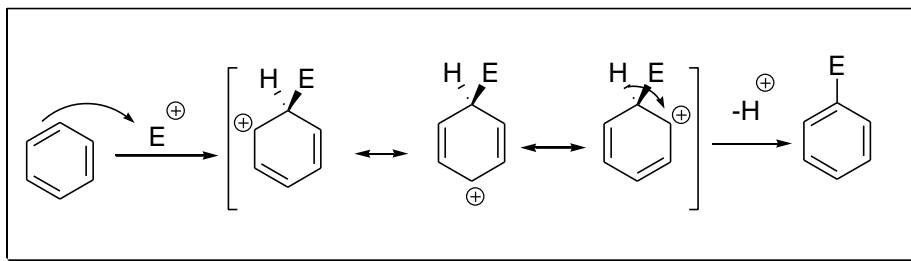


## Lecture 13 Electrophilic Aromatic Substitution I

### 5.1 Principles

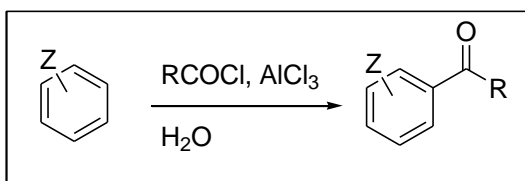
The reaction occurs in two stages: the electrophile adds to one carbon atom of the aromatic ring, yielding a carbocation in which the positive charge is delocalized, and a proton is then eliminated from the adduct.



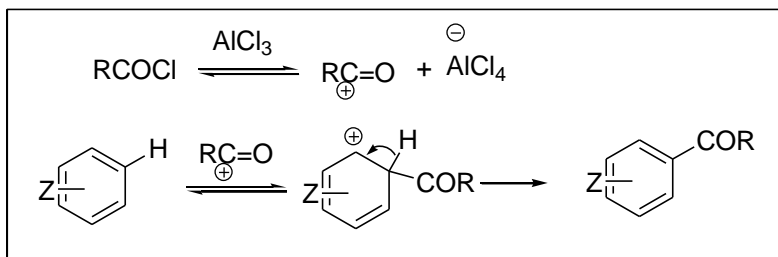
### 5.2 Formation of Carbon-Carbon Bonds

#### 5.2.1 Friedel-Crafts Acylation

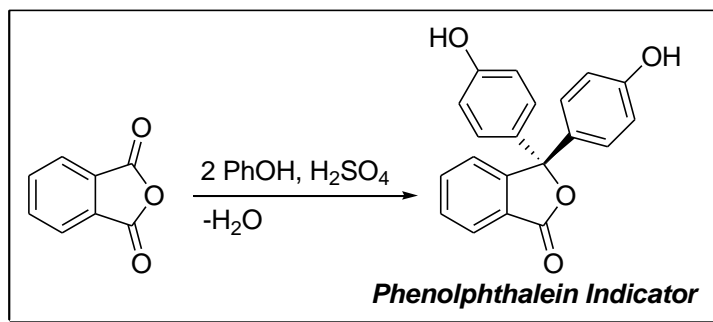
Acylation of aromatic rings is generally performed using acid chloride or acid anhydride as an acylating agent in the presence of Lewis acid.



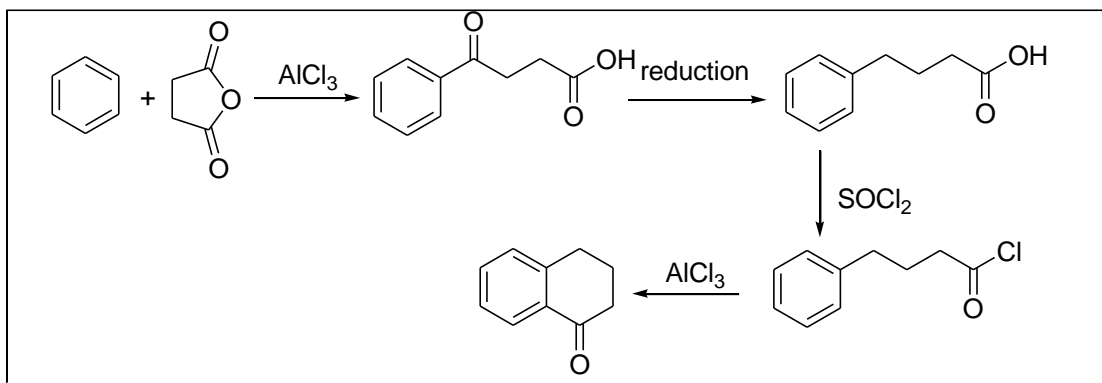
#### Mechanism

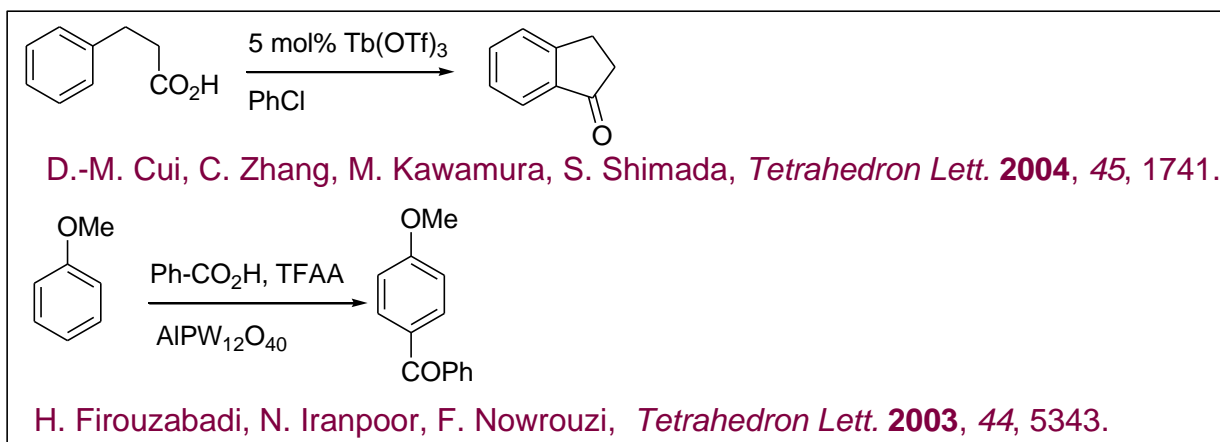


In some circumstances, carboxylic acid is used as an acylating agent in the presence of a proton acid.

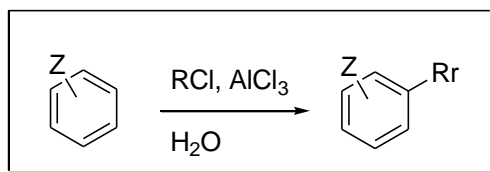
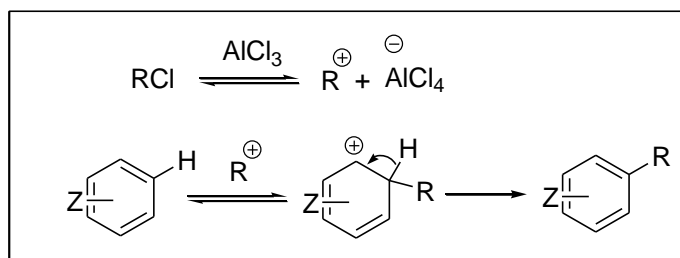


Intramolecular reactions are of particular value to construct cyclic systems. These reactions are usually carried out using dibasic acid anhydrides. For example, the synthesis of  $\alpha$ -tetralone has been accomplished from benzene and succinic anhydride using  $\text{AlCl}_3$  in 80% yield.

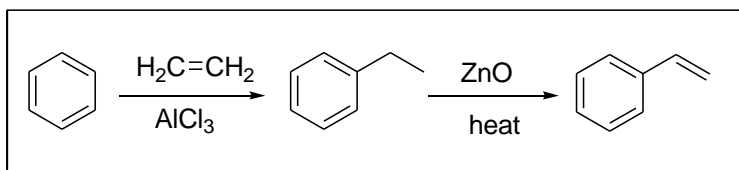


**Examples:****5.2.2 Friedel-Crafts Alkylation**

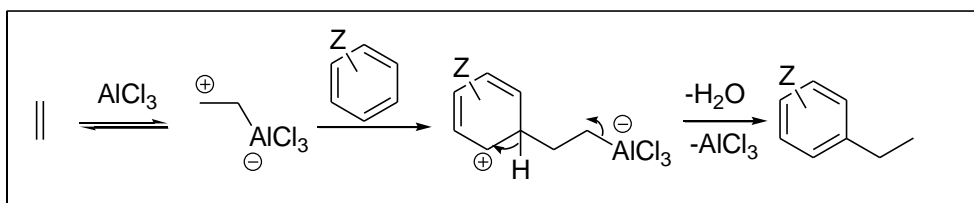
The reaction can be performed using alkyl halides, alcohols, esters, ethers, alkenes, aldehydes and ketones as alkylating agent. Reactions of the first four are accomplished using Lewis acid catalysis, while those of the last three by proton acids.

