CHAPTER 5

Radicals and Radical Anions

I. INTRODUCTION

Radicals are species that contain one or more unpaired electrons. They are encountered in many reactions used in chemical industry (e.g., the production of polyethylene), in the processes responsible for the spoiling of foods (e.g., autoxidation by molecular oxygen), and in many biological systems (e.g., signaling by nitrogen oxide, NO). Radical anions, as their name implies, are radical species that have an unpaired electron and a negative charge.

In chemical structures, the unpaired electron of a radical is represented by a dot. Radical mechanisms are depicted in one of two ways. Most commonly, each individual step of the mechanism is written without the use of arrows to show electron movement. The resulting series of equations shows the order of events, and it is assumed that one-electron transfers are taking place throughout. A second method uses curved, half-headed arrows (⇀) to show electron movement. The half-headed arrow is used to denote movement of a single electron, whereas the normal arrowhead is used to denote movement of a pair of electrons.

Various studies indicate that although radicals tend to be pyramidal, the pyramids are shallow and the barriers to inversion are low. This means that the stereochemical results of radical reactions are very similar to those of carbocations, in other words, stereochemistry is usually lost at a reactive center.

Whereas most carbon free radicals are highly reactive species, there are notable exceptions.

2. FORMATION OF RADICALS

Many radicals are produced by homolytic cleavage of bonds. The energy for this kind of bond breaking comes from thermal or photochemical energy or from electron-transfer reactions effected by either inorganic compounds or electrochemistry. These kinds of processes initiate reactions that proceed by a radical mechanism. Compounds that readily produce radicals are called initiators or free radical initiators.

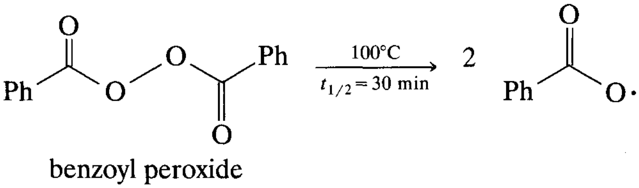
A. Homolytic Bond Cleavage

Radicals produced from chlorine and bromine can be generated photochemically and/or thermally. Because bromine atoms are less reactive than chlorine atoms, brominations are often done in the presence of both heat (Δ) and light ($h\nu$).

$$Cl_2 \xrightarrow{h\nu} 2Cl^\bullet$$

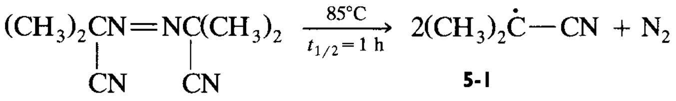
$$Br_2 \xrightarrow[\Delta]{h\nu} 2Br^\bullet$$

Many peroxides and azo compounds can be heated to generate radicals. Peroxides decompose readily because of the weak O—O bond, whereas azo compounds cleave readily because of the driving force provided by the formation of the stable nitrogen molecule. Common examples of these decompositions follow. (The $t_{1/2}$ is the time it takes one-half of the material to decompose.)



$$(CH_3)_3C-O-O-C(CH_3)_3 \xrightarrow[t_{1/2}=1\ h]{150°C} 2(CH_3)_3C-O\cdot$$

di-*t*-butyl peroxide

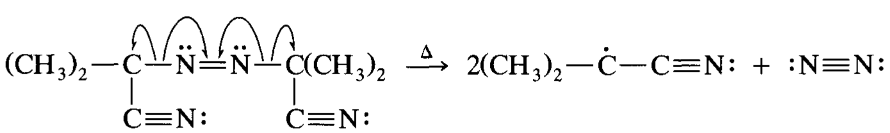


$$\underset{CN}{(CH_3)_2C}N=N\underset{CN}{C}(CH_3)_2 \xrightarrow[t_{1/2}=1\ h]{85°C} 2(CH_3)_2\dot{C}-CN + N_2$$

5-1

Example 5.1. ***Decomposition of AIBN [AIBN = azobisisobutyronitrile].***

Half-headed arrows show the movement of a single electron:



Why is the reaction shown in Example 5.1 a highly favorable process? **PROBLEM 5.1**

B. Hydrogen Abstraction from Organic Molecules

The carbon–hydrogen bond is relatively stable, so that direct formation of an organic radical by homolytic cleavage of a C—H bond is rarely observed. However, many radicals can remove hydrogen atoms from organic molecules to form carbon radicals. This process is known as hydrogen abstraction. For example,

$$F\cdot + CH_4 \longrightarrow HF + \cdot CH_3$$

Some radicals, like fluorine, are so reactive that they form radicals with almost any organic compound, whereas others are so stable that they can abstract hydrogen from very few organic compounds. An example of such a stable radical is **5-1**, formed from AIBN. When selectivity is desired in a radical initiator, a relatively stable radical like the one formed from AIBN is a good choice.

Rates of Hydrogen Abstraction and Relative Stability of Radicals

Because most radicals are electrophilic, the effects of structure on their rate of formation are very similar to those for the formation of carbocations. Thus, the rates of hydrogen abstraction are 1° < 2° < 3°, corresponding to the order of stability of the resulting radicals: 1° < 2° < 3°. Also, it is relatively easy to abstract a hydrogen from an allylic or benzylic position because the resulting radicals are stabilized by delocalization. In contrast, it is quite difficult to abstract vinyl and aromatic hydrogens because the electrophilicity of the resulting radicals is higher due to the higher *s* character of an sp^2-hybridized orbital relative to an sp^3-hybridized orbital. In these cases, the sp^2-hybridized orbital is perpendicular (orthogonal) to the π system; thus, the radical *cannot* be stabilized by resonance. Finally, it is difficult to abstract a hydrogen from the alcohol functional group. The resulting alkoxy radical is quite unstable due to the high electronegativity of oxygen.

The approximate relative stabilities of organic radicals are as follows:

$$\mathrm{Ph\cdot < CH_2{=}CH\cdot < RO\cdot < RCH_2\cdot < R_2CH\cdot}$$
$$\mathrm{< R_3C\cdot < PhCH_2\cdot < RCH{-}CH_2\cdot}$$

C. Organic Radicals Derived from Functional Groups

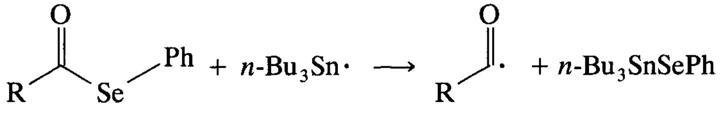
Reactive radicals are often produced by abstraction of a halogen atom from a substrate. A commonly used halogen-abstracting reagent is tri-*n*-butyltin radical, formed from tri-*n*-butyltin hydride using AIBN as an initiator. AIBN generates **5-1**, which abstracts a hydrogen atom from the tri-*n*-butyltin hydride, generating the tri-*n*-butyltin radical. This tin radical can abstract a halogen from a variety of substrates (e.g., alkyl, olefinic, or aryl chlorides, bromides, or iodides) to generate the corresponding radical and tri-*n*-butyltin halide.

$$\mathrm{(CH_3)_2\dot{C}{-}CN + (\mathit{n}\text{-}Bu)_3SnH \longrightarrow (CH_3)_2CH{-}CN + (\mathit{n}\text{-}Bu)_3Sn\cdot}$$

5-1

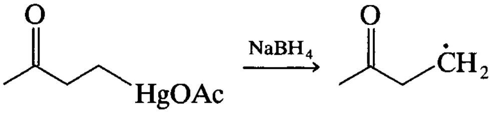
$$\mathrm{(\mathit{n}\text{-}Bu)_3Sn\cdot + RBr \longrightarrow (\mathit{n}\text{-}Bu)_3SnBr + R\cdot}$$

Tri-*n*-butyltin radicals can also be used to generate radicals from selenium compounds. An example is the formation of acyl radicals from seleno esters.



Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1988**, *53*, 3377–3379.

Radicals can also be synthesized by the reduction of alkylmercury salts. For example, in the presence of sodium borohydride, compound **5-2** reacts to form the radical, **5-3**.



5-2 **5-3**

Giese, B.; Horler, H.; Zwick, W. *Tetrahedron Lett.* **1982**, *23*, 931–934.

Despite their toxicity, alkylmercury salts have been used widely in research due to their versatility as synthetic intermediates.

3. RADICAL CHAIN PROCESSES

Most synthetically useful radical reactions occur as chain processes. A radical chain process is one in which many moles of product are formed for every mole of radicals produced. These chain processes include the following steps:

1. *Initiation.* One or more steps produce a radical from starting material.
2. *Propagation.* The radical enters a series of steps that results in the formation of product and a new radical that can start the series of propagation steps over again.
3. *Termination.* Removal of radicals from the propagation steps, thus ending a chain.

Initiation has been discussed in the previous section. In order for propagation to occur, many product molecules need to be formed from just one radical produced in the initiation step, and this occurs *only if the propagation steps are exothermic*. Termination steps include coupling, disproportionation, and abstraction. Abstraction by a chain-transfer agent removes a radical from a propagation step, and a new radical is generated in its place. If this newly generated radical is sufficiently stable, the chain transfer results in termination.

Hint 5.1

The propagation steps of a chain process must add up to the overall equation for the reaction. The overall equation will not contain any radicals. This means that the radical produced in the last propagation step must be the same as a reactant in the first propagation step.

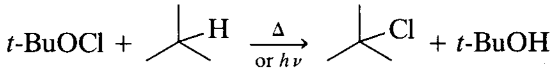
Hint 5.2 In radical reactions, the products are rarely generated by radical coupling.

Radical coupling reactions are those in which two radicals react to form a covalent bond. They are rarely a significant source of product, because both radicals are reactive intermediates and are present in extremely low concentrations. This means that the probability that they will react together is very small, and thus the rate of their reaction, which depends on their concentrations, is very low and other processes will compete effectively.

These various aspects of radical chain processes are illustrated in the following example.

Example 5.2. ***Radical chain halogenation by* t*-butyl hypochlorite.***

The overall process is



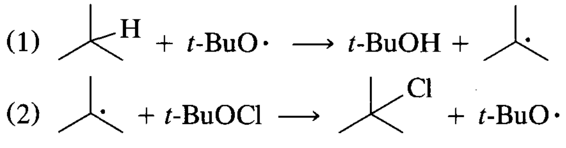
This can be broken down into initiation, propagation, and termination steps.

Initiation Step

$$t\text{-BuOCl} \xrightarrow[\text{or } h\nu]{\Delta} t\text{-BuO}\cdot + \cdot\text{Cl}$$

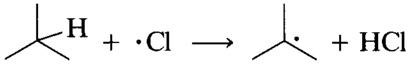
In continuing with the mechanism, consider *t*-BuO· to be the chain-carrying radical. This means that *t*-BuO· will be used up in the first propagation step but regenerated in the last propagation step. In this case, the last propagation step is the second step.

Propagation Steps



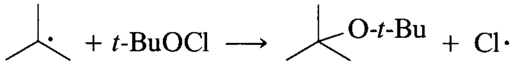
The radical formed in step 2 can start another reaction (step 1); that is why these processes are called chain processes. In this way, just one *t*-BuO· radical can initiate many sets of propagation steps. Addition of steps 1 and 2 gives the equation for the overall reaction; the radicals cancel when the addition is performed.

Is there another possible reaction pathway? Could the chlorine radical be the chain-carrying radical? If so, equation 3, an exothermic reaction, could represent one of the propagation steps.

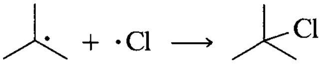
(3) 

Now a step must be found that forms the *t*-butyl chloride product *and* regenerates chlorine radical. This rules out equation 2 as a product-forming step because that reaction does not generate the same radical that is used in equation 3. Addition of equations 2 and 3 does not yield the overall reaction.

If we couple equation 3 with equation 4, we regenerate the chlorine radical but arrive at a different product for the reaction.

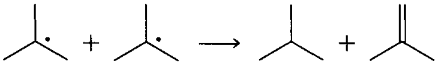
(4) 

Another possible product-forming step would be reaction of the *t*-butyl radical with a chlorine atom. However, because this reaction removes radicals without forming new ones, it could not be one of the propagation steps of a chain process.

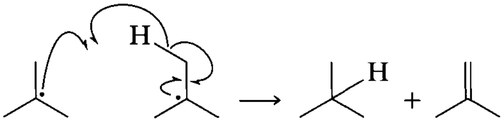


Termination Steps

(1) Disproportionation

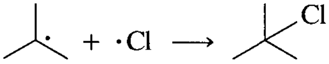


The disproportionation process involves the abstraction of hydrogen by one radical from another radical. Abstraction of a hydrogen atom from the carbon adjacent to the radical produces a double bond:

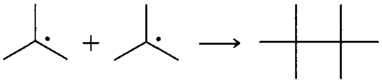


(2) Radical Coupling

Some possible coupling reactions follow:



t-BuO· + t-BuO· ⟶ t-BuOO-t-Bu



The following radical coupling does not affect the chain process because chlorine atoms are not involved in chain propagation.

$$\cdot\mathrm{Cl} + \cdot\mathrm{Cl} \longrightarrow \mathrm{Cl{-}Cl}$$

PROBLEM 5.2 **What other radical coupling reactions are possible for the reaction of t-butyl hypochlorite in Example 5.2?**

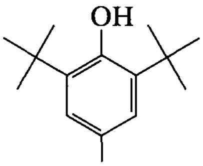
---

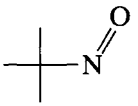
4. RADICAL INHIBITORS

Radical reactions can be slowed or stopped by the presence of substances called inhibitors.

Hint 5.3 A reaction that is slowed by the addition of a free radical inhibitor can be assumed to proceed by a radical mechanism.

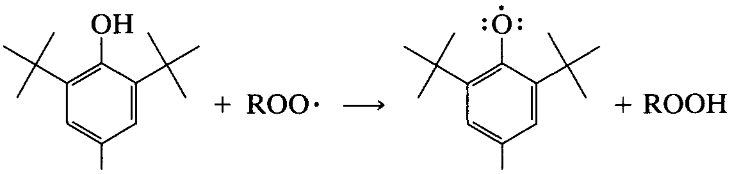
Common radical inhibitors include 2,6-di-*t*-butyl-4-methylphenol (BHT), 2-nitroso-2-propane, and oxygen.





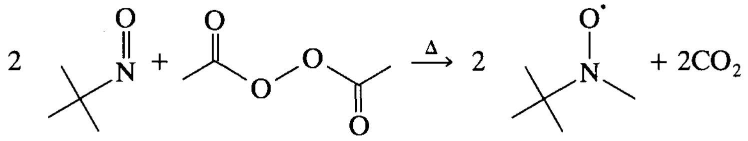
O_2

The acronym BHT stands for butylated hydroxytoluene, the common name for 2,6-di-*t*-butyl-4-methylphenol. It is used widely as an antioxidant in foodstuffs and food packaging. The reaction of oxygen with unsaturated fats gives, after several steps, alkylperoxy radicals (ROO·) that, upon further reaction, give smaller odiferous molecules that can ruin the palatability of foods. BHT acts as a scavenger for alkylperoxy radicals, ROO·, because hydrogen abstraction by ROO· gives the stable free radical, **5-4**. The hydroperoxide ROOH, which also is formed in the reaction, is much less reactive than ROO· and consequently causes much less oxidation. The new radical, **5-4**, which is formed from BHT, is relatively unreactive for two reasons: (i) it is stabilized by resonance, and (ii) the groups attached to the ring sterically hinder further reaction.



5-4

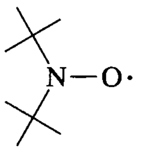
Radicals also can be trapped by addition to the nitroso group to form nitroxide radicals. In the following equation, diacetyl peroxide is a source of methyl radicals, which are trapped by the nitroso compound. (For further discussion of the fragmentation of radicals, see Section 7.)

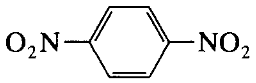


Oxygen can act as an inhibitor by reacting with radicals to produce less reactive hydroperoxyl radicals.

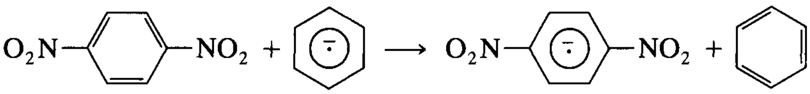
$$R\cdot + O_2 \longrightarrow ROO\cdot$$

Two compounds that effectively inhibit electron-transfer reactions are di-*t*-butyl nitroxide and 1,4-dinitrotoluene:





Transfer of an electron to 1,4-dinitrobenzene gives a radical anion so stable that it is unlikely to transfer an electron to anything else. The reaction of benzene radical anion with 1,4-dinitrobenzene proceeds to the right, because the radical anion of the 1,4-dinitrobenzene is much more stable than the radical anion of benzene itself.



