

Lecture 6

Functional Group Interconversions, including diazonium chemistry

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Reference textbook

- “Organic Chemistry” by Paula Yurkanis Bruice, 8th Edn.
- This lecture – Chapter 18, in particular **18.15**, **18.18**, **18.19**, **18.20**, parts of 18.10

Learning Objectives – Lecture 6

Section 3– Functional group interconversion, Section 6 – synthesis problems

Propose potential syntheses of aromatic target molecules from given starting materials, using the reactions covered in this lecture course

Recall the reagents required to effect a range of functional group interconversions, to include:

protection and deprotection of amine groups by acylation followed by hydrolysis

reduction of nitro groups to amino groups

conversion of amino groups into diazonium ions (**mechanism required**)

substitution of aromatic diazonium groups by Cl-, Br-, CN-, I-, F- and H₂O

reduction of aromatic diazonium groups (replacement by H)

Lecture Outline: L6

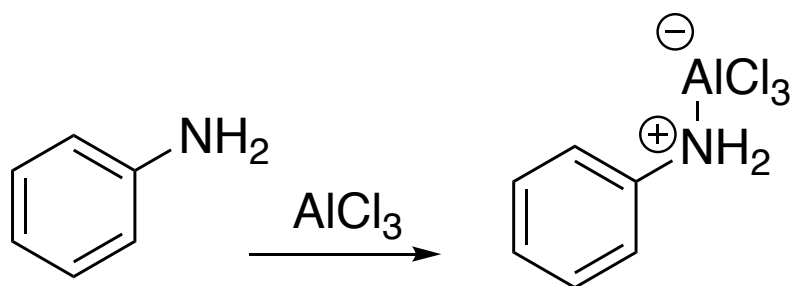
- 1. Protection and deprotection of aryl amines**
- 2. Reduction of nitro to amino**
- 3. Conversion of amino groups to diazonium ions**
- 4. Substitution of aromatic diazonium groups**
- 5. Reduction of aromatic diazonium groups**
- 6. Synthesis of azobenzene**

1. Protection and deprotection of amines

a. Why do we need to do this?

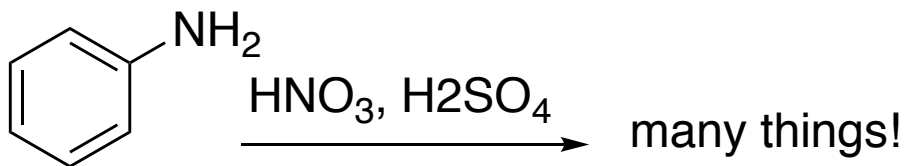
Amines can be quite reactive, and are a good nucleophile

e.g. aniline can not undergo Friedel Crafts S_EAr reactions using $AlCl_3$



- Amine lone pair forms a complex with $AlCl_3$
- Resulting N^+R is strongly deactivating

e.g. aniline can not be nitrated....



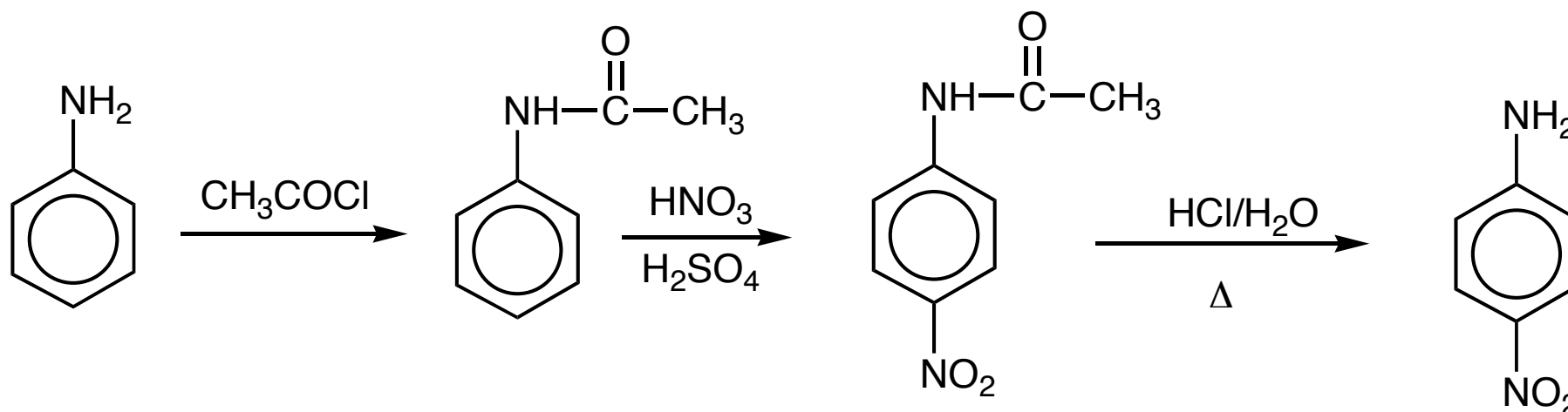
- Nitric acid is an oxidising agent and RNH_2 is easily oxidised
- Can even be explosive!

1. Protection and deprotection of amines

a. What's the solution?

Protect the amine, do the reaction, then deprotect the amine – problem solved!

