

Lecture 8

Nucleophilic Aromatic substitution, and benzyne

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Reference textbook

- “Organic Chemistry” by Bruice, 8th Edn.
- This lecture – Chapter 18, in particular **18.21**
- **And**
 - <https://www.masterorganicchemistry.com/2018/08/20/nucleophilic-aromatic-substitution-nas/>
 - <https://www.masterorganicchemistry.com/2018/09/17/nucleophilic-aromatic-substitution-2-benzyne/>
- (the benzyne mechanism is **not** discussed in depth in Bruice)

Learning Objectives – Lecture 8

Section 4– Aromatic nucleophilic substitution reactions

Account for the general lack of reactivity of benzene towards nucleophiles

Discuss the reactions of aromatic compounds with nucleophiles by the addition/elimination mechanism, to include:

the mechanism of the reaction, including resonance-stabilisation of reaction intermediates

factors affecting reactivity of the aromatic ring towards the nucleophilic addition step

factors affecting the course of the elimination step

Discuss the reactions of aromatic compounds with nucleophiles by the benzyne mechanism, to include:

the mechanism of the reaction

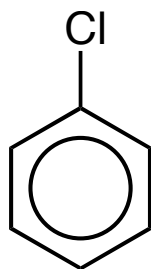
the reactivity of benzyne intermediates

Lecture Outline: L8

- 1. Introduction**
- 2. Nucleophilic Aromatic Substitution**
- 3. Nucleophilic Aromatic Substitution – addition then elimination**
- 4. Nucleophilic Aromatic Substitution – elimination then addition**

1. Introduction

- On the whole, benzene doesn't react easily with nucleophiles because the π cloud repels the approach of a nucleophile
- Benzene derivatives with a leaving group undergo substitution with difficulty.
- A comparison of alkyl and aryl chloride bond strengths indicates why.....



- Aromatic C—Cl, 400 kJ mol⁻¹
- shorter



- Alkyl C—Cl, 346 kJ mol⁻¹
- longer

1. Introduction

NUCLEOPHILIC aromatic substitution CAN occur if

- The aromatic ring is electron poor (one or more EWGs)
- There is a good, incoming nucleophile

AND

- There is a good leaving group

Remember from S_EAr:

~~Strongly Deactivating towards S_EAr~~

—NO₂

—CN

—SO₃H

—NH₃⁺

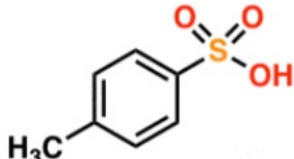
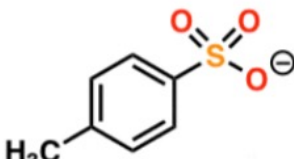
—NR₃⁺

Activating/makes nucleophilic Ar substitution easier/possible

1. Introduction

What makes a good leaving group?

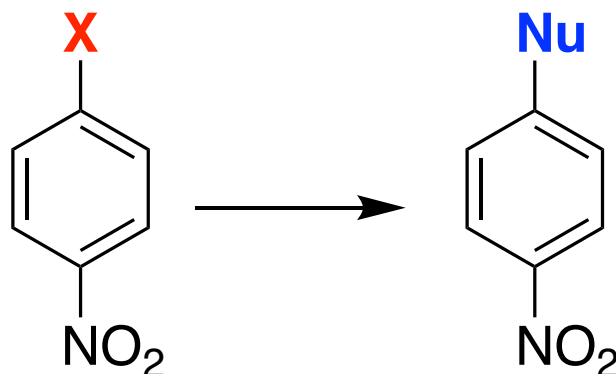
- Good leaving groups are weak bases
- i.e. the conjugate base of strong acids, e.g. halide ions (I^- , Br^- , Cl^-) water (OH_2), and sulfonates

| Functional group / Example | | pKa | Conjugate base (Leaving group) |
|----------------------------|------------------------------------------------------------------------------------------------------|------|---------------------------------------------------------------------------------------|
| Hydroiodic acid | HI | -10 | I^- |
| Hydrobromic acid | HBr | -9 | Br^- |
| Hydrochloric acid | HCl | -6 | Cl^- |
| Sulfuric acid | H_2SO_4 | -3 | HSO_4^- |
| Sulfonic acids |  (tosic acid) | -3 |  |
| Hydronium ion | H_3O^+ | -1.7 | H_2O |

Excellent leaving groups (extremely weak bases)

<https://www.masterorganicchemistry.com/2011/04/12/what-makes-a-good-leaving-group/>

2. Nucleophilic Aromatic Substitution



There are two main types/mechanisms of S_NAr .

