Chapter 14

Free Radicals

Figure 14.1

Processes for initiating free radical chain reactions. Note how initiation with AIBN leads to the formation of bromine atoms, while initiation with peroxides generates an alkyl radical.

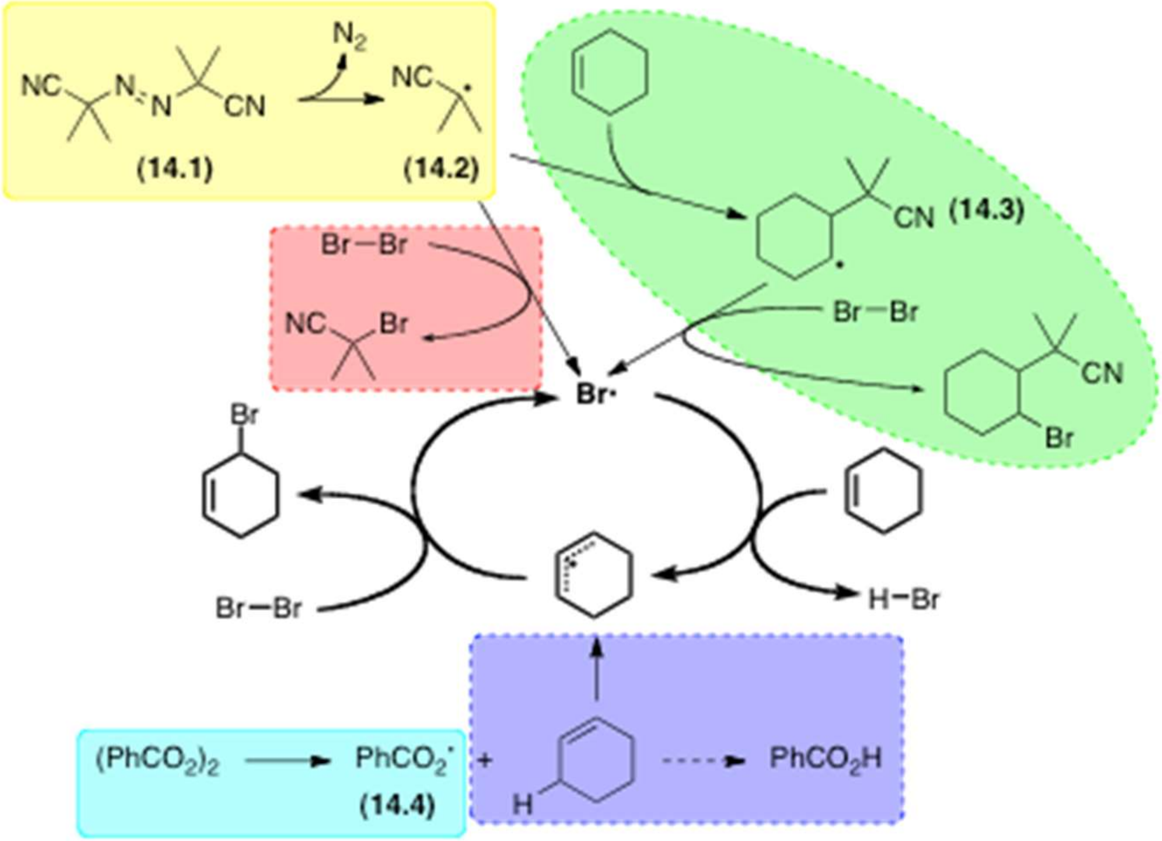
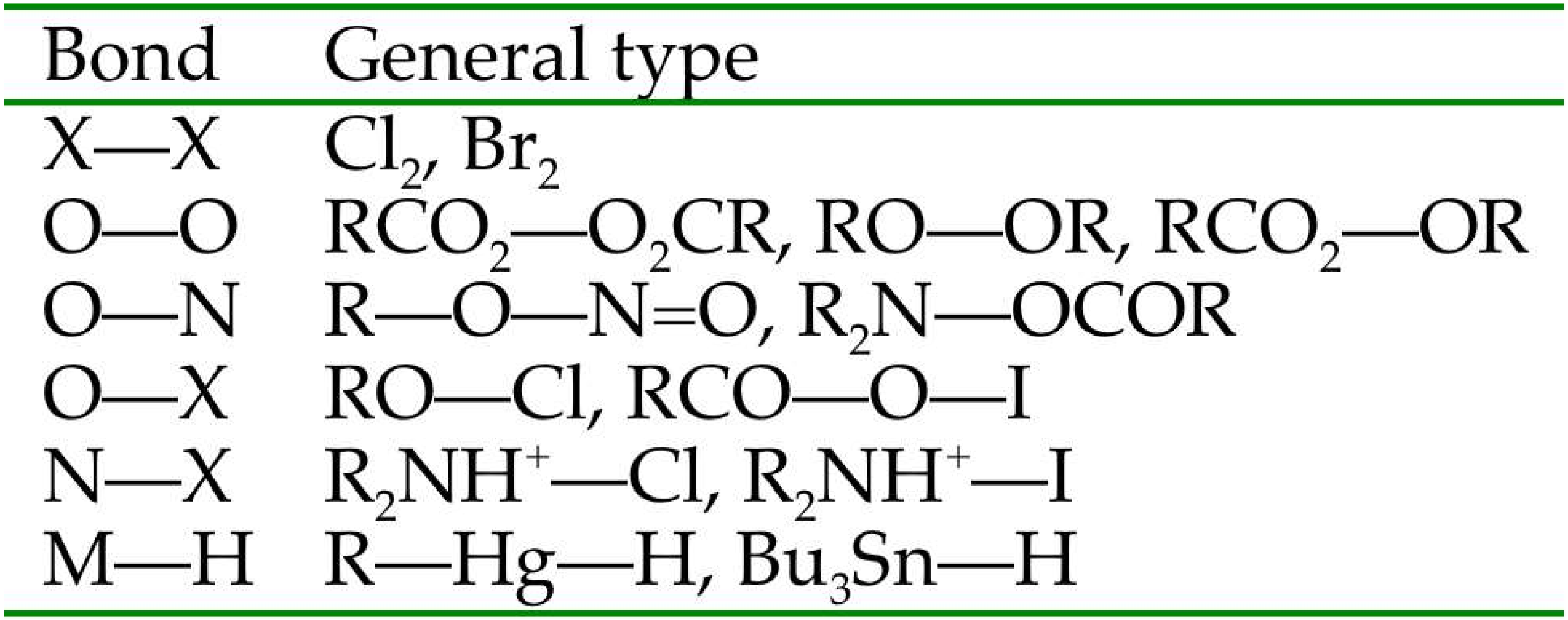


Table 14.1

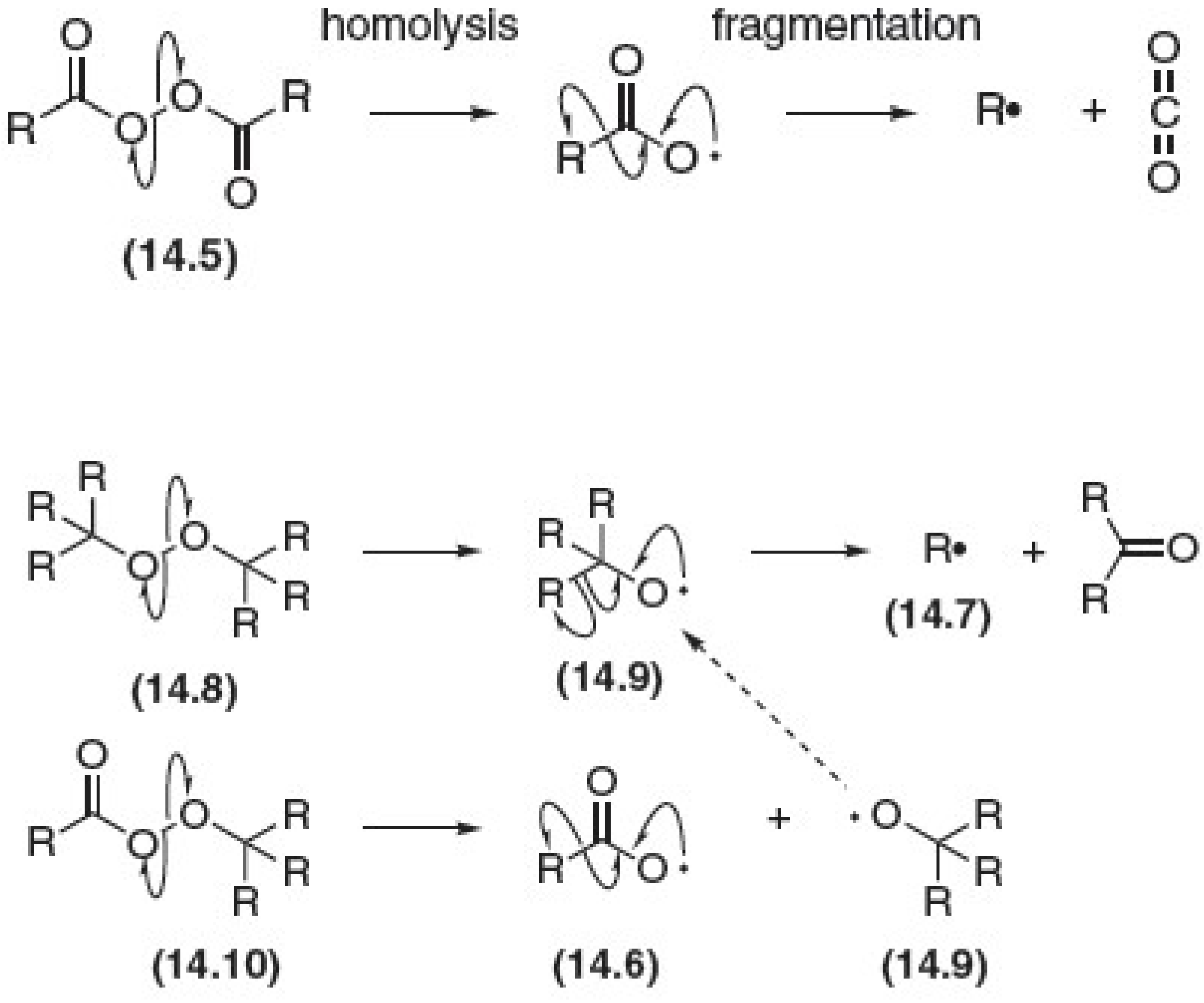
Non-radical precursors to free radicals



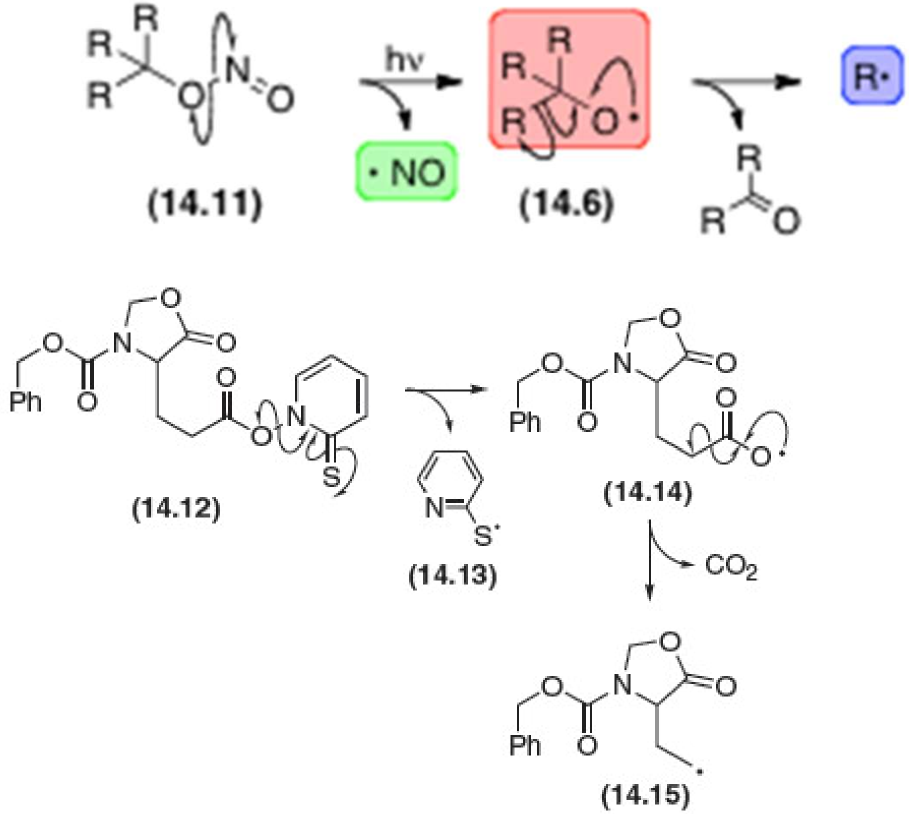
Bond	General type
X—X	Cl_2, Br_2
O—O	RCO_2—O_2CR, RO—OR, RCO_2—OR
O—N	R—O—N=O, R_2N—OCOR
O—X	RO—Cl, RCO—O—I
N—X	R_2NH^+—Cl, R_2NH^+—I
M—H	R—Hg—H, Bu_3Sn—H

O—O homolysis

Homolysis of peroxides gives high energy oxygen-centered radicals (highlighted in red) that can fragment with the elimination of carbonyl compounds (highlighted in green) to give alkyl free radicals (highlighted in blue)

