Metals in Biology
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Lecture - 18
Iron catalyzed oxidation of unactivated sp3 C-H bond-Part II

Hey, welcome back. So, in the last class we were trying to discuss the iron oxo chemistry right, some of the fascinating hydroxylation chemistry. In today's class we will continue on that ok, I think you have got the reactivity pattern correct and that is if you have tertiary carbon hydrogen bond and you have a iron oxo high valent intermediate such as iron V oxo intermediate, you are going to get it reacted very efficiently.

Perhaps, selectively if you have a secondary and a primary C-H bond. If you do not have a primary C-H bond or secondary C-H bond of course, tertiary will still react, but if you do not have a tertiary C-H bond, then the secondary will react; if you do not have tertiary and secondary, then the primary carbon hydrogen will react. So, essentially what it tells you is this reactive iron oxo intermediates are very effective.

And one of the therefore, challenge is to make this reaction selective. Selectivity with respect to a given organic substrate, where one and particularly one carbon hydrogen bond is getting let us say hydroxylated that is going to be a quite big challenge. As you have seen, there could be a number of guiding principle which is responsible for the selectivity and if this guiding principle are strong enough, perhaps we are going to get a good selectivity in this substrate.

Of course, the ligand design, catalyst design, overall reactivity pattern will have a quite a lot of effect by the ligand, but then most importantly the reaction condition has to be suitable also to give the selectivity. Let us look at the suitable ligand metal complex that can give these reactive intermediate quite efficiently and also selectively this reaction can be done.

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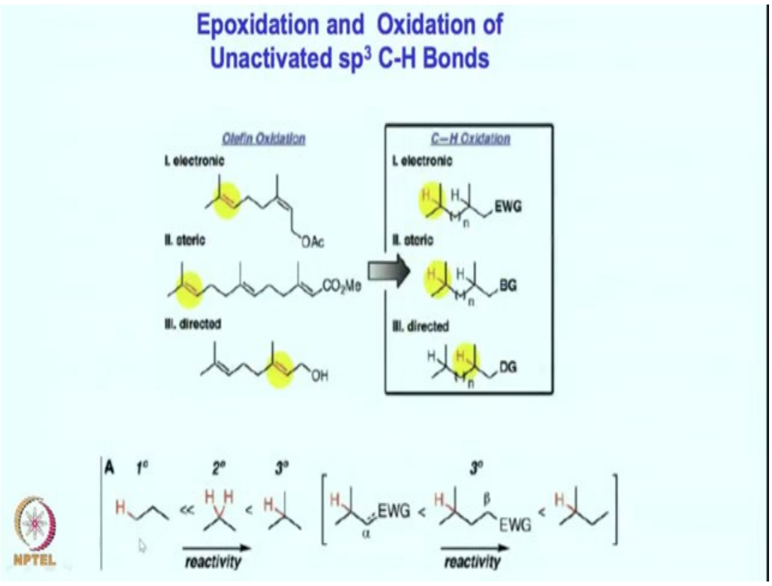

Epoxidation and Oxidation of Unactivated sp^3 C-H Bonds

So, once again remember tertiary is most reactive then secondary, then primary of course, electron withdrawing deactivates the whole thing, this is quite similar to what is shown in the epoxidation chemistry right.

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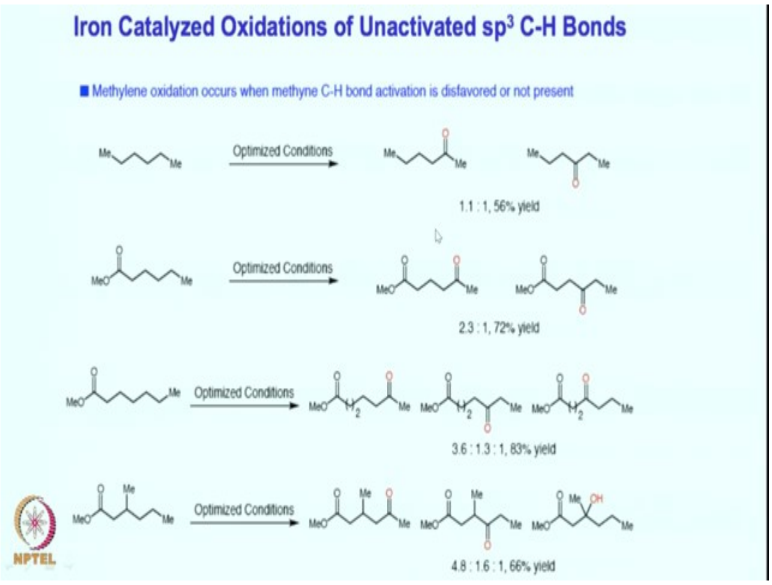

