Principles and Applications of Enolate Alkylation: A Unique Strategy for Construction of C-C (sp3-sp3) bonds in asymmetric fashion

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Module - 08
Miscellaneous method of enolate alkylation of several carbonyl species
Lecture - 37
Memory of chirality in enolate alkylation

Welcome back everyone and today we will be going to start a new module and actually this module is the final module. In this module we have 4 lecture, we are going to start today with the lecture number 37, we are going to start a new concept which entitled as Memory of chirality or MOC in enolate alkylation.

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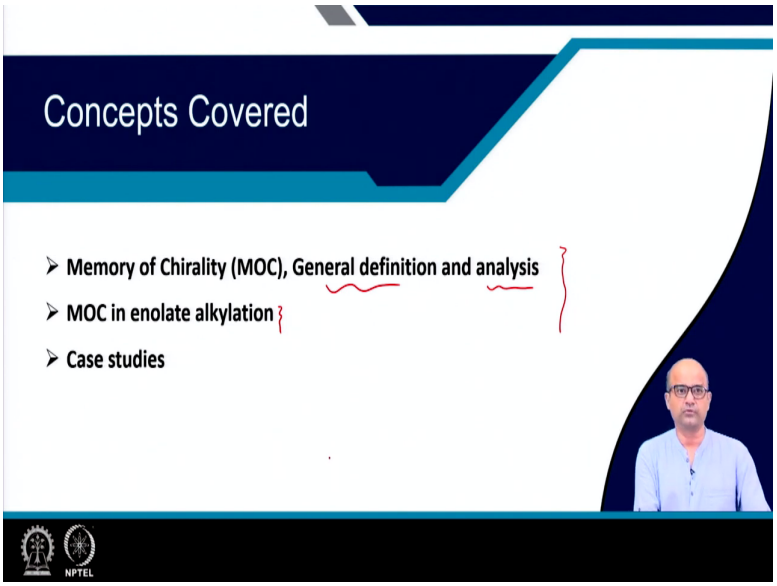

Particularly this lecture we will be talking about MOC conceptual analysis, what is the general definition of MOC and its main analysis. And particularly application of MOC in enolate alkylation as well as we will talk about some case studies.

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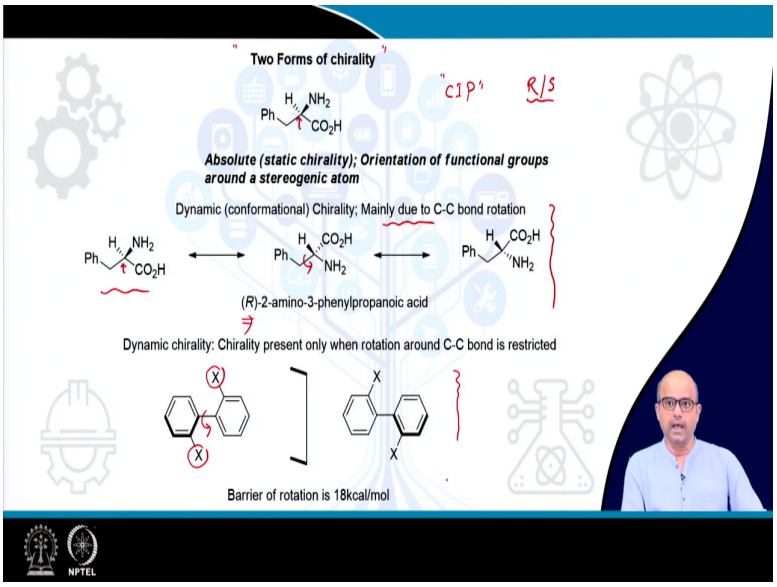

Now, what you talk, what do you understand regarding the term MOC? Before going to that I will just try to talk about little bit of different forms of chirality. Now, in the standard textbook of stereochemistry, often deal with two forms of chirality, mainly the absolute or static chirality which is often derived from the CIP nomenclature, which actually says that, the orientation of different functional groups around the stereogenic carbon.

And that we always designated by R or S nomenclature and this is absolutely fixed wherever you go and the main idea was how you project or view the molecule. Then we describe another form of chirality, which is named as dynamic chirality. And this chirality mainly arises due to C-C bond rotation. Now, this chirality is normally if you take this molecule let say this amino acid, which is R in CIP nomenclature. So, this is the absolute chirality ok.

Now, this particular orientation where NH2 is beta hydrogen is alpha and this benzyl and CO2H in same plane. You can actually change the relative orientation by just rotating around this carbon carbon single bond. But the absolute configuration will not be changing. So, this is the main point in such chirality. So, this chirality mainly arises due to carbon carbon bond rotation.

Now, let us say you are having a molecule; however, the stereogenic carbon is not present, but the restricted rotation you can impose it. The classic example is the biphenyl system or allene system. When a properly substituted biphenyl system these two phenyl ring depending

on the substitution pattern, they may not lie in the same plane and then you are basically restricting a rotation around this particular bond.

Now, the room temperature if the restriction restricted rotation can be imposed, you basically can isolate two enantiomers and these two are not super impossible, they are basically chiral. So, though the molecule does not contain a stereogenic center, you are having a dynamic chirality and these compounds are resolvable.

And such a molecule you will find plenty in case of biphenyl, properly substituted allenes and other molecules and we often said this molecule does possess a chiral axis or chiral plane.

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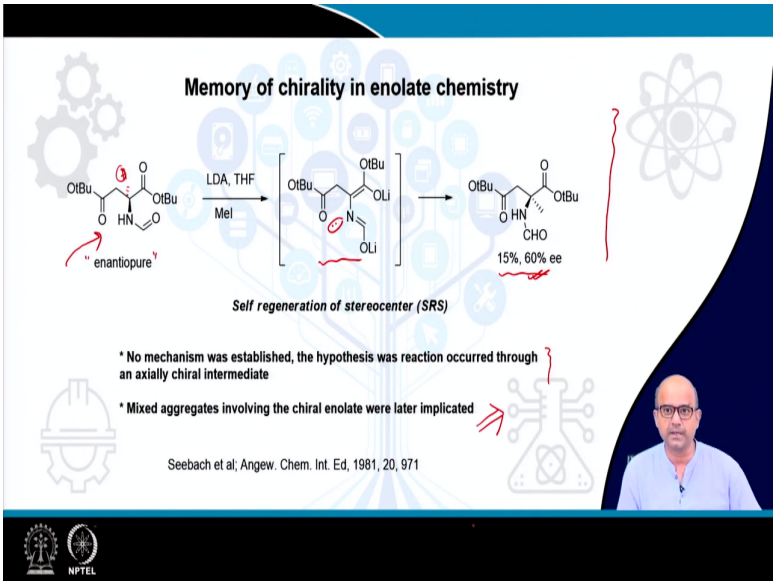

Now, memory of chirality will be now coming to the point. The first reported example of memory of chirality was invented by Professor Dieter Seebach, in the 1981. Now, what happened when Professor Seebach, took an enantiopure amino acid derivative of particular this compound, which contains NH CHO and the CO2 tertiary butyl, you have a hydrogen which is abstractable.

