Reagents in Organic Synthesis
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Lecture 20
Equivalence of Galois extensions and Normal-separable extensions

Welcome again, today we will discuss titanium-based organic reagents. So titanium is a transition metal.

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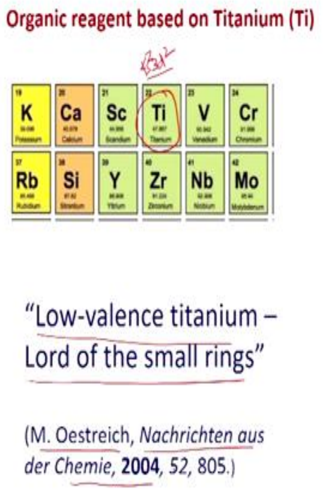
Organic reagent based on Titanium (Ti)

“Low-valence titanium – Lord of the small rings”

(M. Oestreich, *Nachrichten aus der Chemie*, **2004**, *52*, 805.)

This is 4th series, so it is $4s^2$ and $3d^2$. So this is titanium here after scandium and this Low-valance titanium that is very much useful for the generation of small rings, so that is why it is called “Lord of the small rings” and it was in this German general, Nachriten aus der Chemie, 2004,52,805.

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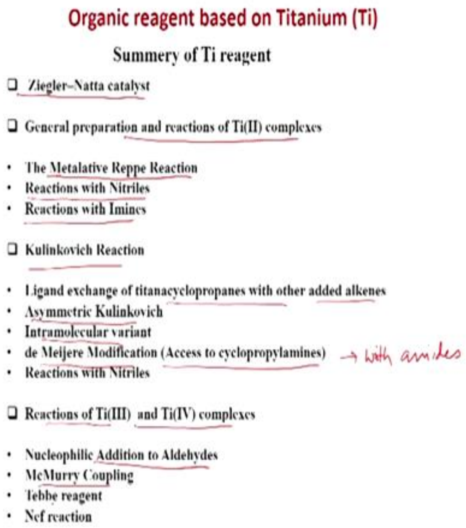

Organic reagent based on Titanium (Ti)

Summery of Ti reagent

❑ Ziegler–Natta catalyst

❑ General preparation and reactions of Ti(II) complexes

- The Metalative Reppe Reaction
- Reactions with Nitriles
- Reactions with Imines

❑ Kulinkovich Reaction

- Ligand exchange of titanacyclopropanes with other added alkenes
- Asymmetric Kulinkovich
- Intramolecular variant
- de Meijere Modification (Access to cyclopropylamines) → with amides
- Reactions with Nitriles

❑ Reactions of Ti(III) and Ti(IV) complexes

- Nucleophilic Addition to Aldehydes
- McMurry Coupling
- Tebbe reagent
- Nef reaction

So first we will discuss how many of Titanium reagents, so Ziegler-Natta catalyst which is Nobel Prize so that we will discuss. Then the general preparation and reaction of titanium complexes. The Metalative Reppe reaction. Reactions with nitrides. Reactions with Imines and Kulinkovich reaction. Ligand exchange of titanacyclopropanes with other added alkenes. Assymmetric Kulinkovich reaction. Intermolecular variant. de Meijere modification access to cyclopropylamines that will see which amides, so this is with amides.

Then reactions with nitriles and lastly we will discuss reactions of titanium(III) and titanium(IV) complexes. Nucleophilic additions to aldehydes. McMurry coupling, Tebbe reagent and Nef reaction.

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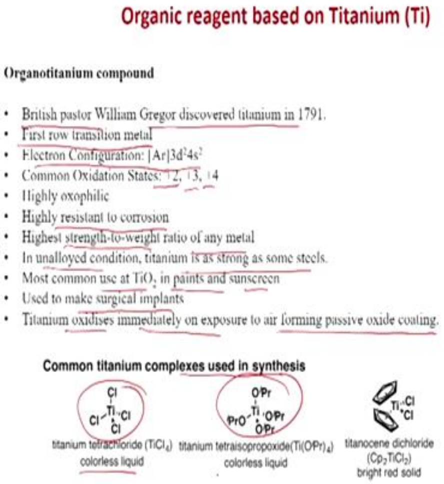

Organic reagent based on Titanium (Ti)

Organotitanium compound

- British pastor William Gregor discovered titanium in 1791.
- First row transition metal
- Electron Configuration: [Ar]$3d^2 4s^2$
- Common Oxidation States: +2, +3, +4
- Highly oxophilic
- Highly resistant to corrosion
- Highest strength-to-weight ratio of any metal
- In unalloyed condition, titanium is as strong as some steels.
- Most common use at TiO_2 in paints and sunscreen
- Used to make surgical implants
- Titanium oxidises immediately on exposure to air forming passive oxide coating.

Common titanium complexes used in synthesis

titanium tetrachloride ($TiCl_4$)
colorless liquid

titanium tetraisopropoxide($Ti(O^iPr)_4$)
colorless liquid

titanocene dichloride
(Cp_2TiCl_2)
bright red solid

So first we will tell some things about Organotitanium compound. So British Pastor William Gregor discovered titanium in 1791. And this is first row transition metal that we have seen earlier. And the electronic configuration is $[Ar]3d^2 4s^2$ and common oxidation are +2, +3, +4. These are highly oxophilic and highly resistant to corrosion also. Highest strength to weight ratio of any metal.

In unalloyed condition, titanium is as strong as some steels. Most common use at titanium oxide in paints and sunscreen. Used to make surgical implants. Titanium oxidises immediately on exposure to air forming passive oxide coating. And these are common titanium complexes used in synthesis. Titanium tetrachloride which is colourless liquid and titanium Tetraisopropoxide which is also a colourless liquid and titanocene dichloride Cp_2TiCl_2. This is bright red solid. This is commercially available and this is a precursor for Tebbe reagent. You can prepare Tebbe reagent from this titanocene dichloride.

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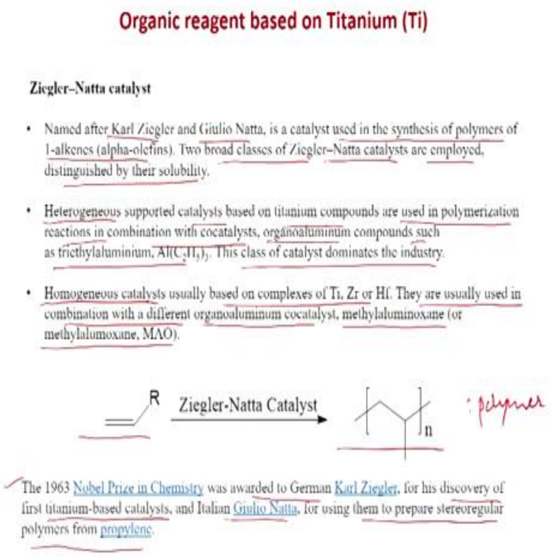

Organic reagent based on Titanium (Ti)

Ziegler–Natta catalyst

- Named after Karl Ziegler and Giulio Natta, is a catalyst used in the synthesis of polymers of 1-alkenes (alpha-olefins). Two broad classes of Ziegler–Natta catalysts are employed, distinguished by their solubility.
- Heterogeneous supported catalysts based on titanium compounds are used in polymerization reactions in combination with cocatalysts, organoaluminum compounds such as triethylaluminium, $Al(C_2H_5)_3$. This class of catalyst dominates the industry.
- Homogeneous catalysts usually based on complexes of Ti, Zr or Hf. They are usually used in combination with a different organoaluminum cocatalyst, methylaluminoxane (or methylalumoxane, MAO).

The 1963 Nobel Prize in Chemistry was awarded to German Karl Ziegler, for his discovery of first titanium-based catalysts, and Italian Giulio Natta, for using them to prepare stereoregular polymers from propylene.

So first we will discuss Ziegler-Natta catalyst. Named after Karl Ziegler and Giulio Natta is a catalyst used in the synthesis of polymers of 1-alkenes alpha olefins. 2 broad classes of Ziegler Natta catalyst are employed, distinguished by the solubility. So one will be homogeneous and other will be heterogeneous. Heterogeneous supported catalyst based on titanium compounds are used in polymerisation reactions in combination with co-catalysts, Organoaluminium compounds such as triethylaluminium. This class of catalyst dominates the industry.

On the other hand homogeneous catalysts usually based on complexes of titanium, zirconium, hafnium. They are usually used in combination with a different organoaluminium co-catalyst, Methyl aluminnoxane or Methylalumoxane MAO. So this is the reaction if you have terminal olefin with Ziegler Natta catalyst you get a Polymer. And as I said earlier the 1963 Nobel Prize in chemistry was awarded to German Karl Ziegler for his discovery of first titanium-based catalyst and Italian Giulio Nara for using them to prepare stereoregular polymers from propylene.

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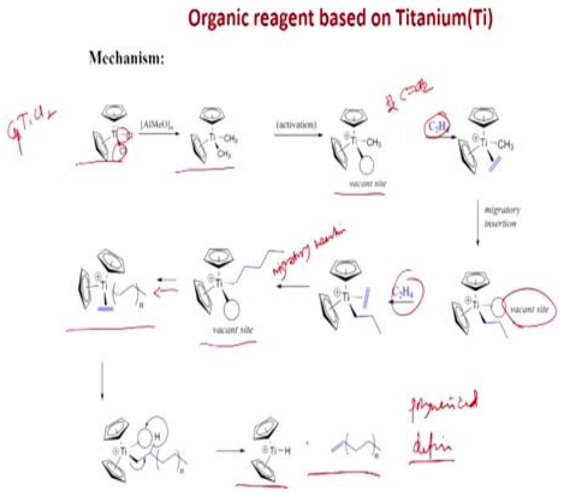

Organic reagent based on Titanium(Ti)

Mechanism:

So now we will see the mechanism of the Ziegler Natta polymerisation reaction. So this is the starting material Cp_2TiCl_2 this is commercially available. Now if you react with this aluminium ethoxyline then you get this. Chlorine is replaced by methyl groups and now the activation can be done on this complex and you get a vacant site because this can eliminate as a methane actually and then C_2H_4, so this is ethylene.

Ethylene comes and ethylene binds to the titanium and now migrator insertion happens. This methyl group goes to the double one. The propyl group is generated and also vacant site. Now another molecule of ethylene can take this vacant site and again the migrator insertion will happen. This propyl group adds to the olefin you get this. Again a vacant site is added. And like this way you get this one polymerization. And with an olefin here ethylene and finally what will happen?

This will go to a double bond, so first this vacant site will be taken up this hydride and you get this one and the olefin, polymerized olefin.

