Structure, Stereochemistry and Reactivity of Organic Compounds and Intermediates: A Problem-solving Approach

Professor Amit Basak
Department of Chemistry
Indian Institute of Technology, Kharagpur

Lecture 27

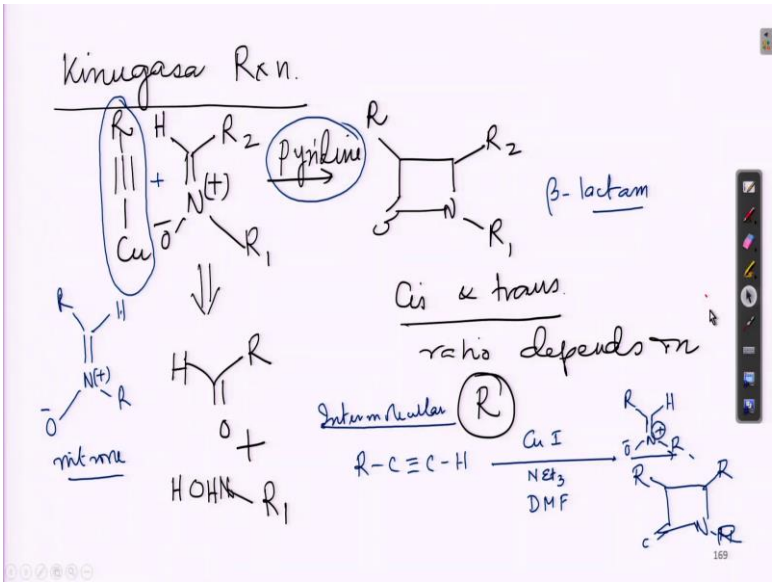
Beta-Lactam synthesis

Hello, everyone. Welcome to this course on Structures, Stereochemistry and Reactivity of Organic Molecules and Intermediates: A Problem-solving Approach. In the last series of lectures this topic was started and we started with the chemistry of alkynes followed by arynes then we discussed a little bit of allenes and then finally the the ketenes.

And in the ketenes, the one of the very famous reaction that we discussed was this Staudinger synthesis, which is basically the addition of an imine to an in C2 generated ketene and to form cis or trans beta lactam or a mixture of both. And we discussed the mechanism. We, very similar reaction was also discovered which was not very popular earlier, but it was discovered in 1972 by some Japanese scientists Kinugasa and Hashimoto. And the reaction I am going to talk about now is what is called the popularly known as Kinugasa reaction.

Now, this is another reaction where the starting precursor is an alkyne. Now, if you want to have a kind of a cycloaddition reaction involving alkyne you need another counterpart. So, in case of in case of Kinugasa reaction, one part is comes from acetylene or an activated acetylene and then the other part comes from a what is called a nitrone.

(Refer Slide Time: 02:14)



The nitrone is so as I said Kinugasa reaction is a reaction between the acetylene a terminal acetylene remember sorry a terminal acetylene which is represented by this as a copper

acetylide, you know the acetylenes with the terminal hydrogen free that can form the copper or the silver acetylide, very quickly.

Here they have started with copper acetylide. So, you convert the acetylene into a copper acetylide and then add another counterpart which is called a nitrone, nitrone is nothing but imine N oxide. So, if you have an imine which is like this and then if you oxidise it. So, it will go to the N oxide, but this N oxide is what is called the nitrone.

So, when you add this copper acetylide and nitrone together and the medium of and the reaction medium is pyridine that was originally developed by Kinugasa. So, they used pyridine as the solvent. So, in presence of pyridine what ends up that you end up with a, with a beta lactam, very interesting reaction, which is otherwise you might think that how a beta lactam can be formed, because what is going on here is a nitrone is nothing but a 1, 3 dipole, it nitrones are very prone to undergo 1, 3 dipolar cycloaddition. So, if you have a double bond and if we have a nitrone then that will form a heterocyclic ring just via a 2 plus 3 cycloaddition.

However, this is ultimately what happened, you are getting a four membered ring. So, formerly although it appeared to be a 3 plus 2 cycloaddition as as is suggested by the substrates, but ultimate product is looks like a 2 plus 2 kind of addition that has taken place. So, this was reported in '72 but was not much discussed at that time.