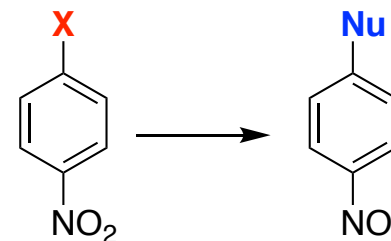
Part **3** of this lecture: Addition THEN elimination

- Requires **electron poor benzene ring** with **electron withdrawing groups** **either ortho or para** to a leaving group. The nucleophile adds, THEN the leaving group is eliminated.

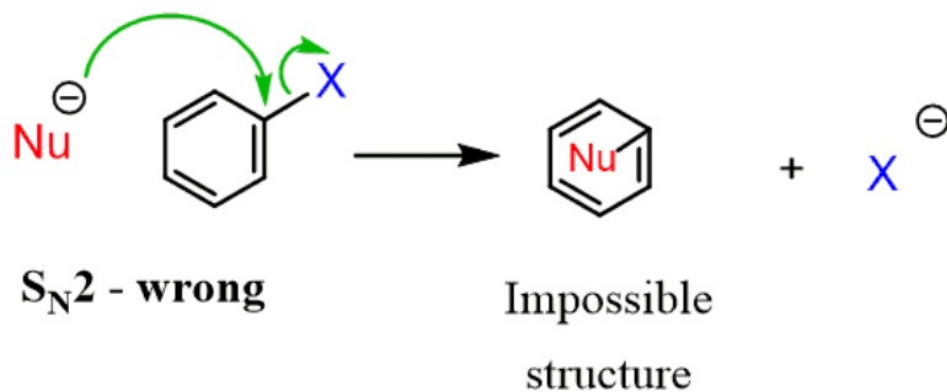
Part **4** of this lecture: Elimination THEN addition

- Requires a **very strong base** (amide anion or molten sodium hydroxide). Elimination of the HX, to give a **benzyne**, THEN addition of a nucleophile (from the base).

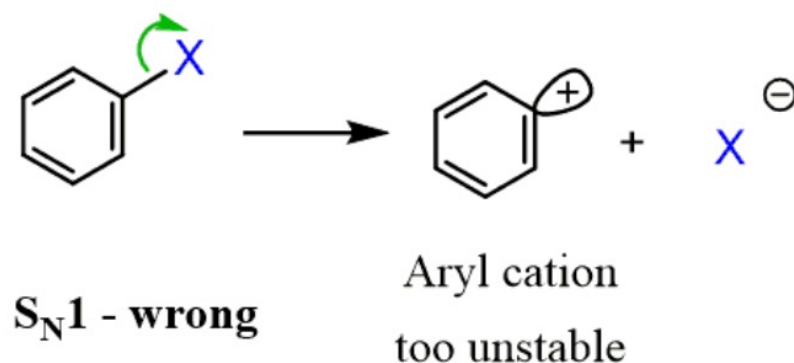
2. Nucleophilic Aromatic Substitution



- Both 'addition then elimination' and 'elimination then addition' for aromatic systems are DIFFERENT to 'alkyl halide' substitution reactions
- Aryl halides DO NOT undergo S_N2 or S_N1**



Backside attack is geometrically (and electronically) impossible

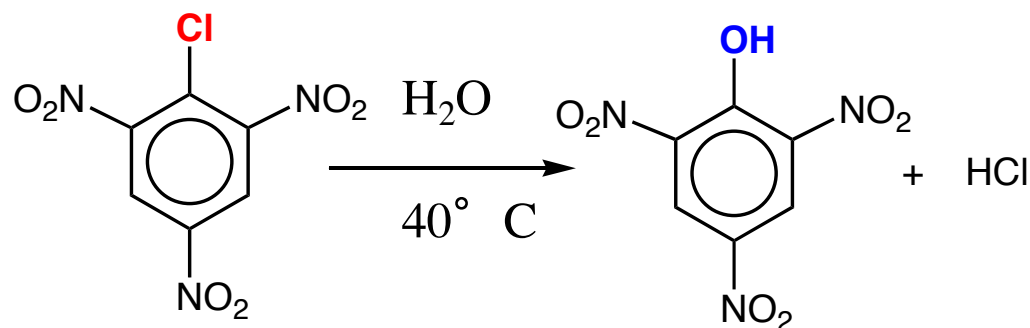
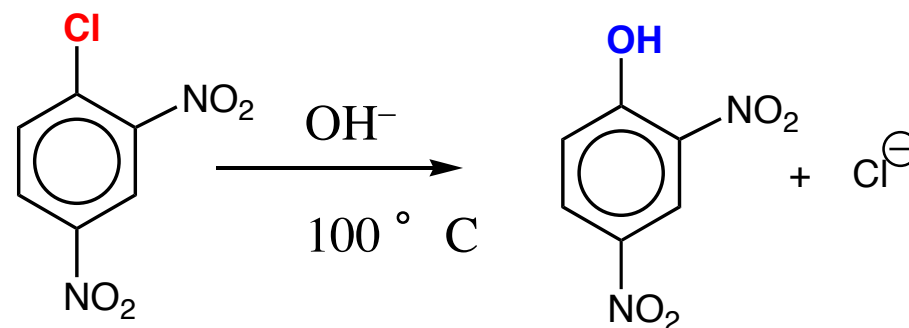
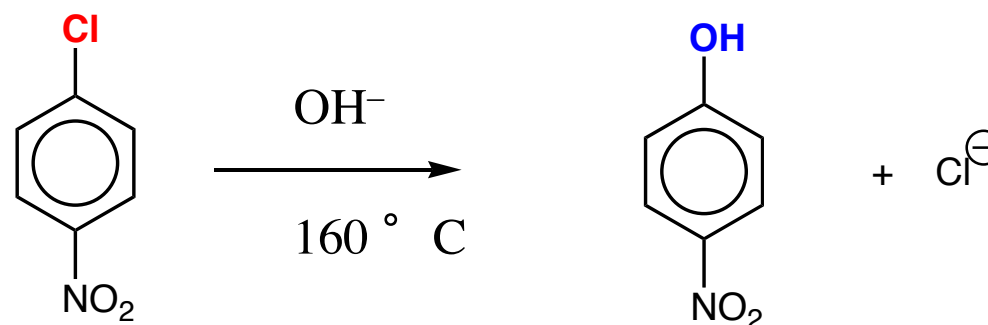


