13. Reazioni del benzene e dei benzeni sostituiti

(1) Nomenclatura dei benzeni mono sostituiti.

(2) Reazioni di sostituzione elettrofila aromatica (S_EAr): alogenazione, nitrazione, solfonazione, acilazione e alchilazione di Friedel-Crafts).

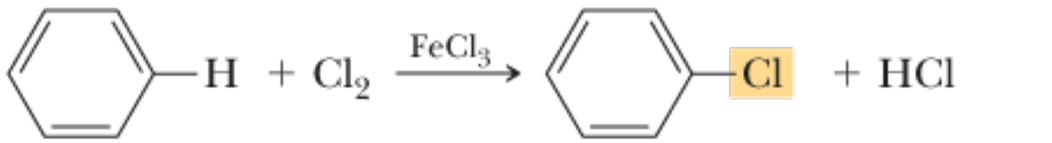
(3) Trasformazioni chimiche dei sostituenti sull'anello benzenico.

(4) Effetto dei sostituenti sulla reattività di un anello benzenico.

(5) Effetto dei sostituenti sull' orientamento di una S_EAr.

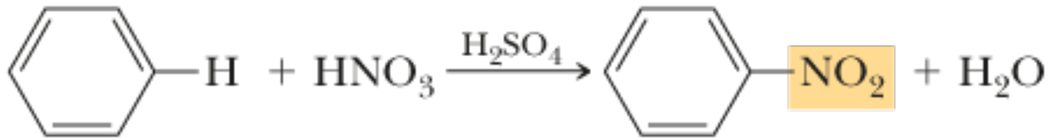
Reazioni di sostituzione elettrofila aromatica (S_EAr): benzene e dei suoi derivati

Alogenazione



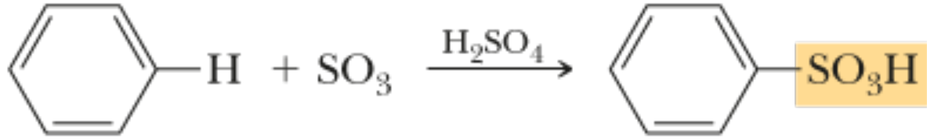
Clorobenzene

Nitrazione



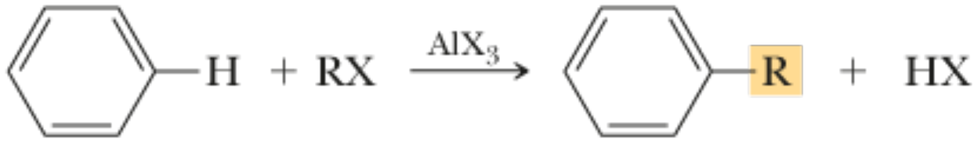
Nitrobenzene

Solfonazione



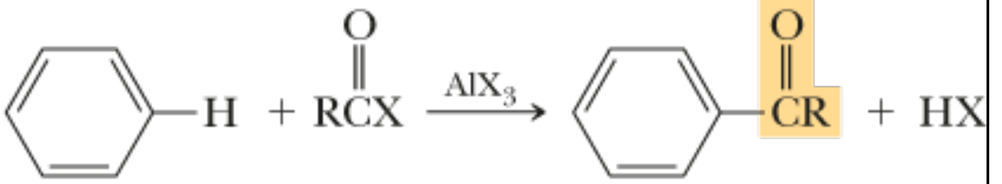
Acido benzensolfonico

Alchilazione



Alchilbenzene

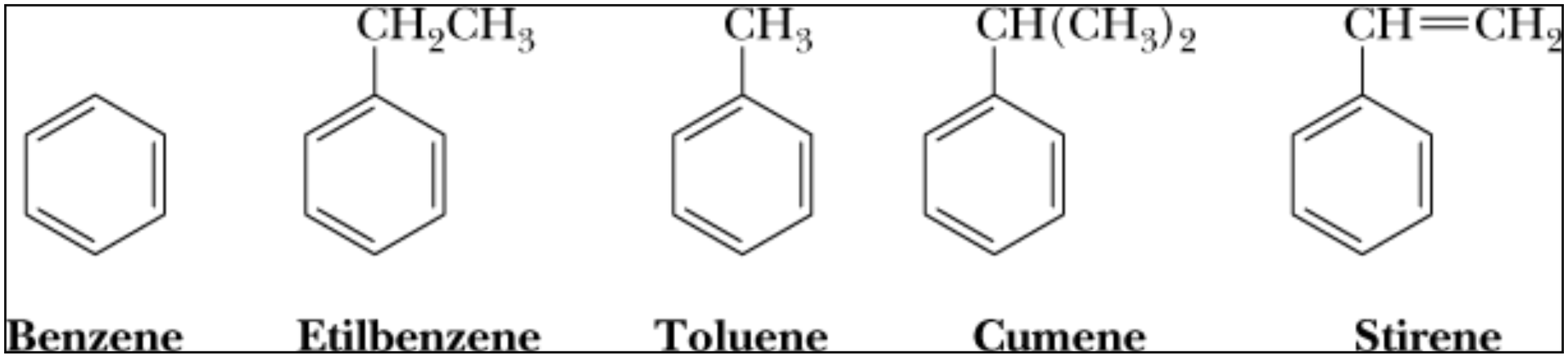
Acilazione

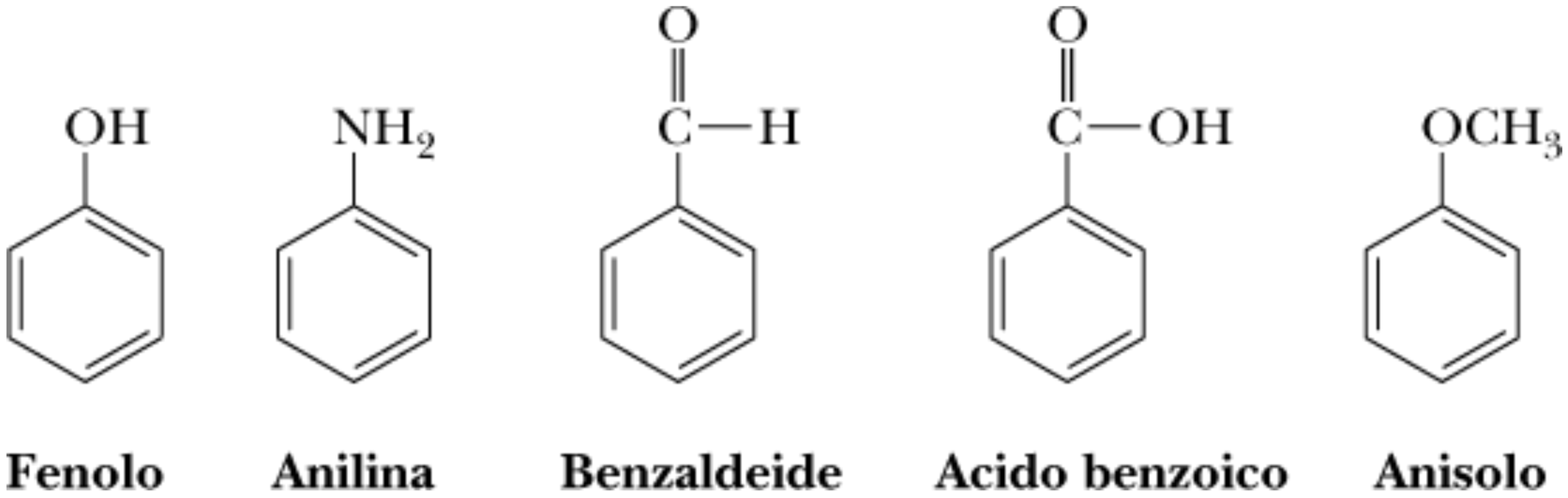


Acilbenzene

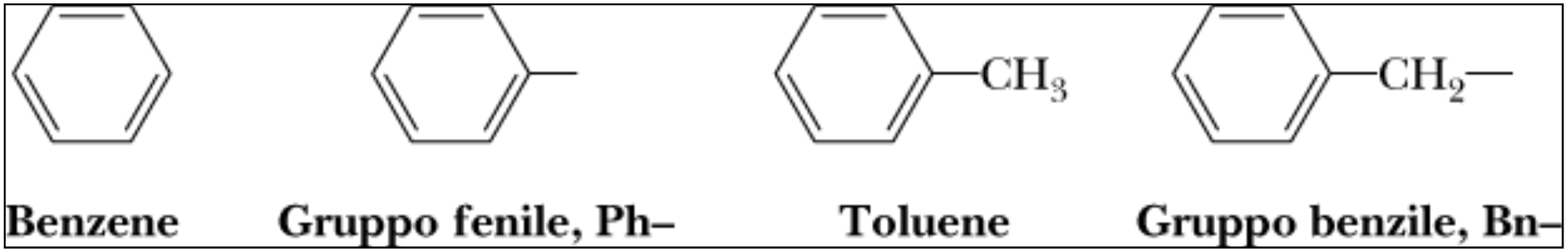
Nomenclatura

A. Benzeni monosostituiti

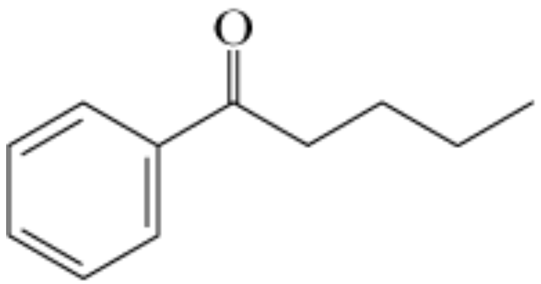




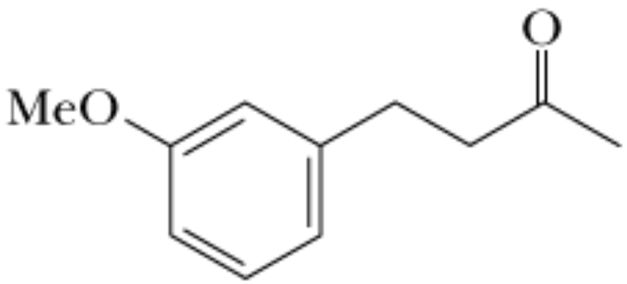
Nomenclatura



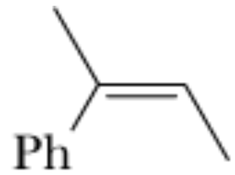
Benzene **Gruppo fenile, Ph–** **Toluene** **Gruppo benzile, Bn–**



1-Fenil-1-pentanone

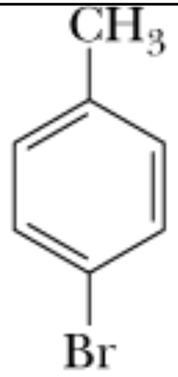


4-(3-Metossifenil)-2-butanone

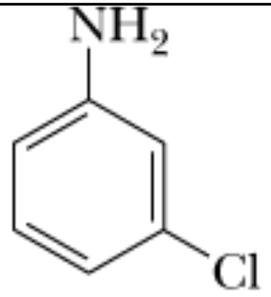


(Z)-2-Fenil-2-butene

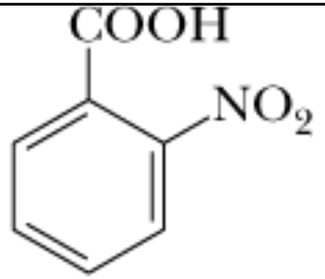
B. Benzeni disostituiti



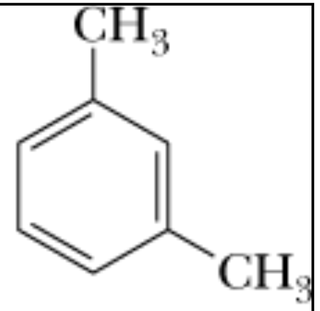
4-Bromotoluene
(*p*-Bromotoluene)



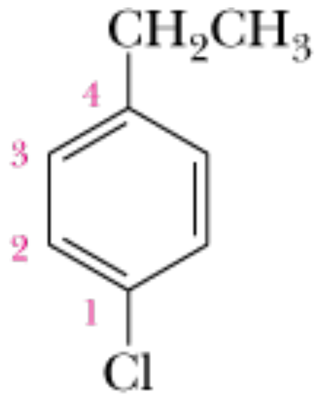
3-Cloroanilina
(*m*-Cloroanilina)



Acido 2-nitrobenzoico
(Acido *o*-nitrobenzoico)

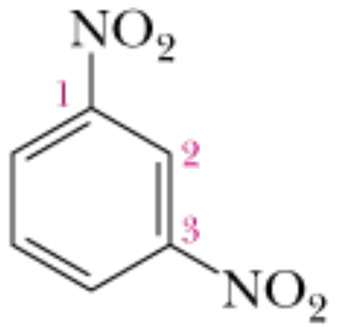


***m*-Xilene**



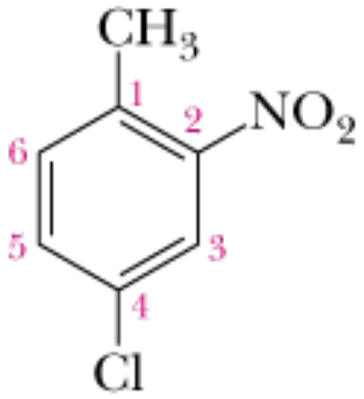
1-Cloro-4-etilbenzene
(*p*-Cloroetilbenzene)

1-Bromo-2-nitrobenzene
(*o*-Bromonitrobenzene)



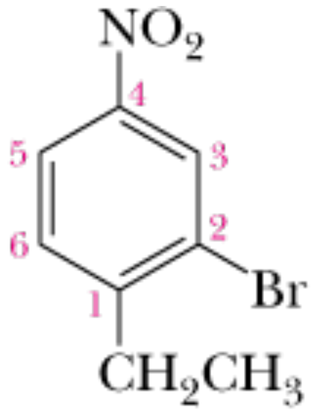
1,3-Dinitrobenzene
(*m*-Dinitrobenzene)

C. Benzeni polisostituiti



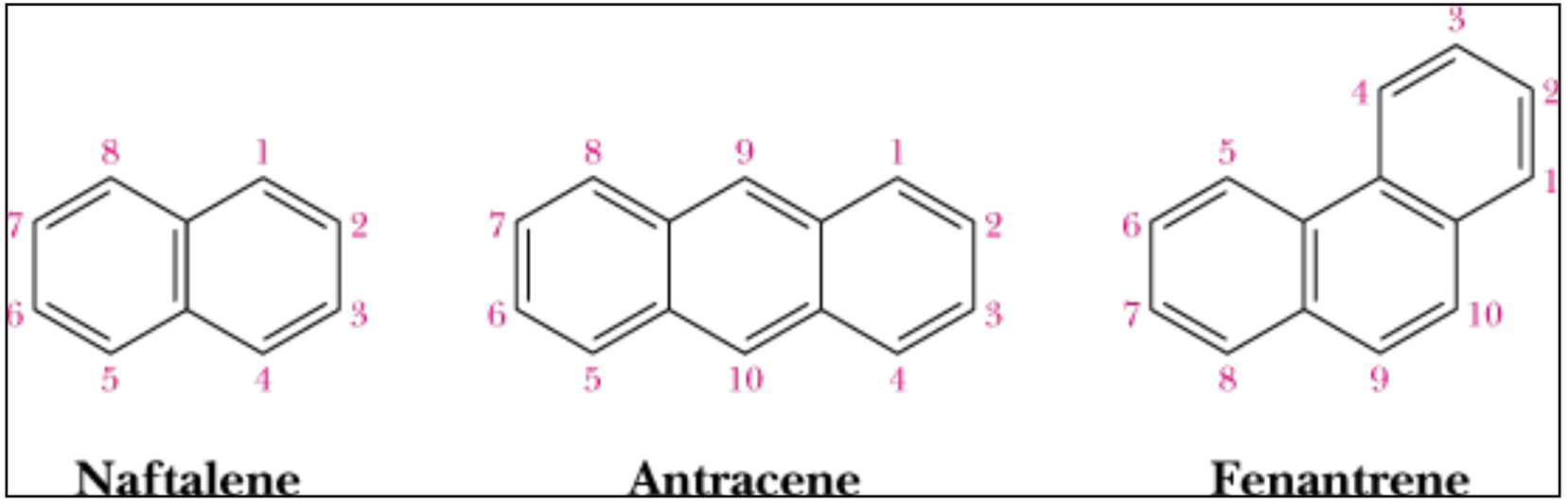
4-Cloro-2-nitrotoluene

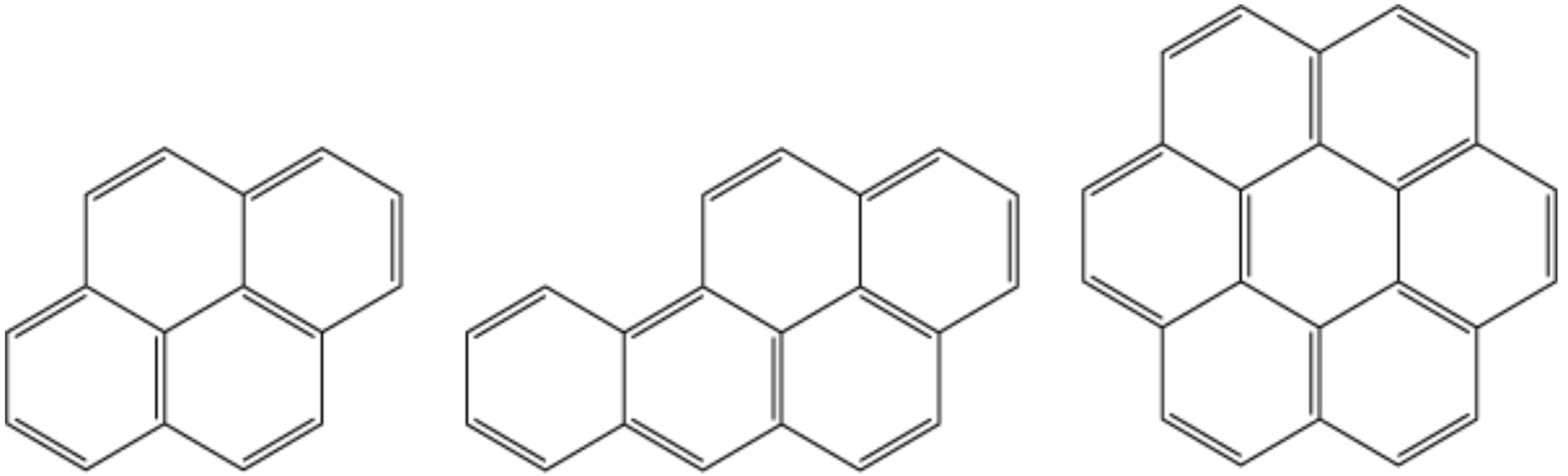
2,4,6-Tribromofenolo



2-Bromo-1-etil-4-nitrobenzene

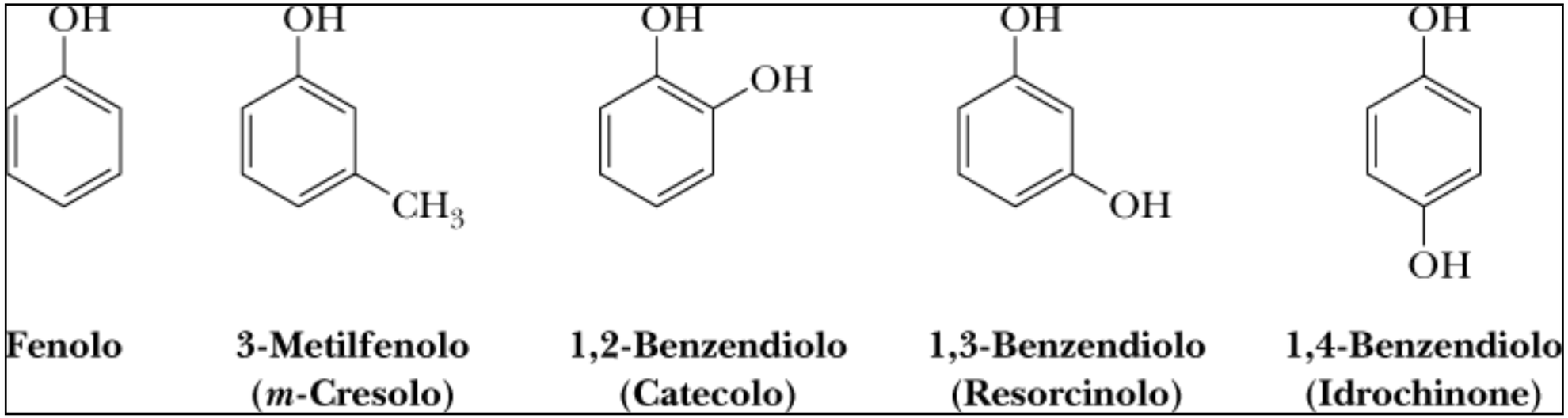
Gli idrocarburi polinucleari aromatici (IPA)



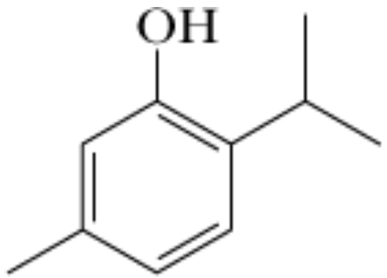


Fenoli

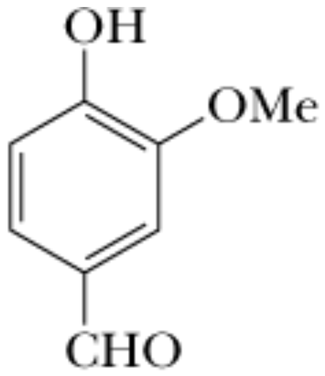
A. Struttura e nomenclatura



Fenolo | **3-Metilfenolo (*m*-Cresolo)** | **1,2-Benzendiolo (Catecolo)** | **1,3-Benzendiolo (Resorcinolo)** | **1,4-Benzendiolo (Idrochinone)**

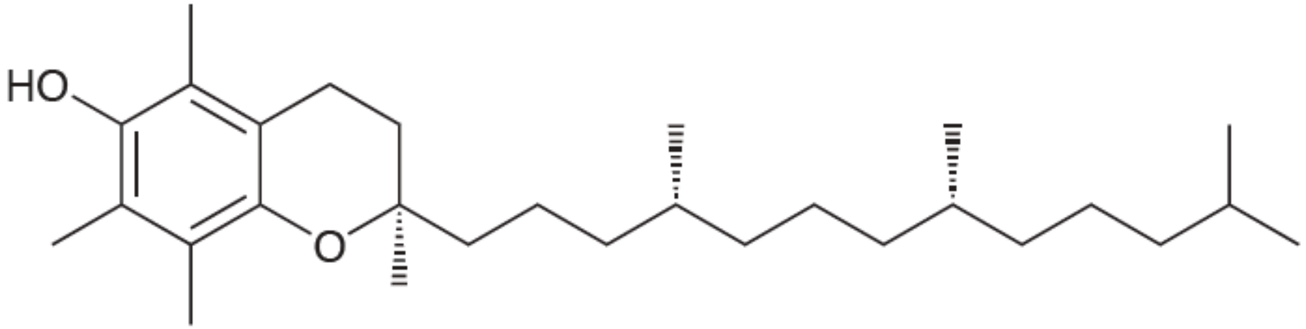


2-Isopropil-5-metilfenolo (Timolo)

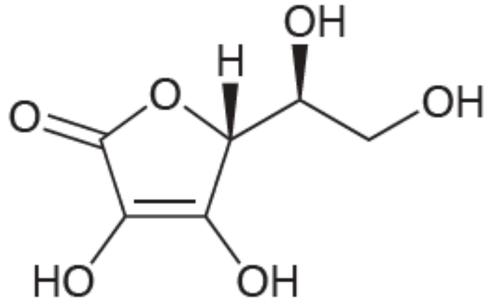


4-Idrossi-3-metossibenzaldeide (Vanillina)

ANTI-OSSIDANTI naturali

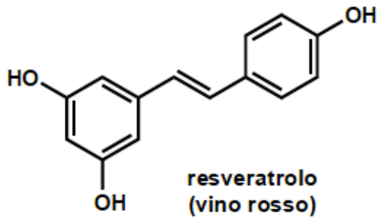


Tocoferolo (Vitamina E) contenuto in molti oli, specialemente nell'olio di germe di grano

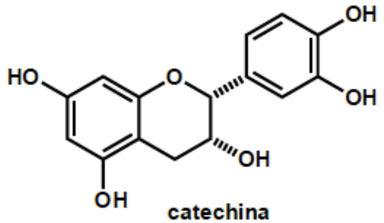


Acido ascrobico (Vitamina C)

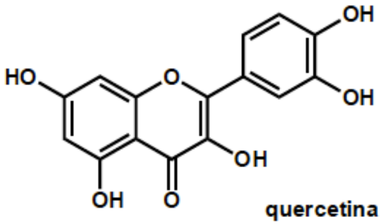
Diversi polifenoli naturali sono antiossidanti ritenuti importanti in campo nutraceutico, quali inibitori dei radicali liberi e dell'invecchiamento



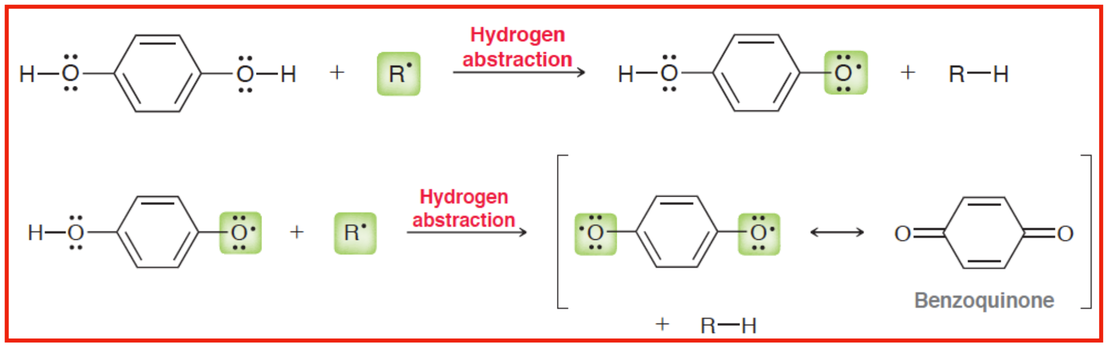
resveratrolo (vino rosso)



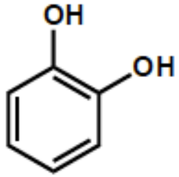
catechina (cioccolato)



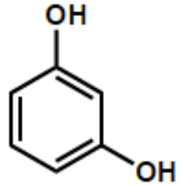
quercetina (un flavonoide) (vino rosso, frutti rossi)



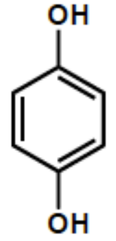
I fenoli sono quindi composti facilmente ossidabili, in particolare quando hanno più gruppi OH ed in ambiente basico.



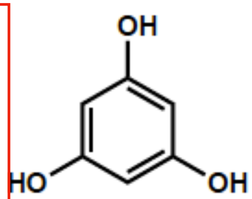
catecolo



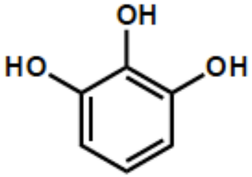
resorcinolo



idrochinone



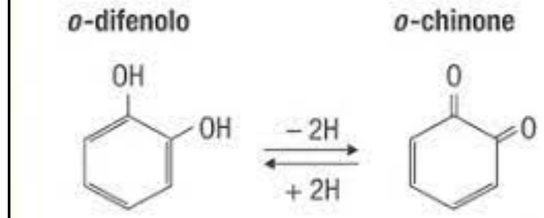
floroglucinolo



pirogallolo

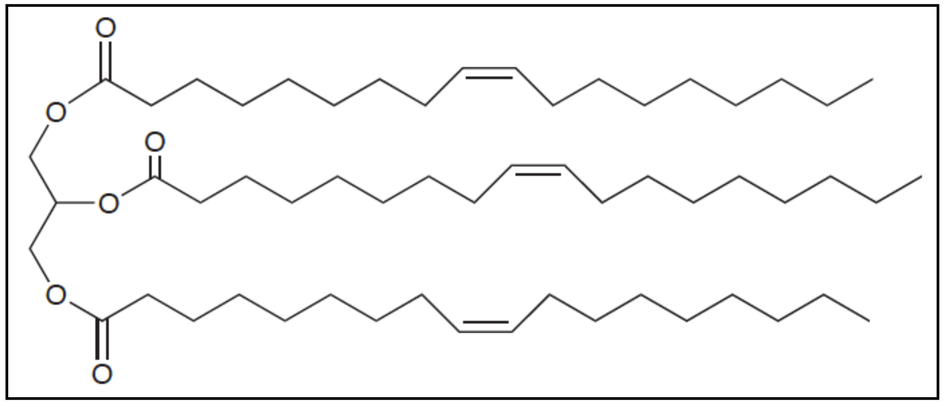
Il pirogallolo in soluzioni fortemente basiche è usato come trappola per l'ossigeno, che assorbe avidamente

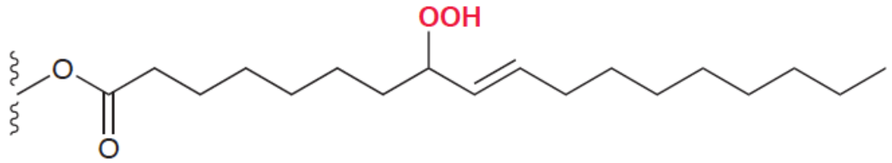
CTF-ORG2_21-A3-9



Tutti i composti fenolici sottraggono ossigeno al vino ed esercitano una naturale azione antiossidante

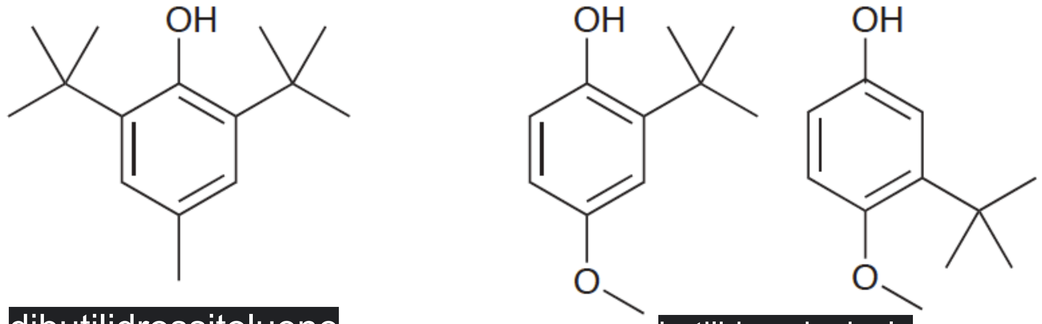
ANTI-OSSIDANTI come ADDITIVI ALIMENTARI





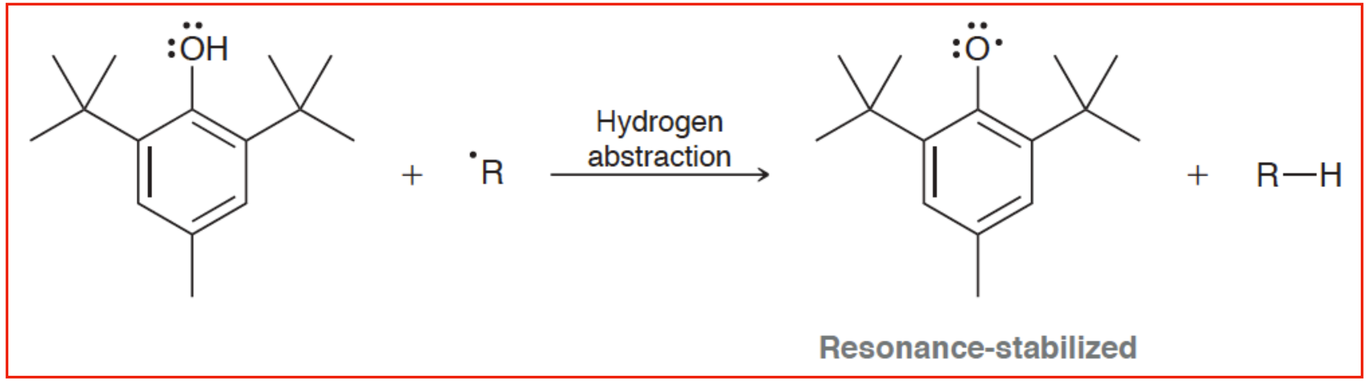
Irrancidimento Ossidativo

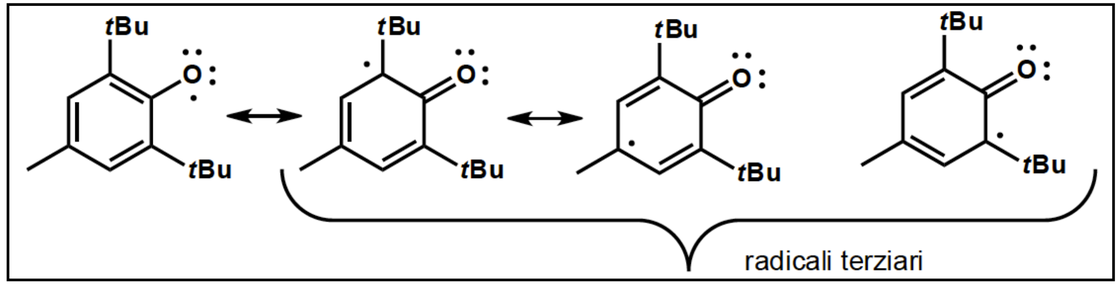
I **trigliceridi** sono suscettibili a auto-ossidazione, specialmente nella posizione allilica. l'Idroperossido (ROOH) risultante contribuisce all'odore rancido contenuto in Oli insaturi (olio di semi e olio d'oliva ricco in omega-3,6 e 9).



dibutilidrossitoluene
Butylated hydroxytoluene
(BHT)

butilidrossianisolo
Butylated hydroxyanisole
(BHA)

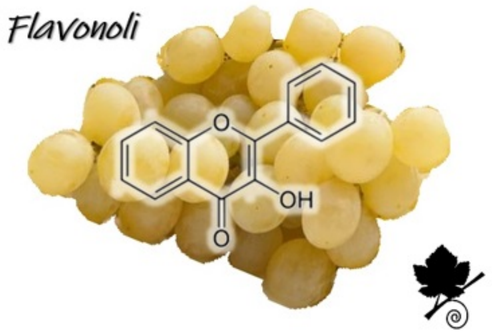


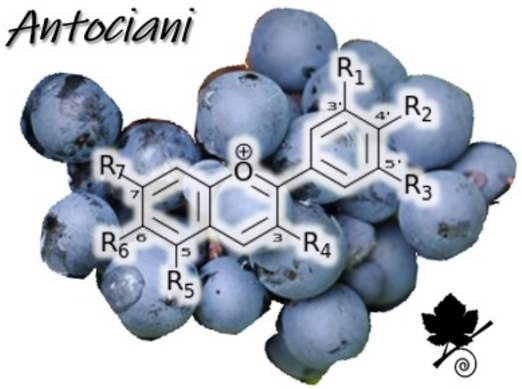


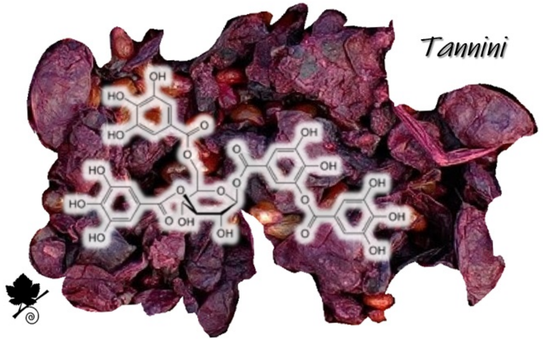
Anti-ossidanti (inibitori radicalici) sono usati per preservare i cibi : **BHT e BHA**.

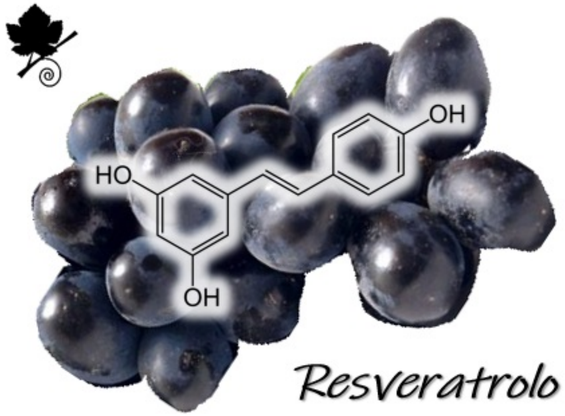
Essi reagiscono con i radicali per generare radicali stabili per risonanza. I gruppi terbutilici a causa dell'impedimento sterico ne riducono la reattività degli inibitori radicalici. Gli anti-ossidnati sono chiamati **"radical scavengers"** perché prevengono l'auto-ossidazione delle molecole alimentari.

