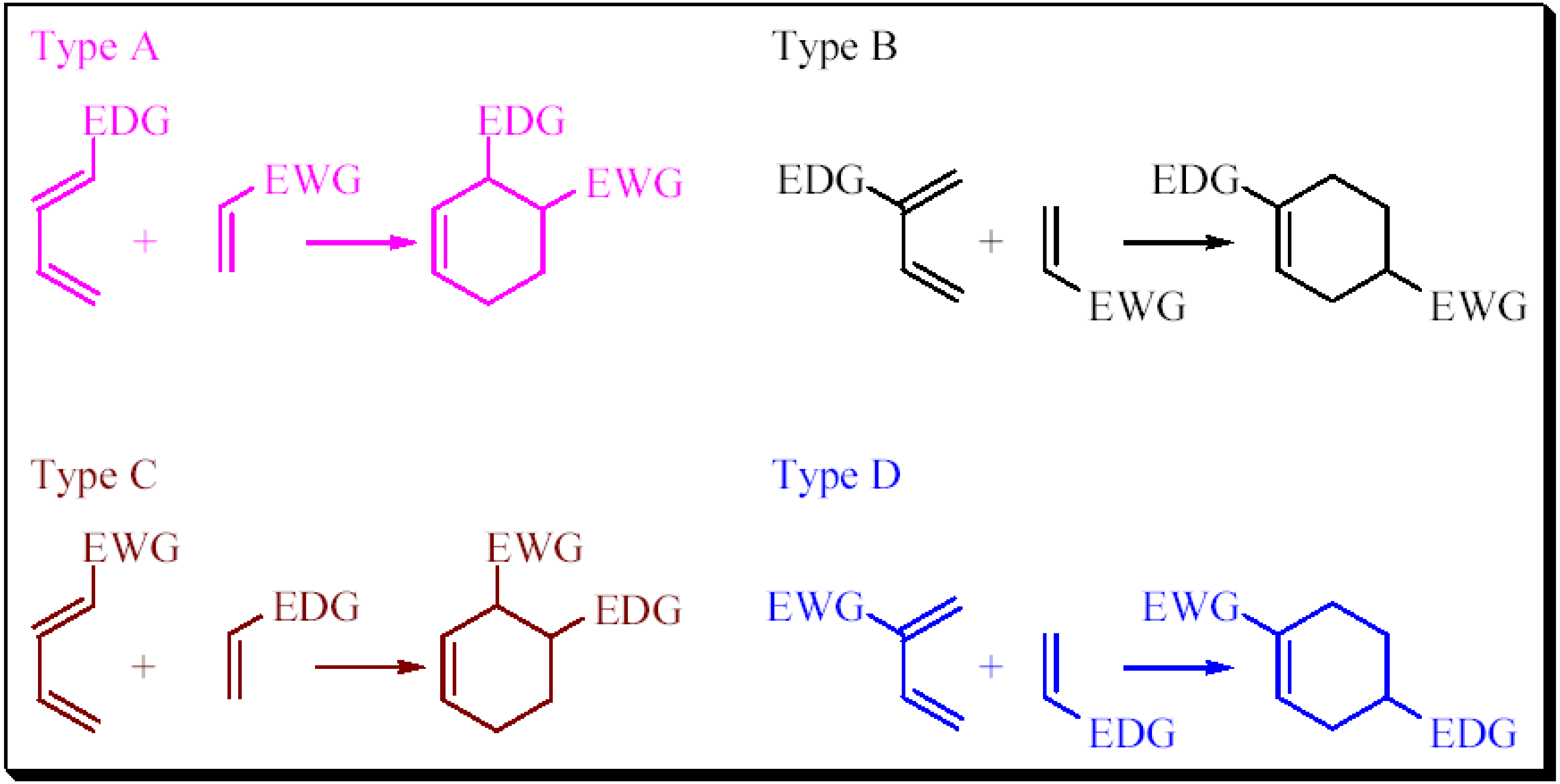


Dienophile:



Diels-Alder Reaction

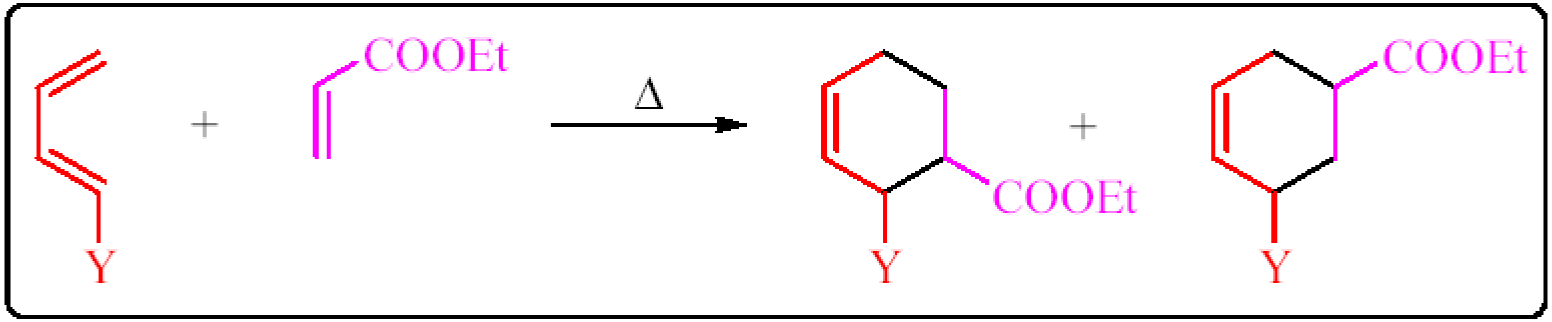
❖ Regioselectivity



Diels-Alder Reaction

❖ Examples

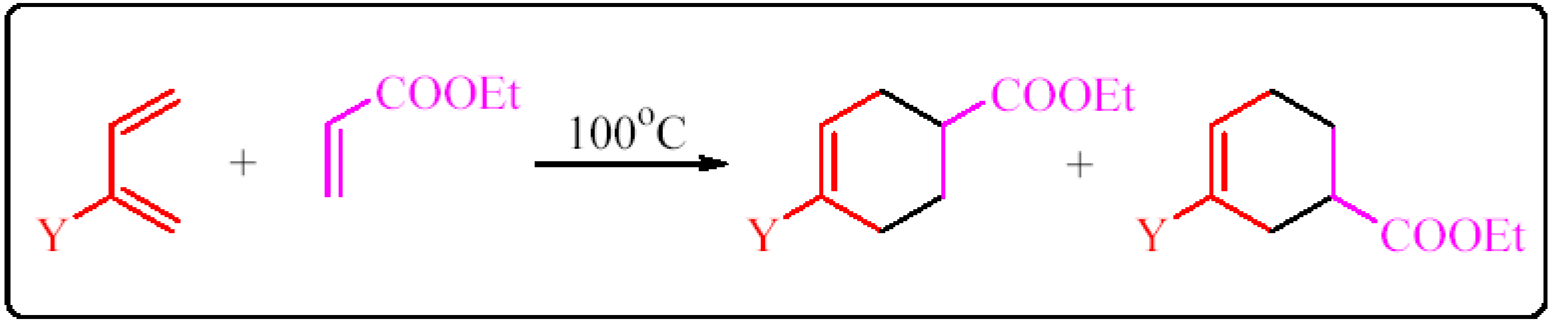
➢ 1-Substituted Buta-1,3-diene



Y	ortho	:	meta
Et_2N	100	:	0