'Sole' loss of leaving group does not occur

3. S_NAr – addition then elimination mechanism

If a benzene ring has:

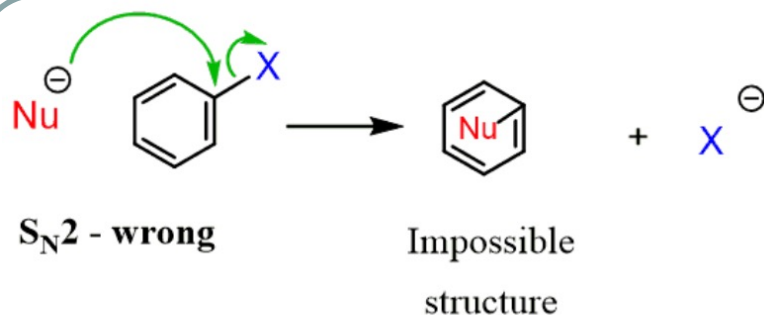
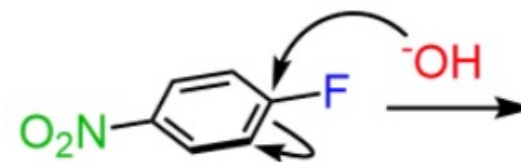
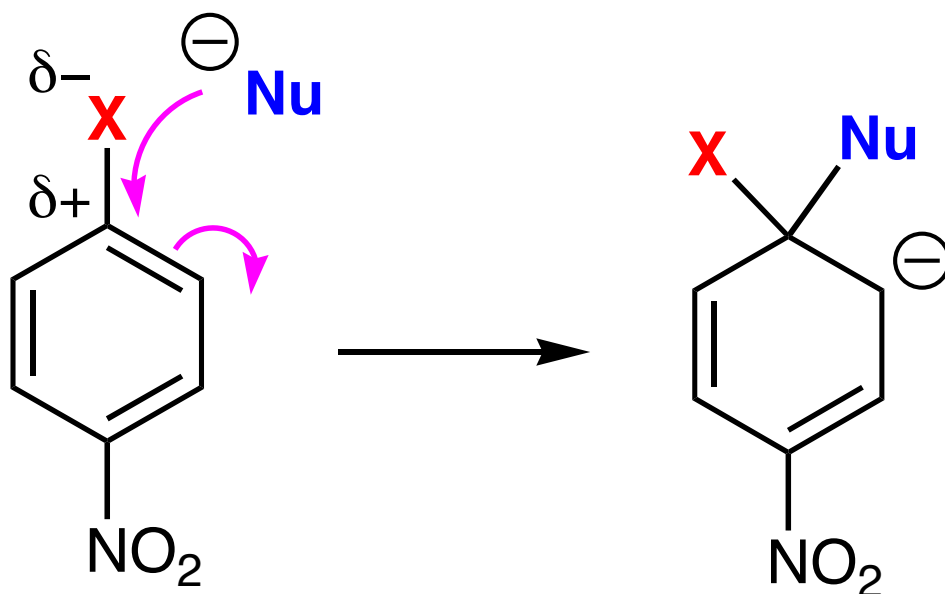
- a good leaving group, **and**
- one or more strongly electron withdrawing substituents either *o* or *p* to the leaving group



3. S_NAr – addition then elimination

Mechanism – Step 1, addition, the slow step

- **Nucleophile** attacks the carbon bearing the leaving group (**X**) **perpendicular** to the Ar ring

