Polynuclear Aromatic Hydrocarbons

- Compounds in which 2 or more benzene rings are fused together.
- They are either:
  - ✓ Isolated

    or
  - ✓ Fused

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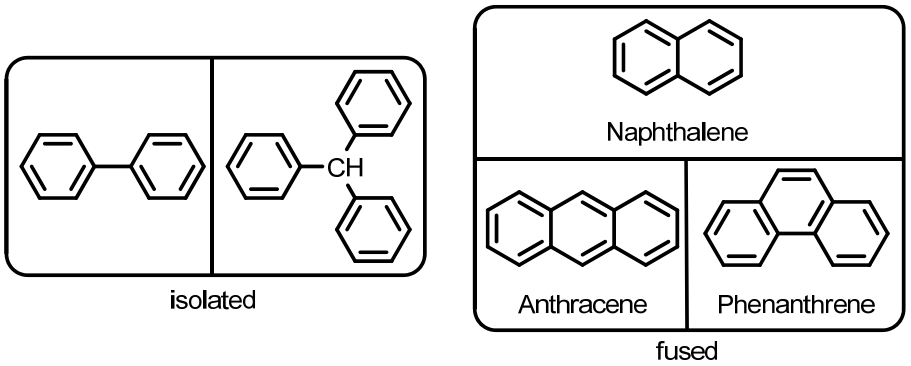
Examples:



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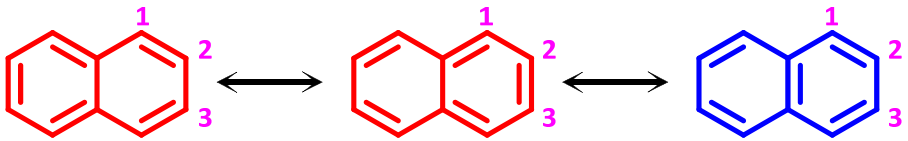
Naphthalene



10 π-electrons

2 benzene rings

- 3 canonical contributors.
- Is Hückel rule obeyed?
- How aromatic is naphthalene?
  - ❖ Naphthalene vs benzene!
- Resonance energy.

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Resonance Energy

- The difference between the potential energy of the actual structure (the resonance hybrid) and that of the contributing structure with the lowest potential energy.

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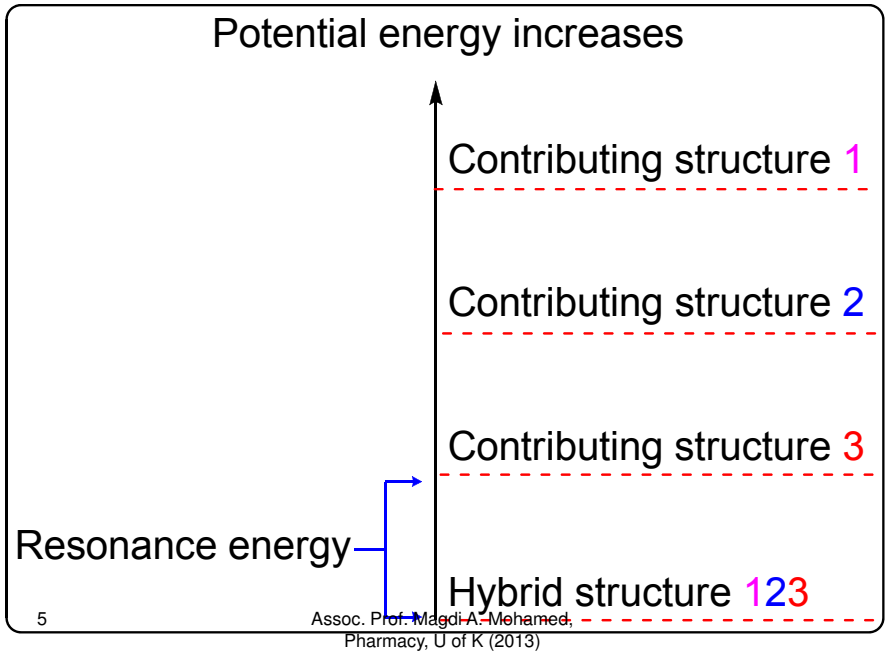
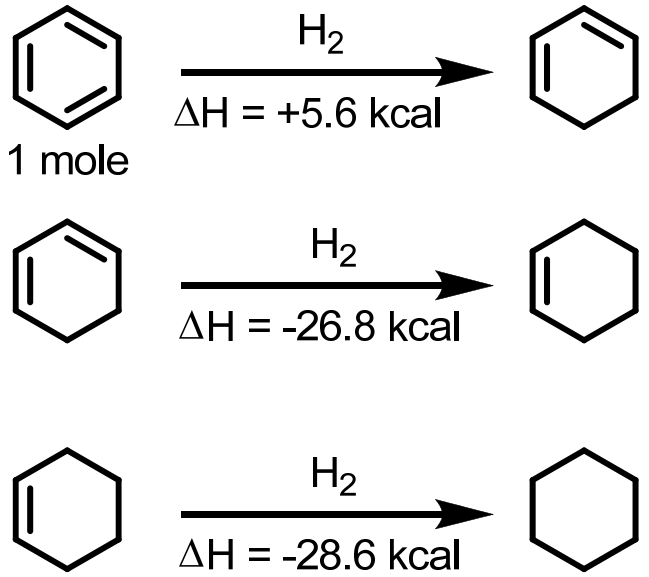
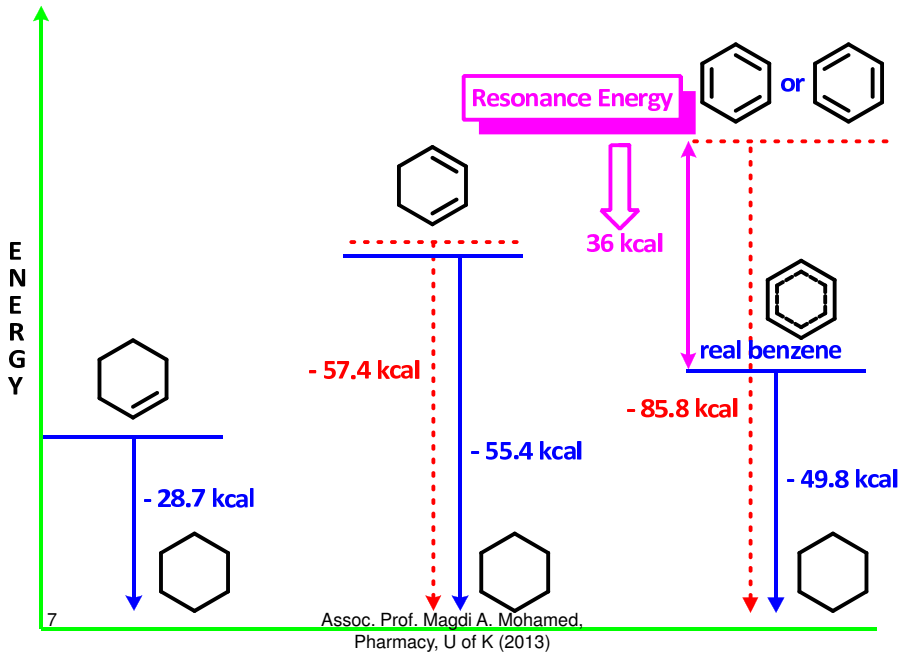
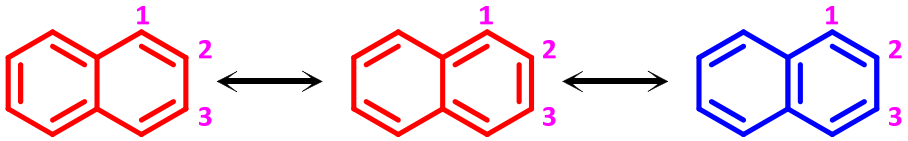






