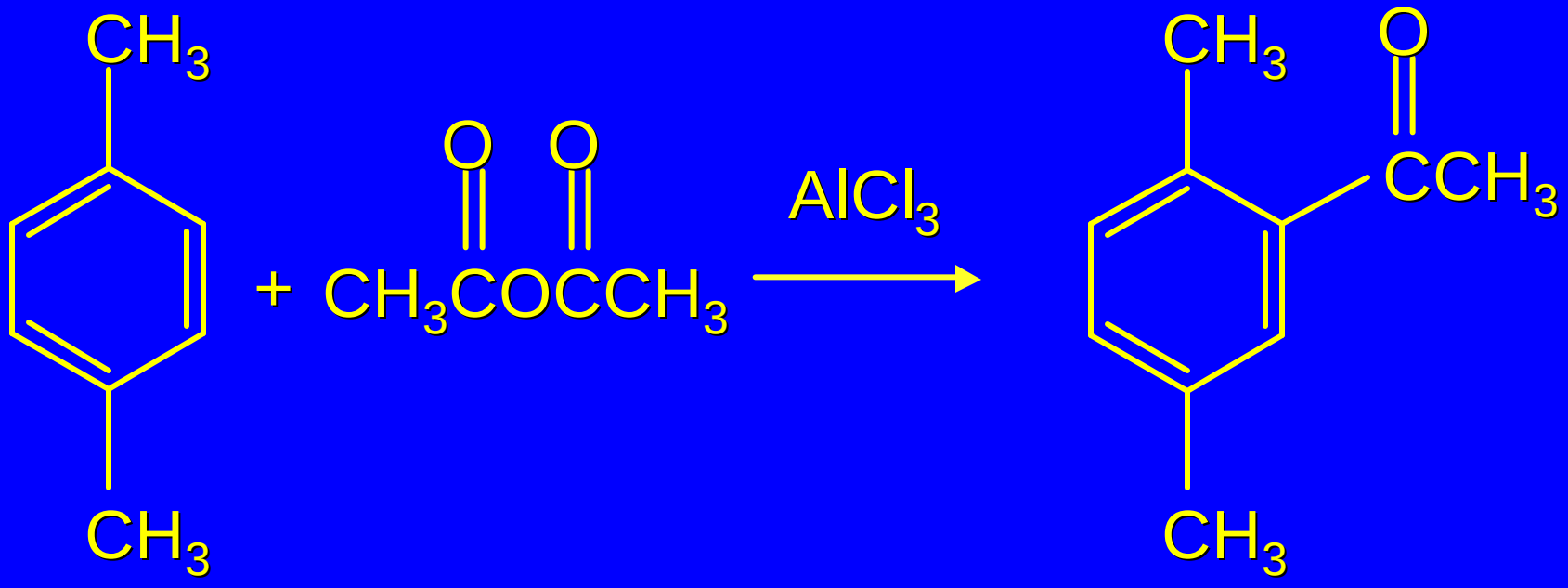
12.15

Multiple Substituent Effects

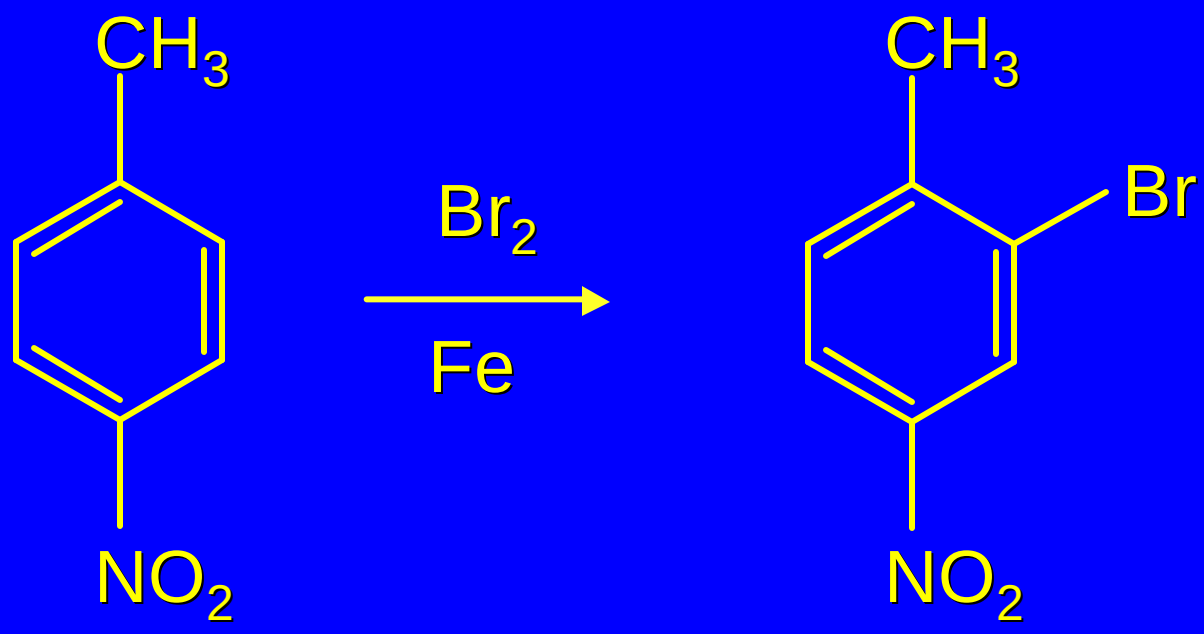
The Simplest Case

all possible EAS sites may be equivalent



99%

Another Straightforward Case



86-90%

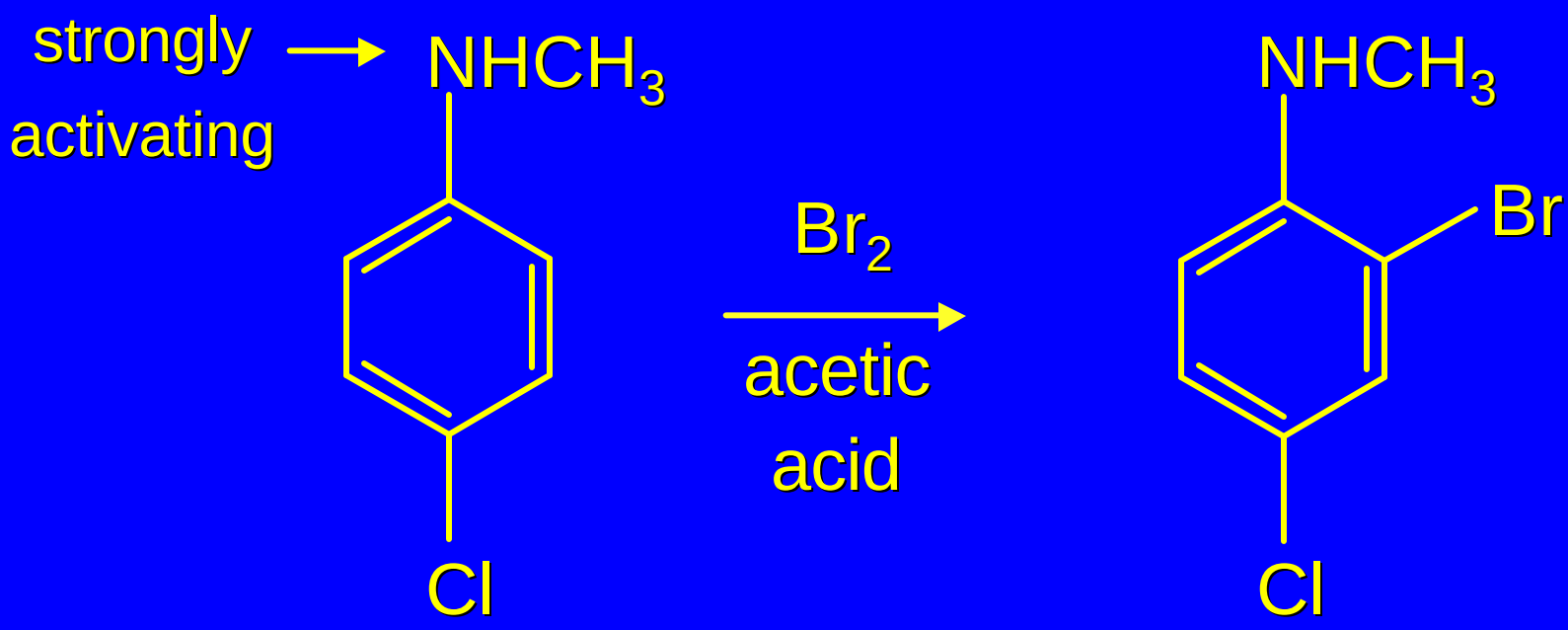
directing effects of substituents reinforce each other; substitution takes place ortho to the methyl group and meta to the nitro group

