

Asymmetric hydrogenation

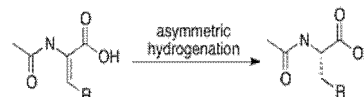
- Asymmetric hydrogenation is a chemical reaction that adds two atoms of hydrogen preferentially to one of two faces of an unsaturated substrate molecule, such as an alkene or ketone.
- The selectivity derives from the manner that the substrate binds to the chiral catalysts.

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Asymmetric Hydrogenation

- This binding transmits spatial information from the catalyst to the target, favoring the product as a single enantiomer.
 - What chemists refer to as chirality**
- This enzyme-like selectivity is particularly applied to bioactive products such as pharmaceutical agents and agrochemicals.



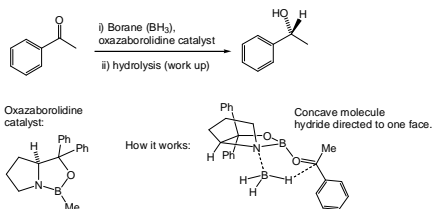
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Asymmetric Hydrogenation

Ketone Reduction

- The reduction of a ketone to a secondary alcohol is a perfect reaction for asymmetric catalysis:

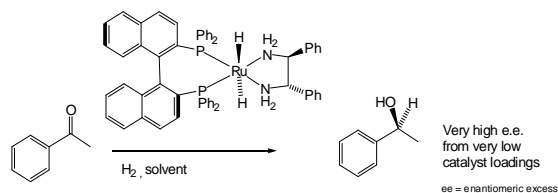


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Asymmetric Hydrogenation

Ketone reduction by pressure hydrogenation (ie Hydrogen Gas)

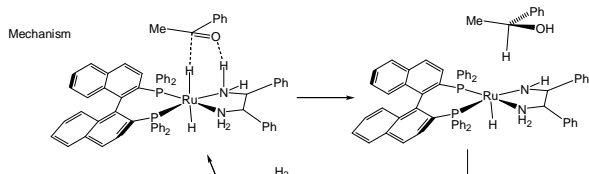


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Asymmetric Hydrogenation

Ketone reduction by pressure hydrogenation (ie Hydrogen Gas)



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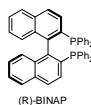
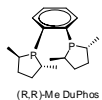
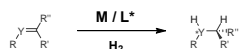
Asymmetric Hydrogenation

- Rh-diphosphine complexes control asymmetric induction by controlling the face of the alkene which attaches to the Rh.
- Hydrogen is transferred, in a stepwise manner, from the metal to the alkene.
- The intermediate complexes are diastereoisomers of different energy.

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Asymmetric Hydrogenation



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Noyori Asymmetric Hydrogenation

- The **Noyori Asymmetric Hydrogenation** of ketones is a chemical reaction for the enantioselective hydrogenation of ketone, aldehydes, and imines.
- This reaction exploits using chiral ruthenium catalysts introduced by Ryoji Noyori.
- He shared half of the Nobel Prize in Chemistry in 2001 with William S. Knowles for the study of the asymmetric hydrogenation.

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Nobel Prize in Chemistry in 2001



William S. Knowles
1/4 of the prize
USA
St. Louis, MO, USA
b. 1917



Ryoji Noyori
1/4 of the prize
Japan
Nagoya University
Nagoya, Japan
b. 1938



K. Barry Sharpless
1/2 of the prize
USA
The Scripps
Research Institute
La Jolla, CA, USA
b. 1941

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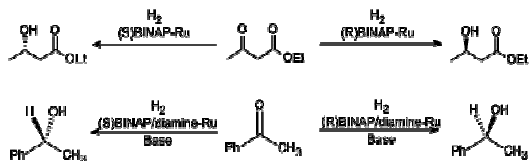
Noyori asymmetric hydrogenation

- BINAP-Ru catalyst is used for the asymmetric hydrogenation of functionalized ketones
 - 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
- BINAP/diamine-Ru catalyst is used for the asymmetric hydrogenation of simple ketones.