PoliFenoli: antiossidanti contenuti in vino, oli e altri alimenti

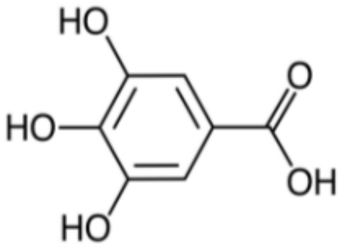






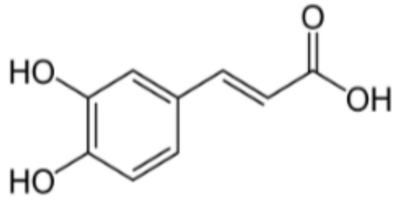


a) Acidi benzoici



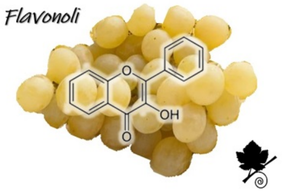
Acido gallico

b) Acidi idrossicinnamici



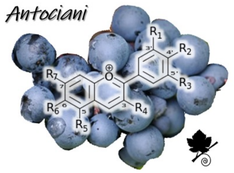
Acido caffeico

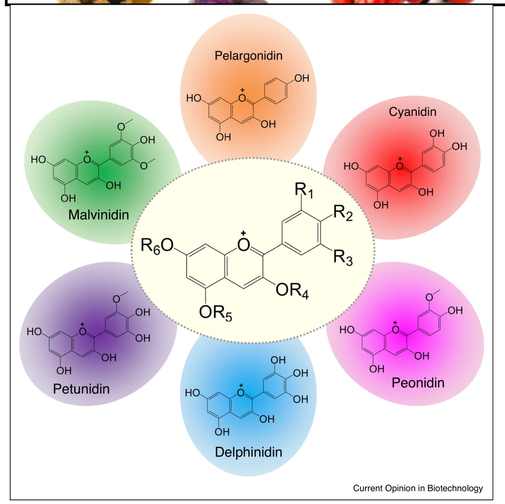
https://www.viviilvino.it/enologia/i-polifenoli-flavonoli-antociania-e-tannini/

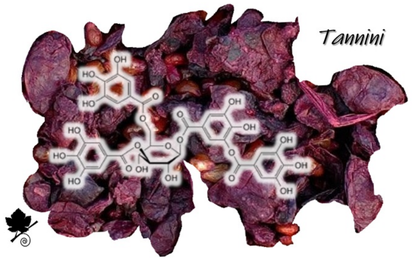


FLAVONOIDI

- FLAVONOLI → Quercetina
- FLAVONI → Apigenina
- FLAVANOLI → Catechine
- FLAVANONI → Esperidina
- ANTOCIANINE → Cianidina
- ISOFLAVONI → Genisteina

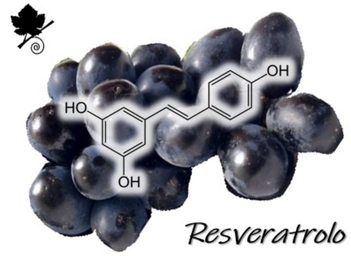






NON FLAVONOIDI

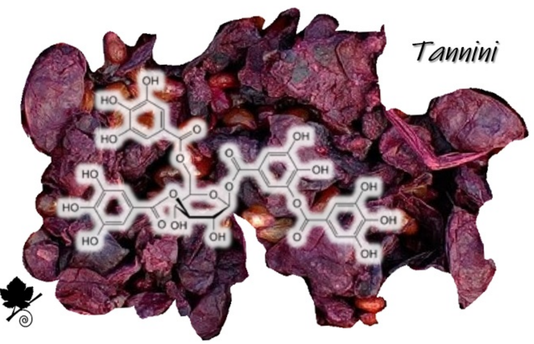
- ACIDI FENOLICI → Acido caffeico, Acido clorogenico
- LIGNANI → Pinoresinolo
- STILBENI → Resveratrolo

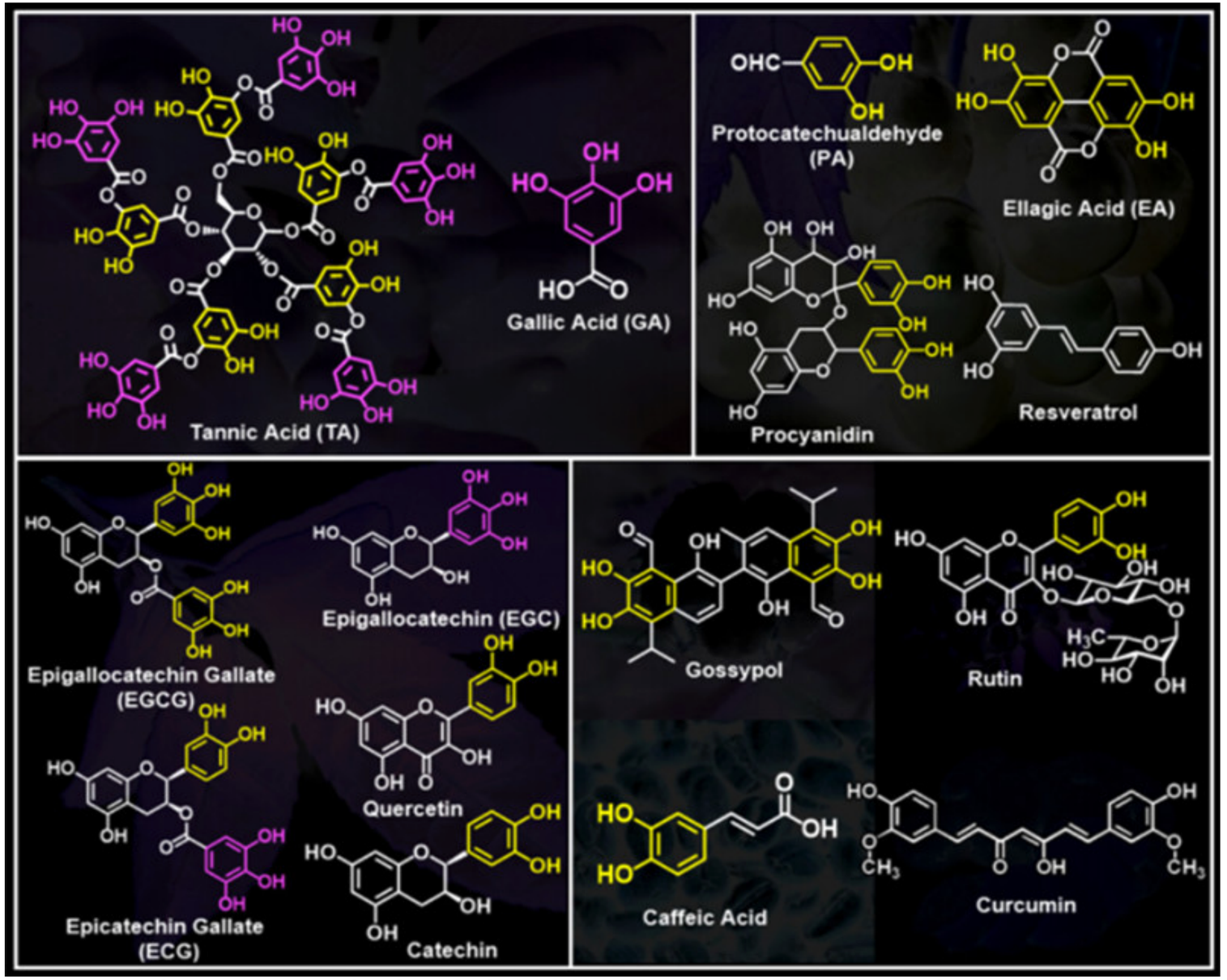


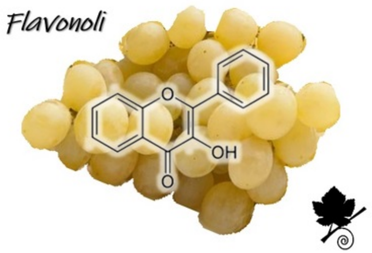
TANNINI

- TANNINI IDROLIZZABILI
- TANNINI CONDENSATI

PoliFenoli: antiossidanti contenuti in vino, oli e altri alimenti

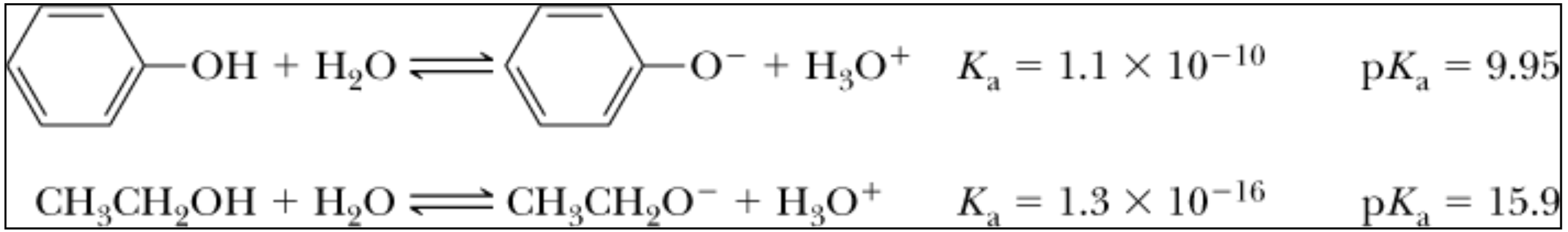


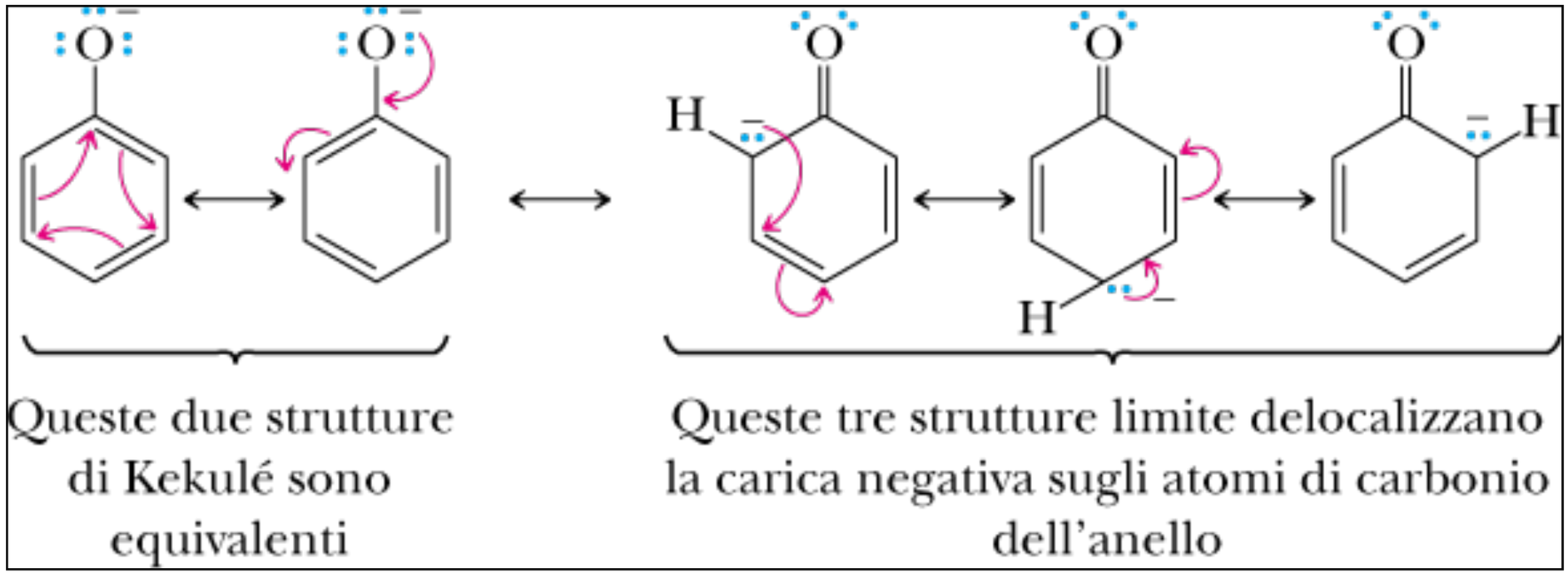




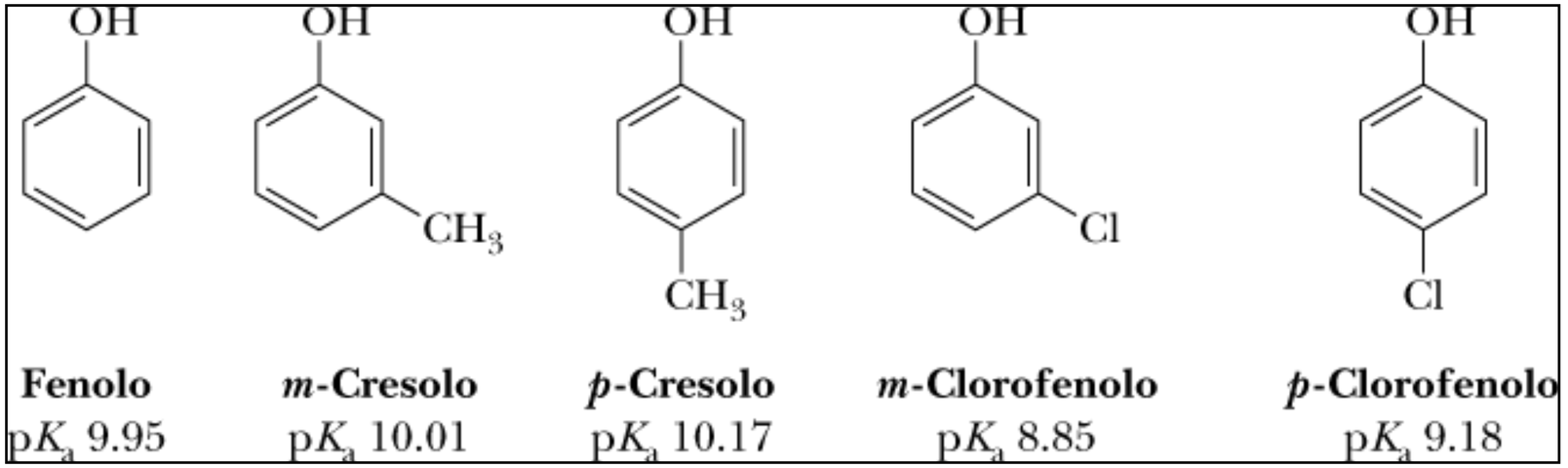
https://www.rainbowextract.com/wp-content/uploads/2022/03/Types-of-Polyphenols.jpg

B. Acidità dei fenoli

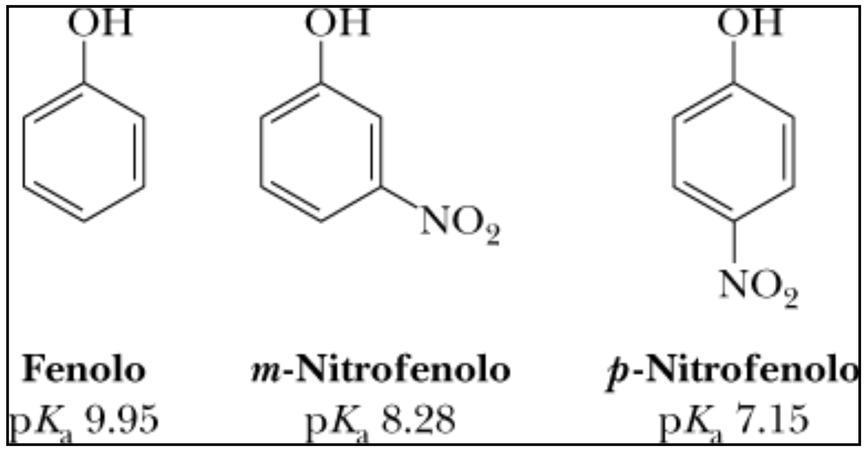




B. Acidità dei fenoli

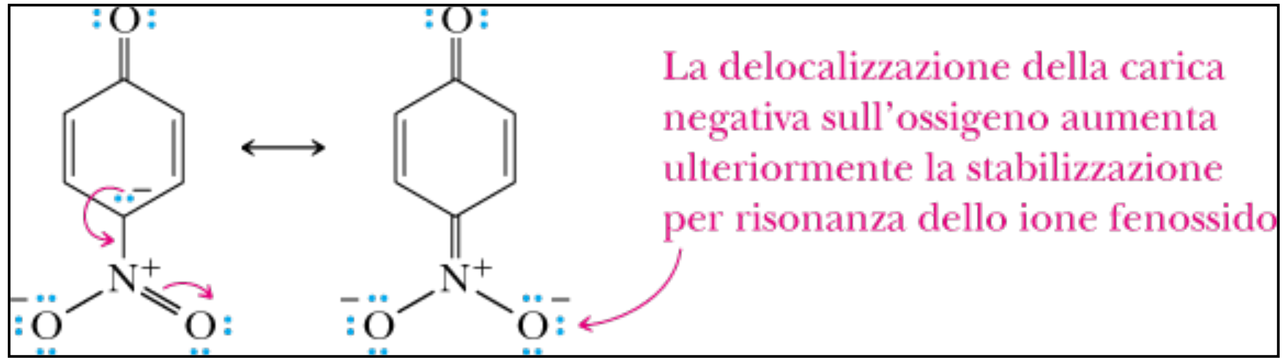


Fenolo	*m*-Cresolo	*p*-Cresolo	*m*-Clorofenolo	*p*-Clorofenolo
pK_a 9.95	pK_a 10.01	pK_a 10.17	pK_a 8.85	pK_a 9.18



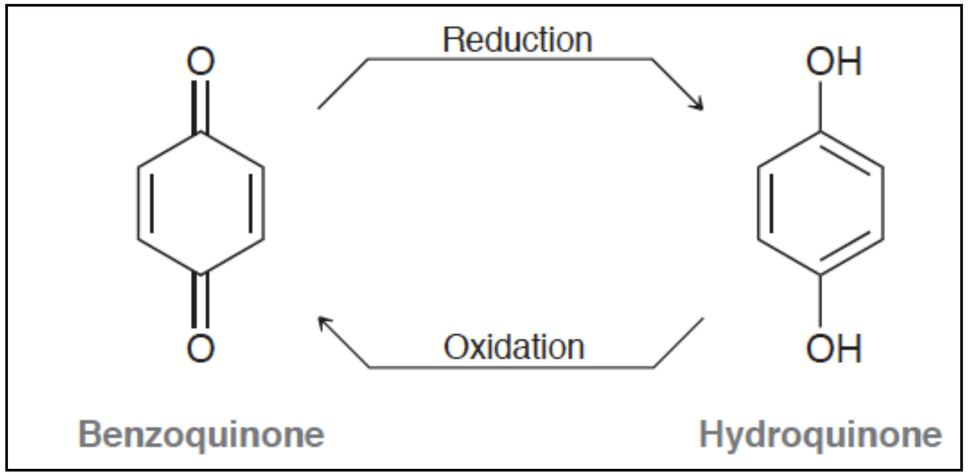
Fenolo	*m*-Nitrofenolo	*p*-Nitrofenolo
pK_a 9.95	pK_a 8.28	pK_a 7.15

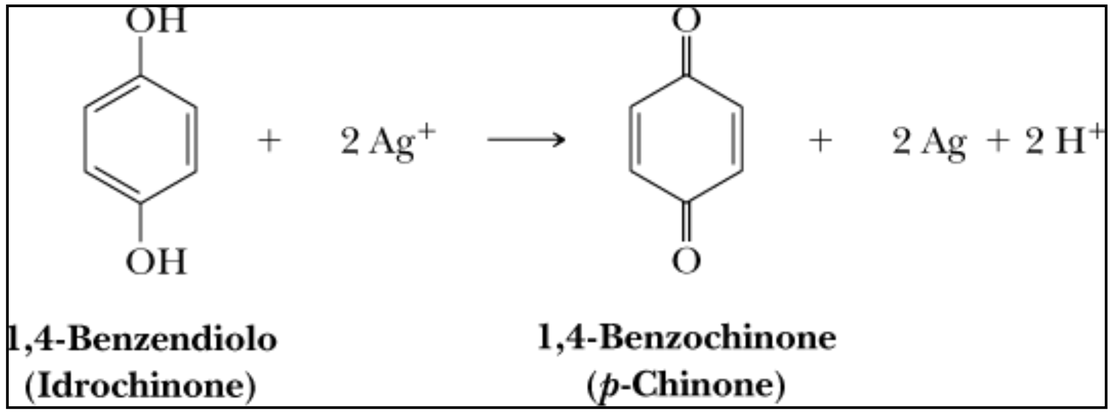
La polarizzazione di questo legame C—C per effetto induttivo elettron-donatore del carbonio sp^3 del gruppo metilico destabilizza questa struttura limite

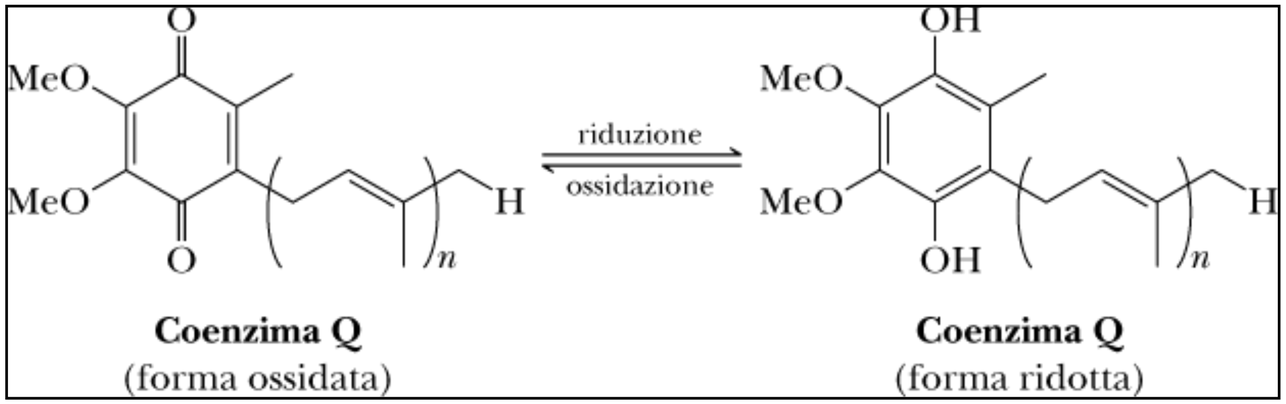


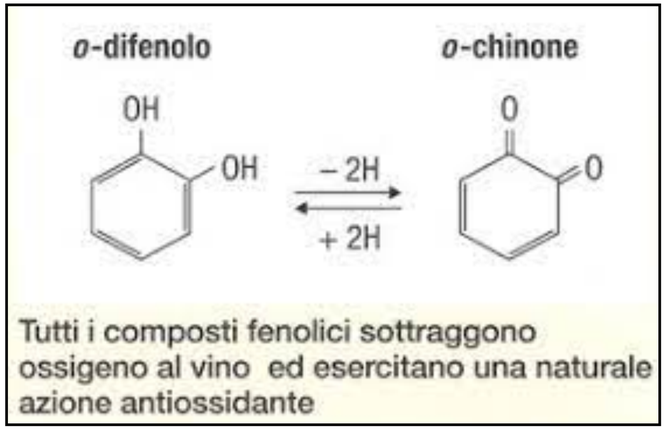
La delocalizzazione della carica negativa sull'ossigeno aumenta ulteriormente la stabilizzazione per risonanza dello ione fenossido

Reazioni di ossido-riduzione degli idrochinoni (difenoli) e chinoni







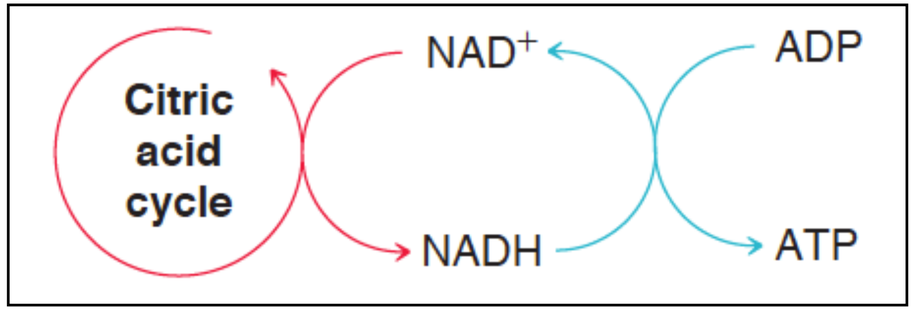


IDROCHINONE CREMA SCHIARENTE

La causa principale della sua azione terapeutica è l'inibizione dell"enzima tirosinasi coinvolto nella sintesi di melanina. La mancata produzione del pigmento produce nel tempo (almeno un mese di terapia) l'auspicato effetto schiarente

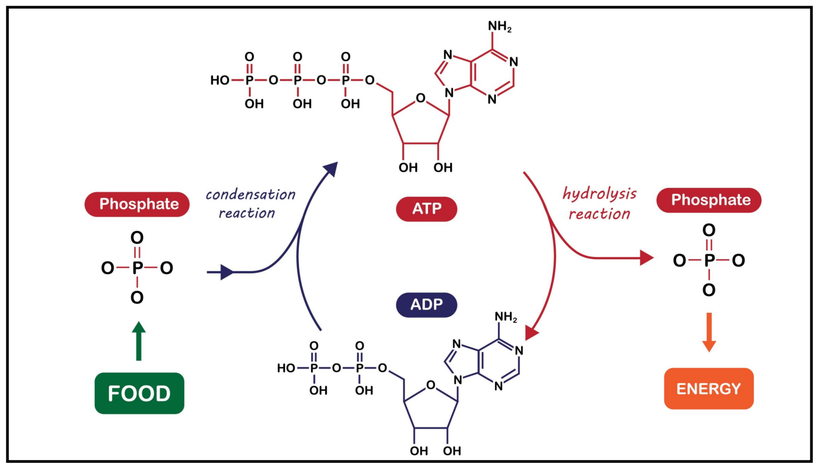
Premio Nobel Peter Mitchell - 1978
Scoperta del ruolo dell'ubichinone nella produzione di energia
(Sintesi del ribonucleoside ATP)

Forma Ossidata

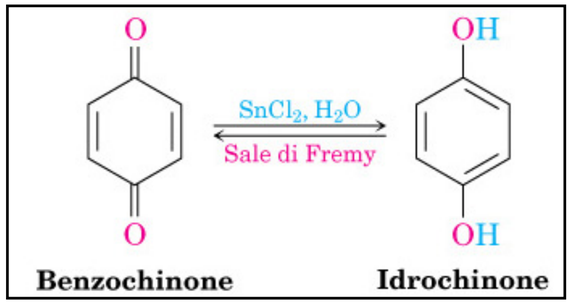


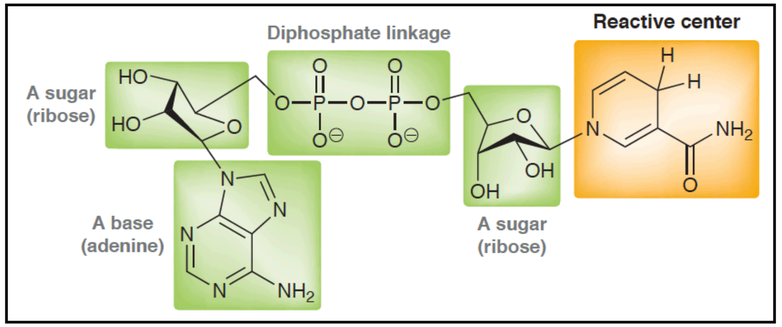
Forma ridotta

Metabolismo del cibo (Ciclo dell'acido Citrico)
con immagazzinamento di energia sotto forma di legami chimici
(Sintesi dell'ATP_ fosforilazione ossidativa).

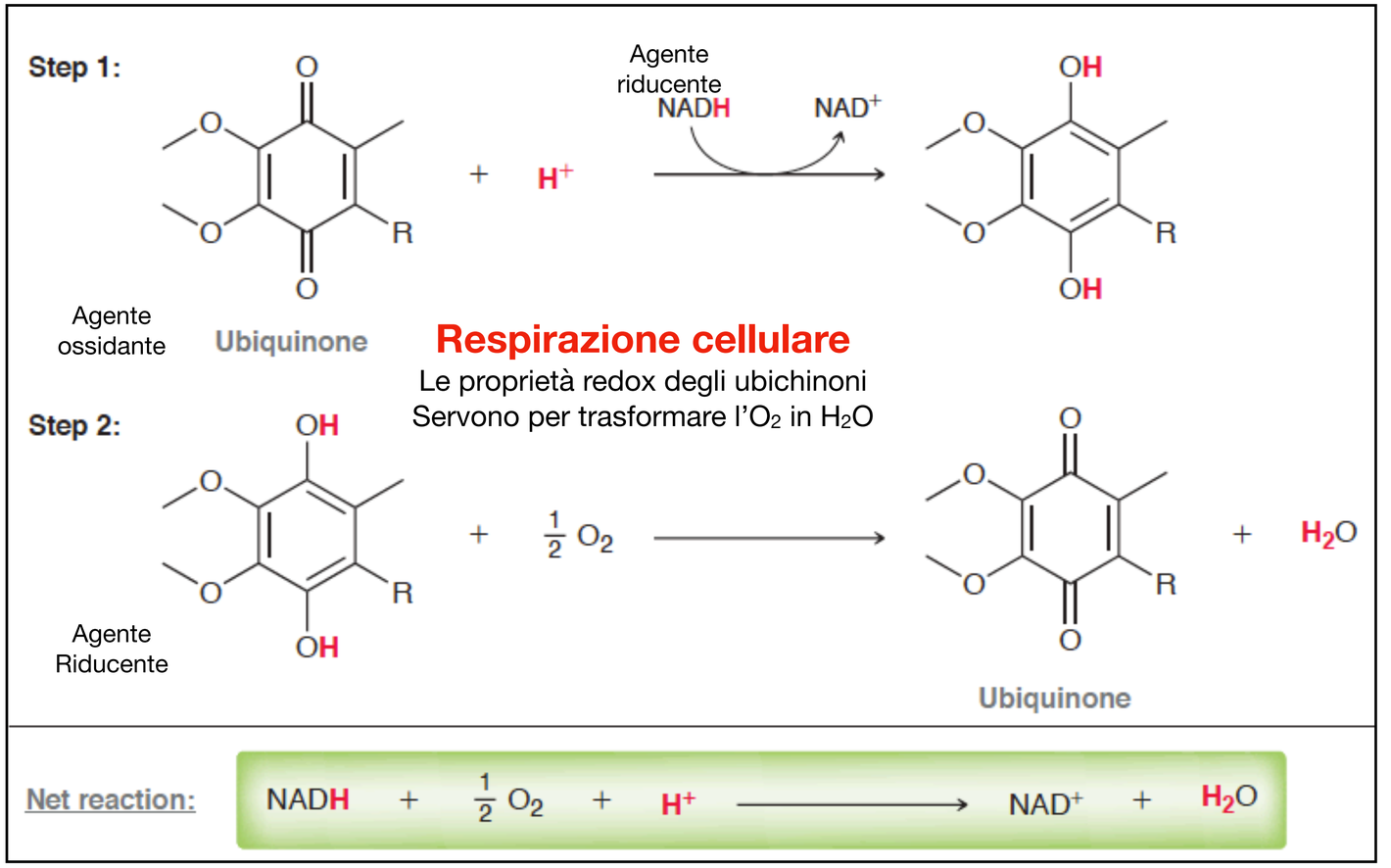


CHINONI e IDROCHINONI (Coppia Redox)

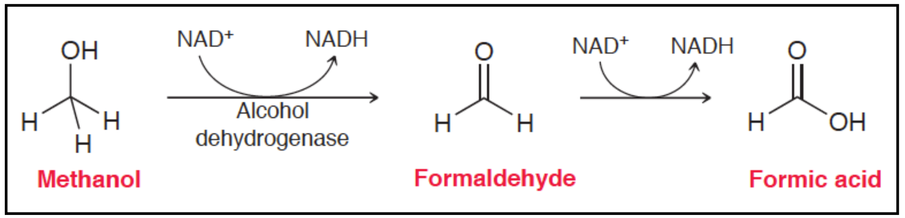




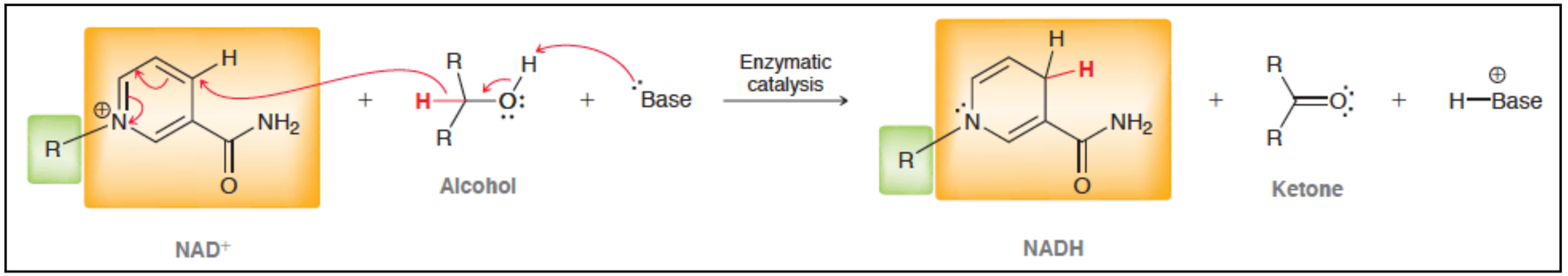
NADH
Nicotinammide **A**denina **D**inucleotide

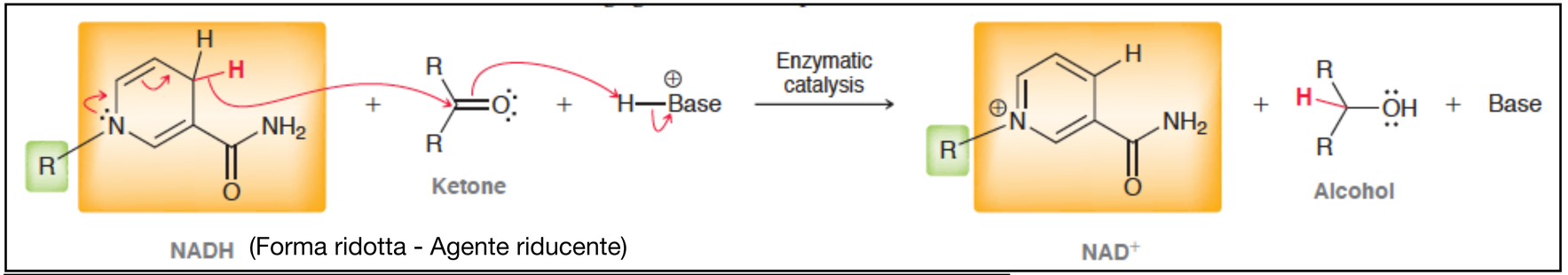


CHINONI e IDROCHINONI (Coppia Redox)
In Natura (respirazione cellulare)

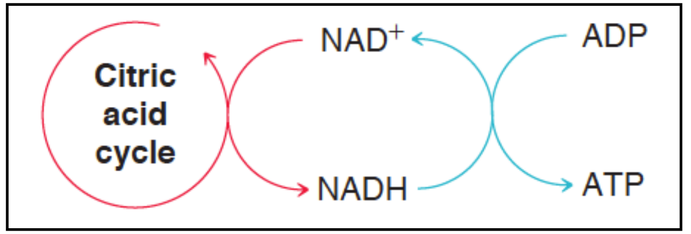


(Forma Ossidata - Agente ossidante)

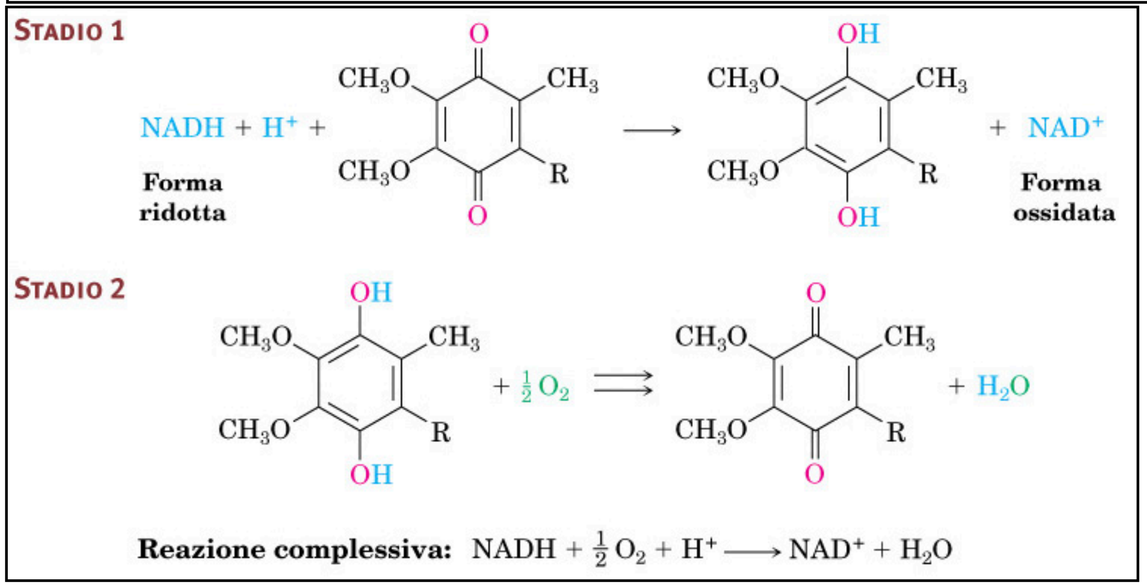


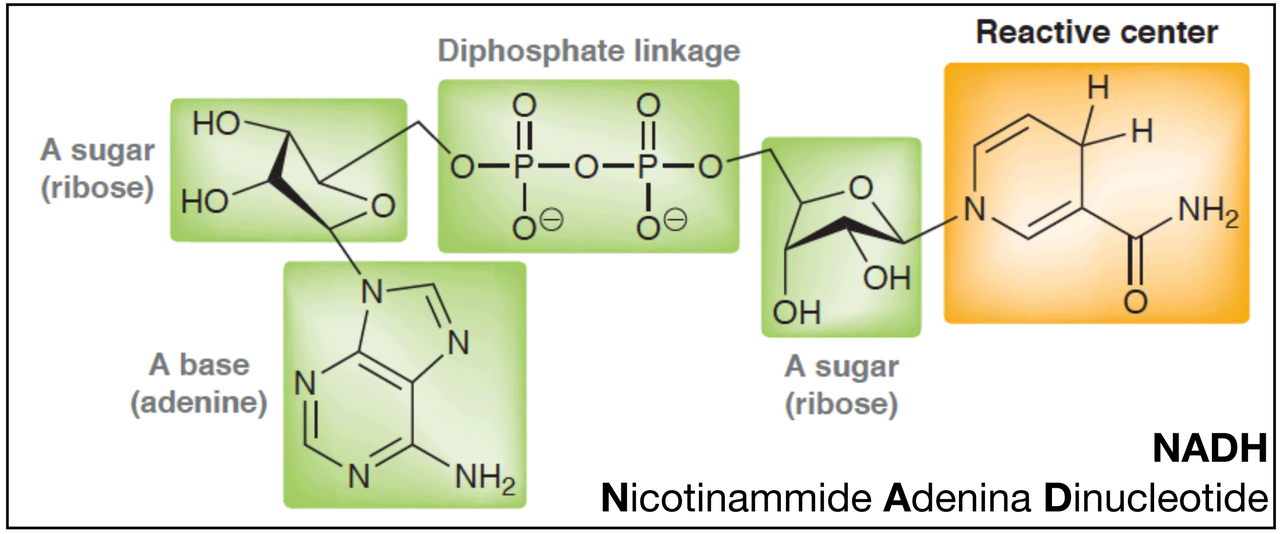


(Forma ridotta - Agente riducente)



Forma ridotta - Agente riducente

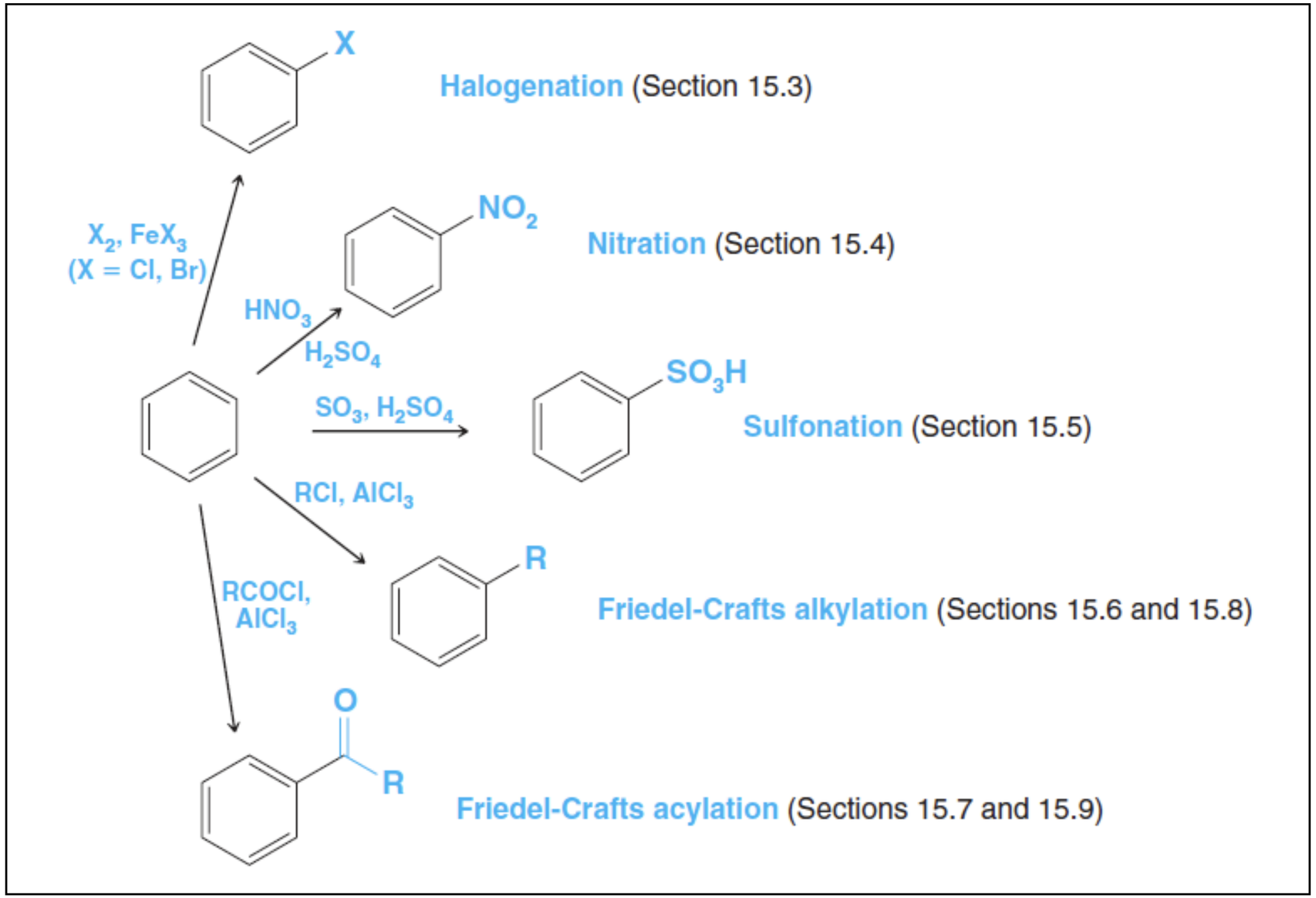




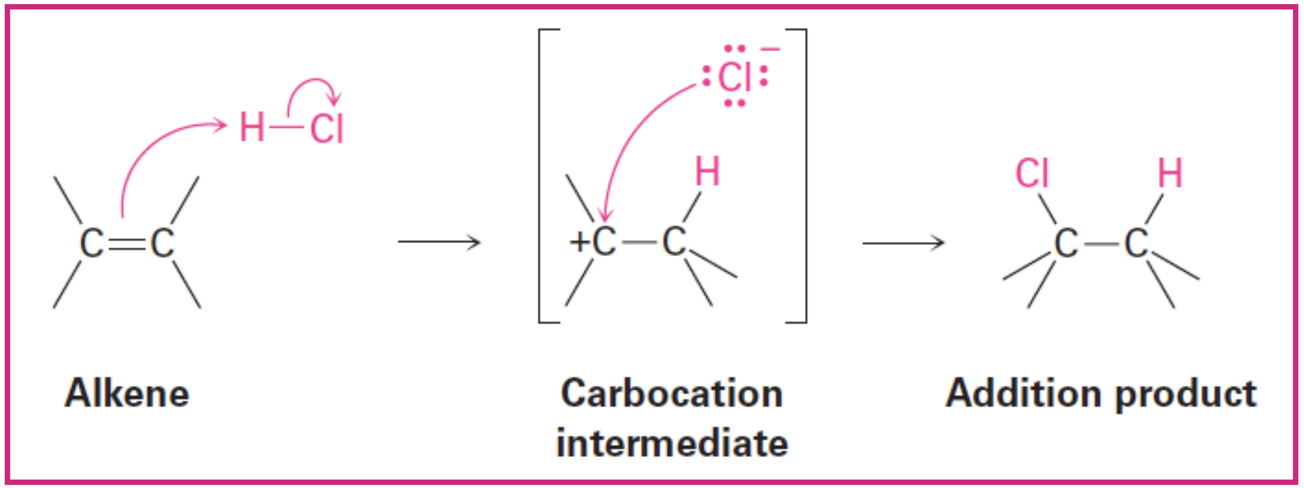
NADH
Nicotinammide **A**denina **D**inucleotide

