Principles of Organic Synthesis
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Lecture 28
Free Radical Reactions

Welcome you all to principles of organic synthesis. So far, we had 27 lectures where we studied aliphatic C-C and C-N bonds formation, organometallic reagents, electrophilic and nucleophilic aromatic substitutions, reactions of aromatic diazonium salts, and phosphorus, sulfur, silicon, boron and tin containing reagents.

Now we will start the free radical reactions. This is last module in this course. In this lecture, we will study the principles of free radical formation. Then, we will study the use of free radical reactions for the formation of carbon-halogen and carbon-carbon bonds.

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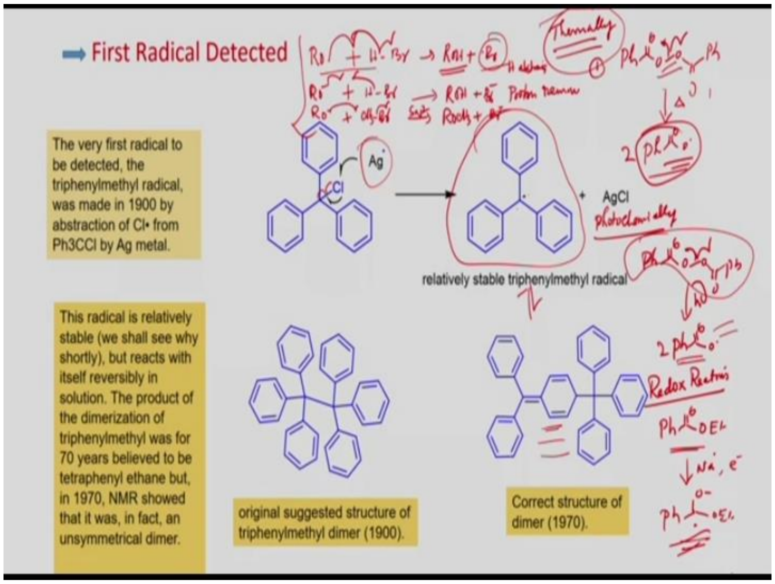

First Radical Detected

The very first radical to be detected, the triphenylmethyl radical, was made in 1900 by abstraction of Cl• from Ph3CCl by Ag metal.

relatively stable triphenylmethyl radical

This radical is relatively stable (we shall see why shortly), but reacts with itself reversibly in solution. The product of the dimerization of triphenylmethyl was for 70 years believed to be tetraphenyl ethane but, in 1970, NMR showed that it was, in fact, an unsymmetrical dimer.

original suggested structure of triphenylmethyl dimer (1900).

Correct structure of dimer (1970).

All of you know free radical is a reactive species and only a few organic free radicals are relatively stable. For example, triphenylmethyl chloride with silver produces triphenylmethyl radical, which exists indefinitely as a dimer in benzene. The stability in part is due to the unpaired electron delocalization and in part by the steric force that inhibits its reaction.

Free radicals can be formed by 3 ways.

Thermal generation: Compound with a weak bond, like peroxide and bromine, can undergo homolysis to give free radical at moderate temperature. In addition, compound, like AIBN, can undergo homolytic cleavage at room temperature because the fragmentation gives a strongly bonded product (N_2).

Photochemical generation: Molecules such as halogen, alkyl nitrites and hypochlorite using light undergo fragmentation to produce radical.

Redox generation: Some covalent bonds undergo hemolysis by the acceptance of an electron from species of one electron donor. For example, sodium is an electropositive element and can give an electron to ester to give a carbon centered radical, which dimerizes to give acyloin.

On the other hand, substrate can also be broken by donating an electron to an electron acceptor. For example, see oxidation of certain phenols with iron(III) salt.

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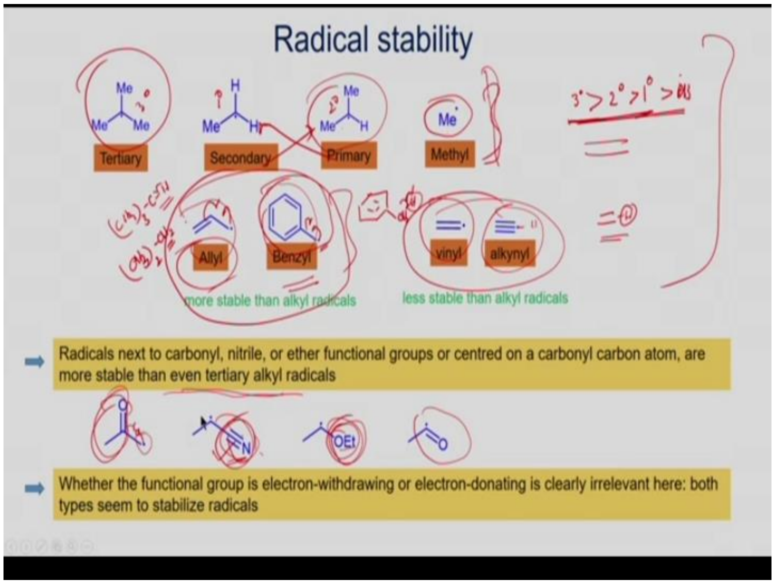

Radical stability

Radicals next to carbonyl, nitrile, or ether functional groups or centred on a carbonyl carbon atom, are more stable than even tertiary alkyl radicals

Whether the functional group is electron-withdrawing or electron-donating is clearly irrelevant here: both types seem to stabilize radicals

Now let us look at the stability of the radicals. Increasing order of the stability of the alkyl radical is: methyl < primary < secondary < tertiary radical.