Although 1,3-dinitrobenzene sometimes is used for the inhibition of electron-transfer reactions, it is not as effective as the 1,4-isomer, because its radical anion is not as stable (see Problem 1.5).

Nitroxides are also used to remove radical anions from a reaction sequence. For example, di-*t*-butyl nitroxide has often been used to inhibit the $S_{RN}1$ reaction (see Section 10). Apparently, nitroxides remove radicals via coupling reactions (Hoffmann, A. K.; Feldman, A. M.; Gelblum, E.; Hodgson, W. G. *J. Am. Chem. Soc.* **1964**, *86*, 639–646).

Hint 5.4 A radical reaction that is initiated only by light can be prevented by omitting light. In this case, any reaction that takes place in the dark must proceed by a nonradical pathway.

5. DETERMINING THE THERMODYNAMIC FEASIBILITY OF RADICAL REACTIONS

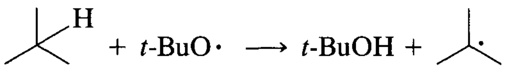
The bond dissociation energies in Table 5.1 can be used to determine the feasibility of radical reactions. In general, a radical process will give reasonable synthetic yields only if all propagation steps are exothermic, so that many propagation steps can occur before termination. The number of propagation steps per initiation step is the *chain length* of the reaction. Highly exothermic propagation steps involve highly reactive radicals, like alkyl radicals, and have a long chain length. More stable radicals, like aryl radicals, may fail to react until they encounter another radical. In this case, there is no chain reaction.

In Example 5.3, calculations show that the radical chlorination of 2-methylpropane by *t*-butyl hypochlorite is an energetically feasible process for the synthesis of *t*-butyl chloride.

Example 5.3. ***Determination of the enthalpy change in chlorination by* t*-butyl hypochlorite.***

Consider the reactions shown in Example 5.2. If both propagation steps are exothermic, the chain length will be long enough that the thermochemistry of the initiation step(s) is unimportant relative to that of the propagation steps.

We will calculate the enthalpy change for the reactions in the propagation steps. In equation 1, the C—H bond broken has a bond dissociation energy (BDE) of 91.0 kcal/mol, and the O—H bond formed has a BDE of 103 kcal/mol. Therefore, this first reaction is exothermic by 91 − 103 or −12 kcal/mol.

(1) 

$\Delta H = -12\ \text{kcal/mol}$

TABLE 5.1 Bond Dissociation Energies (BDEs, kcal/mol) at 298 K[a]

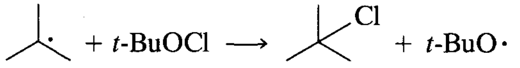
		Cl—Cl[b]	58	Br—Br[b]	46	I—I[b]	36	F—F[b]	37
		H—Cl[b]	103	H—Br[b]	87	H—I[b]	36	H—F[b]	135
CH_3—H	104	CH_3—Cl	73	CH_3—Br	70				
C_2H_5—H	98	C_2H_5—Cl	81	C_2H_5—Br	69	C_2H_5—I	53	C_2H_5—F	106
$CH_3CH_2CH_2$—H	98	*n*-C_3H_7—Cl	82	*n*-C_3H_7—Br	69				
$(CH_3)_2CH$—H	94.5	$(CH_3)_2CH$—Cl	81	$(CH_3)_2CH$—Br	68				
$(CH_3)_3C$—H	91.0	$(CH_3)_3C$—Cl	79	$(CH_3)_3C$—Br	63				
$PhCH_2$—H	85	$PhCH_2$—Cl	68	$PhCH_2$—Br	51				
$CH_2{=}CHCH_2$—H	85								
CCl_3—H	95.7	CCl_3—Cl	73	CCl_3—Br	54				
Ph—H	104			Ph—Br	71				
$CH_2{=}CH$—H	104								
$HOCH_2$—H	92								
CH_3O—H	102								
C_2H_5O—H	102								
i-C_3H_7O—H	103								
t-C_4H_9O—H	103	*t*-C_4H_9O—Cl	44[c]						
CH_3COO—H	112								
CH_3S—H	88								
PhS—H	75								
CH_3—CH_3	88								
PhCO—H	74	PhCO—Cl	74						
HCO—H	88								
CH_3CO—H	88								
CH_3COCH_2—H	92								

[a] All values from Kerr, J. A. *Chem. Rev.* **1966**, *66*, 465–500, unless otherwise noted.

[b] *Handbook of Chemistry and Physics*, 63rd ed.; Weast, R. C.; Astle, M. J., Eds.; CRC Press: Boca Raton, FL, 1982–1983; F186ff.

[c] Walling, C.; Jacknow, B. B. *J. Am. Chem. Soc.* **1960**, *82*, 6108–6112.

For equation 2, the O—Cl bond broken has a BDE of 44 kcal/mol and the C—Cl bond formed has a BDE of 79 kcal/mol. Thus, the second reaction is exothermic by 44 − 79 kcal/mol or −35 kcal/mol. Because both reactions are substantially exothermic.

(2) 

$\Delta H = -25$ kcal/mol

this should be a highly favorable process with a long chain length. The enthalpy change for the overall reaction is [(−12) + (−35)] or −47 kcal/mol.

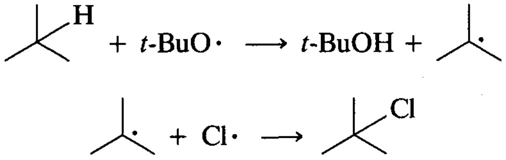
PROBLEM 5.3

What are the defects in the following mechanism for the chlorination of 2-methylpropane by t-butyl hypochlorite? You will need to consider the

PROBLEM 5.3
continued

thermochemistry of the processes, as well as the fact that a chain process is not involved.

$$t\text{-BuOCl} \xrightarrow{\Delta} t\text{-BuO}\cdot + \cdot\text{Cl}$$



---

6. ADDITION OF RADICALS

Radical addition reactions are commonly used in organic synthesis. These additions range from the simple addition of halocarbons to π bonds to cyclization reactions with demanding stereoelectronic requirements.

A. Intermolecular Radical Addition

Hint 5.5

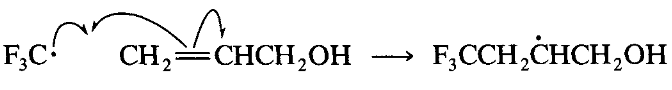
Common types of radicals that add to π bonds are those that can be generated from alkyl halides, mercaptans, thiophenols, thioacids, aldehydes, and ketones. Like the corresponding electrophilic additions to double bonds, many radical additions are either regiospecific or highly regioselective.

Example 5.4. ***Photochemical addition of trifluoroiodomethane to allyl alcohol.***

In the initation step of this reaction, light induces homolytic cleavage of the weak C—I bond.

$$\text{CF}_3\text{I} \xrightarrow{h\nu} \cdot\text{CF}_3 + \cdot\text{I}$$

The trifluoromethyl radical adds to the double bond, giving the most stable intermediate radical:



$$\text{F}_3\text{C}\cdot \quad \text{CH}_2{=}\text{CHCH}_2\text{OH} \longrightarrow \text{F}_3\text{CCH}_2\dot{\text{C}}\text{HCH}_2\text{OH}$$

This radical then abstracts an iodide atom from trifluoroiodomethane to generate product and the chain-propagating radical, the trifluoromethyl radical.

$$F_3CCH_2\dot{C}HCH_2OH + ICF_3 \longrightarrow F_3CCH_2CHICH_2OH + \cdot CF_3$$

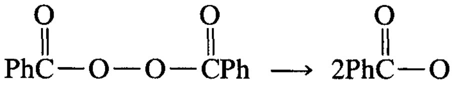
The product shown is the major regioisomer produced. For further details on this reaction, see Park, J. D.; Rogers, F. E.; Lacher, J. R. *J. Org. Chem.* **1961**, *26*, 2089–2095.

Examine the mechanistic steps for the reaction shown. **PROBLEM 5.4**

a. For each step, use half-headed arrows to show the movement of electrons, and dots to indicate all the unpaired electrons.

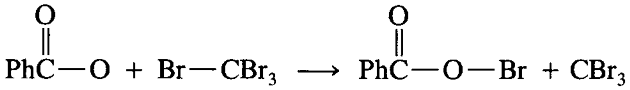
$$CH_2{=}CHC_6H_{13} + CBr_4 \xrightarrow[\Delta]{(PhCO_2)_2} Br_3CCH_2CHBrC_6H_{13}$$

Step 1



$$\text{Ph}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—O—O—}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{Ph} \longrightarrow 2\text{Ph}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—O}$$

Step 2



$$\text{Ph}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—O} + \text{Br—CBr}_3 \longrightarrow \text{Ph}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{—O—Br} + \text{CBr}_3$$

Step 3

$$CBr_3 + CH_2{=}CHC_6H_{13} \longrightarrow Br_3CCH_2CHC_6H_{13}$$

Step 4

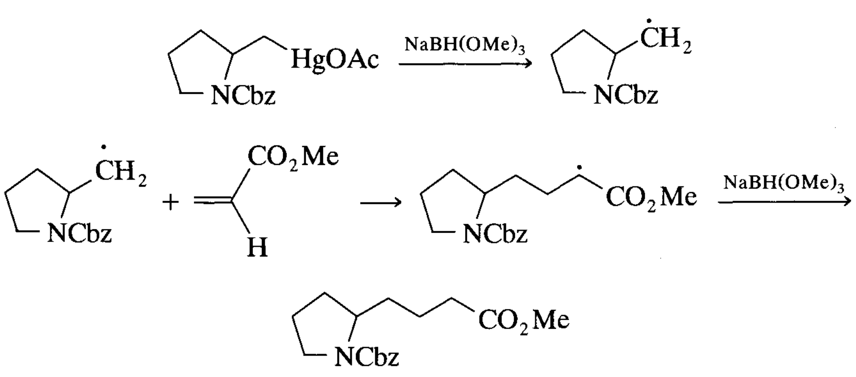
$$Br_3CCH_2CHC_6H_{13} + Br{-}CBr_3 \longrightarrow Br_3CCH_2CHBrC_6H_{13} + CBr_3$$

b. Identify the initation and propagation steps.

c. Why is the addition in step 3 regiospecific?

Example 5.5. ***Addition of a radical formed by reduction of a C—Hg bond.***

Addition of radicals formed from mercury compounds to alkenes often produce good-to-excellent yields. The following mechanism illustrates a reaction with a yield of 64%.



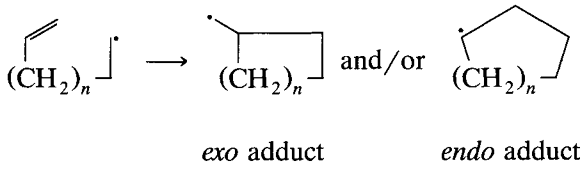
Note: Cbz = $-CO_2CH_2Ph$.

Danishefsky, S.; Taniyama, E.; Webb, R. R., II *Tetrahedron Lett.* **1983**, *24*, 11–14.

B. Intramolecular Radical Addition: Radical Cyclization Reactions

Generation of a radical in a molecule that contains a site of unsaturation presents an opportunity for cyclization. These types of radical cyclizations have been developed into very useful synthetic reactions. The synthetic utility of these cyclizations is enhanced by the ability to predict the regiochemistry of cyclization by applying the Baldwin rules. The Baldwin rules cover the formation of three- to seven-membered rings by various reactions and are based on consideration of both kinetic and thermodynamic factors. (See Beckwith, A. L. J.; Easton, D. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482–483, and Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.)

The Baldwin rules distinguish two types of ring closure, *exo* and *endo*.

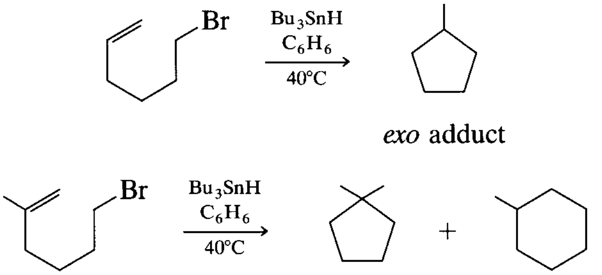


With regard to radical cyclization, the most important guidelines are as follows:

1. For unsubstituted ω-alkenyl radicals containing up to eight carbons, with the general structure previously shown, the preferred mode of cyclization is *exo*. (The symbol ω means that the alkene is at the terminus distant from the radical.) The reaction is controlled kinetically; the major product is the one that forms faster. The rates of formation of the two possible adducts are a result of the stereochemical requirements of their transition states. Often the *endo* product is more stable than the *exo* product. When this is the case, however, the more stable product is not the major product formed.

2. If the alkene is substituted at the nonterminal position, reaction to form the *exo* product is sterically hindered and the percentage of *endo* product increases. With substituted alkenes, the more stable product may predominate.

Example 5.6. ***exo and endo ring closure in radical cyclization.***



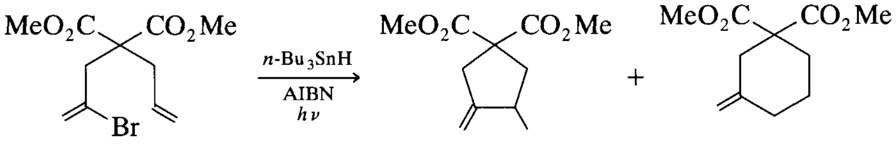
exo adduct

exo adduct *endo* adduct

Julia, M.; Descoins, C.; Baillarge, M.; Jacquet, B.; Uguen, D., Graeger, F. A. *Tetrahedron* **1975**, *31*, 1737–1745.

Example 5.7. ***Intramolecular cyclization of a vinyl radical.***

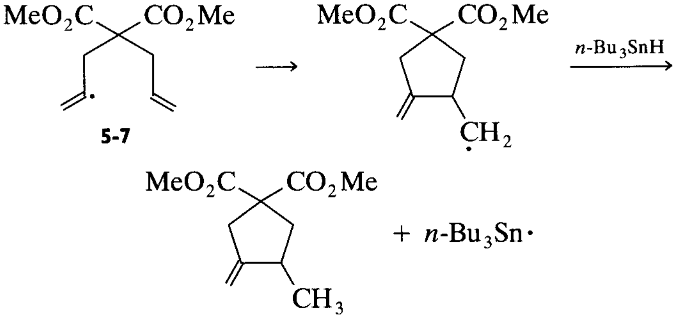
The overall reaction is as follows:



5-5 **5-6**

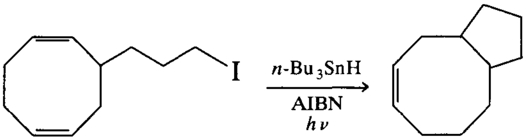
Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321–2323.

The vinyl radical, **5-7**, is formed by the process shown in Section 2. Cyclization of **5-7** can give an *exo* adduct or an *endo* adduct. The resulting radical abstracts hydrogen from n-Bu_3SnH to form products, **5-5** and **5-6**, as well as tri-n-butyltin radical, which continues the chain. As is predicted by the guidelines, the *exo* product (**5-5**) predominates, in this case by a factor of 2.



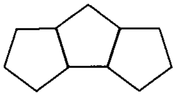
5-7

PROBLEM 5.5 Consider the following reaction:



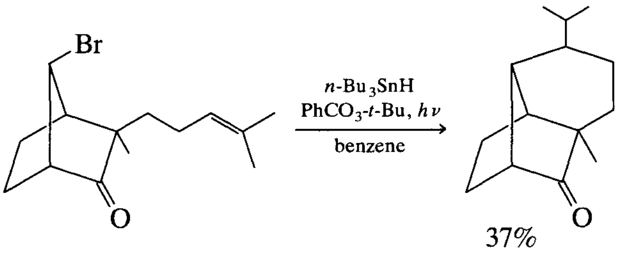
a. Write the initiation and propagation steps.

b. The following structure represents a minor product isolated from the reaction mixture. Show how it might have been formed.



