Lecture 28
Organic Chemistry 1

Professor Duncan Wardrop

April 22, 2010

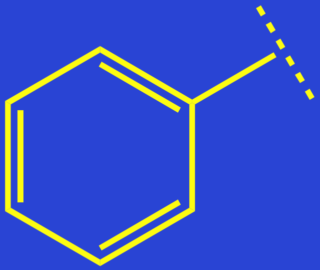
Today's Lecture

Topics Covered:

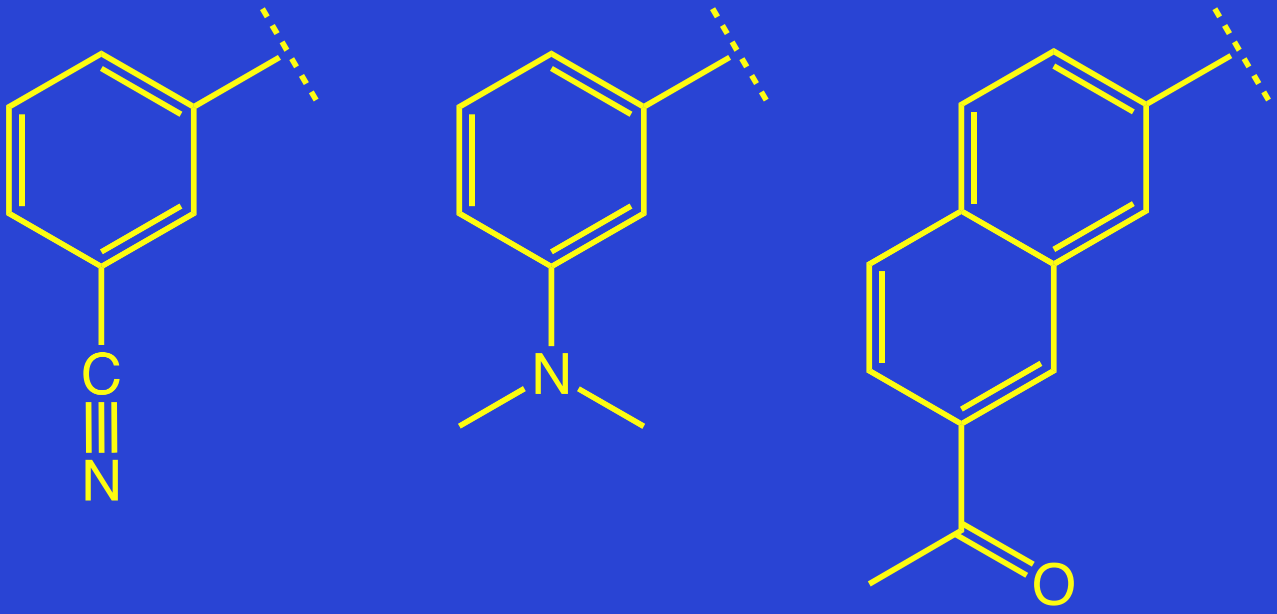
1. Aryl Halides - Bonding, Physical Properties and Reactions
2. Nucleophilic Aromatic Substitution of Chlorobenzene
3. Nucleophilic Aromatic Substitution: Addition-Elimination
4. Floxcin - Application of Nucleophilic Aromatic Substitution
5. Nucleophilic Aromatic Substitution: Elimination-Addition

What’s the Difference Between Ar- and Ph-?

Phenyl refers specifically to this:



Aryl is a general term for <u>all</u> aromatic ring systems:



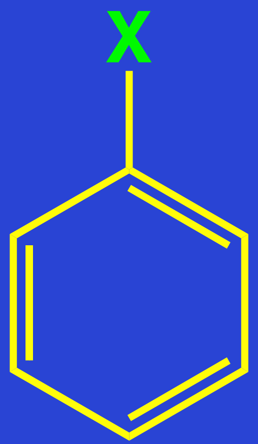
Chapter 23

Aryl Halides

23.1

Bonding in Aryl Halides

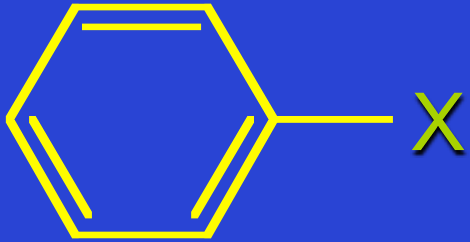
Aryl Halides



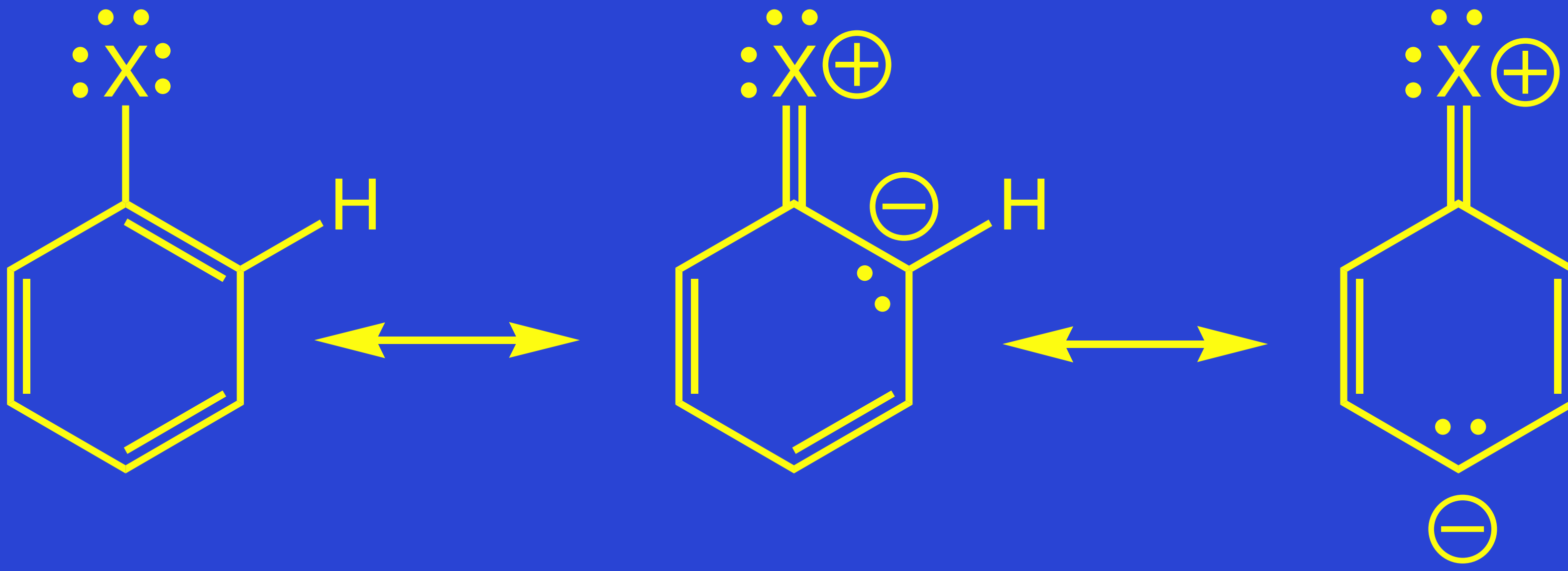
Aryl halides are halides in which the halogen is attached directly to an aromatic ring.

Carbon-halogen bonds in aryl halides are shorter and stronger than carbon-halogen bonds in alkyl halides.

Dissociation Energies of Selected Compounds

		Bond Energy: kJ/mol (kcal/mol)	
		X = H	X = Cl
CH_3CH_2X	sp^3	410 (98)	339 (81)
$H_2C{=}CHX$	sp^2	452 (108)	368 (88)
	sp^2	469 (112)	406 (97)

Resonance Picture



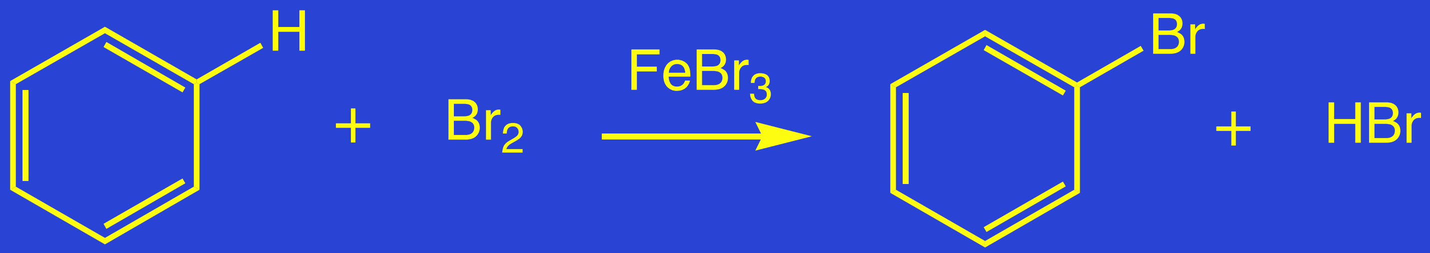
C-X bonds in aryl halides have more double bond character than C-X bonds in alkyl halides

23.2

Sources of Aryl Halides

Preparation of Aryl Halides

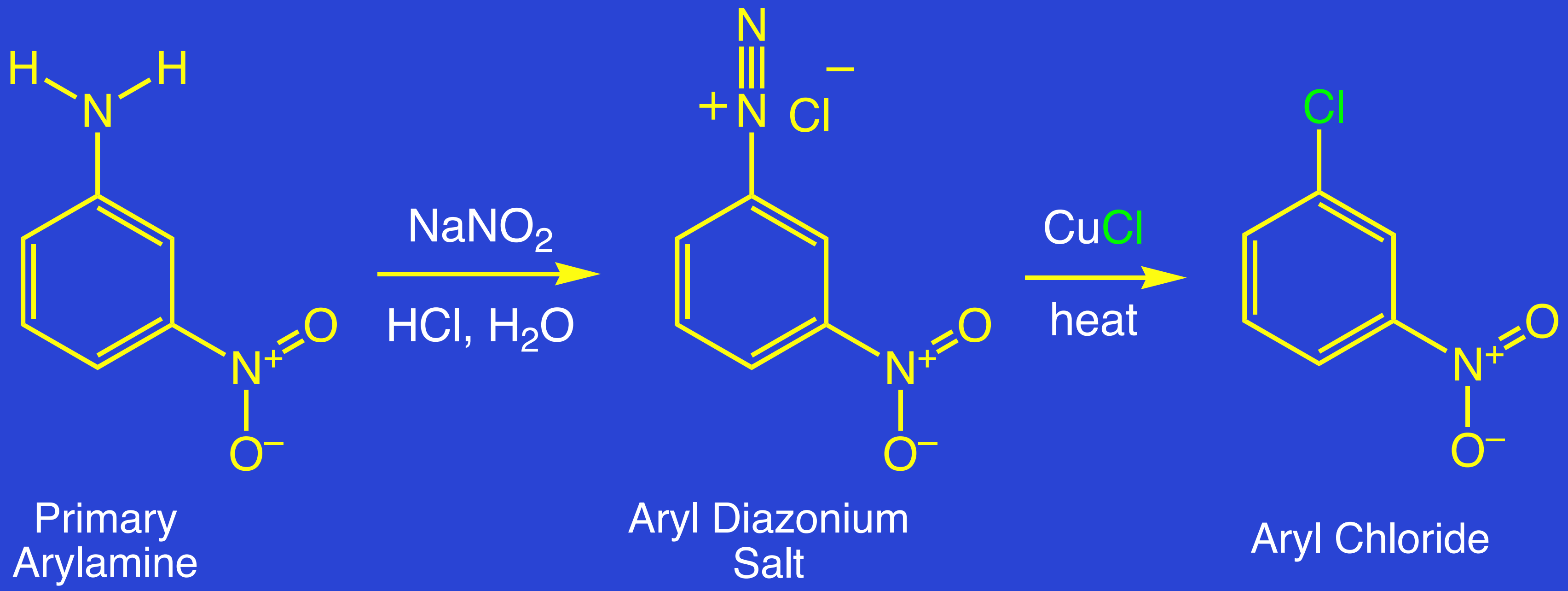
Halogenation of arenes (Section 12.5)



electrophilic aromatic substitution

Preparation of Aryl Halides

The Sandmeyer reaction (Section 22.17)



Primary Arylamine

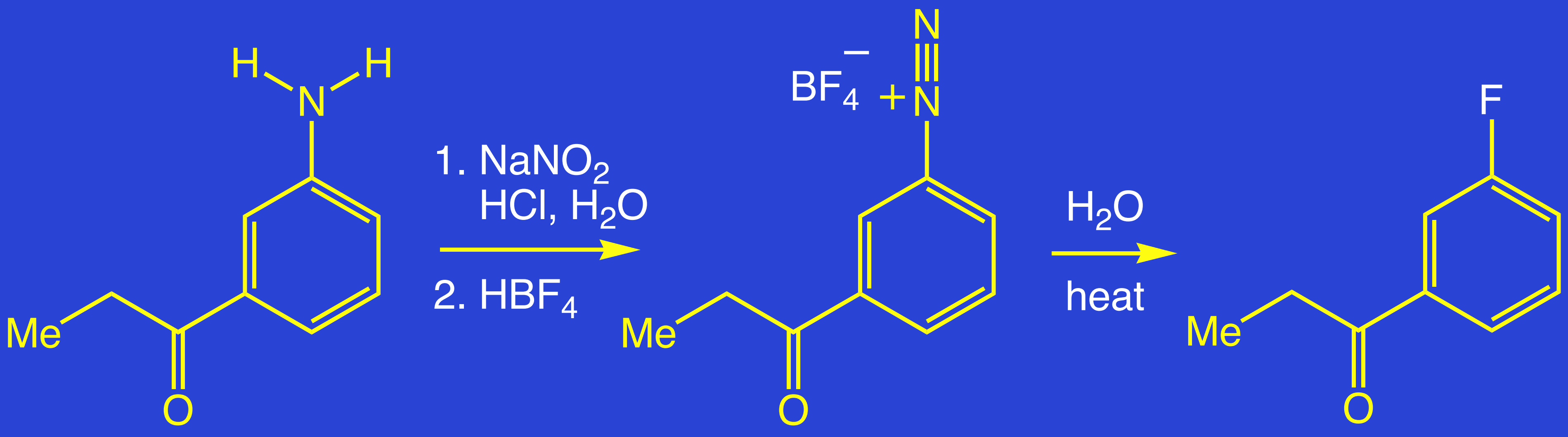
Aryl Diazonium Salt

Aryl Chloride

diazotization-nucleophilic aromatic substitution

Preparation of Aryl Halides

The Schiemann reaction (Section 22.17)



Primary Arylamine

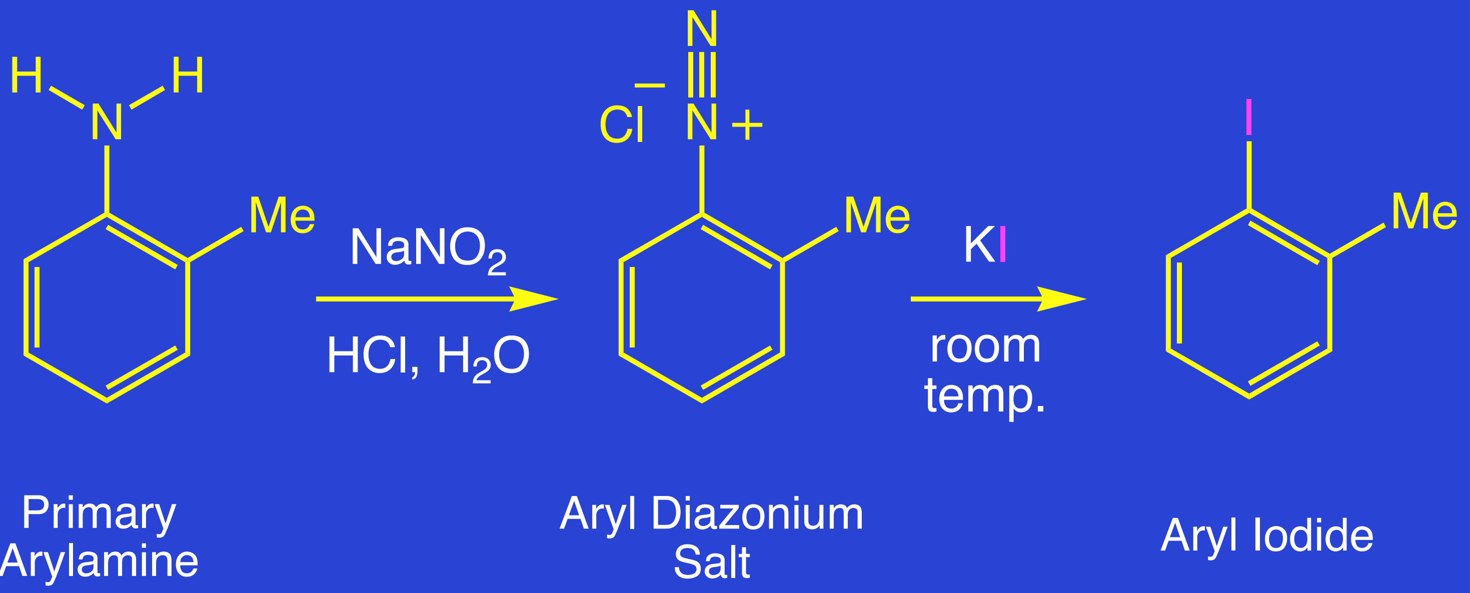
Aryl Diazonium Salt

Aryl Fluoride

diazotization-nucleophilic aromatic substitution

Preparation of Aryl Halides

Reaction of aryl diazonium salts with iodide ion (Section 22.18)



diazotization-nucleophilic aromatic substitution

23.3

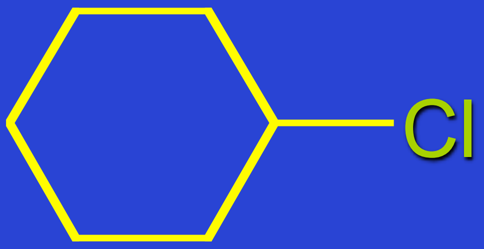
Physical Properties of Aryl Halides

Physical Properties of Aryl Halides

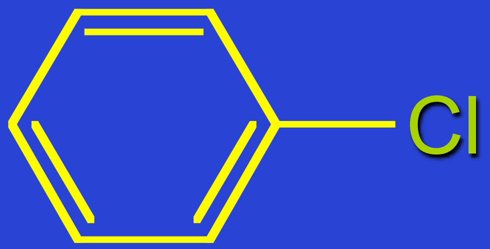
resemble alkyl halides

are essentially insoluble in water

less polar than alkyl halides



μ 2.2 D



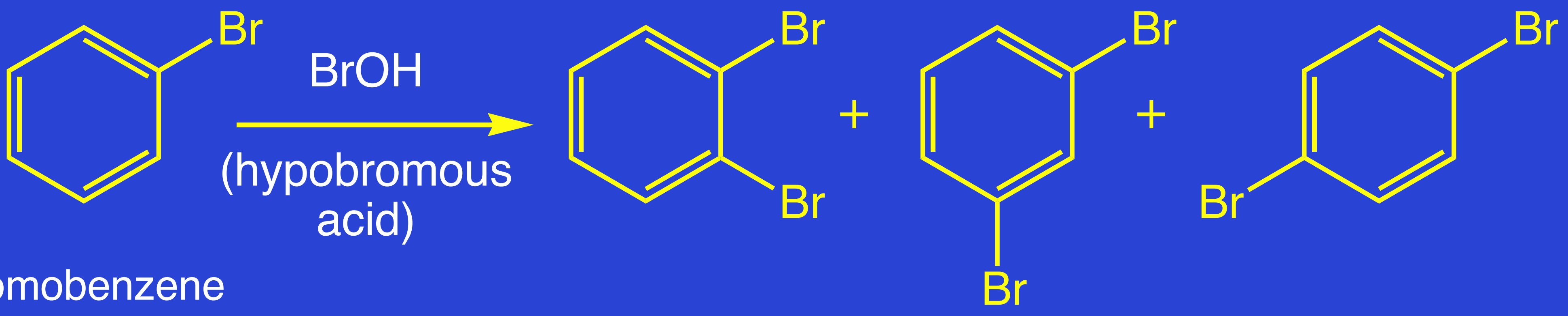
μ 1.7 D

23.4

Reactions of Aryl Halides: A Review and a Preview

Reactions Involving Aryl Halides

Electrophilic aromatic substitution (Section 12.14)



