

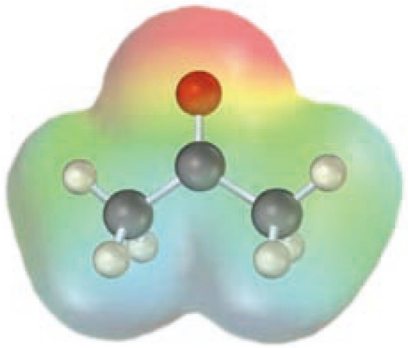
The tear gas used by police and military for riot control is a simple chloro ketone made by a carbonyl α-substitution reaction. Image copyright JustASC 2010. Used under license from Shutterstock.com

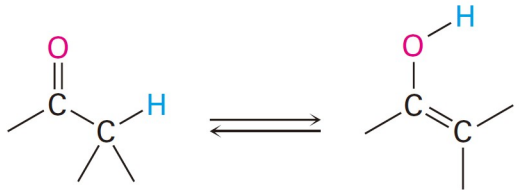
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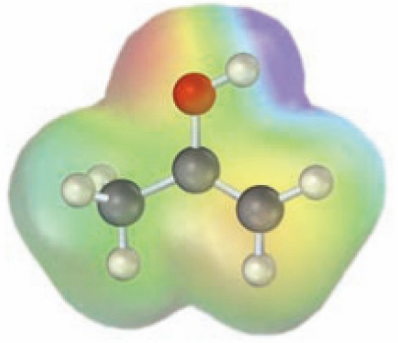
羰基 alpha 位的取代反应

22.1 酮和烯醇式的互变异构

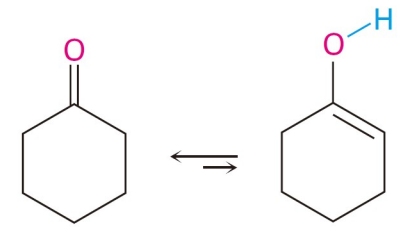
- 互变异构中烯醇式很少，但确实存在这样的平衡。烯醇式的多少和羰基化合物的结构有关。





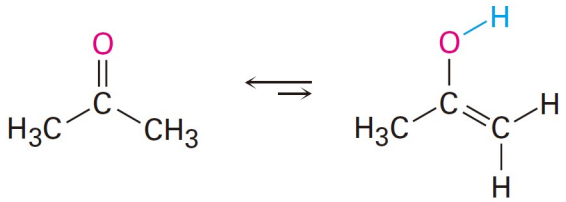


Keto tautomer **Enol tautomer**



99.999 9% 0.000 1%

Cyclohexanone

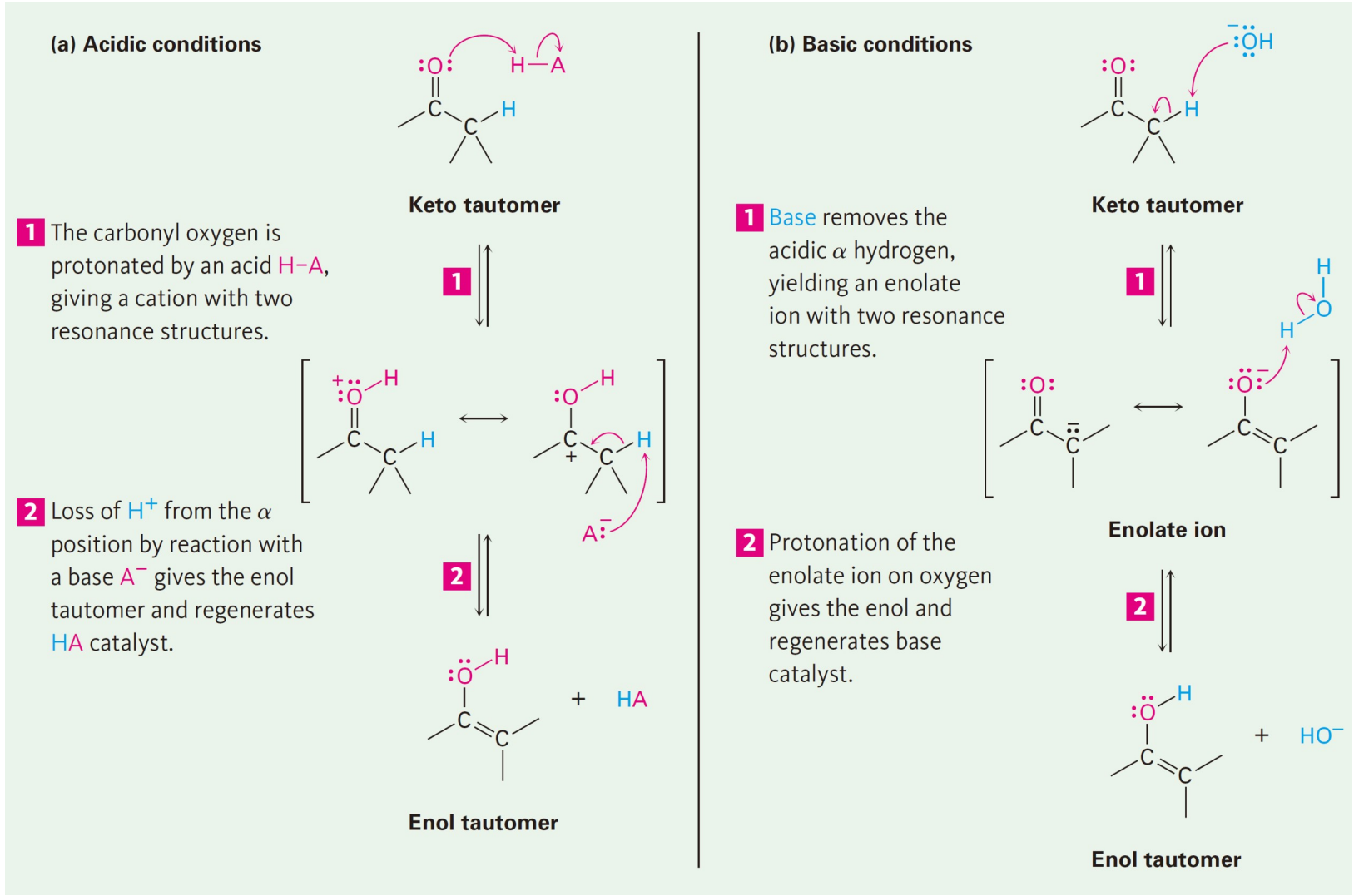


99.999 999 9% 0.000 000 1%

Acetone

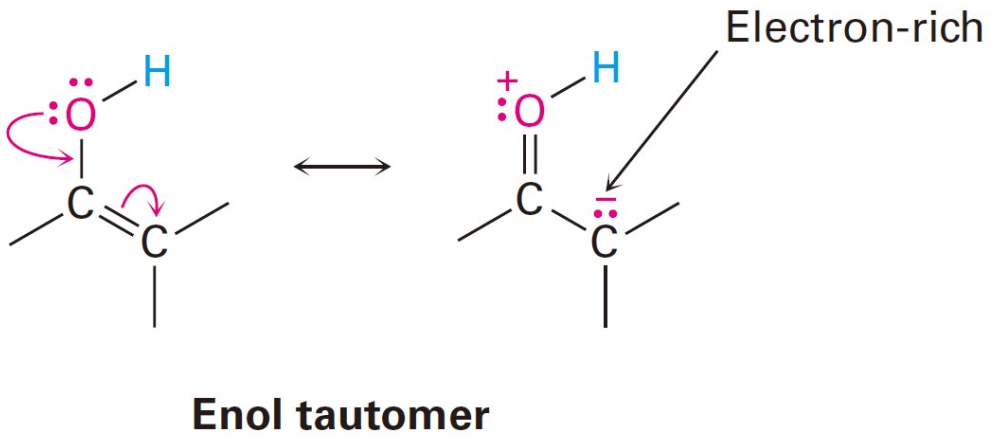
22.1 酮和烯醇式的互变异构

- 酸性条件和碱性条件下都可以互变异构

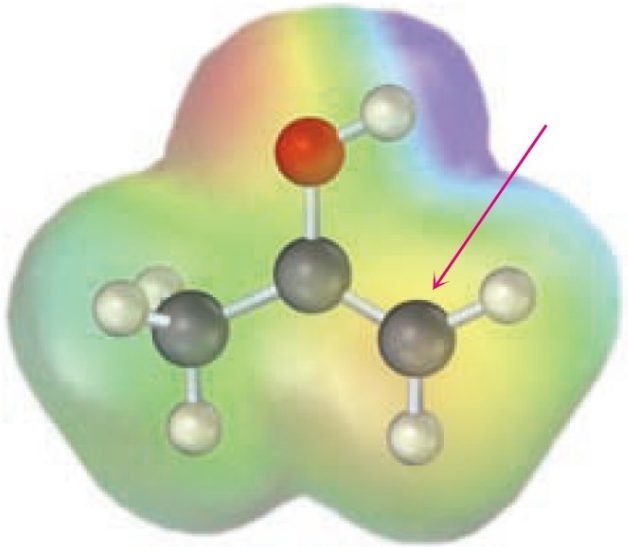


22.2 烯醇的反应性

- 烯醇式具有亲核性



Enol tautomer



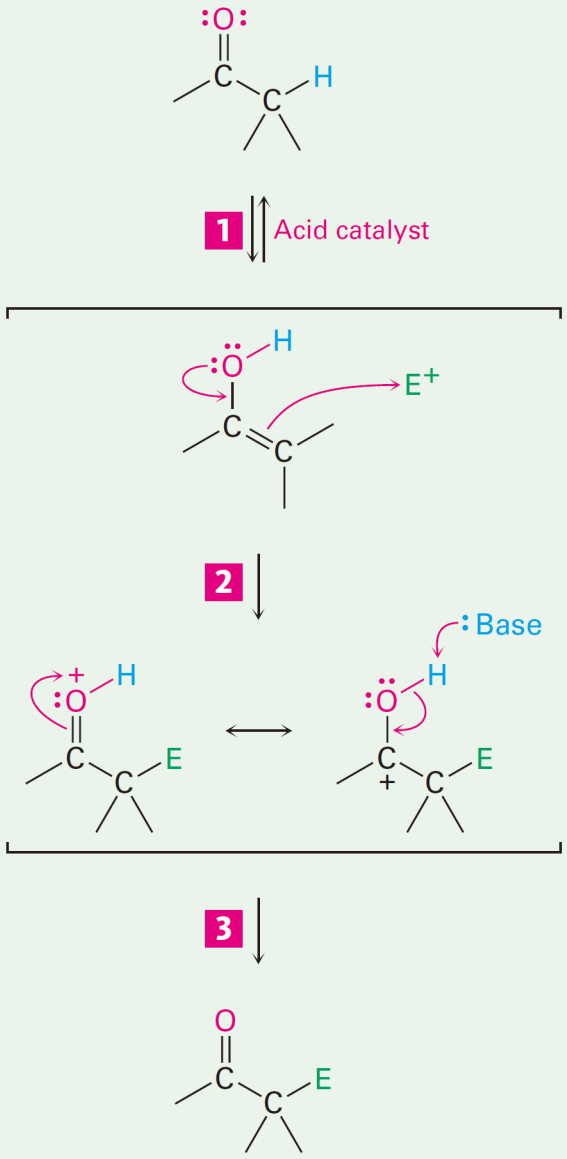
22.2 烯醇的反应性

- 烯醇式对亲电试剂的进攻

1 Acid-catalyzed enol formation occurs by the usual mechanism.

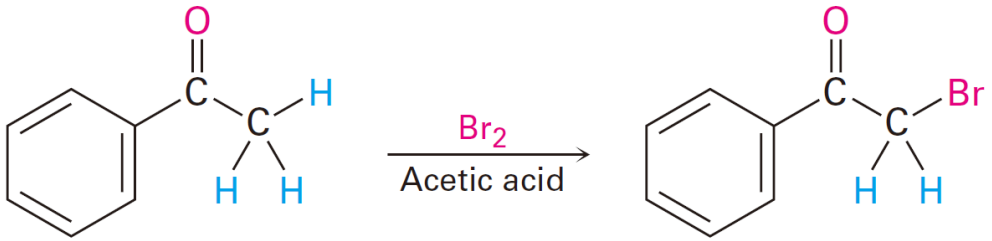
2 An electron pair from the enol oxygen attacks an electrophile (E^+), forming a new bond and leaving a cation intermediate that is stabilized by resonance between two forms.

