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 - 39
Enantioselective alkylation with chiral PTC

Welcome back. So, today in this lecture 39 we will be talking about Enantioselective alkylation with chiral Phase Transfer Catalyst which seems to be again a new concept.

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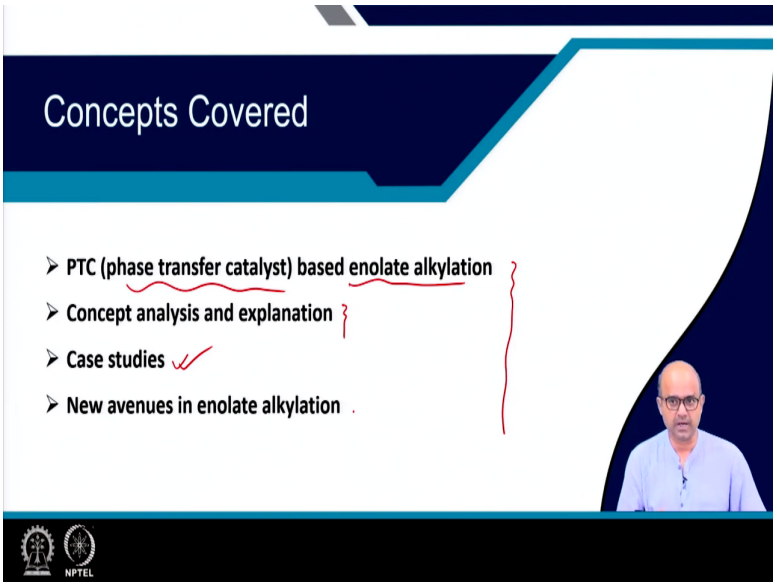

And mainly in this lecture we will be discussing phase transfer catalyst based enolate alkylation in asymmetric form, typical concept analysis and explanation, few case studies. And then finally, new avenues in enolate alkylation we will be having a two three slides to discuss new conceptual analysis in enolate alkylation.

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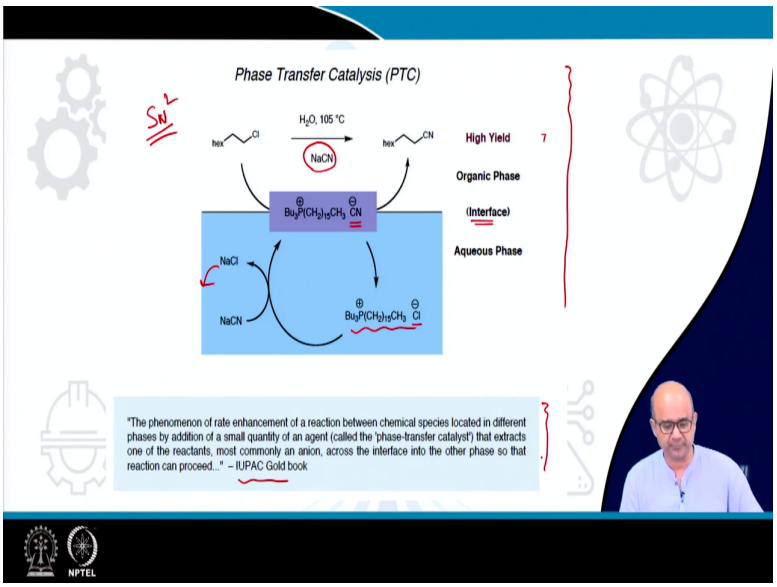

Now, phase transfer catalyst probably all of you are quite familiar, now usually this phase transfer catalyst what did what happens let us say we are talking about the simple SN2 reaction where you are reacting with a long chain alkyl chloride with sodium cyanide in a biphasic reaction.

Now the sodium cyanide probably its solubility in organic phase was very less, it is soluble in aqueous phase. Now, what is happening this compound was used to change that proportion, now what it does it first reacts with sodium cyanide ok and then the chlorine, this chlorine get replaced sodium chloride is precipitate out. So, this phase transfer catalyst now become Bu_3P^+ $(CH2)_{15}$ CN^- and this compound reacts in the interface and then this actually helps in SN2 reaction.

So, phase transfer catalyst in a conventional IUPAC Gold book, you can say that the phenomenon of rate enhancement of a reaction between two chemical components located in a different phase, one is aqueous phase one is organic phase. And you just add a small quantity of agent call the phase transfer catalyst that extracts actually or the brings one of the reactant most commonly mainly anion like here the Cl minus has been replaced by cyanide.

So, cyanide now it basically brings from organic phase to sorry, aqueous phase to organic phase across the interface into the other phase, so that reaction can proceed. So, this was very conventional definition of phase transfer catalyst.

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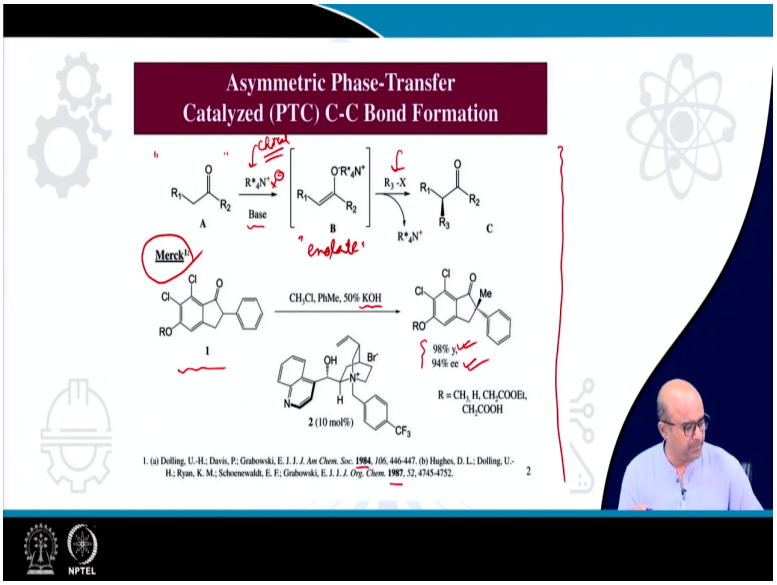

Now, in asymmetric alkylation how this phase transfer catalyst helps and usually this phase transfer catalyst based asymmetric alkylation people are trying to do research, and a significant amount of research has been done by scientist from the Merck chemical company. And they published few good works in 1984 and 1987 now conceptually what they did initially you have a carbonyl compound you treat with a chiral quaternary ammonium salt in presence of a base.

