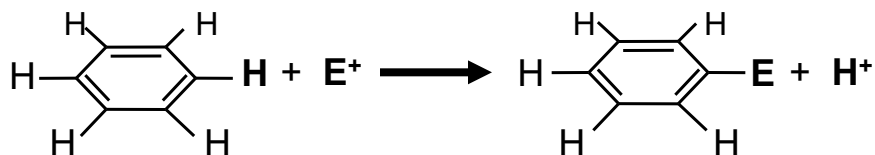


# Lecture 11 and 12

## The Page Lectures

- Electrophilic Aromatic Substitution

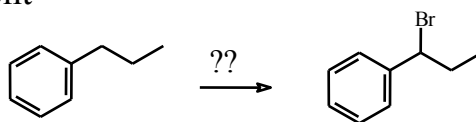


February 26 and 28 2019

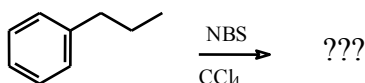
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## Please try Flash Card Trick

- front



- Back



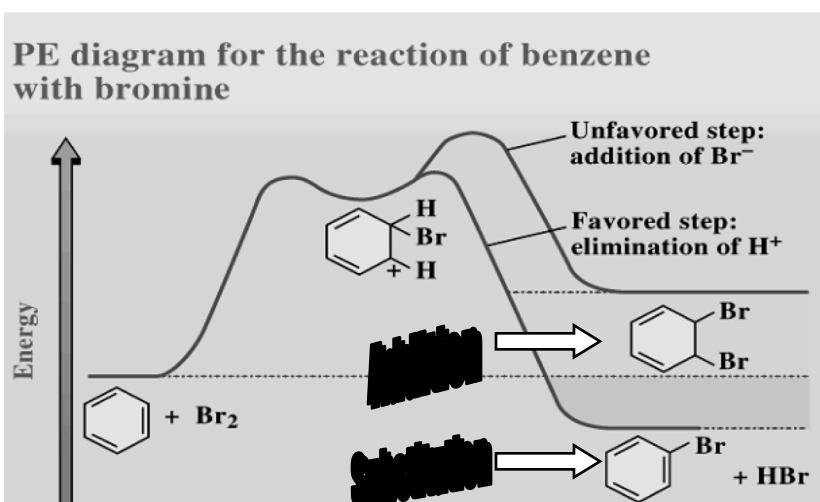
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## Electrophilic Aromatic Substitution

- Electrophilic aromatic substitution: a reaction in which a hydrogen atom on an aromatic ring is replaced by an electrophile
- We study
  - several common types of electrophiles,
  - how they are generated, and
  - the mechanism by which they replace hydrogen, which is the same for all

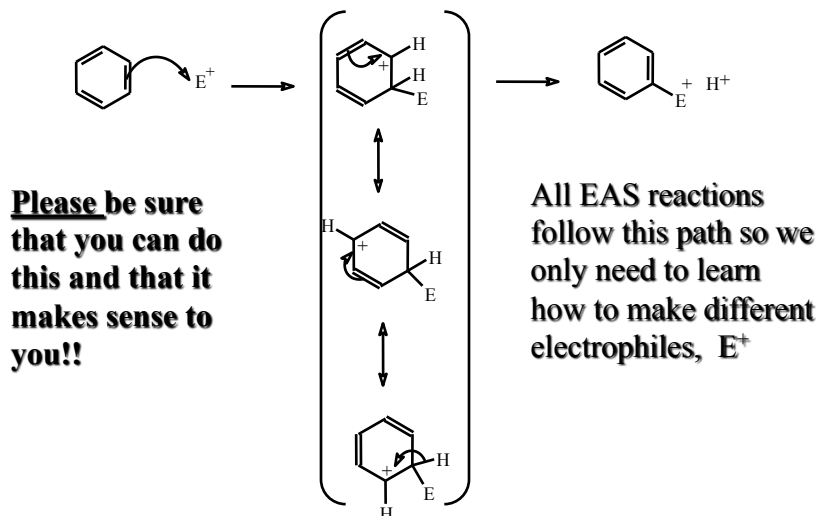
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## Substitution vs Addition



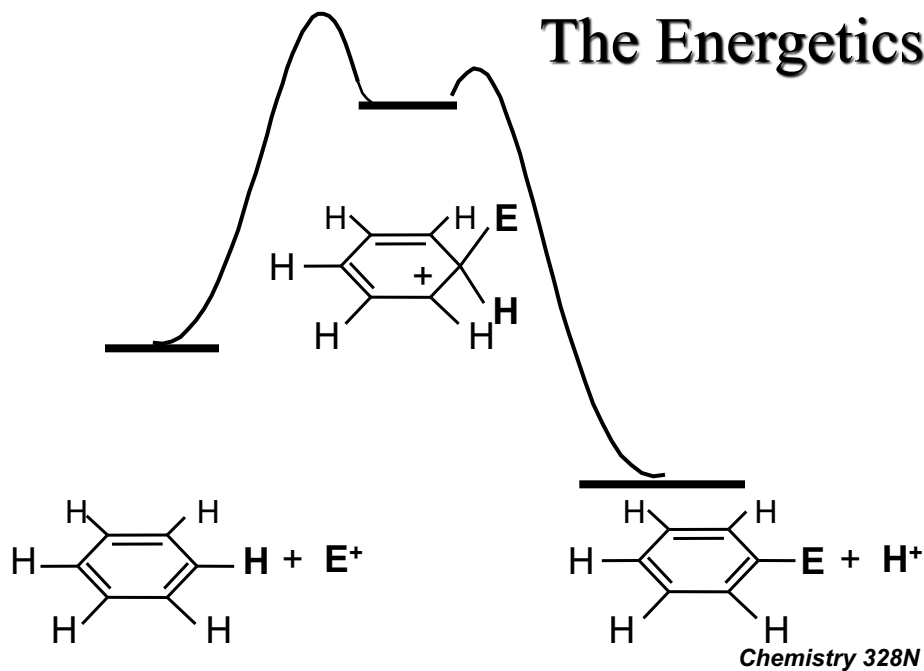
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## Electrophilic Aromatic Substitution

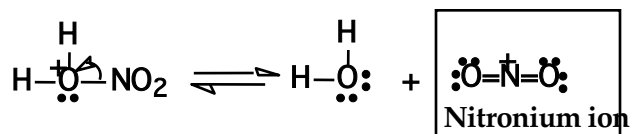
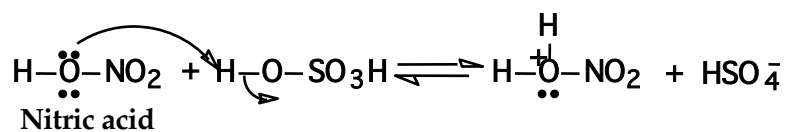
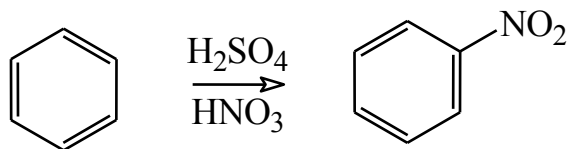


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## The Energetics



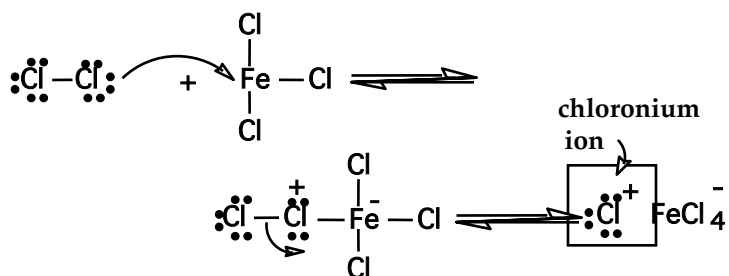
# Nitration



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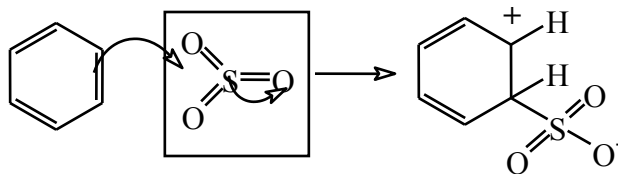
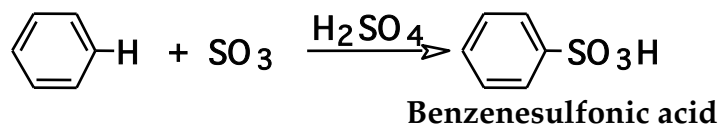
# Chlorination