If we compare the stability of alkyl radical with vinyl, alkynyl, allyl and benzyl radicals, alkyl radical is more stable than vinyl and alkynyl radical, and less stable than allyl and benzyl radical.

Further, the radical next to carbonyl, nitrile or ether functional group or centered on the carbonyl carbon, which is more stable than the tertiary alkyl radical.

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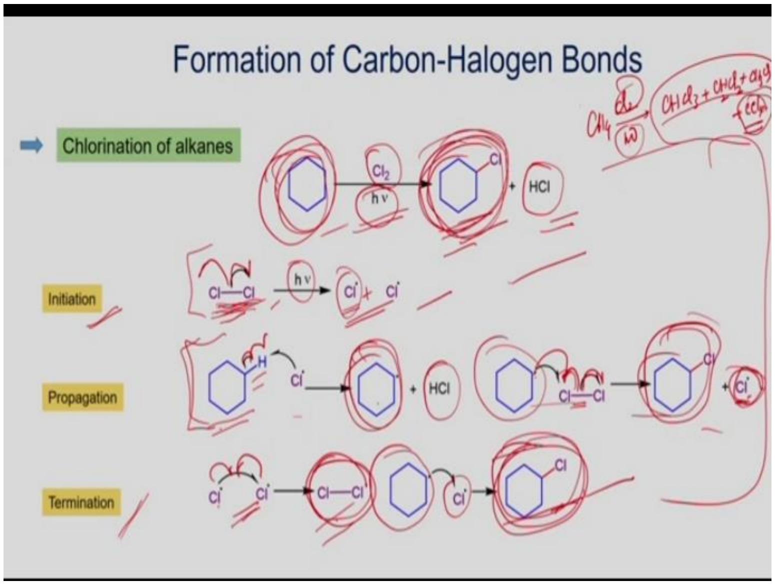

Formation of Carbon-Halogen Bonds

Chlorination of alkanes

Initiation

Propagation

Termination

Now, let us look at the carbon-halogen bond formation. Cyclohexane with chlorine using light produces cyclohexyl chloride.

Chlorine gas in the presence of light undergoes hemolytic cleavage to chlorine radical, which is known as the initiation step. Once the chlorine radical is formed, which reacts with cyclohexane C-H bond to produce cyclohexyl radical. The cyclohexyl radical reacts with chlorine gas to produce cyclohexyl chloride and chlorine radical, which is known as the propagation step. The chlorine radical can react with another chlorine radical to give chlorine gas or with cyclohexyl radical to produce cyclohexyl chloride, which is known as the termination step.

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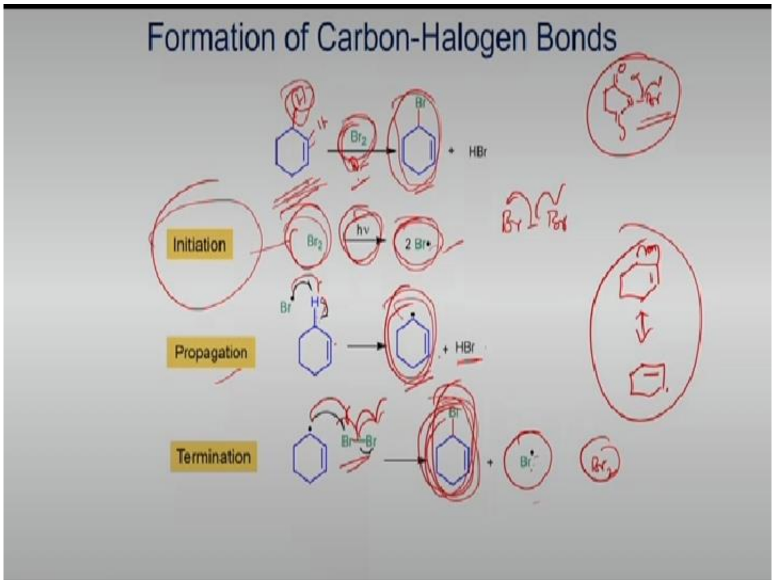

Formation of Carbon-Halogen Bonds

Initiation

Propagation

Termination

Here is the reaction of cyclohexene with bromine under light. As we have seen above, bromine undergoes homolytic cleavage to give a bromine radical that reacts with allylic C-H bond of cyclohexene to give allyl radical, which reacts with bromine to give 3-bromocyclohexene.

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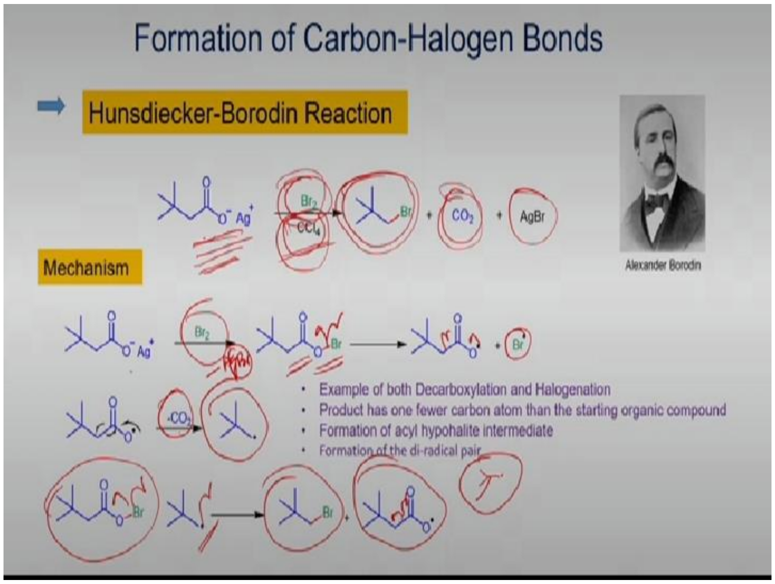

