Reagents in Organic Synthesis
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Lecture 31
Samarium II Iodide in Organic Synthesis

So, today we will continue samarium iodide in organic synthesis.

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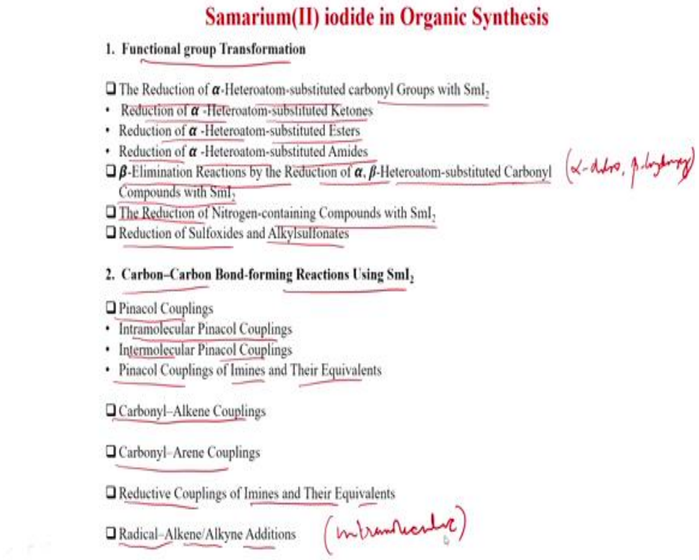

Samarium(II) iodide in Organic Synthesis

1. **Functional group Transformation**

❑ The Reduction of α-Heteroatom-substituted carbonyl Groups with SmI_2
- Reduction of α -Heteroatom-substituted Ketones
- Reduction of α -Heteroatom-substituted Esters
- Reduction of α -Heteroatom-substituted Amides

❑ β-Elimination Reactions by the Reduction of α, β-Heteroatom-substituted Carbonyl Compounds with SmI_2 (α-chloro, β-hydroxy)

❑ The Reduction of Nitrogen-containing Compounds with SmI_2

❑ Reduction of Sulfoxides and Alkylsulfonates

2. **Carbon–Carbon Bond-forming Reactions Using SmI_2**

❑ Pinacol Couplings
- Intramolecular Pinacol Couplings
- Intermolecular Pinacol Couplings
- Pinacol Couplings of Imines and Their Equivalents

❑ Carbonyl–Alkene Couplings

❑ Carbonyl–Arene Couplings

❑ Reductive Couplings of Imines and Their Equivalents

❑ Radical–Alkene/Alkyne Additions (intramolecular)

So, first we will discuss functional group transformation. The reduction of alpha heteroatom substituted carbonyl groups with samarium iodide. And, here we will discuss reduction of alpha heteroatom substituted ketones. Reduction of alpha heteroatom substituted esters also reduction of alpha heteroatom substituted amides. Also, we will discuss beta elimination reactions by the reduction of alpha beta heteroatoms substituted that we will see generally alpha chloro and beta hydroxy is there. Then you can get the beta elimination and alpha beta unsaturated carbonyl compounds you can generate.

The reduction of nitrogen containing compounds is samarium iodide that also you will see nitro compounds. Reduction of sulfoxides and alkylsulfonate that also we will see. Then we will see carbon-carbon bond forming reactions using samarium iodide. And, here we will discuss pinacol couplings, intramolecular pinacol couplings, intermolecular pinacol couplings also. And pinacol couplings of imines and their equivalents also we will discuss. Then we will discuss carbonyl alkene coupling, this is very important C-C bond formation. Carbonyl arene coupling also, then reductive couplings of imines and their equivalents. And, finally we will discuss radical alkene alkyne additions generally these are intramolecular, later we will discuss.

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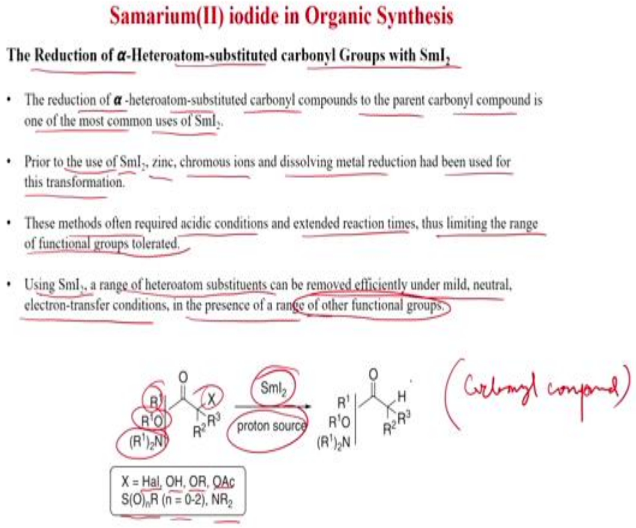

Samarium(II) iodide in Organic Synthesis

The Reduction of α-Heteroatom-substituted carbonyl Groups with SmI_2

- The reduction of α -heteroatom-substituted carbonyl compounds to the parent carbonyl compound is one of the most common uses of SmI_2.
- Prior to the use of SmI_2, zinc, chromous ions and dissolving metal reduction had been used for this transformation.
- These methods often required acidic conditions and extended reaction times, thus limiting the range of functional groups tolerated.
- Using SmI_2, a range of heteroatom substituents can be removed efficiently under mild, neutral, electron-transfer conditions, in the presence of a range of other functional groups.

X = Hal, OH, OR, OAc
$S(O)_nR$ (n = 0-2), NR_2

So, first we will discuss the reduction of alpha heteroatom substituted carbonyl compounds with samarium iodide. So, in the case of samarium last class we have seen when the alpha halo ketones are there, there we have seen that they generate the enolates. So, here also the reduction of alpha heteroatom substituted carbonyl compounds to the parent carbonyl compound is one of the most common uses of samarium iodide. So, here you can generate the enolates and that enolates if you quench with proton source then you can generate the ketone.

Prior to the use of samarium iodide, zinc, chromous ions and dissolving metal reduction had been used for this transformation. Those methods often required acidic condition and extended reactions times, thus limiting the range of functional groups tolerated. So, this is very important the earlier methods the functional groups toleration was very less. However using samarium iodide the range of heteroatoms substituents can be removed efficiently under mild, neutral and electron transfer conditions in the presence of a range of other functional groups.

So, this is very important with samarium iodide you can do this reaction in presence of other functional groups so this very selective. And, this process is very fast that also you will see. So, if you have a carbonyl compound like R1 ketone then OR1 then ester and NR2 then it will be amide and x can be halo OH OR OAc S(O)nR n is equal to 0-2, NR2. So, different x groups can be liberated with samarium iodide and proton source you get the carbonyl compound. So, here the heteroatom which is replaced by a proton.

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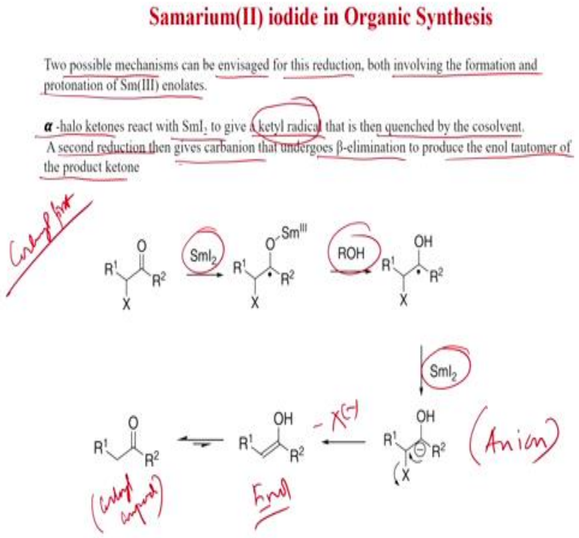

Samarium(II) iodide in Organic Synthesis

Two possible mechanisms can be envisaged for this reduction, both involving the formation and protonation of Sm(III) enolates.

α -halo ketones react with SmI_2 to give a ketyl radical that is then quenched by the cosolvent. A second reduction then gives carbanion that undergoes β-elimination to produce the enol tautomer of the product ketone

Now, what is the mechanism, two possible mechanisms can be envisaged for this reduction both involving the formation and protonation of samarium (III) enolates. Alpha halo ketones react with samarium iodide to give a ketyl radical this is very important ketyl radical is formed that is then quenched by the co solvent. A second reduction then gives carbonion that undergoes beta elimination to produce the enol tautomer of the product ketone. So this is the mechanism here the carbonyl is first actually we can think.

So, carbonyl group is first reduce the samarium iodide to generate the radical anion and then a proton source comes then it becomes OH. And, again another molecular of samarium iodide makes this radical to anion so this is anion is forming. And, then this anion makes the enol after liberation of x minus so x minus is liberated. So, this is the beta elimination and this is enol is formed and this enol is tautomer of course of the carbonyl compound. So, in this mechanism the carbonyl is first reduced and then the elimination of x minus happens and you get the enol and carbonyl compound.

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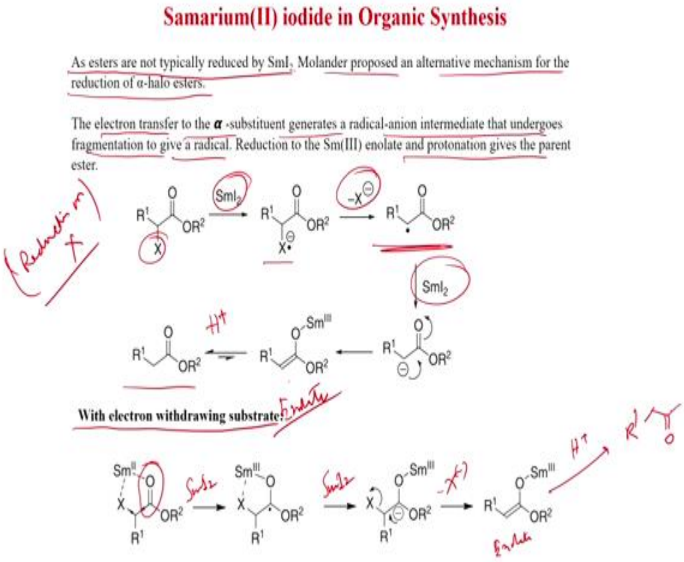

Samarium(II) iodide in Organic Synthesis

As esters are not typically reduced by SmI_2, Molander proposed an alternative mechanism for the reduction of α-halo esters.