Iron Catalyzed Oxidations of Unactivated sp^3 C-H Bonds

- Methylene oxidation occurs when methyne C-H bond activation is disfavored or not present

Let us look at. Now, in iron catalyzed oxidations of unactivated sp3 C-H bond, we will see many different type of carbon hydrogen bond. For example over here, you perhaps immediately noticed that this is a primary sp3 C-H bond this is another primary sp3 C-H bond. These are sp3 C-H bond all, but these are secondary 1, 2, 3, 4. Four secondary sp3

C-H bonds are present, two primary aliphatic sp3 C-H bonds are present, these are primary, these are secondary.

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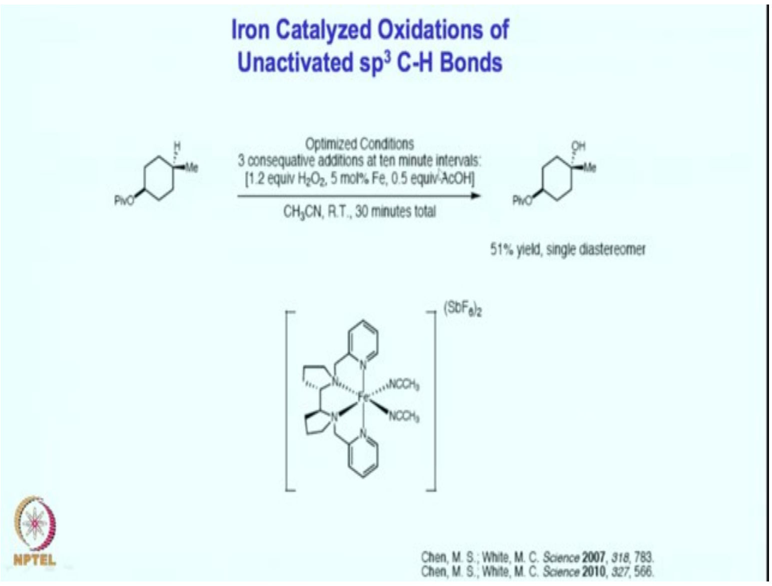

Iron Catalyzed Oxidations of Unactivated sp^3 C-H Bonds

Optimized Conditions
3 consequative additions at ten minute intervals:
[1.2 equiv H_2O_2, 5 mol% Fe, 0.5 equiv AcOH]
CH_3CN, R.T., 30 minutes total

51% yield, single diastereomer

Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783.
Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566.

Now, if you have reacted with that intermediate iron oxo; do you remember that species let me get back, this is the ligand iron complex if you are reacting it with hydrogen peroxide and acetic acid, you are going to get the oxo carboxylate bridged intermediate, let us remind you one more time.

