Principles of Organic synthesis
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Lecture 30
Free-Radical Reactions

Welcome you all to principles of organic synthesis. Presently, we study the free-radical reactions. So far, we studied the methods that can be used for the formation of free-radicals. Then, we studied the application of free-radical for the carbon-halogen and carbon-carbon bond formation. In this class, we will continue the application of free-radical for the C-N and C-O bond formation. Then, we will cover the decarboxylation and C-H functionalization with radical intermediate.

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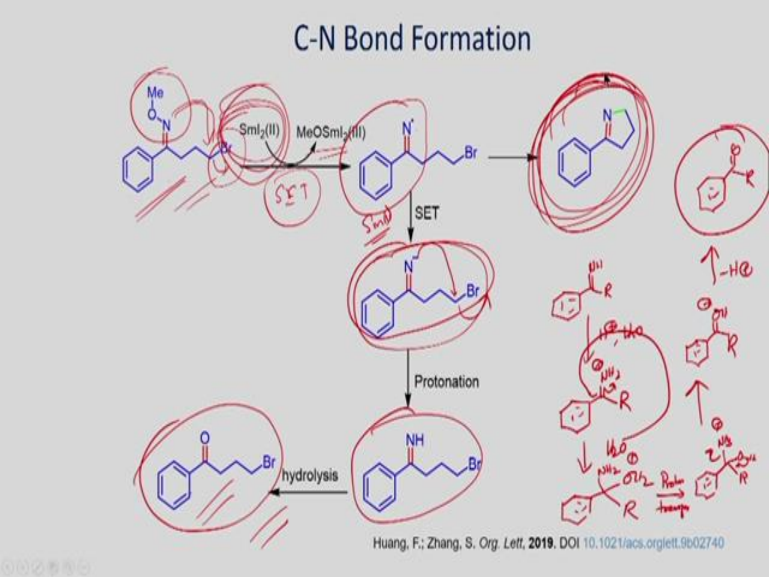
C-N Bond Formation

Huang, F.; Zhang, S. *Org. Lett.* **2019.** DOI 10.1021/acs.orglett.9b02740

In the last class, we have seen the use of SmI_2 for the formation of ketyl radical by single electron transfer (SET). SmI_2 can convert oxime ether to an imine radical, which can be converted to an iminium ion by SET using SmI_2. Intramolecular S_N2 produces 5-phenyl-3,4-dihydro-2H-pyrrole. In addition, protonation of the iminium ion followed by hydrolysis of the imine produces ketone.

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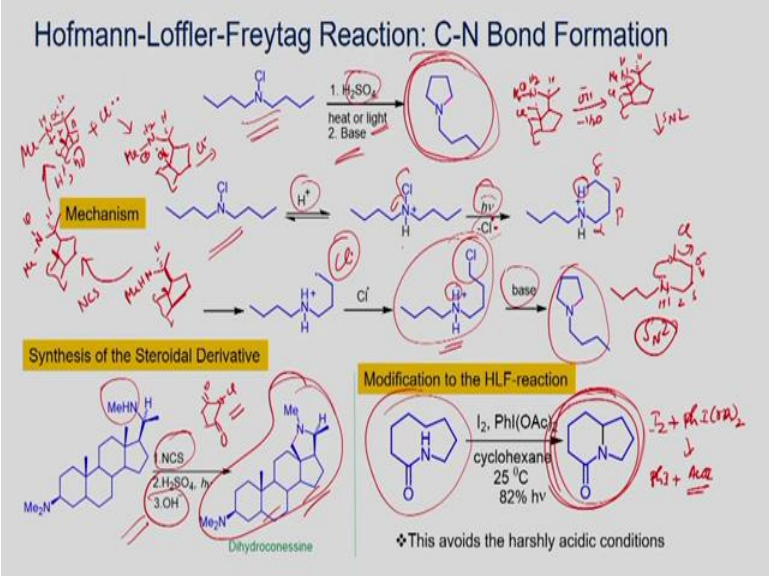

Hofmann-Loffler-Freytag Reaction: C-N Bond Formation

Mechanism

Synthesis of the Steroidal Derivative

Modification to the HLF-reaction

❖This avoids the harshly acidic conditions

Here is the use of photolysis for the *C-N* bond formation. For example, N-chlorobutylamine in 85% sulfuric acid under light gives *N*-butylpyrrolidine. The reaction is general and amines having δ-hydrogen can proceed reaction to give the heterocyclic compound. Protonation followed by photolysis produces the radical cation. Abstraction of the δ-hydrogen atom gives the carbon radical that reacts with chorine radical. Deprotonation followed by S_N2 reaction produces pyrrolidine.

This method provides potential route for the functionalization of less reactive aliphatic C-H bond. The reaction has been utilized for the modification of the angular methyl group in steroids. For example, the synthesis of conessine derivatives has been accomplished. Chlorination of the secondary amine using *N*-chlorosuccinimide and photolysis in the presence of sulfuric acid produces the nitrogen cation radical. Abstraction of the angular methyl δ-hydrogen atom via 1,5-shift produces the carbon radical that reacts with chlorine radical. Deprotonation and intramolecular S_N2 reaction produces *N*-methyl pyrrolidine unit.

