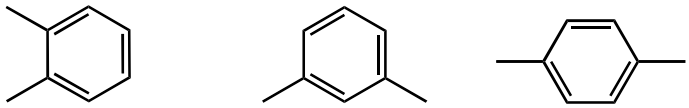
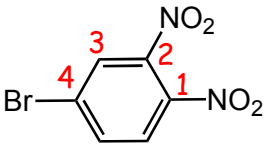
1 Notation Structures and Nomenclature

Disubstituted benzene notation:



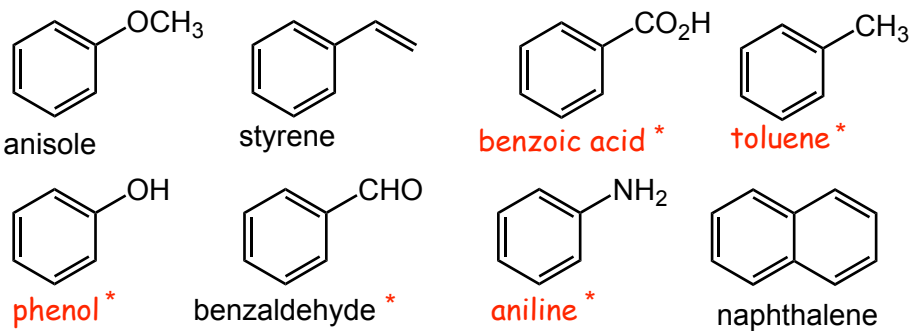
1,2 = ortho-xylene 1,3 = meta-xylene 1,4 = para-xylene

• The terms *ortho-*, *meta-* and *para-* are very useful for describing the substitution patterns on substituted benzenes, but they are not a part of IUPAC nomenclature.
IUPAC: Uses the numbering system.
• Number round the ring to give substituents get the lowest numbers possible as usual.
• All other things equal (and **only** when all other things are equal), then do it alphabetically.

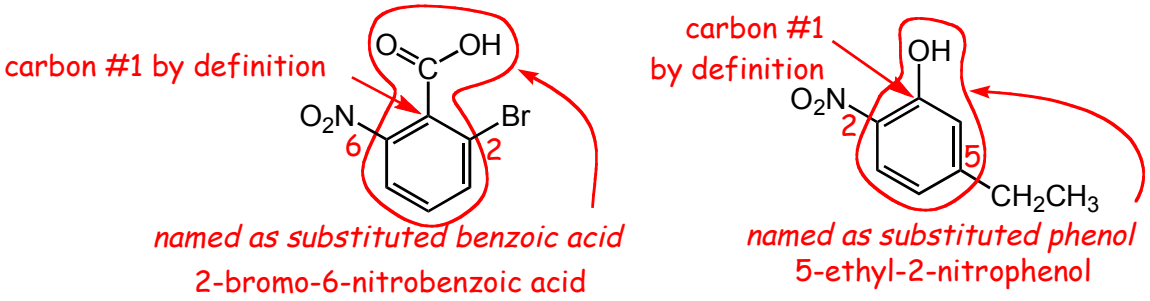


4-Bromo-1,2-dinitrobenzene

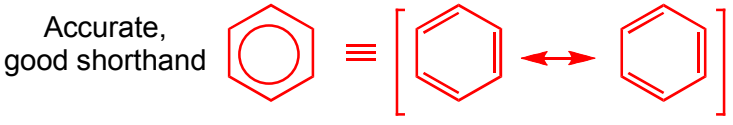
Some aromatic compounds have their own IUPAC names:



* You need to be able to name substituted versions of those indicated with the * symbol for test purposes.



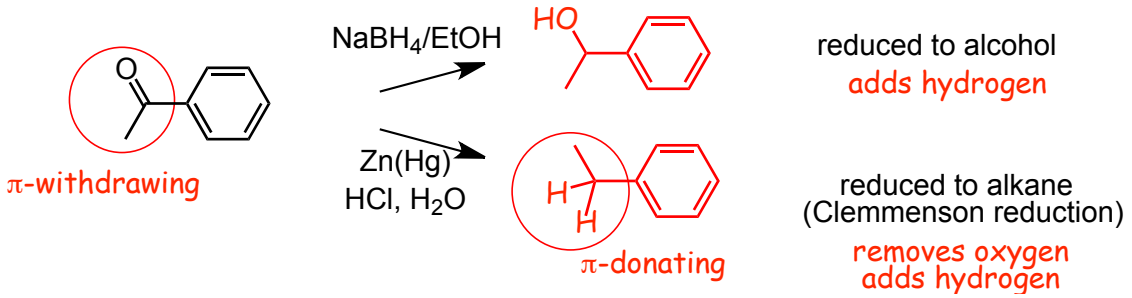
• Drawing structures of benzenes:



2 Some Reactions of Benzenes Around the Periphery of the Ring

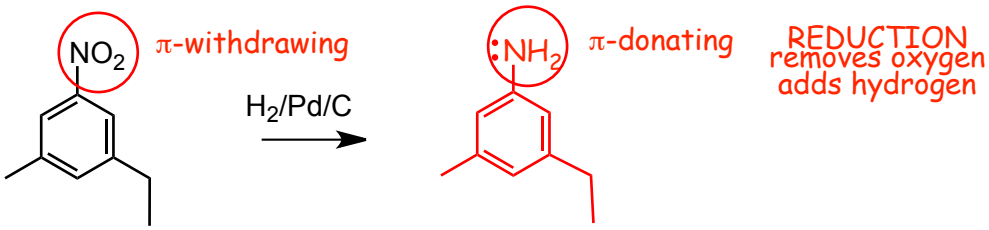
2.1 Reduction : Addition of Hydrogen

Side Chain Reduction



• The first reduction we have already seen.
• The second reduction, a Clemmensen reduction, we have **not seen**. It reduces an aldehyde/ketone all the way to an alkane. We will return to the mechanism later in the semester, for now this is something you just "need to know", sorry!
• The rest of the molecule must be capable of withstanding aqueous acid. If not, there is another reaction we can use, again, see later.

Reduction of nitro to amine

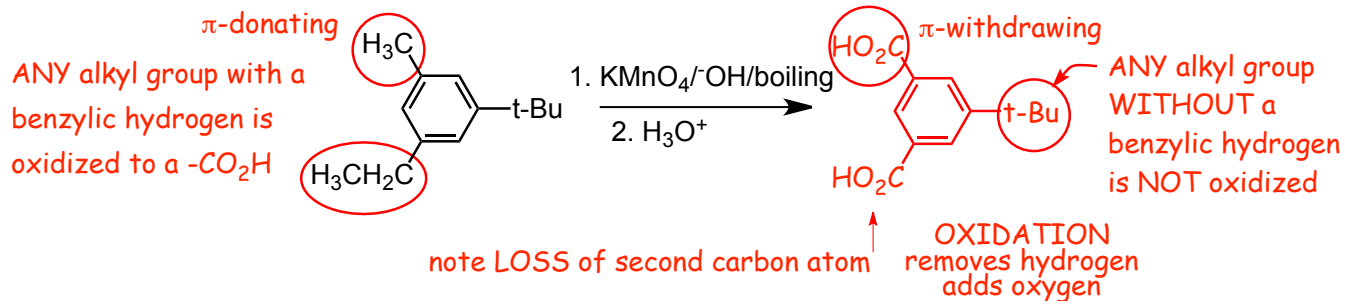


• Catalytic hydrogenation (seen already) reduces a nitro functionality into an amine, which converts a withdrawing group into a donating group. This is going to turn out to be **something important that you need to know!**
• You may see **other** reducing agents used to do this reduction elsewhere (examples are Fe/HCl or Sn/HCl), but we only use H_2/Pd/C in this course because we have seen it before and to minimize the number of reducing agents we need to learn.
• The Clemmensen reduction reduces nitro groups to amines very slowly, therefore we can usually reduce an aromatic aldehyde/ketone using the Clemmensen reduction without also reducing a nitro group that may also be on the benzene ring.

2.2 Side-Chain Oxidation

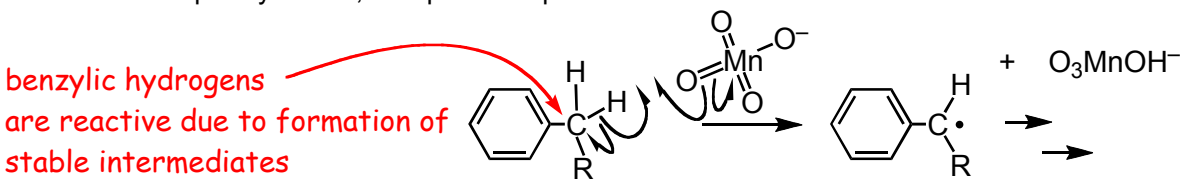
• This is oxidation of an alkyl group connected to a benzene ring using potassium permanganate as the reagent (chromic acid reagents can also be used).
• This reaction oxidizes any 1°, 2°, allyl chain to a benzoate ($-CO_2^-$), which is then converted into a carboxylic acid using H_3O^+ in a second acid workup step.
• Interestingly, 3° carbons connected to a benzene ring are **not** oxidized, a benzylic hydrogen is needed.

Example



• Note: all carbon atoms that are part of the alkyl group being oxidized are **lost**, except the single carbon that is attached to the benzene ring, which becomes the carbon of the carboxylic acid.

