Chapter 5

Electrophilic Substitution

芳香亲电取代反应

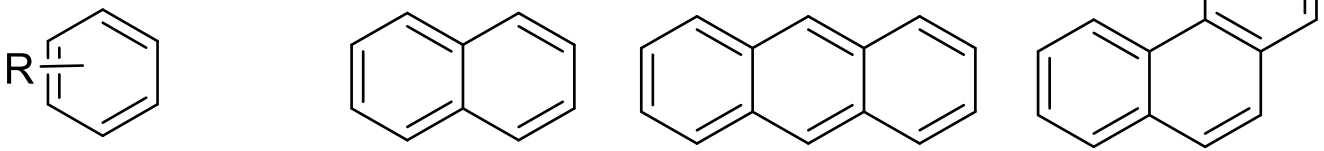
Qiong Li

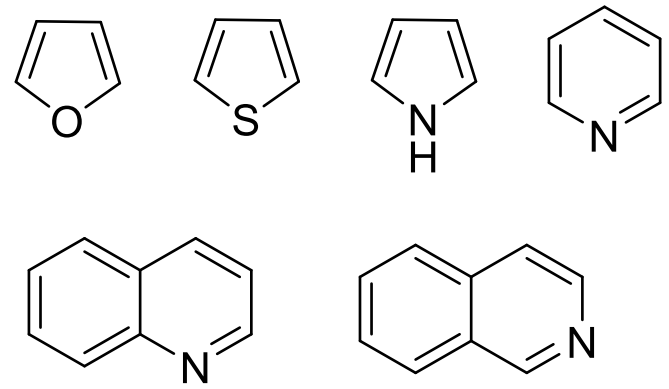
May 13, 2024

Chapter 5 Electrophilic Substitution

Part 1

Electrophilic Aromatic Substitution





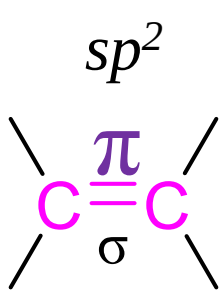
Part 2

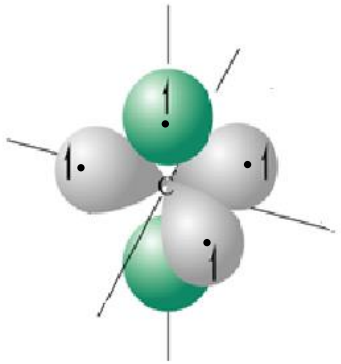
Electrophilic Substitution on α-Carbon of Carbonyl Groups

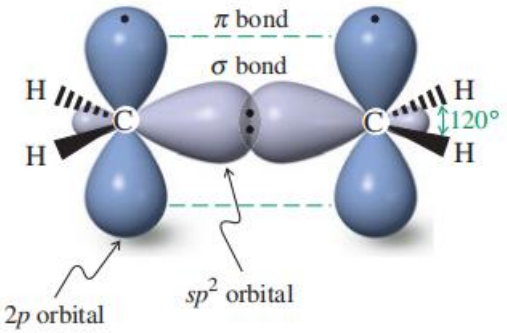
Part 1: Electrophilic Aromatic Substitution

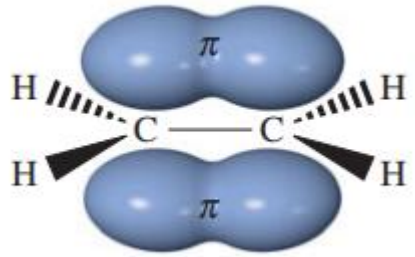
Alkene π bonds are relatively weak

π-键弱；可极化性强，宜参与反应

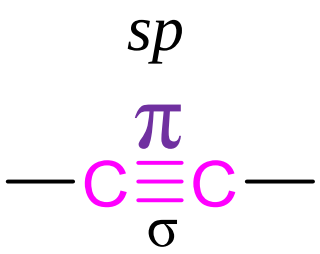


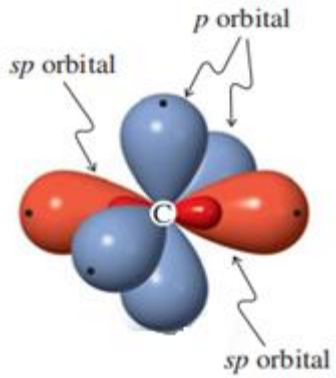


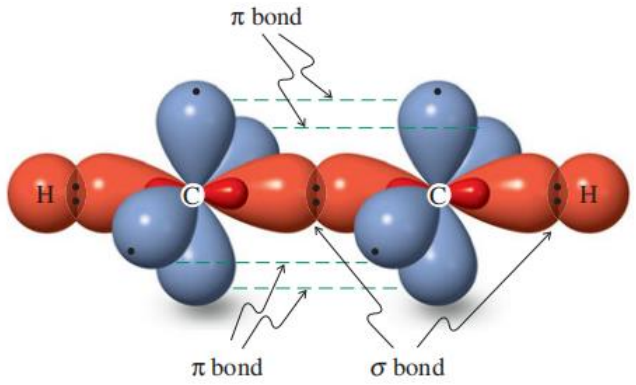


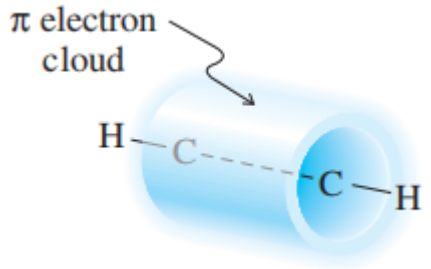


As with alkenes, alkyne π bonds are much weaker than the σ bonds

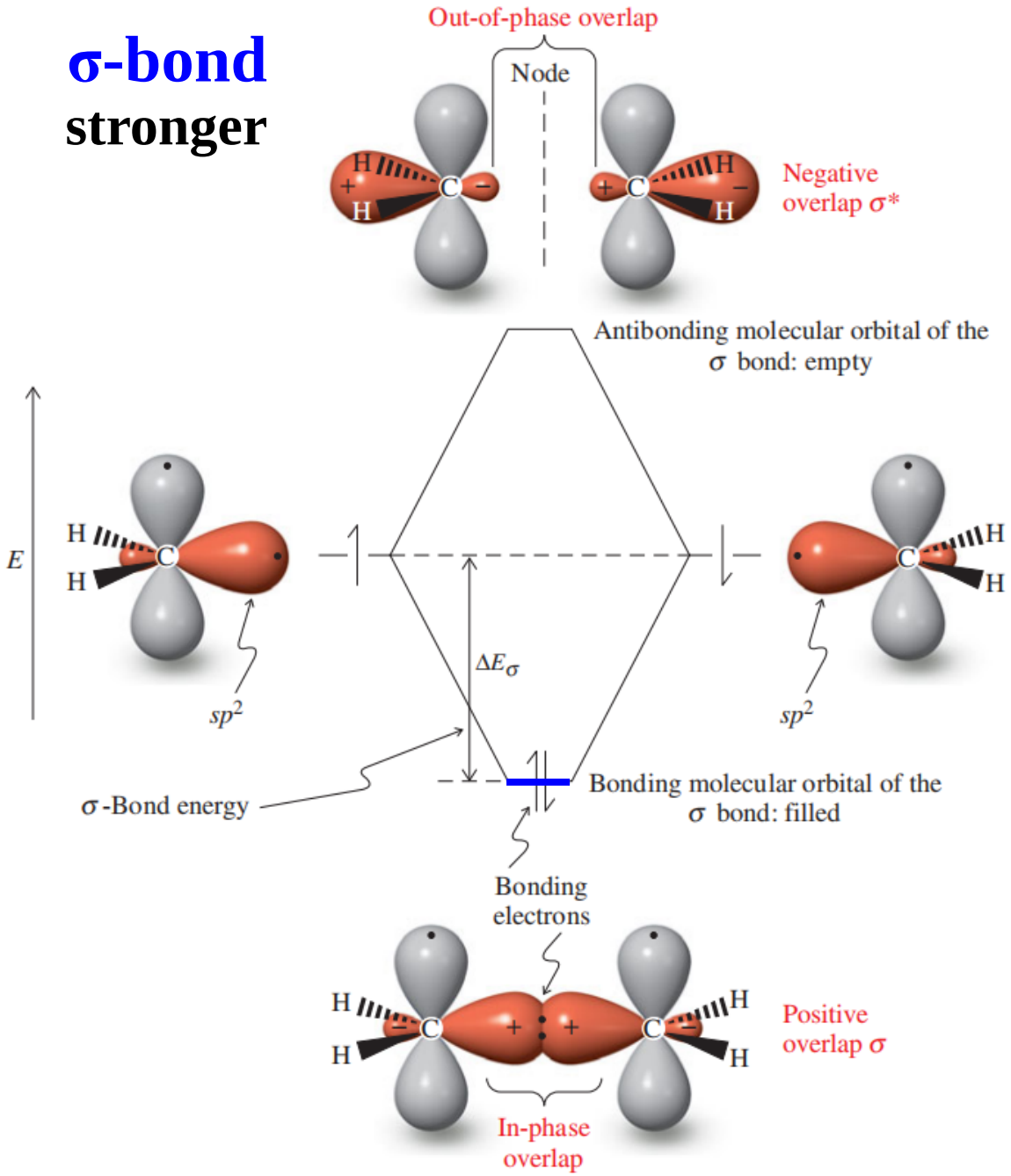




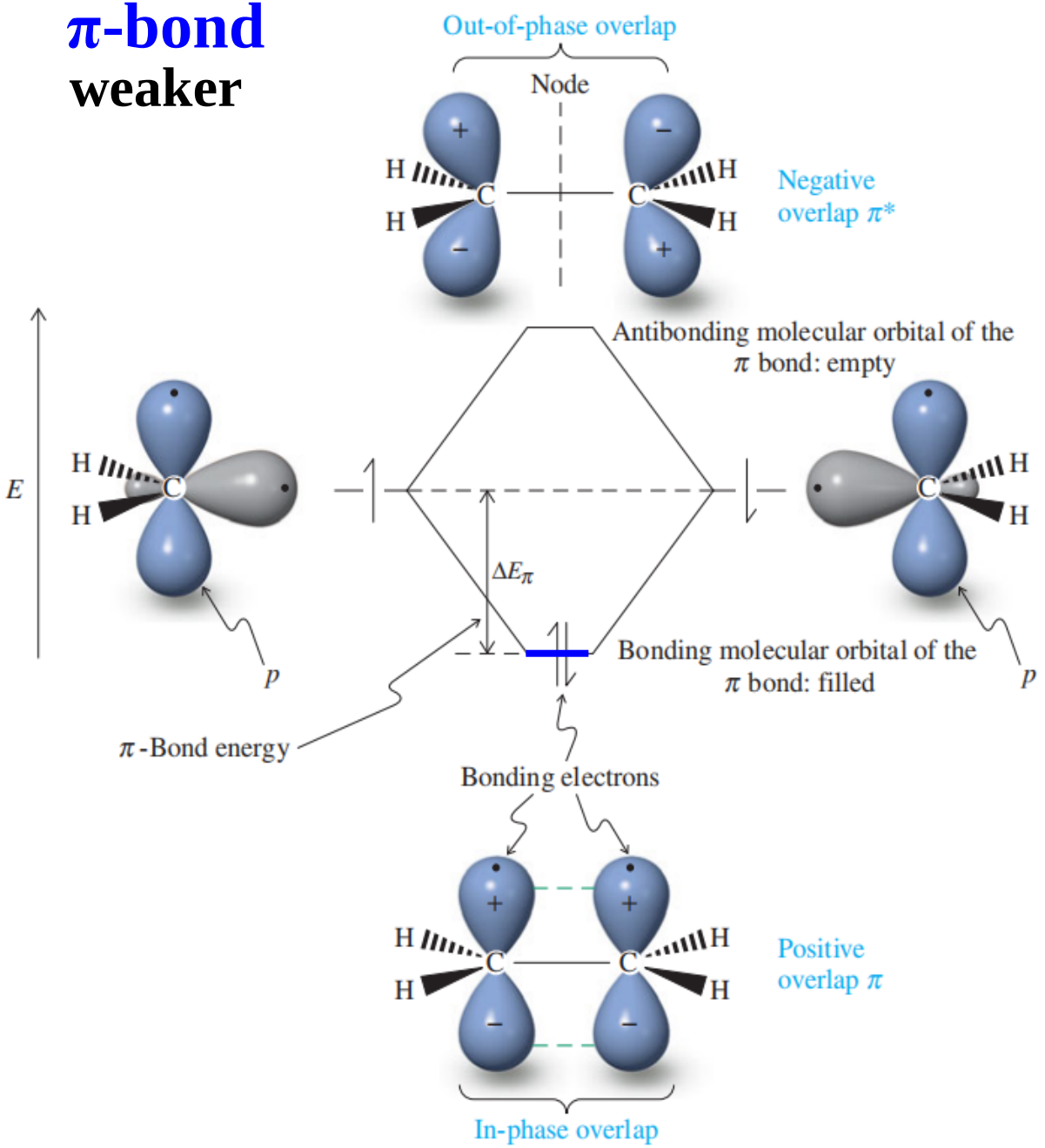




σ-bond
stronger



π-bond
weaker

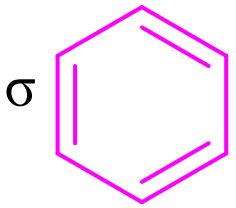


Part 1: Electrophilic Aromatic Substitution

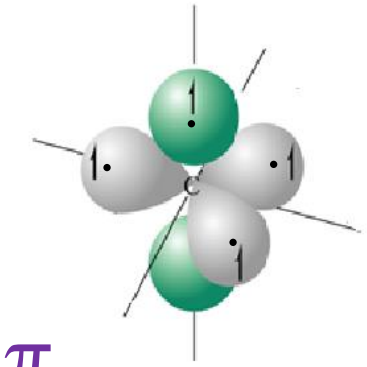
benzene π bond is especially stable

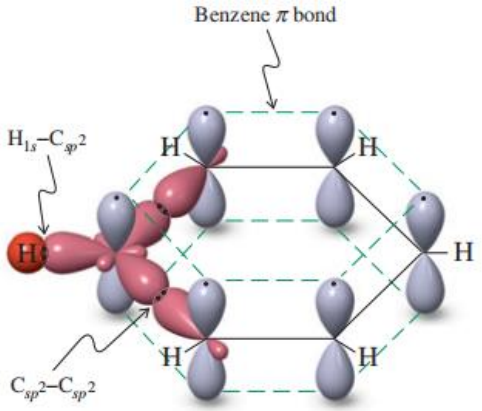
sp^2

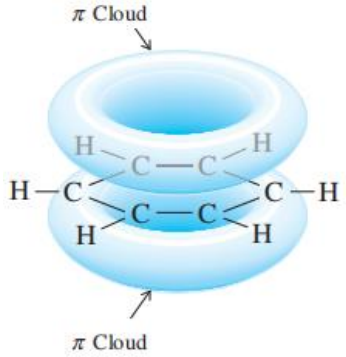
σ

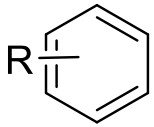


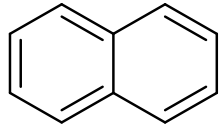
benzene π

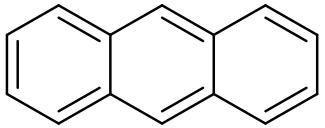


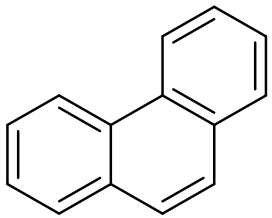


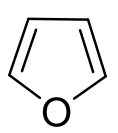


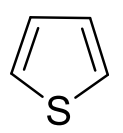


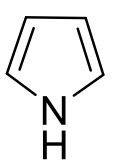


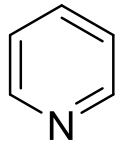


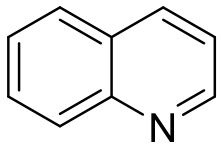


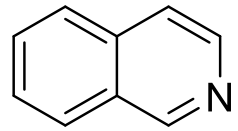






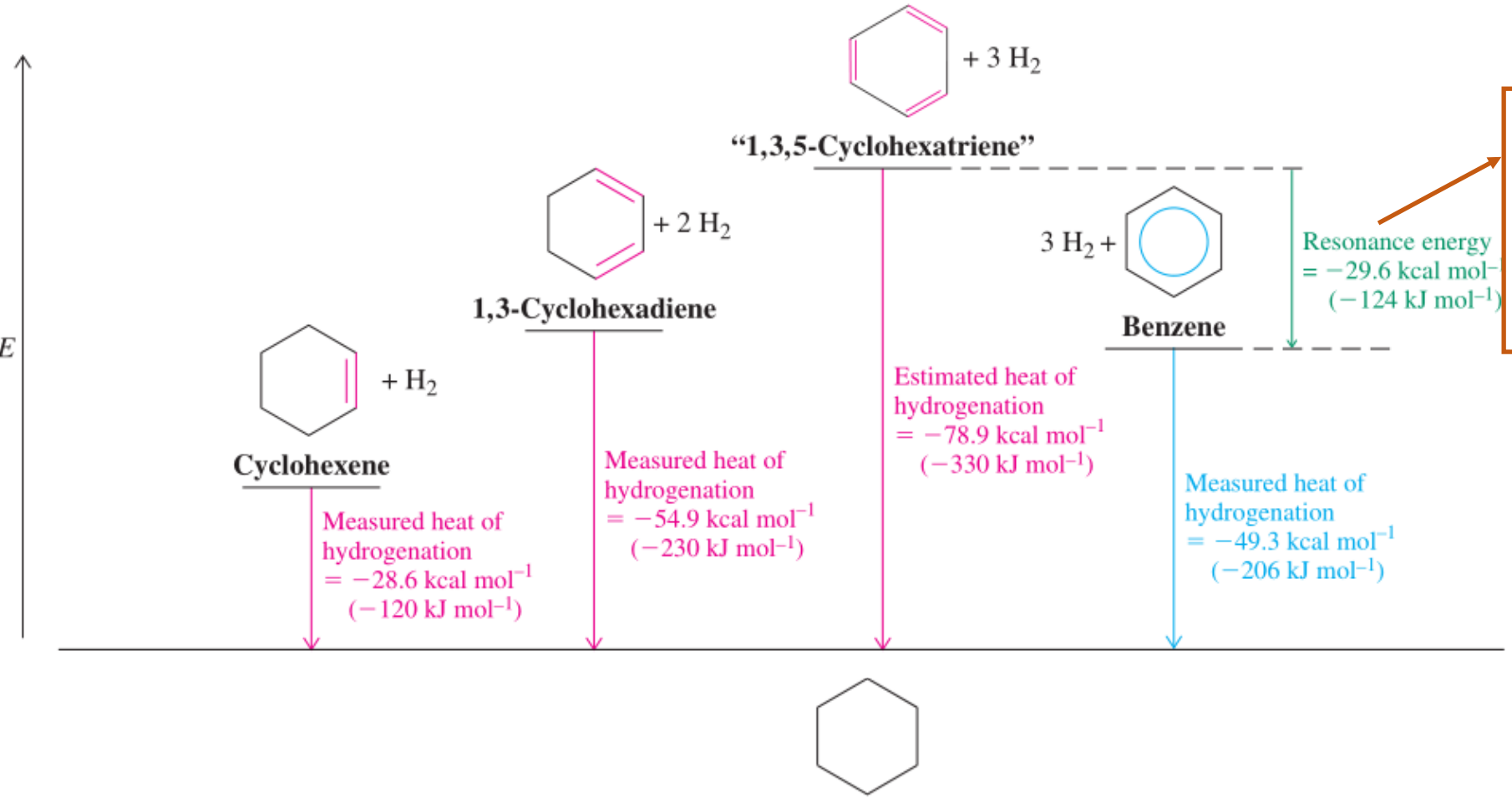






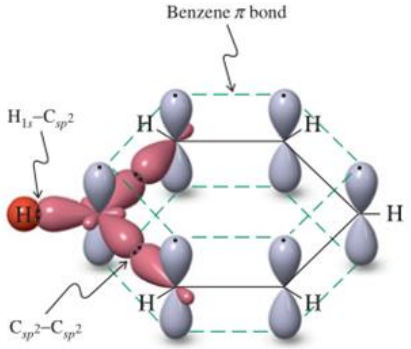
Part 1: Electrophilic Aromatic Substitution

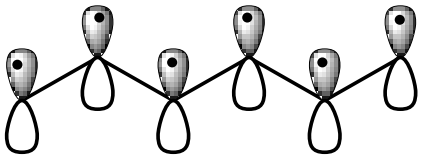
Benzene is especially stable: heats of hydrogenation

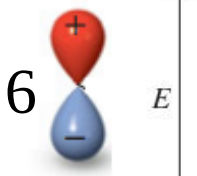


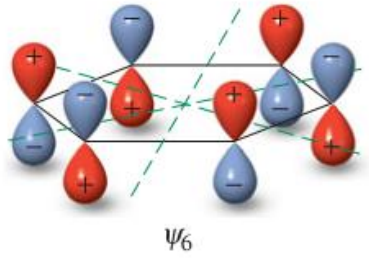
The difference is the resonance energy of benzene. Other terms used to describe this quantity are delocalization energy, or simply the aromaticity of benzene.

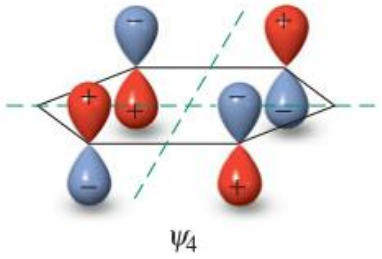
π Molecular Orbitals of Benzene

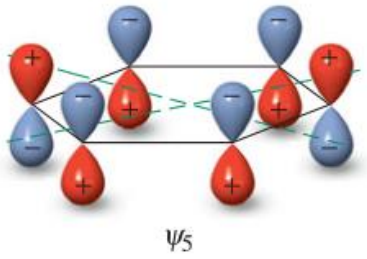


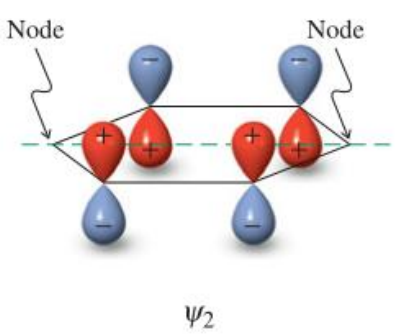


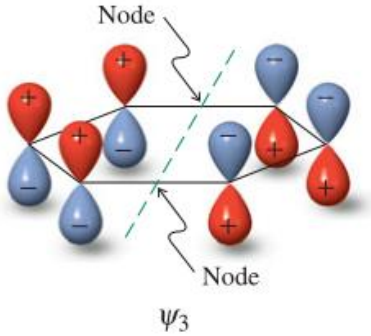


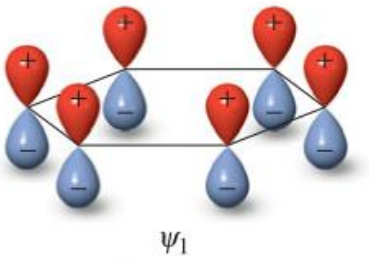




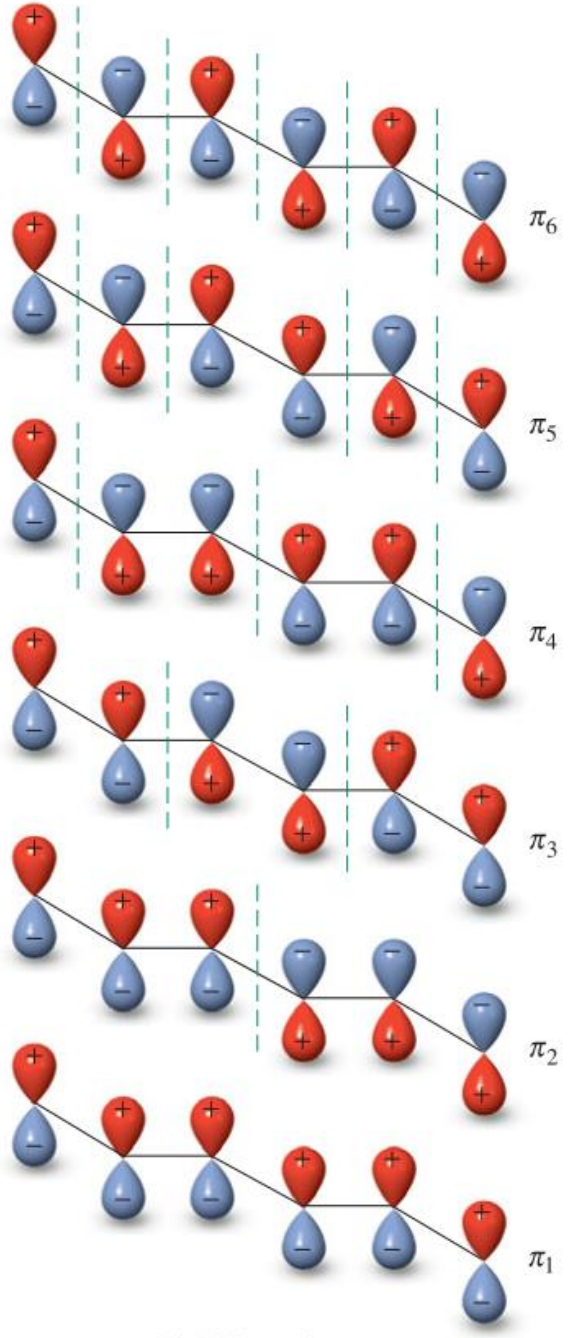






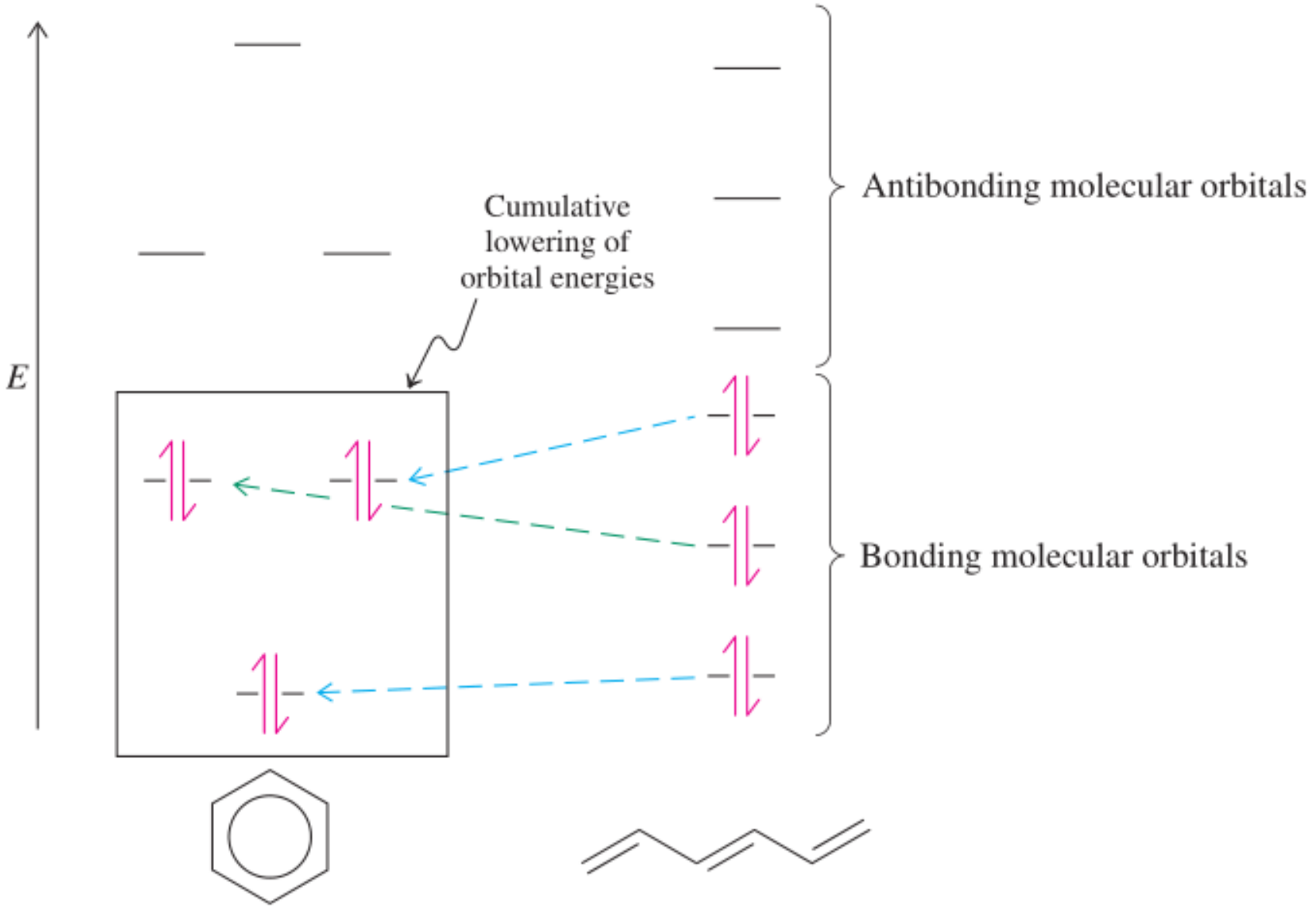


Benzene



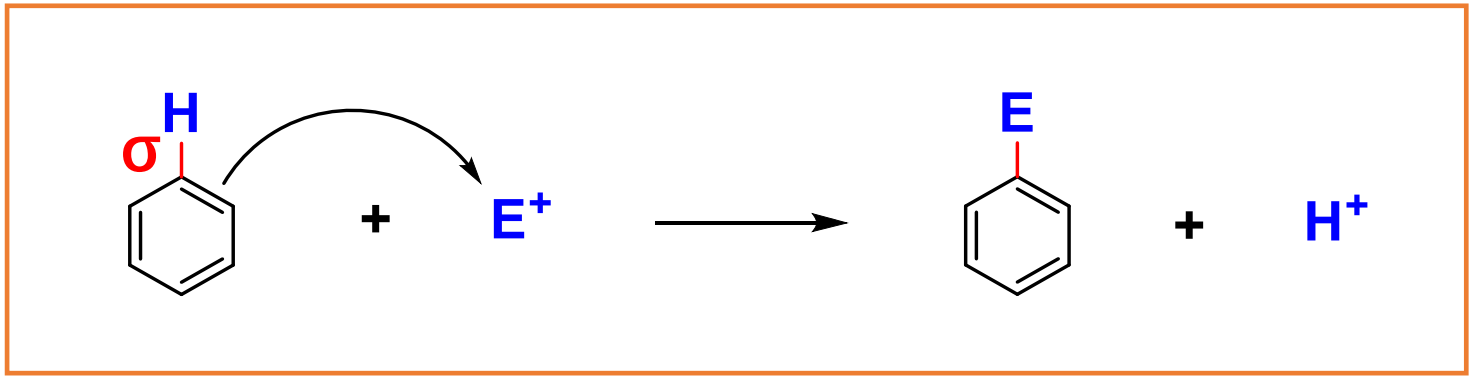
1,3,5-Hexatriene

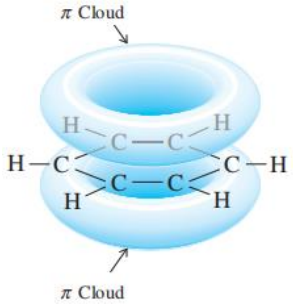
Part 1: Electrophilic Aromatic Substitution

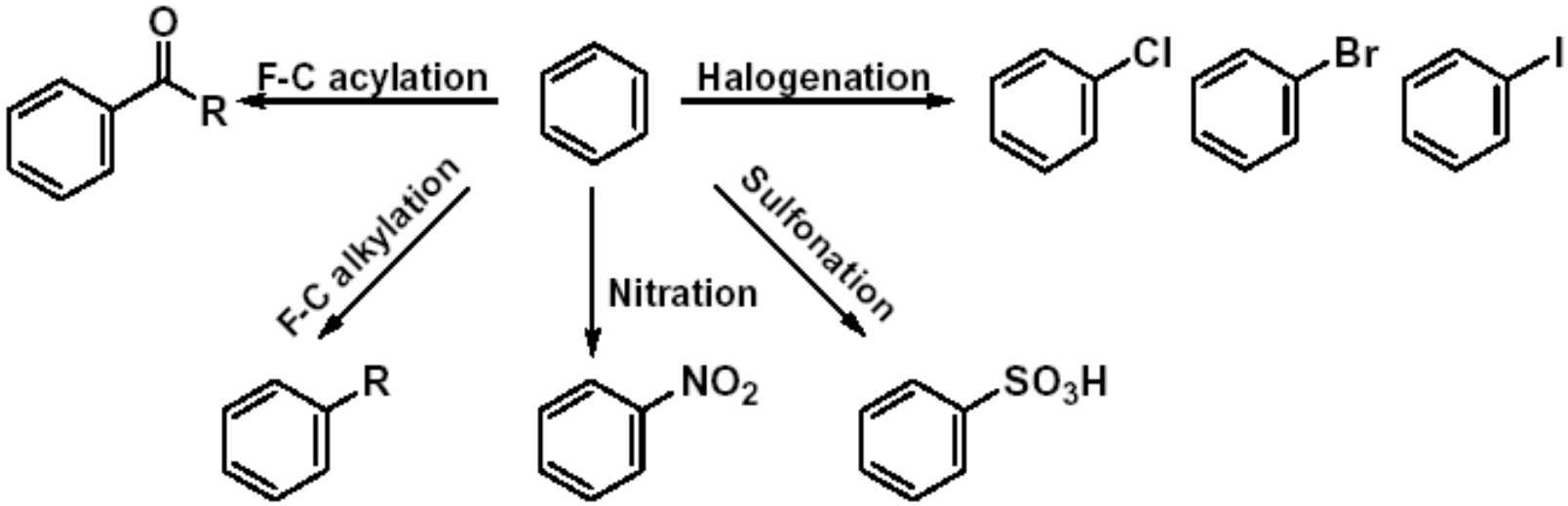


Part 1: Electrophilic Aromatic Substitution

5.1 General Equation of S_E Ar





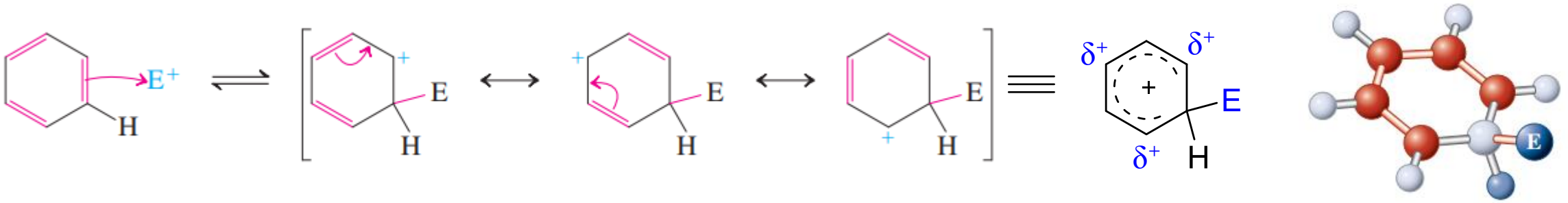


Part 1: Electrophilic Aromatic Substitution

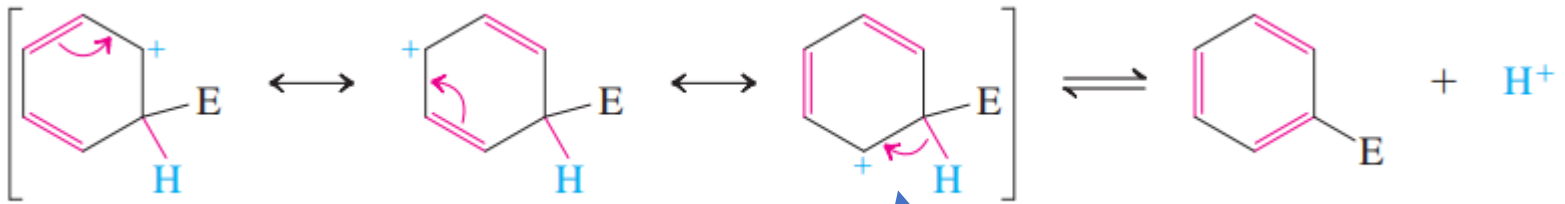
5.2 Mechanism of Electrophilic Aromatic Substitution