3 Loss of a proton from oxygen yields the neutral alpha-substitution product as a new C=O bond is formed.



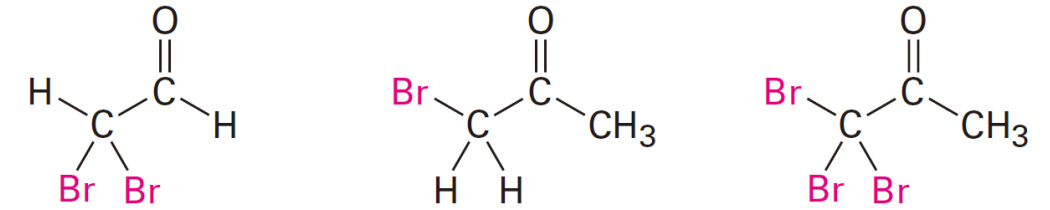
22.3 醛酮的 alpha 位卤化

A particularly common α-substitution reaction in the laboratory is the halogenation of aldehydes and ketones at their α positions by reaction with Cl_2, Br_2, or I_2 in acidic solution. Bromine in acetic acid solvent is often used.



Acetophenone **α-Bromoacetophenone (72%)**

Remarkably, ketone halogenation also occurs in biological systems, particularly in marine alga, where dibromoacetaldehyde, bromoacetone, 1,1,1-tribromoacetone, and other related compounds have been found.



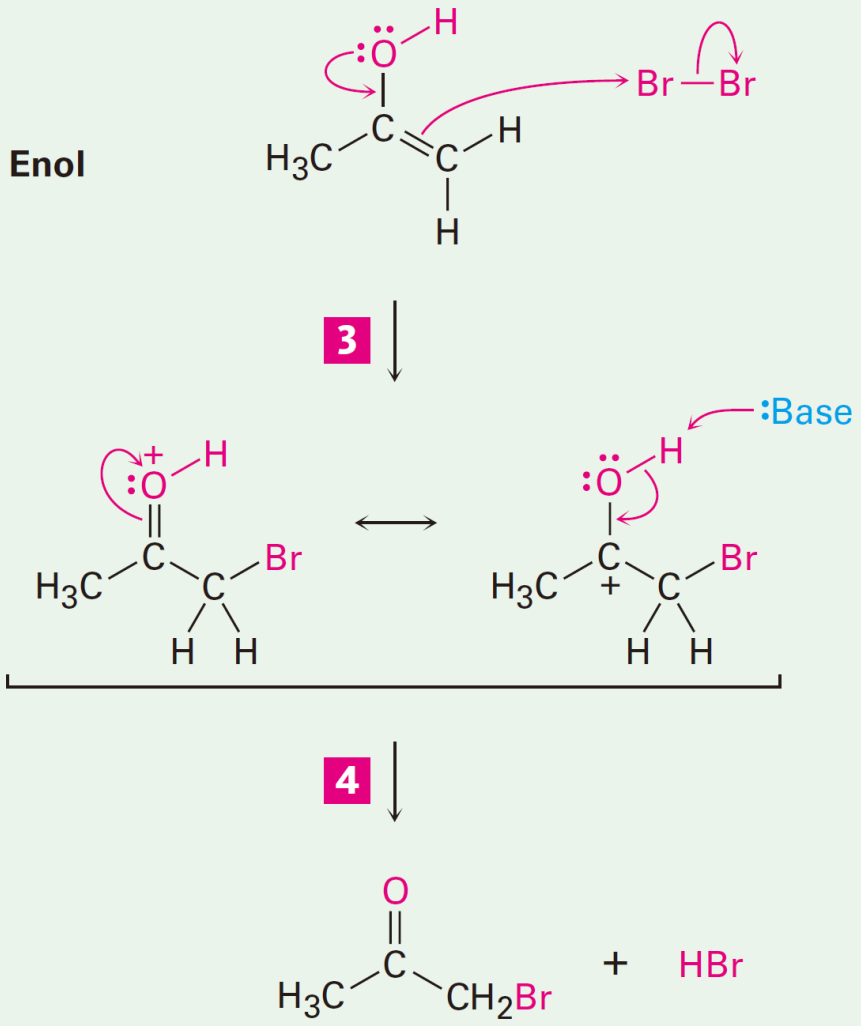
From the Hawaiian alga *Asparagopsis taxiformis*

22.3 醛酮的 alpha 位卤化

- 机理

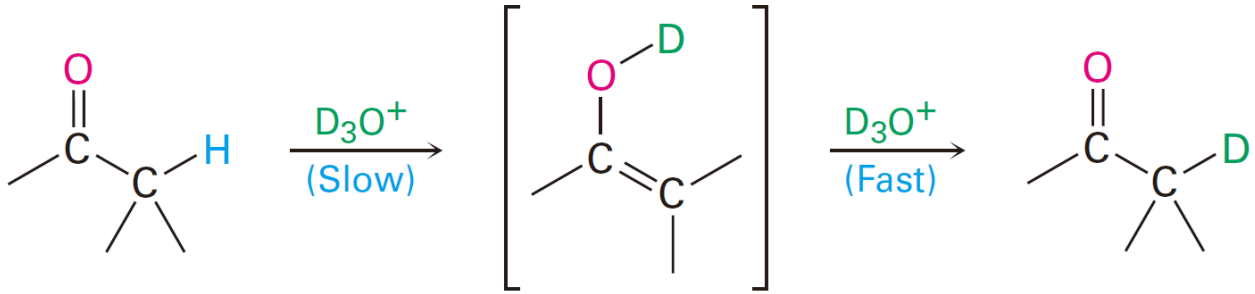
3 An electron pair from the enol attacks bromine, giving an intermediate cation that is stabilized by resonance between two forms.

4 Loss of the –OH proton then gives the alpha-halogenated product and generates more acid catalyst.

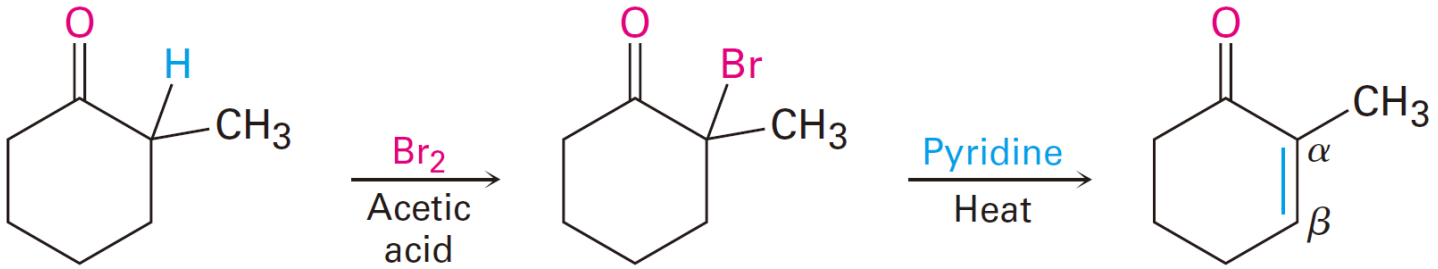


22.3 醛酮的 alpha 位卤化

- 其他应用



Enol



2-Methylcyclo-hexanone

2-Bromo-2-methyl-cyclohexanone

2-Methyl-2-cyclo-hexenone (63%)

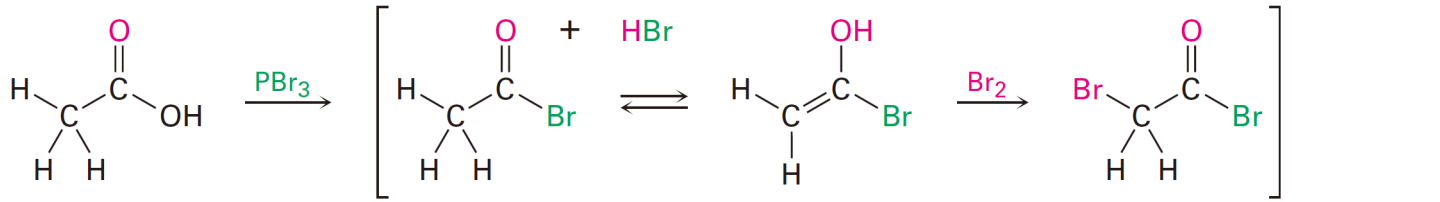
22.4 羧酸的 alpha 位卤化

- 条件和醛酮的 alpha 位卤化有所不同： Br_2, PBr_3

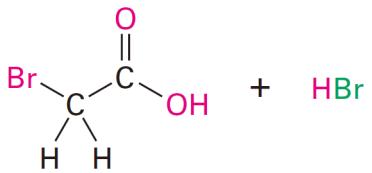
The α bromination of carbonyl compounds by Br_2 in acetic acid is limited to aldehydes and ketones because acids, esters, and amides don't enolize to a sufficient extent. Carboxylic acids, however, can be α brominated by a mixture of Br_2 and PBr_3 in the *Hell–Volhard–Zelinskii (HVZ) reaction*.



Heptanoic acid **2-Bromoheptanoic acid (90%)**



Carboxylic acid **Acid bromide** **Acid bromide enol**



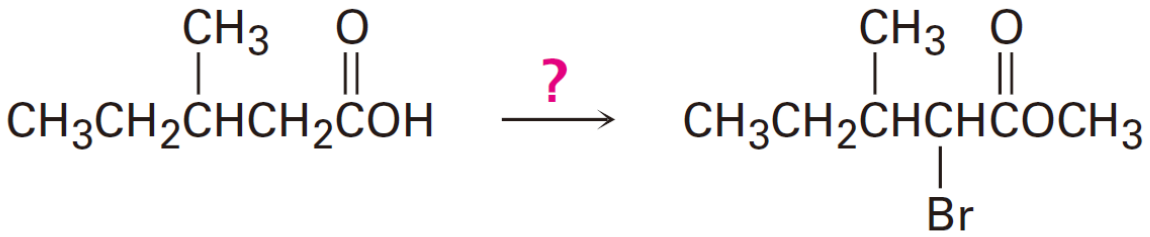
α-Bromo carboxylic acid

22.4 羧酸的 alpha 位卤化

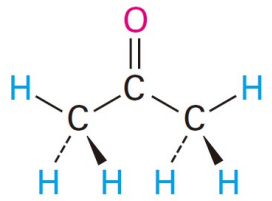
- 课堂练习

Problem 22.6

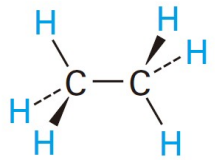
If methanol rather than water is added at the end of a Hell–Volhard–Zelinskii reaction, an ester rather than an acid is produced. Show how you could carry out the following transformation, and propose a mechanism for the ester-forming step.



