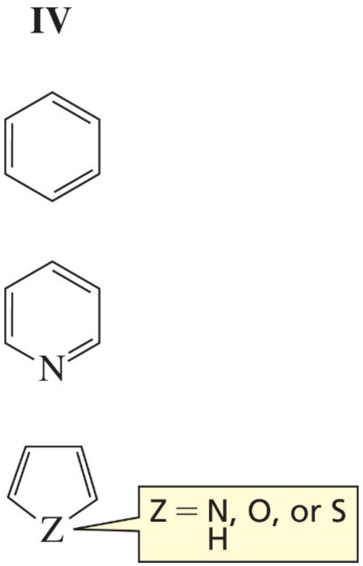
PART 6

Aromatic Compounds

Chapter

18. Bz and subst’d Bz

19. Heterocyclic comp’d



Chapter 18

Reactions of benzene and Substituted Benzenes

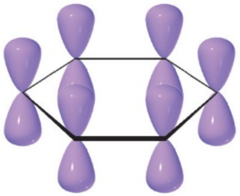
Reactions of aromatics

Aromaticity

- aromatic comp'ds = comp'ds having aromaticity
- 2 requirements for aromaticity
  - cyclic π electron clouds above and below the plane
    - p orbital/cyclic and planar
  - 4n + 2 π electrons

See §8.16 – 20
for aromaticity

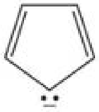
aromatic [芳香族] vs
aliphatic [脂肪族]

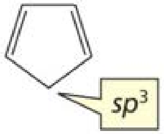

benzene's *p* orbitals


benzene's π cloud

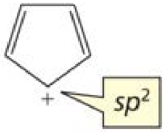

benzene has
3 pairs of π
electrons

- what if 4n π electrons? anti-aromatic
  - aromatic < non-aromatic < anti-aromatic


cyclopentadienyl
anion

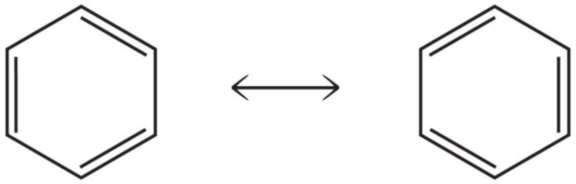


cyclopentadiene

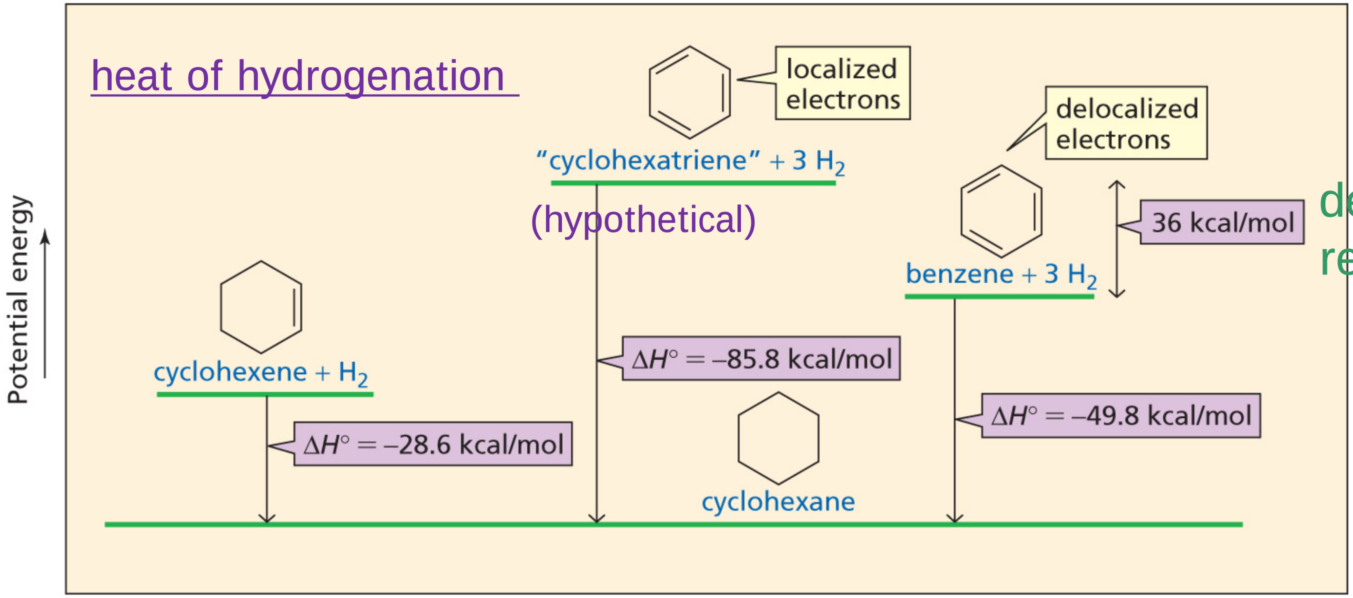


cyclopentadienyl
cation

- result of aromaticity ~ resonance stabilization



large resonance stabiliz’n from
- large # of important resonance forms a/o
- forms of equal importance [contribution]



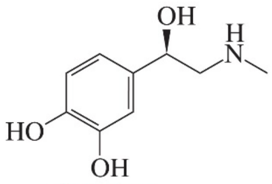
heat of hydrogenation

(hypothetical)

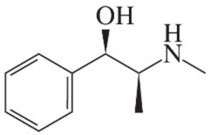
delocalization energy
resonance energy

Substituted benzenes

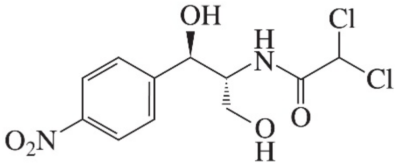
- 2/3 of medicines are aromatic.
  - Some are natural, others synthetic.
  - Some synthesized chemically, others biologically.
  - generic vs biosimilar medicines



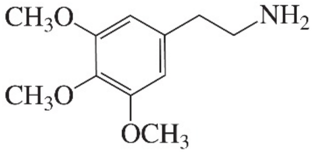
adrenaline
epinephrine
a hormone released
by the body in
response to stress



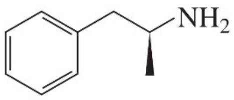
ephedrine
a bronchodilator



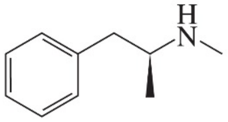
chloramphenicol
an antibiotic that is particularly
effective against typhoid fever