There are several reasons is first of all, pyridine is not a very user-friendly solvent. That is number one and number two is the difficulty of many of these copper acetylides preformed copper acetylides to make them dissolve in organic solvents. Because they are, they are usually if you have seen copper acetylide kind of product, they are usually yellow in colour and extremely insoluble. So, that is why pyridine was used to solubilize the copper acetylide. Then there were some modifications.

The question was raised that whether you have to start with the copper acetylide or whether you can take the acetylene and add the cuprous, now in the copper here is plus 1 state. So, add the cuprous halide mainly the cuprous iodide and then add a base. So, then it will form the copper acetylide in C2, whether that works or not and it was found that yes that worked, you do not need to actually form the preform the copper acetylides you can form that in C2, then the solubility problem is removed and you can use other solvents now, if you are making the copper acetylides in C2.

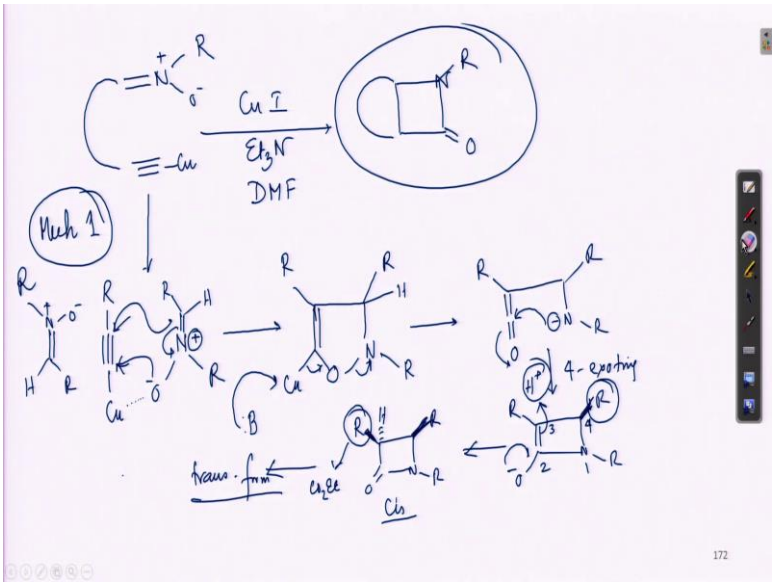
So, you are making small amounts of copper acetylide in C2. So, that small amount will have solubility in many organic solvents and then as it reacts more and more copper acetylide will be formed and go into solution. So, the copper acetylide was formed in C2 that is one solution. The other solution is that you can now have different solvent systems like DMF is a popular solvent in an dimethylformamide which actually is a very good organic solvent.

So, that can dissolve many acetylenes including cuprous iodide and then the base that is used here because you have to use the base because you are starting with a triple bond itself. So, what is now done, that you add copper iodide and then you add a base there are different types of bases possible you can again use pyridine, some people are using triethylamine or other tertiary amines and then the solvent use this DMF and usually that is done and it is start for a while and then you add the nitrone. You add your nitrone and in one step you get the beta lactam.

So, there are these modifications after these modifications the reaction started drawing, drawing attention of the organic chemists, synthetic organic chemists. And now there are several several instances where Kinugasa reaction has been exploited in making complicated molecules containing beta lactam moiety.

In this case, the reaction is intermolecular because the acetylene and and the nitrone are different molecules, but you can have it also in an intramolecular fashion. You can also have it in an intramolecular fashion I will show you, sorry just erase whatever it is here, is intramolecular Kinugasa reactions are also known.

(Refer Slide Time: 08:29)



To have intramolecular you have the nitrone here in one R and the other R you have the acetylene. And then as I said the condition is cuprous iodide triethylamine and DMF or sometimes potassium carbonate also is, any you do not need a very strong base just weak base will do. Sorry, there is a plus here and now you get a bicyclic framework with a beta lactam imine. And you know, this type of bicyclic beta lactam systems are extremely important because they are the pharmacophore present in many antibiotics beta lactam antibiotics like penicillin cephalosporins, terramycin, etc.

