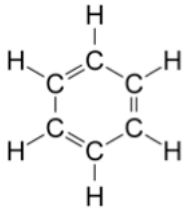
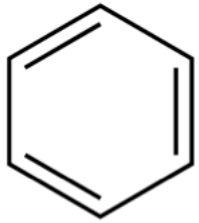
Benzene was once used in shaving cream and as a solvent to decaffeinate coffee beans

~ How far we've come in the world ☺



(1)

Benzene: C_6H_6


(2)


(3)

Chapter 16
Chemistry of Benzene:
Electrophilic ***Aromatic*** Substitution

Outline

Background

Electrophilic aromatic substitution reactions: Bromination

Other aromatic substitutions

Administrative

Alkylation and acylation of aromatic rings:

  The Friedel-Crafts reaction

Substituent effects in electrophilic substitutions

Trisubstituted benzenes: Additivity of effects

Nucleophilic aromatic substitution

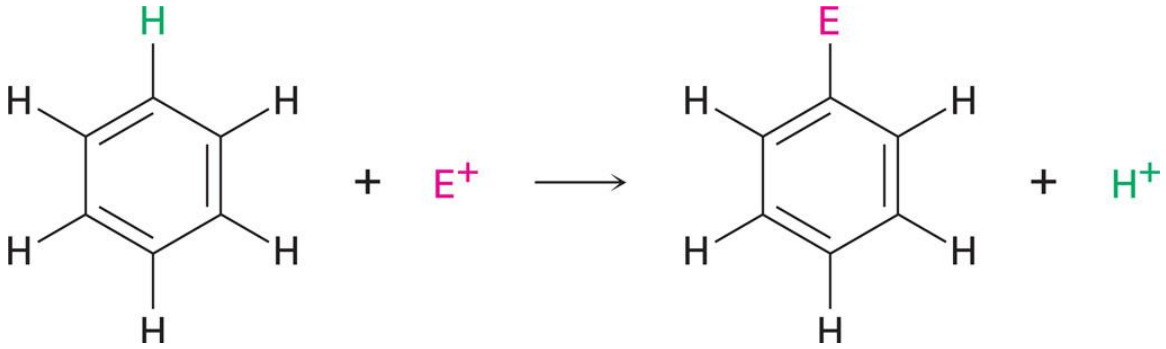
Benzyne

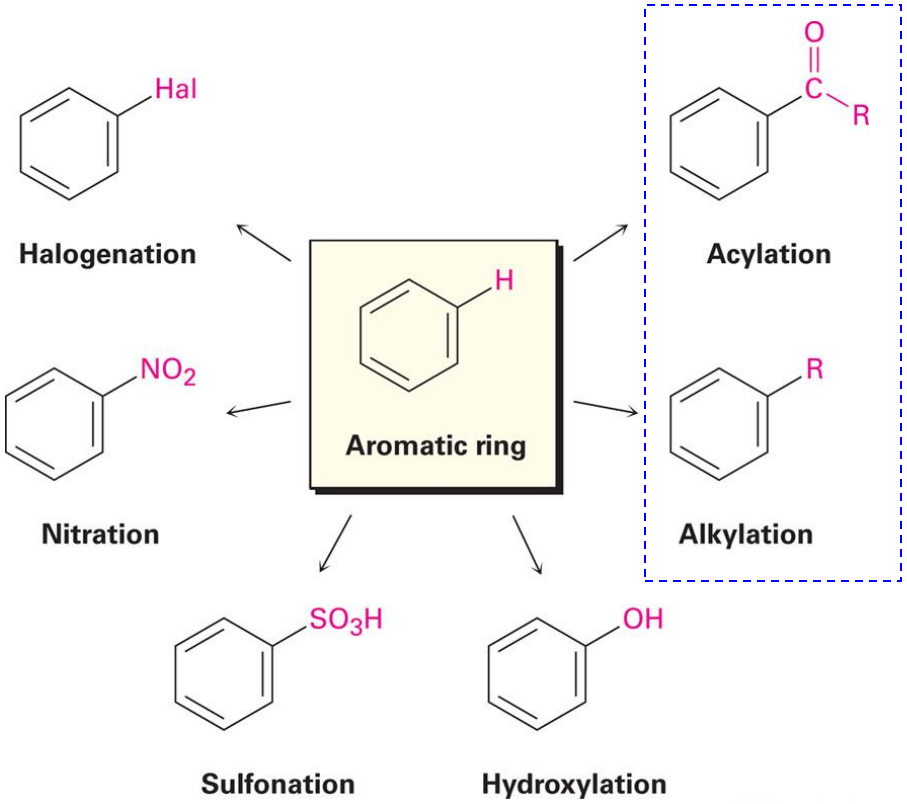
Oxidation of aromatic compounds

Reduction of aromatic compounds

Synthesis of polysubstituted benzenes

Electrophilic ***aromatic*** substitution reactions:

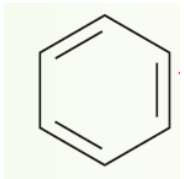




Alkylation & Acylation of Aromatic Rings: The Friedel-Crafts Reaction

One of THE most <u>useful</u> electrophillic *aromatic* substitution rxns in the lab.

alkylation - putting ***alkyl*** group ($-CH_2CH_2CH_3$) onto a benzene ring

Treat ***aromatic*** compound  $\xrightarrow[AlCl_3]{CH_3\underset{Cl}{\underset{|}{C}}HCH_3}$ (alkyl chloride)

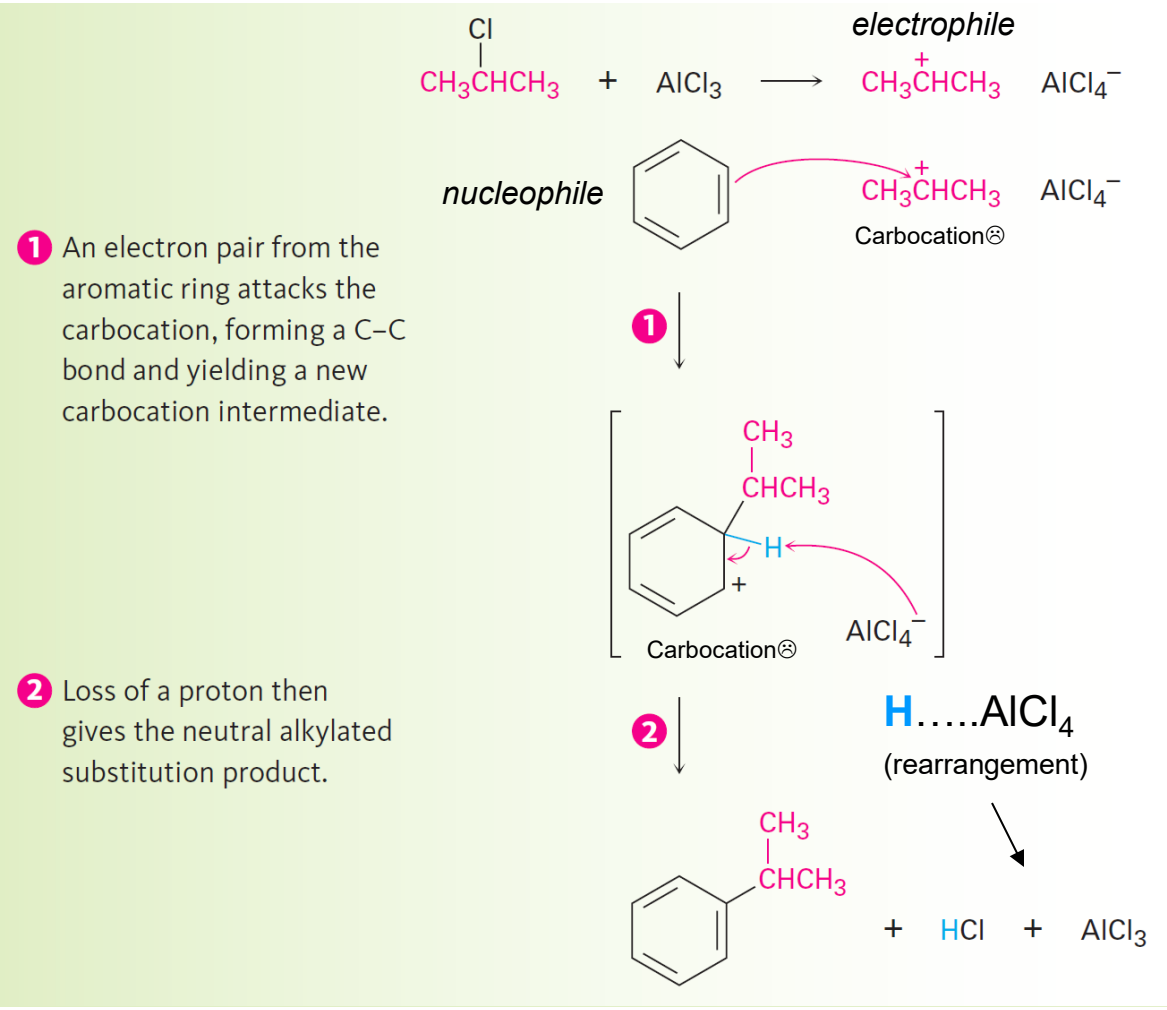
NOTES: $AlCl_3$ catalyzes the rxn by helping the alkyl halide to ***dissociate*** →

(similar to how $FeBr_3$ catalyzes *Aromatic* bromination by polarizing Br_2 ~ last lecture)

Chem 3900
Handout 1
Lecture 4
Chap 16

Mechanism of Friedel-Crafts **Alky**lation RXN

You Draw ☺



1. An electron pair from the aromatic ring attacks the carbocation, forming a C–C bond and yielding a new carbocation intermediate.

2. Loss of a proton then gives the neutral alkylated substitution product.

Despite it's utility ~ there are **five** limitations:

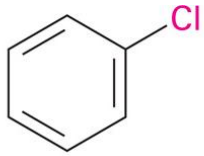
Lets highlight them…(draw)

Assn. professor. P. Still, CSDH

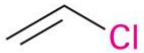
1) Only *alkyl halides* can be used:

Not reactive

2a

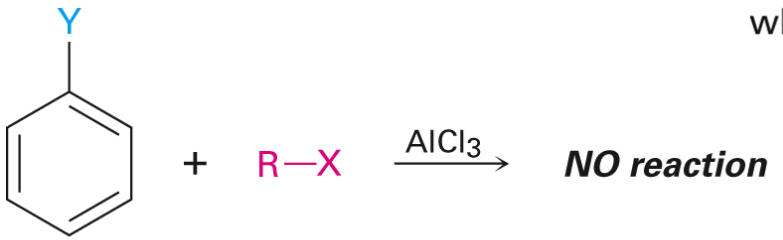


2b

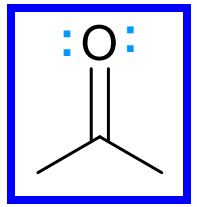


2a) Aromatic (aryl) *halides* and **2b**) vinylic *halides* don't react
their carbocations(+) are too HIGH in E to form under Friedel-Crafts conditions

3) Doesn't work on Aromatic rings with strong ***electronic withdrawing groups*** (**Y**)



where Y = $-\overset{+}{N}R_3$, $-NO_2$, $-CN$,
$-SO_3H$, $-CHO$, $-COCH_3$,
$-CO_2H$, $-CO_2CH_3$
($-NH_2$, $-NHR$, $-NR_2$)