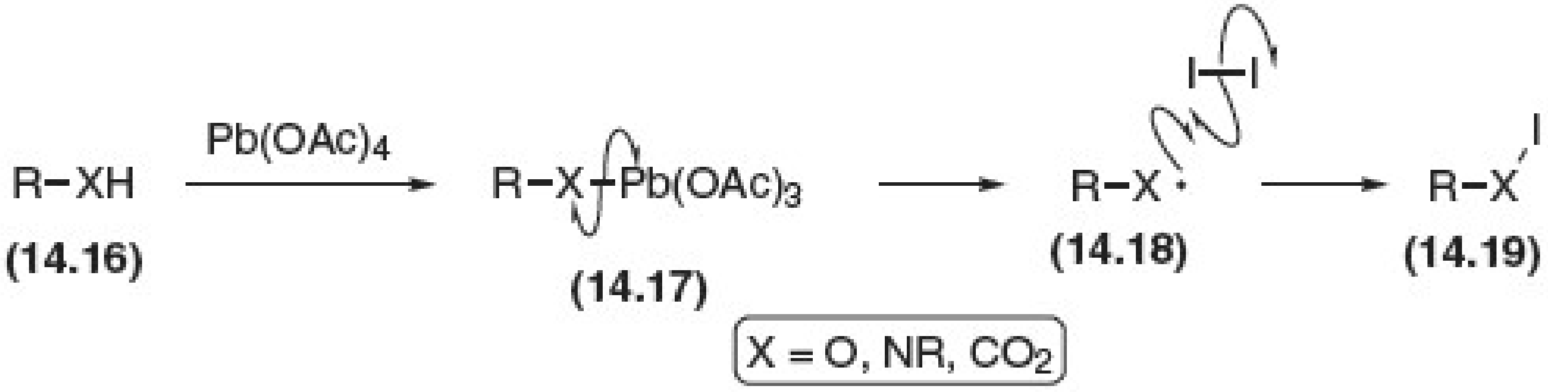


N—O homolysis



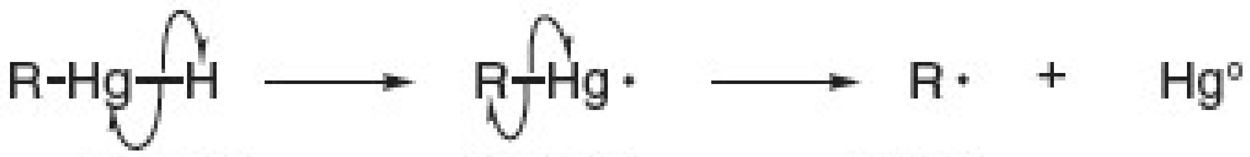
Both these approaches give a very stable free radical (“persistent radical”) as one of the initial products, and a high-energy oxygen-centered radical as the other

Homolysis of N—X and O—X bonds



Precursors can be formed by oxidation of alcohols, amines, carboxylic acids, etc.

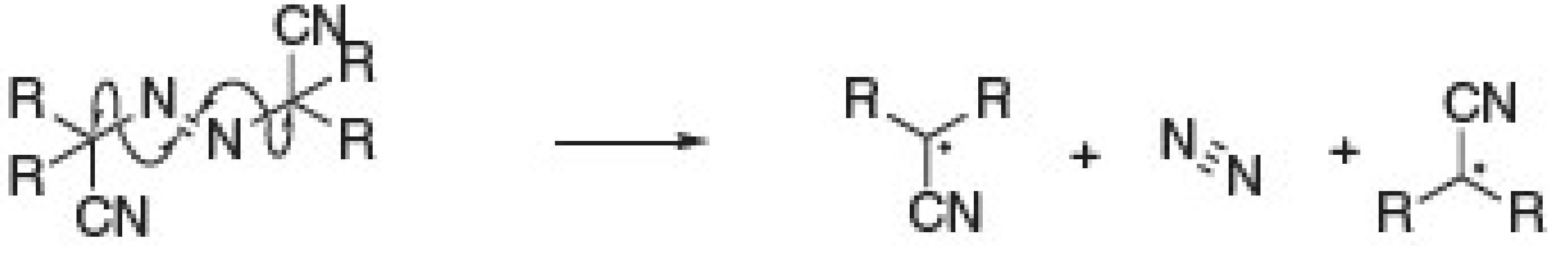
Homolysis of organometallic compounds



(14.20) (14.21) (14.7)

Organomercury hydrides undergo homolysis to give the alkyl radical. The initial hydride may be obtained from an alkene by oxymercuration

Homolysis of other non-radical precursors

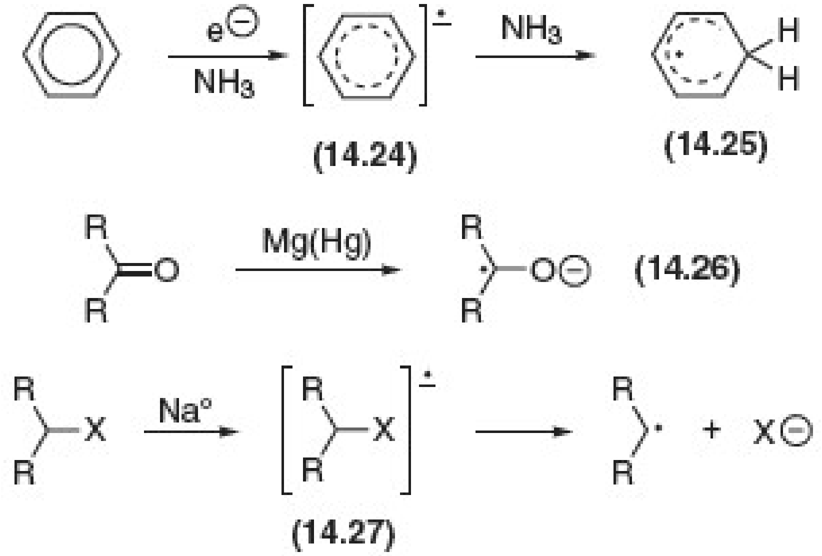


(14.22) (14.23) (14.23)

The most common radical initiators in this class are aliphatic azo compounds

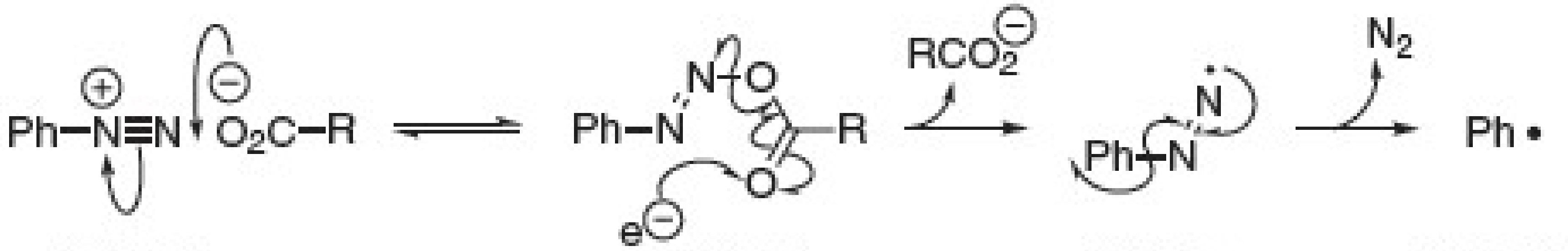
Radicals by reduction

Free radicals are formed by the reactions of unsaturated systems or alkyl halides by active metals



Gomberg-Bachmann reaction

The transfer of a single electron to the aryldiazonium ion forms a diazonyl radical that rapidly loses molecular nitrogen to give the aryl radical. The source of the single electron is not always well defined.



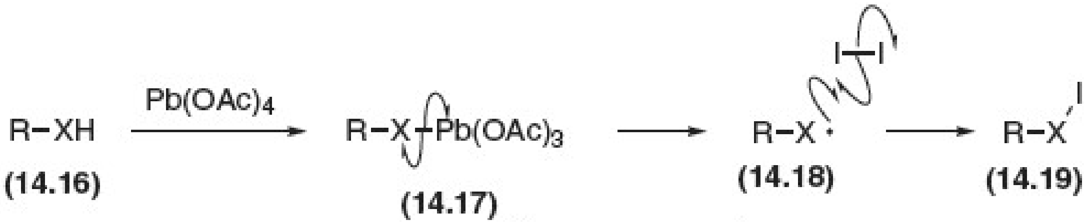
(14.28) (14.29) (14.30) (14.31)

Radicals by oxidation

Electrolysis of carboxylate anions is known as the Kolbe electrolysis. It leads to the carboxy radical that then fragments to carbon dioxide and the alkyl radical. Under conditions of high current, the radical may, in turn, be oxidized to the carbocation.

(14.32)

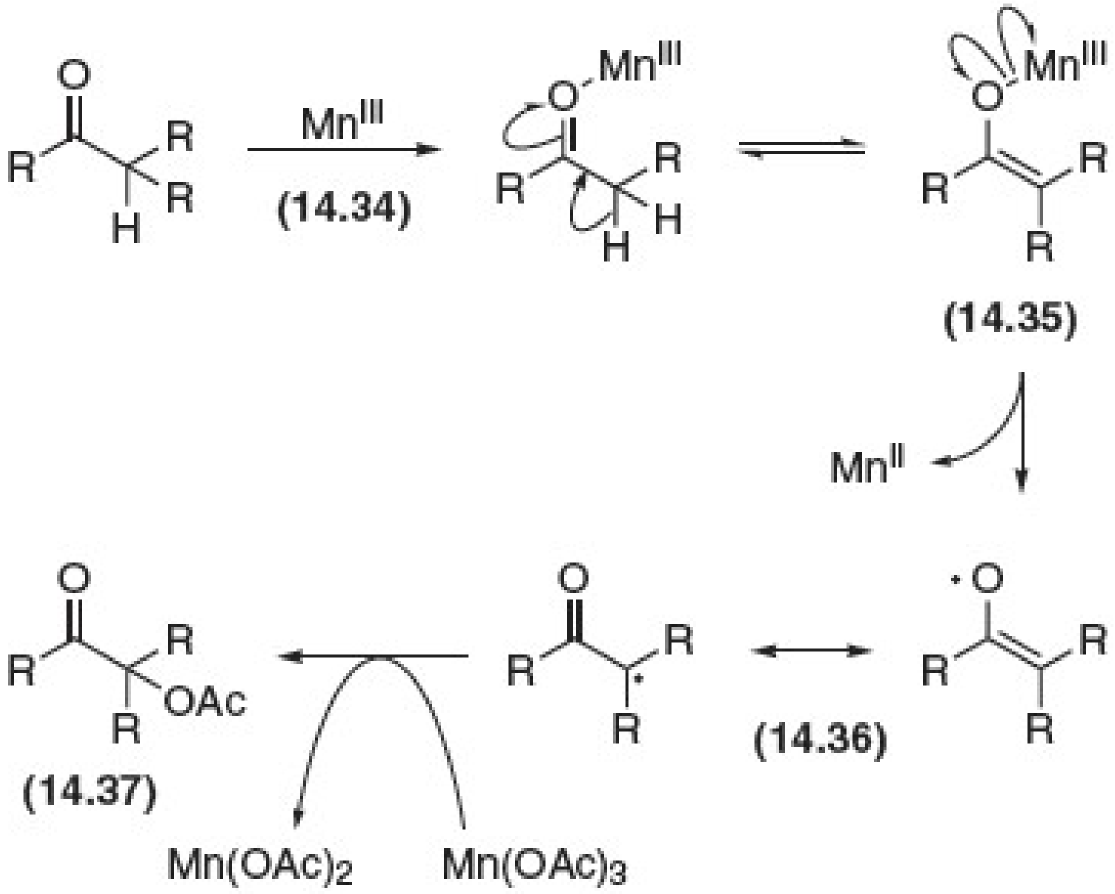
Oxidation of alcohols with lead tetraacetate and iodine gives the alkyl hypoiodite, which is a useful precursor to alkoxy radicals.