Now, initially base abstracts the hydrogen you get the enolate O minus, now this O minus is counter anion is the quaternary ammonium thing. Now this quaternary ammonium thing was chiral. So now, the as this quaternary ammonium is chiral this enolate now becomes a chiral species. As the enolate is chiral with the virtue of this chiral quaternary ammonium and then you can actually discriminate between the two enolate phase and you can react with an electrophile.

Now, this R_4N^+ initially it has a counter anion ok and this counter anion it can again regenerate with the reacting of reaction of electrophile. So, initially if we will be discussing things in detail, but 1884-87 Merck scientist of Merck's group they are basically working on this indanone alkylation. This compound is usually soluble in organic solvent.

Use a 50 percent KOH as an aqueous base and this component as a phase transfer catalyst use a toluene and water biphasic reaction and methyl chloride as the electrophile. Now, it is in found that this asymmetric alkylation occurs through a chiral phase transferred catalyst like

this ok. Yield and enantiomeric excess was excellent 98 percent yield 94 percent enantiomeric excess was obtained. Now, what is the main factor which is responsible here?

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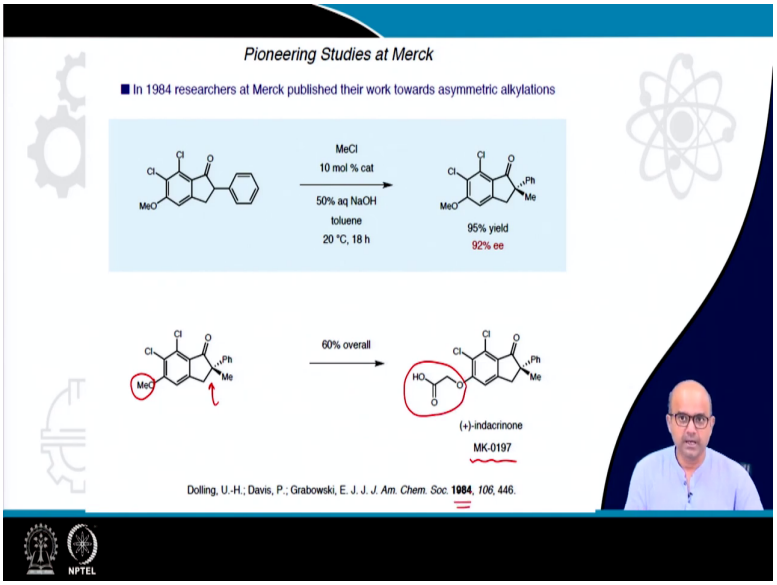

So, we will be basically discussing those things now this compound was basically an active drug intermediate which was later on have been found that, after the alkylation was done this O methoxy group you deprotect and you actually functionalize with a aryl acetic acid and this was reported by again the Merck's scientist by taking this particular lead.

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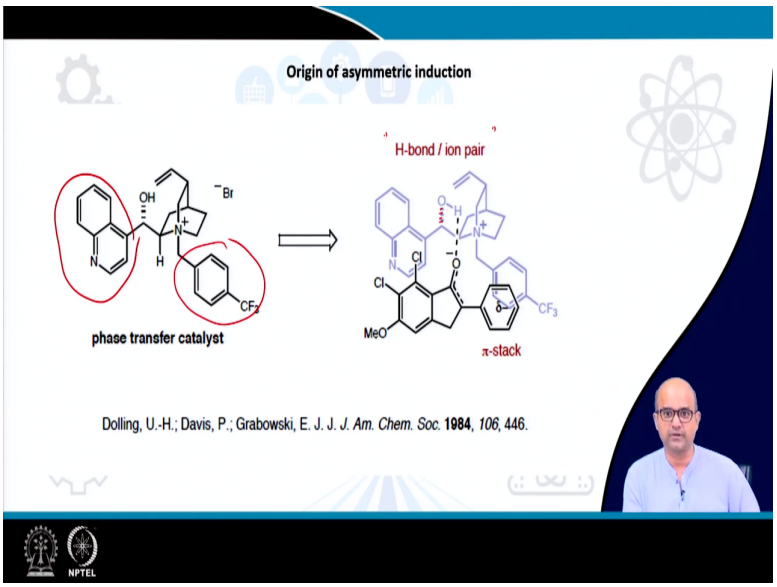

Now, what is happening in this particular reaction we say this is this could be a phase transfer catalyst we will be coming to this later on. Now initially this phase transfer catalyst if you see this phase transfer catalyst has couple of structural motif. This is having a quinoline part this is having an electron withdrawing aryl part and this contains a bicyclic quaternary ammonium species with an OH, it is a N plus and Br minus.

Now the substrates having an indanone, so indanone this part already contains a phenyl. So, this phenyl and this undergoes a π stacking thing, so this is the electron rich phenyl this is the electron deficient probably a π- π stacking sandwich kind of structure taking place. This CO minus 1 the enolate forms it basically gives you the hydrogen bonded ion pair ok.

And then it has been found that the entire back side of this enolate has been shielded because this OH is in the back side and then front side attack of the methyl iodide usually takes place. Now this is how this compound helps in the asymmetric induction, but how this compound is acting as the phase transfer catalyst, it will be quite clear in the next part of slide when we will be discussing few more examples.