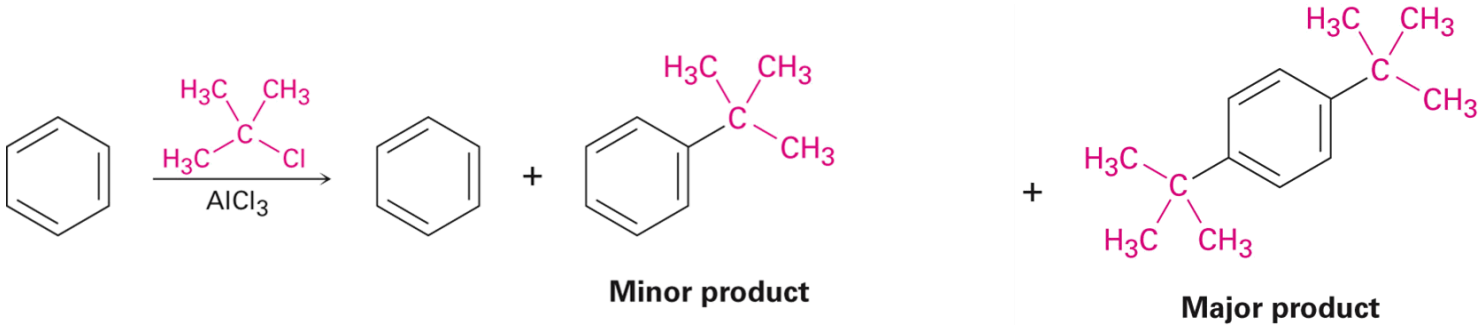


NOTE: Y donates some of their *electron density* into a conjugated π systems via ***resonance*** or ***inductive*** effects, thus making the π system less nucleophilic

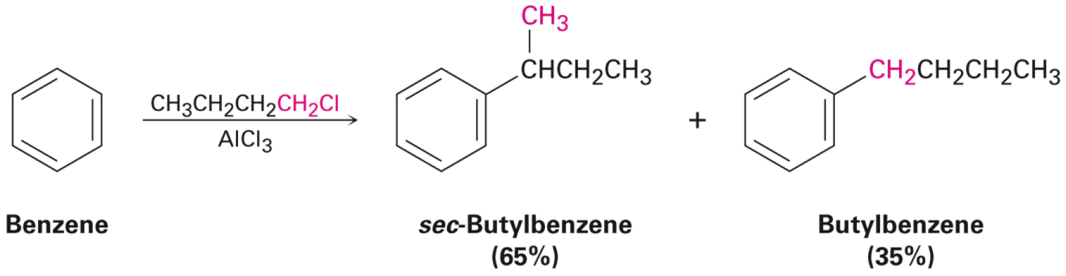
Despite it's utility ~ there are five limitations:

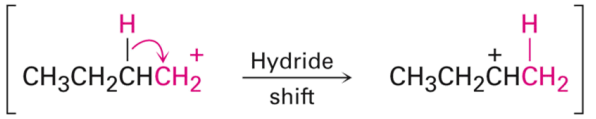
Assn. professor. B. Rubio, HCC

4) Difficult to STOP the reaction after a ***single*** substitution



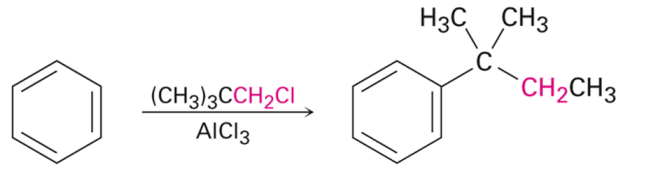
5) Occasional ***skeletal*** structure "rearrangements" occur of the alkyl carbocation ☹

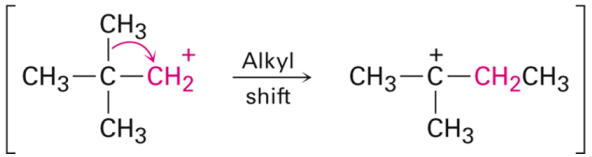




1°carbocation⁺
unstable

2° carbocation⁺
stable ☺





1° carbocation+
unstable

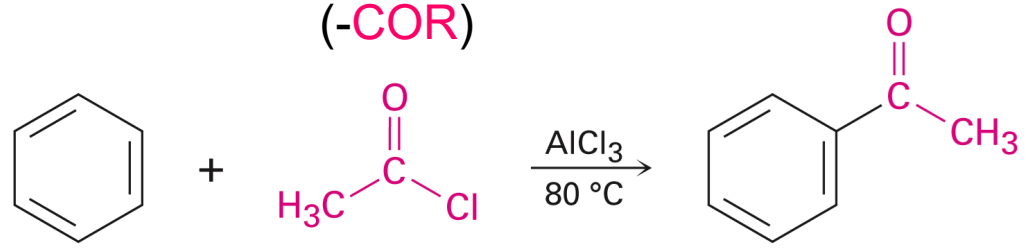
3° carbocation
stable ☺

Recall: *Hydride* & *Alkyl* shifts to stablize carbocation intermediates (**Sect 7-11**)

Mechanism of Friedel-Crafts **Acyl**ation RXN

Background

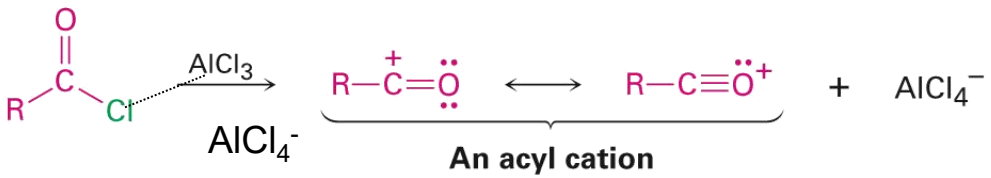
acyl group C=O
(-COR)

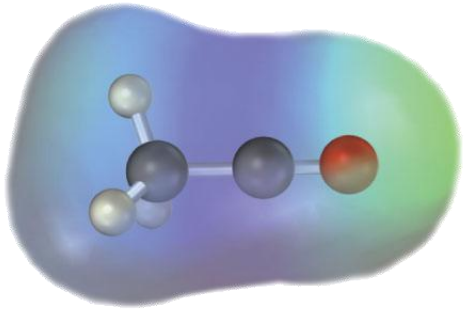


Benzene **Acetyl chloride** **Acetophenone (95%)**

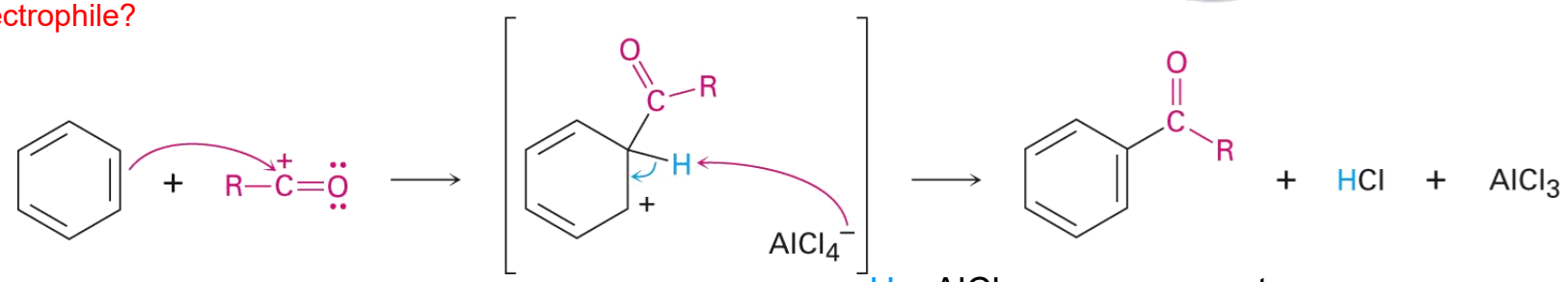
Mechanism is similar to ***akylation*** *(previous slides)*, same limitations (**1-5**) apply

resonance stabilized carbocation+





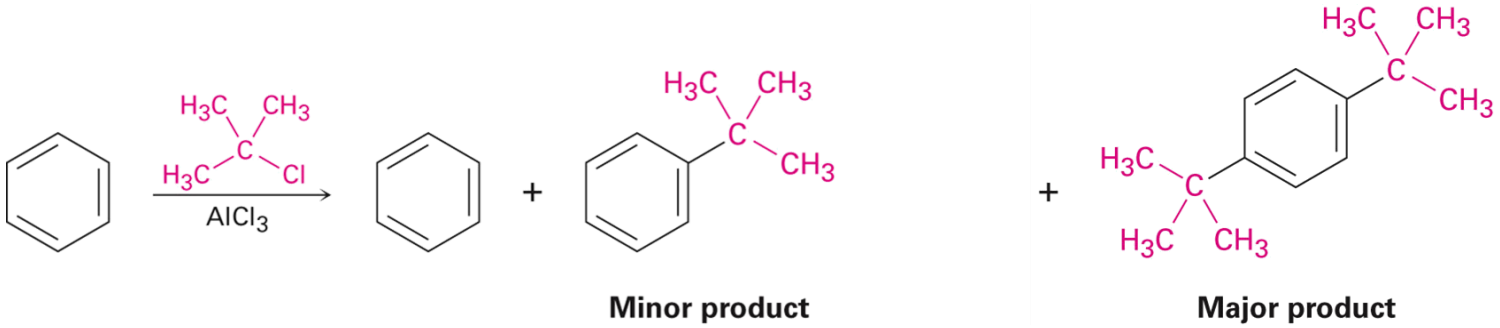
What's the nucleophile?
electrophile?



H + $AlCl_4^-$ rearrangement…

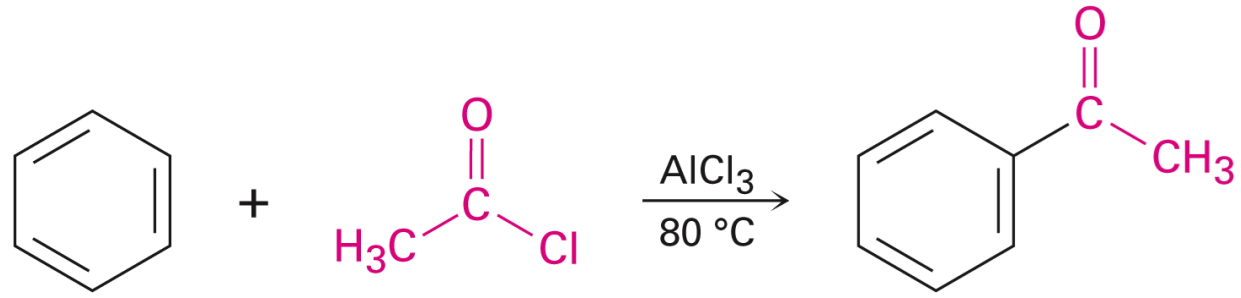
Friedel-Crafts **Acyl**ation RXN

1) Unlike multiple substitutions in Friedal-Crafts ***alkyl***ations…



2) ***Acyl***ations NEVER occur more than once in a ring. ☺

b/c the product (**b**) is *less* reactive than the **non**acylated starting material (**a**)

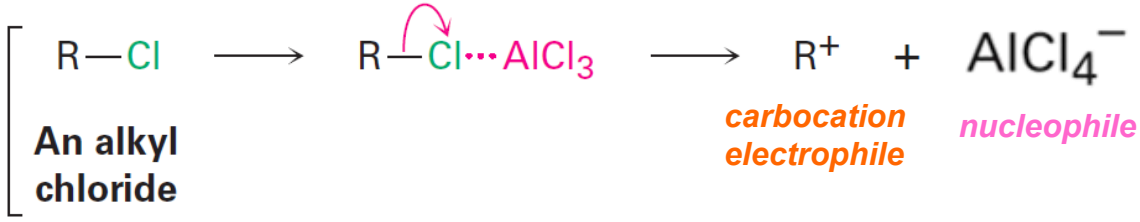


Benzene **Acetyl chloride** **Acetophenone (95%)**

(**a**) (**b**)