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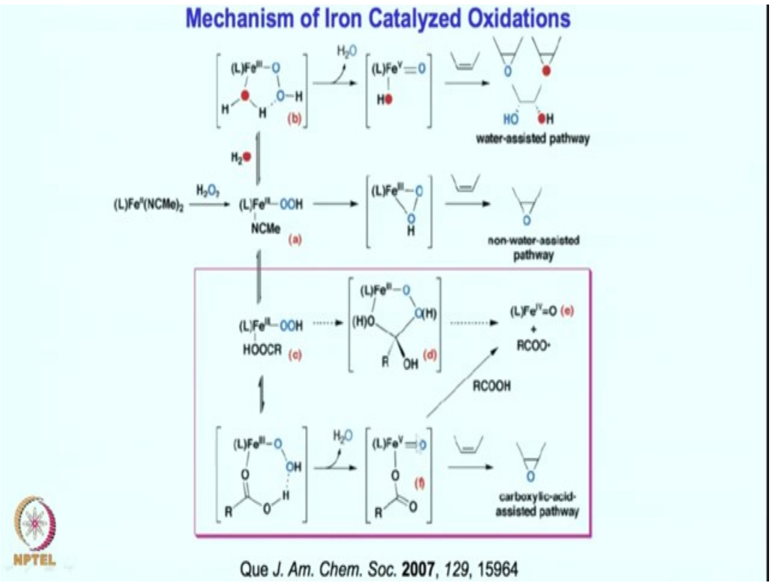

Mechanism of Iron Catalyzed Oxidations

Que *J. Am. Chem. Soc.* **2007**, *129*, 15964

This is the oxo carboxylate bridged intermediate, this intermediate is the one which is facilitating the hydroxylation chemistry of the organic substrate. Let us go back to the organic substrate, this is the reactive intermediate, ligand is the one we have shown, let us go back once again, this is the ligand, this is the iron center oxo carboxylato chemistry we are trying to discuss.

Now, if you see there is not much difference between this center and that center, these are equivalent right. So, this is a primary center, this is not going to be too much reactive; these are secondary center, both of them are going to be equally perhaps reactive, almost equally reactive; this is little bit terminal position, this is internal position, statically this one is less hindered therefore, selectively this position is going to be reacted a little bit more, but again there is almost nothing differentiating between these two center.

You get 1.1:1 selectivity for these product verses that one, so essentially both this center are equally reactive. If you are wondering why not hydroxylated product, why a ketone is forming, because once the hydroxylated product is form, the alcohol secondary alcohol that is way too reactive. Stabilizing such a secondary alcohol is very difficult, you will see that immediately that secondary alcohol will react with another equivalent of the catalyst and can give rise to the ketone.

So, if there is a possibility of ketone or aldehyde formation, it will not stop in terms of the hydroxylated product, it will go on to form the ketone product right all that is fine. So, there is no reaction almost very little or no reaction at this terminal center selectively this one is getting reacted, but equally this one is also reactive right, that is what you get.

Now, let us look at another substrate this is a little bit complex substrate, I would say very complex substrate compared to this one right you agree, I hope so. You have seen that there is a electron withdrawing group right, this is a carboxylate. Now, this is going to be very deactivated, this is not going to give any product perhaps; this is also going to be deactivated, this is somewhat deactivated, this is less deactivated, this is having very less effect, but this is a primary center primary, these are secondary center.

As you have seen in the last slide, secondary is more reactive than primary these three centers or these two centers in particular are very much deactivated by this. These are not going to give too much of the hydroxylation product. In this case, ketone product, oxygenation product, this is between going to be these two center as you see that this is far away from there this is going to be the major product and that is what been seen that are right next to it which is closer to this one is also reactive, because the electron withdrawing ability is not good enough to reach up to this third carbon center. So, we are still going to get decent amount of this product formation.

The selectivity in particular therefore, is going to be nearly 2.3:1, this is the major product. I hope you got it why from this compound oxygenation chemistry with these iron oxo carboxylate species, this is the most reactive position. I will repeat one more once more, this is primary center not too much reactive compared to secondary.

Now, among different four secondary center this is the farthest away from the electron withdrawing group therefore, this reacts mostly. So, the electron richness is highest over here in this whole substrate and that is where this gives the major product. This is the second highest electron rich carbon hydrogen center, it gives you the other product.

Now, what about increasing the linker length or the aliphatic substrate length as one would expect that you know the sp3 C-H center, which is secondary and further away from this electron withdrawing groups such as this one, it can be reacted at this center fantastic right. Selectively, you see the selectivity is 3.6, then it is going to be that center, then that center shown. This is most reactive, because this is far away from the electron withdrawing group.