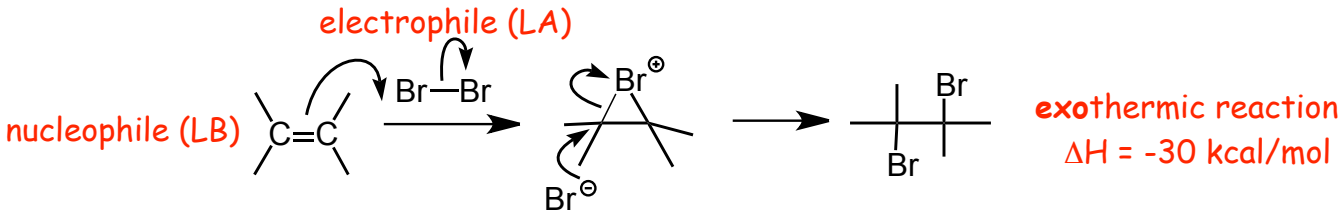
Mechanism - isn't completely known, except first step:



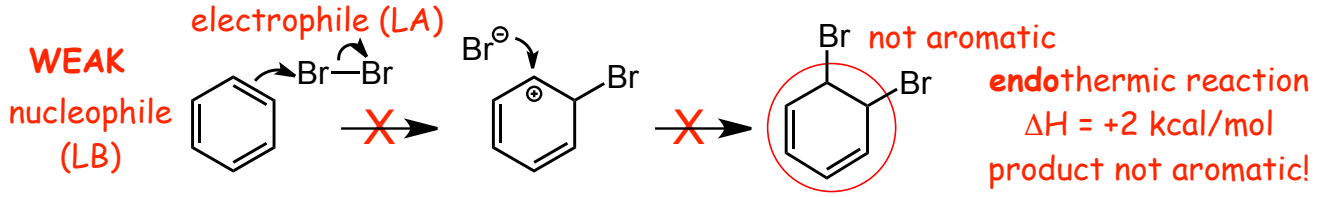
• H-atom abstraction from the carbon attached to the ring (benzylic C-H), explains why 3° alkyl groups are **not** oxidized, they have no such C-H bond.

3 Electrophilic Aromatic Substitution : Many Reactions, One Mechanisms

Recall:

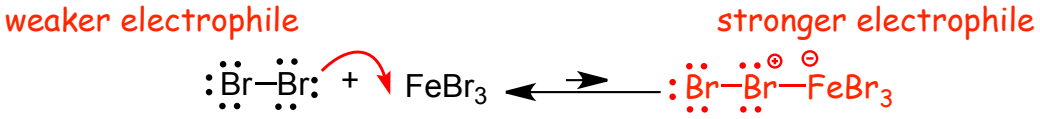


However:9

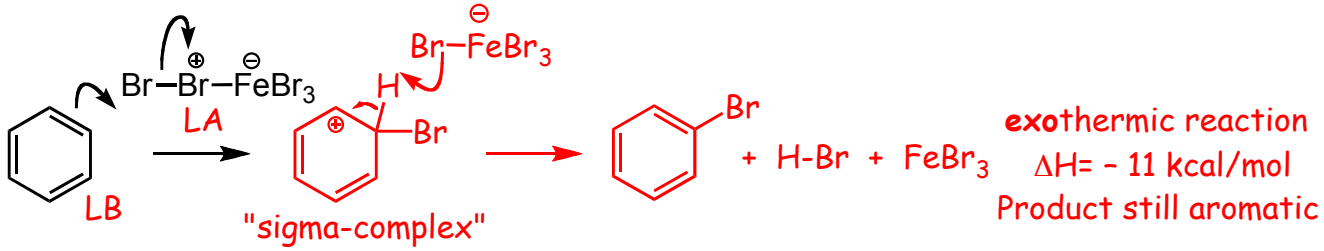


• The first step in the mechanism above is slow, it doesn't really "go" because benzene is a relatively poor nucleophile/Lewis base and this step is particularly endothermic because it breaks aromaticity.
• We need a stronger electrophile to react with the poor benzene nucleophile.

Solution

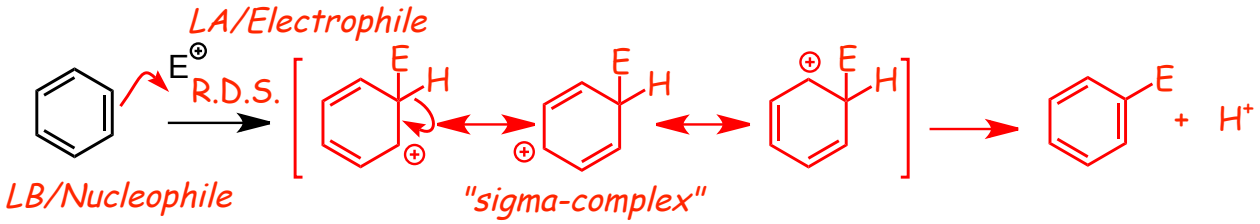


• Ferric bromide ($FeBr_3$) is a Lewis acid catalyst, converts Br_2 into a stronger electrophile:

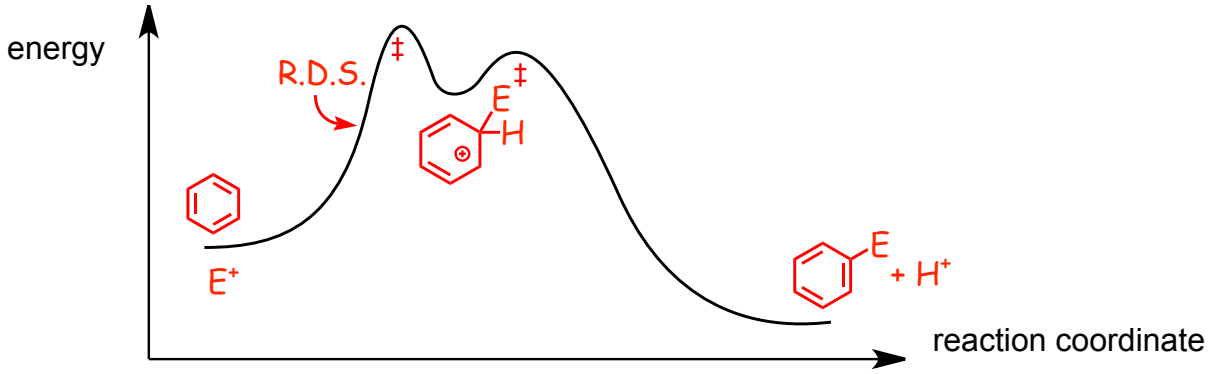


• The reaction is now faster reaction, because we have a **stronger electrophile.**
• The reaction is overall **substitution** instead of addition.
• The Lewis acid is regenerated, it is a true catalyst.

The General Mechanism for Electrophilic Aromatic Substitution:

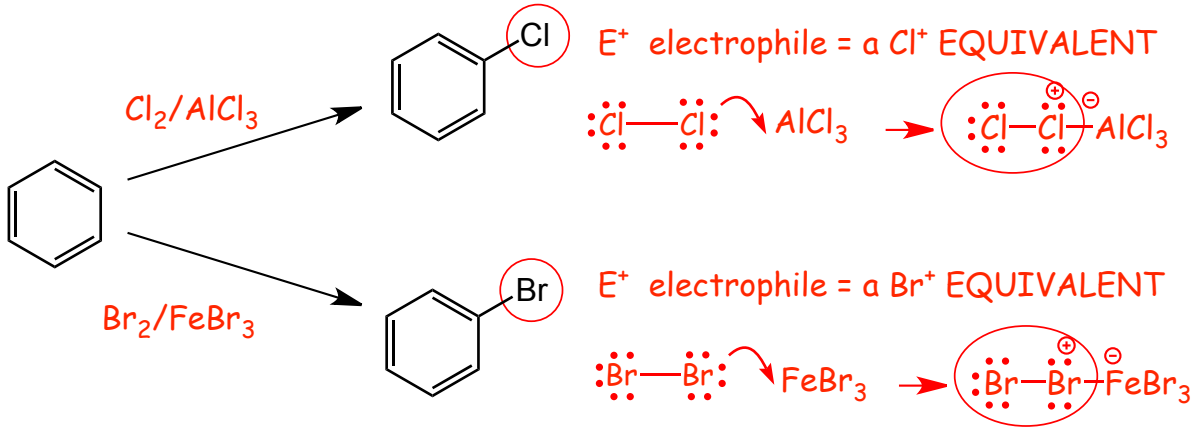


• The **rate determining step** (R.D.S.) is the reaction between the benzene and the electrophile, **the benzene is the Lewis Base/Nucleophile in the R.D.S.**
• As we will see, there are many reactions, depending upon the particular electrophile, they all use the same mechanism.



3.1 Halogenation of Benzene

• Substitution of a halogen for H on a benzene ring via electrophilic aromatic substitution:



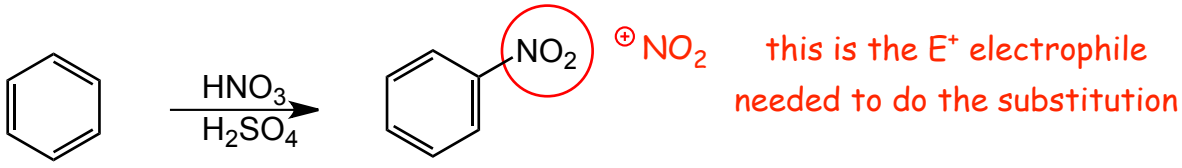
Lewis acid catalysts you can use almost interchangeably:

$FeBr_3$ $FeCl_3$ $AlBr_3$ $AlCl_3$

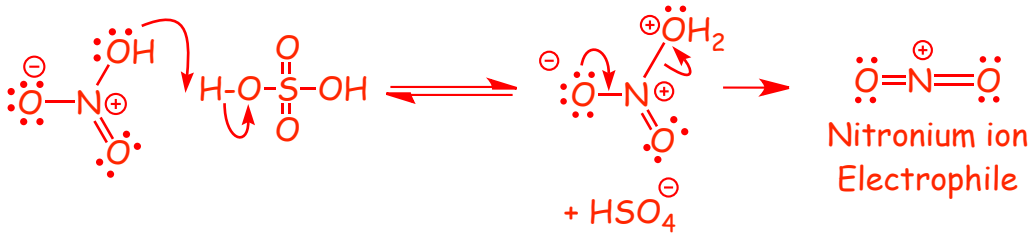
• The electrophile in the reaction is generated using a Lewis acid catalyst.

