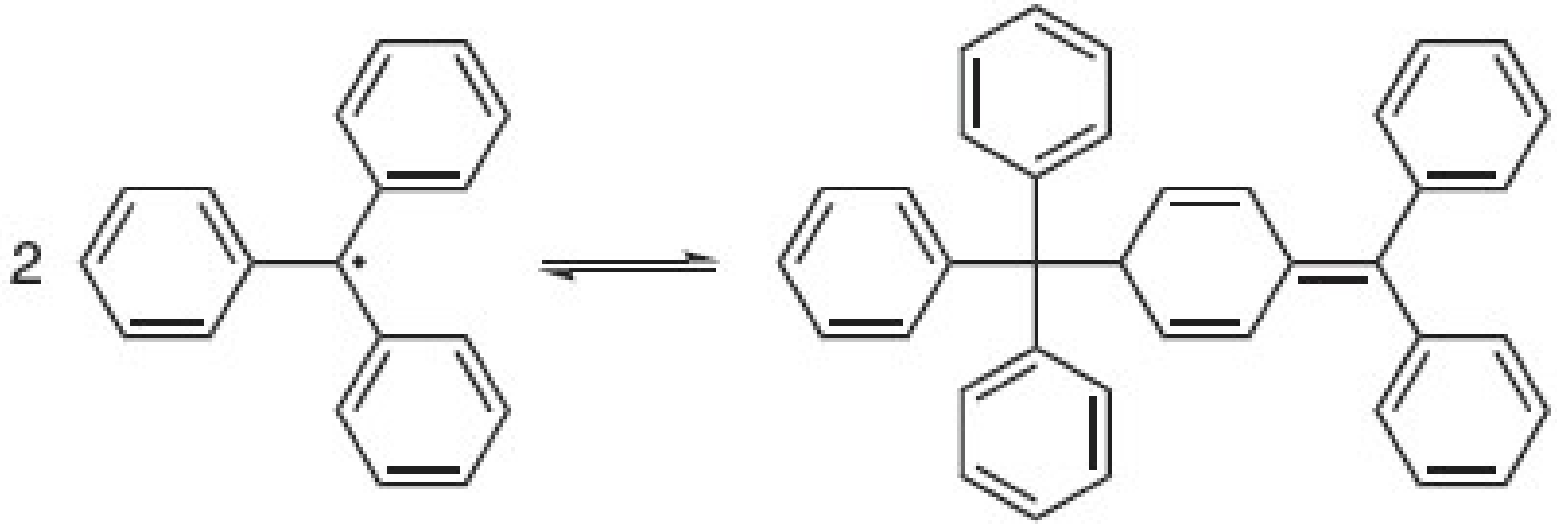
Chapter 13

Free Radicals, Carbenes, Arynes, and Nitrenes

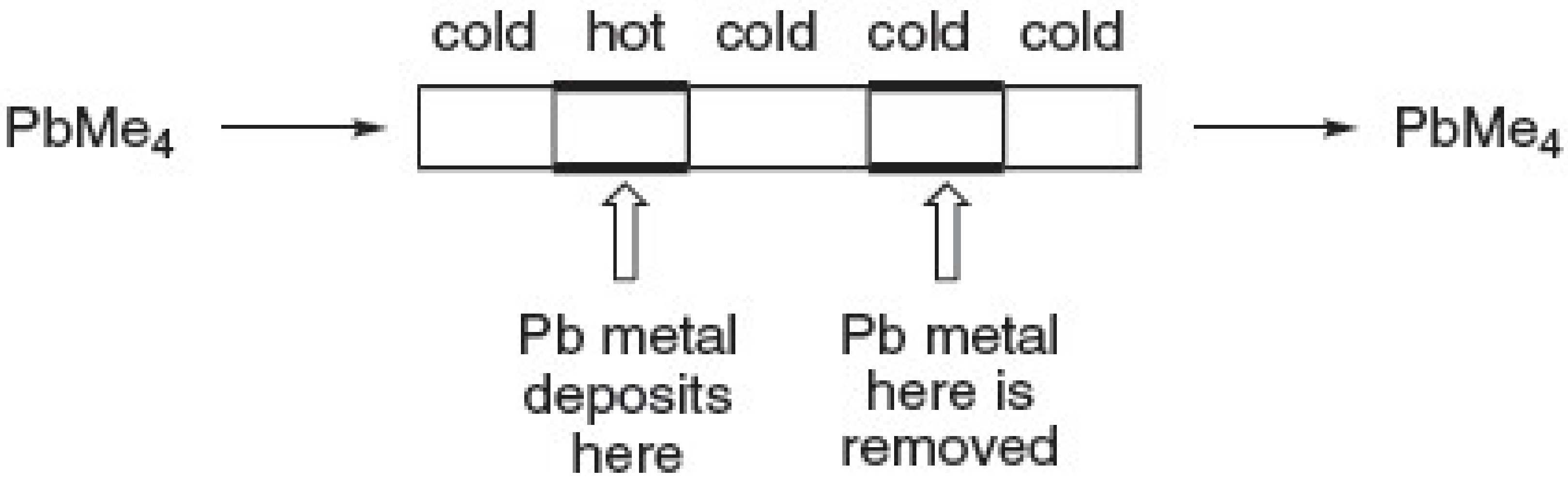
The Gomberg discovery



(13.1)

Gomberg discovered trip[henylmethyl during an attempt to prepare hexaphenylethane. The correct structure for the dimer was not in initially assigned.

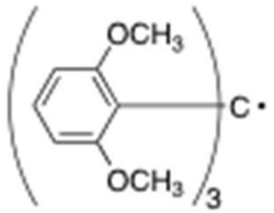
Figure 13.1



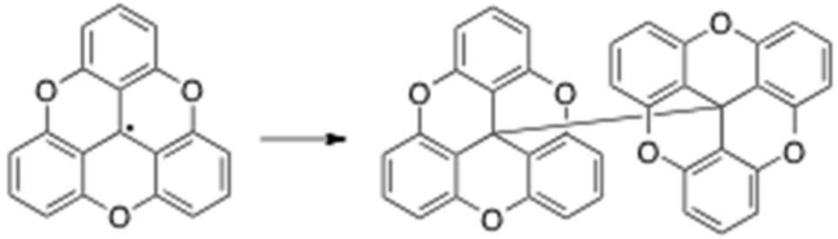
The Paneth and Hofeditz experiment to demonstrate the existence of free radicals. The tetramethyllead is decomposed thermally and deposits lead metal in the front part of the apparatus. Lead metal in the cold region of the tube downstream is gradually removed by the radicals in the effluent gas.

Stability and shape of free radicals

Radical **13.2** is completely unassociated; radical **13.3** dimerizes completely



(13.2)

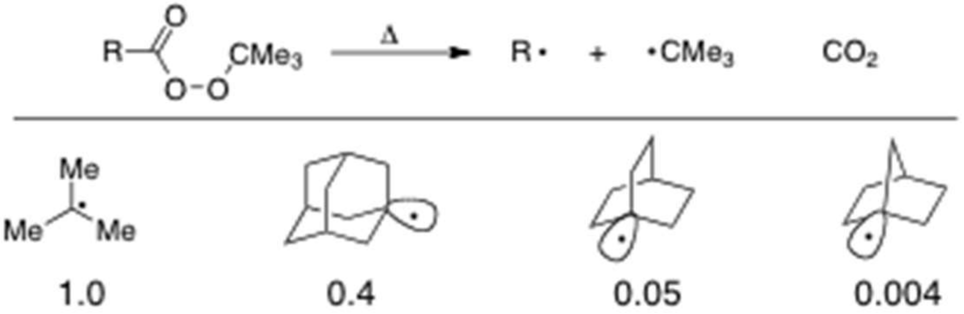


(13.3)

Radical **13.4** is shows that radicals do not have to be planar

(13.4)

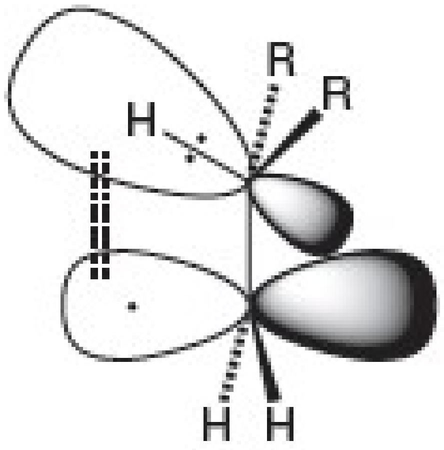
These radicals show that the rate of formation of free radicals decreases as the radical devayes further from planarity



(13.5)

Table 13.1

Dissociation energies[a] of C–H Bonds in hydrocarbons



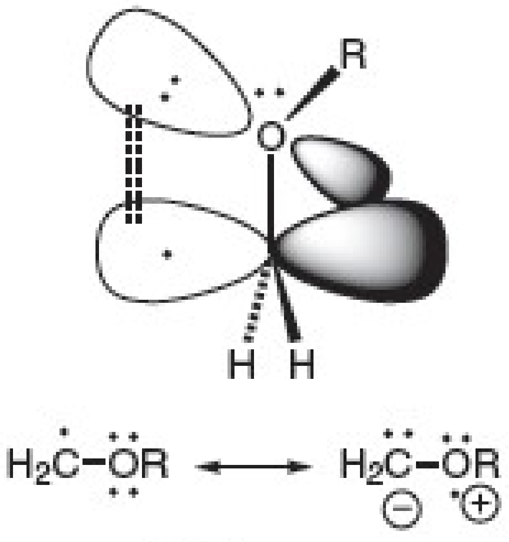
(13.6)

Stabilization by hyperconjugation

Bond	(kcal mol^{Gl})	(kJ mol^{Gl})
C_6H_5Ñ H	110^b	461^b
H_2C=CHÑ H	^{3}108 ^{b}	^{3}452 ^{b}
H_3CÑ H	104	435
$(CH_2)_2$CHÑ H	101	421
RCH_2Ñ H	98	410
R_2CHÑ H^c	95	398
R_3CÑ H	92	385
H_2C=CHĞCH_2Ñ H	89	372
H_2C=CHĞCH(R)Ñ H	83	347
$C_6H_5CH_2$Ñ H	85	356

[a] Experimental error in values is ±1 kcal mol^{-1} (±4 kJ mo^{-1}). [b] ±2 kcal mol^{-1} (±8 kJ mol^{-1}).
[c] Includes cyclopentyl and cyclohexyl groups.

