Reagents in Organic Synthesis
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Lecture 32 - Sm and Yb based reagents in organic synthesis

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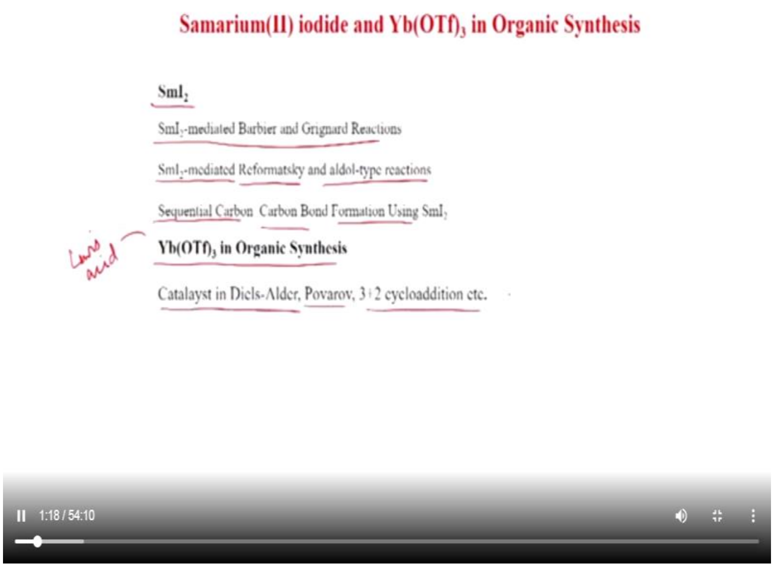

Samarium(II) iodide and Yb(OTf)$_3$ in Organic Synthesis

SmI$_2$

SmI$_2$-mediated Barbier and Grignard Reactions

SmI$_2$-mediated Reformatsky and aldol-type reactions

Sequential Carbon Carbon Bond Formation Using SmI$_2$

Yb(OTf)$_3$ in Organic Synthesis

Lewis acid

Catalayst in Diels-Alder, Povarov, 3+2 cycloaddition etc.

Welcome again, today we will discuss samarium iodide and ytterbium triflate in organic synthesis. So today we will discuss the last of samarium iodide and we will discuss samarium iodide mediated Barbier and Grignard reactions. Then we will discuss samarium iodide mediated Reformatsky and aldol type of reactions and also we will discuss sequential carbon-carbon bond formation using samarium iodide and we will discuss yttererbium triflate because this is a good Lewis acid and different reaction it has been used as a catalyst like in Diels-Alder, Povarov, 3+ 2 cycloaddition reaction, etc.

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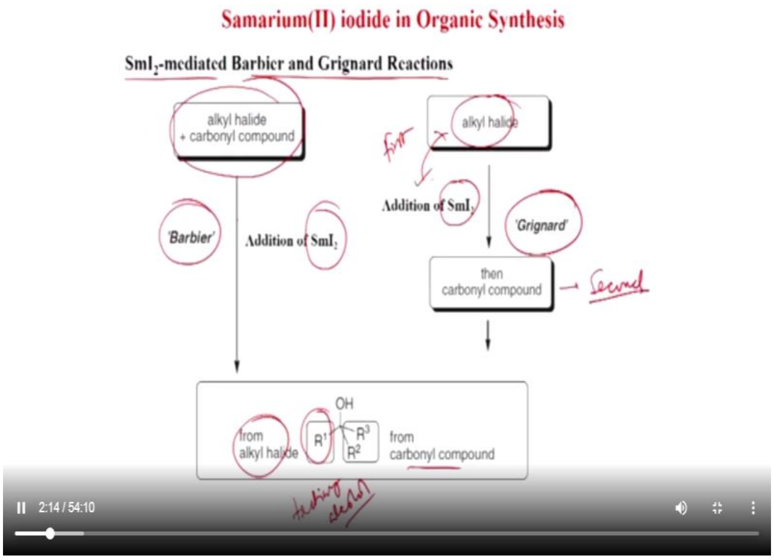

Samarium(II) iodide in Organic Synthesis

SmI_2-mediated Barbier and Grignard Reactions

alkyl halide + carbonyl compound

'Barbier'

Addition of SmI_2

alkyl halide

first

Addition of SmI_2

'Grignard'

then carbonyl compound

Second

from alkyl halide

from carbonyl compound

tertiary alcohol

So samarium iodide meditated Barbier and Grignard reactions, we know this Barbier and Grignard reactions are very important for C-C bond formation. And here we can see this samarium iodide also can perform these reactions.

Like in Barbier condition the alkyl halide and carbonyl compound are mixed together and on that mixture you add samarium iodide. So that is called Barbier condition and you get this tertiary alcohol and this part R1 comes from the alkyl halide and this is comes from the carbonyl group. On the other hand in Grignard condition you mix the alkyl halide with samarium iodide first. So this is the first and in second you add the carbonyl compound. So that is the traditional Grignard method.

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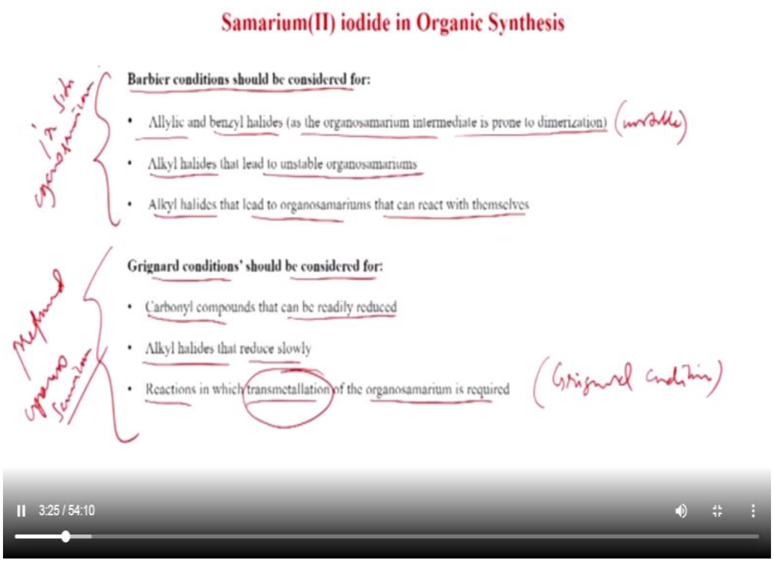

Samarium(II) iodide in Organic Synthesis

in situ organosamarium

Barbier conditions should be considered for:

- Allylic and benzyl halides (as the organosamarium intermediate is prone to dimerization) (unstable)
- Alkyl halides that lead to unstable organosamariums
- Alkyl halides that lead to organosamariums that can react with themselves

preformed organo samarium

Grignard conditions' should be considered for:

- Carbonyl compounds that can be readily reduced
- Alkyl halides that reduce slowly
- Reactions in which transmetallation of the organosamarium is required (Grignard condition)

So, Barbier conditions should be considered for allylic and benzylic halides as the organo samariun intermediate is prone to dimerization. That means they are unstable, if they are unstable then you have to use the Barbier condition. Alkyl halides that lead to unstable organosamariums, alkyl halides that lead to organosamariums that can react with themselves. They are like dimerization. On the other hand Grignard condition should be considered for carbonyl compounds that can be readily reduced, alkyl halides they are reduced slowly and also reactions in which transmetalation of the organosamarium is required.

So if transmetalation is required then you have to use the Grignars condition that means the pre-formed. So, this means the pre-formed organosamarium. Organosamarium and this means in situ, in situ organosamarium mechanism.

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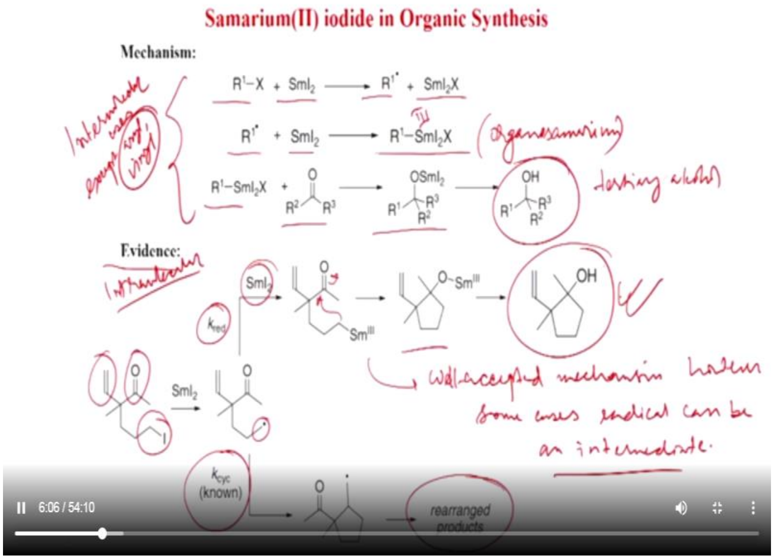

Samarium(II) iodide in Organic Synthesis

Mechanism:

Evidence:

Well-accepted mechanism however some cases radical can be an intermediate.

