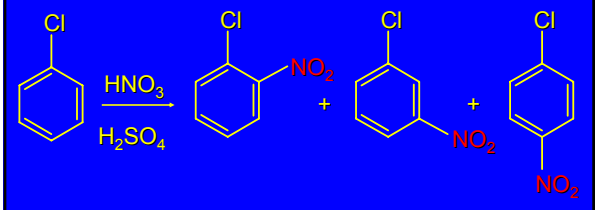
12.14
Substituent Effects in Electrophilic Aromatic Substitution: Halogens

F, Cl, Br, and I are ortho-para directing, but deactivating

Nitration of Chlorobenzene



30% 1% 69%

The rate of nitration of chlorobenzene is about 30 times slower than that of benzene.

Nitration of Toluene vs. Chlorobenzene

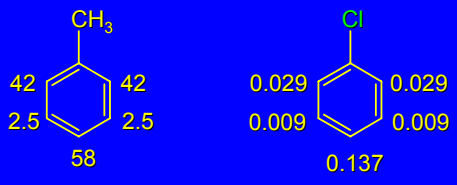


Table 12.2

Classification of Substituents in Electrophilic Aromatic Substitution Reactions

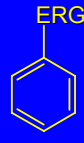
Very strongly activating
Strongly activating
Activating
Standard of comparison is H
Deactivating
Strongly deactivating
Very strongly deactivating

Generalizations

1. All activating substituents are ortho-para directors.
2. Halogen substituents are slightly deactivating but ortho-para directing.
3. Strongly deactivating substituents are meta directors.

Electron-Releasing Groups (ERGs)

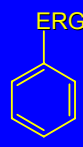
are ortho-para directing and activating



ERGs include —R, —Ar, and —C=C

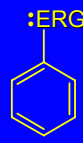
Electron-Releasing Groups (ERGs)

are ortho-para directing and activating



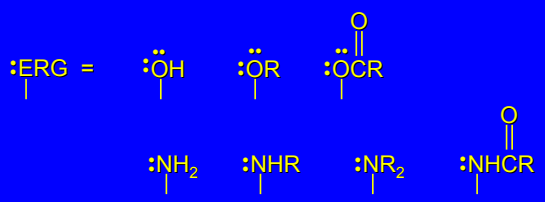
ERGs such as —OH, and —OR
are
strongly activating

Electron-Releasing Groups (ERGs)



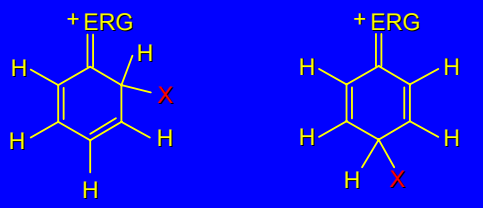
ERGs with a lone pair on the atom directly attached to the ring are ortho-para directing and strongly activating

Examples



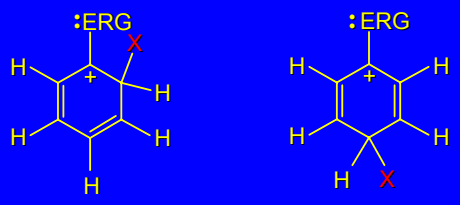
All of these are ortho-para directing and strongly to very strongly activating

Lone Pair Stabilizes Intermediates for ortho and para Substitution

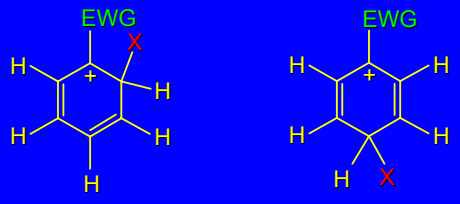


comparable stabilization not possible for intermediate leading to meta substitution

ERGs Stabilize Intermediates for ortho and para Substitution

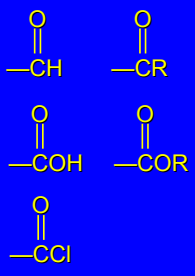


Electron-withdrawing Groups (EWGs) Destabilize Intermediates for ortho and para Substitution



—CF_3 is a powerful EWG. It is strongly deactivating and meta directing

Many EWGs Have a Carbonyl Group Attached Directly to the Ring

—EWG = 

All of these are meta directing and strongly deactivating

Other EWGs Include:

—EWG = —NO_2

—SO_3H

—C≡N

All of these are meta directing and strongly deactivating

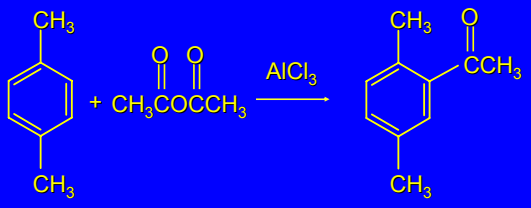
TABLE 12.2 Classification of Substituents in Electrophilic Aromatic Substitution Reactions

