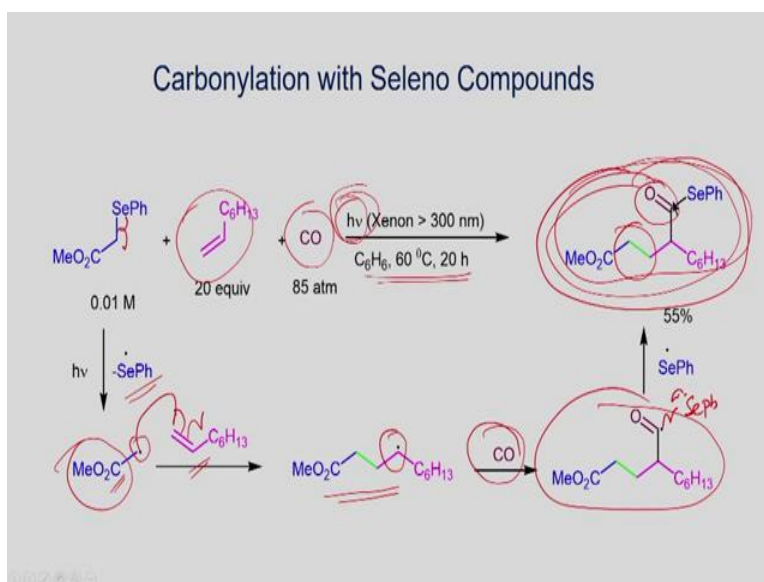


Principles of Organic Synthesis
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Lecture 29
Free-Radical Reactions

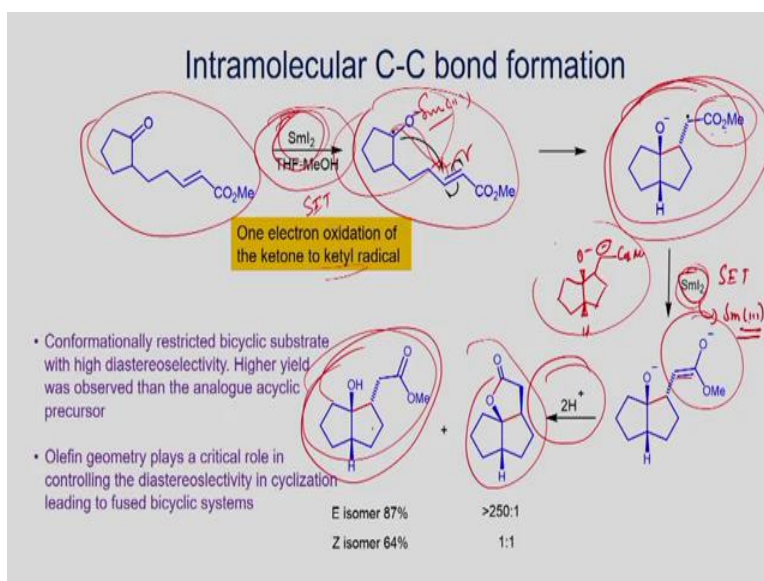
Welcome you all to principles of organic synthesis. Presently, we study the free-radical reactions. In this module, so far, we had one lecture where we studied the methods for the free-radical formation and their reactions for carbon-halogen and carbon-carbon bonds construction. In this lecture, we will continue with the synthetic strategies for the free-radical carbon-carbon bond formation.

