Metals in Biology
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Lecture - 19
Iron catalyzed oxidation of unactivated sp3 C-H bond Part III

Hello, welcome back. So, we will discuss the iron oxo intermediated substrate hydroxylation chemistry and the reactivity pattern, that we were continuing from the last class. Well I hope by now you have get the got the sense that this reactivity pattern is going to be predictable, we can predict. Of course, the catalyst will play a key role in that business, but overall we have increasingly seeing that tertiary, secondary primary in this order the reactivity decreases and electron withdrawing group also decreases. The reactivity steric factors can modulate the reactivity further and a directing group can override all the bias that is present in the molecule and can direct at a position, where a 5 to 6 member ring formation might would be prefer.

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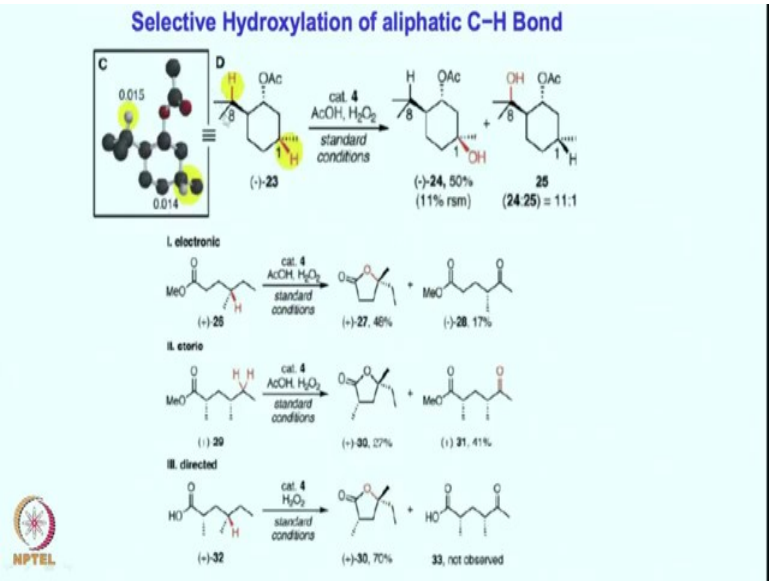

Let us go on and see some more example. In the last class, we have seen these compounds where selectively we have seen that this position is not the major product, but this is the major one giving the major product over here the highlighted positions are the one where C-H bond is getting hydroxylated. In cases where it is a secondary or

primary bond, then we get the ketone, in the cases where it is a tertiary we get the hydroxylated product.

Now, there are other controlling factors as well for which we are going to see the reactivity pattern and how they can influence the selectivity.

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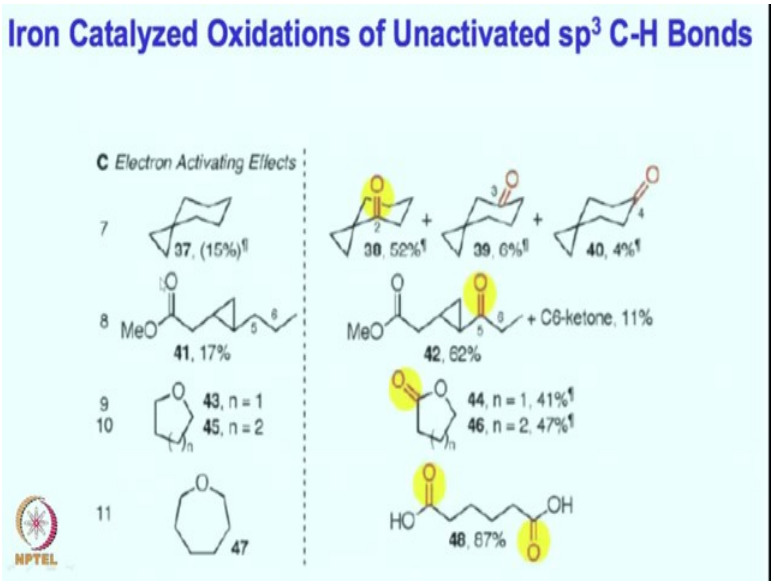

For instance, if you have these you know cyclohexane ring with cyclopropane attached with it, then in this molecule this you know this 3 center 3 membered ring is electron rich. That electron richness can be imparted in this case electron richness of the cyclopropane ring can be imparted on the alpha position of this cyclohexane ring.