The electron transfer to the **α** -substituent generates a radical-anion intermediate that undergoes fragmentation to give a radical. Reduction to the Sm(III) enolate and protonation gives the parent ester.

With electron withdrawing substrate:

There is another possible mechanism because, esters are not typically reduced by samarium iodide that we have seen earlier. Molander proposed an alternative mechanism for the reduction of alpha halo esters. So, the electron transfer to the alpha substituent generates a radical anion intermediate that undergoes fragmentation to give a radical. So, this is the samarium iodide here giving electron to this x. So, x become now x dot minus and after elimination of x minus you get a radical.

This radical again reacts with samarium iodide to generate the anion here and anion will be of course the enolates. So, here the enolate is forming enolate and protonation gives the parent ester. So, after protonation of course H plus x comes, protons source you get the esters reduction on x. So, earlier we have seen reduction carbonyl here reduction on x, x is taking the electron from samarium iodide and becoming x dot minus and after that elimination of x minus you get a radical then anion.

Anion of course will generate the enolate and enolate after proton source you get the ester. Now, if you have electron withdrawing substrate then also this kind of mechanism might operate. Because, x can coordinate with samarium and this ester is getting activated. Once, it is getting activated then the samarium iodide can react to the carbonyl of the ester to generate this radical anion. And, after that again another samarium iodide comes to generate the anion. And after anion you get the elimination of x minus you get the enolate, enolate and this after protons source you get this.

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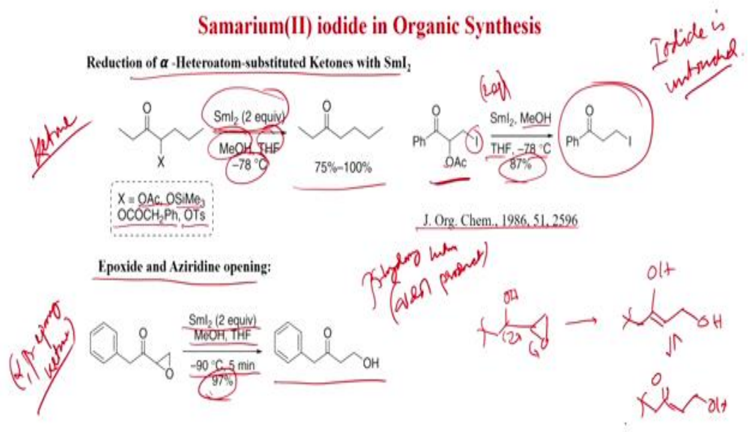

Samarium(II) iodide in Organic Synthesis

Reduction of α -Heteroatom-substituted Ketones with SmI_2

Epoxide and Aziridine opening:

J. Org. Chem., 1986, 51, 2596

Now, we will see some examples of reduction of alpha heteroatoms substituted ketones with samarium iodide. This is a ketone with an alpha substituent so where the substituent can be acetate OSiMe3, OCOCH2Ph, O-tosyl. And only samarium iodide 2 equivalent methanol is the protons source where THF solvent minus 78 degree centigrade you get 75 to 100 percent yield of this ketone where the x is removed. Also, it is interesting in this ketone if you see there is acetate OAc at the alpha and beta there is iodide.

Now, if you add only 2 equivalent of samarium iodide and methanol same condition THF minus 78 degree centigrade, you get this so here the iodide is untouched. That means this removal is very fast process because, here the iodide is not removed. So, generally we know that iodide generates a radical but here the acetoxy removal that is the carbonyl is activated here. So, carbonyl reduction is very fast and after that you eliminate the acetate and you get this product in 87 percent yield. This was published in journal of organic chemistry 1986.

Also, epoxide and aziridine can be open if you have an alpha beta epoxy ketone. So, this is alpha beta epoxy ketone and after samarium iodide equivalent methanol THF minus 90 degree centigrade only 5 minutes you get 97 percent yield of this product. So, this is actually beta hydroxy ketone and this you can generate by aldol reduction so that is why it is called aldol product. Because, in aldol you have the ketone and formaldehyde. So, here also the similar mechanism that negative charge is forming here. OH or O samarium we can think this OH and after that, after that this enol will form. So epoxide will open and it generate this, so you get this product.

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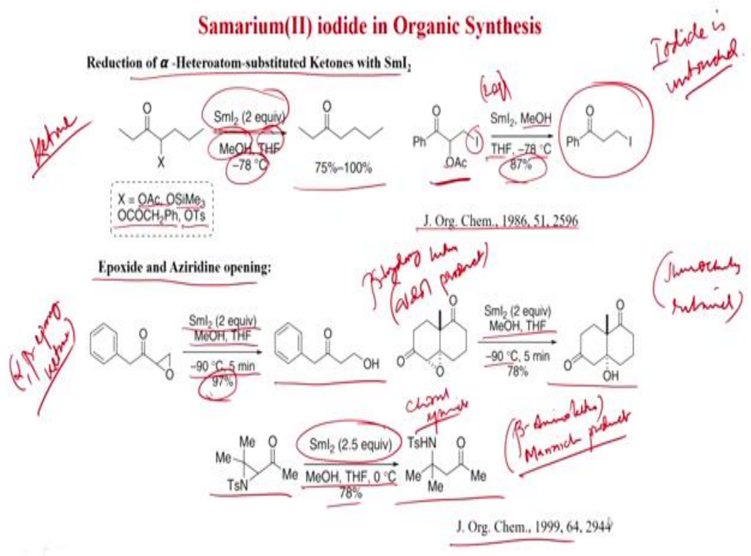

Samarium(II) iodide in Organic Synthesis

Reduction of α-Heteroatom-substituted Ketones with SmI_2

J. Org. Chem., 1986, 51, 2596

Epoxide and Aziridine opening:

J. Org. Chem., 1999, 64, 2944

Similarly, if you have a chiral epoxide so with chiral epoxide also, you can get this product that is the beta hydroxy ketones so this is chiral epoxide. Here also samarium iodide methanol THF condition minus 90 degree centigrade you generate this so this is also chiral so this stereochemistry is retained, stereochemistry retained. So, this is very important that chiral epoxide can open under this condition. Now, this is aziridine so here N- tosyl aziridine is present and with samarium iodide 2.5 equivalent methanol THF 0 degree centigrade you get this beta amino ketone. So, these are actually Mannich product because, by Mannich reaction you can generate this compounds and this work was published in J O C 1999.

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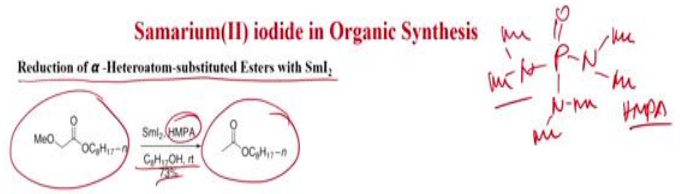

Samarium(II) iodide in Organic Synthesis

Reduction of α-Heteroatom-substituted Esters with SmI_2

Now, we will see reduction of alpha heteroatom substituted esters so far we have seen ketones now we will see esters. And, esters it has been found that if you put HMPA hexamethylene phosphoramide, then the reaction is much faster. So, this is HMPA and you can see there is a methoxy group present and with samarium iodide HMPA this octyl alcohol room temperature you get 73 percent yield of this product. In this ester there is no methoxy group. So, this is very important. Also this one.

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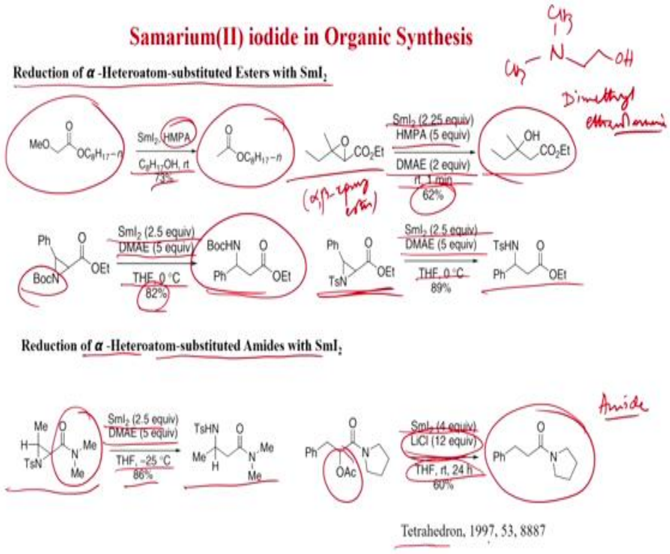

Tetrahedron, 1997, 53, 8887

This one alpha beta epoxy ester, so this alpha beta epoxy ester so like ketones you have seen the esters can also be opened here. Here samarium iodide HMPA and the DMAE is added so DMAE is dimethyl ethanol amine. So, this has two role one role is it is proton source of course and another is at it breaks the samarium ester complex to make free ester. And, this reaction is very fast only 1 minute in room temperature you get beta hydroxy ester by epoxy opening in 62 percent yield.

Also, aziridine here in BOC aziridine is present and samarium iodide here HMPH is not required only DMAE is enough 5 equivalent DMAE and THF 0 degree centigrade you get this beta amino esters in 82 percent yield. Also tosyl aziridine, tosyl aziridine can also be open under similar condition samarium iodide 2.5 equivalent DMAE 5 equivalent THF 0 degree centigrade you get this beta amino tosyl esters. Now we will see reduction of alpha heteroatom substituted amides with samarium iodide.

