Lecture 29

Organic Chemistry 1

Professor Duncan Wardrop

April 27, 2010

Today’s Lecture

Topics Covered:

1. Phenol - Bonding, Physical Properties and Reactions
2. Electrophilic Aromatic Substitution: Halogen, Nitration, Nitrosation
3. O- and C-Acylation of Phenols: Fries Rearrangement
4. Kolbe-Schmitt Reaction: Carboxylation of Phenols
5. Preparation and Cleavage of Aryl Alkyl Ethers

Chapter 24
Phenols

24.1
Nomenclature

Nomenclature of Phenols

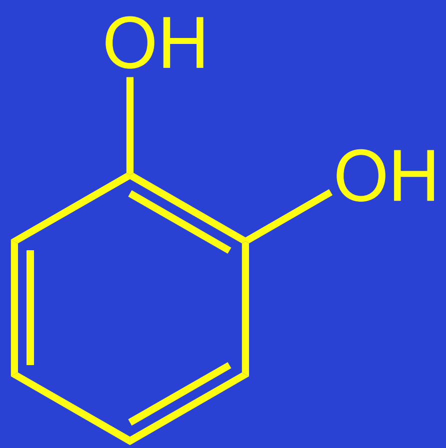
5-chloro-2-methylphenol

named on basis of phenol as parent

substituents listed in alphabetical order

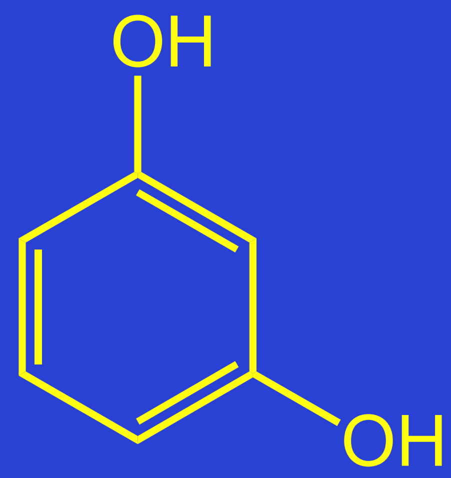
lowest numerical sequence: first point of difference rule

Nomenclature of Hydroxyphenols



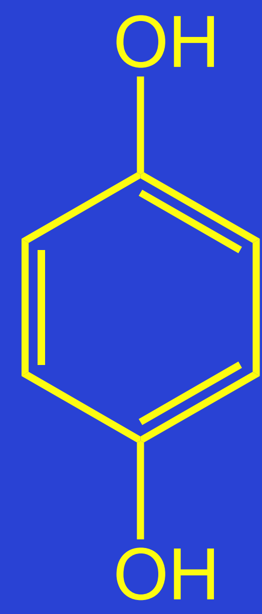
1,2-Benzenediol

(common name: pyrocatechol)



1,3-Benzenediol

(common name: resorcinol)



1,4-Benzenediol

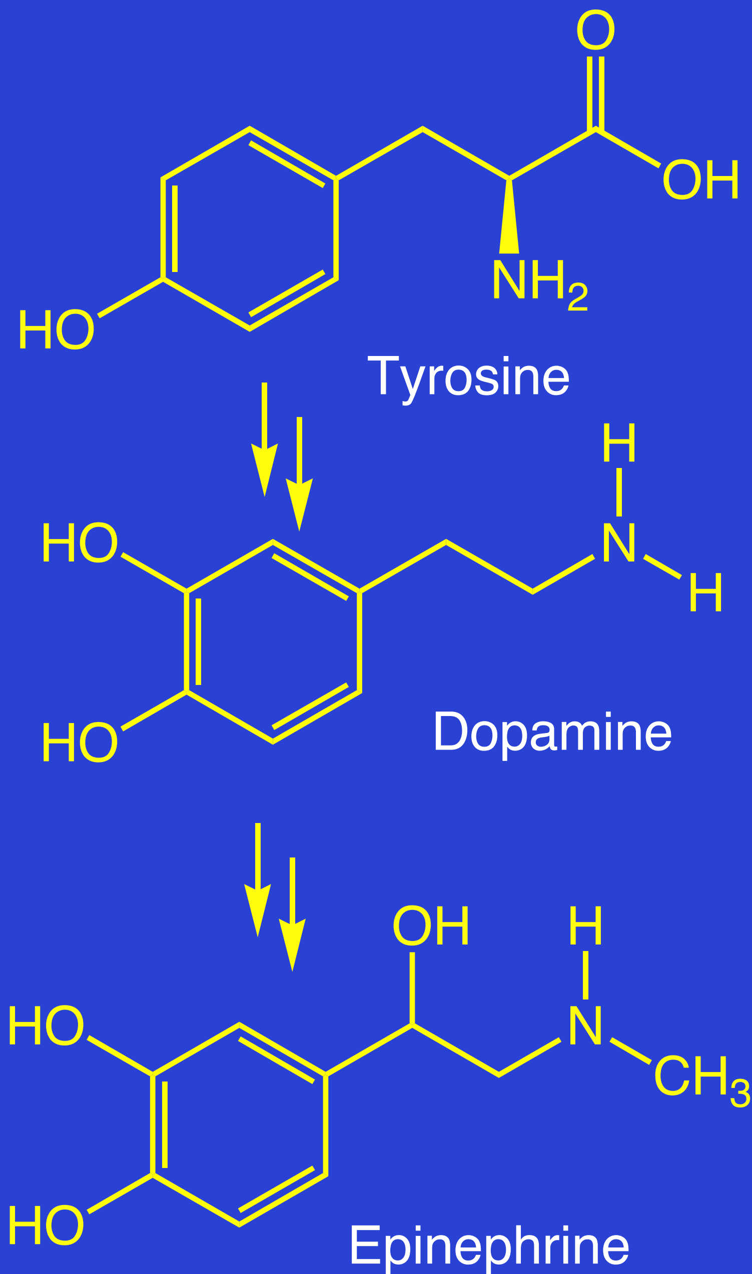
(common name: hydroquinone)

Catechols are Biologically Important

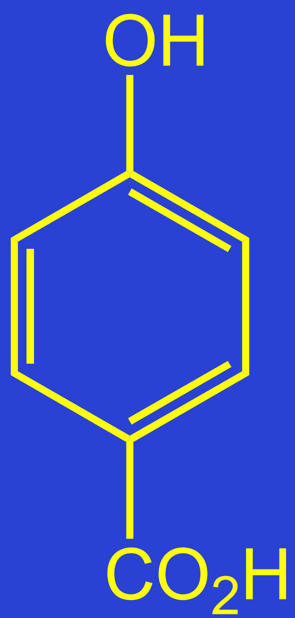
Epinephrine

is the principal hormone governing the "fight or flight" response. This hormone also triggers a variety of physiological events, including increased heart rate. It is biosynthesized from from the amino acid tyrosine by way of DOPA.

http://www.ndrf.org/catechol.htm



Nomenclature of Hydroxyphenols



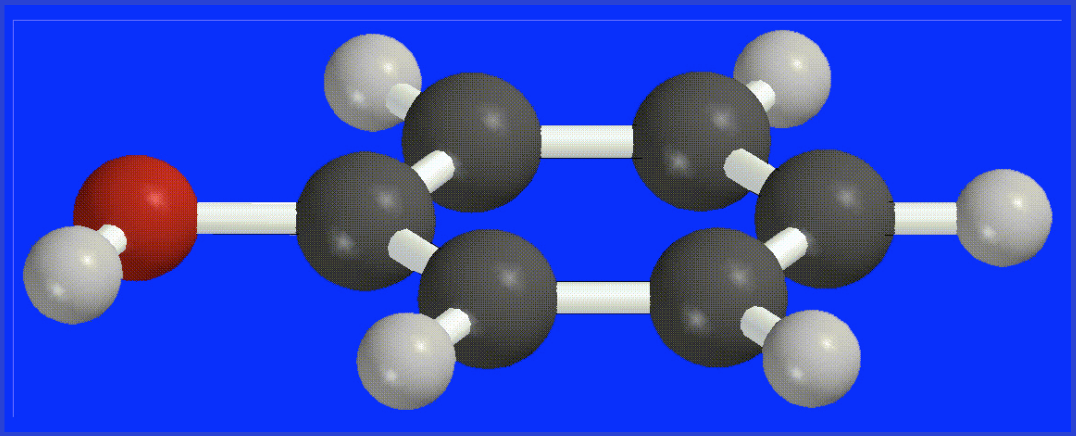
p-Hydroxybenzoic acid

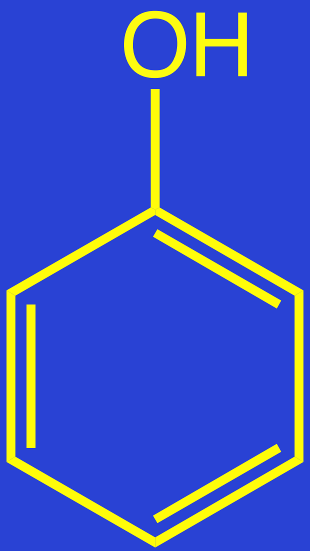
name on basis of benzoic acid as parent

higher oxidation states of carbon outrank hydroxyl group

24.2
Structure and Bonding

Structure of Phenol



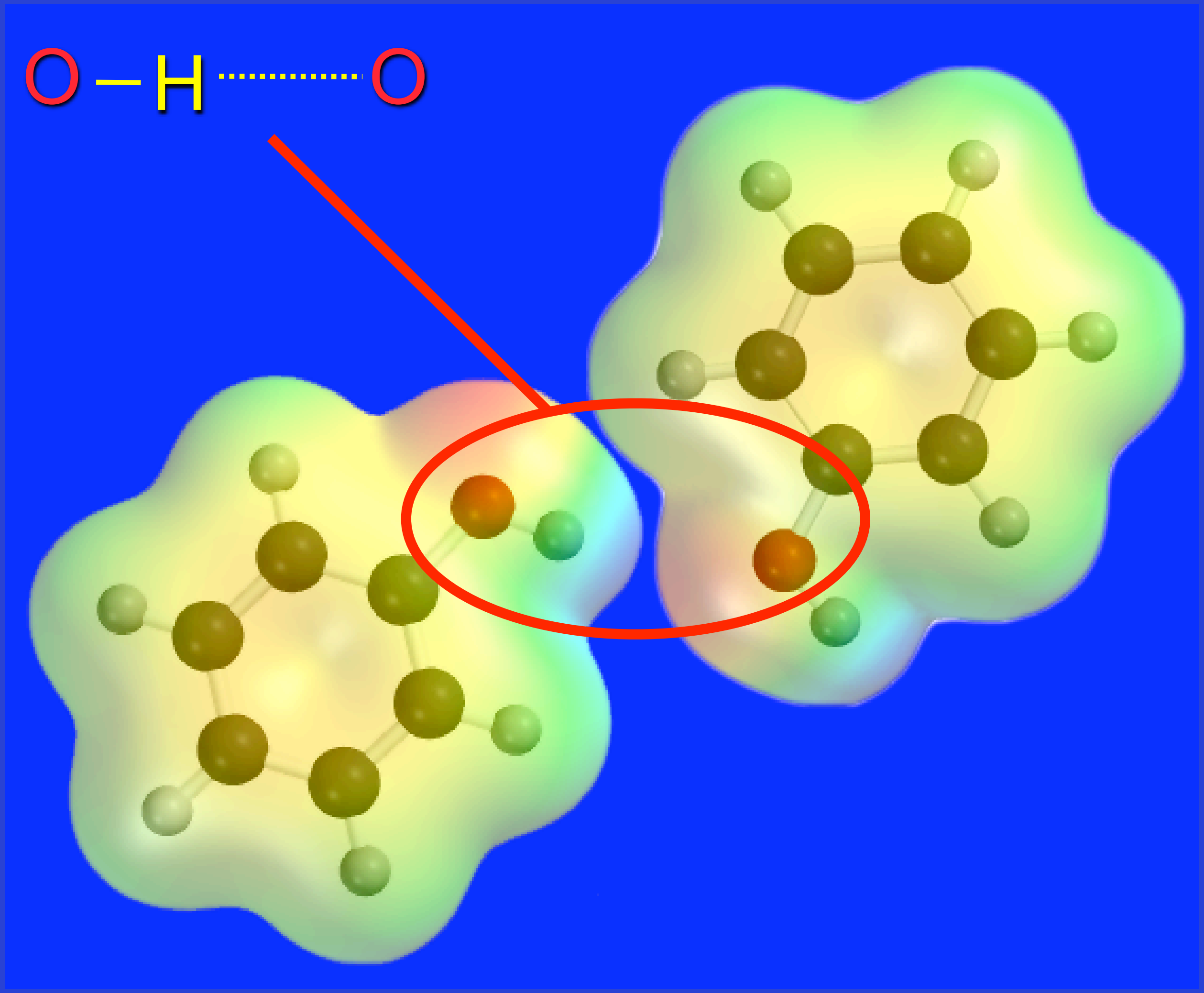


phenol is planar

C—O bond distance is 136 pm, which is slightly shorter than that of CH_3OH (142 pm)

24.3
Physical Properties

Hydrogen Bonding in Phenol



The hydroxyl group of phenols allows hydrogen bonding to other phenol molecules and to water.

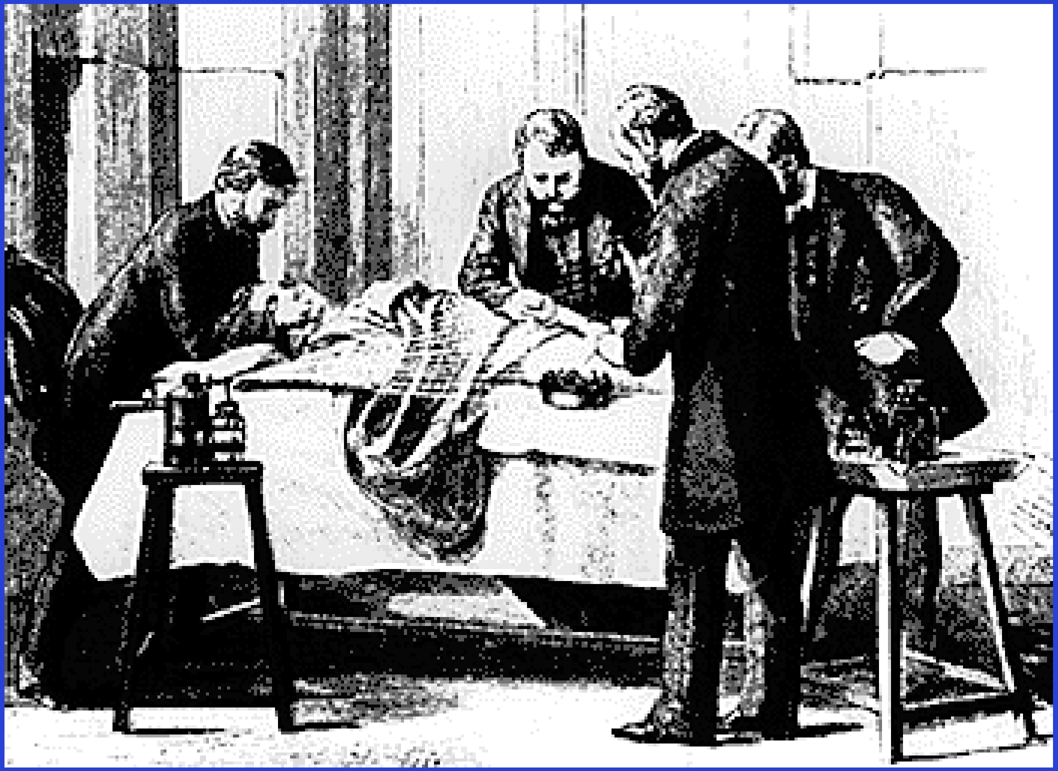
Physical Properties of Phenol

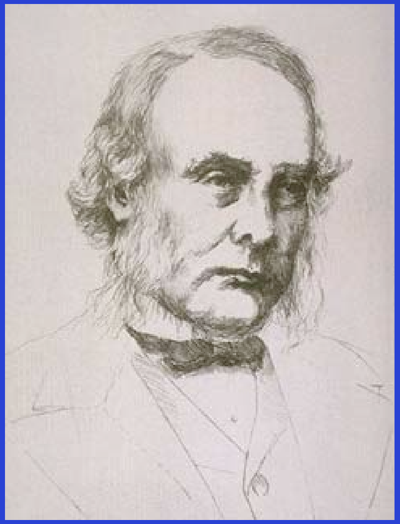
Compared to compounds of similar size and molecular weight, hydrogen bonding in phenol raises its melting point, boiling point, and solubility in water.

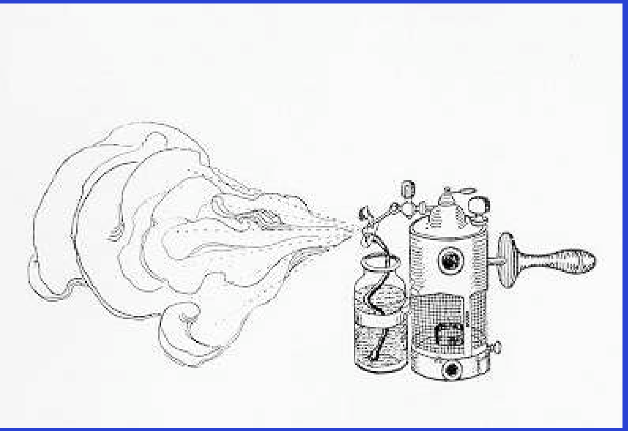
Physical Properties of Phenol

	$C_6H_5CH_3$	C_6H_5OH	C_6H_5F
Molecular weight	92	94	96
Melting point (°C)	–95	43	–41
Boiling point (°C,1 atm)	111	132	85
Solubility in H_2O (g/100 mL,25°C)	0.05	8.2	0.2