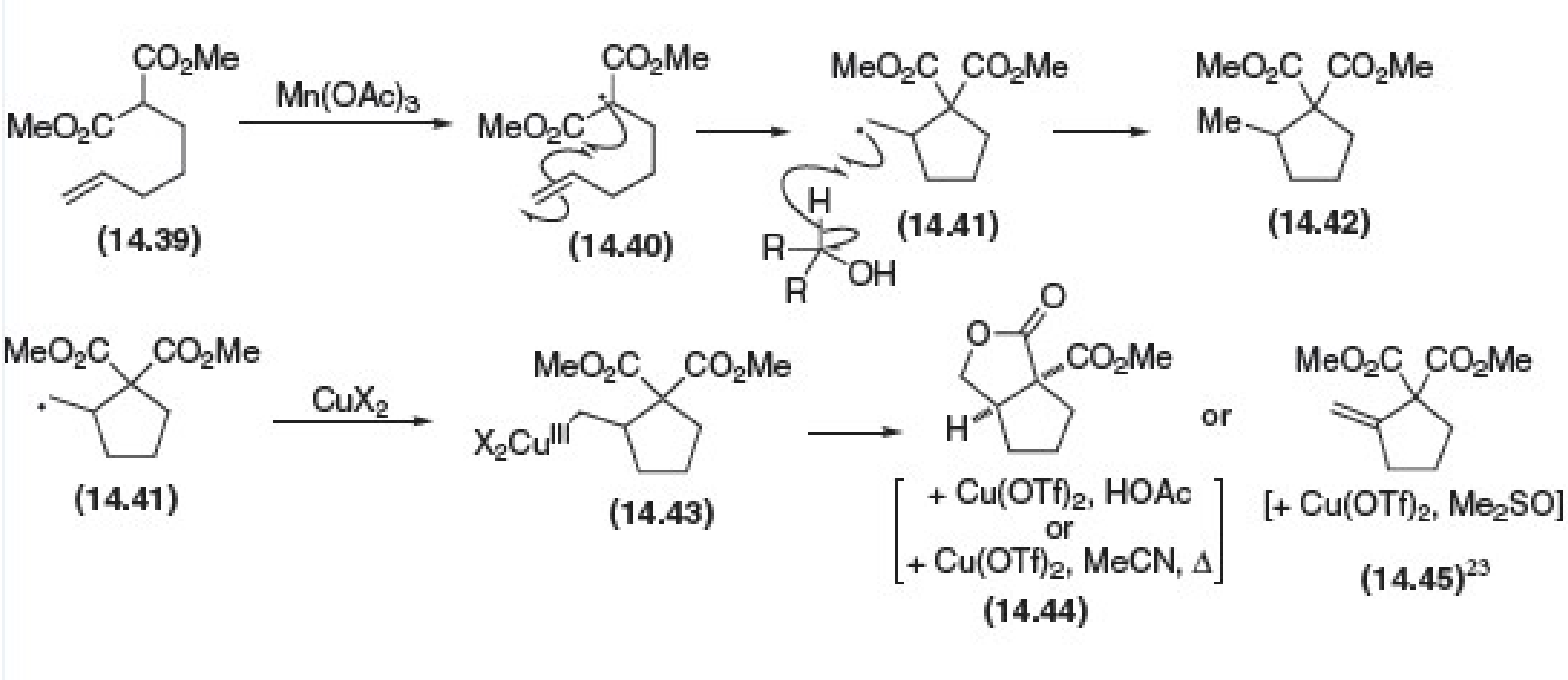
X = O, NR, CO_2

Figure 14.2

Mechanism of α-oxidation of ketones to radicals by Mn(III) acetate

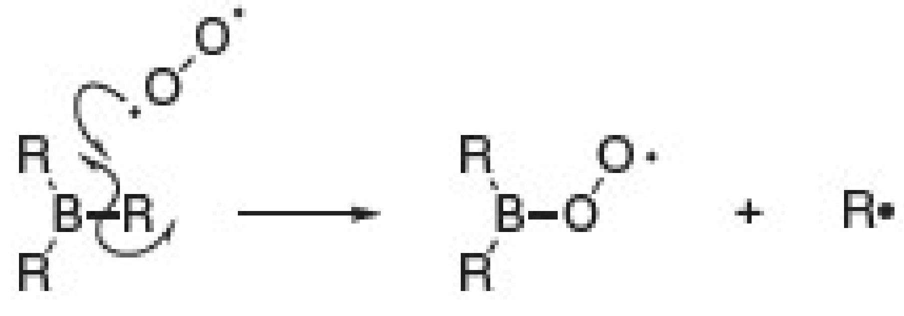


Using Mn (III) acetate in synthesis



copper (II) salts will react with free radicals to give a copper (III) intermediate that exhibits carbocation-like reactivity

Oxidation of trialkylboranes



(14.46)

(14.47)

useful as an initiation reaction for free radical additions to alkenes

Photochemical excitation of carbonyl compounds: Diradicals

(14.48)

Diradical formed may be singlet or triplet; symmetry-forbidden processes (n-π*, ISC) give the longest-lived, most synthetically useful diradicals.

Homolysis: Synopsis

(a) Peroxides

$$\mathrm{RO{-}OR} \xrightarrow{\Delta \text{ or } h\nu} 2\,\mathrm{RO}\bullet$$

Reagents: $(Me_3CO)_2$, $(PhCO_2)_2$, etc.

(b) Aliphatic Azo Compounds

$$\mathrm{RN{=}NR} \xrightarrow{\Delta \text{ or } h\nu} 2\,\mathrm{R}\bullet + \mathrm{N_2}$$

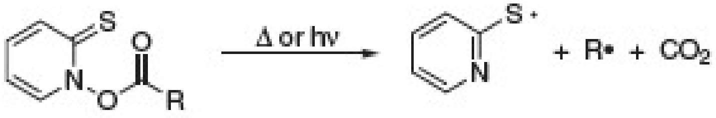
R= $Me_2C(CN)$, AIBN; *c*-$C_6H_{10}(CN)$, ACCN

most widely used radical initiators

(c) Nitrite Esters

$$\mathrm{RO{-}N{=}O} \xrightarrow{\Delta \text{ or } h\nu} \mathrm{RO}\bullet + \bullet\mathrm{NO}$$

(d) Barton Esters



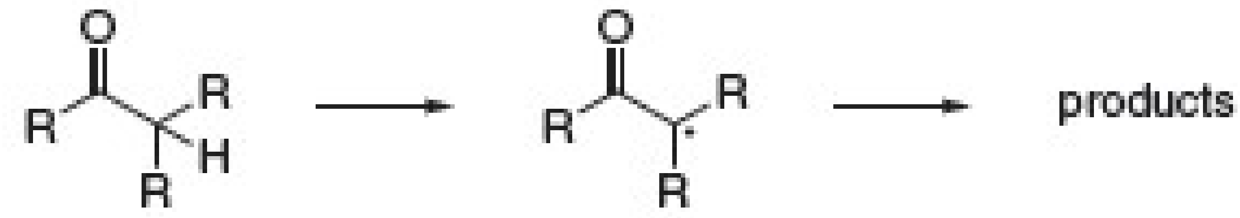
(e) Organomercury Hydrides

$$\mathrm{R{-}Hg{-}X} \xrightarrow[\mathrm{NaOH}]{\mathrm{NaBH_4}} \mathrm{R}\bullet$$

X = Cl, Br, OCOR, etc.

Reagents: $NaBH_4$, NaOH, H_2O; etc.

Oxidation with Mn (III): Synopsis

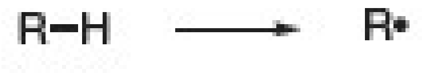


Reagents: $Mn(OAc)_3$, PhH, Δ;

$Mn(acac)_3$, PhH, Δ; etc.

Atom abstraction: Synopsis

(a) Hydrogen



Reagents: ROOR, Δ or $h\nu$; etc.

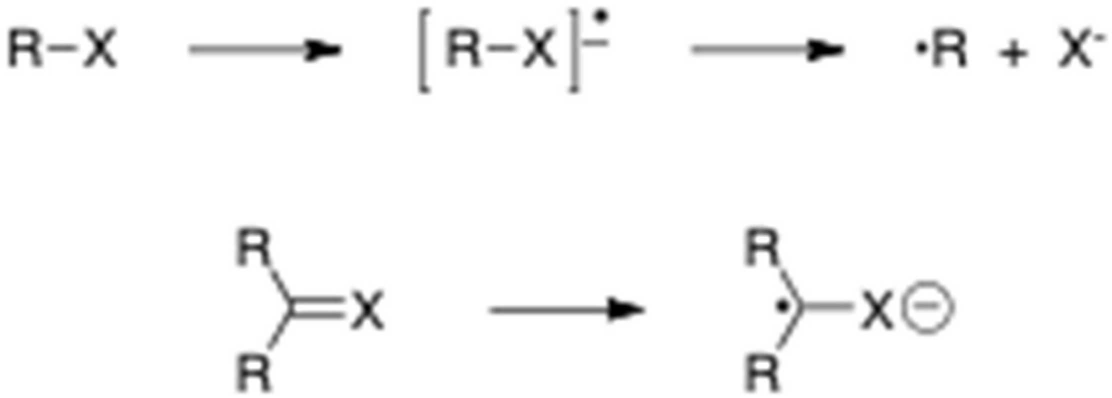
Relatively non-specific unless the C–H bond is activated or the reaction is intramolecular. Intramolecular reaction occurs through a six-membered cyclic transition state.

(b) By Stannyl Radicals

X = Cl, Br, I, SR, OC(=S)–SR SeR, etc.

Reagents: Bu_3SnH, AIBN, Δ or $h\nu$; etc.

Single electron transfer (s.e.t.): Synopsis



Reagents: Li (Na, K, Ca, etc.), NH_3;

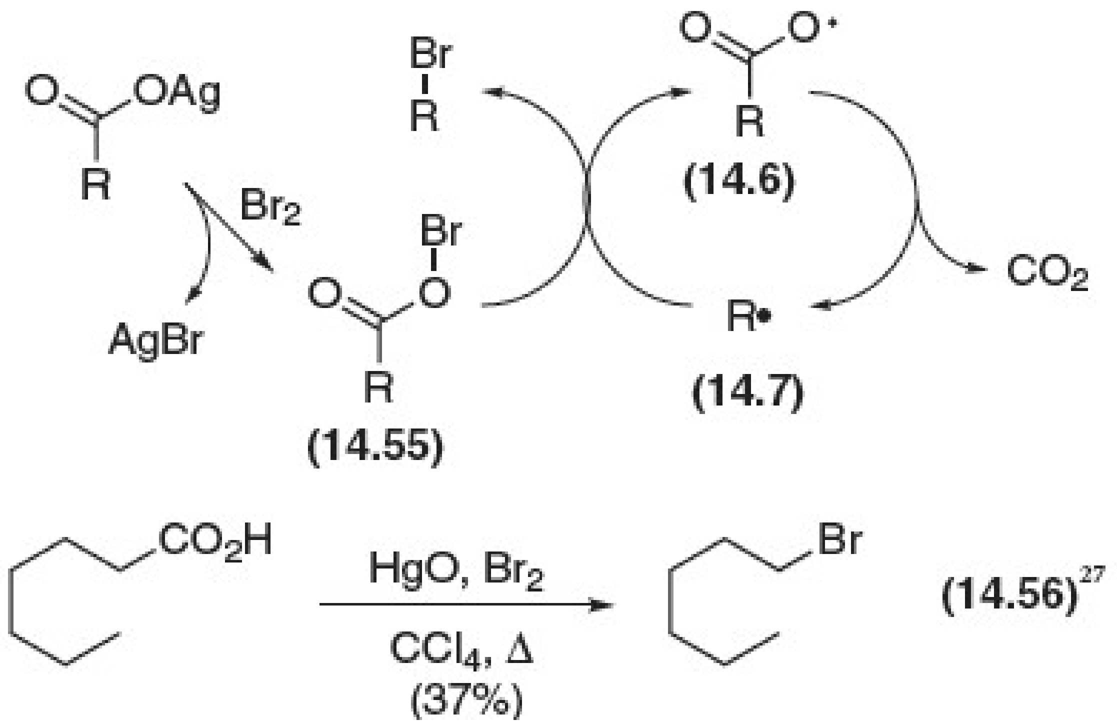
Li (Na, K, Mg, Ca, etc.), PhH; etc.

Table 14.2

Bond dissociation energies of σ bonds to hydrogen

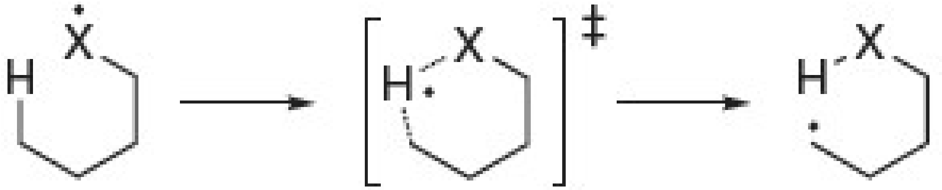
Bond	(kcal mol^{Gl})	(kJ mol^{Gl})	Bond	(kcal mol^{Gl})	(kJ mol^{Gl})
CH_3ĞH	104	435	HOĞH	119	498
RCH_2ĞH	98	410	HOOĞH	90	377
R_3CĞH	92	385	RCH_2OĞH	104	437
$C_6H_5CH_2$ĞH	85	356	RCOOĞH	103-110	431-469
$H_2CCHCHR$ĞH	83	347	C_6H_5OĞH	88	368
$HOCH_2$ĞH	94	393			
$MeOCH_2$ĞH	93	389	H_2NĞH	102	427
$HOCMe_2$ĞH	91	381			
$H_2C{=}CHCH(OH)$ĞH	82	341	HSĞH	95	397
			CH_3SĞH	74	310
C_6H_5ĞH	110	461			
O=CRĞH	87	364			

Borodin-Hunsdiecker reaction



The reaction converts the silver or mercury (I) carboxylate to the alkyl bromide of the next lowest homologue through the acyl hypohalite as the radical precursor

Intramolecular hydrogen atom transfer

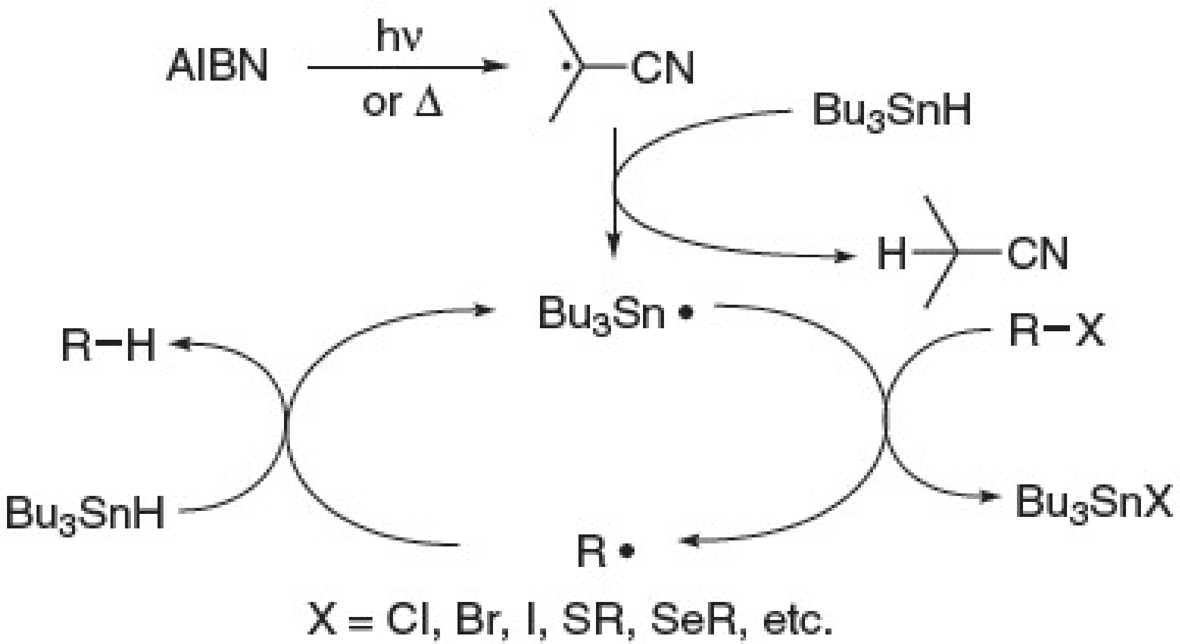


(14.58)

$X = O, NH, NH_2^{\oplus}, NCOR$, etc.

