Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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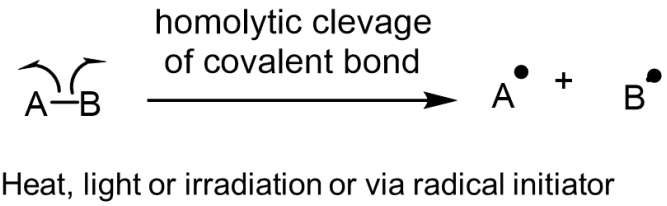
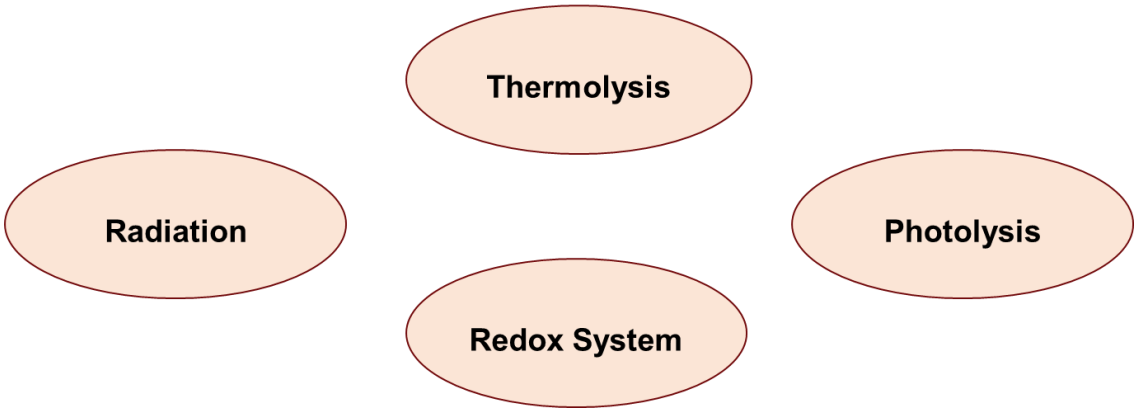
Lecture 18: Radical (Continued)

Welcome back to this NPTEL online lecture on molecular rearrangement and reactive intermediates. so, in the previous class, I started talking about free radicals, and in today's class, I am going to talk about the different methods for the generation of free radicals and different name reactions. In the class, I am going to talk about First the diverse methods for the generation of free radicals, then I am going to talk about various different name reactions like the Barton-McCombie radical decarboxylation, then Barton-McCombie radical deoxygenation, then there will be Hunsdiecker reaction, and the Wohl-Ziegler bromination. And then, there will be several variations of the Hunsdiecker reaction, which I am going to explain in class also. So, let us start talking about the radical, which I started talking about in the last class. The first thing I start talking about is that there will be a homolytic cleavage of the bond.



Classification of Radicals Based on Energy Supplied

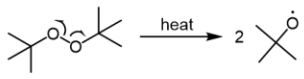


As I mentioned, this homolytic cleavage actually depends on several factors; it can depend on the electronegativity, the polarizability of the bonds, and then several other effects. these are very important for the formation of this type of free radicals. so now we are going to understand there are heat and light or irradiation, which means all the different conditions. Mostly, you can see there is heat and light.

So, it could be thermolysis which means you are giving heat so that the bonds, which are the weaker ones, get cleaved to form the radical there could be radiation or photolysis using UV light, which can also able to cleave those bonds to generate radicals and then I am going to also include the photo redox chemistry which is the recent chemistry using visible light can you do the redox system which can use as a catalytic amount to generate it in a free radical in the reaction. so, the first thing I am going to talk about is thermolysis; I think you are going to see that in thermolysis, under heat, what is going to happen? the compound can absorb heat, and there will be a cleavage of this weak bond. Here you can see these are the bond which is the weakest bond in this dialkyl peroxide under heat, the two-oxygen going to take a single electron to form this species. and then under heat, the other compound, called AIBN so it is an Azobisisobutyronitrile. this Azobisisobutyronitrile was the compound where under heat, it is going to actually is going to get out as an N_2. So, to form N_2, you have to take a single electron from this bond and a single electron from this bond, this will end up generating this corresponding radical and these are the very stable radical so that it can do some other things in the reaction.

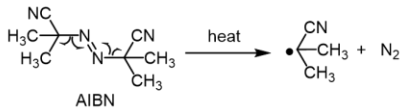
Some types of compounds dissociate to give free-radicals at moderate temperature

- Compounds that have an intrinsically weak bond such as Dialkyl Peroxides (BDE O-O = 155 KJ mol^{-1})



Dialkyl Peroxide

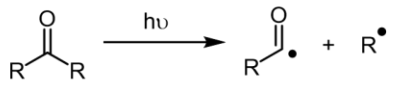
- Compounds that, on fragmentation, form strongly bonded products, such as (Azobisisobutyronitrile) **AIBN** which releases N_2.



AIBN

And you can see why I am saying because this is again a electrophilic radical because there is a cyano group here attached to it. So, now there are some reactions. You can take some of this carbonyl compound, and then under UV light, it can also generate this type of acyl radical. So, we are going to also talk about some of the generation of the acyl radical and some of the reactions.

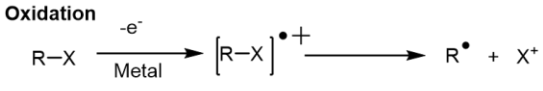
Light is absorbed by a substance allowing an electron in a lower orbital level to be elevated to a higher energy level. Consequently, various photoreactions can take place such as bond cleavage



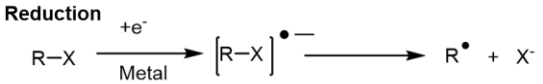
As light source **UV light (200nm - 400 nm)** or **visible light (400nm - 800nm)** can be used

and then, as I was saying, using some sort of metal like sodium, magnesium, tin, and samarium can also give you an electron. So, they can give you electrons for this type of reduction reaction. You guys must have heard about acyloin condensation and then several reactions like the formation of pinacol using magnesium. Then, some of the chemistry uses samarium where it can generate the radical that can form pinacol, and then it can also add to the olefin. So, there are several different reactions we are going to discuss about samarium, and I am also going to talk about some of the photoredox systems using the photoredox catalyst as well.

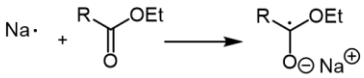
Oxidation or reduction (redox reaction) generate radicals by an intermolecular electron transfer.



Metal: Na, Mg, Sn, Sm etc

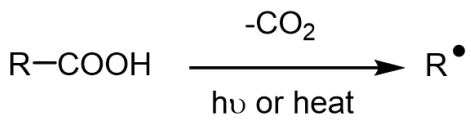


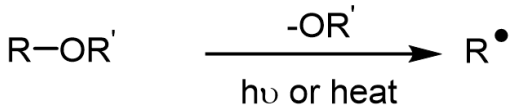
Example:



In this particular class, I am going to focus on this decarboxylation reaction. So, the reaction is mostly photochemical and thermal, which means there are some photochemical reactions and thermal reactions that go by the thermal pathway for generating radicals. I am going to discuss them first. so here I am going to start with these three different reactions, as I mentioned, the Barton McCombie decarboxylation reaction. Here what is happening? From carboxylic acid, you can generate this R•, this type of radical, and then using the Hunsdiecker reaction also from carboxylic acid, you will be generating this R• which can able to take a proton which can take a H•, so there will be hydrogen atom abstraction to form the corresponding RH or it can participate some sort

of intramolecular reaction as well. and then also i am going to talk about the Barton deoxygenation reaction starting from this corresponding alcohol, you can make a derivative of alcohol, and then under hv or heat, you can generate the corresponding radical. Again, this radical can go for a hydrogen atom abstraction to form the RH, or it can go for an intermolecular cyclization reaction.