Bromobenzene

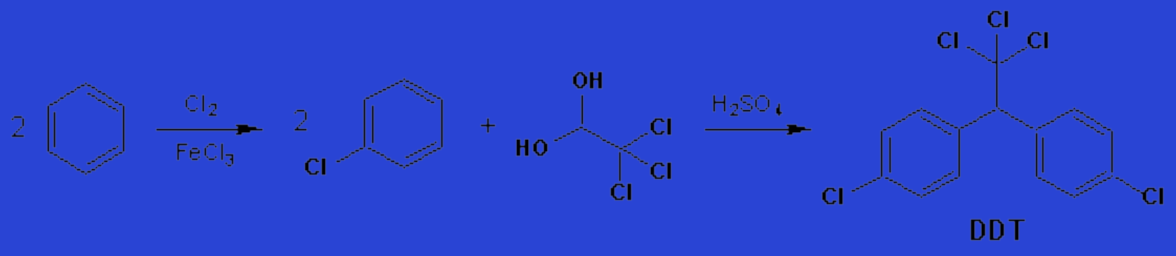
35.7% 1.0% 64.3%

halide substituents are *ortho-para* directing & deactivating

Reactions Involving Aryl Halides

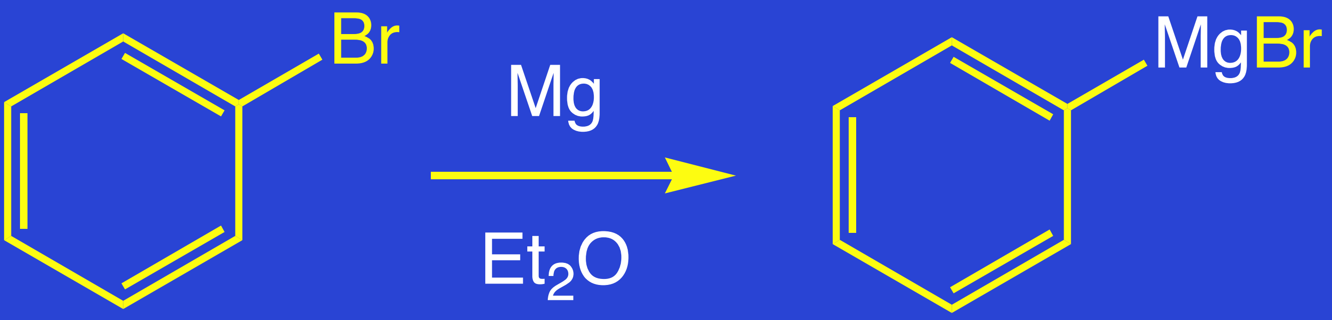
Electrophilic aromatic substitution (Section 12.14)

ADD DDT SYNTHESIS



Reactions Involving Aryl Halides

Formation of aryl Grignard reagents (Section 14.4)



Bromobenzene

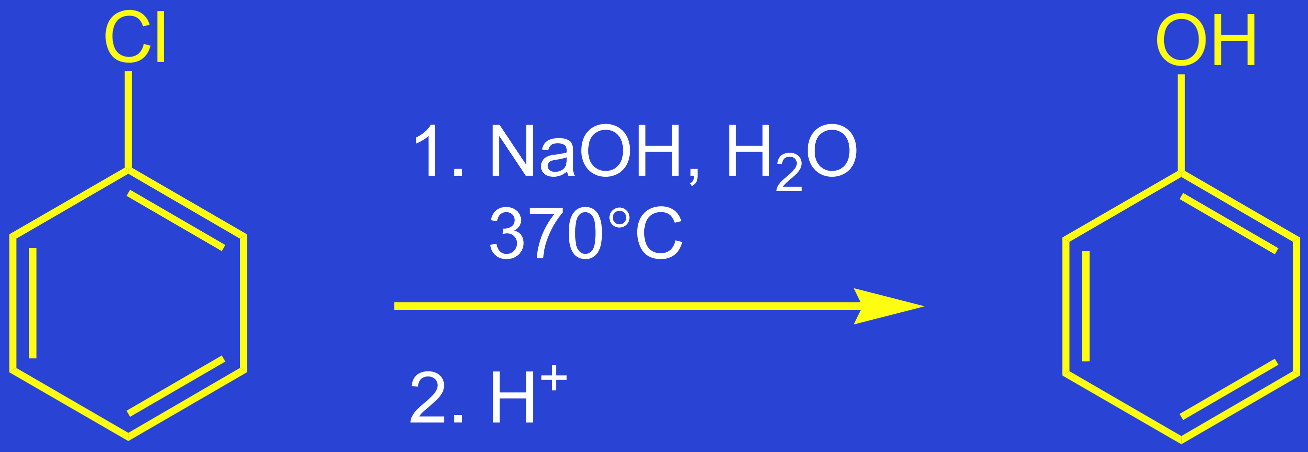
Phenylmagnesium
bromide

Substitution Reactions Involving Aryl Halides

We have not yet seen any nucleophilic substitution reactions of aryl halides.

Nucleophilic substitution on chlorobenzene occurs so slowly that forcing conditions are required.

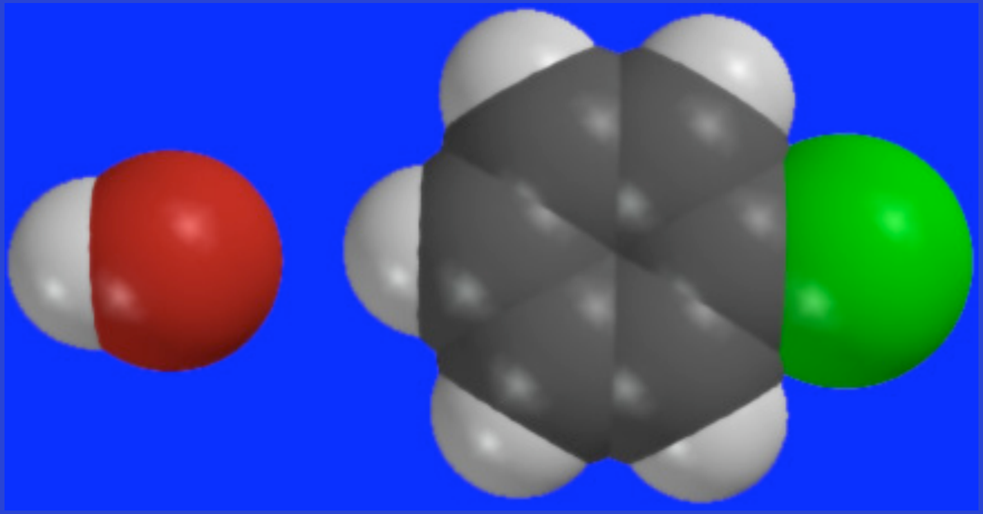
Nucleophilic Substitution of Chlorobenzene



(97%)

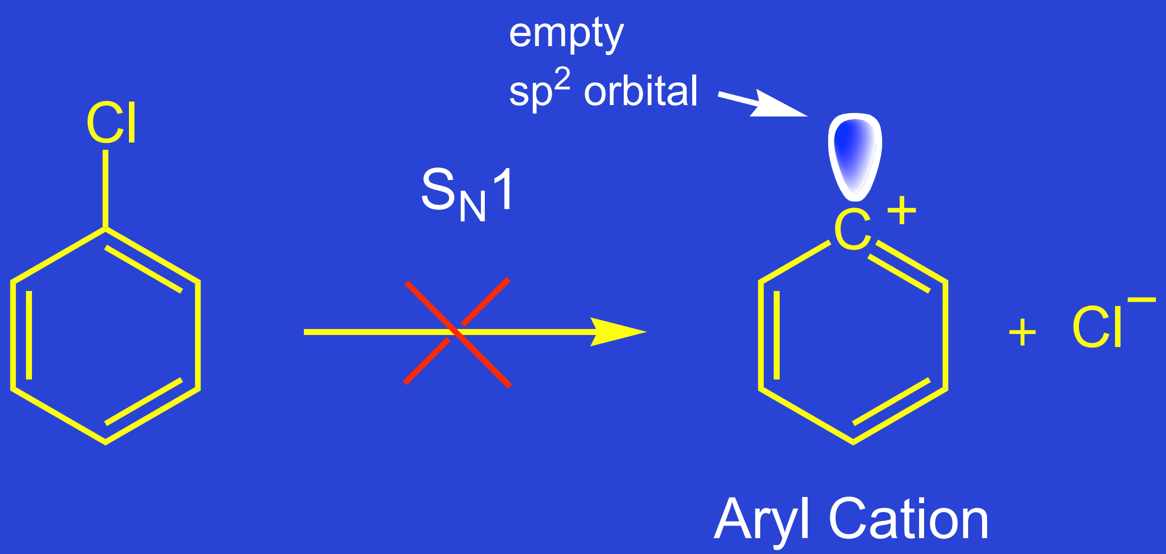
This reaction does not proceed via SN2……..

Why is Chlorobenzene Unreactive?



the S_N2 is not reasonable because the aromatic ring blocks back-side approach of the nucleophile. Inversion is not possible.

SN1 Also Unlikely: Aryl Cations are Highly Unstable

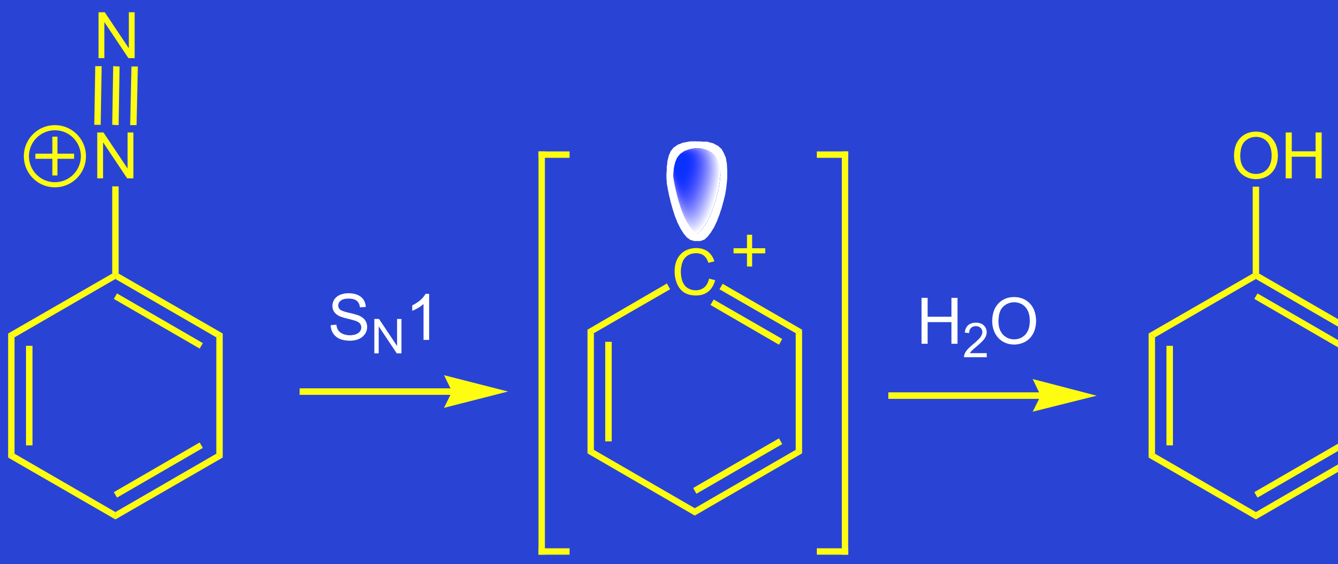


SN1 not reasonable because:

1) C—Cl bond is strong; therefore, ionization to a carbocation is a high-energy process

2) aryl cations are highly unstable

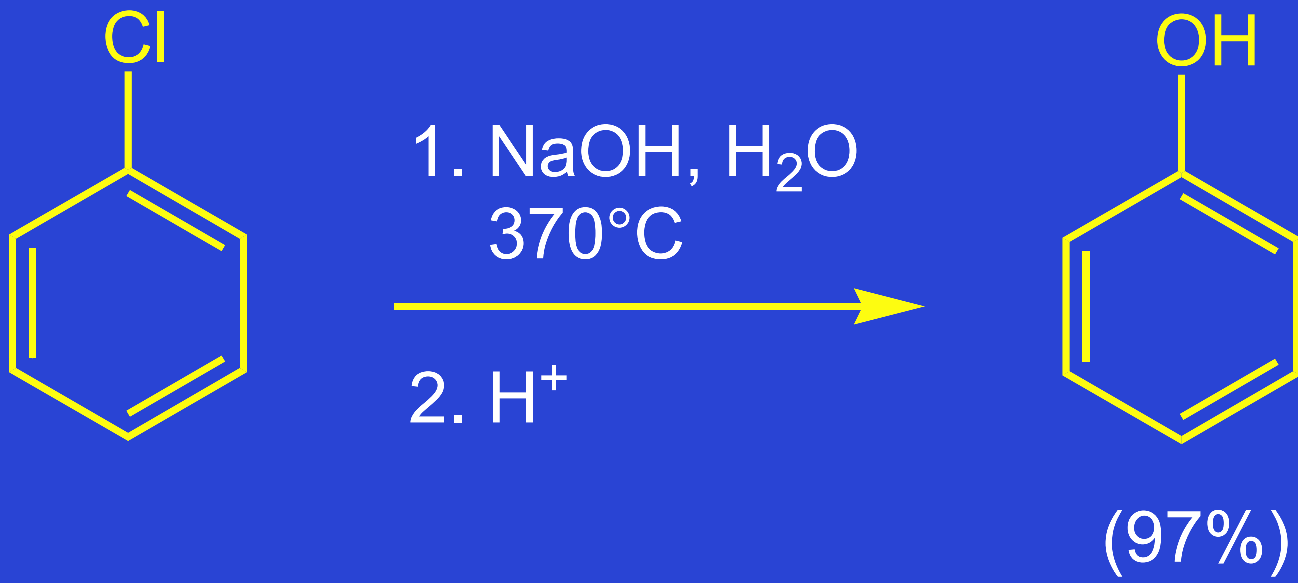
S_N1 Reaction is Possible with Very Powerful Leaving Groups such as Dinitrogen



Aryl Cation

This is a unique case: halides are not good enough leaving groups for this process to occur.

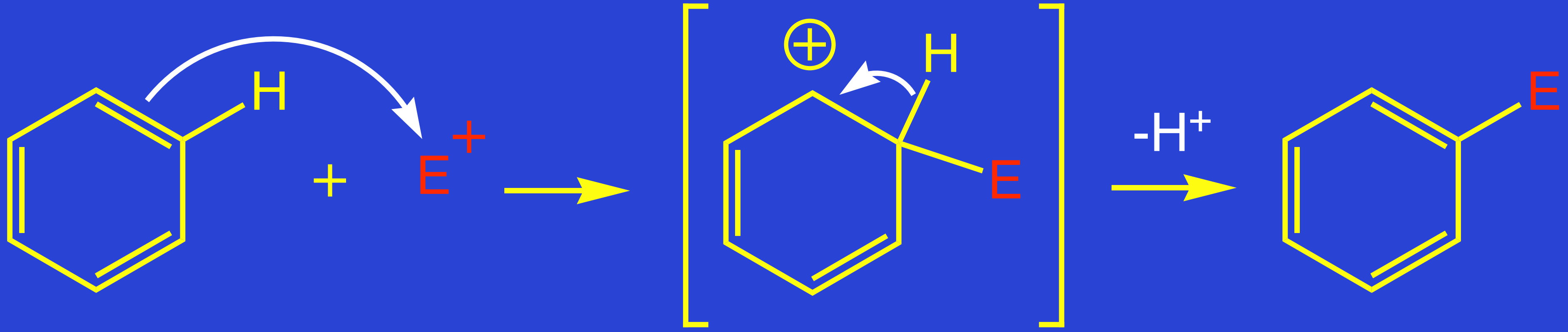
What is the Mechanism of This Reaction?



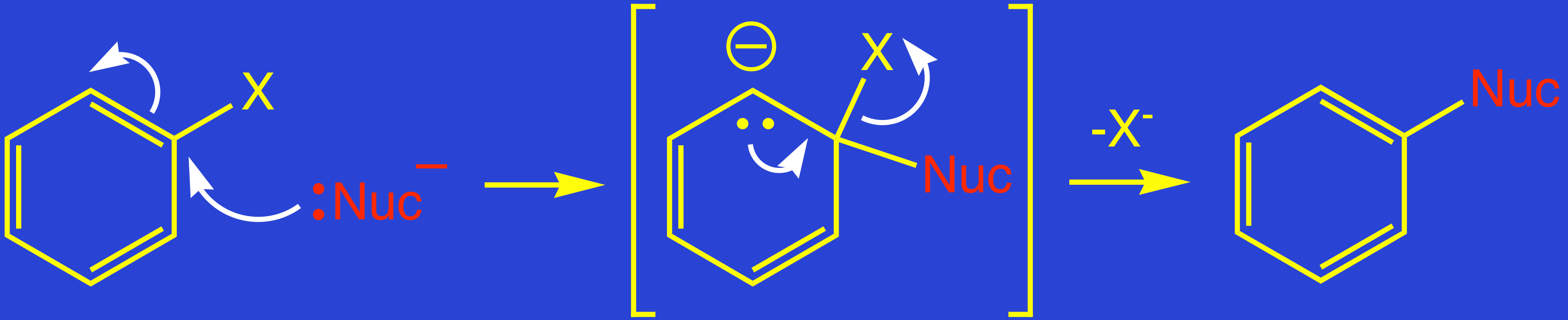
23.5

Nucleophilic Substitution in Nitro-Substituted Aryl Halides

Nucleophilic Aromatic Substitution (S_NAr)?



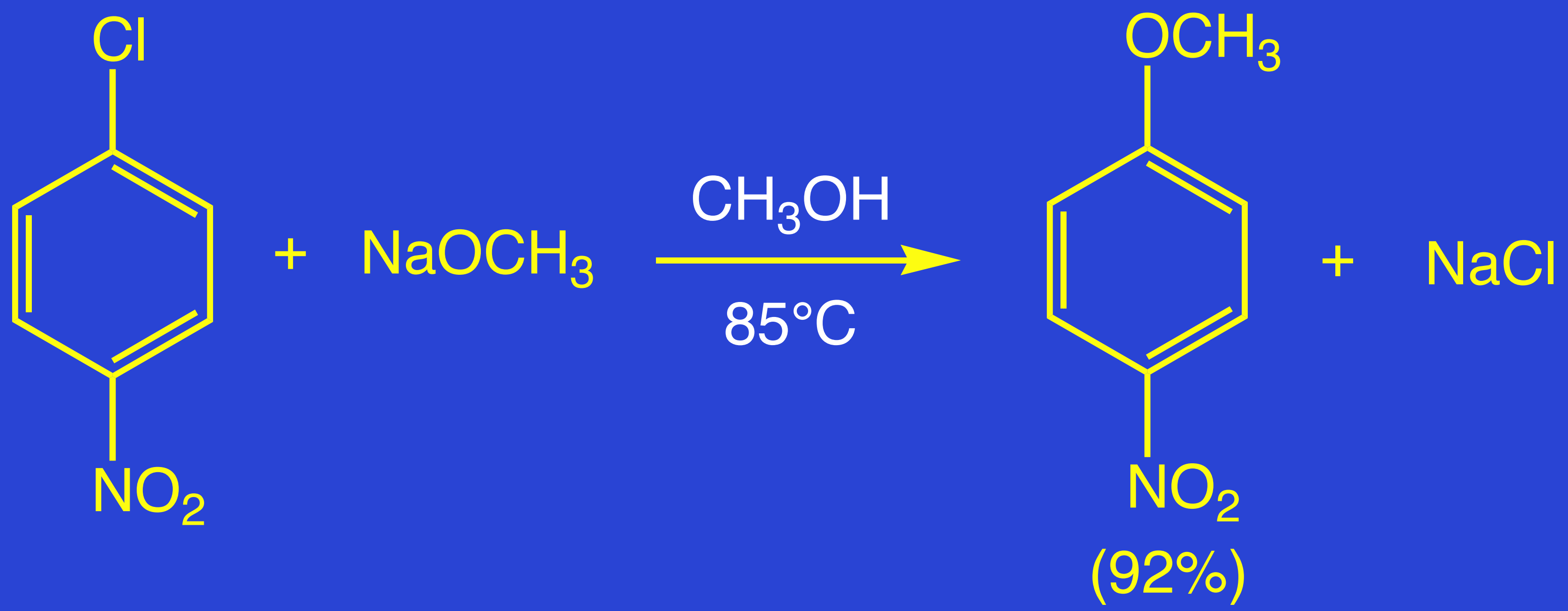
Electrophilic Aromatic Substitution



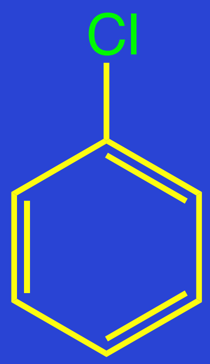
Nucleophilic Aromatic Substitution?