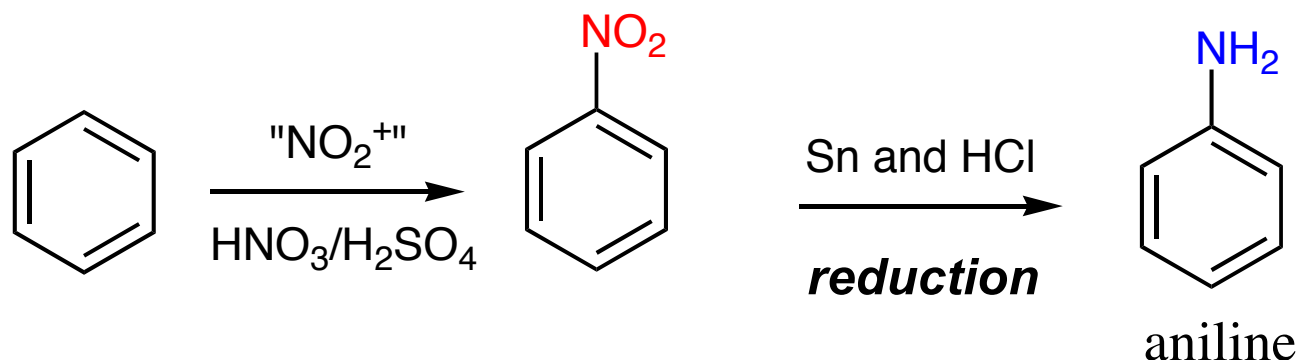
Nitration example -



1. Protect the amine as an amide (weakly activating and *o/p* directing)
2. Nitration gives the *para* product because of steric and electronic reasons
3. Then hydrolyse the amine under acid conditions to the amine

2. Reduction of nitro to amino

- Often the reason for 'carrying' a nitro through a synthesis and then converting to an amine is because amines can be a pain during a synthesis (e.g. last few slides)
- Aminobenzenes or anilines can be formed from nitro groups by reduction

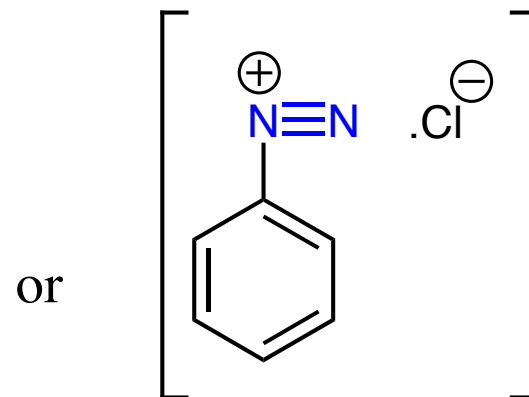
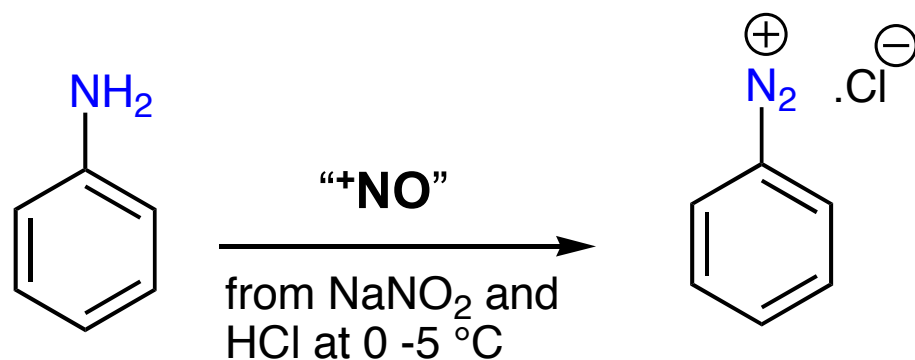


Other **reductants** such as Fe and HCl, SnCl_2 and HCl, H_2 and a catalyst (e.g. Pd/C), or H_2S can also be used.

The reduction is **NOT** a 'Clemmensen reduction' which is a named reaction for reducing aldehydes or ketones to hydrocarbons using Zn/Hg, HCl.

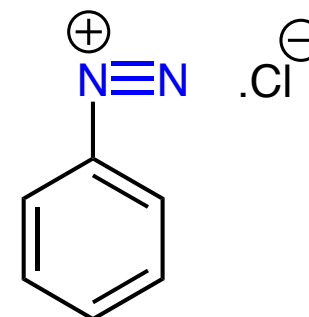
3. Conversion of amino groups to diazonium ions

- As we will shortly see..... arenediazonium ions can be used to introduce a wide variety of substituents on the aryl ring.
- Primary aryl amines can react with a **nitrosonium ion** (^+NO), which is generated from sodium **nitrite** (NaNO_2) and HCl at 0°C .



3. Conversion of amino groups to diazonium ions

- Nitrogen is such a good leaving group that arenediazoniums are only stable around 0°C and are used immediately in the desired reaction



