A Study Guide in Organic Retrosynthesis: Problem Solving Approach

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Lecture - 52
Stereochemical Strategies

So welcome back students. As discussed in the last class, today we will be talking about stereochemical strategies.

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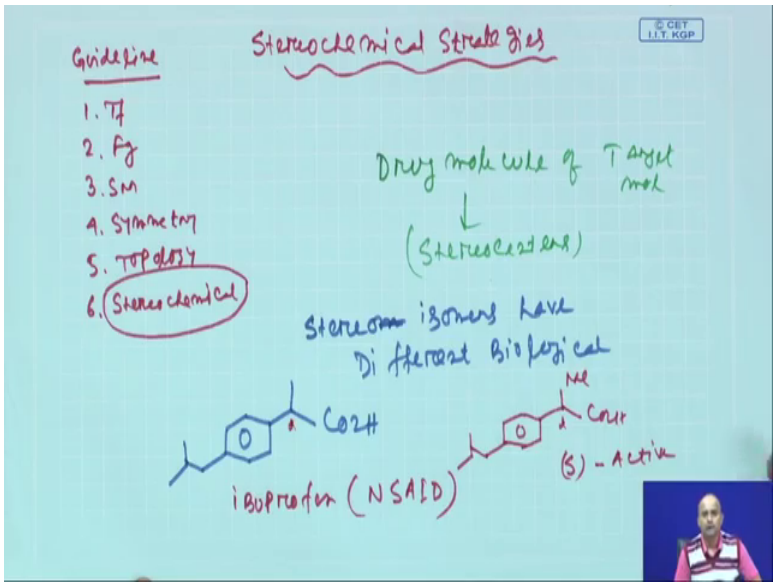

And this is our 6, or final guidelines, the 6 guidelines or 6 different instruction, which I am telling from the very beginning, that our main guideline was basically to follow 6 different points, those guidelines were starting from transformation based strategies, your functional group based strategies, starting material based strategies, 4 is symmetry based strategies which you have discussed, the 5 is topology which you have just finished, and then our final strategy is stereochemical based strategies.

Now, as the name implies, basically this particular strategy is very important, whenever you will find, a molecule contains oil defense your center.

And normally ah, maximum natural products ah, which you are isolated from the nature ah, are having rich stereochemical information, means that, they contain stereo centers in their structure. So, it is often very much challenging or demanding, to synthesize the pure

enantiomer or the pure stereoisomers in a substantial quantity so that, you can do the possible biological evolution.

And probably, it is now quite mandatory, if you have a drug molecule or a given target molecule, drug molecule of a, or a target molecule, where, particularly for drug molecule is very important, if you have stereo centers, then you need to prepare all the stereoisomers for the given molecule, because we know that, individual stereo isomers have different biological, biological profiles.

So, stereomers, or stereoisomers also, individual stereoisomers, have different biological property, different biological property, this is very important, or to synthesize the ah, particular or the proper stereoisomers, which you are looking for. Let us give a very classic example, this molecule is, ibuprofen. Now it is a very well known painkiller, all of us probably take it, basically falls in the class of this drug, non steroidal anti inflammatory drug. And, I will see the structure; this compound is having a stereo center here.

And in reality the s isomer of ibuprofen, was having the main biological activity, the s enantiomer, s enantiomer is the active form, the r isomer is inactive basically.

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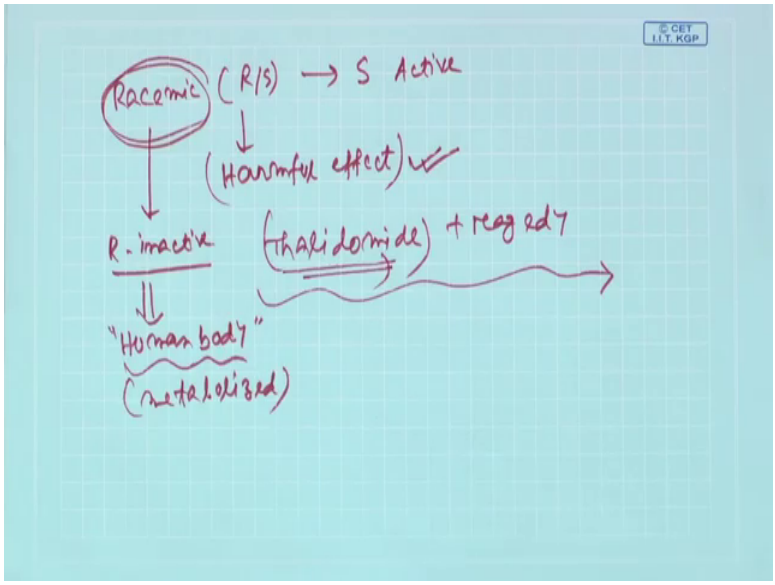

So, now, if, ah, if it, if a drug supplier, make a racemic drug, racemic ibuprofen, means that you are having R and S together, the s isomer is active, active, the point is, if r isomer is inactive, that is fine.