- 49.8 kcal is delivered on complete hydrogenation of benzene (1 mole) to cyclohexane via 1,3-cyclohexadiene and cyclohexene.
- The difference between the hydrogenation energy of three 'non-resonance' double bonds and the measured hydrogenation energy: (3×28.6) - 49.8 = 36 kcal (resonance energy).

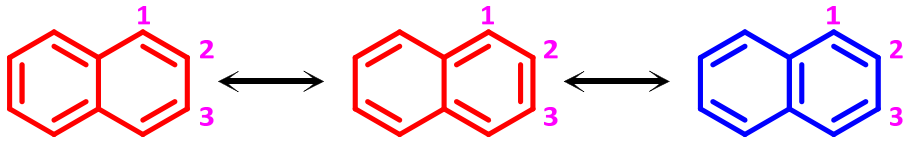
Naphthalene vs Benzene



10 π-electrons 2 benzene rings

- 3 canonical contributors.
- Resonance energy is 61 kcal/mole.
- Resonance energy for benzene is 36 kcal/mole.
- 11 kcal/mole less than that of 2 benzene rings.

Naphthalene vs Benzene



10 π-electrons 2 benzene rings

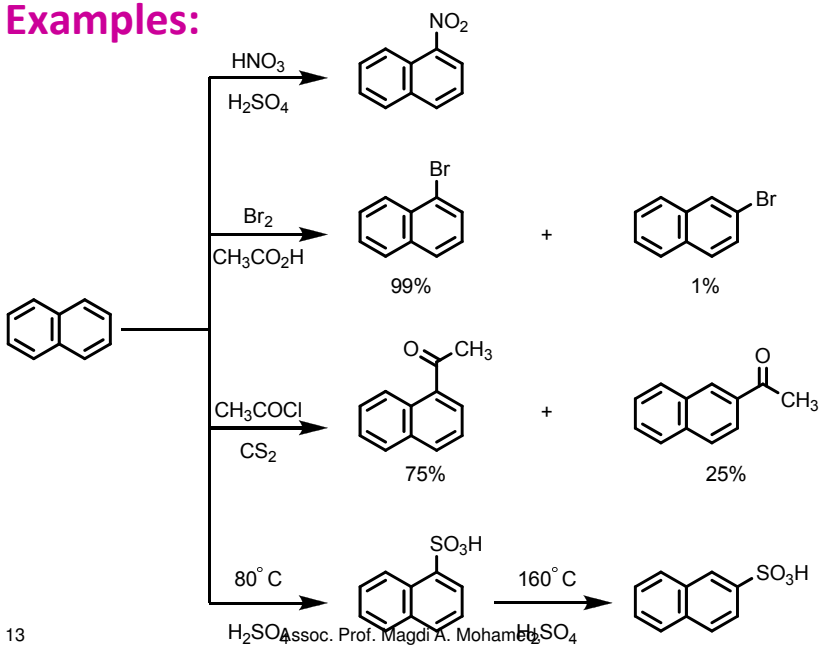
- C_1–C_2 is 1.36 Å (more π character).
- C_2 –C_3 1.42 Å (more σ character).
- Contrast with benzene; C–C bond length is common = 1.39 Å.