Improvement in the reaction has been made using $PhI(OAc)_2$ in the presence of iodine under irradiation. This reaction avoids the use of acid and functions under neutral conditions. For example, the cyclic amide converts to oxoindolizidine. First, iodine reacts with amine to produce iodoamine, which undergoes photolysis to produce nitrogen radical. 1,5-Hydrogen abstraction and coupling of the carbon radical with iodine radical and intramolecular S_N2 reaction affords the lactam

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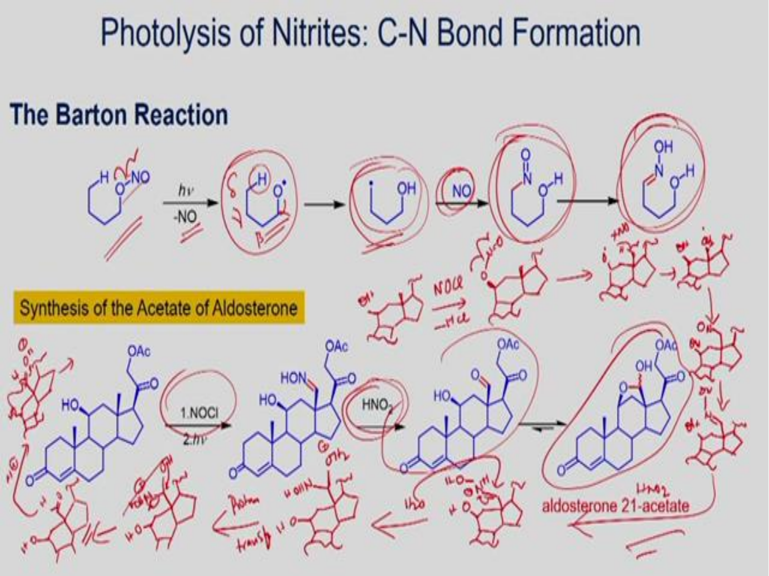

Photolysis of Nitrites: C-N Bond Formation

The Barton Reaction

Synthesis of the Acetate of Aldosterone

Here is the Barton reaction, which involves the photolysis of nitrite O-N bond to give an alkyoxyl radical that abstracts a hydrogen from the δ–carbon. The alkyl radical couples with the nitrosyl radical to give the nitroso compound that tautomerizes to oxime.

The reaction has been utilized for the synthesis of aldosterone acetate. Corticosterone acetate with nitrosyl chloride produces the nitrite. Irradiation under inert atmosphere followed by treatment with HNO_2 produces the oxime. Acetylation followed by the hydrolysis of the oxime yields the natural product hemiacetal.

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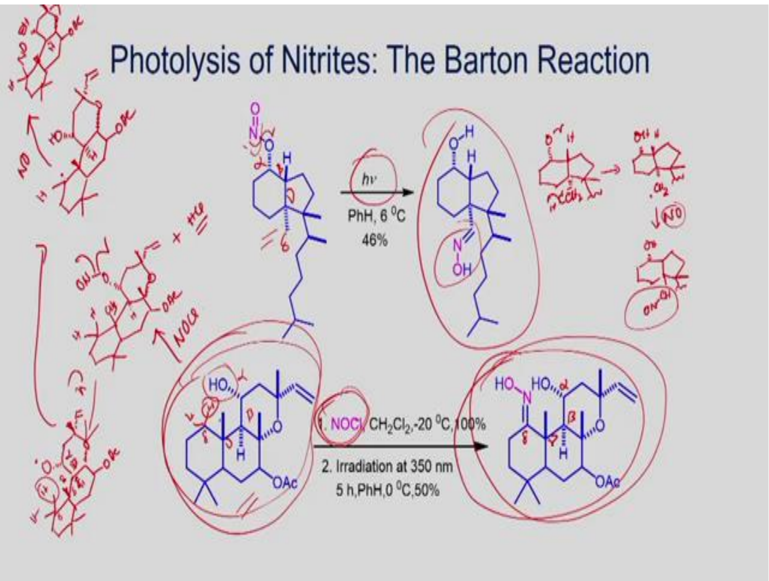

Photolysis of Nitrites: The Barton Reaction

Here are two more examples for the Barton reaction. The first one involves the homolysis of the nitrite ester to produce alkyoxyl radical, which abstracts a hydrogen atom from δ–methyl group via 1,5-hydrogen shift. Coupling of the alkyl radical with nitrosyl radical produces nitroso compound that tautomeries to oxime.

The second example shows the reaction of alcohol with nitrosyl chloride to produce nitrite ester, which undergoes O-N cleavage under photolysis to produce alkyoxyl radical that abstracts a hydrogen from δ-carbon. The alkyl radical couples with nitrosyl radical to give nitroso derivative, which tautomerizes to oxime.

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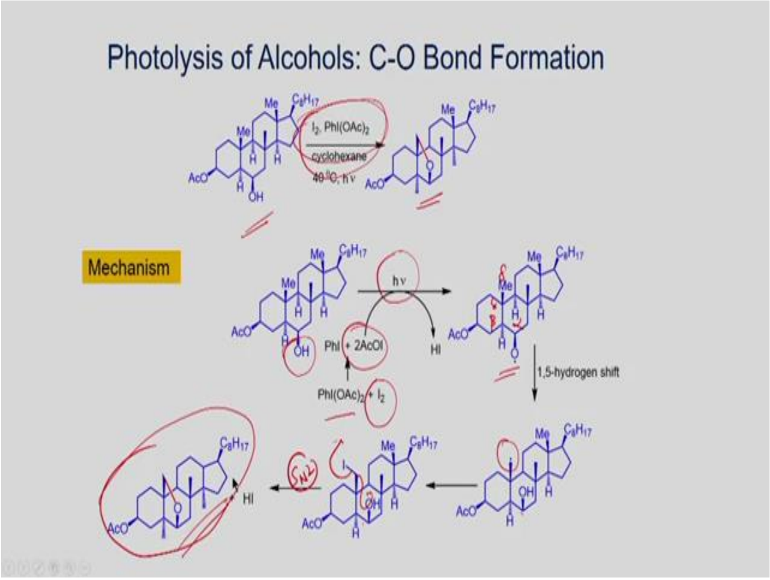

Photolysis of Alcohols: C-O Bond Formation

Mechanism

Here is an example for the photolysis of alcohol for the formation of ether. $PhI(OAc)_2$ with iodine produces AcOI, which reacts with OH group to produce alkyoxyl radical. As we have seen in the previous example, the alkyoxyl radical abstracts a hydrogen atom from the δ-carbon via 1,5-hydrogen shift. The coupling of alkyl radical with iodine radical produces alkyl iodide, which undergoes S_N2 reaction with OH group to yield the ether.

