

Lecture 21 Free-Radical Reactions I

9.1 Principles

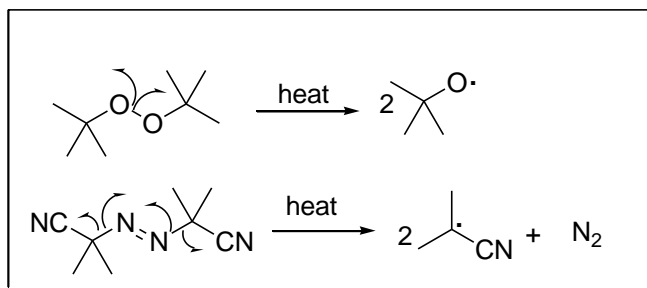
Free radicals may be defined as the species that contain one or more unpaired electrons. They are generally less stable and react in fraction of seconds with another species.

9.1.1 Formation of Free Radicals

Three general methods are used for the generation of free radicals.

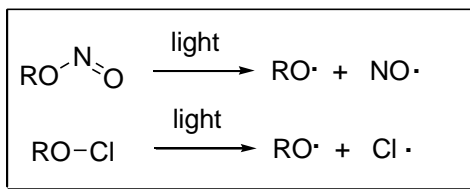
9.1.1.1 Thermal Generation

Two types of compounds dissociate to give free-radicals at moderate temperature: (i) compounds that have an intrinsically weak bond such as dialkyl peroxides ($D_{O-O} = 155 \text{ KJ mol}^{-1}$), and (ii) compounds that, on fragmentation, form strongly bonded products, such as AIBN which releases N_2 .



9.1.1.2 Photochemical Generation

Light can bring the fragmentation of a compound if the wavelength of the light is correspond both to an energy greater than that of the bond to be cleaved, and to an electronic excitation of the molecule concerned. This procedure is suitable for the formation of alkoxy radicals from alkyl nitrite or hypochlorites.



9.1.2 Reactions of Free Radicals

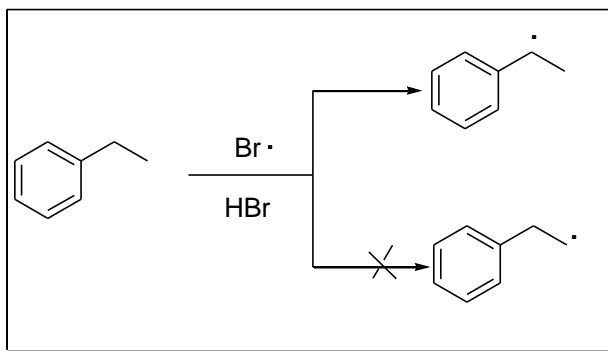
Four types of reactions are possible with free-radicals.

9.1.2.1 Abstraction

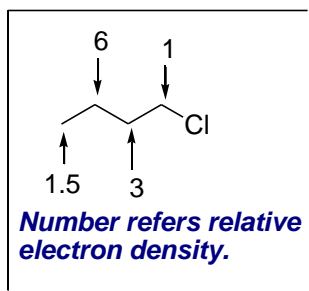
Free radicals proceed reactions with saturated organic molecules by abstracting an atom from carbon. The selectivity of the free radicals towards C-H bonds of different types is determined by bond dissociation energy and polar effects. The rate of the abstraction process increases as bond dissociation energy decreases. For examples:

Bond:	H-CH ₃	H-CH ₂ Me	H-CHMe ₂	H-CMe ₃
Bond Dissociation Energy (KJmol ⁻¹)	426	401	385	372
Reactivity Order::	H-CH ₃ <	H-CH ₂ Me <	H-CHMe ₂ <	H-CMe ₃

Allylic and benzylic C-H bonds are weaker than those of saturated systems and exhibit greater reactivity and selectivity with free radicals.



Secondly, polar effect is also operative in radical reactions. For example, the relative reactivity of C-H bonds in butyl chloride towards chlorine atom follows:

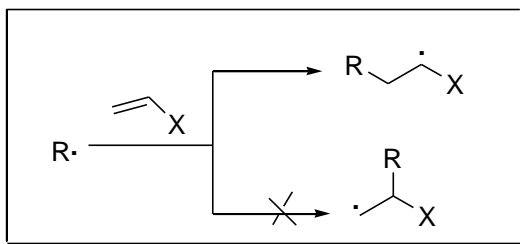


Chlorine atom is electronegative and preferentially reacts at C-H bonds of relatively high electron density.

In contrast, alkyl radicals which are called nucleophilic radicals react preferentially at C-H bonds with electron density low.

9.1.2.2 Addition

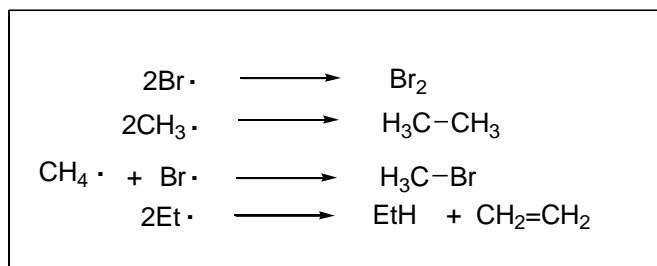
Free radicals undergo addition to carbon-carbon double bonds. The reaction is generally selective. For example, addition to $\text{CH}_2=\text{CHX}$ takes place exclusively at the methyl group, irrespective of the nature of X.



Alkynes also exhibit similar reactivity with free radicals.

9.1.2.3 Combination and Disproportionation

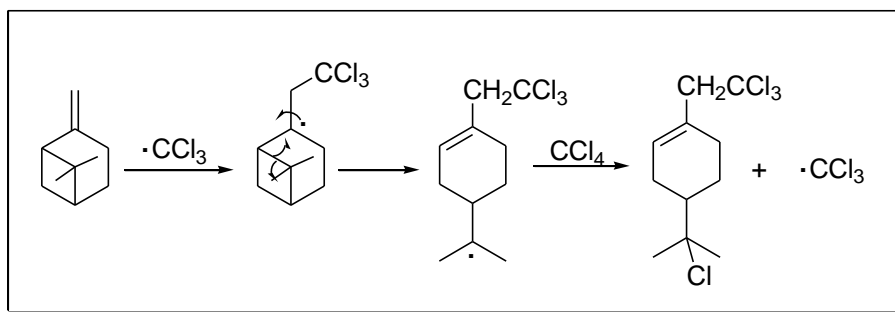
Two free radicals can combine by dimerization or disproportionation.



These reactions are generally fast, some having negligible activation energies.