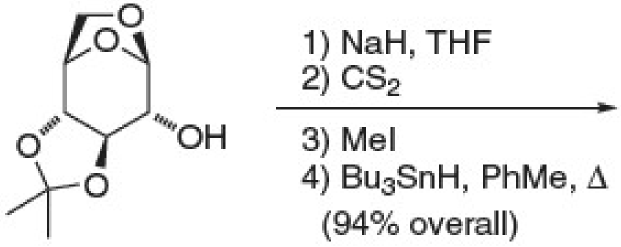
intramolecular transer of the hydrogen atom from carbon to the heteroatom occurs through a six-membered transition state

Figure 14.3

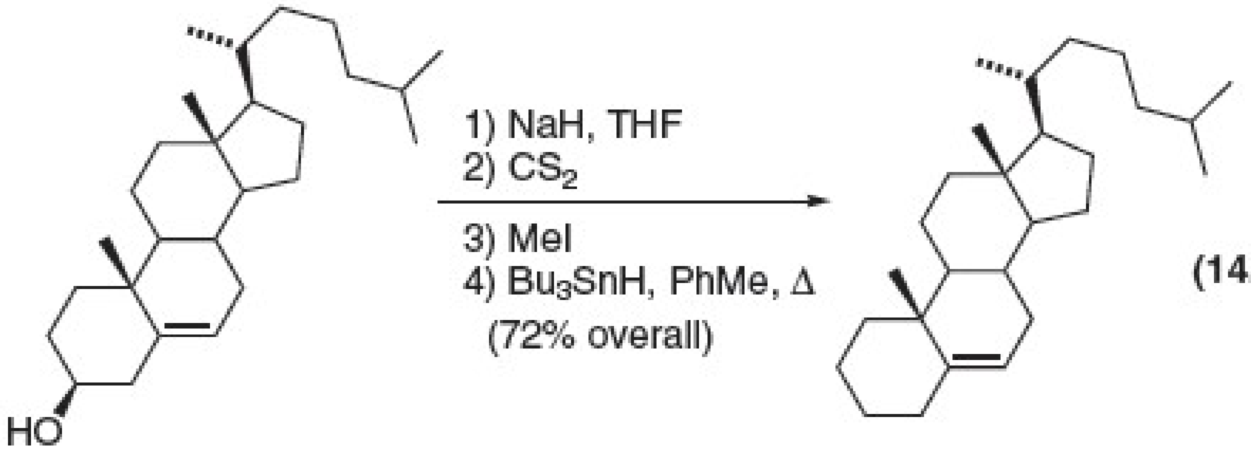


Stannane reduction of alkyl halides

Barton-McCombie reaction



(14.61)



(14.62)

alcohols are reduced to hydrocarbons through the xanthate ester

Figure 14.4

Frontier orbital overlap in addition of radicals (top) and cations (bottom) to alkenes

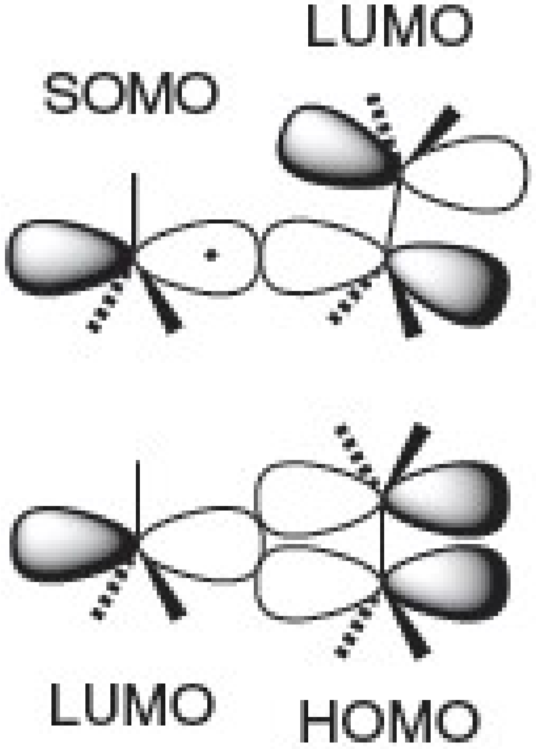
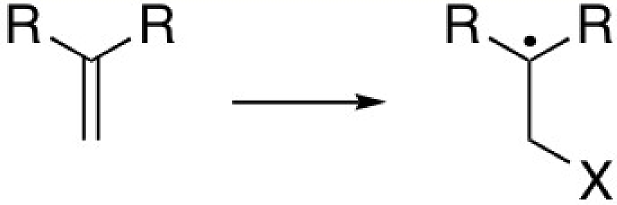
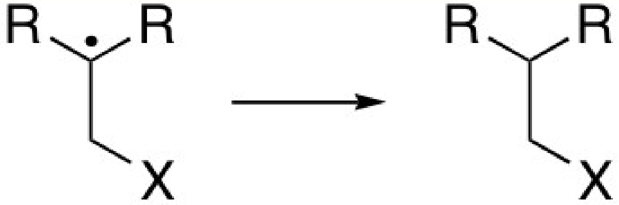


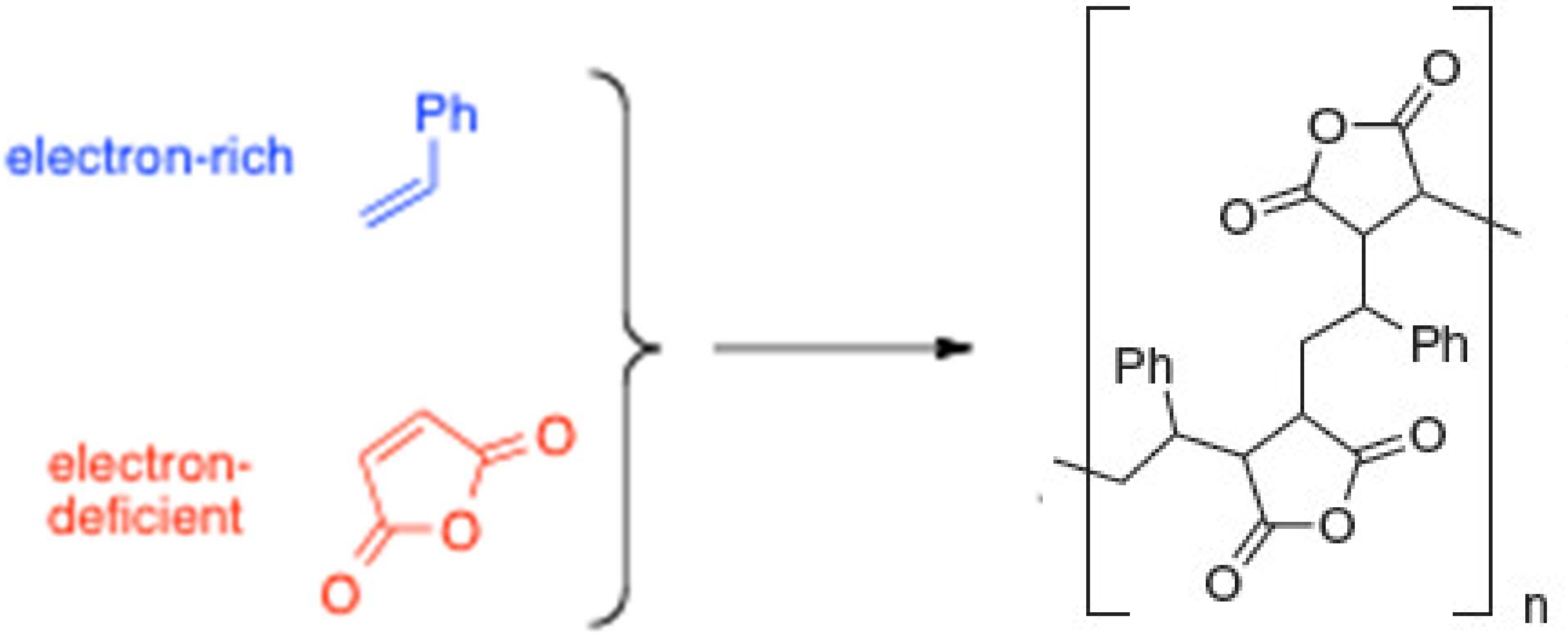
Table 14.3

Reaction enthalpies for free radical addition of HX to alkenes

HX		
HF	-46	+36
HCl	-17	+4
HBr	-3	-11
HI	+12	-27

addition to the alkene occurs with Markovnikov regiochemistry

Radical addition; polymers

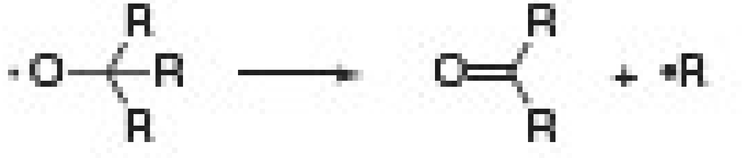


(14.65)

copolymerization of styrene and maleic anhydride gives a polymer where the two monomers alternate (i.e. the electron-deficient radical adds to the more electron-rich alkene, and vice-versa)

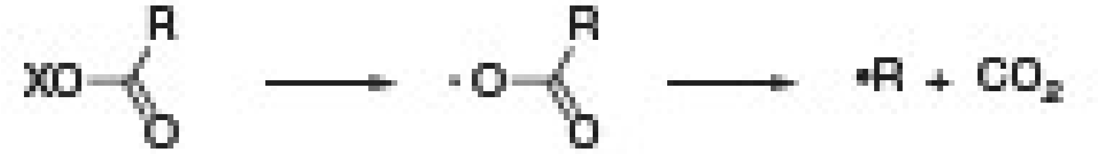
Radical fragmentation: Synopsis

(a) Alkoxy Radicals



Reagents: $(Me_3CO)_2$, etc.

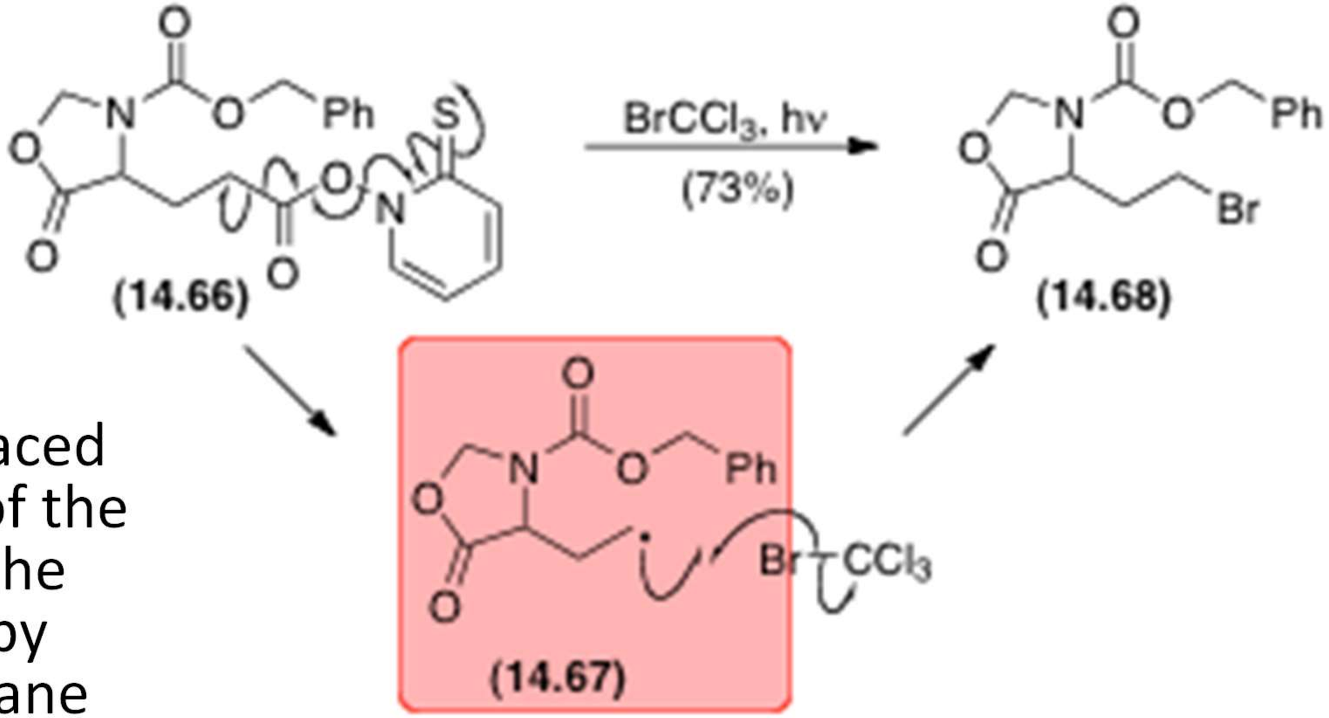
(b) Carboxy Radicals



X = Br, OCOR, OR, etc.