Here also the tosyl aziridine with an amide motif can be opened, with samarium iodide 2.5 equivalent DMAE 5 equivalent THF minus 25 degree centigrade, you get 86 percent yield of this beta amino tosyl amides. Here, an acetate group is present and when samarium iodide 4 equivalent lithium chloride here is used 12 equivalent. And, under this condition THF room temperature 24 hours you get 60 percent yield of this product. So, this is very important the acetate group here is eliminated and you get the unsubstituted amide in 60 percent yield. This work was published in Tetrahedron 1997.

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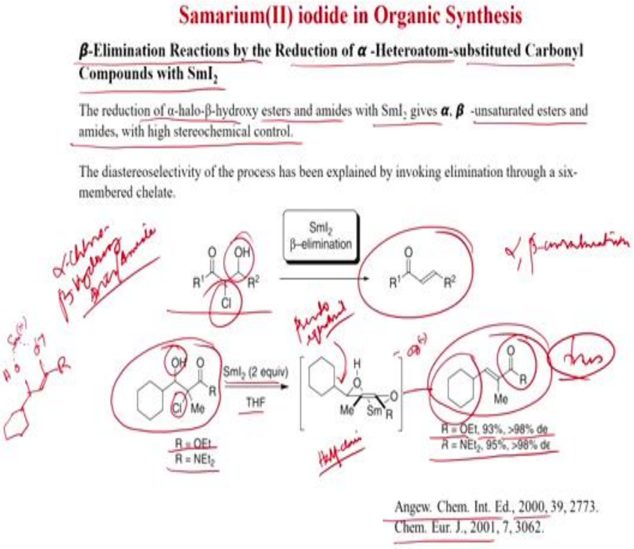

Samarium(II) iodide in Organic Synthesis

β-Elimination Reactions by the Reduction of α-Heteroatom-substituted Carbonyl Compounds with SmI_2

The reduction of α-halo-β-hydroxy esters and amides with SmI_2 gives **α, β** -unsaturated esters and amides, with high stereochemical control.

The diastereoselectivity of the process has been explained by invoking elimination through a six-membered chelate.

Angew. Chem. Int. Ed., 2000, 39, 2773.
Chem. Eur. J., 2001, 7, 3062.

Also, beta elimination reactions by the reduction of alpha hetero substituted carbonyl compounds with samarium iodide is possible. And the reduction of alpha halo beta hydroxy esters and amides with samarium iodide give alpha beta unsaturated esters and amides with high stereochemical control. So, this very important if you have an alpha halo beta hydroxy esters amides then you get alpha beta also the ester or amide. So, here the hydroxy group is eliminated because hydroxy group is activated by samarium (III) and that is why it can be eliminated.

So, like this is alpha chloro beta hydroxy ester or amide under this conditions samarium iodide beta elimination can happen and you can get this alpha beta unsaturation. For example, here you can see this is R is equal to OEt then it is ester R is equal to NEt2. Then it is amide here an alpha chloro beta hydroxy is present and with samarium iodide 2 equivalent THF condition you get this. So, alpha beta unsaturated ester or amide. And when R is equal to OEt then you get 93 percent yield of this product and 98 percent diastereomeric excess.

So, here this cyclohexyl and this ester motive are in the trans. So, this product is trans also with amide you can get similar yield as similar diastereomeric excess greater than 98 percent. So, what is the possibility of this high diastereomeric excess, you can get this half chair form and this chair form actually of this one. This enolate as you can see there is OH is there, there is double bond so this is cyclohexane kind of intermediate is forming. And, this samarium is coordinate with this OH as well as this O minus. And, methyl is here R is here so this is in the pseudoequatorial position. And, then the elimination of OH minus after OH minus elimination you get this, and this is very much serious selective after elimination it gives this trans orientation. This was published in Angew Chem E 2000 also Chemistry European Journal 2001.

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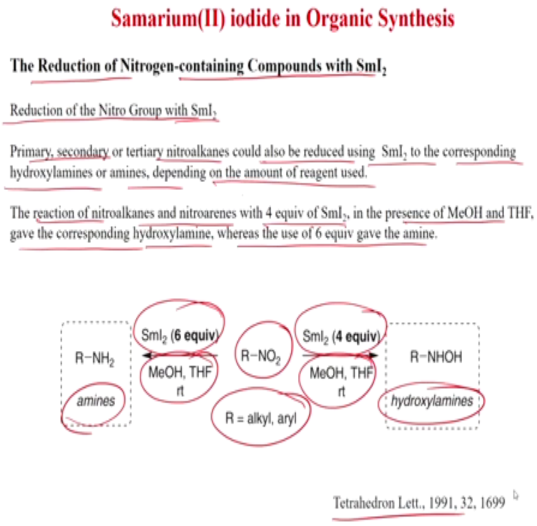

Samarium(II) iodide in Organic Synthesis

The Reduction of Nitrogen-containing Compounds with SmI_2

Reduction of the Nitro Group with SmI_2

Primary, secondary or tertiary nitroalkanes could also be reduced using SmI_2 to the corresponding hydroxylamines or amines, depending on the amount of reagent used.

The reaction of nitroalkanes and nitroarenes with 4 equiv of SmI_2, in the presence of MeOH and THF, gave the corresponding hydroxylamine, whereas the use of 6 equiv gave the amine.

Tetrahedron Lett., 1991, 32, 1699

Now, we will discuss reduction of nitrogen containing compound with samarium iodide. We will discuss reduction of the nitro group with samarium iodide. So, we know primary secondary or tertiary nitroalkanes could also be reduce using samarium iodide to the corresponding hydroxylamines or amines, depending on the amount of reagent used. And, the reaction of nitroalkanes and nitroarenes with 4 equivalent of samarium iodide in the presence of methanol and THF gave the corresponding hydroxylamine, whereas the use of 6 equivalent gave the amine.

So, we know the nitro group is a useful group inorganic chemistry and various reduction methods are well known. And, with Sn/HCl and like here we can see the samarium iodide can also do this reduction. Like R NO2 if is there nitroalkane R is equal to alkyl or aryl and samarium iodide 4 equivalent methanol THF condition you get this hydroxylamine. On the other hand if you put 6 equivalent samarium iodide methanol THF room temperature condition you get the amine. So, that means hydroxylamine is an intermediate for the formation of amines this was published in Tetrahedron Letter in 1991.

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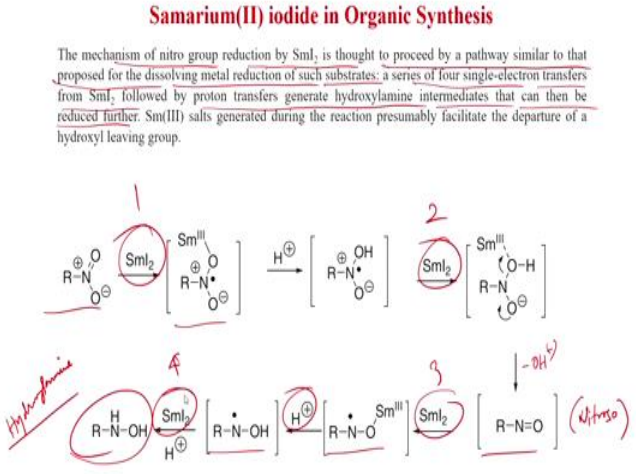

Samarium(II) iodide in Organic Synthesis

The mechanism of nitro group reduction by SmI_2 is thought to proceed by a pathway similar to that proposed for the dissolving metal reduction of such substrates: a series of four single-electron transfers from SmI_2 followed by proton transfers generate hydroxylamine intermediates that can then be reduced further. Sm(III) salts generated during the reaction presumably facilitate the departure of a hydroxyl leaving group.

The mechanism of nitro group reduction by samarium iodide is thought proceed by a pathway, similar to that proposed for the dissolving metal reduction of such substrates. A series of four single electron transfers from samarium iodide followed by proton transfers generate a hydroxylamine intermediates that can then be reduced further. So, this is the mechanism you can see the nitro compound first samarium comes you generate this dot O minus then H plus comes you get this OH here again samarium iodide comes here it becomes O minus.

And, nitrogen positive charge is vanished here now after elimination of hydroxide. So, this is very important the hydroxide elimination is common in samarium iodide reaction because, the hydroxy is activated by samarium 3 and you get this nitroso compound. And, another equivalent samarium iodide here then you get dot O minus and this O minus quenched by H Plus and this dot getting negative again another equivalent samarium iodide after proton source you get this, this is the hydroxylamine. So, with 4 equivalent this is 1 2 3 4 with 4 equivalent you get the hydroxylamine.

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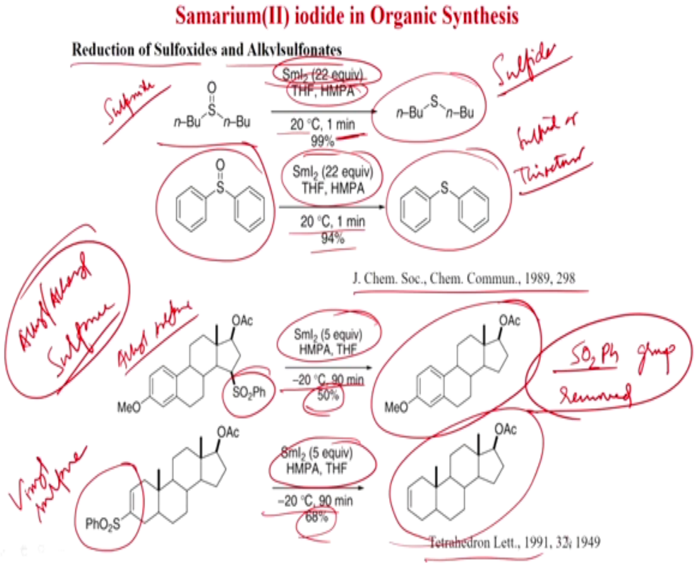

Samarium(II) iodide in Organic Synthesis

Reduction of Sulfoxides and Alkylsulfonates

J. Chem. Soc., Chem. Commun., 1989, 298

Tetrahedron Lett., 1991, 32, 1949

Now, we will see reduction of sulfoxide and alkylsulfonates. So, this is sulfoxide like here this is alkyl sulfoxide 2 nbutyl group is there and is samarium iodide here you need excess 22 equivalent THF HMPA condition 20 degree centigrade temperature just 1 minute you get this sulfide in 99 percent yield. Also, an aromatic groups so this aromatic biphenyl is there sulfoxide with samarium iodide THF HMPA same condition 20 centigrade 1 minute you get 94 percent yield of this compound. This is also sulfide or thioether. This was published in Journal of Chemical Society Chem Commun 1989.