Figure 13.2



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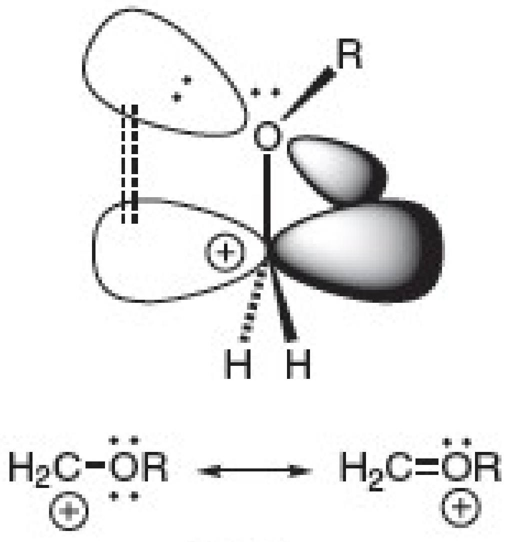
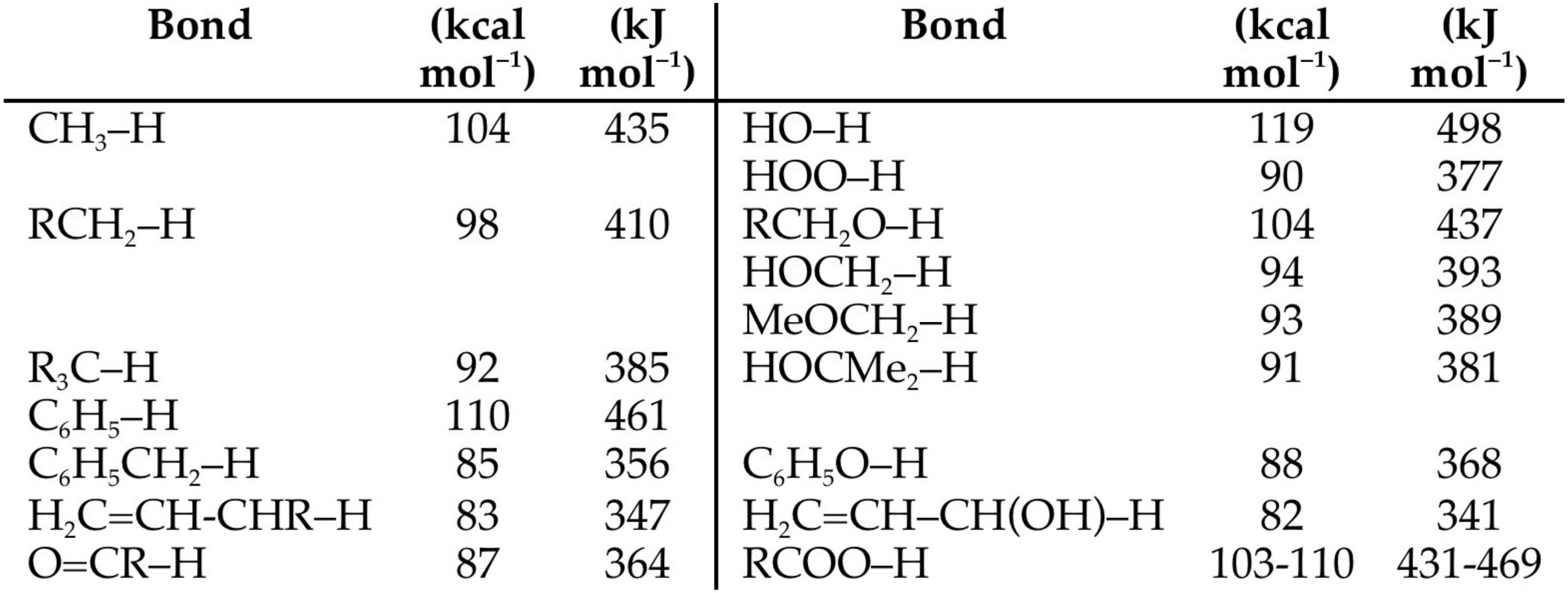


(13.8)

Comparison between the stabilization of a free radical by an adjacent oxygen atom (left) and the stabilization of a carbocation by an adjacent oxygen atom (right). Both involve delocalization of electron density from oxygen to carbon.

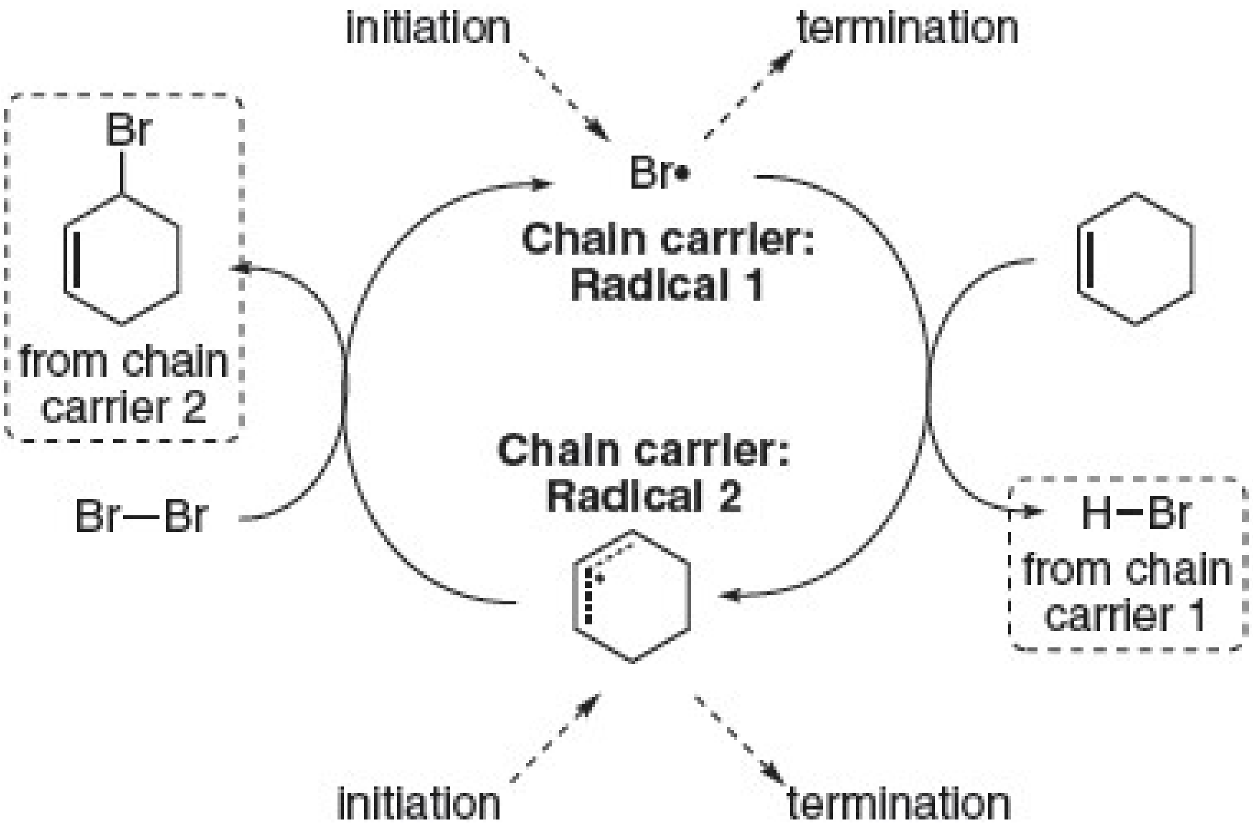
Table 13.2

Bond dissociation energies of O—H and C—H bonds in organic compounds



Bond	**(kcal mol^{-1})**	**(kJ mol^{-1})**	**Bond**	**(kcal mol^{-1})**	**(kJ mol^{-1})**
CH_3–H	104	435	HO–H	119	498
			HOO–H	90	377
RCH_2–H	98	410	RCH_2O–H	104	437
			$HOCH_2$–H	94	393
			$MeOCH_2$–H	93	389
R_3C–H	92	385	$HOCMe_2$–H	91	381
C_6H_5–H	110	461			
$C_6H_5CH_2$–H	85	356	C_6H_5O–H	88	368
H_2C=CH-CHR–H	83	347	H_2C=CH–CH(OH)–H	82	341
O=CR–H	87	364	RCOO–H	103-110	431-469

Figure 13.3



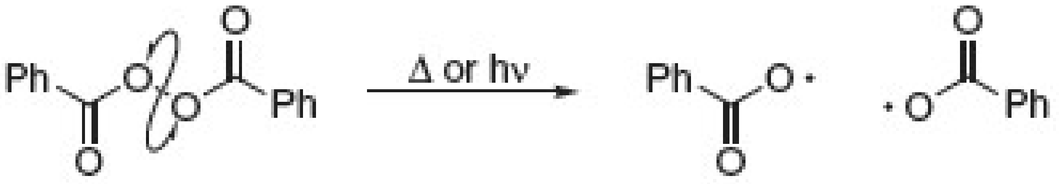
Cycle diagram for the free radical bromination of cyclohexene

Note how the two brominated products (HBr, RBr) are formed from different bromine molecules

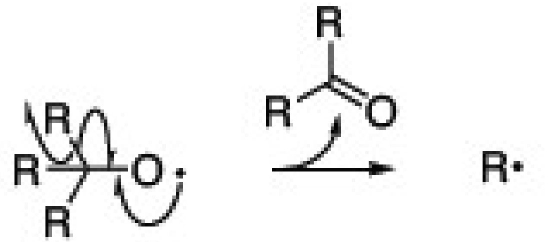
Initiation of free radical reactions


AIBN

(13.10)


benzoyl peroxide

(13.11)



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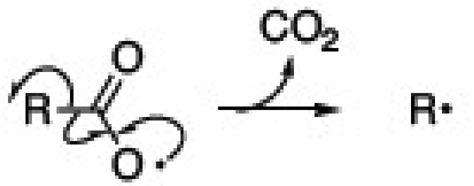
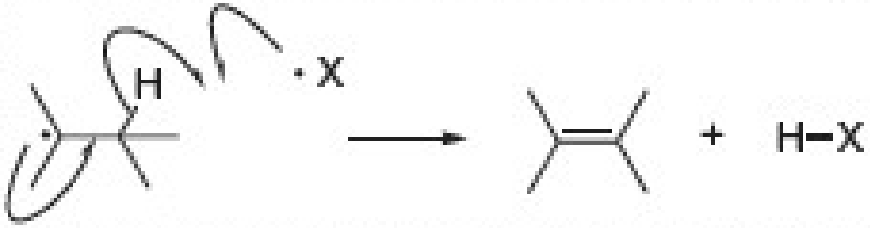


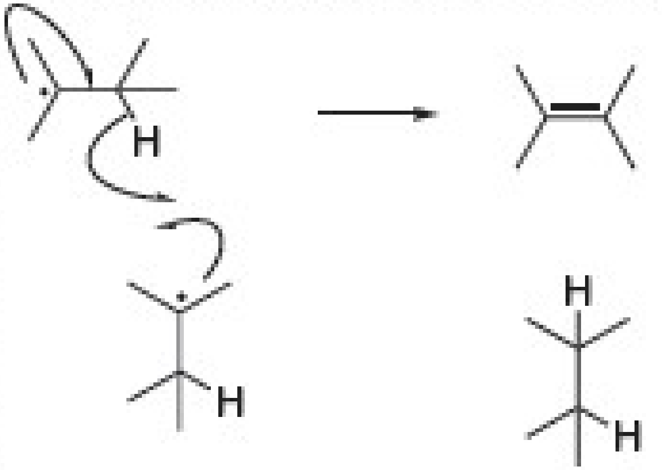
(13.13)

Termination steps

Atom transfer



(13.15)



(13.16)

Radical recombination

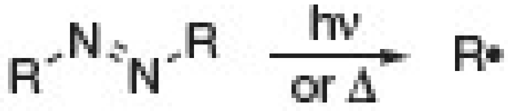
$$R\bullet + R\bullet \longrightarrow R{-}R$$

$$R\bullet + X\bullet \longrightarrow R{-}X$$

$$X\bullet + X\bullet \longrightarrow X{-}X$$

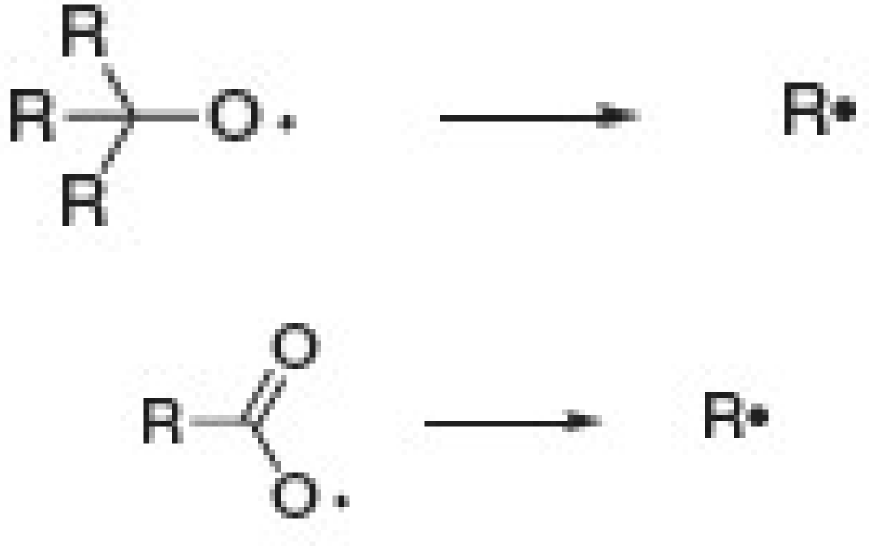
(13.14)

Methods for generating free radicals: Synopsis



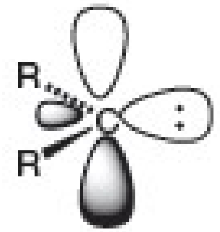
- Peroxide initiators: $(PhCO_2)_2$; $Me_3CO—OH$; H_2O_2, Fe^{2+}; etc.
- Azoalkane initiators: AIBN, etc.

