Chapter 3

Nucleophilic Addition to Carbonyl Group

羰基的亲核加成

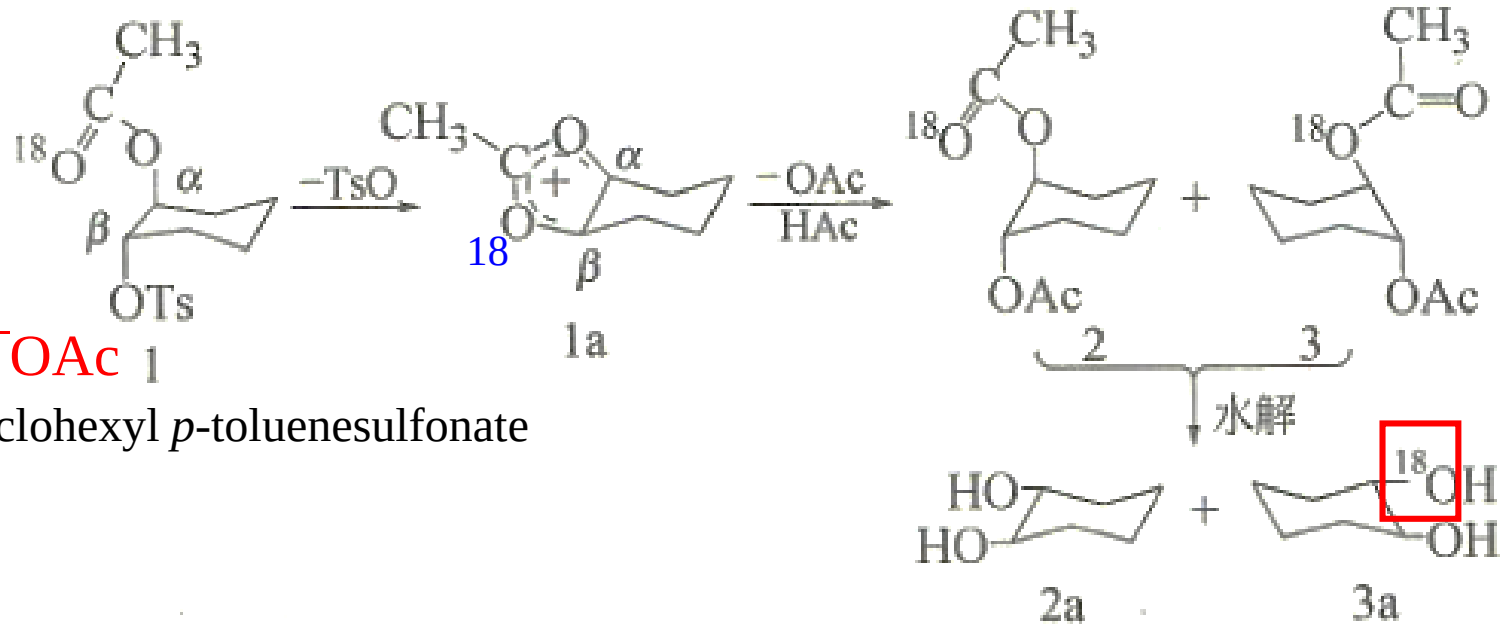
Qiong Li

April 15, 2024

The Neighboring-Group Mechanism

例3：1-O-乙酰基-2-O-对甲苯磺酰基-反-1，2-环己醇的乙酸解（同位素标记）（羰基作为邻近基团）

Solvolysis of 2-acetoxy cyclohexyl p-toluenesulfonate



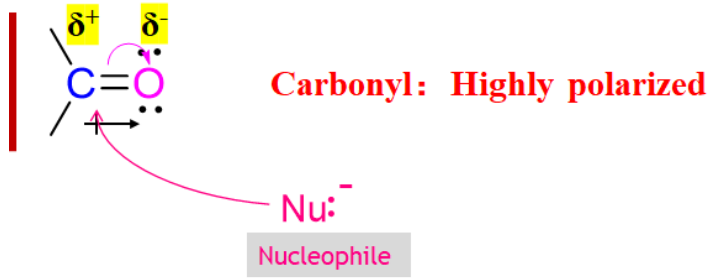
Nu: $^{-}$OAc 1

2-acetoxy cyclohexyl *p*-toluenesulfonate

The rates of solvolysis of the cis and trans isomer of 2-acetoxy cyclohexyl p-toluenesulfonate differ by a factor of about 670, the trans isomer being be more reactive .

?

Chapter 3: Nucleophilic Addition to Carbonyl Group

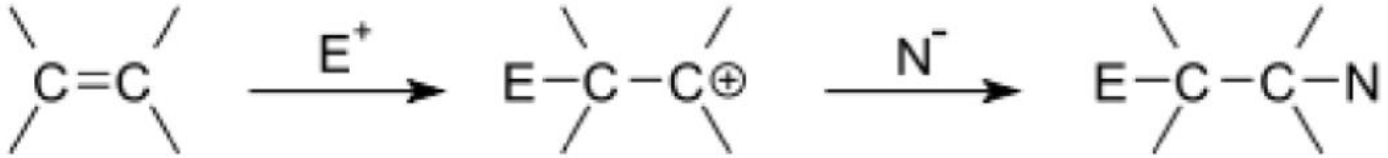


Content

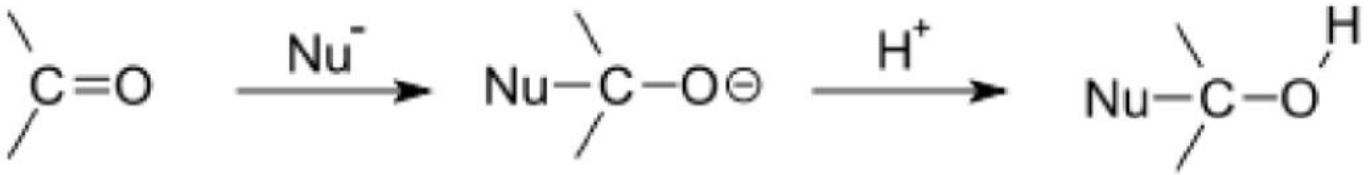
1. Mechanism and Reactivity
2. Nucleophilic addition reactions of carbonyl groups
3. Nucleophilic addition on other unsaturated bonds
4. Diastereoselectivity in nucleophilic addition reactions

Addition Reaction

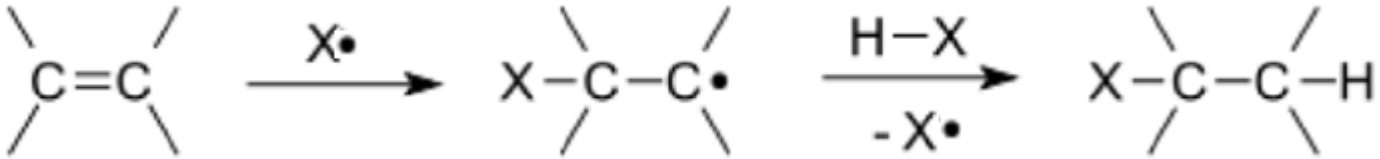
Electrophilic Addition



Nucleophilic Addition



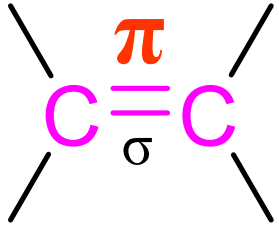
Free Radical Addition

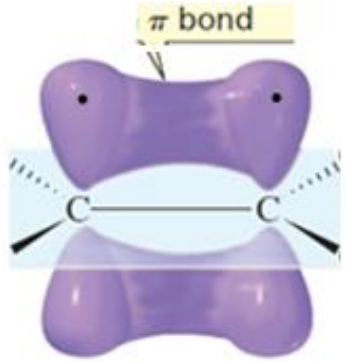


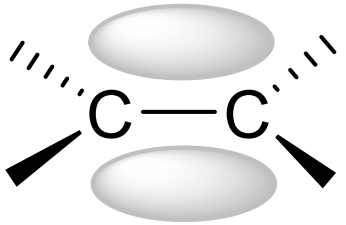
Electrophilic Addition and Nucleophilic Addition

Electrophilic Addition

sp^2



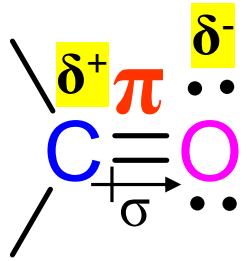


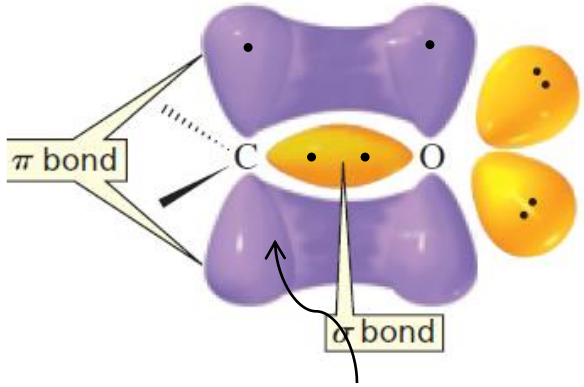


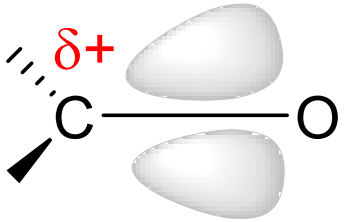
π - 电子云分布

Nucleophilic Addition

sp^2



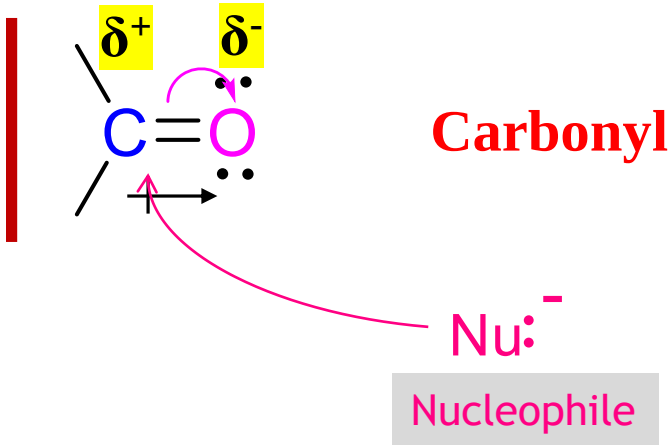




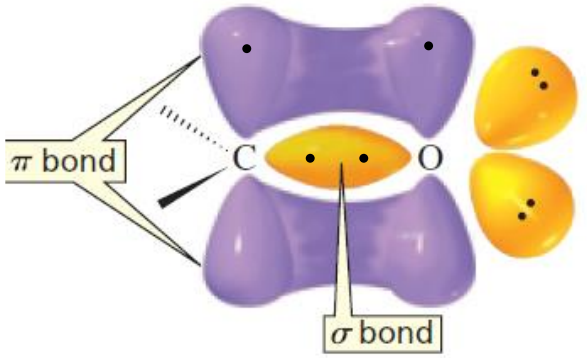
π-电子云分布

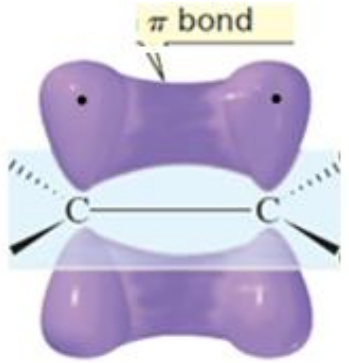
Highly Polarized

8.1 Structure and Reactivity

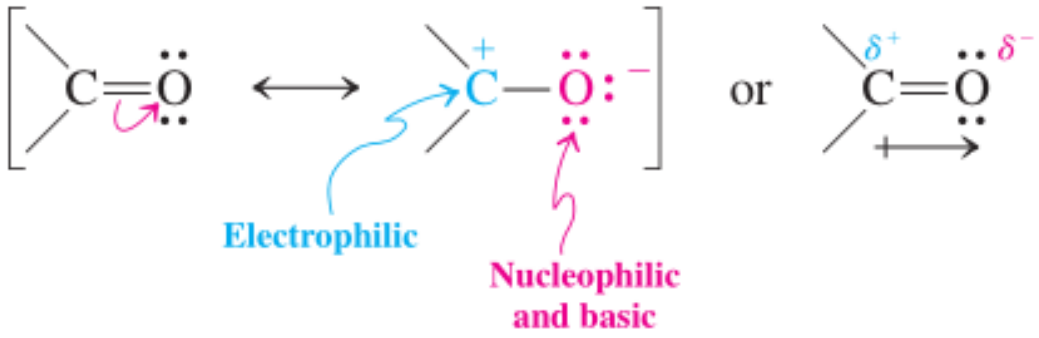


Carbonyl：Highly polarized



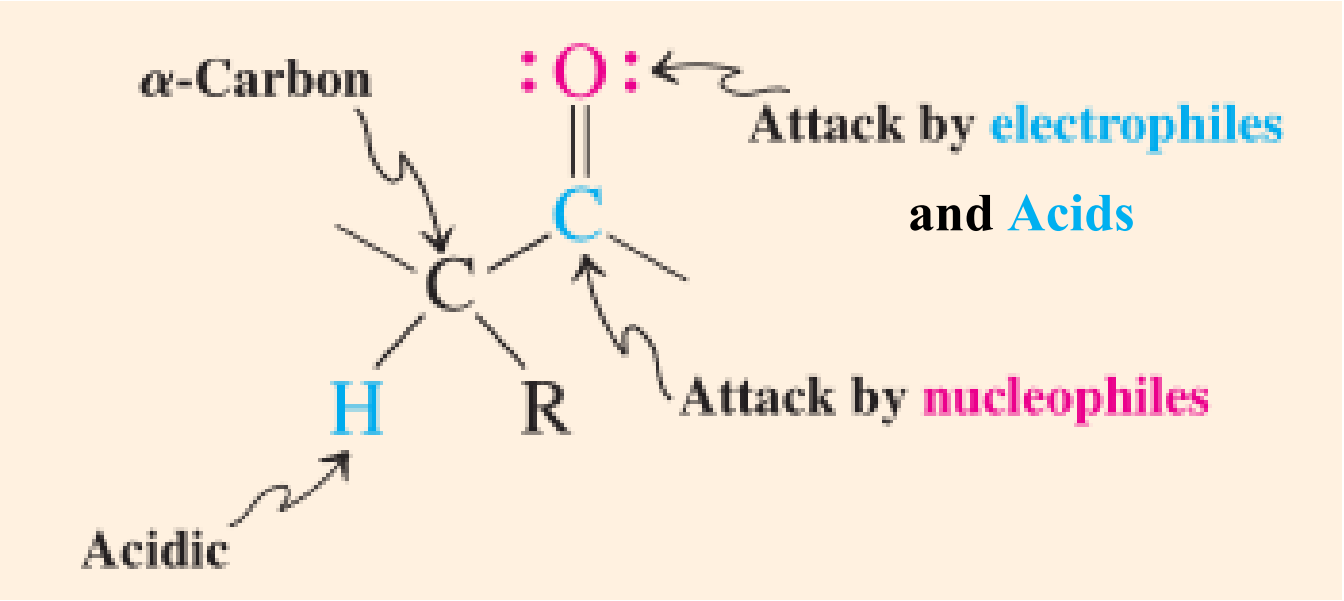


Descriptions of a Carbonyl Group



8.1 Structure and Reactivity

Regions of Reactivity in Carbonyl Compounds



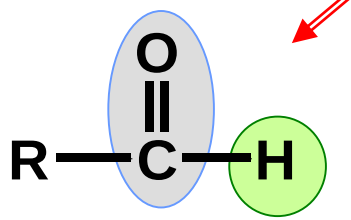
The Carbonyl Compounds

A_N

"S_N"

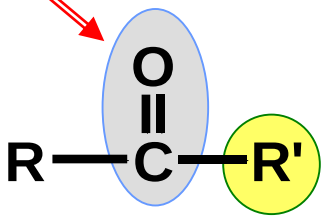
carbonyl

羰基



Aldehyde

醛

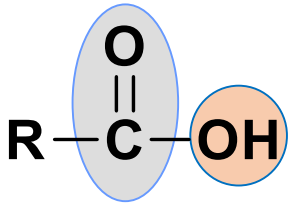


Ketone

酮

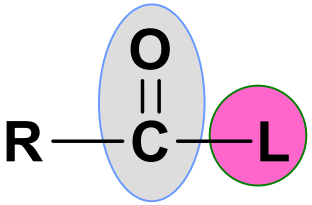
carbonyl

羰基



Carboxylic Acid

羧酸



Carboxylic Acid Derivatives

羧酸衍生物

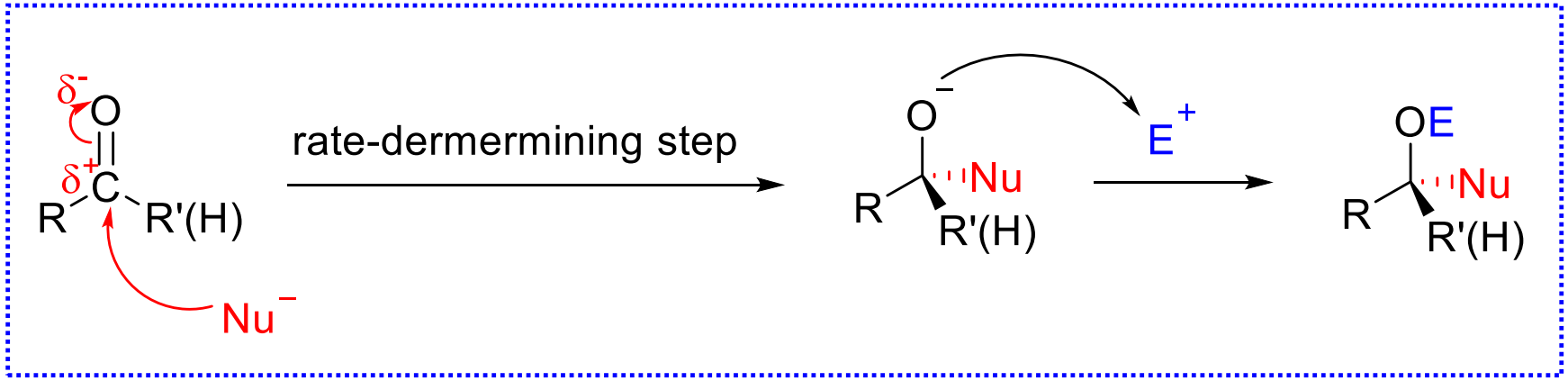
8.2 Nucleophilic Addition to Carbonyl Groups

8.2.1 General reaction, Mechanisms, and Reactivity

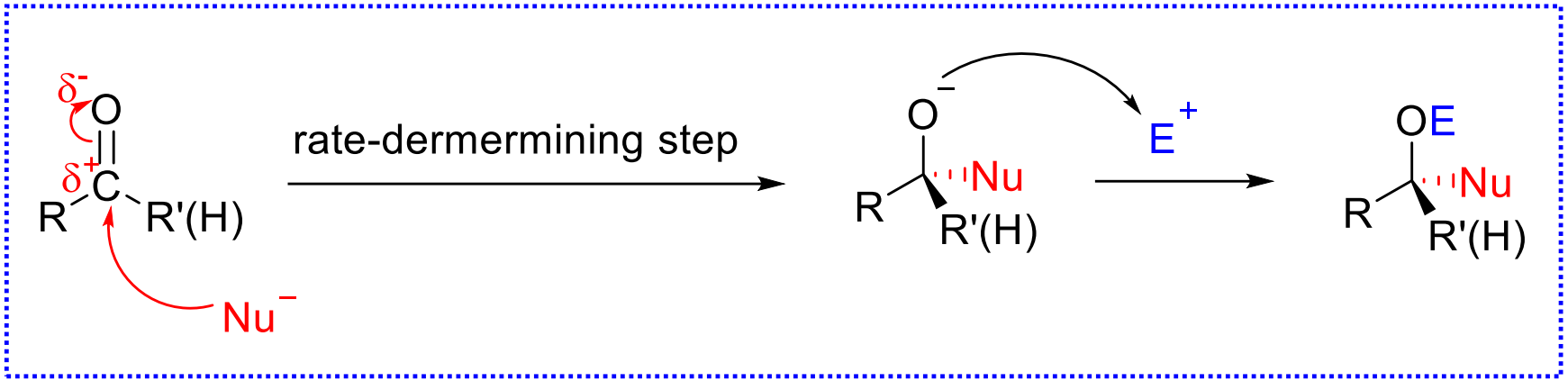
The carbonyl group is Highly polarized and the partial positive charge on the carbonyl carbon

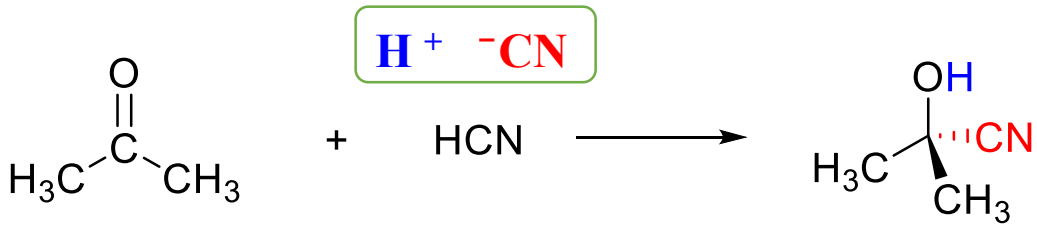
a. Reaction

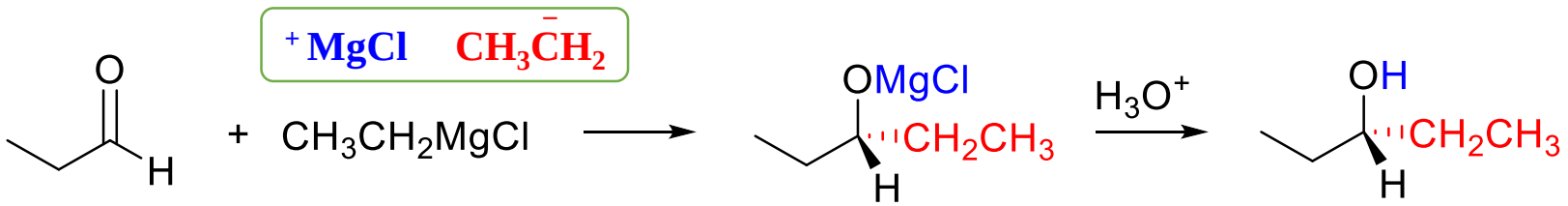
Ionic Additions to the Carbonyl Group



8.2 Nucleophilic Addition to Carbonyl Groups



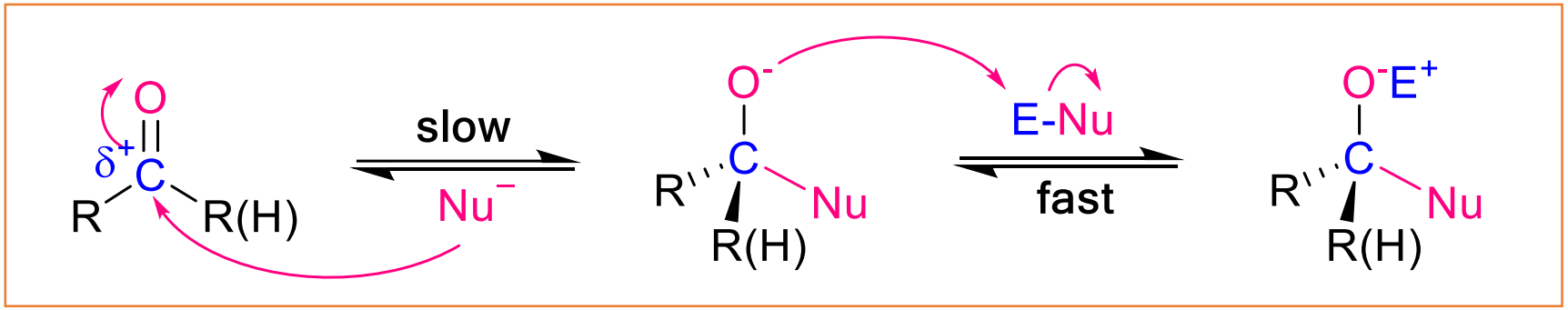


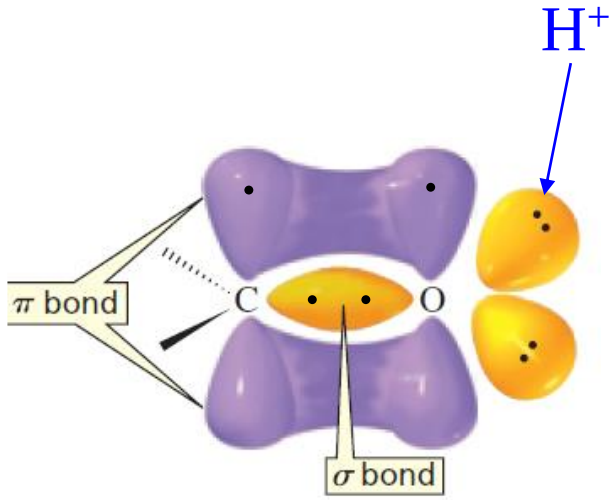


Nucleophilic Addition to Carbonyl Group

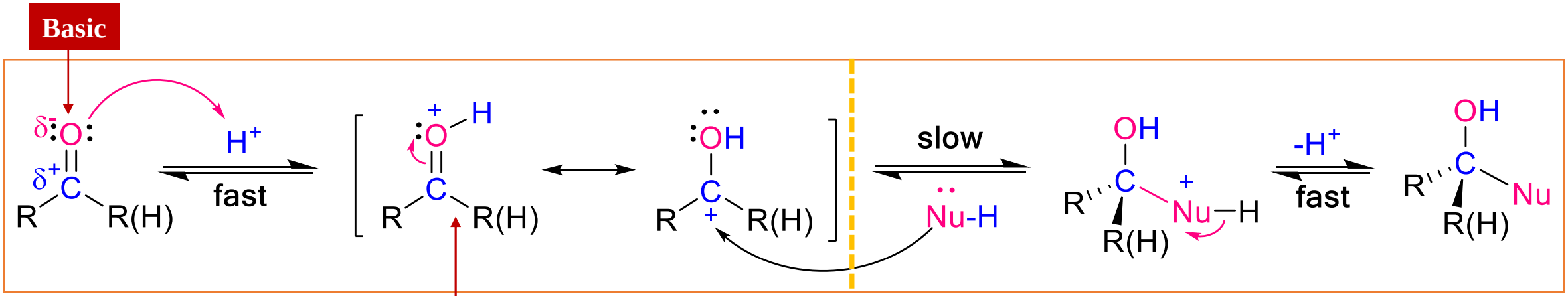
b. Mechanisms

1. Basic Conditions: Nu^- relatively strong nucleophile





2. Acidic Conditions: $\ddot{H}Nu$ relatively weak nucleophile

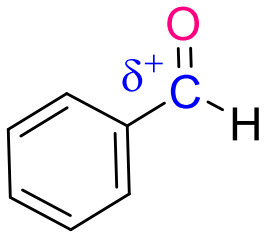


Nucleophilic Addition to Carbonyl Group

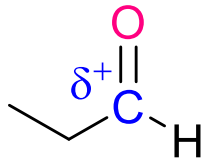
c. Structure and Reactivity

Electronic effect δ^+ ↑ reactivity ↑

Conjugated effect

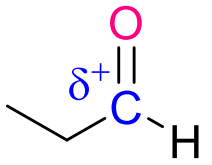


<

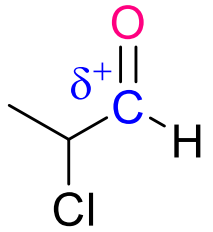


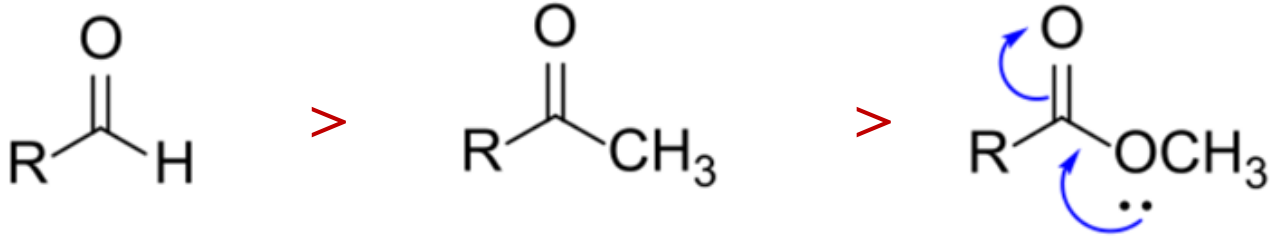
aromatic aldehyde aliphatic aldehyde

Inductive effect



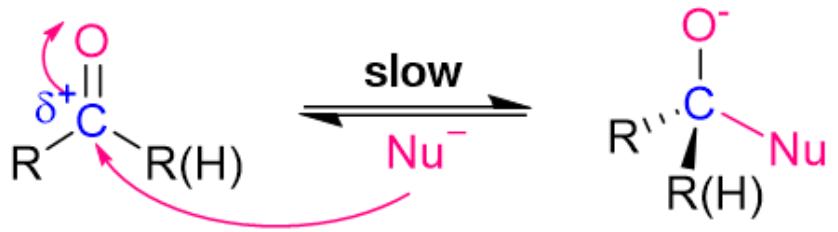
<





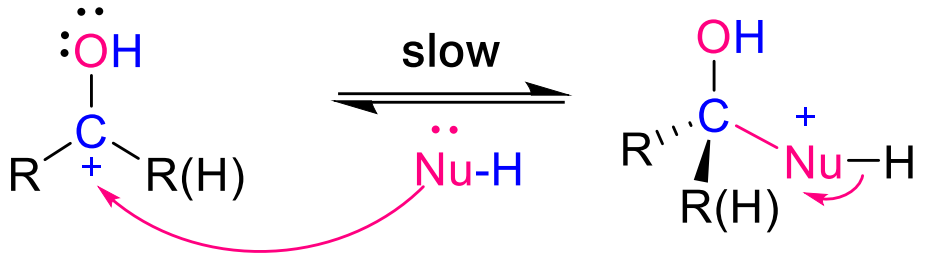
Nucleophilic Addition to Carbonyl Group

Steric effect R，R’ Steric hindrance ↑ reactivity ↓



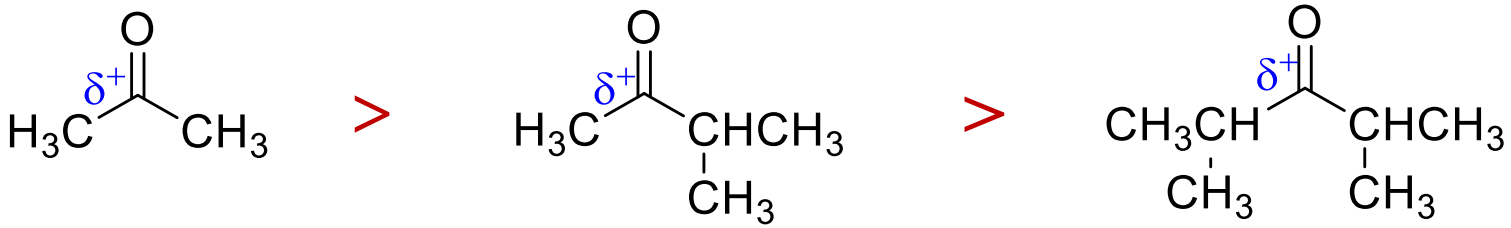
SP^2 planar → SP^3 tetrahedron

Steric hindrance increase



SP^2 planar → SP^3 tetrahedron

Steric hindrance increase



8.2.2 Typical nucleophilic addition reactions

Nucleophile:

Heteroatoms: O， S， N。。。

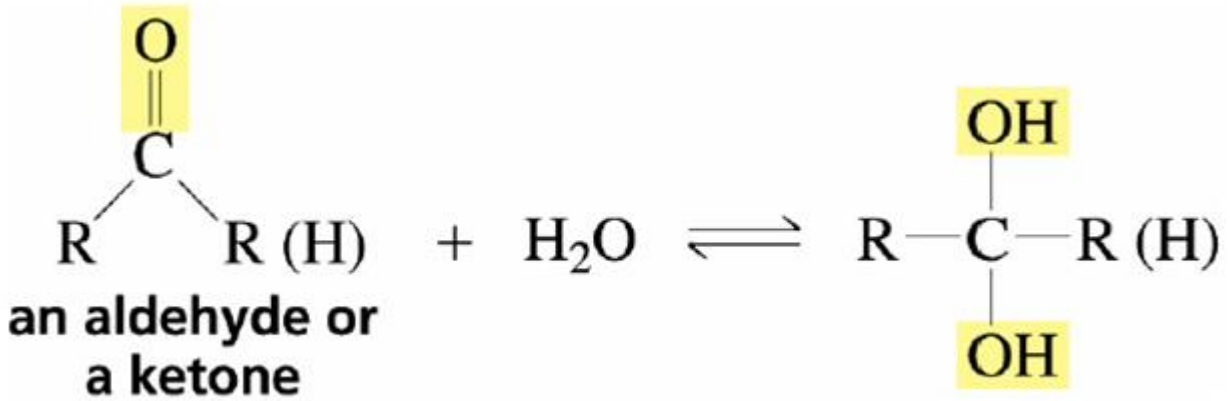
Carbon atoms: carboanion， cyanide， enolate，

enol， enamine。。。

Nucleophilic Addition to Carbonyl Group

a. with oxygen nucleophiles

1. The addition of $H_2\ddot{O}$ Hydration

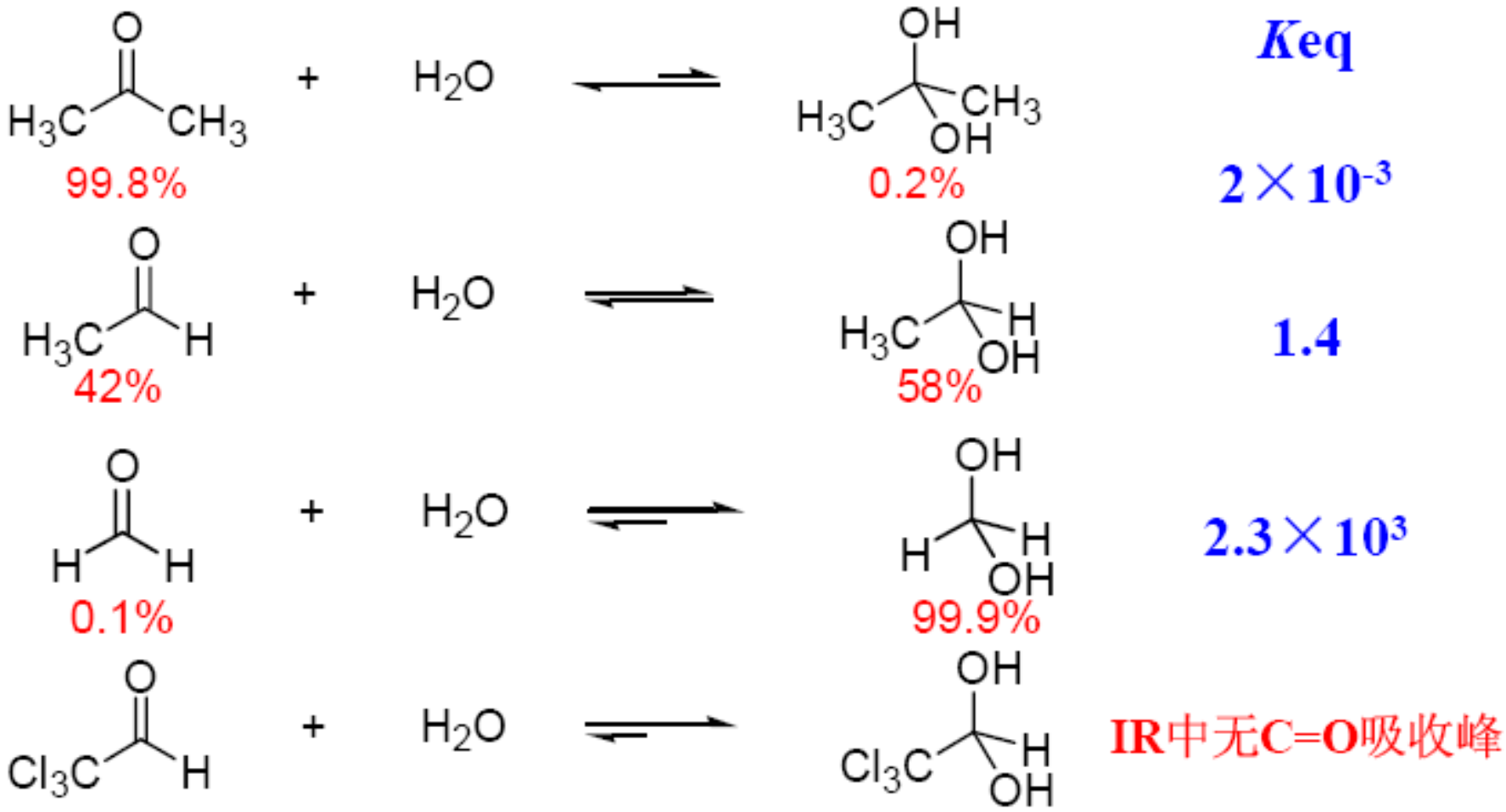


geminal diol 偕二醇

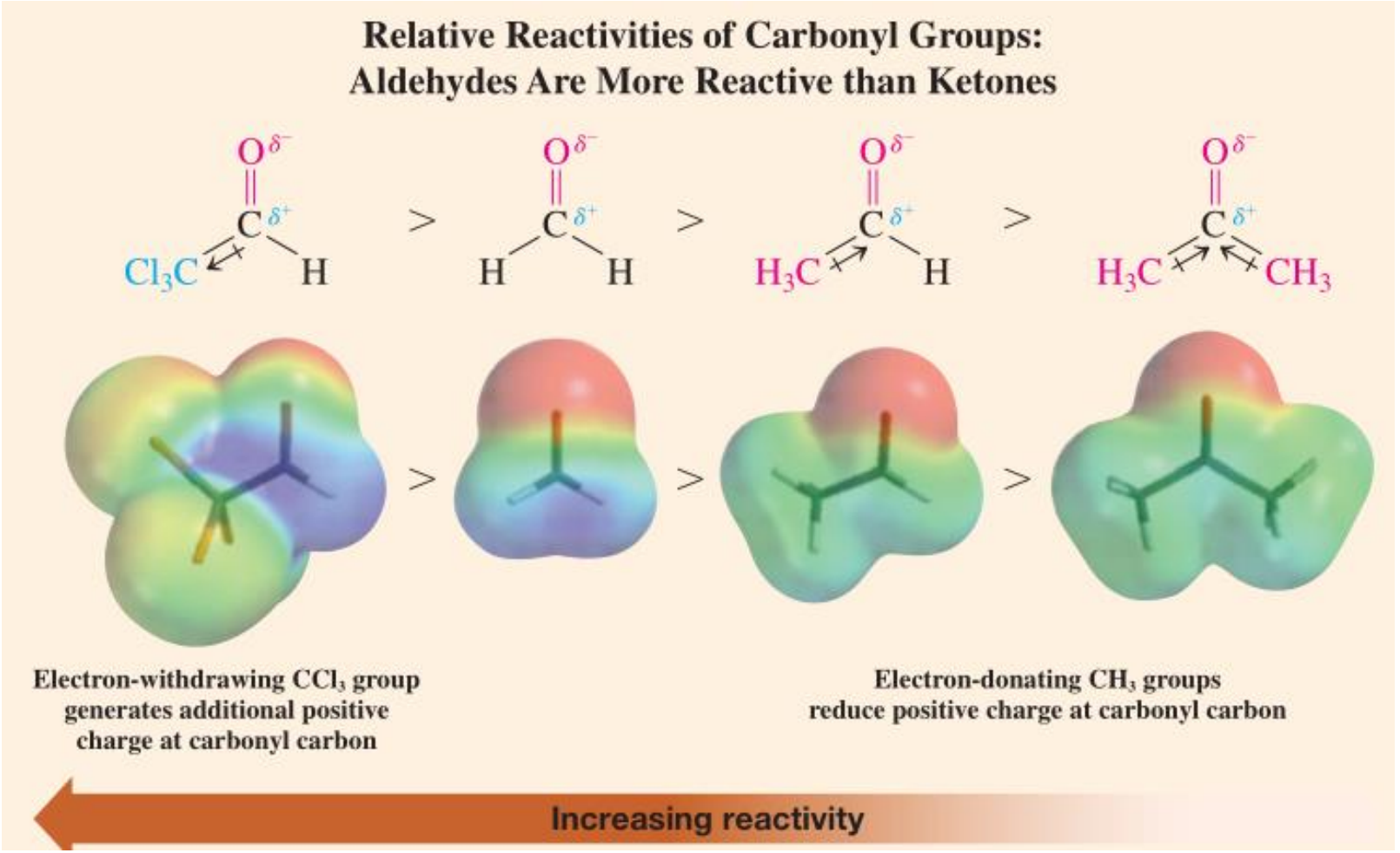
carbonyl hydrate 羰基水合物

Nucleophilic Addition to Carbonyl Group

Hydration is reversible

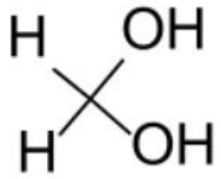


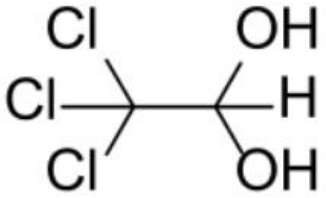
Nucleophilic Addition to Carbonyl Group

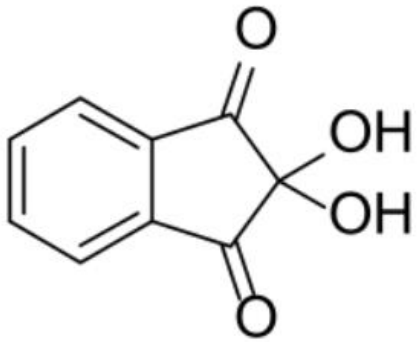


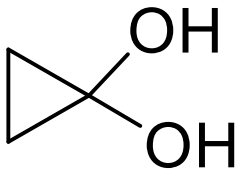
Nucleophilic Addition to Carbonyl Group

Some of the more stable gem-diols





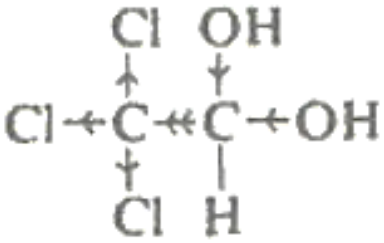


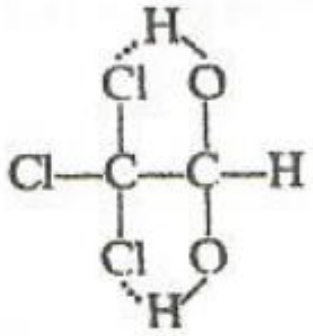


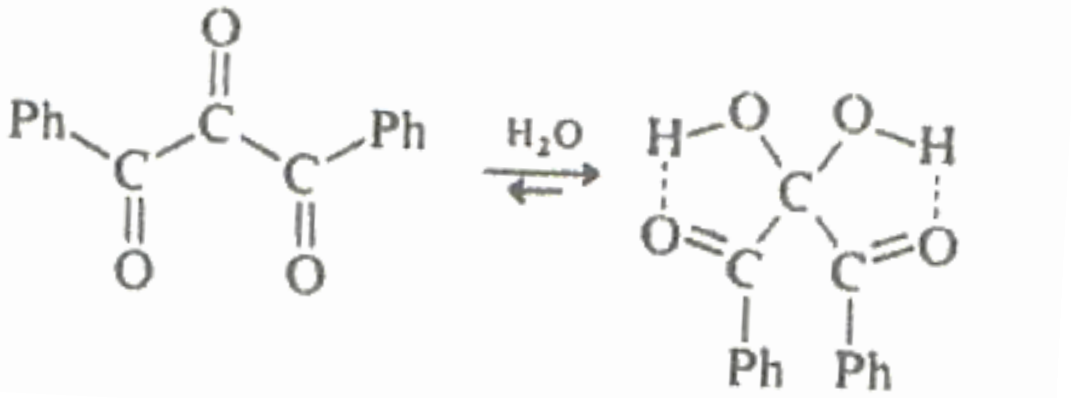
Nucleophilic Addition to Carbonyl Group

Some of the more stable gem-diols

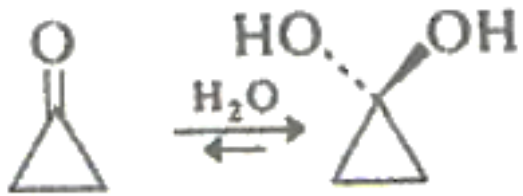
H-Bond







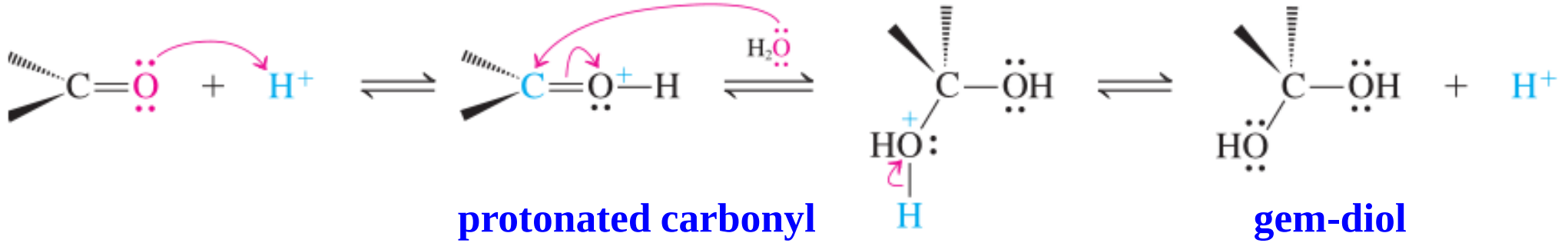
Release of angle strain



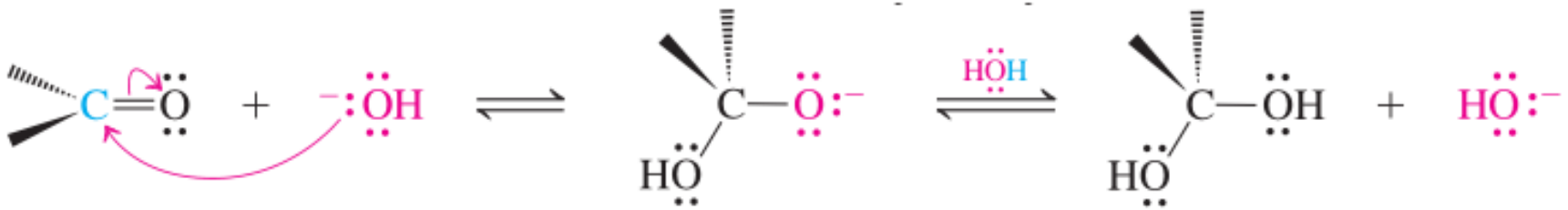
(21) (20)

Nucleophilic Addition to Carbonyl Group

Mechanism of Acid-Catalyzed Hydration

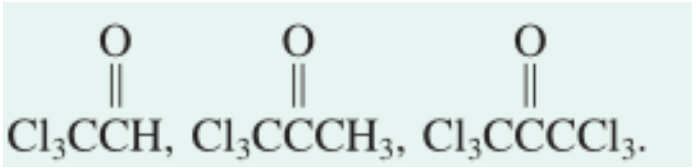


Mechanism of Base-Catalyzed Hydration

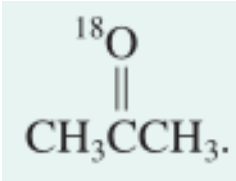


Exercise 1

Rank in order of increasing favorability of hydration:



Treatment of acetone with $H_2{}^{18}O$ and catalytic amount of HCl results in the formation of labeled acetone,



Explain. (Hint: hydration is reversible)

Exercise 2

Rank in order of decreasing favorability of nucleophilic addition.

1. CF_3CH_2CHO > CH_3CH_2CHO > $CH_3COCH_2CH_3$ > $CH_3CH_2COCH_2CH_3$

2. $ArCH_2COR$ > $ArCOR$ > Ar_2CO

3. $ClCH_2CHO$、$BrCH_2CHO$、$CH_2{=}CHCHO$、CH_3CH_2CHO、CH_3CF_2CHO

4. CH_3CHO、CH_3COCH_3、CF_3CHO、$CH_3CH{=}CHCHO$、$CH_3COCH{=}CH_2$

Chapter 3

Nucleophilic Addition to Carbonyl Group

羰基的亲核加成

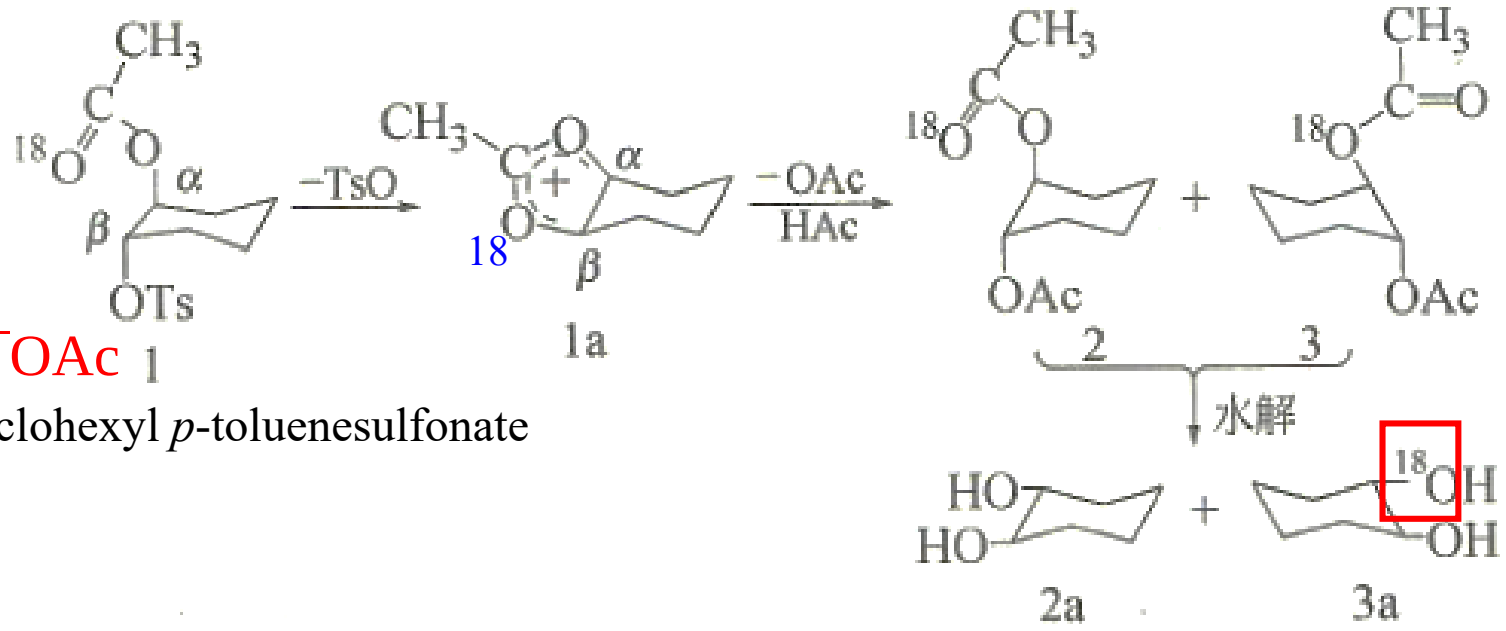
Qiong Li

April 15, 2024

The Neighboring-Group Mechanism

例3：1-O-乙酰基-2-O-对甲苯磺酰基-反-1，2-环己醇的乙酸解（同位素标记）（羰基作为邻近基团）

Solvolysis of 2-acetoxy cyclohexyl p-toluenesulfonate

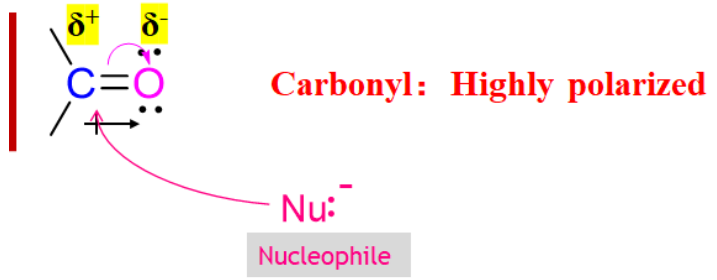


Nu: $^{-}$OAc 1

2-acetoxy cyclohexyl *p*-toluenesulfonate

The rates of solvolysis of the cis and trans isomer of 2-acetoxy cyclohexyl p-toluenesulfonate differ by a factor of about 670, the trans isomer being be more reactive .

Chapter 3: Nucleophilic Addition to Carbonyl Group

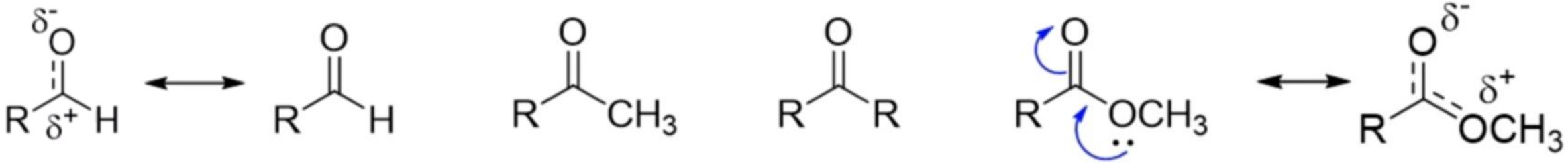


Content

1. Mechanism and Reactivity
2. Nucleophilic addition reactions of carbonyl groups
3. Nucleophilic addition on other unsaturated bonds
4. Diastereoselectivity in nucleophilic addition reactions

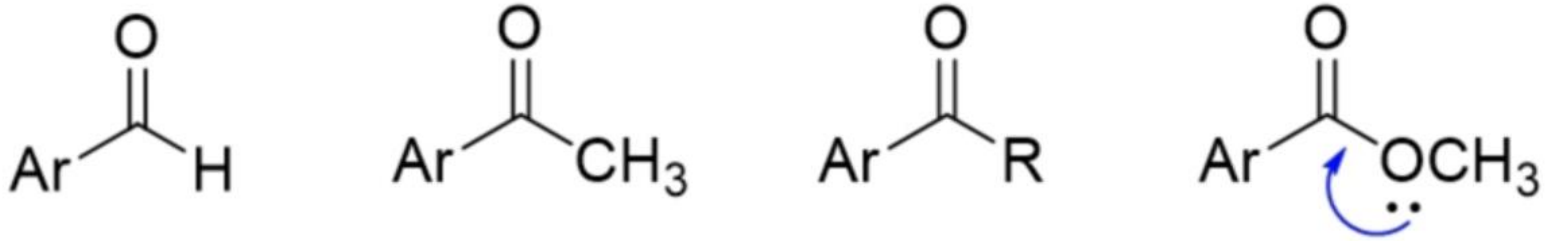
Nucleophilic Addition to Carbonyl Group

Structure and Reactivity



Electronic effect δ^+ ↑ reactivity ↑

Steric effect R, R' Steric hindrance ↑ reactivity ↓



3.2.2 Typical nucleophilic addition reactions

Nucleophile:

Heteroatoms: O， S， N。。。

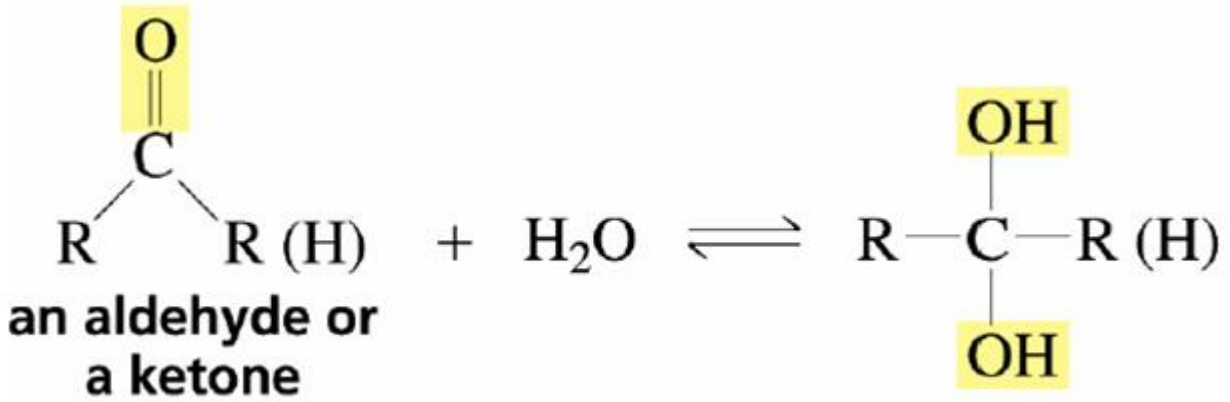
Carbon atoms: carboanion， cyanide， enolate，

