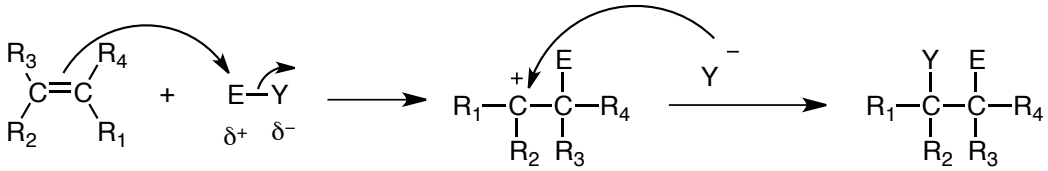
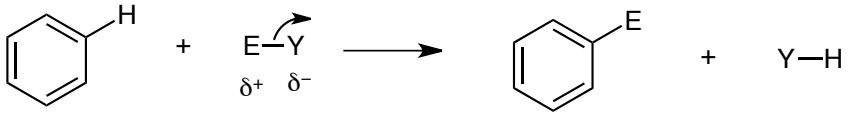
Chapter 13
Reactions of Arenes
Electrophilic Aromatic Substitution

Electrophiles add to aromatic rings in a fashion somewhat similar to the addition of electrophiles to alkenes.

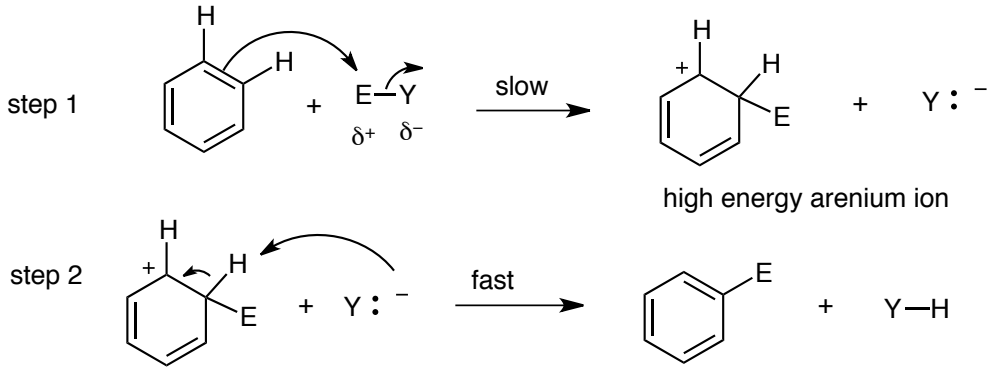
Recall:



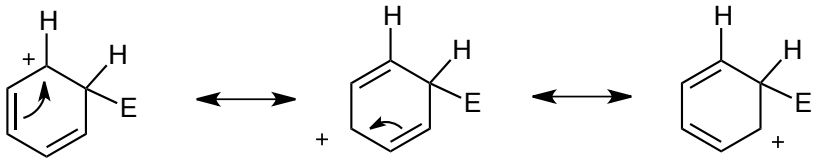
In aromatic rings, however, we see substitution of one of the benzene ring hydrogens for an electrophile.



The mechanism is the same regardless of the electrophile. It involves two steps: (1) Addition of the electrophile to form a high-energy carbocation. (2) Elimination of the proton to restore the aromatic ring system.

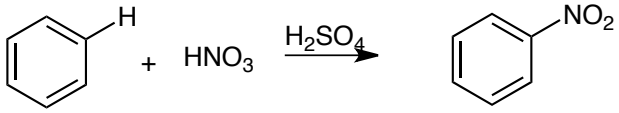


The first step is the slow step since the aromaticity of the benzene ring system is destroyed on formation of the arenium ion intermediate. This is a high energy species but it is stabilized by resonance with the remaining two double bonds. The second step is very fast since it restores the aromatic stabilization.

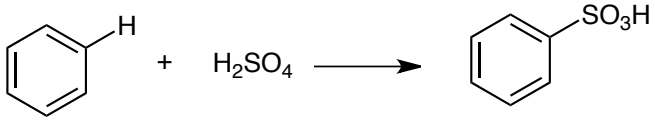


There are five electrophilic aromatic substitution reactions that we will study.

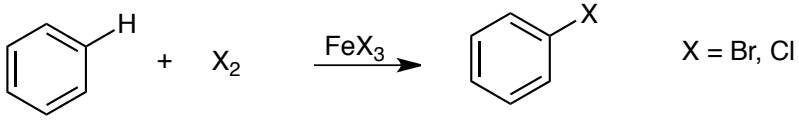
(1) Nitration



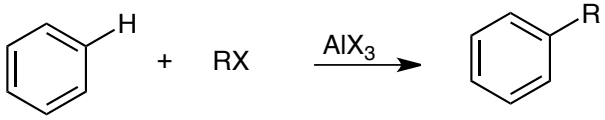
(2) Sulfonation



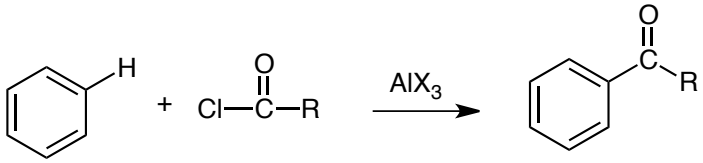
(3) Halogenation with bromine or chlorine



(4) Friedel-Crafts Alkylation

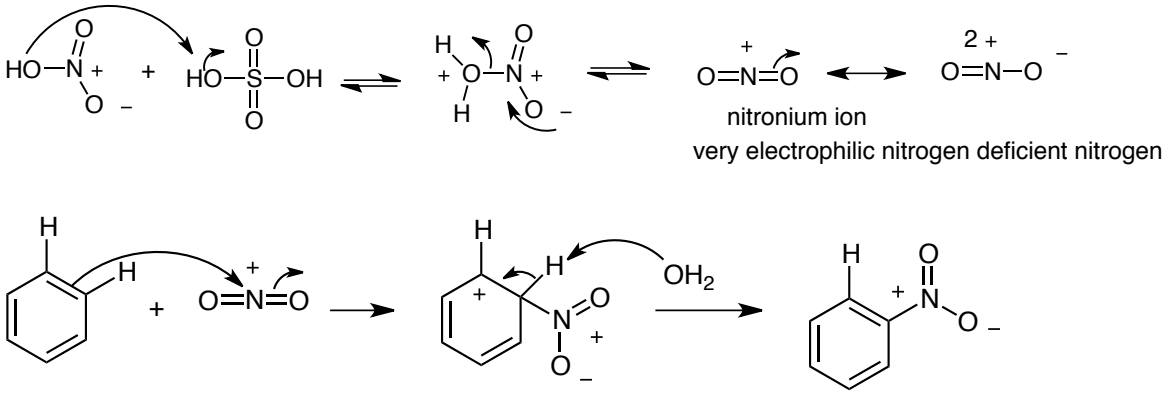


(5) Friedel-Crafts Acylation

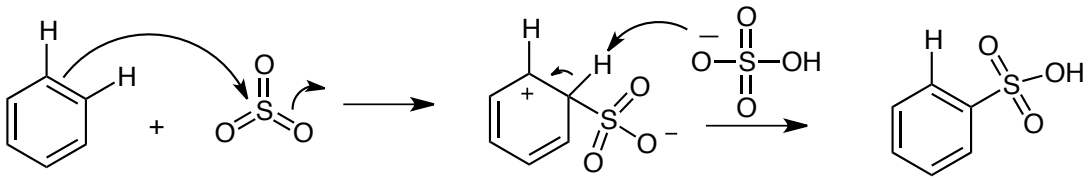


Nitration of Benzene

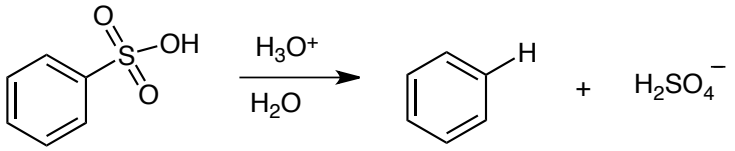
We generate the highly electrophilic nitronium ion *in situ* using sulfuric acid to dehydrate nitric acid. The nitronium ion is then attacked by the π–electrons to give the arenium ion, which then loses a proton to regain its aromaticity.



Sulfonation of Benzene

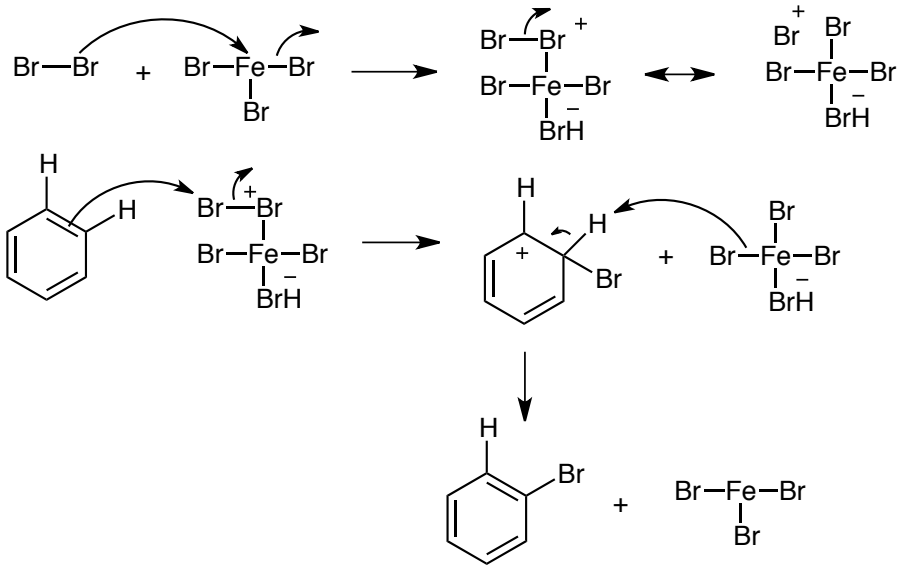


The sulfonation reaction is reversible. Heating the benzene sulfonyl compound in aqueous acid removes the sulfonyl group and replaces it with a proton.