S_EAr in benzene proceeds by addition of the electrophile followed by proton loss

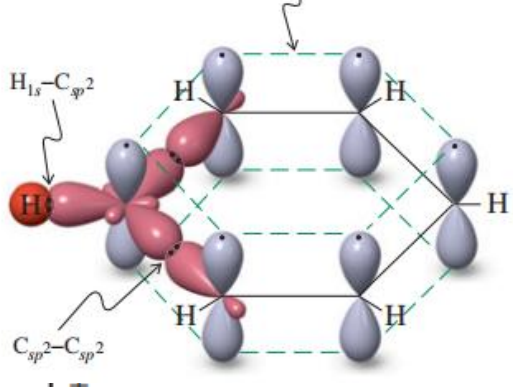
Step 1. Electrophilic attack This step in the mechanism is not favored thermodynamically

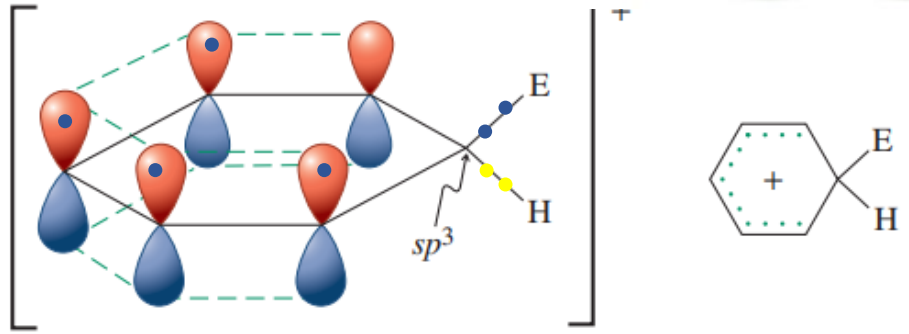


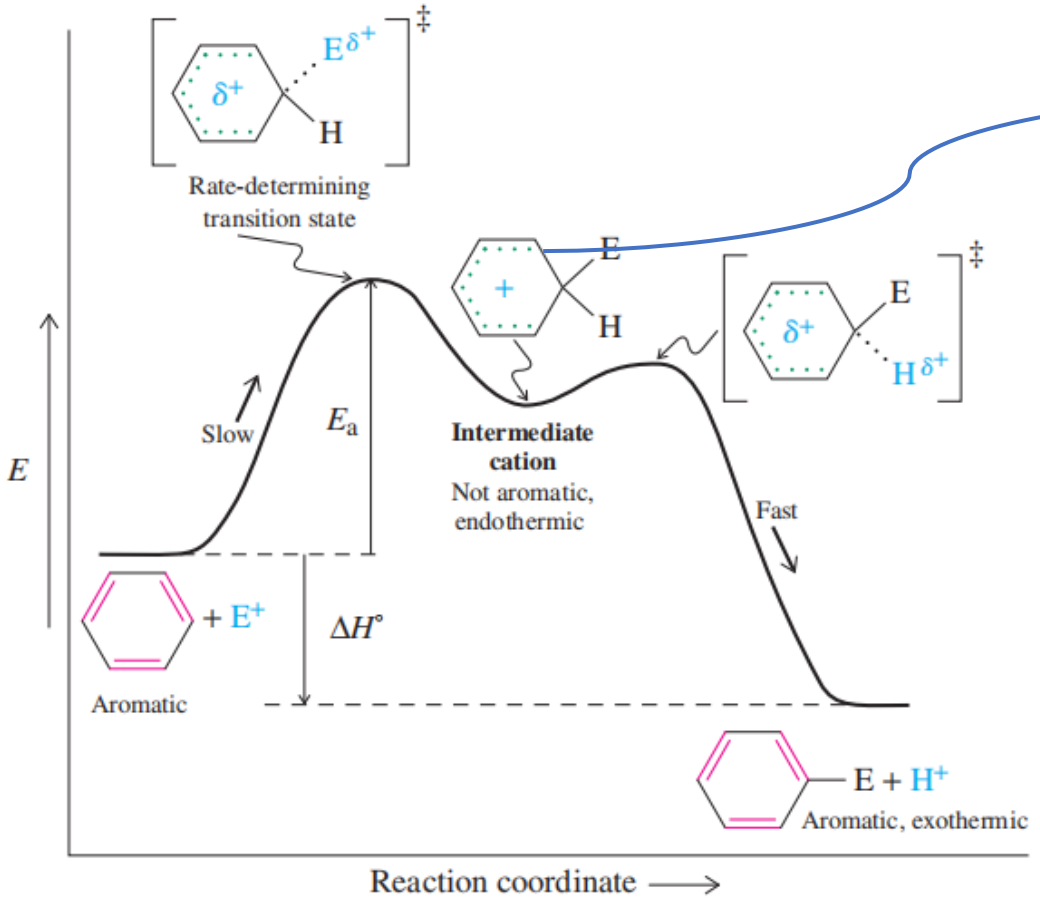
Step 2. Proton loss The loss of proton leads to the aromatic product



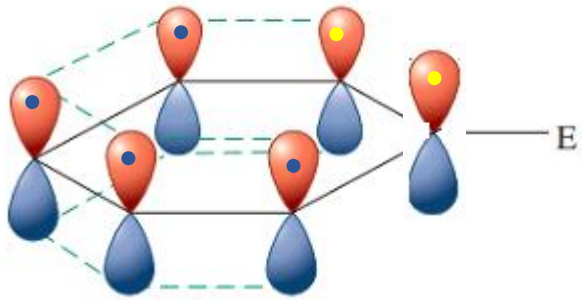
Part 1: Electrophilic Aromatic Substitution



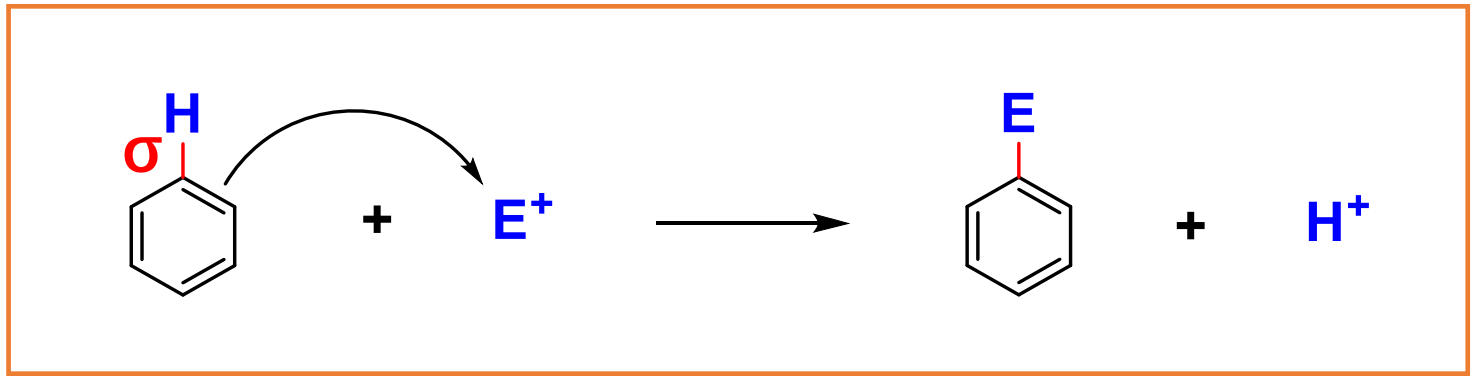


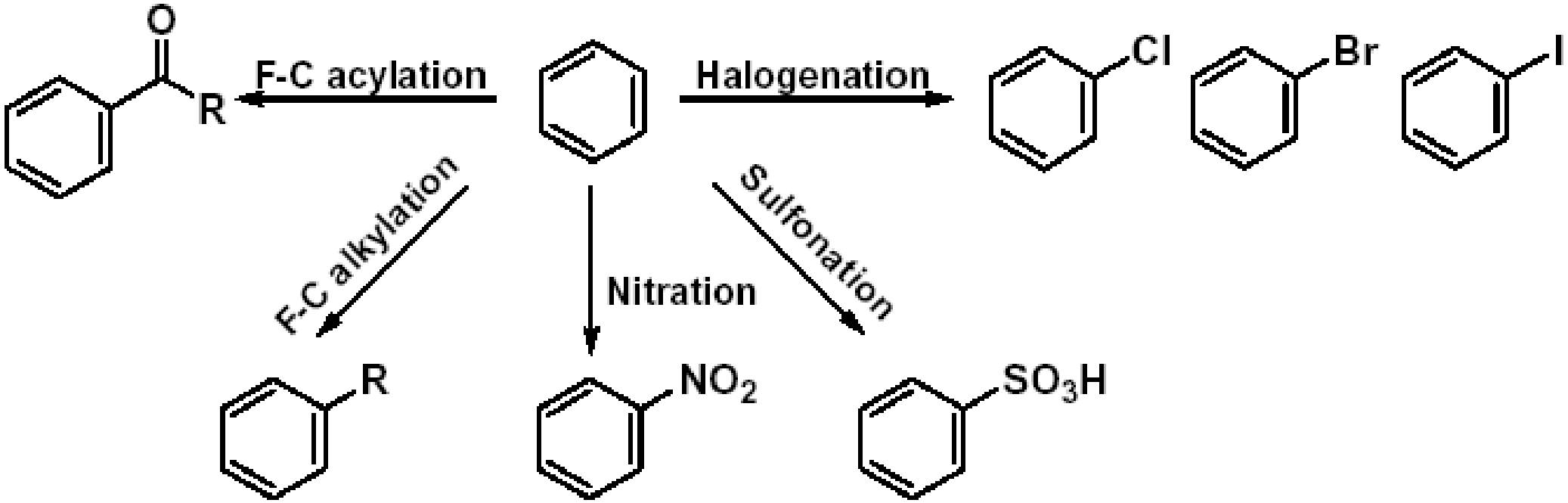


The first transition state is rate determining.
Proton loss is relatively fast.
The overall rate of the reaction is controlled by *E*a
the amount of exothermic energy released is given by ΔH



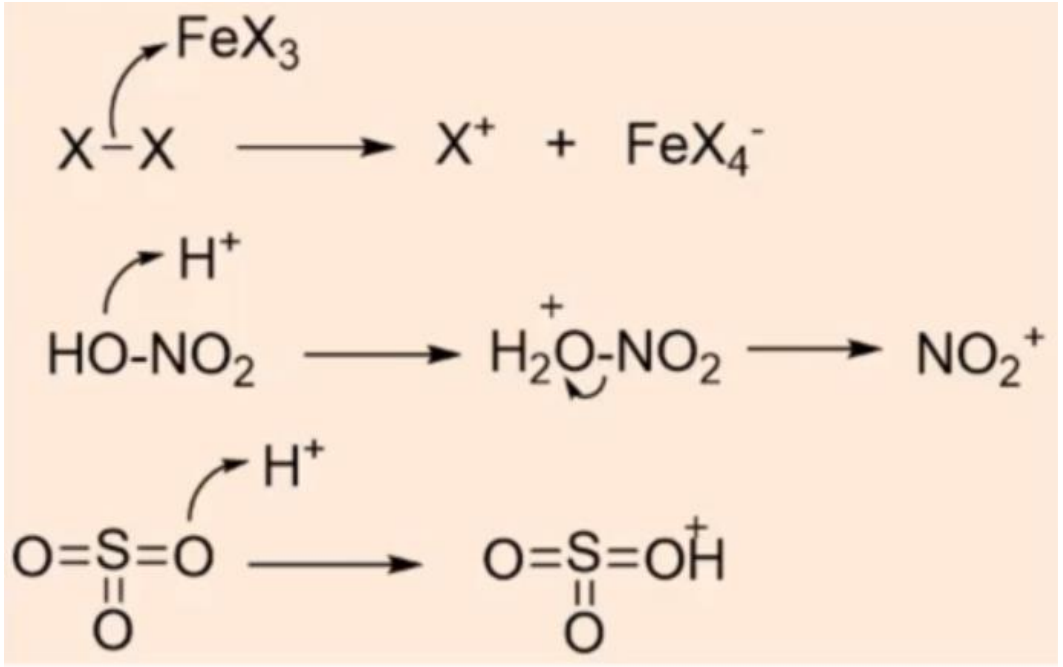
Part 1: Electrophilic Aromatic Substitution



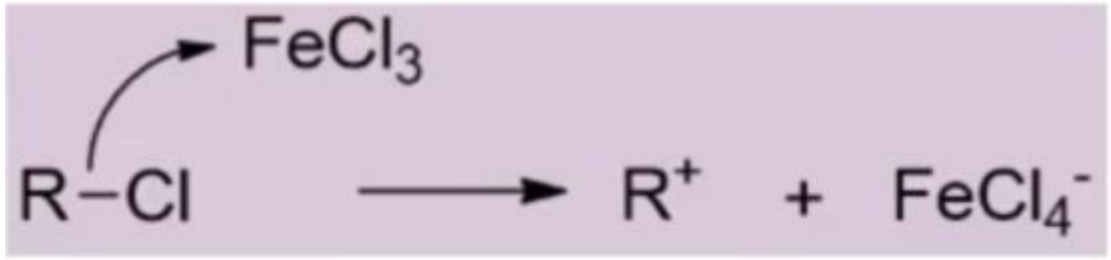


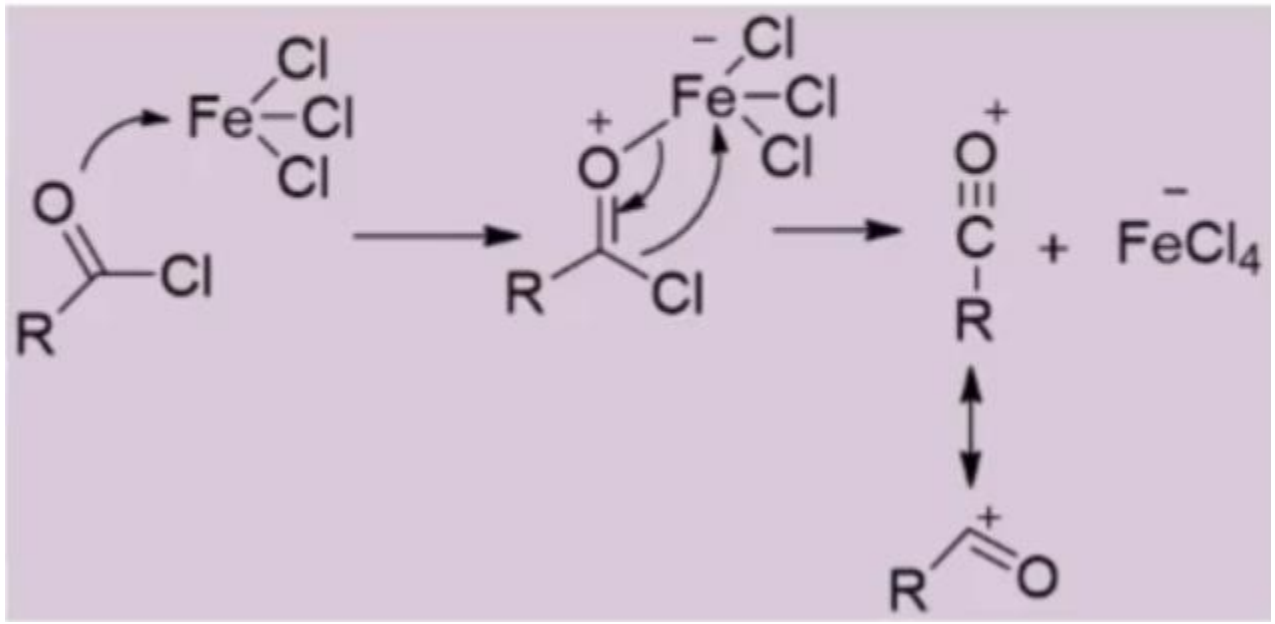
Part 1: Electrophilic Aromatic Substitution

Formation of heteroatomic electrophiles



Formation of carbon electrophiles

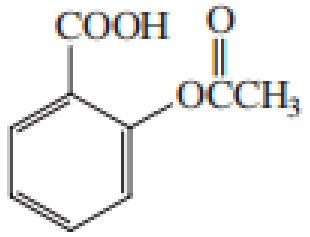




Part 1: Electrophilic Aromatic Substitution

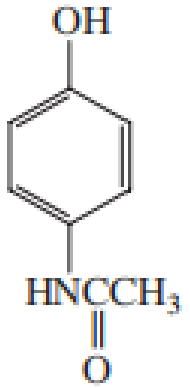
5.3 Orientation

Substituents Control Regioselectivity



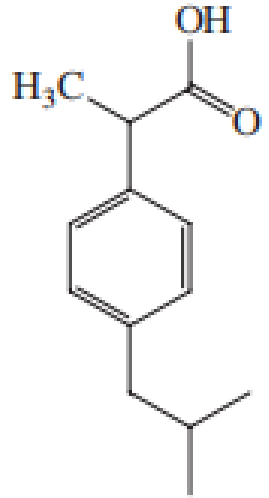
2-Acetyloxybenzoic acid
(Aspirin)

Aspirin



N-(4-Hydroxyphenyl)acetamide
(Acetaminophen)

Tylenol

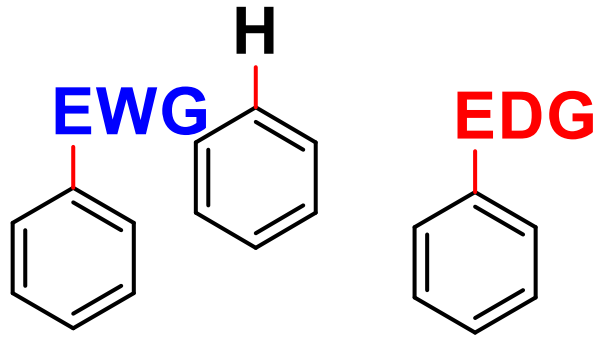


2-[4-(2-Methylpropyl)-
phenyl]propanoic acid
(Ibuprofen)

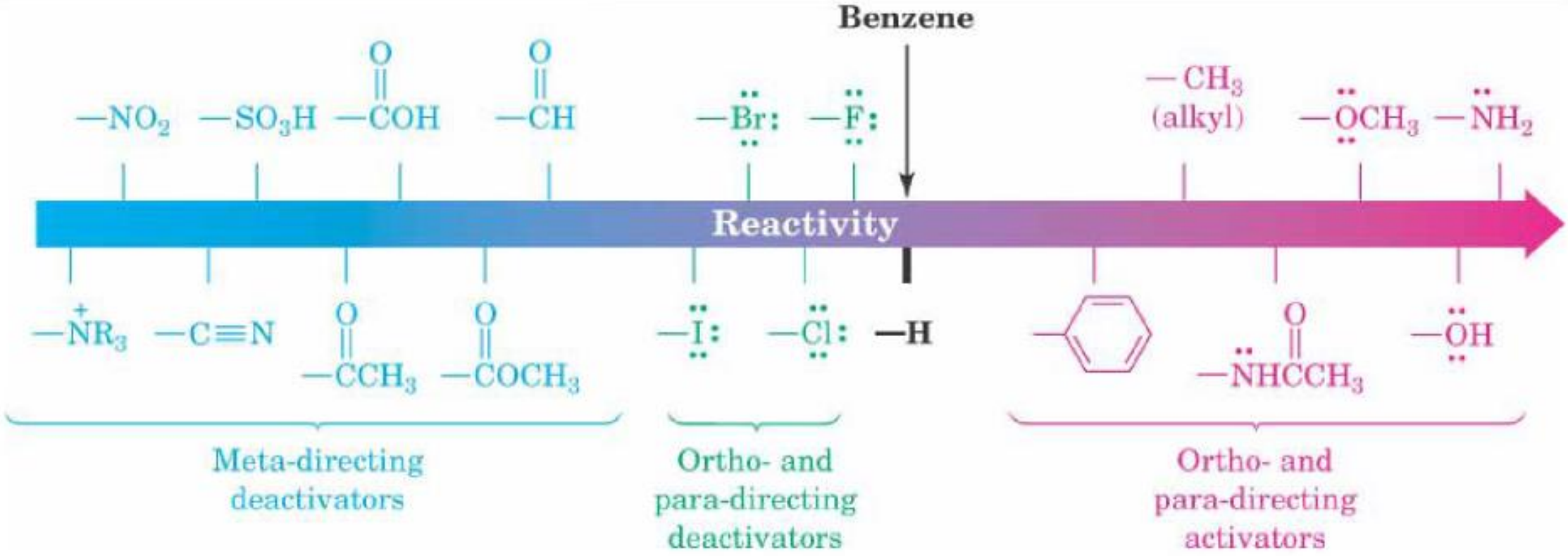
Advil

Part 1: Electrophilic Aromatic Substitution

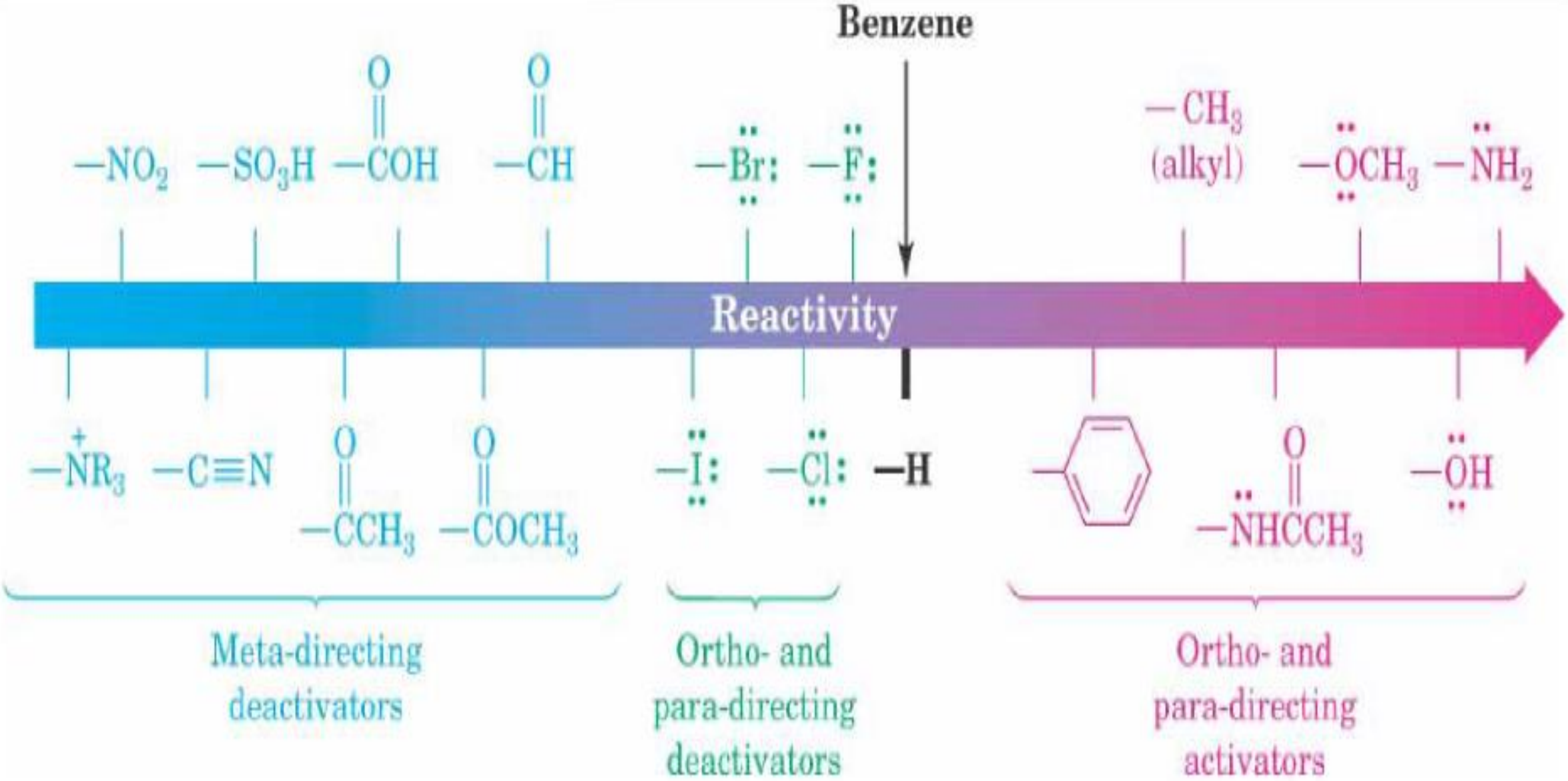
5.3.1 Reactivity



Classification



Part 1: Electrophilic Aromatic Substitution

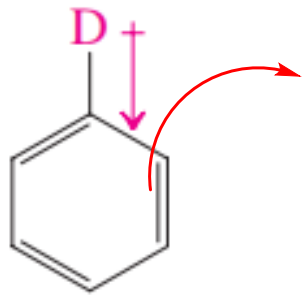


Part 1: Electrophilic Aromatic Substitution

5.3.1 Activation or Deactivation by Substituents on a Benzene Ring

Inductive Effects of Some Substituents on the Benzene Ring

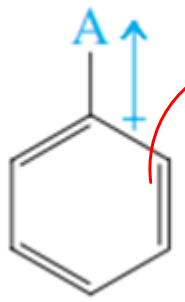
Donors D



E^+ (electrophile)

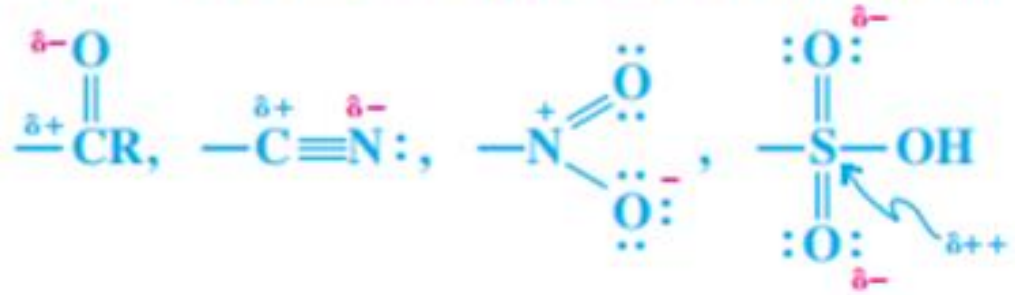
D = $-CH_3$, other alkyl groups

Acceptors A



E^+ (electrophile)

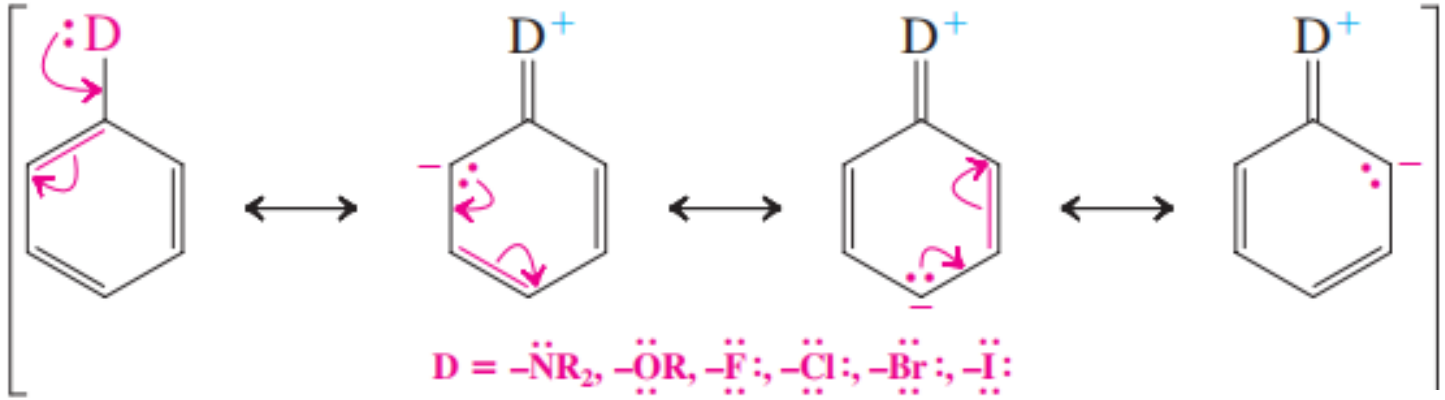
A = $-CF_3$, $-NR_2$, $-OR$, $-X$ ($-F$, $-Cl$, $-Br$, $-I$),



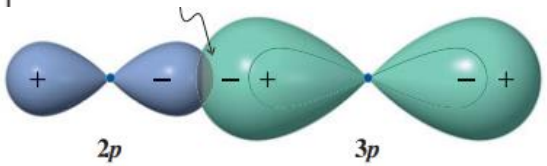
Part 1: Electrophilic Aromatic Substitution

Resonance Donation to Benzene

Resonance donors bear at least one electron pair capable of delocalization into the benzene ring.