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Noyori asymmetric hydrogenation

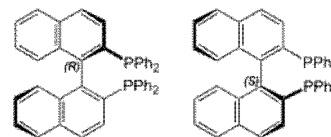


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BINAP

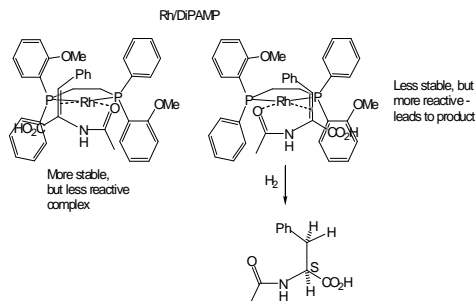
- BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) is an organophosphorus compound.
- This chiral ligand is widely used in asymmetric synthesis.



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Asymmetric Hydrogenation



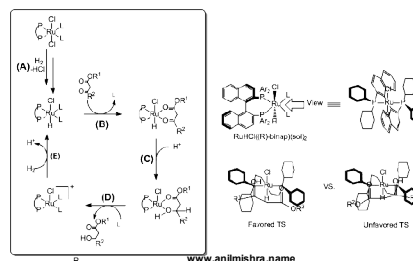
Using Rh(DIPAMP) complexes, asymmetric reductions may be achieved in very high enantioselectivity.

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BINAP-Ru Mechanism

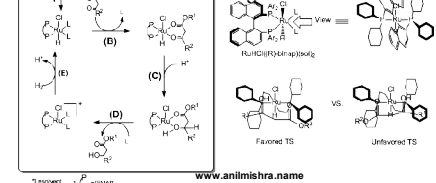
- The BINAP-Ru dihalide precatalyst gets hydride from H₂ and forms Ru-monohydride Reaction intermediate while giving off HCl (A).



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BINAP-Ru Mechanism

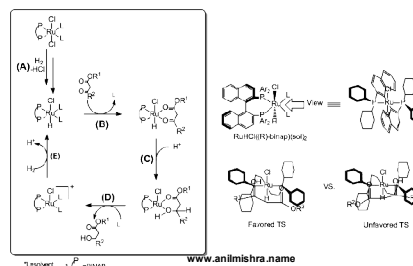
- The ruthenium center of the catalyst coordinates to the oxygen atoms in the ester compound. Because of the chirality of the BINAP ligand, one of the two possible diastereomeric transition states is favored (B).
- The transition state on the left is favored over the other because of the large R₁/ Ph steric hindrance.



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BINAP-Ru Mechanism

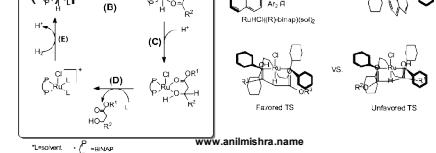
- Ester gets proton, and hydride transfers from the catalyst to the carbonyl carbon (C).



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BINAP-Ru Mechanism

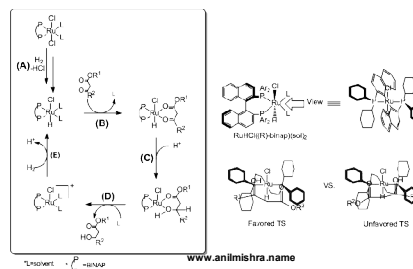
- Hydrogenated ester compound leaves the catalyst and solvent coordinate back to the catalyst (D).
- The (R)-BINAP-Ru catalyze the synthesis the (S)-Product
- The (S)-BINAP Ru catalyze the synthesis the (R)-product



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BINAP-Ru Mechanism

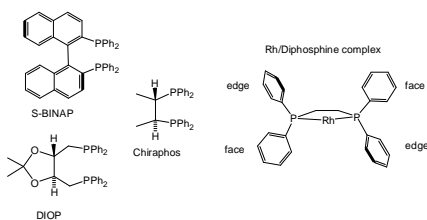
- Again, the dehydrated BINAP-Ru catalyst is utilized by the addition of another hydride from H₂. The newly activated Ru-monohydride re-participates in the catalytic cycle (E).