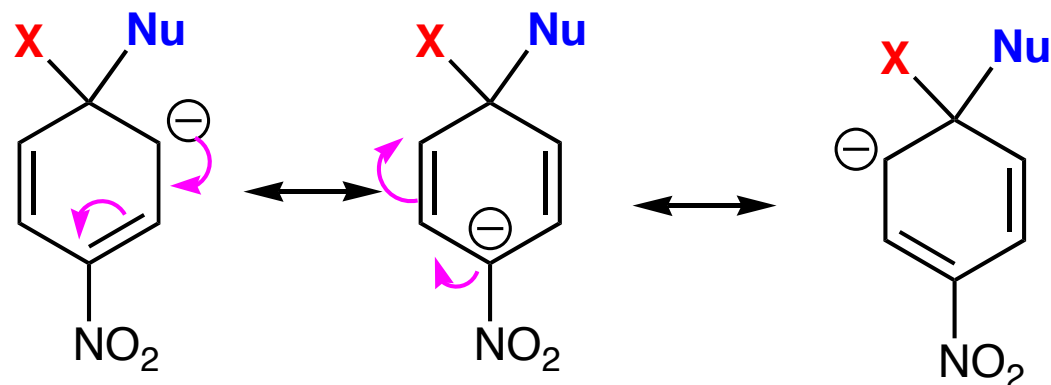


Remember – backside attack **is not possible**

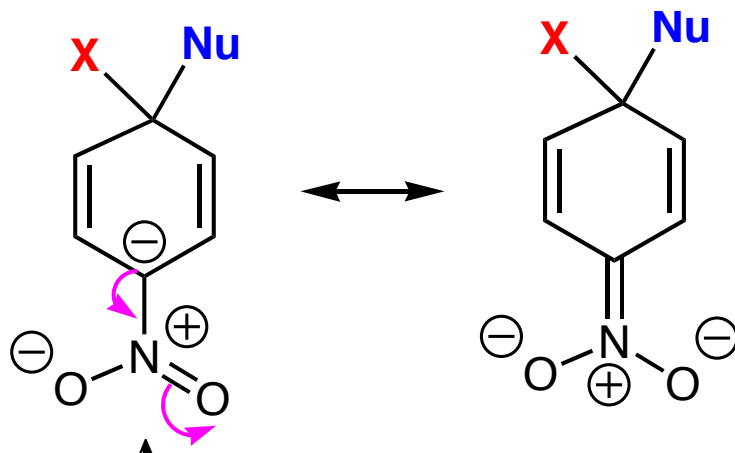
3. S_NAr – addition then elimination

Mechanism – Step 1, addition, the slow step

- The **carbanion** is resonance stabilized, called a “**meisenheimer complex**”



- The reason an EWG substituent(s) helps is the resonance contributor(s) -

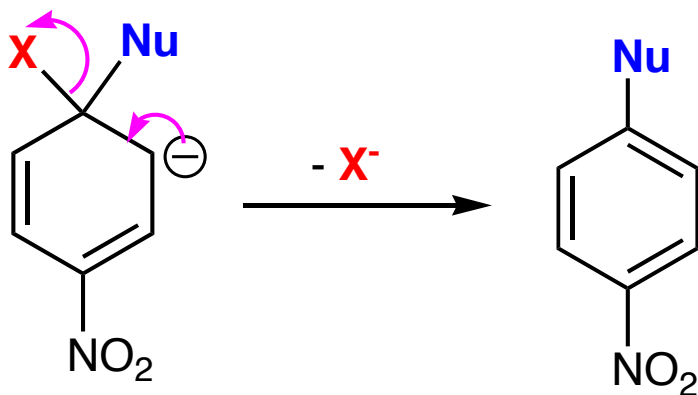


All the resonance contributors are termed the “**meisenheimer complex**” however this is the most stabilised contributor

3. S_NAr – addition then elimination

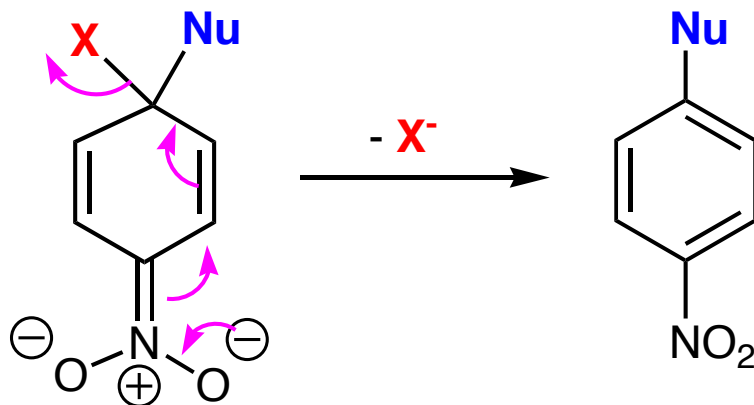
Mechanism – Step 2, elimination of X⁻

- X must be a BETTER leaving group than Nu, i.e. the incoming Nu must be a stronger base than X.