So, at these positions it becomes much more reactive all of them are obviously, secondary center, but these and this position these are equivalent positions, these are becoming much more reactive compared to these other places. And therefore, selectively these positions these alpha positions are going to get hydroxylated. Since it is a secondary carbon center we get ketone upon hydroxylation and further oxidation. This is the major product obviously, there are going to be other products such as these and these are not so much of product formation from this starting material.

Well, we can we can bring this cyclopropane ring in another context some example like these species is quite exciting. I would say, as you can see for example, over here this cyclopropane ring can enrich this position alpha position and this position both the alpha

position or thus consequent position or these two position can be activated by this cyclopropane ring due to its electron richness, but this is next to an electron withdrawing group.

So, this is not going to be too much a reactive, this is the one which is going to be very reactive due to the presence of this cyclopropane ring and then subsequently these other product at C6 position will happen. In this case of course, this electron withdrawing group has effect in deactivating these bonds, but this is not too much close to the center therefore, still this is reactive and now further reactivity is enhanced by this cyclopropane ring, and selectively this position then can be hydroxylated up upon hydroxylation, it further undergo oxidation to give the ketone product.

If you are seeing this cyclo cyclopentane or cyclohexane THF type of ring pyran type of ring, you we will see that this alpha position once again the lone pair in this case of the oxygen atom can activate this position and this C-H bond activation becomes much easier due to presence of this lone pair. Essentially this lone pair can donate into the antibonding orbital of the C-H bond to eventually making this per more reactive compared to all other carbon hydrogen bond that is present into this cyclic molecule.

So, alpha 2 and oxygen atom having lone pair are going to be quite reactive and that is what we see over here. Similarly alpha 2, this oxygen that carbon centers are going to be reactive, both of them gets the ketone formation. So, the ester formation and the ester hydrolysis ring opening gives rise to this dicarboxylic acid product and this is the kind of major product and the only product that can form in these cases.

So, oxygen lone pair can activate the alpha position and the cyclopropane ring can also activate the alpha position this cyclopropane ring is also can activate the alpha position of this molecule, which are quite powerful I would say for this sort of selective functionalization reaction right. So, these are electron activating effects; these are activating, we have seen previously deactivating effect these are electron with activating effect.

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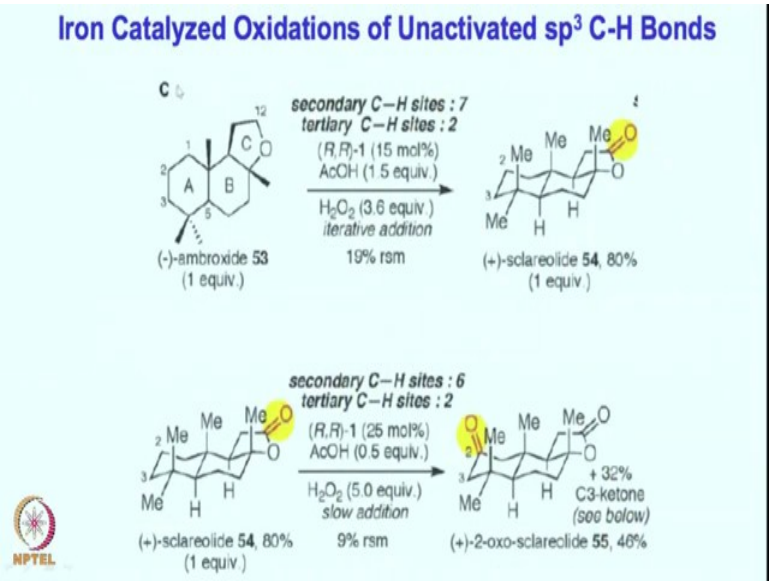

Now, we would like to see some of the natural products such or its analogs or complicated molecule. Can we predict the selectivity in this molecule? For instance over here you have diff, we have different types of carbon hydrogen bond, these are primary, primary, primary, primary, secondary, secondary, tertiary, primary sorry secondary, secondary, secondary and tertiary secondary, secondary primary right.

So, since this is an activating effect of course, these positions are in a bridged position not so, reactive sterically crowded also. So, this is not going to be easy to react these positions are too much available. So, in this sense since this is having an electron activating effect at the alpha position, this is the ring that gets activated and gives you the product selectively that one.