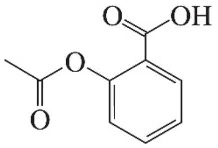
mescaline
active agent of
the peyote cactus



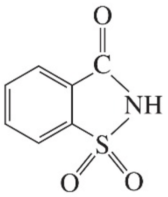
amphetamine
an appetite
suppressant



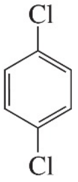
methamphetamine
"speed"



acetylsalicylic acid
aspirin



saccharin
an artificial
sweetener

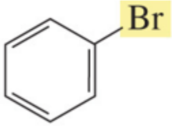


***p*-dichlorobenzene**
in mothballs and
air fresheners

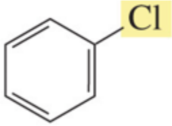
- Benzene is a carcinogen. Use toluene as a solvent.

Naming monosubst'd bz

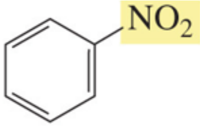
- --bz



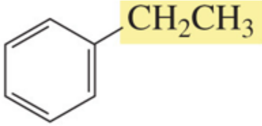
bromobenzene



chlorobenzene

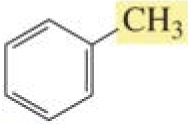


nitrobenzene

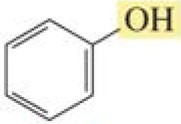


ethylbenzene

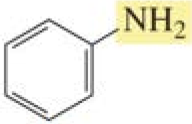
- own name



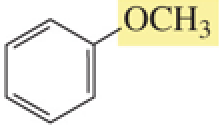
toluene



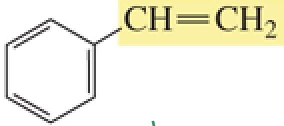
phenol



aniline



anisole



styrene

↓ ROOR

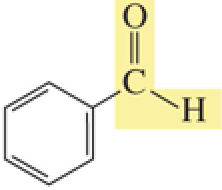
polystyrene [PS]

↓ C_5H_{12}

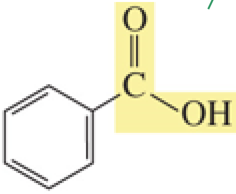
Styrofoam? EPS

(In principle,) only these three are allowed in the systematic [IUPAC] nomenclature.

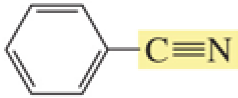
- benz--



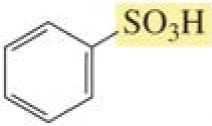
benzaldehyde



benzoic acid

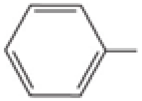


benzonitrile

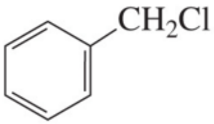


benzenesulfonic acid

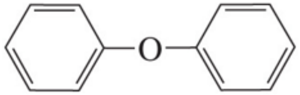
- bz as subs ~ phenyl or benzyl



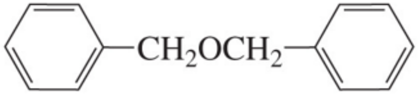
a phenyl group



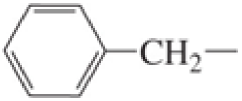
chloromethylbenzene
benzyl chloride



diphenyl ether

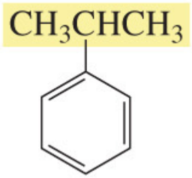


dibenzyl ether

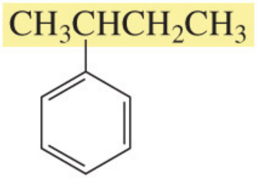


a benzyl group

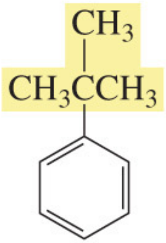
- alkyl benzene or phenyl alkane
  - alkyl bz if alkyl has own name [no confusion]



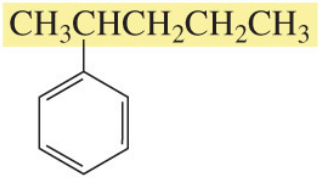
isopropylbenzene
cumene



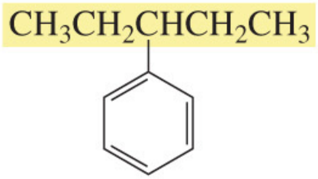
***sec*-butylbenzene**



***tert*-butylbenzene**



2-phenylpentane

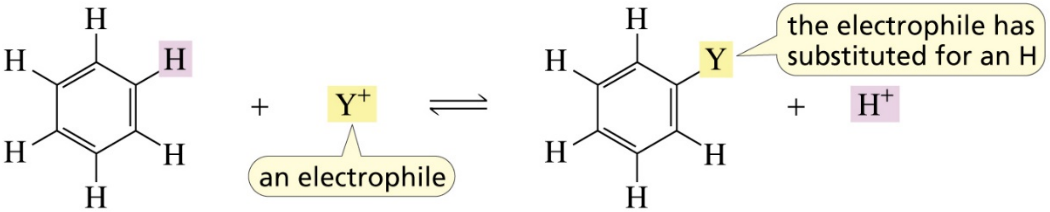


3-phenylpentane

- aryl [Ar] ~ general; <cf> alkyl [R]