Generalization

regioselectivity is controlled by the most activating substituent

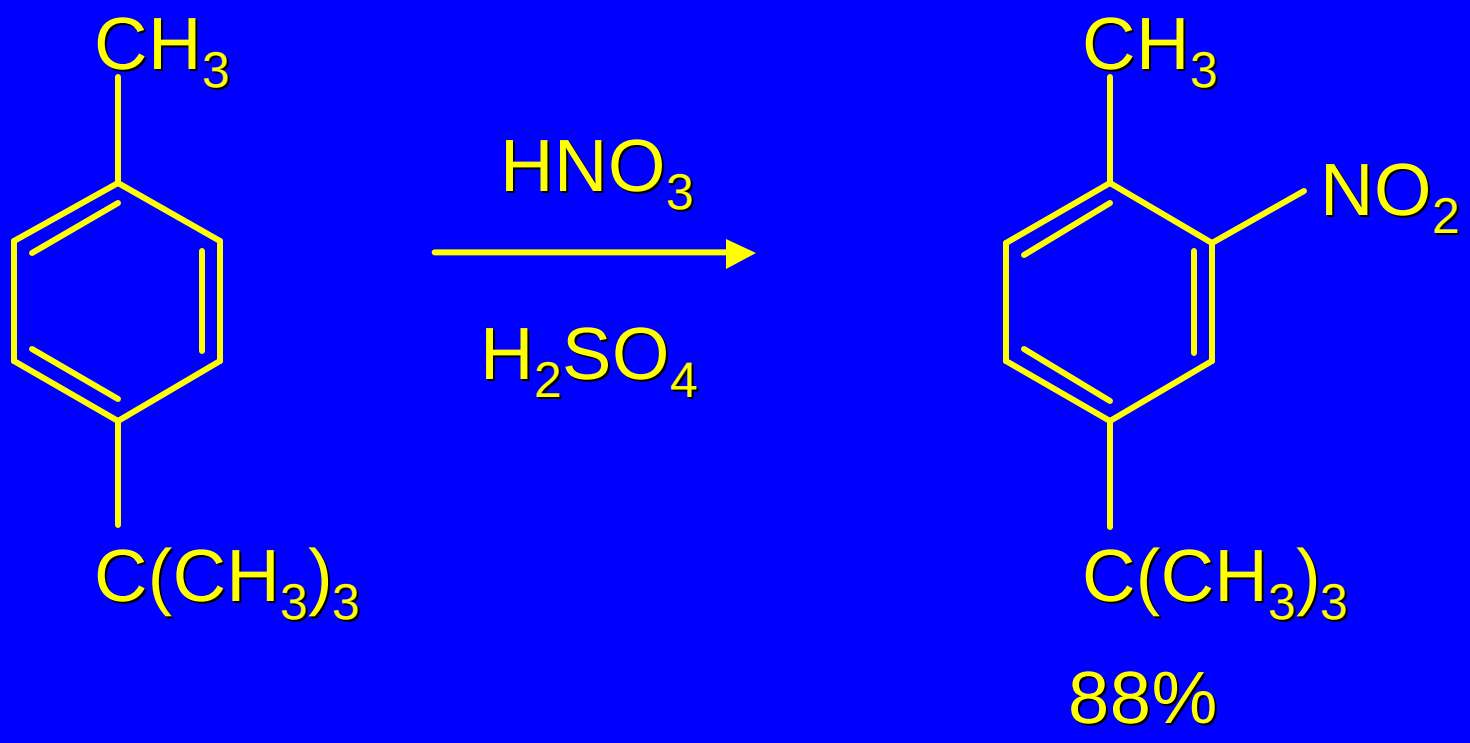
The Simplest Case

all possible EAS sites may be equivalent



87%

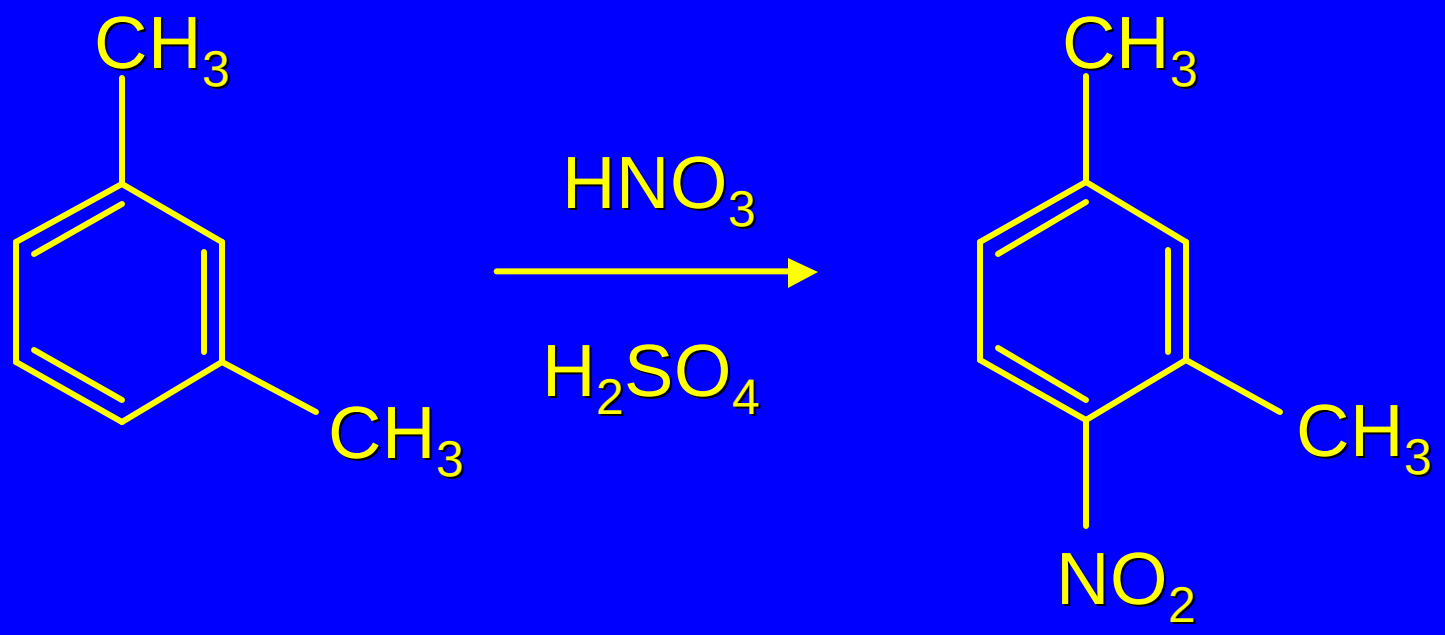
When activating effects are similar…



88%

substitution occurs ortho to the smaller group