Now, initially the treatment of LDA, THF, MeI you basically get an enolate, where the point of chirality has been lost or removed. Then we are assuming that probably in the final compound the alkylated product you have a loss of enantiomer excess. But in reality it is found that 60 percent enantiomer excess was obtained. But as the product was enantiopure, the transition state or the enolate does not contain any form of point chirality.

So, where from the chirality is coming in the final product? Though at that time no mechanism was established, but usually it was thought that probably the enolate which contains nitrogen might have a transiently formed axially chiral enolate intermediate. So, point chiral to axial chiral and then this axial chiral may have a different facial orientation and then electrophile might approach from a specific phase. So, the stereo- selectivity might be obtained what you are expecting.

But initially at the time no mechanism was proposed, but then later on it has been found that probably a supramolecular aggregates or a chiral form of enolate having a supra molecular aggregates might be the real intermediate. Now, this was initially the main exciting factor for the memory of chirality and its related research.

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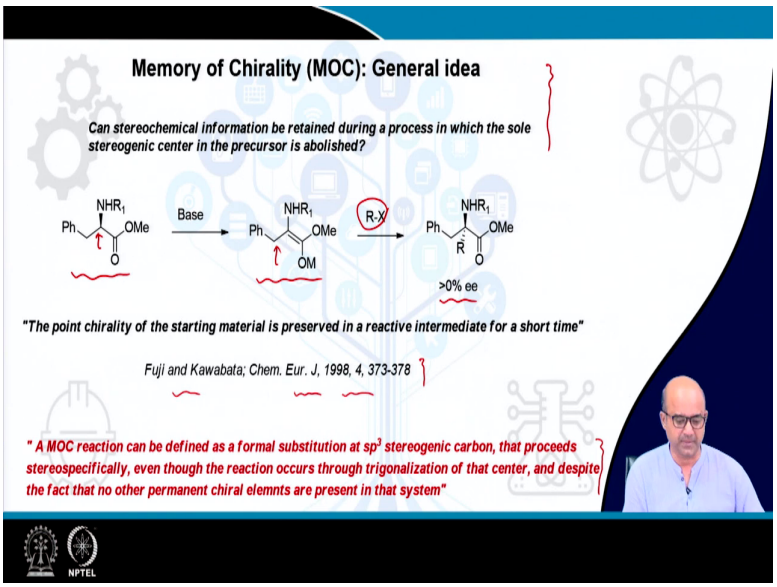

Then we try to take a general view that whether if you are taking an amino acid derived compound or a similar compound, where the point chirality you can basically destroy or abolish during the deprotonation or enolization step. And then when electrophile is attacked, if you get a enantiomeric excess it might be mainly responsible due to some form of a transient intermediate, which may be arising due to a axially chiral enolate intermediate or a intermediate which contains a chiral plane.

Now, initially this two fellows Fuji and Kawabata have been done a significant or seminal contribution in this field and they have defined a very classical concept of this MOC. And they said that a MOC reaction can be defined as a formal substitution at a sp 3 stereogenic

center or carbon, that proceeds stereo specifically means you are getting one enantiomer excess than the other enantiomer.

Even though the reaction occurs through trigonalization of that center. Means at the transition state, the stereogenic centre is lost and despite the fact that in the enolate there are no other permanent chiral element was present. In the enolate if this was lost, you do not have any other permanent chiral element. So, this was the initial findings where which professor Fuji and Kawabata in 1998 they have derived some system.

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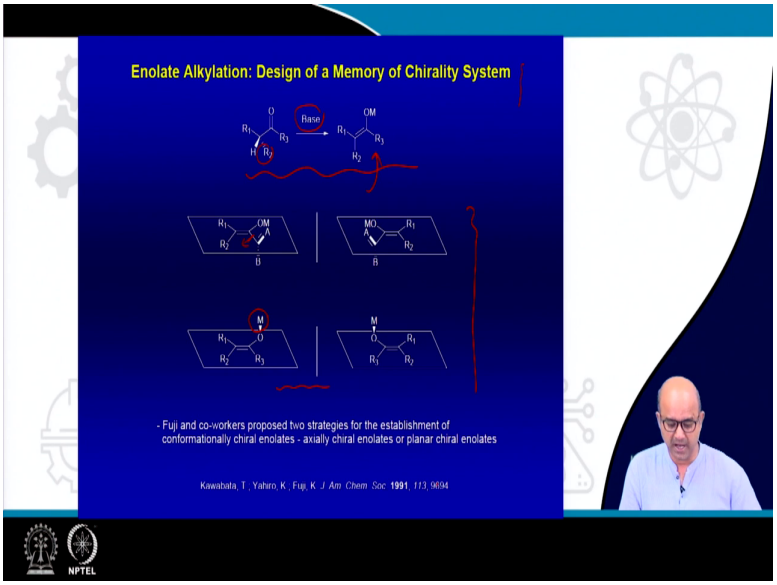

Now, let us have a very close look on such system. Now, enolate alkylation as I said probably this is the very classical system where a amino acid derived compound or a carbonyl compound, which may contain a stereogenic center you first add a base and then you are basically having enolate, where subsequent trigonalization or a flat sp2 carbon you are generating.

Now, eventually you may think that or you probably the origin of this transient enolate intermediate might be having an extra form of chirality, mainly due to a chiral axis, because if the substitution pattern in R2 will be having some transient element of chirality, like a substitution on nitrogen. And then it is been found that this carbon carbon bond rotation can be restricted and you may have a chiral axis around this carbon carbon bond.

Now, this two intermediate having an axially chiral or chiral axis might be the might be the originating or main factor, which might be responsible to have a transient intermediate, which contains an element of chirality. In addition a chiral plane also can be viewed where you might get an enolate which might be having a chiral metal element. And then probably you can have two enantiomers of chiral plane and then basically these are non-superimposition.

So, this kind of non stereogenic form of chirality, where a stereo centre is not present, but other elements like chiral axis and chiral plane might be the responsible factor to have a transient chiral species.