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Asymmetric Hydrogenation

- Other chiral diphosphines are not chiral at P, but contain a chiral backbone which ~~relays~~ relays chirality to *conformation* of the arene rings.

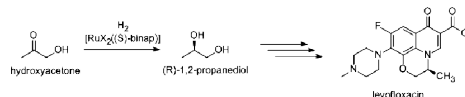


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Applications

- An antibacterial levofloxacin is synthesized using (R)-1,2-propanediol, which is synthesized from hydroxyacetone using Noyori asymmetric hydrogenation

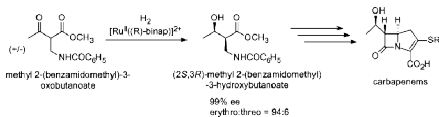


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Applications

- An antibiotic **carbapenem** is also prepared using Noyori asymmetric hydrogenation via (2S,3R)-methyl 2-(benzamidomethyl)-3-hydroxybutanoate, which is synthesized from racemic methyl 2-(benzamidomethyl)-3-oxobutanoate by dynamic kinetic resolution.



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Reducing Agents

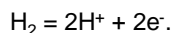
- There are three types of reductions differing in how H₂ is added.
- The simplest reducing agent is H₂.
- Reductions using H₂ are carried out with a metal catalyst.

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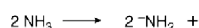
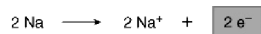
Reducing Agents

- A second way is to add two protons and two electrons to a substrate



- Reductions of this sort use alkali metals as a source of electrons, and liquid ammonia as a source of protons.

- These are called **dissolving metal reductions**.



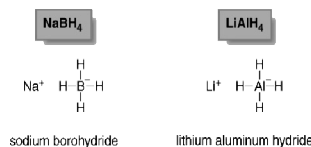
an equivalent of H₂ for reduction

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Reducing Agents

- The third way to add H₂ is to add hydride (H⁻) and a proton (H⁺).
- The most common hydride reducing agents contain a hydrogen atom bonded to boron or aluminum.
 - Simple examples include sodium borohydride (NaBH₄) and lithium aluminum hydride (LiAlH₄).
- NaBH₄ and LiAlH₄ deliver H⁻ to the substrate, and then a proton is added from H₂O or an alcohol.



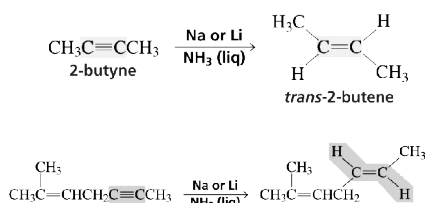
sodium borohydride

lithium aluminum hydride

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Dissolving-Metal Reduction



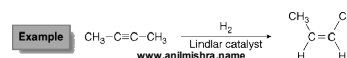
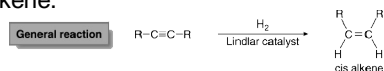
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Dissolving-Metal Reduction

Alkyne reduction to a Cis Alkene

- Reduction of an alkyne to a cis alkene is a stereoselective reaction, because only one stereoisomer is formed.
- Hydroboration-acidification instead of Lindlar's catalyst can be used to get a cis alkene.



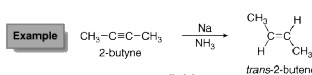
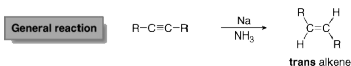
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Dissolving-Metal Reduction

Alkyne reduction to a Trans Alkene

- In a dissolving metal reduction (such as Na in NH_3), the elements of H_2 are added in an anti fashion to form a trans alkene.
- Na has only one electron, so, electrons for the reduction are added sequentially from 2 Na atoms.



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Dissolving-Metal Reduction

Alkyne reduction to a Trans Alkene

- Dissolving metal reduction of a triple bond with Na in NH_3 is a stereoselective reaction because it forms a trans product exclusively.
- Dissolving metal reductions always form the more stable trans product preferentially.

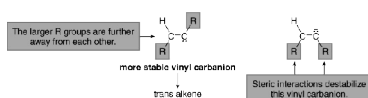
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Dissolving-Metal Reduction

Alkyne reduction to a Trans Alkene

- The trans alkene is formed because the vinyl carbanion intermediate that is formed is more stable when the larger R groups are further away from each other to avoid steric interactions. Protonation of this anion leads to the more stable trans adduct.



