Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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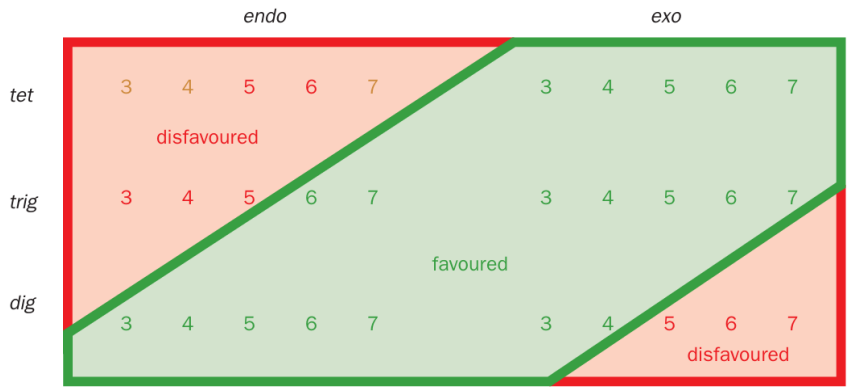
Lecture 26: Radical

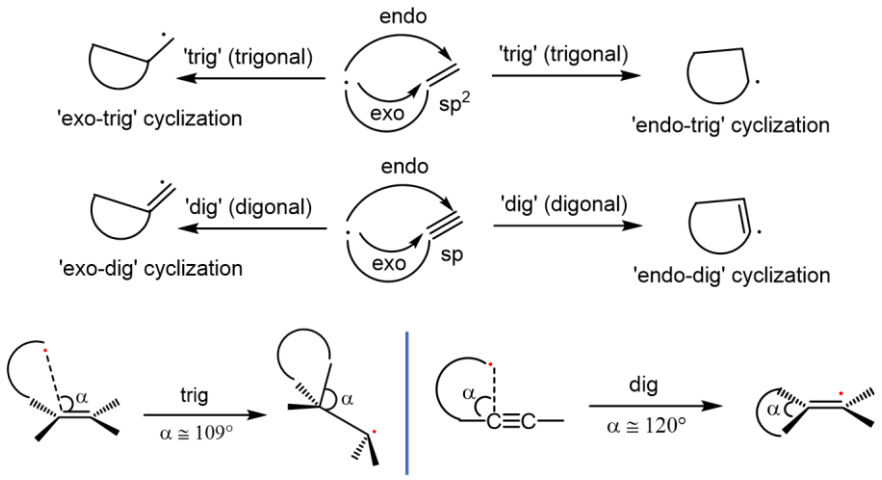
Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediates. In the last class, I talked about the hydrogen atom transfer, and there, I talked about the two important name reactions, the Barton nitrite ester reaction and the Hofmann–Löffler–Freytag reaction. And, there, if you remember, in the end, I was talking about some intermolecular radical cyclization. So, I thought about giving a separate lecture about intermolecular radical cyclization because this is a very important reaction, and it was used for several natural product synthesis.

I am going to talk about Baldwin's rule, and then I am going to talk about the stereochemistry in radical cyclization. So, what will be the product? So, what will the corresponding diastereoselectivity be? I am going to talk about some of the oxidative radical cyclization. Finally, I am going to talk about one or two reactions to samarium iodide.

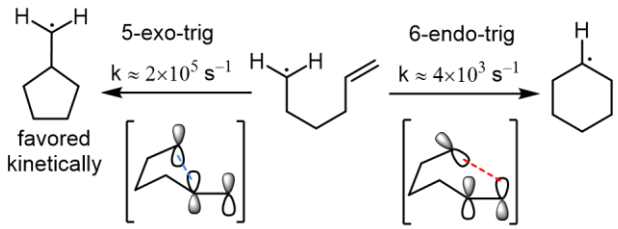
So, let us start with the Baldwin's rule. So, we know about the intramolecular cyclization. So, if you go for any type of cyclization to form a ring, Baldwin's actually proposed a rule. So, this is a very important rule. It was used if you use a corresponding anion for a cyclization, but here, we are going to show that these rules are very similar if you go for a radical cyclization. And again, if you see some of them, this number corresponds to the ring size 3, 4, or 5, and here are the tet, trig, and dig. These are for the tetrahedral, this is for the sp^2, and this is for the sp. So, where is the ring cyclization happening in that carbon hybridization we are talking about? So, some of them are favored. I think you have already learned this in Baldwin's rule for the formation of the ring, but what I am going to talk about is the important part of radical chemistry.



What we are going to see majorly is these two different types. We will not see much of this tet type of thing, but we will see mostly the trig and the diagonal. So, we are going to see the trigonal and the diagonal here. So, what we are going to see here is if you see you have a radical and you have an olefin, how are they getting cyclized? So, there could be an exo-trig cyclization, or there will be endo-trig cyclization. Also, if you have an alkyne and there is a radical. So, then, it is possible to go for exo-cyclization or endo-cyclization. Again, I think we are still going to follow a very similar rule to Baldwin's rule that once the radical is approaching, in the case of the trigonal one, then it tries to approach in such a way. So, if this is the sp^2 carbon, it is approaching such a way that this angle will be 109 degrees. So, that will be the best approach. At the same time, if the radical is approaching the alkyne for the cyclization, this angle will be close to 120 degrees. So, that will be the best approach.