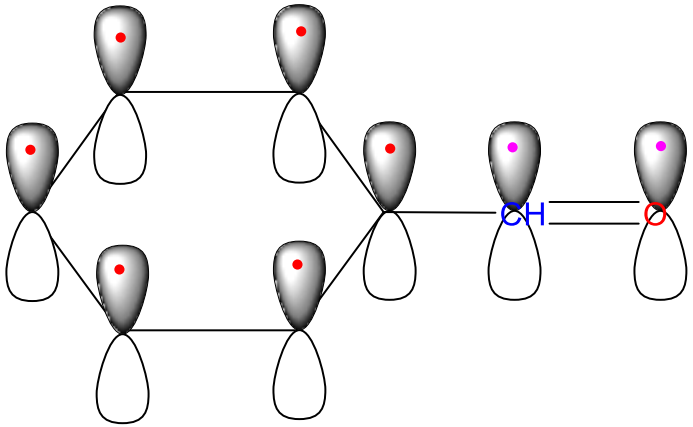
here the two phenomena, Induction and Resonance, are opposing each other

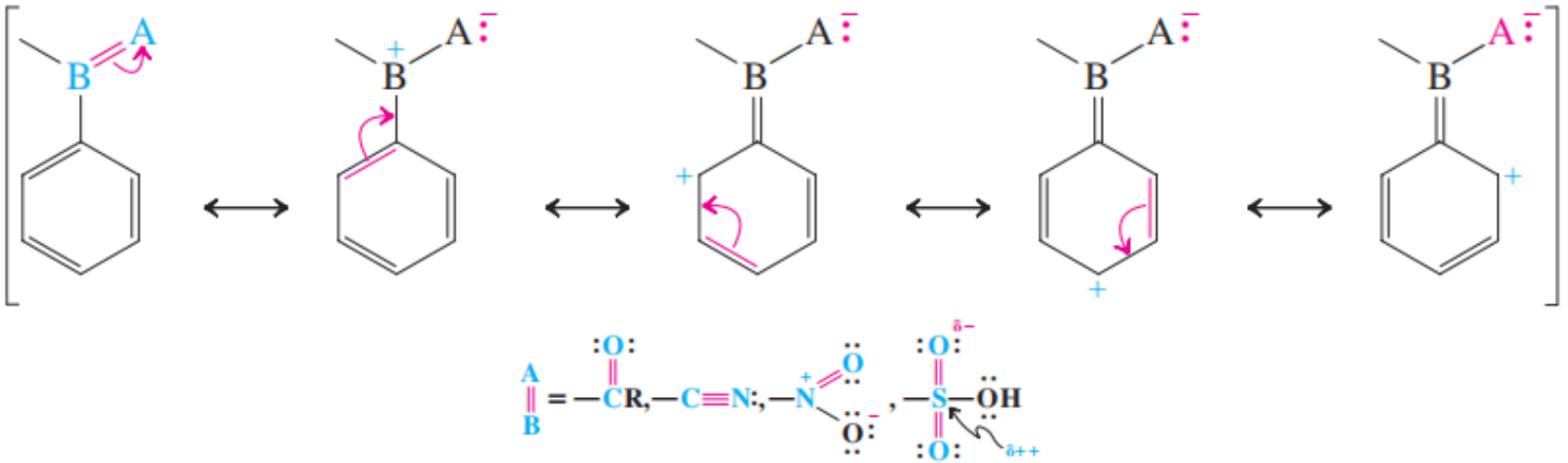


Part 1: Electrophilic Aromatic Substitution

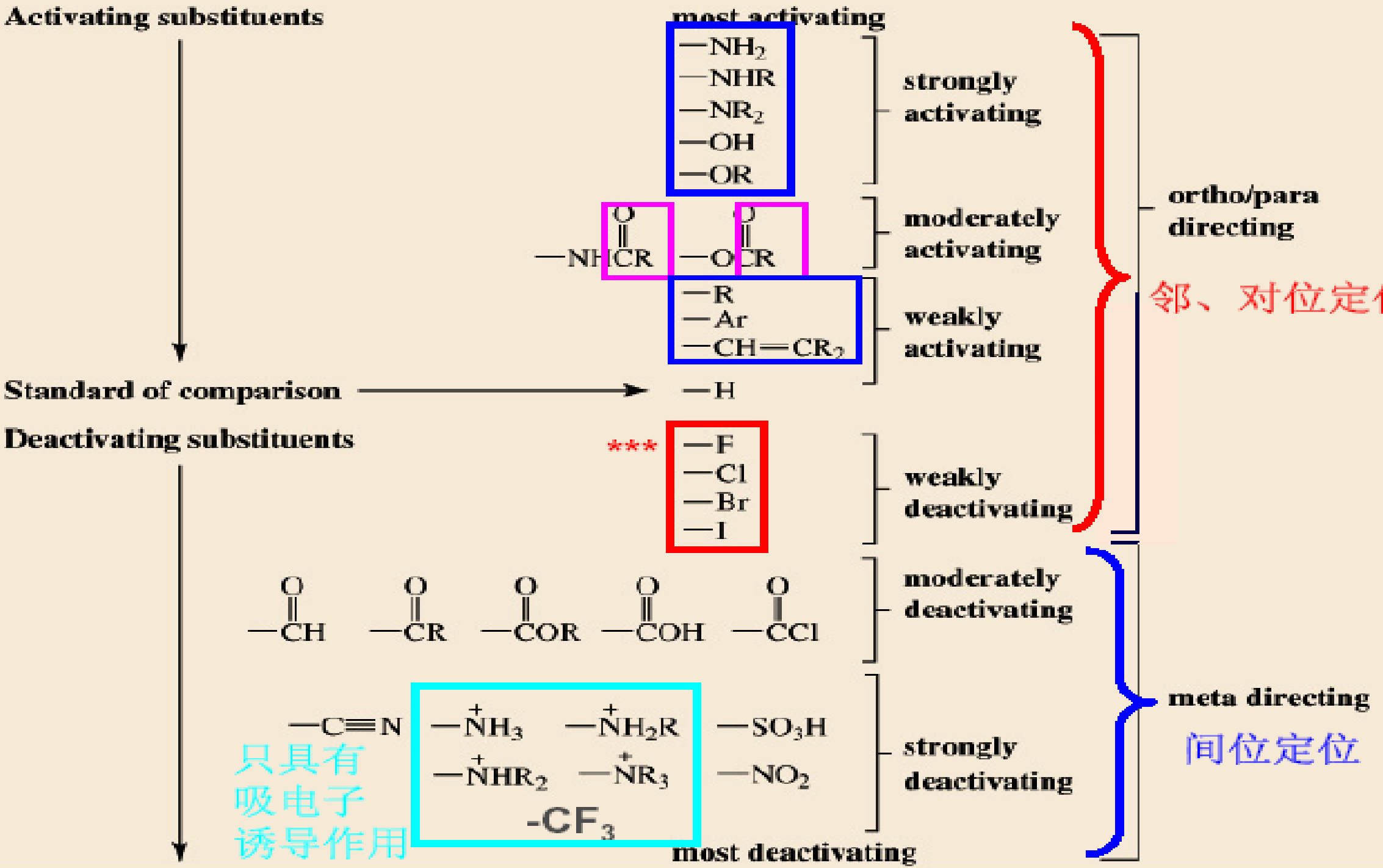
Resonance Acceptance from Benzene

groups bearing a polarized double or triple bond





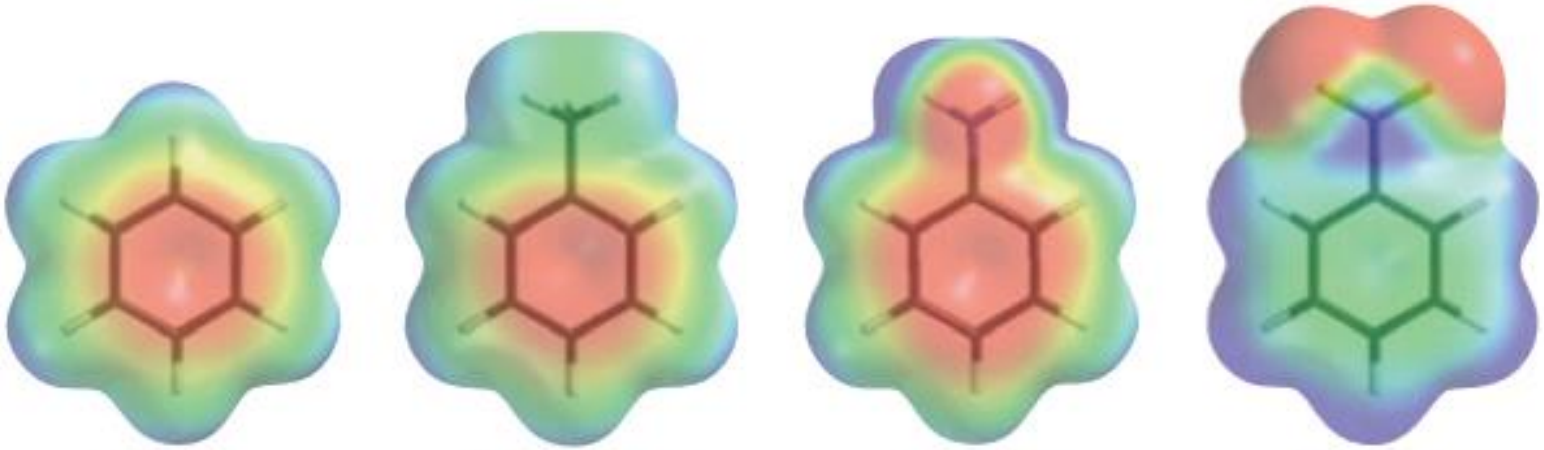
here, Resonance Reinforces Induction


Activating substituents
most activating
—NH2
—NHR
—NR2
—OH
—OR
strongly activating
—NHCR
—OCR
moderately activating
—R
—Ar
—CH=CR2
weakly activating
ortho/para directing
邻、对位定位
Standard of comparison
—H
Deactivating substituents
***
—F
—Cl
—Br
—I
weakly deactivating
—CH
—CR
—COR
—COH
—CCl
moderately deactivating
—C≡N
—NH3+
—NH2R+
—SO3H
—NHR2+
—NR3+
—NO2
-CF3
只具有吸电子诱导作用
strongly deactivating
meta directing
间位定位
most deactivating

Exercise 1

Explain why (a) $-NO_2$, (b) $^{+}NR_3$ are deactivating groups ? and (c) Why should phenyl and vinyl be activating groups?

Part 1: Electrophilic Aromatic Substitution



Benzene | Methylbenzene (Toluene) | Benzenamine (Aniline) | Nitrobenzene

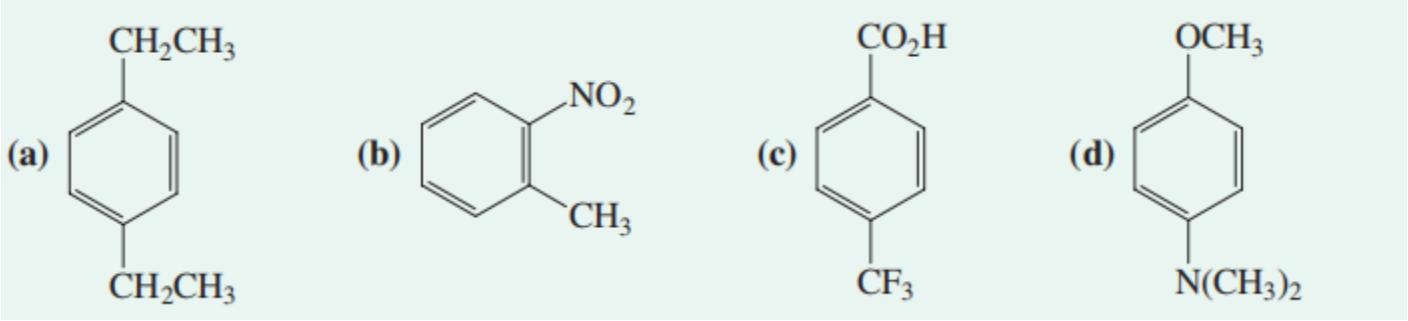
Relative Rates of Nitration of C_6H_5X

X =	$NH(C_6H_5)$	> OH	> CH_3	> H	> Cl	> $CO_2CH_2CH_3$	> CF_3	> NO_2
	10^6	1000	25	1	0.033	0.0037	2.6×10^{-5}	6×10^{-8}

Increasing rate of nitration

Exercise 2

Specify whether the benzene rings in the compounds below are activated or deactivated

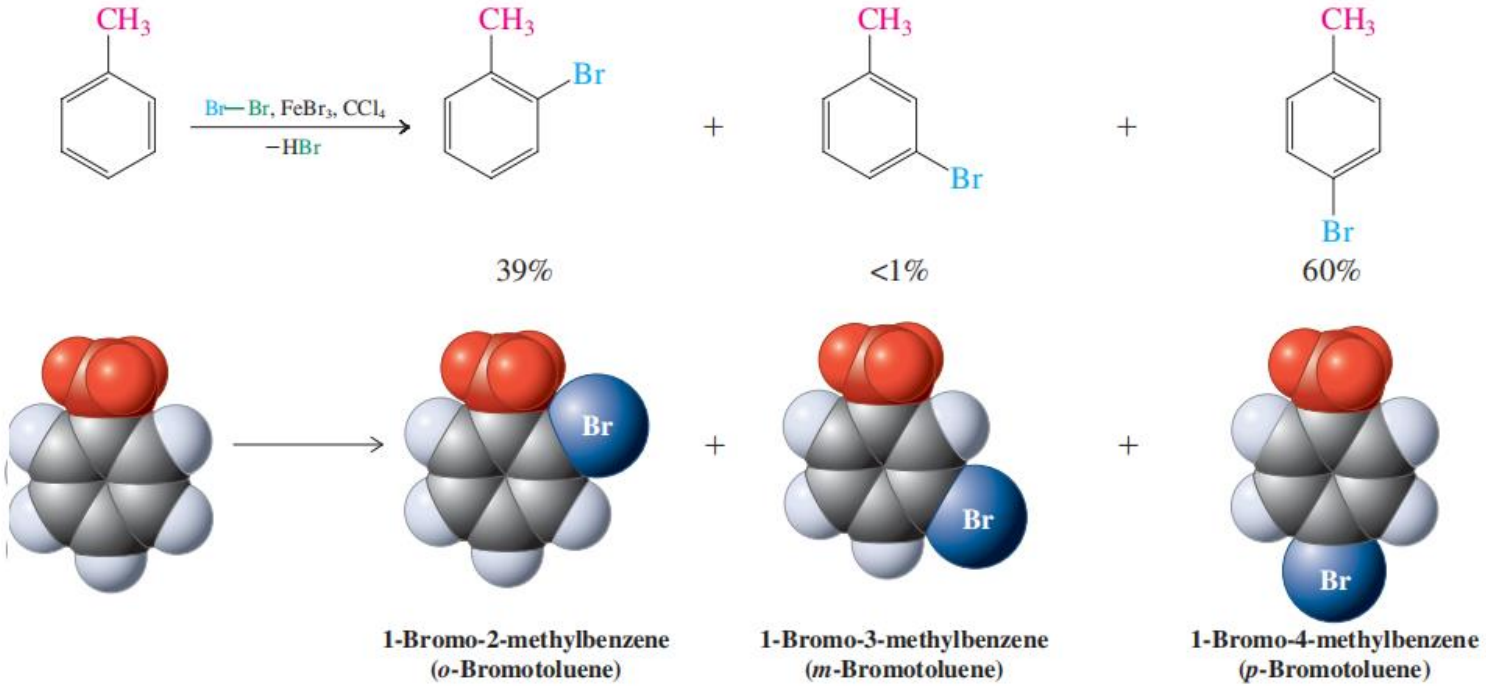


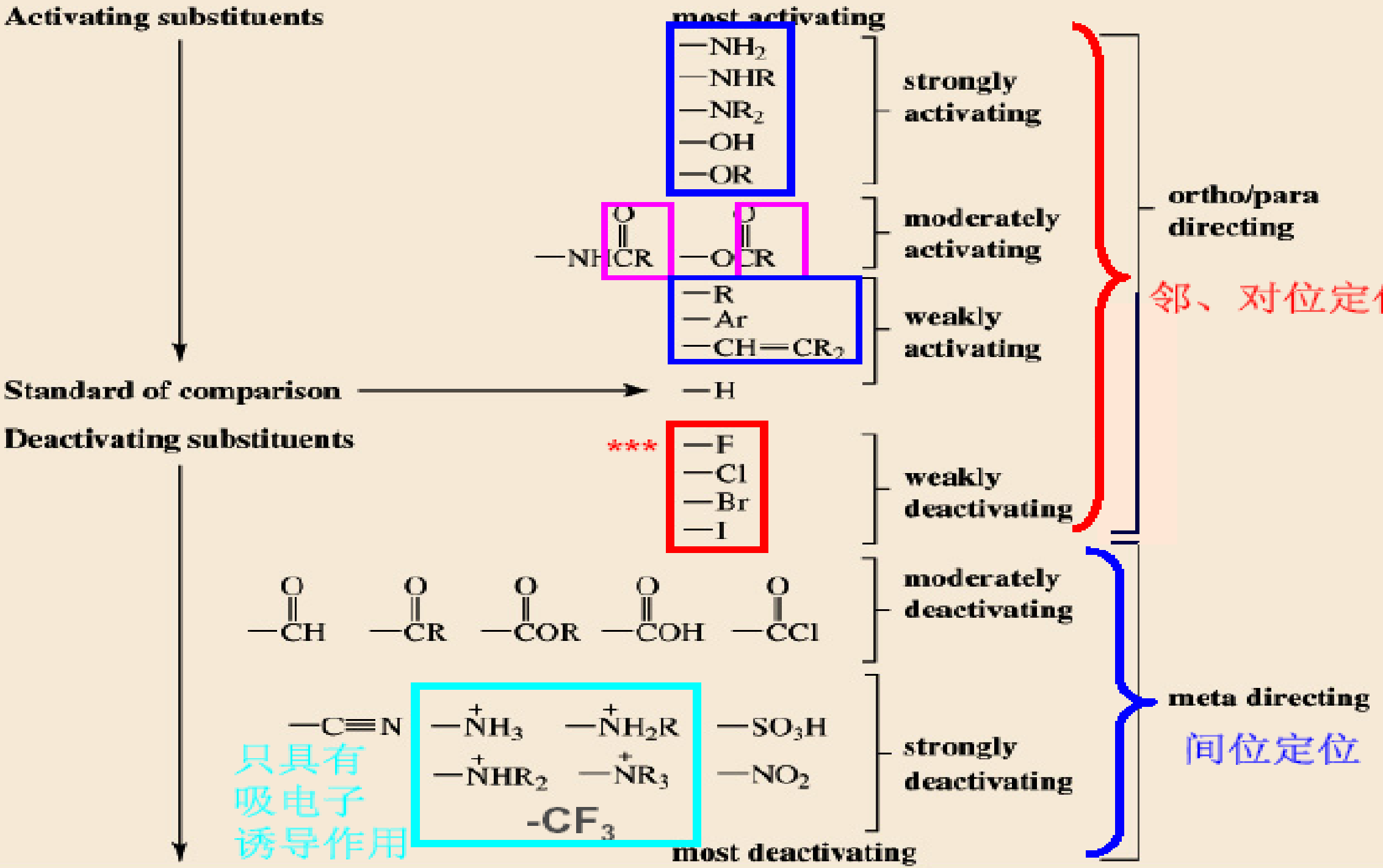
Part 1: Electrophilic Aromatic Substitution

5.3.2 Regioselectivity

A. Activators (electron donors) generally, direct a second electrophilic attack to the ortho and para positions

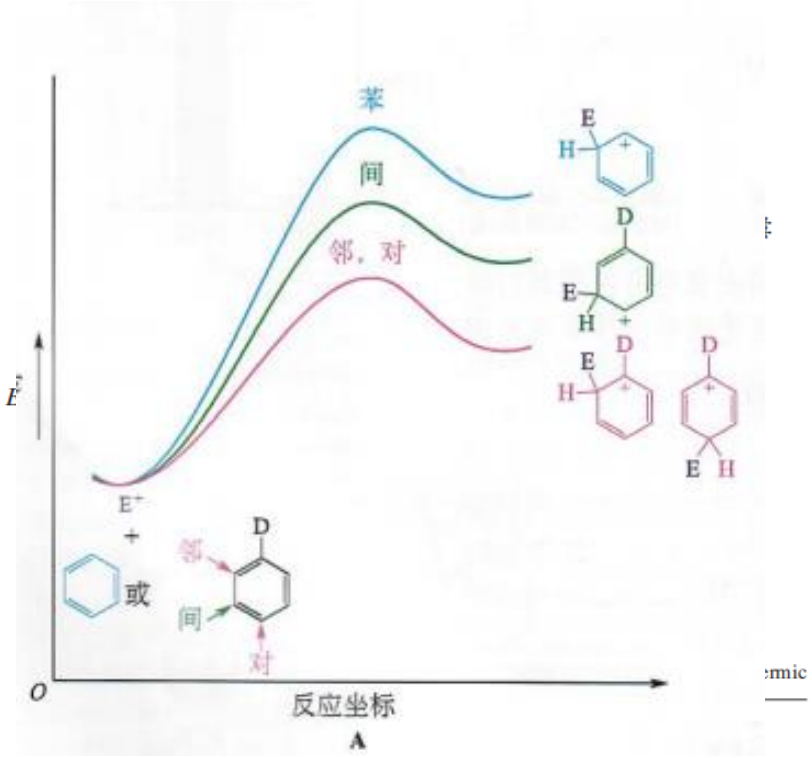
a. Groups that donate electrons by induction and hyperconjugation. (Alkyl Group) **Weakly Activating**

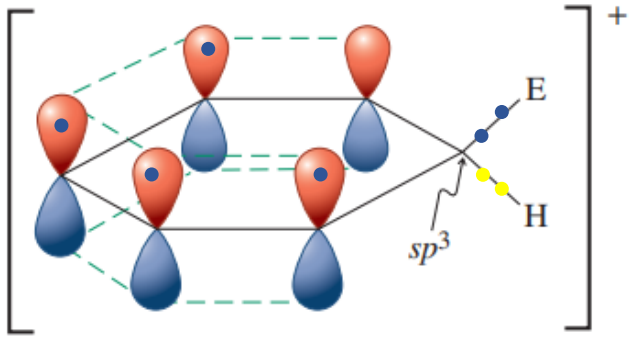


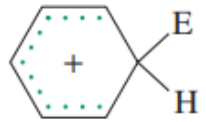

Activating substituents
most activating
—NH2
—NHR
—NR2
—OH
—OR
strongly activating
—NHCR
—OCR
moderately activating
—R
—Ar
—CH=CR2
weakly activating
ortho/para directing
邻、对位定位
Standard of comparison
—H
Deactivating substituents
***
—F
—Cl
—Br
—I
weakly deactivating
—CH
—CR
—COR
—COH
—CCl
moderately deactivating
—C≡N
—NH3+
—NH2R+
—SO3H
—NHR2+
—NR3+
—NO2
-CF3
只具有吸电子诱导作用
strongly deactivating
meta directing
间位定位
most deactivating

Part 1: Electrophilic Aromatic Substitutic

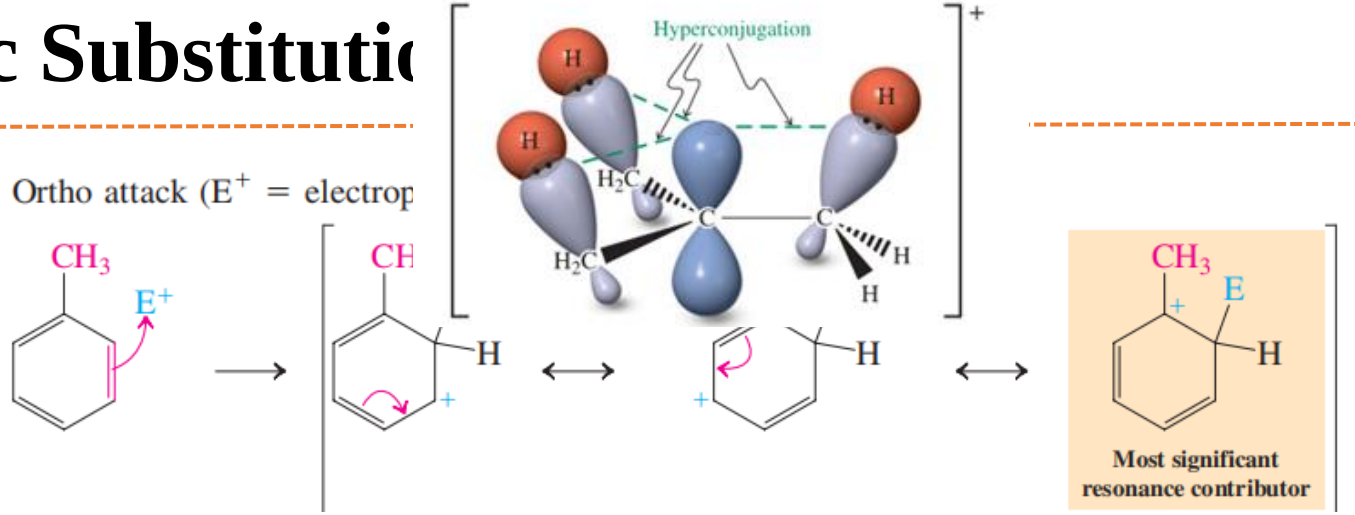
Explain this regioselectivity by the mechanism



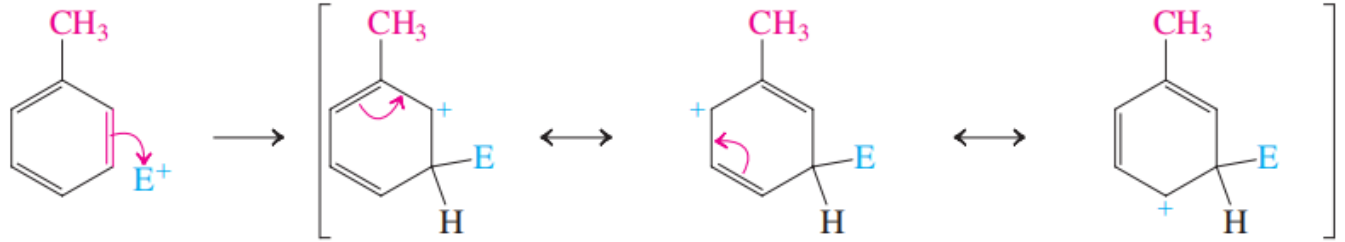




Ortho attack (E^+ = electrop

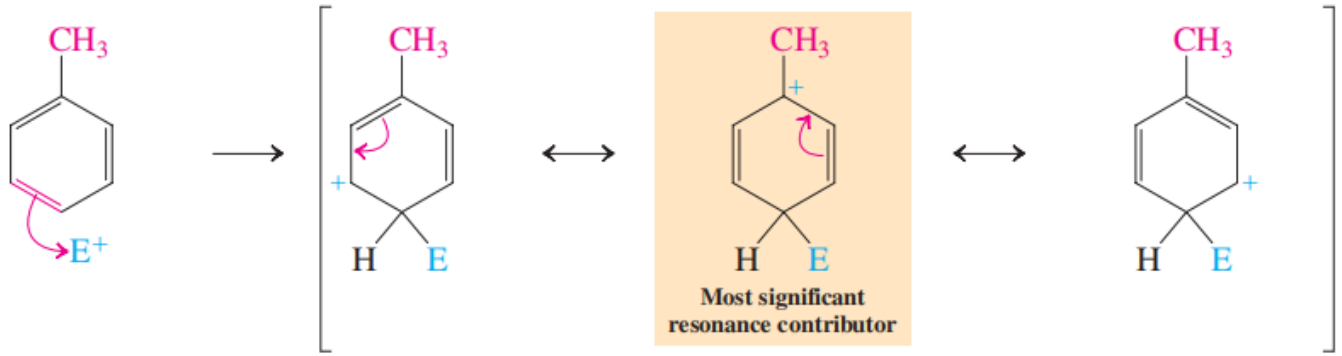


Meta attack



Less stable cation

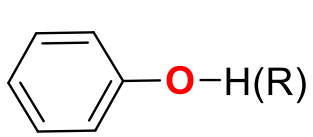
Para attack

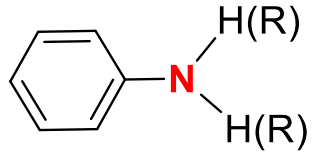


More stable cation

Part 1: Electrophilic Aromatic Substitution

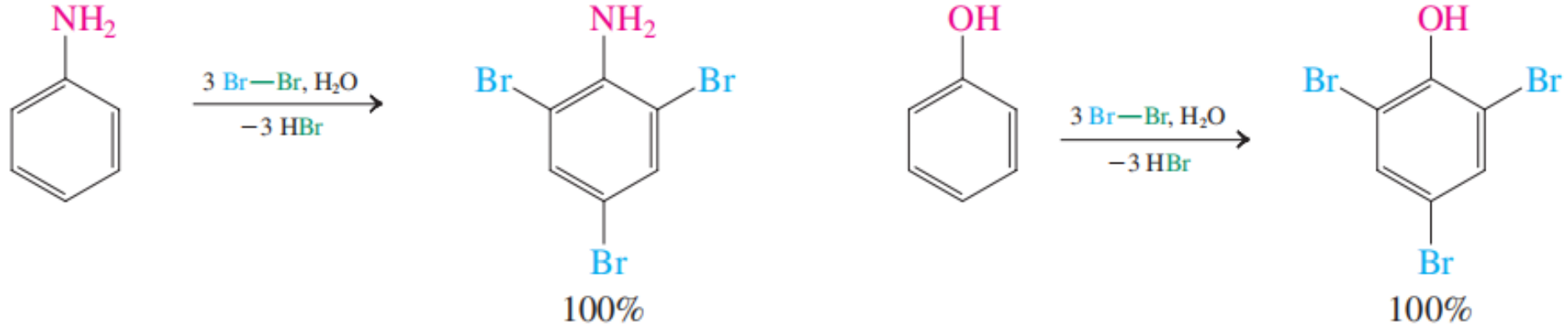
b. Groups that donate electrons by resonance.





Strongly Activating

Electrophilic Brominations of Benzenamine (Aniline) and Phenol Give Ortho and Para Substitution



Benzenamine (Aniline)

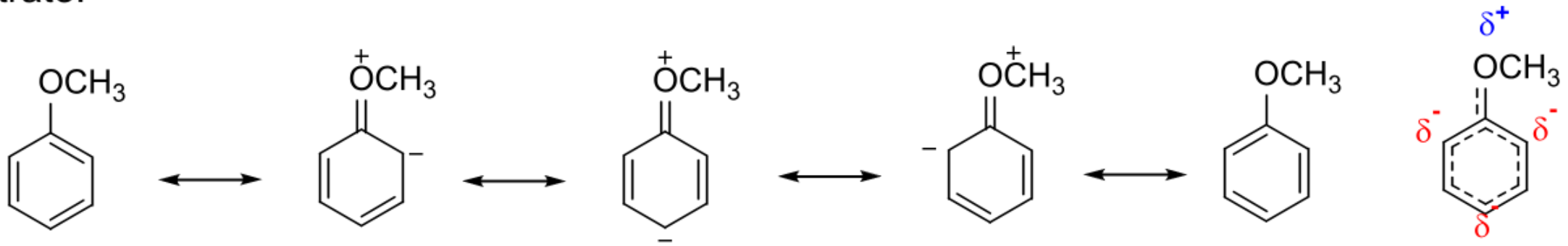
2,4,6-Tribromobenzenamine (2,4,6-Tribromoaniline)

Phenol

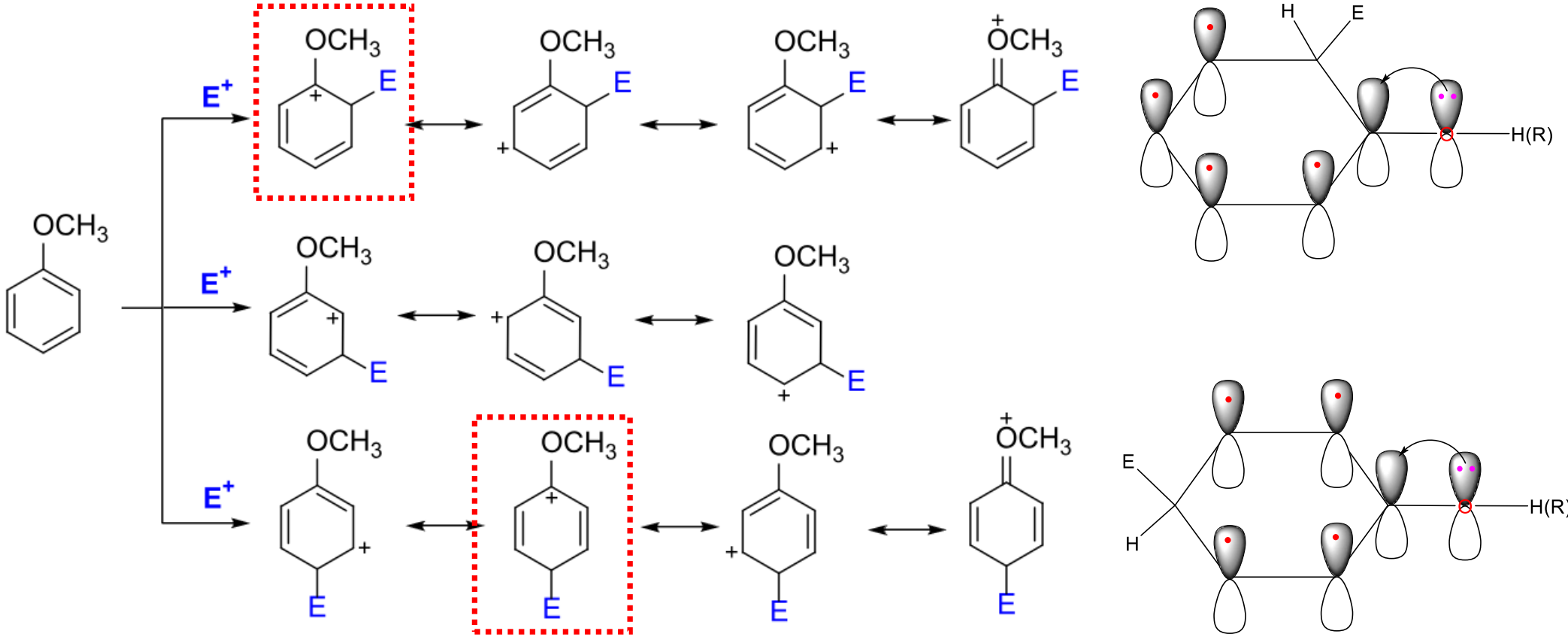
2,4,6-Tribromophenol

Part 1: Electrophilic Aromatic Substitution

From substrate:



From intermediate:



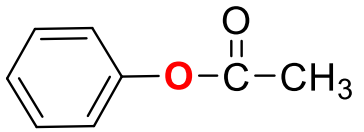
Exercise 3

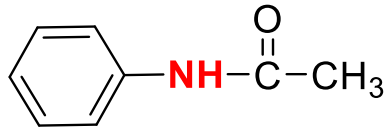
Explain (1) why should vinyl be activating groups? (2) why should vinyl be ortho- and para-directing group.(from structure of substrate and the stability of intermediate)

Explain (1) why should amino be activating groups? (2) why should amino be ortho- and para-directing group.(from structure of substrate and the stability of intermediate)

Part 1: Electrophilic Aromatic Substitution

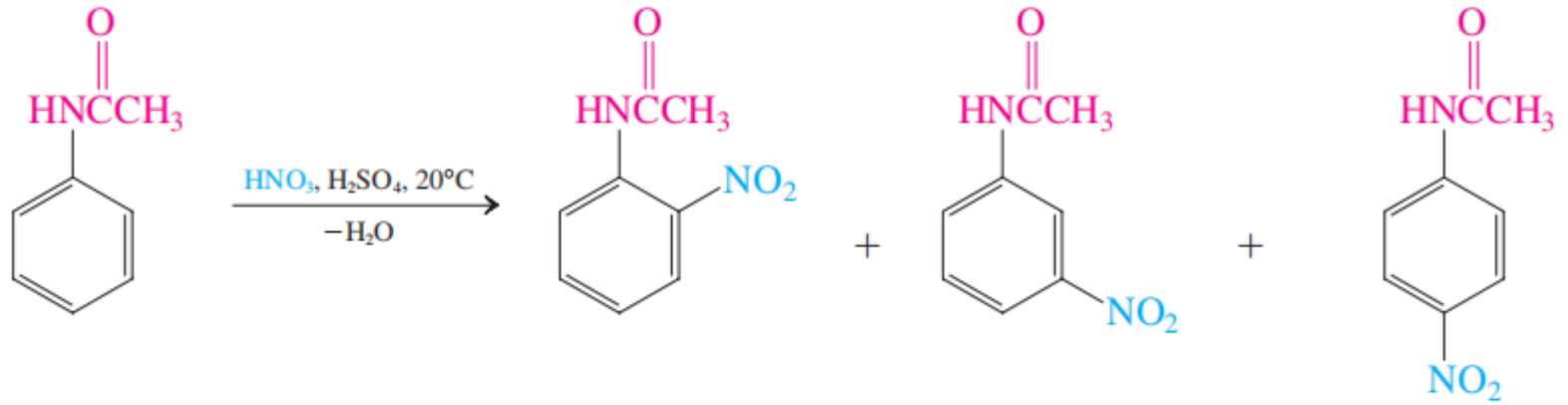
c. Groups that donate electrons by resonance.





Moderately Activating

Electrophilic Nitration of *N*-Phenylacetamide (Acetanilide)

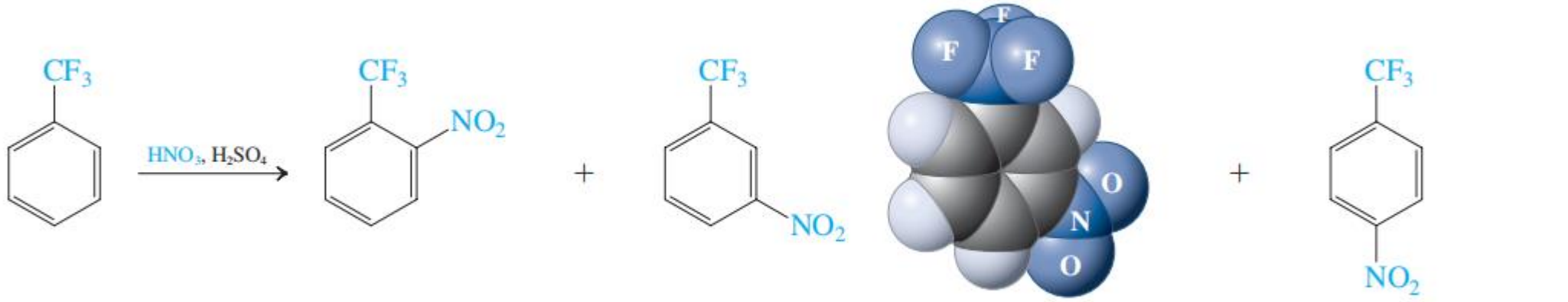


Part 1: Electrophilic Aromatic Substitution

B. Deactivators (electron acceptors) (except X) generally direct electrophiles to the meta positions.

a. Groups that withdraw electrons by induction.