❖ Barton deoxygenation reaction

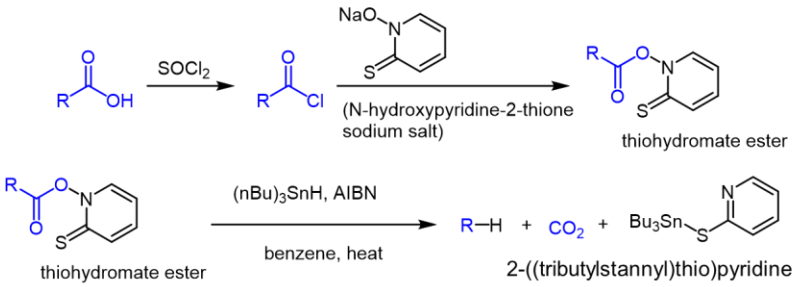
❖ BartonMcCombie decarboxylation

❖ Hunsdiecker rection

❖ Wohl-Ziegler Bromination

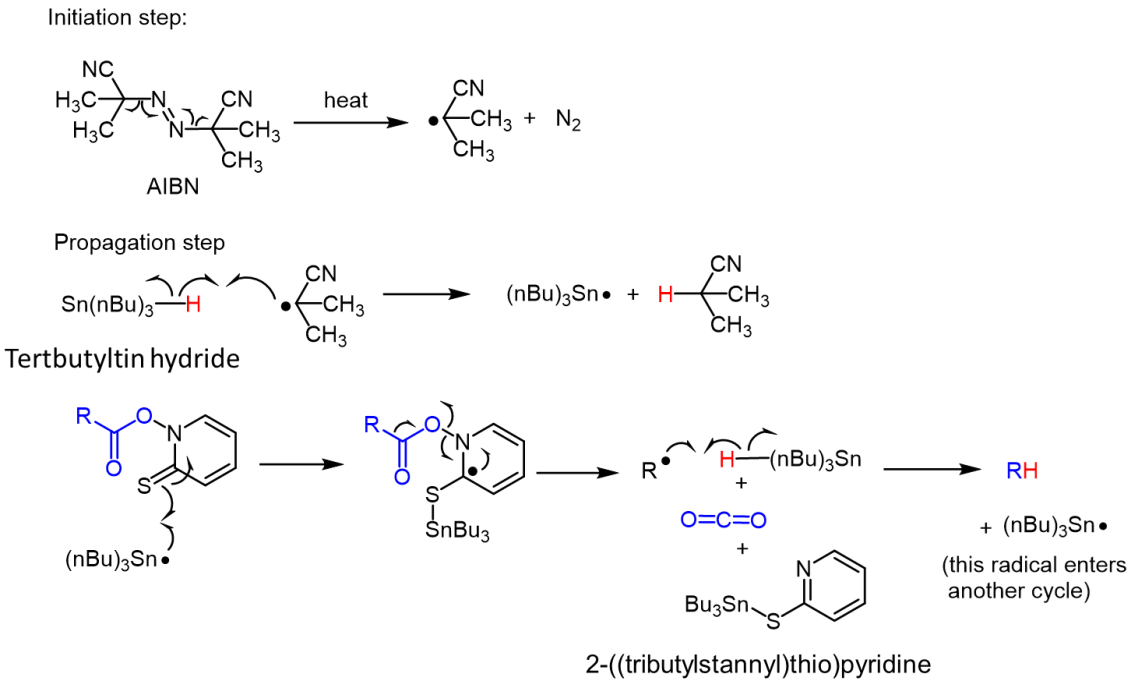
So, the first thing is the Barton McCombi decarboxylation reaction. So, here you can see the carboxylic acid is getting converted to the corresponding acid chloride using thionyl chloride and then once you use this N-hydroxy pyridine-2-thione. So, this is a N-hydroxy pyridine-2-thione, that sodium salt of it once treated with here. Now, this O-minus can attack here to this corresponding acid chloride, get rid of the Cl to form this type of thiohydromate ester.

Synthesis of carboxylic acid to alkane via radical intermediate with expulsion of CO_2 in presence of heat is known as **Barton McCombie reaction**



now this thiohydramate ester is going to participate in a decarboxylation reaction in the presence of tributyltin hydride and AIBN in presence of benzene and heat, so what is happening?it is this R is becoming R• to form this RH and there then there will be formation of the CO_2 and then you will see this 2-(tributylstannyl)thiopyridine which will be a by-product going to form So, now we are going to learn about the mechanism of the Barton McCombie decarboxylation reaction first thing is the initiation step where the AIBN get decomposed in presence of heat to generate this radical and N_2. So, now

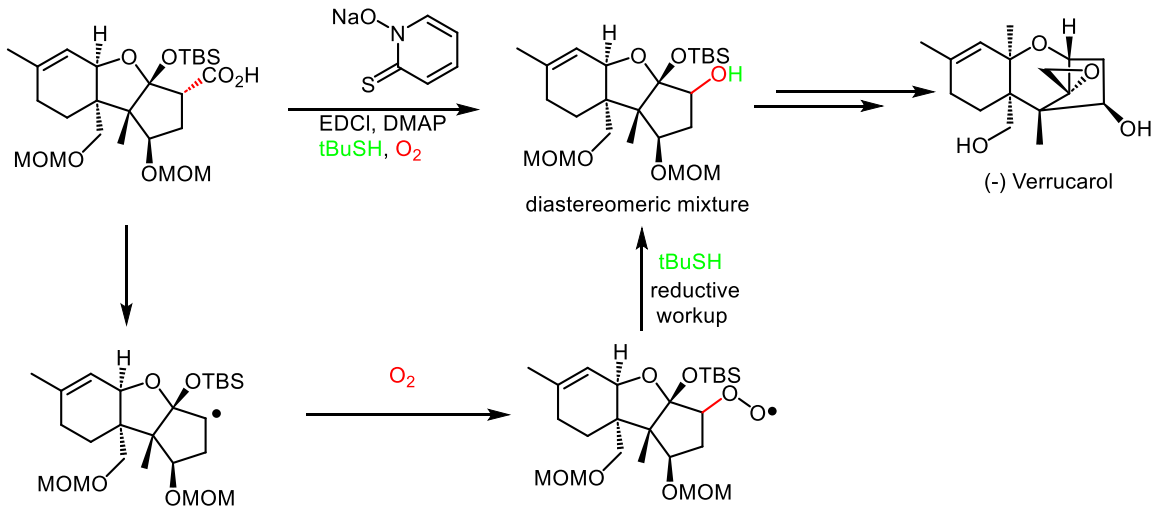
what is going to happen? this radical can take another weak bond getting cleaved between the tin and the hydrogen. So, now it is going to generate this type of radical which can cleave this bond to generate the tributyltin radical here. a tributyltin radical can now interact with this carbon-sulfur double bond. So, that bond is getting cleaved to generate next generate a radical next to nitrogen, which is going to form a bond here, and it is going to allow this cleavage of this nitrogen-oxygen bond.