How bz reacts

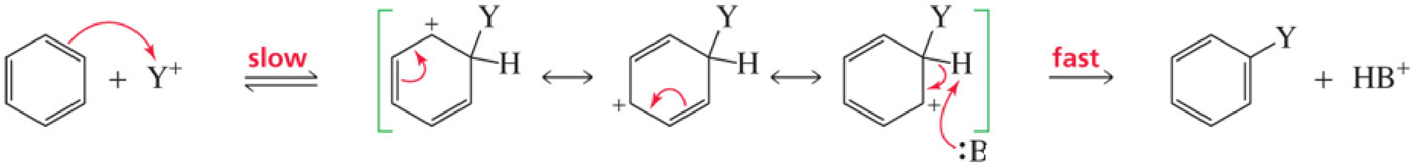
- electrophilic aromatic substitution



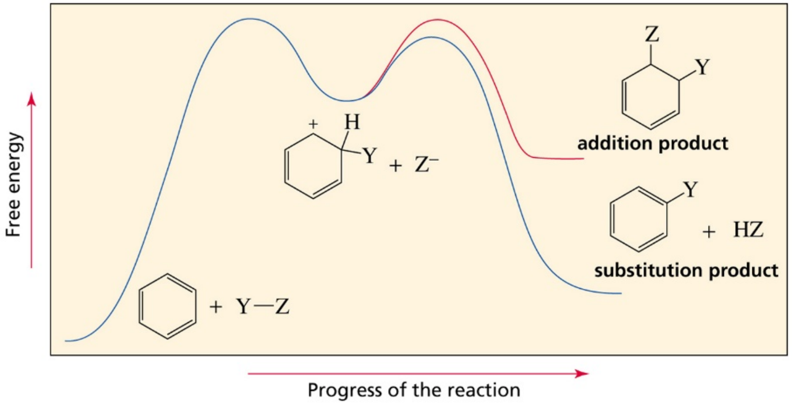
See also §8.21

- 2-step rxn with C^+ [arenium ion] interm

arene = aromatic HC

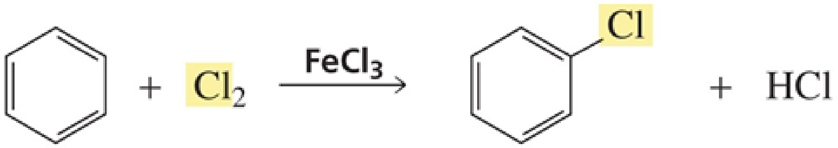


  - 1st step ~ forming C^+ ~ RDS
    - breaking aromaticity
  - 2nd step ~ substitution
    - not an addition
      ← recovering aromaticity
    - H^+ removed from the original site



Halogenation

- chlorination and bromination



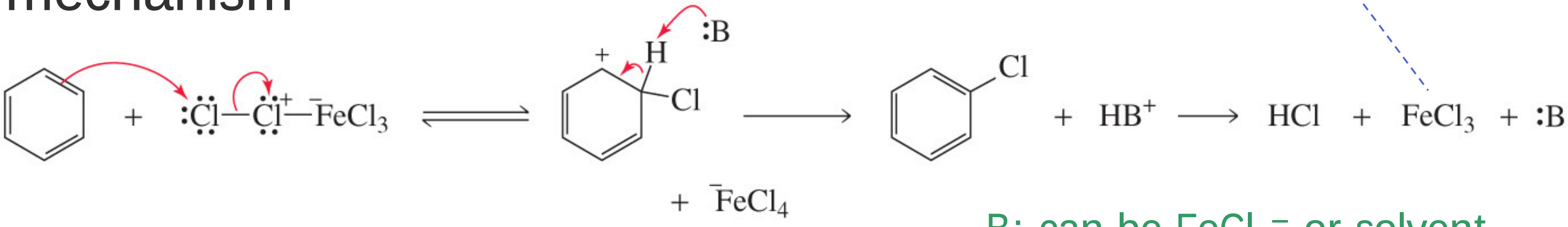
  - with Lewis acid catalyst
    - why catalyst? aromatic reactant
    - LA weakens X–X bond, forming better E^+

catalyst for addition to alkene?

    - $FeCl_3$ for chlorin'n, $FeBr_3$ for bromin'n ← regenerated and reused
      - has to be made in situ ← moisture-reactive

$$2\ Fe + 3\ Cl_2 \longrightarrow 2\ FeCl_3$$

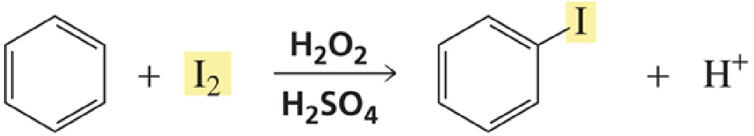
  - mechanism



B: can be $FeCl_4^-$ or solvent.

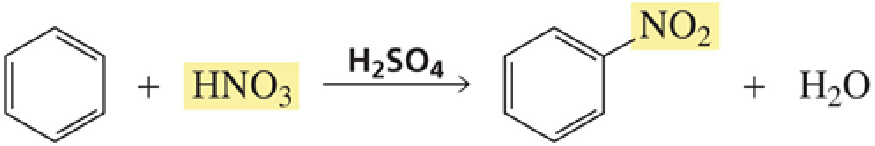
- iodination
  - with Lewis acid? I_2 too stable.
  - with oxidizing agent like H_2O_2/H_2SO_4 or HNO_3

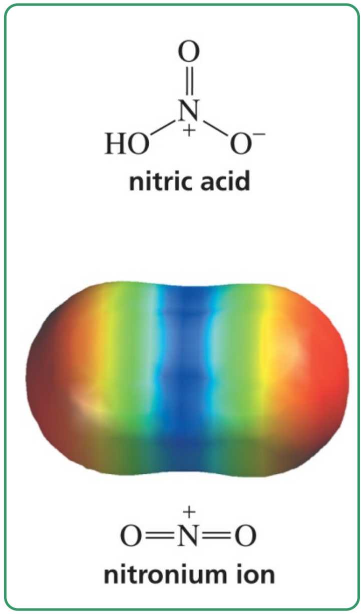
$$I_2 + H_2O_2 + 2H_2SO_4 \longrightarrow 2\,I^+ + 2\,H_2O + 2\,HSO_4^-$$



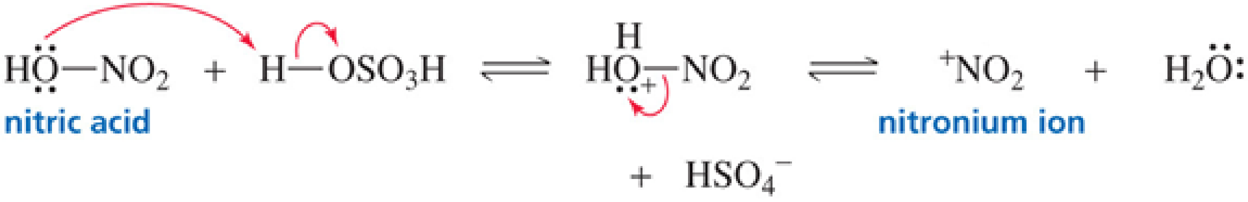
- fluorination
  - too reactive → gives bz-F6
  - for fluorobz, thru indirect method (using N_2Cl) sl#46