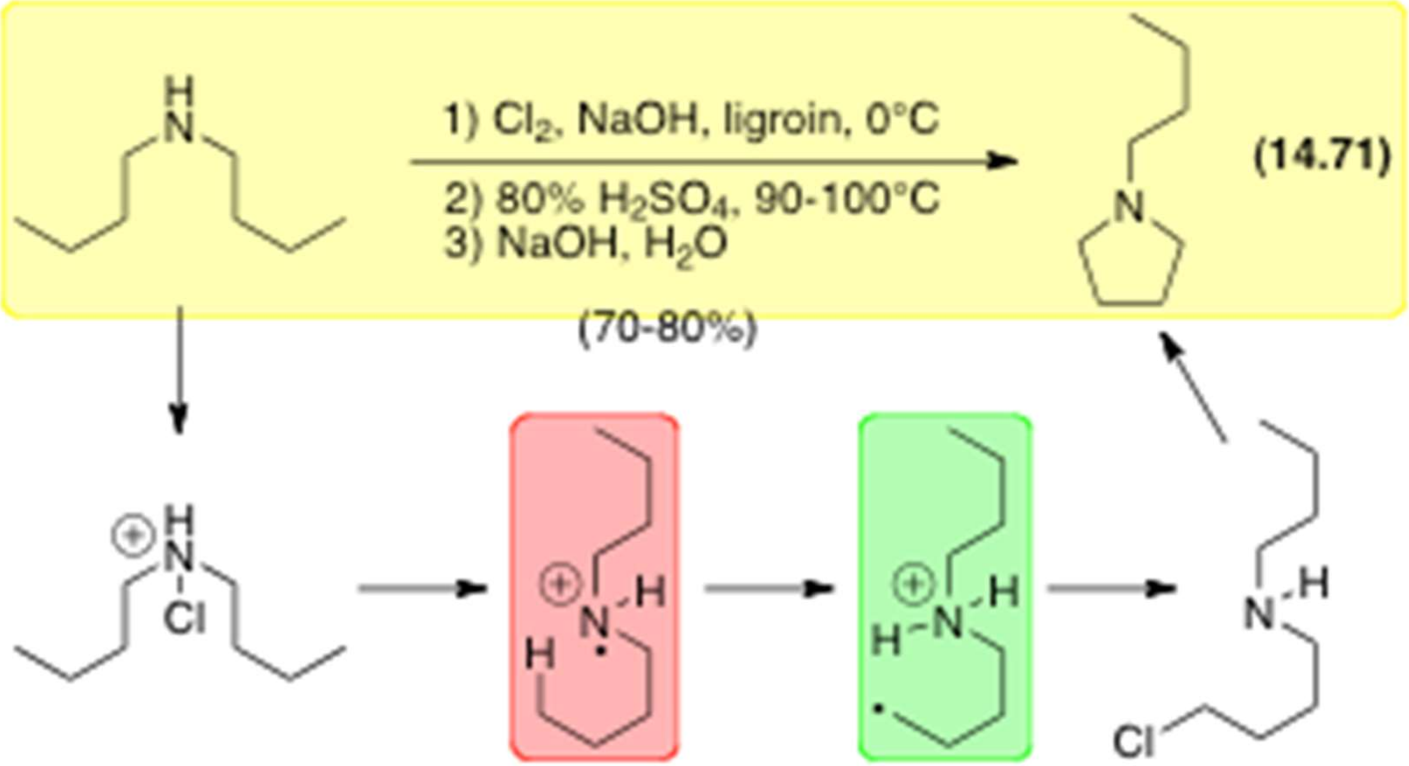
Reagents: RCO_2OR'; RCO_2Ag, Br_2; $(RCO_2)_2$; etc.

Barton modification of Borodin-Hunsdiecker reaction



The silver salt is replaced by the Barton ester of the carboxylic acid, and the bromine is replaced by bromotrichloromethane

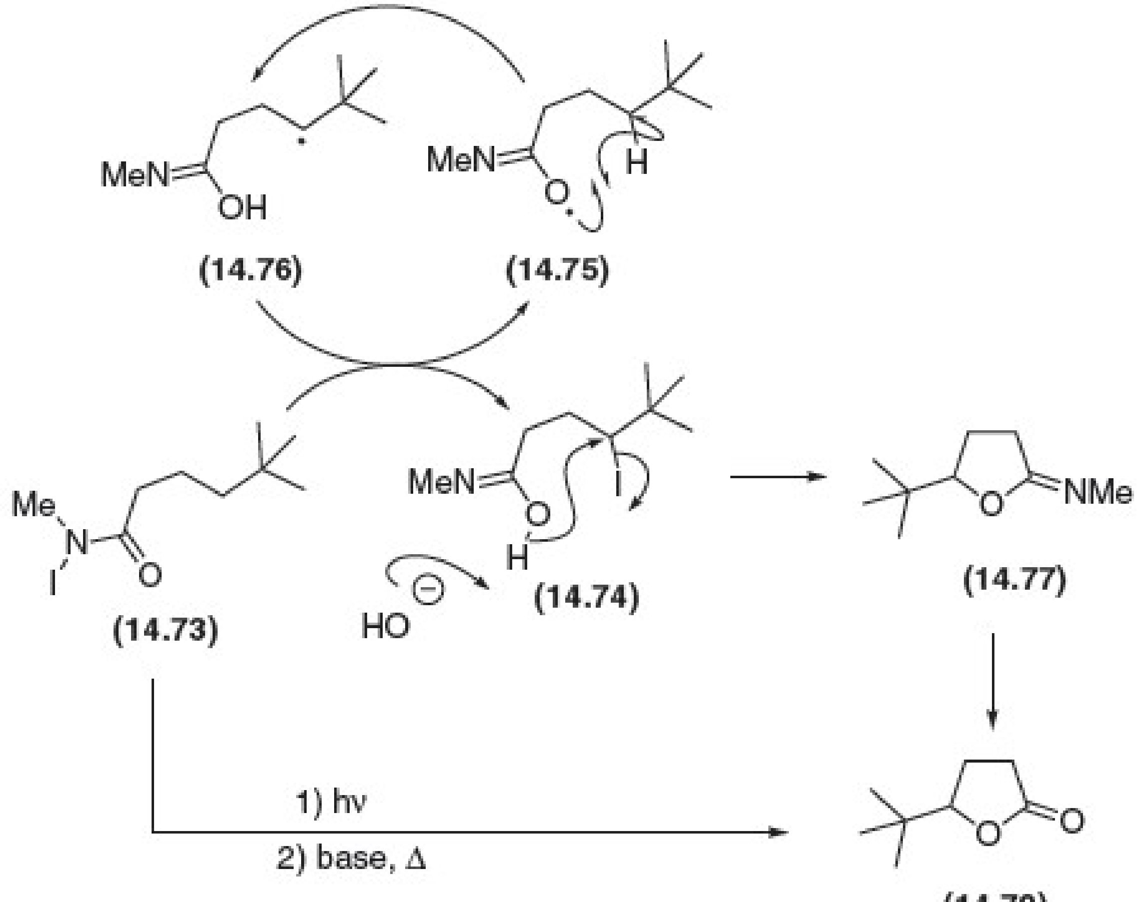
Hofmann-Löffler-Freytag reaction



The homolysis of the N—halogen bond leads to a radical that then abstracts a hydrogen atom from carbon through a six-membered transition state. Trapping of the radical with the halogen gives a δ-haloamine that can then be cyclized by base.

Figure 14.5

Synthesis of δ-haloamides and δ-lactones from *N*-haloamides



Radical coupling: the McMurry reaction

This titanium (III) promoted pinacol reaction gives increasing amounts of the *trans* (racemic) diol (**14.83**) with an increase in the size of the ring formed. The formation of the six-membered ring leads to the *cis* (*meso*) diol only.

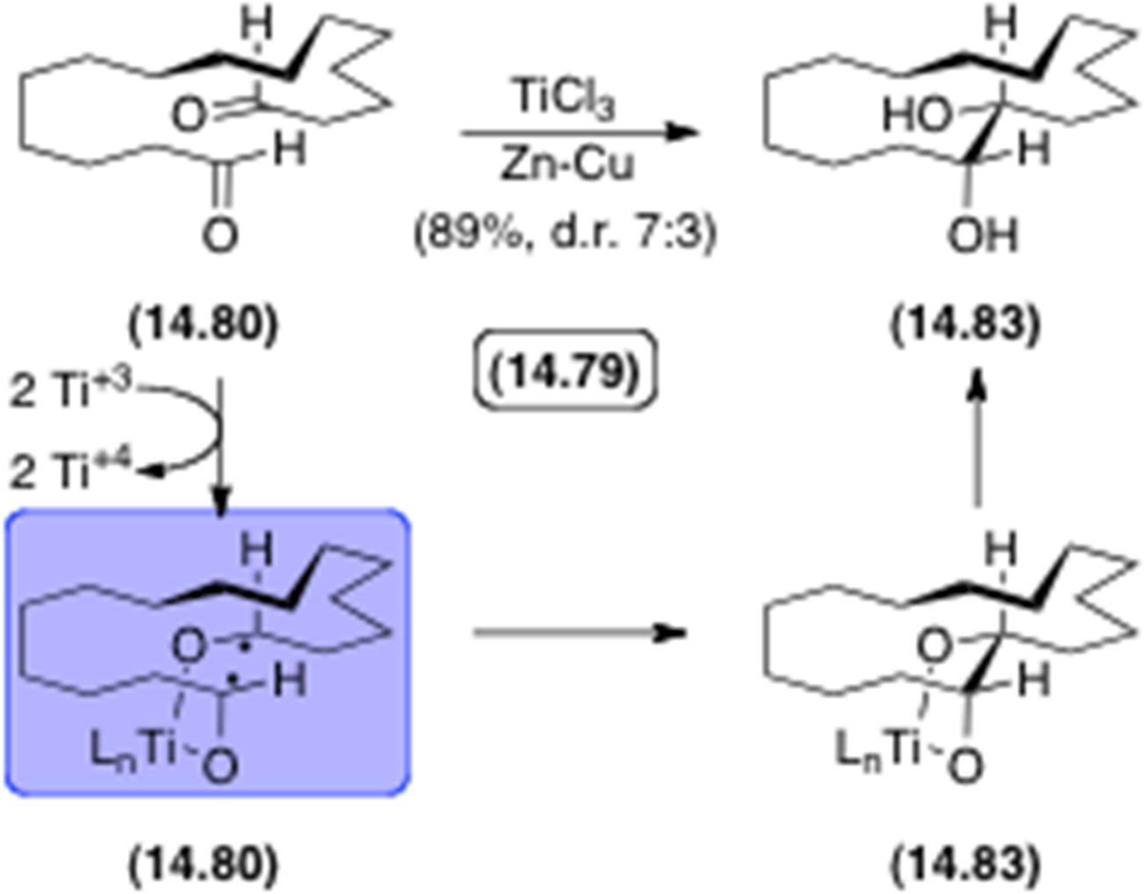


Figure 14.6

Proposed mechanism of the SmI_2-promoted pinacol reaction that accounts for the observed stereochemistry of the reaction.

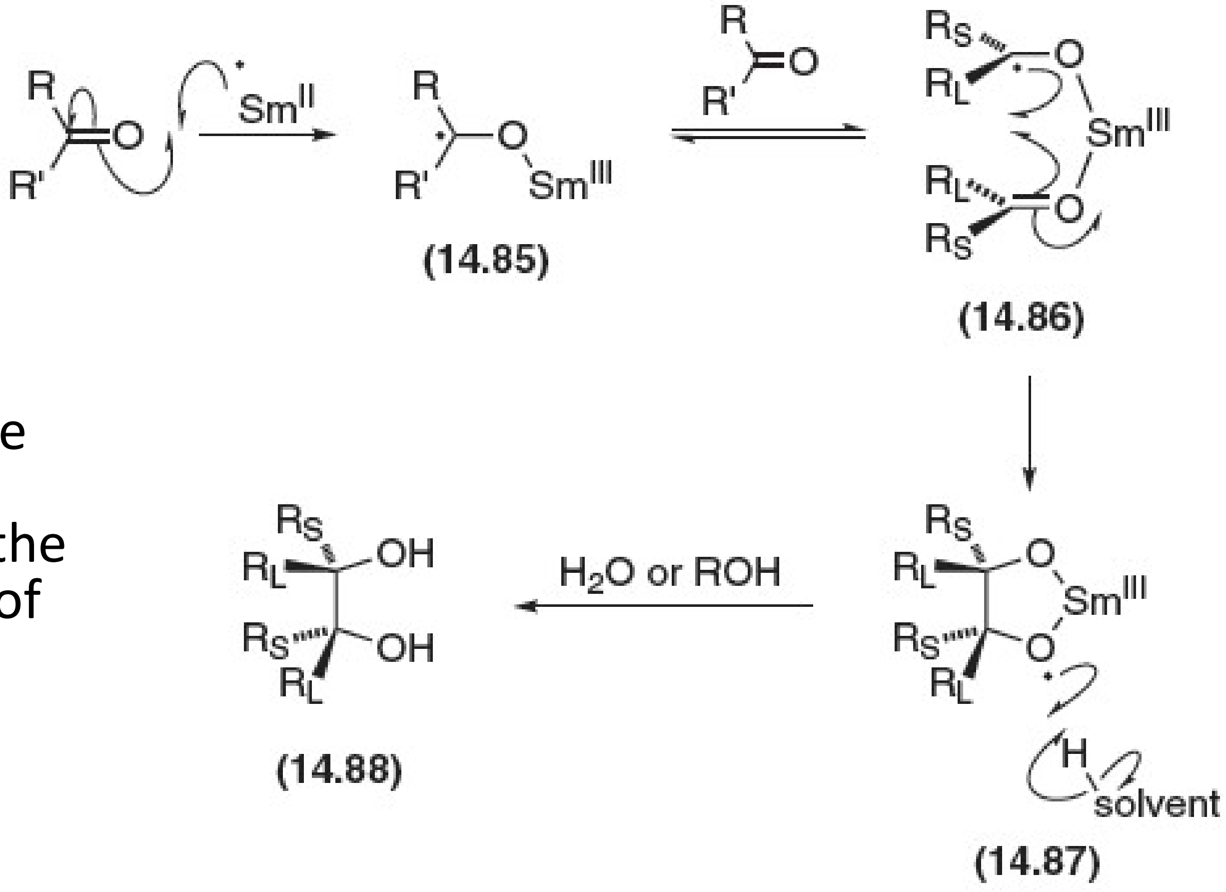
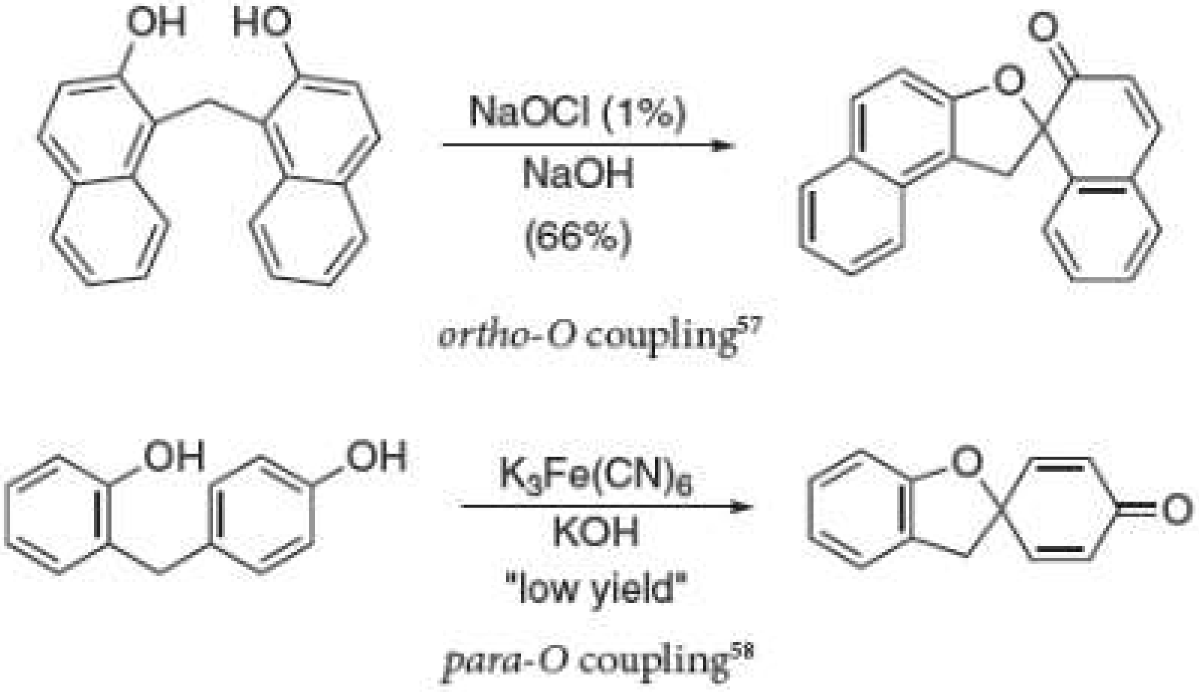