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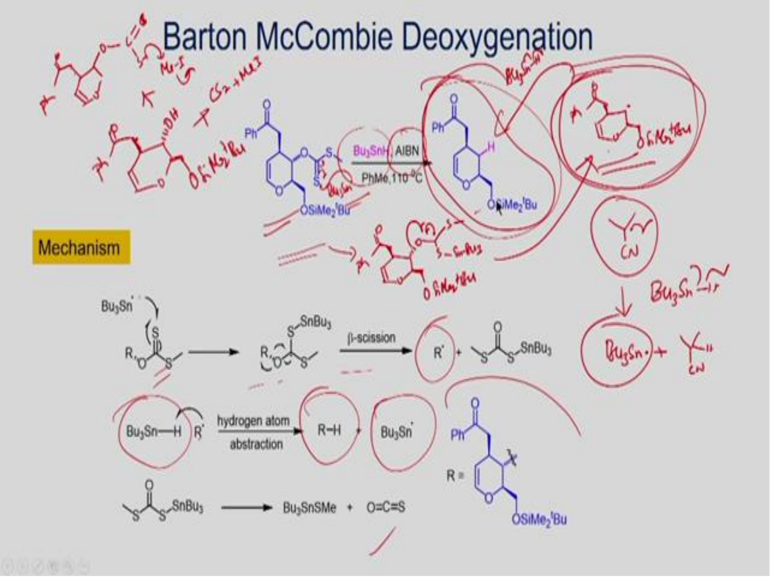

Barton McCombie Deoxygenation

Mechanism

Here is an example for the Barton-McCombie deoxygenation. The alcohol is converted to the more reactive xanthate. Tributyltin radical adds to S=C of the xanthate and β-scission occurs to give the carbon centered radical and tributyltin xanthate. The S-Sn is very stable, which is the driving force for this transformation. The carbon radical reacts with tributyltin hydride to yield the deoxygenated compound.

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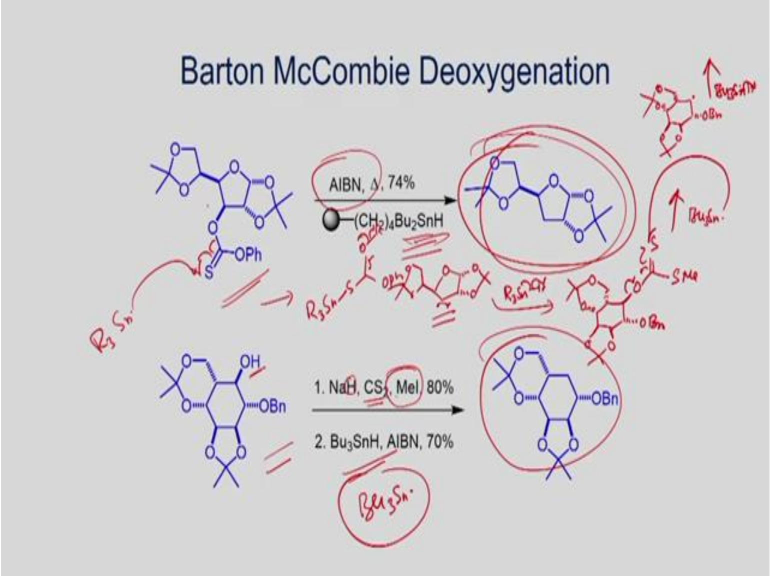

Barton McCombie Deoxygenation

Here are two more examples for the Barton-McCombie deoxygenation. The first one shows the reaction of monothiocarbonate with a polymer anchored trialkyltin radical to produce a carbon radical that reacts with trialkyltin hydride to yield the deoxygenated compound.

Similarly, the second example reacts with CS_2 and MeI in the presence of NaH to produce the xanthate, which reacts with tributyltin radical to give the deoxygenated compound.

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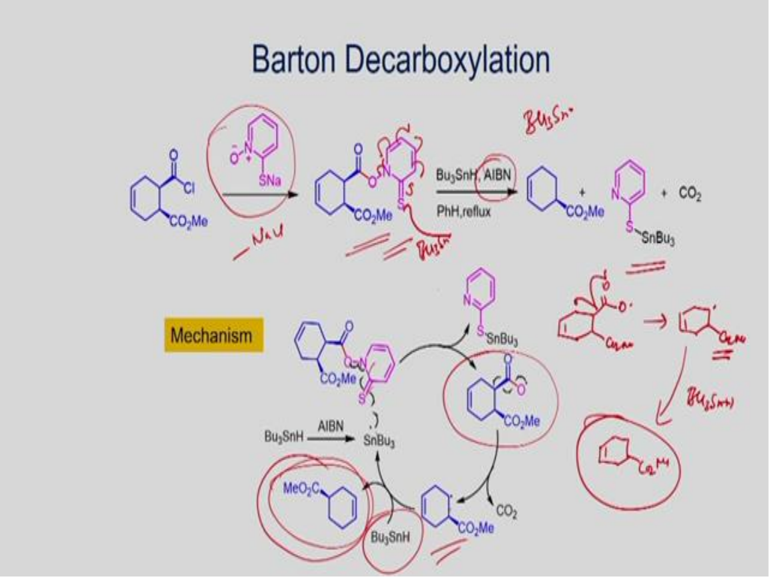

Barton Decarboxylation

Mechanism

Here is the Barton decarboxylation in which an acyl chloride is converted to thiohydroxamate ester. Tributyltin radical attacks the sulfur atom of the thiohydroxamate ester and the N-O bond undergoes homolytic cleavage to produce a carboxyl radical. Removal of the CO_2 produces a carbon centered radical that abstracts hydrogen from tributyltin hydride to give the decarboxylation compound.