Radical fragmentation: Synopsis

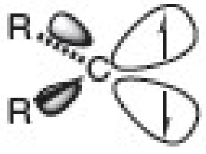


- Fragmentation of alkoxy radicals produces an aldehyde or ketone.
- Fragmentation of acyloxy radicals produces carbon dioxide.

Carbene structures

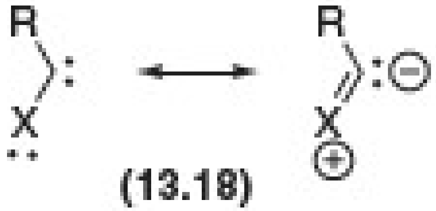


(13.17a)

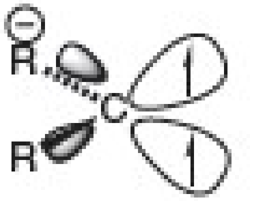


(13.17b)

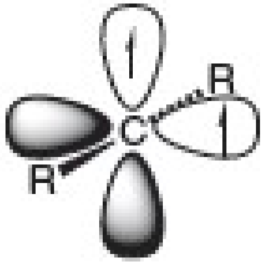
singlet carbene



(13.18)



(13.19a)



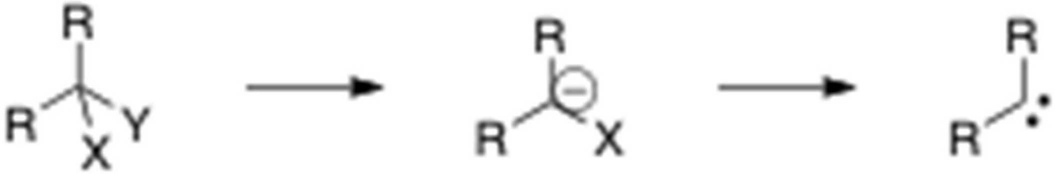
(13.19b)

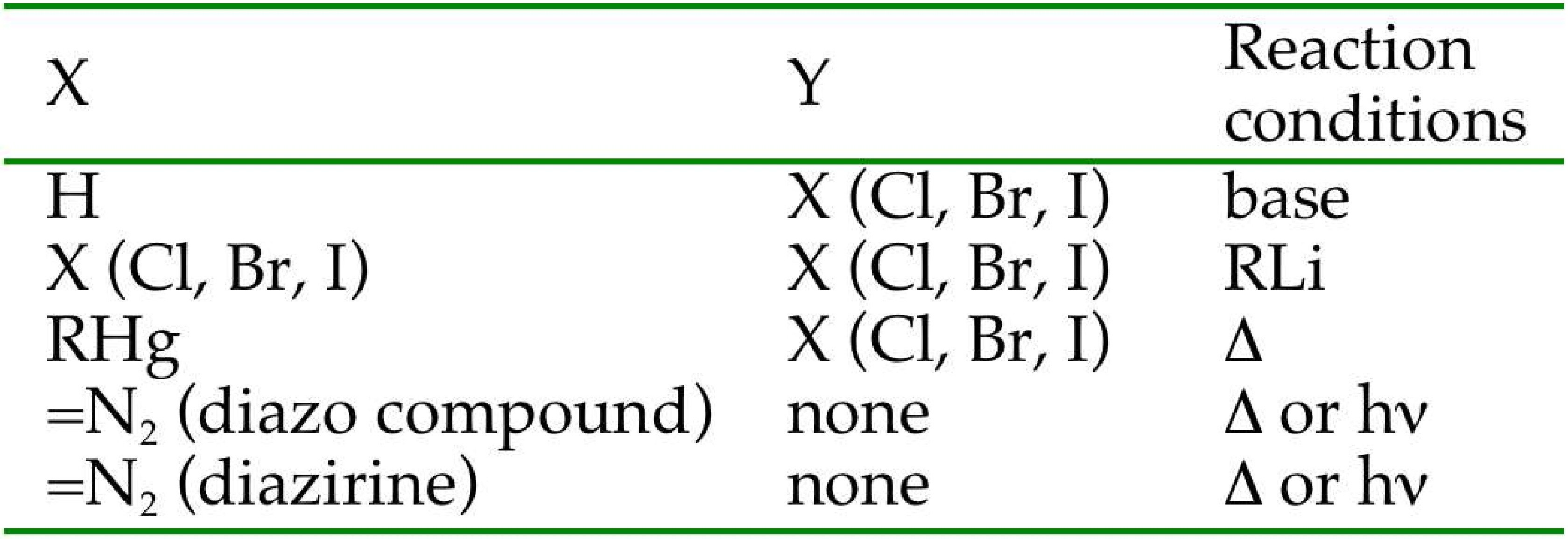
triplet carbene

- singlet carbenes may be represented as an sp^2-hybridized zwitterion or a sp^3-hybridized singlet diradical
- singlet carbenes are bent, regardless of which model is adopted
- triplet carbenes are diradicals that may be either sp^2- or sp-hybridized.
- triplet carbenes are bent, but with an angle that indicates that the hybridization of carbon is between these two extremes

Table 13.3

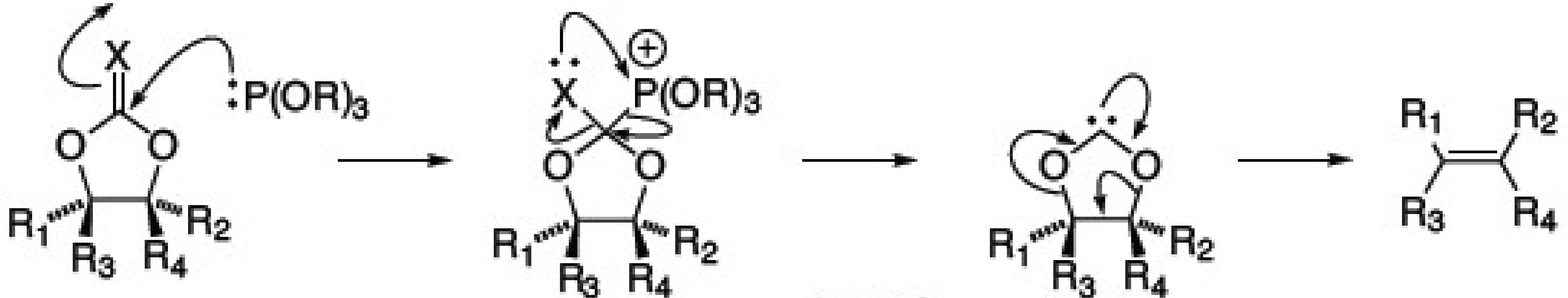
Generation of carbenes by α-elimination





X	Y	Reaction conditions
H	X (Cl, Br, I)	base
X (Cl, Br, I)	X (Cl, Br, I)	RLi
RHg	X (Cl, Br, I)	Δ
$=N_2$ (diazo compound)	none	Δ or $h\nu$
$=N_2$ (diazirine)	none	Δ or $h\nu$

Corey-Winter elimination



(13.20)

This elimination proceeds through a singlet carbene

Table 13.4

Relative rates of additions of halocarbenes to alkenes

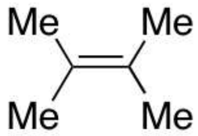
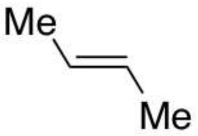
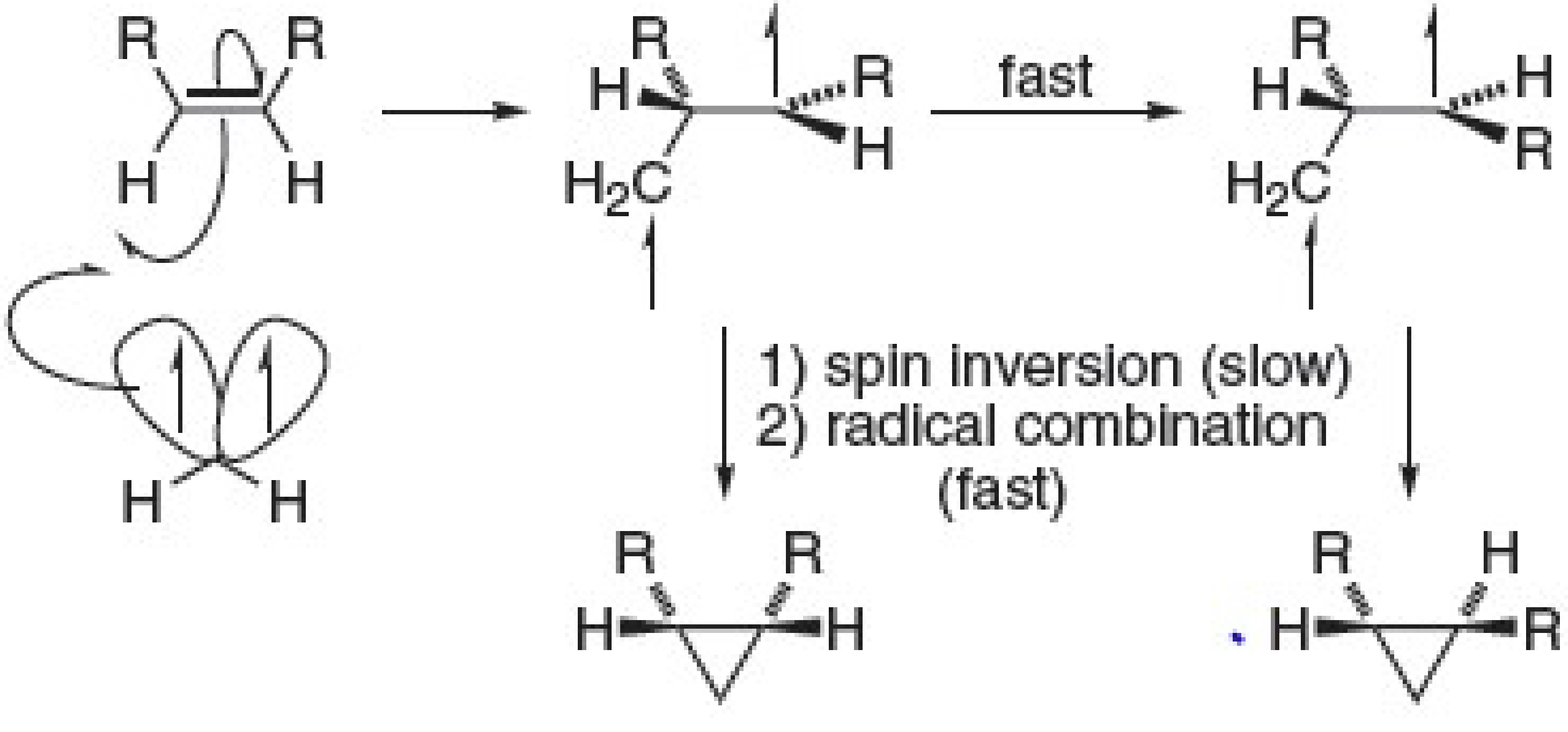
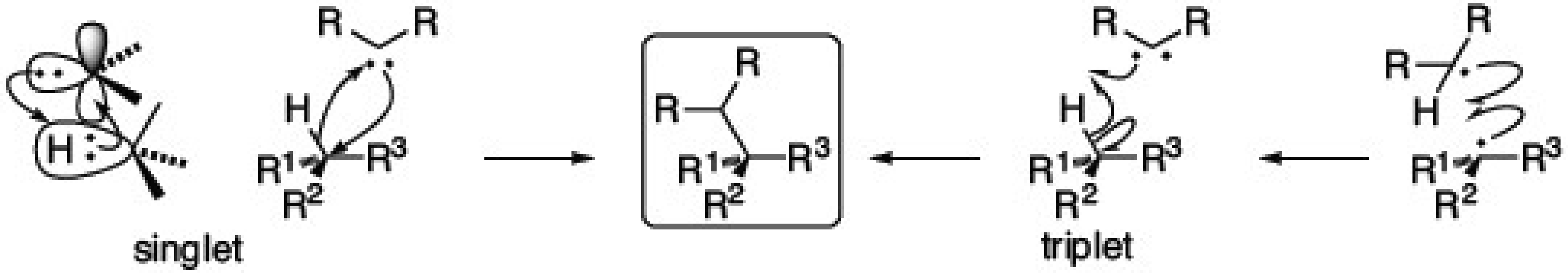
Alkene	CFCl	CCl_2	CBr_2
	31	6.5	3.5
	6.5	2.8	3.2
	1	1	1
	0.14	0.23	–
	0.097	0.15	–
	0.0087	0.011	–
	–	0.023	0.07
	–	0.12	0.4