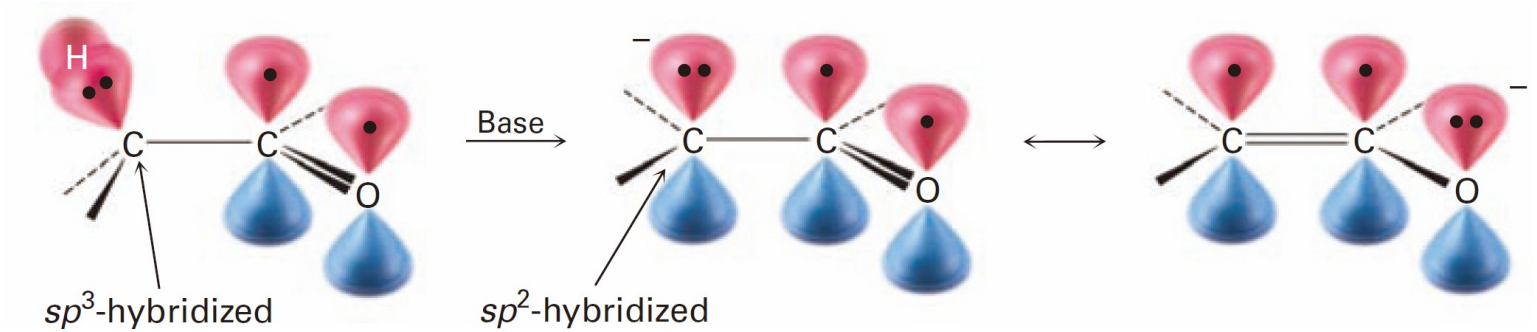
22.5 Alpha 氢的酸性

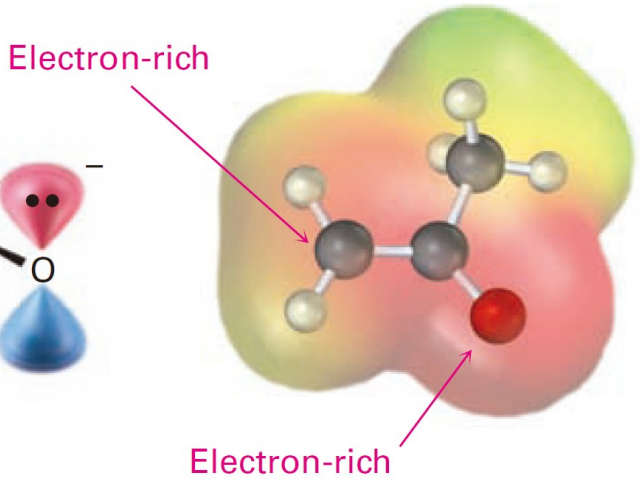


Acetone
(pK_a = 19.3)



Ethane
($pK_a \approx 60$)





22.5 Alpha 氢的酸性

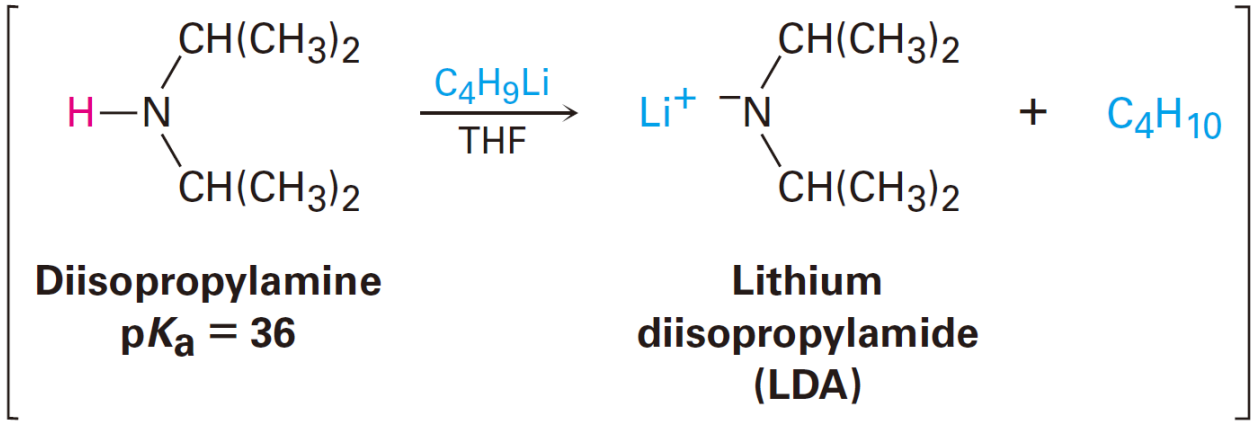
- 酸性比较

Table 22.1 Acidity Constants for Some Organic Compounds

Functional group	Example	pK_a
Carboxylic acid	CH_3COH	5
1,3-Diketone	$CH_3CCH_2CCH_3$	9
3-Keto ester	$CH_3CCH_2COCH_3$	11
1,3-Diester	$CH_3OCCH_2COCH_3$	13
Alcohol	CH_3OH	16
Acid chloride	CH_3CCl	16
Aldehyde	CH_3CH	17
Ketone	CH_3CCH_3	19
Thioester	CH_3CSCH_3	21
Ester	CH_3COCH_3	25
Nitrile	$CH_3C{\equiv}N$	25
N,*N*-Dialkylamide	$CH_3CN(CH_3)_2$	30
Dialkylamine	$HN(i\text{-}C_3H_7)_2$	36

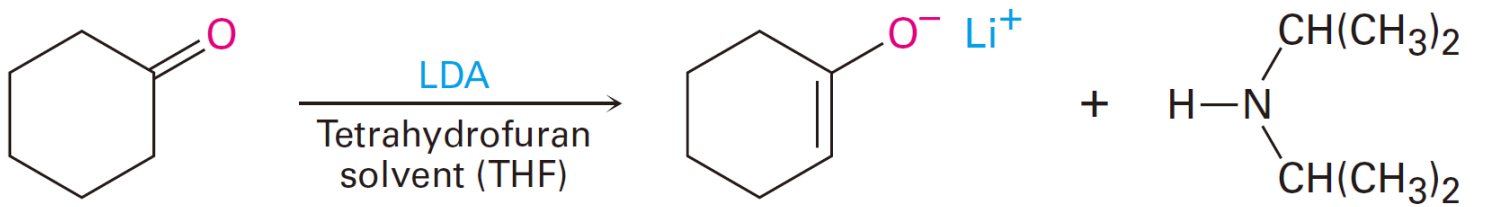
22.5 Alpha 氢的酸性

- LDA ：一种实验室常用的大位阻的碱，广泛用于羰基化合物 alpha 位去质子



Diisopropylamine
$pK_a = 36$

Lithium diisopropylamide (LDA)



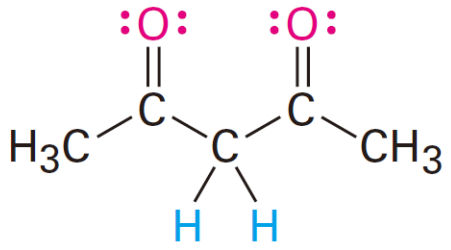
Cyclohexanone

Cyclohexanone enolate ion

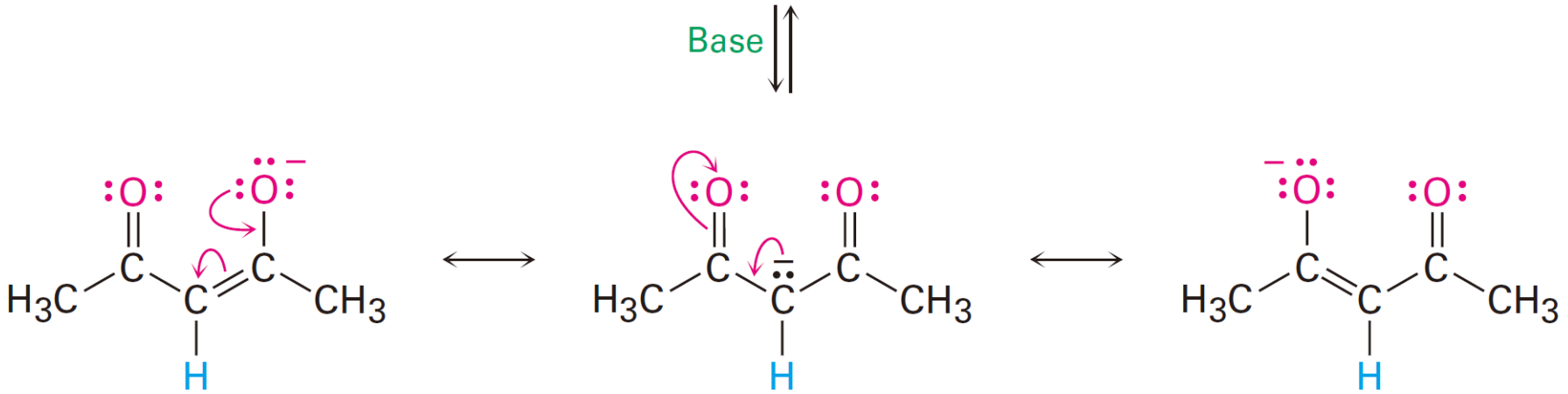
Diisopropylamine

22.5 Alpha 氢的酸性

- 1, 3 双羰化合物， alpha 位氢酸性很强



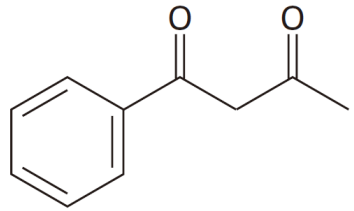
2,4-Pentanedione ($pK_a = 9$)

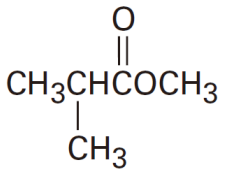


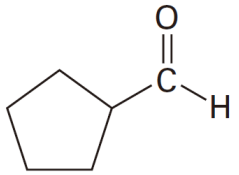
22.5 Alpha 氢的酸性

Identifying the Acidic Hydrogens in a Compound

Identify the most acidic hydrogens in each of the following compounds, and rank the compounds in order of increasing acidity:

(a) 

(b) 

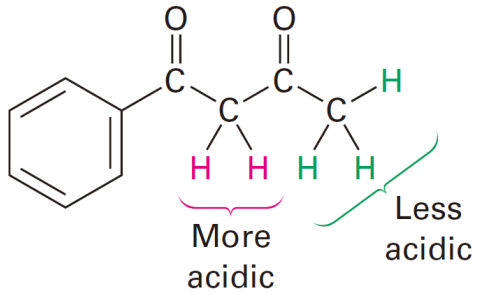
(c) 

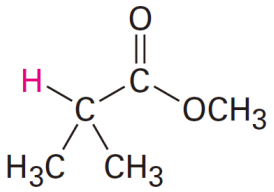
Strategy

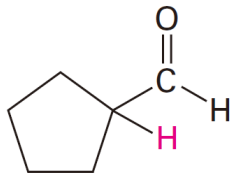
Hydrogens on carbon next to a carbonyl group are acidic. In general, a β-dicarbonyl compound is most acidic, a ketone or aldehyde is next most acidic, and a carboxylic acid derivative is least acidic. Remember that alcohols, phenols, and carboxylic acids are also acidic because of their —OH hydrogens.

Solution

The acidity order is (a) > (c) > (b). Acidic hydrogens are shown in red.