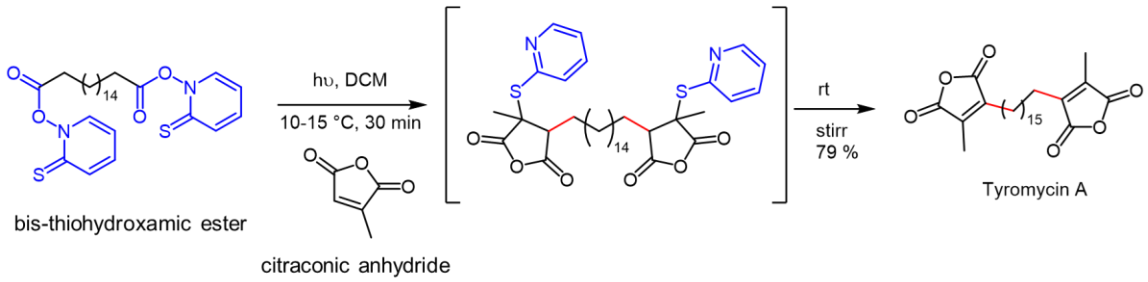
So, what is happening? After this stage you are generating this type of radical species. you are generating this one and now you can see, you are generating this N•, then there is a S, Sn(^{n}Bu)$_3$, they are forming a bond to generate this corresponding so this can go to the forming this compound to tributyl stannyl thiopyridine and then this one going to happen. it will go for a decarboxylation to get rid of the CO_2 to generate a R•. This R• will abstract a hydrogen from this tributyltin hydride to generate this RH.

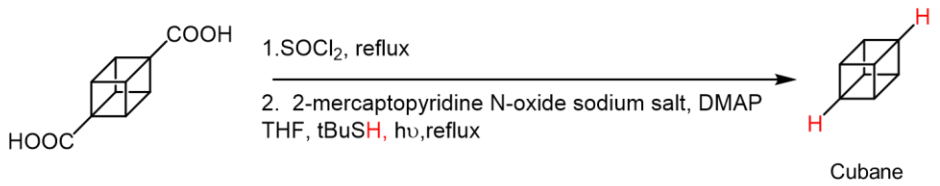
So now we will see some of the examples in this compound we can see there is a COOH here under this type of Barton McCombie decarboxylation condition what is going to happen? so you can form this type of this type of ester species here, which can generate this type of radical. Now if you have oxygen here, as I mentioned, it can give the electron to the oxygen to form this compound which after reductive workup it can form the corresponding alcohol after that, it can be converted to this compound after a few steps so that means you can you can not only get to H you can also convert to corresponding OH so here is another interesting example. you can see, you have this bis-thiohydroxamate ester so which means you have both sides this is a dicarboxylic acid. From this dicarboxylic acid, you can make this compound, as I mentioned, by making the

corresponding acid chloride, and then you take this corresponding sodium salt. you can take an amide coupling reagent to make this. now what is happening? under this hv and DCM, and if you take this citraconic anhydride, it is forming a radical, and it is going for a 1,4- addition. Once this radical is added here, it generates another radical in this position, which is a tertiary radical.



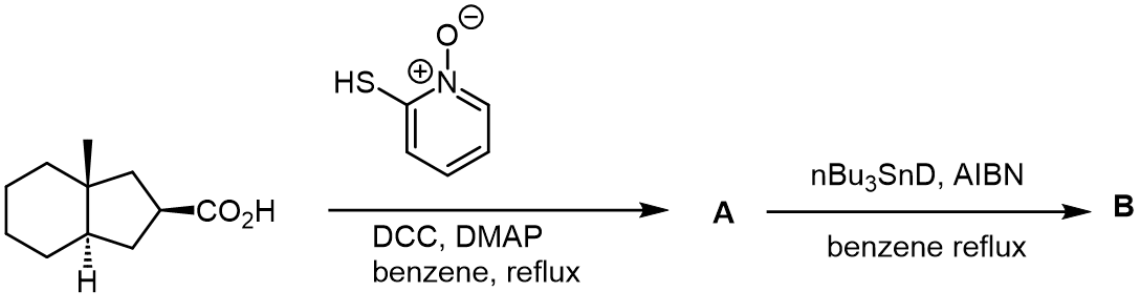
At the same time, this is next to a carbonyl group here, which is getting stabilized. so what is going to happen? it can also interact with this radical, which is forming in the reaction. So, it can interact with this radical to form this species. that means you can see there is a di-functionalization happening of this olefin, and then under room temperature, there is an elimination happening of this group. So, it can eliminate the form of this corresponding olefin here to get to this compound.

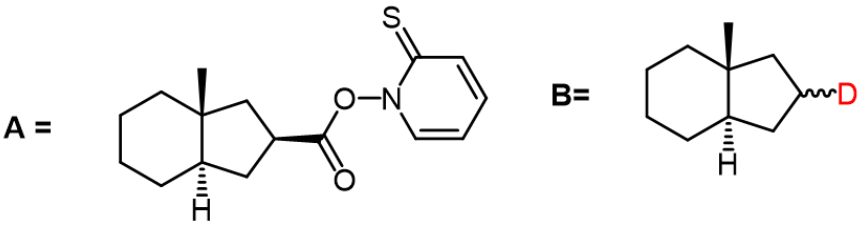




there is another example here, so you have two carboxylic acid here which can first form this corresponding hydroxamate ester first and then using this condition after the SOCl to

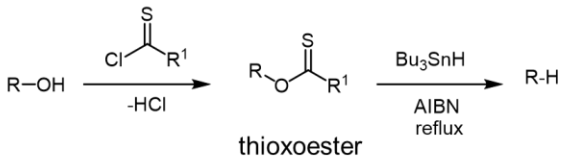
form the corresponding acid chloride, then the corresponding thiohydroxamate ester, and then finally, it is abstracting the hydrogen from here corresponding thiol to get to the cubane. there is another example here, so this is an exam question if you start with this carboxylic acid and then what will be your A? What will be your B if you use the tributyltin-D? instead of the hydrogen, there will be a deuterium abstraction going to happen so i think I have already discussed that you end up getting to this will be A that means under this amide coupling condition, you are going to end up making this compound and then once you try with a tributyltin hydride it is going to cleave here, so there will be decarboxylation going to happen, and then it is going to after this tin and the deuterium bond getting cleaved to introduce the deuterium here so that will be your B.





now i am going to talk about the other important reaction is Barton McCombi radical deoxygenation. so, we talked about the decarboxylation now we are starting from the corresponding alcohol. So, if we start from corresponding alcohol using this R double bond SCl using this compound, what you can do we can able to convert to corresponding thiooxoester.

The Barton–McCombie deoxygenation is an organic reaction in which a hydroxy functional group in an organic compound is replaced by a hydrogen atom.



