PHA284

Organic Chemistry II

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Department of Pharmaceutical Chemistry

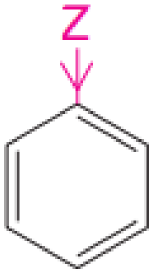
Ring-Activating and Ring-Deactivating Substituents

Substituents Can Affect Both the Reactivity of the Ring and the Orientation of the Incoming Group

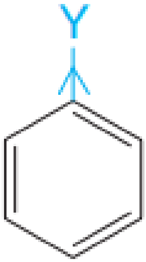
A substituent group present on a benzene ring can affect both the **reactivity of the ring toward electrophilic substitution** and **the orientation that the incoming group takes on the ring**.

- A substituent can make the ring more reactive than benzene. Such a group is called an **activating group.**
- A substituent can make the ring less reactive than benzene. Such groups are called **deactivating groups.**

How Do Substituents Affect Reactivity?



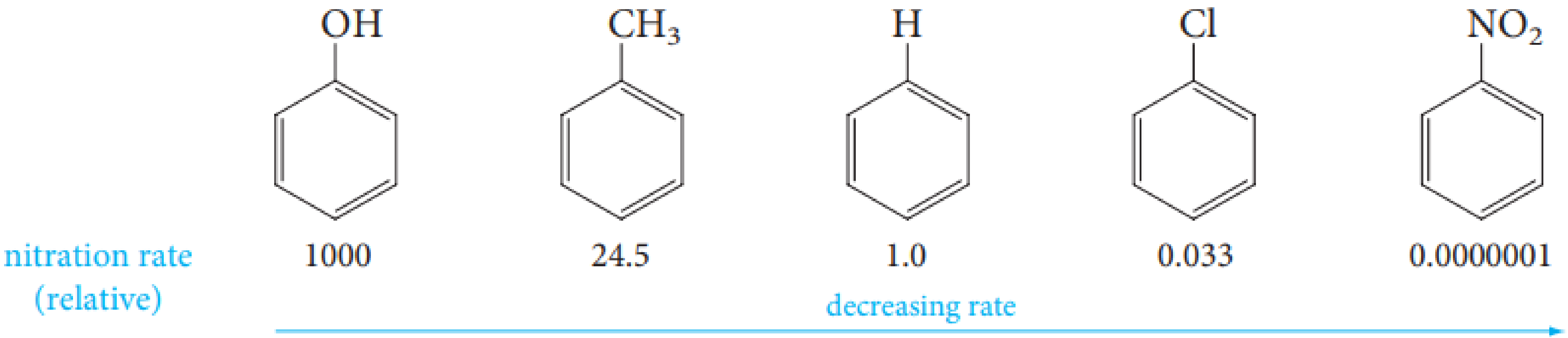
If **Z** donates electrons the ring is more electron rich and it reacts faster with an electrophile.



If **Y** withdraws electrons the ring is electron poor and it reacts more slowly with an electrophile.