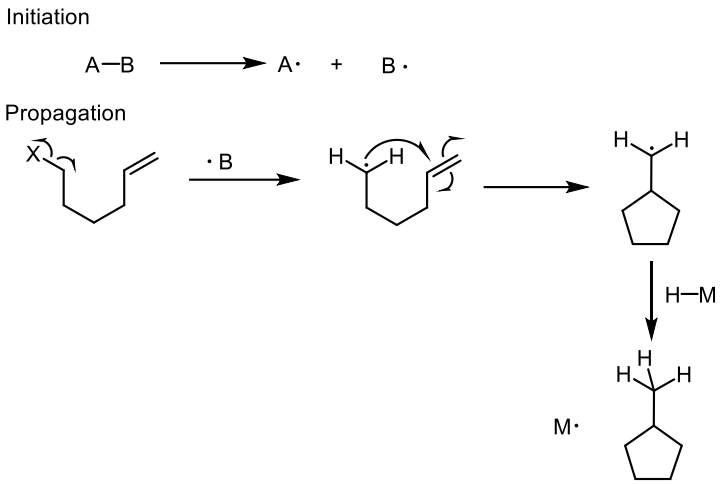
Now, we will learn that the endo-trig will favor the exo-trig, or correspondingly, the exo-trig will be favored. So, that I think can be explained from this corresponding transition state that the 5-exo versus the corresponding 6-endo because once you generate a radical species here and you have an olefin, then there are two possibilities it can go for a 5-exo-trig to get to this product or it can go for a 6-endo-trig to get to this product. Again, the relative rate of cyclization is 5-exo is much greater than 6-endo greater than 6-exo greater than the corresponding 7-endo. So, what is happening? We are saying that this is a kinetically favor product. So, this is a kinetically favorable product that is being formed here. So, why is it forming? You can see here that we have also mentioned the corresponding ring size. When it is 5 and 6 member formation happening here in this scenario, the calculation is 10:1 is found, as 50:1. So, you can see there is a preference for the formation of this corresponding 5-exo-trig, and this cyclization is you can see the corresponding rate of cyclization. Also, you can see that this rate is much higher than this one. So, we can explain them from the corresponding chair-like transition state here. So, what is happening is that there is a better orbital overlap. Once we are trying to draw this chair-like exo transition state, there is a better overlap between this orbital compared to the other transition state. So, that is the main driving force behind the corresponding exo-trig cyclization.



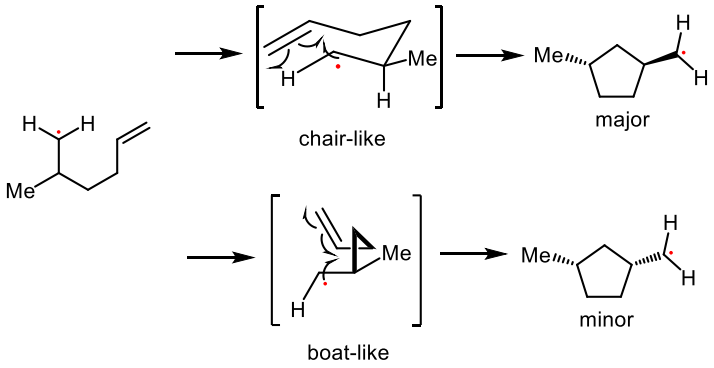
	exo:endo Ratio	
Ring size	Calculated	Found
5:6	10:1	50:1
6:7	> 100 : 1	10:1
7:8	1:5.8	< 1 : 100

See here, and I think in this type of reaction, you will see that we are going to talk about different types of radical sources. X could be halide, or X could be some other group, which can be where the carbon and the X can be cleaved in the presence of an initiator, which could be an AIBN/tributyltin hydride, which can generate this type of radical species that can cleave this carbon halogen bond and generate a radical. Now, it can go for an intramolecular cyclization. Again, you can see that, as I mentioned from this exo-

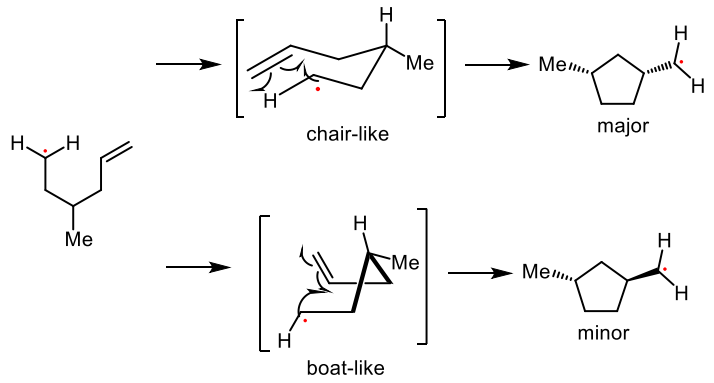
trig, we can make this 5-member, which can go for another hydrogen atom abstraction to get to the corresponding product.