So, any method new method, which can generate a beta lactam is always, will always draw and continue to draw attention of organic chemistry, because this pharmacophore has given us a lot of life saving drugs. So, this is intramolecular. Now, the next the next development that took place was the asymmetric version of Kinugasa reaction.

Now, there are there are asymmetric versions, see Kinugasa reaction, when you do Kinugasa reaction is symmetric, symmetric substrates, then what you will get? You will get the plus minus mixture of cis and the plus minus mixture of trans. If suppose the cis isomers dominate and that what was found that the cis isomer usually predominates in the mixture, then you have some sort of diastereoselectivity, because you have shut down one pair of diastereomer, and that is the that is the trans diastereomer and you are getting more of the cis diastereomer.

So, diastereoselectivity can be pretty high. However, whatever cis isomer you have got that is a plus or minus mixture. So, if you want to make only one cis isomer that is where comes the asymmetric synthesis. And in the last 10-20 years, there are a lot of developments in the asymmetry synthesis of Kinugasa reaction, but we are not going to, we will give you some examples of intramolecular Kinugasa reaction, but our major focus will be on the mechanism of this reaction, because as organic chemists, we must try to understand how the reaction goes to give the beta lactam.

There are two kinds of two schools of thought regarding the mechanism of the reaction and still not very clear. However, in the in the last few years, there were some papers, I believe that have come out and they wanted to clarify the mechanism. Now, I will talk about the existing whatever was the the two schools of thought what they what they believe at that time, I will highlight those and then extremely modern way of looking at it, I am not going to discuss that. But broadly speaking, they are actually basically some correction of the mechanism what has been proposed, but it is at this point, it is better that we should know

what are the two schools of thought? What are the two possible mechanisms that were proposed?

The first, the first one is a common state both the mechanisms have a common state, the common state is the cycloaddition, it is a 1, 3 cycloaddition or what is called a dipolar cycloaddition between the alkyne and the nitrone. And this cycloaddition has already been known that this is this becomes facile, if you have the terminal acetylene hooked to a metal like copper. That means, the reaction of the temperature that this reaction takes place to have a 1, 3 dipolar cycloaddition will be much higher.

But as soon as you put a copper here, then the reaction can occur even at room temperature. So, very facile. It is a metal mediated acceleration of the 1, 3 dipolar cycloaddition. This is very famous, there is a famous reaction called the click reaction, the click chemistry which is also based on the on a cycloaddition reaction. But that was also speeded up by the formation of the copper complex.

So, that is why in Kinugasa reaction in order to speed up the cycloaddition process, you have to have a terminal acetylene with a copper, that is number one. So, when let me actually do a mechanism which, which is intermolecular. So, you have the copper acetylide which is extremely prone to the cycloaddition.

And not only that, formation of the copper also gives very good regioselectivity of this cycloaddition reaction. Where from the regio selectivity comes? Because you have the acetylene, there are two carbons where you have the addition. Now, the addition of the nitrone can take place in two ways, either the way I am writing the nitrone is like this or I can have the nitrone o minus on this side and R and hydrogen. So, this is the other possibility. So, they will give different products.

However, the because you have started with this copper acetylide, what happens, this oxygen gets chelated to the copper, or the oxygen donates the electrons and copper becomes chelated by the oxygen. And if that be the case, then the nitrone will only come from the way I have depicted. So that controls the regiochemistry. So, copper helps in both ways. It speeds up the reaction as well as it gives selectivity, regioselectivity, complete regioselectivity for the cycloaddition reaction.

And so, once the cycloaddition takes place like this, then what you get is a heterocyclic compound and isoxazole. Here it is copper. Let me see there was a study, just a second there

is some mistake here. So, this is R then you have these R the hydrogen that is coming from the nitrone, then you have the nitrogen, then the oxygen and this is the acetylene carbon containing copper and there is a double bond. And there is another substituent, sorry there must be a substituent on the nitrogen.