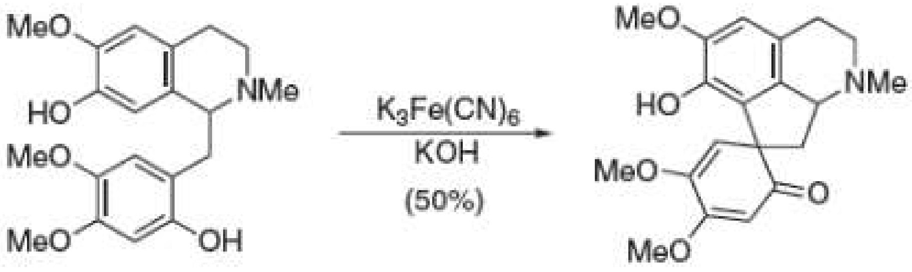
Figure 14.7 A



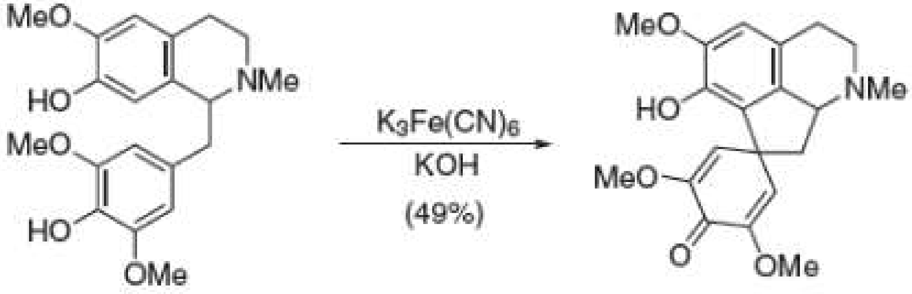
Regioisomeric products that can be formed by free radical coupling of phenols with one ring coupling through the oxygen atom

Figure 14.7 B

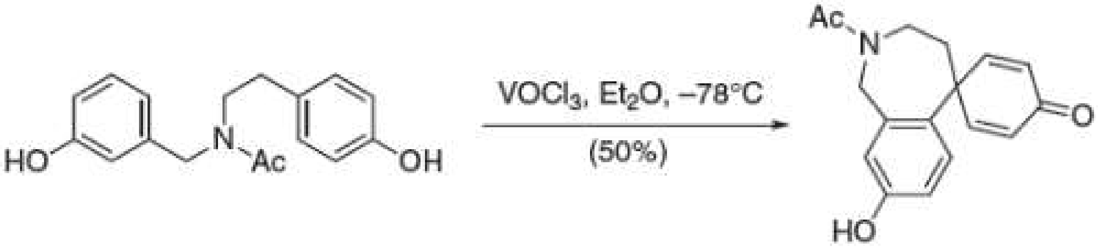
Regioisomeric products that can be formed by free radical coupling of phenols through the ring carbon atoms



ortho-ortho coupling[59]



ortho-para coupling[60]



para-para coupling[61]

Borodin-Hunsdiecker reaction: Synopsis

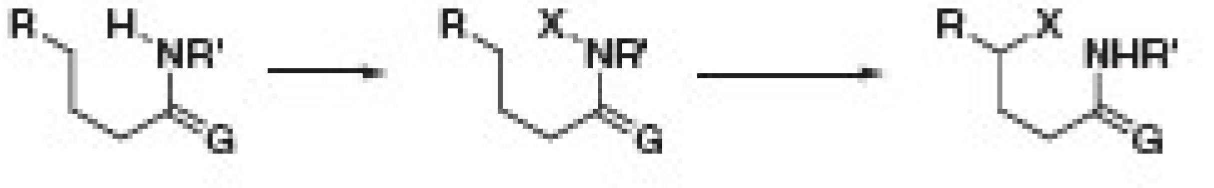
Reagents: Ag_2O, Br_2, Δ; etc.

or 1) $(COCl)_2$; 2) $Na^+ \, ^-ONC_5H_4S$; 3) CCl_3Br or CCl_4, Δ;

or $Pb(OAc)_4$, I_2, hν;

or *t*-BuOI, hν.

Hofmann-Löffler-Freytag and related reactions: Synopsis



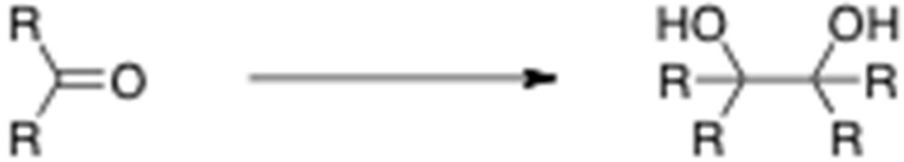
$G=H_2$, O; X=Cl, Br, I

Reagents:

$G=H_2$: 1) Cl_2, NaOH; 2) H_2SO_4, Δ; or
1) Cl_2, NaOH; 2) CF_3CO_2H, hν; or
1) NCS, Et_2O; 2) CF_3CO_2H, hν; etc.

G=O: I_2, $Pb(OAc)_4$, CCl_4, Δ or hν; or
t-BuOI, PhH, hν

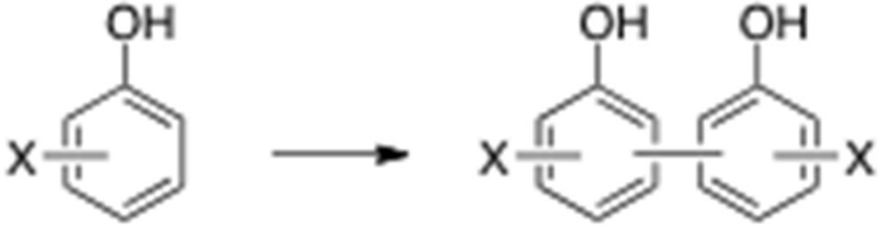
Pinacol and McMurry reactions: Synopsis



Reagents: Mg(Hg), Et_2O; or
$TiCl_3$, Zn-Cu, THF; or
SmI_2, THF

Stereochemistry: *meso* isomer favored in cyclizations that give small (≤6 members) rings; *dl* isomer is favored from open-chain compounds and in cyclizations that give large rings

Oxidative coupling of phenols: Synopsis



Reagents:

- Fe (III): $K_3Fe(CN)_6$/KOH; $FeCl_3$/*m*-CPBA; $Fe(ClO_4)_3$; etc.
- V (V): $VOCl_3/Et_2O$; VOF_3/CH_2Cl_2; etc.
- Pb (IV): $Pb(OAc)_4$/AcOH; etc.
- Mn (IV): MnO_2/CF_3CO_2H; MnO_2, MsOH; etc.
- other: NaOCl/NaOH; etc.

Adition of radicals to alkenes

Addition always occurs with Markovnikov regiochemistry. The synthesis of a key intermediate in this synthesis of a pyrethroid insecticide is accomplished by free radical addition of CCl_4 to an alkene.

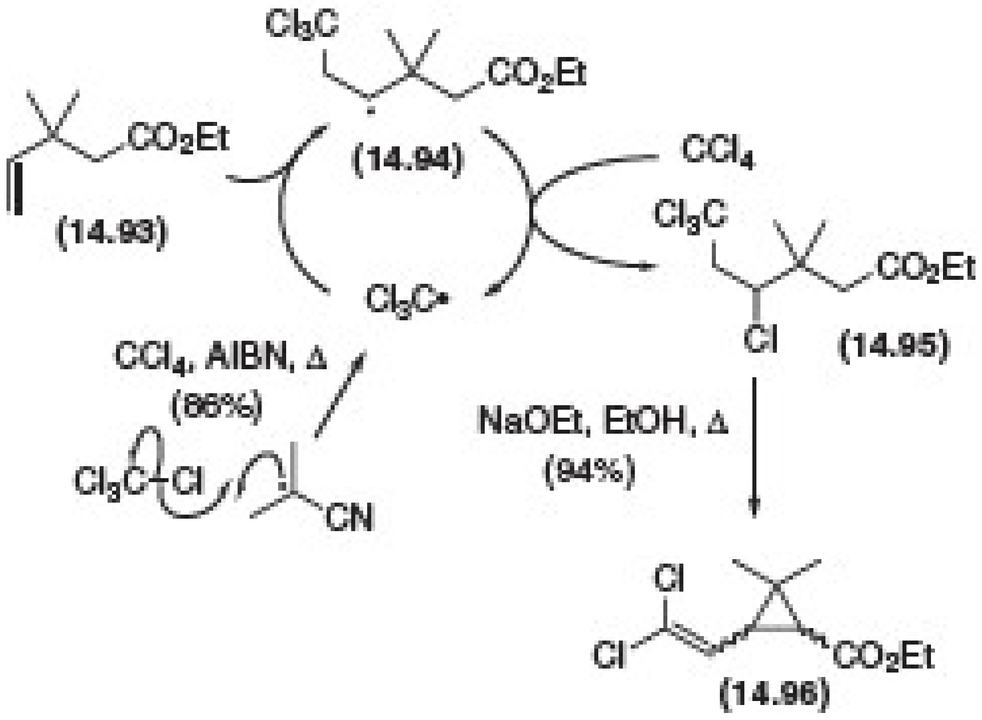
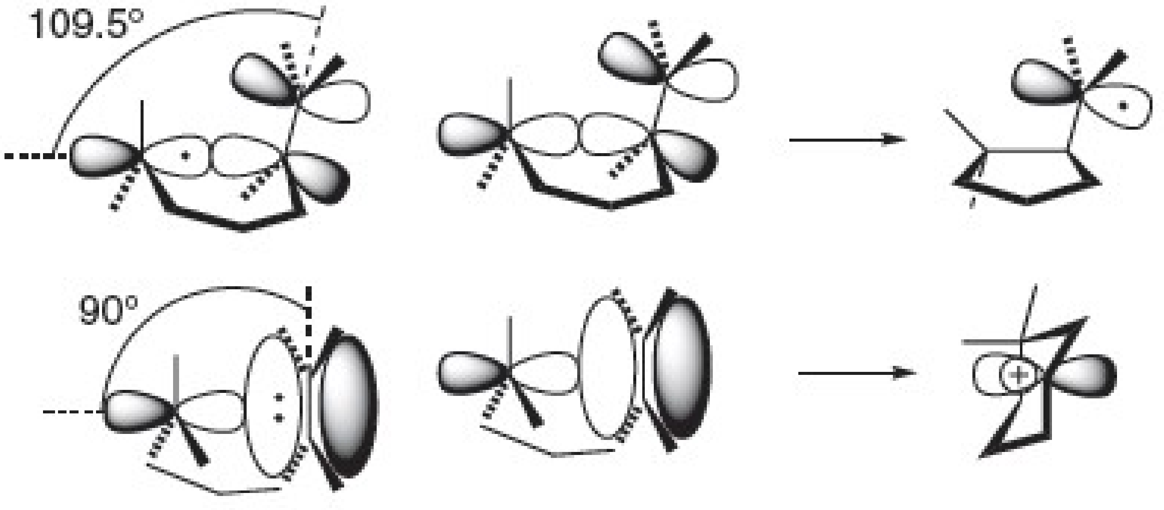