Electron-Deficient Haloarenes Undergo Nucleophilic Aromatic Substitution

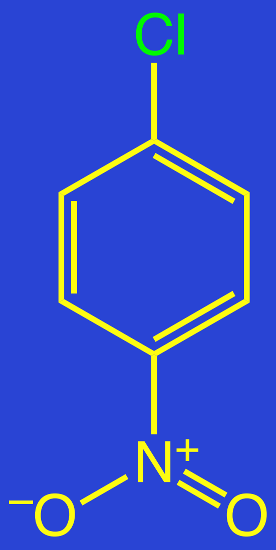
In contrast to chlorobenzene, nitro-substituted aryl halides undergo nucleophilic aromatic substitution at reasonable temperatures



The More Electron-Deficient the Haloarene, the Faster the Substitution



1.0

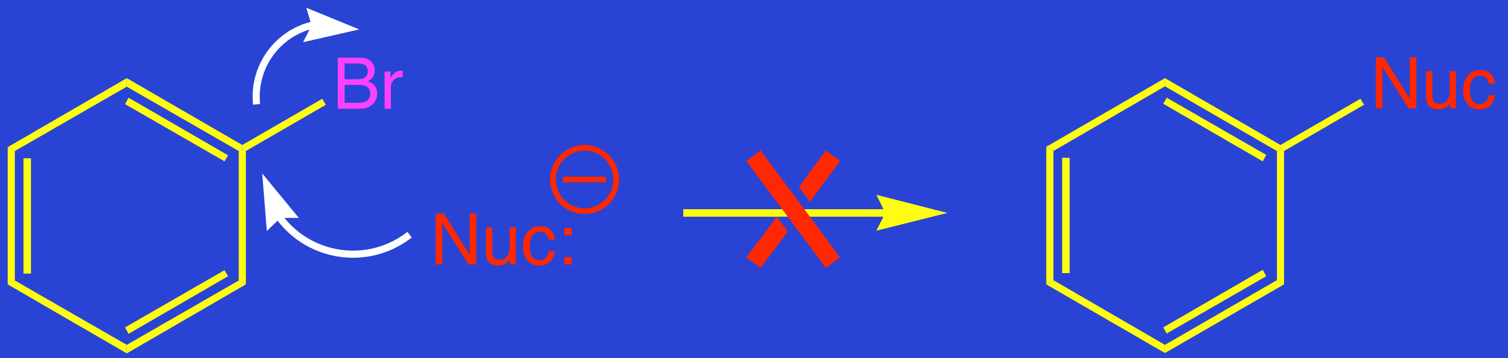


7 x 10^{10}

2.4 x 10^{15}

too fast to measure

Direct Displacement Doesn’t Occur!



Kinetics of Nucleophilic Aromatic Substitution

follows second-order rate law:

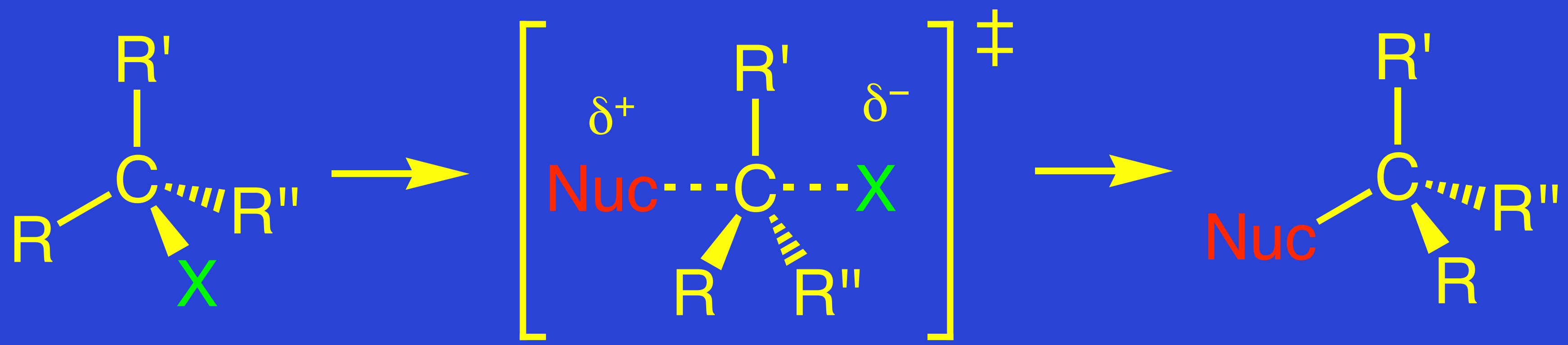
rate = *k* [aryl halide] [nucleophile]

inference:

both the aryl halide and the nucleophile are involved in rate-determining step

Effect of Leaving Group Upon Rate of SN2

During SN2 reactions, the C-X bond breaks during the rate-determining step

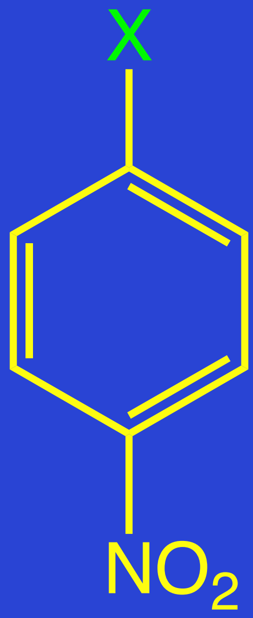


Reaction Rate Depends on X: I > Br > Cl > F

C-F (485 kJ/mol), C-Cl (327 kJ/mol)

C-Br (285 kJ/ml, C-I (213 kJ/mol)

Effect of Leaving Group in Nucleophilic Aromatic Substitution



X	Relative Rate*
F	312
Cl	1.0
Br	0.8
I	0.4

*$NaOCH_3$, CH_3OH, 50°C

C-F (485 kJ/mol), C-Cl (327 kJ/mol)

C-Br (285 kJ/ml, C-I (213 kJ/mol)

General Features of Mechanism

1. bimolecular rate-determining step in which nucleophile attacks aryl halide
2. rate-determining step precedes carbon-halogen bond cleavage
3. rate-determining transition state is stabilized by electron-withdrawing groups (such as NO_2)

23.6

The Addition-Elimination Mechanism of Nucleophilic Aromatic Substitution

Addition-Elimination Mechanism

Two step mechanism:

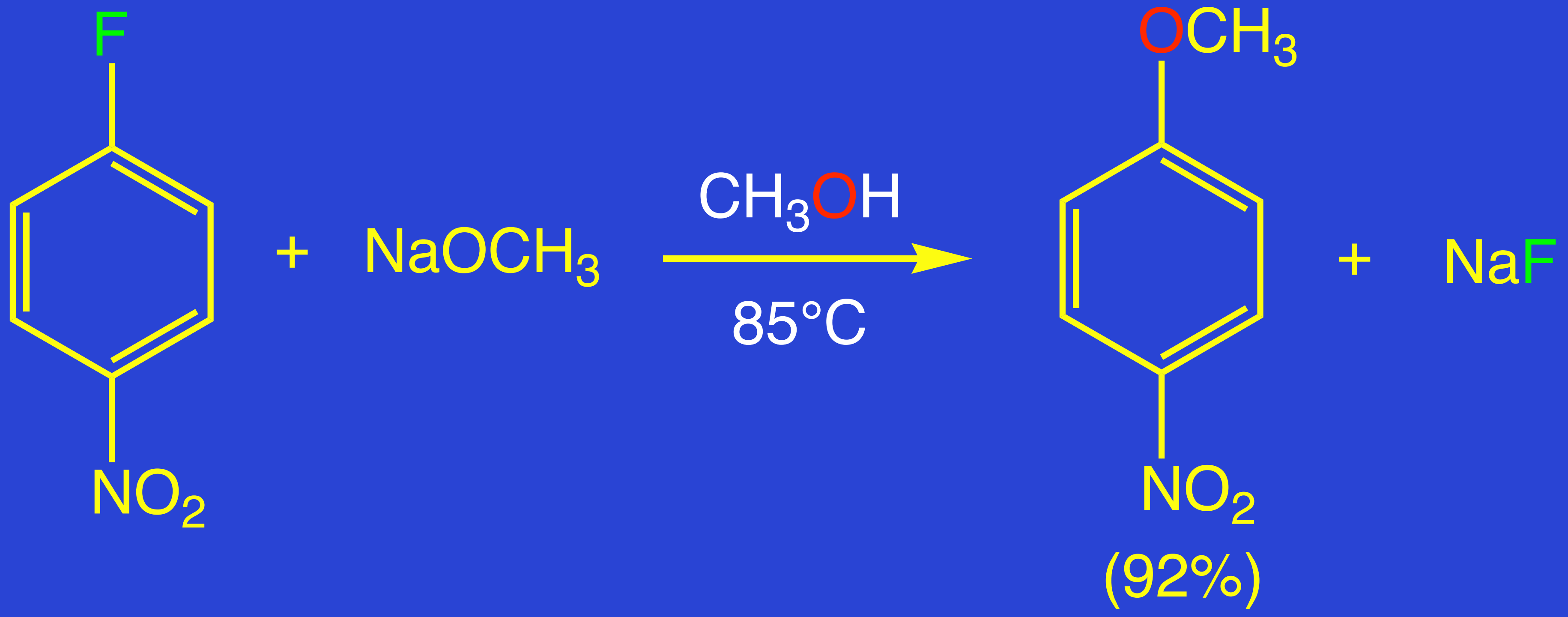
Step 1

nucleophile attacks aryl halide and bonds to the carbon that bears the halogen
(slow: aromaticity of ring lost in this step)

Step 2

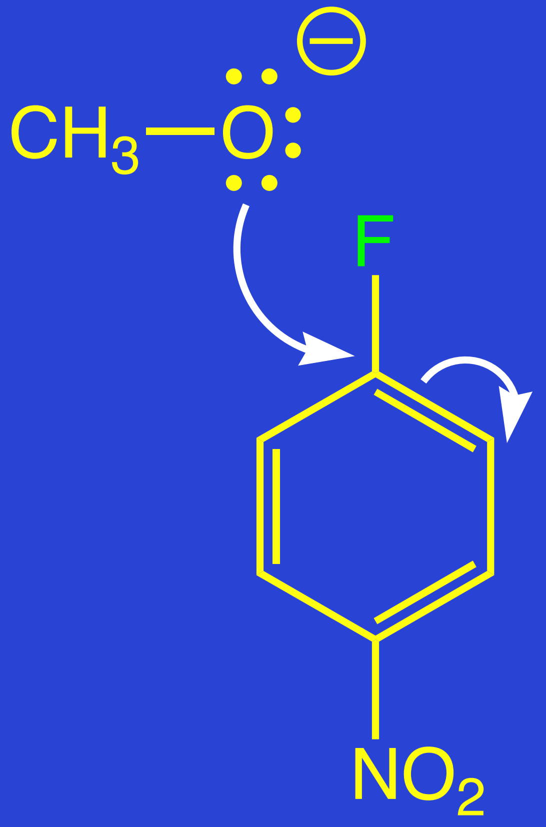
intermediate formed in first step loses halide
(fast: aromaticity of ring restored in this step)

Addition-Elimination Mechanism



Addition-Elimination Mechanism

Step 1 - Addition



bimolecular

consistent with second-order kinetics;

first order in aryl halide,
first order in nucleophile

Rate = k [CH_3ONa] [arene]

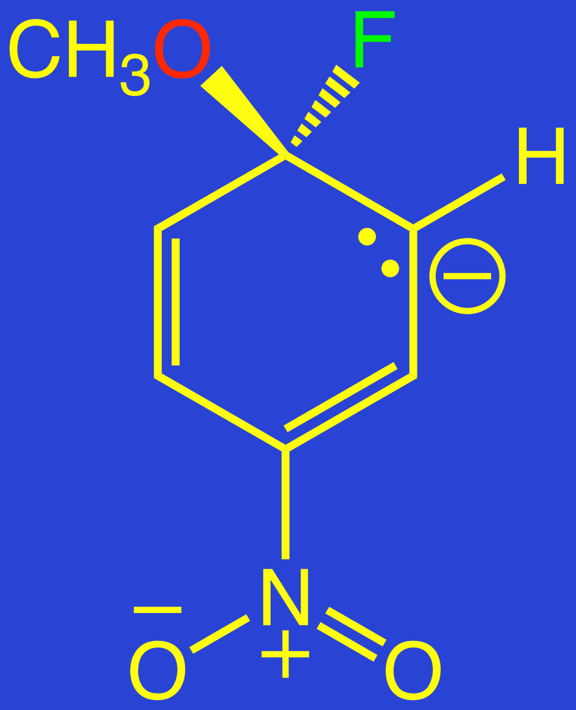
Addition-Elimination Mechanism

Step 1 - Addition

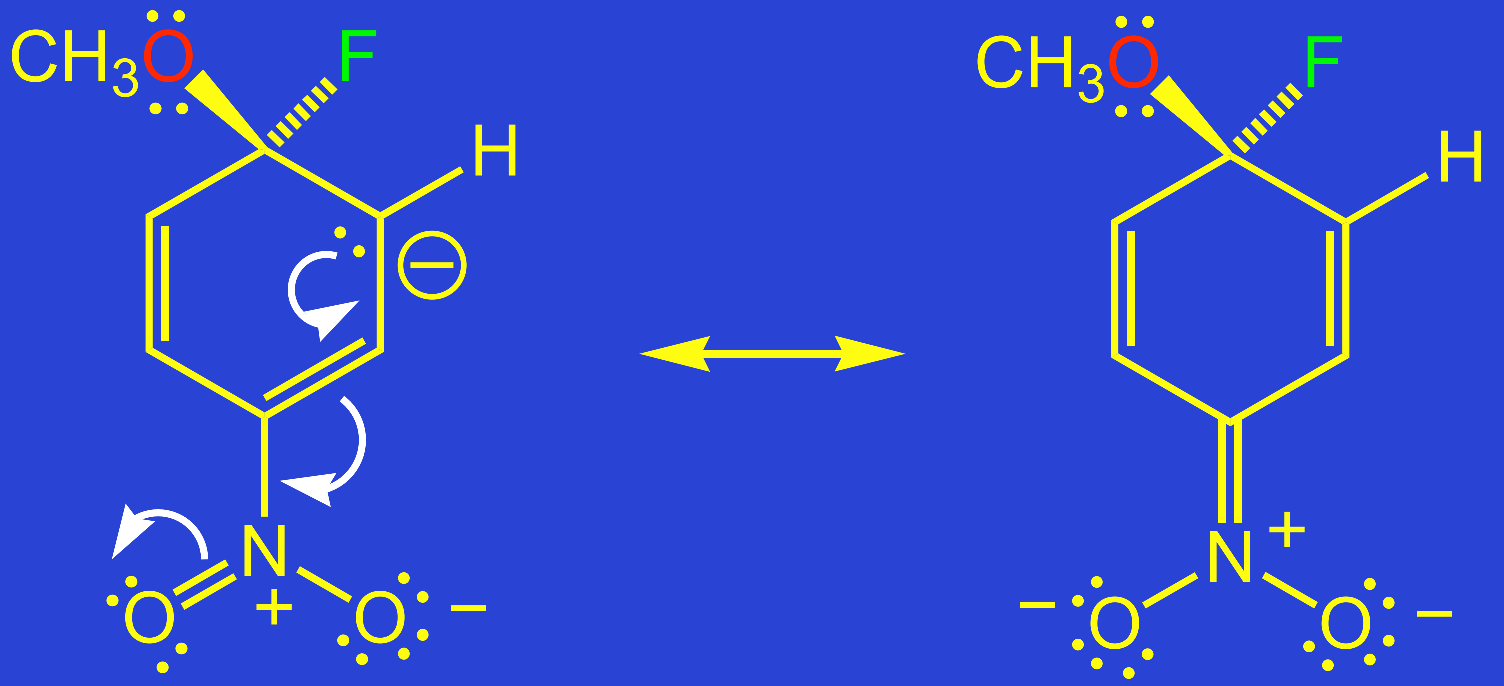
Reaction Involves an Anionic Intermediate

intermediate is negatively charged

formed faster when ring bears electron-withdrawing groups such as NO_2 because negative charge is stabilized……..

