Chapter 21
The Radical Chemistry

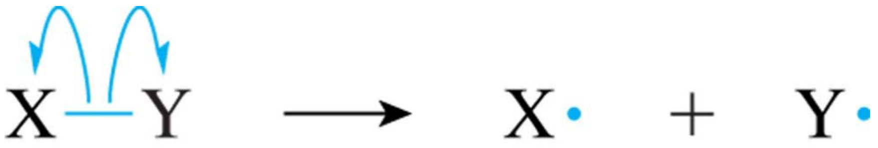
Until now: Reactions of electrophiles with nucleophiles

This chapter: a new reactive intermediate

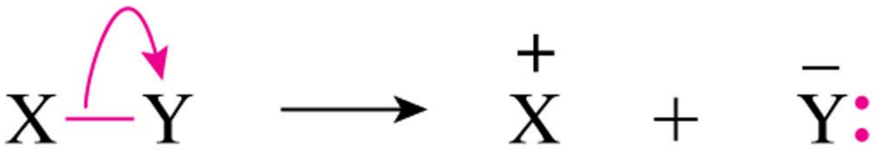
radical

21.1 Radicals

A radical is a species with an odd number of electrons, which is generated by homolytic bond cleavage



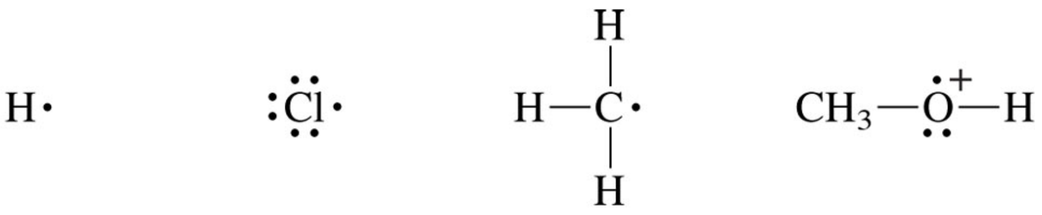
Homolytic bond cleavage



Heterolytic bond cleavage

Radicals are normally neutral

Examples



Hydrogen atom

Chlorine atom

Methyl radical

Methanol radical cation

21.2 Stability of Radicals

Radicals have an odd number of electrons

→ Octect rule cannot be satisfied

→ Unstable and exists as an transient intermediate, same as the carbocation

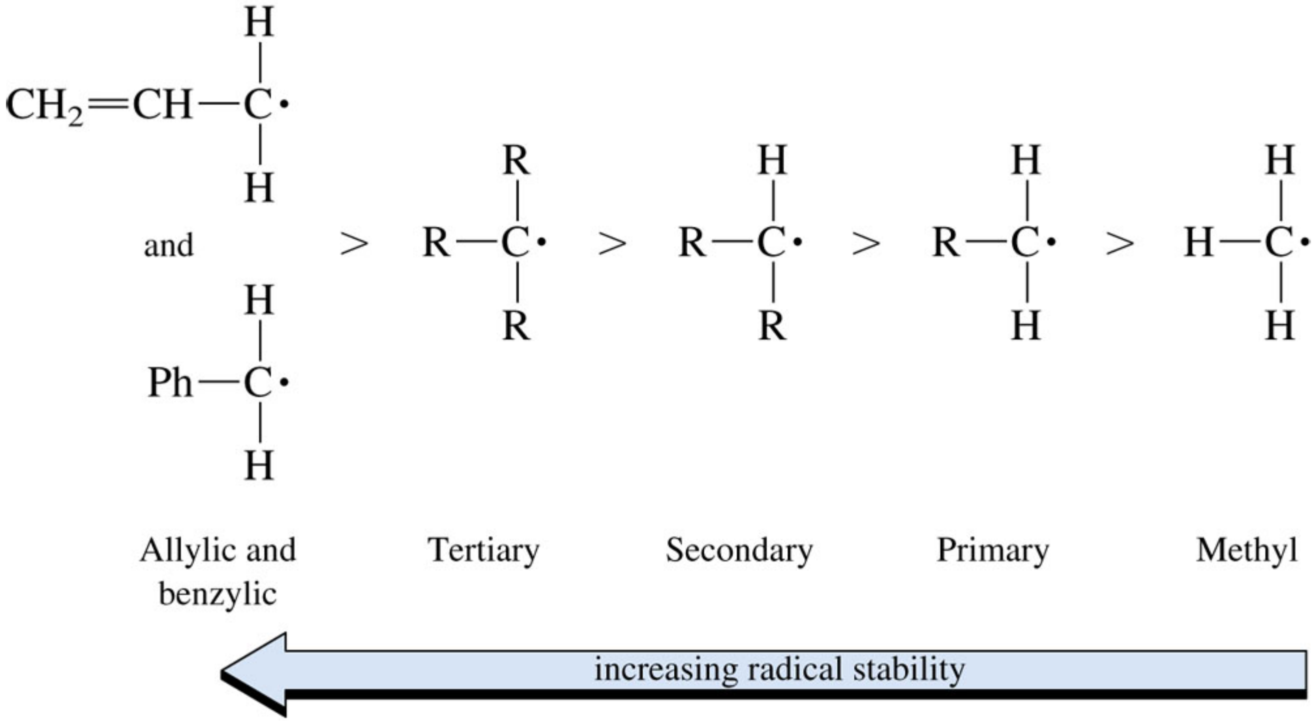
Still the radical is more stable than the carbocation, because the radical has 7 electrons while the carbocation has 6 electrons

⇒ Methylene radical in methanol at 77K has 10min life time

The order of radical stabilities parallels the order of carbocation stability because the stabilities are due to the same reasons

See next page

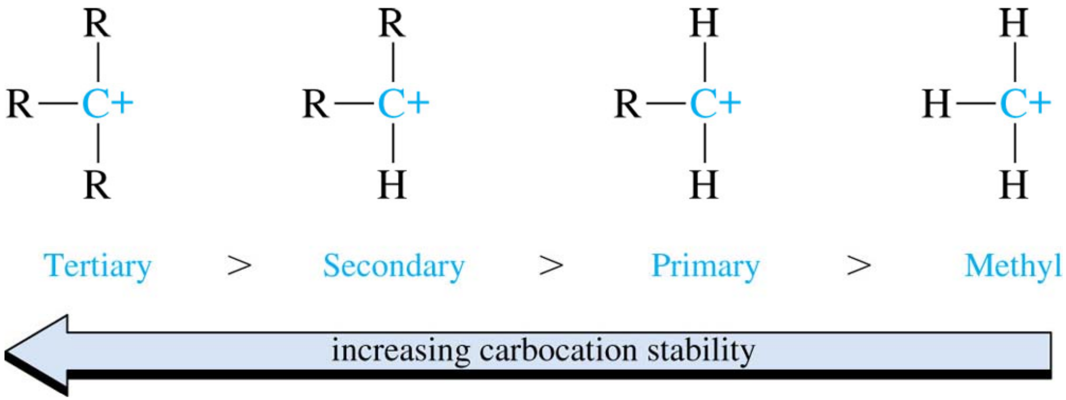
Radical stability



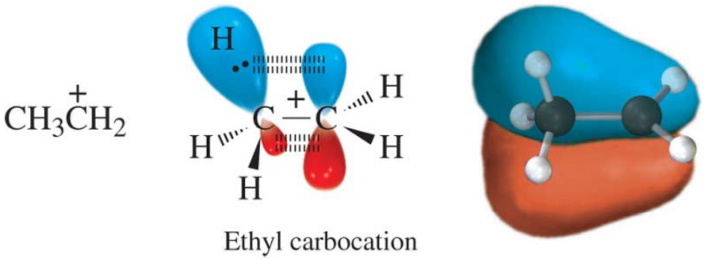
The differences in stabilities between the radicals are smaller than the differences in stabilities between the corresponding cations, therefore radicals are not as prone to rearrange as the carbocations are.

The lower the bond dissociation energy, the higher the stability of the resulting radical. See table 21.1

Cation stability



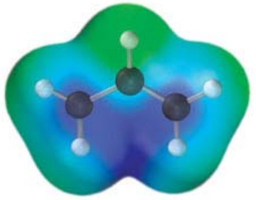
Hyperconjugation

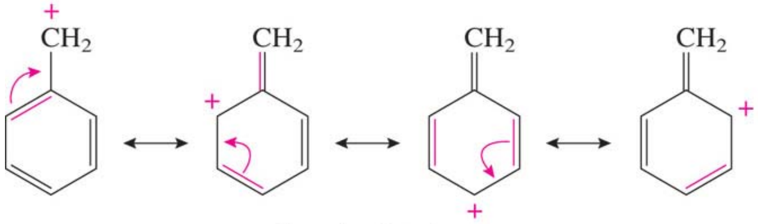


Ethyl carbocation

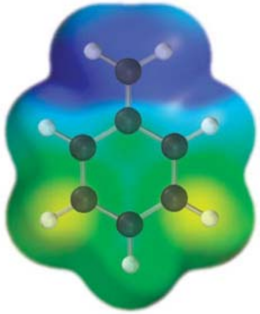
Resonance stabilization

Allyl carbocation





Benzyl carbocation



21.3 Geometry of Radicals

⇒ not clear yet

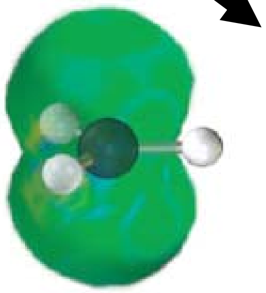
Two possibilities

1. A radical carbon is *sp*^{2} hybrized with trigonal geometry

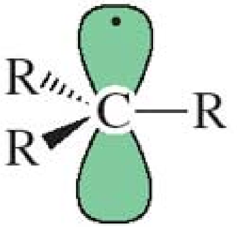
⇒the odd electron is in p orbital

2. A radical carbon is *sp*^{3} hybrized with tetrahedral geometry

⇒ the odd electron is in *sp*^{3} orbital

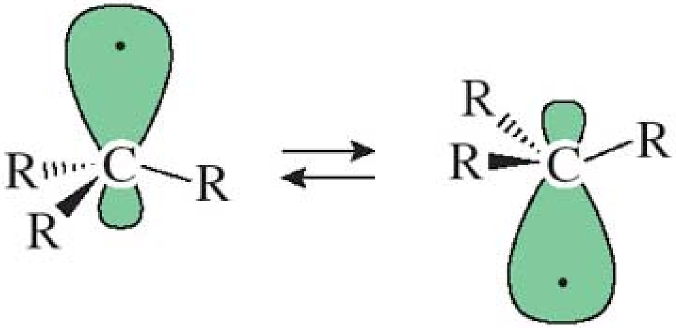


This model shows the electron density for the odd electron of the planar methyl radical. The radical electron is in a *p* orbital perpendicular to the plane of the atoms.



A trigonal planar radical

or



A rapidly inverting pyramidal radical

21.4 Generation of Radicals

When an weak bond is heated not clear yet

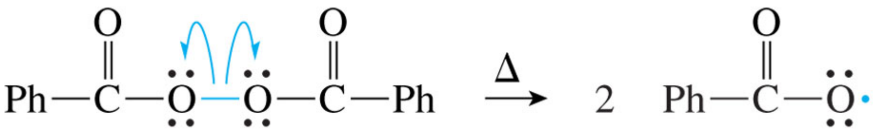
⇒ the weak bond is cleaved to generate radicals

Examples

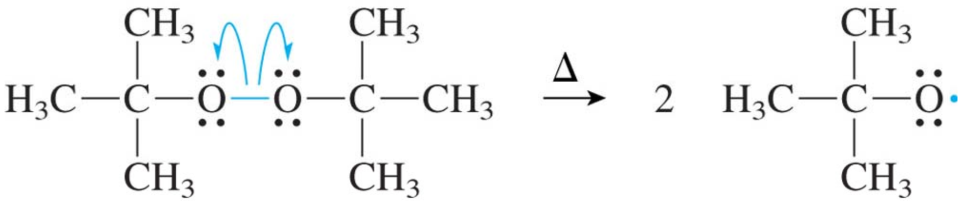
1. **Peroxide**

O—O bond dissociation E = 30 Kcal/mol *(ex) C — C, 80 Kcal/mol)*

bond homolysis at 80 – 100 ^oC



Benzoyl peroxide

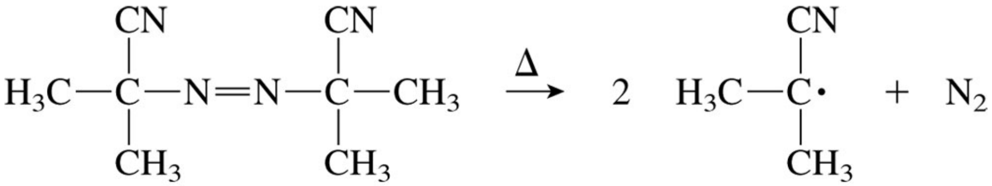


tert-Butyl peroxide

2. Azo compound

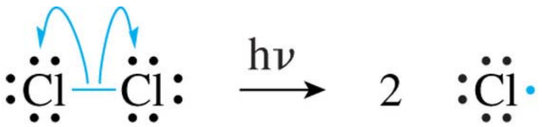
C — N bond is not weak (70Kcal/mol), but the N_2 product which evaporate enable the reaction to occur at lower temperture