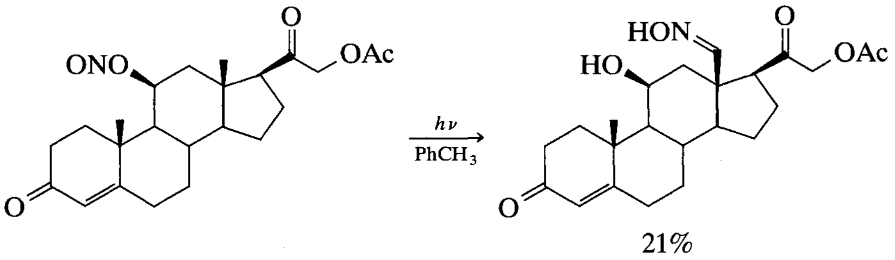
Winkler, J. D.; Sridar, V. *J. Am. Chem. Soc.* **1986**, *108*, 1708–1709.

PROBLEM 5.6 Write the initiation and propagation steps for the following reaction:



Hart, D. J. *Science* **1984**, *223*, 883–887.

PROBLEM 5.7 Propose a mechanism for the following transformation.



Barton, D. H. R.; Beaton, G. M.; Geller, L. E.; Bechet, M. M. *J. Am. Chem. Soc.* **1960**, *82*, 2640.

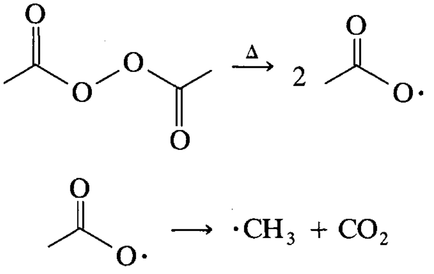
7. FRAGMENTATION REACTIONS

Hint 5.6

Many radical processes involve the loss of small, stable molecules, such as carbon dioxide, nitrogen, or carbon monoxide. These kinds of reactions are called fragmentations.

A. Loss of CO_2

The radical initiator, diacetyl peroxide, homolyzes at the O—O bond to form carboxy radicals, which then readily lose CO_2 to give methyl radicals. In fact, between 60°C and 100°C, acetyl peroxide can be a convenient source of methyl radicals.



(See Walling, C. *Free Radicals in Solution*; John Wiley: New York, 1957; p. 493.) Aryl-substituted carboxy radicals also lose CO_2, but they do so much less readily (e.g., the initial radical formed from benzoyl peroxide, Section 2).

Fragmentation with loss of CO_2 also occurs in the Hunsdiecker reaction, in which a silver salt of a carboxylic acid reacts with bromine to produce an alkyl halide. The reaction results in shortening of the carbon chain by one carbon. The overall reaction is as follows:

$$RCO_2Ag + Br_2 \xrightarrow{\Delta} RX + CO_2 + AgBr$$

The mechanism is

$$RCO_2Ag + Br_2 \longrightarrow RCO_2Br + AgBr$$

Initiation:

$$RCO_2Br \longrightarrow RCO_2\cdot + Br\cdot$$

Propagation 1:

$$RCO_2\cdot \longrightarrow R\cdot + CO_2$$

Propagation 2:

$$R\cdot + RCO_2Br \longrightarrow RBr + RCO_2\cdot$$

B. Loss of a Ketone

The radical initially produced by homolytic decomposition of a dialkyl peroxide can undergo further scission. The rate of scission depends on the temperature and the stability of the resulting radical(s). For example, *t*-butoxy radicals decompose on heating to methyl radicals and acetone.

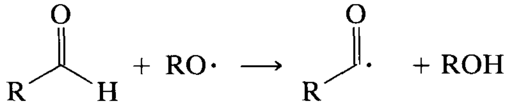
$$t\text{-BuO}\cdot \longrightarrow \cdot CH_3 + CH_3COCH_3$$

C. Loss of N_2

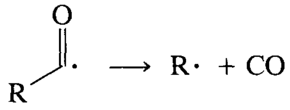
Azo compounds often decompose with loss of nitrogen. The decomposition of the initiator, AIBN, is an example (see Section 2).

D. Loss of CO

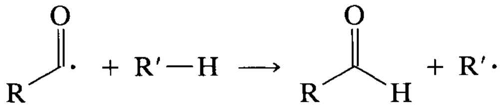
At elevated temperatures, the radical, **5-8**, generated by hydrogen abstraction from the aldehyde functional group fragments to give a new carbon radical and carbon monoxide. The fragmentation is temperature-dependent; the higher the temperature, the more favorable the loss of CO from the initial radical.



5-8

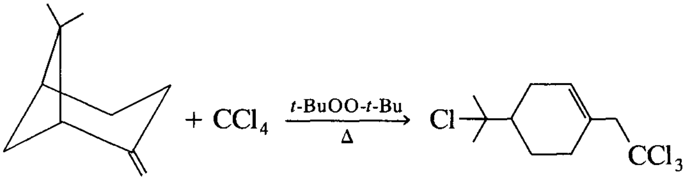


In the presence of a suitable compound, hydrogen abstraction may compete with loss of CO, as in the following example.



Example 5.8. ***Addition followed by fragmentation.***

The radical reaction of carbon tetrachloride with aliphatic double bonds involves addition of the trichloromethyl radical to the double bond, followed by chlorine atom abstraction from carbon tetrachloride by the intermediate radical to give the product. After the addition of the trichloromethyl radical to β-pinene, a fragmentation occurs prior to formation of the product.

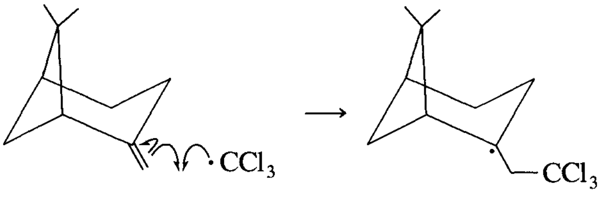


The mechanism for this reaction starts with the generation of the trichloromethyl radical:

$$t\text{-BuOO-}t\text{-Bu} \xrightarrow{\Delta} 2t\text{-BuO}\cdot$$

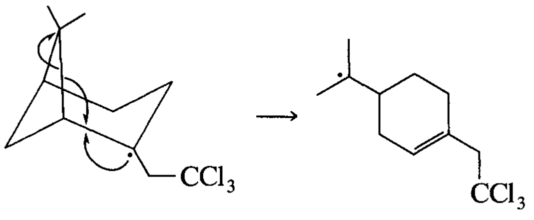
$$t\text{-BuO}\cdot \quad \text{Cl—CCl}_3 \longrightarrow t\text{-BuOCl} + \cdot\text{CCl}_3$$

The trichloromethyl radical now adds regiospecifically to the double bond to form a new carbon radical, **5-9**:

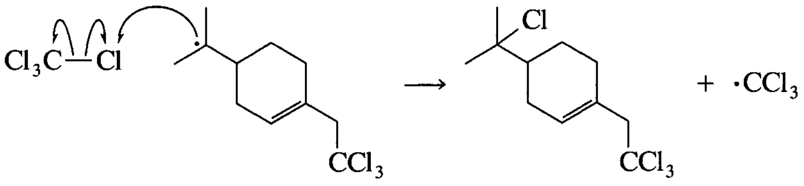


5-9

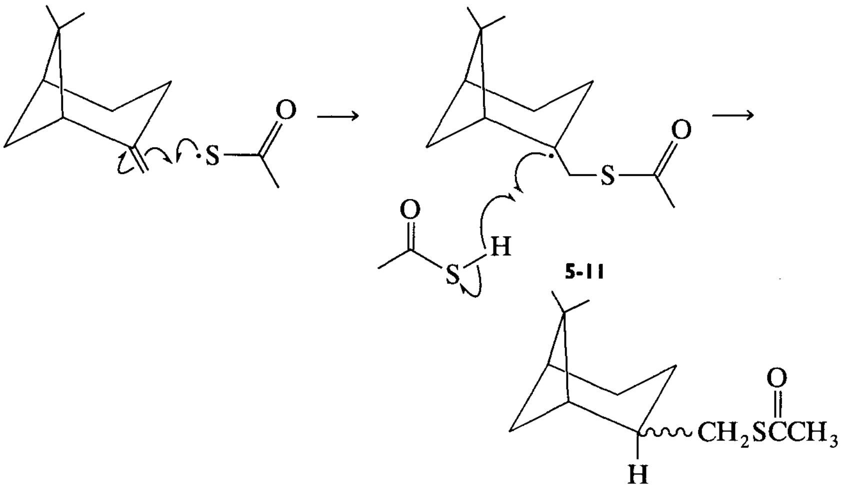
This radical can now fragment to give another radical, **5-10**, which then abstracts a chlorine atom from another molecule of CCl_4 to give the product:



5-10



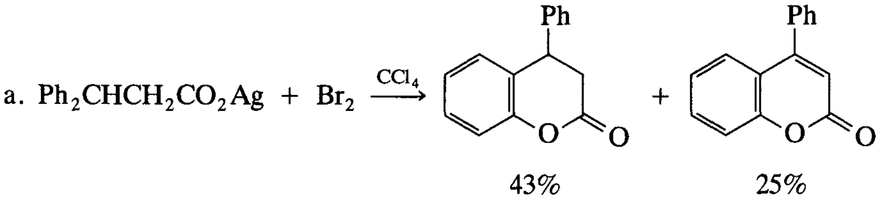
The radical addition of thiolacetic acid to β-pinene gives unrearranged product. This result is evidence for the discrete existence of radical **5-9**. That is, the rate of abstraction of a hydrogen atom from thiolacetic acid by **5-11** is faster than its rate of fragmentation. Note that the product is a mixture of stereoisomers, as indicated by the wavy bond lines.



5-11

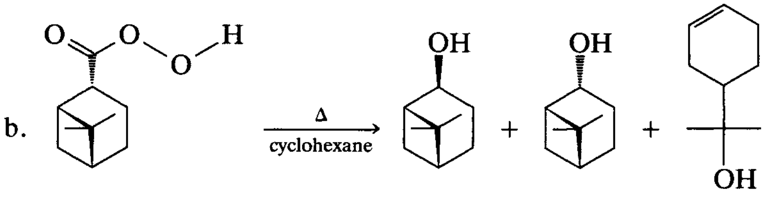
(See Claisse, J. A.; Davies, D. I.; Parfitt, L. T. *J. Chem. Soc. C* **1970**, 258–262.)

Write step-by-step mechanisms for the following reactions. **PROBLEM 5.8**



5-12 **5-13**

Pandet, U. K.; Dirk, I. P. *Tetrahedron Lett.* **1963**, 891–895.



5-14 **5-15** **5-16** **5-17**

In writing your mechanism, take into account the following experimental observations: (i) the other isomer (with the peracid group up) of the starting material reacts to give roughly the same ratio of **5-15** and **5-16**, and (ii) the ratio of bicyclic to ring-opened products increases with increasing peracid concentration.

Fossey, J.; Lefort, D.; Sorba, J. *J. Org. Chem.* **1986**, *51*, 3584–3587.

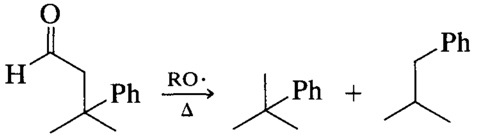
8. REARRANGEMENT OF RADICALS

Rearrangements of radicals are much less common than rearrangements of carbocations.

In radical rearrangements, the migrating groups are those that can accommodate electrons in a π system (vinyl, aryl, carbonyl) or atoms that can expand their valence shell, i.e., all halogens but fluorine. *Hydrogen and alkyl do not migrate* to **_Hint 5.7_** radicals. However, an addition – elimination pathway could give the appearance of alkyl migration (see Example 5.11). For a discussion of the reasons why alkyl and hydrogen do not migrate, see Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York, 1990; p. 704.

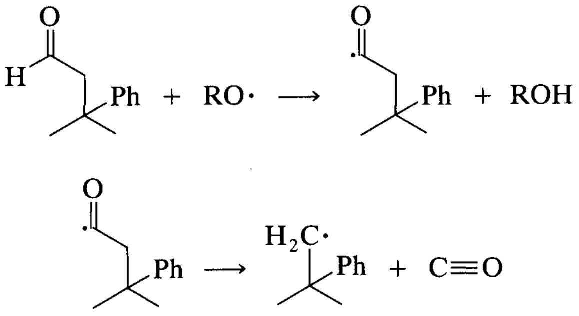
Example 5.9. ***Aryl migration.***

In the following reaction, **5-19** is a product resulting from migration of an aryl group, and **5-18** is a nonrearranged product. Thus, there is competition between rearrangement and hydrogen abstraction by a radical intermediate.



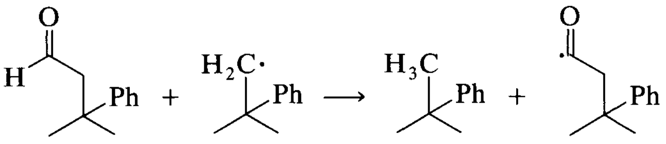
5-18 **5-19**

The mechanism for formation of **5-18** and **5-19** involves formation of a hydrocarbon radical from the starting aldehyde. The radical from the initiator abstracts the aldehyde proton to give a carbonyl radical. This loses carbon monoxide to give **5-20**.

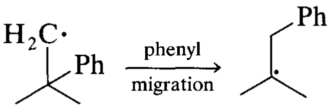


5-20

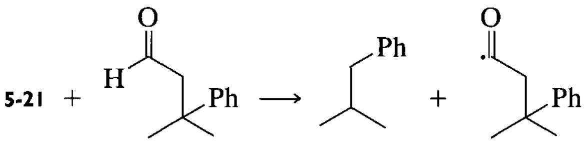
Radical **5-20** can either abstract a hydrogen atom from the starting aldehyde to give nonrearranged product, **5-18**, or rearrange via phenyl migration to **5-21**, which then abstracts a hydrogen atom to give **5-19**.



5-20 **5-18**



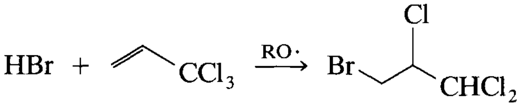
5-20 **5-21**



5-19

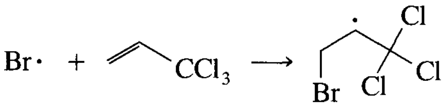
Example 5.10. *Halogen migration.*

The radical addition of HBr to 3,3,3-trichloropropene, involves migration of a chlorine atom in an intermediate step.

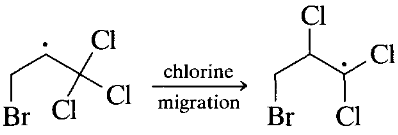


The mechanism for the reaction involves a regiospecific addition of bromine radical to the double bond.

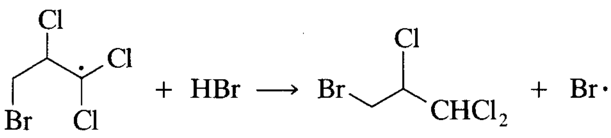
$$RO\cdot + HBr \longrightarrow ROH + Br\cdot$$



A chlorine atom then migrates to the adjacent radical, giving **5-22**. Finally, **5-22** abstracts a hydrogen from HBr to form the product plus another bromine radical to continue the chain.



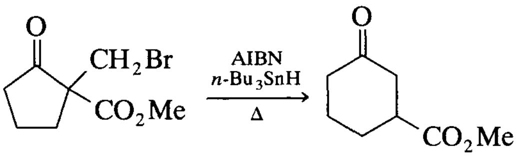
5-22



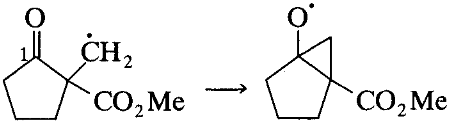
5-22

Example 5.11. ***An apparent acyl migration mediated by radical addition to a carbonyl group.***

The overall reaction is as follows:

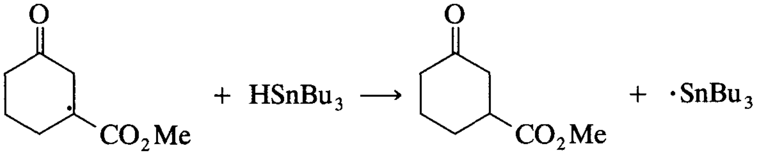


In this reaction, the tri-*n*-butyltin radical, formed by the usual initiation steps, removes the bromine atom from the starting material to give **5-23**. This radical then adds to the carbonyl carbon, forming a three-membered ring that then opens at a different bond to give **5-24**. On the basis of Hint 5.7, we would not expect direct formation of **5-24** by migration of carbon C-1 in **5-23** to the radical center.