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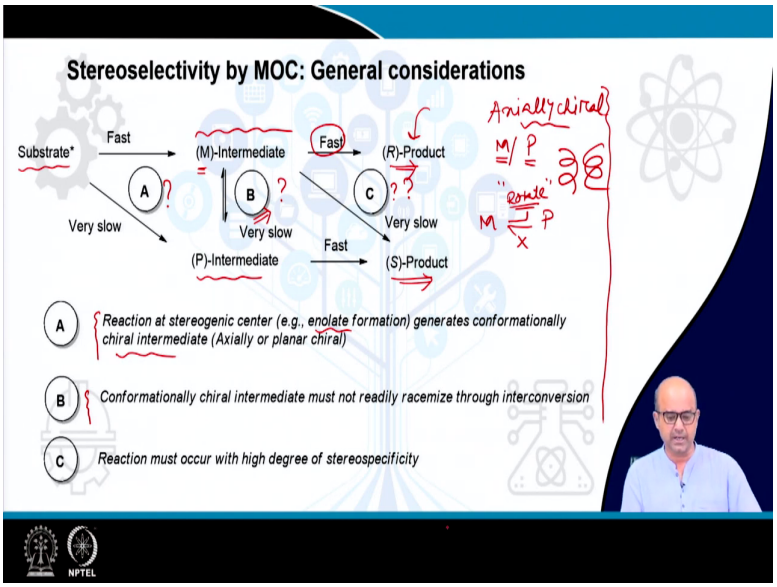

Again we will try to give you a conceptual analysis because that is quite important. So, initially what I am trying to say, you have a substrate which contains a chiral center ok. Now, substrates may react in two different pathways, first it gives a transient chiral intermediate, this M; M stands for normally minus or P stands for plus.

So, for axially chiral molecule, axially chiral molecule, if I am not sure whether all of you are familiar with axially chiral molecule like binol or binaphthyl, they have a two form of chirality M and P. So, M is for minus, P is for (Refer Time: 10:37) plus isomer. Normally they are a helical form of chirality ok.

So, you have one intermediate which contains a chiral axis which contains a M form of chirality. This is very fast and then this intermediate undergoing the enolization on alkylation

for particular case and you get a R product. So, stereogenic center, here no stereogenic center, here you are again regenerating the stereogenic center now there are other competing reaction. Now, the substrate might undergo a very slow process to give you another intermediate which is enantiomeric to the original intermediate M ok.

Now, this M and P there must be a prerequisite the that they should not racemize under given condition ok. Then this P intermediate, if it forms it can have a possibility to give you a S product or the other enantiomer of the product. From the M intermediate there should not be any possibility or a very slow possibility that it can give you this product.

Now, there are three factors this circle A, this circle B, this circle C. What are those things? Circle A: circle A says that you have to think about the reaction at a stereogenic center ok, means an enolate formation, that actually first abolish the point chirality and creates a chiral intermediate through axial or planar chiral.

So, the point chirality basically creates a form of a transient chirality. Now B: B is another circular condition, this says that once one of this chiral axis or chiral plane containing intermediate is formed, it must not readily racemize through inter conversion. Means, if M is formed. Now M and P, what is the, how they can easily inter convert? They can rotate around carbon carbon single bond.

Now, this rotation should be, rotational barrier should be quite high. So, they cannot easily rotate under reaction condition. The condition C another optimization factor, reaction must occur with high degree of stereo specificity. So, if these three forms … you can optimize or you can control, you can actually generate a nice system containing a MOC or memory of chirality system.

This was definitely little bit of difficult or different to understand, but it is not that difficult to perceive.

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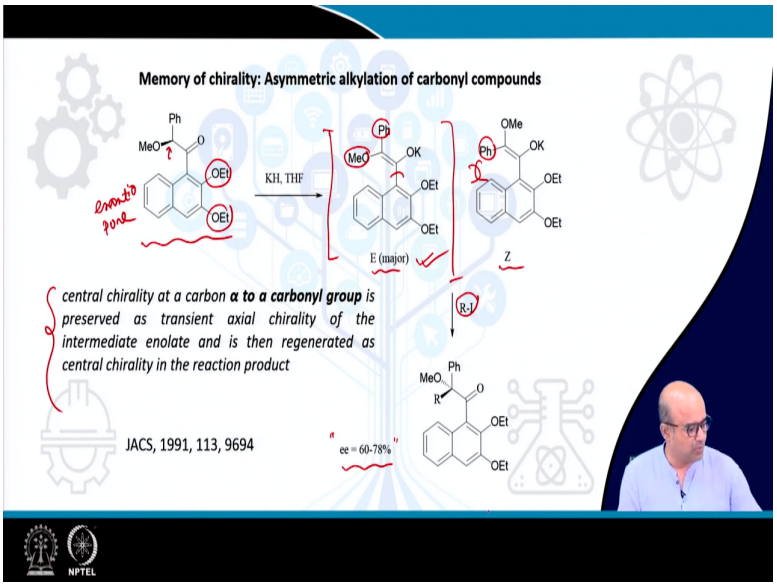

So, let us go back to the system where Fuji and Kawabata initially contributed lot. So, initially Professor Fuji and Kawabata took a naphthyl derived system, where this naphthoic acid contains a bulky OEt …..OEt group and here you having a enol contain or a carbon containing compound where is a stereogenic center is present, is a carbonyl compound.

Now, this is abstractable hydrogen. So, this initial compound is enantiopure, this compound is enantiopure, which was taken as a substrate ok. You put a base potassium hydride and THF. Now, there are two chances of enolate formation ok. Now, the enolate will be definitely E will be major, because the MeO is a smaller group than the phenyl, if phenyl comes here there will be substantially steric repulsion with this phenyl and the naphthalene.

So, E will be major ok, and then the alkyl iodide which was added it was found that 60 to 68 percent it is enantiopure. Now, how to explain it? The point of chirality has been abolished or destroyed in the reaction condition, but still you are able to get a substantial good amount of asymmetric induction. Now, the main factor which is responsible, the central chirality at a carbon alpha two carbonyl group is preserved as a transient axial chirality.

Now, see the compound which is the enolate, it might have an axial chirality because this contains a bulky substitution around a carbon-carbon thing. So, this enolate and this naphthalene might not in the same plane ok, and then you add something. So, this enolate is the discriminant factor. We will just go to the next slide for a better understanding of the every system.

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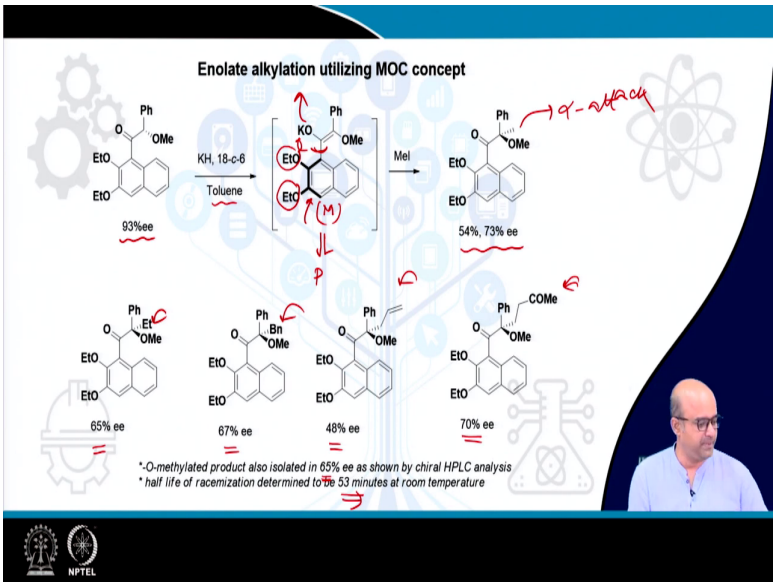

So, initially first starting compound we took 93 percent enantiomeric excess, which was the main precursor for enolate alkylation. Potassium hydride, 18 crown 6 as the phase transfer catalyst toluene as the solvent. So, first what you get? An E enolate. Now, see this E enolate it basically fixes. So, this point chirality initially which was present it forces this naphthyl ring to adopt in a different plane with the enolate. So, this bold things basically means that this was little bit above the plane and this is in a different plane.