Now, if you have a sulfone so this is called sulfone and generally alkyl alkenyl sulfone alkyl alkenyl sulfone it gets completely eliminated under samarium iodide condition. So, here samarium iodide 5 equivalent HMPA THF minus 20 degree centigrade 90 minutes 50 percent yield of this product. So, what happens most likely radical is formed the radical reacts with samarium to generate to anion and then the proton source come. So, this sulfonyl SO2Ph group completely removed. This is very important we will see later that this radical is formed that can add to olefin. But, here just if you add the proton source then you get this removal. And, here this vinyl sulfone is there so this alkyl sulfone and this is vinyl sulfone. So, in vinyl sulfone also the samarium iodide 5 equivalent HMPA THF minus 20 degree centigrade 90 minutes 68 percent yield of this compound is obtained. This was published in Tetrahedron Letter 1991.

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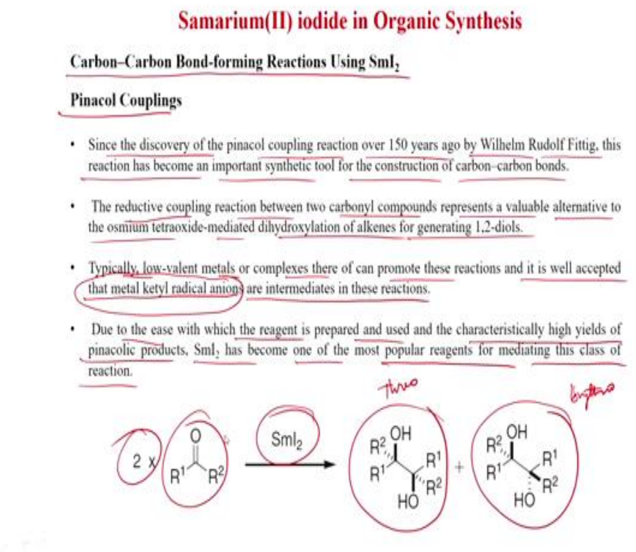

Samarium(II) iodide in Organic Synthesis

Carbon–Carbon Bond-forming Reactions Using SmI_2

Pinacol Couplings

- Since the discovery of the pinacol coupling reaction over 150 years ago by Wilhelm Rudolf Fittig, this reaction has become an important synthetic tool for the construction of carbon–carbon bonds.
- The reductive coupling reaction between two carbonyl compounds represents a valuable alternative to the osmium tetraoxide-mediated dihydroxylation of alkenes for generating 1,2-diols.
- Typically, low-valent metals or complexes there of can promote these reactions and it is well accepted that metal ketyl radical anions are intermediates in these reactions.
- Due to the ease with which the reagent is prepared and used and the characteristically high yields of pinacolic products, SmI_2 has become one of the most popular reagents for mediating this class of reaction.

Now, we will discuss carbon-carbon bond formation reaction using samarium iodide. So, far we have seen different reaction with functional groups. Now, we will see that whether we can combine this strategy with C-C bond formation reaction. So, first we will discussed pinacol couplings since the discovery of the pinacol coupling reaction over 150 years ago by Wilhelm Rudolf Fitting this reaction has become an important synthetic tool for the construction of carbon-carbon bonds.

The reductive coupling reaction between two carbonyl compounds represents a valuable alternative to the osmium tetroxide mediated dihydroxylation of alkenes for generating 1, 2 diols. So, this very important this as an alternative to the osmium tetroxide mediated dihydroxylation. Typically, in low valent metals or complexes thereof can promote this reaction and it is well accepted that metal ketyl radical anions are intermediate in these reactions.

So, like that we have seen that carbonyl group reduction the ketyl radical anion also is forming and that will generate the pinacol product. Due, to the ease with which the reagent is prepared and used and the characteristically high yields of pinacolic products samarium iodide has become one of the most popular agent for mediating this class of reaction. So, here you can see carbonyl compound is present and with 2 equivalent you get either threo so this is threo product, or erythro product two products you can get and we will see the selectivity later and samarium iodide only can do this pinacol coupling.

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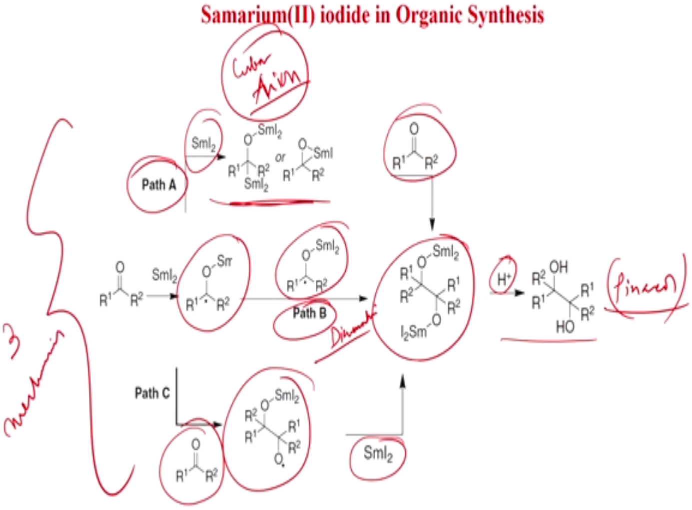
Samarium(II) iodide in Organic Synthesis



So, this is the path b is here you can see this radical anion is generated and in the path b process it reacts with another radical anion so it is actually dimerization. And, then you get this pinacol O samarium compound and after proton source you get the pinacol products. Alternatively, in path A you can see this radical again can be converted to anion that we have seen earlier also it is samarium iodide. And, then you get this anion so this is anion is forming here carbanion is forming. And then it is reacting with carbonyl compound to generate the same intermediate. And, this radical also can it can react with carbonyl compound. Then you can generate this O dot here and this O dot this are very less common and with samarium iodide you get this O dot it becomes O minus after protons source you get this pinacol. So, there are 3 mechanisms possible.

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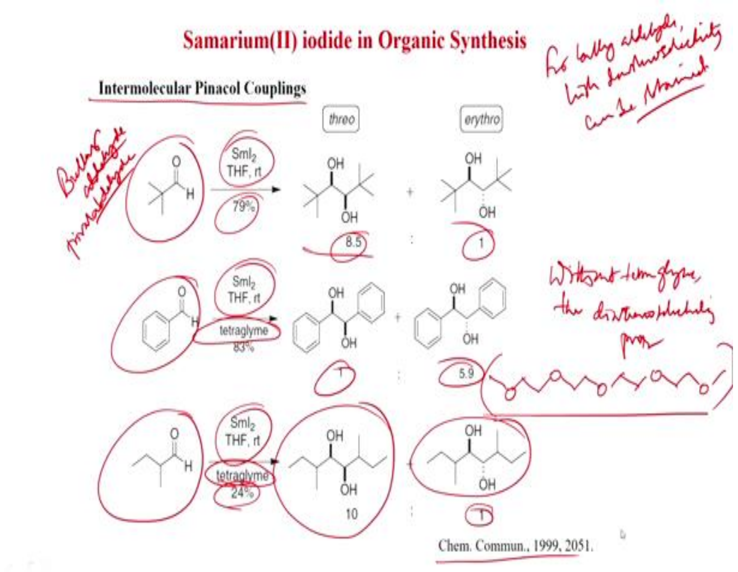
Samarium(II) iodide in Organic Synthesis

Intermolecular Pinacol Couplings

Chem. Commun., 1999, 2051.

Now, we will see intermolecular pinacol couplings. So in the intermolecular coupling cases if it is bulky aldehyde so this is pivalaldehyde so tertiary butyl group is present and with samarium iodide THF room temperature only you get these two products in 8.5 is to 1 ratio. This is the threo product and this is erythro and you get this product in 79 percent yield. So, for bulky aldehydes high diastereoselectivity can be obtained like here 8.5 is to 1. Now, if simple benzaldehyde is there this reaction it has been found that with samarium iodide if you add tetraglyme then the diastereoselectivity can be improved.

So, in this case of course the opposite erythro is forming and measured 5.9 is to one. So, without tetraglyme the diastereoselectivity is poor. And, this is the structure of tetraglyme so there are 5 oxygen atoms are present. This is the structure of tetraglyme this of course coordinate with samarium. Also, this one this is the not so bulky like alpha methyl butyl aldehyde with samarium iodide THF and tetraglyme you get this product threo product in high diastereoselectivity 10 is to 1. So, this erythro is formed here 1 percent minor. However, the yield of this reaction is low 24 percent only. And this was published in Chem Commun 1999.

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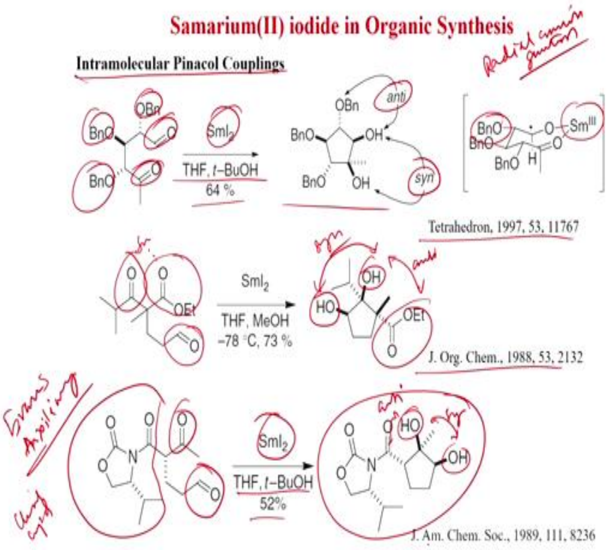

Samarium(II) iodide in Organic Synthesis

Intramolecular Pinacol Couplings

Tetrahedron, 1997, 53, 11767

J. Org. Chem., 1988, 53, 2132

J. Am. Chem. Soc., 1989, 111, 8236

Now, we will see intramolecular pinacol coupling so we have seen the intermolecular pinacol coupling the diastereoselectivity is less. But, in intramolecular cases we can see the diastereoselectivity sometimes is very high. Because, you can take the cyclic transition state. Like here this compound you can see aldehyde is there, ketones is there and three O benzyl groups are there and with samarium iodide THF tat butanol you get this product in 64 percent yield. And this very highly diastereoselectivity you can see this OH are newly generated hydroxy groups are syn and with the bulky group is hydroxy is anti.