Y = SMe, imidazolyl, OPh, OMe; X = Cl, imidazolyl; base: NaH

- Hindered tertiary and secondary alcohols are also compatible
- This deoxygenation reaction is a radical substitution reaction.

it will form the corresponding thiooxoester a under the tributyltin hydrate, and AIBN in a reflux condition it can replace this corresponding OH by H. So, Here, deoxygenation is happening. So, now what is happening the hindered tertiary and secondary alcohols are also compatible here. so, what is happening? it is some sort of way you are converting this corresponding ROH to the corresponding RH. So, we are going to understand the mechanism here.

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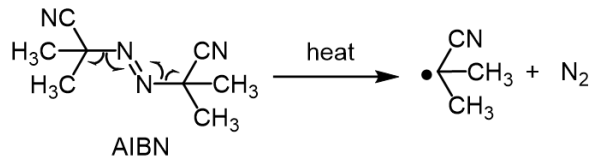
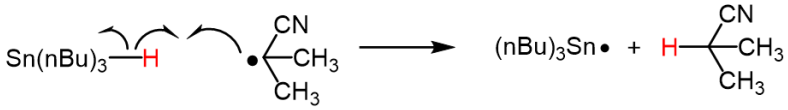
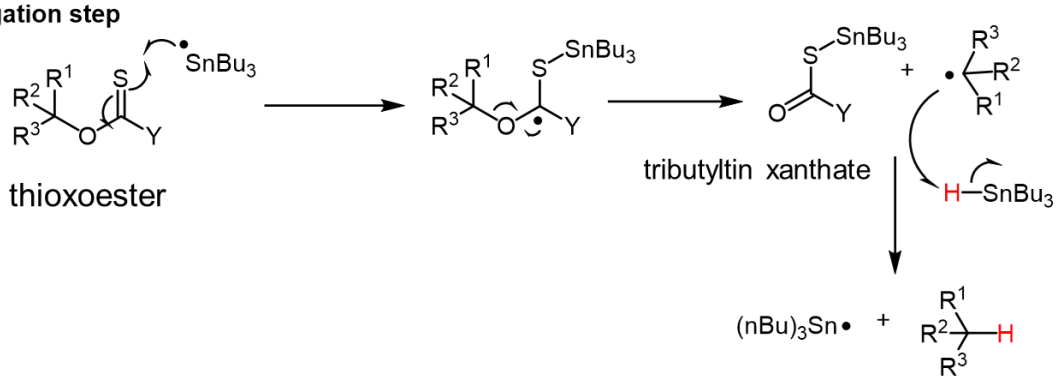
Initiation step:

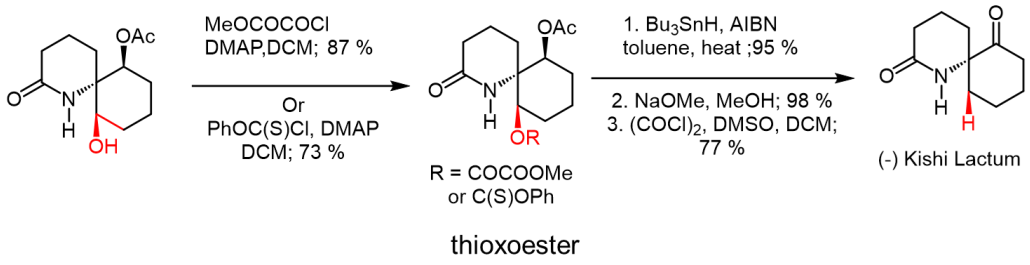




Propagation step



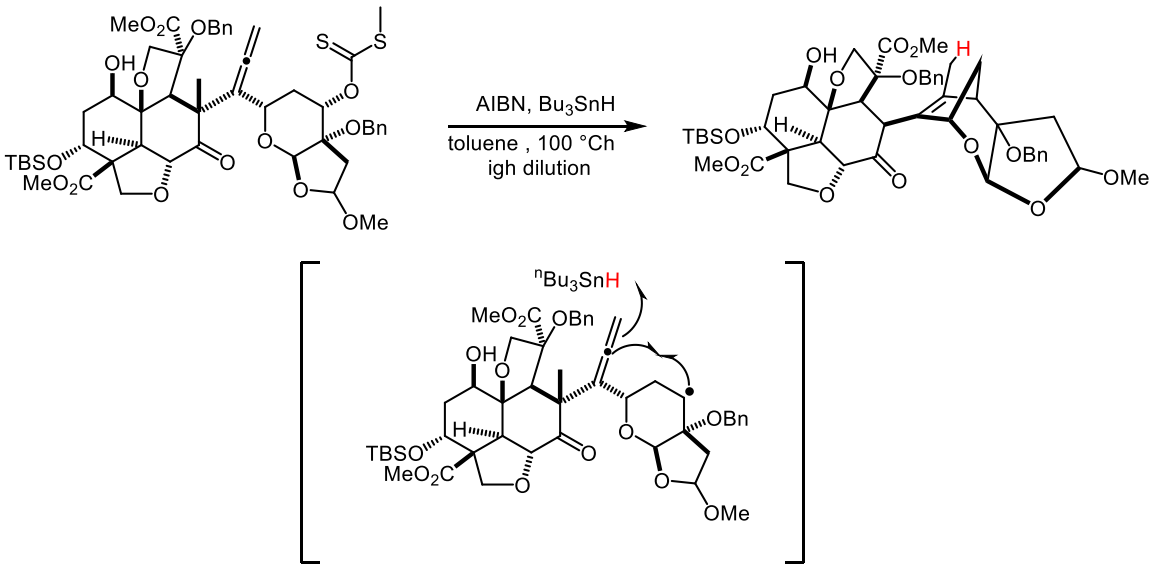
what is happening? the first step is the initiation; that is, the AIBN is getting decomposed to generate this radical. After the expulsion of the N_2, it is the cleaving of this tin-hydrogen bond to generate this tributyltin radical. which can again be very similar to the other reaction here; the decarboxylation reaction here is very similarly interacting with this carbon-sulfur double bond to generate a radical species here. Now, it is going to allow you to cleave this carbon-oxygen bond to generate a radical at the same time you are making this tributyltin xanthate. because we are forming a carbon-oxygen double bond, and at the same time, we are forming this tertiary radical, which is going to abstract a proton from the tributyltin hydride to generate this corresponding species. So, here are some examples: this chemistry can be applied in the natural product synthesis. Here, you can see at the beginning what is happening. You have this carbonyl group. So, what is actually happening? starting from the product, you want to replace this carbonyl group by a hydrogen.



So, what you will do? if you have a carbonyl group, you can go for some other reaction. I am sure you know how to convert the carbonyl to the corresponding CH_2 but we can go for other approaches. we can also convert the carbonyl to the corresponding alcohol first and then corresponding alcohol so we can make these thioesters under the Barton McCcombie condition, and then we can use the tributyltin hydride and the AIBN. So the job is to convert this corresponding CO to the corresponding H and you have a another CO group which is in the protected form. So, you can now open up in the presence of HCl, and then you can use the the Wittig condition to introduce the olefin here.