Formation of Carbon-Halogen Bonds

Hunsdiecker-Borodin Reaction

Mechanism

- Example of both Decarboxylation and Halogenation
- Product has one fewer carbon atom than the starting organic compound
- Formation of acyl hypohalite intermediate
- Formation of the di-radical pair

Alexander Borodin

Carboxylic acid can be converted to halo substrate via a radical decarboxylation. For example, sodium salt of 3,3-dimethylbutanoic acid with silver nitrate gives the silver carboxylate, which with bromine in CCl$_4$ produces neopentyl bromide. The silver salt reacts with bromine to give acyl hypobromite. Which undergoes homolysis to give acyloxy radical that loses carbon dioxide to give alkyl radical. Reaction with acyl hypobromite yields neopentyl bromide.

So far we have seen carbon-halogen bond formation via substitution reaction. Now let us focus on addition to carbon-carbon double bond for the carbon-halogen bond formation. These reactions are carried out in the presence of peroxide as the radical initiator.

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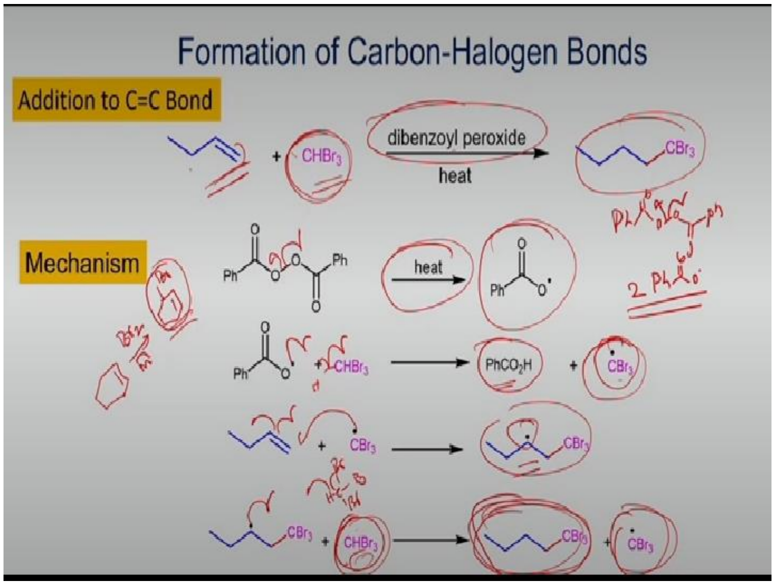

Formation of Carbon-Halogen Bonds

Addition to C=C Bond

Mechanism

Here is the addition reaction of butene with bromoform in the presence of benzoyl peroxide as the radical initiator. Peroxide undergoes cleavage to produce benzoyl radical that reacts with bromoform to yield benzoic acid and CBr_3 radical. Addition reaction to butene gives the secondary radical, which can react with bromoform to yield the addition compound that is synthetically useful.

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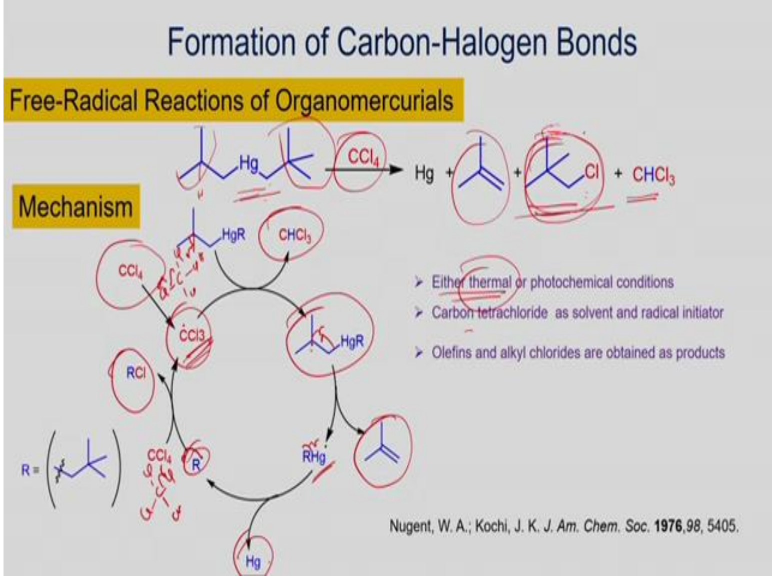

Formation of Carbon-Halogen Bonds

Free-Radical Reactions of Organomercurials

Mechanism

- Either thermal or photochemical conditions
- Carbon tetrachloride as solvent and radical initiator
- Olefins and alkyl chlorides are obtained as products

Nugent, W. A.; Kochi, J. K. *J. Am. Chem. Soc.* **1976**,*98*, 5405.