Mechanism: So this is the well accepted mechanism. The halide reacts with samarium iodide, first radical is formed and this is the byproduct then again R1 dot samarium iodide it becomes the organosamarium species where samarium is in the (III). And now this organosamarium reacts with carbonyl compound to join first this, so this is the addition product and then you get this tertiary alcohol.

And this mechanism is well accepted for intermolecular cases. Intermolecular cases except aryl and vinyl because in aryl, vinyl cases, it goes by radical that we will see later. Now for intramolecular, so intramolecular case whether this organism is forming or not, we have to choose a substrate like this one here a double bond is there, carbonyl is there and alkyl iodide is there.

Now in samarium iodide this alkyl iodide has to react with samarium iodide to generate this radical. Now this radical will get reduced. So we will take another electron from samarium iodide and will become negative. That is the organosamarium anion here and this then attacks to carbonyl compound to generate this species and after work up you get this tertiary alcohol. So this is well accepted, alternatively is that this radical can be formed and this radical then adds to the double bond. So this can be also possible, this radical can add to the double bond and then rearrange product. However, in this case, this product is formed. So this is the well accepted mechanism.

However in some cases, this is radical can be an intermediate. So most cases this anion is forming and then this anion is attacking to the carbonyl compound and you get this tertiary alcohol.

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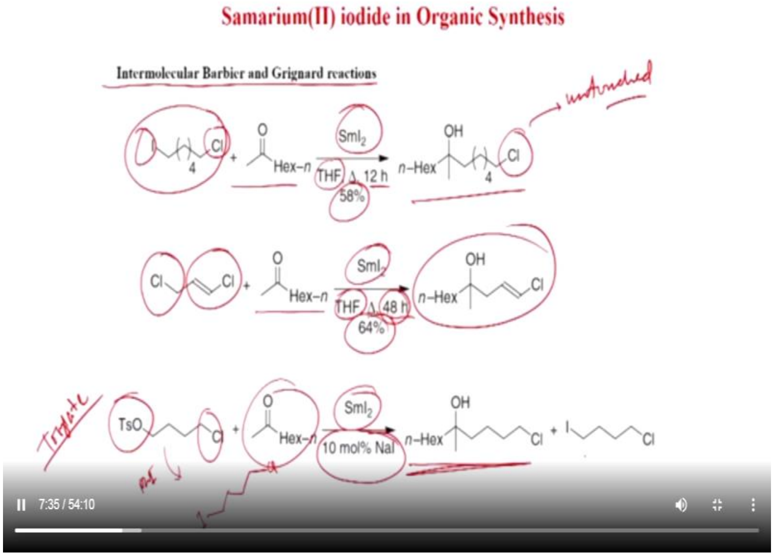

Samarium(II) iodide in Organic Synthesis

Intermolecular Barbier and Grignard reactions

So now we will see examples for intermolecular Barbier and Grignard reactions, like this one long chain alkane with iodide and chloro substituent when it is treated with this ketone with samarium iodide THF heating condition 12 hours, only this iodide react with the samarium iodide and chloro is untouched. And you get this tertiary alcohol in 58 percent yield. Also if you have a chloride and vinyl chloride then also this selectivity will come and only this chloride reacts.

Sp3 carbon chloride that is reacting and with the same ketone with samarium iodide THF heating here the condition is 48 hours. Earlier 12 hours here, you have to use long reaction time and you get this tertiary alcohol in 64 percent yield. Now, here chloride and tosylate, this is tosylate and if 10 mole percent sodium iodide is added with samarium iodide then what happens? This exchange happens. So this will go to iodide and that will react with samarium to generate the organosamarium and then will react with the ketone to generate this tertiary alcohol.

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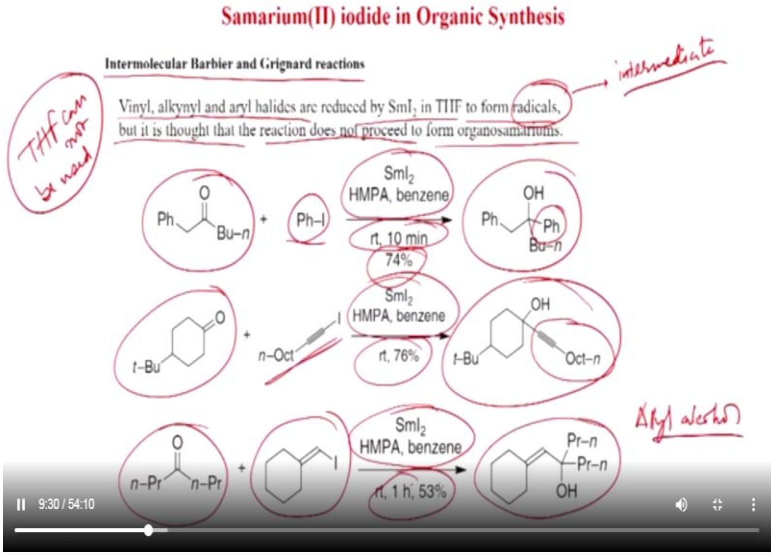

Samarium(II) iodide in Organic Synthesis

Intermolecular Barbier and Grignard reactions

Vinyl, alkynyl and aryl halides are reduced by SmI_2 in THF to form radicals, but it is thought that the reaction does not proceed to form organosamariums.

THF can not be used

intermediate

Now, we will see intermolecular Barbier and Grignard reaction in vinyl, alkenyl and aryl halides. So vinyl, alkenyl and aryl halides as I told already that they are cases the radical will form and radical will react or reduce by samarium iodide in THF to form radicals, but it is thought that the reaction does not proceed to form organosamarium. So this is very important, radical is intermediate for vinylic aryl cases.

Like here this iodobenzene when treated with this ketone with samarium iodide HMPA benzene and in this case also THF cannot be used, so this also tells the radical is forming and that is intermediate. So if you use THF solvent, then there will be a problem. So we have to use the benzene solvent and HMPA is the additive with room temperature only 10 minutes. The reaction is quite fast and this product tertiary alcohol you get in 74 percent yield.

So this is the phenyl that is coming from the iodobenzene. Also if 4-tertiary butyl cyclohexanone is treated with this alkynyl iodide with samarium iodide HMPA benzene and room temperature condition, you get this propargyl alcohol in 76 percent yield. So this is coming from the propargyl iodide part. So these reactions are very important and if vinyl iodide is present, that also can generate the radical and it can react with this symmetrical ketone with samarium iodide HMPA benzene condition at room temperature here also reaction first one hour you get this allyl alcohol. So this is allyl alcohol in 53 percent yield.

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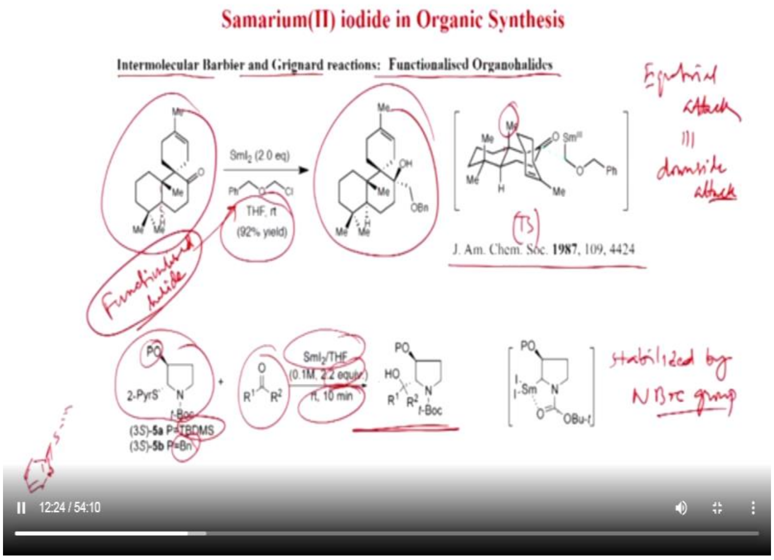

Samarium(II) iodide in Organic Synthesis

Intermolecular Barbier and Grignard reactions: Functionalised Organohalides

J. Am. Chem. Soc. **1987**, 109, 4424

Now we will see intermolecular Barbier and Grignard reaction functionalize organohalide. So functionalized organohalide also is important because in normal organo-magnesium compound these functional organohalides cannot be used. So that means the samarium compounds are much milder.

Like here if this chiral ketone and this is the functionalized halide. And this functionalized halide this is the O-benzyl group is there and O CH 2 Cl here samarium iodide can generate the organosamarium and that can react with the ketone to generate this tertiary alcohol and here also, the selectivity is there, the addition takes place diasteroselectively from the down face and this could be the transition state of this reaction.

And now this is the ketone and this group is drawn here, all are chair. And now if you see this axial group, there is a methyl, on the other hand equatorial attack is favorable. So equatorial attack is happening and that is actually down face attack, downside attack and it is attacking from the downside. So there this alcohol is in the top side and you get this product in THF room temperature 92 percent yield. This was published in JACS 1987 page number 4424.

Also if this kind of functionalized substrate is there and S pyridine is actually this is S and so this is the S 2 pyridine that can generate the organosamarium and that is stabilized by this Boc group and OP that can be OTBDMS or O-benzyl and that can be reacted with the ketone with samarium iodide THF 0.1 molar 2.2 equivalent room temperature 10 minutes, you get this tertiary alcohol.