Conclusion

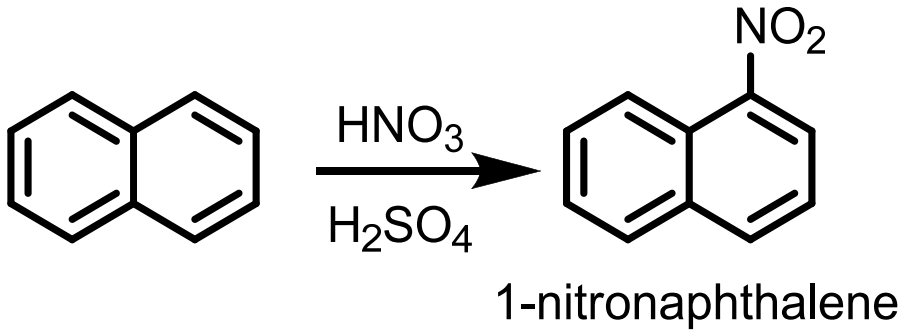
- Naphthalene is less aromatic than benzene.
- Hence, more reactive than benzene both in substitution and addition reactions.

Electrophilic Aromatic Substitution Reactions of Naphthalene

Examples:

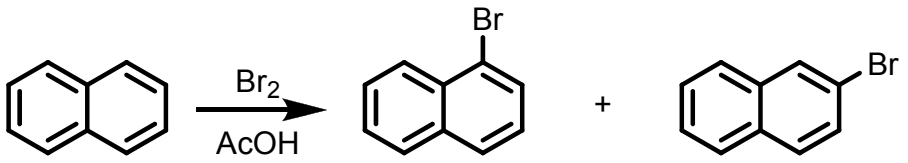


Nitration



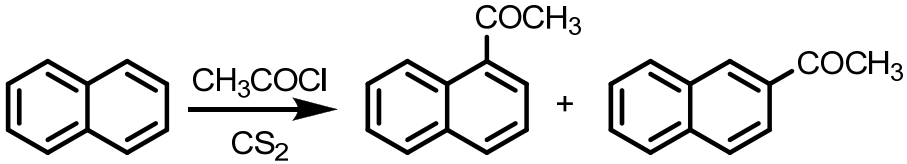
1-nitronaphthalene

Halogenation



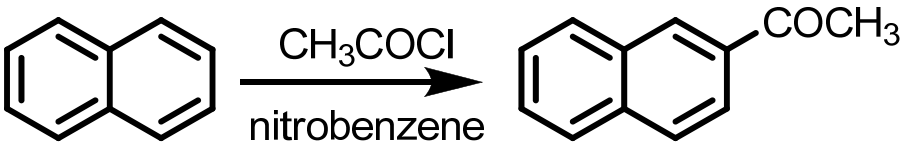
1-bromonaphthalene 99% 2-bromonaphthalene 1%

Friedel-Crafts Acylation

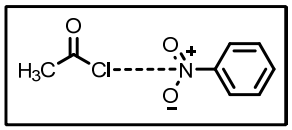


75% 25%

Friedel-Crafts Acylation: Solvent Effect



- Steric effect!



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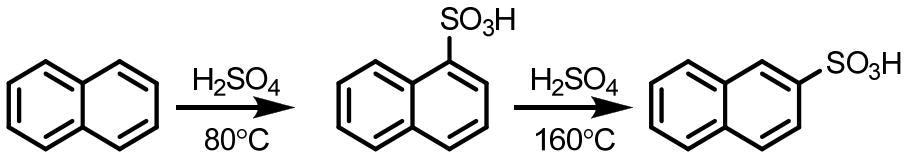
Sulfonation



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Rationale for Regioselectivity!?

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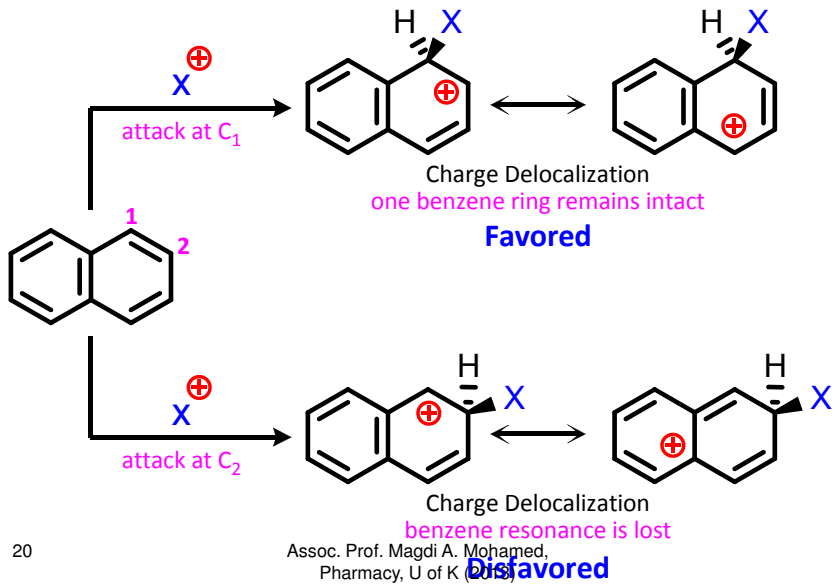
C_1–Isomer is Kinetically Favored!