3.2 Nitration of Benzene

• Substitution of a $-NO_2$ group for H on a benzene ring via electrophilic aromatic substitution:



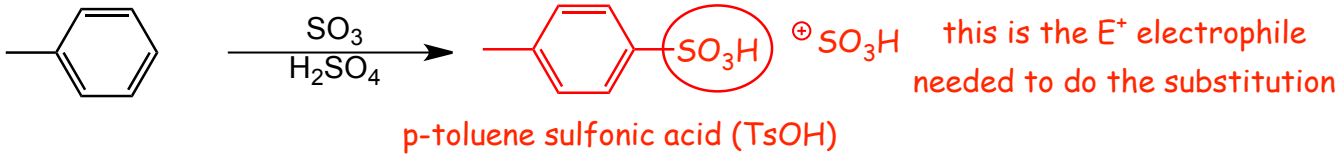
• Where does the $^{+}NO_2$ electrophile come from?



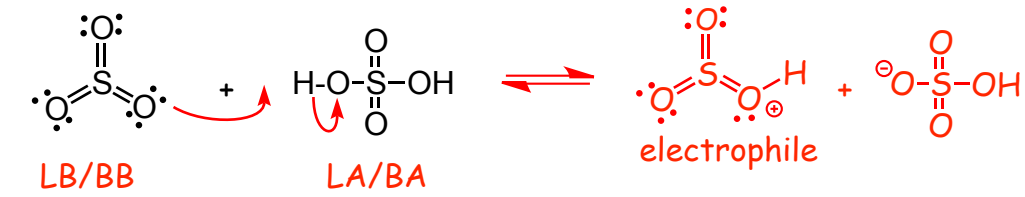
• You may not need to know exactly how the $^{+}NO_2$ electrophile is formed, but you should know the mechanism of the subsequent electrophilic aromatic substitution reaction.

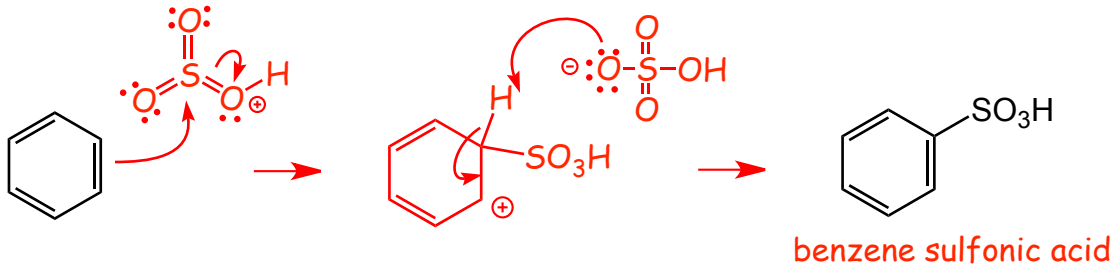
3.3 Sulfonation of Benzene

• Substitution of a -SO_3H group for H on a benzene ring via electrophilic aromatic substitution:



• Where does the $^{+}SO_3H$ electrophile come from?

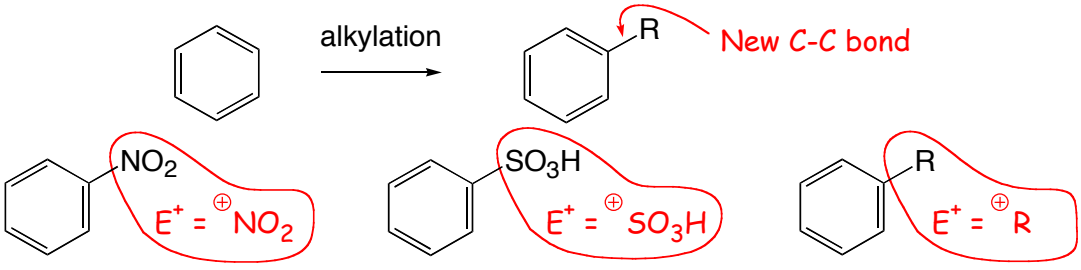




• Dissolve SO_3 (sulfur trioxide, gas) in concentrated H_2SO_4, makes fuming sulfuric acid.
• A Lewis/Brønsted acid/base reaction protonates the sulfur trioxide, this is where the E+ electrophile comes from for this reaction.

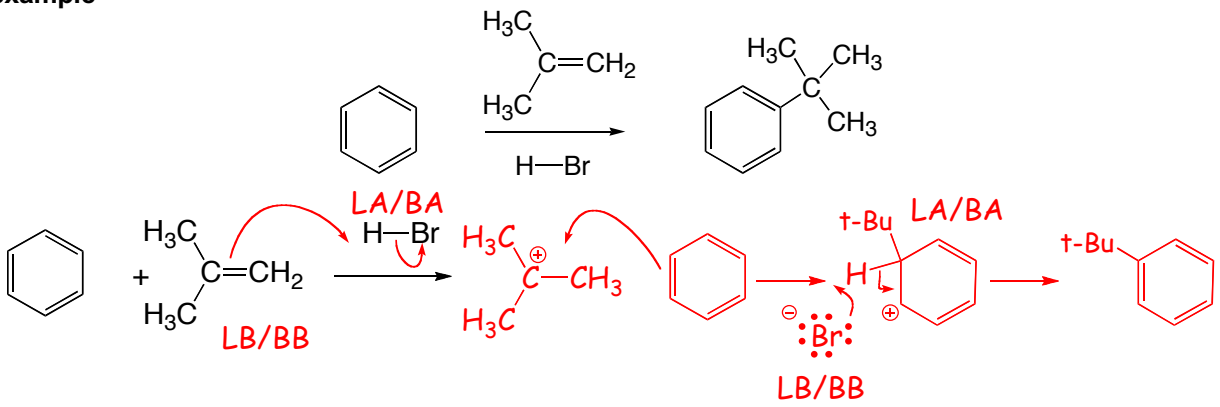
3.4 Alkylation and Acylation of Benzene

• Carbon-carbon bond forming reactions, important!



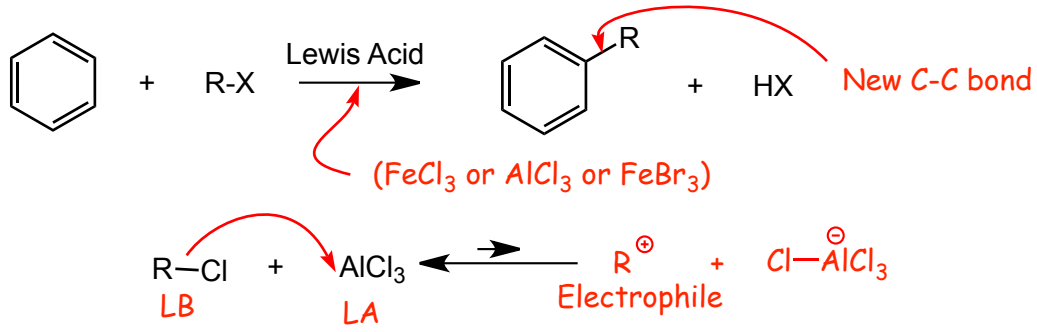
• So, all we need is an alkyl cation, i.e. a carbocation, and we have seen lots of ways to make those!

For example

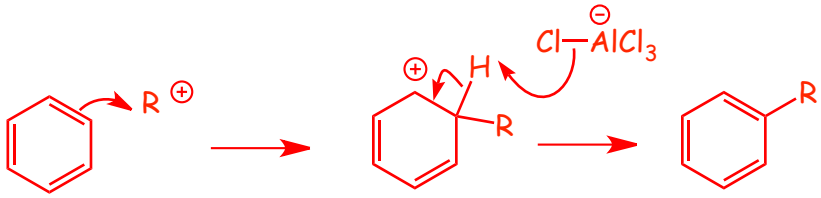


• Any carbocation should react with benzene to do substitution, carbocations are very strong electrophiles.
• However, the standard conditions to make carbocations are not always convenient (strong acid, silver salts, heating in polar protic solvents etc.), and a better Lewis catalytic method has been developed.