Carbolic Acid & the History of Antisepsis

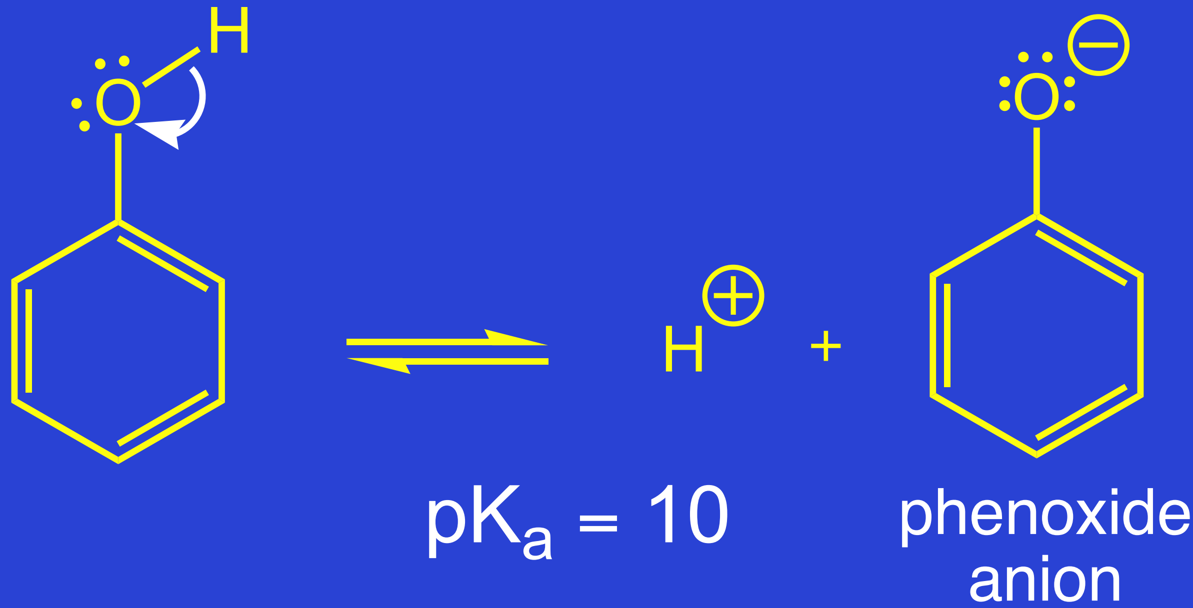




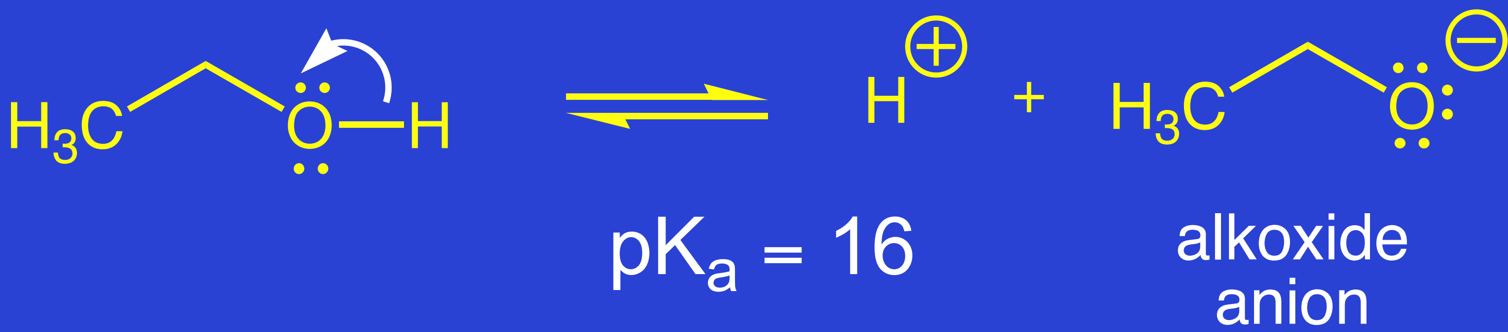


24.4
Acidity of Phenols

Comparative Acidity of Phenol

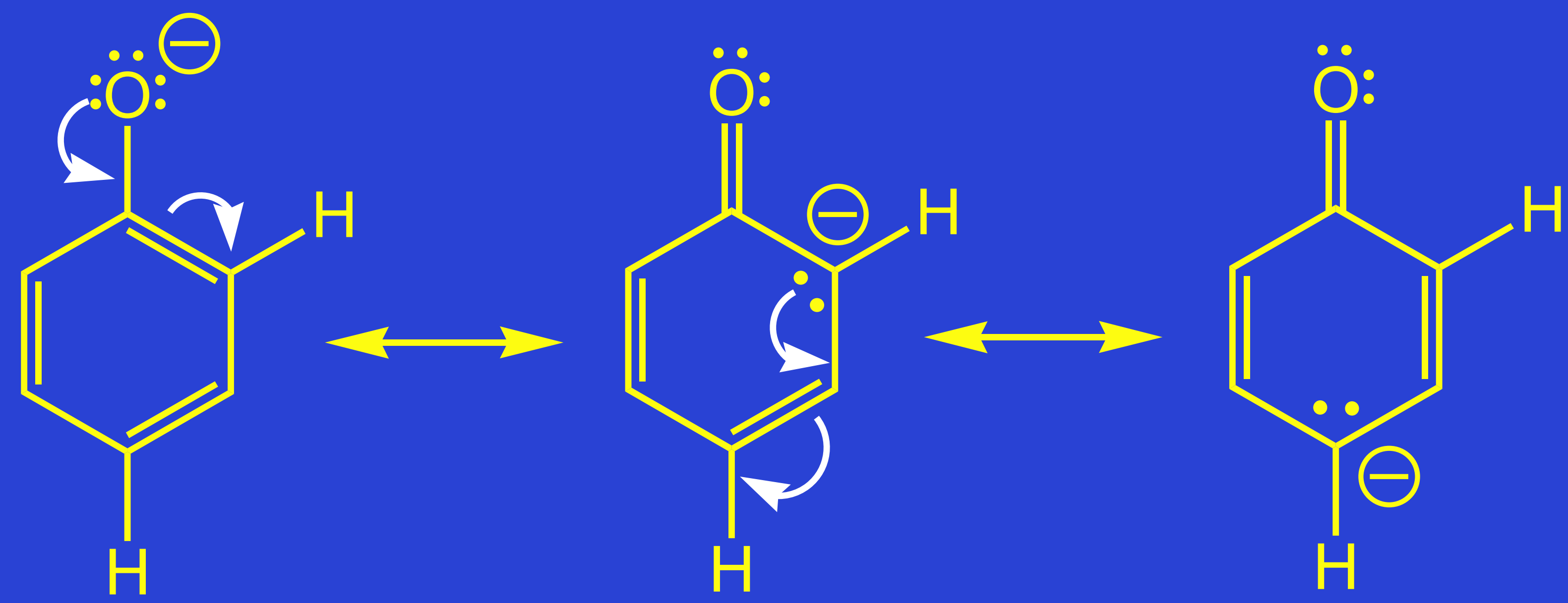


Stabilized by solvation and resonance

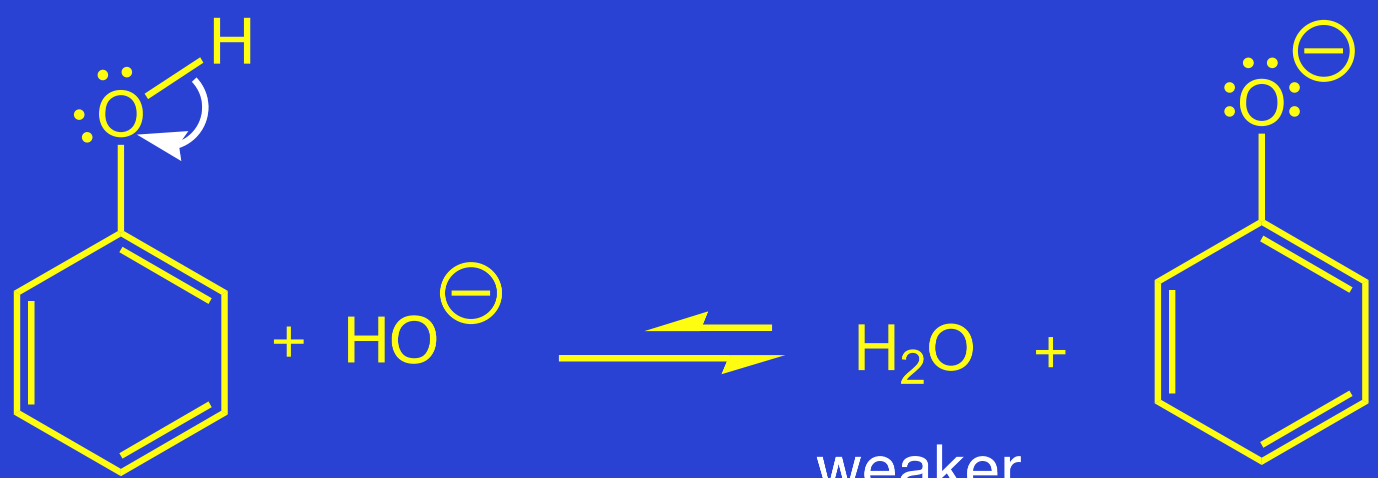


Stabilized by solvation alone

The Phenoxide Anion is Stabilized Through Resonance



Phenols are Converted to Phenoxide Ions in Aqueous Base



stronger acid

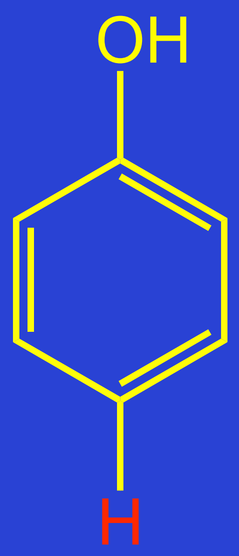
stronger base

weaker acid

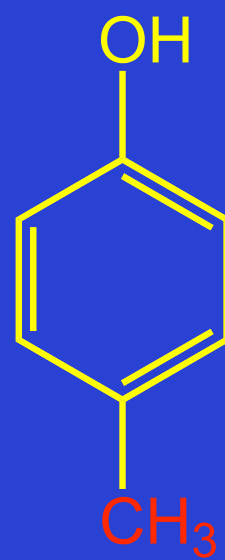
weaker base

24.5
Substituent Effects on the Acidity of Phenols

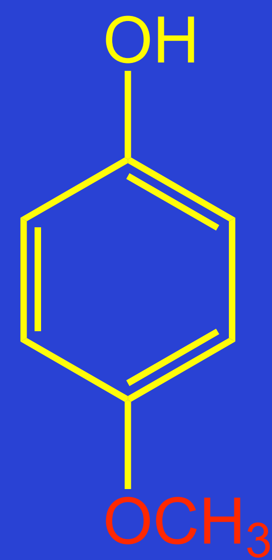
Electron-Releasing Substituents have Little Effect on the pKa of Phenols



pK_a 10

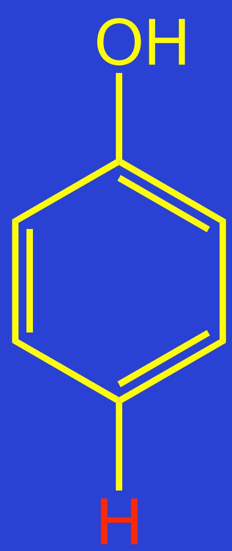


pK_a 10.3

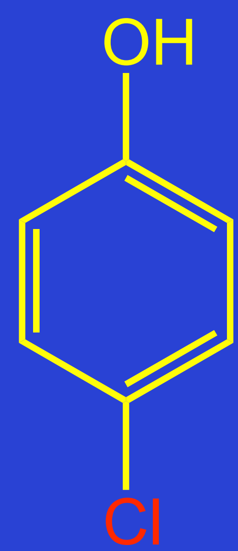


pK_a 10.2

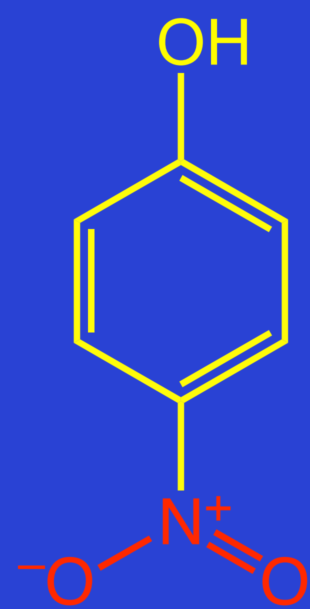
Electron-Withdrawing Substituents Lower the pKa of Phenols



pK_a 10

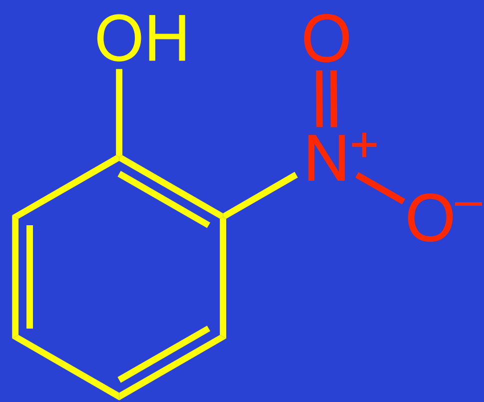


pK_a 9.4

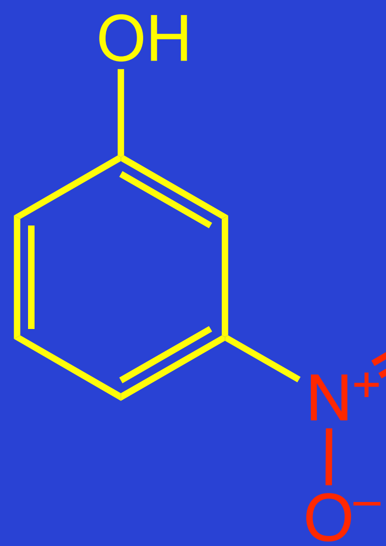


pK_a 7.2

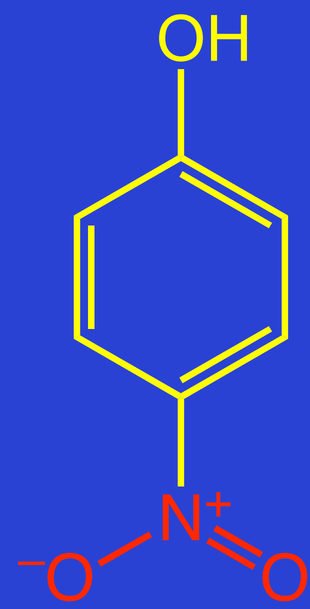
Effect of Electron-Withdrawing Groups is Most Pronounced at *Ortho* and *Para* Positions



pK_a 7.2

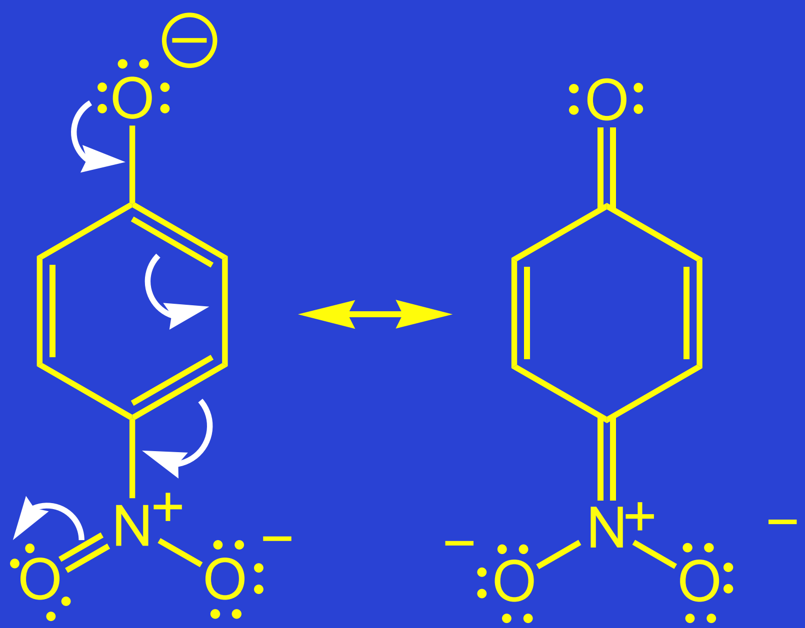


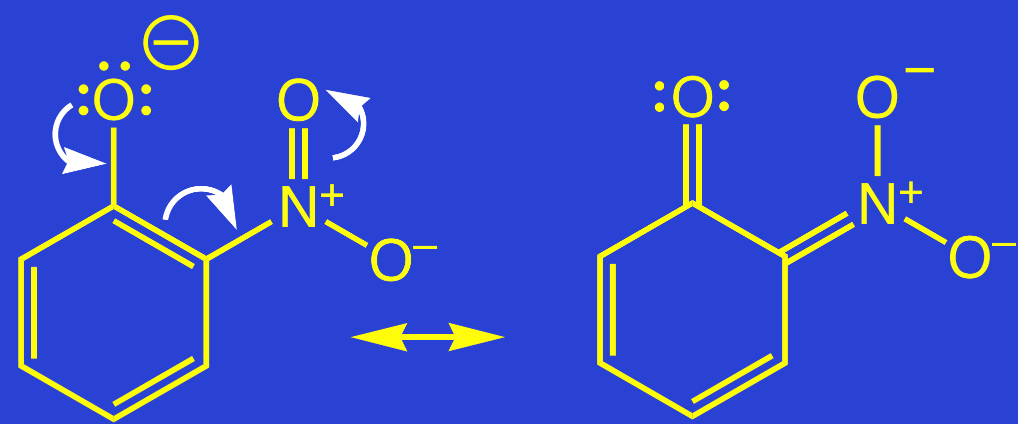
pK_a 8.4



pK_a 7.2

Direct Conjugation of the Negatively Charged Group with the Nitro Substituents is Possible

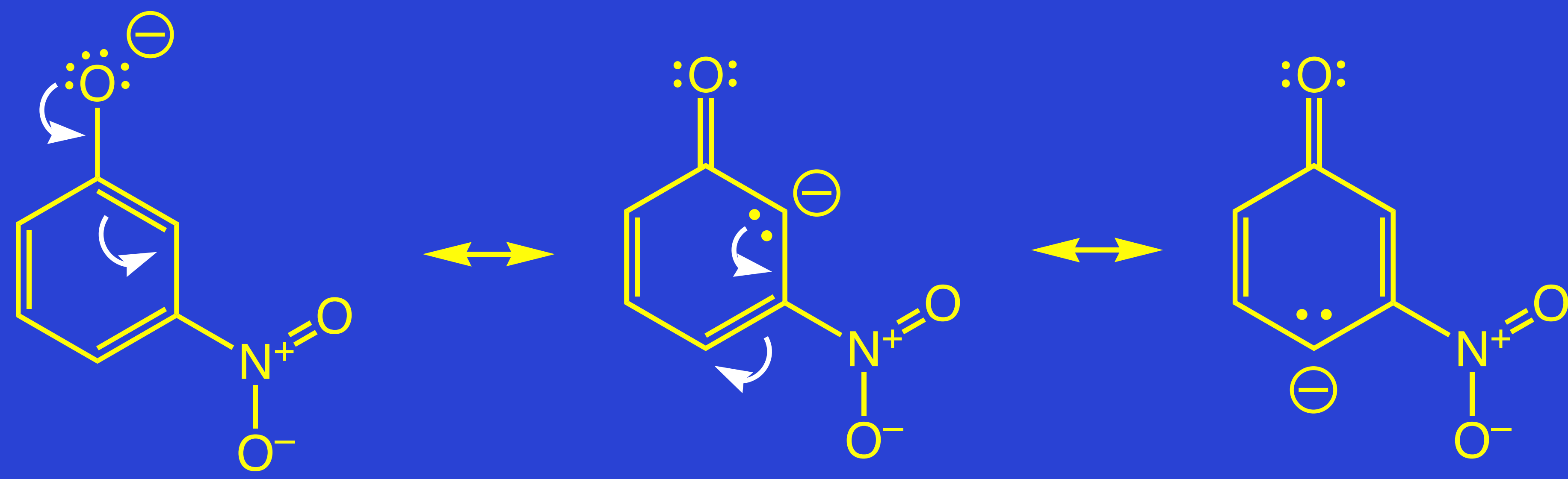




Consequence?

Electron-withdrawing substituents (inc. NO_2) have larger effect on the pKa of a phenol group when in an *ortho* or *para* relationship

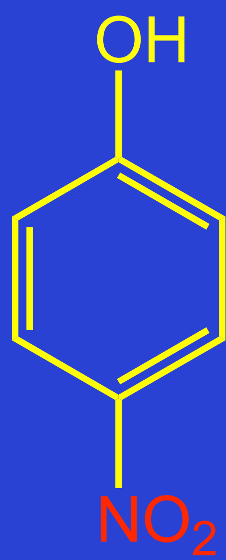
Direct Conjugation of the Negatively Charged Group with the Nitro Substituents is not Possible



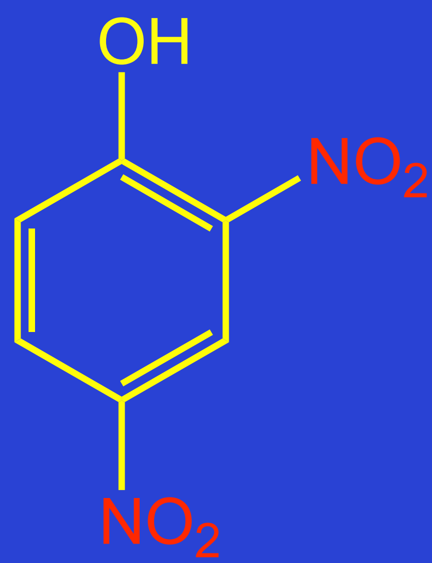
Consequence?

Electron-withdrawing substituents (inc. NO_2) have a smaller effect on the pKa of a phenol group when in a *meta* relationship

The Effect of Electron-Withdrawing Substituents on pKa of Phenols is Cumulative



pK_a 7.2



pK_a 4.0

pK_a 0.4

Picric Acid

24.6
Sources of Phenols

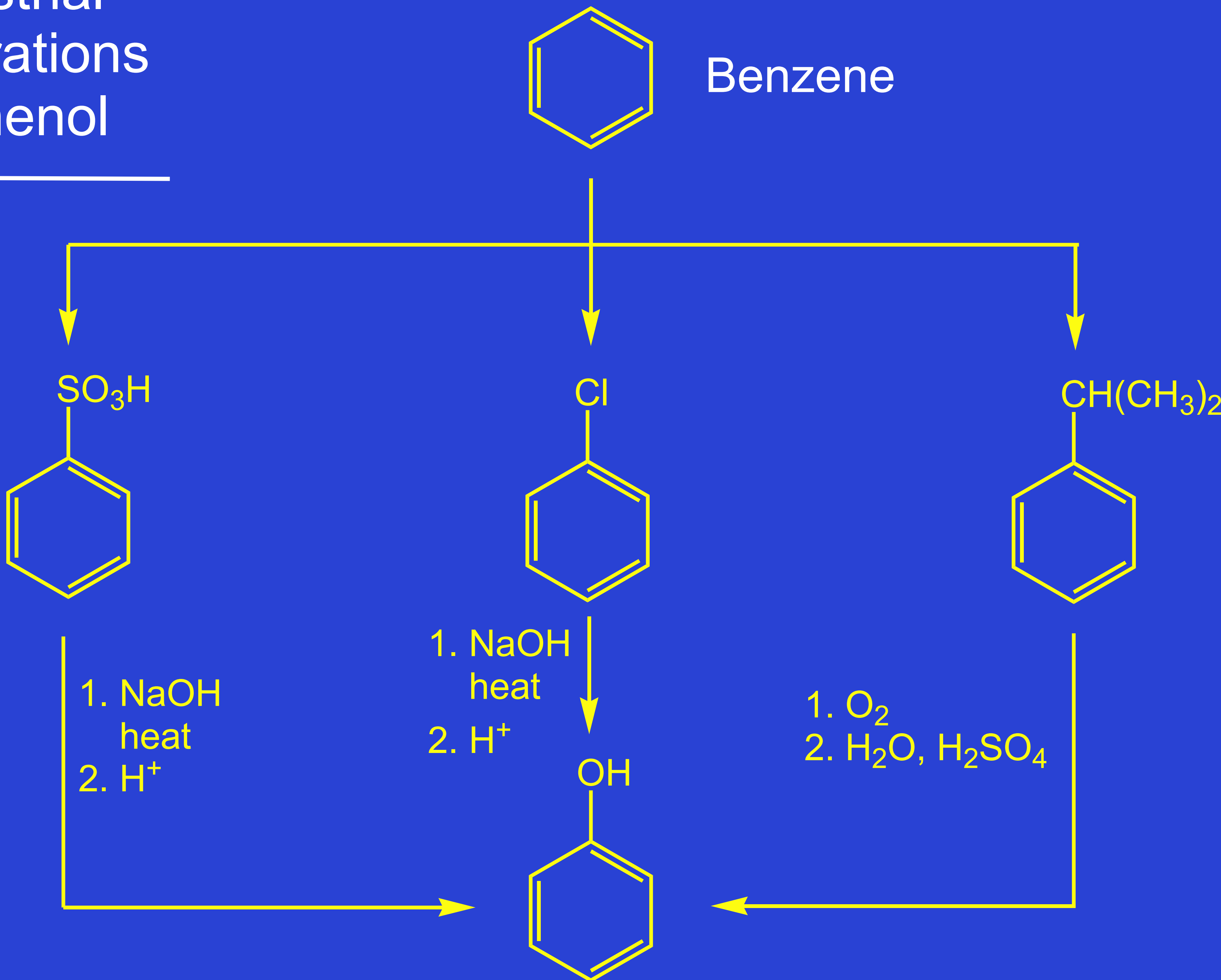
Phenol - An Industrial Chemical

Phenol is an important industrial chemical.