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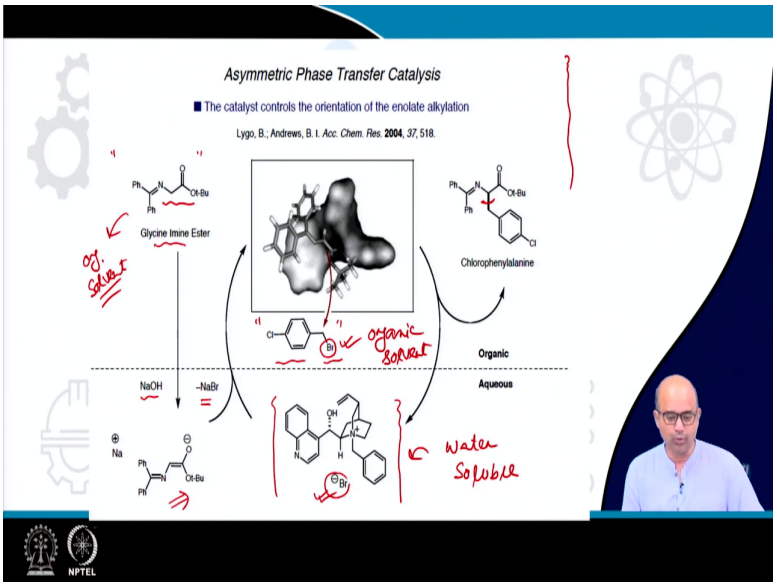

Then later on people like Lygo as well as ODonnell actually trying to do a asymmetric alkylation on the glycine imine ester. So, what they do they took glycine derivative NH2 CH2CO tertiary butyl, fuse with benzophenone they get glycine imine ester. Now this glycine imine ester you can actually treat with sodium hydroxide as a base ok and then use this similar kind of phase transfer catalyst used by Merck scientist for this asymmetric alkylation.

Now, what is happening the moment you use sodium hydroxide you basically get the enolate which is O minus Na plus ok, now this is the aqueous solution this enolate is aqueous soluble. Now, phase transfer catalyst your quaternary ammonium salt this is also aqueous soluble. Now, what is happening? This O minus and this N plus exchange the counterpart and sodium and Br it is getting precipitated. Now this entire thing is the organic part it is actually from aqueous it comes to organic part this is the entire species.

So, phase transfer means first anion exchanging takes place. So, this Br minus and the sodium now recombines that gives you this initial enolate negative charge with the quaternary ammonium phase transfer catalyst cation.

Now everything has been pulled out in the organic phase. Then you have an electrophile ClCH2Br. Now this electrophile contains bromine ok this CH2Cl attacks at this enolate carbon. And then this bromine recombines again with the N plus Br minus the moment it becomes N plus Br minus it comes again to aqueous phase because this is the water soluble.

So, this compound is water soluble and this compound is soluble in organic solvent. So, the phase transfer catalyst basically helps this initial fine the once you forms the enolate that enolate actually comes in the water soluble, but the reaction has to be taken place because this chlorobenzyl bromide is an organic compound and this is a soluble in organic solvent.

But the enolate is not soluble in organic solvent. So now, you add a phase transfer catalyst this O minus exchange the counter ion it is having O minus Na plus, but this having a Br minus. So, sodium bromide easily precipitates outs and now this enolates with the chiral counter ion repairs combines and that comes to organic solvent and then you have a para chloro benzyl bromide para chloro benzyl bromide this actually reacts.

Now, the beauty is this para chloro benzyl bromide having bromine after the reaction this is the electrophile this quaternary ammonium phase transfer catalyst has to regenerate. So, it again N plus and Br minus and again it comes to aqueous phase the further catalytic cycle goes on. So, this was a simplistic example or simplistic explanation which was nicely documented by this Lygo and O'Donnell.

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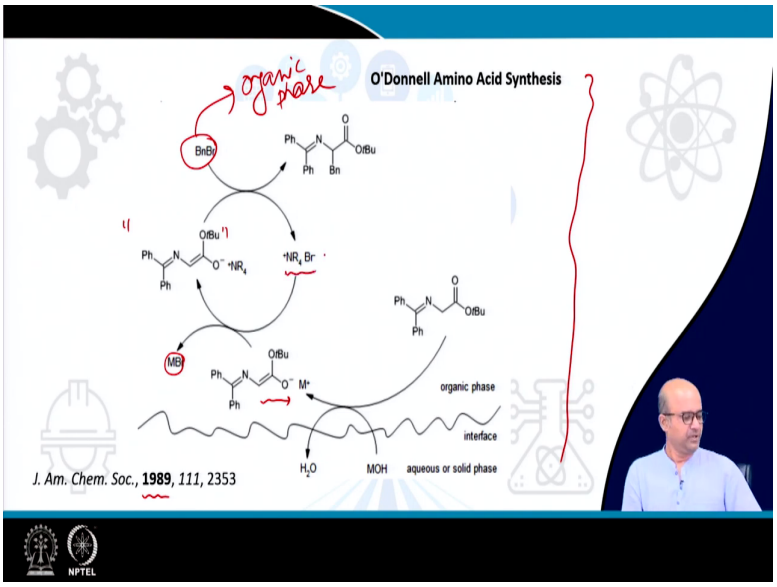

O'Donnell was the actually the pioneer who first termed out this coin this particular concept in 1989 way before the Lygo's work. This is also similar thing which we just now talked about you have this enolate species which you can initially you can generate from the corresponding glycine amino derivative ok. Now, sodium hydroxide was the base because it is very cheap base, the moment you use sodium hydroxide you get the alkoxide means enol…… enolate O minus metal plus.

Now your counter anion or the charge quaternary ammonium species which is also organic solvent you mix it. Now this rapid exchange of anion cation takes place and sodium and Br are precipitates out as NaBr……..and this O-minus recombines with N plus quaternary ammonium that brings everything to the organic phase. Your benzyl bromide is the electrophile which is also soluble in the organic phase. So, now the reaction takes place in the organic phase and Br or benzyl bromide the bromine comes back to the quaternary ammonium salt the reaction takes place.