5-23

Radical **5-24** can abstract a hydrogen atom from tri-*n*-butyltin hydride to give the product and a new radical to propagate the chain:

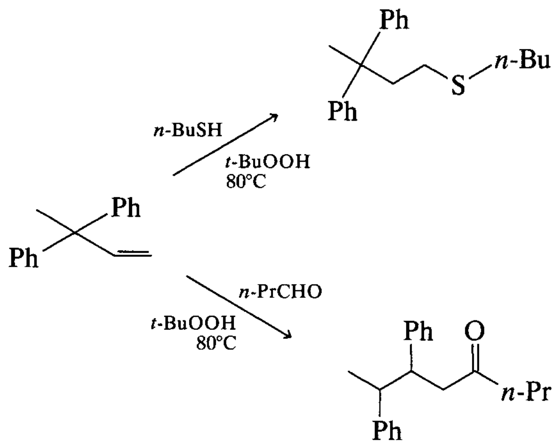


5-24

Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 3493–3494.

PROBLEM 5.9 **Compare the two reactions shown and explain why one process gives rearrangement and the other does not. Write step-by-step mechanisms for both processes.**

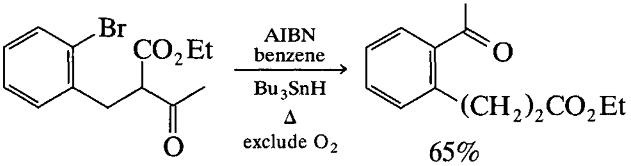
PROBLEM 5.9
continued



Weinstock, J.; Lewis, S. N. *J. Am. Chem. Soc.* **1957**, *79*, 6243-6247.

PROBLEM 5.10

Write a complete mechanism for the following process.



Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565-2575.

9. THE $S_{RN}1$ REACTION

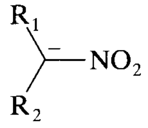
The $S_{RN}1$ reaction, a versatile synthetic tool, is initiated by generation of a radical anion. The designation $S_{RN}1$ indicates that the reaction is a nucleophilic substitution proceeding through a radical intermediate and that the rate-limiting step is unimolecular decay of the radical anion intermediate formed from the substrate (see a review by Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413-420). $S_{RN}1$ reactions occur with both aliphatic and aromatic compounds.

For the general case, the propagation steps for the $S_{RN}1$ reaction can be represented as follows:

$$[RX]^{\cdot-} \longrightarrow R\cdot + X^-$$
$$R\cdot + Y^- \longrightarrow [RY]^{\cdot-}$$
$$[RY]^{\cdot-} + RX \longrightarrow RY + [RX]^{\cdot-}$$

Note that the radical anion consumed in the first propagation step is regenerated in the third propagation step.

$S_{RN}1$ reactions can be initiated by photochemical excitation, electrochemical reduction, and solvated electrons (alkali metal in ammonia). In some cases, spontaneous thermal initiation can also take place. The leaving group, X^-, is often a halide—frequently bromide or iodide, never fluoride. The nucleophile, Y^-, is commonly a nitroalkane anion (**5-25**) or another anion such as thiolate (RS^-), phenolate (PhO^-), or various enolates.



5-25

Because these are free radical reactions, they are inhibited by the addition of free radical inhibitors such as di-*t*-butyl nitroxide and 1,4-dinitrobenzene.

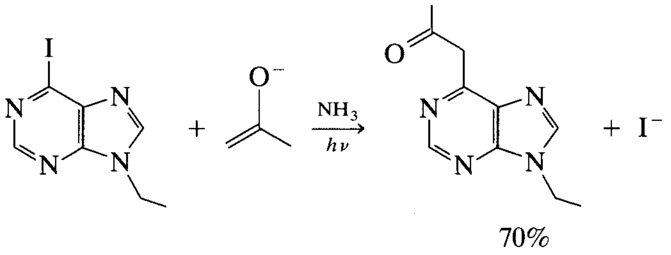
Addition of the propagation steps of the general mechanism for an $S_{RN}1$ reaction gives the following equation for the overall reaction:

$$RX + Y^- \longrightarrow RY + X^-$$

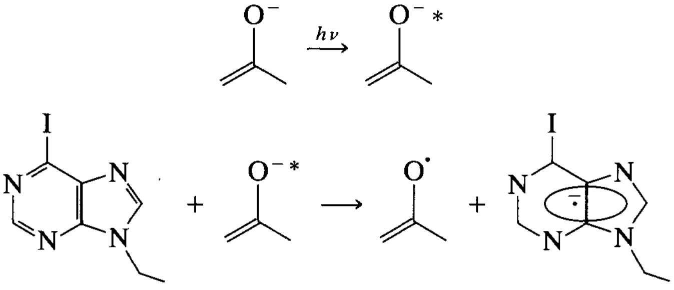
This equation also describes the overall reaction of either an S_N2 or a nucleophilic aromatic substitution process. In some cases, the only way to distinguish an $S_{RN}1$ reaction from these processes is that an $S_{RN}1$ is inhibited by radical inhibitors. Another distinguishing feature is that the order of the relative leaving group abilities of halides are opposite that found for nucleophilic aromatic substitution by the addition–elimination mechanism (see Chapter 3).

Example 5.12. ***Reaction of an enolate with an aromatic iodide.***

The overall reaction is as follows:

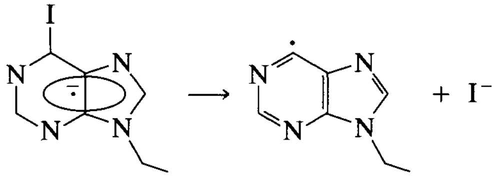


The mechanism involves photochemical excitation of the enolate. (An excited state is indicated by an asterisk, *.) The excited enolate transfers an electron to the aromatic π system. Because a single electron has been added, there must be an unpaired electron present; thus, the new intermediate, **5-26**, is a radical. Because an electron has been added to a neutral system, there must be a negative charge. Thus, **5-26** is both an anion and a radical or what is usually called a radical anion or an anion radical.

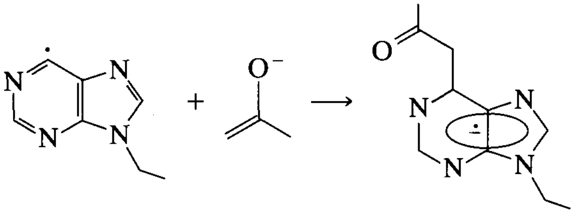


5-26

The radical anion now loses iodide ion to give a radical.

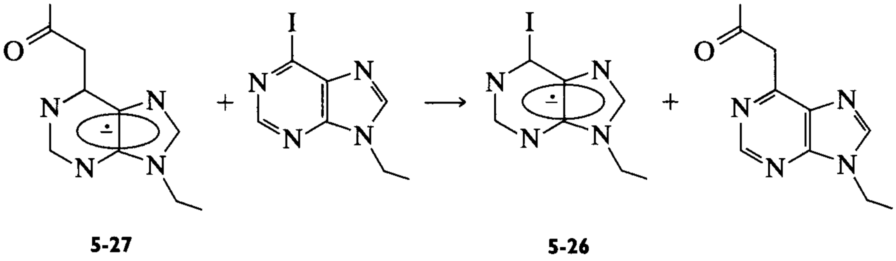


This radical couples with the enolate to give a new radical anion, **5-27**.



5-27

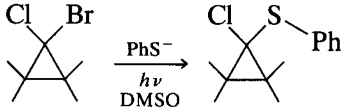
Intermediate **5-27** transfers an electron to starting material to give a molecule of product and a new molecule of **5-26** to propagate the chain.



Nair, V.; Chamberlain, S. D. *J. Am. Chem. Soc.* **1985**, *107*, 2183–2185.

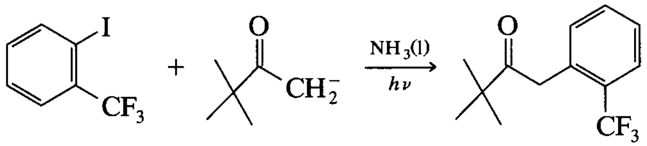
PROBLEM 5.11 **Write step-by-step mechanisms for the following reactions:**

a.



Meijs, G. F. *J. Org. Chem.* **1986**, *51*, 606–611.

b.

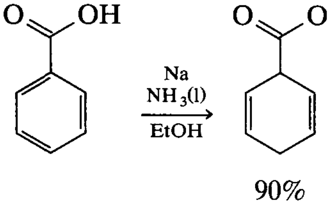


Bunnett, J. F.; Galli, C. *J. Chem. Soc., Perkin Trans. I* **1985**, 2515–2519.

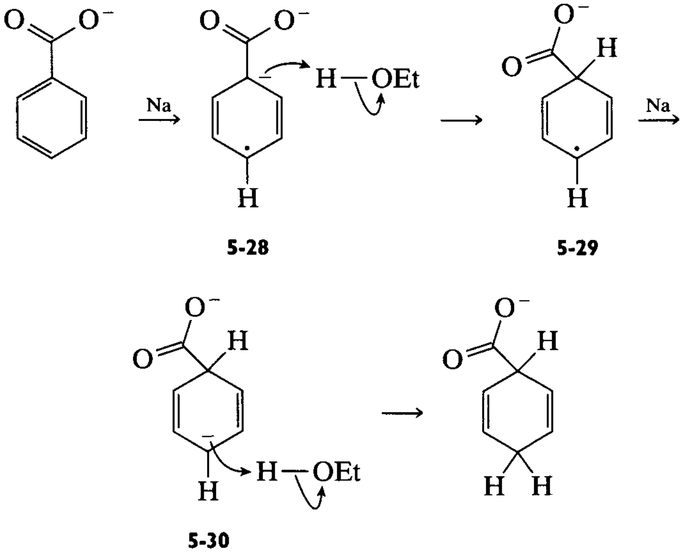
10. THE BIRCH REDUCTION

The typical conditions for the Birch reduction are sodium in liquid ammonia that contains a small amount of ethanol. Workup generally is in acid.

Example 5.13. ***Birch reduction of benzoic acid.***



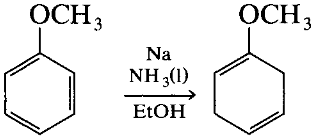
Under the basic reaction conditions, the carboxylate ion is formed from benzoic acid. Sodium then transfers a single electron to the aromatic system to produce a pentadienyl radical anion, **5-28**. Protonation of **5-28** gives the radical, **5-29**, which will be reduced to the corresponding anion, **5-30**, by another sodium atom. Finally, **5-30** is protonated, giving the product.



Molecular orbital (MO) calculations indicate that the intermediate radical anions have more anionic character at the positions *ortho* or *meta* to a π-donating substituent and *para* or *ipso* (*ipso* means at the substituent-containing carbon) to a π-accepting substituent. (See Birch, A. J.; Hinde, A. L.; Radom, L. *J. Am. Chem. Soc.* **1980**, *102*, 3370–3376). The pentadienyl anions formed after transfer of the second electron have more anionic character on the central carbon, and that is where the second protonation occurs.

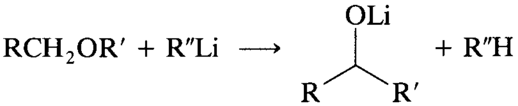
The result of the various factors is that in the product 1,4-cyclohexadienes, π-withdrawing groups (e.g., $-CO_2H$) are found on the saturated carbons, whereas π-donating groups (e.g., $-OCH_3$) are found on the unsaturated carbons.

PROBLEM 5.12 **Write a mechanism for the following reaction that is consistent with the regiochemistry observed.**



11. A RADICAL MECHANISM FOR THE REARRANGEMENT OF SOME ANIONS

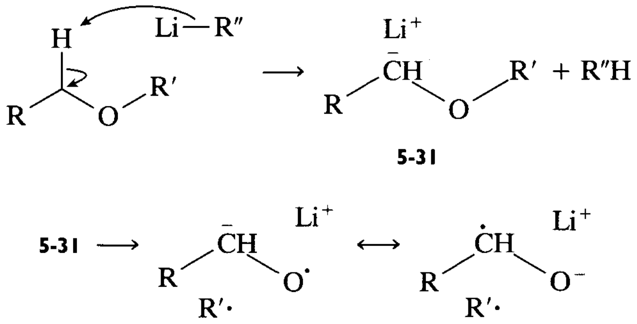
In the Wittig rearrangement, an anion derived from an ether rearranges to the salt of an alcohol.



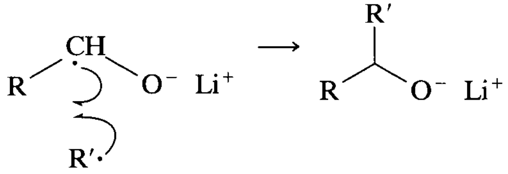
$$RCH_2OR' + R''Li \longrightarrow R(R')CH{-}OLi + R''H$$

In some cases, the mechanism for the formation of at least some of the product(s) of reaction appears to be radical scission of the anion produced initially.

The radicals can now recombine to form the product:



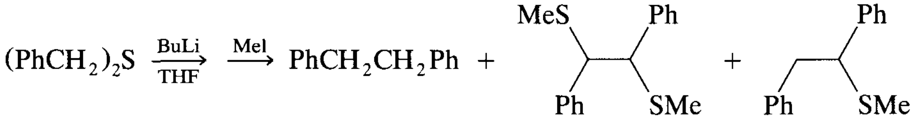
There is evidence to suggest that some of these reactions go by an ionic



There is evidence to suggest that some of these reactions go by an ionic mechanism. The purpose in introducing a radical mechanism here is to indicate that when there are several possible mechanisms for a reaction, some may be radical in character.

PROBLEM 5.13

Write reasonable mechanisms for the formation of each of the products in the following reaction.

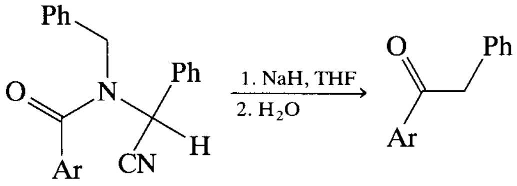


Biellmann, J. F.; Schmitt, J. L. *Tetrahedron Lett.* **1973**, 4615–4618.

Other reactions that may involve radical scission of anion intermediates include the rearrangement of anions adjacent to either trivalent or tetravalent nitrogen.

Example 5.14. ***Unusual rearrangement of an anion α to a nitrogen.***

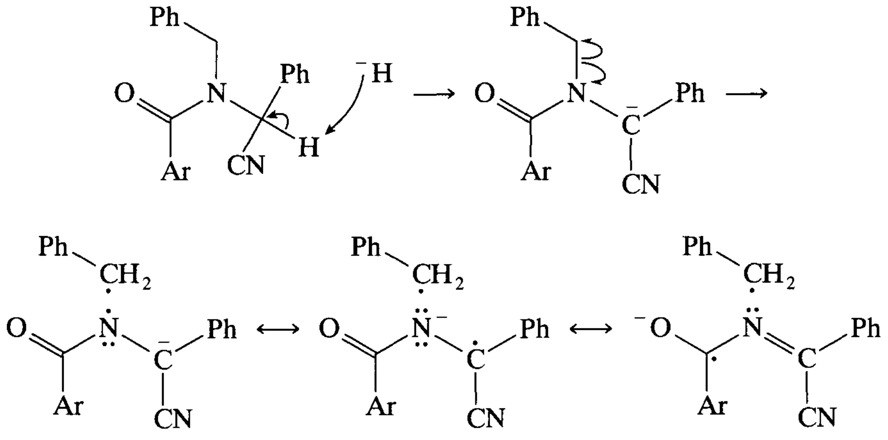
In this example, an anion formed initially undergoes radical scission, recombination, and then anionic rearrangement to the final product.



When Ar = *p*-tolyl, the yield is 57%.

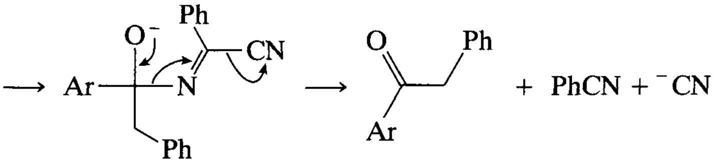
Stamegna, A. P.; McEwen, W. E. *J. Org. Chem.* **1981**, *46*, 1653–1655.