Nitration

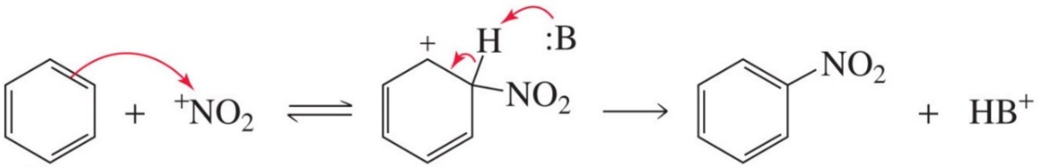




- needs H_2SO_4 to form nitronium ion E^+

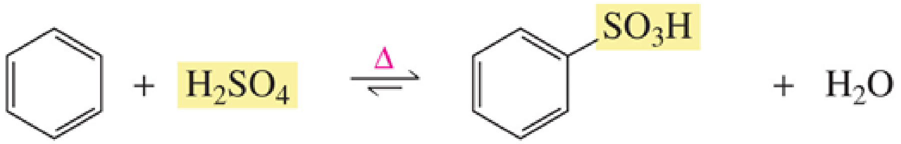


- follows general mechanism



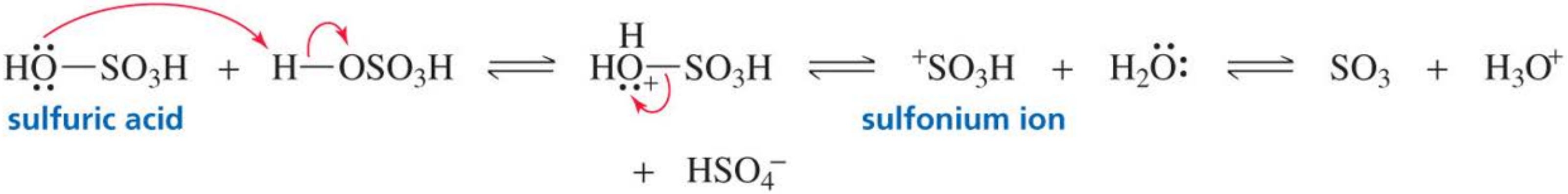
  - B: can be H_2O, HSO_4^-, or solvent

Sulfoantion



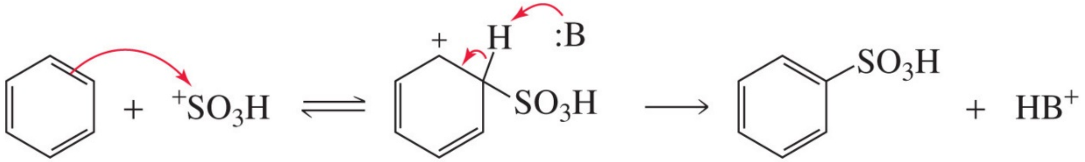
sulfonic acid ~ RSO_3H
sulfuric acid ~ R = OH
술폰산, 黃酸, 硫酸

- using conc. or fuming sulfuric acid



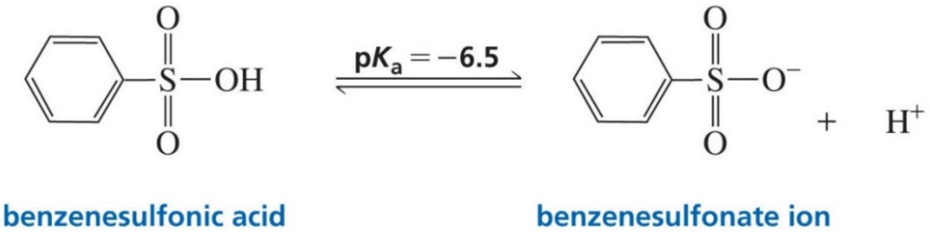
  - E^+ = sulfonium ion

- mechanism ~ general



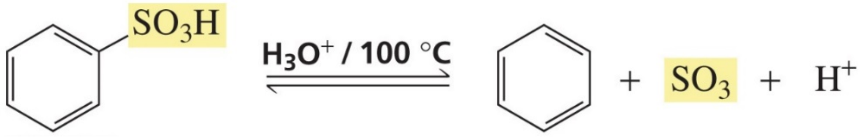
  - B: can be H_2O, HSO_4^-, or solvent

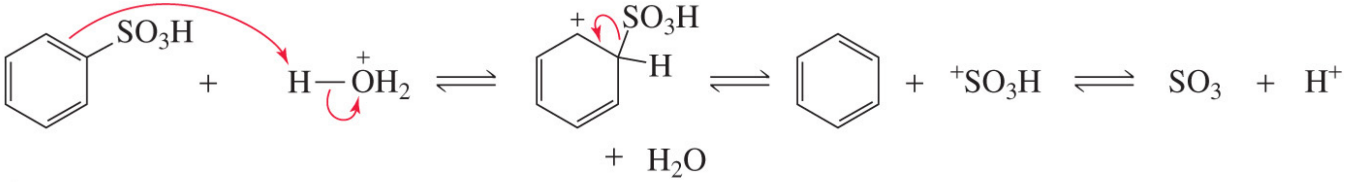
- Sulfonic acids are very strong acids.



delocalized to 3 O's

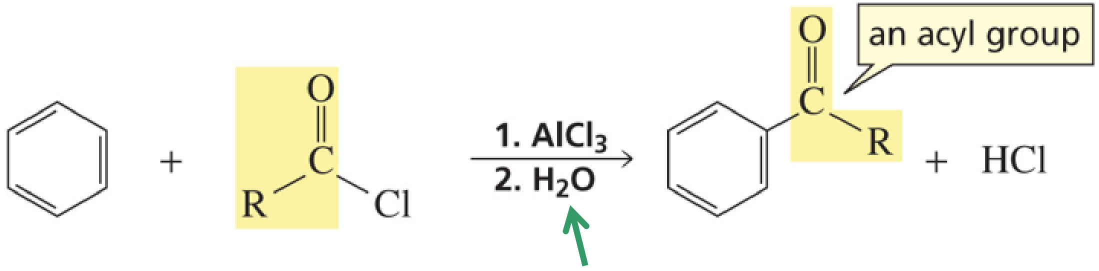
- Sulfonation is reversible. ~ desulfonation