Here is an example for the transformation of isobutylneopentylmercury compound to isobutene and neopentyl chloride in CCl_4 via a radical pathway. CCl_4 undergoes homolytic cleavage to produce CCl_3 and chlorine radicals. The CCl_3 radical reacts with substrate to produce chloroform and isobutyl radical that converts to isobutene via the homolytic cleavage of C-Hg bond. Elimination of mercury give neopentyl radical that reacts with CCl_4 to produce neopentyl chloride

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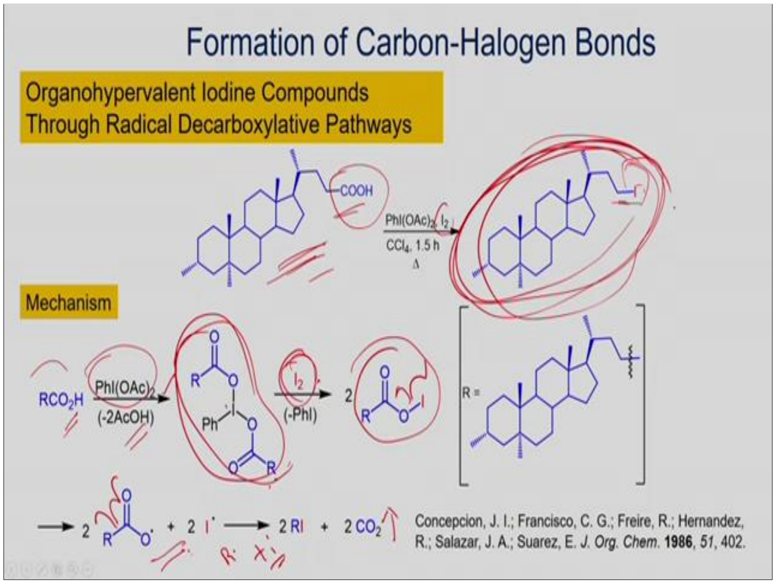

Formation of Carbon-Halogen Bonds

Organohypervalent Iodine Compounds
Through Radical Decarboxylative Pathways

Mechanism

Concepcion, J. I.; Francisco, C. G.; Freire, R.; Hernandez, R.; Salazar, J. A.; Suarez, E. *J. Org. Chem.* **1986**, *51*, 402.

Here we see the use of hypervalent iodine for the decarboxylative radical carbon-halogen bond formation. Carboxylic acid with $PhI(OAc)_2$ produces iodozobenzene dicarboxylate, which reacts with iodine to yield acyl hypoiodite. Homolytic cleavage gives iodine and acyloxy radicals. Decarboxylation gives alkyl radical that react with iodine radical to produce alkyl iodide.

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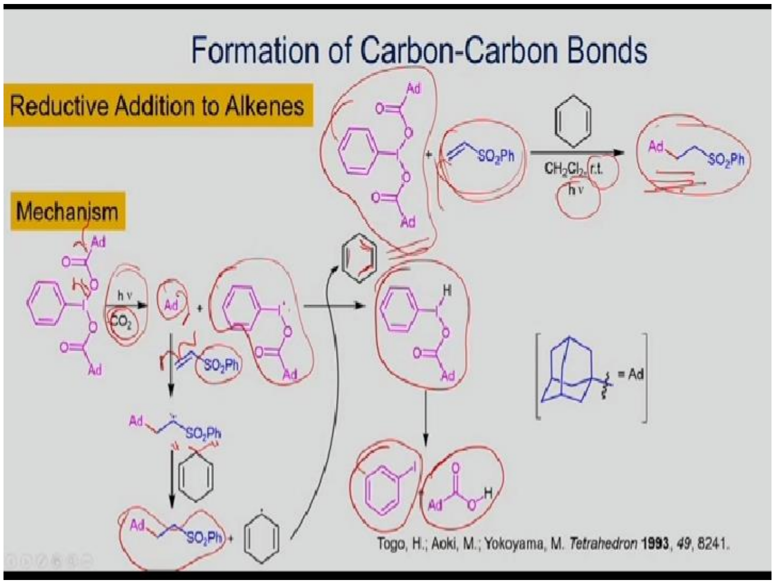

Formation of Carbon-Carbon Bonds

Reductive Addition to Alkenes

Mechanism

Togo, H.; Aoki, M.; Yokoyama, M. *Tetrahedron* **1993**, *49*, 8241.

The above strategy has been extended to the addition reaction of activated carbon-carbon double bond. Homolysis of iodozobenzene dicarboxylate gives the adamantyl radical, which undergoes addition reaction with vinyl sulfone to give the secondary carbon radical that abstracts hydrogen from cyclohexadiene.

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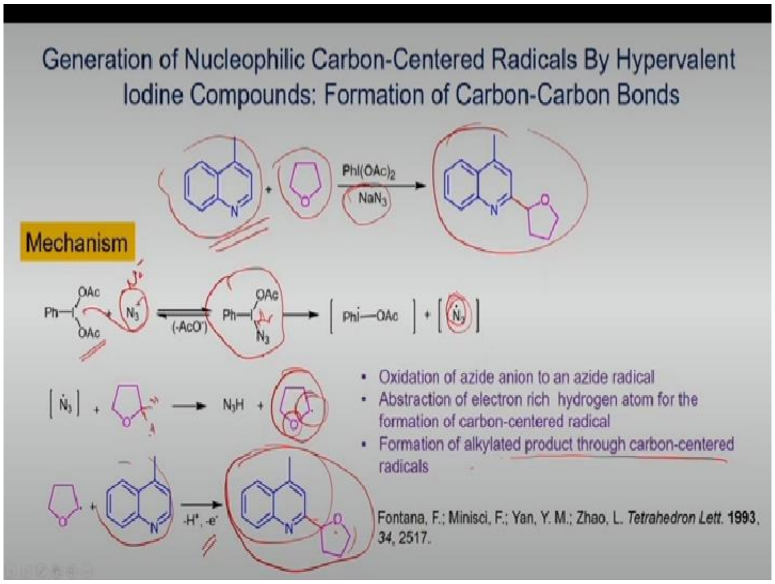
Generation of Nucleophilic Carbon-Centered Radicals By Hypervalent Iodine Compounds: Formation of Carbon-Carbon Bonds

- Oxidation of azide anion to an azide radical
- Abstraction of electron rich hydrogen atom for the formation of carbon-centered radical
- Formation of alkylated product through carbon-centered radicals

Fontana, F.; Minisci, F.; Yan, Y. M.; Zhao, L. *Tetrahedron Lett.* **1993**, *34*, 2517.