In the paper cited, the following mechanism was proposed. The hydride removes the proton on the carbon α to the nitrile, leaving a carbanion. Then a benzyl radical cleaves, leaving a resonance-stabilized radical anion, **5-32**.

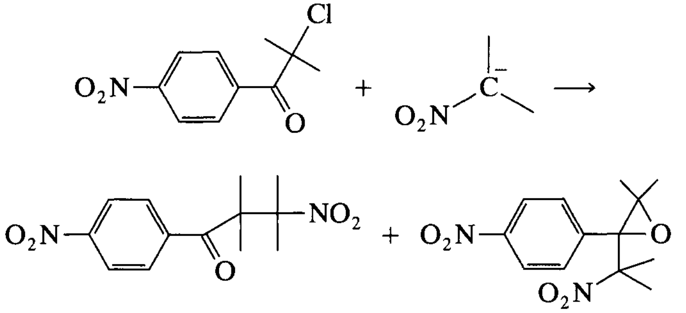


5-32-1 **5-32-2** **5-32-3**

The benzyl radical then recombines at the carbon of the carbonyl group in **5-32**, and subsequent elimination of benzonitrile and cyanide ion gives the product.



PROBLEM 5.14 Consider the following data and then write reasonable mechanisms for the formation of 5-33 and 5-34.



5-33 **5-34**

(a) 10 mol% di-*t*-butyl nitroxide completely suppressed formation of **5-33**.

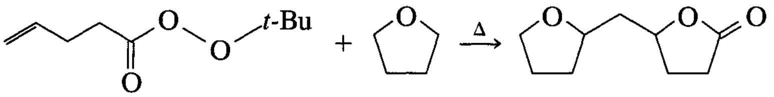
PROBLEM 5.14 *continued*

(b) The yield of **5-34** was higher in the dark or in the presence of nitroxide.
(c) The yield of **5-33** was lower in the dark than with sunlamp irradiation.

Russell, G. A.; Ros, F. *J. Am. Chem. Soc.* **1985**, *107*, 2506–2511.

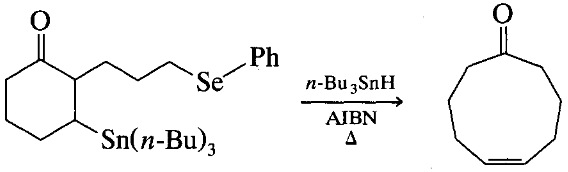
Write step-by-step mechanisms for the following reactions. **PROBLEM 5.15**

a.



Kharrat, A.; Gardrat, C.; Maillard, B. *Can. J. Chem.* **1984**, *62*, 2385–2390.

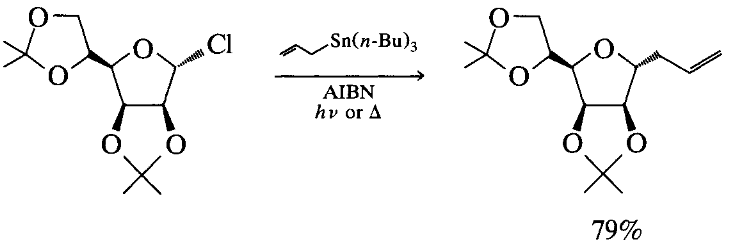
b.



Only 10 mol% tin hydride is used.

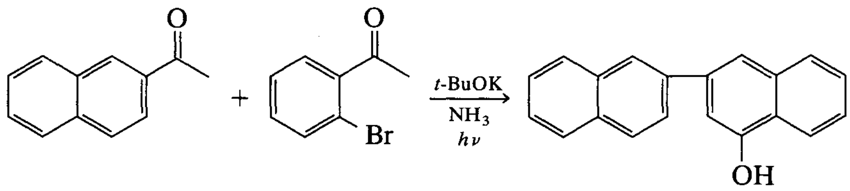
Baldwin, J. E.; Adlington, R. M.; Robertson, J. *J. Chem. Soc., Chem. Commun.* **1988**, 1404–1406.

c.



Hart, D. J. *Science* **1984**, *223*, 883–887.

d.

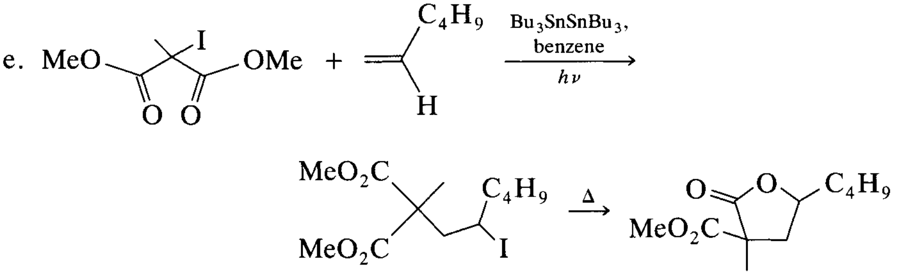


5-35

The yield of **5-35**, when the reaction mixture is irradiated, is 72%; in the dark, none of this product is formed.

Beugelmans, R.; Bois-Choussy, M.; Tang, Q. *J. Org. Chem.* **1987**, *52*, 3880–3883.

PROBLEM 5.15
continued



5-36 **5-37**

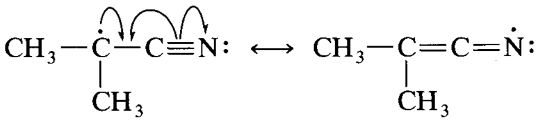
Hexabutylditin was present in 10 mol%. The yield of **5-37** from 1-hexene and iodomalonate was 69%.

Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872–8878.

ANSWERS TO PROBLEMS

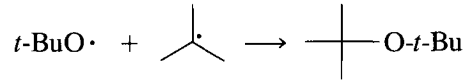
Problem 5.1

The radical formed is stabilized by resonance and by two alkyl groups. In addition, the small, stable molecule N_2 is formed in the process (see Hints 2.13 and 2.14).



$$\mathrm{CH_3{-}\underset{CH_3}{\overset{\cdot}{C}}{-}C{\equiv}N{:}} \longleftrightarrow \mathrm{CH_3{-}\underset{CH_3}{C}{=}C{=}\dot{N}{:}}$$

Problem 5.2



t-BuO· + Cl· ⟶ t-BuOCl

The last coupling is the reverse of an initiation process. It removes t-butoxy radical from the chain propagation steps and, thus, is a termination process.

Problem 5.3

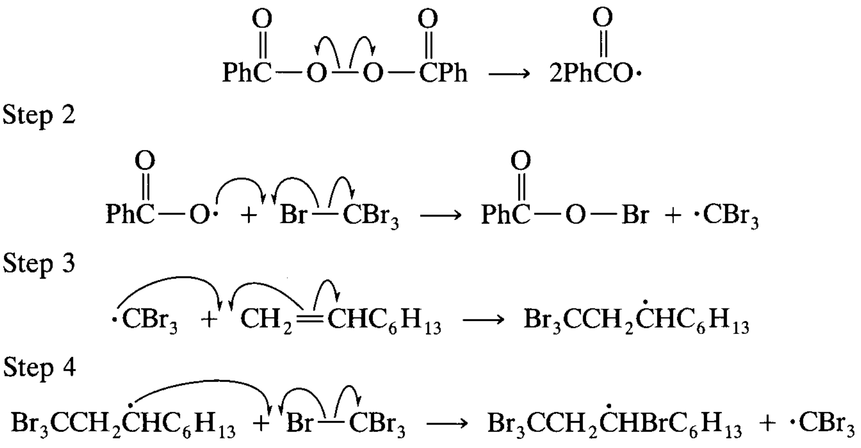
The three equations shown add up to the same overall reaction as equations 1 and 2 in Example 5.3. Thus, the total enthalpy change, −47 kcal/mol is the same as the total enthalpy change calculated in Example 5.3. Why then do these equations not represent a mechanism for

Problem 5.3
continued

the reaction? There are two reasons. First, the equations in the problem do not represent a chain process, so the thermochemistry of each step, *including the first one*, must be considered. Because this first reaction is highly endothermic, the overall process would be very slow. Second, the third step involves the coupling of two radicals. Whereas the enthalpy for this reaction is very favorable, both radicals will be present in very low concentrations. Thus, the probability that they will collide and react is very low. In contrast, both propagation steps in Example 5.3 have a radical colliding with a stable molecule whose concentration is much higher than that of any radical intermediate.

Problem 5.4

a. Step 1



$$Ph\overset{O}{\overset{\|}{C}}-O-O-\overset{O}{\overset{\|}{C}}Ph \longrightarrow 2Ph\overset{O}{\overset{\|}{C}}O\cdot$$

Step 2

$$Ph\overset{O}{\overset{\|}{C}}-O\cdot + Br-CBr_3 \longrightarrow Ph\overset{O}{\overset{\|}{C}}-O-Br + \cdot CBr_3$$

Step 3

$$\cdot CBr_3 + CH_2{=}CHC_6H_{13} \longrightarrow Br_3CCH_2\dot{C}HC_6H_{13}$$

Step 4

$$Br_3CCH_2\dot{C}HC_6H_{13} + Br-CBr_3 \longrightarrow Br_3CCH_2\dot{C}HBrC_6H_{13} + \cdot CBr_3$$

5-38

b. The initiation steps are steps 1 and 2. The propagation steps are steps 3 and 4.

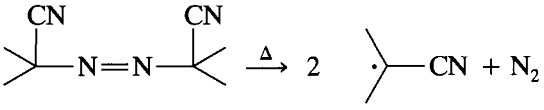
c. Addition of the tribromomethyl radical to the double bond could give either a primary or a secondary radical. Regiospecific addition leads to the more stable secondary radical, **5-38**.

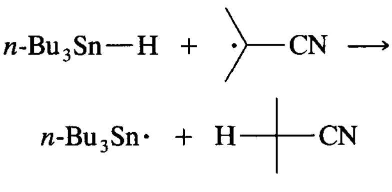
Problem 5.5

a. ***Initiation steps***

Thermal decomposition of AIBN and then hydrogen abstraction from tri-*n*-butyltin hydride.

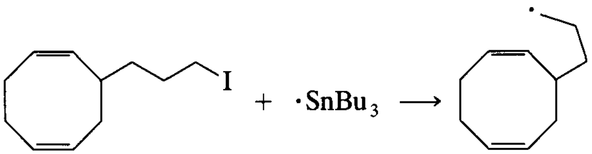
Problem 5.5
continued



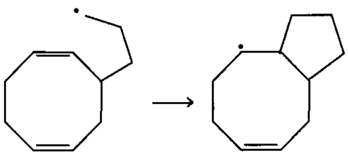


Propagation steps

(1) The tin radical abstracts an iodine atom.

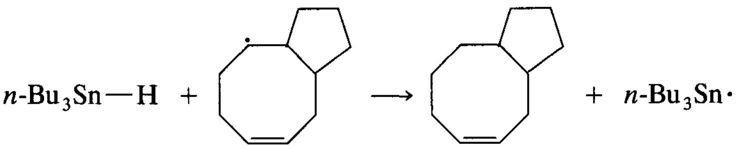


(2) The resulting radical cyclizes.



5-39

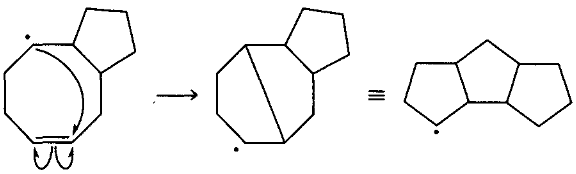
(3) The cyclized radical abstracts a hydrogen atom from tri-*n*-butyltin hydride to give the product and a new tri-*n*-butyltin radical to continue the chain.



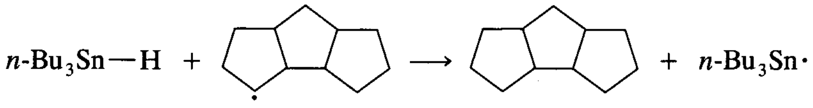
5-39

b. Radical **5-39** can undergo further cyclization across the ring. Such transannular reactions are common in medium-sized rings.

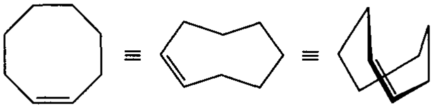
Problem 5.5
continued



The resulting radical also can abstract a hydrogen from tri-*n*-butyltin hydride to produce the hydrocarbon and a tin radical to continue the chain.



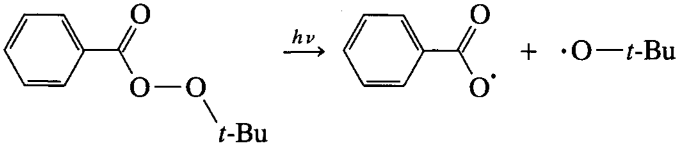
The relative ease with which transannular reactions occur in medium-sized rings becomes apparent when we look at the actual three-dimensional structure of these rings. In their most stable conformations, the hydrogen atoms attached to the ring are staggered, and this means that the carbon atoms across the ring are sufficiently close to form bonds when the appropriate functionality is present. Although medium-sized rings are often represented as regular polygons, alternative representations give a much more realistic picture of the molecular configuration.



These kinds of pictures make it easier to rationalize transannular reactions.

Problem 5.6

Initiation steps



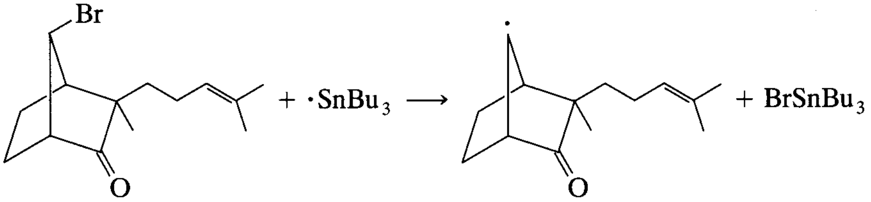
Problem 5.6 *continued*

Either of the resulting radicals can remove a hydrogen from tri-*n*-butyltin hydride.

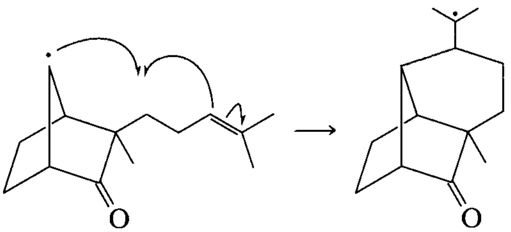
$$t\text{-BuO}\cdot + \text{H—SnBu}_3 \longrightarrow t\text{-BuOH} + \cdot\text{SnBu}_3$$
$$\text{PhCO}_2\cdot + \text{H—SnBu}_3 \longrightarrow \text{PhCO}_2\text{H} + \cdot\text{SnBu}_3$$

Propagation steps

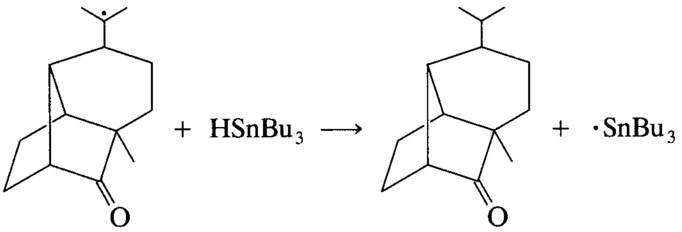
The tributyltin radical abstracts a bromine atom from the starting material.



The radical undergoes intramolecular cyclization. This cyclization is regiospecific to form a new radical on the exocyclic carbon. This is expected on the basis of the Baldwin–Beckwith guidelines (Section 6.B).