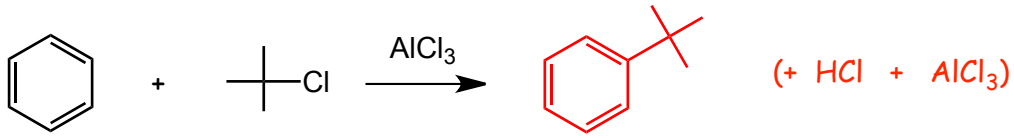
Friedel-Crafts Alkylation:



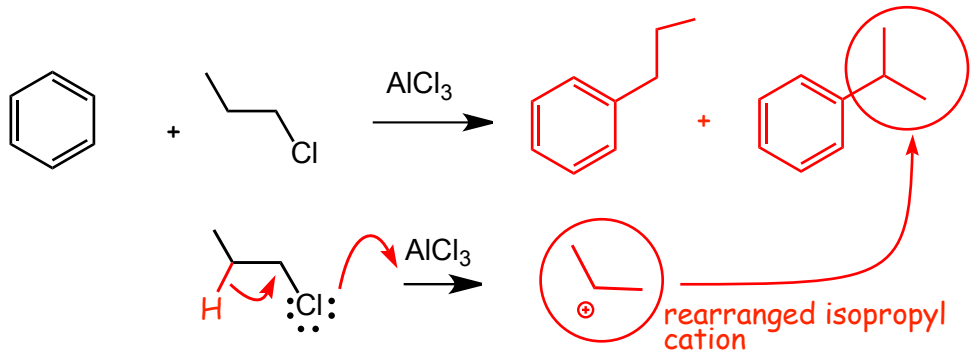
The Mechanism:



Example:

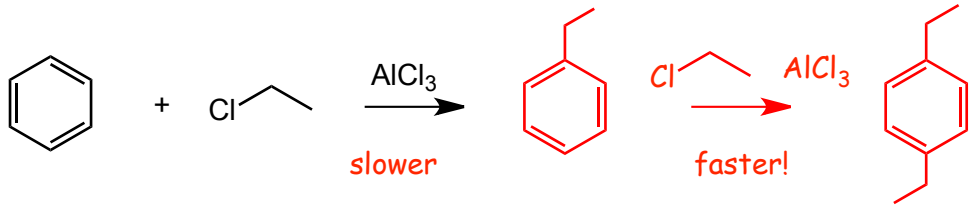


But:



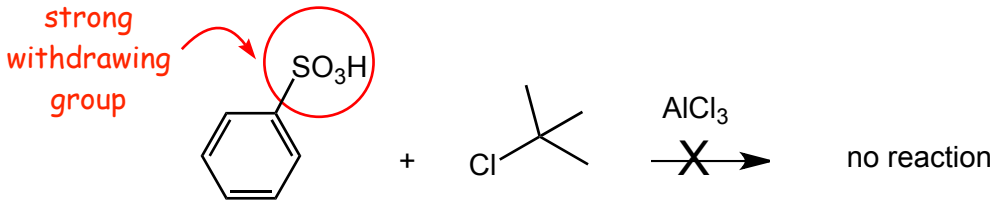
• Rearrangement of carbocation intermediate occurred, this is the usual carbocation problem.

Also:



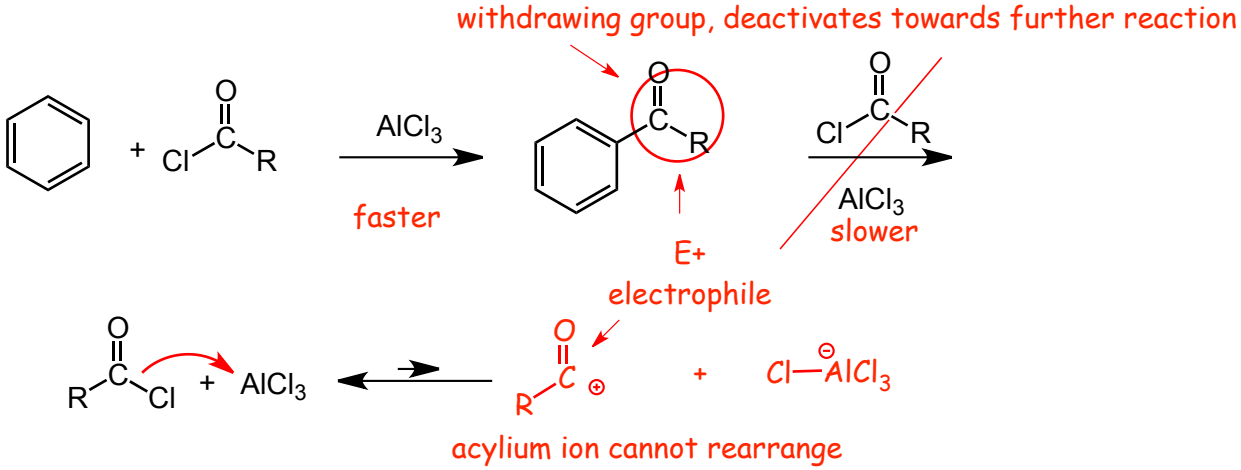
• Multiple additions occur because when 1 alkyl group adds, because the new alkylated benzene becomes more reactive than benzene itself.

Three Problems with Friedel-Crafts Alkylation.....
1. Rearrangements
2. Multiple Additions
3. I doesn't work with benzenes that have already have strong electron withdrawing groups.....

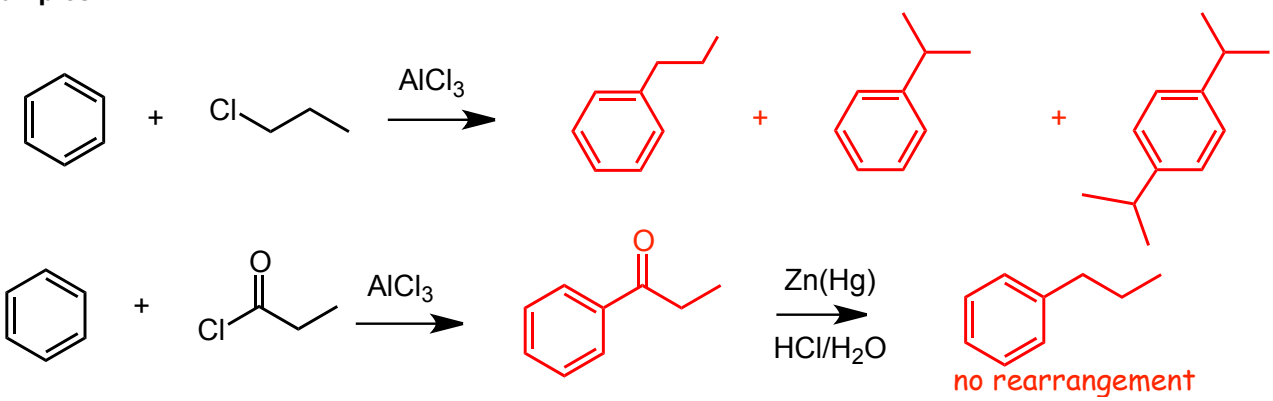


• Withdrawing groups "pull" electrons from the ring making it less reactive as a Lewis base/Nucleophile.
• Because the Friedel Crafts reaction is among the slowest of the electrophilic aromatic substitution reactions, it is the most sensitive to strong withdrawing groups on the benzene ring, a Friedel Crafts reaction won't go when other electrophilic aromatic substitution reactions will.

Friedel-Crafts Acylation: Solves problems 1 and 2 (above), but not 3:

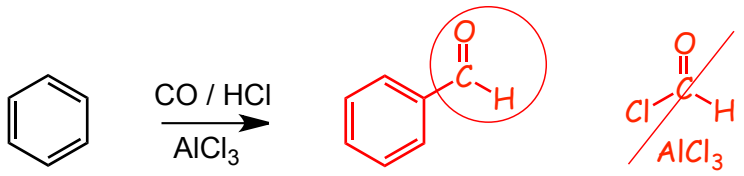


Examples:

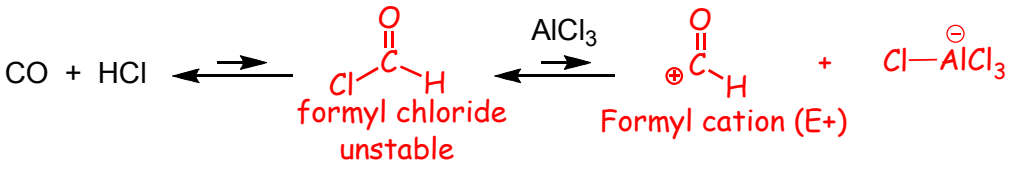


• Acylation followed by reduction is the "approved" method for alkylating benzenes in this course!

3. Friedel-Crafts for "1 carbon" (Gatterman-Koch Reaction)

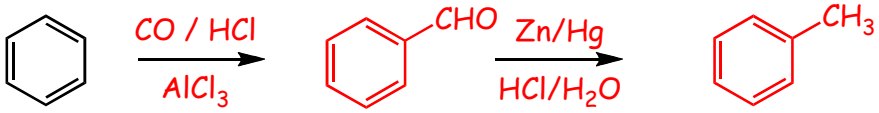


• The Friedel Crafts reagent you would **want** to use in this case, formyl chloride, unfortunately does not exist, since it is unstable and spontaneously dissociates into carbon monoxide (CO) and hydrogen chloride (HCl).
• Therefore you have to make it "in situ", i.e. by mixing CO and HCl, a small of formyl chloride will form, as shown below, which can then react with aluminum trichloride to produce a small amount of the formyl cation that will then undergo electrophilic aromatic substitution with benzene:



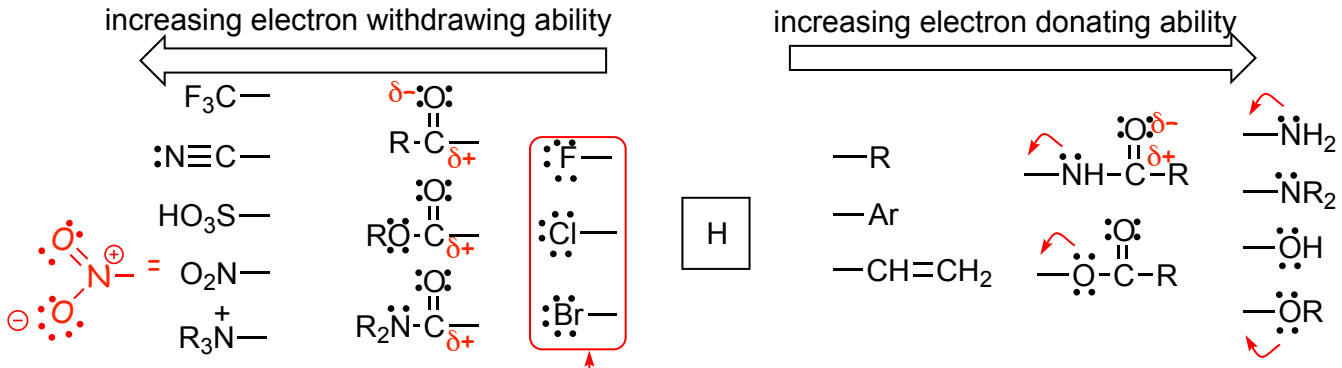
• CuCl is also often included as a catalyst in addition to $AlCl_3$, but we omit it here for simplicity to minimize reagent memorization, but be aware that you may see CuCl elsewhere.

