Reagents in Organic Synthesis
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Lecture 21
Ru Based Reagents in Organic Synthesis

Welcome again, today we will discuss ruthenium-based reagents in organic synthesis.

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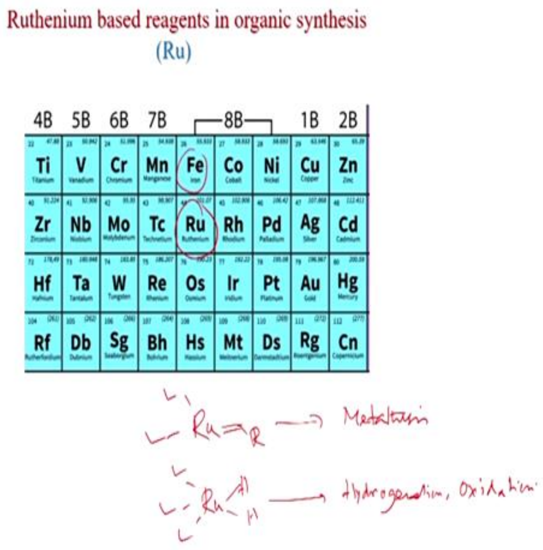

Ruthenium based reagents in organic synthesis

(Ru)

4B	5B	6B	7B	8B			1B	2B
Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn
Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd
Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg
Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cn

So ruthenium is a 5th row element as you can see here, and it is in the same group with iron. And ruthenium chemistry is mainly the alkylidene complexes which are used for metathesis catalyst we will see. And also ruthenium has a property to take hydrogen so it can take hydrogen and that is why it is useful for hydrogenation, oxidation reaction.

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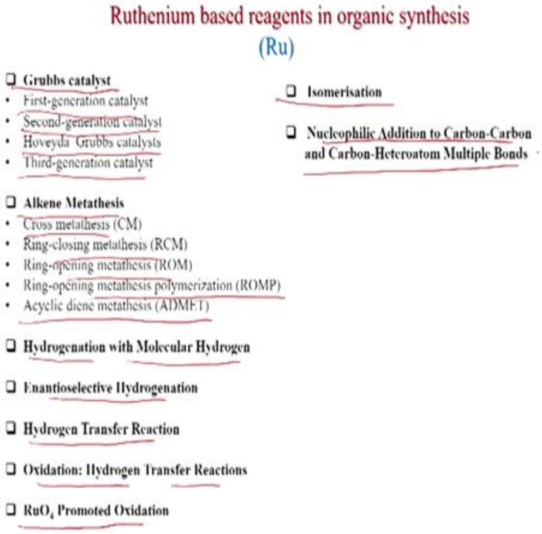

Ruthenium based reagents in organic synthesis
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❑ **Grubbs catalyst**
- First-generation catalyst
- Second-generation catalyst
- Hoveyda Grubbs catalysts
- Third-generation catalyst

❑ **Alkene Metathesis**
- Cross metathesis (CM)
- Ring-closing metathesis (RCM)
- Ring-opening metathesis (ROM)
- Ring-opening metathesis polymerization (ROMP)
- Acyclic diene metathesis (ADMET)

❑ **Hydrogenation with Molecular Hydrogen**

❑ **Enantioselective Hydrogenation**

❑ **Hydrogen Transfer Reaction**

❑ **Oxidation: Hydrogen Transfer Reactions**

❑ **RuO_4 Promoted Oxidation**

❑ **Isomerisation**

❑ **Nucleophilic Addition to Carbon-Carbon and Carbon-Heteroatom Multiple Bonds**

So we will see details, so Grubbs catalyst has been very popular for metathesis catalyst and there are several versions of this Grubbs catalyst, first one is first-generation catalyst which was first developed, then second-generation catalyst, then Hoveyda Grubbs catalyst, third generation catalyst. In Alkane metathesis there are different versions are there; Cross metathesis, Ring closing metathesis, Ring opening metathesis, Ring opening metathesis polymerisation ROMP and Acyclic diene metathesis that is also polymerisation ADMET.

And as I told, hydrogenation also is possible with molecular hydrogen, Enantioselective hydrogenation also possible, hydrogen transfer reaction, both intra and inter molecularly, oxidation hydrogen transfer reaction is also possible and ruthenium oxide promoted oxidation that is a strong oxidising agent. And isomerisation also is possible, double bond isomerisation we will see Nucleophilic addition to carbon-carbon and carbon heteroatom multiple bonds that we will also see.

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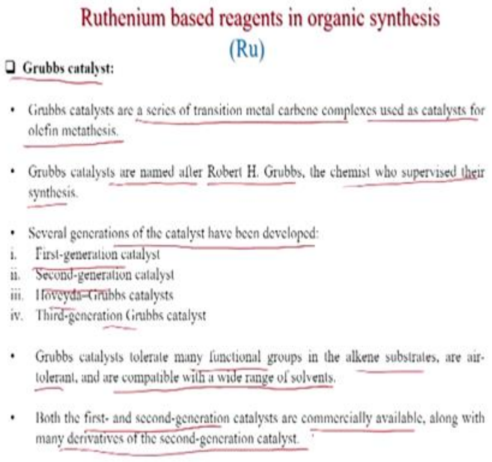

Ruthenium based reagents in organic synthesis

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❑ **Grubbs catalyst:**

- Grubbs catalysts are a series of transition metal carbene complexes used as catalysts for olefin metathesis.
- Grubbs catalysts are named after Robert H. Grubbs, the chemist who supervised their synthesis.
- Several generations of the catalyst have been developed:

i. First-generation catalyst
ii. Second-generation catalyst
iii. Hoveyda–Grubbs catalysts
iv. Third-generation Grubbs catalyst

- Grubbs catalysts tolerate many functional groups in the alkene substrates, are air-tolerant, and are compatible with a wide range of solvents.
- Both the first- and second-generation catalysts are commercially available, along with many derivatives of the second-generation catalyst.

So first we will discuss Grubbs catalyst, Grubbs catalyst are a series of transition metal carbene complexes used as catalyst for olefin metathesis and you know Grubbs got noble prize for discovery of this catalyst. Grubbs catalysts are named after Robert H Grubbs, the chemist who supervised their synthesis. Several generation of the catalyst have been developed; first-generation catalyst we have already told, second-generation, Hoveyda Grubbs catalyst and third-generation Grubbs catalyst. Grubbs catalyst tolerate many functional groups in the alkane substrate, are air-tolerant and are comfortable with wide range of solvents so that is why it is very useful. Both the first and second generation catalysts are commercially available along with many derivatives of the second-generation catalyst, so you can buy this catalyst

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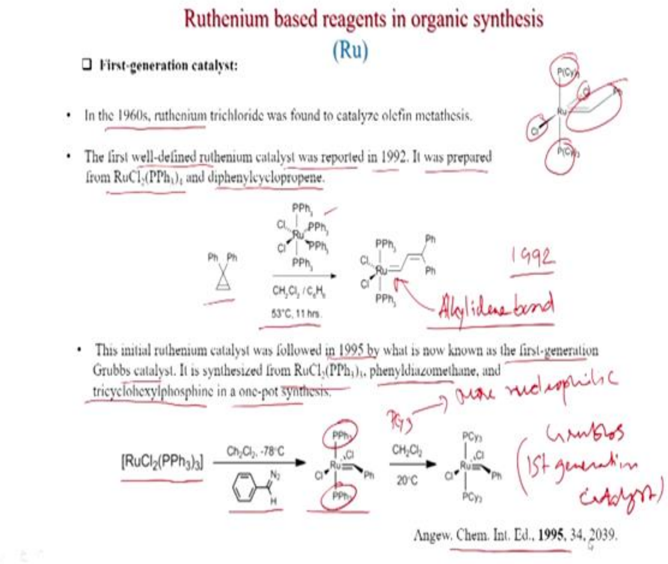

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❑ **First-generation catalyst:**

- In the 1960s, ruthenium trichloride was found to catalyze olefin metathesis.
- The first well-defined ruthenium catalyst was reported in 1992. It was prepared from $RuCl_2(PPh_3)_4$ and diphenylcyclopropene.
- This initial ruthenium catalyst was followed in 1995 by what is now known as the first-generation Grubbs catalyst. It is synthesized from $RuCl_2(PPh_3)_3$, phenyldiazomethane, and tricyclohexylphosphine in a one-pot synthesis.

Angew. Chem. Int. Ed., **1995**, 34, 2039.

So this is the first-generation catalyst, the structure you can see; two chlorine is there, $2P(Cy)_3$ and this is the benzylidene group is there. In the 1960, ruthenium trichloride was found to catalyse olefin in metathesis. The first well-defined ruthenium catalyst was reported in 1992, it was prepared from $RuCl_2(PPh_3)_4$ and diphenylcyclopropene. So this is the reaction, it was developed in 1992.

First this catalyst was developed, so you can see this is the starting material diphenylcyclopropene and this is the $RuCl_2(PPh_3)_4$ and now this alkylidene bond was formed here, so this is alkylidene bond that is very important because this bond only reacts with the olefin and 53 degree centigrade 11 hours you get this catalyst. So inspired by this study, then in 1995 what is known as the first-generation Grubbs catalyst.

It is synthesised from $RuCl_2(PPh_3)_3$ phenyl diazomethane and tricyclohexylphosphine in one pot synthesis, so this is the synthesis $RuCl_2(PPh_3)_3$ then this phenyl diazomethane then you get this one this also is catalyst, but if you put now $P(Cy)_3$ tricyclohexylphosphine because those are more nucleophilic more nucleophilic, so they can displace this PPh_3 group and you get this, so this is the first-generation catalyst, Grubbs first-generation and this was reported in Angew Chem 1995.

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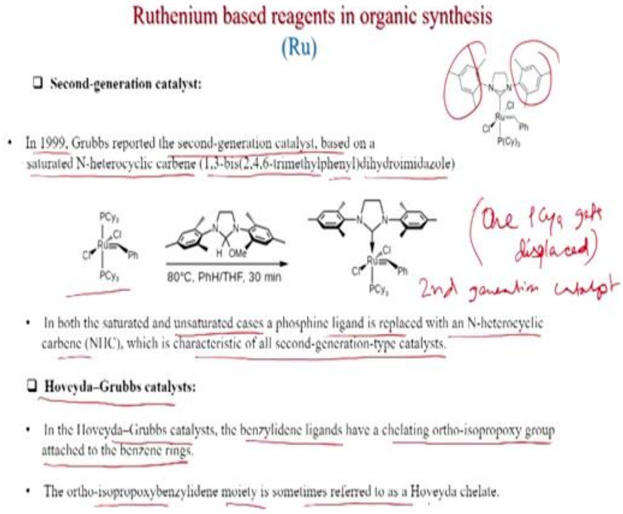

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❑ **Second-generation catalyst:**

- In 1999, Grubbs reported the second-generation catalyst, based on a saturated N-heterocyclic carbene (1,3-bis(2,4,6-trimethylphenyl)dihydroimidazole)

(One PCy3 gets displaced)

2nd generation catalyst

- In both the saturated and unsaturated cases a phosphine ligand is replaced with an N-heterocyclic carbene (NHC), which is characteristic of all second-generation-type catalysts.

❑ **Hoveyda–Grubbs catalysts:**

- In the Hoveyda–Grubbs catalysts, the benzylidene ligands have a chelating ortho-isopropoxy group attached to the benzene rings.
- The ortho-isopropoxybenzylidene moiety is sometimes referred to as a Hoveyda chelate.

The second-generation carbene, you can see the N-heterocyclic carbene is there, dihydroimidazole moiety is present here and this is a mesityl group for the extra stabilisation. In 1999, Grubbs report the second-generation catalyst based on saturated N heterocyclic carbene 1.3-bis-2,4,6-trimethylphenyl dihydromidazole, this is this moiety. And this can be prepared from this first-generation catalyst, if you put because they are more nucleophilic than one $P(Cy)_3$ so they can displace one $P(Cy)_3$ gets displaced.

And then you get the second-generation catalyst. In both the saturated and unsaturated cases, phosphine ligand is replaced with an N-heterocyclic carbene which is characteristic of all second-generation type catalysts. Hoveyda Grubbs catalyst, in the Hoveyda Grubbs catalyst the Benzylidene ligands have a chelating ortho-isopropoxy group attached to the benzene rings. The ortho-isopropoxy Benzylidene moiety is sometimes referred to as Hoveyda chelate.