So, the actually this OEt….. OEt groups are main responsible factor, if there is no OEt group because this is a bulky OEt.. OEt group and that is why it causes substantially steric bulk and definitely this enolate and this aryl system are not in the same plane. So, this is this molecule contains a chiral axis around this carbon-carbon bond. And then you will be having 73 percent enantiomeric excess because as this is the above the plane of this enolate.

So, methyl iodide attacks from the opposite phase and that is why you are getting an alpha attack. So, we will be trying to explain these things little bit later on again, substrate scope if you think ethyl iodide is giving 68 percent enantiomeric excess, benzyl 67 percent, allyl 48 percent, other group gives you 70 percent. So, all the compounds give good I mean not excellent, but good to moderate enantiocontrol.

And we found that sometimes if you add simple methyl iodide the O minus also be O alkylated and this compound also isolated 65 percent enantiomeric excess, because this compound contains a chiral axis ok, no point chirality. And the most important thing is if this

is the M form of chiral axis, the corresponding P form. So, means this rotational barrier is at the room temperature 53 minutes.

So, it takes 53 minutes to racemize M to P. So, whatever you have to do you have to fetch or you have to do the reaction with this 53 minute time frame. Otherwise, the M and P will be dynamically equilibrated.

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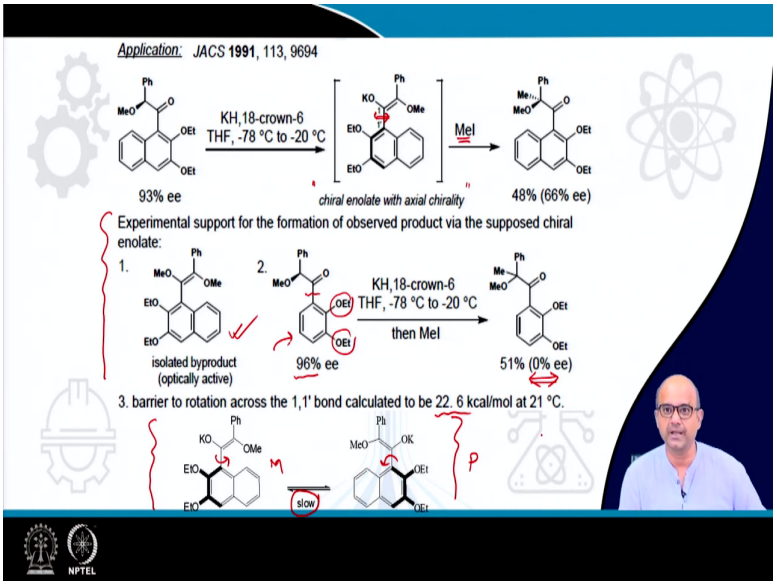

So, with this background information you can eventually try to get a little bit more structural features. So, this is one of the intermediate M, initially what we have drawn. So, if this is M this is the P and this is arising mainly due to rotation around this carbon-carbon bond ok. And usually a room temperature is been found that this is 22.6 kilo calorie per mole and normally it stays 53 minutes one form.

So, 93 percent excess initial starting material you get a M form of chirality in the form of chiral axis. So, this is the transient chirality, this restriction gives you this thing. So, now, this enolate and this naphthyl are in different plane and then methyl iodide attacks opposite from this napthyl ring. So, you get this thing.

Experimental support also gives you further evidence if O alkylated product like you do not, you definitely react MeI, but it happened that sometimes you get a O alkylated product not the C alkylated product. You isolate this product and this product also you isolate as an enantiopure compound, mainly this is the chiral axis or axially chiral molecule.

Now, the interesting point is if you take a simple phenyl derivative, this does not give you any enantiomeric excess it means that you need a naphthyl system is sterically bulky and then this carbon-carbon bond restricted rotation can take place. So, simple phenyl system does not give you a any memory of chiral derived alkylation.

Though alkylation took place (Refer Time: 20:04) 96 percent enantiomeric excess, but at the end you get 0 percent enantiomeric excess. So, with the substrate has to be properly tuned or properly framed.

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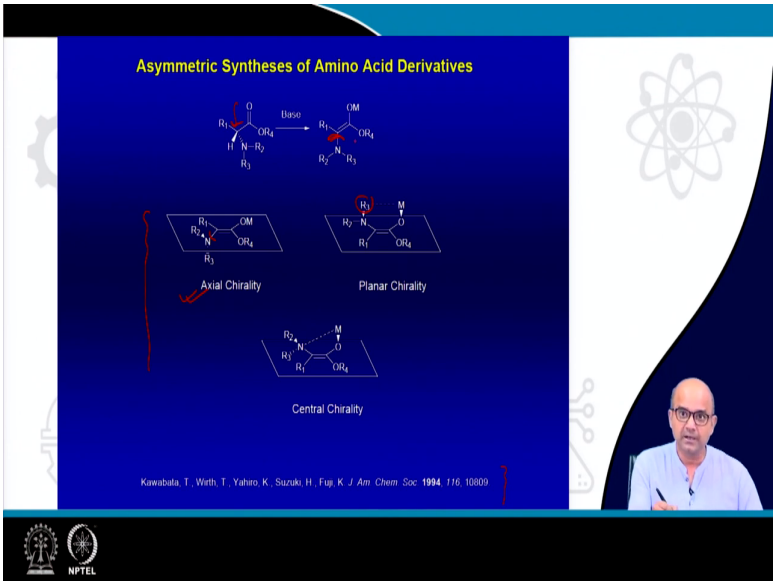

Now, with this information of this naphthyl derived chiral axis, later on Professor Kawabata derived an amino acid derived system which also might be exhibiting a memory of chirality derived enolate alkylation. So, this particular compound which contains a stereogenic center at this carbon, you treat with base initially you get an enolate. So, original stereo center has been abolished.

So, you have a sp3 to sp2, a trigonal system. Now, this trigonal system what I am trying to figure it out that this carbon-carbon bond restricted rotation you might think about. Now, if you have this restricted bond rotation with the nitrogen substitution in a some bulky or other group you will be having axial chirality form ok. This is one form chirality.