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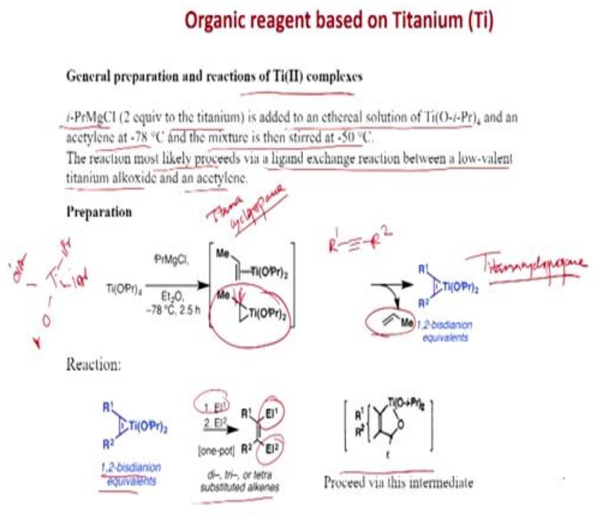

Organic reagent based on Titanium (Ti)

General preparation and reactions of Ti(II) complexes

i-PrMgCl (2 equiv to the titanium) is added to an ethereal solution of Ti(O-*i*-Pr)$_4$ and an acetylene at -78 °C and the mixture is then stirred at -50 °C.
The reaction most likely proceeds via a ligand exchange reaction between a low-valent titanium alkoxide and an acetylene.

Preparation

Reaction:

Proceed via this intermediate

General preparation and reactions of titanium II complexes, so this is very important. Titanium II can be said Tetanus cycloproane and Tetanusclyclopropen that we will see. Like isopropyl magnesia chloride 2 equivalent of titanium is added to ethereal solution of titanium isopropoxide and acetylene at -70 degrees centigrade and the mixture is then stirred at -50 degrees centigrade.

The reaction most likely proceeds via a Ligand exchange reaction between a low valent titanium alkoxide and an acetylene. So this is the preparation, so isopropyl magnesium chloride this mechanism we will see later also. So isopropyl magnesium chloride and ether and titanium isopropoxide then you get this tetanuscyclopropane because 2 equivalents of isopropyl, so this will form o isopropyl, o isopropyl and isopropyl go to here and here isopropyl group.

And then one isopropyl group will eliminate and generate this one tetanus cyclopropane which will be in equilibrium with this and now if you react with an alkyne the Ligand exchange will happen. Now if you react with an alkyne this propylene will eliminate and you get this tetanus cyclopropene you can tell this, so this is formed. And this has been exploited in many reactions.

Like this one, this is 1,2 bis-dianion equivalents because carbon titanium bond you can break it. If you put suitable electrophile like E1 you can put here and another electrophile EI2 di,tri or tetra substituted alkanes you can prepare and this follows by this intermediate. Suppose if you react with an electrophile then this kind of five membered intermediate is formed.

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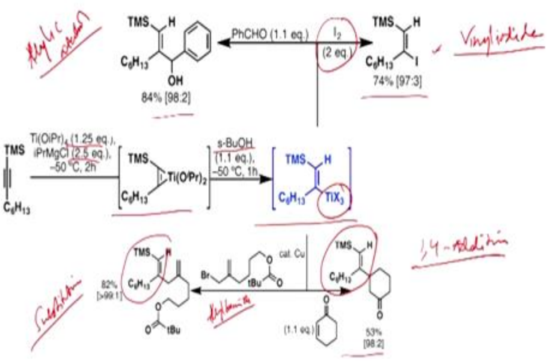
Organic reagent based on Titanium(Ti)

(η2-alkyne)Ti(O*i*Pr)$_2$ reactions



JACS 1999, 121, 2931

So we will see details, first we will discuss this (alkyne) Ti(OiPr)$_2$ reactions. So suppose this TMS and disubstituted alkyne, if you put with titanium di-isopropoxide 1.2 equivalent, 2.5 equivalent isopropyl magnesium chloride at minus 50 degrees centigrade you get these titanuscyclopropane. Now if you react with secondary butanol, s butanol then 1 equivalent minus 50 degrees centigrade, you get this.

And which in situ if you treat with iodine then you get this one is substituted with iodine, you get this one Vinyl iodide and you can react with an aldehyde also then you get this allylic alcohol. So this is a chemistry that alkyne can be reductively converted with titanium reagent to generate this and then you can do a substituted reaction here or addition reactions with iodine as well as benzaldehyde to get these products. Also you can do copper chemistry, so then this is actually 1, 2 addition reactions slide Also you can do 1, 4. Like if you react a cyclohexanone then this group is coming from here and this is the 1,4 addition, you get 53 percent yield.

Also if you react with this allyl bromide then a substitution reaction. So this is substitution reaction is happening here, so this group is coming from the titanium part and this is the product is forming exactly. This was published in JACS 99.

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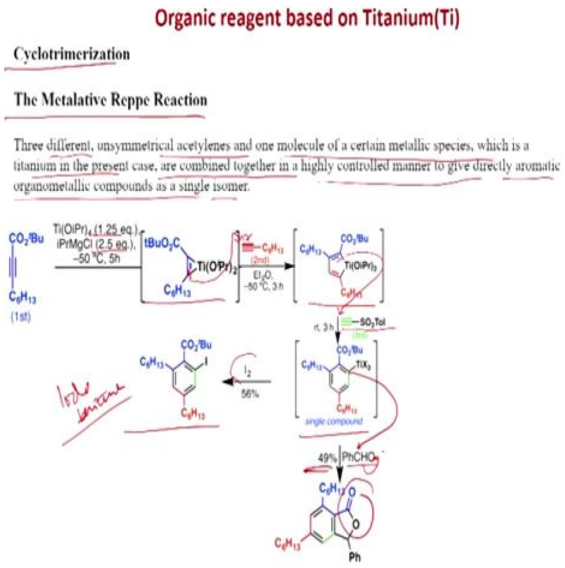

Organic reagent based on Titanium(Ti)

Cyclotrimerization

The Metalative Reppe Reaction

Three different, unsymmetrical acetylenes and one molecule of a certain metallic species, which is a titanium in the present case, are combined together in a highly controlled manner to give directly aromatic organometallic compounds as a single isomer.

Cyclotrimerisation reaction that is called Metalative Reppe reaction, so that is also exploited with this. And here in this Metalative Reppe reaction we will see 3 different alkynes are used and you can get benzene derivatives. So this is an important reaction, 3 different unsymmetrical Acetylenes and one molecule of a certain metallic species which is a titanium in the present case are combined together and in highly controlled manner to give directly aromatic organometallic compounds as a single isomer.

Like here this is disubstituted alkyne and if you treat with titanium isopropoxide 1.2 equivalent, isopropyl magnesium chloride 2.5 equivalent you get this tetanus cyclopropene this then reaction with this terminal alkyne here and Ether minus 50 degrees centigrade. Here what happens, this one this carbon titanium bond breaks first, so the addition happens here and this is quite regioselective as you can see.

So this adds here and like this, so you get this 5 membered titanuscyclopentadine intermediate and now again if you react with the sulfonyl alkyne then selectively this compound is formed. The detail mechanism we will show in the next slide but if you see the regioselectivity here also this bond is breaking and this is adding to here.

And this intermediate if you put with iodine then you get this Iodobenzene is formed with substitution also. Alternated with this one if you react with benzaldehyde what happens? This reacts with the carbonyl group and that oxygen cyclize with the ester, so you get a lactone here and this compound is formed in 49 percent yield. So this is maybe useful reaction and you can see all alkyne component are present. This is your blue then red and the green, all alkyne component are… So this is a useful reaction.

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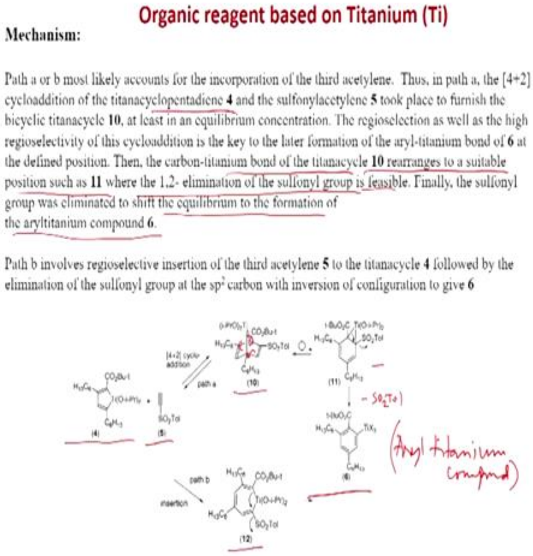

Organic reagent based on Titanium (Ti)

Mechanism:

Path a or b most likely accounts for the incorporation of the third acetylene. Thus, in path a, the [4+2] cycloaddition of the titanacyclopentadiene **4** and the sulfonylacetylene **5** took place to furnish the bicyclic titanacycle **10**, at least in an equilibrium concentration. The regioselection as well as the high regioselectivity of this cycloaddition is the key to the later formation of the aryl-titanium bond of **6** at the defined position. Then, the carbon-titanium bond of the titanacycle **10** rearranges to a suitable position such as **11** where the 1,2- elimination of the sulfonyl group is feasible. Finally, the sulfonyl group was eliminated to shift the equilibrium to the formation of the aryltitanium compound **6**.

Path b involves regioselective insertion of the third acetylene **5** to the titanacycle **4** followed by the elimination of the sulfonyl group at the sp^2 carbon with inversion of configuration to give **6**

So what could be the mechanism? So this could be the mechanism that the last step actually, the sulphonyl alkyne that mechanism we will see. So this one was formed Titanacyclopentadine 4 and if you react with sulfonylacetylene then you can think of 4+2 reaction is bicyclic intermediate might formed and then this one is formed. If you see this one, this carbon titanium bond breaks and now the Olefin will isomerize and you get this one and after that elimination of SO_2Tol group you get this, 6.

Alternatively, so this titanaicular the carbon titanium bond of the titanacyle 10 rearranges to a suitable position such as 11 where the 1, 2 elimination of the sulfonyl group is feasible. Finally, the sulfonyl group was eliminated to shift the equilibrium for the formation of aryltitanium compound 6. So this is aryltitanium compound. That we have seen earlier, this aryltitanium compound will form.

Alternatively, the insertion reaction also is possible like this one reacts with this. This is insertion and then a rearrangement happens to get this aryltitanium benzene derivative.