Major use is in phenolic resins for adhesives and plastics.

Annual U.S. production is about 4 billion pounds per year.

Industrial Preparations of Phenol



Preparation of Phenol from Diazonium Salts

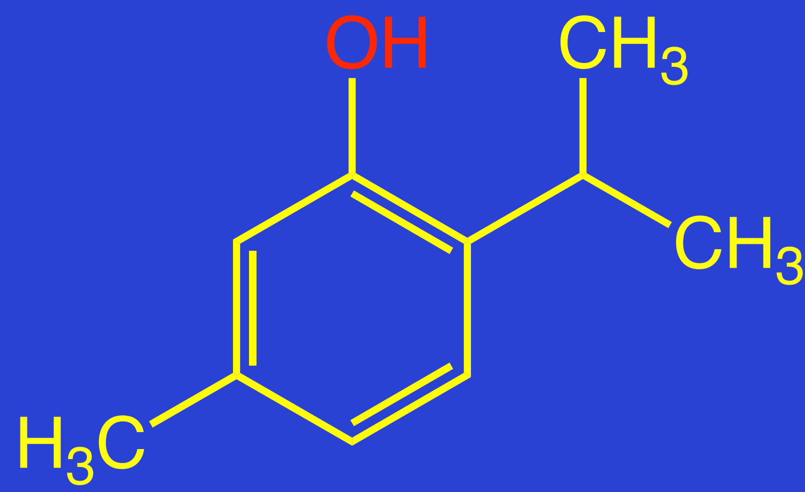
Remember - reaction proceeds via aryl cation

24.7
Naturally Occurring Phenols

An Antiseptic with a Pleasant Smell

Thymol

a major constituent of oil of thyme, was used in ancient Egyptian religious ceremonies

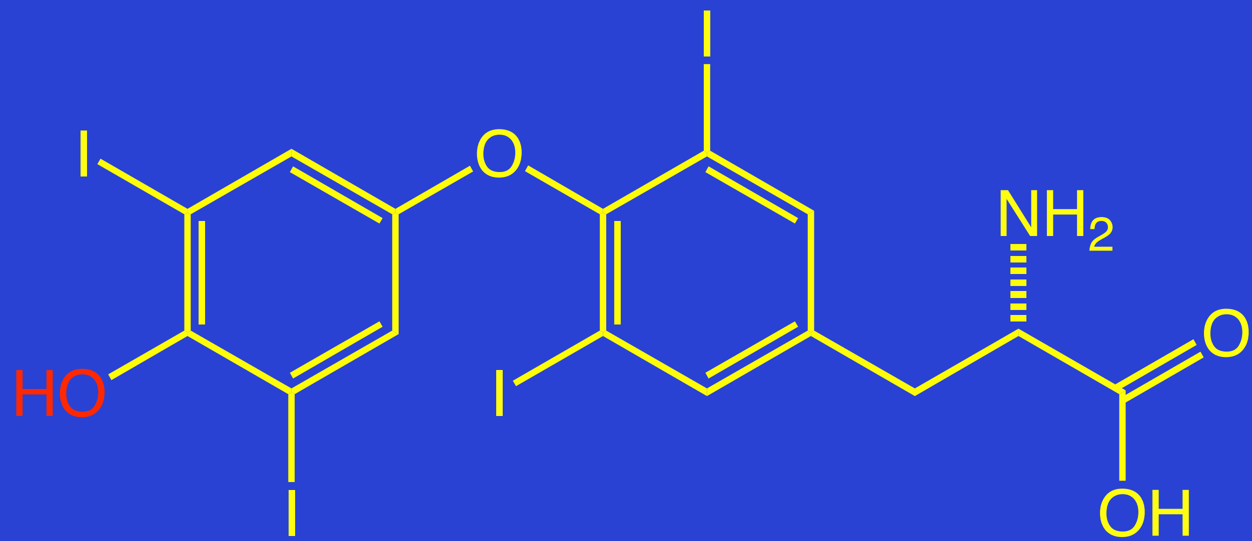


A Red Pigment Isolated from ‘Young’ Red Wine

Malvin

this phenolic compound belongs to a family of plant pigments called anthocyanins

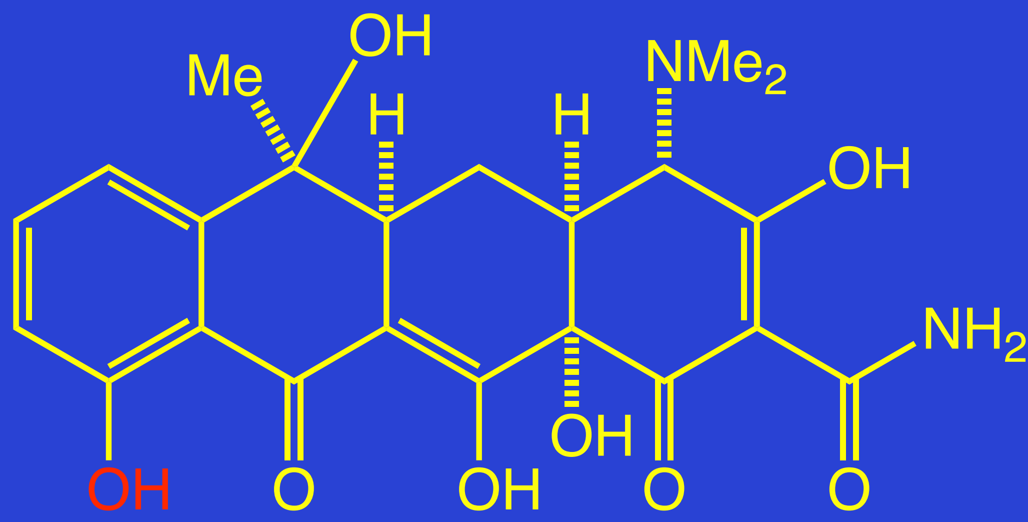
A Major Hormone of the Thyroid Gland



Thyroxine

is one of the major hormones secreted by the human thyroid gland. Its principle function is to stimulate the metabolism of cells

An Antibiotic



Tetracycline

the tetracyclines are a family of antibiotics produced by various strains of microorganisms of the genus *Streptomyces*. Bacterial resistance to these antibiotics is a major problem

24.8
Reactions of Phenols: Electrophilic Aromatic Substitution

Electrophilic Aromatic Substitution in Phenols

Halogenation

Nitration

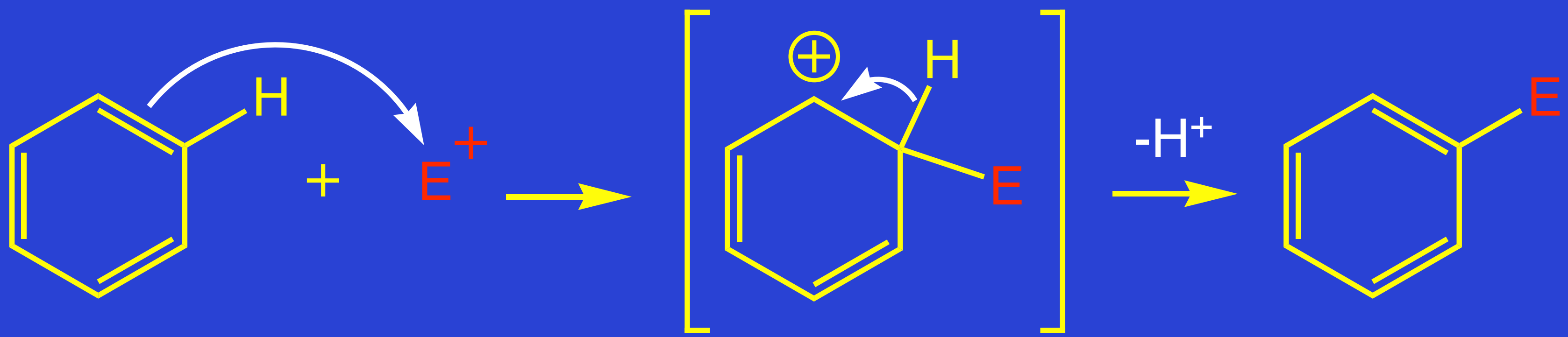
Nitrosation

Sulfonation

Friedel-Crafts Alkylation

Friedel-Crafts Acylation

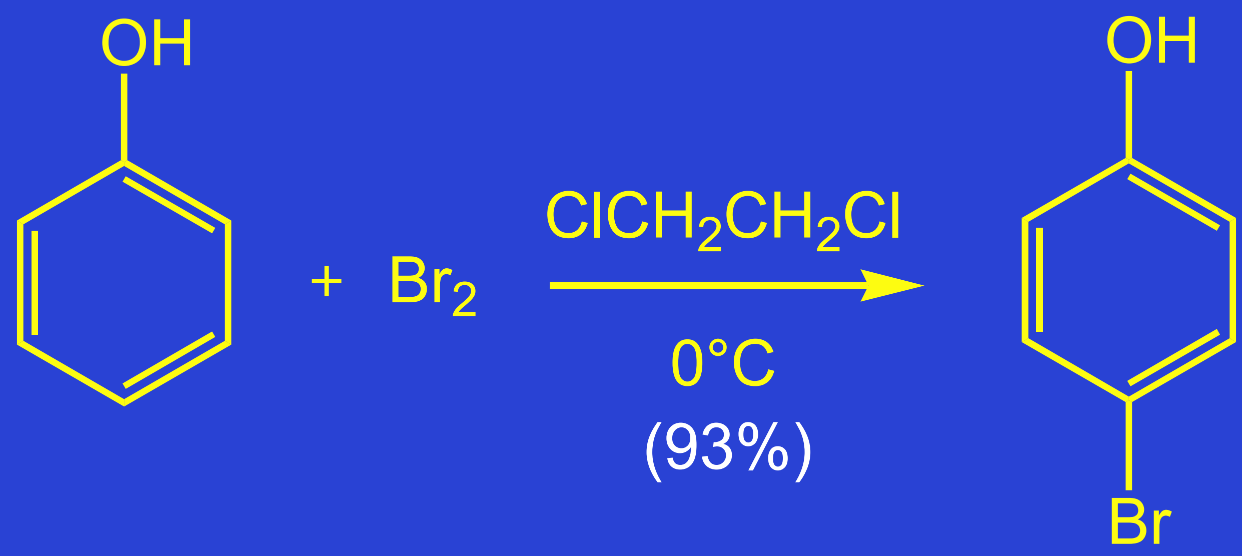
Electrophilic Aromatic Substitution



Sigma Complex
or
Wheland Intermediate

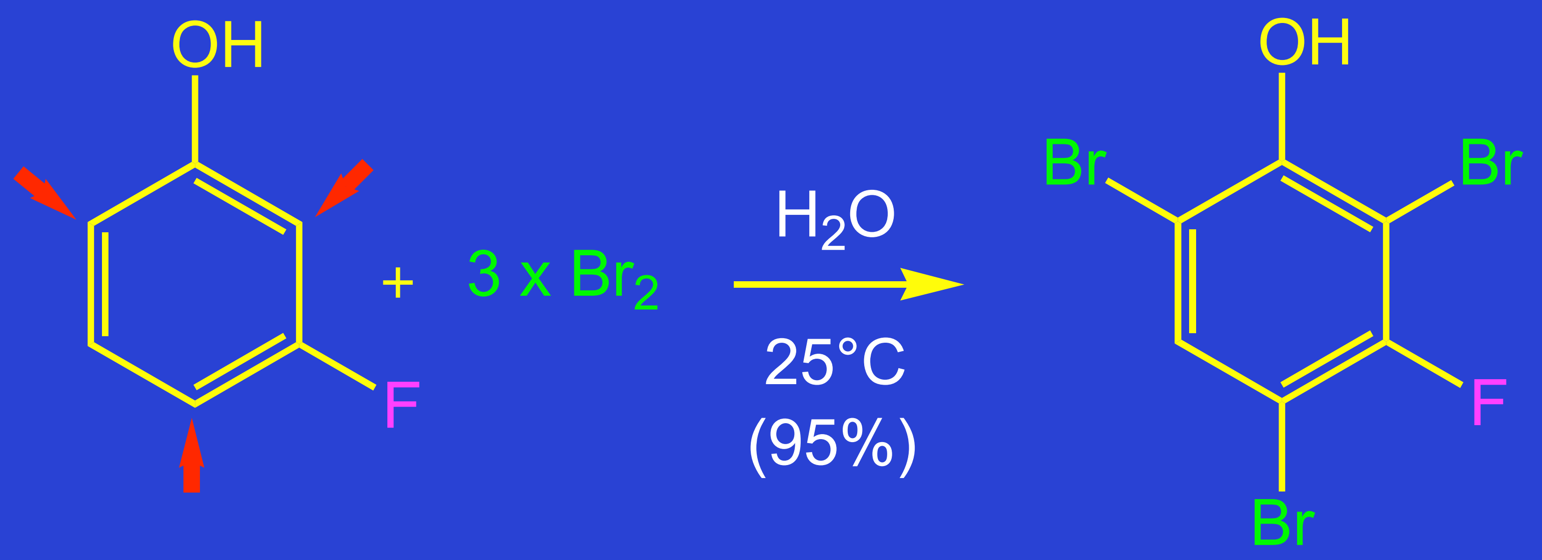
OH groups on benzene rings are *ortho, para-* directing and strongly activating

Halogenation of Phenols - Non-Polar Solvents



monohalogenation occurs in non-polar solvents (1,2-dichloroethane)

Halogenation of Phenols - Polar Solvents

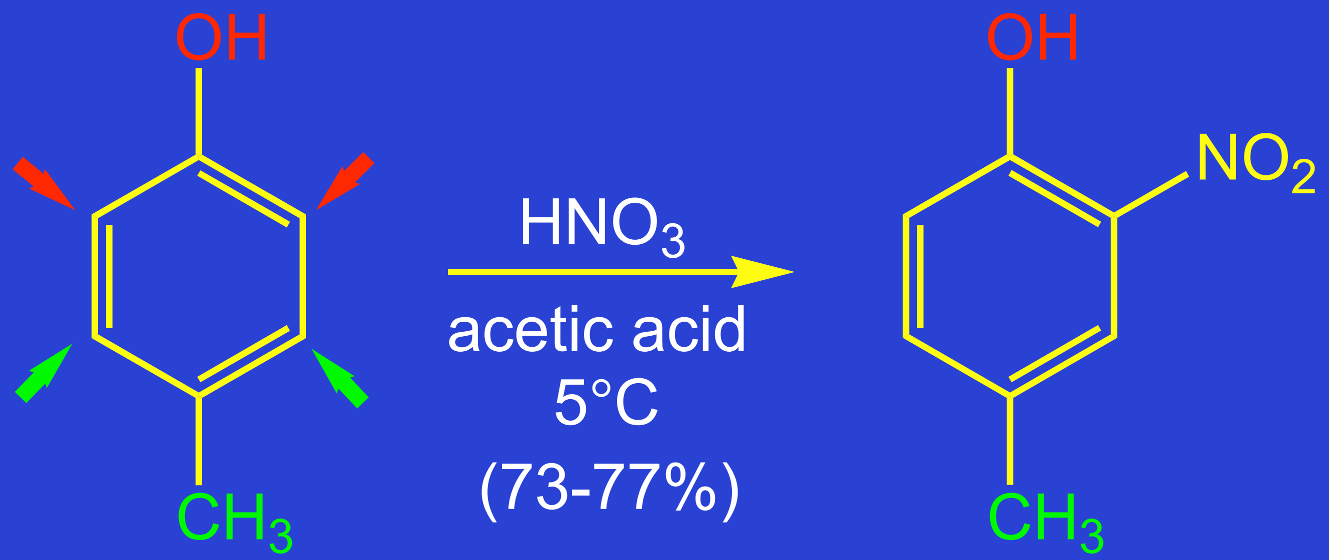


multiple halogenation in polar solvent (water)

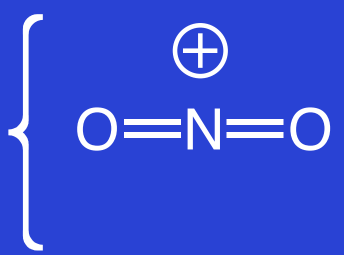
Electrophilic Aromatic Substitution in Phenols

- Halogenation
- Nitration
- Nitrosation
- Sulfonation
- Friedel-Crafts Alkylation
- Friedel-Crafts Acylation

Nitration of Phenols

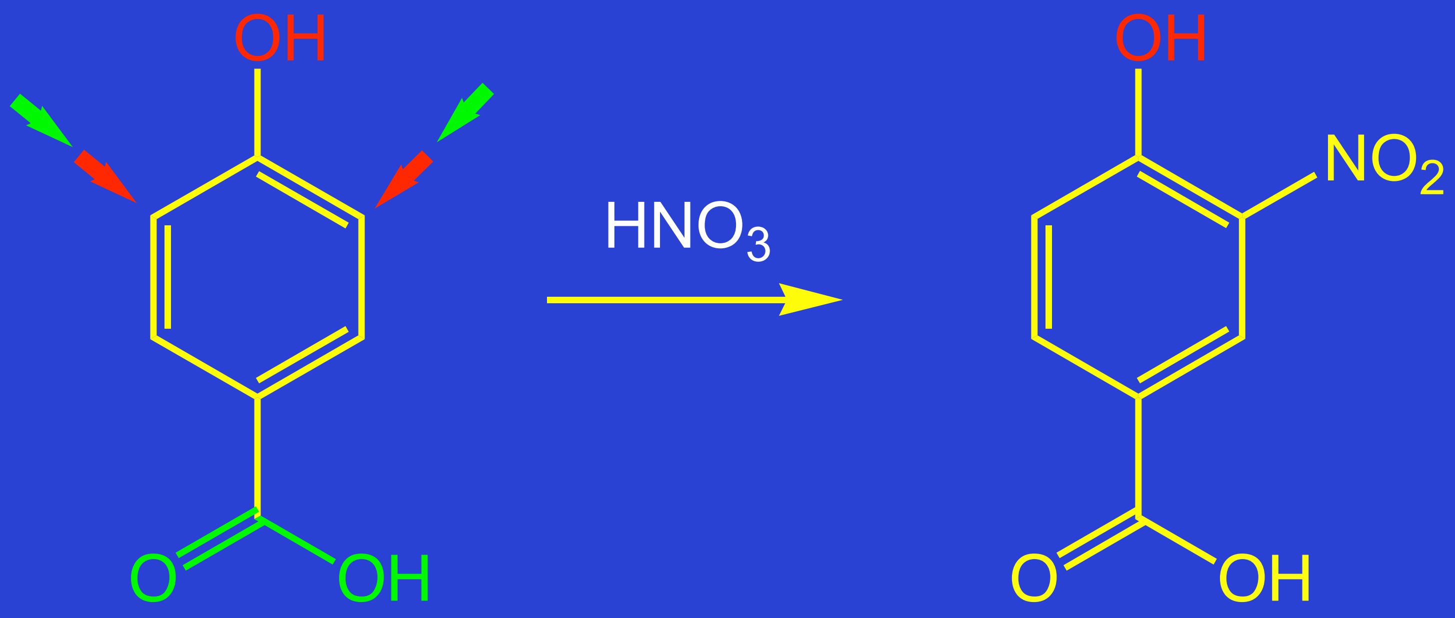


Active Electrophile



the OH group is more electron donating than the methyl group and consequently controls the regiochemistry of this reaction

Nitration of Phenols

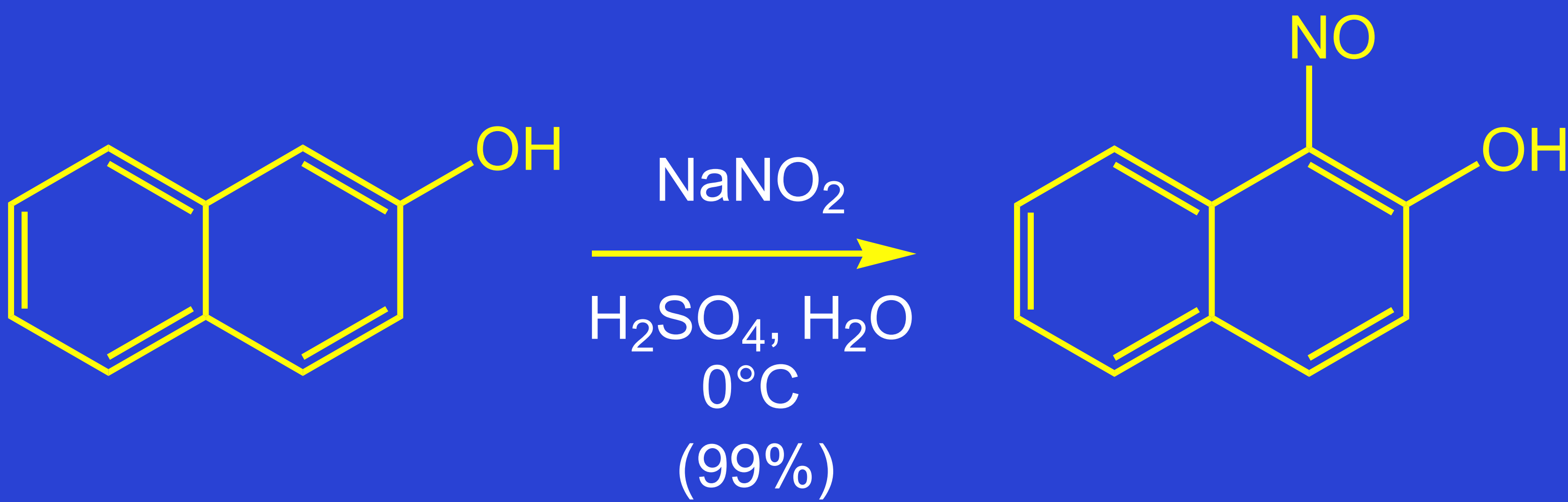


Hydroxyl groups are *ortho, para*-directing, while carboxylate groups are *meta*-directing. In this example, these effects reinforce each other and a single product is obtained