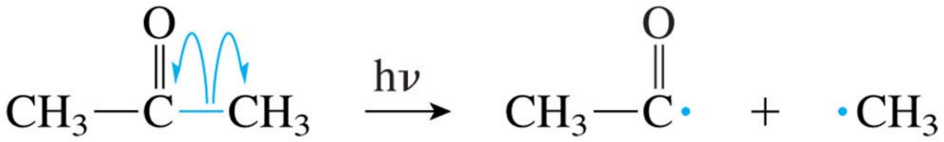
An azo compound



Azobis(isobutyronitrile)
AIBN

3. Photochemically induced homolytic bond cleavage

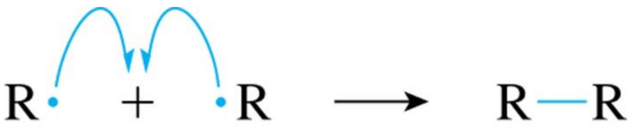




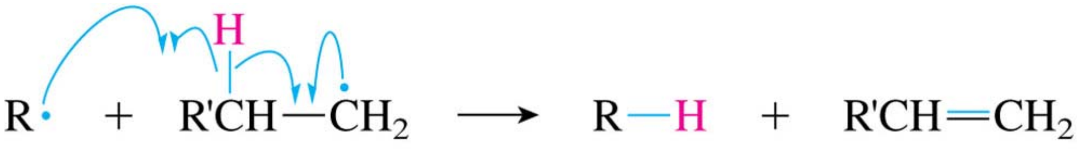
21.5 General Radical Reactions

1. Coupling and Disproportionation

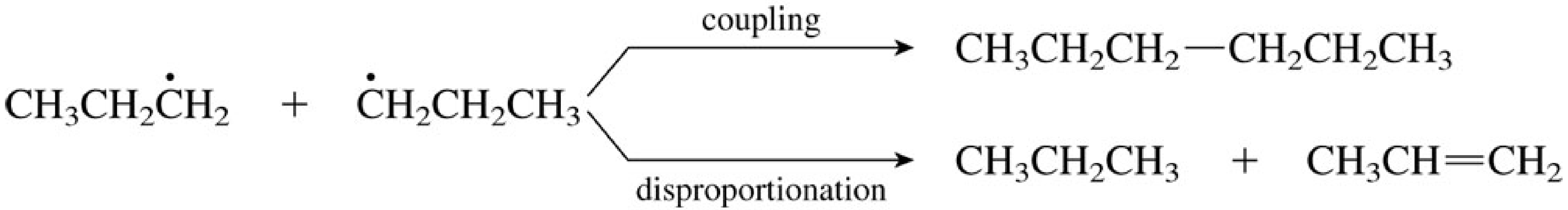
two radicals produce stable products

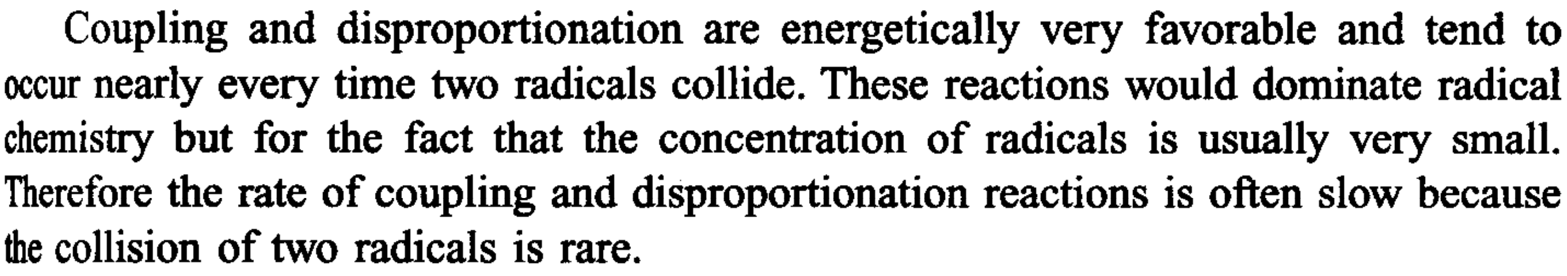


Coupling



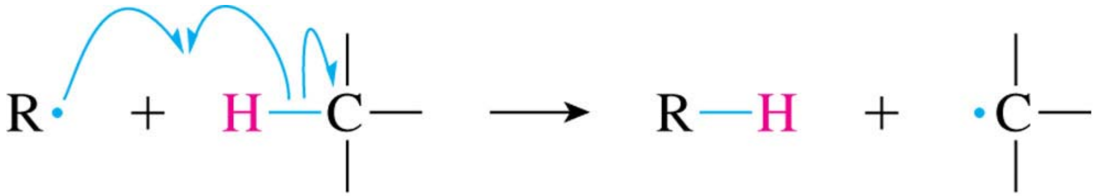
Disproportionation





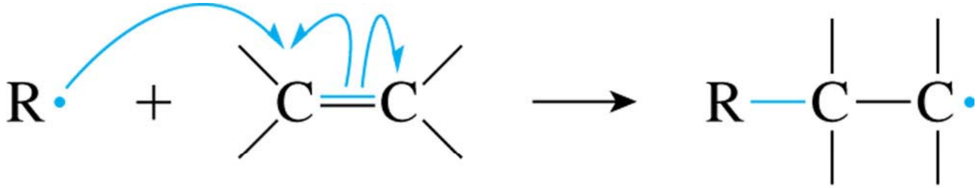
Coupling and disproportionation are energetically very favorable and tend to occur nearly every time two radicals collide. These reactions would dominate radical chemistry but for the fact that the concentration of radicals is usually very small. Therefore the rate of coupling and disproportionation reactions is often slow because the collision of two radicals is rare.

Therefore the following reactions are common

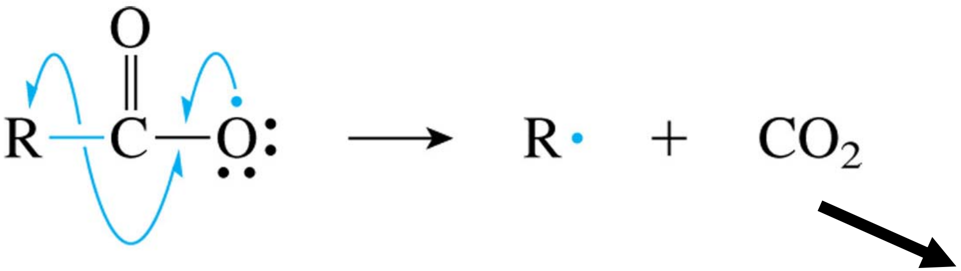


Abstraction

Abstraction and addition is not energetically favored, while can be very common when the concentration of the normal molecules are high.



Addition



Fragmentation

Radicals from carboxylic acids can eliminate CO_2 very rapidly.

Very stable

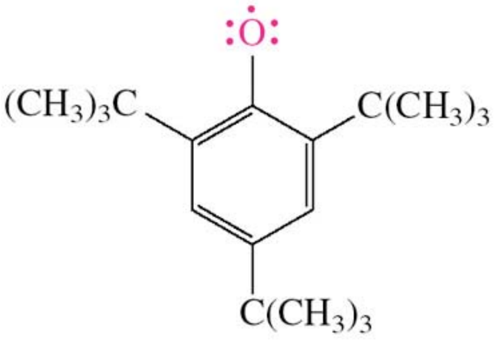
The rate of the radical reactions are affected by the same factor that affects the rate of other reactions

⇒**Stability of the product**

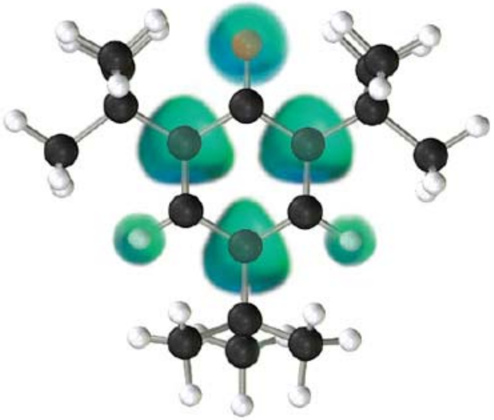
⇒**Steric effect…….**

Very stable radical

No coupling



2,4,6-tri-*tert*-Butylphenoxy radical



The green areas in this model show the locations of the odd electron density in the radical, primarily on the oxygen and the positions ortho and para to it. (This is consistent with the location of the odd electron in the resonance structures that can be written for this radical.) Note how the positions with odd electron density are shielded by the bulky *tert*-butyl groups.

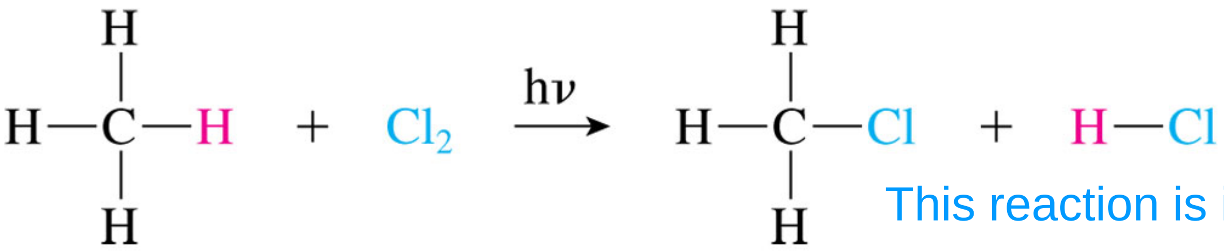
21.6 Halogenation

Bond dissociation E of very common bonds

C —C : 80 kcal/mol *Cl — Cl : 58 kcal/mol*

C —H : 80 kcal/mol *Br — Br : 46 kcal/mol*

C —N: 70 kcal/mol



$$\mathrm{H{-}\overset{\displaystyle H}{\underset{\displaystyle H}{C}}{-}H} + \mathrm{Cl_2} \xrightarrow{h\nu} \mathrm{H{-}\overset{\displaystyle H}{\underset{\displaystyle H}{C}}{-}Cl} + \mathrm{H{-}Cl}$$

This reaction is induced by light

Three steps

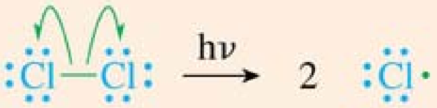
Initiation step: In this step, a normal compound undergoes homolytic bond cleavage to generate radicals.

Propagation steps: There are often several propagation steps in a radical chain reaction. In each of these steps, a radical reacts with a normal compound to produce a new radical. The final propagation step of a chain reaction produces the same radical that reacts in the initial propagation step, so the process can begin anew.

Termination steps: In termination steps, two radicals react to give nonradical products by coupling or disproportionation. These steps destroy radicals.

Initiation

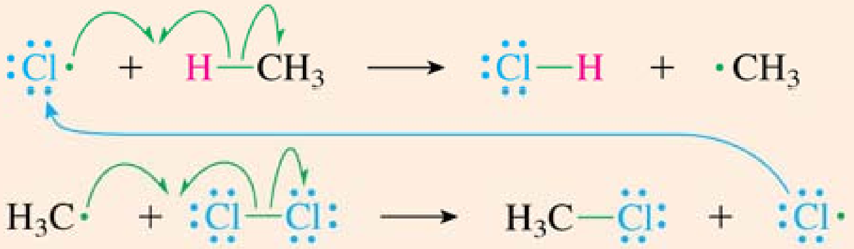
The weak chlorine–chlorine bond is broken by light.



one initiation reaction,
many propagation cycles,
one termination reaction.

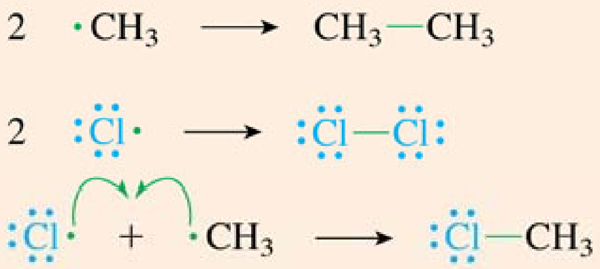
Propagation

A chlorine atom abstracts a hydrogen atom from methane in the first propagation step. Then the methyl radical that is formed abstracts a chlorine atom from Cl_2. The chlorine atom that is produced in the second propagation step reacts again as in the first propagation step. This cycle of two propagation steps is repeated many times in a chain reaction.



Termination

The termination steps include all of the possible radical coupling reactions.



While the initiation and termination steps are important in the mechanism of a chain reaction, almost all of the products are formed as the result of the propagation steps because there are so many more of them. An equation for the overall reaction can be obtained by summing the propagation steps and canceling species that appear on both sides of the equation:

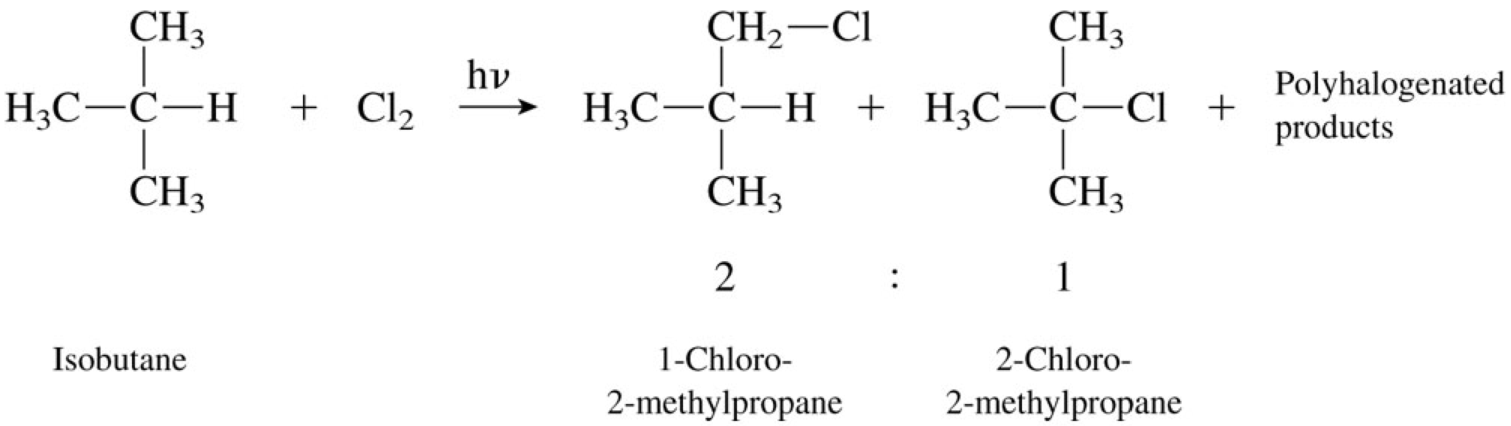
$$
\begin{array}{lllllll}
:\underset{\cdot\cdot}{\overset{\cdot\cdot}{\cancel{Cl}}}\cdot & + & CH_4 & \longrightarrow & HCl & + & \cdot\cancel{CH_3} \\
\cdot\cancel{CH_3} & + & Cl_2 & \longrightarrow & CH_3Cl & + & :\underset{\cdot\cdot}{\overset{\cdot\cdot}{\cancel{Cl}}}\cdot \\
\hline
CH_4 & + & Cl_2 & \longrightarrow & CH_3Cl & + & HCl
\end{array}
$$

Radical chlorination is a difficult reaction to control.

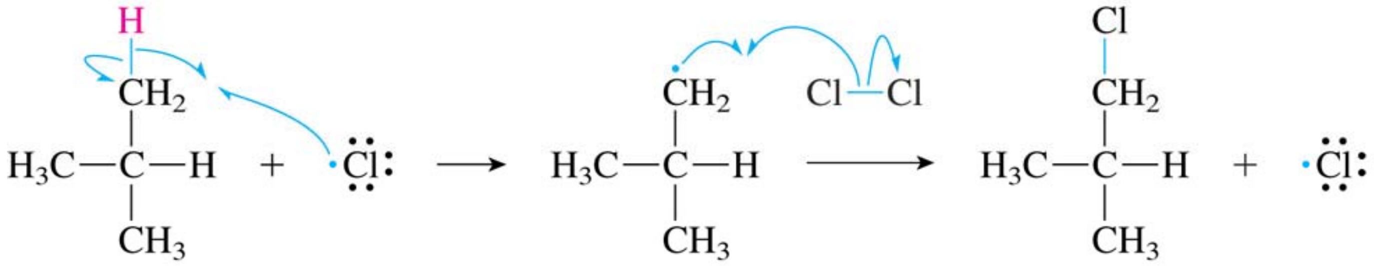
The reaction of a 1:1 ratio of methane and chlorine at 440°C (at this high temperature, homolytic fission of the chlorine–chlorine bond occurs without light) results in the product mixture shown in the following equation:

$$
CH_4 + Cl_2 \xrightarrow{440°C} \underset{47\%}{CH_4} + \underset{20\%}{CH_3Cl} + \underset{22\%}{CH_2Cl_2} + \underset{10\%}{CHCl_3} + \underset{1\%}{CCl_4} + HCl
$$