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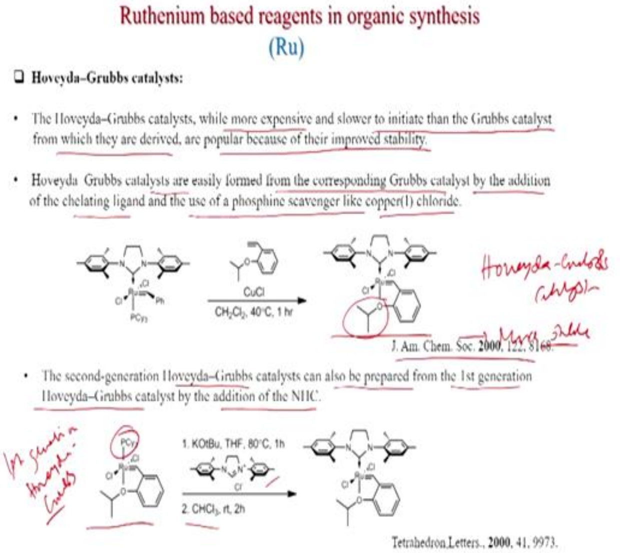

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☐ **Hoveyda–Grubbs catalysts:**

- The Hoveyda–Grubbs catalysts, while more expensive and slower to initiate than the Grubbs catalyst from which they are derived, are popular because of their improved stability.
- Hoveyda Grubbs catalysts are easily formed from the corresponding Grubbs catalyst by the addition of the chelating ligand and the use of a phosphine scavenger like copper(I) chloride.

J. Am. Chem. Soc. **2000**, 122, 8168.

- The second-generation Hoveyda–Grubbs catalysts can also be prepared from the 1st generation Hoveyda–Grubbs catalyst by the addition of the NHC.

Tetrahedron Letters., **2000**, 41, 9973.

So, we will see the structure, so this is the structure of Hoveyda Grubbs catalyst and these are more expensive and slower to initiate than Grubbs catalyst from which they are derived are popular because of their improved stability. So, they are more stable because here this isopropoxyl additional binding with the benzylidene moiety, so that is why this is more stable. Hoveyda Grubbs catalysts are easily formed from the corresponding Grubbs catalyst by the addition of the chelating ligand and the use of a phosphine scavenger like copper chloride. This was published in JACS 2000.

The second-generation Hoveyda Grubbs catalysts can also be prepared from the first-generation Hoveyda Grubbs catalyst by the addition of the NHC. So from this first-generation Hoveyda Grubbs catalyst is the first-generation Hoveyda Grubbs with phosphines are there, this is the P(Cy)$_3$ is there, now you have to displace with this carbene you can generate with potassium tertiary butoxide and this salt and then in chloroform room temperature 2 hours you get this Hoveyda Grubbs catalyst. This was published in Tetrahedron Letters.

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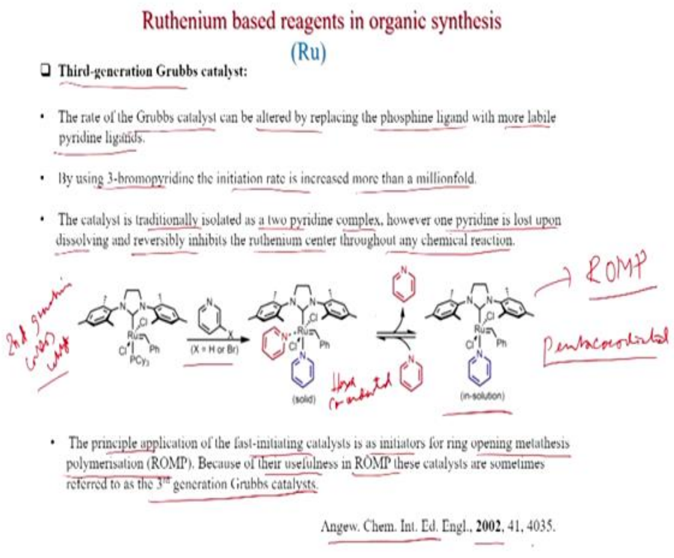

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❑ **Third-generation Grubbs catalyst:**

- The rate of the Grubbs catalyst can be altered by replacing the phosphine ligand with more labile pyridine ligands.
- By using 3-bromopyridine the initiation rate is increased more than a millionfold.
- The catalyst is traditionally isolated as a two pyridine complex, however one pyridine is lost upon dissolving and reversibly inhibits the ruthenium center throughout any chemical reaction.

- The principle application of the fast-initiating catalysts is as initiators for ring opening metathesis polymerisation (ROMP). Because of their usefulness in ROMP these catalysts are sometimes referred to as the 3rd generation Grubbs catalysts.

Angew. Chem. Int. Ed. Engl., **2002**, 41, 4035.

Third-generation Grubbs catalyst is also there, the rate of the Grubbs catalyst can be altered by replacing the phosphine ligand with more labile pyridine ligands, so here pyridine is present. By using 3-bromopyridine the initiation rate is increased more than millionfold. The catalyst is traditionally isolated as a two pyridine complex, however, one pyridine is lost upon dissolving and reversibly inhibits the ruthenium centre throughout any chemical reaction.

So this is the second-generation catalyst second-generation Grubbs catalyst and now if you put the 3-bromopyridine X is equal to H or Br then 2 pyridine moiety attached and this becomes you can see hexa-coordinated, so one pyridine can go out in the solution and in the solution now it will become penta co-ordinated like usual and this reversibly inhibits the ruthenium centre throughout any chemical reaction.

The principal application of the first initiating catalyst is as initiated for ring opening metathesis polymerisation, so this is very useful for ROMP ring opening metathesis polymerisation this third-generation because their usefulness in ROMP these catalysts are sometimes referred to as the third-generation Grubbs catalyst, this was published in Angew Chem 2002.

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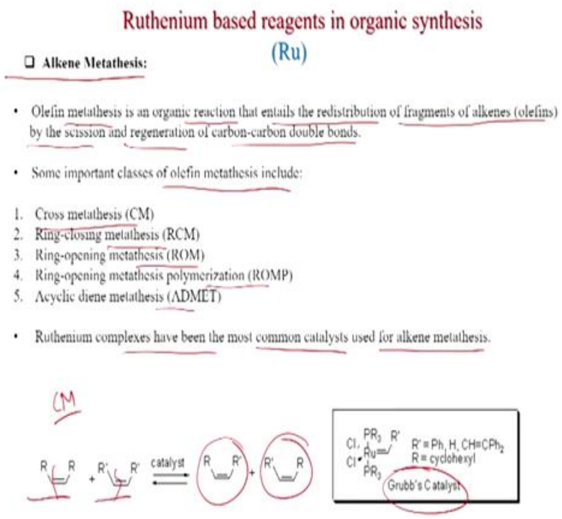

Ruthenium based reagents in organic synthesis

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☐ **Alkene Metathesis:**

- Olefin metathesis is an organic reaction that entails the redistribution of fragments of alkenes (olefins) by the scission and regeneration of carbon-carbon double bonds.
- Some important classes of olefin metathesis include:

1. Cross metathesis (CM)
2. Ring-closing metathesis (RCM)
3. Ring-opening metathesis (ROM)
4. Ring-opening metathesis polymerization (ROMP)
5. Acyclic diene metathesis (ADMET)

- Ruthenium complexes have been the most common catalysts used for alkene metathesis.

Now, we will discuss different versions of alkene metathesis, so olefin metathesis is an organic reaction that entails the redistribution of fragments of alkenes (Olefins) in the scission regeneration of carbon-carbon double bonds. So, carbon-carbon double bonds are breaking and regenerated, some important classes of Olefin metathesis include Cross metathesis, then Ring closing metathesis, Ring opening metathesis, Ring opening metathesis polymerisation and Acyclic diene metathesis.

Ruthenium complexes have been the most common catalyst used for the alkene metathesis. This is like Cross metathesis, you can see one olefin is there, another olefin is there, then you put this Grubbs catalyst, there different generations are there and now you get the cross products. So one substance comes from here, another come here and you get this cross product so these are the cross olefin or hetero heterodimer.

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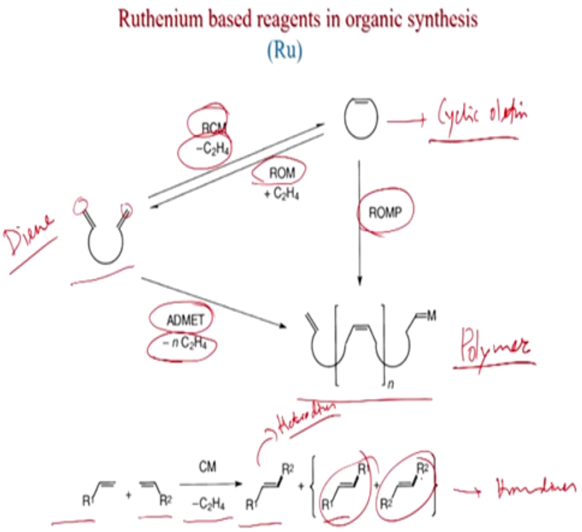

Ruthenium based reagents in organic synthesis

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So this is the overall metathesis reaction if you have diene like this, this is diene. Then you can do the ring closing metathesis to get this one, this is cyclic olefin so a diene is converted to cyclic olefin by ring closing metathesis and one molecule of ethylene is eliminated in this process because this you can say two carbons unless here. Alternatively, if you put ring opening metathesis ethylene, the cyclic olefin can be converted to this diene so this is called the ring opening metathesis.

On the other hand, if you do not put any diene, just a cyclic olefin, you put under this condition ring opening metathesis polymerisation, you can get a polymer like this. And this diene also can be converted to polymer that is called the Acyclic diene metathesis polymerisation, here also ethylene minus nC_2H_4 is eliminated in this process.

And this is the Cross metathesis that we have seen here, R1 substituted olefin, R2 substituted olefin then cross metathesis, you eliminate one molecule of ethylene and you get this heterodimer and this is homodimer. So because this is from the same molecular reacting to give this one, and this one reacting to give this one.

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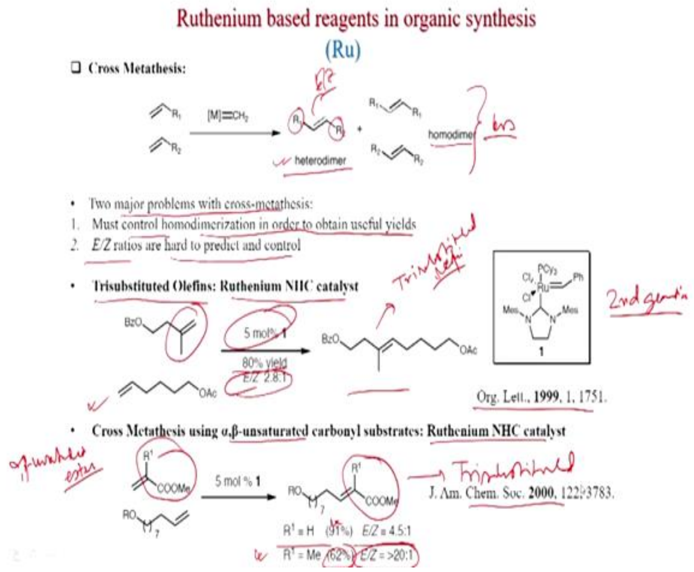

Ruthenium based reagents in organic synthesis

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☐ Cross Metathesis:

- Two major problems with cross-metathesis:
1. Must control homodimerization in order to obtain useful yields
2. *E/Z* ratios are hard to predict and control

- Trisubstituted Olefins: Ruthenium NHC catalyst

Org. Lett., **1999**, 1, 1751.

- Cross Metathesis using α,β-unsaturated carbonyl substrates: Ruthenium NHC catalyst

J. Am. Chem. Soc. **2000**, 122, 3783.

Cross metathesis we are interested in this heterodimer because here you get, can get olefin with both substituents R1, R2 and if you put this ruthenium alkylidene catalyst then you can get this heterodimer and these are the homodimer. So, the challenges are in the Cross metathesis that must control homodimerization in order to obtain useful yields. So, if you want to get selectively the heterodimer then this should be less. And E Z ratios are hard to predict and control because here you can see a substituted olefin is generated so E Z stereochemistry should be important.