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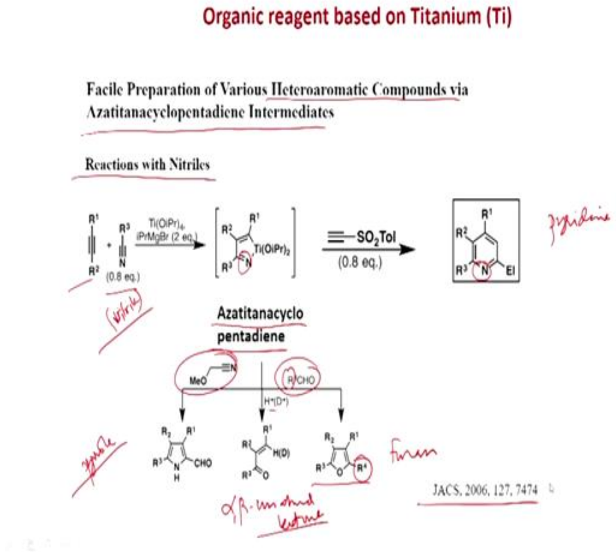
Organic reagent based on Titanium (Ti)

Facile Preparation of Various Heteroaromatic Compounds via Azatitanacyclopentadiene Intermediates

Reactions with Nitriles

Azatitanacyclo pentadiene

JACS, 2006, 127, 7474

So with this we can develop also facile preparation of various Heteroaromatic compounds via Azatitancyclopentadine intermediate. So the cyclopentadine intermediate if you generate as a titanacyclopropane Pentadine intermediate then it will be also useful and that is possible only with reactions with nitriles. So this alkyne is there and then instead of other alkyne here we have put the nitrile.

And this is the intermediate earlier it was carbon here. So here it is Azatitanacyclopentadiene. So Aza works in this one and this also has been useful. So if you react with sulfonyl Acetylene you get pyridine. So remember this nitrogen is here, so that is why the pyridine derivative is formed and the mechanism will be similar, we will see details also. And if you put another equivalent of nitrile then you can get pyrrole.

If you put an aldehyde then you get Furan and if you see this R4, it is here. So it is substituted Furan. Alternatively, if you put this intermediate just with H+ then the hydrolysis of imine is happened and you get this Alpha beta unsaturated ketone. So Alpha beta unsaturated ketone is formed, if we do not put another electrophile then you will get this ketone and this work has published in JACS 2006.

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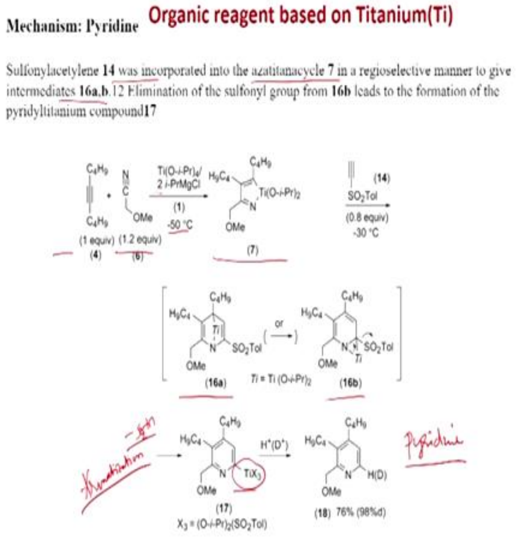

Mechanism: Pyridine Organic reagent based on Titanium(Ti)

Sulfonylacetylene **14** was incorporated into the azatitanacycle **7** in a regioselective manner to give intermediates **16a,b**.12 Elimination of the sulfonyl group from **16b** leads to the formation of the pyridyltitanium compound**17**

So we will discuss first the mechanism of the formation of pyridine where the sulfonyl alkyne was used. Sulfonylacetylene 14 was incorporated into the azatitanacycle 7 in a regioselective manner to give intermediate 16ab. So first this is formed you have seen earlier as a titanacyclopentadine will be formed with titanium ispropoxide 2 equivalent of isopropyl magnesium chloride -50 degrees centigrade with alkyne and nitrile.

After this you put this one and now this 4+2 will happen and now this will be formed and this 16a which will be converted into 16b like earlier we have seen and now the elimination of SO_2Tol group, so this is the elimination SO_2Tol group with this titanium metalated pyridine derivatives. So this way the SO_2Tol is eliminating this bond in nitrogen titanium is breaking and you get double one. That is the aromotization also, so this aromatzation is happening here and you get this titanium carbon bond here which can be of course protonated to get this pyridine compound.

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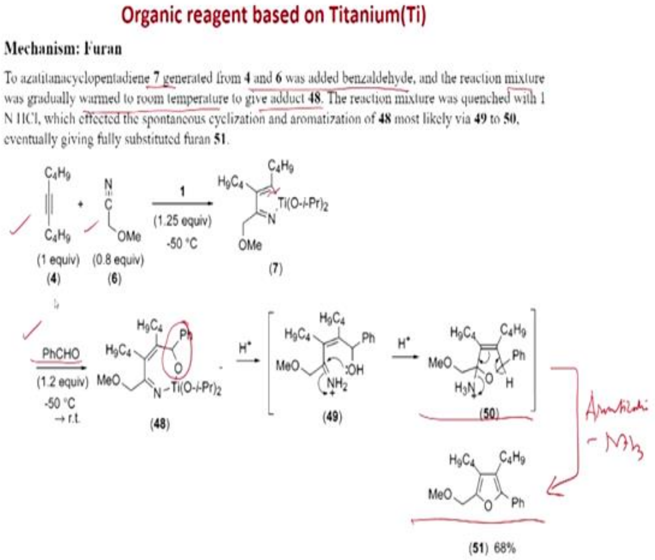

Organic reagent based on Titanium(Ti)

Mechanism: Furan

To azatitanacyclopentadiene 7 generated from 4 and 6 was added benzaldehyde, and the reaction mixture was gradually warmed to room temperature to give adduct **48**. The reaction mixture was quenched with 1 N HCl, which effected the spontaneous cyclization and aromatization of **48** most likely via **49** to **50**, eventually giving fully substituted furan **51**.

For the Furan formation you have seen that you have to use another aldehyde. So as a cyclopentadine 7 generated from 4 and 6 was added benzaldehyde and the reaction mixture was gradually warmed to room temperature to give adduct 48, so this was the common intermediate, azatitanacyclopentadine and now if you react with benzaldehyde and here the benzaldehyde will add to this carbon titanium bond because this is more reacting, so this one will break and the benzaldehyde will come.

So this is the benzaldehyde substance here. Benzyl group is here, benzaldehyde after addition and now if you put the acid what will happen? This alcohol will adduct to the Iminium ion to generate this intermediate and then the aromatization will happen to give this Furan, Aromatization. Also one equivalent of ammonia is eliminated as you can see. So ammonia is a leaving group here. So you get a Tetra substitute in Furon. So this is a very useful method to generate Tetra substituted in Furan. The alkyne, nitrile and aldehyde.

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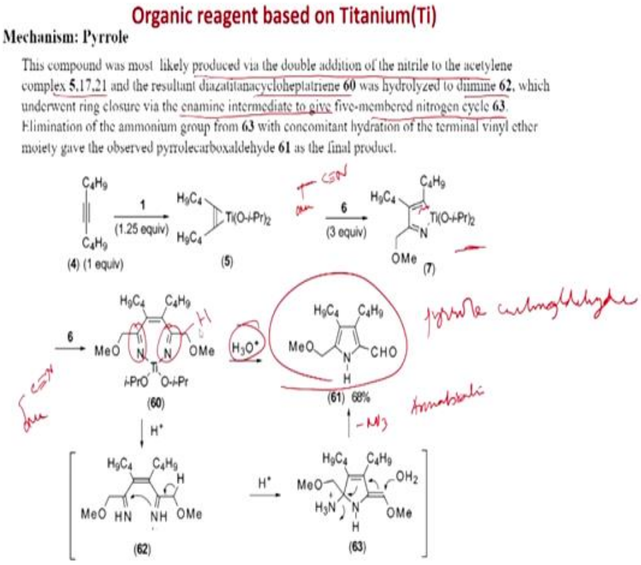

Organic reagent based on Titanium(Ti)

Mechanism: Pyrrole

This compound was most likely produced via the double addition of the nitrile to the acetylene complex 5,17,21 and the resultant diazatitanacycloheptatriene **60** was hydrolyzed to diimine **62**, which underwent ring closure via the enamine intermediate to give five-membered nitrogen cycle **63**. Elimination of the ammonium group from **63** with concomitant hydration of the terminal vinyl ether moiety gave the observed pyrrolecarboxaldehyde **61** as the final product.

And now Pyrrole we have told that 2 equivalent of nitrile is used then the Pyrrole formation happens and this is the mechanism, the compound was most likely produced via the double addition of the nitrile to the Acetylene complex 5,17,21 and the resultant diazatatanacycloheplatine 60 was hydrolysed to diimine 62 which underwent ring closure. So this is formed and now 6, this is 6 the nitrile.

The nitrile is 6, so after this common intermediate form and now the nitrile again is added, 6 is again added and selectively as well as in this one will break and they have the addition happens and nitrile addition you get imine. So this is the clean intermediate diazatitanacycloheptatiene 60 is formed. So here you can see 2 imine is present. And now because this is a hydrogenic acidic, so this kind of isomerization will happen.

Of course this is happening because of aromatization and now this enamine will attack to the iminium ion that is what to generate this this five-member nitrogen cycle 63 and elimination of ammonium group followed by aromatization will give you Pyrrole. Pyrrole carboxaldehyde 61 is the final product, so this is very important reaction Pyrrole carboxaldeyde. So this is useful reaction, if you use one equivalent of alkyne and 2 equivalent of nitrile then you can get this pyrrol with titanium chemistry. So this is the (()) (21:50) here finally.

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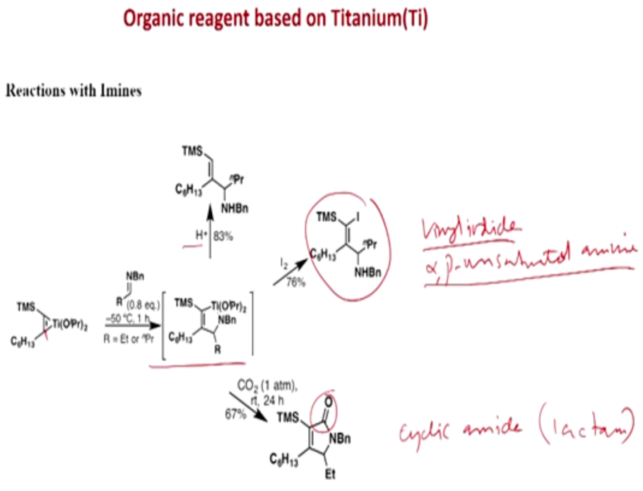
Organic reagent based on Titanium(Ti)

Reactions with Imines

Now we will see what happens with imine. So instead of nitrile if you react with imine then again this bond will break here, so if TMS is there then this bond will break and you get an addition reaction and here you can put with iodine then this carbon titanium will be replaced by iodine, so you get vinyl iodide.