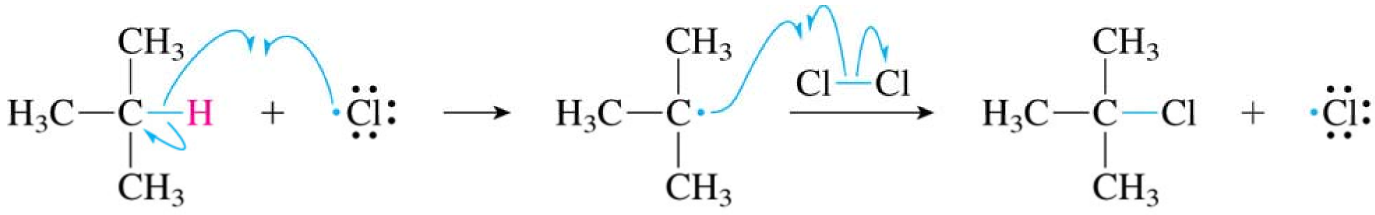
Selectivity



Statistical ratio: 9 : 1

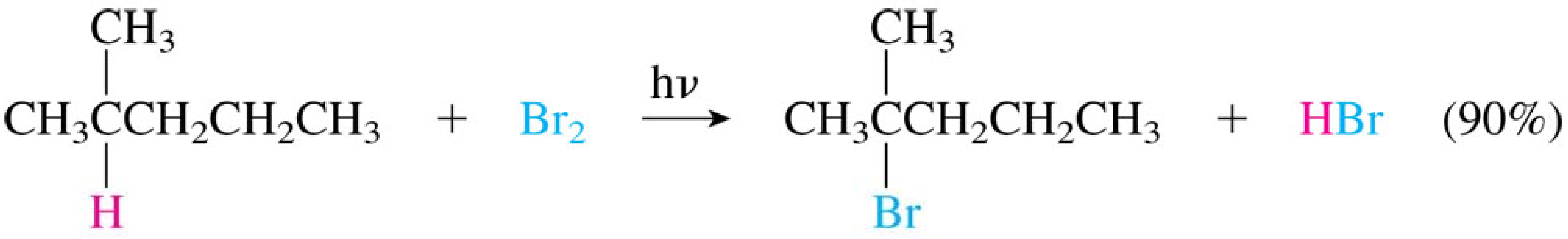


A primary radical



A tertiary radical

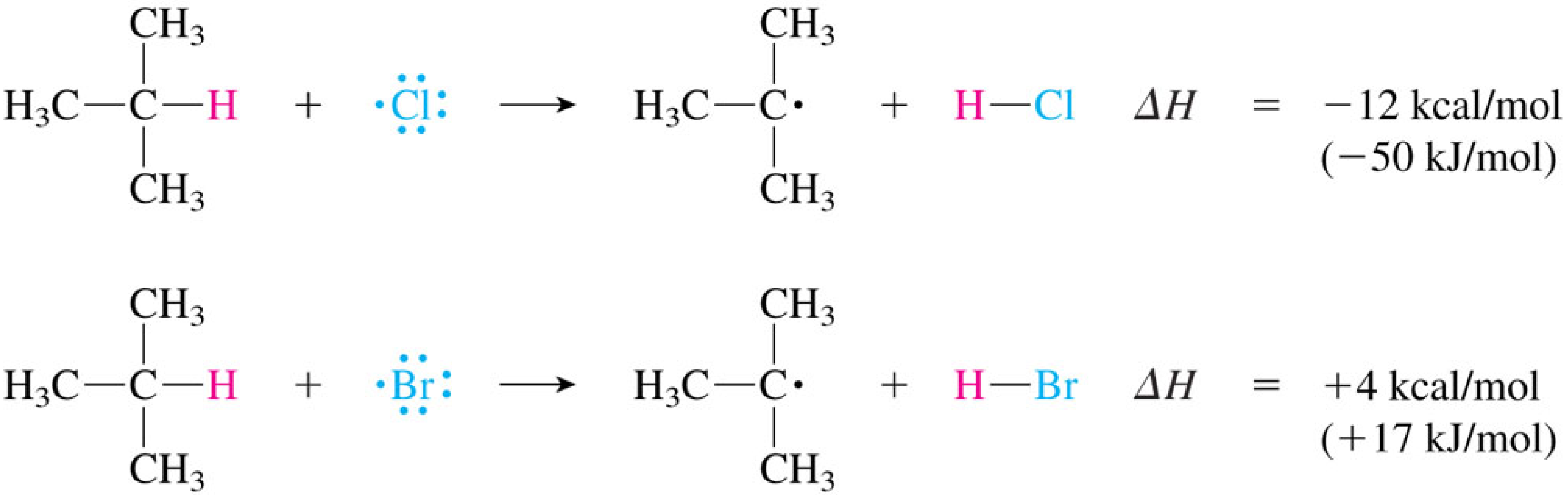
However, bromination is very selective



$$CH_3\underset{\textstyle H}{\overset{\textstyle CH_3}{\overset{|}{\underset{|}{C}}}}CH_2CH_2CH_3 + Br_2 \xrightarrow{h\nu} CH_3\underset{\textstyle Br}{\overset{\textstyle CH_3}{\overset{|}{\underset{|}{C}}}}CH_2CH_2CH_3 + HBr \quad (90\%)$$

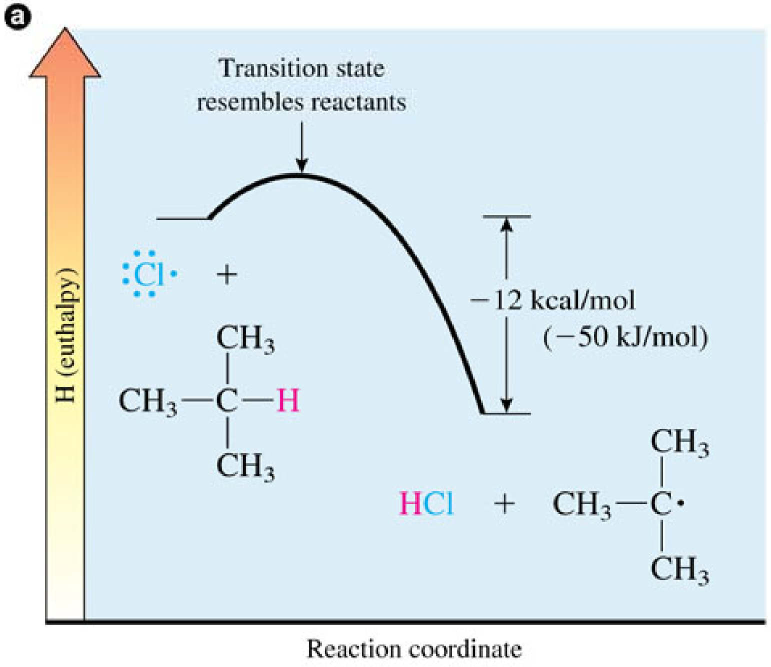
2-Methylpentane

Why?

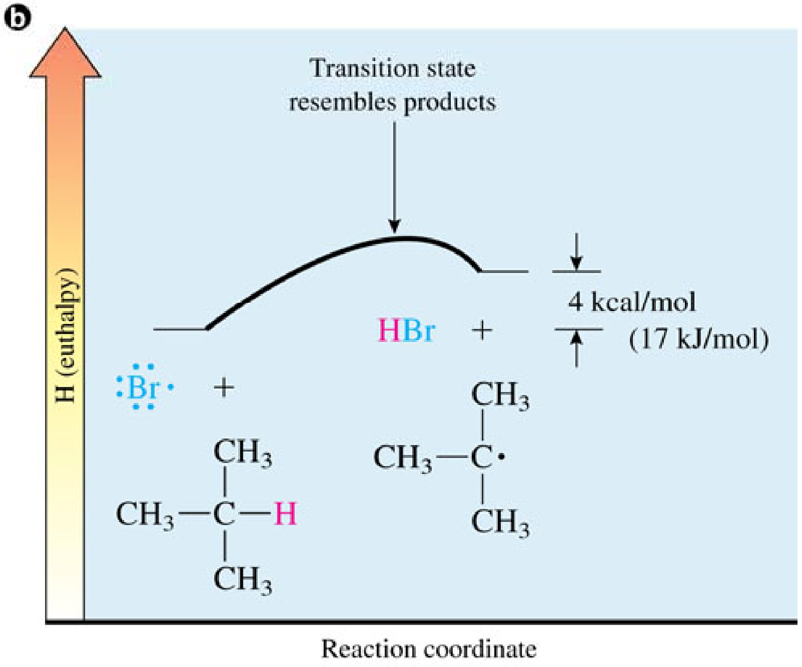


$$H_3C-\underset{\textstyle CH_3}{\overset{\textstyle CH_3}{\overset{|}{\underset{|}{C}}}}-H + \cdot\ddot{\underset{\cdot\cdot}{Cl}}\colon \longrightarrow H_3C-\underset{\textstyle CH_3}{\overset{\textstyle CH_3}{\overset{|}{\underset{|}{C}}}}\cdot + H-Cl \quad \Delta H = -12\ \text{kcal/mol}\ (-50\ \text{kJ/mol})$$

$$H_3C-\underset{\textstyle CH_3}{\overset{\textstyle CH_3}{\overset{|}{\underset{|}{C}}}}-H + \cdot\ddot{\underset{\cdot\cdot}{Br}}\colon \longrightarrow H_3C-\underset{\textstyle CH_3}{\overset{\textstyle CH_3}{\overset{|}{\underset{|}{C}}}}\cdot + H-Br \quad \Delta H = +4\ \text{kcal/mol}\ (+17\ \text{kJ/mol})$$



By the Hammond postulate, the transition state for abstraction of a hydrogen by a chlorine atom resembles the reactants and has only a small amount of radical character. Therefore, the transition state leading to a tertiary radical is only slightly more stable than the transition state leading to a primary radical.

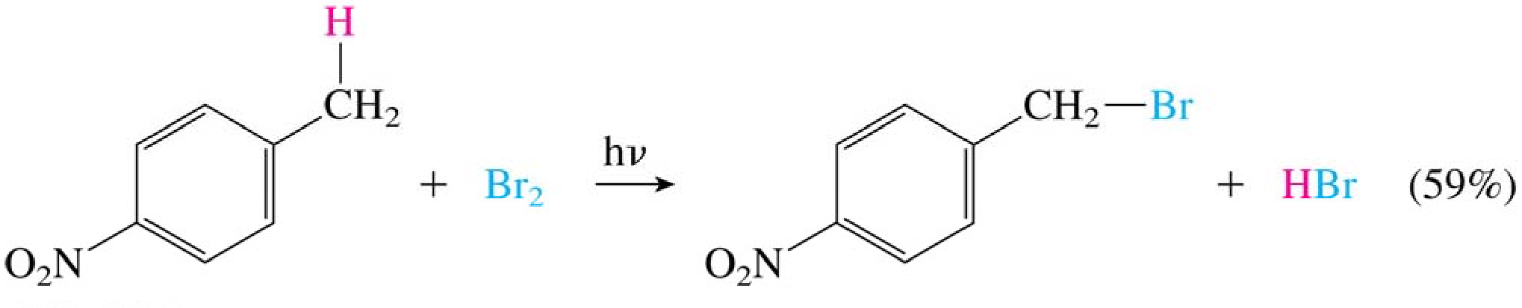


In contrast, the transition state for abstraction of a hydrogen atom by a bromine atom resembles the product and has a large amount of radical character. Therefore, the transition state leading to a tertiary radical is considerably more stable than the transition state leading to a primary radical.

In chlorination, the transition state resembles the reactant (small radical character), therefore the tertiary radical is slightly more stable than the primary one

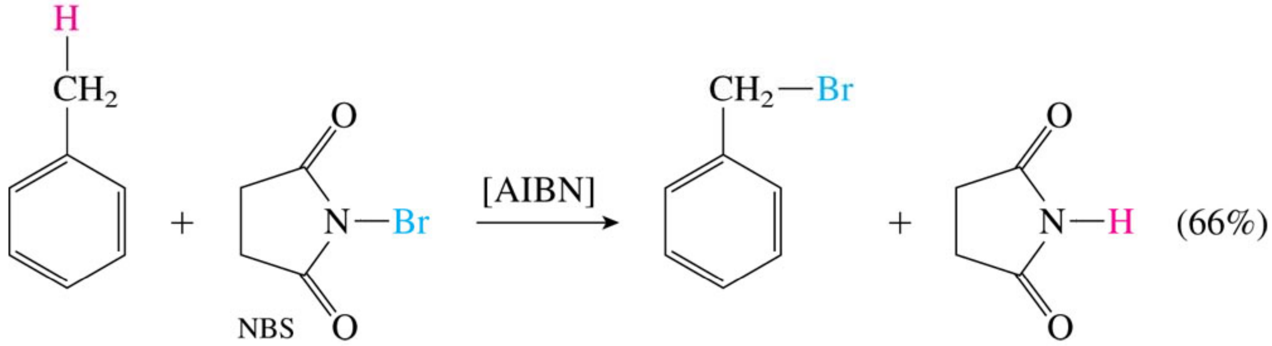
In bromination, the transition state resembles the product (mostly radical character), therefore the tertiary radical is much more stable than the primary one

Radical bromination is very selective, as long as the compound to be brominated has one hydrogen that is considerably more reactive than others

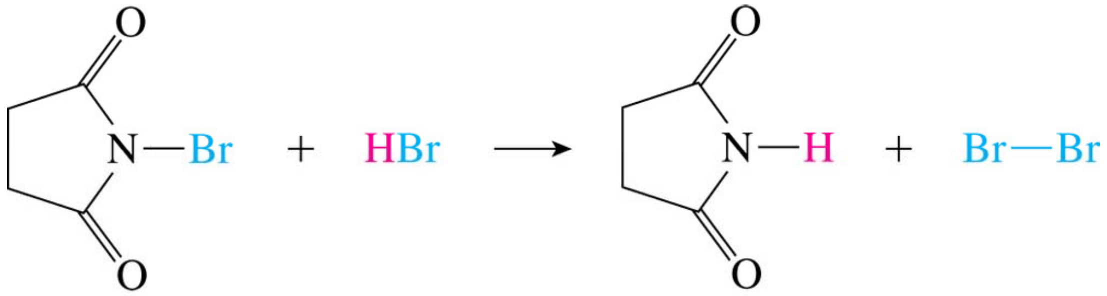


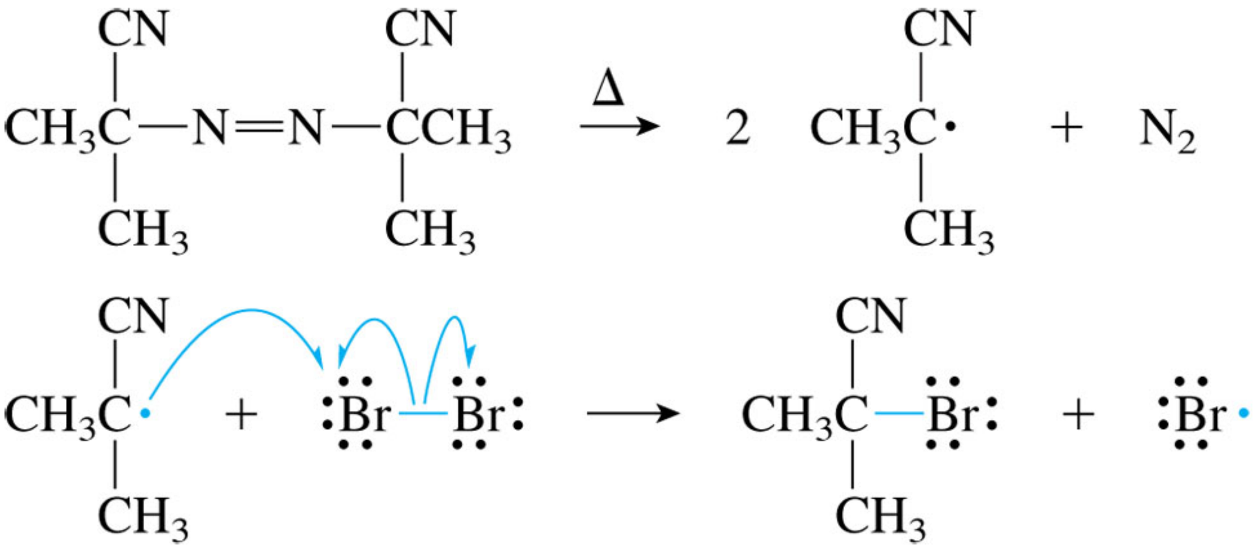
NBS (*N*-bromosuccinimide)