For Trisubstituted olefin, ruthenium NHC catalyst has been mostly used so this is the second-generation catalyst. If you have a trisubstituted here you can say here this is disubstituted olefin, and here also the trisubstituted olefin is generated, so this is trisubstituted forming. And in this case it has been found that the second-generation catalyst is very useful, suppose if you react this one with this one with 5 mol% **1** that is 5 mol percent second-generation catalyst to get 80 percent yield for this product.

However, E Z ratio is 2.8:1 so the selectivity is not very high and this was published in Organic Letters. Also with this ruthenium NHC catalyst you can do Cross metathesis of alpha-Beta unsaturated carbonyl substrates like here, this is alpha-beta unsaturated ester, unsaturated ester and with this here also a trisubstituted ester is forming here, disubstituted here, another substitution so total trisubstituted so this is trisubstituted.

And here also this 5 mol% catalyst same catalyst is useful, and if you have R1 is equal to hydrogen then E Z is 4.5:1 with 91 percent yield. When R1 is methyl then the yield gets reduced to 62 percent but E Z ratio is higher than 20:1, so this is very important that when you have methyl substituent here then the geometry is E, so this is very important and this was first published in JACS 2000.

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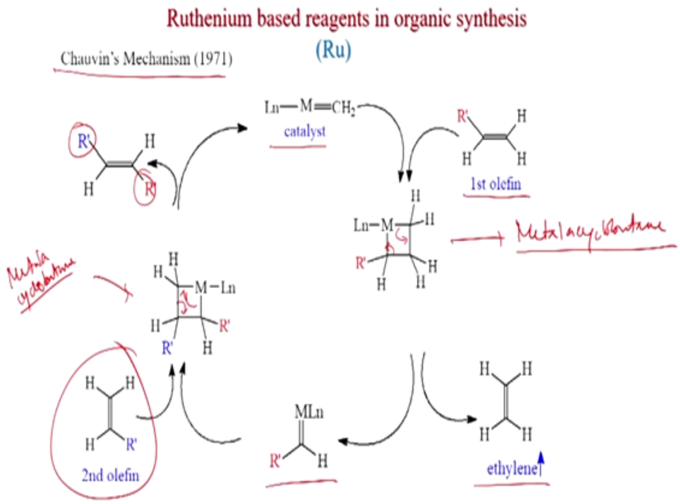

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Chauvin's Mechanism (1971)

Now, the mechanism we will discuss about Cross metathesis, this was first proposed by Chauvin who also shared the Nobel Prize with Grubbs in the same year. This mechanism was proposed in 1971, so this is the catalyst and this is the first olefin, with this first olefin and you get with this catalyst you get this metallocyclobutane, so this is very important that metallocyclobutane is formed because then only the redistribution will happen. And after that this bond will break and this will get a double bond so you get ethylene out, ethylene is eliminated and you get this one, now with R'

Now second olefin will come and second olefin will react with this alkylidene complex to generate another metallocyclobutane. So two metallocyclobutanes are formed and through that only the redistribution happens and you get a heterodimer product. And, now you get a heterodimer olefin product, here the trans-geometry has been shown and the catalyst is regenerated. So, catalyst is regenerated, so catalyst is regenerated and you get a substituted olefin.

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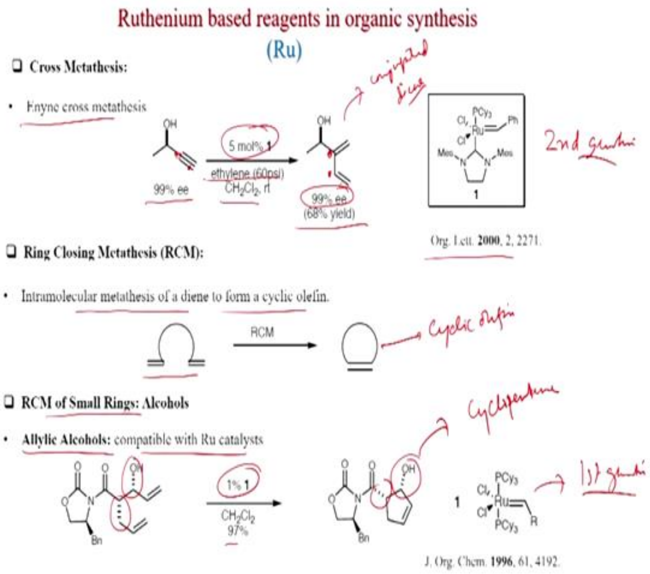

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❑ **Cross Metathesis:**

- Enyne cross metathesis

Org. Lett. **2000**, 2, 2271.

❑ **Ring Closing Metathesis (RCM):**

- Intramolecular metathesis of a diene to form a cyclic olefin.

❑ **RCM of Small Rings: Alcohols**

- **Allylic Alcohols:** compatible with Ru catalysts

J. Org. Chem. **1996**, 61, 4192.

Cross metathesis different examples, Enyne cross metathesis also is possible like you have this propargylic alcohol, chiral alcohol having 99 percent enantiomeric excess and with the second-generation catalyst 5 mol% of this catalyst in ethylene 60 Psi dichloromethane room temperature the enantioselectivity is retained 99 percent and you get 68 percent of this diene so this is conjugated diene is formed.

We will see the mechanism later, but what I want to say now that these two carbon atoms are here so this triple bond is becoming a single bond and these are coming from the ethylene. This was published in Organic Letters 2000. Ring closing metathesis, intramolecular metathesis of diene to form a cyclic olefin, this is very important reaction if you have a diene then with our ring closing metathesis you can get this cyclic olefin.

And RCM of small ring alcohols is also possible, allylic alcohols compatible with ruthenium catalyst. Suppose, if you have a this chiral alcohol with chiral centre here here and with 1 mol% catalyst, so this is first-generation catalyst is enough for this reaction here and 1 mol of the catalyst dichloromethane 97 percent yield of the cyclopentene so cyclopentene is formed and these chiral centres are not disturbed in this process, so this is very important and it was published in JOC, 1996.

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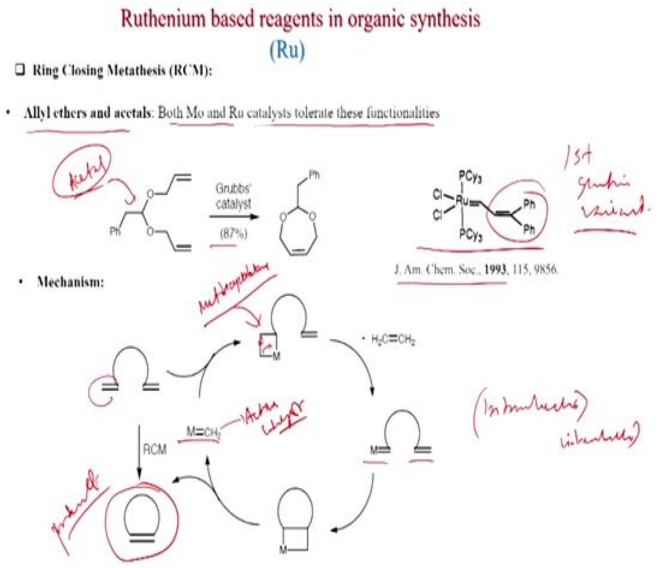

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❑ **Ring Closing Metathesis (RCM):**

- **Allyl ethers and acetals**: Both Mo and Ru catalysts tolerate these functionalities

J. Am. Chem. Soc., **1993**, 115, 9856.

- **Mechanism:**

Some more examples of ring closing metathesis, allyl ethers and acetals, both molybdenum and ruthenium catalyst tolerate these functionalities like here you can see this is acetal, so this is acetal. So you can see this acetal gives this cyclic acetal. Cyclisation happens with this catalyst so this is first-generation variant and with this catalyst you can get this product in 87 percent yield so this is very useful reaction. This was published in JACS 1993.

What is the mechanism of ring closing metathesis? So if you have a diene like this, then this comes catalyst which already reacted this catalyst comes and to get this metallocyclobutane, metallocyclobutane and after ethylene elimination so here if you do this then the ethylene gets eliminated and you get this one. Now this will react with this olefin because this is accessible now to this olefin compared to other starting material.

Because intramolecular will be faster always, intra-molecular faster than intermolecular, so this will react with this olefin and you get this metallocyclobutane and we generate this active catalyst so this is the active catalyst. So, this active catalyst and you get your product so this is the product, cyclic olefin product is formed, so overall an acyclic diene is converted to cyclic olefin by ring closing metathesis.

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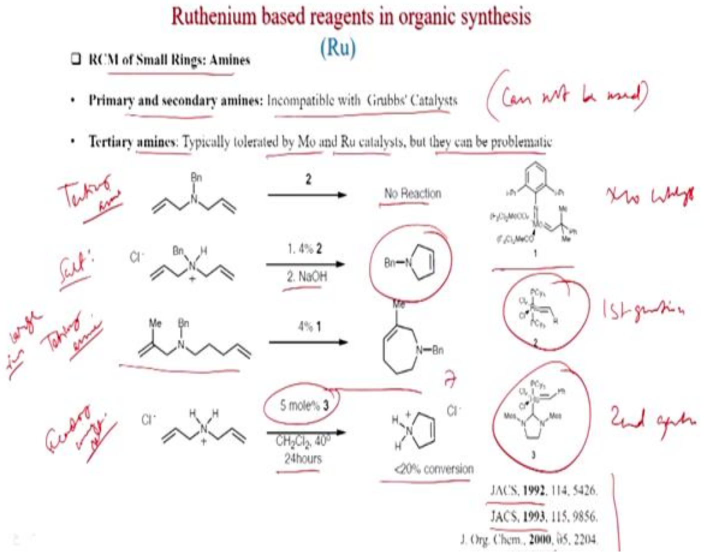

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❑ RCM of Small Rings: Amines

- **Primary and secondary amines:** Incompatible with Grubbs' Catalysts (Can not be used)
- **Tertiary amines**: Typically tolerated by Mo and Ru catalysts, but they can be problematic

JACS, **1992**, 114, 5426.

JACS, **1993**, 115, 9856.

J. Org. Chem., **2000**, 65, 2204.

Small ring is also possible like amines. Here, primary and secondary amines they are incompatible with Grubbs catalyst. so primary-secondary amines cannot be used, so this is very important because they are basic they can might react with the catalyst. And tertiary amines typically tolerated by molybdenum and ruthenium catalyst, but they can be also problematic like here this tertiary amine this is tertiary amine, this with catalyst **2** this is the first-generation and this is **3** is second-generation and this is molybdenum catalyst **1** so with catalyst **2** no reaction.

Interestingly, if you destroy the nucleophilicity of this tertiary amine by this salt formation, so if you make a salt, now with 4% of catalyst **2**, you can get this ring closing metathesis and you get this 5 membered ring heterocycle in good yield, also you have to work up with sodium hydroxide. Also for large ring formation, **1** molybdenum catalyst has been found to be useful, so here tertiary amine this is again tertiary amine and large ring formation.

Here a 7 membered ring is formed. 7 membered heterocycle is formed with this molybdenum catalyst when it is secondary amine salt, so now this is secondary amine salt. Secondary amine salt and 5 mol% **3** second-generation catalyst in dichloromethane 40 degree centigrade 24 hours, you get only less conversion. So, tertiary amine salt is very good for the cyclisation part, secondary amine salt is not good for the cyclisation reaction, these are the papers JACS 1992, JACS 1993 and JOC 2000.

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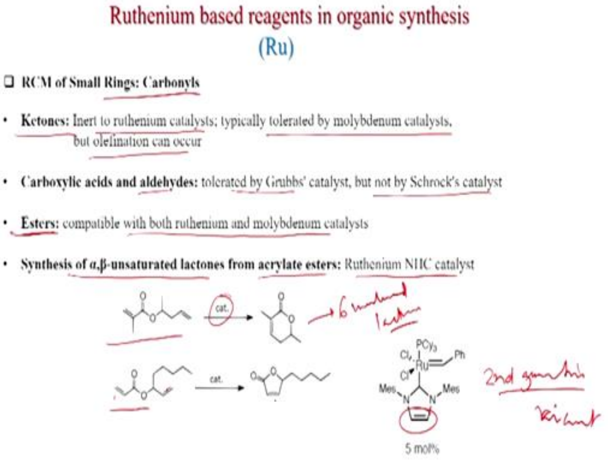

Ruthenium based reagents in organic synthesis

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❑ RCM of Small Rings: Carbonyls

- **Ketones:** Inert to ruthenium catalysts; typically tolerated by molybdenum catalysts, but olefination can occur
- **Carboxylic acids and aldehydes:** tolerated by Grubbs' catalyst, but not by Schrock's catalyst
- **Esters:** compatible with both ruthenium and molybdenum catalysts
- **Synthesis of α,β-unsaturated lactones from acrylate esters:** Ruthenium NHC catalyst

RCM of small rings carbonyl, so carbonyl groups are also very useful functionalities present in many natural products, so if you get the carbonylated cycles that could be useful. Like Ketones, here they are inert to ruthenium catalyst typically tolerated by molybdenum catalysts, but olefination can occur. Carboxylic acid and aldehyde is tolerated by Grubbs catalyst but not by Schrock's catalyst.