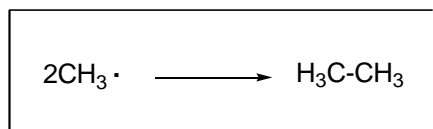
9.1.2.4 Rearrangement

Free radicals are known to rearrange in certain circumstances. For example, the addition of free radical leads to rearrangement due to relief of strain in the cyclic system.

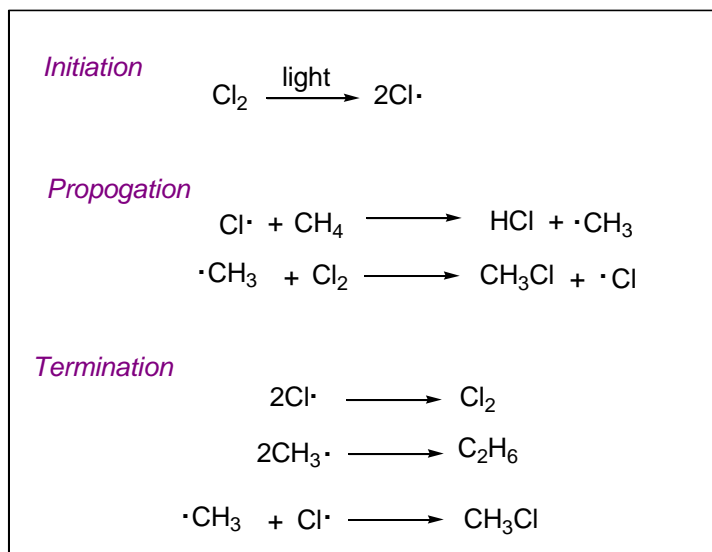


9.1.3 The Characteristics of Free radical Reactions

Free radical reactions may be broadly classified into two groups. In the first, the product formation occurs from the combination of two radicals.



In the second class, the product formation results from the reaction of a radical with a molecule by chain process.

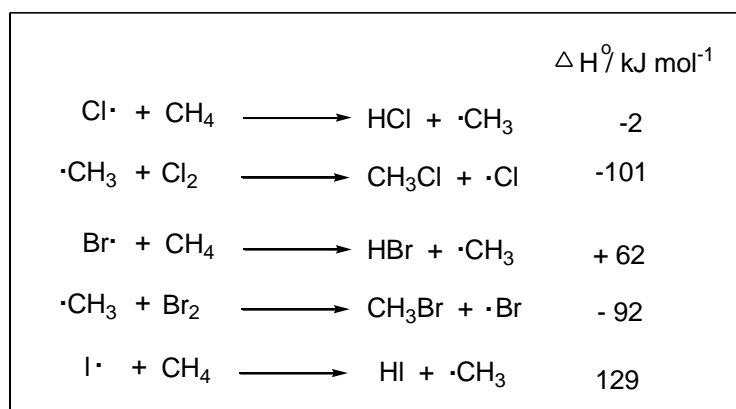


9.2 Formation of Carbon-Halogen Bonds

9.2.1 Substitution in Saturated Carbons

9.2.1.1 Energetics

Radical catalyzed chlorination and bromination can be performed both in gas and liquid phases. The energetic comparison of chlorination, bromination and iodination of methane follows:



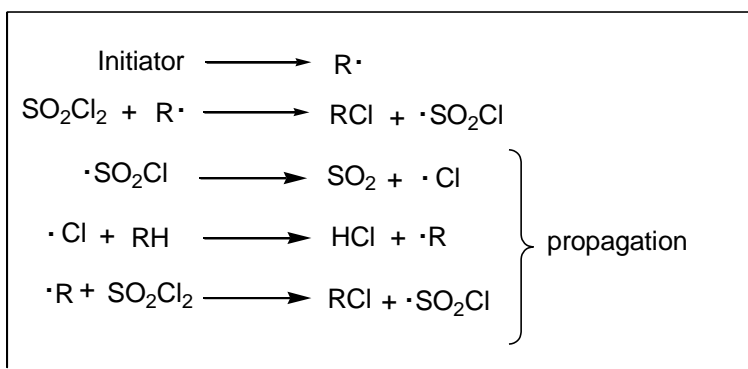
As we can see, in chlorination, both the propagating steps are exothermic reactions. Thus, the chain reaction competes very effectively with the termination steps and the chains are long.

In contrast, in bromination, the first of the propagating steps is endothermic and its activation energy is essentially at least as great as 62 kJ mol^{-1} . Thus, the reaction is slower than compared to chlorination. As a result, the terminating process competes with the propagating step that leads to the chains short.

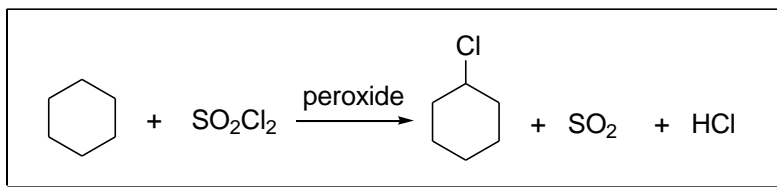
In iodination, the reaction is strongly endothermic (129 kJ mol^{-1}) that lead to ineffective. In the case of fluorination, both the propagating steps are exothermic that leads to violent reaction with fragmentation of the alkyl groups. Thus, fluorination is usually carried out by other methods.

9.2.1.2 Applications

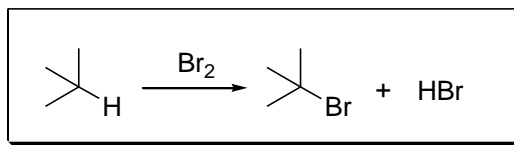
Radical-catalyzed chlorination and bromination of alkanes take place readily, both in gas and liquid phases. Both the thermal and photochemical generation of the halogen atoms are used.



For example, cyclohexane reacts with sulfuryl chloride in the presence of dibenzoyl peroxide to give cyclohexyl chloride in 89% yield.

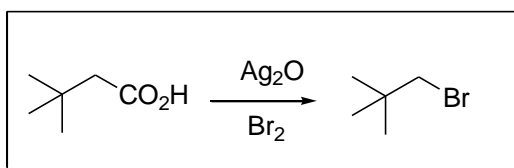


Similarly, the gas phase bromination of isobutane gives t-butyl bromide exclusively.