This is a primary center, not too much question of reacting it right now. So, these are the secondary center if you have a suitable catalyst with you the iron I oxo carboxylato species, it will end up reacting at this center selectively, selectivity is quite good. Of course, this is not too far behind, this is far from the electron withdrawing group compared to this one this is not too much reactive and therefore, the reactivity is 3.6:1.3 and the next center is also going to give you the product, as you see that these all these three centers are little far from this electron withdrawing group.

So, its the electronic factor that is biasing the selectivity, where there is no biasness present there is selectivity is almost nothing right 1:1 or 1.1:1 the moment we introduce an electron withdrawing group, the substrate C-H hydroxylation chemistry is going to be quite exciting and simple I would say and this is going to be very selective.

Over here, we you have seen that this substrate is going to be quite interesting and giving rise to the exciting product in terms of selectivity right. Well, as you have seen that this substrate is quite interesting it gives three products, but obviously this is going to be the terminal one. The terminal sp3 C-H with the secondary center is going to be the most reactive.

Now, you might be thinking what about a tertiary center. So, far there is no tertiary center in these three substrate. If you have introduced a tertiary center over there selectively at this position, well this is still going to be very close to this electron withdrawing center right. So, this is deactivated this is also significantly deactivated, although this is a tertiary center; one may be thinking that selectively this position is going to be hydroxylated that is not going to be the case. This electron withdrawing nature of this deactivates even a secondary C-H center and a tertiary C-H center if it is close to it.

And then still I would say, this is little more reactive and this is the one which is most reactive. As you see, this is the major product at this position where hydroxylation and further oxidation takes place to give you the ketone from there on the next position, next to that is this one which is away from the ester is giving the next major product and subsequently of course, this hydroxylation product happens since it is a tertiary center. At this position, this hydroxylation product was not too much forming, but over here since it is a tertiary center, still it is bit reactive and it gives you 4.8:1.6:1 product.

So, once again if you look at this substrate, there is primary center, primary center; these are not that very reactive, these are secondary center; 1, 2, 3 secondary centers. This is a tertiary center, one could expect that this should be very reactive, but that is not the case ok. This is not reacting over secondary, because this is close to an electron biasing or withdrawing substrate. Although still it is reactive, but the most reactive one is the one over here this reacts mostly, then that one then this one and this can be explained by this electron withdrawing nature of this.

But despite having this electron withdrawing substrate, you can still see that this tertiary C-H is reacting somewhat to give you the product. Hydroxylated product in this case, because there is no question of forming a ketone product; ketone product would have formed if there was another H available for in other cases, these are not ketone product.

So, I hope you understand now that it is indeed possible to predict the selectivity in the aliphatic substrate in terms of their hydroxylation. Of course, this is not going to be always very simple, because it will be controlled by the biasness such as electron withdrawing group or the sterical demanding group, present in the molecule as well as how effectively those biasness can overcome, the inherent reactivity pattern of tertiary versus secondary versus primary. So, in a given substrate if everything is defined of course, everything is defined, then we will be able to see that we can perhaps predict what is going to happen.

Let us see some more examples with some other biasing element. Here we have electron withdrawing group, as well as tertiary secondary and primary bias. Let us look at some more well, if you do not have any other option, these are I we did not have the aliphatic substrate drawing.

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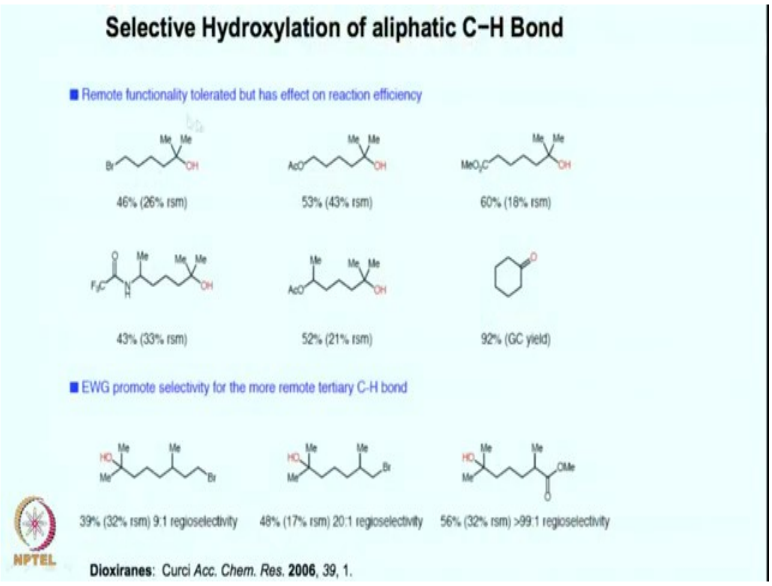