So, upon formation of this ester product cyclic ester product, we can take this major product or this product as a substrate once again. This is the same substrate over here now it is actually completely different ballgame right. It was activating in this case at the alpha position. So, therefore, alpha ketone formation is feasible, this is a secondary center that is why hydroxyl leads to the ketone product. But once it is esterified or once this cyclic ester here compound is form, this ring whole ring is deactivated. This deactivating effect can be also affecting this ring in its hydroxylation chemistry. So, this ring also gets deactivated in turn also

Now, overall we have this axial position available for hydroxylation. So, this ring gets deactivated due to this carbox this due to this ester moiety. Therefore, this is not really activating anything, it is deactivating this is deactivating itself as well as this ring this is the one which is relatively reactive these are also I would say deactivated its positions all these positions. So, the competition for hydroxylation is between this center that center and that center overall this is a primary centers. So, this is not in competition, these two centers are going to be most reactive in these cases right.

Now, selectively or majorly this product is giving as the key product, as you can see that upon hydroxylation and ketone formation, there is this strain can be removed from this 1,3 axial position right. In the cyclo hexane ring this is an axial methyl, this is an axial methyl, this axial C-H bond is under tremendous strain tremendous strain. So, once this 1,3 bicyclic on 3 strain can be removed once it is hydroxylated equatorial position and then subsequently oxidation is happening. So, this ketone formation which going to be the major product. Of course, this is not far behind as you can see that this is this is also forming in quite good amount 46 percent and 32 percent.

So, what we have seen in these two product or 2 compound that these are very complicated molecule or relatively complicated molecule I would say. These are natural product analogues and in this case, we have activating factor in once we have got this product this can then further be incorporated once again under the reaction condition and adding new catalyst amount.

These are once again not so, catalytic reaction, but in any case this can be deactivating the whole ring as well as this ring leaving these 3 position available for functionalization still this is deactivated to some extent, 2 and 3 are the ones where the possibly reaction can happen. 2 by reacting with 2 1 gains, the release of strain and therefore, this is turning out to be the major product and this position it is not really too much of a bias. So, if we cannot prevent the formation of the ketone product over here, because this is the major product next major product or subsequent product is going to be at this position and that is what we see over here right. Ok.

Let us see some more examples may be the final examples we have, as I think you are increasingly seeing more complicated the substrate is it is becoming much better or

easier to react right. Complicated substrates are easy to predict or relatively easier to predict where the reaction is going to be.

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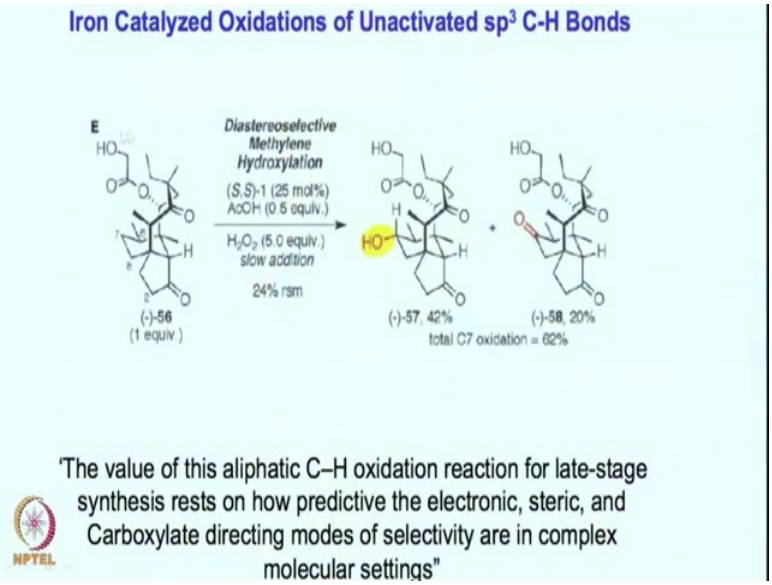

Now, this is a really a beautiful compound and very complex one

Now, this product natural product analogues, we can see that there are many carbon hydrogen bond that is present, we can leave out the primary ones right; primary ones primary secondary and we can focus on the secondary and the tertiary one ok.

Now, as you can see this is a ketone molecule, cyclic ketone now being electron withdrawing this ketone molecule will deactivate this whole ring significantly so, that any of the C-H bond that is present into this ring will not be reacting with this.