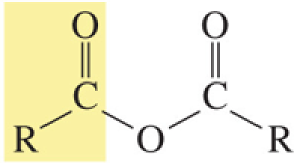


  - useful in some synthesis p935

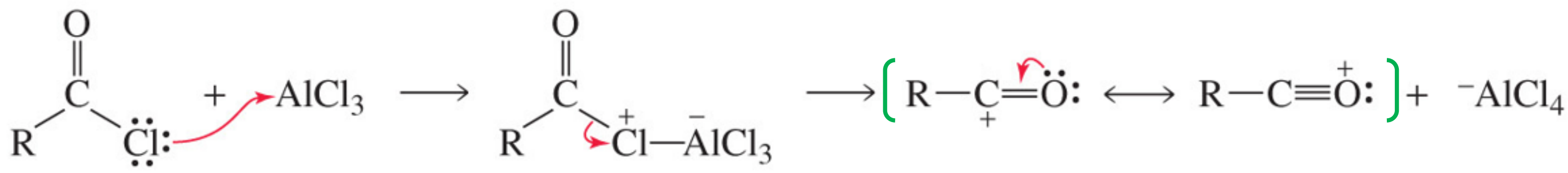
Friedel-Crafts acylation



an acyl group



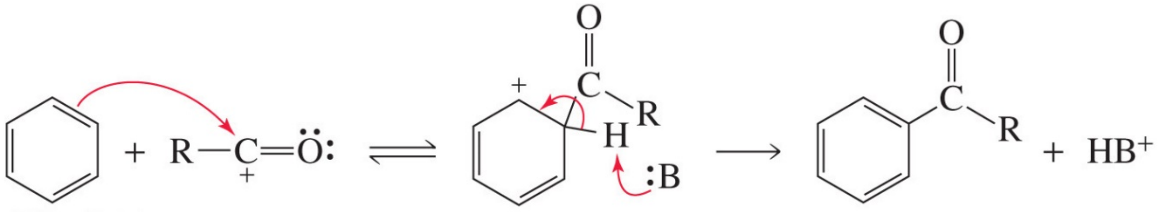
- acyl group from RCOCl or $(RCO)_2O$ w/ LA
  - Less reactive carbonyls do not give RC^+O with LA.



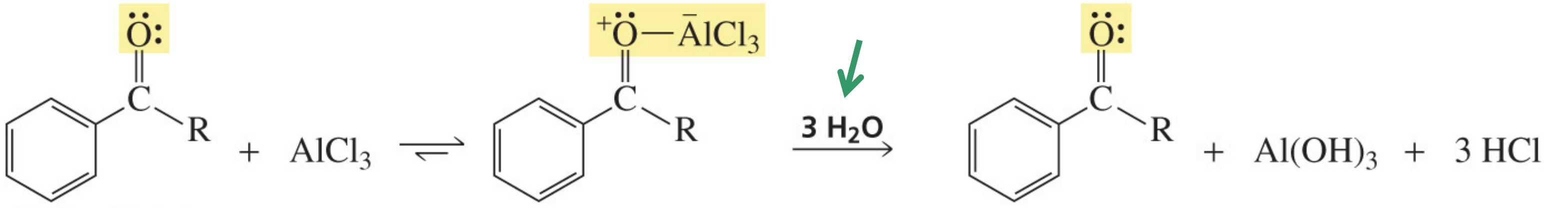
an acyl chloride

an acylium ion

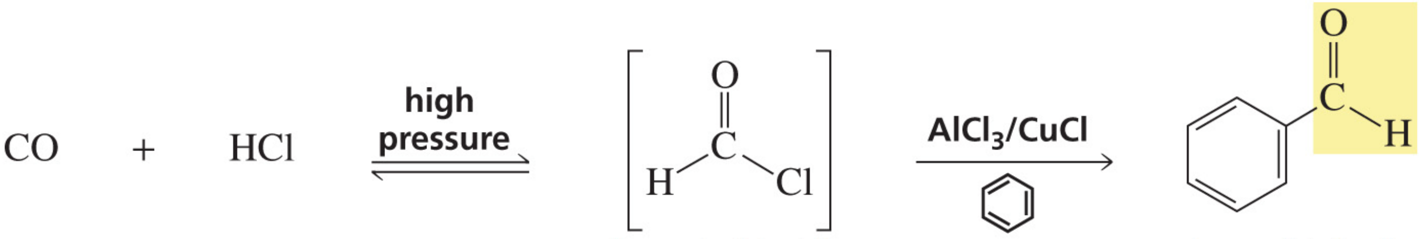
- mechanism ~ general



- More than 1 equiv of LA should be used.
  - LA complexes to C=O ~ removed after rxn (by water)



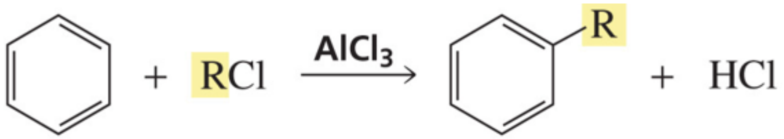
- For benzaldehyde, use Gatterman-Koch rxn



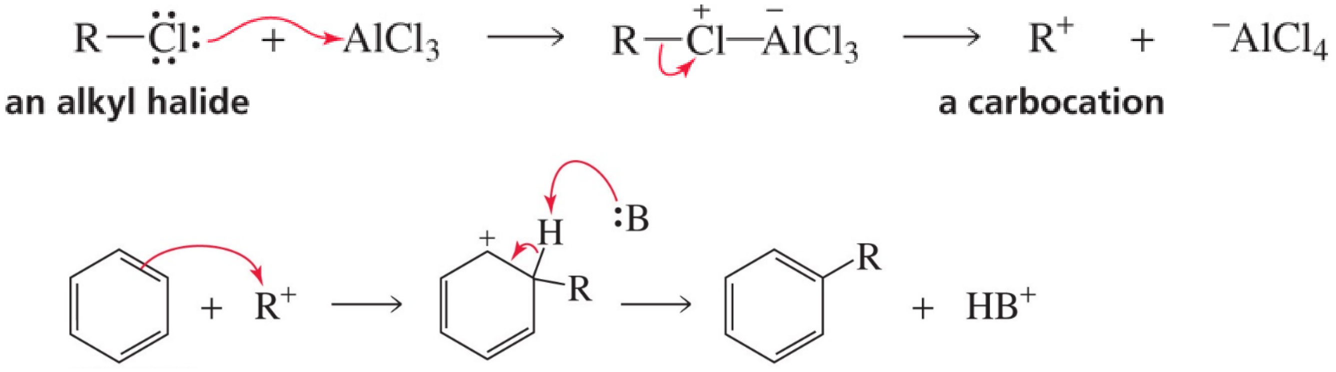
formyl chloride
unstable
prepared *in situ*