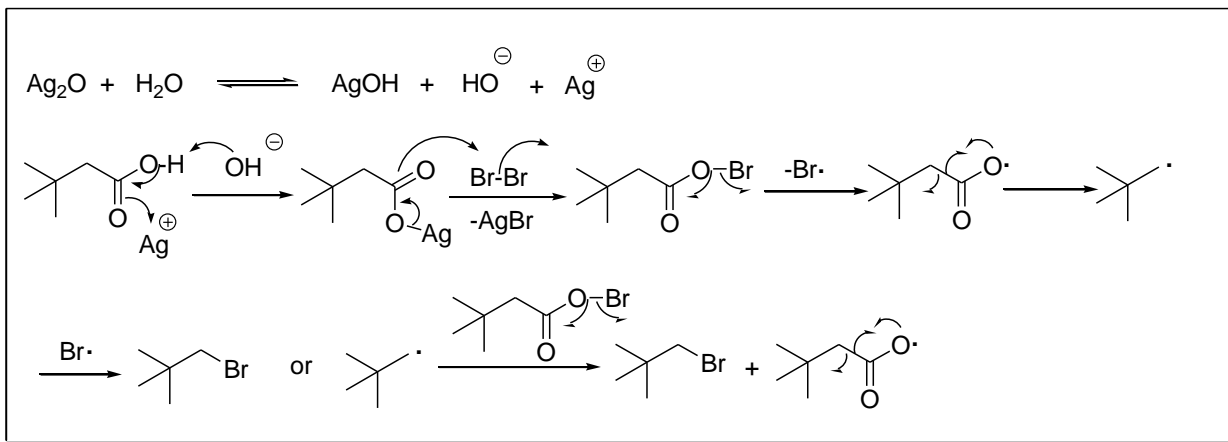
9.2.2 Hunsdiecker Reaction

Treatment of aqueous solution of silver oxide with carboxylic acid gives silver salt of carboxylic acid which reacts with Br₂ to give a bromo-compound with elimination of CO₂.

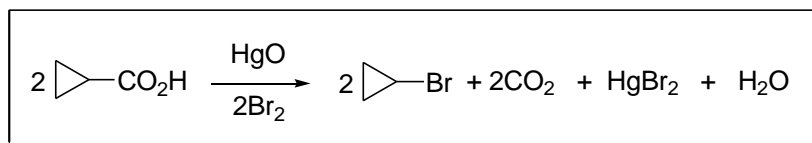


Mechanism

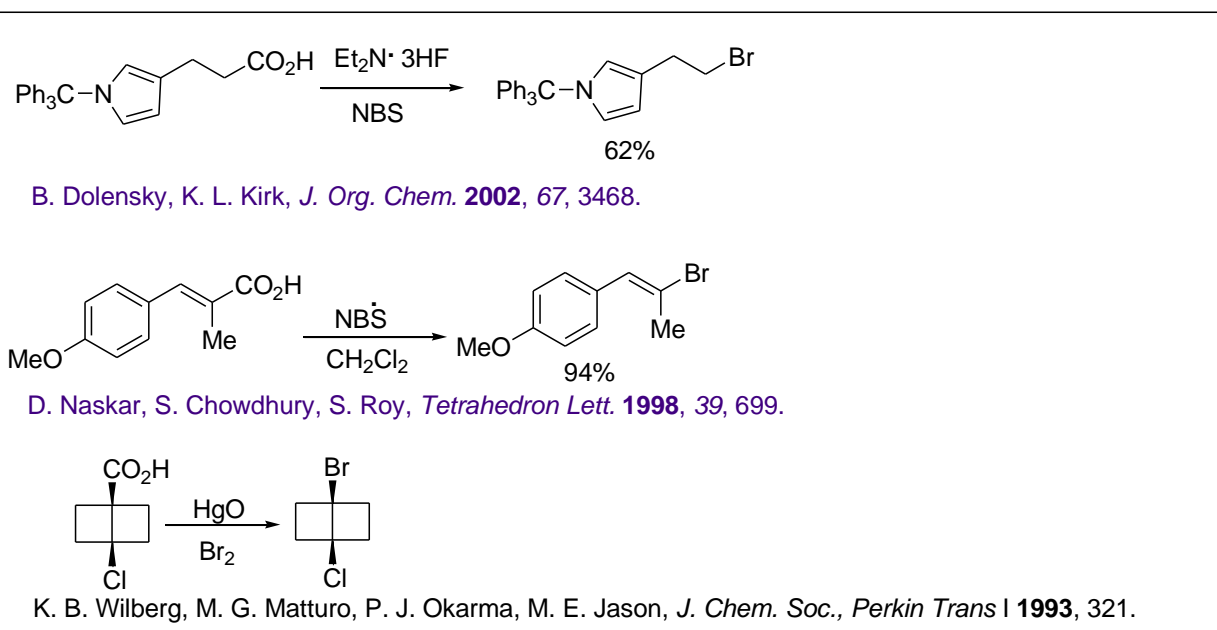
The reaction involves the formation of acyl hypobromite and its homolytic cleavage to give acyloxy radical which loses CO₂ and the resulting radical reacts with bromine radical or abstracts bromine from a second molecule of the hypobromite.



Mercury(II) and lead(IV) compounds are also known to react similarly. For example, cyclopropanecarboxylic acid with HgO and Br₂ affords bromocyclopropane in 45% yield.

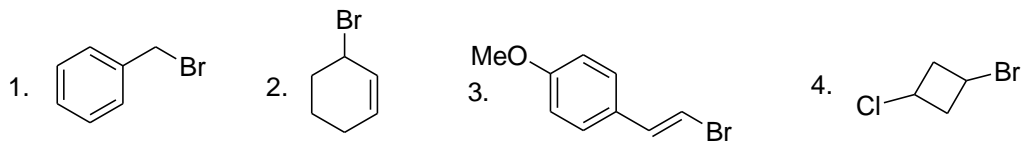


Examples:

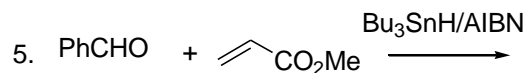
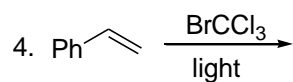
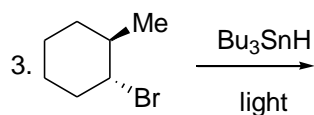
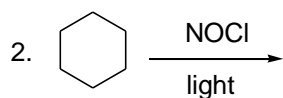
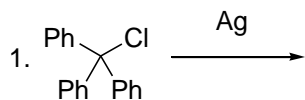


Problems:

A. How would you employ radical reactions in the synthesis of the following compounds?



B. Complete the following reactions.



Text Books:

R.O.C. Norman and C. M. Coxon, *Principles of Organic Synthesis*, CRC Press, New York, 2009.