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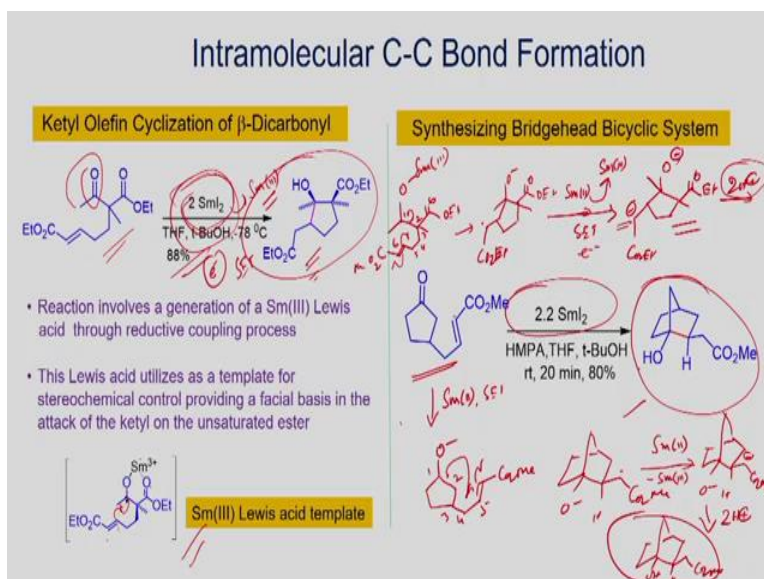
The first example involves the homolytic cleavage of the weak C-Se bond using light to produce the free-radical. The carbon radical bearing electron withdrawing ester group adds to terminal alkene to yield secondary carbon radical. CO trapping gives the acyl radical that reacts with phenylselenanyl radical to produce the selenoate.

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Here is an example for the formation of the free-radical by the redox process using SmI_2 . SmI_2 gives an electron to the ketone to produce the ketyl radical. Intramolecular addition to the conjugated double bond produces a stabilized carbon radical. SmI_2 transfers an electron (SET) to form an enolate, which undergoes protonation. The compound with *syn* substituents proceeds an intramolecular cyclization to give the five membered lactone. Thus, the reaction requires two equiv of SmI_2 to complete the process.

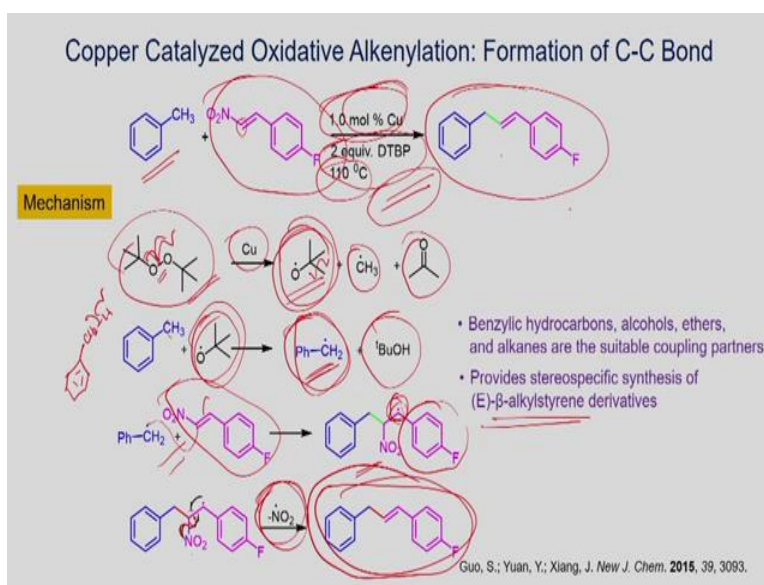
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As the previous example, here SmI_2 reduces the β -ketoester by giving an electron to produce the ketyl radical, which undergoes cyclization to produce the five membered cyclic compound. The stereochemistry can be controlled by the chelation of Sm(III) with the ester carbonyl group.

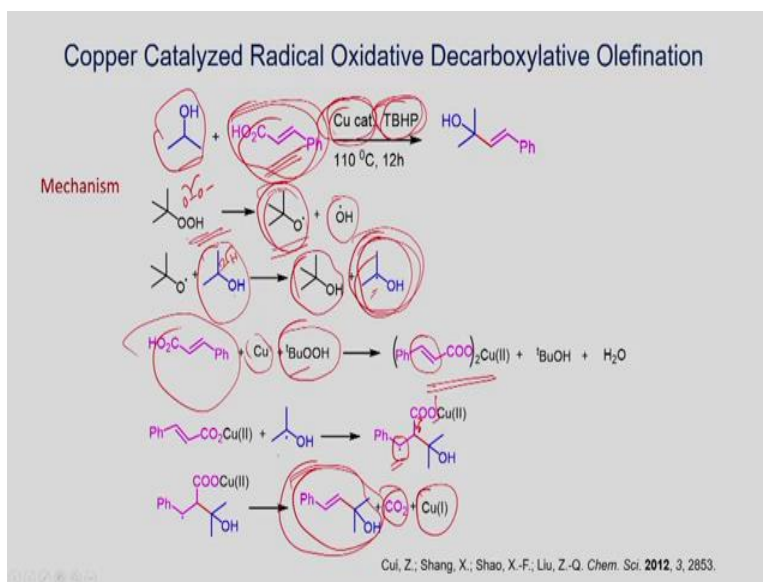
Similarly, the cyclopentanone is converted to ketyl radical by SET from SmI_2 . Intramolecular cyclization followed SET produces the carbanion, which is subsequently protonated to give the bicyclic compound.