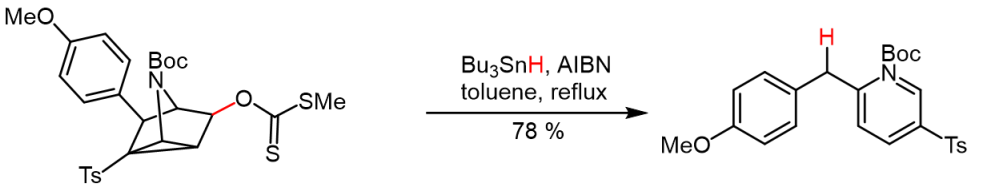
So, there is another example here you can see you have this alcohol here. So, which is under the Barton-McCombie condition, which generates the thioxoesters and which can, in the presence of tributyltin hydride and AIBN, form this compound called Kishi-lactam

to convert this OH to the corresponding H. there is another very interesting example. this is very important because, this particular chemistry of Barton McCombie radical deoxygenation is actually used for the synthesis of one of the key intermediates of Azadirachtin. so it is a very important natural product from the neem tree, which was synthesized by Steve Blake's group in Cambridge.



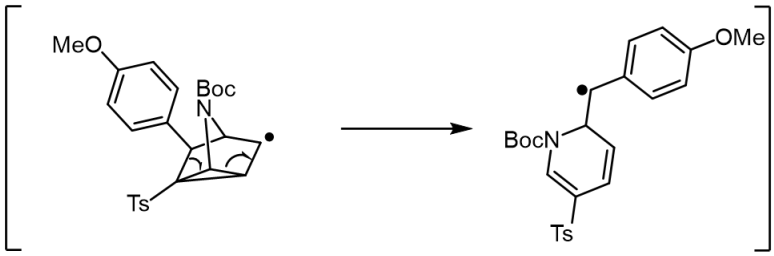
So, in their synthesis what they found that one of the important steps they have actually from this alcohol. they have generated the thioxoester and then using the AIBN and tributyltin hydride they generate this radical but this radical can take part in an intermolecular cyclization as I mentioned this radical fate is not always going to this corresponding H. It can also participate in an intermolecular reaction, so that is happening here, it is attacking here participating in an intermolecular cyclization reaction between this allene. and this radical can end up making this type of product here. So, there is another very interesting example of this Barton-McCombie radical deoxygenation reaction.

Again, you can see first this thioxoester is formed from the corresponding alcohol, and now, under this Barton-McCombie condition, what is happening? First it is forming this radical. Once it is forming this radical, now you can see there is a cyclopropane ring here. So, now that ring is getting chopped here, forming of a radical here and here to generate this type of species. So, you can see this entire thing becoming another pyridine ring here at the end of the reaction. And this now at the end it is generating one radical here to generate this species and finally, it can able to take a hydrogen from the tributyltin hydride to get to this type of species.



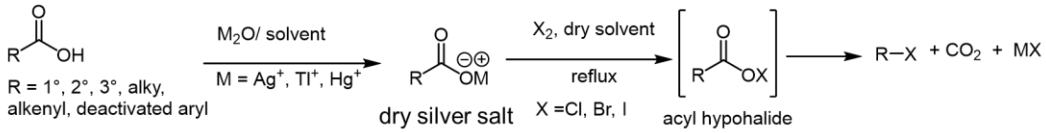
Thioxoester of epibatidine derivative (alkaloid)

Dihydropyridine derivative

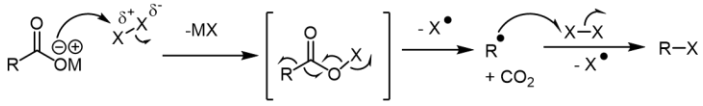


So, now I am going to talk about the Hunsdiecker reaction. here in 1963 the Hunsdiecker reported when dry silver salt of aliphatic carboxylic acid was treated with bromine, the corresponding 1-carbon shorter alkyl bromide was formed. it is a very important reaction because you started from this corresponding carboxylic acid, and your carboxylic acid is actually gone. this part goes for a decarboxylation, and instead of the Barton-McCombie reaction here, you end up getting an X, which means you can take a halogen, which means starting from the corresponding acid, you can synthesize a corresponding alkyl halide using a silver salt. so here is what is happening this reaction can be done with silver, thallium and mercury, so it is forming the dry silver salt first and then once you treat with the corresponding halogen source in presence of dry solvent in the reflux it is forming the acyl hypohalide so once it is forming the hypohalite then after that it is forming the CO2 and then corresponding RX.

In 1963, **H. Hunsdiecker** reported when dry silver salt of aliphatic carboxylic acid were treated with bromine, the corresponding one carbon shorter alkyl bromide were obtained.



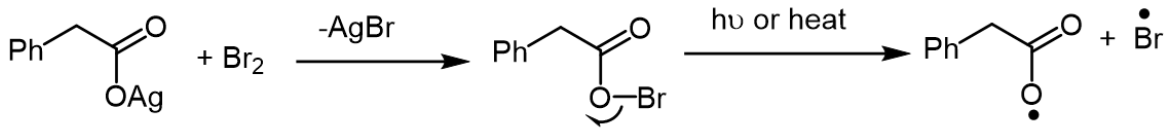
Classical Mechanism



So you can see mechanistically after this what is happening? this minus is attacking to

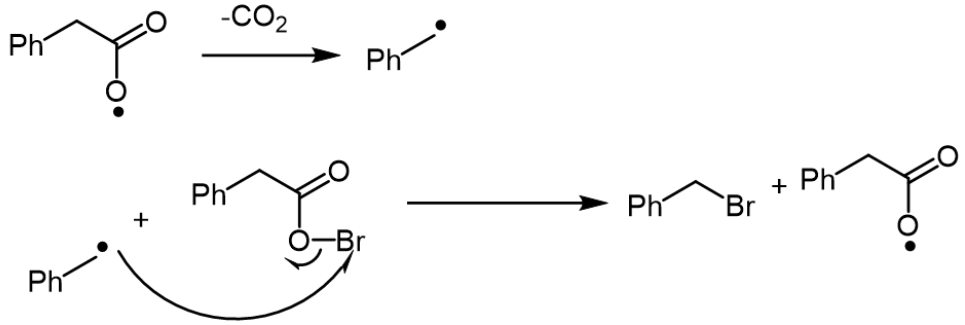
the X forming this hypohalide and then there will be cleavage happening between the O and the halogen bond. this is a weaker bond here to generate X• and after that, once you are generating this species, it will not going to stay there, it will immediately go for generating a free radical at the same time, a CO_2 will be expelled from here to generate this R• which now going to take a X• from here from X_2 to generate RX. So, again there is a mechanism given here. once you have this silver salt of benzyl acetic acid, first this formation of the hypohalide then under hv or heat it will generate this species here, which can participate in a decarboxylation to generate this benzyl radical which will take the bromine from here to generate this corresponding benzyl bromide.

