Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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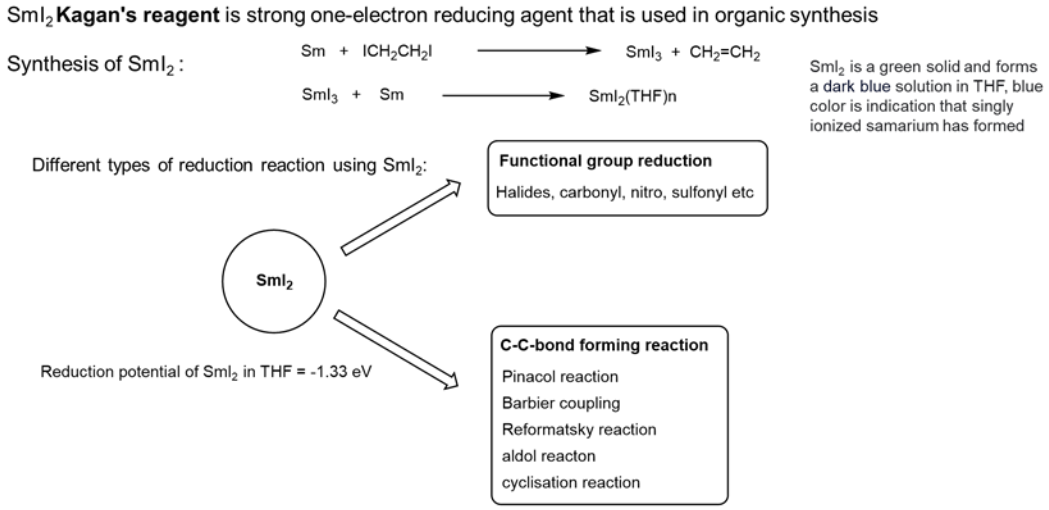
Lecture 24: Free radical reactions

Welcome back to this NPTEL online certification course on molecular rearrangement and reactive intermediates. In the last couple of classes, I was talking about the single electron transfer reagents. So, that can be used for the generation of a radical, and now this radical species can take part in a pinacol coupling or a Barbier reaction. So, in today's class, I am going to focus on the samarium because there are several important reactions to the samarium. I am going to talk about how samarium iodide was synthesized and what are the different reactions using samarium iodide.

So, first thing I am going to talk about the alkyl iodide reduction reaction. Then the pinacol reaction, of course, the ketone and aldehyde reduction reaction, cyclization. So, then there will be some Grignard or the Barbier reaction, Reformatsky reaction and I am going to talk about the Aldol reaction at the end. So, first thing, I think the Kagan group actually developed the method of how to generate the samarium iodide. So, it is an one-electron or a single-electron reducing agent. It can be generated starting from the samarium. If you use this 1, 2 diiodo ethane, it will generate the SmI_3 which is going to react with the samarium to form the SmI_2 and there will be one important thing, solvent plays very important role. So, the solvent will make a coordinated complex with the samarium. So, once you make them also you have to use the THF in the reaction. So, actually, samarium iodide is a green solid, but once it is combined with the THF. you will go to see a very deep blue color. So, that blue color actually indicates that yes you got to the samarium iodide which is now ready for the reaction. So, what is that mean of the color, that kind of showing that it is a slightly ionized samarium has formed. That means, you already have electron density there which can now take part in the different type of chemical transformations. So, there are different types of reduction reactions using samarium iodide and we can talk about functional group reduction which means you start with different functional groups like alkyl halide, carbonyl group and then the corresponding nitro. So, that can be reduced because having a so, it has a wide range of reduction potential. So, this is a reduction potential using THF, -1.33 ev, but this is not the reduction potential of samarium iodide it can go up to 2.6 or even up to 3 ev. If you change the additives and the different solvents. So, it not only go for the functional group reduction that can be also done with other different type of reducing agents or other different single electron transfers. But the important thing is this can participate in a very important type of reaction like the pinacol reaction, I am going to talk about the Barbier reaction, the Reformatsky reaction, and some of the most importantly intramolecular radical cyclization. That is still nowadays also you will see a publication where this samarium iodide is still very useful for the formation of carbon-carbon bonds.



SmI_2 **Kagan's reagent** is strong one-electron reducing agent that is used in organic synthesis

Synthesis of SmI_2 :

$$Sm + ICH_2CH_2I \longrightarrow SmI_3 + CH_2{=}CH_2$$

$$SmI_3 + Sm \longrightarrow SmI_2(THF)n$$

SmI_2 is a green solid and forms a dark blue solution in THF, blue color is indication that singly ionized samarium has formed

Different types of reduction reaction using SmI_2:

SmI_2

Functional group reduction

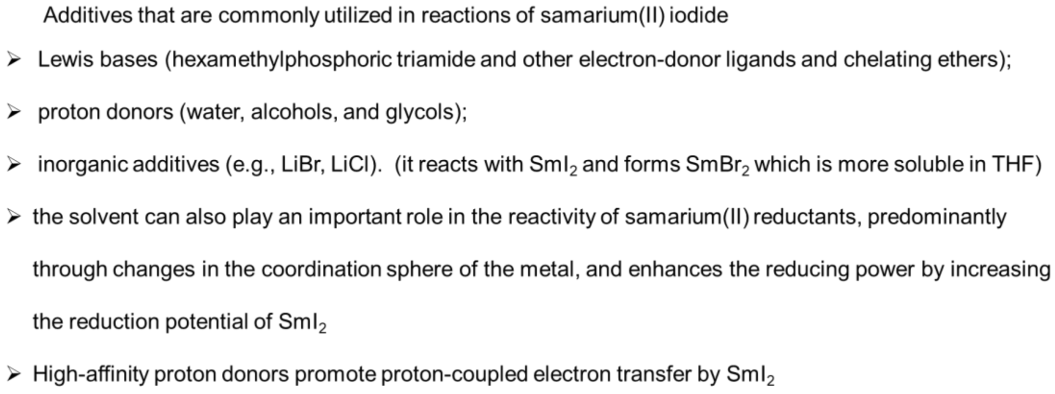
Halides, carbonyl, nitro, sulfonyl etc

C-C-bond forming reaction

Pinacol reaction
Barbier coupling
Reformatsky reaction
aldol reacton
cyclisation reaction