Steric effects control regioselectivity when electronic effects are similar



98%

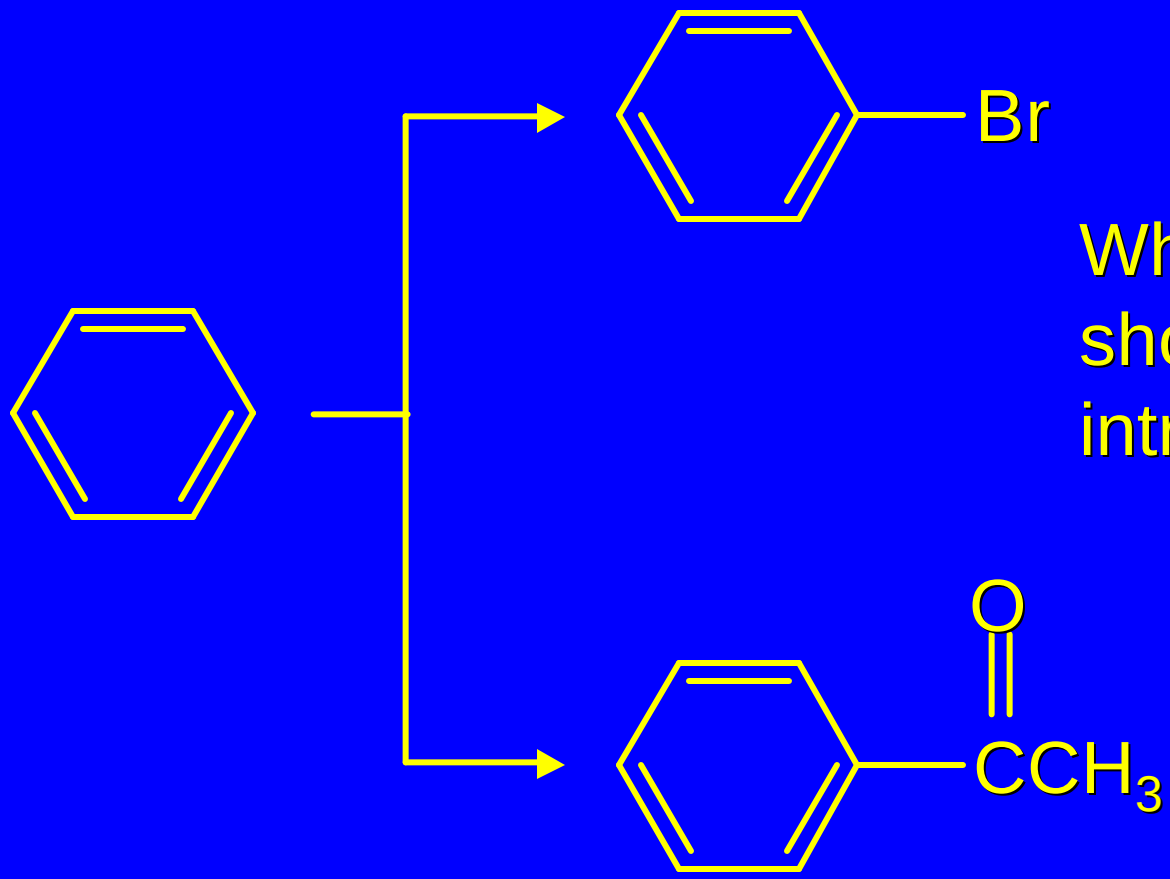
position between two substituents is last position to be substituted

12.16
Regioselective Synthesis of Disubstituted Aromatic Compounds

Factors to Consider

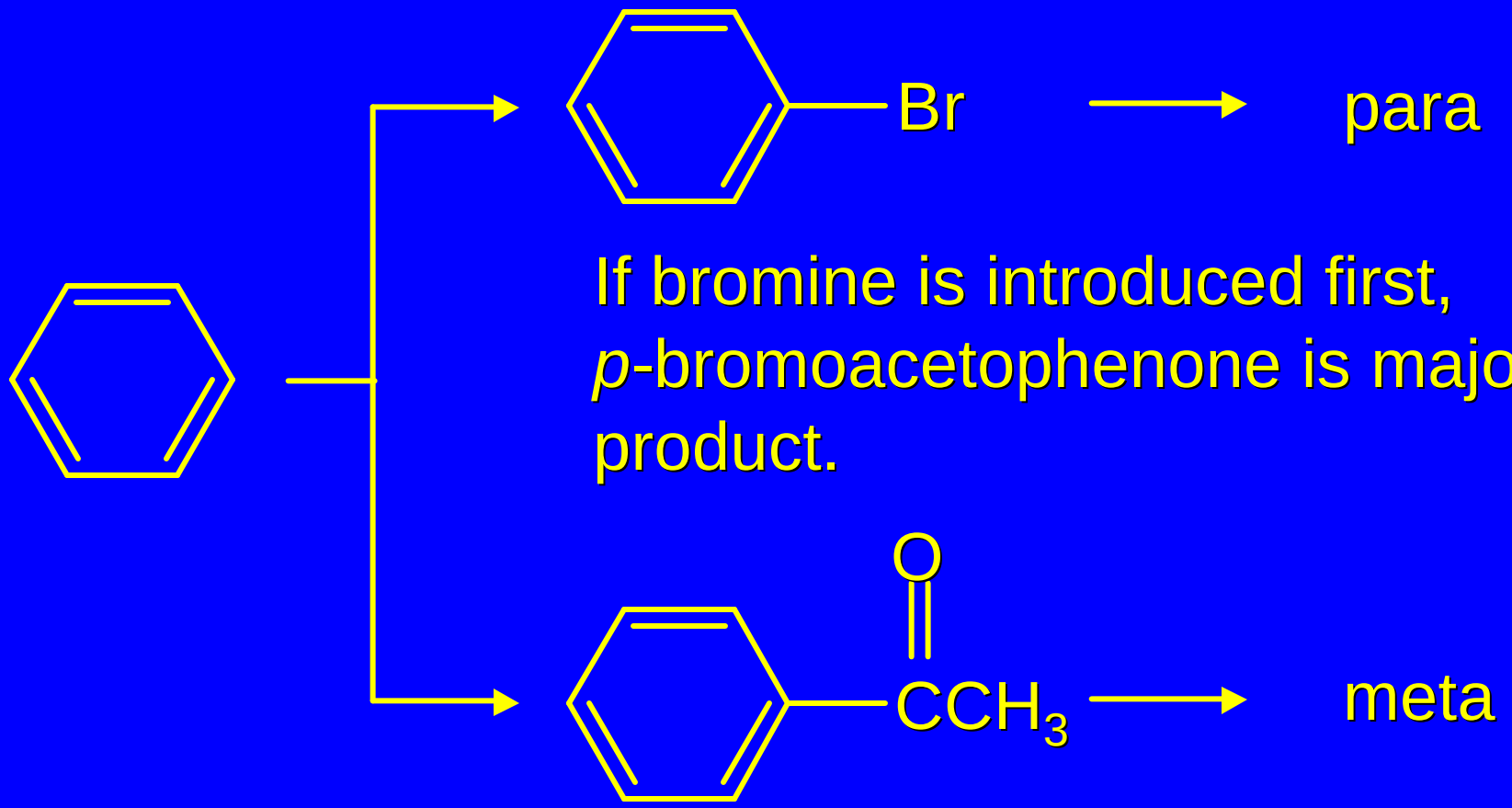
order of introduction of substituents to ensure correct orientation