COOH	100	:	0
Ph	98	:	2
Me	95	:	5

Diels-Alder Reaction

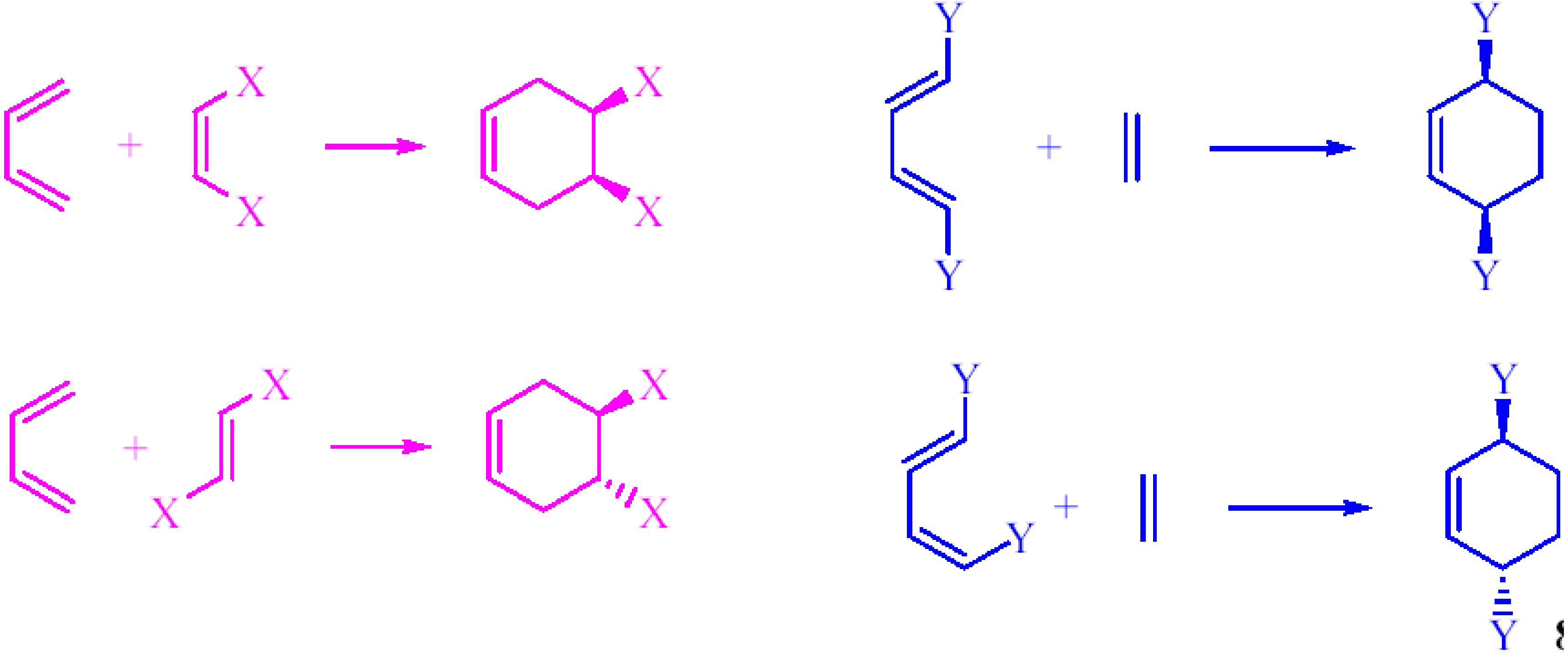
❖ Examples



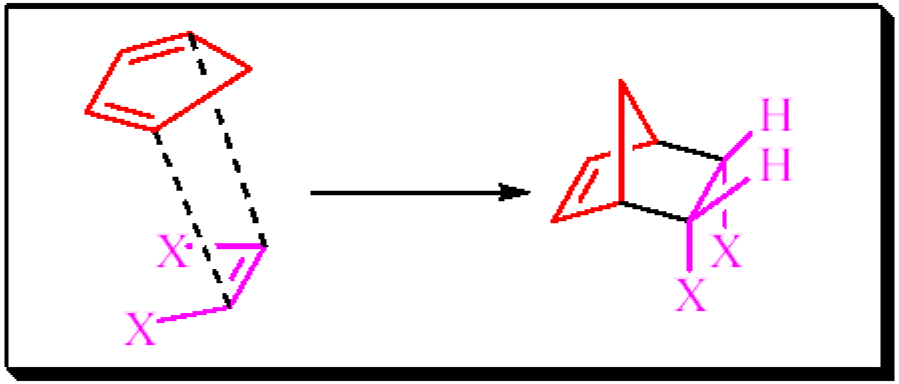
Y	para	:	meta
EtO	100	:	0
Cl	100	:	0
Ph	82	:	18
Me	83	:	17