Effect on rate	Substituent		Effect on orientation
Very strongly activating	—$\ddot{N}H_2$	(amino)	Ortho, para-directing
	—$\ddot{N}HR$	(alkylamino)	
	—$\ddot{N}R_2$	(dialkylamino)	
	—$\ddot{O}H$	(hydroxyl)	
Strongly activating	—$\ddot{N}HCR$ (O)	(acylamino)	Ortho, para-directing
	—$\ddot{O}R$	(alkoxy)	
	—$\ddot{O}CR$ (O)	(acyloxy)	
Activating	—R	(alkyl)	Ortho, para-directing
	—Ar	(aryl)	
	—CH=CR_2	(alkenyl)	
Standard of comparison	—H	(hydrogen)	
Deactivating	—X (X = F, Cl, Br, I)	(halogen)	Ortho, para-directing
	—CH_2X	(halomethyl)	
Strongly deactivating	—CH (O)	(formyl)	Meta-directing
	—CR (O)	(acyl)	
	—COH (O)	(carboxylic acid)	
	—COR (O)	(ester)	
	—CCl (O)	(acyl chloride)	
	—C≡N	(cyano)	
	—SO_3H	(sulfonic acid)	
	—CF_3	(trifluoromethyl)	
Very strongly deactivating	—NO_2	(nitro)	Meta-directing

12.15
Multiple Substituent Effects

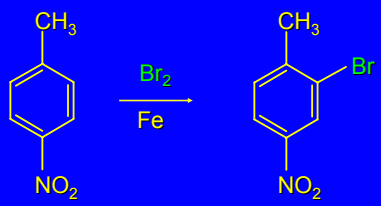
The Simplest Case

all possible EAS sites may be equivalent



99%

Another Straightforward Case



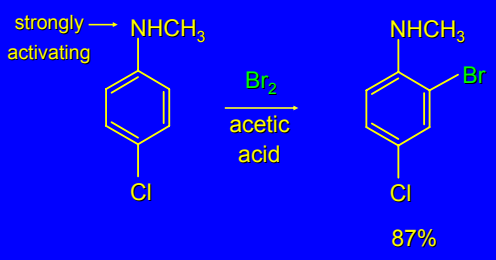
86-90%

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

Generalization

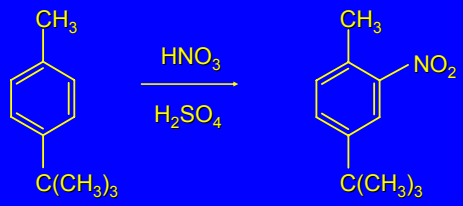
regioselectivity is controlled by the most activating substituent

Example



87%

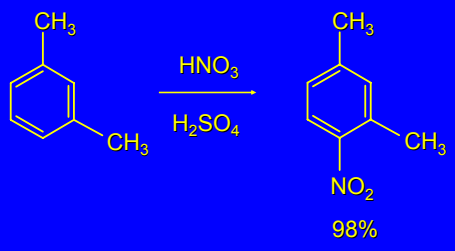
When activating effects are similar...



88%

substitution occurs ortho to the smaller group

Steric effects control regioselectivity when electronic effects are similar



98%

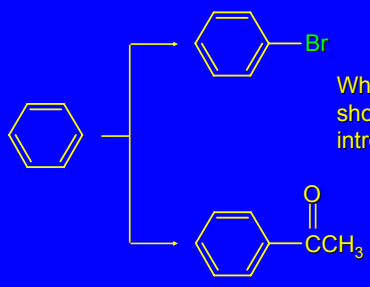
position between two substituents is last position to be substituted

12.16
Regioselective Synthesis of Disubstituted Aromatic Compounds

Factors to Consider

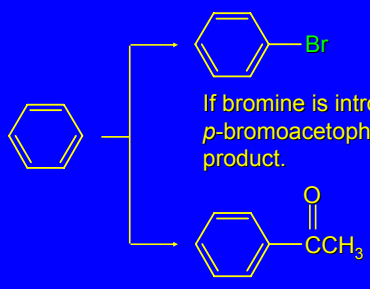
order of introduction of substituents to ensure correct orientation

Synthesis of m-Bromoacetophenone



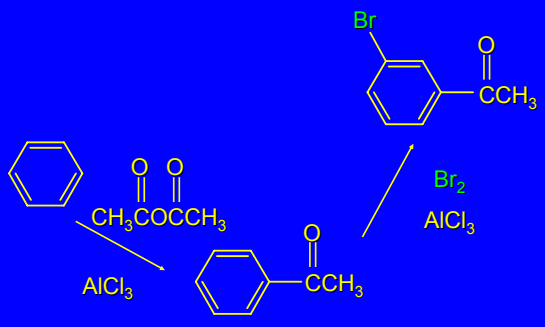
Which substituent should be introduced first?