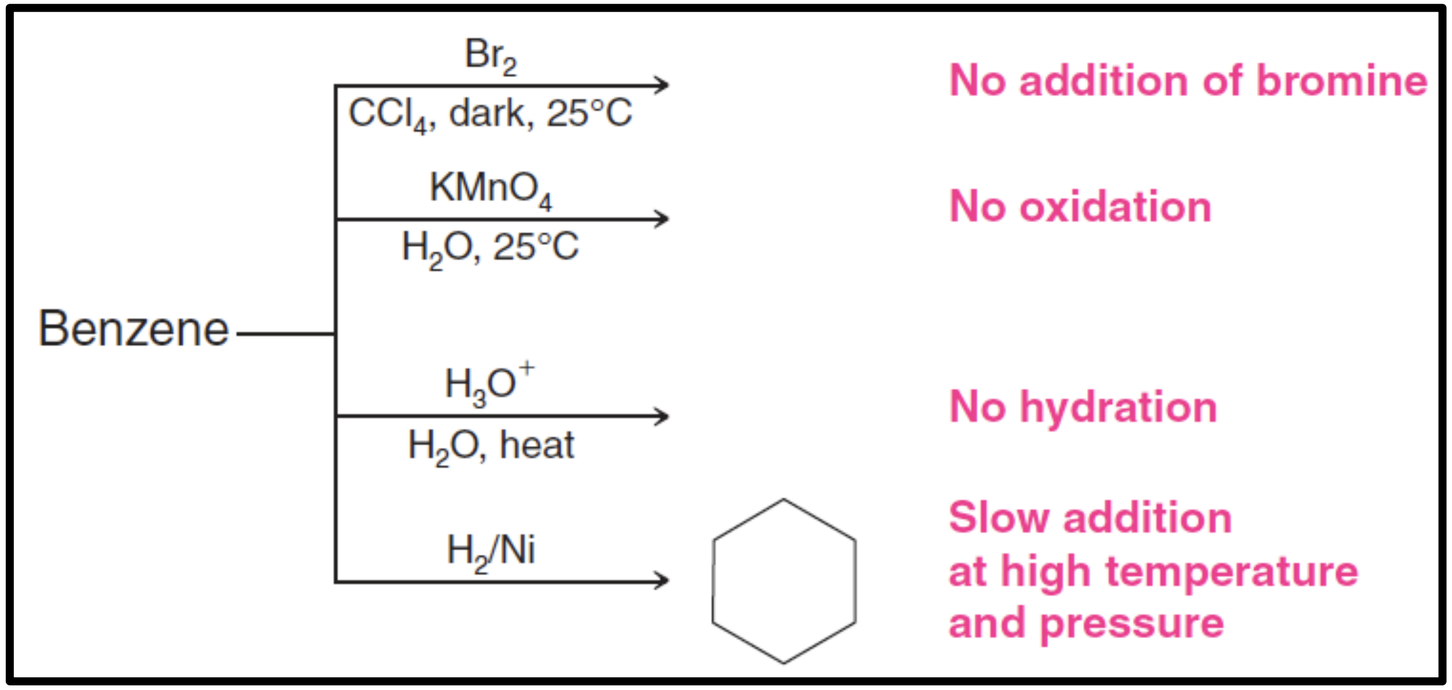
Reazioni del benzene e dei suoi derivati

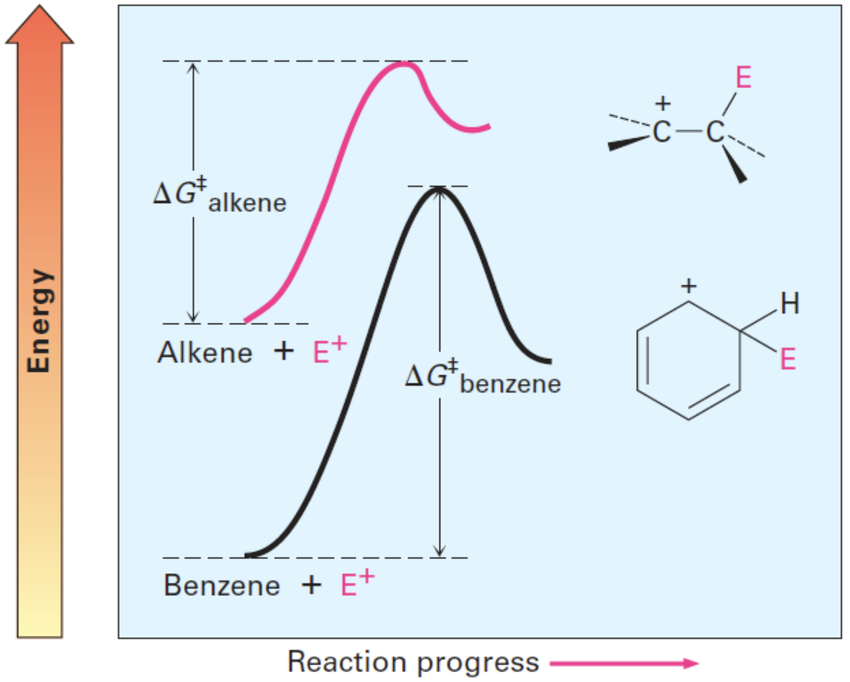
Sostituzione elettrofila aromática (S_EAr)



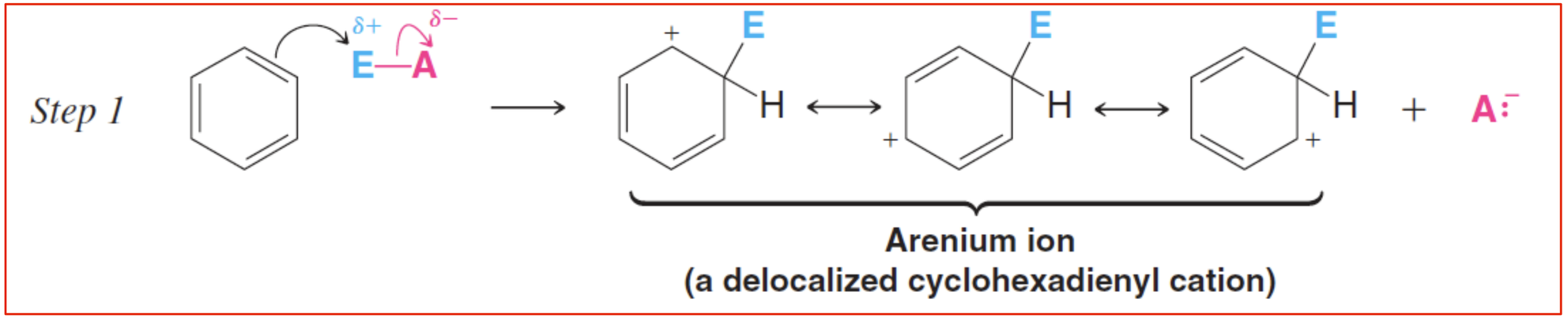
Sostituzione elettrofila aromatica (S_EAr) è diversa dall'addizione degli alcheni

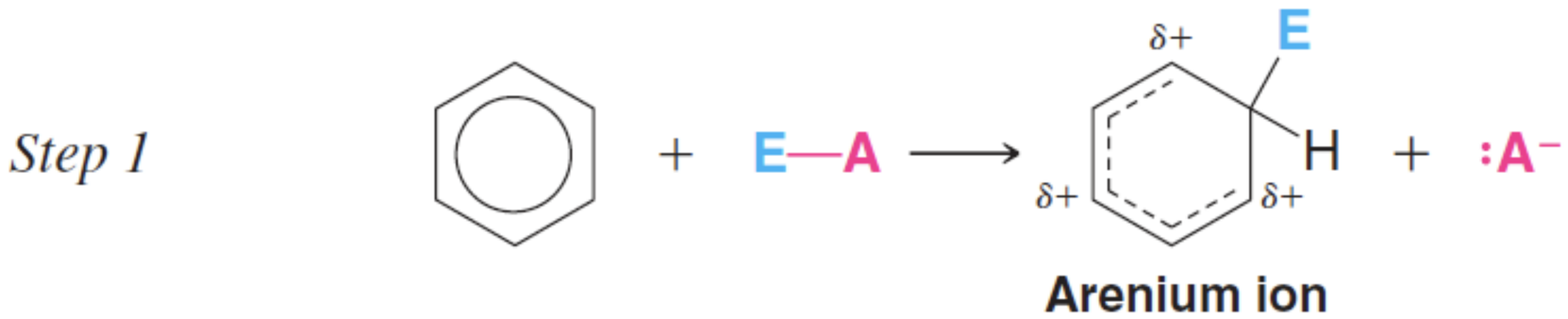


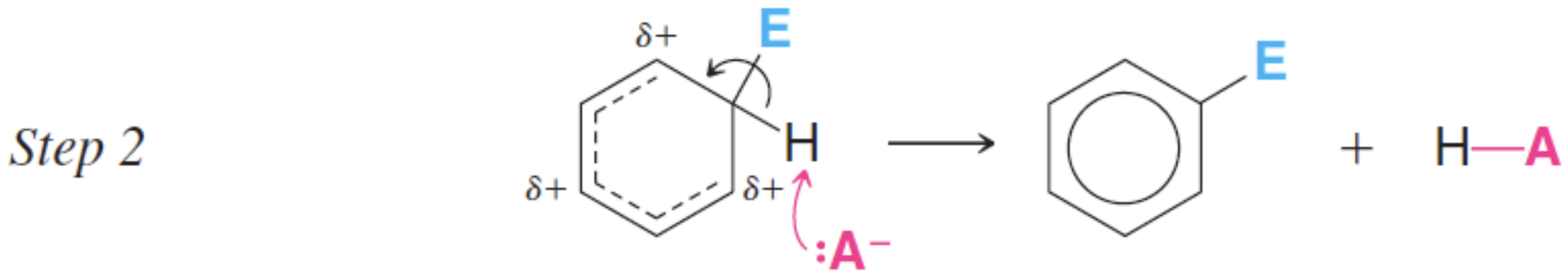




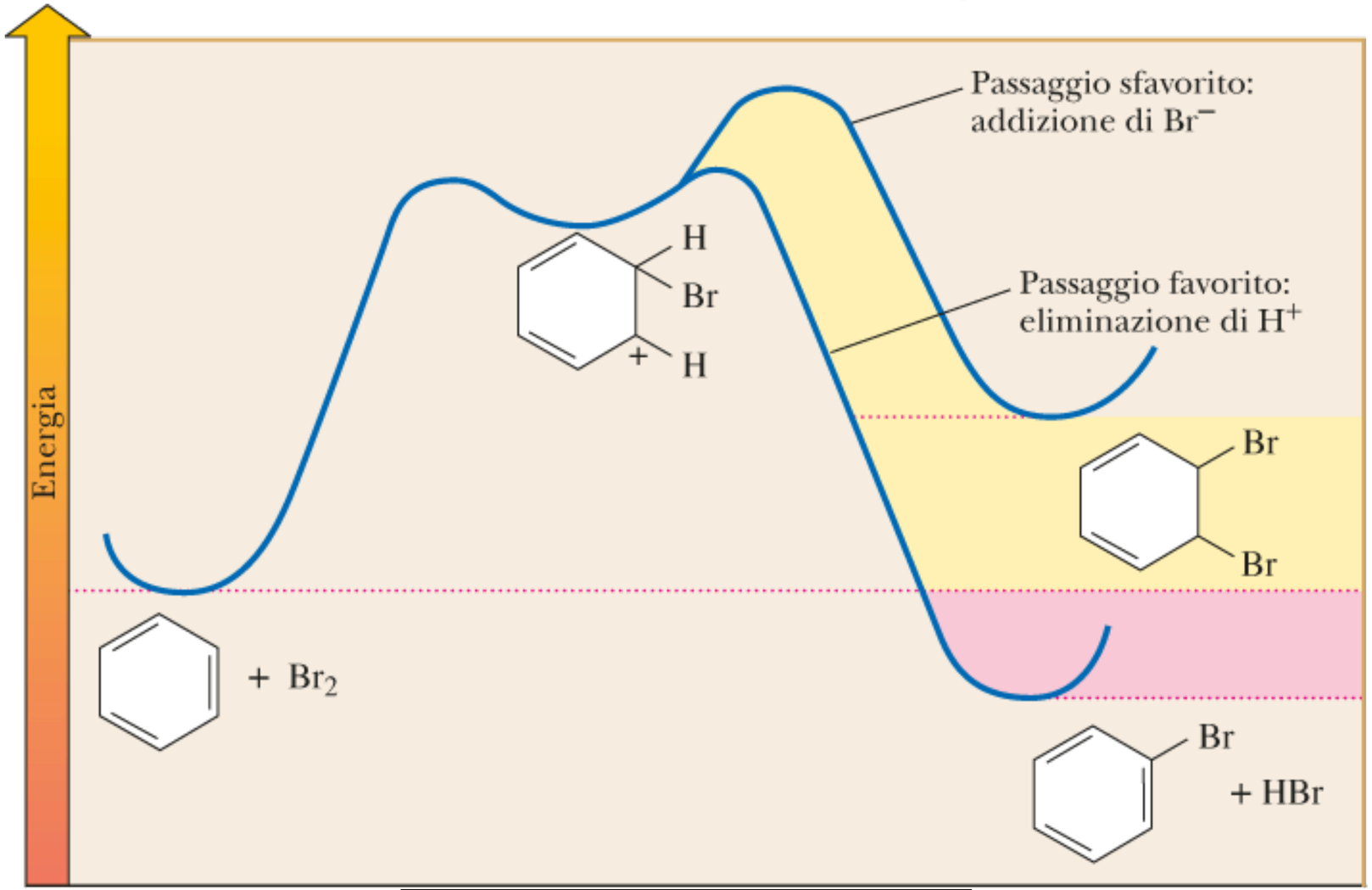
MECCANISMO: Sostituzione elettrofila aromática (S_EAr)

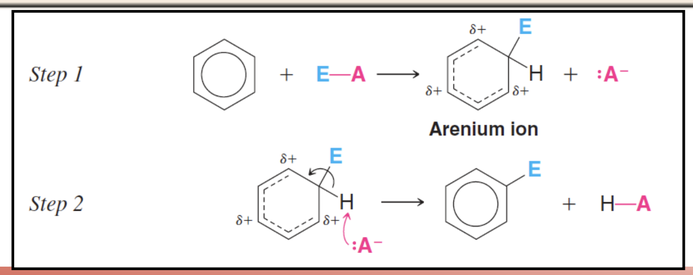




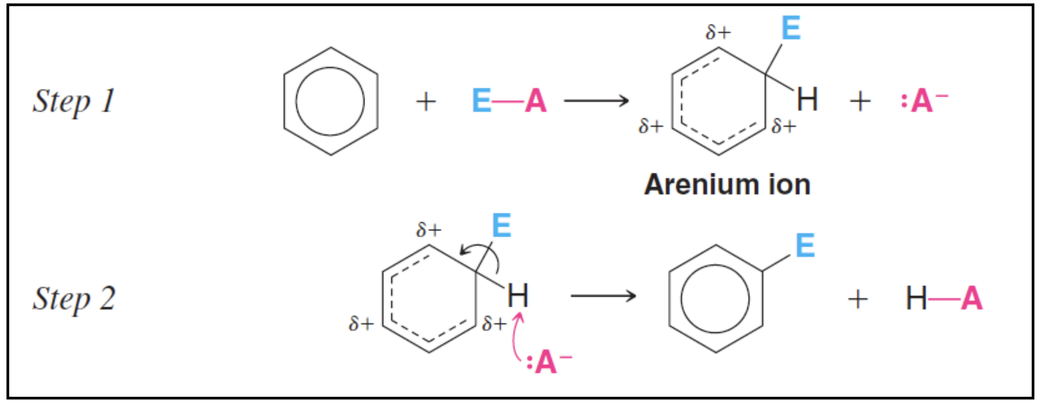


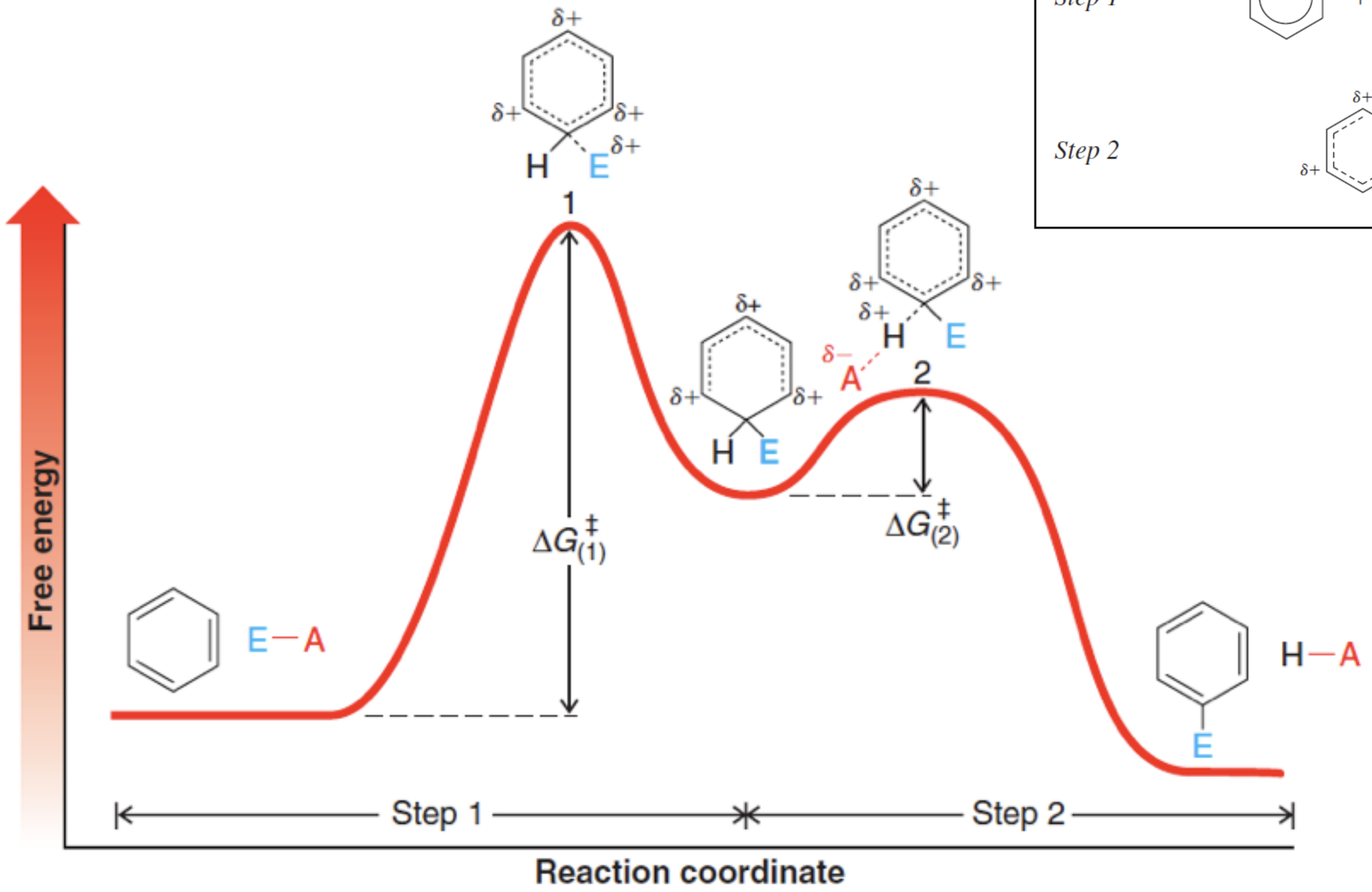
Sostituzione elettrofila aromática (S_EAr) è diversa dall'audizione degli alcheni



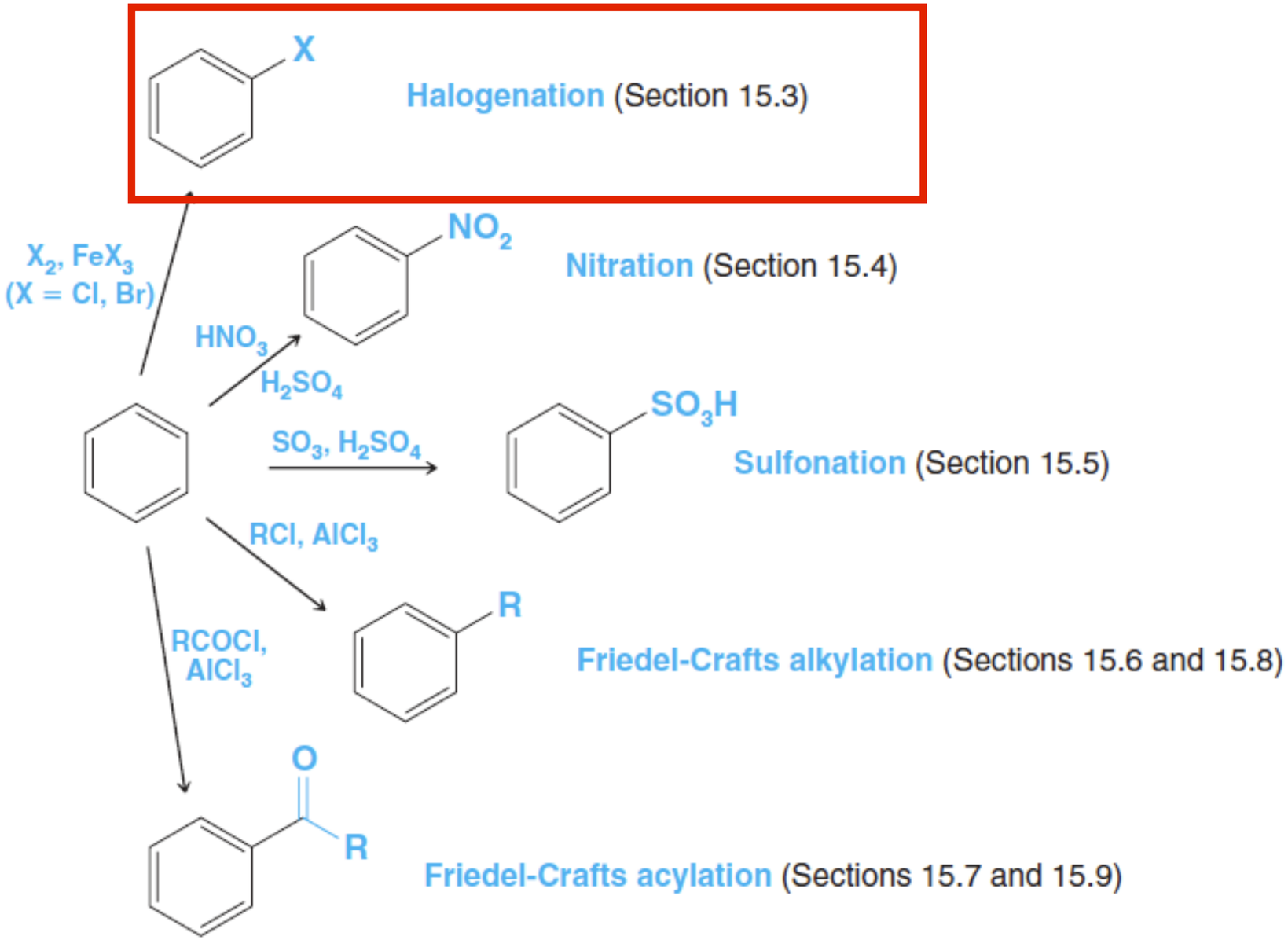


MECCANISMO: Sostituzione elettrofila aromática (S_EAr)

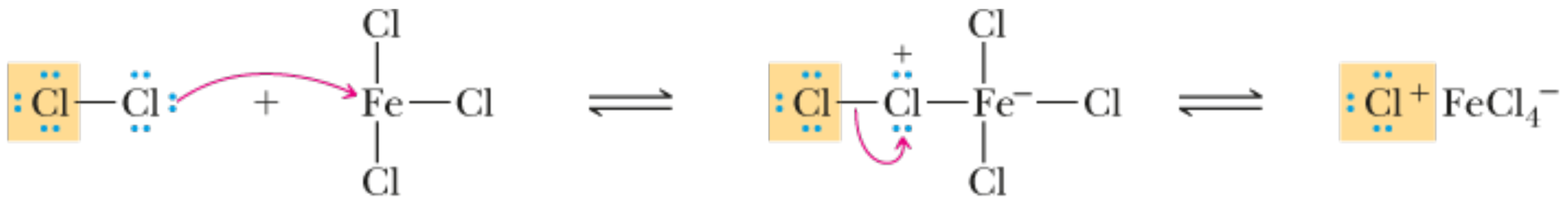




ALOGENAZIONE del BENZENE



Sostituzione elettrofila aromatica: clorurazione

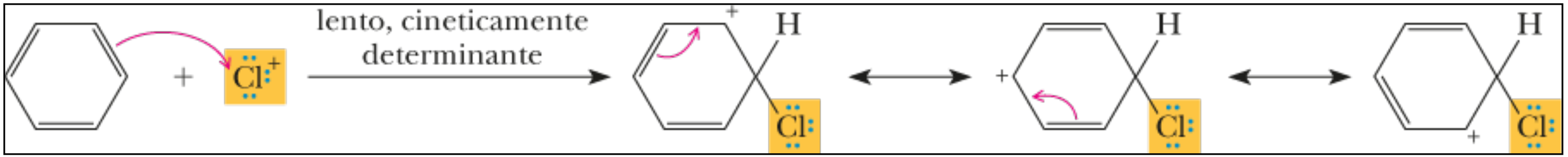


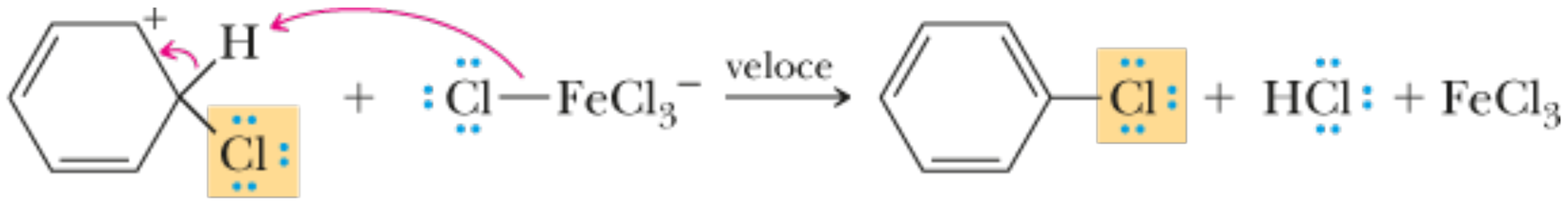
Cloro
(base di Lewis)

Cloruro ferrico
(acido di Lewis)

Complesso molecolare con una carica positiva sul cloro e una carica negativa sul ferro

Coppia ionica che contiene lo ione cloronio

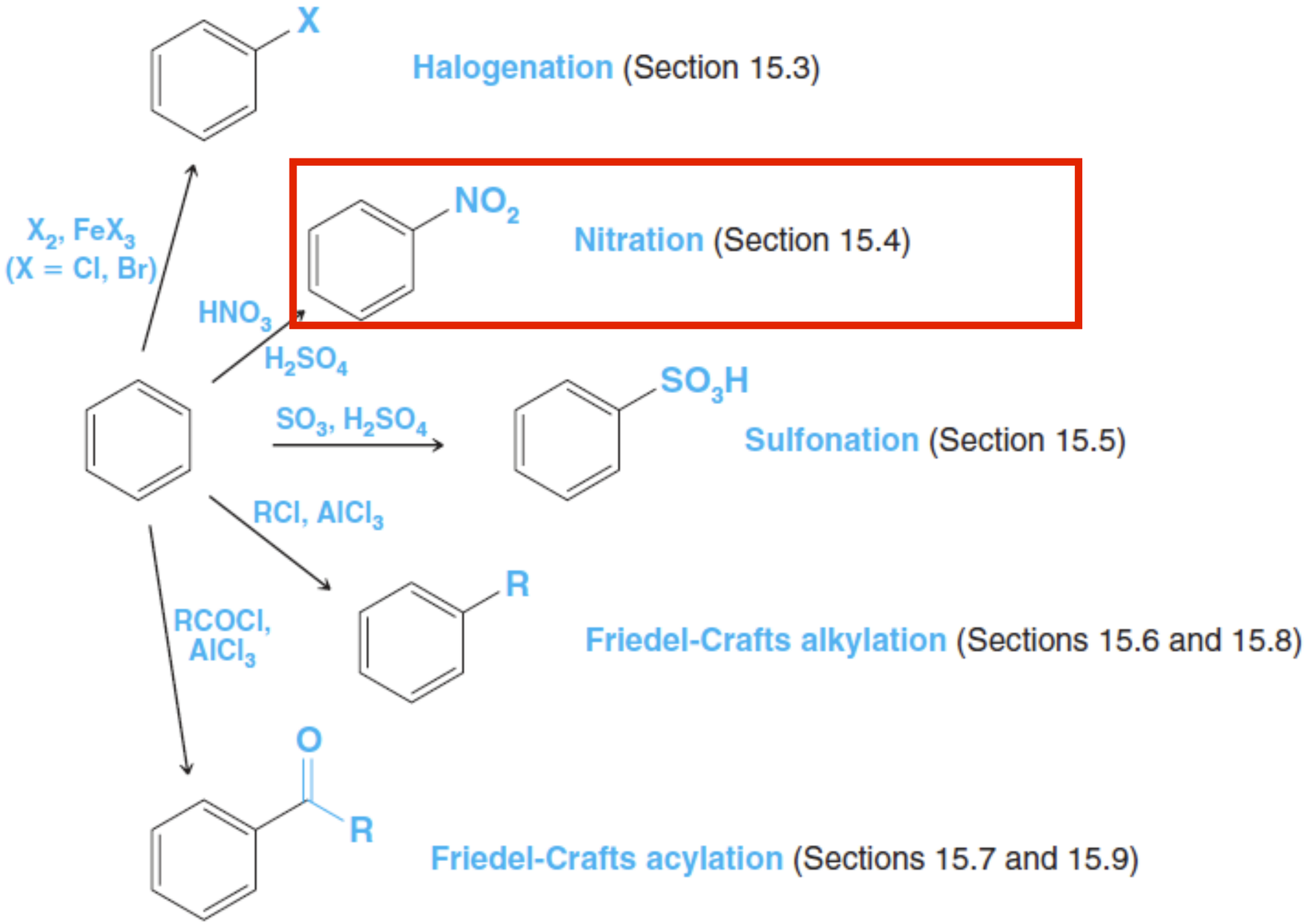




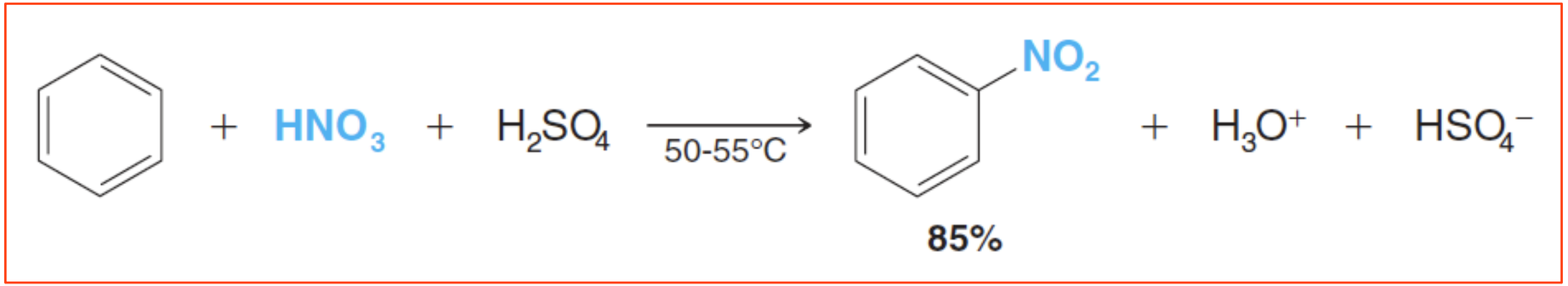
Catione intermedio

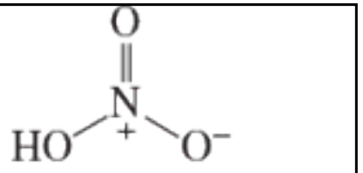
Clorobenzene

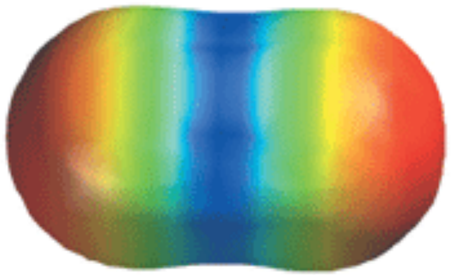
NITRAZIONE del BENZENE

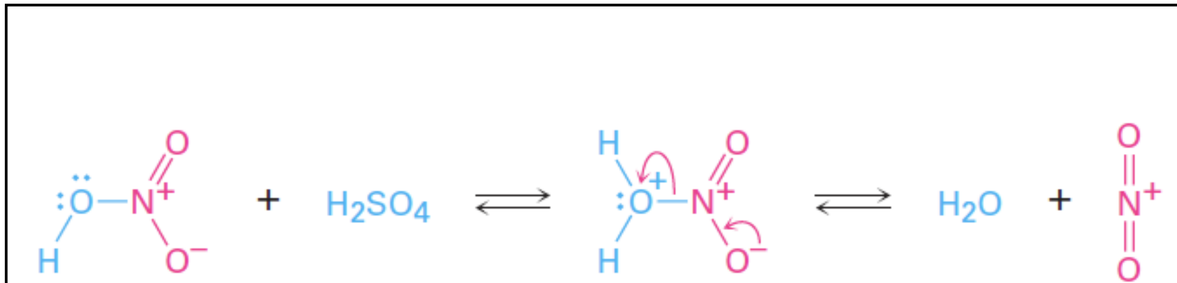


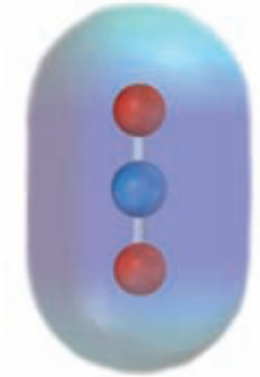
NITRAZIONE del BENZENE

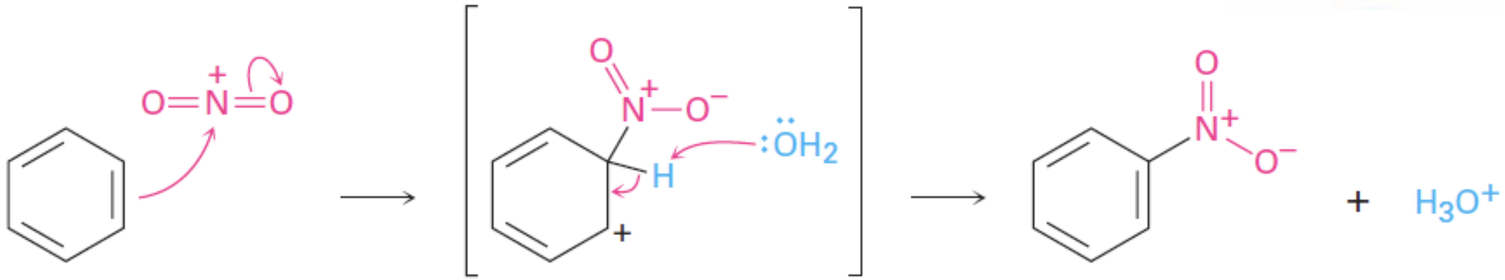




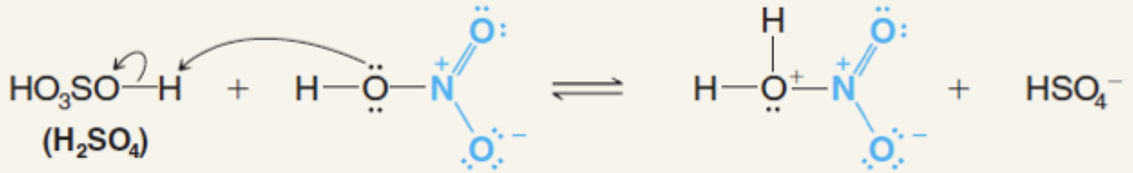








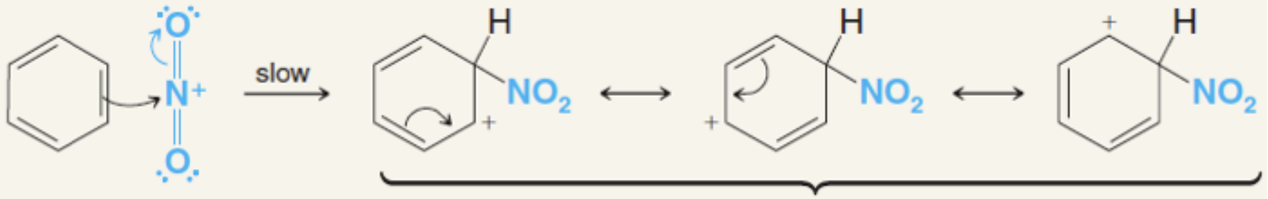
MECCANISMO: NITRAZIONE DEL BENZENO



In this step nitric acid accepts a proton from the stronger acid, sulfuric acid.

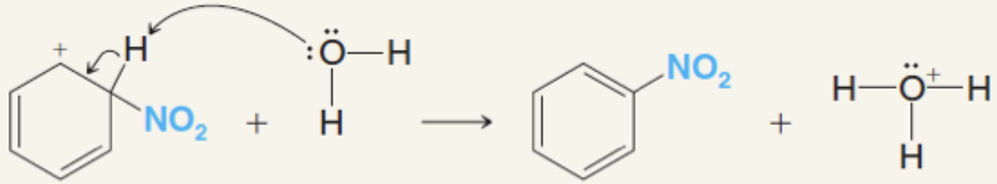
Nitronium ion

Now that it is protonated, nitric acid can dissociate to form a nitronium ion.



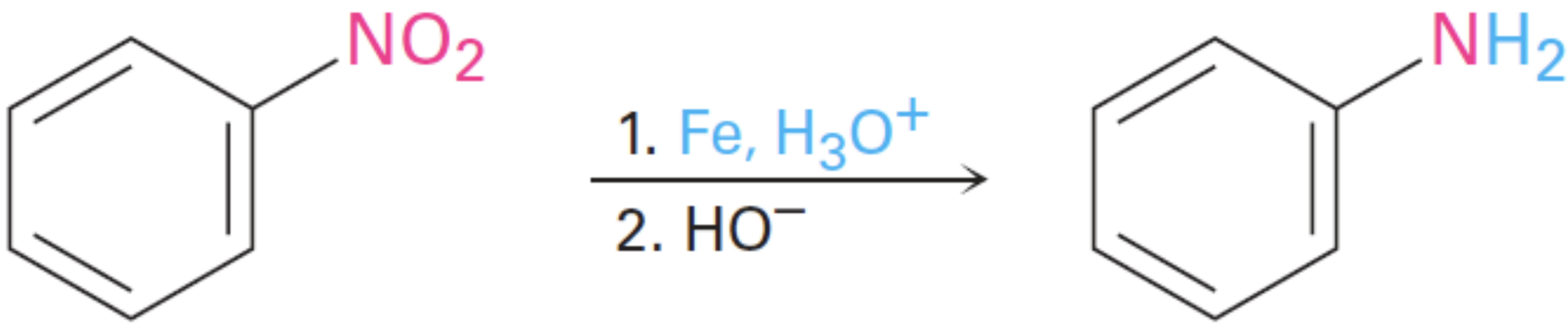
Arenium ion

The nitronium ion is the electrophile in nitration; it reacts with benzene to form a resonance-stabilized arenium ion.



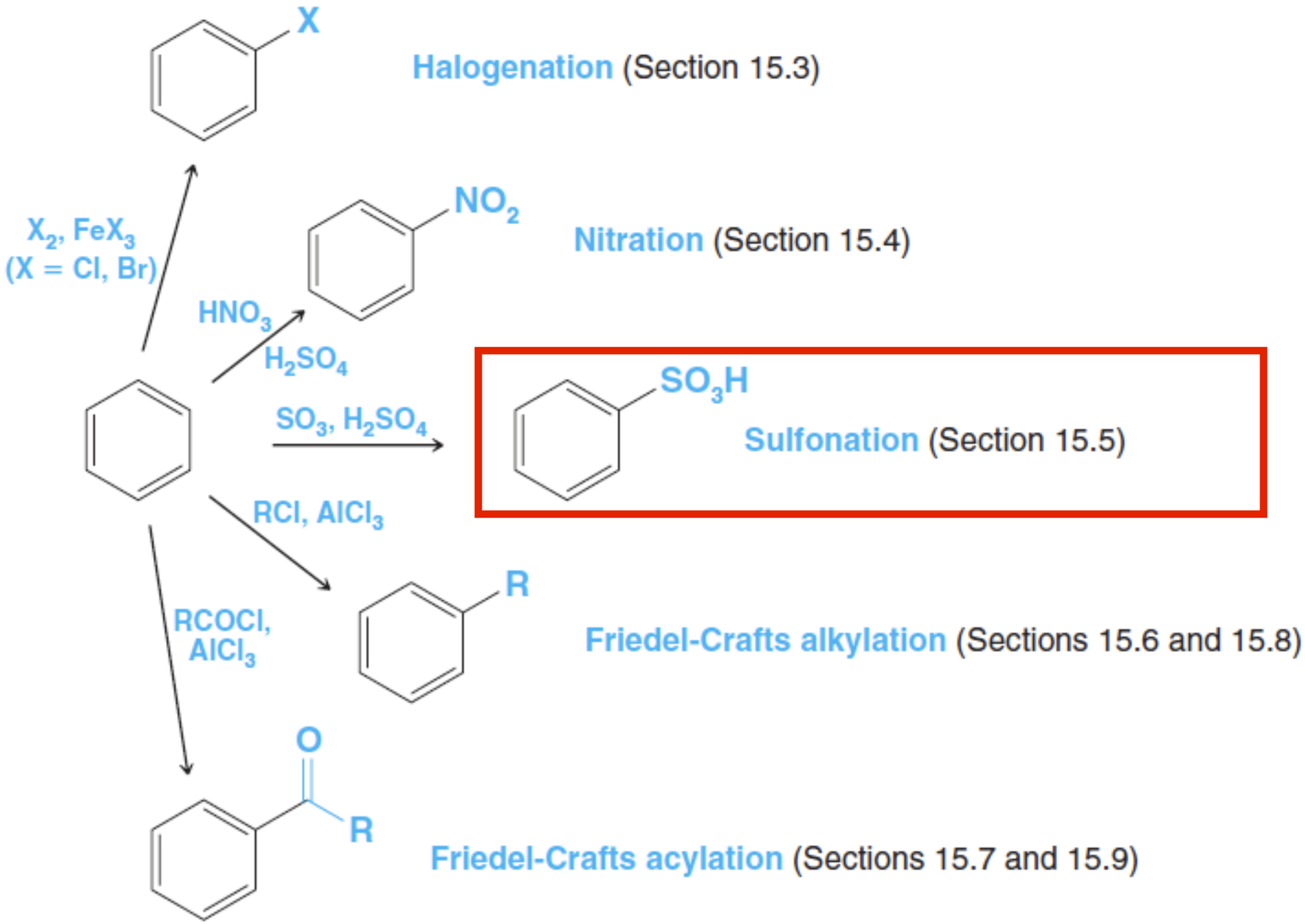
The arenium ion then loses a proton to a Lewis base and becomes nitrobenzene.