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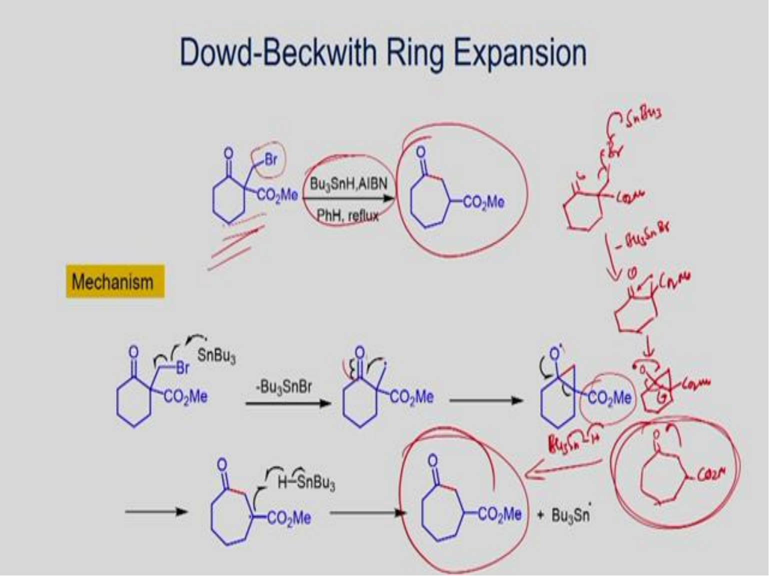

Dowd-Beckwith Ring Expansion

Mechanism

Here is an example for ring expansion of β-ketoester by radical intermediate, which is known as Dowd-Beckwith ring expansion. The tributyltin radical abstracts the bromide atom to form an alkyl radical, which undergoes addition to the carbonyl group to produce a bicyclic ketyl. It rearranges with ring expansion to give a new carbon radical, which reacts with tributyltin hydride to give the ring expansion product. This reaction can be utilized for the ring expansion up to four carbons.

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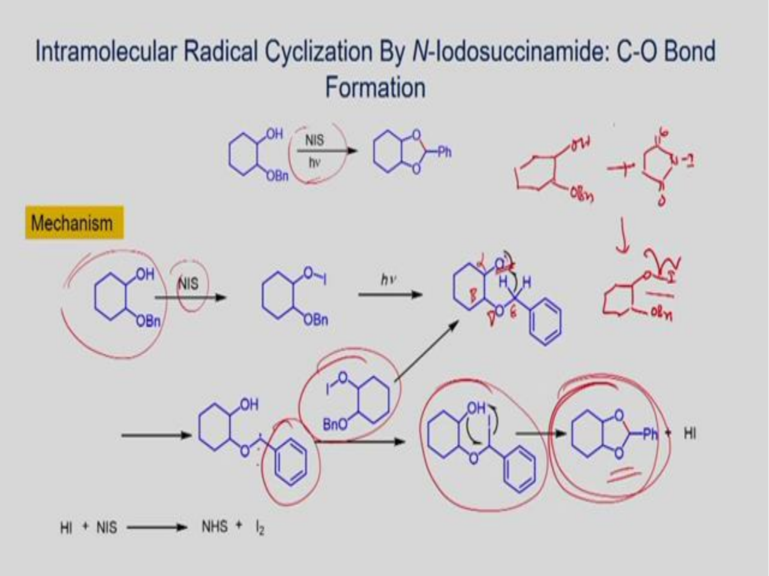

Intramolecular Radical Cyclization By *N*-Iodosuccinamide: C-O Bond Formation

$HI + NIS \longrightarrow NHS + I_2$

Here is an example for the radical C-O bond formation using *N*-iodosuccinimide (NIS). Alcohol undergoes reaction with NIS to produce hypoiodite, which leads to homolysis under light to yield alkyoxyl radical. Abstraction of a hydrogen atom from δ-carbon to yield benzyl radical, which couples with iodine radical to yield the benzyl iodide. Intramolecular cyclization yields 2-phenyhexahydrobenz[*d*][1,3]-dioxole.

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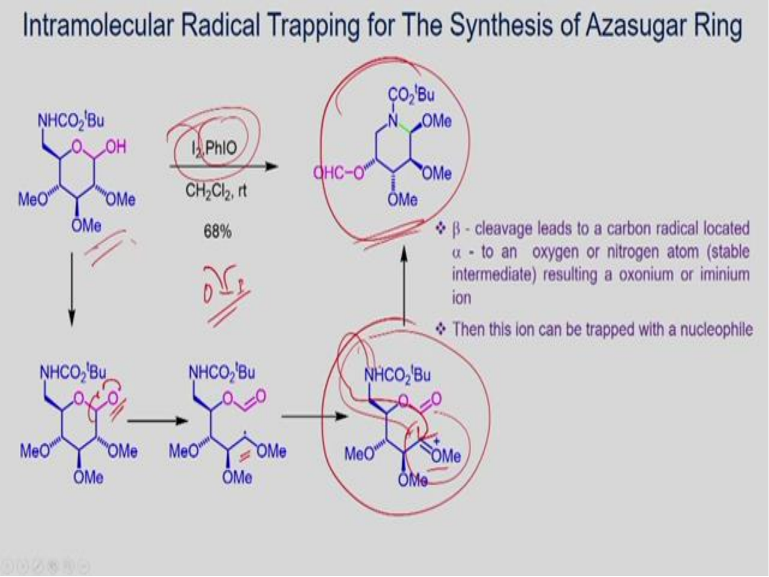