But if the r isomer is having some harmful effect, then you will be in trouble, and it happens many time that other enantiomer, which is not biologically active, if they have some harmful effect, will be absolutely damaging, or absolutely tragic incident may occur, there are a few cases, which have been already, taken places in the human civilization, particularly if I talk about this thalidomide tragedy.

Now, you will not discuss it in detail, we just saying that, this particular compound thalidomide was given as a drug molecule. Now, one of this enantiomer is the active component, the remaining enantiomer was not the active component, and the remaining enantiomer, basically having a harmful effect, which causes severe defects in a certain human bodies. So, that is why, now later on, all the drug related companies have clearly instructed that, whenever you are trying to market it a drug or a pharmaceutical intermediates, which contains stereo center, you need to prepare all the stereoisomers in pure form.

And then I say, they are biological profile individually. So, that except that stereoisomers, if the other compounds have a say, biological profile then it is fine.

But if, those compounds, does not have a say, biological profile, those compound, sorry, immediately banned, or were not even marketed, in case of ibuprofen, as I said, the r isomer is inactive. Now, inactive means, though it does not do any significant activity in the human body, still, once you take in the human body, it has to be metabolized, it has to be metabolized, it has to be metabolized, it has to be metabolized.

Metabolize means, you need to, produce some extra energy to degrade the compound. So, means, your body system need some extra thing, it needs to produce some extra enzyme, or extra biomolecules, which can degrade the r enantiomer. And then, it can be secreted out from their body, in form of urine or something like that. So, in those cases basically, your body needs to, needs to, spend some extra energy, which is also not recommended.

Why you are, why your body should produce some extra energy, to degrade some molecules which is not beneficial to us. So, in those, in, in particular keeping view of those minds ah, whenever you are dealing with a stereo chemical, with the pure compound, or target is stereo chemically pure, you need to think about that, you ah, should have a proper guideline, or proper strategical outline, that you can, you will be certain to make or synthesize the molecule in a stereo pure form, or enantio stereo pure form.

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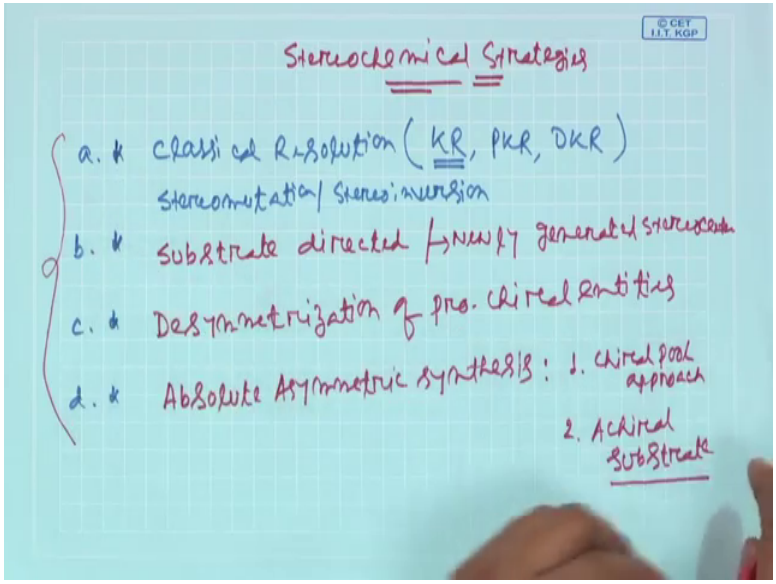

Now, we, definitely under the stereochemical strategies, we have some guideline, we have some guidelines, or, rules, we will try to outline those, or, we try to try to highlight those rules, which is basically, simplify your ah, your ideas. We say that, our main idea, or main thing, regarding stereo chemical strategies, will be focused on 4 different topics, and by, by adapting these 4 different topics, you can basically create some stereo centers, or you can bring some new stereo centers in the given molecule.

