Objective 8. Understand electrophilic aromatic substitution reactions (EAS) of di- and polysubstituted aromatics.

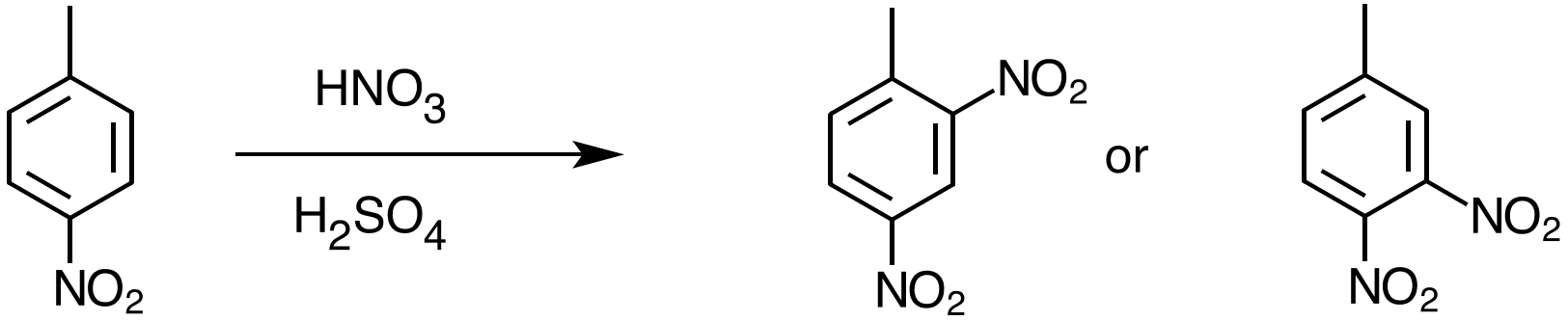
Skills: Draw structure
ID structural features and reactive sites (alpha C, beta C, LG, etc.)
ID Nu^- and E^+
use curved arrows to show bonds breaking and forming
show delocalized electrons with resonance structures.

Key ideas:
Some groups activate ring, others deactivate ring.

Draw resonance structures of carbocation intermediate to ID most stable to determine product.

EAS to Functionalize Benzene

Objective: predict EAS product of disubstituted benzene



A B

If 2 or more groups on benzene, which group directs the substitution?

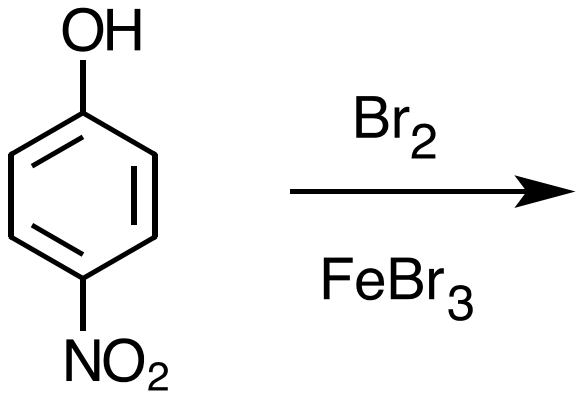
A. most activating

B. most deactivating

EAS to Functionalize Benzene

The ***more activating*** group directs the position of substitution

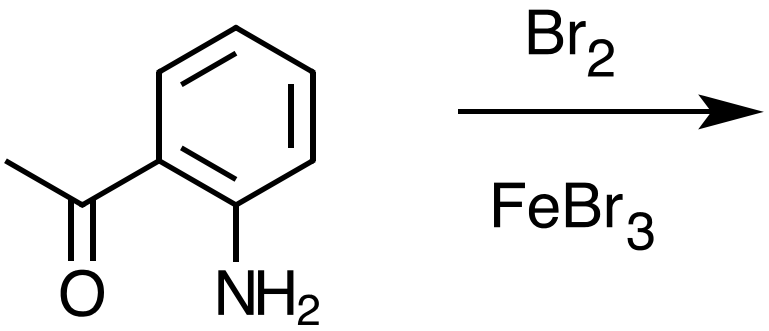
For each reaction, ID the group that directs EAS. Then, predict the product.



EAS to Functionalize Benzene

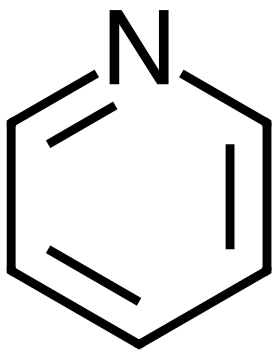
The ***more activating*** group directs the position of substitution

For each reaction, ID the group that directs EAS. Then, predict the product.



EAS to Functionalize Aromatics

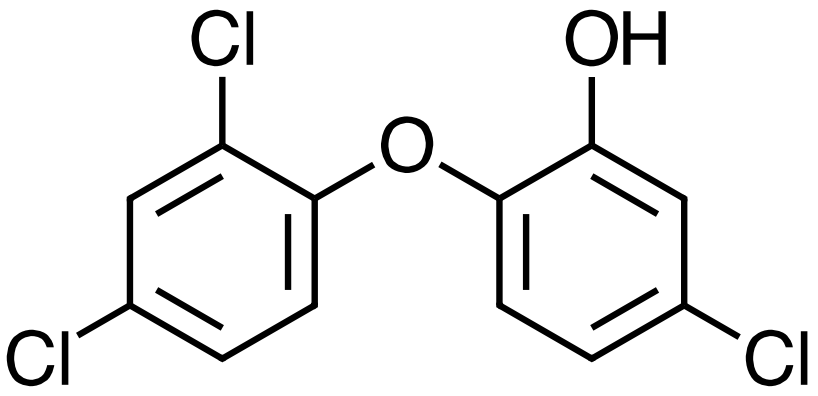
Pellagra is a disease caused by a deficiency of niacin ($C_6H_5NO_2$) in the diet. Niacin can be synthesized in the lab by the side chain oxidation of 3-methylpyridine with chromic acid or potassium permanganate. Suggest a reasonable structure for niacin.



Pyridine
(note: it stinks)

See Practice Problems

What is Triclosan used for?



At which ring will EAS occur in Triclosan?

Biology Reaction or Industrial Reaction Application

Work in a Group of 2 to 4

Apply 2 or more Course Objectives (except Objective 16) to a Biology or Industrial Reaction.
This means a Chem 12A or 12B reaction.
Show reaction, conditions, and mechanism.

Proposal due 4/7/17 (include group names)

5 minute presentation on 5/1/17

Biology Reaction or Industrial Reaction Application

Biology Examples:

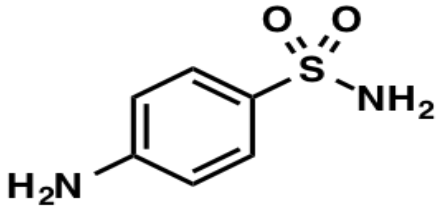
- Glucuronidation Metabolism
- Benzo(a)pyrene Metabolism
- Squalene → cholesterol
- Tylenol toxicity in liver (pharm chem)
- Antibiotic mechanism, e.g., beta-lactams

Industry Examples:

- phenol → BPA → polycarbonate
- phenol → BPA → epoxy resins
- nylon synthesis
- vanillan synthesis
- Drug synthesis, e.g., Ibuprofen

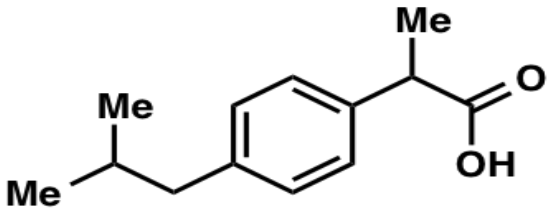
Organic Synthesis sites: http://www.synarchive.com/
http://www.orgsyn.org/

From LearnBacon.com: Friedel-Crafts reactions are used in chemical biology, polymer chemistry, and pharmaceutical synthesis, e.g., sulfanilamide, ibuprofen, and diazepam.



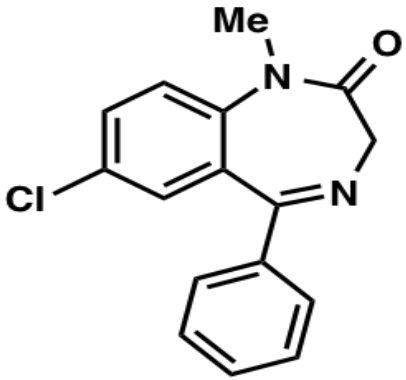
sulfanilamide

antibiotic



ibuprofen

treatment of pain & inflammation

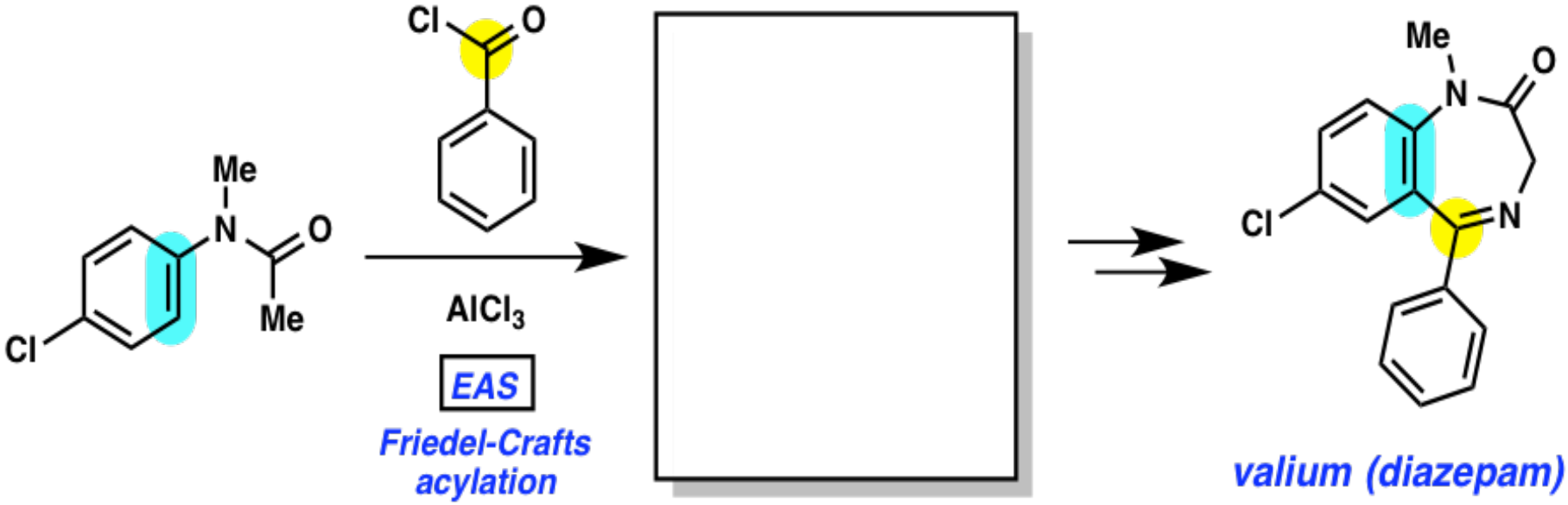


diazepam

treatment of anxiety

From LearnBacon.com: diazepam (Valium) binds to GABA type A receptor, which controls chloride ion channels in brain – causes influx of chloride ions to enter brain, which results in fewer neurons being fired.