or

Any of the resonance contributors can be used to show this elimination step

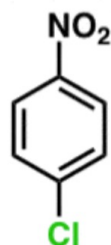


3. S_NAr – addition then elimination

Factors influencing the reaction

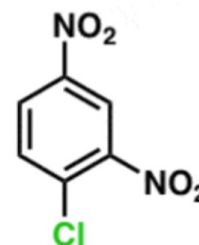
- The more electron poor the Ar ring is, the faster the reactions

one EWG
slowest



two EWGs
faster

(by a factor of about 10⁵)

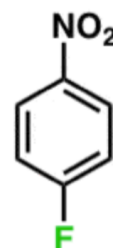


three EWGs
fastest



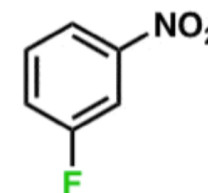
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p-fluoronitrobenzene

Fast



m-fluoronitrobenzene

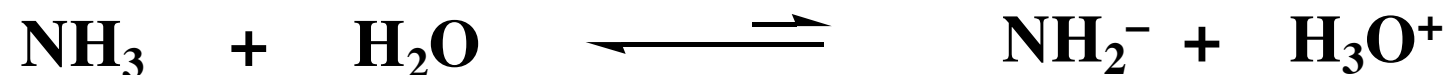
Slow

BREAK

4. S_NAr – elimination then addition mechanism

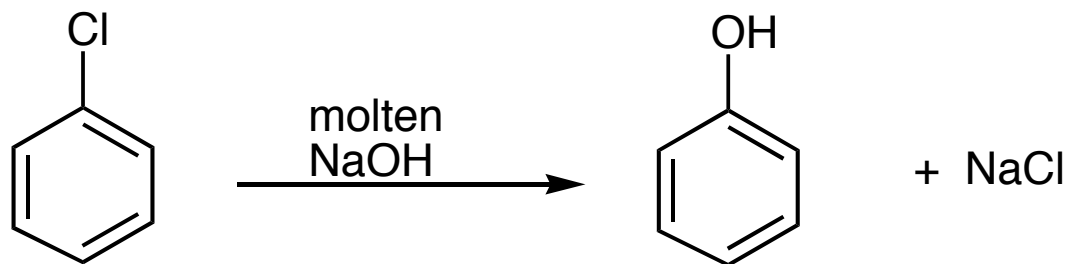
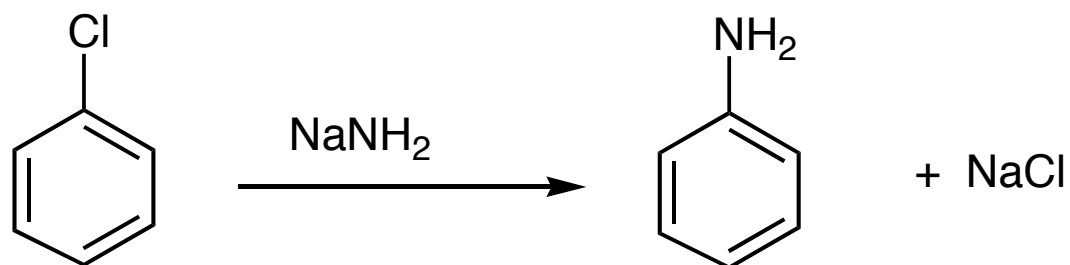
Aryl halides **without** an electron withdrawing group(s) can undergo nucleophilic substitution in the presence of **very strong bases** such as sodium amide (NaNH₂).

- e.g. NH₃ has a pK_a of 43.



4. S_NAr – elimination then addition

The overall reaction (i.e. substituted product) is the same.....



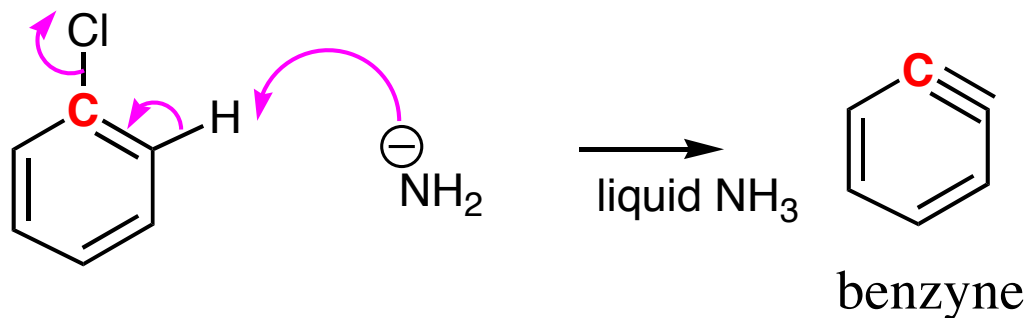
.....but the mechanism is different to section 3 of this lecture, and the nucleophile must be a **very strong base**