If you having an enolate oxygen linked with a metal and then this might have coordination with the substitution at this R3, this gives you a chiral plane ok. And sometimes this nitrogen

with a three different group can have a central chirality, though the carbon chirality is vanished you get ……..you get a nitrogen containing chirality. So, this three chiral element might be present in the enolate formation.

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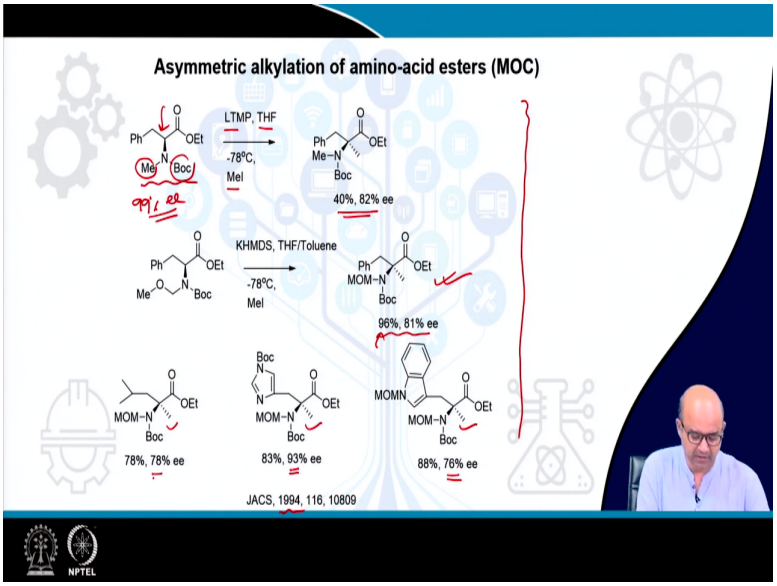

So, let us give you a case study. Professor Kawabata in 1994 first reported this amino acid derived memory of chirality based alkylation. A phenyl glycine derivative was taken mainly phenyl alanine, with n-methyl and N Boc, LTMP based THF methyl iodide electrophile starting with 99 percent enantiomeric excess of this compound. So, this center is going to be vanishing, you get 82 percent enantiomeric excess with 40 percent yield.

So, how to explain? Later on more system like N-Boc and N-MOM are giving you a better yield and better control, the yield is 96 percent. Now, this system was later on optimized and you will find a series of electrophile like this methyl, this methyl this methyl and the system contains a this kind of unnatural amino acid, all gives good to moderate enantiomeric induction asymmetric induction. Now, how this thing is happening?

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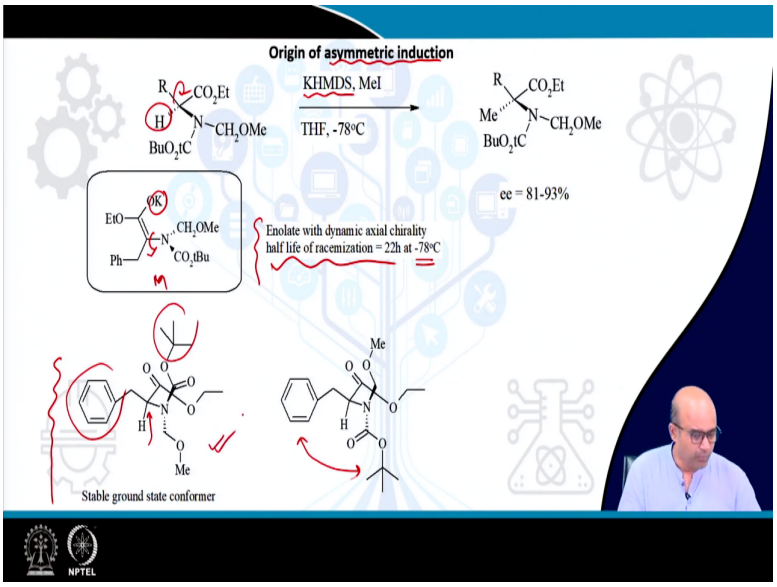

So, initial idea or the origin of asymmetric induction might be explained due to the fact that once you abstract this hydrogen to generate the enolate, you basically abstract it and then you get an O enolate which is metal. If you use potassium hexamethyldisilazide you get a potassium enolate. Now, this potassium enolate will have a dynamic chirality dynamic axial chirality in this form ok.

Now, this restrictive rotation is mainly imposed here and the half-life of racemization is 22 hour at minus 78 degree centigrade. So, this is M, the corresponding P form it can racemize after 22 hour at minus 78 degree centigrade. This has been proved by that the variable temperature NMR analysis; now fine.

Now, what could be the mode of asymmetric induction? Stable ground state conformer could be the left hand side, where you will find that the phenyl and the tertiary butyl are little bit far apart. So, this is your nitrogen MOM CO tertiary butyl and this is the stereo center original …….stereo center. This phenyl and this tert butyl are far apart ok.

Now, you have another conformer which seems to be not very stable because this phenyl and the tert butyl seem to lie in the close proximity. Now, based on this assumption we will now produce or we will now try to explain something.

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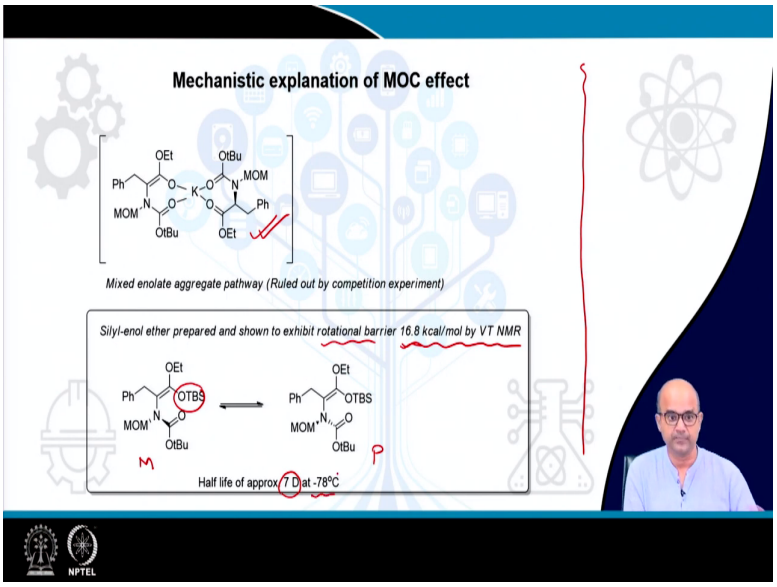

Now, coming to the mechanism part initially people are thinking that probably MOC is not operating, instead you are getting a mixed enolate aggregation which is supra molecular enolate aggregate are formed and you get a chiral enolate aggregate.

But this was ruled out by computation experiment and then the most interesting part it part of this thing is when enol was trapped by the silyl ether, now this axial chirality M and P are found to exhibit rotational barrier of 16.8 kilo calorie mole by this VT NMR. And this half-life is seems to be 7 day, more than quite high half-life at minus 78 degree centigrade. So, this is kind of a very interesting factor responsible.