NITRAZIONE E RIDUZIONE DEL NITROBENZENE

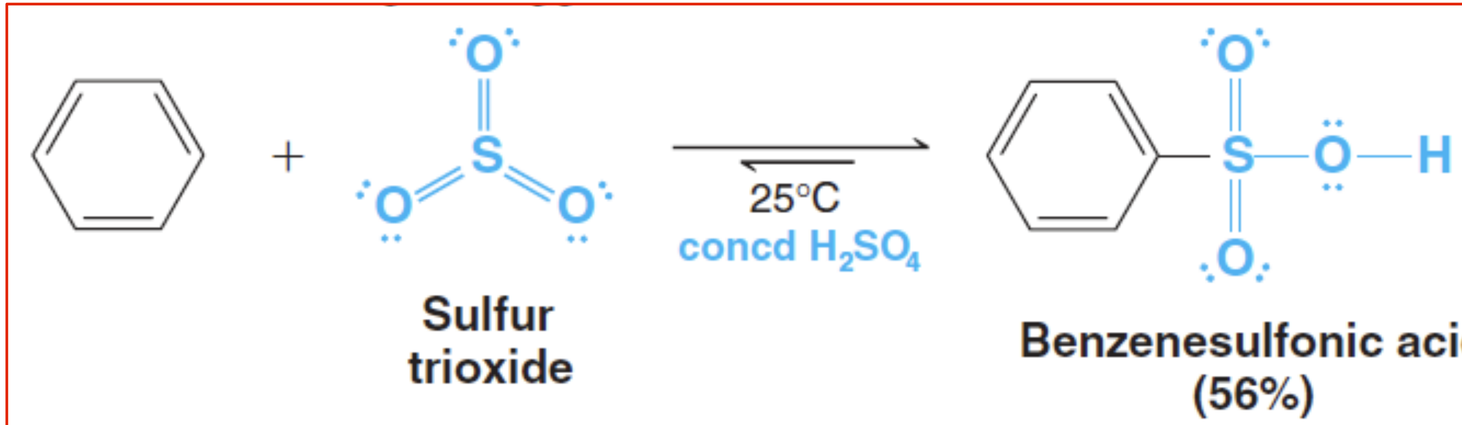


Nitrobenzene **Aniline (95%)**

SOLFONAZIONE del BENZENE



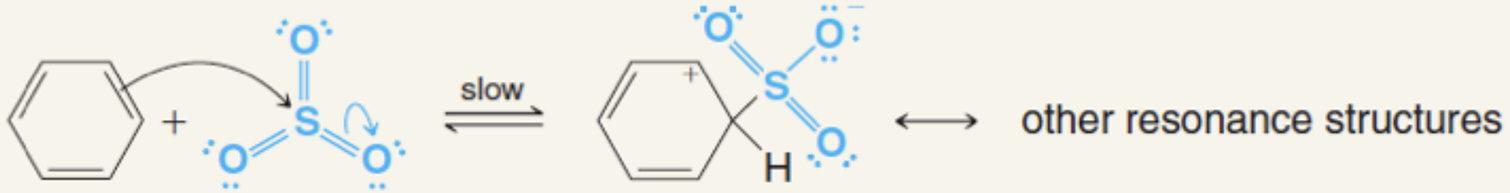
SOLFONAZIONE del Benzene



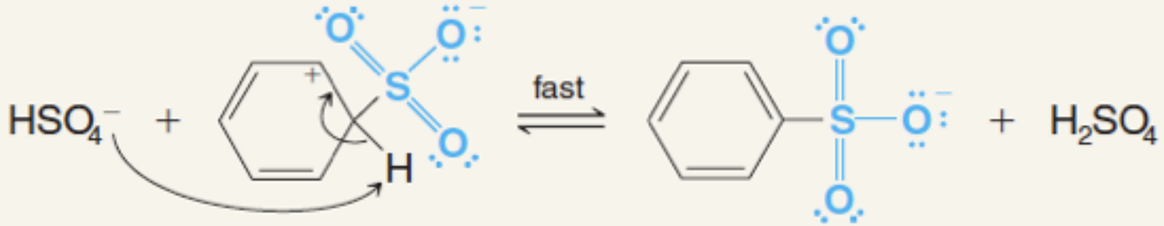
MECCANISMO: SOLFONAZIONE DEL BENZENE

$$2\,H_2SO_4 \rightleftharpoons SO_3 + H_3O^+ + HSO_4^-$$

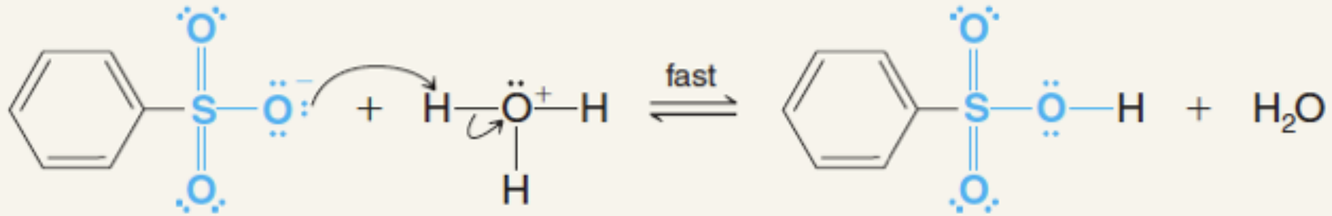
This equilibrium produces SO_3 in concentrated H_2SO_4.



SO_3 is the electrophile that reacts with benzene to form an arenium ion.

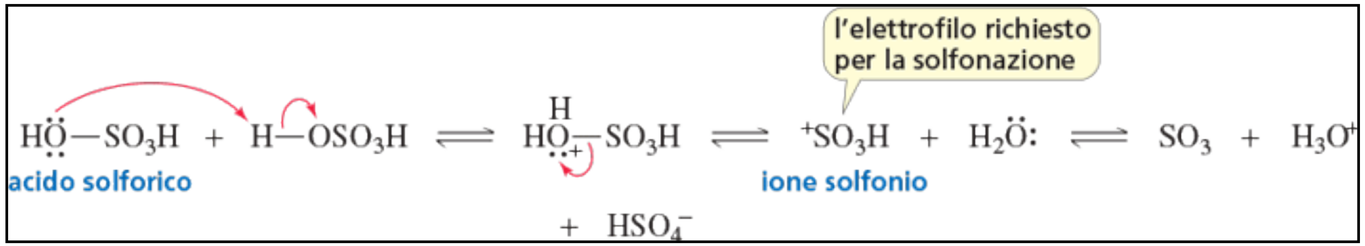


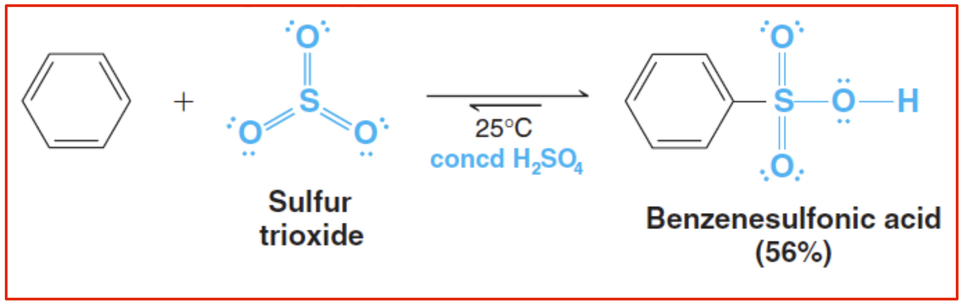
A proton is removed from the arenium ion to form the benzenesulfonate ion.

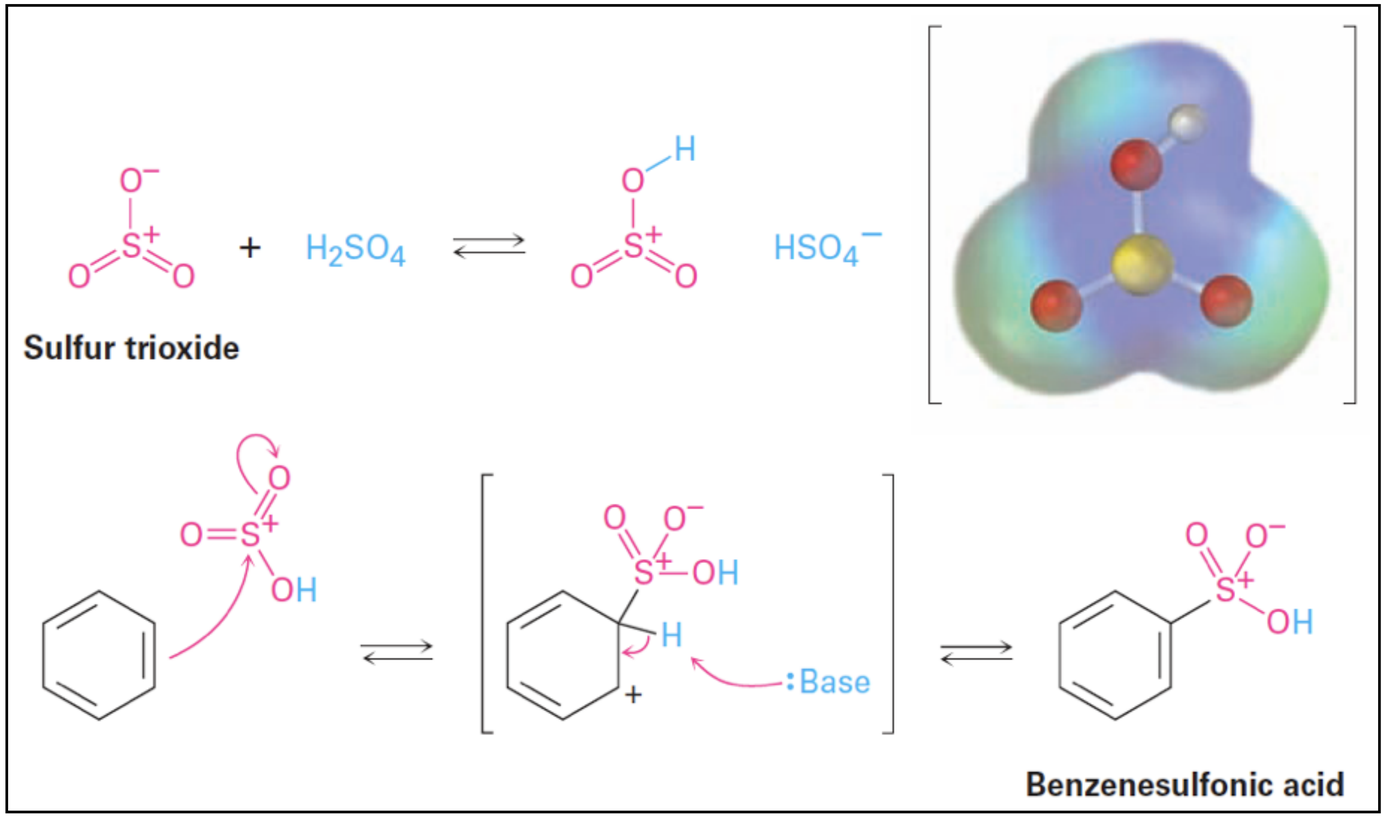


The benzenesulfonate ion accepts a proton to become benzenesulfonic acid.

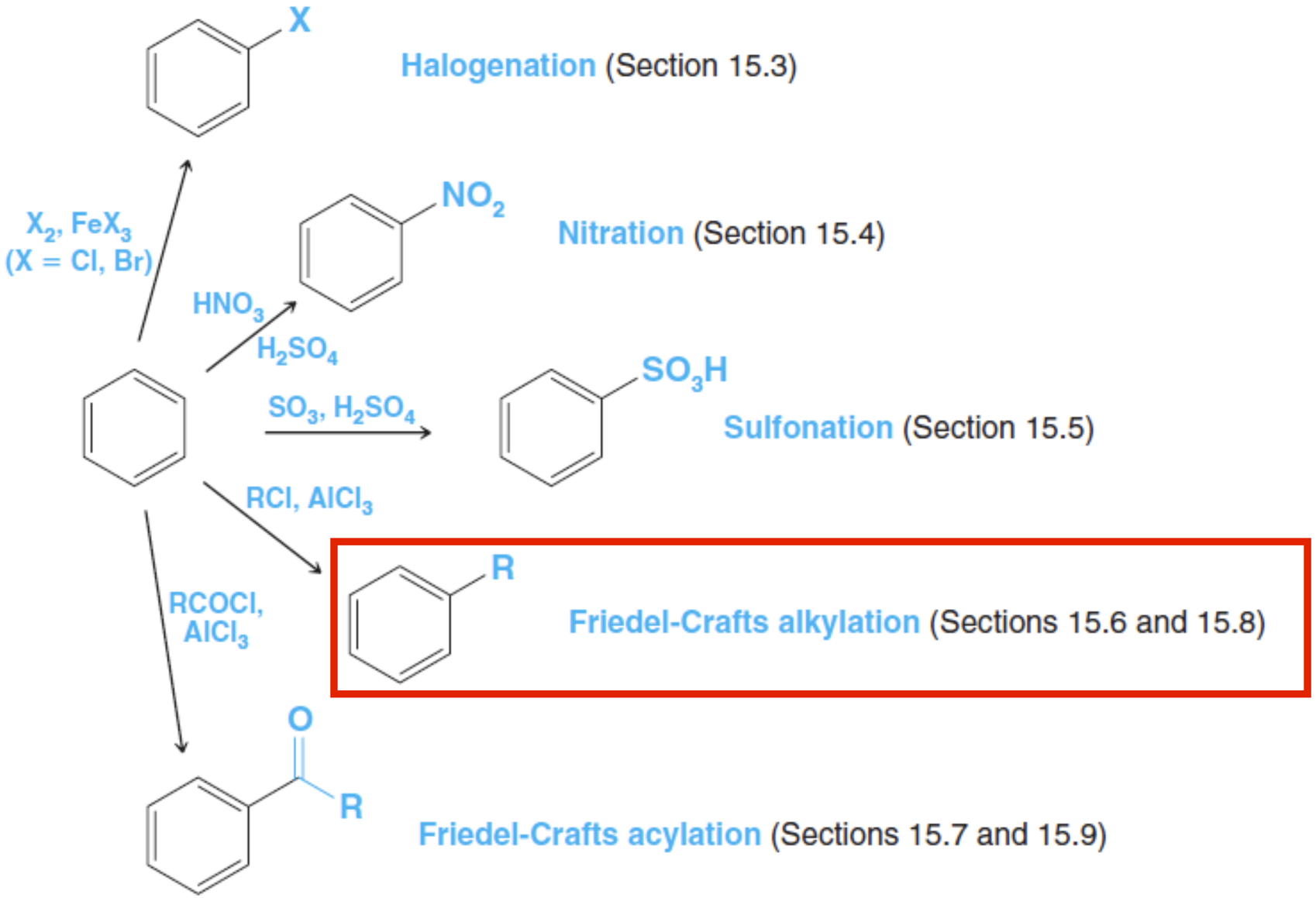
SOLFONAZIONE del Benzene



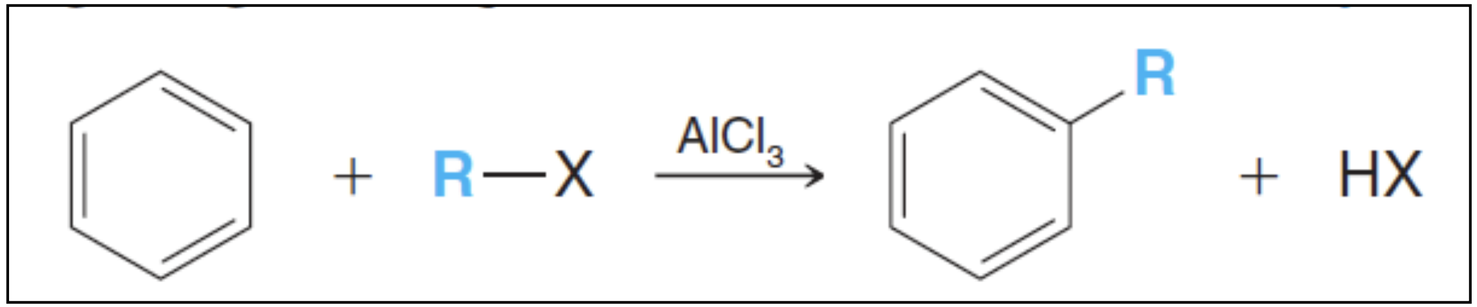




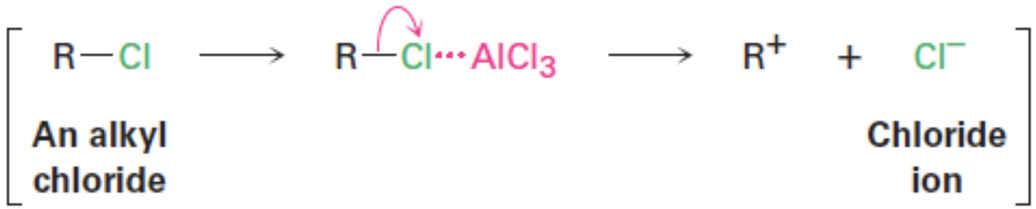
ALCHILAZIONE DI FRIEDEL-CRAFTS

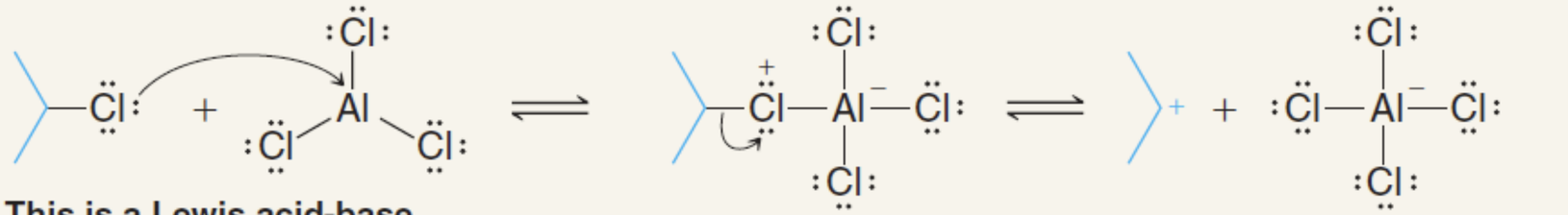


ALCHILAZIONE DI FRIEDEL-CRAFTS



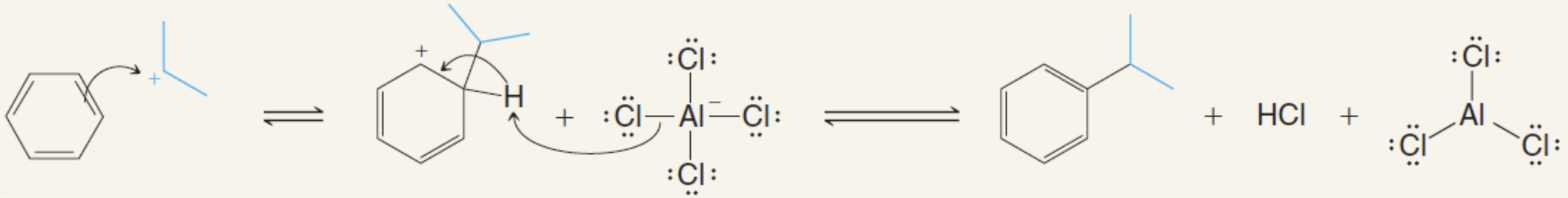
ALCHILAZIONE DI FRIEDEL-CRAFTS





This is a Lewis acid-base reaction (see Section 3).

The complex dissociates to form a carbocation and $AlCl_4^-$.



The carbocation, acting as an electrophile, reacts with benzene to produce an arenium ion.

A proton is removed from the arenium ion to form isopropylbenzene. This step also regenerates the $AlCl_3$ and liberates HCl.

3 LIMITAZIONI DELLE ALCHILAZIONI DI FRIEDEL-CRAFTS

Ci sono tre importanti limitazioni nell'alchilazione di Friedel-Crafts.

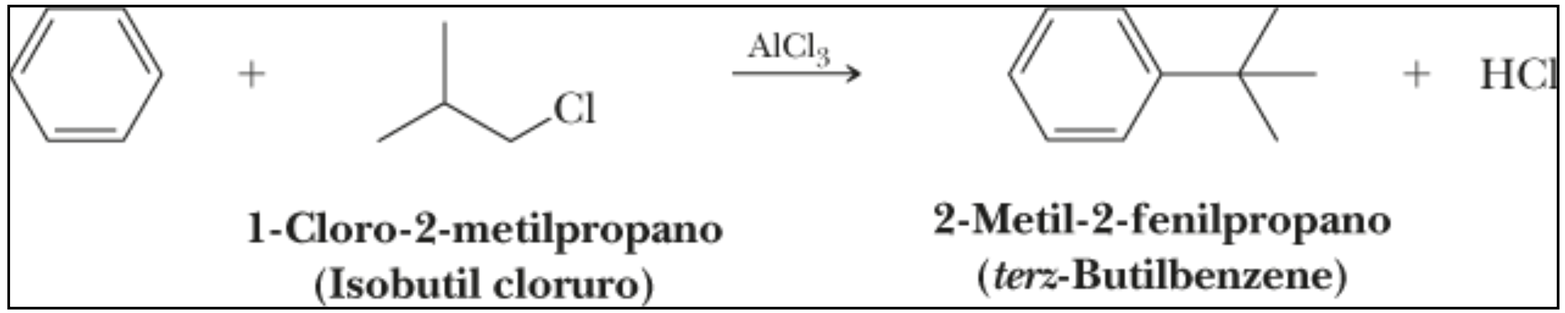
La prima è dovuta a possibili trasposizioni del gruppo alchilico.

La seconda limitazione nell'alchilazione di Friedel-Crafts risiede nel fatto che essa fallisce quando nell'anello aromatico sono presenti uno o più gruppi fortemente elettron-attrattori.

La terza limitazione all'alchilazione di Friedel-Crafts sta nel fatto che risulta difficile fermare la reazione a livello del prodotto monosostituito, in quanto quest'ultimo risulta più reattivo del benzene stesso.

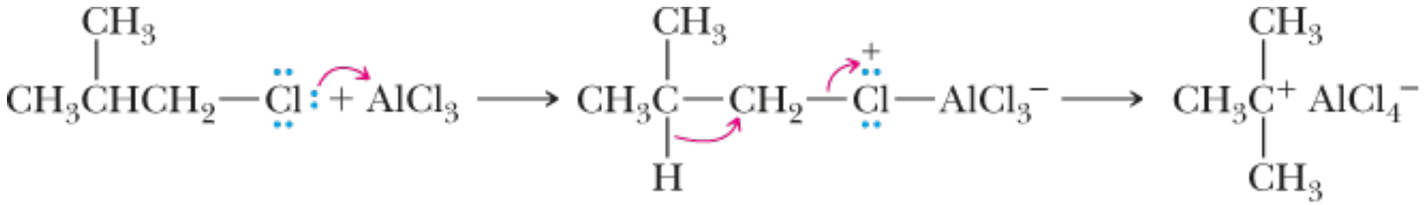
3 LIMITAZIONI DELLE ALCHILAZIONI DI FRIEDEL-CRAFTS

La prima è dovuta a possibili trasposizioni del gruppo alchilico.



1-Cloro-2-metilpropano (Isobutil cloruro)

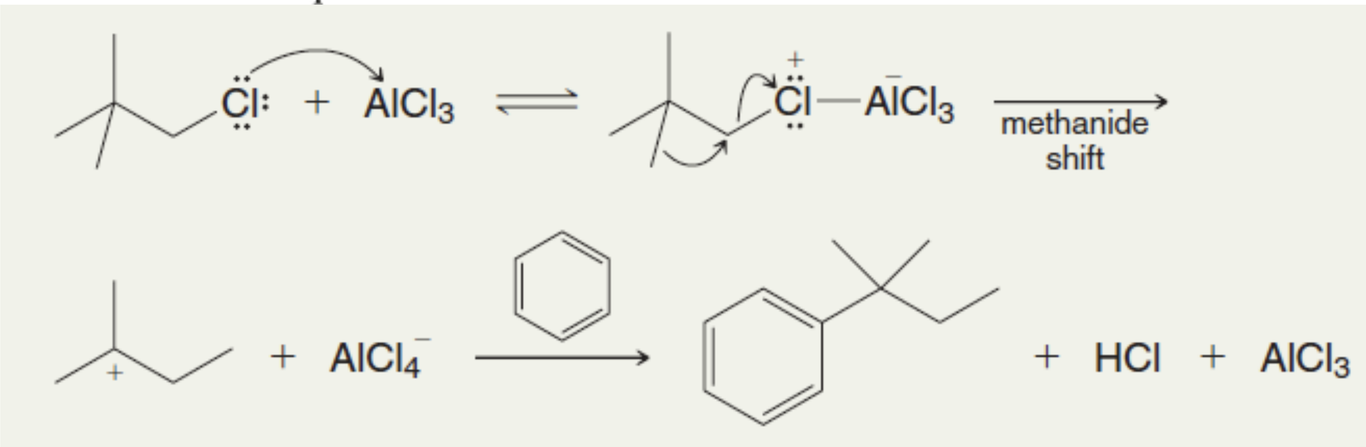
2-Metil-2-fenilpropano (*terz*-Butilbenzene)



Isobutil cloruro

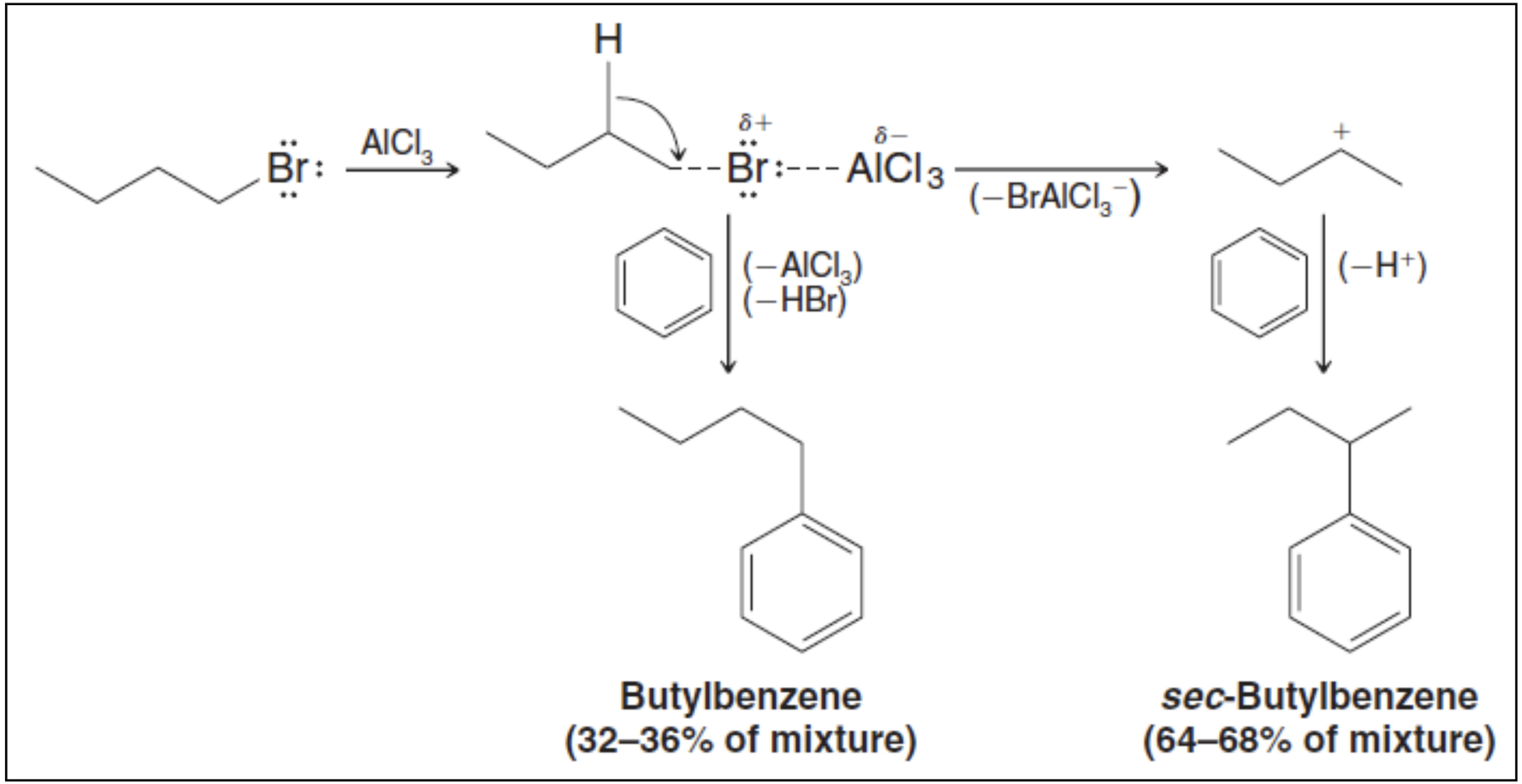
Complesso isobutil cloruro/ cloruro di alluminio

Coppia ionica catione *terz*-butilico/ $AlCl_4^-$



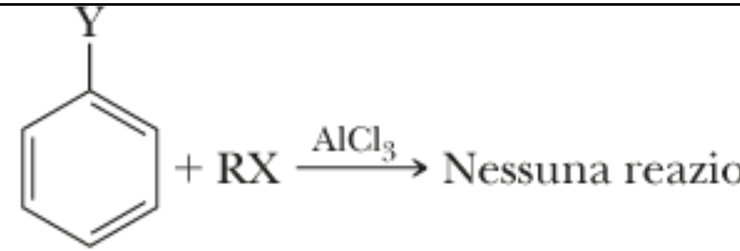
3 LIMITAZIONI DELLE ALCHILAZIONI DI FRIEDEL-CRAFTS

possibile trasposizione del gruppo alchilico.



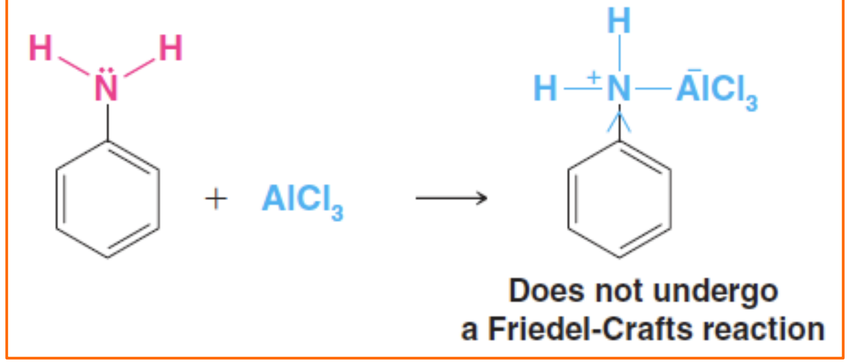
3 LIMITAZIONI DELLE ALCHILAZIONI DI FRIEDEL-CRAFTS

La seconda limitazione nell'alchilazione di Friedel-Crafts risiede nel fatto che essa fallisce quando nell'anello aromatico sono presenti uno o più gruppi fortemente elettron-attrattori.



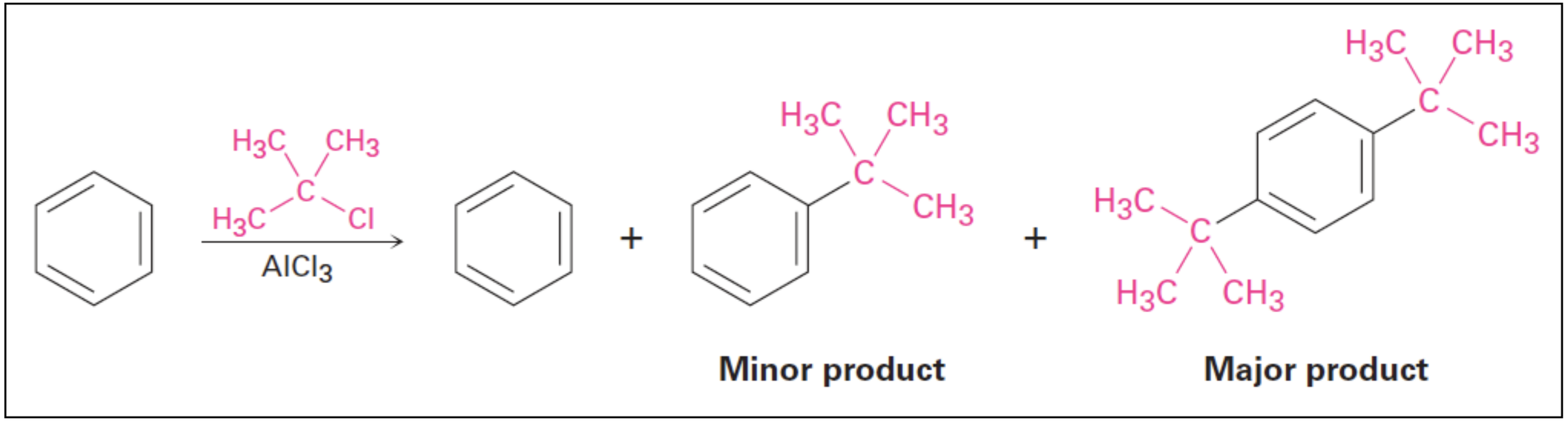
Quando Y è uno qualsiasi di questi gruppi, l'anello benzenico non subisce l'alchilazione di Friedel-Crafts

—CH	—CR	—COH	—COR	—CNH_2
—SO_3H	—C≡N	—NO_2	—NR_3^+	
—CF_3	—CCl_3			

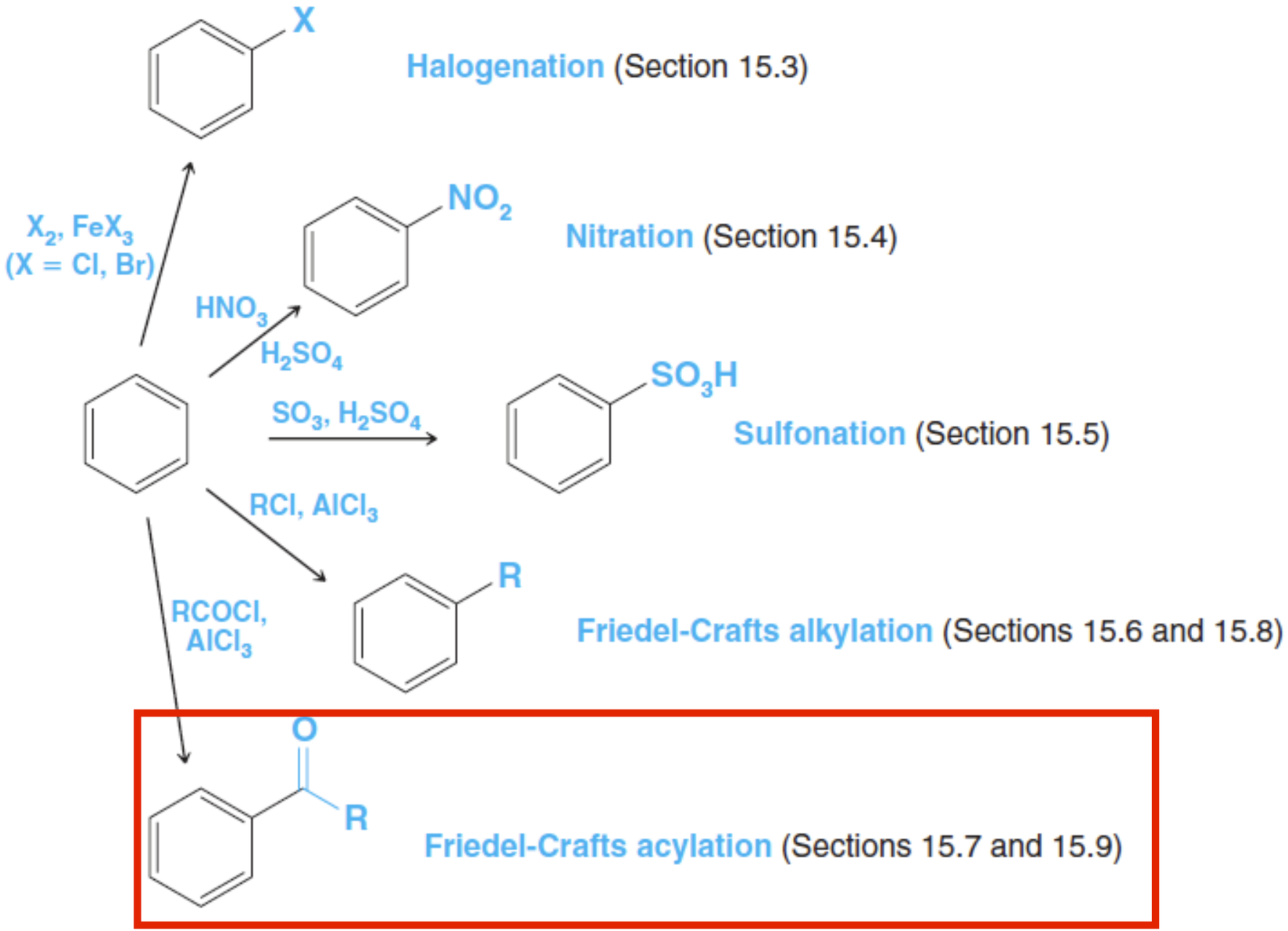


3 LIMITAZIONI DELLE ALCHILAZIONE DI FRIEDEL-CRAFTS

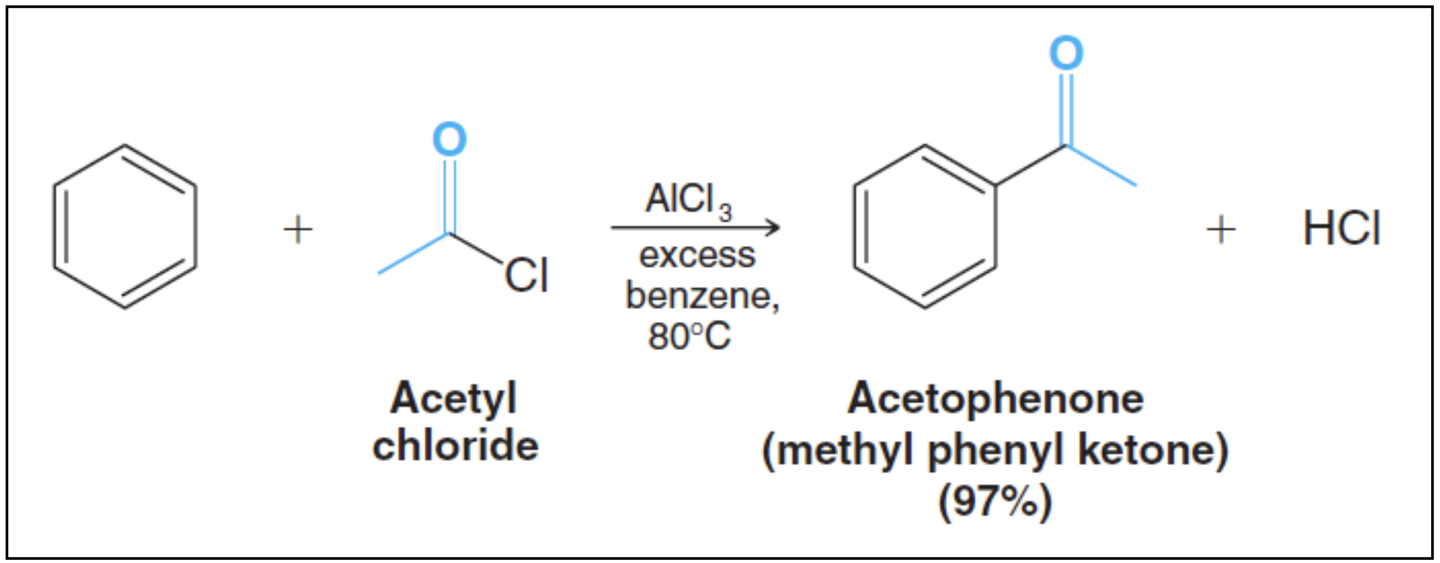
La terza limitazione all'alchilazione di Friedel-Crafts sta nel fatto che risulta difficile fermare la reazione a livello del prodotto monosostituito, in quanto quest'ultimo risulta più reattivo del benzene stesso.