Esters they are compatible with, so esters are very useful, they are compatible with both ruthenium and molybdenum catalyst. Synthesis of alpha-beta unsaturated lactones from acrylate esters, ruthenium NHC catalyst. So, here you can see this alpha-beta unsaturated ester when reacts with catalysts so this is also second-generation catalyst, this is a double bond is there, of course, so second-generation variant. And you get the 6 membered lactone so cross metathesis happens.

So as I told esters are very useful for this cross metathesis, here also alpha-beta unsaturated ester is present and now these two carbonyl items with cycle, so you get a 5 membered lactone here, this is 5 membered. Also, if you have substitution in the double bond substitution in the double bond that case also reaction was for 5 members and you get good yield for this product. And if you have substitution at both olefin then also you get good yield of this product, this is also 5 membered lactone, 5 membered lactone with double bond substitution. So this was published in JOC 2000.

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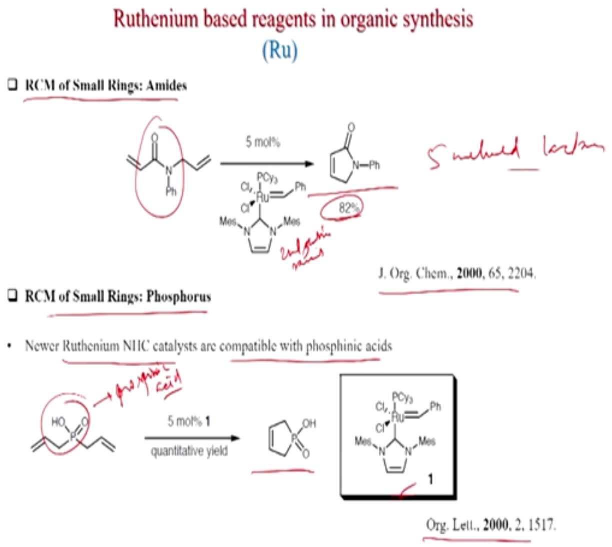

Ruthenium based reagents in organic synthesis
(Ru)

❑ RCM of Small Rings: Amides

J. Org. Chem., 2000, 65, 2204.

❑ RCM of Small Rings: Phosphorus

- Newer Ruthenium NHC catalysts are compatible with phosphinic acids

Org. Lett., 2000, 2, 1517.

Some more examples, RCM of small rings amides like here this is alpha-beta unsaturated amide, you can see here and with second-generation the similar catalyst that we have told earlier second-generation variant you get 5 membered lactam 5 membered lactam is formed in 82 percent yield, this was published in JOC 2000.

Also, phosphorus atoms can be incorporated new ruthenium NHC catalysts are compatible with phosphinic so this is the catalyst second-generation variant and this has been found to be useful for this cyclisation reaction, this is the phosphinic acid, phosphinic acid, and these 2 double bonds can be cyclized to get a 5 membered ring and this was published in organic letters 2000.

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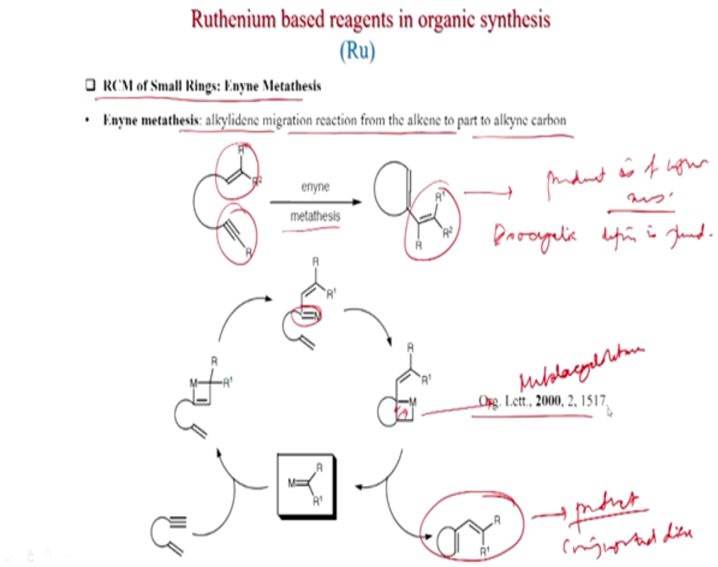

Ruthenium based reagents in organic synthesis

(Ru)

❑ **RCM of Small Rings: Enyne Metathesis**

- **Enyne metathesis**: alkylidene migration reaction from the alkene to part to alkyne carbon

Org. Lett., **2000**, 2, 1517

Some more examples, and now we will discuss RCM of small rings enyne metathesis. Enyne metathesis alkylidene migration reacts from the alkene part to the alkyne carbon, like here if you have a double bond earlier it was both double bond, now if you have a triple bond then the enyne metathesis will happen and here you can see that nothing is eliminated because R1, R2, R all staying in the product so product is of higher mass compared to cycle. Earlier the cycle was formed here, what happened the exocyclic olefin so this is very important exocyclic olefin is formed.

And we will see the mechanism now, so this reacts with the activated catalyst to generate this triple bond reaction to get this metallocyclobutane, now this will break like this and this will form, now this will react with this one because as I told the intramolecular will be first term to generate this metallocyclobutane, metallocyclobutane will be formed with this double bond present and now this will eliminate and give this product so this is the product and this is also conjugated diene with exocyclic double bond is present and you get this is the catalyst back, this was published in organic letters 2000.

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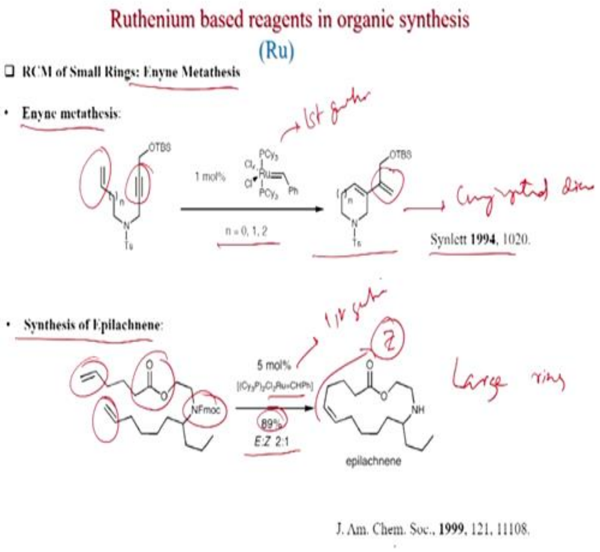

Ruthenium based reagents in organic synthesis

(Ru)

- RCM of Small Rings: Enyne Metathesis
- Enyne metathesis:

Synlett **1994**, 1020.

- Synthesis of Epilachnene:

J. Am. Chem. Soc., **1999**, 121, 11108.

RCM of small rings enyne metathesis, enyne metathesis examples like here you can see there is a double bond is there, this is the substituted alkyne and what will happen when it reacts with 1 mol% first-generation catalyst, this first-generation catalyst n can be 0, 1, 2, you get these products cyclised products with this double bond here, and this is the conjugated diene, conjugated diene and this substituents is present so nothing is lost here, this was published in Synlett 1994.

Synthesis of epilachnene so this cross metathesis has been used in many natural product synthesis, one example is this epilachnene, this one is large ring the product and this is the starting material you can see this is ester also NFmoc group is there and this terminal olefins are present. With 5 mol% $(PCy_3)_2Cl_2Ru{=}CHPh$ that is the first-generation, so first-generation works for this enyne metathesis and this is the cross metathesis, of course. So you get this cyclisation, and this is large ring and their products is formed in 89 percent yield with 2:1 E to Z stereochemistry, actually whatever structure is shown this is Z but E is major so E is formed in 2:1 ratio, this was published in JACS 1999.

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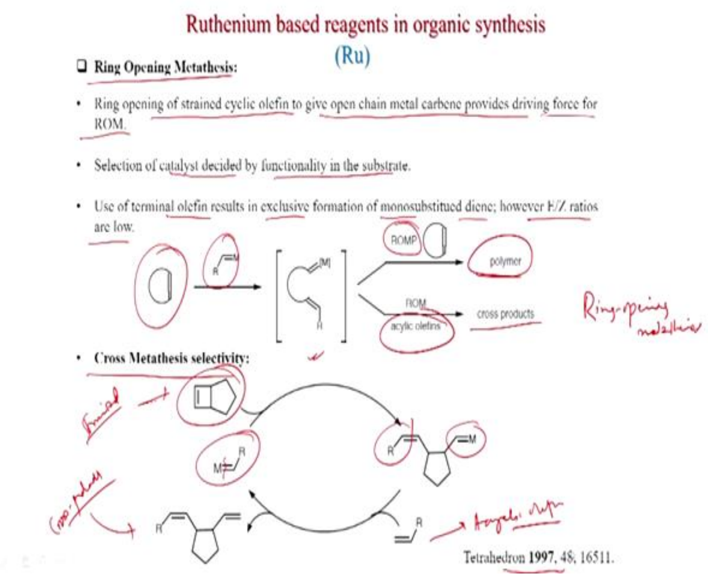

Ruthenium based reagents in organic synthesis

(Ru)

☐ **Ring Opening Metathesis:**

- Ring opening of strained cyclic olefin to give open chain metal carbene provides driving force for ROM.
- Selection of catalyst decided by functionality in the substrate.
- Use of terminal olefin results in exclusive formation of monosubstitued diene; however E/Z ratios are low.
- **Cross Metathesis selectivity:**

Tetrahedron **1997**, 48, 16511.

Ring opening metathesis, now we will discuss ring opening metathesis, so far we have discussed ring closing metathesis, now we will discuss ring opening metathesis. Ring opening of strain cyclic olefin so that should be strained to give open chain metal carbene provides driving force for Ring opening metathesis. Selection of catalyst decided by functionality in the substrate, use of terminal olefin results in exclusive formation of Monosubstituted diene, however, E Z ratios are low, so this is important that E Z ratios are low.

If you use a terminal olefin, so here this cyclic olefin is reacted with the active catalyst to get this, and now if the cyclic olefin only reacts then you get the ring opening metathesis polymerisation that is called polymer. Alternatively, if you put other acyclic olefin, then you can get ring opening metathesis ring opening metathesis, so no polymerisation happens because here you are quenching with another olefin then you get cross products so that both examples we will see.

So cross metathesis selectivity so this is the reaction is happening, this is the active catalyst which reacts with the cyclic olefin, this is strained as you can see here is a bicyclic compound there is a strain here and now this will open and this active catalyst you can see one part is going to one carbon, another part is double bonds are coming to the another part. And now if you react with acyclic olefin so this is the acyclic olefin then you can get this cross product, so this is the cross product. So this is the cross product and this has used many applications, this was published in Tetrahedron in 1997.

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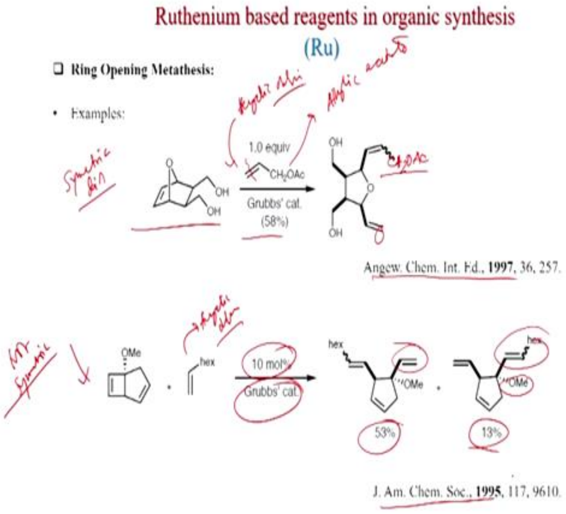

Ruthenium based reagents in organic synthesis

(Ru)

❑ **Ring Opening Metathesis:**

- Examples:

Angew. Chem. Int. Ed., **1997**, 36, 257.