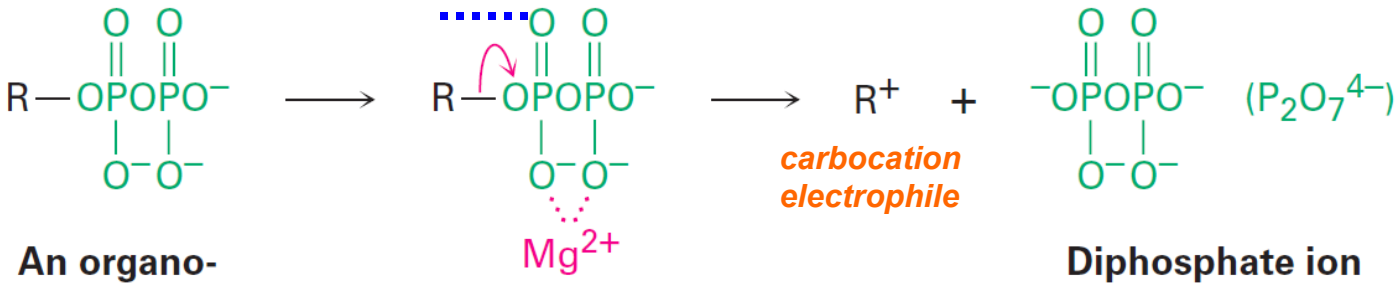
Aromatic acylations occur in numerous ***BIOLOGICAL*** *pathways*

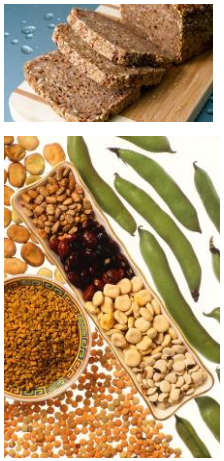
(however no $AlCl_3$ is availb. to be an electrophile ☹ like below)



Instead in **Nature** the ***carbocation electrophile*** is typically formed by ***dissociation*** of an Organo-di-**phosphate** assisted by complexation to a divalent metal cation e.g. **Mg^{2+}**

(just like the dissociation of an alkyl chloride is assisted by $AlCl_3$ above)

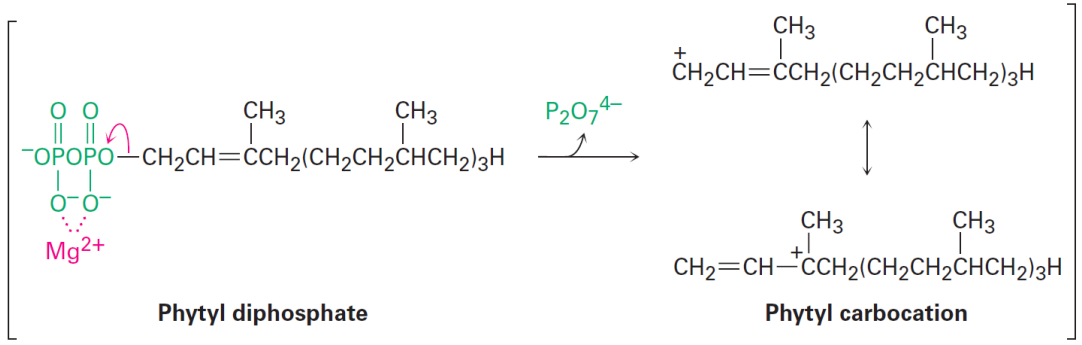


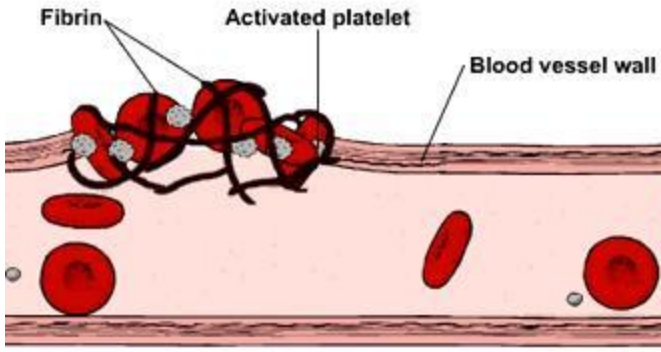


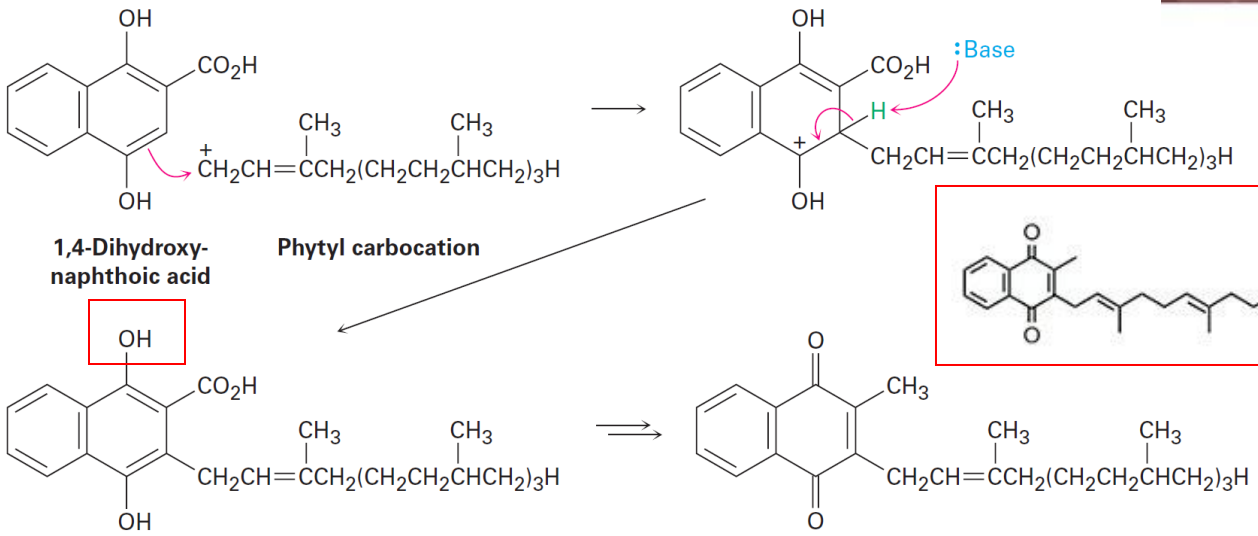
Sources of **Mg^{2+}**

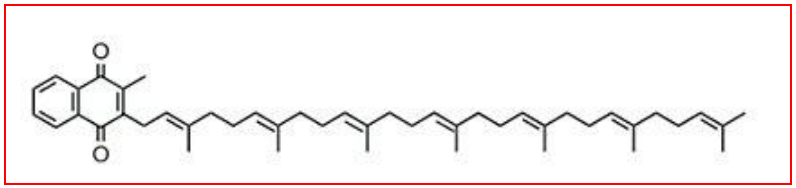
BIOLOGICAL *pathways* ~ Friedel-Crafts **Alkyl**ation (in **Nature**)

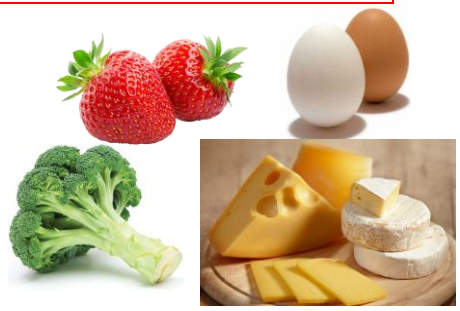
Background











Dietary sources

NOTES: Vitamin K is an essential precursor for proteins involved in ***blood clotting*** and controlling binding of Ca^{2+} in bones and other tissues (related to *osteoporsis*). Our body can't produce ample amt. (some microbes in our gut can ~ antibiotics can destroy ☹). Crohns disease, celiac patients and small children are at risk for Vit K. deficiency. Babies often get an injection ~ beneficial for early development. https://www.webmd.com/vitamins-and-supplements/supplement-guide-vitamin-k#2-3

Challenge Question

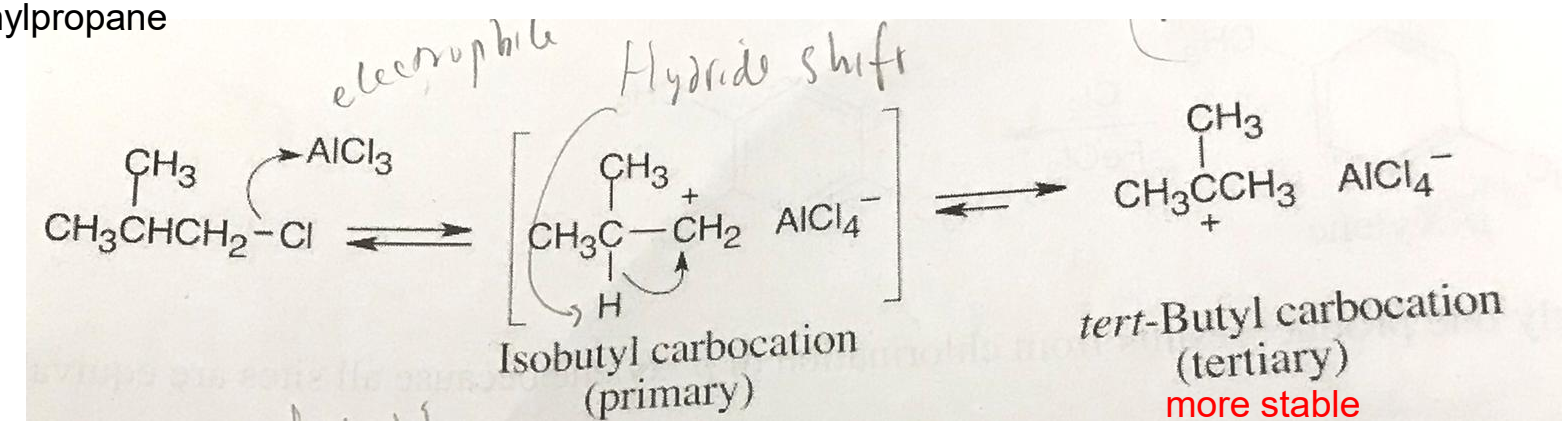
What is the major monosubstitution product from the Friedel-Crafts rxn of: Benzene with 1–chloro-2-methylpropane in the presence of $AlCl_3$?

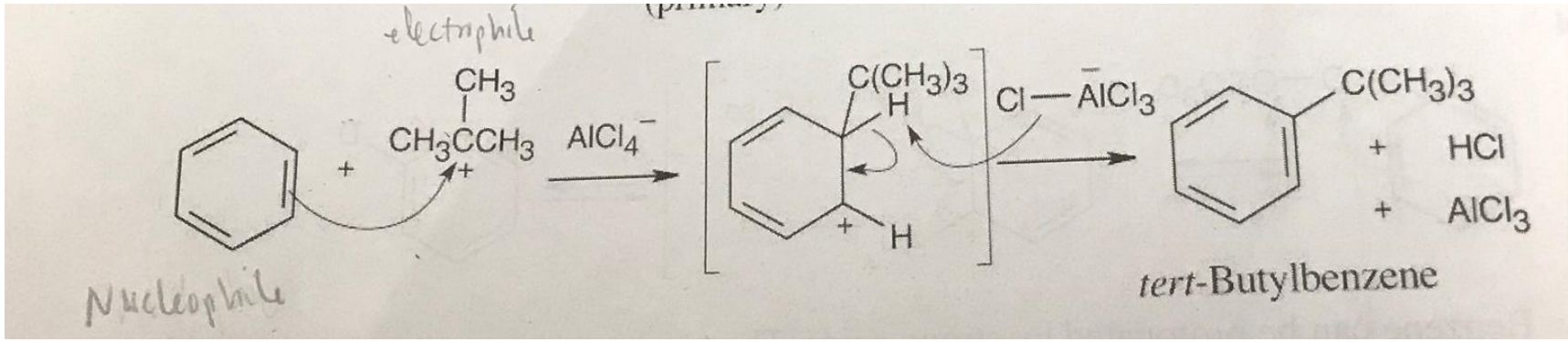
Hint 1: Draw structures of:

a) 1-chloro-2-methylpropane reacting w/ $AlCl_3$

b) Benzene

c) Write out the Mechanism(s) (see prev. notes)





Hint 2: *What is no. 5 limitation of the "Friedal Crafts reaction" (see previous notes)*

Outline

Background

Electrophilic aromatic substitution reactions: Bromination

Other aromatic substitutions

Alkylation and acylation of aromatic rings:

  The Friedel-Crafts reaction

Substituent effects in electrophilic substitutions

Trisubstituted benzenes: Additivity of effects

Nucleophilic aromatic substitution

Benzyne

Oxidation of aromatic compounds

Reduction of aromatic compounds

Synthesis of polysubstituted benzenes

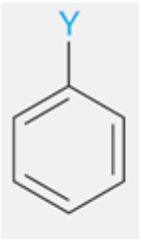
Substituent effects in electrophilic substitutions

What happens if we carry out a rxn on an ***Aromatic*** ring that already has a substituent?