Vinyl iodide and also this is Alpha beta unsaturated amine, so imine is converted to amine and also if you put the acidic work up then this titanium bond can be break. Alternatively, you can put carbon dioxide then you get an amide, cyclic amide which is called Lactum. So formation of Lactum is observed. So this carbonyl group is coming from carbon dioxide and the double cyclisation is happening to get this cycle.

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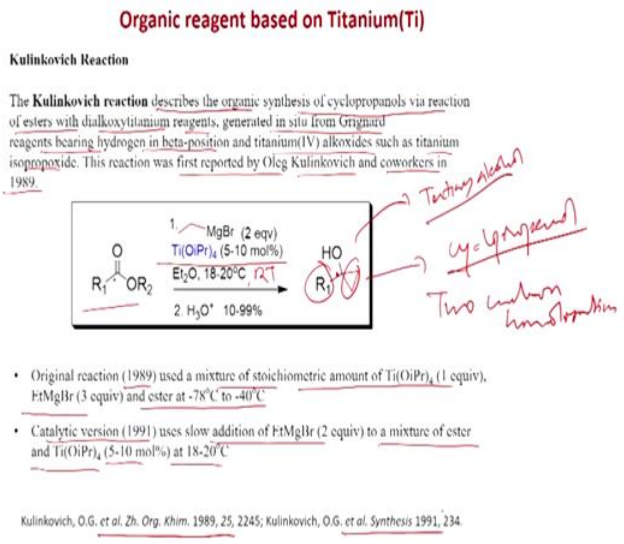
Organic reagent based on Titanium(Ti)

Kulinkovich Reaction

The **Kulinkovich reaction** describes the organic synthesis of cyclopropanols via reaction of esters with dialkoxytitanium reagents, generated in situ from Grignard reagents bearing hydrogen in beta-position and titanium(IV) alkoxides such as titanium isopropoxide. This reaction was first reported by Oleg Kulinkovich and coworkers in 1989.

- Original reaction (1989) used a mixture of stoichiometric amount of $Ti(OiPr)_4$ (1 equiv), EtMgBr (3 equiv) and ester at -78°C to -40°C
- Catalytic version (1991) uses slow addition of EtMgBr (2 equiv) to a mixture of ester and $Ti(OiPr)_4$ (5-10 mol%) at 18-20°C

Kulinkovich, O.G. *et al. Zh. Org. Khim.* 1989, *25*, 2245; Kulinkovich, O.G. *et al. Synthesis* 1991, 234.

Now we will discuss Kulinkovich reaction, this is also a powerful reaction for the generation of cyclopropanols from Esters. The Kulinkovich reaction described the organic synthesis of cyclopropanols via reactions of Esters with dialkoxytitanium reagents generated in situ from Grignard reagents bearing hydrogen in beta position and titanium(IV) alkoxides such as titanium isopropoxide. This reaction was first reported by Oleg Kulinkovich and co-workers in 1989.

So here also the mechanism involves the Titanacyclo-propane that you will see. So if you have an ester and 2 equivalents of Grignard and titanium isopoproxide this you can use catalytic amount also 5 to 10 percent ether, so this is room temperature reaction followed by acidic work up you get 10 to 99 percent yield of this compound. So cyclopropanol and you can see this is 2 carbon homologation because these 2 carbons are coming from the Grignard and this is the ester part and this carbon is this carbon.

Carbonyl carbon become a, this is quaternary centre this is tertiary alcohol. Tertiary alcohol is formed. Original reaction 1989 used a mixture of stoichiometric amount of titanium isopropoxide one equivalent, Ethyl magnesium bromide 3 equivalent and ester at -78 degrees to -40 degrees centigrade. And the catalytic version 1991 uses slow addition of Ethyl magnesium bromide 2 equivalent to a mixture of ester and titanium isopropoxide 5 to 10 mole percent at 18 to 20 degrees centigrade.

So catalytic version was developed later as you can see here and this was the paper, initial paper and then the catalytic version.

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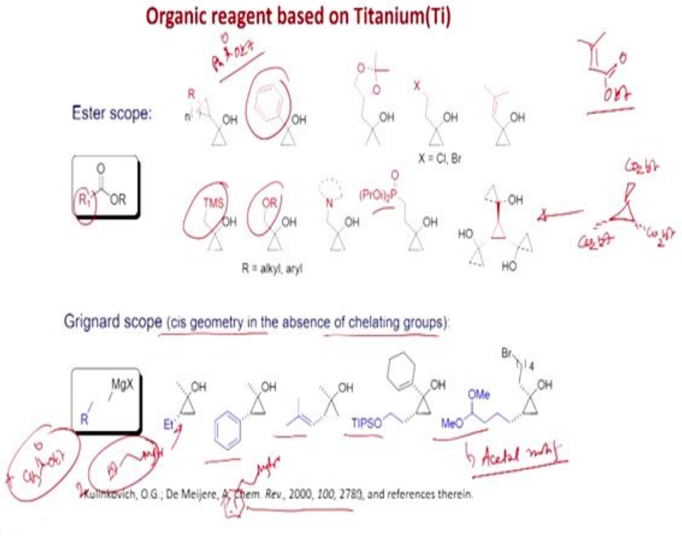

And the scope of this reaction is very broad define Esters can be used as we can see here this R1 is shown in the red here, so this is the cyclopropyl ester, this is benzoate derivatives like PhCOOEt Ethyl Benzoate. This is the functionalised esters, this is also substituted Esters, this is Alpha beta unsaturated ester, so like COOEt, and this part is coming from the Grignard and the TMS group containing, OR group, amino group containing, phosphoryl containing and this the triple ester, so triester is present, so the starting material will be CO_2Et, CO_2Et and CO_2Et, so chiral Centre will not be disturbed in this reaction. So, 3 cyclopropane ring is formed.

Grignard scope cis geometry in the absence of chelating groups, so this kind of grignard you have to use these 2 carbon will be there, so the olefin formation will happen. And now if you use this starting material will be Et, this, this magnesium bromide plus CH_3COOEt. So these 2 will give you this product and this will be 2 equivalents. Also this one, this kind of Phenyl Ethyl magnesium bromide suppose than Alpha beta unsaturated where also functionalised acetal motif, so this also is tolerable under the reaction condition.

So this is a chemical review 2000 that all details are discussed.

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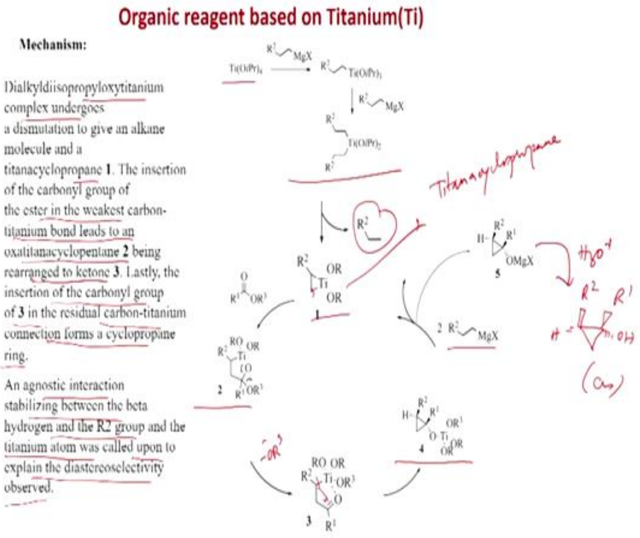

Organic reagent based on Titanium(Ti)

Mechanism:

Dialkyldiisopropyloxytitanium complex undergoes a dismutation to give an alkane molecule and a titanacyclopropane **1**. The insertion of the carbonyl group of the ester in the weakest carbon-titanium bond leads to an oxatitanacyclopentane **2** being rearranged to ketone **3**. Lastly, the insertion of the carbonyl group of **3** in the residual carbon-titanium connection forms a cyclopropane ring.

An agnostic interaction stabilizing between the beta hydrogen and the R2 group and the titanium atom was called upon to explain the diastereoselectivity observed.

Now what will be the mechanism? So the mechanism also inverses like earlier that titanacyclopropane Dialkyldiisopropyloxytitanium complex, okay this was the mechanism first 2 alkyl groups comes from the Grignard reagent, this one is formed then after that elimination of this alkane you get this titanacyclopropane, so this is very important. So titanacyclopropane is formed and now the insertion of the carbonyl group of the ester in the weakest carbon titanium bond leads to an oxatitanacyclopentane 2, so this is formed.

So the weakest means this less substituted carbon titanium bond breaks and you get this and this oxatitanacyclopentane can be rearranged to ketone, of course here this OR^3 group will eliminate $-OR^3$ group will eliminate, you get this or it will bind to titanium also. And ketone will form here. Lastly the insertion of the carbonyl group of 3 in the residual carbon titanium connection forms a Cyclopropane ring. So after this, this bond will break.

So what we have seen here that this titanacyclopropane the both bond will break. So first this bond is breaking to add to the ester and lastly the second carbon titanium bond will break, so that the cyclisation will happen and you get this, so the cycle again happens the displacement by the Grignard to generate this active titanium complex. This of course acidic work up, you get this.

And this is also important that both group R switched to each other, so cis compound is formed. And an agnostic interaction stabilisation between the beta hydrogen and the R2 group and the titanium atom was called upon to explain the diastereoselectivity observe, so this is very important. This is very much diastereoselective reaction also. So the cyclopropanol is formed as one isomer and mainly the cis isomer is formed because of the agnostic interaction.

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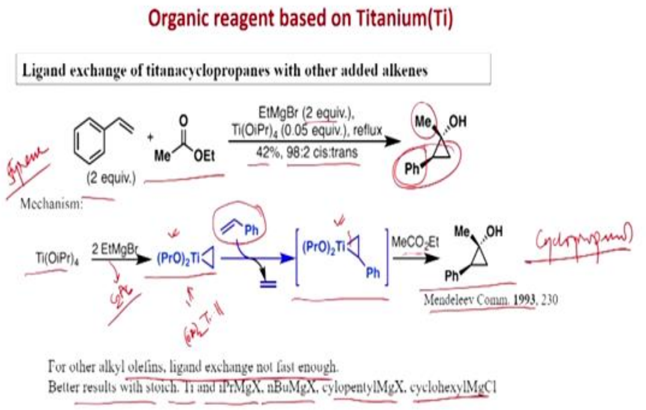

Organic reagent based on Titanium(Ti)

Ligand exchange of titanacyclopropanes with other added alkenes

Mendeleev Comm. 1993, 230

For other alkyl olefins, ligand exchange not fast enough.
Better results with stoich. Ti and iPrMgX, nBuMgX, cylopentylMgX, cyclohexylMgCl

Ligand exchange of titanacyclopropane with other added alkenes this is very important because many times the Grignard reagent formation is not easy then you can use alkane and then the actions would be possible. Like here styrene 2 equivalent with ethyl acetate, Ethyl magnesium bromide 2 equivalent titanium isopropoxide this is catalytic amount, reflux 42 percent yield of 98:2 cis:trans, so this 2 groups are cis to each other and as you can see this styrene motif is here.