Now, the question comes. I think initially we have mentioned that when we mention that from there, it will be going to the Exo. Now, the question arises: There are different positions. Suppose I give them the numbers 1, 2, 3, 4, and 5. In that case, the problem is that depending on the substitution in this position, there will be a different selectivity because the question arises once the radical attacks the olefin. After the hydrogen atom abstraction, you are generating a methyl group at the end. So, now the question comes up: If you are generating these things, the question comes up. There will be two methyl groups here: there is a methyl at the C-2 position, and there will be methyl at the C-5 position. So, now, are they going to be syn or anti, and which one will be the major one? So, that is the answer we are going to find here. So, here we can see from this compound: if you try to see this, it is going to be the anti, which is going to be the major, and the syn, which is going to be the minor. So, we try to explain them again in a very similar way to this chair-like exo-transition state. In this chair-like exo-transition state, the most preferred option is where you can make any substitution. You have to find an equatorial position instead of the axial position. You guys know that if you have an axial group in the chair-transition state, then you will have more di-axial interactions. That is why the transition state will be favored, where this group will be in the equatorial position. Now, if you see a radical cyclization happening, this double bond is actually here in the down. So, now, this methyl and this methyl will actually be in the opposite phase. The methyl will be up, and this methyl is going to form, which is going to be down, going to get to this product. In the other case, what is going to happen if you try to go for a boat-like transition state? Only then will you have a chance of being a minor, but this transition state will have a higher energy.

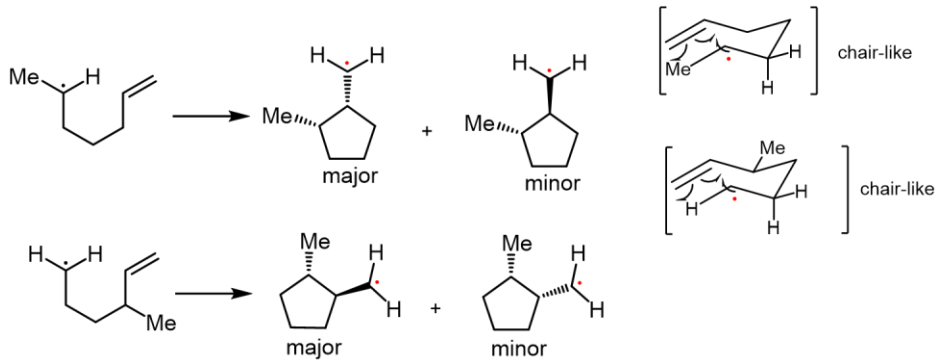


Now, we have moved from this C-2 to a C-3 position here. So, what is going to happen if I have a methyl? What will be the major product? Again, if you see this type of exo-transition state chair-like exo-transition state, you can see now the methyl will be here, and you have to put the methyl in the as I mentioned, the methyl will always be in the equatorial position. Once you put methyl in the equatorial position, this radical has to be added here. So, now, this methyl group will be down, and methyl is already down. So, this syn a product will be a major product. So, this can go for a hydrogen atom abstraction to get to the methyl, and here, if you try to go for a boat-like transition state, that will have a higher energy. So, anti will be the minor one.

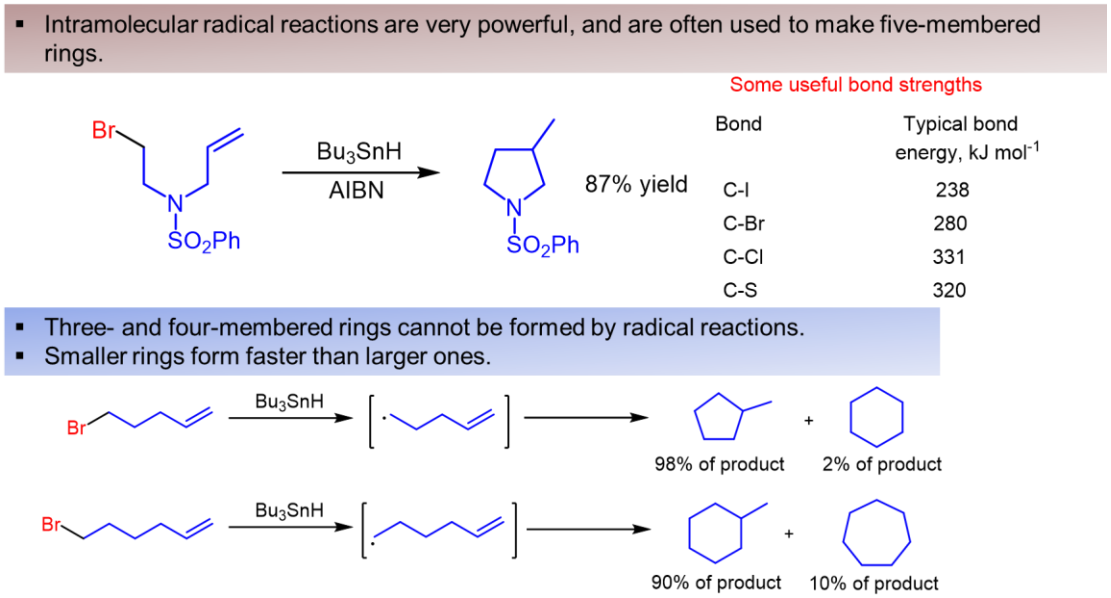


So, now, we have put the methyl in two other positions. As I mentioned, I mentioned C-2 and C-3. Now, this is the C-1. If I give them a name, this will be your C-4. So, starting from C-1, we see this will be a major product, which is the two methyl in the same site, or if you start from this C-4 methyl, then the major where these two methyl will be in the anti-position. So, what is happening here? You can see we are making the very same