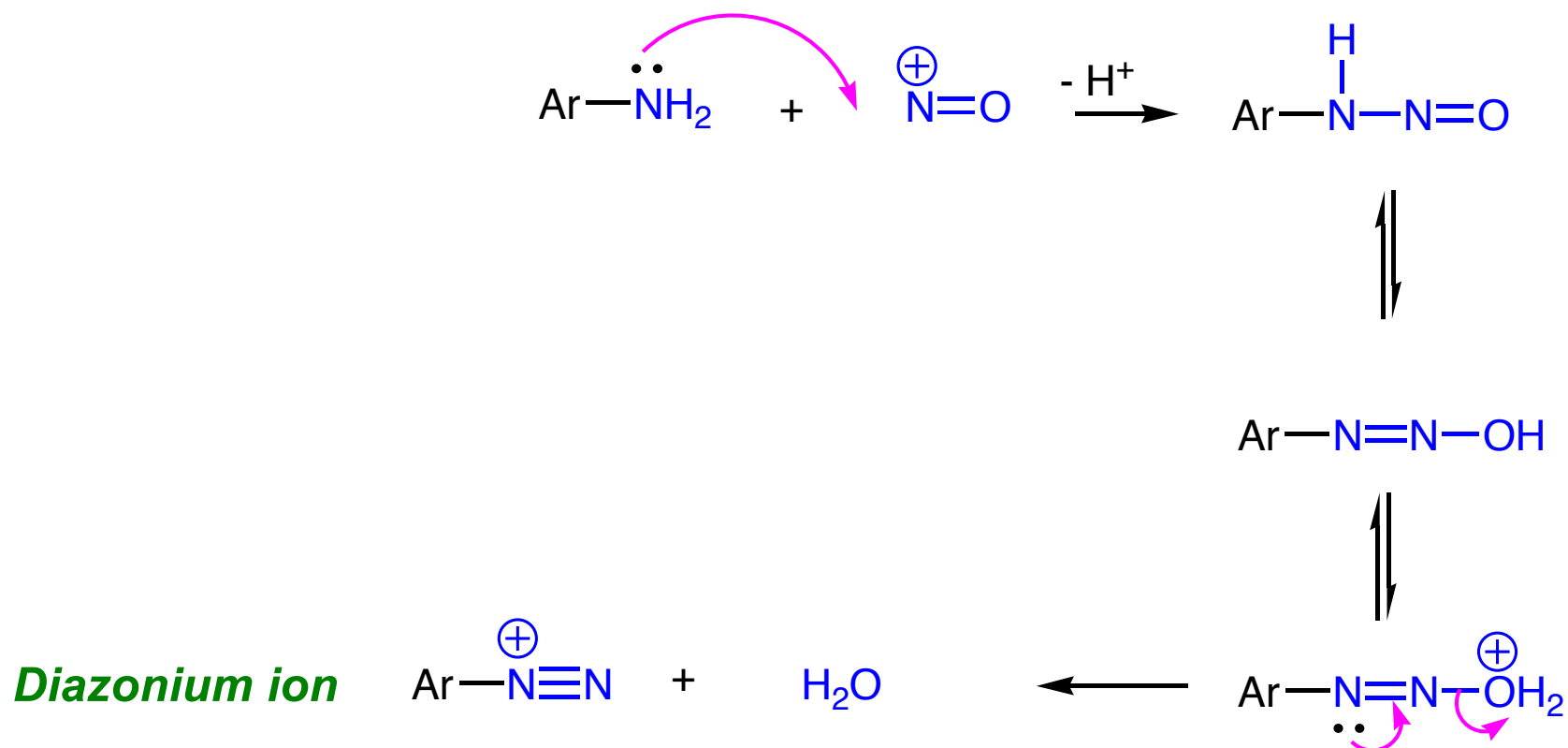
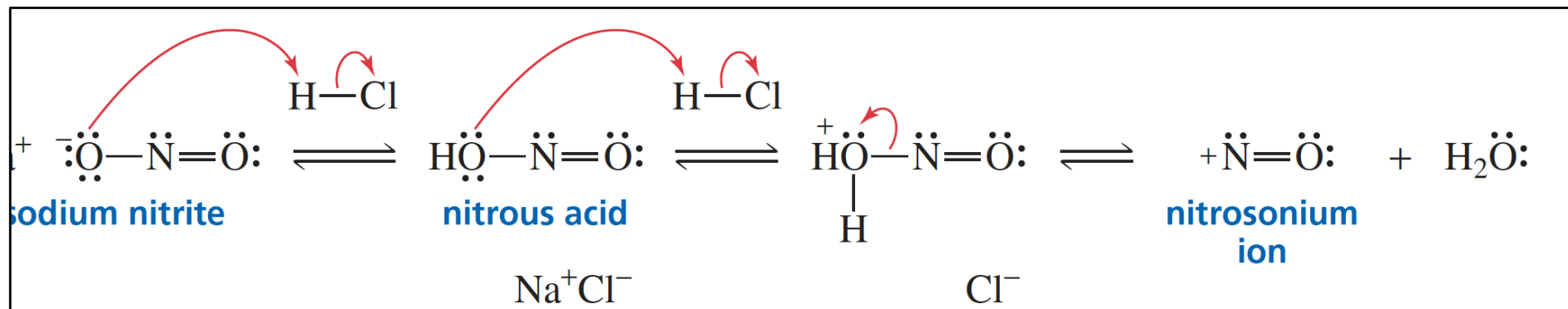
- Diazonium salts are very sensitive to touch, heat, pressure...*
- If a diazonium solution is warmed up, or dried to remove water ...*



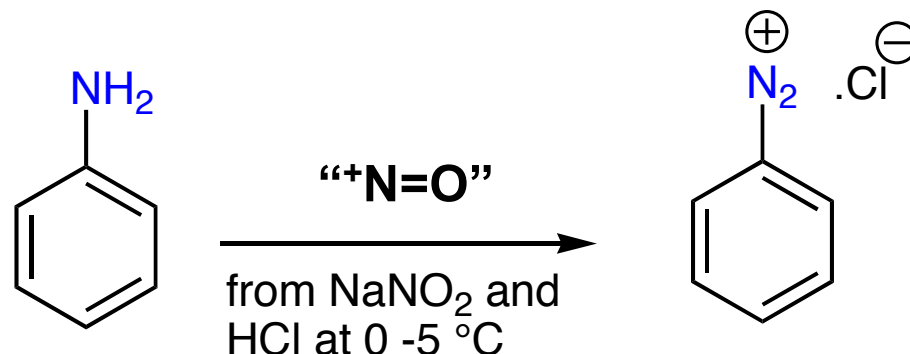
Aryl diazonium salts are more stable than alkyl as are stabilised by the aromatic electron system