Figure 13.3

Addition of a triplet carbene to an alkene π bond results in stereochemical equilibration.



Carbene insertion

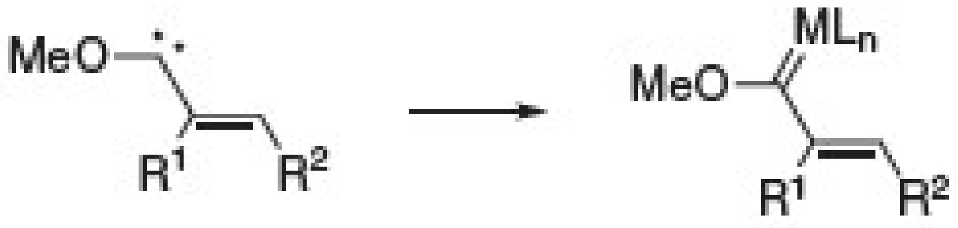


(13.24)

Insertion singlet carbenes into C—H σ bonds occurs through a radical pair, and is selective for the most stable free radical intermediate

Insertion of singlet carbenes into C—H σ bonds is a concerted process with retention of configuration, and shows lower regioselectivity than the triplet

Fischer carbene complexes

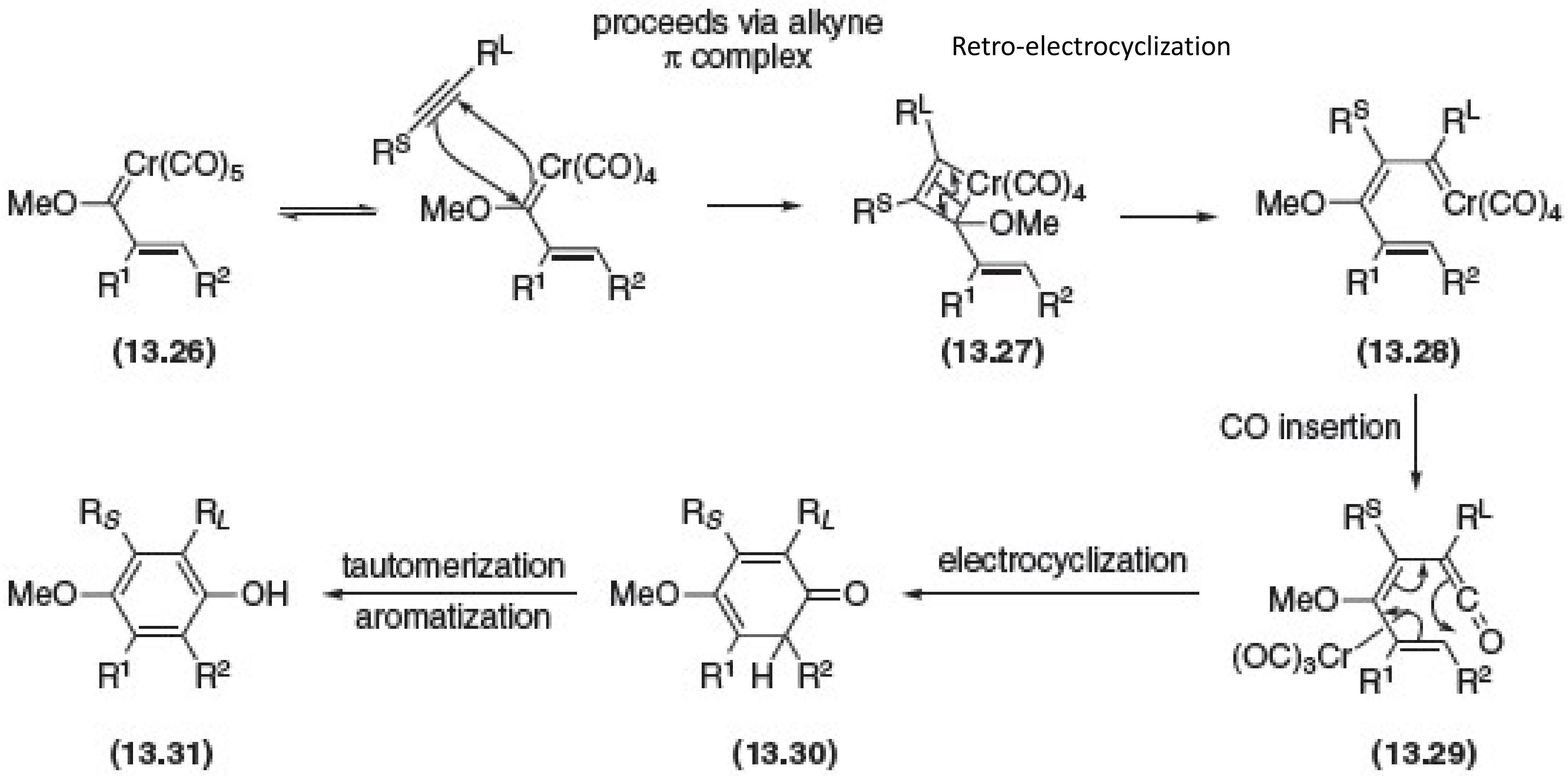


(13.26)

M = Cr, Mo, W

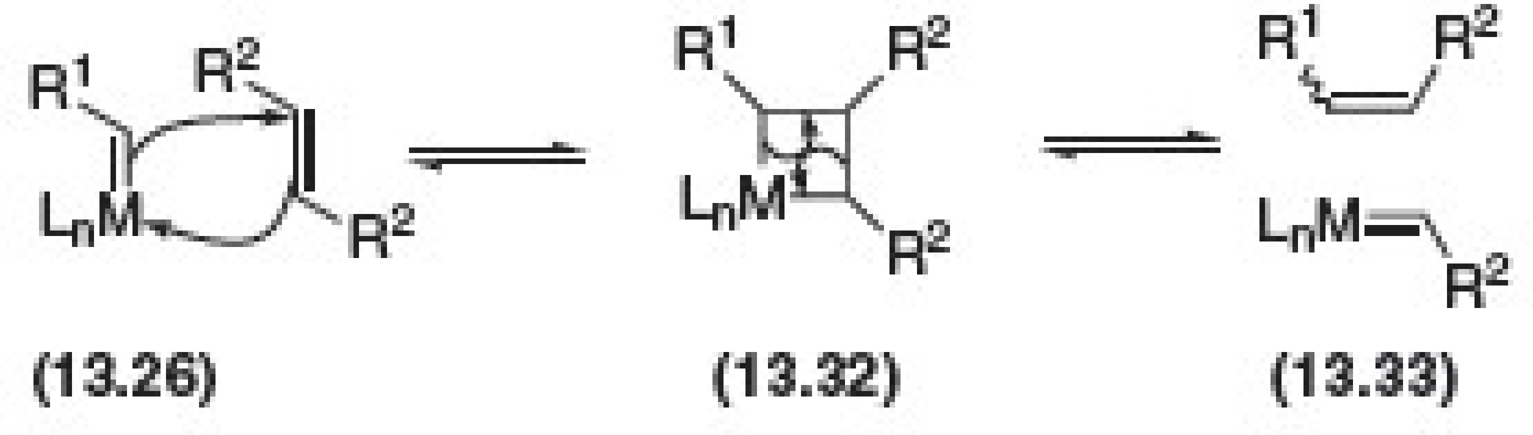
Transition metal carbene complexes are important intermediates in a number of modern synthetic reactions

Figure 13.4



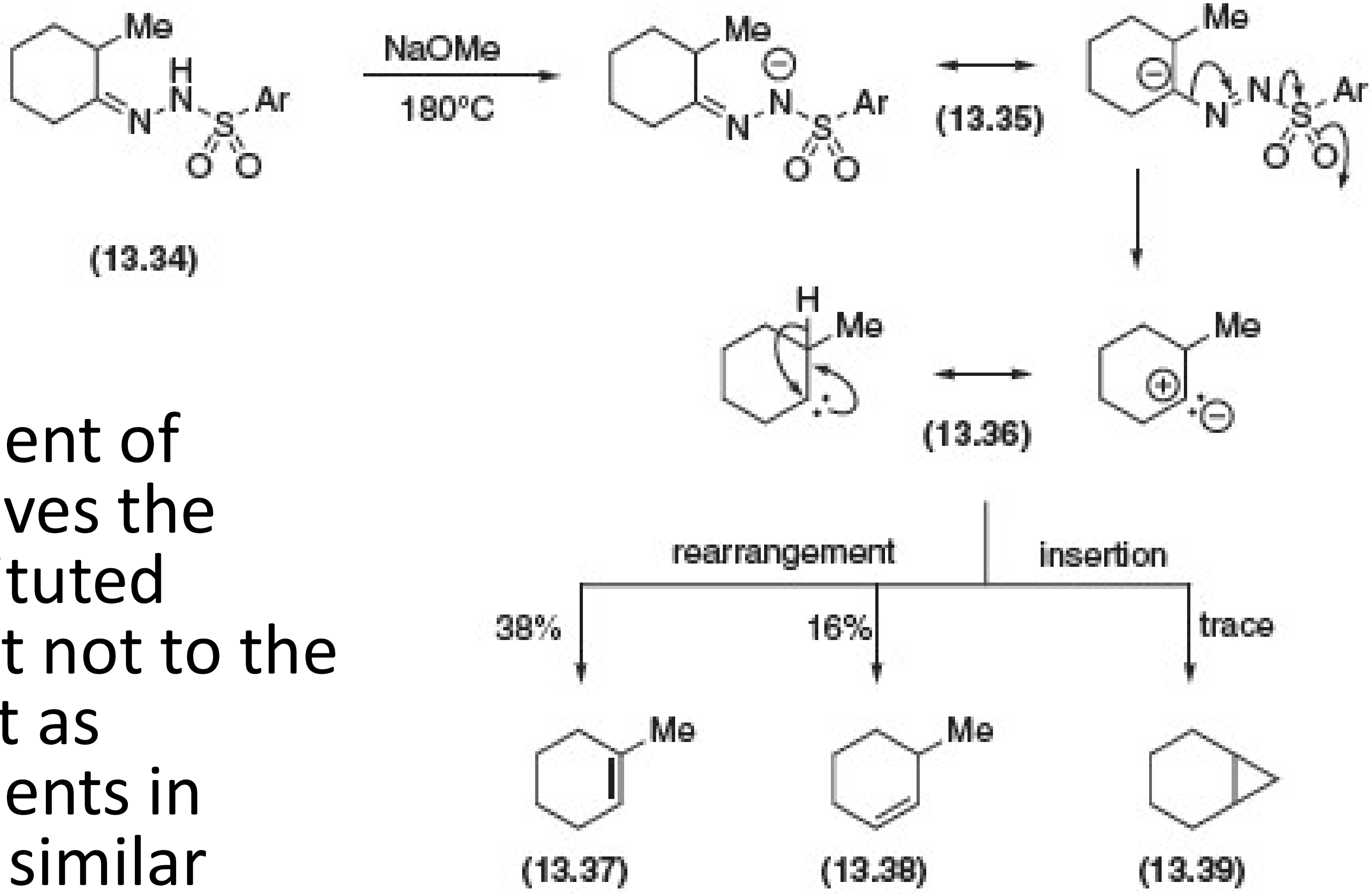
Formation of a phenol by addition of a Fischer carbene complex to an alkyne.