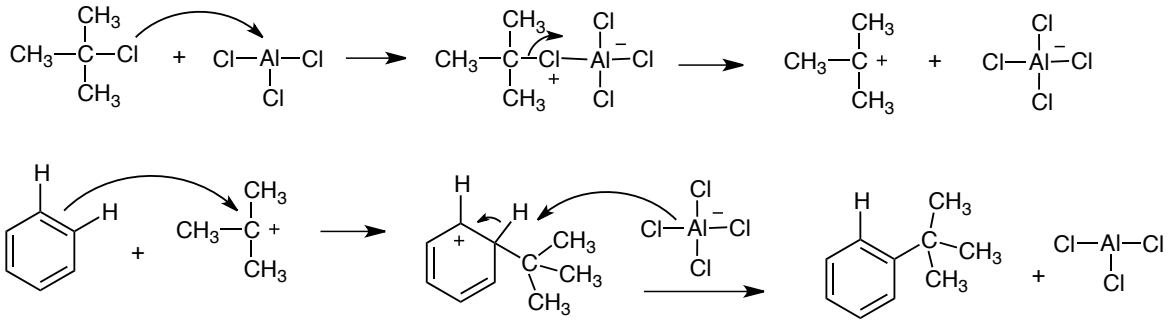
Halogenation of Benzene

Generally a Lewis acid catalyst is needed to activate the bromine and make it into a better electrophile. Bromine itself does not react with benzene.

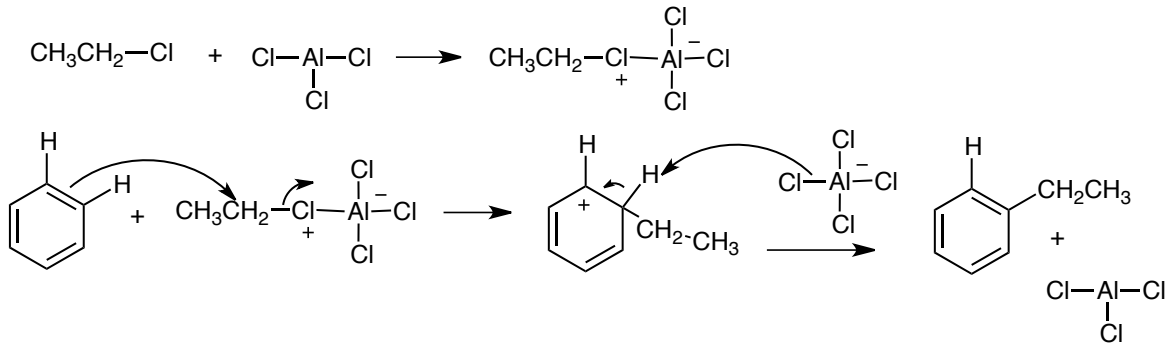


Friedel-Crafts Alkylation

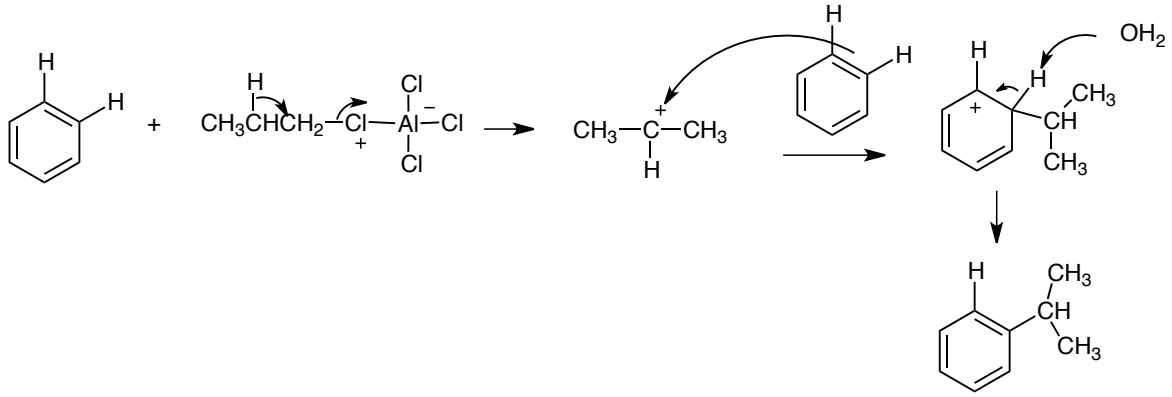
With secondary and tertiary alkyl halides, a carbocation intermediate is formed by reaction of a secondary or tertiary alkyl halides with a Lewis acid such as aluminum trichloride, $AlCl_3$. The carbocation intermediate is then attacked by the π–system to form a new carbon-carbon bond and an arenium ion, which rapidly loses a proton to re-aromatize.

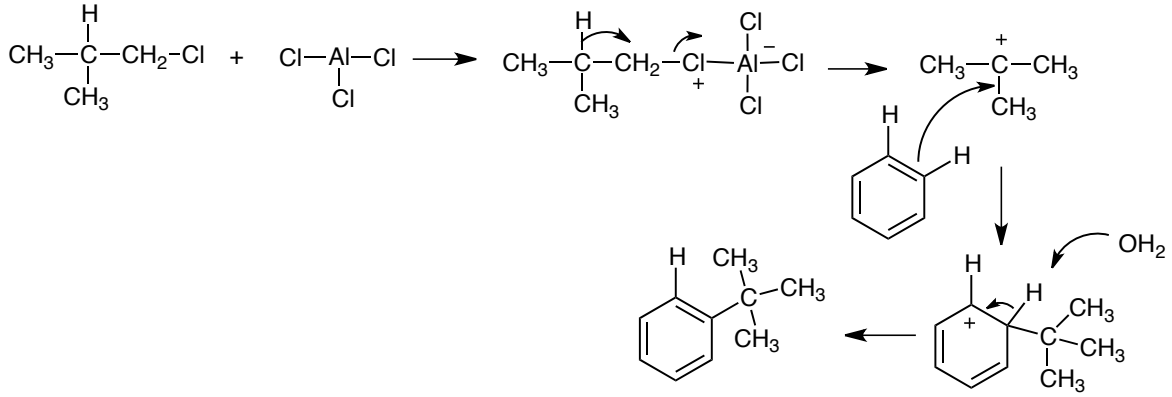


With primary alkyl halides there is no primary carbocation formed. They are too high in energy. The benzene π–system attacks the Lewis acid-alkyl halide complex directly.

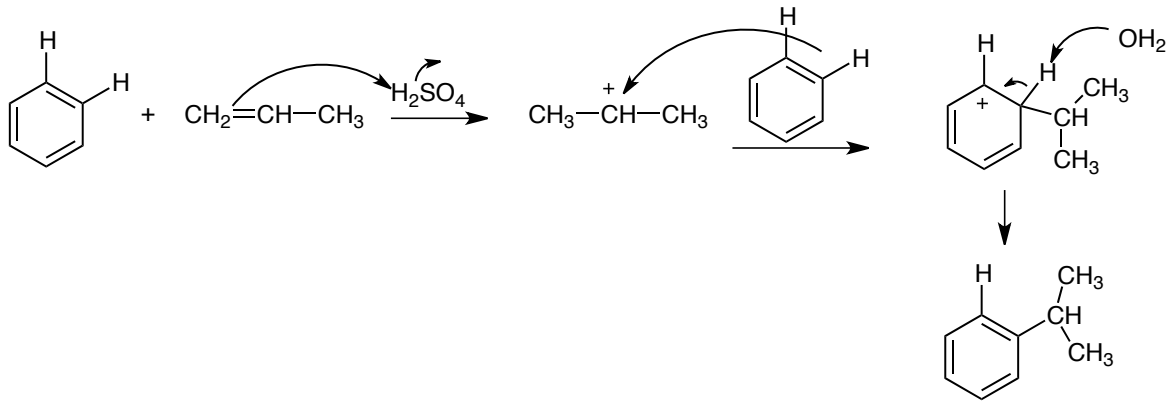


We do see rearrangements so as to form the more stable carbocations so it is not possible to make straight chain alkyl benzene derivatives having more than two carbons in the chain. The secondary derivative is always formed as the major product.



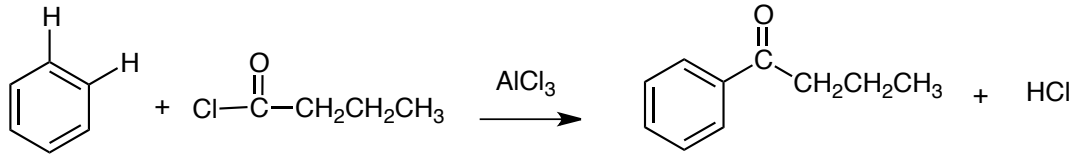


We can also generate carbocations for Friedel-Crafts alkylations from alkenes in acidic conditions. We protonate the alkene to form the more stable carbocation according to Markovnikov's rule.