We are now talking about not different substituents for the sake of simplicity, we are putting the similar substituents at all the centres. So, this is the intermediate the isoxazole. Then, what happens? Then there is a because you have the base present there, the base now will because copper carbon bond is a, is a weak bond and it is because there is a change of hybridization from Sp3 Sp to Sp Sp going to Sp2, so, there is a change of electronegativity and that we can see carbon copper bond.

So, then for the base to break the carbon copper bond is easier. So, this way it breaks. Now, this is one school of thought that you form what is called a ketene by the way, the copper is gone and you get something which looks like this R and then R and then R. So, a ketene and this nitrogen in nucleophilic nitrogen.

So, now, what will happen? This nucleophilic nitrogen will attack the ketene in an intramolecular fashion. So, that is nothing but 4 exo-trig. So, 4 exo-trig and in so, this is again the product is basically the enolate of a beta lactam which is which will not be stable in the enolate form. So, it will immediately go to the keto form.

So, this is one mechanism which involves a ketene. After the cycloaddition, there is a decomposition of the copper carbon bond to form the imine and the nitrogen nucleophile and which then intramolecularly attacks in a 4 exo-trig fashion and then subsequently tautomerized to the beta lactam.

The formation of the cis or trans beta lactam actually depends from which side the protonation takes place. That is the important thing and that will decide whether you get cis or trans arrange junction. Usually, the protonation comes from the side opposite to this this group, protonated species, protonating species is maybe the code that trimethylammonium ion trimethylammonium ion. So, which is a little bulky.

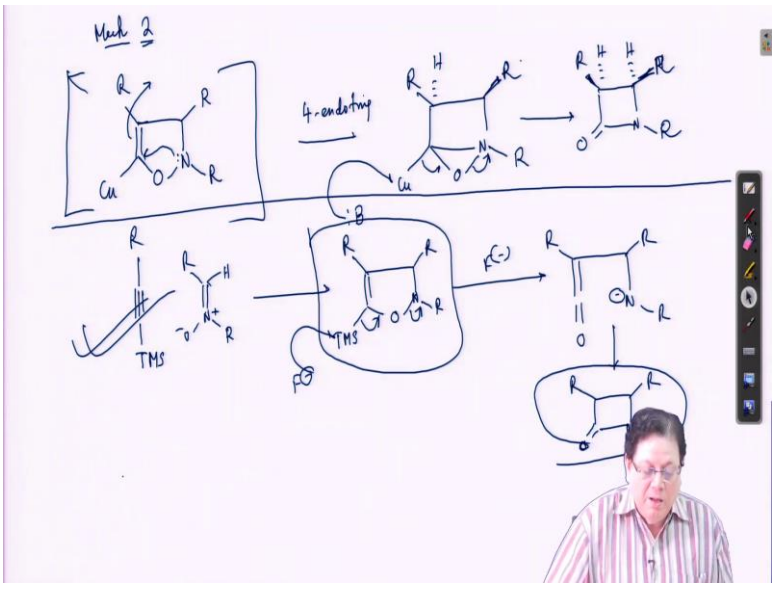
So, the hydrogen source is not a BR hydrogen plus. So, that will be delivered from the side opposite to the R group at the 4 position, this is one, this is two, this is three and the four. So, that gives the first a cis beta lactam. You understand, because the protonation is happening for a less crowded face.

However, if this R is a very electronegative element like CO2Et electronegativity group CO2Et. Then what will happen? In the base medium, because the medium is already basic and if you allow some time to equilibrate, then this hydrogen will now equilibrate into the transform. Otherwise, if R is alkyl, those type of groups which are not only which are electron donating, not acceptor, so that will reduce the acidity of this hydrogen. So, we will slow down this isomerization process.

So, if basically what I am saying that if these R groups are alkyl or aryl groups, then you end up in getting the cis product as the major product, but if the R at the three position happens to be an electron withdrawing group like the ester or the cyanide or any other carbonyl etc. Then what you have? You will have a tautomerization, you will have the racemization that is possible and you may end up getting the trans isomer as the plus minus trans isomer as the major product. So, this is mechanism number one.

And another mechanism is there, which was actually originally proposed by the by some of the scientists who worked on this Kinugasa reaction right after the after Kinugasa reported this reaction. The mechanism was not reported by Kinugasa. It was reported by some other scientists who worked on this reaction.