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Dissolving-Metal Reduction

- Metal (Li, Na, K) is reducing agent;

- H_2 is not involved
- There are four steps
 - Electron transfer
 - Proton transfer
 - Electron transfer
 - Proton transfer

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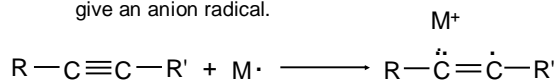
Reduction

Dissolving-Metal Reduction

Mechanism

Step 1 (Electron Transfer)

- Transfer of an electron from the metal to the alkyne to give an anion radical.



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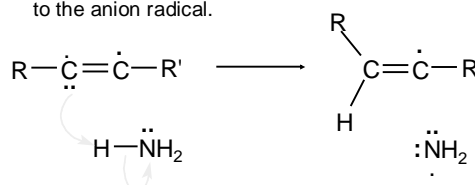
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Dissolving-Metal Reduction

Mechanism

Step 2 (Proton Transfer)

- Transfer of a proton from the solvent (liquid ammonia) to the anion radical.



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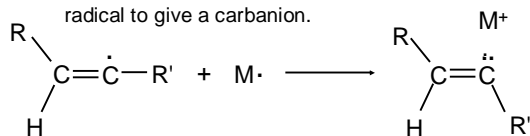
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Dissolving-Metal Reduction

Mechanism

Step 3 (Electron Transfer)

- Transfer of an electron from the metal to the alkenyl radical to give a carbanion.



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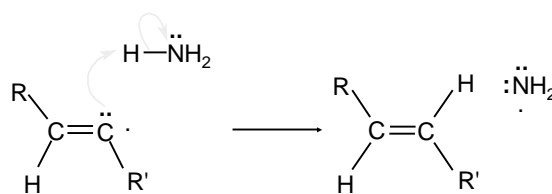
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Dissolving-Metal Reduction

Mechanism

Step 4 (Proton Transfer)

- Transfer of a proton from the solvent (liquid ammonia) to the carbanion.



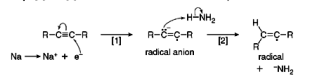
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Dissolving-Metal Reduction

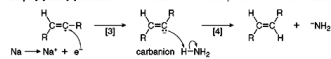
Alkyne reduction to a Trans Alkene:

Steps [1] and [2]: Addition of one electron and one proton to form a radical



- Addition of an electron to the triple bond in Step [1] forms a radical anion, a species containing both a negative charge and an unpaired electron.
- Protonation of the anion with the solvent NH_3 in Step [2] yields a radical. The net effect of Steps [1] and [2] is to add one hydrogen atom (H^+) to the triple bond.

Steps [3] and [4]: Addition of one electron and one proton to form the trans alkene



- Addition of a second electron to the radical in Step [3] forms a carbanion.
- Protonation of the carbanion in Step [4] forms the trans alkene. These last two steps add the second hydrogen atom (H^+) to the triple bond.

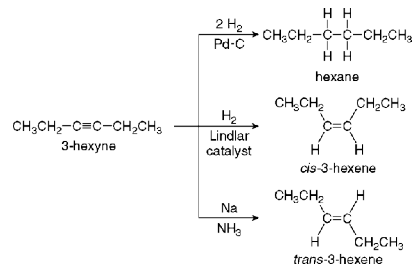
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Dissolving-Metal Reduction

Summary of Alkyne Reductions

Three methods to reduce a triple bond



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Birch Reduction

- It converts aromatic compounds having a benzenoid ring into a product, 1,4-cyclohexadienes, in which two hydrogen atoms have been attached on opposite ends of the molecule.
- It is the organic reduction of aromatic rings in liquid ammonia with sodium, lithium or potassium and an alcohol, such as ethanol and tert-butanol.
- This reaction is quite unlike catalytic hydrogenation, which usually reduces the aromatic ring all the way to a cyclohexane.