Synthesis of m-Bromoacetophenone



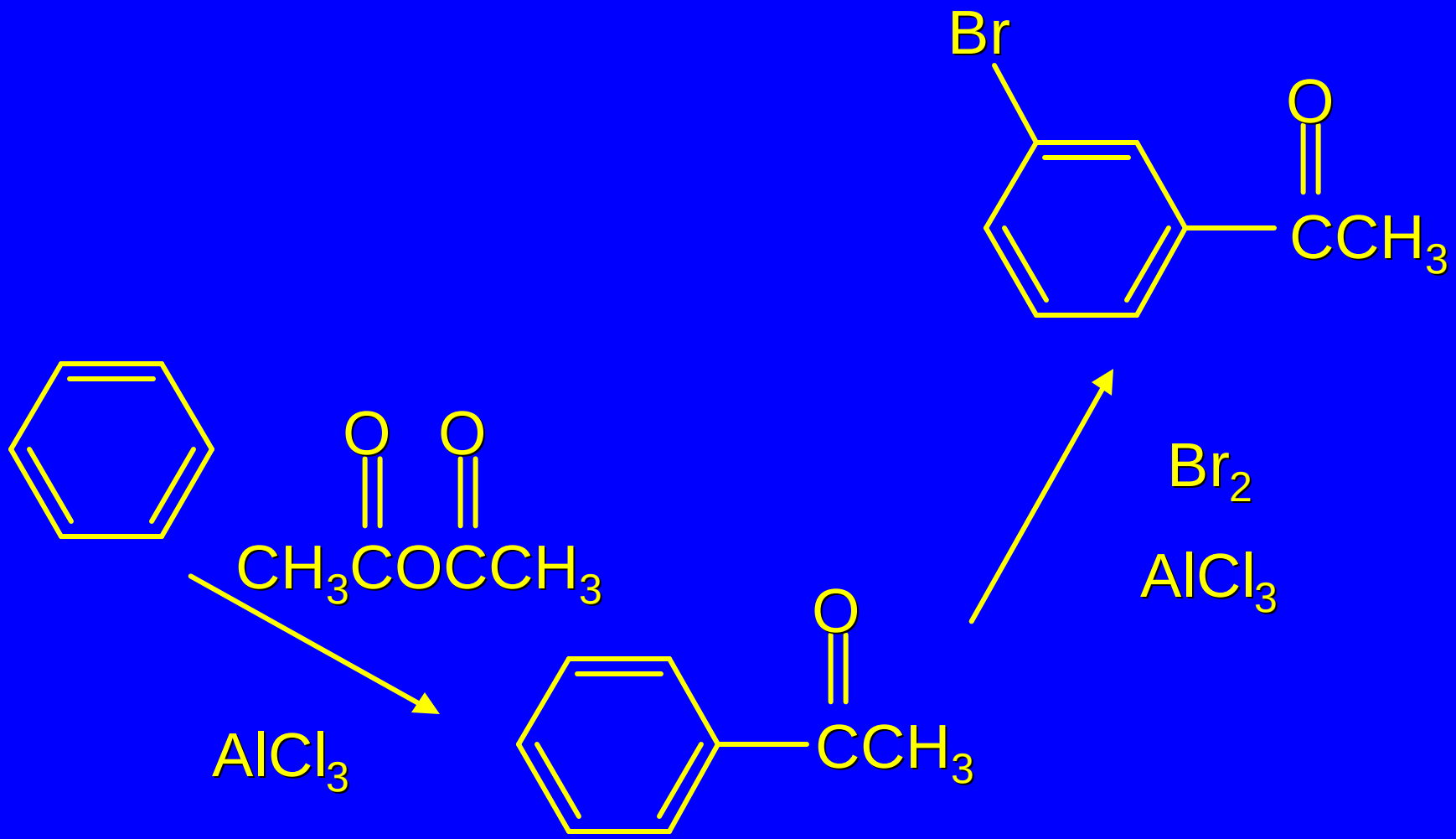
Which substituent should be introduced first?

Synthesis of m-Bromoacetophenone



If bromine is introduced first, *p*-bromoacetophenone is major product.