Intramolecular Radical Trapping for The Synthesis of Azasugar Ring

- β - cleavage leads to a carbon radical located α - to an oxygen or nitrogen atom (stable intermediate) resulting a oxonium or iminium ion
- Then this ion can be trapped with a nucleophile

Now let us look at the use of the radical chemistry for the construction of the azasugar. As we gave seen in the previous example, the substrate reacts with iodine in the presence PhIO to produce hypoiodite, which undergoes homolytic cleavage to give the carbon centered radical that exists as an oxonium ion. Intramolecular addition with carbamate produces the azasugar.

So far we have seen the use of the radical reactions for the C-N and C-O bond formation, and deoxygenation, decarboxylation and ring expansion reactions. Now, let us the see few example for the C-H functionalization using transition-metal-catalysts, which involve single electron transfer oxidation.

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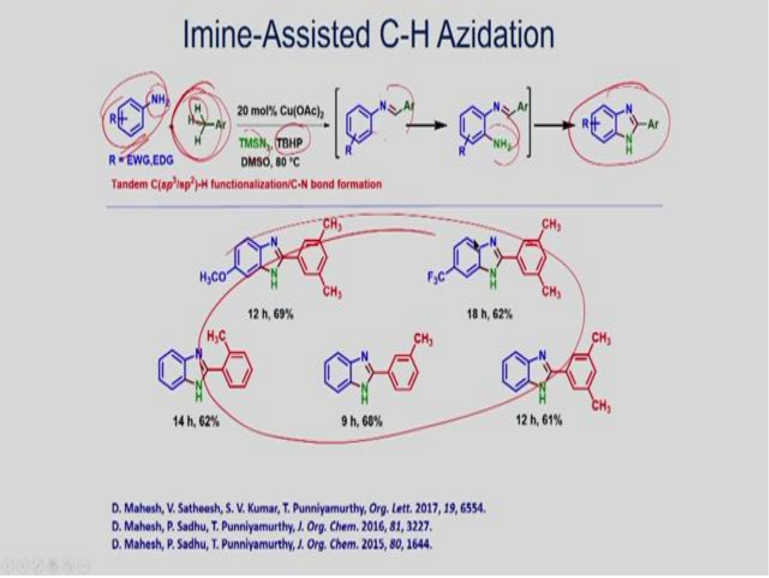

Imine-Assisted C-H Azidation

Tandem C(sp^3/sp^2)-H functionalization/C-N bond formation

D. Mahesh, V. Satheesh, S. V. Kumar, T. Punniyamurthy, *Org. Lett.* 2017, *19*, 6554.
D. Mahesh, P. Sadhu, T. Punniyamurthy, *J. Org. Chem.* 2016, *81*, 3227.
D. Mahesh, P. Sadhu, T. Punniyamurthy, *J. Org. Chem.* 2015, *80*, 1644.

In this reaction, aniline couples with benzylic C-H bond to produce an imine that makes chelation with copper(II) species and activates the *ortho*-C-H bond of aromatic ring and the azidation takes place. Subsequent intramolecular cyclization produces 2-aryl benzimidazole. This three component C-H functionalization involves a tandem C-N bond formation.

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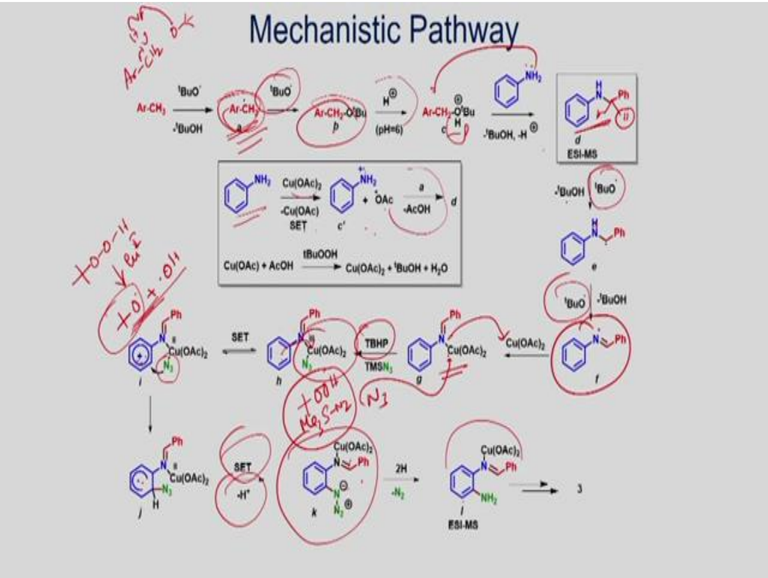

Copper(II) with THBP produces *tert*-butoxy radical, which abstracts benzylic hydrogen atom to produce benzyl radical. Coupling of the benzyl and *tert*-butoxy radicals produces the ether, which protonates as the reaction medium is acidic and then leads to S_N2 with aniline to give *N*-benzylaniline. Oxidation to imine using *tert*-butoxy radical and chelation with copper(II) species followed by reaction with azide radical generates copper(III) species. Aromatic ring reduces Cu(III) to Cu(II) vis SET. The resultant radical cation reacts with azide anion to give the radical intermediate, which aromatizes by SET. The reduction of azide amine using copper and intramolecular cyclization gives the cyclic compound.