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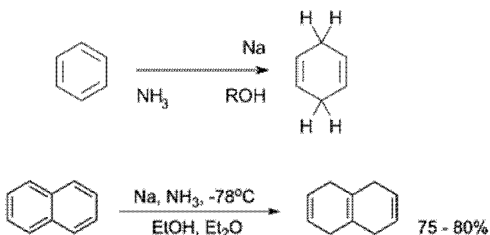
Birch Reduction

- The original reaction reported by Arthur Birch in 1944 utilized sodium and ethanol.
- Subsequently A. L. Wilds noted that better yields result with lithium.
- Also the use of t-butyl alcohol has become common.
- The reaction is one of the main organic reactions utilized in all types of syntheses.

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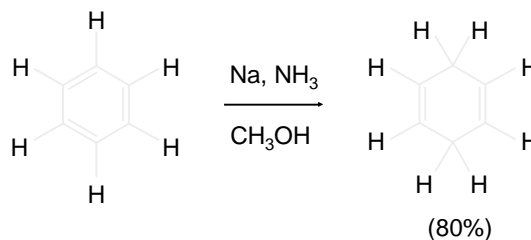
Birch Reduction



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Birch Reduction of Benzene



Product is non-conjugated diene.

Reaction stops here. There is no further reduction.

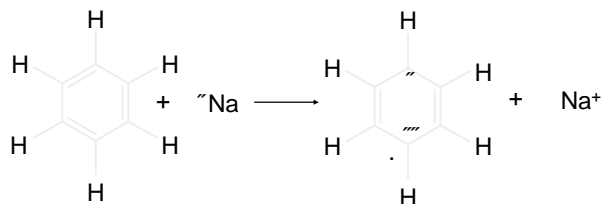
Reaction is not hydrogenation. H₂ is not involved in any way.