Initiation:



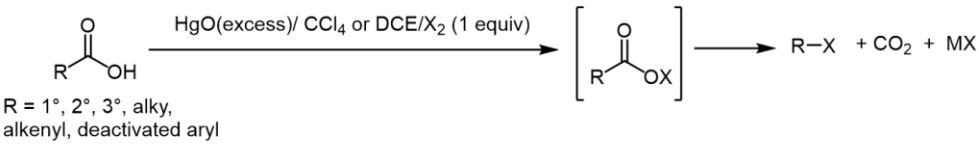
hypohalide

Propagation:

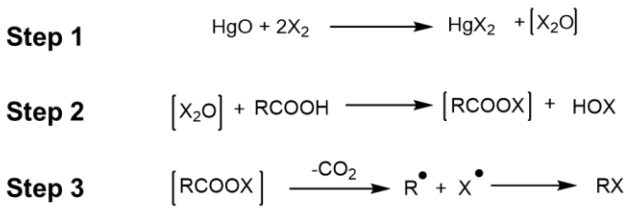


there is a modified version of this reaction so this is called the modified Hunsdiecker reaction or the crystol-firth modification. So what is happening here? in this reaction, they are starting from the carboxylic acid using the mercuric oxide excess and the CCl_4 or the DCE and X_2 that means these are the conditions. so instead of the silver now so these are the different variation actually developed. So, the most important thing is from here to here the corresponding hypohalide. So, this is the development happen. how to form the hypohalide in a different route.

Cristol-Firth modification



Mechanism



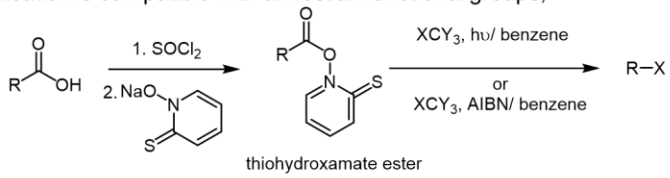
❑ One Pot reaction of excess red HgO and 1 equiv of halogen But in Classical method first silver salt has to be prepared from carboxylic acids

Once you generate the hypohalide, under hv or heat, it is going to generate this corresponding product. So, it is actually a one-pot reaction of excess red mercuric oxide and one equivalent of halogen.

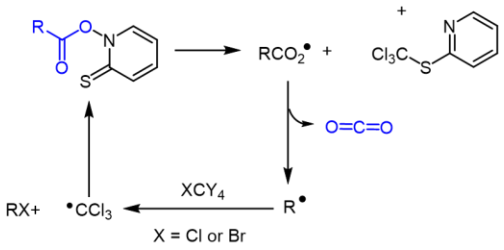
so now i can give you some Barton modification this reaction. So, what is happening here? first, starting from this corresponding carboxylic acid, it is actually forming this acid chloride, I can give you some Barton modifications to then forming this thiohydroxamate ester. So now, if you see in the Barton decarboxylation reaction, we know it is forming the R•.

Barton modification

Thermal or photolytic decomposition of thiohydroxamate esters in halogen donor solvents (e.g., $BrCCl_3$, CHI_3) and this modification is compatible with almost all functional groups;



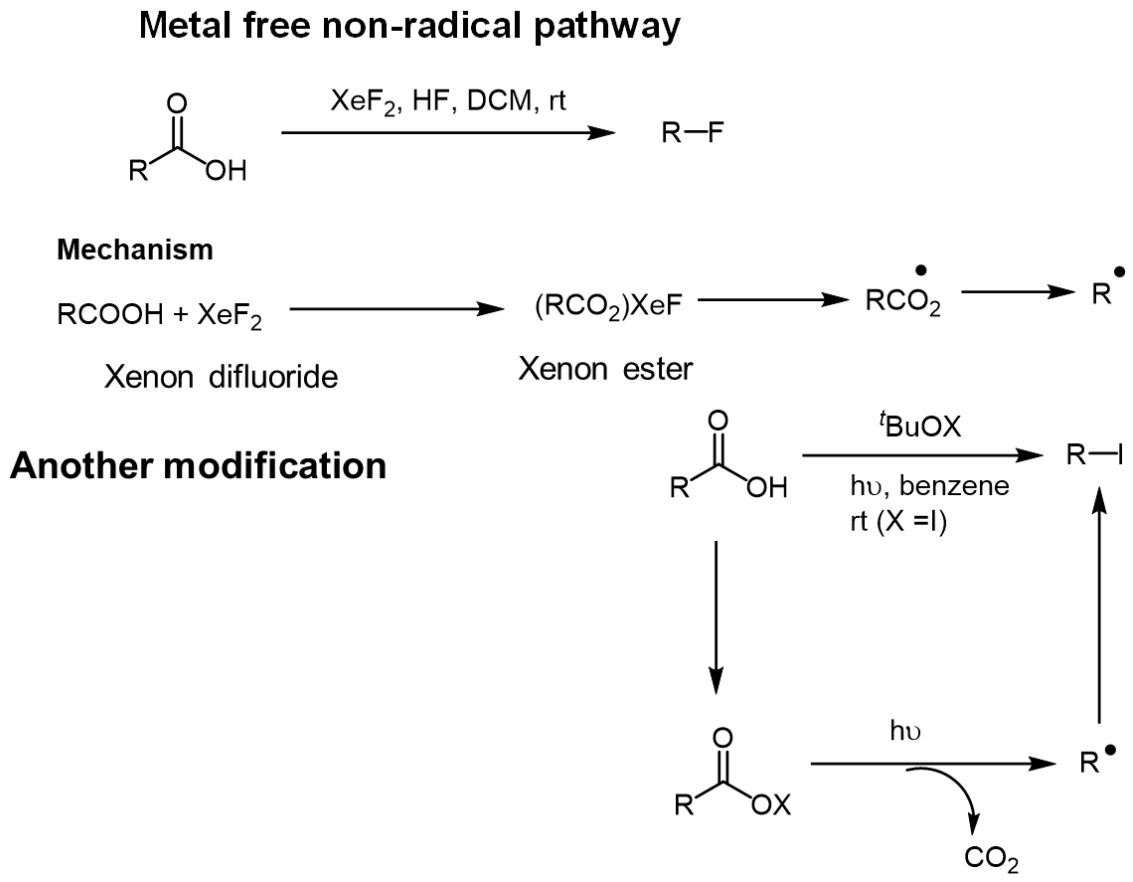
Mechanism



just because there is a tributyltin hydride at the end that is why the reaction is going from formation of the RH but now if you able to bring this some sort of a XCY_3 where the X

can be transferred, then you can able to synthesize corresponding RX. so that is happening here once you have a CCl_4, once you have some other species here, there are R• can able to abstract the corresponding chlorine or bromine to form the RX and then the corresponding CCl_3• or the CBr_3•. So, this can further go back to the system. what is happening? once you form the CCl3, it is actually interacting with this, to generate this corresponding S-CCl_3 species. It is very similar to the tributyltin hydride, where the tributyltin is actually at the end attached to the sulfur here.

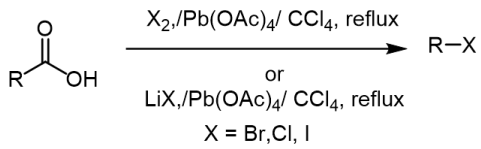
you have this CCl_3, which is actually attached here, so there is some of the other modifications using the xenon fluoride using HF. again, I think there is a formation of this xenon ester here. As I mentioned, once you form there, it is going to cleave the bond and formation of that species, which is going to form the R•. Again, you can see, once you have R•. if you use the tertbutyl-OX, the X could be halide then it is going to abstract this halogen to form the corresponding RX.