(a) 

(b) 

(c) 

22.5 Alpha 氢的酸性

- 课堂练习

Problem 22.7

Identify the most acidic hydrogens in each of the following molecules:

(a) CH_3CH_2CHO **(b)** $(CH_3)_3CCOCH_3$ **(c)** CH_3CO_2H

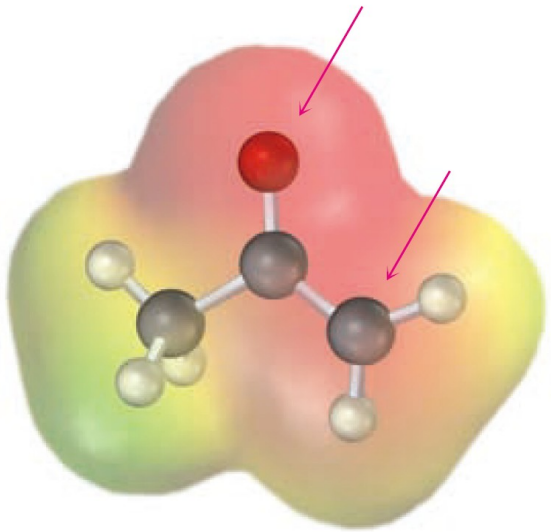
(d) Benzamide **(e)** $CH_3CH_2CH_2CN$ **(f)** $CH_3CON(CH_3)_2$

Problem 22.8

Draw a resonance structure of the acetonitrile anion, $^{-}{:}CH_2C{\equiv}N$, and account for the acidity of nitriles.

22.6 烯醇负离子的反应性

- 作为亲核试剂，对亲电试剂进攻



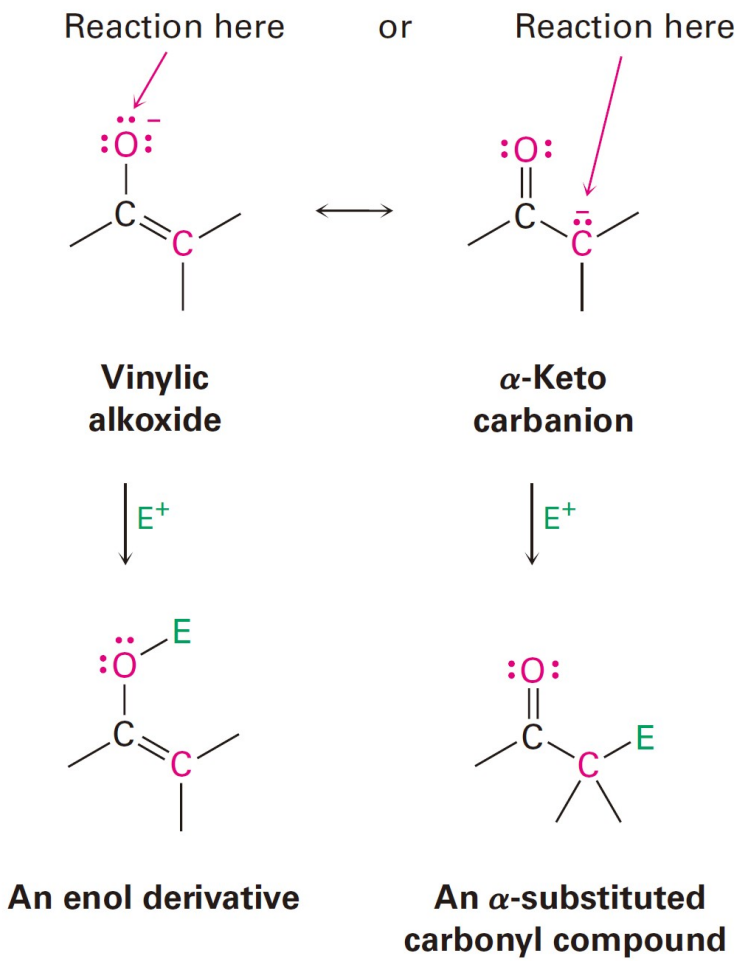
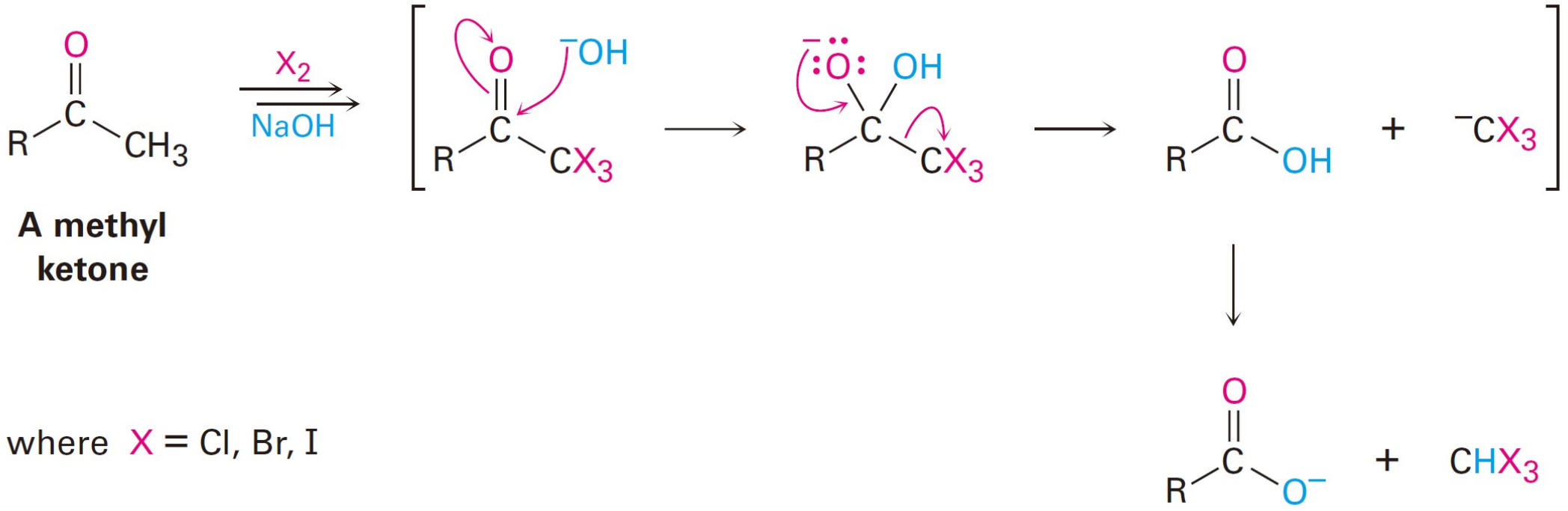


Figure 22.5 The electrostatic potential map of acetone enolate ion shows how the negative charge is delocalized over both the oxygen and the α carbon. As a result, two modes of reaction of an enolate ion with an electrophile E^+ are possible. Reaction on carbon to yield an α-substituted carbonyl product is more common.

22.6 烯醇负离子的反应性

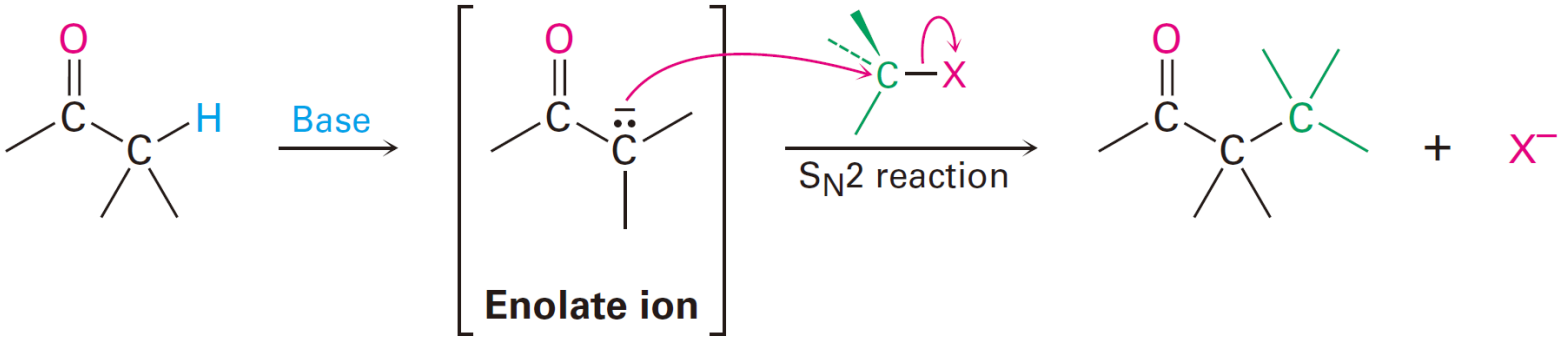
- 卤仿反应



22.7 烯醇负离子的烷基化反应

- 重要：构建 C–C 键

Perhaps the most useful reaction of enolate ions is their alkylation by treatment with an alkyl halide or tosylate, thereby forming a new C–C bond and joining two smaller pieces into one larger molecule. Alkylation occurs when the nucleophilic enolate ion reacts with the electrophilic alkyl halide in an S_N2 reaction and displaces the leaving group by backside attack.



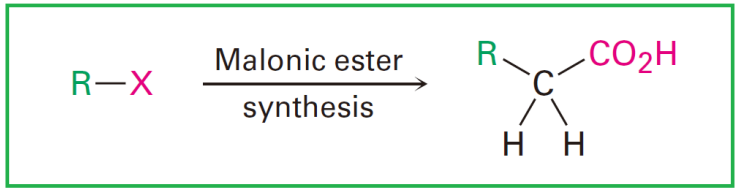
R—X
- —X: Tosylate > —I > —Br > —Cl
- R—: Allylic ≈ Benzylic > H_3C— > RCH_2—

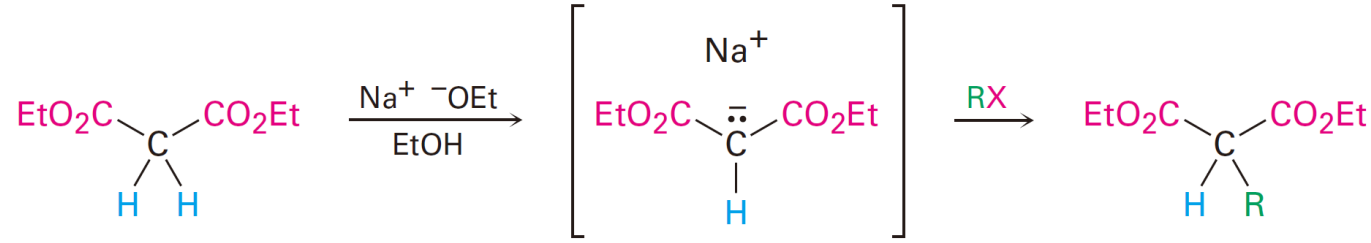
22.7 烯醇负离子的烷基化反应

- 丙二酸酯的合成应用

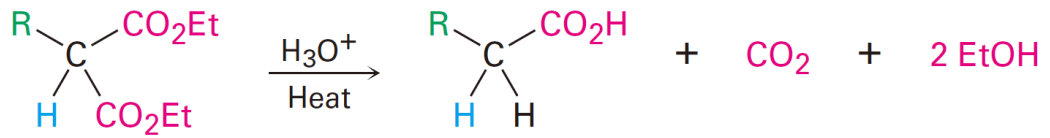
The Malonic Ester Synthesis

One of the oldest and best known carbonyl alkylation reactions is the **malonic ester synthesis**, a method for preparing a carboxylic acid from an alkyl halide while lengthening the carbon chain by two atoms.