Electrophilic Nitration of (Trifluoromethyl)benzene Gives Mainly Meta Substitution



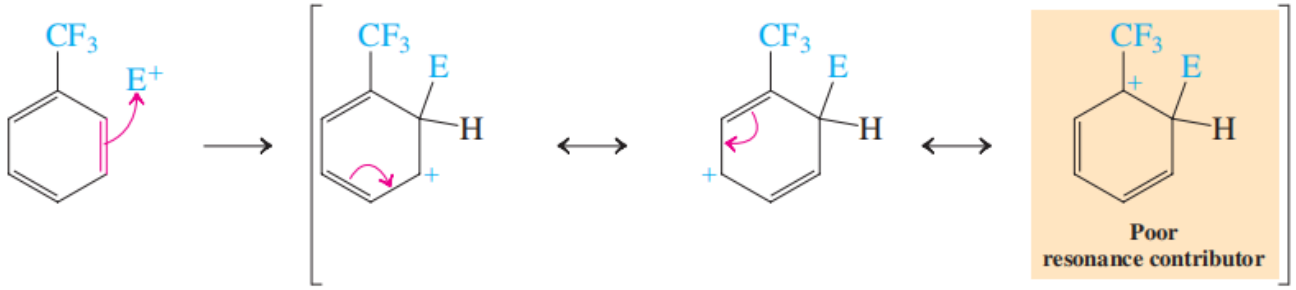
6%
1-Nitro-2-(trifluoromethyl)benzene
[*o*-Nitro(trifluoromethyl)benzene]

91%
1-Nitro-3-(trifluoromethyl)benzene
[*m*-Nitro(trifluoromethyl)benzene]

3%
1-Nitro-4-(trifluoromethyl)benzene
[*p*-Nitro(trifluoromethyl)benzene]

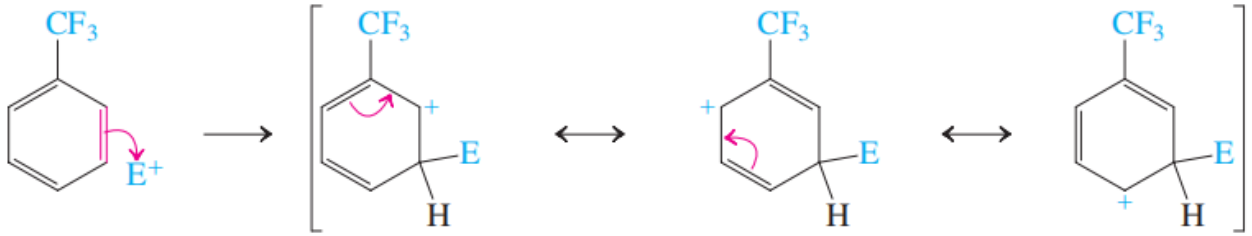
Part 1: Electrophilic Aromatic Substitution

Ortho attack



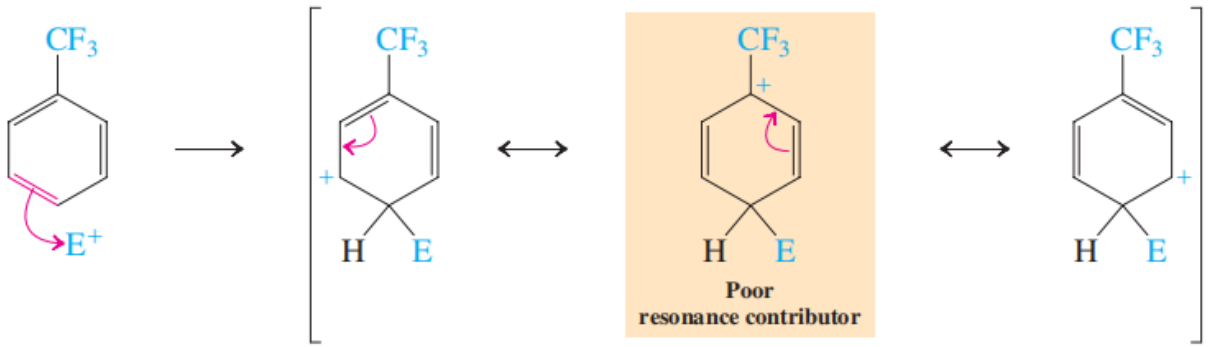
Strongly destabilized cation

Meta attack

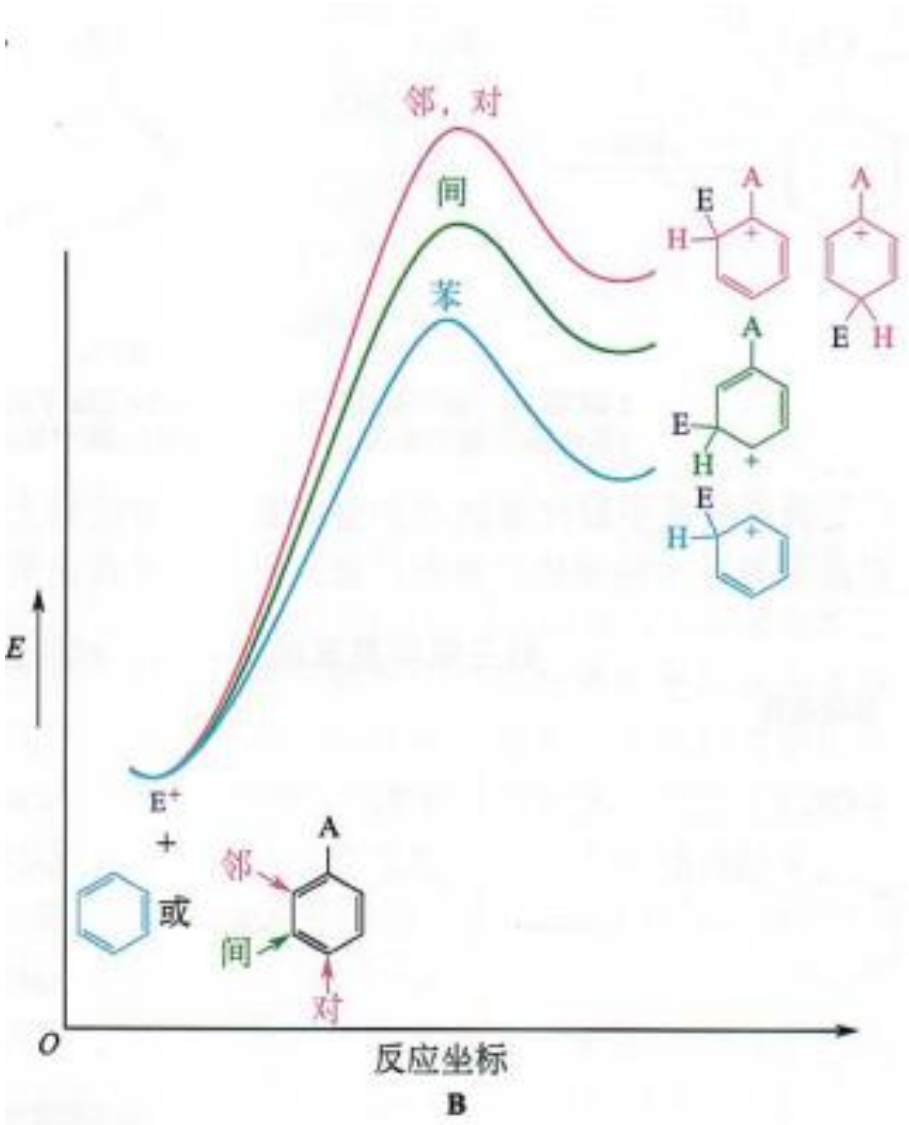


Less destabilized cation

Para attack



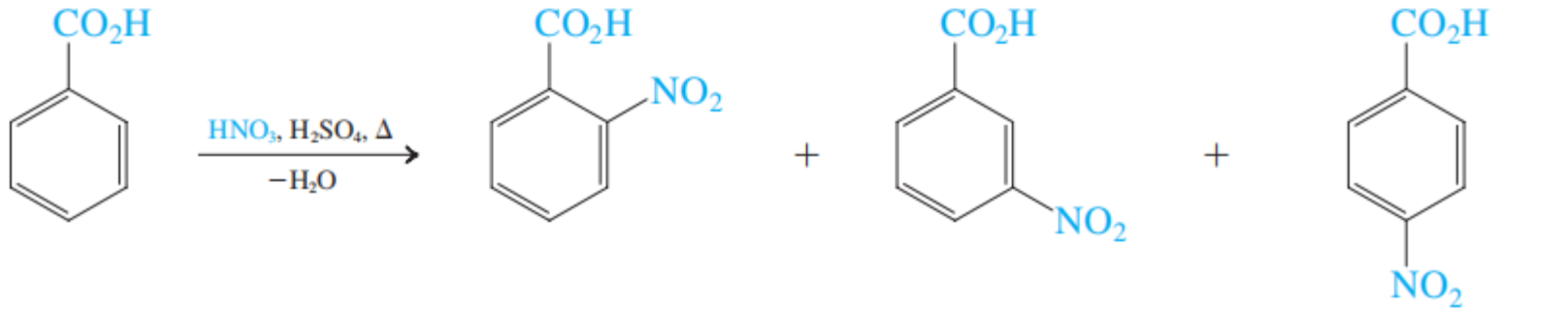
Strongly destabilized cation



Part 1: Electrophilic Aromatic Substitution

b. Groups that withdraw electrons by **resonance.**

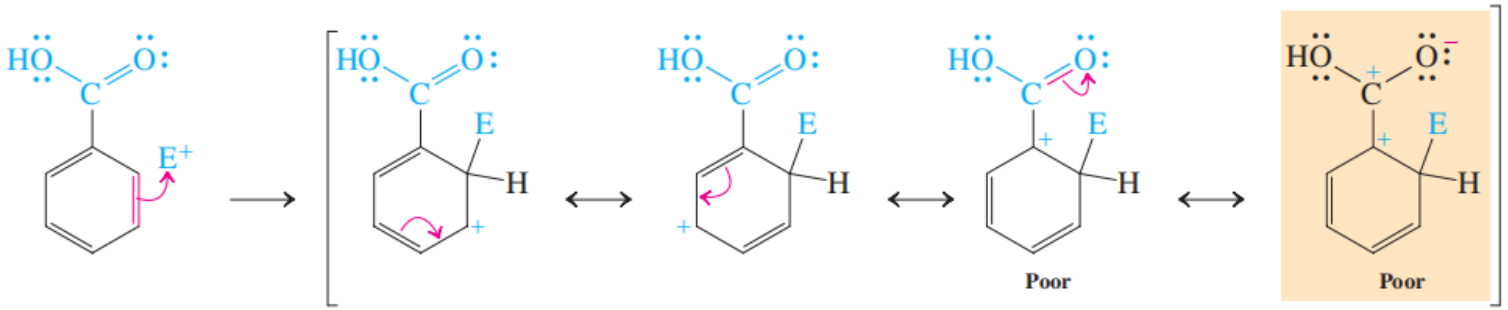
Electrophilic Meta Nitration of Benzoic Acid



18.5%	80%	1.5%
2-Nitrobenzoic acid (*o*-Nitrobenzoic acid)	**3-Nitrobenzoic acid (*m*-Nitrobenzoic acid)**	**4-Nitrobenzoic acid (*p*-Nitrobenzoic acid)**

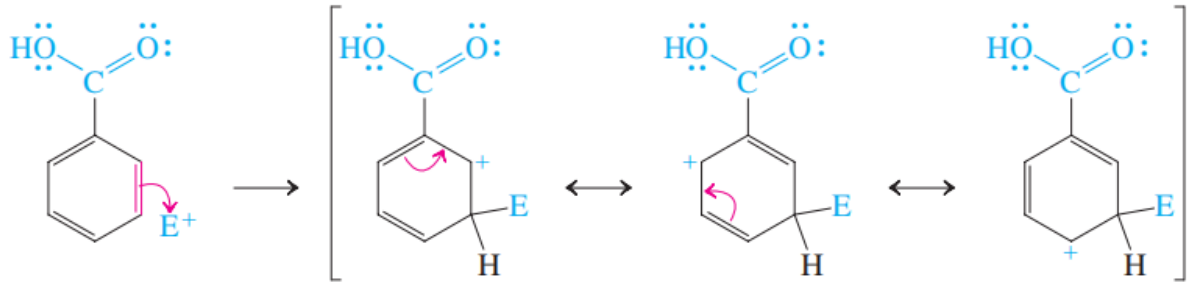
Part 1: Electrophilic Aromatic Substitution

Ortho attack



Strongly destabilized cation

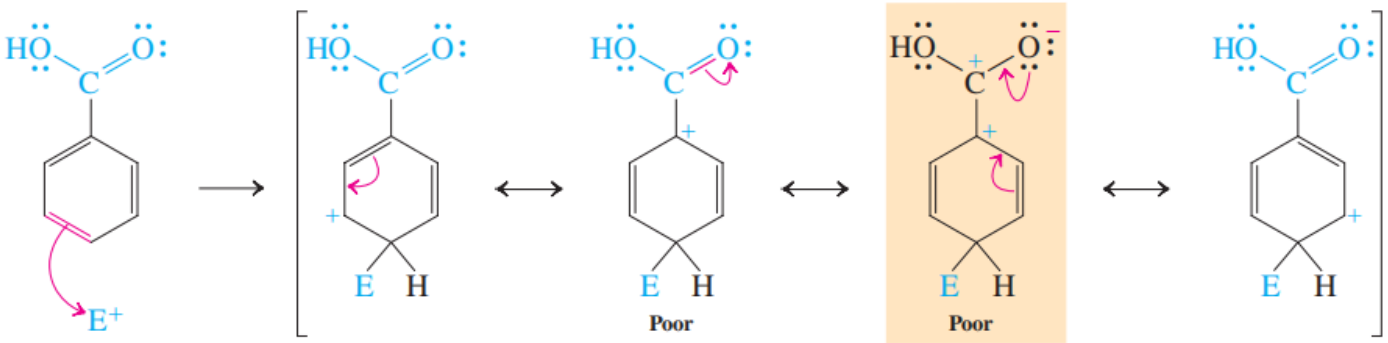
Meta attack



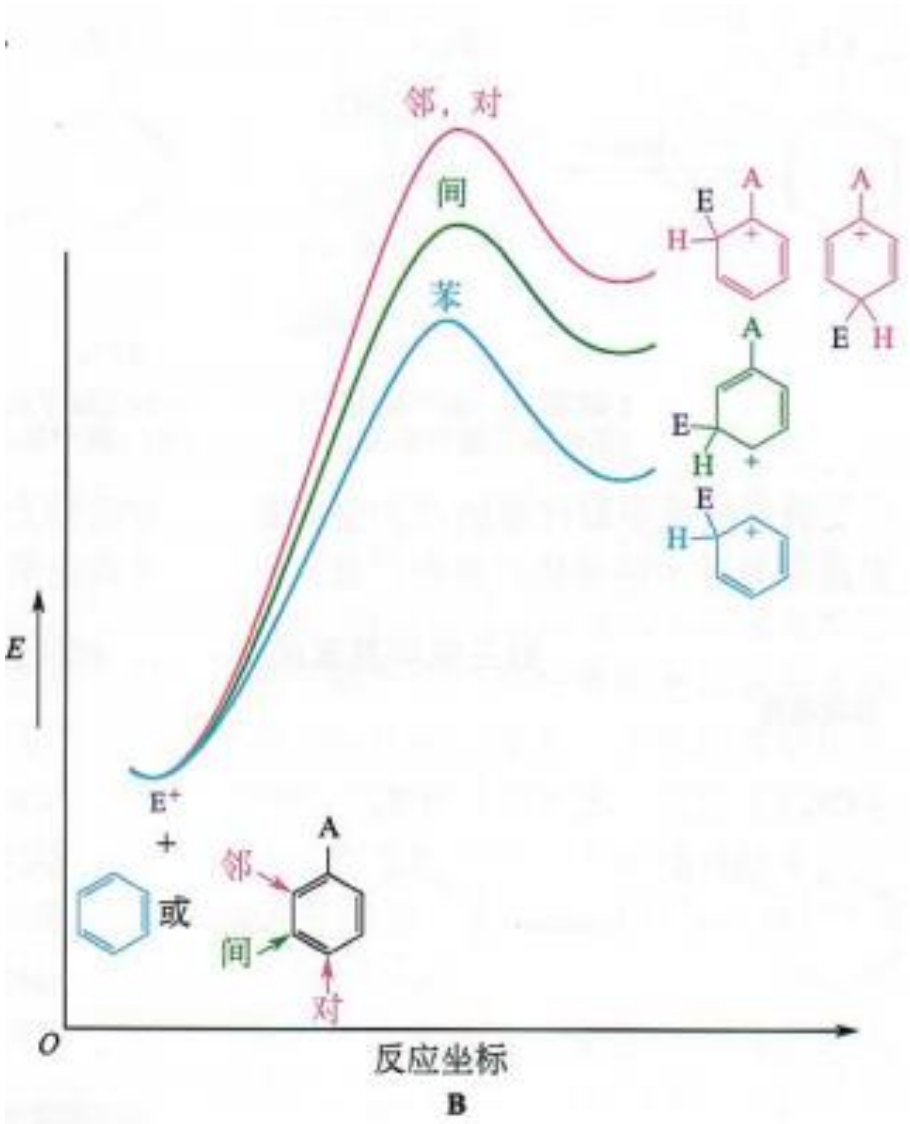
None is poor

Less destabilized cation

Para attack



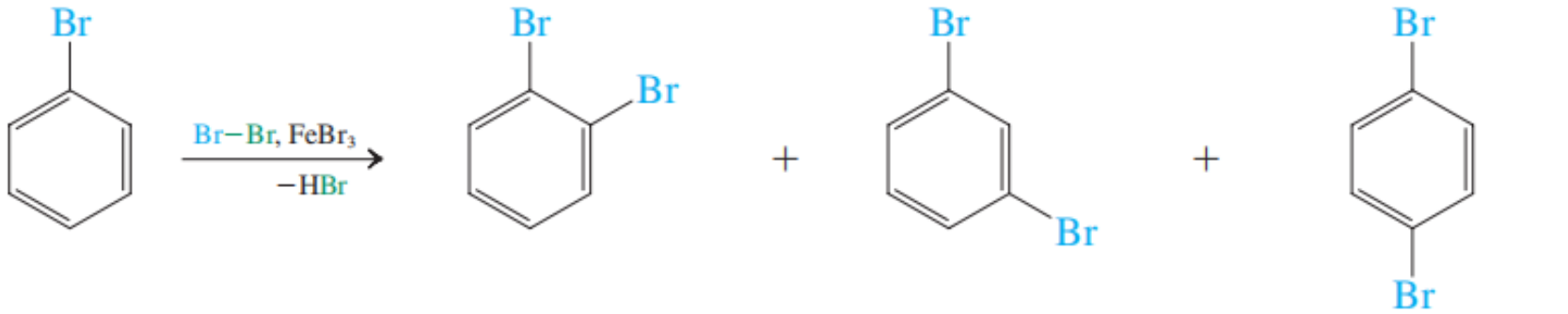
Strongly destabilized cation



Part 1: Electrophilic Aromatic Substitution

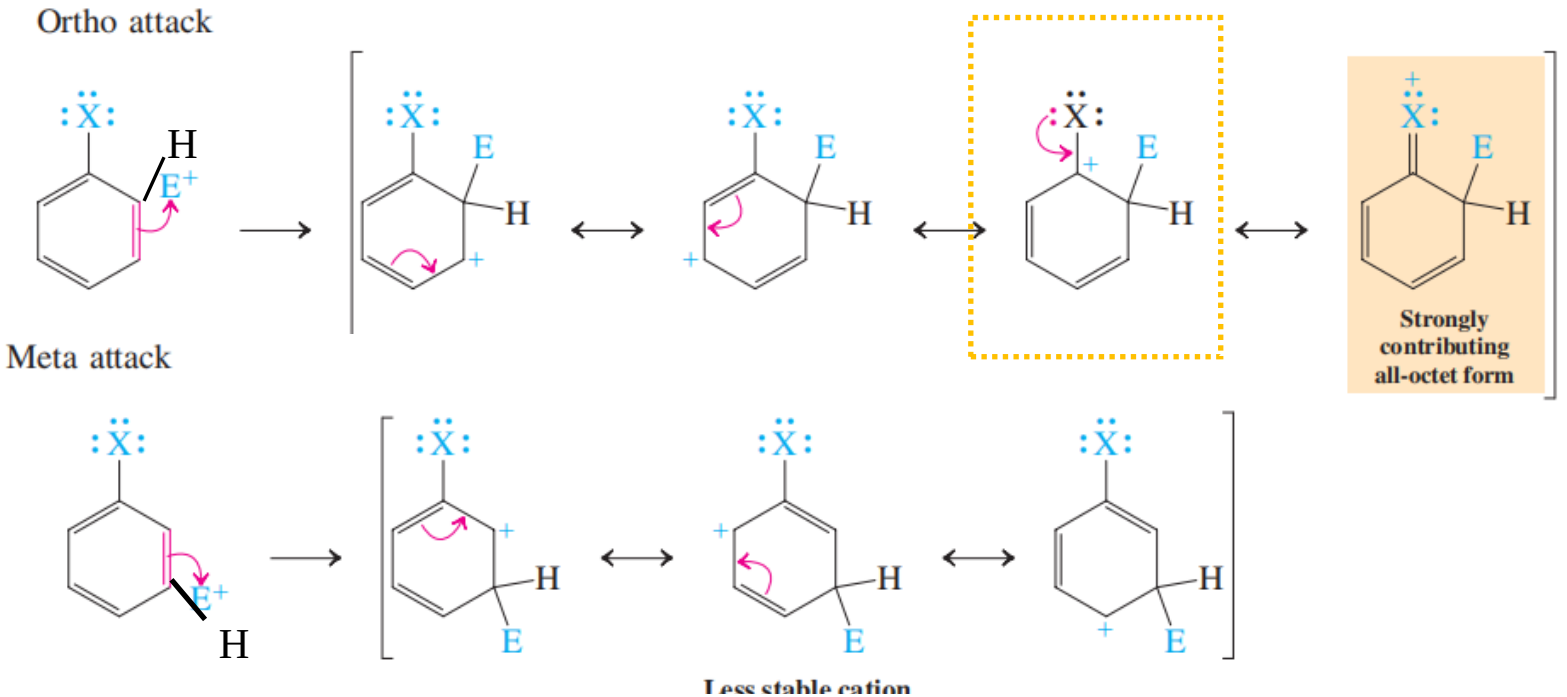
C. There is always an exception: halogen substituents, although deactivating, direct ortho and para

Electrophilic Bromination of Bromobenzene Results in *ortho*- and *para*-Dibromobenzene



13%	2%	85%
1,2-Dibromobenzene (*o*-Dibromobenzene)	**1,3-Dibromobenzene (*m*-Dibromobenzene)**	**1,4-Dibromobenzene (*p*-Dibromobenzene)**

Part 1: Electrophilic Aromatic Substitution

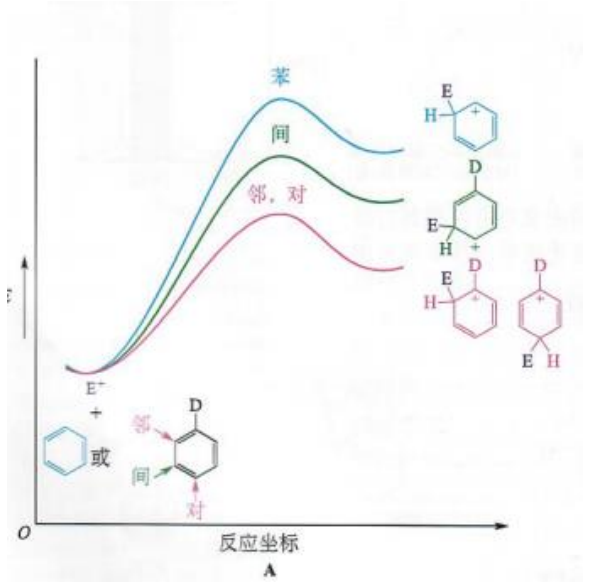


√

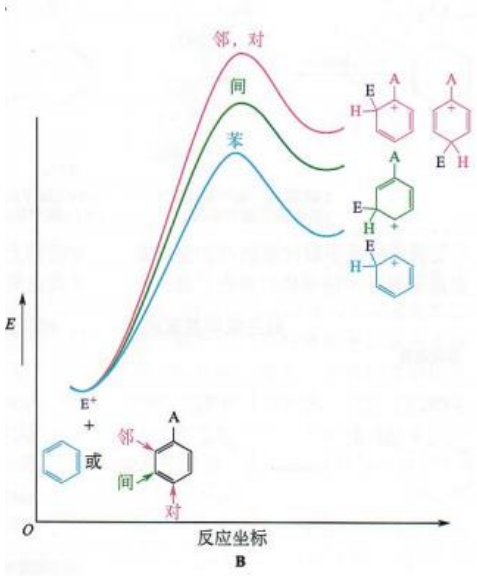
√

Orientation

A. **Activators** (electron donors) generally, direct a second electrophilic attack to the **ortho and para positions**



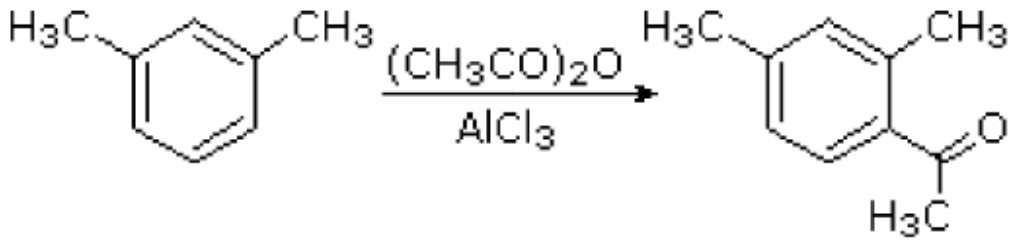
B. **Deactivators** (electron acceptors) (**except X**) generally direct electrophiles to the **meta** positions.

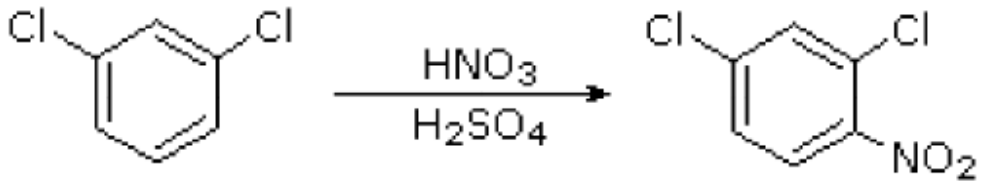


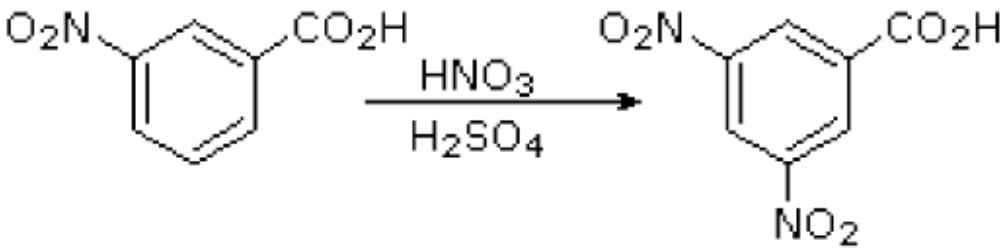
C. There is always an exception: **halogen substituents, although deactivating,** direct **ortho and para**

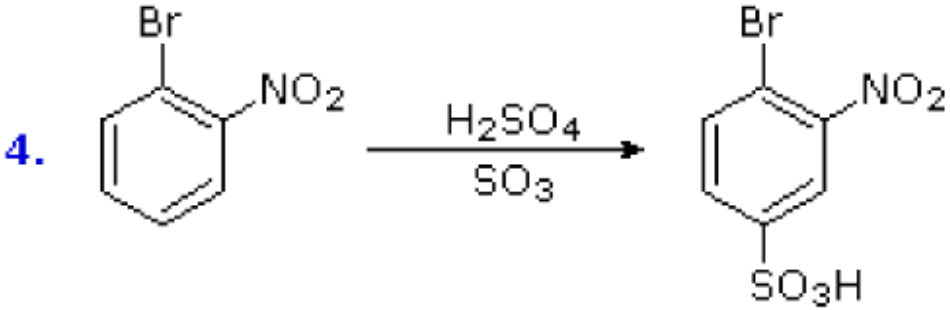
Part 1: Electrophilic Aromatic Substitution

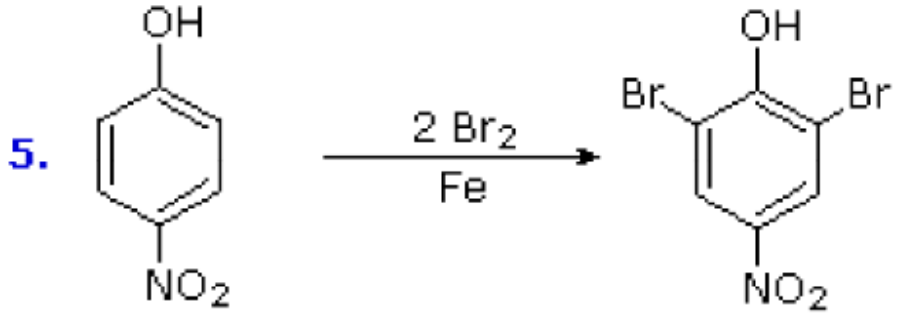
苯环上有两个取代基，且定位效应一致。

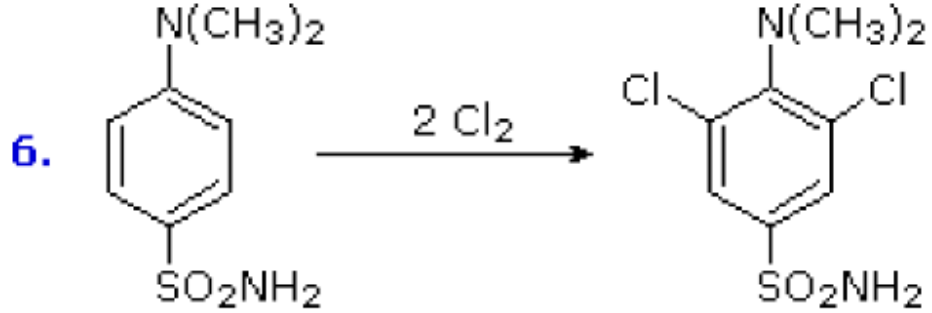
1. 

2. 

3. 

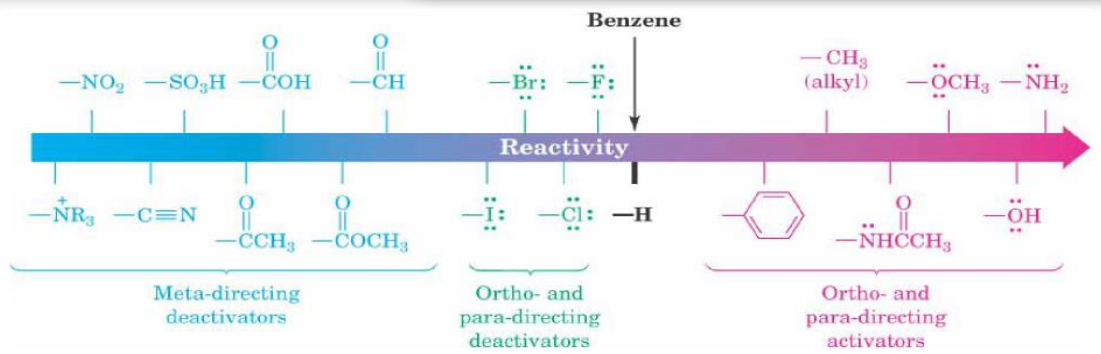
4. 

5. 

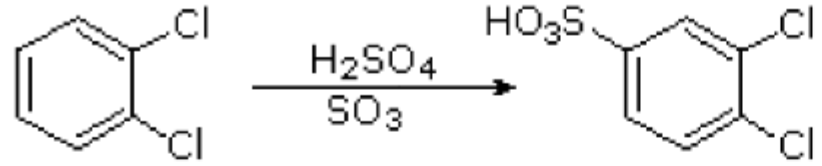
6. 

Part 1: Electrophilic Aromatic Subst

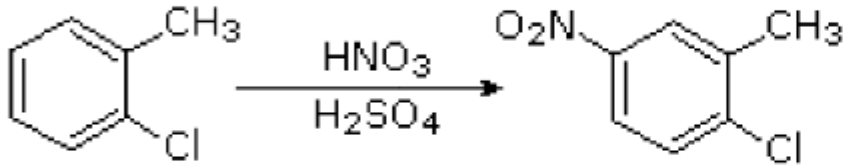
苯环上有两个取代基，且定位效应不一致。



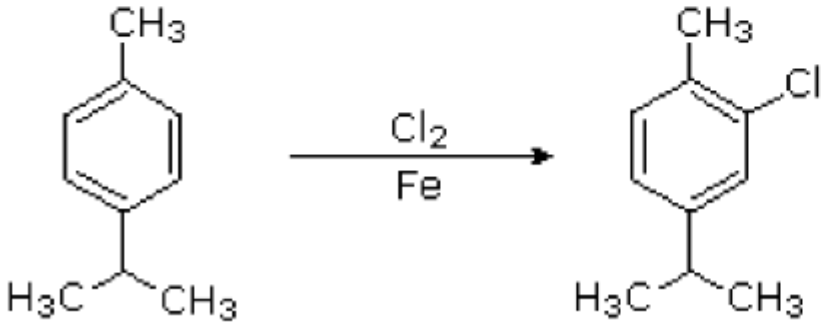
1.