J. Am. Chem. Soc., **1995**, 117, 9610.

Ring opening metathesis examples, so this is the acyclic olefin here acyclic olefin, this is allylic acetate and this is the symmetrical diol so symmetric diol, one advantage of symmetric diol that you do not get mixture, here that is why the substituents are different here but you do not get mixture because these two are same. And as you can see as I told earlier this olefin, one part will go to here, here this CH_2OAc is missing, another part will come here. So one part is going here that CH_2 part and this part CH CH_2OAx is going here and you get this product with Grubbs catalyst 58 percent yield this was published in Angew Chem in 1997.

Also this, this one is not symmetric so this is not symmetric and in this case this is the acyclic olefin one octene here, 10 mol% Grubbs catalyst must be the first-generation because this is now not symmetric so when there is a symmetric then you get one product, if it is not symmetric then you get mixture product so this product is forming 53 percent yield, one case the methoxy has this substituent, on the other hand, methoxy has this substituent so 53 percent for this one might be for the steric reason and with this is forming this one is forming in 13 percent yield, this was published in JACS 1995.

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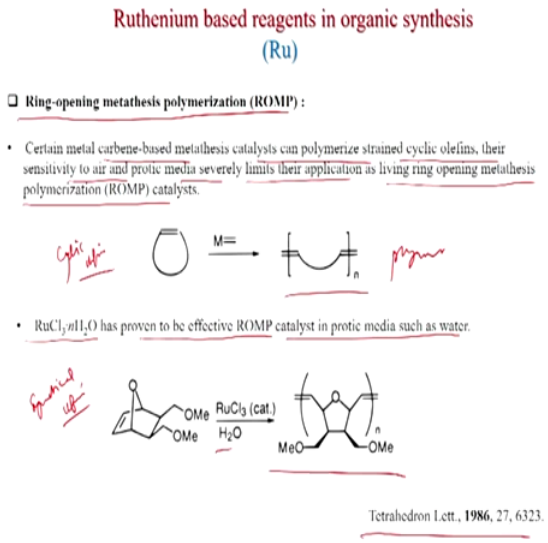

Ruthenium based reagents in organic synthesis

(Ru)

☐ **Ring-opening metathesis polymerization (ROMP) :**

- Certain metal carbene-based metathesis catalysts can polymerize strained cyclic olefins, their sensitivity to air and protic media severely limits their application as living ring opening metathesis polymerization (ROMP) catalysts.

- $RuCl_3 \cdot nH_2O$ has proven to be effective ROMP catalyst in protic media such as water.

Tetrahedron Lett., **1986**, 27, 6323.

Now we discuss ring opening metathesis polymerisation, certain metal carbene based metathesis catalyst can polymerise strained cyclic olefins, they are sensitive to air and protic media severely limits their applications as ring opening metathesis polymerisation ROMP catalysts. Like this, the cyclic olefin reacts to this active catalyst and you get this polymer. $RuCl_3$ and H_2O has proven to be effective, ROMP catalysts in protic media such as water, and this is an example. Suppose this is the symmetrical olefin, symmetrical olefin and this one is ruthenium chloride, water you get this polymer so this is very important reaction and it was published in Tetrehedron letter 1986.

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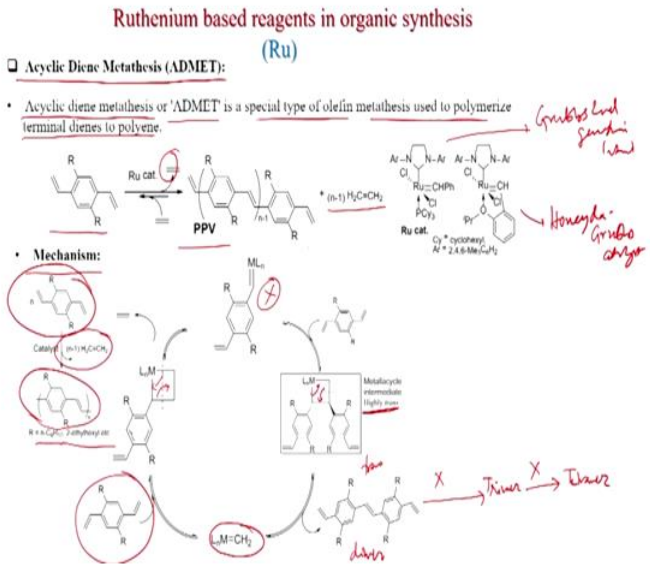

Ruthenium based reagents in organic synthesis

(Ru)

☐ **Acyclic Diene Metathesis (ADMET):**

- Acyclic diene metathesis or 'ADMET' is a special type of olefin metathesis used to polymerize terminal dienes to polyene.

- **Mechanism:**

Now we discuss acyclic diene metathesis polymerisation that is called ADMET. Acyclic diene metathesis or ADMET is a special type of olefin metathesis used to polymerise terminal dienes to polyene. So if you see this is olefin, here one side is there another side another olefin is there, and if you put ruthenium catalyst this is Grubbs second-generation catalyst and this is Hoveyda Grubbs catalyst. And if you put this diene with this ruthenium catalyst and after the elimination of ethylene you get this polymer which is called PPV, so this is polypropylene vinylene.

And N-1 molecule of ethylene is eliminated so here N-1 is there so what could be the mechanism of this reaction so this catalyst after reaction with ethylene we generate these active catalysts and then this will react with this monomer and to generate the metallocyclobutane is formed and this metallocyclobutane after elimination of ethylene it will generate this active intermediate and this again will react with another molecular monomer to generate another metallocyclobutane intermediate and this is highly trans and after that this again gets eliminated to generate this, this is active catalyst and you get this trans olefin so this is dimer.

And now if you see this structure, if this is X then this again reacts with X, it will generate the trimer and trimer again will react with X then will generate tetramer. So like this the polymerisation will happen and N molecules of monomer after elimination of N-1 ethylene it will generate a polymer having N molecules of this monomer. So R is equal to n-C_8H_{17} or 2-ethylhexyl.

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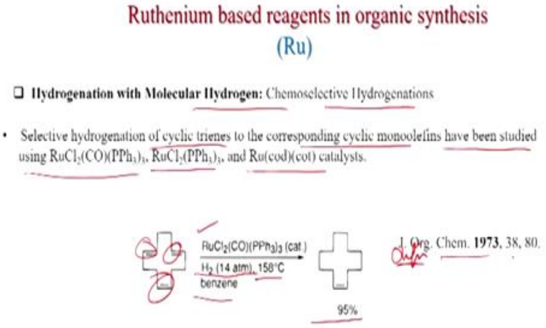

Ruthenium based reagents in organic synthesis
(Ru)

❑ **Hydrogenation with Molecular Hydrogen:** Chemoselective Hydrogenations

- Selective hydrogenation of cyclic trienes to the corresponding cyclic monoolefins have been studied using $RuCl_2(CO)(PPh_3)_3$, $RuCl_2(PPh_3)_3$, and Ru(cod)(cot) catalysts.

J. Org. Chem. **1973**, 38, 80.

Hydrogenation with molecular hydrogen chemoselective hydrogenation, selective hydrogenation of cyclic trienes to the corresponding cyclic mono olefins have been studied using $RuCl_2(CO)(PPh_3)_3$, $RuCl_2(PPh_3)_3$ and Ru(cod)(cot) catalyst. Like here there are 3 double bonds are present and with this catalyst with hydrogen 14 atmosphere pressure, 158 degrees centigrade benzene solvent you get this olefin, so 2 double bonds gets reduced this was published in JOC in 1973.

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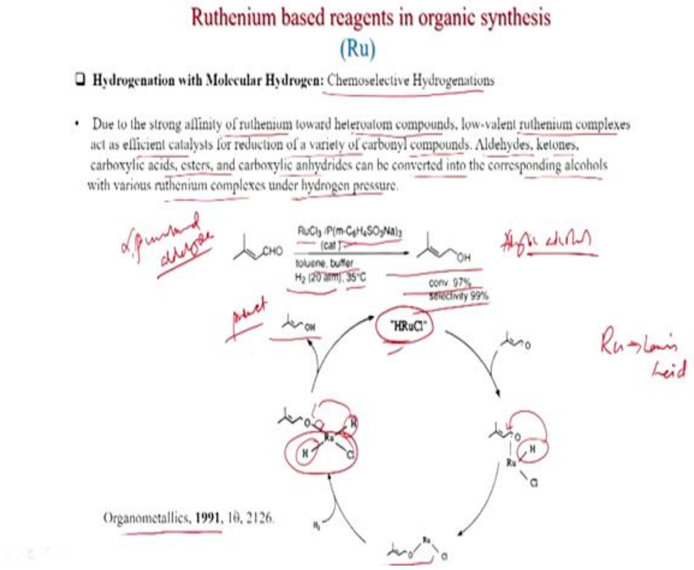

Ruthenium based reagents in organic synthesis

(Ru)

❑ **Hydrogenation with Molecular Hydrogen:** Chemoselective Hydrogenations

- Due to the strong affinity of ruthenium toward heteroatom compounds, low-valent ruthenium complexes act as efficient catalysts for reduction of a variety of carbonyl compounds. Aldehydes, ketones, carboxylic acids, esters, and carboxylic anhydrides can be converted into the corresponding alcohols with various ruthenium complexes under hydrogen pressure.

Organometallics, **1991**, 10, 2126.

Now we will discuss hydrogenation with molecular hydrogen and chemoselective hydrogenation are possible. Due to the strong affinity of ruthenium towards hetero atom compounds, low valent ruthenium complexes act as efficient catalyst for reduction of a variety of carbonyl compounds. Aldehydes, ketones, carboxylic acid, ester and carboxylic anhydrides can be converted into the corresponding alcohols with various ruthenium complexes under hydrogen pressure.

So as I have told that ruthenium can take up hydrogen and it can the hydride can be transferred. Like here, this is alpha-beta unsaturated aldehyde, this will react with this $RuCl_3$ then sulphonate ester is there, phosphorus has this sulphonate ester derivative with this is the catalyst and toluene, buffer, H_2, so hydrogen will be taken up by ruthenium first and 35 degrees centigrade you get this allylic alcohol, so allylic alcohol is formed in 97 percent conversion with 99 percent selectivity.

So what could be the mechanism, as I told that ruthenium will take up the hydrogen so HRuCl is the active catalyst here and HRuCl will react with first the carbonyl, it will bind like this because this is also Lewis acid ruthenium also Lewis acid so it will bind with carbonyl, and now the hydride will deliver to the carbonyl and it becomes alcoxy so this ruthenium oxygen bond will form now.

And now hydrogen will come to make this hydride because ruthenium always will take up hydrogen and again another hydride will transfer to oxygen and this bond will break so you get HRuCl, HRuCl is here present and you get the allylic alcohol so this is the product. SO as you can see HRuCl is the active catalyst which will bind to the carbonyl then transfer the hydrogen, and again hydrogen would come to make this dihydride ruthenium then the hydride will transfer to the oxygen and the alcohol will form, this was published in organometallic in 1991.