Reduction potential of SmI_2 in THF = -1.33 eV

First I am going to talk about the different type of additives. So, of course, samarium forms a complex with the THF as you can see samarium iodide in a THF complex. Now, people have also used different type of additives because what happen once the additives. So, there are different types of additives. So, let us talk about them. There are one is the Lewis bases. One of the important one which is often used with the samarium is the HMPA, hexamethyl phosphoric triamide. So, these are the electron donor ligand or a chelating ligand which forms some sort of a complex with the samarium. I am going to also talk about them in the later slides. Then there are other type of additives called the proton donor. So, they become last two decades this proton donor become very popular in the samarium reaction. So, they can be water, alcohol, or glycols, all they are can be used as a proton donor. And people have found out using water, they can found there is some sort of a proton couple. So, there is some sort of PCET also happening. I am going to explain also them in the later on. There is something called the inorganic additives that could be lithium bromide or lithium chloride. Again this can react to samarium iodide, and samarium bromide which can form more solubility in the THF. So, that can help with the solubility. Again the solvent can play a very important role as I mentioned. Generally, you can see mostly the ether type of solvent was used, but again if you can add some of the other solvents that is the reactivity has changed. Because there is a change in the reduction potential of the samarium iodide. So, I think the high-affinity proton donor promotes the proton-couple electron transfer as I mentioned at the beginning if you use the water or the corresponding alcohols. So, the most important fact is in these additives, there are some the additives like lithium bromide has helped with solubility, but other additives HMPA or the protic additives, they actually form some sort of a complex with the samarium iodide. So, there is a change in the redox potential that is the important factor.

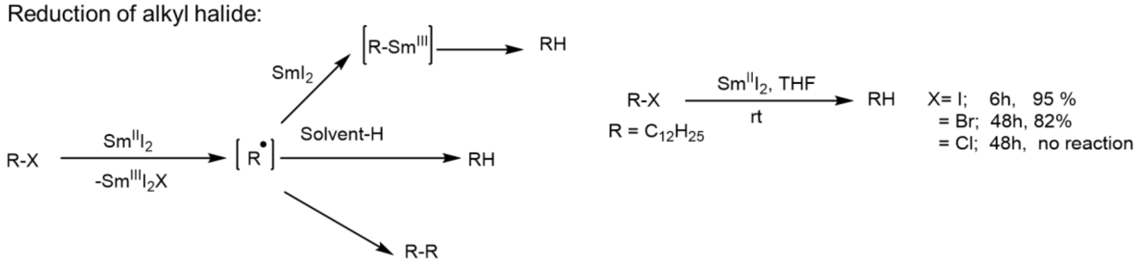


Additives that are commonly utilized in reactions of samarium(II) iodide

- Lewis bases (hexamethylphosphoric triamide and other electron-donor ligands and chelating ethers);
- proton donors (water, alcohols, and glycols);
- inorganic additives (e.g., LiBr, LiCl). (it reacts with SmI_2 and forms $SmBr_2$ which is more soluble in THF)
- the solvent can also play an important role in the reactivity of samarium(II) reductants, predominantly through changes in the coordination sphere of the metal, and enhances the reducing power by increasing the reduction potential of SmI_2
- High-affinity proton donors promote proton-coupled electron transfer by SmI_2

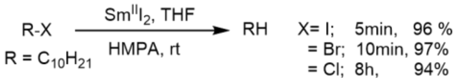
So, first thing I am going to talk about the in the reduction of alkyl halide here. So, first, if you have an R-X and the samarium iodide, it is going to form this in R• through a single electron transfer, samarium will be converted to Sm(III)and it is going to form the R• which can again take another SmI_2 to form this R-Sm(III) which can finally, take some proton to get to the RH or it can abstract. So, there could be a hydrogen atom abstraction from the solvent to form the RH or there is a process called a radical recombination to form a dimer. Again you can see here if you are doing this reaction then if you have a X= I vs Br vs Cl what is happening. As the carbon halide bonds energy is getting increases your reaction becomes slower and slower. That is kind of understandable that your bond dissociation energy.

Reduction of alkyl halide:



Reduction of halides: iodide> bromide> chloride

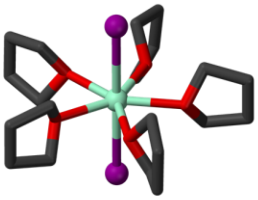
Reduction of alkyl halide (HMPA solvent):



Again very similar things here, and now the thing is if you use HMPA what is happening here? So, HMPA is making a huge difference because at the beginning you have seen for X= Br, 48 hours and Cl even no reaction. But here once you use HMPA, we can see in the case of bromo and chloro which is almost, it is a very long reaction now under 10 minutes or 8 hours, these reactions are possible. What is happening here? Once you add HMPA, this change the redox potential that is allowing you to reduce this carbon-chlorine bond much faster. So, this is a complex. So, you can see there are five THF unit with the samarium iodide. So, this is a samarium in the center, there are two iodine here with the purple color and there are THF units here. So, this samarium iodide THF complex getting, first, it is formed in the presence of THF, but once you add this HMPA, it actually dissociates this complex. So, it actually makes kind of form aggregation at the beginning with the THF, but HMPA kind of break this aggregation. So, that is a very important part of the HMPA. So, it breaks the aggregation, makes the samarium free from the THF.