- Chlorination requires requires a Lewis acid catalyst, such as  $\text{AlCl}_3$  or  $\text{FeCl}_3$



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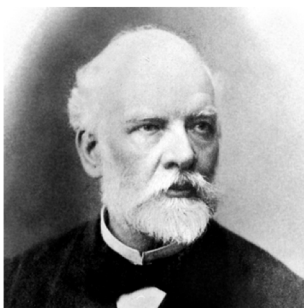
# Sulfonation



Sulfonation can be reversed by Heating in H<sub>2</sub>O

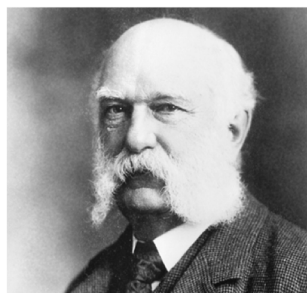
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## *The Friedel-Crafts Reaction.. Circa 1877*



Courtesy Edgar Fahs Smith Collection,  
Van Pelt Library, University of Pennsylvania

Charles Friedel



Courtesy Edgar Fahs Smith Collection,  
Van Pelt Library, University of Pennsylvania

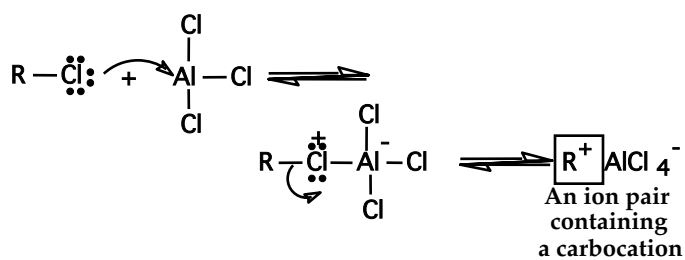
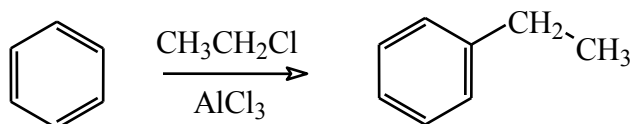
James Craft

Making C-C bonds is....

~~not~~ **a BIG deal**

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## Friedel-Crafts Alkylation

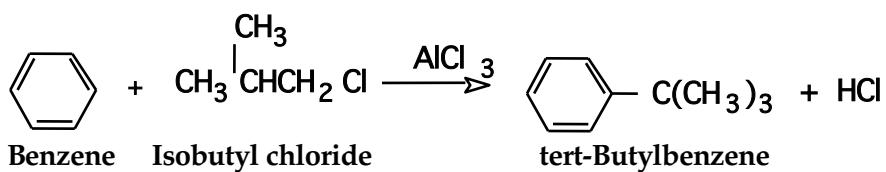


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## A word about the Friedel-Crafts Alkylation

### Caution!!!

1. Carbocation rearrangements are common



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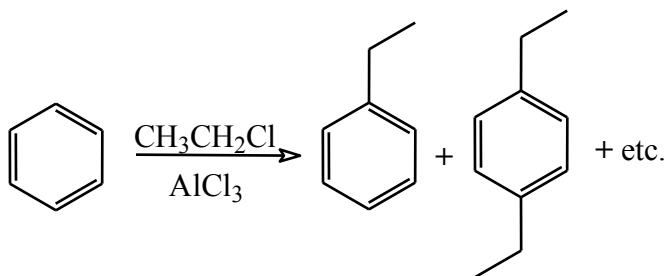
## Friedel-Crafts Alkylation

### Caution!!!!

2. They are tough to stop!

Product is more reactive than the starting material

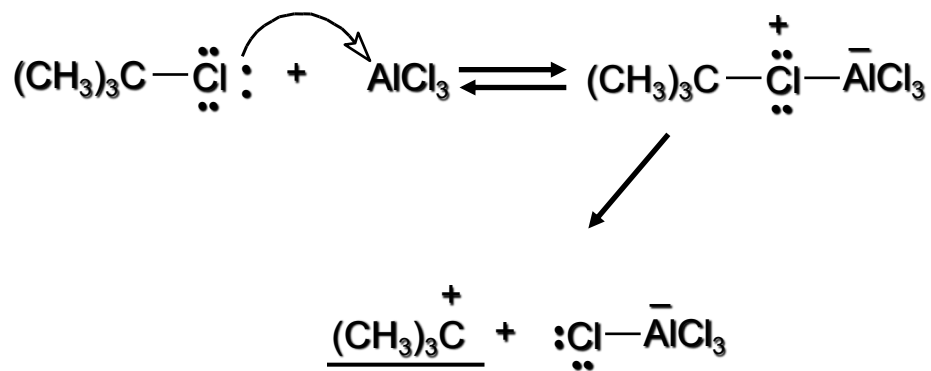
Hence. Terrible mixtures result....



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## Role of $\text{AlCl}_3$

Acts as a Lewis acid to promote ionization of the alkyl halide

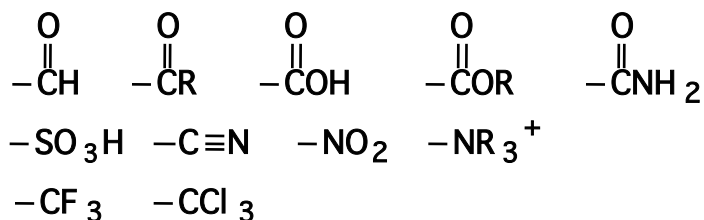


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## Friedel-Crafts Alkylation

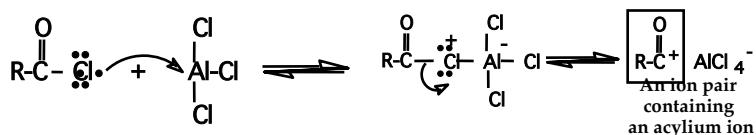
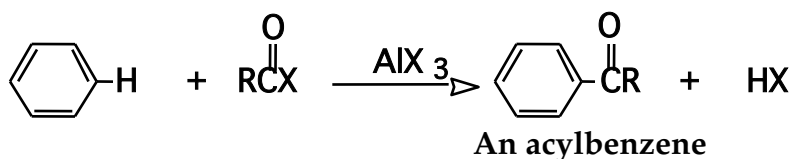
### Caution!!!!

alkylation **fails** on benzene rings bearing one or more strongly electron-withdrawing groups



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## Friedel-Crafts Acylation

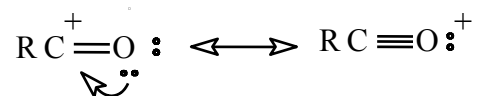


Chemistry 328N



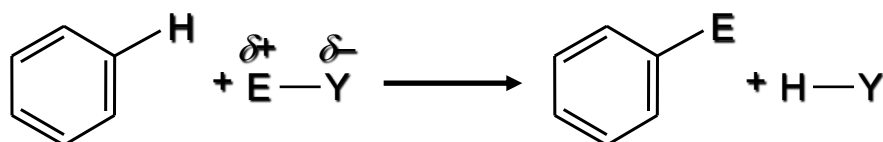
## Friedel-Crafts Acylation

- An acylium ion is a resonance hybrid of two major contributing structures



- F-C acylations are free of TWO major limitation of F-C alkylations; acylium ions do not rearrange and the product is deactivating so the reaction stops after one substitution!!!