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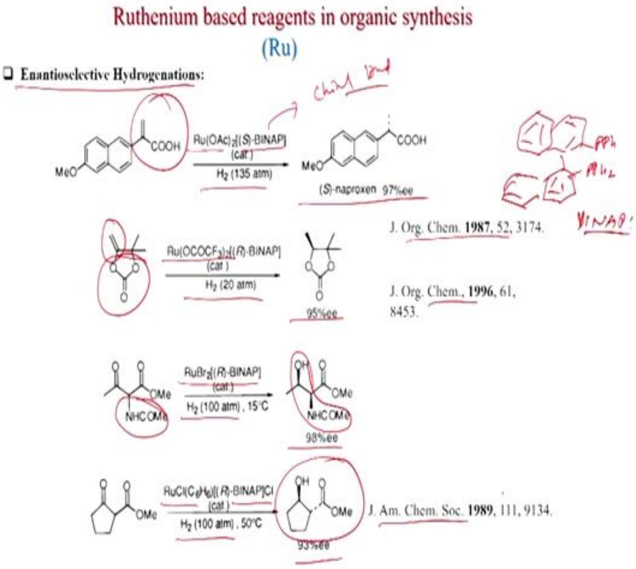

Ruthenium based reagents in organic synthesis

(Ru)

☐ **Enantioselective Hydrogenations:**

J. Org. Chem. **1987**, 52, 3174.

J. Org. Chem., **1996**, 61, 8453.

J. Am. Chem. Soc. **1989**, 111, 9134.

Enentioselective hydrogenation also is possible, suppose if you use chiral catalyst that enhances selectivity can be obtained. Like this one, this is the alpha-beta unsaturated carboxylic acid and with ruthenium acetate if this is the chiral ligand BINAP chiral ligand. So PPh_2, PPh_2 this is chiral, this is the BINAP and with H_2 135 atmosphere you get this product which is useful drug (S)-naproxen with 97 percent ee this was published in JOC 1987. Also, this anhydride and this double bond is present so double bond will be selectively reduced because it generates a chiral centre with $Ru(OCOCF_3)_2$ [(R)-BINAP] catalyst and hydrogen 20 atmosphere you get 95 percent yield, this was published in JOC.

Also this one, there is a stereogenic centre will form here after the reduction, this is the beta ketone ester and with $RuBr_2$[(R)-BINAP] catalyst, H_2 100 atmosphere you get this product so 2 chiral centre because after reduction this centre is stable with 98 percent ee. Also this cyclic beta ketone ester with $RuClC_6H_6[(R)\text{-}BINAP]Cl$ provide catalyst H_2 100 atmosphere, 50 degree centigrade you will get this beta hydroxyl ester in 93 percent yield, this was published in JACS 1989.

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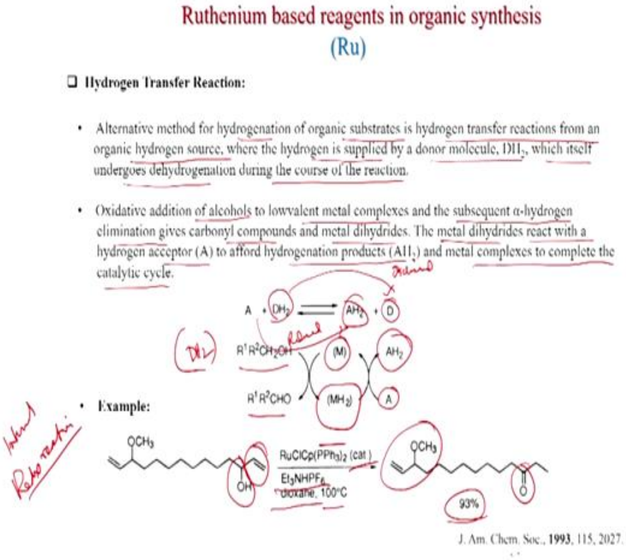

Ruthenium based reagents in organic synthesis

(Ru)

❑ **Hydrogen Transfer Reaction:**

- Alternative method for hydrogenation of organic substrates is hydrogen transfer reactions from an organic hydrogen source, where the hydrogen is supplied by a donor molecule, DH_2, which itself undergoes dehydrogenation during the course of the reaction.
- Oxidative addition of alcohols to lowvalent metal complexes and the subsequent α-hydrogen elimination gives carbonyl compounds and metal dihydrides. The metal dihydrides react with a hydrogen acceptor (A) to afford hydrogenation products (AH_2) and metal complexes to complete the catalytic cycle.
- **Example:**

J. Am. Chem. Soc., **1993**, 115, 2027.

Hydrogen transfer reaction also is possible, alternative method for hydrogenation of organic substances is hydrogen transfer reaction from an organic hydrogen source, where the hydrogen is applied by a donor molecule DH_2 which itself undergoes dehydrogenation during the course of the reaction. So in this case hydrogen transfer reaction the external hydrogen is not required. Oxidative addition of alcohols to low valent metal complexes and the subsequent alpha hydrogen elimination gives carbonyl compounds and metal dihydrides.

The metal dihydrides reacts with a hydrogen acceptor to afford hydrogenation products AH_2 and metal complexes to complete the catalytic cycle. So here what will happen, the DH_2 which wants to give hydrogen to the acceptor, the acceptor take the hydrogen AH_2 and D will from. So what will happen, D will be oxidised so in this process D is getting oxidised and A is getting reduced.

And this is the cycle so suppose here in this case the alcohol is actually DH2 so this is the alcohol which is DH_2 and AH_2, A you have to use that we will see sometimes enone is present and what will happen? This metal takes up the hydrogen from the alcohol to convert the alcohol to aldehyde and it will become MH_2. MH_2 will transfer hydrogen to acceptor because MH_2 has to be converted to again M so that it can take up the hydride again so MH has to be free and that process is only possible if you put an another acceptor will take up the hydrogen so that MH_2 will convert to M again.

In the example of this, here interestingly this alcohol will be oxidised so this is like a redox reaction because internal redox reaction because here with this alcohol is getting oxidised and this double bond is reduced so both acceptor and donor are in the same molecule and with $RuClCp(PPh_3)_2$ catalyst this is the additive Et_3NHPF_6 and dioxane 100 degrees centigrade you get 93 percent yield of this product, so double bond gets reduced and alcohol gets oxidised and this part is not affected, this was published in JACS 1993.

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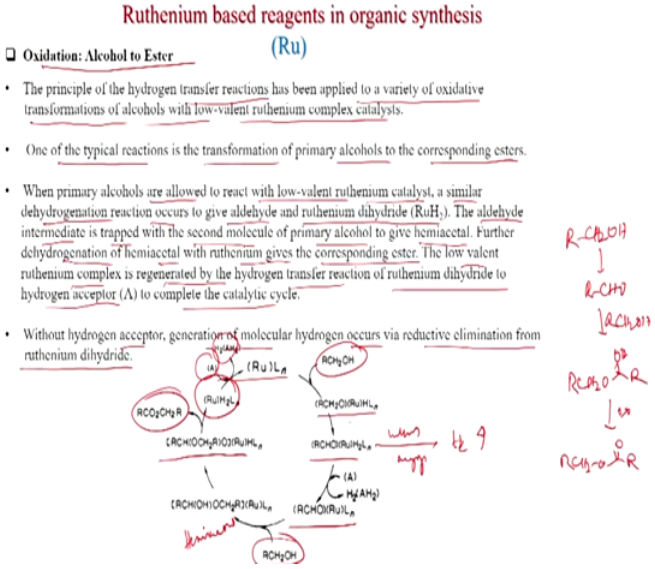

Ruthenium based reagents in organic synthesis

(Ru)

❑ **Oxidation: Alcohol to Ester**

- The principle of the hydrogen transfer reactions has been applied to a variety of oxidative transformations of alcohols with low-valent ruthenium complex catalysts.
- One of the typical reactions is the transformation of primary alcohols to the corresponding esters.
- When primary alcohols are allowed to react with low-valent ruthenium catalyst, a similar dehydrogenation reaction occurs to give aldehyde and ruthenium dihydride (RuH_2). The aldehyde intermediate is trapped with the second molecule of primary alcohol to give hemiacetal. Further dehydrogenation of hemiacetal with ruthenium gives the corresponding ester. The low valent ruthenium complex is regenerated by the hydrogen transfer reaction of ruthenium dihydride to hydrogen acceptor (A) to complete the catalytic cycle.
- Without hydrogen acceptor, generation of molecular hydrogen occurs via reductive elimination from ruthenium dihydride.

Now we will see this kind of transfer hydrogenation application of alcohol to ester. So alcohol can be converted to ester also, principle of the hydrogen transfer reaction has been applied to a variety of oxidative transformation of alcohols with low-valent ruthenium complex catalyst. One of the typical reaction is the transformation of primary alcohol to the corresponding esters. When primary alcohols are allowed to react with low valent ruthenium catalyst, a similar dehydrogenation reaction occurs to give aldehyde and ruthenium dihydride.

The aldehyde intermediate is trapped with the second molecule of primary alcohol to give hemiacetal. Further dehydrogenation of hemiacetal with ruthenium catalyst give the corresponding ester. So as you know, the alcohol suppose this is the alcohol this will convert to aldehyde and now this aldehyde will react with the alcohol to generate this hemiacetal. And now this hemiacetal will be oxidation will give this ester.

The low valent ruthenium complex is regenerated by the hydrogen transfer reaction of ruthenium dihydride to hydrogen acceptor to complete the catalytic cycle. Without hydrogen acceptor, generation of molecule hydrogen occurs by reductive elimination from ruthenium dihydride, so this is also possible. If you do not put the hydrogen acceptor then the hydrogen gas will eliminate that is also possible if you have the system where the hydrogen can be eliminated.

So this is the catalyst and now the alcohol will react and this alcohol hydrogen will go to the ruthenium so RCHO will come so 2 hydrogen goes to the ruthenium. Now if you put the acceptor so without acceptor hydrogen will be eliminated. Now if you put the acceptor then acceptor will take up the hydrogen, it go to AH_2 and you have this complex. Now again this RCH_2 will react to generate the hemiacetal so this is hemiacetal as we have shown here hemiacetal will form and this hemiacetal will again get oxidation.

So here the hemiacetal is getting oxidised RCHO OCH_2R and you get this ester and you get this ruthenium hydride. And again this acceptor will come so acceptor will take up the hydrogen, whenever ruthenium has excess of hydrogen the acceptor will take up the hydrogen so that the metal can again take up the hydrogen from the substrate and in this process you can get the ester.

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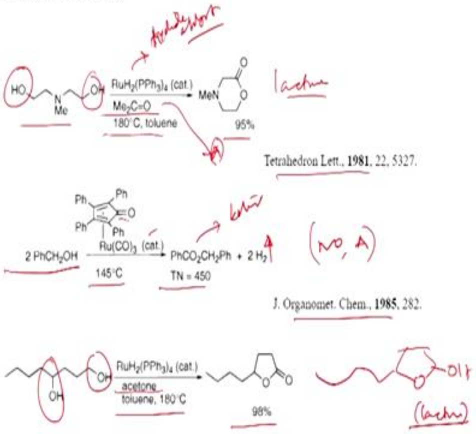
Ruthenium based reagents in organic synthesis

(Ru)

❑ **Oxidation: Hydrogen Transfer Reactions:**

- Examples:



Tetrahedron Lett., **1981**, 22, 5327.

J. Organomet. Chem., **1985**, 282.

J. Org. Chem., **1987**, 52, 4319.

Now we will see some examples of this kind of reactions like here 2 alcohol is there so this is a diol with $RuH_2(PPh_3)_4$ so this is already hydride catalyst where hydride is present here already hydride catalyst and acetone, so this is the A so this will take the hydrogen so acceptor is here acetone because acetone can be reduced to alcohol. And 180 degrees centigrade toluene you get this lactone in 95 percent yield, it was published in tetrahydron letter.

Also if you have this benzylic alcohol 2 equivalent with this ruthenium carbonyl cyclopentadiene carbonyl complex, catalyst in catalytic amount 145 degree centigrade you can get this ester and hydrogen gas is eliminated. So here no acceptor but hydrogen has to be eliminated and turnover number is 450, it was published in Journal of organic chemistry 1985.

If you have diol like this one primary secondary then the primary alcohol will be oxidised to the aldehyde first and then this will react so lactol will form so this is going like this, this is a lactol so lactol is forming and this lactol is converted to lactone and we have the acceptor is acetone with this ruthenium hydride catalyst toluene 180 degree centigrade you get this product 98 percent yield, this was published in JOC 1987.

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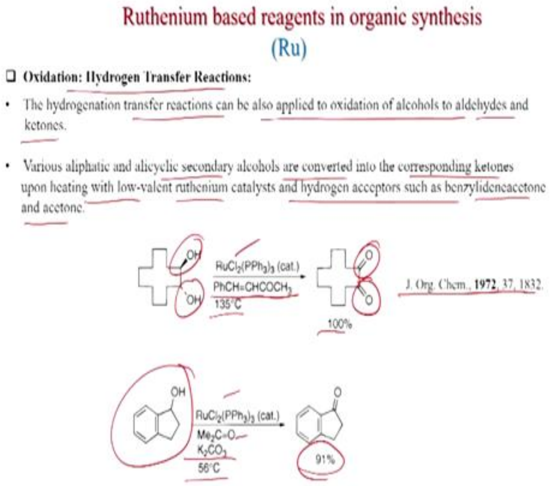

Ruthenium based reagents in organic synthesis
(Ru)

☐ **Oxidation: Hydrogen Transfer Reactions:**

- The hydrogenation transfer reactions can be also applied to oxidation of alcohols to aldehydes and ketones.
- Various aliphatic and alicyclic secondary alcohols are converted into the corresponding ketones upon heating with low-valent ruthenium catalysts and hydrogen acceptors such as benzylideneacetone and acetone.