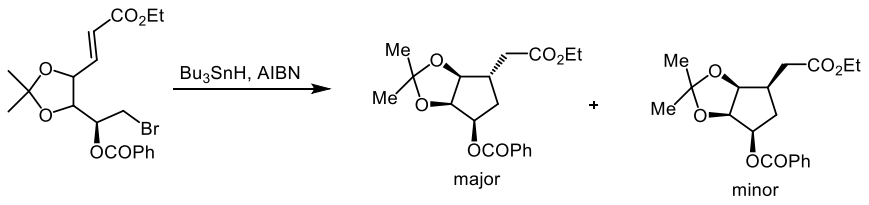
product, but in one case, they are syn another case, they are anti. So, if you try to explain them very similarly to what we have tried to explain in the previous case from this chair-like transition, here again, the idea is you always try to put this group in the equatorial position. So, what is going to happen here for this one? We are showing here this will be in the equatorial position. Now, once this is radically attacked here, both of the methyls will actually be on the same side. They both will be down to form this compound. And, then again, what is going to happen once you are here? In this scenario, we can draw the corresponding transition state here. What is going to happen now here? The methyl is in this position here. Sorry, I think it will be the wrong position we have drawn. So, we are talking about the methyl in this position because that is where the methyl will be, and as I mentioned, there will be hydrogen here. We can say this is H, H in this position; there will be methyl up and hydrogen here. So, the axial position will be this hydrogen, and the equatorial position will be the methyl. Once this radical cyclization is happening, this methyl will be down, and this methyl will be up. So, you end up getting to the corresponding anti-product as the major product.



So, now, as I mentioned in all the different cases you have seen, this corresponding 5-exo-trig is the one that is the major product. What is happening? In this reaction, we end up making the 5-member ring. So, it is very useful to make this type of pyrrolidine ring. Now, depending on the group you have, if you have bromine versus iodine versus chlorine, you can see their bond dissociation energy. So, depending on the bond dissociation energy, one will be faster than the other. Also, what is often observed in this intramolecular radical cyclization is that the smaller size ring forms faster compared to the larger size ring. Again, this could be due to the entropy factor.

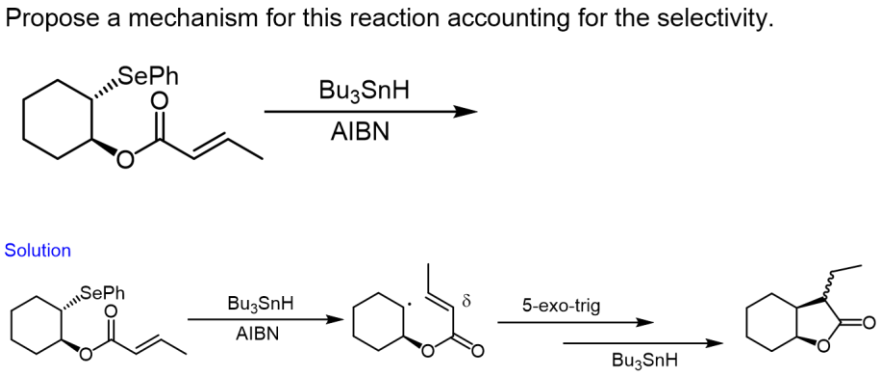


Here, I will show you another example; if you have a tributyltin hydride and corresponding AIBN, again, it will make their corresponding tin radical, which will cleave this and generate the radical species here. This radical can participate in the so you can see, so this will be a nucleophilic radical. I am sure you have learned about the nucleophilic radical. So, it is going to act as an alpha, beta-unsaturated compound, which will be olefin with the electron-withdrawing group. And you have a nucleophilic radical here, which is adding. So, now, if you see it again, I think it is forming a 5-membered ring here. So, this is the major product for these two groups. You can see here this is already up. So, you can draw here that this is already up. Now you can see that once this bond is forming here, this will be down to avoid the steric class in the corresponding transition state and give this product the major product.