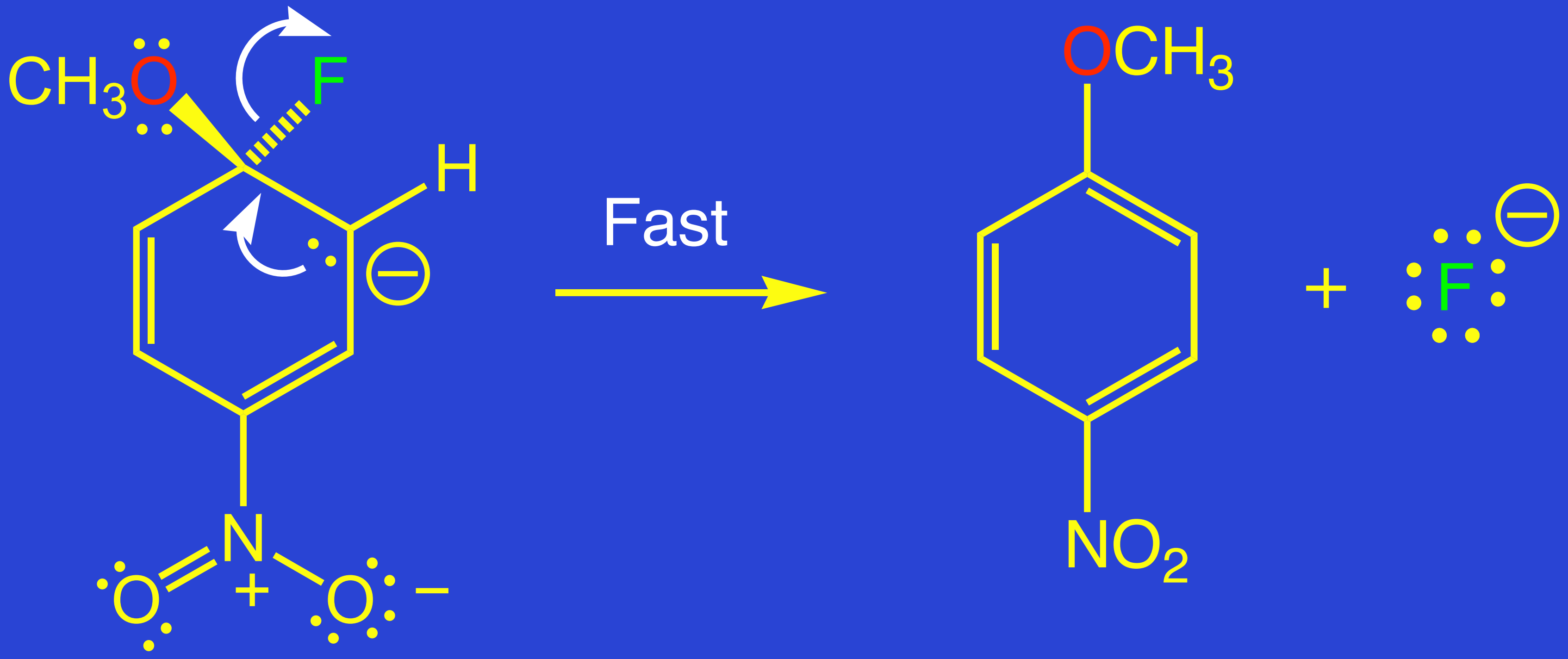


Stabilization of Addition Product by Electron-Withdrawing Group



Rapid Collapse of Cyclohexadienyl Anion Intermediate

Step 2 - Elimination



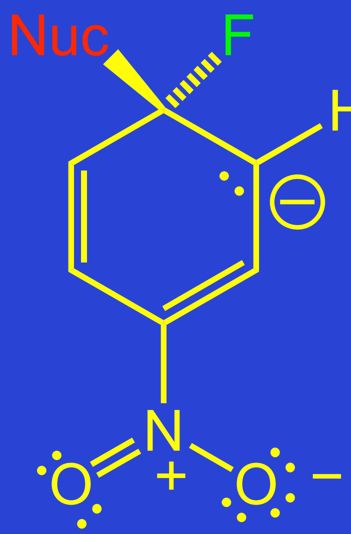
The Role of Leaving Groups

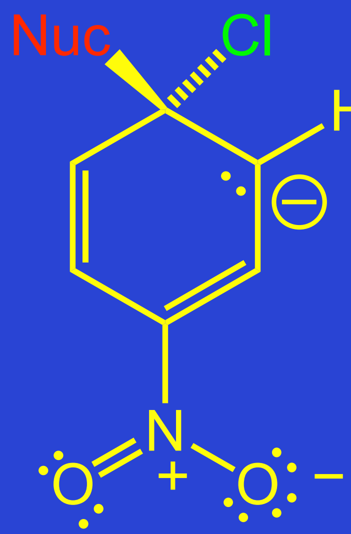
F > Cl > Br > I is unusual, but consistent with mechanism

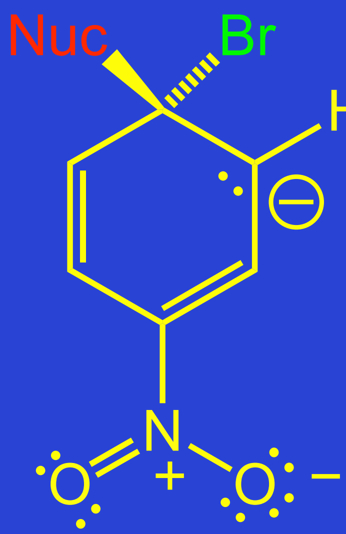
carbon-halogen bond breaking does not occur until after the rate-determining step

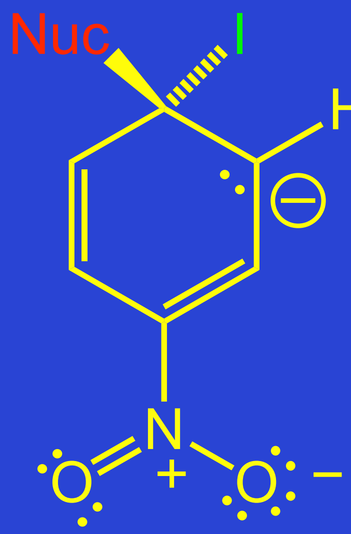
electronegative F stabilizes negatively charged intermediate

The Role of Leaving Groups







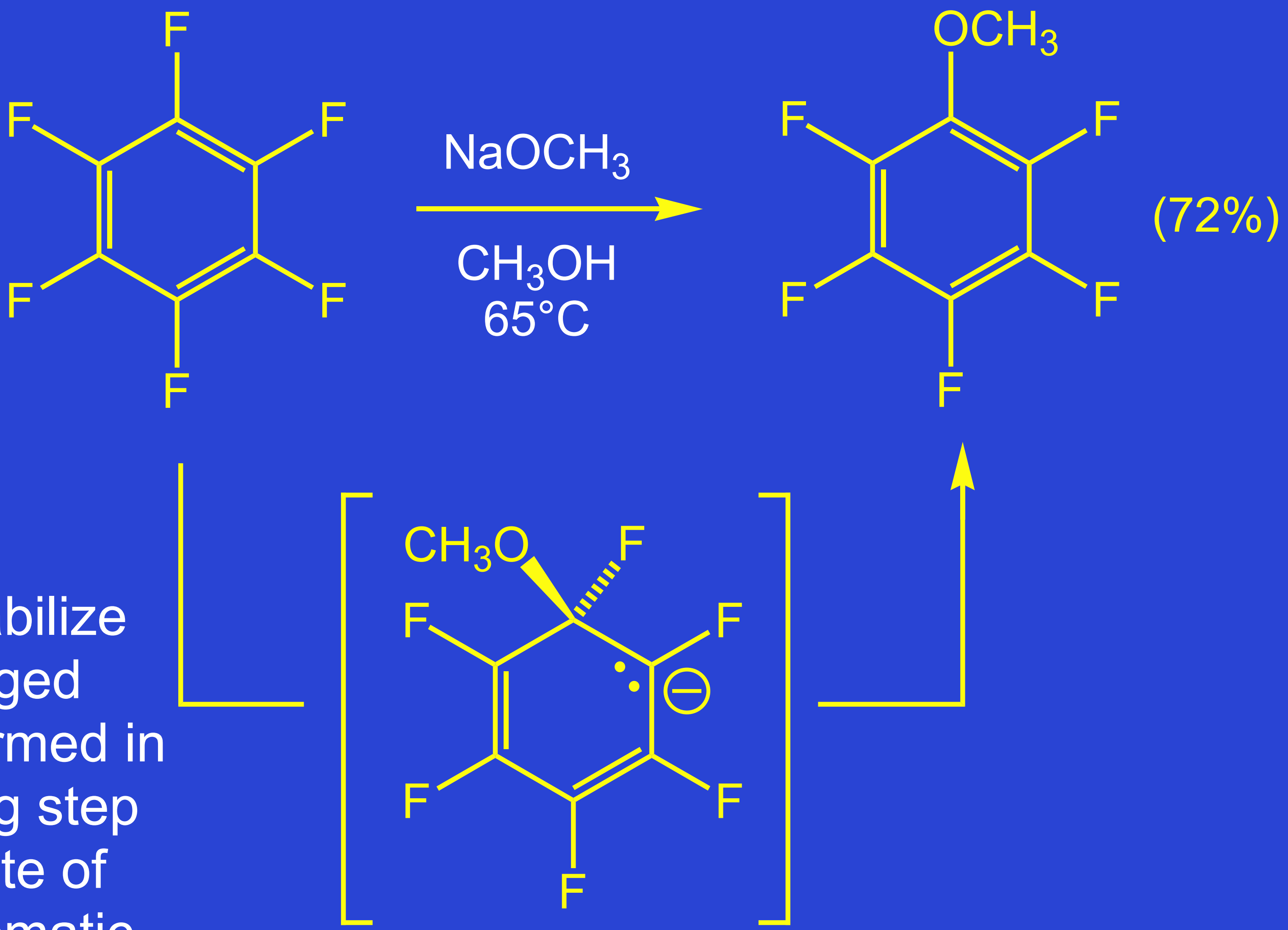


Most Stabilized → Least Stabilized

23.7

Related Nucleophilic Aromatic Substitution Reactions

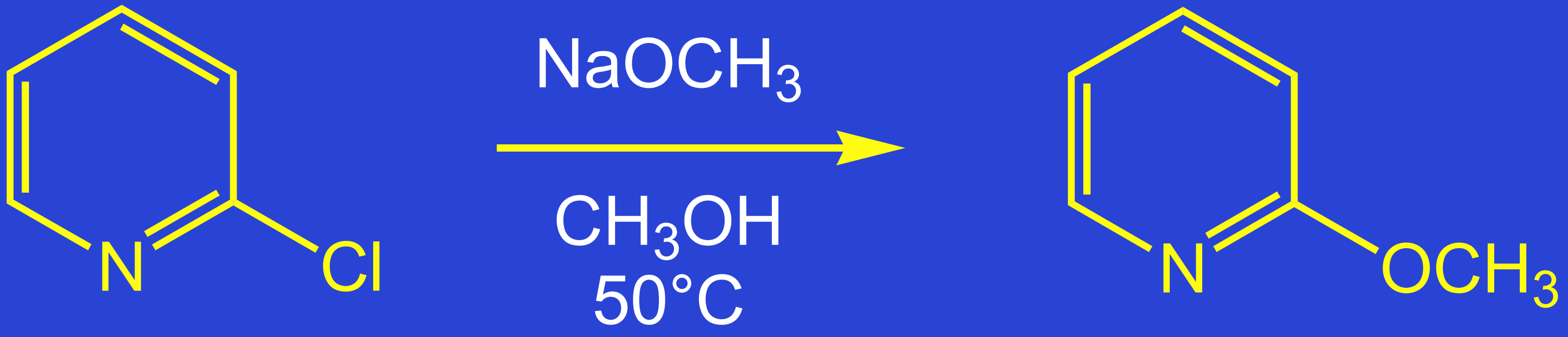
Substitution of Hexafluorobenzene



Anionic Intermediate

Six fluorine substituents stabilize negatively charged intermediate formed in rate-determining step and increase rate of nucleophilic aromatic substitution.

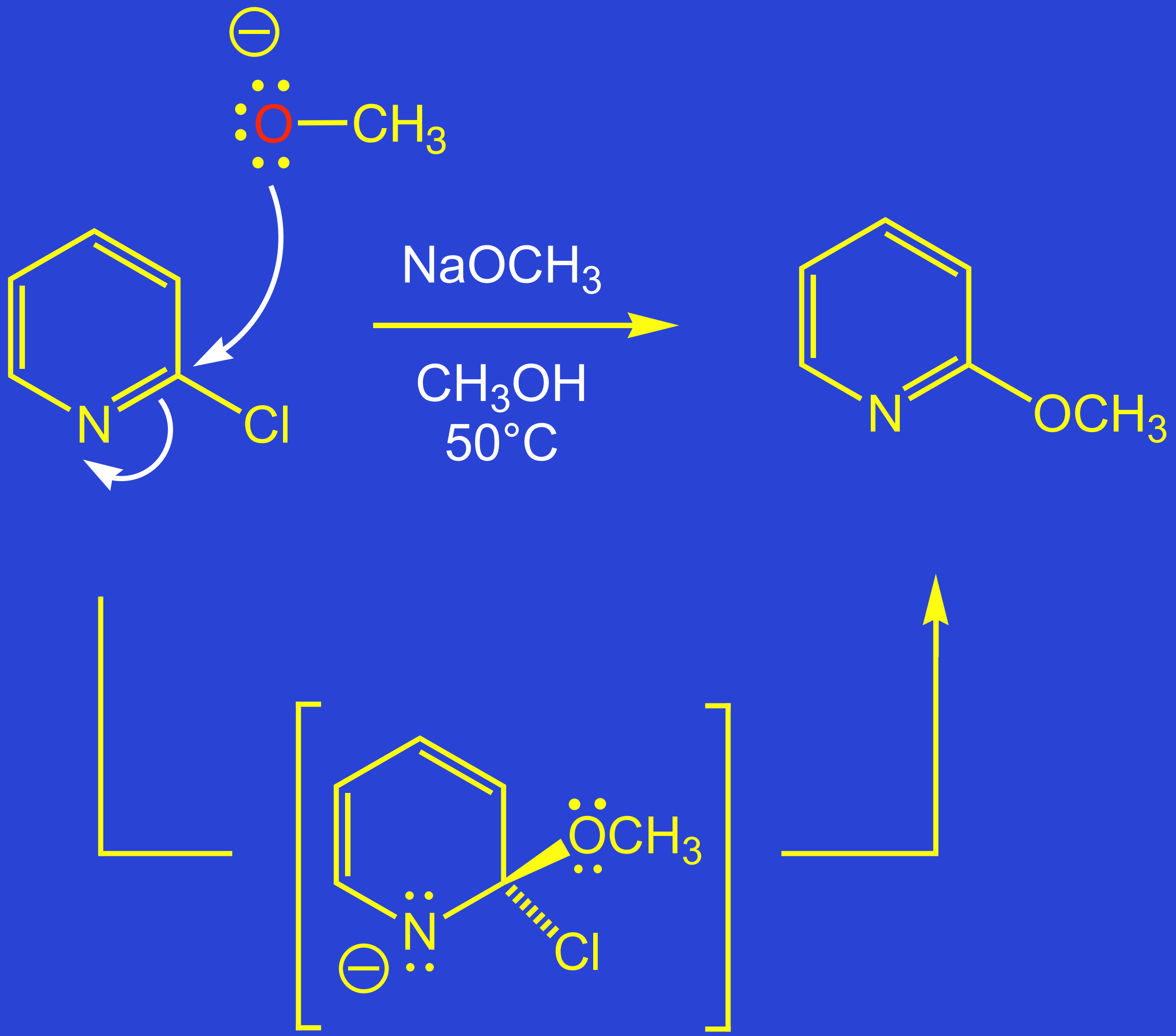
Substitution of 2-Chloropyridine



2-Chloropyridine reacts 230,000,000 times faster than chlorobenzene under these conditions.

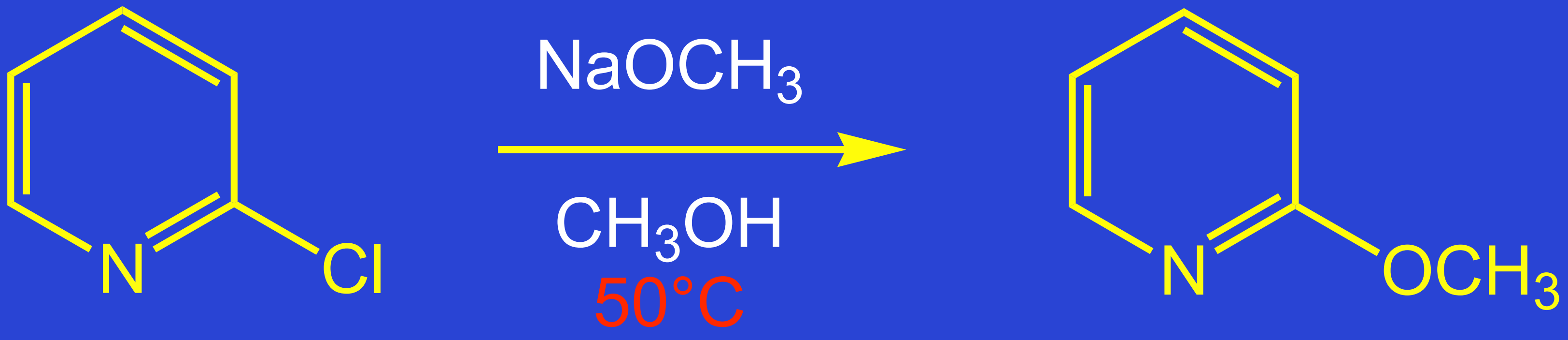
Substitution of 2-Chloropyridine

Nitrogen is more electronegative than carbon, stabilizes the anionic intermediate, and increases the rate at which it is formed.



Anionic Intermediate

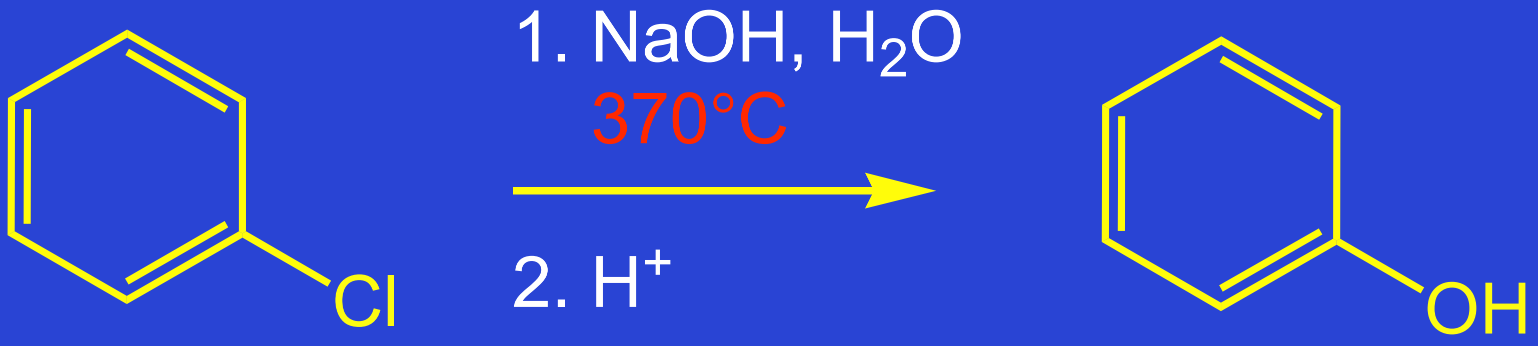
Compare 2-Chloropyridine with Chlorobenzene