Synthesis of m-Bromoacetophenone

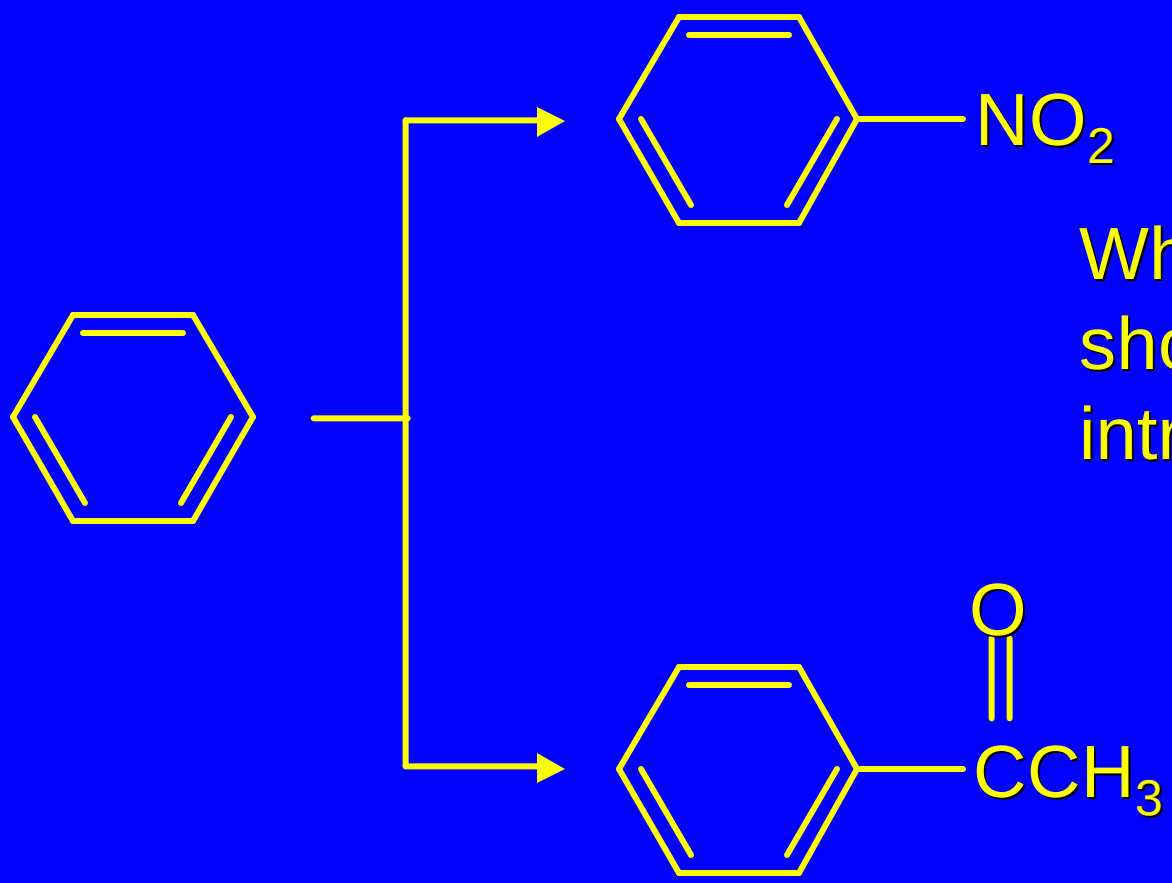


Factors to Consider

order of introduction of substituents to ensure correct orientation

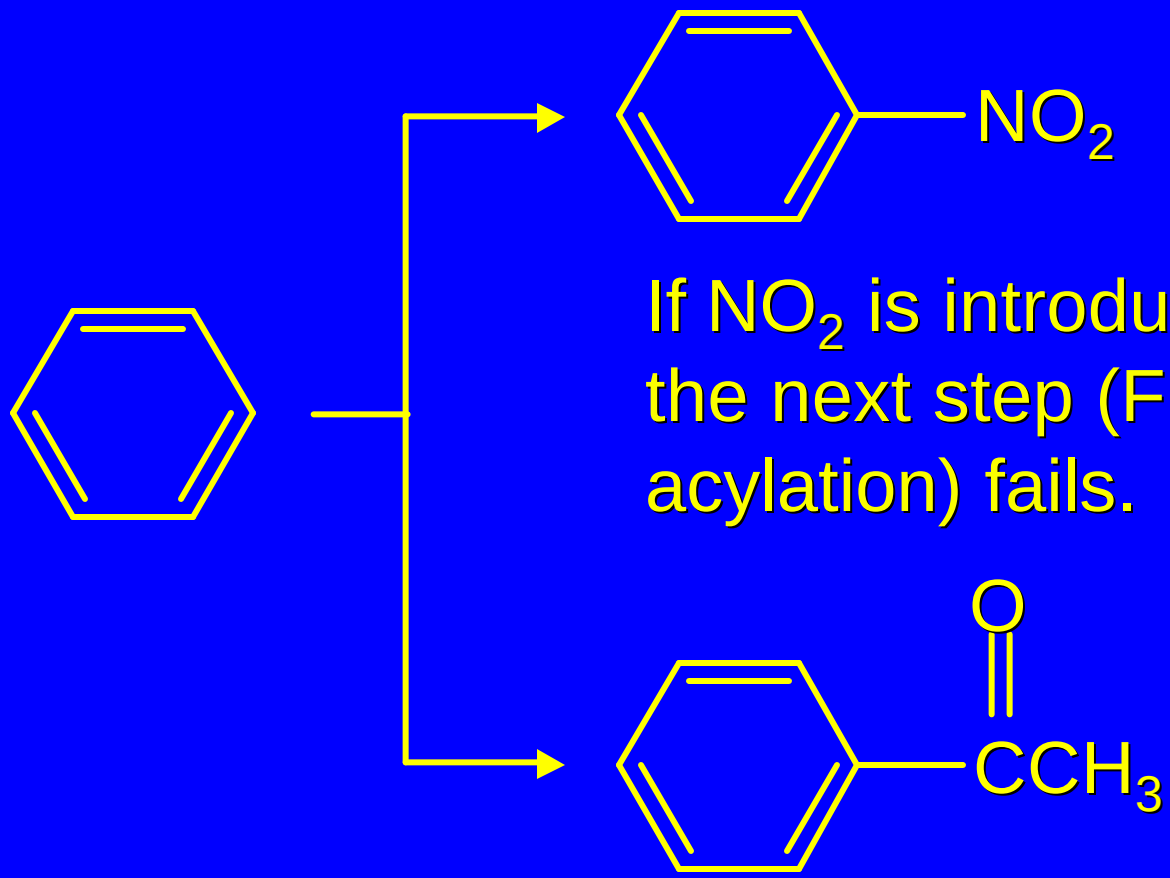
Friedel-Crafts reactions (alkylation, acylation) cannot be carried out on strongly deactivated aromatics

Synthesis of m-Nitroacetophenone



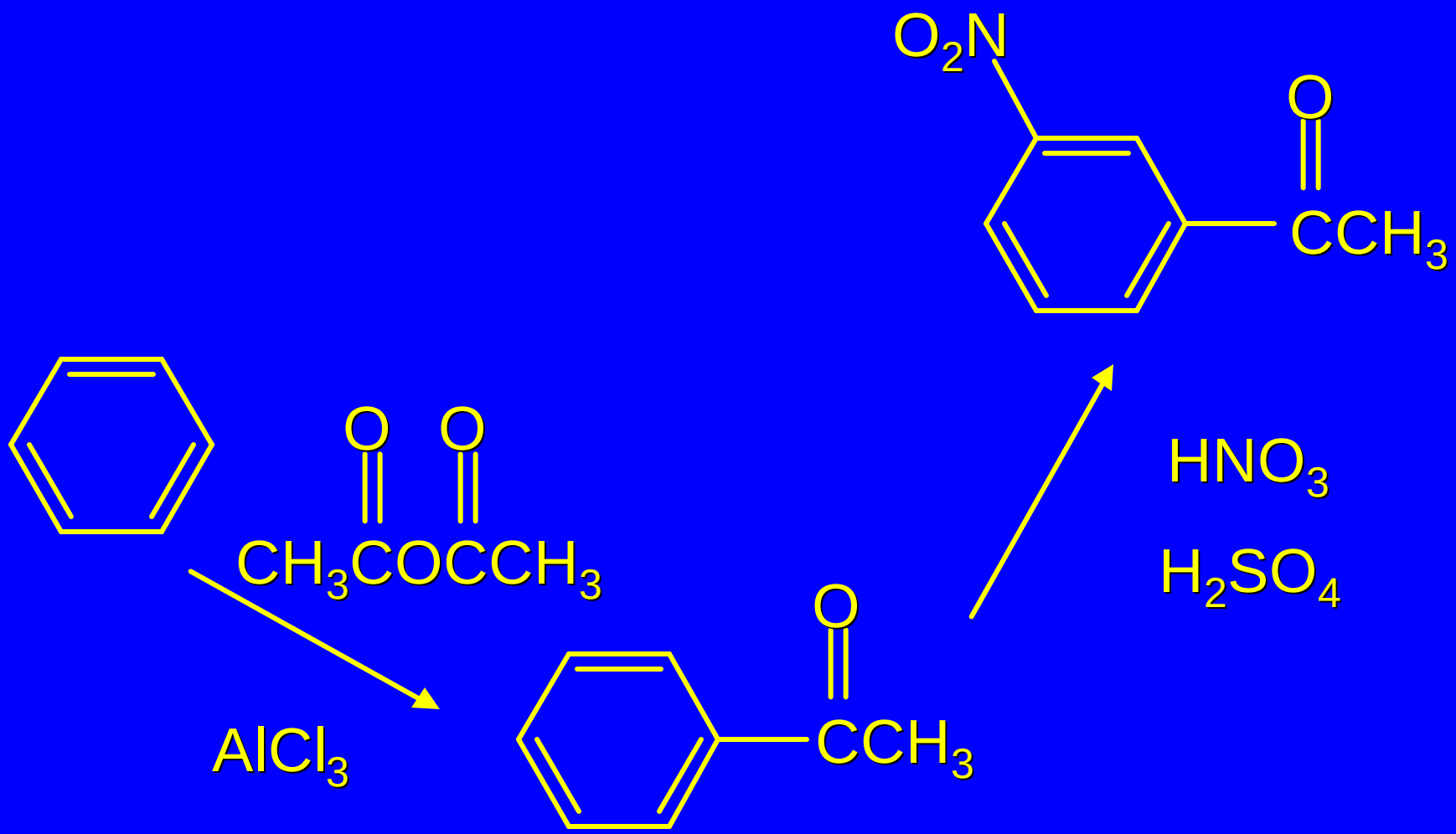
Which substituent should be introduced first?

Synthesis of m-Nitroacetophenone



If NO_2 is introduced first, the next step (Friedel-Crafts acylation) fails.