Example: To add a methyl group to benzene, first add the corresponding formyl group to form an aldehyde, then reduce:

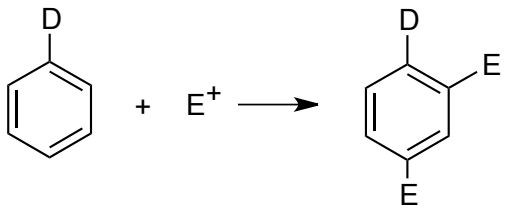


4 Reactions of Disubstituted Benzenes

• **Directing** and **activating** effects of substituents.
Recall electron donating and withdrawing groups on π–systems:

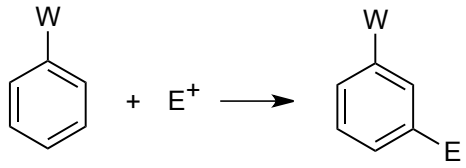


Summary of electron donating and withdrawing effects on electrophilic aromatic substitution:



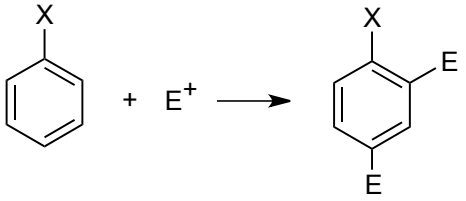
increasingly faster rates with increasingly stronger (activating) electron donating groups

D-groups are ortho- and para-directing



increasingly slower rates with increasingly stronger (deactivating) electron withdrawing groups

W-groups are meta-directing



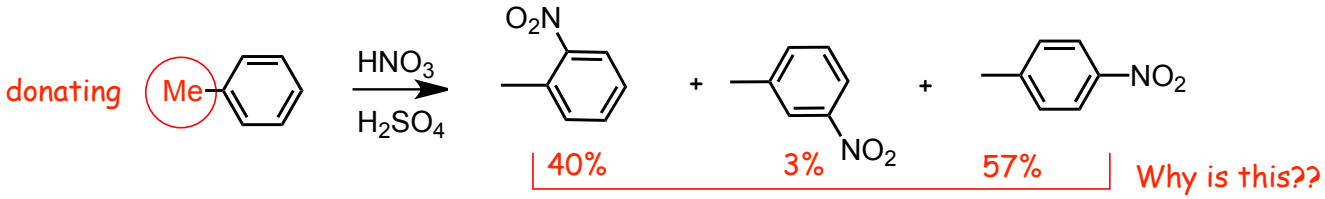
the "exceptions"

somewhat slower rates with halogens (X), weakly deactivating

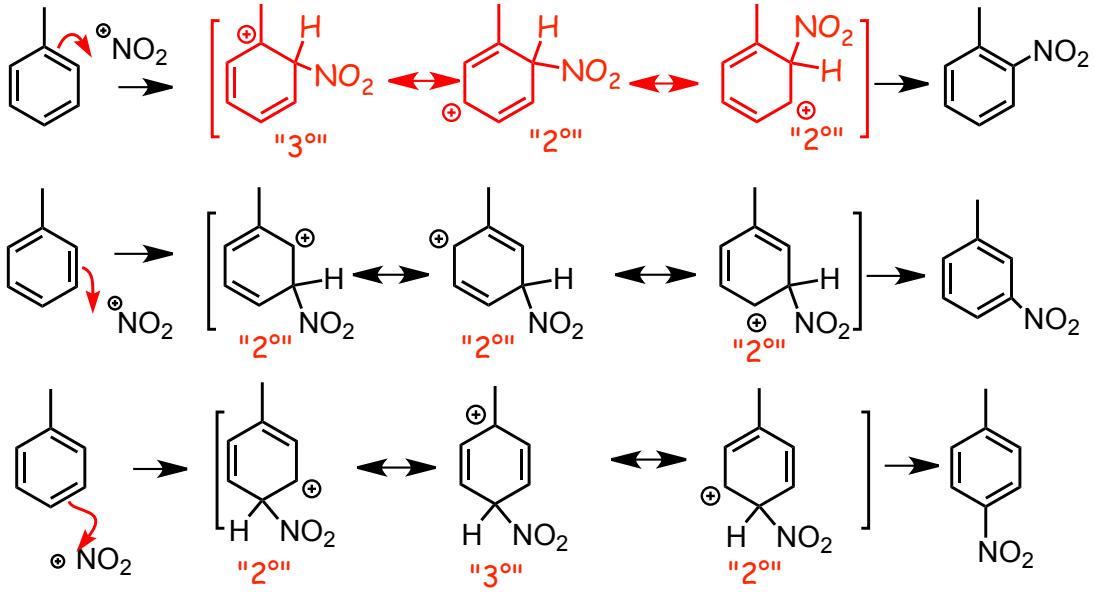
X- are ortho- and para-directing

4.1 Donating Groups : Activating and *ortho*- and p*ara*-Directing

• Let's see what happens when we do an electrophilic aromatic substitution reaction (EAS) on a benzene ring that already as an electron donating substituent (-D), a -Me group in this case:

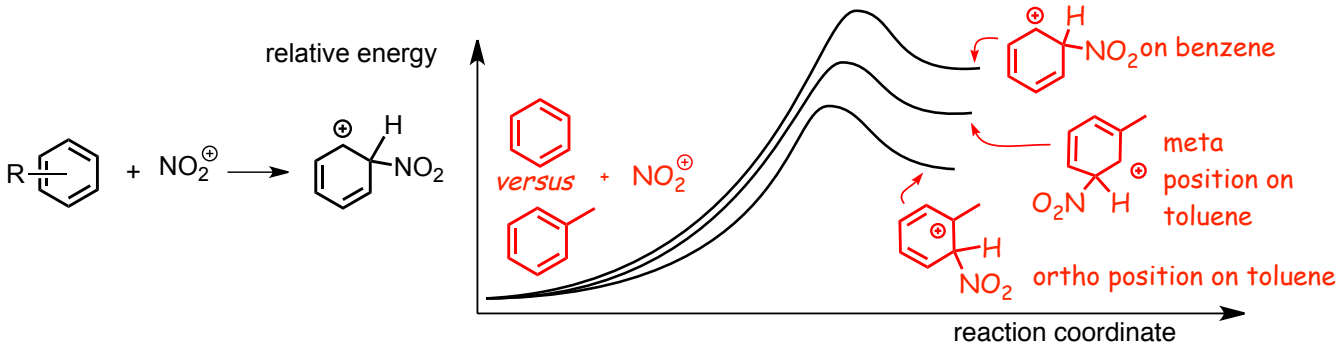


• The explanation for this product distribution lies in looking at the various intermediate cations, and their resonance contributors:



• The methyl donor group stabilizes the charge for reaction at the *ortho*- and *para*-positions, but **not** for reaction at the *meta*-position.

• Here is a **partial** reaction energy diagram for the first step in the mechanism comparing benzene and toluene (methylbenzene):

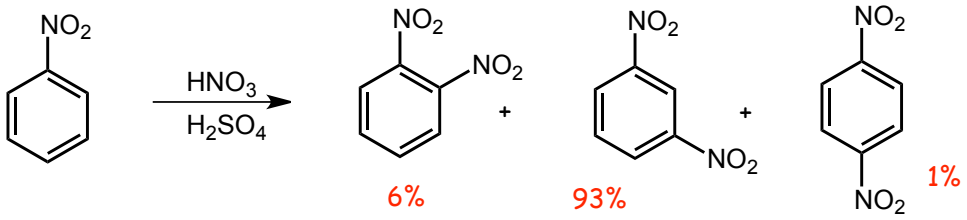


• The donating group makes attack at **both** the *meta*- and the *ortho*-/*para*- positions faster than for simple benzene (the Ea smaller for both reactions with the methyl substituent).
• **But** reaction at the *ortho*- and *para*-positions is faster than for reaction at the *meta*-position.
• Reaction does not occur at the *meta*-position because reaction there is slow, it is **not slow**, it is just not as fast as reaction at the *ortho*- and *para*-positions.