enol， enamine。。。

Nucleophilic Addition to Carbonyl Group

a. with oxygen nucleophiles

1. The addition of $H_2\ddot{O}$ Hydration

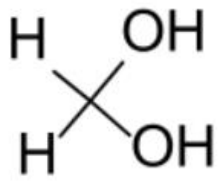


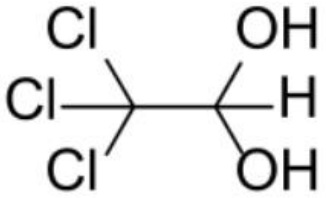
geminal diol 偕二醇

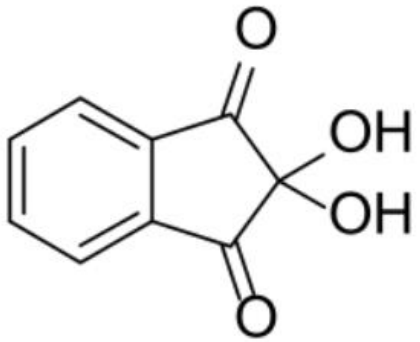
carbonyl hydrate 羰基水合物

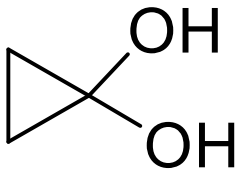
Nucleophilic Addition to Carbonyl Group

Some of the more stable gem-diols



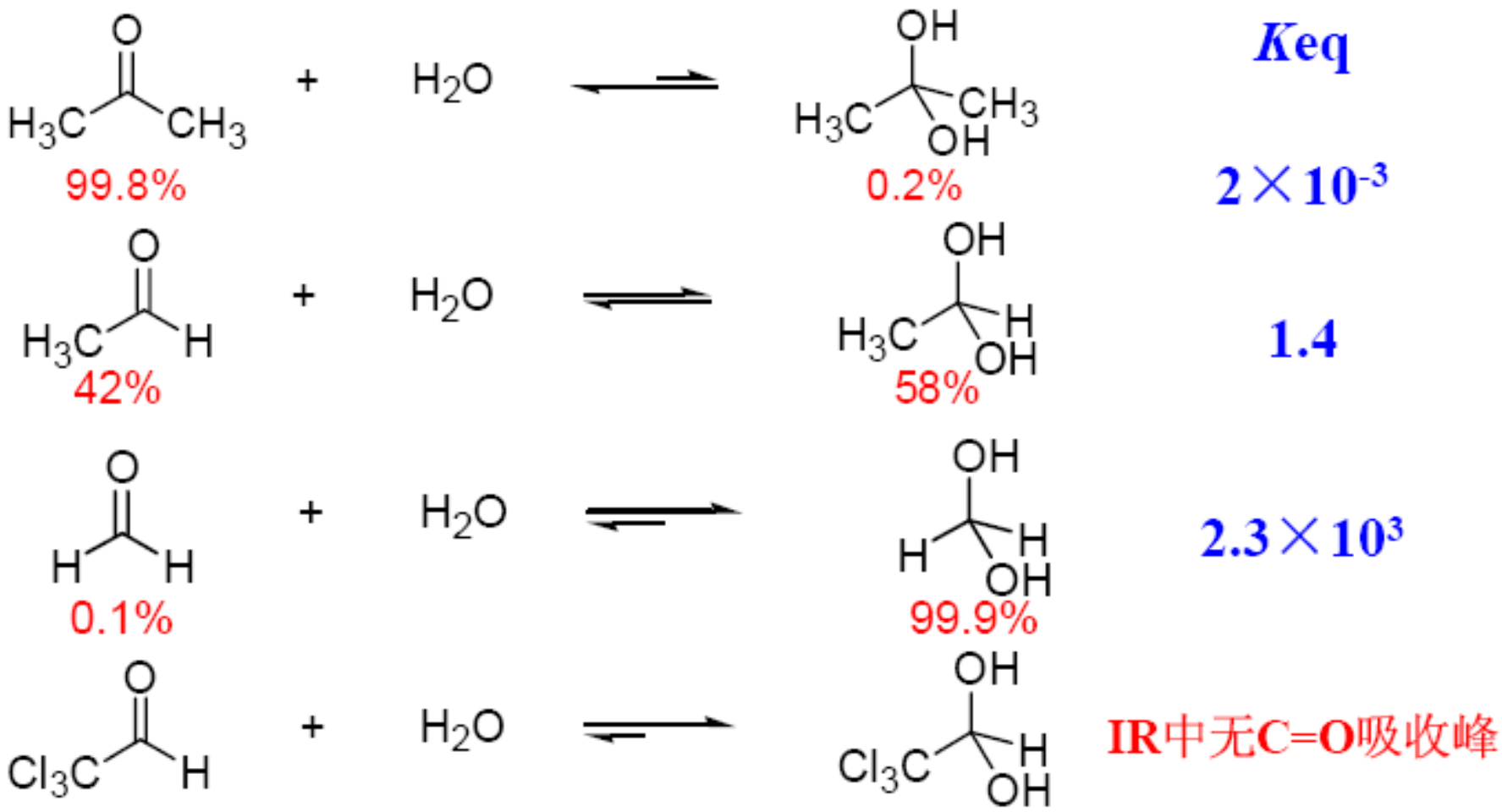






Nucleophilic Addition to Carbonyl Group

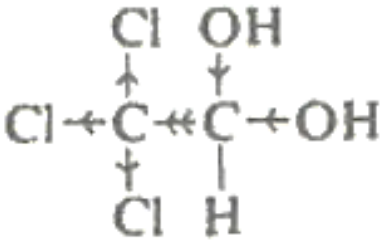
Hydration is reversible

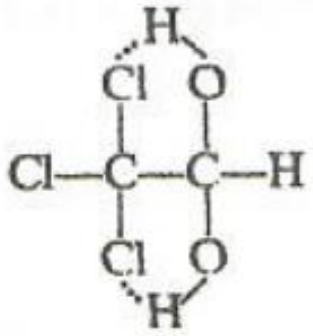


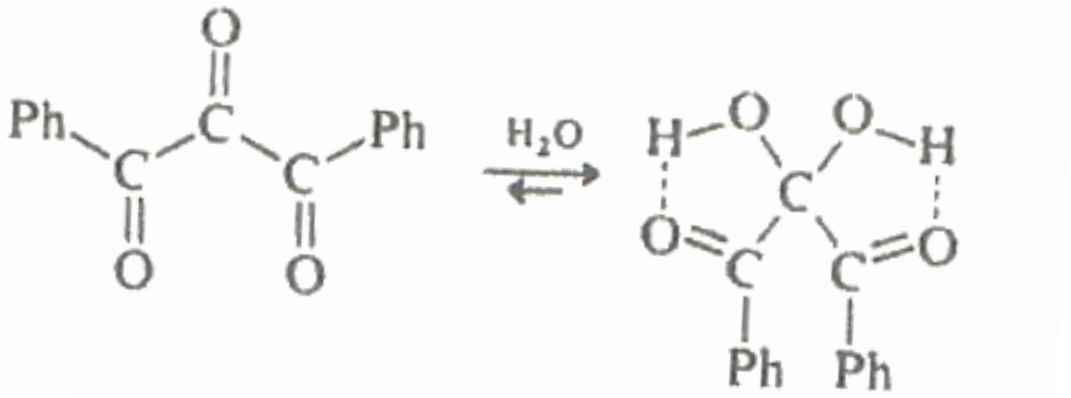
Nucleophilic Addition to Carbonyl Group

Some of the more stable gem-diols

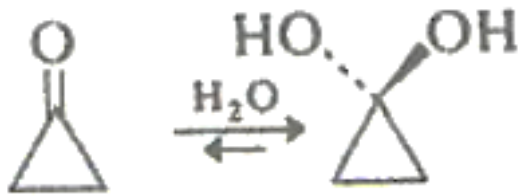
H-Bond





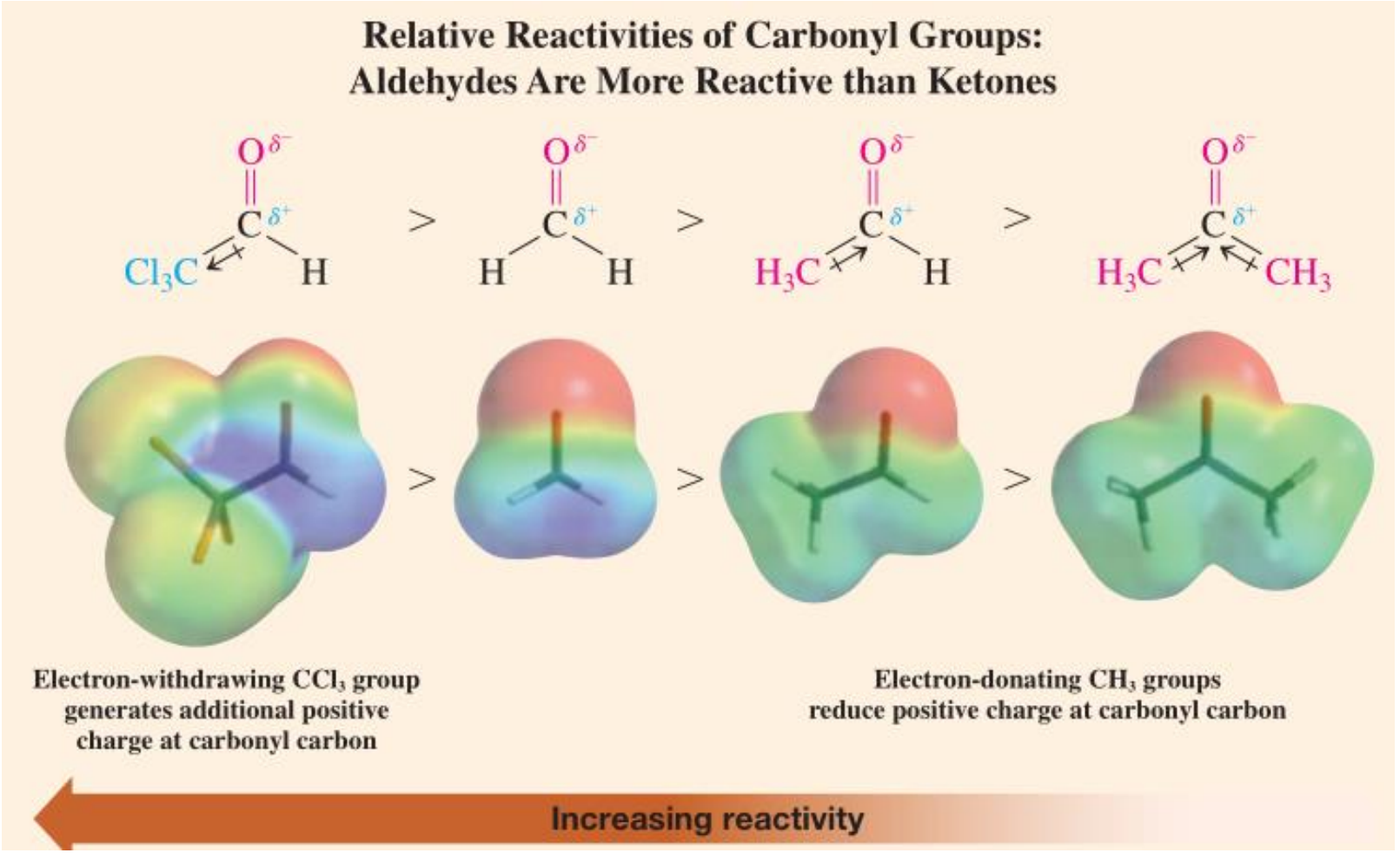


Release of angle strain



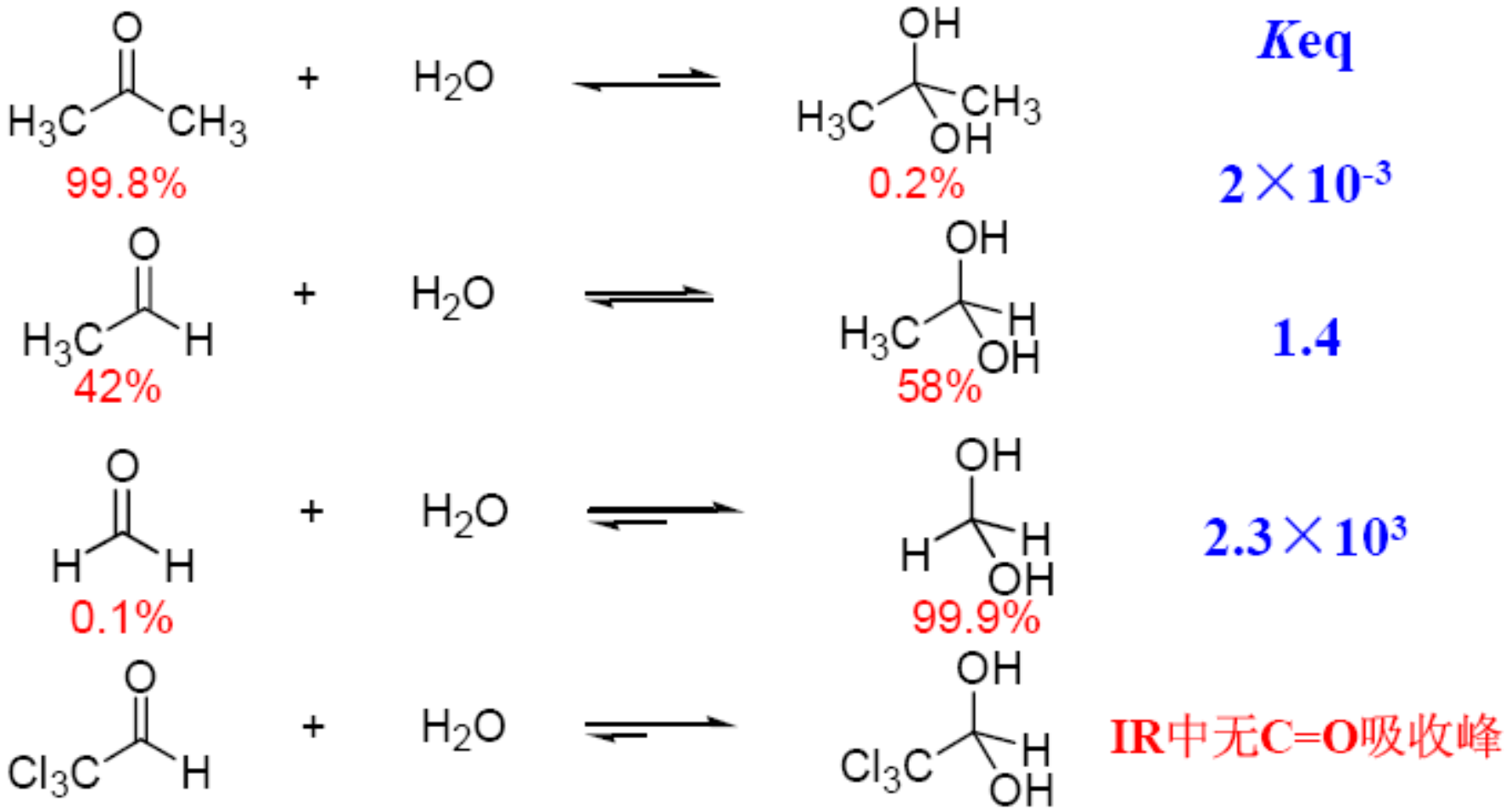
(21) (20)

Nucleophilic Addition to Carbonyl Group



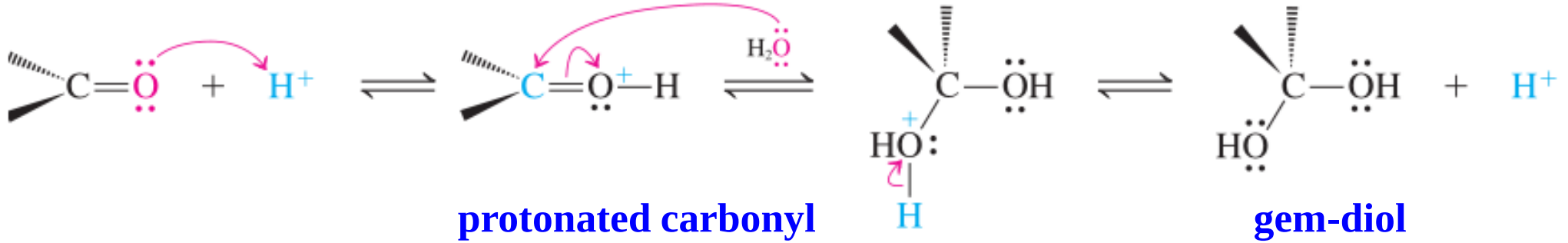
Nucleophilic Addition to Carbonyl Group

Hydration is reversible

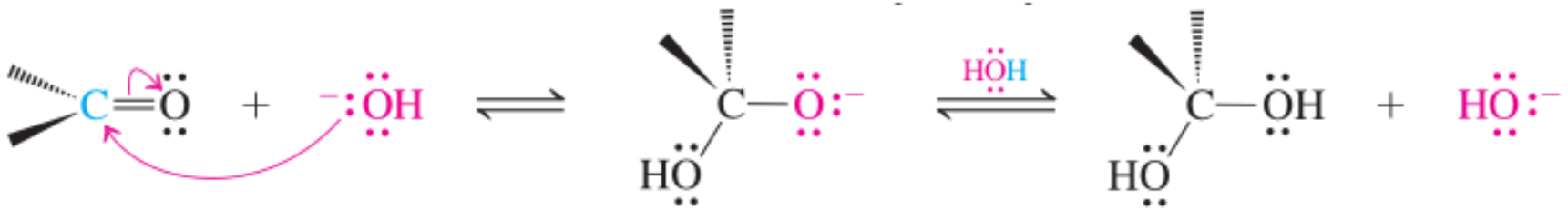


Nucleophilic Addition to Carbonyl Group

Mechanism of Acid-Catalyzed Hydration

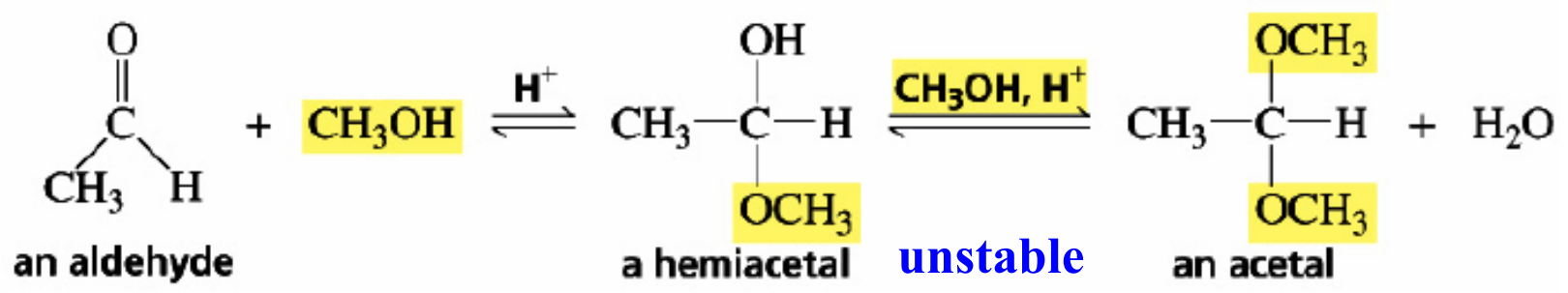


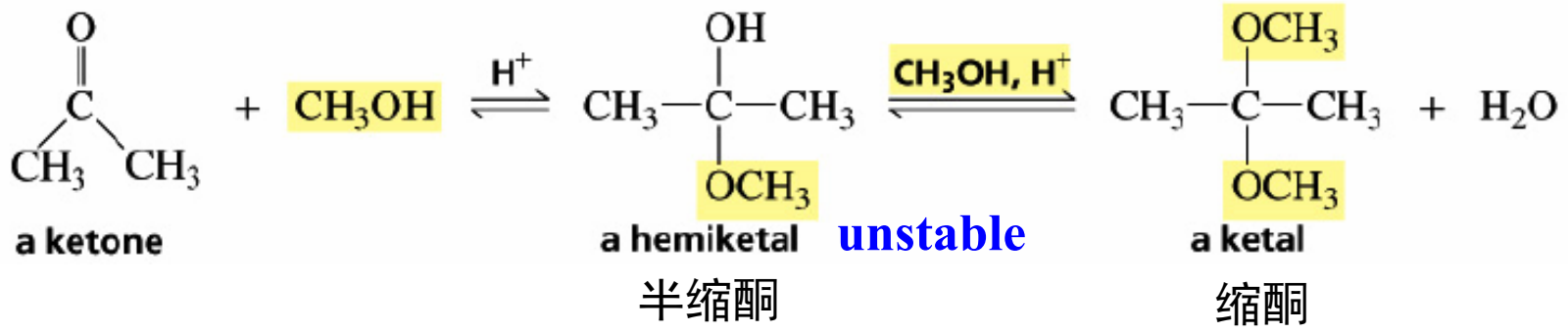
Mechanism of Base-Catalyzed Hydration



Nucleophilic Addition to Carbonyl Group

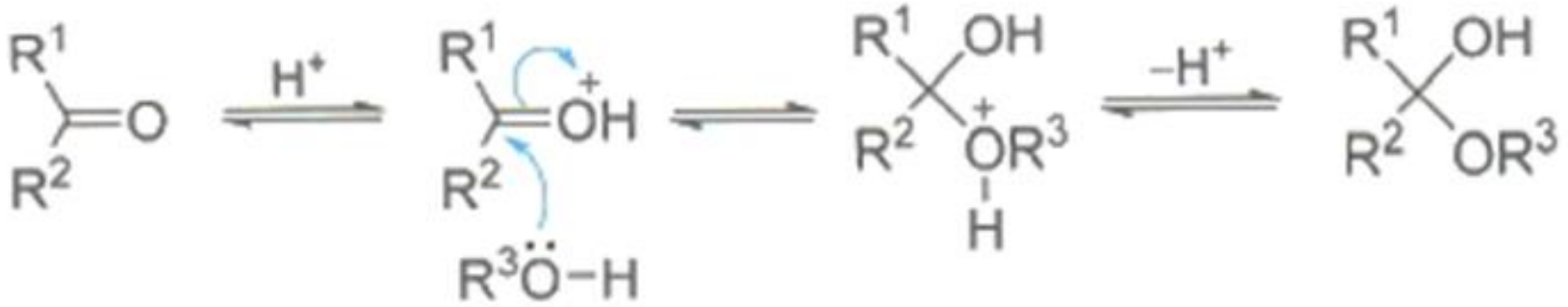
2. The addition of R$\ddot{\text{O}}$H





Nucleophilic Addition to Carbonyl Group

Mechanism of forming hemiacetal

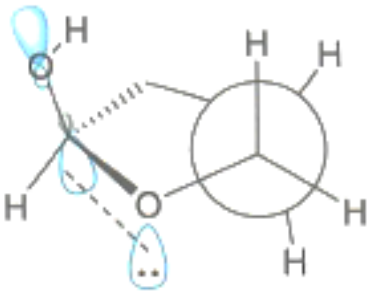


hemiacetal (hemiketal)

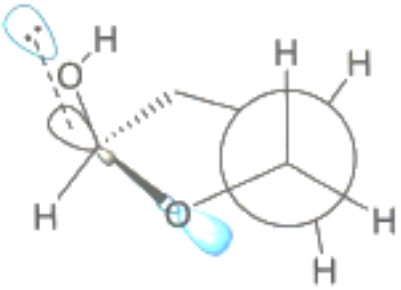
Nucleophilic Addition to Carbonyl Group

Some stable hemiacetal

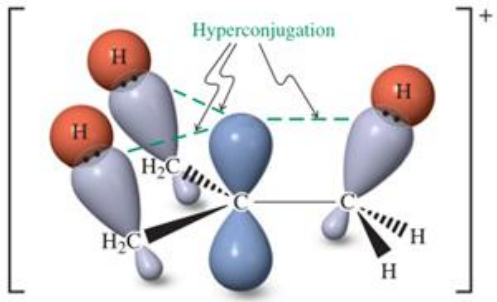
Release of angle strain

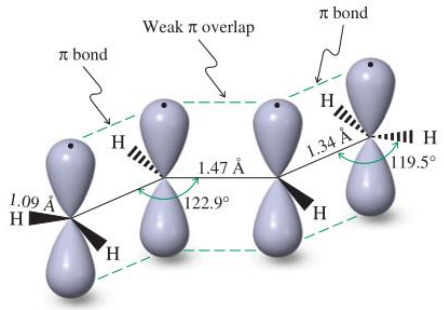


内型端基效应



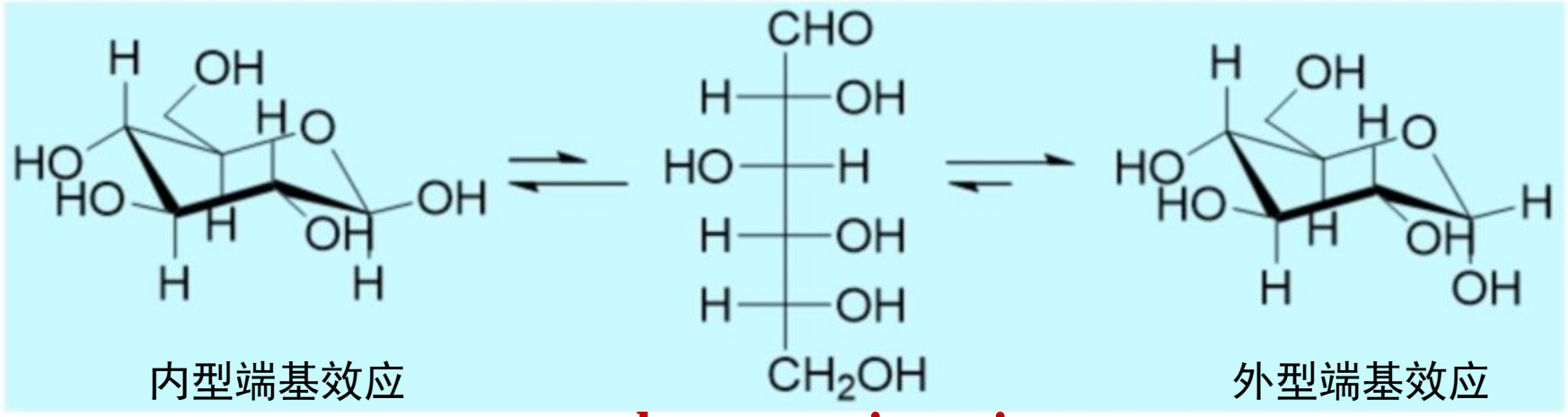
外型端基效应



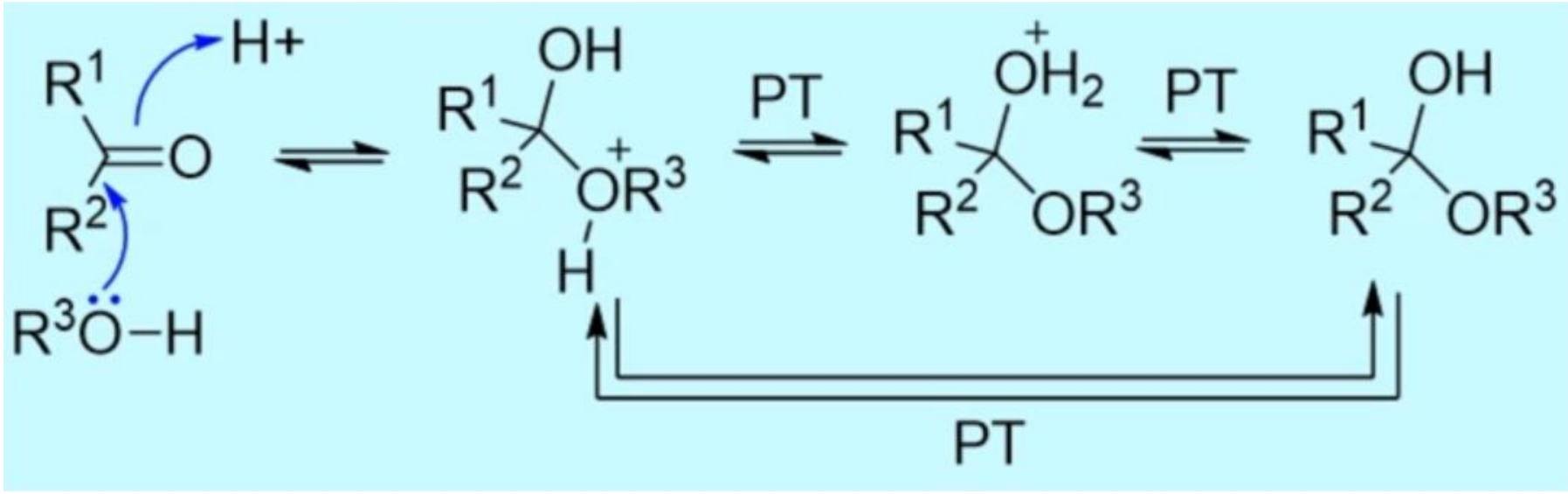


n-σ* hyperconjugation

Nucleophilic Addition to Carbonyl Group

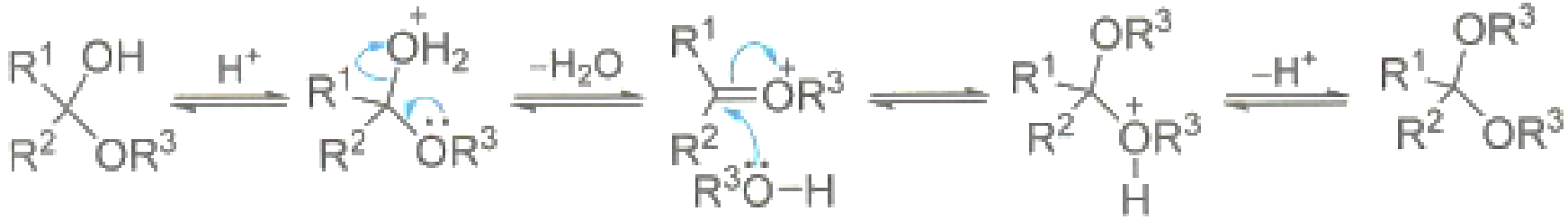


n-σ* hyperconjugation



Nucleophilic Addition to Carbonyl Group

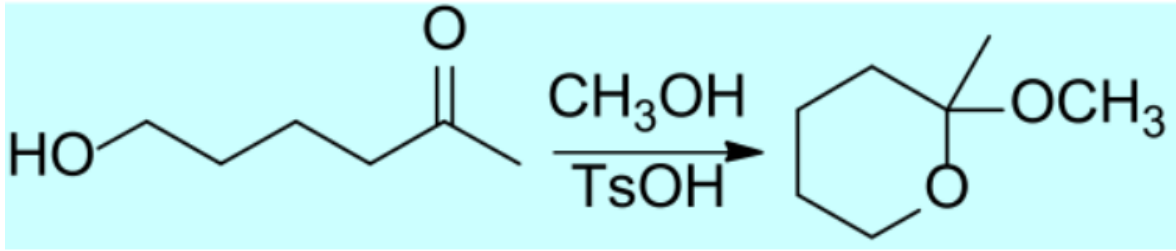
Mechanism of forming acetal



acetal (ketal)

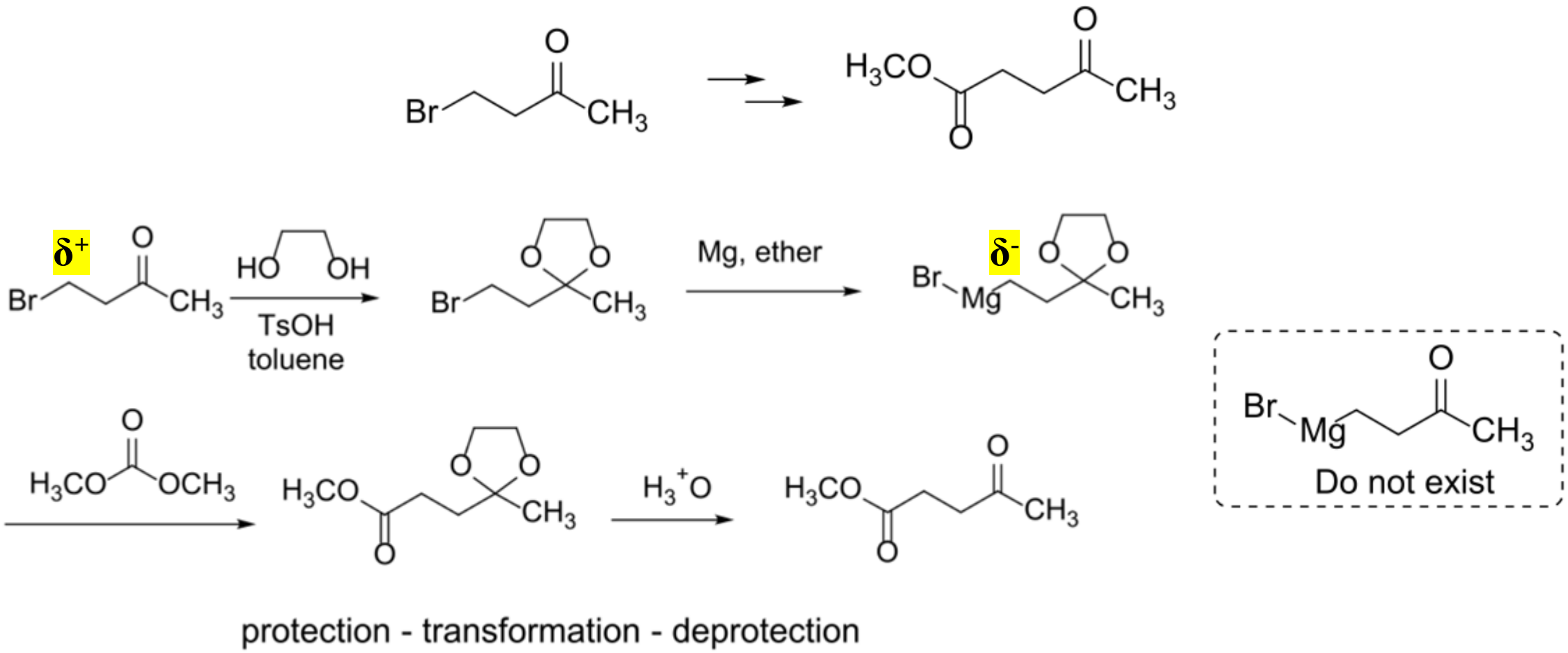
Exercise 3

Provide the mechanism for the reaction below



Nucleophilic Addition to Carbonyl Group

Application: Protection of Carbonyl (Acetals as Protecting Groups)

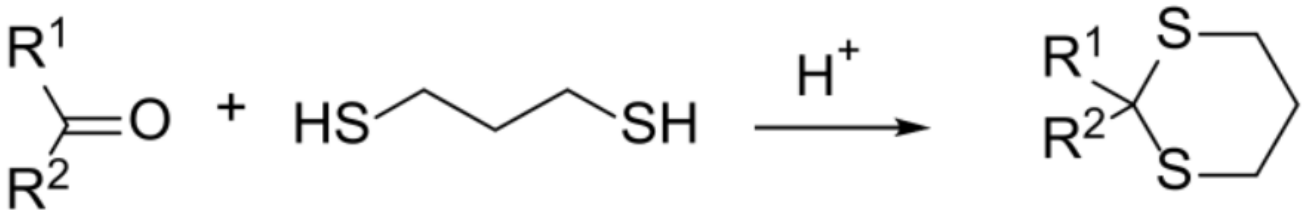


Nucleophilic Addition to Carbonyl Group

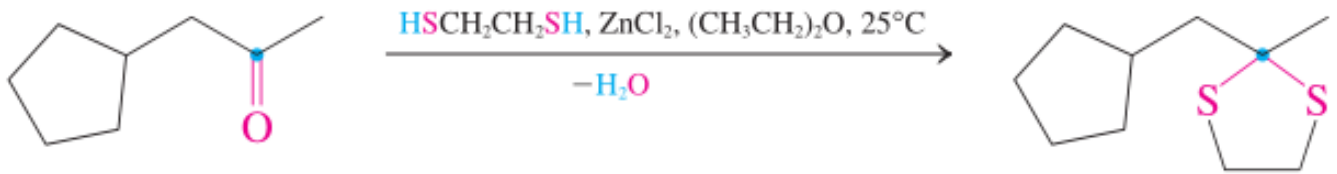
b. with sulfur nucleophiles

1. The addition of $\ddot{R}\ddot{S}H$ $\quad\quad$ $R\ddot{O}H$

Thiols react with the carbonyl group to form thioacetals



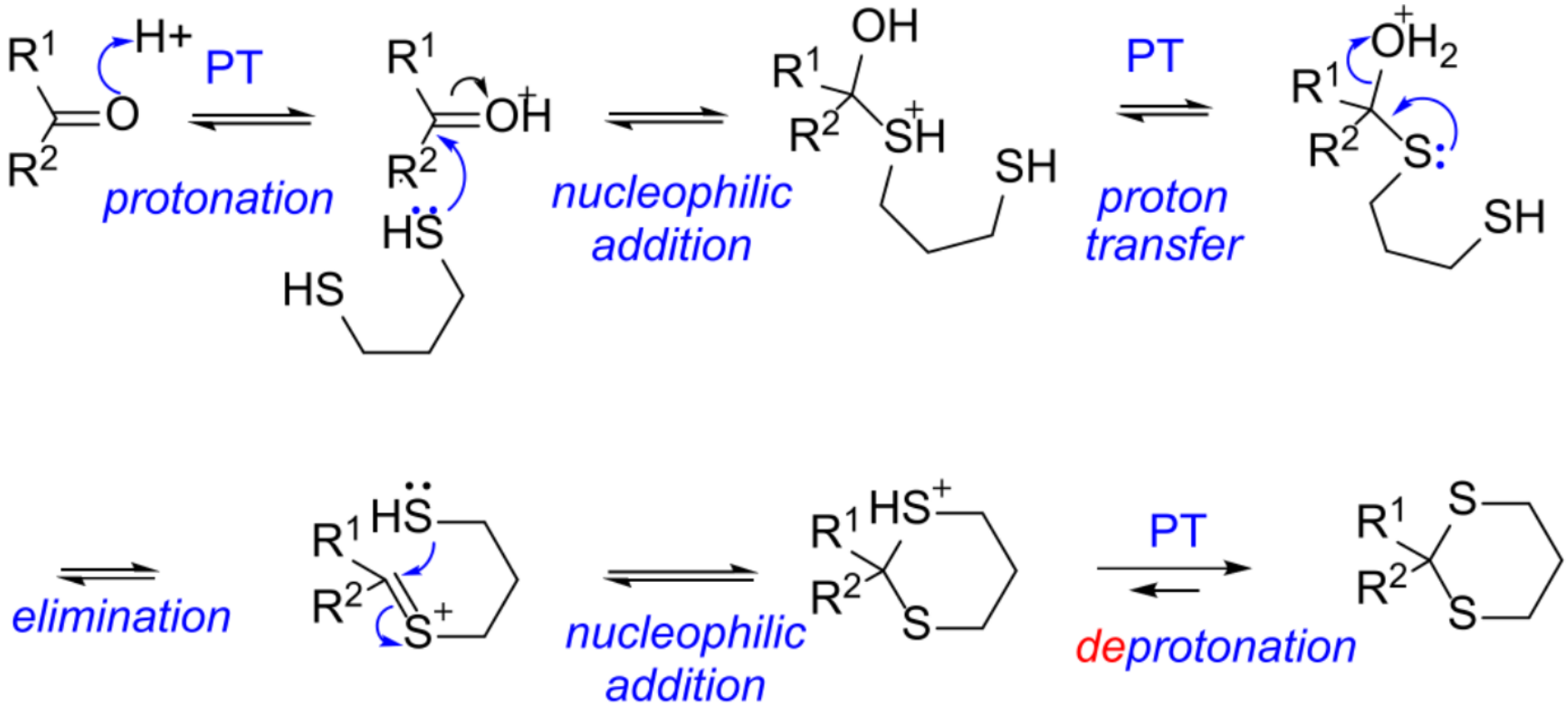
thioacetal (thioketal)