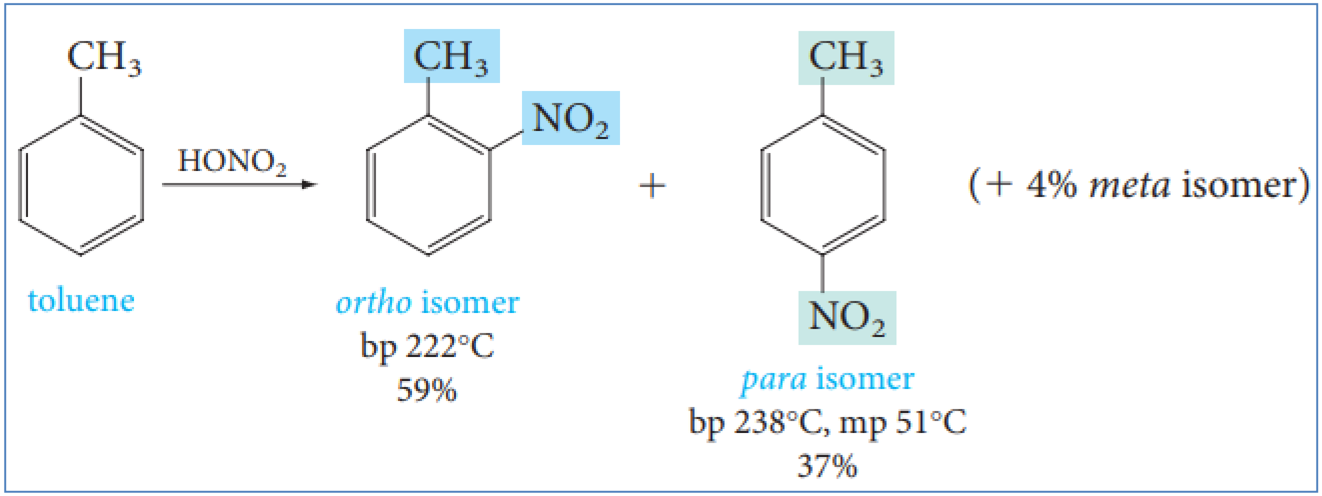
Ring-Activating and Ring-Deactivating Substituents

Consider the relative nitration rates of the following compounds, all under the same reaction conditions:



- Taking benzene as the standard, we see that some substituents (for example, OH and CH_3) speed up the reaction, and other substituents (Cl and NO_2) retard the reaction.
- We know from other evidence that hydroxyl and methyl groups are more electron donating than hydrogen, whereas chloro and nitro groups are more electron withdrawing than hydrogen.
- The electrostatic potential maps illustrate the effects of electron-donating and electron-withdrawing groups on the electron density in the benzene ring.