Olefin metathesis



- Metathesis occurs through the [2+2] cycloaddition of the metal carbene complex to the alkene, and retro-cycloaddition to generate a new metal-carbene complex

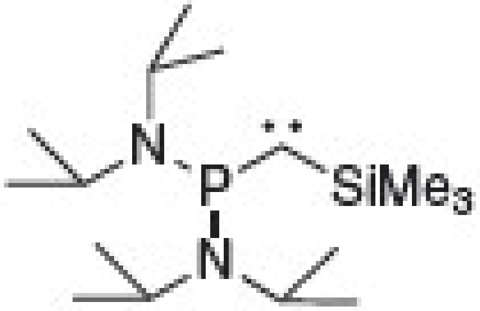
Carbene rearrangements



rearrangement of hydrogen gives the more substituted product, but not to the same extent as rearrangements in structurally similar carbocations

Stable carbenes

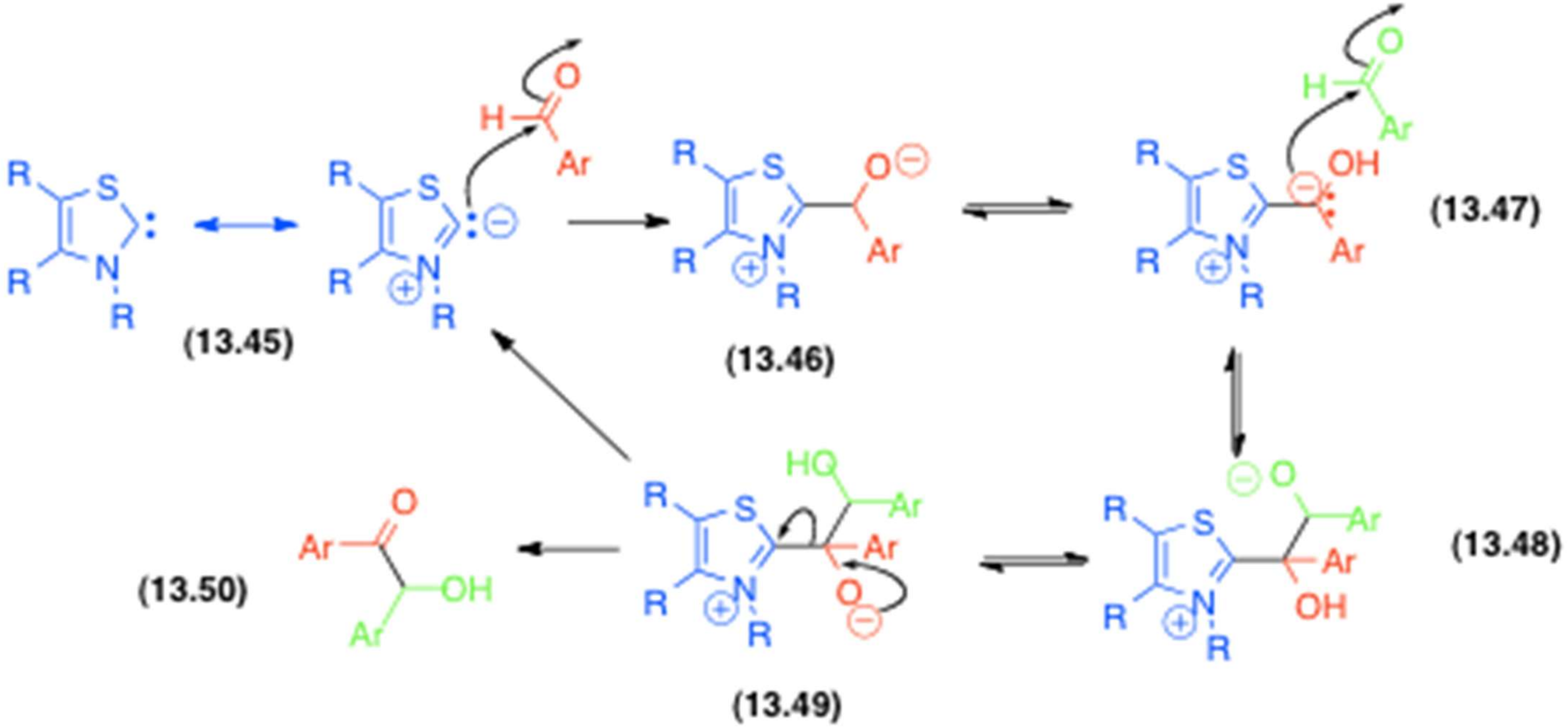
(13.43)



(13.44)

N-heterocyclic carbenes (e.g. **13.43**) are now important ligands in a variety of applications

Figure 13.5

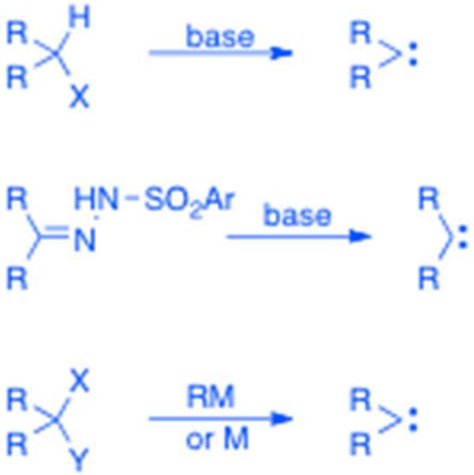


Reactivity of a thiazolium ion as a heterocyclic carbene.

Preparation of carbenes: Synopsis

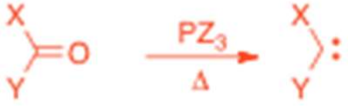
Carbenes from α-elimintion

- Reagents: BuLi/THF; Et_2Zn/THF; Zn(Cu)/Et_2O; etc.
- or KOBu^t/pentane; $NaNH_2$/THF; LDA/THF; etc.



X = Cl, Br, I
Y = F, Cl, Br, I
M = Li, Zn
base = RO^-, NR_2^-

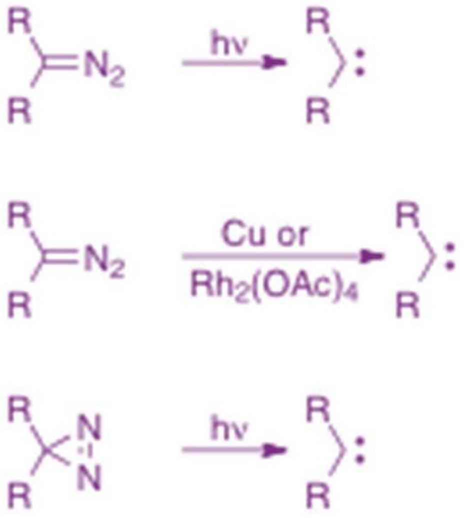
Carbenes by deoxygenation



X, Y = OR, NR_2, etc.
Z=alkyl, alkoxy

Carbenes by photolysis or thermolysis

- Carbene is often triplet when generated photochemically, and singlet when generated via the metal carbenoid.

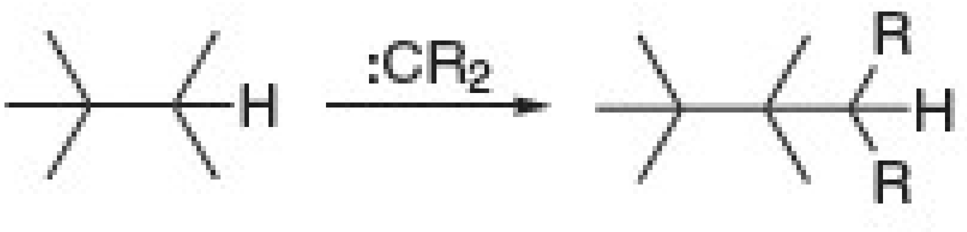


Carbene addition: Synopsis

Reagents: $CHCl_3$/KOBu^t; CH_2I_2/Et_2Zn; etc.

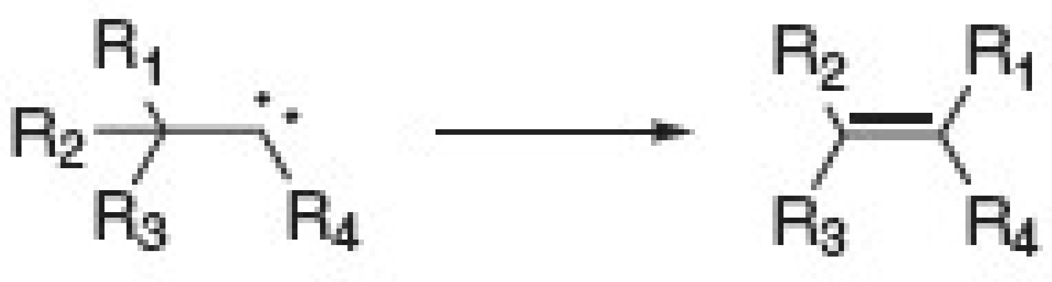
- Stereochemistry: addition is *syn* (suprafacial) with singlet carbenes, and stereochemistry of alkene is retained in cyclopropane product.

Carbene insertion: Synopsis



- Stereochemistry: Insertion occurs with retention of stereochemistry.
- Regiochemistry: insertion into C—H bonds is usually preferred over insertion into C—C bonds; insertion into sp^3-C—H bonds is preferred over insertion into sp^2-C—H bonds.

Carbene rearrangements: Synopsis



- Rearrangement of hydrogen is usually preferred.