95%

Nucleophilic Addition to Carbonyl Group

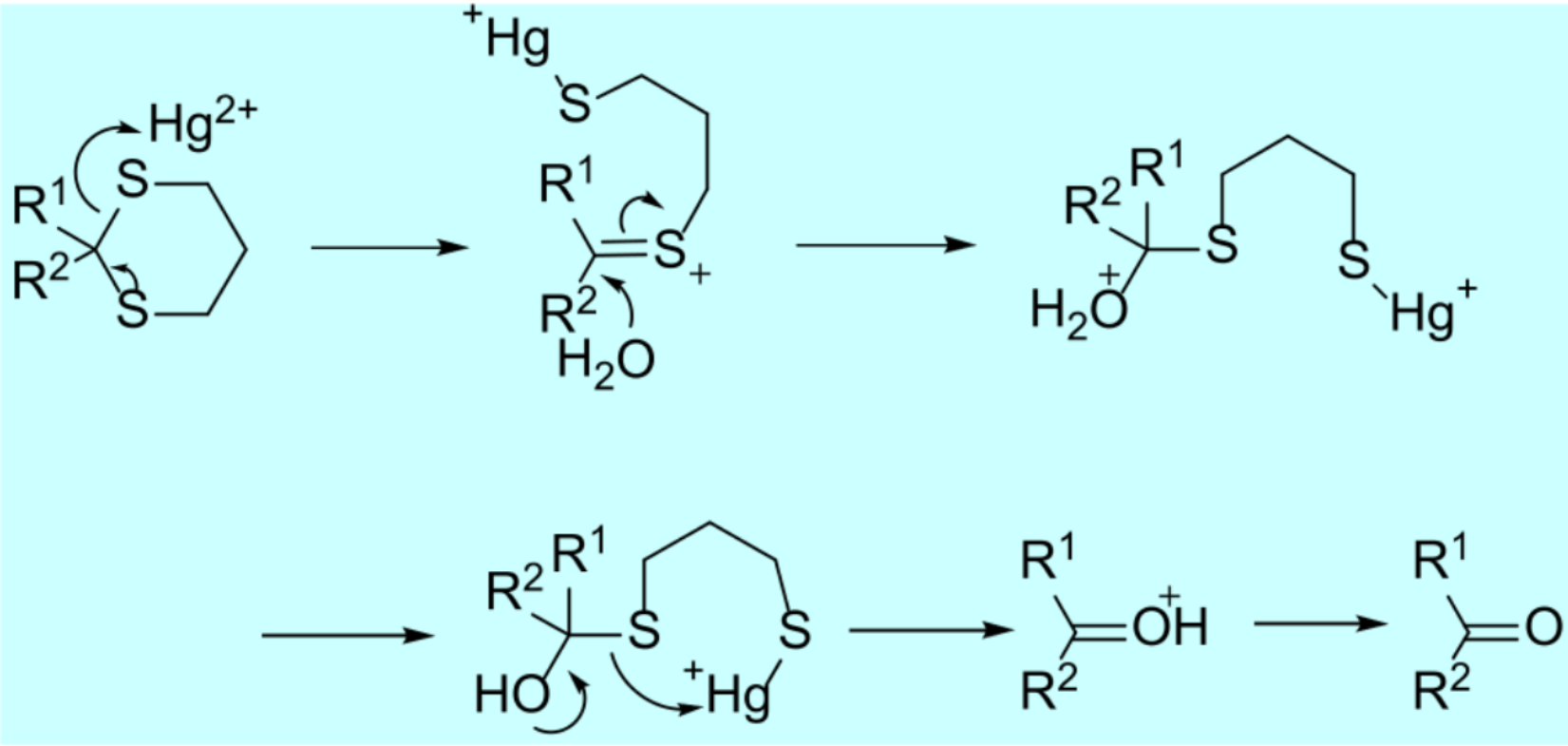
Mechanism of forming thioacetal



Nucleophilic Addition to Carbonyl Group

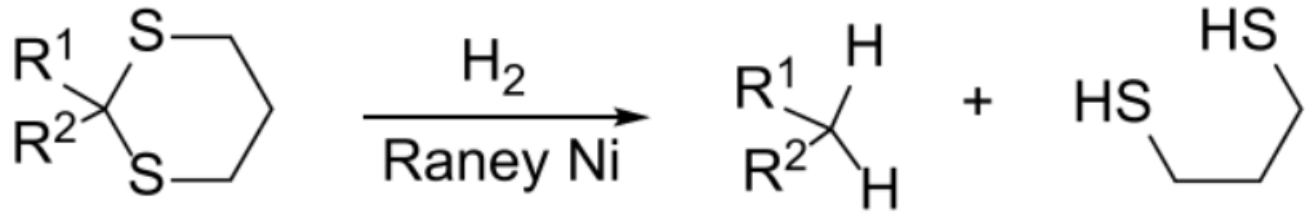
Application 1: Protection of Carbonyl (thioacetals as Protecting Groups)

Deprotection

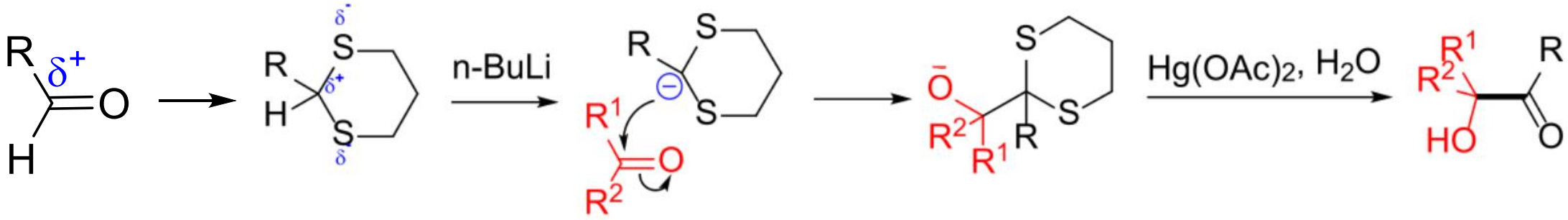


Nucleophilic Addition to Carbonyl Group

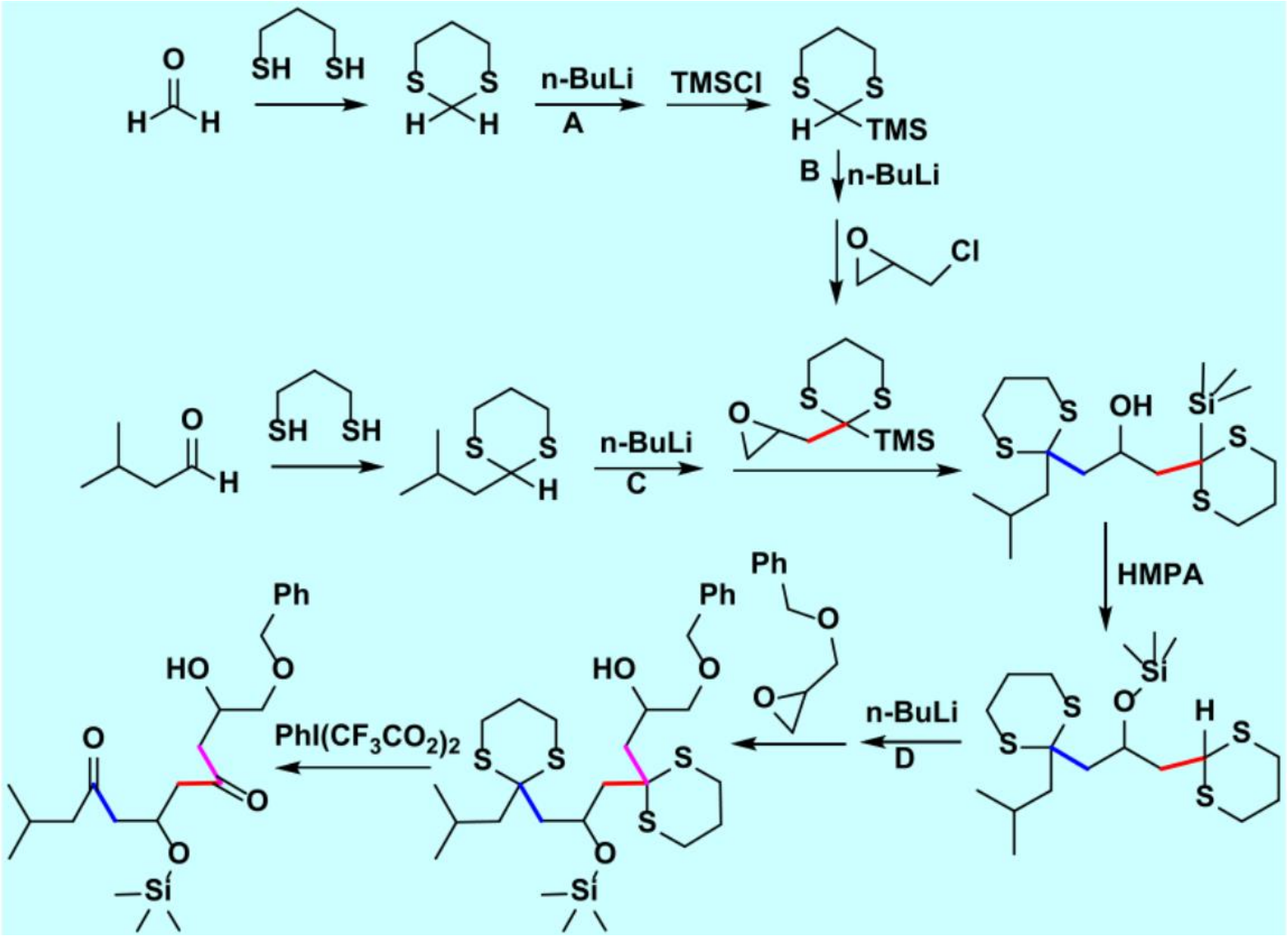
Application 2: Reduction of the carbonyl group to methylene



Application 3: Umpolung



Nucleophilic Addition to Carbonyl Group



Smith A. B., Journal of the American Chemical Society, 2006, **128** (1): 66–67

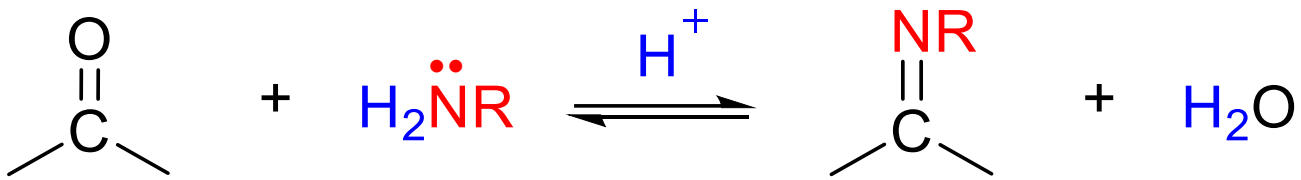
Nucleophilic Addition to Carbonyl Group

c. with nitrogen nucleophiles

NH_3, RNH_2, R_2NH, R_3N

1. Nucleophilic addition of Ammonia and Its Derivatives

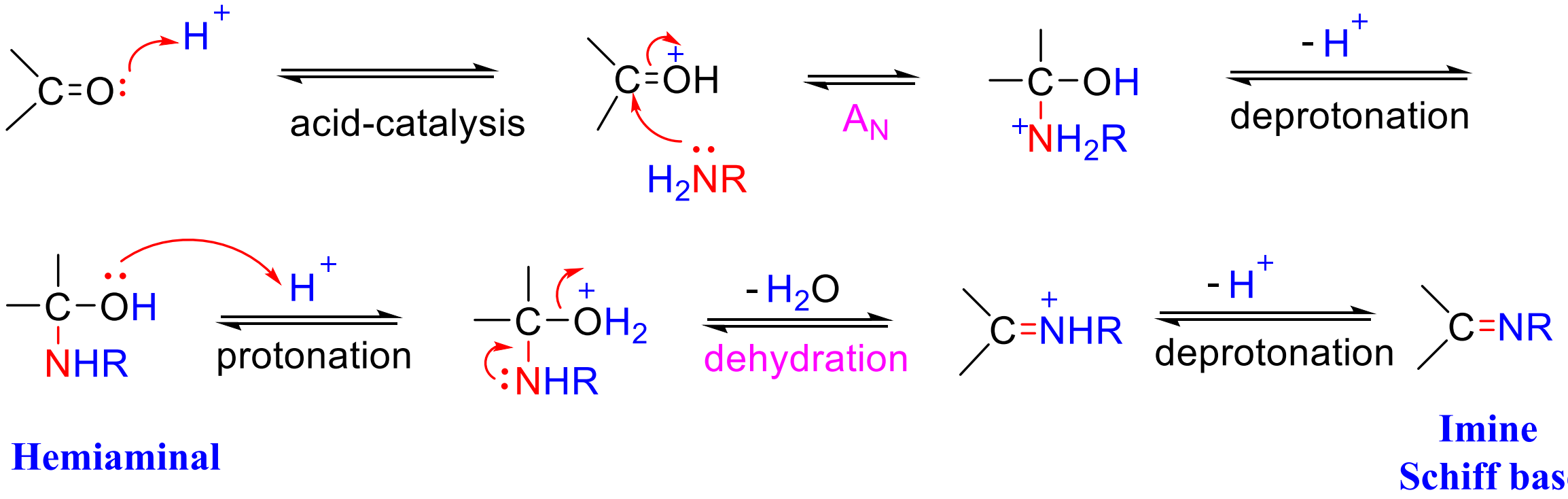
a. ammonia and primary amines form imines $\ddot{N}H_3$ and $R\ddot{N}H_2$



Imine (Schiff base)

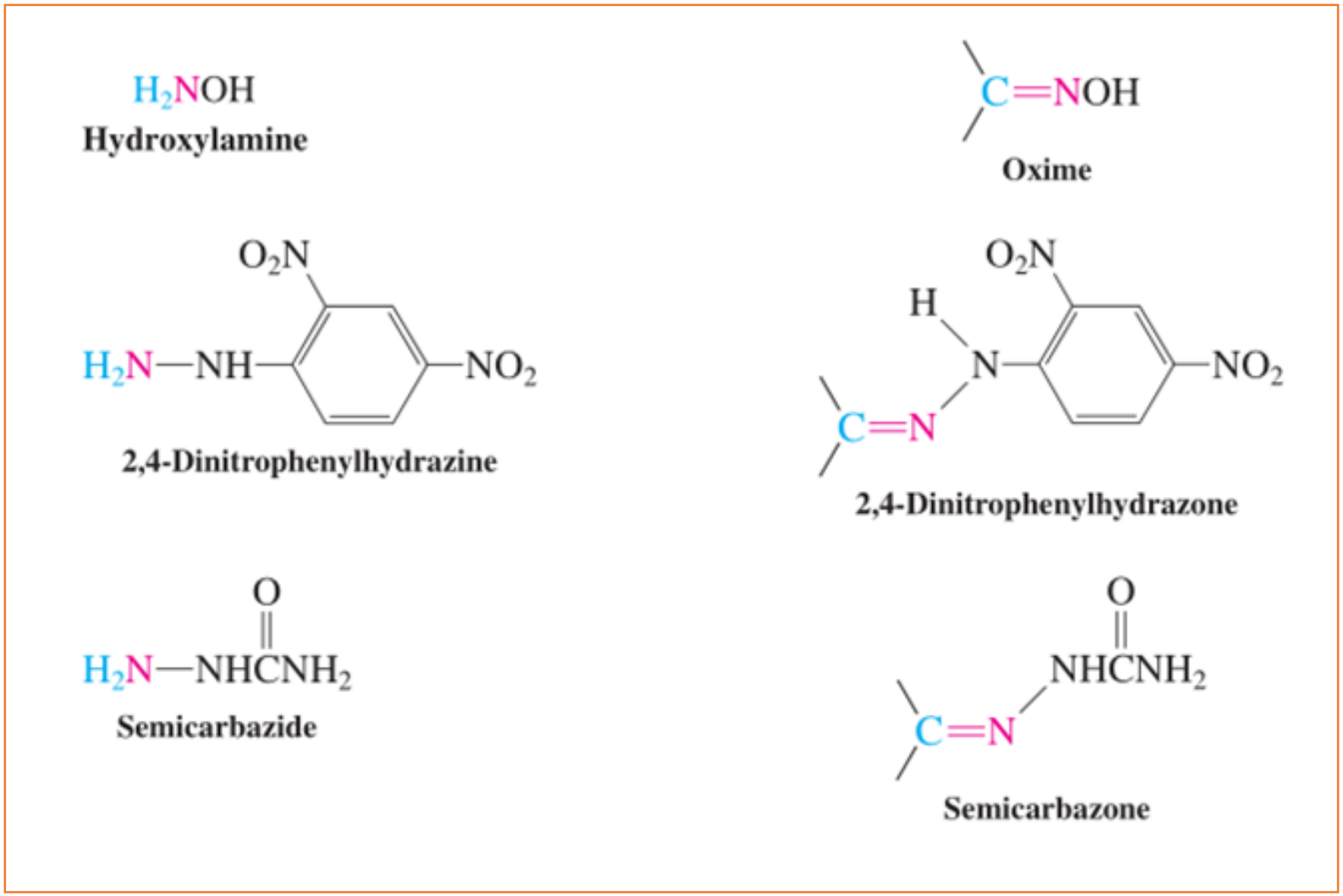
Nucleophilic Addition to Carbonyl Group

Mechanism of Imine Formation from primary amines and aldehydes or ketones

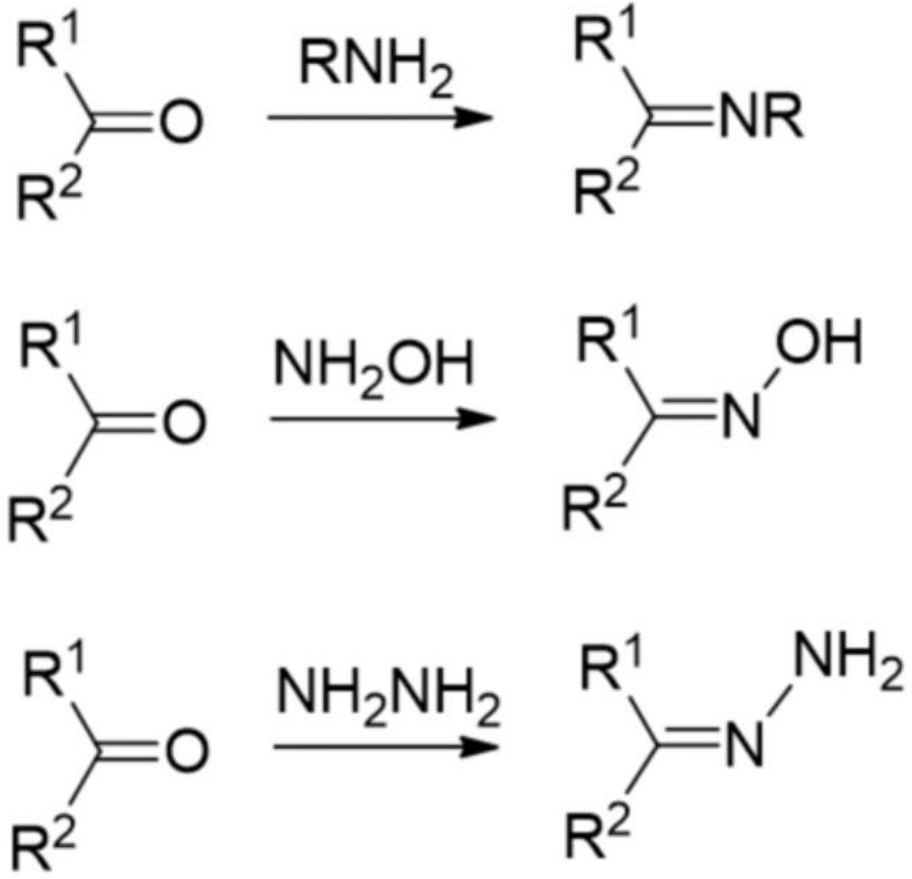


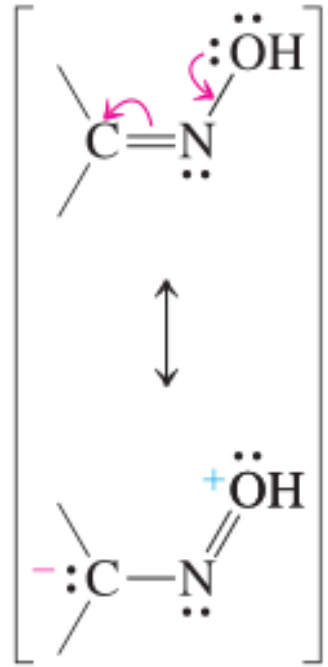
Nucleophilic Addition to Carbonyl Group

b. With ammonia derivatives $\ddot{N}H_2Y$



Nucleophilic Addition to Carbonyl Group





Resonance stabilization in oximes

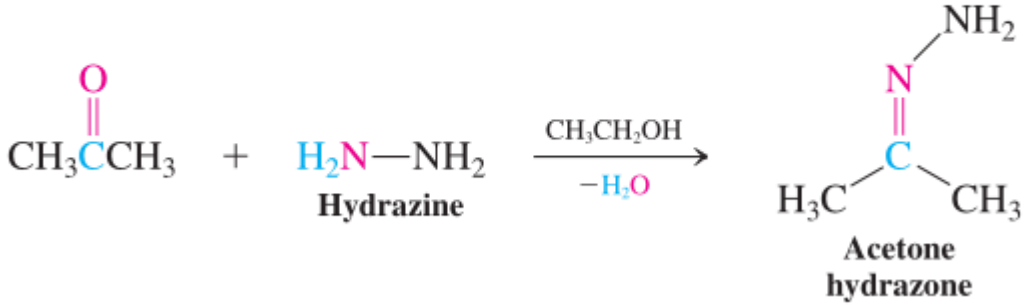
Nucleophilic Addition to Carbonyl Group

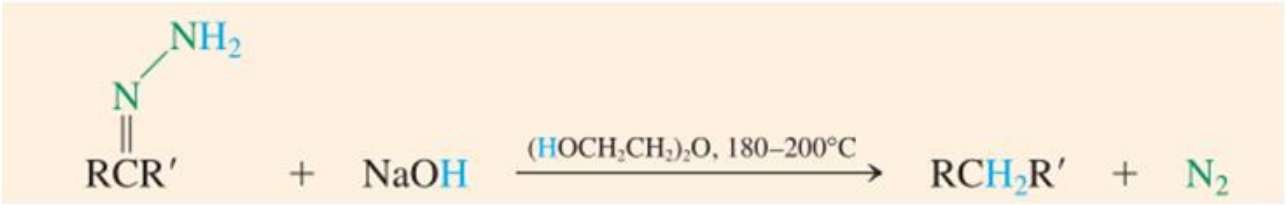
Application 1: Reduction of the carbonyl group to methylene

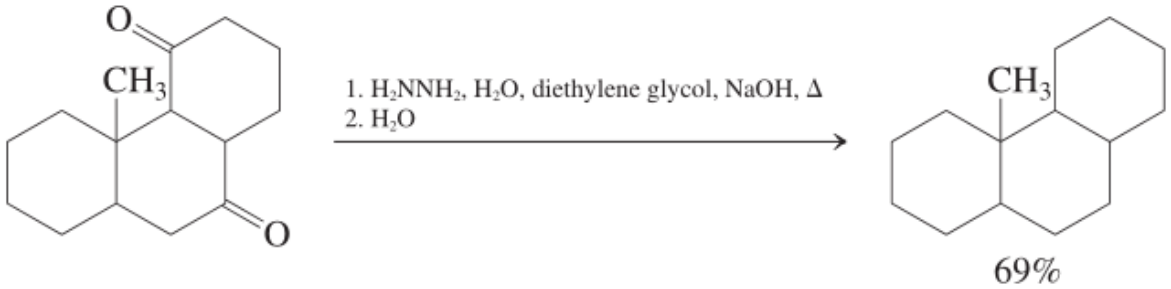
Deoxygenation of the Carbonyl Group

Wolff-Kishner-Huang Reduction

Synthesis of a Hydrazone



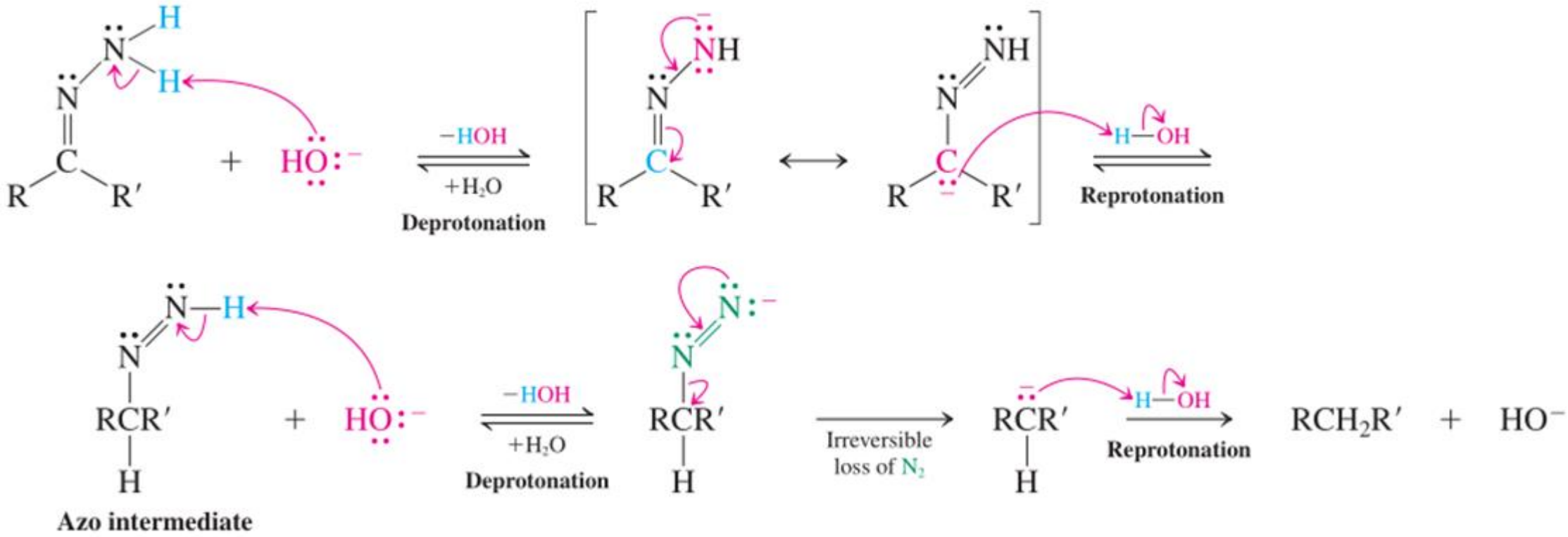




Nucleophilic Addition to Carbonyl Group

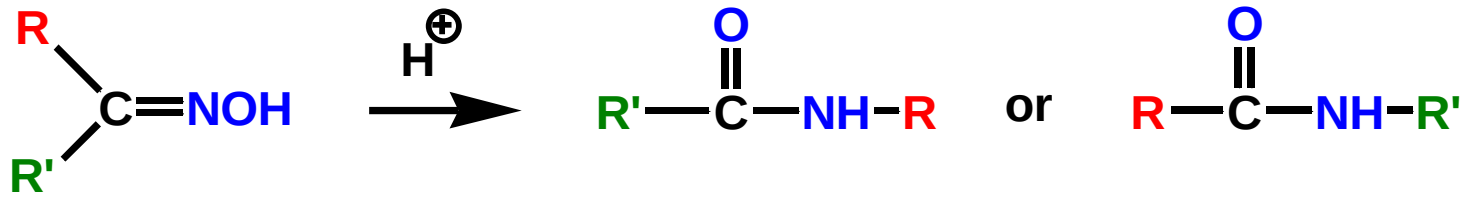
Mechanism of Nitrogen Elimination in the Wolff-Kishner-Huang Reduction

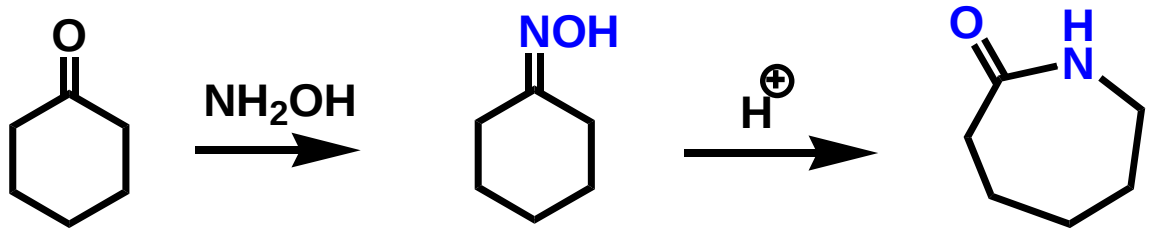
The mechanism of nitrogen elimination includes a sequence of base-mediated hydrogen shifts.