**Mechanism**

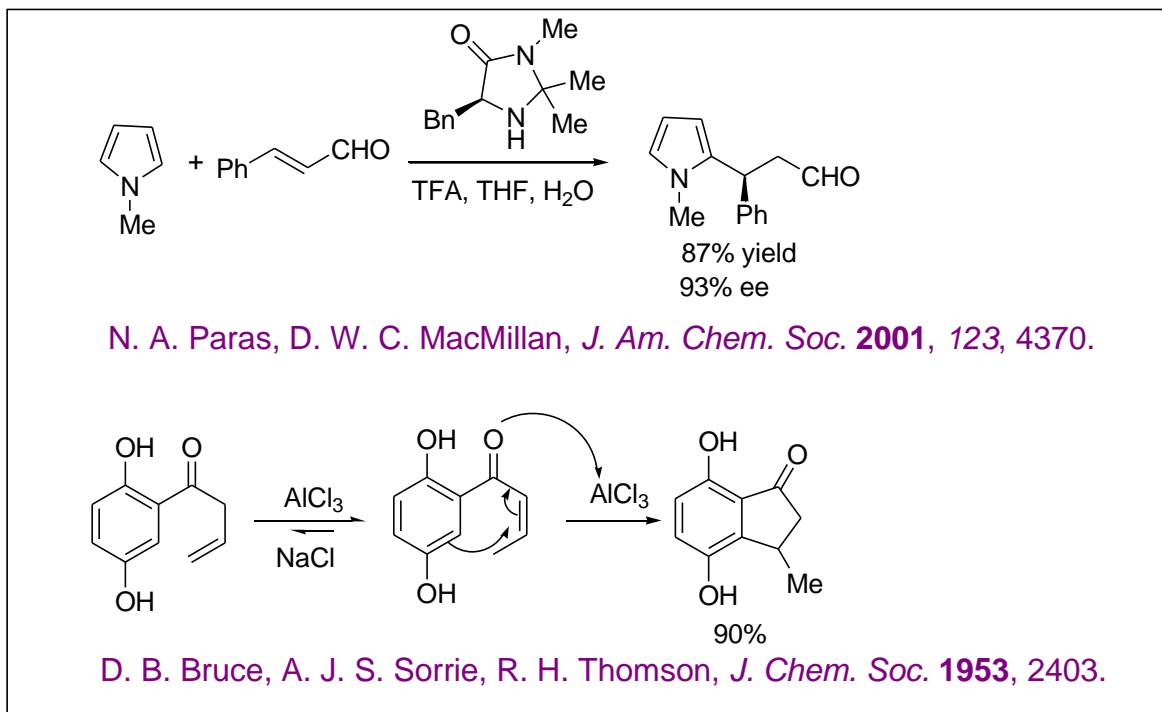
For examples, the industrial production of styrene involves the ethylation of benzene using  $\text{AlCl}_3$  followed by dehydrogenation.



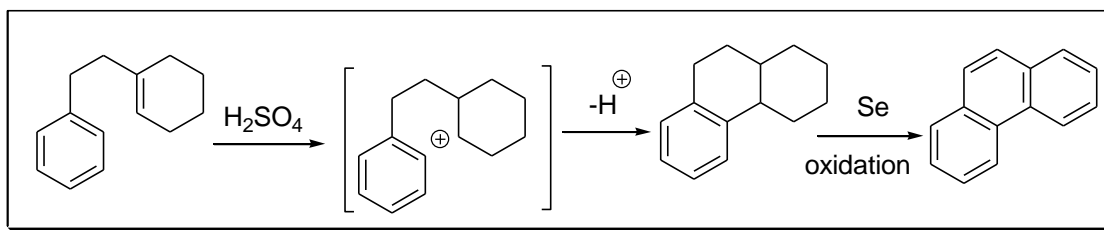
### Mechanism



### Examples:

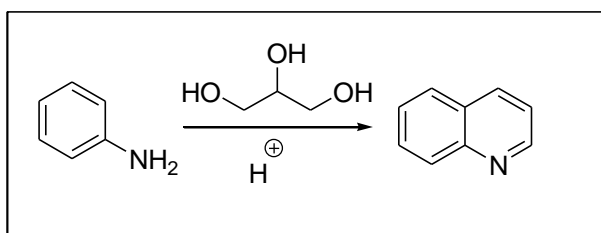


While the Bogert-Cook phenanthrene synthesis uses intramolecular alkylation as intermediate in the presence proton acid.

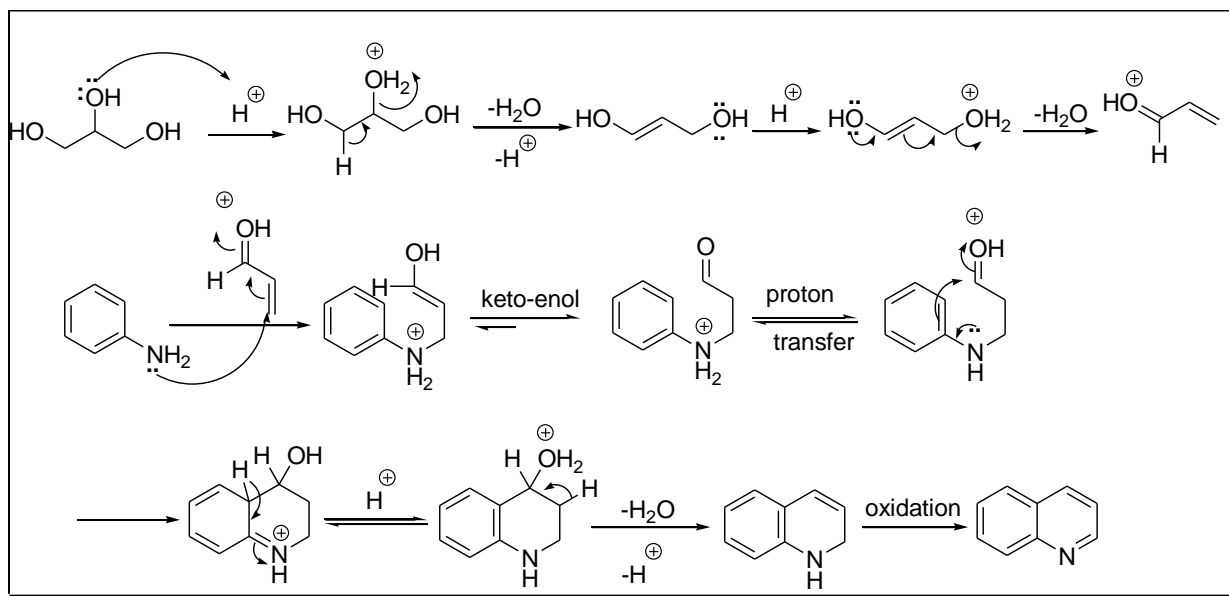


### Skraup Synthesis

Skraup quinoline synthesis is an example for the reaction which involves aldehyde as alkylating agent. The process with aldehydes and ketones is useful when the reaction is intramolecular and stereochemically controlled.



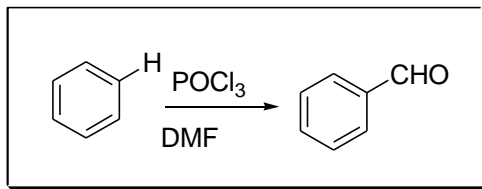
### Mechanism



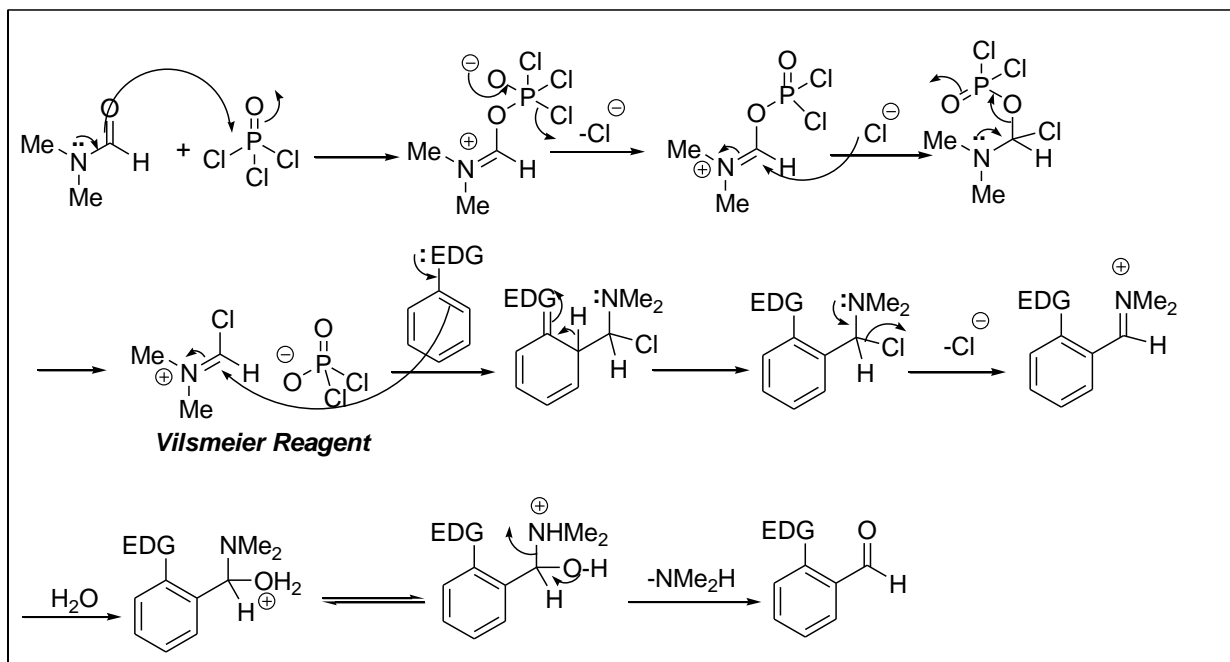
Aromatic compounds whose reactivity is comparable with or greater than that of benzene can be successfully alkylated.