Synthesis of m-Nitroacetophenone



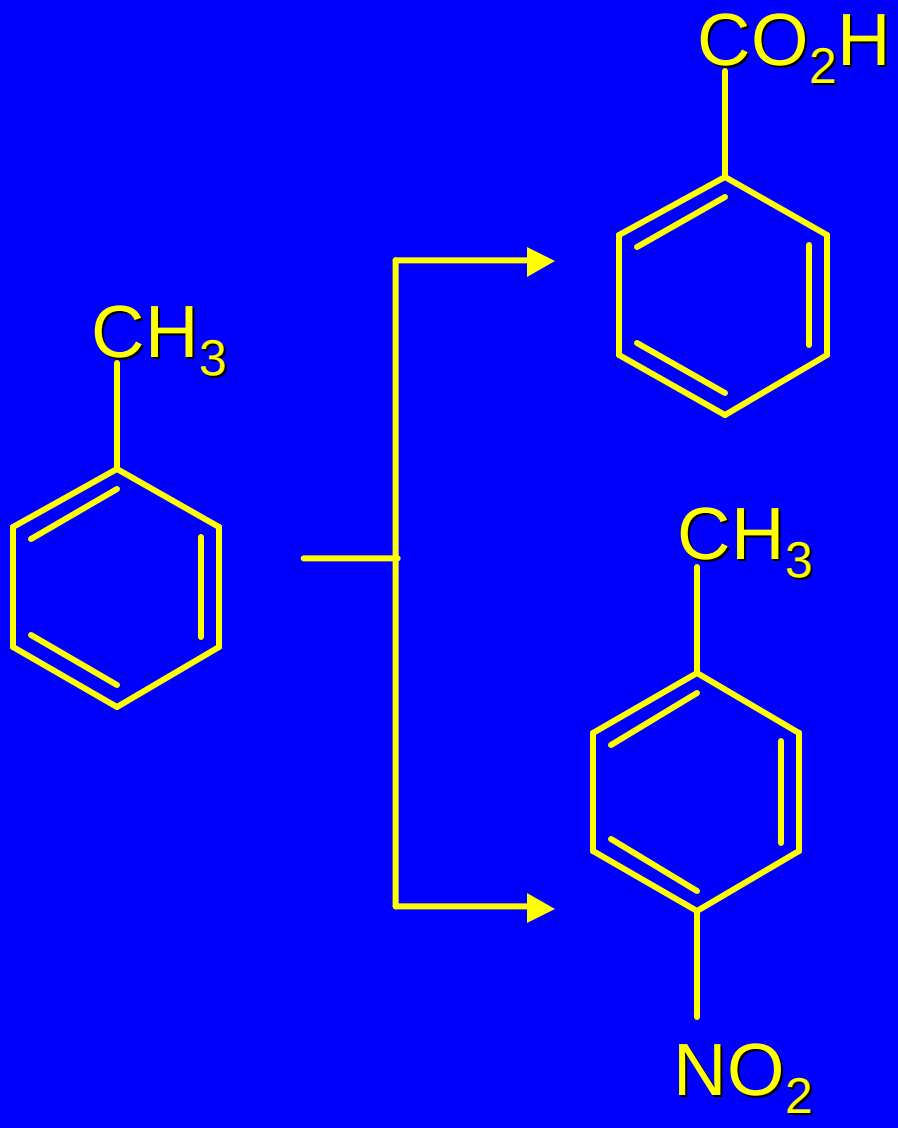
Factors to Consider

order of introduction of substituents to ensure correct orientation

Friedel-Crafts reactions (alkylation, acylation) cannot be carried out on strongly deactivated aromatics

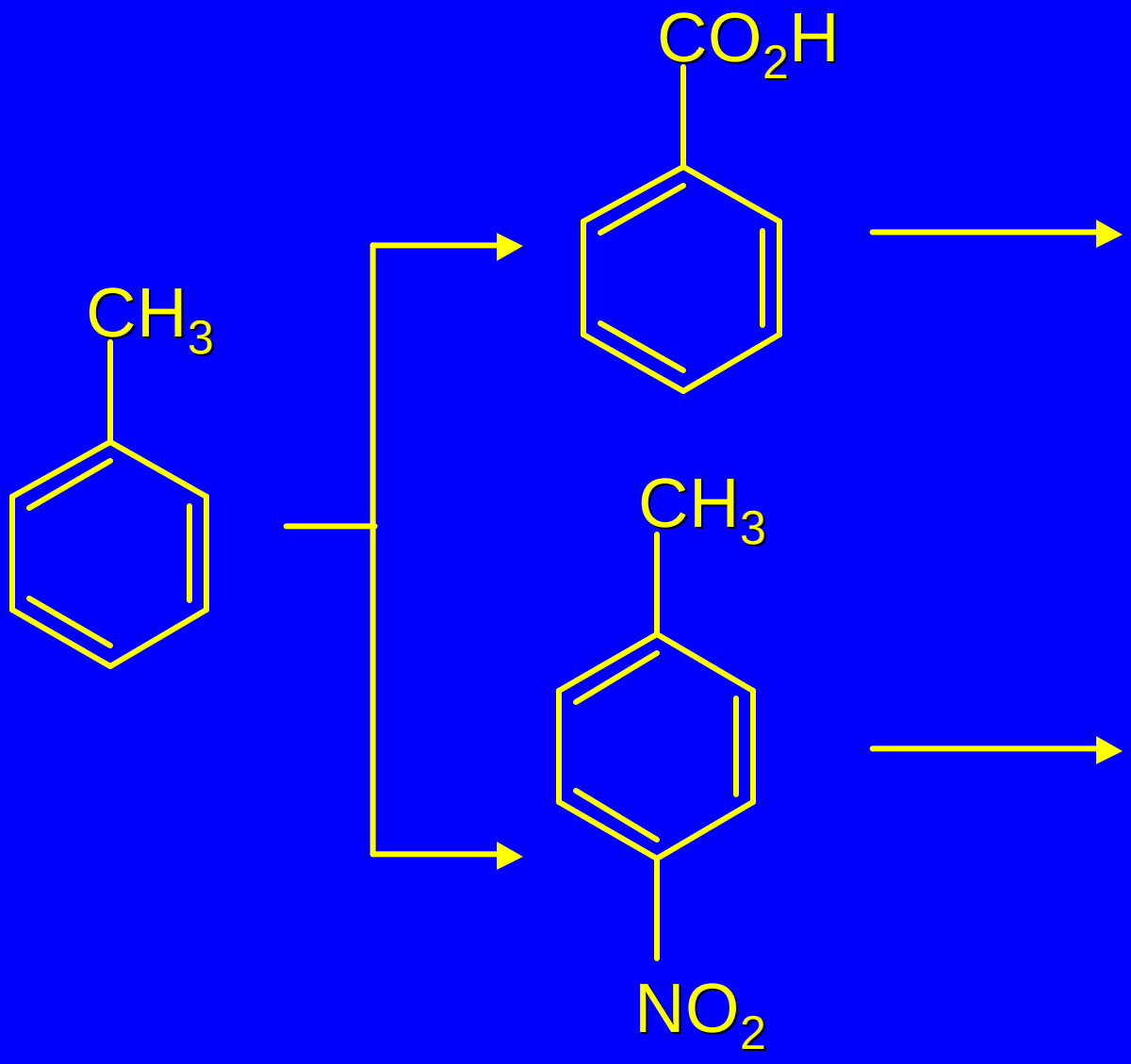
sometimes electrophilic aromatic substitution must be combined with a functional group transformation

Synthesis of p-Nitrobenzoic Acid from Toluene



Which first?
(oxidation of methyl group or nitration of ring)

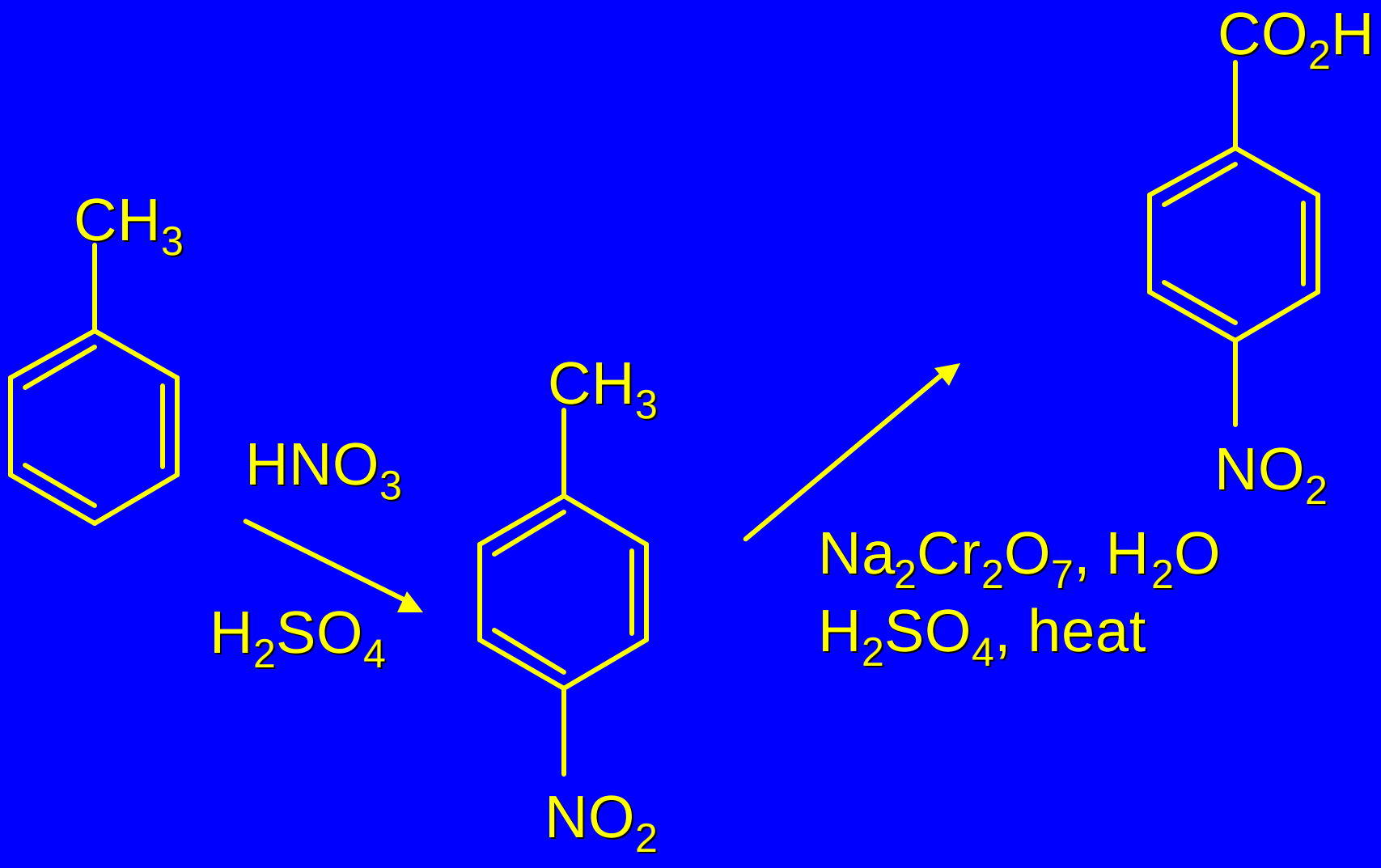
Synthesis of p-Nitrobenzoic Acid from Toluene