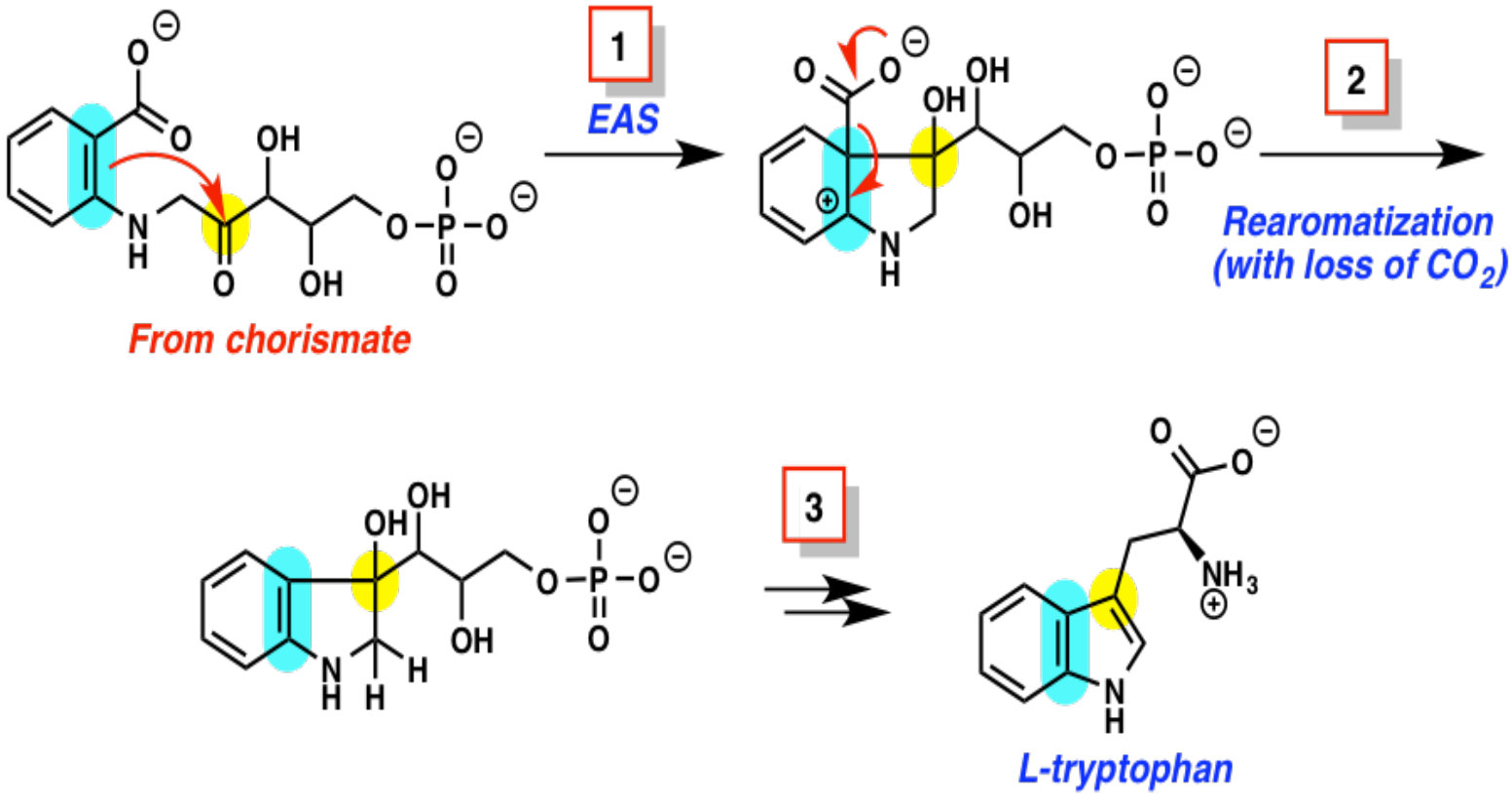
biosynthesis of diazepam



Which group directs EAS?
Draw structure of intermediate.

Think of Thanksgiving!

From LearnBacon.com: biosynthesis of L-tryptophan

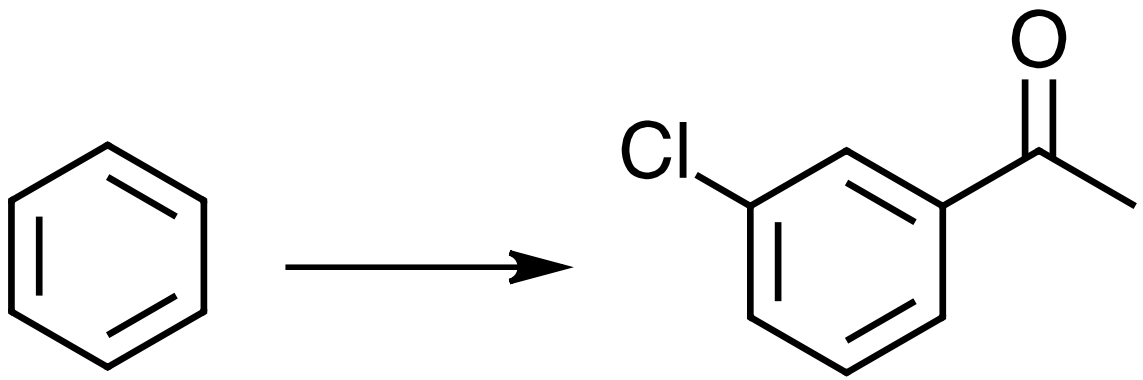


Which group directs EAS?

Is carbonyl Carbon a good E^+?

Objective: Use EAS to Functionalize Benzene in Synthesis

The order in which substituents are introduced onto a benzene ring requires **planning** due to o, p or m directing effects.



Which method works for this synthesis?

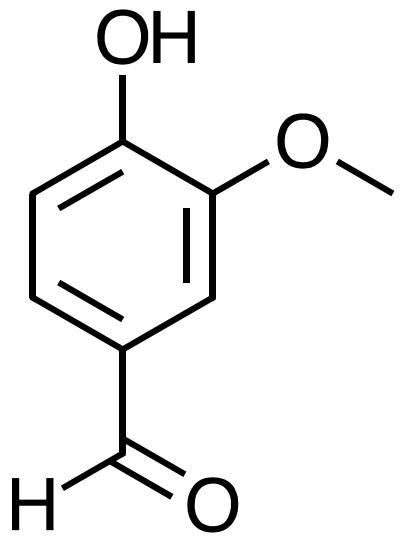
A: 1. Friedel-Crafts acylation, 2. Chlorination

B: 1. Chlorination, 2. Friedel-Crafts alkylation, 3. NBS, 4. OH^-, 5. Oxidation

C: 1. Chlorination, 2. Friedel-Crafts acylation

Objective: Propose a synthesis.

Starting from benzene, in what order would you perform EAS to synthesize vanillan?



vanillan

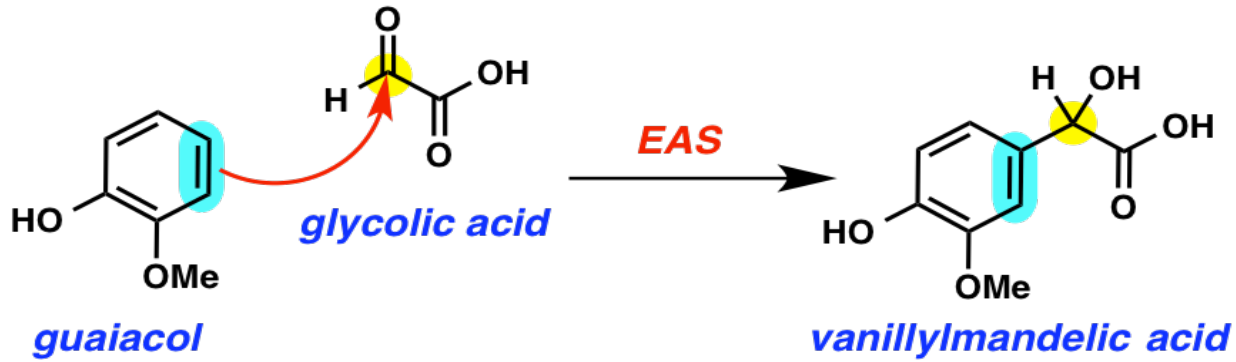
a. –OH, -OR, -CHO

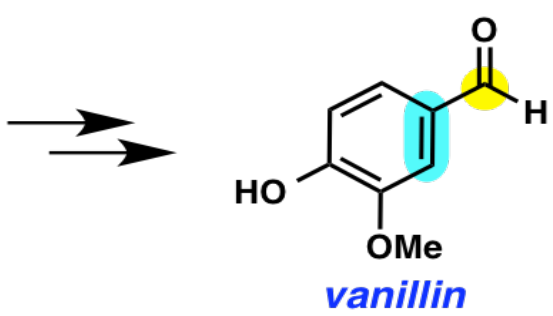
b. –OR, -OH, -CHO

c. –CHO, -OR, -OH

We will learn how to substitute –OH on benzene later.

From LearnBacon.com: Guaiacol is present in wood smoke, resulting from the pyrolysis of lignin.