⇒ useful in substituting bromine for hydrogen at allylic and benzylic position



The possible mechanism

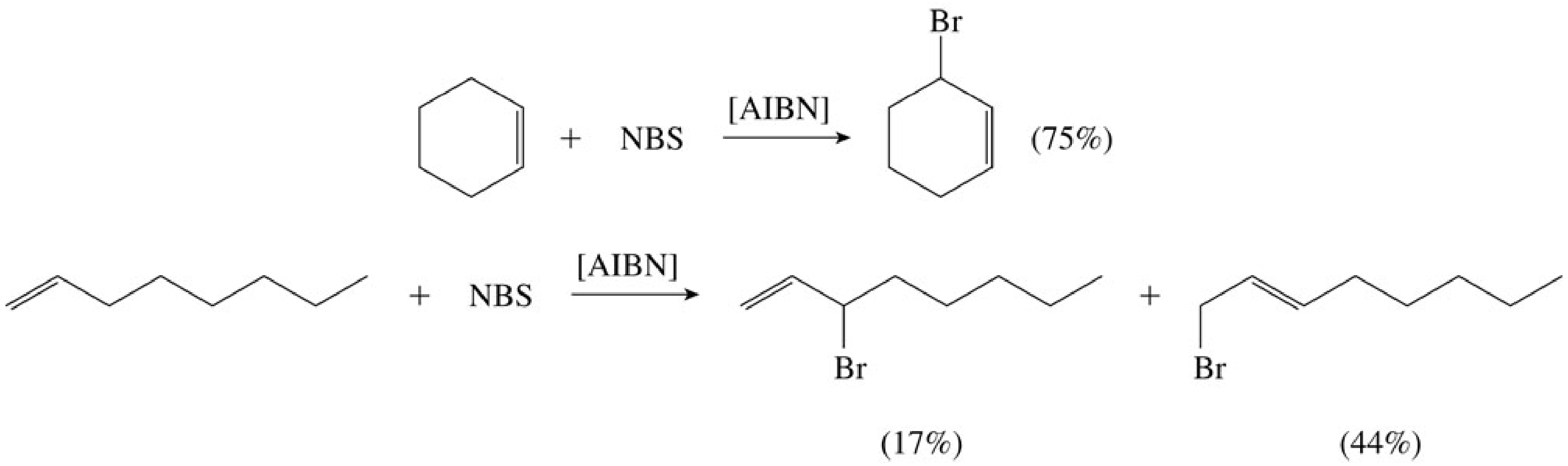


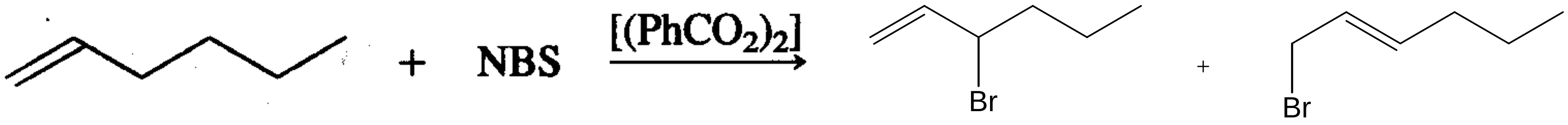


The actual brominating agent is probably the Br_2

Single product if only a single type of allylic hydrogen is available

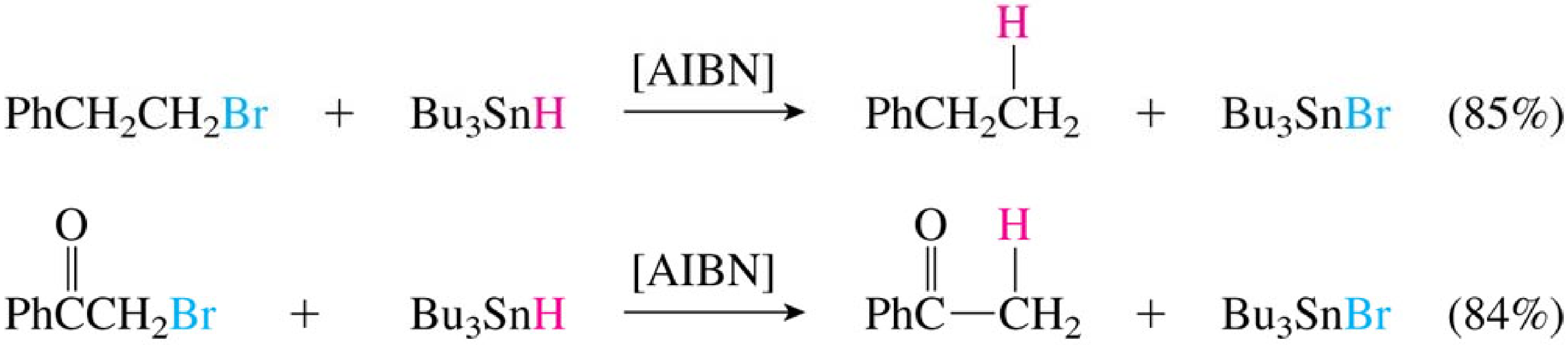
Two products if the resonance stabilized allylic radical provide two radical sites





21.7 Dehalogenation

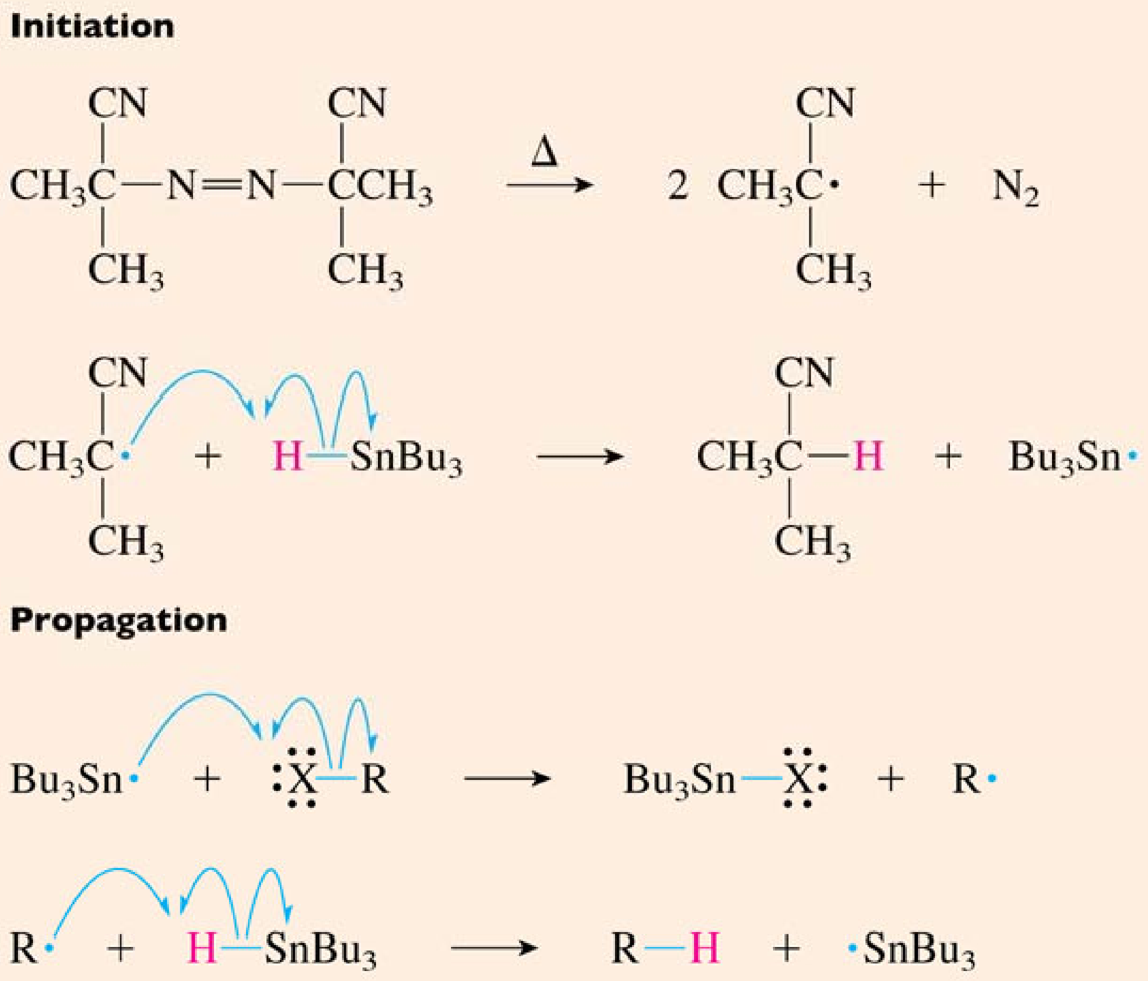
The reaction of an alkyl halide with tributyltin hydride, using a radical initiator, results in the replacement of the halogen by hydrogen.



$$PhCH_2CH_2Br + Bu_3SnH \xrightarrow{[AIBN]} PhCH_2CH_2\text{—}H + Bu_3SnBr \quad (85\%)$$

$$PhC(=O)CH_2Br + Bu_3SnH \xrightarrow{[AIBN]} PhC(=O)\text{—}CH_2\text{—}H + Bu_3SnBr \quad (84\%)$$

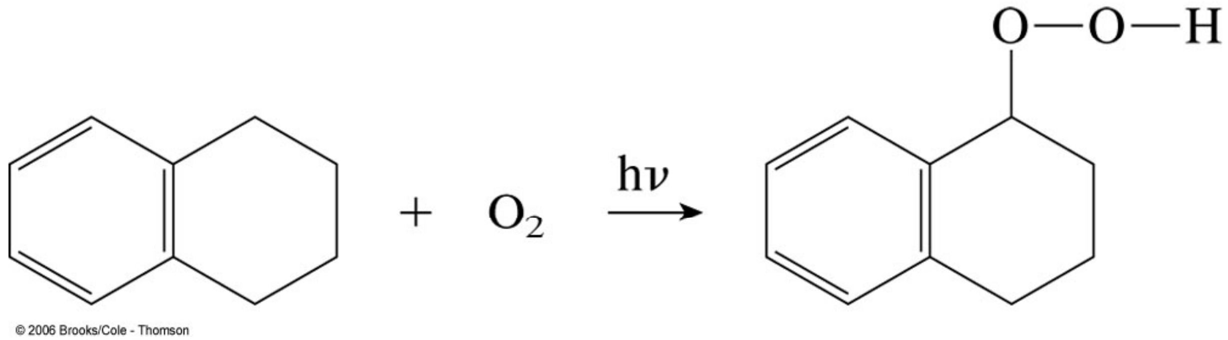
Mechanism


Initiation
CN
CH3C—N=N—CCH3
CH3
Δ
2 CH3C·
+ N2
CH3C· + H—SnBu3
CH3C—H + Bu3Sn·
Propagation
Bu3Sn· + :X—R
Bu3Sn—X: + R·
R· + H—SnBu3
R—H + ·SnBu3

21.8 Autooxidation

The slow oxidation of organic materials that are exposed to oxygen in the atmosphere is termed **autooxidation**

A simple example



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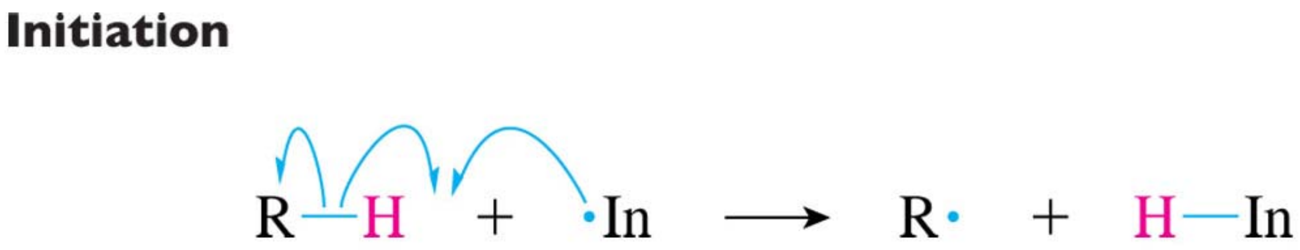
This process follows a radical chain mechanism and is catalyzed by light.

⇒ **Chemicals are normally stored in brown bottle or plastic bottle**

Mechanism



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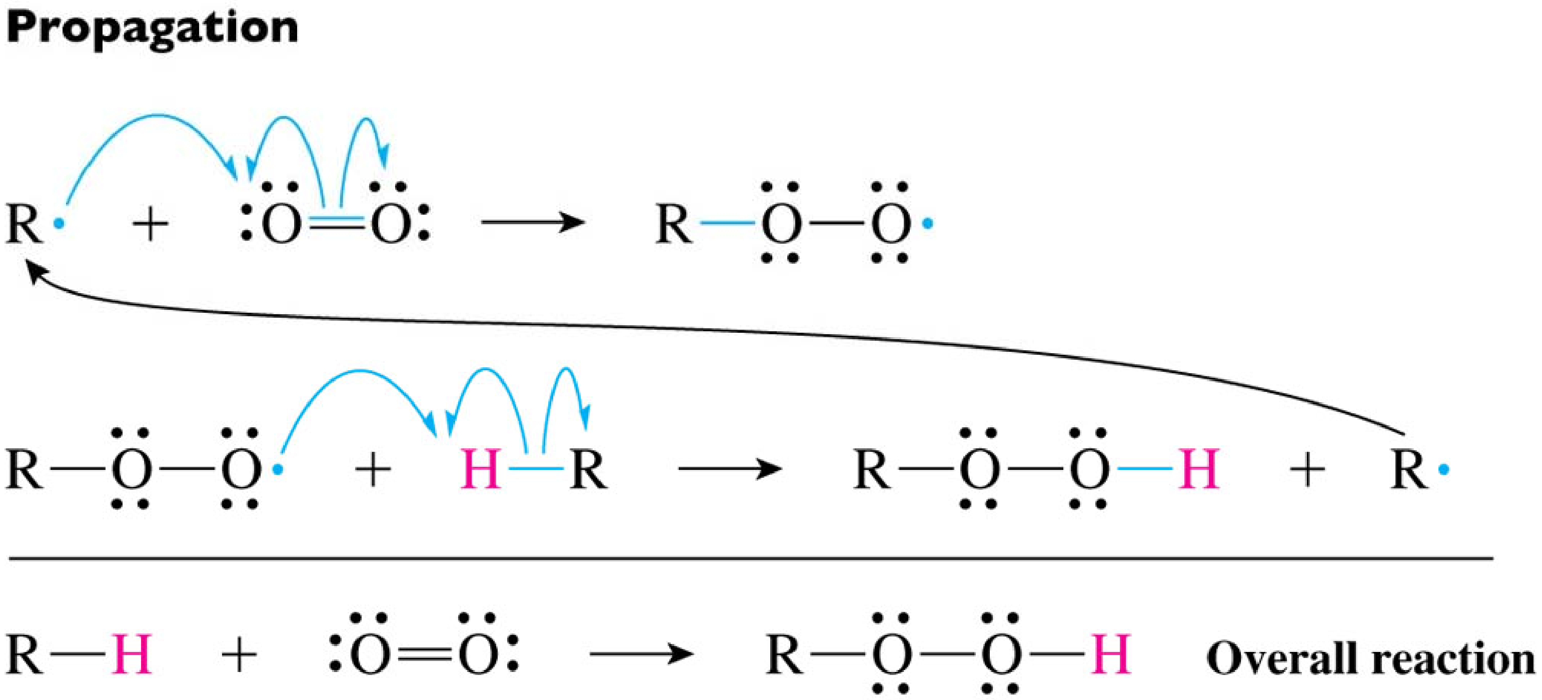

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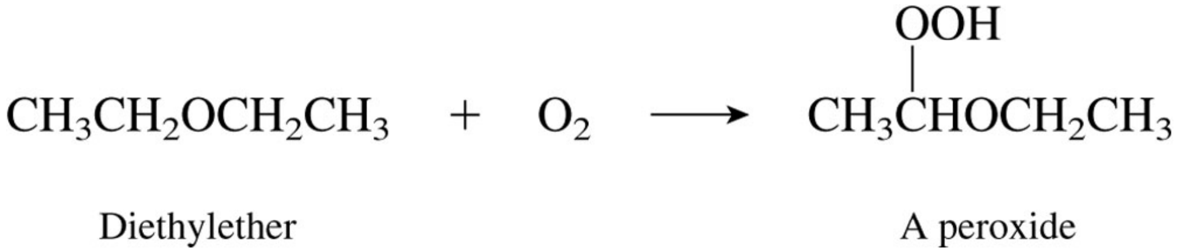
The autoxidation reaction is difficult to control, so it is not often used for synthetic purposes.

However, it is a very important natural process. The slow deterioration of organic materials, such as rubber, paint, and oils, and that of many foods, such as butter and fats, is due to autoxidation.