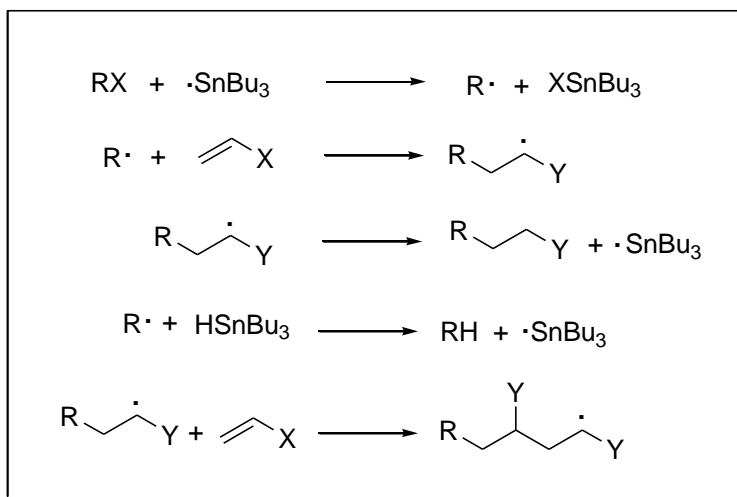
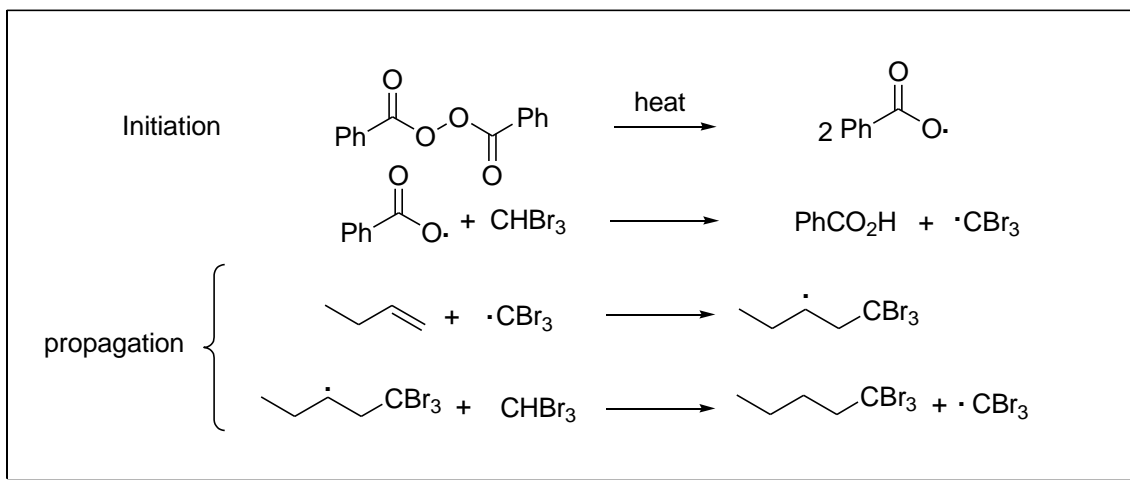
J. March, *Advanced Organic Chemistry*, 4th ed, Wiley Interscience, New York, 1992.

Lecture 22 Free-Radical Reactions II

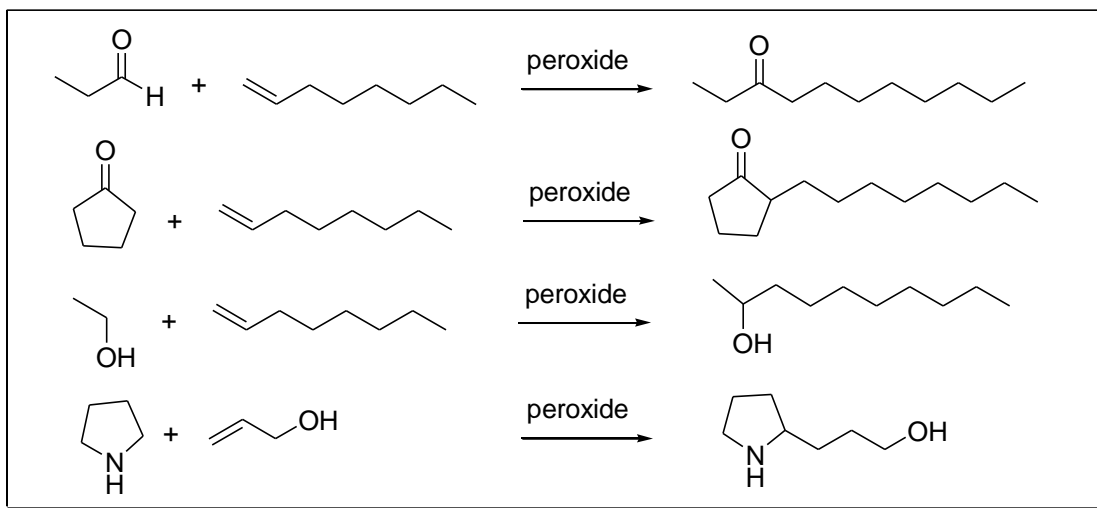
9.3 Formation of Carbon-Carbon Bonds

9.3.1 Addition to Carbon-Carbon Double bonds

The addition of aliphatic free radical to carbon-carbon double has wide applications. The reaction of bromoform with 1-butene is illustrative:

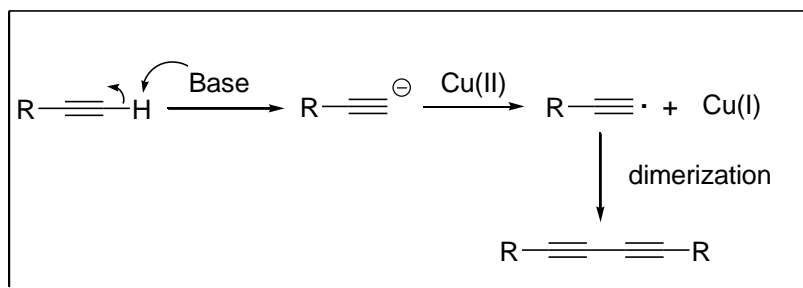


The following are some examples for radical addition to carbon-carbon double bond with a variety of types of starting material.