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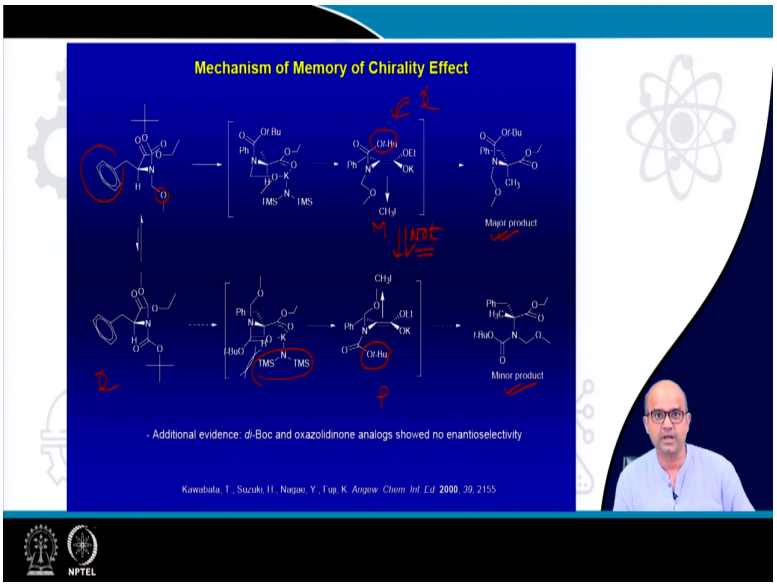

Now, coming to the mode of asymmetric induction. So, initially we said this benzyl group and this tertiary butyl group lies little bit far apart. So, benzyl is pointing towards below CO tertiary butyl is above and this is the least stable conformer. So, mainly your equilibrium lies in favor of this, potassium hexamethyldisilazide.

Now, what it does it basically gives you a 6…… 7 member chelated form where this CO OEt, this oxygen and the MOM oxygen, the MOM group contains the oxygen it helps in the chelation and this is the TMS of the base ok. Now, once you abstract the hydrogen, you basically get the corresponding enolate. Now, this enolate you will find that whatever the ground state, the benzyl seems to be little bit apart and tart butyl are the oppositely oriented. So, enolate this face seems to be blocked and below face is available.

So, now you see you can have only below face attack. Now, the less stable conformation isomer can might be also abstractable by the base, with the hydrogen abstraction. Now, here the point is the tertiary butyl group seems to be below and the TMS also seems to be coordinating these groups are quite bulky.

So, for this least stable ground state conformation, hydrogen abstraction seems to be quite impossible. And if it happens probably now you can find that a tertiary butyl is pointing below towards the enol, the methyl iodide attack from the top phase. So, you get this one as a major product, this one as the minor product. So, this is the form of axial chirality M and this is the P and they are not rapidly inter convertible, not rapidly inter convertible.

So, based on these things Professor Kawabata actually proposed this memory of chirality in original form. So, this was the system where the amino acid derived thing you can talk about.

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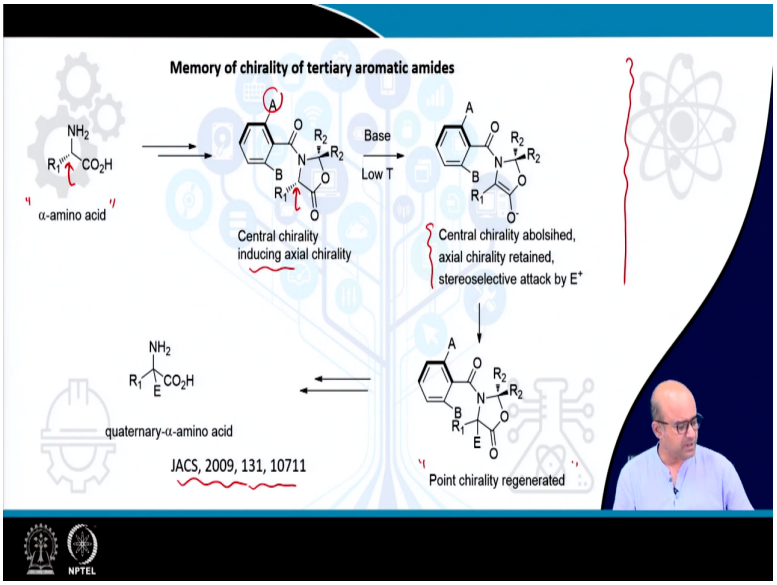

We will conclude with one such system, which was little bit recent and published in 2009 from a Czechoslovakia group, a Czech group they basically reported these things. Now, initially the idea was simple, a point chiral containing amino acid was converted to a oxazolidinone, this oxazolidinone in addition to the point chirality you are also imposing a axial chirality with the help of a napthyl containing or aryl containing group, with proper substitution ok.

Then low temperature you are applying base. So, this point chirality was vanished you get a trigonal enolate. Now, this axial chirality remains. So, central chirality actually inducing the axial chirality and then central chirality was abolished and the based on this point chirality, sorry this axial chirality stereo selective attack of the electrophile to the enolate and you are again regenerating the point chirality and you can get quaternary alpha amino acid. Let have a closer look for such system.

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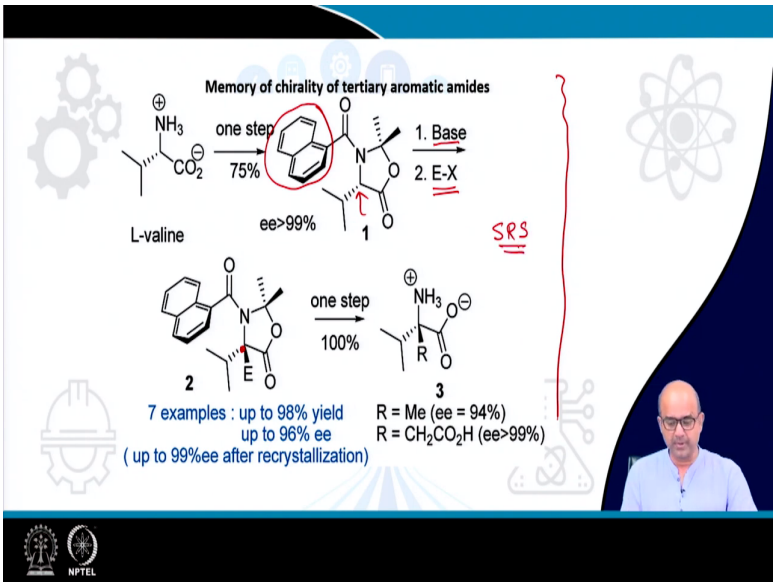

Initially valine was the compound which was chosen and valine was first converted to a naphthoic acid containing oxazolidinone of this system ok. Now, this system we will be try to discuss its feature little bit later on. So, this is the axial chirality part which is coming from the naphthoic acid, this point chirality was abolished in the base treatment and then electrophile actually regenerates the point chirality again, ok.