So what could be the intermediate? So this is the intermediate because this organosamarium is stabilized. So this is stabilized by N Boc group because this samarium can coordinate with the carbonyl of the N Boc moiety and that is quite stable and then it can react to the carbonyl compound to generate this tertiary alcohol.

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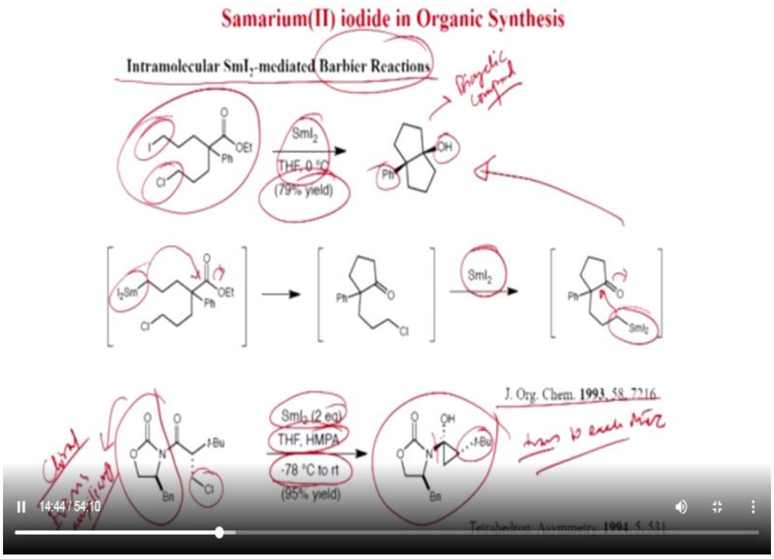

Samarium(II) iodide in Organic Synthesis

Intramolecular SmI_2-mediated Barbier Reactions

J. Org. Chem. 1993, 58, 7216

Tetrahedron: Asymmetry 1994, 5, 531

Now we will see intramolecular samarium iodide and intramolecular case, it is always the Barbier condition. Like here, if you see this compound, this is a quaternary center. There is ester, there is iodide and there is a chloride and samarium iodide THF is zero degree centigrade you get this bicyclic compound in 79 percent yield and also this geometry is cis so this is 5-5 fused case so cis can be stable here.

So what could be the mechanism? So, first this iodo will react fast to generate the organosamarium here. And then this reacts with the ester and this generates the ketone. So, now cyclic ketone is formed. Now this chloro will react with samarium iodide again, and this will react here and you get this product and selectively the cis product is formed. This was published in Journal of Organic Chemistry 1993.

Also, if you have a this chiral one, so chiral and this is called Evans auxiliary and if there is a chloride substituent with samarium iodide 2 equivalent THF HMPA condition in minus 78 degree to room temperature you get this product in 95 percent yield and here also you can see this stereochemistry is very important. This one and this tertiary butyl, they are trans to each other. So this and this are trans to each other.

So this is very important. You can use the chiral one and the stereochemistry is not disturbed in this reaction and you can get this chiral cyclopropyl alcohol in good yield. This was published in Tetrahedron Asymmetry in 1994.

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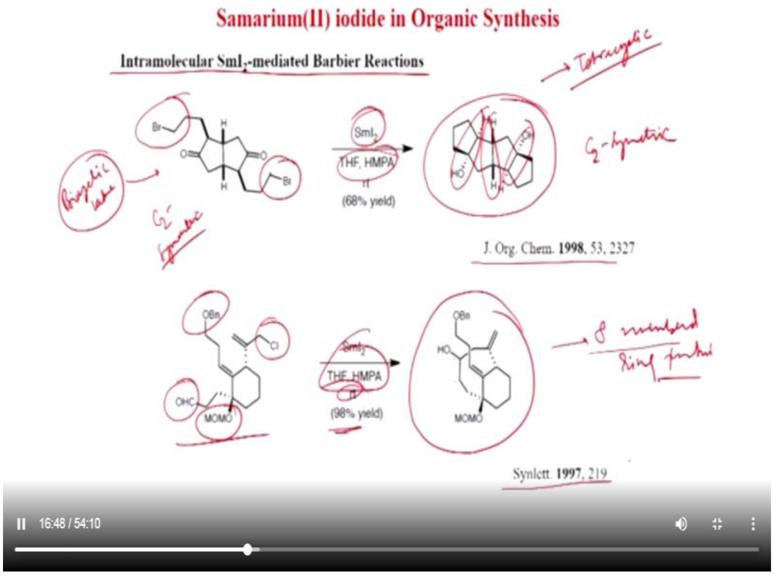

Samarium(II) iodide in Organic Synthesis

Intramolecular SmI_2-mediated Barbier Reactions

J. Org. Chem. **1998**, 53, 2327

Synlett. **1997**, 219

Now we will discuss intramolecular samarium iodide mediated Barbier reaction, some more examples like this one. This is bicyclic ketone, bicyclic ketone and there are two bromine there bromide and here bromide. So this is also C2 symmetric and when it is treated with samarium iodide THF HMPA room temperature you get this tetracyclic motive. So this is 4 cycle is there so this is tetracyclic motive and you can see this is also C2 symmetric.

So most likely this will generate the organosamarium here and then will react to the carbonyl and form here, here and that is also selectively so that this fusion is always cis. So this is cis, this is cis, this is cis. So 5-5 system the cis geometry is stable and this was published in Journal of Organic Chemistry 1998.

Also, if you have this compound, this is also chiral and here you can see aldehyde motif is there, a chloro substituent is there, also O-benzyl and O-MOM is there and there are two chiral centers present and with samarium iodide THF HMPA condition only room temperature you get this product in 98 percent yield. So what could be the mechanism? So here the organosamarium will form and that will react to the aldehyde and to generate a long chain so you can see here 1, 2, 3, 4, 5, 6, 7, 8. So, 8-membered ring is forming. This was published in Synlett 1997.

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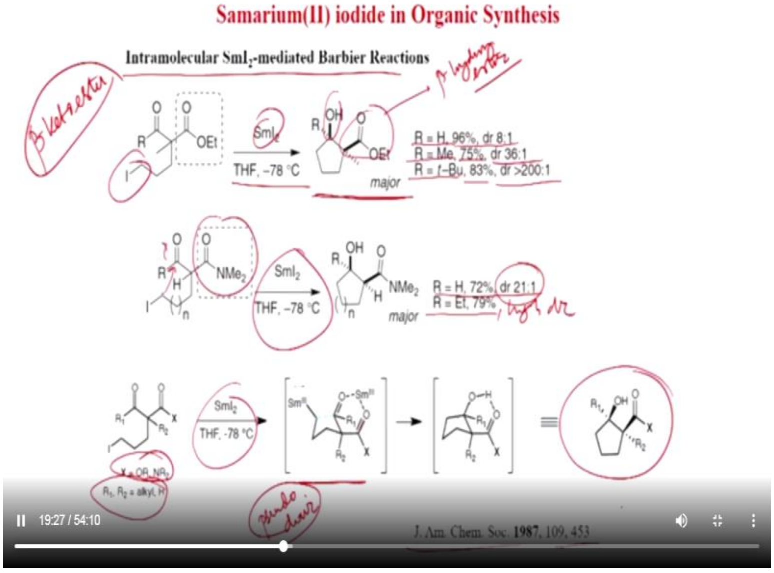

Samarium(II) iodide in Organic Synthesis

Intramolecular SmI_2-mediated Barbier Reactions

J. Am. Chem. Soc. 1987, 109, 453

Some more example of intermolecular samarium iodide mediated Barbier reaction and these are beta-ketoester. Beta-ketoester with an alkyl substituent here and with samarium iodide THF minus 78 degree centigrade you can get this beta-hydroxy ester. So beta-ketoester is converted to beta-hydroxy ester and these products are formed in high diastereo-selectivity here.

You can see this OH and this CO2Et they are same to each other and when R is equal to hydrogen that means this is aldehyde then you get 96 percent yield with 8:1 diastereomeric ratio, R is equal to methyl in that case you get 75 percent yield 36 :1 diastereomeric ratio. R is equal to tertiary-butyl, you get 83 percent yield with diastereomeric ratio greater than 200:1. Also if you have amide here, that case also the cyclization occurs, samarium iodide at THF minus 78 degree centigrade.

So what is happening? The organosamarium is forming and it is adding but the addition is selective so that you can get the high diastereomeric excess. When R is equal to hydrogen then you get 72 percent yield, diastereomeric ratio 21:1, R is equal to ethyl you get 79 percent yield, here also high dr.

So what could be the mechanism? Like here X is equal to OR NR 2, R 1, R 2 can be alkyl or hydrogen with samarium iodide THF minus 78 degrees centigrade. You get this kind of intermediate. So what happens, this organosamarium is formed and another samarium will coordinate with the carbonyl as well as this ester or amide carbonyl. So that these two will be same to each other and this takes a pseudo-chair conformation.