The very earlier approach was, classical resolution technique, classical resolution technique, we will explain these things in detail. In the classical resolution, you have kinetic resolution, you have parallel kinetic resolution, you have dynamic kinetic resolution, those are basically abbreviated form. In addition, you do have some other methods, which named as stereo mutation, or stereo inversion, means, you are doing a inversion of stereochemistry.

Then the second part, which is very well known a substrate directed strategy, means that, your starting material, having etched existing stereo centers, based on this existing stereo center, your newly generated stereo centers can be created. So, it is basically substrate directed approach, to newly generated stereocenters. So, if the substrate has some pre existing stereocenter, you can use that, to create, or you can bring new stereo centers in the given molecule.

This particular, we have, explained little bit, but we did not talk about in detail, we say that, if you are having a pro chiral unit, you can do a desymmetrization of a pro chiral entities, to bring new stereo centers. We have explained in certain examples that, a, like a symmetrical molecule, where you have a sigma v, both, the groups are enantio topic, you can do a sequential reaction either one end or the other end, you can create 2 enantiomers.

And the final thing is, which I called, absolute asymmetric synthesis. Now this is also, this fourth point is the most important, or most challenging one, which is again classified into 2 different part, one is the chiral pool approach, we will explain, what is chiral pool approach little bit we are going to bear a, deep or detail.

And the second one is, starting from a achiral substrate. This is the most challenging, you know substrate is achiral, you react with a chiral reagent, or with a chiral catalyst, to bring new stereo center, or to bring asymmetry, in a given molecule.

So, our main focus on the stereochemical strategies will be centered on these 4 topics. We will first start with the, classical resolution technique, classical resolution technique.

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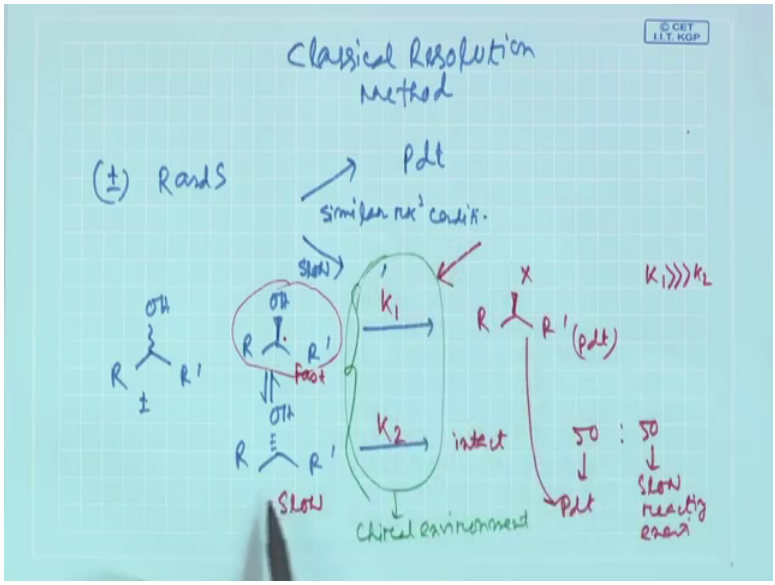

So, in classical resolution, as the name implies, classical resolution method. As the name implies, basically you are having a, racemic mixture, r and s together, and you allow them, to react in a similar condition.

You allow them to react under similar condition, similar reaction condition. Find that, the one of the enantiomer, out of this 2, will react, to give you a product, the other enantiomer reacts slowly, very slow, very slow. So, means that, you now will be trying to give you example ah. So, that basically simplifies, your whole concept, I say you are having this alcohols, which is in a racemic from.

So, now, what does it mean you basically having, this enantiomer as well as the other enantiomer, ok?

Now, these are in equilibrium, or basically you are having a 1 is to 1 mixture, what I am saying, one of the enantiomer, let us say that, top enantiomer reacts with a red constant K 2, second one is K 2. Now this I say, this is fast reacting enantiomer, and this is slow reacting enantiomer, the fast acting enantiomer, reacts in a some fashion, to give you a compound x.

The second enacting reactiomer, is absolutely slow reacting, and we say, the prerequisite is K 1 is much greater than K 2. So, K 2 remains intact, now what happen? If it reacts very fast, the one enantiomer, you will get this product, now this enantiomer does not

react, after this reaction is over, or a 50 percent, of this enantiomer reacts, because you only have 50 percent, as it is a resin mixture.

So, this 50 percent is reacted, you get this product. Now this 50%, is slowly reacting enantiomer, does not react. So, it remains intact. So, in principle, after this reaction is over, you will get a 50 50 mixture of, one case you get this product, which is nothing but this one, and 50 percent of this slow reacting enantiomer, slow reacting enantiomer ok. So, this is called kinetic resolution.