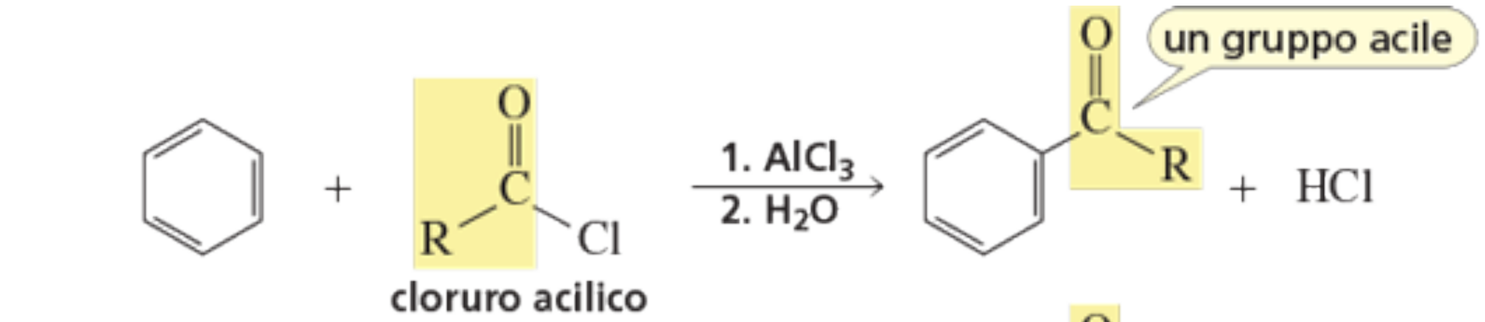


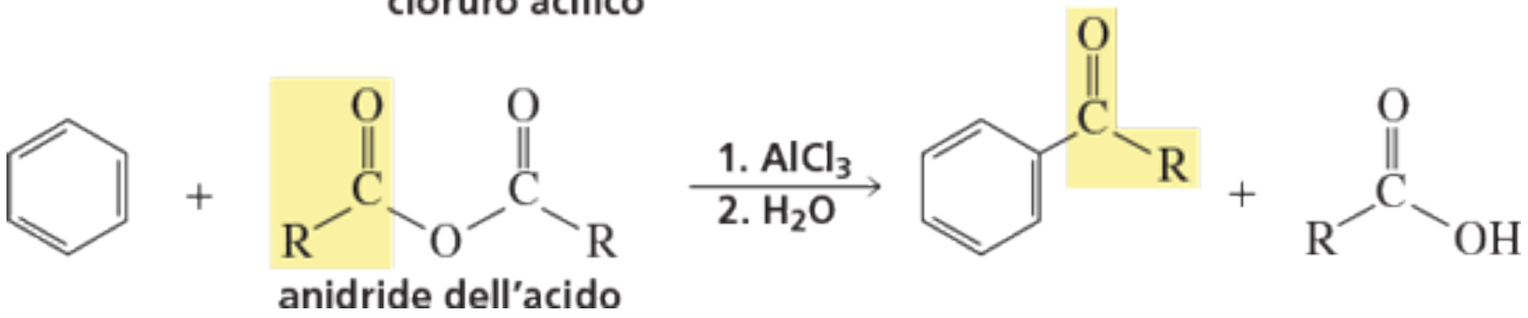
ACILAZIONE DI FRIEDEL-CRAFTS



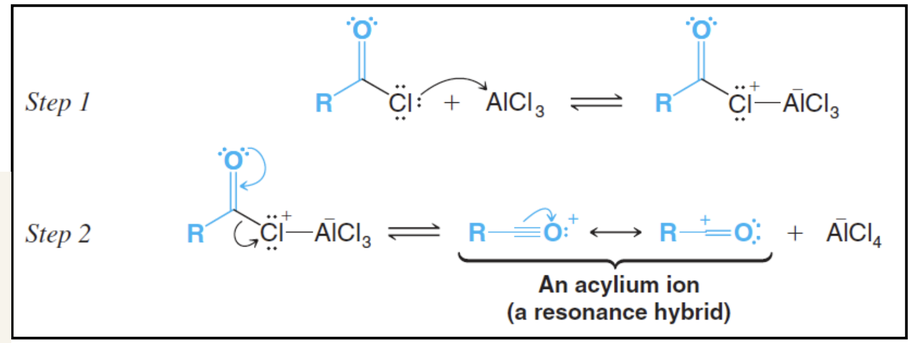
ACILAZIONE DI FRIEDEL-CRAFTS







MECCANISMO: ACILAZIONE DI FRIEDEL-CRAFTS



Step 3

other resonance structures
(draw them for practice)

The acylium ion, acting as an electrophile, reacts with benzene to form the arenium ion.

Step 4

A proton is removed from the arenium ion, forming the aryl ketone.

Step 5

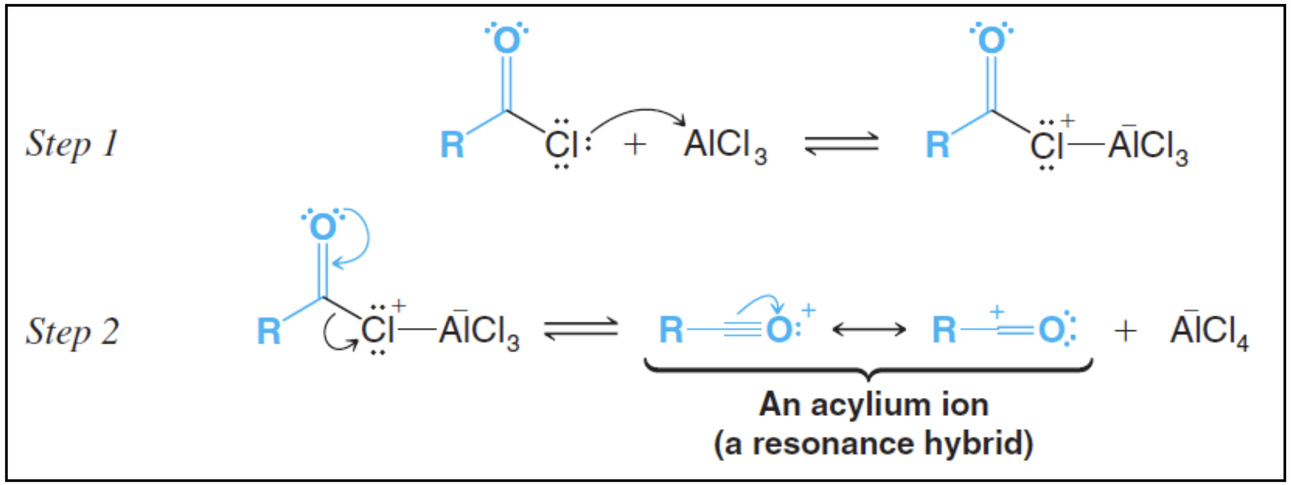
The ketone, acting as a Lewis base, reacts with aluminum chloride (a Lewis acid) to form a complex.

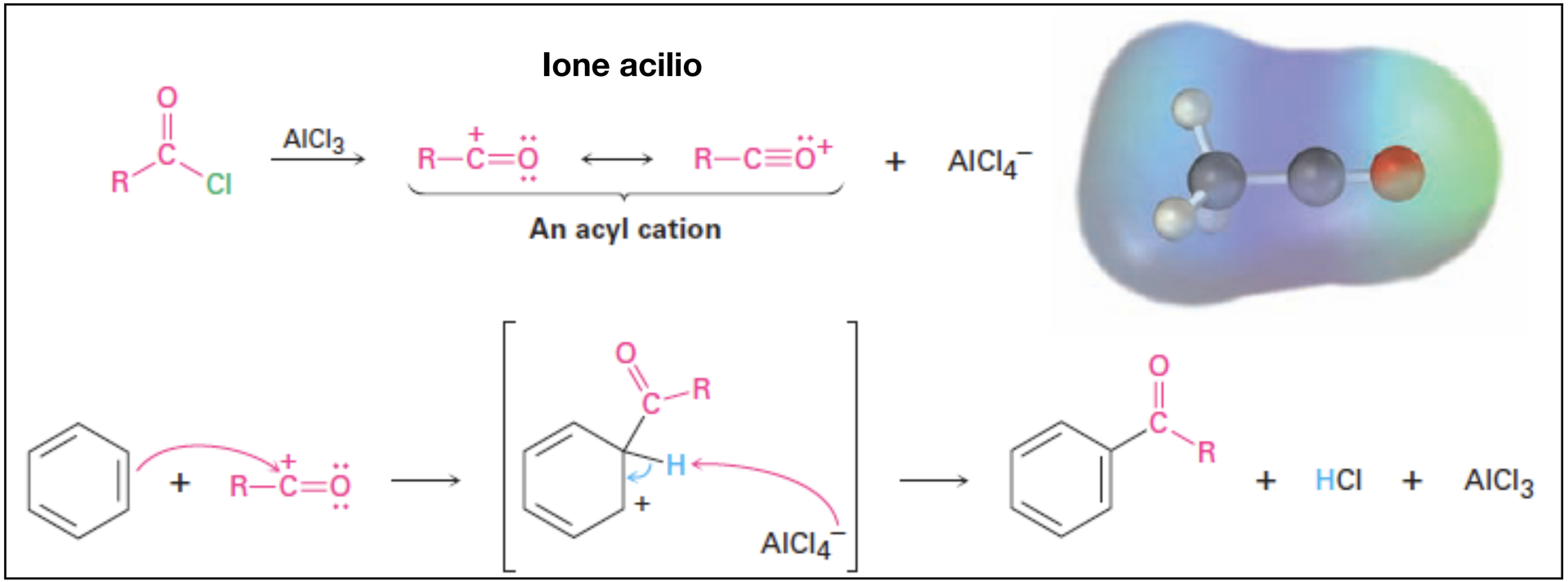
Step 6

Treating the complex with water liberates the ketone and hydrolyzes the Lewis acid.

Poiché il prodotto di una reazione di acilazione di Friedel-Crafts contiene un gruppo carbonilico che può formare un complesso con l'$AlCl_3$, l'acilazione di Friedel-Crafts deve essere condotta con più di un equivalente di $AlCl_3$. Quando la reazione è terminata, si aggiunge acqua alla miscela di reazione per liberare il prodotto dal complesso.

MECCANISMO: ACILAZIONE DI FRIEDEL-CRAFTS

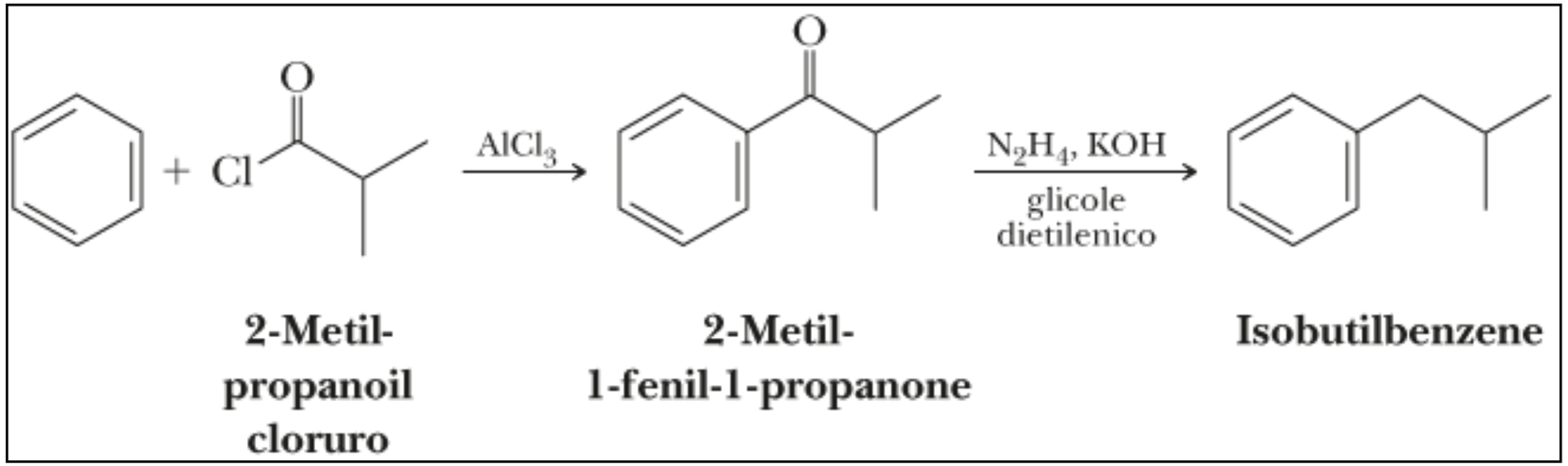




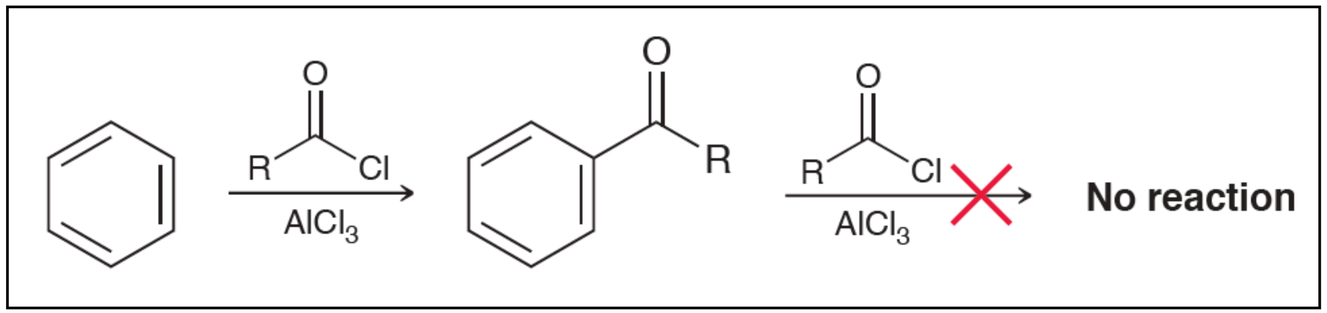
2 VANTAGGI: ACILAZIONE DI FRIEDEL-CRAFTS

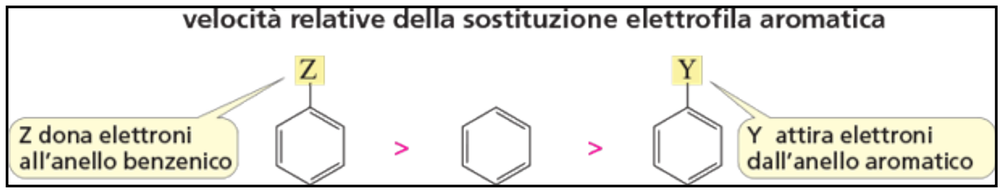
L'acilazione di Friedel-Crafts non soffre nemmeno della prima limitazione dell'alchilazione di Friedel-Crafts: i cationi acilici non traspongono. Pertanto, lo scheletro carbonioso dell'alogenuro acilico viene trasferito invariato sull'anello aromatico.
Il fatto che un acilbenzene sia meno reattivo (o addirittura inerte, in molti casi) del reagente iniziale evita il terzo inconveniente dell'alchilazione di Friedel-Crafts.

La trasposizione dello ione acilio è osservata

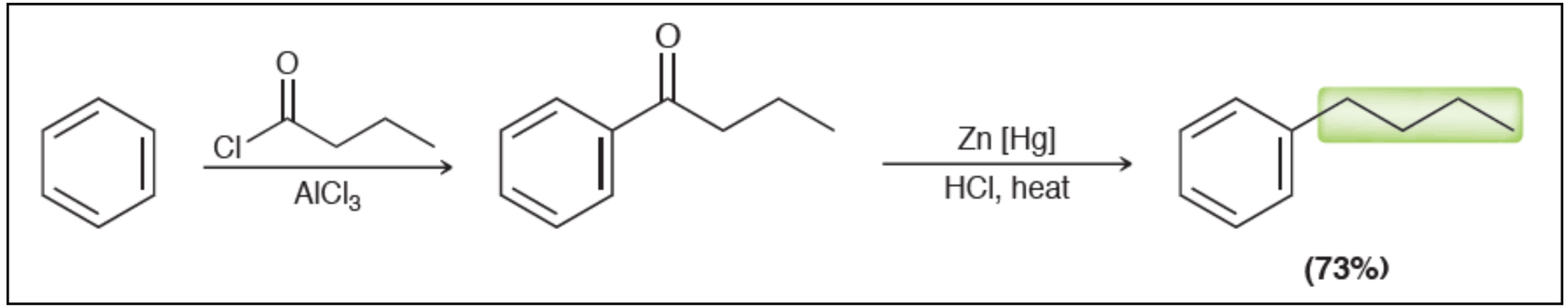


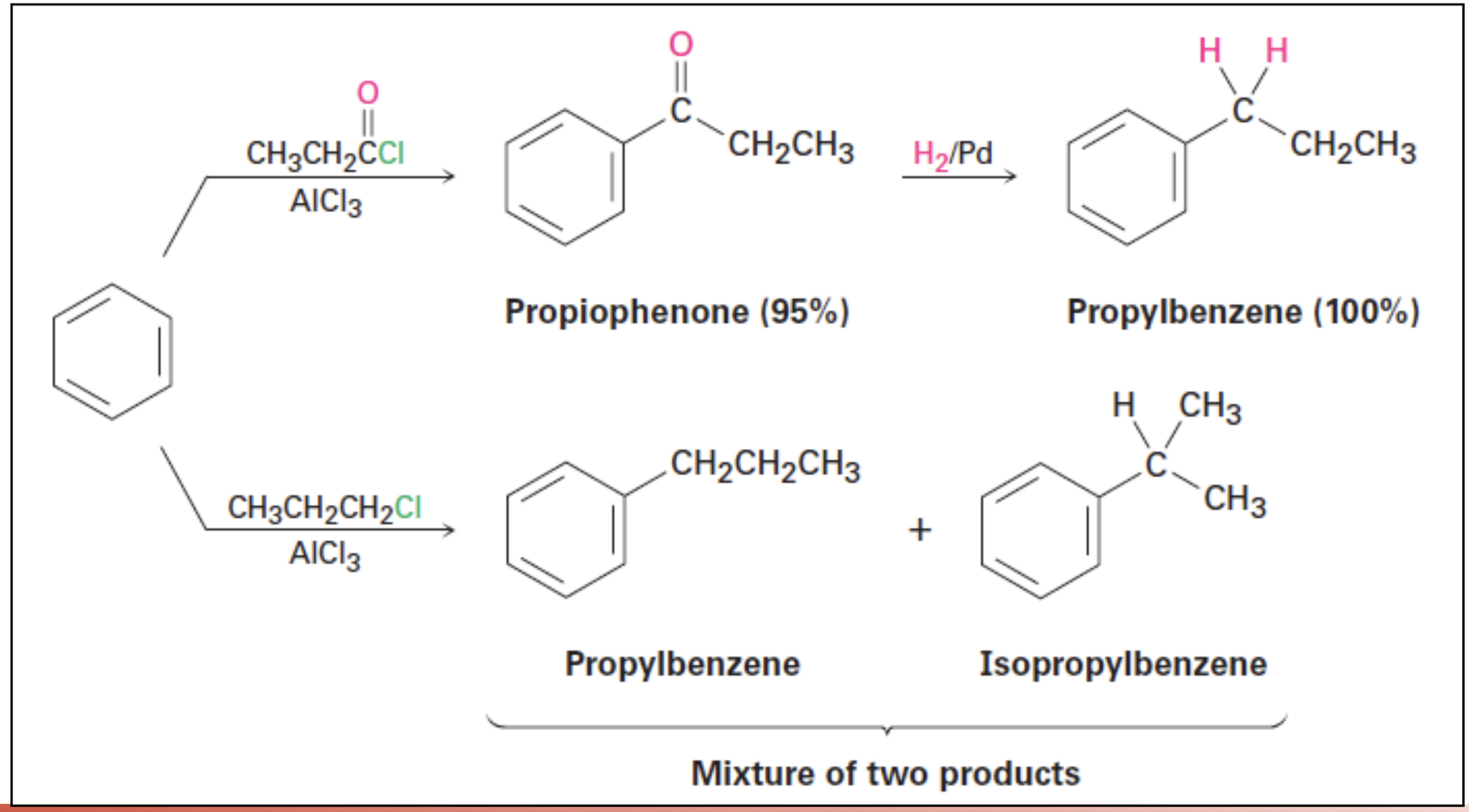
La poliacilazione non è osservata



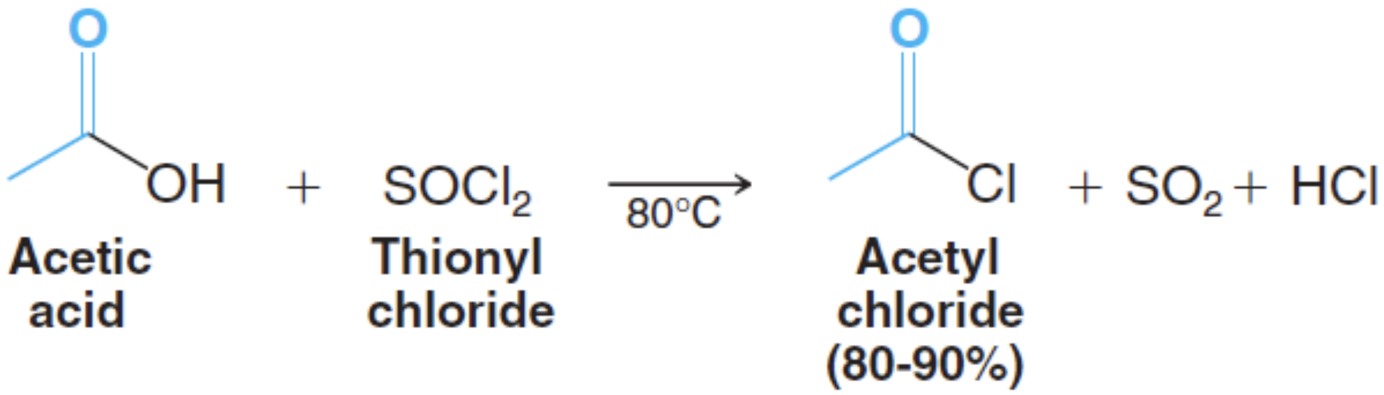


RIDUZIONE DEGLI ARIL-ALCHIL-CHETONI

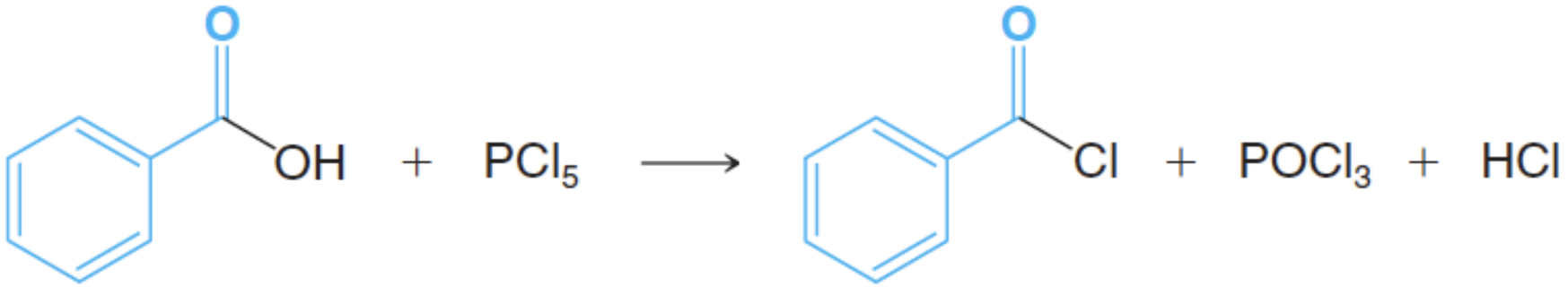




ACILAZIONE DI FRIEDEL-CRAFTS



Acetic acid + **Thionyl chloride** → **Acetyl chloride (80-90%)** + SO_2 + HCl

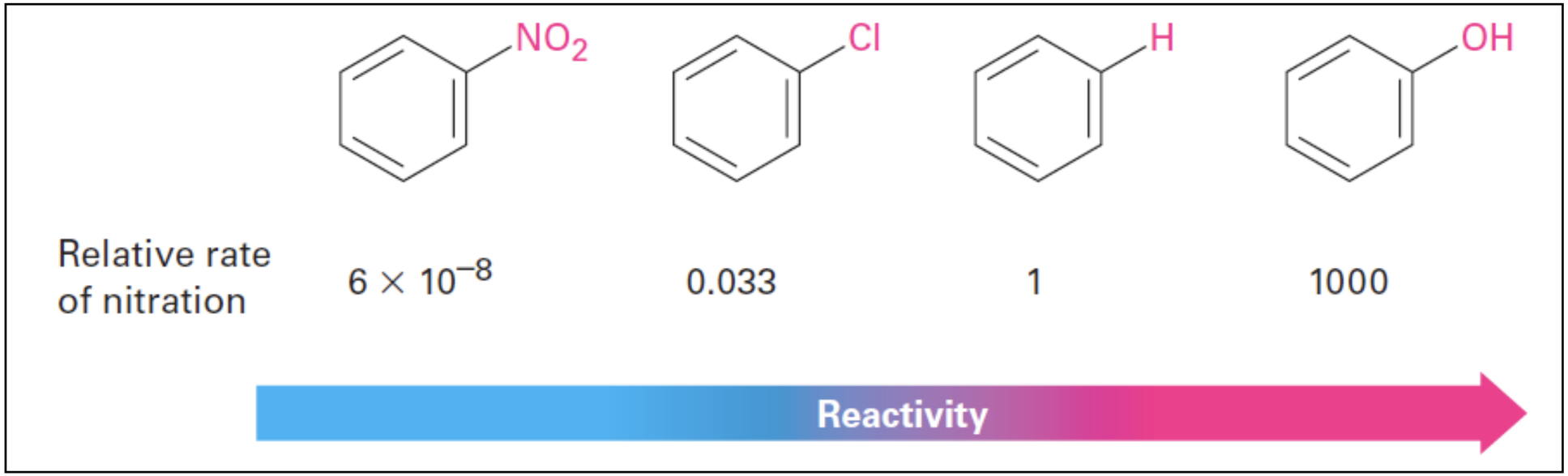


Benzoic acid + **Phosphorus pentachloride** → **Benzoyl chloride (90%)** + $POCl_3$ + HCl

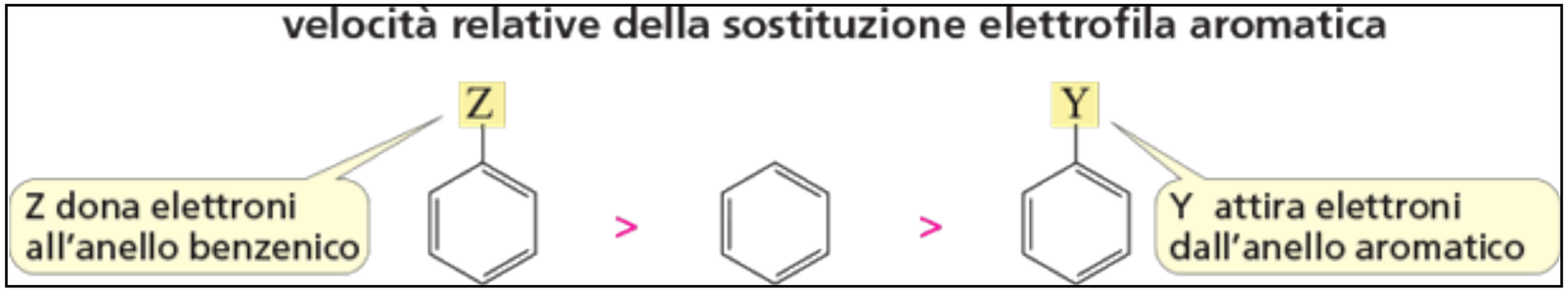
A. Effetti di un sostituente sulla reattività
B. Teoria degli effetti orientanti: EFFETTO DEI SOSTITUENTI SULL'ORIENTAMENTO
C. Effetti attivanti e disattivanti in benzeni polisostituiti

A. Effetti di un sostituente sulla reattività

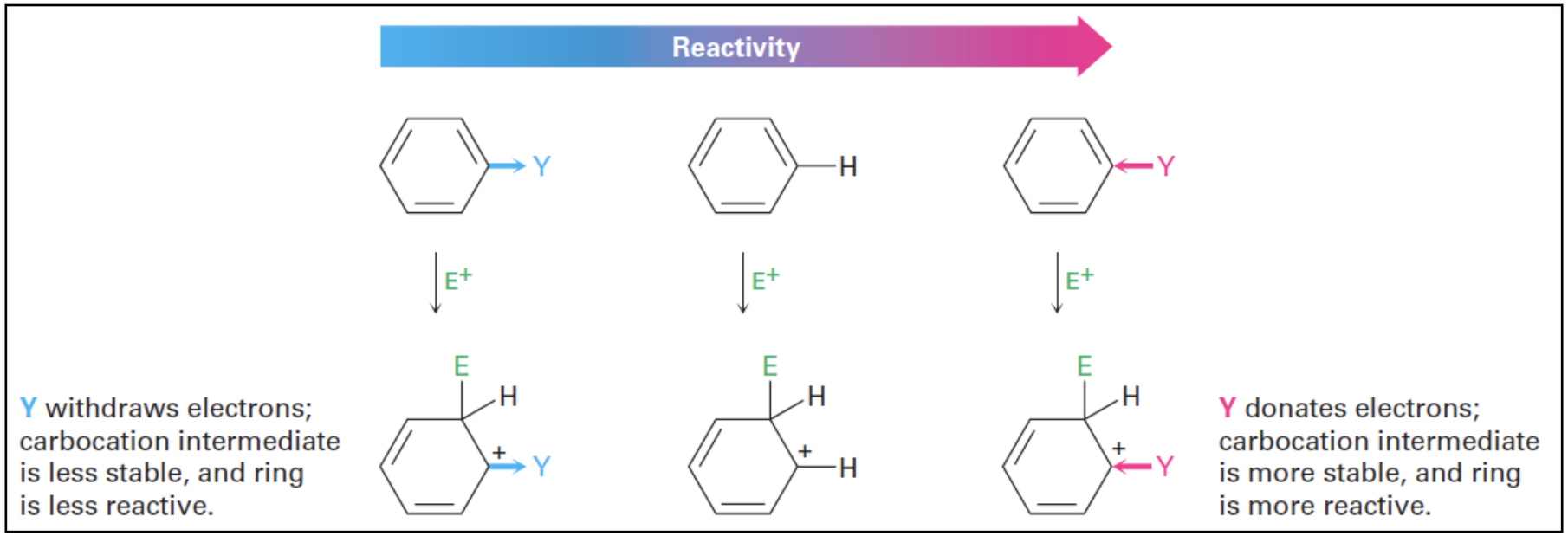
Effetti dei sostituenti dell'anello aromatico: DISATTIVATORI e ATTIVATORI

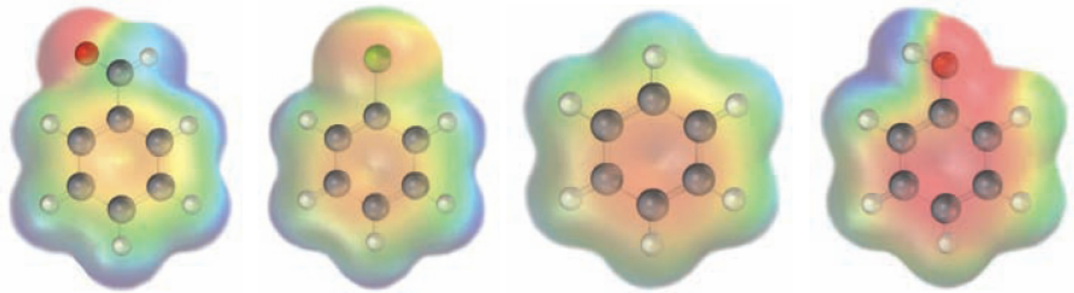


I sostituenti attivanti rendono l'anello benzenico più reattivo nei confronti della sostituzione elettrofila aromatica, mentre i sostituenti disattivanti rendono il benzene meno reattivo.



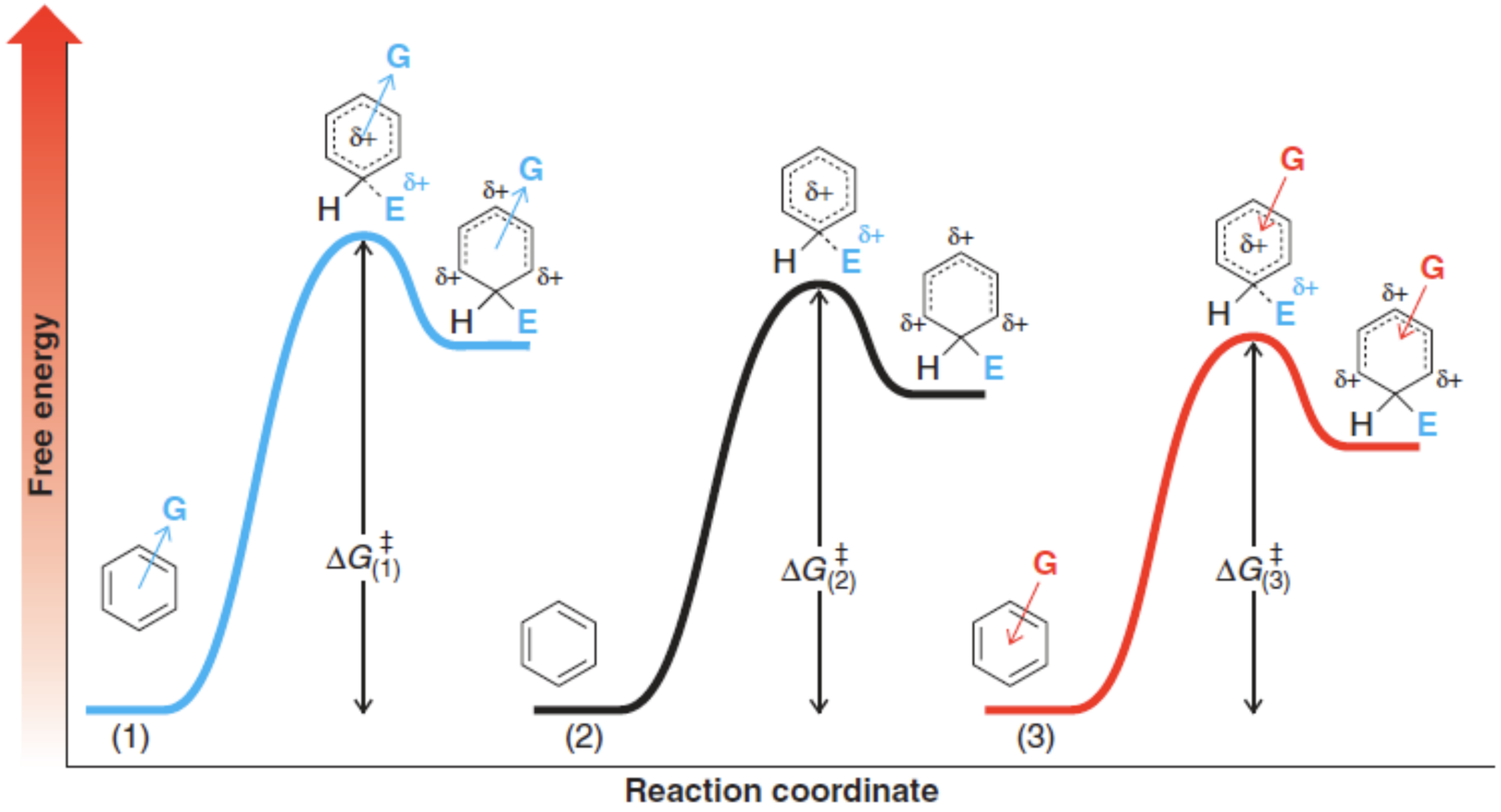
Effetti dei sostituenti dell'anello aromatico: DISATTIVATORI e ATTIVATORI

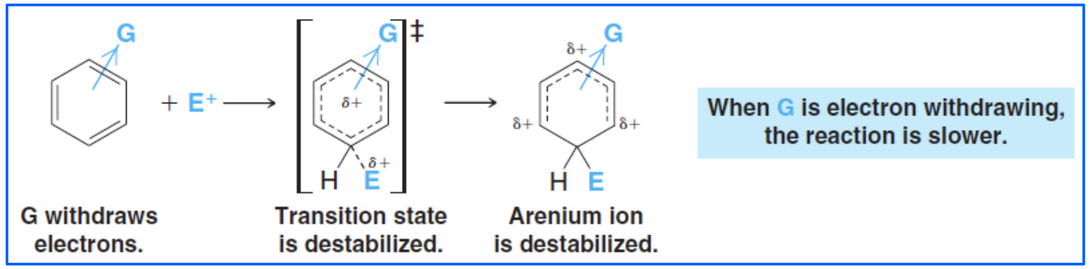




Benzaldehyde Chlorobenzene Benzene Phenol

Effetti dei sostituenti dell'anello aromatico: DISATTIVATORI e ATTIVATORI





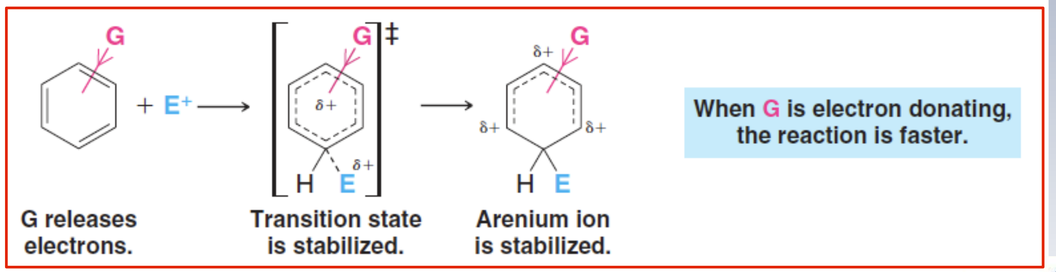
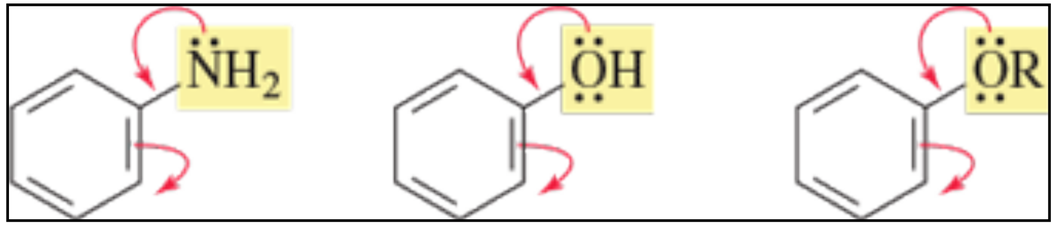


Tabella 18.1 L'effetto dei sostituenti sulla reattività di un anello benzenico nei confronti della sostituzione elettrofila aromatica

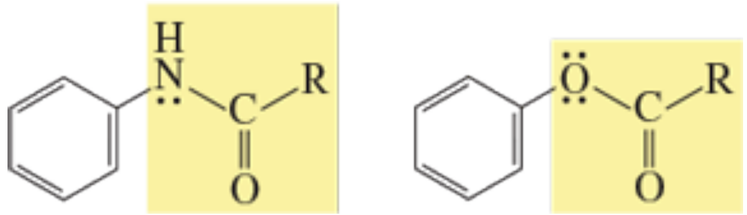
	Più Attivanti		
Sostituenti attivanti	$-NH_2$, $-NHR$, $-NR_2$, $-OH$, $-OR$	Fortemente attivanti	Orto/para orientanti
	$-NHCR$ (O), $-OCR$ (O)	Moderatamente attivanti	
	$-R$, $-Ar$, $-CH{=}CHR$	Debolmente attivanti	
Modello di comparazione →	$-H$		
Sostituenti disattivanti	$-F$, $-Cl$, $-Br$, $-I$	Debolmente disattivanti	
	$-CH$ (O), $-CR$ (O), $-COR$ (O), $-COH$ (O), $-CCl$ (O)	Moderatamente disattivanti	Meta orientanti
	$-C{\equiv}N$, $-SO_3H$, $-\overset{+}{N}H_3$, $-\overset{+}{N}H_2R$, $-\overset{+}{N}HR_2$, $-\overset{+}{N}R_3$, $-NO_2$	Fortemente disattivanti	
	Più disattivanti		