❖ Stereochemistry

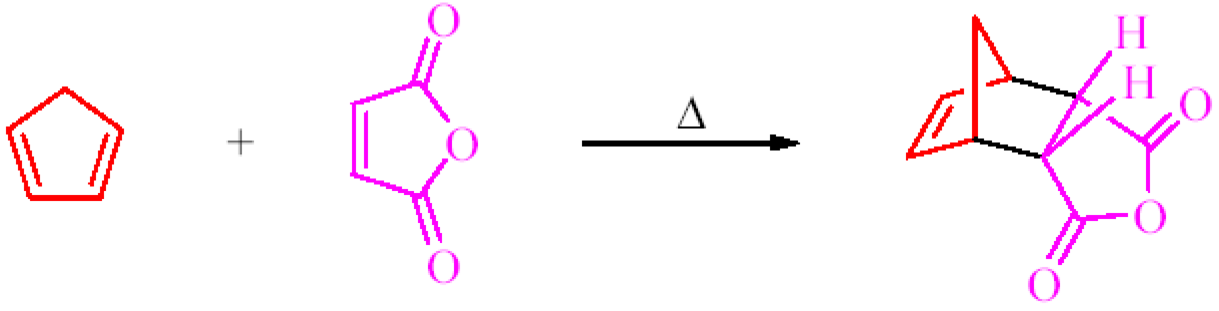
- ➢ Relies on products derived from kinetic control
- ➢ Stereochemistry of reactants preserved, Orbital Symmetry requires <u>suprafacial</u> nature of reaction
- ➢ Stereospecific reaction



❖ Alder-*Endo* Rule



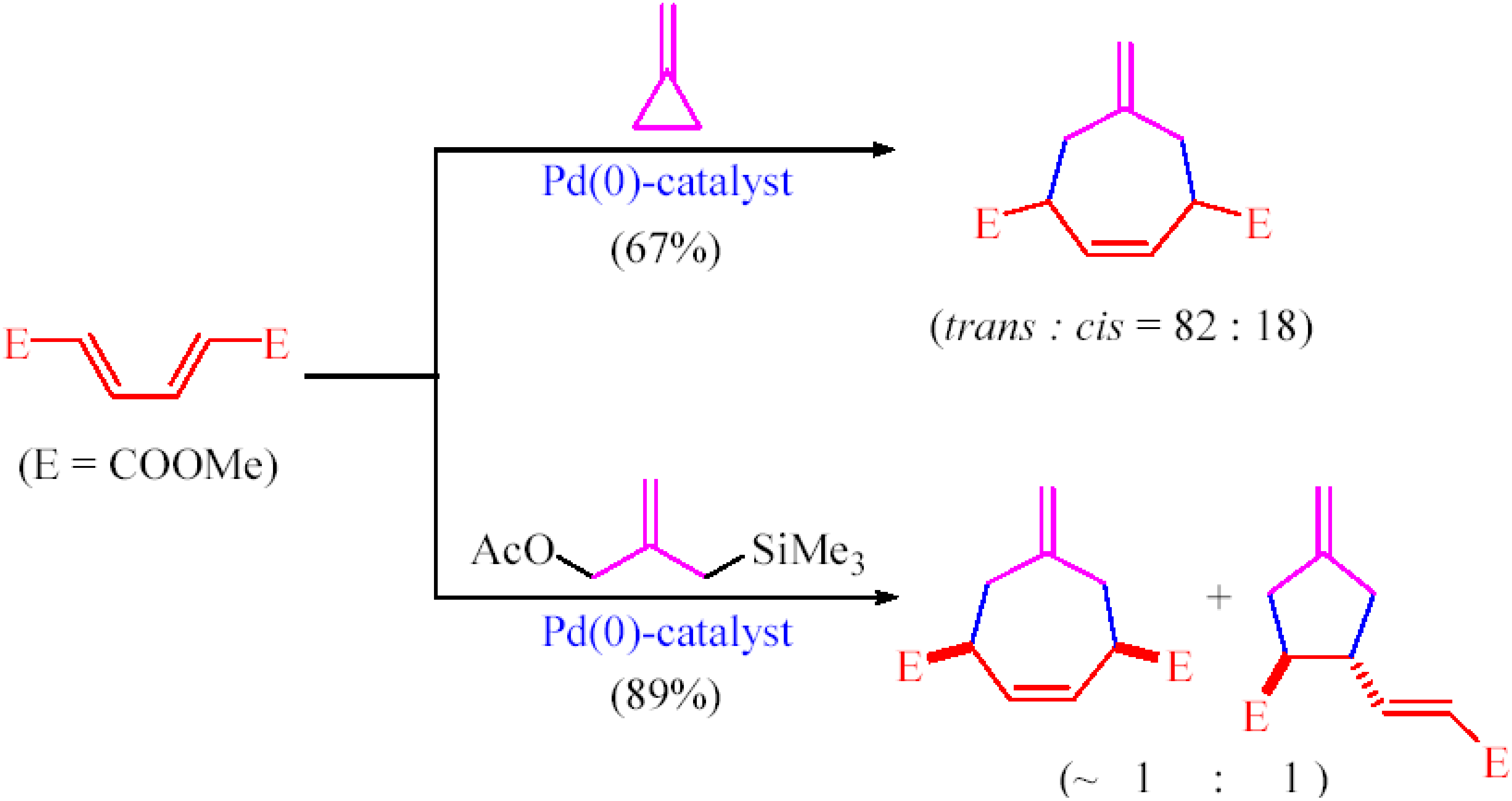
e.g.