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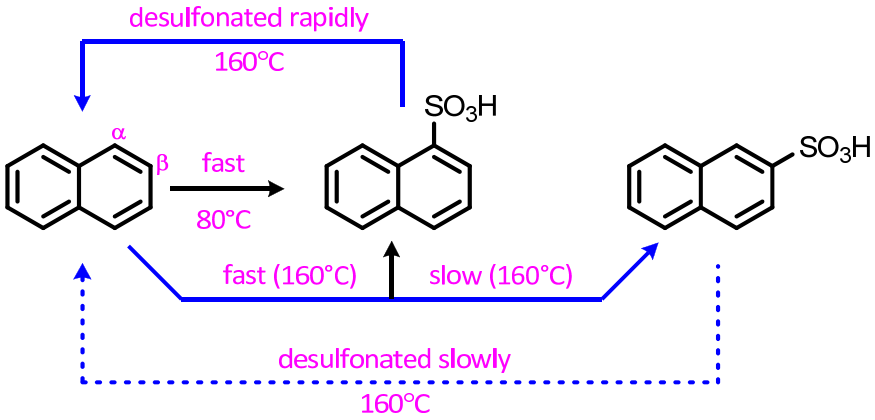
C_2–Isomer is Thermodynamically Favored!



- α-isomer is formed rapidly and desulfonated rapidly. β-isomer is formed slowly and desulfonated slowly.

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Sulfonation: Regioselectivity

- Kinetically controlled reaction favors α-isomer (kinetically stable isomer).
- Thermodynamically controlled reaction favors β-isomer (thermodynamically stable isomer).

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Oxidation & Reduction Reactions of Naphthalene

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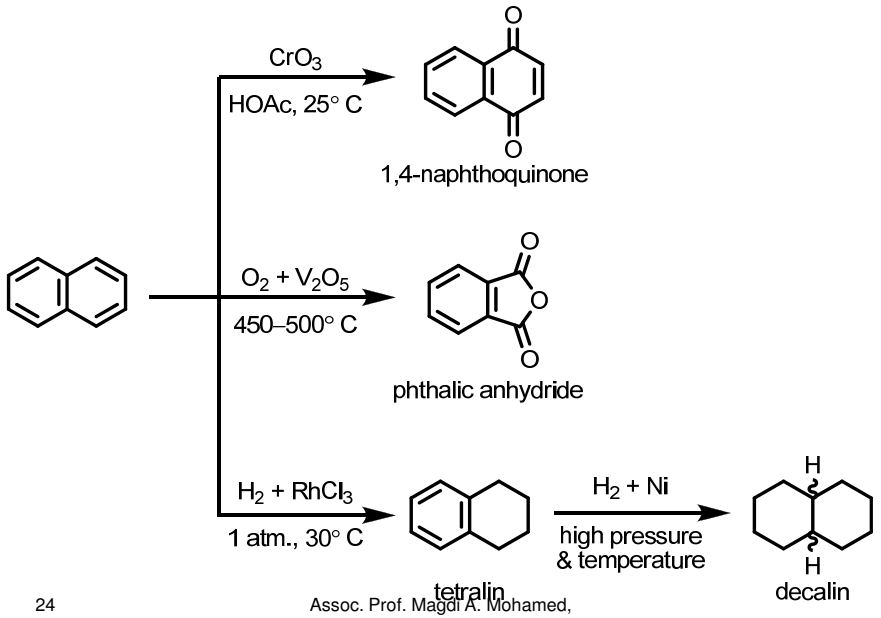

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- Deactivated rings resist oxidation.
- Activated rings are oxidized more easily than benzene ring.

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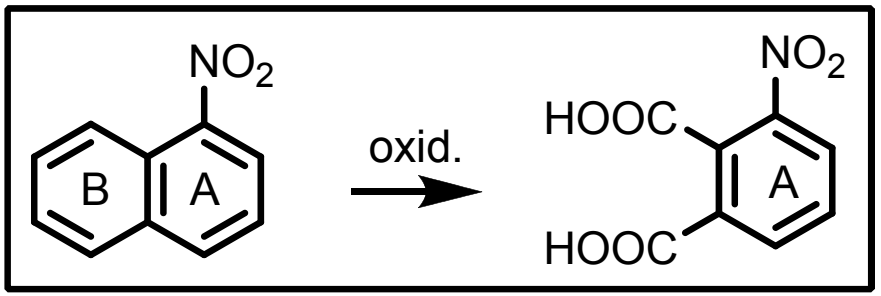