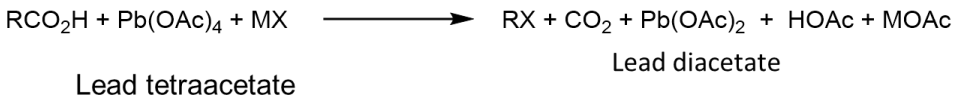
So, there is a Kochi modification here using the lead tetraacetate. the X_2, lead tetraacetate, carbon tetrachloride in reflux condition what is happening? the lead tetraacetate is forming this type of lead diacetate at the end forming of the RX. it is happening this corresponding to the tetrahedral reacting with this acid and then after that

you can see very similar type of reactivity that at the end it will be formation of the R• and then it will take a X from corresponding MX source and then the Cl will be transferred to make the corresponding RX. The detailed mechanism is given here.

Kochi modification



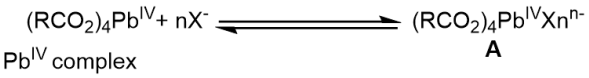
General mechanism



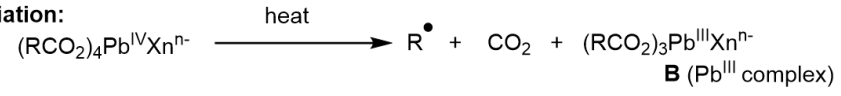
how this formation is happening. So, it is a lead tetraacetate going to react with the carboxylic acid as I mentioned to form this type of species which can under heat it is going to generate the R• which can finally take the X form corresponding MX.

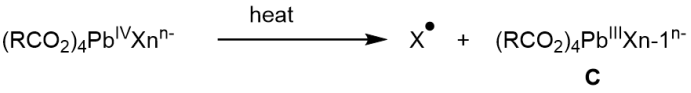
Mechanism:

preequilibrium:

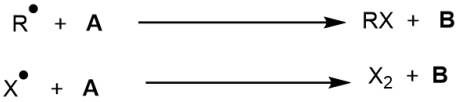


Initiation:

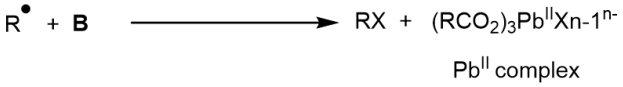




propagation:

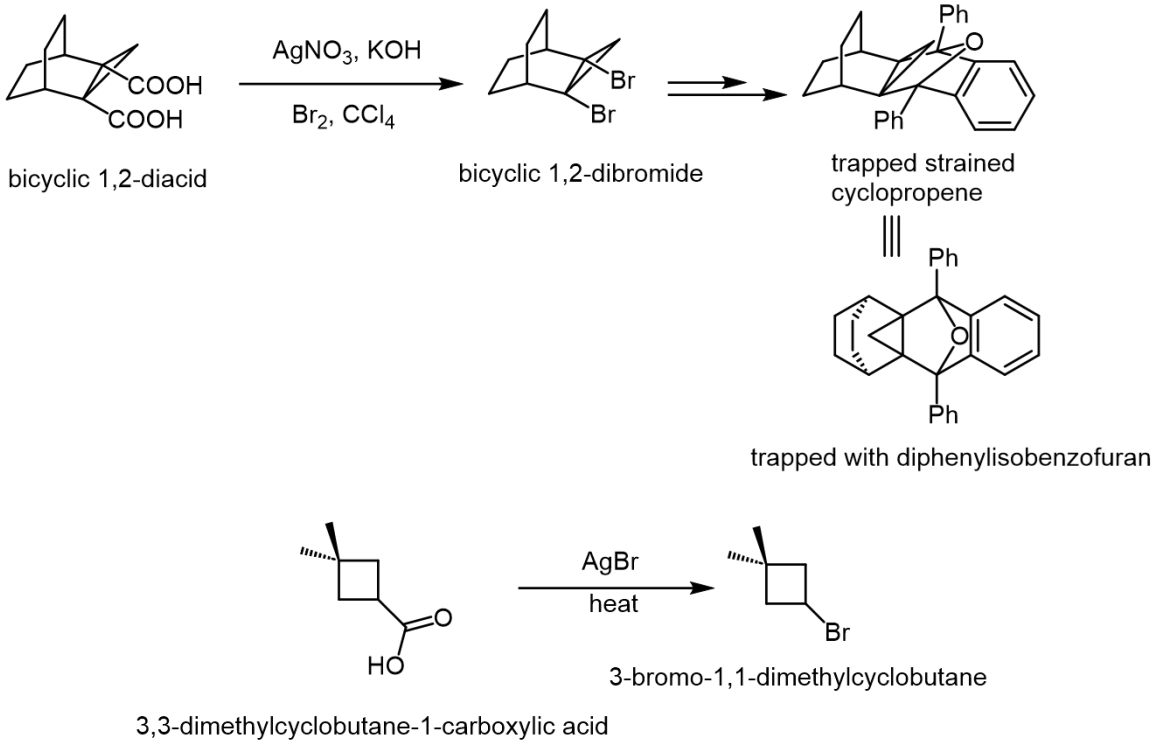


Termination:



Here are some of the applications of the Hunsdiecker reaction. there are several applications, but we have just brought some of the examples here. If you have this bicyclic 1,2-diacid, then this bicyclic diacid can form this corresponding bromide here, which can be trapped with this type of species to make some sort of a trap and strain cyclopropane. you can see, you have this cyclopropane already there now, this bromine can be trapped with this species to form this type of trapped cyclopropane, and then there

is another example here you can see starting from the carboxylic acid, using the silver bromide and heat (it is the original condition) you can make corresponding bromide here.



bicyclic 1,2-diacid

bicyclic 1,2-dibromide

trapped strained cyclopropene

trapped with diphenylisobenzofuran

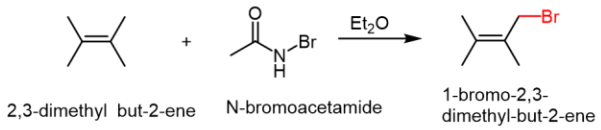
3,3-dimethylcyclobutane-1-carboxylic acid

3-bromo-1,1-dimethylcyclobutane

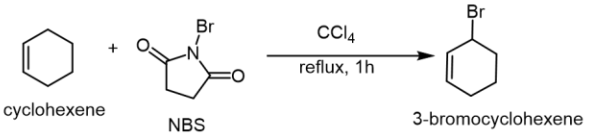
then the final one for this class is the Wohl-Ziegler bromination. So, what is happening? we all know that if you have an olefin with an allylic position here, then this allylic hydrogen can be abstracted and can be replaced with a bromine if you do allylic bromination. So this was discovered by Wohl and Ziegler in 1942; here, they used the NBS and CCl_4 under reflux conditions to get this corresponding cyclohexene to the 3-bromocyclohexene so this reaction is called the allylic bromination. And currently, this reaction can be done with the visible light instead of using the UV light. So what is happening here? if you take the alkane and the NBS and if you give a radical initiator, it can end up making the corresponding allylic bromide.

The introduction of a bromine substituent at the **allylic position** of olefins or at the **benzylic position** of alkylated aromatic or heteroaromatic compounds in known as the **Wohl-Ziegler bromination**.