3. Conversion of amino groups to diazonium ions

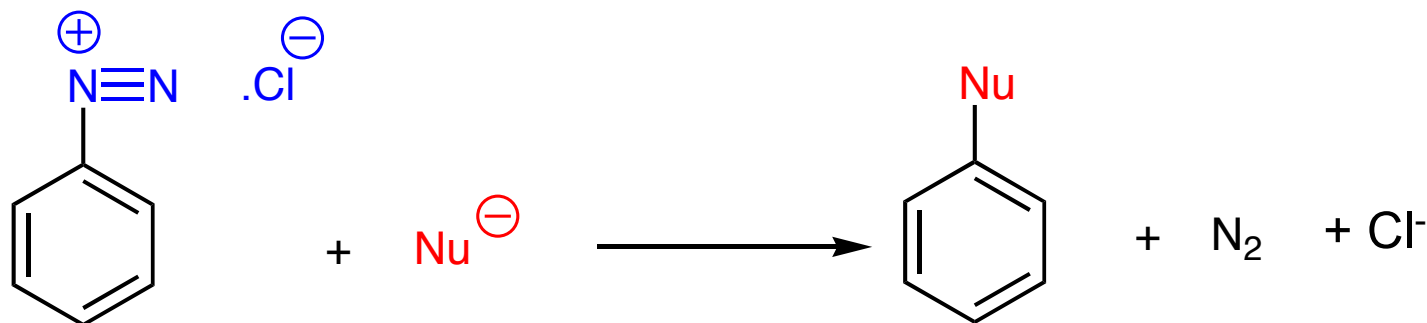
- The reaction mechanism (page 941, section 18.20)



4. Substitution of aromatic diazonium groups



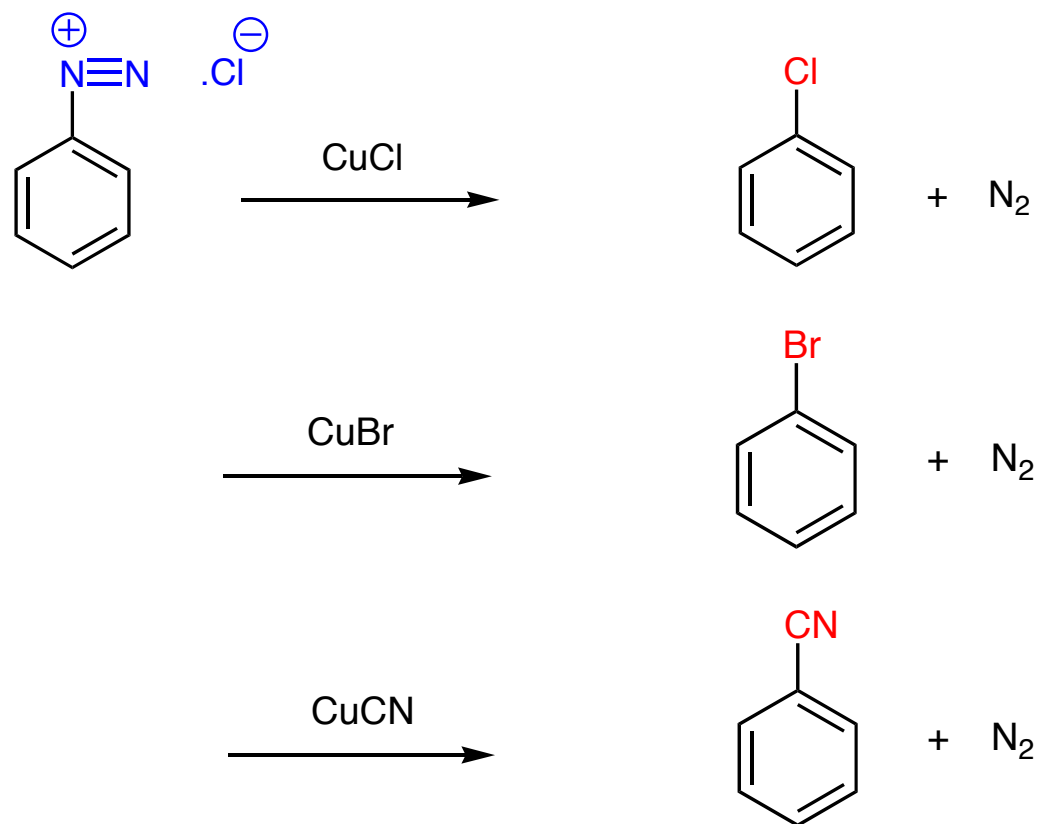
- Once a diazonium is formed (e.g. from an aniline) a **substitution reaction** can be carried out



- Note – although this is a type of Aromatic Substitution reaction, it **does NOT** proceed via $\text{S}_{\text{N}}\text{Ar}$ mechanism in next weeks lecture.
- Here, diazonium salts react via either $\text{S}_{\text{N}}1_{\text{Ar}}$ (loss of N_2 gas as first step) or S_{RN} (radical mechanism, Sandmeyer rx) (you don't need to know these mechanisms)

4. Substitution of aromatic diazonium groups

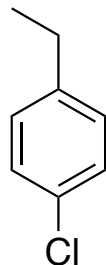
- A **Sandmeyer reaction** is when an arenediazonium salt is substituted with a nucleophile of a **cuprous** (copper (I)) salt.