Now, the whole ring once it is deactivated, then we can also think of another ring over here this is also completely deactivated due to the presence of this ketone right. This ring as well as this whole ring is deactivated that leaves only this middle ring over here this cyclohexane ring over here that is left for activation, but despite having many different sp3 secondary centers, we can see that only selectively this is going to be giving the product and that is particularly due to the fact that this is more accessible C-H bond over here and since equatorial position will be getting oxidized first, because axial position approach will not be really feasible due to the sterically crowded atmosphere.

So, equatorial position get hydroxylated first and then subsequently, it can get oxidized to form the ketone. Although due to the steric strain what will happen, this even in this situation a alcohol a secondary alcohol can still remain as a secondary alcohol slowly only 20 percent of this product, it is giving the ketone formation. Essentially in absence of this steric crowding the secondary alcohol will not be stable, but under this special situation overall geometry and steric strain are such that that it can still remain as the hydroxyl.

So, in this complicated molecule you can see despite having many different types of carbon hydrogen bond that is present over there, selectively this is the product that is forming and this is the major one that is over there right. So, well I think what perhaps then terms where that this value of this aliphatic C-H oxidation reaction for late stage synthesis rests on how predictive the electronic steric and carboxylate directing modes of selectivity are in complex molecular setting right.

So, both the electronic properties steric properties and the directing ability will be the key for dictating the selectivity. It is not going to be one factor absolutely that is going to determine what is going to be the selectivity in this reactions, but overall we can expect that these reactions are going to be predictive or we can tell essentially where and how the selectivity pattern might would be. Well things still gets complicated, but overall this is a great guiding principle which tells us that more the more the complex the substrate becomes the better it is or easier it is for the substrates, for giving a selective product rather than multiple products.

Let us moving on; well essentially this understanding can be extrapolated to other functionalization as well specifically radical type of reaction mechanism whereas, let us say for example, halogenation reaction. If aliphatic halogenation catalysts exist, one can think of a similar type of reactivity might be observed during those cases as well right.

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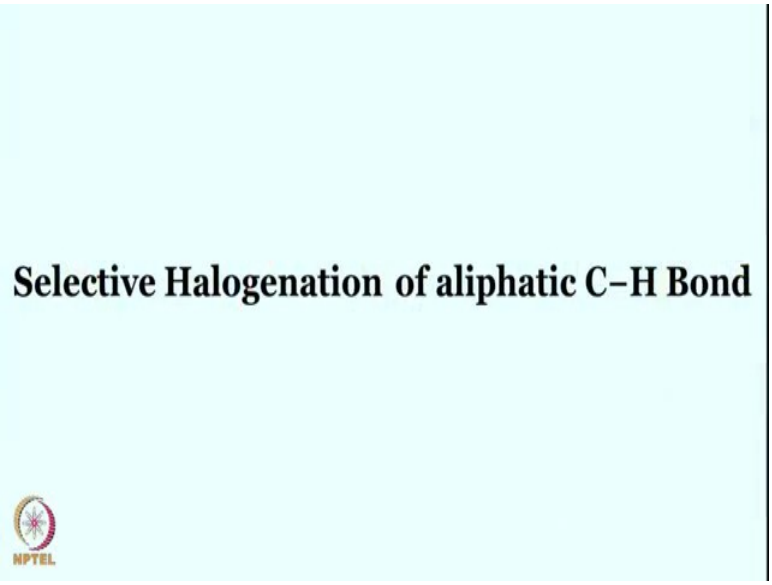

So, we will discuss very briefly selective halogenation of aliphatic C-H bond. These halogenation are quite prominent quite available in nature well this is a fascinating enzyme. We are seeing a very very special enzyme mechanism here.

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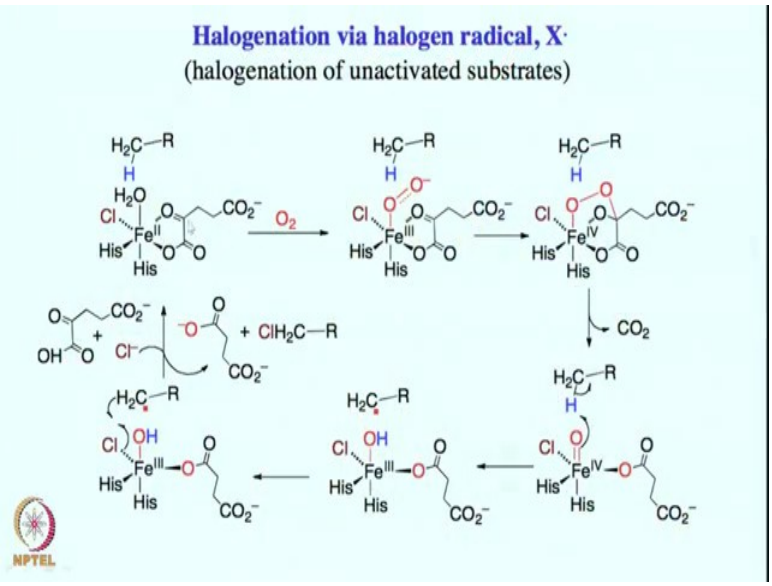