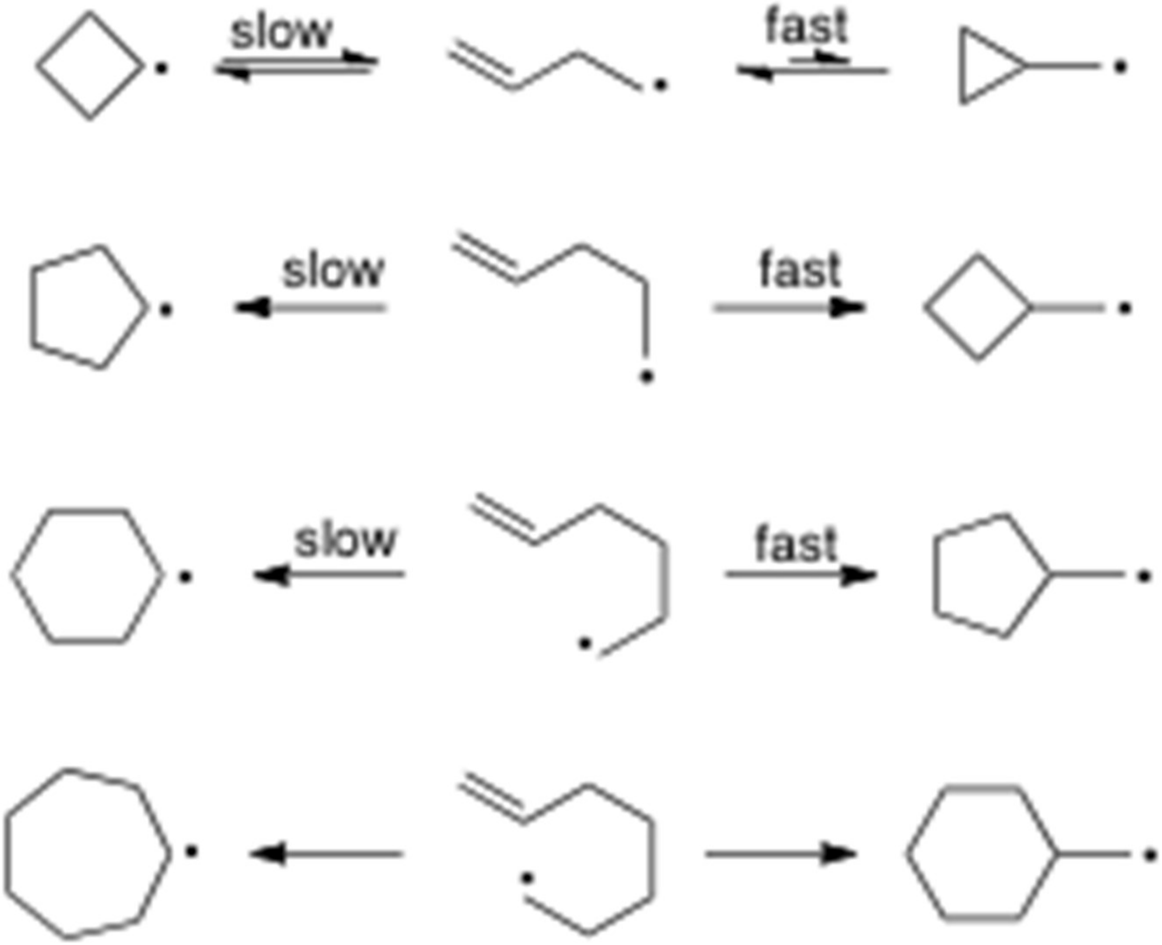
Figure 14.8



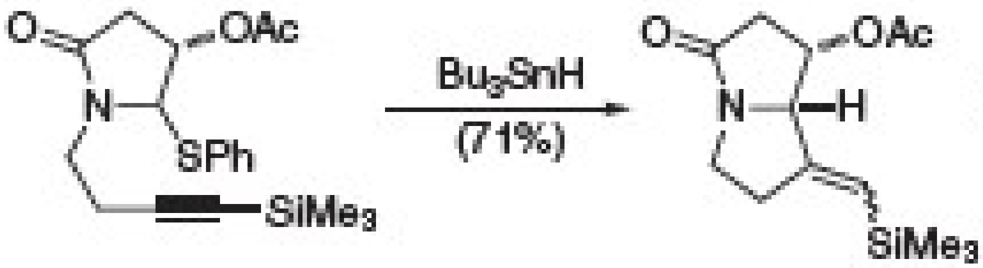
The cyclization of a free radical requires a different set of orbitals, and so leads to a different product from carbocation cyclization.

Cyclizations

Cyclizations to small- to medium-size rings are under stereoelectronic control that leads to the primary radical formed by the *exo* mode being the kinetically favored product.

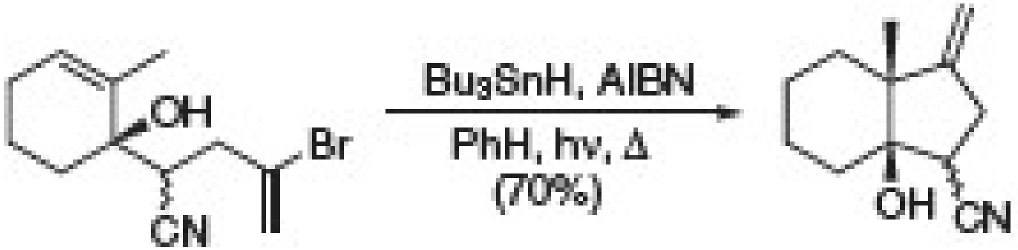


Radical cyclizations to give small rings



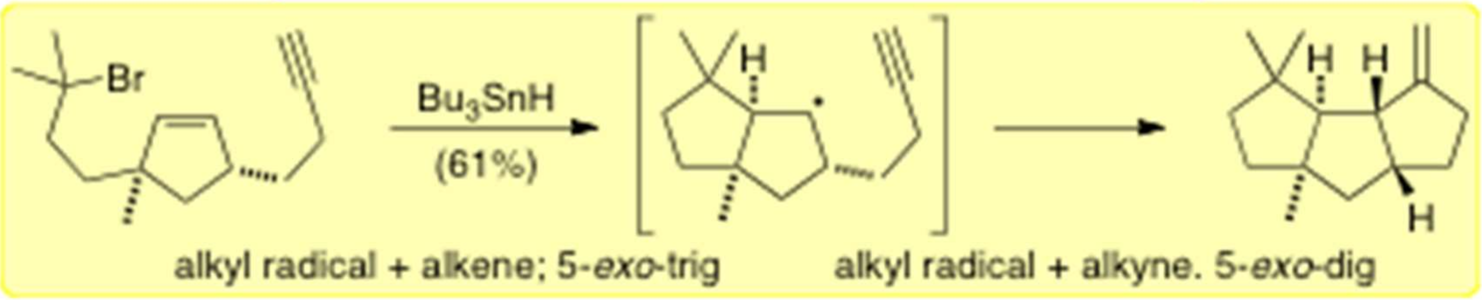
(14.100)[73]

alkyl radical + alkyne; 5-*exo*-dig



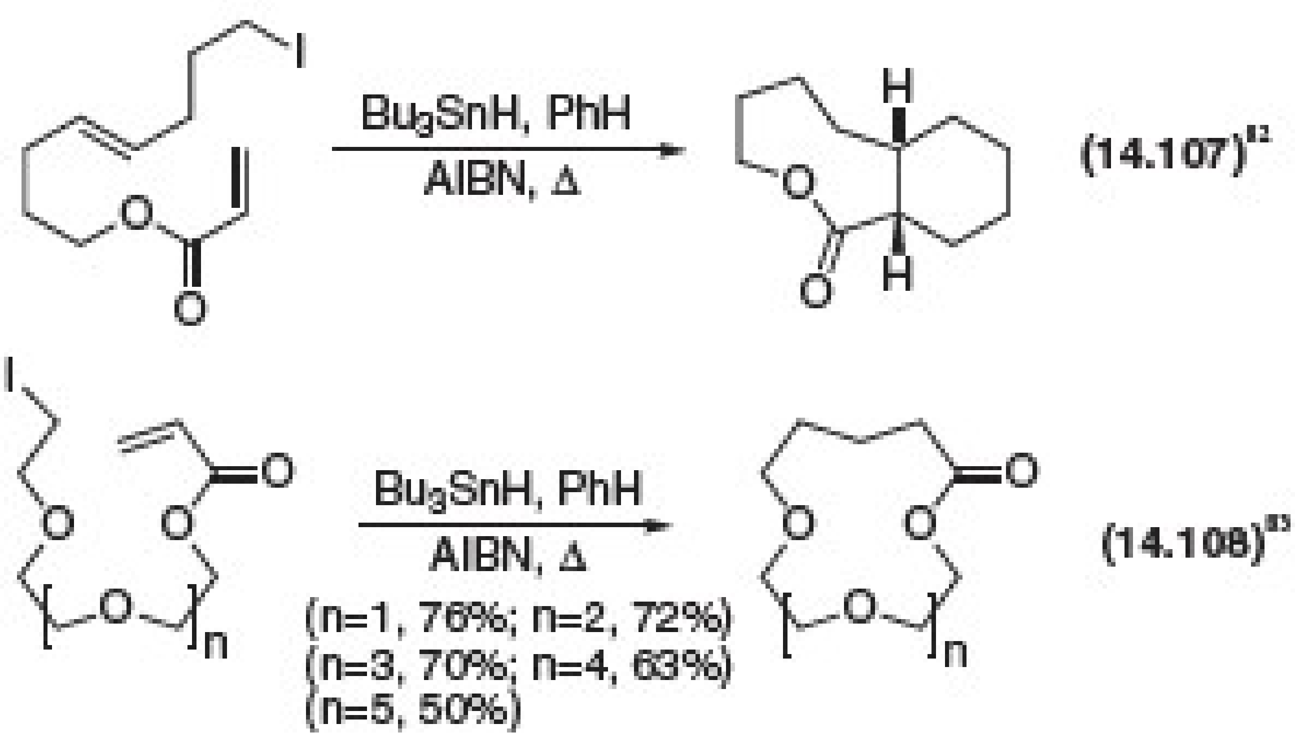
(14.101)[73]

vinyl radical + alkene; 4-*exo*-trig



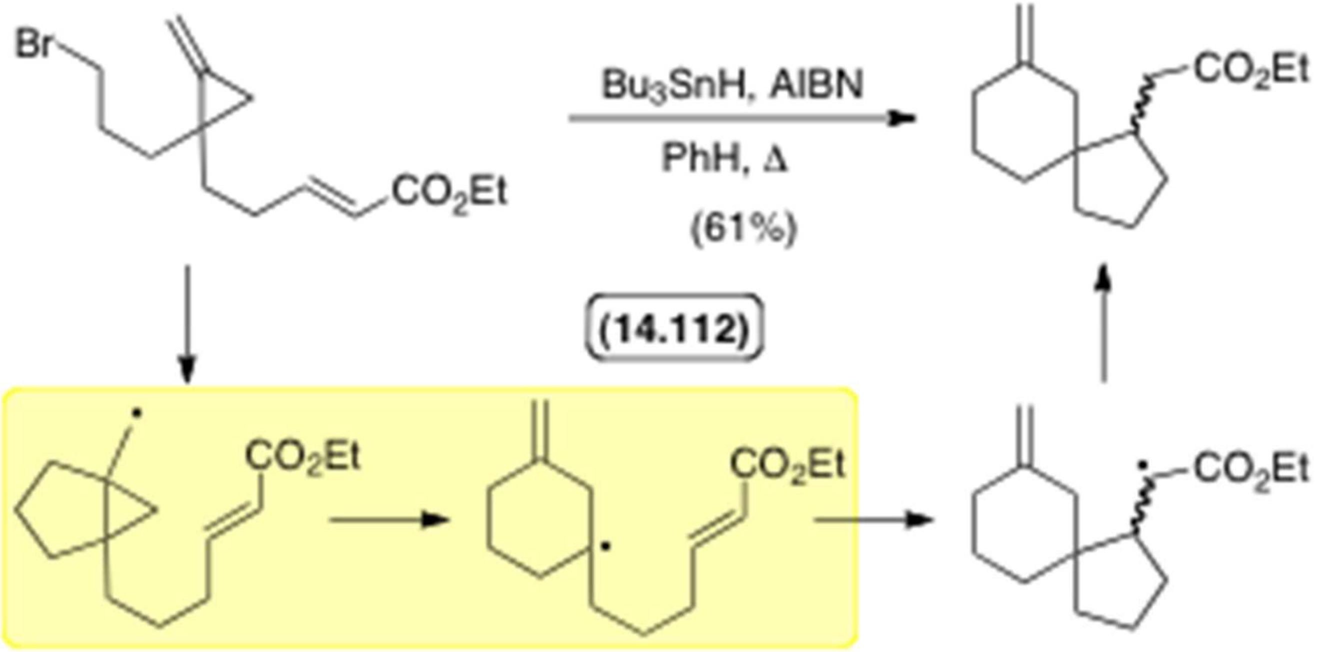
These cyclizations all occur under stereoelectronic control to form cyclopentane-based products in the 5-*exo* mode instead of cyclohexane-based products by the 5-*endo* mode