The hypervalent iodine chemistry has been further utilized for the coupling of quinoline with THF. In this reaction, iodozobenzene diacetate reacts with NaN$_3$ to give N$_3$ radical, which abstracts electron rich hydrogen atom from THF to yield THF radical, which adds to quinoline at 2-position to yield the C-C coupled product.

So far we have seen the use of hypervalent reagent for the radical C-C bond formation. Now, let us see the use of tin chemistry for the radical C-C bond formation, which has been well explored.

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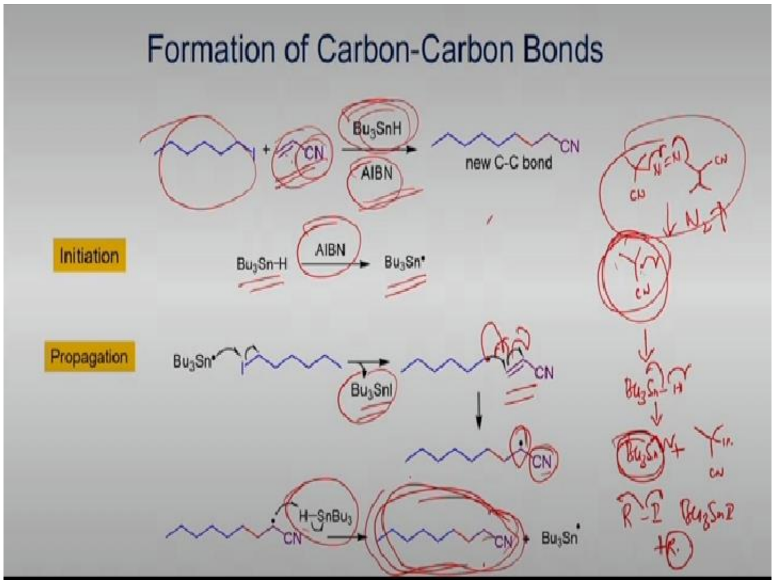
Formation of Carbon-Carbon Bonds

Homolysis of AIBN produces isobutyronitrle radical. It reacts with tributyltin hydride to produce tributyltin radical that reacts with hexyl iodide to produce tributyltin iodide and hexyl radical. The hexyl radical adds to acrylonitrile to give a secondary carbon centered radical that reacts with tributyltin hydride to give alkyl nitrile. AIBN is the radical initiator and the fragmentation occurs due to the formation of strongly bonded nitrogen molecule.

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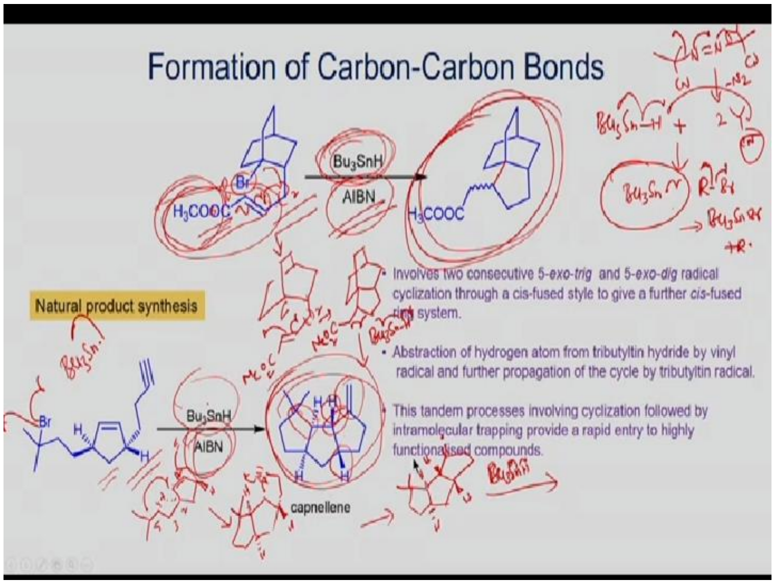

Formation of Carbon-Carbon Bonds

Natural product synthesis

- Involves two consecutive 5-*exo-trig* and 5-*exo-dig* radical cyclization through a cis-fused style to give a further *cis*-fused ring system.
- Abstraction of hydrogen atom from tributyltin hydride by vinyl radical and further propagation of the cycle by tributyltin radical.
- This tandem processes involving cyclization followed by intramolecular trapping provide a rapid entry to highly functionalised compounds.

Here two examples illustrate the power of tributyltin hydride chemistry. First example shows the formation of bridgehead radical and subsequent intramolecular addition to the activated double bond to give the tricyclic compound. This is an important transformation as radical reaction is normally difficult due to the bridgehead radical can not achieve the planar geometry. The second example involves the formation of a tertiary radical and subsequent addition to a double bond to give a secondary radical that further reacts with tripled bond to give the tricyclic compound.