### 5.2.3 Vilsmeier-Haack Reaction

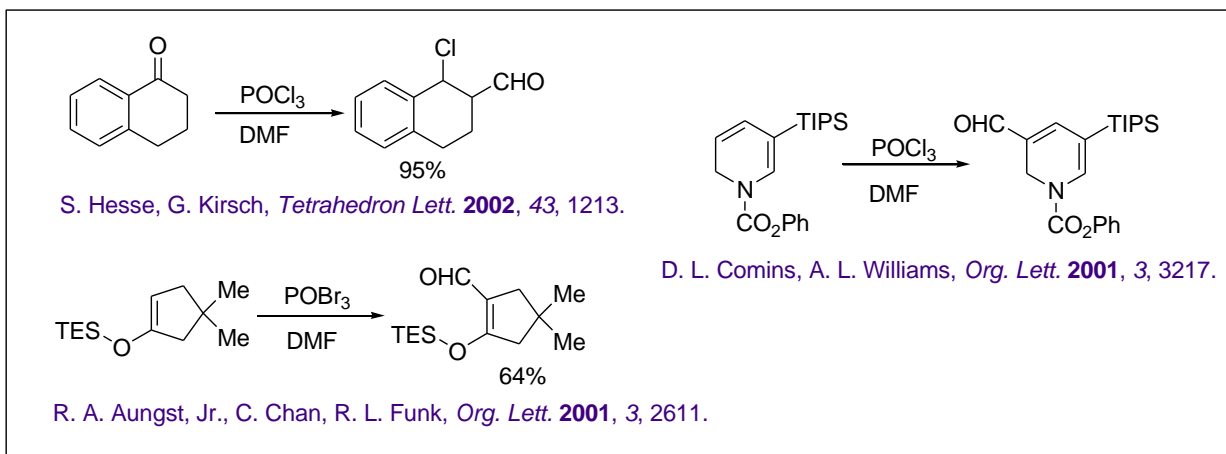
Reaction of secondary amines with formic acid gives N-formylamines which formylate aromatic compounds in the presence of phosphorus oxyhalide.



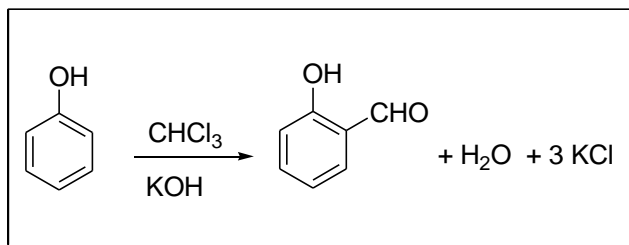
#### Mechanism

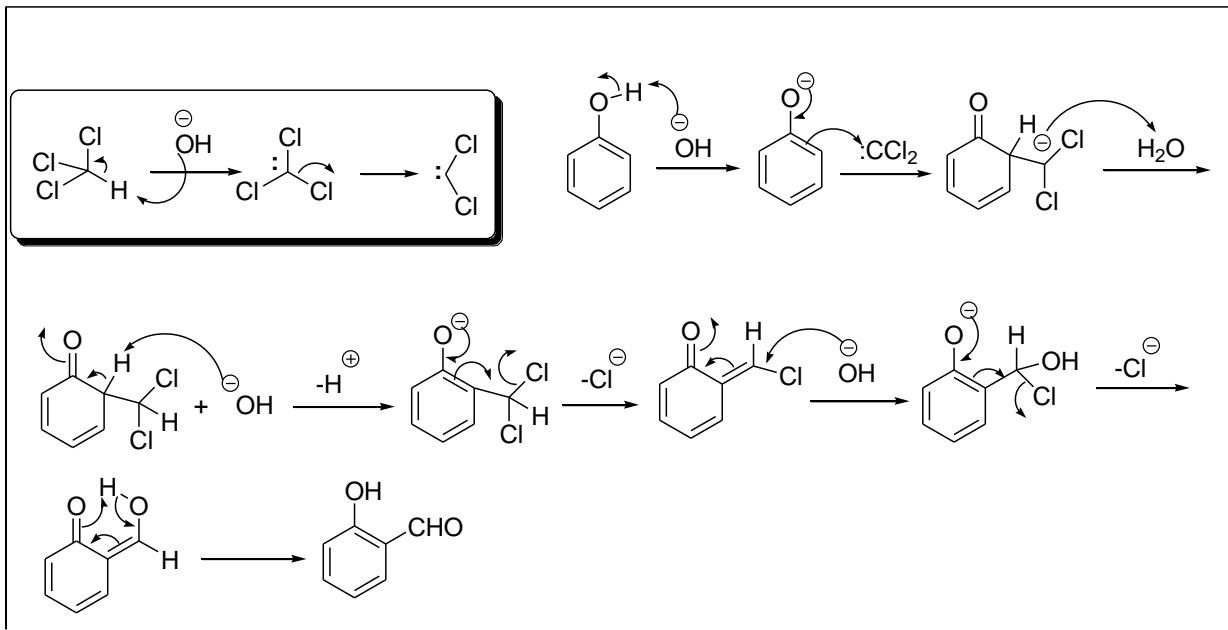


- Heterocycles are also common substrates.
- The reaction can also be performed on alkene.
- The reaction is more efficient with aromatic ring having electron donating group (EDG).

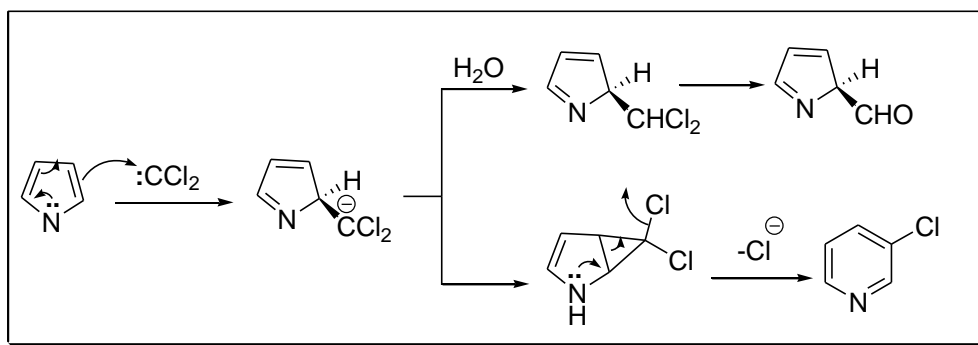
**Examples:****5.2.4 Reimer-Tiemann Formylation**

The reaction involves formylation of phenol and analogues using chloroform in the presence of base. First, chloroform reacts with base to give electrophilic dichlorocarbene which in situ undergoes reaction with phenoxide ion. The resulting benzal chloride can be converted into salicylaldehyde by hydrolysis followed by acidification.



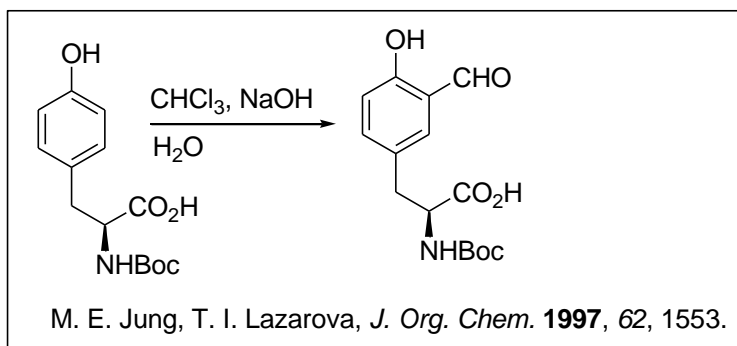
**Mechanism**


Pyrrole, which resembles phenol in reactivity towards electrophiles, undergoes reaction to give pyrrole 2-aldehyde along with 3-chloropyridine as by-product. Both products form from the same intermediates.