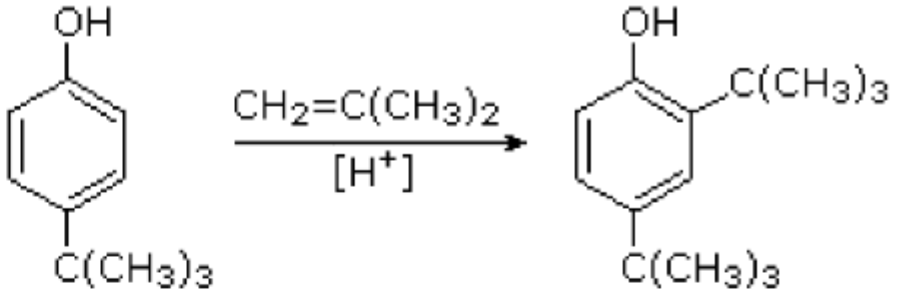
2.



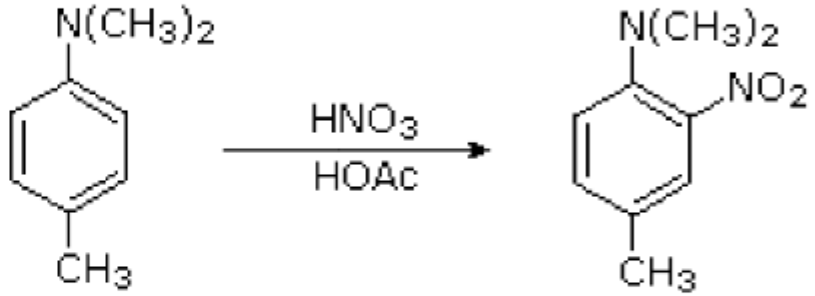
3.



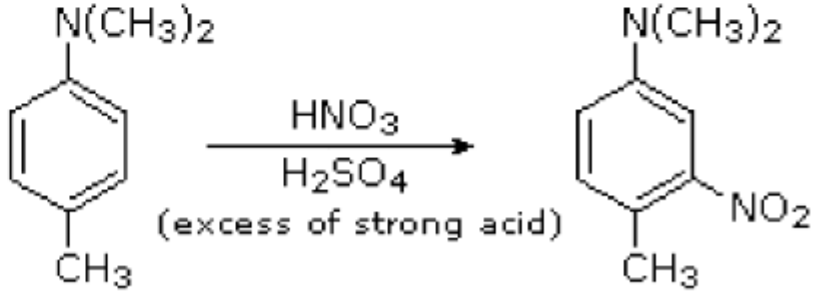
4.



5.

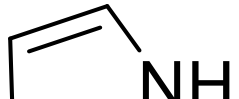


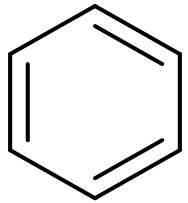
6.

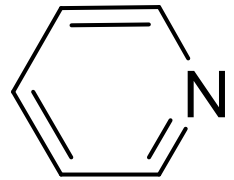


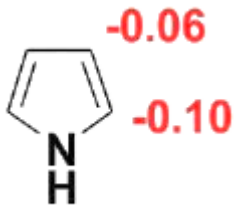
Exercise 4

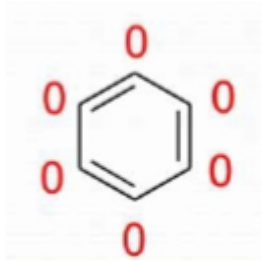
Rank the following compounds in order of decreasing reactivity toward S_EAr reaction.

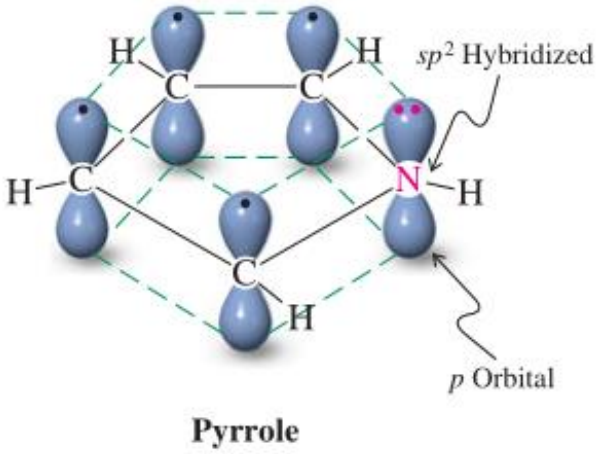




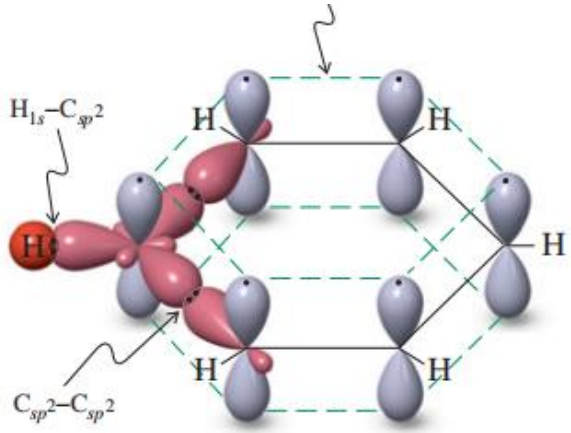


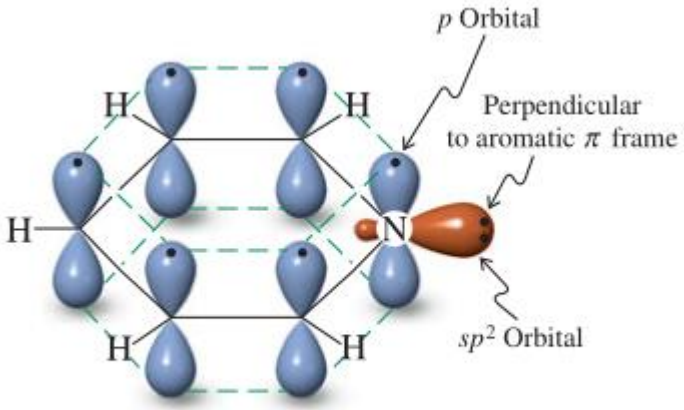






Pyrrole



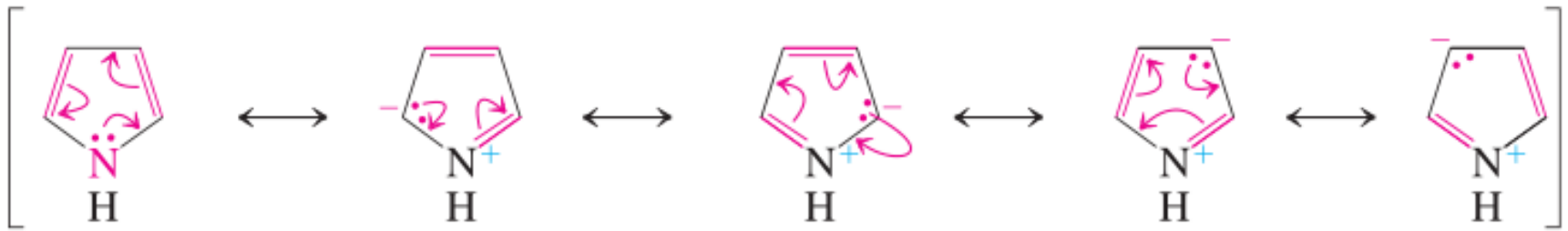


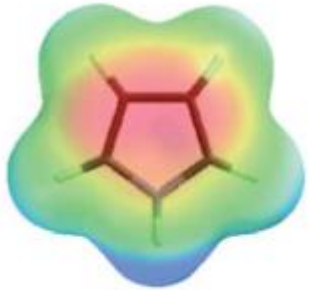
Part 1: Electrophilic Aromatic Substitution

5.4 S_EAr reactions of Other Aromatic Compounds

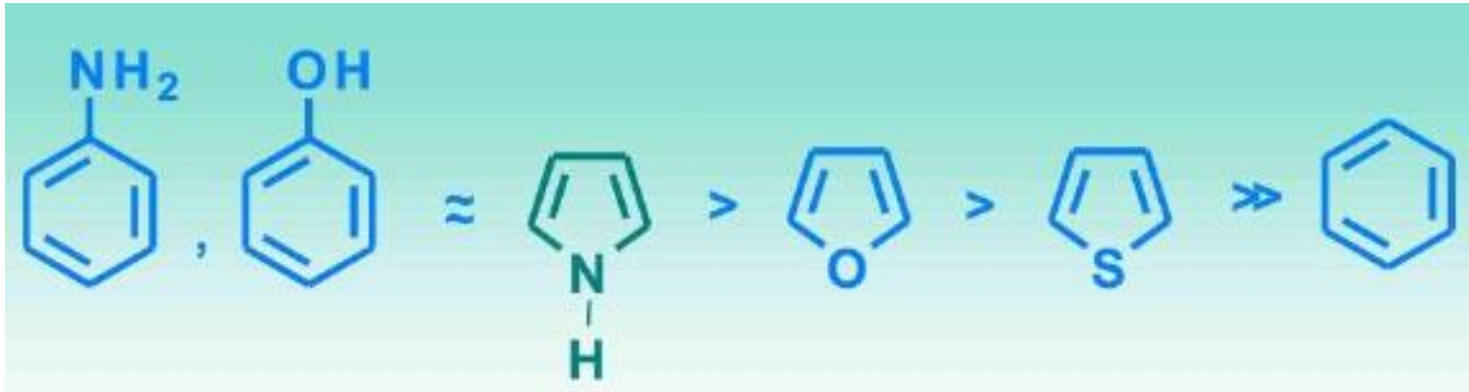
5.4.1 S_EAr reactions of Aromatic Heterocycle compound （芳香杂环）

Resonance Forms of Pyrrole

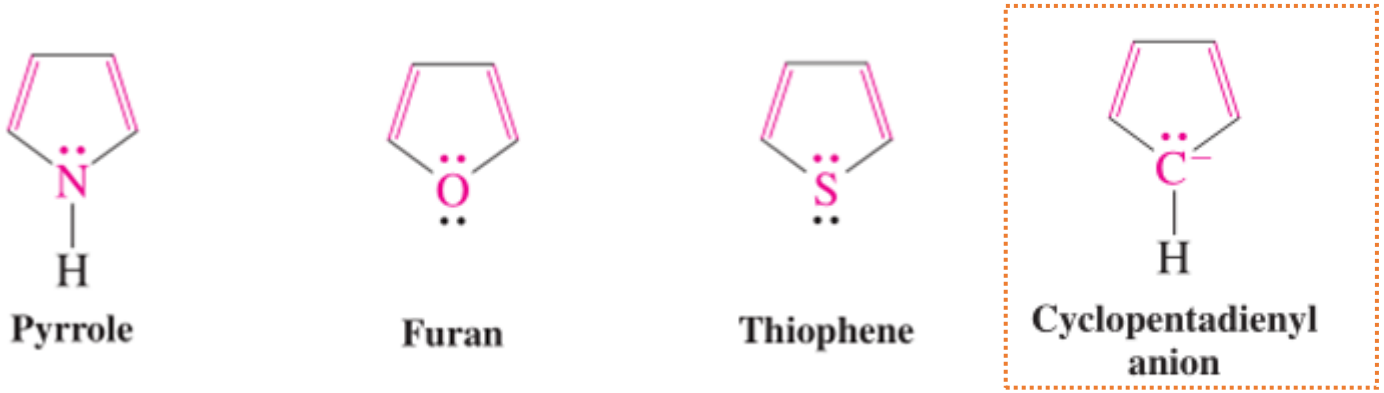




Pyrrole

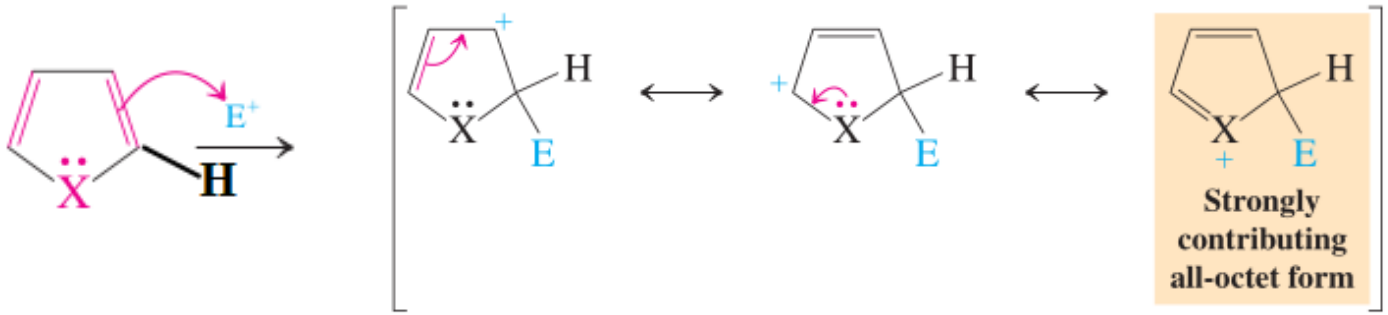


Part 1: Electrophilic Aromatic Substitution

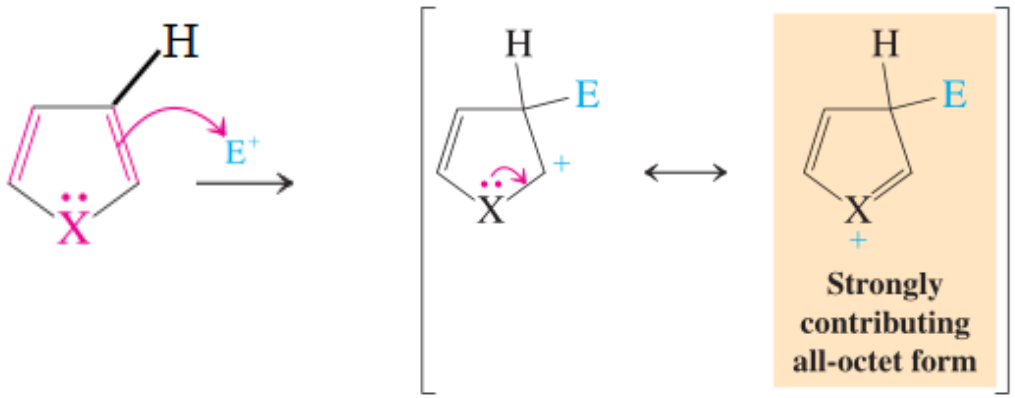


Regioselectivity：

α-substitution



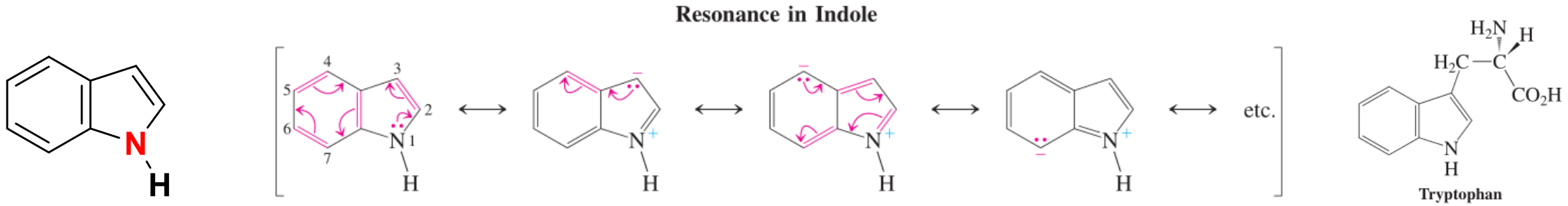
β-substitution



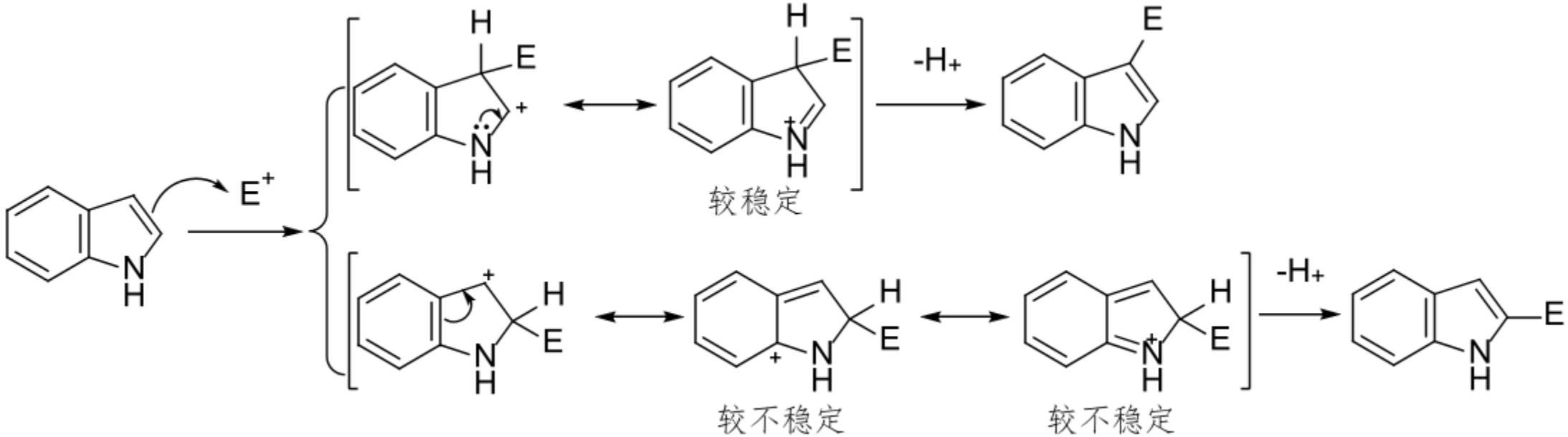
Exercise 5

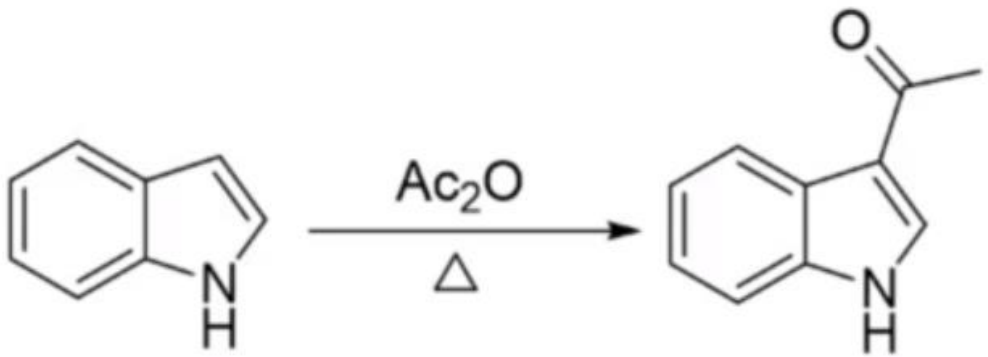
Predict the preferred site of electrophilic aromatic substitution in indole. Explain your choice.

Indole is a benzopyrrole



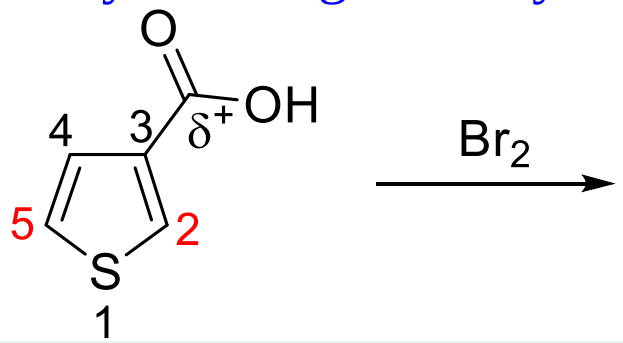
Exercise 5



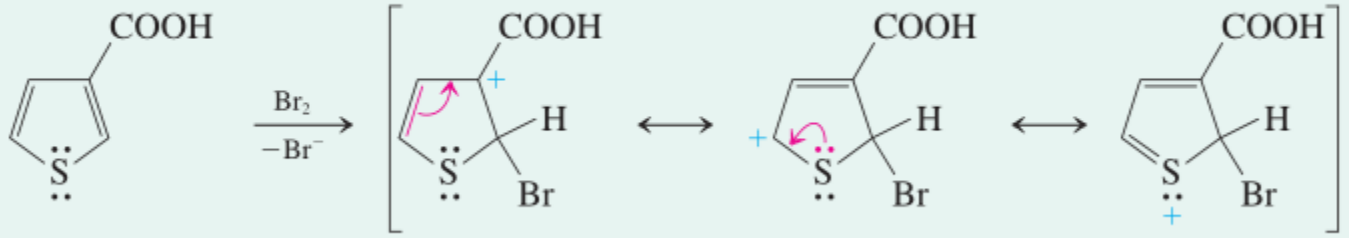


Exercise 6

The monobromination of thiophene-3-carboxylic acid gives only one product. What is its structure, and why is it the only product formed?

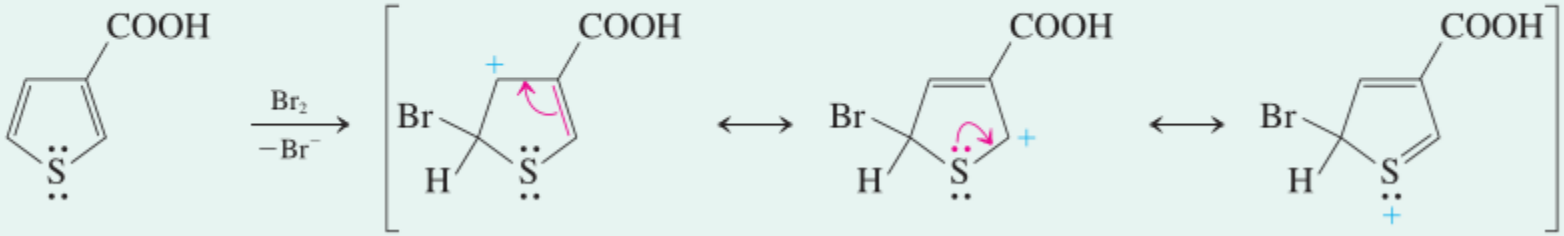


• Attack at C2



A

• Attack at C5

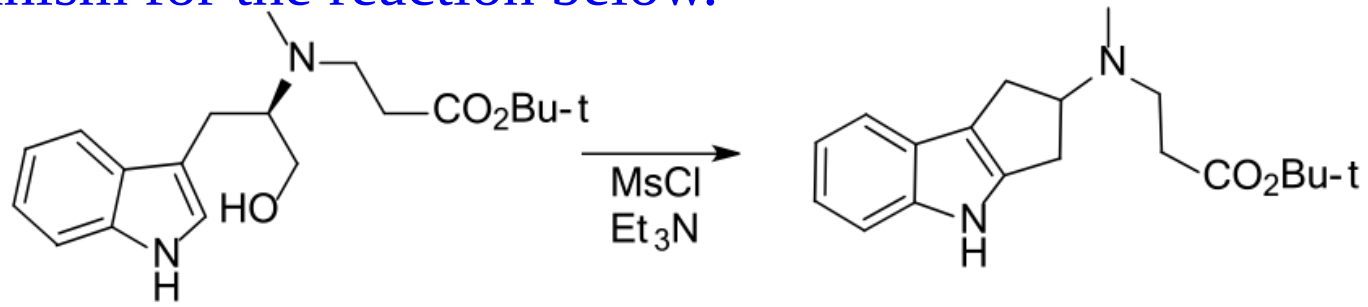


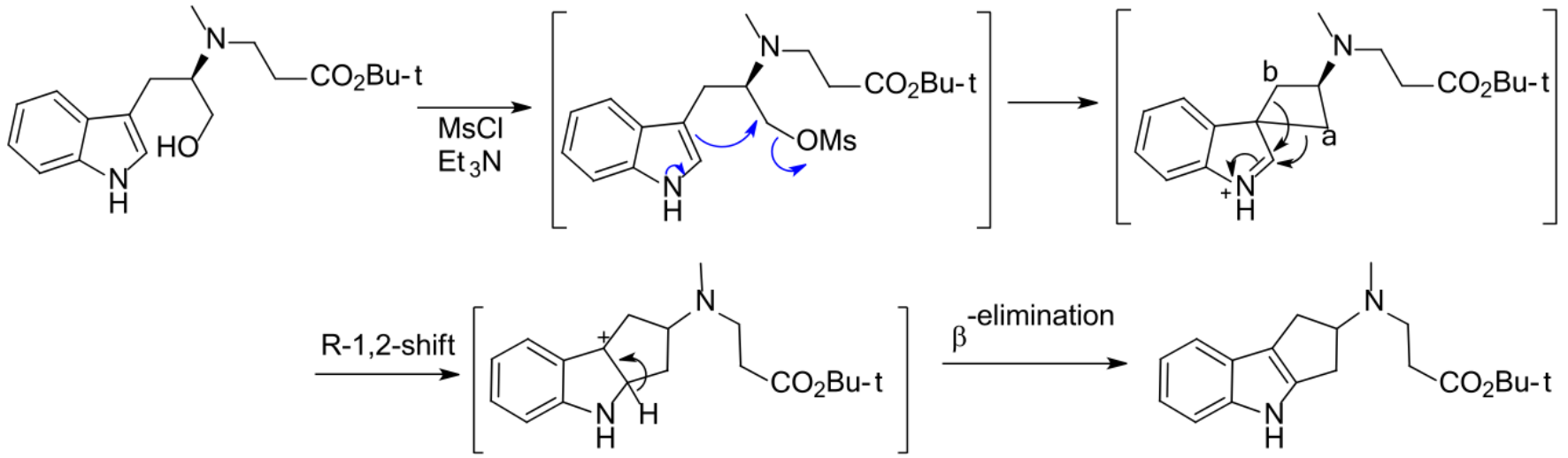
• Result: Attack on C5 avoids placing the positive charge on C3, as in A, bearing the electron-withdrawing carboxy function. Therefore, the only product is 5-bromo-3-thiophenecarboxylic acid.

Part 1: Electrophilic Aromatic Substitution

当吲哚3-位有取代基时，S_EAr反应仍发生在3-位

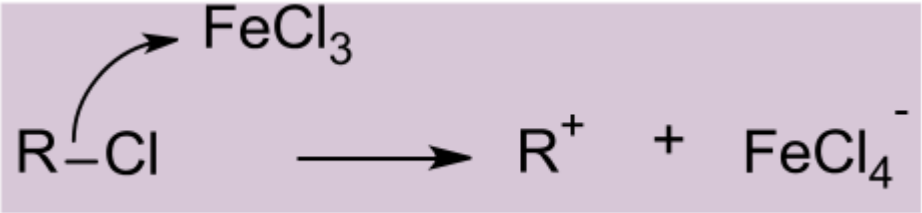
Propose the mechanism for the reaction below.



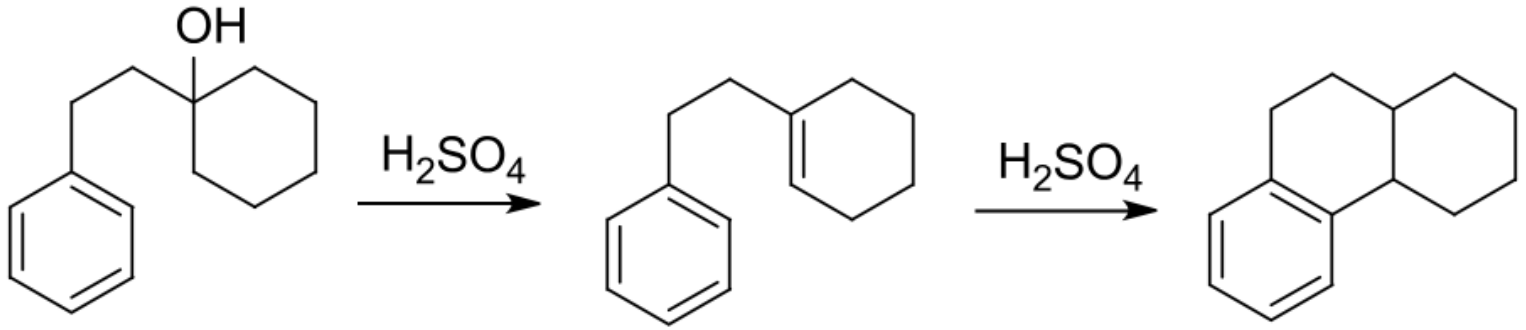


Part 1: Electrophilic Aromatic Substitution

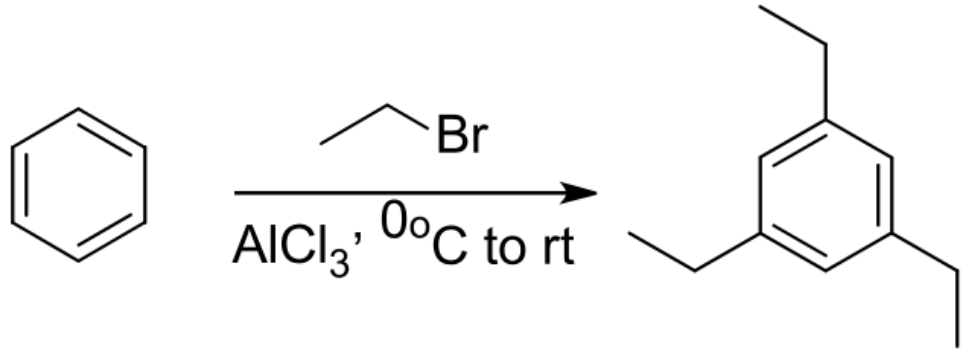
Friedel-Craft alkylation



醇和烯烃都可生成烷基化试剂

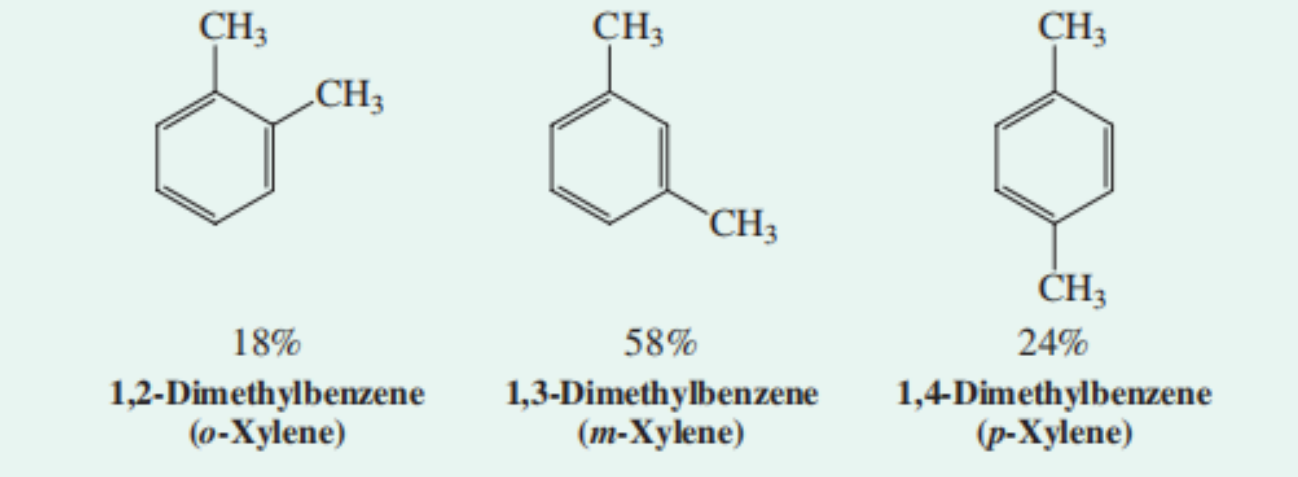


F-C alkylation is reversible

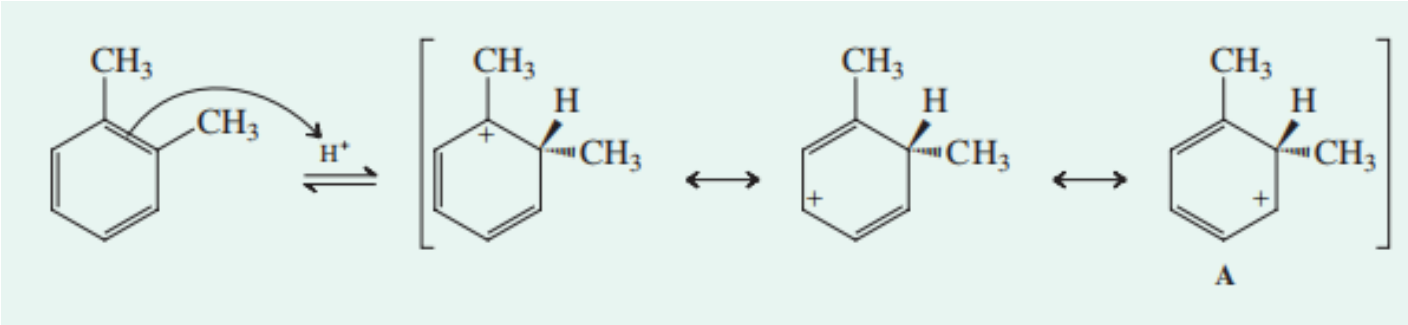


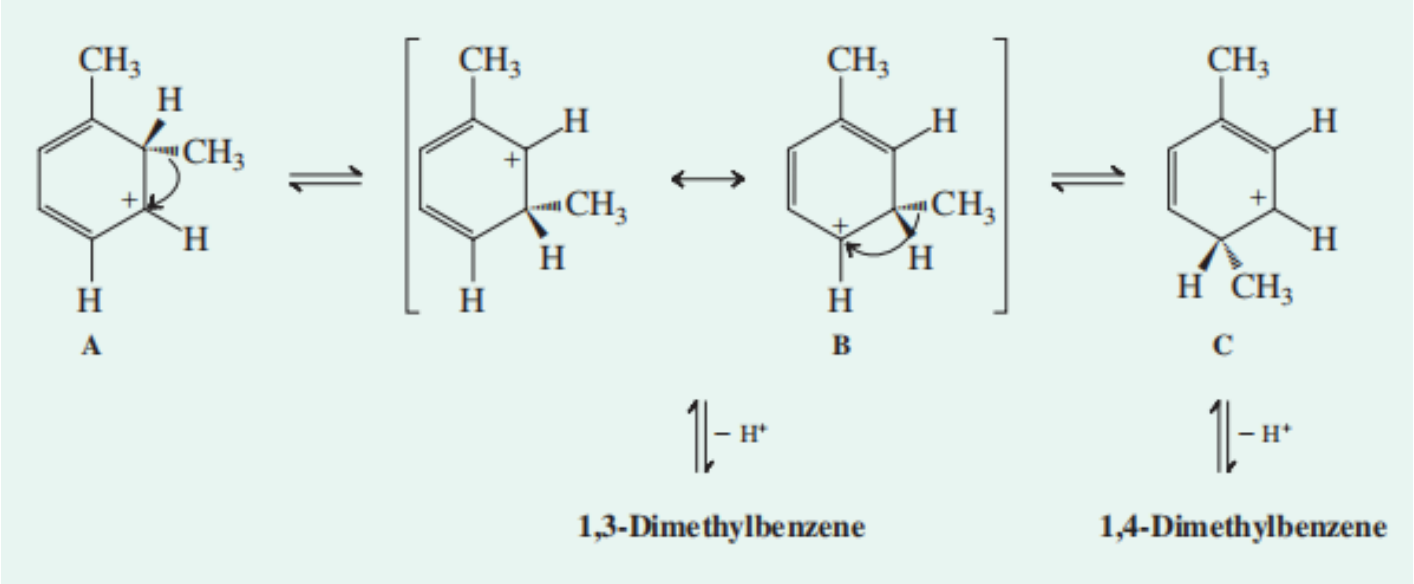
Part 1: Electrophilic Aromatic Substitution

Heating 1,2-dimethylbenzene with H^+ leads to the equilibrium mixture shown below. Formulate a mechanism for these isomerization.