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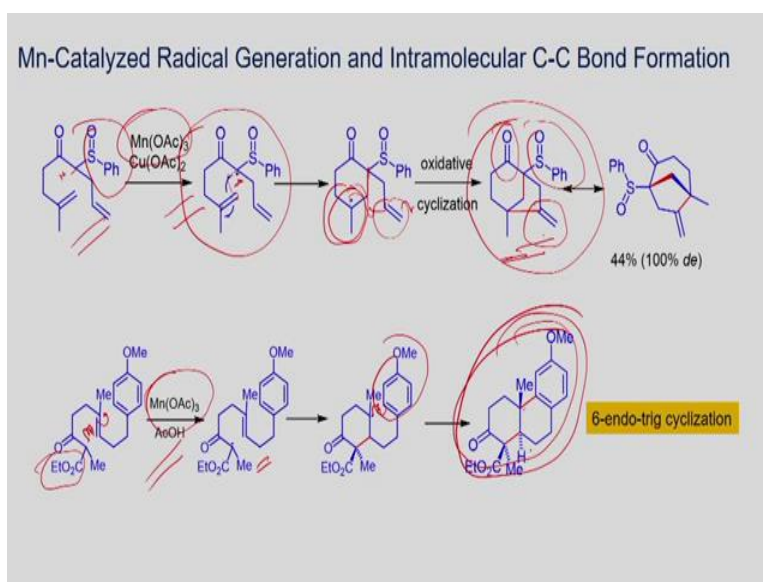
Now let us focus on Cu-catalyzed oxidative alkenylation of toluene using peroxide as the oxidant. The coupling of benzyl radical with *E*-(2-nitrovinyl)benzene gives β -benzylstyrene derivative using a catalytic amount of copper and 2 equiv of DTBP. Copper catalyzes the homolysis of DTBP to produce the *tert*-butoxy radical, which reacts with benzylic C-H bond. The benzyl radical adds to *E*-(2-nitrovinyl)benzene double bond to give the benzyl radical that converts to double bond by the elimination of NO_2 radical.

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Here is a Cu-catalyzed oxidative decarboxylative alkenylation of 2-propanol using TBHP as the oxidant. Homolysis of TBHP gives *tert*-butoxy radical, which reacts with 2-propanol to give the carbon radical, while cinnamic acid couples with Cu to produce Cu(II) cinnamate using TBHP. Addition of the radical to the double bond of cinnamate gives benzyl radical that converts to double bond by the removal of CO₂ and Cu(I) species via an homolytic cleavage.

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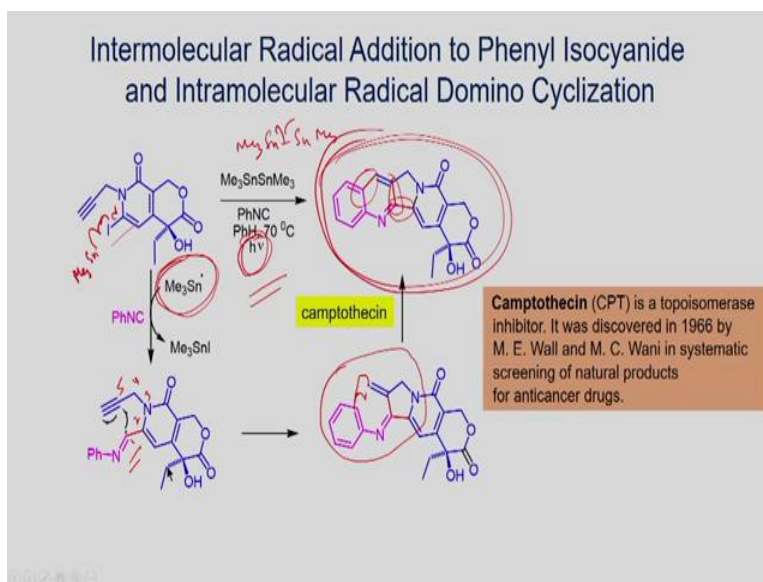
Here are two more examples of activated ketones for the formation of radical by redox process using Mn(OAc)₂ and subsequent cyclization to produce cyclic compounds. The first example has