J. Org. Chem., **1972**, 37, 1832.

Some more examples of oxidation hydrogen transfer reaction, the hydrogenation transfer reaction can also be applied to oxidation of alcohols to aldehydes and ketones. Various aliphatic and acyclic secondary alcohols are converted into the corresponding ketones upon heating with low-valent ruthenium catalyst and hydrogen acceptor such as benzylideneacetone and acetone.

Like here the diol is converted to diketone with this catalyst the same catalyst and this is the acceptor, it is the acceptor of hydrogen and 135 degrees centigrade you get 100 percent yield almost quantitative yield and this was published in JOC 1972, this is the interval derivative and here with this catalyst this is the acceptor, Potassium carbonate is base, 56 degrees centigrade you get this compound in 91 percent yield, the alcohol oxidation the first published in Chem comm 1992.

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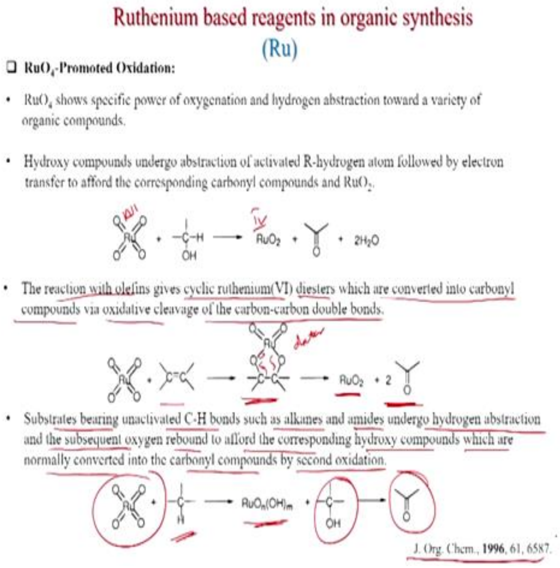

Ruthenium based reagents in organic synthesis

(Ru)

❑ **RuO_4-Promoted Oxidation:**

- RuO_4 shows specific power of oxygenation and hydrogen abstraction toward a variety of organic compounds.
- Hydroxy compounds undergo abstraction of activated R-hydrogen atom followed by electron transfer to afford the corresponding carbonyl compounds and RuO_2.
- The reaction with olefins gives cyclic ruthenium(VI) diesters which are converted into carbonyl compounds via oxidative cleavage of the carbon-carbon double bonds.
- Substrates bearing unactivated C-H bonds such as alkanes and amides undergo hydrogen abstraction and the subsequent oxygen rebound to afford the corresponding hydroxy compounds which are normally converted into the carbonyl compounds by second oxidation.

J. Org. Chem., **1996**, 61, 6587.

Now we will discuss ruthenium oxide promoted oxidation, earlier we have seen that TPAP reagent which has ruthenium 7 that time we told that TPAP is a mild reagent, on the other hand ruthenium oxide ruthenium is in 8 oxidation state so it is quite strong. Ruthenium oxide for specific power of oxidation and hydrogen abstraction towards a variety of organic compounds.

Hydroxy compounds undergo abstraction of activated or hydrogen atoms followed by electron transfer to afford corresponding carbonyl compounds and RuO_2. So it is converted after oxidation to RuO_2, this is 4 oxidation state and this is 8. Here this alcohol is converted to ketones, secondary alcohol is converted to ketones and 2 molecule of water is eliminated.

The reaction with olefins gives cyclic ruthenium(VI)diester which are converted into carbonyl compounds by oxidative cleavage of the carbon-carbon double bond. So this is very interesting, ruthenium tetraoxide with reaction with olefin to generate this ruthenium diester so this is diester, then diester then cleaves like osmate ester to generate the ruthenium dioxide and 2 molecules of ketone is formed, so this is a very important reaction.

Also, substrate bearing unactivated C-H bonds such as alkanes and amides undergo hydrogen abstraction and the subsequent oxygen rebound to afford the corresponding hydroxy compounds which are normally converted into the carbonyl compounds by second oxidation. So ruthenium tetraoxide reacts also with alkanes to generate this ruthenium hydroxide compound and you generate the alcohol, the alcohol is converted to carbonyl compound again by oxidation, and this work was published in JOC 1996.

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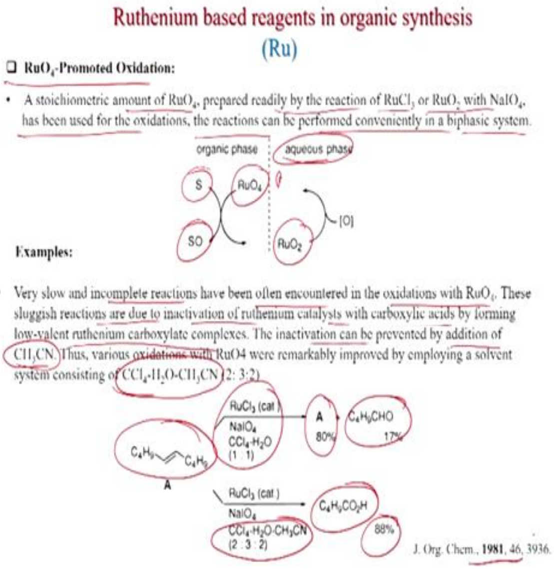

Ruthenium based reagents in organic synthesis

(Ru)

❑ **RuO_4-Promoted Oxidation:**

- A stoichiometric amount of RuO_4, prepared readily by the reaction of $RuCl_3$ or RuO_2 with $NaIO_4$, has been used for the oxidations, the reactions can be performed conveniently in a biphasic system.

Examples:

- Very slow and incomplete reactions have been often encountered in the oxidations with RuO_4. These sluggish reactions are due to inactivation of ruthenium catalysts with carboxylic acids by forming low-valent ruthenium carboxylate complexes. The inactivation can be prevented by addition of CH_3CN. Thus, various oxidations with RuO4 were remarkably improved by employing a solvent system consisting of CCl_4-H_2O-CH_3CN (2: 3:2)

J. Org. Chem., **1981**, 46, 3936.

Some more examples of ruthenium oxide promoted oxidation is stoichiometric amount of ruthenium oxide prepared readily by the reaction of $RuCl_3$ or RuO_2 with Sodium periodate has been used for the oxidation reactions can be performed conveniently in a biphasic system. Like here, in the aqueous phase the RuO_2 is getting oxidised to RuO_4 the aqueous phase, now it is going to organic phase. RuO_4 is going to organic phase after oxidation from RuO_2, and now in the organic phase it is oxidising substrate to SO substrate oxide.

Examples, very slow and incomplete reaction often we encounter in the oxidation of RuO_4, these sluggish reactions are due to inactivation of ruthenium catalyst with carboxylic acid by forming a low valent ruthenium carboxylate complex. The inactivation can be prevented by the addition of acetonitrile, and thus the solvents are used we will see some examples acetonitrile.

Suppose this olefin if you put with ruthenium chloride catalyst, sodium periodate CCl_4, H_2O you get **A** that is the starting material remain and you get the aldehyde 17 percent yield. On the other hand, if you use CCl_4, H_2O, acetonitrile solvent 2:3:2 then you get this acid in 88 percent yield so that says that acetonitrile is very important for converting olefin to carboxylic acid, this was published in JOC 1981.

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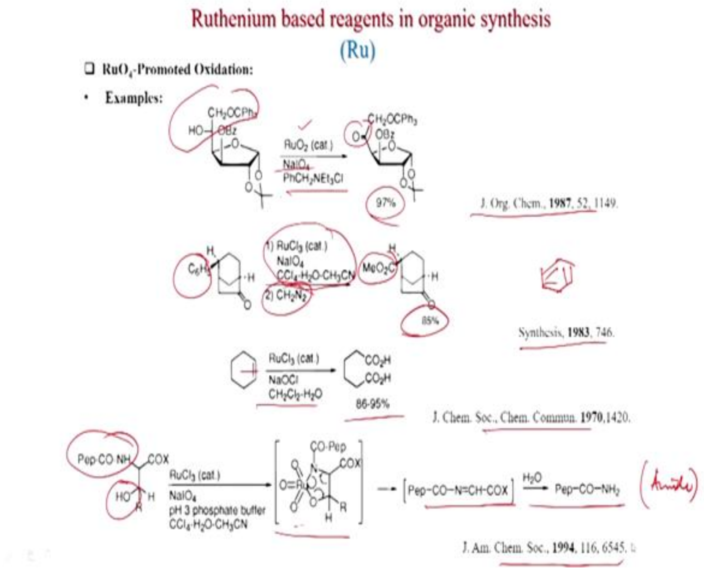

Ruthenium based reagents in organic synthesis

(Ru)

❑ RuO_4-Promoted Oxidation:

- Examples:

J. Org. Chem., **1987**, 52, 1149.

Synthesis, **1983**, 746.

J. Chem. Soc., Chem. Commun. **1970**,1420.

J. Am. Chem. Soc., **1994**, 116, 6545.

Some more examples like here the secondary alcohol getting oxidised to the carbonyl here so ruthenium oxide and $NaIO_4$ which in situ form the, this is the additive you get 97 percent yield for the product, this was published in JOC 1987. Here also an important reaction that benzene getting oxidised, this is phenyl and this phenyl group getting oxidised to the first carboxylic acid so one carbon only remains and that can be converted to ester with diazomethane so this is very strong oxidising agent $RuCl_3$, $NaIO_4$, carbon tetrachloride, water acetonitrile solvent you get 85 percent yield for this product, this was published in Synthesis 1983.

And the Olefin can be cleaved as we have seen earlier with the system NaOCl here dichloromethane water is enough to give this di-acid in 86 to 95 percent, this was published in Chem Comm 1970. And if you have an amino group and OH then this kind of reaction is happening, the cyclisation happens first and then the bond isomerisation as you can see bond breaking and making here so you get this imine and after hydrolysis you get the amide so amide is formed. Pep-CO-NH_2 is formed, this was published in JACS 1994.

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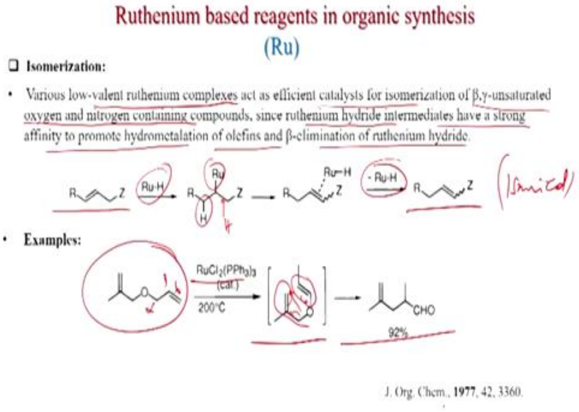

Ruthenium based reagents in organic synthesis

(Ru)

☐ **Isomerization:**

- Various low-valent ruthenium complexes act as efficient catalysts for isomerization of β,γ-unsaturated oxygen and nitrogen containing compounds, since ruthenium hydride intermediates have a strong affinity to promote hydrometalation of olefins and β-elimination of ruthenium hydride.

- **Examples:**

J. Org. Chem., **1977**, 42, 3360.

Now isomerisation also is an important reaction in organic chemistry and ruthenium can take up the hydrogen and transfer. So as we have seen so this isomerisation can be carried out by ruthenium complexes and generally low valent ruthenium complexes act as efficient catalyst for isomerisation of beta-gamma unsaturated oxidation and nitrogen containing compounds, say ruthenium hydride intermediates have a strong affinity to promote hydrometalation of olefins and beta elimination of ruthenium hydride.