Nitrenes: structure and preparation

singlet and triplet nitrenes exist

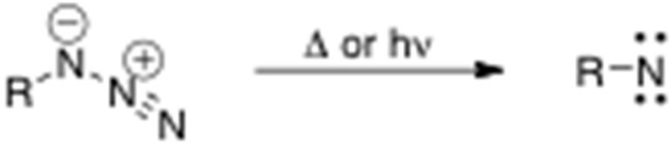
nitrenes can be formed by α-elimination from azides and *N*-acylsulfonamide anions

SINGLET

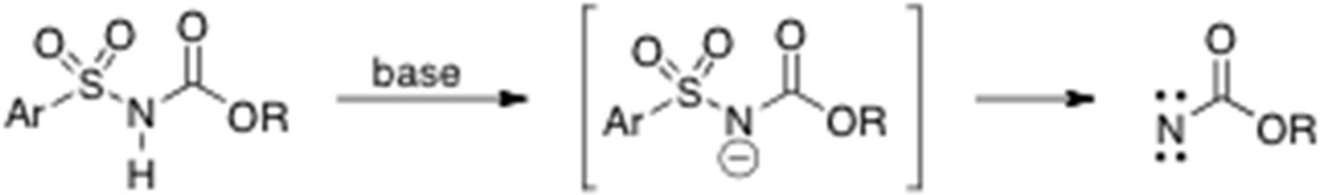
(13.51)

TRIPLET

(13.52)



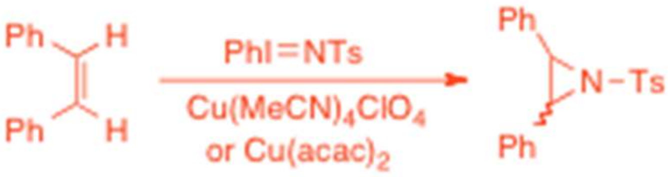
(13.53)

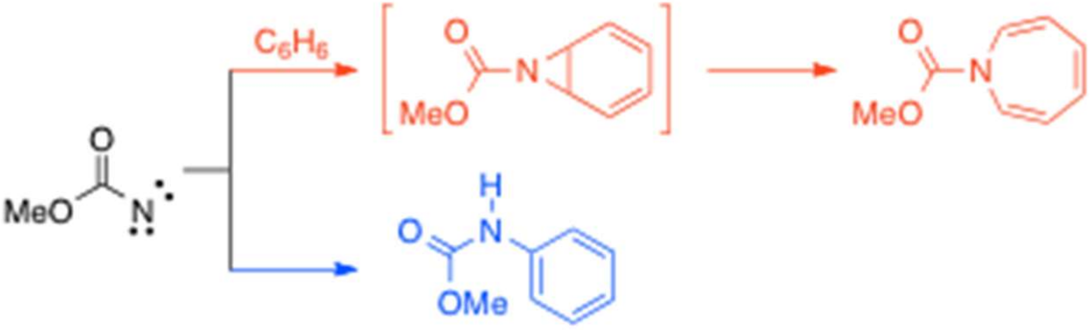


(13.54)

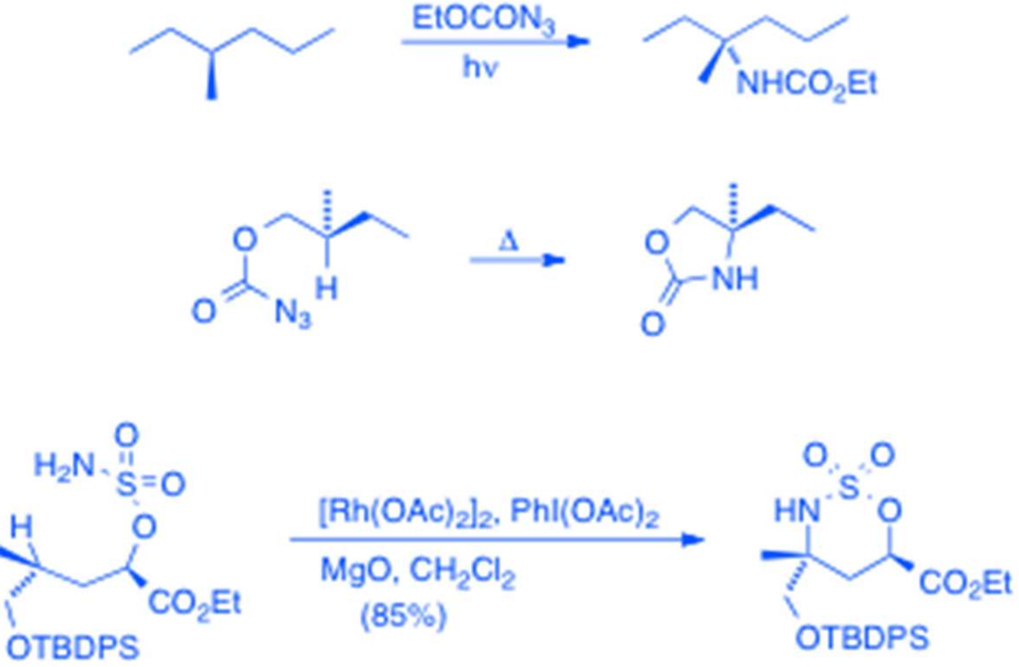
Representative nitrene reactions

nitrenes add to alkenes to give aziridines

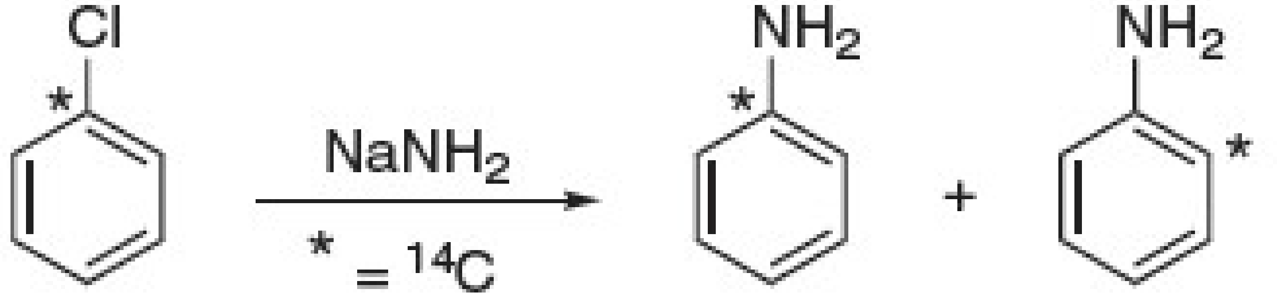




nitrenes insert into both C—H and C—C bonds; insertion into C—H bonds occurs with retention of configuration

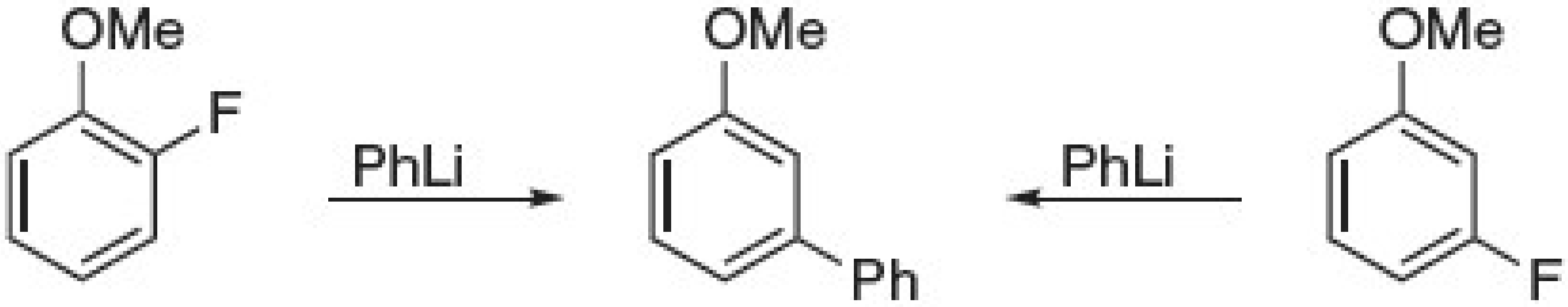


Initial experiments with benzyne intermediates



(13.60)

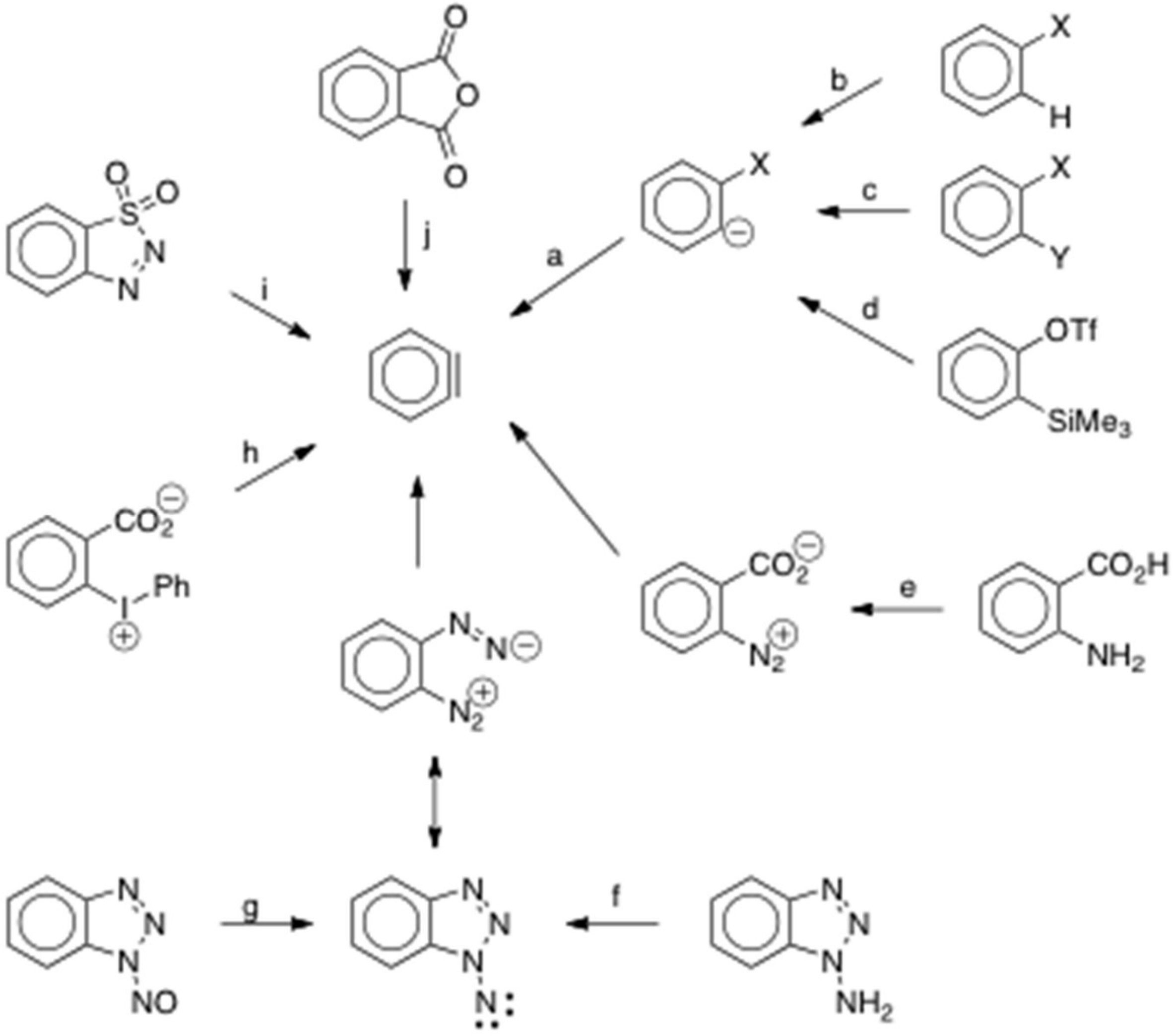
X = Cl	43%	53%
X = I	46%	52%



(13.61)