- KCl and KBr **do not work** in this reaction, Cu(I) is required
- This indicates that the Cu(I) is involved in the reaction and is most likely serving as a radical initiator (*you don't need to know the mechanism*)

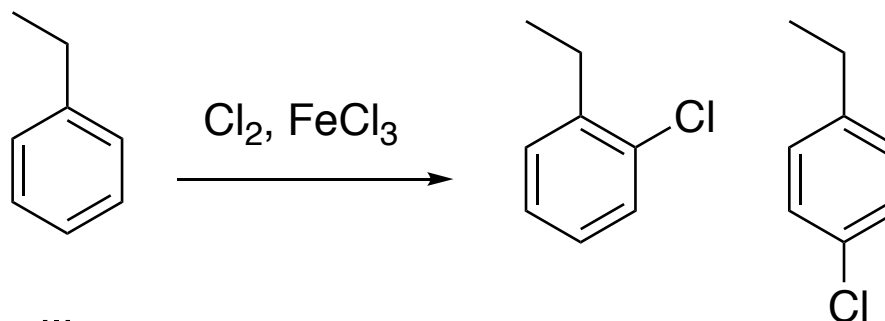
4. Substitution of aromatic diazonium groups

- Answer – because S_EAr may give the undesired or a mixture of products.....



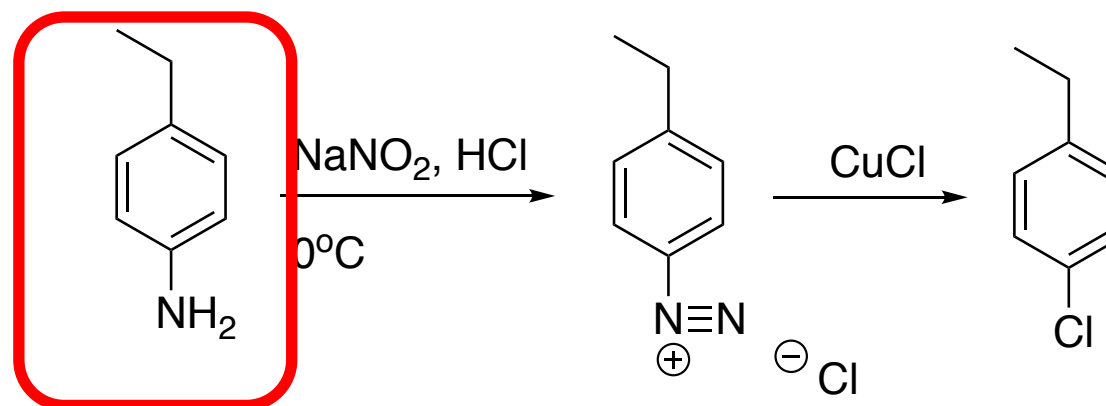
e.g. this is our target compound, *p*-chloroethylbenzene