This mechanism is less common because of the extreme reaction conditions

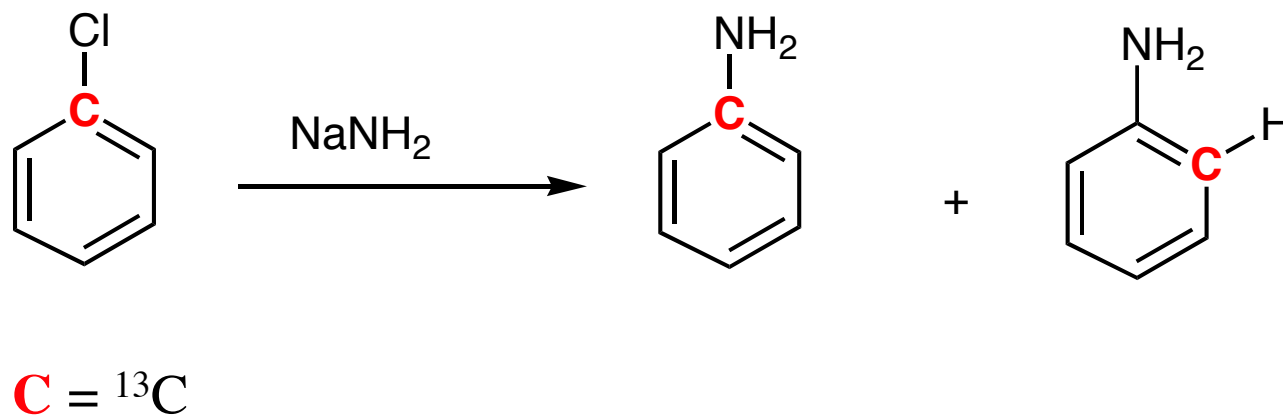
4. S_NAr – elimination then addition

Mechanism – Step 1, elimination of halide (but NOT just ‘directly’)