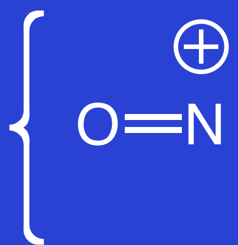
Electrophilic Aromatic Substitution in Phenols

- Halogenation
- Nitration
- Nitrosation
- Sulfonation
- Friedel-Crafts Alkylation
- Friedel-Crafts Acylation

Nitrosation of Phenols



Active Electrophile



only strongly activated rings undergo nitrosation when treated with nitrous acid

Electrophilic Aromatic Substitution in Phenols

Halogenation

Nitration

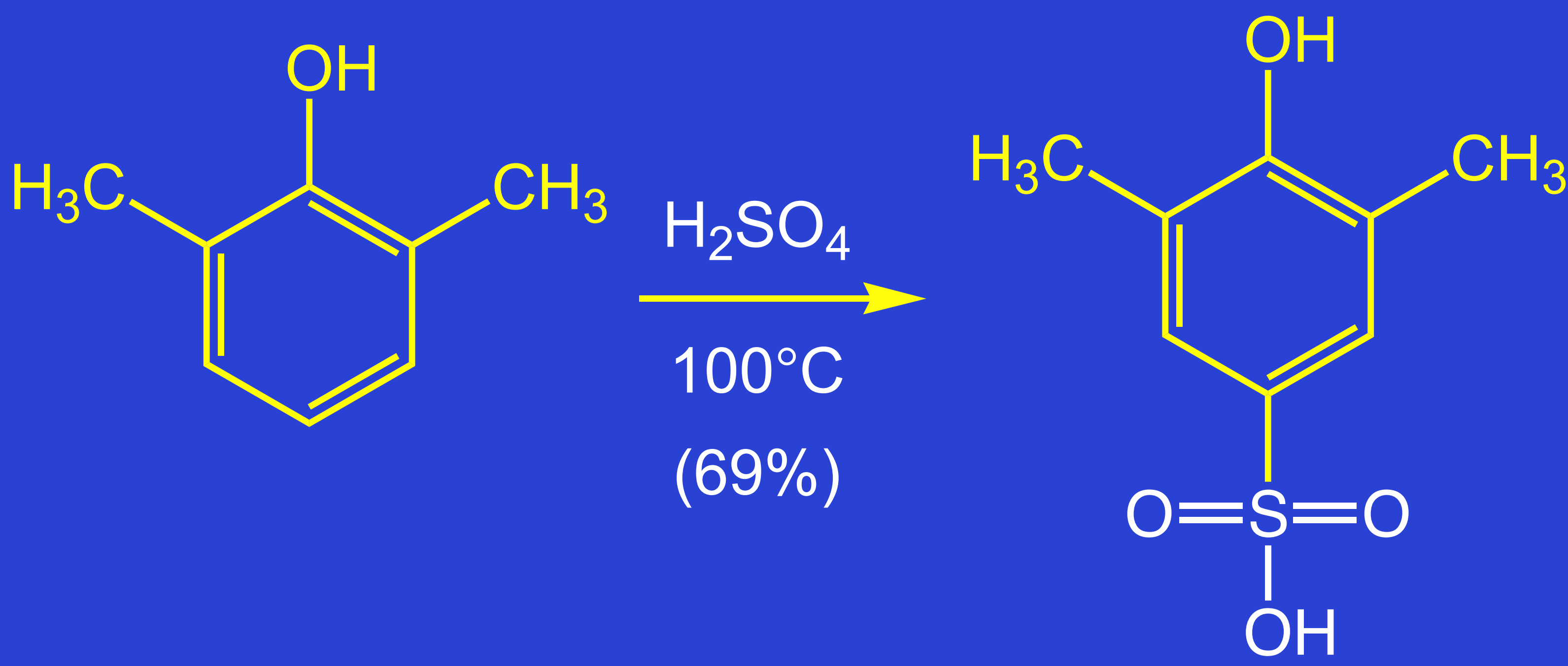
Nitrosation

Sulfonation

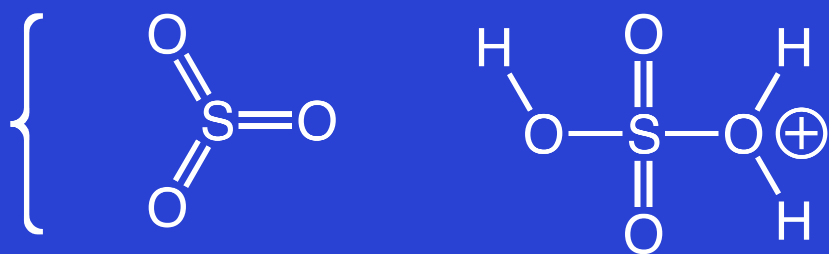
Friedel-Crafts Alkylation

Friedel-Crafts Acylation

Sulfonation of Phenols



Possible
Active
Electrophiles



Electrophilic Aromatic Substitution in Phenols

Halogenation

Nitration

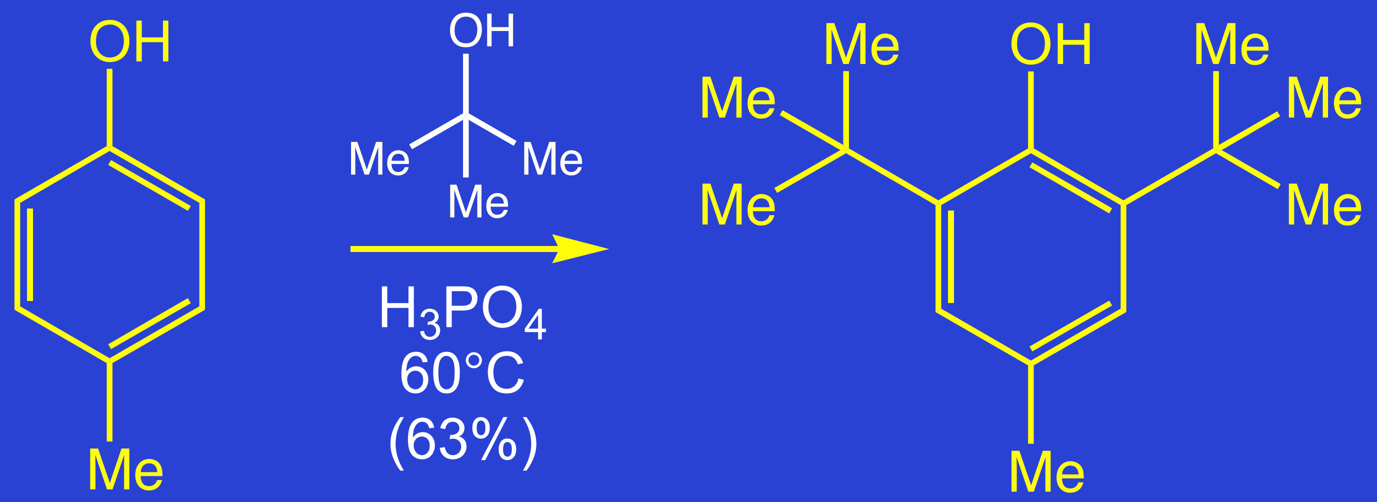
Nitrosation

Sulfonation

Friedel-Crafts Alkylation

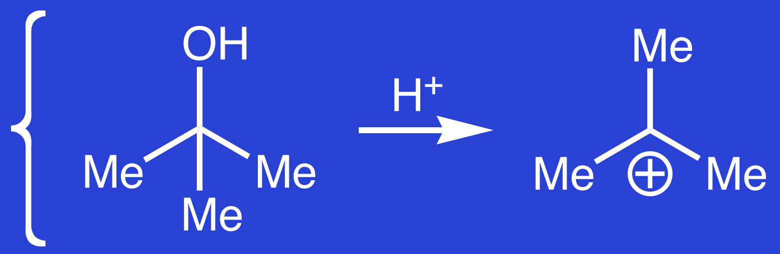
Friedel-Crafts Acylation

Friedel-Crafts Alkylation

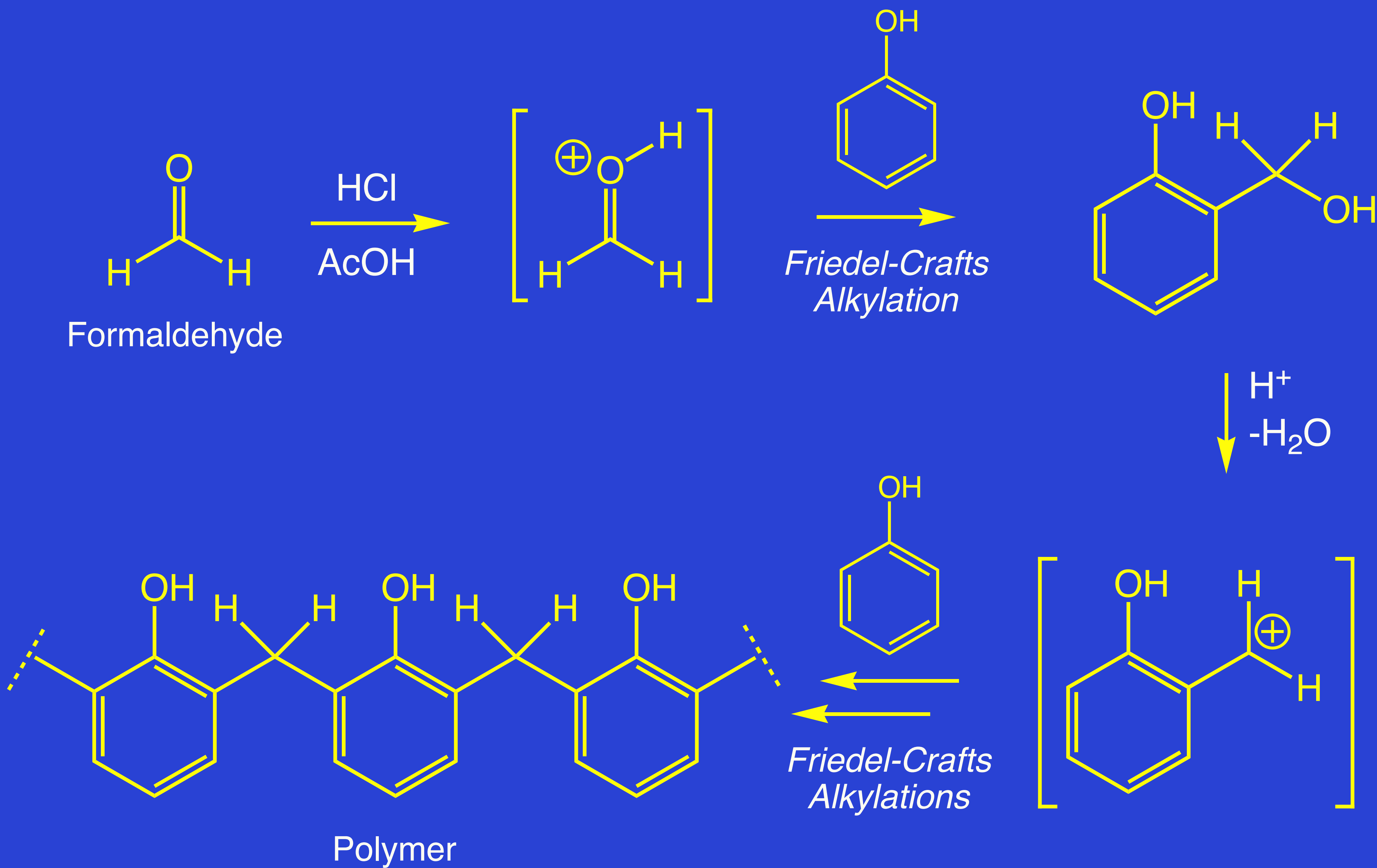


BHT
(butylated hydroxy toluene)

Active
Electrophile



Phenol-Formaldehyde Resins



Bakelite - The First Commerical Synthetic Polymer

http://www.bakelite.de/eng/

Electrophilic Aromatic Substitution in Phenols

Halogenation

Nitration

Nitrosation

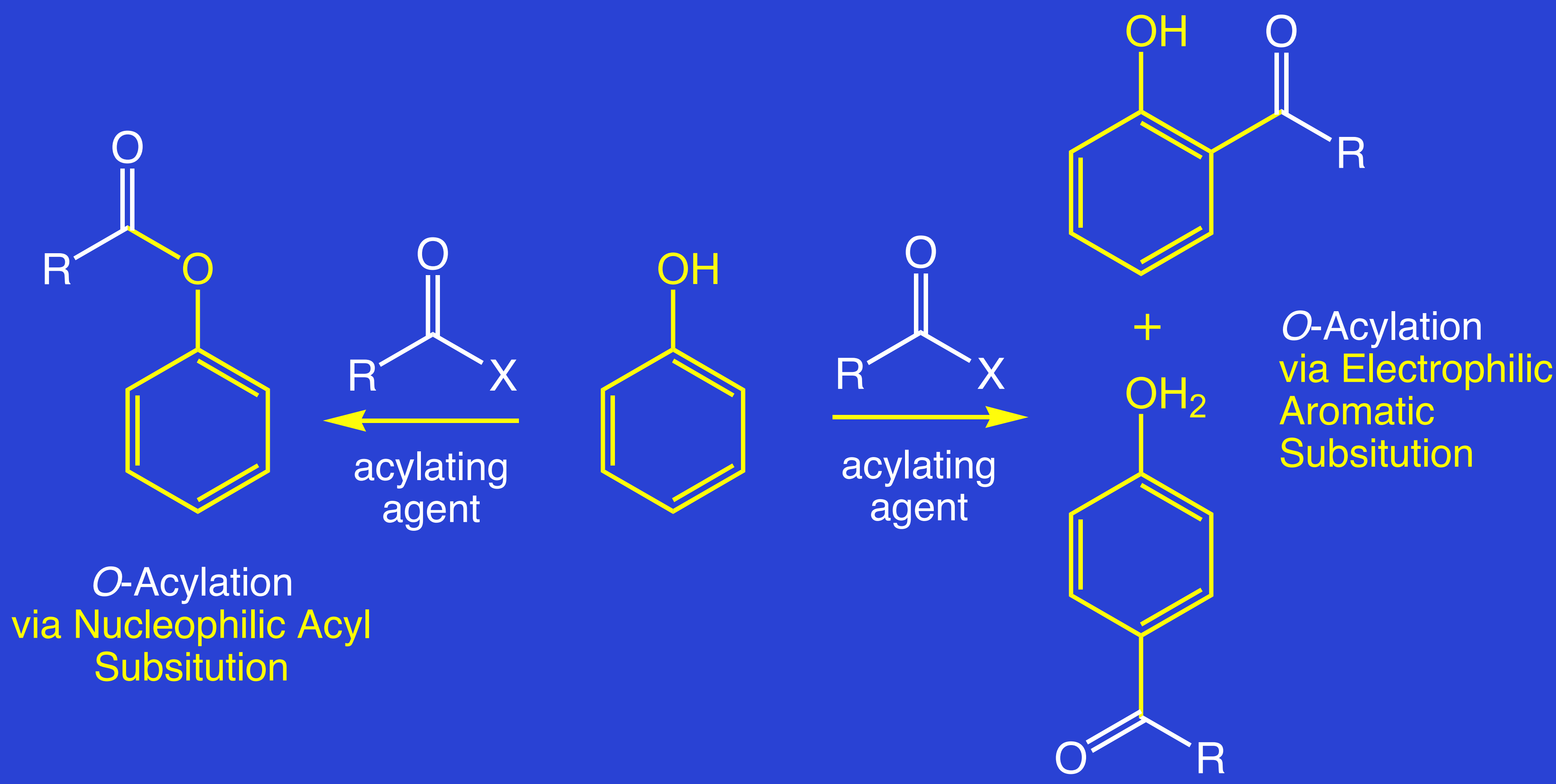
Sulfonation

Friedel-Crafts Alkylation

Friedel-Crafts Acylation

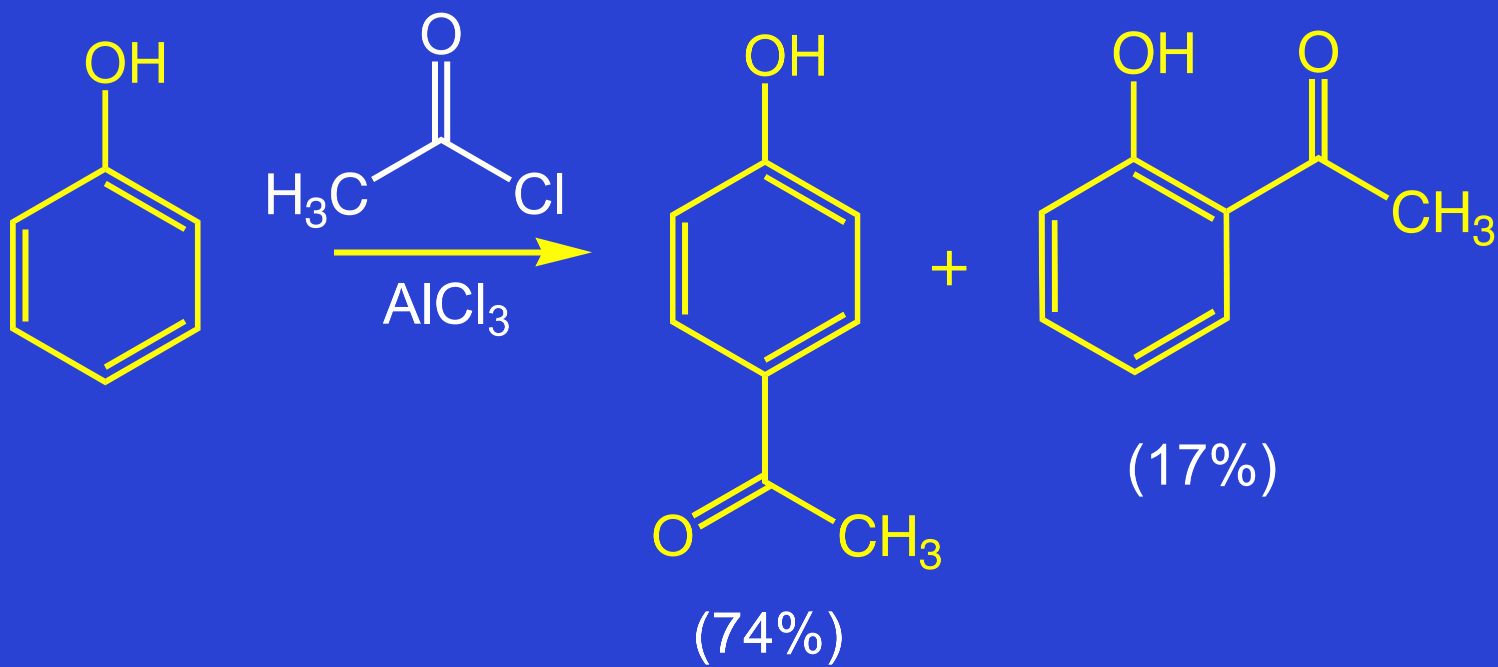
24.9
Acylation of Phenols

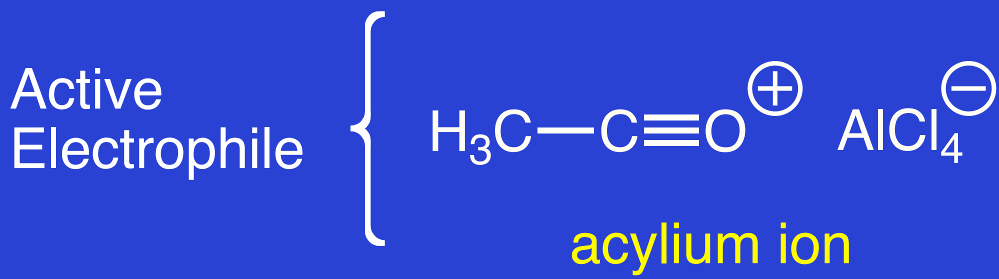
Phenol Acylation: A Question of Regioselectivity and Chemoselectivity