sulfinyl substituent at β -position of the carbonyl group. Which undergoes the enol formation and reacts with $\text{Mn}(\text{OAc})_3$. Homolysis produces a tertiary radical, which is stabilized by the carbonyl as well as sulfinyl group. Intramolecular *6-endo-trig* cyclization with the double bond produces a tertiary radical that leads *5-exo-trig* cyclization with another double bond to yield primary radical that converts to double bond. $\text{Cu}(\text{OAc})_2$ oxidizes $\text{Mn}(\text{II})$ to $\text{Mn}(\text{III})$ to catalyze the reaction.

The second example shows a $\text{Mn}(\text{OAc})_3$ -mediated radical formation in the β -ketoester. Tandem *6-endo-trig* cyclization produces the tricyclic compound. The reaction is stereospecific, which can be understood by drawing the six membered chair conformation.

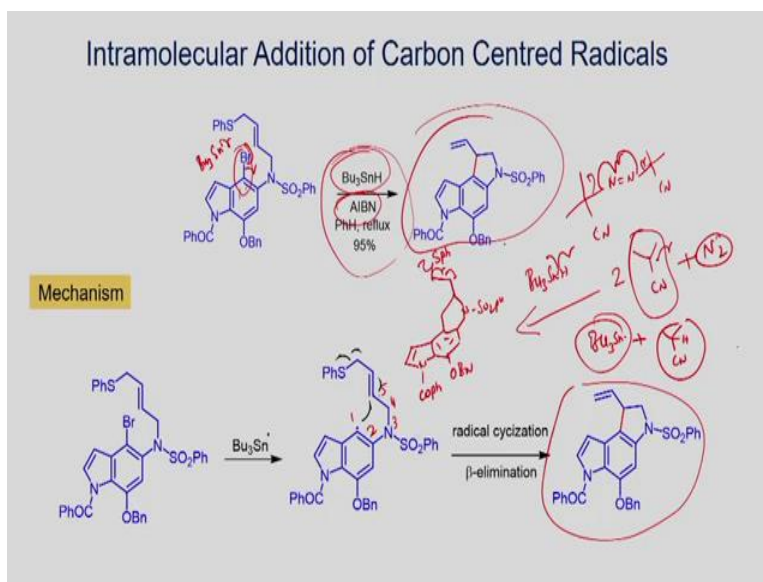
So far we have seen few interesting examples for the formation of radical by redox process and their application for the tandem cyclization.

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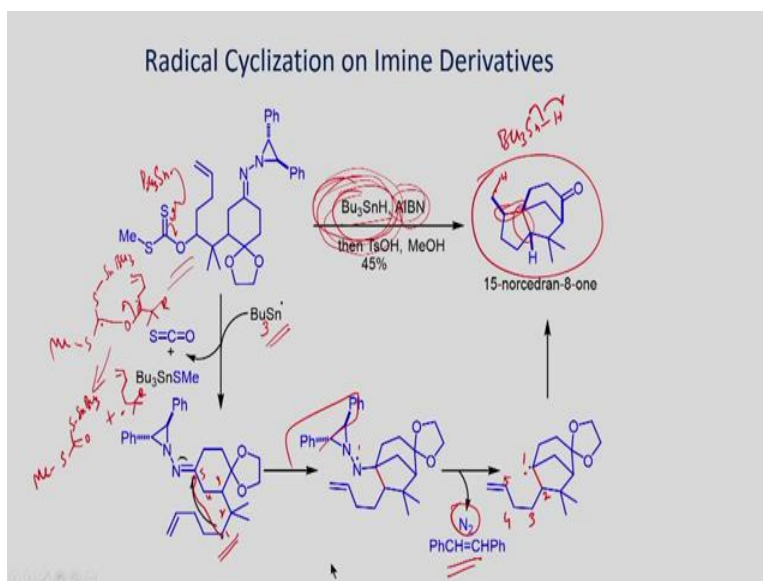
Now, let us see some examples for trialkyltin radical mediated C-C bond formation. Homolytic cleavage of the weak Sn-Sn bond of hexamethylditin yields trimethyltin radical, which cleaves the C-I bond. The alkenyl radical adds to phenyl isocyanide to give iminyl radical that undergoes *5-exo-dig* cyclization. The alkenyl radical undergoes cyclization with aromatic ring to produce polycyclic compound.