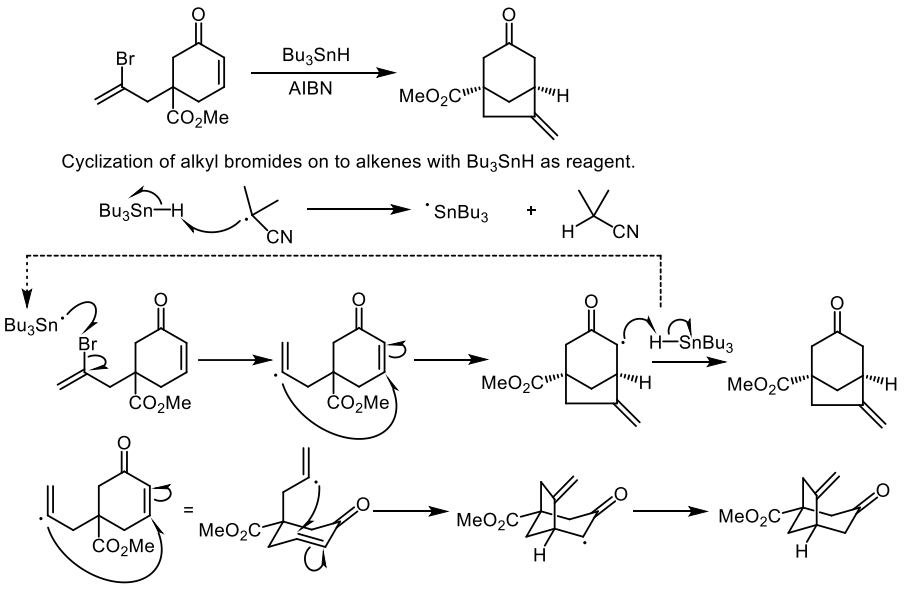


Another example here, so if you look at this, I think it came in the exam. So, one of the important factors if you think about the corresponding cyclohexane geometry is that these two groups are not on the same side. They are anti. So, what is happening in the reaction? We end up getting to a radical here, which is going to act in this manner. You can see this

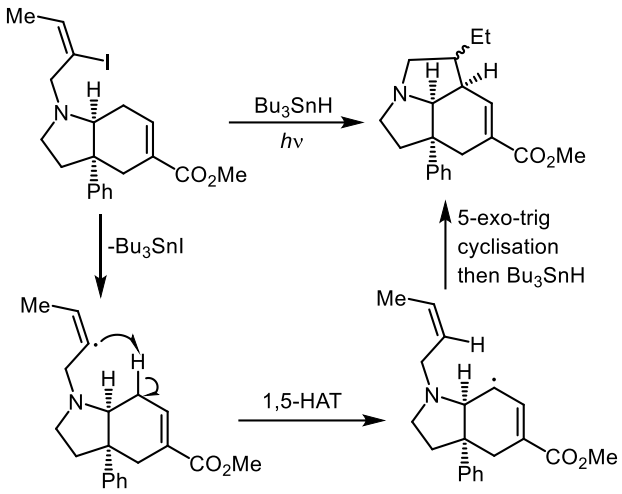
is a nucleophilic radical, which is going to act on this corresponding alpha, beta-unsaturated carbonyl compound, and go for a 5-exo-trig. Then, it will go for the hydride abstraction from tributyltin hydride to get to this product.



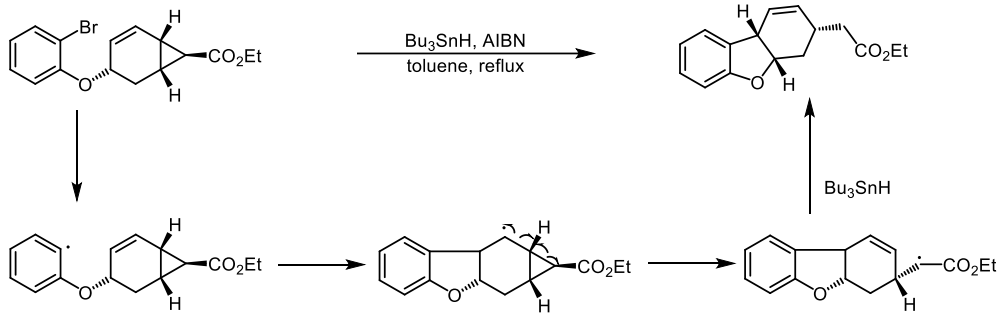
Another interesting example in the exam is that if you start with this compound using tributyltin hydride and AIBN, what will be your product? So, we can see this will be your product at the end. So, let us try to understand how this is happening. So, you can see that once you have this AIBN/tributyltin hydride, as I have already mentioned, you are generating tributyltin in radical, which is going to cleave this carbon bromine bond after the de-bromination. It will generate a radical species. Here, we can draw the radical like that. And now, if you try to draw this corresponding confirmation, you can understand that after the formation of this radical. So, this is a vinyl radical that will be very reactive, and at the same time, it is going to act on this corresponding alpha, beta-unsaturated carbonyl compound here. So, there will be a radical addition here to the formation of this species. And then, in this case, what is going to happen? From there, it is going to go for a hydrogen atom abstraction. So, hydrogen atom abstraction from this type of tributyltin hydride will be used to get to this corresponding product.



Another important example here is in this particular compound. You just have to look for if it is. So, actually, this also came in the exam. So, what is going to happen if you take this compound tributyltin hydride under hv. Again, the tributyltin radical that is going to form here to generate this corresponding radical is a vinyl radical, as I mentioned in the last slide. What is happening here? From this vinyl radical to come and add to this alpha, beta-unsaturated carbonyl will be very difficult. So, instead of that, what is going to happen? It is going to go for a hydrogen atom abstraction here, 1,5 hydrogen atom abstraction. Because the other cyclization will be you can see if you want to cyclize, then it will be 1, 2, 3, 4, 5, 6, and as I was saying in there, we talk about 5-exo, but this is going to be 6-exo here. So, that is why this will go for this 1,5 hydrogen atom abstraction because these are very reactive radicals, and if you mention, I have already mentioned that if you have vinyl radical, then the hydrogen abstraction rate will be much faster compared to the corresponding alkyl radical. Then, it will form this corresponding allyl radical, which will be stabilized. So, once you have this allyl radical, what is going to happen? It can now go for a radical addition here to this double bond. So, a 5-exo-trig cyclization will happen again to form this corresponding product.