Nucleophilic Addition to Carbonyl Group

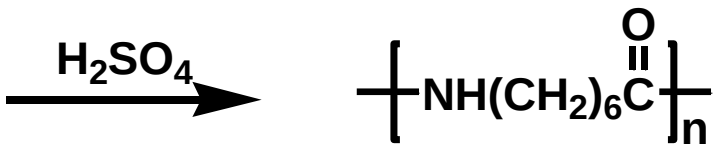
Application 2: Beckmann Rearmament





Hexanolactam

己内酰胺

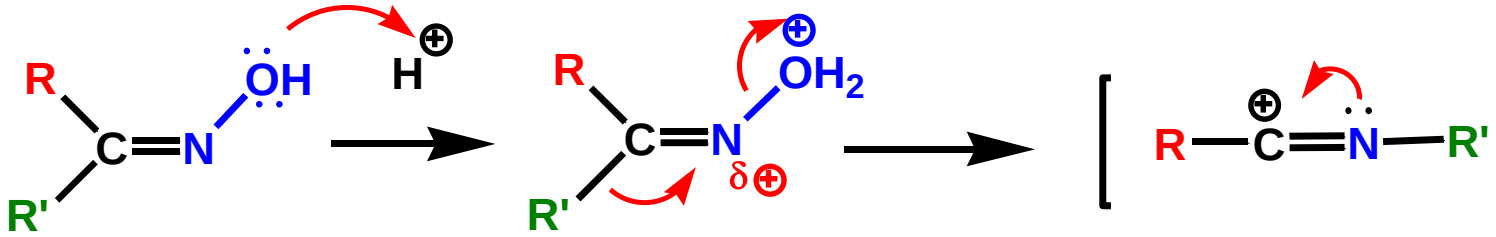


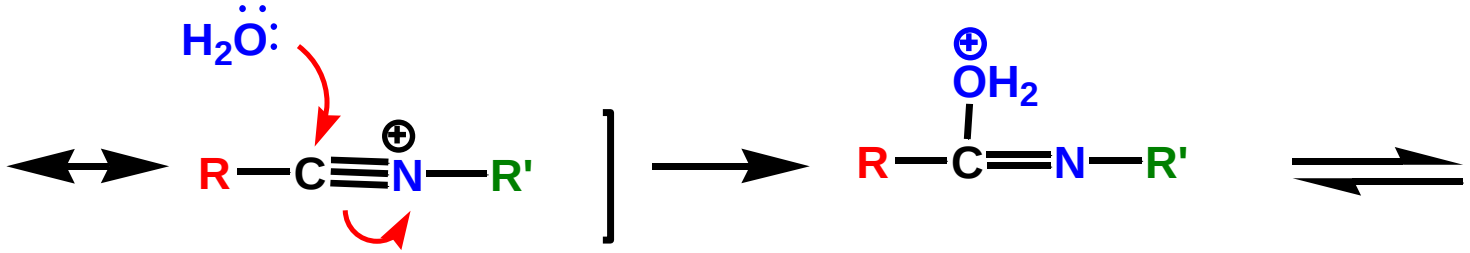
nylon-6

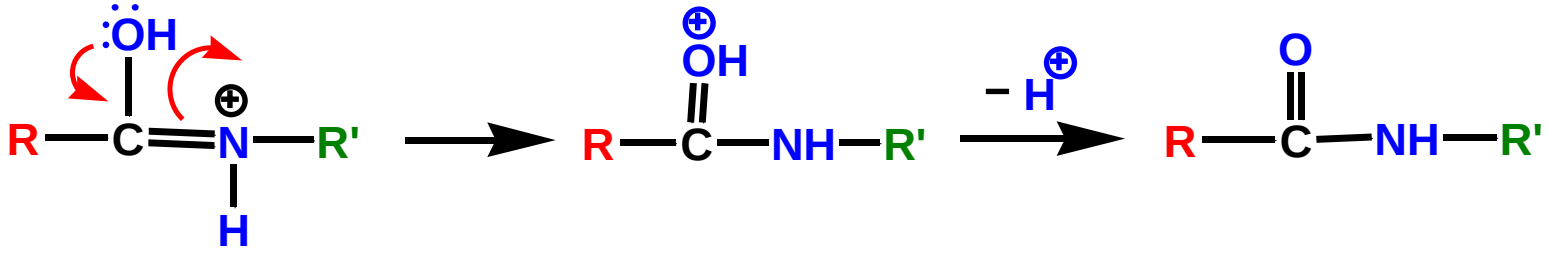
聚己内酰胺

Nucleophilic Addition to Carbonyl Group

Mechanism of Beckmann Rearrangement

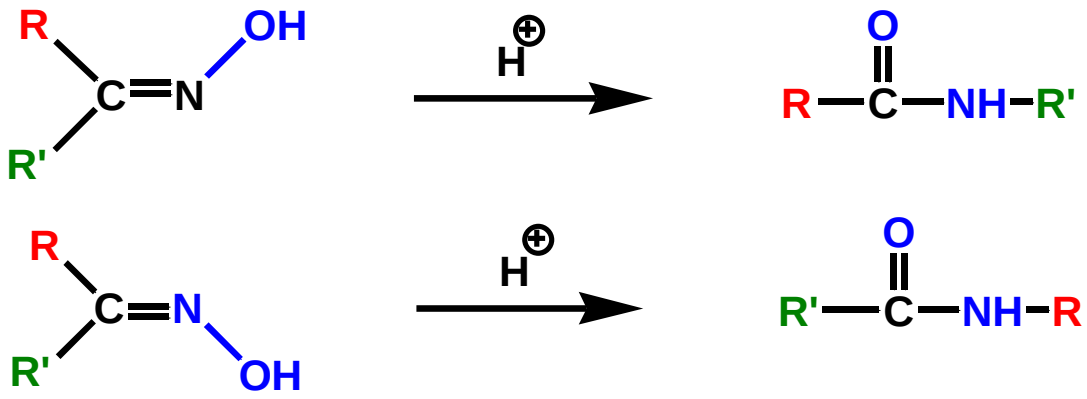




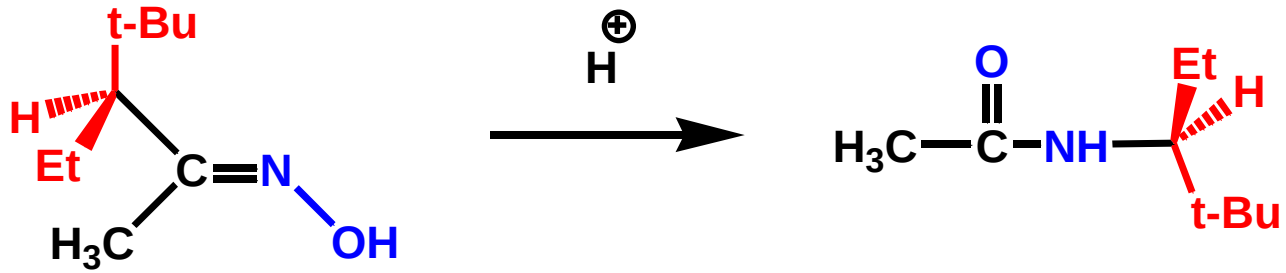


Stereochemistry of Beckmann Rearrangement

Trans co-migration-elimination

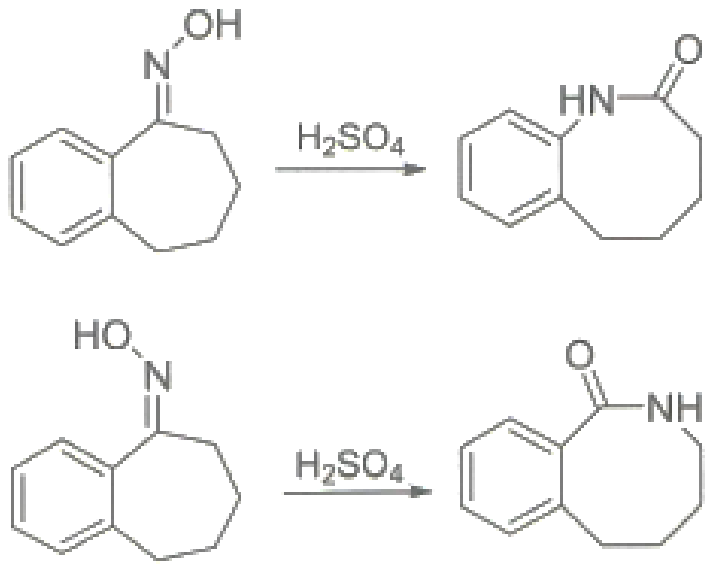


The configuration of the migrating group remained.



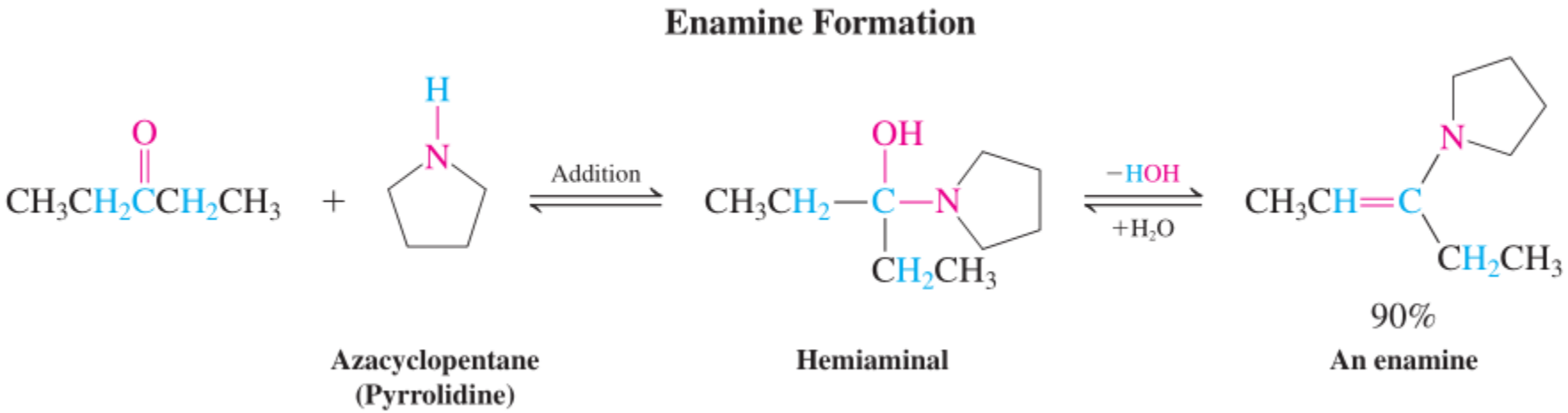
Exercise 5

Propose the mechanisms for the reactions below



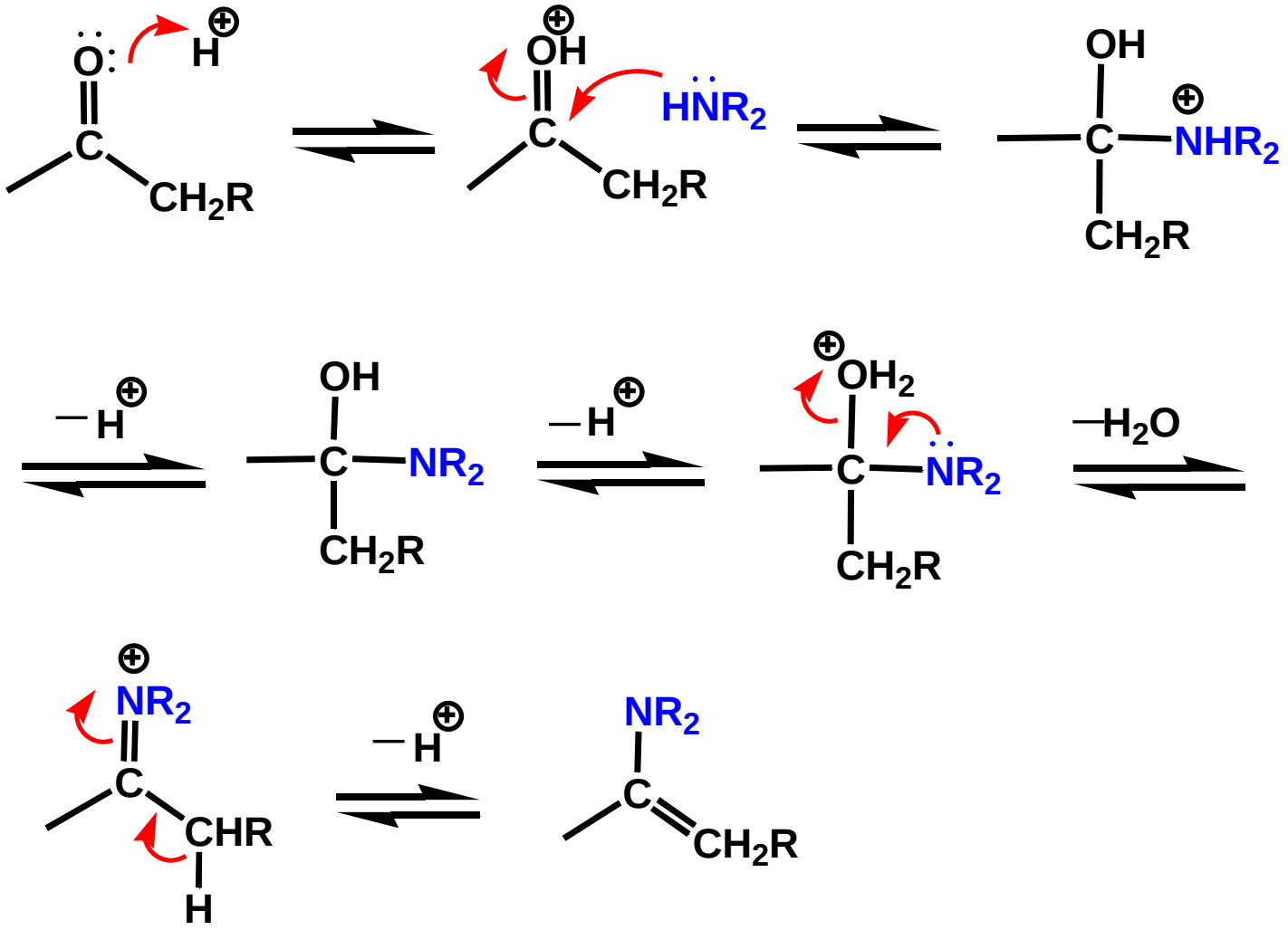
Nucleophilic Addition to Carbonyl Group

c. With secondary amines form enamines $R_2\ddot{N}H$



Nucleophilic Addition to Carbonyl Group

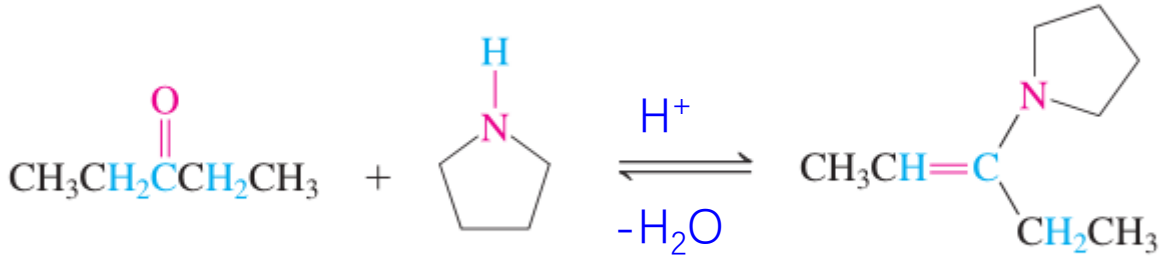
Mechanism of enamine Formation from secondary amines and aldehydes or ketones



Exercise 6

Formulate a detailed mechanism for the acid-catalyzed enamine formation shown below.

Enamine Formation

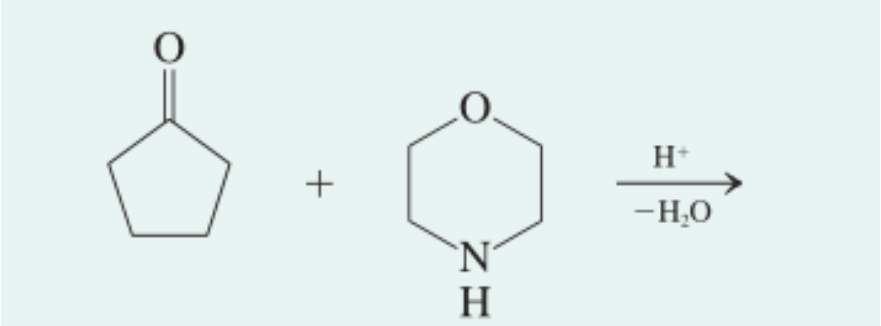


90%

An enamine

Exercise 7

Write the product, in addition to the mechanism of its formation, for the following acid-catalyzed reaction.

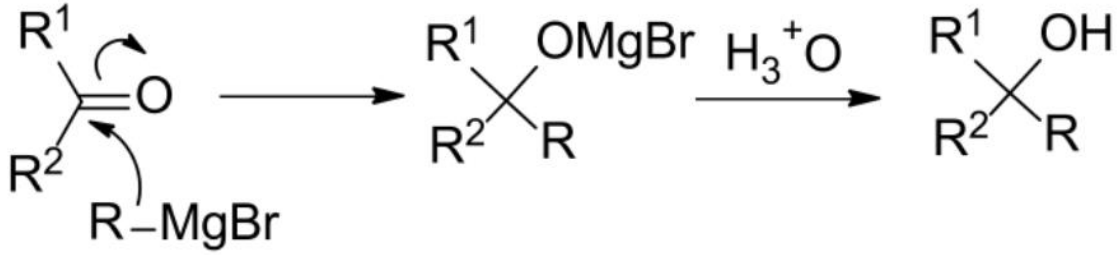


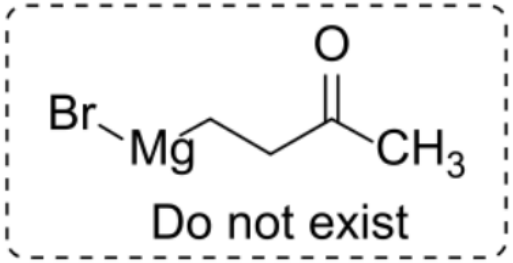
Nucleophilic Addition to Carbonyl Group

d. with carbon nucleophiles

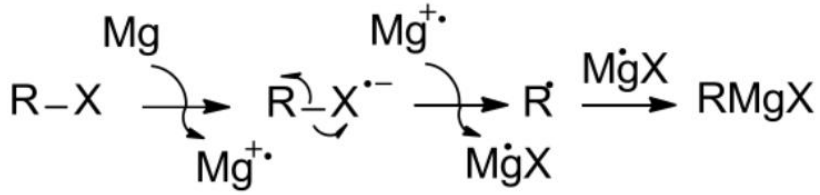
1. Nucleophilic addition of Organometallic Reagent

a. With Grignard Reagent RMgX (R^-)





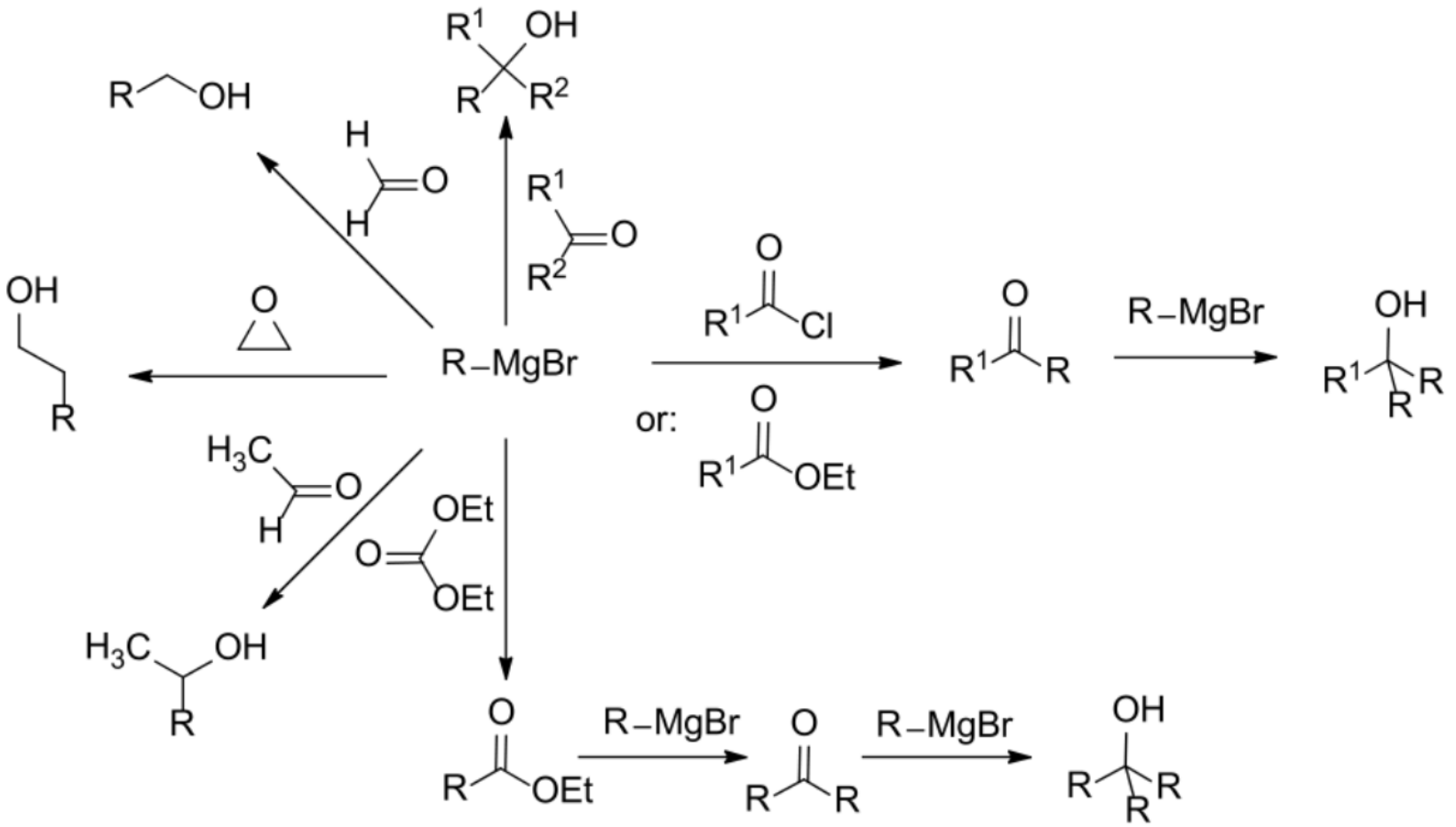
Formation of RMgX:
single electron transfer(SET) mechanism

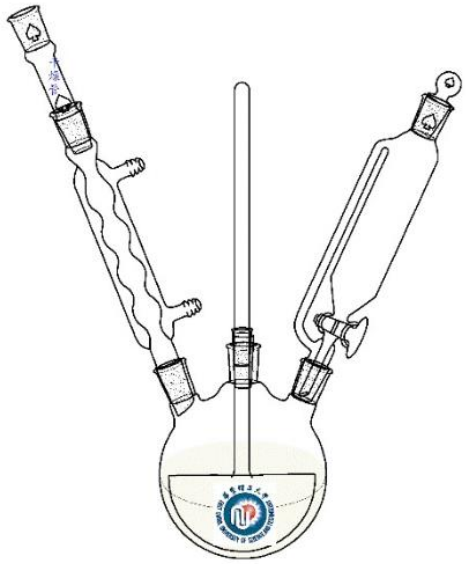


Sensitive to: $C^{\delta+}$, Carbonyl group (CO_2……), **H^+** (acid, H_2O, ROH, RCOOH, RNH_2……)

Nucleophilic Addition to Carbonyl Group

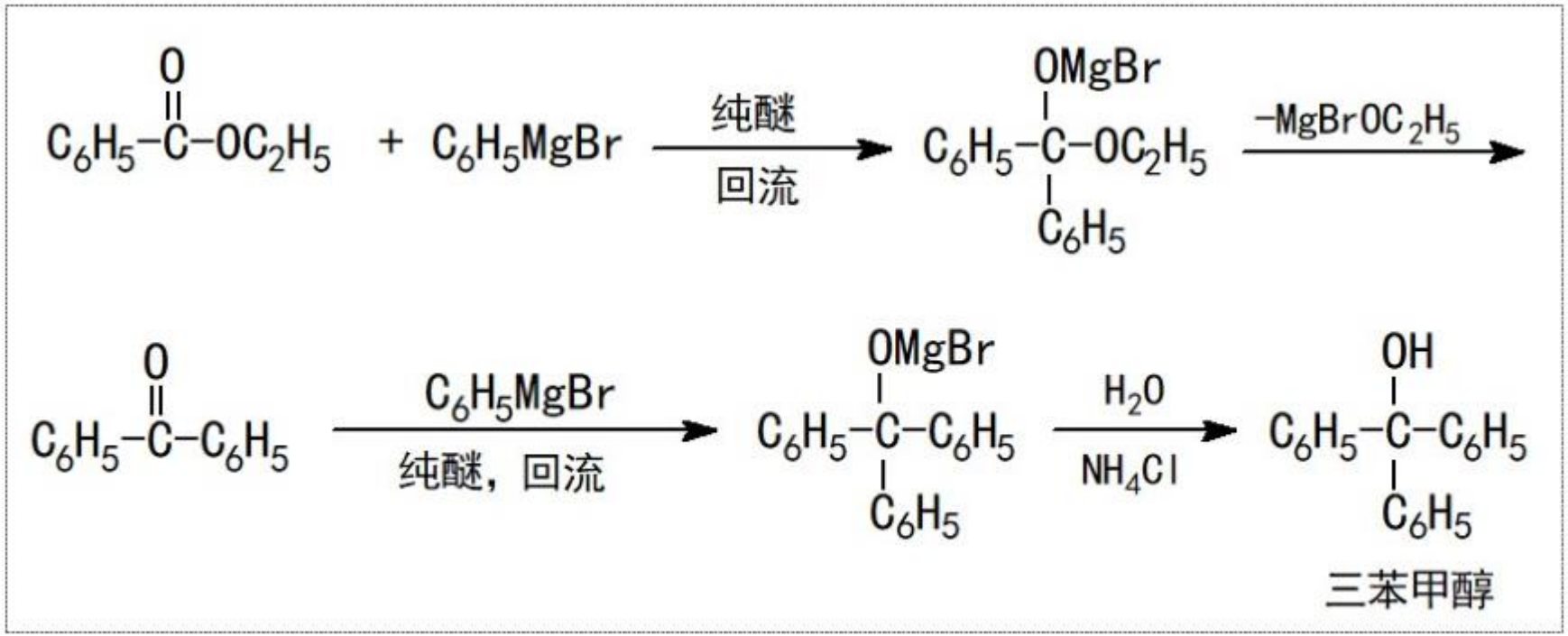
Application: Preparation of Alcohols

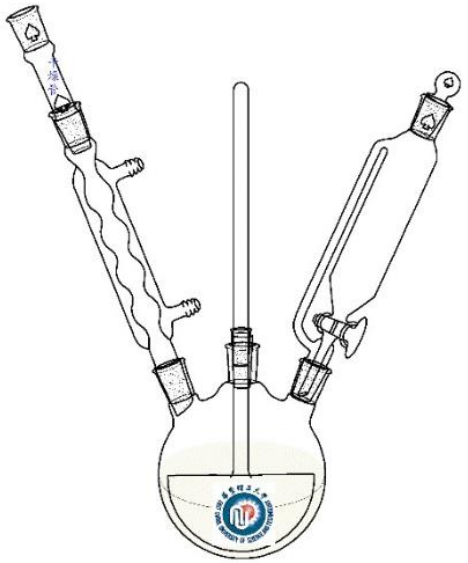




Nucleophilic Addition to Carbonyl Group

Preparation of Triphenylmethanol

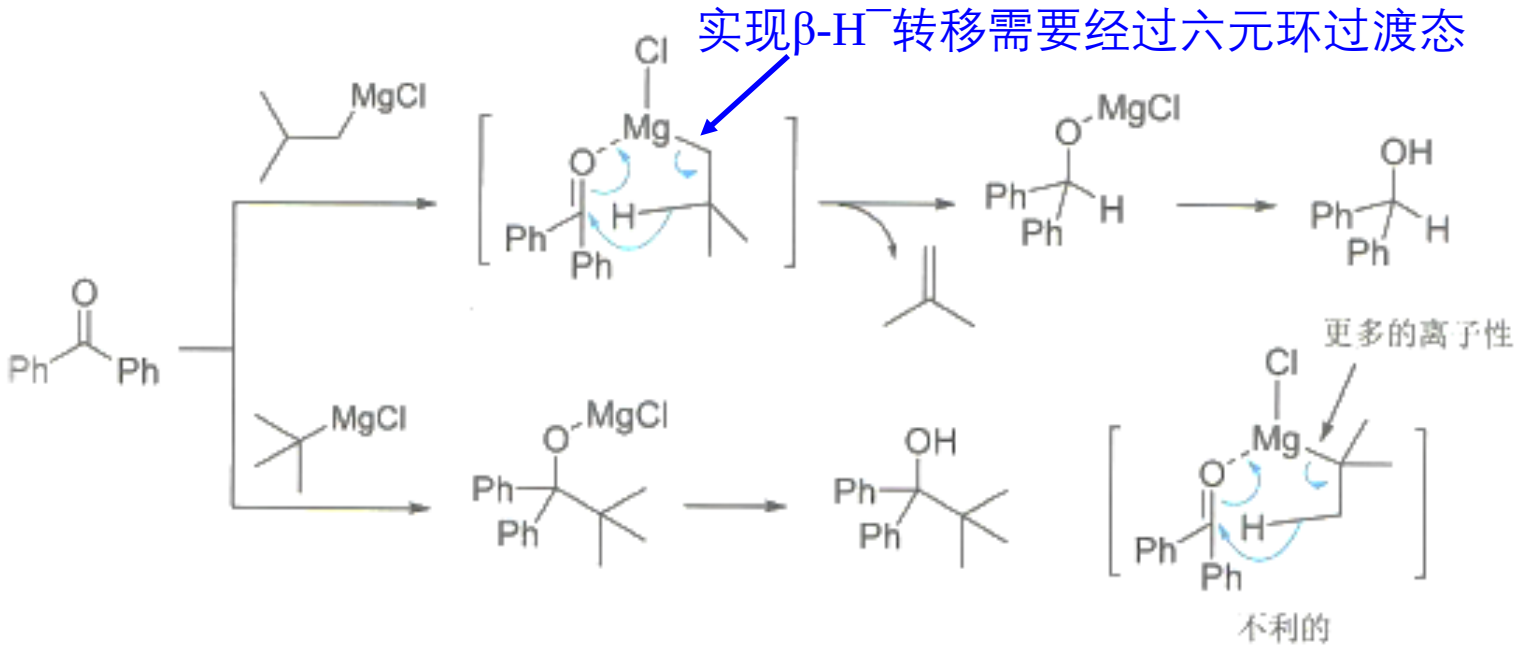




Nucleophilic Addition to Carbonyl Group

Competitive reactions in Grignard reaction:

1. Competition between nucleophilicity and basicity.
2. For some Grignard's reagent with β-H, pay attention to the competition between carbon nucleophiles (R^-) and hydrogen nucleophiles (H^-) "



两种格式试剂C-Mg键的性质不同，造成了反应性的差异。

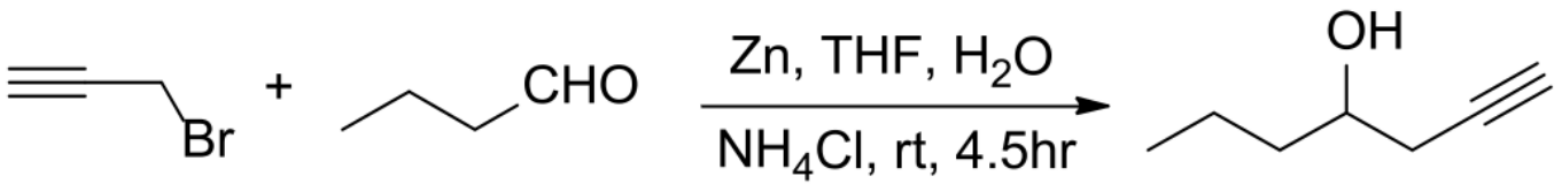
Nucleophilic Addition to Carbonyl Group

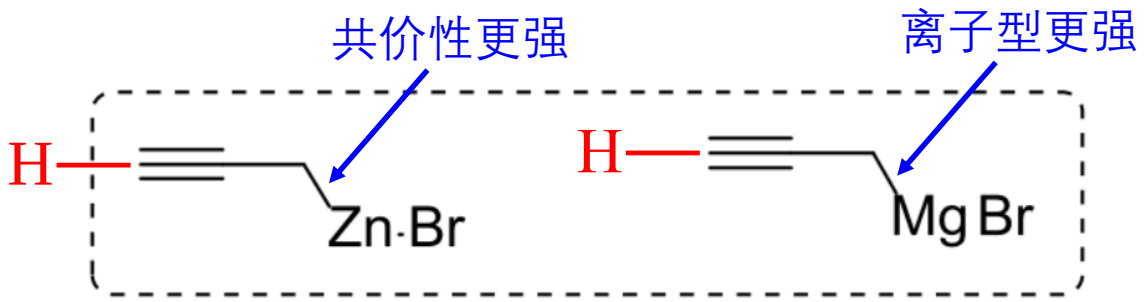
b. With Organozinc Reagent

The advantages are their safety and simplicity

1) Barbier coupling reaction (RZnX, RSnX……)

This transformation cannot be achieved with Grignard reagent, Why?