Ortho, Para-Directing and *Meta*-Directing Groups

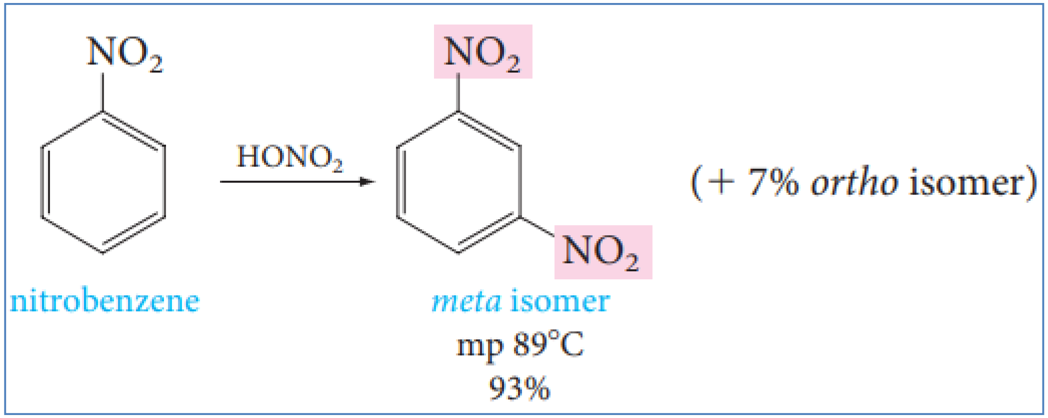


toluene

ortho isomer
bp 222°C
59%

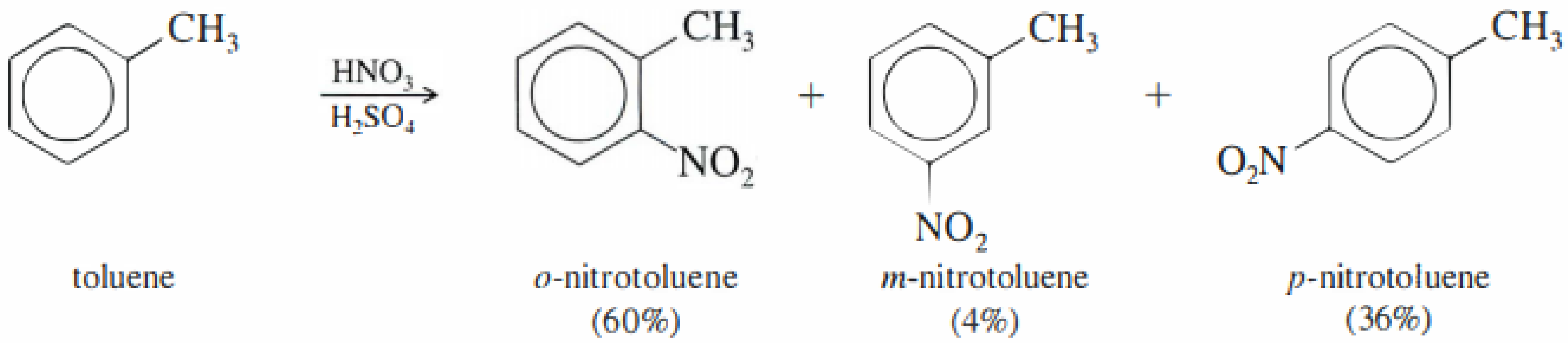
para isomer
bp 238°C, mp 51°C
37%

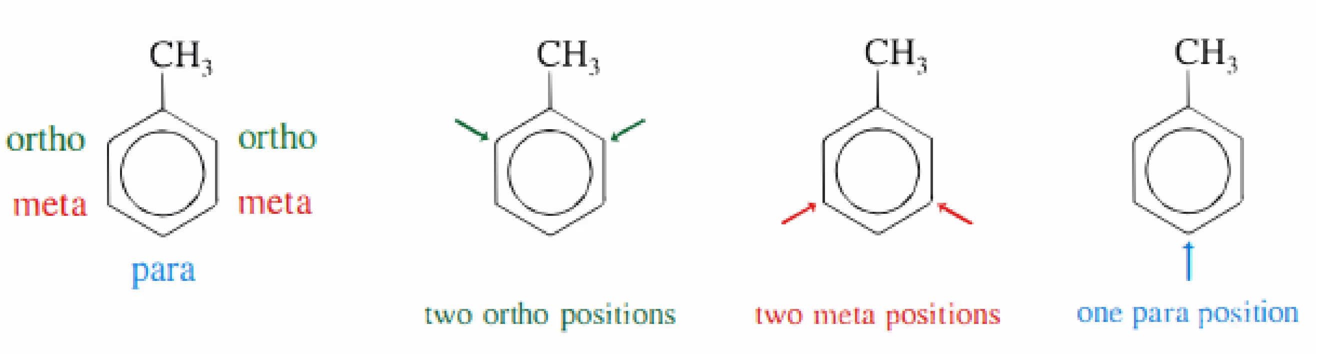
Ortho, Para-Directing and *Meta*-Directing Groups