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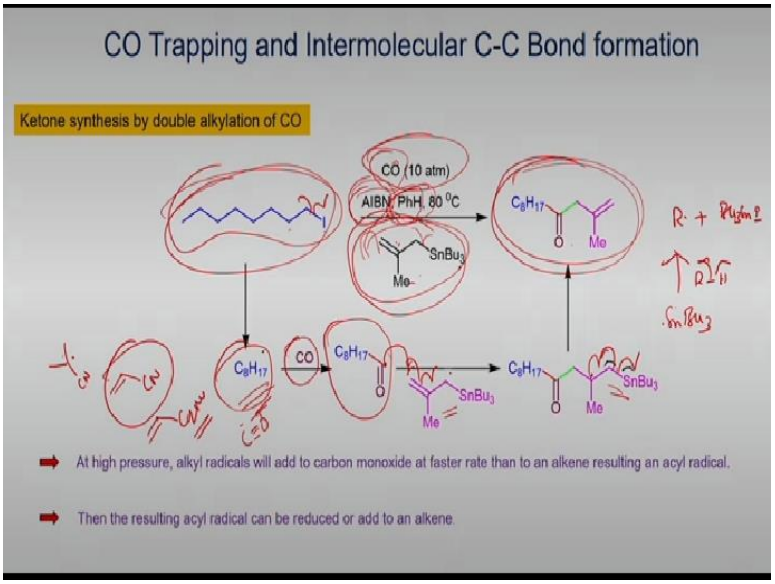

CO Trapping and Intermolecular C-C Bond formation

Ketone synthesis by double alkylation of CO

- At high pressure, alkyl radicals will add to carbon monoxide at faster rate than to an alkene resulting an acyl radical.
- Then the resulting acyl radical can be reduced or add to an alkene.

Now let us look at CO trapping and carbon-carbon bond formation. At high pressure, alkyl radical adds to CO compared to alkene. Here octyl iodide adds to CO to give the acyl radical that undergoes reaction with allyl tin to give a ketone.

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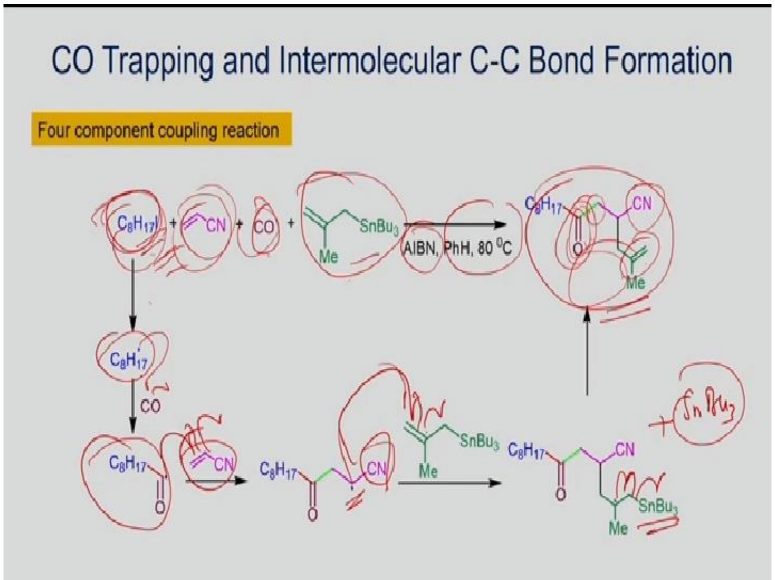

CO Trapping and Intermolecular C-C Bond Formation

Four component coupling reaction

Here octyl iodide converts to octyl radical, which reacts with CO to yield the acyl radical. Addition of an electron deficient acrylonitrile followed by allyl tin gives the four component coupling functionalized ketone.

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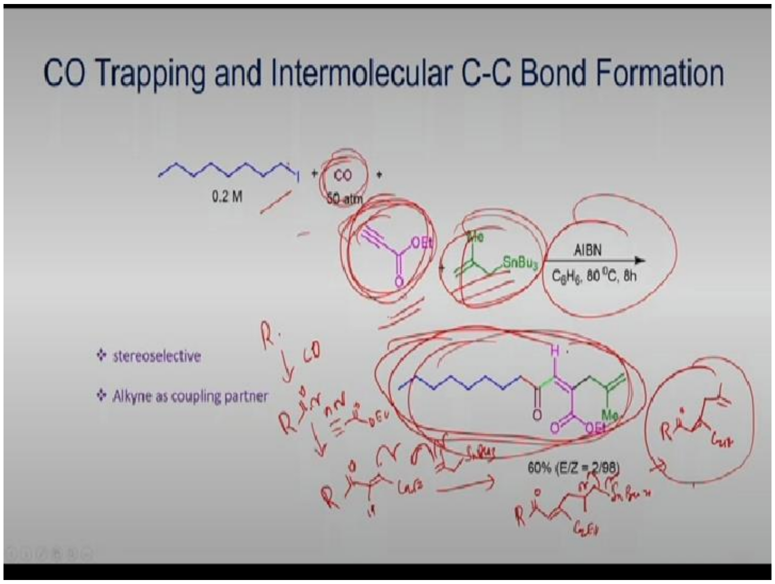

CO Trapping and Intermolecular C-C Bond Formation

- stereoselective
- Alkyne as coupling partner

Here is an another example for the four component coupling reaction. As the previous example, octyl iodide converts to octyl radical that adds to CO. The resultant acyl radical further adds to the activated propargyl ester and allyl tin to give the functionalized carbonyl compound.