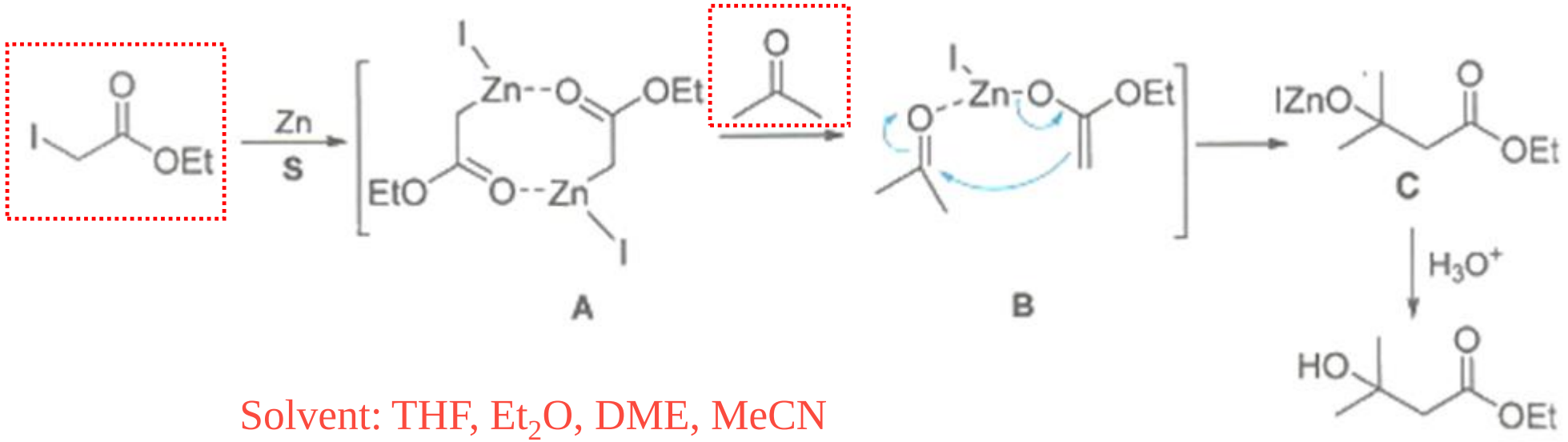




Nucleophilic Addition to Carbonyl Group

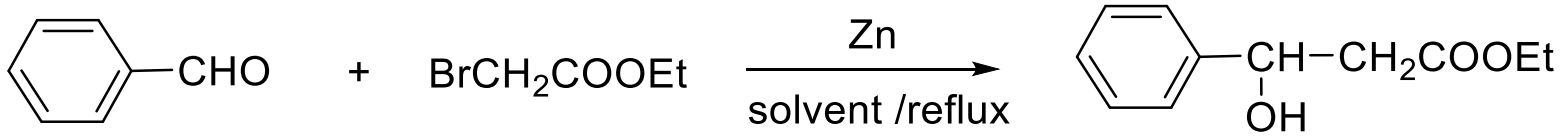
2) Reformatsky Reaction

醛酮与 α –卤代酸酯的有机锌试剂反应生成β–羟基酯



Solvent: THF, Et_2O, DME, MeCN

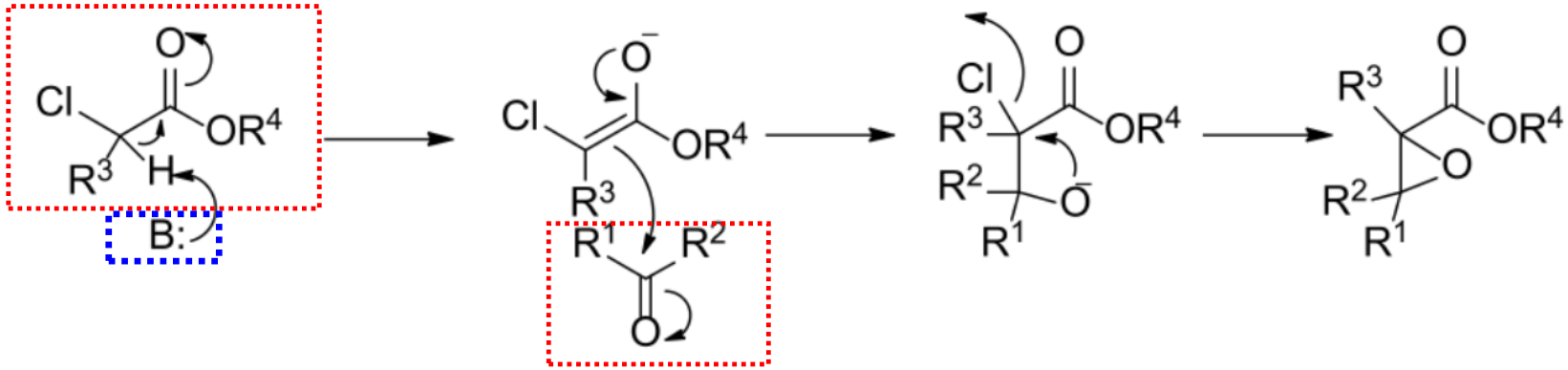
Propose the mechanisms for the reactions below

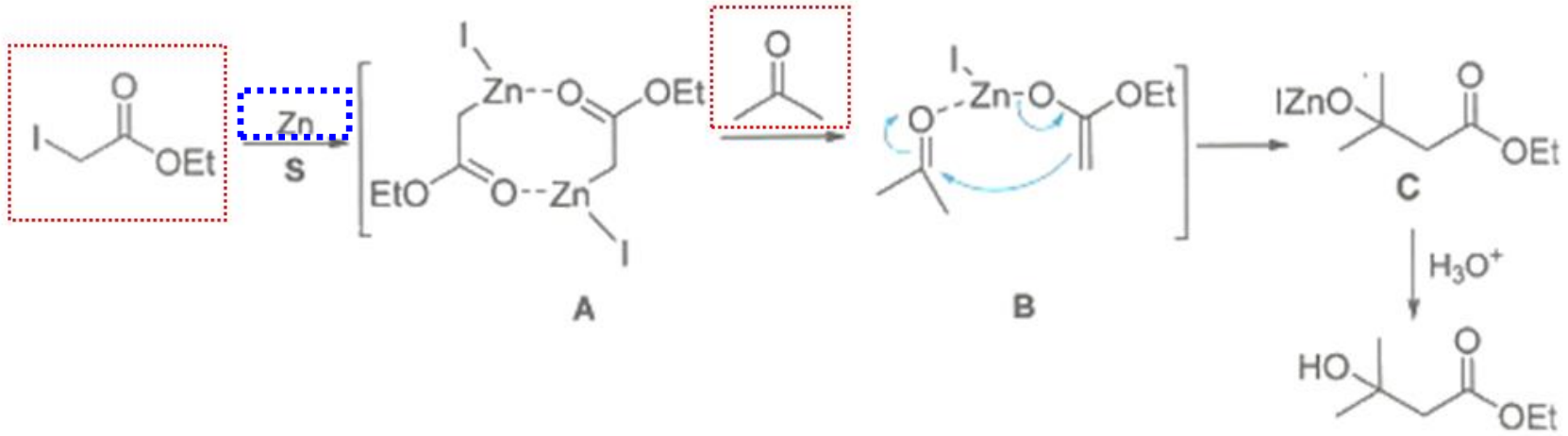


Nucleophilic Addition to Carbonyl Group

2') Darzens Reaction

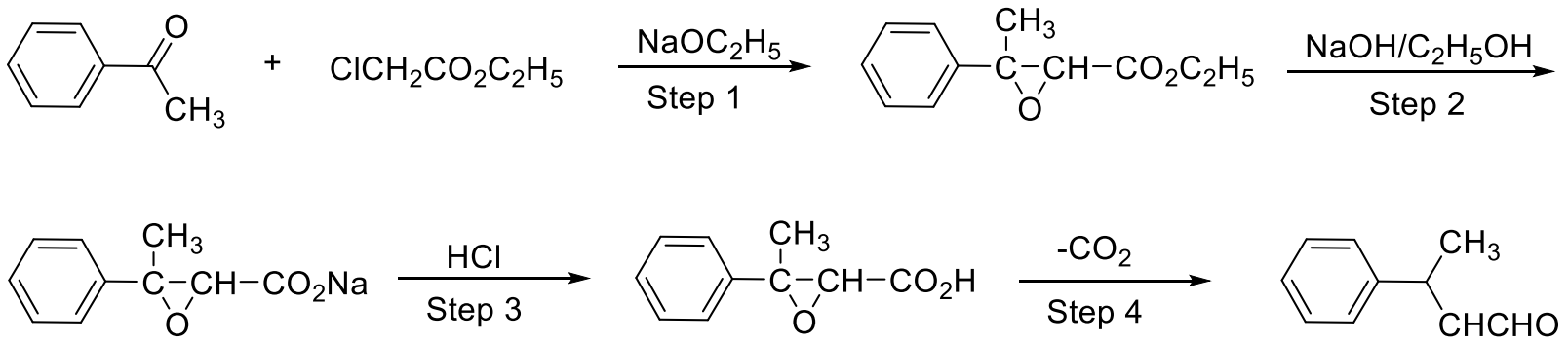
醛酮在碱作用下与α-卤代酸酯反应生成α，β-环氧酯



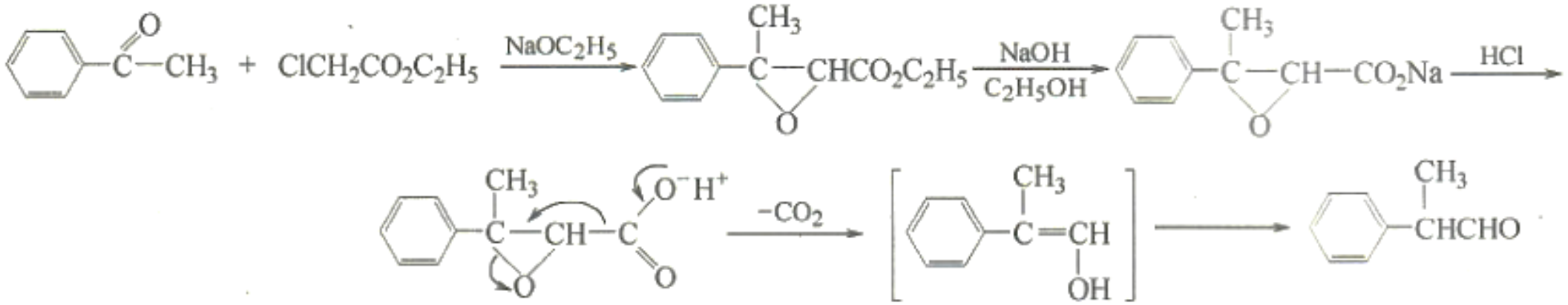


Nucleophilic Addition to Carbonyl Group

Application: Preparation of Epoxy Compounds



mechanism

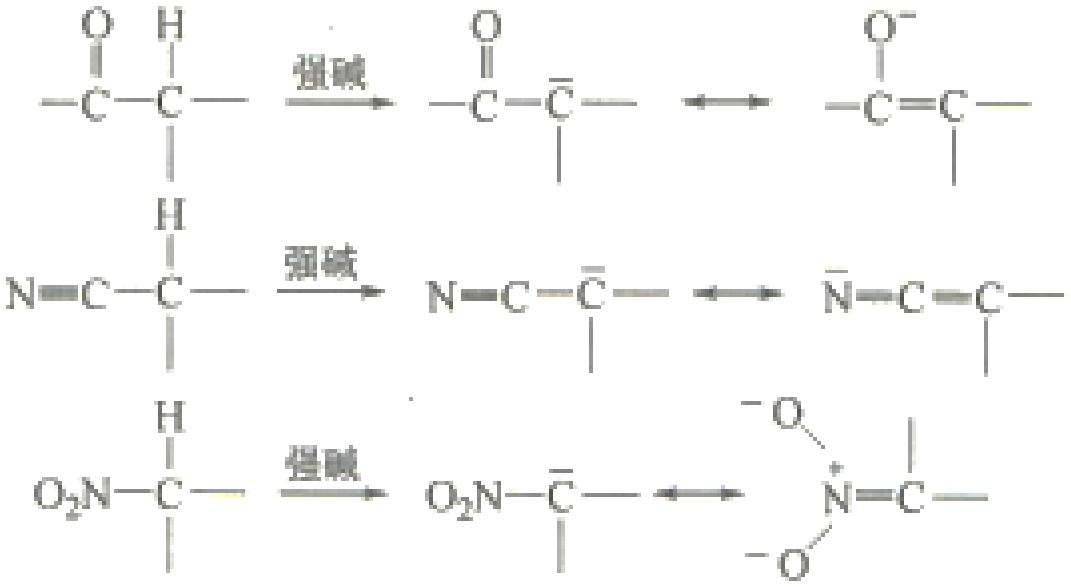


6.4 Carbanion

碳亲核试剂的来源

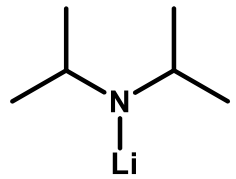
1. 金属有机化合物

2. 有机分子中的C-H键失去质子后形成的共轭碱



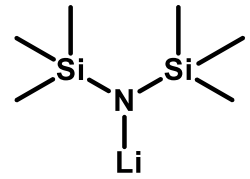
Strong Base:

$(CH_3)_3COK$　　$NaNH_2$　　NaH



lithium diisopropylamide

LDA



lithium bis(trimethylsilyl)amide

LHMDS

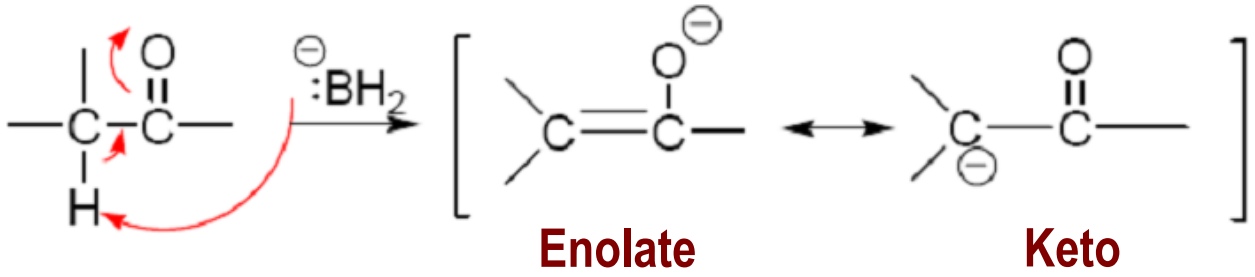
大位阻碱（亲核性弱，副反应少）

Nucleophilic Addition to Carbonyl Group

2. Nucleophilic addition with Enolate or Enol

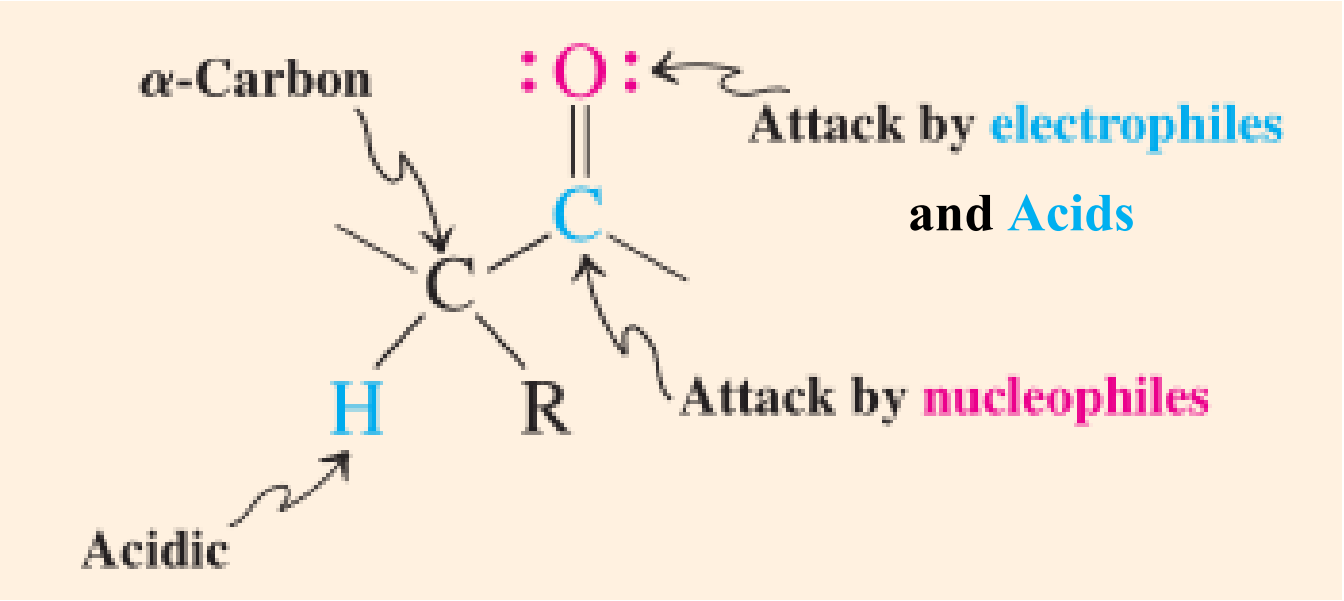
碳负离子在反应中是亲核试剂，在很多情况下，以烯醇负离子结构形式存在。

α-H acidity



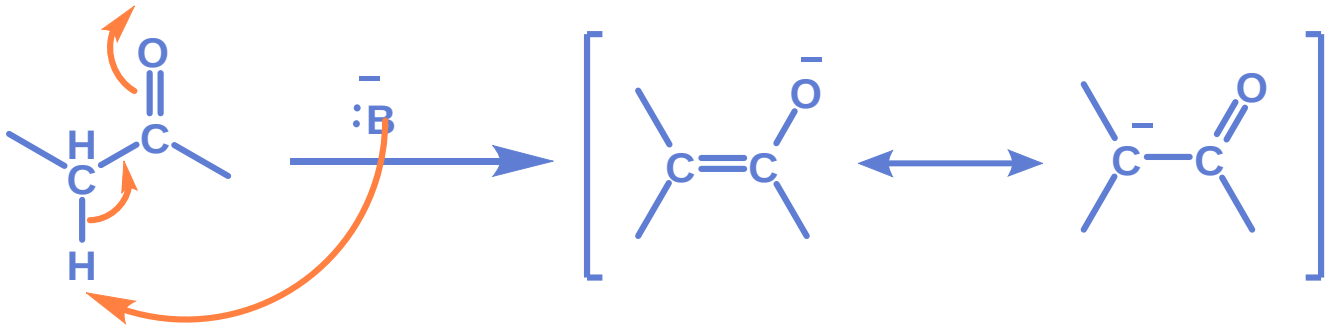
8.1 Structure and Reactivity

Regions of Reactivity in Carbonyl Compounds



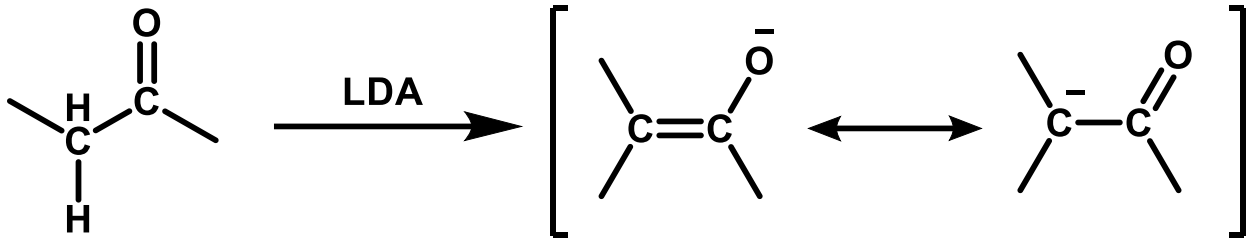
Nucleophilic Addition to Carbonyl Group

Formation of enolate

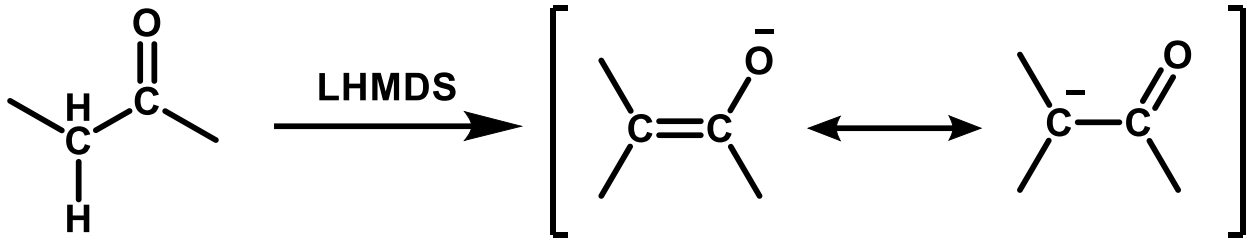


Which "Base"?

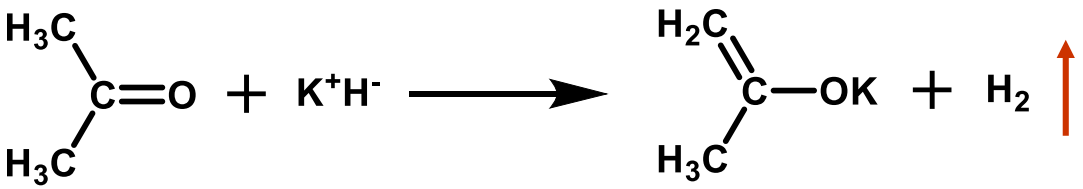
Nucleophilic Addition to Carbonyl Group



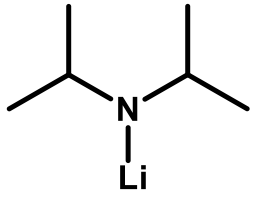
enolate



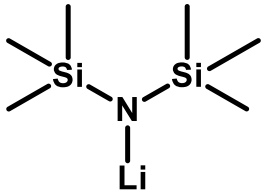
enolate



enolate



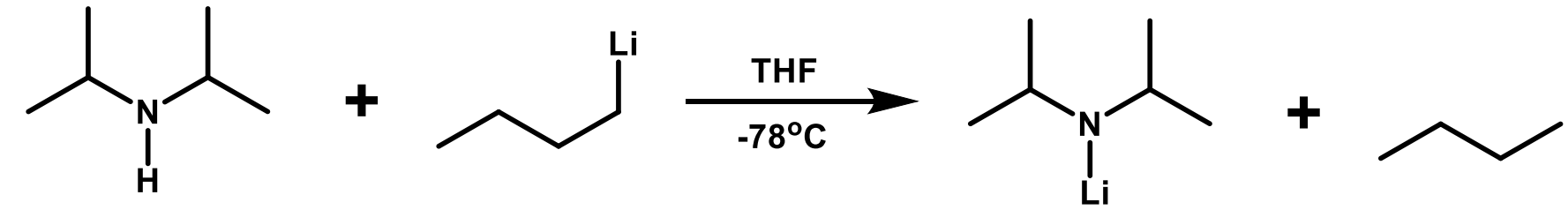
lithium diisopropylamide



lithium bis(trimethylsilyl)amide

LDA 大位阻强碱 LHMDS

Nucleophilic Addition to Carbonyl Group



diisopropylamine

pK_a = 35

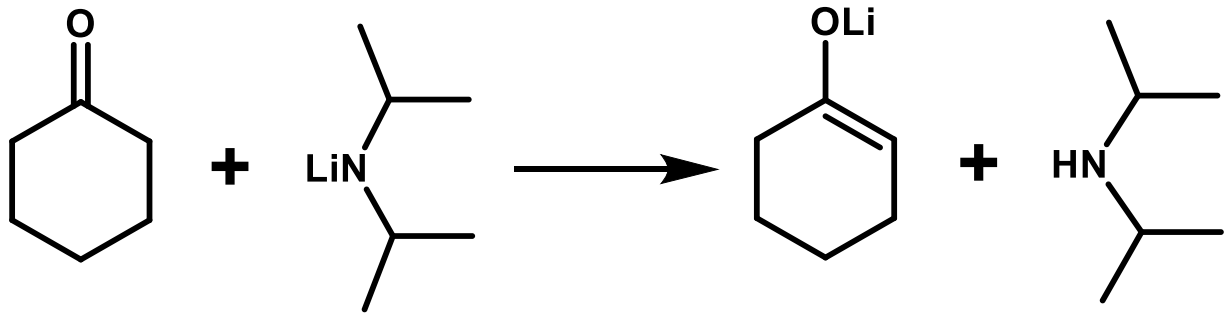
butyllithium

lithium diisopropylamide

LDA

butane

pK_a ~ 50

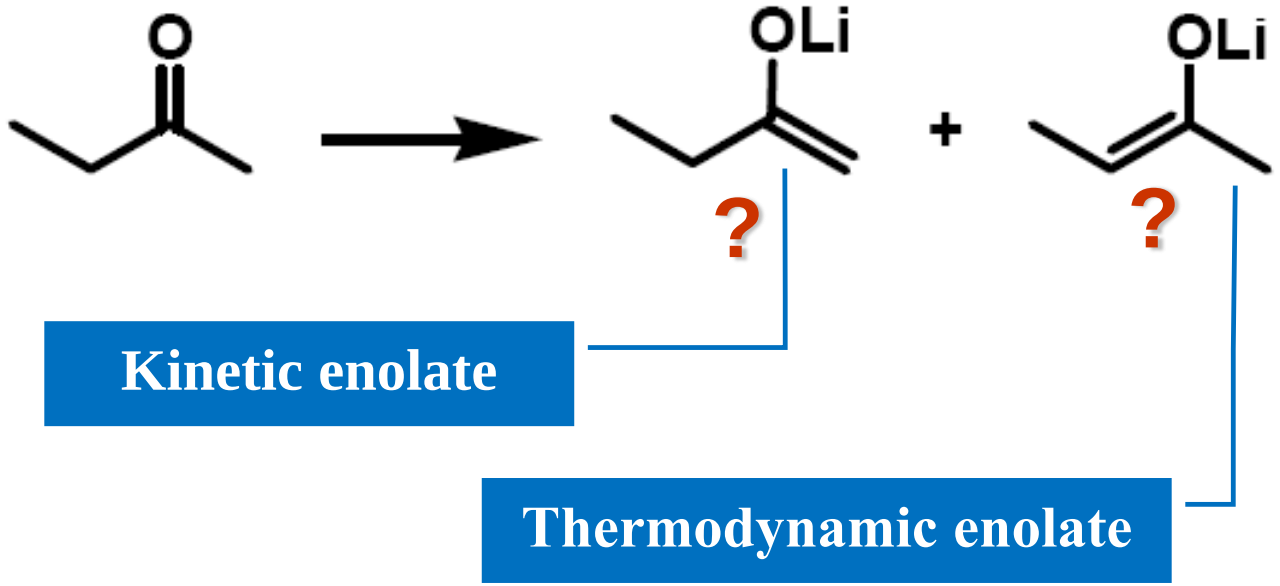


pK_a=17

p*K*a = 35

Nucleophilic Addition to Carbonyl Group

Regioselective Formation of Enolate Anions

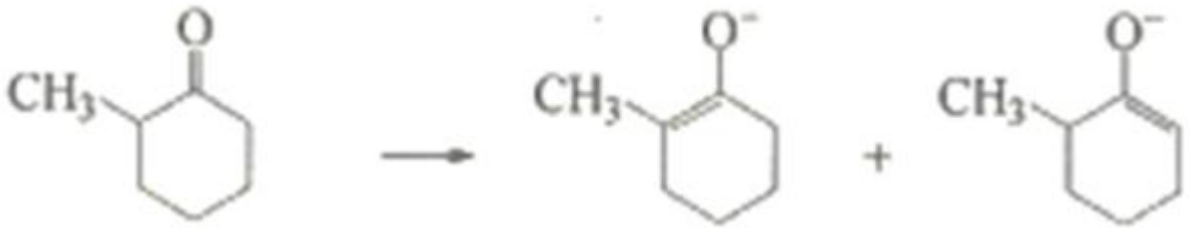


Generally:

1. Low temperature gives the kinetic enolate.

2. High temperature, relatively weak base in a protic solvent gives the thermodynamic enolate.

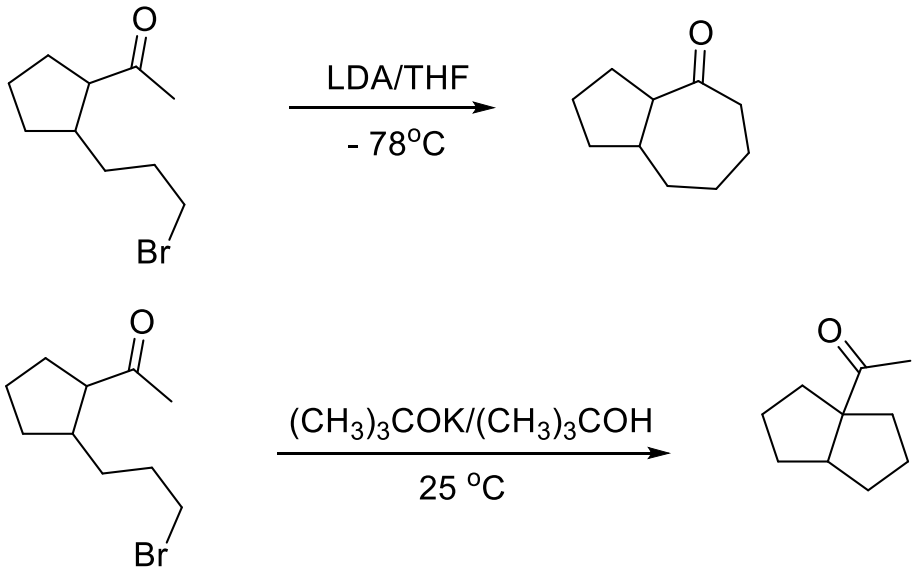
Nucleophilic Addition to Carbonyl Group



Kinetic control	1%	99 %	**LDA/-78 °C**
Thermodynamic control	78 %	22 %	**Et_3N**

Exercise 8

Propose the mechanisms for the reactions below

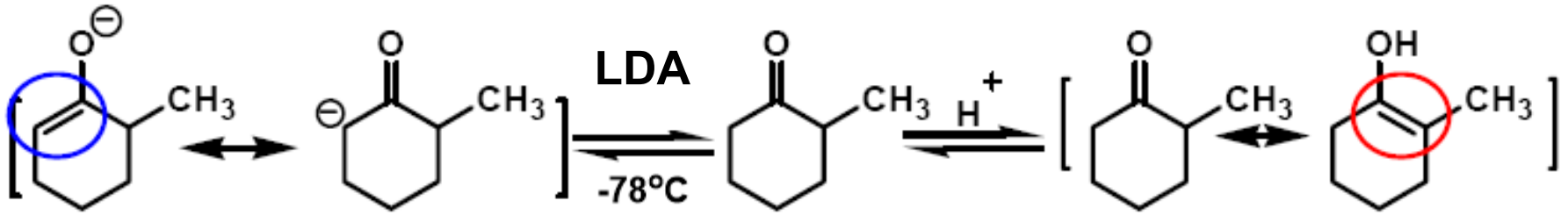


Nucleophilic Addition to Carbonyl Group

α-H acidity

Carbonyl oxygen basicity

α-H acidity



kinetically favored

enolate

thermodynamic

enol

Two special examples:

1. **The kinetically favored enolate can be formed cleanly through the use of LDA.**
2. **In acid conditions, the thermodynamic enol is formed predominantly.**