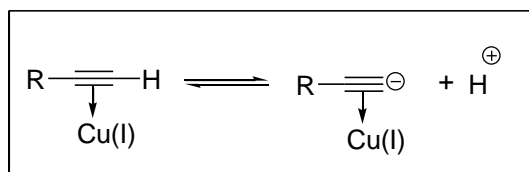


9.3.2 The Coupling of Alkynes

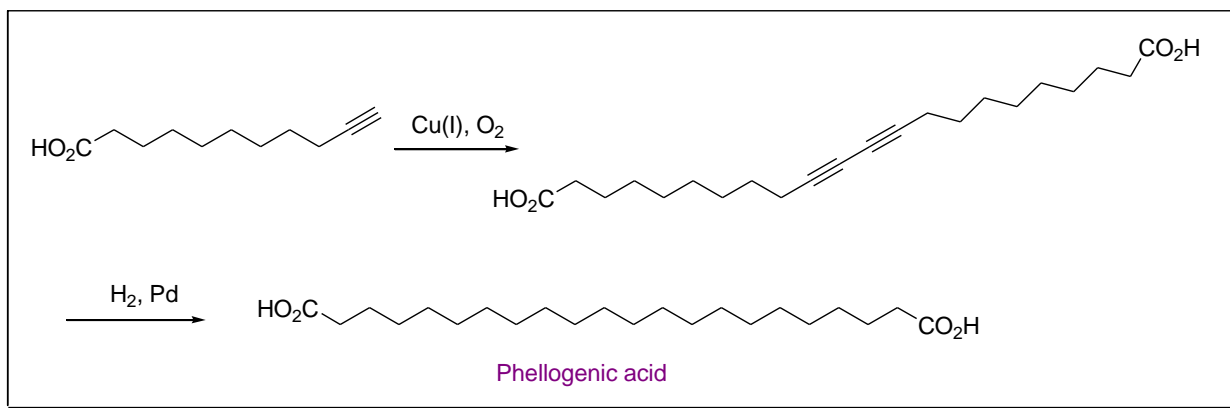
Copper(II) complex catalyzes the coupling of acetylene and monosubstituted acetylenes to yield diynes in the presence of base such as pyridine. The reaction probably takes place via one-electron oxidation of the acetylide anion by copper(II) ion followed by dimerization of the resulting acetylide radicals:



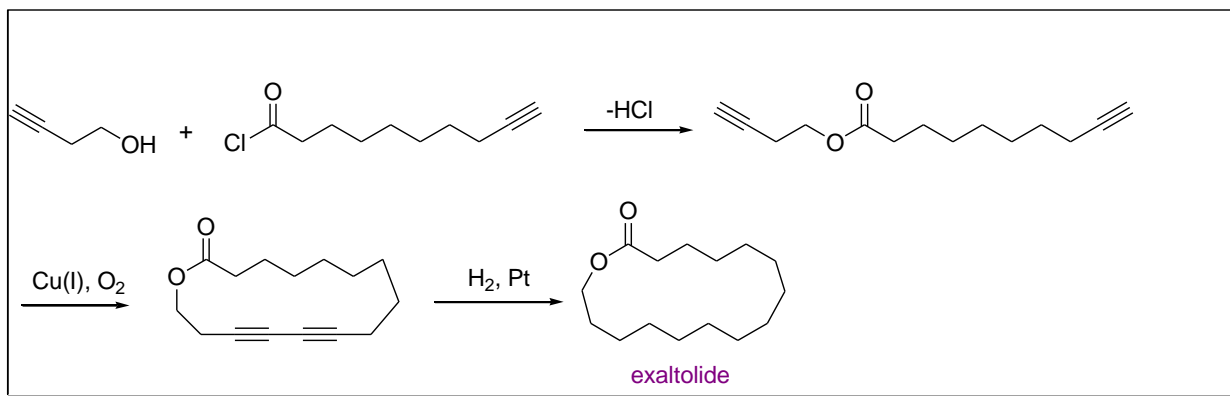
Alternative method has also been developed using an aqueous mixture of copper(I) chloride and ammonium chloride under air. Under these conditions, removal of the proton may be facilitated by complexing between the carbon-carbon triple bond and copper(I) ion.



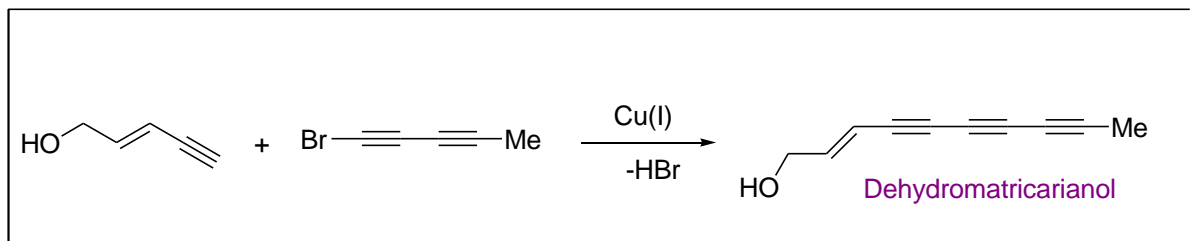
Since the reaction functions under air, some of the Cu(I) could be oxidized to Cu(II) which in turn could oxidize the acetylide ion to the acetylide radical that could dimerize to yield diynes. The following are examples of many synthetic applications. The synthesis of phellogenic acid has been accomplished from undecylenic acid:



In some cases, intramolecular coupling of terminal alkynes may also occur to produce cyclic compounds, if the resulting ring is not highly strained. For example, the synthesis of macrocyclic lactone, exaltolide, that is partly responsible for the sweet odour of the angelica root, could be accomplished with high yield.

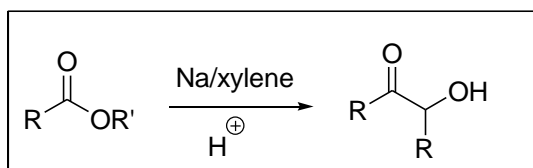


Coupling of monosubstituted acetylene with 1-bromoalkyne can be performed to afford hetero coupled product in good yield.