100% *endo*

Formation of 7-Membered Ring

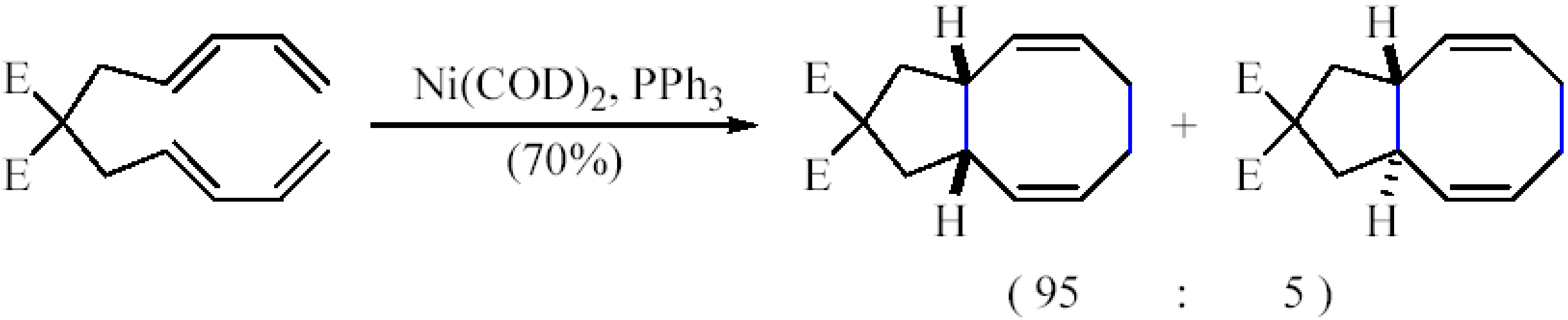
❖ [4+3] Cycloadditions



Formation of 8-Membered Ring

❖ [4+4] Cycloadditions

➢ **Transition Metal Catalyzed [4+4] Cycloaddition**



有机钯化学

在所有的过渡金属中，钯在有机合成中的应用可谓最为广泛。

零价钯的主要来源则是$[Pd(PPh_3)_4]$，$[Pd_2$（$dba)_3]$以及一些诸如$[Pd(OAc)_2]$，$[Pd(PPh_3)_2Cl]$的二价钯的原位还原。

由氧化加成形成的有机钯可以与有机金属化合物以及含Π键的化合物，如炔烃活着烯烃等进行反应。

Still 偶联反应