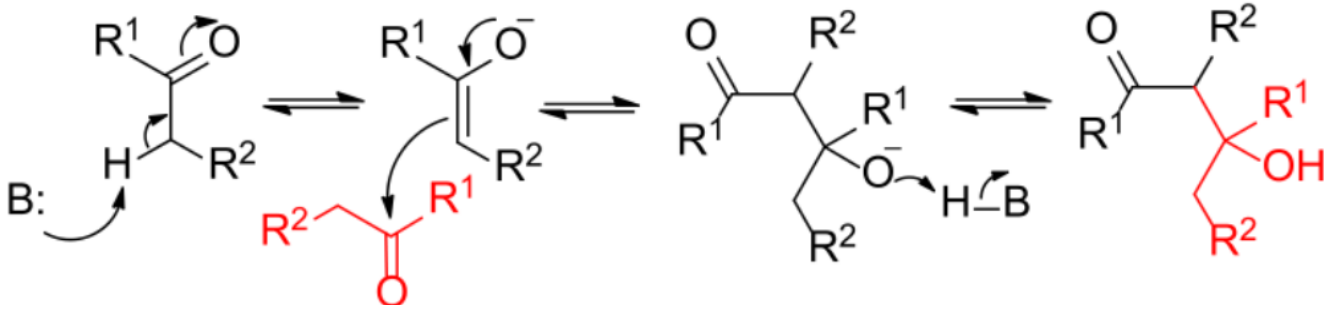
Nucleophilic Addition to Carbonyl Group

a. Aldol Reaction

Enolate as Nucleophile **Base-catalyzed**

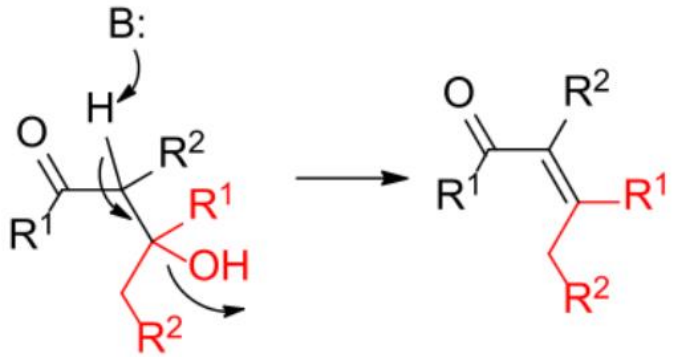
Mechanism

Base-catalyzed Condensation



Nucleophilic Addition

Base-catalyzed Hydration



Elimination

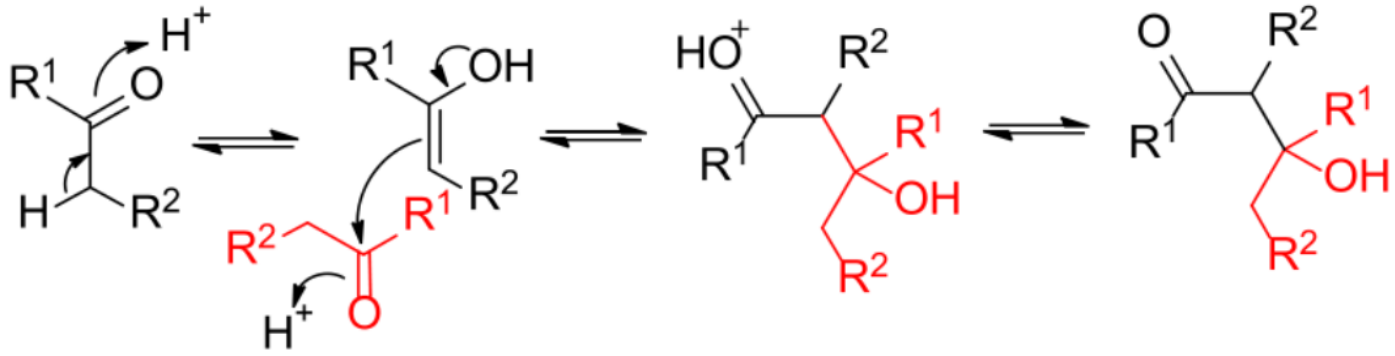
Nucleophilic Addition to Carbonyl Group

a. Aldol Reaction

Enol as Nucleophile **Acid-catalyzed**

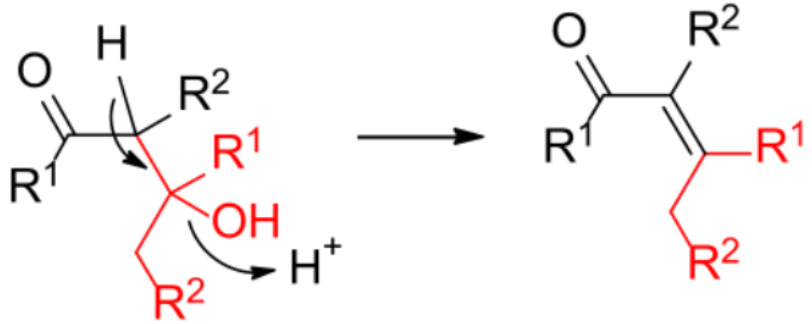
Mechanism

acid-catalyzed Condensation



Nucleophilic Addition

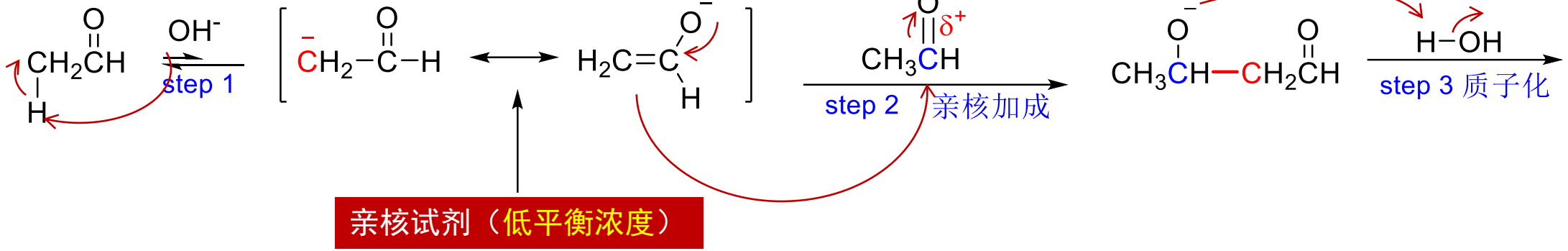
acid-catalyzed Hydration

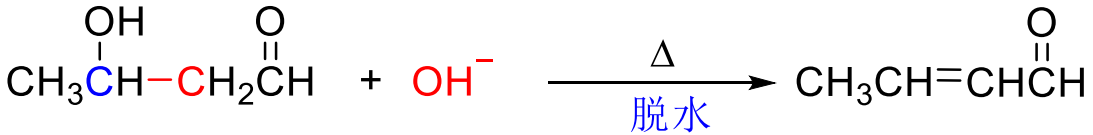


Elimination

Nucleophilic Addition to Carbonyl Group

Mechanism

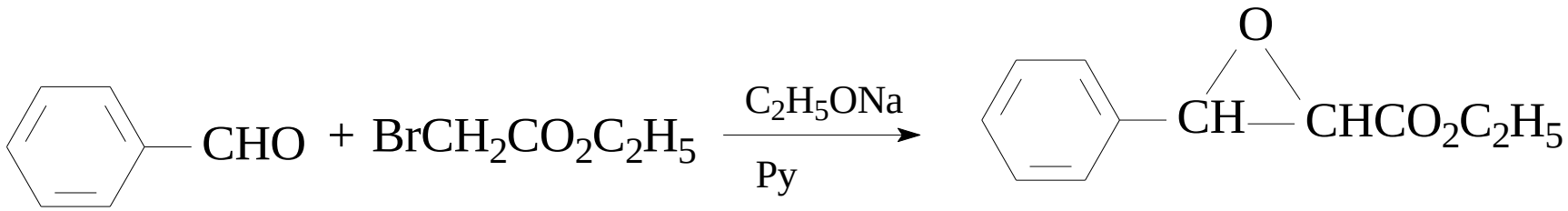




β-羟基醛　　催化剂再生　　α, β-不饱和醛

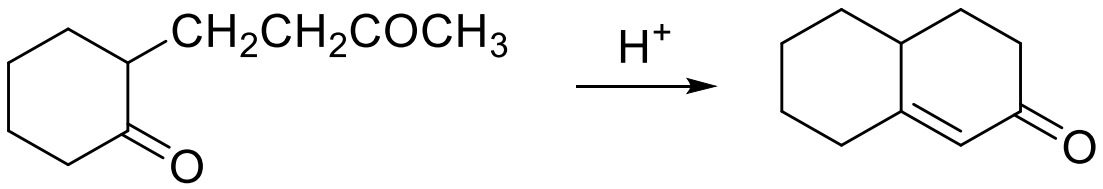
Exercise 9

Propose the mechanisms for the reactions below



Darzens Reaction

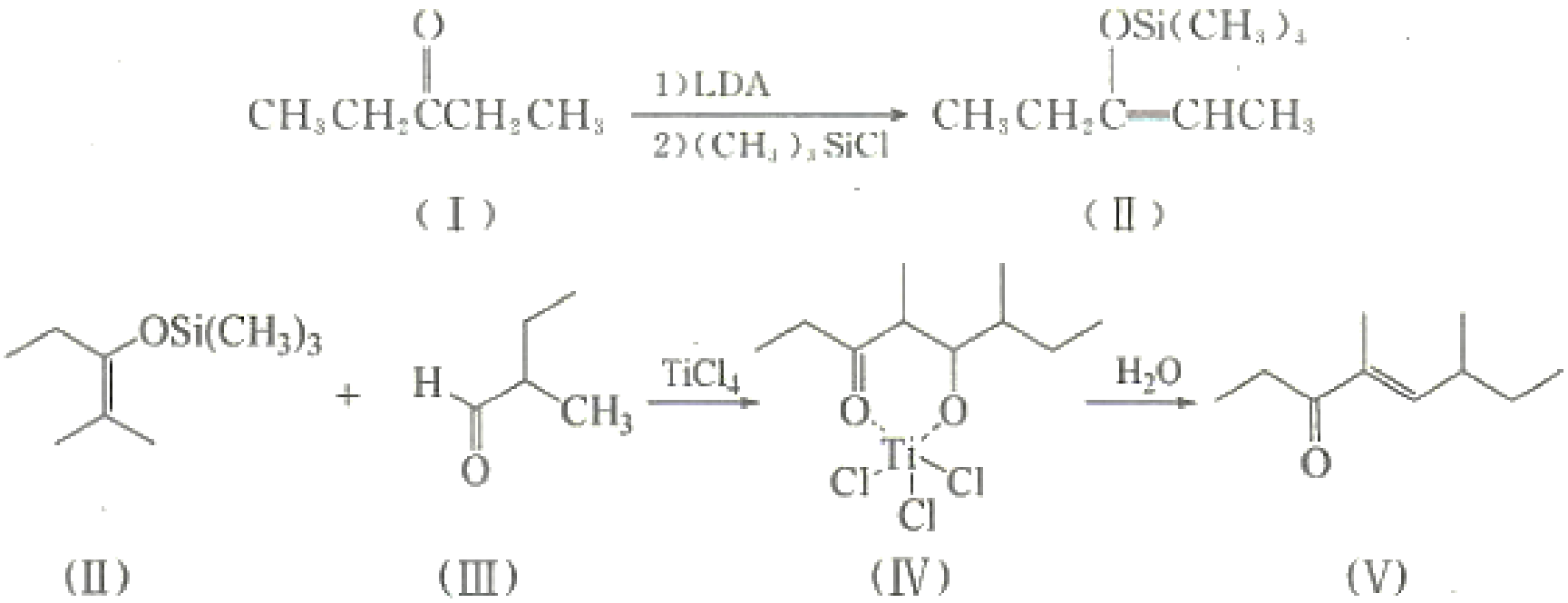
醛酮在碱作用下与α-卤代酸酯反应生成α，β-环氧酯



Acid-catalyzed Aldol Reaction

6.5 Condensation Reactions

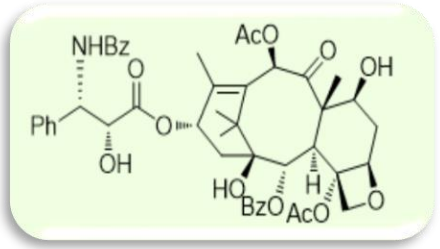
Mukaiyama-Carreria Aldol Reaction 对交叉羟醛缩合的改进



药物发现、人类健康、与生态保护

红豆杉

制约瓶颈：天然稀缺资源获取



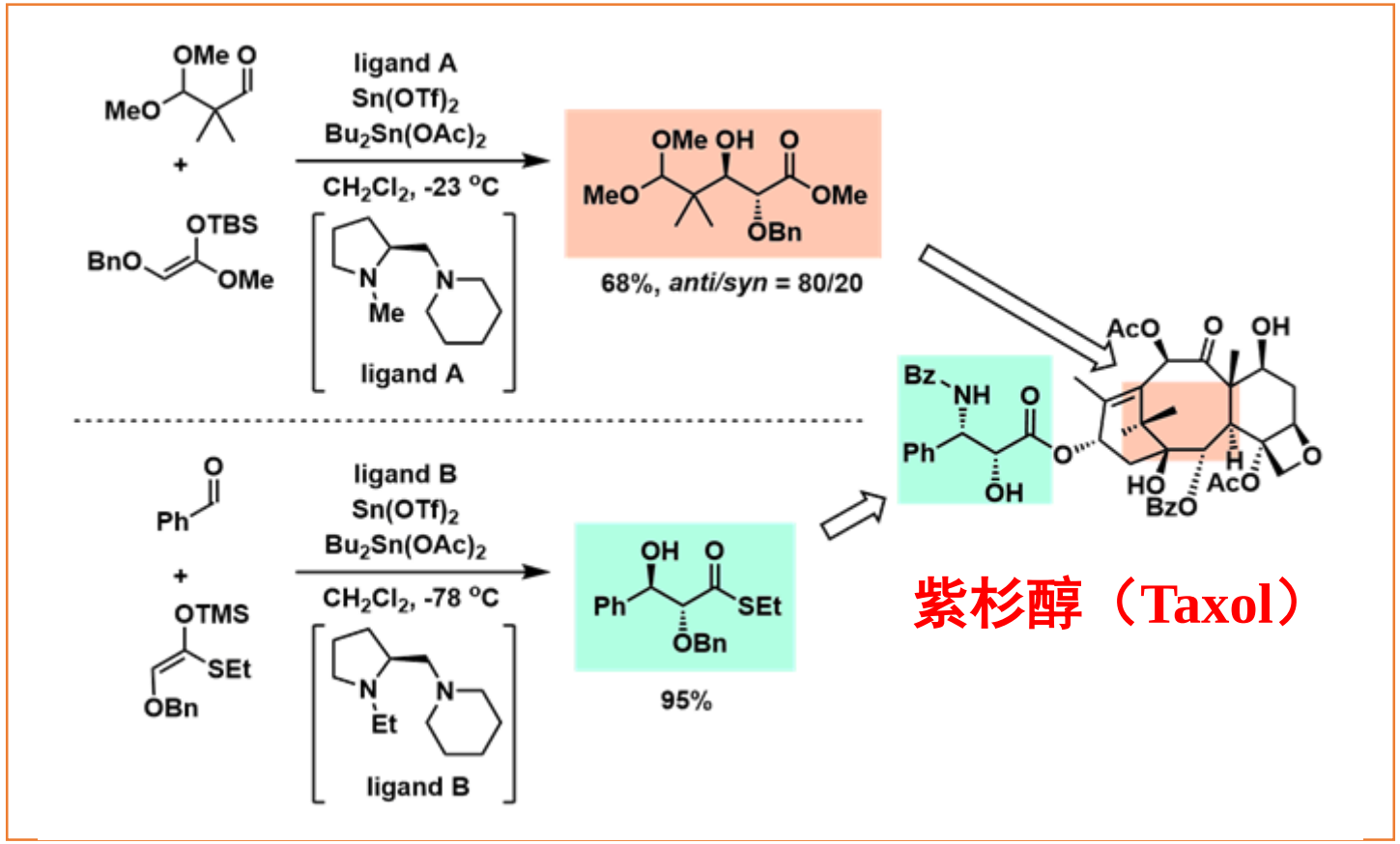
紫杉醇（Taxol）

汉德事件

90年代，云南红豆杉资源消耗80%

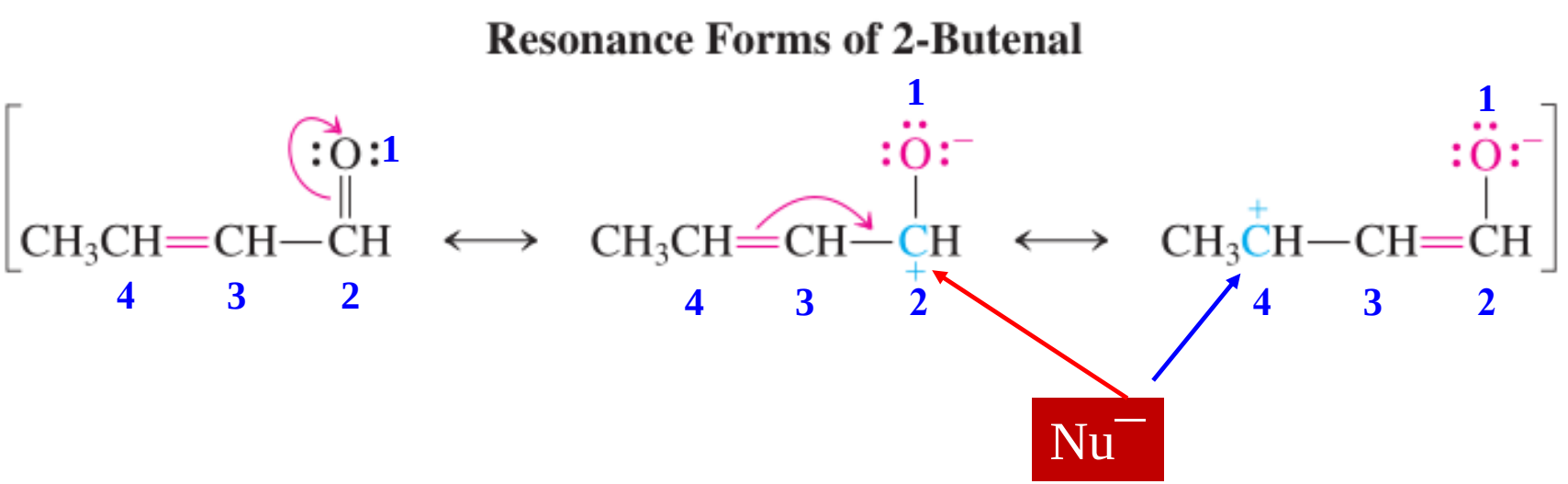
合成方法学在药物合成中的作用

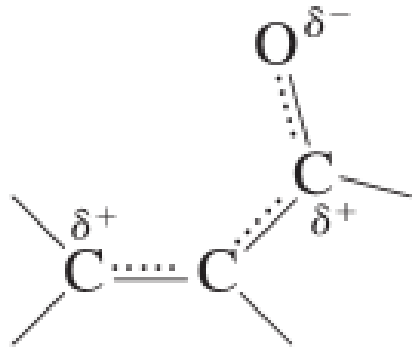
Mukaiyama采用羟醛缩合反应，实现紫杉醇人工全合成



Nucleophilic Addition to Carbonyl Group

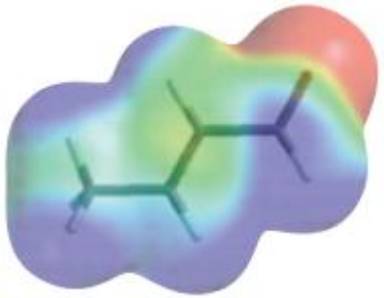
2'. Conjugate Additions of Enolate Ions: Michael Addition and Robinson Annulation





Competing reaction ⟶ **1, 2- addition**

1, 4- addition (conjugate addition)

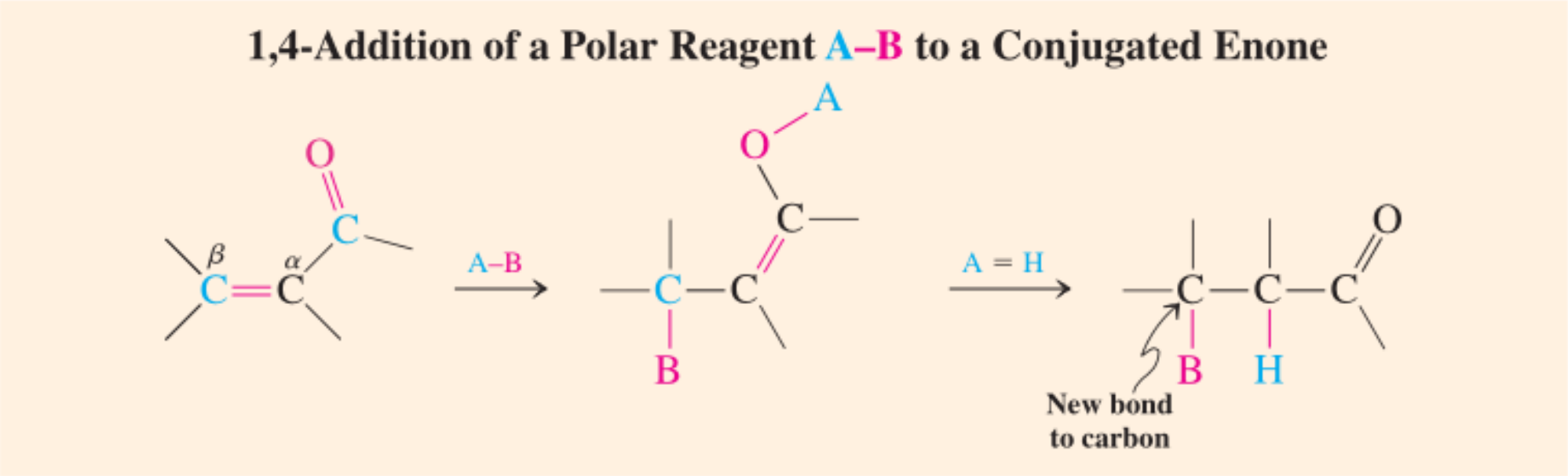


Nucleophilic Addition to Carbonyl Group

1, 4- addition (conjugate addition) ⟶ the end result appears to be that of **3,4-addition**

The initial product of conjugate addition to an α, β-unsaturated carbonyl compound is an enol, which subsequently rapidly tautomerizes to its keto form.

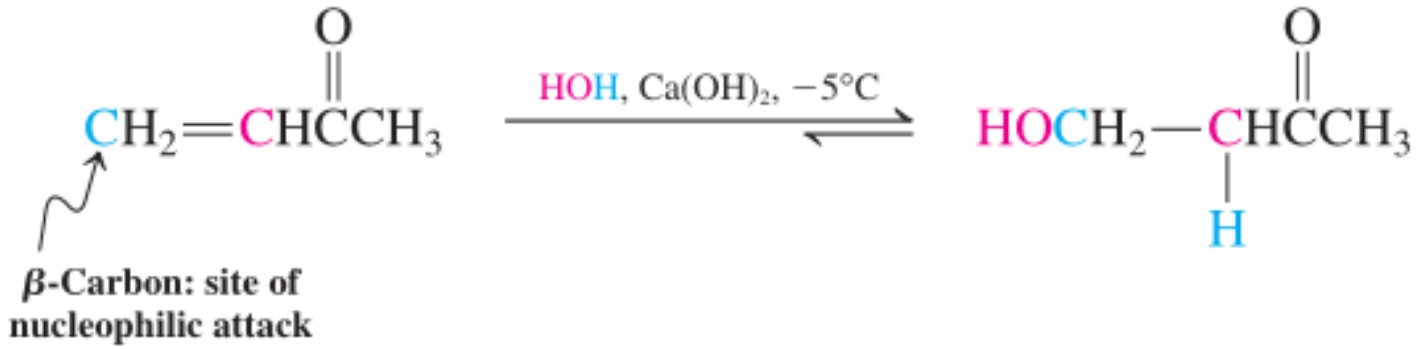
1, 4- addition + tautomerism



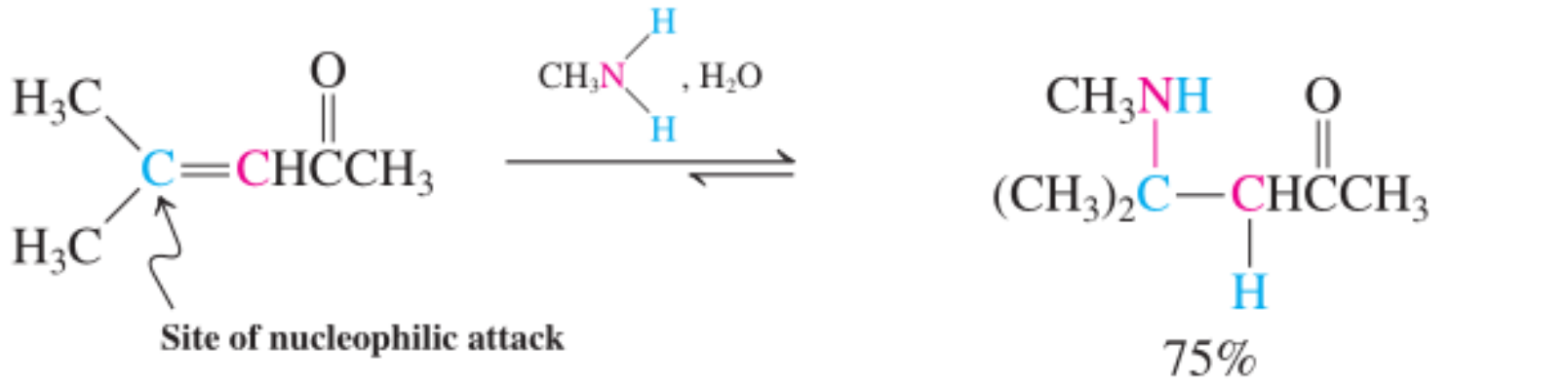
Nucleophilic Addition to Carbonyl Group

Oxygen and nitrogen nucleophiles undergo conjugate additions

Hydrogen cyanide also undergoes conjugate addition



3-Buten-2-one **4-Hydroxy-2-butanone**



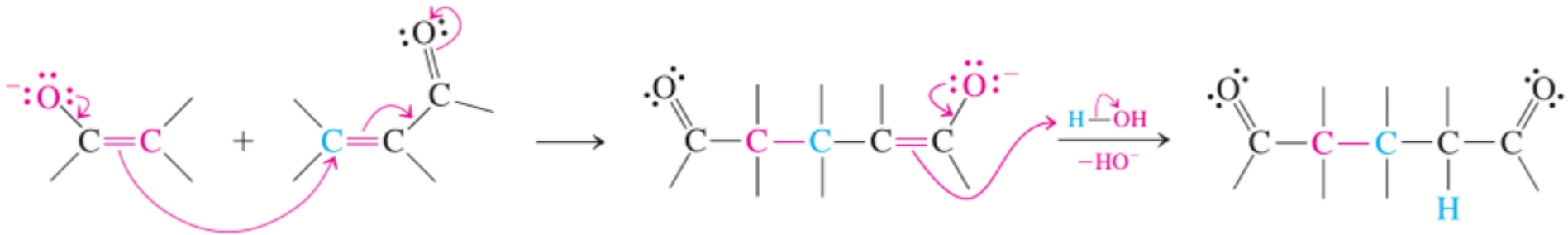
4-Methyl-3-penten-2-one **4-Methyl-4-(methylamino)-2-pentanone**

Nucleophilic Addition to Carbonyl Group

a. Michael Addition

1) 1,4-Additions(conjugate addition) of Enolate Ions

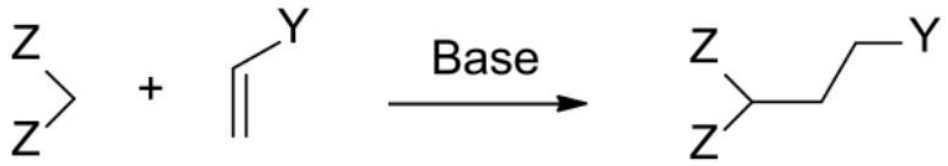
Mechanism Michael Addition



Nucleophilic Addition to Carbonyl Group

General equation of Michael Addition

Preparation of 1, 5-dicarbonyl compounds　　碳亲核试剂对a,β–不饱和羰基化合物的共轭加成



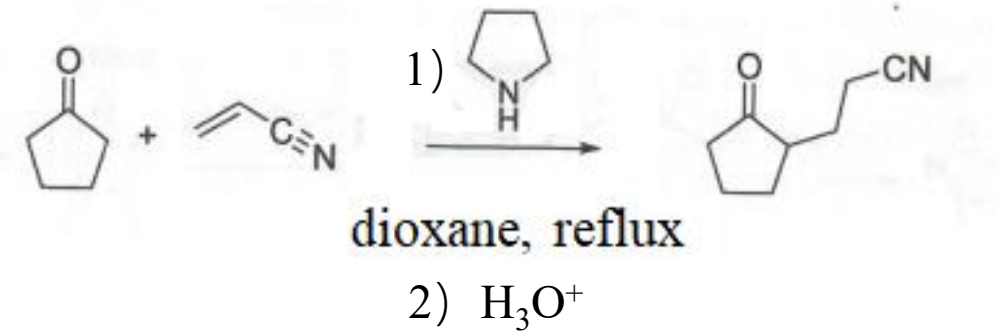
Z, Y = electron withdrawing groups

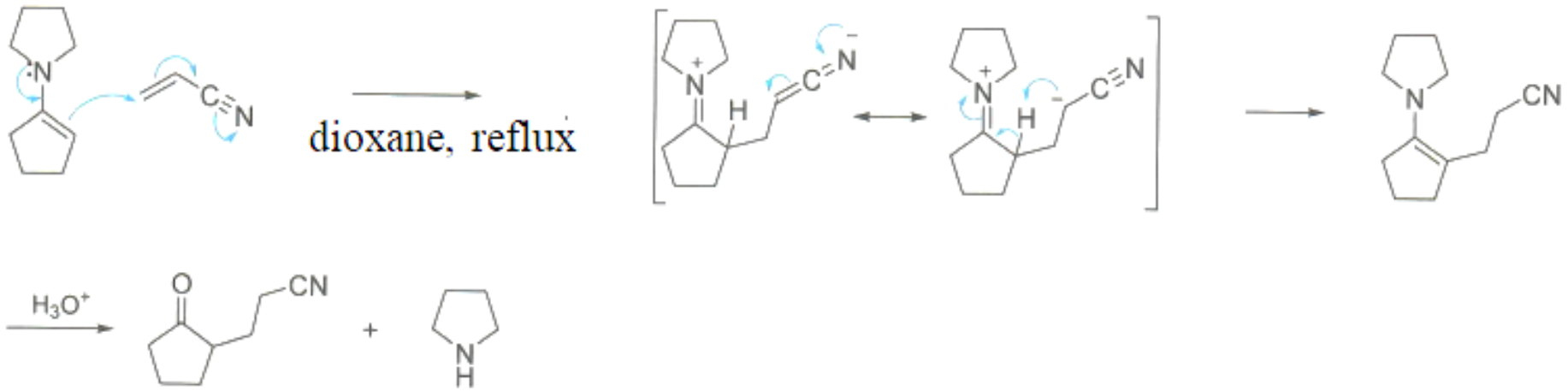
2) 1,4-Additions (conjugate addition) of Silyl Enol Ether　　Mukaiyama Michael Addition