And, we can propose a transition state like this pseudo chair that all O benzyl are in the pseudo equatorial position. And this is actually the radical anion so radical anion geometry. This radical anion O minus here at this accordance with the ketones. So, aldehyde will get first reduced to radical anion and that radical anion it will bring 2 oxygen atoms in the same side with samarium (III) will coordinate with both the oxygen atoms here. And, you can get this kind of geometry and that is why this is syn selectivity is observed and this was published in tetrahedron 1997.

Also you can see this O benzyl and this OH are in the anti. Also, if you have an ester groups this ester is interesting that when this carbonyl wants to coordinate with this aldehyde by samarium. Then this you show to it does not coordinate because this interaction is less important here samarium samarium here the important is this and this. Because, here the radical anion will form and that wants to coordinate ketone that is why these two hydroxide groups are the syn and this ester group is actually anti.

Because, this is the more bulky here compare to methyl so this is anti and this two hydroxy groups are in the syn. This was published in J O C 1988. Also you can see this aldehyde and ketone is present also Evans auxiliary is present, this Evans auxiliary oxazolidinone. So, this is a chiral compound samarium iodide condition THF tertiary butanol 52 percent yield of this product. So, here also the chiral product is form in highly diastereoselectivity fashion this two ways are in the seen. And, this hydroxy and this group is anti there in these anti orientation. And this was published in J S 1989.

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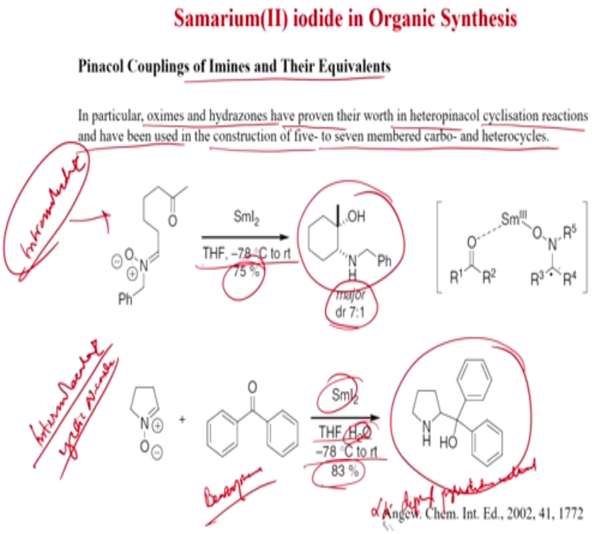

Samarium(II) iodide in Organic Synthesis

Pinacol Couplings of Imines and Their Equivalents

In particular, oximes and hydrazones have proven their worth in heteropinacol cyclisation reactions and have been used in the construction of five- to seven membered carbo- and heterocycles.

Angew. Chem. Int. Ed., 2002, 41, 1772

Now, this pinacol couplings can be extended to imines also and their equivalents. And in particular oximes and hydrazones because we know define imines are available but oximes and hydrazones they are less electron deficient. So, if they are neutral have proven their worth in heteropinacol cyclisation reactions and have been used construction of 5 to 7 membered carbo and heterocycles. So, generally the intramolecular is favorable so intramolecular with high diastereoselectivity can be obtained.

So, this is intramolecular and this carbonyl and imines you can say here and this is obtained also in high diastereoselectivity major diastereomer 7 is 1. And, samarium iodide THF minus 78 degree centigrade to room temperature you will get 75 percent yield of this product. And, also you see this NH-OH is bond here that also cleaved so this bond is cleaved so you get the imine here. First then the nitrous is getting reduced with the samarium iodide and this then coordinates with the carbonyl compound like earlier we have seen the radical anion coordinate with the carbonyl and that is why this syn selectivity is observed.

Also, intermolecular also it is possible this is a cyclic N oxide and reacts with benzophenone. And, this compound is very important alpha-alpha diphenyl pyrrolidine methanol. And, this compound is obtained with samarium iodide THF water, here water is added minus 78 degree centigrade to room temperature you get 83 percent yield. So, water enhanced the reactivity of samarium iodide. And, here also the similar mechanism is operating that here the reduction is happening first. And then this radical can reacts here and then second samarium iodide will convert the radical to the carbanion and you get after protons source you get this. This are published in Angew Chem international edition 2002, page number is 1772.

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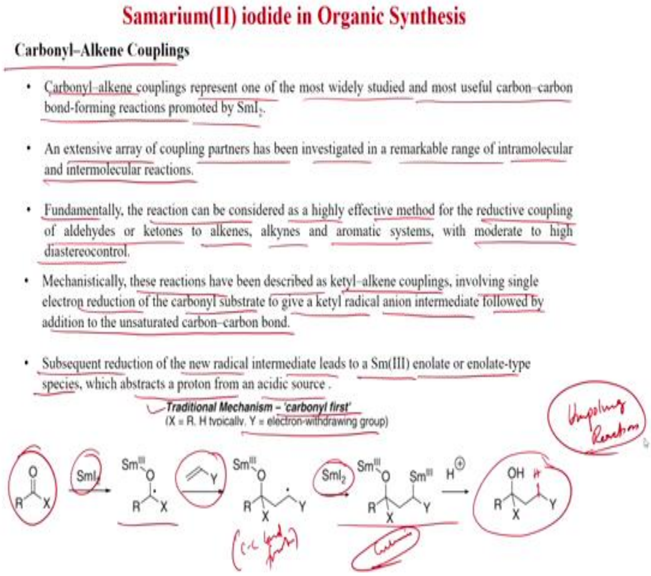

Samarium(II) iodide in Organic Synthesis

Carbonyl–Alkene Couplings

- Carbonyl–alkene couplings represent one of the most widely studied and most useful carbon–carbon bond-forming reactions promoted by SmI_2.
- An extensive array of coupling partners has been investigated in a remarkable range of intramolecular and intermolecular reactions.
- Fundamentally, the reaction can be considered as a highly effective method for the reductive coupling of aldehydes or ketones to alkenes, alkynes and aromatic systems, with moderate to high diastereocontrol.
- Mechanistically, these reactions have been described as ketyl–alkene couplings, involving single electron reduction of the carbonyl substrate to give a ketyl radical anion intermediate followed by addition to the unsaturated carbon–carbon bond.
- Subsequent reduction of the new radical intermediate leads to a Sm(III) enolate or enolate-type species, which abstracts a proton from an acidic source .

Traditional Mechanism – 'carbonyl first'
(X = R, H typically, Y = electron-withdrawing group)

Now, we will discuss another important reaction carbonyl alkene couplings this is also very important reaction. So, carbonyl group reduction we have seen then the carbonyl dimerization we have seen and now we will discuss that carbonyl whether it can be reacted with electron deficient olefins and whether C-C born formation is possible. So, carbonyl alkene couplings represent one of the most widely studied and most useful carbon-carbon bond forming reactions promoted by samarium iodide.

And, extensive array of coupling partner has been investigated in a remarkable range of intramolecular and intermolecular reactions. Fundamentally the reaction can be considered as a highly efficient method for the reductive coupling of aldehyde ketones to alkenes alkynes and aromatic systems with moderate to high diastereocontrol. Mechanistically, these reactions have been described as ketyl alkene couplings, involving single electron reduction of the carbonyl substrate to give a ketyl radical anion intermediate followed by addition to the unsaturated carbon-carbon bond.

Subsequent reduction of the new radical intermediate leads to a samarium (III) enolate or enolate type species, which abstract a proton from an acidic source. Here two kinds of mechanism is possible that in one case we can think that carbonyl group is first reduced and another case it is possible that the electron deficient olefin is reduced. So, in the tradition mechanism the carbonyl is first so carbonyl first means this is the carbonyl compound with samarium iodide it generates the radical anion.

And then this radical anion reacts to the electron deficient olefin because y is electron withdrawing group. And, then this C-C bond is forming so this is C-C bond formation. And, now this radical also if it is stable by electron withdrawing group can react with another equivalent of samarium iodide to generate the anion. So, here cabanion is forming and after proton source you get this OH become and here also H. And this can be considered that umpolung reaction. Because, the carbonyl group we have this anion is generating or radical is generating and that is adding to the electron deficient olefins.

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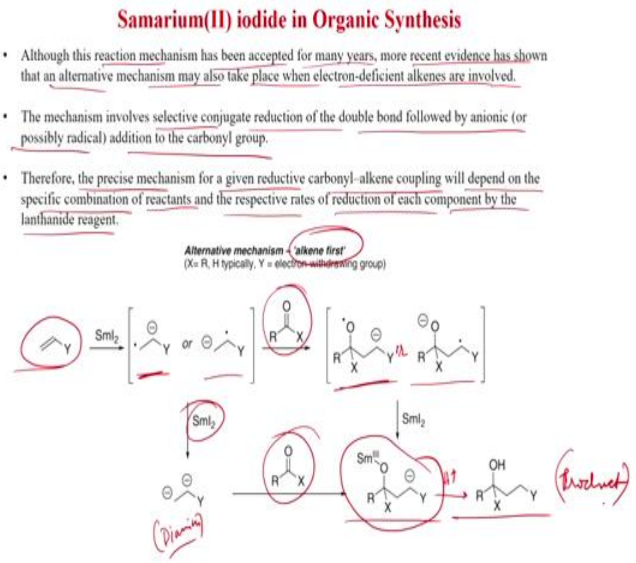

Samarium(II) iodide in Organic Synthesis

- Although this reaction mechanism has been accepted for many years, more recent evidence has shown that an alternative mechanism may also take place when electron-deficient alkenes are involved.
- The mechanism involves selective conjugate reduction of the double bond followed by anionic (or possibly radical) addition to the carbonyl group.
- Therefore, the precise mechanism for a given reductive carbonyl–alkene coupling will depend on the specific combination of reactants and the respective rates of reduction of each component by the lanthanide reagent.