Working with the Concepts: Reversible Friedel-Crafts Alkylations

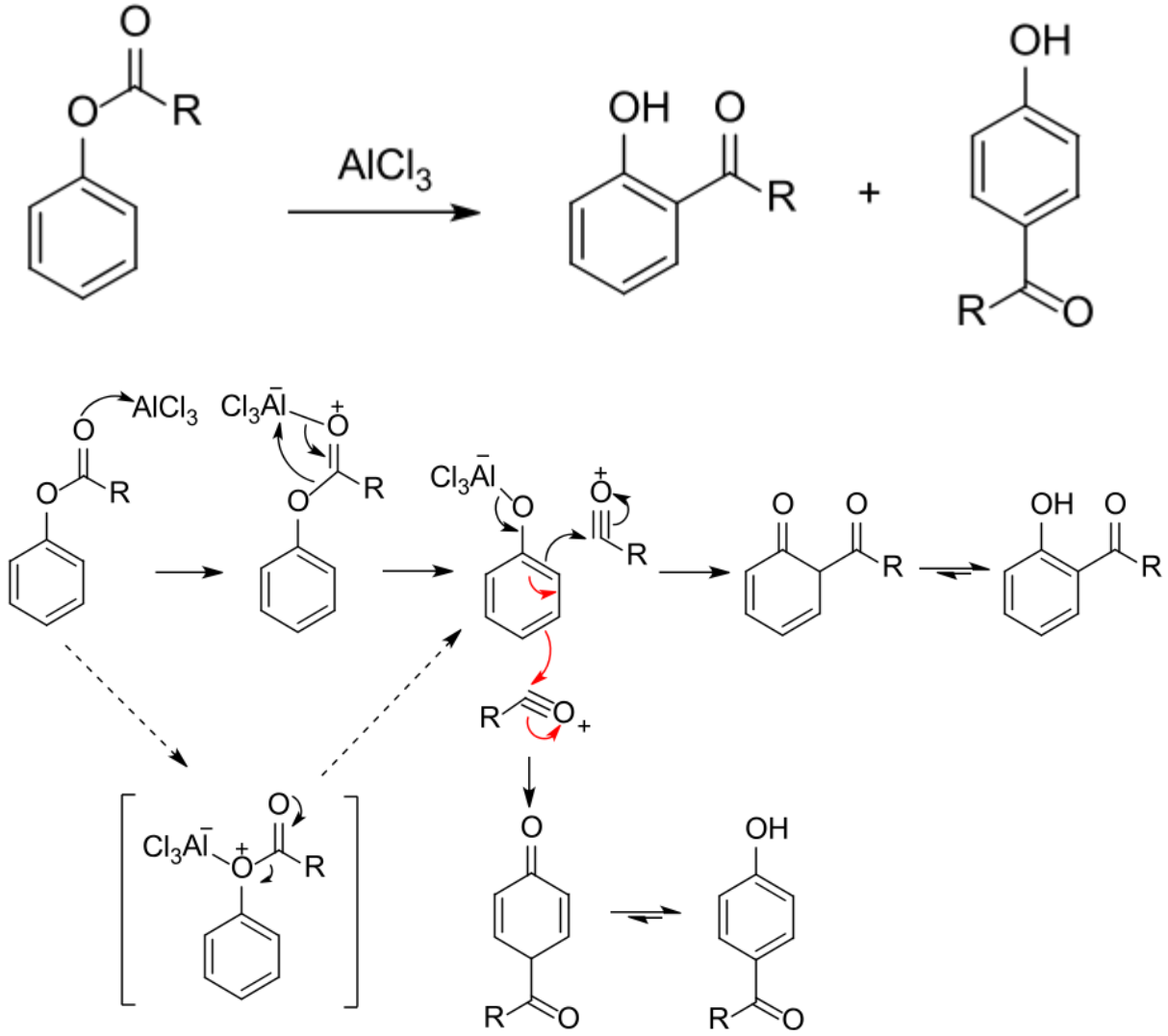




Part 1: Electrophilic Aromatic Substitution

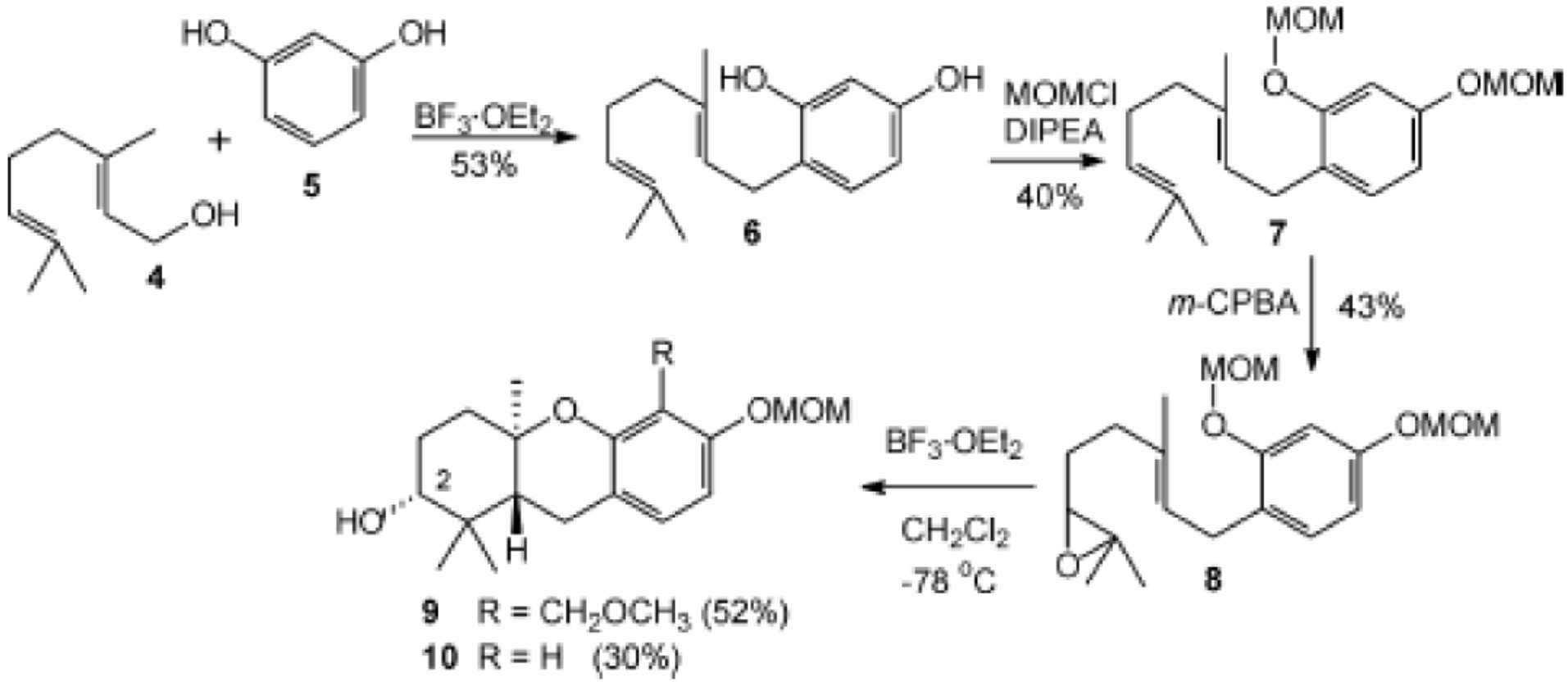
Fries rearrangement

Intramolecular F-C acylation



Part 1: Electrophilic Aromatic Substitution

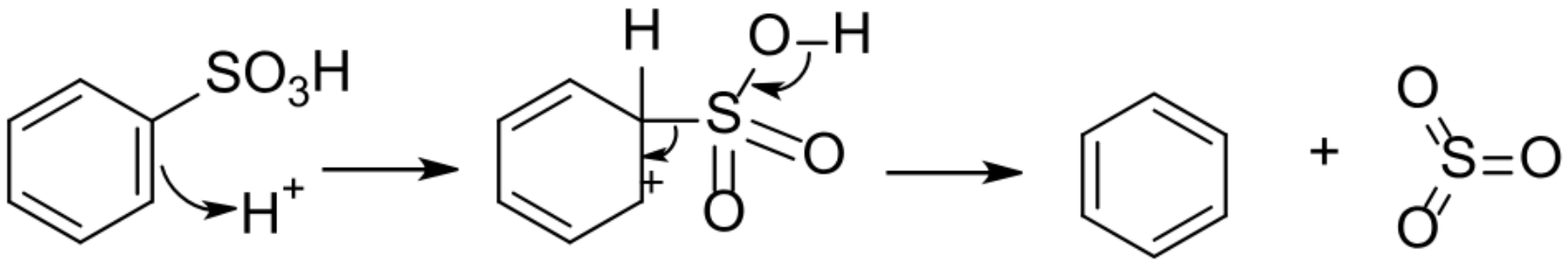
Intramolecular F-C alkylation Cascade Cyclization- S_EAr

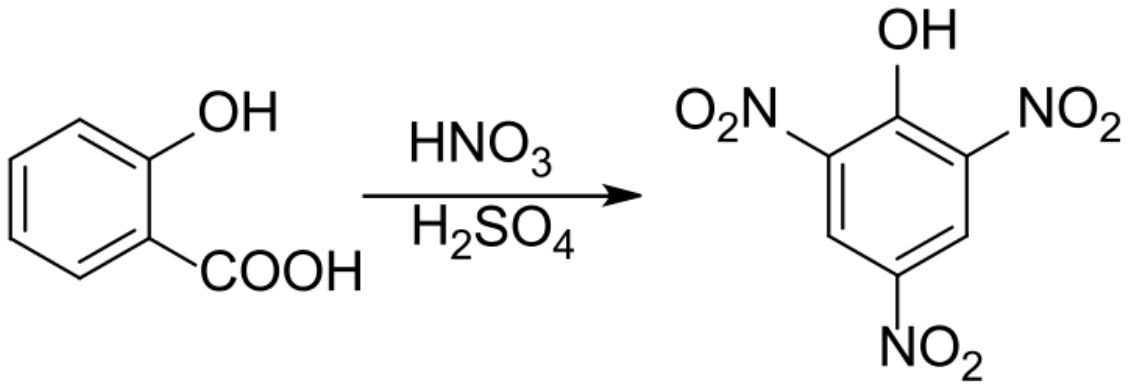


J. AM. CHEM. SOC. 2009, *131*, 14630–14631

Part 1: Electrophilic Aromatic Substitution

ipso　芳香烃同位亲电取代

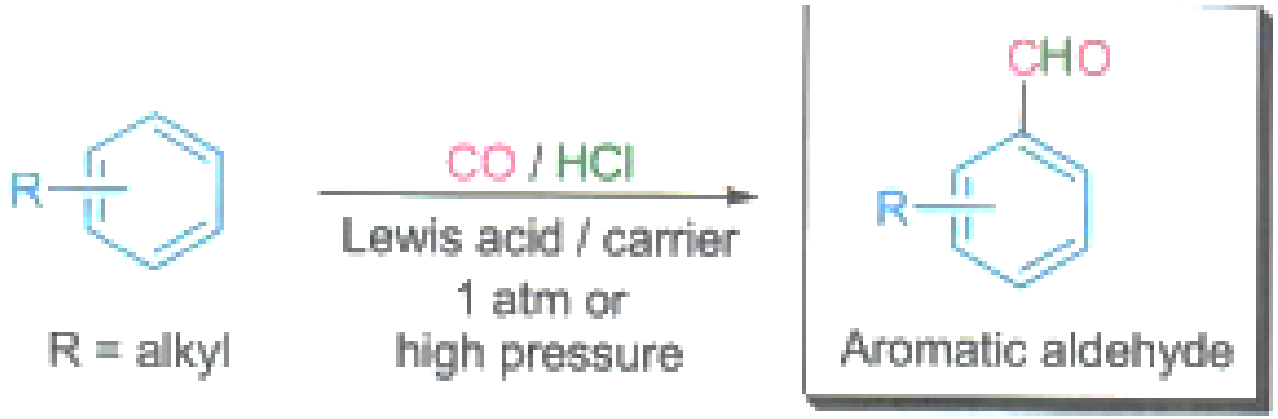


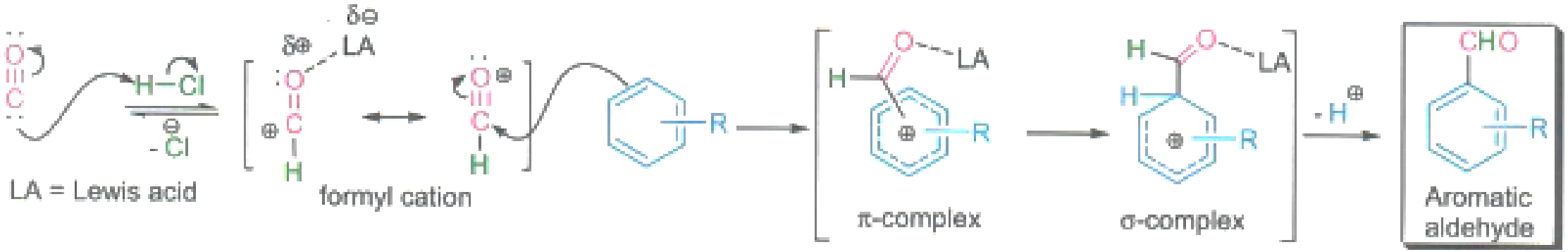


Electrophilic substitution-related reactions on aromatic rings

1. Gattermann-Koch Formylation

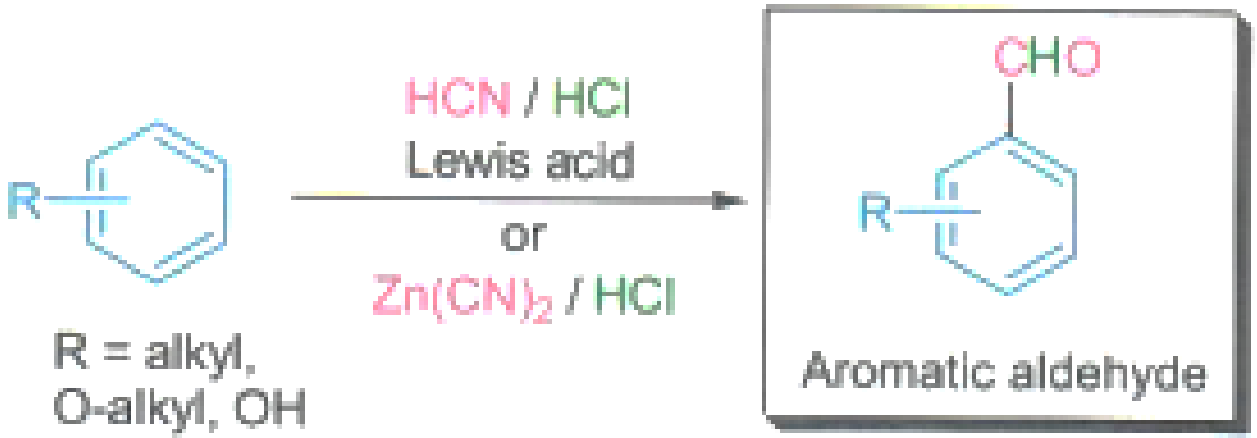
此反应试用与底物为苯或者烷基苯

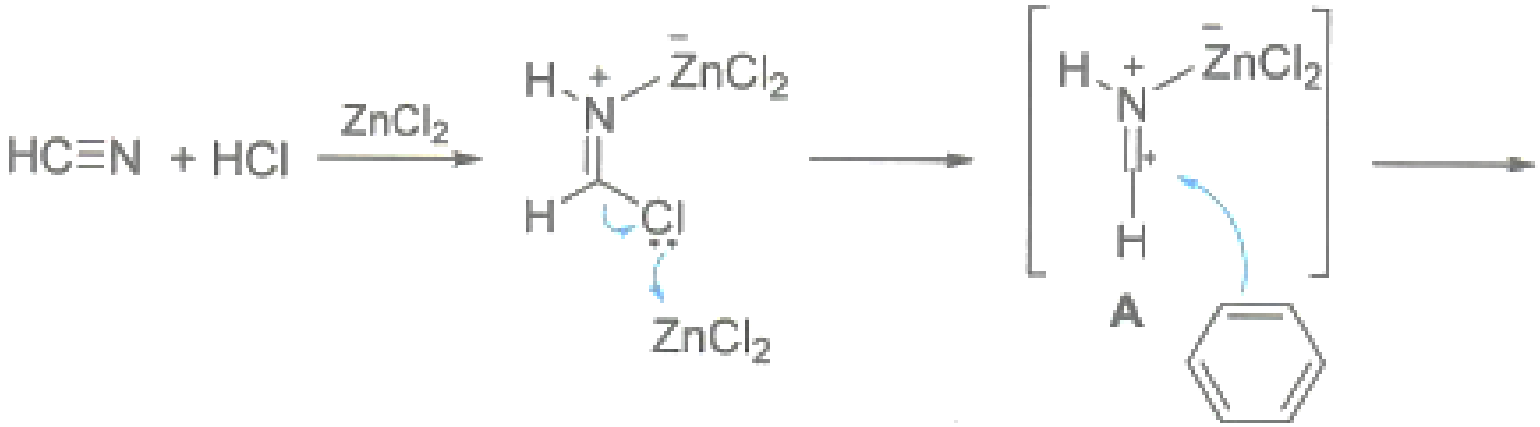


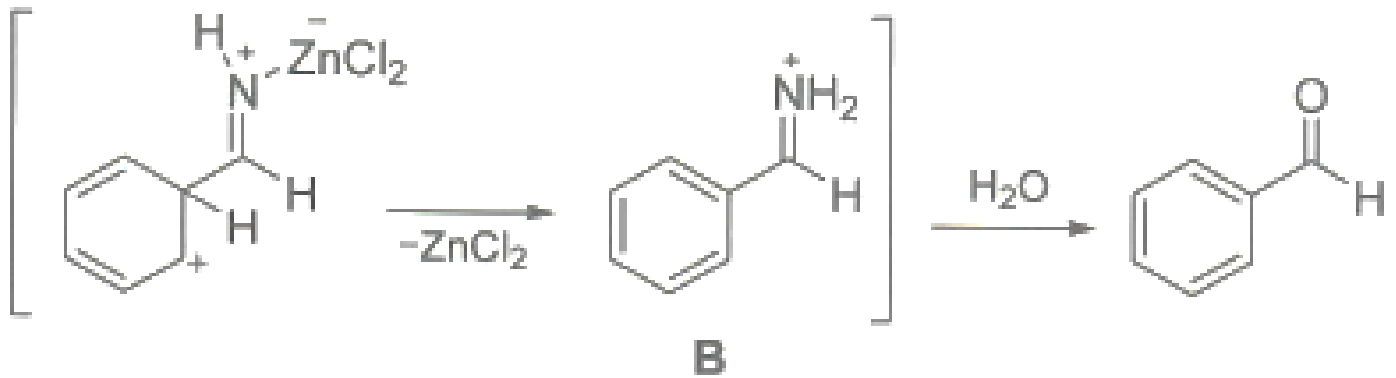


Electrophilic substitution-rel

2. Gattermann Formylation

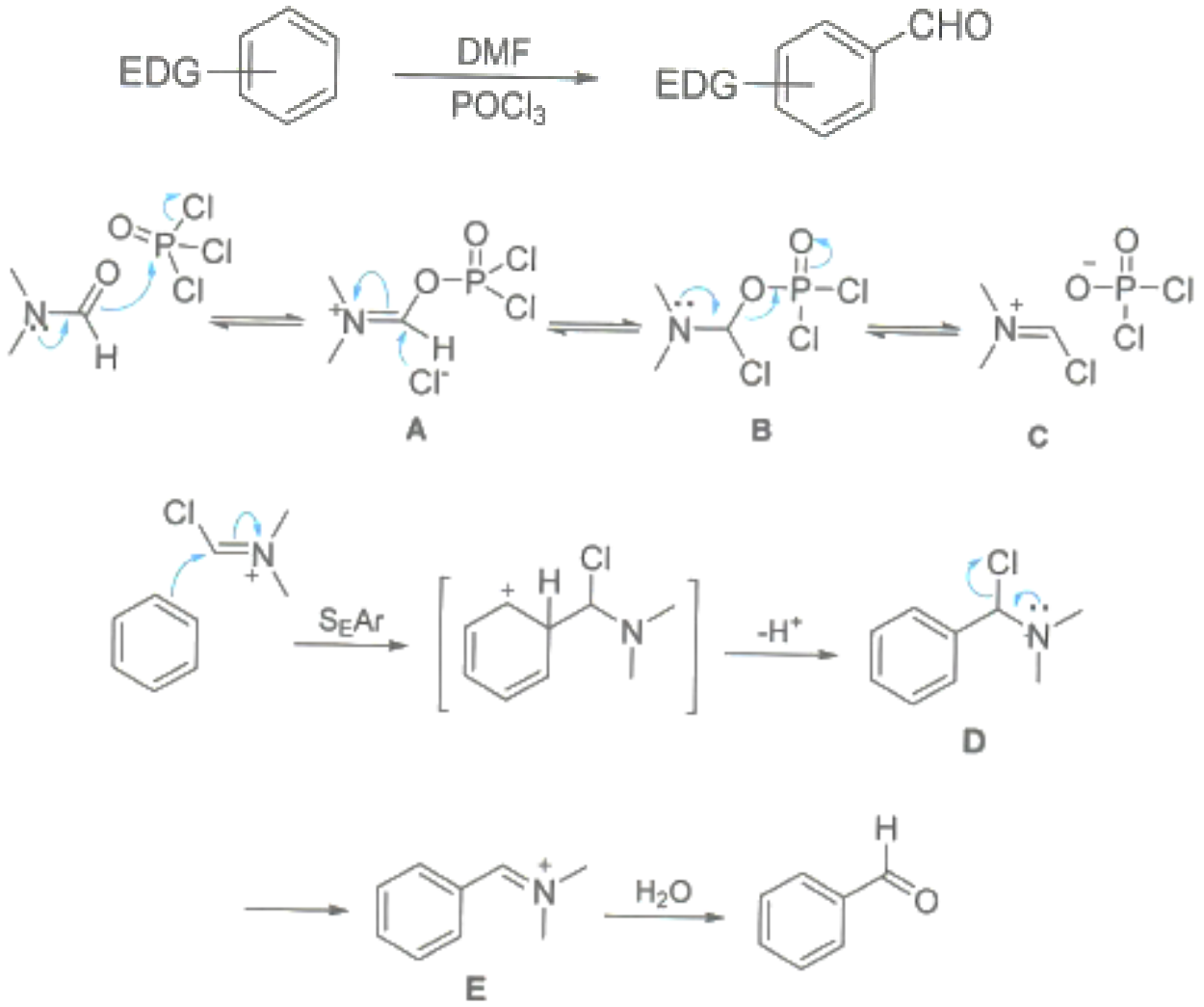






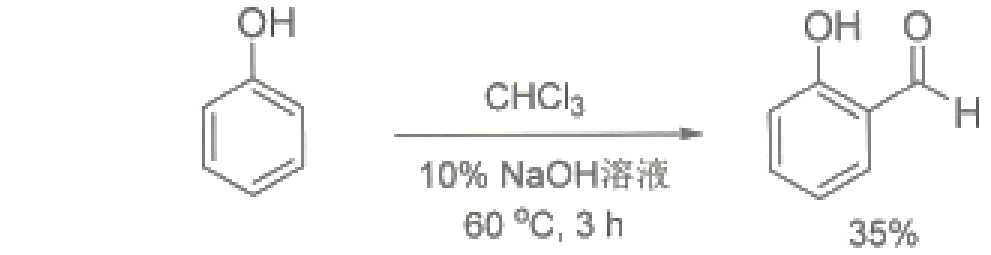
Electrophilic substitution-related reactions on aromatic rings

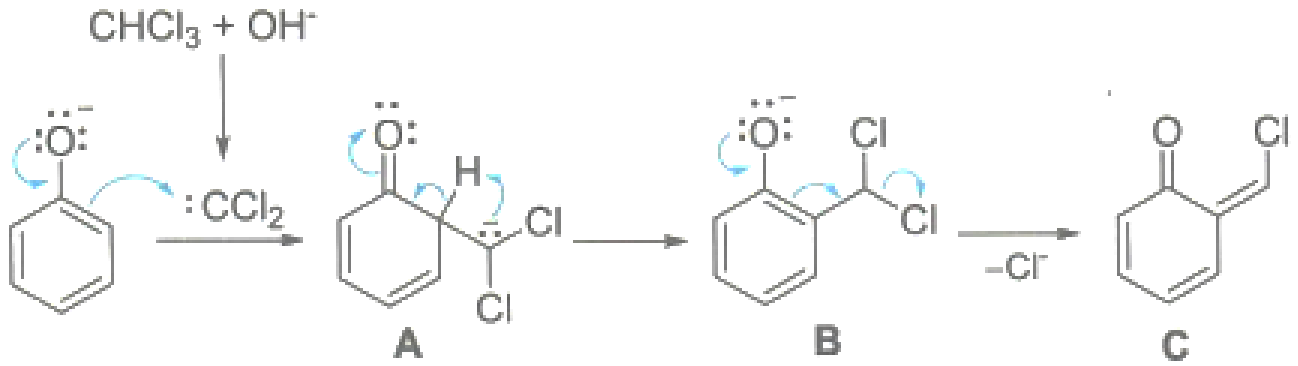
3. Vilsmeier-Haack Formylation

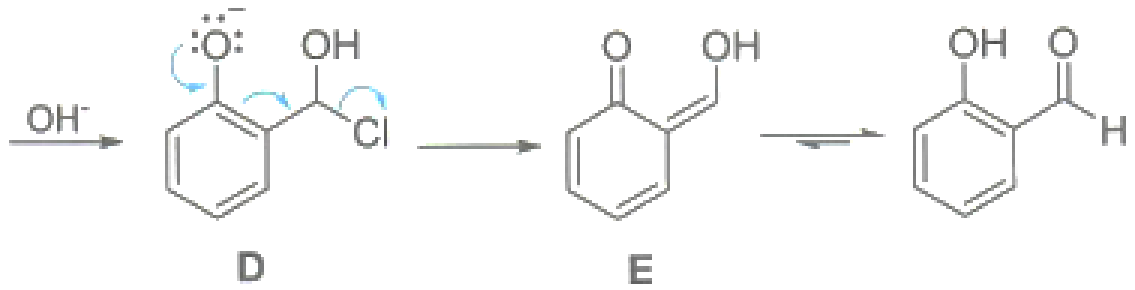


Electrophilic substitution-related reactions on aromatic rings

4. Reimer-Tiemann Reaction alkaline condition

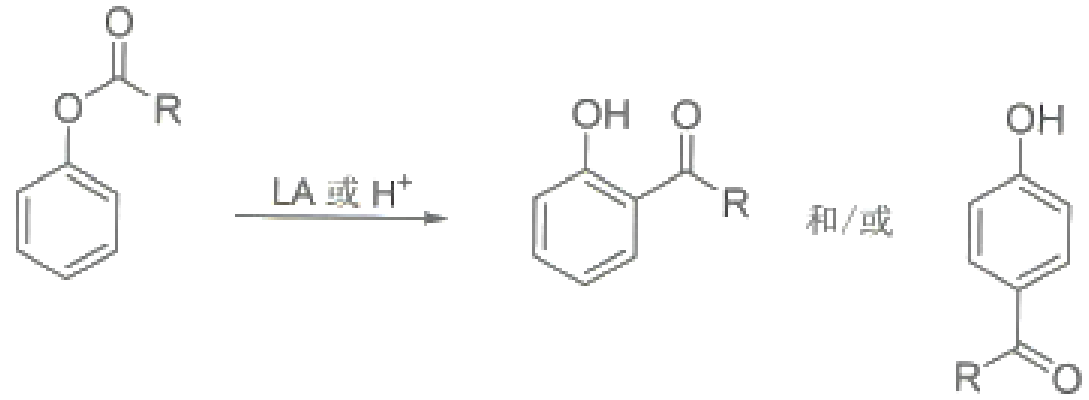


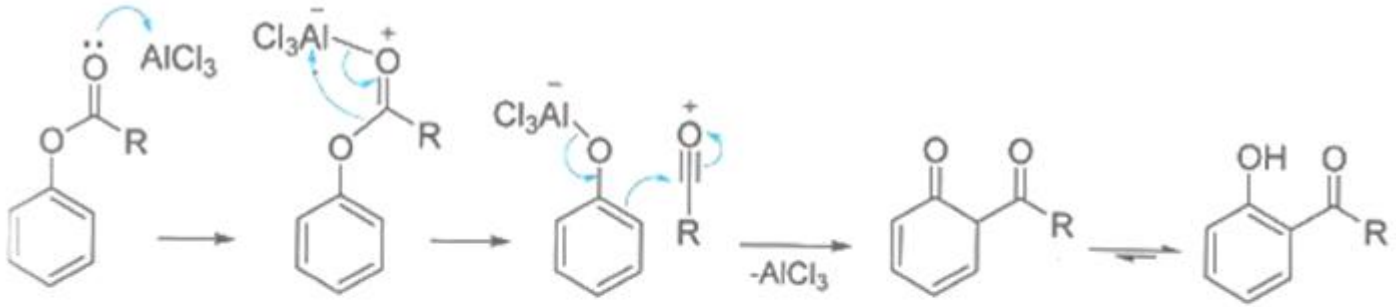


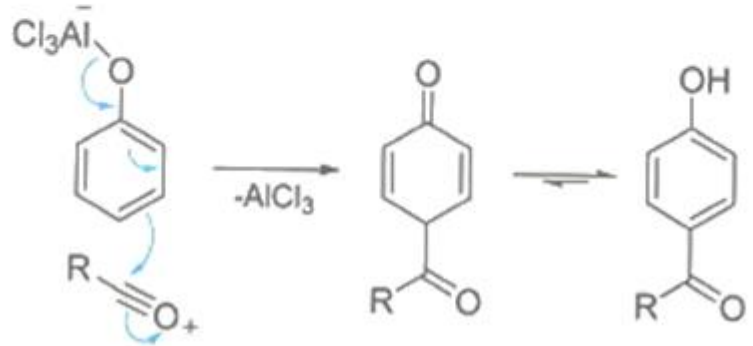


Electrophilic substitution-related reactions on aromatic rings

5. Fries Rearrangement

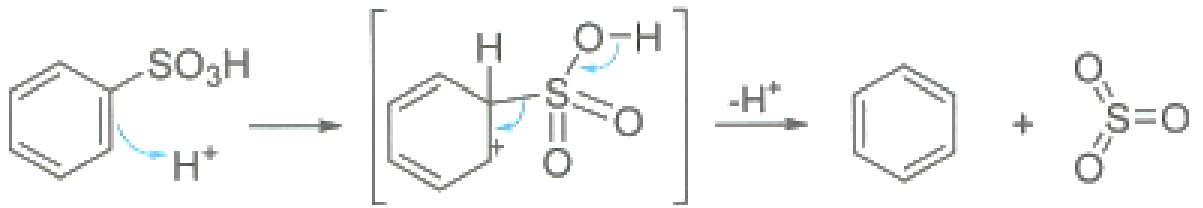


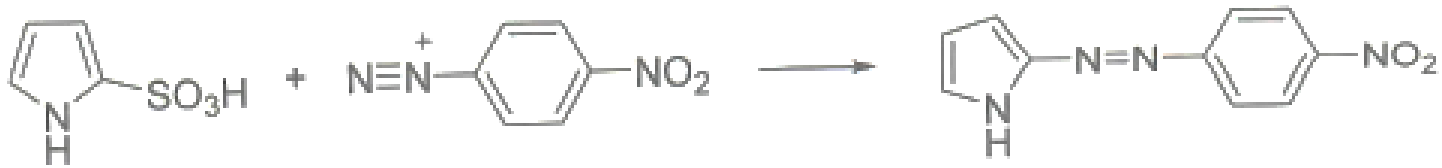




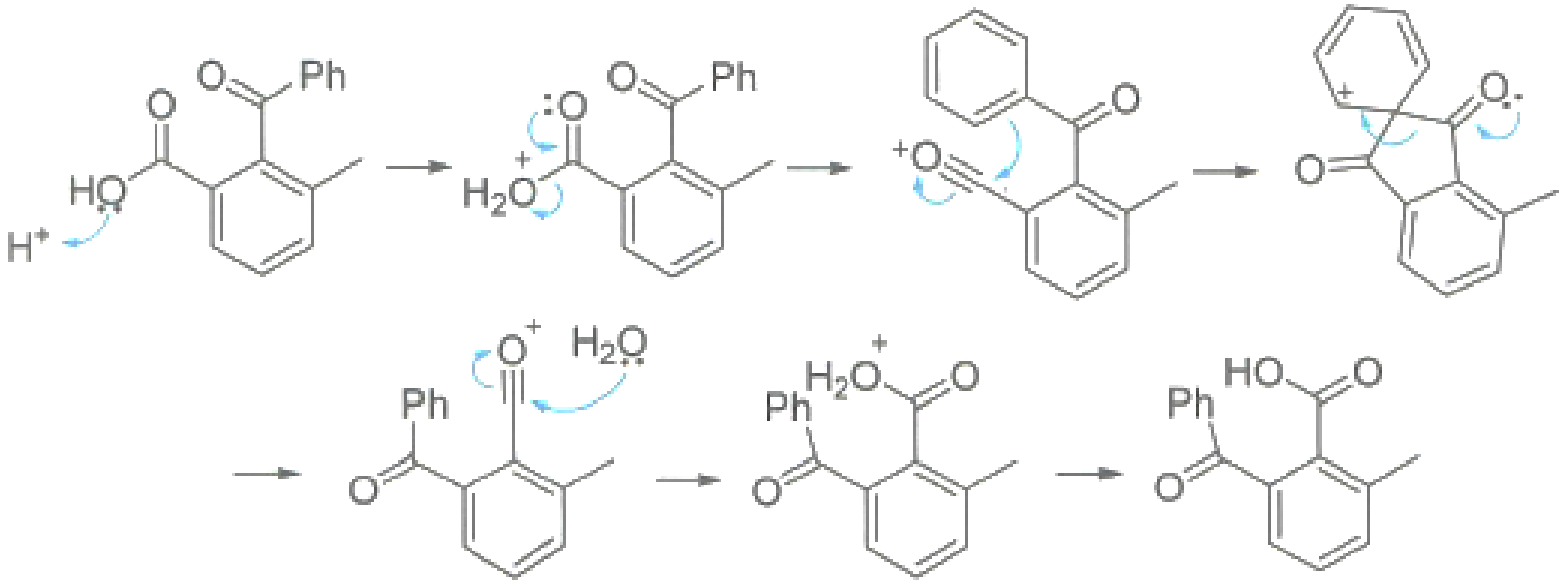
Electrophilic substitution-related reactions on aromatic rings