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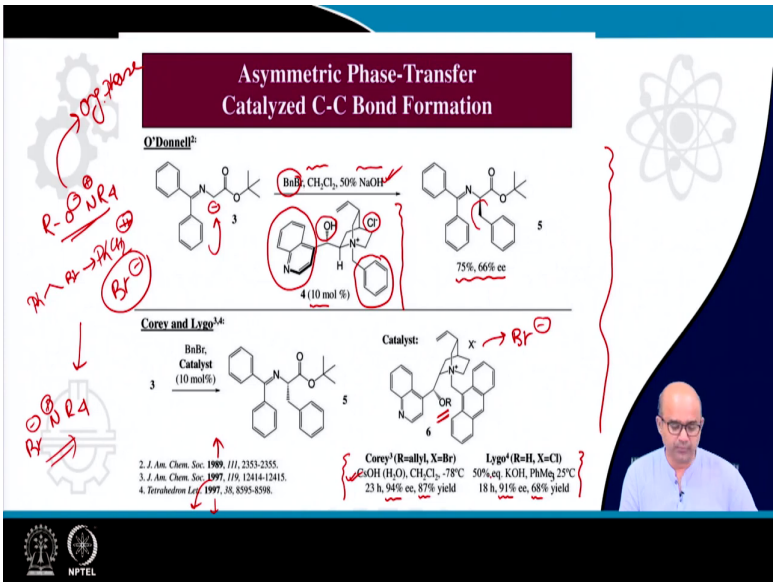

So, O'Donnell was first which who first discovered the entire thing. Now based on the O'Donnell's work later on people like Corey and Lygo have been doing or optimizing this entire condition. Now, initially what professor O'Donnell did he actually took glycine derived compound with a benzophenone based compound and this compound reacted with benzyl bromide as an electrophile. And then he used this cinchonidine based compound which was used as a 10 mol percent as a 4.

Now this compound as I said has different structural features it contains an aryl ring at this point it contains a quinoline part this aryl ring is used for the π-π stacking interaction. Normally, this glycine enolate ester having a phenyl ring so π-π stacking interaction. The main idea was one of the enolate phase needs to be blocked and then the concept of phase transfer catalyst also is working. Because most of the cases the reaction was done in biphasic convention DCM and sodium hydroxide.

50 percent sodium hydroxide normally probably this is the very few cases where we use the inorganic base for the enolate generation. Now, what is happening you can just take the lead from the earlier slide your phase transfer catalyst having N plus Cl minus. To react with NaOH means that the hydrogen abstraction takes place you get o minus Na plus ok. And then you add your phase transfer catalyst which contains N plus Cl minus which is aqueous soluble ok.

Then this counter ion exchanging Cl minus combines with sodium NaCl precipitates out you have this O minus the O minus of the substrates with the counter ion is coming from the phase transfer catalyst. Now, this everything goes to the organic phase and there in the organic phase you have some substrate like benzyl bromide ok this benzyl bromide then act as an electrophile. So, benzyl bromide means PhCH2Br it basically gives you a benzyl cation PhCH2 plus and Br minus.

Now this PhCH2 plus reacts with this thing the Br minus its basically again regenerates to the quaternary ammonium thing RN_4 and Br minus. So, now you will get back your catalyst. Now, O'Donnell was probably 1989, he got good yield, but enantio selectivity was not very good probably the main reason was the counter anion was Cl minus, so the exchange was a bit difficult ok. So, then professor Corey and Lygo; so O'Donnell in 1989, Corey 1997, Lygo 1997 almost after 10 years later on.

So, they have taken similar kind of substrates and then the counter anion they have changed it. So, x is now Br minus and this free alcohol was not there because this free alcohol sometimes this also gets deprotonated in place of NaOH. So, they replace this free alcohol hydrogen with an allyl or a benzyl group. And usually if you can see the yield and everything was seems to be improved little bit better than the O'Donnell's original work from 66 percent ee you now get a 94 percent ee yield was definitely also improved from 80 75 to 87 percent.

And Lygo's work 91 percent enantiomeric excess and 68 percent yield was obtained. So, Lygo's system and Corey system is a modified version of O Donnell's system, but the mode of asymmetric induction was similar will be explaining little bit later on, but the basic concept what of chiral phase transfer catalyst seems to be quite applicable.

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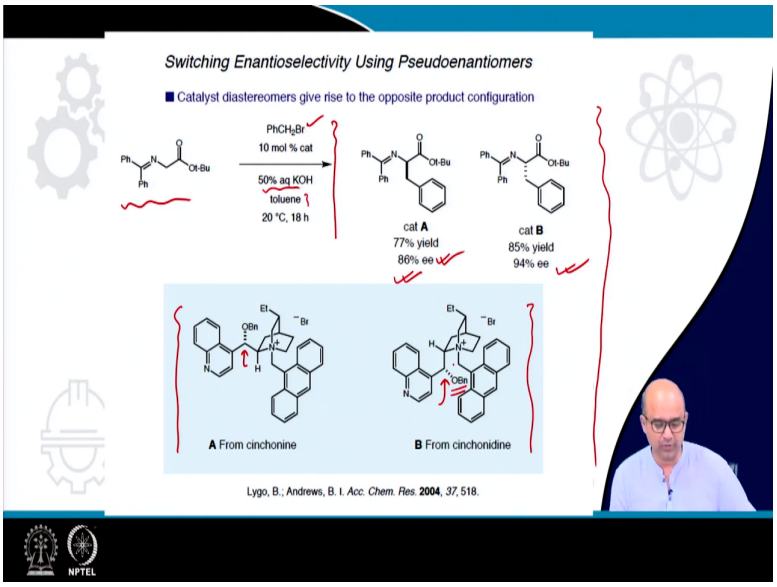

Now, based on this O'Donnell's early work Lygo has later on derived two pseudo enantiomeric chiral phase transfer catalyst; one is this compound A and another is this compound B. Now the basic difference was the stereo center in this two was pseudo enantiomeric ok. So, one is I mean you we have we have just written a different way this compound and this compound basically these are pseudo enantiomer if this center is R this center becomes S remaining everything are similar.