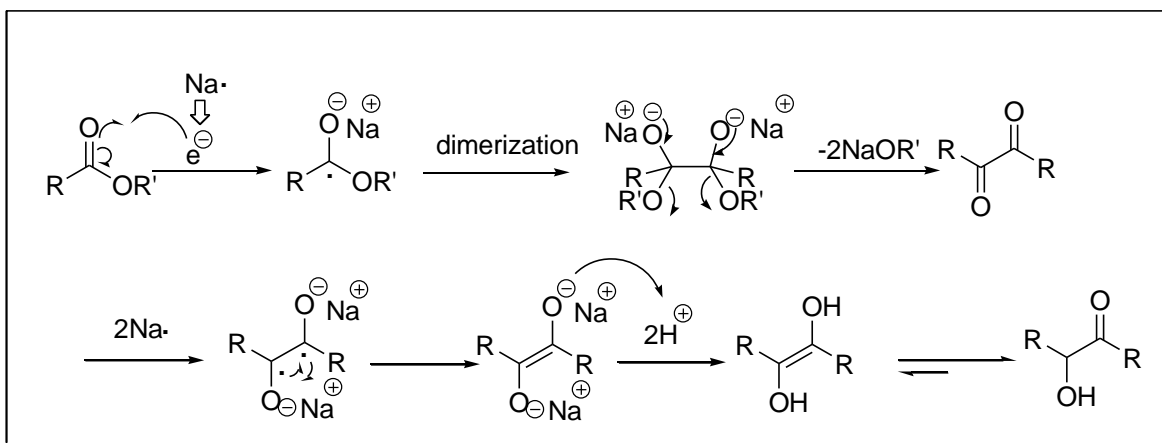
9.3.4 Acyloin Condensation

Aliphatic ester reacts with molten sodium in hot xylene to yield the disodium derivative of acyloin which is converted into acyloin in the presence of acid. The reaction is to be carried out under nitrogen because acyloins and their anions are prone to undergo oxidation with air.

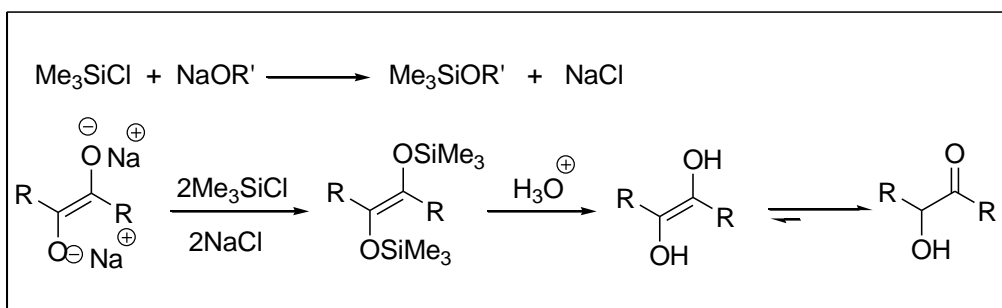


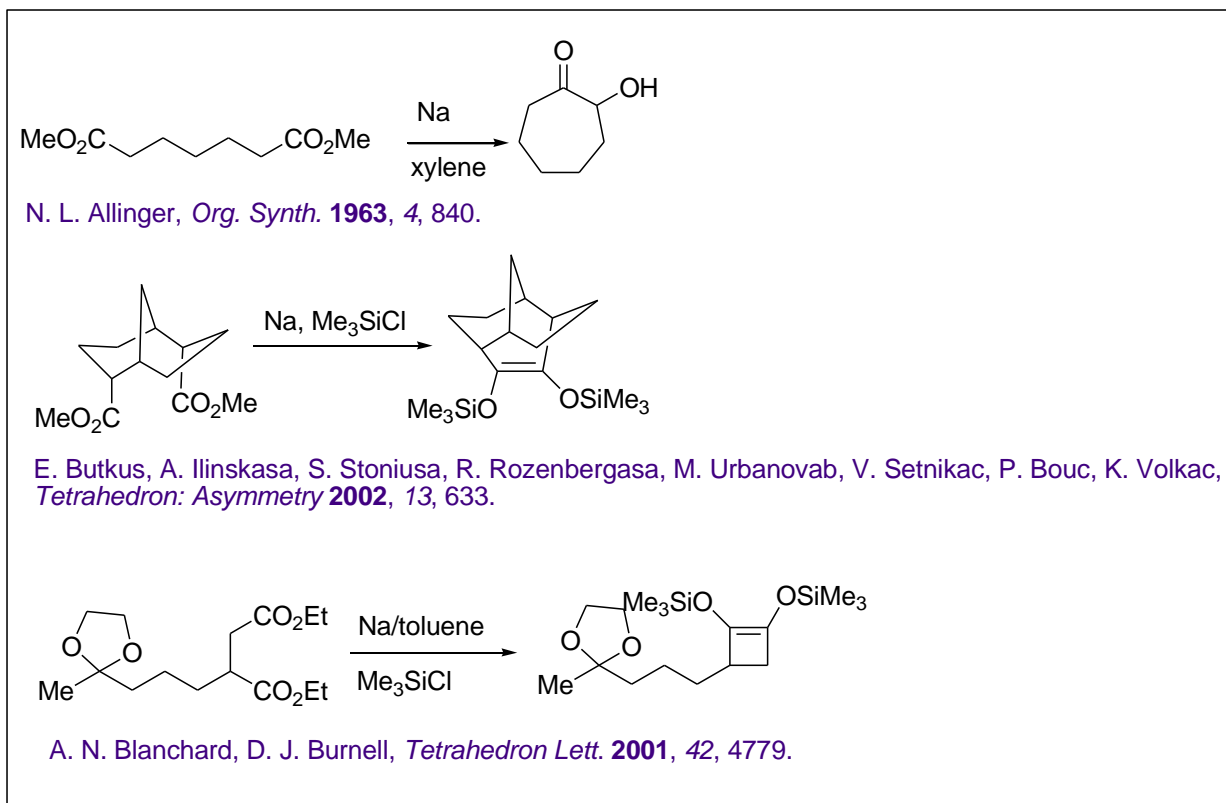
Mechanism

The reaction is initiated by electron transfer from sodium to the carbonyl group of the ester. The resulting radicals dimerize and the alkoxides are eliminated. The diketone further reacts with sodium to give disodium derivative which reacts with acid to give acyloin.



The alkoxide generated during the reaction can catalyze condensation of the ester. To prevent this competitive reaction, the alkoxides are trapped using chlorotrimethylsilane and the acyloin is then released with acid. This procedure gives better results compared to the traditional Dieckmann cyclization for preparation of larger rings.