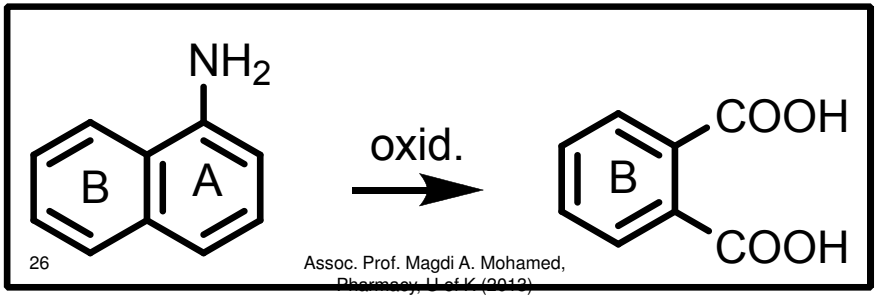

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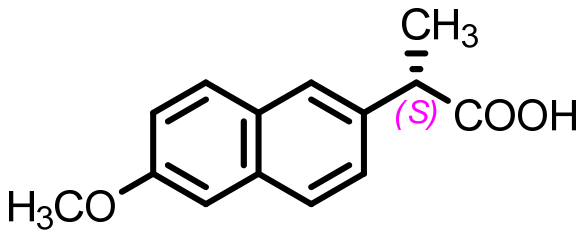
Naproxen



(*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid

- Stereogenic center (*R*/*S* enantiomers).
- (*S*)-enantiomer is the biologically active form and is 28 times more active than (*R*)-enantiomer.

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- How could we obtain an enantiomerically pure compound!?
  - ✓ Natural sources.
  - ✓ Optical resolution of racemic mixtures.
  - ✓ Asymmetric synthesis.

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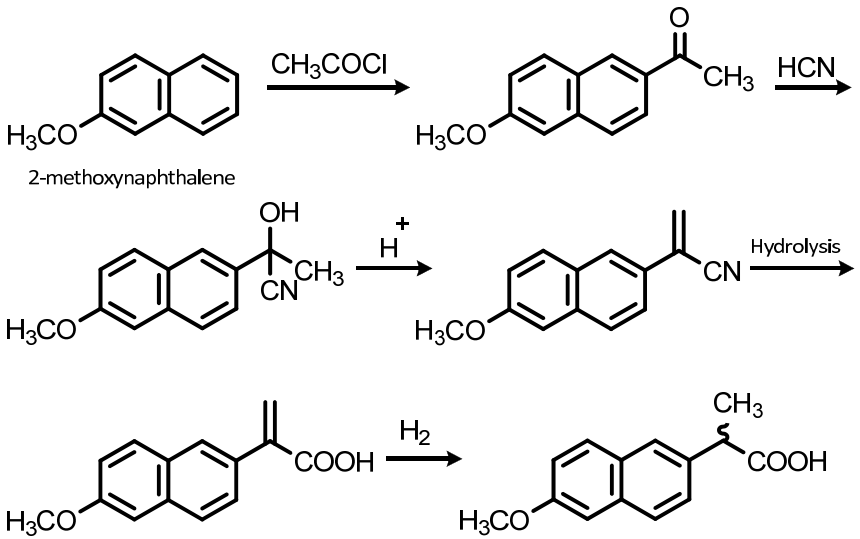
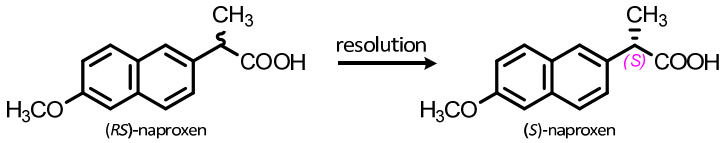
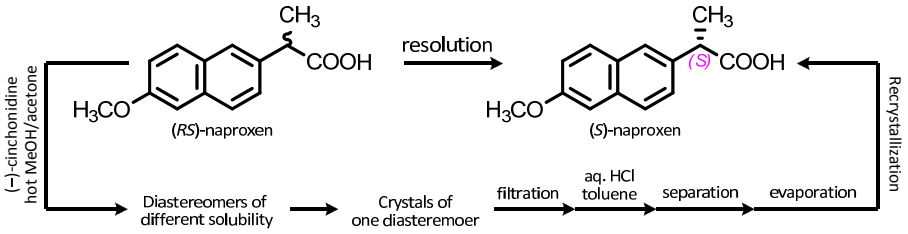
Racemic Synthesis of (*RS*)-Naproxen