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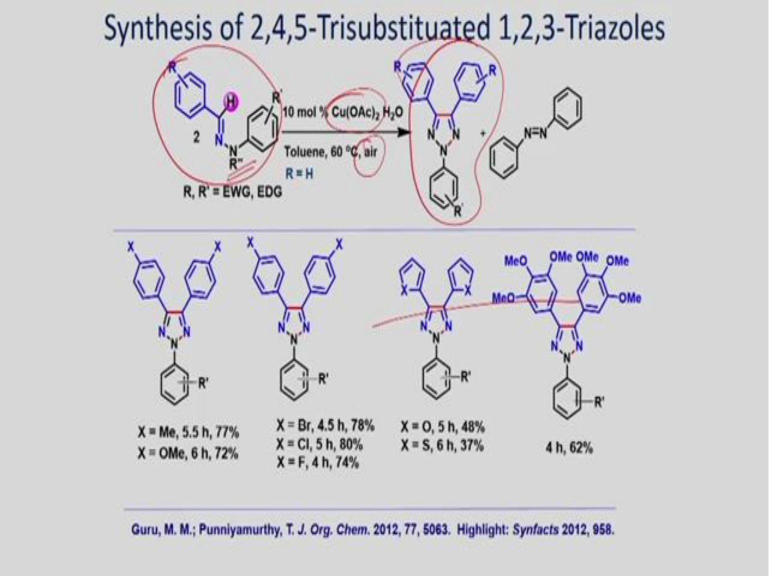

Synthesis of 2,4,5-Trisubstituted 1,2,3-Triazoles

X = Me, 5.5 h, 77%
X = OMe, 6 h, 72%

X = Br, 4.5 h, 78%
X = Cl, 5 h, 80%
X = F, 4 h, 74%

X = O, 5 h, 48%
X = S, 6 h, 37%

4 h, 62%

Guru, M. M.; Punniyamurthy, T. *J. Org. Chem.* 2012, 77, 5063. Highlight: *Synfacts* 2012, 958.

Here copper(II) acetate catalyzes the dehdyrogenative *C-N* coupling of diarylhydrazone to produce 1,2,3-triazoles. This reaction involves a radical pathway via SET oxidation.

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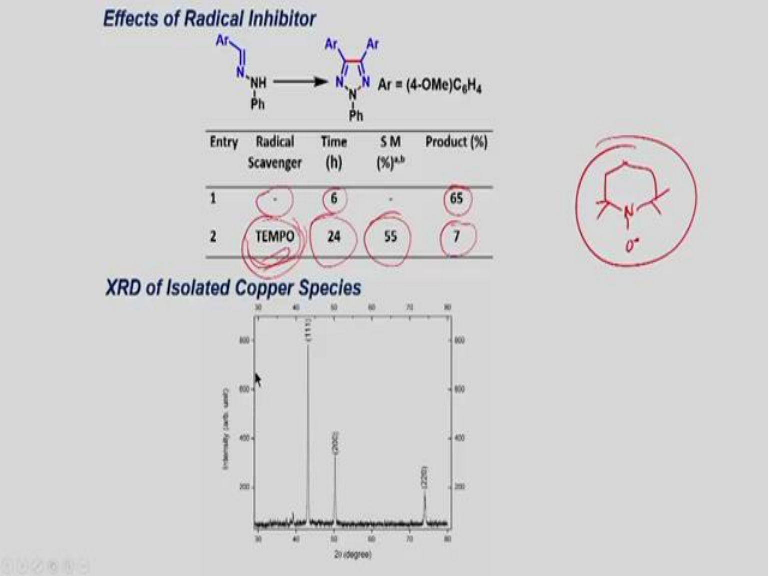

Effects of Radical Inhibitor

Entry	Radical Scavenger	Time (h)	S M (%)[a,b]	Product (%)
1	-	6	-	65
2	TEMPO	24	55	7

XRD of Isolated Copper Species

The experiment using the trapping agent TEMPO shows the reaction is less effective, which suggests that the reaction may involve a radical intermediate. In addition, the powder X-ray analysis shows the presence of copper(0) species, which suggest that copper(II) is reduced to copper(0) during the reaction by the substrate via SET.

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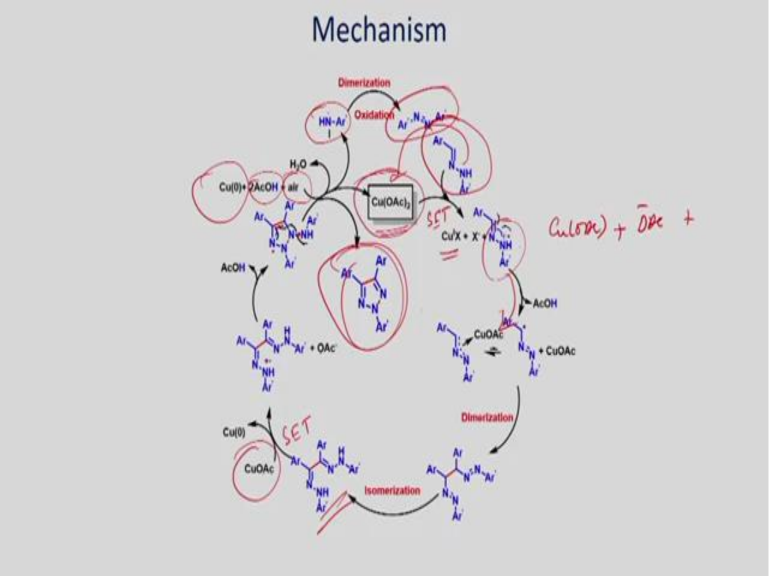

Mechanism

Thus, SET reduction of copper(II) to copper(I) by the substrate can produce the benzyl radical. Dimerization followed by isomerization and SET of the substrate to copper(I) can produce copper(0) species. The resultant nitrogen cataion radical undergoes intramolecular cyclization and homolytic cleavage of the N-N bond to give the triazole. The ArNH radical can dimerize to give the azo compound.