$NaOCH_3$

CH_3OH

50°C



1. NaOH, H_2O

370°C

2. H^+

Synthetic Application of Nucleophilic Aromatic Substitution

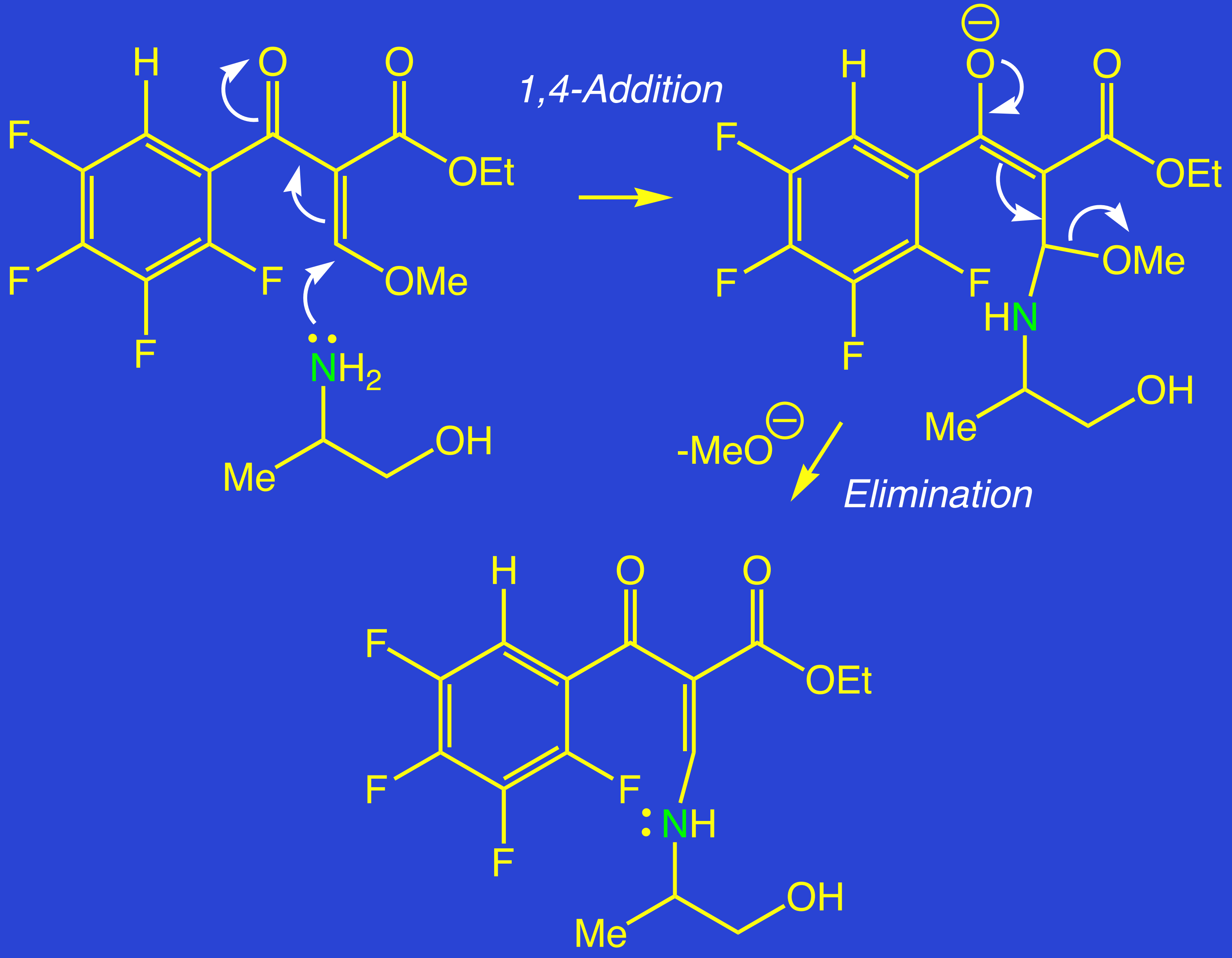
Ofloxacin

Ofloxacin (trade name Floxin) is a broad-spectrum quinolone antibiotic

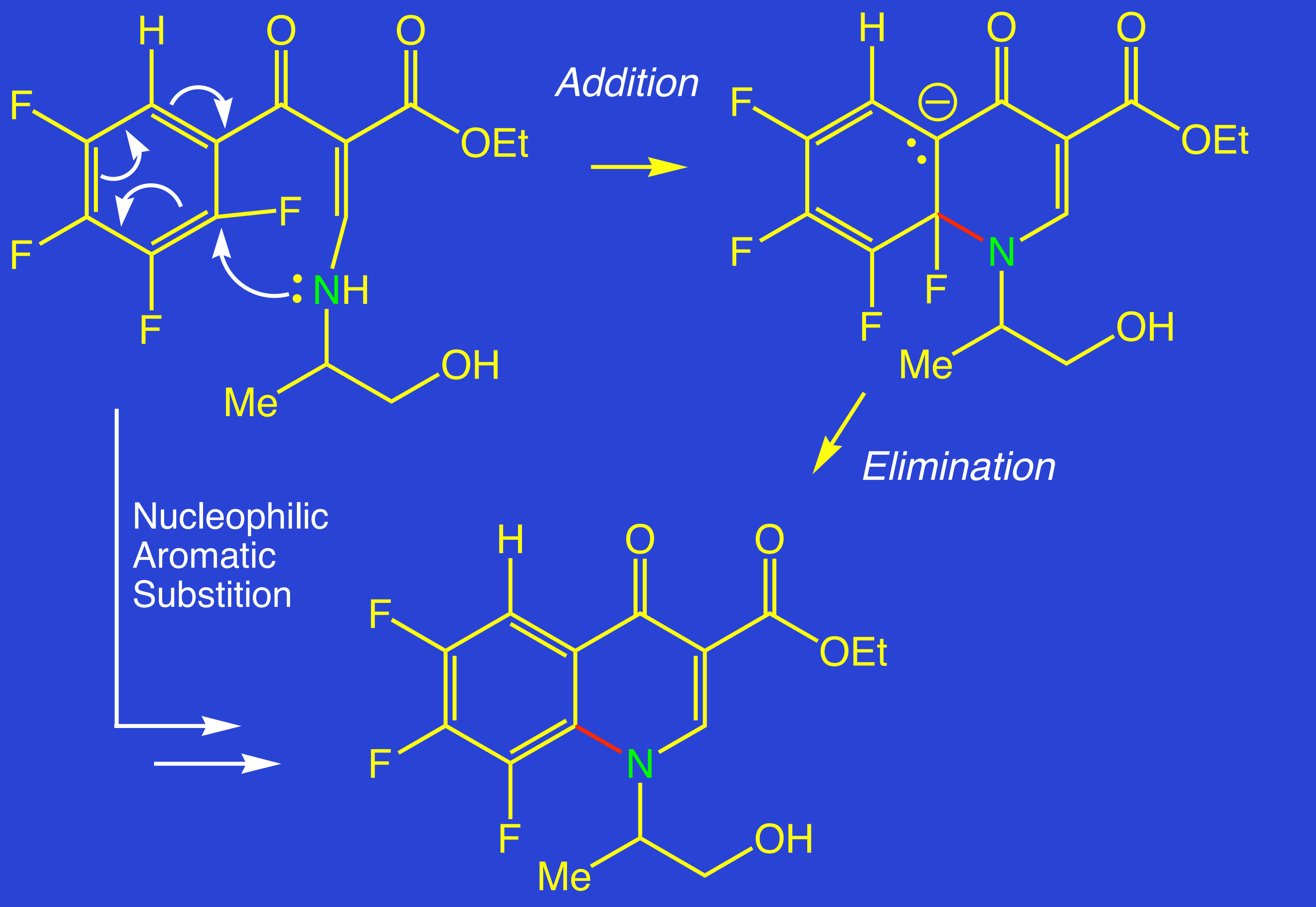
Ofloxacin

http://www.ofloxacin.com/

Synthesis of Ofloxacin, Part 1



Synthesis of Ofloxacin, Part 2

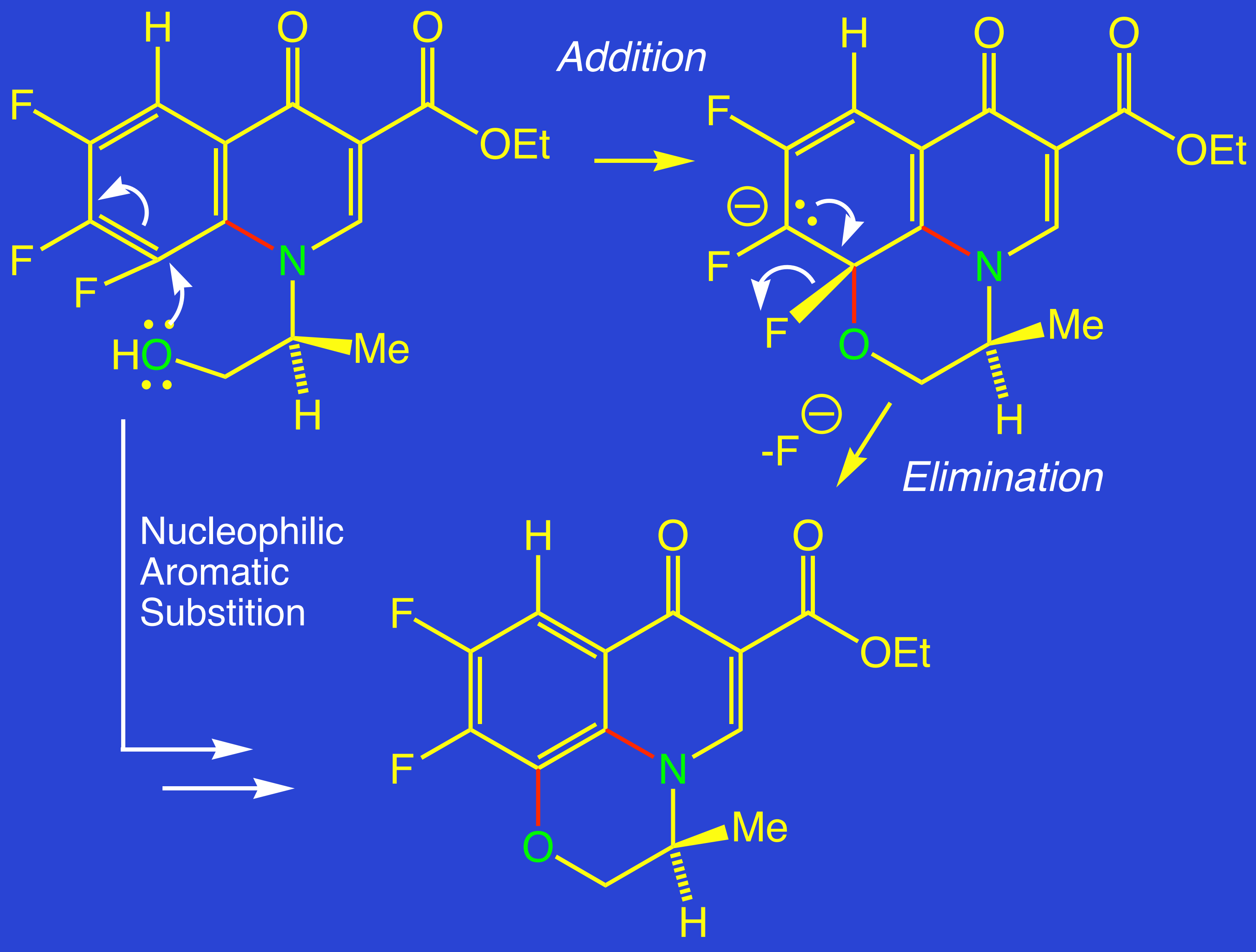


Addition

Elimination

Nucleophilic
Aromatic
Substition

Synthesis of Ofloxacin, Part 3



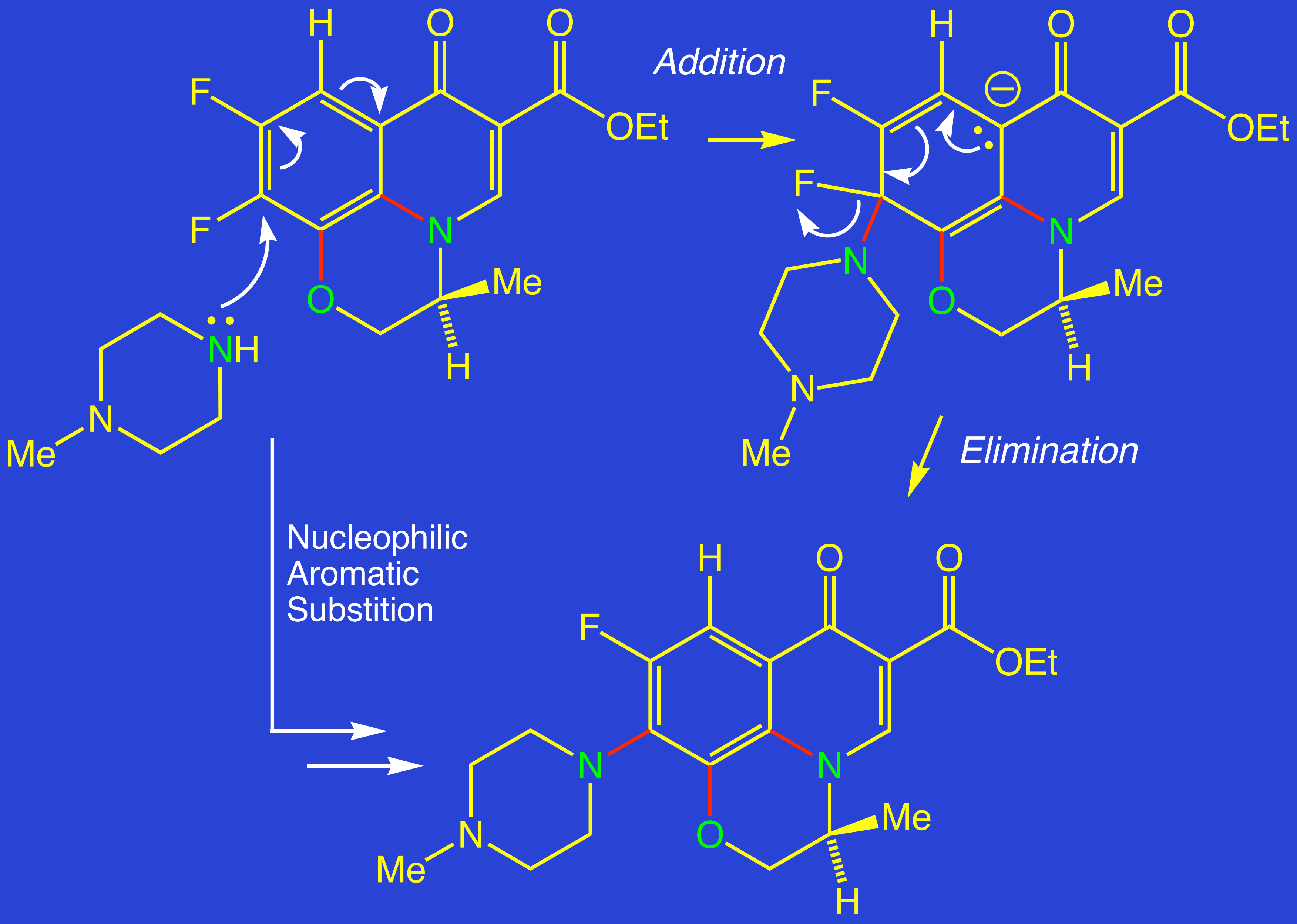
Addition

$-F^{\ominus}$

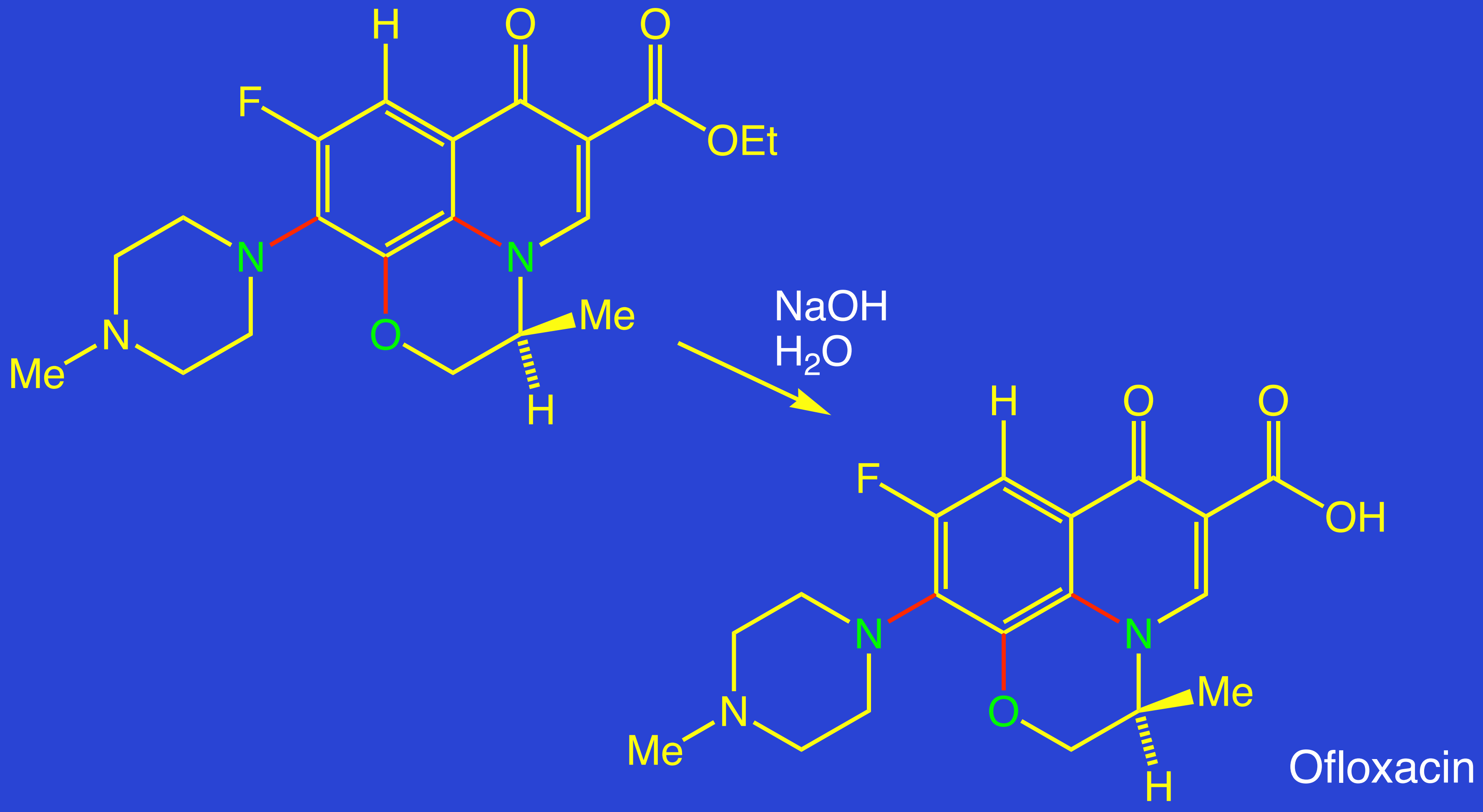
Elimination

Nucleophilic
Aromatic
Substition

Synthesis of Ofloxacin, Part 4



Synthesis of Ofloxacin, Part 5



Ofloxacin

Synthetic Application of Nucleophilic Aromatic Substitution

Page 238 Furosemide

Ofloxacin (trade name Floxin) is a broad-spectrum quinolone antibiotic

Prozac another good idea

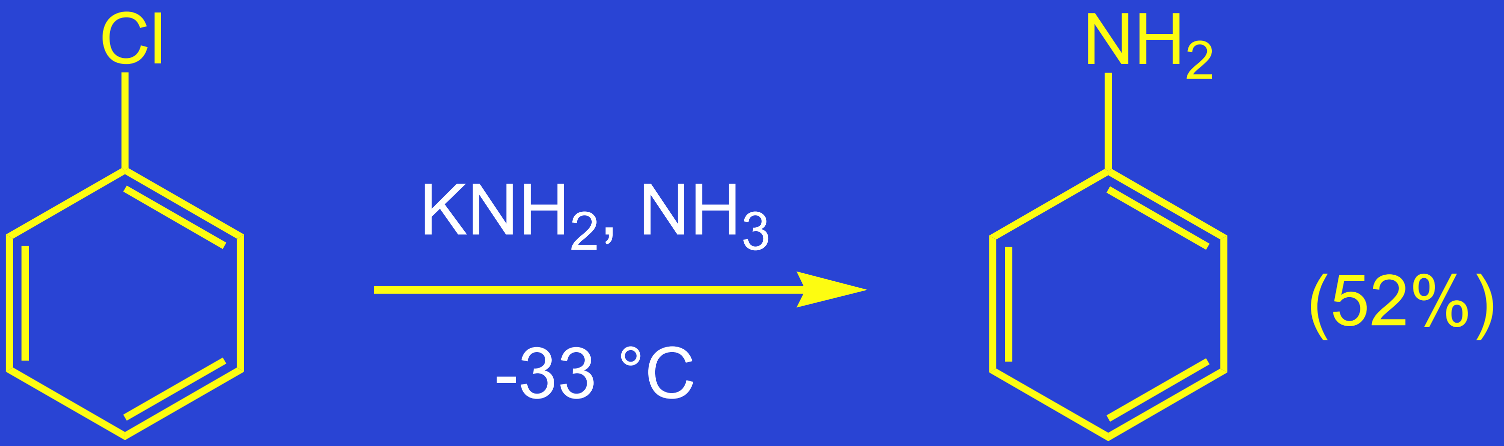
Ofloxacin

http://www.ofloxacin.com/

23.8

Benzyne & the Elimination-Addition Mechanism of Nucleophilic Aromatic Substitution

Aryl Halides Undergo Substitution When Treated With Very Strong Bases



Ammonia: pKa = 34; b.p. = -33 °C

Potassium Amide: strong base

Regiochemistry

new substituent becomes attached to either the carbon that bore the leaving group or the carbon adjacent to it

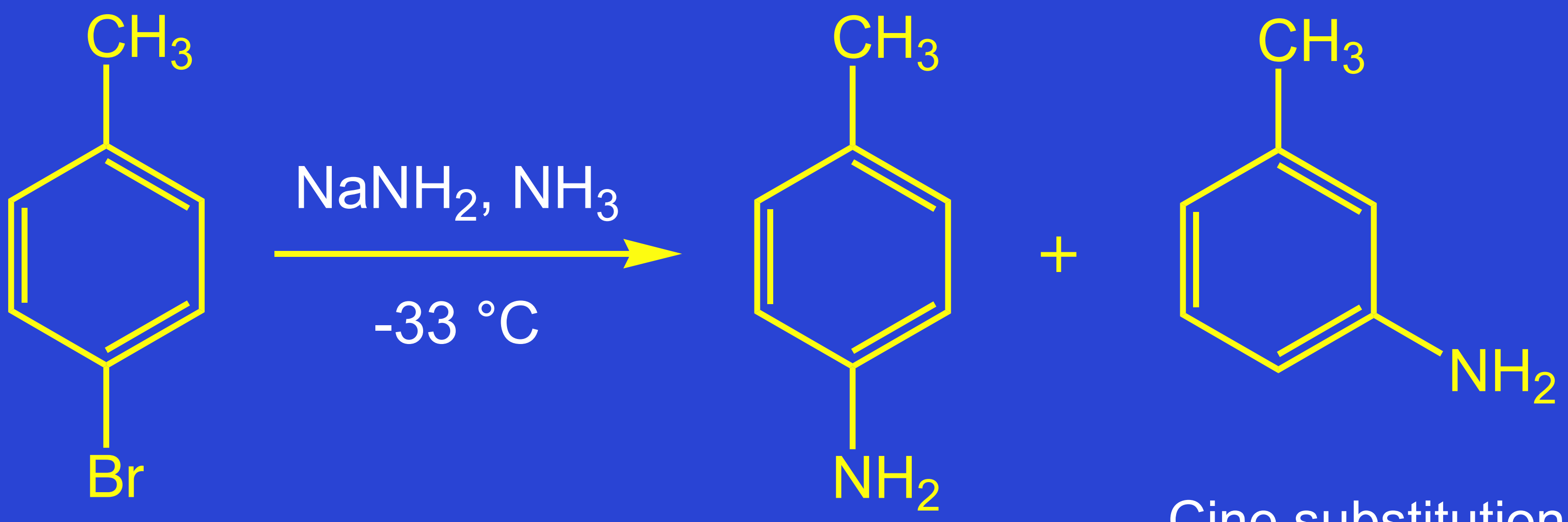
Cine substitution product

Cine Substitution Defined

cine-substitution
A substitution reaction (generally aromatic) in which the entering group takes up a position adjacent to that occupied by the leaving group.