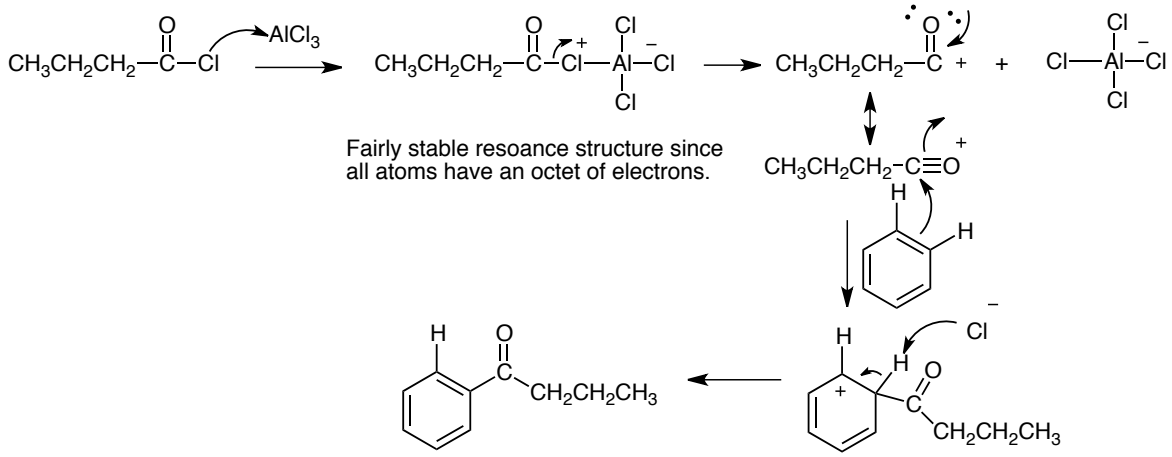


Friedel-Crafts Acylations

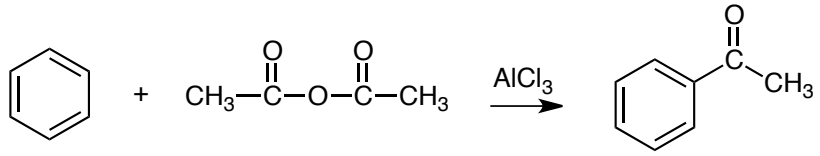
Friedel-Crafts acylations use a carboxylic acid chloride (or acid chloride for short) and catalysis by a Lewis Acid such as aluminum trichloride, $AlCl_3$, to give acyl benzene derivatives. We do not see rearrangements with Friedel-Crafts acylations.



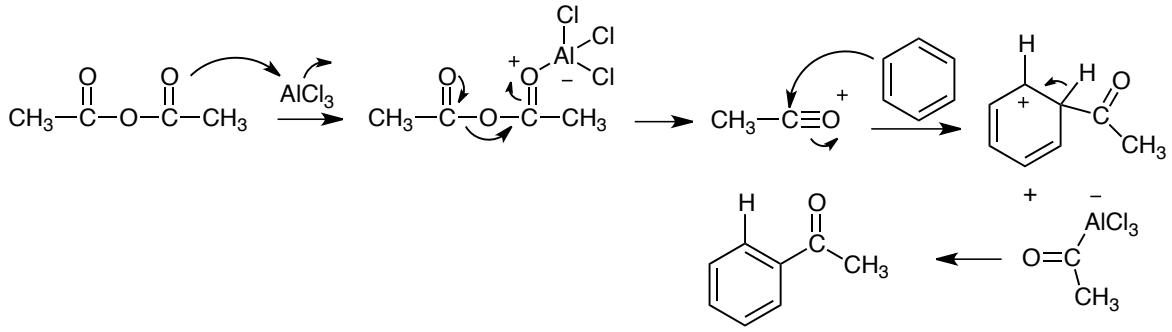
The mechanism involves the formation of a quite stable acylium ion. The Lewis acid is attacked by the chlorine lone pair. The chlorine is then removed to form the acylium ion. This is an sp^2 carbocation but is reasonably stable since one of the lone pair of the oxygen donates electrons to form a resonance structure in which all of atoms have an octet. Due to this stabilization of the carbocation by the oxygen lone pair, no rearrangements occur. The acylium ion is attacked by the benzene π–system to give an arenium ion, which then loses a proton to restore the aromatic system.



We can also do Friedel-Crafts acylations using anhydrides.

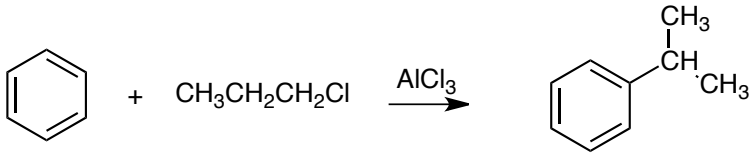


The mechanism is similar to that using the acid chloride. We first form an acylium ion, which is attacked by the π–system of the benzene ring.

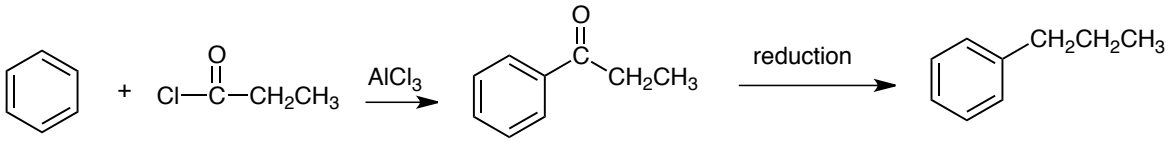


Synthesis of Straight Chain Alkyl Benzenes

In order to synthesize benzene rings with straight chain alkyl substituents with more than two carbons in the alkyl chain, we can not simply use Friedel-Crafts alkylation because there will be a rearrangement reaction and we will get a 2-substituted derivative.

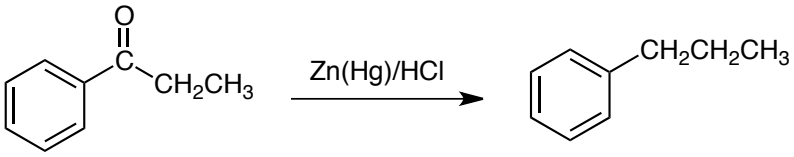


The way to make straight chain alkyl benzene derivatives is to use a two step sequence involving (1) Friedel-Crafts acylation, which occurs without rearrangements, followed by (2) reduction of the resulting carbonyl to the methylene (CH_2).

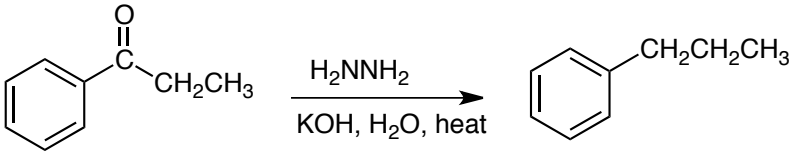


There are two useful methods for reducing the benzylic carbonyl to a methylene group. The Clemmenson reduction uses acidic conditions [Zn(Hg)/HCl] and the Wolff-Kishner reduction uses basic conditions (H_2NNH_2, KOH, H_2O, heat).

Clemmenson Reduction



Wolff-Kishner Reduction



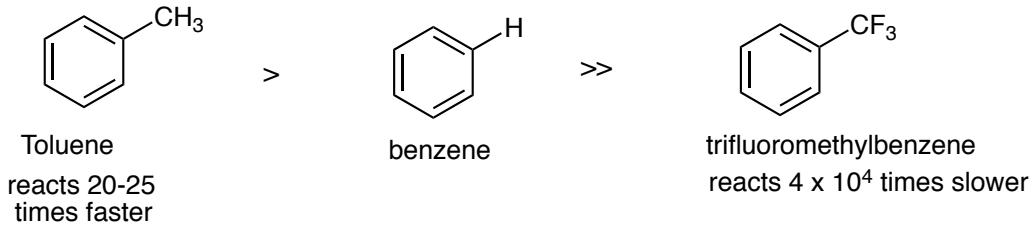
Substituent Effects on Rate and Regioselectivity

Next, we will examine substituted benzene rings and how they react in electrophilic aromatic substitution reactions. There are two things we need to consider:

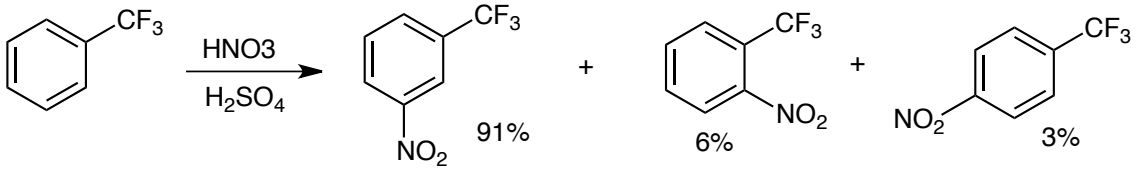
(1) The effect of a substituent on the rate of addition of a second substituent.
(2) The effect of a substituent on the regioselectivity of the addition of a second substituent. In other words, where will the second substituent go in relation to the first substituent? We will see that there are well defined rules that govern this process.