Selective Hydroxylation of aliphatic C–H Bond

- Remote functionality tolerated but has effect on reaction efficiency

46% (26% rsm)

53% (43% rsm)

60% (18% rsm)

43% (33% rsm)

52% (21% rsm)

92% (GC yield)

- EWG promote selectivity for the more remote tertiary C-H bond

39% (32% rsm) 9:1 regioselectivity

48% (17% rsm) 20:1 regioselectivity

56% (32% rsm) >99:1 regioselectivity

Dioxiranes: Curci *Acc. Chem. Res.* **2006**, 39, 1.

These are directly product drawing. So, if you imagine that there was the C-H bond over here that was tertiary that is getting selectively hydroxylated, you have aliphatic all other secondary C-H bond, sp3 C-H bond these are not that very reactive compared to this tertiary C-H bond which is now getting hydroxylated selectively.

Of course, you know you cannot prevent completely any other product formation. Some amount of some other product formation will happen in all the examples, but the we are mainly trying to discuss about the major product formation and as you see this tertiary C-

H bond is getting hydroxylated majorly to give you this product only. This center which you would have give otherwise the ketone product is not getting reacted too much. And of course, these are electron withdrawing as well, electron deficient as well, little bit by this bromine group, but still this could have been perhaps very reactive, but it is not too much compared to this hydroxyl.

Now, if you look at the another substrate once again you have a clear tertiary C-H bond, it is getting hydroxylated despite having an electron withdrawing group. You have an another electron withdrawing group still, you see that selectively hydroxylation is happening at this center.

Here the competition is between the tertiary C-H and the secondary C-H. Secondary C-H anywhere does not have much chance over tertiary and on top of that these are little bit biased electron withdrawing group is attached. So, things are going to be little bit electron deficient anyway.

So, tertiary selectively is working if you have a substrate like here, where cyclohexane is taken as a substrate. There is no question of any selectivity, because all the 6 carbon hydrogen positions are similar. So, one of them reacts any one of them react and once hydroxylated cyclohexanol; cyclohexanol is form, then it can further oxidized to give you cyclohexanone.

Here is another substrate, you have a tertiary sp3 C-H center and another tertiary sp3 C-H center, all this is electron withdrawing group. So, selectively this is going to be hydroxylated. So, this is very very reactive compared to that one, this secondary one does not have much of a choice, so we get predominantly this product.

If you are looking at this one, this is once again go to be similar; this is a tertiary center that is a tertiary center if you have H over there, and these two center will compete with each other and this one will be getting near exclusively reacted, because this is next to an electron withdrawing group or biasness is there. These are the secondary sites once again tertiary wins and we have this product as the major product.

Now, if you are looking at other substrates such as this you have a tertiary C-H over there, so which is getting hydroxylated. So, tertiary C-H over here, tertiary C-H over there, this center is next to an electron withdrawing group therefore, this is not really that much reactive, selectively this one is getting reacted all others are secondary C-H including this one. So, these are not going to be that much decay reactive, a tertiary C-H, a tertiary C-H selectively this one is going to be reactive.

Over here, if you see that this is a tertiary C-H and this is a tertiary C-H and we are going to get predominantly this as the major product over here, just like over here ok, but as you have seen here this is the major product minor product is at the center right. Here this is the major product, minor product is at that center, but this bromine was very far relatively a little bit far from this center two carbon away, this is one carbon away.