- Believed to be via a **benzyne**

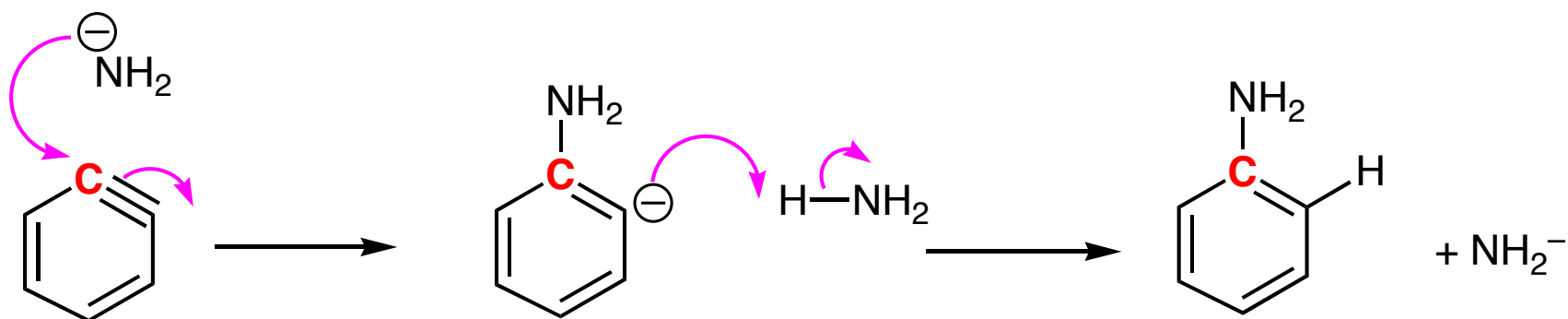


- The mechanism has been studied using ¹³C

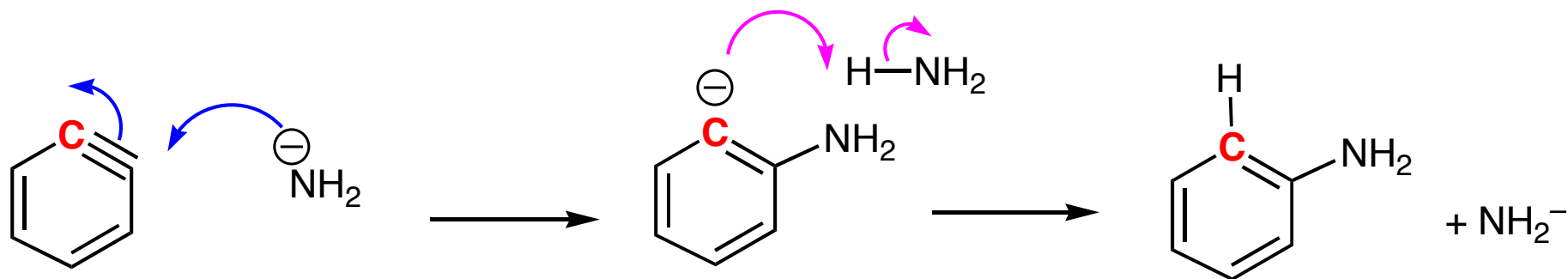


4. S_NAr – elimination then addition

Mechanism – Step 2, nucleophile attacks the benzyne

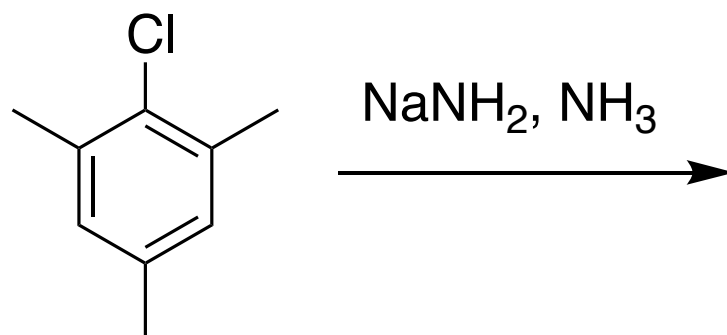


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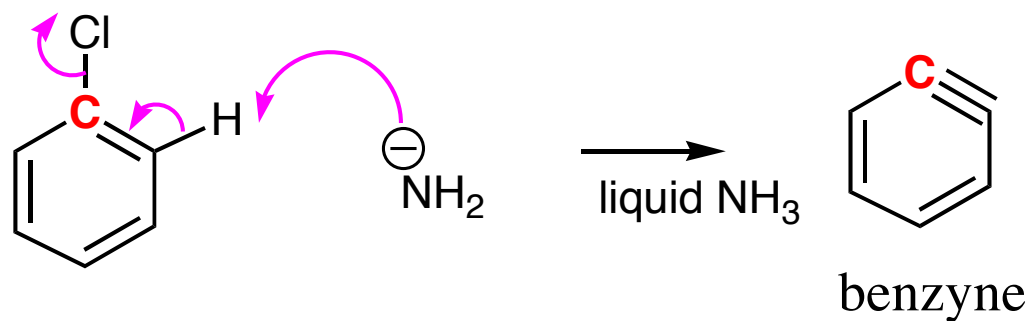


4. S_NAr – elimination then addition

There must be a hydrogen adjacent (*ortho to*) the leaving group



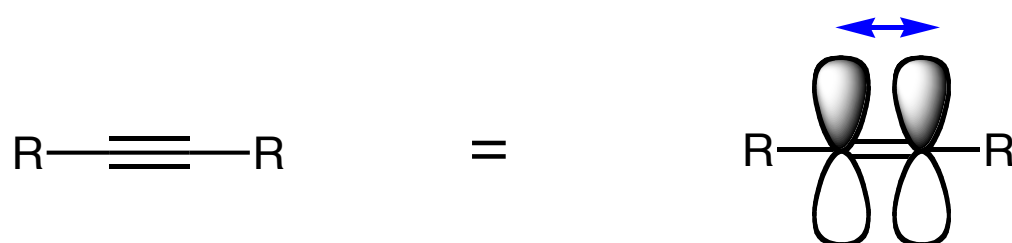
Remember the mechanism....



4. S_NAr – elimination then addition

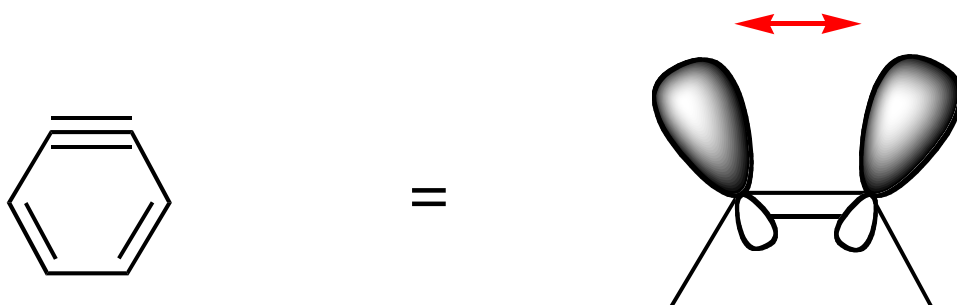
The benzyne intermediate is very reactive...