Now, mode of binding will be definitely different… ok. So, in one case it will be bind from the top in one case of the……. it will bind from the top, but the respective enolate geometry if you do in one case you will get this product and one case you will get the other enantiomer of the product. This was usually done on the same system which was originally reported by O'Donnell benzyl bromide is the electrophile, 10 mol percent of catalyst, 50 percent aqueous KOH in a toluene biphasic reaction. The reactions are done in the room temperature 20 degree centigrade yield was definitely good to excellent.

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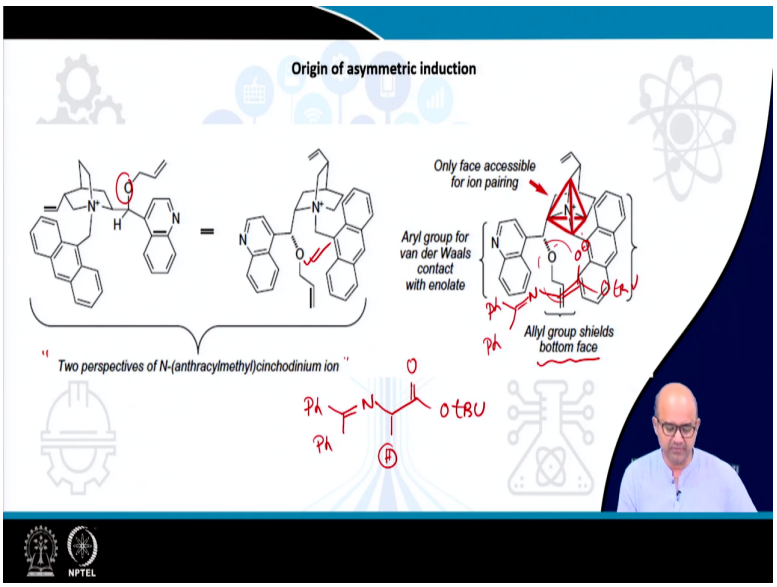

Now let me talk about how you can think about the origin of asymmetric induction for such system. So, initially if you now have to do the compound the compound which we take it is usually this compound the glycine derivative as the enolate. Now the catalyst of the phase transfer catalyst basically having this kind of structure the O allyl. So, you can just rewrite these things with an O allyl which O allyl seems to be alpha, so two perspectives I have written ok.

Now, the enolate actually as allyl is below the enolate seems to be now, sits over the allyl part. So, you can eventually write the allyl part on top of this compound and this with this I mean you just write O minus O tertiary butyl this O minus having the N plus, so see this is the N plus the quaternary salt ok. And so this is the face accessible for the ion pairing because back face is blocked by this O minus and this is the red colored thing the tetrahedral geometry which is just consider by taking this N plus it is this things and then you have this thing.

Now, attack of alkyl group as this way this is the allyl group of shields the bottom face or the back side of the enolate. So, definitely the top face attack will be possible with this particular compound now this particular compound means either OBn or O-allyl ok. So, in this way you can or you can if you can go back to the original work here is the O allyl see the O allyl this is the O allyl and attack from the top face.

So, this benzyl bromide attacks from the top face. So, O allyl as well as benzyl both is similar kind of thing, but free hydroxy group was not recommended. bases usually you can use

sodium hydroxide as reported by O'Donnell later on professor Corey used sodium hydroxide in a system water and DCM. It is and it is a low temperature, but then 50 percent aqueous KOH was used with toluene solvent which was reported by the Lygo and other people.

Now, asymmetric induction as I am said this could be nicely explained by taking any of the pseudo enantiomeric compounds. So, this compound if you can use it. So, this hydrogen will be abstracted by your base then you get the enolate now the enolate it is O minus it has to be (Refer Time: 21:40) with the N plus ok. And the ion pair actually attacks from the top face because bottom face is shielded by this O allyl group.

So, so this was main factor and eventually if you see the original thing you can see here is O benzyl it could be like this and then here is your another O benzyl which is pseudo enantiomeric. So, these two forms you can just write side by side and you can compare the asymmetric induction, is usually quite good.

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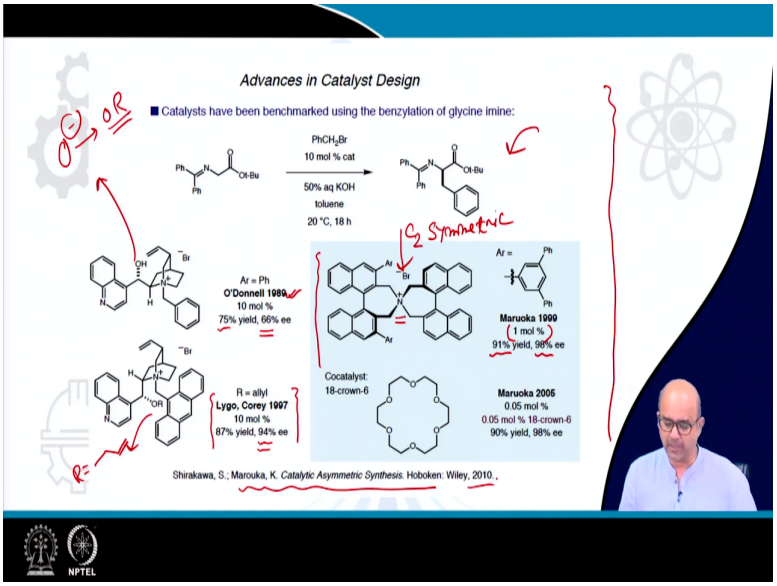

Then it has been found that on the similar way people are trying to work on different perspective that what could be the more futuristic approach. So, initially O'Donnell in 1989, 10 mol percent 75 percent yield hydroxy is free ok that gives you 66 percent enantiomeric excess. Later on Corey and Lygo almost 10 years later they come up with new solution when R group is usually allyl, so free hydroxy group has been removed which just now we have discussed ok.