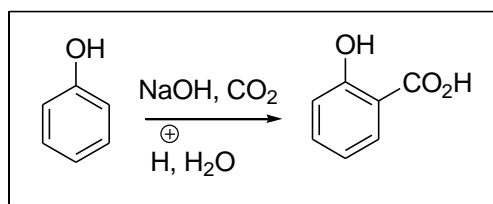


**Example:**



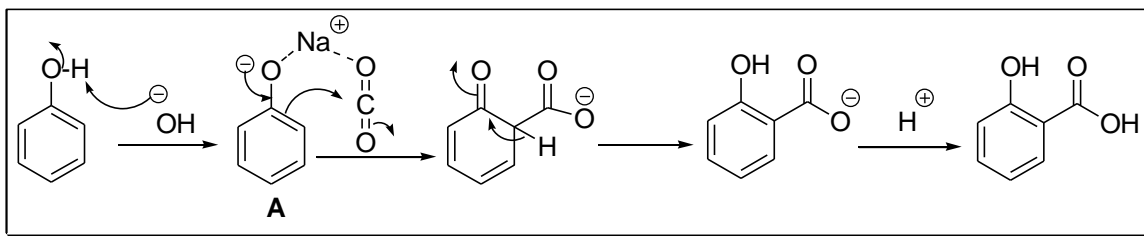
**5.2.5 Kolbe-Schmidt Carboxylation**

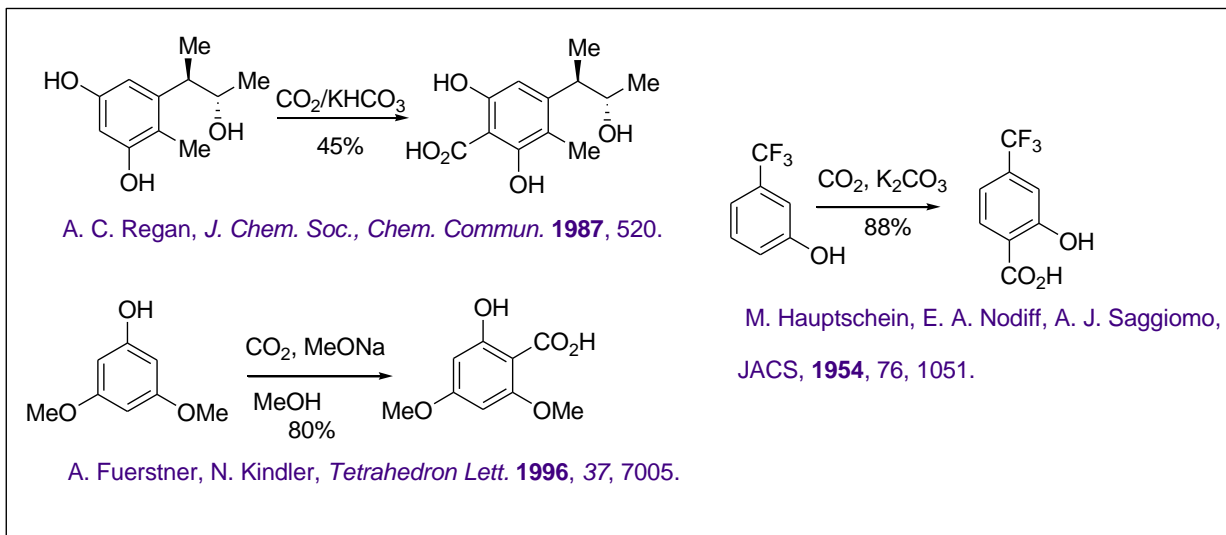
Phenoxide ions react with  $\text{CO}_2$  (weak electrophile) under pressure at about  $100^\circ\text{C}$  to give *ortho* substitution.



**Mechanism**

The formation of *ortho* product predominates which may be due to the stabilizing influence of chelation on the transition state **A**.



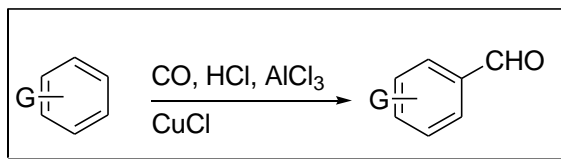
**Examples:**

However, the Kolbe-Schmidt carboxylation is reversible at about 240 °C and the formation of more stable *para*-isomer predominates.

The reaction conditions are also compatible with heterocyclic compounds. For example, pyrrole undergoes reactions at 120 °C to give pyrrole-2-carboxylic acid.

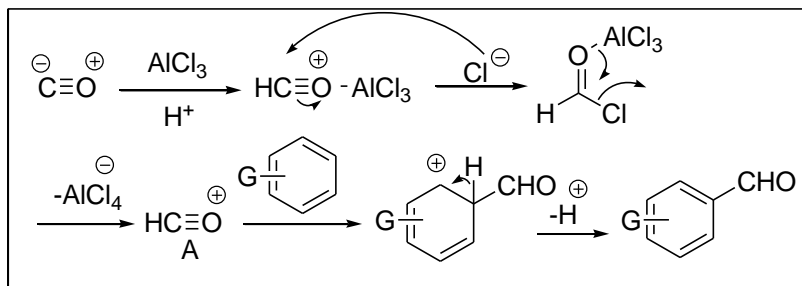
**5.2.6 Gattermann-Koch Reaction**

The formylation of aromatic compound can be accomplished by treatment with CO and HCl in the presence of Lewis acid. The reaction is performed either under pressure or using copper(I) chloride whose role may be to aid the reaction between CO and HCl *via* the complex which it forms with CO.



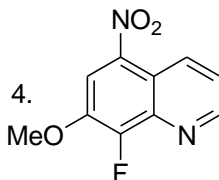
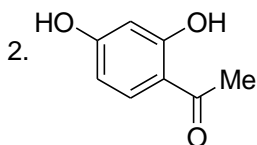
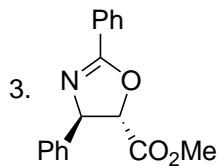
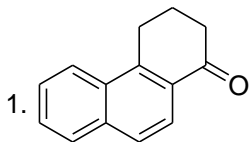
**Mechanism**

In this reaction, presumably the electrophile is the formyl cation A.

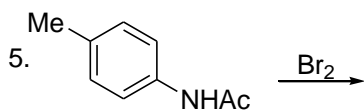
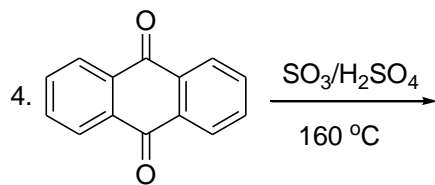
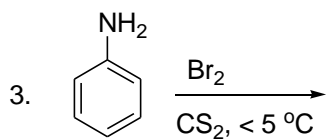
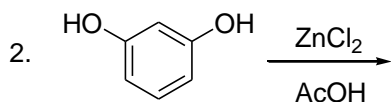
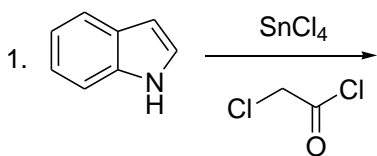


**Problems:**

A. Outline synthetic routes to the following compounds.



B. What major products would you expect from the following reactions?



**Text Books:**

R.O.C. Norman and C. M. Coxon, *Principles of Organic Synthesis*, CRC Press, New York, 2009.

B. P. Mundy, M. G. Ellerd, F. G. Favaloro Jr, *Name Reactions and Reagents in Organic Synthesis*, Wiley Interscience, New Jersey, 2005.

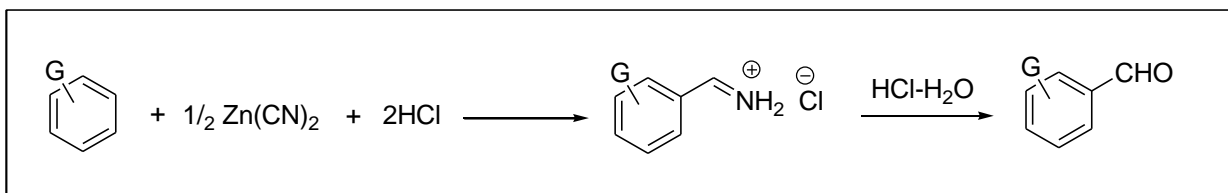
J. March, *Advanced Organic Chemistry*, 4<sup>th</sup> ed, Wiley Interscience, New York, 1992.



## Lecture 14 Electrophilic Aromatic Substitution II

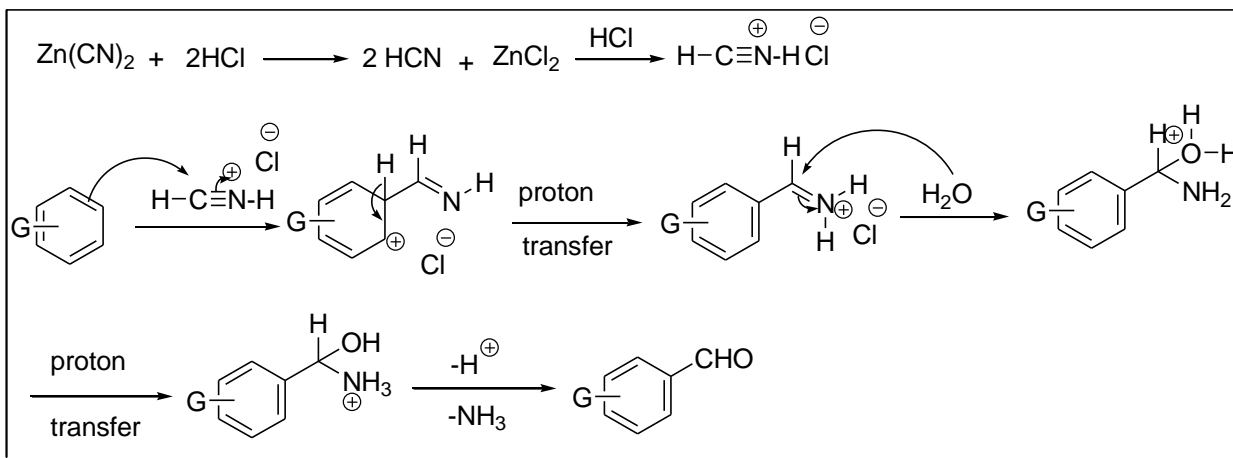
### 5.2.7 Gattermann Formylation

This is an alternative to the Gatterman-Koch reaction for formylation of aromatic compounds.