The use of hexamethylphosphoramide (HMPA) as a co-solvent in samarium(II) iodide reductions increases the Sm(II)/Sm(III) reduction potential

1. Basic cosolvents dissociate SmI_2 aggregates in THF
2. Basic cosolvents increase the Sm(II)/Sm(III) reduction potential



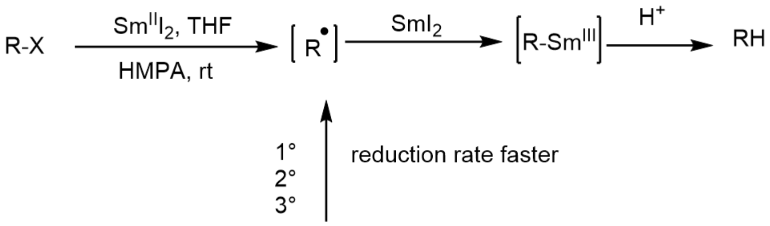
SmI_2-5THF complex

Reduction potential of **SmI_2 in THF is -1.33eV**

But in 6 equiv of HMPA reduction potential is **-2.05 eV**

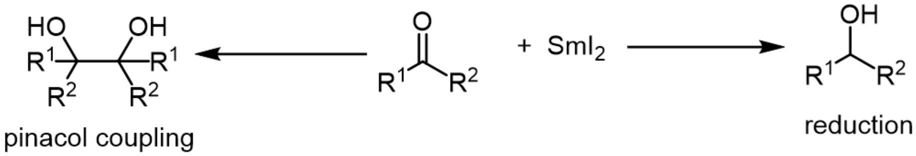
So, that means, samarium now has the chance to coordinate with this some of the like with oxygen of the carbonyl or other things. So, that means, that can remove some of this THF unit and also make a change in the redox potential. So, this is in the THF, that is in the HMPA which I was telling in the previous slide. And again that is also depend on how much equivalent of HMPA you are using. It is not that if you use one equivalent HMPA you will achieve to this redox potential. So, what is going to happen? If you have a samarium iodide in THF and now you are adding HMPA one equivalent after another equivalent, you are seeing a change in the redox potential, but after a certain amount you will not see. So, there will be saturation. Again we are seeing here in this reaction, that once you are doing the reduction here the samarium is going to reduce the corresponding alkyl halide to the corresponding RH after it is getting to the proton from the corresponding if you have a proton source.

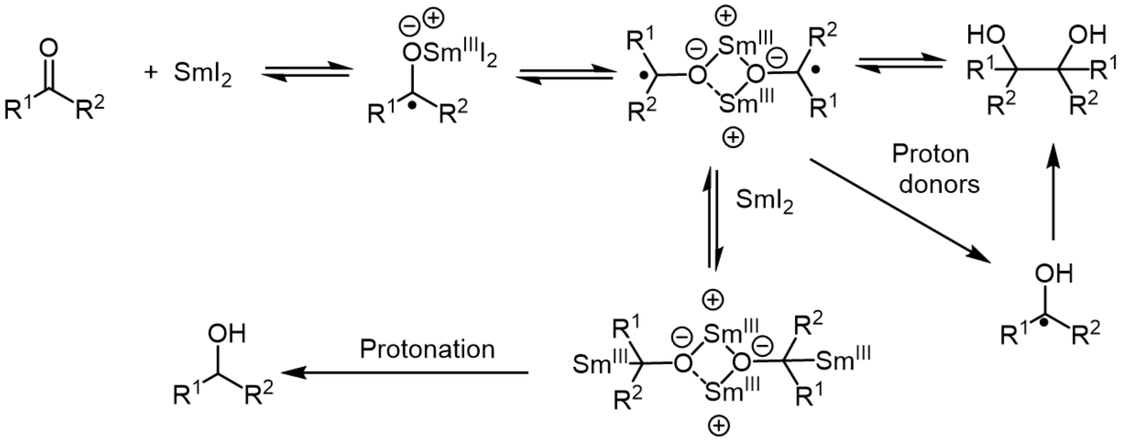
Reduction of alkyl halide (HMPA solvent):



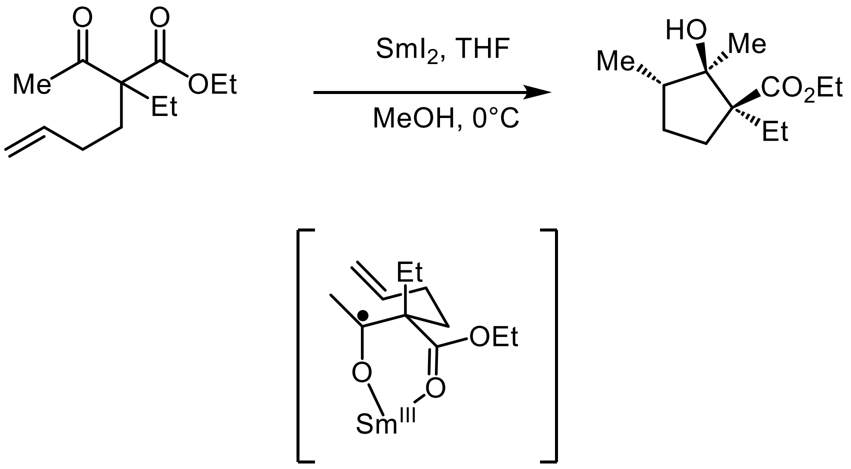
So, now I am going to talk about the pinacol reaction vs the reduction. So, if you have a carbonyl group here, What is happen? First thing once you have a carbonyl group here and you have a samarium iodide. Samarium acts as a single electron transfer agent. That means, now it is going to end up making this samarium ketyl radical. that is the very important species. So, you will see lot of reaction happening from this samarium ketyl radical which is happening after the reduction of the carbonyl species. First thing again, it can form this species here, you can see that it can go for another molecule of this can form this type of. So, both of the molecule, two of the molecules can form this species can take two of the samarium unit. So, after that, it can take a, it can convert here. How this is conversion happening? You can see from here there is a radical species here which is generating, that can be also taken with the samarium in the presence of samarium iodide which can be after the protonation, it can form the corresponding alcohol or from here it can also form the corresponding pinacol. So, for the pinacol what is going to happen, these two radicals can go for a radical recombination. If there is a radical recombination happening it can form the pinacol, but if it is taking another samarium iodide and going for a protonation then it is forming this corresponding alcohol.