First we will examine the effect of a substituent on the rate of addition of a second substituent. Consider the nitration of benzene versus the nitration of trifluoromethylbenzene and toluene (methylbenzene). We see that the trifluoromethylbenzene reacts much, much slower (4×10^4 times slower) than benzene. It is therefore a deactivating group.

Toluene reacts faster than benzene by a factor of 20-25 times. Therefore, the methyl group is an activating group.

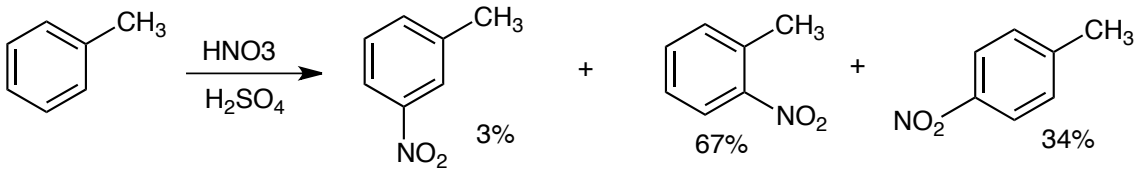


If we look at the regioselectivity of the addition reaction we see very different results between that of the trifluoromethylbenzene and toluene. Nitration of trifluoromethyl-benzene puts the nitro group mainly in the *meta* position with high selectivity.



So, we see that the trifluoromethyl group is a *meta* director. An important point is that it does not matter what the incoming group is; the trifluoromethyl group will always direct a second group to the *meta* position.

In the nitration of toluene, we see that the nitro group ends up mainly in the *ortho* and *para* positions relative to the methyl group. The methyl is therefore an *ortho/para* director. Note also that we see roughly twice as much *ortho* nitration as *para*. This is a statistical result since there are two *ortho* positions and only *para* position so reaction at the *ortho* position is twice as likely.



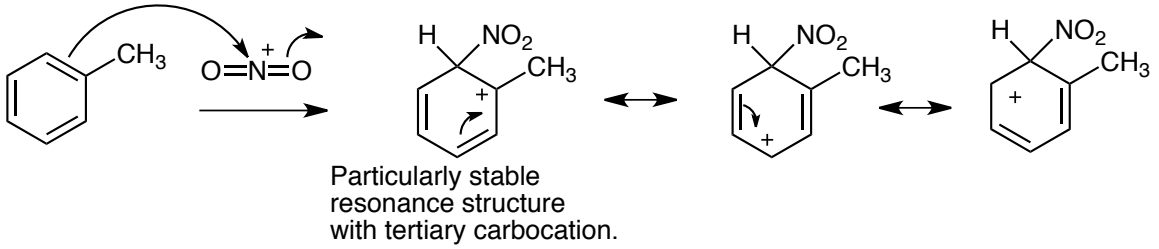
We see that the trifluoromethyl group is deactivating and a *meta* director.

The methyl group is an activating group and *ortho*/*para* directing.

We need to understand why this is the case and in order to do this we need to look at the mechanism and to examine the effect of the substituent on the initially formed carbocation or arenium ion. Formation of the carbocation is the slow, rate determining step and as we have seen, the more stable carbocation is formed faster because it is lower in energy. Therefore, in order to understand the directing group effects, we need to look at the relative stabilities of the carbocations involved.

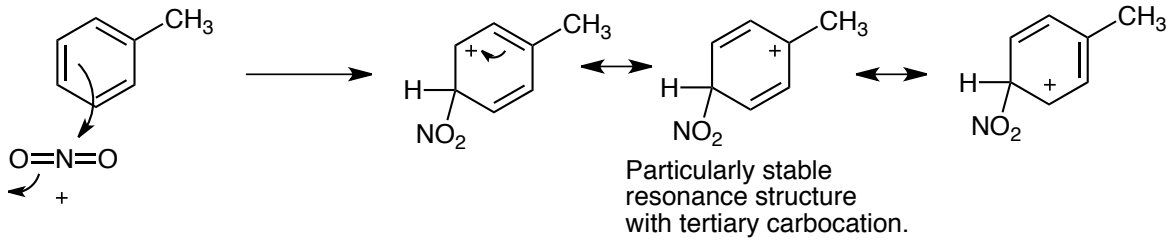
First consider *ortho* attack in the nitration of toluene. We see that if nitration occurs in the *ortho* position, there will be a relatively stable tertiary carbocation as one of the resonance structures.

***Ortho* Nitration**



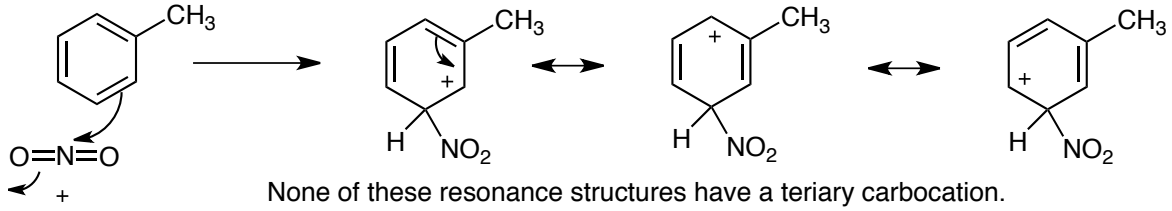
For attack at the *para* position, we get a similar result.

***Para* Nitration**



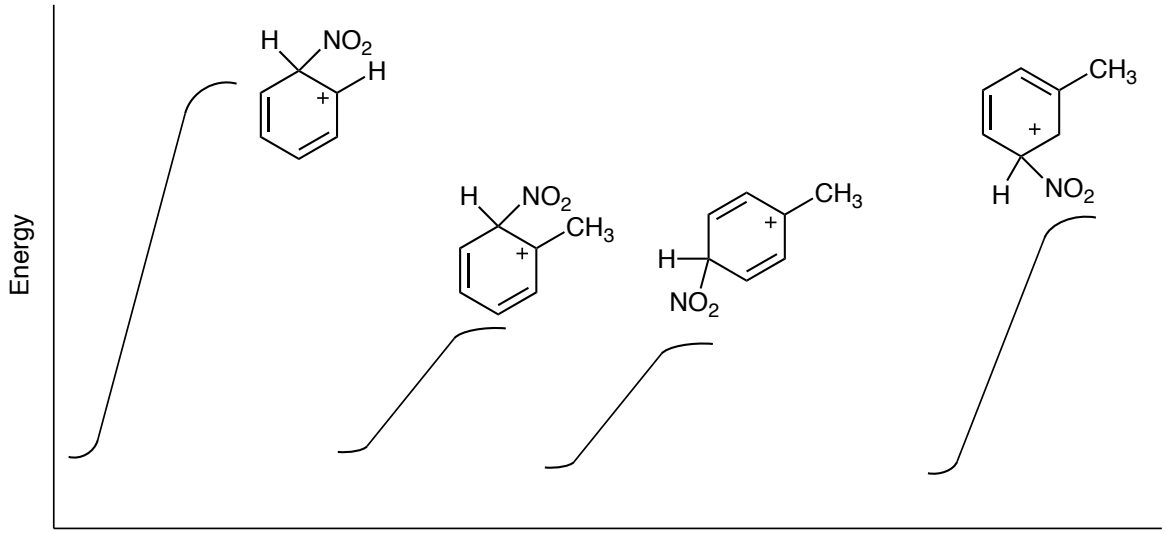
For attack at the *meta* position, we do not see the stabilized carbocation. We have only secondary carbocations that skip the tertiary carbocation that is observed in the *ortho* and *para* cases.

***Meta* Nitration**



None of these resonance structures have a teriary carbocation.

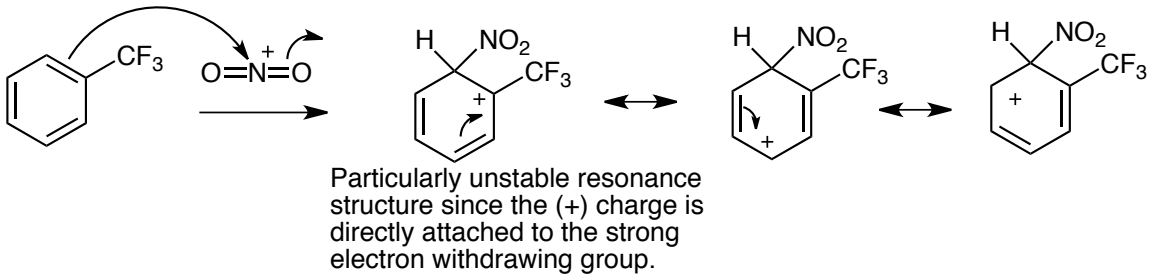
The net effect of this is that the carbocation formed in the first step of nitration of toluene is lower in energy if it occurs in the *ortho* and *para* positions. And, since the methyl group is an activating group, the carbocation formed by nitration in any of the three positions is lower in energy than that formed by nitration of benzene.



The trifluoromethyl group is strong electron withdrawing group. The central carbon has a partial (+) charge due to the strong electronegativity of the three fluorines. The trifluoromethyl group will destabilize a carbocation. The more stable resonance structures will have the trifluoromethyl group on a carbon away from the carbocation. The high energy structures will have the trifluoromethyl group on a carbon directly attached to the trifluoromethyl group.