Nitration of Toluene: The Effect of Alkyl Substitution

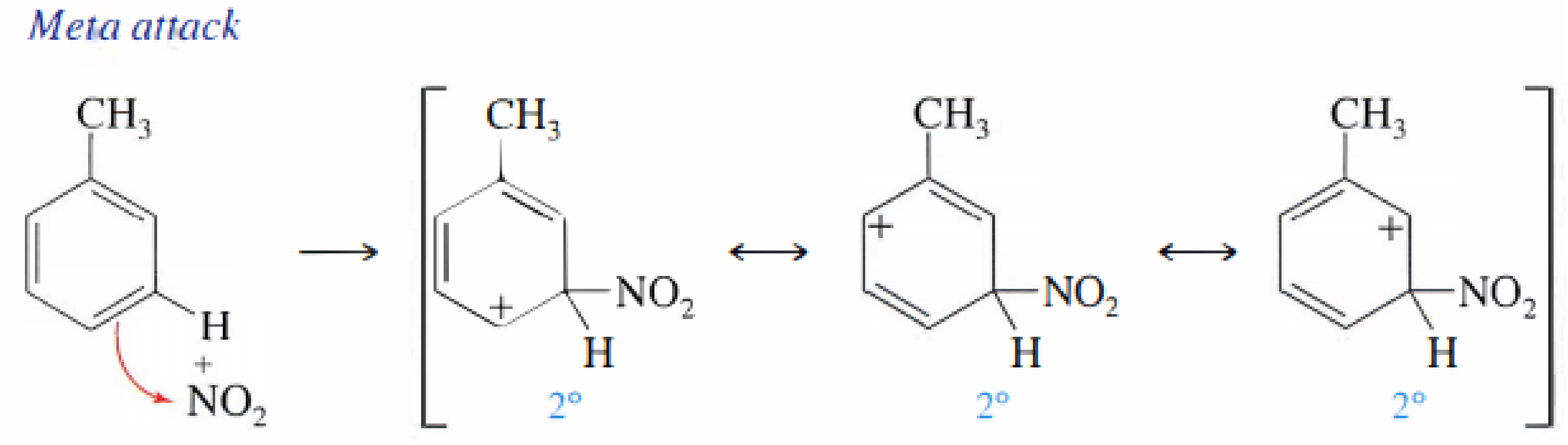
1. Toluene reacts about 25 times faster than benzene under the same conditions.
2. Nitration of toluene gives a mixture of products.





In ortho or para substitution of toluene, the positive charge is spread over two secondary carbons and one tertiary (3^0) carbon (bearing the CH_3 group).

Meta substitution of toluene does not show the large rate enhancement seen with ortho and para substitution.



Ortho, Para-Directing Groups

Consider now the other ortho, para-directing groups listed in Table.

In each of them, the atom attached to the aromatic ring has an unshared electron pair.

$$—\ddot{\underset{..}{F}}: \qquad —\ddot{\underset{..}{O}}H \qquad —\ddot{N}H_2$$

EFFECT OF SUBSTITUENTS ON ELECTROPHILIC AROMATIC SUBSTITUTION

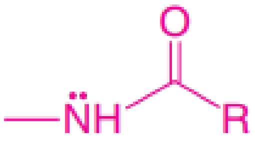
Ortho–Para Directors

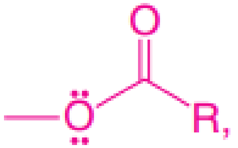
Strongly Activating

$-\underset{\cdot\cdot}{\ddot{N}}H_2$, $-\underset{\cdot\cdot}{\ddot{N}}HR$, $-\underset{\cdot\cdot}{\ddot{N}}R_2$

$-\underset{\cdot\cdot}{\ddot{O}}H$, $-\underset{\cdot\cdot}{\ddot{O}}:^-$

Moderately Activating





$-\underset{\cdot\cdot}{\ddot{O}}R$

Weakly Activating

$-R$ (alkyl)

$-C_6H_5$ (phenyl)

Weakly Deactivating

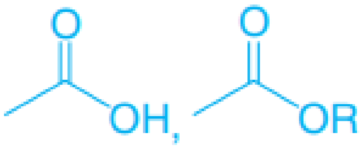
$-\underset{\cdot\cdot}{\ddot{F}}:$, $-\underset{\cdot\cdot}{\ddot{Cl}}:$, $-\underset{\cdot\cdot}{\ddot{Br}}:$, $-\underset{\cdot\cdot}{\ddot{I}}:$