6. 芳香烃同位亲电取代反应

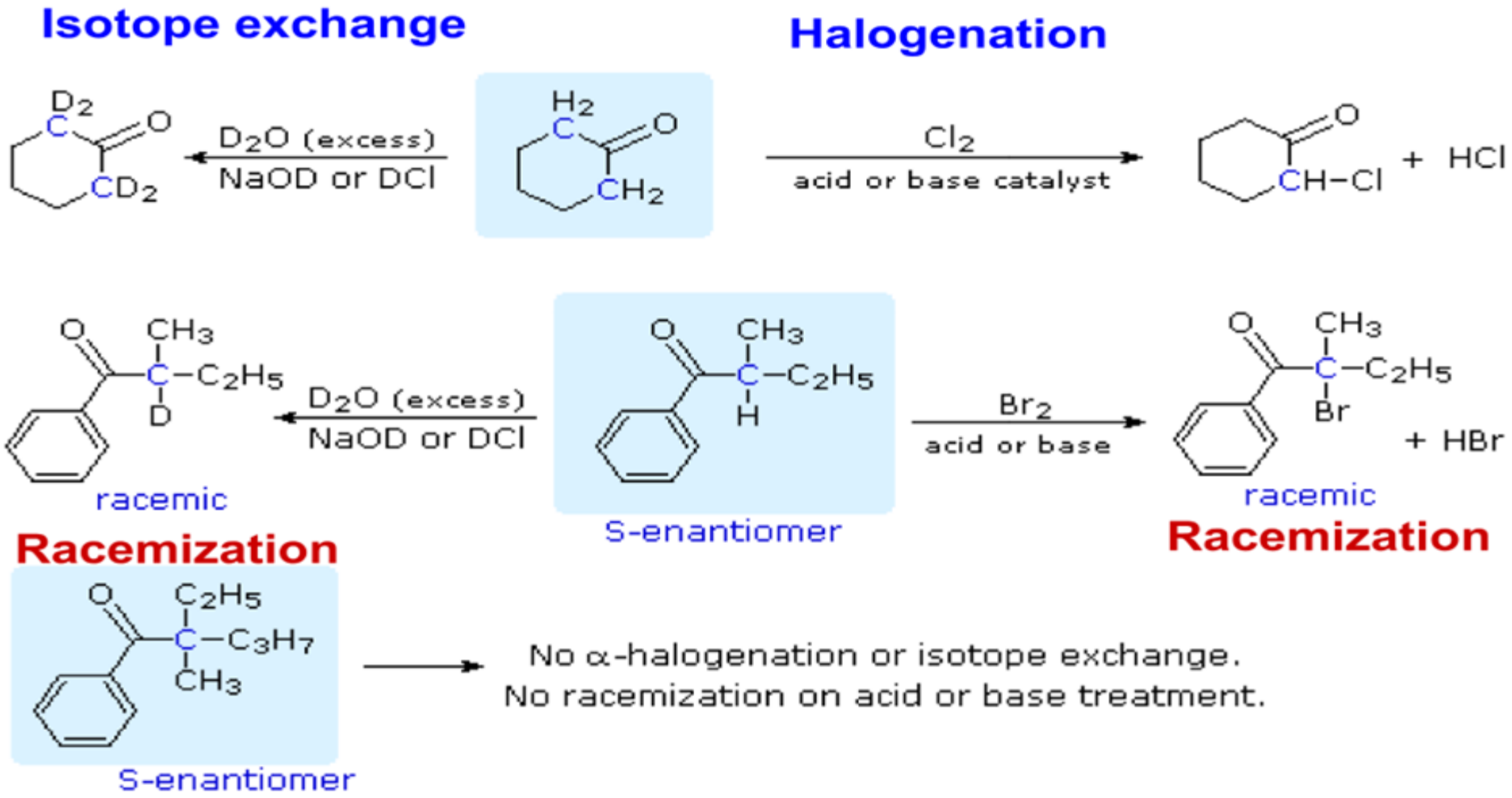




Electrophilic substitution-related reactions on aromatic rings

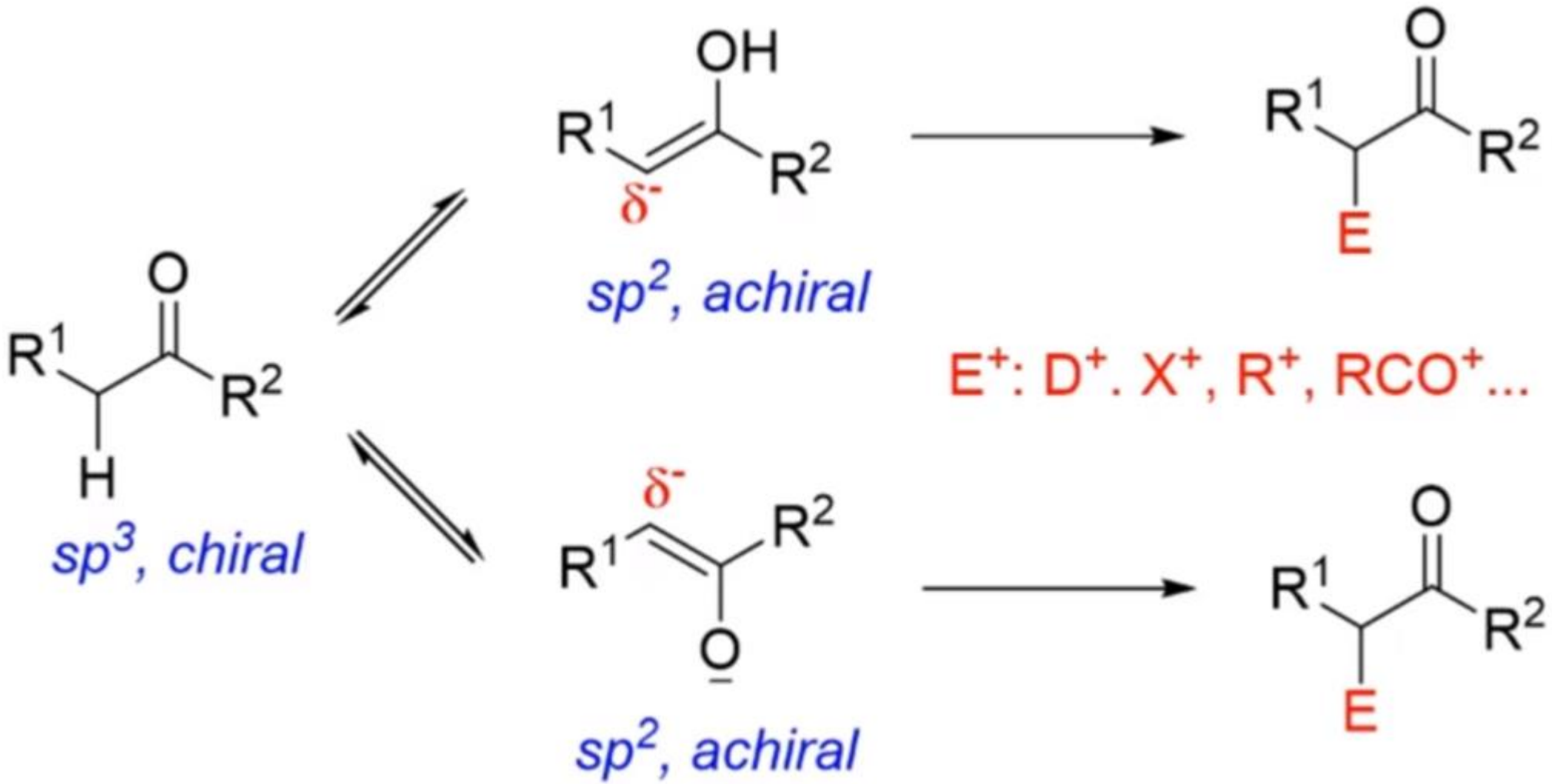


Part 2: Electrophilic Substitution on α-Carbon of Carbonyl Groups



- Isotope exchange, halogenation, alkylation, acylation, racemization
- Either acid or base catalyzed
- Limited to C-H alpha to the carbonyl group.

Part 2: Electrophilic Substitution on α-Carbon of Carbonyl Groups

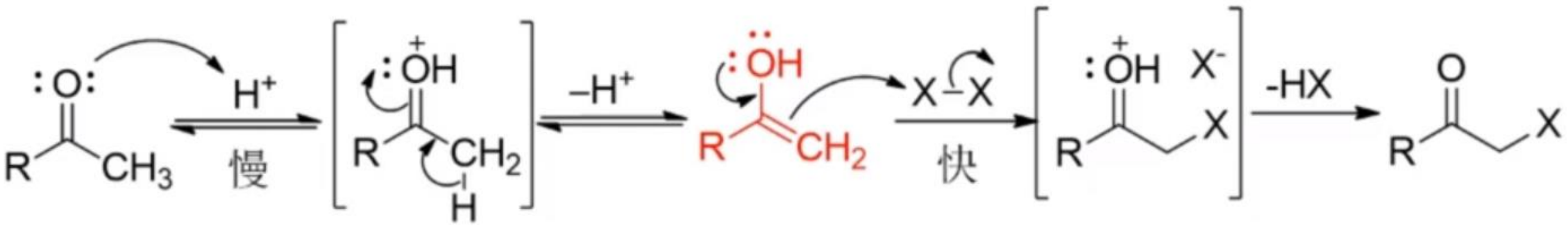


Part 2: Electrophilic Substitution on α-Carbon of Carbonyl Groups

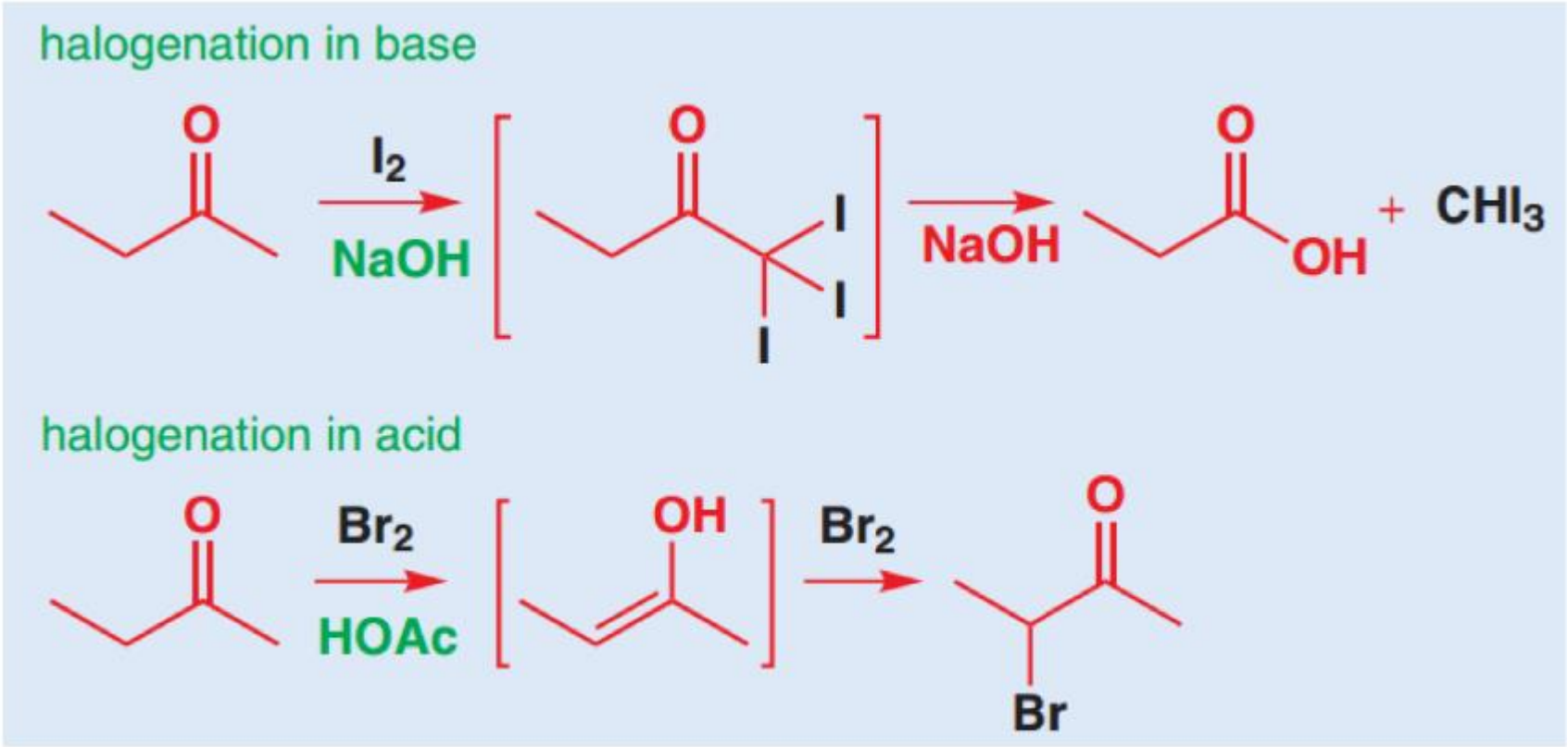
5.5 Halogenation on α-Carbon of Carbonyl groups

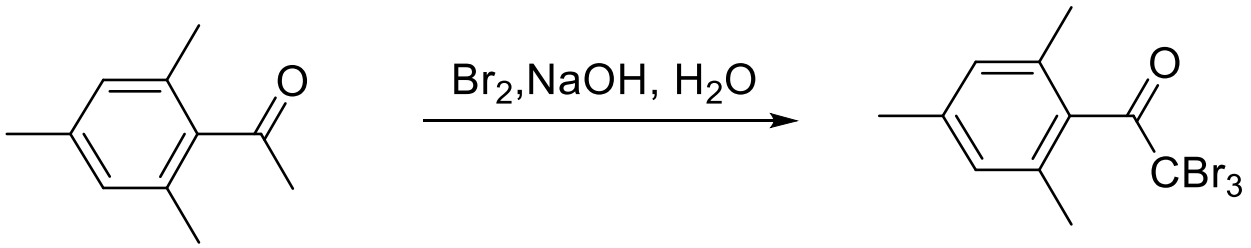
Base-Catalyzed -Halogenation

Acid-Catalyzed -Halogenation



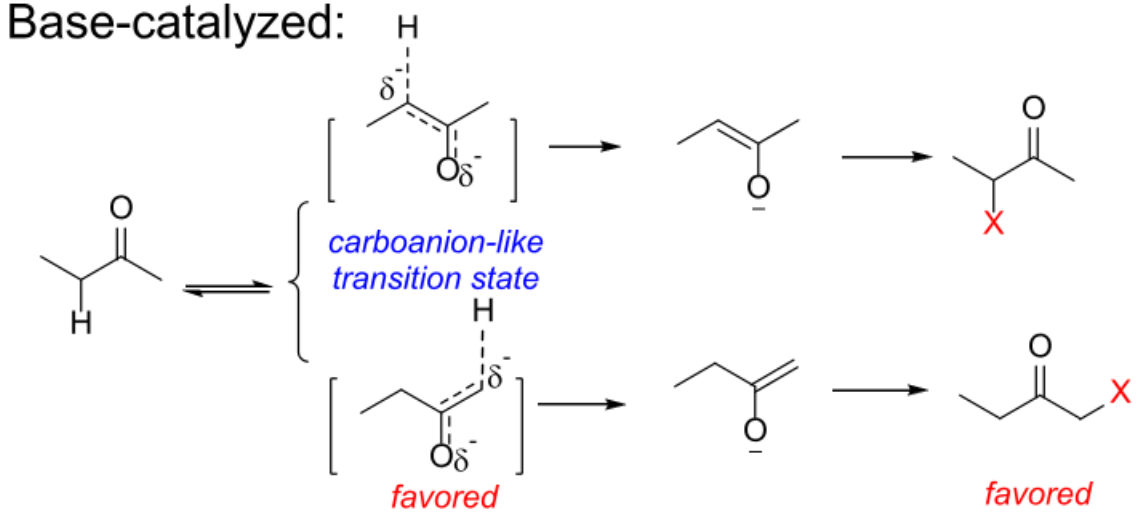
Part 2: Electrophilic Substitution on α-Carbon of Carbonyl Groups

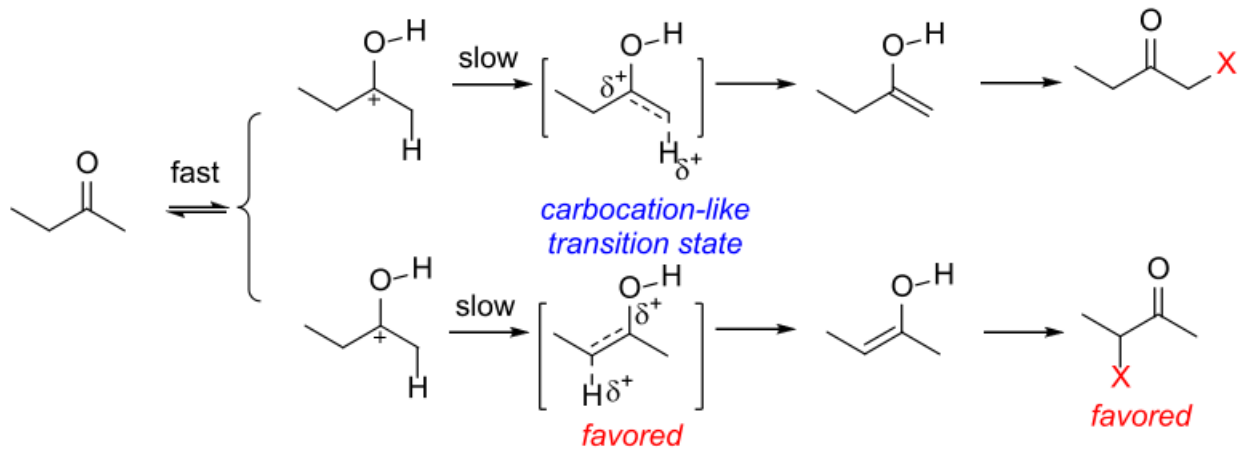


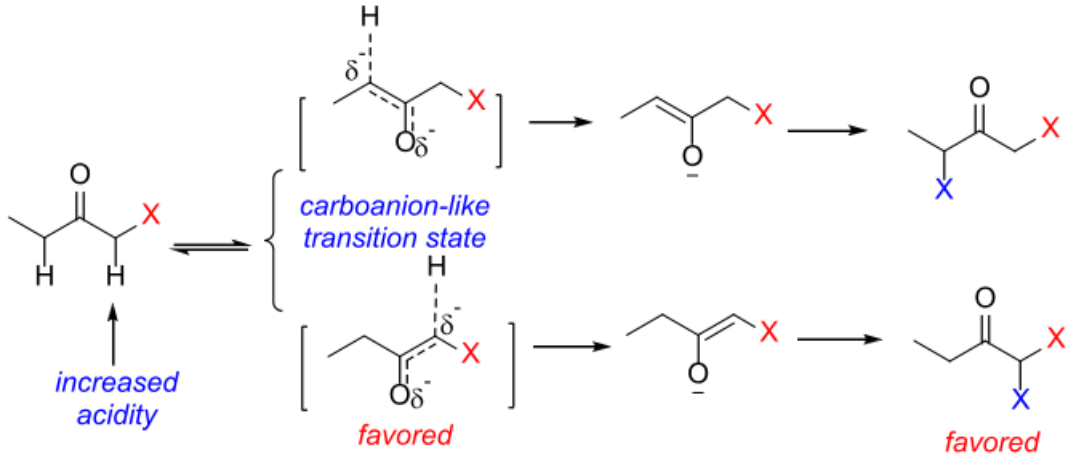


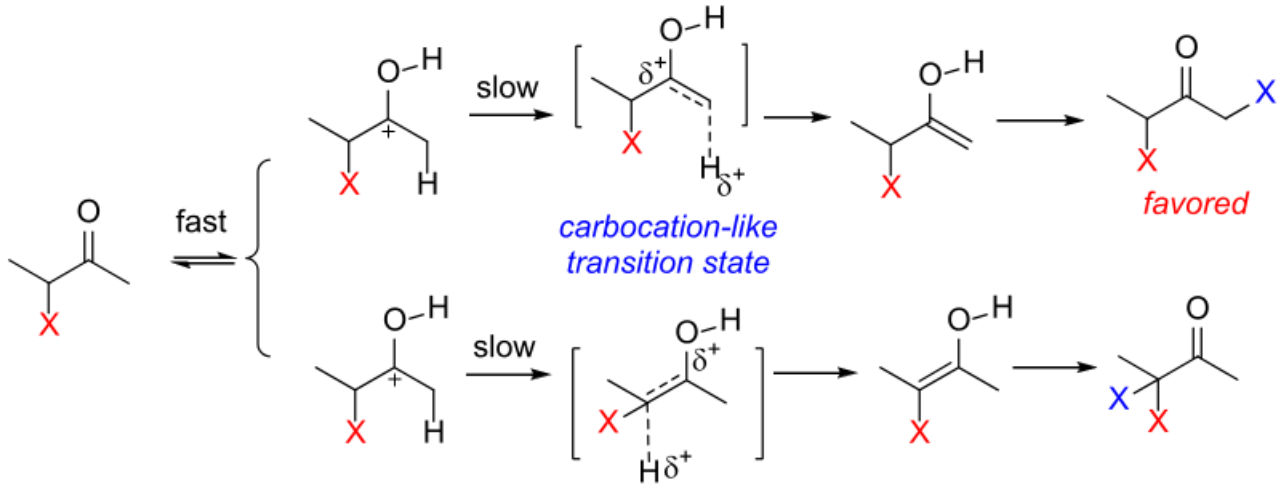
89%

Part 2: Electrophilic Substitution on α-Carbon of Carbonyl Groups



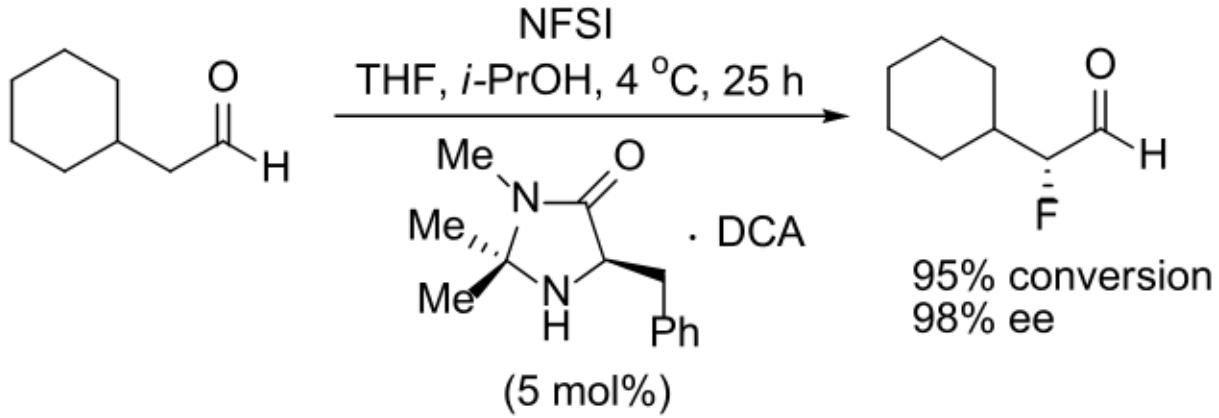


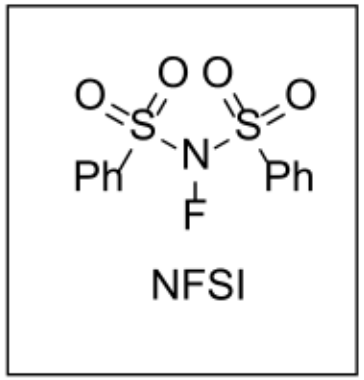




Part 2: Electrophilic Substitution on α-Carbon of Carbonyl Groups

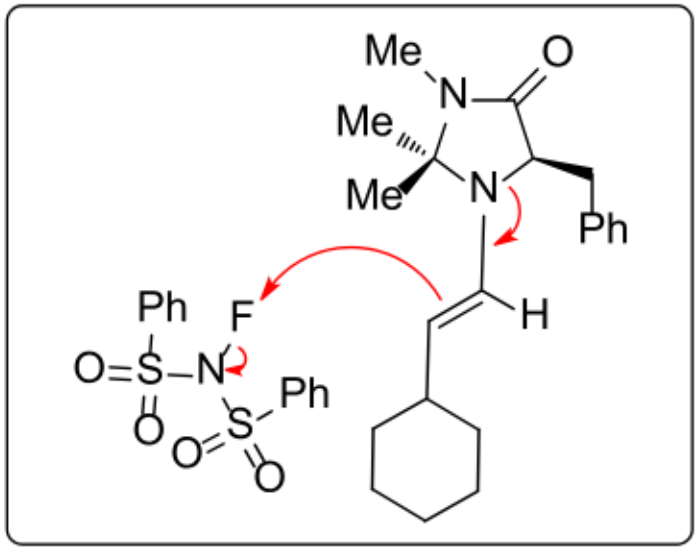
Organic Compound-Catalyzed -Halogenation





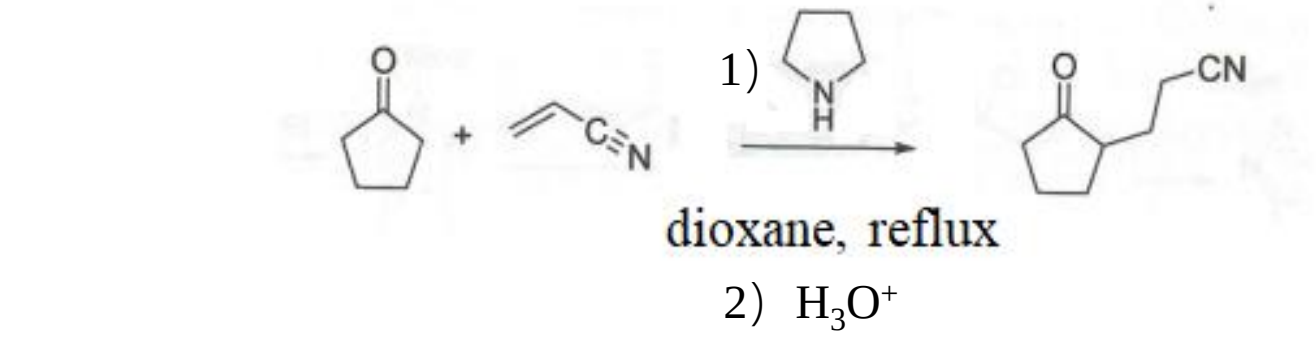
enamine formation

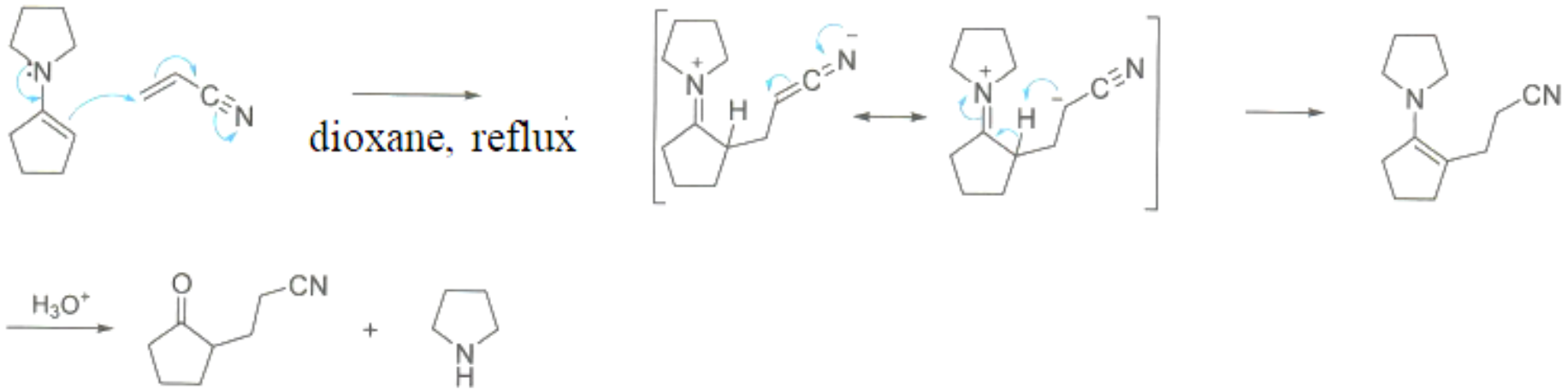
enhanced nucleophilicity



Nucleophilic Addition to Carbonyl Group

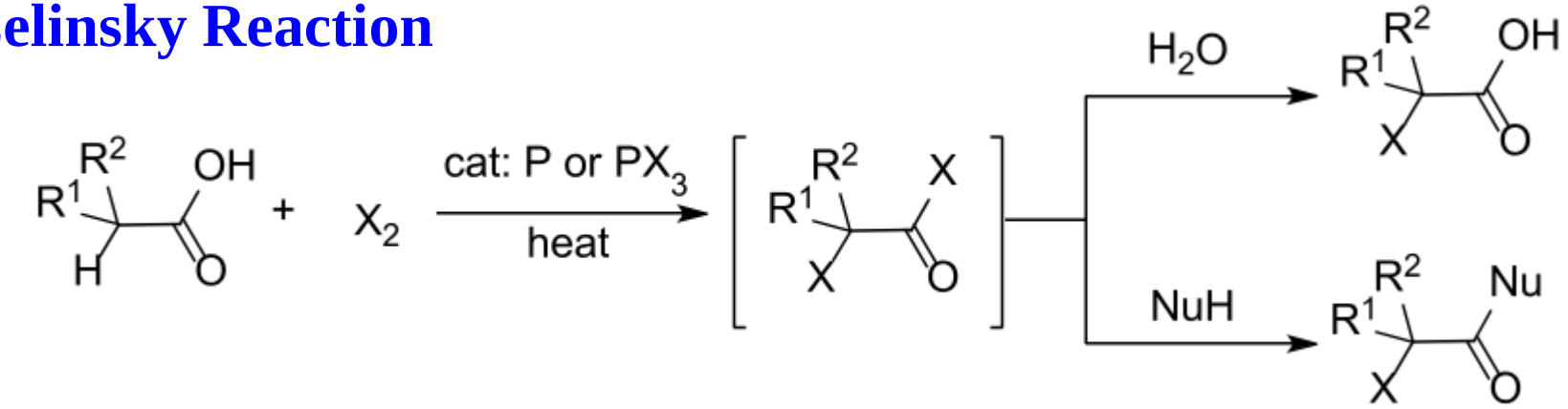
3) 1,4-Additions (conjugate addition) of enamine