Because, there is a huge kinetic rate differences between these 2 enantiomers now what causes this huge kinetic rate differences? Now in, particularly, this kind of kinetic resolution, as the compounds are racemic, and both the compounds are having different stereo orientation, in the stereo racemic center. So, you basically need to create a chiral environment, you, need to create a chiral environment through a chiral catalyst, or something like that so, which I called, chiral atmosphere or chiral environment.

Now, this chiral environment, might be created through a chiral reagent, or through a chiral catalyst. So, that, 2 enantiomers are having some kind of interaction, through a ionic interaction, or to a non covalent interaction so that, it can reacts to this chiral entity, and then, one enantiomer reacts faster, and if the slow reacting enantiomer probably does not intact with the, or does not interact with the chiral environment, it probably would not be reactive.

So, the essential criteria these, you have to fix a, chiral atmosphere, or chiral environment, through which you have a kind of recognition.

That one of the enantiomer is recognized, or interacted through some, non covalent or ionic interaction, or kind of a small charged, charged kind of interaction. So that, one enantiomer effectively interacts with this chiral atmosphere, and then it reacts, the slowly acting enantiomer does not react another condition. So, that will give ah, you a very good condition of kinetic resolution.

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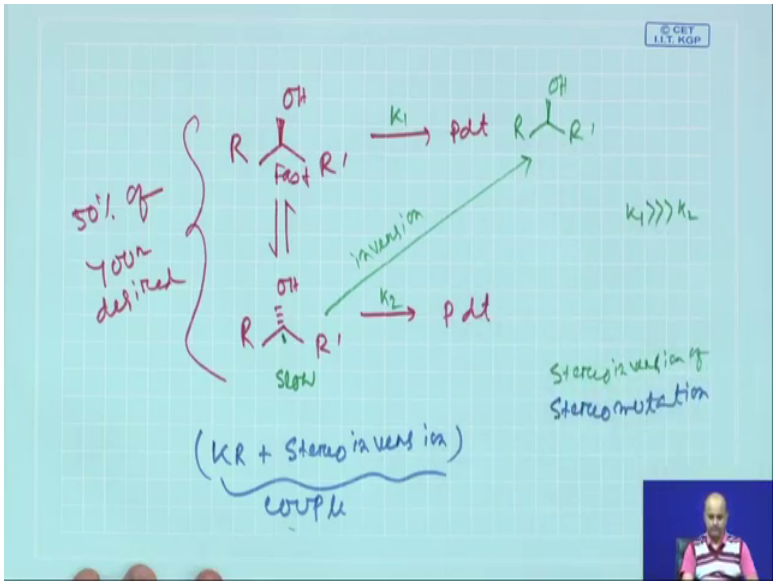

So, this is the kinetic resolution case now, you do have a similar kind of scenario, if you now draw the same equilibrium, for the kinetic resolution, to explain certain other phenomenas, now we say kinetic resolution is very useful, but only drawback is, you will basically get 50 percent of your desired product, 50 percent of your desired product, means that, if your desired product is the fast acting enantiomer you get 50%.

If the second reacting, or slow reacting enantiomer, is the desired product, you get 50%. So, 50 percent product has to be thrown out. So, this is your kinetic resolution, which we explained in the earlier slide. Now I am saying, after the 50 percent fast reacting enantiomer, which basically reacts, and this slope is K 1 and K 2. So, then the kinetic resolution K 1 is greater than K 2.

Now, if we I am saying that, your 50 percent desired product has to be thrown. So, what you can do?

Now, if there is a possibility that, slow reacting enantiomer, can be converted to the fast reacting enantiomer, through some stereo inversion, then it is possible, that you get your 50%, particular product, starting from this, fast reacting enantiomer, ok, that is done.

Then, the slow reacting enantiomer, if you can do some inversion, at this stereogenic center, this is also possible. Now this particular point, we called, stereo inversion, inversion, or stereo mutation, mutation means, you basically, mutate is that terminology

often used in the biology, but stereo mutation means changing, it is stereo center has been changed.

So, sometimes kinetic resolution plus stereo inversion, is coupled together, inversion is coupled, if you can couple this 2 path way together, you have a very good pathway, to get one enantiomer, exclusively. This all depends, which, which kind of a compound you are dealing with. Now next we will be talking about, something else, which is named as D K R.