And mol percent was 10 mol percent here also they get 10 mol percent yield was 75 percent to 87 percent, but substantial differences from the 66 percent enantiomeric excess of the O'Donnell's work with 94 percent almost like 30 percent jump in the asymmetric induction that is a definitely a clear cut indication that this system the free hydroxy group was not required. You need to change the free hydroxy group with the free hydroxy group the main drawback seems to be that O minus is already there.

Now, this O minus and the enolate O minus they are basically two competing species. So, you do not want extra competing species …… now this O minus can actually inter molecularly coordinates with this or ion pairing with this quaternary ammonium salt. So, you do not want something like this, so this O minus should be protected as OR and Corey and Lygo rightly address these things.

Now, later on professor Maruoka a Japanese scientist, Maruoka after 2 years later he actually derived a C2 symmetric Binol based quaternary ammonium phase transfer catalyst which is definitely complex, but it is a C2 symmetric this compound is C2 symmetric in nature and this is binol based compound. Now, this binol based compound everything was nicely done, but only one mol percent catalyst loading was needed, so that is the further more improvement.

Yield was definitely 91 percent and then 98 percent asymmetric induction on the similar O'Donnell system the glycine imine was reported. Now, Maruoko's catalyst was definitely quite good because you have to use a pretty bulky C2 symmetric binol based catalyst similar kind of mode of induction this is the N plus. So, initially N plus Br minus the reaction was done in the aqueous organic biphasic reaction.

You first generate the enolate which is O minus Na plus you add this phase transfer catalyst ion exchange takes place, this N plus combines with enolate that brings everything to the organic solvent like toluene, sodium bromide is not soluble in toluene it precipitates out. And then you can eventually try to write the correct transition state similarly based on the cinchonidine based and then you eventually if you are trying to go through the corresponding references the Maruoka reported these things in 2010 ok.

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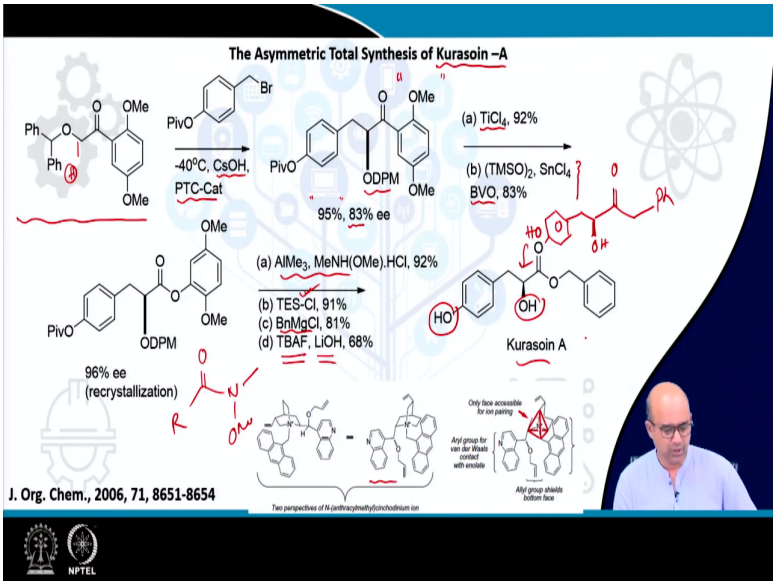

Now, fine based on these things you will be now trying to give you an idea that, how this phase transfer based catalyst can be applied in the field of asymmetric organic synthesis. One such example we just talking about which basically describes asymmetric total synthesis of Kurasoin A, Kurasoin A is a natural product it contains a single stereo genic center. Now this was first reported in 2006 the idea was you having a kind of a carbonyl compound similar like your glycine derived system, but it is not you take this three four dimethoxy phenyl based a carbonyl species or a glycolic acid.

Now, this glycolic acid you use cesium hydroxide as a base with a phase transfer catalyst and a 4 pivaloyl benzyl bromide as an electrophile. The catalyst we use the same as Lygo's catalyst the quaternary ammonium N plus Br minus. Now this N plus Br minus you first abstract this hydrogen definitely you get O minus cesium plus. Now you have this thing with N plus Br minus rapid exchange you get O minus I mean after this enolization O minus N plus this is below ok. So, now, the electrophile attack from the top this ODPM group is the phenyl group ok

Now, next the asymmetric induction was not that good, but still 83 percent enantiomeric excess you could obtained. 95 percent was yield initially this ODPM group was deported using titanium tetrachloride and then a SnCl4 for mediated and di siloxane based hydrogen peroxide containing Baeyer-Villiger oxidation reaction was done. So, this Baeyer-Villiger oxidation was done means that this phenolic this electron rich aromatic nucleus will migrate and you get a …….. ok.

Then a transamination reaction was there you replace this electron rich nucleophile with this aromatic ring with the O N (Refer Time: 28:40) amine ok you get the corresponding C double bond O N Me OMe this O N (Refer Time: 28:48) amine this R remains same everything. Then there is a DPM group has been deprotected you protect with TES-chloride triethylsilyl chloride, then you react with benzyl magnesium chloride you basically get I think there is a small mistake probably. I think this structure will be C double bond OCH_2Ph yeah final structure.

So, probably I did some mistake anyway that I think this could be the final structure of Kurasoin because I think during the drawing I did some mistake ok. Anyway nevertheless, you basically get the benzyl magnesium chloride on this when the amine and then you react with this you get the C double bond this particular benzyl ketone. And then TBAF lithium hydroxide TBAF is eventually displacing this test group with OH and pivaloyl group was hydrolyzed by lithium hydroxide, you get the compound which is Kurasoin A.

Asymmetric induction you can definitely explain this was a nice synthesis of a naturally occurring compound by using phase transfer catalyst based asymmetric alkylation. There are few other reports, but we will be not talking about.