So in the pseudo-chair, you can see these two wants to syn to each other like here. This is the 5-member ring is forming here. So this is the newly generated bond and now this OH and COR will be syn to each other, so here both are top side and this will give this product. So this is the important that the both carbonyl are coordinate to the samarium and that is why the addition is taking place selectively. This was published in JACS 1987 page number 453.

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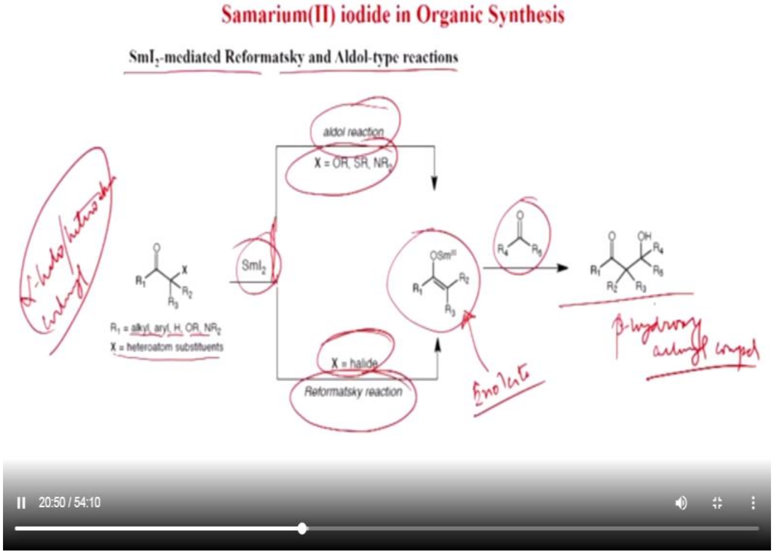

Samarium(II) iodide in Organic Synthesis

SmI_2-mediated Reformatsky and Aldol-type reactions

Samarium iodide mediated Reformatsky and aldol-type reactions. So now we will discuss Reformatsky and aldol reactions. So if you have alpha halo carbonyl, alpha halo or alpha heteroatom carbonyl, then this kind of reaction Reformatsky and aldol will happen. So here you can see R1 can be alkyl, aryl, hydrogen, OR NR 2 X is equal to heteroatoms substituents, with samarium iodide you get this enolate.

And when X is equal to halide that time only it is called a Reformatsky reaction. And with this O-samarium enolate which reacts with the carbonyl compound to generate the beta-hydroxy carbonyl compound.

Alternatively if PX is equal to OR, SR, NR 2, then we call it aldol reaction. So this is very important. If X is equal to halide then will call Reformatsky reaction. That is the alpha halo substituent. And if alpha heteroatom like OR, SR, NR 2, is there then we call the aldol reaction and you generate the same samarium enolate and then it reacts with carbonyl compound to generate the beta-hydroxy carbonyl.

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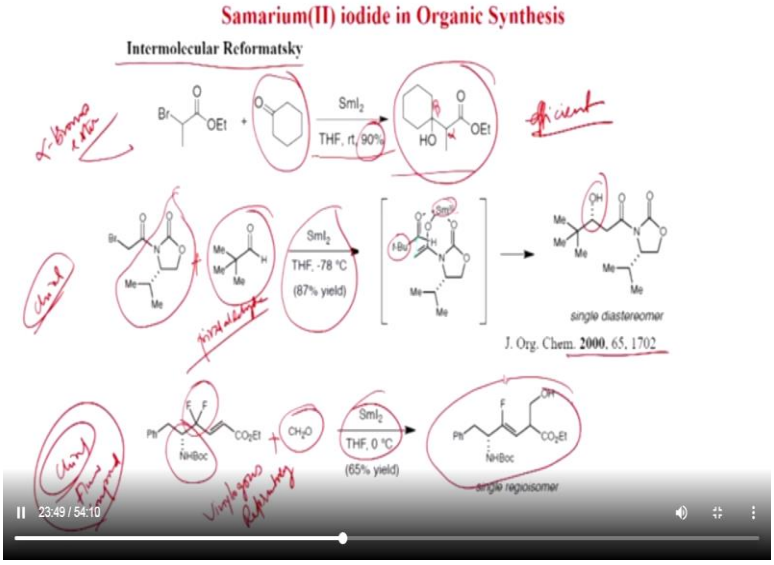

Samarium(II) iodide in Organic Synthesis

Intermolecular Reformatsky

J. Org. Chem. 2000, 65, 1702

So now we see the examples like here intermolecular Reformatsky. This is the alpha bromo ester. Alpha bromo-ester reacting with cyclohexanone to generate this beta-hydroxy. So this is alpha, this is beta, beta hydroxy ester. So what happens, this enolate is generated here and that is reacting to cyclohexanone to generate this compound beta-hydroxy ester and with samarium iodide room temperature condition you get 90 percent yield of this product. So this method is quite efficient.

Now if you have a chiral one, so this is chiral compound and you can see this is Evans auxiliary and here also we know that Evans auxiliary has been used for many aldol kind of reaction. So here this is alpha bromo substituent is there so this we will call the Reformatsky, and that is samarium enolate will react with this pivalaldehyde so this called pivalaldehyde and with samarium iodide THF minus 78 degree centigrade what will happen, you get this product single diastereomer. So this is very important, this is chiral.

So newly generated center also is determined by this chirality and because this takes a chair like transition state, here you can see this is the samarium enolate and this samarium is coordinated with this as well as this oxygen. So this samarium is coordinated to three oxygens and they are all keeping like this kind of geometry. You can see this is the chair here, this tertiary-butyl is in the equatorial position and this motive is here and after the addition takes place, so this is the newly generated bond will form here that is the enolate reacting to the aldehyde and you get this hydroxyl group and that is selectively is forming and you get only single diastereomer. This was published in JOC 2000 page number is 1702.

Also, this is a chiral fluoro compound and here you can see this NH Boc. This is the chiral center and two fluorine substituent is there and alpha beta unsaturated ester is there. So this can be called vinylogous Reformatsky and when it reacts with para-formaldehyde with samarium iodide THF 0 degree centigrade you get this. So here this product is forming and this part is coming from the formaldehyde.

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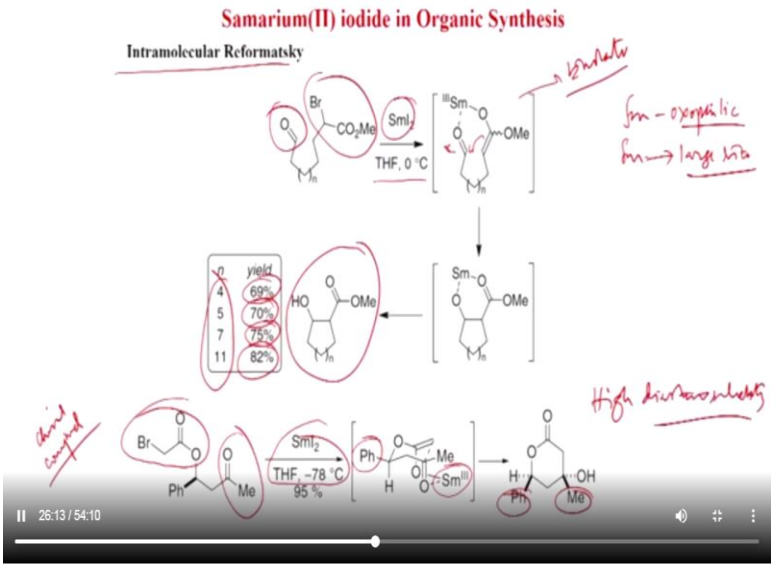

Samarium(II) iodide in Organic Synthesis

Intramolecular Reformatsky

n	yield
4	69%
5	70%
7	75%
11	82%

Now, we will discuss intramolecular Reformatsky, so intramolecular case also you have the carbonyl and this alpha bromo ester in the same molecule. And here you can see n is there, n can be 4 to 11. So large ring can also be formed in this process, that is the special of samarium and with samarium iodide THF 0 degree centigrade you generate this enolate. So this is the enolate and this enolate is binding with the carbonyl compound also. So this is very important because samarium is oxophilic.

So always it binds with oxygen and in this case samarium also helps to make large rings because samarium also has large size. So because of its large size, you can generate large ring also. And after this activation of the aldehyde now this bond will form here C-C Bond and you get this cyclic compound. This is the beta hydroxy ester is forming and when n is equal to 4, then you get 69 percent yield; n is equal to 5, 70 percent yield; n is equal to 7, 75 percent yield; n is equal to 11, 82 percent yield.

Now if you have a chiral compound, so here chiral compound and this is also intramolecular because there is a ketone is there and this is alpha bromo ester. And now what will happen, the enolate will form with samarium iodide THF minus 78 degrees centigrade. This kind of enolate will form and this will take a chair orientation. You can see this phenyl takes the equatorial orientation and this enolate oxygen and this carbonyl will be always syn because it wants to coordinate with samarium that makes them in the same side here.

So methyl becomes now same side of phenyl, methyl and phenyl is the same side. And this compound is formed in high diasterero-selectivity. So high diastereo selectivity and this was published in JACS 1991 page number is 8036.