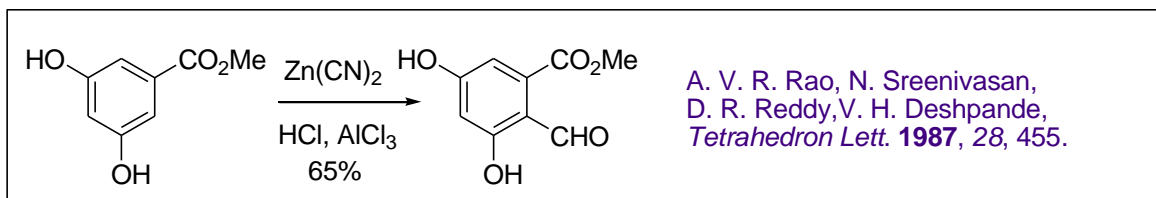


#### Mechanism

This reaction employs  $\text{Zn(CN)}_2$  and  $\text{HCl}$  instead of  $\text{CO}$  (Gatterman-Koch reaction). The initial product is an iminium chloride which is converted into the aldehyde by acid hydrolysis.

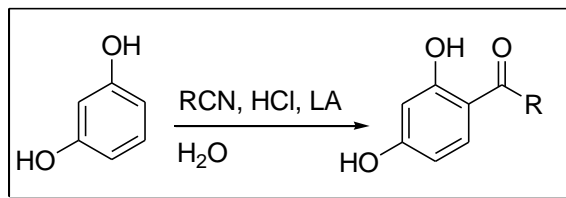


#### Example:

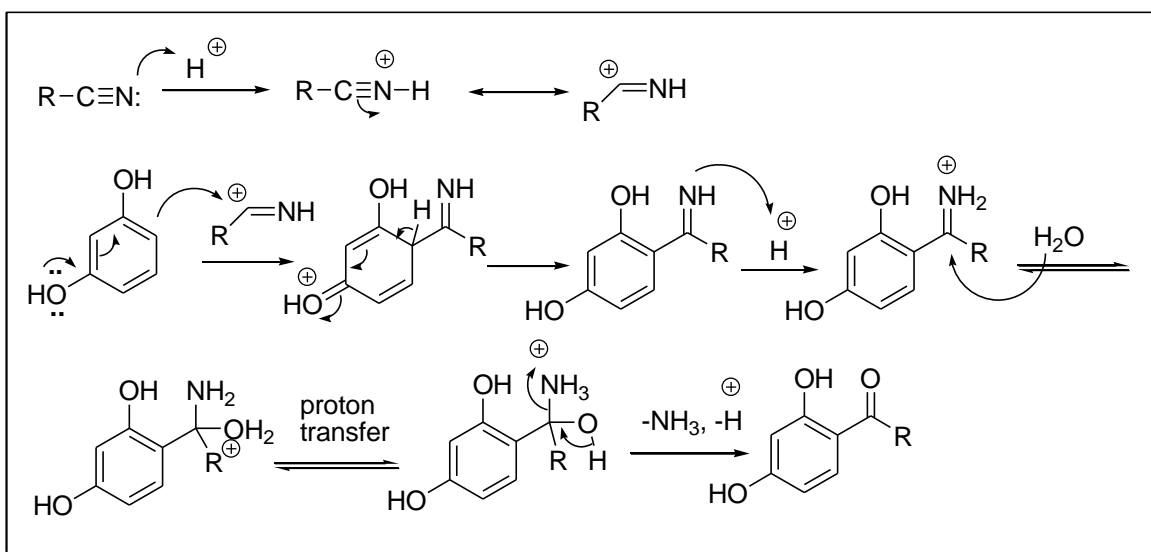


## 5.2.8 Houben-Hoesch Reaction

This reaction refers the acylation of phenols using nitrile, hydrochloric acid and Lewis acid.

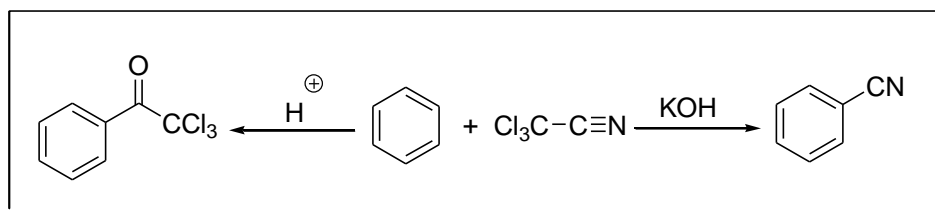


### Mechanism

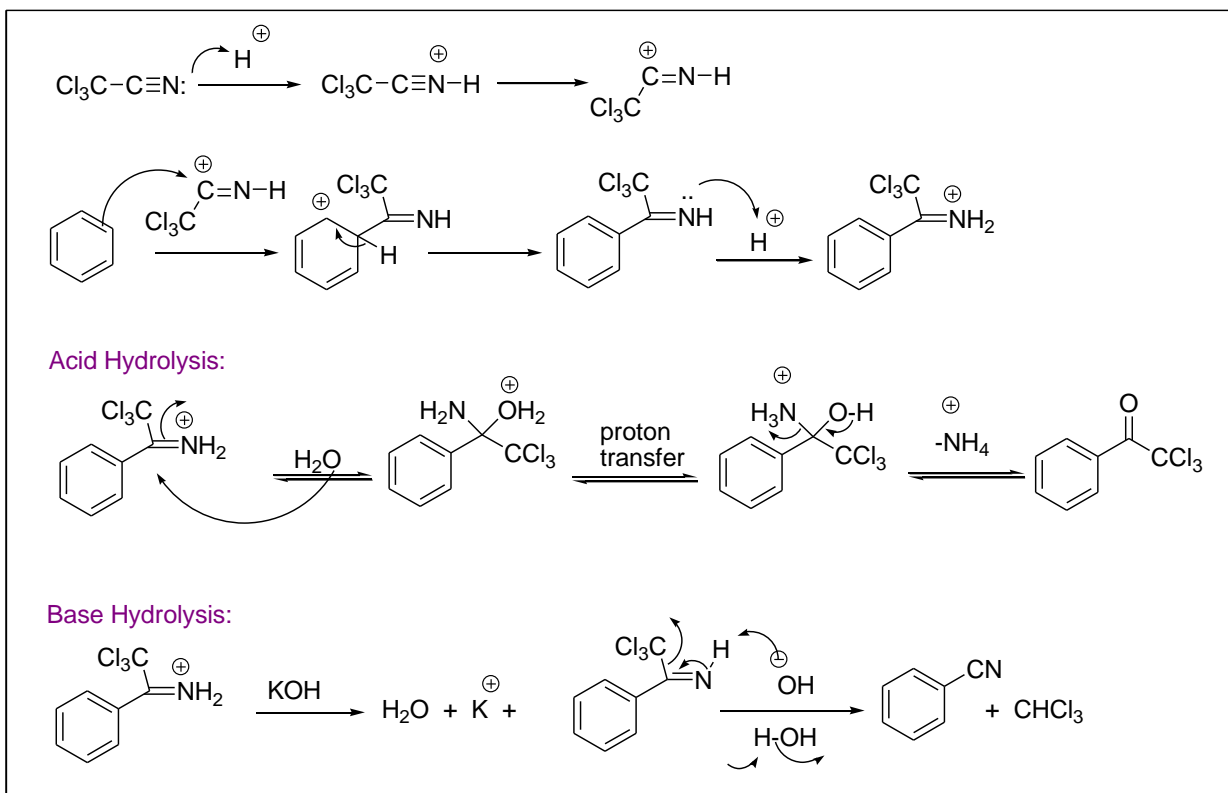


## 5.2.9 Houben-Fischer Synthesis

Base hydrolysis of trichloromethyl aryl ketimines gives aromatic nitriles, while acid hydrolysis leads to the formation of ketones.