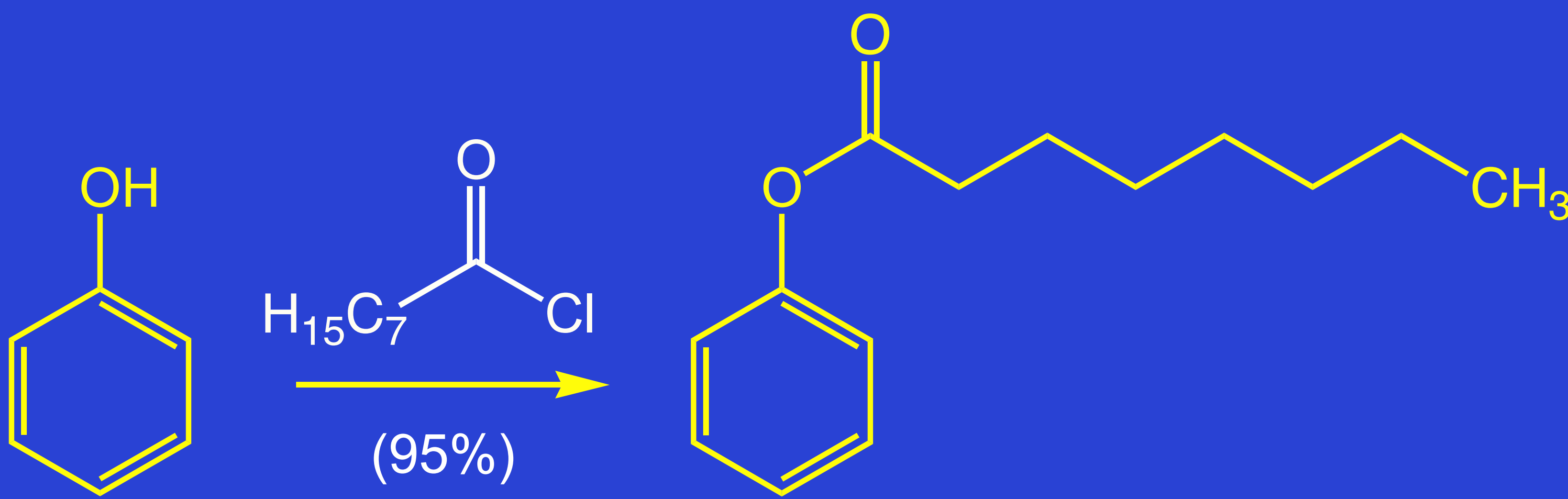
Acylation of phenolic compounds can take place either on the ring by electrophilic aromatic substitution or on oxygen by nucleophilic acyl substitution

Friedel-Crafts Conditions Yield Aryl Ketones via *C*-Acylation



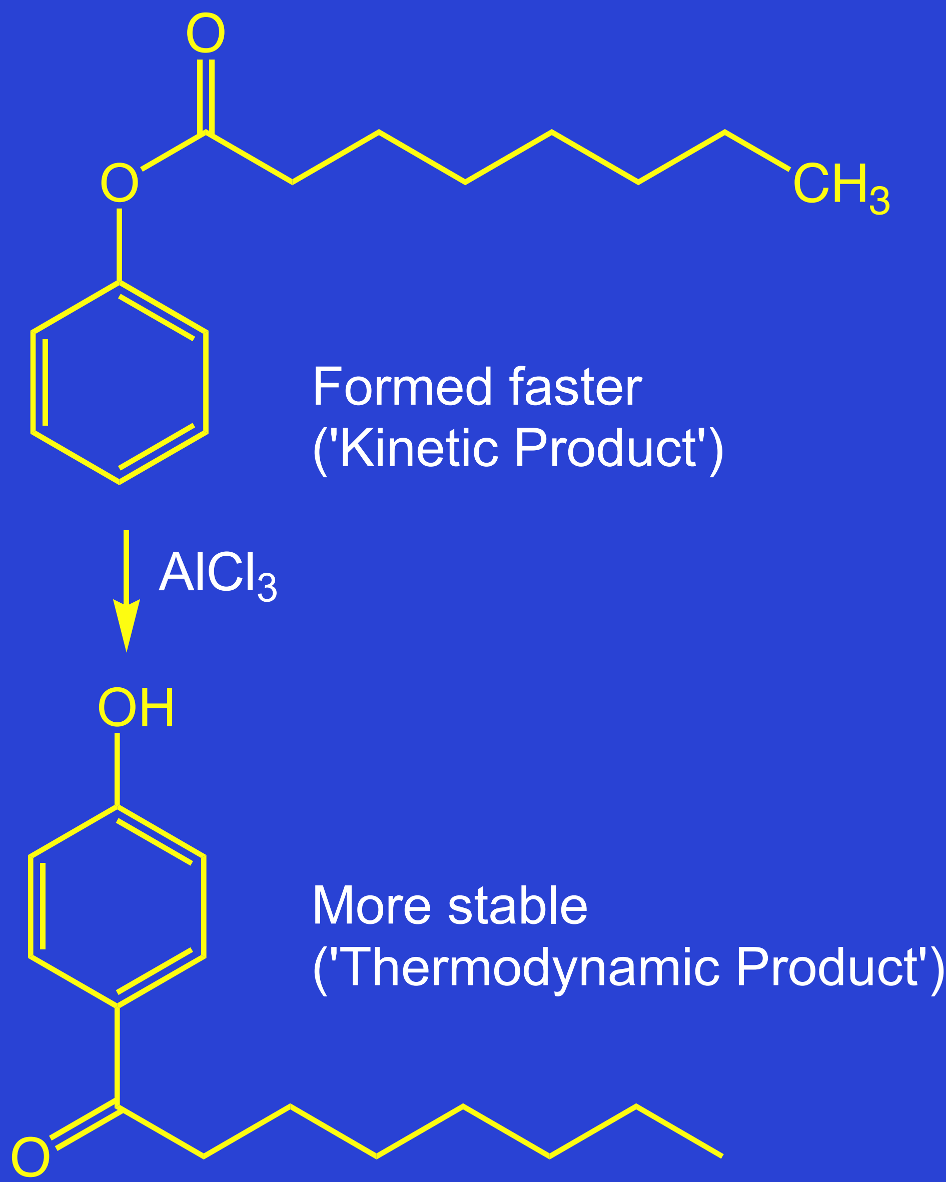


‘Unactivated’ Acylating Reagents Provide Aryl Esters via *O*-Acylation



in the absence of $AlCl_3$, acylation of the hydroxyl group occurs (O-acylation)

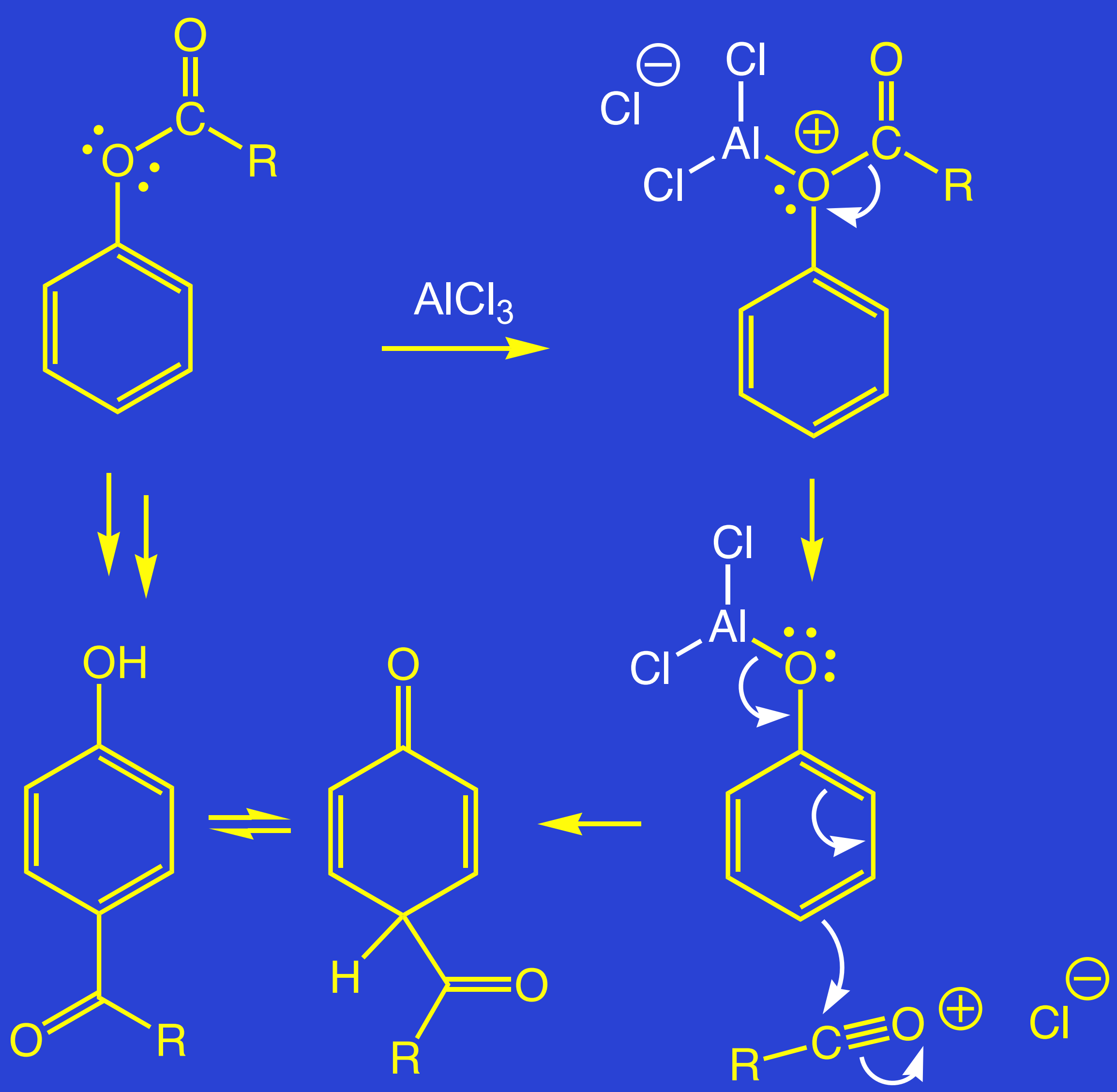
O-Acylation *vs.* *C*-Acylation



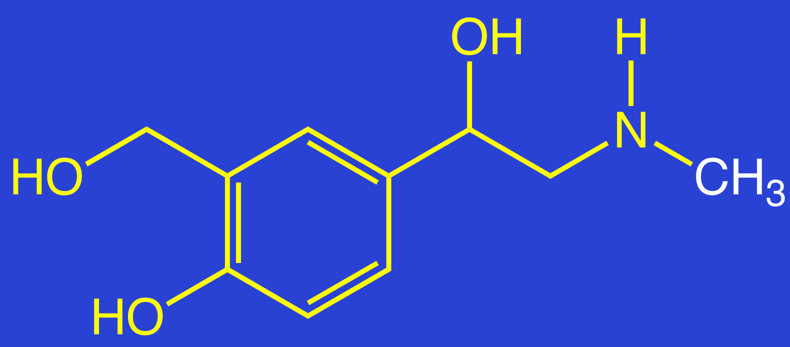
O-Acylation is kinetically controlled process; *C*-acylation is thermodynamically controlled

$AlCl_3$ catalyzes the conversion of the aryl ester to the aryl alkyl ketones; this is called

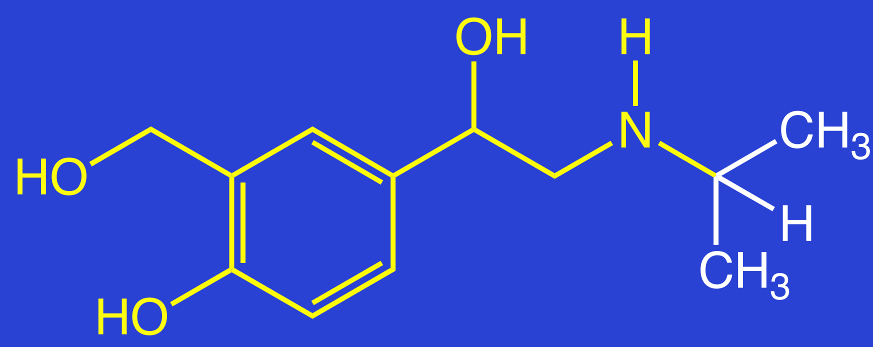
Mechanism of Fries Rearrangement



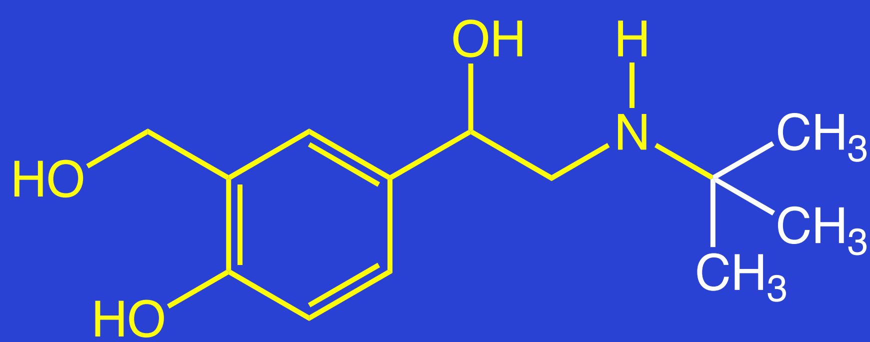
Albuterol Mimics Epinephrine
Alleviates the Symptoms of Asthma



Epinephrine

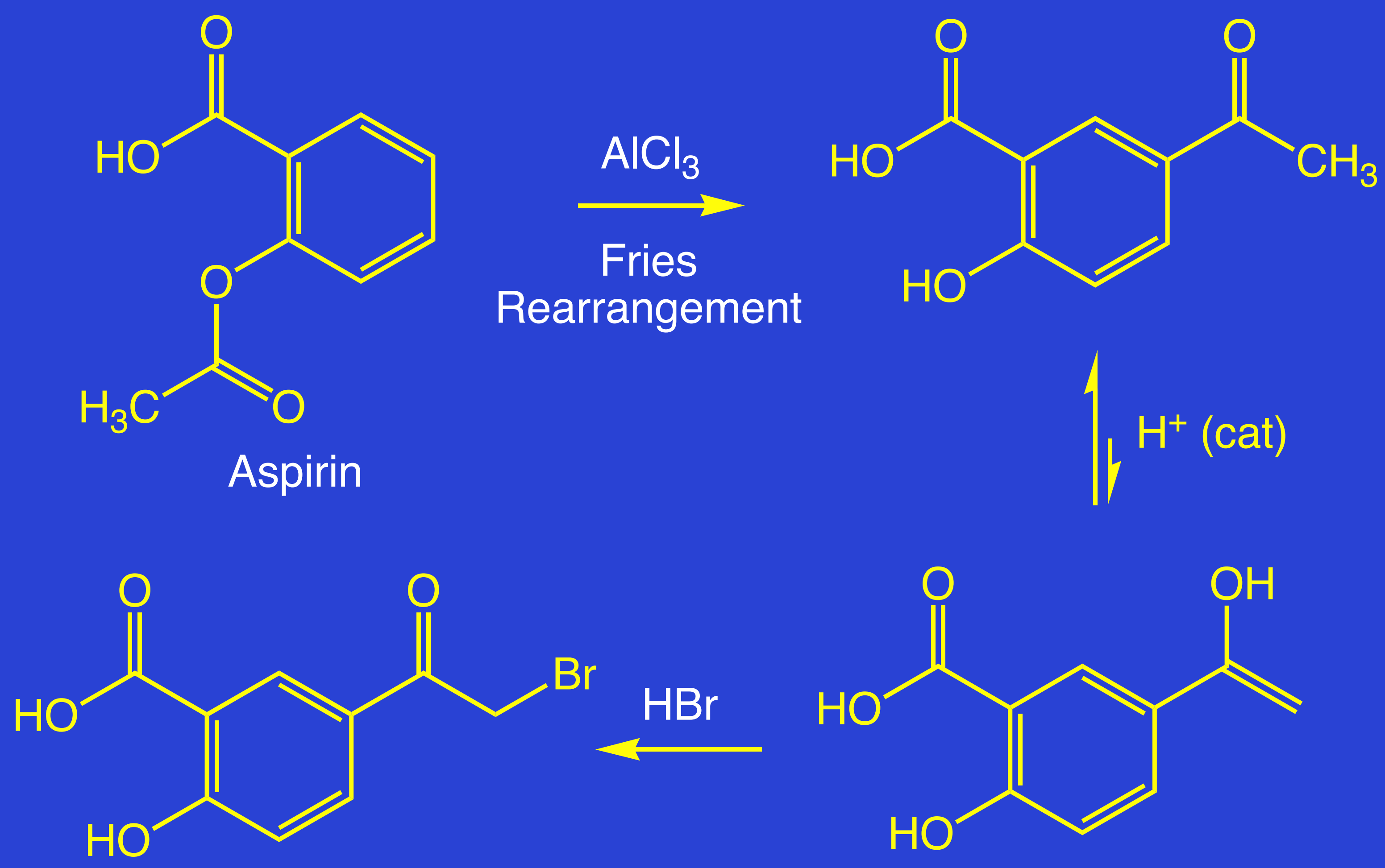


Isoproterenol

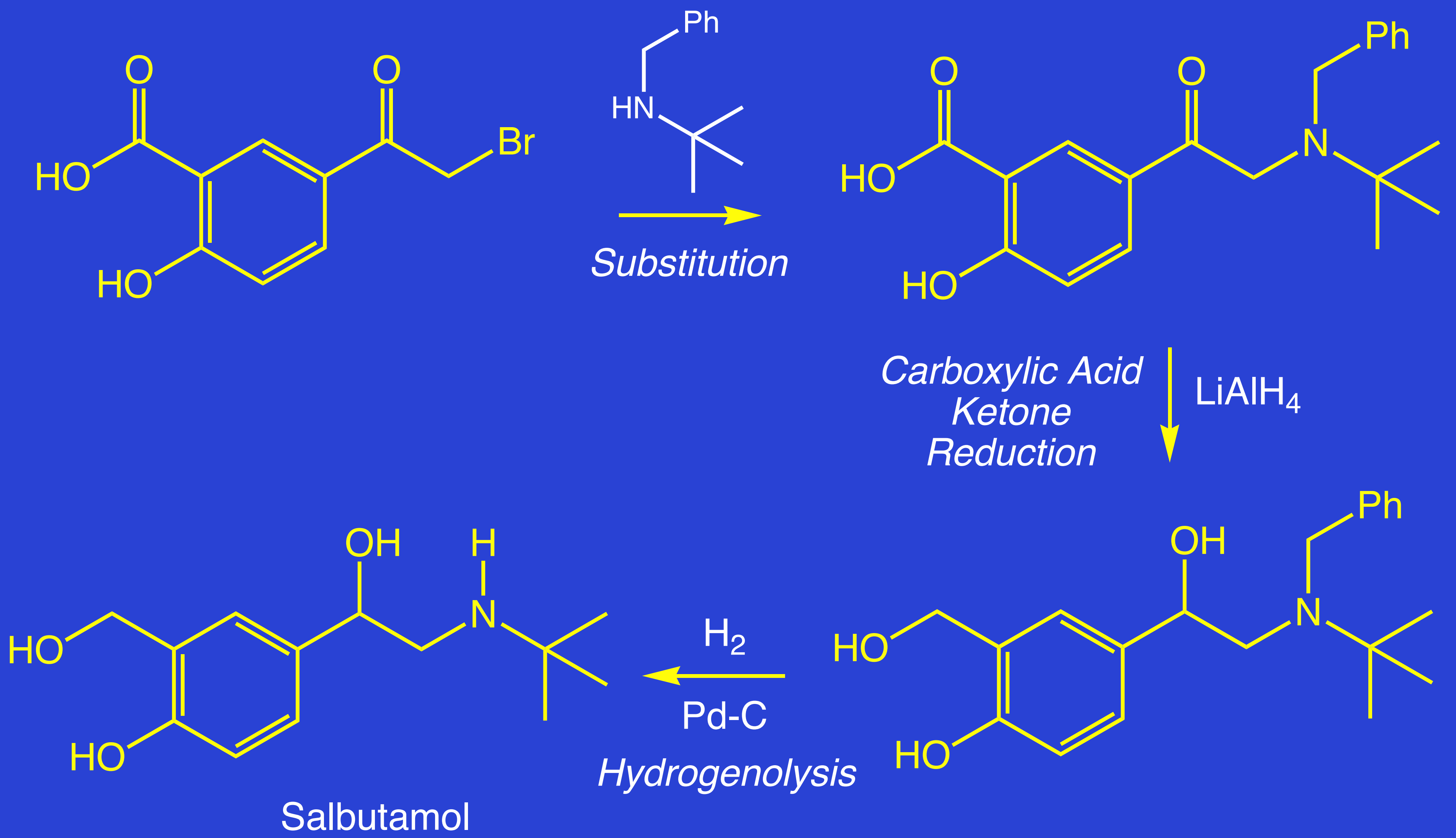


Salbutamol

Synthesis of Albuterol



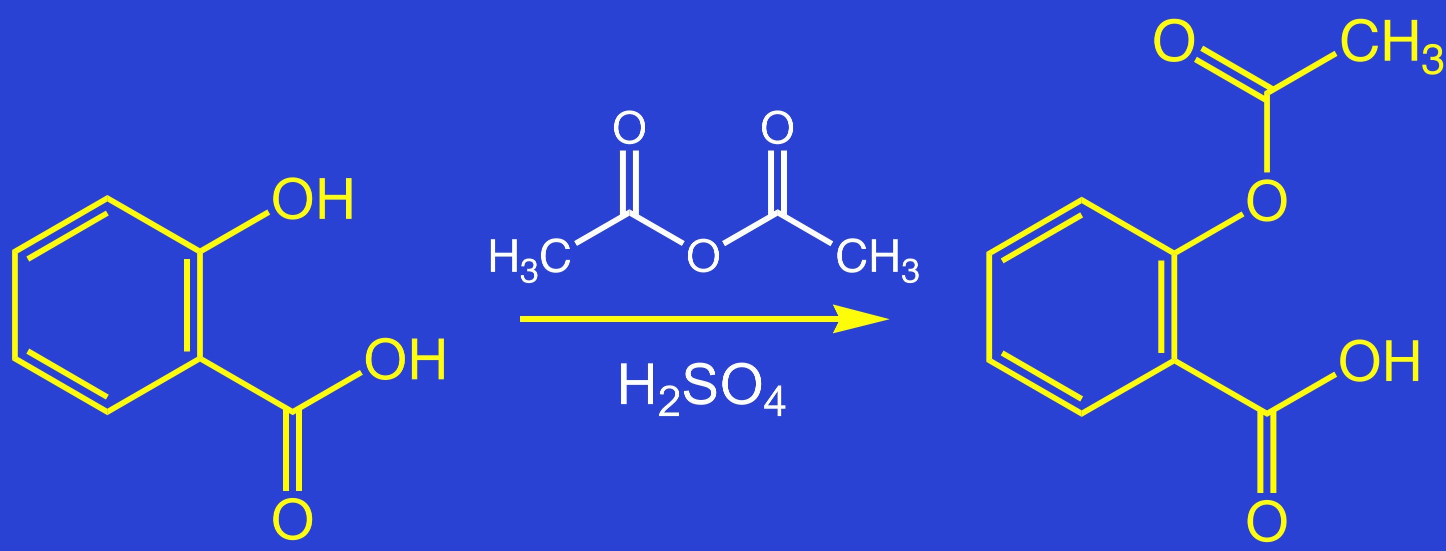
Synthesis of Albuterol



Difference Between Hydrogenation and Hydrogenolysis

24.10
Carboxylation of Phenols

Aspirin is Prepared Through *O*-Acylation of Salicylic Acid



Salicylic Acid

Aspirin

how is salicylic acid prepared?