So, there are two possibilities it can go for reduction or it can go for a pinacol coupling.

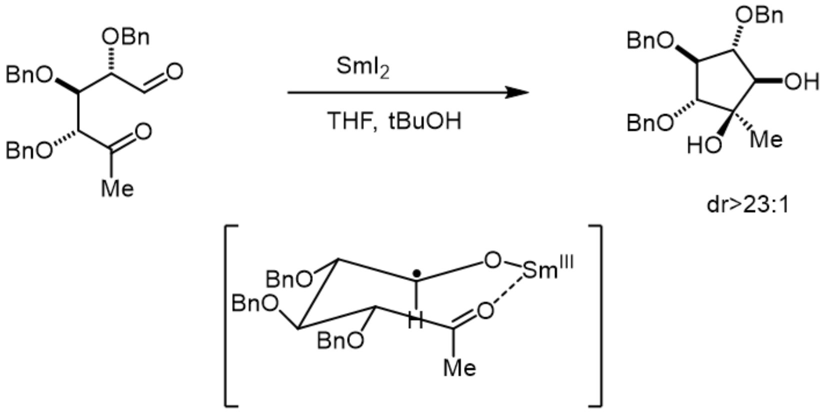




I am going to show you some of the examples here. So, you have a carbonyl group and you have an ester here. So, these are some of the examples of intramolecular reactions. So, you have learned about I think I have already talked about that if you are forming a radical species, then if you have a double bond there that can participate in an intramolecular radical cyclization which I am going to talk about when I talk about the radical intramolecular reaction. So, here what is going to happen? If you have a carbonyl group here, the important, if you have a ketone and ester that ester can also combine with the samarium. So, the important part is the kind of keeping both this ester and this oxygen on the same side. And now this radical going to participate in a 5-exo-trig cyclization to get to this product. And if you see here the important part is here, Once the radical is added here this methyl group which is here and the newly formed methyl group actually going to be down because going to be on the same side that is the important thing. Both the methyl will be on the same side. And then you can see this corresponding ester and this corresponding oxygen, the OH which is going to form are also in the same side. because of the chelation with the samarium.

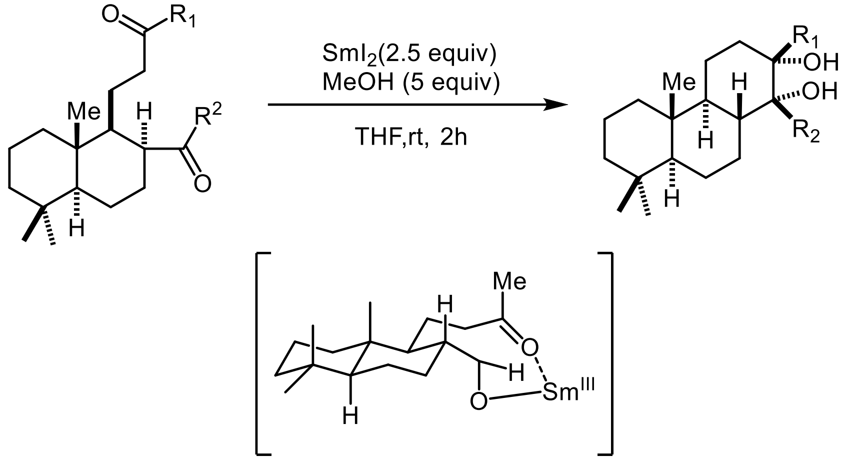


So, here what is happening, first there is reduction and then an intramolecular cyclization. So, now what is going to happen? It is going to participate in a pinacol reaction.

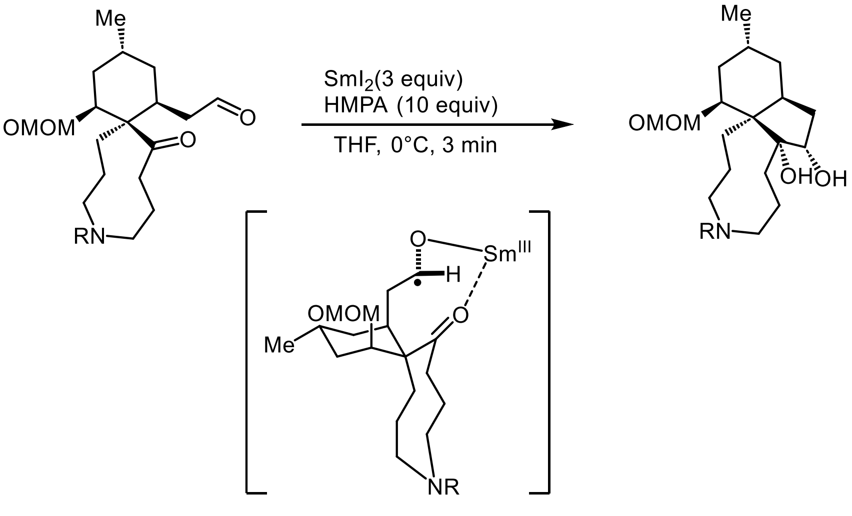


So it is an intramolecular pinacol reaction happening. How this reaction is taking place that first thing is you can see there is an aldehyde and there is a ketone. So, aldehyde is getting reduced with the samarium and now it can go for one round of reduction of this. So, it can either be added here or the samarium can able to reduce this carbonyl group, the ketone can be reduced to the samarium to generate a radical species here, which can recombine to form this product. Again the important factor you can see this oxygen and this oxygen will be on the. So, these two OH are on the same side.