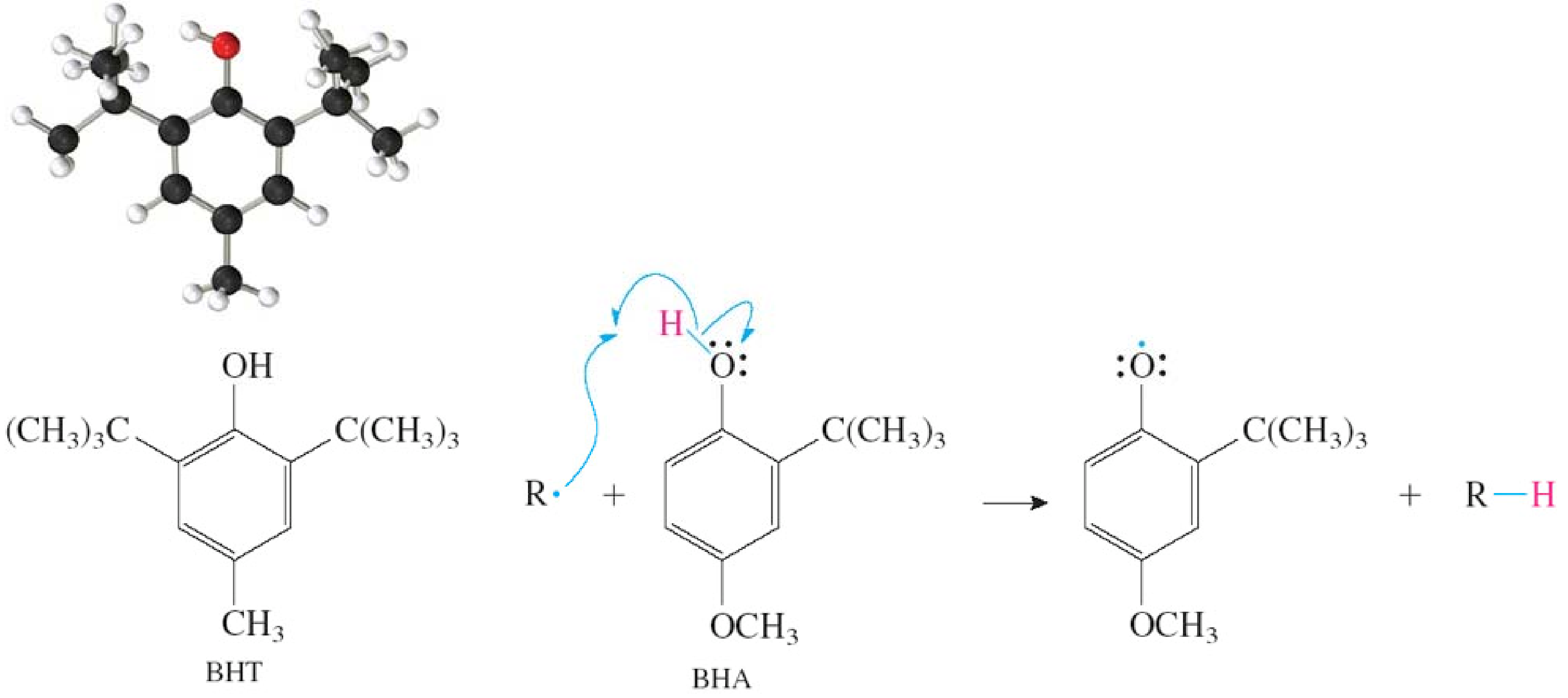
As one example, peroxides are formed in solvents such as diethyl ether or THF that are stored for long periods of time in contact with air:



$$CH_3CH_2OCH_2CH_3 + O_2 \longrightarrow CH_3\overset{\overset{\displaystyle OOH}{|}}{C}HOCH_2CH_3$$

Because peroxides are explosive, the use of such contaminated solvents leads to a very dangerous situation. Numerous explosions have resulted in the laboratory when peroxides have been concentrated as the solvent is removed by distillation during the workup of a reaction. Therefore it is important to be certain that ether and THF are free of peroxides before they are employed as solvents and solutions of ether, and THF should never be distilled to dryness.

Antioxidant: added to organic materials to prevent autooxidation



2,6-di-*tert*-butyl-4-methylphenol

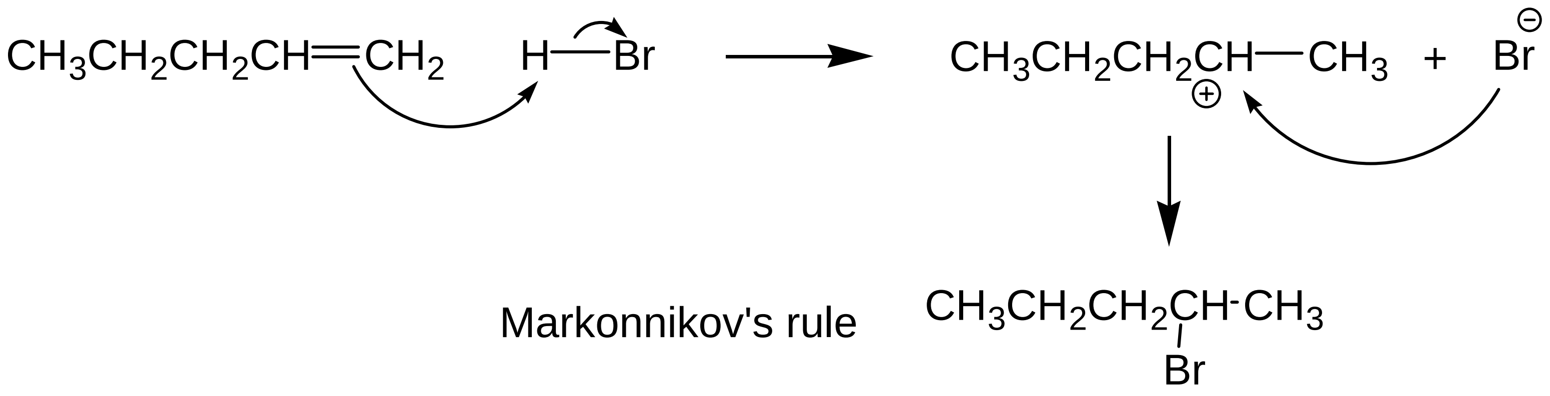
<u>b</u>utylated <u>h</u>ydroxy<u>t</u>oluene

2-*tert*-butyl-4-methylphenol

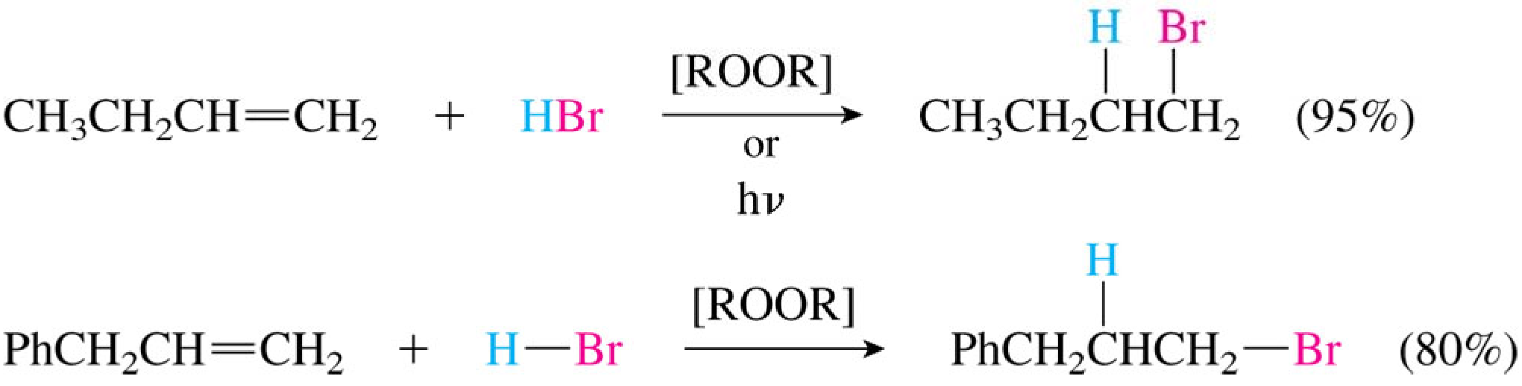
<u>b</u>utylated <u>h</u>ydroxy<u>a</u>nisole

21.9 Radical Additions to Alkene

Electrophilic addition of HBr to alkene



Radical addition occurs in anti-Markonikov’s manner

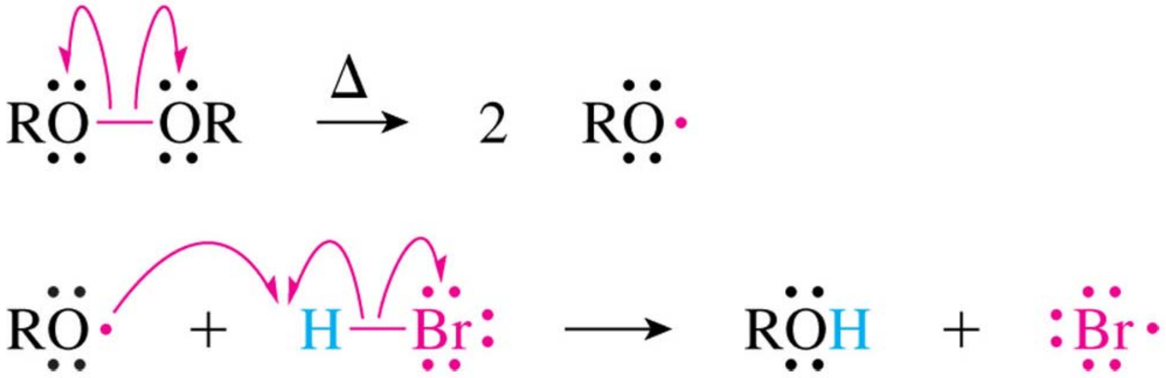


$$CH_3CH_2CH{=}CH_2 + HBr \xrightarrow[\text{or } h\nu]{[ROOR]} CH_3CH_2\overset{H}{C}H\overset{Br}{C}H_2 \quad (95\%)$$

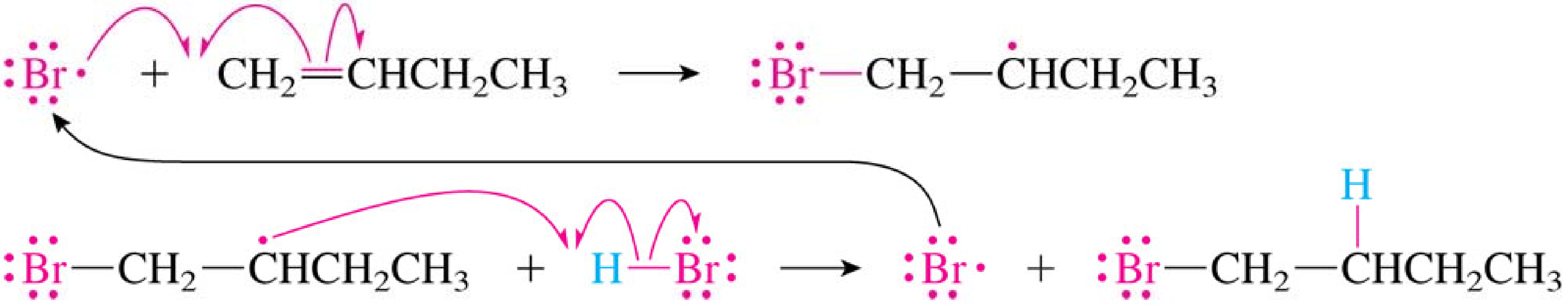
$$PhCH_2CH{=}CH_2 + H—Br \xrightarrow{[ROOR]} PhCH_2\overset{H}{C}HCH_2—Br \quad (80\%)$$

Radical Chain Mechanism

Initiation

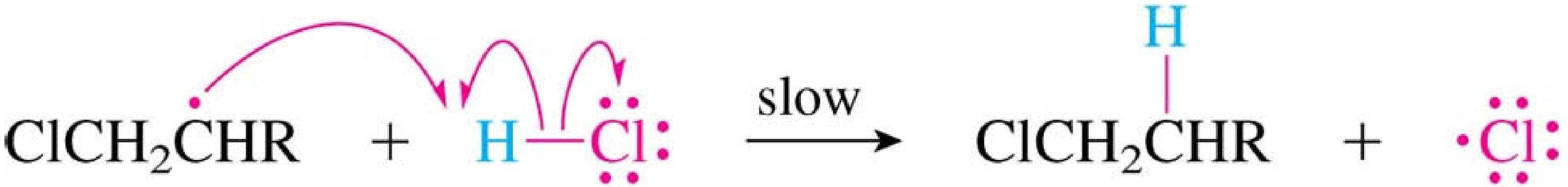


Propagation



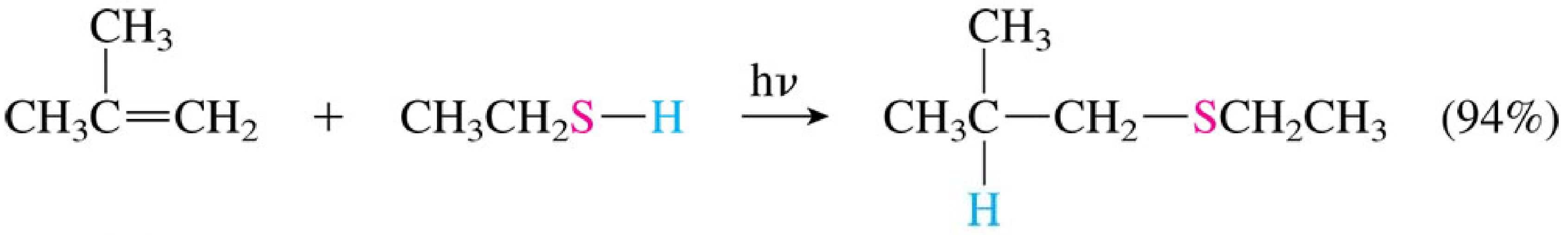
HCl and HI cannot be used in the Radical Additions to Alkene

HCl: strong H – Cl bond (bond dissociation E = 103 kcal/mol), then abstraction step is slow

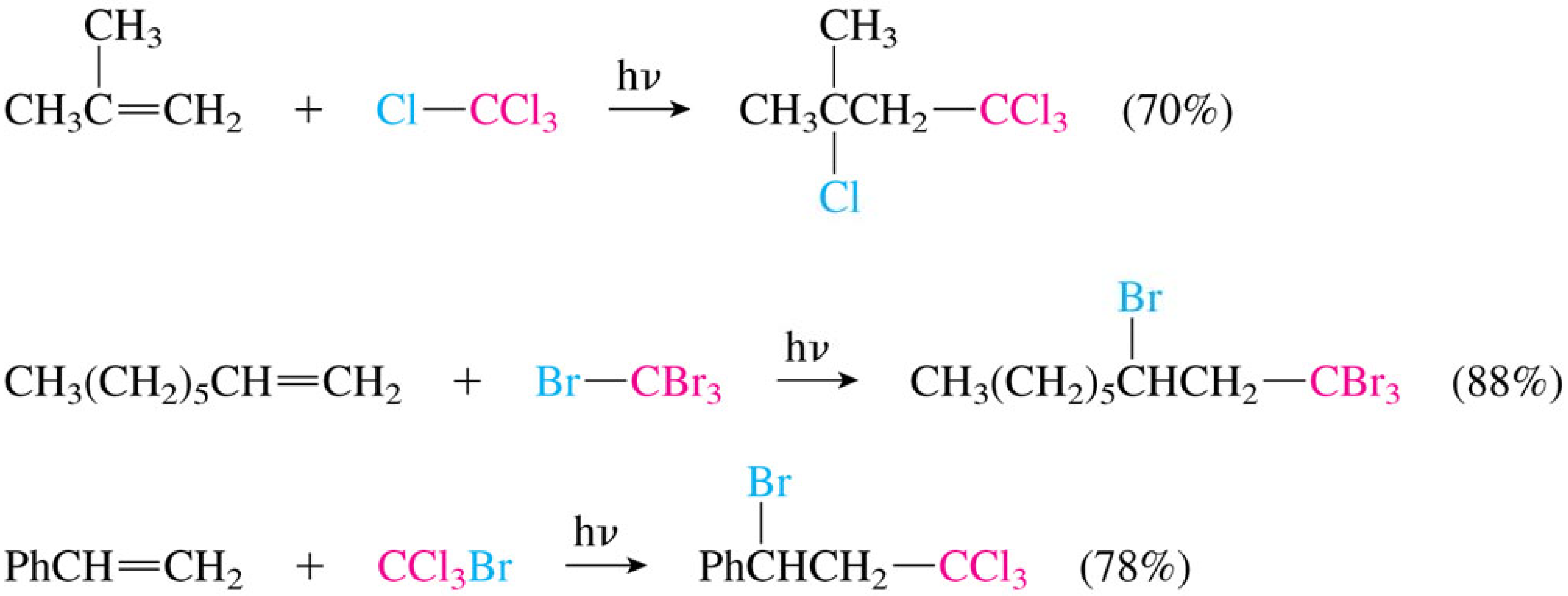


HI: week H – I bond (bond dissociation E = 52 kcal/mol), then addition step is slow