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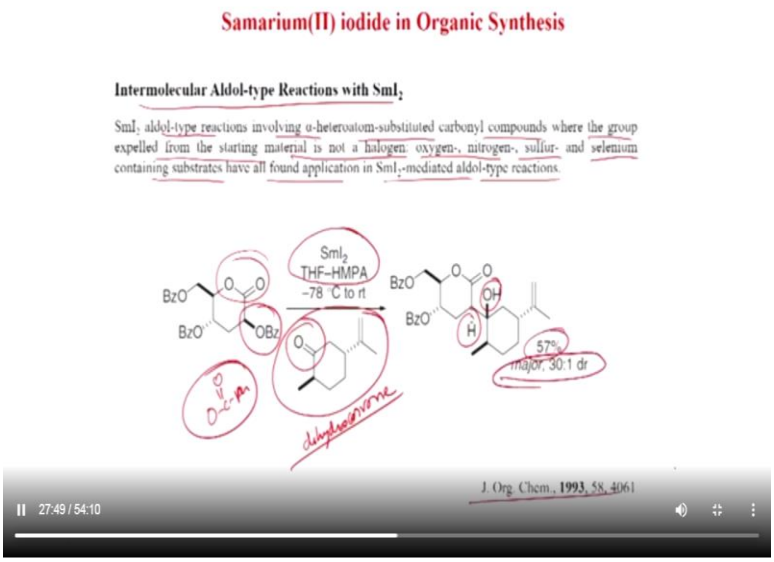

Samarium(II) iodide in Organic Synthesis

Intermolecular Aldol-type Reactions with SmI_2

SmI_2 aldol-type reactions involving α-heteroatom-substituted carbonyl compounds where the group expelled from the starting material is not a halogen: oxygen-, nitrogen-, sulfur- and selenium containing substrates have all found application in SmI_2-mediated aldol-type reactions.

J. Org. Chem., **1993**, 58, 4061

Intermolecular aldol type reactions is also possible. So samarium iodide aldol type reactions involving alpha heteroatom substituted carbonyl compounds where the group expelled from the starting material is not a halogen, oxygen, nitrogen, sulfur and selenium containing substrates have all found application in samarium mediated aldol type reaction. So when it is halide, that time we call it as Reformatsky otherwise we call it aldol.

So we will see now examples like oxygen here. You can see this O benzyl group is present here. So, O CO Ph and this is connected with lactone motif. So what will happen, when it is treated with samarium iodide THF HMPA at minus 78 degree to room temperature you get the samarium enolate here and that will react with this compound which is dihydrocarbone. So this is chiral, a carbonyl group is present. So the addition will take place here and this you can see they are trans here this hydrogen and OH, so this is very good diastereoselectivity 30 is to 1, diastomeric ratio and this product is formed in 57 percent yield. This was published in Journal of Organic Chemistry, 1993 page number 4061.

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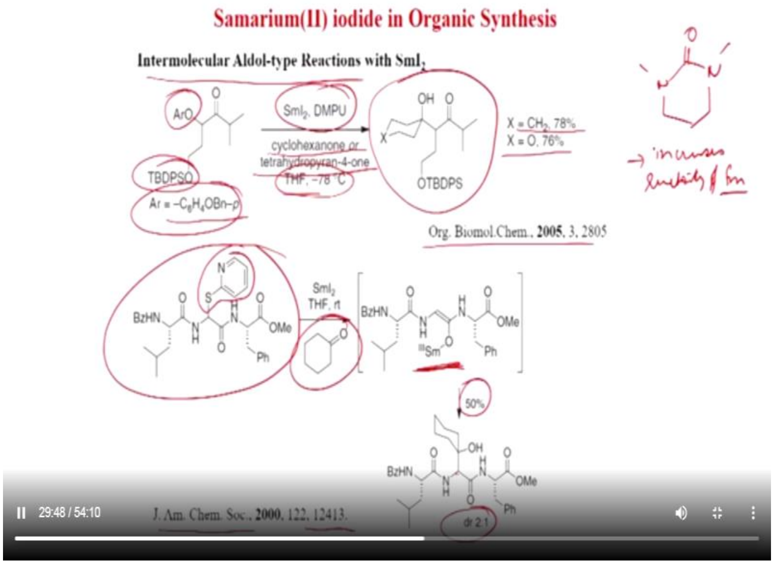

Samarium(II) iodide in Organic Synthesis

Intermolecular Aldol-type Reactions with SmI_2

Org. Biomol.Chem., **2005**, 3, 2805

J. Am. Chem. Soc., **2000**, 122, 12413.

Some more examples of intermolecular aldol type reactions. Like here you can see this is O benzyl group is there, Ar is equal to C6 H4 O Bn-p and this is the ketone, this is OTBDPS and samarium iodide DMPU. So DMPU is this. This is urea and this increases reactivity of samarium. So DMPU, samarium iodide and then cyclohexanone that is the electrophile or tetrahydropyran 4-one and THF minus 78 degree centigrade you get this addition product beta-hydroxy carbonyl.

When X is equal to CH 2, then you get 78 percent yield, X is equal to oxygen with 76 percent yield and this work was published in Organic Biomolecular Chemistry and here you can see this is a chiral, this is peptide kind of molecule and here this threo pyridine motif is there that we have seen earlier also.

So samarium can cleave this one and will generate this enolate here. So this carbon center you can see this is the enolate now and now when it is treated with cyclohexanone the aldol reaction will happen. So this is the carbon here the addition is taking place to the cyclohexanone. So this is the aldol product you are getting 2:1 diastereomeric ratio and 50 percent yield. So here diastereomeric ratio is little less and this work was published in JACS 2000 page number is 12,413.

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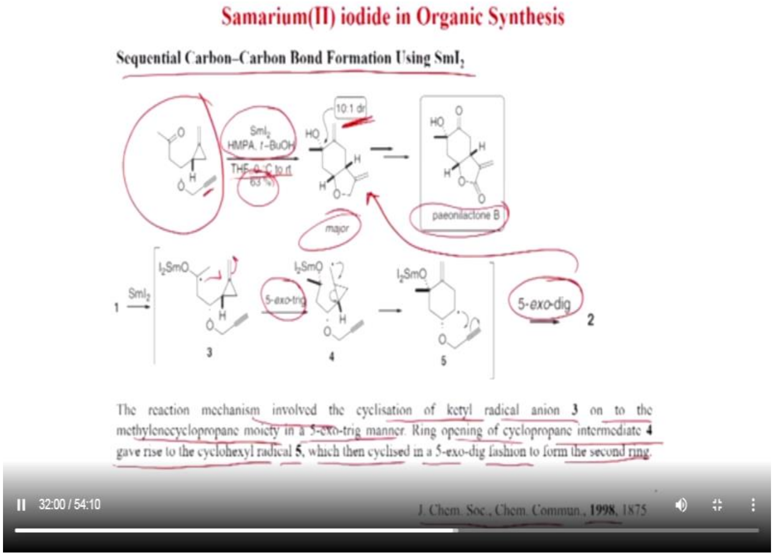

Samarium(II) iodide in Organic Synthesis

Sequential Carbon–Carbon Bond Formation Using SmI_2

The reaction mechanism involved the cyclisation of ketyl radical anion **3** on to the methylenecyclopropane moiety in a 5-exo-trig manner. Ring opening of cyclopropane intermediate **4** gave rise to the cyclohexyl radical **5**, which then cyclised in a 5-exo-dig fashion to form the second ring.

J. Chem. Soc., Chem. Commun., **1998**, 1875

Now we will discuss sequential carbon-carbon bond formation so using samarium iodide. So this is very important samarium iodide can do many bond formations. This substrate if you see this is a carbonyl is there but no iodide is there. So when carbonyl is there samarium iodide reacts to the carbonyl first and it double bond connected with cyclopropyl group is present and a triple bond is here.

Now if it is treated with samarium iodide HMPA tert-butanol, tert- butanol is the potent source, with THF 0 degree centigrade to room temperature you get this product. This is the product 10:1 diastereomeric ratio and 63 percent yield and this can be converted to this natural product Paeonilactone B.

So what could be the mechanism? So here the samarium iodide first reacts with carbonyl to generate this radical. This kind of cyclization we have seen in last class. Now this will add to this, this will add here and a radical will form here. So this is the 5 exo-trig cyclisation, name this radical 4 is formed and now this ring will open, it will generate another radical cyclohexyl. The cyclohexyl radical again do another cyclization 5 exo-dig and after that this compound is formed that is 2.

So the reaction mechanism involved the cyclization of ketyl radical anion 3 onto the methylene cyclopropane moiety in a 5 exo-trig manner. Ring opening of cyclopropane intermediate 4 gave rise to the cyclohexyl radical 5, who is then cyclized in a 5 exo-dig fashion to form the second ring. So there are many bond is forming by samarium iodide. So this is very important. You can get multi-cyclic compound by samarium iodide. This was published in Chem Commun 1998 page number 1,875.