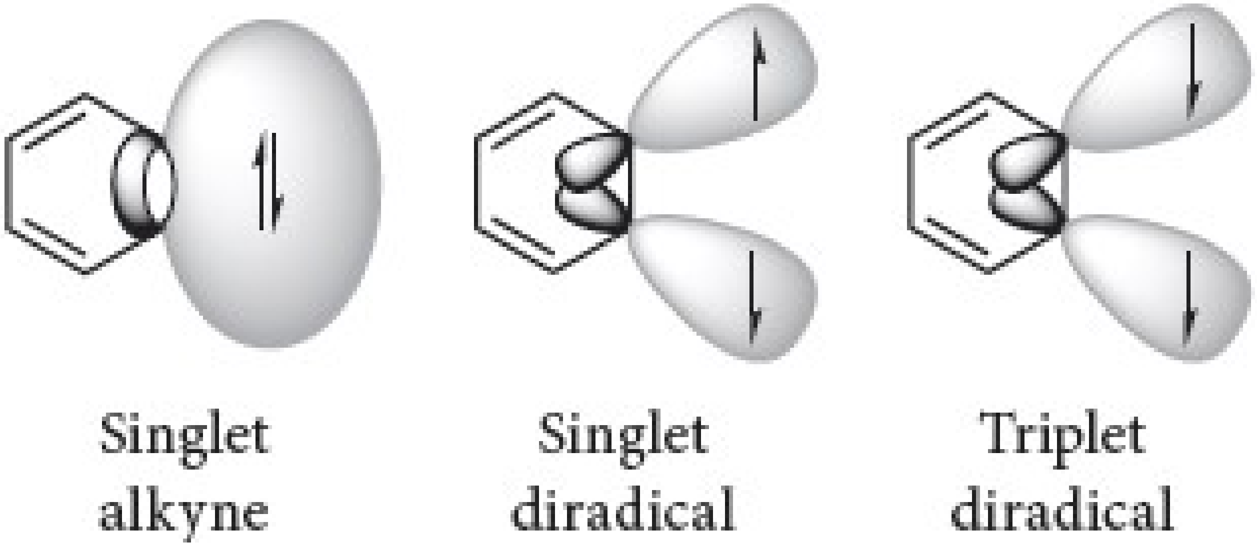
Figure 13.6

Reagents: (a) room temp. (b) $NaNH_2$, PhLi, etc. (c) Mg, Et_2O. (d) CsF, MeCN. (e) RONO. (f) $Pb(OAc)_4$. (g) $(PhO)_2P(O)H$. (h) hν or Δ. (i) Δ. (j) Δ or hν.



Methods for the production of benzyne

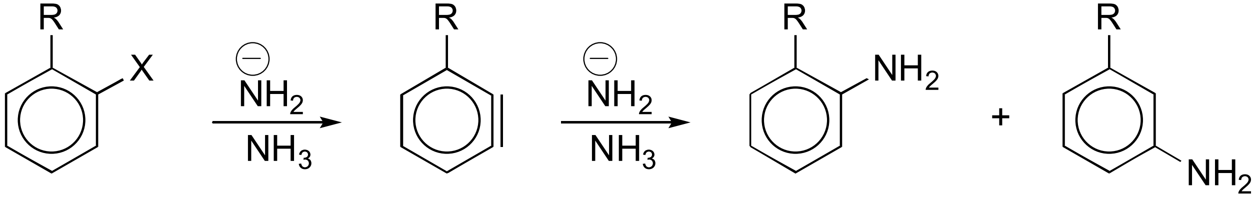
Electronic structures for benzyne



- Calculations support the singlet alkyne as the most likely structure of benzyne

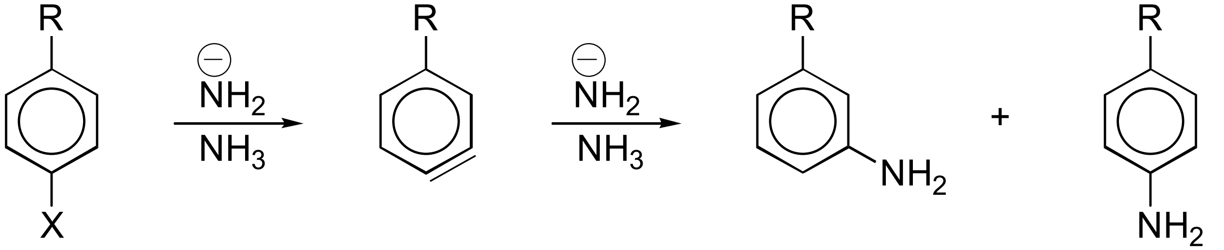
Table 13.9 (A): Regiochemistry of formation and addition of benzyne

o-ArX



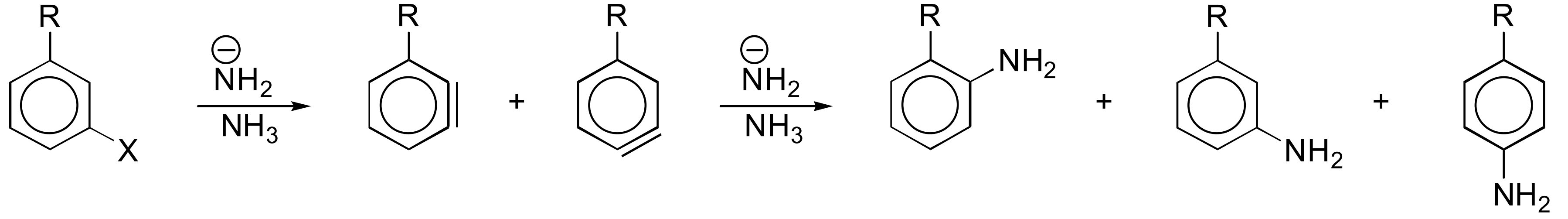
R = CF_3; X = Cl	0	100
R = CH_3; X = Cl	45±4	55±4
R = CH_3; X = Br	48.5±2	51.5±2
R = OCH_3; X = Br	0	100

m-ArX



R = CF_3; X = Cl	50±5	50±5
R = CH_3; X = Cl	62±4	38±4
R = OCH_3; X = Br	49±1	51±1
R = F; X = Br	20±1	80±1

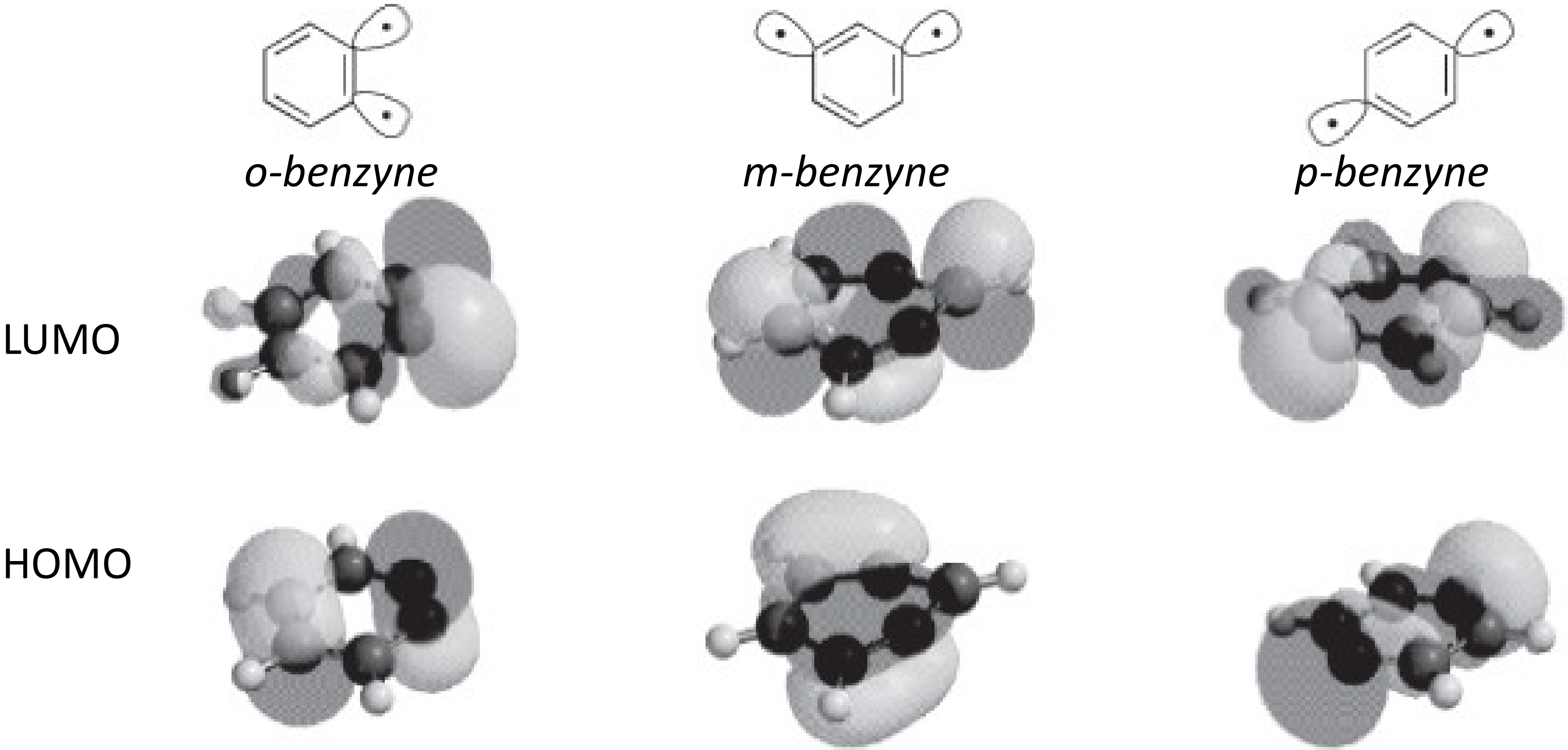
Table 13.9 (B): Regiochemistry of formation and addition of benzyne