Chlorination of ethylbenzene



However starting with *p*-ethylaniline

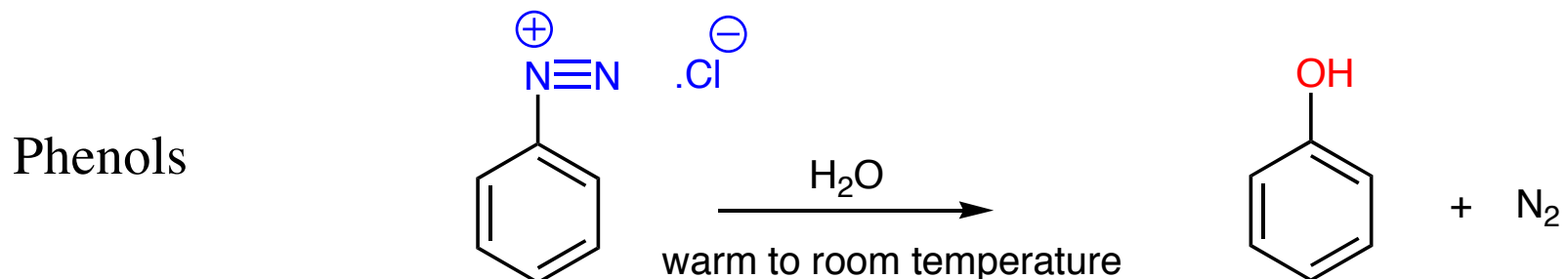
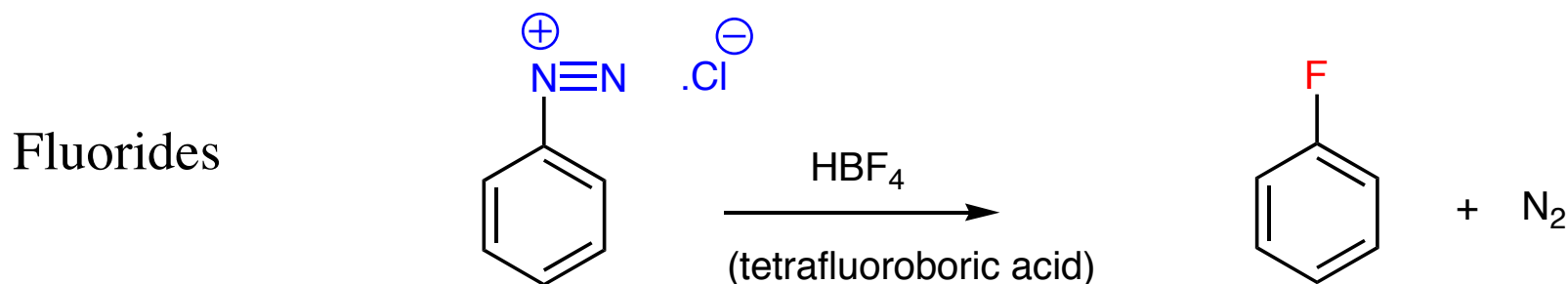
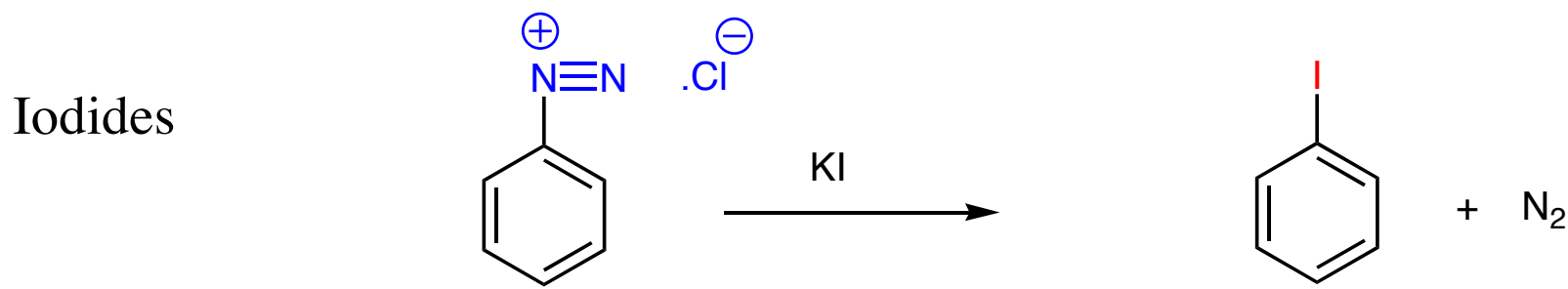
How would you make this?



BREAK

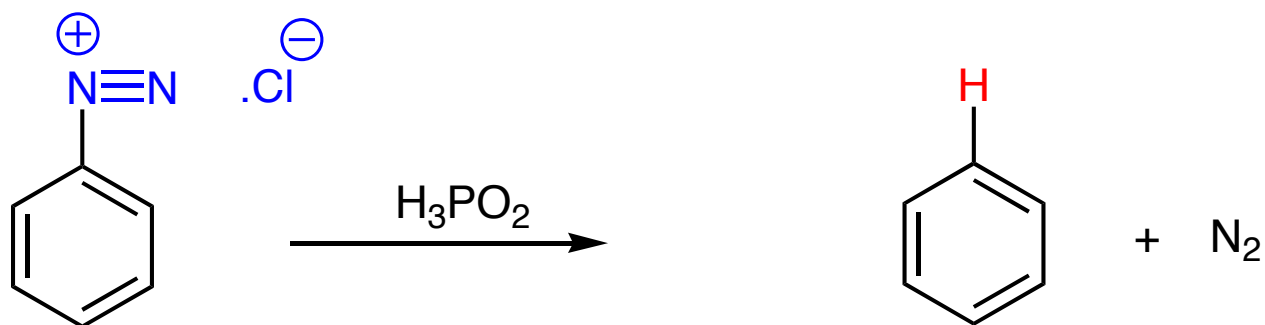
4. Substitution of aromatic diazonium groups

- The Sandmeyer reaction (cuprous salt) is **just one way** diazonium salts can be substituted.
- If the nucleophile is strong enough, and/or if the reaction is heated, copper(I) is not required (**so is not called a Sandmeyer reaction**)



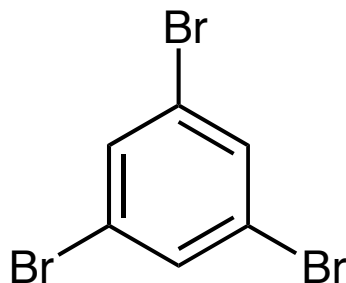
5. Reduction of aromatic diazonium groups

- Diazonium ions can be reduced with hypophosphorus acid (H_3PO_2)



5. Reduction of aromatic diazonium groups

- This 'deamination' type reaction (ie eventual replacement of diazonium with H) is useful if an amino or nitro group is needed for directing purposes, as can then be 'removed' at the end.....