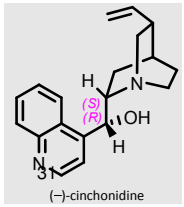


Optical Resolution of (*S*)-Naproxen

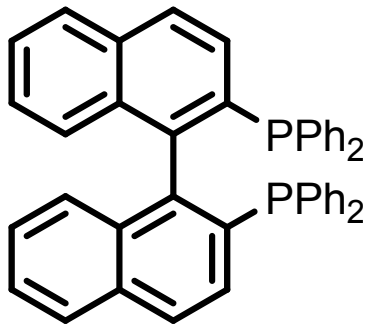


Optical Resolution of (*S*)-Naproxen

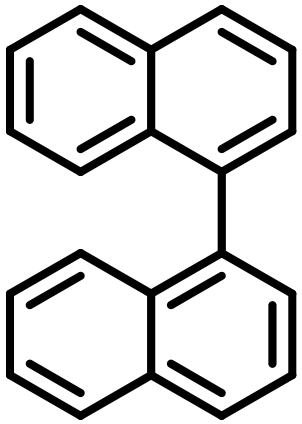




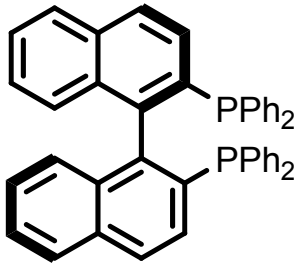
BINAP



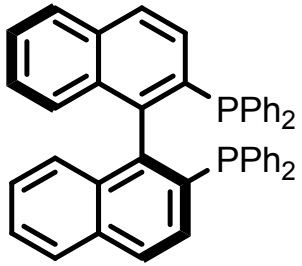
- 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
- Can you see any sort of isomerism!!?????



BINAP



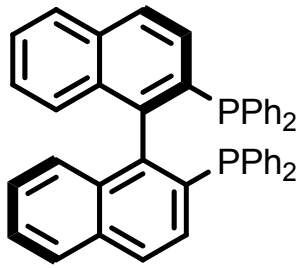
(*R*)-BINAP



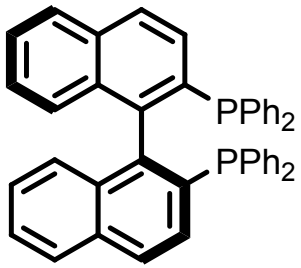
(*S*)-BINAP

- Restricted rotation (axial chirality).
- Not possible to interconvert.

BINAP



(*R*)-BINAP



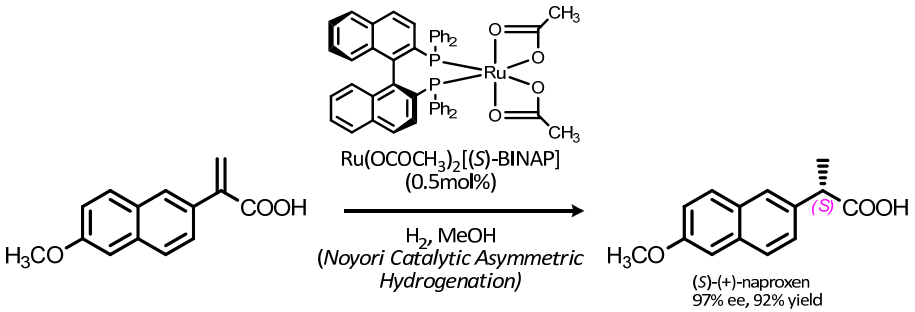
(*S*)-BINAP

- Chelating diphosphine chiral ligand (*R* or *S*).

Asymmetric Synthesis

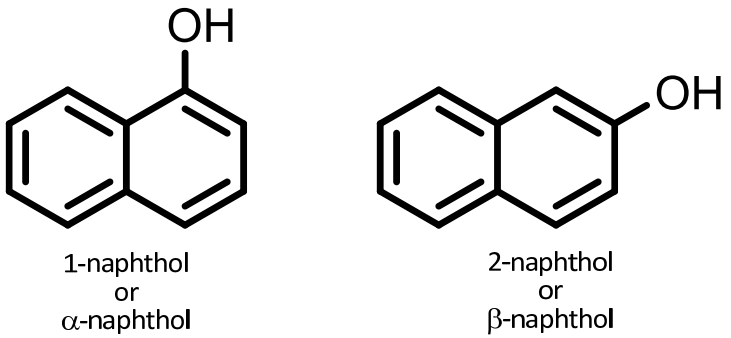
- Synthesis of an stereoisomer in a pure (or nearly pure) stereoisomeric form.
- Most important strategies are:
  - ✓ Chiral pool.
  - ✓ Chiral ligand controlled.
  - ✓ Chiral auxilliary.
  - ✓ Substrate controlled.

Chiral Ligand-Controlled Asymmetric Synthesis of (*S*)-Naproxen



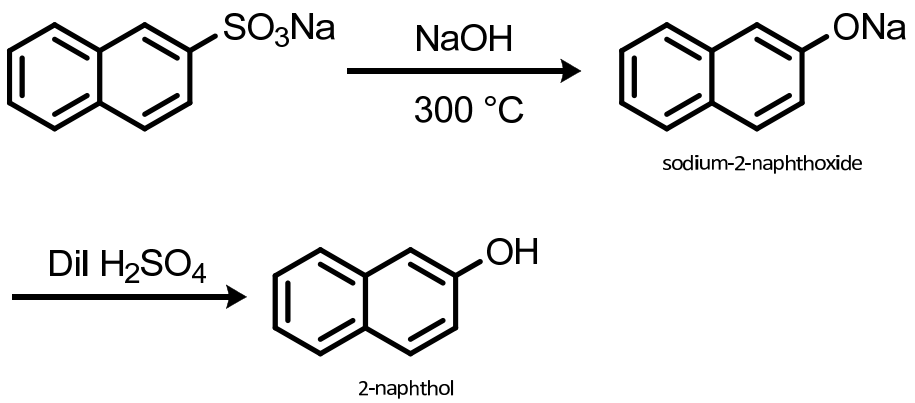
- The metal sits between the two phosphorous atoms firmly anchored in a chiral environment.
- The catalyst selects enantiotopic face of the double bond and adds hydrogen across it.