Radical cyclizations to give medium and large rings



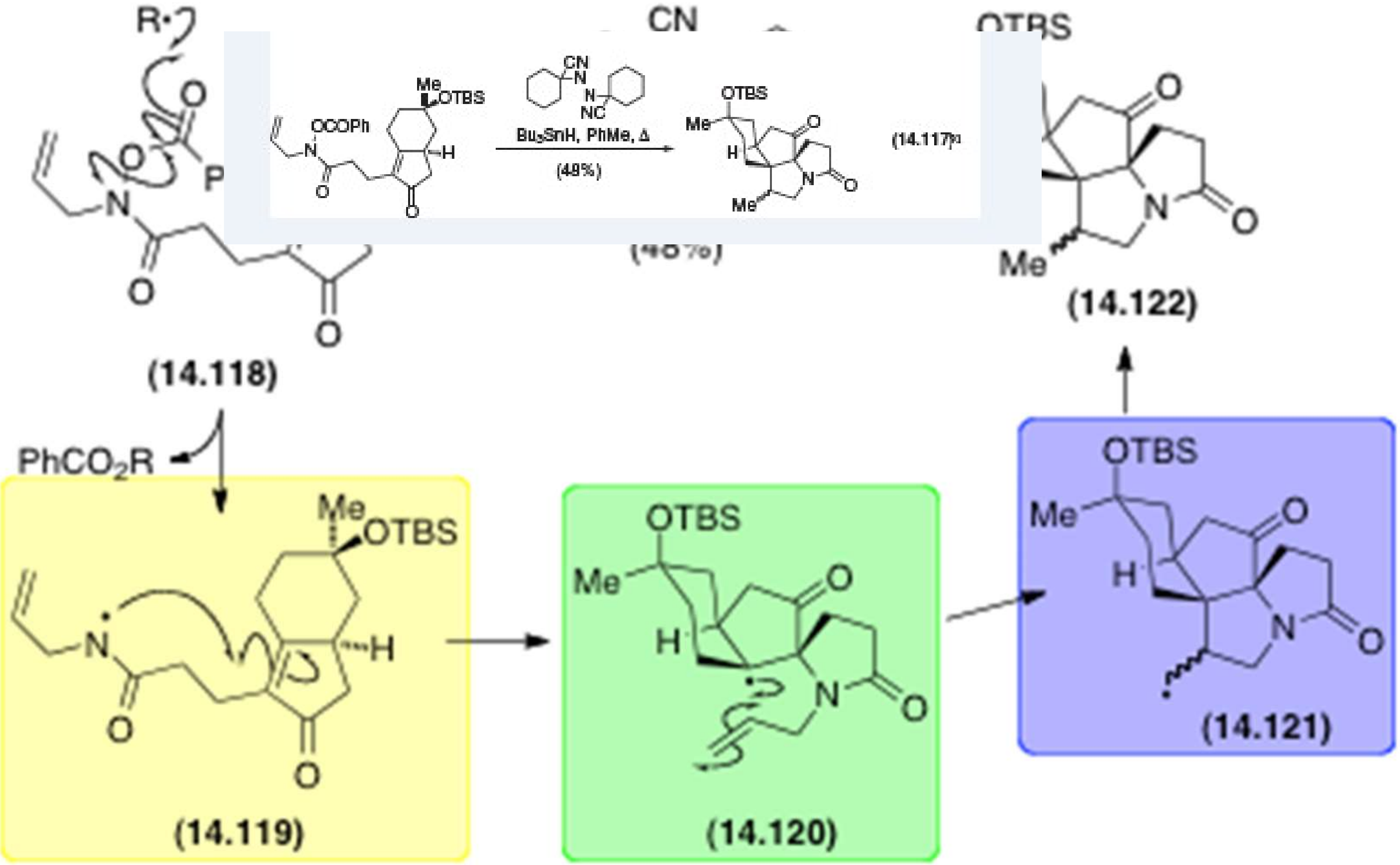
These cyclizations all occur kinetically in the *n-endo* mode to give the macrocyclic products (and the more stable secondary radical intermediates)

Using radical ring opening in synthesis



the formation of a cyclopropylcarbinyl radical by one addition can permit the formation of cyclohexyl radicals by ring opening in the following step

Cascade cyclizations with free radicals



This radical cascade reaction involves three sequential radical cyclizations

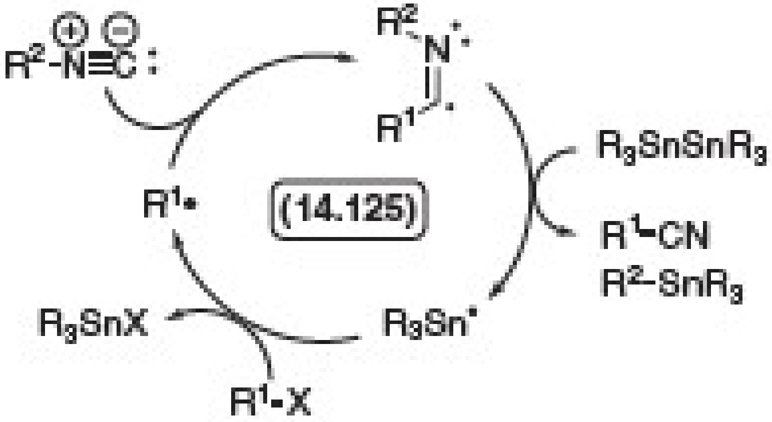
Carbon monoxide and alkyl isocyanides

(14.123)

(14.124)

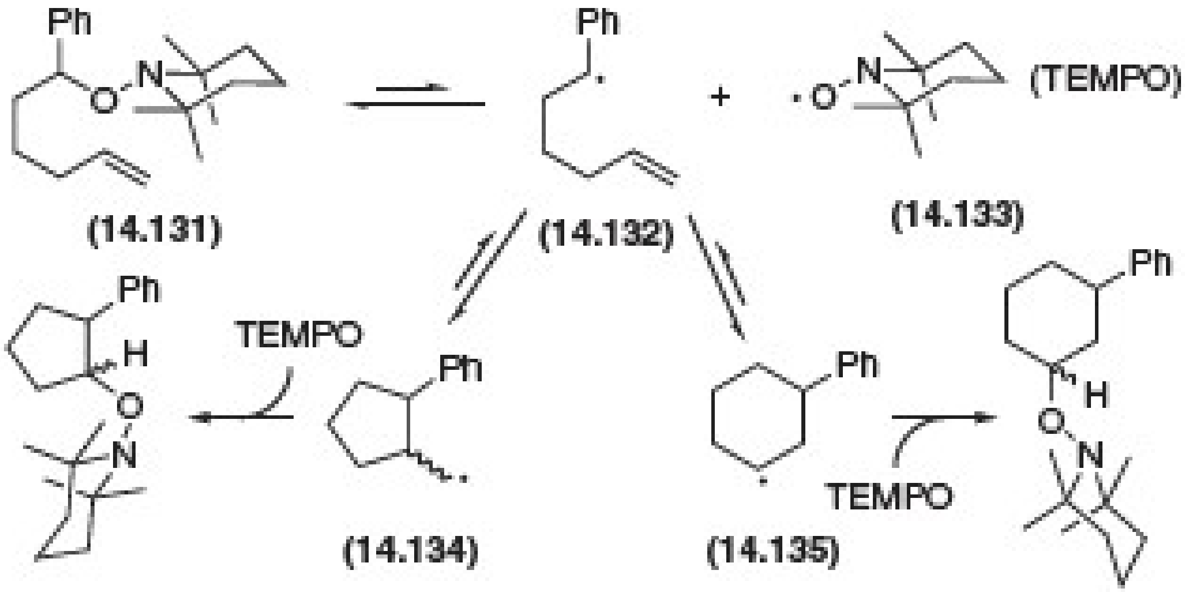
Carbon monoxide and alkyl isocyanides are bipolar molecules that have two carbenoid canonical forms that can react with free radicals

Cyanation of free radicals



Addition of the radical to the isocyanide gives an iminyl radical that then loses the alkyl group from nitrogen to generate the nitrile product

Persistent radical effect



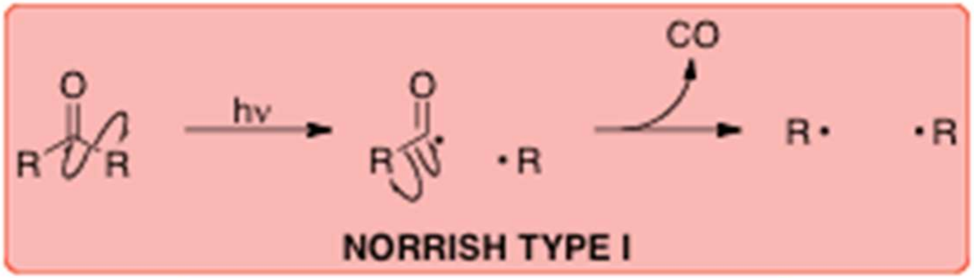
Stable (persistent) radicals do not self-couple, so they form only cross-coupled products

Norrish photochemical reactions through diradicals

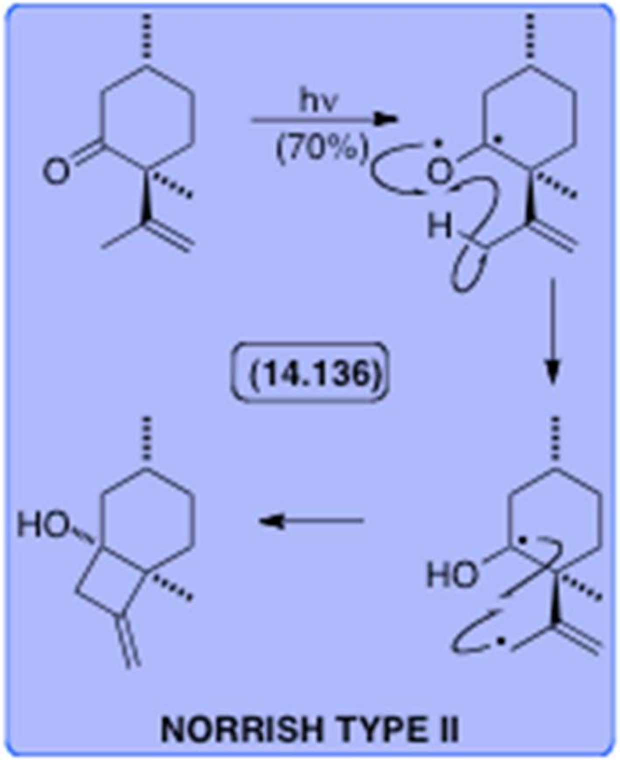
Both fragmentations proceed through the photochemically excited state of the ketone, which is a diradical.

The Norrish Type I reaction results in cleavage of the excited state an alkyl and an acyl radical, followed by decarbonylation of the acyl radical to give two separate radicals.

The Norrish Type II reaction results in intramolecular hydrogen atom transfer from carbon to oxygen in the excited state of the ketone, and subsequent collapse of the resultant diradical to the cyclobutanol

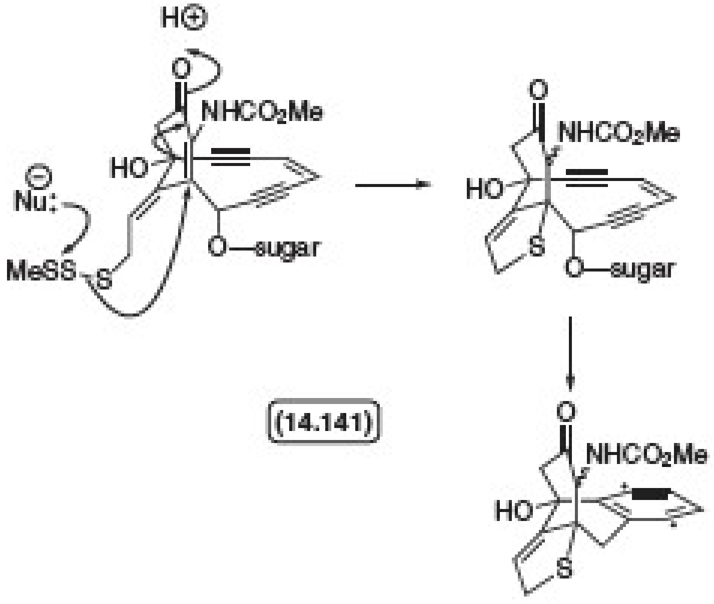


NORRISH TYPE I



NORRISH TYPE II

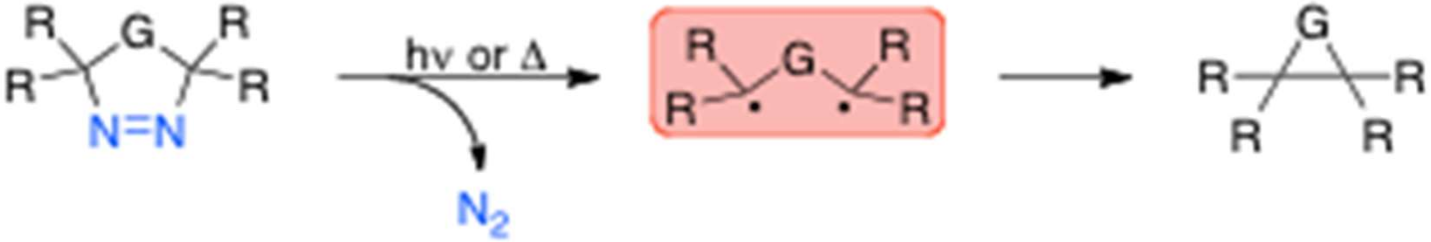
Bergman cycloaromatization

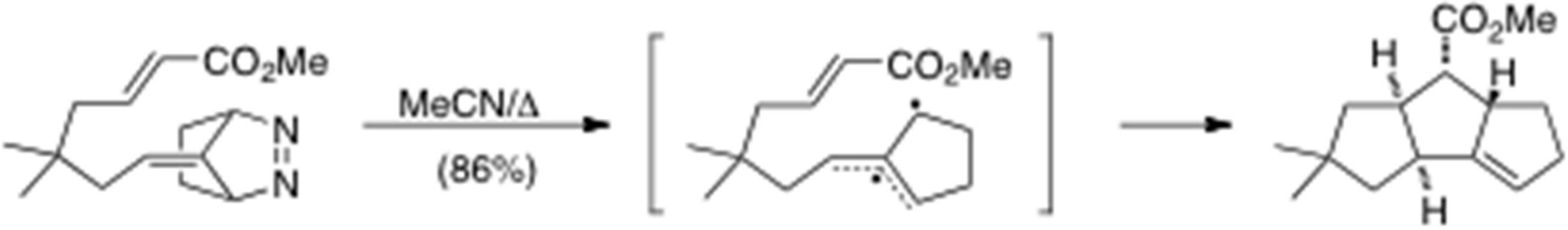


(14.141)

The *cis*-enediyne undergoes ring closure to a benzene-1,4-diyl (a *p*-benzyne) when the two ends of the system are close enough together.

Homolysis of cyclic azo compounds





Homolysis of cyclic azo compounds gives a diradical that can cyclize, or react with an intramolecular alkene or alkyne