These are called beta ketoglutarate dependent halogenase, this is beta keto glutamic acid and this is the one what which is used as a substrate or the mediator for this chemistry.

Let us say in the active site of the enzyme in this alpha ketoglutarate dependent halogenase enzyme, we have two histidine and one halogen ok. If there are alpha

ketoglutarate dependent hydroxylases, where this would be a essentially a carboxylate unit. Now this sort of motive are called facial triad motive when you have carboxylate group over there.

Now, these two histidine and one chlorine over there. So, iron chloride complex is formed along with this beta ketoglutarate. Now this is a bidentate ligand. It binds with iron effectively. As you can see in the active site, this is the real active intermediate to start with and the substrate the aliphatic substrate is sitting right next to it.

It can react with oxygen to give you the iron III superoxo intermediate, which can then abstract hydrogen atom from this substrate or it in this case since this is an going to be an intermolecular reaction to activate this C-H bond. Intramolecular reactions are much more fascinated or much more common in these cases; exclusively it will attack at this ketocentre to give you this nice 6 membered ring, which is now ready for further cleavage to give the iron IV oxo species.

So, overall if you are following it properly, you will be able to see that it is going to be iron for oxo carboxylate intermediate ok. This is glutarate glutamic acid, now this as you can see this is ligated with this iron center and this iron oxo is now ready to activate this aliphatic substrate.

In this case both the chloride and oxo are sitting close to this, and more importantly the substrate is perhaps positioned closer to the chloride upon hydrogen atom abstraction CH2 radical gets generated, then it is a competition between the chloride and hydroxo the present studies shows that this radical will be generated very close to the chloride. And therefore, chloride can transfer selectively without forming any hydroxylation product whatsoever in this beta ketoglutarate dependent halogenase enzyme. So, chlorine gets transferred to this carbon radical to give the halogenated product without formation of any hydroxylation product.

Now, chloride comes in. So, in this case gives the product another chloride comes in and regenerate the whole catalytic cycle and this diacid goes out and the alpha ketoglutarate also comes in to complete the catalytic cycle this is going to be the succinic acid right succinate.

So, overall what you have seen that, a non heme iron center supported by alpha ketoglutarate and a halide appended with 2 histidine and water molecule undergo intramolecular reaction to form a high valent oxo halide intermediate which selectively promote hydrogen atom abstraction and chloride rebound to give a halogenated product ok. Now this short of reactions which can give halogenation products are quite interesting, but no synthetic chemistry studies are closer to this which can effectively form these halogenation product exclusively without forming the hydroxylated product.

So, following this mechanism or exactly this mechanism it is not much easy or it is not easy at all to form the selective halogenation product in synthetic setup so far not much model studies are successful in towards this direction. So, in absence of such suitable catalyst for promoting halogenation reaction, people tried to come up with synthetic complexes which perhaps can do the halogenation chemistry. Towards this one of the metal center that is turning out to be quite efficient. Of course, that is manganese, this is not going to be the structural mimic. This is more of a activity mimic. So, instead of iron which is not really very successful or people are so far not very successful in following this chemistry synthetically in the laboratory, the manganese chemistry is trying out to be quite exciting.