nitration gives *m*-nitrobenzoic acid

oxidation gives *p*-nitrobenzoic acid

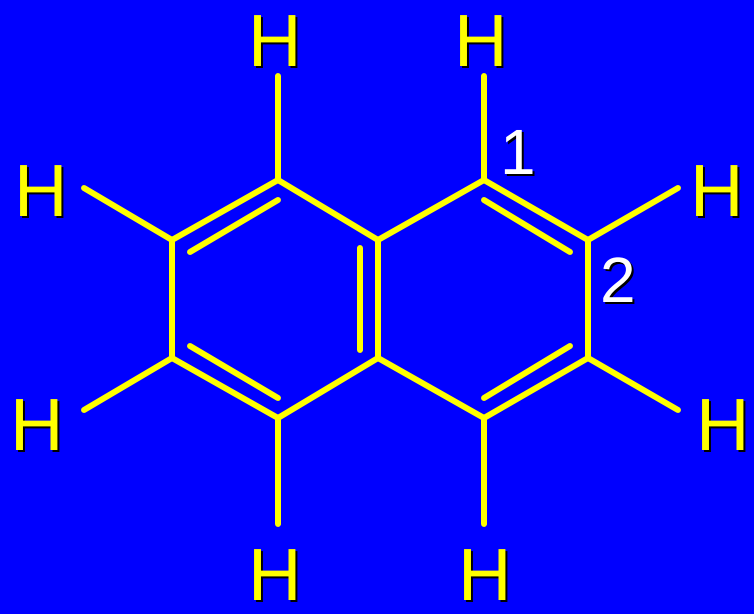
Synthesis of p-Nitrobenzoic Acid from Toluene