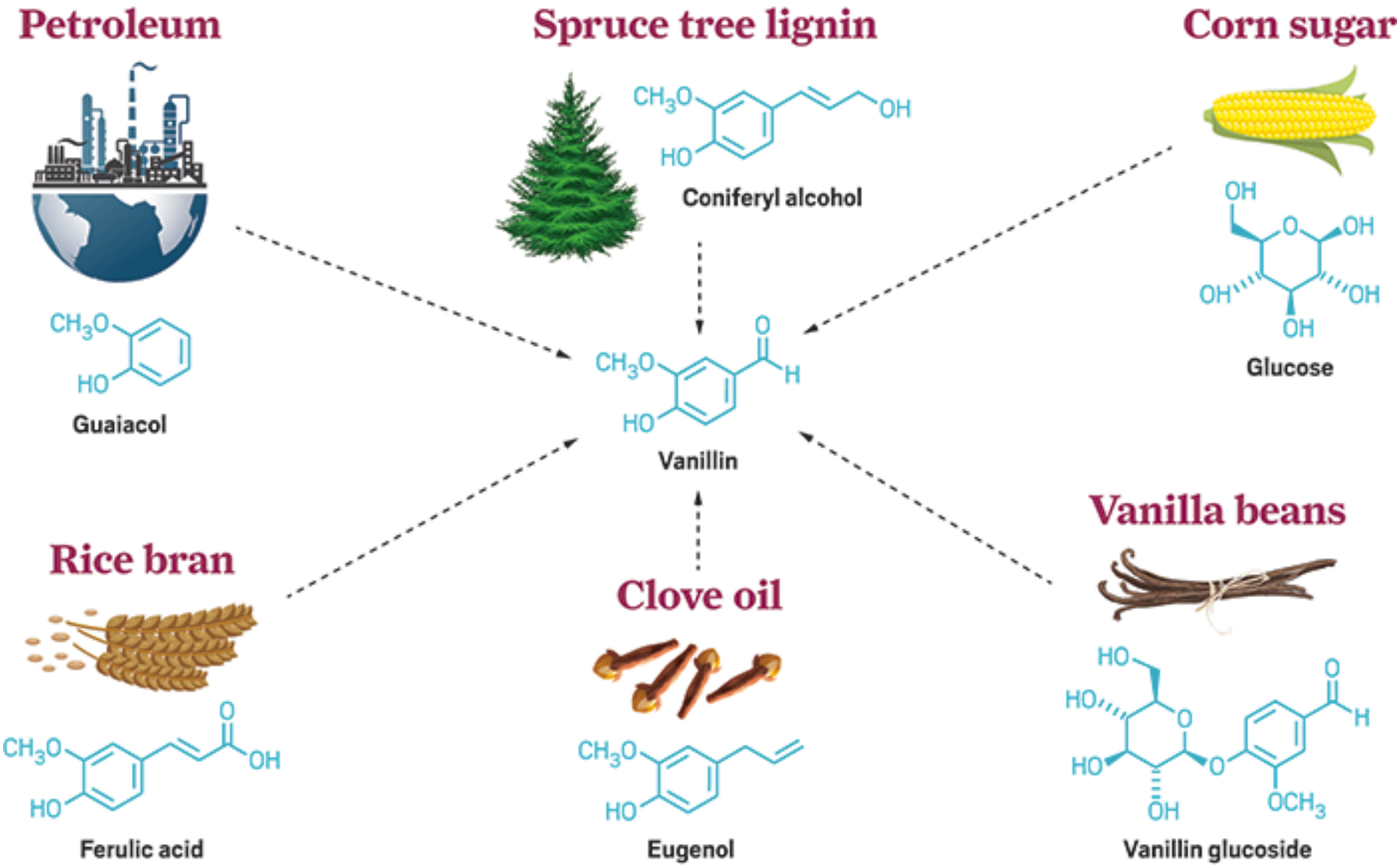


Which group directs EAS?
Aromatic pi bond is a weak Nu:$^{-}$. Is E^{+} in this reaction strong or weak?

CEN, 9/12/16, Vanilla shortage

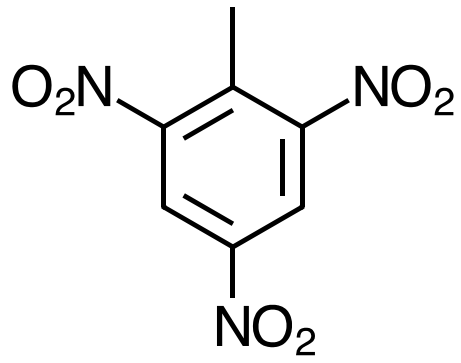
http://cen.acs.org/articles/94/i36/problem-vanilla.html

Propose a synthesis of vanillin from each source.



Objective: Propose a synthesis.

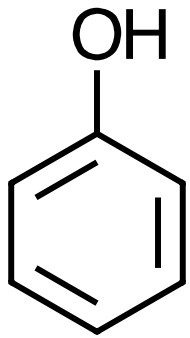
Propose a synthesis of TNT starting from benzene.



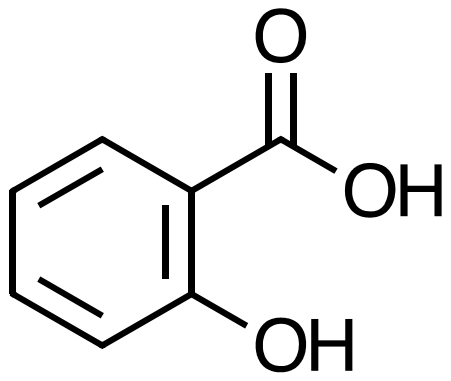
TNT

EAS to Functionalize Benzene in Synthesis

Starting from phenol, propose a synthesis of salicylic acid.



phenol



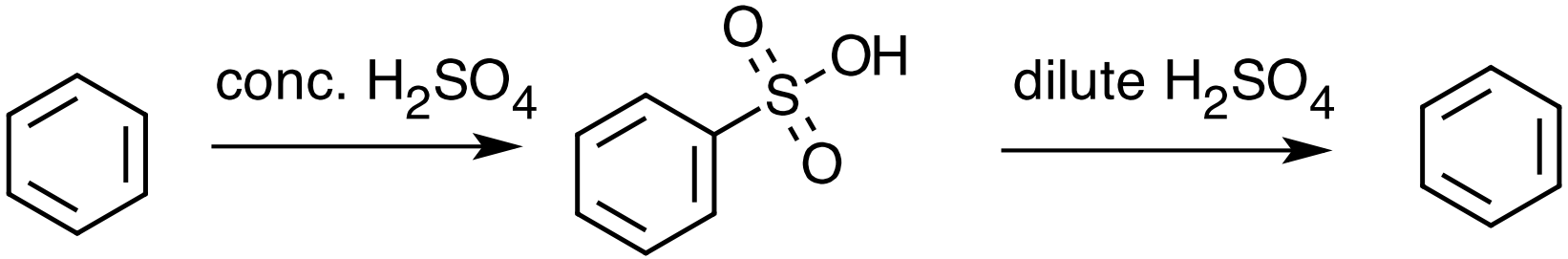
salicylic acid

See Practice Problems

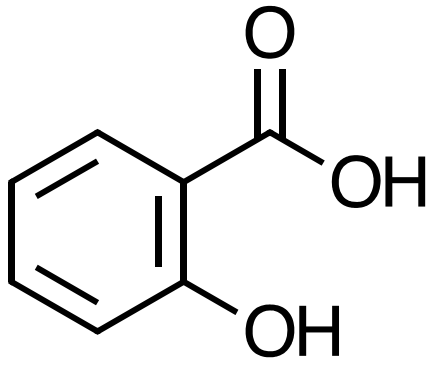
Objective: Propose a synthesis

What if you wanted to substitute a group on the ortho position but not the para?

Use a "blocking" group.



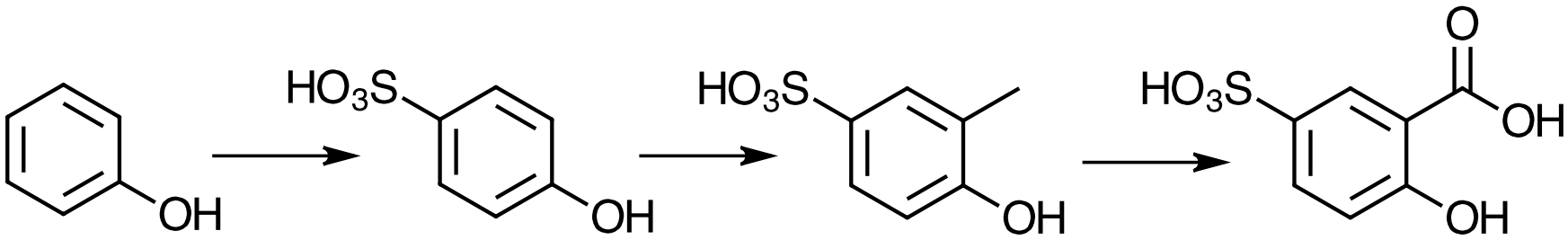
How can $–SO_3H$ be used as a blocking group to make salicylic acid from phenol? Would the yield be higher?



Objective: Propose a synthesis

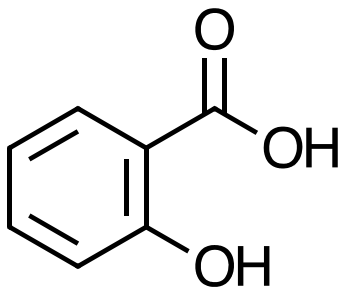
What if you wanted to substitute a group on the ortho position but not the para?

How can –SO_3H be used as a blocking group to make salicylic acid from phenol?



ID the reaction conditions for each step.

The yield is higher because _____



http://cen.acs.org/articles/91/i12/Drug-Fight-Both-Indigestion-Pain.html

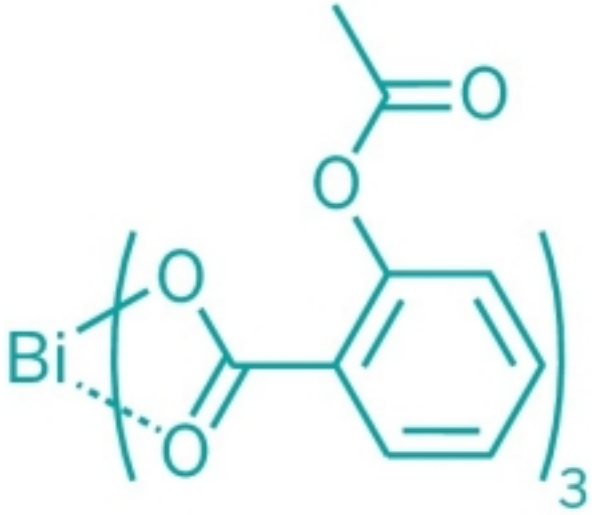
3/25/13, CEN, p. 34 “Drug To Fight Both Indigestion And Pain”

Bismuth acetylsalicylate effectively kills ulcer-causing bacteria and might also work as a pain reliever.

Bismuth carboxylate compounds kill ulcer-causing Helicobacter pylori bacterium.

Bismuth subsalicylate is the active ingredient in Pepto-Bismol.

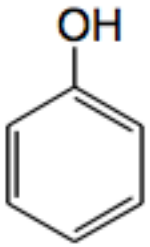
Aspirin is a common pain reliever.



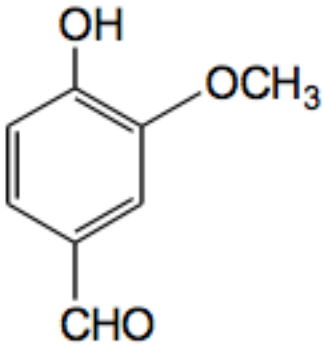
Bispirin

Describe a synthesis of the organic part starting from phenyl acetate.