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In this reaction, tributyltin hydride reacts with AIBN to produce tributyltin radical that cleaves the C-Br bond. The aryl radical undergoes *5-exo-trig* cyclization followed by the β -elimination of phenyl sulfide radical to produce the tricyclic compound.

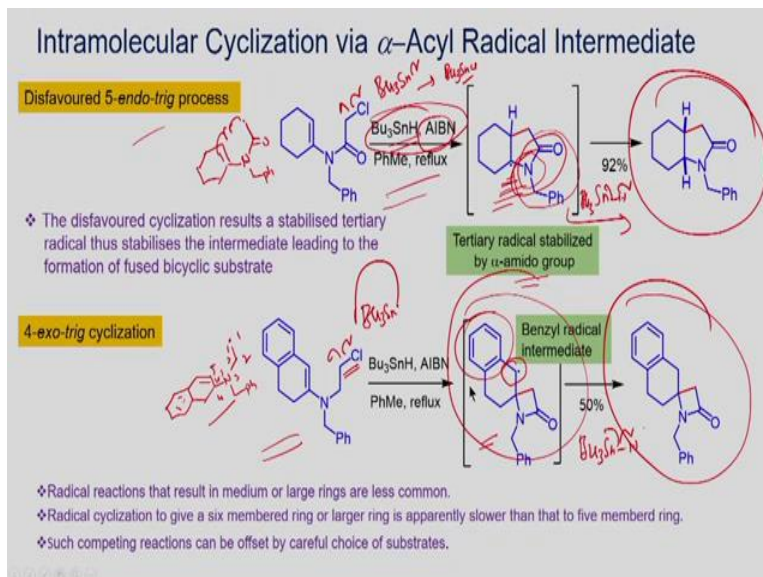
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So far, we have seen the cleavage of carbon-halogen bond with tin radical to form carbon radical. Here is an example where tin radical cleaves xanthate to produce carbon radical. The radical

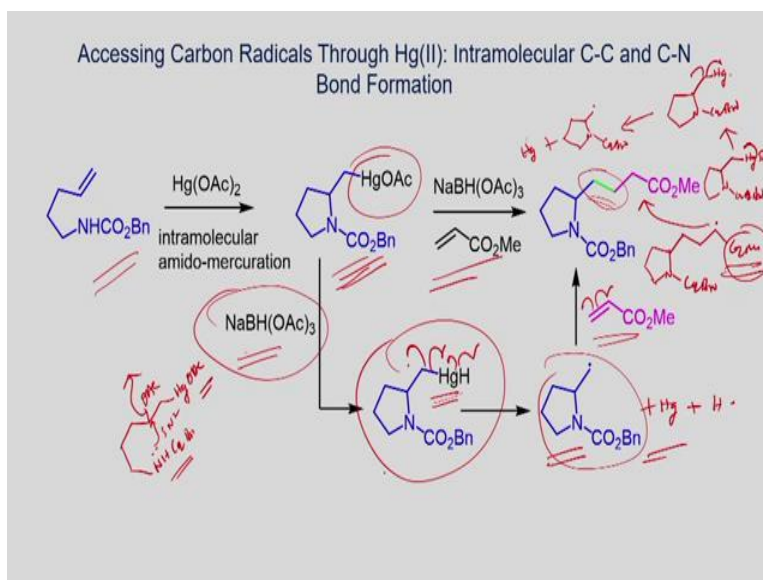
undergoes cyclization to C-N double bond followed by elimination of nitrogen and 5-*exo-trig* cyclization to give the tricyclic compound.