Naphthols

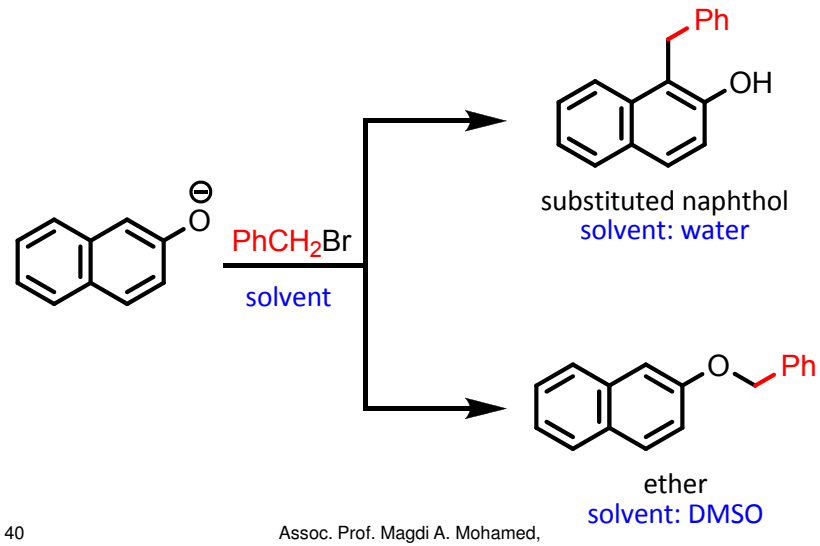


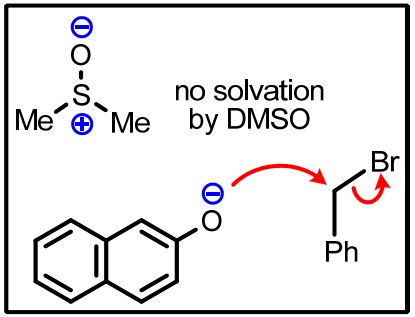
- Homologous of phenol.
- More reactive than phenol (why?).

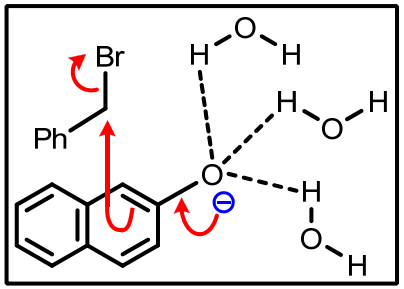
General Synthesis of Naphthols



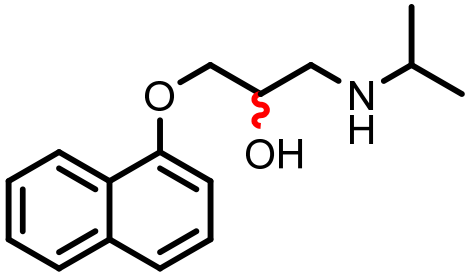
How can you account for the following?







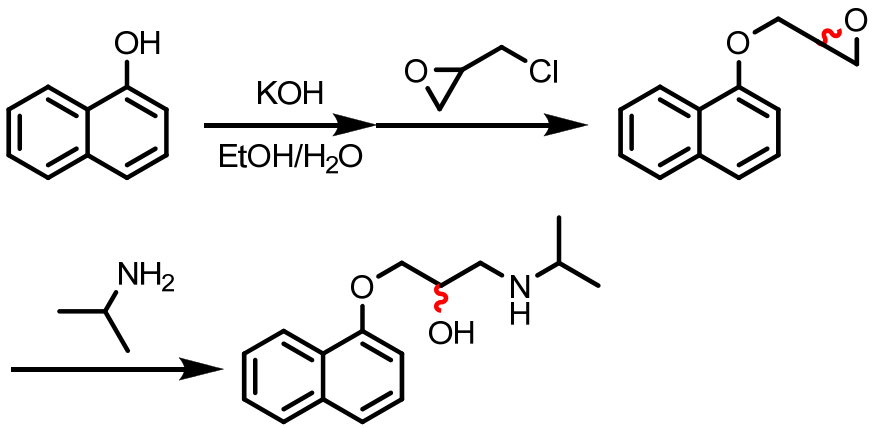
Propranolol



(*RS*)-propranolol

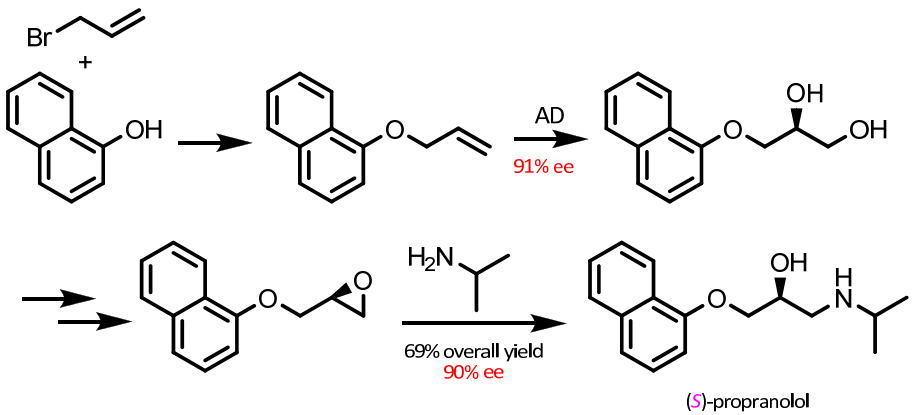
- Nonselective adrenergic antagonist (β1, β2-blocker).
- Treatment of angina and hypertension.