Acceptor　　Donor

Nucleophilic Addition to Carbonyl Group

3) 1,4-Additions (conjugate addition) of enamine

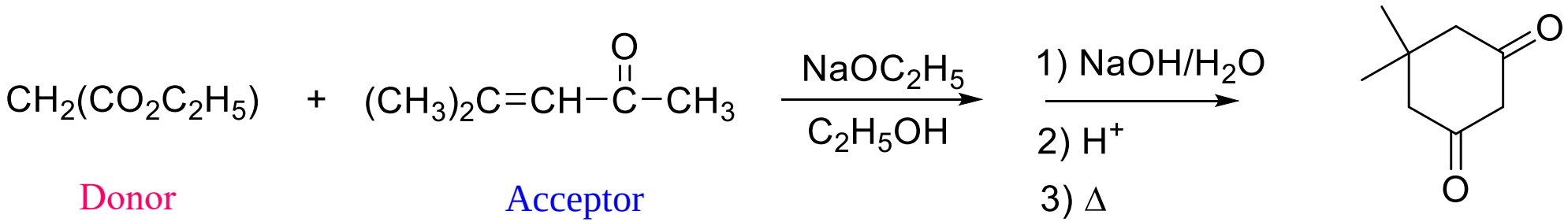




Exercise 10

Propose the mechanism for the reaction below

Michael addition + Intramolecular Claisen Ester Condensation+ Decarboxylation



Donor

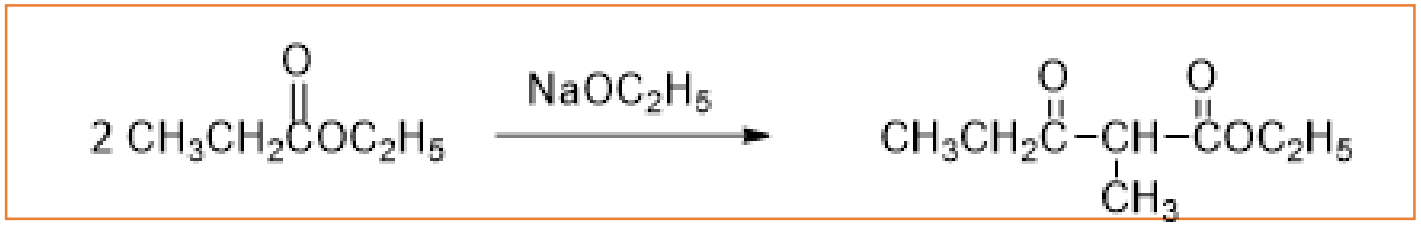
Acceptor

6.5 Condensation Reactions

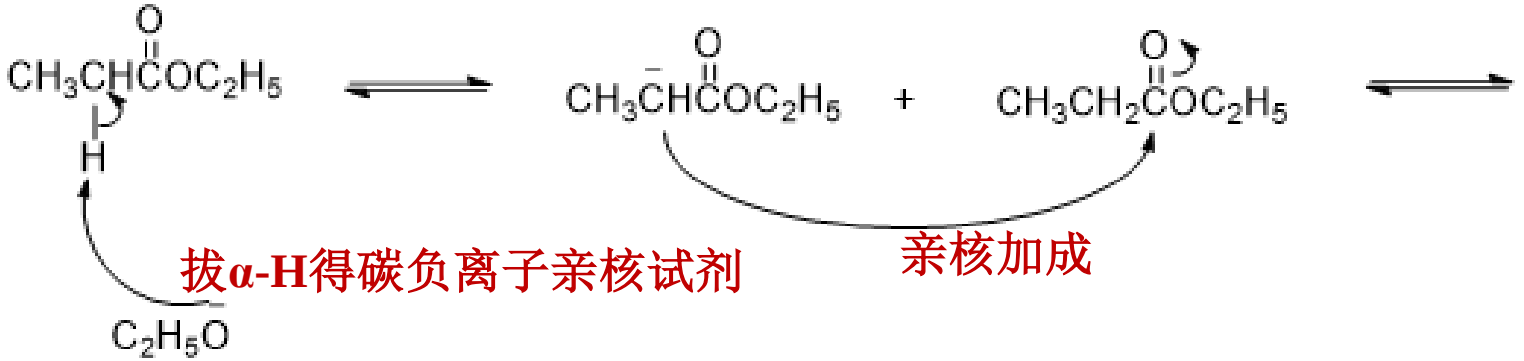
Claisen Condensation

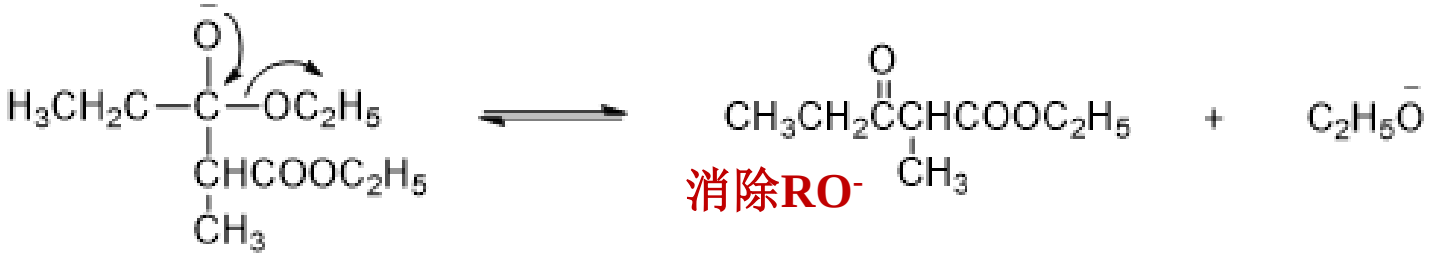
含活泼α-氢的酯在碱作用下的缩合得到酮酯

self-condensation

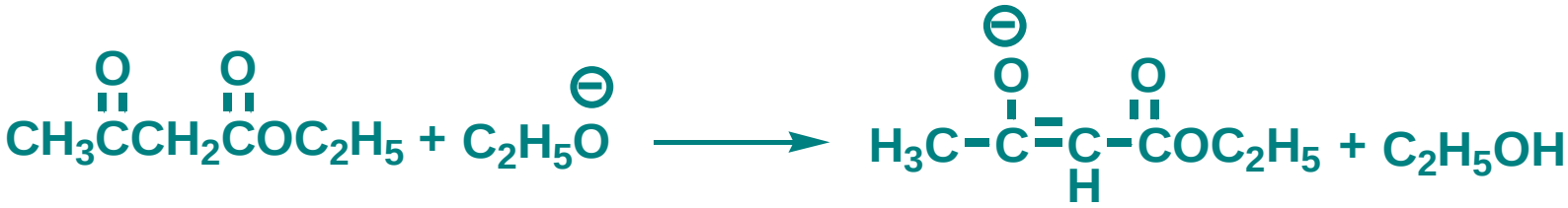


Mechanism





6.5 Condensation Reactions

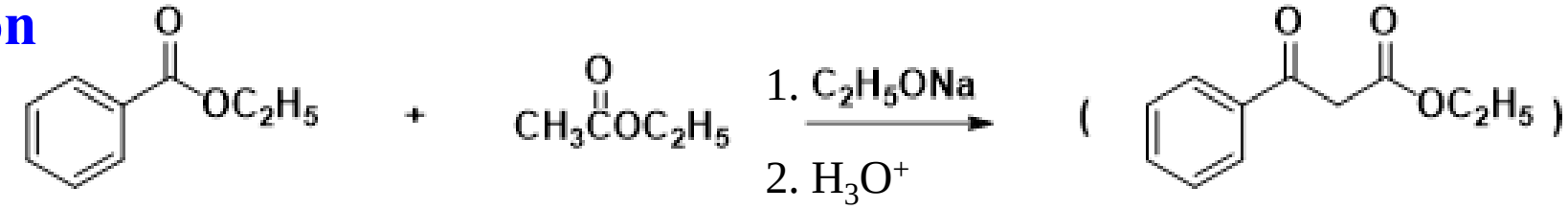


pKa = 11　　不可逆　　pKa = 17

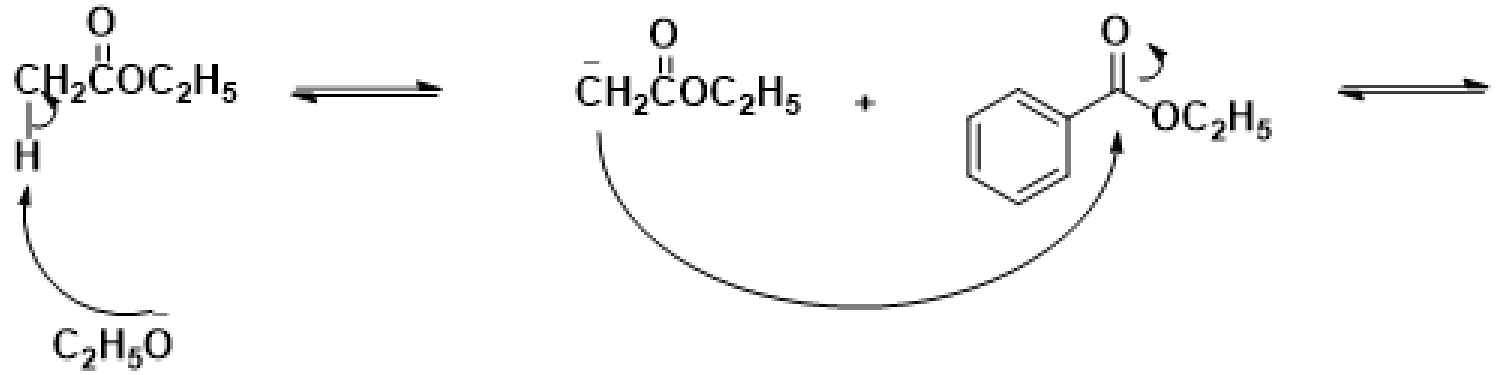
$$[CH_3COCHCOOC_2H_5]^- Na^+ + HAc \longrightarrow CH_3COCH_2COOC_2H_5 + NaAc$$

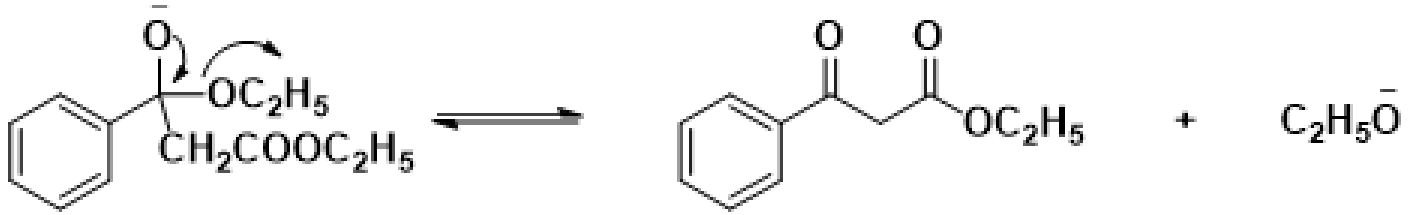
6.5 Condensation Reactions

Mixed-condensation



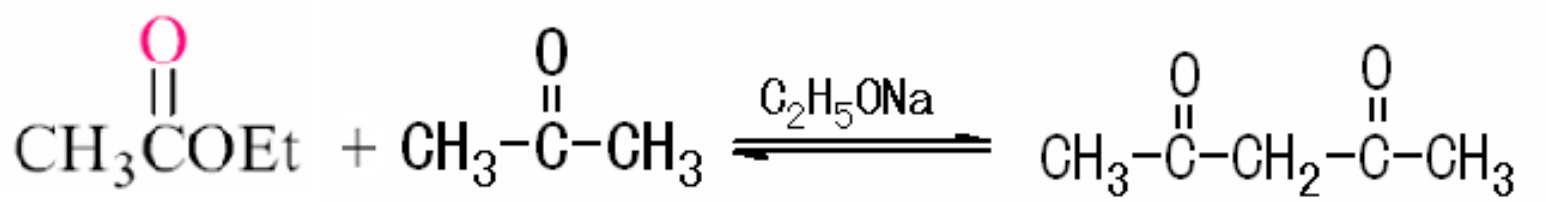
Mechanism



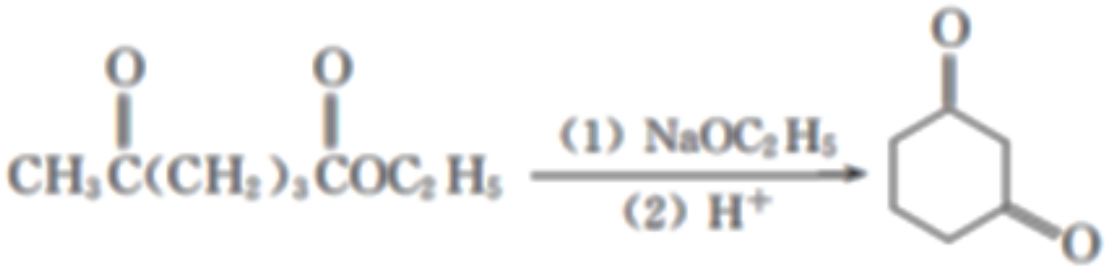


6.5 Condensation Reactions

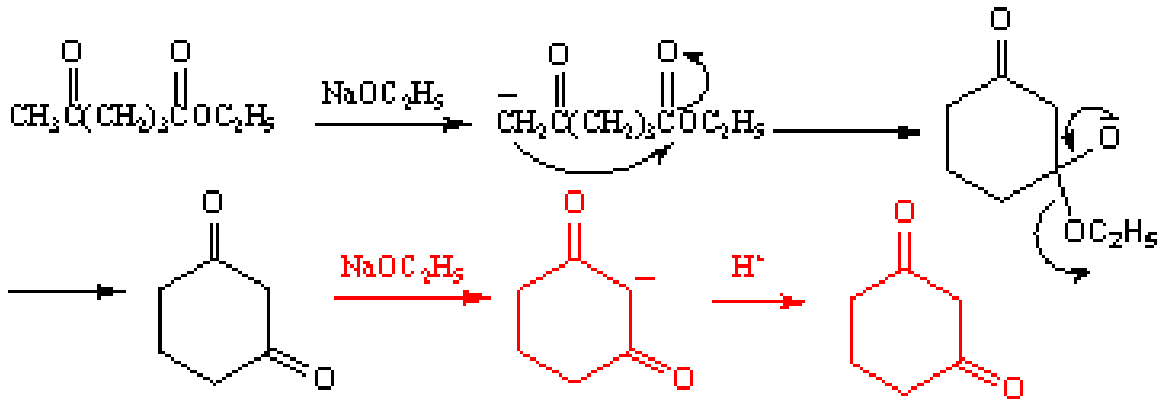
Ketone ester condensation



6.5 Condensation Reactions



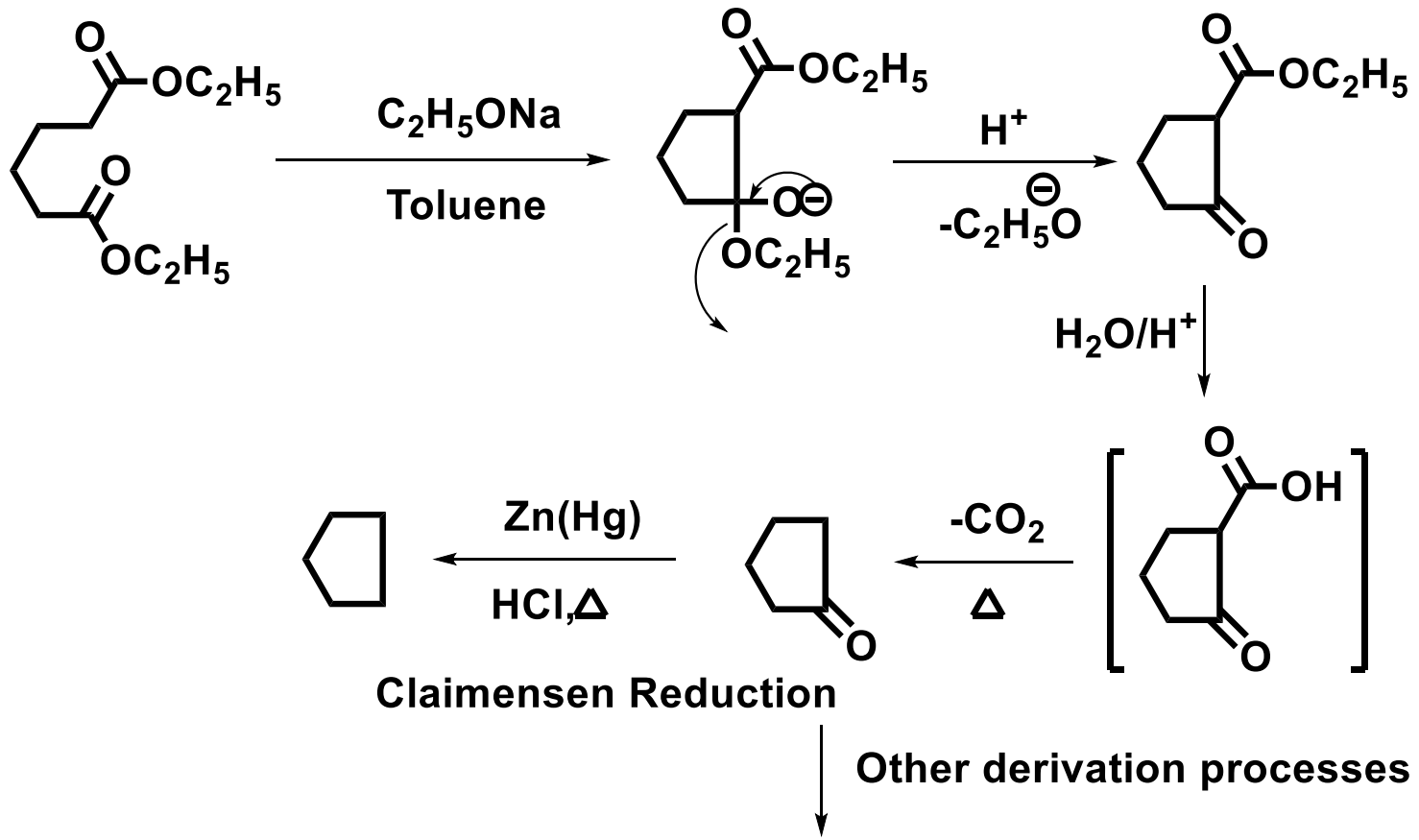
Mechanism ★



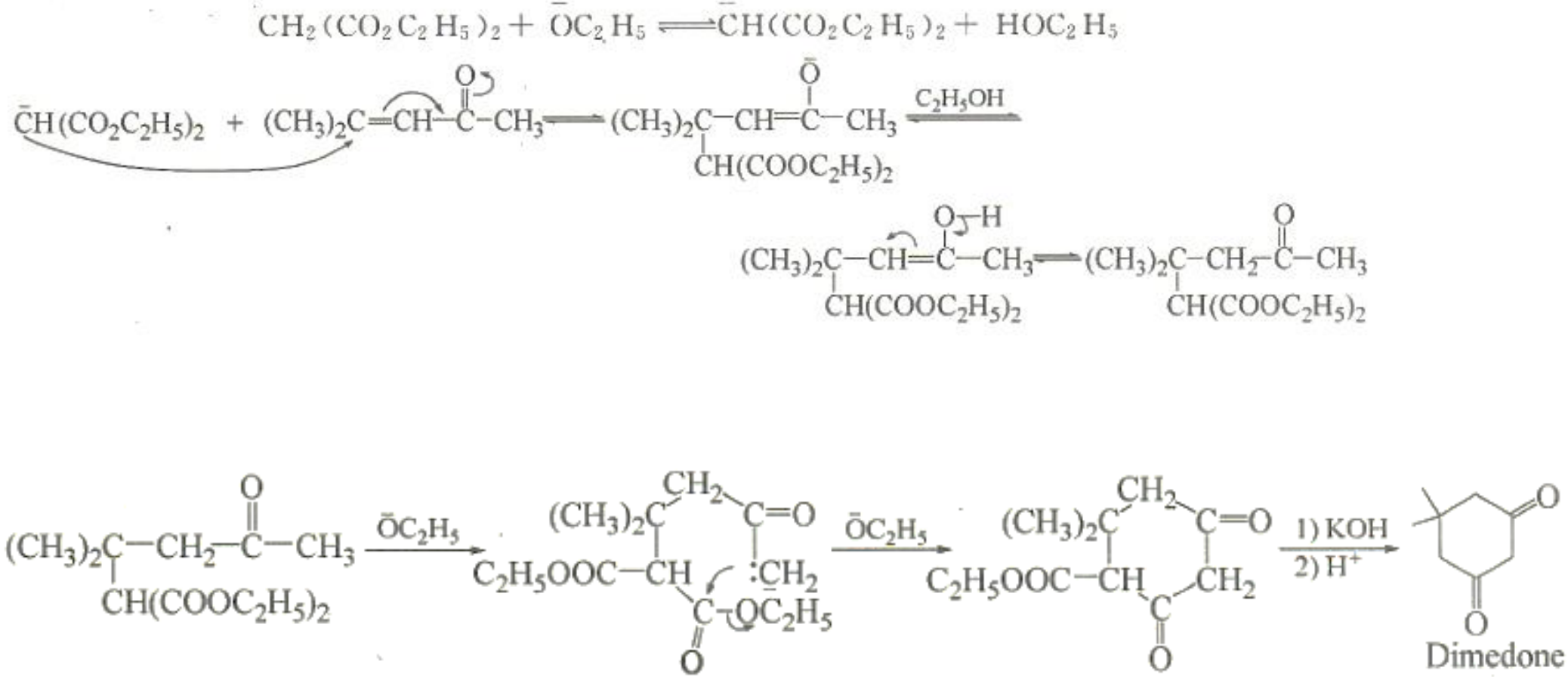
6.5 Condensation Reactions

Dieckmen Condensation

分子内酯缩合反应，用于五、六元环化合物的制备。



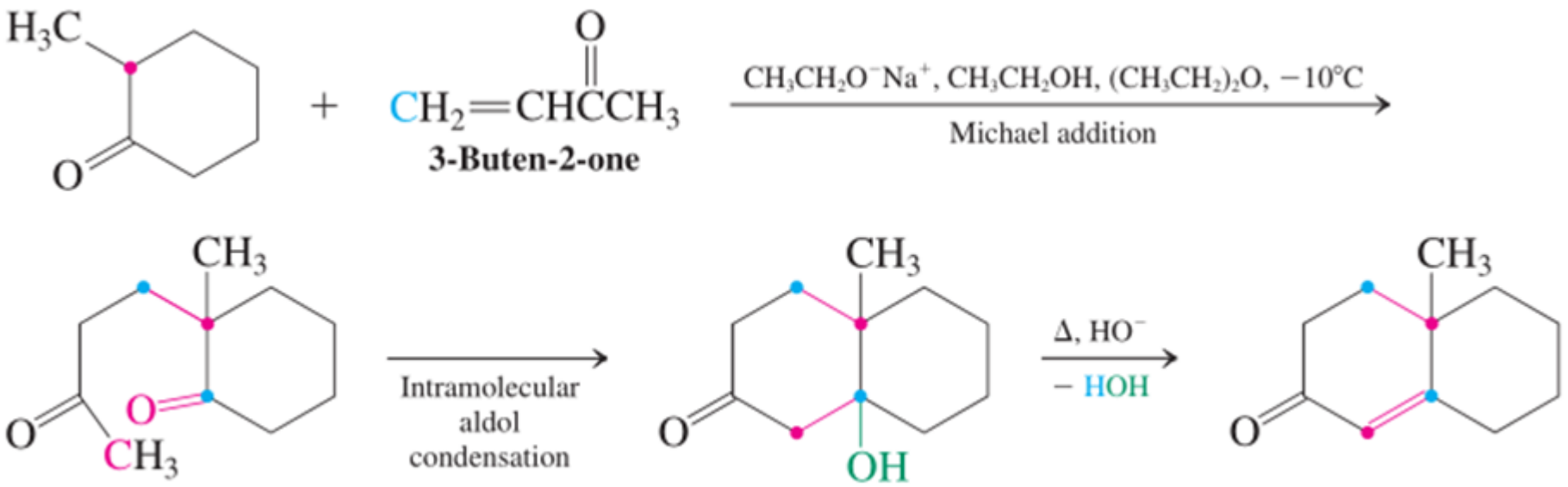
Exercise 10



Nucleophilic Addition to Carbonyl Group

b. Robinson Annulation

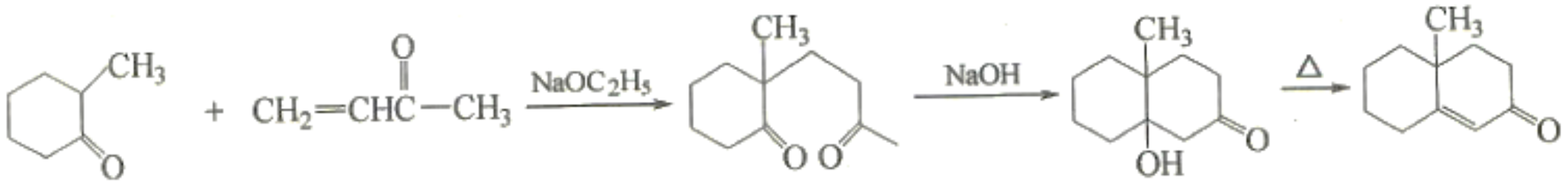
Michael Addition Followed by Intramolecular Aldol Condensation



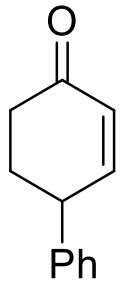
Exercise 11

Propose the mechanism for the reaction below Robinson Annulation

Michael addition + Intramolecular Aldol Condensation



Exercise 12

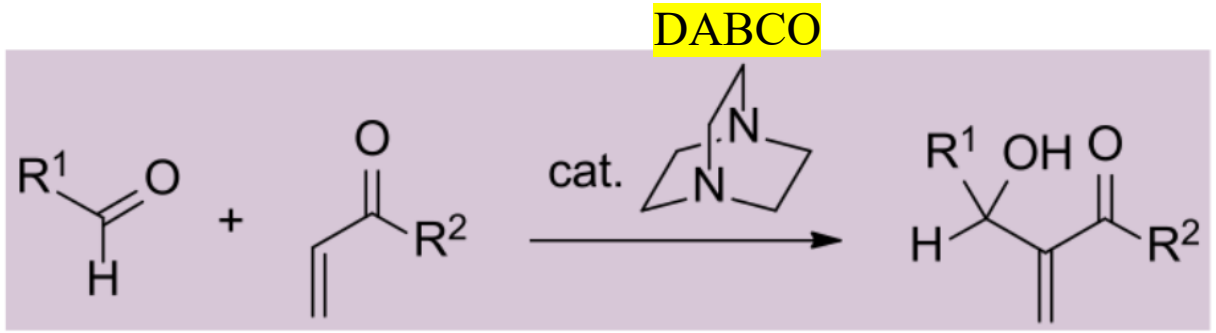
Propose a synthesis of 

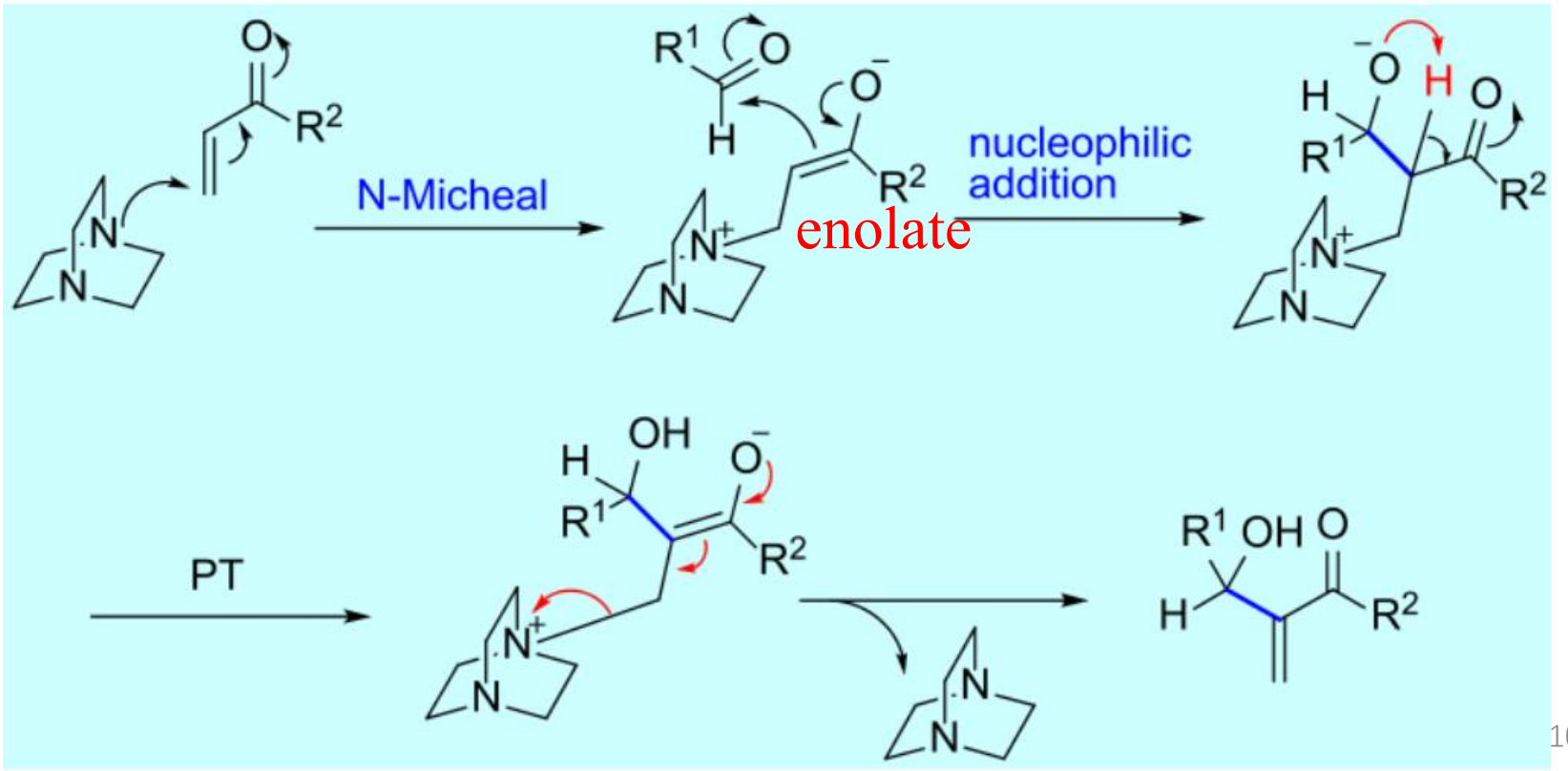
using Michael or Robinson reactions.

Nucleophilic Addition to Carbonyl Group

c. Morita-Baylis-Hillman Reaction

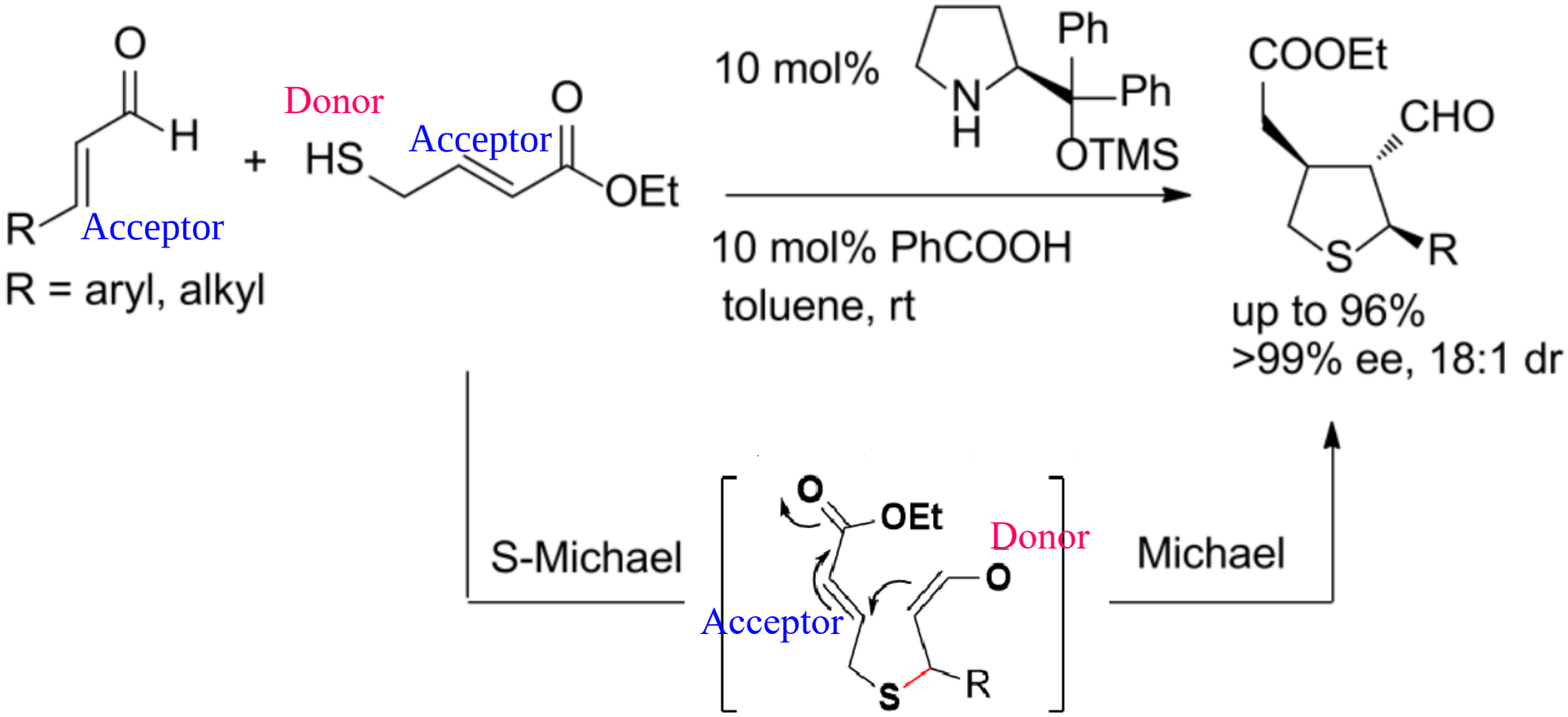
N-Michael Addition





Nucleophilic Addition to Carbonyl Group

S-Michael Addition



Nucleophilic Addition to Carbonyl Group

O-Michael Addition Michael Addition---Nitroalkene as acceptor (了解)