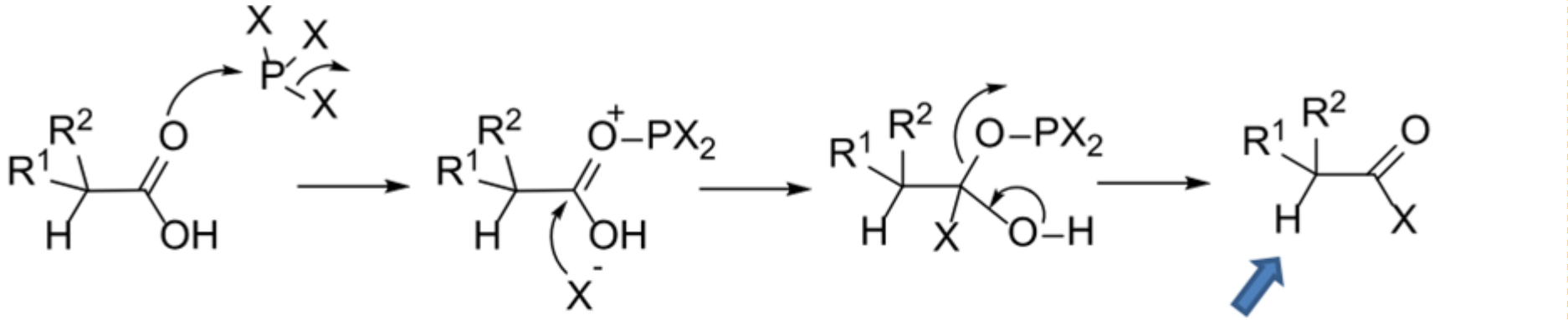


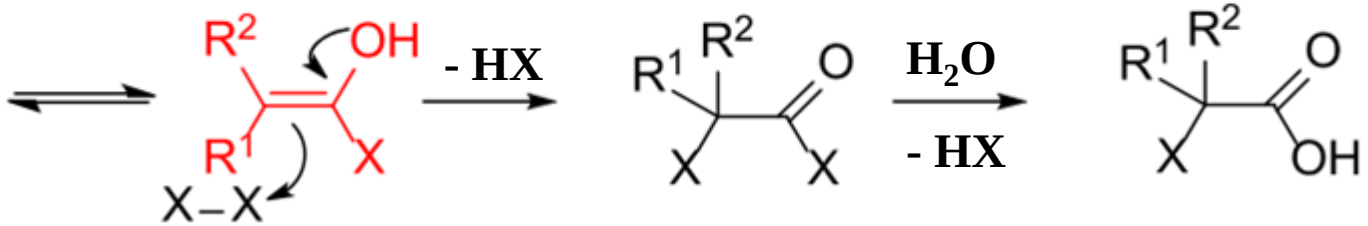


Part 2: Electrophilic Substitution on α-Carbon of Carbonyl Groups

Hell-Volhard-Zelinsky Reaction

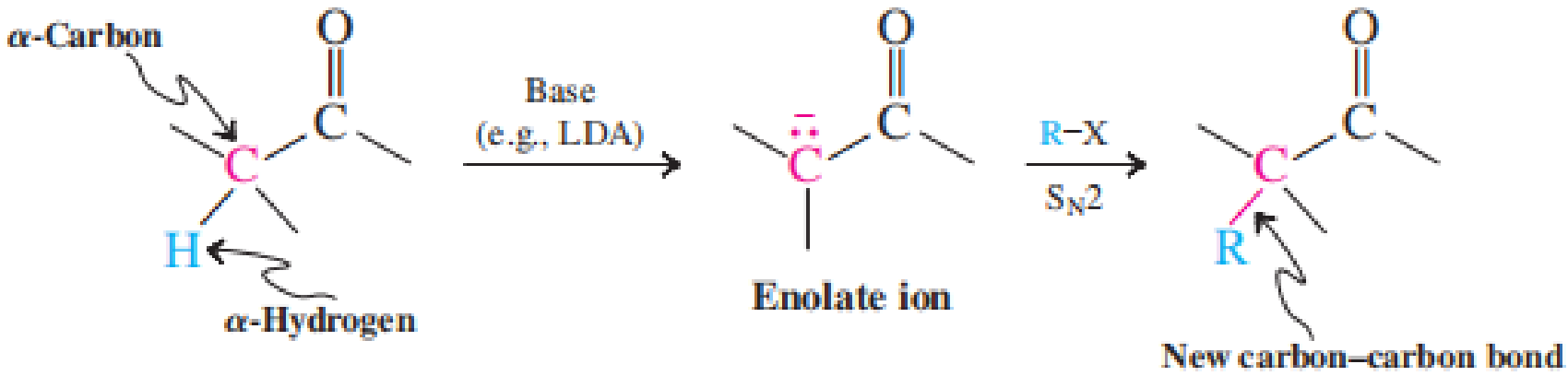




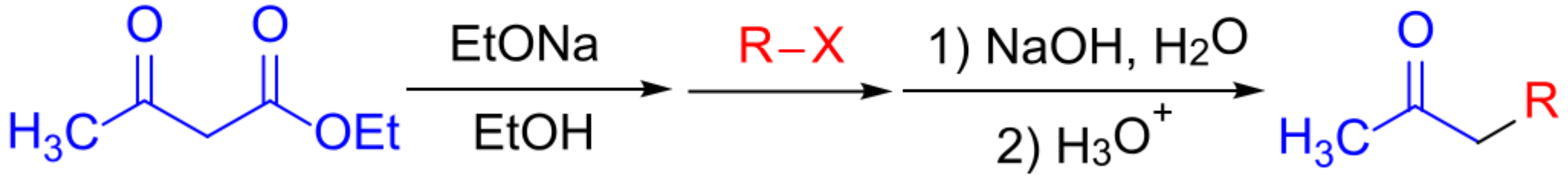


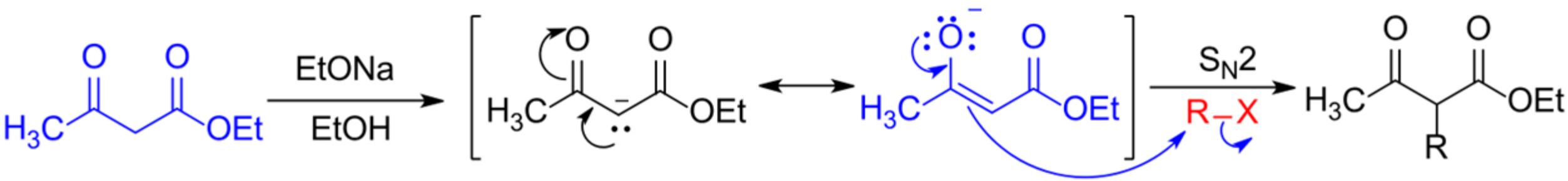
Part 2: Electrophilic Substitution on α-Carbon of Carbonyl Groups

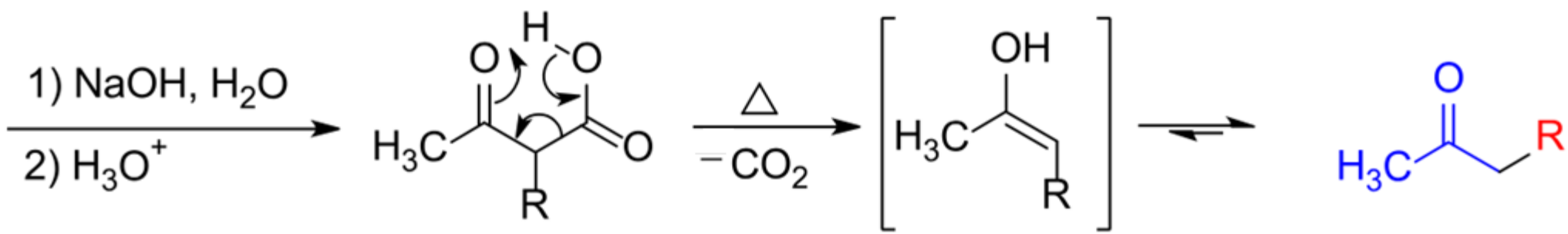
5.6 Alkylation on α-Carbon of Carbonyl groups



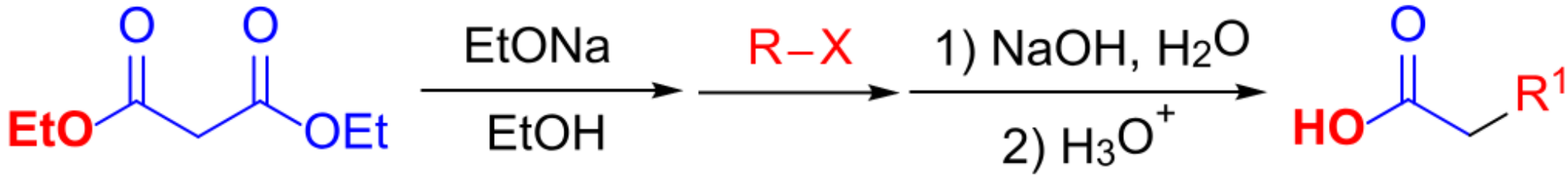
乙酰乙酸乙酯：

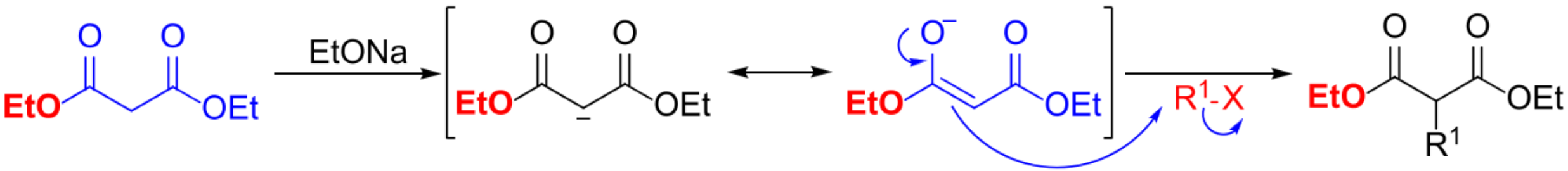

EtONa
EtOH
R–X
1) NaOH, H2O
2) H3O+

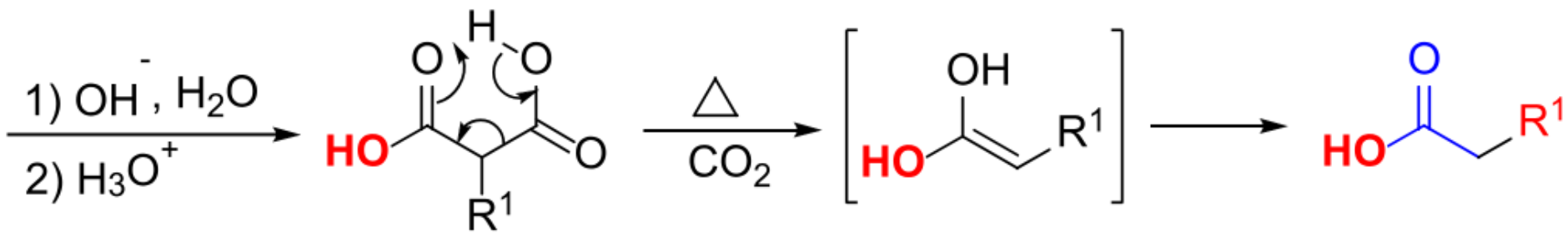

EtONa
EtOH
SN2
R–X


1) NaOH, H2O
2) H3O+
△
−CO2

丙二酸二乙酯：

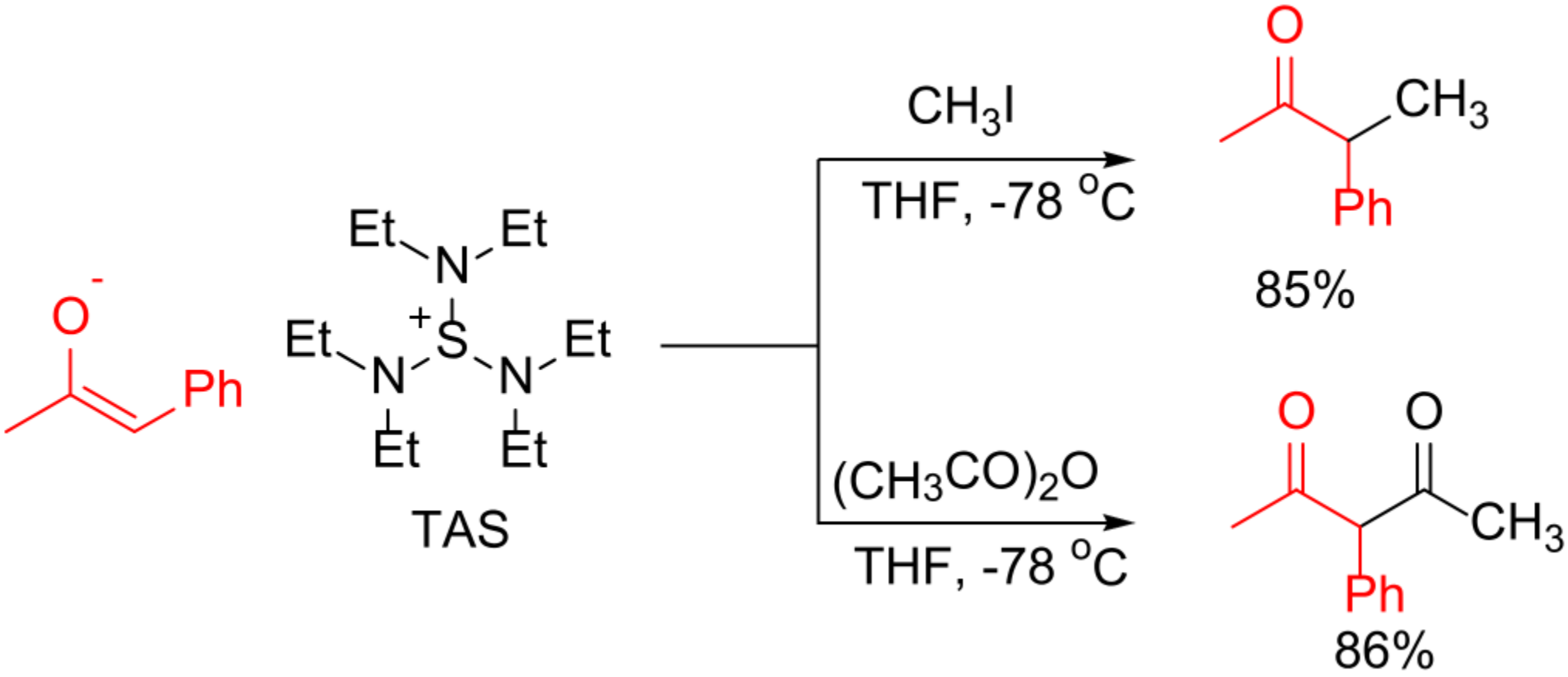

EtO
O
O
OEt
EtONa
EtOH
R–X
1) NaOH, H2O
2) H3O+
HO
R1


EtO
O
O
OEt
EtONa
R1-X
R1


1) OH-, H2O
2) H3O+
HO
H
O
R1
△
CO2
OH
HO
R1

Part 2: Electrophilic Substitution on α-Carbon of Carbonyl Groups

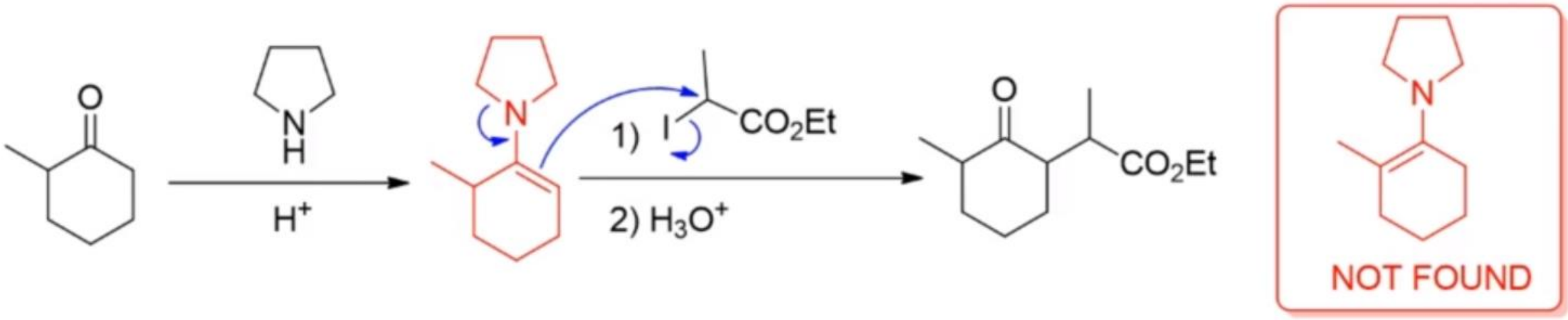
Nucleophile with bulky cation



大位阻阳离子，提高亲核试剂的亲核性

Part 2: Electrophilic Substitution on α-Carbon of Carbonyl Groups

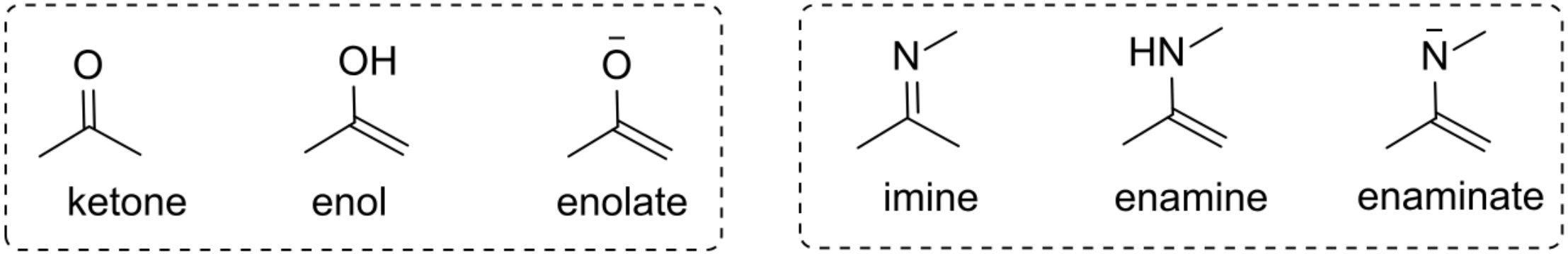
Nucleophile-enamine

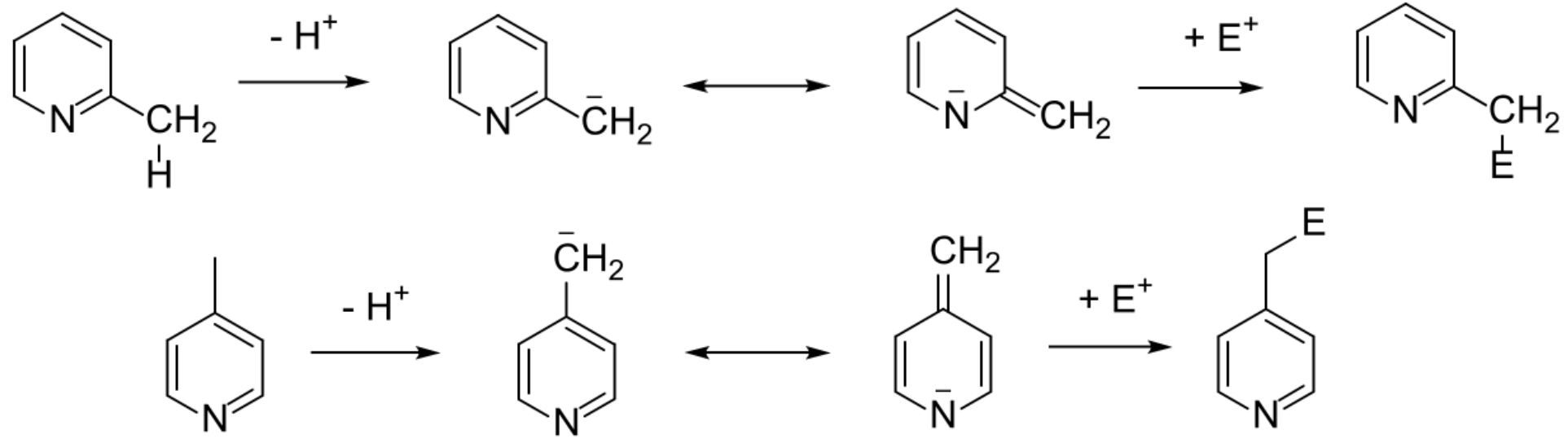


利用烯胺提高区域选择性

Part 2: Electrophilic Substitution on α-Carbon of Carbonyl Groups

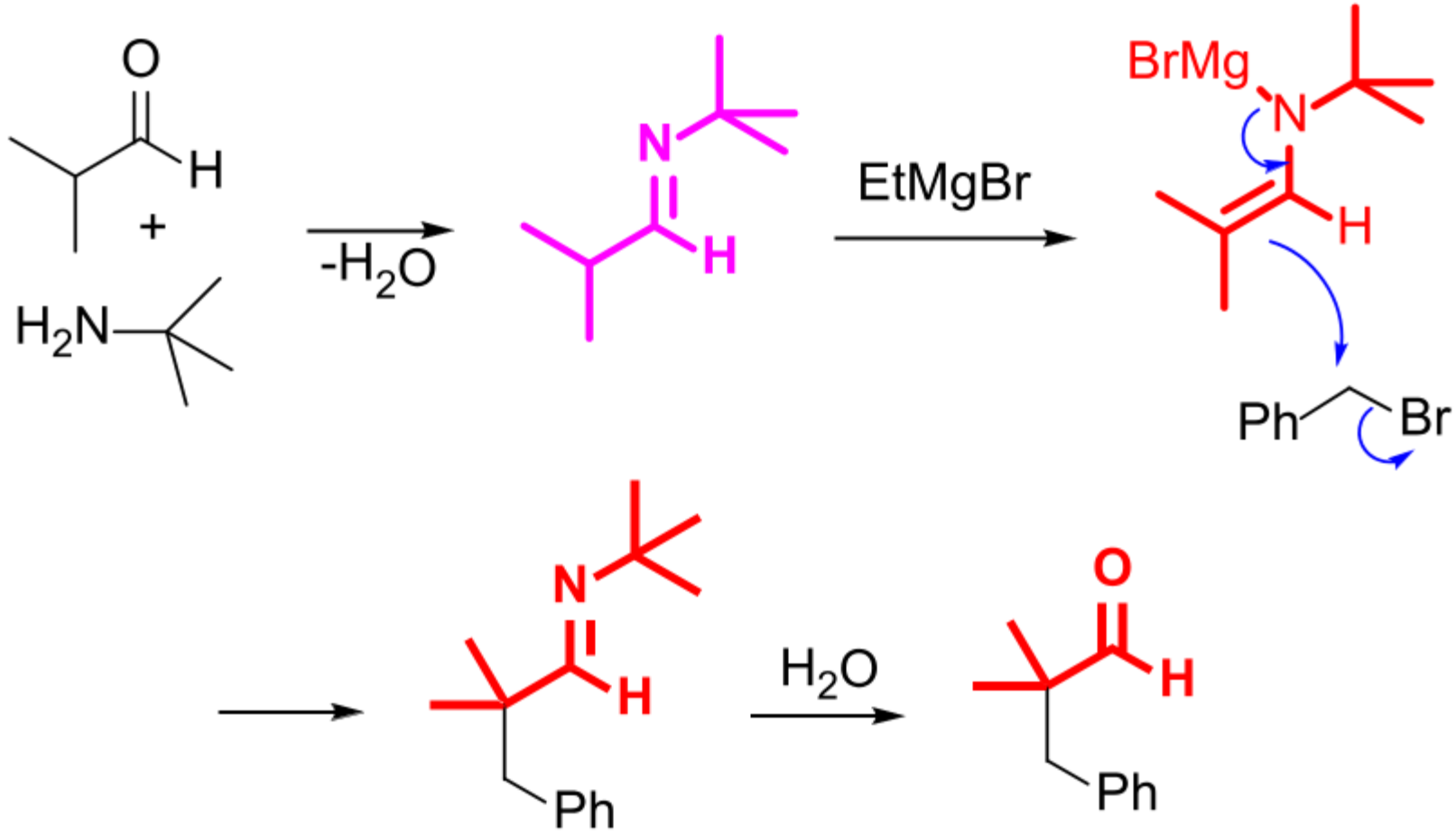
Nucleophiles – enaminates





Part 2: Electrophilic Substitution on α-Carbon of Carbonyl Groups

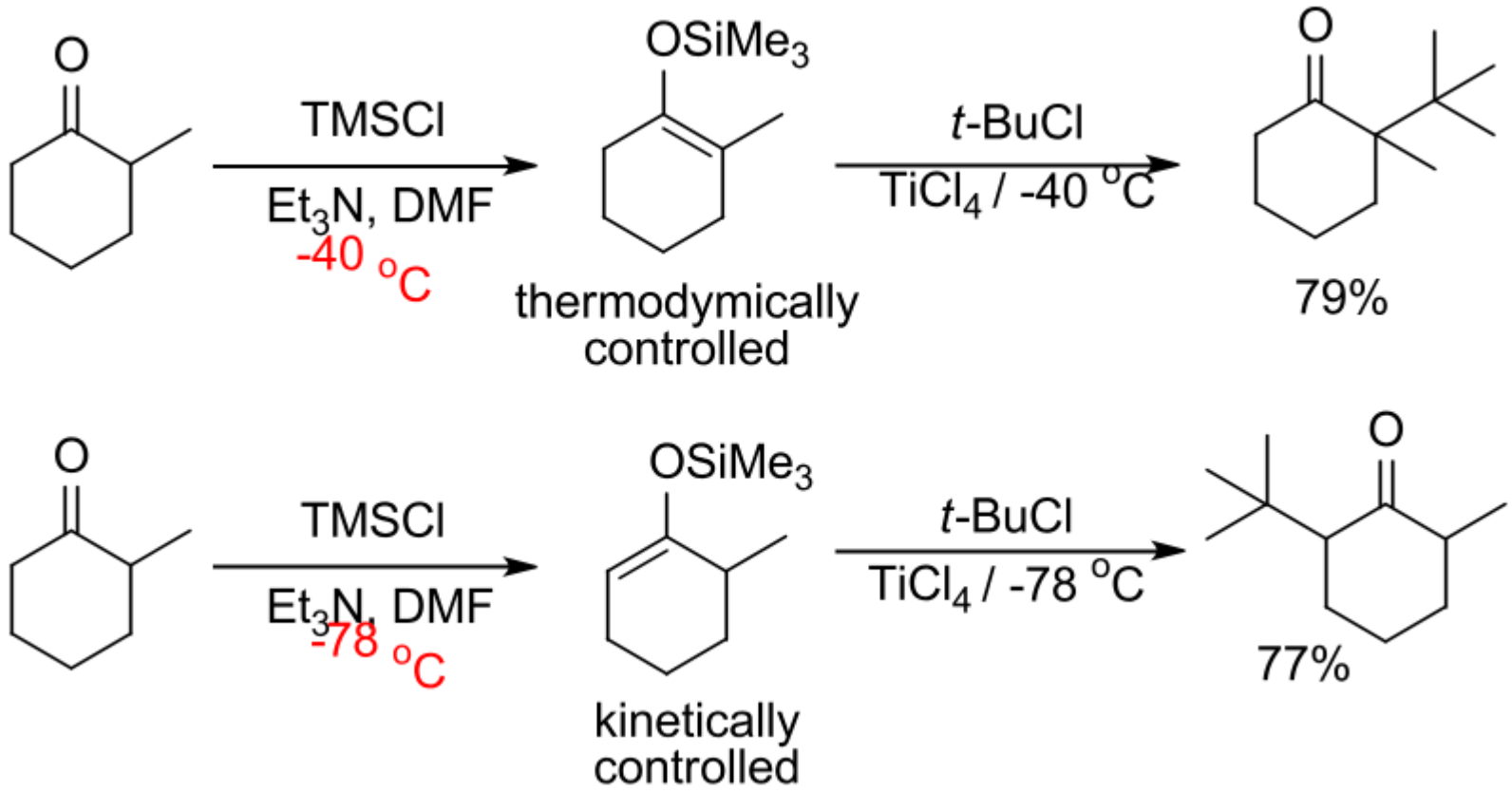
Nucleophiles – enaminates



利用烯胺负离子提高亲核性

Part 2: Electrophilic Substitution on α-Carbon of Carbonyl Groups

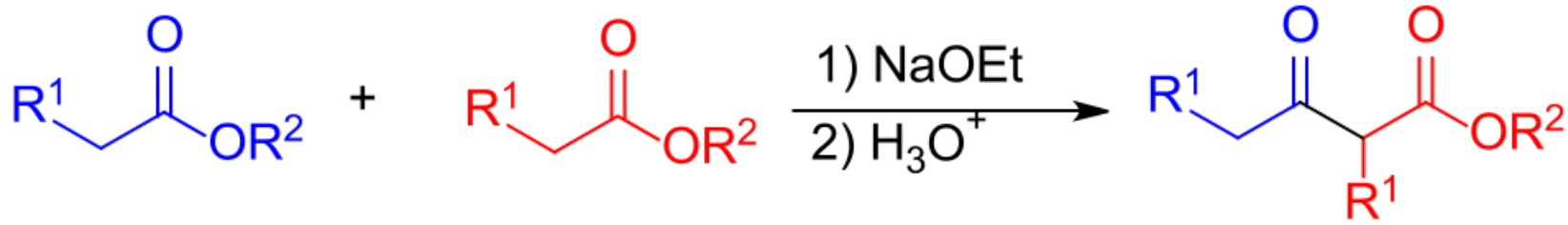
Nucleophile – silyl enol ether

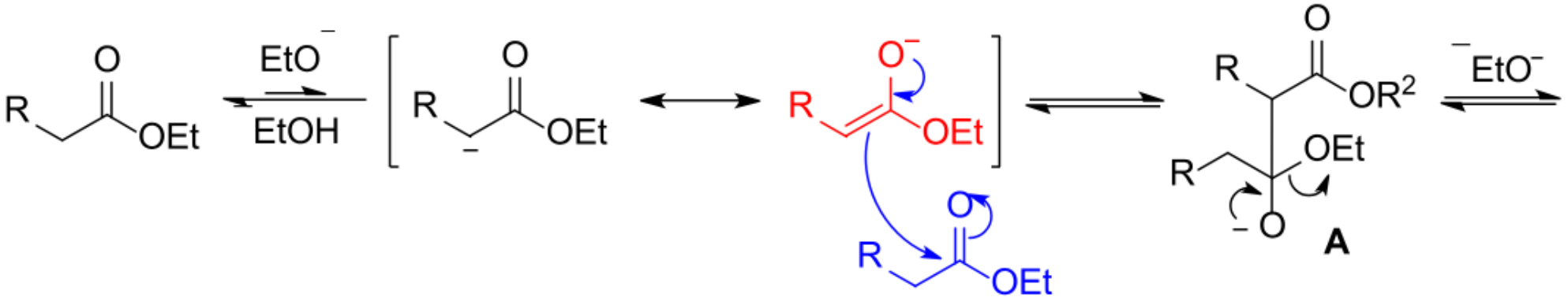


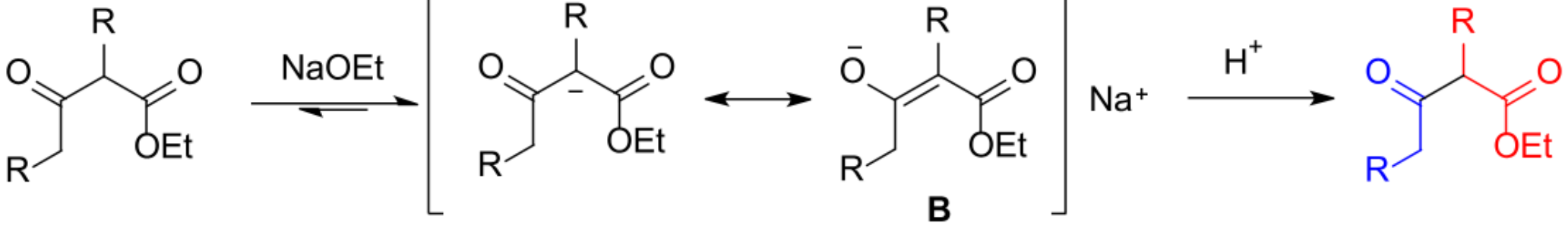
利用烯醇硅醚控制反应的区域选择性

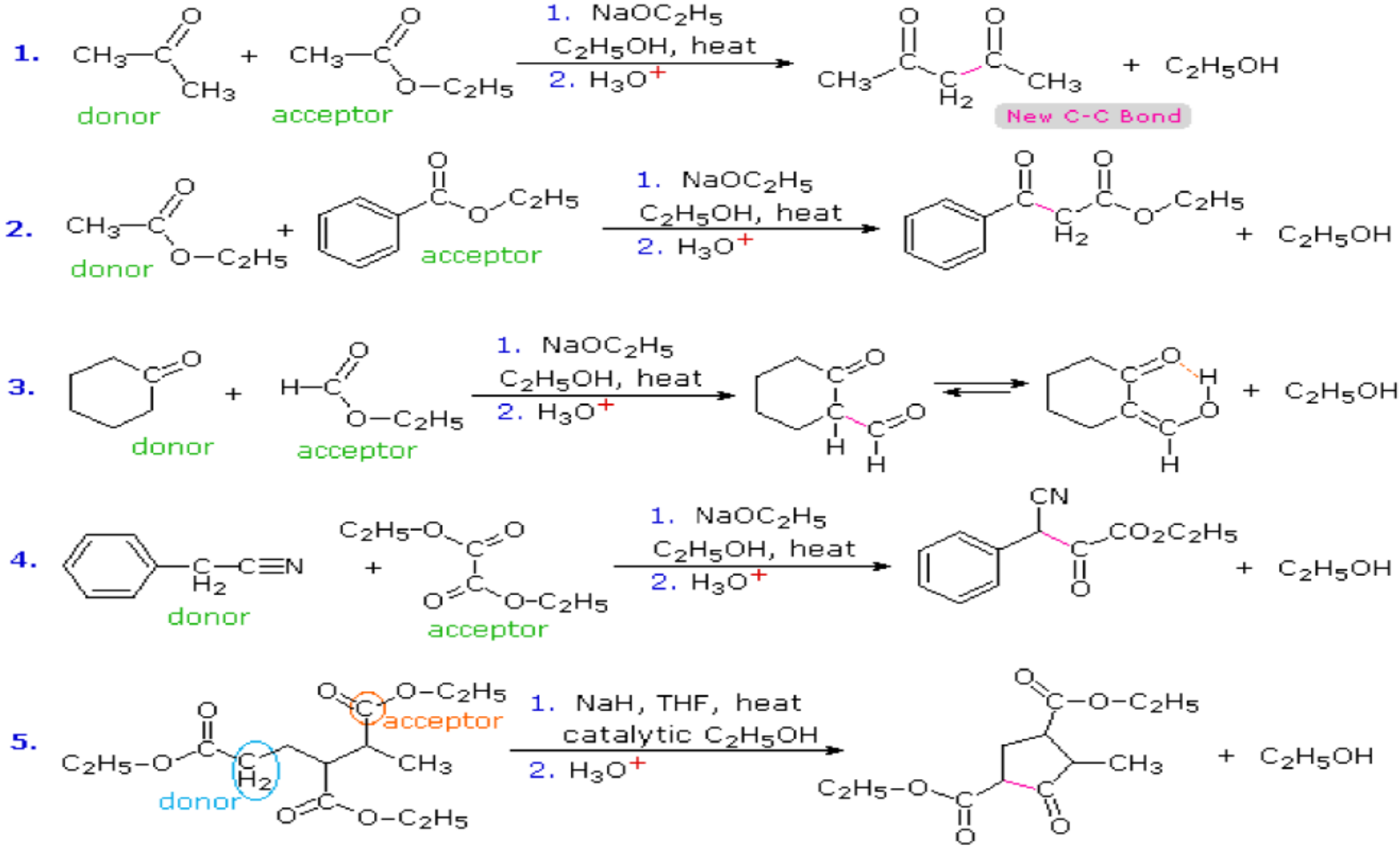
Part 2: Electrophilic Substitution on α-Carbon of Carbonyl Groups

5.7 Acylation on α-Carbon of Carbonyl groups








1.
donor
acceptor
1. NaOC2H5
C2H5OH, heat
2. H3O+
New C-C Bond
+ C2H5OH
2.
donor
acceptor
1. NaOC2H5
C2H5OH, heat
2. H3O+
+ C2H5OH
3.
donor
acceptor
1. NaOC2H5
C2H5OH, heat
2. H3O+
+ C2H5OH
4.
donor
acceptor
1. NaOC2H5
C2H5OH, heat
2. H3O+
+ C2H5OH
5.
donor
acceptor
1. NaH, THF, heat
catalytic C2H5OH
2. H3O+
+ C2H5OH

quiz

1. Explain (1) why should vinyl be activating groups? (2) why should vinyl be ortho- and para-directing group.(from structure of substrate and the stability of intermediate)

2. Explain (1) why should amino be activating groups? (2) why should amino be ortho- and para-directing group.(from structure of substrate and the stability of intermediate)

3. Propose the mechanism for the reaction below.