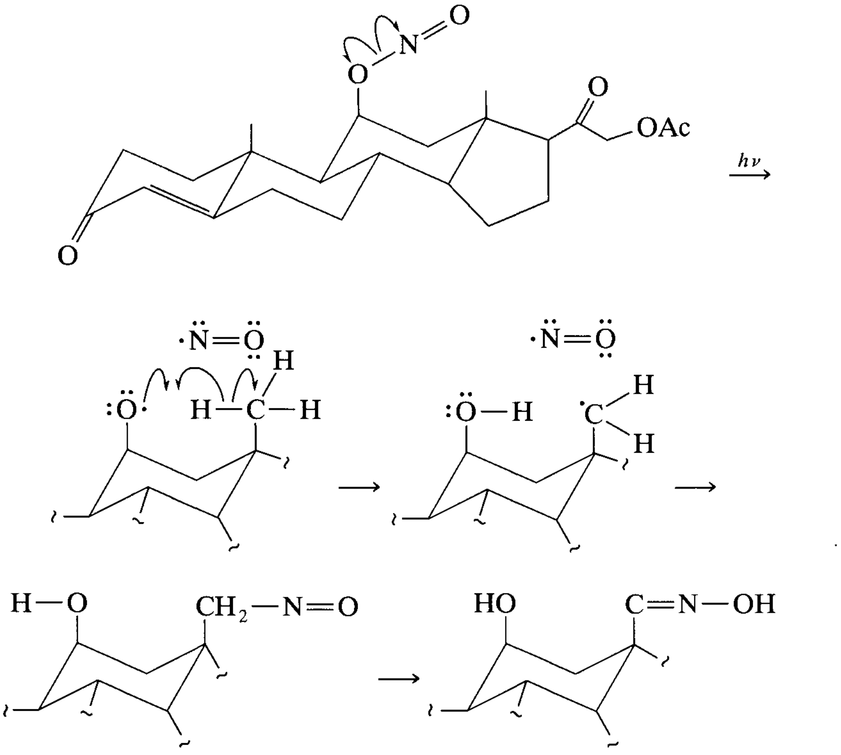
The cyclized radical abstracts a hydrogen from another molecule of tributyltin hydride to generate the product and another tributyltin radical.



Problem 5.7 Note that this is not a chain process. The reaction, known as the Barton nitrite photolysis, was developed to functionalize steroids in positions that

Problem 5.7
continued

are difficult to activate by other routes. The first step is photolysis of the nitrite ester, cleaving the relatively weak N—O bond.



Because of the conformational rigidity of the steroid ring system, the nitrite ester and the methyl group that becomes functionalized are in close proximity, and the oxyradical formed by photolysis of the nitrite ester is well-positioned to abstract a hydrogen from the methyl group via a six-membered cyclic transition state. (The formation of a five- or six-membered ring is a common feature of the transition state for many reactions because bond lengths, bond angles, and entropy all combine to stabilize these ring sizes.) Presumably the intramolecular hydrogen abstraction is so rapid that the nitroso radical is still close enough to recombine with the primary carbon radical. The resulting nitroso compound tautomerizes to the oxime on workup.

Problem 5.8

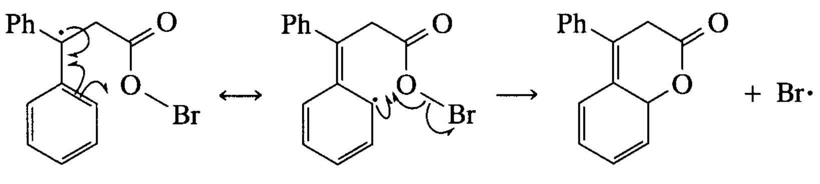
Bromine reacts with the silver salt to form silver bromide and the acyl hypobromite. The latter undergoes homolytic scission to give the carboxy radical, **5-40**.

$$Ph_2CHCH_2CO_2Ag + Br_2 \longrightarrow Ph_2CHCH_2CO_2Br + AgBr$$

$$Ph_2CHCH_2CO_2Br \xrightarrow{\Delta} \underset{\textbf{5-40}}{Ph_2CHCH_2CO_2\cdot} + Br\cdot$$

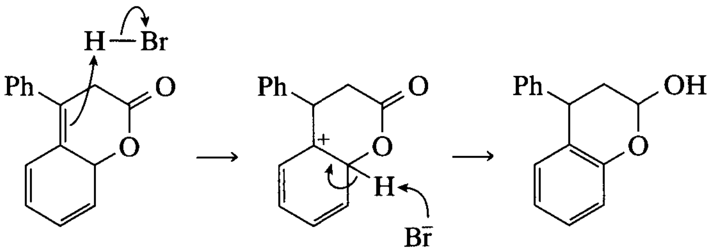
Hydrogen abstraction by the bromine radical gives the radical **5-41**, which cyclizes, regenerating a bromine radical.

$$Ph_2CHCH_2CO_2Br + Br\cdot \longrightarrow \underset{\textbf{5-41}}{Ph_2\dot{C}HCH_2CO_2Br} + HBr$$



5-41-1 **5-41-2** **5-42**

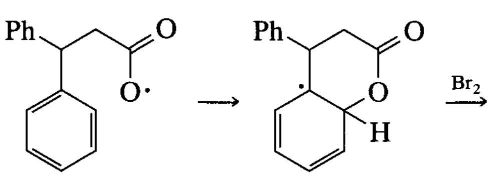
The intermediate **5-42** can isomerize to product **5-12** by a protonation-deprotonation mediated by the strong acid HBr formed in the reaction medium.



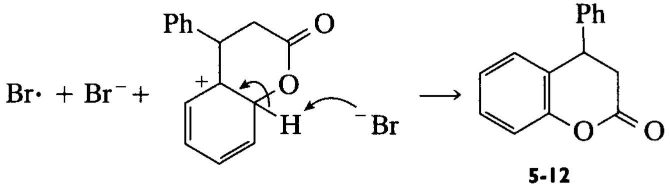
5-42 **5-12**

An alternative mechanism can be written in which **5-40** cyclizes to **5-43**, which is then oxidized by bromine to the corresponding carbocation. The product is then obtained by abstraction of a proton by bromide ion.

Problem 5.8
continued



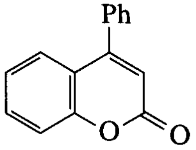
5-40 **5-43**



5-12

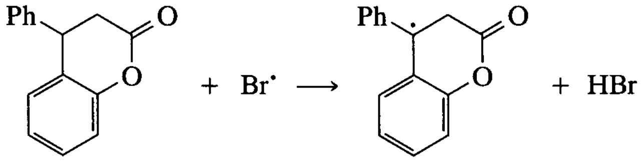
This second mechanism is less satisfactory because cyclization of the carboxy radical **5-40** is unlikely. Alkyl carboxy radicals are highly unstable and they decarboxylate so rapidly that fragmentation would be expected to occur faster than cyclization. The previous mechanism has at least two other advantages. First, it proceeds through the radical **5-41**, which is stabilized by resonance with two phenyl substituents, so that hydrogen abstraction to form **5-41** should compete effectively with homolytic scission of the acyl bromide to form **5-40**. Second, it will occur rapidly because it is a radical chain process; the bromine radical formed in the cyclization of **5-41** regenerates **5-41** from the acyl hypobromite.

Product **5-13** can be produced via hydrogen atom abstraction



5-13

from **5-12** to form radical **5-44**, followed by mechanistic steps analogous to those for the transformation of **5-43** to **5-12**.

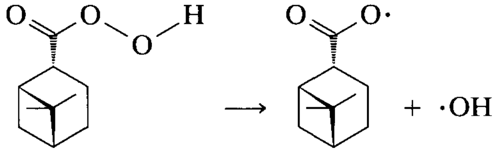


5-12 **5-44**

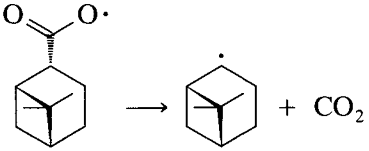
Problem 5.8
continued

b. Note that the bicyclic structure of the starting material is the same as the bicyclic structure in Example 5.8. It has been written in a different (more old-fashioned) way. Once this is recognized, a mechanism can be written for the reaction, which is analogous to Example 5.8.

The first step is homolysis of the weakest bond in **5-14**, the O—O bond. This is followed by loss of CO_2.

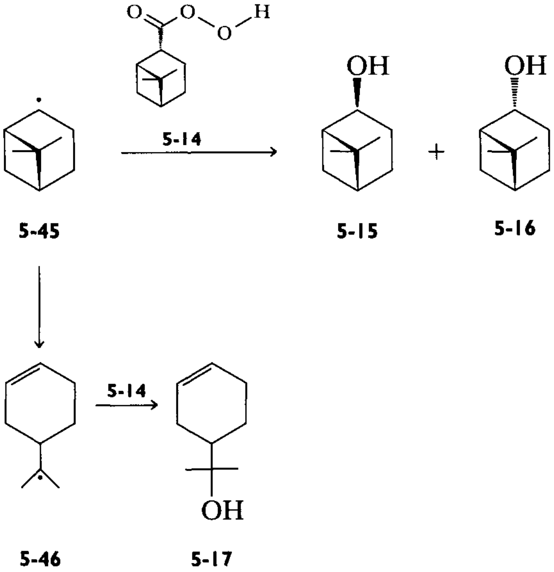


5-14



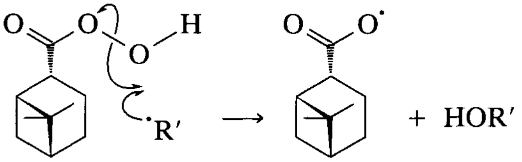
5-45

Because the ratio of bicyclic to ring-opened products increases with increasing peracid concentration, the bicyclic products (**5-15** and **5-16**) must be formed by reaction of the intermediate **5-45** with **5-14**. This bimolecular process competes with the unimolecular fragmentation of **5-45** that leads to the ring-opened product **5-17**.

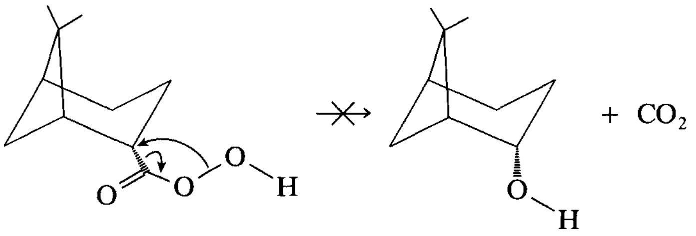


Problem 5.8
continued

The intermediate radicals **5-45** and **5-46**, symbolized by ${}^{\bullet}R'$ in the following equation, can abstract OH from **5-14** to produce the product alcohols.



Because roughly the same amounts of **5-15** and **5-16** are produced from either isomer of starting material, **5-14**, the mechanism of the reaction cannot be concerted:

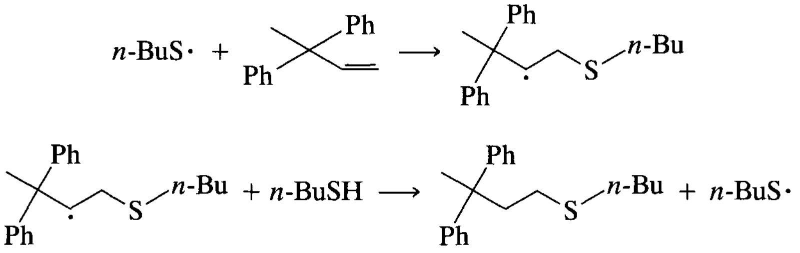


Problem 5.9

n-Butylmercaptan is a better chain-transfer agent than the aldehyde, because hydrogen abstraction from the mercaptan is much easier. Thus, the radical, formed by addition of *n*-butylthio radical to the aliphatic double bond, is captured by mercaptan before it can rearrange. This is not the case for reaction with aldehyde.

$$t\text{-BuOOH} \longrightarrow t\text{-BuO}\cdot + \cdot\text{OH}$$

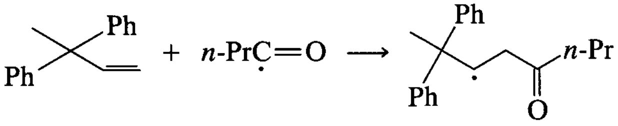
$$t\text{-BuO}\cdot + n\text{-BuSH} \longrightarrow t\text{-BuOH} + n\text{-BuS}\cdot$$



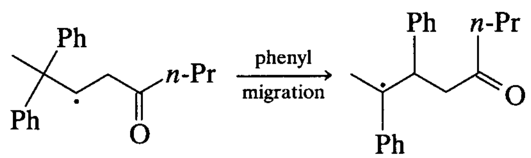
Problem 5.9
continued

The reaction with aldehyde is as follows:

$$t\text{-BuO}\bullet + n\text{-PrCHO} \longrightarrow t\text{-BuOH} + n\text{-Pr}\underset{\bullet}{\mathrm{C}}{=}\mathrm{O}$$

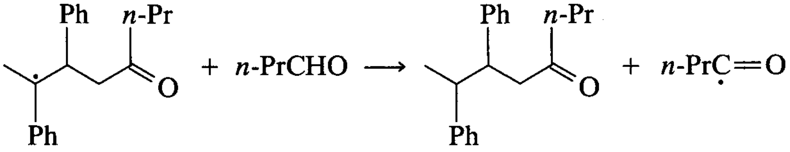

5-47

In this case, rearrangement of **5-47** competes effectively with its abstraction of hydrogen from starting material.



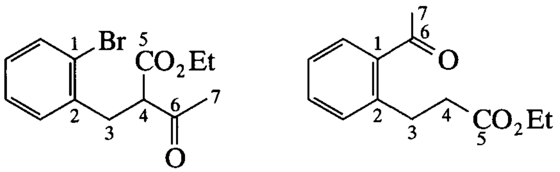
5-47

The rearranged radical abstracts a hydrogen from aldehyde to continue the chain.



Problem 5.10

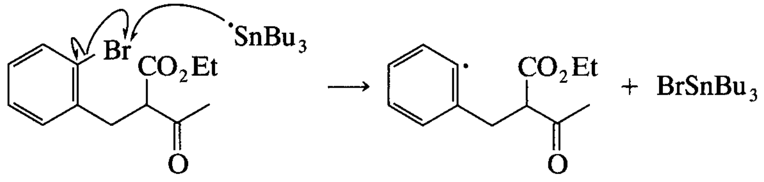
Numbering of the critical carbon atoms in the starting material and product gives a good indication of the course of the reaction.



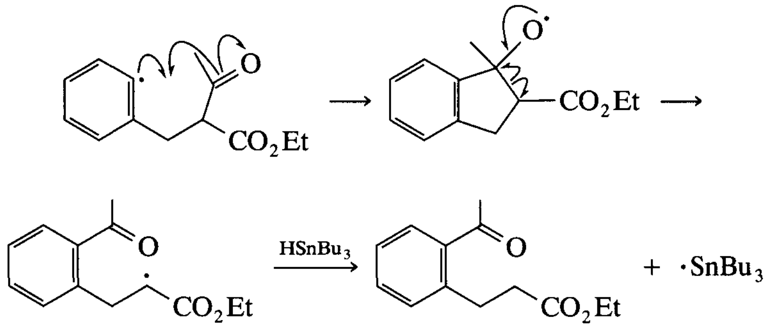
The acetyl group has "migrated" from C-4 in the starting material to C-1 in the product. Thus, the following sequence of events can be anticipated: (i) removal of the bromine atom from C-1, (ii) addition of the resulting radical to C-6, (iii) cleavage of the C-6 to C-4 bond, and (iv) reaction with tri-*n*-butyltin hydride to give the product and a radical to continue the chain.

Problem 5.10
continued

The initiation steps, to form the tri-*n*-butyltin radical, are the same as those in Problem 5.5. This radical then abstracts bromine from the starting material.



The aryl radical adds to the carbonyl group, a bond cleaves, and the resulting radical abstracts hydrogen from tri-*n*-butyltin hydride to form the product and a new chain-carrying radical.



Problem 5.11

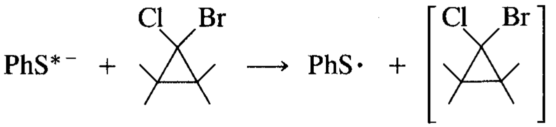
The fact that reactions in both (a) and (b) require light suggests that a radical mechanism is involved for each of them. This rules out a simple S_N2 substitution in part a or a nucleophilic aromatic substitution by an addition–elimination reaction in part b. When substitution occurs under basic conditions in the presence of light, the most likely mechanism is $S_{RN}1$.

Problem 5.11
continued

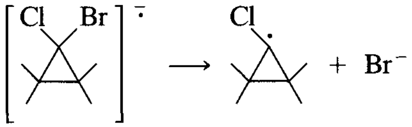
a. The thiolate anion is excited by the light.

$$\mathrm{PhS^-} \xrightarrow{h\nu} \mathrm{PhS^{*-}}$$

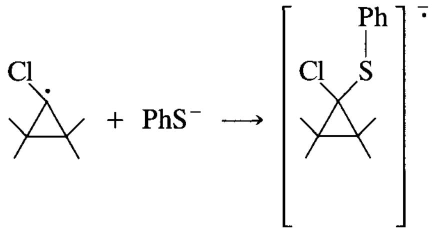
The excited thiolate anion transfers an electron to cyclopropane.