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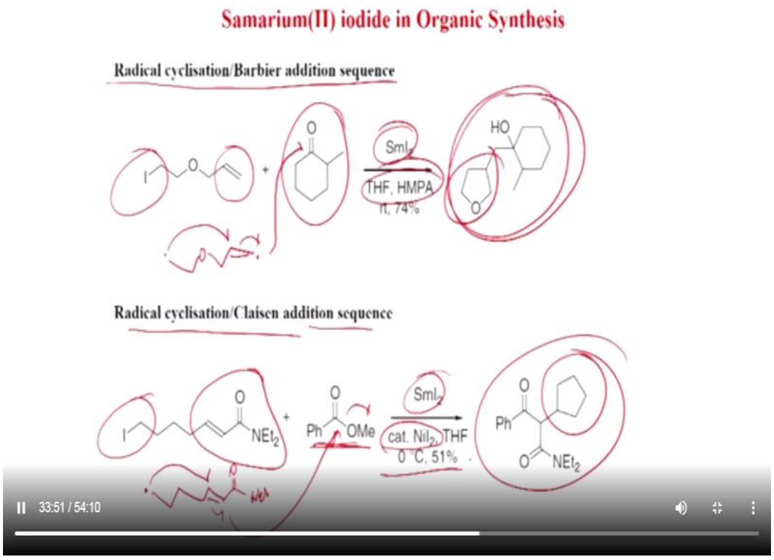

Samarium(II) iodide in Organic Synthesis

Radical cyclisation/Barbier addition sequence

Radical cyclisation/Claisen addition sequence

Now will see more sequence like radical cyclization, Barbier addition sequence. So here you can see alkyl iodide is there and a double bond is present, also 2-methylcyclohexanone is present with samarium iodide THF HMPA condition you get this product. So what could be the mechanism? So a radical will form here, this radical react here. So 1, 2, 3, 4, 5, this tetra hydrofuran motif will form and here a radical will generate and that radical then react to cyclohexanone and you get this. Radical cyclization, Claisen addition sequence also is possible. So here this is the iodide, this is alpha beta unsaturated amide and ester motif is there.

So when there is a possibility that intramolecular functionality is there then the radical will react first with the intramolecular functionality and then will react intermolecular fashion because intramolecular reactions are always much faster. Like here iodide and alpha beta unsaturated amide is present, so this radical will form. This can react now here. So a 5-member cyclopentane ring is forming and this then can add to ester and Claisen kind of reaction can happen with catalytic nickel iodide, that will activate the amide actually as well as the ester and samarium iodide THF 0 degree centigrade you get 51 percent yield of this product.

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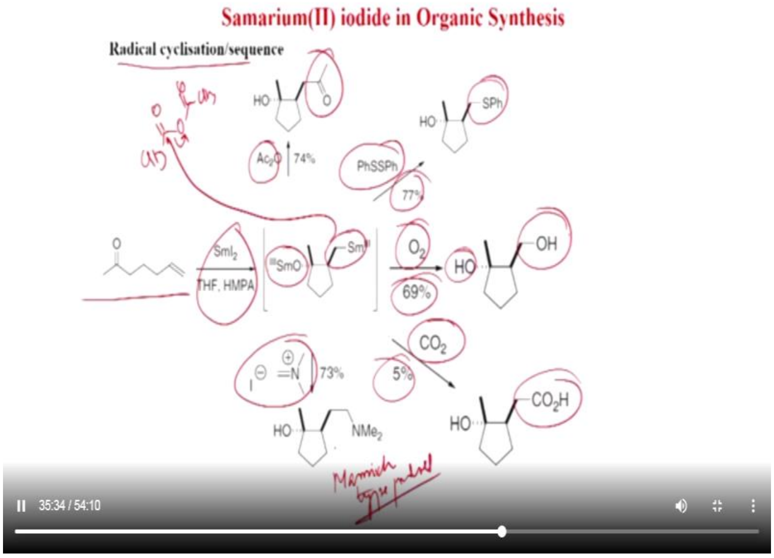

Samarium(II) iodide in Organic Synthesis

Radical cyclisation/sequence

Radical cyclization sequence, this already we have seen in the last class that a carbonyl compound and olefin is present with samarium iodide HMPA, you can get the cyclization of the ketyl radical and you get this kind of intermediate, we have seen already O samarium and this moiety are trans in case of methyl, so they are trans here. So we will see now that this intermediate can be converted to other useful products.

Now like if it is treated with oxygen then this OH is formed here. This already OH was there that was after proton source you can get this but this OH is forming after treatment with oxygen and this product diol is forming in 69 percent yield. Also if it is treated with the diethyl PhSSPh and you can get this thioether in 77 percent yield. Also if it is treated with acetic anhydride, so this is the structure of acetic anhydride.

And this nucleophile this can react with the acetic anhydride to generate this acyl group here. Also, it can react with carbon dioxide and then carbon dioxide is formed in 65 percent yield and this is the iminium ion and it can react to generate the Mannich product. So this is Mannich type product and you get this product in high yield 73 percent.

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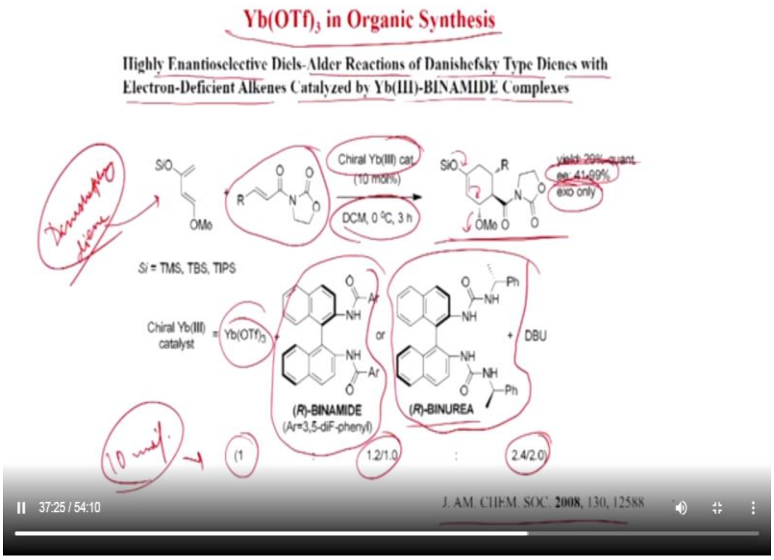

Yb(OTf)$_3$ in Organic Synthesis

Highly Enantioselective Diels-Alder Reactions of Danishefsky Type Dienes with Electron-Deficient Alkenes Catalyzed by Yb(III)-BINAMIDE Complexes

J. AM. CHEM. SOC. **2008**, 130, 12588

Now we will discuss ytterbium triflate in organic synthesis. So ytterbium triflate is a good Lewis acid and we will see that it has been used in many reactions like highly enatioselective Diels Alder reactions of Danishefsky type dienes with electron deficient alkenes catalyzed by ytterbium-3 binamide complexes, like this one. So, this is Danishefsky diene and this is the oxazolidinone alpha beta unsaturated.

So this is the diene, this is dienophile with chiral ytterbium-3 catalyst 10 mole percent. So ytterbium triflate plus this binamide is there, they are C2 symmetric. Also here bi-urea is present. So either of these two catalyst and plus DBU in DCM 0 degree centigrade you get this Diels Alder product.

And in this case, you get preferentially exo-products and yield is 29 percent to quantitative and ee is 41 to 99 percent yield. So this is the ratio 1-ytterbium triflate 1.2 or 1 equivalent of this and 2.4 equivalent of DBU. So this is of the 10 mole percent and these products are very useful, you can convert to here also. If you treat with acid then this group can be removed actually. So enone can be found from here, this work was published in JACS 2008 page number 12,588.

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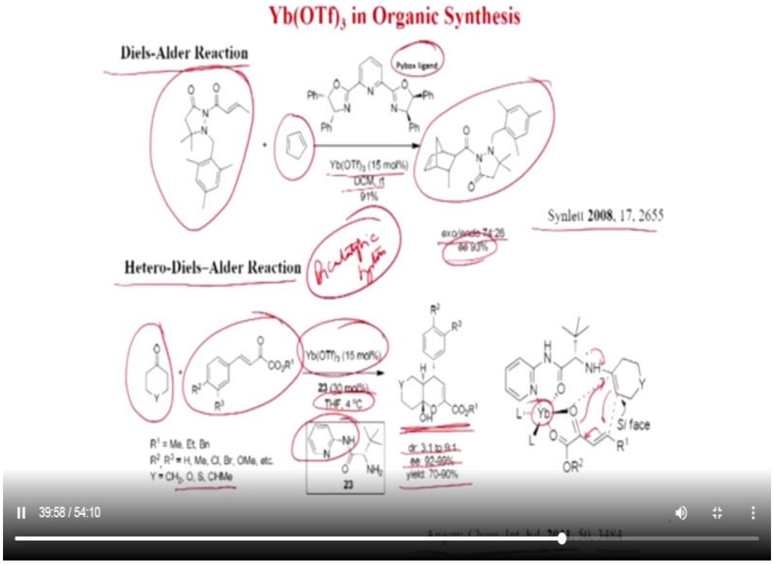

Yb(OTf)$_3$ in Organic Synthesis

Diels-Alder Reaction

Synlett **2008**, 17, 2655

Hetero-Diels–Alder Reaction

Diels-Alder reaction like this cyclopentadiene, this is alpha beta unsaturated imide and with the pybox ligand. So this is pyridine and this is the oxazoline. You can see the motif is present and with ytterbium triflate the same room temperature you get these Diels Alder products and here also exo is measured 74 is to 26 and ee is 93 percent. So ee is very high for this product with a pybox and this work was published in Synlett 2008.