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Here are two examples for the tributyltin radical mediated cleavage of C-Cl bond to form carbon radical. The first example involves 5-*endo-trig* cyclization to give the bicyclic lactam. Similarly, the second example forms radical, which undergoes 4-*exo-trig* cyclization to give the lactam.

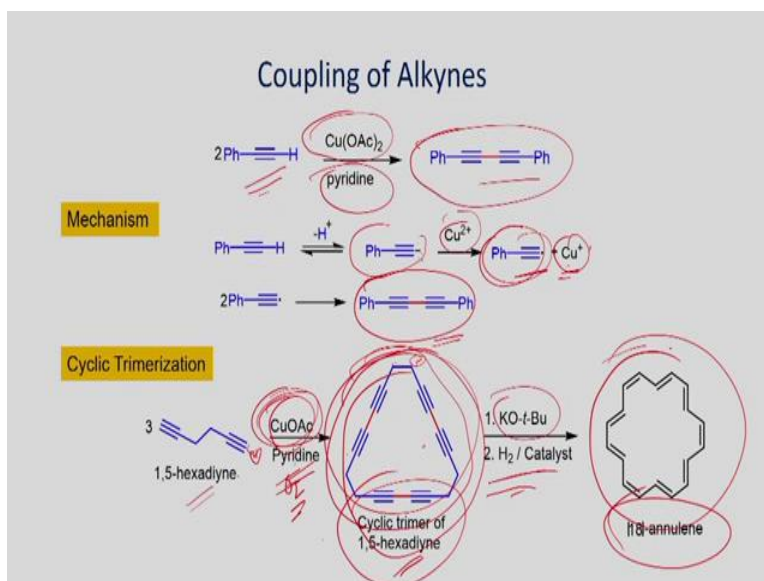
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Here the use of $\text{Hg}(\text{OAc})_2$ for the formation of radical is presented. $\text{Hg}(\text{OAc})_2$ with the double bond form mercuronium ion, which opens by the carbamate via the nucleophilic substitution. Reduction using $\text{NaBH}(\text{OAc})_3$ followed by homolysis of the C-Hg bond gives the methyl radical, which adds to methyl acrylate to produce the C-C coupled product.

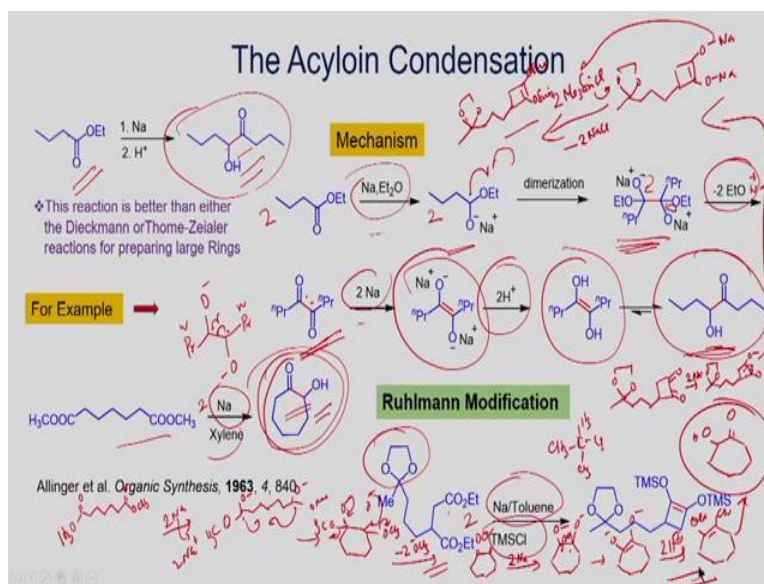
So far, we have seen several radical reactions for the carbon-carbon bond formation. Now let us coupling terminal alkynes via radical pathway.

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Here the use of radical chemistry is illustrated for the coupling of terminal alkyne. Deprotonation of the terminal alkyne and subsequent reaction with copper(II) salts gives alkynylcopper, which undergoes homolytic cleavage to give the acetylide radical that can be coupled with another acetylide radical. For an example, phenylacetylene dimerizes using $\text{Cu}(\text{OAc})_2$ in the presence of pyridine. Similarly, 1,5-hexadiyne can be trimerized, which can be converted to [18]-annulene via the deprotonation and hydrogenation sequence.