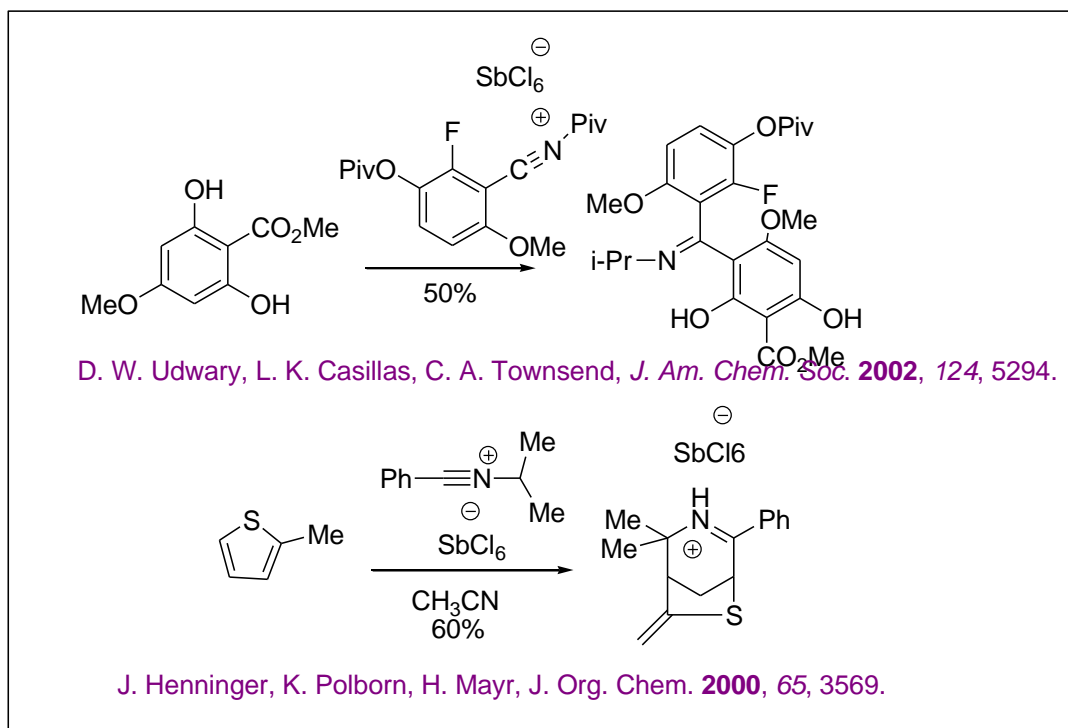


**Mechanism**



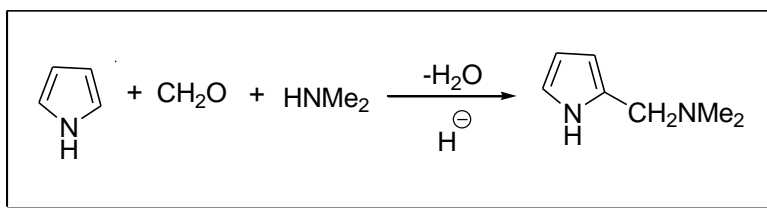


**Examples:**

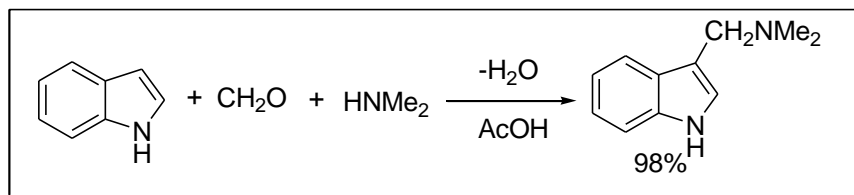


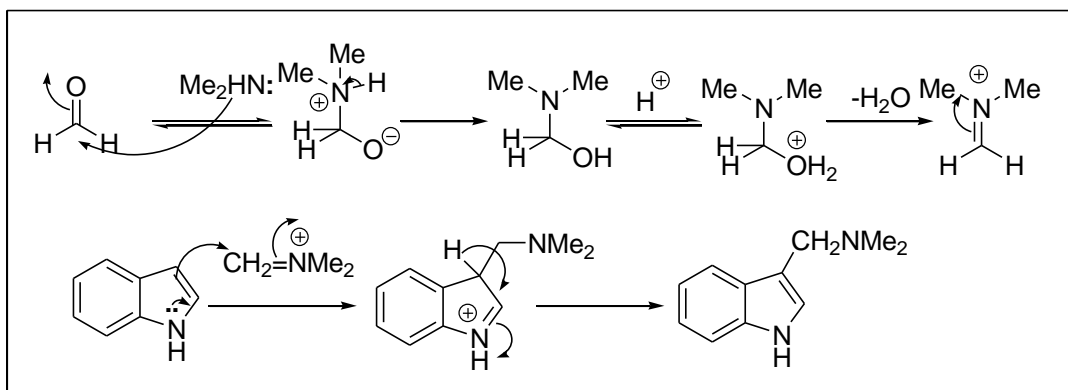
**5.2.9 Mannich Reaction**

This three-component condensation reaction is useful for bonding aliphatic carbon to the reactive positions of phenols, pyrroles and indoles. For examples, pyrrole reacts with HCHO and dimethylamine to give 2-dimethylaminomethylpyrrole.

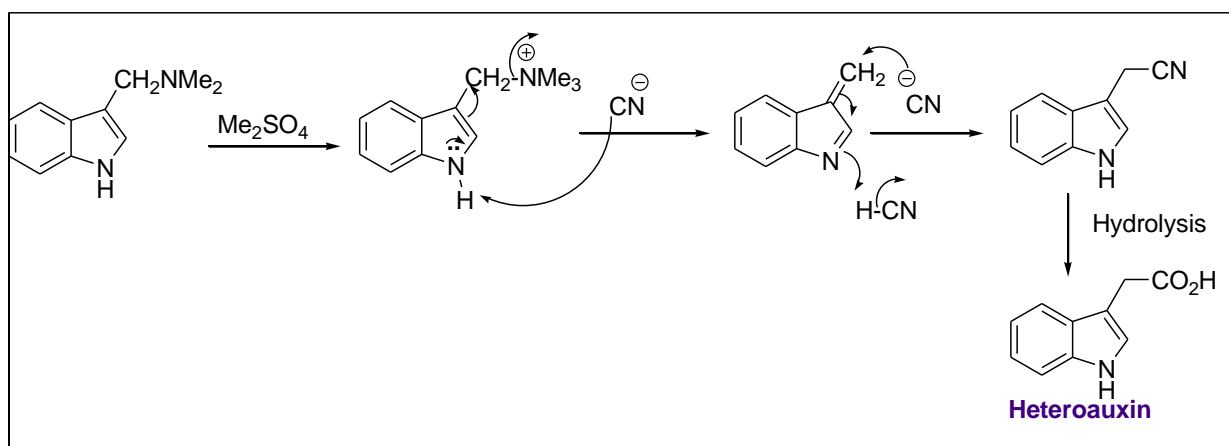


A similar result has been observed with indole. The substitution takes place at 3-position to give gramine.

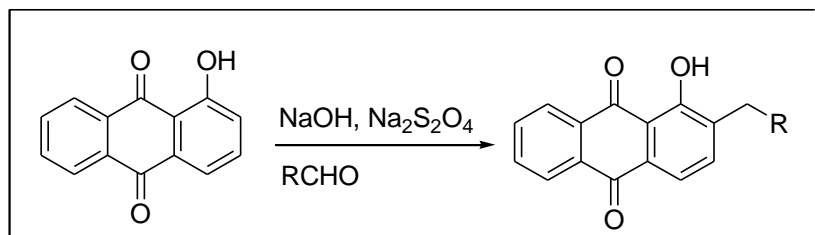


**Mechanism**

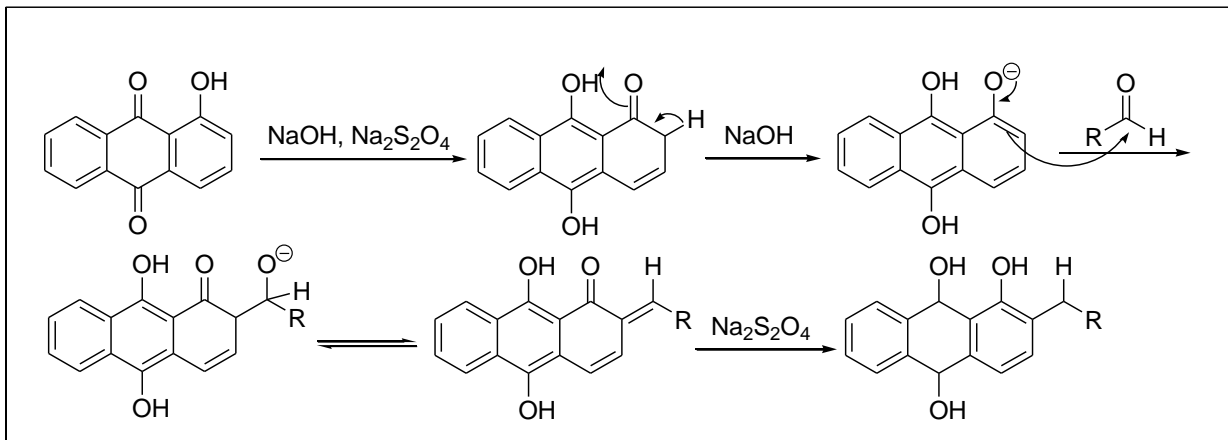
Gramine can be readily converted into heteroauxin via methylation followed by treatment with NCN and hydrolysis.

**5.2.10 Marschalk Reaction**

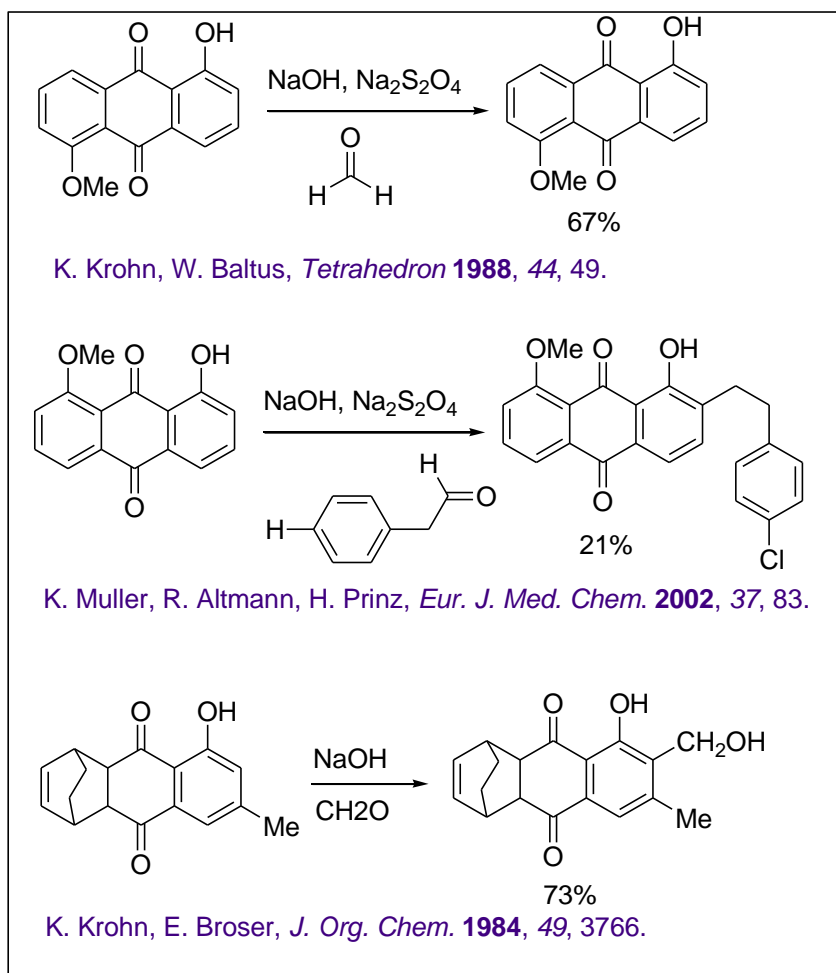
Phenolic anthraquinones react with aldehydes to afford a substituted phenolic anthraquinones in the presence of sodium dithionite.