Other useful radical addition reactions



$$\mathrm{CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}{=}CH_2} + \mathrm{CH_3CH_2S{-}H} \xrightarrow{h\nu} \mathrm{CH_3\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}{-}CH_2{-}SCH_2CH_3} \quad (94\%)$$



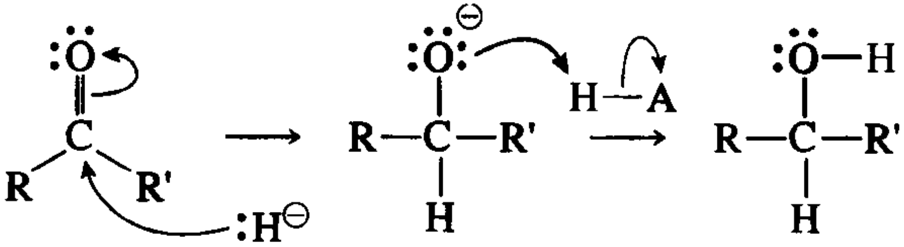
$$\mathrm{CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}{=}CH_2} + \mathrm{Cl{-}CCl_3} \xrightarrow{h\nu} \mathrm{CH_3\underset{\underset{\displaystyle Cl}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}CH_2{-}CCl_3} \quad (70\%)$$

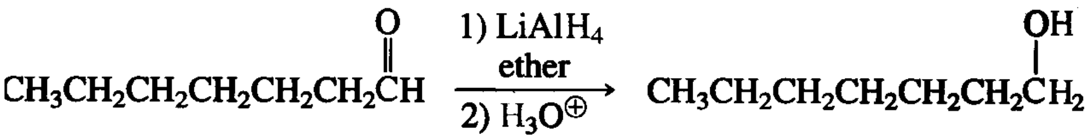
$$\mathrm{CH_3(CH_2)_5CH{=}CH_2} + \mathrm{Br{-}CBr_3} \xrightarrow{h\nu} \mathrm{CH_3(CH_2)_5\overset{\overset{\displaystyle Br}{|}}{C}HCH_2{-}CBr_3} \quad (88\%)$$

$$\mathrm{PhCH{=}CH_2} + \mathrm{CCl_3Br} \xrightarrow{h\nu} \mathrm{Ph\overset{\overset{\displaystyle Br}{|}}{C}HCH_2{-}CCl_3} \quad (78\%)$$

Summary of reductions in this semester

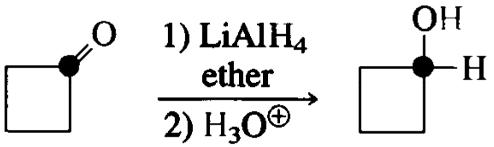
1. addition of hydride: reduction of aldehyde and ketones



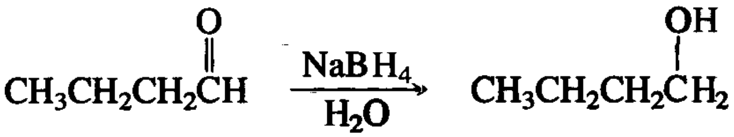


$$CH_3CH_2CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}H \xrightarrow[2)\ H_3O^{\oplus}]{1)\ LiAlH_4,\ ether} CH_3CH_2CH_2CH_2CH_2CH_2\overset{OH}{\overset{|}{C}}H_2$$

(86%)

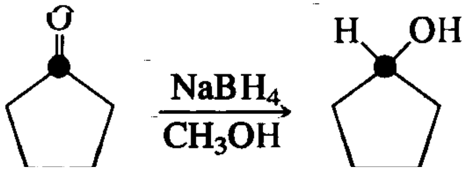


(90%)

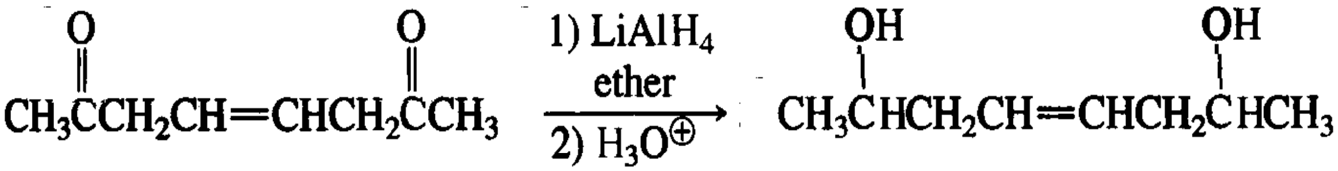


$$CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}H \xrightarrow[H_2O]{NaBH_4} CH_3CH_2CH_2\overset{OH}{\overset{|}{C}}H_2$$

(85%)



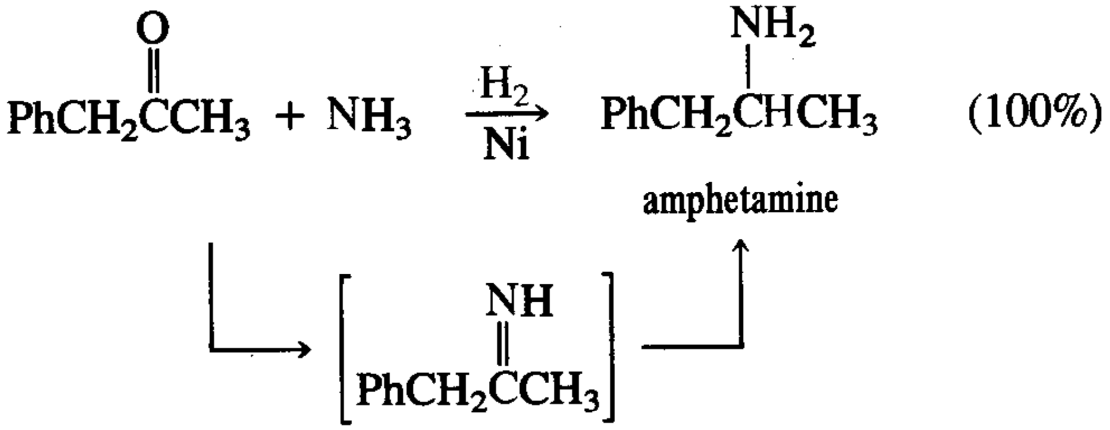
(90%)

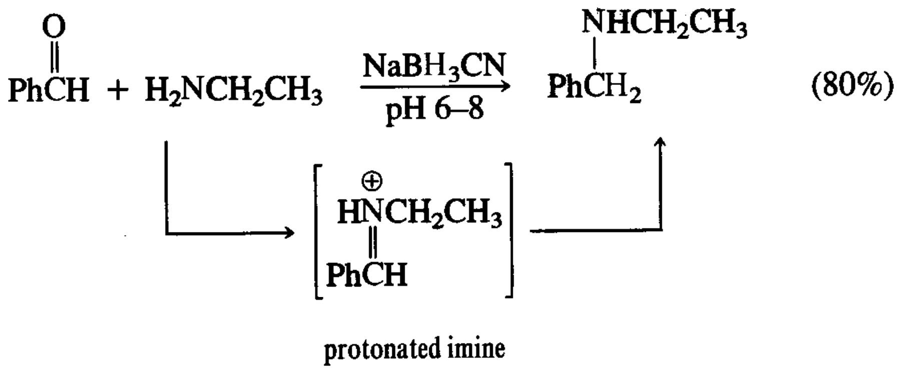


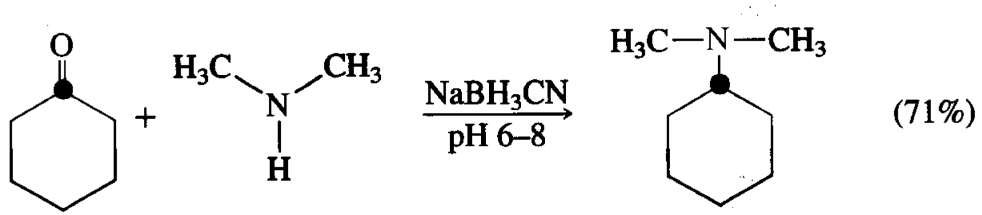
$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH{=}CHCH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[2)\ H_3O^{\oplus}]{1)\ LiAlH_4,\ ether} CH_3\overset{OH}{\overset{|}{C}}HCH_2CH{=}CHCH_2\overset{OH}{\overset{|}{C}}HCH_3$$

(79%)

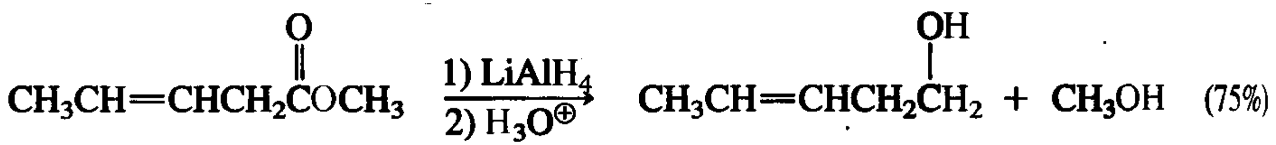
2. Using sodium cyanoborohydride: does not react with aldehyde and ketones, do react with imine or enamine



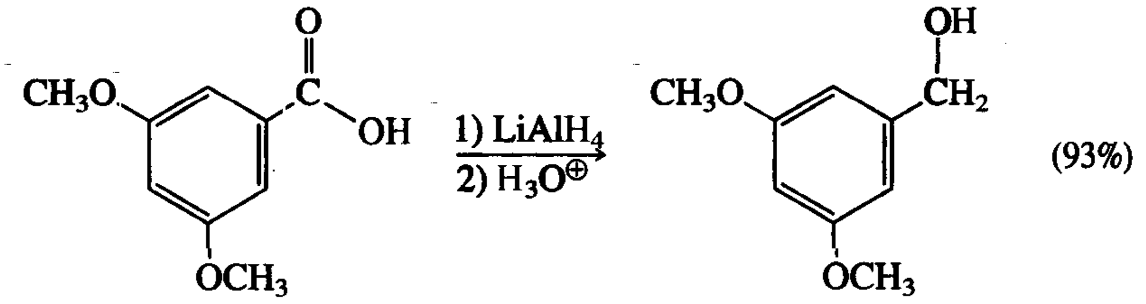


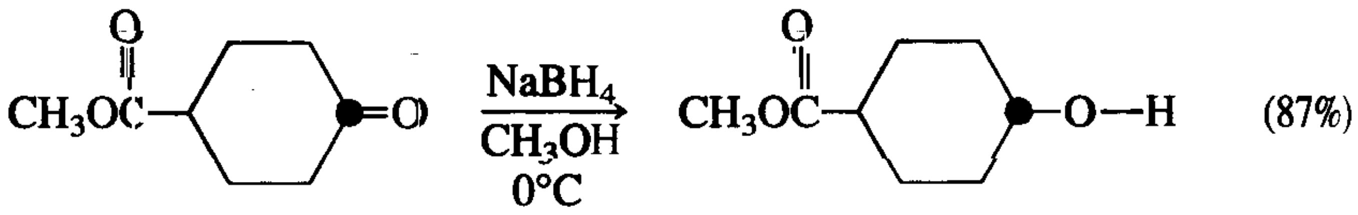


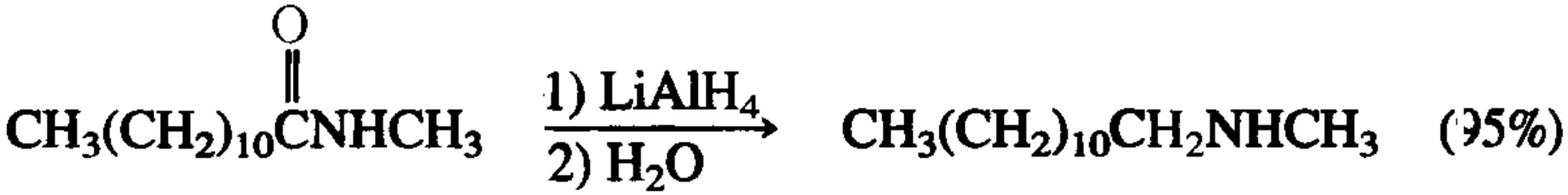
3. reduction of carboxylic acid derivatives



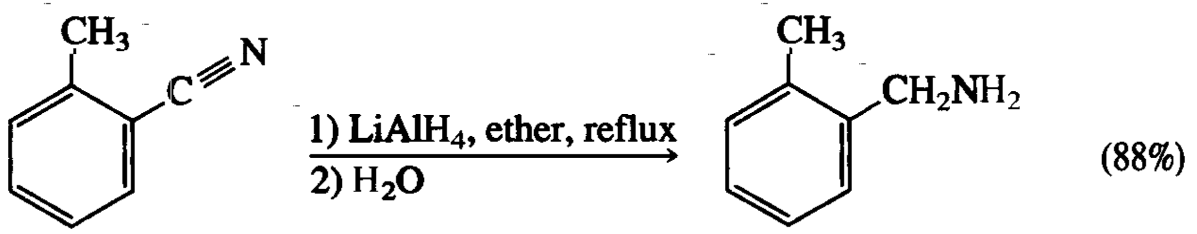
$$CH_3CH{=}CHCH_2\overset{\overset{O}{\|}}{C}OCH_3 \xrightarrow[2)\ H_3O^{\oplus}]{1)\ LiAlH_4} CH_3CH{=}CHCH_2\overset{\overset{OH}{|}}{C}H_2 + CH_3OH \quad (75\%)$$