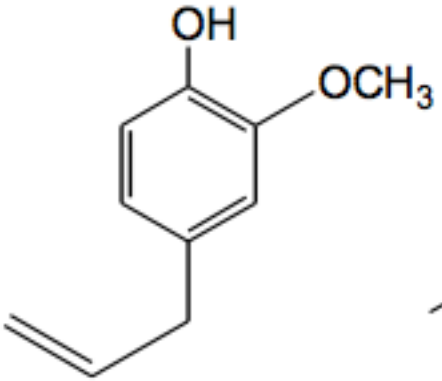
Phenols Are Found in Many Products



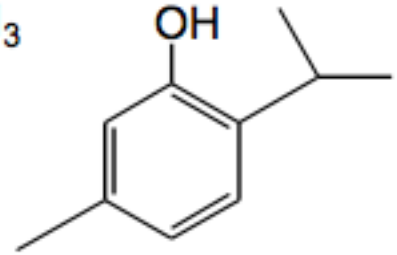
phenol - antiseptic
in Chloraseptic
and Carmex



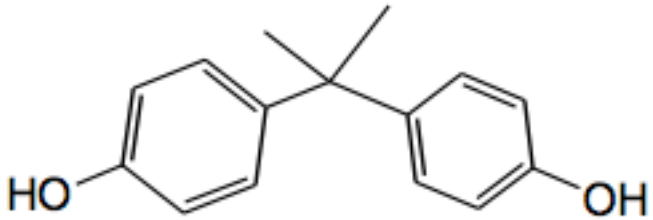
vanillan
(vanilla)



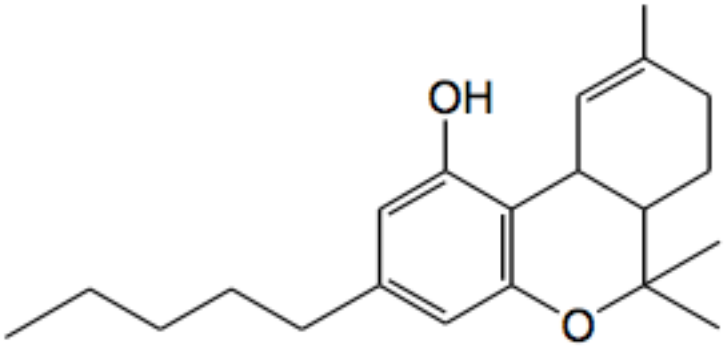
eugenol
(cloves)



thymol
(thyme)



Bisphenol A



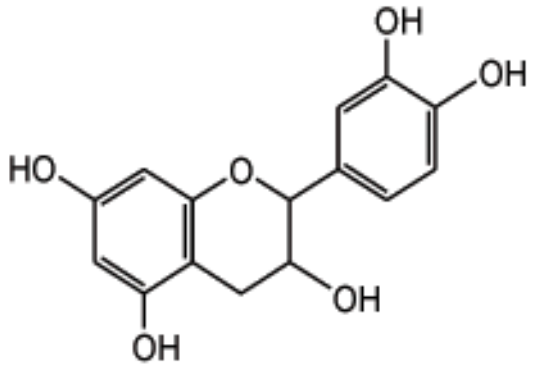
THC

Some **Antioxidants** Are Phenols

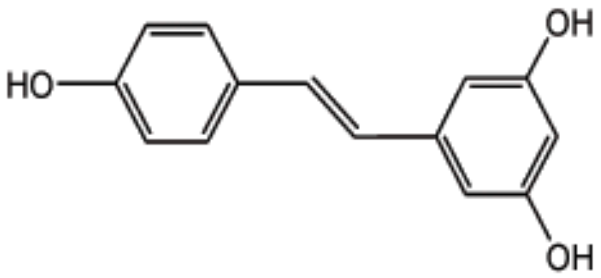
Reactive oxygen species (ROS) are byproducts of energy production and storage. ROS include peroxides and radicals.

Oxidative stress is an imbalance in ROS levels.

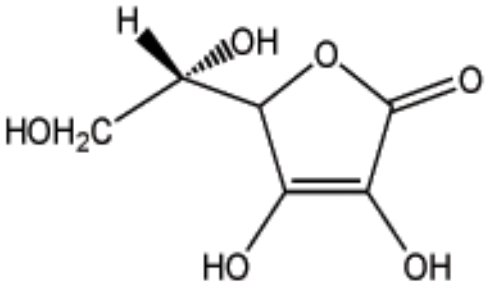
Antioxidants scavenge radicals and lower ROS levels.



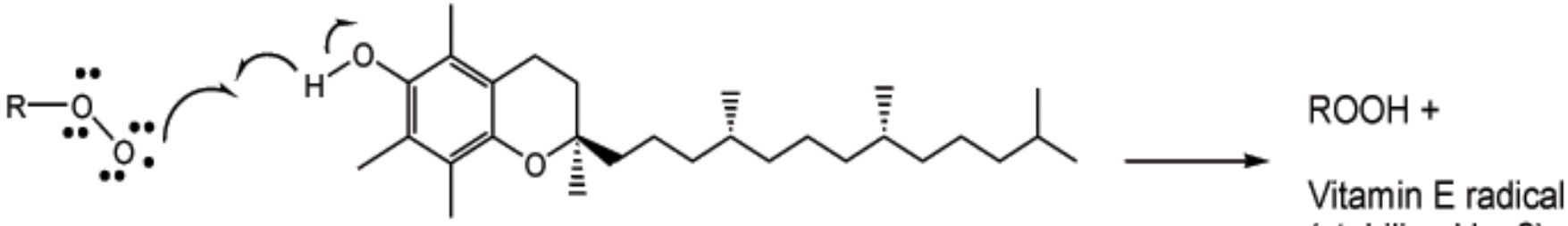
catechin - flavanoid antioxidant in green tea and red wine



reservatrol - in red grapes and red wine



Vitamin C



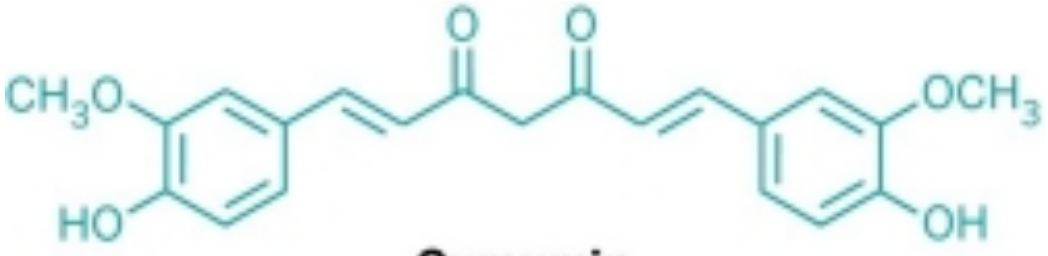
peroxyl radical

Vitamin E (α-tocopherol)

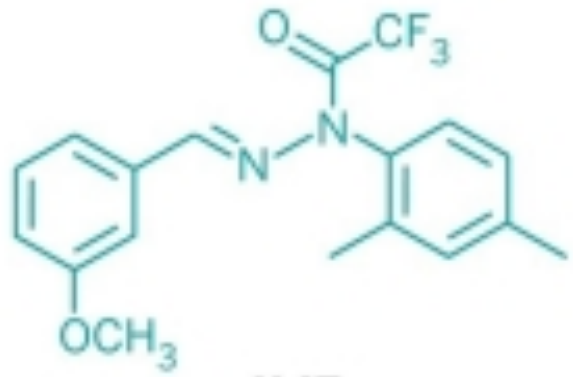
http://cen.acs.org/articles/90/i31/Tumeric-Derived-Compound-Curcumin-Treat.html

7/30/12, CEN, p. 44 Curcumin (from turmeric plant) decreases inflammation and reactive oxygen species in mice brains with Alzheimer's symptoms; inhibits aggregation of amyloid-β strands in nerve cells.