Wohl (1919)

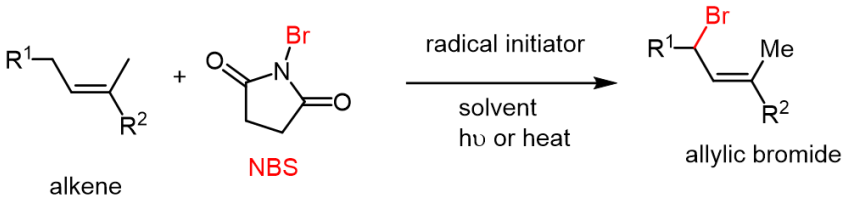


Ziegler (1942)

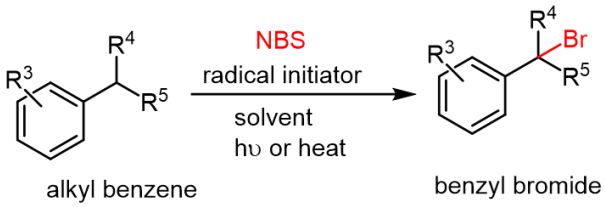


so from corresponding alkyl benzene, if you have a benzylic position here, it can end up making the corresponding benzylic bromide. this is a very good method if you want to make a benzylic bromide or an allylic bromide as well. so i think the first thing is you have to use an initiator that means if you have this benzoic hydroperoxide, what is going to happen? this peroxide going to cleave and then this it is going to form this species. as I said once that once you are forming this species you can generate this Ph• here and now at the same time what is happening? The Ph• can interact with this Br_2 to form this Br•. So, now this the Br• is the active species which is going to cleave this carbon-hydrogen bond to generate a radical which is just 2° and allylic.

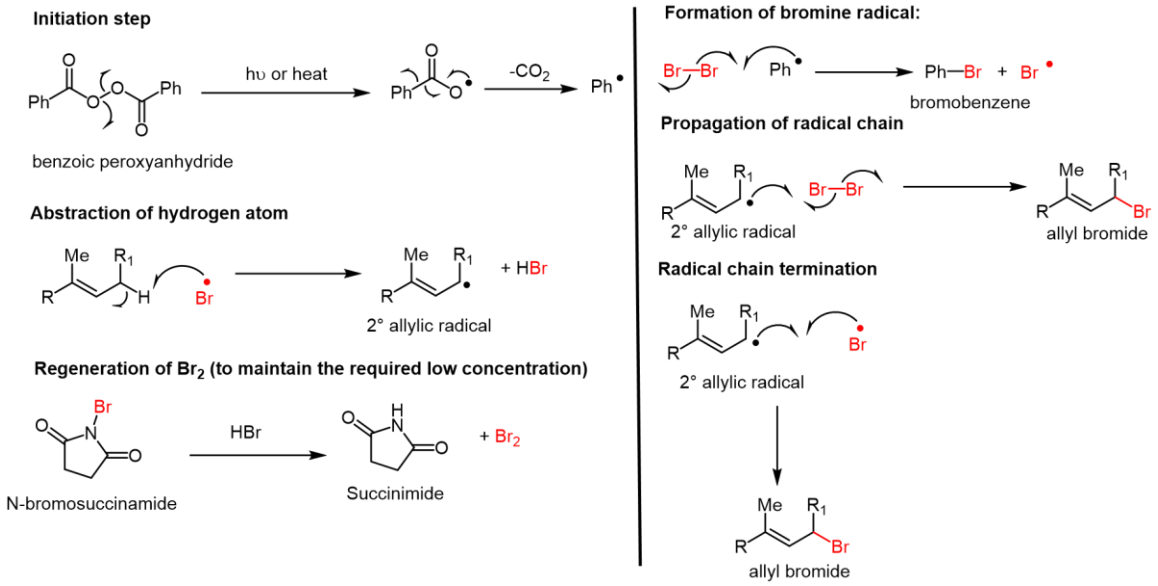
Wohl-Ziegler bromination



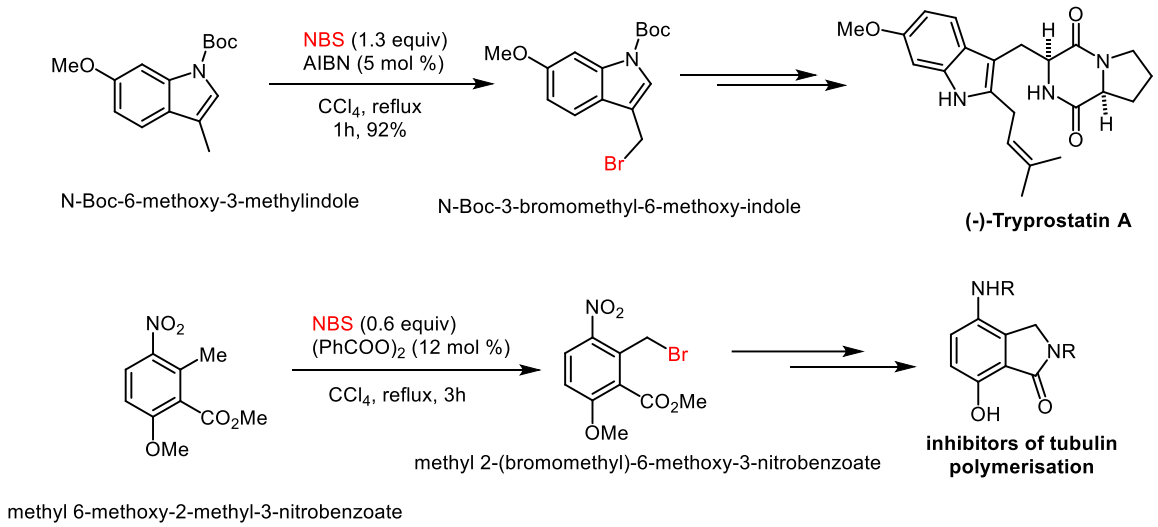
R^1 = alkyl, R^2= H, alkyl, COR, CO_2R, R^3=H, alkyl,aryl, O-alkyl, NR_2 R^{4-5}= H, alkyl, aryl
radical initiator: ROOR, Bz_2O_2, AIBN



now once you have this allylic radical it can interact with this bromine to form this allylic bromide so there, once you form the bromine, there will be radical chain termination happening to form this corresponding allylic bromide.



So, there are some of the applications here. starting from these corresponding indoles if you have a 3- methyl indoles then using the NBS and AIBN under CCl_4 reflux condition. now this benzylic position will be brominated which after some steps can able to get to this corresponding Tryptostatin-A.



So you can have another example here. you have a methyl group which is in a benzylic poison it can form this corresponding benzylic bromide which can be converted to a bioactive compound. So, in the today's class we have learned about the Barton-

McCombie decarboxylation reaction. you have learned about the Barton-McCombie deoxygenation reaction. you have learned about the Hunsdiecker reaction, the Wohl-zieglar bromination. and I am sure there are more reactions of the radical chemistry, which I am going to bring to the next class.

Again, there are very similar textbooks you can follow for this topic, and then thank you all for coming to the class, and I am sure you are going to come back to the next class. Thank you.