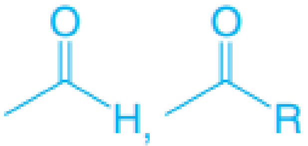
Meta Directors

Moderately Deactivating

$-C\equiv N$

$-SO_3H$





Strongly Deactivating

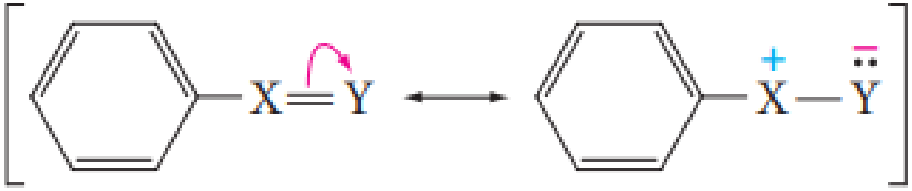
$-NO_2$

$-NR_3^+$

$-CF_3$, CCl_3

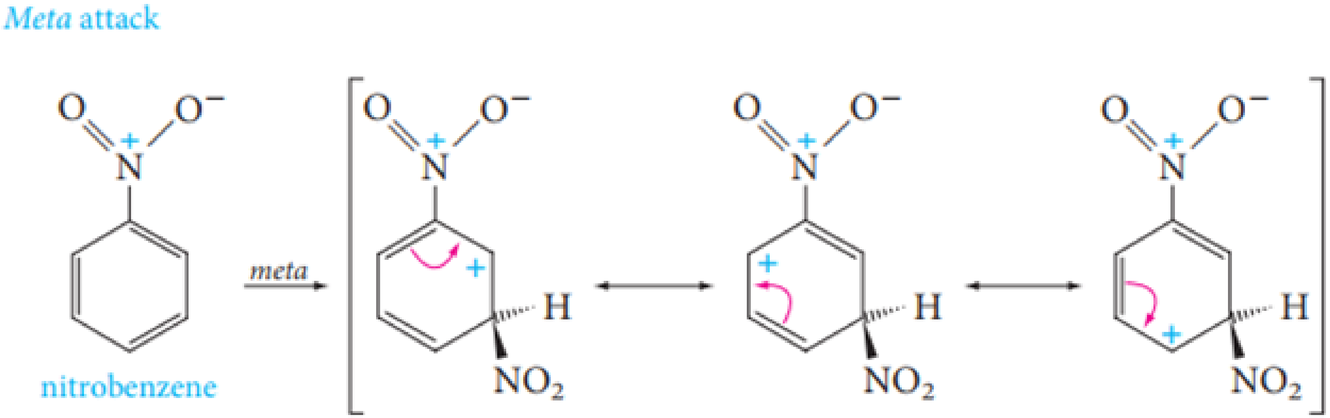
Meta-Directing Groups

In the Table, notice that each meta-directing group is connected to the aromatic ring by an atom that is part of a double or triple bond, at the other end of which is an atom more electronegative than carbon (for example, an oxygen or nitrogen atom).



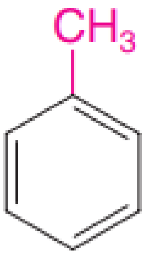
Y is an electron-withdrawing atom such as oxygen or nitrogen; atom X carries a positive charge in one of the resonance contributors.

In nitrobenzene, the nitrogen has a formal charge of +1, as shown on the structures. The equations for forming the intermediate benzenonium ion are:

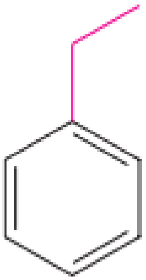


Reactions of the Side Chain of Alkylbenzenes

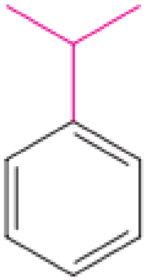
Hydrocarbons that consist of both aliphatic and aromatic groups are also known as arenes. Toluene, ethylbenzene, and isopropylbenzene are alkylbenzenes. Phenylethene, usually called styrene, is an example of an alkenylbenzene. :



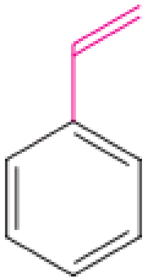
Methylbenzene
(toluene)