Look at *ortho* substitution. Attack at the *ortho* position is disfavored because in one of the resonance structures, the (+) charge is on the carbon that bears the trifluoromethyl group. This is a very high energy resonance structure

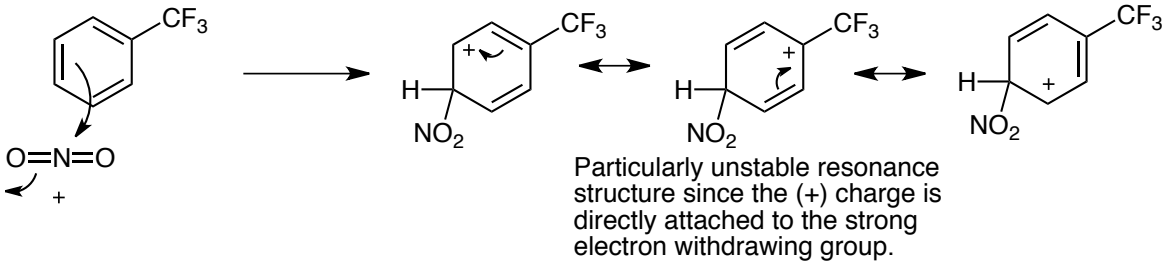
***Ortho* Nitration**



Particularly unstable resonance structure since the (+) charge is directly attached to the strong electron withdrawing group.

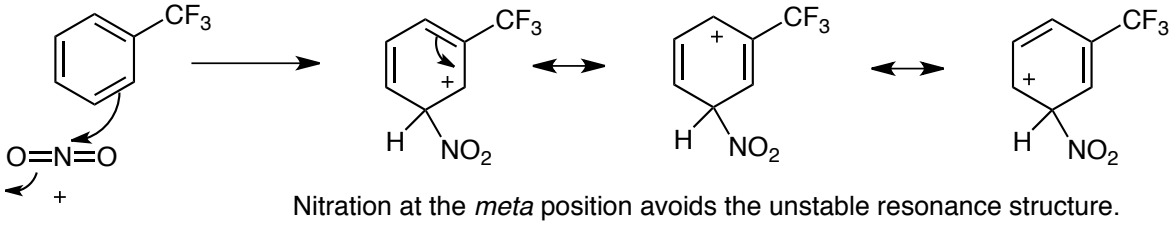
We see the same situation in attack at the *para* position. *Para* attack puts the (+) charge on the carbon bearing the trifluoromethyl group. Again, this is a very high energy resonance structure.

***Para* Nitration**



Particularly unstable resonance structure since the (+) charge is directly attached to the strong electron withdrawing group.

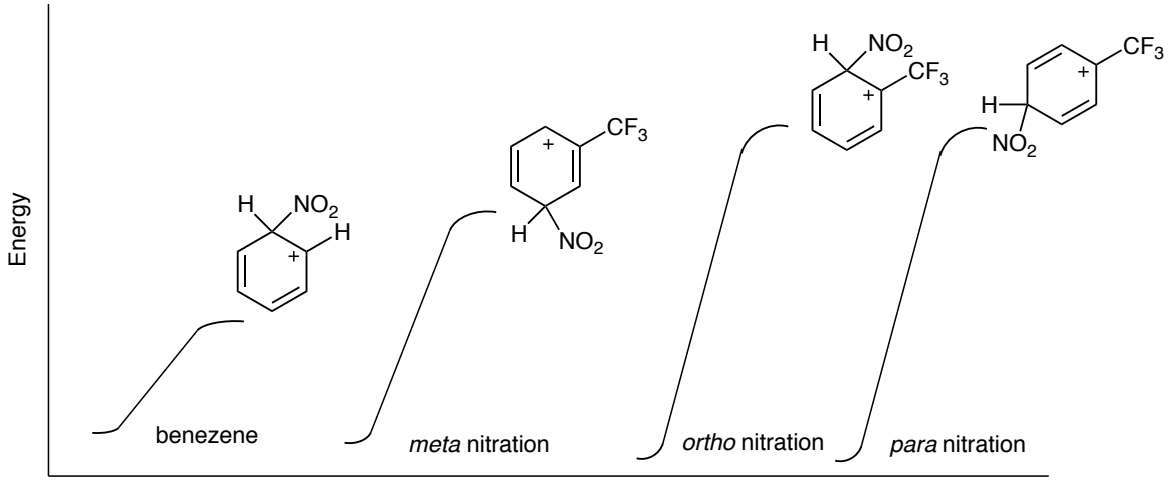
***Meta* Nitration**



Nitration at the *meta* position avoids the unstable resonance structure.

We see that *meta* nitration avoids the very high energy resonance structure where the positive charge is on the carbon that is directly attached to the electron withdrawing trifluoromethyl group.

Nitration at all three positions of trifluoromethylbenzene is slower than for benzene but it is less slow at the *meta* position. Looking at an energy diagram showing the relative stabilities of the carbocations intermediates involves illustrates this. The carbocation formed from addition of the nitronium ion at the *meta* position is lower in energy than the carbocation formed from addition at the *ortho* or *para* positions and therefore the *meta* product forms faster.



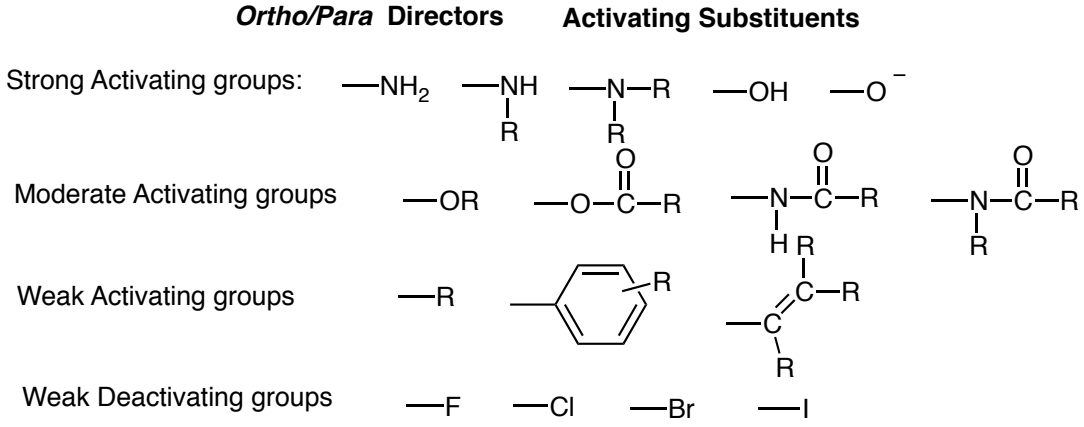
The trifluoromethyl and toluene examples can be extended to include more substituents and we can make general rules regarding activating and directing effects.

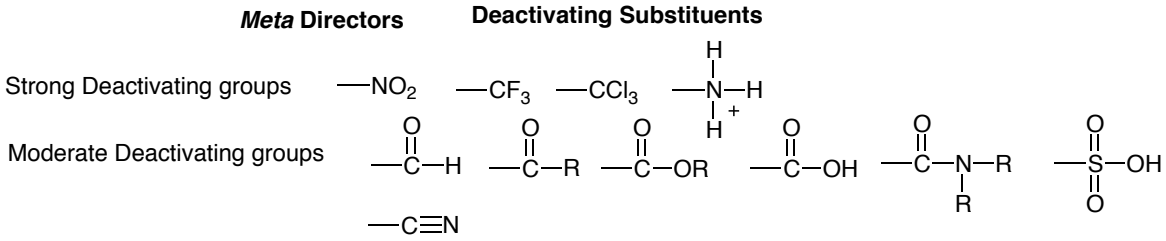
All electron donating groups are activating and direct the in-coming substituent to the *ortho* and *para* positions.

All electron withdrawing substituents are deactivating and direct *meta*.

The one exception to this rule is the halogens. These are deactivating but direct incoming substituents to the *ortho* and *para* positions.

The common substituents and their effects are grouped below. It is essential to be able to look at a substituent and predict its directing effect.





Activating Substituents

The strongest activating substituents, those having an oxygen or nitrogen directly attached to the benzene ring, have a lone pair that is capable of donation into the benzene ring by means of overlap of the lone pair with the adjacent p orbitals of the π–system through resonance.

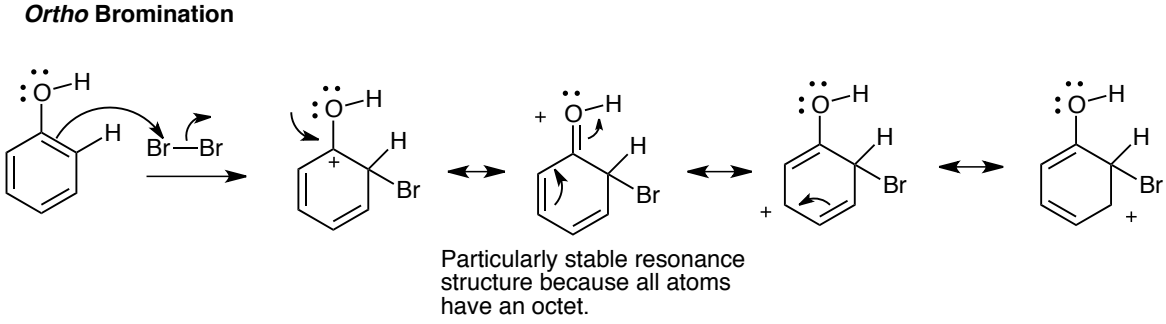
Note that there are two opposing trends:

(1) There is an inductive effect in which the oxygen, being more electronegative than the sp^2 carbon, withdraws electrons through the sigma bond. This acts to decrease the electron density of the benzene ring.