benzaldehyde

Friedel-Crafts alkylation

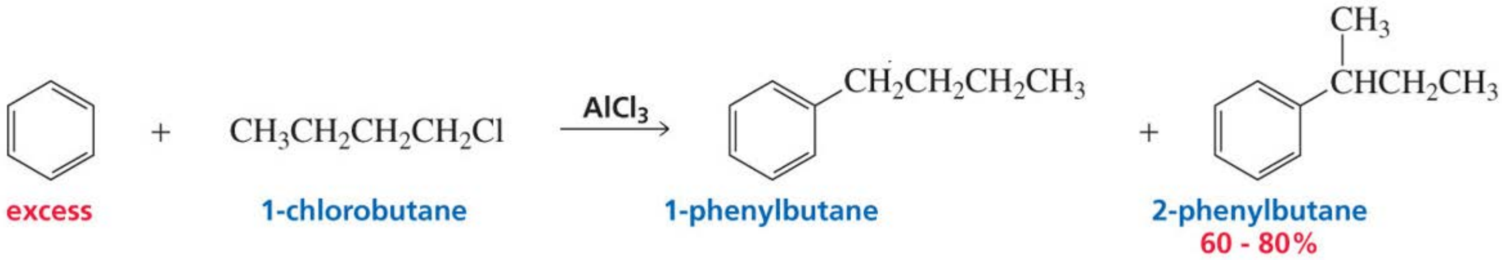


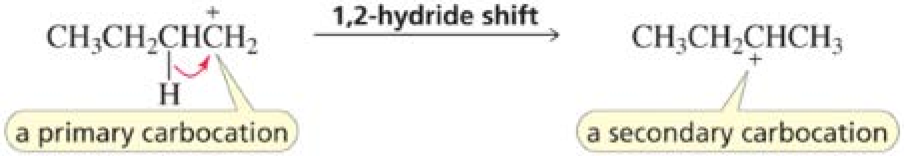
- with LA following general mechanism

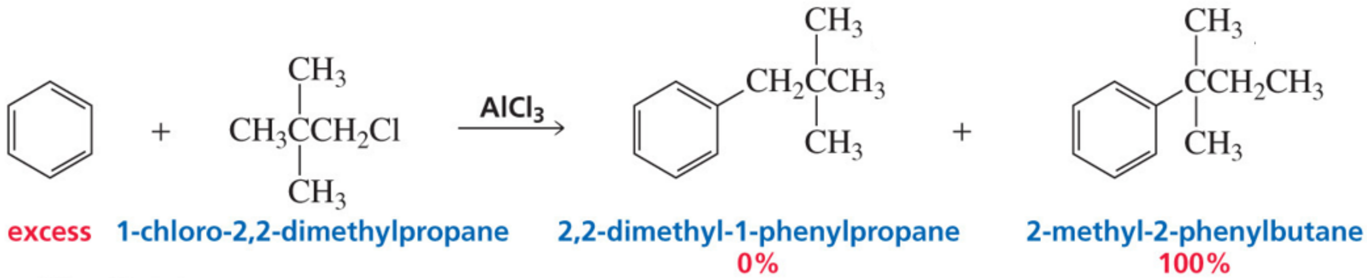


- Multiple alkylation occurs.
  - Alkyl bz is more reactive than bz. ← ED R
  - For monosubstitution, use xs bz.

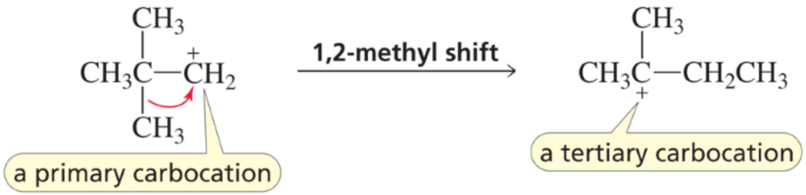
- C^+ rearrangement occurs.