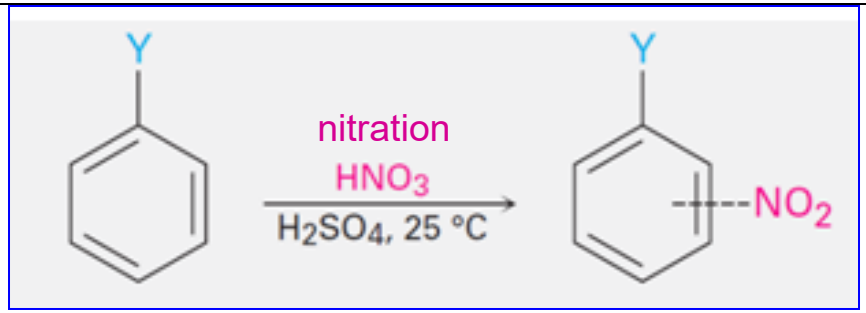
Two effects:

1) Some ***activate*** the ring (making it ***more Reactive*** than **Benzene**)

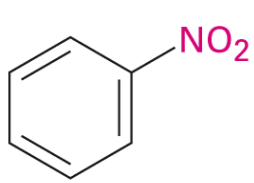
2) Some *de-**activate*** the ring (making it *less reactive* than **Benzene**)

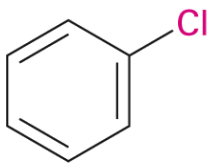


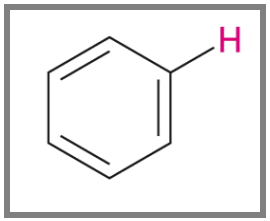
e.g.

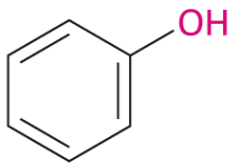


Y =









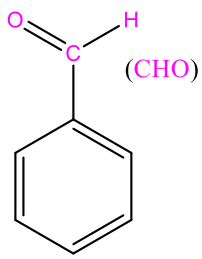
Relative rate of nitration	6×10^{-8}	0.033	1	1000 X ***more reactive*** ☺
2)	10 Million times *less reactive* ☹		**1**)	

Reactivity

Handout 2a

(HNO_3)

Substituents affect the ***orientation*** of the reaction.



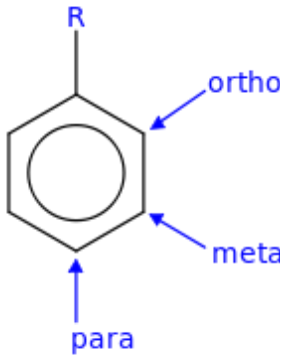
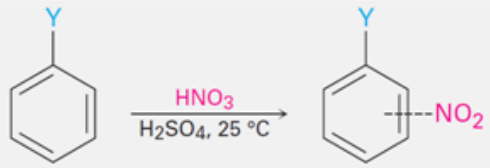


Table 16.1 Orientation of Nitration in Substituted Benzenes



	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
1) $-CHO$	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
2) $-OH$, $-NH_2$	50	0	50
$-NHCOCH_3$	19	2	79

The 3 possible disubstituted products: *ortho* (***o***), *meta* (***m***), *para* (***p***) are **NOT** formed in equal amounts.

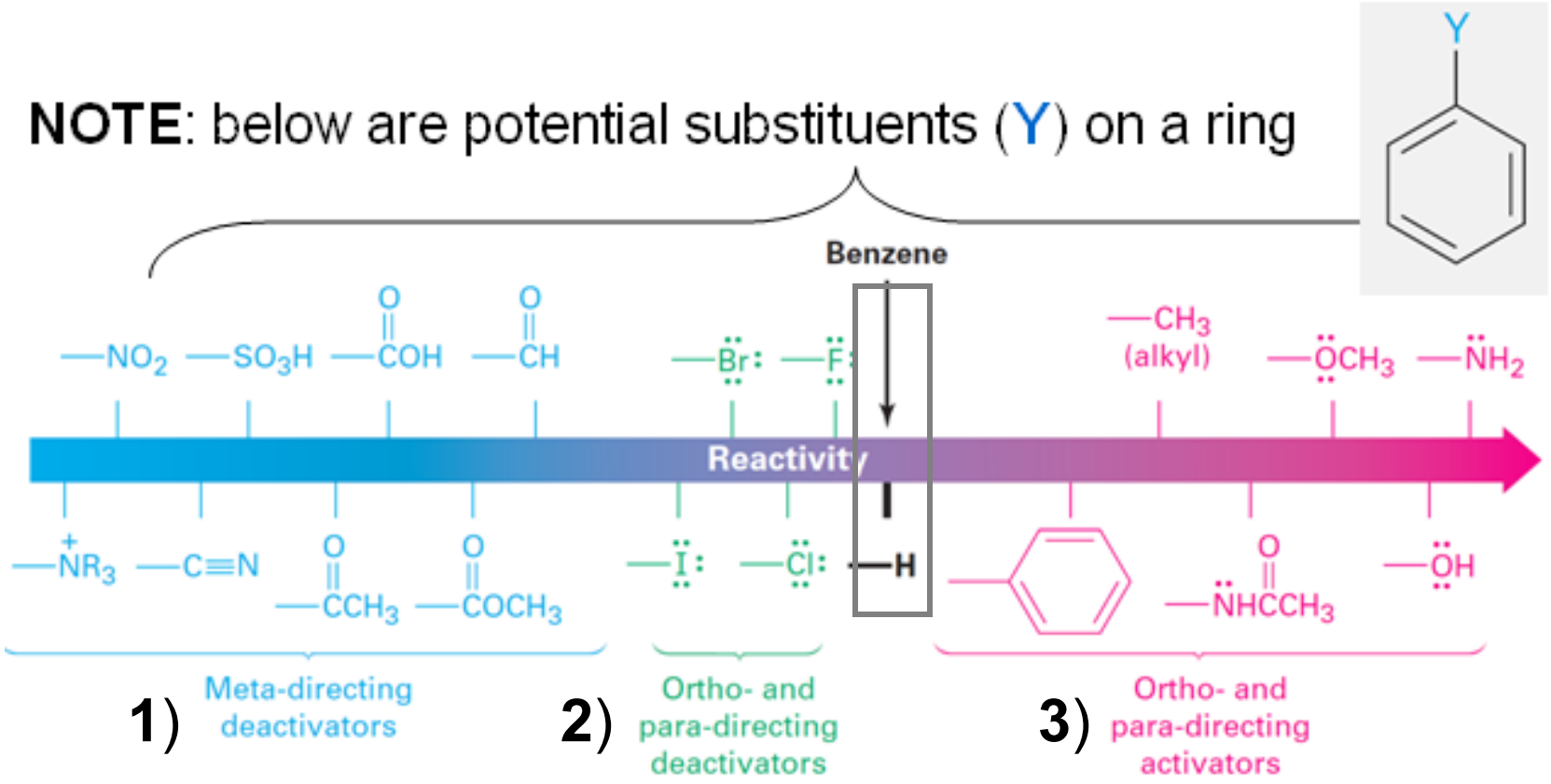
The chemical ***nature*** of the 1st substituent (Y, e.g. -CHO, $-CH_3$, -OH…) on benzene ring determines the position of **2nd** *substituent…*

e.g. **1**) if Y = -CHO (structure above), this directs NO_2 *mainly to* ***meta*** positions (72%)

2) If Y = -OH, this directs NO_2 *to* the ***ortho*** (50%) & ***para*** (50%) positions

Handout 2b

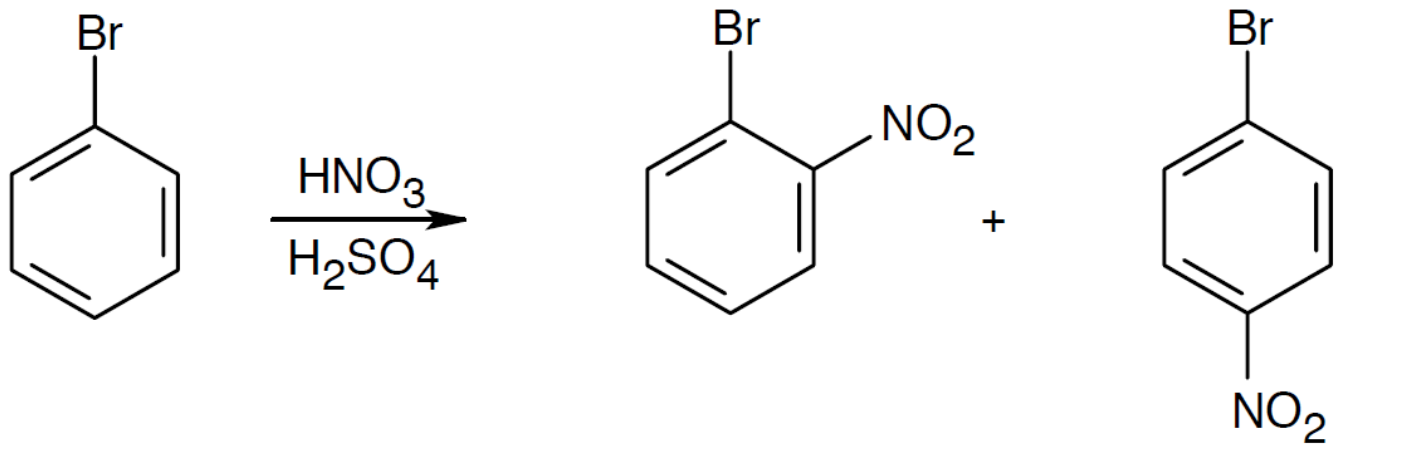
Substituents can be classified into three groups (please ***annotate*** below)



NOTES: 1) There are ***Meta***-directing de-activators.
2) Halogens are weakly *-ortho* & *-para* directing **de**-activators
3) *Ortho and-para* directing activators

Confirming Your Knowledge

Predict the major product(s) in the nitration (NO_3) of bromobenzene?