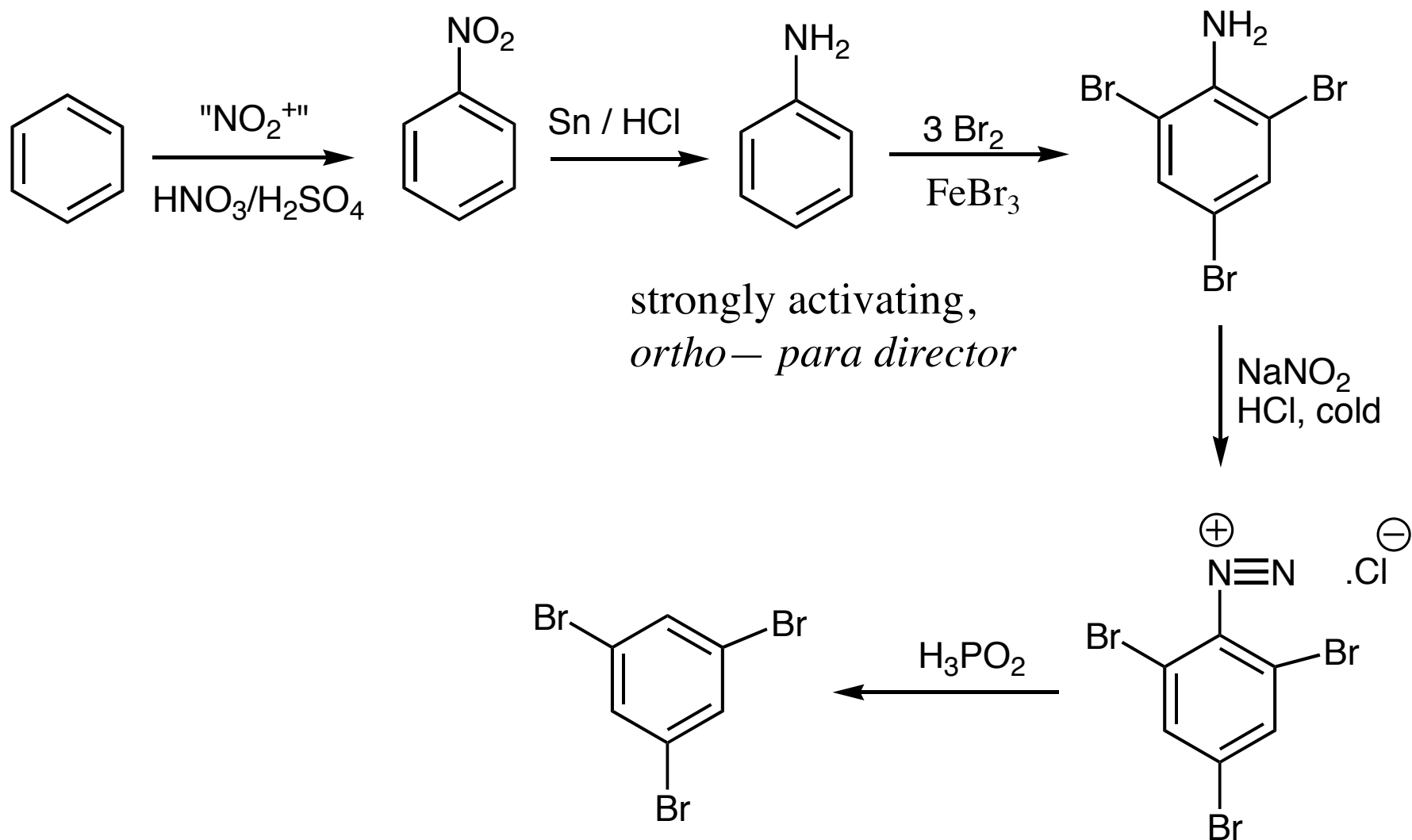


Target compound
1,3,5-tribromobenzene

Some problems if starting from benzene....

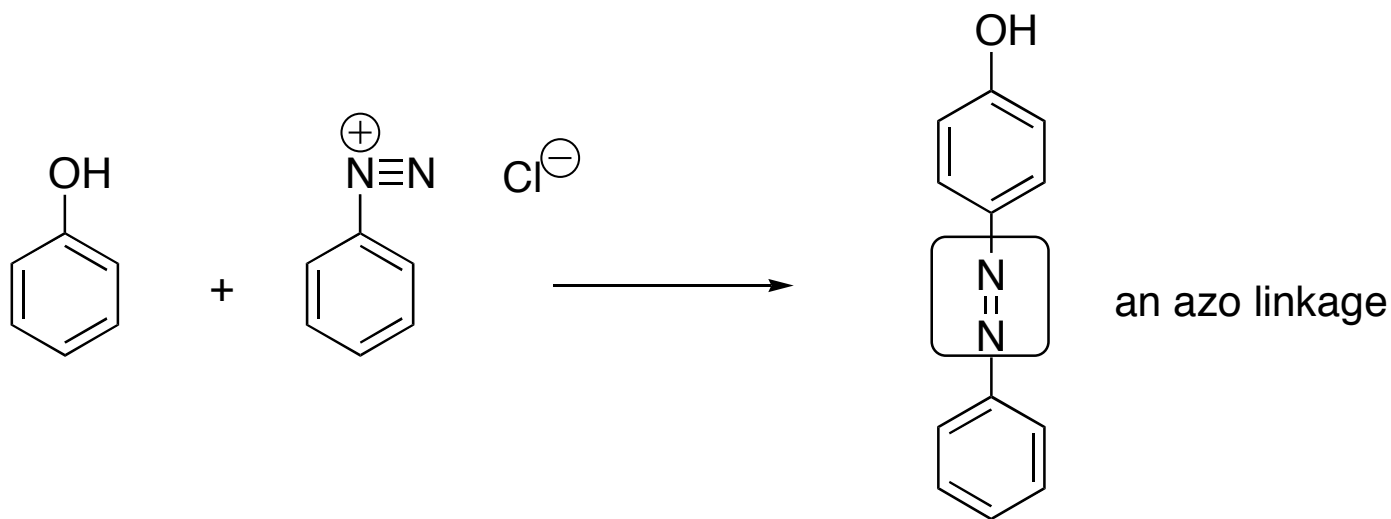
- Bromine substituents **direct ortho/para**, so the above substitution pattern is not obtainable directly.
- Also, bromine substituents are **deactivating**, so tribromination is not likely.
- One solution could be**