So the ligand exchange happened, yeah this is the mechanism the titanium isopropoxide 2 Ethyl magnesium you get this one with one molecule elimination of this C_2H_6 ethane you get this titanacyclopropane and now the styrene comes tie and eliminate the olefin because this one is in equilibrium with this. So that proves that ligand exchange is possible. After ligand exchange you get this styrene motif. So phenyl substituted titanacyclopropane is formed.

And now this carbon titanium bond will break first this addition and then the cyclisation will happen to get this cyclopropanol. So this ligand exchange is very much important. This is published in 1993. However other alkyl olefins ligand exchange not fast enough. And better results with stoichiometric titanium and isopropyl magnesium X instead of Ethyl you can use isopropyl also n butyl, cyclopentyl magnesium and cyclohexyl. So these are most useful that we will see in the next slide because it has to be this complex formation. So this should be more stable than this.

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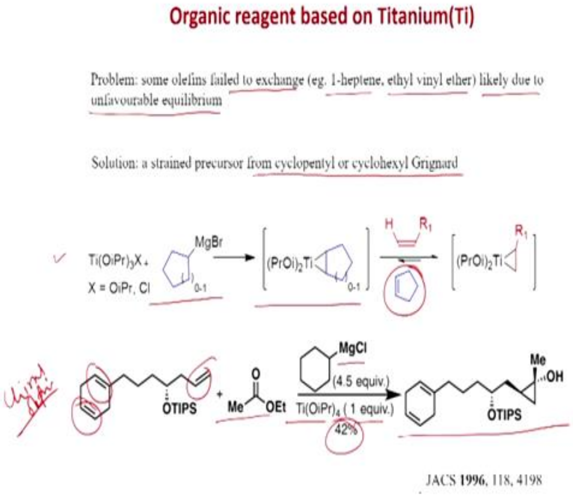

Organic reagent based on Titanium(Ti)

Problem: some olefins failed to exchange (eg. 1-heptene, ethyl vinyl ether) likely due to unfavourable equilibrium

Solution: a strained precursor from cyclopentyl or cyclohexyl Grignard

JACS 1996, 118, 4198

However this equilibration is not always first like some olefins failed to exchange as for example one heptane, Ethyl vinyl ether likely due to unfavourable equilibrium. And what could be the solution? The solution will be a strained precursor from cyclopentyl or cyclohexyl Grignard.

Like here if you put this titanium isopropoxide with this one cyclopentyl or cyclohexyl magnesium bromide you get this and now this equilibrium will be faster. So this cyclopentene elimination will be much faster and this reaction will be in the forward direction. The exchange will be in the forward direction. Like this one a chiral olefin, so this is a chiral olefin and if you see the structure there are 3 olefins, motifs are present.

And now with this condition with ethyl acetate cyclohexyl magnesium chloride 4.5 equivalent, titanium isopropoxide 1 equivalent only this terminal olefin reacts and you get this product selectively 42 percent yield. So what happens here? The exchange happens with cyclohexyl magnesium chloride. First this complex will form then this olefin will react here to generate this substituted titanacyclopropane which reacts with the methyl acetate to generate this cyclopropanol. This was published in JACS 1996.

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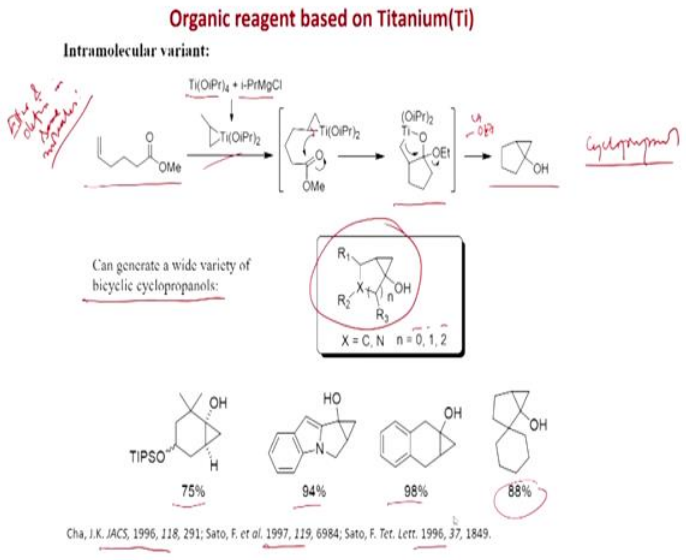
Organic reagent based on Titanium(Ti)

Intramolecular variant:

Can generate a wide variety of bicyclic cyclopropanols:

Cha, J.K. *JACS*, 1996, *118*, 291; Sato, F. *et al.* 1997, *119*, 6984; Sato, F. *Tet. Lett.* 1996, *37*, 1849.

Now intra-molecular variant also is possible, so here ester and olefin means same molecule. So this exchange can be exploited particularly for intramolecular version because here the Grignard immediately reacted with ester, so for this system intramolecular variant only ligand exchange will be useful. So here you can react titanaisopropyl magnesium chloride to get this and now this complex which formed titanacyclopropane, the bond which is close to ester that bond will break.

So this bond will break first to generate this and now the elimination of ethoxide this is substitution will happen, this carbon titanium bond will attack here to eliminate ethoxide to generate this cyclopropanol and this method has been used for a variety of bicyclic cyclopropanols like this kind of system. Bicyclic cyclopropanol, here the x can be carbon and nitrogen, n can be 0, 1, 2.

So it can be cyclopentane, cyclohexane, cycloheptane like this example you can see 75 percent yield of the cyclohexyl this is fuse system 94, this is 98 percent yield and this is 88 percent. So different kind of bicyclic cyclopropanol can be formed and these are the paper JACS 1996 from Cha group, Sato group 1997, also 1996.

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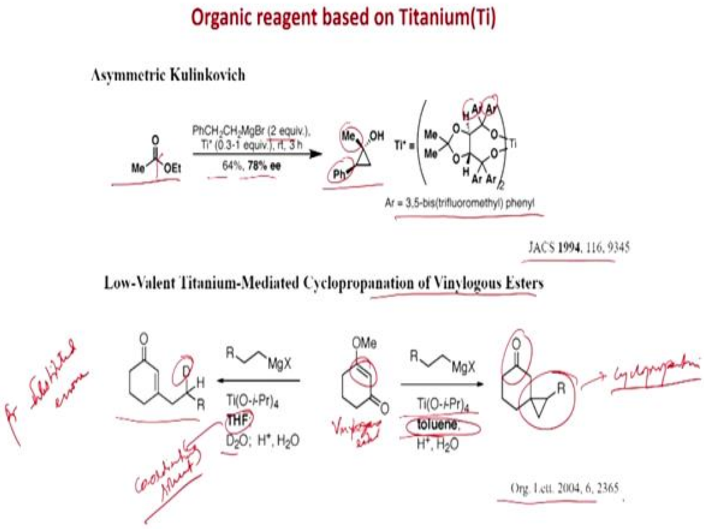

Organic reagent based on Titanium(Ti)

Asymmetric Kulinkovich

JACS 1994, 116, 9345

Low-Valent Titanium-Mediated Cyclopropanation of Vinylogous Esters

Org. Lett. 2004, 6, 2365

Assymmetric Kulinkovich is also possible and here you have to of course use a ligand and Corey group use this Taddol derivative, so with ethyl acetate, phenyl Ethyl magnesium bromide 2 equivalent titanium 0.321 equivalent room temperature three-hours and with this titanium complex, so which is 0.321 equivalent stoichiometric amount 30 mole percent and this Ar= 3,5 bistrifluoromethyl phenyl. So this is the Taddol derivative and you can get 64 percent yield, 78 percent ee to generate this cyclopropanol. Here also the cis stereochemistry is maintained. This is published in JACS 1994.

And another variant was developed where the Vinylogous ester has been used in this Kulinkovich reaction, so this is called Vinylogous ester because between this there is a double bond here as you can see here and if you put this Grignard with titanium isopropoxide in toluene as a solvent then this cyclopropanation happens so not cyclopropanol, so this is cyclopropanation. So we will see the mechanism and this becomes ketone.

Alternatively, if you use coordinating solvent like THF, so THF is coordinating that we will see in the mechanism also. This is coordinating solvent. So in coordinating solvent you get product like this and if you put D_2O then this deuterium comes here. This is an Enone compound, substituted Enone, beta substituted Enone. This was published in organic Lett 2004.

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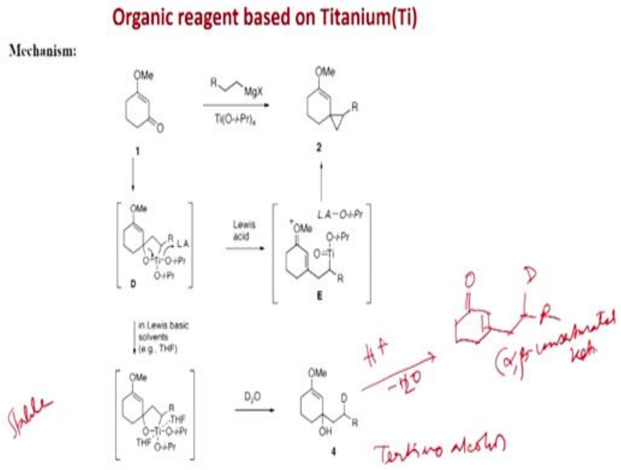

Organic reagent based on Titanium(Ti)

Mechanism:

So the mechanism will be for this formation, first this the titanacyclopropane. So this R titanacyclopropane reacts like this way to the carbonyl group, this carbon titanium bond will break to give this 5 membered ring here and then with Lewis acid you get this, so this happens, isomerisation here and this one breaks. So alkoxy group is breaking here and that is going to carbonyl with the titanium.

And now this one will cyclise with this carbon titanium bond will break and this will add here. Okay, this is now electrophilic carbon. This carbon titanium bond will break, so you get the cyclopropanation and this double bond will be here, here. Alternatively, if you use coordinating Lewis basic solvent such as THF then what happens? This coordination happens with THF and this becomes stable.

And after D_2O only it breaks, so this oxygen titanium, carbon titanium bond will break and you get this tertiary alcohol, this is tertiary alcohol, this form. So in non-coordinating solvent the cyclopropanation happens but in coordinating solvents the intermediate get stable and then the hydrolysis of this intermediate gives the tertiary alcohol. So this tertiary alcohol if you put acid then the hydrolysis will happen that this inner ether will go to carbonyl because it will deprotect first Enol and then Tautomerization.

Water will eliminate because it has a hydroxy group, so water will eliminate to get a double bond that is the Alpha beta unsaturated ketone.