EFFETTO DEI SOSTITUENTI SULLA REATTIVITÀ

sostituenti fortemente attivanti



sostituenti moderatamente attivanti



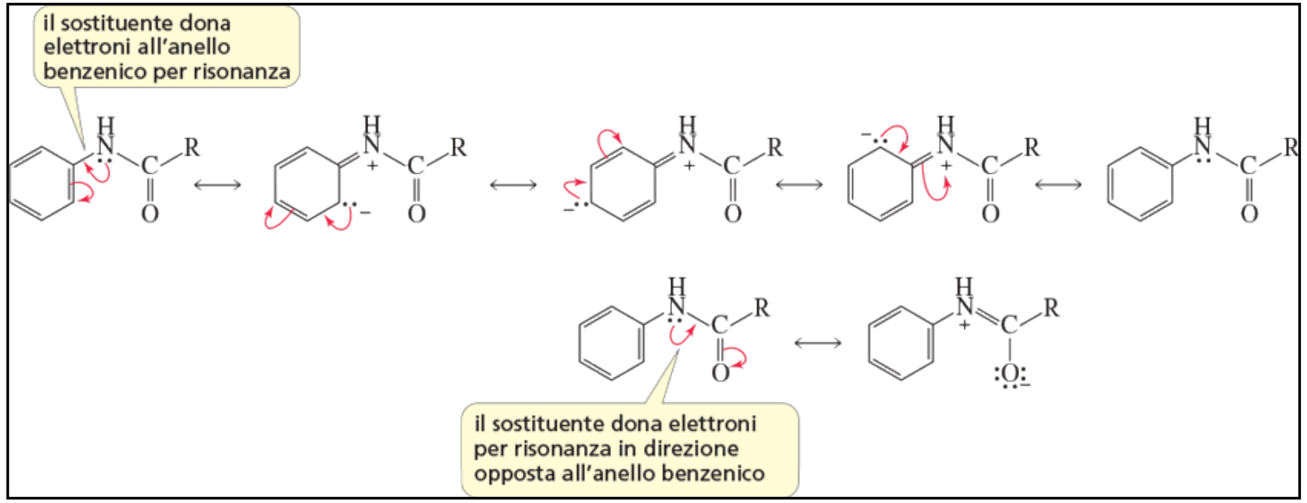
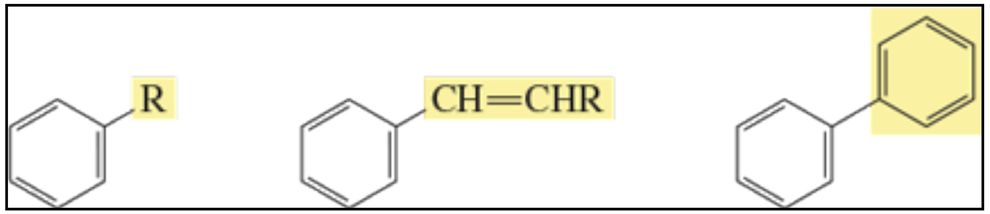


Tabella 18.1 L'effetto dei sostituenti sulla reattività di un anello benzenico nei confronti della sostituzione elettrofila aromatica

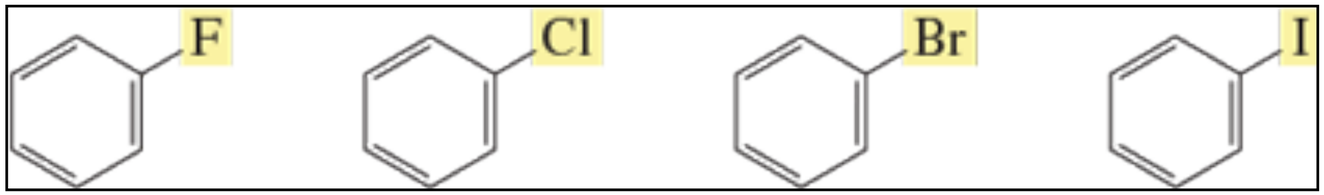
	Più Attivanti		
Sostituenti attivanti	$-NH_2$, $-NHR$, $-NR_2$, $-OH$, $-OR$	Fortemente attivanti	Orto/para orientanti
	$-NHCR$ (O), $-OCR$ (O)	Moderatamente attivanti	
	$-R$, $-Ar$, $-CH{=}CHR$	Debolmente attivanti	
Modello di comparazione →	$-H$		
Sostituenti disattivanti	$-F$, $-Cl$, $-Br$, $-I$	Debolmente disattivanti	
	$-CH$ (O), $-CR$ (O), $-COR$ (O), $-COH$ (O), $-CCl$ (O)	Moderatamente disattivanti	Meta orientanti
	$-C{\equiv}N$, $-SO_3H$, $-\overset{+}{N}H_3$, $-\overset{+}{N}H_2R$, $-\overset{+}{N}HR_2$, $-\overset{+}{N}R_3$, $-NO_2$	Fortemente disattivanti	
	Più disattivanti		

EFFETTO DEI SOSTITUENTI SULLA REATTIVITÀ

sostituenti debolmente attivanti



Sostituenti debolmente disattivanti



Sostituenti moderatamente disattivanti

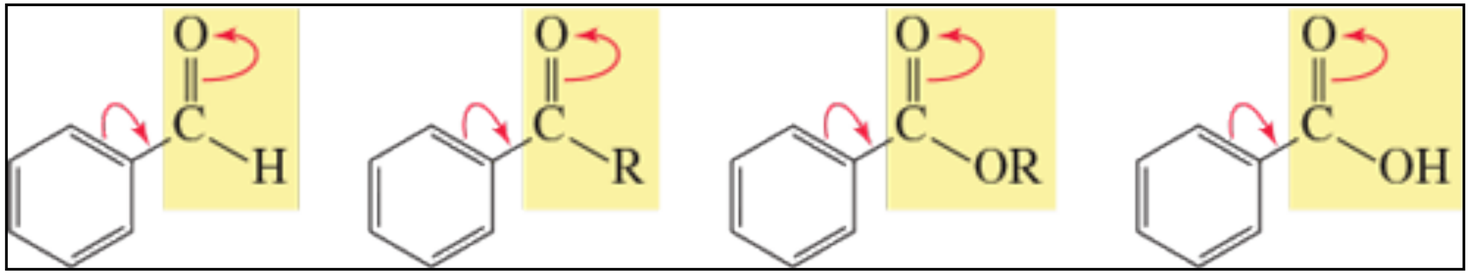


Tabella 18.1 L'effetto dei sostituenti sulla reattività di un anello benzenico nei confronti della sostituzione elettrofila aromatica

	Più Attivanti		
Sostituenti attivanti	$-NH_2$, $-NHR$, $-NR_2$, $-OH$, $-OR$	Fortemente attivanti	Orto/para orientanti
	$-NHCR$ (O), $-OCR$ (O)	Moderatamente attivanti	
	$-R$, $-Ar$, $-CH{=}CHR$	Debolmente attivanti	
Modello di comparazione →	$-H$		
Sostituenti disattivanti	$-F$, $-Cl$, $-Br$, $-I$	Debolmente disattivanti	
	$-CH$ (O), $-CR$ (O), $-COR$ (O), $-COH$ (O), $-CCl$ (O)	Moderatamente disattivanti	Meta orientanti
	$-C{\equiv}N$, $-SO_3H$, $-\overset{+}{N}H_2R$, $-\overset{+}{N}R_3$, $-NO_2$; $-\overset{+}{N}H_3$, $-\overset{+}{N}HR_2$	Fortemente disattivanti	
	Più disattivanti		

Sostituenti fortemente disattivanti

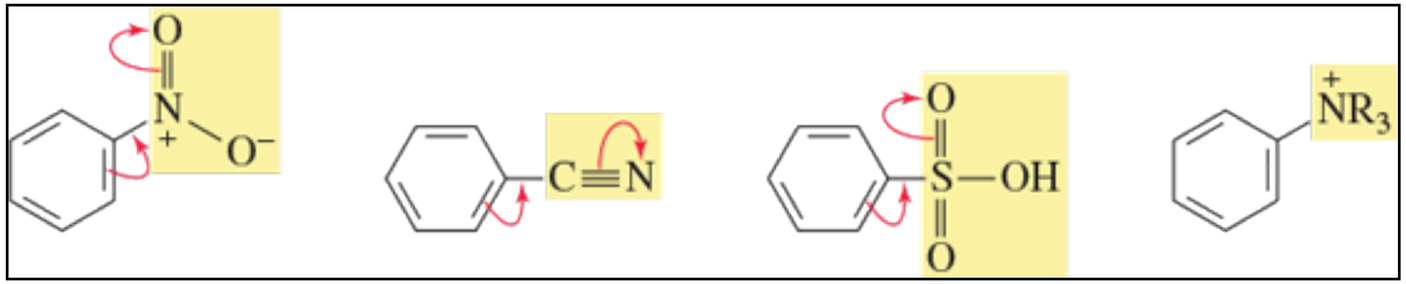
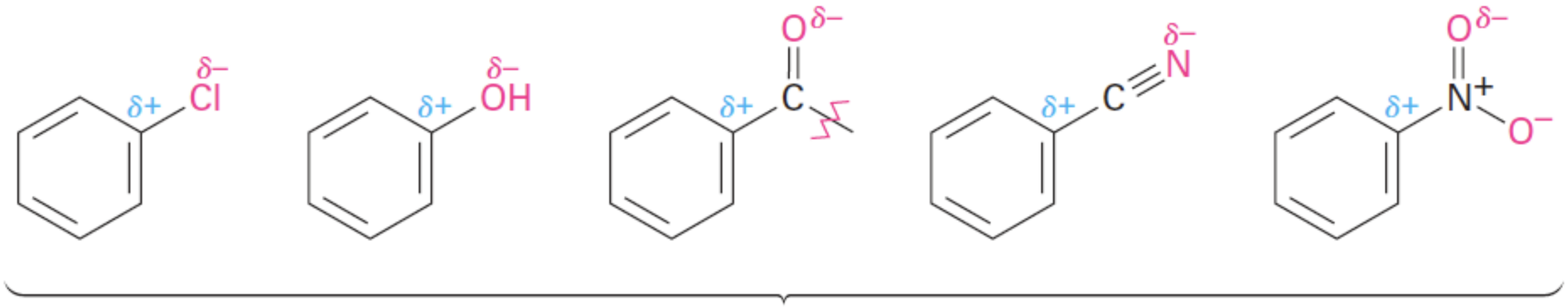


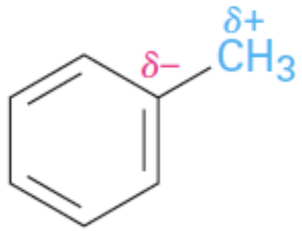
Table 16.2 Substituent Effects in Electrophilic Aromatic Substitution

Substituent	Reactivity	Orienting effect	Inductive effect	Resonance effect
$-CH_3$	Activating	Ortho, para	Weak donating	—
$-OH$, $-NH_2$	Activating	Ortho, para	Weak withdrawing	Strong donating
$-F$, $-Cl$, $-Br$, $-I$	Deactivating	Ortho, para	Strong withdrawing	Weak donating
$-NO_2$, $-CN$, $-CHO$, $-CO_2R$, $-COR$, $-CO_2H$	Deactivating	Meta	Strong withdrawing	Strong withdrawing

EFFETTO INDUTTIVO dei DISATTIVATORI e ATTIVATORI



Inductive electron withdrawal

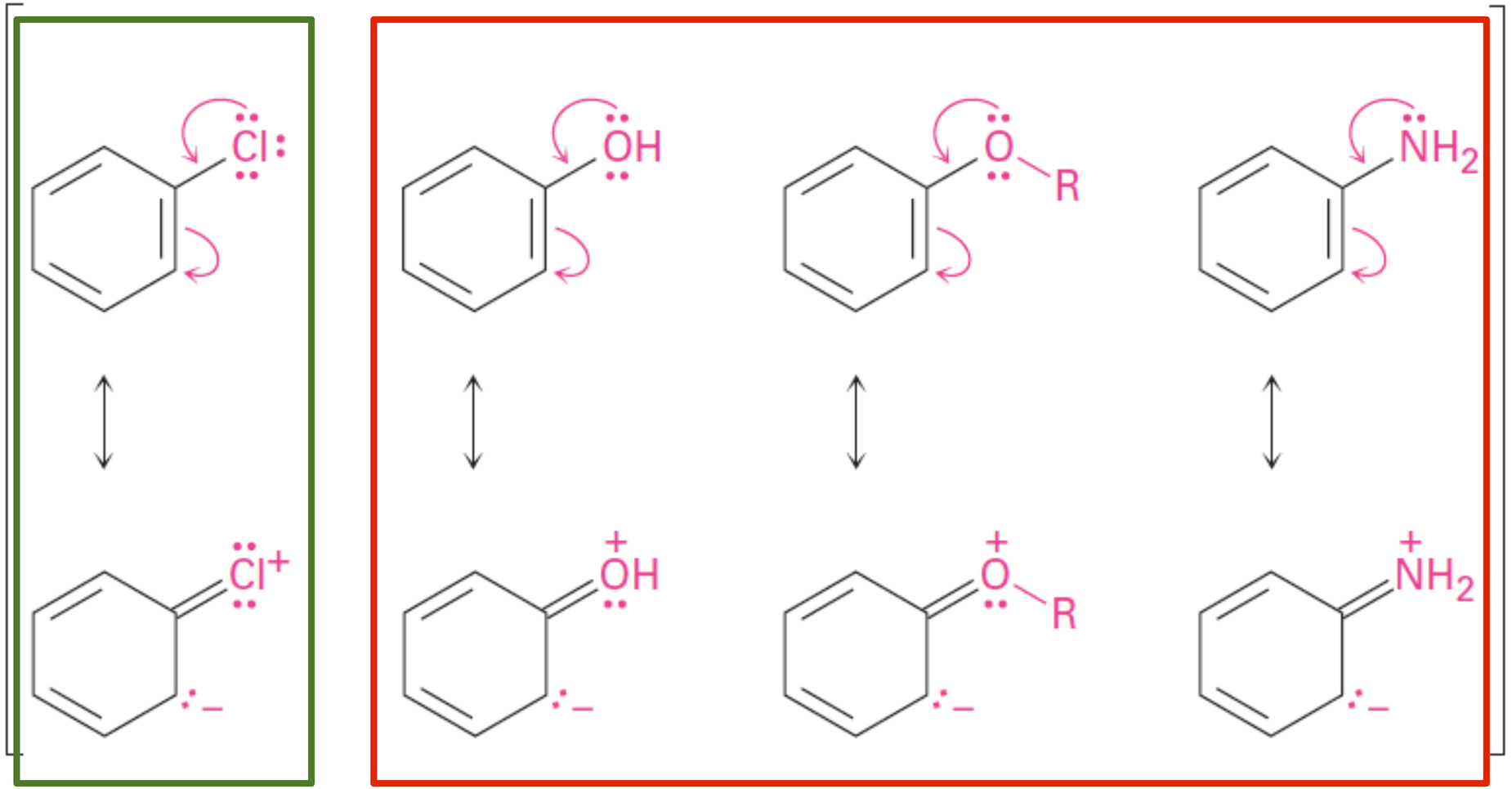


Inductive electron donation

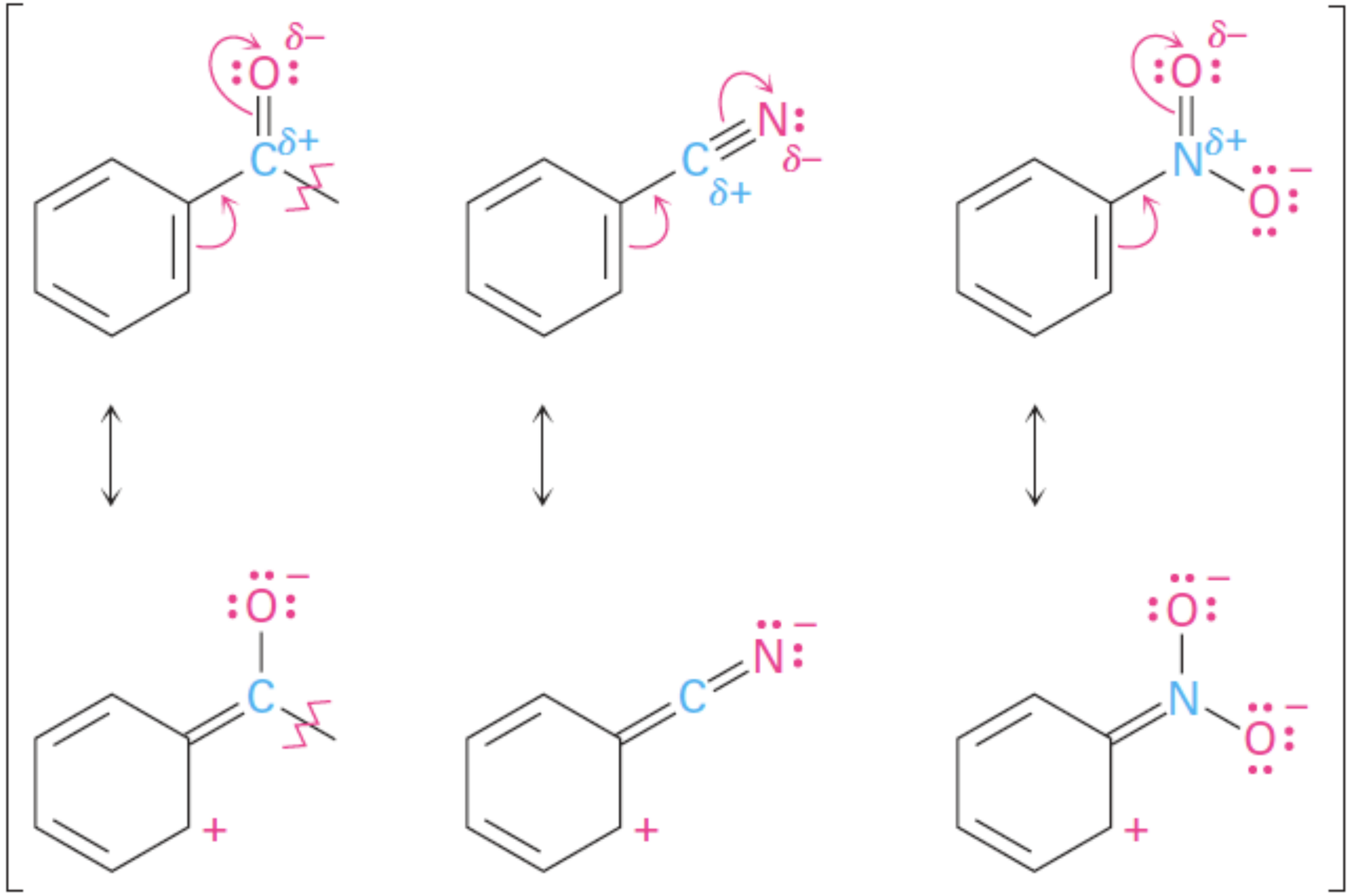
Table 16.2 Substituent Effects in Electrophilic Aromatic Substitution

Substituent	Reactivity	Orienting effect	Inductive effect	Resonance effect
$-CH_3$	Activating	Ortho, para	Weak donating	—
$-OH$, $-NH_2$	Activating	Ortho, para	Weak withdrawing	Strong donating
$-F$, $-Cl$ $-Br$, $-I$	Deactivating	Ortho, para	Strong withdrawing	Weak donating
$-NO_2$, $-CN$, $-CHO$, $-CO_2R$ $-COR$, $-CO_2H$	Deactivating	Meta	Strong withdrawing	Strong withdrawing

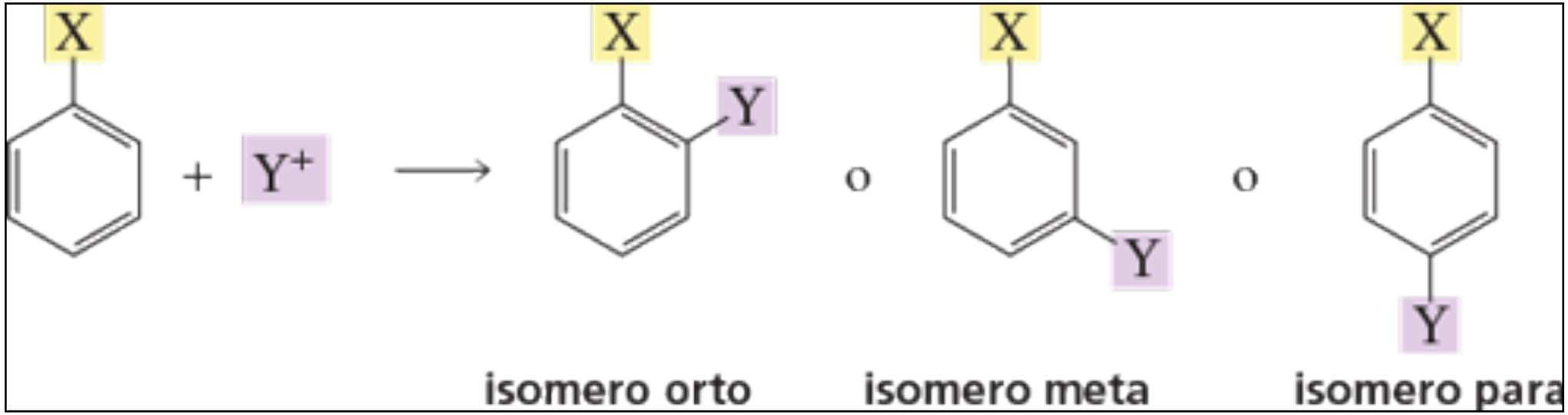
EFFETTO di RISONANZA dei gruppi ATTIVATORI



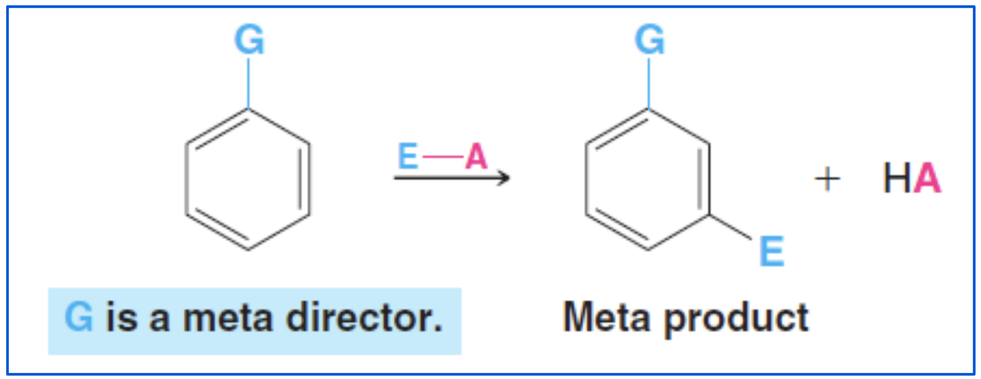
EFFETTO di RISONANZA dei DISATTIVATORI

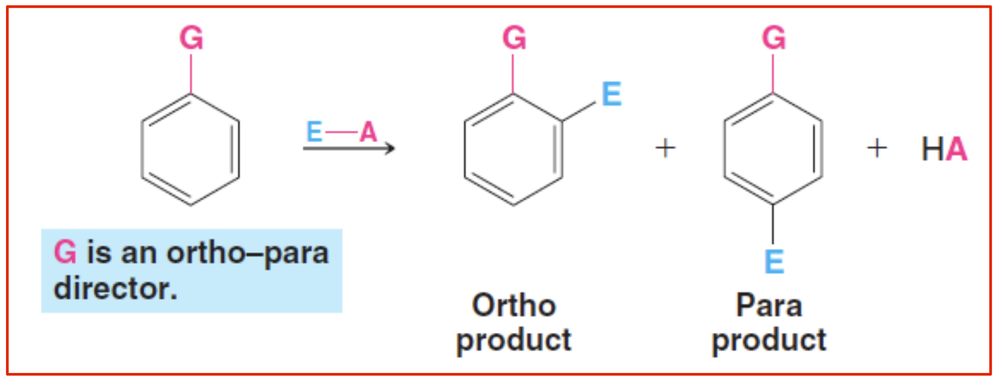


B. Teoria degli effetti orientanti: EFFETTO DEI SOSTITUENTI SULL'ORIENTAMENTO

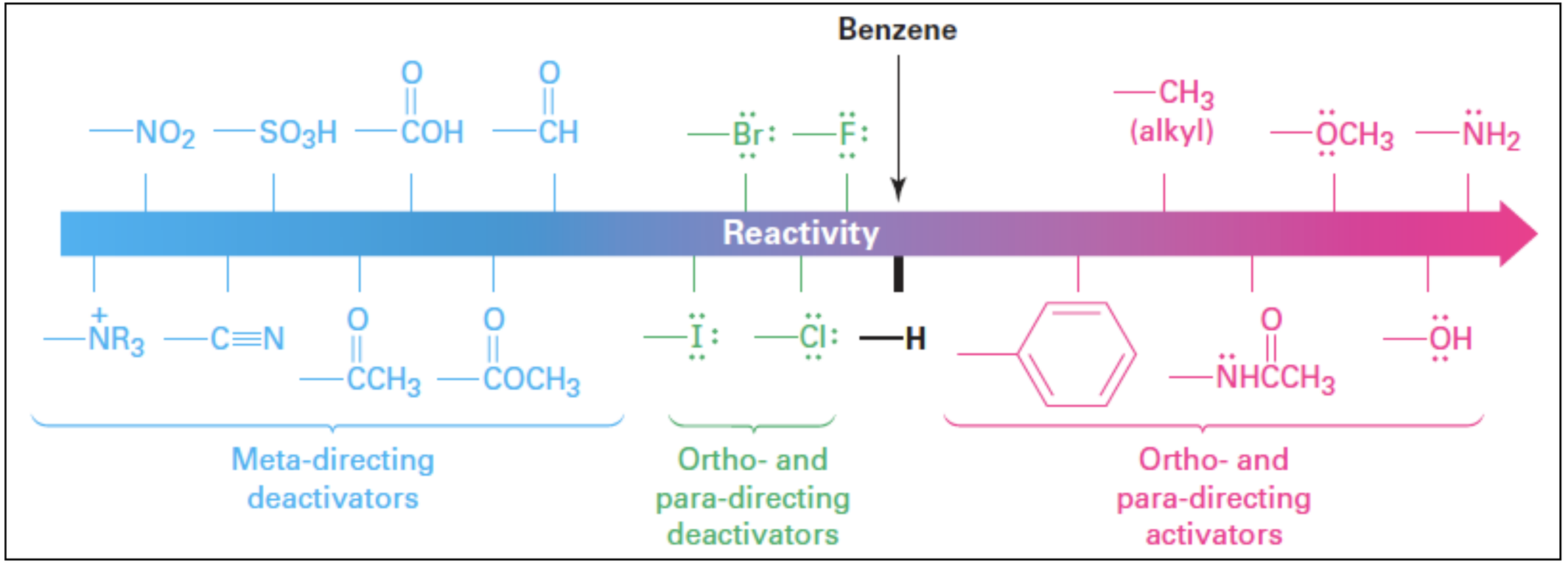


DISATTIVATORI (META orientatori) **e ATTIVATORI (ORTO e PARA orientatori)**



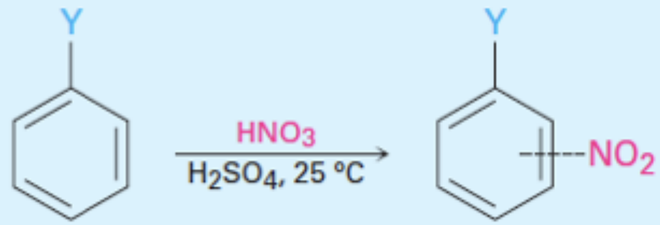


DISATTIVATORI (META orientatori) , DISATTIVATORI (ORTO e PARA Orientatori)
ATTIVATORI (ORTO e PARA orientatori)



DISATTIVATORI (META orientatori) , DISATTIVATORI (ORTO e PARA Orientatori)
ATTIVATORI (ORTO e PARA orientatori

Table 16.1 Orientation of Nitration in Substituted Benzenes

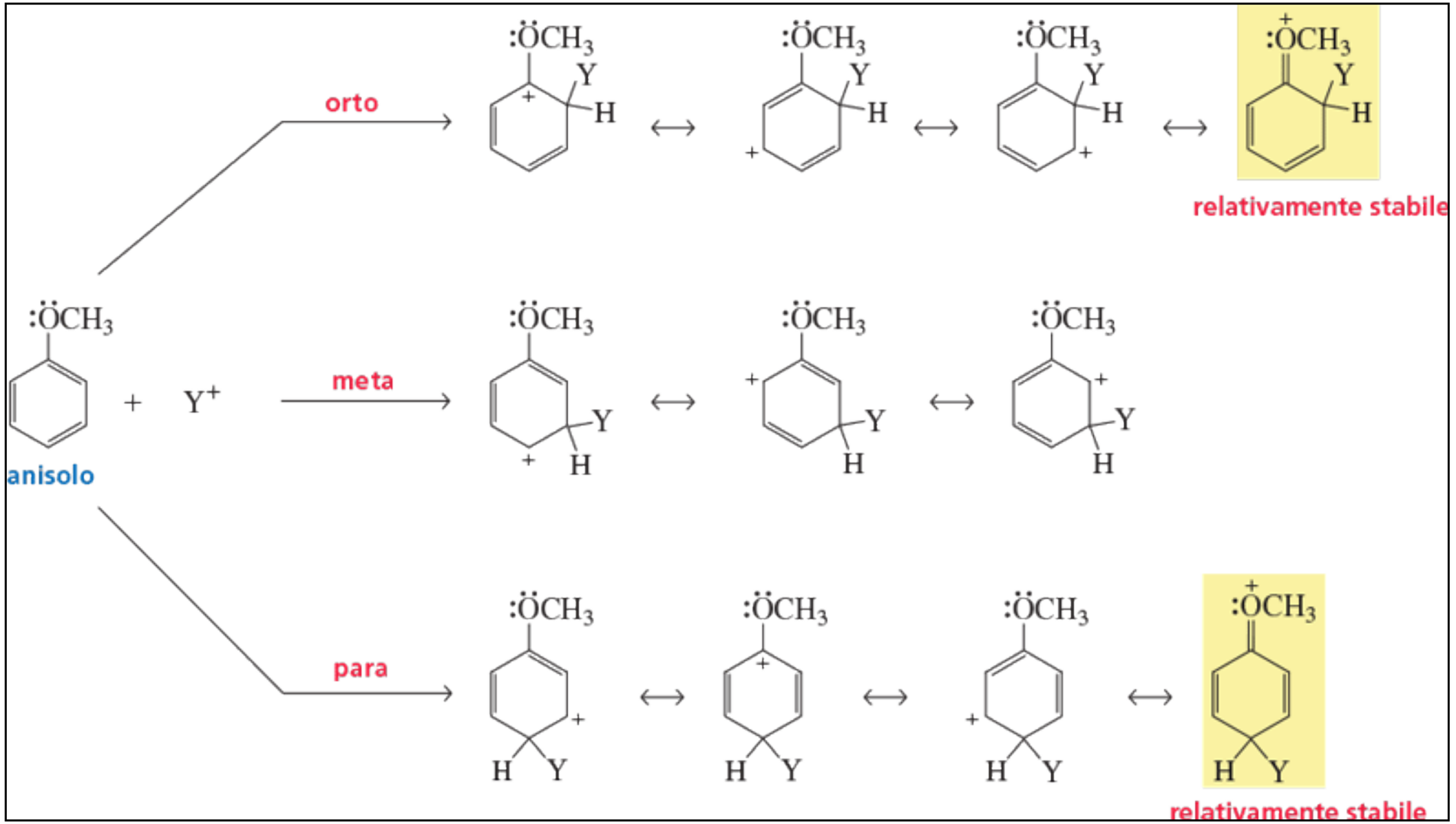


	Product (%)		
	Ortho	Meta	Para
Meta-directing deactivators			
$-\overset{+}{N}(CH_3)_3$	2	87	11
$-NO_2$	7	91	2
$-CO_2H$	22	76	2
$-CN$	17	81	2
$-CO_2CH_3$	28	66	6
$-COCH_3$	26	72	2
$-CHO$	19	72	9

	Product (%)		
	Ortho	Meta	Para
Ortho- and para-directing deactivators			
$-F$	13	1	86
$-Cl$	35	1	64
$-Br$	43	1	56
$-I$	45	1	54
Ortho- and para-directing activators			
$-CH_3$	63	3	34
$-OH$	50	0	50
$-NHCOCH_3$	19	2	79

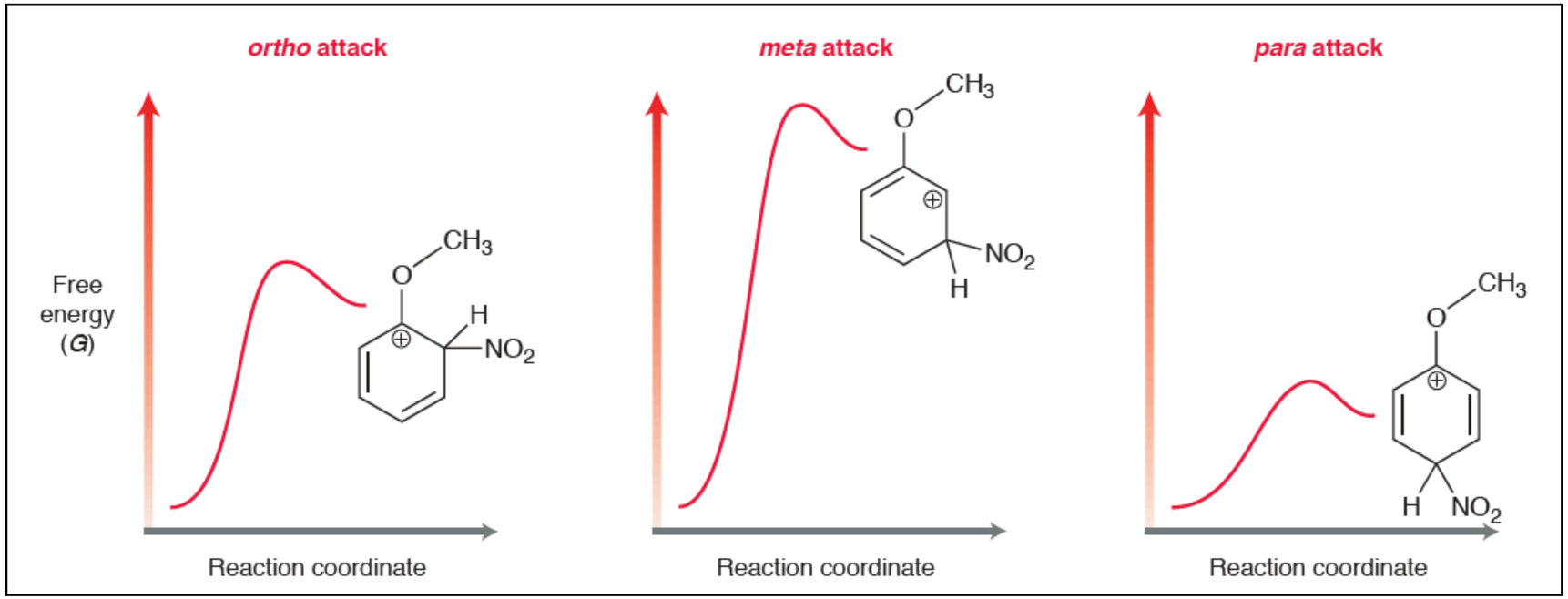
B. Teoria degli effetti orientanti:
EFFETTO DEI SOSTITUENTI SULL'ORIENTAMENTO

I sostituenti che donano elettroni per risonanza sono orto-para orientanti



	Product (%)		
	Ortho	Meta	Para
Ortho- and para-directing deactivators			
–F	13	1	86
–Cl	35	1	64
–Br	43	1	56
–I	45	1	54
Ortho- and para-directing activators			
$-CH_3$	63	3	34
–OH	50	0	50
$-NHCOCH_3$	19	2	79

I sostituenti che donano elettroni per risonanza sono orto-para orientanti



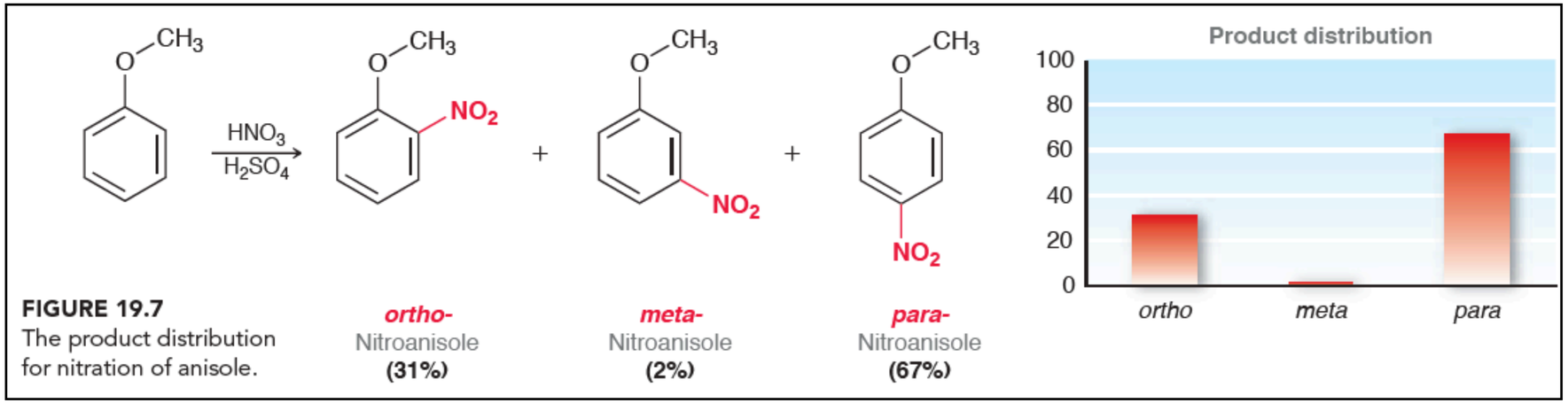


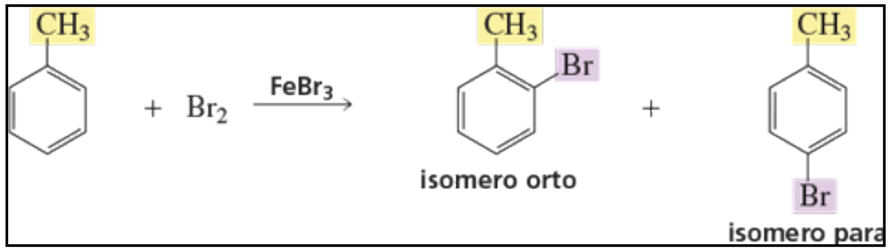
FIGURE 19.7
The product distribution for nitration of anisole.