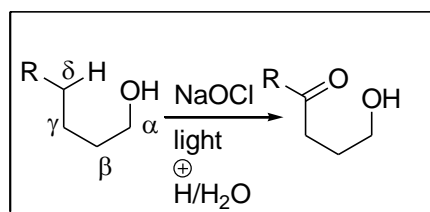




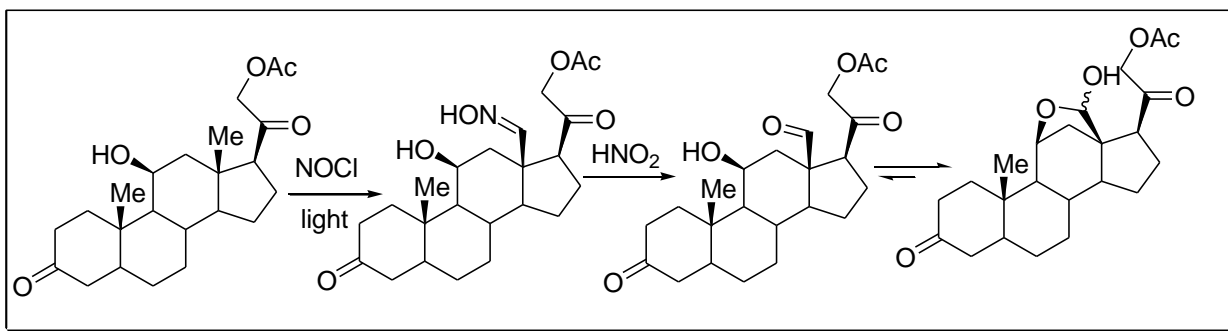
9.4 Formation of Carbon-Nitrogen Bonds

9.4.1 Barton Nitrite Photolysis Reaction

Photolysis of organic nitrites can be utilized to introduce functionality at unreactive aliphatic δ -carbon.

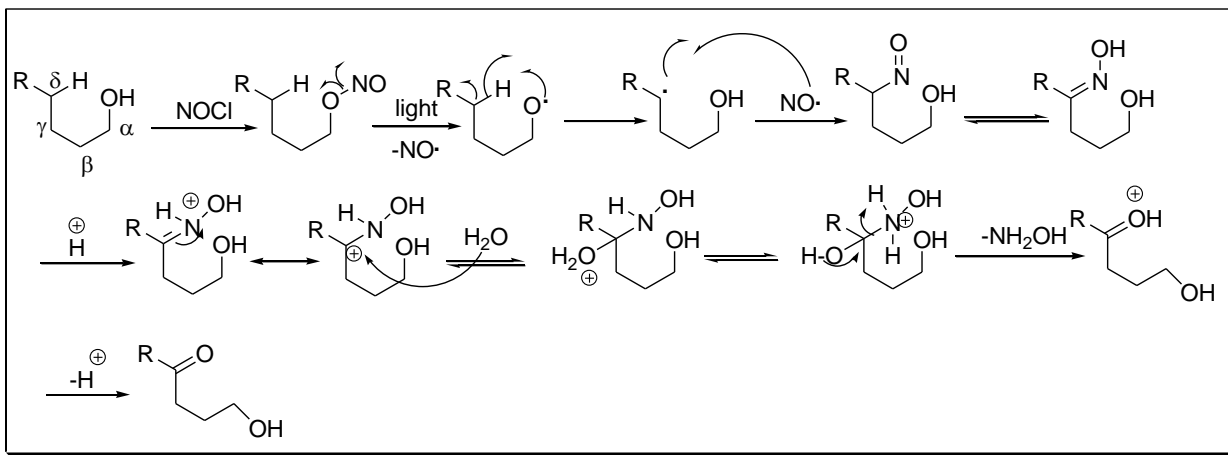


For example, the synthesis of aldosterone 21-acetate from corticosterone acetate has been demonstrated.



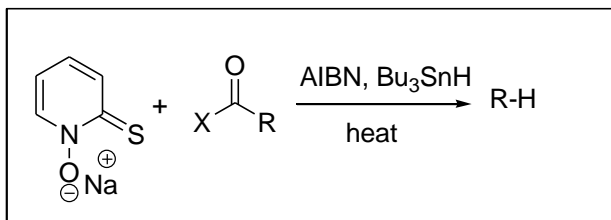
Mechanism

Photolysis of organic nitrites gives oxy-radical which abstracts hydrogen from a δ -CH bond. The resulting alkyl radical reacts with nitric oxide liberated during the photolysis to yield a nitroso-derivative which tautomerizes to oxime that can be hydrolyzed to carbonyl group.



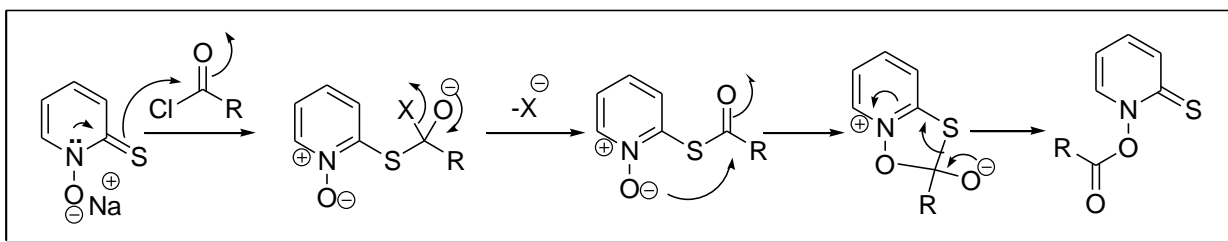
9.4.2 Barton Decarboxylation

Thiohydroxamate ester (commonly referred to as a Barton ester) with tributyltin hydride or t-butylmercaptan in the presence of a radical initiator undergoes decarboxylation to give alkanes. The driving for this reaction is the S-Sn bond formation.