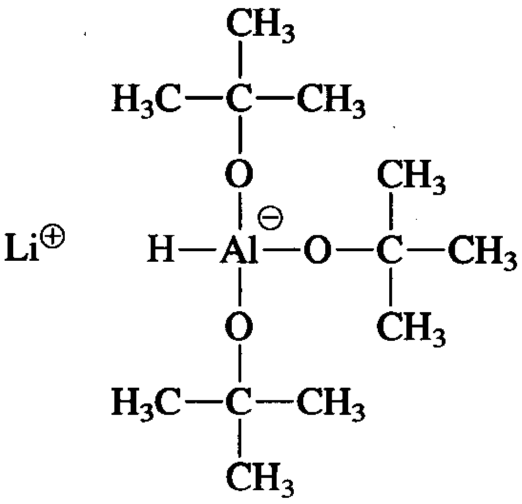




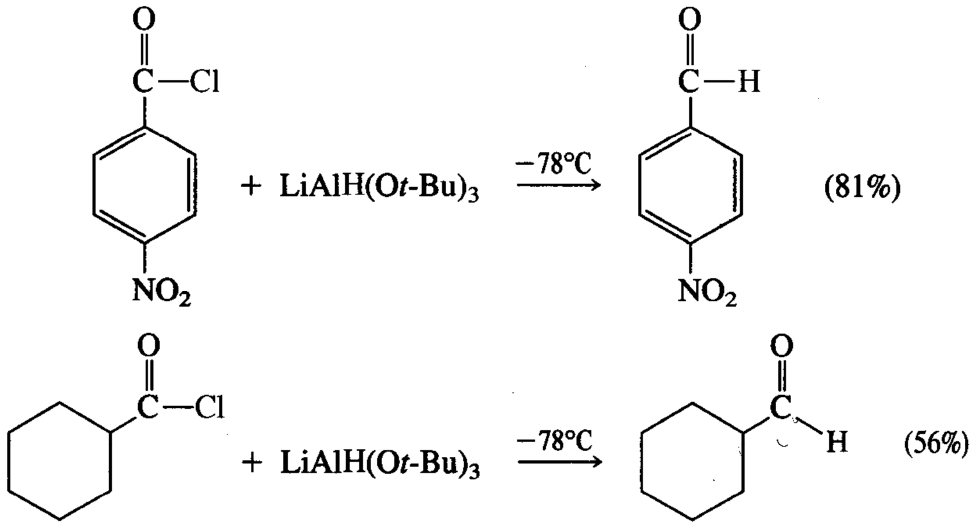
$$CH_3(CH_2)_{10}\overset{\overset{O}{\|}}{C}NHCH_3 \xrightarrow[2)\ H_2O]{1)\ LiAlH_4} CH_3(CH_2)_{10}CH_2NHCH_3 \quad (95\%)$$

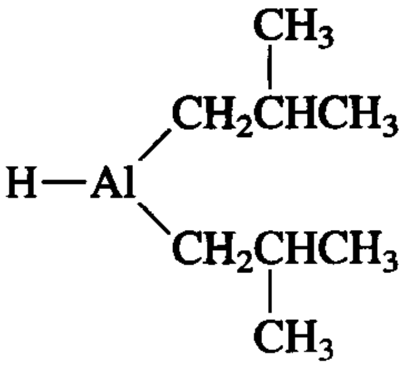


4. Reduction to aldehyde

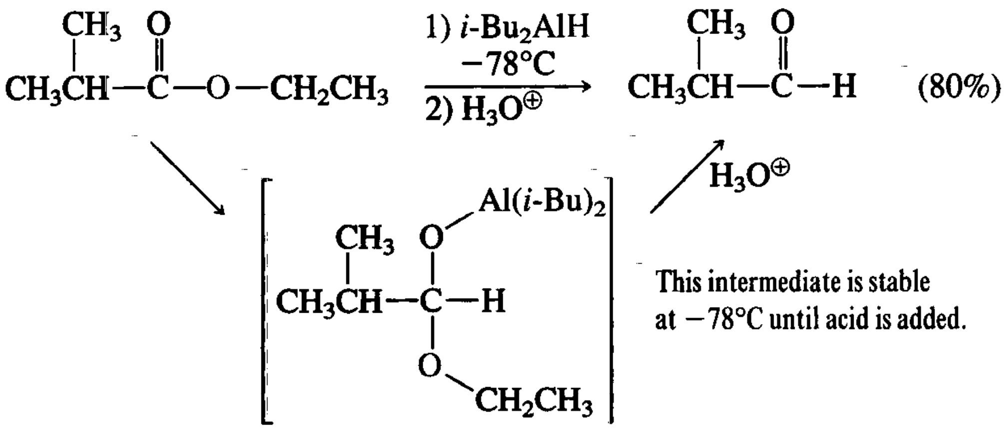


lithium tri-*t*-butoxyaluminum hydride





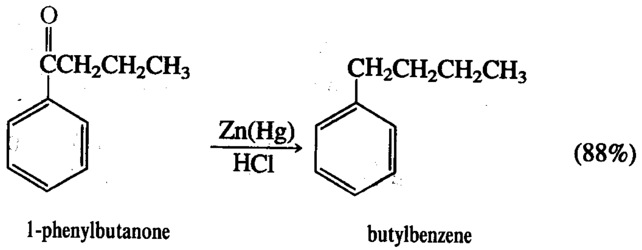
diisobutylaluminumhydride
DIBAH or *i*-Bu_2AlH



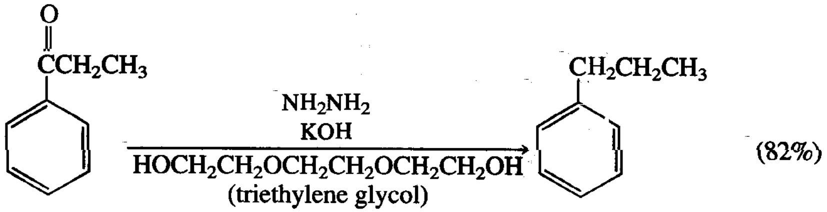
This intermediate is stable
at −78°C until acid is added.

5. Reduction of carbonyl group (aldehyde or ketone) to a methylene group

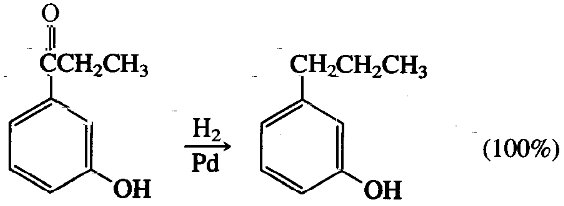
1. Clemmenson reduction



2. Wolff-Kishner reduction



3. Catalytic hydrogenation



H_2/Pt reduction vs Wolff-Kishner and Clemmenson reduction

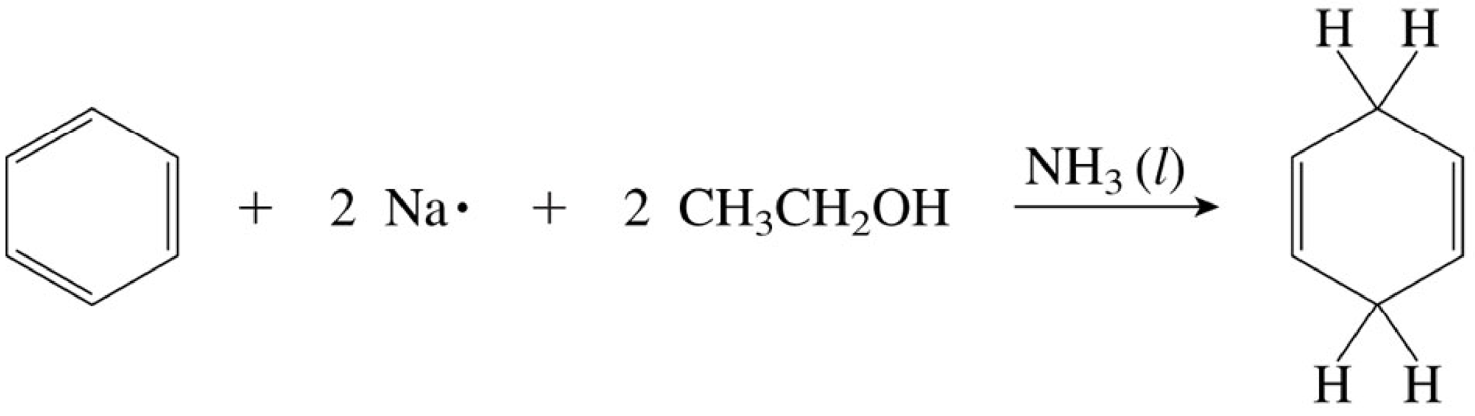
-H_2/Pt works for the carbonyl attached to the aromatic ring

-Wolff-Kishner and Clemmenson reduction do not have this restriction

21.10 Reductions of Radical Anions

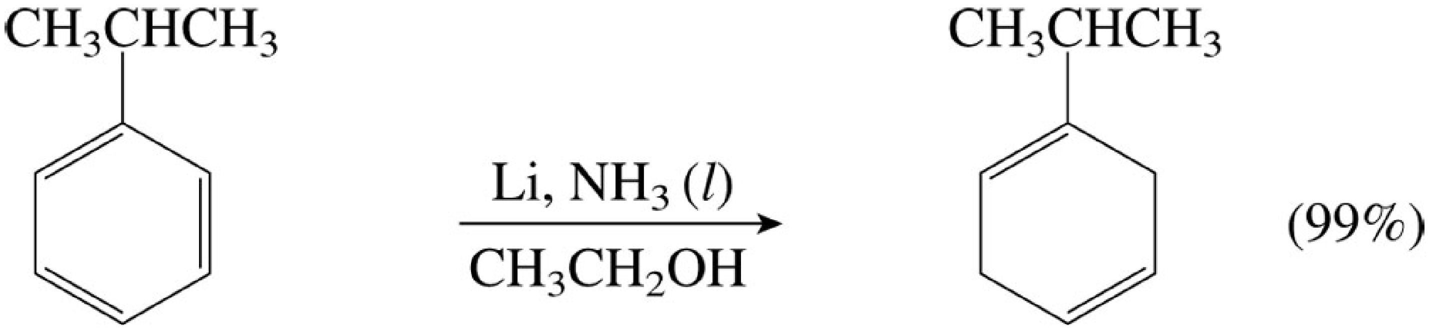
Birch reduction:

- **Sodium or lithium: electron source**
- **A small amount of alcohol: proton source**
- **Liquid ammonia: solvent**



Benzene

1,4-Cyclohexadiene



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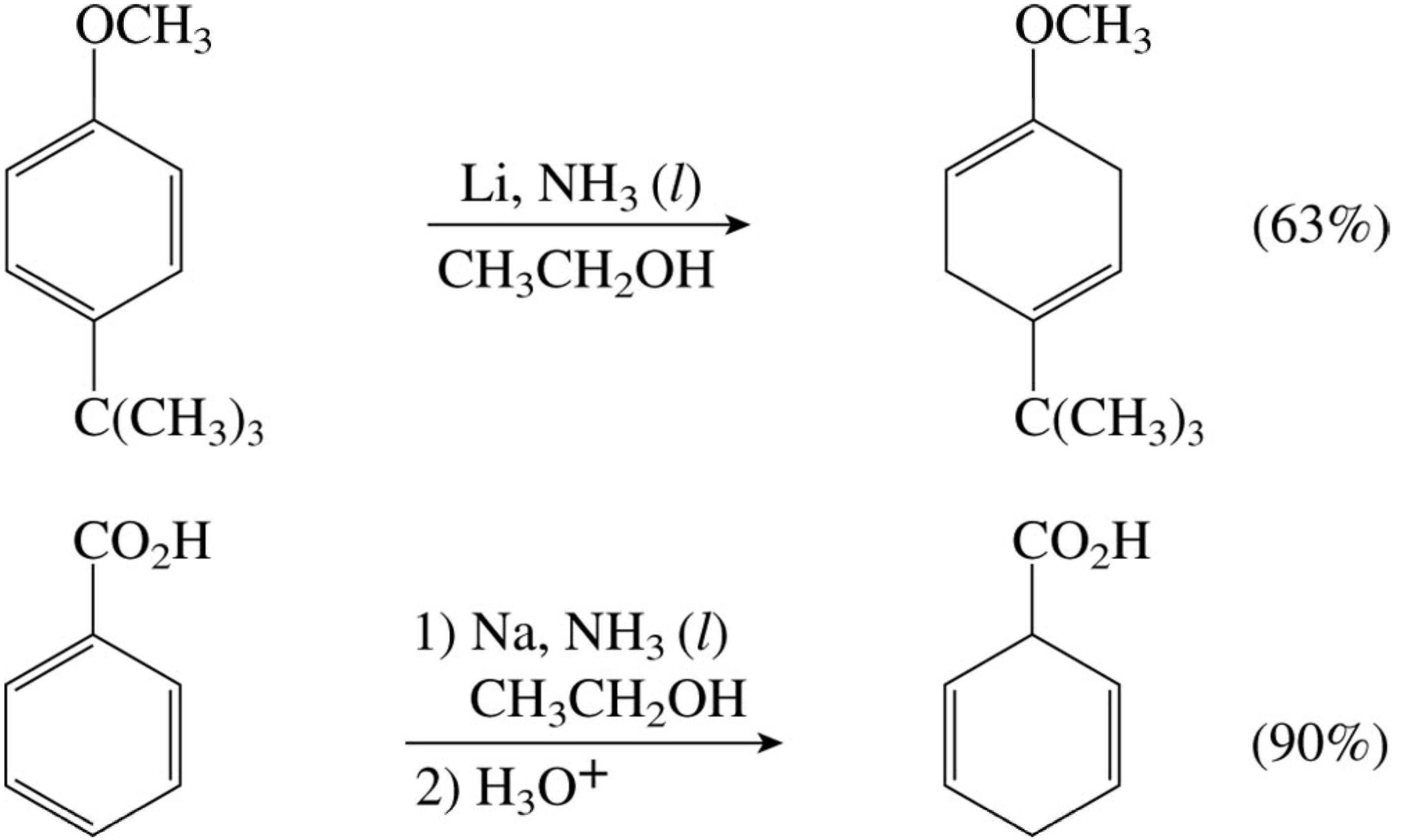

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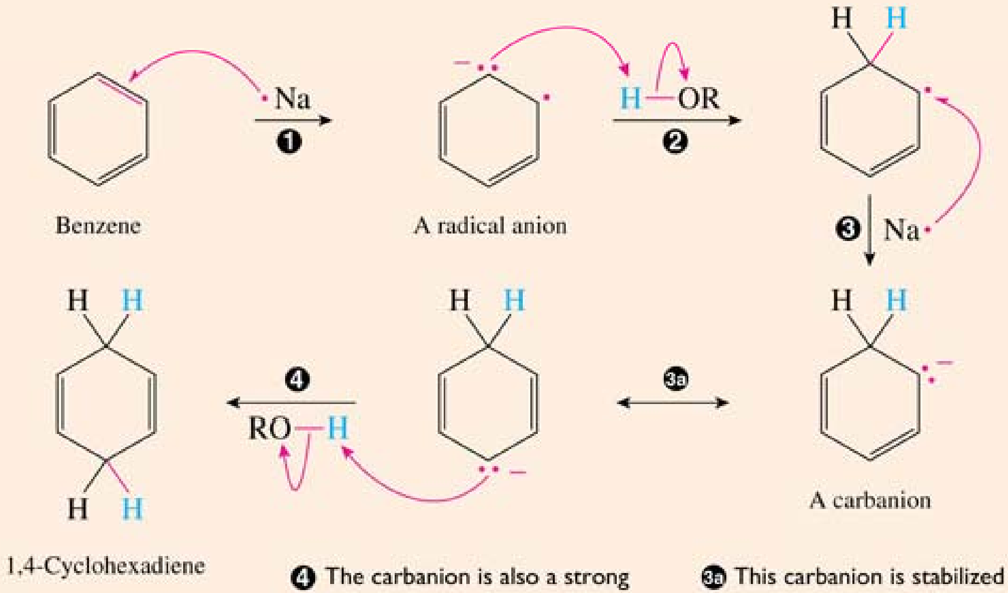
Mechanism

❶ An electron is transferred from a sodium atom to a benzene molecule. This electron is added to the lowest-energy orbital that is available, a pi antibonding MO in this case.

The product of the first step has an odd number of electrons and a negative charge so it is called a radical anion. It has seven electrons in its pi MOs. This Lewis structure is one way to represent it. It has a number of resonance structures.

❷ The radical anion is a very strong base and removes a proton from the alcohol. The product of this step is a radical.

❸ A second electron is added to the radical, producing a carbanion.