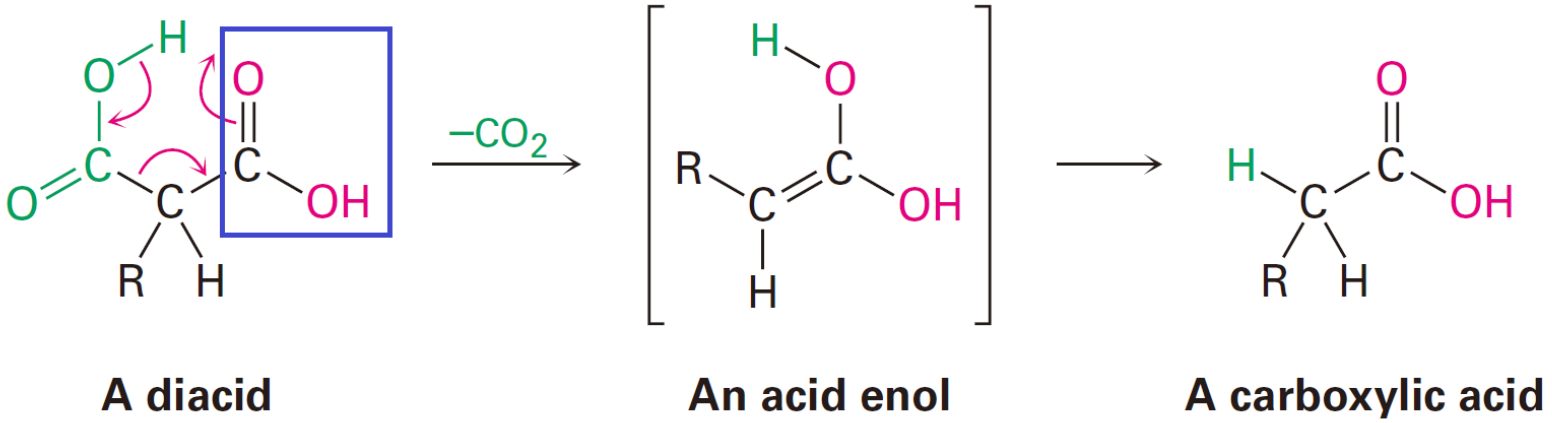
Diethyl propanedioate (malonic ester) | **Sodio malonic ester** | **An alkylated malonic ester**



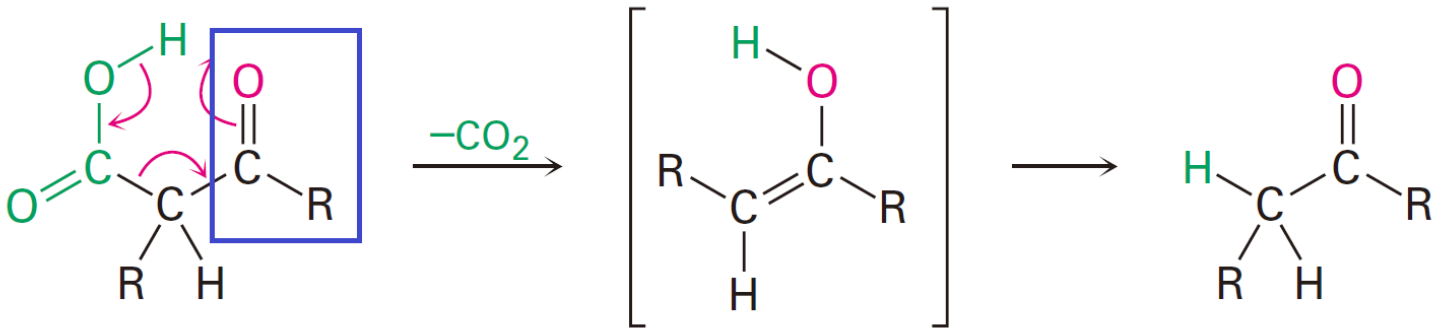
An alkylated malonic ester | **A carboxylic acid**

22.7 烯醇负离子的烷基化反应

- 机理



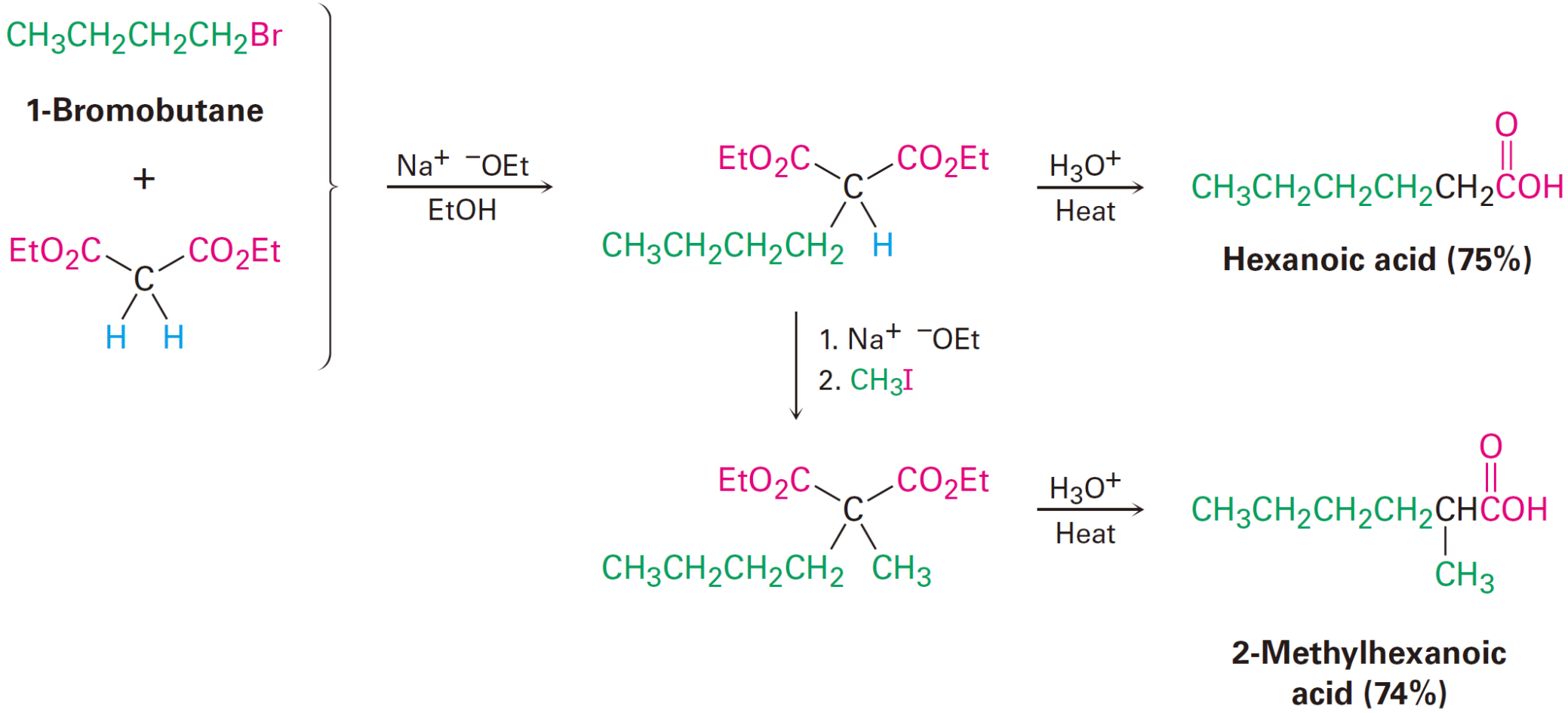
A diacid　　An acid enol　　A carboxylic acid



A β-keto acid　　An enol　　A ketone

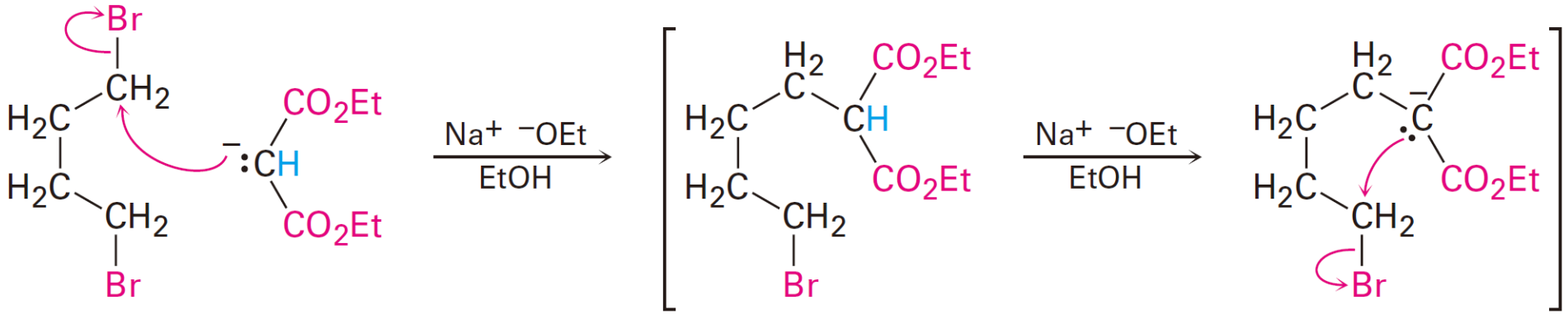
22.7 烯醇负离子的烷基化反应

- 应用举例

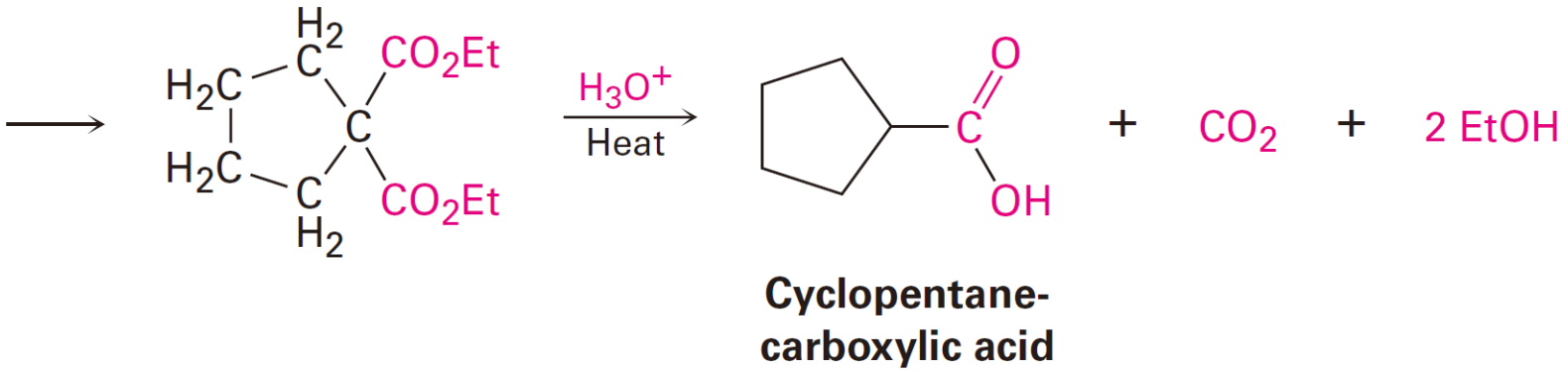


22.7 烯醇负离子的烷基化反应

- 应用举例



1,4-Dibromobutane



Cyclopentane-carboxylic acid

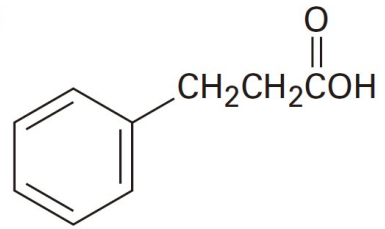
22.7 烯醇负离子的烷基化反应

- 课堂练习

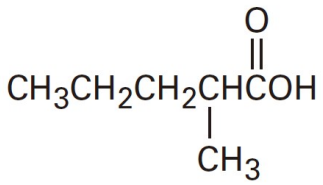
Problem 22.10

How could you use a malonic ester synthesis to prepare the following compounds? Show all steps.