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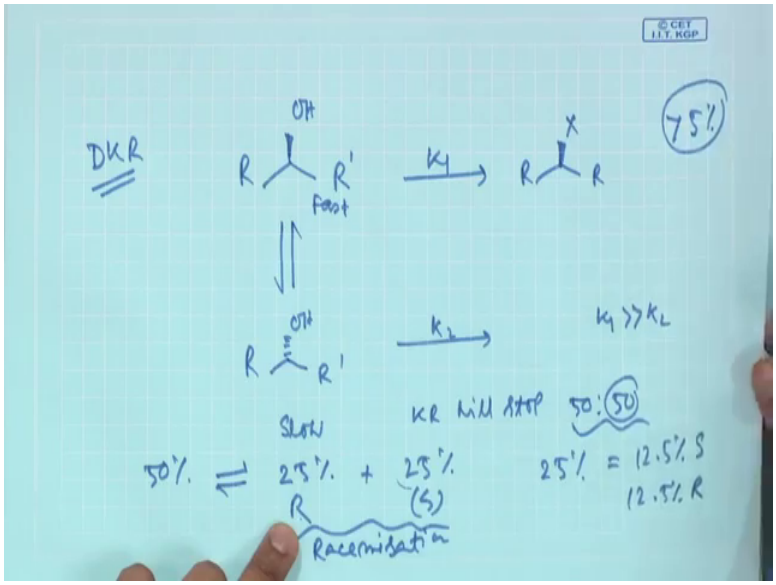

Now, we will again draw the same, same kinetic equation. And we are saying that, this, D K R, this is the process; the idea has to be essentially taken from this kinetic resolution.

Which is, this is fast reacting, and this is slow reacting. Now I am saying that, this fast reacting enantiomer react, there is absolutely no doubt,, it reacts to give you the product.

Now, slow reacting enantiomer remains in the reaction mixture. Now, if there is a possibility that, slow reacting enantiomer can instantly so, your kinetic revolution is taking place, K 1 K 2, we said K 1 much greater than K 2. So, kinetic resolution is stopped, K R will stop, when all the fast reacting enantiomer reacts. So, 50 50 it will stop.

Now, the slow reacting enantiomer is, 50 percent is there. Now is it possible that, a 50 percent slow reacting enantiomer, you can again convert it to 25 percent R and 25 percent of S, means that, you will be trying to do a Racemisation. Now, why this is helpful? Now, if your rasemisation, you can coupled with kinetic resolution, then the 50 percent slow reaction enantiomer will again give, 25 percent R 25 percent S.

Now, this 25 percent R, which is the fast acting enantiomer, now again undergo kinetic resolution, to give you this product. So, in principle now 50 percent plus 25 percent 75 percent have been reacted, you have 25 percent of slow reacting enantiomer, again this 25 percent you convert it to 12.5 percent of S and 12.5 percent of R, then again mix your this kinetic resolution is triggered it up. So, you have to have a system.

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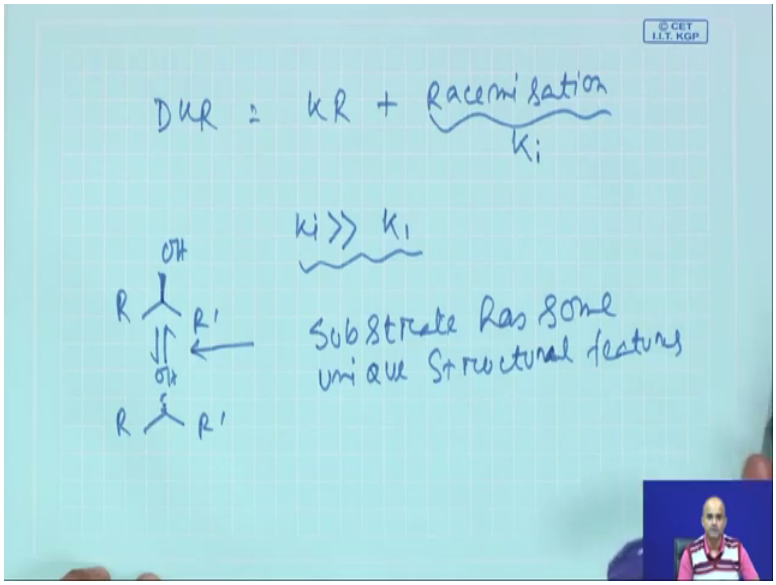

So, D K R basically consists of, a kinetic resolution, coupled to, with a Racemisation protocol.