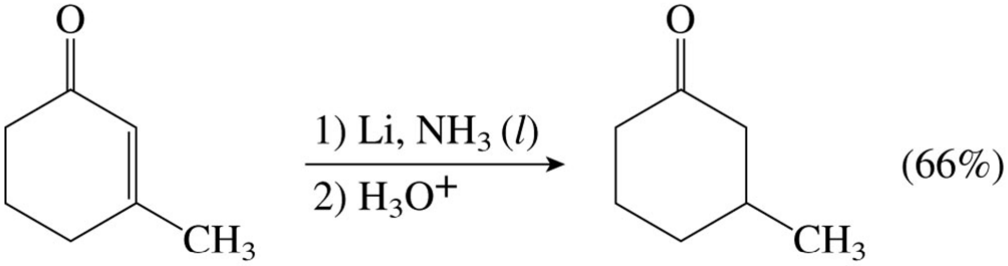


❹ The carbanion is also a strong base and removes a proton from the alcohol. Although it could potentially be protonated either ortho or para to the site of the first protonation, para protonation is faster. The product is a nonconjugated diene, 1,4-cyclohexadiene.

3a This carbanion is stabilized by resonance. Two resonance structures are shown here. A third resonance structure that resembles the first is not shown.

A normal alkene is not reduced under the conditions of the Birch reduction because its pi antibonding MO is too high in energy for an electron from a sodium atom to be readily added to it.

carbon-carbon double bond that is conjugated with a carbonyl group is readily reduced by lithium or sodium metal in liquid ammonia solvent, without any added alcohol.



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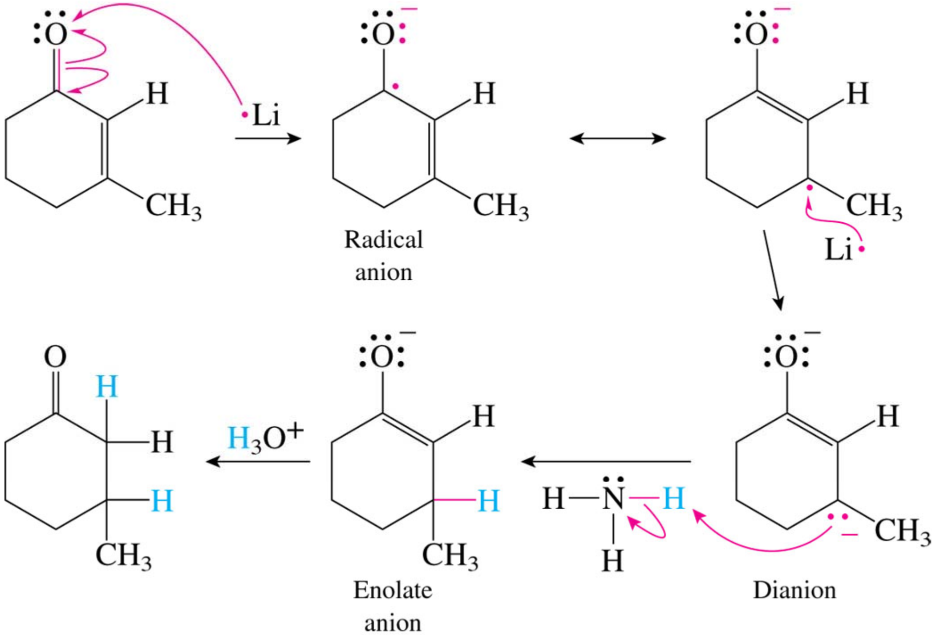
Mechanism



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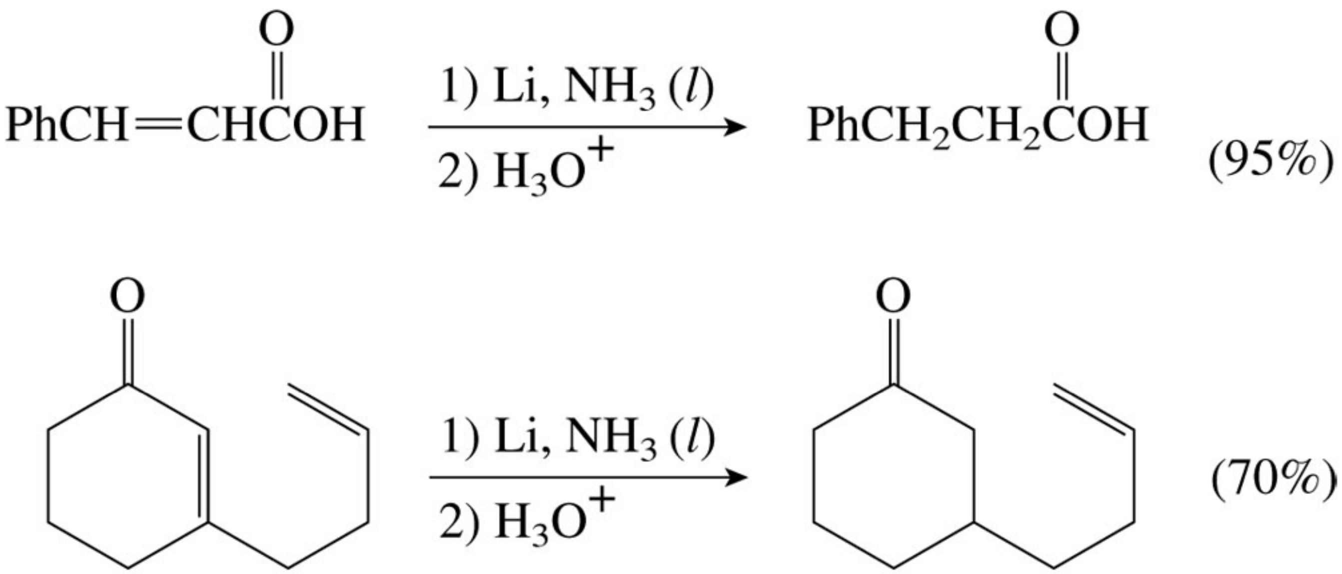
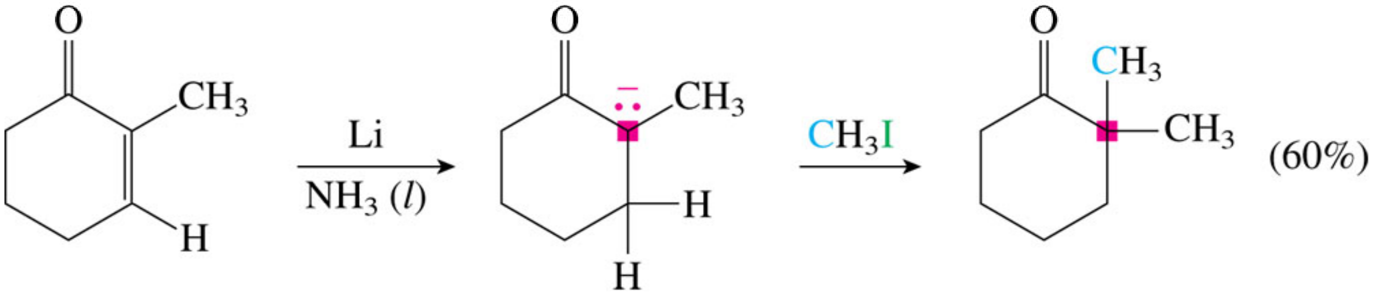
Examples

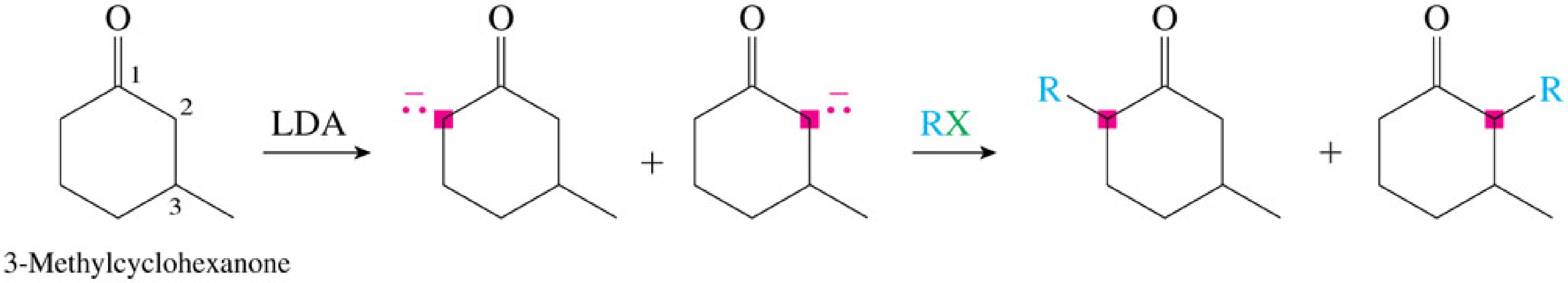


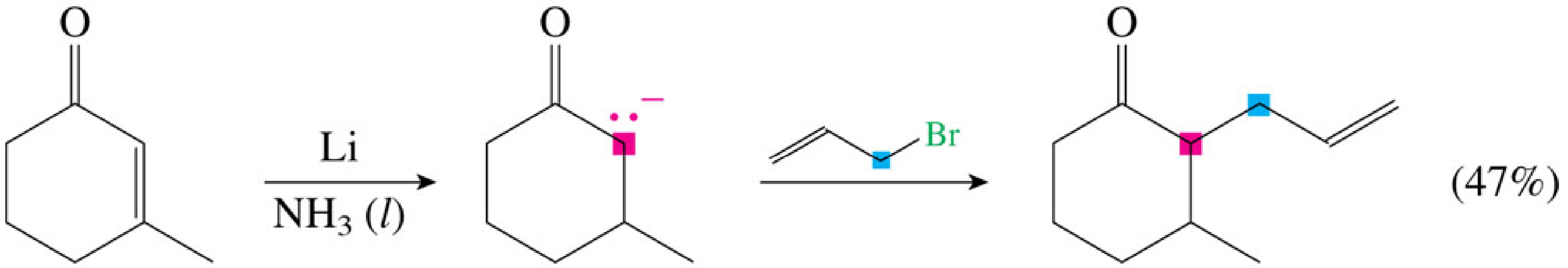
Application



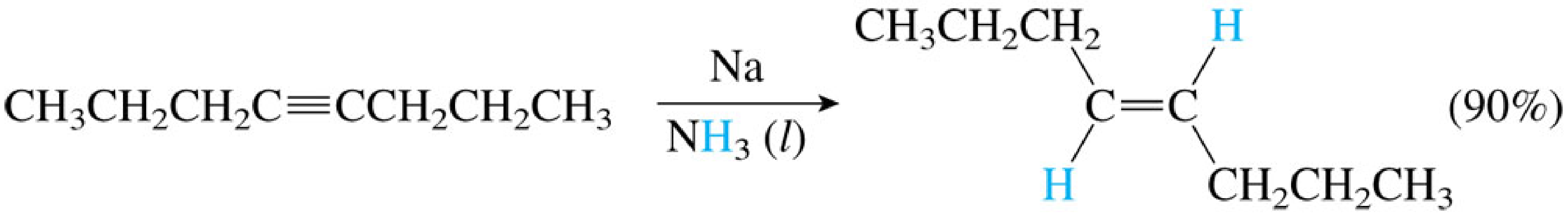
Advantage of using Li/NH2 system over LDA

LDA: lithium diiospropylamide, basic but not nucleophilic

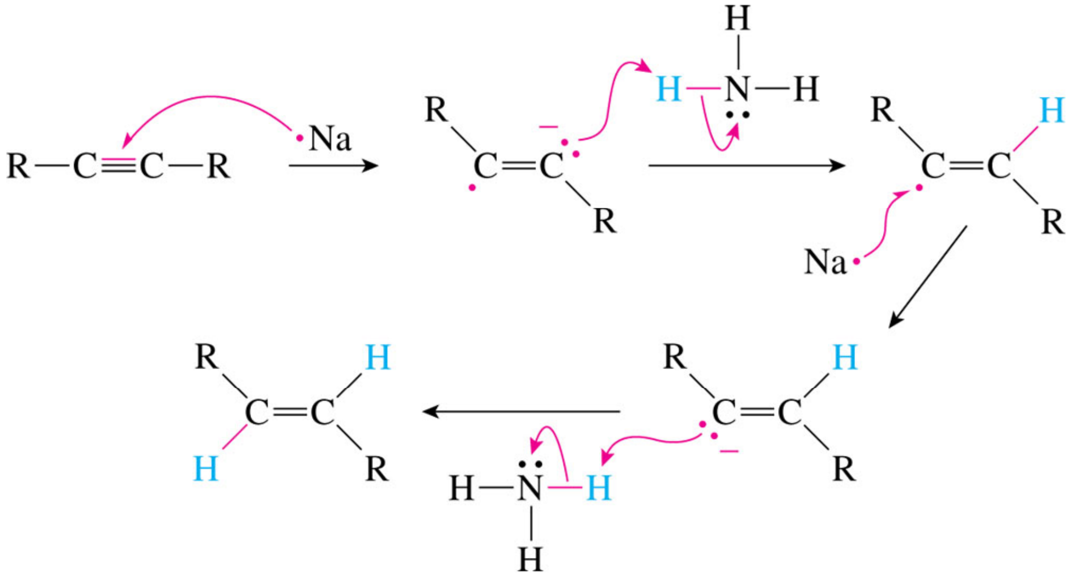




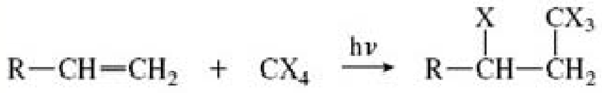
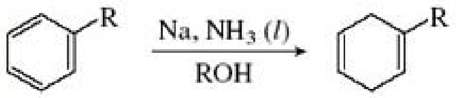
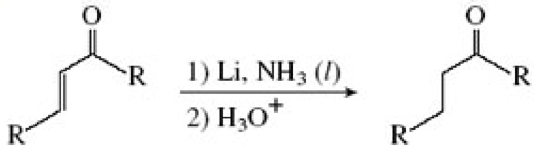
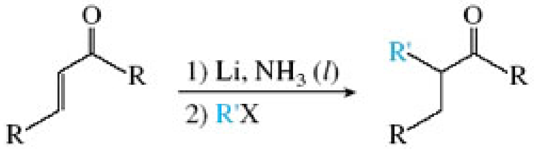
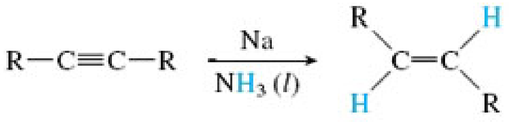
Reduction of carbon-carbon triple bond



Mechanism



This reaction is very useful because it produces the E-isomer of the alkene product. (Z-isomers are produced by catalytic hydrogenation of the alkyne. See Ch. 11.12)

Reaction	Comments
$R{-}H + Cl_2 \xrightarrow{h\nu} R{-}Cl$	**Section 21.6** Chain mechanism, not very selective, multiple chlorinations occur
$R{-}H + Br_2 \xrightarrow{h\nu} R{-}Br$	**Section 21.6** Chain mechanism, more selective, can use NBS + initiator
$R{-}X + Bu_3Sn{-}H \xrightarrow{[AIBN]} R{-}H$	**Section 21.7** Chain mechanism
$R{-}H + O_2 \xrightarrow{h\nu} R{-}OOH$	**Section 21.8** Autoxidation, chain mechanism, not very selective
 $R{-}CH{=}CH_2 + HBr \xrightarrow{[ROOR]} R{-}\overset{H}{CH}{-}\overset{Br}{CH_2}$	**Section 21.9** Anti-Markovnikov addition, chain mechanism, HCl and HI do not add
 $R{-}CH{=}CH_2 + R'SH \xrightarrow{h\nu} R{-}\overset{H}{CH}{-}\overset{SR'}{CH_2}$	**Section 21.9** Anti-Markovnikov addition, chain mechanism
 $R{-}CH{=}CH_2 + CX_4 \xrightarrow{h\nu} R{-}\overset{X}{CH}{-}\overset{CX_3}{CH_2}$	**Section 21.9** Chain mechanism
	**Section 21.10** Birch reduction, Li can also be used, radical anion mechanism
	**Section 21.10** Radical anion mechanism
	**Section 21.10** Alkylation of enolate anion
	**Section 21.10** *Trans*-alkene is formed