So, this is much more electron deficient compared to this one right. So, this is relatively electron rich compared to this center over here. Therefore, the selectivity is not that very great this is 9:1, this is great; but you know here since it is furthermore deactivated. So, selectivity factor is much better here this is 20:1, this is much more deactivated compared to there. So, selectivity is pretty good.

If you are looking at further biasing or different type of biasing, you can see these are very very electron withdrawing group or very much electron withdrawing group compared to this bromo and no wonder almost very little product is forming over there, selectively or near exclusively this is the product that is getting formed in this case. So, quite amazing right.

So, you can essentially predict where these hydroxylation chemistry is going to happen in the organic substrate. These certainly will have a lot of implication in terms of synthesizing hydroxylated product, once again there are synthetic methodologies not many available or if any of course, oxidant chemistry is one of the chemistry one can look at, but otherwise there is no synthetic toolbox, no tool in that synthetic toolbox that can hydroxylate this sort of aliphatic substrate, these are going to be very challenging substrate.

Of course there are many limitation of the method, we did not mention these are not too much a catalytic reaction. I would say rather this is a stoichiometric reaction and it is not like other products are not forming, they are forming, but minor amount. So, isolating this compound and purifying is going to be very challenging. It is going to have mixture of product, but there is a clear cut message that one of the product would be the major product.

Now, if you want to get that major product in large quantity well, you have to really bias the substrate. If you have unbiased substrate, there is no way you can prevent it; if you are able to bias the substrate completely, reaction is going to be great. So, more complicated the substrate is going to be that means, more biasness would be there, easy at the reaction is that is quite interesting.

Usually, you know people think on the other way right, more complicated the substrate is reaction will be complicated, but here it is just the opposite of it. More biasness you can bring, more complex substrate you can bring, perhaps you have an opportunity. Perhaps of course, perhaps you have an opportunity to get a selective product, maybe only one product well that is never going to be easy no matter how the literature is, but it is going to be very tricky to get only one product or exclusive product or near exclusive product, other products are going to be there and these reactions are not too much catalytic.

Once again no matter what is what we see, it is not going to be too much of a of a selectivity. Of course, there is a selectivity pattern, selectivity since these reactions are selective, but the selectivity factors are not going to be very simple and it is not like other products will not form. Reactions are not too much catalytic selectivity is problematic, but can be somewhat guided, some guiding principle can come up.

Let us look at some more substrate, I hope this is similar you are finding similar to what you see in the epoxidation chemistry right. This is I would say quite interesting, because such sort of predictable selective chemistry is difficult to get. Once again, you have to have it with a pinch of salt, its not like 100 percent crystal clear clean reaction; this is going to be mixture of product formation, from there you have to fish out the major product right. Let us look at some more example.

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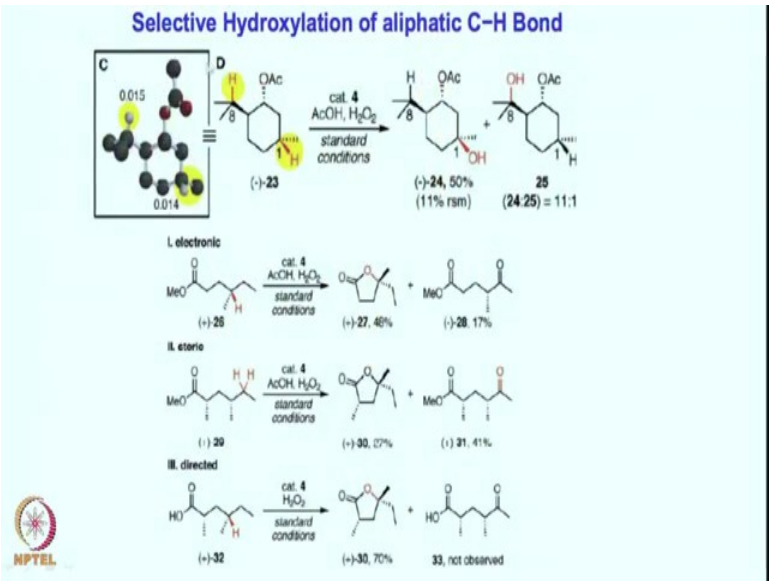

Selective Hydroxylation of aliphatic C–H Bond

Well, in this slide what you see is the one substrate over here, you have a tertiary C-H bond, you have another tertiary C-H bond, these are two tertiary C-H bonds; of course, there is another one over here. So, this is a tertiary C-H bond that is a tertiary C-H bond and that is a tertiary C-H bond, all others are secondary.