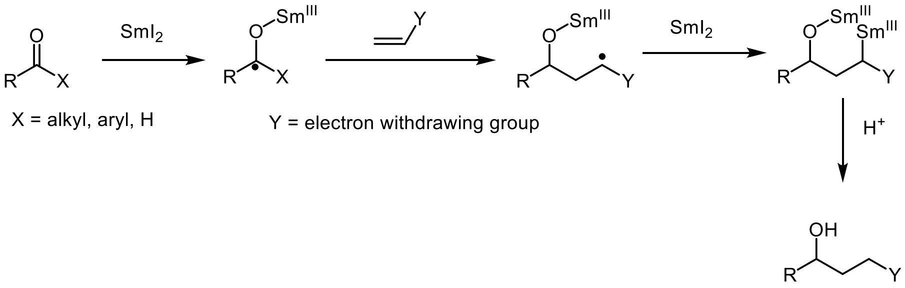
So, there is another example here of the pinacol reaction. Now the important thing is you have a carbonyl compound. So, there are two different carbonyl compounds here, and as I said what is happening at the beginning? So, this is forming a radical species here. So, it is forming this samarium ketyl radical, and then it is going to go for another round of reduction of this carbonyl species to to generate another round of ketal radical here and these double bonds will be vanished. So, then samarium will make a coordination. So, there could be a once the samarium coordinates now these two ketyl radicals go for radical recombination to form this 6-member product. Here you can see both the OH, as the samarium is coordinating with both oxygen it is going to be on the same side. So, they are actually in the down you can see in this molecule there is methyl in the up, and both the oxygen is down in the product.



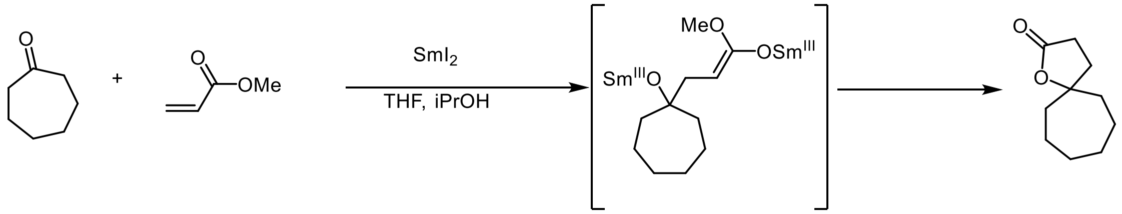
There is another example of the intramolecular pinacol reaction. Here you can see there is a generation of a radical in this species. There is an aldehyde here which is generating radical and then there is another carbonyl species here which at the end forming this pinacol. Again as I said both the OH will be on the same side. So, again in this reaction, you need more, I think they have used 10 equivalents of HMPA with the samarium iodide for this reaction to happen. So, this actually, also depends on the substrates as well.



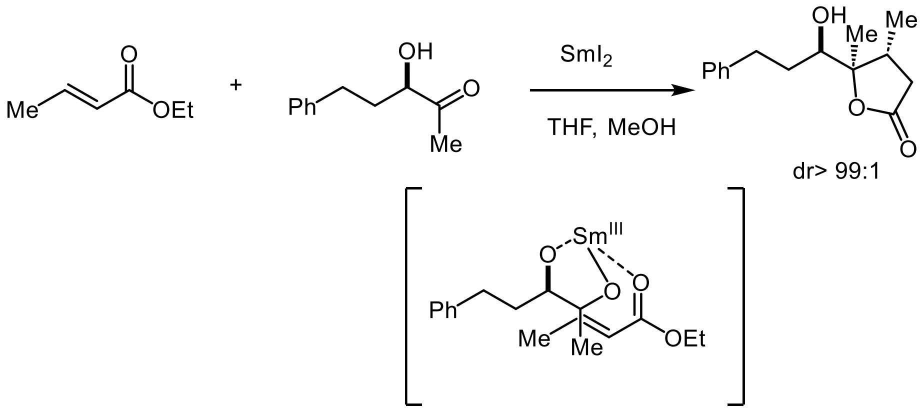
So, I talk about I think in the previous slide there is an intramolecular reaction that once you form the samarium ketyl radical, if you have an olefin then it can add there and if you have an olefin with electron withdrawing group then also it going to add because you can see. So, this is a radical which will be a nucleophilic radical which will add here with a electron withdrawing group to make this radical species. Then another samarium iodide is going to come into the picture from this samarium species. And it can take a proton from a proton source to get to this corresponding product.



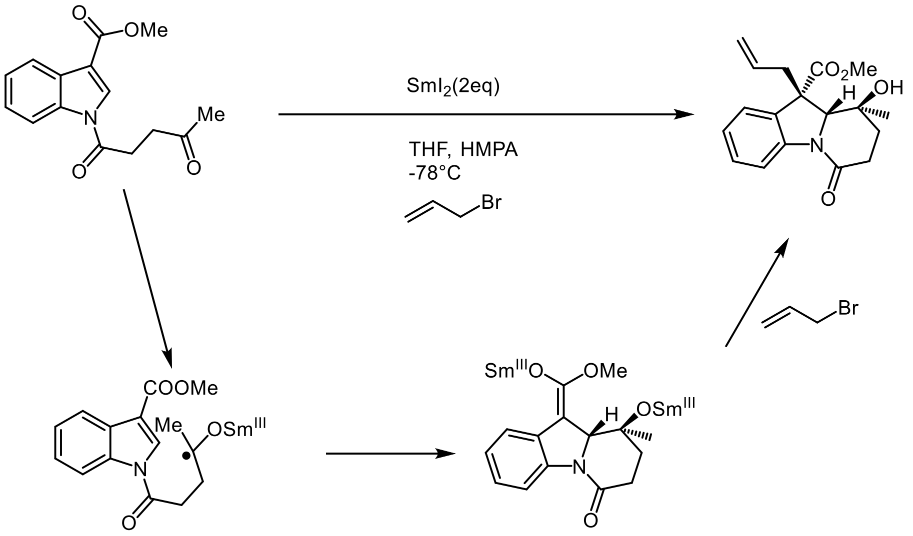
So, what is happening here, literally this carbonyl group is converting to the corresponding alcohol and it is going to take part in some sort of a 1,4-addition to this. So, what is happening here, you start with this corresponding ketone, formation of this samarium with the ketyl radical here which will generate here and now it will going to take part in the radical addition here. and then what is going to happen, there will be a samarium iodide that are going to come and then form this type of intermediate species. You can see here, there is oxygen with the samarium. So, there is some sort of a negative character and there is an ester here. So, which going to recombine to form this product.