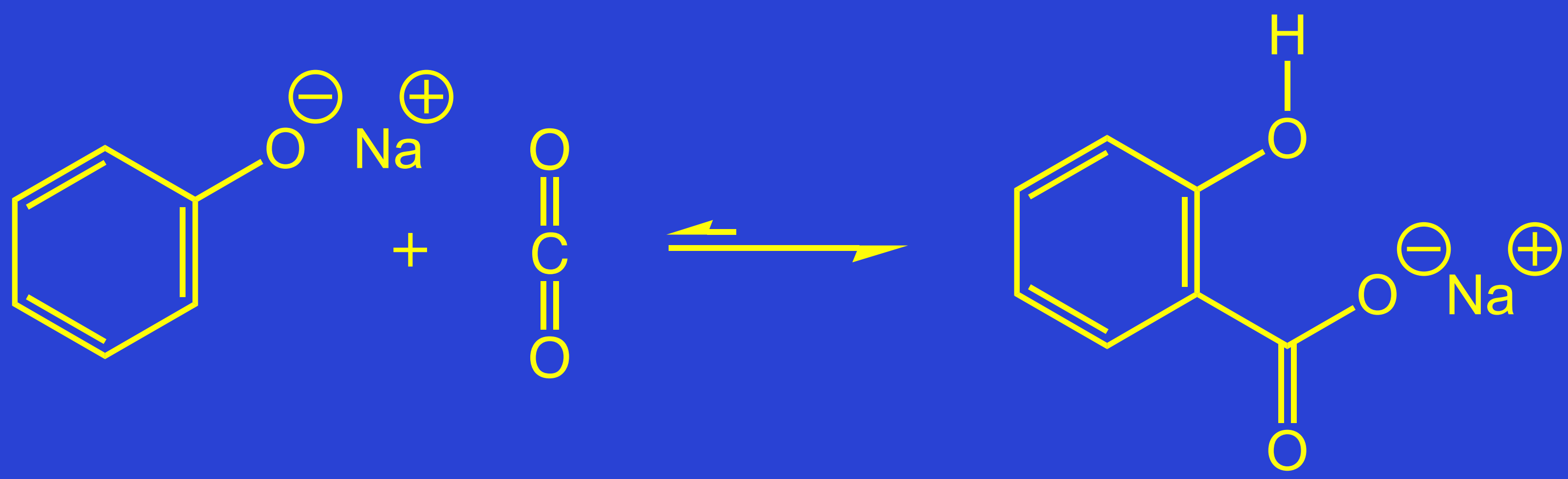
Aspirin & the Kolbe-Schmitt Reaction

this process is called the Kolbe-Schmitt reaction

acidification converts the sodium salt shown above to salicylic acid

Why is the Formation of the Salicylate Anion Thermodynamically Favored?

acid-base considerations provide an explanation:
stronger base on left; weaker base on right



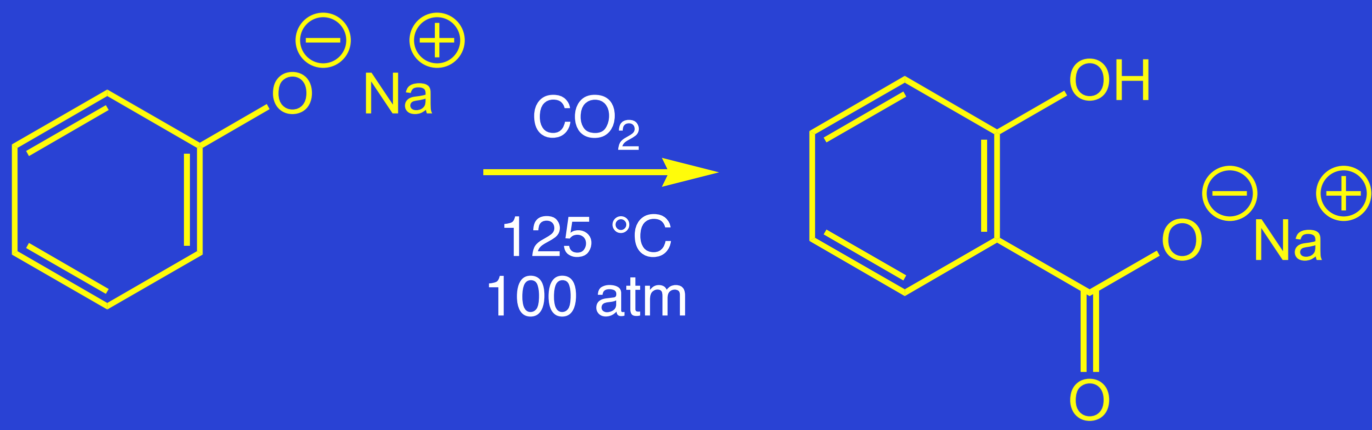
Sodium Phenoxide

Salicylate Anion

stronger base:
pK_a of conjugate acid = 10

weaker base:
pK_a of conjugate acid = 3

Industrial Synthesis of Salicylic Acid



how does carbon-carbon bond form?

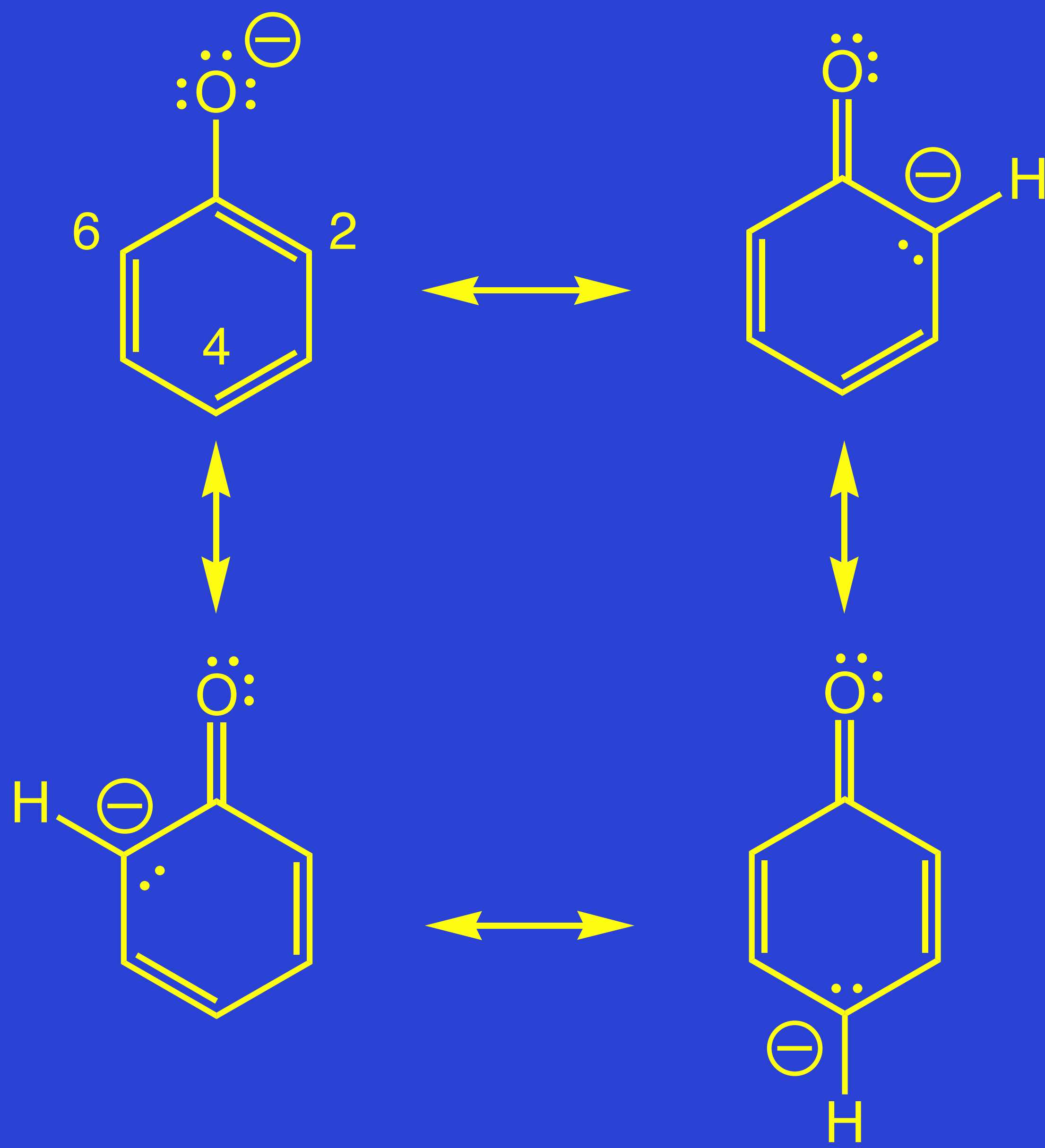
recall electron delocalization in phenoxide ion

negative charge shared by oxygen and by the ring carbons that are ortho and para to oxygen

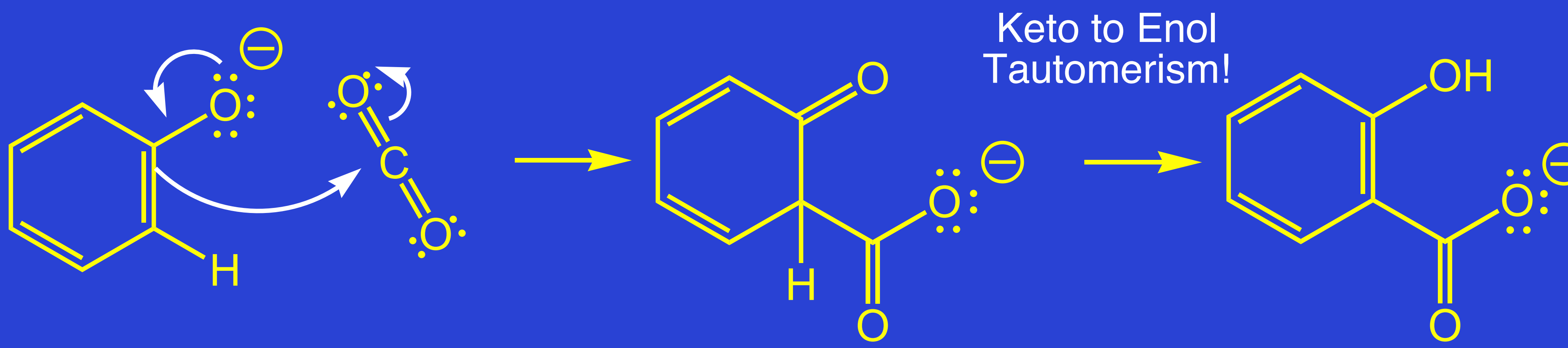
Mechanism of Kolbe-Schmitt Reaction

Note the high charge density at the C-2, C-4 and C-6 positions of the phenoxide anion

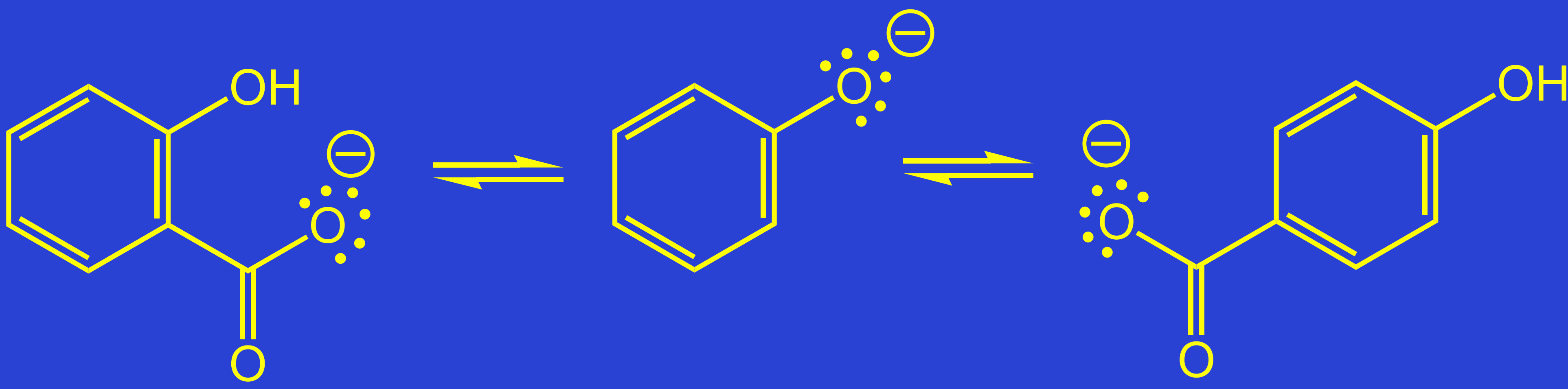
The alkoxide group is a strongly activating *ortho*, *para*-directing group



Mechanism of *Ortho* Carboxylation



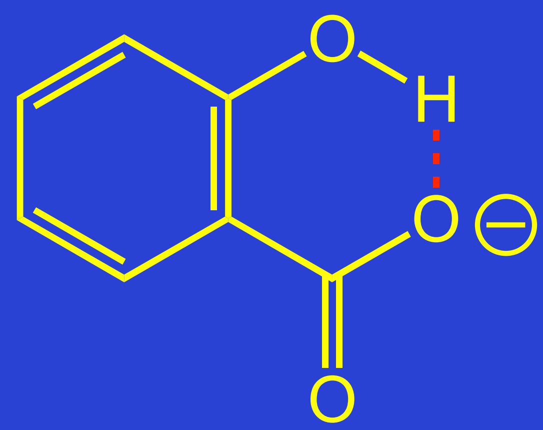
Why is *Ortho* Carboxylation Preferred? A Question of Regioselectivity



weaker base:
pK_a of conjugate acid = 3

stronger base:
pK_a of conjugate acid = 4.5

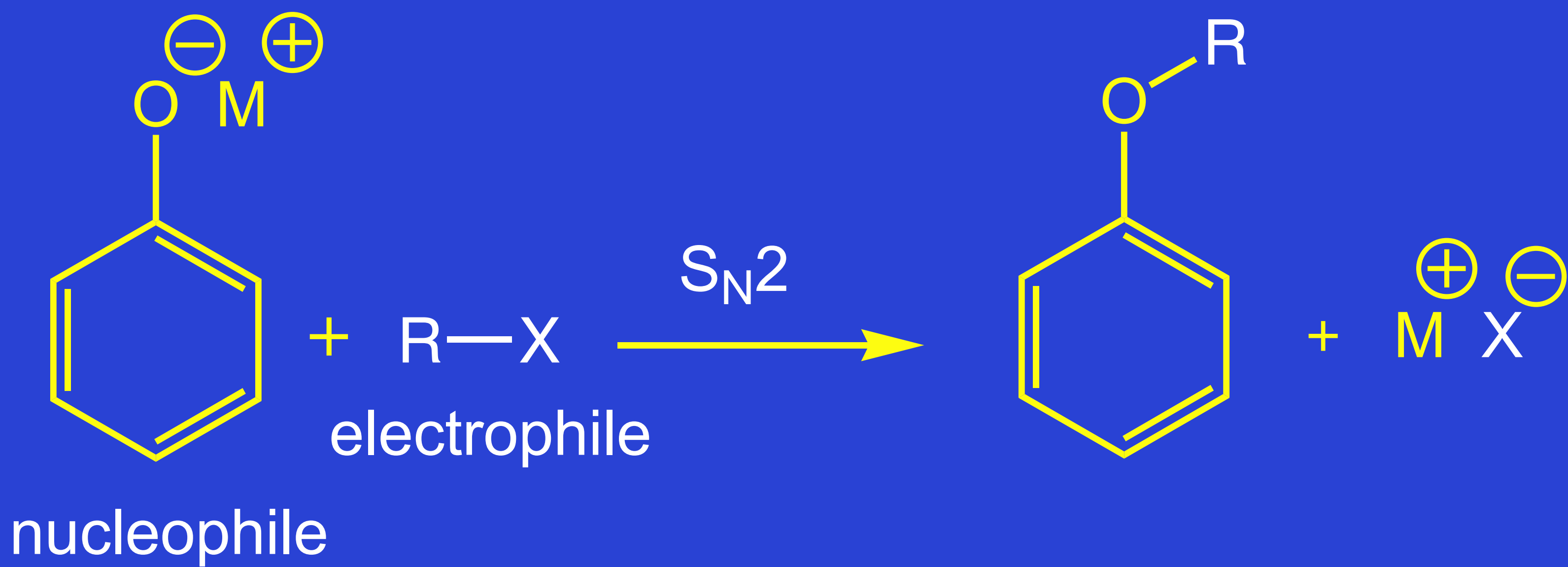
Intramolecular Hydrogen Bonding in Salicylate Ion



Hydrogen bonding between carboxylate and hydroxyl group stabilizes salicylate ion. Salicylate is less basic than *para* isomer and predominates under conditions of thermodynamic control.