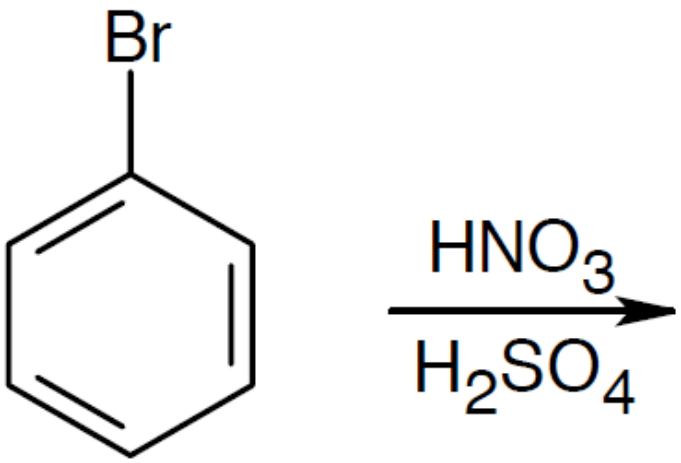
(~43% yield) **(~56% yield)**

Hint: see Handout 2a, Table 16.1

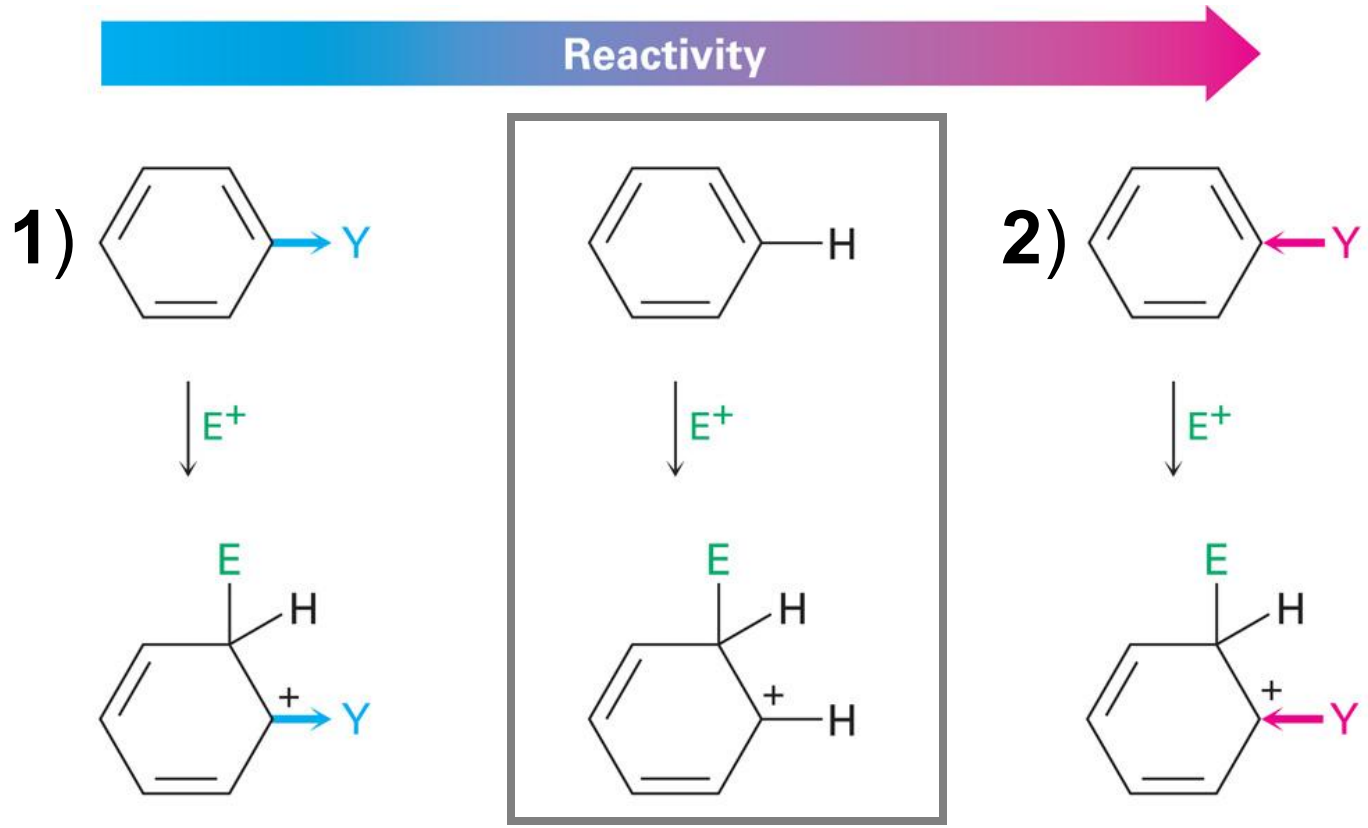
Now lets talk about:

de-*activating* or ***activating*** effects

that influence the reaction on rings in more detail…



What makes a group either: 1) de-*activating* *or* 2) ***activating***?



If substituent-
Y withdraws electrons;
carbocation intermediate
is less stable, and ring
is less reactive.

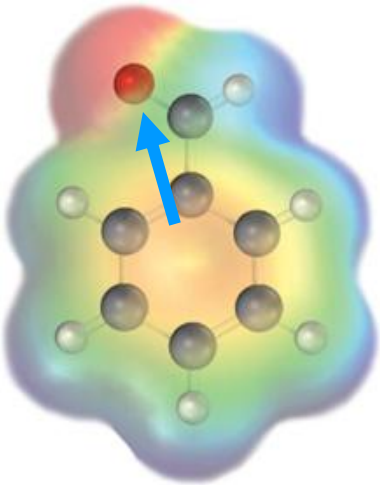
benzene = standard.
(neutral)

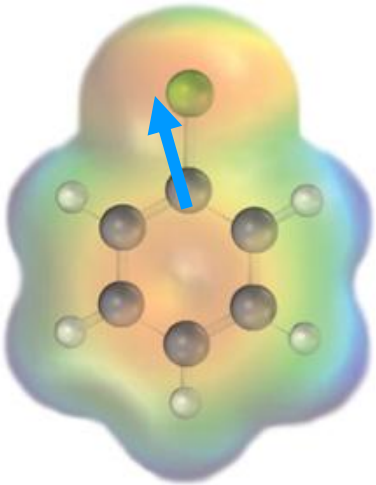
If substituent-
Y donates electrons;
carbocation intermediate
is more stable, and ring
is more reactive.

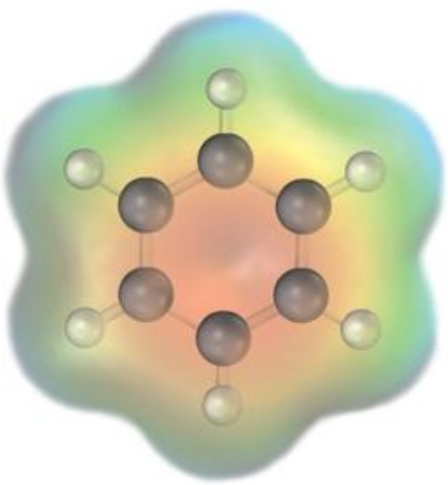
Note: compare the *electrostatic* potential Map below

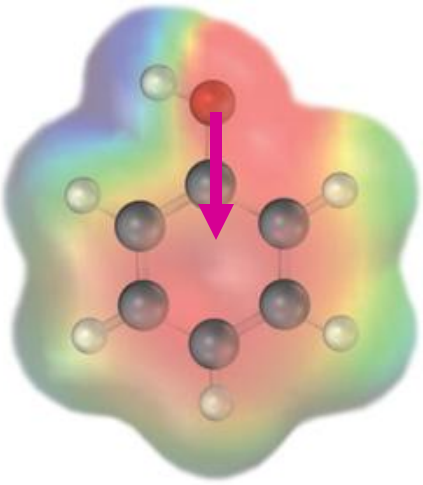
Ring is more POSITIVE (yellow-green) when *e- withdrawing groups* are present: **A** & **B**

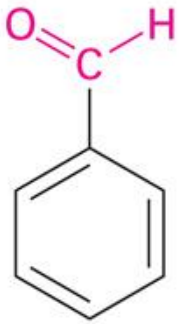
Ring is more negative (red) when *e- donating group* is present **C**:

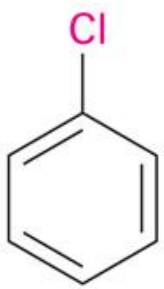




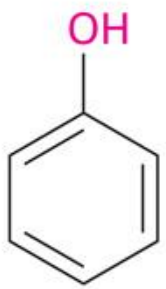








neutral = standard



A) Benzaldehyde **B)** Chlorobenzene Benzene **C)** Phenol

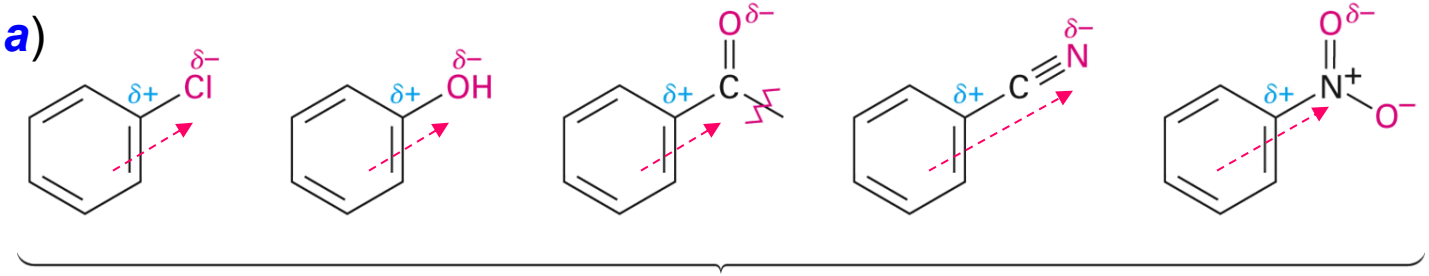
All influenced by…. →

RECALL
Chap 2.1

*1) **Inductive** effects:*

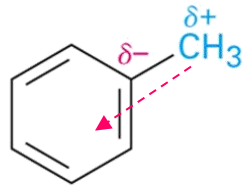
***a**) withdrawal* or ***b**) donation* of e- thru a σ bond
(based on ***electronegativity***)

a)



Inductive electron withdrawal

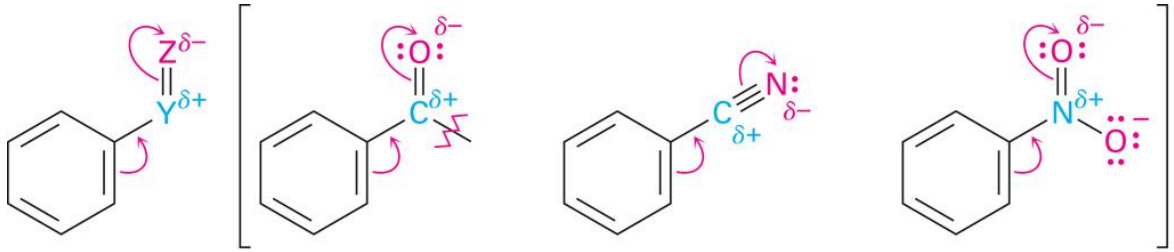
b)



Inductive electron donation

*2) **Resonance** effects:*

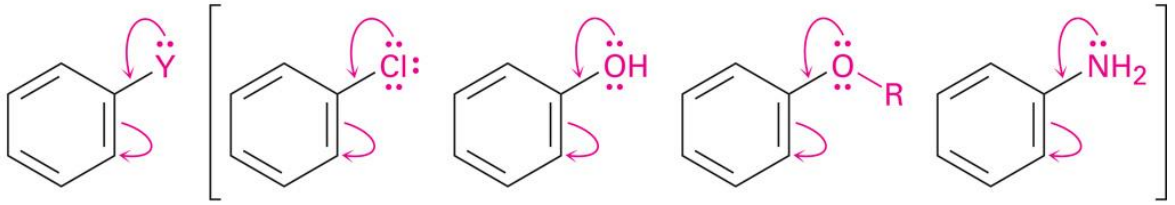
a) withdrawal



Resonance electron-withdrawing groups

or

b) donation



Resonance electron-donating groups

of **e-** thru a π bond due to overlap
of a *p* orbital on substituent *(*Z or Y*) w/ p*-orbital on ring