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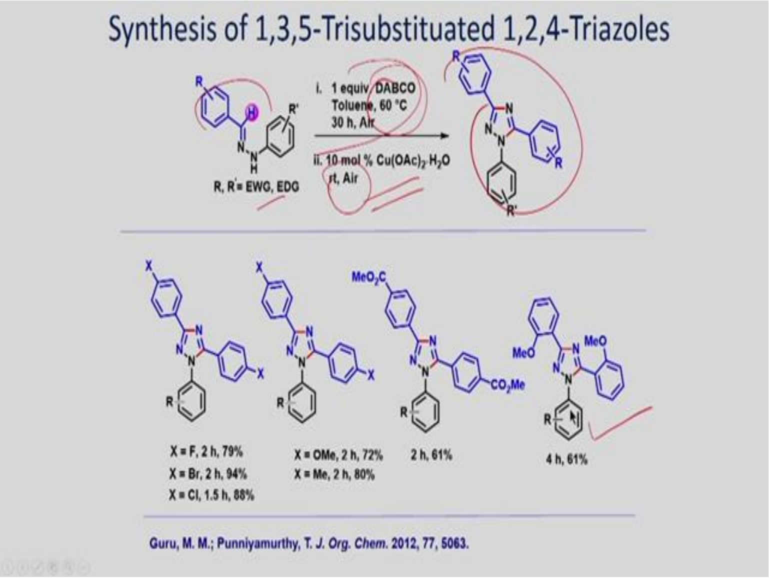

Synthesis of 1,3,5-Trisubstituted 1,2,4-Triazoles

Guru, M. M.; Punniyamurthy, T. *J. Org. Chem.* 2012, 77, 5063.

The above reaction using DABCO produces 1,2,4-triazole via the radical pathway. In this two steps reaction, first DABCO deprotonates and the resultant nitrogen anion undergoes addition reaction with another hydrazone C=N bond. The resultant compound undergoes oxidation, and then reacts with copper(II)-DABCO complex to produce the 1,2,4-triazole.

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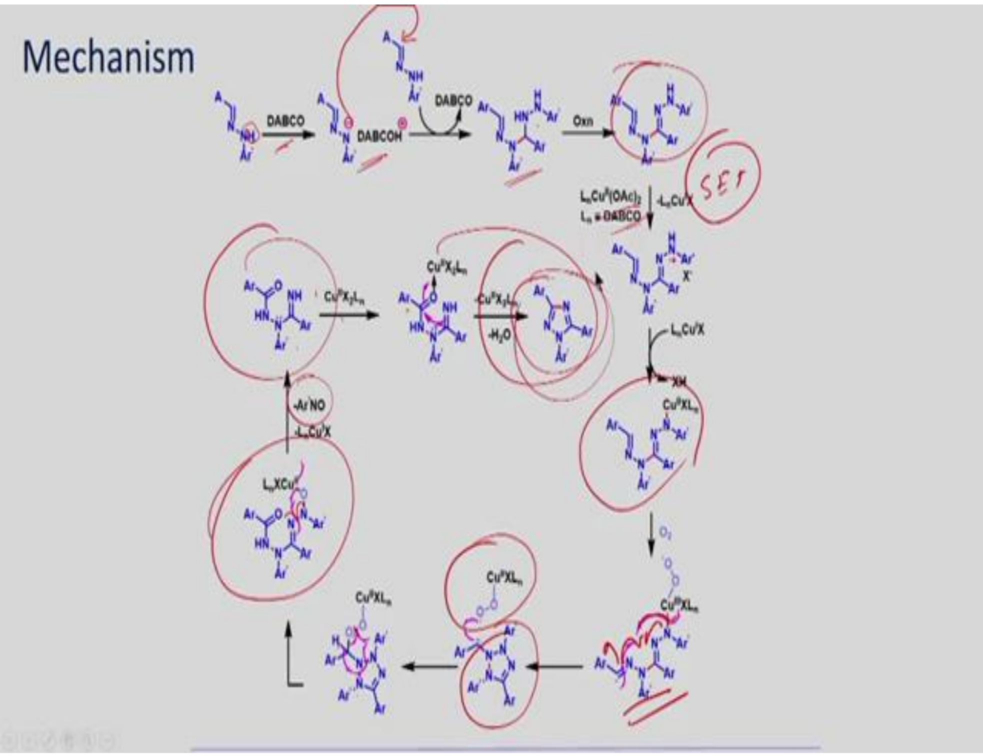

Mechanism

Deprotonation using DABCO followed addition to C=N of an another hydrazone followed by oxidation gives the intermediate, which reduces copper(II) to copper (I) by SET. The nitrogen cation radical with copper(I) and oxygen molecule yield the copper(III) peroxy radical. Homolytic cleavage of the N-Cu bond and the radical cyclization yields benzyl radical that reacts with copper(II) peroxy radical. Cleavage of O-O bond, rearrangement and ring opening leads to the formation of N-O-Cu(II) species. Cleavage of N-N bond produces hydrazide derivative that undergoes intramolecular cyclization to yield triazole.