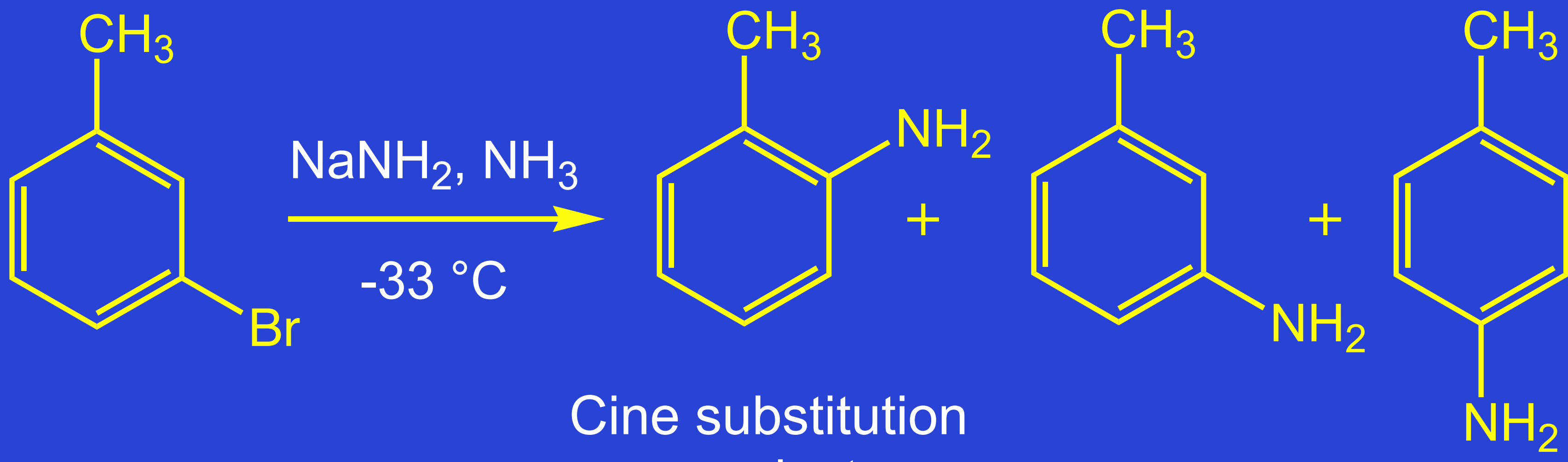
Regiochemistry

new substituent becomes attached to either the carbon that bore the leaving group or the carbon adjacent to it



Cine substitution product

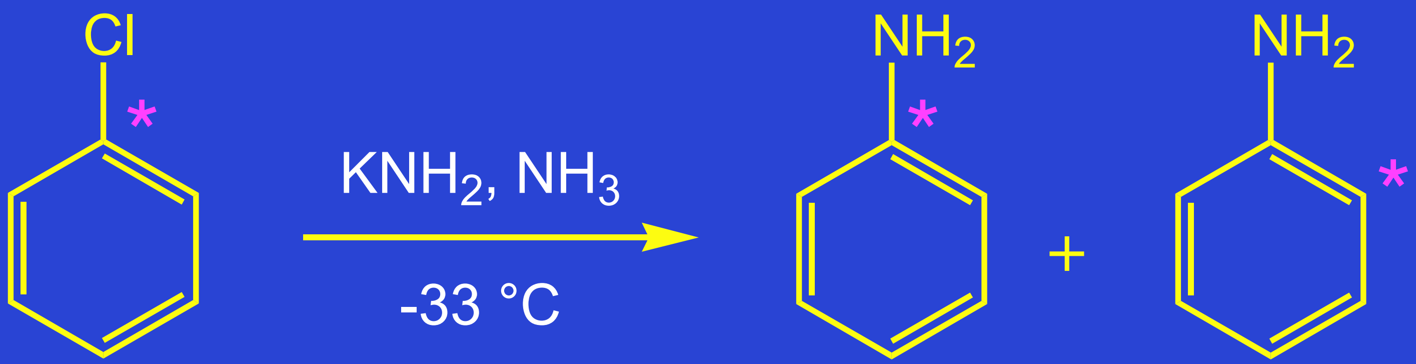
Regiochemistry



Cine substitution product

Cine substitution product

Further Proof of Cine Substitution via ^{14}C Label



KNH_2, NH_3

-33 °C

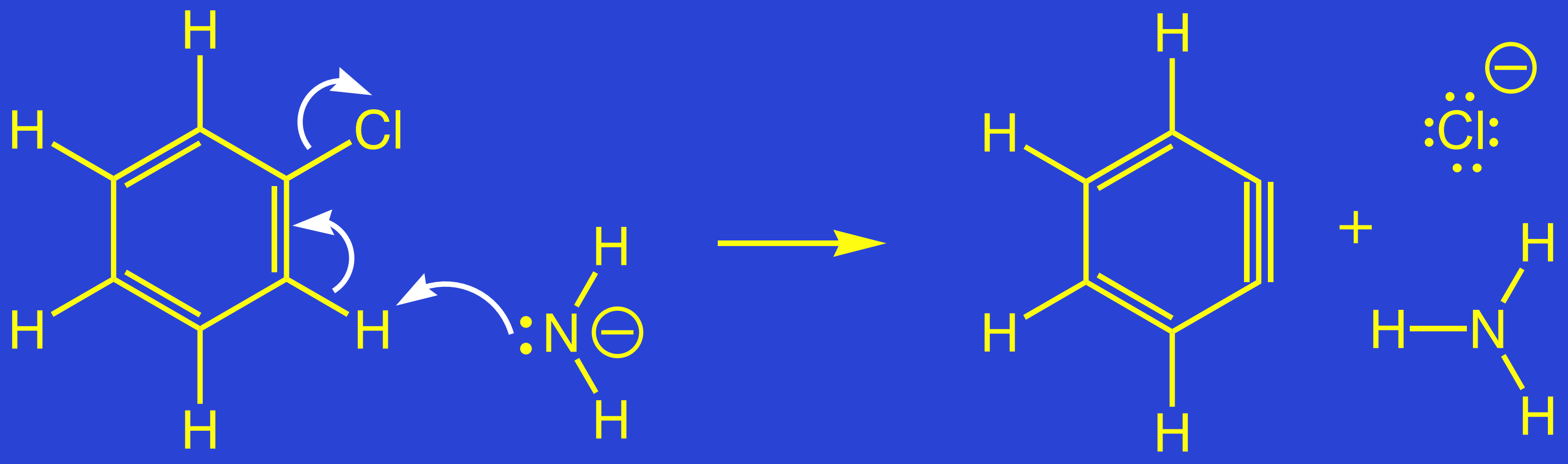
(48%)

(52%)

Cine substitution product

Rationalization of Cine Substitution

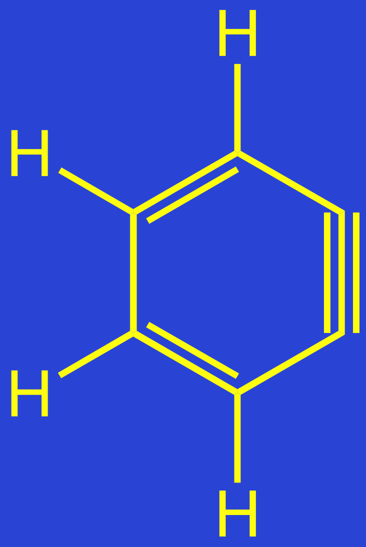
Step 1 - Elimination



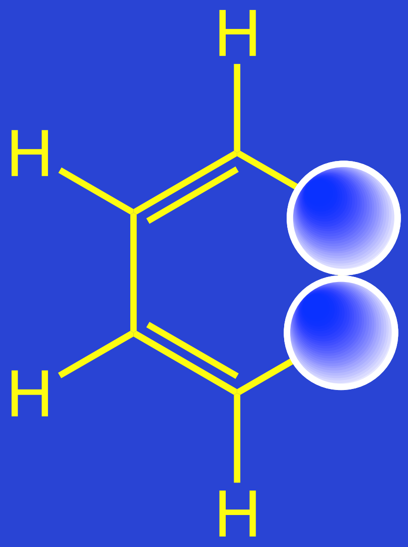
Benzyne

compound formed in this step is called *benzyne*

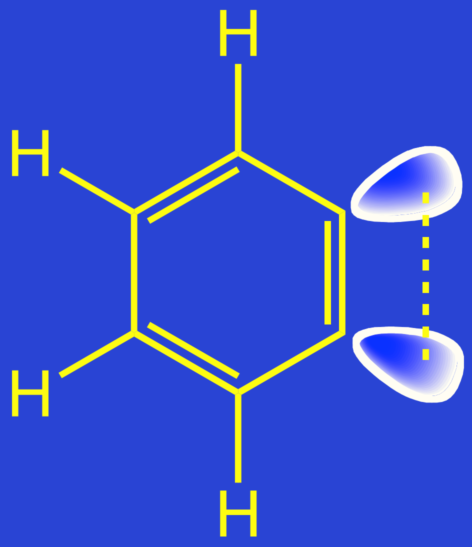
Benzyne - A Reactive Molecule With an Abnormal π-Bond



Benzyne



$2p_Z$-$2p_Z$
π Bond

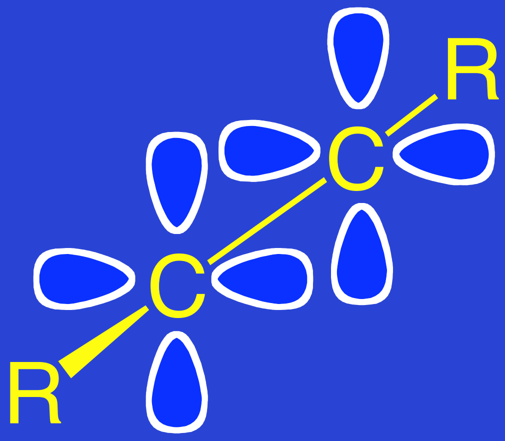


sp^2-sp^2
π Bond

Benzyne has a reactive triple bond.

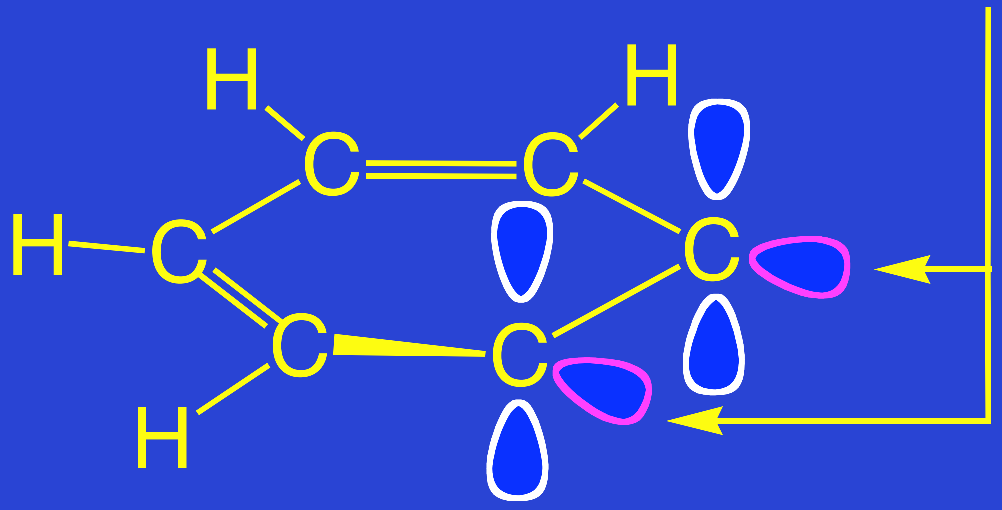
It cannot be isolated in this reaction, but is formed as a reactive intermediate.

Benzyne - A Reactive Aromatic Molecule With An Abnormal, In-Plane π-Bond



'Normal' C-C Triple Bond

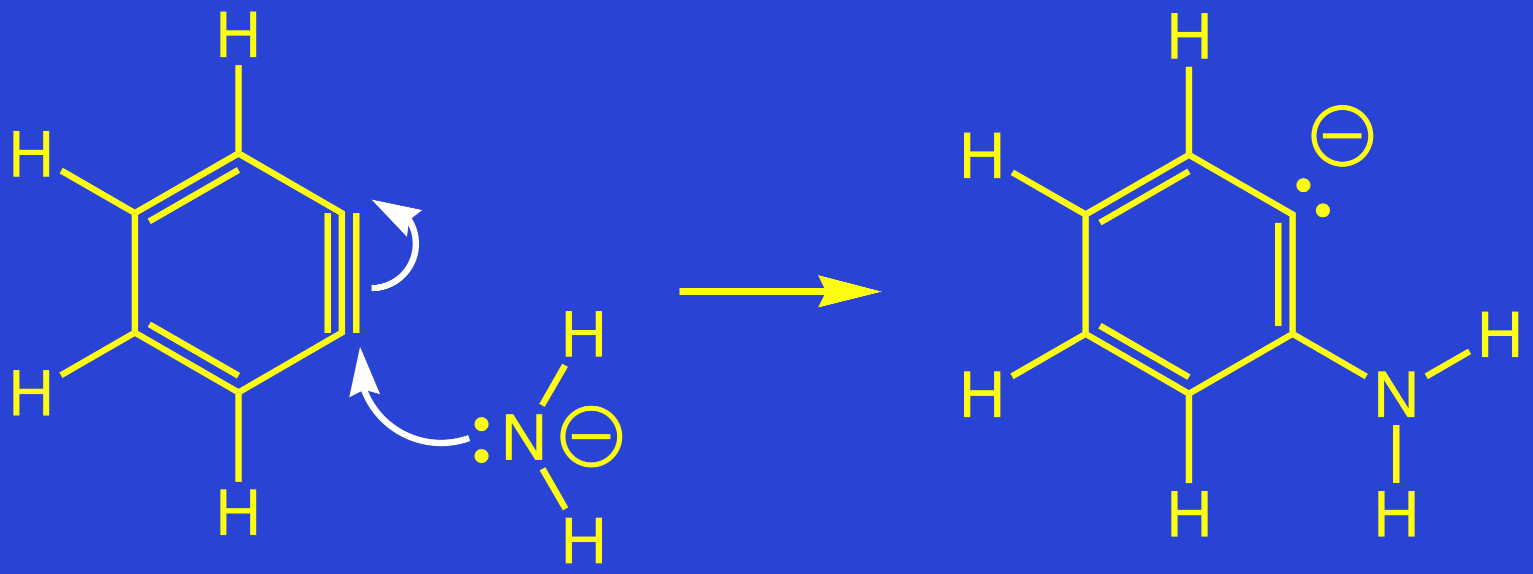
overlapping sp^2 orbitals
poor overap results
in a weak, reactive bond