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Electrophilic aromatic substitutions include:

Nitration

Sulfonation

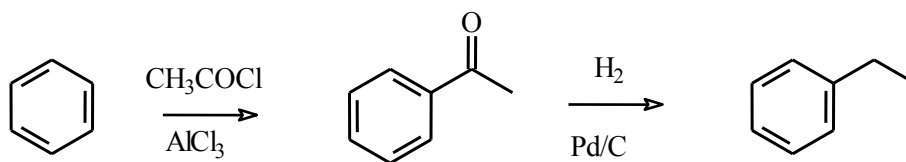
Halogenation

Friedel-Crafts Alkylation

Friedel-Crafts Acylation

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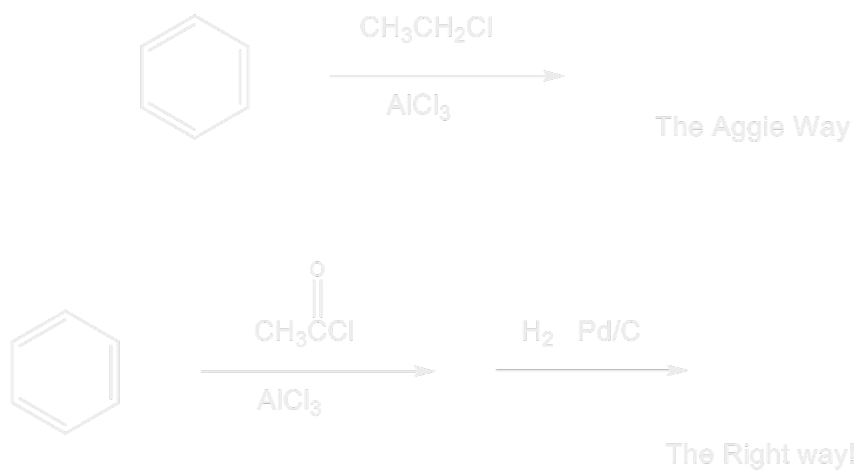
# Hydrogenolysis



There are two nice tricks hidden here  
Works on benzylic alcohol and ethers as well.  
Please be sure to remember this reaction!!!

*Chemistry 328N*

# How to make ethyl benzene



*Chemistry 328N*

## Di- and Polysubstitution

- Existing groups on a benzene ring influence further substitution in both **orientation** and rate
- Orientation:
  - certain substituents direct preferentially to ortho & para positions; others direct preferentially to meta positions
  - substituents are classified as either  
**ortho-para directing..... or  
meta directing**

*Chemistry 328N*

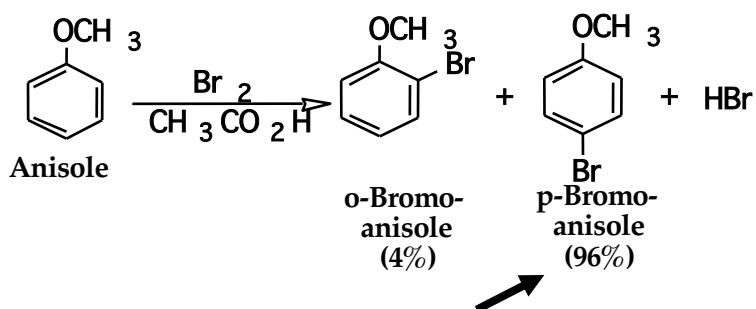
## Di- and Polysubstitution

- Rate:
  - certain substituents cause the rate of a second substitution to be greater than that for benzene itself; others cause the rate to be lower
  - substituents are classified as
    - activating toward further substitution, or
    - deactivating

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## Di- and Polysubstitution

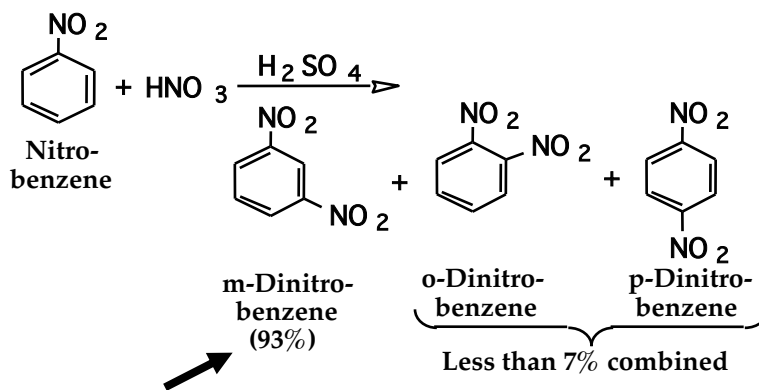
- $-\text{OCH}_3$  is ortho-para directing and activating



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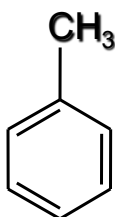
## Di- and Polysubstitution

- $-\text{NO}_2$  is meta directing and deactivating!



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## Methyl Group

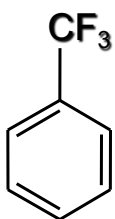


Toluene undergoes nitration 1000 times faster than benzene.

A methyl group is an **activating** substituent.

*Chemistry 328N*

## Trifluoromethyl Group

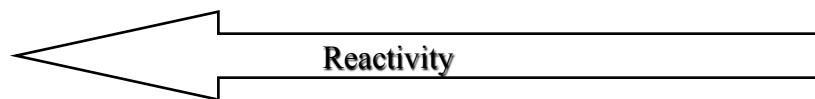
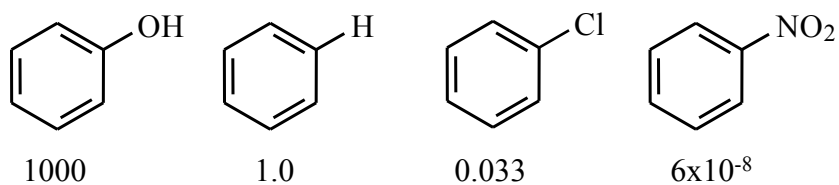


Trifluoromethylbenzene undergoes nitration 40,000 times more slowly than benzene .

The trifluoromethyl group is a **deactivating** substituent.

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# Relative rates of Nitration



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## Effects of substitution on further electrophilic aromatic substitution

Ortho-Para Directing	Strongly activating	<chem>N</chem>	<chem>NHR</chem>	<chem>NR2</chem>	<chem>O</chem>		Real Fast
	Moderately activating	<chem>NHCR</chem>	<chem>NHCAr</chem>	<chem>OR</chem>	<chem>OCR</chem>	<chem>OCAr</chem>	Pretty fast
	Weakly activating	<chem>R</chem>	<chem>c1ccccc1</chem>				Kinda slow
	Weakly deactivating	<chem>F</chem>	<chem>Cl</chem>	<chem>Br</chem>	<chem>I</chem>		Pretty slow
Meta Directing	Moderately deactivating	<chem>CH</chem>	<chem>CR</chem>	<chem>COH</chem>	<chem>COR</chem>	<chem>CNH2</chem> <chem>SOH</chem>	Slow
	Strongly deactivating	<chem>NO2</chem>	<chem>NH3+</chem>	<chem>CF3</chem>	<chem>CCl3</chem>	<chem>C#N</chem>	Real Slow

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## Di- and Polysubstitution

### Some observations

- Alkyl groups, phenyl groups, and all groups in which the atom bonded to the ring has an *unshared pair of electrons* are ortho-para directing. All other groups are meta directing.
- All ortho-para directing groups except the halogens are activating toward further substitution. The halogens are weakly deactivating

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## Effect on Regioselectivity

- *Ortho-para directors* direct an incoming electrophile to positions ortho and/or para to themselves.
- *Meta directors* direct an incoming electrophile to positions meta to themselves.
- *All meta directors* are deactivating
- *All ortho-para directors* are activating *except* halogen

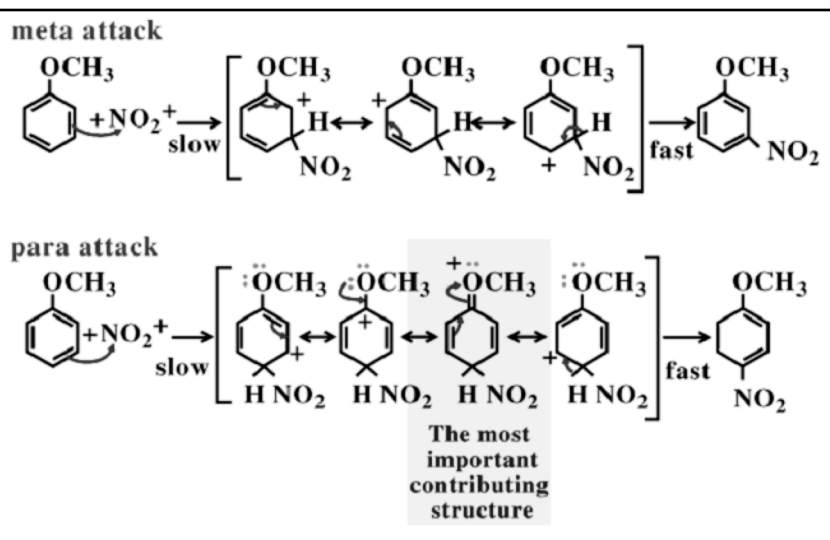
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## Theory of Directing Effects