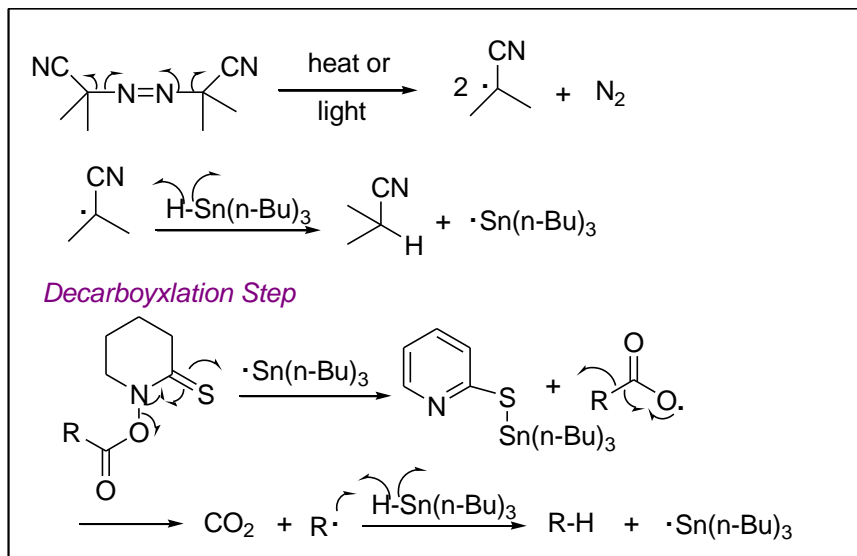


Mechanism

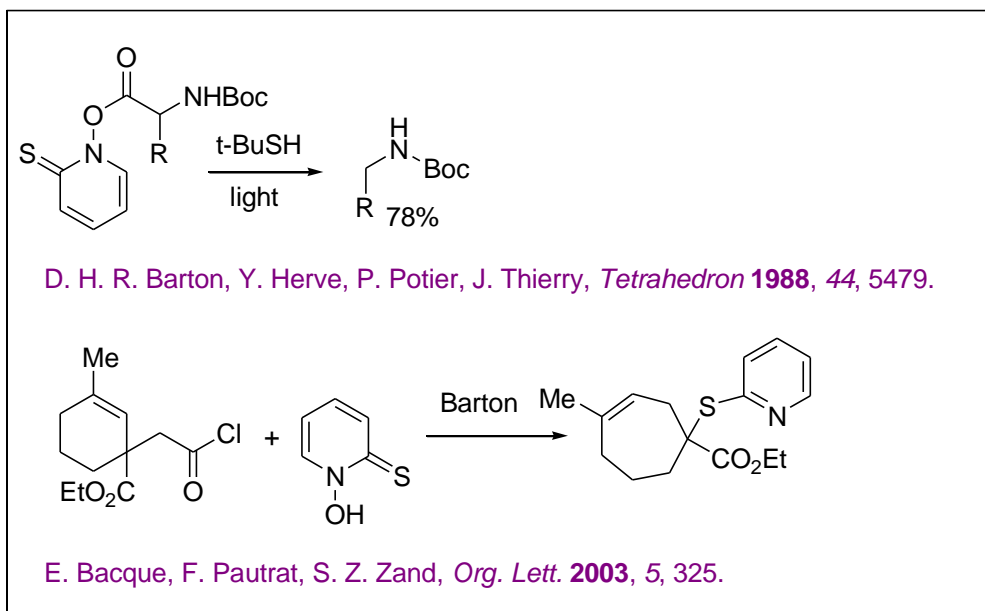
Instead of direct reaction of oxygen with the acid chloride, the following occurs:



Decarboxylation

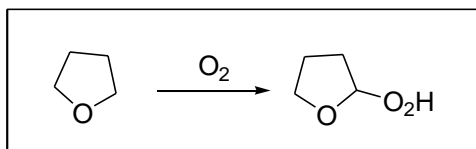


Examples:



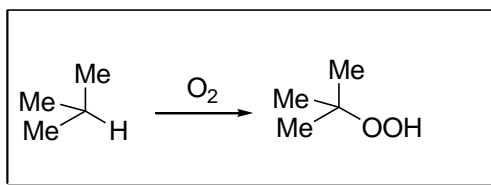
9.5 Formation of Carbon-Oxygen Bonds

In a wide variety of environments, C-H bond undergoes oxidation on standing in air to give hydroperoxides. For example, ethers proceed autoxidation to give α -hydroperoxide.

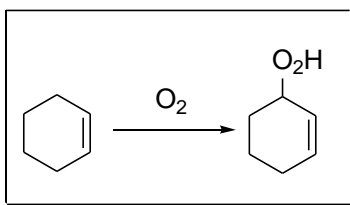


Since hydroperoxides are known to explode on heating, it is essential to remove them (e.g. by reduction with aqueous iron(II) sulfate) from ethers before their use as solvents for the reactions.

Isobutane can be transformed into t-butyl hydroperoxide in the presence of initiator.

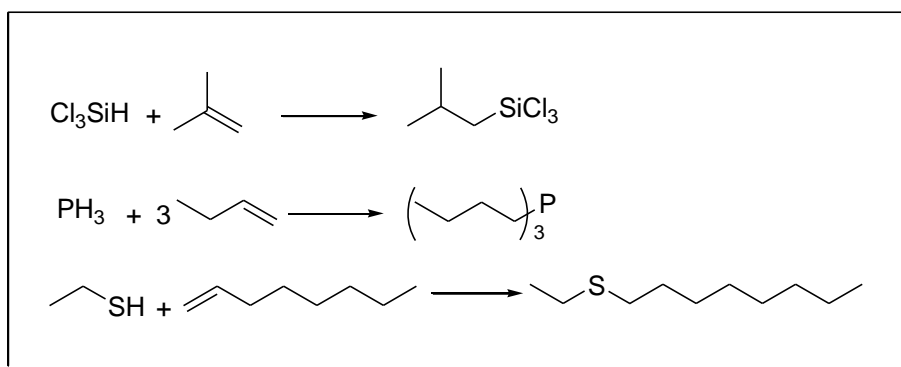


Alkenes are more reactive compared to alkanes due to greater stability of allyl radicals compared to alkyl radicals.



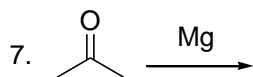
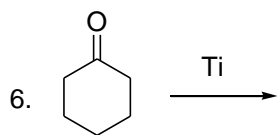
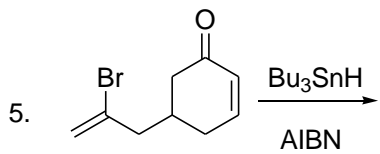
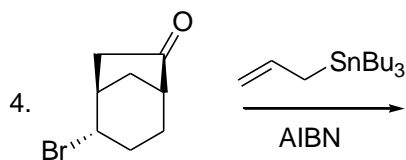
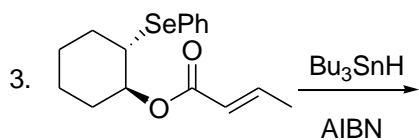
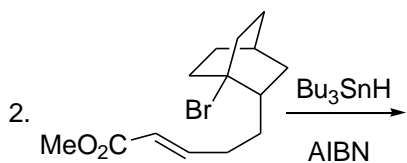
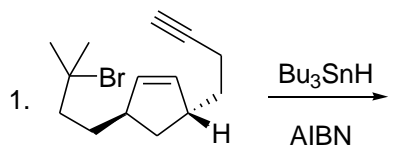
9.6 Formation of Bonds to Other Elements

Elements such as sulfur, phosphorus and silicon can proceed reactions with alkenes and alkynes via radical catalyzed process. The characteristics of these reactions are similar to those described above. For example,



Problems:

What would be the products for the following reactions?



Text Books:

R.O.C. Norman and C. M. Coxon, *Principles of Organic Synthesis*, CRC Press, New York, 2009.

J. March, *Advanced Organic Chemistry*, 4th ed, Wiley Interscience, New York, 1992.