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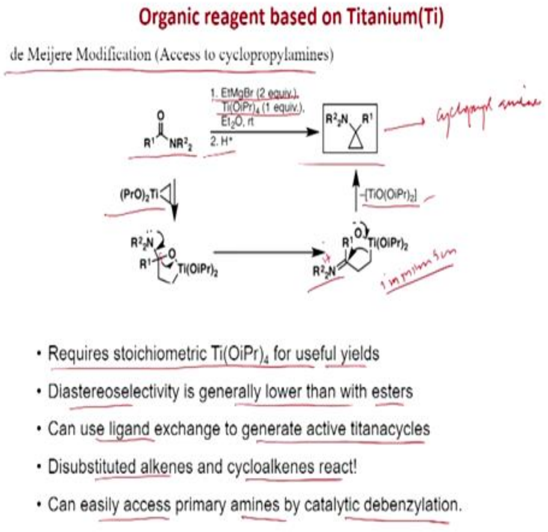

Organic reagent based on Titanium(Ti)

de Meijere Modification (Access to cyclopropylamines)

- Requires stoichiometric Ti(OiPr)$_4$ for useful yields
- Diastereoselectivity is generally lower than with esters
- Can use ligand exchange to generate active titanacycles
- Disubstituted alkenes and cycloalkenes react!
- Can easily access primary amines by catalytic debenzylation.

De Meijere modification, de Mejere also develop a modification and that is using amides, we will see the tertiary amides only. So if you have a tertiary amide with identical condition Ethyl magnesium bromide 2 equivalent and titanium isopropoxide 1 equivalent, ether solvent after that acidic workup you get this cyclopropyl amine, so this is the mechanism that here also titanacyclopropane is formed and the addition happens to the amide and now if you have a tertiary amide then this nitrogen is more Lewis basic, so this nitrogen will push electrons to break this carbon oxygen bond and after this breakage then the carbon titanium will attack to the iminium.

So this is iminium ion because there will of course a positive charge here and this iminium ion on cyclization give the cyclopropylamine and this will eliminate. So this method request stoichiometric titanium isopropoxide for useful yield because this is the formation of titaniumisopropoxide. Diastereoselectivity is generally lower than with esters. Can use ligand exchange to generate active Titanacycles that you will see.

Disubstituted alkenes and cycloalkenes react can easily access primary amines by catalytic debenzylation that we will also see the tertiary amine you can do if it is a benzoyl group easily with hydrogenation condition you can debenzyl.

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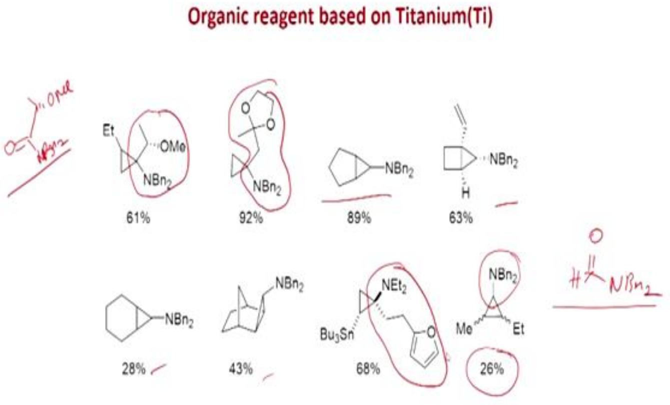
Organic reagent based on Titanium(Ti)

So these are the scope of this reaction, so here you can see this coming from the amide. So this $OMeCONBn_2$ is the amide, here also this is the amide part, so you had to put a carbonyl group and this is of course the ligand exchange that we will see. This was ligand exchange. This ligand exchange. This was the amide and here also this was the amide.

So $HCONBn_2$ formamide, formamide is the… Here you get 26 percent yield.

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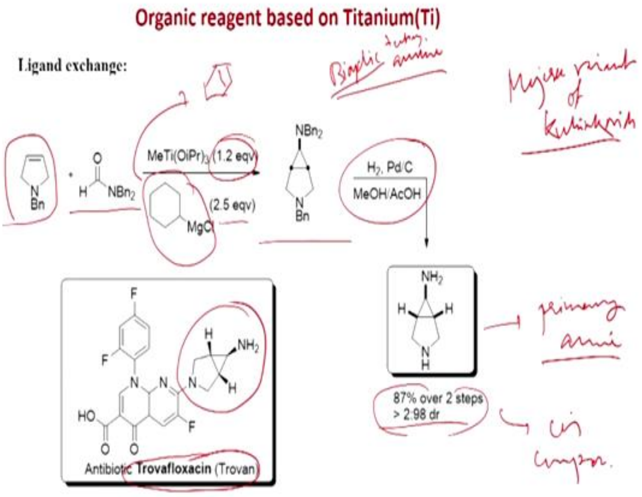
Organic reagent based on Titanium(Ti)

Ligand exchange:

And the regioselectivity is not good, so this is the ligand exchange that we are telling this was the formamide and this is the 5 membered aza cycle this will do the exchange because methyl titanium isopropoxide is 1.2 equivalent and this is the Grignard, so here the cyclopropanation will happen with this cyclohexyl magnesium chloride 2.5 equivalent and you have seen this will eliminate like the cyclohexyl. So the ligand exchange will happen you get this one, the product.

This is the bicyclic tertiary amine is formed which under hydrogenation condition H_2 palladium charcoal you get a primary amine. So this becomes primary amine now and this kind of structures are present in many natural products such as this compound. This is antibiotic compound Trovafloxcin, so you can see this motif is present and this motif can be easily obtained from this Mejeire variant, so this is Mejeire variant of Kulinkovich and where the ligand exchange happened, so that you get this one bicyclic compound in 87 percent yield over 2 steps greater than 2:98 dr.

So for this case the diastereoselectivity is good and cis compound is formed.

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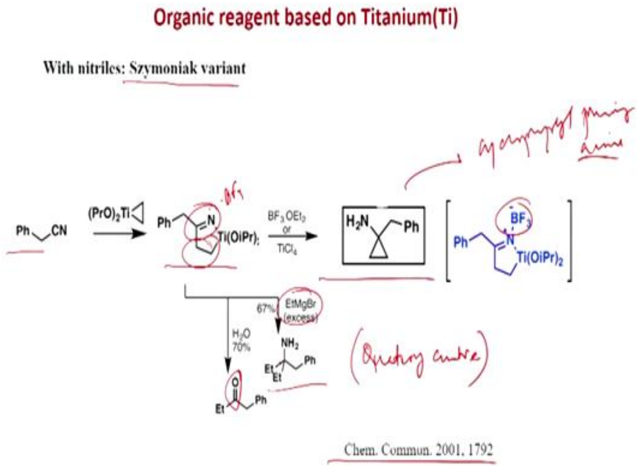

Organic reagent based on Titanium(Ti)

With nitriles: Szymoniak variant

Chem. Commun. 2001, 1792

Now we will see the reaction with nitriles, so this you call Szymoniak variant with nitriles you get this 5 membered titanacycle and with BF_3 what happens? This imine generally will not cycle because this imine is not activated enough, so that this will attack but if you put BF_3 then this cyclisation will happen because BF_3 will activate the iminium ion and this cyclisation would happen to generate the cyclopropyl amine. Cyclopropyl primary amine you will get directly here.

Earlier we have seen tertiary amine was forming here, primary amine. If you do just hydrolysis you get a carbonyl because this imine gets hydrolysed and if you put ethyl magnesium bromide excess then you get ethyl addition also to get an amine. So this is quaternary center.

Quarternary center formation is happening. This ethyl is present already here and another ethyl coming from the Grignard. This was published in Chem Comm 2001. This is very important that nitriles variant of the Kulinkovich reaction.

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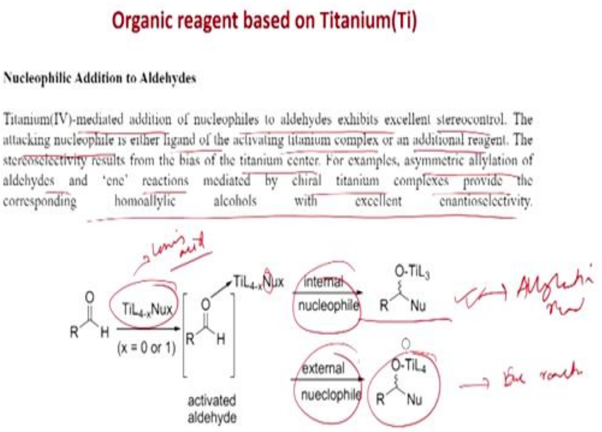

Organic reagent based on Titanium(Ti)

Nucleophilic Addition to Aldehydes

Titanium(IV)-mediated addition of nucleophiles to aldehydes exhibits excellent stereocontrol. The attacking nucleophile is either ligand of the activating titanium complex or an additional reagent. The stereoselectivity results from the bias of the titanium center. For examples, asymmetric allylation of aldehydes and 'ene' reactions mediated by chiral titanium complexes provide the corresponding homoallylic alcohols with excellent enantioselectivity.

Now we will discuss titanium(IV) chemistry. So first titanium(IV) mediated addition of nucleophiles to aldehydes exhibits excellent stereo control. The attacking nucleophile is either ligand of the activating titanium complex or an additional reagent. The stereoselectivity results from the bias of the titanium center for example asymmetric allylation of aldehydes and ene reactions mediated by Chiral titanium complexes provide the corresponding homoallylic alcohols with excellent enantioselectivity.

Like here this is the overall reaction the titanium complex that can activate because this is Lewis acid also, so it can activate carbonyl compound and this nucleophile can be internal from the titanium which was bind to titanium we will see like allylation you get this compound, the addition product and external nucleophile like ene reaction we will see, you get this product. Nucleophile is adding outside, this example is ene reaction we will see and this is allylation reaction.

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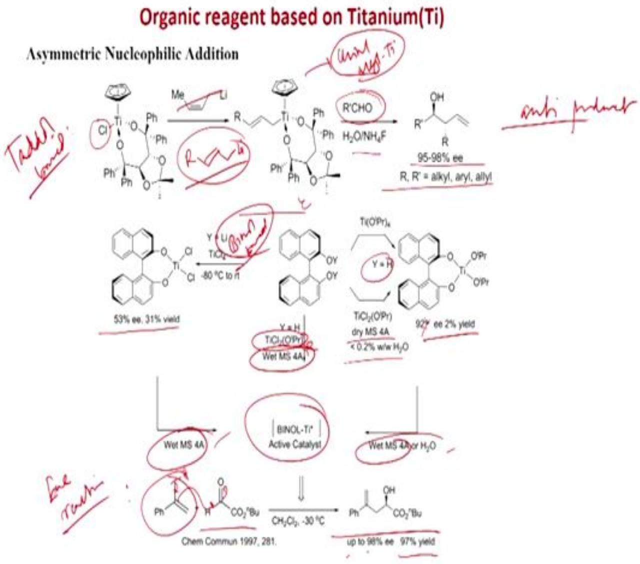

So this is the allylation. So in this case actually the trans was used, so trans allyllithium, trans allylithium and this is the taddol derivative with titanium, you can see here one chlorine is there of course which will be displaced by this lithium to get this intermediate and now if you react this is a chiral allyl titanium. Chiral allyl titanium is formed here and now if you react with aldehyde after work up you get this product. So this is anti-product is forming. Anti-product in 95 to 98% ee, R, R’ can be alkyl, aryl, allyl, so different substance can be tolerated.