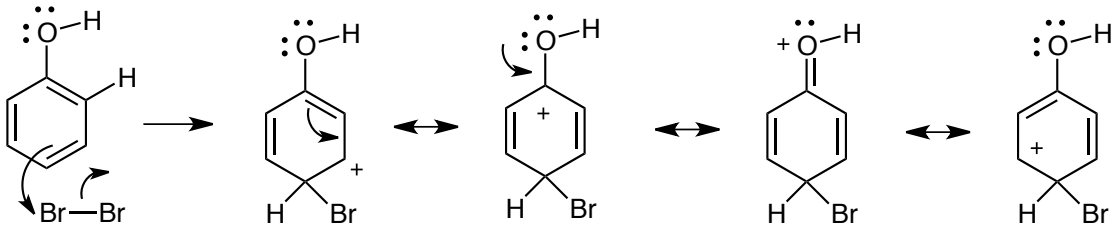
(2) There is an opposite resonance effect that donates electrons through the oxygen lone pair as described above.

In the case of oxygen, the resonance effect is much larger than the inductive effect and so overall the hydroxyl (-OH), alkoxy (-OR) and acyloxy (-O_2CR) is electron donating and therefore activating and *ortho*/*para* directing.

Look at the bromination of phenol. The phenol ring is so electron rich that no Lewis Acid catalyst is needed. Bromination at the *ortho* position gives a particularly stable arenium ion in which the positive charge is directly on a carbon to which the oxygen is attached. This allows for lone pair donation to the carbocation, stabilizing it.

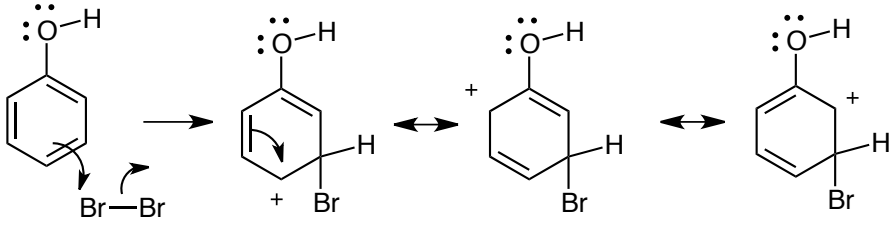


***Para* Bromination**



Attack at the *meta* position would result in a higher energy arenium ion because there would be no carbocation that is directly stabilized by the oxygen lone pair.

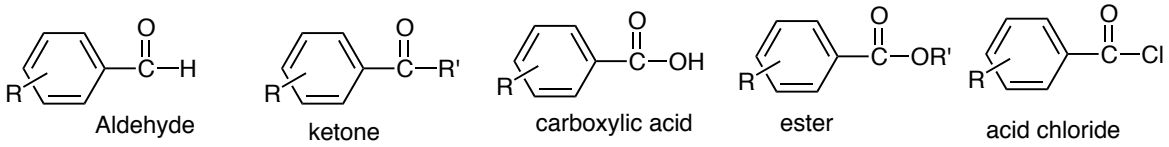
***Meta* Bromination**



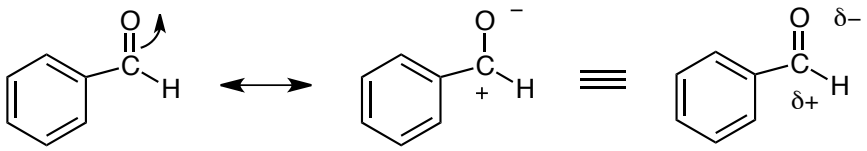
Amines are even stronger activating groups since the resonance overlap of the lone pair is even more effective than with oxygen and inductive effect is less than with oxygen since nitrogen is less electronegative than oxygen.

Deactivating Substituents – *Meta* Directors

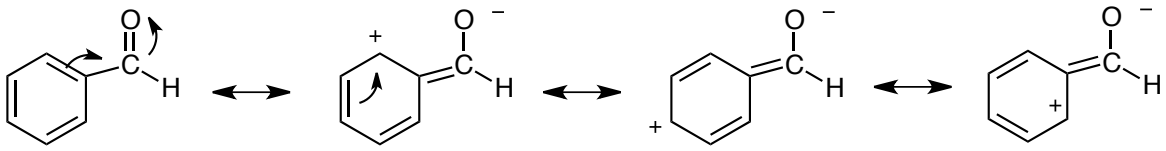
All substituents in which a carbonyl group is attached directly to the benzene ring are deactivating. This includes the following compounds:



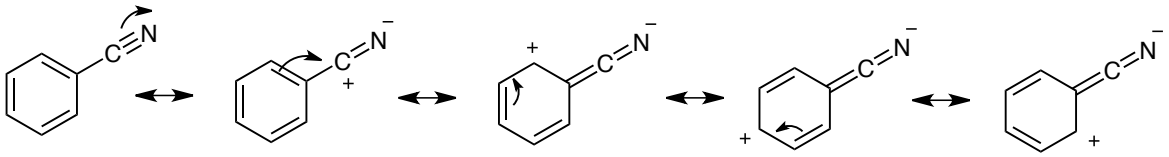
The carbonyl carbon has a partial (+) charge (δ+) that withdraws electrons from the benzene ring in an inductive effect.



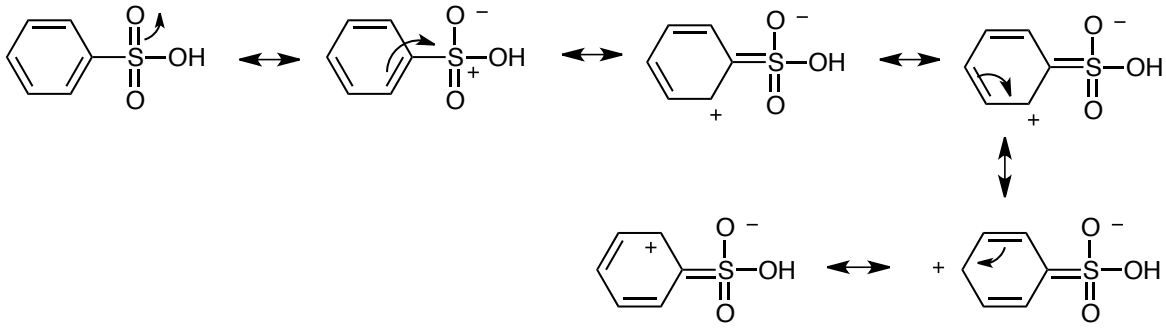
There is also a resonance delocalization of the benzene π–system onto the carbonyl. This also withdraws electrons from the benzene ring and is deactivating. This is shown below for benzaldehyde.



The cyano group (-CN) has a similar effect.



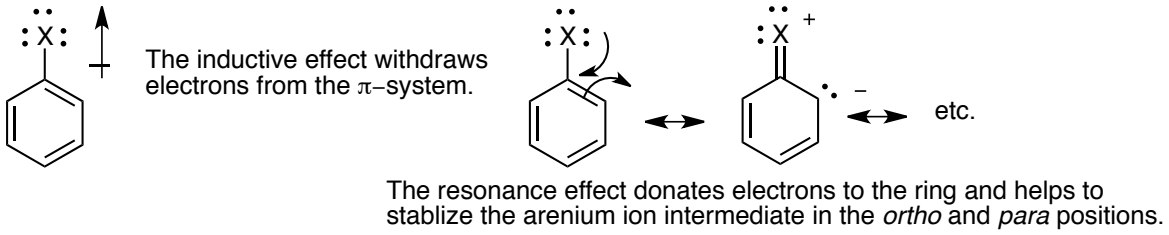
And also the sulfonyl group.



Halogens

Halogens (I, Br, Cl, F) are the exception to the general rule. They are electron withdrawing substituents and deactivating but they direct to the *ortho* and *para* positions. This is a combination of the two factors, the inductive effect and the resonance effect. Since they are electronegative, they with draw electrons from the benzene π–system (inductive effect) but they are also good at stabilizing the arenium ion intermediate through resonance donation of the lone pair. This is similar to the situation with oxygen and

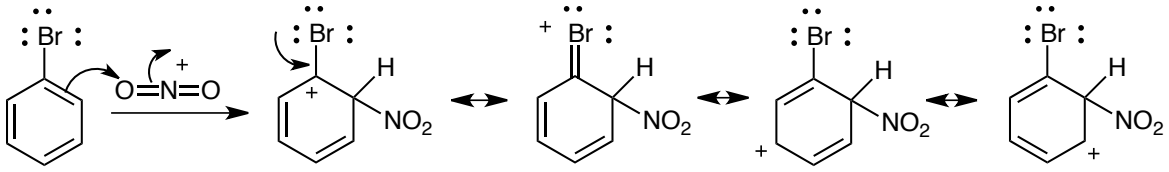
nitrogen substituents but in the case of the halogens, the inductive effect is stronger than the resonance effect (With oxygen and nitrogen it is the opposite; the resonance effect is larger than the inductive effect.).



The resonance effect donates electrons to the ring and helps to stablize the arenium ion intermediate in the *ortho* and *para* positions.