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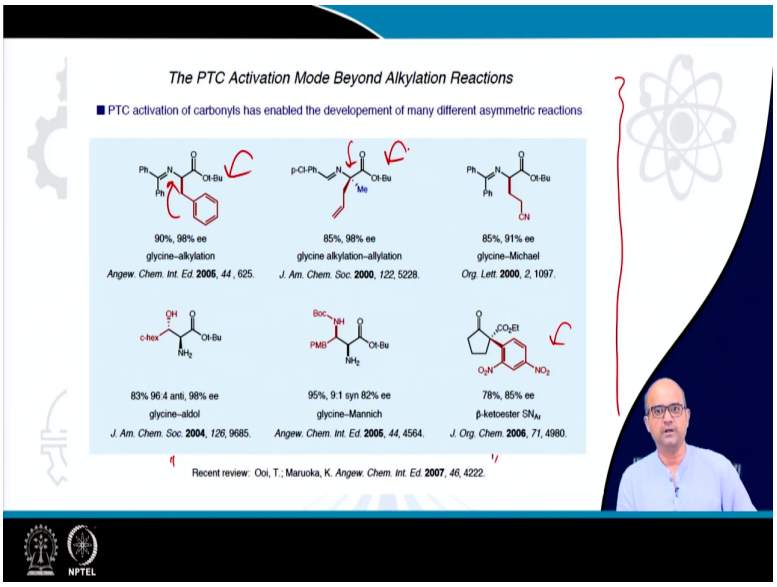

So, finally, what you can do with phase transfer catalyst actually you can do many things you can do a glycine alkylation, the work which we have talking about the O'Donnell's Corey and Lygo's. Glycine alkylation followed by quaternary based thing, so you can actually create

quaternary derived quaternary glycine derivative. You can do a Michael reaction which when I talking about you can generate the minus thing and with the phase transfer catalyst you can do a Michael addition. You can do a aldol reaction, you can do a manic reaction, even you can do other substitution nucleophilic aromatic reaction.

So, everything can be done on the phase transfer catalyst and this was recently nicely reviewed by professor Maruoka, but for the alkylation part this could be interesting this could be interesting which is our main concern in the enolate alkylation.

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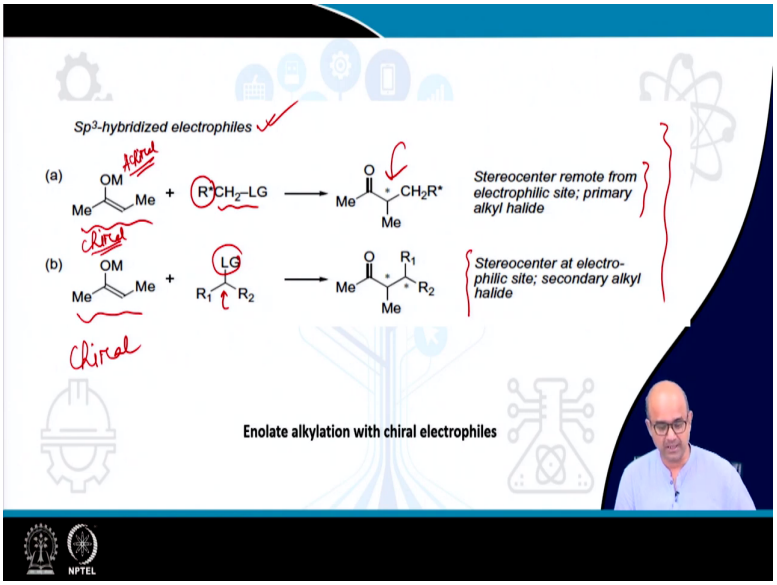

So, next we will just trying to stop with a new direction. Normally throughout this enolate alkylation we talked about that always you take an enolate which seems to be a chiral precursor an electrophile was never taken as a chiral electrophile, always we took an electrophile which seems to be a chiral. Now, what will be happening if you take, I mean normally we do with the sp3 hybridized electrophile. Now electrophile could be a chiral, so you have a CH2 LG and if this contains a chiral thing and may be something like this when you have a chiral electrophile.

So, then it might happen that stereocenter removed from electrophilic site you might get asymmetric induction due to this chiral electrophilic nature. So, in this case enolates will be a chiral in the. Till now what are the systems we talked about? Always in most of the cases enolates are chiral like your Evan's, Meyer's, Mayor's, Boeckman junior (Refer Time: 32:22) everything.

Now if we try to use a chiral electrophile you can definitely create further round of asymmetric induction and this could be new avenues and definitely this will be beyond the scope of our current discussion, may be in the future we will talk about chiral electrophile induced asymmetric alkylation ok.

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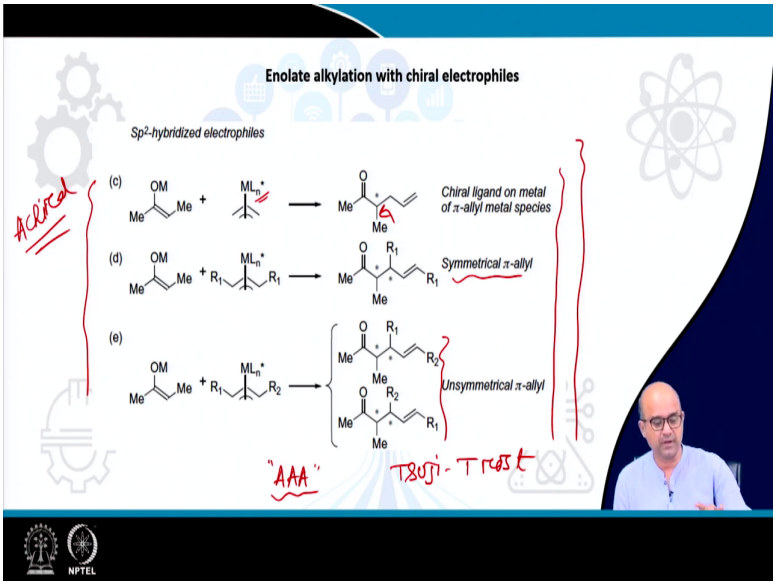

And then finally, if you have a sp2 hybridized electrophile last slide we talk about sp3 hybridized chiral electrophile, if you try to talk about sp2 hybridized electrophiles. Most of the enolates will be now talking about an achiral enolates the enolates are achiral fine. Now, the electrophile might be sp2 containing and there is a metal coordinating with a chiral ligand. So, electrophiles are sp2 and then you try to have a symmetrical electrophile with this or you have a un-symmetrical electrophile. So, if you have a π- allyl electrophile with three carbon containing electrophile.