So, this is kind of sometimes you say self regeneration of stereo center. Now, but usually it basically goes through a memory of chirality system. Now, how it is happening?

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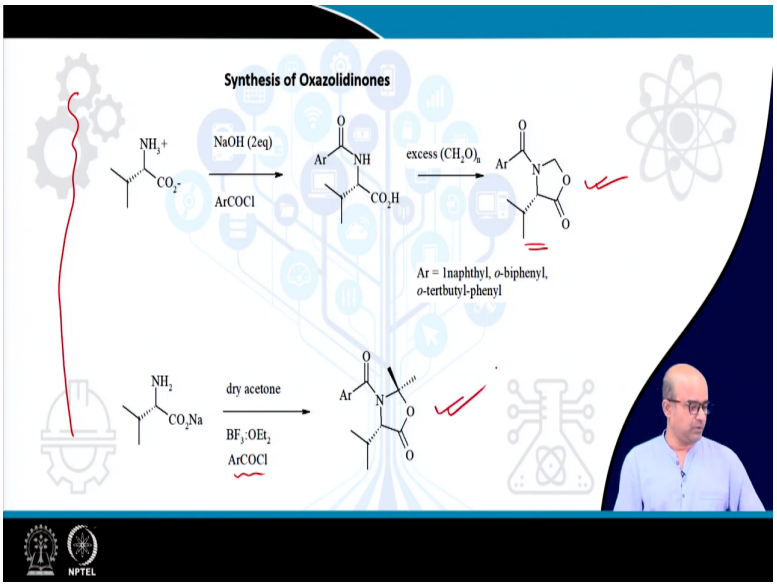

The compound can be easily synthesized by different way, first you take the amino acid, take a sodium hydroxide ArCOCl, initial this NHCO Ar means a acylation forms, excess formaldehyde react with this NH and CO2H it gets CH2OH followed by lactonization you get the oxazolidinone.

You put a sodium salt of this valine, treat with dry acetone you can get this one followed by ArCOCl. So, this is the usual way you can make it, you can make formaldehyde based oxazolidinone, you can make acetone based oxazolidinone.

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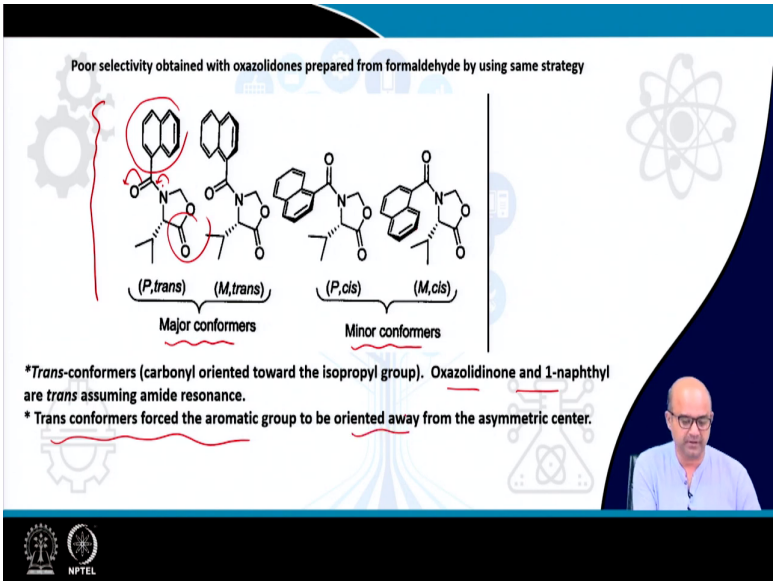

Now, initially you will find that this compound contains two form of chirality. What are those forms? P; P is the positive chirality P and M is negative, trans these are major conformer have been found in the x ray structure, this is the minor conformer. Now, why it is called *trans*? Trans-conformer the carbonyl oriented towards the isopropyl group fine, oxazolidinone and the naphthyl group are trans.

So, oxazolidinone is this way and naphthalene is this way. So, basically this naphthalene and this oxazolidinone part are basically trans to each other if you are assuming a amide resonances just by this. So, this double bond contains this group here, this group here this is more of like an E isomer.

Same thing happens here. Now this P trans M trans, what is the main differences? In one case the rear ring is above in other case the former ring is above. Similarly, you have a Cis where

this oxazolidinone and the napthyl in Cis confirmation, the near ring is above the former ring is above ok.

So, you can have two different things. In the trans conformer you will find that force the aromatic group, the aromatic group oriented away from the asymmetric center, the transform fine.

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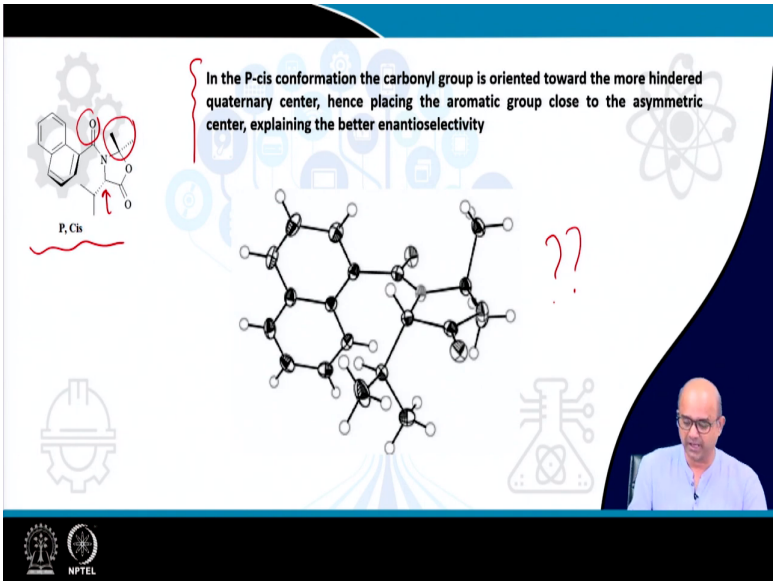

Now, actually it has been found that the P Cis form or the cis form is the main responsible factor for the memory of chirality. And this was been later on proved by the some cases that normally P Cis form for some of the oxazolidinones are really you can get a nice excess structure.

And you can find that in the P Cis conformation, the carbonyl group is oriented towards the more hindered quaternary center. So, this is the carbonyl group, it is oriented towards quaternary center and placing the aromatic group, this aromatic group close to the asymmetric carbon which has to be vanished Cis ok. And then if this is very close when this hydrogen was abolished you can get the attack by the electrophile.