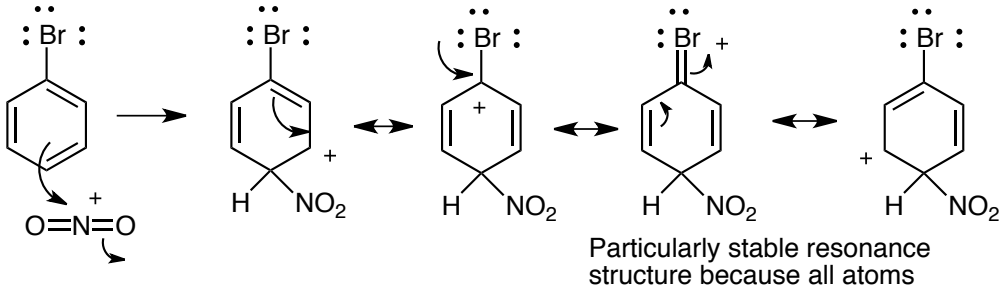
For nitration of bromobenzene, the intermediate arenium ion is more stable (lower in energy) when the nitronium ion adds in the *ortho* and *para* positions. This allows for a resonance structure in which the positive charge ends up on the carbon that bears the bromine. Lone pair donation from the benzene π–system helps to stabilize it and all atoms have an octet of electrons. This direct donation cannot occur when addition of the nitronium ion electrophile occurs at the *meta* position.

***Ortho* Nitration**



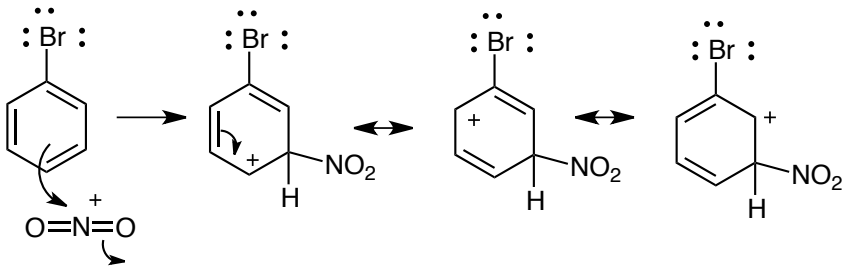
Particularly stable resonance structure because all atoms have an octet.

***Para* Nitration**



Particularly stable resonance structure because all atoms have an octet.

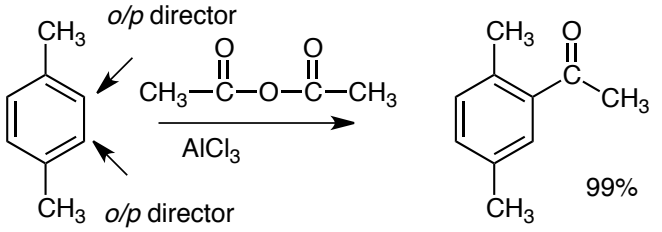
***Meta* Nitration**



Multiple Substituents

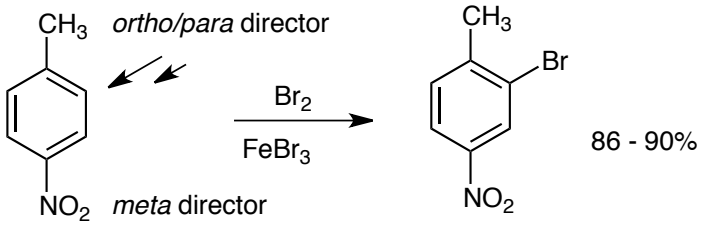
When there are two or more substituents on a ring, the directing group effects of both substituents must be taken into effect.

If both substituents have the same directing effect, the effects reinforce each other and usually one major product is formed in good yield. For example, in the Friedel-Crafts acylation of 1,4-dimethylbenzene (*para*-xylene), both substituents direct *ortho*/*para* and by symmetry the two *ortho* positions are the same. Note that an incoming electrophile will only replace a hydrogen, not another substituent, so the *para* position is blocked and so the only available position is the *ortho* to either methyl group.



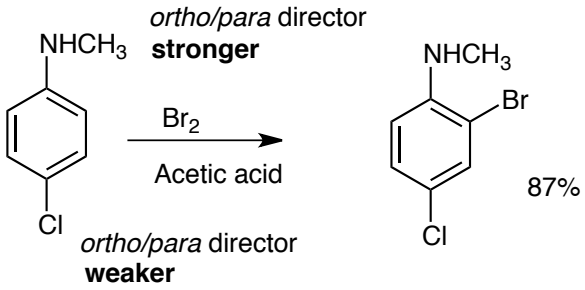
Both susbstituents reinforce each other.

Another example in which both existing substituents reinforce each other is *para*-nitrotoluene. The nitro group directs *meta* and the methyl group directs *ortho* and *para*. The *para* position is blocked by the nitro substituent so the directing effects of both groups reinforce each other to give excellent yields of 2-bromo-4-nitrotoleune. To repeat, the directing effect of the incoming electrophile is not important. The result is the same for bromination, nitration, alkylation, etc.

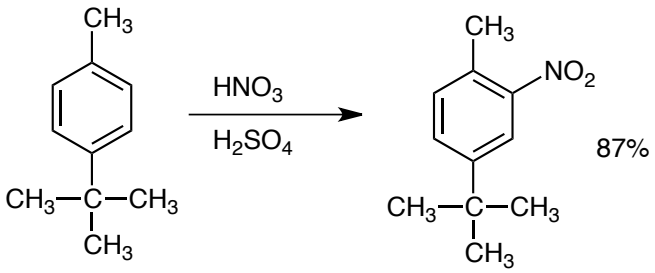


If the directing effects oppose each other, then the stronger activating group dominates and controls the regioselectivity.

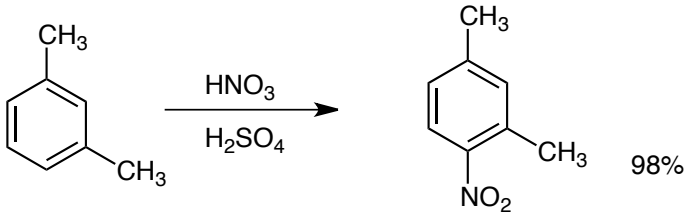
For example in the bromination of 4-chloro-N-ethylaniline, the methylamino substituent is a strong *ortho*/*para* director than the chloride and so the major product results from reaction at the position *ortho* to the amino group.



If two positions are comparably activated, substitution occurs at the less hindered position.



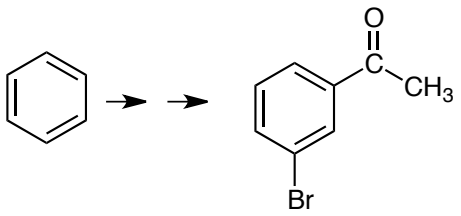
The position between two other substituents is usually the last position to be substituted, again due to steric hindrance. In the nitration of *meta*-xylene (1,3-dimethylbenzene) the nitronium ion adds *ortho* to one methyl group and *para* to the other. There are two possible positions for this to occur but by symmetry the two possible positions are the same. Nitration does not occur between the two methyl groups. This would make a very hindered 1,2,3-trisubstituted benzene derivative.

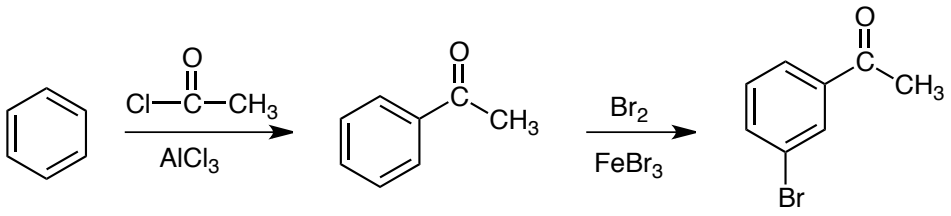


Synthesis of Disubstituted Derivatives

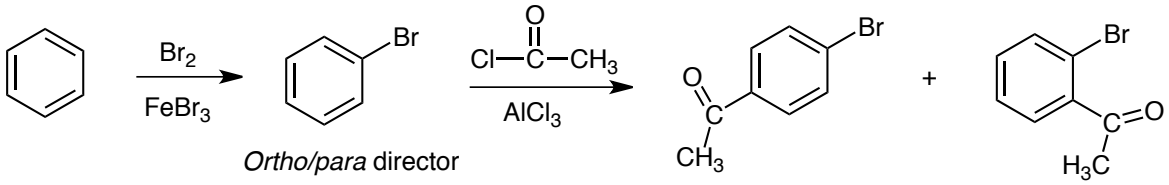
When preparing disubstituted benzene derivatives, attention must be paid to the correct order of adding the substituents so that the directing groups effects will give the desired product.

For example, in synthesizing 3-bromoacetophenone, we want to do the acylation step first because the acetyl group is a *meta* director.





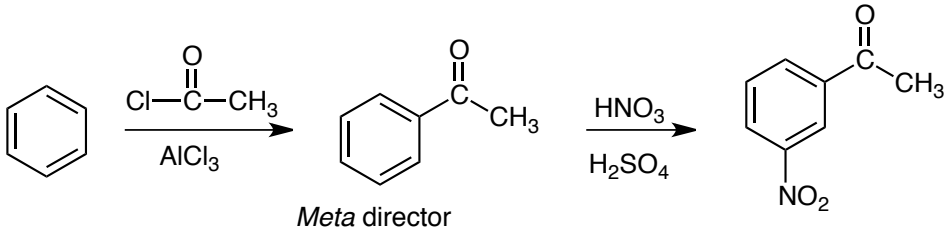
If the steps were done in the reverse order, the wrong isomer would be obtained.