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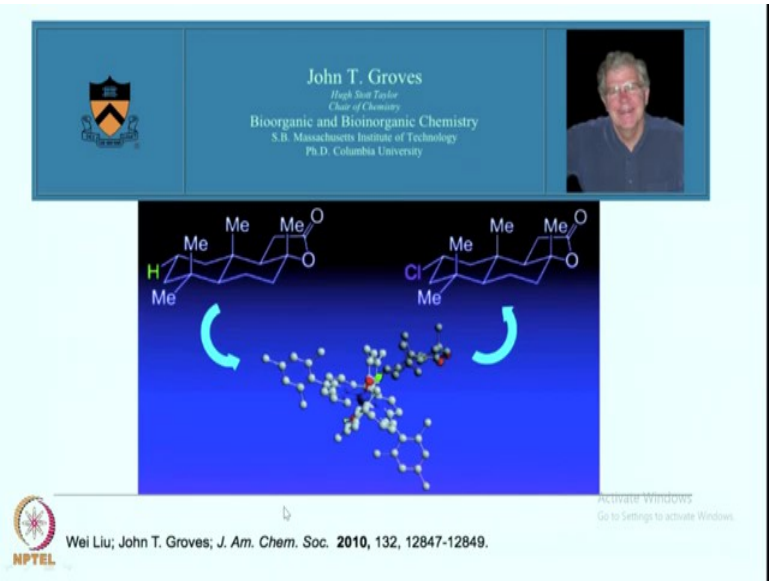

As you have seen that this molecule is or will go and give the halogenation product perhaps over there, similar to what one can see in the hydroxylation cases.

Here you we do not have any possibilities of formation of the ketone product or dichloride product and therefore, we are going to get a mono chloride product right over here.

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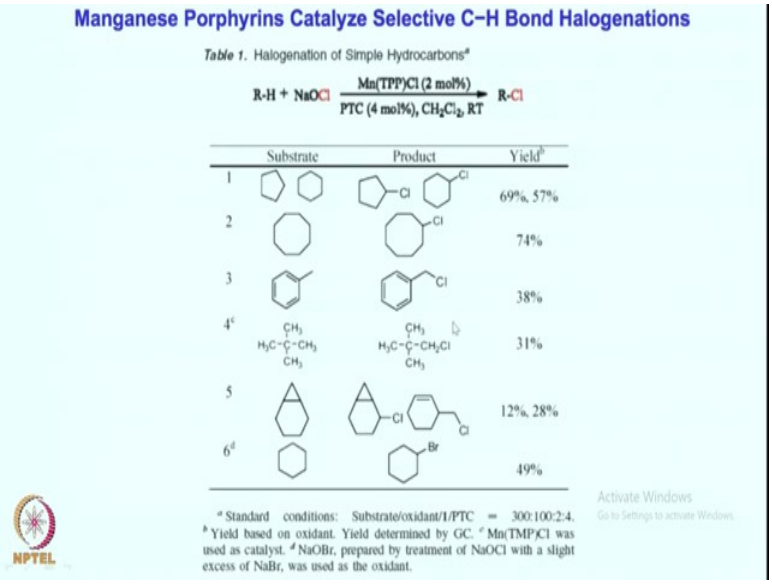

If a suitable manganese catalyst exists indeed there is since this is the work from J. T. Groves group, these are early work even the manganese TPP complex can do such chemistry with the formation of hypo hypo chloride, which is working in a electrophilic manner or the chlorine is really a chloride plus. In any case, these different aliphatic substrate can be halogenated by utilizing this manganese hypo chloride formation and subsequent OCl cleavage.

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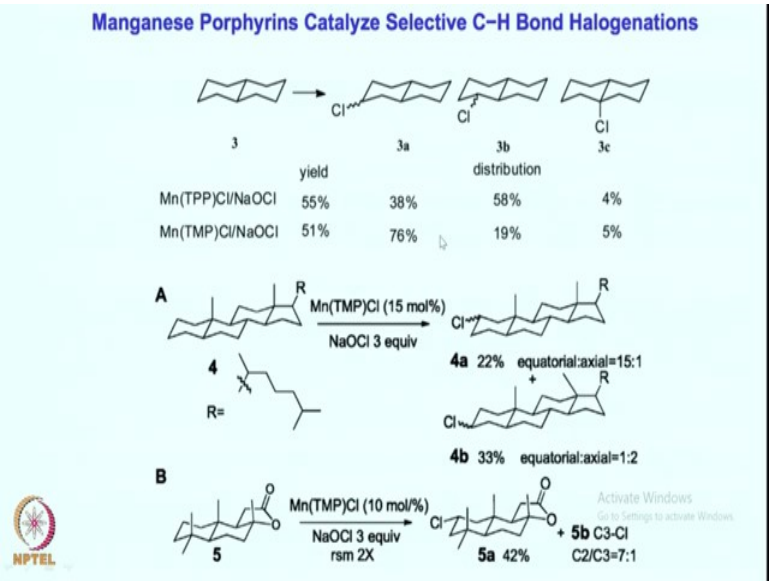

Over here if you look at in i the substrate in J. T. Groves case, where this manganese catalyst was used and then we see that the sodium hypochloride in presence of sodium hypochloride. This halogenation reactions are possible, but these equatorial product is going to be major product in some cases. In other cases, it is just the 3b that becomes the major product depending on the ligand, one can tune the reactivity of this compound ok.