Ethylbenzene

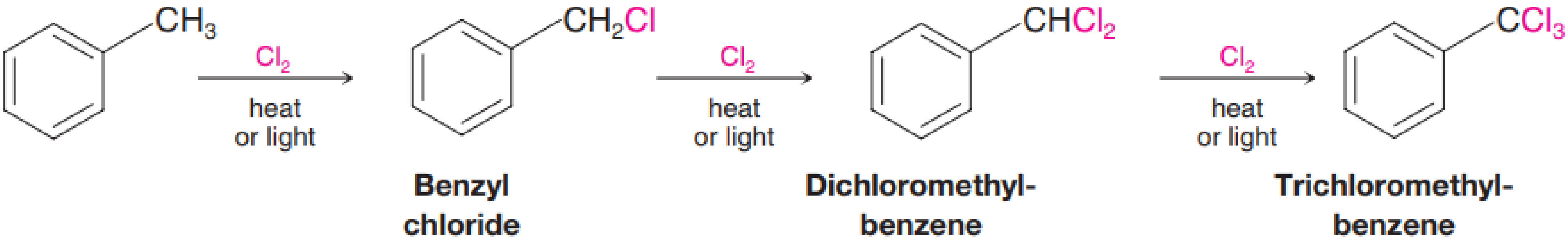


Isopropyl-benzene
(cumene)



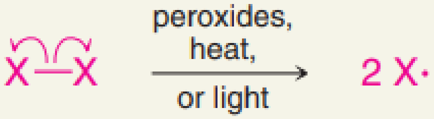
Phenylethene
(styrene or vinylbenzene)

A- Benzylic Halogenation of the Side Chain



Chain Initiation

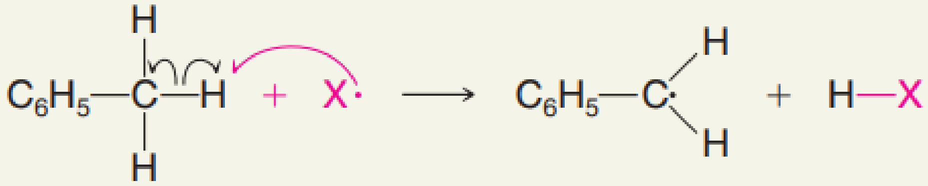
Step 1



Peroxides, heat, or light cause halogen molecules to cleave into radicals.

Chain Propagation

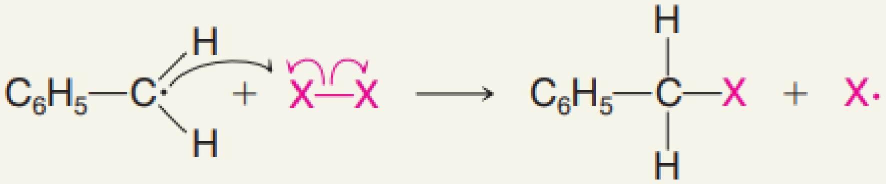
Step 2



Benzyl radical

A halogen radical abstracts a benzylic hydrogen atom, forming a benzylic radical and a molecule of the hydrogen halide.

Step 3



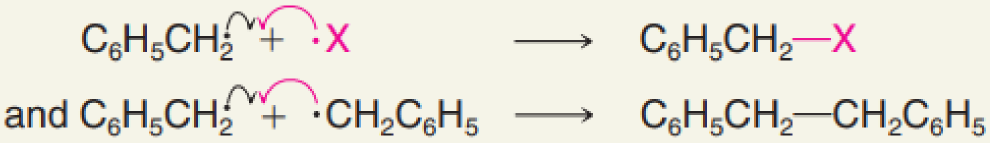
Benzyl radical

Benzyl halide

The benzylic radical reacts with a halogen molecule to form the benzylic halide product and a halogen radical that propagates the chain.