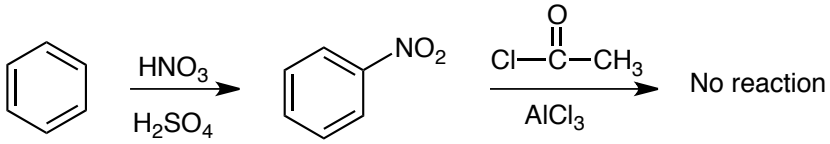
Another important consideration when planning syntheses is that both Friedel-Crafts alkylation and acylation are relatively difficult reactions and do not work well if there is a

strong deactivating group on the benzene ring. The strongest deactivating group allowable for a Friedel-Crafts reaction to work well is a halogen.

For example of make 3-nitroacetophenone, it is best to put the acetyl group on first.

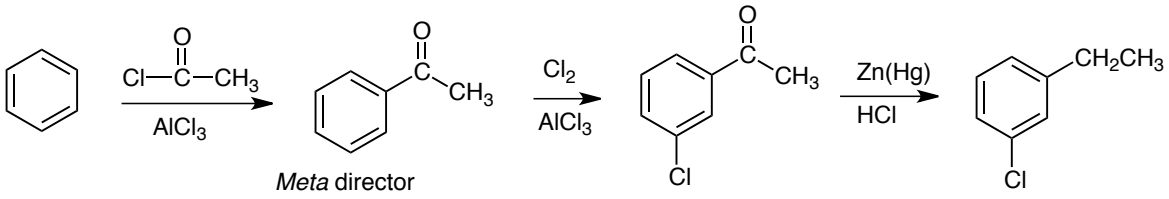


If the nitro group were put on first, then the Friedel-Crafts acylation step would not work, even though the directing group effects are correct.

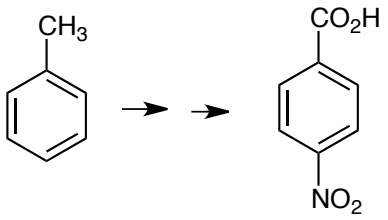


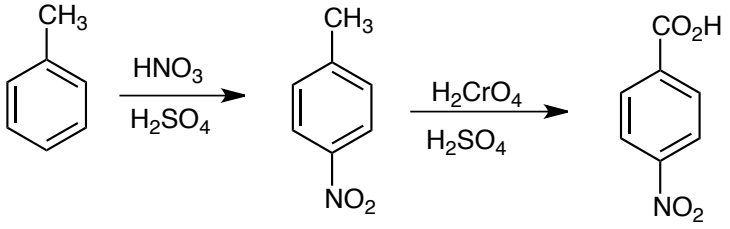
Monohalogenated benzene rings will undergo Friedel-Crafts reactions.

For the following synthesis we want a 1,3-(or meta) relationship between an ethyl group and a chlorine. This is achievable if the molecule is acylated first to give a *meta* directing acetyl group. The chlorine can then be added and then the acyl group is reduced.



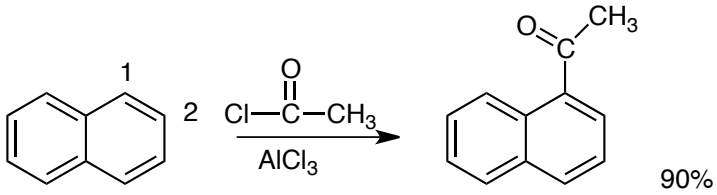
Another synthetic example where the order of steps is critical is synthesis of 4-nitrobenzoic acid from toluene. The methyl group of toluene is an *ortho/para* director while the carboxylic acid is a *meta* director so the correct order of steps is to nitrate toluene first and then oxidize the methyl group to the carboxylic acid.





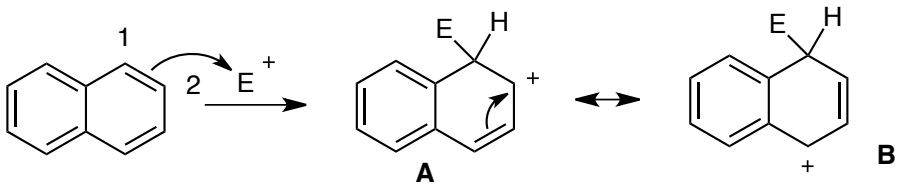
Substitution in Naphthalene

Polycyclic systems react with the same reagents as benzene and they are generally more reactive than benzene itself. In naphthalene, the C1 carbon is the more reactive site.



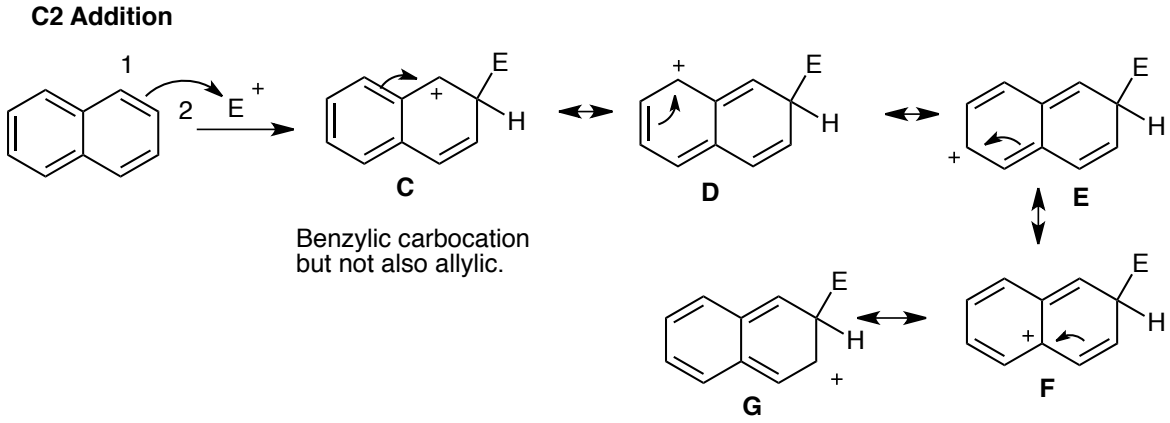
The preference for reaction at C1 rather than C2 can be seen by looking at the resonance structures involved. When the electrophile adds to the C1 position, it forms a more stable carbocation that is lower in energy since in resonance structure **B** there is both benzylic stabilization and allylic stabilization and the full aromaticity of the benzene aromatic system is preserved.

C1 Addition



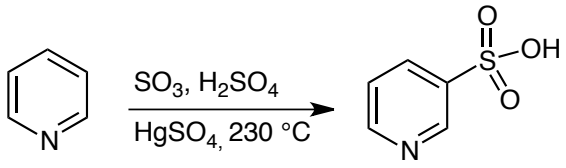
Here in this resonance structure we have allylic and benzylic type resonance stabilization of the carbocation in which the benzene aromatic system in the other ring is fully intact.

Addition at C2, however, gives a carbocation that is higher in energy. In resonance structure **C** we have benzylic stabilization (but not also allylic as in resonance structure **B** above).

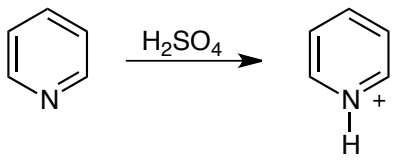


Heterocyclic Compounds

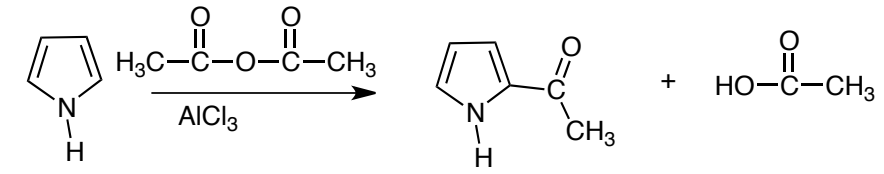
Pyridine is much less reactive to substitution than benzene due to the electron withdrawing nitrogen in the ring. It is similar in reactivity to nitrobenzene. Pyridine can be sulfonated at high temperature at the 3-position.



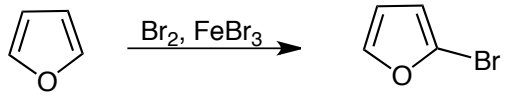
One reason for the low reactivity of pyridine is due to the electronegativity of the nitrogen and another reason is that the nitrogen can be protonated under the acidic conditions to make it an even strong electron withdrawing group.



Pyrrole, furan and thiophene are all electron rich aromatic rings and are extremely reactive to electrophilic aromatic substitution reactions. They are similar to phenol and aniline in terms of reactivity. There are five atoms sharing 6 π–electrons, whereas in benzene there are 6 π–electrons shared by six atoms.

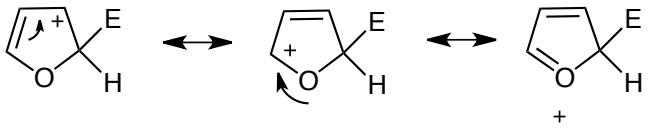


pyrrole



furan

Attack at the 2-position is preferred since the resulting carbocation is lower in energy. Because the (+) charge is spread out over three different atoms, carbon-3, carbon-2 and the oxygen.



The (+) charge is spread out over three atoms: C3, C2, and the oxygen.

But in attack at the 3-position, the (+) charge is spread out over only two atoms, carbon-2 and the oxygen.