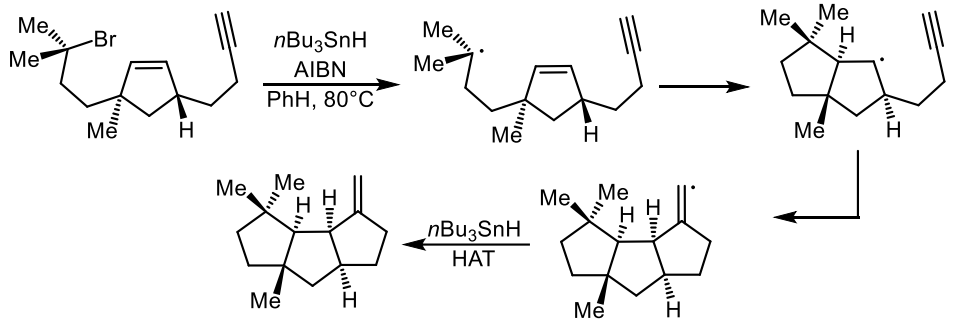


Another important example again which come in the gate exam. So, what is going to happen from here if you use tributyltin hydride, AIBN? First, this carbon bromine bond will be cleavage in the homolytic cleavage to generate a radical, which you can see here in this space. There are no other things except there is a double bond here. It will add to the double bond to generate a radical species here. Now you have a strained ring. So, once you see you have this type of cyclopropane, where you can see there is a double bond attached with the corresponding cyclopropane, then they are once we add a radical, they are prone to cleavage. So that it can cleave here to generate radicals. That is a very similar thing happening here. This will open this corresponding cyclopropane, and you are generating a stable radical. It is a radical next to the ester, and then what is going to happen is it is going to take hydrogen from the tributyltin hydride to get to the corresponding product.

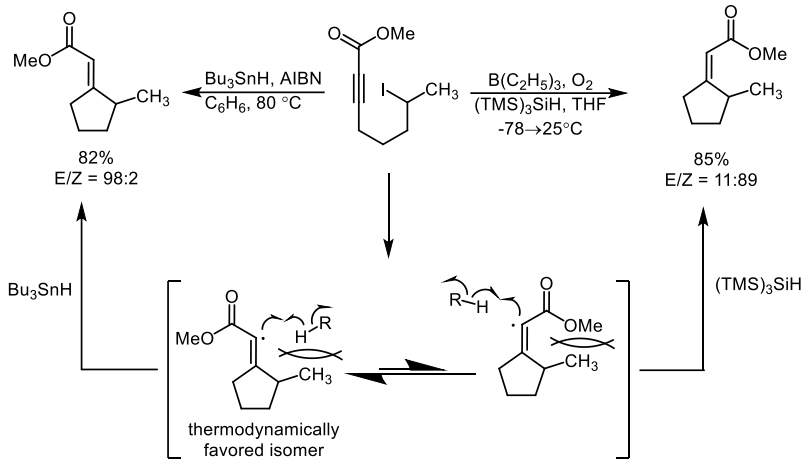


Another interesting example here is that this also came in an exam. So, what is happening here, you see, is that there is a carbon bromine bond going to get cleaved to generate radical, which is going to add here to the double bond first, and then it will add to the

triple bond. So, you can see what is happening here. First, a 5-exo-trig happens, and then a 5-exo-dig happens here to get to these compounds, which we can show here in the mechanism. Finally, hydrogen atom transfer will be used to get to this product.