(Refer Slide Time: 20:49)



So, at that time the first mechanism was proposed involved again the formation of the same isoxazole thing that they are basically it is a, so, here it is the carbon of the nitrone then the nitrogen and then the oxygen and here it is R, we are putting all R groups here. So, this is our intermediate. There is no, that is there is no discrepancy between the formation of this intermediate.

After that one school of thought thinks that this is the becoming the ketene. And another school of thought, thinks that the nitrogen internally attacks this double bond, and picks up the that that picks up the proton. So, that is a 4 endo-trig process. And if you look at the Baldwin's rule, you will know that this is not a facile process. This is not the favoured one. This is a disfavoured process.

However, this was the mechanism that was proposed. Actually, the timing was right at the right when Sir Baldwin was proposing his rules, I think this paper showing the mechanism came in 1975 and Baldwin's rule was published in 1976. So, people may not be well aware of this that this cyclisation is not, is not stereo electronically possible. But anyway, let me draw what is the mechanism that was the proposed at that time.

So, you get N C and then there is the O, so oxaziridine, this is aziridine is only a nitrogen, a three membered nitrogen ring, if you have another oxygen in the ring then oxaziridine. So, you get a very strange oxaziridine. So, this is R, that is R and this will be R and this will now take the hydrogen.

Suppose it takes the hydrogen from the opposite side of this R, so that is the intermediate, then the subsequent steps which was earlier proposed in the formation of the ketene that takes place now, this collapses into a carbonyl and with the result that ultimately a beta lactam is formed. So, in this case, straight away the beta lactam is formed, via the formation of an oxaziridine, a strained intermediate. So, this is a mechanism number two.

I think the mechanism one has a has a lot of plus point has a lot of plus point in the sense that in the sense that suppose, you take instead of copper, if you take a TMS compound and do the same reaction sorry, do the same reaction with a nitrone, with a nitrone, in this case, instead of copper you have a TMS R hydrogen and when you add these two, here obviously the condition will be a little different, you have to heat these two and then you get the same intermediate, but here it is copper is not present instead there is a silicon now. So, this is the intermediate TMS.

Now, earlier mechanism there was copper here and the copper is lost, carbon copper bond is lost because of the vulnerability of that bond and that is induced by a base. Similarly, carbon TMS also you can you can break you know that fluoride is the reagent which breaks the breaks easily the carbon silicon bond because fluoride has a very strong bond with the silicon.

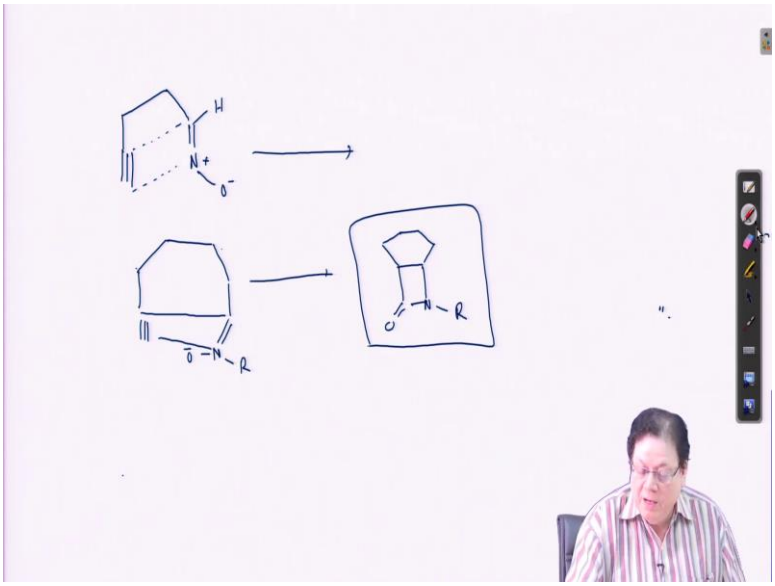
So, now the fluoride should do in a very similar way generate this intermediate which was the which was one of the intermediate suggested by the mechanism one of Kinugasa reaction. So, you see that this is the ketene minus R R. So, if you take this TMS compound and do the same, try to do the similar sort of reaction like Kinugasa and then the intermediate you can isolate here this is not unstable and then treat that with the fluoride.