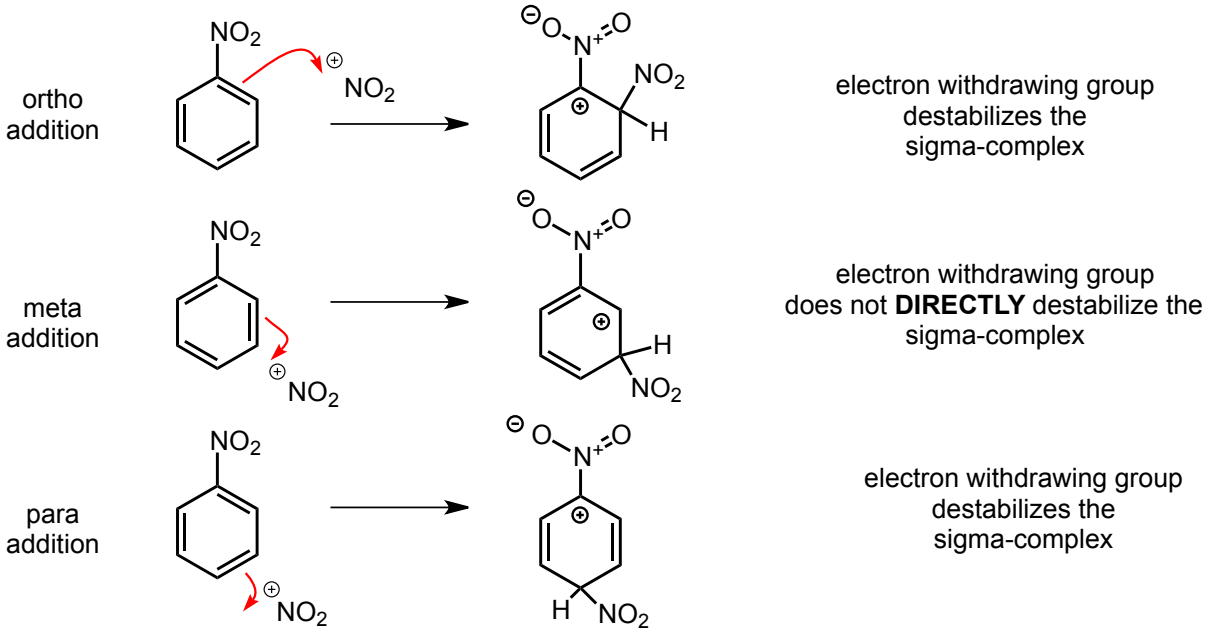
• Electron Donating groups are ***ortho*- and *para*-directing.**
• Electron Donating groups are **activating** (make reaction go faster).
• The **stronger** the electron donating group, the **faster** the reaction.

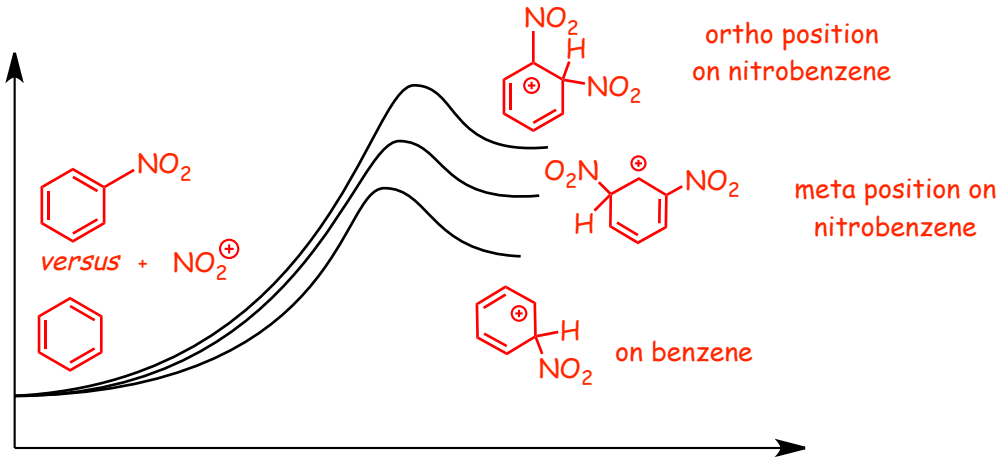
4.2 Withdrawing Groups : Deactivating and *meta*-Directing

• Let's see what happens when we do an electrophilic aromatic substitution reaction (EAS) on a benzene ring that already as an electron withdrawing substituent (-W), a -NO_2 group in this case:



• The intermediate cation (the sigma complex) is **least** destabilized for reaction at the *meta*-position:



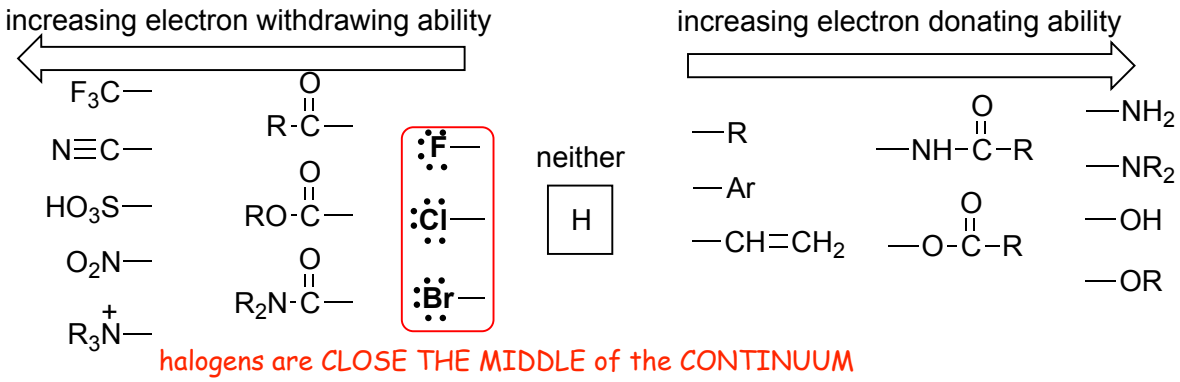


• Reaction does not occur at the *meta*-position because reaction there is fast, it is **not**, it is just not as slow as reaction at the *ortho*- and *para*-positions.

• Electron Withdrawing groups are ***meta*-directing.**
• Electron Withdrawing groups are **deactivating** (make reaction go slower).
• The **stronger** the electron withdrawing group, the **slower** the reaction.

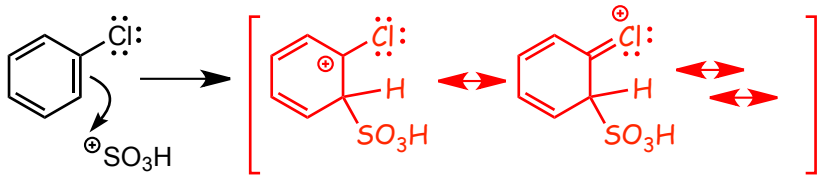
4.3 Halogens are different! They are Deactivating but *ortho*- and *para*-Directing!

• Electron donation versus withdrawing isn't black versus white, it isn't really binary like that.
• There is a **continuum**, from very strong withdrawing, to weaker withdrawing to not withdrawing or donating at all (H), to weakly donating to strongly donating.
• So we shouldn't be surprised that there are substituents that are very close to the middle, like H.
• **This** is the **halogens**, they are **very close to the middle.**



• The halogens are **electronegative**, therefore withdrawing via the **inductive effect**, **but**, the **halogens** also have non-bonding electrons that could, in principle, be donating.
• **The halogens thus have mixed behavior as substituents.**
• The **halogens** are electron-withdrawing, and therefore **deactivating.**
• **However, the halogens** are also ***ortho***- and ***para***-directing since they can stabilize the intermediate cation (sigma complex) by **resonance donation** of a pair of **non-bonding electrons** for reaction in the *ortho*- and *para*-positions, but not in the *meta*-position.

Example

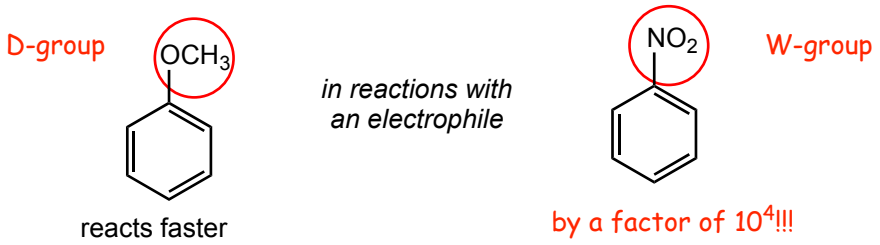


• **We should not be surprised that there is a substituent type that is in the middle, this is the halogens!**

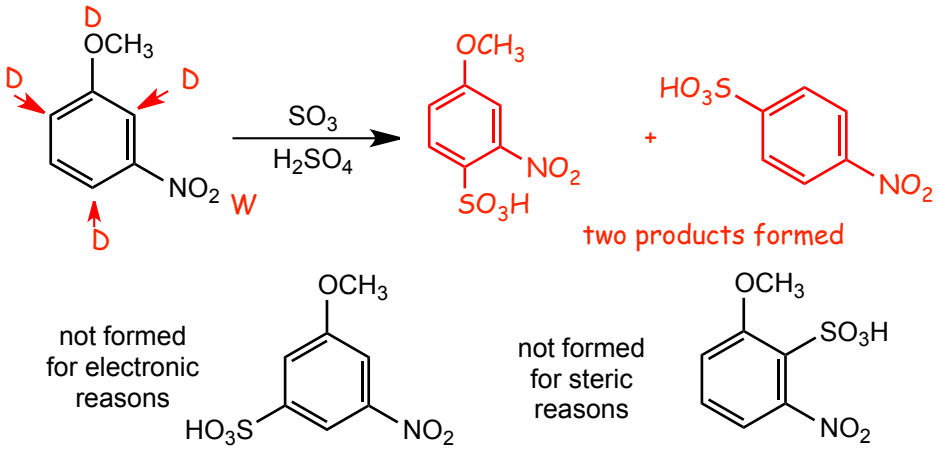
4.4 Predicting Products for Multiply-Substituted Benzenes

• When there is more than one substituent, consider the following....