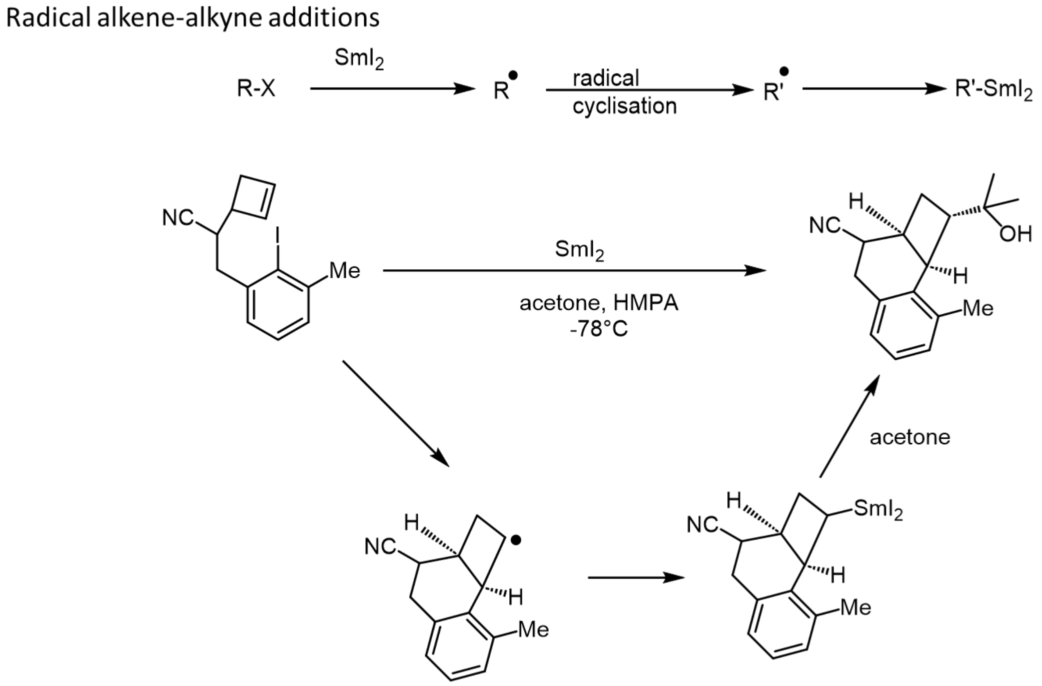
It is going to form some sort of lactone here and then there is another example here if you have an ester and you have a carbonyl group. So, you have an α-hydroxy carbonyl group. If you have an α-hydroxy carbonyl group, again this hydroxy kind of acts as a directing group here. So, this samarium going to bind and form this type of species first, and now what is going to happen, it can form this type of ketyl radical here and this ketyl radical now is going to add here to the α, β- unsaturated compound. Now you can see here finally, in the product. So, if you see so these two have actually these two oxygen in the same side this OH and then it is going to now add to this ester. So, it is going to add here first, and then at the end, this alcohol which is going to form, it is going to form a lactone by reacting with the ester. Here the methanol was used as a protic acid like which can give a proton source.



Then there is another interesting example here, you can see there is an indole where C-3 position, there is electron withdrawing group. Now, if you can see there is a carbonyl group here and some sort of an amide group here. So, of course, the carbonyl group going to be participate in the reduction in the presence of samarium iodide and going to form this type of ketyl samarium species which going to take part in the 1,4-addition here. So, it is going to add to the corresponding indole in the C-2 position. So, it is going to add here form this species. Again now it is going to form this species here and then what is going to happen, you can see now this has some sort of enolate character if you use corresponding allylic bromide, it can trap the allyl group here to form this.



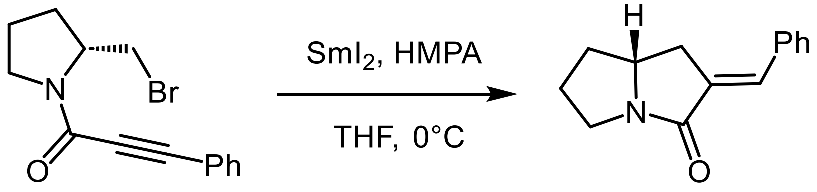
Now it can form you can see you have a quaternary center here, you have a tertiary center here, you have a quaternary center here. It forms because you can see here as you have a samarium here which is forming at the beginning then it is going to take the allyl bromide here to get to this corresponding product.



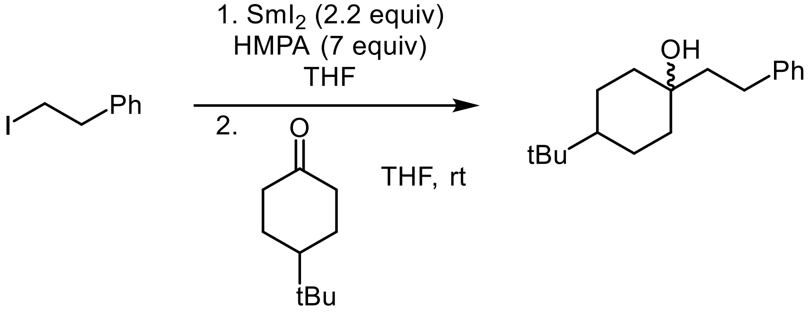
I have talked about some of the radical cyclization. So, now what is going to happen here, from the R-X you are going to generate R•, which I already mentioned at the beginning and now what is going to happen, that can take part in a radical cyclization reaction. Here first this carbon iodine bond is getting cleaved in the presence of the samarium. Now, it is going to add to this corresponding double bond here and it is going to generate this radical species, once the radical going to form here what is going to happen, it can take a samarium iodide to form this species. Now, if you have acetone in the reaction what is going to happen, the acetone is also going to end up forming the corresponding ketyl radical. So, there will be a radical recombination going to happen between these two. So, that can form this product.