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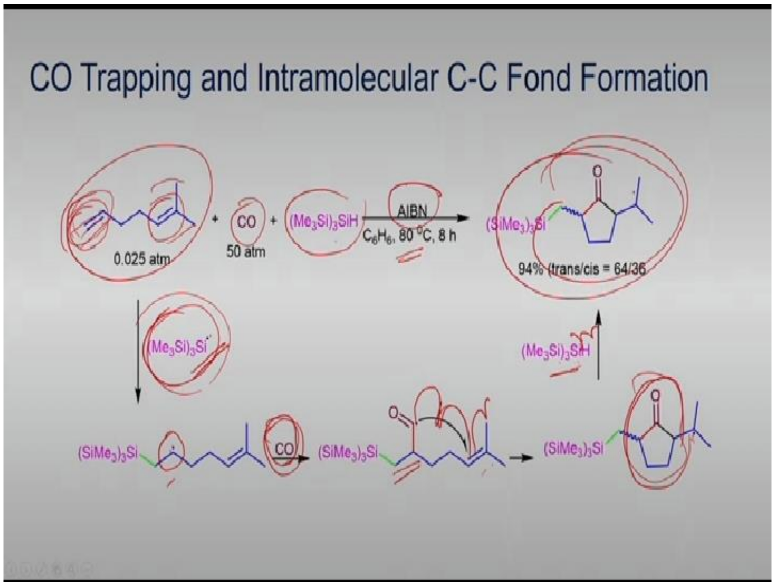

CO Trapping and Intramolecular C-C Fond Formation

In this example, silyl hydride is converted to silyl radical that adds to the double bond to give a secondary radical that reacts with CO to give the acyl radical. Intramolecular cyclization with double bond produces a tertiary radical that reacts with silyl hydride to give a cyclic ketone.

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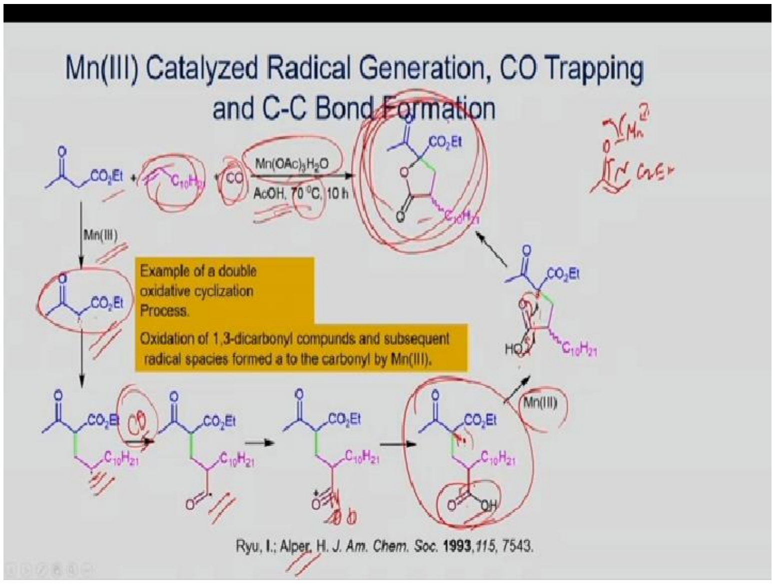

Mn(III) Catalyzed Radical Generation, CO Trapping and C-C Bond Formation

Example of a double oxidative cyclization Process.

Oxidation of 1,3-dicarbonyl compunds and subsequent radical spacies formed a to the carbonyl by Mn(III).

Ryu, I.; Alper, H. *J. Am. Chem. Soc.* **1993**, *115*, 7543.

Let us look at here the synthesis of five membered lactone using the CO trapping chemistry. β-Ketoester converts to methylene radical in the presence of Mn(III), which adds to an alkene to give the secondary radical. Reaction with CO produces the acyl radical that converts to acid. Mn(III) catalyzed radical cyclization gives the lactone. This chemistry has been well explored.

It is noteworthy to mention that electron rich radical reacts with CO compared to addition to electron deficient double bond. On the other hand, electron deficient radical reacts with electron rich alkene compared to CO. The reactivity can thus be controlled by the reaction conditions.

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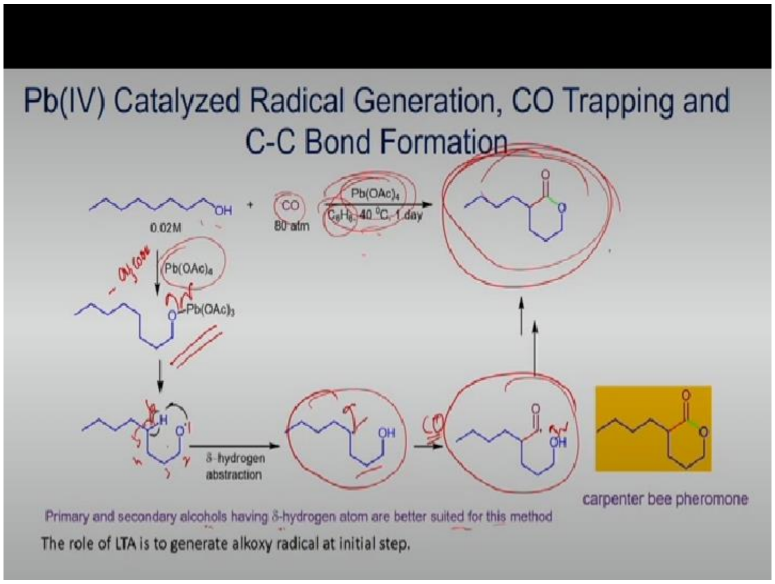

Pb(IV) Catalyzed Radical Generation, CO Trapping and C-C Bond Formation

Primary and secondary alcohols having δ-hydrogen atom are better suited for this method

The role of LTA is to generate alkoxy radical at initial step.