Also hetero Diels Alder reaction is possible. So, like here if cyclohexanone or their derivatives like oxygen, sulfur can be here and this is alpha beta unsaturated ketoester and with ytterbium triflate 15 mole percent and this primary amine. So this is actually bi-catalytic system. Bi-catalytic system this primary amine reacts with the cyclohexanone to generate the enamine.

And this ketoester is activated by ytterbium. So here you can see also this pyridine motif is important so that it can coordinate with the ytterbium. So here you can see ytterbium coordinated with four atoms here oxygen, oxygen this oxygen, this primary amine and this pyridine and then this enamine is forming here and then this reaction will happen.

So like this and this will generate a carbonyl but when this reaction is happening, it will go to the alcohol. So this kind of product will form bicyclic and because of this tight transition state, you can get high diastereo as well as enantiomeric excess like 3 is to 1 to 9 is to 1 dr and ee is equal to 92 to 99 percent and yield is equal to 70 to 90 percent in THF 4 degree centigrade.

So this ytterbium triflate will be 15 mole percent and this catalyst it will be 30 mole percent. So this will be two times and this work was published in Angew Chem International Edition 2011, page number 3,484.

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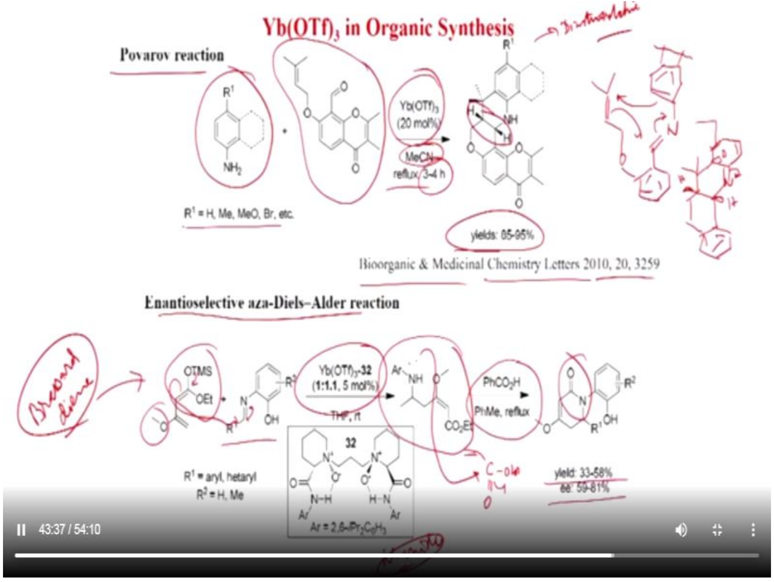

$Yb(OTf)_3$ in Organic Synthesis

Povarov reaction

R^1 = H, Me, MeO, Br, etc.

$Yb(OTf)_3$ (20 mol%)
MeCN reflux, 3-4 h

yields: 85-95%

Bioorganic & Medicinal Chemistry Letters 2010, 20, 3259

Enantioselective aza-Diels–Alder reaction

$Yb(OTf)_3$-32 (1:1.1, 5 mol%)
THF, rt

PhCO$_2$H
PhMe, reflux

R^1 = aryl, hetaryl
R^2 = H, Me

Ar = 2,6-$iPr_2C_6H_3$

yield: 33-58%
ee: 59-81%

Now, we will discuss Povarov reaction. And here you can see this is aromatic amine, here this R1 can be H, methyl, methoxy, Br etc. And this is the aldehyde and here you can see a double bond. So this amine will react with the carbonyl that is the aldehyde motif to generate the imine. So if we react amine with aldehyde then you get the imine here.

Now you can see this reaction will happen. So most likely this will react here. This is 4 plus 2, 4 plus 2 will give this product. So initially this will happen. Now this will be diastereomeric product also and now the aromatization will happen here. So, here this aromatization will happen and so that you can get the amine. So this is Povarov reaction with ytterbium triflate 20 mole percent in acetonitrile reflux condition 3 to 4 hours, you get 85 to 95 percent yield of this product and this is highly diastereoselective also.

So diastereoselective here this is fused is formed and this was published in Bioorganic and Medicinal Chemistry Letters 2010. Now enantioselective aza-Diels-Alder reaction we will see. Now enantioselective variance we have already seen. So here this kind of diene is present. This is called Brassard diene. This is also electron rich diene, here OTMS OEt and here the methoxy group is present. Now if it is treated with this imine, so first what happened?

First this is the stepwise here with ytterbium triflate as well as this is the co-catalyst, this is the N-oxide and this is C 2 symmetric also. So with ytterbium triflate and Ar is equal to 2, 6 isopropyl 2C6H3 so they are also bulky here and then first this addition takes place. And then this ester group reacts with the amine. So ester if you draw like this COOEt then what happened, this nitrogen is reacting so that the cyclization is happening here. So this second step is forming after benzoic acid toluene reflux condition and this product is formed in 33 to 58 percent yield and enantiomeric excess is 59 to 81 percent.

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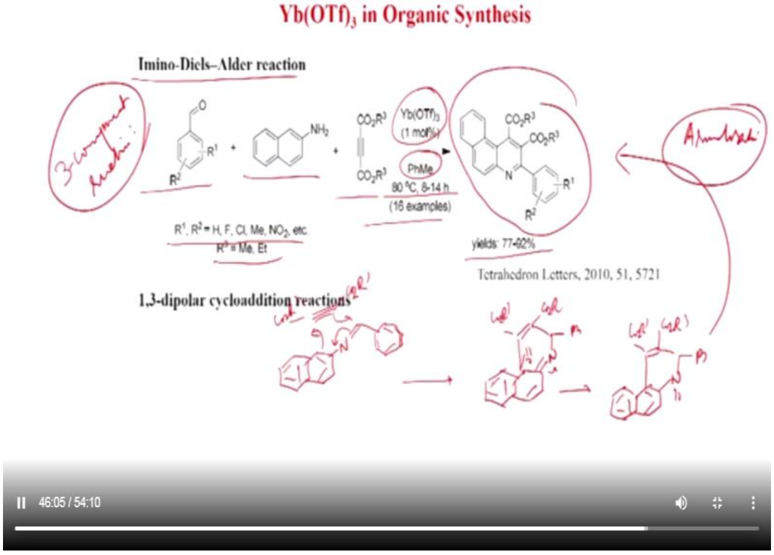

Yb(OTf)$_3$ in Organic Synthesis

Imino-Diels–Alder reaction

R^1, R^2 = H, F, Cl, Me, NO_2, etc.
R^3 = Me, Et

yields: 77-92%

Tetrahedron Letters, 2010, 51, 5721

1,3-dipolar cycloaddition reactions

Another example, imino-Diels-Alder reaction. This is also Povarov kind of reaction. So, here also amine, aldehyde and ester. So alkynyl ester is present. So this is 3 component reaction, 3 component reaction and you get this aromatic compound in 77 to 92 percent yield with ytterbium triflate 1 mole percent, toluene 80 degree centigrade 8 to 14 hours and different substituents can be tolerated R1, R2. So, this is R1, R2. Also R3 is equal to methyl, ethyl; R1, R2 can be hydrogen fluoride, chloride methyl, nitro etc.

So what could be the mechanism? So here also like Povarov kind of mechanism will happen. So this is the amine and of course it will generate the imine with this phenyl and CO2 R’. So now again this kind of reaction will happen this, this. So then this becomes double bond and here a new double bond will form. So like earlier, the aromatization will take place here. So this ring will be aromatized now. But since there is a double bond present, so with air if you heat it 80 degree centigrade then the aromatization will happen. So after aromatization you get this pyridine.

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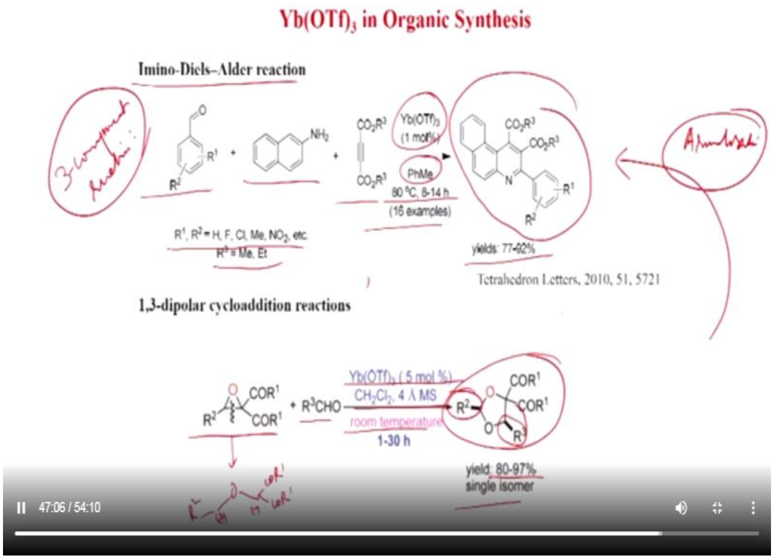

$Yb(OTf)_3$ in Organic Synthesis

Imino-Diels–Alder reaction

$R^1, R^2 = H, F, Cl, Me, NO_2$, etc.
$R^3 = Me, Et$

yields: 77-92%

Tetrahedron Letters, 2010, 51, 5721

1,3-dipolar cycloaddition reactions

yield: 80-97%
single isomer

Now we will discuss 1, 3-dipolar cycloaddition reactions. Ytterbium triflate can also do this kind of reaction, like here epoxy ketone is present with aldehyde. Ytterbium triflate 5 mole percent, dichloromethane 4 Armstrong molecular sieves with room temperature you get this cyclic acetal in 80 to 97 percent yield and this is single isomer. So this R3 and R2 are from the same side. So most likely so this bond is breaking and you get a dipole. So oxygen, this will be minus COR1, COR1 and this of course will be plus and then this aldehyde reacts.