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Birch Reduction Mechanism

Step 1: Electron transfer from sodium

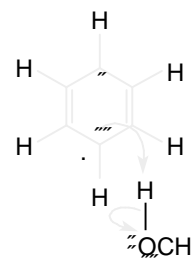


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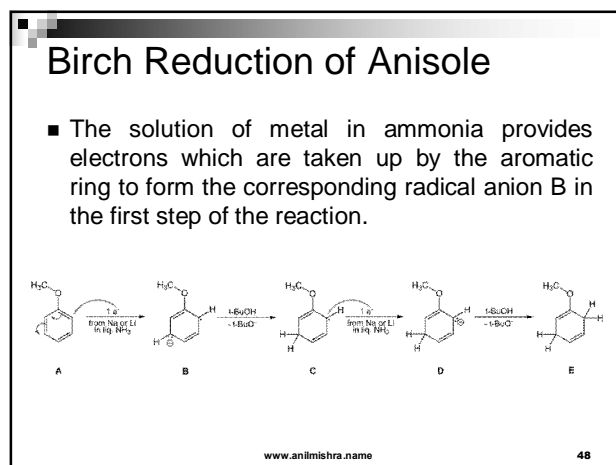
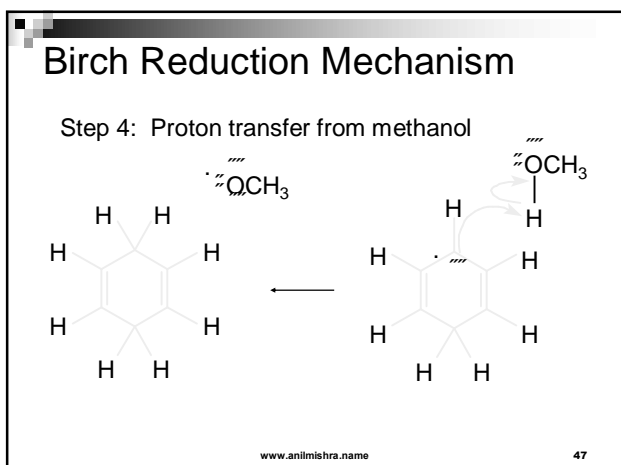
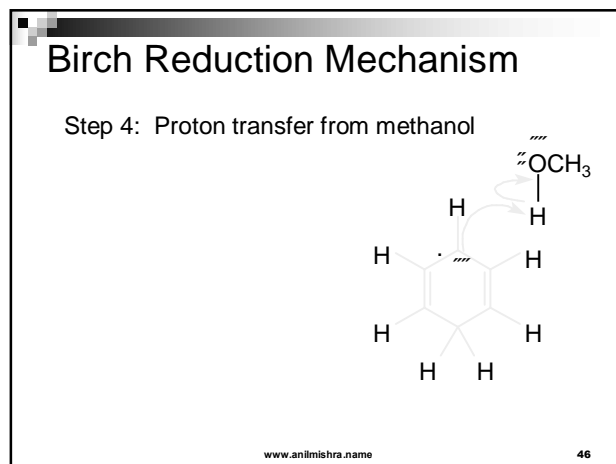
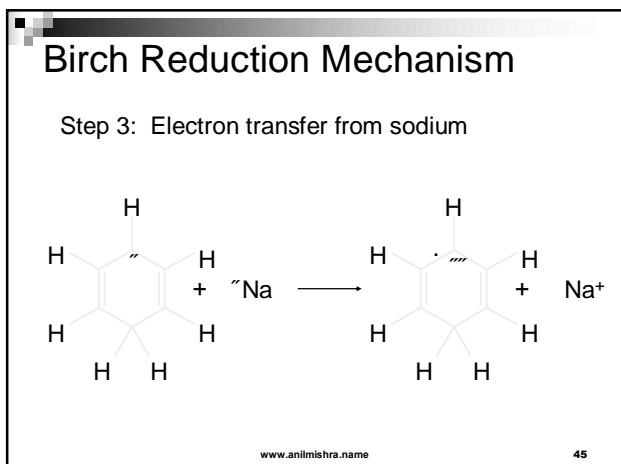
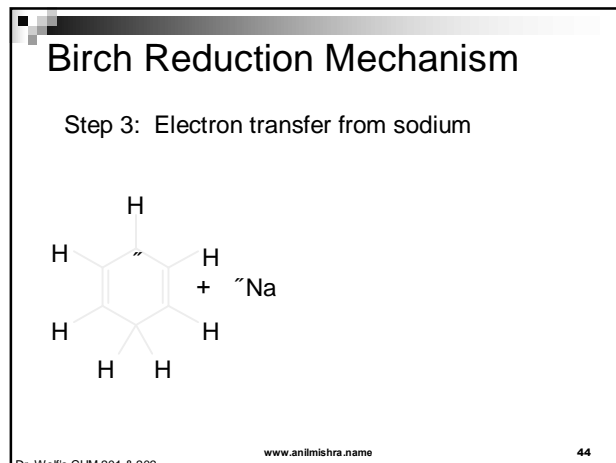
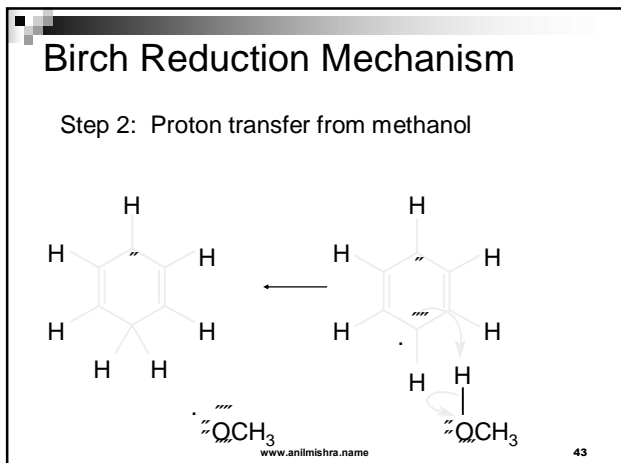
Birch Reduction Mechanism

Step 2: Proton transfer from methanol



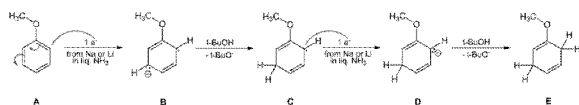
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Birch Reduction of Anisole

- This is followed by protonation by the alcohol to form a cyclohexadienyl radical C.