Three tertiary C-H bonds 1, 2 and 3 this is right next to OAc, electron withdrawing group this is no way going to be reactive, this center and that center can undergo competition. These are secondary center, therefore those are not going to be reactive these secondary centers; these are primary centers that is also not going to be reactive, these three are primary centers not going to be reactive.

So, the reactivity or the competition for reactivity is between these two tertiary center, because tertiary is more reactive than secondary than primary. Now, whether this is going to react or that is going to react ok, as you can see by this modelling or as such that there is a steric crowding involved in these cases.

And this is statically hindered site compared to this one and overall then we see that this is the one, which is going to be the major product and the ratio is 11:1. This is going to be the major product, this is going to be the minor product, nonetheless these two tertiary centers are the one which is reacting others are not too much reactive that is fantastic.

So, therefore we have seen that we can predict the reactivity. Let us look at some other examples, over here what you have, you have a bunch of 1, 2, 3 sp3 secondary center, this is a primary center, but this is as you know this is going to be electron withdrawing group. And therefore, these are deactivated anyway they are secondary, this is the only tertiary C-H bond that is going to be reactive over here.

And this is little bit deactivated, but not too much you end up hydroxylating this position these are secondary not much reactive, this is primary not much reactive, but this carboxylate or ester group is close to this. Therefore still it has an opportunity to react, but it is little bit deactivated. So, hydroxylation will happen of course, once hydroxylation happen, it can cyclize to give you this ester or cyclic ester product and subsequently, you can since this is little bit deactivated you are also going to see some reactivity at this center and that is what is happened.

Although this is a secondary site, still it is reacting these are completely deactivated by this ester, this is primary. So, this is going to be the next product major product is going to be this and the minor product is going to be this, as you can see selectivity is not that great despite this being the tertiary C-H.

On the other hand, if you are having this substrate organic substrate over here, which is nothing but introducing another substituent over there. So, two dye methyl groups are now there into one organic substrate this is a tertiary center, this is a tertiary center, this is next to it, so not too much reactive and due to this reason that this we don’t get any product of course, this can react, but what you see that these are one these are going to be sterically crowding and these sp3 C-H hydroxylation product formation is going to be challenging right.

So, 1,3 interaction would be there which is going to challenge the activation of the C-H bond due to the steric hindrance arising from this one anyway this electron withdrawing effect is there. So, combining the steric effect as well as electron withdrawing ability of this moiety render this center not to reactive although these forms, but the major product although two tertiary centres are there still it is the secondary site, in this case that is the major product.

So, this product which were the minor product by introducing a steric group we can make it as a major product that you can see it is completely steric and electronic driven process electronic properties driven process in presence of two tertiary bond, it is possible to even react a secondary center, but once again these are a bias substrate, you have to take a complex substrate. These are complex substrate, more complex the substrate is reactivity pattern becomes more predictable that is what it is in this case, this becomes the major product.

On the other hand, if you have still this substrate, you want to remove this ester group, make it acid hydrolysis. This acid is now actually capable to override all those problem that we were discussing and it can very easily go on to form this 5 membered ring. All the steric problem disappears electron biasness, disappears this directing group directs it right over here to form a preferred intermediate like this upon hydroxylation chemistry.

So, we will come back to this selectivity pattern. In the next class with few more examples, I hope you are excited to see these subtle things that is affecting the reactivity pattern, these are very very minor thing, but are very effective as you can see right so that is quite amazing, all right. We will come back soon on discussing the reactivity pattern in the iron hydroxylation chemistry.

Thank you very much, take care.