Turmeric give Indian dishes their color



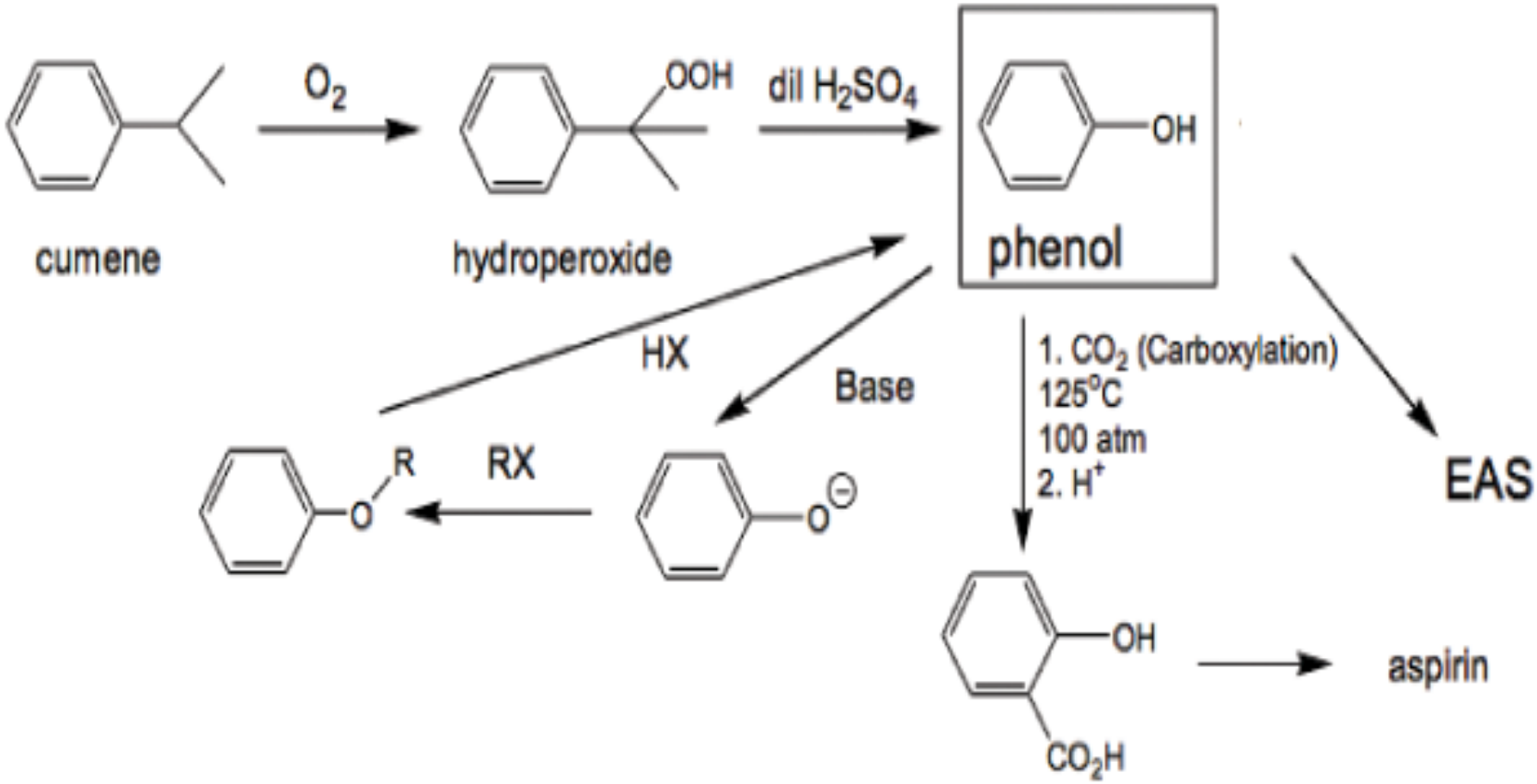
Curcumin



J147

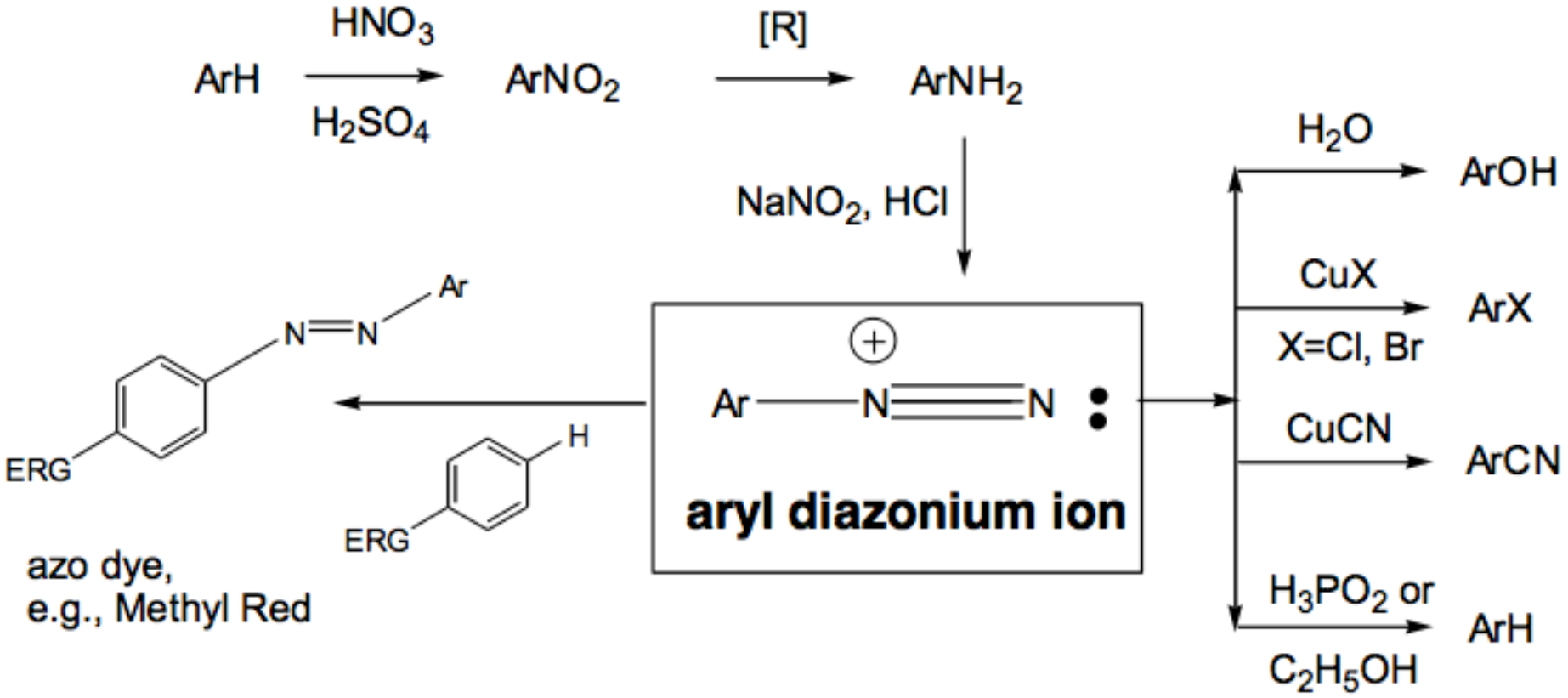
Curcumin has poor bioavailability (not much gets into bloodstream; converted to curcumin glocuronide or curcumin sulfate; hydrolyzed at pH>7). J147 (hybrid of curcumin and cyclohexyl bisphenol A) has increased bioavailability with similar properties.

Industry: 4 billion lbs of Phenols Are Produced Annually
Most of the Phenol Is Use to Make Phenolic Resins in Adhesives and Plastics (see BPA)



The *Aryl Diazonium* ion makes Substituted Arenes and Azo Dyes

Make phenol in the lab



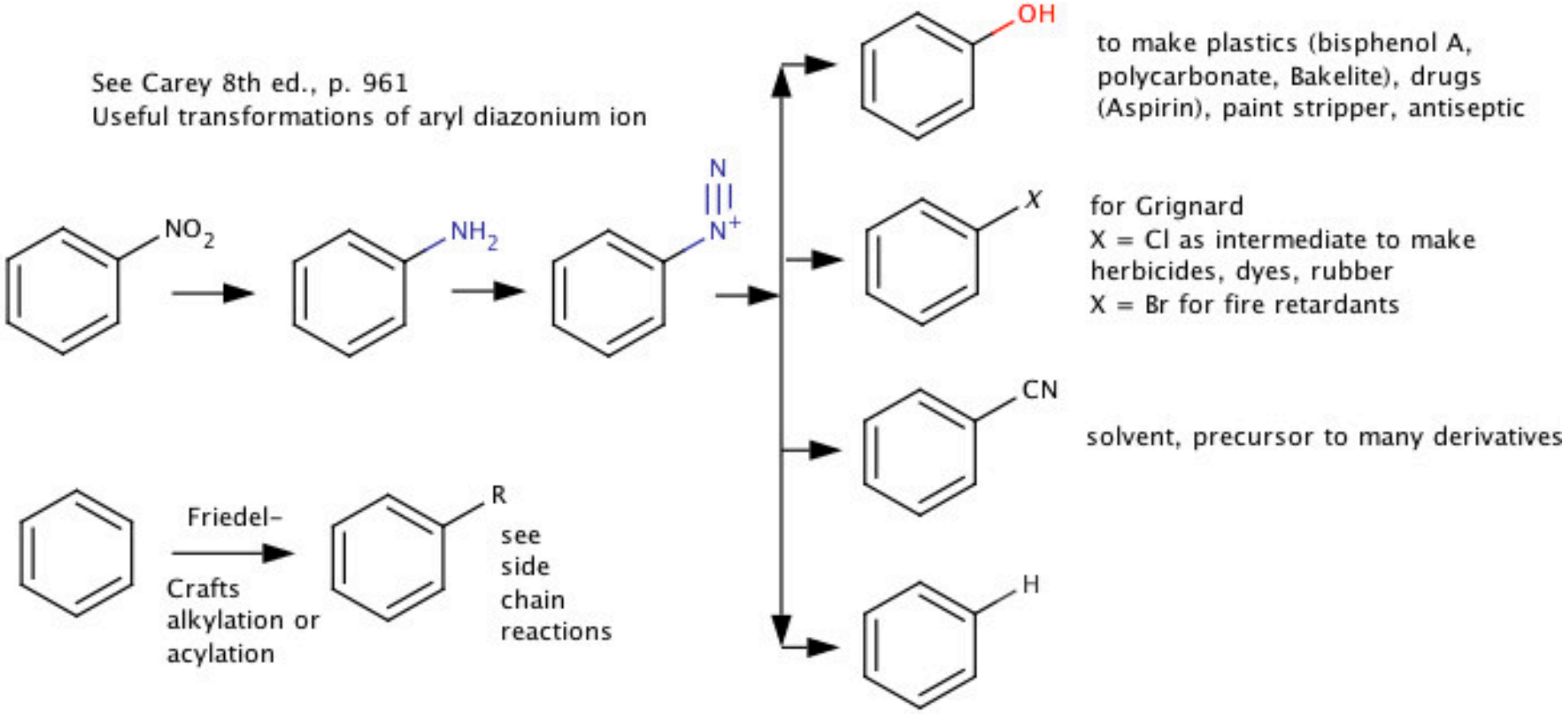
Is the aryl diazonium ion a $Nu:^-$ or E^+?

What is "ERG"?

How does this ion react to form dye?

Hint: see resonance.

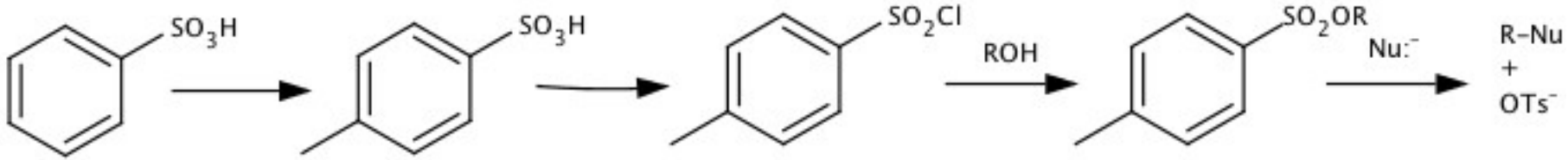
See Carey 8th ed., p. 961
Useful transformations of aryl diazonium ion