- *So...what's going on here????*
- The rate of EAS is limited by the slowest step in the mechanism...duh
- For EAS, the rate-limiting step is attack of  $E^+$  on the aromatic ring to form a resonance-stabilized cation intermediate
- The more stable this cation intermediate, the faster the rate-limiting step and the faster the overall reaction

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### Adding a Second Substituent

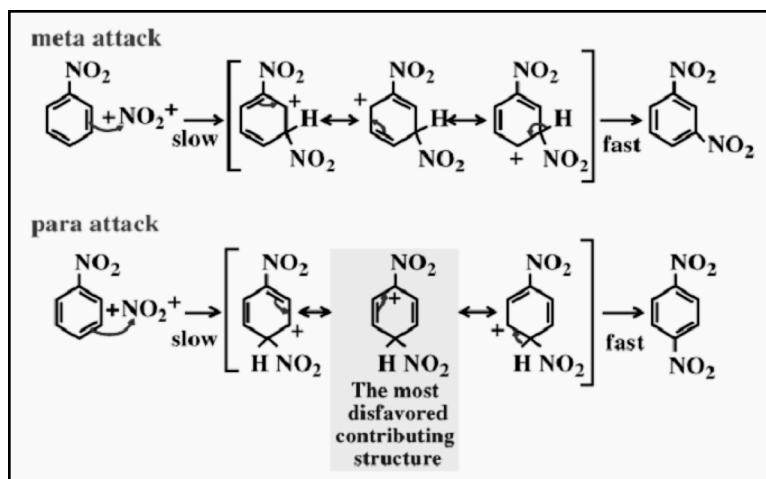


Methoxy is therefore an "o-p director"

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## Adding a Second Substituent

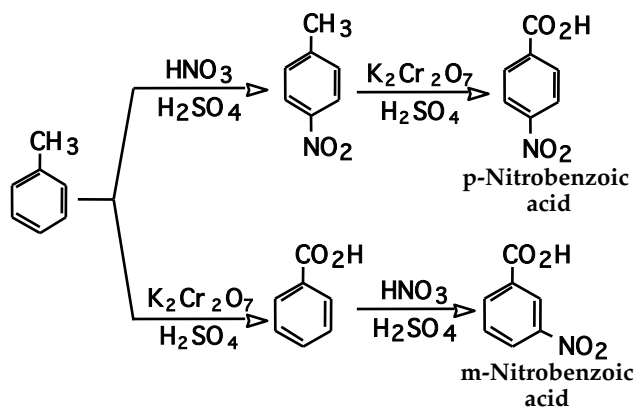


Meta attack is not good, but better than the alternative!

Nitro is therefore a “meta director”

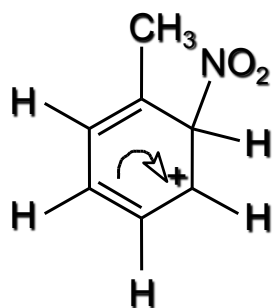
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## Di- and Polysubstitution



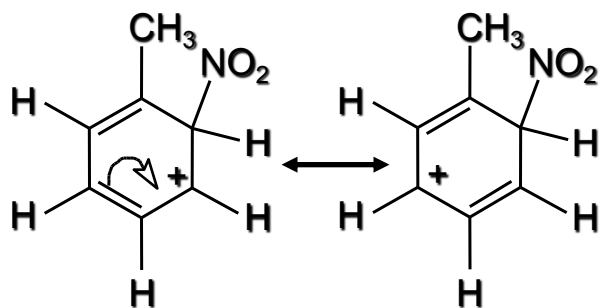
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*ortho Nitration of Toluene*



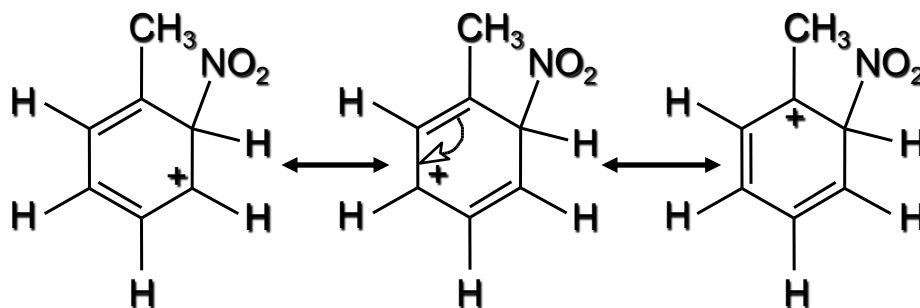
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*ortho Nitration of Toluene*



Chemistry 328N

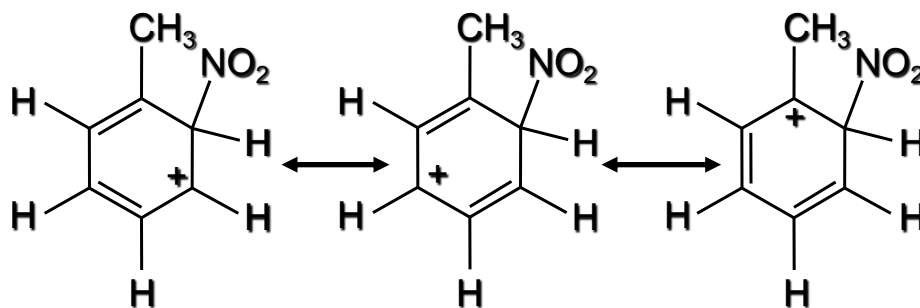
*ortho Nitration of Toluene*



this resonance form is a tertiary carbocation

*Chemistry 328N*

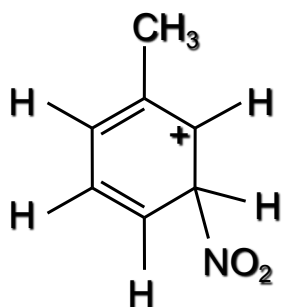
*ortho Nitration of Toluene*



the rate-determining intermediate in the ortho nitration of toluene has tertiary carbocation character

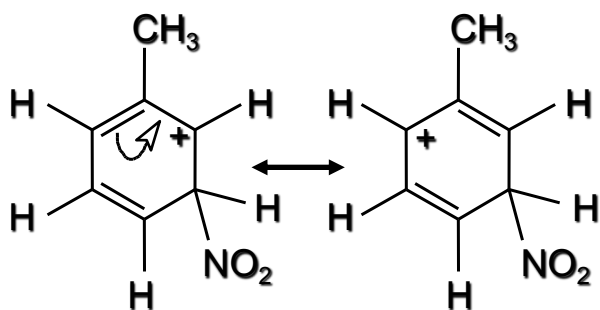
*Chemistry 328N*

*meta Nitration of Toluene*



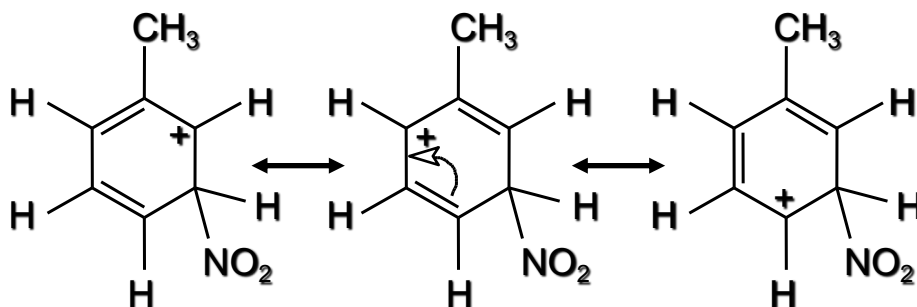
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*meta Nitration of Toluene*



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### *meta Nitration of Toluene*



all the resonance forms of the rate-determining intermediate in the meta nitration of toluene have their positive charge on a secondary carbon

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## *Nitration of Toluene: Interpretation*

- The rate-determining intermediates for ortho and para nitration each have a resonance form that is a tertiary carbocation. All of the resonance forms for the rate-determining intermediate in meta nitration are secondary carbocations.
- Tertiary carbocations, being more stable, are formed faster than secondary ones. Therefore, the intermediates for attack at the ortho and para positions are formed faster than the intermediate for attack at the meta position. This explains why the major products are *o*- and *p*-nitrotoluene.