## Mechanism



## Examples:



## 5.3 Carbon-Nitrogen Bond Formation

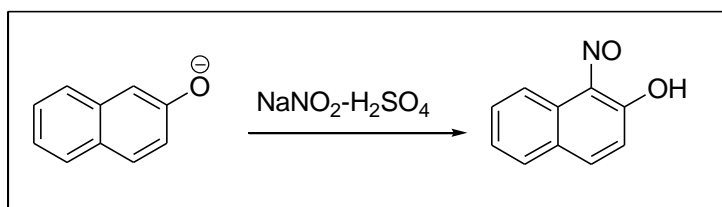
### 5.3.1 Nitration

The most common method used for bonding nitrogen to aromatic system is nitration. This is because a variety of nitration conditions are available. The most frequently used methods for nitration follow:

- A mixture of concentrated nitric acid and concentrated sulfuric acid.
- Fuming nitric acid in acetic anhydride
- Nitric acid in glacial acetic acid.

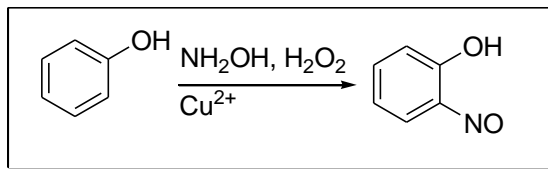
### 5.3.2 Nitrozoation

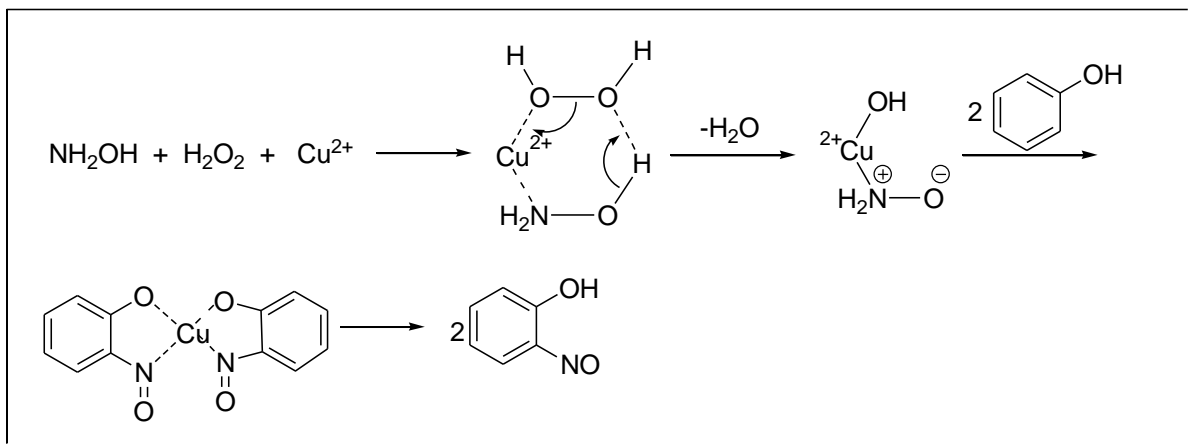
Sodium nitrite with strong acids such as sulfuric acid gives nitrosonium ion which undergoes reaction with aromatic compounds. The reaction is limited with the reactive nuclei of phenols and tertiary aromatic amines.



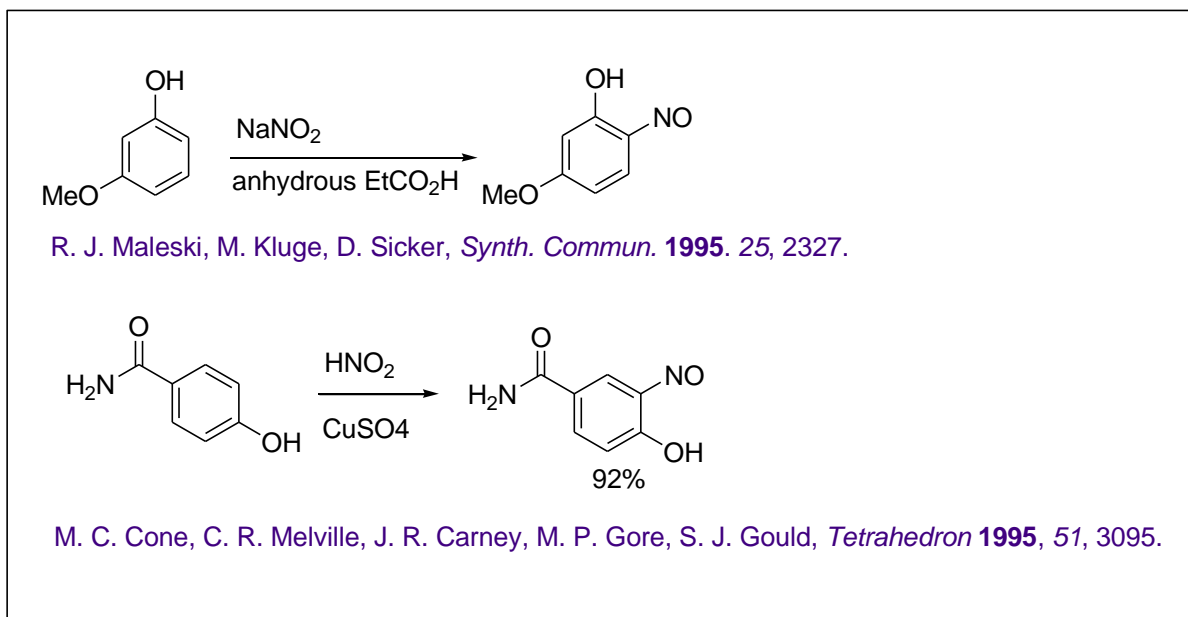
### Baudisch Reaction

It involves the combination of hydroxylamine, hydrogen peroxide and copper(II) salt for the nitrozoation of phenol derivatives.





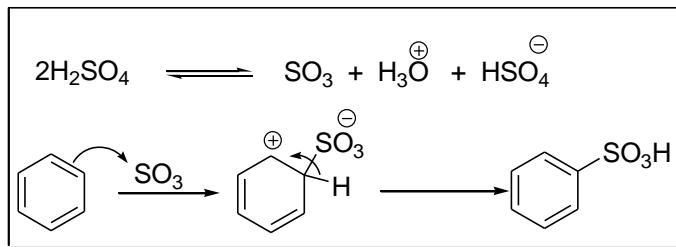
### Examples:



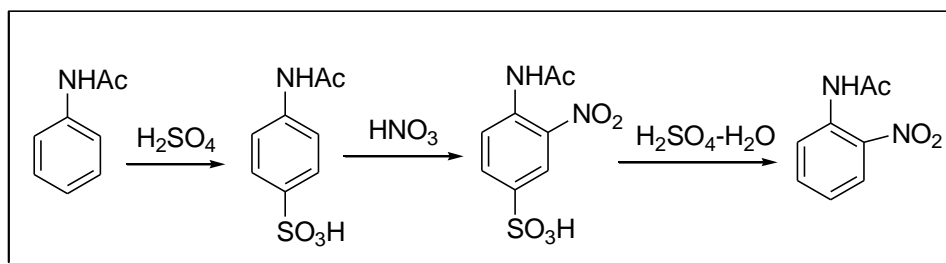
## 5.3 Carbon-Sulfur Bond Formation

### 5.3.1 Sulfonation

As in nitration, the sulfonation of both strongly activated and strongly deactivated nuclei can be performed at varied reaction conditions. The electrophile is  $\text{SO}_3$ , which is present in concentrated  $\text{H}_2\text{SO}_4$  as the result of the equilibrium. The mechanism of sulfonation is similar to that of other electrophilic substitutions.