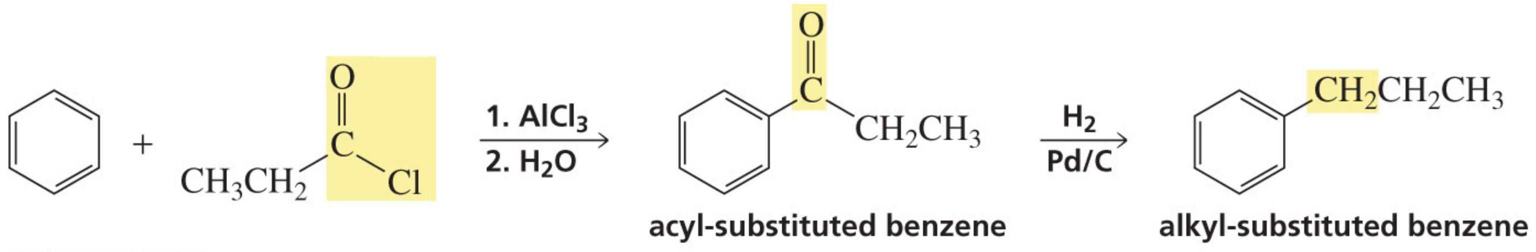




- 3° > 2° >> 1 °

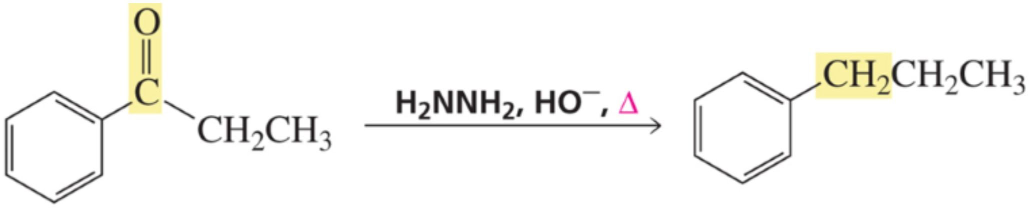


Aklkylation by acylation-reduction

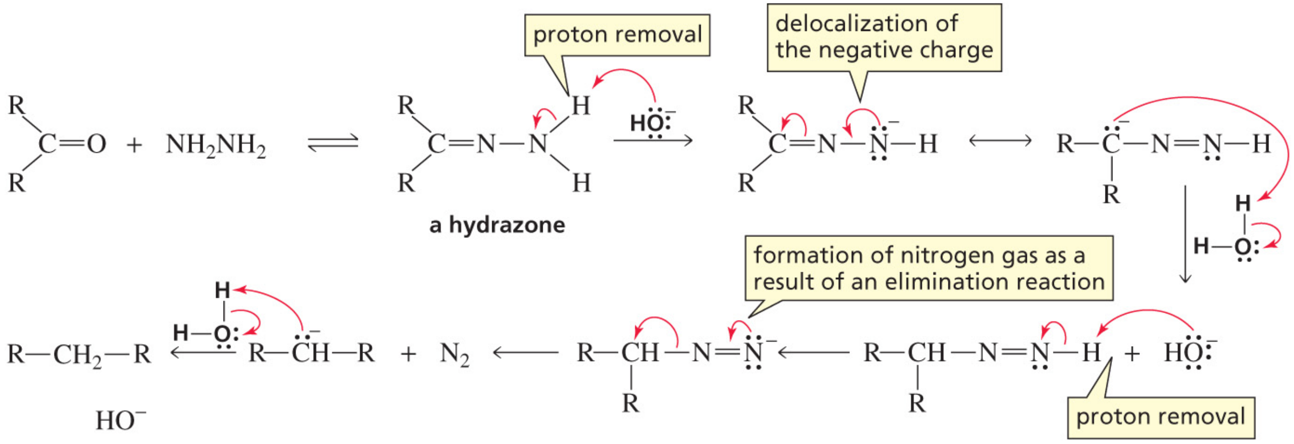


- F-C acylation then reduction
  - to obtain straight-chain alkyl bz
    - Acylium ion [acyl cation] does not rearrange.
    - (EW) acyl bz less reactive than bz → only one equiv bz needed
  - C=O reduced to CH_2 with H_2/Pd/C?
    - effective only for aroyl [C=O next to ring]
    - aliphatic C=O
      - NR with H_2/Pd/C
      - to CH–OH with H_2/Raney Ni or $NaBH_4$ §16.6

- F-C acylation then reduction
  - another method for C=O to CH_2 = Wolff-Kishner reduction

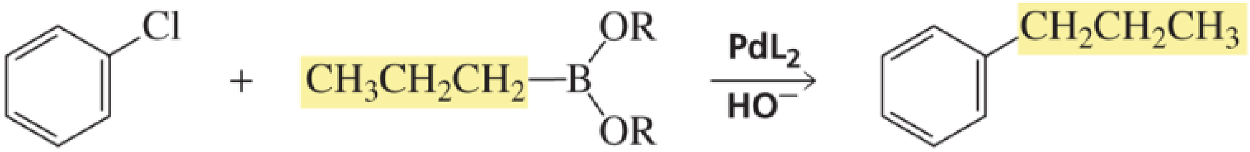


  - for all ketones [not only for aroyls]