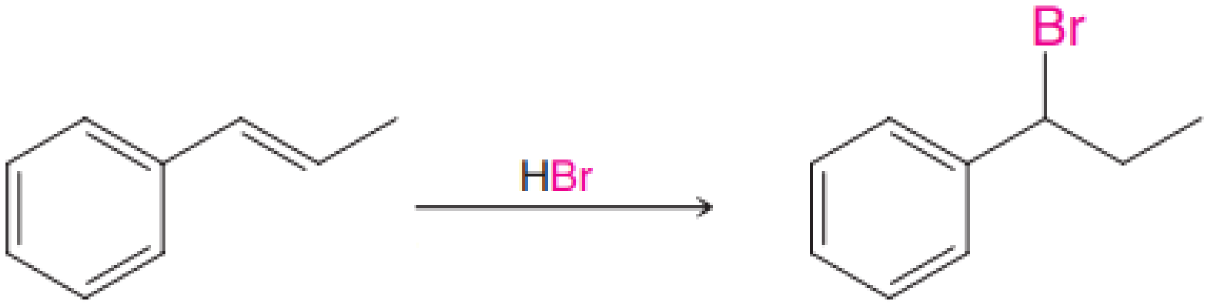
Chain Termination

Step 4



Various radical coupling reactions terminate the chain.

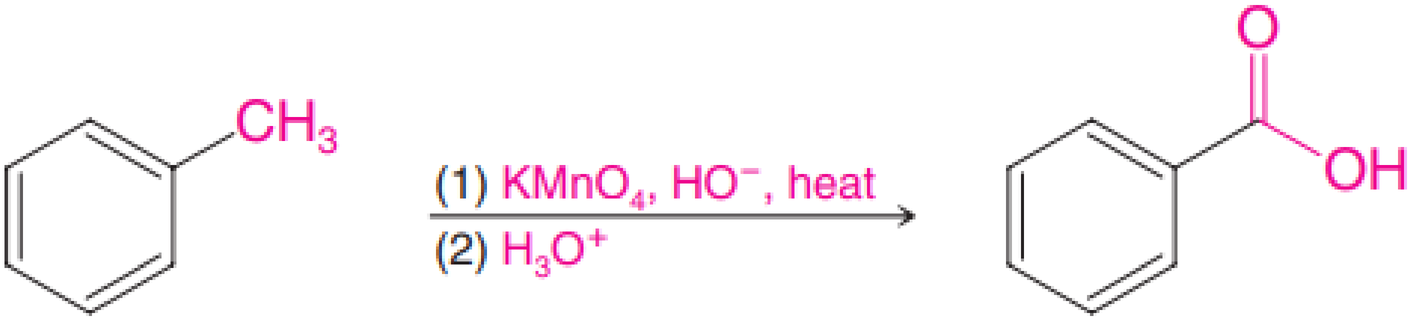
B- Additions to the Double Bond of Alkenylbenzenes



1-Phenylpropene

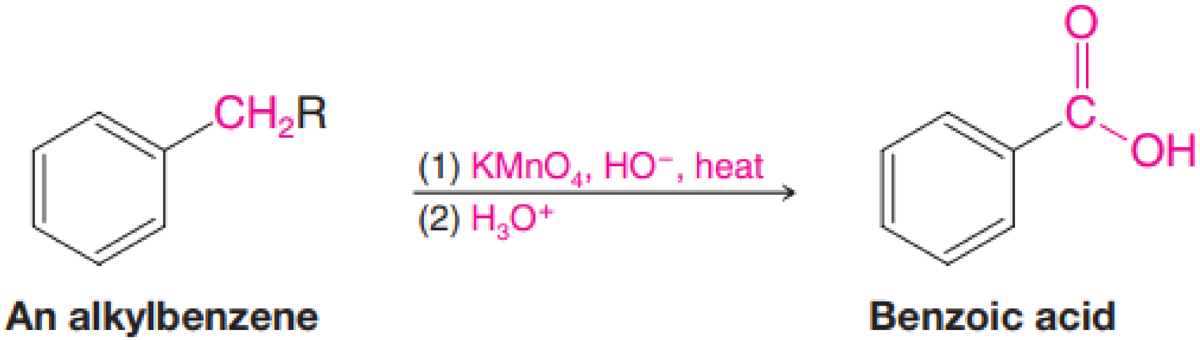
1-Bromo-1-phenylpropane

C- Oxidation of the Side Chain



Benzoic acid
(~100%)

An important characteristic of side-chain oxidations is that oxidation takes place initially at the benzylic carbon.



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