Alternative mechanism – 'alkene first'
(X= R, H typically, Y = electron-withdrawing group)

Although this reaction mechanism has been accepted for many years, more recent evidence has shown that an alternative mechanism may also take place when electron deficient alkenes are involved. So, here this is the other way, have the olefin is first. The mechanism involves selective conjugate reduction of the double bond followed by anionic or possibly radical addition to the carbonyl group. Therefore, the precise mechanism for a given reductive carbonyl alkene coupling will depend on the specific combination of reactants and the respective rates of reduction of each component by the lanthanide reagent.

So, here the alkene first is happening same substrates electron deficient olefin samarium iodide the reduction is happening. And, you get this radical anion this can stay or like this or this and this can react with carbonyl compound to generate this. So, if the radical reacts then you generate this or the anion reacts then the radical stays is here so this two can form. And with samarium iodide again you get this O dot or C dot becomes anions so here this carbanion is generated along with O anion. Alternatively, this radical anion can react with samarium to generate this dianion which is less likely though. Dianion, can react with carbonyl compound to generate this. And this on proton source generates this neutral compound which is the product.

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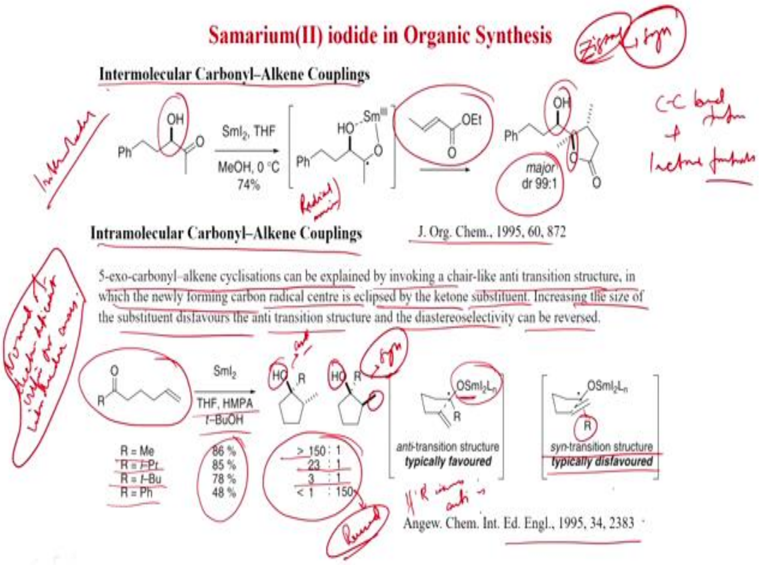

Samarium(II) iodide in Organic Synthesis

Intermolecular Carbonyl–Alkene Couplings

J. Org. Chem., 1995, 60, 872

Intramolecular Carbonyl–Alkene Couplings

5-exo-carbonyl–alkene cyclisations can be explained by invoking a chair-like anti transition structure, in which the newly forming carbon radical centre is eclipsed by the ketone substituent. Increasing the size of the substituent disfavours the anti transition structure and the diastereoselectivity can be reversed.

R = Me	86 %	> 150 : 1
R = i-Pr	85 %	23 : 1
R = t-Bu	78 %	3 : 1
R = Ph	48 %	< 1 : 150

Angew. Chem. Int. Ed. Engl., 1995, 34, 2383

And, we will discuss now this reaction intermolecular carbonyl alkene couplings examples. So, here it has been seen that if a hydroxy group is present hydroxy all are minds is samarium. And, whether this reaction can be done in highly diastereoselective fashion or not. So, here this radical anion is forming radical anion. And, if its minds is samarium then this also will be same side of hydroxy. That is what you have seen this hydroxy this hydroxy there are in the zigzag. And in the zigzag they are in the syn orientation.

And, when treated with alpha beta unsaturated ester. Then C-C bond formation along with lactone formation C-C bond formation plus lactone formation is happening. This OH reacting to ester to generate a lactone and this product is formed in highly diastereomeric ratio dr is equal to 99 is to 1. So, this two OH group this OH and this is the lactone CO bond they are in the syn orientation. And, this two methyl’s are also syn here and this lactone is formed in high dr. This was published in J O C 1995.

So, this is intermolecular now intramolecular cases also that we have already scene intramolecular pinacol coupling. Similarly, intramolecular carbonyl alkene coupling can be also diastereoselective. Like here if you have this ketone here a double bond is present also this double bond is here in this case you do not need the electron deficient. So, no need of electron deficient olefin in intramolecular cases. Because, intramolecular are always first so do not need an electron deficient here simple olefin is enough to do this cyclisation.

And, you can see this is ketone R is equal to methyl R is equal to isopropyl R is equal to tertiary butyl, R is equal to phenyl to get moderate to good use with this condition samarium iodide THF HMPA transfer butanol. But, when you change the substituent you get different diastereoselectivity. So, this is OH and methyl this are anti and here OH and methyl they are syn. So, in general the anti is more when R is equal to methyl then get greater than 150 is to 1 R is equal to isopropyl 23 is to 1, R is equal to tertiary butyl you get 3 is to 1 so it is getting reduced when it is the bulky increases.

And, R is equal to Ph you get comparably reverse so in this case reversed. So, here 150 percent of syn is form and 1 percent only trans is obtained. So, what could be the mechanism? So, this kind of transition structure might operate that a 5 exo carbonyl alkene cyclisation can be explained by invoking a chair like anti transitions state structure in which the newly forming carbon radical center is eclipsed by the ketone substituent. So, here this O samarium take this anti with this double bond.

Increasing the size of the substituent disfavors the anti-transition structure and the diastereoselectivity can be reversed. So, in this anti transition state you can see this is big of course compare to R so that is why we are calling anti. However, if R increases then anti is less stable. Then this interaction also because R is with this double bond. And syn case of course the syn transition state typically disfavored. Because, this is in the same side with O samarium so this will feel the steric interaction. And this favor R is big so when R is big then this syn transition state is major. Because, that case the double bond wants to stay anti to the R group. And, this case when R is equal to small then double bond wants to stay anti with the O samarium and this work was published in Angew Chem international edition 1995, page number is 2383.

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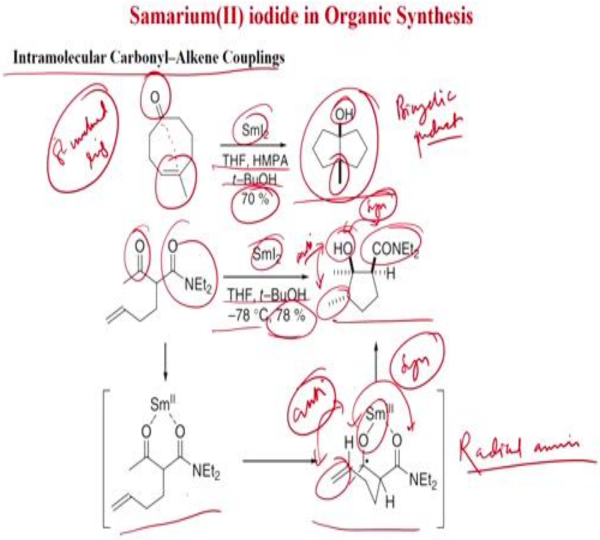
Samarium(II) iodide in Organic Synthesis

Intramolecular Carbonyl–Alkene Couplings

Some more examples of intramolecular carbonyl alkene couplings so we have already told that this carbonyl alkene coupling intramolecular cases you do not need the activated olefin. That is why this scope can be broad and you can see here this is a 8 member ring and carbonyl is there the olefin is there samarium iodide THF HMPA tat butanol you get this bicyclic compound product in 70 percent yield. And this is the reaction is happening so here this reacts here 1 2 3 4 5 at this case also 5,5.

So, 5,5 bycyclic product is formed in 70 percent yield and highly diastereoselectivity OH and methyl are in the syn here this kind of substrate we have seen. That the carbonyl and amide is present. So, earlier we have seen that when there is an earlier it then the samarium iodide wants to coordinate with this. Because, this radical anion will form from the aldehyde and that will continue the ketones. So, that cases we have seen the syn observation and this was anti with the new generated hydroxy component.

Now, in this case the olefin cases we will see that they want to coordinate. So, this two are syn here so this is very interesting because samarium does not bind with double bond but, instead coordinates with this two oxygen and they are in the syn. And, this newly generated center methyl that we have already seen this wants to stay anti. So, this is anti with samarium iodide THF tertiary butanol minus 78 degree centigrade you get 78 percent yield of this product and we can think mechanism like this.

So, samarium (II) first coordinates with both ketone and amide and then this kind of radical anion transitions state takes. So, this is the radical anion you can see the carbonyl already reduced here dot O minus samarium and it takes syn orientation with this as amide so there syn. Because, they want to coordinate with samarium (III). And, olefin takes this kind of geometry so this olefin and O samarium because here methyl group is there only O samarium wants to stay anti. And, after cyclisation you get this geometry. So, this is very important in pinacol coupling we have seen that aldehyde and ketone are in the same side but here if the aldehyde is replaced with olefin then the ketone and amide are in the same side and the newly generated methyl will be anti.