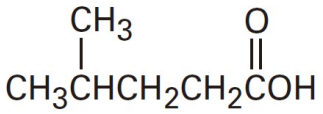
(a)



(b)



(c)

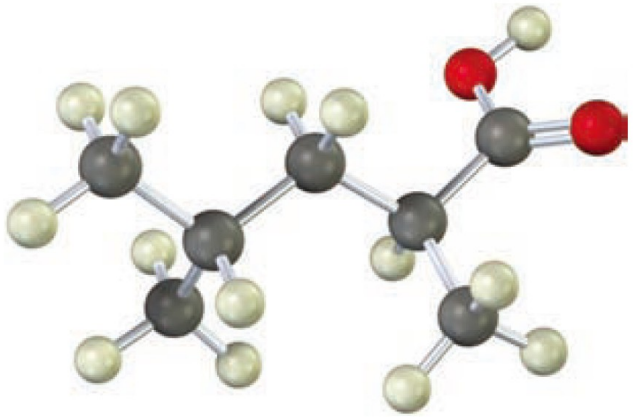


Problem 22.11

Monoalkylated and dialkylated acetic acids can be prepared by the malonic ester synthesis, but trialkylated acetic acids (R_3CCO_2H) can't be prepared. Explain.

Problem 22.12

How could you use a malonic ester synthesis to prepare the following compound?

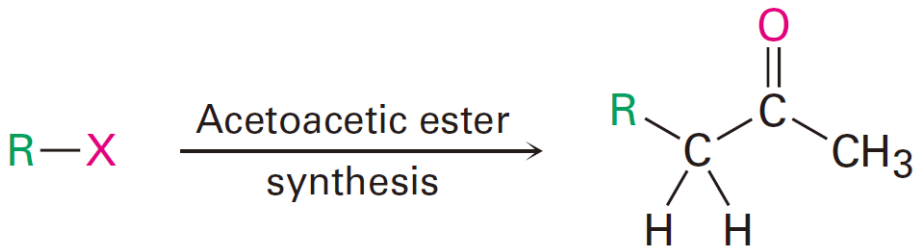


22.7 烯醇负离子的烷基化反应

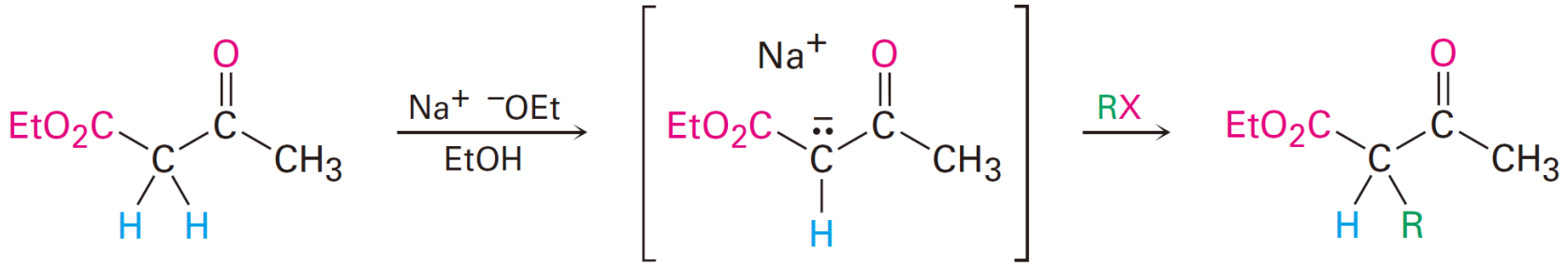
- 乙酰乙酸乙酯的合成应用

The Acetoacetic Ester Synthesis

Just as the malonic ester synthesis converts an alkyl halide into a carboxylic acid, the **acetoacetic ester synthesis** converts an alkyl halide into a methyl ketone having three more carbons.



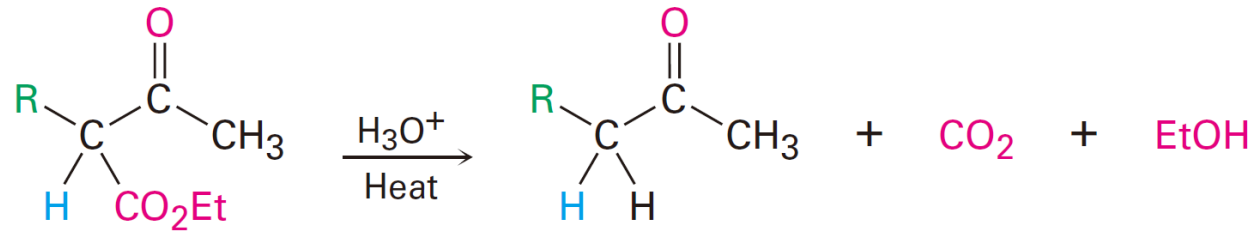
22.7 烯醇负离子的烷基化反应



Ethyl acetoacetate (acetoacetic ester)

Sodio acetoacetic ester

A monoalkylated acetoacetic ester

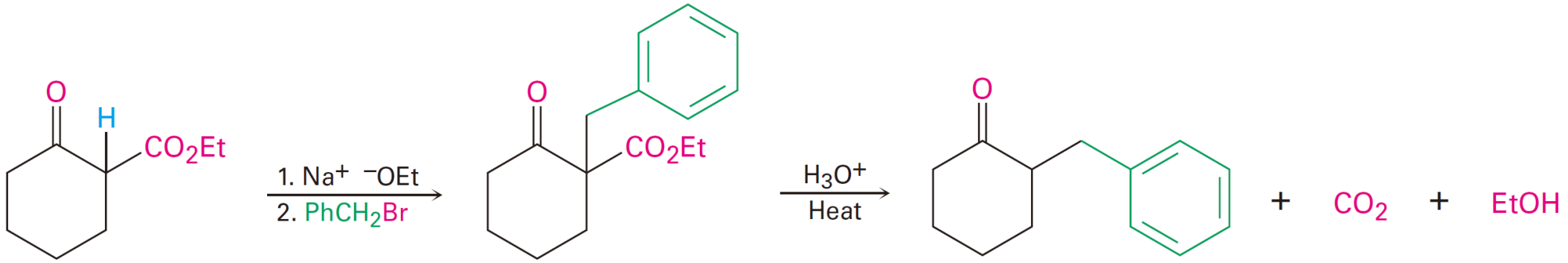


An alkylated acetoacetic ester

A methyl ketone

22.7 烯醇负离子的烷基化反应

- 应用举例



Ethyl 2-oxocyclohexane-carboxylate (a cyclic β-keto ester)

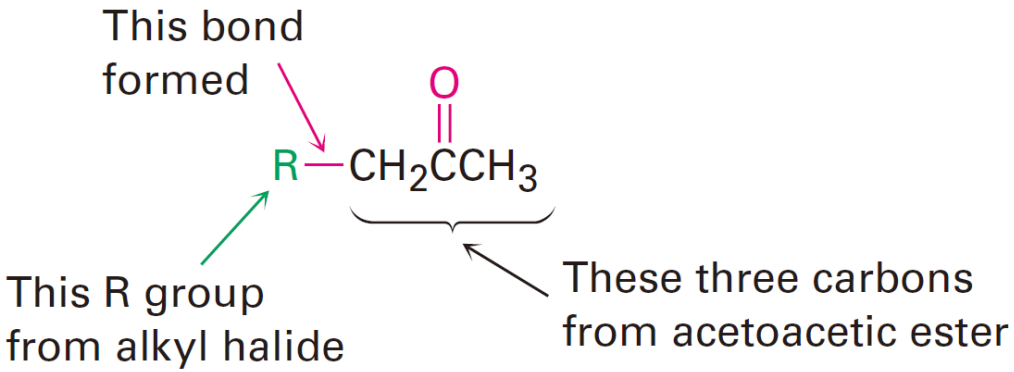
2-Benzylcyclohexanone (77%)

22.7 烯醇负离子的烷基化反应

- 应用举例

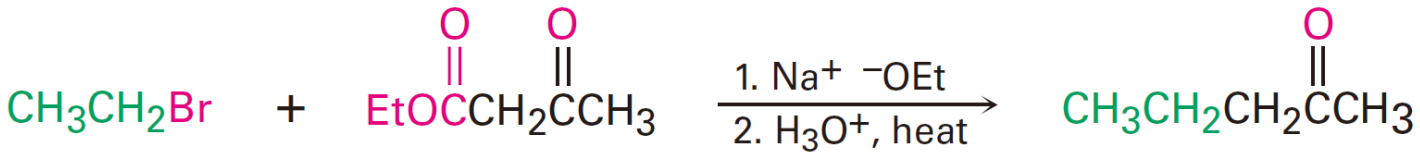
Strategy

The acetoacetic ester synthesis yields a methyl ketone by adding three carbons to an alkyl halide.



Thus, the acetoacetic ester synthesis of 2-pentanone must involve reaction of bromoethane.

Solution



2-Pentanone

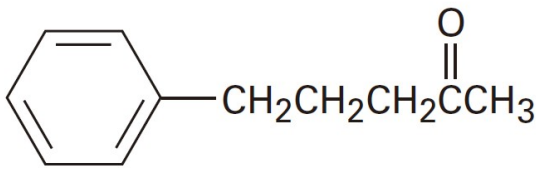
22.7 烯醇负离子的烷基化反应

- 课堂练习

Problem 22.13

What alkyl halides would you use to prepare the following ketones by an acetoacetic ester synthesis?

(a) $CH_3CHCH_2CH_2CCH_3$ (with CH_3 and O)

(b) 

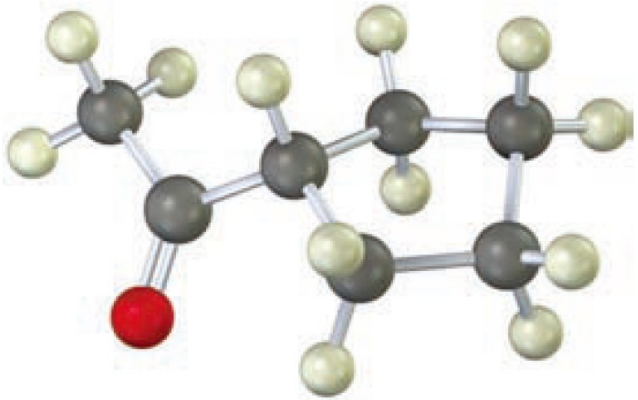
Problem 22.14

Which of the following compounds *cannot* be prepared by an acetoacetic ester synthesis? Explain.

(a) Phenylacetone **(b)** Acetophenone **(c)** 3,3-Dimethyl-2-butanone

Problem 22.15

How would you prepare the following compound using an acetoacetic ester synthesis?