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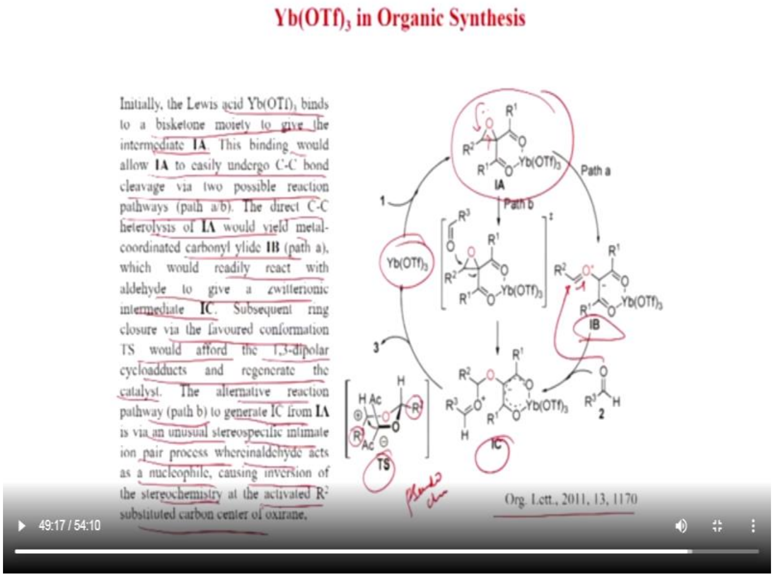

$Yb(OTf)_3$ in Organic Synthesis

Initially, the Lewis acid $Yb(OTf)_3$ binds to a bisketone moiety to give the intermediate **IA**. This binding would allow **IA** to easily undergo C-C bond cleavage via two possible reaction pathways (path a/b). The direct C-C heterolysis of **IA** would yield metal-coordinated carbonyl ylide **IB** (path a), which would readily react with aldehyde to give a zwitterionic intermediate **IC**. Subsequent ring closure via the favoured conformation TS would afford the 1,3-dipolar cycloadducts and regenerate the catalyst. The alternative reaction pathway (path b) to generate IC from **IA** is via an unusual stereospecific intimate ion pair process whereinaldehyde acts as a nucleophile, causing inversion of the stereochemistry at the activated R^2 substituted carbon center of oxirane.

Org. Lett., 2011, 13, 1170

So that we will see the mechanism now details. So with ytterbium triflate, the Lewis acid binds to a bis-ketone moiety to give the intermediate 1A. So it binds first with these two carbonyl motif. This binding would allow 1A to easily undergo CC bond cleavage via two possible reaction pathways, path A or B. So the C-C bond this bond is breaking, that direct C-C hydrolysis of 1A would yield metal coordinated carbonyl ylide 1B.

So if like this, this will be oxonium ion and here a negative charge will form. 1B will generate which will readily react with aldehyde to give a zwitterionic intermediate 1C. So, this aldehyde now react here to generate this. This will be oxonium ion here now on the aldehyde. Subsequent ring closure via the favored conformation transition state would afford the 1, 3 dipolar cycloadducts and regenerate the catalyst. So here you can see this kind of transition state will form. So this is pseudo chair, pseudo chair so both are in the downside and after that you get your product and ytterbium triflate catalyst back.

The alternate reaction pathway path 1B to generate 1C from 1A via an unusual stereo specific intimate ion pair process where an aldehyde acts as a nucleophile causing inversion of the stereochemistry at the activated R2 substituted carbon center of oxirane. So here this aldehyde is reacting directly to here. And now this is the same intermediate will form and then this geometry will determine the product formation. So this work was published in Organic Letters 2011, page number 1170.

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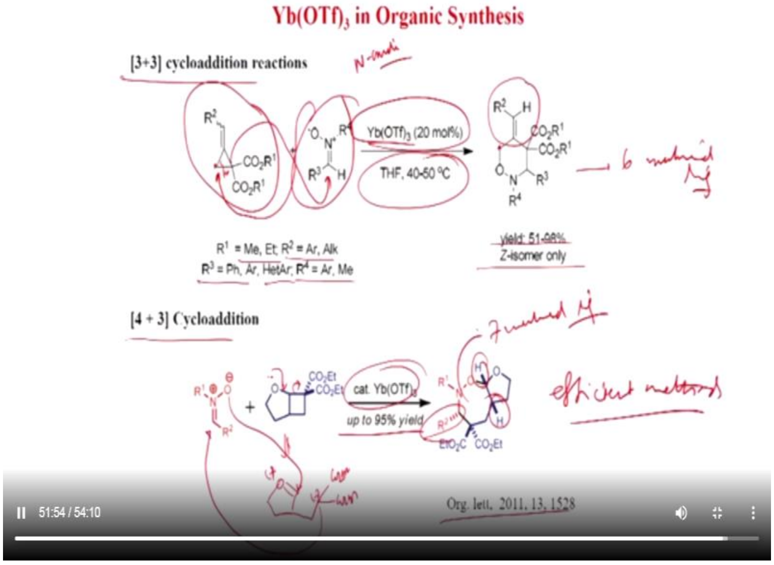

Yb(OTf)$_3$ in Organic Synthesis

[3+3] cycloaddition reactions

R^1 = Me, Et; R^2 = Ar, Alk
R^3 = Ph, Ar, HetAr; R^4 = Ar, Me

yield: 51-98%
Z-isomer only

[4 + 3] Cycloaddition

Org. lett., 2011, 13, 1528

Now we will discuss 3+ 3 cycloaddition reaction also is possible. Like here the cyclopropyl ester is present and this is the N-oxide with ytterbium triflate 20 mole percent, THF 40 to 50 degree centigrade this 3-3 plus cycloaddition product. This is the 6-member ring, 6-member ring is forming. So what is happening here?

This bond is breaking and this one is attacking to here and this bond is breaking then it is attacking to this imine. So you can see this oxygen is with this carbon, this carbon is here and this one is attacking to the imine carbon. So R3 carbon is here. And different substituents like R1 is equal to methyl ethyl, R2 is equal to aryl, alkyl; R3 phenyl, aryl, methyl; R4, aryl, methyl and with this 40 to 50 degree centigrade you can get this product, yield is 51 to 98 percent and Z isomer only. So this is the olefin geometry and you get Z isomer.

Now 4+ 3 cycloaddition. So 4+ 3 cycloaddition also is possible and you can see here also this kind of intermediate is formed. So this will equilibrate to positive negative. So this negative reacts here and this oxygen reacts here. And this is 4+ 3, you can get a 7-member ring.

So this is 7-member ring with ytterbium triflate the geometry is very important, here also syn geometry is formed and this is downside. So these products are found in up to 95 percent yield. So this is very efficient method and this work was published in Organic Letters, 2011 page number 1528.

So in today's class we have seen the samarium iodide mediated Barbier and Grignard reactions. So Barbier condition, we have seen that carbonyl compound halide and samarium iodide are added together. On the other hand in Grignard condition, you have to add first the halide with the samarium iodide and then the carbonyl compound will be added. So in cases where the radical is unstable, like it can give dimer like allyl, benzyl case, in that case you have to use the Barbier cases and all intermolecular reactions like this kind are Barbier condition.

So we have seen that different groups can be tolerated. Also we have seen in these cases the functionalized halides can be also used, that is very important of samarium mediated Grignard reaction. And later we have seen the aldol as well as the Reformatsky reactions. So when Alpha halo substituent is present with a carbonyl compound that time we call this Reformatsky and when alpha heteroatom like O CO Ph or S sulfur moiety are present then we called it aldol products and you get this beta hydroxy carbonyl compounds in very high yield and we have seen that different products are forming with high diastereoselectivities.

Then we have seen ytterbium triflate and it acts as a Lewis acid in many cycloaddition reactions. We have seen it is in Diels Alder reaction, then hetero Diels Alder reaction, then reactions with Danishefsky and Brassard diene. Also with chiral catalyst the reaction can be done in enantioselective way. And lastly we have seen 3 plus 3 cycloaddition with N-oxide also 4 plus 3 cycloaddition. So, this is the last class. I hope you have enjoyed all classes. Thank you.