R = CF_3; X = Cl	0	100	0
R = CH_3; X = Cl	40±4	52±4	8±4
R = CH_3; X = Br	22±4	56±4	22±4
R = OCH_3; X = Br	0	100	0

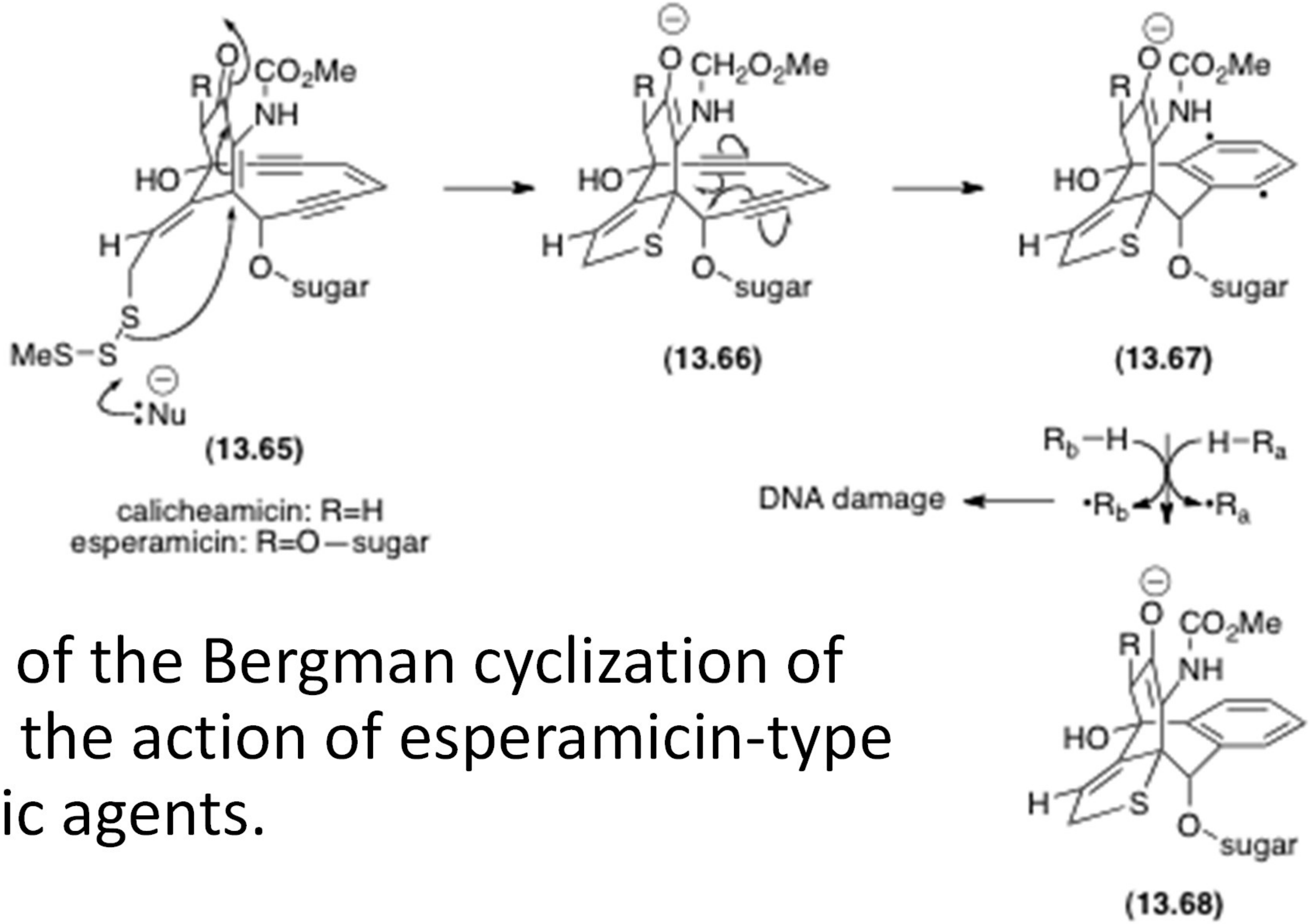
p-ArX

Figure 13.7



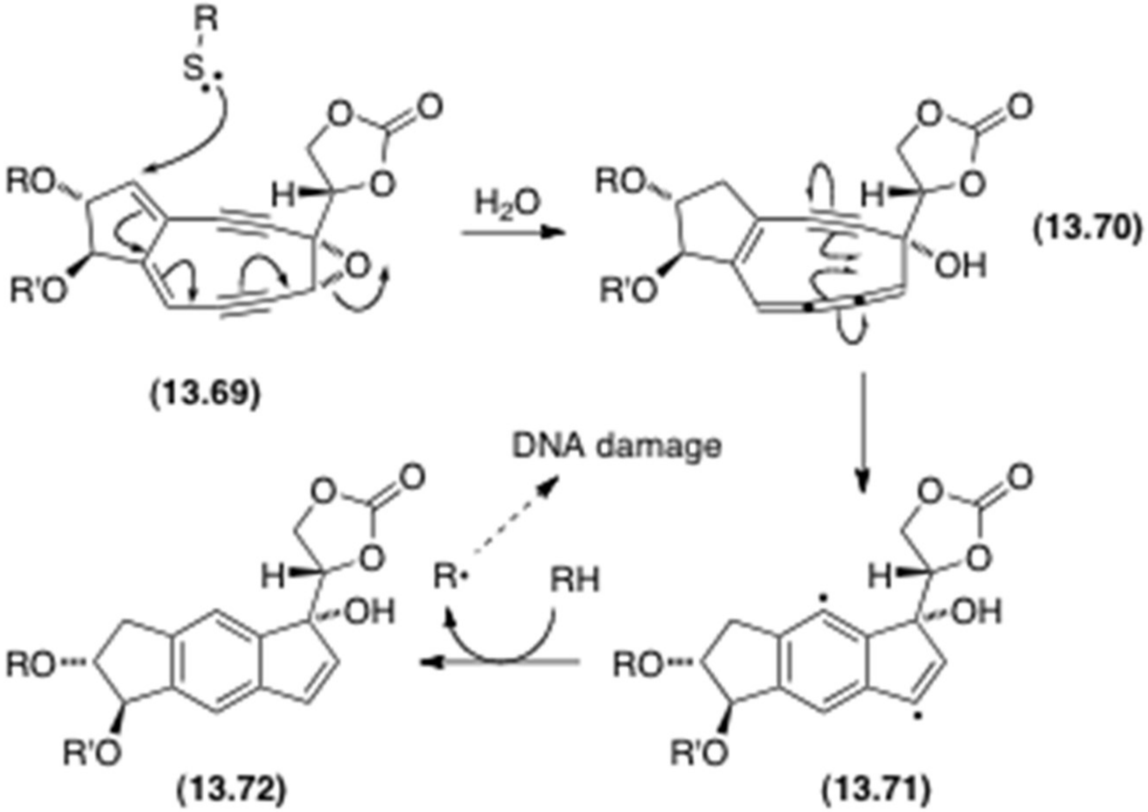
Frontier orbitals of isomeric benzynes. The LUMO is the upper orbital of each pair, and the HOMO is the lower orbital of each pair.

Figure 13.8



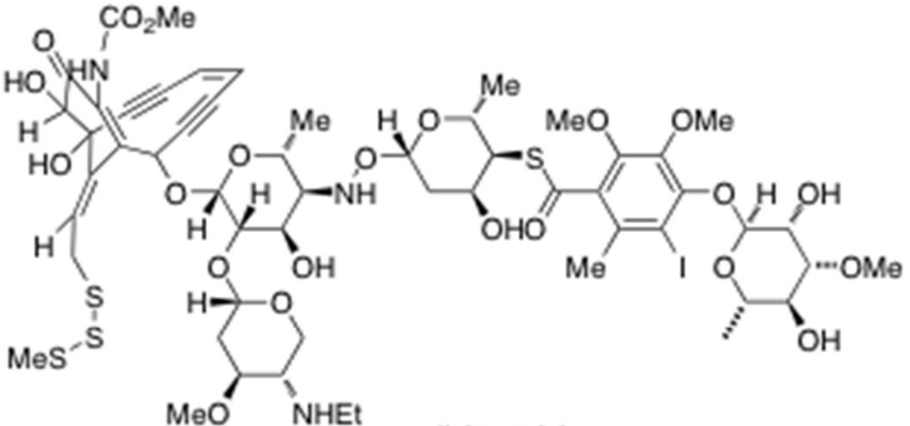
Involvement of the Bergman cyclization of enediynes in the action of esperamicin-type antineoplastic agents.

Figure 13.9

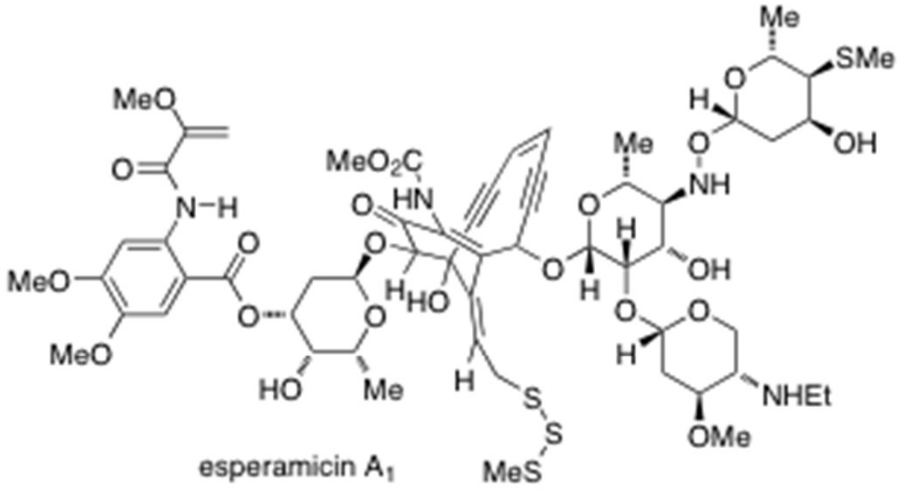


Involvement of the Myers-Saito cyclization of eneyne-allenes in the action of neocarzistatin chromophore antineoplastic agents.

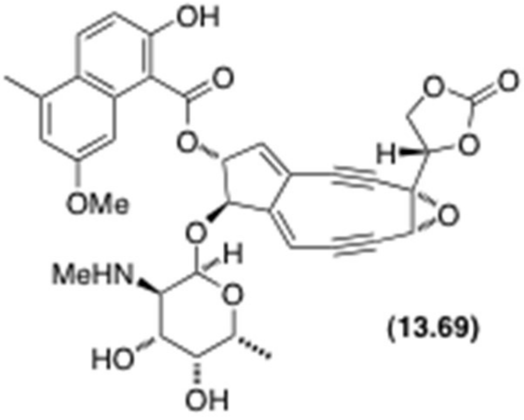
Antineoplastic compounds that act through diradical intermediates



calicheamicin γ_1



esperamicin A$_1$



(13.69)

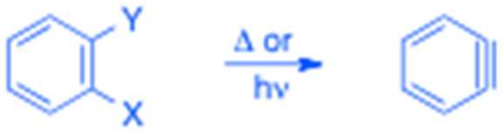
neocarzinostatin chromophore

Methods for generating arynes: Synopsis

- *From substituted phenyl anions*

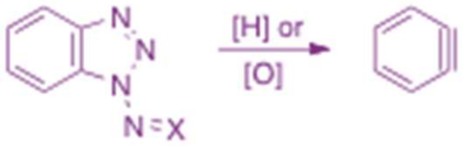
X=H, SiR_3 halogen; Y=halogen, OSO_2R, N_2^+, etc.

- Reagents: X=H: $NaNH_2/NH_3$; LDA/THF; PhLi; etc.
  X=SiR_3: CsF/MeCN
  X=halogen: Mg/Et_2O; BuLi/THF; etc.
- *By thermolysis or photolysis*



X, Y = CO-O-CO; N=N-SO_2; CO_2^- and PhI^+; CO_2^- and N_2^+

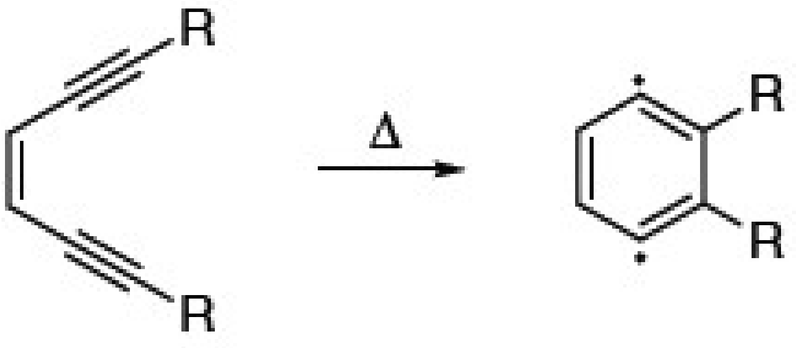
- *From benzotriazole derivatives*



X = H_2, O

- Reagents: X=O: $(MeO)_3P$;
-   X=H_2: $Pb(OAc)_4$

Bergman cyclization of enediynes



- Reaction proceeds spontaneously if the termini of the ene-diyne are close enough together.

Myers-Saito cyclization of enyne-allenes