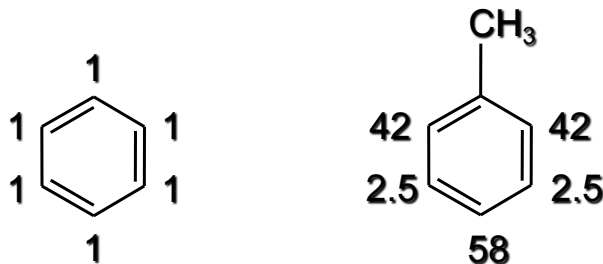
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## Nitration of Toluene: Partial Rate Factors

- The experimentally determined reaction rate can be combined with the ortho/meta/para distribution to give *partial rate factors* for substitution at the various ring positions.
- Expressed as a numerical value, a partial rate factor tells you by how much the rate of substitution at a particular position is faster (or slower) than at a single position of benzene.

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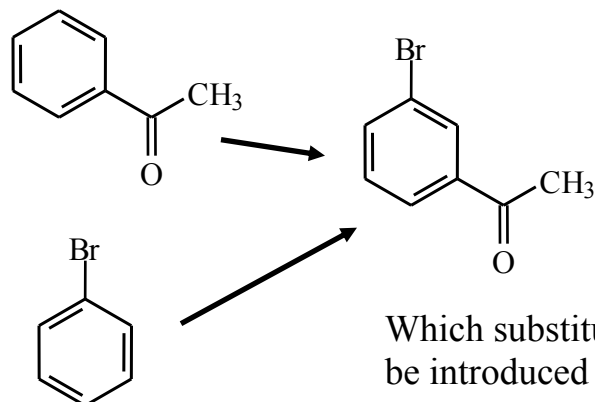
## Nitration of Toluene: Partial Rate Factors



- All ring positions in toluene are more reactive than any position of benzene.
- A methyl group activates all of the ring positions but the effect is greatest at the ortho and para positions.
- Steric hindrance by the methyl group makes each ortho position slightly less reactive than para.

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## Synthesis of m-Bromoacetophenone



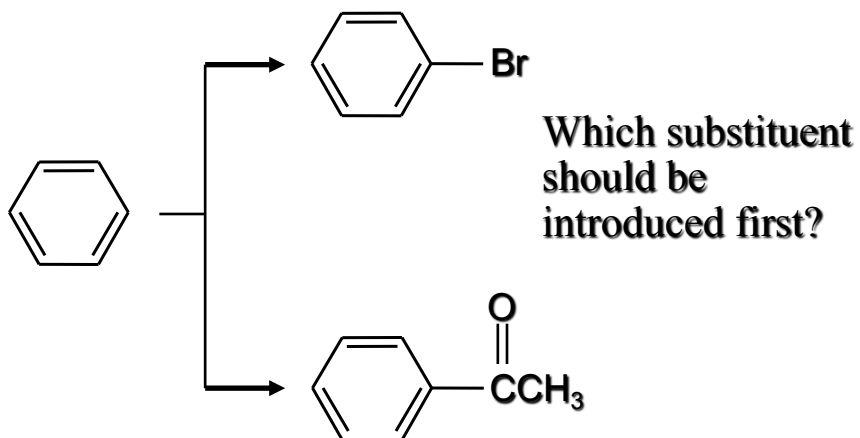
*Chemistry 328N*

## Factors to Consider

The order of the introduction of substituents must be carefully designed to ensure correct orientation

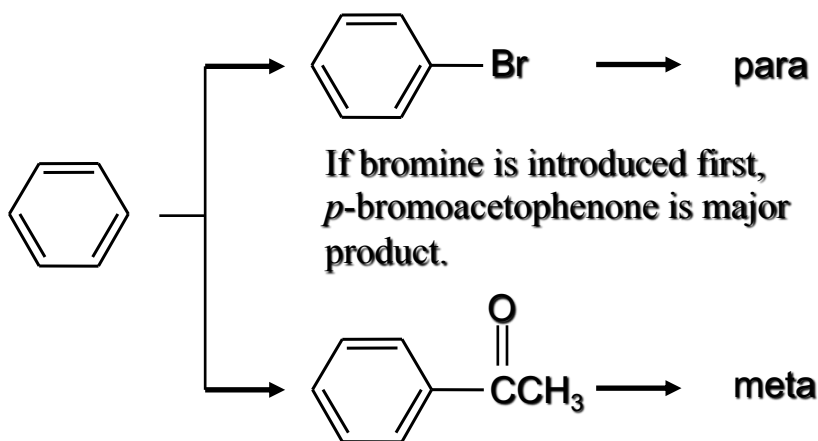
*Chemistry 328N*

### Synthesis of *m*-Bromoacetophenone



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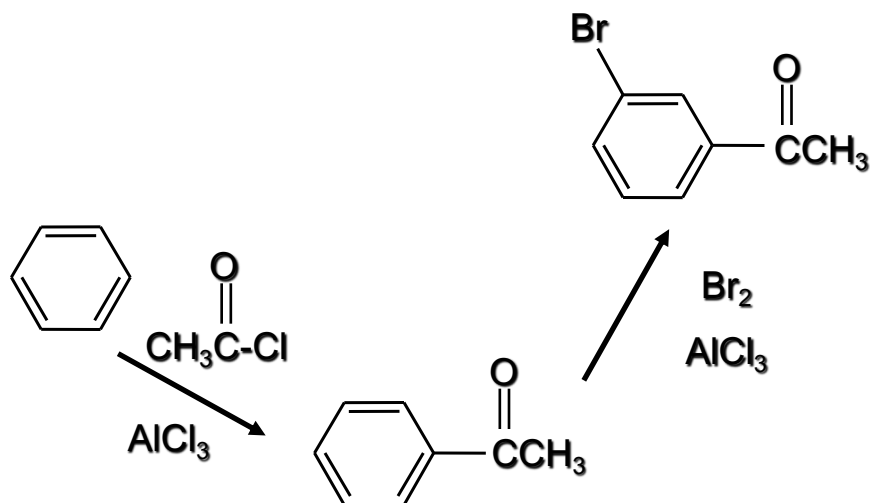
### Synthesis of *m*-Bromoacetophenone



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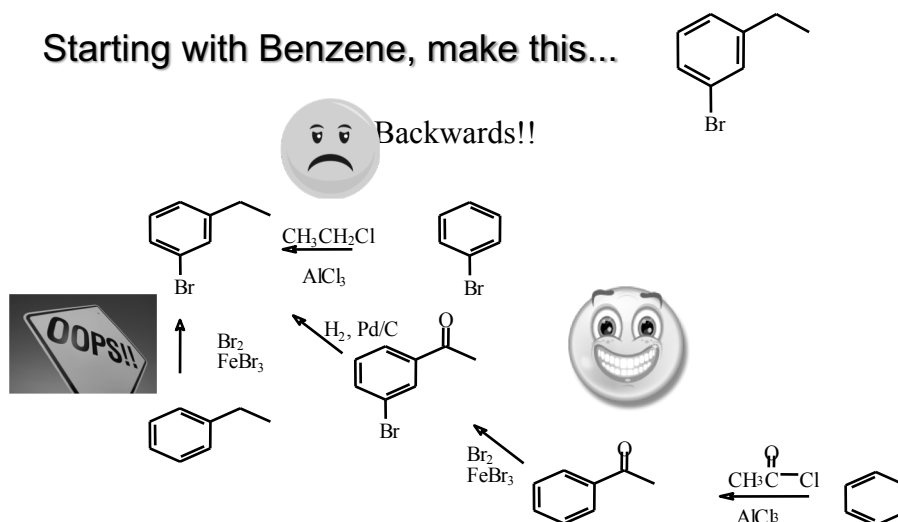