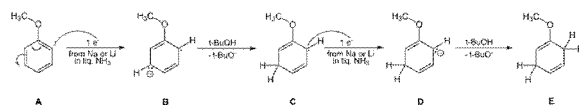


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Birch Reduction of Anisole

- Next, a second electron is transferred to the radical to form a cyclohexadienyl carbanion D.

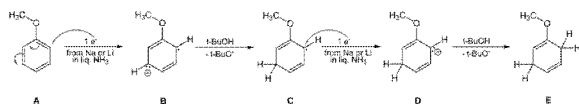


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Birch Reduction of Anisole

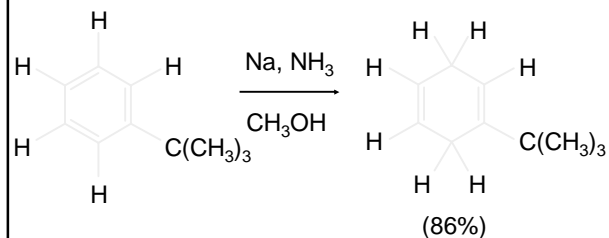
- In the last step a second proton leads the cyclohexadienyl carbanion to the unconjugated cyclohexadienyl product.



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Birch Reduction of Alkylbenzene

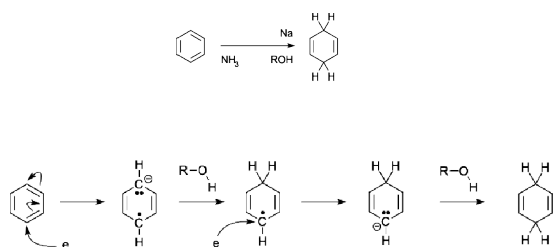


If an alkyl group is present on the ring, it ends up as a substituent on the double bond.

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Birch Reduction Mechanism



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Birch Reduction Mechanism



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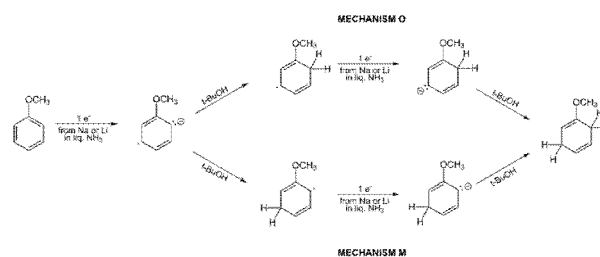
Birch Reduction Mechanism

- The original mechanism of the Birch reduction invoked protonation of a radical anion that was meta to the ring methoxy and alkyl groups.
- It further propose that the last step, protonation of a cyclohexadienyl anion, occurred ortho with respect to these substituents.

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Birch Reduction Mechanism



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Birch Reduction Mechanism

- Birch's original mechanism was based on qualitative reasoning,
 - That the radical anion's electron density, resulting from the addition of an electron, would be highest meta to an electron donor (such as methoxy or methyl) due to avoiding the usual ortho-para high density in the neutral species

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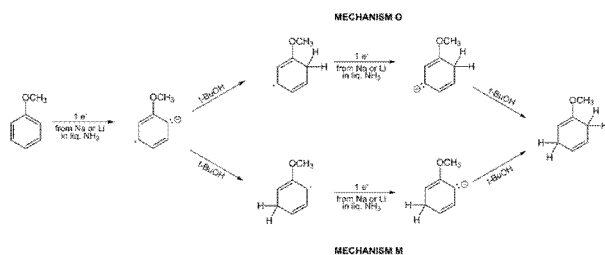
Birch Reduction Mechanism

- In 1961, simple Hückel computations showed that Birch's proposed mechanism was incorrect.
 - The correct mechanism O
 - The two a-priori alternative mechanisms O and M:

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Birch Reduction Mechanism



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Birch Reduction

- The original Birch reduction conditions have some drawbacks, one of which is the use of liquid ammonia as solvent.
- The use of other electron donating reagents can permit the use of THF as solvent.

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