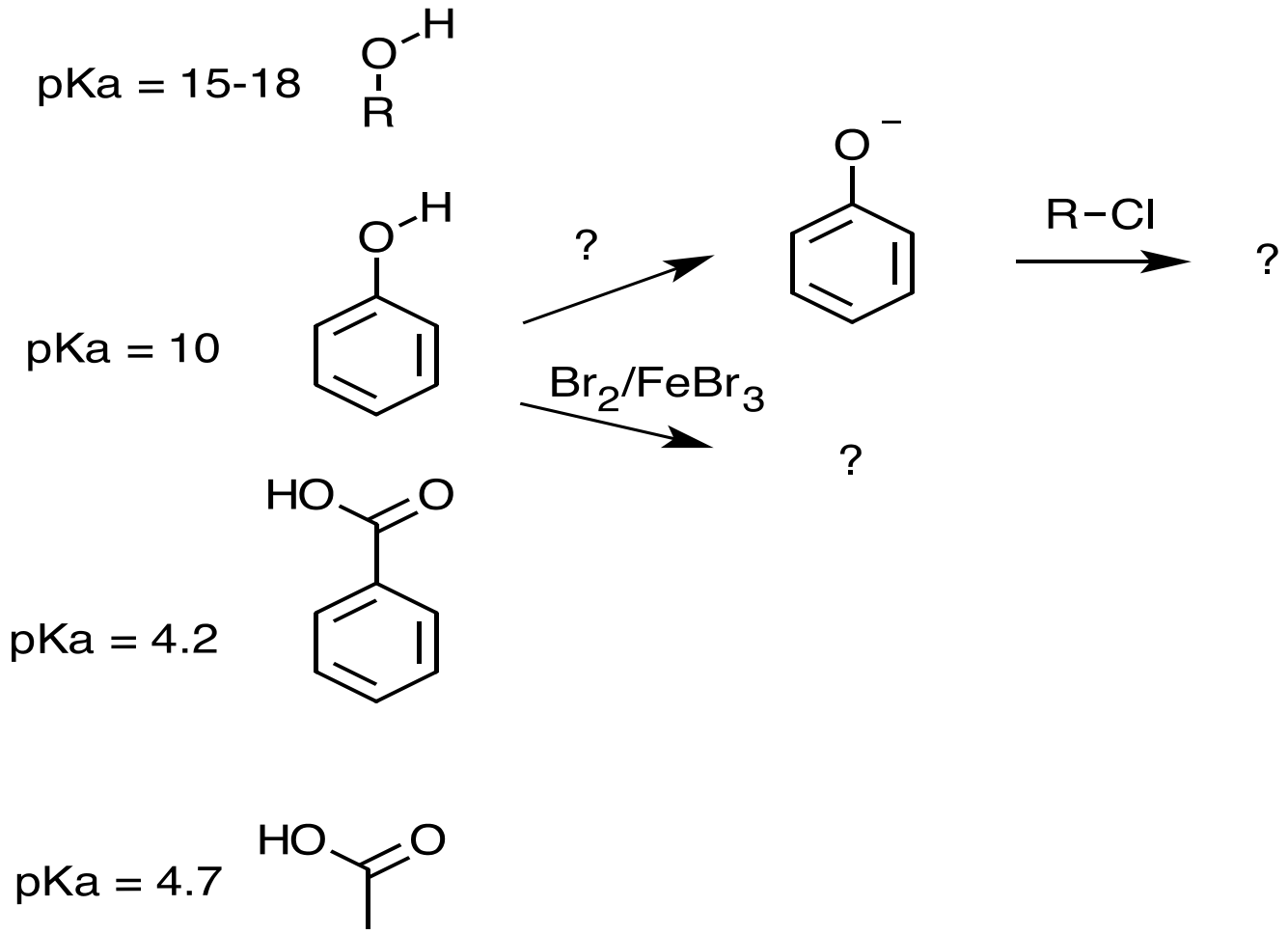
to make plastics (bisphenol A, polycarbonate, Bakelite), drugs (Aspirin), paint stripper, antiseptic

for Grignard
X = Cl as intermediate to make herbicides, dyes, rubber
X = Br for fire retardants

solvent, precursor to many derivatives



p-toluenesulfonic acid (HOTs)



Circle the acidic H's. Where does phenol rank in acid strength?

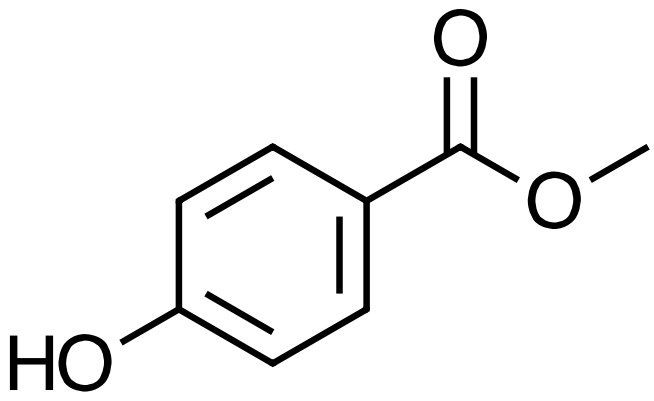
Does -OH activate or deactivate the ring?

Predict the product or reaction conditions for each "?"

Parabens are used as preservatives in Personal Care Products

C&EN, 6/9/14, p. 22
(http://cen.acs.org/articles/92/i23/Close-Scrutiny-Cosmetic-Preservatives-Continues.html)

Microbes in H_2O-based cosmetics can cause rashes or infection.

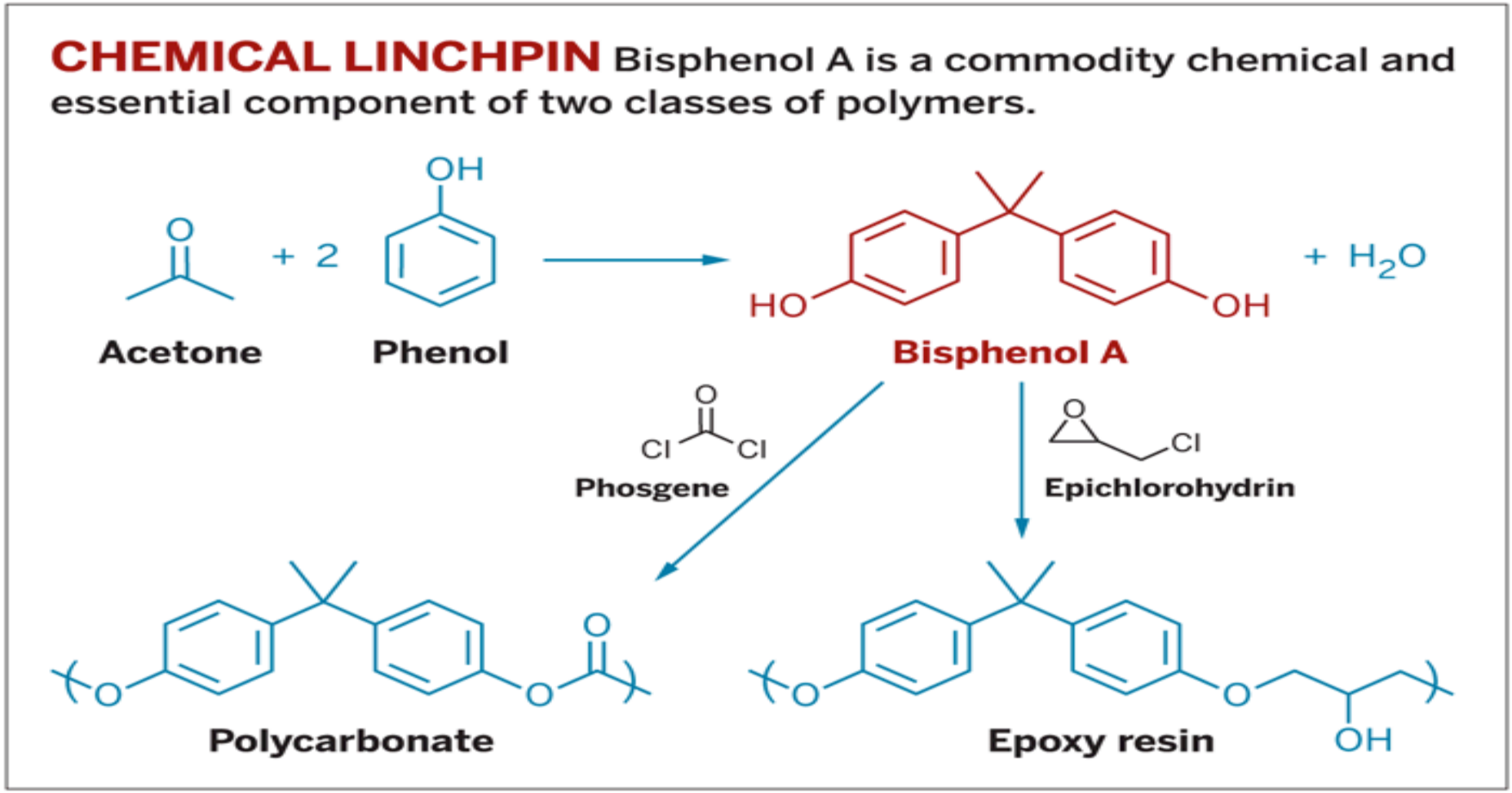


Methylparaben

Propose a synthesis of methylparaben from benzene.

BPA is used in polycarbonate hard plastics (drink containers, DVDs, cell phones, eyeglass lenses) ***and epoxy resins*** (food and drink can liners, paints and coatings, adhesives).

BPA is <u>BIG</u> business: 12 billion lbs in 2011.



CEN, 6/6/11, p. 14-19.

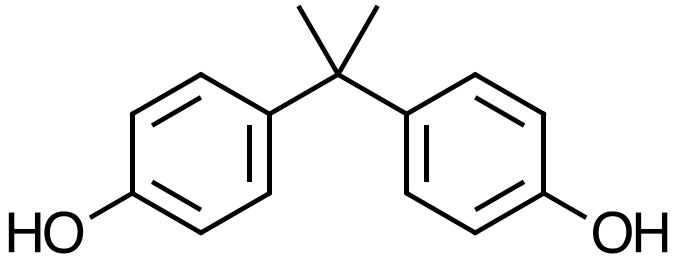
BPA is an endocrine disruptor (triggers changes in hormone concentration, enzyme function, protein synthesis, …) (CEN, 6/6/11, p. 14)

Note: German Society of Toxicology: BPA "represents no noteworthy risk to the health of the human population, including newborns and babies" (CEN, 4/25/11, p. 28)

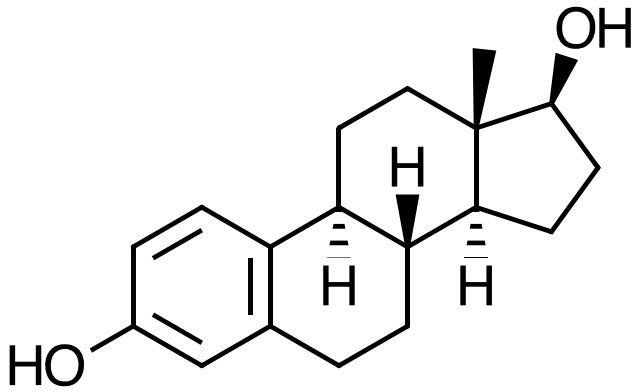
California must remove BPA from its list of chemicals known to cause reproductive toxicity until an industry-led lawsuit challenging the listing is resolved (CEN, 4/29/13, p. 7).

A common type of endocrine disruption is ***Estrogenic Activity*** - the ability to simulate the effects of female sex hormones.

But estrogenic activity is *not* necessarily toxic.