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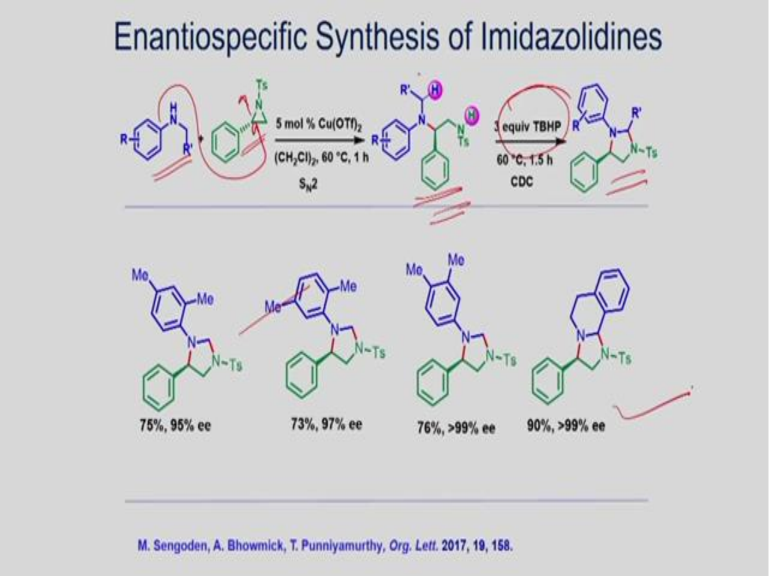

Enantiospecific Synthesis of Imidazolidines

M. Sengoden, A. Bhowmick, T. Punniyamurthy, *Org. Lett.* **2017**, *19*, 158.

Here Cu(OTf)$_2$-catalyzes S$_N$2 opening of aziridine with N-methylaniline to give 1,2-diamine, which undergoes oxidative radical cyclization using TBHP to produce imidazolidine.

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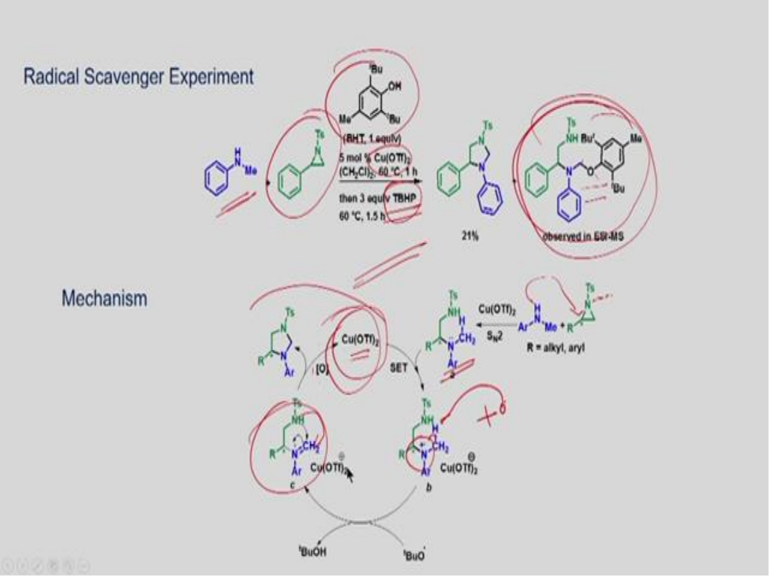

Radical Scavenger Experiment

Mechanism

Regarding the mechanism, the reaction using radical scavenger BHT produced the adduct, which has been confirmed by the mass analysis. Thus, copper(II) triflate may activate the aziridine and S$_N$2 opening occurs to give the 1,2-diamine. SET reduction of Cu(II) to Cu(I) can form the nitrogen cation radical. *tert*-Butoxy radical can abstract the methyl hydrogen atom to form the iminium ion, which can undergo intramolecular cyclization to yield imidazolidine. Oxidation of copper(I) to copper(II) complete the catalytic cycle. In this reaction, copper(II) triflate acts as the Lewis acid as well as the redox catalyst.

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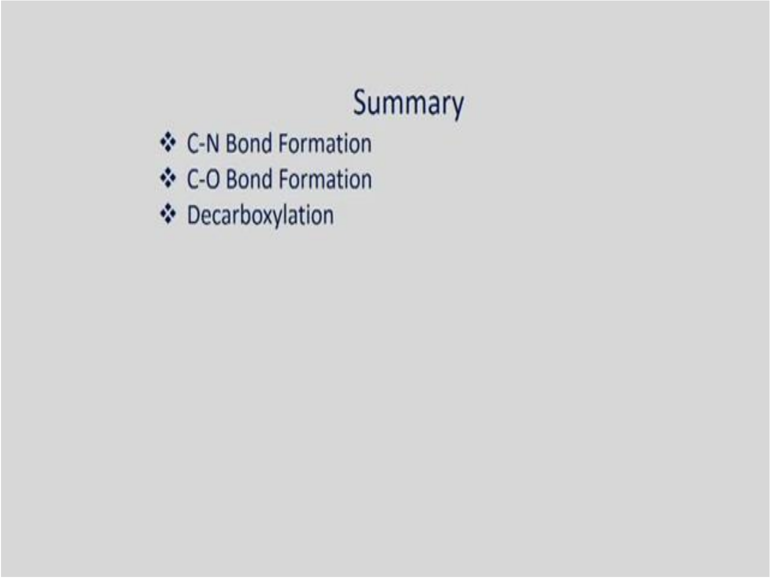

Summary

- C-N Bond Formation
- C-O Bond Formation
- Decarboxylation

In summary, we have seen the use of free-radical chemistry for the C-N and C-O bond formation. Then, we have seen the deoxygenation and decarboxylation reactions. Finally, we have seen the C-H functionalization for the C-N bond formation using copper-based catalytic systems. These reactions take place via SET. As you can see, the radical reaction plays an important role in synthetic chemistry to construct complex molecule at neutral conditions.

I would like to thank you all for taking this course. I am sure that you were able to learn many new things, and the course was useful to you to understand the basics of the organic transformations and reaction mechanisms. With this let us conclude this course. Wish you all the best.