Synthesis of m-Bromoacetophenone



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

Synthesis of m-Bromoacetophenone

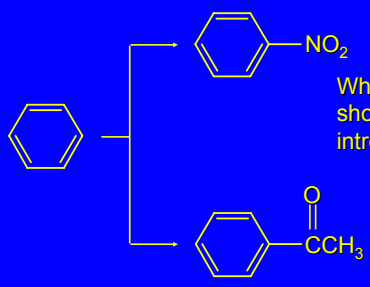


Factors to Consider

order of introduction of substituents to ensure correct orientation

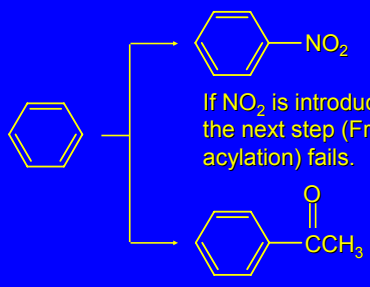
Friedel-Crafts reactions (alkylation, acylation) cannot be carried out on strongly deactivated aromatics

Synthesis of m-Nitroacetophenone



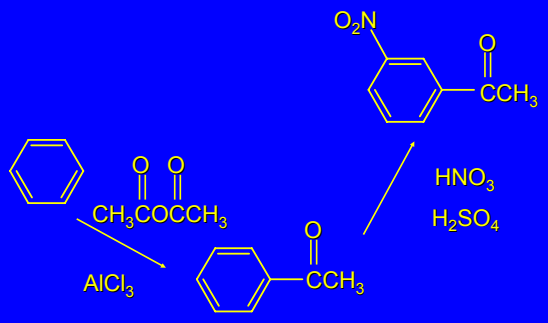
Which substituent should be introduced first?

Synthesis of m-Nitroacetophenone



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

Synthesis of m-Nitroacetophenone



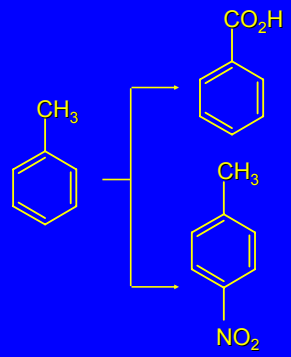
Factors to Consider

order of introduction of substituents to ensure correct orientation

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

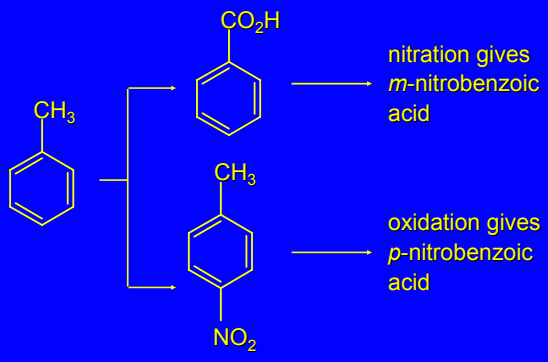
sometimes electrophilic aromatic substitution must be combined with a functional group transformation

Synthesis of p-Nitrobenzoic Acid from Toluene

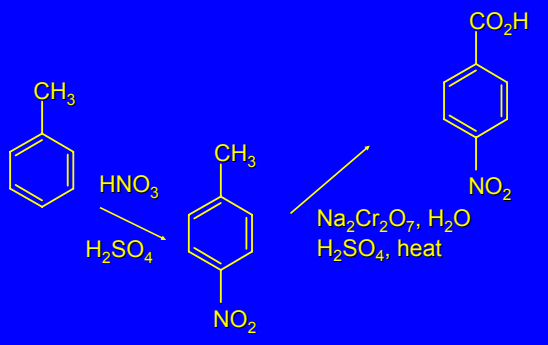


Which first? (oxidation of methyl group or nitration of ring)

Synthesis of p-Nitrobenzoic Acid from Toluene



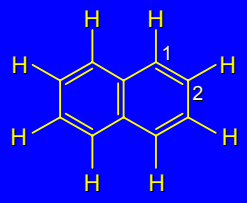
Synthesis of p-Nitrobenzoic Acid from Toluene



12.17

Substitution in Naphthalene

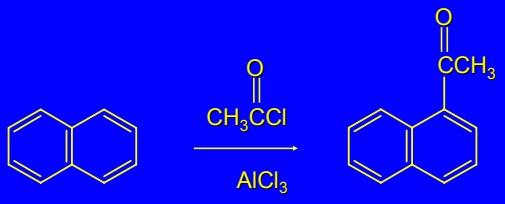
Naphthalene



two sites possible for electrophilic aromatic substitution

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

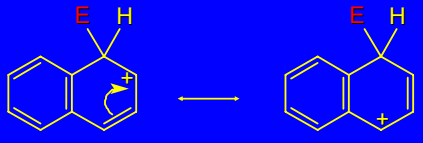
EAS in Naphthalene



90%

is faster at C-1 than at C-2

EAS in Naphthalene

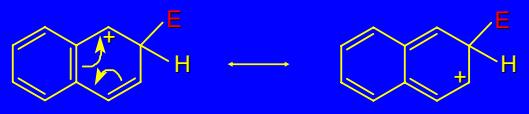


when attack is at C-1

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

Example: Furan

75-92%

undergoes EAS readily

C-2 is most reactive position