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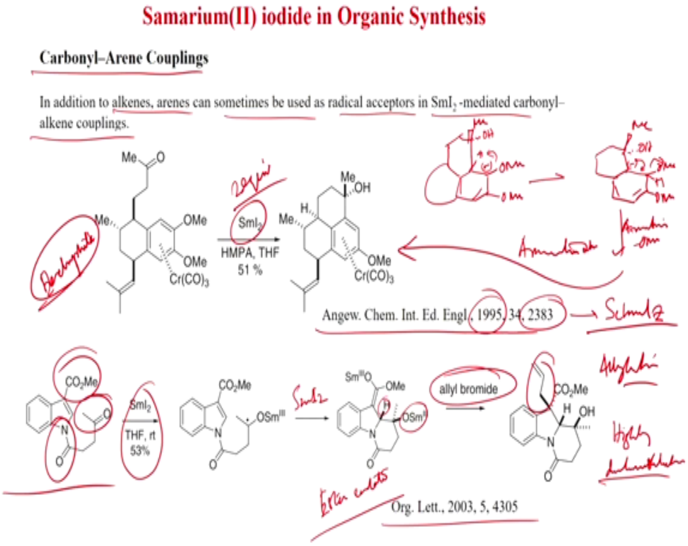

Samarium(II) iodide in Organic Synthesis

Carbonyl–Arene Couplings

In addition to alkenes, arenes can sometimes be used as radical acceptors in SmI_2-mediated carbonyl–alkene couplings.

Angew. Chem. Int. Ed. Engl., 1995, 34, 2383 → Schmalz

Org. Lett., 2003, 5, 4305

Now, we will discuss carbonyl-arene coupling in addition to alkenes arenes can sometimes be used as radical acceptors in samarium iodide mediated carbonyl alkene couplings. We have already discussed when we discuss chromium. That this chromium tricarbonyl arene complex is electrophilic. So, electrophilic in nature and this dot O minus that dot can react here and after samarium iodide again so this is 2 equivalent you generated anion here.

So, most likely this will form methyl OH and this is the O methyl and now after cyclisation first a radical of course and then a negative charge will form C minus here and this C minus because this is unstable this can take the H plus there and you can get anion there. So, hydrogen come here anion goes there and this anion and then the aromatization this will happen. Aromatization minus OMe group or OMe group will eliminate and you get this product.

Where you can see one methoxy group is eliminated because of this aromatization. So, aromatization this was published in Angew Chem E International Edition 1995, 2383 this is from Schmalz group form Germany. Also this kind of indole system where you can see esters motive is there amide is there ketone is there. And now if samarium iodide is added to this substrate in THF room temperature you get first the reduction of the ketone of course then the radical anion forms.

And, then the diaaromatization will happen because this radical will add to here and another equivalent of samarium i2 will generate this enolate. So, this is ester enolate is formed you can see this also in highly diastereoselective this O samarium and this hydrogen in the same side. And now, this enolate if you treat with allyl bromide where allylation will happen so this is allylation. So, this enolate can be treatment with allyl bromide again this product is high diastereoselective. And, this work was published in Organic Letters 2003 page number is 4305.

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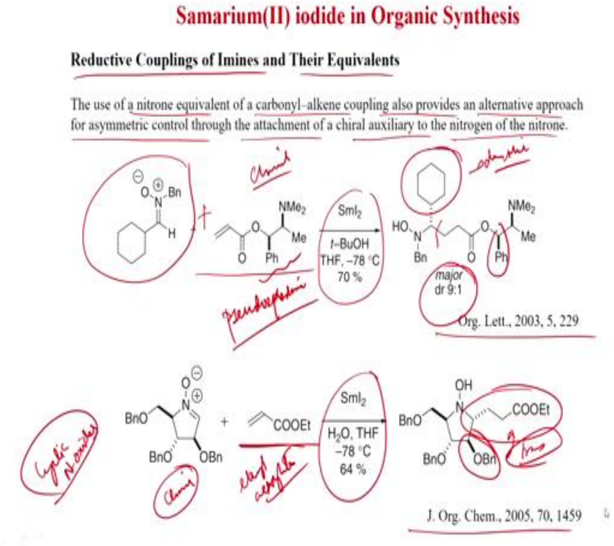

Samarium(II) iodide in Organic Synthesis

Reductive Couplings of Imines and Their Equivalents

The use of a nitrone equivalent of a carbonyl–alkene coupling also provides an alternative approach for asymmetric control through the attachment of a chiral auxiliary to the nitrogen of the nitrone.

Org. Lett., 2003, 5, 229

J. Org. Chem., 2005, 70, 1459

And lastly you will see reductive couplings of imines and their equivalents. The use of a nitrone equivalent to a carbonyl alkene coupling also provides an alternative approach for asymmetric control through the attachment of a chiral auxiliary to the nitrogen of the nitrone. So, here you can see this is the nitrile oxide. And, when treatment with this this is chiral of course and this is pseudo ephedrine it is present here. And, now this C-C bond will form so this the newly generate C-C bond and this newly generated C-C bond is formed in highly diastereoselective fashion.

So, that the cyclohexyl group is in the down side so this is down side. And, the diastereomeric excess is 9 is to 1 under this conditions samarium iodide tertiary butanol THF minus 78 centigrade you get 70 percent yield of this product. And this was also published in organic letters 2003, page number 229. And, this is cyclic N oxide this already we have seen similar but here this is chiral so this is chiral. So, here the chiral olefin is chiral here the n oxides is chiral. And, when in ethyl acrylate thus treated with samarium iodide water THF minus 78 degree centigrade this newly generated C-C bond is found in the diastereoselective fashion and this is down so this is up so this two are trans so this is very important here this two are trans here this and phenyl are in the trans and this are published in J O C 2005.

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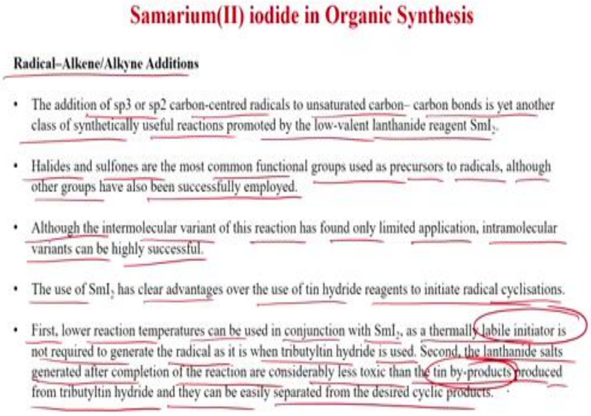

Samarium(II) iodide in Organic Synthesis

Radical–Alkene/Alkyne Additions

- The addition of sp3 or sp2 carbon-centred radicals to unsaturated carbon– carbon bonds is yet another class of synthetically useful reactions promoted by the low-valent lanthanide reagent SmI_2.
- Halides and sulfones are the most common functional groups used as precursors to radicals, although other groups have also been successfully employed.
- Although the intermolecular variant of this reaction has found only limited application, intramolecular variants can be highly successful.
- The use of SmI_2 has clear advantages over the use of tin hydride reagents to initiate radical cyclisations.
- First, lower reaction temperatures can be used in conjunction with SmI_2, as a thermally labile initiator is not required to generate the radical as it is when tributyltin hydride is used. Second, the lanthanide salts generated after completion of the reaction are considerably less toxic than the tin by-products produced from tributyltin hydride and they can be easily separated from the desired cyclic products.

Radical alkene alkyne additions, the addition of sp3 sp2 carbon centered radicals to unsaturated carbon-carbon bonds is yet another class of synthetically useful reactions promoted by the low valent lanthanide reagent samarium iodide. So, so far we have discussed the carbonyl alkene reaction now we will see the radical is adding to the olefin that is also possible. Halides and sulfones are the most common functional groups used as precursors to radicals although other groups have also been successfully employed.

Although the intermolecular variant of this reaction has found only limited application intramolecular variants can be highly successful. The use of samarium iodide has clear advantage over the use of tin hydride reagents to initiate radical cyclisations. First lower reaction temperatures can used in conjunction with samarium iodide, as a thermally labile initiator is not required to generate the radical as it is when tributyltin hydride is used. Here the initiator is not required, second the lanthanide salts generated after completion of the reaction are considerably less toxic than tin byproducts produced from tributyltin hydride and they can be easily separated from the desired cyclic products.

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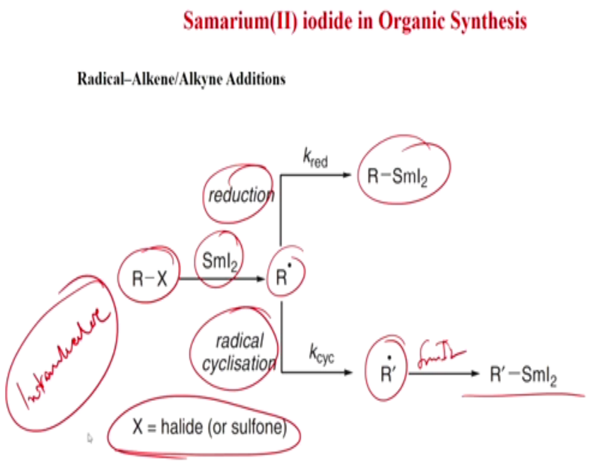

Samarium(II) iodide in Organic Synthesis

Radical–Alkene/Alkyne Additions

So, this is the reaction that we know that if you halide is there then samarium iodide generate this radical. And this radical of course with reduction it can generate this R samarium I2 alternatively if there is a double bond is present then the radical cyclisation will happen that will generate a new radical. And, after quenched this samarium iodide will generate this anion and anion after protons source will generate the neutral compound. And, x can be halide or sulfone. And, this is mainly for intramolecular cases because, then this radical immediately reacts.