The most electron donating group determines the directing effects (an electronic effect).

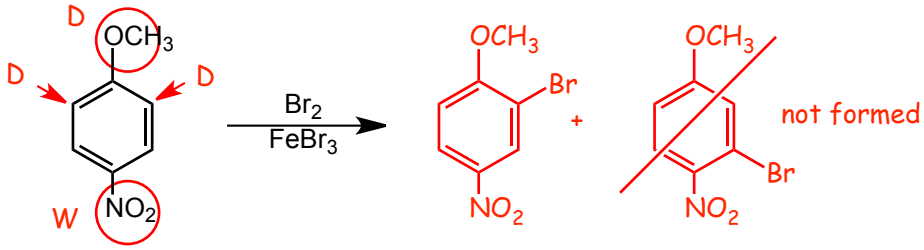


But we also need to **consider steric effects:**



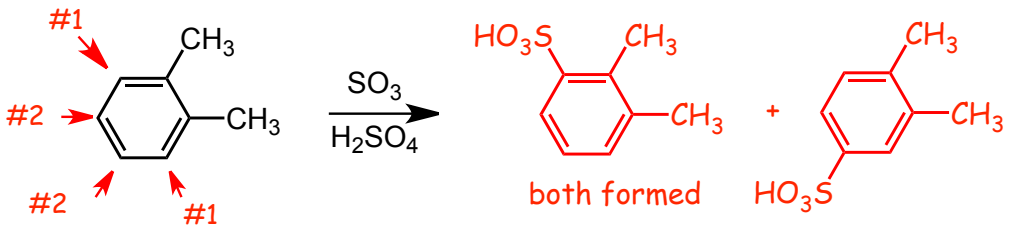
• The -OCH_3 group **directs** the reactivity because it is **activating.**
• Reaction occurs at the *ortho*- and *para*-positions with respect to the -OCH_3 group, except that **one** of the *ortho*-positions is "blocked" due to steric hindrance.

Examples

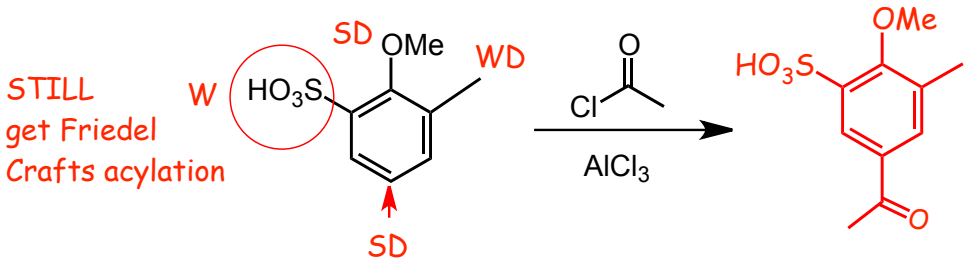


• The -OCH_3 group **directs** the reactivity because it is **activating.**
• Reaction occurs at the *ortho*-position with respect to the -OCH_3 group, the para-position in this case is **blocked**, we can't substitute the -NO_2 substituent.
• The two *ortho*-positions in this case are equivalent (by symmetry), reaction at either gives the same product.

• Reaction at positions #1 (above) is equivalent, gives the same products, reaction at position #2 does not occur for steric reasons.



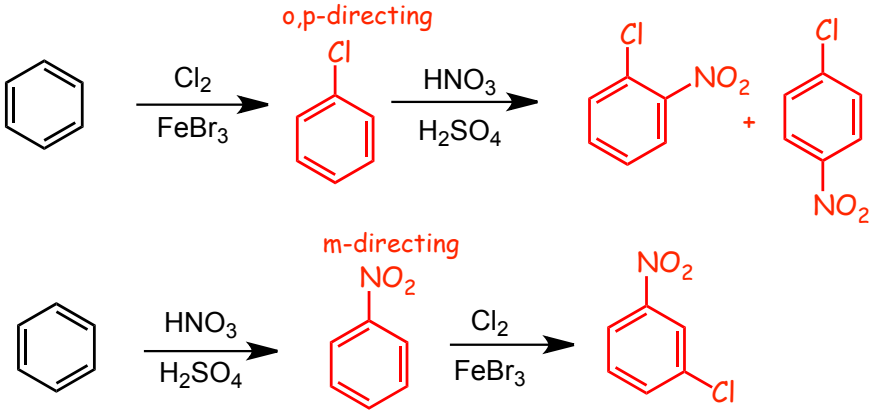
• Positions #1 and positions #2 (above) are equivalent, reaction at each #1 gives the same product same for #2.
• Electrophilic aromatic substitution reactions **can** give more than one product, we need to be aware of this!



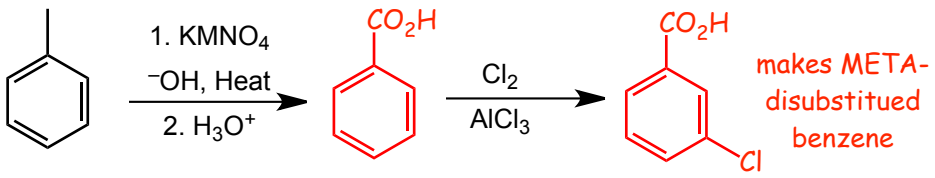
• The -OMe is the **strongest donating** group, **it directs** the reactivity because it is **more activating** than the weakly donating -Me substituent.
• Reaction occurs at one *para*-position with respect to the -OMe group, the two *ortho*-positions are **blocked**, we can't substitute the -SO_3H or the -CH_3 substituents.
• **But wait!** How can we have a Friedel Crafts reaction on a ring that has a strong -W substituent, the -SO_3H, doesn't that break our "rule? This is a problem with rules! Note that we also have 2 donating (activating) substituents that offset the deactivating effect of the withdrawing -SO_3H. And so, we have to use some common sense and adapt the "rule" that there is no Friedel Crafts reactions with strongly withdrawing substituents accordingly when there are also strong donating substituents.

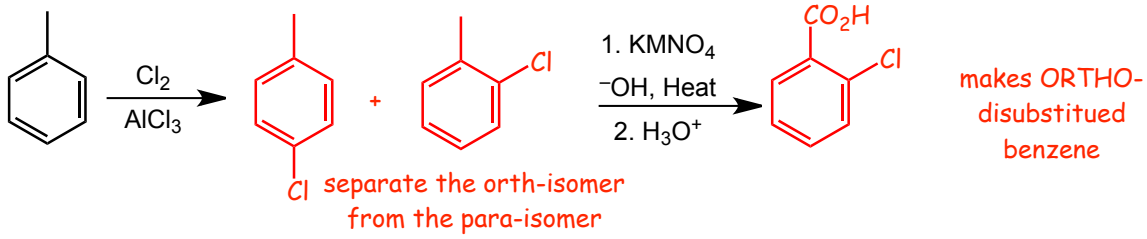
5 Synthesis of Substituted Benzenes

Putting a series of reactions together (in the correct order!) to build complex substituted benzenes.
Examples

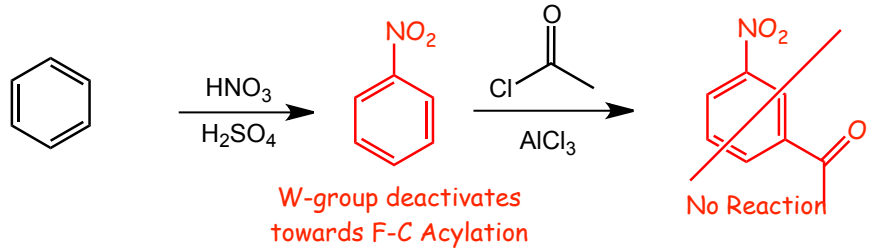


• Note the different products from the two last reaction sequences, the **order matters.**