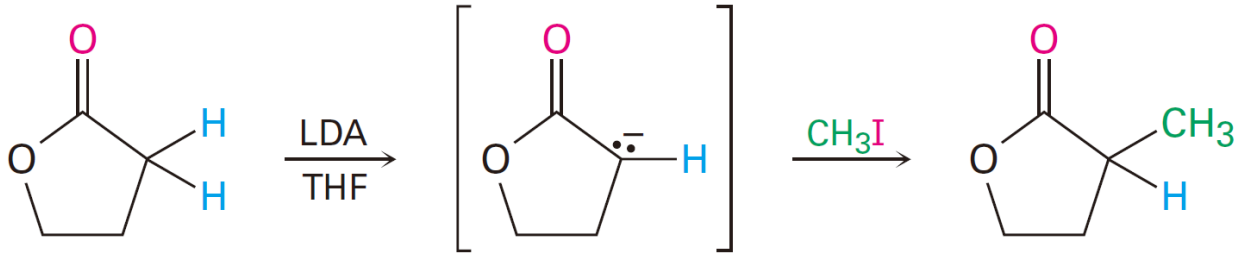


22.7 烯醇负离子的烷基化反应

- 酮，酯和腈的直接 alpha 位烷基化

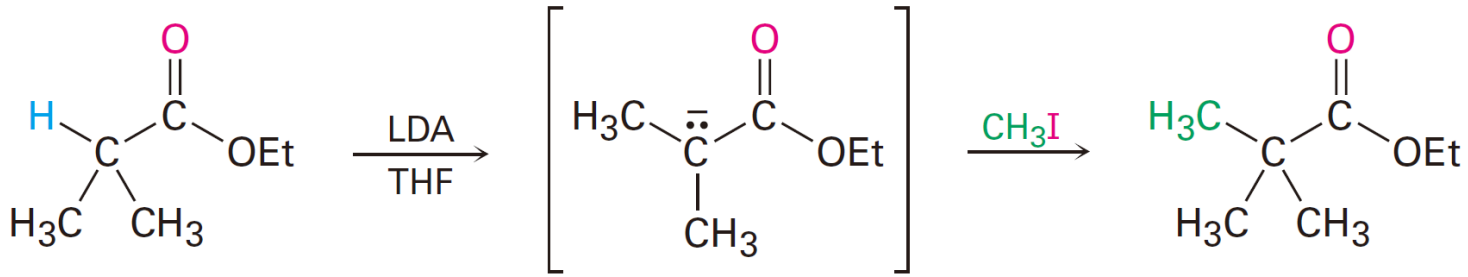
Direct Alkylation of Ketones, Esters, and Nitriles

Lactone



Butyrolactone **2-Methylbutyrolactone (88%)**

Ester

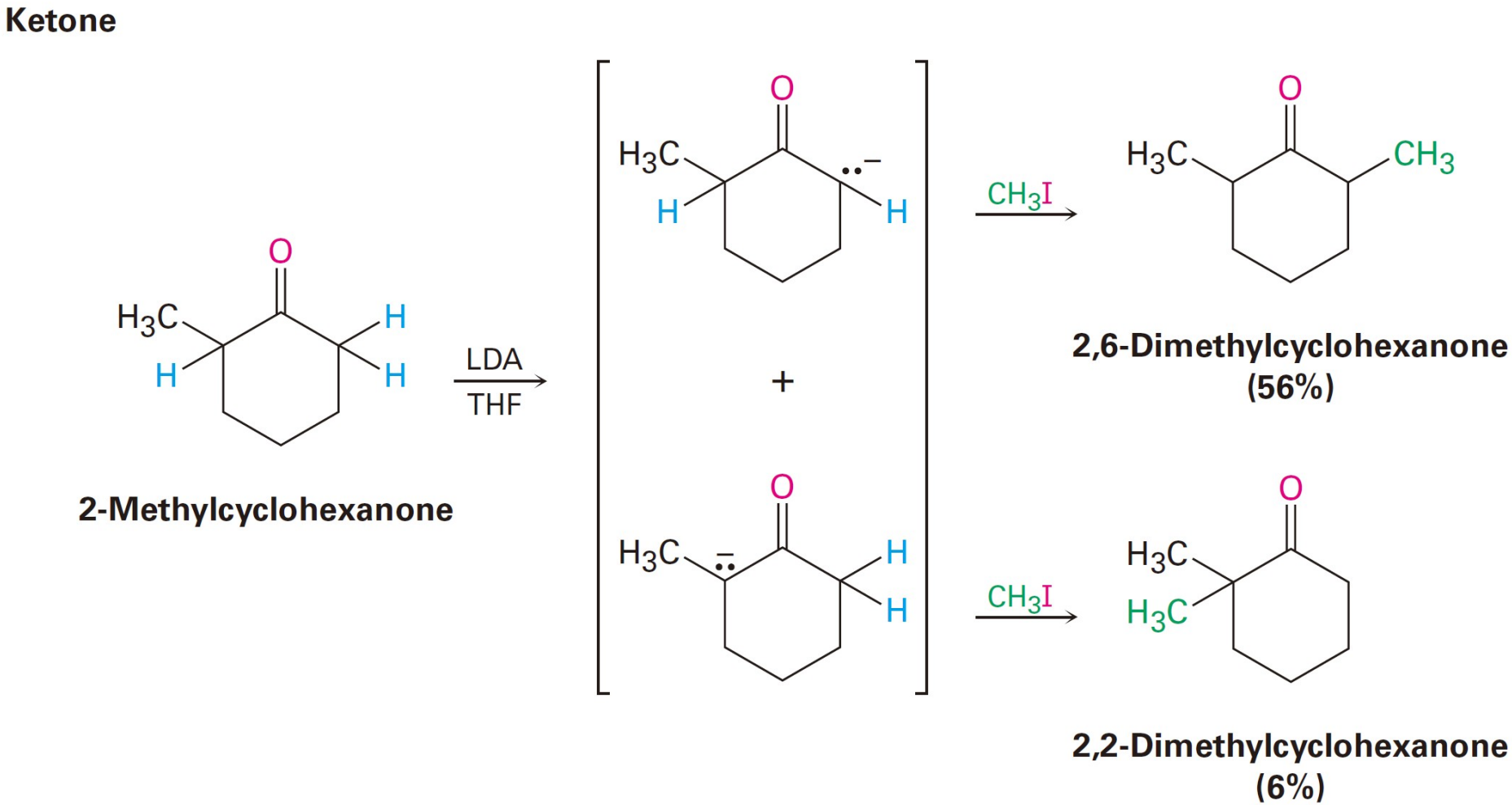


Ethyl 2-methylpropanoate

Ethyl 2,2-dimethylpropanoate (87%)

22.7 烯醇负离子的烷基化反应

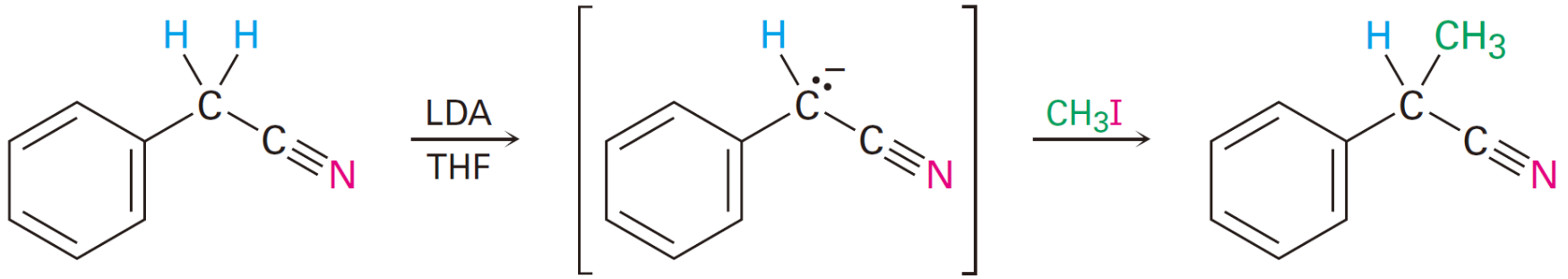
- 酮的 alpha 位烷基化，使用 LDA 作为碱



22.7 烯醇负离子的烷基化反应

- 腈的 alpha 位烷基化，使用 LDA 作为碱

Nitrile



Phenylacetonitrile

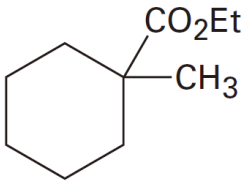
2-Phenylpropane-nitrile (71%)

22.7 烯醇负离子的烷基化反应

- 举例

Using an Alkylation Reaction to Prepare a Substituted Ester

How might you use an alkylation reaction to prepare ethyl 1-methylcyclohexanecarboxylate?

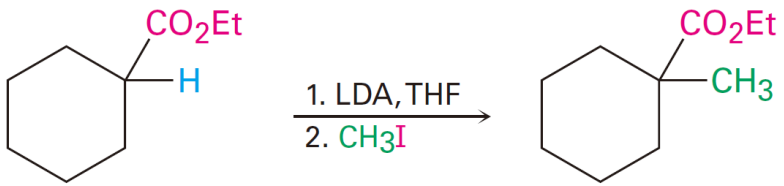


Ethyl 1-methylcyclohexanecarboxylate

Strategy

An alkylation reaction is used to introduce a methyl or primary alkyl group onto the α position of a ketone, ester, or nitrile by S_N2 reaction of an enolate ion with an alkyl halide. Thus, we need to look at the target molecule and identify any methyl or primary alkyl groups attached to an α carbon. In the present instance, the target has an α methyl group, which might be introduced by alkylation of an ester enolate ion with iodomethane.

Solution



Ethyl cyclohexane-carboxylate

Ethyl 1-methylcyclo-hexanecarboxylate

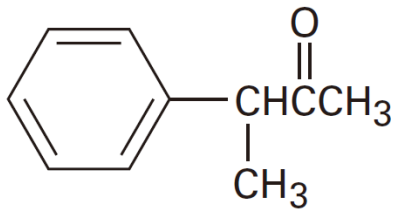
22.7 烯醇负离子的烷基化反应

- 练习

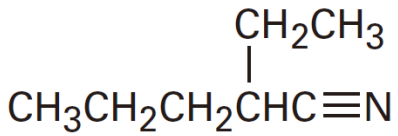
Problem 22.16

Show how you might prepare the following compounds using an alkylation reaction as the key step:

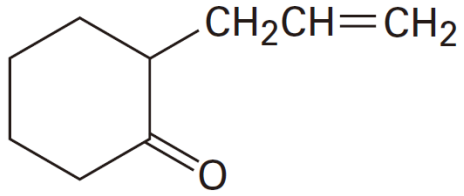
(a)



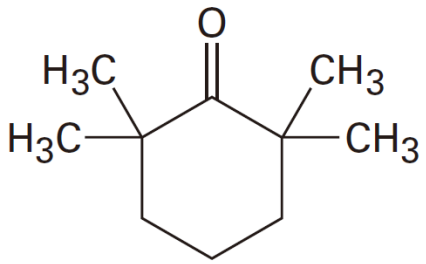
(b)



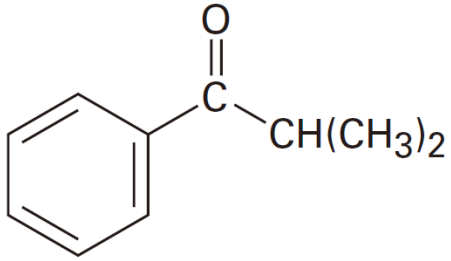
(c)



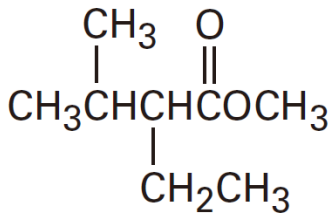
(d)



(e)



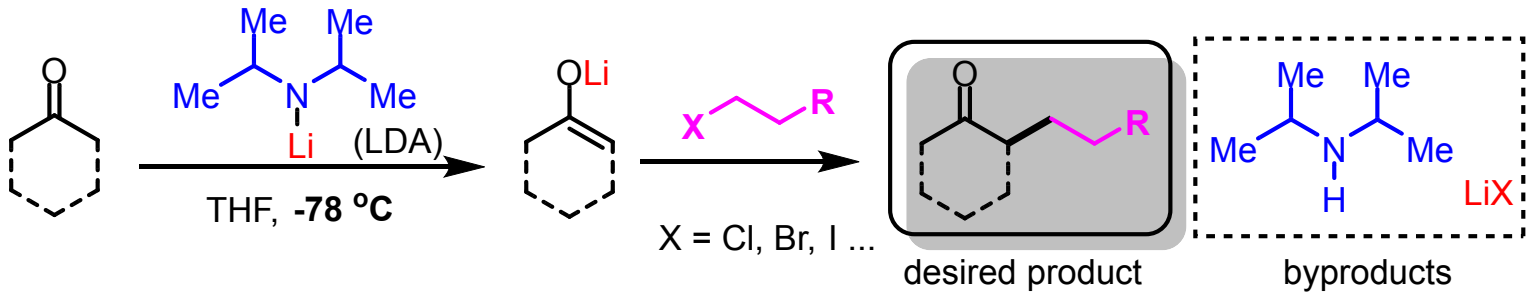
(f)