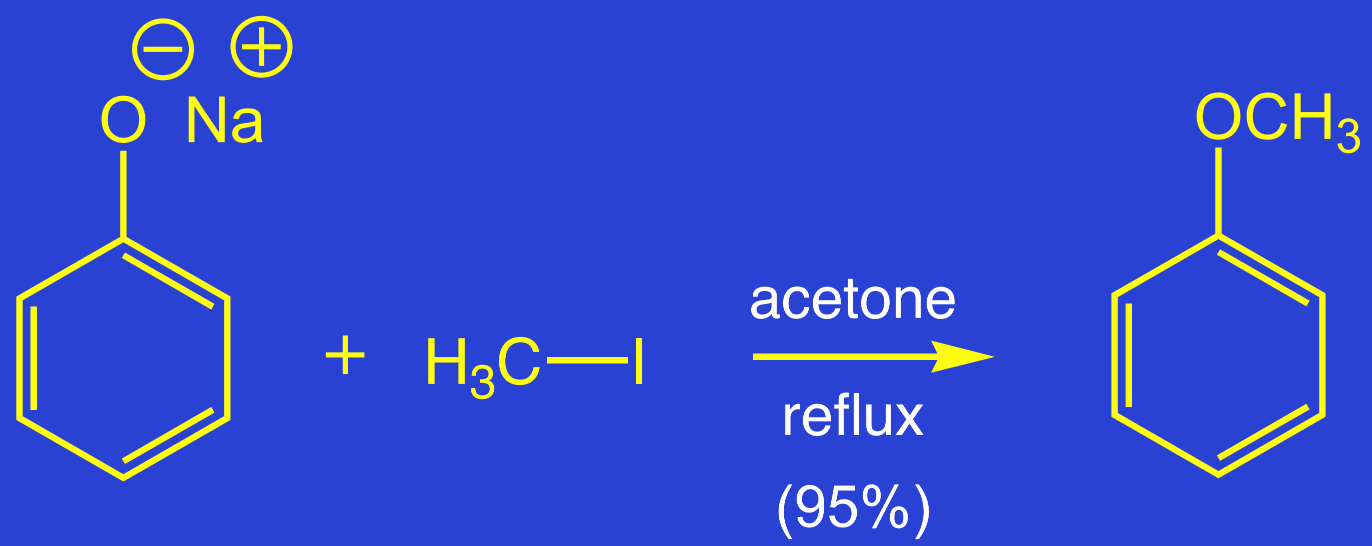
24.11
Preparation of Aryl Ethers

Preparation of Aryl Alkyl Ethers *O*-Alkylation of Phenols

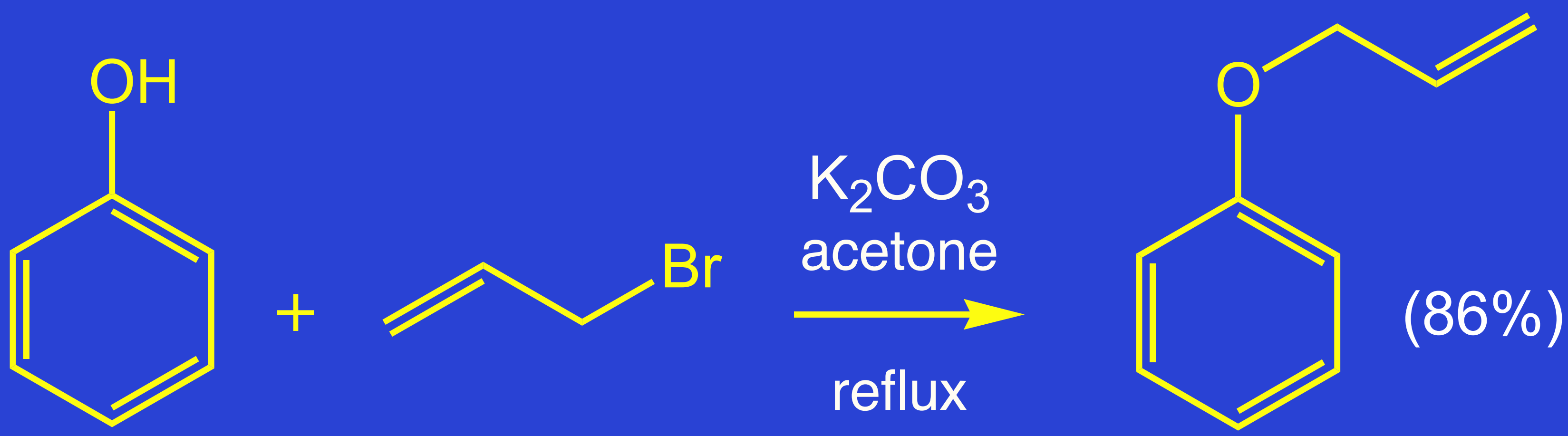


this reaction is an example of a Williamson ether synthesis

O-Alkylation of Phenols

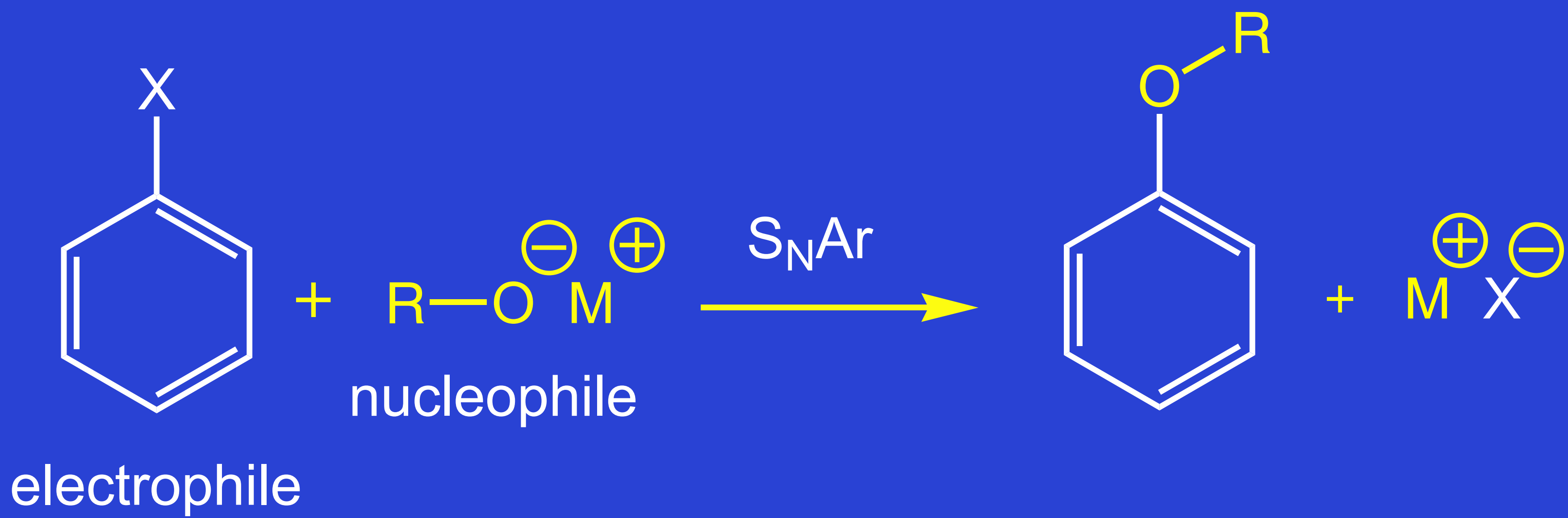


O-Alkylation of Phenols



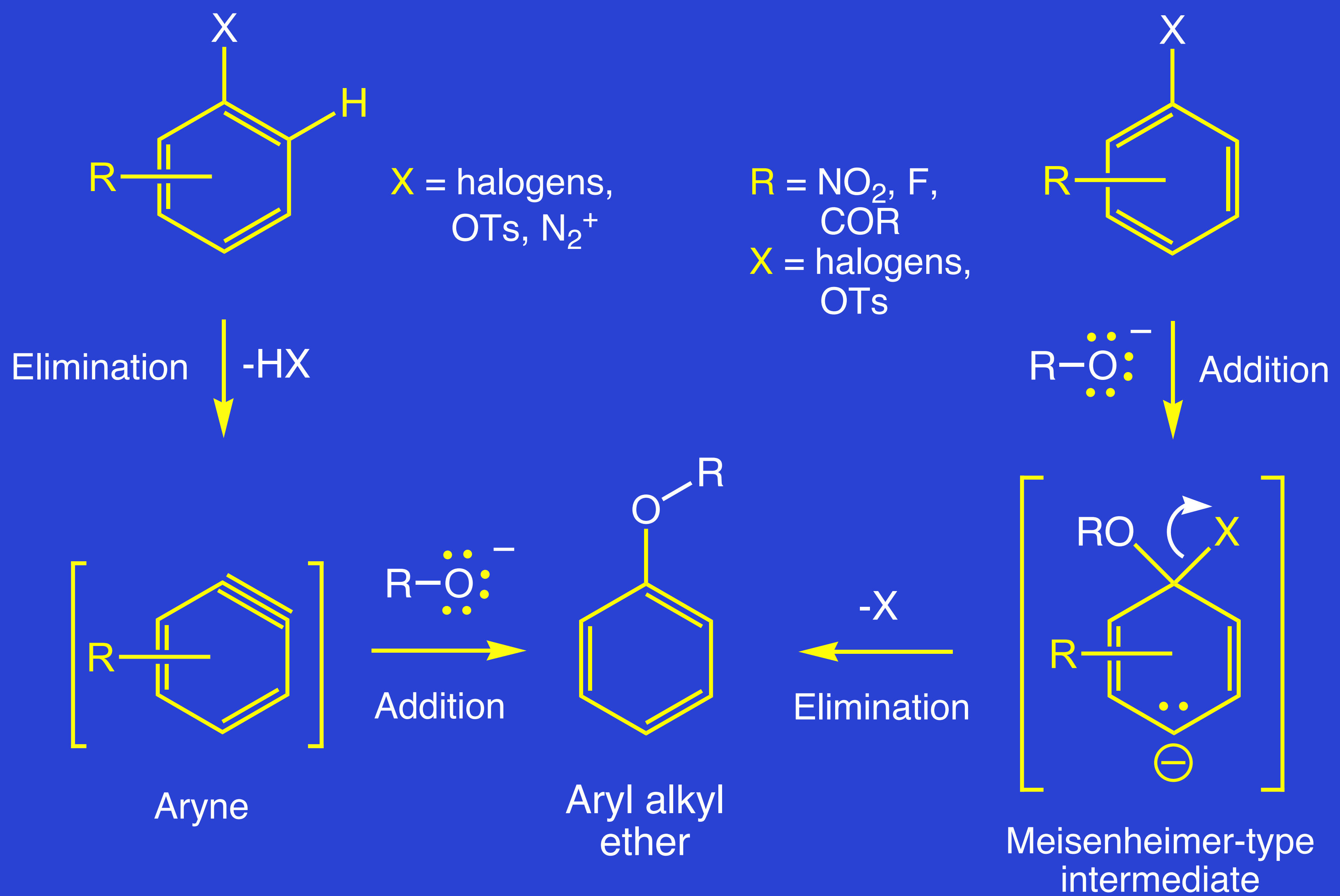
Potassium carbonate is sufficiently basic to deprotonate phenol

Preparation of Aryl Alkyl Ethers
Nucleophilic Aromatic Substitution (S_NAr)

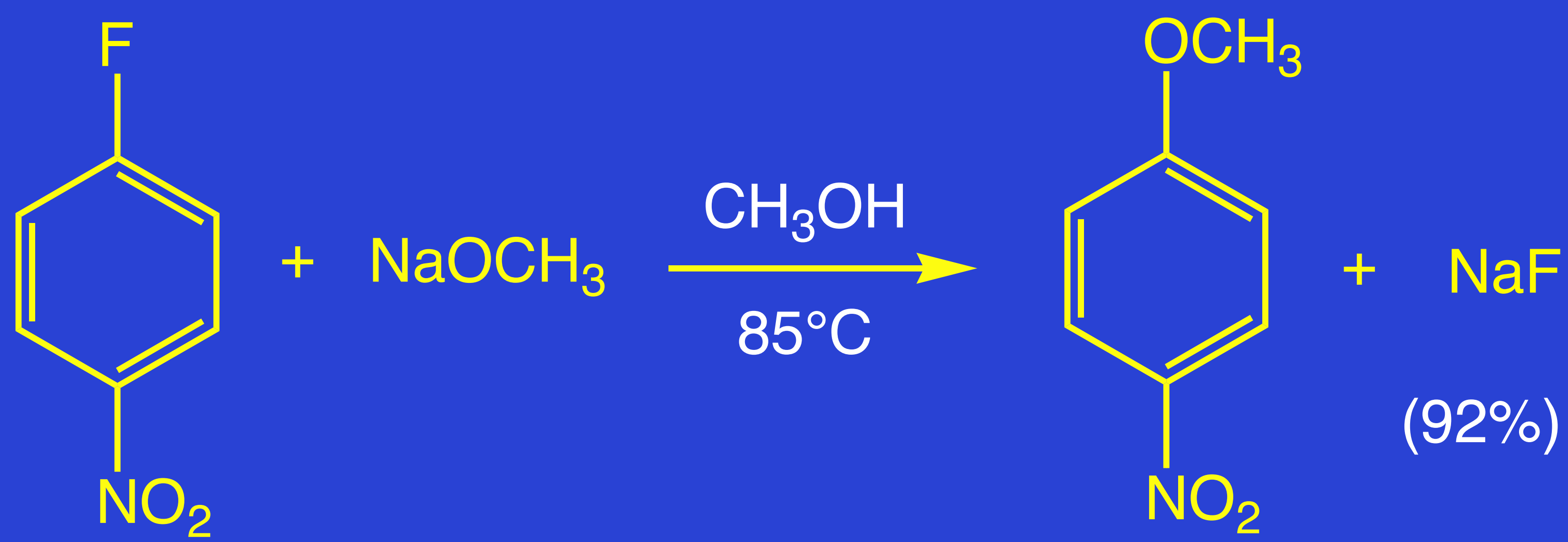


This type of reaction is considerable more demanding than *O*-alkylation. Nonetheless, for certain aromatic substrates, this can be a useful strategy

Two Viable Pathways to Achieve Nucleophilic Aromatic Substitution (S_NAr)

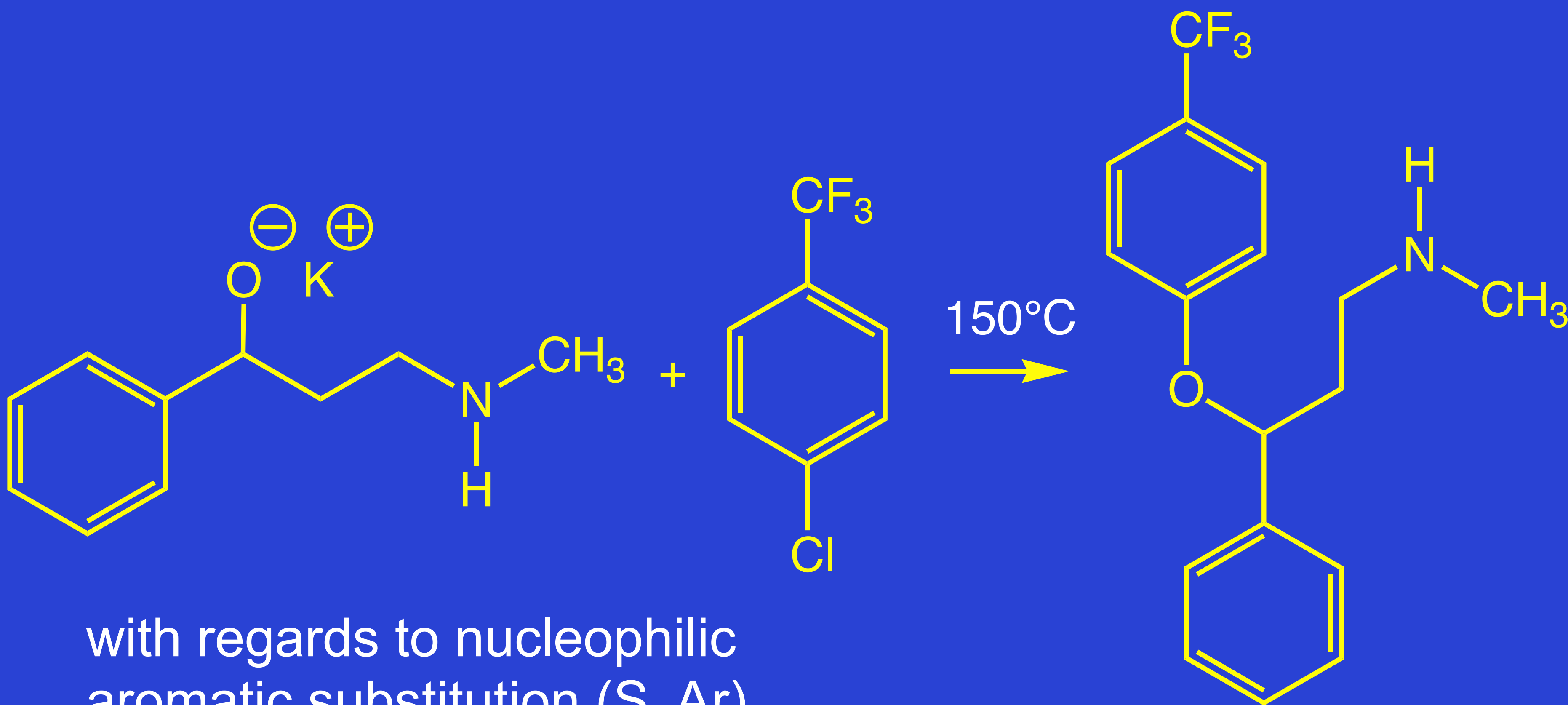


Preparation of Aryl Alkyl Ethers Addition-Elimination Substitution



nucleophilic aromatic substitution is effective with nitro-substituted (ortho and/or para) aryl halides

Preparation of Aryl Alkyl Ethers Addition-Elimination Substitution

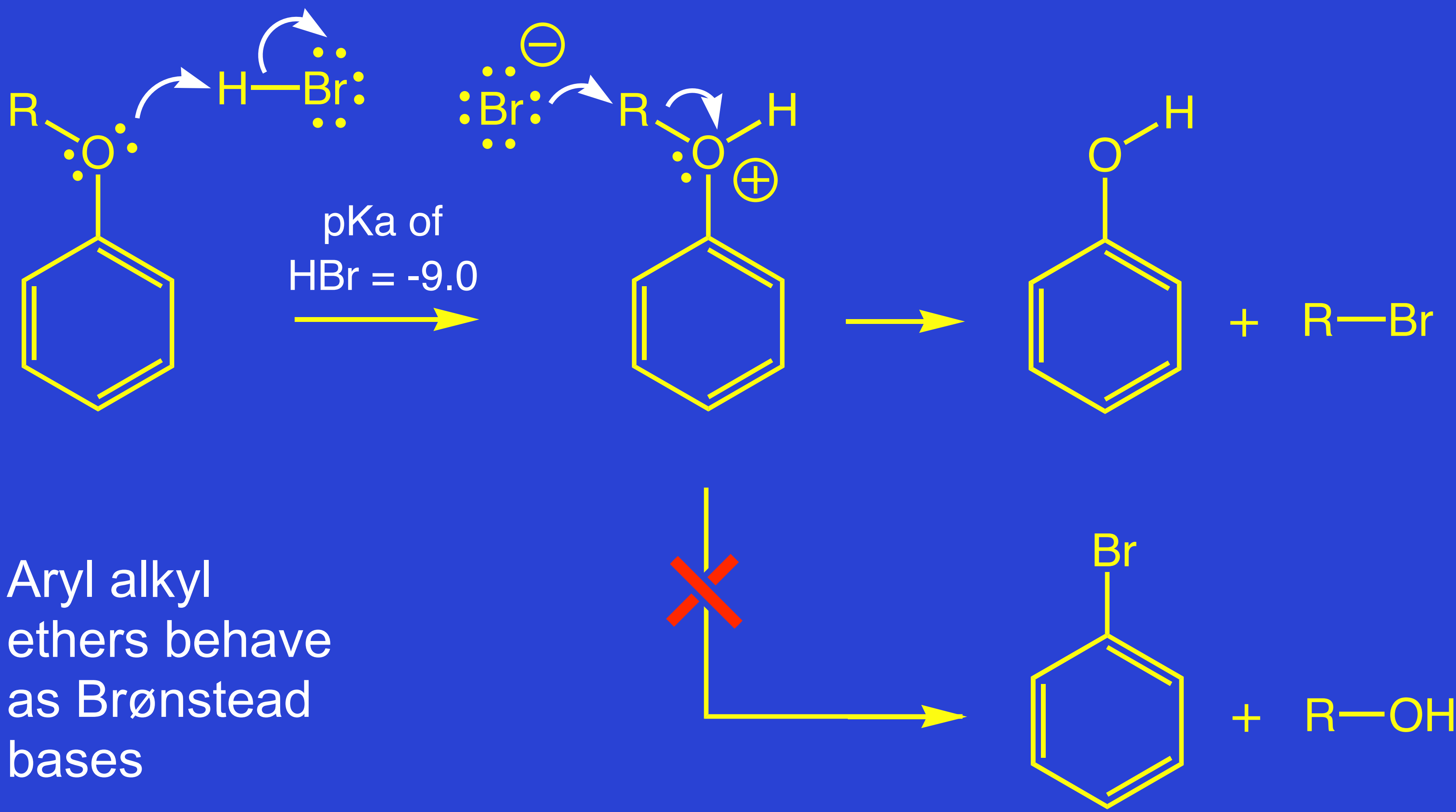


with regards to nucleophilic aromatic substitution (S_NAr), trifluoromethyl groups function like the nitro groups

Fluoxetine (Prozac)

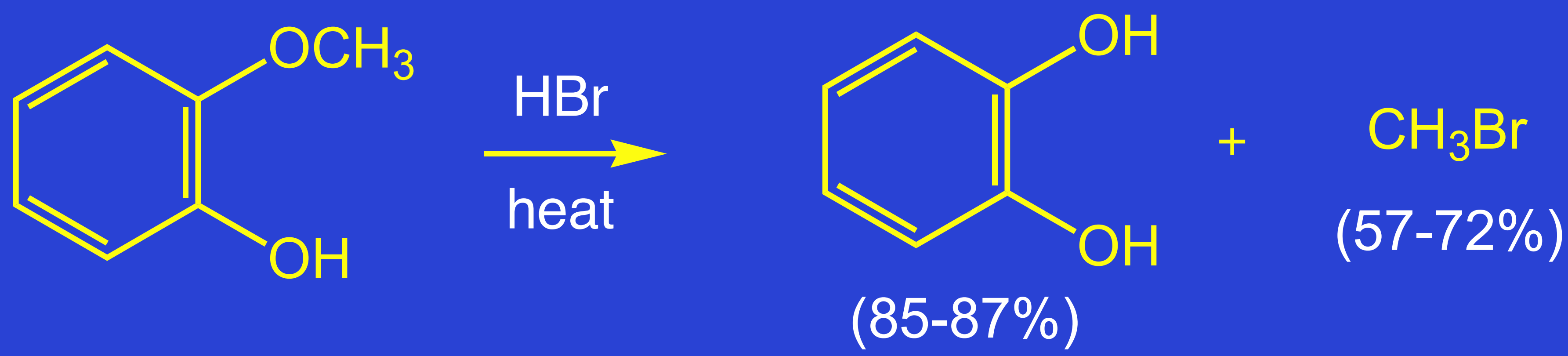
24.12
Cleavage of Aryl Ethers by Hydrogen Halides