So like this the ruthenium hydride first will hydrogenate this one and add like this, and now this hydrogen will be taken. This hydrogen will be taken and so the double bond will be formed and ultimately -RuH you get the isomerised product so this is isomerised. Examples like here so this is alpha, beta, gamma so this is beta-gamma unsaturated ether and when you put this ruthenium catalyst you get this alpha beta unsaturated ether. So this you can say this is a claisen substrate O allyl and O vinyl, this is O vinyl, this is O allyl, now the claisen rearrangement will happen like this way and you get this aldehyde 92 percent yield this was published in JOC 1977.

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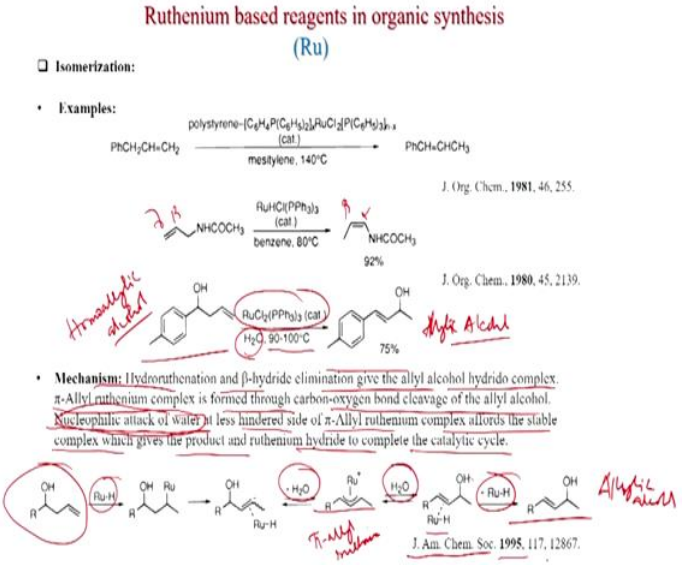

Ruthenium based reagents in organic synthesis

(Ru)

☐ **Isomerization:**

- **Examples:**

J. Org. Chem., **1981**, 46, 255.

J. Org. Chem., **1980**, 45, 2139.

- **Mechanism:** Hydroruthenation and β-hydride elimination give the allyl alcohol hydrido complex. π-Allyl ruthenium complex is formed through carbon-oxygen bond cleavage of the allyl alcohol. Nucleophilic attack of water at less hindered side of π-Allyl ruthenium complex affords the stable complex which gives the product and ruthenium hydride to complete the catalytic cycle.

J. Am. Chem. Soc. **1995**, 117, 12867.

Some more examples, suppose if you have a double bond here then you can get the conjugated with the phenyl olefin is forming here with polystyrene this catalyst mesitylene solvent 140 degrees centigrade, this was published in JOC 1981. Also this one will converted to alpha beta unsaturated so what we have seen that beta-gamma if it is there beta-gamma then it goes to alpha-beta that is the reaction is happening because this is more stable product and here cis product is forming with this catalyst already hydrogenated and benzene 80 degree centigrade 92 percent yield of this product.

Also this is an homoallylic alcohol so homoallylic alcohol, and this homoallylic alcohol when treated with this catalyst $RuCl_2(PPh_3)_3$ and H_2O this is very important, the water solvent 90 to 100 degree centigrade then you get allylic alcohol. So what could be the mechanism of this reaction, hydroruthenation and beta hydride elimination gives the allyl alcohol hydrido complex, pi-allyl ruthenium complex is formed through the carbon-oxygen bond cleavage of the allyl alcohol.

For the nucleophilic attack of water so this is very important, nucleophilic attack of water at less hindered side of pi-allyl ruthenium complex affords the stable complex which gives the product and ruthenium hydride to complete the catalytic cycle. So this is the mechanism this is the homoallylic alcohol, now that in the double bond this ruthenium hydride will add so ruthenium hydride generally attack the double bond and then you can see the migration of the double bond happens, so double bond has become now internal and it will be coordinate with ruthenium hydride.

And after elimination of water this pi-allyl ruthenium will form. So this pi-allyl ruthenium intermediate is very important and water then attack because this is an electrophilic species, water can attack and mostly attack this side to generate this allylic alcohol and where the double bond is coordinated with ruthenium hydride and after elimination of ruthenium hydride you get this allylic alcohol, so this is an important reaction and this was published in JACS 1995 page number is 12867.

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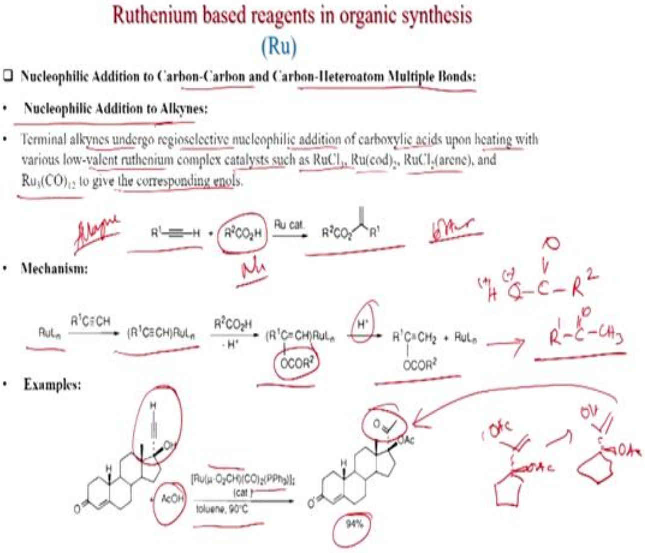

Ruthenium based reagents in organic synthesis
(Ru)

☐ **Nucleophilic Addition to Carbon-Carbon and Carbon-Heteroatom Multiple Bonds:**

- **Nucleophilic Addition to Alkynes:**
- Terminal alkynes undergo regioselective nucleophilic addition of carboxylic acids upon heating with various low-valent ruthenium complex catalysts such as $RuCl_3$, $Ru(cod)_2$, $RuCl_2(arene)$, and $Ru_3(CO)_{12}$ to give the corresponding enols.
- **Mechanism:**
- **Examples:**

Lastly we will discuss nucleophilic addition to carbon-carbon and carbon-heteroatom multiple bonds. First we will discuss nucleophilic addition to alkynes, terminal alkynes undergo regioselective nucleophilic addition of carboxylic acid upon heating with various low valent ruthenium complex catalyst such as $RuCl_3$, $Ru(cod)_2$, $RuCl_2$(arene) and $Ru_3(CO)_{12}$ to give the corresponding enols. So like this you can say this is alkyne and this is carboxylic acid so this is the nucleophile and with ruthenium catalyst the triple bond we can add this so you get this ester.

So ester is formed after addition of carboxylic acid and the mechanism is there, this is the catalyst, it is first reacting with the alkyne to generate this and after the activation now the addition will take place $OCOR^2$, so adding is $OCOR^2$ so this is adding this minus this is a nucleophile, this minus is adding here and you get this vinyl ester and after protonation you get this olefin and of course this will isomerise this can isomerise to the Ketone bond R-CO-CH_3 R1-CO-CH_3 after hydrolysis.

So like this, this one you can say the hydroxy and the triple bond is present and if you treat with acetic acid with this complex Ru carbonyl PPh_3 catalyst in toluene 90 degree centigrade so what happens here the alcohol is converted into acetate, also this triple bond is converting to the ketone. And here what is happening? Here this is the intermediate of course OAc, so this is converting to the first this OAc is forming this is going to OH and this OH is going to carbonyl, the enol is converted into carbonyl and you get this product in 94 percent yield, this was published in Chem comm, 1994.

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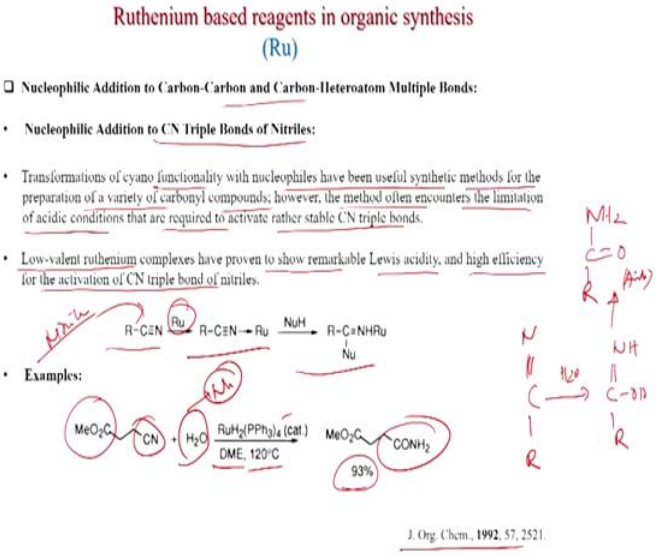

Ruthenium based reagents in organic synthesis
(Ru)

❑ **Nucleophilic Addition to Carbon-Carbon and Carbon-Heteroatom Multiple Bonds:**

- **Nucleophilic Addition to CN Triple Bonds of Nitriles:**
- Transformations of cyano functionality with nucleophiles have been useful synthetic methods for the preparation of a variety of carbonyl compounds; however, the method often encounters the limitation of acidic conditions that are required to activate rather stable CN triple bonds.
- Low-valent ruthenium complexes have proven to show remarkable Lewis acidity, and high efficiency for the activation of CN triple bond of nitriles.
- **Examples:**

J. Org. Chem., 1992, 57, 2521.

Nucleophilic addition to carbon-carbon heteroatoms, so now we will discuss CN triple bonds of nitrites. Transformation of cyano functionality with nucleophiles have been useful synthetic methods for the preparation of a variety of carbonyl compounds, however the method often encounters the limitation of acidic conditions that are required to activate rather stable CN triple bonds. Low valent ruthenium like aldehyde low-valent ruthenium complexes have proven to show remarkable Lewis acidity and high efficiency for the activation of CN triple bond to nitrile.

So here you can see the triple bond C that is the nitrile so nitrile bond is getting activated by ruthenium so that the nucleophilic addition will take place now, the carbon center. Examples, like here CO_2Me and cyano group is there with water, water is the nucleophile and with this catalyst $RuH_2(PPh_3)_4$ catalyst DME solvent 120 degrees centigrade temperature you get this amide in 93 percent yield.

So what happens, C triple bond N it adds water so what happens OH adds here and it becomes C double bond NHR and this after tautomerisation this becomes C double bond O NH_2 so this is the amide. Cyanide is getting converted to amide, and this was published in JOC 1992. So today we have discussed ruthenium catalyst and first we have discussed the Grubbs first metathesis catalyst, so Grubbs first generation we have discussed. first generation has the Benzylidene substituent and cyclone hexyl phosphine.

On the other hand, second-generation had the more nucleophilic N heterocyclic carbene and 3rd generation has pyridine and the third-generation catalyst have been found to be useful for ring opening metathesis polymerisation and Hovyeda Grubbs catalyst where also isopropoxy group is present which is binding to ruthenium and giving extra stability. And we have seen different kinds of metathesis reactions, cross metathesis we have seen then the ring closing metathesis. And in the ring closing metathesis we have seen that different substrates can be tolerated like esters are very useful substrate, also carboxylic acid.

So esters can be converted to lactones because after cyclisation we call it lactones and these processes are very efficient to generate cyclic compounds. Also, ring closing metathesis we have seen for the synthesis of larger rings, one challenge is the E Z stereochemistry then we have seen the ring opening metathesis polymerisation. In the ring opening metathesis polymerisation we have seen that with symmetrical olefin if you put an acyclic olefin then you can get a single product, on the other hand if it is not symmetrical if the double bond is not symmetric if it is not symmetric then you will get a mixture of products depending on the steric.

And ruthenium can take up hydrogen and this chemistry has been exploited in many reactions like oxidation, induction we have been the reduction of aldehyde functionality like alpha-beta unsaturated aldehyde can be converted to allylic alcohols. Also double bond can reduce with ruthenium catalyst and we have seen that with BINAP ligand and with hydrogen as the reducing agent you can generate chiral centre of Alpha-beta unsaturated carboxylic acid you can get very high enantioselectivity.

And then we have seen that this system can be also useful for oxidation, in the oxidation case we have seen that it can be used with an acceptor like acetone or para benzoquinone which take up the hydrogen liberated during the oxidation process. And in this way we have seen the oxidation of alcohol to esters and lastly we have seen the isomerisation so isomerisation of beta-gamma unsaturated alcohols or amines can be converted to alpha-beta unsaturated efficiently by this isomerisation process, thank you.