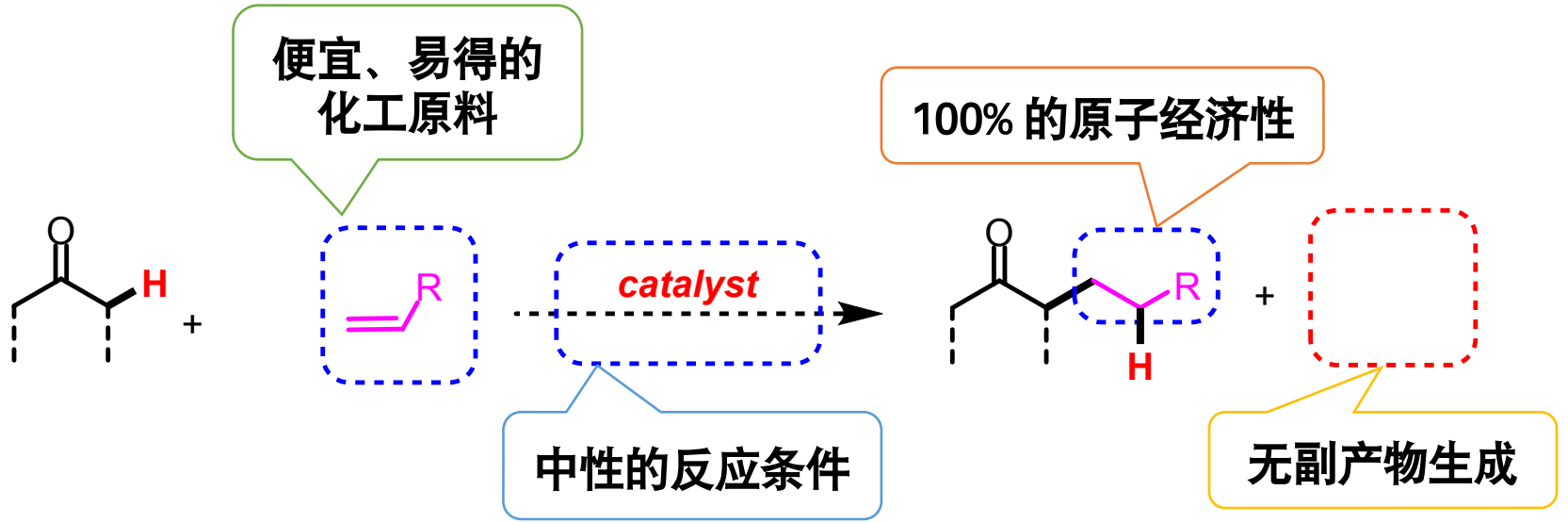
作业

- 22.25, 22.29, 22.31, 22.36, 22.47, 22.50, 22.54

传统方法的一些局限性

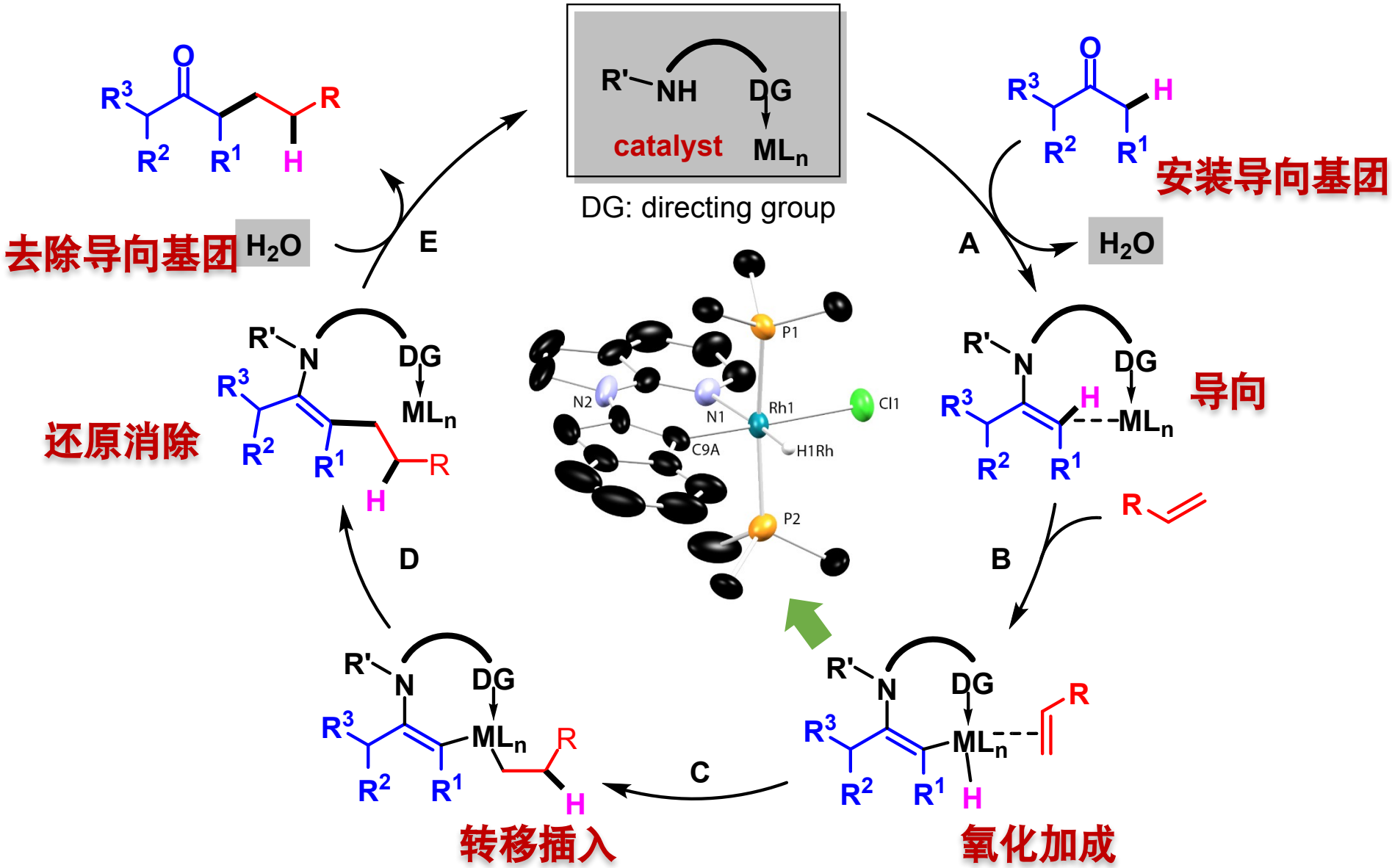


- 低温——能耗
- 强碱——底物适用性
- 卤代烃的使用——环境不友好
- 副产物——原子经济性差

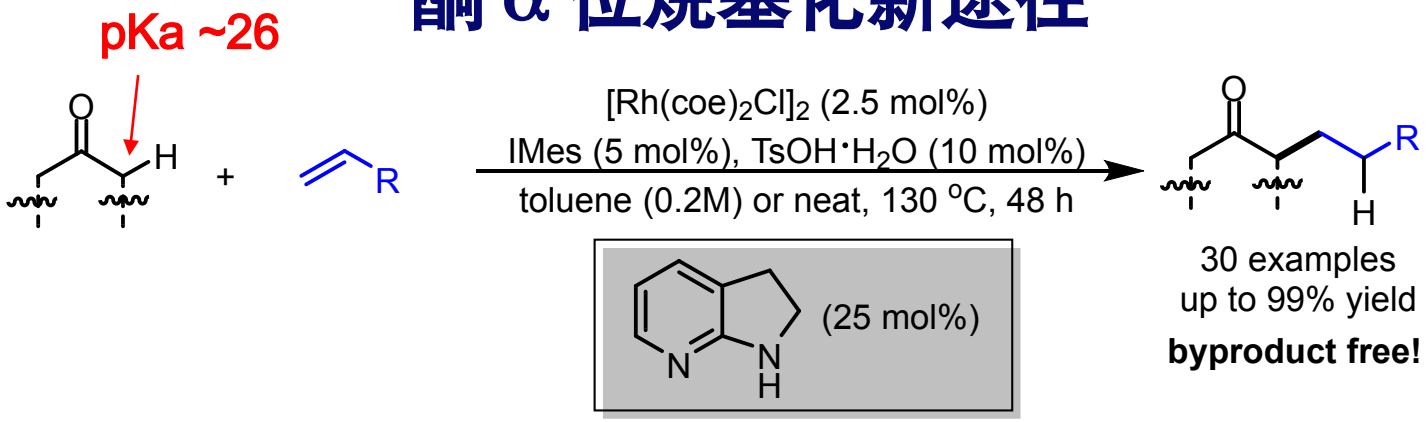


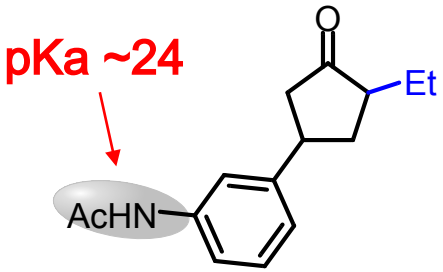
$H_2C{=}CH_2$	\$1/kg	**\$0.028/mol**
	VS	
ICH_2CH_3	\$280/kg	\$43.7/mol
$BrCH_2CH_3$	\$55/kg	\$6.0/mol

反应过程设计——机理

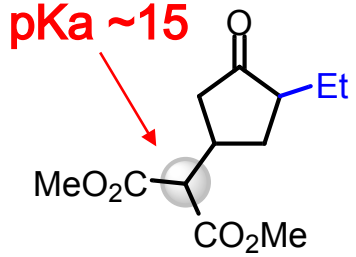

R'
NH
DG
catalyst
ML_n
DG: directing group
安装导向基团
H_2O
A
导向
B
氧化加成
C
转移插入
D
还原消除
E
去除导向基团
H_2O
P1
P2
Rh1
Cl1
N1
N2
C9A
H1Rh

酮 α 位烷基化新途径

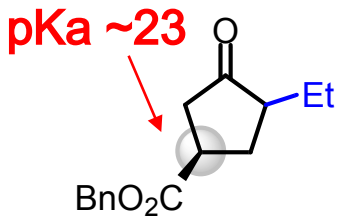




84%, 1.9:1 dr

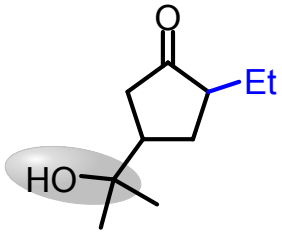


87%, 1.9:1 dr

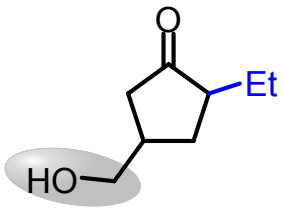


90%, 1.3:1 dr

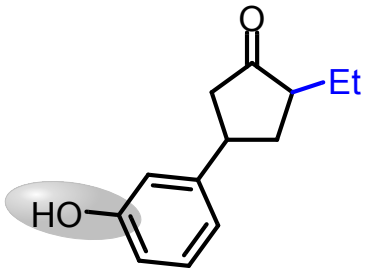
具有竞争性反应位点的底物



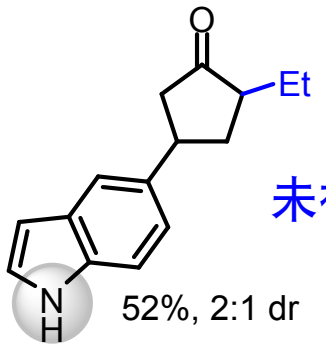
88%, 2.1:1 dr



95%, 1.6:1 dr



65%, 2:1 dr



52%, 2:1 dr

未被保护的醇、酚和吲哚

Mo, Fanyang.; Dong, Guangbin.* *Science* **2014**, *345*, 68.
http://www.sciencemag.org/content/345/6192/68.abstract