## Synthesis of *m*-Bromoacetophenone



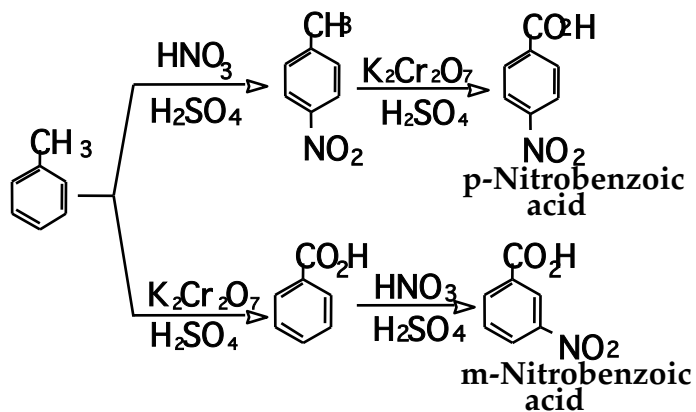
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Starting with Benzene, make this...



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## Di- and Polysubstitution



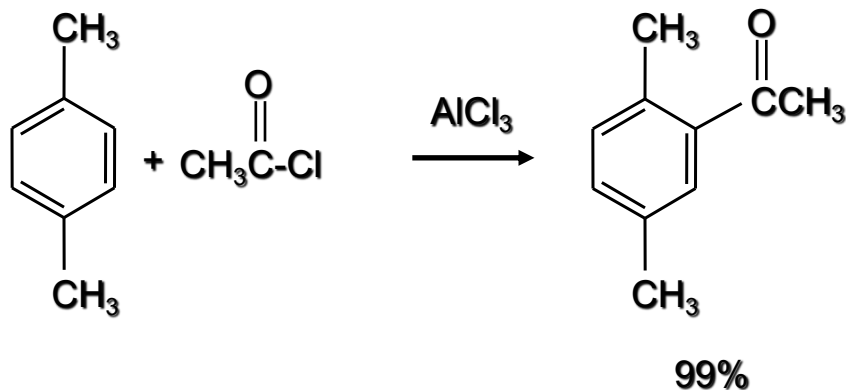
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## Multiple Substituent Effects

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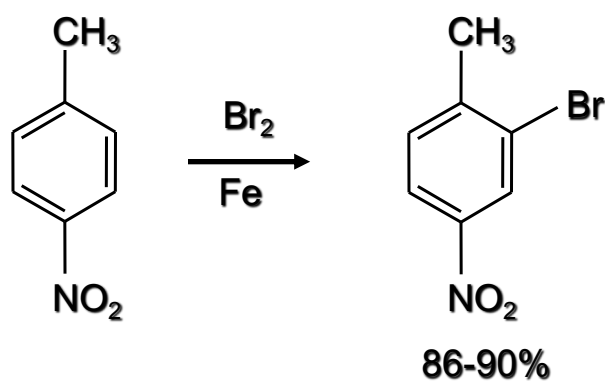
## The Simplest Case

all possible EAS sites may be equivalent



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## Another Straightforward Case



directing effects of substituents reinforce each other; substitution takes place ortho to the methyl group and meta to the nitro group

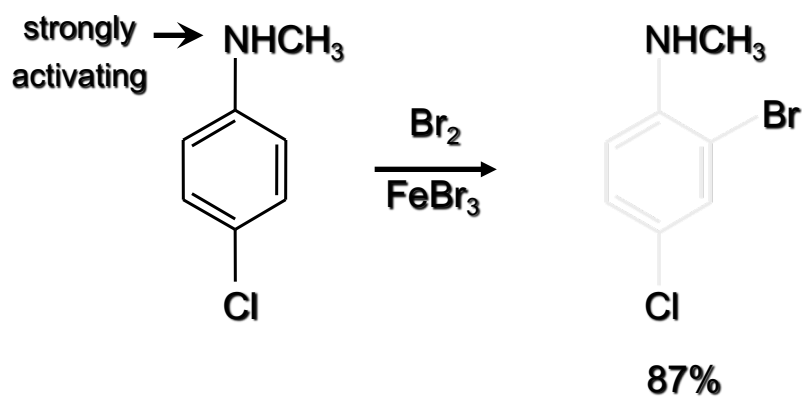
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## Generalization

regioselectivity is controlled by the most activating substituent

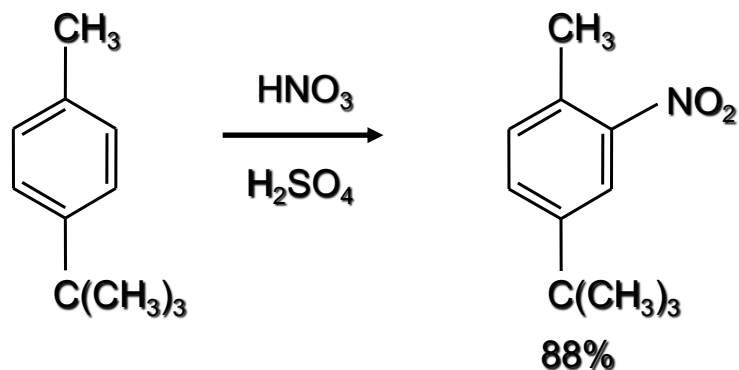
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## The “Best Man Wins”



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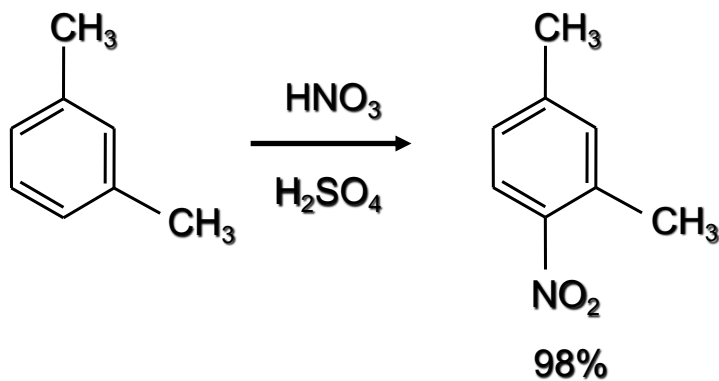
*When activating effects are similar...*



substitution occurs ortho to the smaller group

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*Steric effects control regioselectivity when electronic effects are similar*



position between two substituents is last position to be substituted

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## ***Factors to Consider***

**order of introduction of substituents to ensure correct orientation**

**Friedel-Crafts reactions (alkylation, acylation) cannot be carried out on strongly deactivated aromatics**

*Chemistry 328N*

## **Substitution in Heterocyclic Aromatic Compounds**

*Chemistry 328N*

## *Generalization*

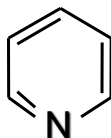
There is none.

There are so many different kinds of heterocyclic aromatic compounds that no generalization is possible.

Some heterocyclic aromatic compounds are very reactive toward electrophilic aromatic substitution, others are very unreactive..

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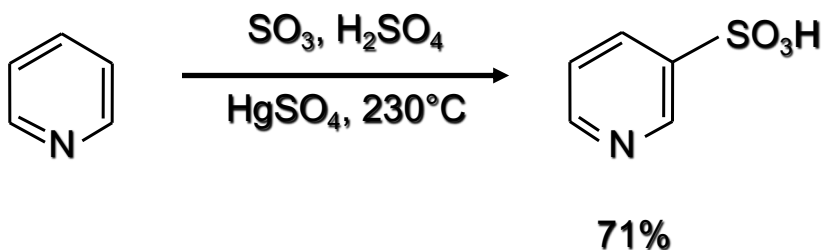
## *Pyridine*



- Pyridine is very unreactive; it resembles nitrobenzene in its reactivity.
- Presence of electronegative atom (N) in ring causes  $p$  electrons to be held more strongly than in benzene.