So, now, there is a reaction where I talk about the reaction of the radical species to the corresponding alkene. Here I am going to talk about a reaction where you have samarium iodide and HMPA. I mentioned that what is the role of HMPA, it is going to coordinate, first, it is going to dissociate the THF samarium complex and then it is going to coordinate with the samarium and then change the redox potential. And also I talked about that if you have a carbon bromine bond, then it is going to form the corresponding radical very fast. You have seen that the reaction depends if you have a chloro vs bromo vs iodo. Now, once you form this corresponding radical, what is going to happen here?

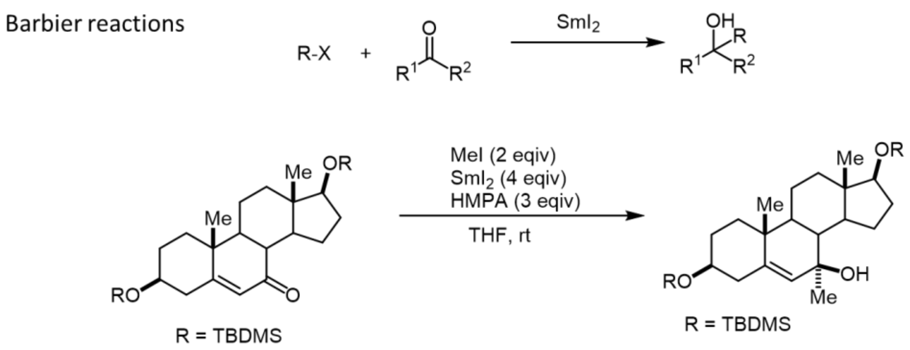
So, now, you are generating this radical species in this position. So, there are two different types of cyclization that can happen. It can either go for some sort of an exo-dig cyclization or it can go for. So, it can be a 5 exo or it could be a 6 endo. And you can see this will be more favorable compared to others. So, that is how it is going to end up, adding here and that is going to generate a radical species here, a samarium species. Which can able to take a proton or it can go for a hydrogen atom abstraction to get to this product.



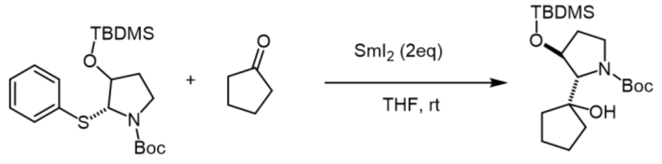
So, now I am going to talk about some of the Grignard reactions here that you have learned about. If you have corresponding alkyl iodide and if you have a samarium iodide. It is forming this radical species and then the samarium iodide can come in and form the corresponding some sort of a R·. So, you will end up making some sort of SmI_2 species form. Now if you can consider very similar to some sort of a Grignard type of reagent, you have an anionic character here which can add to this corresponding carbonyl group here. Once you add it here, you end up making to these corresponding alcohols.

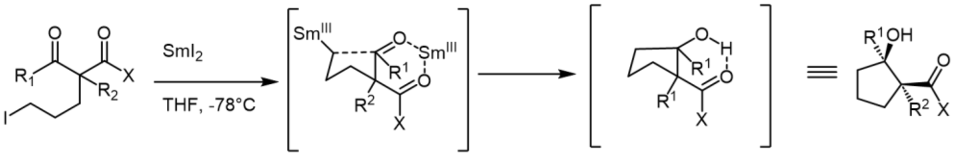


Again there is the Barbier reaction. I explained during the Barbier reaction that if you make samarium as I was telling you that methyl iodide and samarium iodide going to make this methyl samarium species. Which is going to now add to this species through the bottom phase because the top phase is hindered because of the methyl groups. So, that is why it is end up forming this product as a major product.

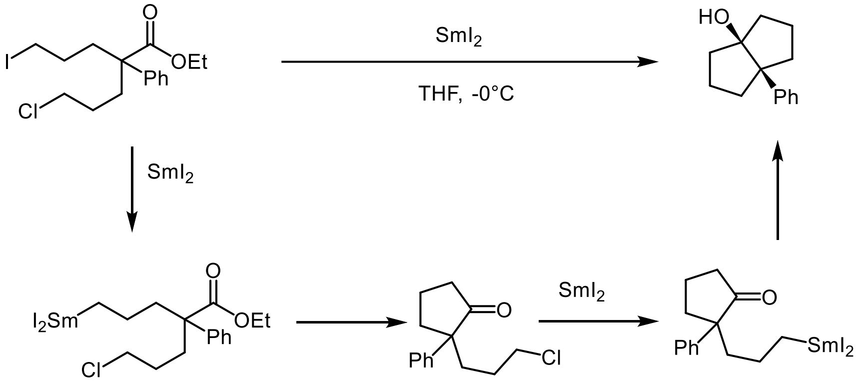


There is another example of the Barbier reaction here. So, what is happening here you can see in this starting material to product. Let us try to understand what is happening here. If you see this carbon-sulfur bond getting cleaved and then we are seeing this particular group is getting into the system. So, what is happening, again if you see the samarium iodide going to form some sort of a, first it will cleave this bond and form the corresponding. So, very similar to the carbon-iodine bond, it is going to cleave this carbon-sulfur bond to generate a samarium species from here. it will generate a samarium species. So it will generate a radical first and then it will generate a samarium species after the reaction with samarium iodide. And now this samarium iodide can able to act as a Barbier reaction to react with the corresponding carbonyl group here to get to this product.