Also this is Taddol based and this is Binal based. Binal based, what happens? The formation is little bit tricky if you put titanium like Y is equal to hydrogen, Y is equal to hydrogen is Binal titanium isopropoxide but you get very less yield but ee is good and also dry molecular sieves also the yield is not good. Also, with this one titanium chloride you can get a product but the ee is dropped here 53 percent, 31 percent yield.

And it has been found that if you wet molecular sieves 4 angstrom with TiCl$_2$(OiPr)$_2$ of course you get this binary titanium active catalyst better yield. So like this you have to use wet molecular sieve or wet, wet molecular sieves is important and that you get this binary titanium active catalyst and this active catalyst then it can use for ene reaction, so this is the ene reaction. There is a double bond and this is the keto ester and this addition is happening, so this hydrogen will add to carbonyl that is called ene reaction and you get this product in 97 percent yield and 98 percent ee, so this is very useful reaction.

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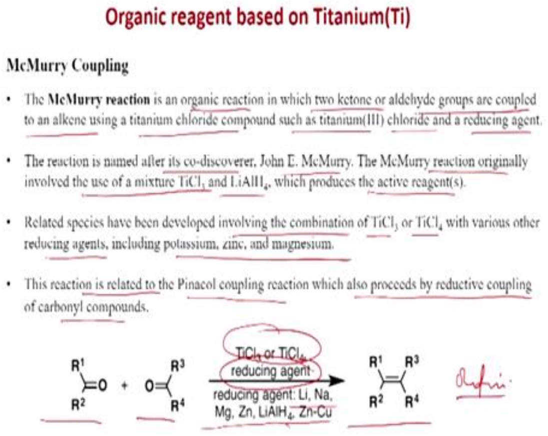

Organic reagent based on Titanium(Ti)

McMurry Coupling

- The **McMurry reaction** is an organic reaction in which two ketone or aldehyde groups are coupled to an alkene using a titanium chloride compound such as titanium(III) chloride and a reducing agent.
- The reaction is named after its co-discoverer, John E. McMurry. The McMurry reaction originally involved the use of a mixture $TiCl_3$ and $LiAlH_4$, which produces the active reagent(s).
- Related species have been developed involving the combination of $TiCl_3$ or $TiCl_4$ with various other reducing agents, including potassium, zinc, and magnesium.
- This reaction is related to the Pinacol coupling reaction which also proceeds by reductive coupling of carbonyl compounds.

$TiCl_3$ or $TiCl_4$, reducing agent

reducing agent: Li, Na, Mg, Zn, $LiAlH_4$, Zn-Cu

Now we will discuss McMurry coupling. McMurry reaction is an organic reaction in which 2 ketone or aldehyde groups are coupled to an alkene using a titanium chloride compound such as titanium(III) chloride and a reducing agent. The reaction is named after its co-discoverer John E. McMurry. The McMurry reaction originally involve the use of a mixture of $TiCl_3$ and lithium aluminium hydride which produces the active reagents.

Related species have been developed involving the combination of $TiCl_3$ or $TiCl_4$ with various other reducing agents including potassium, zinc and magnesium. We will see the mechanism with magnesium. This reaction is related to the pinacol coupling reaction which also proceeds by reductive coupling of carbonyl compounds. So this is the reaction 2 carbonyl compounds with $TiCl_3$ or $TiCl_4$ as well as reducing agents.

So reducing agents like lithium, sodium, magnesium, zinc, lithium aluminium, hydride zinc copper couple to generate the Olefin. So this Olefin is formed like pinacol coupling here.

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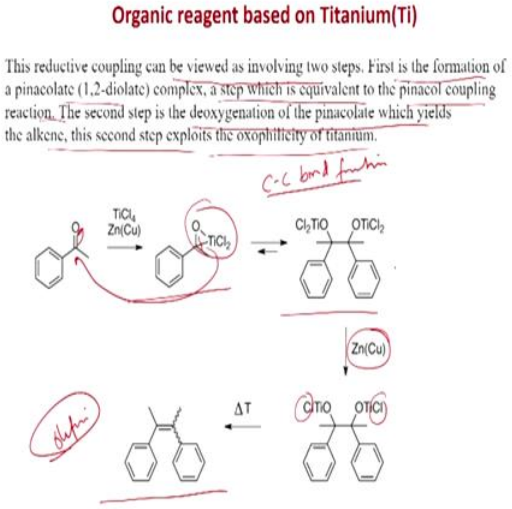

Organic reagent based on Titanium(Ti)

This reductive coupling can be viewed as involving two steps. First is the formation of a pinacolate (1,2-diolate) complex, a step which is equivalent to the pinacol coupling reaction. The second step is the deoxygenation of the pinacolate which yields the alkene, this second step exploits the oxophilicity of titanium.

And the reductive coupling can be viewed as involving 2 steps, first is the formation of the pinacolate complex, step which is equivalent to the pinacol coupling reaction. So this is formed titanium chloride zinc copper couple this ring is formed, three-member ring.

And now the carbon carbon bond formation will happen, so like pinacol coupling to generate this one which if you put zinc copper than one chlorine will displace it will be 2 chlorine here and this will elimination the second step is the deoxygenation on the pinaolate which yields alkene, this second step exploits the oxophilicity of titanium. So if you heat then this elimination will happen and you get the olefin.

So this step is very important, this is the carbon carbon bond formation. So this carbon or titanium bond will break this can attack to the carbonyl and you get this intermediate.

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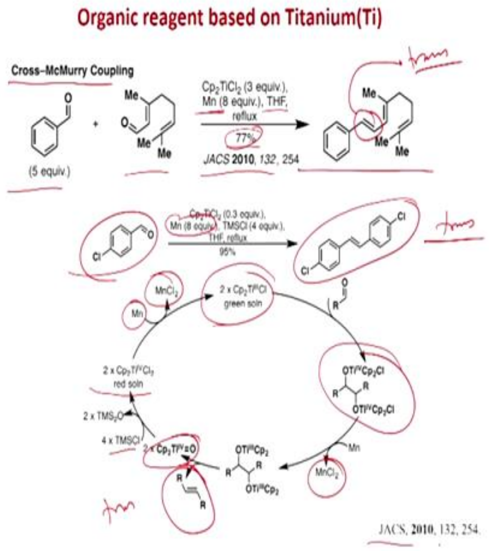

Organic reagent based on Titanium(Ti)

JACS, 2010, 132, 254.

Cross McMurry coupling also is possible if you use two different aldehydes like this and this aldehyde then with Cp_2Ti provide and with manganese 8 equivalent THF reflux 77 percent yield of this product, so this is very important and you get this trans product in 77 percent yield, this was published in JACS 2010. So this mechanism with manganese is described here though this is a Homo coupling to get this trans olefin here also it is forming.

So what could be the mechanism? Now Cp_2TiCl_2 with manganese it becomes manganese chloride and it becomes Ti(III)Cl, so this is the active reagent now it reacts with aldehyde to generate this carbon carbon bond formation happens here and again the manganese comes. Manganese becomes oxidised to $MnCl_2$, Ti(IV) reduces to Ti(III) like this then the elimination happens and generally the trans product is formed.

Then this is formed, this again reacts with TMS chloride to generate this, Cp_2TiCl_2. This was published in JACS 2010.

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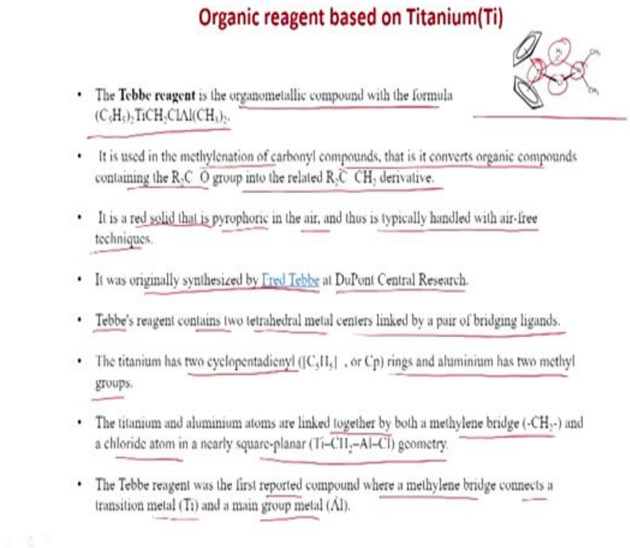

Organic reagent based on Titanium(Ti)

- The **Tebbe reagent** is the organometallic compound with the formula $(C_5H_5)_2TiCH_2ClAl(CH_3)_2$.
- It is used in the methylenation of carbonyl compounds, that is it converts organic compounds containing the R_2C O group into the related R_2C CH_2 derivative.
- It is a red solid that is pyrophoric in the air, and thus is typically handled with air-free techniques.
- It was originally synthesized by Fred Tebbe at DuPont Central Research.
- Tebbe's reagent contains two tetrahedral metal centers linked by a pair of bridging ligands.
- The titanium has two cyclopentadienyl ($[C_5H_5]$, or Cp) rings and aluminium has two methyl groups.
- The titanium and aluminium atoms are linked together by both a methylene bridge ($-CH_2-$) and a chloride atom in a nearly square-planar ($Ti–CH_2–Al–Cl$) geometry.
- The Tebbe reagent was the first reported compound where a methylene bridge connects a transition metal (Ti) and a main group metal (Al).

Another reagent which is Tebbe reagent, this is very useful reagent for conversion of carbonyl compounds to double bond CH_2 like Wittig reaction. The Tebbe reagent is the Organometallic compound with the formula $(C_5H_5)_2TiCH_2ClAl(CH_3)_2$ is a structure and you can see there is a bridge CH_2 as well as bridge chlorine is there and 2 atoms are present titanium metal atoms, titanium and aluminium are there.

It is used in the methylenation of carbonyl compounds that it converts organic compounds containing R_2CO group into the related R_2C double bond CH_2 derivative. It is a red solid that is Pyrophoric in the air and thus is typically handled with air free techniques. It was originally synthesised by Fred Tebbe at DuPont Central research. Tebbe's reagent contains 2 Tetrahedral metal centres linked by a pair of bridging ligands.