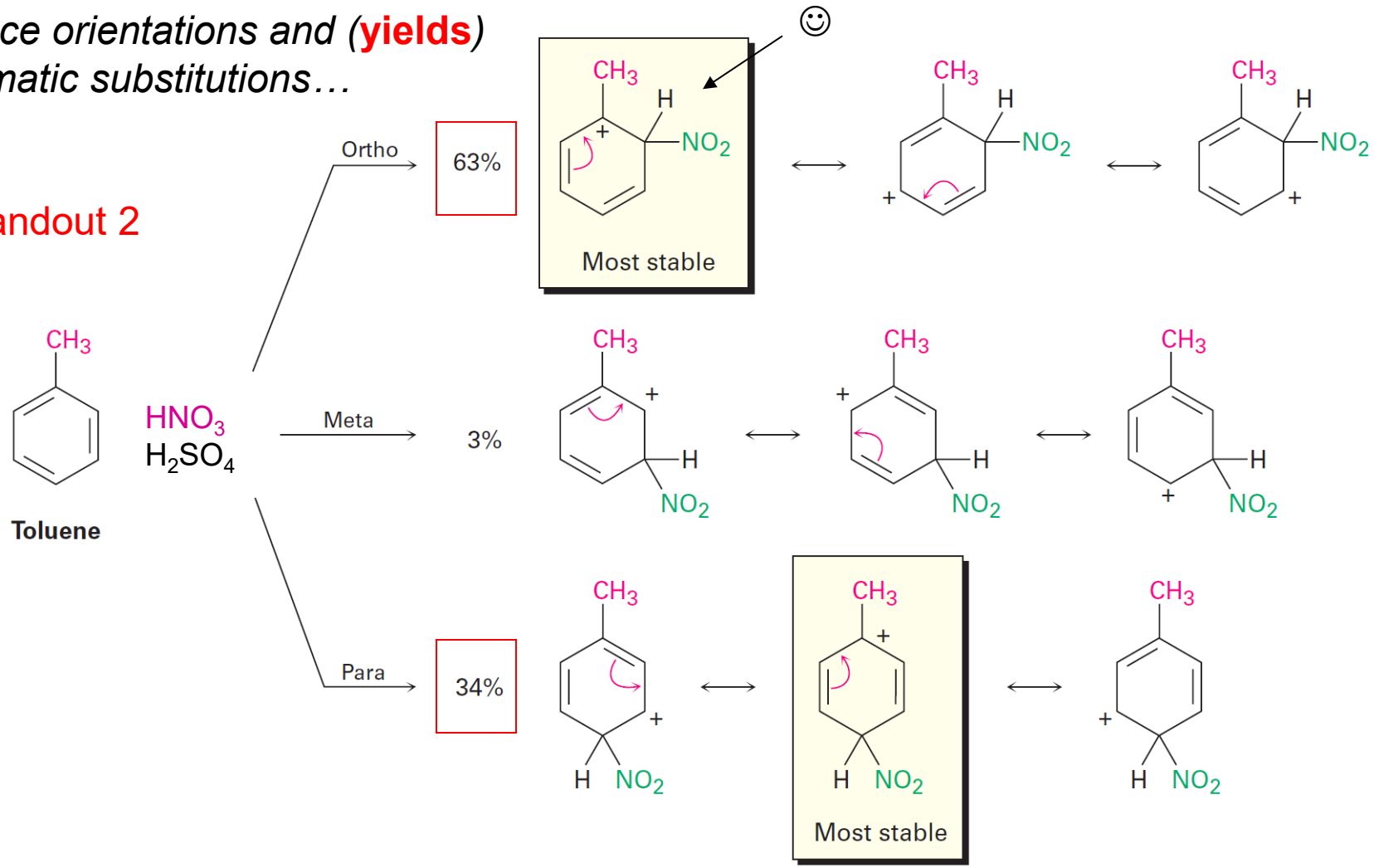
So what’s happening and why?

Alkyl groups *Ortho*- and *para*-Directing activators:

Figure 16-13

Inductive *and* ***resonance*** *effects influence orientations and (***yields***) of aromatic substitutions…*

e.g.
see Handout 2

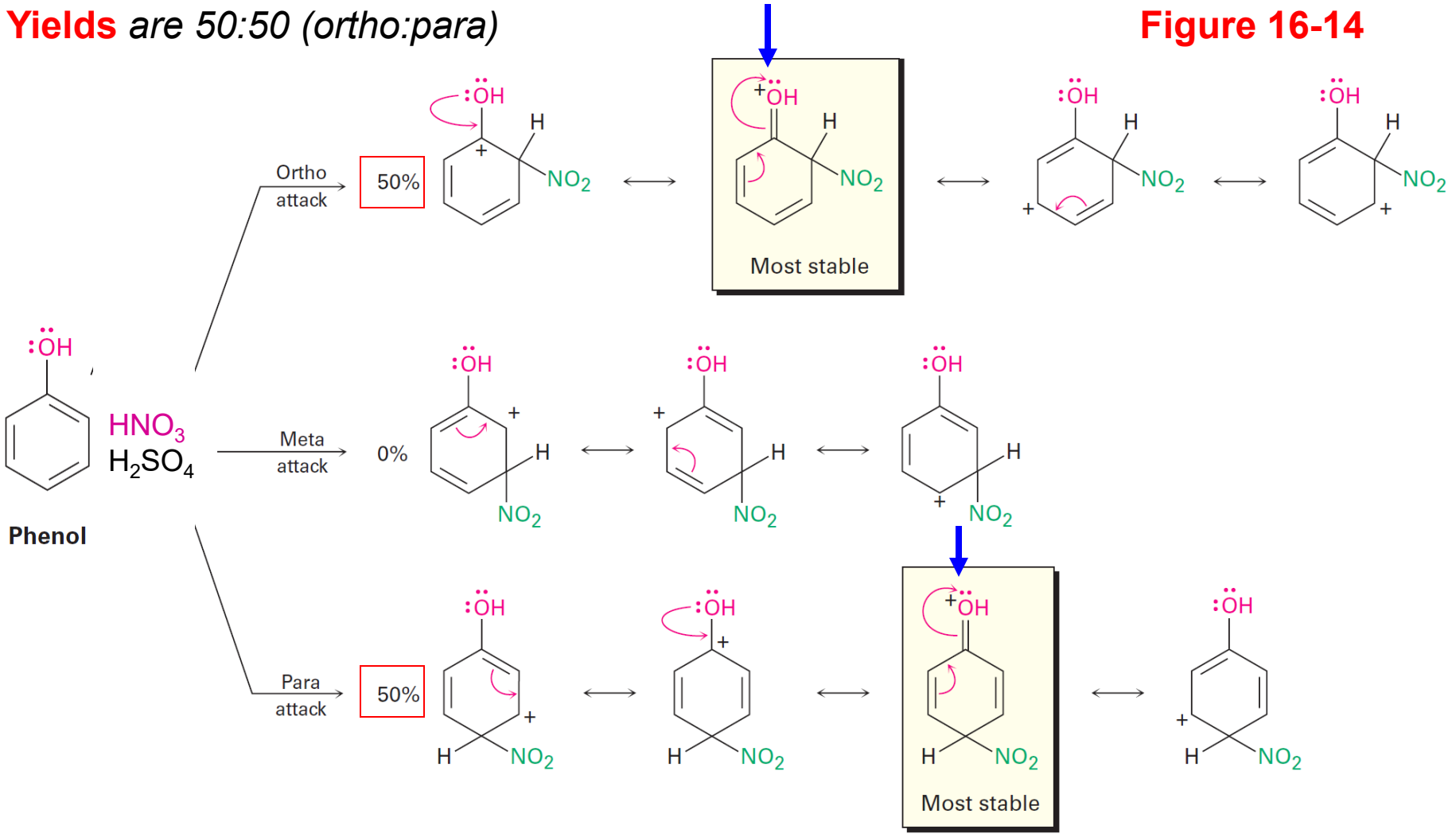


NOTES: *Ortho* and *Para* carbocation⁺ compounds are more stable than *Meta* b/c their + charge is on **3°** (boxed) vs 2° carbon (all the rest)

OH & NH_2 groups *Ortho*- and *para*-Directing activators:

Yields *are 50:50 (ortho:para)*

Figure 16-14

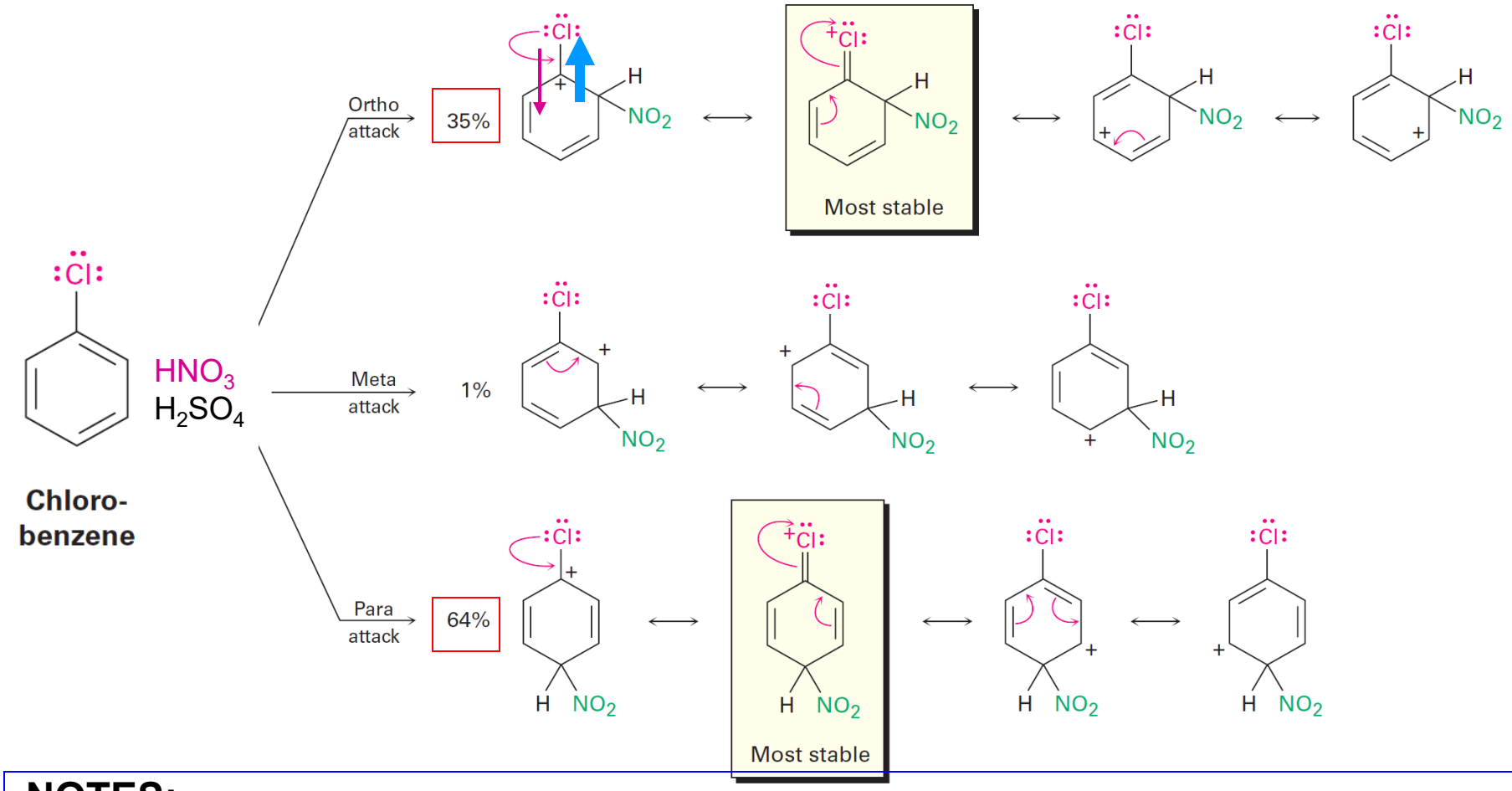


NOTES: *Ortho* and *para* carbocation$^+$ compounds are more stable b/c they have more resonance forms (4) vs the *meta* form (3) shown above.
The most favorable form (boxed) has + charge stabilized on lone pair of :OH

Halogens

Ortho- and *para*-Directing De-activators:

Figure 16-15



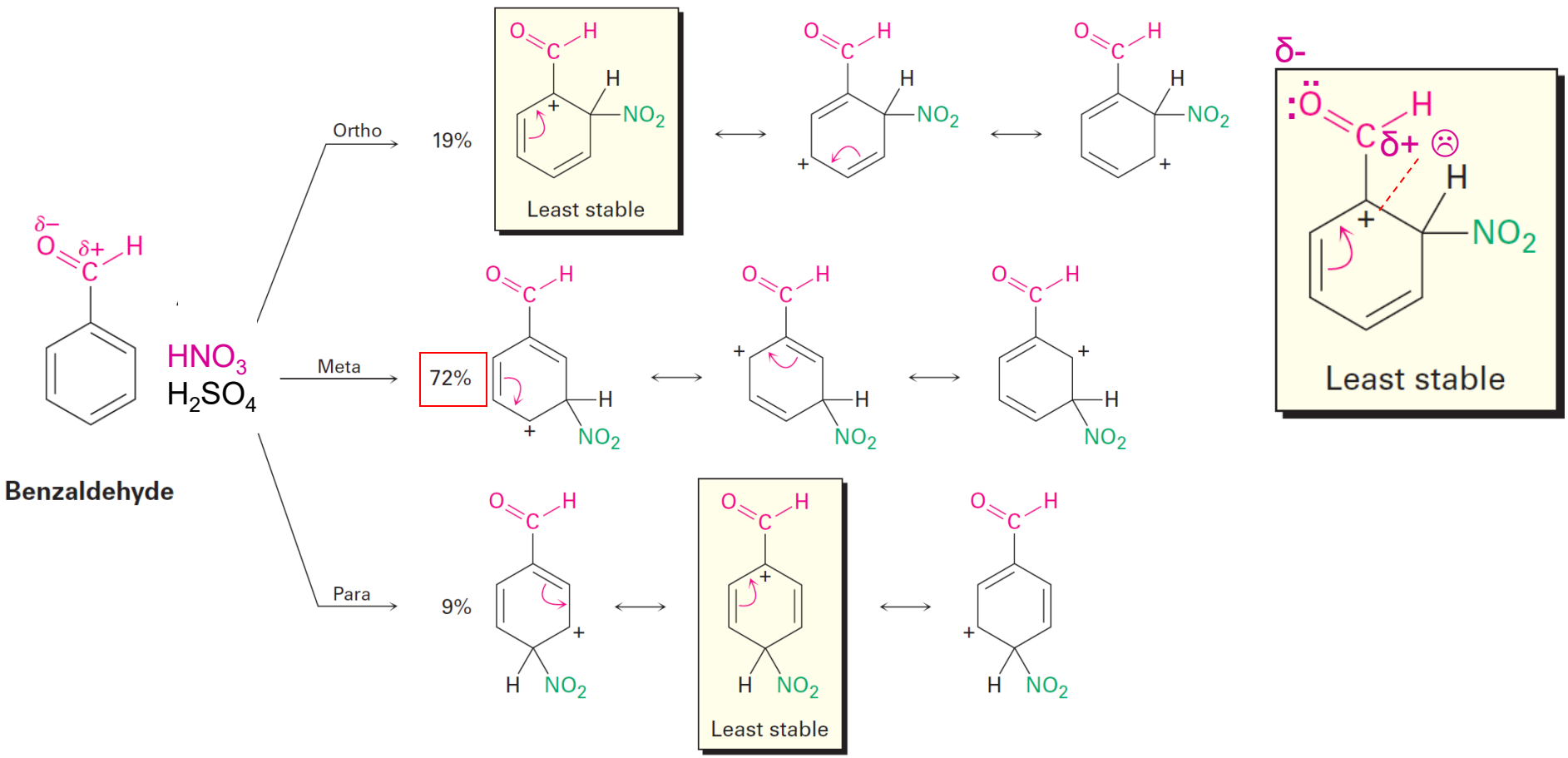
NOTES:

Halogens are De-**activators** b/c their strong **a**) electron ***withdrawing inductive effects*** outweighs their weaker **b**) ***electron donating resonance*** effects

The most favorable carbocation(s)$^+$ (boxed) have + charge stabilized on :Cl lone pair

Meta-Directing De-activators:

Figure 16-16



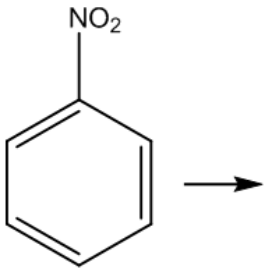
NOTES:

Here the *Meta* carbocations have 3 favorable resonance forms, while the *ortho* and *para* carbocations have two. The least stable resonance forms (boxed) are *unfavorable* (---) b/c they place a **+** charge on the carbon next to a positively polarized carbon (δ+).

Chem 3900
Lecture 4
Worksheet 3

Take Home Challenge (THC) Question - HW (5 min.)

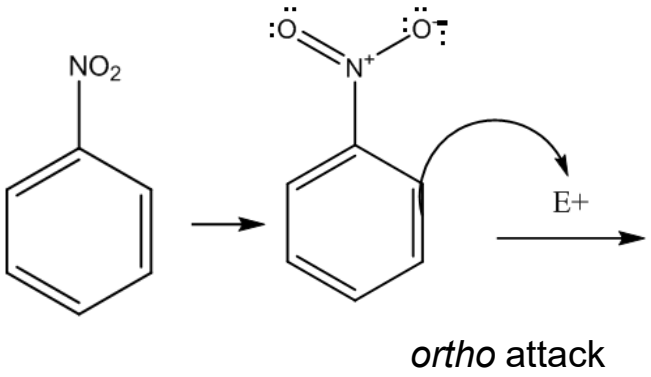
Draw the resonance structure(s) for the intermediate(s) from the reaction of a electrophile (E^+) at the: *ortho position (below)* of ***nitrobenzene***, and circle the least stable.



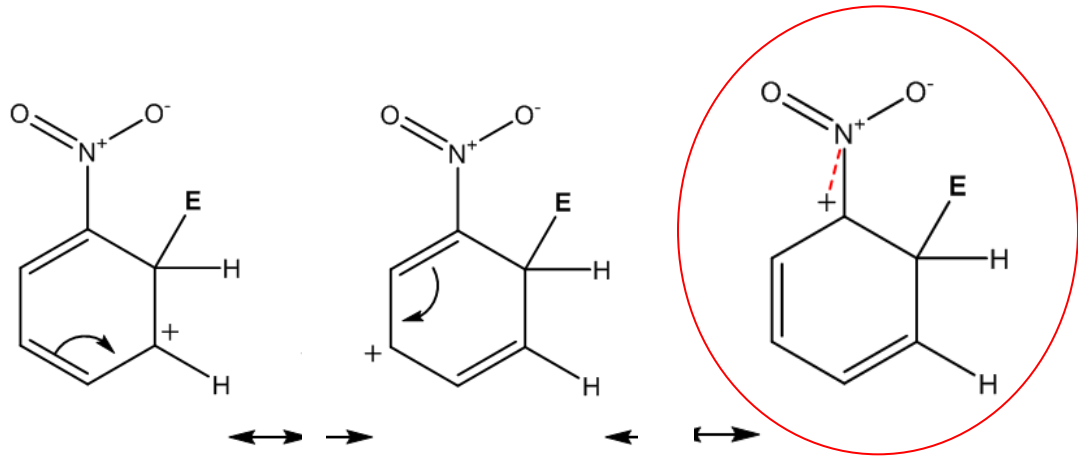
Note: see prev. slides Handout 2a
solution available @ Faculty office hours or contact our TAs for assistance –

Take Home Challenge (THC) Question - HW

Draw the resonance structure(s) for the intermediate(s) from the reaction of a electrophile (E^+) at the: *ortho position (below)* of ***nitrobenzene***, and circle the least stable.



ortho attack



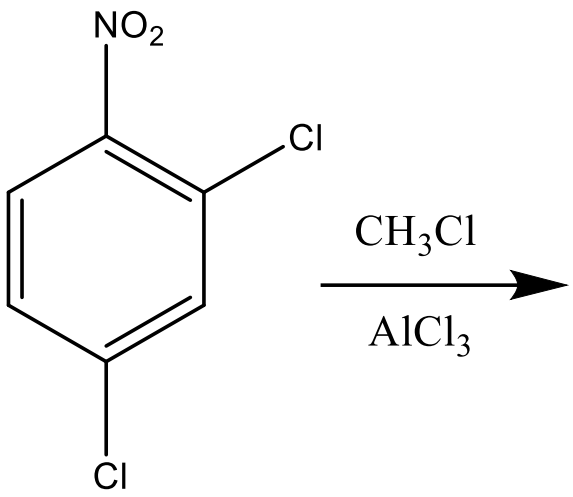
Hint:

Challenge Question

What is the major monoalkylation product(s) you would expect to obtain from the rxn of chloromethane (CH_3Cl), $AlCl_3$ and 2,4, dichloronitrobenzene?

Hint:
Draw the structure of
2,4, dichloronitrobenzene

SKIP



NO_2
meta
directing de-activators

Cl (X)
ortho, para -
directing de-activators
(weak activators)

Hint 2: see Handout 2a (Table 16.1)

Outline

Background

Electrophilic aromatic substitution reactions: Bromination

Other aromatic substitutions

Alkylation and acylation of aromatic rings:

  The Friedel-Crafts reaction

Substituent effects in electrophilic substitutions

Trisubstituted benzenes: Additivity of effects

Nucleophilic aromatic substitution

Benzyne

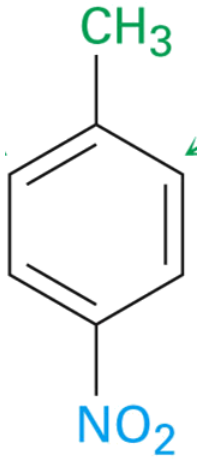
Oxidation of aromatic compounds

Reduction of aromatic compounds

Synthesis of polysubstituted benzenes

Tri-***substituted*** Benzenes: Additivity of Effects

Start w/ **di-*substituted*** rings



Guided by same ***inductive*** and ***resonance*** effects as ***mono-substituted*** rings (previous slides)