Here is an example for the CO trapping and carbon-carbon bond formation using hypervalent iodine. Octanol with iodozobenzene diacetate produces octyloxy radical that abstracts the δ–hydrogen to give the secondary radical. Addition to CO followed cyclization gives the lactone. This method is found to be successful with primary and secondary alcohols that bear δ hydrogen.

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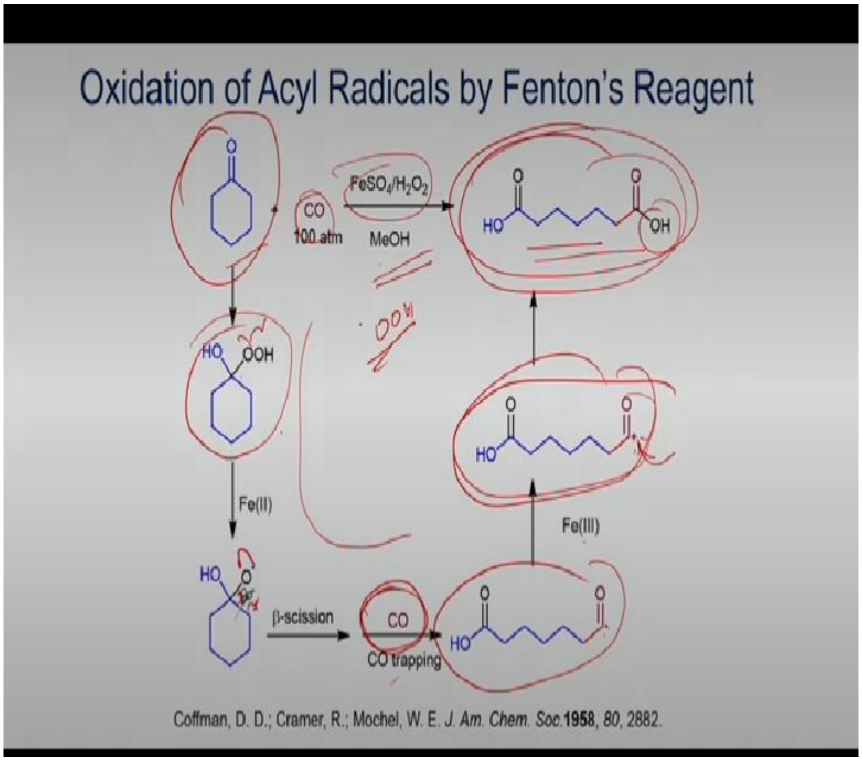

Oxidation of Acyl Radicals by Fenton's Reagent

Coffman, D. D.; Cramer, R.; Mochel, W. E. *J. Am. Chem. Soc.* **1958**, *80*, 2882.

Here the use of Fenton’s reagent is demonstrated for the oxidation of cyclohexanone to suberic acid by trapping CO. Addition of hydrogen peroxide radical to cyclohexanone followed by homolysis and β-scission provides the alkyl radical that adds to CO. The acyl radical is converted to acylium ion and subsequently carboxylic acid.

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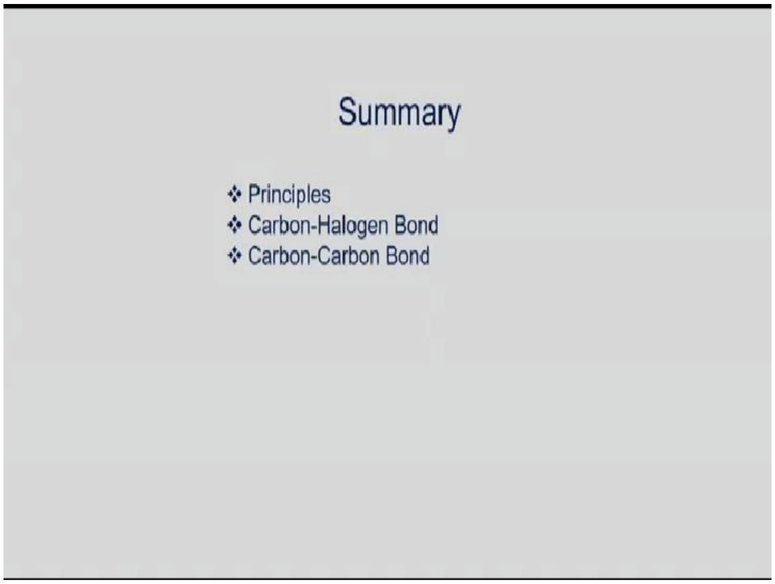

Summary

- ❖ Principles
- ❖ Carbon-Halogen Bond
- ❖ Carbon-Carbon Bond

In summary, we have seen the methods for the radical formation.

We have then seen the utilities of the radical chemistry for the carbon-halogen bond formation. We have seen examples for the substitution reaction with C-H bond. We have also seen examples for the addition reaction with double and triple bonds.

We have seen the utilities of the radical chemistry for the carbon-carbon bond formation. The radicals are formed by the radical initiator and add to the double and triple bonds. We have seen the use of tributyltin hydride, which affords powerful synthetic tool for the coupling of alkyl halides with double and triple bonds. This reaction finds greater applications in tandem cyclization, which will be difficult to accomplish by other methods.

We have seen several examples for the CO trapping to form acyl radical. Using this strategy, the synthesis of ketone, lactone and carboxylic acid can be accomplished. As you can see, the radical chemistry plays an important role in synthetic chemistry for the construction carbon-halogen and carbon-carbon bonds. With this we conclude this lecture, Thank you very much.,