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## Pyridine

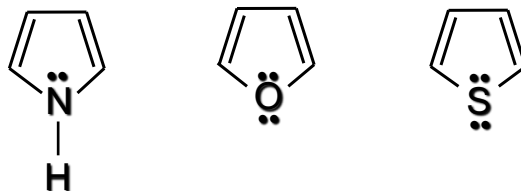


Pyridine can be sulfonated at high temperature.

EAS takes place at C-3.

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## Pyrrole, Furan, and Thiophene



Have 1 less ring atom than benzene or pyridine to hold same number of  $p$  electrons (6).

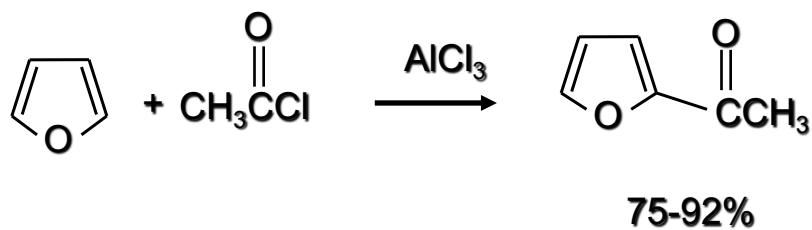
$p$  electrons are held less strongly...rings are more "electron rich".

These compounds are quite reactive toward EAS..

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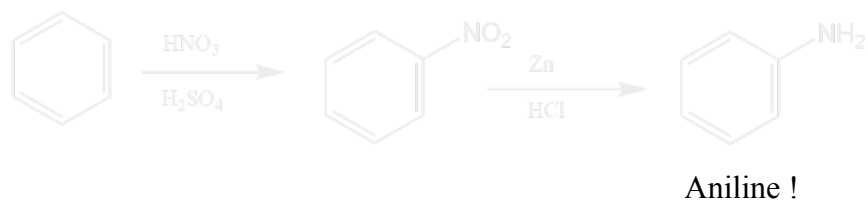
### Example: Furan



undergoes EAS readily  
C-2 is most reactive position

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## Reduction of the Nitro Group



The Nitro group is easily reduced. Many reducing agents can be employed for this transformation including Sn or Fe in HCl, H<sub>2</sub> with Pd/C, etc

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## Aniline dyes (Tyrian Purple)



Aniline Dye



Royal Purple Previously  
from shell fish secretions



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## Diazonium Salts



Diazonium Salt

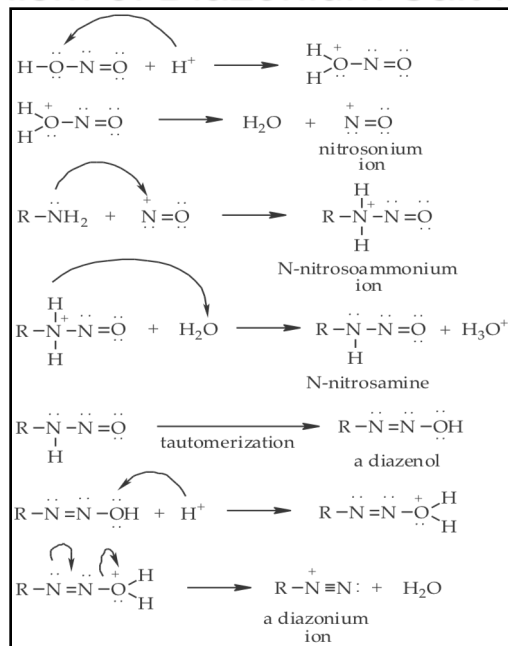


Acts like



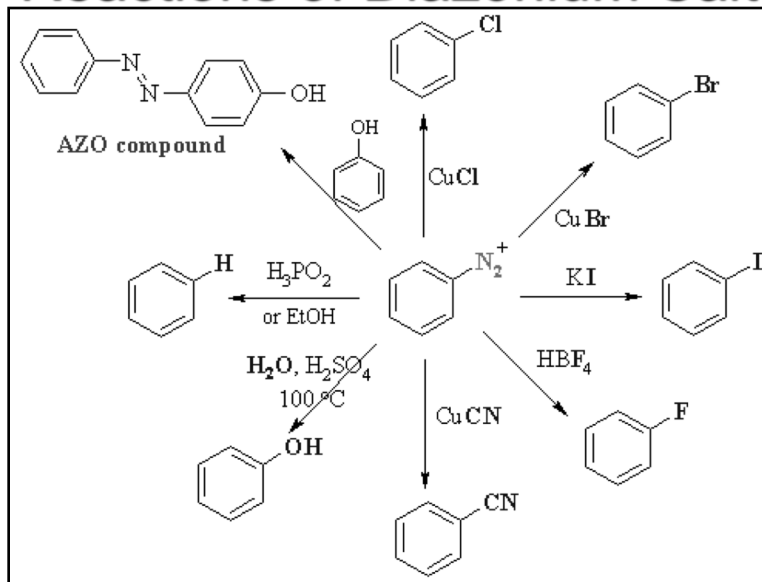
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## Mechanism of Diazonium Salt formation



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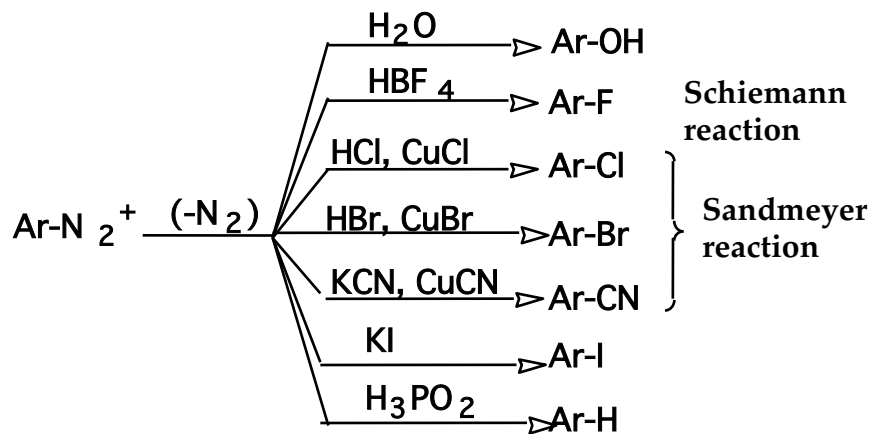
## Reactions of Diazonium Salts



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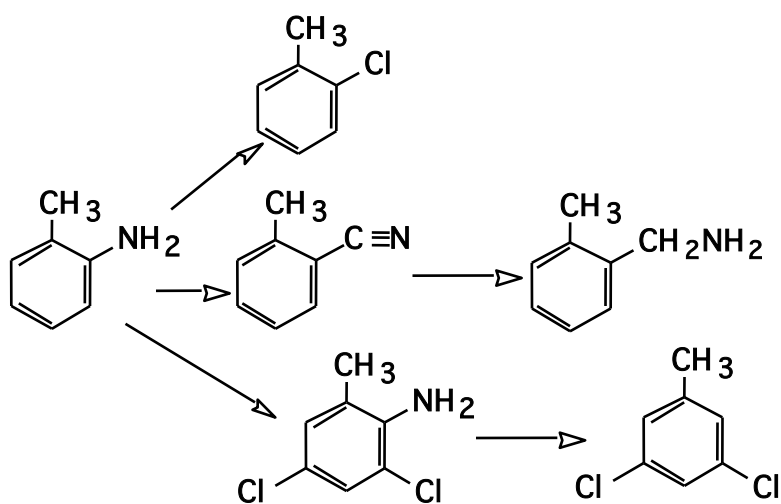
## Diazonium Salts

- The  $-N_2^+$  group of an arenediazonium salt can be replaced in a regioselective manner by these groups