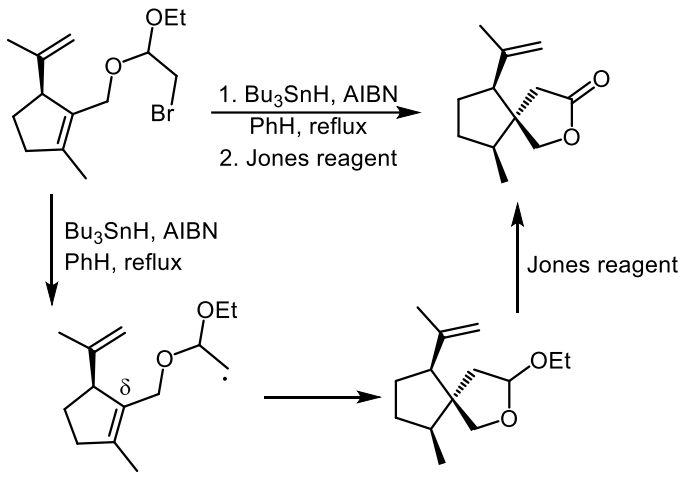


So, now we are talking about, so we already talked about the radical cyclization in case of when you have olefin, now we are talking about when you have alkyne here, and here your first thing is tributyltin hydride and AIBN, you are generating this product where you can see this group is actually an opposite side of this methyl. So, you are getting this product with 98:2, so E versus Z selectivity. Here, E versus Z selectivity, your Z is major. You are getting the product where this ester and the methyl are on the same side, which means the E to Z is 11:89. So, here is the difference in what you are making here: you are using a different hydrogen donor source. So, you are using this $(TMS)_3SiH$ versus a tributyltin hydride. So, the important thing is first thing once this radical is going to form. So, here, it is forming from the AIBN, and here, the corresponding boron and oxygen, the trialkyl boron. I am going to explain them again in more detail when I am going to talk about organoboron chemistry. Then, once you treat this trialkyl boron with oxygen, it will generate an alkyl radical, which is going to cleave this carbon iodine bond here to generate this radical species. Now, it can go for once you form the radical, it will go for this intermolecular radical cyclization, and it will come to this type of intermediate species, but here, the important catch is that it can go from this step to this step. So, there could be internal isomerization happening because once you see these cases, you can think about the ester on this side compared to the other side, but depending on now, the question is what type of hydrogen acceptor you are using if you are using a less bulky corresponding tributyltin hydride. Then, what is happening is the radical abstraction happening from the thermodynamically favor isomer because this will be thermodynamically favorable compared to this. As you can see here, the methyl and this group have a steric class compared to this one.

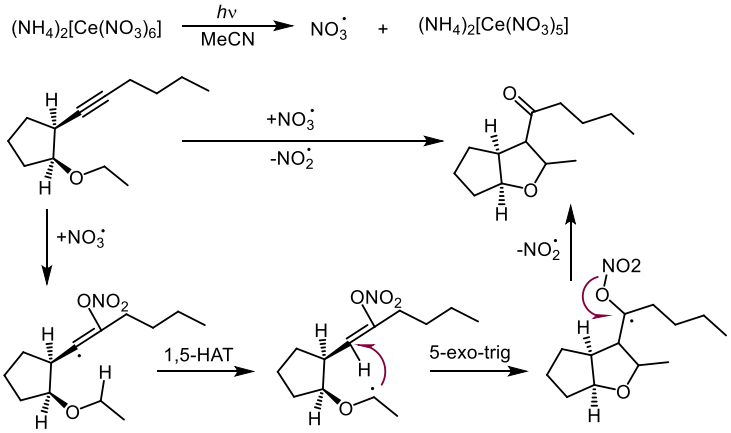


So, this will be a thermodynamically favor isomer. So, if you have a less bulky-sized hydrogen donor, then it will form this product after the hydrogen atom abstraction, but if you have a bulkier one here, then what is going to happen is it is going to go from this particular intermediate. What is going to happen is that it cannot go from the other one because of the above hydrogen. The donor is also going to have a steric clash. That is why it is going to be abstracted. It is going for the hydrogen abstraction from here in the case of this particular silane and going to get to this product as a major product.

Another important example here is tributyltin hydride, and the AIBN will generate the radical here, which will go for the intermolecular cyclization. Here, you can see that it is going to attack and then form a compound after the attack. So, it is going to attack for a radical attack to happen this double bond. If it goes to another double bond, the ring size will be bigger. So, it is going to attack here to form this compound, and then once the Jones reagent, it can convert this one to the corresponding lactone.

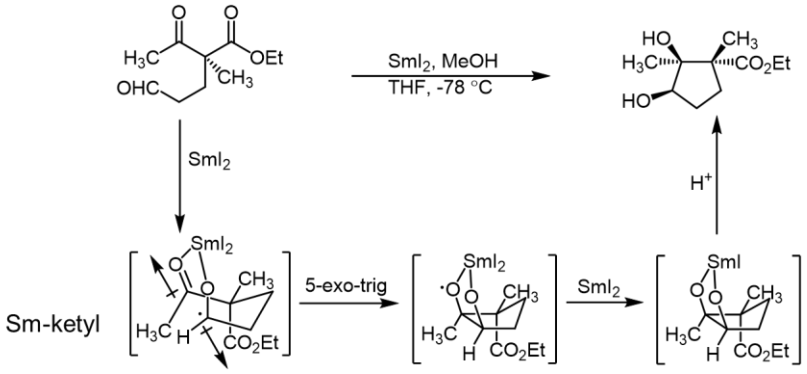


There is another example where it generates this type of nitrate radical from this compound under the hv. The nitrate radical will attack the alkyne, and then it will form this species here. This is going for 1,5 hydrogen atom transfer because this is a vinyl radical, which will go for a hydrogen atom abstraction. As I mentioned, the vinyl radicals are much more reactive, and their reactivity for the hydrogen atom abstraction is much faster. So, then it will generate this type of stable radical species, which can now go for this addition reaction because you have this corresponding double bond here. This can go for a 5-exo-trig and form this product. It is going to get out, and then it will generate a radical here. So, there will be O·, and then there will be C·, which can finally convert to corresponding carbonyl.



So, now I am going to talk about some of this chemistry I had already mentioned in the samarium chemistry when I was talking, but here I am going to again explain to you that