The titanium has 2 cyclopentadine rings and aluminium has two methyl groups that we can see in the structure and the titanium and aluminium atoms are linked together by both a methylene bridge we have seen already chloride atom nearly square-planar geometry. Tebbe reagent was the first reported compound where methylene bridge connects a transition metal and main group metal, aluminium.

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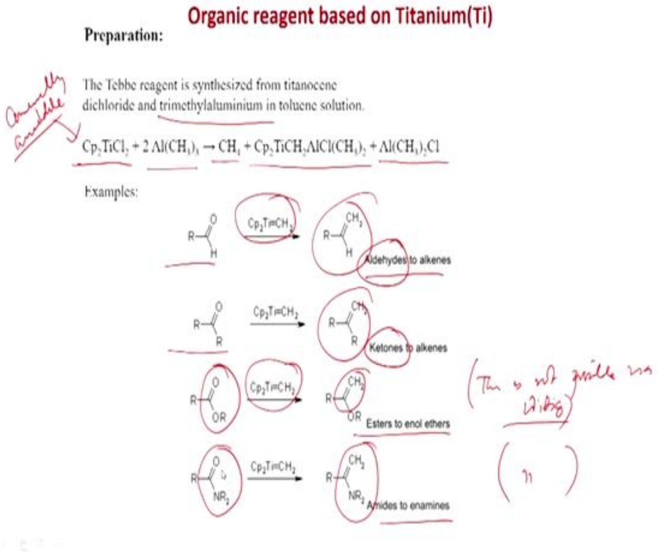

Organic reagent based on Titanium(Ti)

Preparation:

The Tebbe reagent is synthesized from titanocene dichloride and trimethylaluminium in toluene solution.

Commercially available

$Cp_2TiCl_2 + 2\,Al(CH_3)_3 \rightarrow CH_4 + Cp_2TiCH_2AlCl(CH_3)_2 + Al(CH_3)_2Cl$

Examples:

Aldehydes to alkenes

Ketones to alkenes

Esters to enol ethers

Amides to enamines

(This is not possible via Wittig)

(")

So the preparation we will see first. The Tebbe reagent was prepared from this, this is commercially available we already discussed in initial slide. The Cp_2TiCl is commercially available and there it can react with trimethylaluminium which is commercially available to generate methane and this is the Tebbe reagent $Cp_2TiCH_2AlCl(CH_3)_2$ and this is the byproduct $Al(CH_3)_2Cl$.

Examples you can do different carbonyl compounds can be olefinated with this Tebbe reagent like aldehyde, so this is the active species Cp_2Ti double bond CH_2 is formed to generate… So this you will see in the mechanism also. You get the olefin. Aldehyde to alkenes, Ketone, so this is aldehyde then ketones to alkenes which is also possible. Then Esters, if you have an ester, if you put this Cp_2Ti double CH_2 that is a Tebbe reagent ester to enol ether, so this is not possible with wittig reaction. So this is very important that if I have ester you can get enol ether with this Tebbe reagent and also amide.

This is also not possible with wittig reagent. So if you have amide with Tebbe reagent you get this enamines their carbonyl becomes double bond CH_2, so these are very useful reactions.

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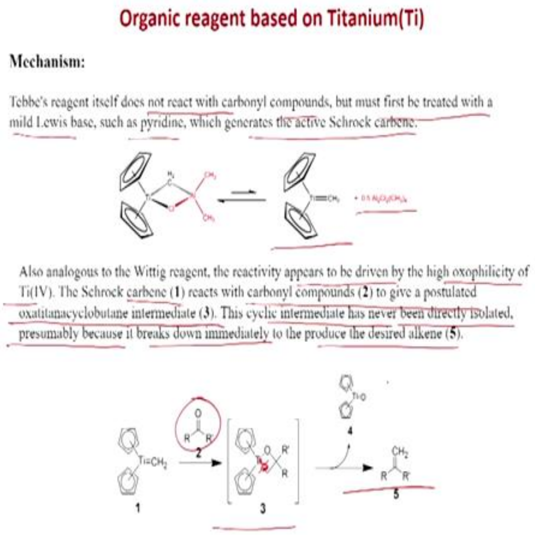

Organic reagent based on Titanium(Ti)

Mechanism:

Tebbe's reagent itself does not react with carbonyl compounds, but must first be treated with a mild Lewis base, such as pyridine, which generates the active Schrock carbene.

Also analogous to the Wittig reagent, the reactivity appears to be driven by the high oxophilicity of Ti(IV). The Schrock carbene (**1**) reacts with carbonyl compounds (**2**) to give a postulated oxatitanacyclobutane intermediate (**3**). This cyclic intermediate has never been directly isolated, presumably because it breaks down immediately to the produce the desired alkene (**5**).

And what could be the mechanism? The Tebbe reagent itself does not react with carbonyl compounds but must first be treated with a mild Lewis base such as pyridine which generates the active Schrock carbene that is the double bond CH_2, so this is formed, this is the Schrock carbene, this is active species and it will break like this. Also analogous to the Wittig reagent the reactivity appears to be driven by the high oxophilicity of Ti(IV). The Schrock carbene (**1)** reacts with carbonyl compounds to give a postulated oxatitanacyclobutane intermediate. Like Wittig reaction oxaphospatane here, oxatitanacyclobutane. This cycle intermediate has never been directly isolated presumably because it breaks down immediately to the product to produce the desired alkene. So this is the reaction, schrock carbene reacts with the carbonyl to generate this cycle oxatitanacyclobutane and this, so you can think that a double bond titanium double bond is forming and the olefin is generated here like Wittig reaction.

And in Wittig reaction you get the phosphine oxide here, you get the titanium double bond oxide and you get the olefin.

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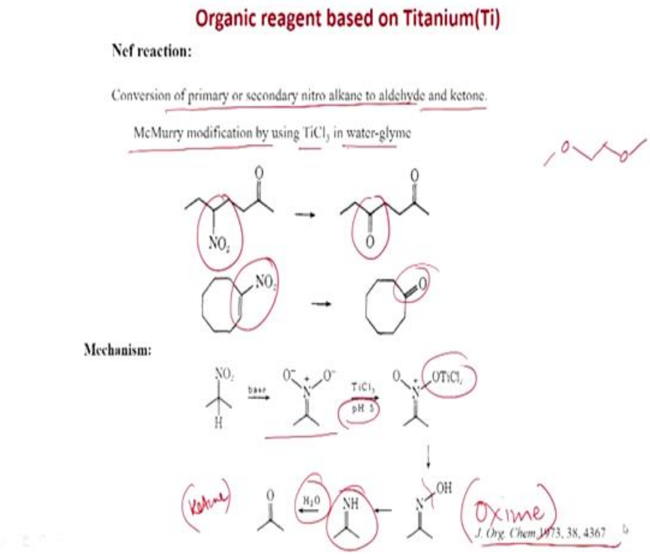

Organic reagent based on Titanium(Ti)

Nef reaction:

Conversion of primary or secondary nitro alkane to aldehyde and ketone.

McMurry modification by using $TiCl_3$ in water-glyme

Mechanism:

J. Org. Chem 1973, 38, 4367

And lastly we will discuss Nef reaction that is also powerful reaction to convert Nitro compounds to carbonyl and you will see that is the McMurry variant. Conversion of primary or secondary nitrile alkanes to aldehydes and ketone. McMurry modification using titanium chloride and water-glyme. So this is glyme structure. So in wate- glyme and titanium chloride also the pH is important.

pH has to be below 7 then you can get this Nitro 2 carbonyl. Also if you have alpha beta unsaturated Nitro compound and then also it goes to carbonyl compound and what could be the mechanism? So with base or acid you get this isomerisation, to get this N oxide and now titanium chloride pH 5 to give this intermediate which goes out to give this oxime. So this is very important it goes by Oxime.

And this Oxime again in presence of acid you get this imine because this imine without substitution is not stable and reacts with water it will go to the ketone. So Nef reaction is a powerful reaction for the conversion of Nitro compounds to carbonyl compounds. Research published in JOC 1973, 48, 4367 is the page number.

So today we have discussed the titanium-based reagents. First we have discussed titanium(II) and we have seen the Ziegler Natta catalyst where the olefin is converted to a polymer compound with the Ziegler Natta catalyst that is a very useful reaction and Ziegler Natta got a Nobel Prize. Then we have seen the Reppe reaction and in the Reppe reaction we have seen that 3 alkynes can be used.3 alkynes gives the benzene derivatives.

Also we have seen the Nitrile variant. And with nitrile we have seen that you can generate pyridine. Also you can generate pyrrole, when 2 equivalent of nitrile are used then pyrrole is formed and if you use the benzaldehyde or aldehyde derivatives then you get the Furan. And then we have seen the titanium(II) chemistry for the cyclopropanol formation which is called the Kulinkovich reaction.

And in the Kulinkovic reaction an ester is converted into cyclopropanol. If you use 2 equivalent of Grignard and this method is very useful. The product is formed selectively also cis product is the major product. Then we have seen the variant of Kulinkovich that is the asymmetric variant we have seen that titanium Taddol complex can give the asymmetric product and also we have seen the vinylogous ester also can be used and you can get different products depending on the solvent.

If toluene is there, then you get the cyclopropanation on the other hand THF you get the alcohol product. Also we have seen the de Mejiere variation, that in the de Mejiere variation the amides are used, tertiary amides are used. That case you get the cyclopropyl amine and this N benzyl group can be deprotected with Palladium hydrogenation condition, you get the primary amine.

And this also we have seen that in, here the distereoselectivity, a little bit less and like Kulinkovich reaction here also ligand exchange is possible and different olefins can be used to give this bicyclic cyclopropyl amines. Then we have seen the reaction with nitriles and nitriles with Grignard we have seen that if you use BF_3 then also cyclopropyl amine is formed. Alternatively, if you hydrolysed you get the ketone.

Alternatively, if you use the Grignard reagent you get an amine, primary amine with a quaternary center. And lastly we have seen the reaction of titanium(IV) and here the addition to aldehyde derivatives we have seen also the asymmetric variation we have seen the internal nucleophile like allyl. You can give the product in high yield. Also we have seen the external like in reaction we have seen that you can get the high enantioselectivity from the product.

Then we have seen the McMurry coupling, carbon carbon bond formation and olefin is formed and the mechanism is similar like the pinacol coupling. And here the reducing agent is agent used to live lithium aluminium hydride, manganese magnesium, zinc copper couple to give this olefin. Then we have seen the Nef reaction. In the Nef reaction we have seen the Nitro compound can be converted to carbonyl compound and this is also a useful method, here the titanium chloride and diglyme is used and under this condition the oxime is an intermediate and you get the carbonyl compound in very good yield, thank you.