Racemic Synthesis of (*RS*)-Propranolol



(*RS*)-propranolol

Enantioselective Synthesis of (*S*)-Propranolol



(*S*)-propranolol

Regioselectivity in E.A.S. Reactions in Naphthalene Derivatives

- Activating group directs substituent to the same ring (homonuclear substitution):
  - ✓ Activating group at position 1 directs substituent to position 4 and to a lesser extent position 2.
  - ✓ Activating group at position 2 directs substituent to position 1.
- Deactivating group (at position 1 or 2) directs substitution to other ring:
  - ✓ α-Position in case of nitration or halogenation.
  - ✓ β-Position in case of sulfonation.

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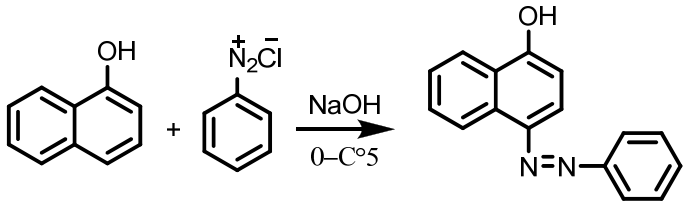
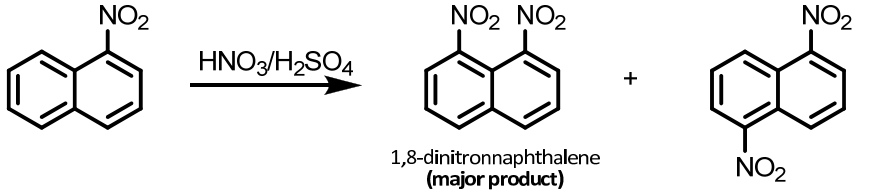
ACTIVATING GROUP:



DEACTIVATING GROUP:



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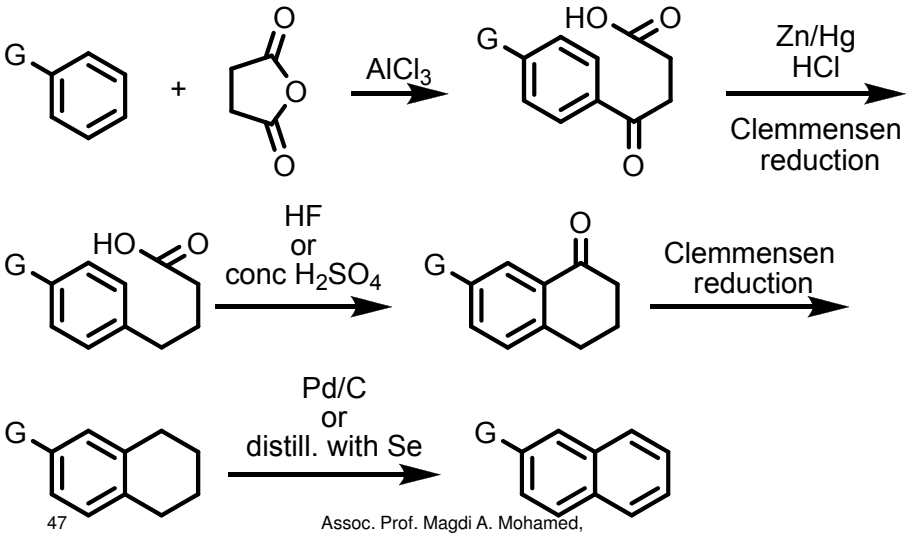
Synthesis of Naphthalene Derivatives



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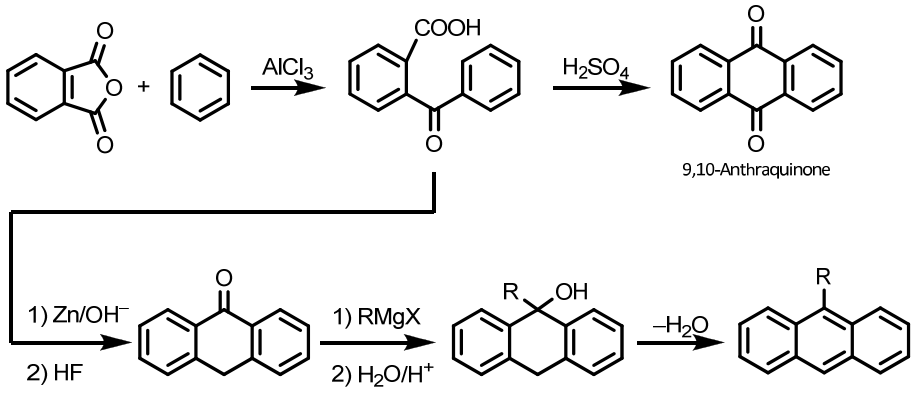
Synthesis of Anthracene Derivatives



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Synthesis of Phenanthrene