Examine a normal alkyne:



Very good orbital overlap
Strong π bond

Examine a benzyne

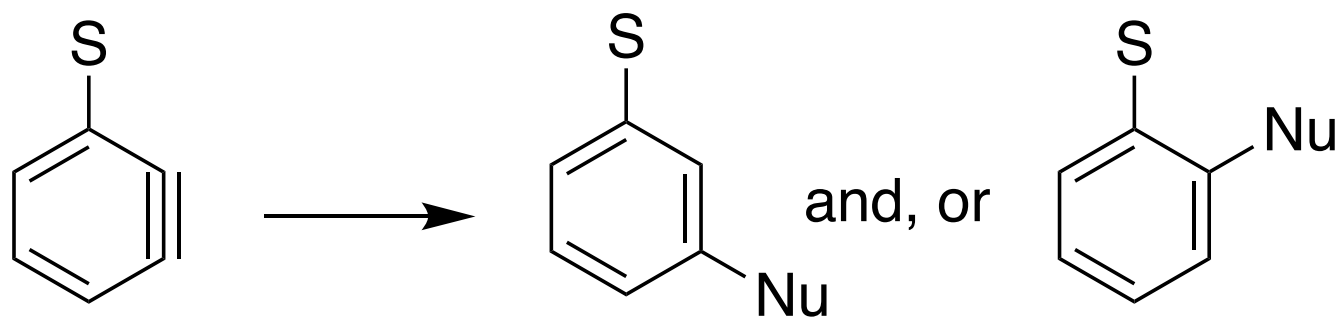


Poor overlap
Weak π bond

4. S_NAr – elimination then addition

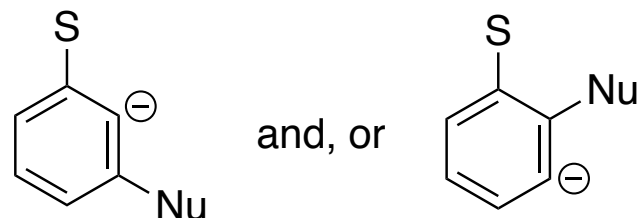
- There can be 'substituent directing effects' but not quite in same way as we saw for S_EAr
- Remember if there is a strong EWG then the 'addition then elimination' mechanism will likely occur
- But the 'elimination then addition' mechanism can occur with other substituents present.....

If the benzyne is not symmetrical then regioisomers could form



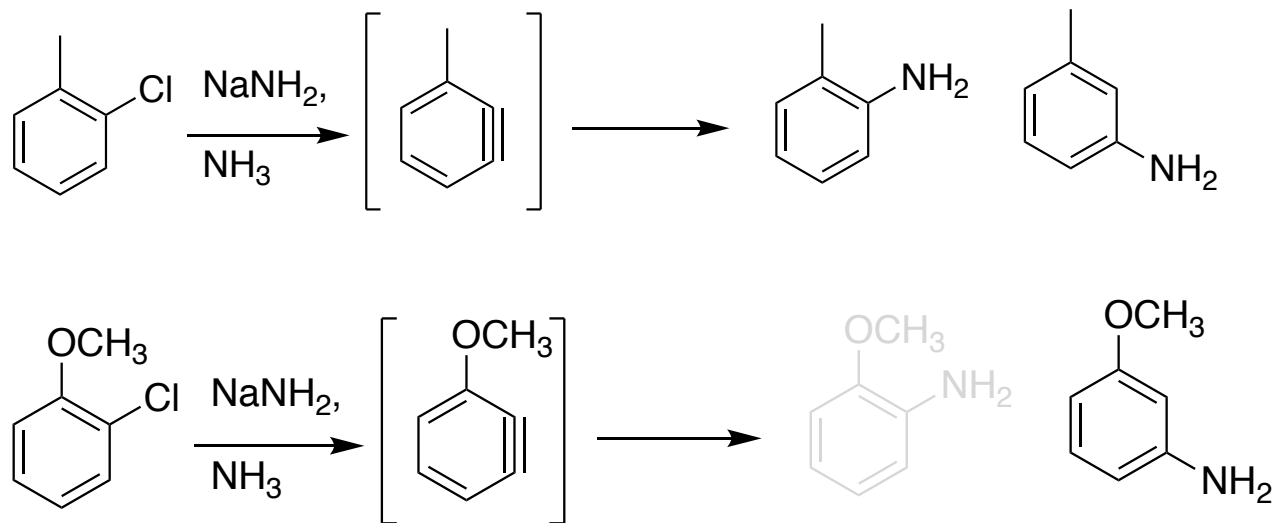
4. S_NAr – elimination then addition

- The regiochemistry depends on the stability of the anion formed when the nucleophile attacks in step 2



Since the aromatic pi-system is at right angles to the triple bond, what's NOT relevant is the substituent's ability to donate the lone electron pair to the ring (like OCH₃) , or accept a lone pair from it (like NO₂). **i.e. no +M or –M**

The negative charge can only be stabilised by –I (inductive effects)



4. S_NAr – elimination then addition

Home work exercises:

Predict the products formed upon reaction with sodium amide in liquid ammonia.