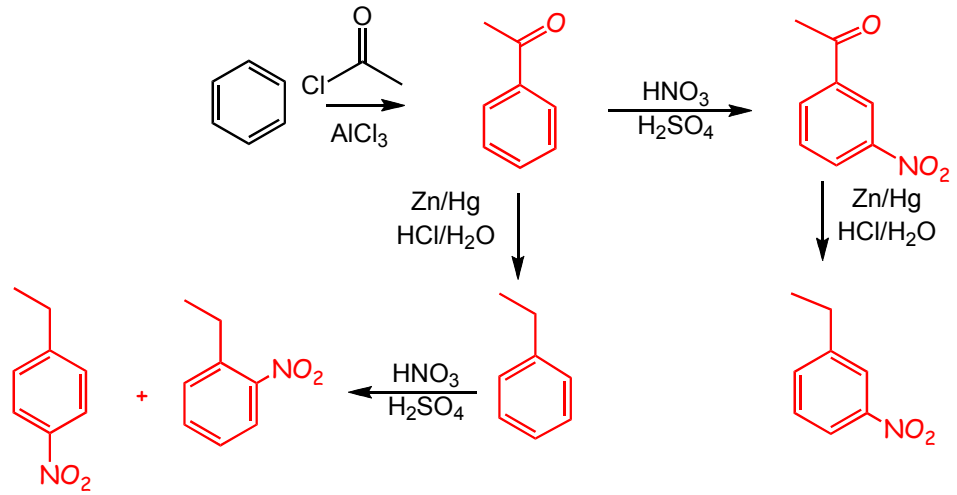




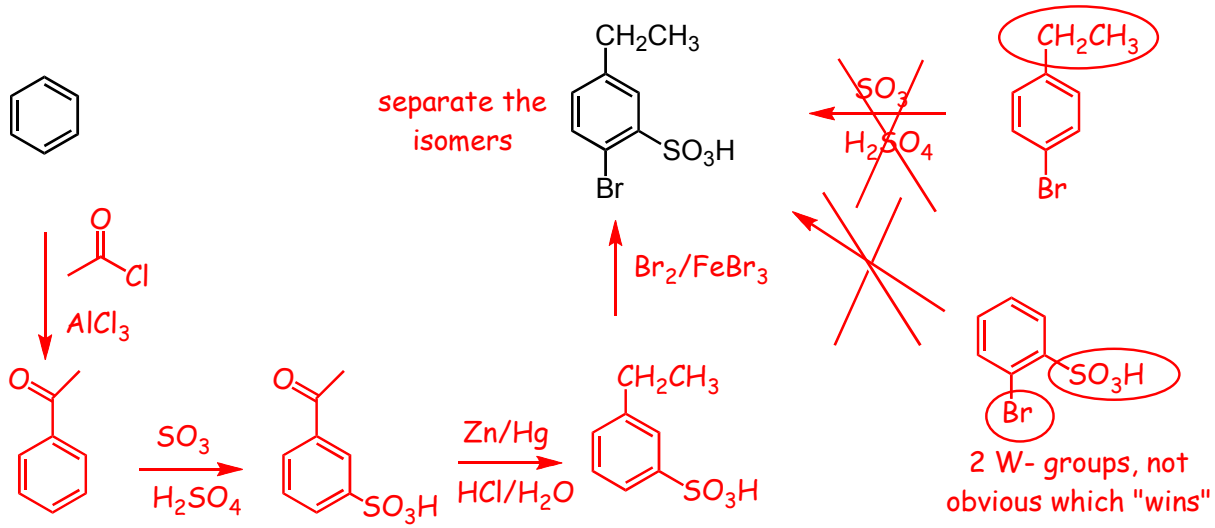
• Again, different isomeric products can be formed by performing the reactions in a different sequence.
• Where necessary, "separate the isomers" to complete a benzene synthesis sequence (this is not only allowed, if you form isomers then you have to indicate so).



Recall: Friedel Crafts acylation (above) cannot be performed on the benzene that has a strong electron withdrawing substituent.
Compare:

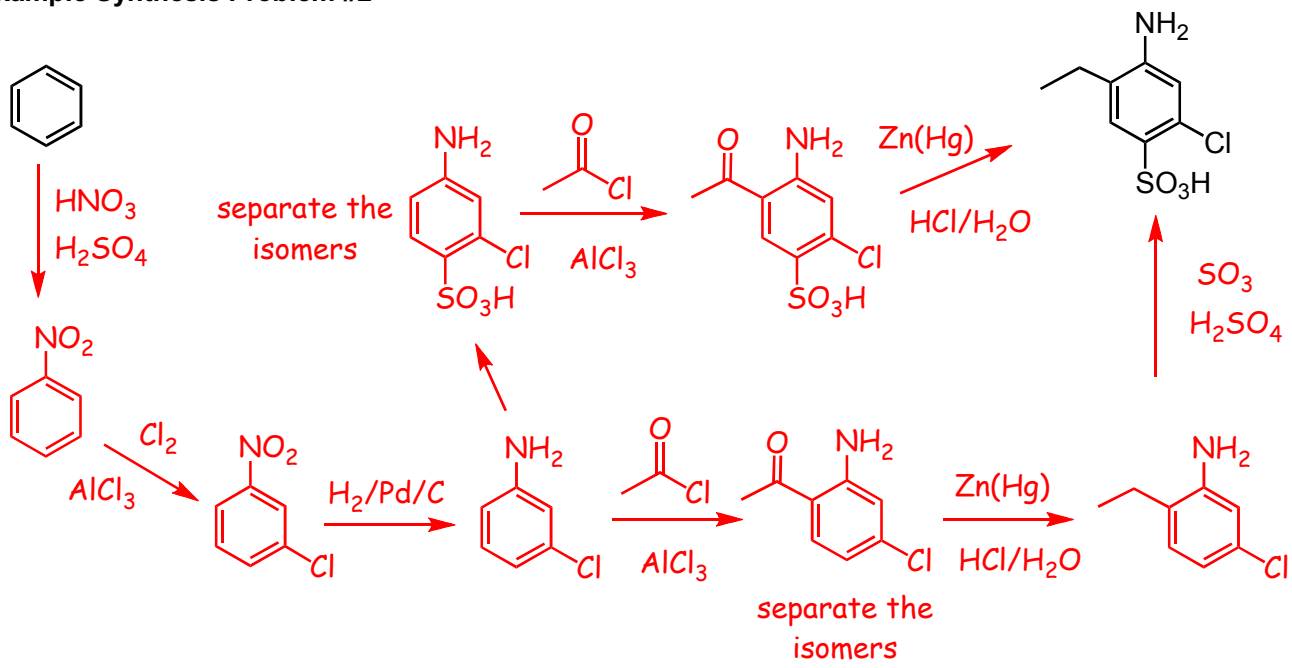


Example Synthesis Problem #1
Synthesize the trisubstituted benzene derivative on the right from benzene:
• Work backwards using retrosynthetic approach, ask which substituent you are able to "add" backwards.



• At each step (backwards), ask "which of the substituents can be generated, decide which reaction to do on that basis
• Eventually you don't have to actually write out all of the possible reactions, you can analyze the possibilities in your head.
• It would be difficult to predict that Friedel-Crafts acylation should be the first step in the synthesis problem above, these problems are definitely best solved backwards.

Example Synthesis Problem #2

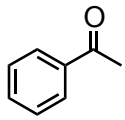


• Of course, there may be more than one possible solution to these problems, as above.
• In reality even these reactions have complications that we don't really have the time to get into here, specifically, once the amine is formed the Freidel crafts reaction becomes very slow again even though the amine is very activating, because the amine will also undergo a Lewis acid base reaction with the $AlCl_3$, making it less donating, organic can be complicated sometimes!

7 Summary of Aromatic Reactions

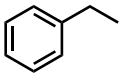
Do not start studying by trying to memorize the reactions here!
Work as many problems as you can, with this list of reactions in front of you if necessary, so that you can get through as many problems as you can without getting stuck on the reagents/conditions, and so that you can learn and practice solving reaction problems. Use this list **after** you have worked all of the problems, and just before an exam. By then you will have learned a lot of the reagents/conditions just by using them and you will only have to memorize what you haven't learned yet. Then do the following:
• Cover the entire page of reagents/conditions with a long vertical strip of paper, see if you can write down the reagents/conditions for each reaction, check to see which you get correct, if **completely** correct, circle Y, if incorrect or even slightly incorrect, circle N. In this way you keep track of what you know and what you don't know.
• Keep coming back to this list and so the same thing only for those reactions you circled N, until all are circled Y.

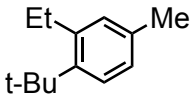
Knowing the reagents/conditions on this page is **insufficient** to do well on an exam since you will **also** need to recognize how to use and solve reaction problems in different contexts, this page **only** helps you to learn the reagents/conditions that you have **not yet** learned by working problems.



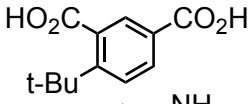
$\xrightarrow[\text{HCl /H}_2\text{O}]{\text{Zn (Hg)}}$ Y / N

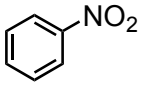
(Clemmenson reduction)



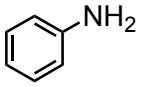


$\xrightarrow[\text{2. } H_3O^+]{\text{1. } KMnO_4 \text{ / }^-OH\text{/boil}}$ Y / N

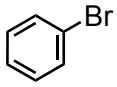




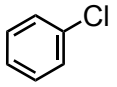
$\xrightarrow{H_2/Pd/C}$ Y / N



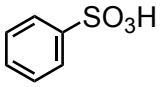
$\xrightarrow[FeBr_3]{Br_2}$ Y / N



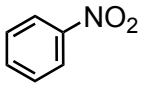
$\xrightarrow[AlCl_3]{Cl_2}$ Y / N

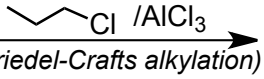


$\xrightarrow[H_2SO_4]{SO_3}$ Y / N



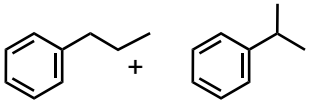
$\xrightarrow[H_2SO_4]{HNO_3}$ Y / N

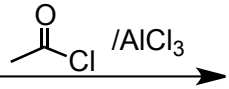




Y / N

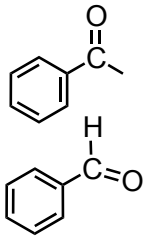
(Friedel-Crafts alkylation)
do not use in synthesis





Y / N

(Friedel-Crafts acylation)



$\xrightarrow[\text{(Gatterman Koch reaction)}]{\text{CO/HCl/AlCl}_3\text{ (CuCl)}}$ Y / N

CuCl should be included, we omit it for simplicity