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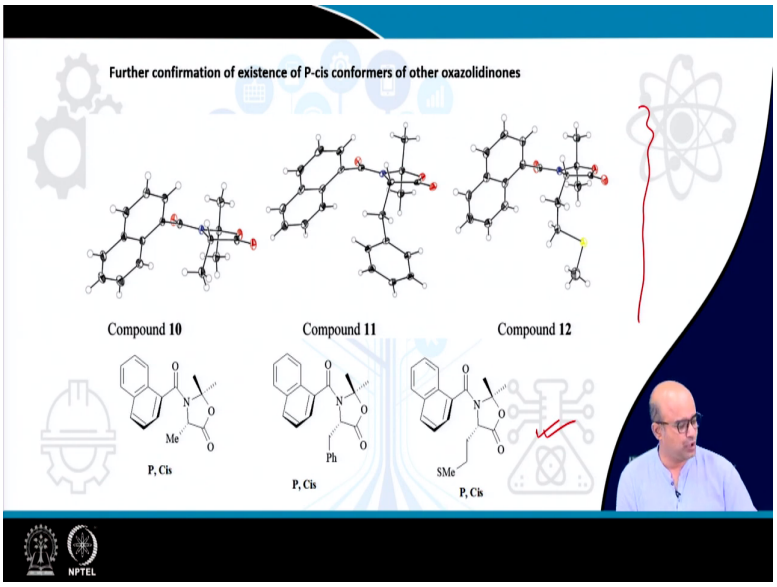

So, let us the based on this excess structure, similar kind of compound you all get P-Cis and P-Cis is the main conformer which actually displays the memory of chirality effect.

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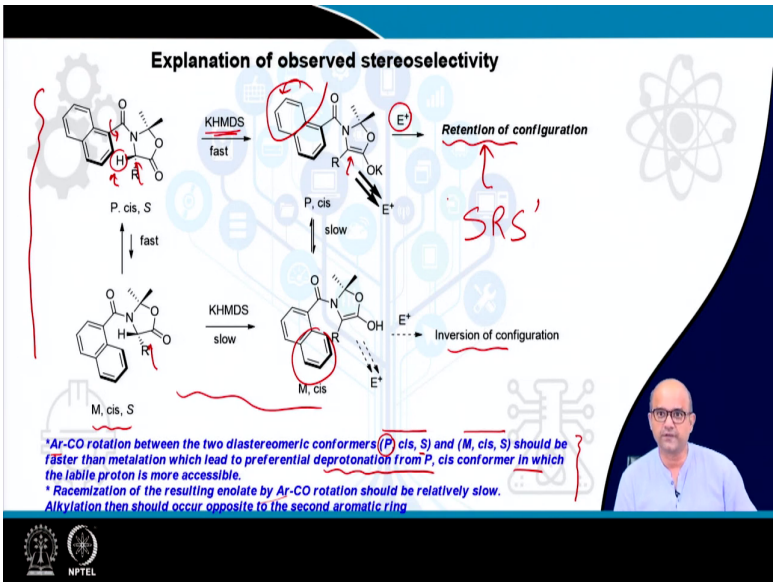

Now, let talk about the real system. So, first you take a P-Cis system ok and; obviously, you have a M cis system. So, P cis……. and M cis are seems to be quite fast equilibrating thing. Eventually you have to identify couple of you have to think about couple of assumption the aryl group and CO rotation. So, aryl and co rotation between the two diastereomeric conformer of P, cis, S and M, cis, S.

So, S is the point chirality present already here, this is the S ok and P is the form of the chiral axis and M is from the negative form ok, cis is the amide resonances. Now, this should be faster these are very rapidly inter convertible. And then that basically gives you one of the ring above here, if it rotates the rear ring comes here ok. Now, fine these are in very fast dynamic equilibrium ok. So, first KHMDS, in the cis form you will find that cis form contains a hydrogen where which the aryl ring little bit far apart.

But in the M cis form the hydrogen is deeply buried with the aryl ring; that means, that this one, the P cis h form the hydrogen could be easily abstracted. So, that is what only from this P cis form the hydrogen is getting abstracted. Now, once you are abstracting the hydrogen, you get a trigonal sp3, then you add the E plus and as the ring aryl ring contains a near phenyl ring which is above it, means that the this phenyl ring is below ok.

So, the retention of configuration means electrophile attack in the top face, because the the phenyl ring which is far apart that actually controls the stereo selectivity. Now, this P cis to M cis these are very slow, this interconversion has to very slow. And if this operates you get inversion of configuration. But in reality of this system retention of configuration or self regeneration of stereo center took place.

So, usually you can find that the preferential deprotonation from P cis conformer in which the labile proton is more accessible. Then the racemization of the resulting enolate by arco rotation is very slow, alkylation then should occur opposite to the second aromatic ring, see the second aromatic ring, second aromatic ring, the second aromatic ring. So, this was roughly the explanation for this good or excellent asymmetric induction in such system which exhibits a memory of chirality.

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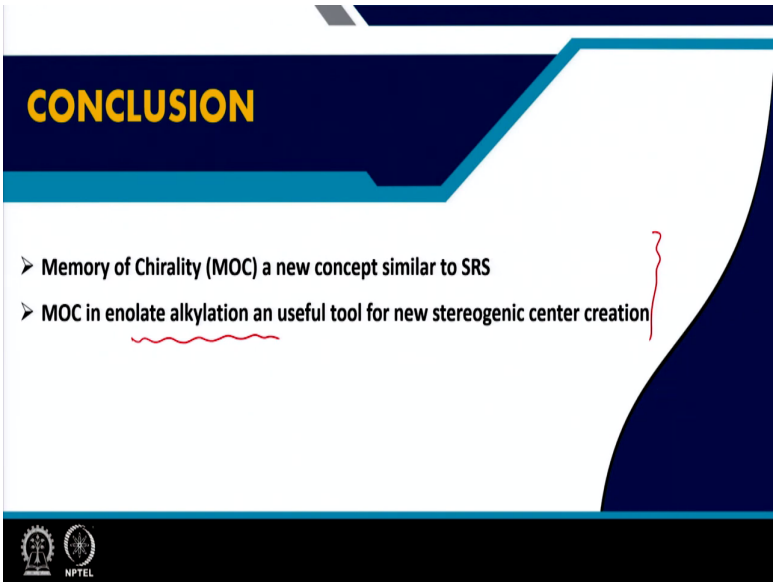

So, anyway in concluding remarks we can say that memory of chirality is definitely a new concept you have to understand a couple of ideas that a transient chirality has to be generated in the intermediate. The point of chirality in the original molecule has to be vanished and the transient chirality might be in the form of non-conventional chiral molecule like chiral axis, chiral plane and even nitrogen containing chirality.

And you can find that MOC still is in is in fancy state, but still you can create quite good asymmetric induction or new stereogenic center based on enolate alkylation.

So, thank you. In the subsequent lecture we will talk about asymmetric alkylation through an organocatalytic fashion.

Thank you.