So, you might get a chiral center based on the ligand chirality, which is associated with the electrophile ok. You get a symmetrical π- allyl…….. there are two stereocenter you are creating two contiguous stereo center, if there is a unsymmetrical you might have to regiochemical issues on this thing. So, these things are definitely can create you new avenues for further thinking anomaly based on these strategies some name reactions are definitely well known like Tsuji Trost asymmetric allylic alkylation ok.

Tsuji and Trost asymmetric allylic alkylation was one of the most important reactions we call it AAA reaction asymmetric allylic alkylation reaction. Now these reactions we are not

discussing it, but that will basically based on the similar concept you actually generate a achiral enolate and these electrophiles are chiral electrophiles.

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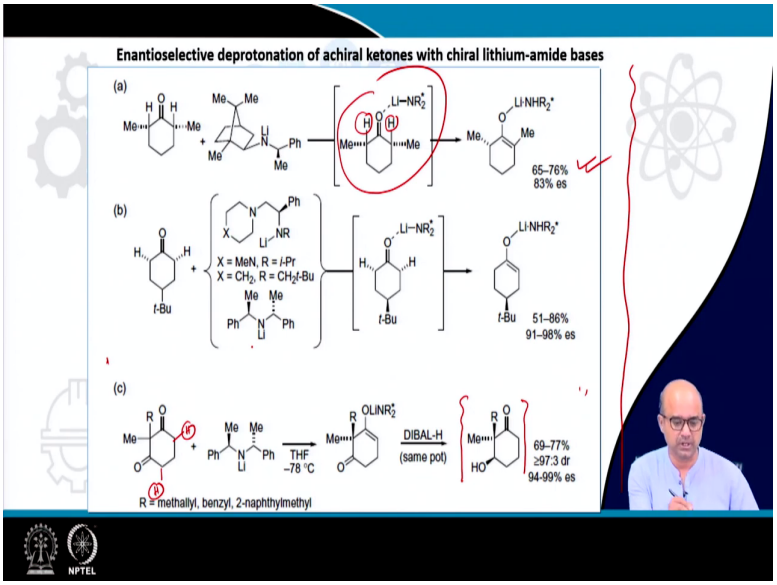

And finally, there are a few other scopes which also could be quite interesting you can have an enantio selective deprotonation on a meso or pro chiral a pro chiral carbonyl compounds with the help of chiral bases. Now this chiral bases what it does is basically picks up the enantiotropic proton, so initially they coordinates with this kind of meso compound with this chiral bases and then they pick up one of these enantiotopic hydrogen and they give you a chiral enolate ok.

The similar kind of things happens here and also there are other scopes where this starting material contains a chiral center like this, but this is a pro chiral center ok. Now if you can analyze any of these two enantiotopic hydrogen which is C2 symmetric chiral base you can basically get a resolution means one of the pro chiral system is accepted by this compound and creates a enolate with a specific point chirality.

Now, next what you do? You do not do enolate alkylation you do a typical one pot reduction on this system. So, you are basically getting a fully functionalized cyclohexanone system with two contiguous stereo center. So, these are few fine aspects final aspects on the selective deprotonation and this selective deprotonation was nicely explained by different people mainly Koga's asymmetric deprotonation method with this chiral bases.

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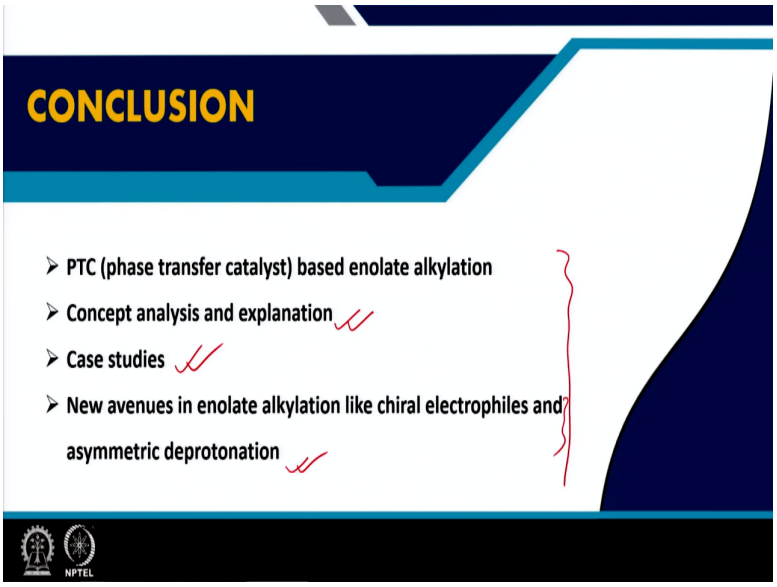

So, finally, we can say there is a concluding remark this phase transfer based catalyst was seems to be pretty useful for the enolate alkylation we have talked about its few concept analysis few case studies and finally, new avenues for the enolate alkylation and asymmetric deportation. Now during the lecture there might be some typing mistake which might happen because most of the lectures I am doing it my pen and paper drawing.

So, definitely being a human being some error might be creeping in. So, please forgive me, if I have some errors I have tried to correct the errors definitely and you are always welcome to point out me that if sir you did some error. So, these things are definitely I will appreciate from all of you, so please just try to help me to correct the errors during the drawing purpose.

So, thank you all in the final lecture we will be mainly discussing the summary of all 39 lectures which we have discussed and we will try to give you a scope for the future direction.

Thank you and see you in the final lecture.