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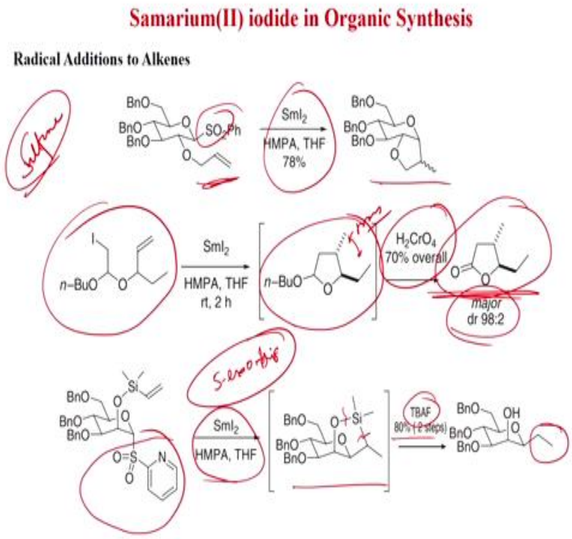

Samarium(II) iodide in Organic Synthesis

Radical Additions to Alkenes

And, we will see some examples now so this is sulfone. So, as if you have seen the intramolecular cases so here, mostly you can see that intramolecular because the radical will immediately react it olefin. And, this olefin is not electron deficient so simple olefins also can be used for intramolecular cases. So, sulfone here is generate the radical and that radical reacts here so you get this product with samarium iodide HMPA. And, this kind of substrate is present then this iodide the radical will form the radical add to this olefin and you get this product.

So, here you can see they are trans so newly generate like chiral center is trans to the and after chromic acid treatment you can get this lactone butyrolactone in 98 is to 2 ratio. Also, if you have sulfonyl in like pyridine sulfonyl group and this can kind of olefin is present then also similar cyclisation will happen so 1 2 3 4 5 so 5 exo trig, 5 exo trig cyclisation is happening you get this samarium iodide HMPA THF. And, if you treat with TBAF then this two bonds are cleaved, O silicon, carbon silicon bond is cleaved. And, you get the free hydroxy group and this the ethyl group. This product is obtained in 80 percent yield after two steps.

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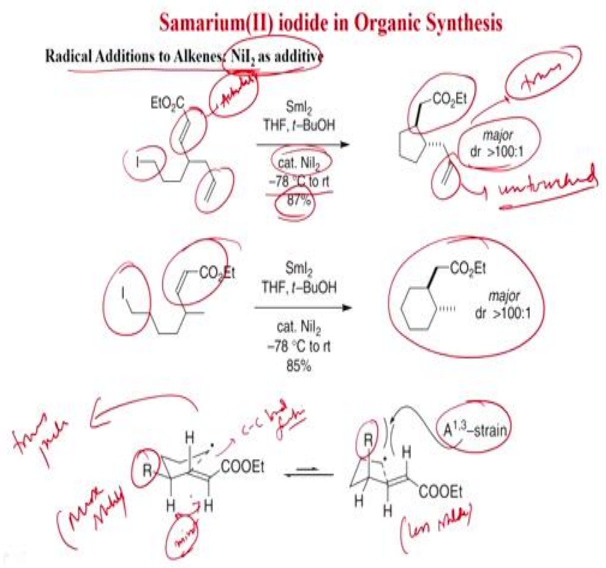

Samarium(II) iodide in Organic Synthesis

Radical Additions to Alkenes: NiI_2 as additive

And, in cases that if you had nickel iodide as additive then the reaction is very fast this has been found that if you this radical alkene coupling if you add nickel iodide catalytic amount then the reaction efficient is very high. Of course two kind of olefin is present of course this is activated olefin so, this is activated. And, in this case the radical that is forming in adding to the activated olefin and this olefin is untouched, this is untouched. However, the diastereoselectivity also here is very high this is trans again trans and you get this diastereomer greater than 100 is 1 is to 1.

This case also you get this trans product in grater then 100 is to 1 and this is the transitions state so the radical will add to this so this is the C-C bond formation is happening here C-C bond formation. And, in this case there is no A 1, 3 strain though it is here but, this is minor because hydrogen-hydrogen is minor. But, in this case if it is R is up so R and newly generated bond is in the same side then you can get this R hydrogen. And there you can get this allylic 1,3 strain that is why this one is less stable so this is more stable. And this will give you trans product because R and this are in the opposite side.

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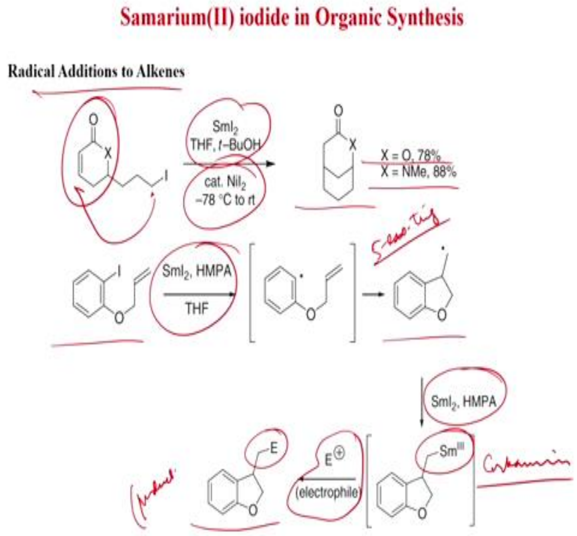

Samarium(II) iodide in Organic Synthesis

Radical Additions to Alkenes

Some more examples radical additions to alkenes like here cyclohexane one system x is equal to oxygen x is equal to NMe. So, lactone are lactam then samarium iodide THF tat butanol catalytic nickel iodide you get this bicyclic compounds so this radical is adding here. Also if you have a these kind of substrate and here also this is the aromatic iodide and with samarium iodide you get the aryl radical and this radical immediately react in high exo trig fashion. So this is not activated and in this case you get this and with samarium iodide THF HMPA you get the carbanion so this is carbanion. The electrophile can react with this carbanion and you get this kind of product.

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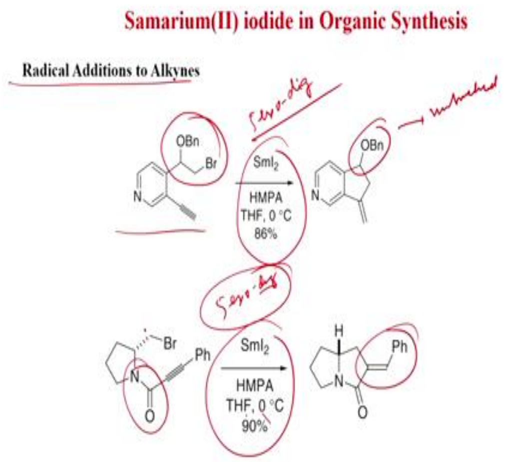

Samarium(II) iodide in Organic Synthesis

Radical Additions to Alkynes

And, lastly we will discuss radical additions to alkynes so like this alkynes this is the OBn CH2Br is there and OBn is untouched. And, in this case 5 exo dig reaction is happening. So, here radical is adding to the alkyne with samarium iodide HMPA THF condition you get 86 percent yield. And, this case also 5 exo dig is happening so dot will generate 1 2 3 4 5 so add and then you get this exo cyclic olefin. Because this is amide here and exo dig is very favorable under this condition you get this product in 90 percent yield.

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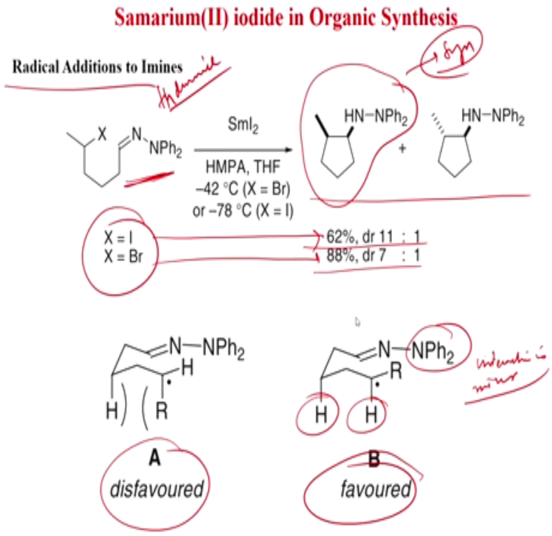

Samarium(II) iodide in Organic Synthesis

Radical Additions to Imines

Now we will discuss radical addition to imines this is also possible like here if you have a iodide bromide and if you have a hydrazine so this is hydrazine. Then this kind of products can be obtained and in this case they are syn so the syn products are form major that we will discuss while. And, you can see dr can be 7 is 1 when x is equal to Br x is equal to iodide you get high dr. So, this is the mechanism the transitions state here if you put HR then you get a interaction and this is disfavored. On the other hand if you put R here so there might be some interaction with nitrogen but this group is far so this interaction is minimum or interaction is minor here this interaction. That is why this hydrogen-hydrogen interaction is also minimum so that is why this favored. And, that means this nitrogen and this R will be in the same for the imine cases.

So, today we have discussed samarium iodide mediator reaction first you have discuss the alpha bromo ketones amide as well as the ester reactions. And in this we have seen that the alpha substance can be removed and then you have seen if it is alpha chloro beta hydroxy esters amides are there then the alpha beta unsaturated esters or amides can be produced. And then we have seen the nitro group reduction. We have seen that the nitro group go to the four equivalent can go to the hydroxyl amine and which 6 equivalent it can go to the amine. And, then we have discussed different C-C bond formation reactions we have seen the pinacol coupling cases we have seen the carbonyl group can react with another carbonyl compound.

And in this case you can get high diastereoselectivity for the bulky aldehyde like triple aldehyde and other case you have to add some additive then this additive can increase the like tetraglyme this additive can give the high diastereoselectivity. Then we have seen the carbonyl alkyne coupling and this carbonyl alkyne coupling we have seen that the both operation is possible that the carbonyl first as well as the alkyne first. And we have seen this carbonyl alkyne coupling the reaction can occur in high diastereoselective fashion.

And depending on the substituent R generally the anti products is forming but if R is equal to phenyl we have seen the syn product is major. So, highly diastereoselectivity way you can get this product. And then we have seen the lastly radical alkene and this is mainly the intramolecular cases also in this cases intramolecular cases the olefin can be normal that is no electron with the group is required. And, in this case also we have seen the highly diastereoselectivity where you can get this product.

Generally, you get the trans product because, the allylic strain in the transition state will be minimum. And, for the imine alkene cases we have seen that the syn product is major because, here also the interaction will be minimum when it takes the syn orientation we have seen. And in the pinacol coupling cases we have seen that the intramolecular cases also you can get high diastereoselectivity, thank you.