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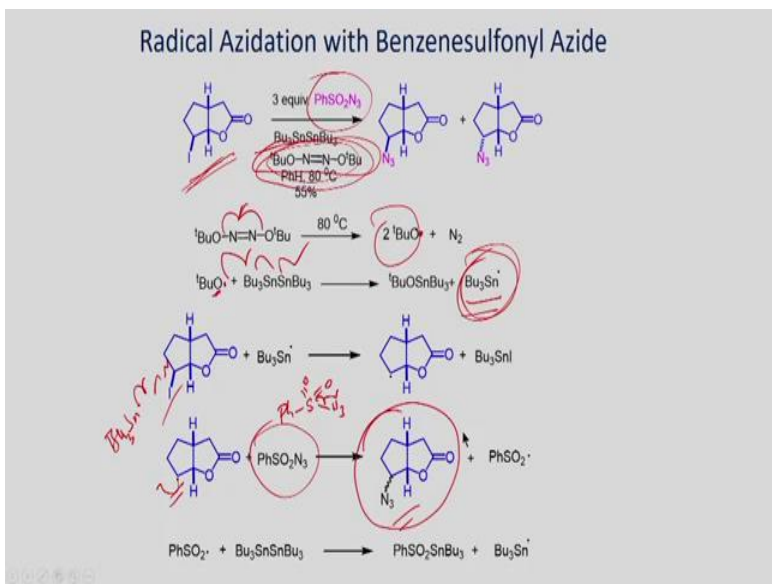


Now, let us look at the reductive coupling of two carboxylic esters using metallic sodium to yield α -hydroxyketone. The reaction is performed in aprotic solvent such as benzene under oxygen free condition. The reaction involves four steps. First, sodium transfers an electron to the ester group to produce carbon radical. Coupling of the carbon radical and elimination of alkoxy group produces a 1,2-diketone, which further reacts with two equiv of sodium to produce sodium enediolate. Neutralization with proton source gives enediol, which tautomerizes to α -hydroxyketone.

In case of diester, intramolecular acyloin condensation can be carried out to produce the cyclic compound. For example, heptane-1,7-dioic ester undergoes acyloin condensation to yield α -hydroxyheptanone.

Since alkoxide is generated in the reaction, base catalyzed condensation occurs. To minimize the side reaction, Rühlmann trapped the sodium enediolate using trimethylchlorosilane and the hydrolytic cleavage of the silylether gives the acyloin. Using this approach, the yield of the acylation can be increased. In addition, the base catalyzed side reaction can be minimized.

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Here the diastereoselective azidation of C-I bond of the bicyclic lactone is presented. Homolysis of 1,2-di-*tert*-butoxydiazene produces *tert*-butoxy radical. Which reacts with hexabutylditin to give tributyltin radical, which cleaves the C-I bond to generate carbon radical. Reaction with sulfonyl azide yields the alkyl azide. The azidation takes place to give a mixture of *syn* and *anti* stereoisomers.

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Summary

- ❖ Cu-Based Reactions
- ❖ Mn-Based Reactions
- ❖ Sm-Based Reactions
- ❖ Sn-Based Reactions
- ❖ Acyloin Condensation

In summary, we have seen the use of redox methods for the radical carbon-carbon bond formation. SmI_2 -mediated reactions are useful for the generation of ketyl radical, which can be reacted with double bond to give the cyclic compounds. Similarly, β -ketoester can be reacted with $\text{Mn}(\text{OAc})_3$ to produce carbon radical that can be reacted with double bond to give the cyclic compound. Further, copper(II) salt can be used to cleave peroxide to produce alkoxy radical that can be used to initiate the radical reactions. In addition, mercuration of alkene followed by reduction produce radical, that can be utilized for the addition to double bond. These are complimentary to the tin radical mediated reactions.

We have seen the coupling of terminal alkynes via radical pathway. This strategy can be used for the construction annulenes.

We have then seen the acyloin condensation and azidation of organic halides via radical pathway. With this we conclude this lecture. Thank you very much.