Benzyne C-C Triple Bond

Arynes are Highly Reactive Electrophiles

Step 2 - Addition

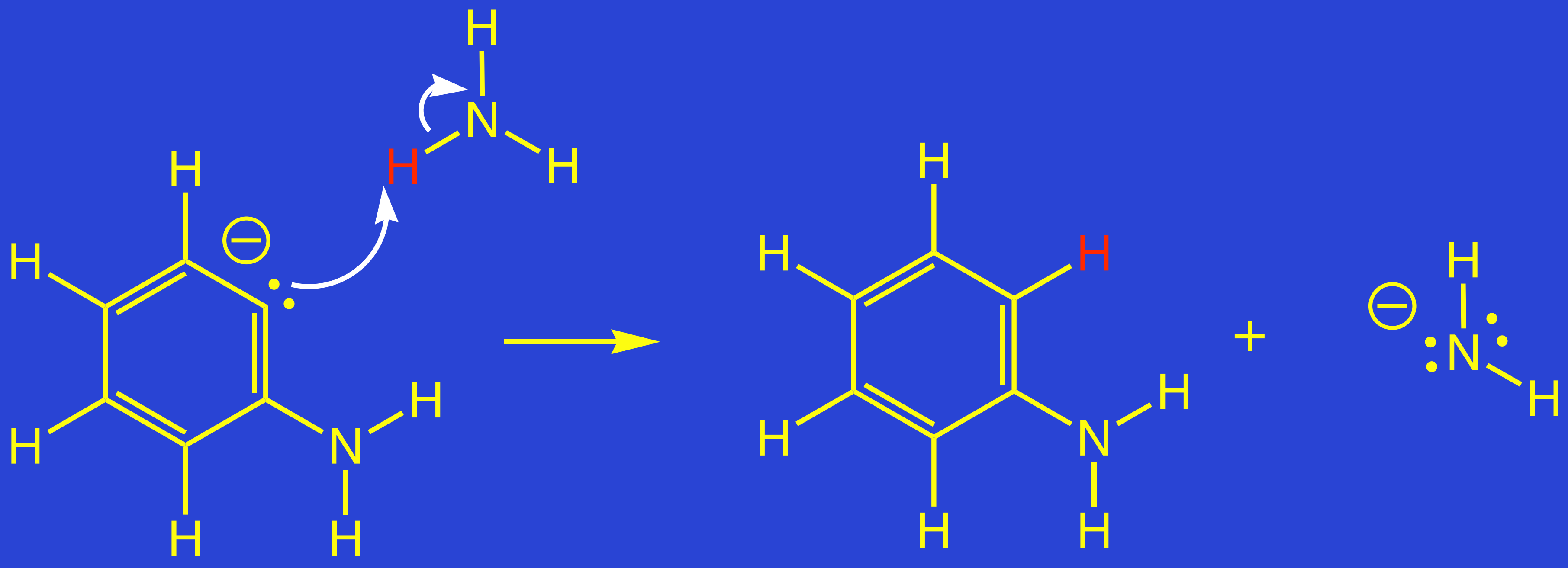


Benzyne

Aryl Anion

Aryl Anions are Strongly Basic

Step 3 - Protonation

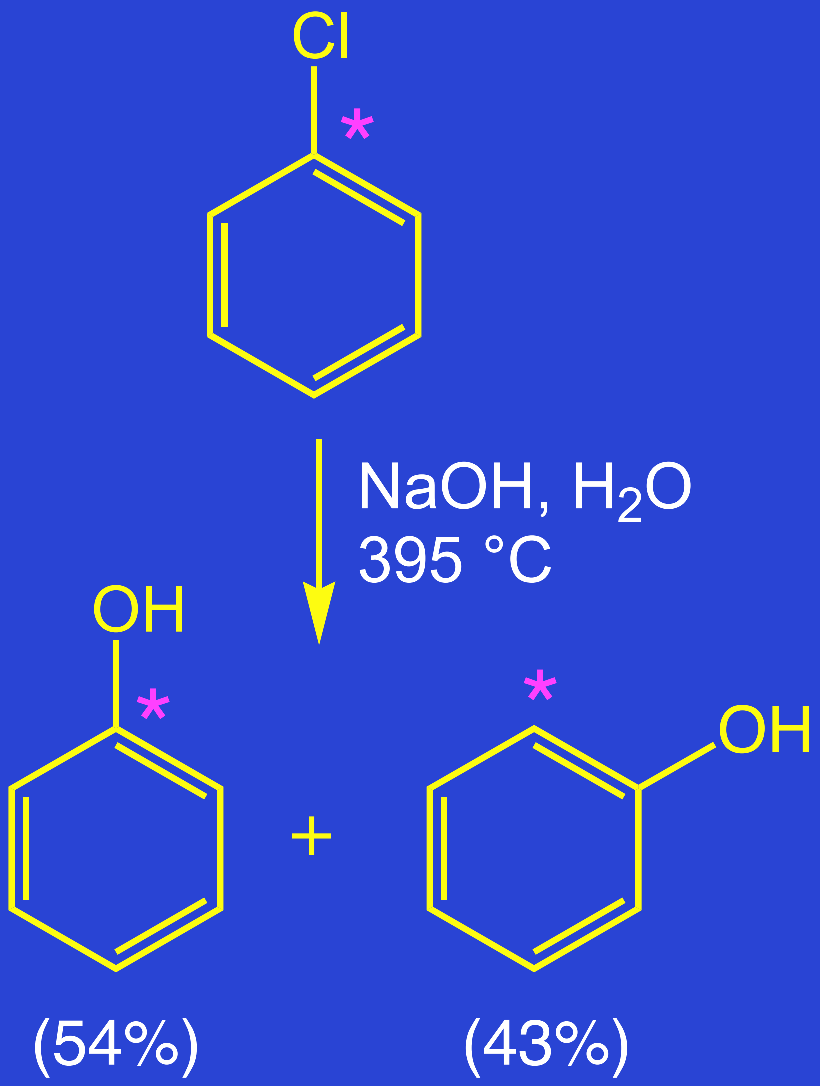


Benzyne

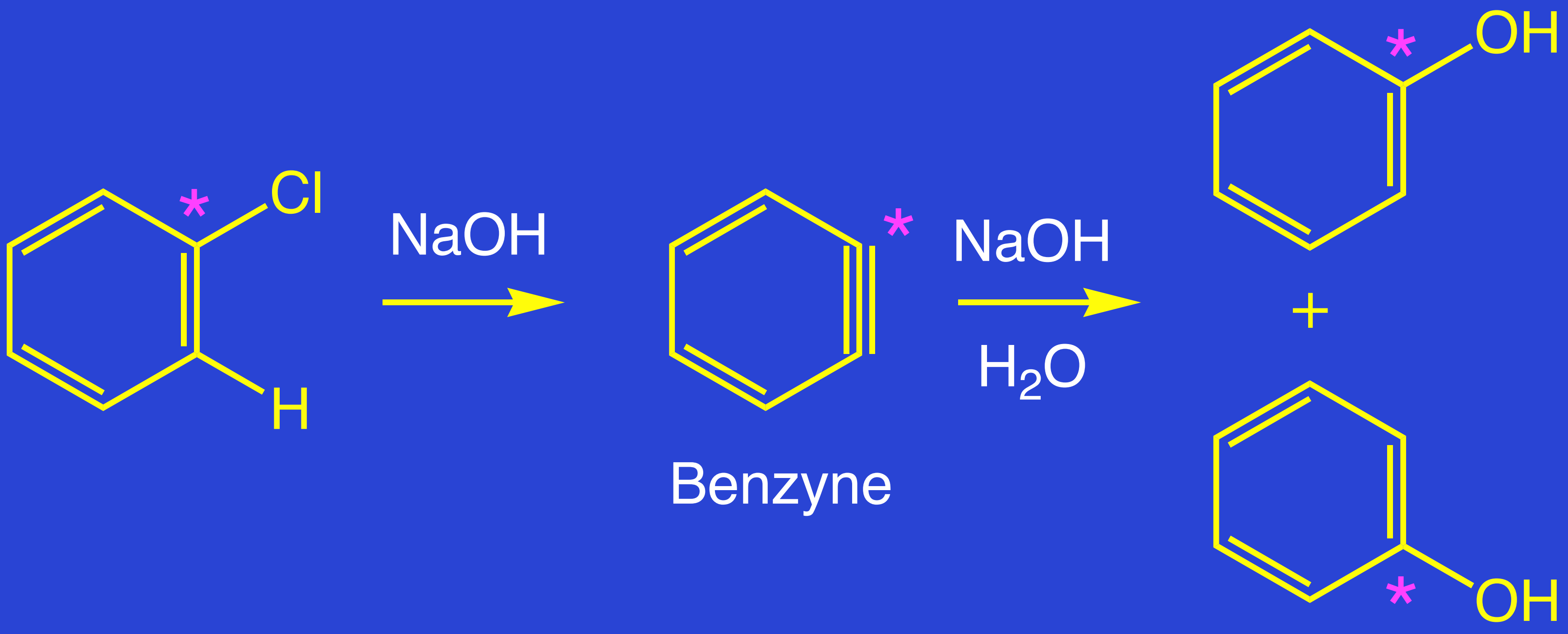
Substitution
Product

Hydrolysis of Chlorobenzene

^{14}C labeling indicates that the high-temperature reaction of chlorobenzene with NaOH proceeds via benzyne.



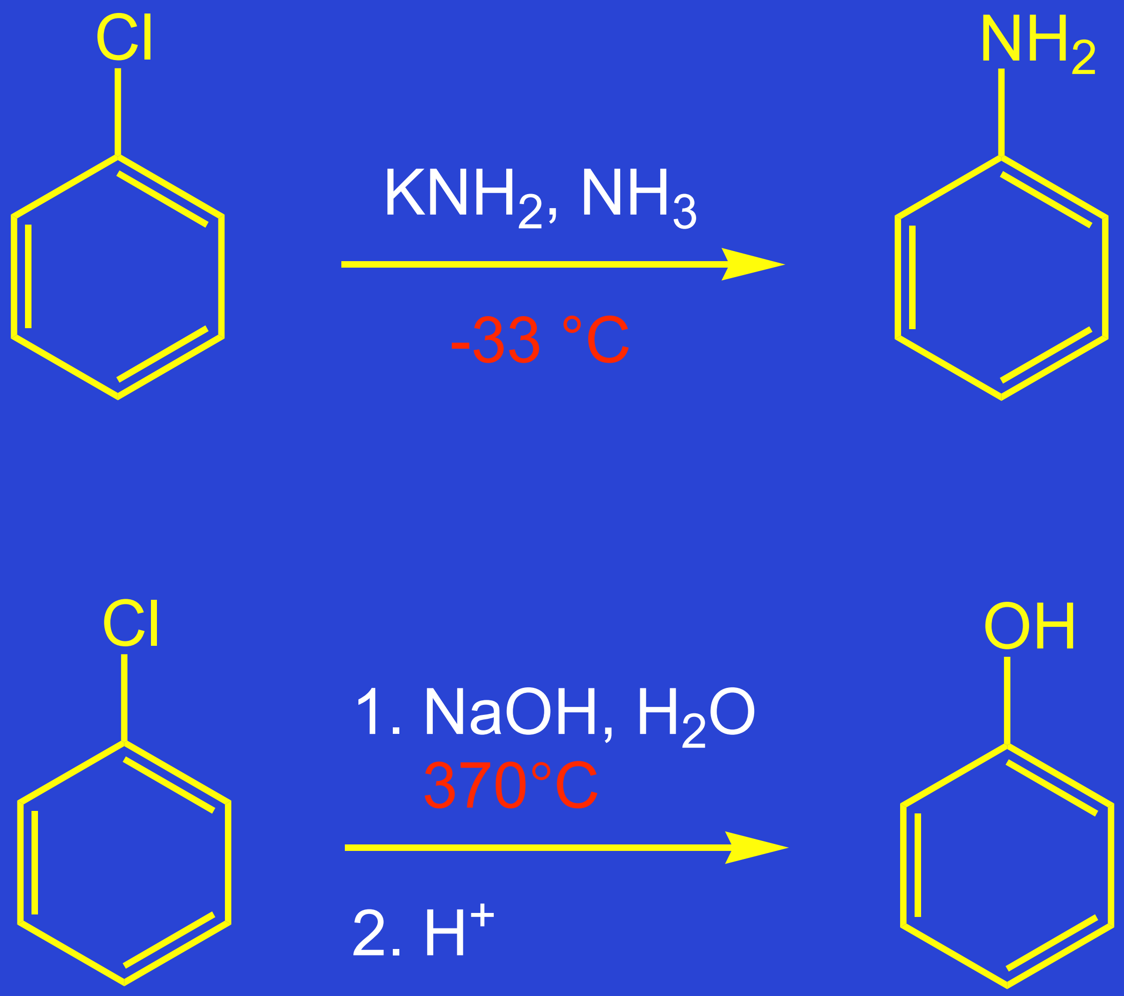
Substitution of Chlorobenzene Proceeds via Benzyne



Benzyne

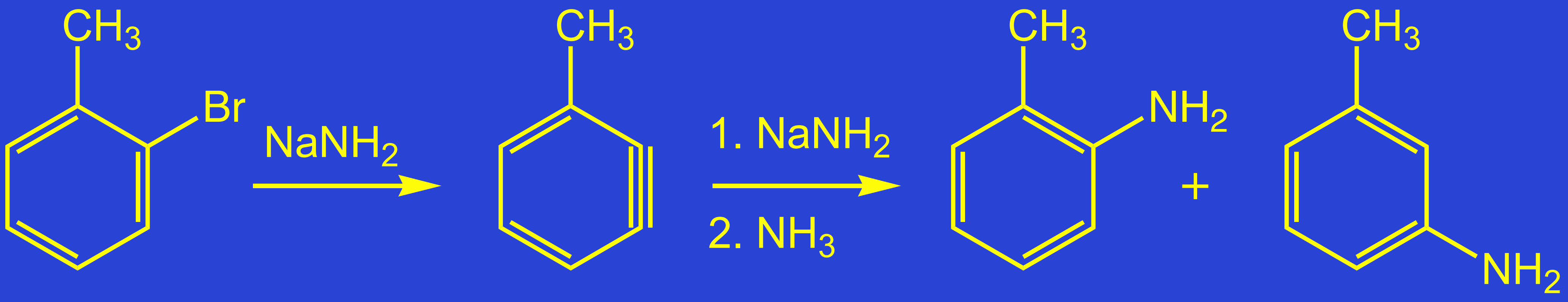
Cine substitution product

Why the Temperature Difference?

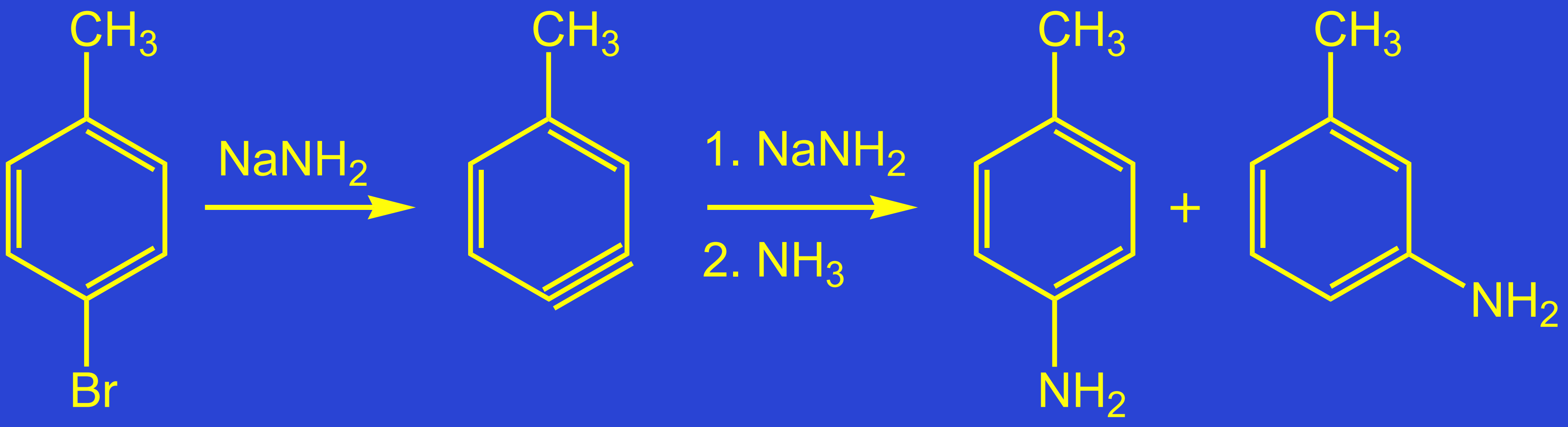


Sodium amide is a considerably stronger base than hydroxide and consequently better able to carry out the rate-determining step

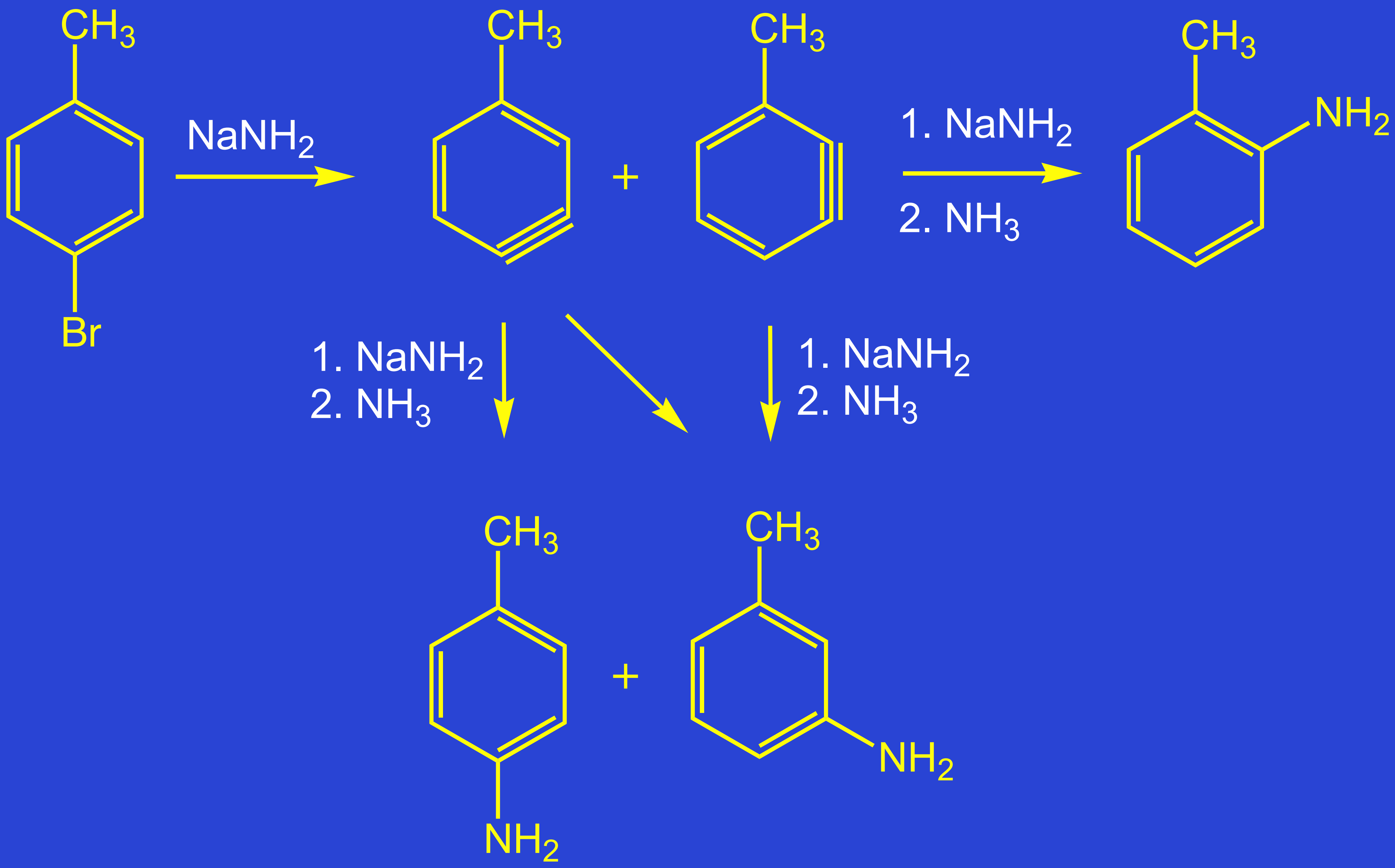
All is Revealed



All is Revealed



All is Revealed

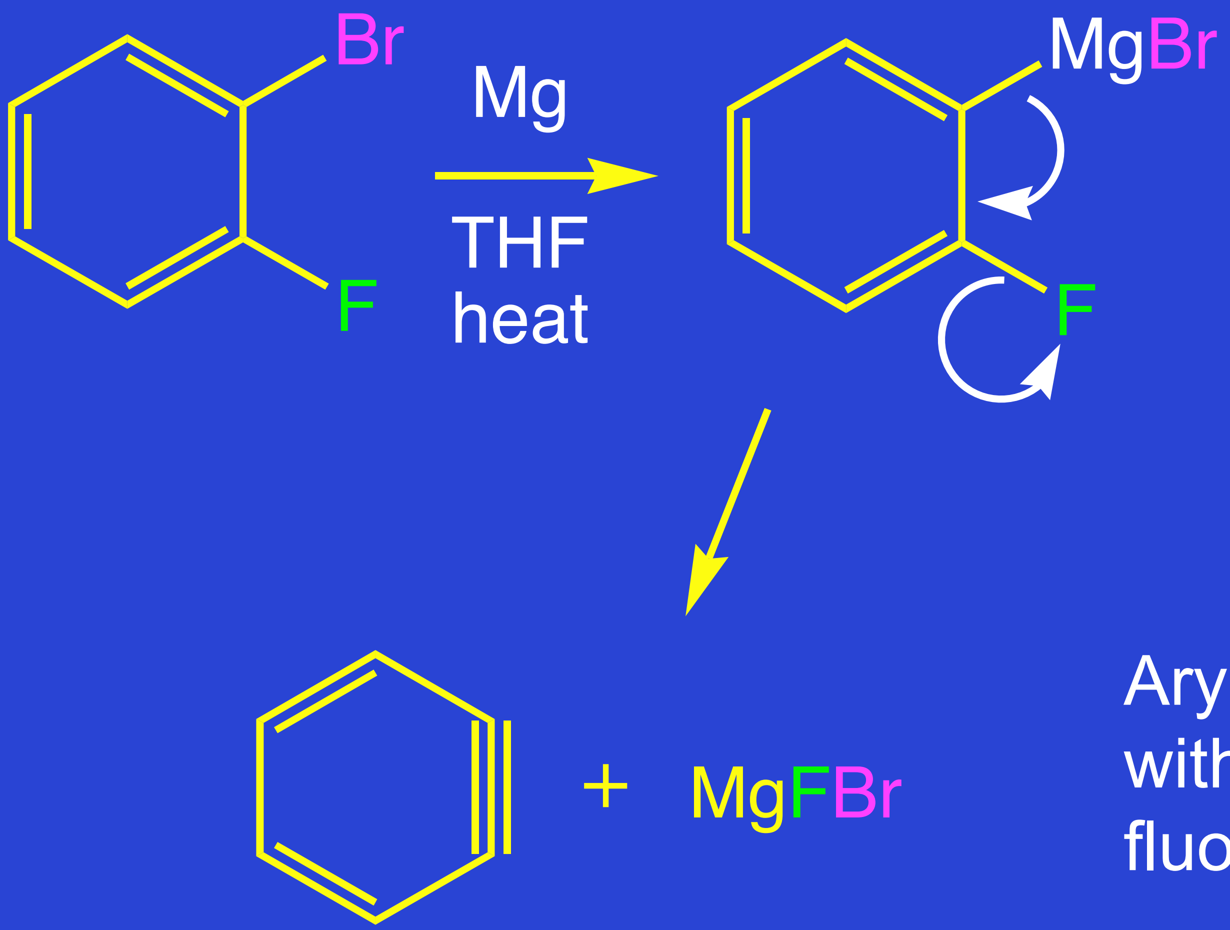


Other Methods for the Preparation of Benzyne

Benzyne can be prepared as a reactive intermediate by methods other than treatment of chlorobenzene with strong bases.