Once again if you look at this compound over here, halogenation is not possible. In this ring, this is going to be the similar mechanism as we have seen or similar reactivity pattern, as we have seen in case of the hydroxylation. This rings gets deactivated and that makes also this ring somewhat deactivated, and these two are the available position where one can think of doing the reactions, and out of these this is the equatorial position which sterically least hindered that and is going to get reacted efficiently.

And that is what has happened and therefore, one can see that these are both the hydroxylation and halogenation reaction chemistry or the selectivity pattern predominantly follow that of what had been seen in the iron oxygen chemistry or iron high valent oxo intermediate.

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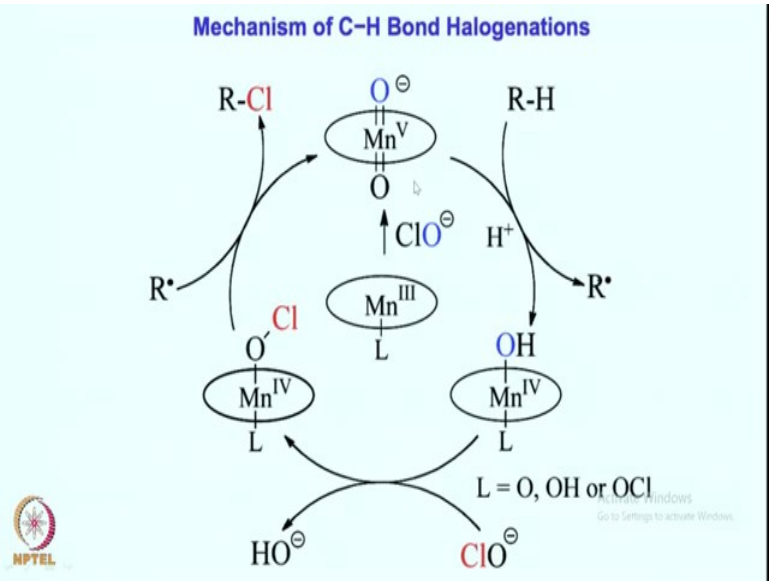

Here reaction mechanism is little bit different compared to what we have seen in terms of the iron chemistry right iron oxo species was forming. Here is a manganese bis oxo intermediate which can abstract hydrogen atom to give the R dot and the manganese hydroxo radical. This hydroxy radical can then react with a hypo chloride or this hydroxide can react with hypo chloride to give rise to an intermediate where manganese hypo chloride intermediate is formed. Subsequently a radical intermediate can be promoted from here because this R dot is already generated over there. This R dot and this chlorine or chlorine radical Cl dot from here will give (Refer Time: 25:27) into R-Cl and manganese gets oxidized to manganese IV.

So, I hope overall we were able to see that even in complicated organic aliphatic substrate where essentially there is no difference in reactivity. Still we can extract out some sort of reactivity pattern for these complexes. And these patterns are quite exciting; we have seen that tertiaries more reactive than secondary than primary electron withdrawing group can make or reverse the reactivity pattern, directing group also override all sorts of electronic and steric bias. There are activating factor such as cyclopropane ring and you have the oxygen ring in the oxygen atom inside the ring. These are the factors that can influence greatly, but overall more complex the substrate is better it is for us to predict easier it is for us to predict and this becomes very predictive; if the complex if the compound is complex.

If seemingly no differentiation is there among the different carbon centers, then the C-H bond hydroxylation or halogenation is going to complicated all in a sense that it will form multiple products. If one wishes to get them get selected product, the substrate has to be biased.

Of course, this is not a generalized solution, but this is quite exciting seeing that by seeing that there are not many solution available for doing even the halogenation of the aliphatic substrate or hydroxylation of the aliphatic substrate. Doing this chemistry selectively, it is going to have further implication of the catalyst development and overall implications of this methodology in complex molecular set of application and various other avenues. With this, we will come back to you in the next class. Till then keep studying. If there is any queries, let us know. See you.

Thank you very much.