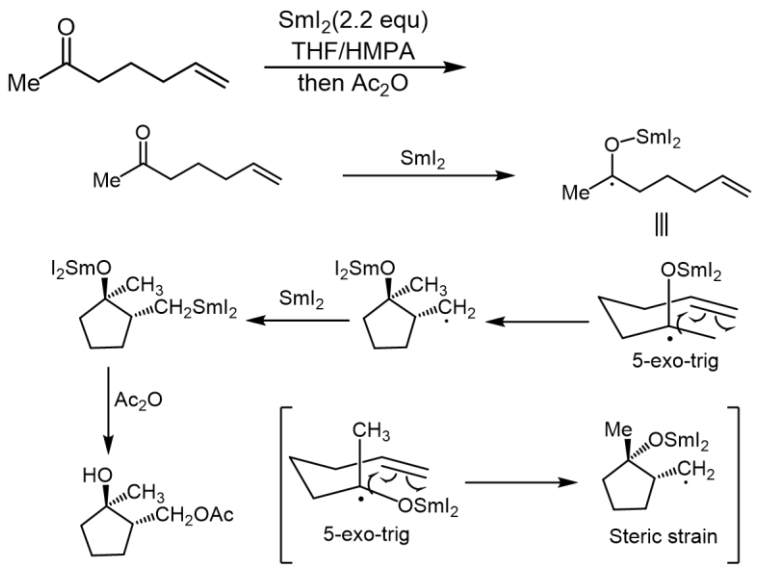
I think I have already mentioned that once you see samarium iodide, what is going to happen it is going to reduce this corresponding carbonyl compound here you have the carbonyl and the ester, but once you have this, 1, 3 diketones it is going to make a chelate. It is going to form a chelate here, and then it is going to form the first thing it is going to form this type of samarium ketal radical. So, I think there is an error here. I think this will be H instead of OEt. So, sorry for that. So, instead of the OEt, this will be H. So, samarium is going to make a radical here, ketal radical, which is going to go in addition to this carbonyl group.



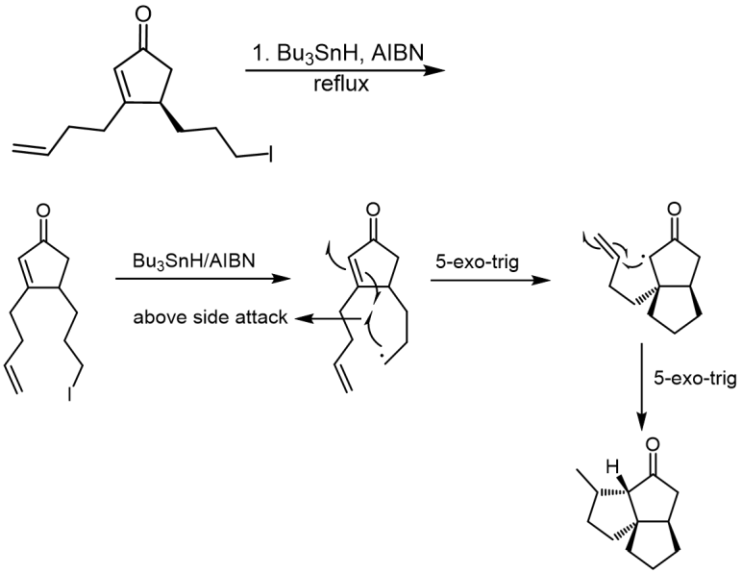
Now, what is happening? Samarium actually binds with these two oxygen. So, one of the important things is that one of these is binding these two oxygen molecules, and the newly formed carbon-oxygen bond after the radical addition will be on the same side. So, both of these oxygen will be on the same side. So, you can see in the product you make a 1,2-diol where these two OHs will be on the same side. And the other important thing is that there is a dipole thing here. So, there is a minimization of the dipole happening here in this transition state in this particular transition state there is a minimization of dipole which allows this corresponding exo-trig cyclization, which I mentioned, and then after that, the samarium is getting out in the presence of the H+ to get to this corresponding product.

Here is another example of this particular reaction that is happening very similarly as you have seen: samarium is the first formation of the corresponding samarium ketal radical after the reduction of this carbonyl group here, and then once it is generated, this ketal radical is going for this exo-trig cyclization. As I mentioned and after the exo-trig cyclization here, you can see from this again that I think I have already mentioned the samarium chemistry the samarium can add with this radical. Then, there will be acetic anhydride to replace samarium, and in the end, what will happen? You end up forming this corresponding product. Again, you can see we try to explain the formation of this

corresponding product from this transition state, where you can see in this exo-trig transition state where you have this oxygen. Here, you can see the difference. Hence, there is a steric strain going to happen versus this.



There is a tandem radical cyclization here in this compound again, and you can see there are two double bonds here. Once you form this radical, it is going to go for this first radical cyclization. Here, it is going to be added. Here, you can see this is a nucleophilic radical. It will add to this alpha, beta-unsaturated radical, which will be the preferred one. First, the 5-exo-trig is going to happen; then, there will be another 5-exo-trig that will get up because this is a radical that is going to form here next to a carbonyl group. So, this is becoming an electrophilic radical. So, now, this electrophilic radical will prefer to add to a corresponding double bond. Once that is happening, you can see what we have mentioned at the beginning. If you remember this 5-exo-trig cyclization, you ended up making the syn product at the beginning when I was talking about the first slide and this corresponding chair-like exo transition state. So, once the first cyclization happens, they are in syn geometry, and again, the next cyclization happens in the 5-exo-trig, given this particular product after the hydrogen atom abstraction.



So, in this particular part, I have talked about intermolecular radical cyclization. I talked about why the 5-exo-trig is in favor compared to the 6-endo-trig. I have also talked about the several different variations of this reaction. If you bring different substitutions in different positions, then the selectivity varies. Then, at the end, I discussed some of the samarium catalyst intermolecular and radical cyclization reactions. References: Thank you for coming to the class. I am going to see you guys in the next class. Thank you.