Bisphenol A
(BPA)



Estradiol

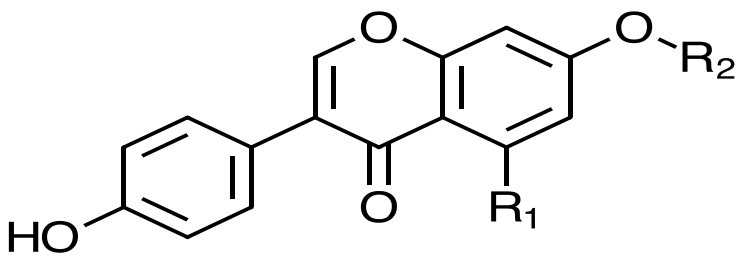
Most plastic products, including BPA-free products, release estrogenic chemicals (CEN, 3/7/11, p. 48)

Sources of endocrine disruptors often contain phenolic structures

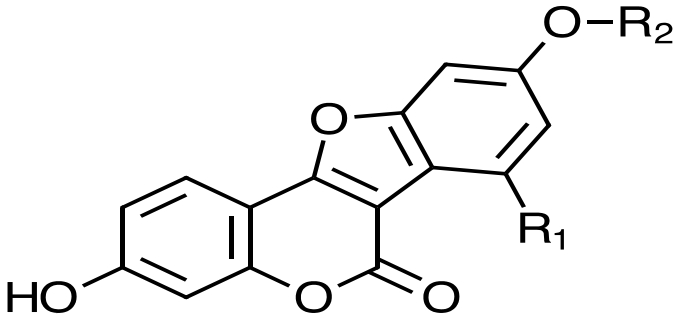
BPS - replace isopropylidene group with -SO_2 group.

Natural sources in foods and beverages - **Phytoestrogens**

isoflavones, coumestans, lignans found in beans, olive oil, some fruits and vegetables, grains, tea, coffee, wine, beer, chocolate. (CEN, 6/6/11, p. 20)



Isoflavones

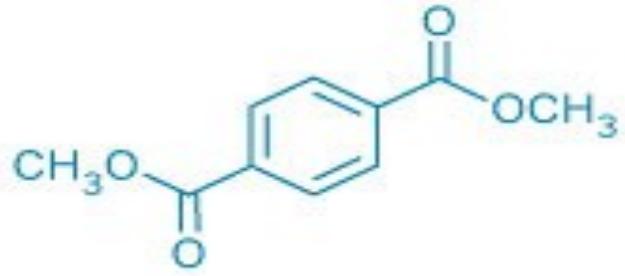


Coumestrol

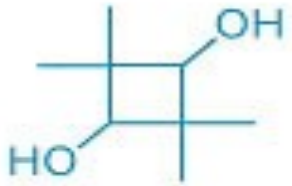
	R_1	R_2
Daidzein (soy)	H	H
Formononetin (beans)	H	CH_3
Genistein (tofu)	OH	H
Biochanin A (peanuts)	OH	CH_3

	R_1	R_2
Coumestrol (soy)	H	H
4’ - methoxycoumestrol	H	CH_3
Repensol	OH	H
Trifoliol	OH	CH_3

Tritan copolyester is a BPA-free substitute for Polycarbonate and has similar properties and production costs.
(CEN, 6/6/11, p. 14)



Dimethyl terephthalate



2,2,4,4-Tetramethyl-1,3-cyclobutanediol

1,4-Cyclohexanedimethanol

Tritan is thought to be assembled from a combination of dimethyl terephthalate, 2,2,4,4-tetramethyl-1,3-cyclobutanediol, and 1,4-cyclohexanedimethanol.

Properties: toughness, clarity, and temperature resistance
Tritan is more dishwasher-durable than polycarbonate, which tends to develop cracks, called crazing, at molded-in stress points.

BPA-free alternatives, including some grades of Tritan, still display estrogenic activity.

http://cen.acs.org/articles/89/i38/Breaking-New.html

9/19/11, CEN, p. 10 New Polymers

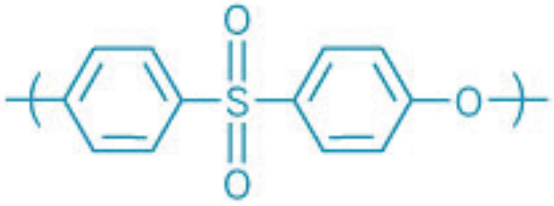
WORLDS TO CONQUER

Makers of new polymers have their sights set on major applications

POLYMER	COMPANY	APPLICATIONS
Ingeo polylactic acid	NatureWorks	Thermoformed containers, injection molding, fibers
Mirel polyhydroxyalkanoate	Metabolix/Telles	Film and other agricultural applications, plastic bags
Polyethylene furanoate	Avantium	Bottles, containers
Polypropylene/polyethylene carbonate	Novomer	Packaging, industrial coatings, specialty polymers
Stanyl ForTii high-temperature polyamide	DSM	Electronics, automotive uses
Topas cyclic olefin polymers	Topas Advanced Polymers	Protective packaging, shrink-wrap, optical components
Tritan polyester copolymer	Eastman Chemical	Housewares, baby bottles, medical applications

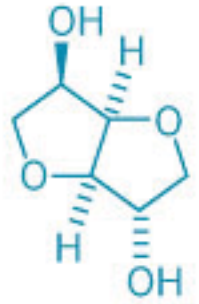
Tritan replaced polycarbonate (made from BPA) in water bottles

Other BPA-free plastics:



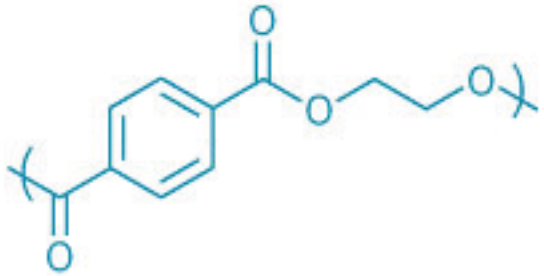
Polyether sulfone

Very stable and holds its properties over wide T range but expensive and trigger (+) estrogen activity response



Isosorbide

Derived from sorbitol
Not as tough or clear as BPA



Polyethylene terephthalate

Clarity but not as tough or heat stable as polycarbonate and more expensive

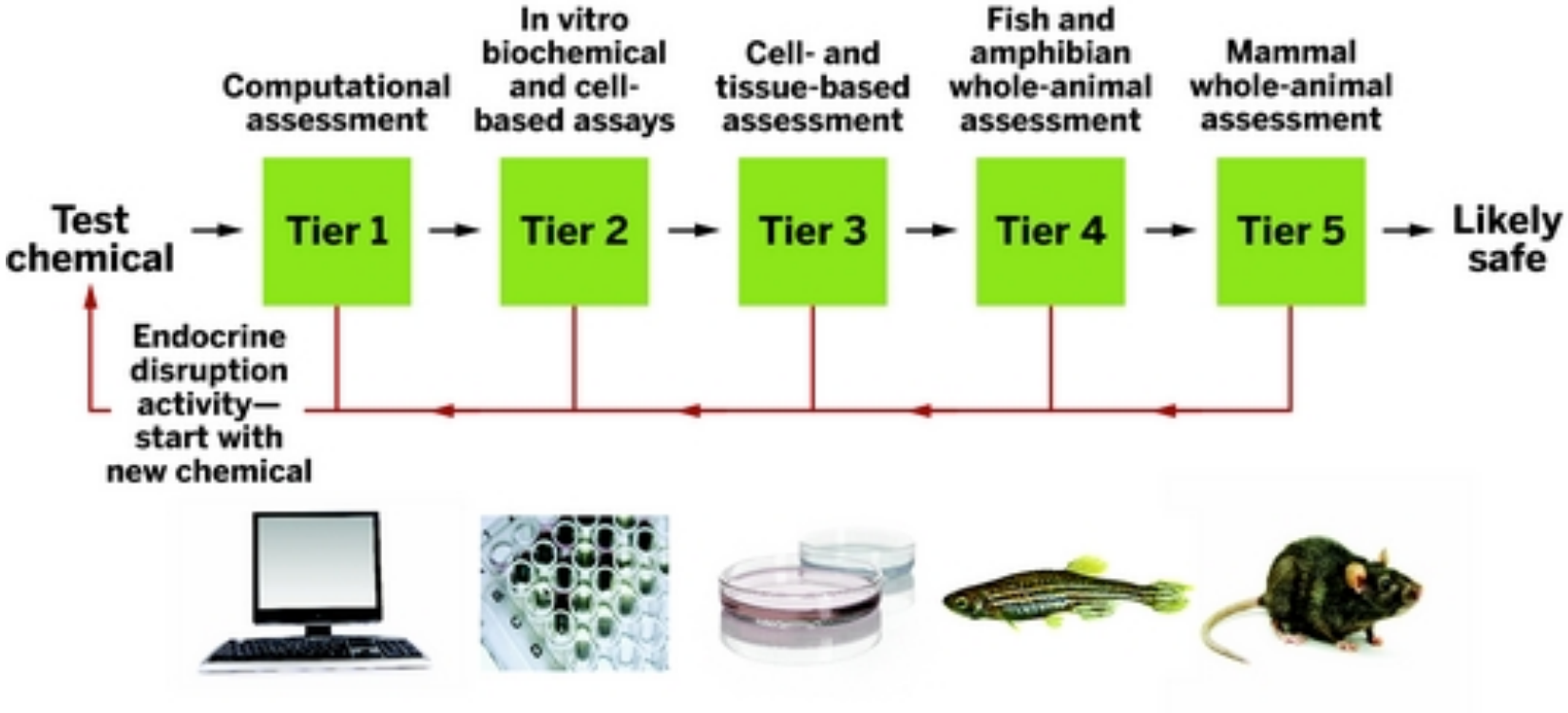
Cyclic olefin copolymer

Inexpensive, tough, highly processable, chemically inert but not as clear as polycarbonate

http://cen.acs.org/articles/90/i51/Designing-Away-Endocrine-Disruption.html

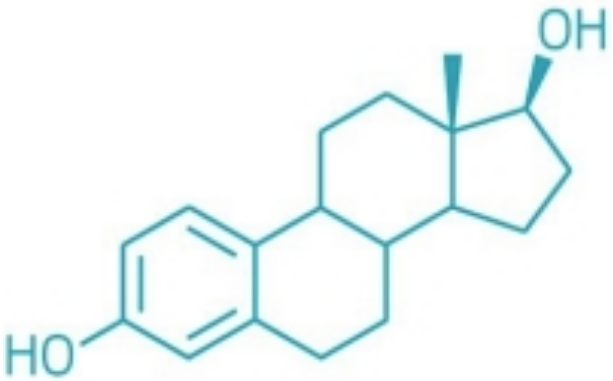
12/17/12, CEN, p. 33 “Designing Away Endocrine Disruption”

Tiered Protocol for Endocrine Disruption (TiPED) screening tool walks chemists through the process of selecting assays to test chemicals during design or redesign phases for potential endocrine-disrupting activity.