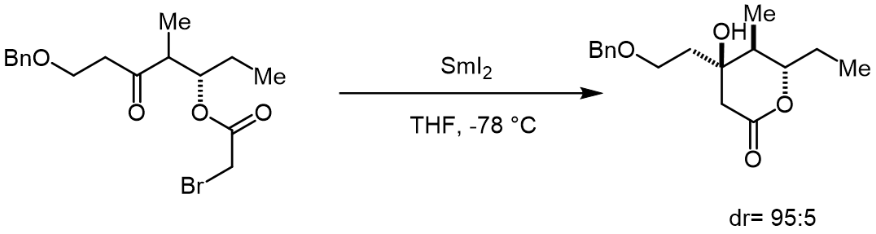
There is another example of an intramolecular reaction happening here. So, in this reaction what is happening, you can think that samarium iodide is leaving this bond, forming this corresponding samarium species here. So, it can form the radical and then the samarium species which can now able to add to this corresponding carbonyl group here and once it is added to the carbonyl group, you can see, it is going through some sort of a transition state here and then it is forming this corresponding alcohol. So, the important thing is once you have this other carbonyl group which could be ester then that is the samarium is going to bind with that in the corresponding transition state, making sure these two oxygen will be on the same side. So, this OH and the carbonyl group will be in the same side. So, that will be the product in the reaction after taking a proton.

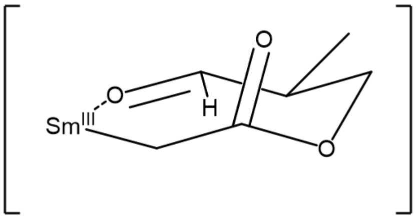


Another example here forming a samarium species first with the corresponding iodo and then it can participate. So, there are you can see, it can react with the ester also. It is not only reacting with the corresponding aldehyde or ketone, it can react with the ester and then there will be in this OEt going to get out to form this carbonyl species. Here what is going to happen, you have this corresponding chloride here, now this corresponding chloride can also form a samarium species in the presence of samarium iodide and that can also going to add here.

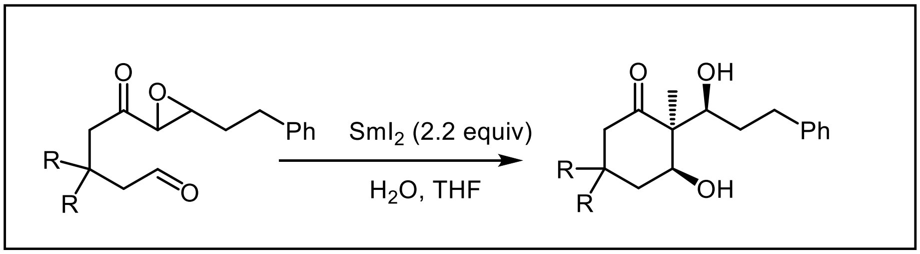
So, it can add to this type of carbonyl group here. And we can see if you think about this phenyl is up if you think this phenyl is up, the addition of this nucleophile is going to happen from the bottom phase. So, it is going to come back after it is forming the samarium species, it can form through the bottom phase. and it can going to form this, if you see now this OH going to form the up. So, this OH and phenyl will be on the same side because the nucleophile is attacking from the bottom phase.

Another important example here. So, these are a type of a reformatsky reaction happening because you have a compound which has a α-bromo esters are present here. So, now, if you use samarium iodide what is happening here? Now you can see from this type of mechanistic drawing, first, there will be cleavage of this carbon bromine bond and it will going to generate this corresponding samarium species there. And now what is going to happen, that corresponding samarium species going to add to this corresponding carbonyl group. So, it will form this corresponding samarium here and then it is going to connect here and then this is going to add here to this corresponding carbonyl group to form the alcohol. So, it is some sort of Reformatsky reaction. We have learned about reformatsky reaction using the zinc, but here we are using the samarium for the same transformation as well.





There are several different types of other reactions also I am just going to talk about the other important reaction is the aldol reaction. What is the aldol reaction? If you remember the aldol reaction, you end up synthesis of β- hydroxycarbonyl compound. This is α, β. So, now, what is happening by using this samarium iodide chemistry we can also able to make a β-hydroxy carbonyl compound. So, let us learn how this reaction is happening. So, again if you have a carbonyl group here it can form this corresponding ketyl radical and once it is forming the ketyl radical that means, what is going to happen, you make this radical here and a samarium species here. So, now if you have this species here what is going to happen? Now that can participate in two different way, it can go for finally, convert to the corresponding anion, and then it can add to this epoxide. Now if you see in this epoxide you have this carbonyl group. So, means that position will be more electrophilic compared to the other position. So, that is why the nucleophile going to attack here. So, it is going to form an anion here and some sort of a Barbier type reaction going to, it is going to add to the epoxide to form this corresponding product here. And again you can see here this. If you see in this reaction in this particular position you end up forming this H here. That means, this will be attacking from the position from the bottom phase of this to form this corresponding product. So, you end up again forming this β-hydroxy carbonyl compound.



So, in this part, I talk about samarium iodide generation. How you generate samarium iodide by starting from this 1,2-di-iodo ethane using samarium. Then I talk about the pinacol reaction and different types of pinacol reactions, which could be intramolecular or intermolecular. Then there are the ketone aldehyde reduction reaction and intramolecular cyclization reaction to the olefin and alkyne. Then there are the Barbier reaction and the Reformatsky reaction, the aldol reaction. So, I think these are important references if you want to learn about samarium chemistry more. And again thank you for coming to the class and I am going to see you guys in the next class. Thank you.