However NOW we must consider the additive effects of **TWO** different groups…

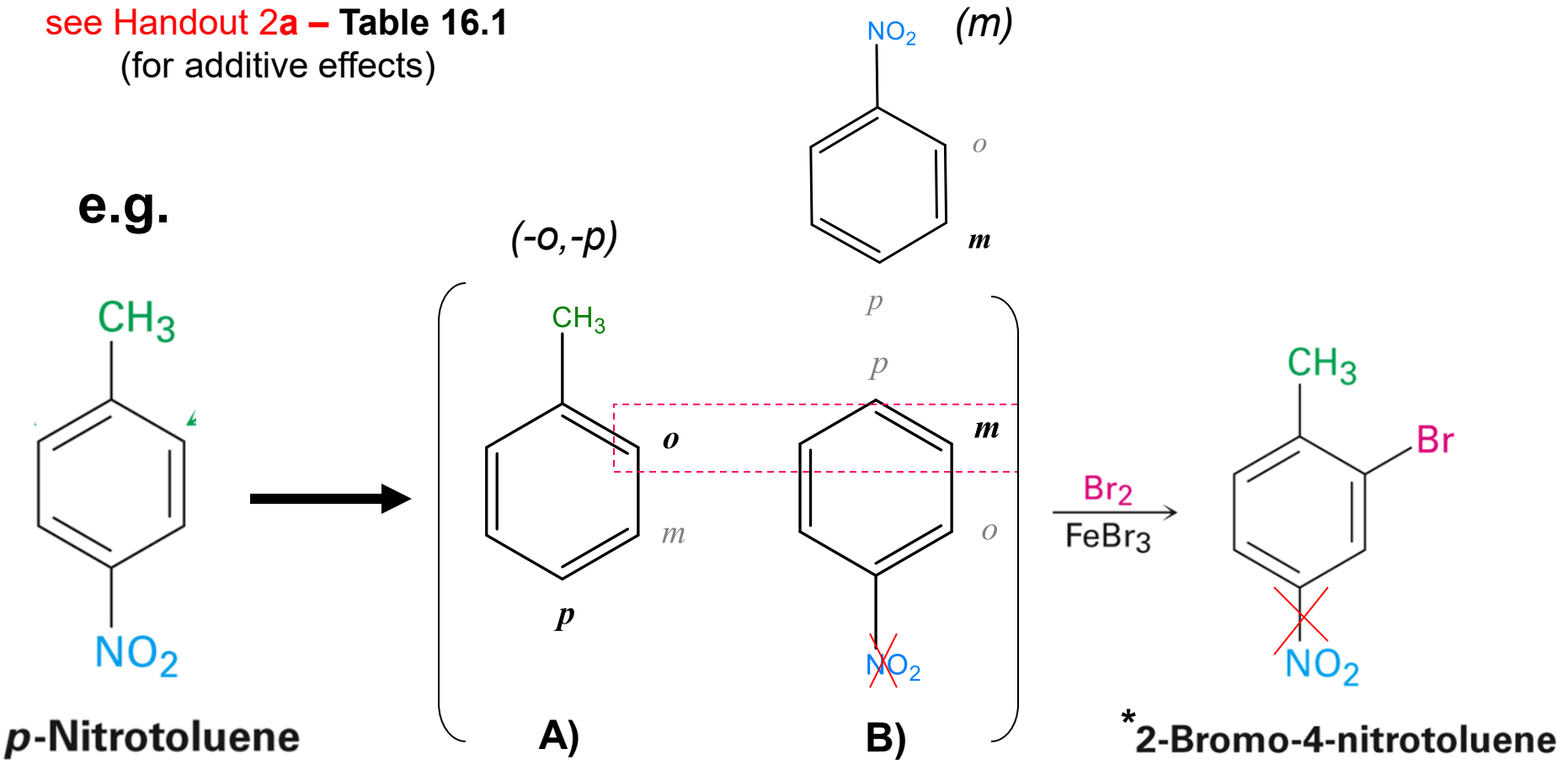
Three Rules Apply…

Tri-***substituted*** Benzenes

Rule 1 If the directing effects of two groups ***reinforce*** each other – it's somewhat *straight forward*

see Handout 2**a** – **Table 16.1**
(for additive effects)

e.g.



***p*-Nitrotoluene**

***2-Bromo-4-nitrotoluene**

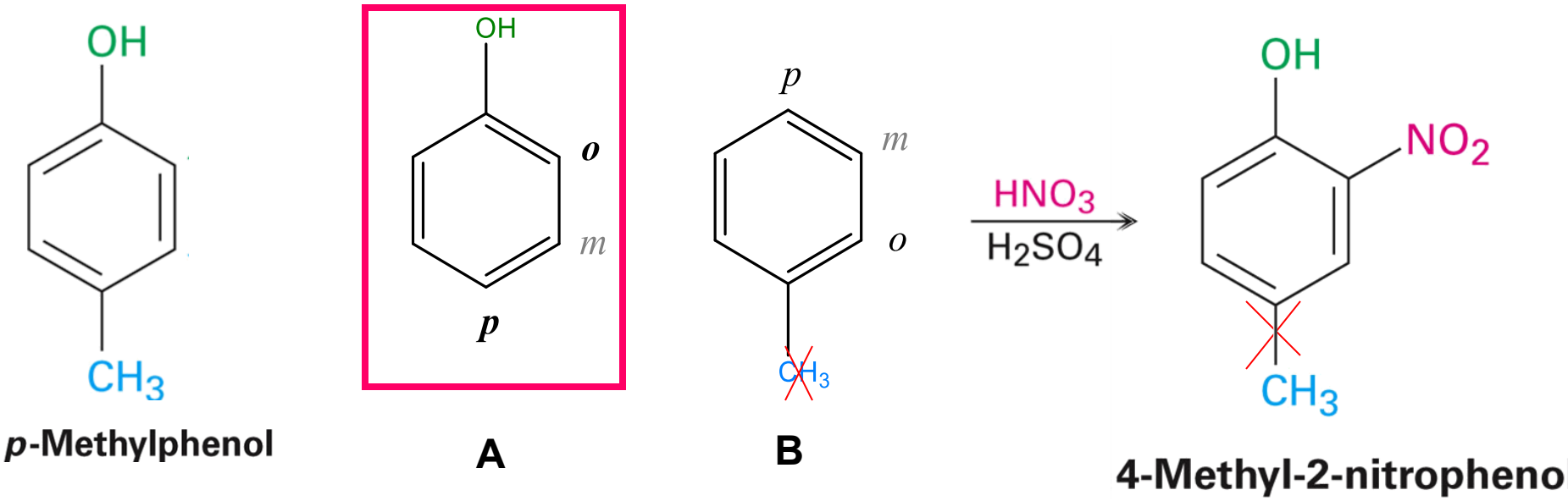
***Note:** **1)** **Br** can't add (✗) at *para*-position in **A** b/c **NO_2** is already there**!**
2) **Br** can add at *ortho*-position in **A** b/c there is no subtituent there, however not favored…
3) **Br** adds at *meta*-position in **B** b/c it's favored there (see Table 16.1)
2-3 and compliment each other ☺

Tri-***substituted*** Benzenes

Rule 2 If the directing effects of two groups ***oppose*** each other –
The more ***Reactive*** activating group has the ***dominant*** influence.

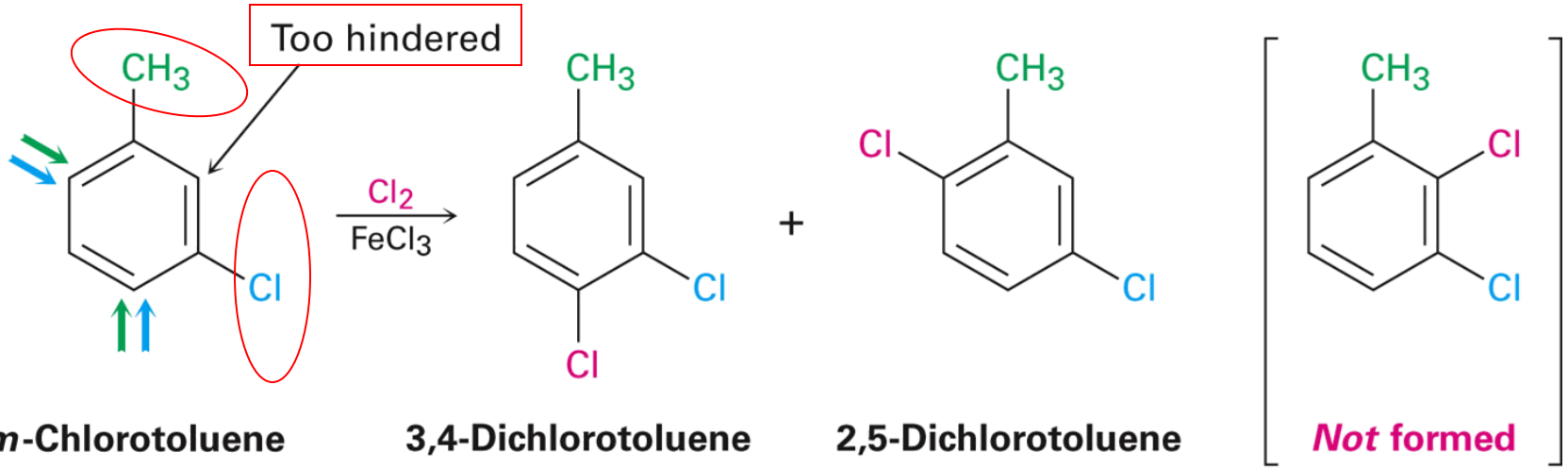
see Handout 2**b**

see Handout 2**a** **– Table 16.1**
(for additive effects)

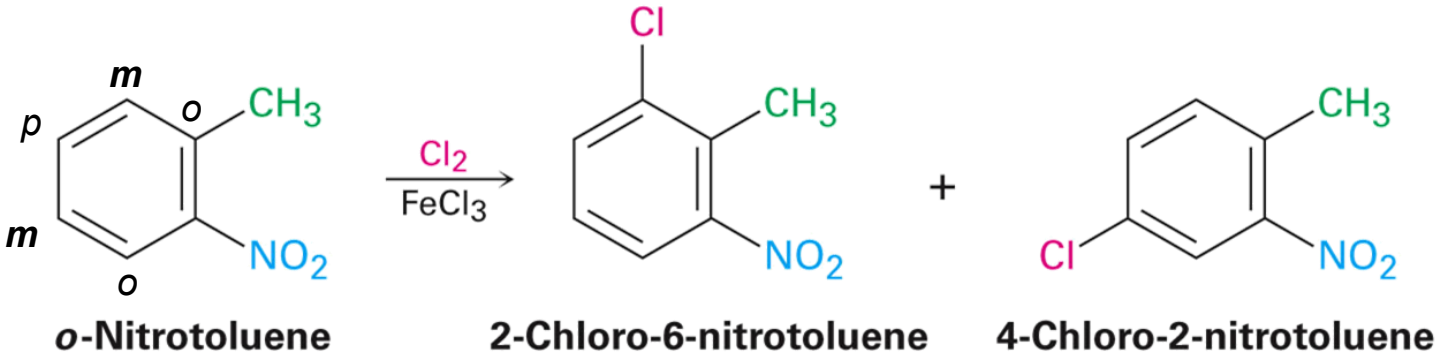


***Note:** 1) NO_2 can't add (X) at *para*-position in **A** b/c CH_3 is already there**!**
2) NO_2 can add at *ortho*-position in **A** b/c there is no subtituent there.
3) NO_2 could have added at the *ortho*-position in **B** but doesn't b/c A is more ***Reactive*** group
2-3 compete with each other

Rule 3 Substitution rarely occurs between two groups in ***meta*** di-substituted compounds b/c the site is Too hindered.

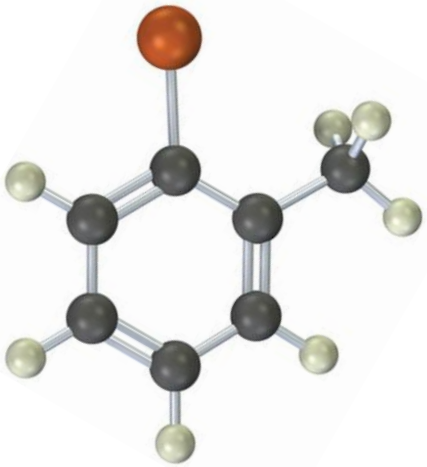


But:



Confirming Your Knowledge

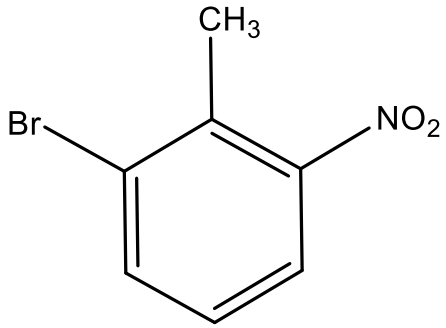
What is the major product(s) from the reaction of the following substances with:

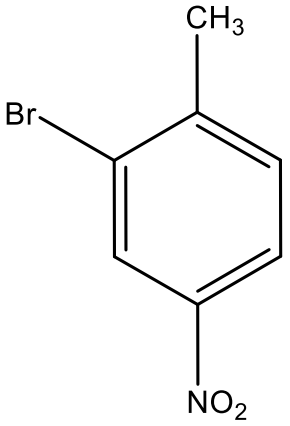


o-Bromotoluene

orange is **Br**

1) HNO_3
2) H_2SO_4





Hint: Methyl (-CH_3) group has directing priority over Br

HW 16

1, 3, 7, 8, 9, 13, 14, 49 (skip c, d, g)