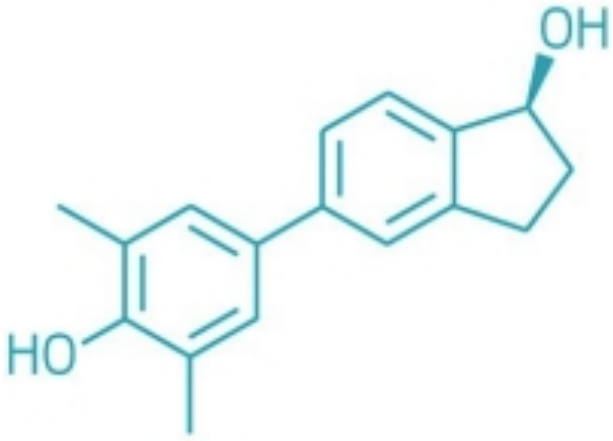
Estrogen replacement therapy

http://cen.acs.org/articles/94/i22/Pathway-preferentialestrogens-target-avoid-bad.html



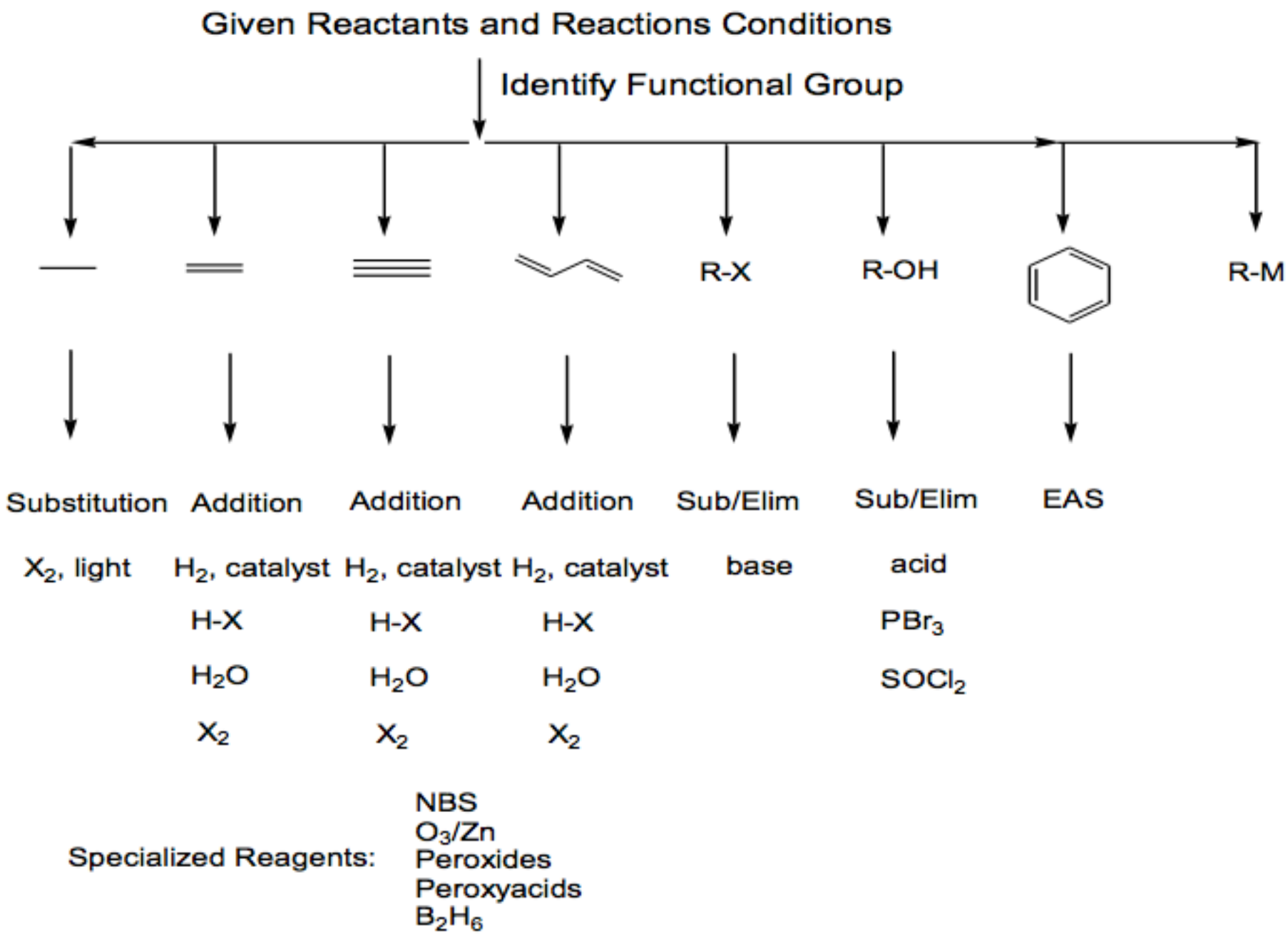
Estradiol

Binds to estrogen receptors, which triggers:
extranuclear signaling pathway → controls metabolism in adipose tissue and in liver to reduce fat accumulation and repair blood vessels.
nuclear signaling pathway → stimulates activity in reproductive and breast tissue, including cancer cells.
Side effects: increased risk of breast and uterine cancer



PaPE-1 estrogen analog

Estrogen analog preserves essential chemical features of estrogens but reduces estrogen binding activity → triggers extranuclear signaling pathway but not nuclear signaling pathway


Given Reactants and Reactions Conditions
Identify Functional Group
R-X
R-OH
R-M
Substitution
Addition
Addition
Addition
Sub/Elim
Sub/Elim
EAS
X2, light
H2, catalyst
H-X
H2O
X2
H2, catalyst
H-X
H2O
X2
H2, catalyst
H-X
H2O
X2
base
acid
PBr3
SOCl2
Specialized Reagents:
NBS
O3/Zn
Peroxides
Peroxyacids
B2H6

Objective: Identify the atom or bond in a compound that reacts

Most organic reactions are:

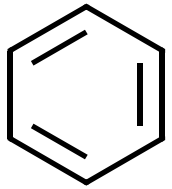
a. polar b. radical c. pericyclic

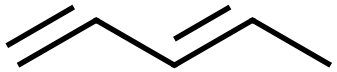
Polar reactions involve a:

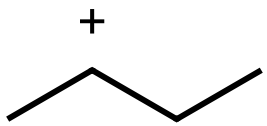
a. $Nu:^-$ and E^+ b. light c. diene/dienophile

Identify each as a nucleophile or electrophile:

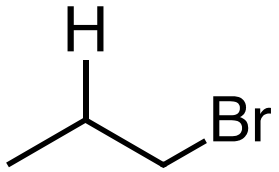
Lone pair
Pi bond
HBr
Br-Br
RMgBr
$NaBH_4$

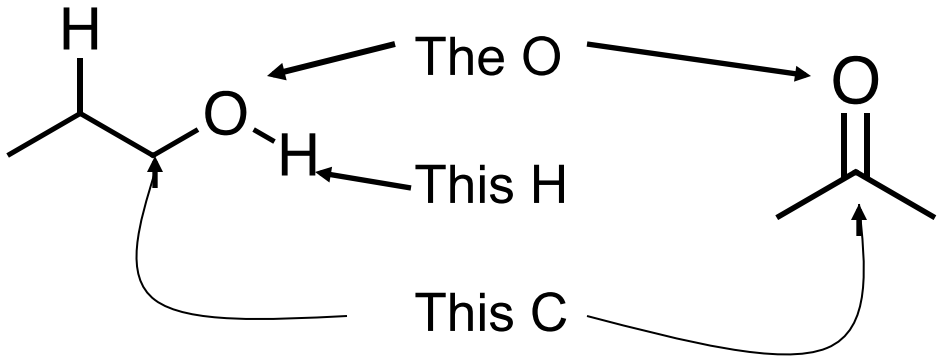






The H in

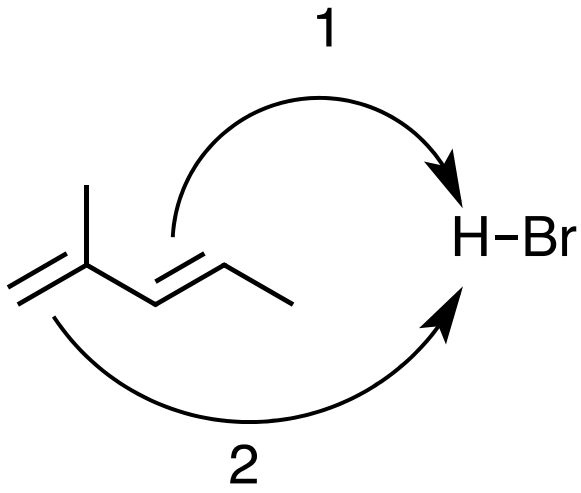




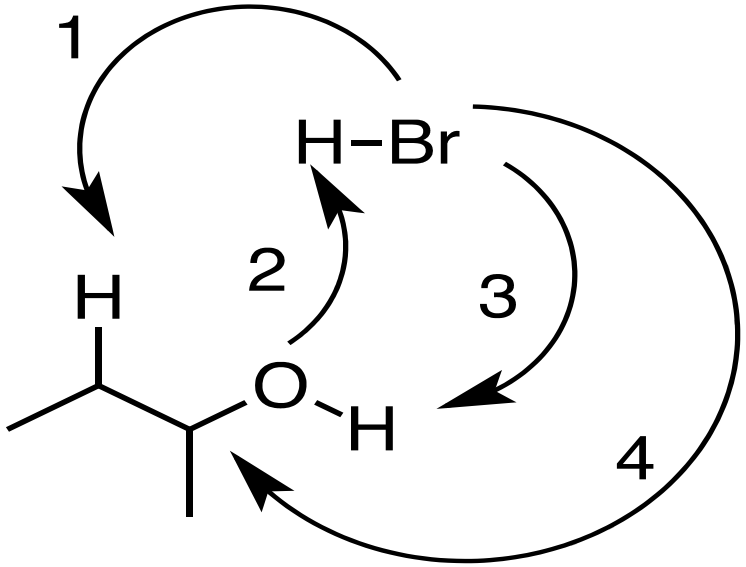
How can you make Br_2 a better one?

Objective: Identify the atom or bond in a compound that reacts

Which bond reacts with H-Br? Why?

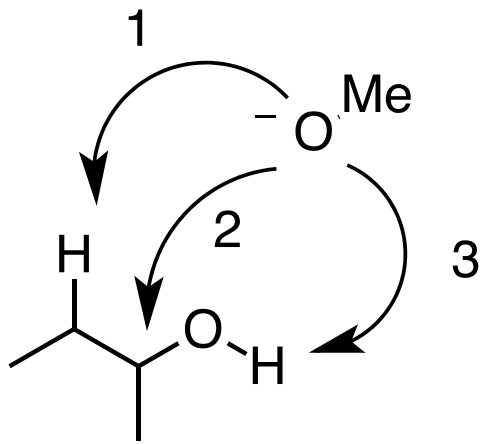


At which atom does HBr react? Why?



Objective: Identify the atom or bond in a compound that reacts

At which atom does MeO^- react? Why?



Which bond reacts with CH_3Cl? Why?