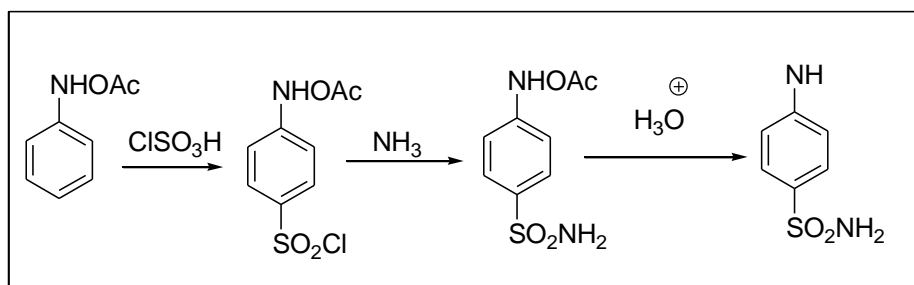


However, the process is reversible which led to employ sulfonic acid as protecting group for regioselective substitutions. For example, sulfonation of acetanilide give p-sulfonic acid which could be nitrated at *ortho* position and then, the sulfonic acid group can be eliminated by treatment with dil.  $\text{H}_2\text{SO}_4$ .



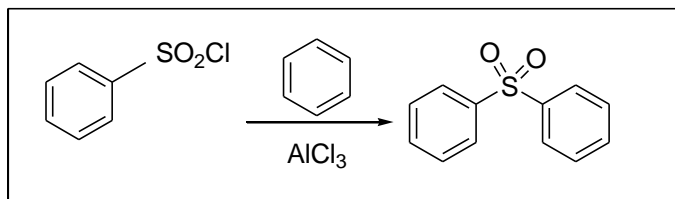
### 5.3.2 Chlorosulfonation

Aromatic compounds that are either deactivated or unstable towards acids react with chlorosulfonic acid to give arylsulfonyl chloride in good yield.



### 5.3.3 Sulfonylation

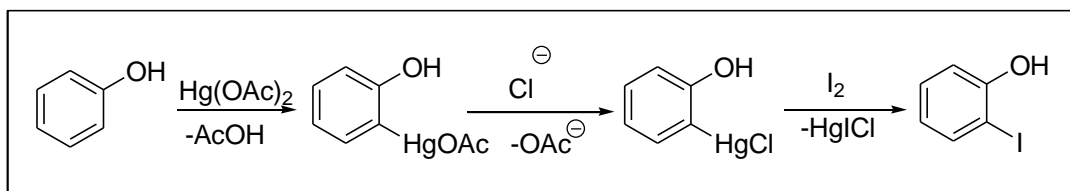
Benzenesulfonyl chloride reacts with benzene in the presence of Lewis acid to give diphenyl sulfone. The reaction is similar to that of Friedel-Crafts acylation and has the same limitations as chlorosulfonation.



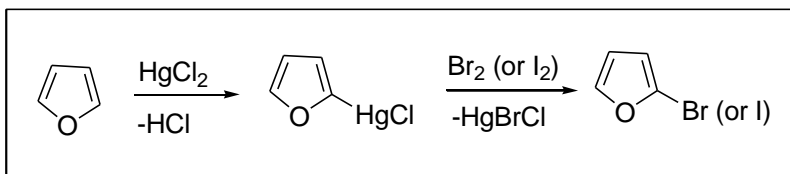
## 5.4 Formation of Carbon-Halogen Bonds and Other Reactions

### 5.4.1 Metallation

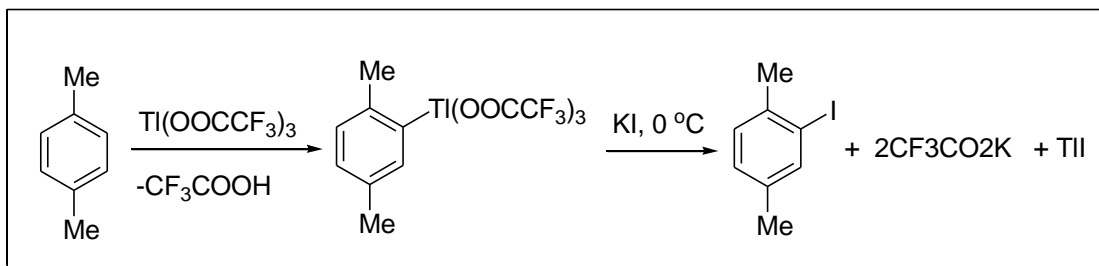
Aromatic compounds react with divalent mercury salt under dry and air free conditions to give mercury derivatives which find useful applications. For example, the synthesis of *o*-iodophenol can be conveniently accomplished via mercuration of phenol with  $\text{Hg}(\text{OAc})_2$  followed by transformation of *o*-acetoxymercury derivative into *o*-chloromercury derivative and treatment with iodine.



Similarly, the transformation of furan to 2-bromo- and 2-iodofuran can be accomplished.



Thallium(III) salts contains similar applications. For example, the reaction of *p*-xylene with thallium(III) trifluoroacetate gives the thallium derivative that, with KI at 0 °C, provides the iodo-compound in good yield.

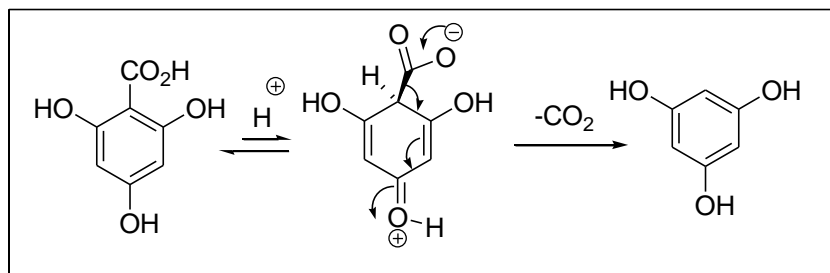


## 5.4.2 Displacement of Groups

There are electrophilic substitutions in which atoms and groups other than hydrogen are displaced from the aromatic ring (*ipso*-substitution). Some examples follow:

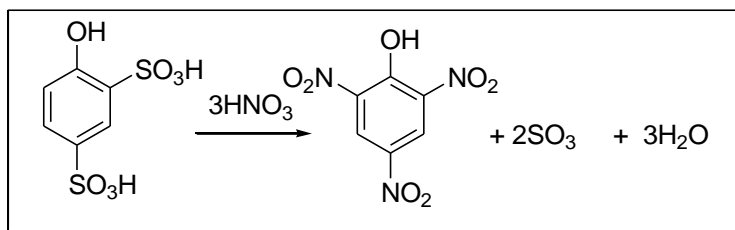
### 5.4.2.1 Decarboxylation

In aromatic compounds, activating substituents lead to displacement of carboxyl group. For example, 2,4,6-trihydroxybenzoic acid on heating leads to decarboxylation with an internal electrophilic substitution by hydrogen.



### 5.4.2.2 Desulfonation

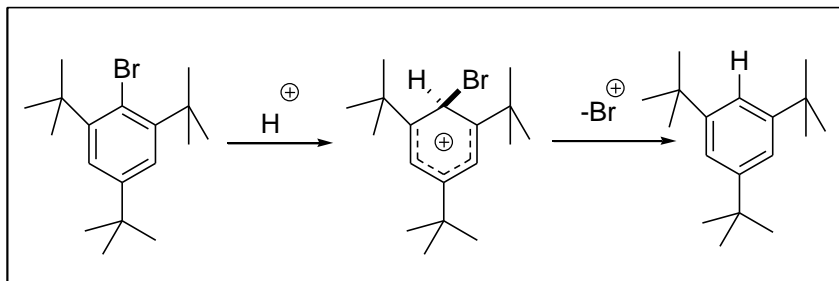
Acids displace sulfonic acid group from aromatic rings. For example, phenol-2,4-disulfonic acid could be converted into picric acid in the presence of nitric acid.





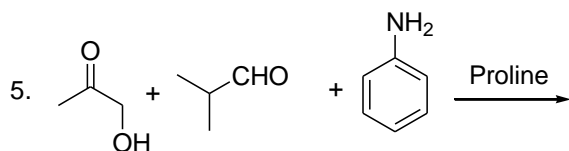
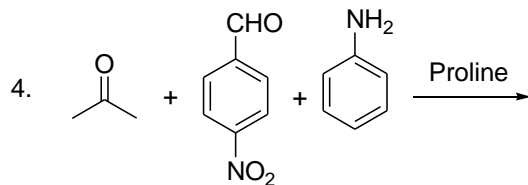
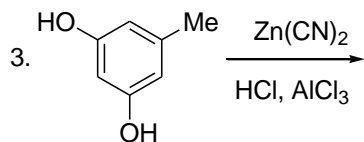
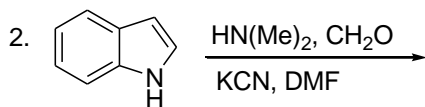
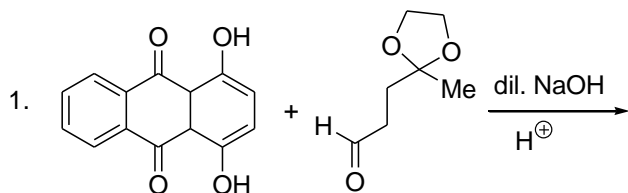
### 5.4.2.3 Dehalogenation

Dehalogenation takes place when the halogen atom is adjacent to two very bulky substituents. For example, 2,4,6-tri-*t*-butylbromobenzene undergoes debromination with strong acid.



#### Problems:

What products would you expect from the following reactions. Provide mechanistic rationale.



**Text Books:**

R.O.C. Norman and C. M. Coxon, *Principles of Organic Synthesis*, CRC Press, New York, 2009.

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