Another method involves loss of fluoride ion from the Grignard reagent of 1-bromo-2-fluorobenzene.

Other Methods for the Preparation of Benzyne

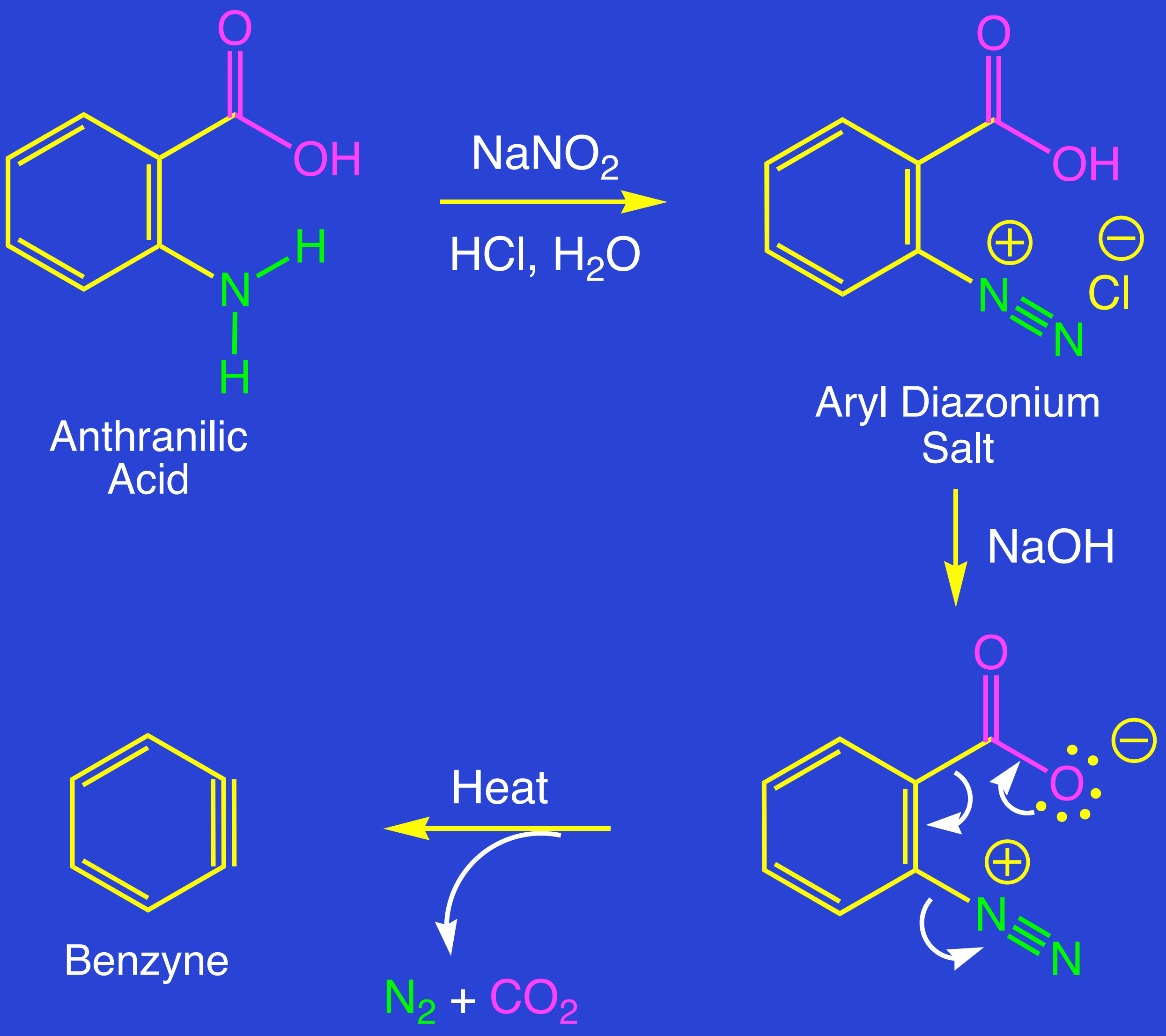


Benzyne

Aryl bromide faster with Mg than aryl fluoride

Preparation of Benzyne via Diazotization of Anthranilic Acid

See Question 23.23



23.9

Cycloaddition Reactions of Benzyne

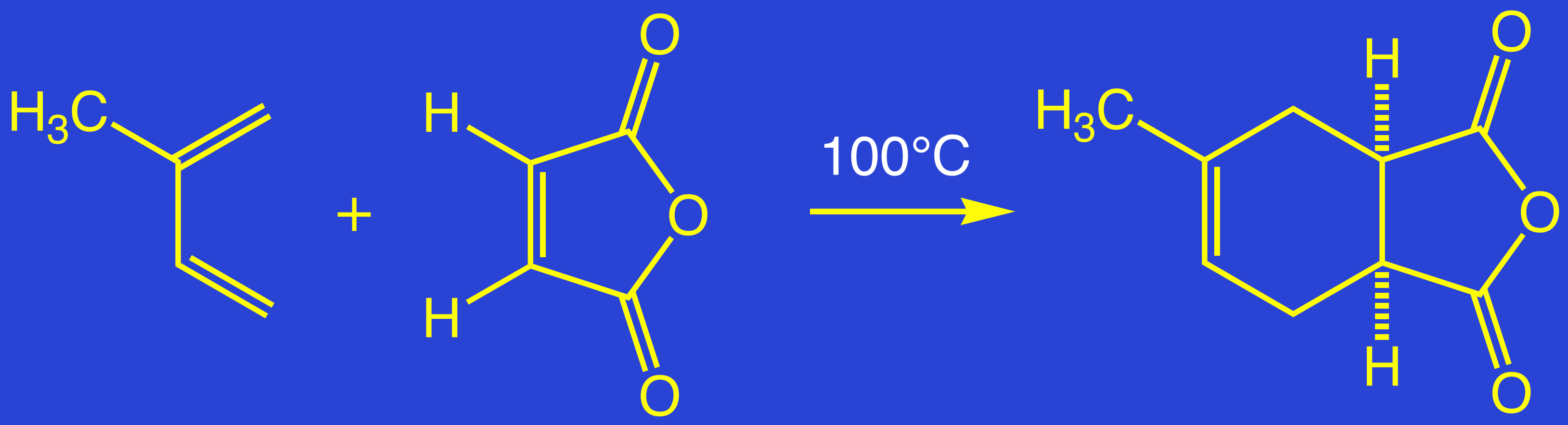
What is a Cycloaddition?

Cycloaddition, *n.*
a reaction in which two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic *adduct* in which there is a net reduction of the bond multiplicity.

The Diels-Alder Reaction Revisited

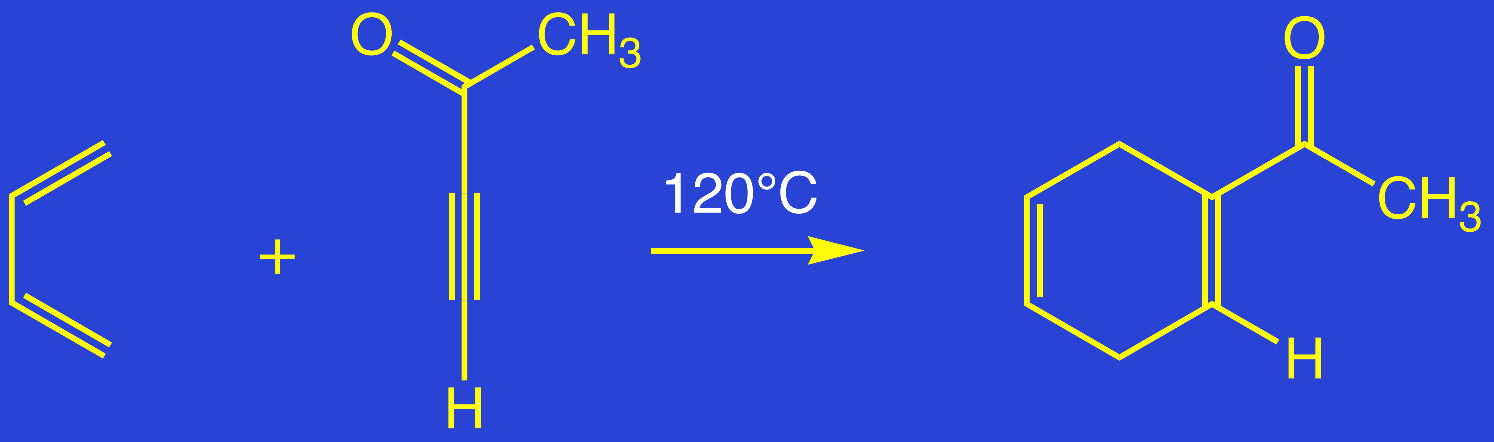
Section 10.12

diene dienophile cycloadduct



isoprene maleic anhydride cycloadduct

Electron-Deficient Alkynes Behave as Dienophiles

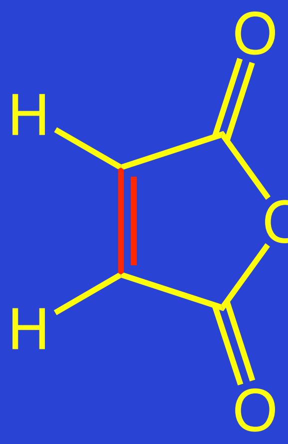


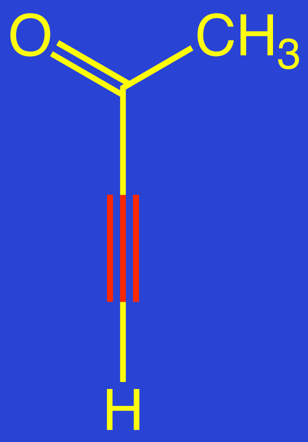
butadiene

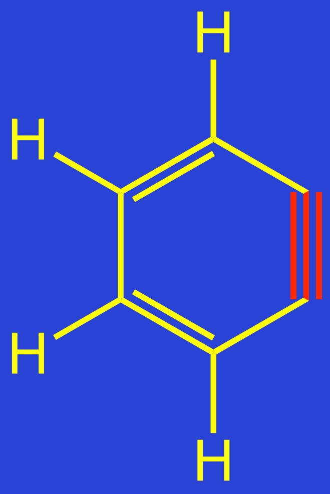
but-3-yn-2-one

cycloadduct

Benzyne Behaves as a Dienophile



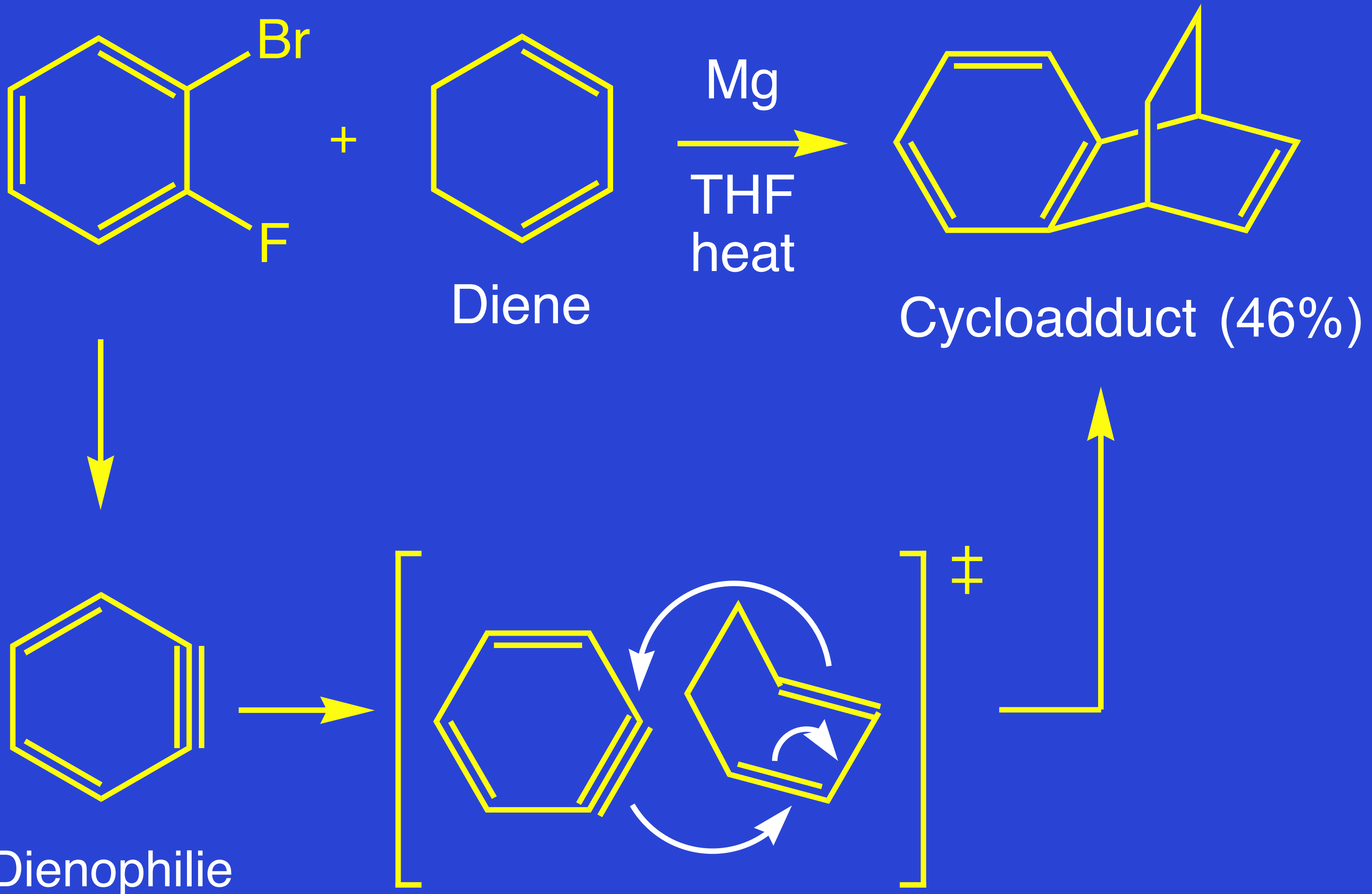




Benzyne

Benzyne is a fairly reactive dienophile, and gives Diels-Alder adducts when generated in the presence of conjugated dienes.

Benzyne Participates in Diels-Alder Reactions

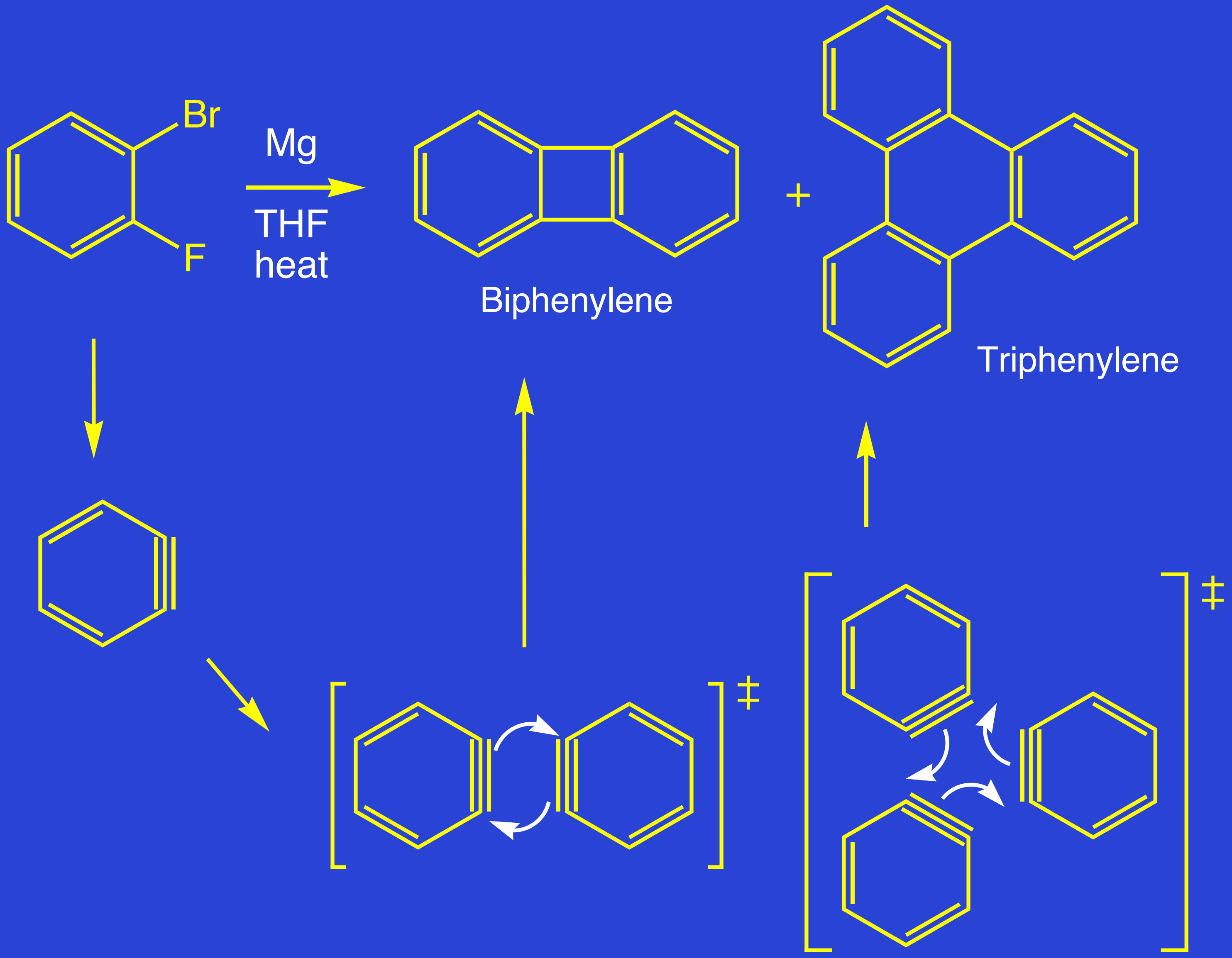


Diene

Cycloadduct (46%)

Dienophilie

In the Absence of Dienes (or other nucleophiles) Benzyne Undergoes Dimerization and Trimerization



Today’s Lecture

Topics Covered:

1. Aryl Halides - Bonding, Physical Properties and Reactions
2. Nucleophilic Substitution of Chlorobenzene
3. Nucleophilic Aromatic Substitution: Addition-Elimination
4. Synthetic Application of Nucleophilic Aromatic Substitution
5. Nucleophilic Aromatic Substitution: Elimination-Addition
6. Benzyne: Generation, Bonding and Reactions

Information & Suggested Problems

Suggested Problems: 23.10-23.27