Deprotection of Aryl Alkyl Ethers



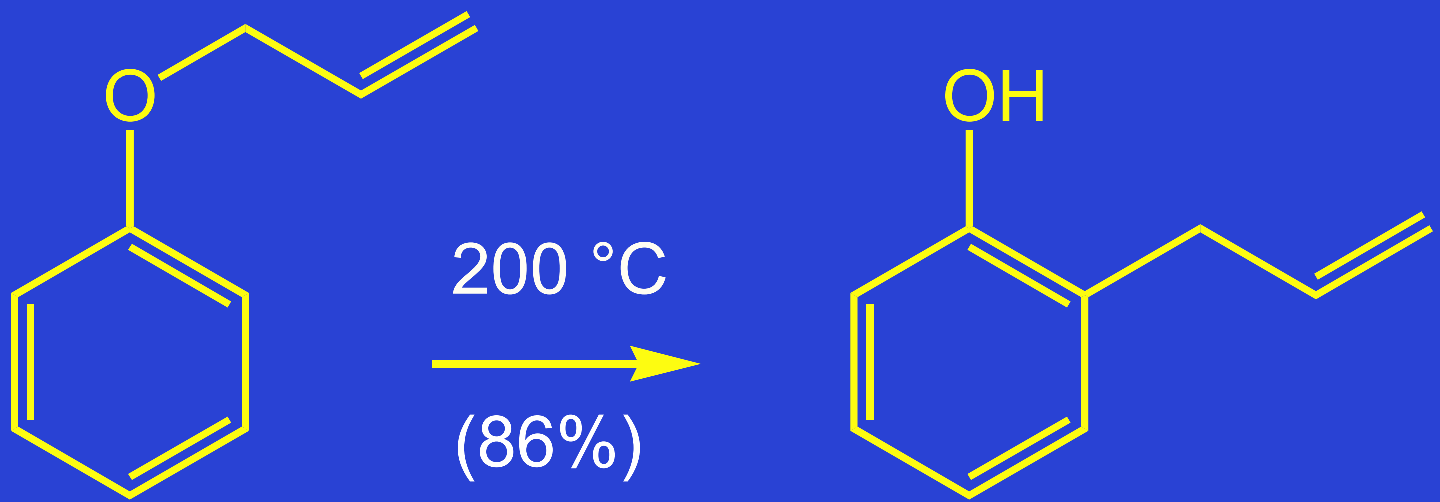
Aryl alkyl ethers behave as Brønstead bases

Cleavage of Aryl Methyl Ethers

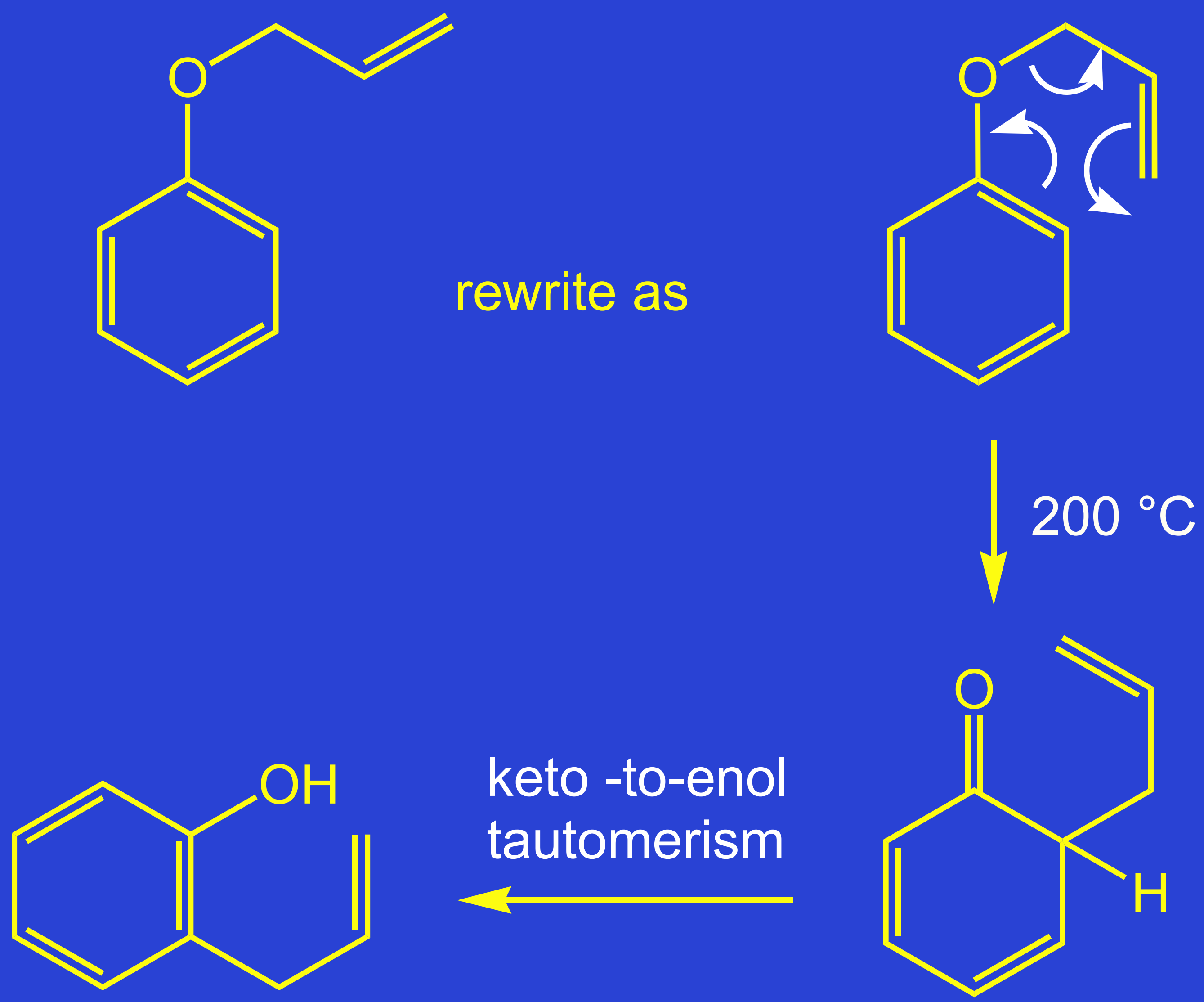


24.13
Claisen Rearrangement of Allyl Aryl Ethers

Claisen Rearrangement of Aryl Allyl Ethers



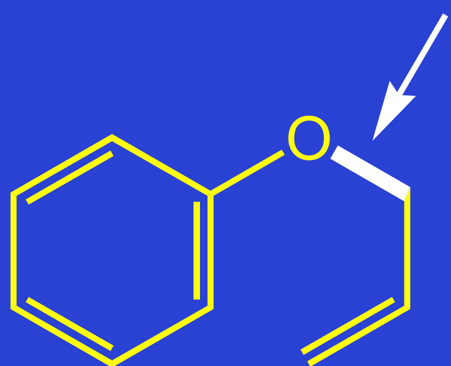
Mechanism of Claisen Rearrangement

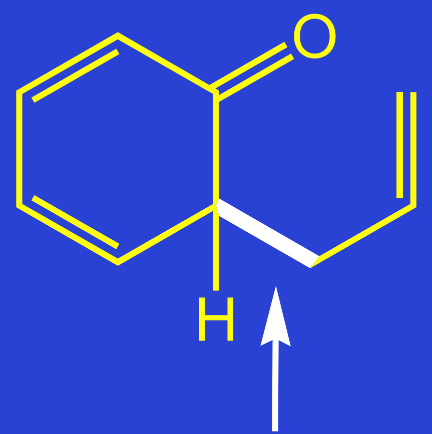


Sigmatropic Rearrangement

The Claisen rearrangement is an example of a sigmatropic rearrangement. A sigma (σ) bond migrates from one end of a conjugated π electron system to the other.

this α bond breaks during reaction





“conjugated π electron system” is the allyl group

this α bond forms during reaction

Pericyclic Reactions Defined

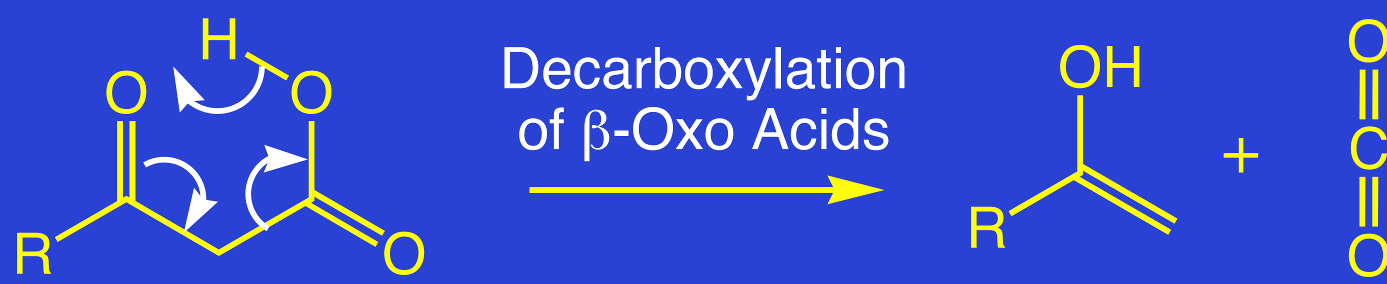
pericyclic reaction

a *chemical reaction* in which *concerted* reorganization of bonding takes place throughout a cyclic array of continuously bonded atoms. It may be viewed as a reaction proceeding through a fully *conjugated* cyclic transition state. The number of atoms in the cyclic array is usually six, but other numbers are also possible.

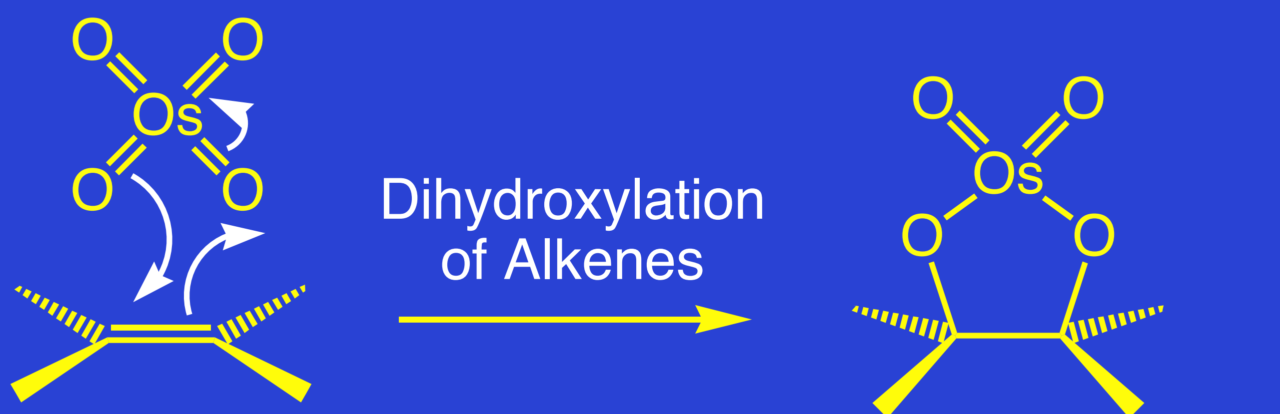
Other Pericyclic Reactions in Chem 234

[4+2]
Cycloaddition

Retro-Ene
Reaction

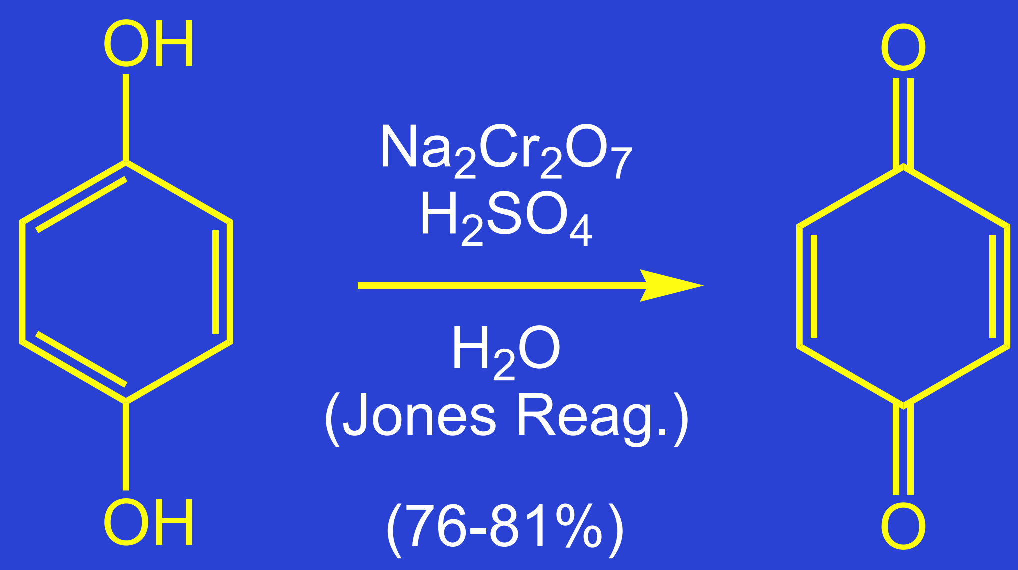


[2+3]
Cycloaddition



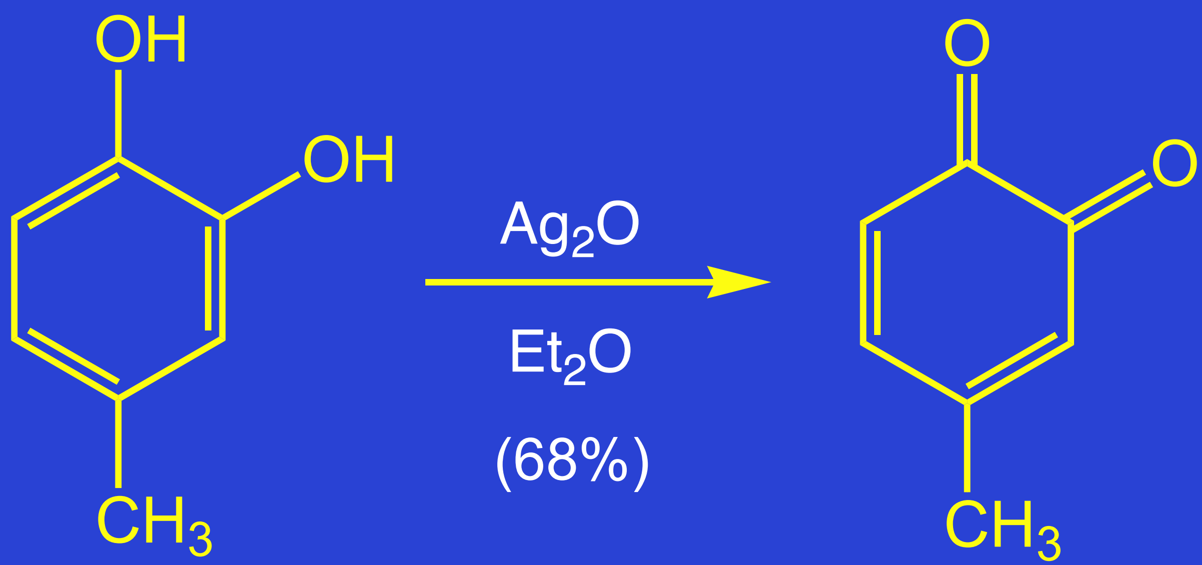
24.14
Oxidation of Phenols: Quinones

Hydroquinones are Oxidized to Quinones

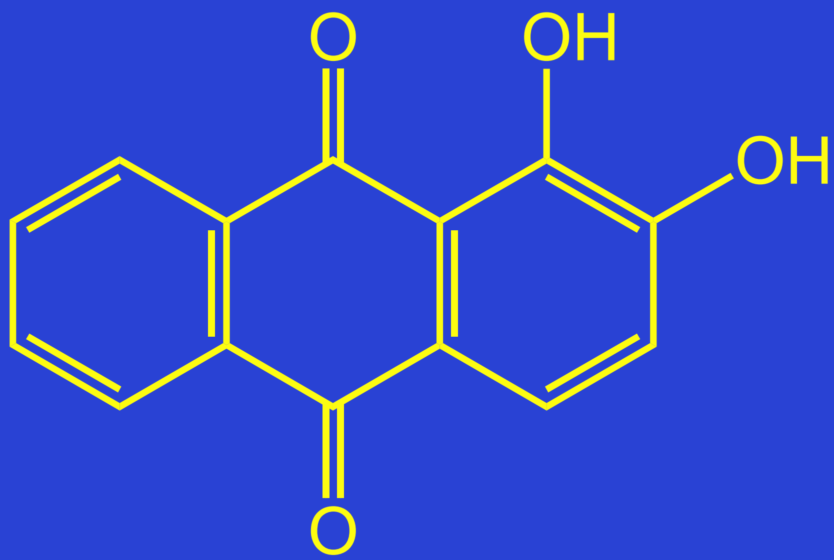


The most common examples of phenol oxidations are the oxidations of 1,2- and 1,4-benzenediols to give quinones.

Catechols are Oxidized to Orthoquinones

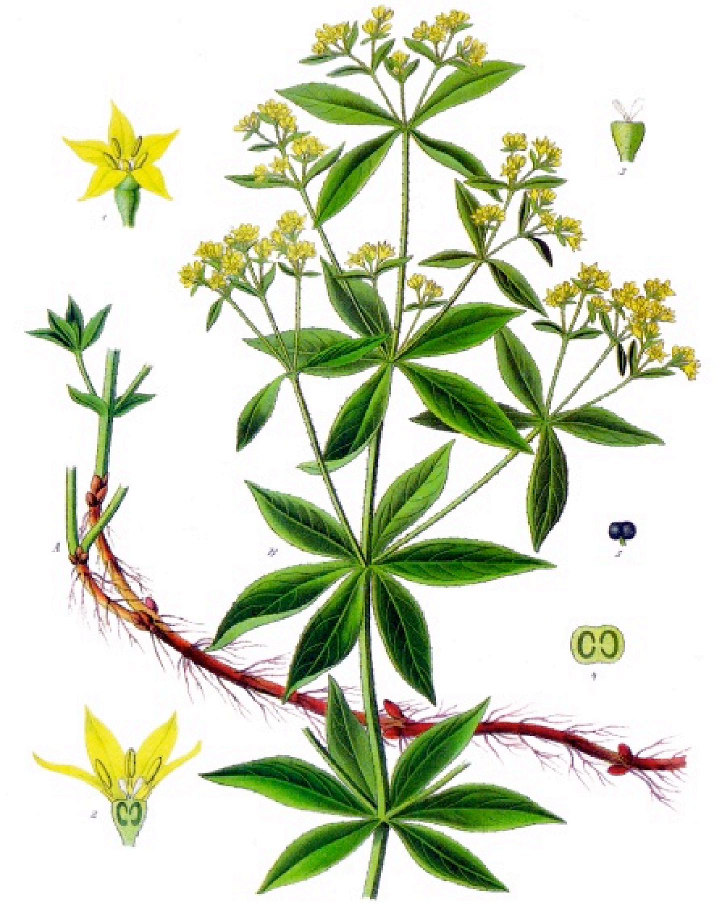


Many Quinones are Highly Colored



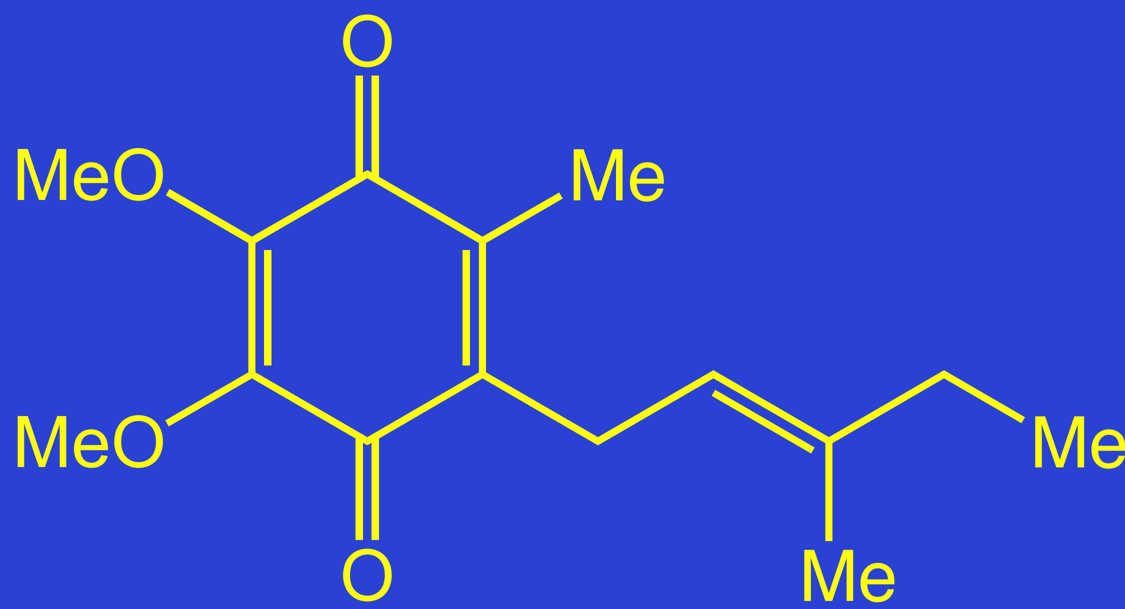
Alizarin

is a red dye originally obtained from the root of the common madder plant, *Rubia tinctorum*. Use of this dye in India predates the 10th century.



Rubia tinctorum

Biologically Important Quinones



Ubiquinone (Coenzyme Q)

n = 6-10

involved in biological electron transport

Biologically Important Quinones

Vitamin K
(blood-clotting factor)

Today's Lecture

Topics Covered:

1. Phenols - Bonding, Physical Properties and Reactions
2. Electrophilic Aromatic Substitution: Halogen, Nitration, Nitrosation
3. O- and C-Acylation of Phenols: Fries Rearrangement
4. Kolbe-Schmitt Reaction: Carboxylation of Phenols
5. Preparation and Cleavage of Aryl Alkyl Ethers

Information & Suggested Problems

Suggested Problems: 24.11-24.26