And eventually, the Racemisation rate constant must be very high, the kinetic. So, the Racemisation rate constant, say I say K i. So, K i must be very high, than the rate constant of the faster enantiomer, means that, it, there will be always a dynamic equilibrium, there will be always a dynamic equilibrium between the, slow reacting enantiomer and the fast reacting enantiomer, there will be always a dynamic equilibrium.

Now, this dynamic equilibrium ah, you can basically do it chemically, you can do it enjoymetically, you can do it by different way. And it will be quite interesting, if your substrate, substrate has some unique structural features, has some unique structural features so that, the substrate itself can undergo a, very efficient decay reaction. Now, I will show you only one example.

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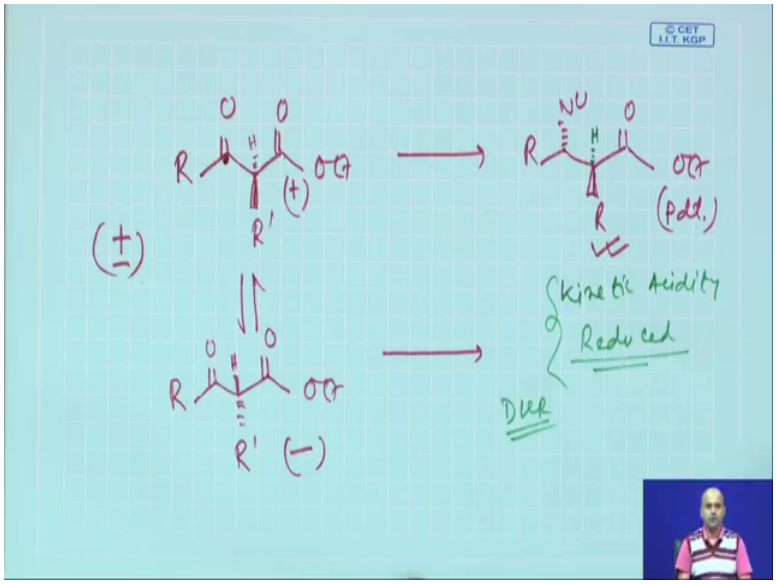

This particular example is very important. I am giving you a, substrate which is basically alpha substituted beta keto ester. Now this substrate, if you see their structure, I am saying that, these 2 enantiomer is a dynamic equilibrium. Now why? This substrate is having, extremely acidic kinetic hydrogen. So, in reality ah, probably you just need to keep those substrates, but they will be epimerized instantly, because the epimerization is driven by this high kinetic acidity of this compound.

So, now if you take a racemic mixture of both this compound, plus minus, and you are saying that, the, in our chiral environment only plus isomer reacts. So, this is the plus isomer, this is minus isomer. Now, I am saying that, plus isomer reacts to this carbonyl

group, now if this compound is basically a pro chiral compound. So, probably this compound gives a particular nucleophilic addition, in this way.

Because this compound is a pro chiral so, it is having 2 phase, re phase, psi phase, the nucleophile conduct from psi phase or re phase, I assume that nucleophile attacks from a not particularly one phase. So, basically have, only this product ok. Now I am saying that, if fast isomer reacts faster, what the slow isomer is doing? Ok. Now your dynamic kinetic resolution, or the Racemisation will come into picture. This slow reacting enantiomer, due to presence of this highly lavile kinetic acidic hydrogen, it will instantly again epimerize.

So, there will be, no matter, whether the fast reacting enantiomer reacts or not, that we always a steady supply of racemic mixture. So, one of the slow reacting enantiomer, again a epimerizes back, the fast reacting enantiomer then reacts, slow reacting again epimerize reacts. So, the reaction will continue, till you get the final product. Now the final product, now you see, the epimerization has to be suppressed, because the kinetic acidity has been now substantially reduced.

You earlierly having 2 carbonyl, which is extremely acidic, now one of the carbonyl has been functionally, inter converted to a, another functional group. So, now, the kinetic acidity has been reduced, kinetic acidity of this product, has been now reduced. So, this is a very classic example of D K R. Now, basically we are talking about the proof of concept.

We are not giving you, any example ah. So, now, we will be trying to discuss the similar kind of strategies say, or other explanation, will give you a pure case studies of kinetic resolution strategies, that how kinetic resolution was done in the lab, lab scale, and how you can separate the 2 enantiomers.

And then, basically proceed to a valuable intermediate, or valuable enantiomeric intermediate, in a stereo selective fashion. So, we will continue discussing on these topics in the next class, till then good bye.