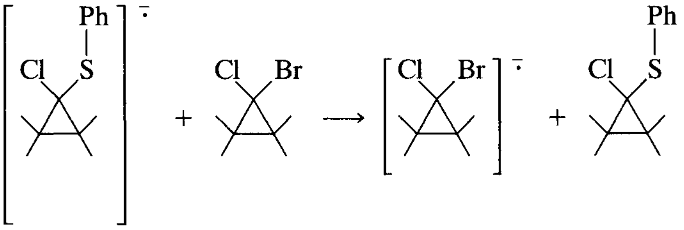
The better leaving group, bromide, leaves.



Thiolate reacts, as a nucleophile, with the electrophilic radical to produce the radical anion of the product.



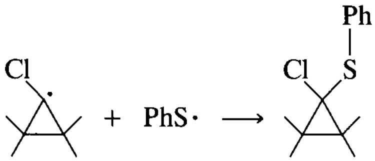
Electron transfer to another molecule of starting cyclopropane gives the product and another cyclopropane radical anion to continue the chain.



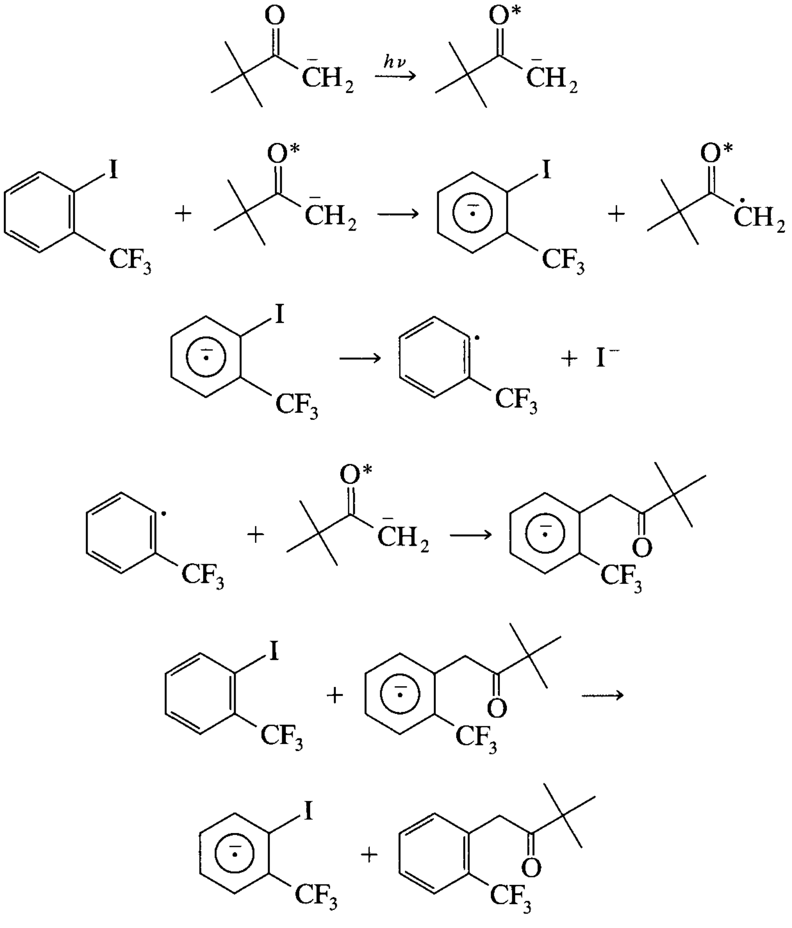
The following is not a proper product-forming step because it does not also produce a radical to continue the chain. It actually is a termination step, involving the coupling of two radicals. Formation of a major product

Problem 5.11
continued

by the coupling of two radicals is unlikely because the concentration of radical intermediates usually is quite low.



b. Each step in the mechanism for this reaction has a direct counterpart in the mechanism for part a.

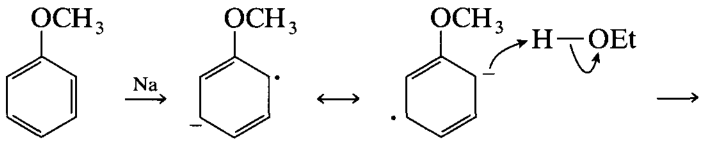


Problem 5.12

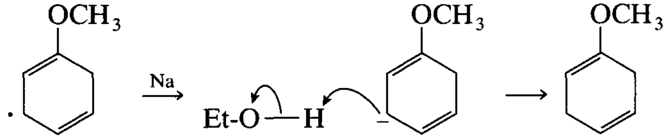
Sodium transfers a single electron to the aromatic system to produce a pentadienyl radical anion, **5-48**. This anion is protonated at the position either *ortho* or *meta* to the π-donating methoxy group to give an interme-

Problem 5.12
continued

diate radical. When a second electron is added to this radical, the pentadienyl anion is again protonated at its central carbon, *ortho* or *meta* to the methoxy substituent.

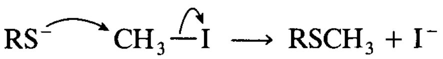


5-48-1 **5-48-2**



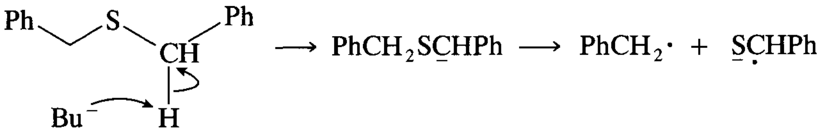
Problem 5.13

Comparison of the starting material with products shows that methyl iodide is used to methylate sulfur. The reaction takes place in base, so that the most likely mechanism for the methylation is an S_N2 reaction with thiolate ion:



$$RS^- + CH_3{-}I \longrightarrow RSCH_3 + I^-$$

Despite the fact that radical coupling is rarely a significant source of reaction products, the structural symmetry of the first two products suggests that they are formed by this route. Butyllithium can remove a proton from the carbon *α* to the sulfur. The resulting anion could then fragment into a radical and a radical anion by scission of the S—C bond.

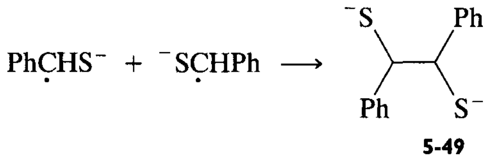


Problem 5.13
continued

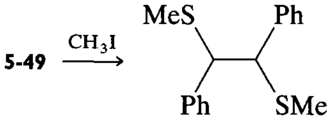
Two benzyl radicals can couple to give the first product.

$$\mathrm{PhCH_2\cdot + \cdot CH_2Ph \longrightarrow PhCH_2CH_2Ph}$$

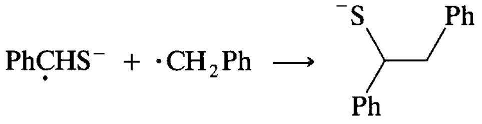
Two thiolate radical anions can couple to give the dithiolate precursor, **5-49**, of the second product. This is analogous to the well-documented coupling of ketyls (radical anions derived from one-electron reduction of carbonyl compounds), which results in the formation of pinacols (1,2-diols).



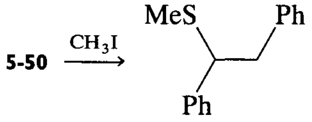
5-49



Finally, the two radicals formed initially can couple, at carbon, to give the thiolate precursor, **5-50**, of the third product.



5-50



This is one of those relatively few reactions that proceed through radical coupling. The reaction occurs in part because the radicals involved are sufficiently stable to remain in existence until they can couple with another radical.

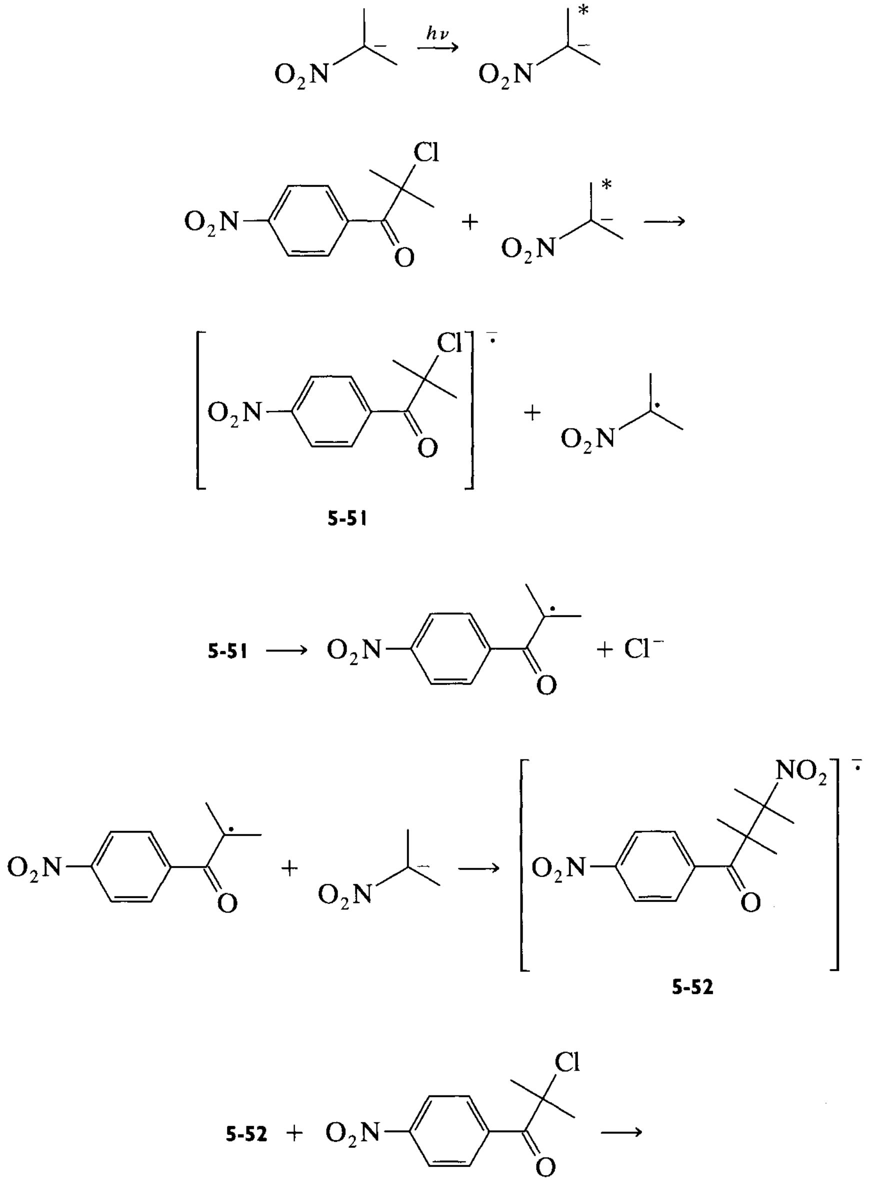
Problem 5.14

The evidence suggests that **5-33** and **5-34** are formed by different types of mechanisms: structure **5-33** by a radical process and structure **5-34** by a non-radical process. Formation of **5-33** is suppressed completely by addition of a free radical inhibitor, but is stimulated by light. These observations strongly support a radical pathway to **5-33**. Other factors also make ionic $\mathrm{S_N}$ pathways unlikely. An $\mathrm{S_N2}$ reaction is ruled out because **5-33** is formed by substitution at a tertiary carbon. An $\mathrm{S_N1}$ ionization also is unlikely because formation of a carbocation next to the partially positive

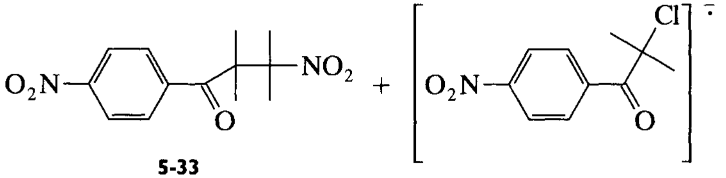
Problem 5.14
continued

carbonyl would be required. Therefore, we are left with the strong possibility that **5-33** is formed by an $S_{RN}1$ mechanism. On the other hand, **5-34** forms in better yield in the dark or in the presence of a radical inhibitor, data which support a nonradical reaction. Note the regiochemistry of addition is different in the formation of **5-33** and **5-34**.

An $S_{RN}1$ mechanism for the formation of **5-33** can be written as follows:

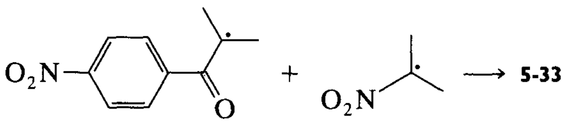


Problem 5.14
continued

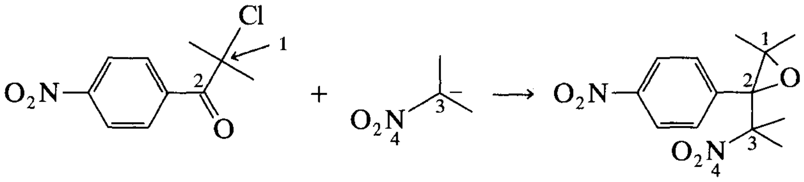


5-33

It is tempting to write a radical coupling to form product **5-33**, because it involves fewer steps. However, this mechanism would be energetically inefficient because it does not continue the chain process. Thus, the following *is not* the major product-forming step:

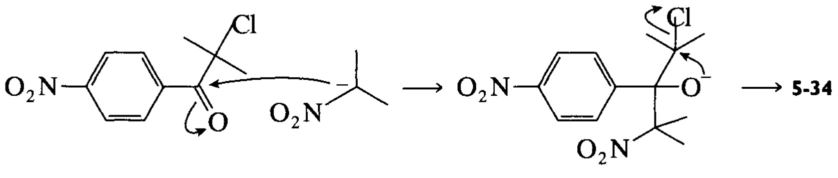


Noting the formation of the epoxide group and numbering the atoms in the starting materials and in **5-34** help to indicate how **5-34** must be formed.



5-34

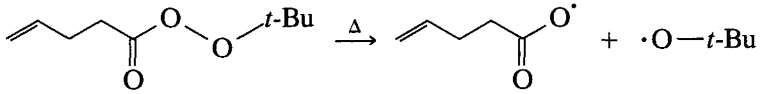
Because C-3 becomes attached to C-2, a nucleophilic reaction of the nitranion at the electrophilic carbonyl carbon must take place. Sterically this carbon is the most accessible. This step is followed by an intramolecular nucleophilic reaction of the alcoholate with the adjacent carbon (numbered 1 in the previous equation).



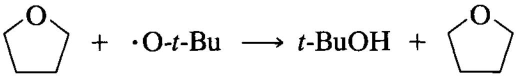
Problem 5.15

a. The perester could serve as a free radical initiator. At first glance, it appears that two tetrahydrofuran molecules form the two rings of the product, but the product contains one additional carbon atom. Therefore, the perester must be the source of the atoms of one ring, as well as a source of radicals. Because the perester contains a carbonyl group, the simplest explanation is that the lactone ring is derived from the perester. These considerations suggest the following chain mechanism:

Initiation

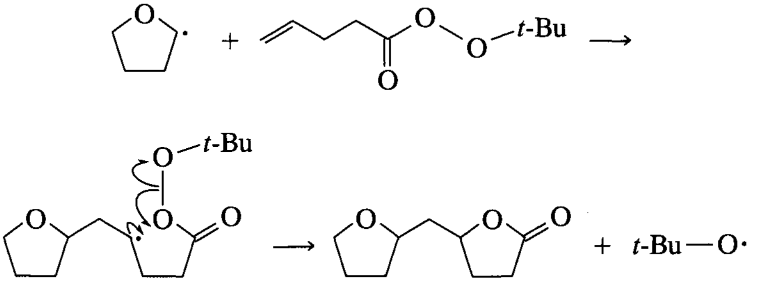


Propagation

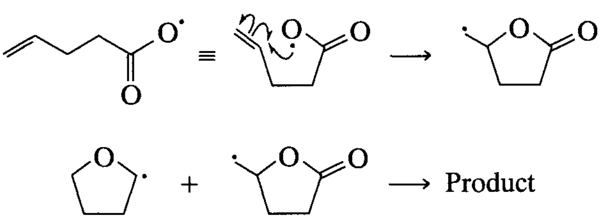


5-53

The tetrahydrofuranyl radical, **5-53**, adds to the carbon–carbon double bond of the perester.