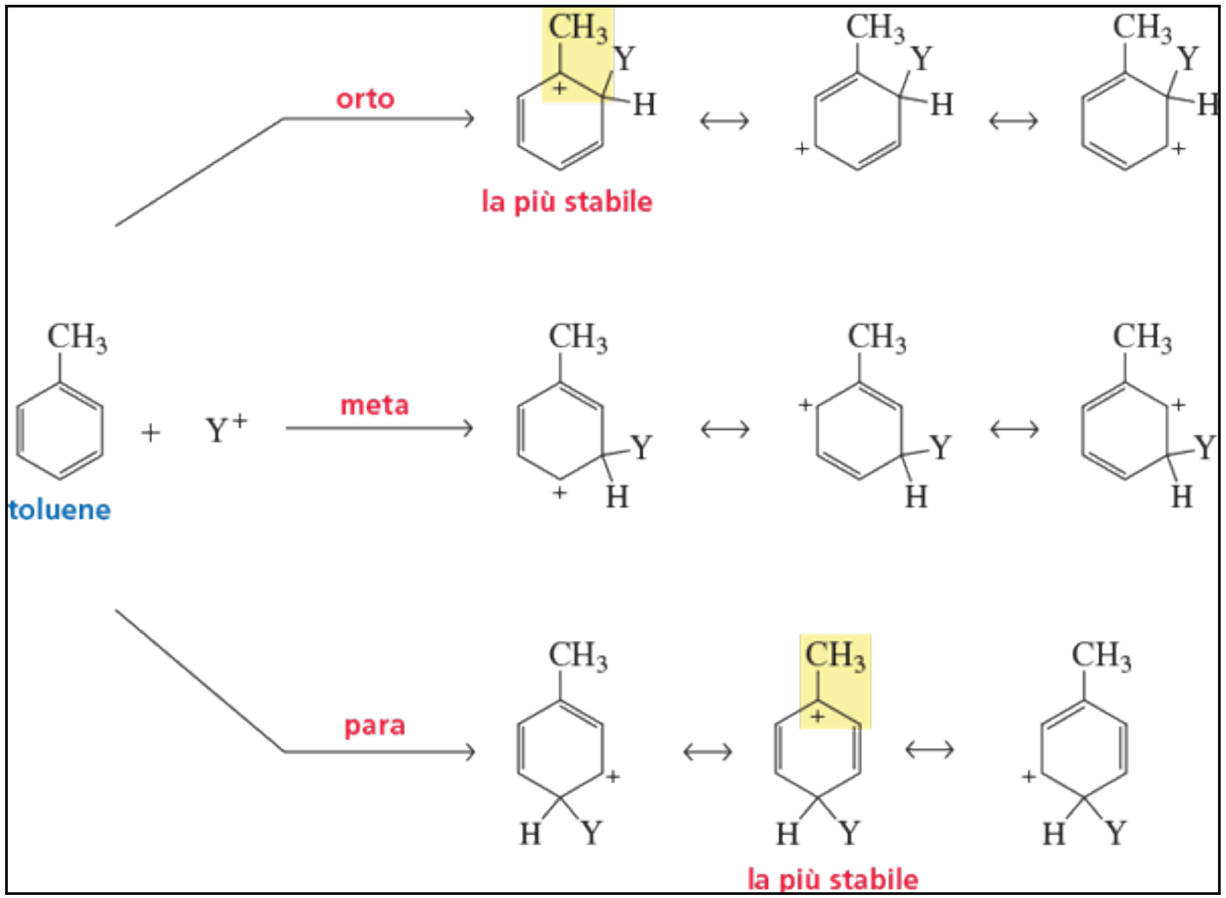
ortho- Nitroanisole **(31%)**

meta- Nitroanisole **(2%)**

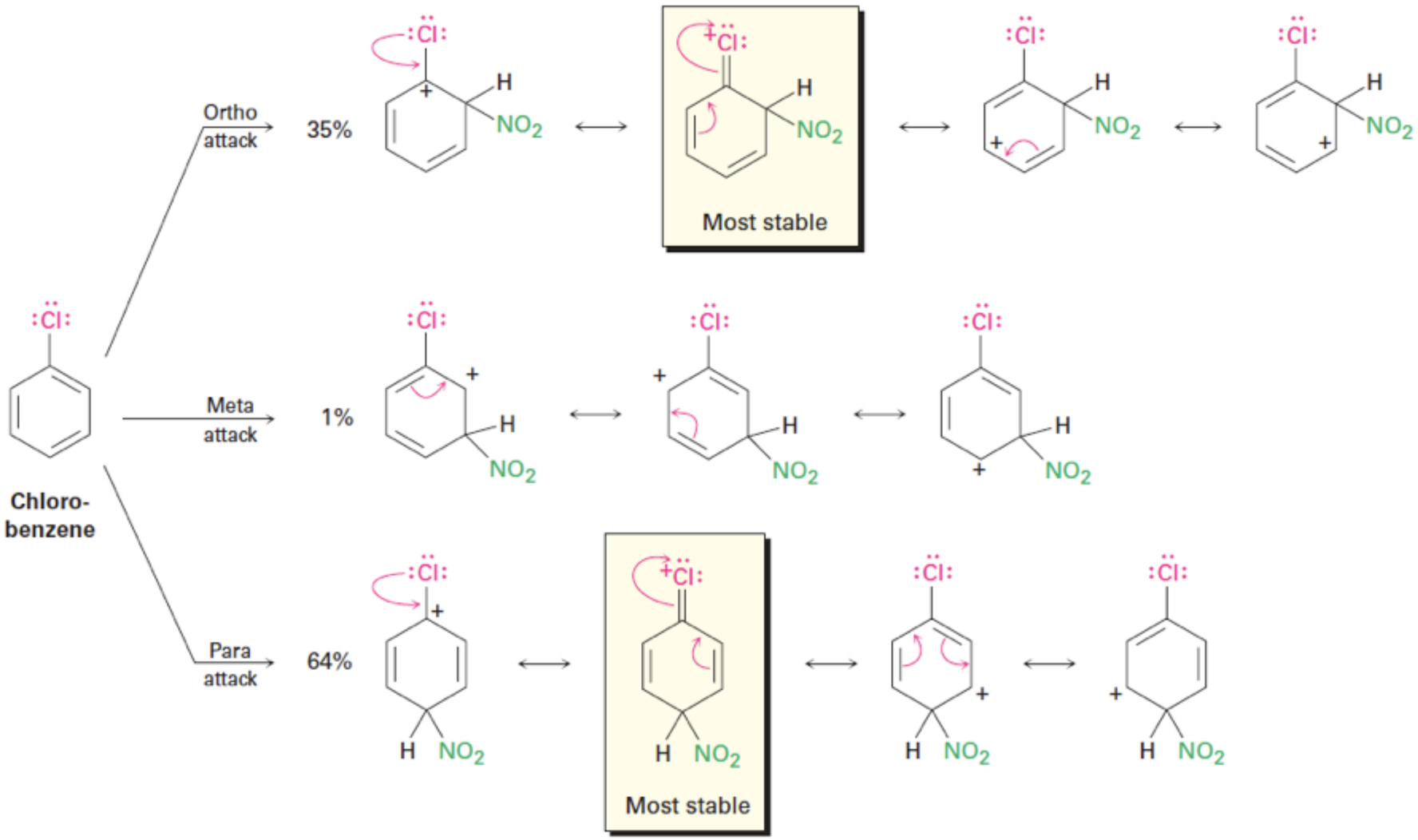
para- Nitroanisole **(67%)**

I sostituenti che donano elettroni per iperconiugazione sono orto-para orientanti

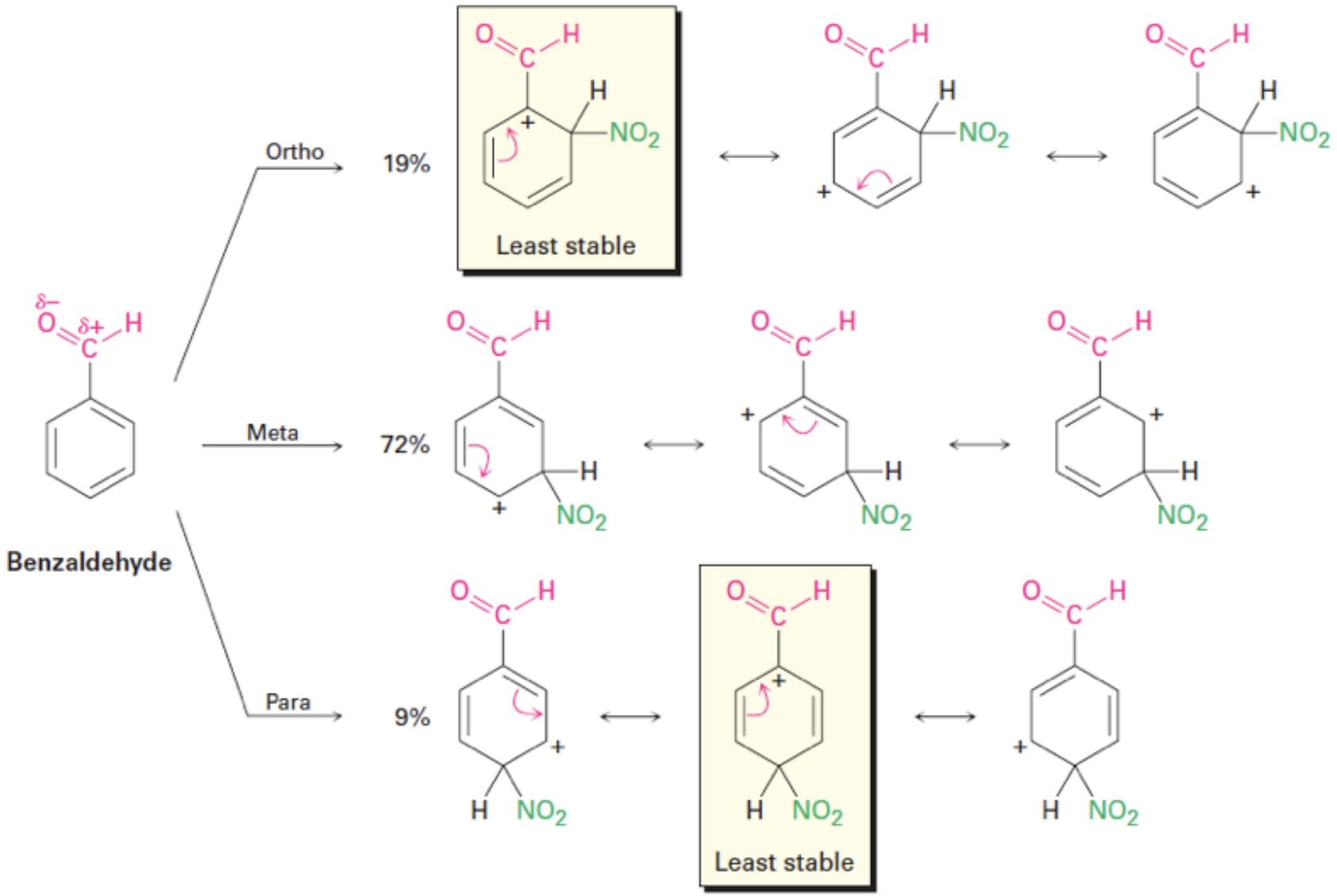




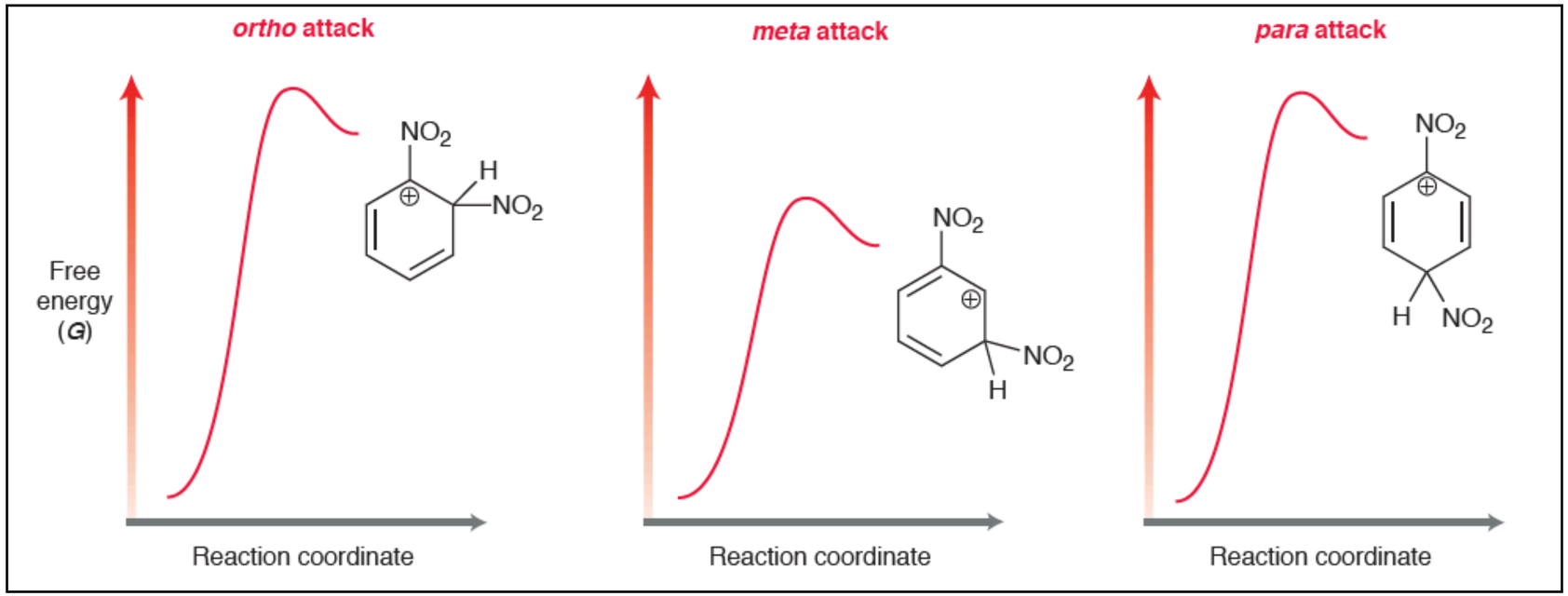
I sostituenti che sottraggono elettroni per efffetto induttivo sono orto-para orientanti



I sostituenti che sottraggono elettroni per efffetto induttivo e risonanza sono METÀ orientanti



I sostituenti che sottraggono elettroni per efffetto induttivo e risonanza sono METÀ orientanti



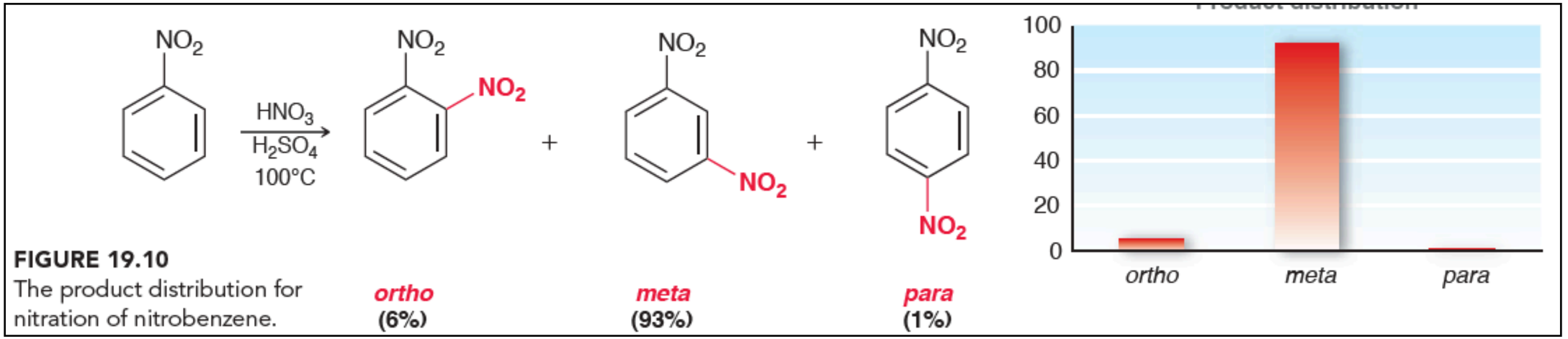
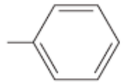


FIGURE 19.10
The product distribution for nitration of nitrobenzene.

Disostituzione e polisostituzione

A. **Effetti di un sostituente su un'ulteriore sostituzione**
B. **Teoria degli effetti orientanti**
C. **Teoria degli effetti attivanti e disattivanti**

Table 22.2 Directing Effects of Substituents on Further Substitution

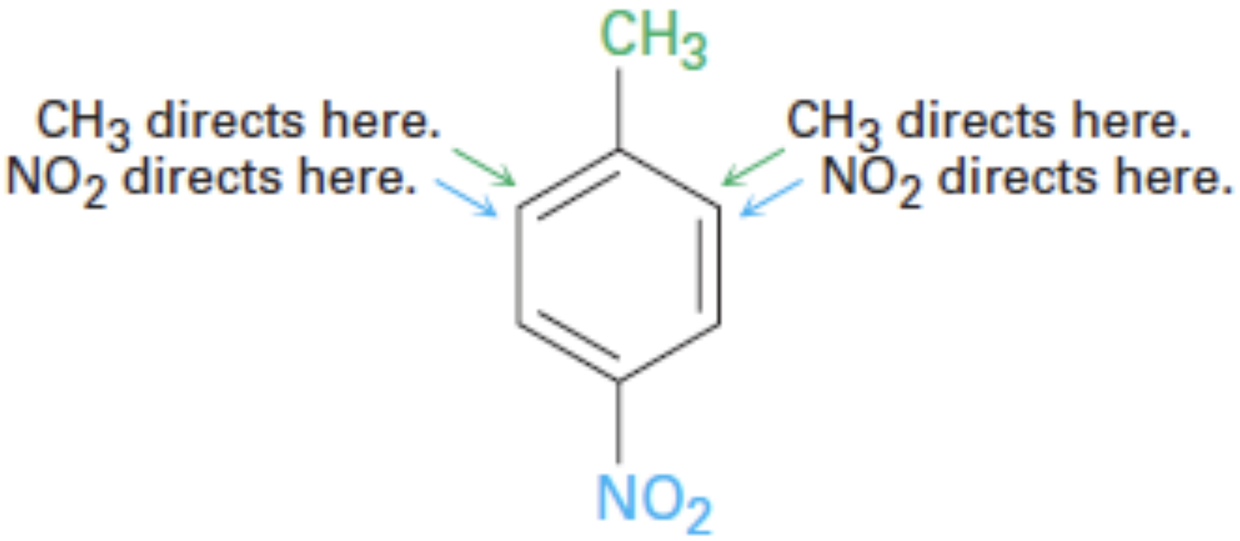
Ortho-Para Directing	Strongly activating	$-\ddot{N}H_2$	$-\ddot{N}HR$	$-\ddot{N}R_2$	$-\ddot{O}H$	$-\ddot{O}R$				
	Moderately activating	$-\ddot{N}HCR$ (O)	$-\ddot{N}HCAr$ (O)	$-\ddot{O}CR$ (O)	$-\ddot{O}CAr$ (O)					
	Weakly activating	$-R$								
	Weakly deactivating	$-\ddot{F}:$	$-\ddot{Cl}:$	$-\ddot{Br}:$	$-\ddot{I}:$					
Meta Directing	Moderately deactivating	$-CH$ (O)	$-CR$ (O)	$-COH$ (O)	$-COR$ (O)	$-CNH_2$ (O)	$-SOH$ (O,O)	$-C\equiv N$		
	Strongly deactivating	$-NO_2$	$-NH_3^+$	$-CF_3$	$-CCl_3$					

Relative importance in directing further substitution

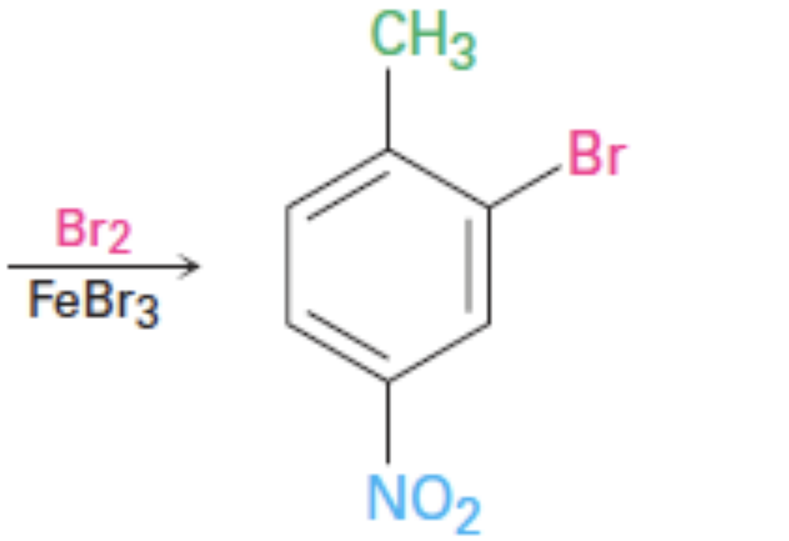
Table 16.2 Substituent Effects in Electrophilic Aromatic Substitution

Substituent	Reactivity	Orienting effect	Inductive effect	Resonance effect
$-CH_3$	Activating	Ortho, para	Weak donating	—
$-OH$, $-NH_2$	Activating	Ortho, para	Weak withdrawing	Strong donating
$-F$, $-Cl$ $-Br$, $-I$	Deactivating	Ortho, para	Strong withdrawing	Weak donating
$-NO_2$, $-CN$, $-CHO$, $-CO_2R$ $-COR$, $-CO_2H$	Deactivating	Meta	Strong withdrawing	Strong withdrawing

Teoria degli effetti attivanti e disattivanti sull'anello

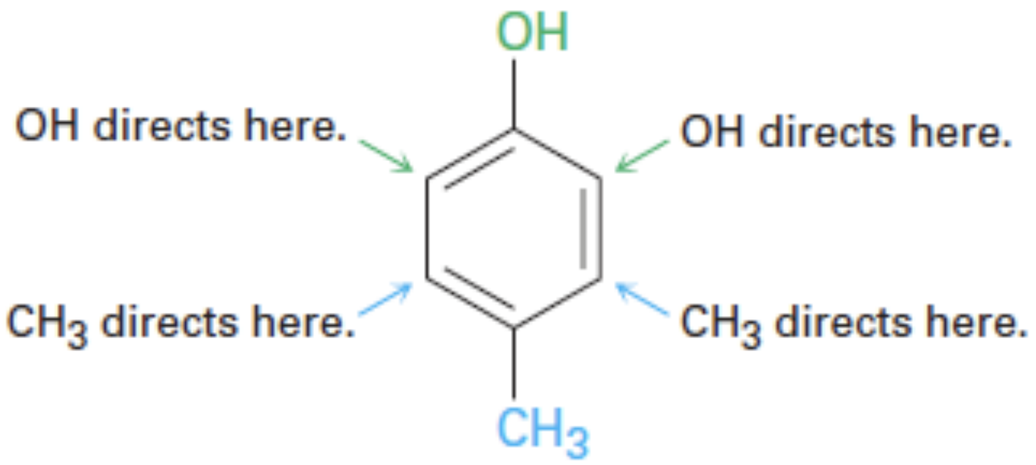


p-Nitrotoluene

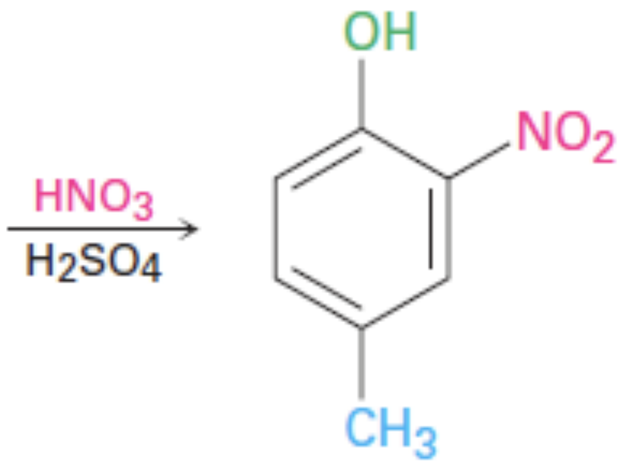


2-Bromo-4-nitrotoluene

Teoria degli effetti attivanti e disattivanti sull'anello

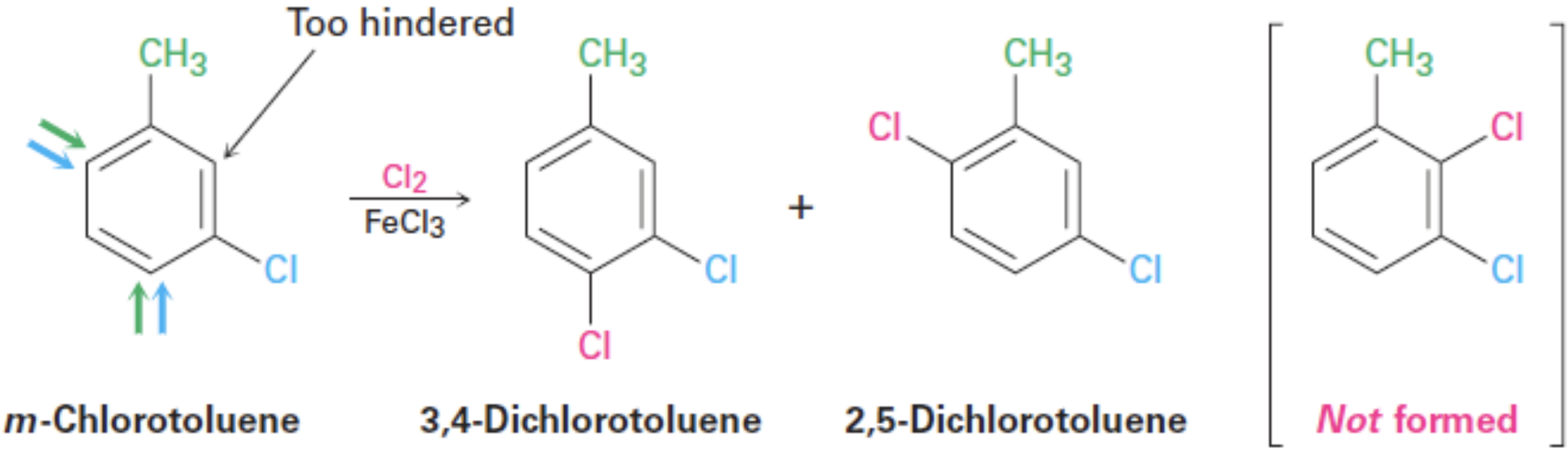


p-Methylphenol



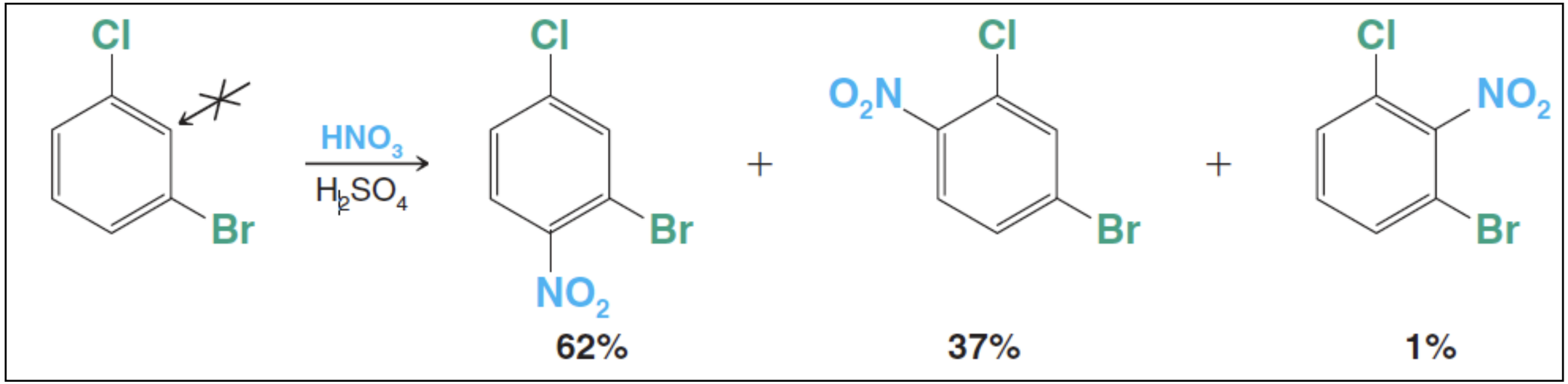
4-Methyl-2-nitrophenol

Effetti dei sostituenti attivanti e disattivanti sull'anello , e effetto sterico

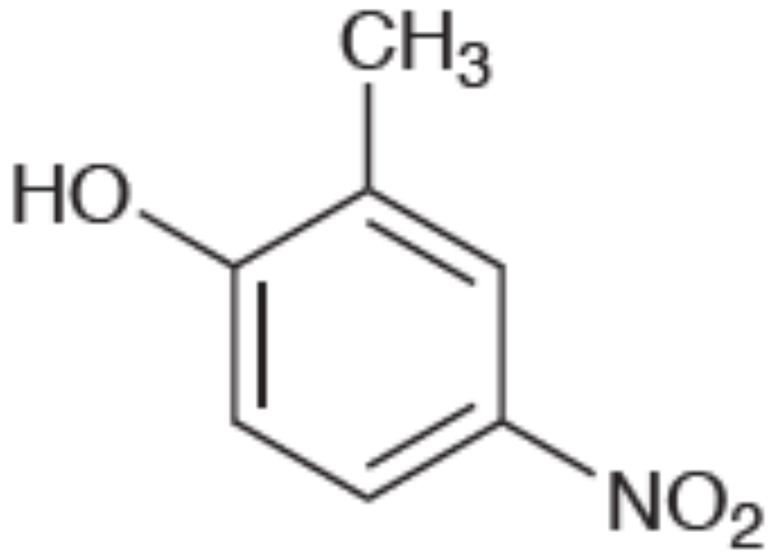


m-Chlorotoluene 3,4-Dichlorotoluene 2,5-Dichlorotoluene

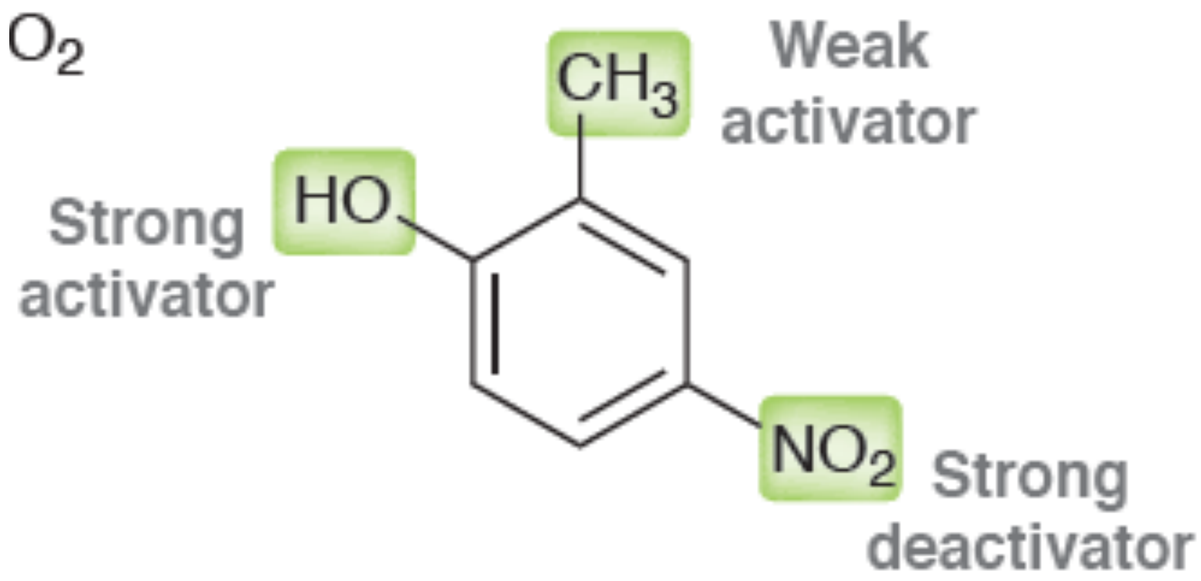
Gli effetti sterici sono importanti anche nelle sostituzioni aromatiche.
La sostituzione non avviene di forma apprezzabile tra sostituenti META se è disponibile un'altra posizione.



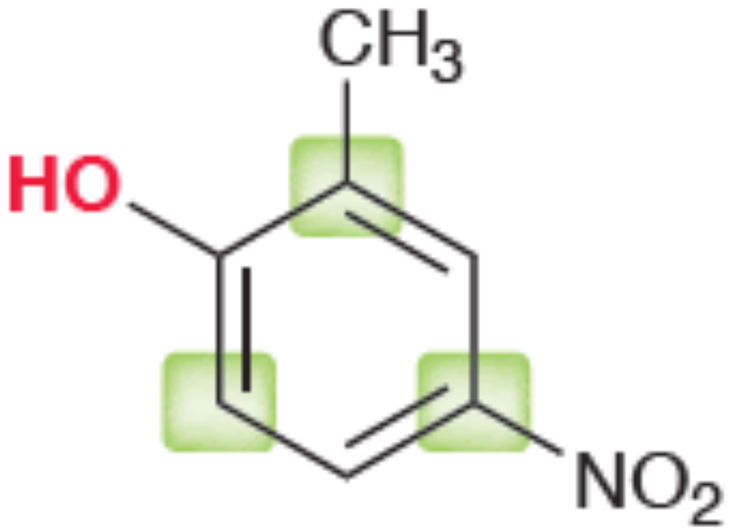
PROBLEMA. Identificare, nella sostanza vista di seguito, la posizione che è più suscettibile Ad una reazione di sostituzione elettrofilica aromatica.

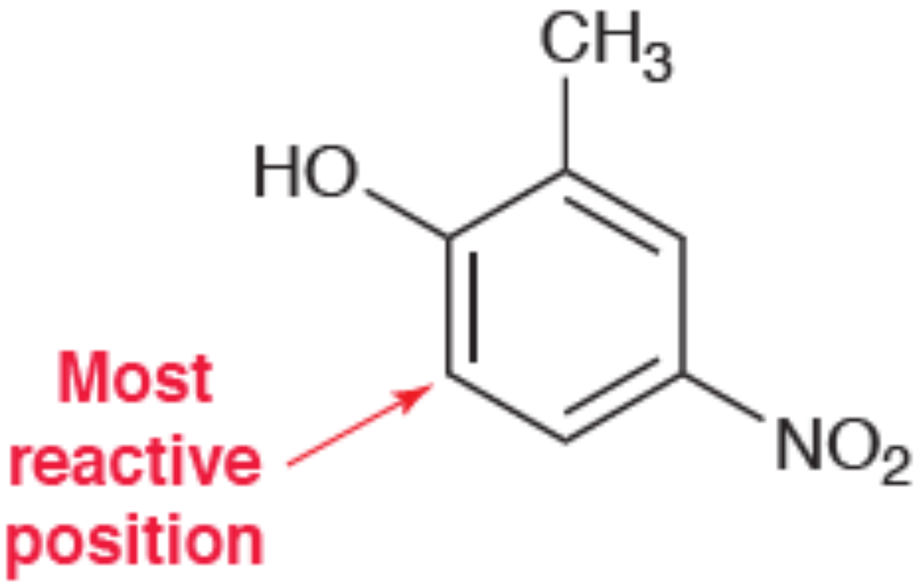


PROBLEMA. Identificare, nella sostanza vista di seguito, la posizione che è più suscettibile per essere sottoposta a una reazione di sostituzione elettrofilica aromatica.

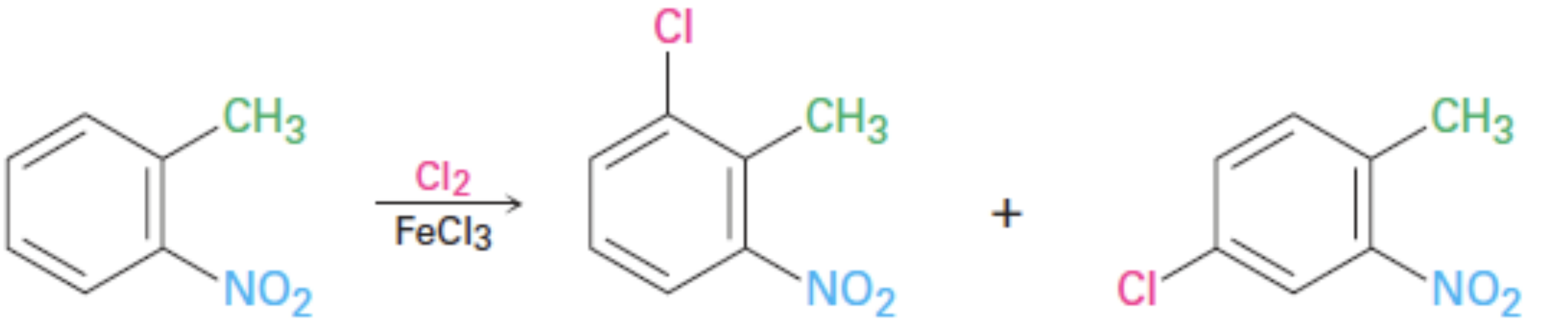


PROBLEMA. Identificare, nella sostanza vista di seguito, la posizione che è più suscettibile per essere sottoposta a una reazione di sostituzione elettrofilica aromatica.



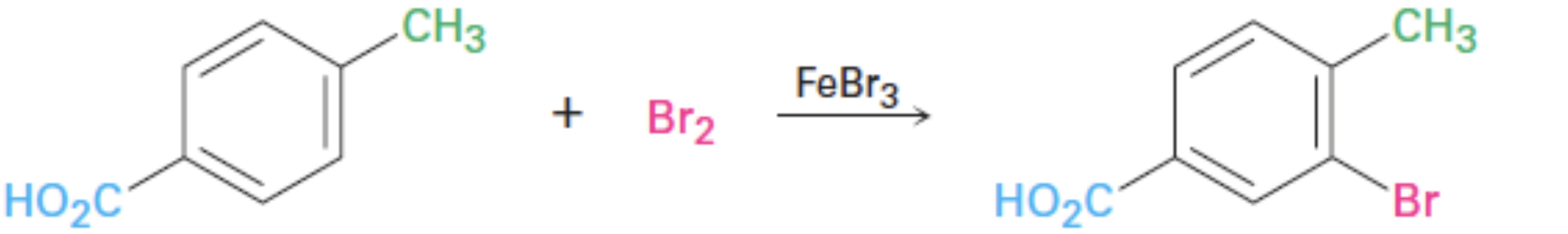


Effetti dei sostituenti attivanti e disattivanti sull'anello



o-Nitrotoluene 2-Chloro-6-nitrotoluene 4-Chloro-2-nitrotoluene

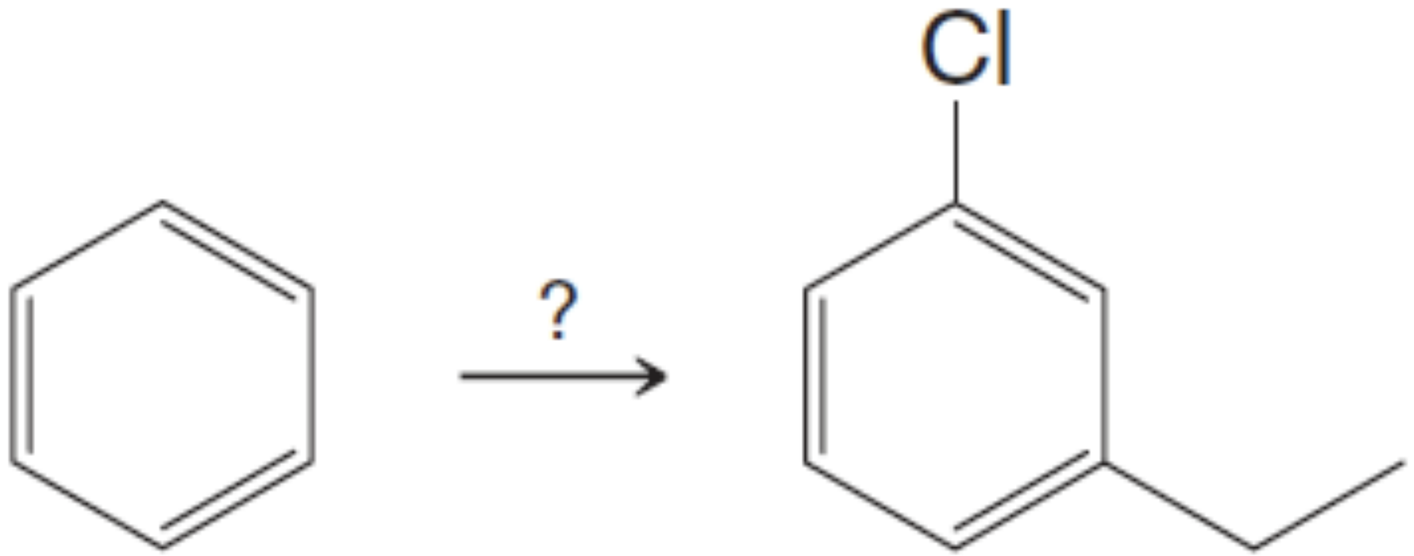
Effetti dei sostituenti attivanti e disattivanti sull'anello



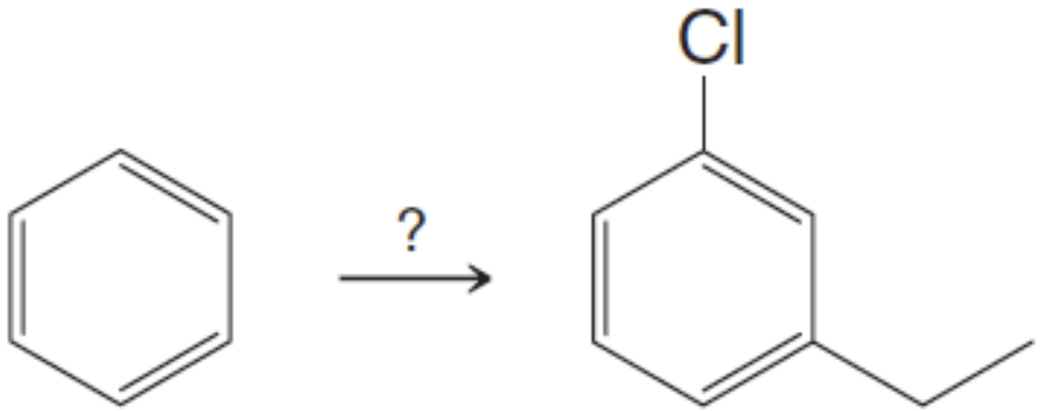
p-Methylbenzoic acid

3-Bromo-4-methylbenzoic acid

Problema: Supponiamo di dover sintetizzare il m-cloroetilbenzene dal benzene. C'è un metodo in tre fasi che funzionerà se i passi sono fatti nell'ordine corretto. Qual è questo metodo?



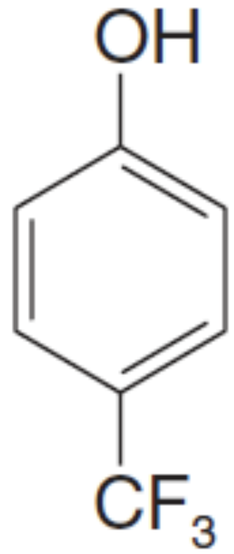
Problema: Supponiamo di dover sintetizzare il m-cloroetilbenzene dal benzene. C'è un metodo in tre fasi che funzionerà se i passi sono fatti nell'ordine corretto. Qual è questo metodo?



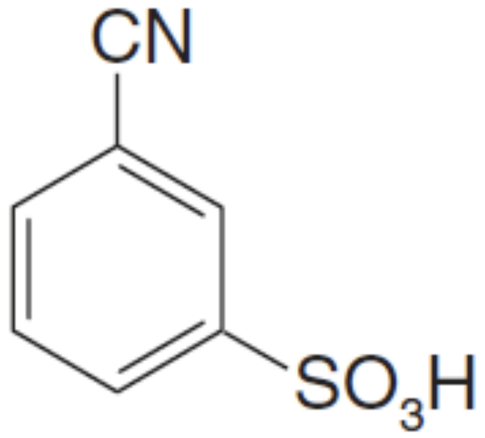
1) Acilazione di F-C
2) Clorurazione
3) Idrogenazione catalitica del gruppo carbonilico

Problema: Prevedere il prodotto (o i prodotti) principale della reazione di nitrazione di ciascuno dei seguenti composti.