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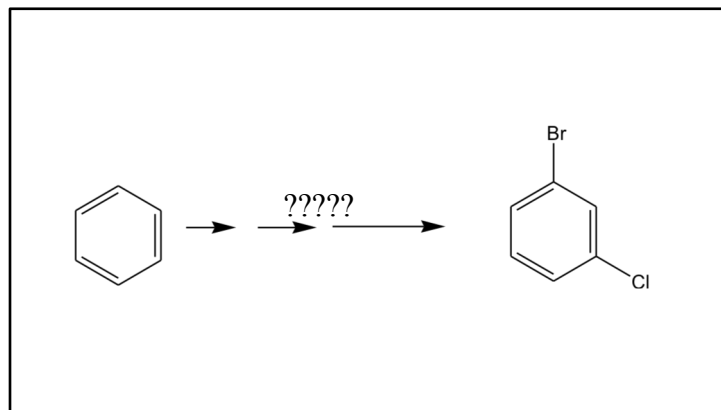
## Practice



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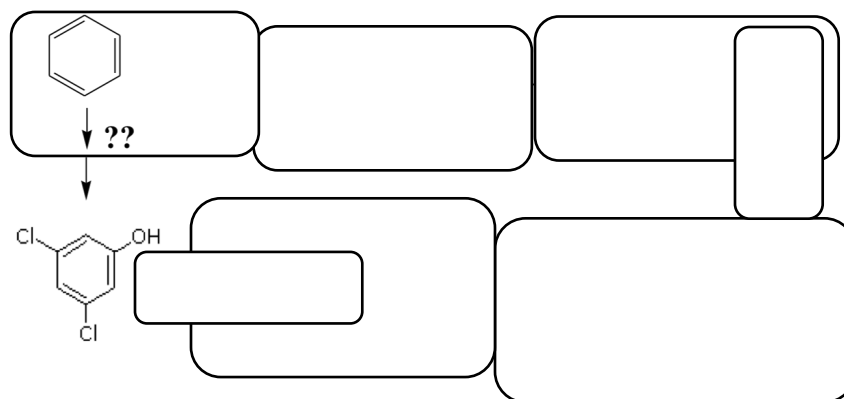
## Practice...work backwards

Oh No....two o,p directors meta to one another???



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## Synthesis Strategy



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## Substitution Reactions

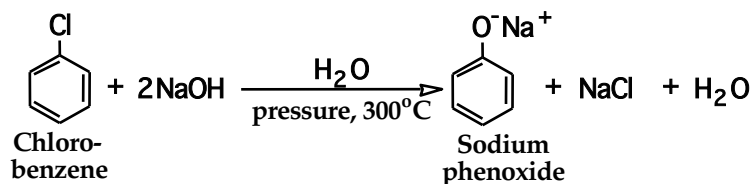
- Aryl halides do not undergo nucleophilic substitution by either  $S_N1$  or  $S_N2$  pathways!

But.....

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## But...this is fact

- When heated under pressure with aqueous NaOH, chlorobenzene is converted to sodium phenoxide

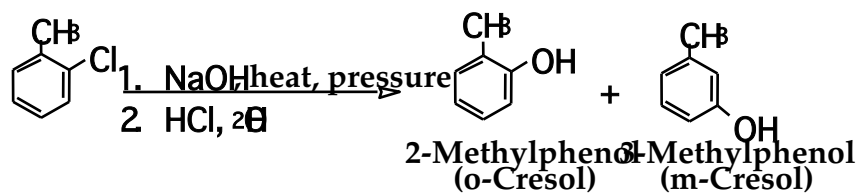


– neutralization with HCl gives phenol????? What is this??

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## Also fact....

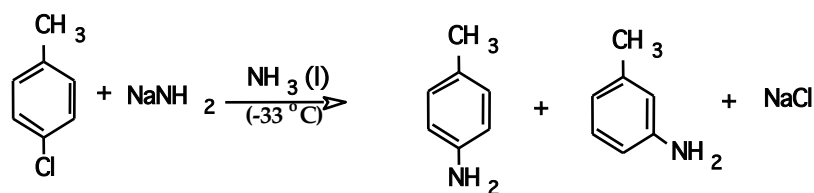
- The same reaction with 2-chlorotoluene gives a mixture of ortho- and meta-cresol???? Ortho and meta....huh????



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## Also true

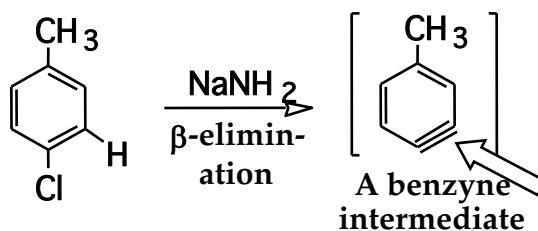
- The same type of reaction can be brought about by the use of sodium amide in liquid ammonia



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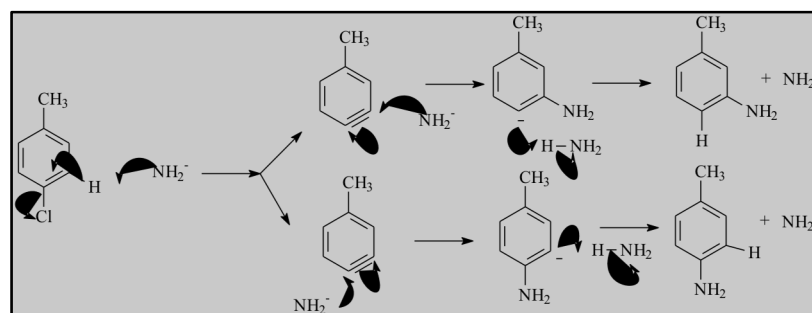
## Proposed Benzyne Intermediate

- $\beta$ -elimination of HX gives a “benzyne” intermediate, that then adds the nucleophile to give products



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## Proposed Benzyne Intermediate

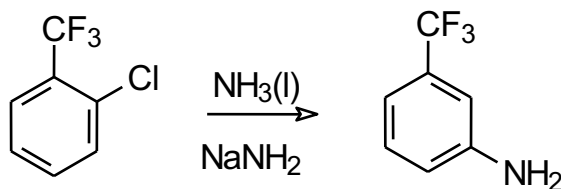


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## Proposed Benzyne Intermediate

Another Mystery??

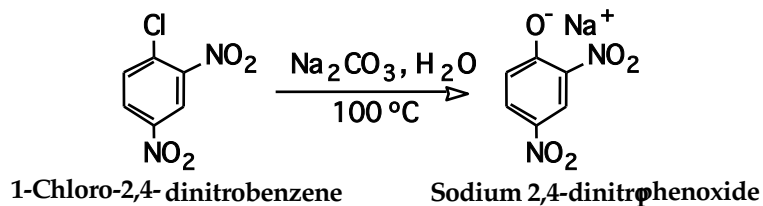


More than 95% of the product is the meta isomer??

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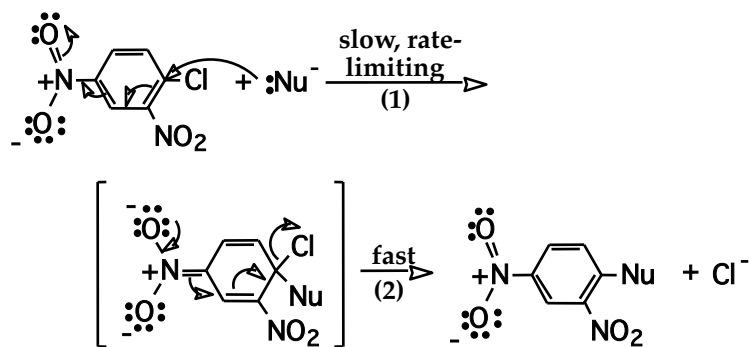
## Nucleophilic Addition-Elimination

- When an aryl halide contains strongly electron-withdrawing  $-\text{NO}_2$  groups ortho and/or para to X, nucleophilic aromatic sub. takes place readily



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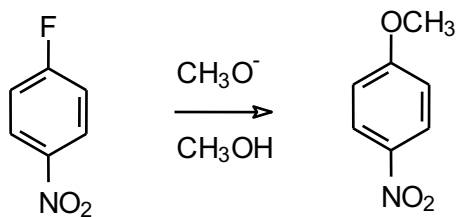
## Meisenheimer Complex



**A Meisenheimer complex**

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## Addition Elimination



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