The following mechanism is not as satisfactory.

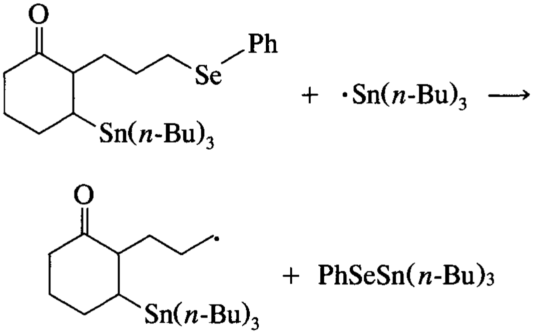


Problem 5.15
continued

Rapid decarboxylation of the alkyl carboxyl radical to the corresponding alkyl radical would be expected to compete with intramolecular cyclization. Moreover, the reaction scheme shown would not be efficient. Not only would the reaction be slow because two radicals must collide in order to form the product, but the step fails to regenerate a radical to continue the reaction. (Note: Aryl carboxyl radicals lose carbon dioxide more slowly than alkyl carboxyl radicals.)

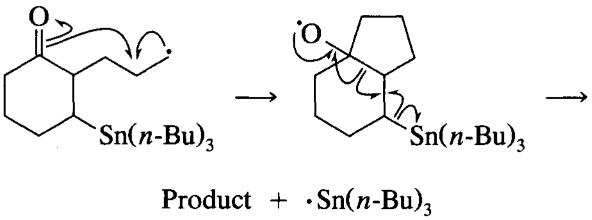
b. From the reaction conditions, we can make the following speculations and/or conclusions: (i) the tri-*n*-butyltin radical will be the chain carrier. (ii) Tri-*n*-butyltin will be lost from the starting material. (iii) A bond in the six-membered ring breaks at some point in the mechanism.

In Section 2, we learned that tri-*n*-butyltin radicals react with selenium compounds to produce radical intermediates. Therefore, this might be a logical first step, after the initiation reaction between AIBN and tri-*n*-butyltin hydride has produced tri-*n*-butyltin radicals.



5-54

The carbonyl group of radical **5-54** can undergo an intramolecular cyclization reaction with the alkyl radical. The shared bond between the five- and six-membered rings then breaks to form the product and a new tri-*n*-butyltin radical, which continues the chain.

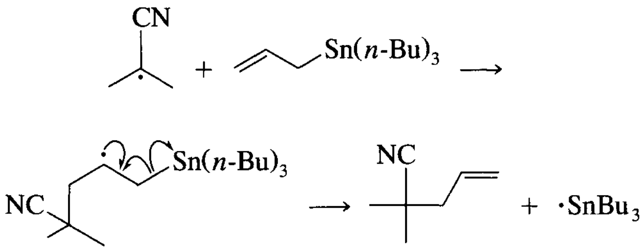


The major difference between this reaction and that of Example 5.11 is that only 10 mol% tin hydride is present. This is enough to initiate the reaction, but not enough to reduce intermediate radicals significantly.

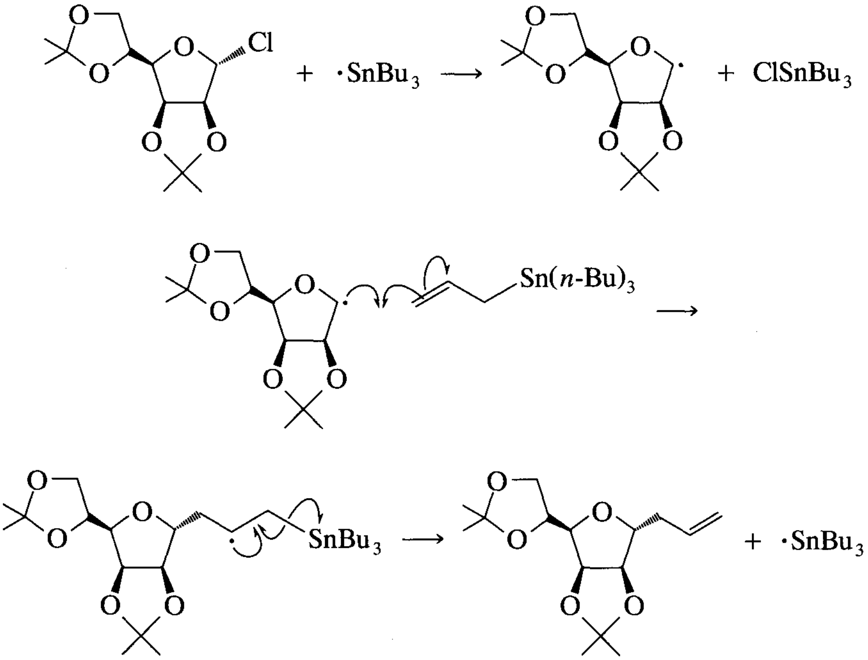
Problem 5.15 *continued*

c. Clues to the reaction mechanism are (i) chlorine is missing from the product, (ii) AIBN is present as an initiator, and (iii) the tributyltin group is present. Thus, it appears that tributyltin radicals abstract chlorine from the starting material. In the initiation steps, AIBN forms 2-cyano-2-propyl radicals in the usual way, and these radicals react with allyltri-*n*-butyltin to produce tri-*n*-butyltin radicals by an addition–elimination mechanism.

Initiation

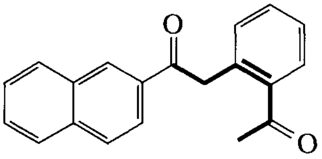


Propagation



Problem 5.15
continued

d. Reaction in the presence of light and strong base suggests the involvement of a radical anion intermediate and the $S_{RN}1$ mechanism for at least part of the reaction pathway. In the initiation steps, the anion of the naphthyl ketone, excited by light, donates an electron to the bromo ketone to form a radical anion. The product of an $S_{RN}1$ reaction would be **5-55**.

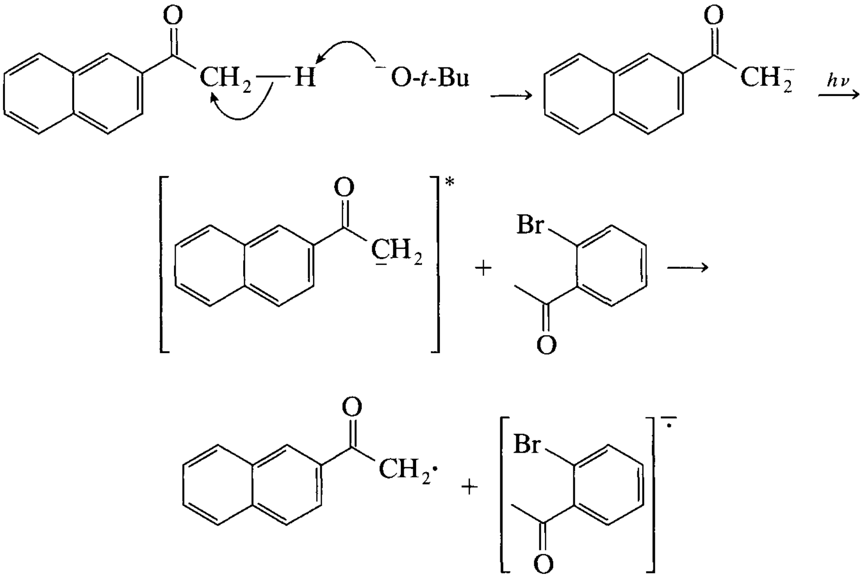


5-55

If the six highlighted carbon atoms in **5-55** form a six-membered ring, the correct carbon skeleton for the final product is obtained. In fact, an intramolecular aldol condensation (discussed in Chapter 3), followed by elimination of water, gives the final product.

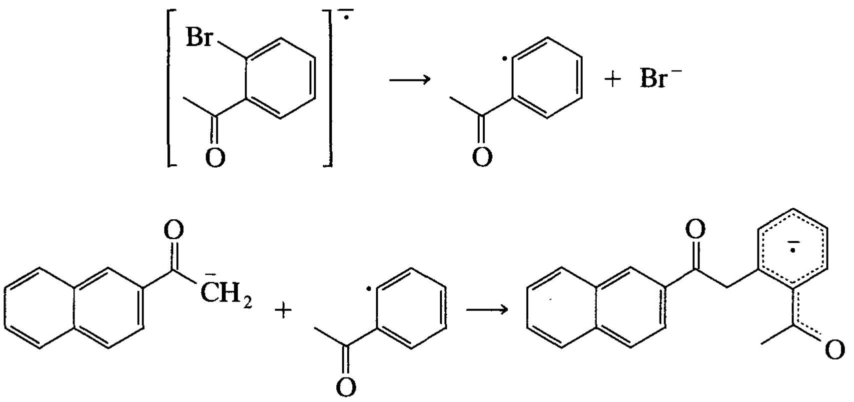
$S_{RN}1$ Reaction

(1) Initiation Steps



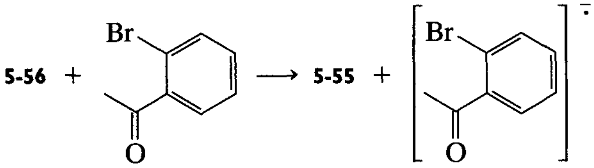
Problem 5.15
continued

(2) Propagation Steps



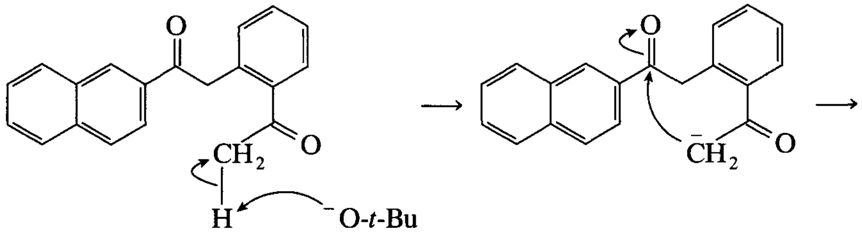
5-56

In the last step, a new radical anion of the starting bromo compound is formed, which continues the chain.



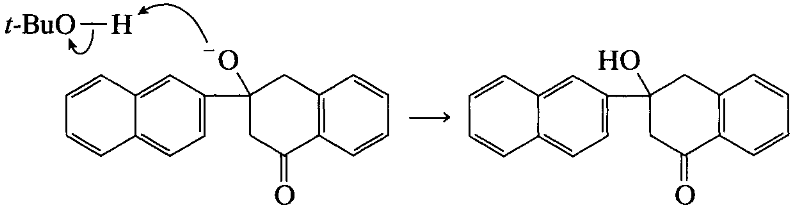
Aldol Condensation

The aldol condensation of **5-55** involves several steps. First, a proton is removed from the methyl group by the *t*-butoxide ion. (If the proton were removed from the methylene group α to the other carbonyl, condensation would be at the carbonyl attached to the methyl. This would produce a five-membered ring.) The resulting enolate adds to the other carbonyl group.



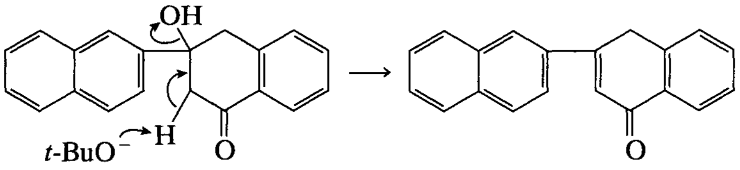
Problem 5.15
continued

Protonation of the resulting alkoxide ion gives alcohol **5-57**.

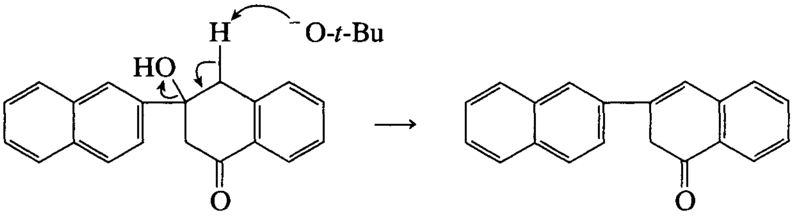


5-57

The alcohol can undergo base-promoted elimination to give two possible products, **5-58** or **5-59**. The new double bond in each of these products is stabilized by conjugation with the carbonyl group and at least one of the aromatic rings.



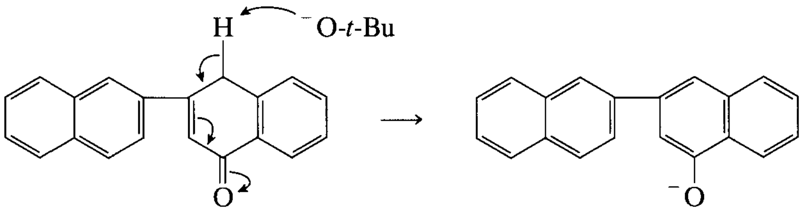
5-58



5-57 **5-59**

Either **5-58** or **5-59** can readily tautomerize to give the final product. Both mechanisms are very similar, so only one is shown.

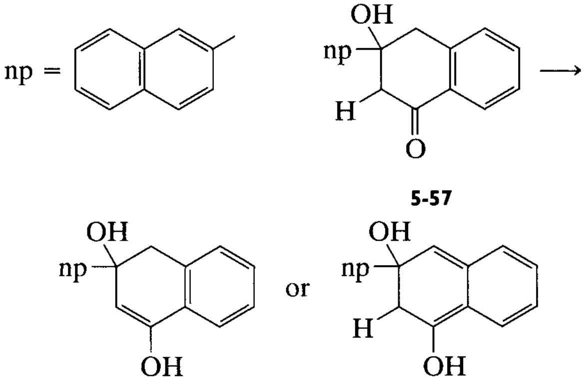
Problem 5.15
continued



5-58 **5-60**

Upon acidic workup, the naphthoxide ion **5-60** is protonated to give **5-35**.

Another plausible mechanism for the final stages of the reaction is tautomerization of **5-57** to **5-61**, followed by elimination directly to the phenol. (Structure **5-62** would not be produced because the aromaticity of the right-hand ring is interrupted.) However, the mechanism previously discussed is preferable because alcohol **5-61** would not be as stable as **5-58** or **5-59**.



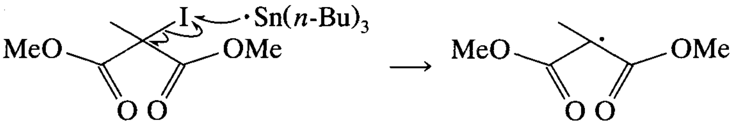
5-57

5-61 **5-62**

e. The overall reaction yield is 69%, with only 10 mol% hexabutylditin present, which indicates that this must be a chain process. Because iodide is present, probable initiation steps would be photochemical decomposition of the ditin compound to tri-*n*-butyltin radicals, followed by abstraction of iodine from the starting material.

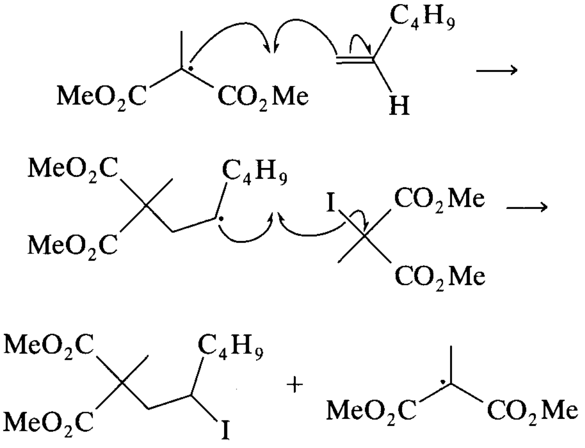
Problem 5.15
continued

$$(n\text{-Bu})_3SnSn(n\text{-Bu})_3 \xrightarrow{h\nu} 2n\text{-Bu}_3Sn\cdot$$



5-63

Radical **5-63** can add regiospecifically to the 1-alkene to produce an intermediate radical, which can then abstract iodine from the starting ester to produce **5-36** and a new radical to continue the chain.



5-36

Because both homolytic and heterolytic cleavages readily occurs with C—I bonds, plausible reaction mechanisms can be written with either radical or ionic intermediates. However, in the nonpolar solvent benzene, the radical mechanism is more likely because the ionic mechanism requires the

Problem 5.15
continued

carbocation and anion to be separated, and these species cannot be stabilized by interaction with the nonpolar solvent.