So, you should end up with the beta lactam. And that was that was done and so, that lends support that possibly this is the correct mechanism, that means, the formation of the ketene their involvement of the ketene is the it should be the should be the right one. However, there is no direct evidence yet that whether the ketene has been isolated or the ketene the ketene intermediate formation has been has been proved conclusively by spectroscopic bids. So, that debate still continues.

However, from organic chemistry's logic point of view and this support of the TMS acetylene it appears at the second, the first mechanism. The first mechanism involving the ketene intermediate and not the oxaziridine intermediate is should be the more plausible one. We will, at this stage we will say that this is more plausible, because in organic chemistry mechanisms are suggested and they have been provided with a lot of experimental supports.

But ultimately all mechanisms are, they are plausible mechanisms because different substrates may behave little differently, you must understand that. That is why organic chemists are very careful in proposing a mechanism and they always put the word plausible or possible, these are the two words that are often used just to make sure that the the student who is reading that do not get obsessed that this is the only mechanism followed by all the substrates belonging to that category.

(Refer Slide Time: 27:56)



So, now, let us give one example of sorry, of intramolecular reaction, intramolecular Kinugasa reaction. Not this one, sorry, let me erase this. So, in order to do first of all, in order to do intramolecular Kinugasa reaction, what you need is a nitrone in one hand and sorry maybe I will write the oxygen on the other side that will be better.

So, you take nitrone like this, and, and then, no not this sorry. If we are doing intramolecular then you have to have a triple bond here, make it more simple. A triple bond here and that will give you, this will be a little bit difficult because that will give you four four that is a 4 membered ring fused to another 4 membered ring. So, this may not work.

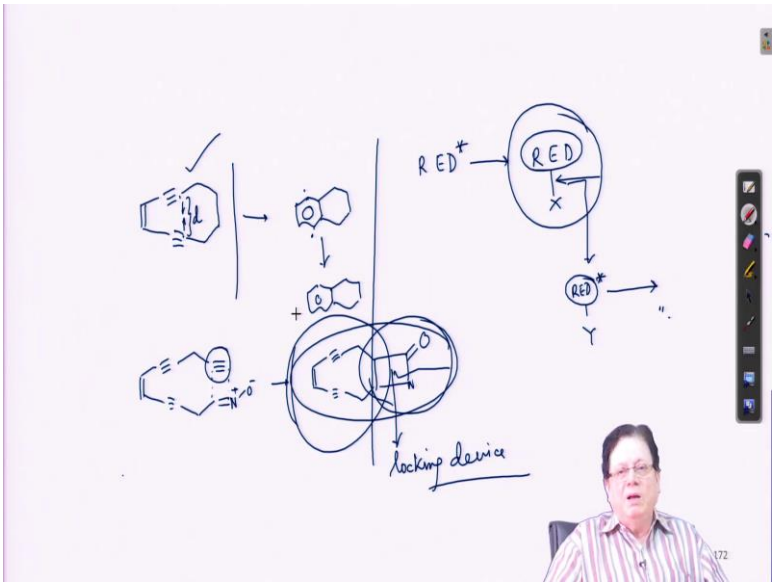
So, you have to be careful means in in figuring out the type of substrate that you should take. So, better leg than this the arm, this is acetylene and then you have a nitrone suppose, O minus R. And that will give ultimately 1 so, there will be a connection between this and there will be a connection between these and that. So, you get 1, 2, 3, 4, 5, 6. So, it will be a 6 membered ring followed by the beta lactam.

So, these type of reaction has is is now quite well known in the literature. The one I want to show you was very challenging and it was connected to the kind of kind of functionality which was already told to you in the last few lectures, that there is a class of compounds which are called enediyne compounds and they can spontaneously generate para-benzyne diradicals para-benzynes.