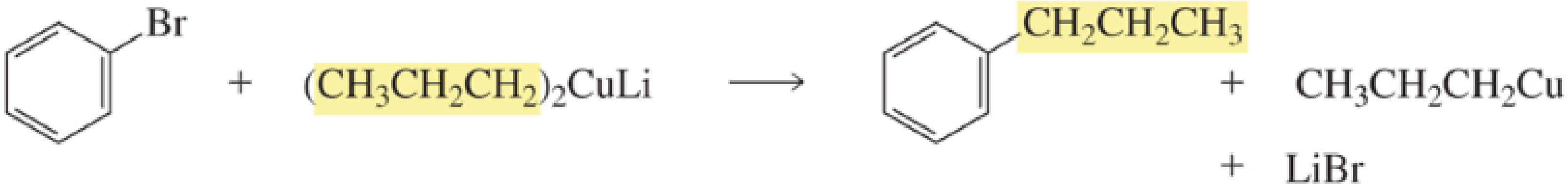


Alkyl bz using coupling rxn

- Suzuki rxn

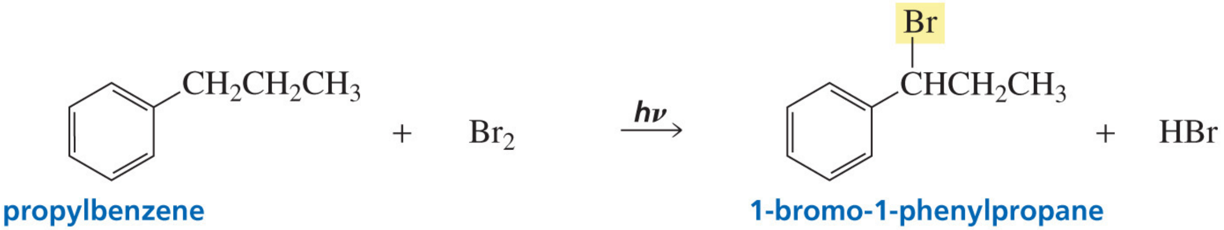


- Gilman reagent

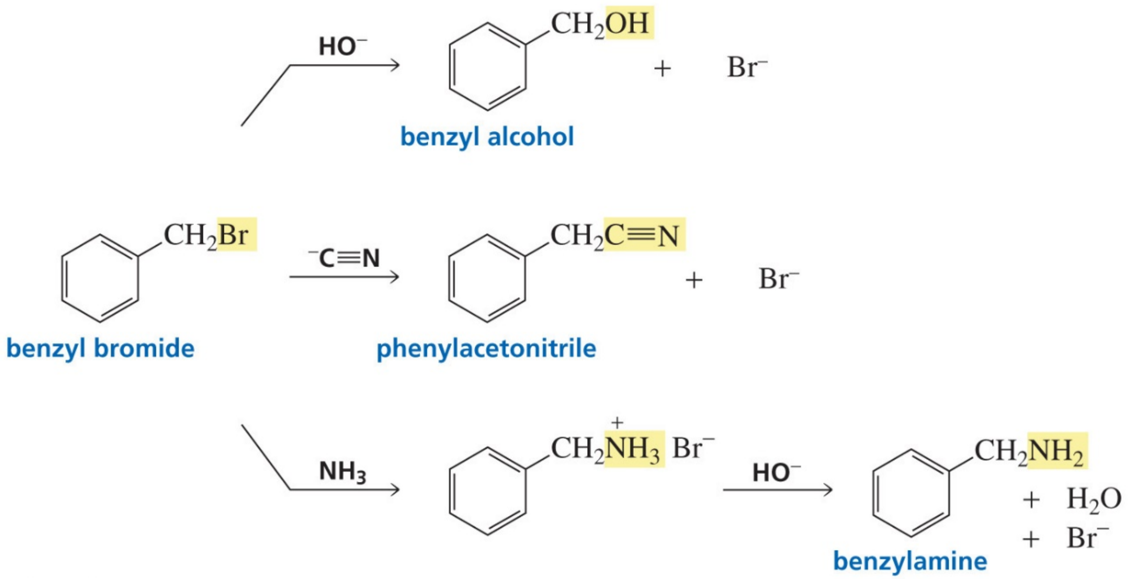


Converting subs

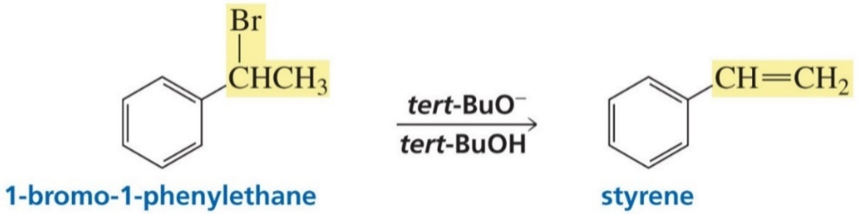
- alkyl



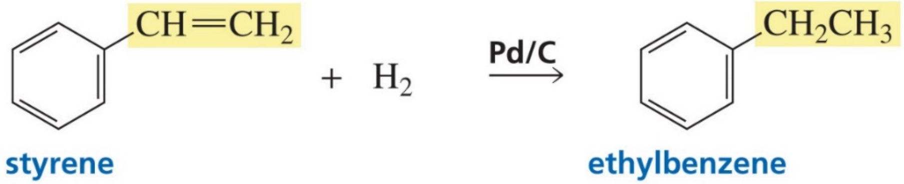
- benzyl halide
  - S_N1 or S_N2

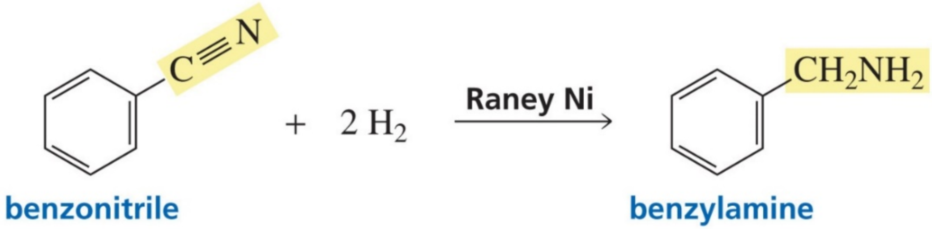


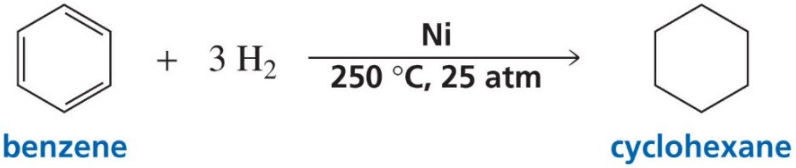
  - E1 or E2

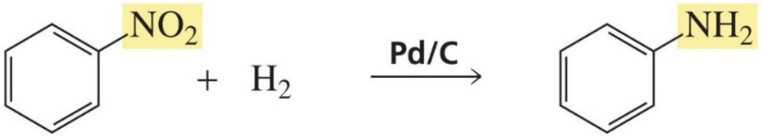


- reduction

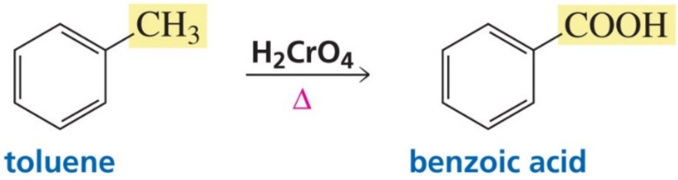

CH=CH2
+ H2
Pd/C
CH2CH3
styrene
ethylbenzene


C≡N
+ 2 H2
Raney Ni
CH2NH2
benzonitrile
benzylamine

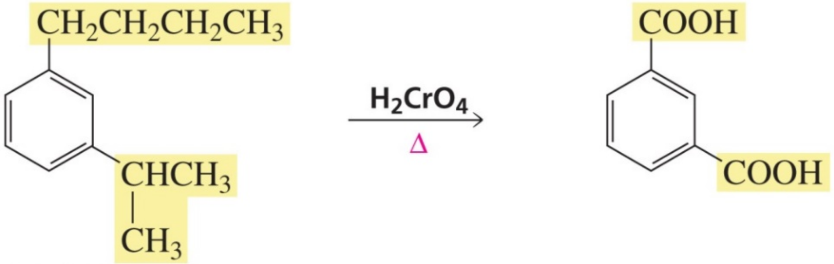

+ 3 H2
Ni
250 °C, 25 atm
benzene
cyclohexane


NO2
+ H2
Pd/C
NH2

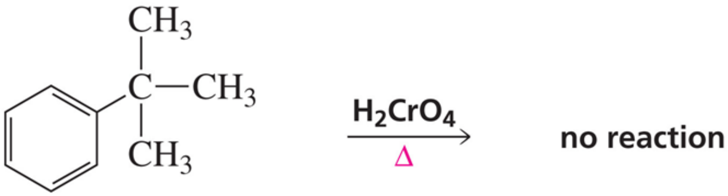
- oxidation



  - Oxidation at benzylic C
    - All alkyl oxidized to COOH.



    - No oxidation if no benzylic H



  - Other oxidizing agent like $KMnO_4$, $K_2Cr_2O_7$ can also be used.