12.17

Substitution in Naphthalene

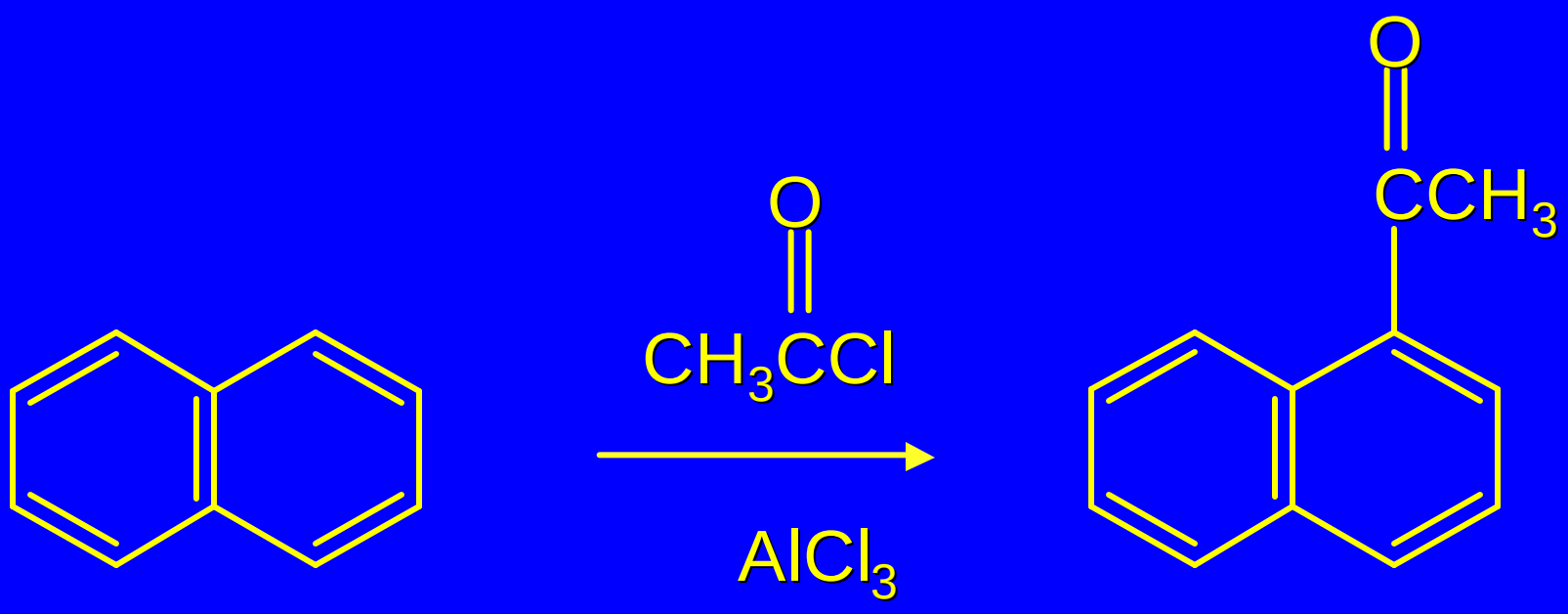
Naphthalene



two sites possible for electrophilic aromatic substitution

all other sites at which substitution can occur are equivalent to 1 and 2

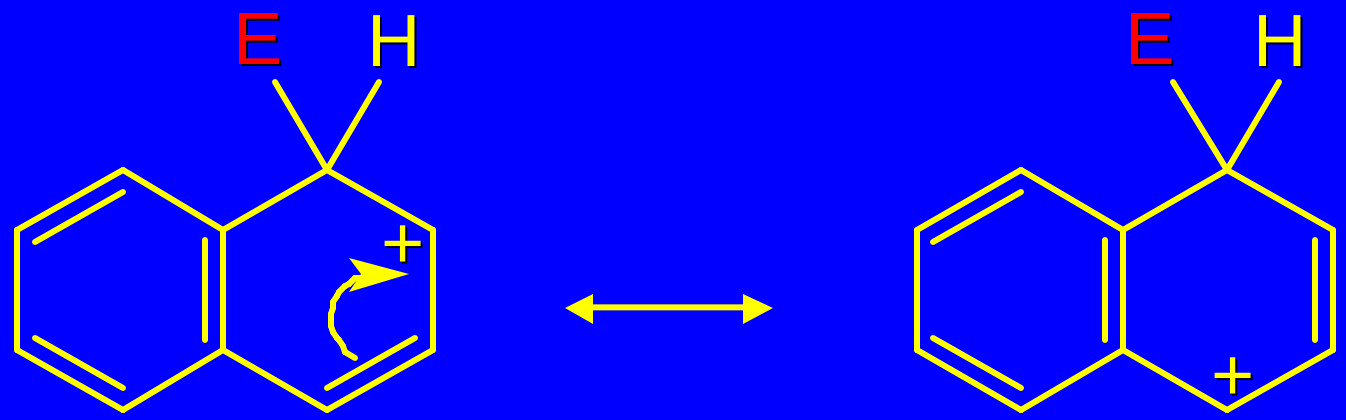
EAS in Naphthalene



90%

is faster at C-1 than at C-2

EAS in Naphthalene

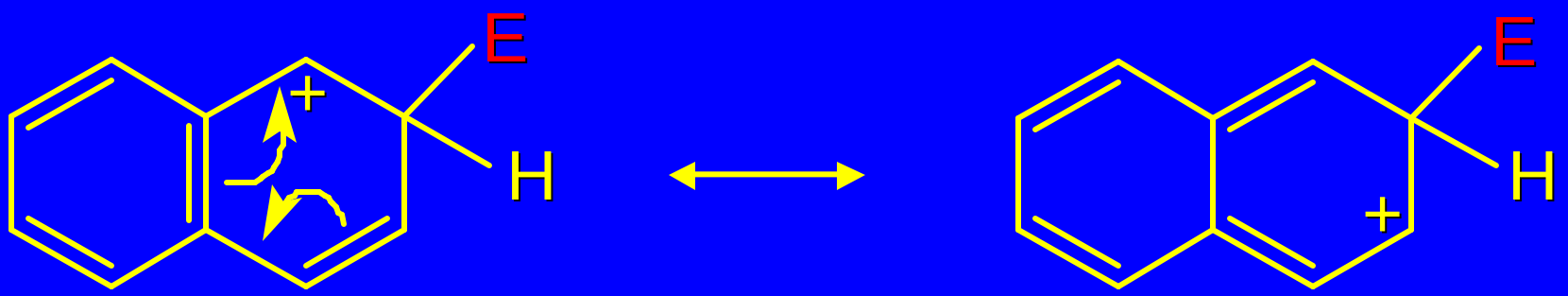


when attack is at C-1

carbocation is stabilized by allylic resonance

benzenoid character of other ring is maintained

EAS in Naphthalene



when attack is at C-2

in order for carbocation to be stabilized by allylic resonance, the benzenoid character of the other ring is sacrificed

12.18
Substitution in
Heterocyclic Aromatic Compounds

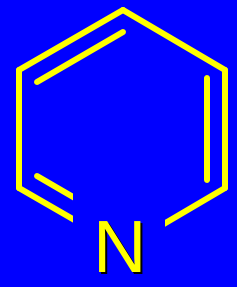
Generalization

There is none.

There are so many different kinds of heterocyclic aromatic compounds that no generalization is possible.

Some heterocyclic aromatic compounds are very reactive toward electrophilic aromatic substitution, others are very unreactive..

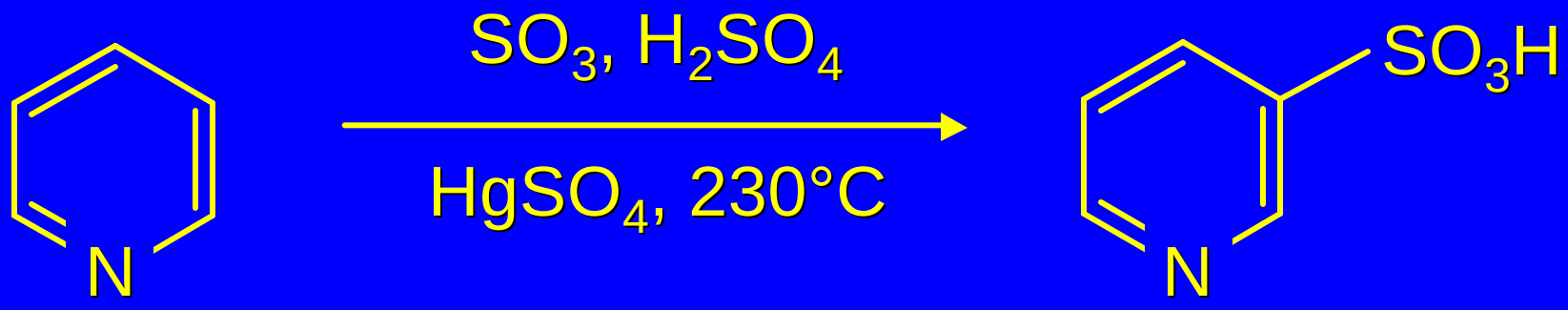
Pyridine



Pyridine is very unreactive; it resembles nitrobenzene in its reactivity.

Presence of electronegative atom (N) in ring causes *p* electrons to be held more strongly than in benzene.

Pyridine

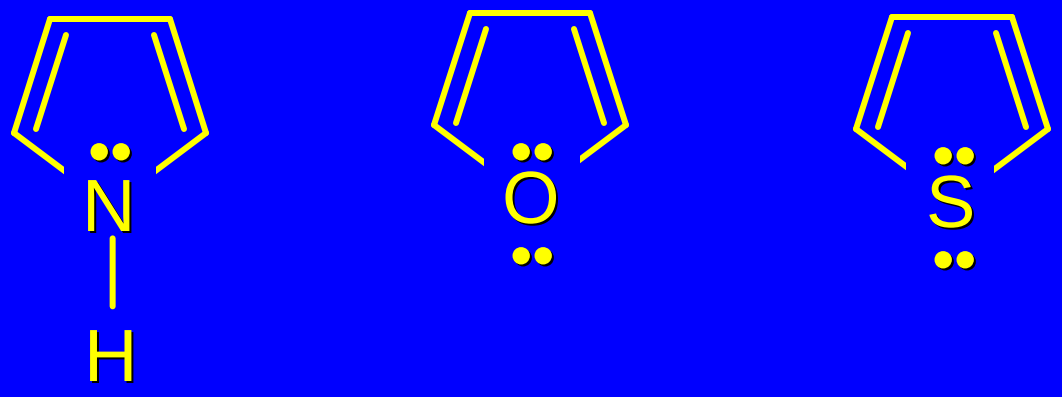


71%

Pyridine can be sulfonated at high temperature.

EAS takes place at C-3.

Pyrrole, Furan, and Thiophene

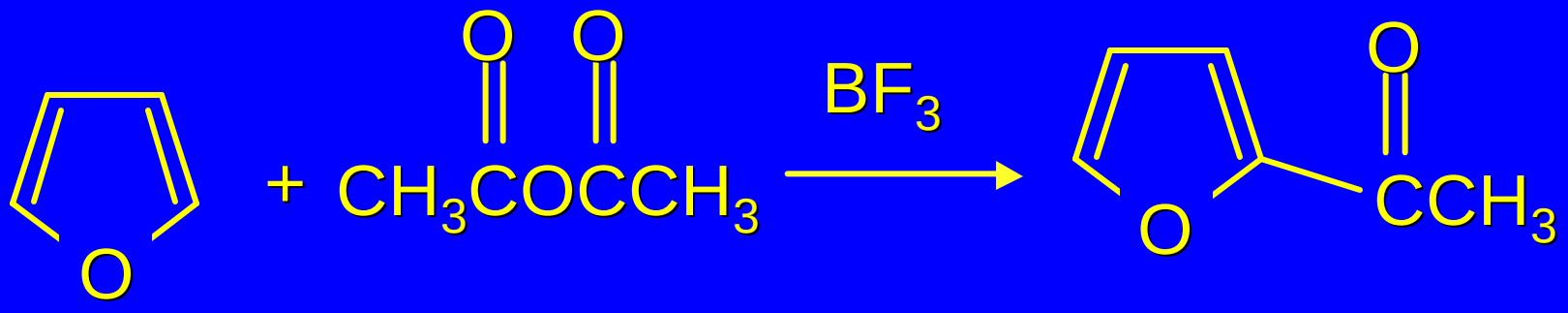


Have 1 less ring atom than benzene or pyridine to hold same number of *p* electrons (6).

p electrons are held less strongly.

These compounds are relatively reactive toward EAS..

Example: Furan



75-92%

undergoes EAS readily

C-2 is most reactive position