And the para-benzynes have an importance in biology because they can abstract the hydrogen from the two complimentary strands of DNA. Of course, provided they are situated right at

the right position, but if they are situated at the right position, they can abstract hydrogen from the complimentary strands of DNA. And as a result, the DNA strand gets cleaved, both the strands get cleaved, it is a double strand breakage. So, there are many anti-cancer compounds which work on this principle. They just go enter the cell and chop the DNA basically, kill the DNA. And if you can kill the DNA the cell will be will be gone, the cell cannot, the cell is the lost, cell die.

(Refer Slide Time: 31:19)



Now, we know that to form this diradical from enediyne requires a particular type of structure that a cyclic enediyne a cyclic enediyne, they can form diradicals only when heated at a very high temperature. But that you cannot do in biology. In biology, it should be spontaneously happening at the biological temperature of 37 degrees centigrade. So, that is why it was found, I also mentioned earlier that you have to put the enediyne in a cyclic network.

What is the advantage of putting in the cyclic network? Is that these two carbons are pushed towards each other, that means the distance between these decreases as they are close enough. So, that favourable entropy speeds up the speeds up the Bergman cyclization process. So, to again just to again, just to summarise that, what I am saying is that enediynes are naturally not that reactive if they are in a cyclic framework.

But if they are in a cyclic framework and if the cycle, size of the cycle is 10 then it is very optimum that they will have a decent half-life and they will slowly make the diradical slowly make the diradical. Now, if you want to utilise enediynes as an anti-cancer agent, suppose I make this back to a cyclic enediyne, I know that it has got a half-life say two days or three days.

Now, the question is where do I store it? Because I may need this molecule one month later. So, if I make this and try to store it in the refrigerator, as it has got a half-life of reaction, so slowly, after 7 days, I will not see any enediyne present, what I will see is the generation of the naphthalene nucleus, that means the complete conversion into the Bergman cyclization product via these diradical and then the tetra hydro naphthalene system.

So, basically it cannot be used as a drug, because that storage, it does not have shelf life. What is called shelf life? So, you have to have some, some system attached to this molecule, which is acting, which is called acting as a locking device that will lock the system from undergoing the Bergman cyclization.

So, basically, what I am saying that you have a reactive system, but you have to modulate the reactivity with the help of a lock. And what is a lock? It is not a chemical, it is not a mechanical lock, it is a chemical lock that is a type of functionality that is present in the molecule which can be removed or which can be modified in such a way that the molecule becomes reactive again.

So basically, what is the strategy, you have is you have a reactive enediyne, very reactive star means reactive, you add something to the enediyne moiety X and then the reactivity is gone. And then what you do? Do some reaction on this bond that is connecting this RED. So, convert it into something else X going to say suppose Y so, change that locking device into Y. But Y is such a, it is innocent that it again brings back the activity of the RED. And then it can show the biological activity.

So, basically you have to store this in the shelf. So, that was the strategy that is always used in these type of molecules, molecules which are extremely unstable, because you have to remember that molecules which are cytotoxic that kills the cells, they are also, they are not stable, they are also very reactive. So, sometimes at ambient temperature it is difficult to stabilise them.

So, this is the strategy and the molecule that was made by Kinugasa reaction was, that was by intramolecular Kinugasa reaction was this. So, if you have this acetylene intramolecular one arm is acetylene another arm is a nitrone. So, when they react, so, that reaction will be basically between this carbon and this carbon.

So, what you will get is a molecule which will look like this and that is now, this part is what is the locking device, these beta lactam ring. So, this is a nice example of various aspects of

chemistry, one is that how to introduce a locking device, what is the importance of locking device and then actually the locking device is usually very small rings, which can be broken very easily like epoxide is one, aziridine is another one, beta lactam is the third one.

So, you can have beta lactam but the question is how to make it, how to convert an acyclic enediyne into a bicyclic enediyne containing a beta lactam moiety. The beta lactam will act as a lock and once you remove this lock, it is very easy you can just hydrolyse it or it can enzymatically cleave this bond, then this one as it is cleaved, the molecule becomes reacting. It can show that formation of the benzene, the para-benzyne diradical and show the biological activity.

I think that is all about the Kinugasa reaction. You can read it there are many good reviews on Kinugasa reaction. If you want to learn more, I did not mention the asymmetric version of universal reaction that also you can learn by looking at different literature's that are present in the internet. Thank you very much.