5. Reduction of aromatic diazonium groups



6. Synthesis of azobenzenes

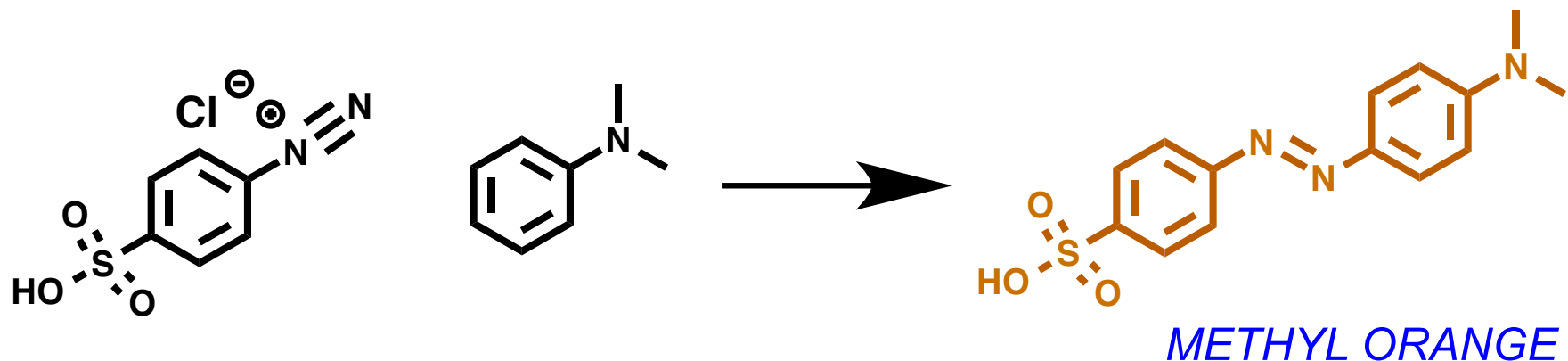
- To date in this lecture, we have discussed replacement of the diazonium salt with something else, resulting in the leaving group of N₂ gas.
- Arene diazonium ions can be the **electrophile** in **S_EAr**, forming an **azo compound**



- Require a **strongly activated** benzene ring as a **nucleophile**
- Reaction generally occurs **para** to the activating group
- If the *para* position is blocked reaction will take place at the *ortho* position

6. Synthesis of azobenzenes

- Azobenzenes are an important class of compounds



The azo group is a pH-sensitive chromophore

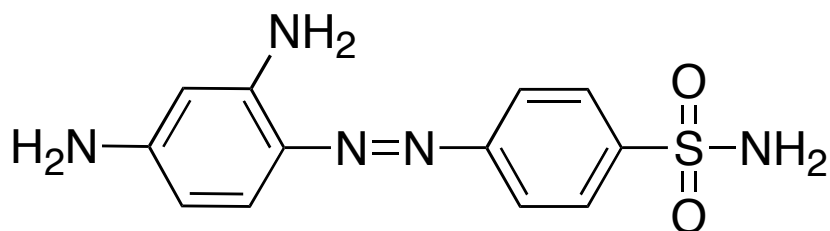


Azo dyes common in textiles



6. Synthesis of azobenzenes

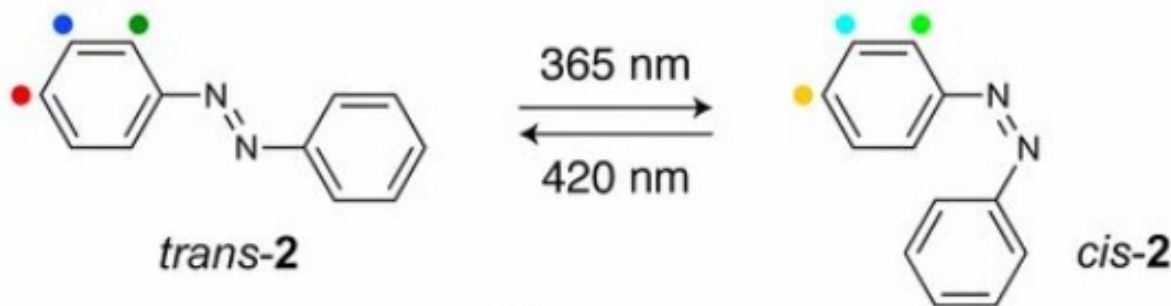
- Azobenzenes are an important class of compounds



Some drugs have azo bonds

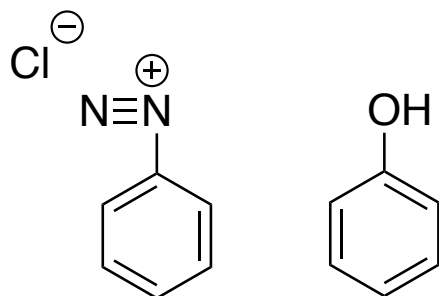
Prontosil a sulfur drug (antibiotic)

Also very interesting
'photoswitches' via
photoisomerisation



6. Synthesis of azobenzenes

- The two compounds below react with each other in an S_EAr reaction, with the diazonium ion acting as the electrophile....



Have a go at drawing out the mechanism