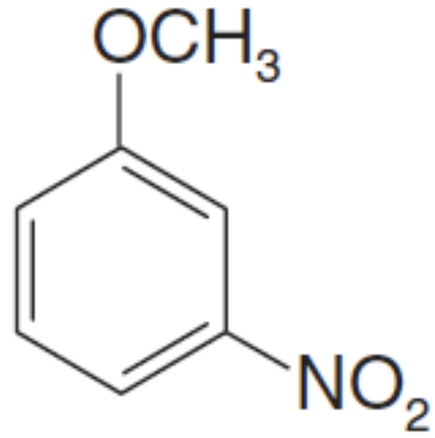
(a)



(b)

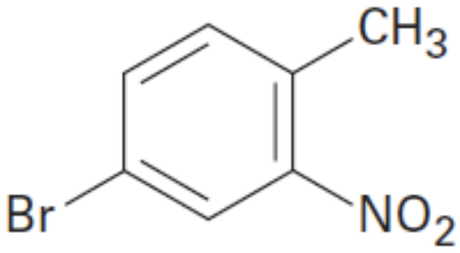


(c)



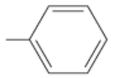
PROBLEMA: Sintesi del Benzene trissubstituita:

Sintetizzare il 4-Bromo-2-nitrotoluene dal benzene



4-Bromo-2-nitrotoluene

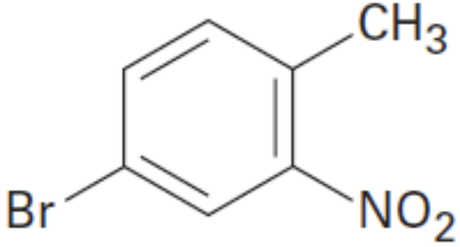
Table 22.2 Directing Effects of Substituents on Further Substitution

Ortho-Para Directing	Strongly activating	$-\ddot{N}H_2$	$-\ddot{N}HR$	$-\ddot{N}R_2$	$-\ddot{O}H$	$-\ddot{O}R$		
	Moderately activating	$-\ddot{N}HCR$ (O)	$-\ddot{N}HCAr$ (O)	$-\ddot{O}CR$ (O)	$-\ddot{O}CAr$ (O)			
	Weakly activating	$-R$						
	Weakly deactivating	$-\ddot{F}:$	$-\ddot{Cl}:$	$-\ddot{Br}:$	$-\ddot{I}:$			
Meta Directing	Moderately deactivating	$-CH$ (O)	$-CR$ (O)	$-COH$ (O)	$-COR$ (O)	$-CNH_2$ (O)	$-SOH$ (O, O)	$-C\equiv N$
	Strongly deactivating	$-NO_2$	$-NH_3^+$	$-CF_3$	$-CCl_3$			

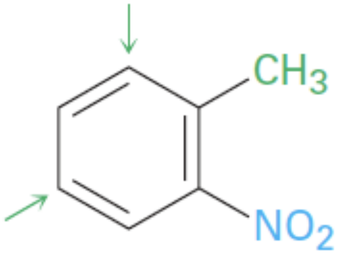
Relative importance in directing further substitution

PROBLEMA: Sintesi del Benzene trissubstituita:

Sintetizzare il 4-Bromo-2-nitrotoluene dal benzene

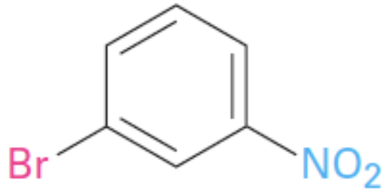


4-Bromo-2-nitrotoluene



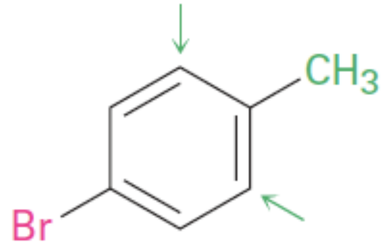
***o*-Nitrotoluene**

This ring will give a mixture of isomers on bromination.



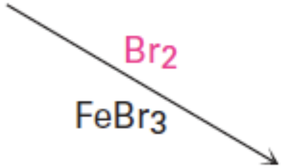
***m*-Bromonitrobenzene**

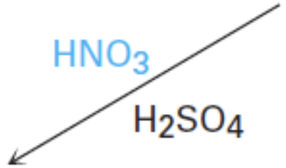
This deactivated ring will not undergo a Friedel–Crafts reaction.



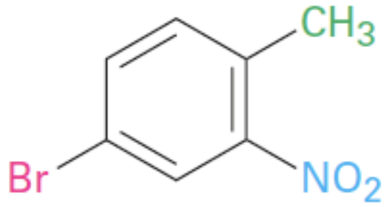
***p*-Bromotoluene**

This ring will give only the desired isomer on nitration.





1) Alchilazione F-C
2) Nitrazione
3) Alogenazione

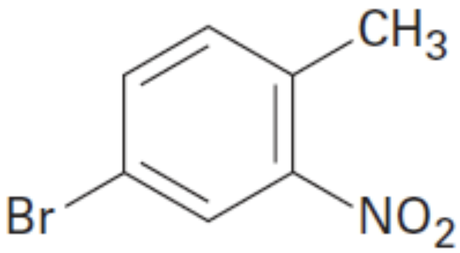


4-Bromo-2-nitrotoluene

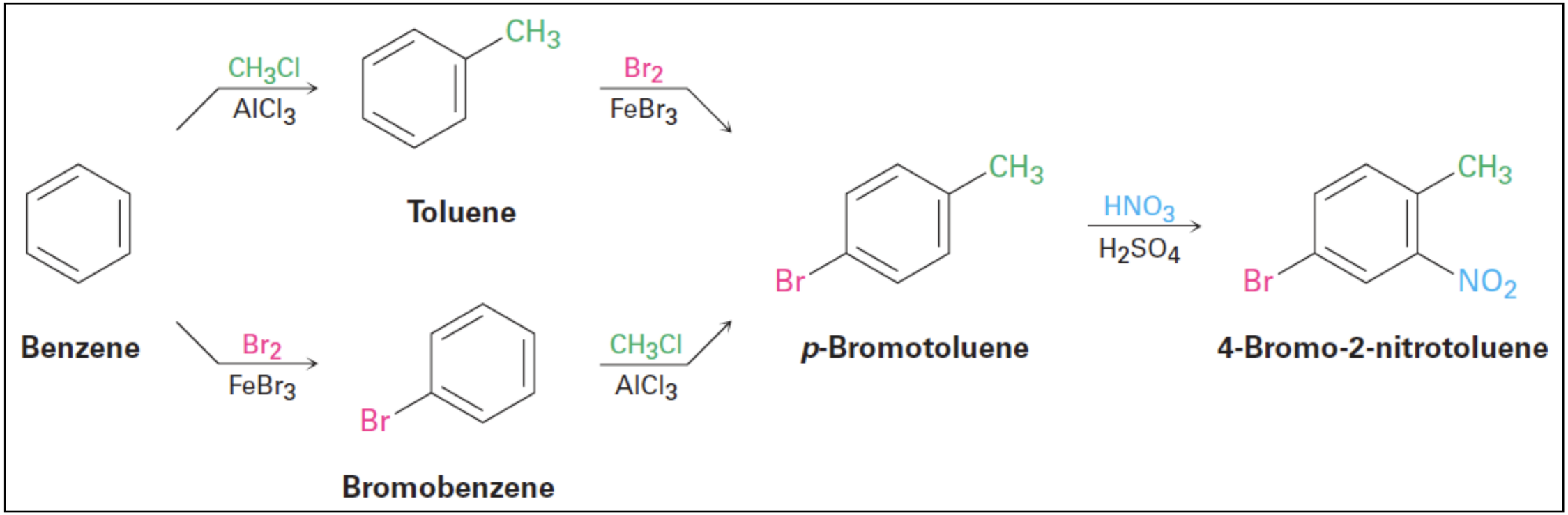
1) Bromurazione
2) Alchilazione F-C
3) Nitrazione

PROBLEMA: Sintesi del Benzene trissubstituita:

Sintetizzare il 4-Bromo-2-nitrotoluene dal benzene

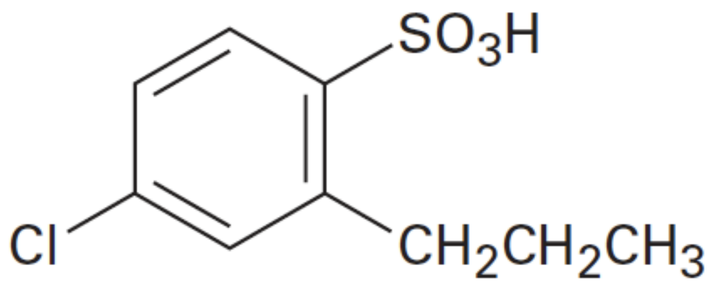


4-Bromo-2-nitrotoluene



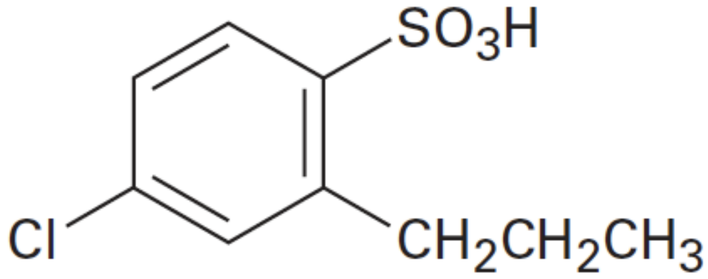
Sintesi di un Benzene trisostituito:

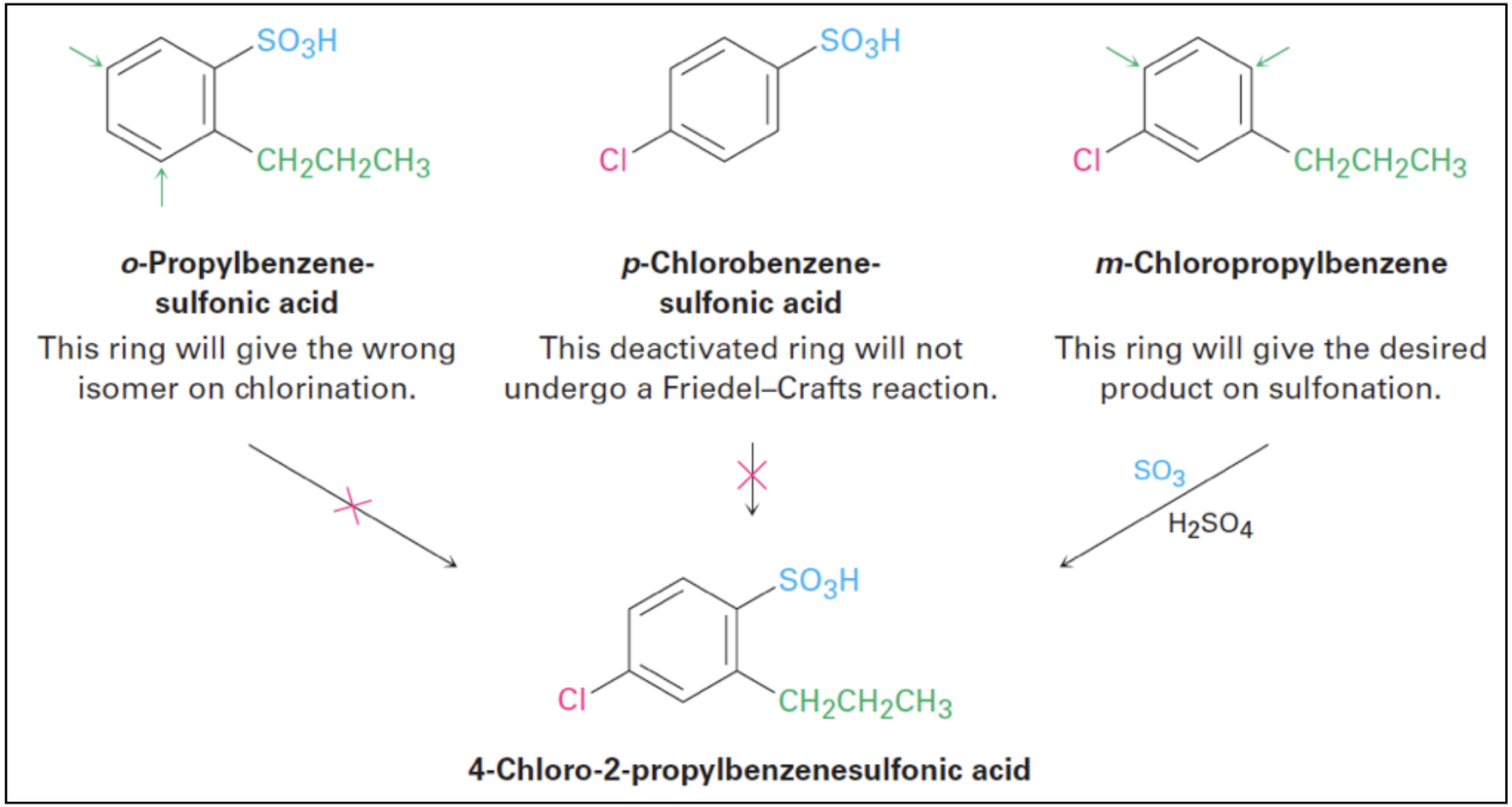
Sintetizzare l'acido 4-cloro-2-propilbenzenesolfonico dal benzene



Sintesi di un Benzene trisostituito:

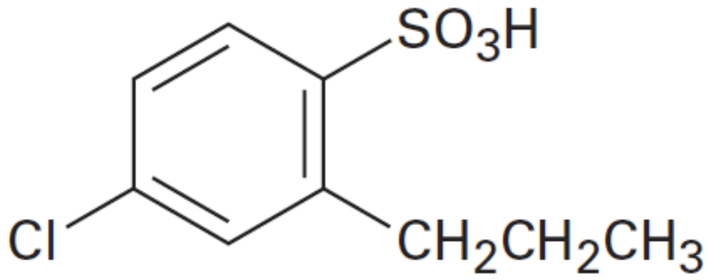
Sintetizzare l'acido 4-cloro-2-propilbenzenesolfonico dal benzene

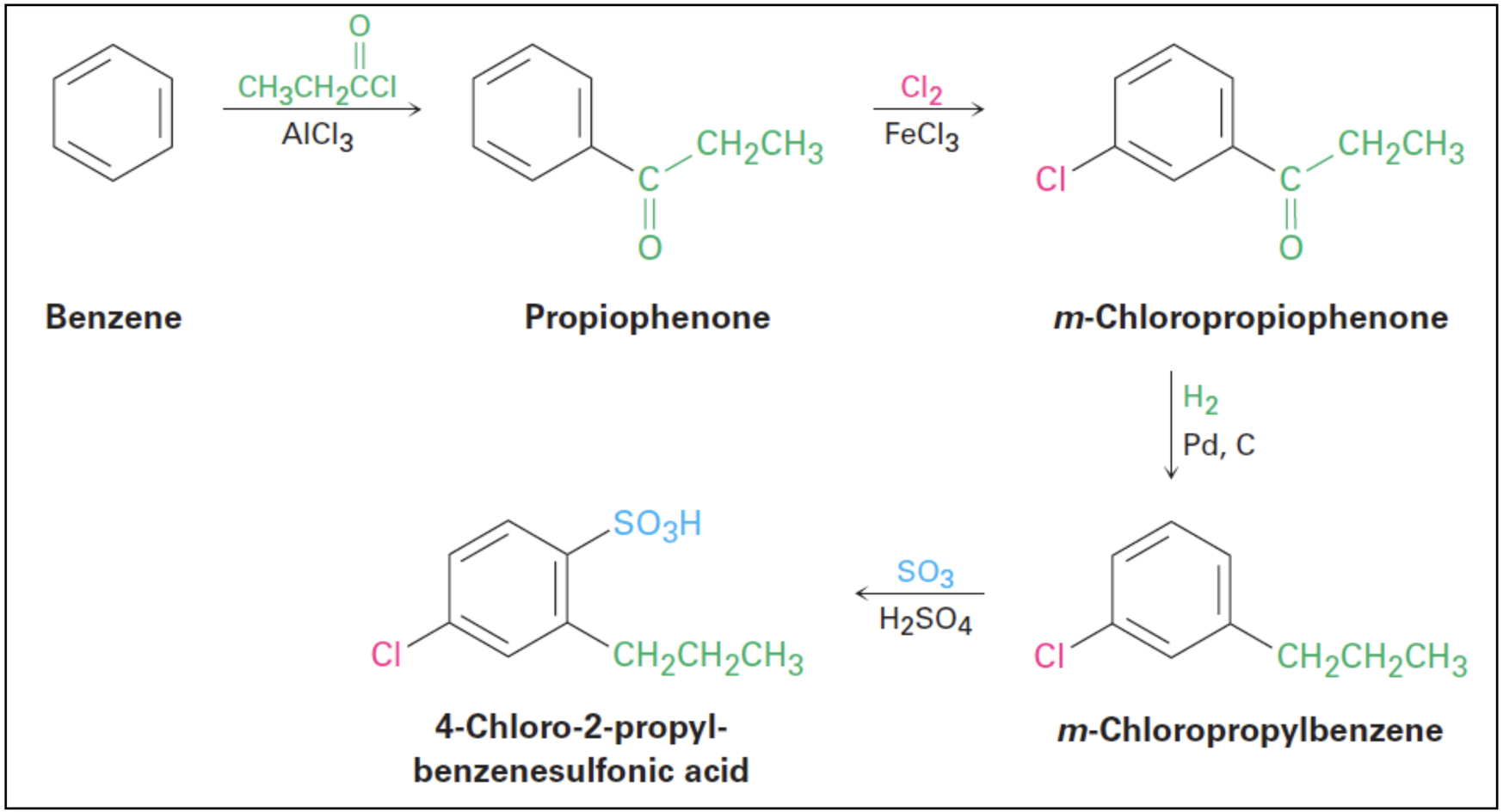




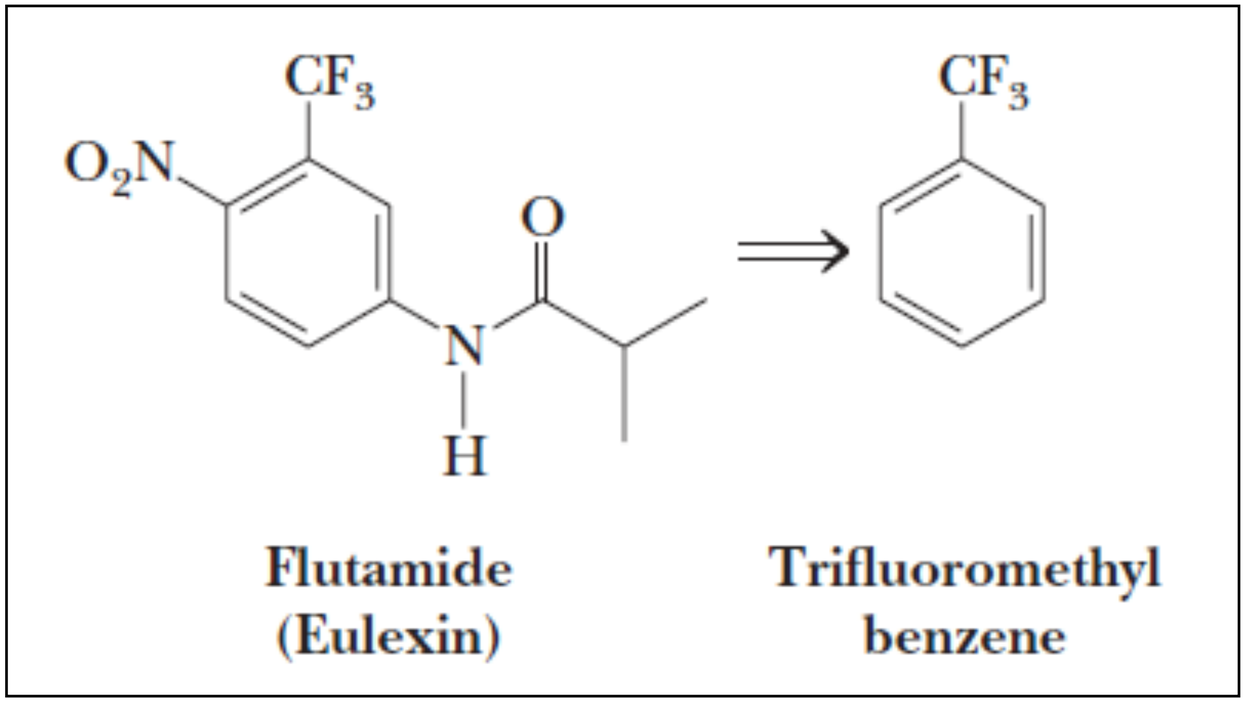
Sintesi di un Benzene trisostituito:

Sintetizzare l'acido 4-cloro-2-propilbenzenesolfonico dal benzene





PROBLEMA: Come prepareresti il seguente composto dal trifluormetil-benzene? Il cancro alla prostata è la seconda causa di morte negli Stati Uniti. Il testosterone e l'androsterone sono le cause della proliferazione di questo cancro. Il farmaco Flutamide riduce i livelli degli ormoni androgeni preducendo la proliferazione del cancro. Indica i reagenti necessari e se hai più di un prodotto puoi assumere la separazione dei prodotti orto e per i prodotti sostituiti.



Flutamide (Eulexin)

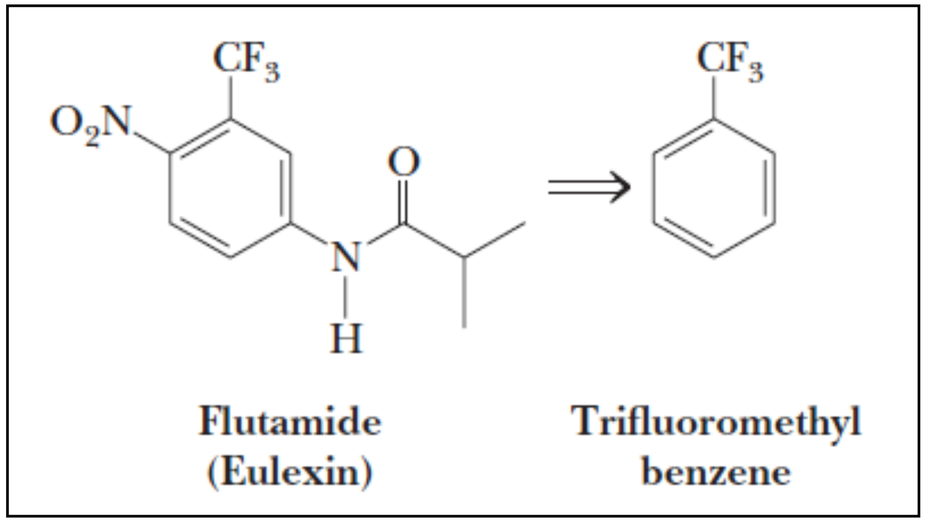
Trifluoromethyl benzene

Table 22.2 Directing Effects of Substituents on Further Substitution

Ortho-Para Directing	Strongly activating	—$\ddot{N}H_2$	—$\ddot{N}HR$	—$\ddot{N}R_2$	—$\ddot{O}H$	—$\ddot{O}R$			
	Moderately activating	—$\ddot{N}HCR$ (O)	—$\ddot{N}HCAr$ (O)	—$\ddot{O}CR$ (O)	—$\ddot{O}CAr$ (O)				
	Weakly activating	—R							
	Weakly deactivating	—$\ddot{F}$:	—$\ddot{C}l$:	—$\ddot{B}r$:	—$\ddot{I}$:				
Meta Directing	Moderately deactivating	—CH (O)	—CR (O)	—COH (O)	—COR (O)	—CNH_2 (O)	—SO_2OH	—C≡N	
	Strongly deactivating	—NO_2	—NH_3^+	—CF_3	—CCl_3				

Relative importance in directing further substitution

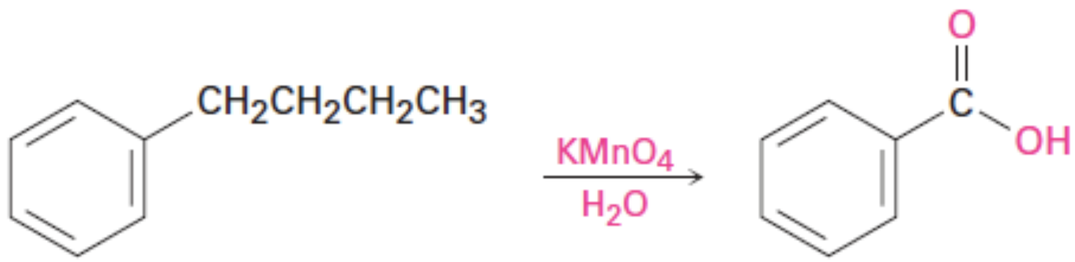
PROBLEMA: Come prepareresti il seguente composto dal trifluormetil-benzene? Il cancro alla prostata è la seconda causa di morte negli Stati Uniti. Il testosterone e l'androsterone sono le cause della proliferazione di questo cancro. Il farmaco Flutamide riduce i livelli degli ormoni androgeni preducendo la proliferazione del cancro. Indica i reagenti necessari e se hai più di un prodotto puoi assumere la separazione dei prodotti orto e per i prodotti sostituiti.



Flutamide (Eulexin) — Trifluoromethyl benzene

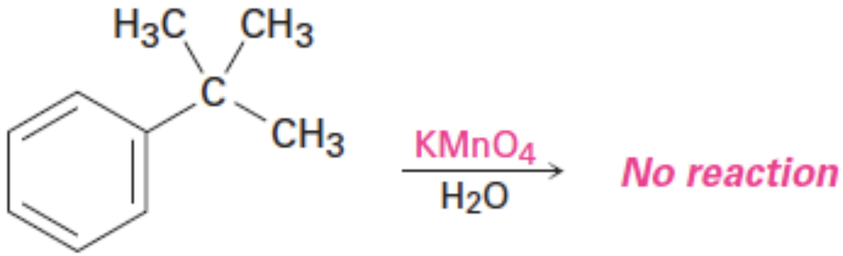
1) Nitrazione
2) Riduzione ad ammina (Ar-NH_2)
3) Acilazione $(CH_3)_2CHCOCl$
4) Nitrazione

OSSIDAZIONE DI ALCHIL BENZENI



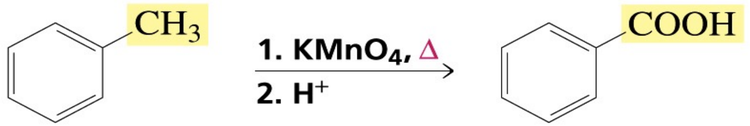
Butylbenzene

Benzoic acid (85%)



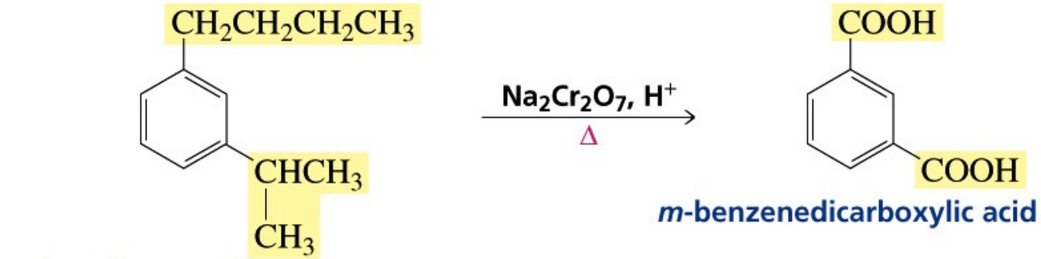
No reaction

tert-Butylbenzene



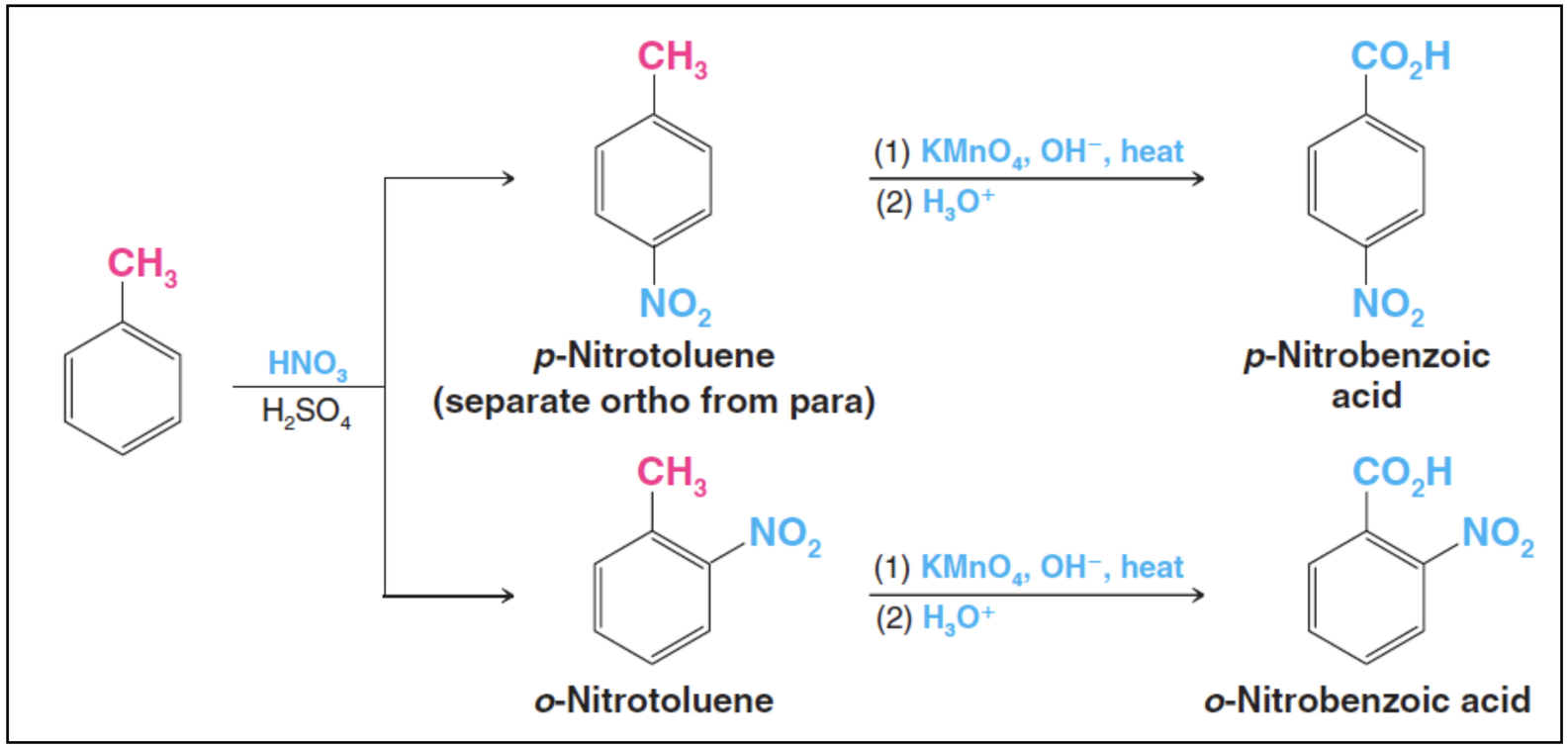
toluene

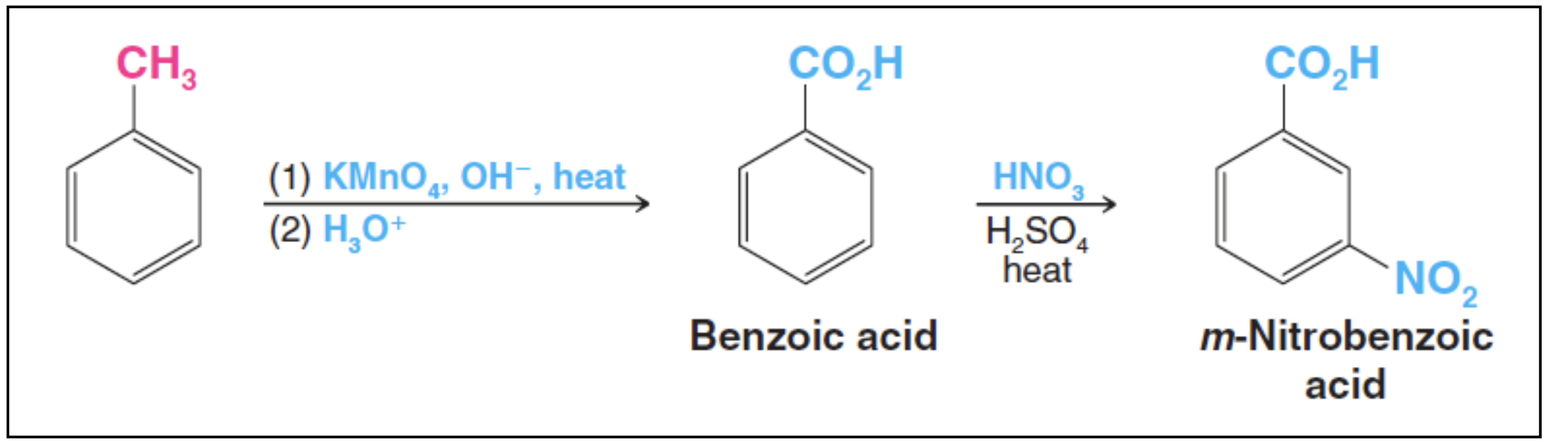
benzoic acid

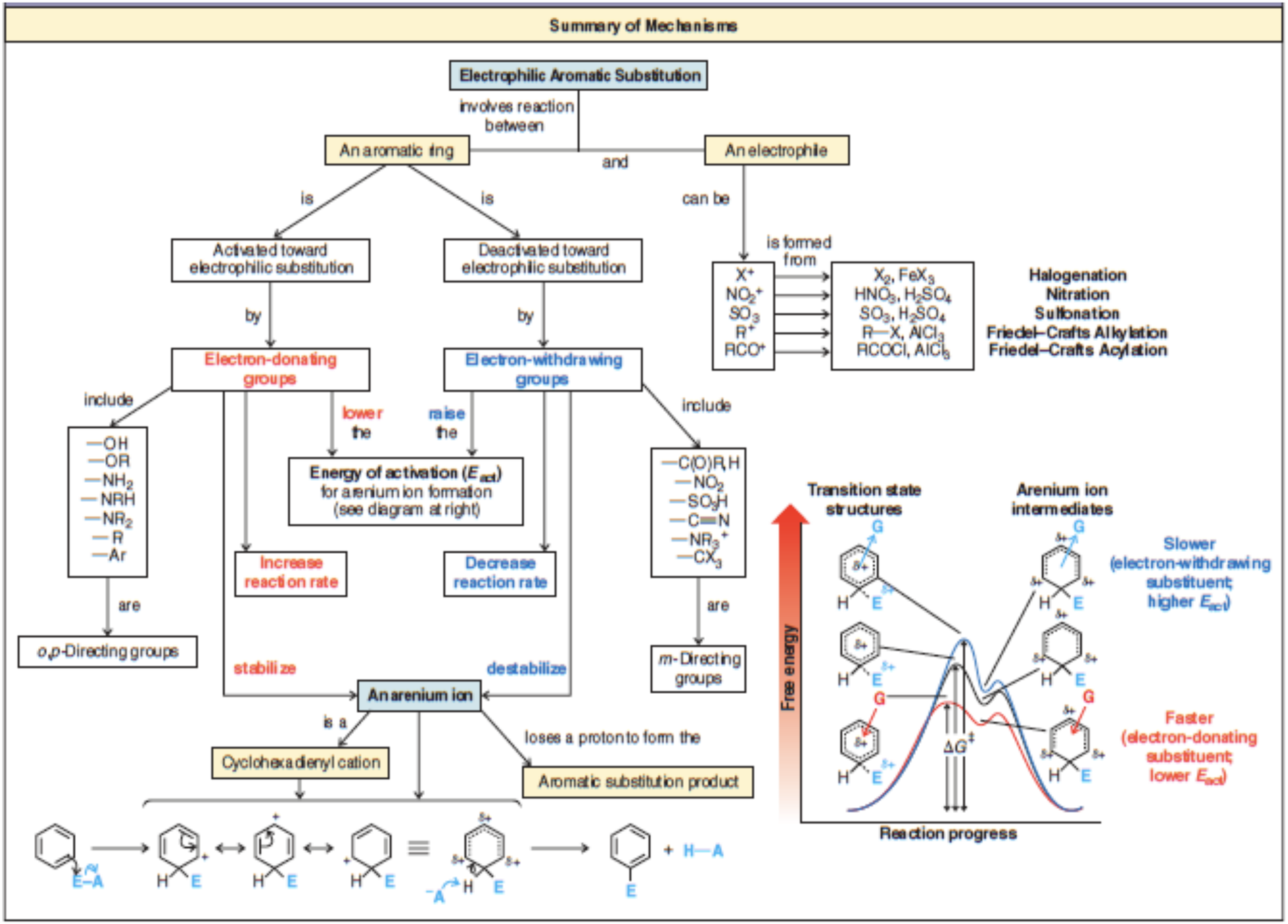


m-butylisopropylbenzene

m-benzenedicarboxylic acid


CH3
HNO3
H2SO4
CH3
NO2
p-Nitrotoluene
(separate ortho from para)
(1) KMnO4, OH−, heat
(2) H3O+
CO2H
NO2
p-Nitrobenzoic acid
CH3
NO2
o-Nitrotoluene
(1) KMnO4, OH−, heat
(2) H3O+
CO2H
NO2
o-Nitrobenzoic acid

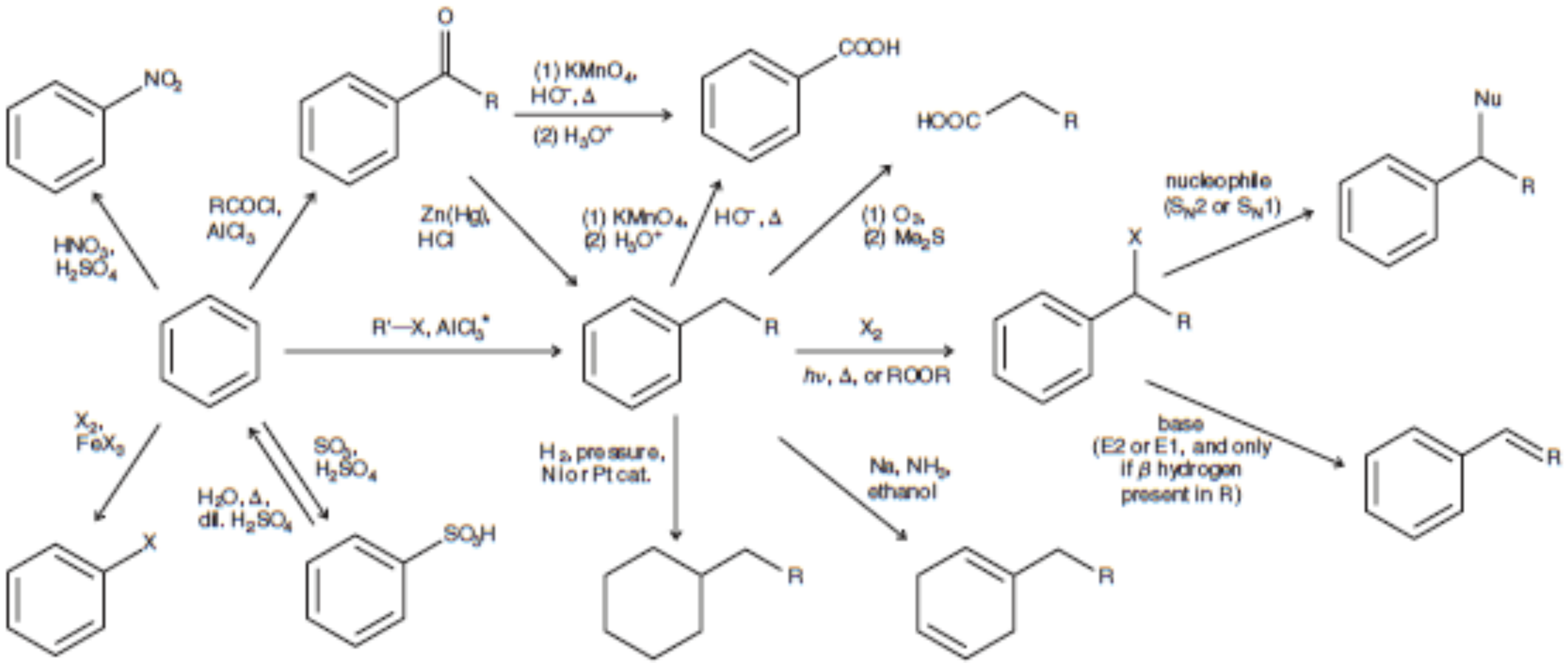

CH3
(1) KMnO4, OH−, heat
(2) H3O+
CO2H
Benzoic acid
HNO3
H2SO4
heat
CO2H
NO2
m-Nitrobenzoic acid


Summary of Mechanisms
Electrophilic Aromatic Substitution
involves reaction between
An aromatic ring
and
An electrophile
is
is
can be
Activated toward electrophilic substitution
Deactivated toward electrophilic substitution
by
by
is formed from
X+
NO2+
SO3
R+
RCO+
X2, FeX3
HNO3, H2SO4
SO3, H2SO4
R—X, AlCl3
RCOCl, AlCl3
Halogenation
Nitration
Sulfonation
Friedel–Crafts Alkylation
Friedel–Crafts Acylation
Electron-donating groups
Electron-withdrawing groups
include
include
—OH
—OR
—NH2
—NRH
—NR2
—R
—Ar
—C(O)R, H
—NO2
—SO3H
—C≡N
—NR3+
—CX3
lower the
raise the
Energy of activation (Eact) for arenium ion formation (see diagram at right)
Increase reaction rate
Decrease reaction rate
are
are
o,p-Directing groups
m-Directing groups
stabilize
destabilize
An arenium ion
is a
loses a proton to form the
Cyclohexadienyl cation
Aromatic substitution product
E–A
H E
H E
H E
–A
H E
E
+ H—A
Transition state structures
Arenium ion intermediates
Free energy
Reaction progress
ΔG‡
G
Slower (electron-withdrawing substituent; higher Eact)
Faster (electron-donating substituent; lower Eact)

CONCEPT MAP

Some Synthetic Connections of Benzene and Aryl Derivatives

- Nitration
- Halogenation
- Sulfonation/desulfonation
- Friedel–Crafts alkylation
- Friedel–Crafts acylation
- Clemmensen reduction
- Side-chain oxidation
- Ring oxidation
- Catalytic hydrogenation of ring
- Birch reduction
- Benzylic radical halogenation
- Benzylic substitution/elimination



*In the Friedel–Crafts alkylation example shown here, R' is a primary alkyl halide. If carbocation rearrangements are likely, then Friedel–Crafts acylation followed by Clemmensen reduction should be used to incorporate a primary alkyl group.