Reduction

Reduction (Syllabus)

- Catalytic Hydrogenation
  - Heterogeneous
    - Pd/Pt/Rh/Ni etc
  - Homogeneous
    - Wilkinson
- Noyori Assymmetric Hydrogenation

Reduction (Syllabus)

- Metal based reduction using Li/Na/Ca in liquid Ammonia, Sodium, Magnesium and Zinc
  - Birch
  - Pinacol formation
  - McMurray
  - Acyloin formation
  - Dehalogenation
  - Deoxygenations

Reduction (Syllabus)

- Hydride transfer reagents
  - $NaBH_4$
  - Triacetoxyborohydride
  - $LiAlH_4$
  - DIBAL-H
  - Meerwein Pondorff Verley reduction

Reduction (Syllabus)

- Stereoselective reduction
- Enantioselective reductions
  - Chiral Boranes
  - Corey-Bakshi-Shibata

Oxidation and Reduction

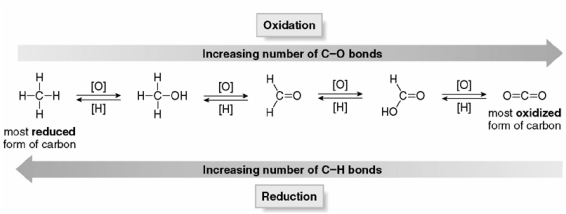
- Oxidation:
  - The loss of electrons
    - Alternatively, the loss of H, the gain of O, or both
- Reduction:
  - The gain of electrons
    - Alternatively, the gain of H, the loss of O, or both

Oxidation and Reduction

- Oxidation results in an increase in the number of bonds between C and a more electronegative atom, C—Z, (usually C—O) or decrease in the number of C—H bonds.
- Reduction results in a decrease in the number of C—Z bonds (usually C—O) or an increase in the number of C—H bonds.

Oxidation and Reduction

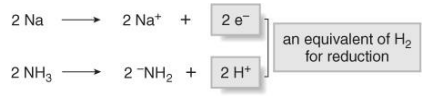
- A general scheme for the oxidation and reduction of a carbon compound



Oxidation and Reduction

There are three ways of introducing 2 Hs in a reduction.

- The first method uses H_2 gas. Catalytic hydrogenation requires a metal catalyst (usually Pt, Pd or Ni) with H_2.
- A second method adds two protons and two electrons to a substrate, and $2H^+ + 2e^- = H_2$
  - Reductions of this sort use alkali metals as a source of electrons, and liquid ammonia as a source of protons, Na in NH_3 (liq) or Li in NH_3 (liq).
  - These are called dissolving metal reductions.



Oxidation an Reduction

- The third way 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 ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$).
  - $NaBH_4$ and $LiAlH_4$ deliver H^- to the substrate, and then a proton is added from H_2O or an alcohol.

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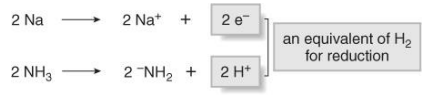

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Oxidation and Reduction

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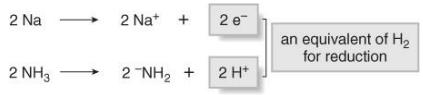


Oxidation and Reduction

Some common reducing agents

	Reducing agents	Acts on
Catalytic Hydrogenation	H_2 / Pt, Pd or Ni	C=C, C≡C C=O
Hydroboration	BH_3 / THF	C=C, C≡C
Dissolving Metal	Na / NH_3 (liq.) Li / NH_3 (liq.)	C≡C
Metal Hydride	$NaBH_4$ / alcohol $LiAlH_4$ / ether	C=O C=O
Other	ZnO / HOAc $(CH_3)_2S$	Malozonide

Hydrogenation

- Hydrogenation typically constitutes the addition of pairs of hydrogen atoms to a molecule, generally an alkene.
  - To treat with hydrogen
  - It is a chemical reaction between molecular hydrogen (H_2) and another compound or element.
- The process is commonly employed to reduce or saturate organic compounds.
  - Hydrogenation reduces double and triple bonds in hydrocarbons.

Two Ways to Add Hydrogen:

- Hydrogenation:
  - Addition across Pi bonds

- Hydrogenolysis:
  - Cleavage of Sigma bonds

Catalytic Hydrogenation

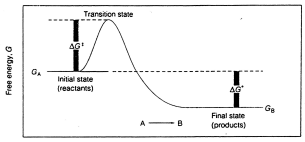
- Hydrogenation is usually carried out in the presence of a catalyst such as nickel, palladium or platinum.
- Such reaction is known as **catalytic hydrogenation.**
  - Catalysts are required for the reaction to be usable
  - Non-catalytic hydrogenation takes place only at very high temperatures.

Catalysis

- Catalysts increase reaction rate without themselves being changed
- Can accelerate a reaction in both directions
- Do not affect the state of equilibrium of reaction
  - simply allow equilibrium to be reached faster

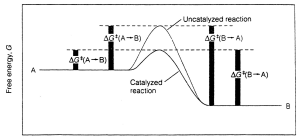
Activation energy

- Molecules must be activated before they can undergo a reaction
  - Reactants must absorb enough energy from surroundings to destabilize chemical bonds (energy of activation)
- Transition state
  - Intermediate stage in reaction where the reactant molecule is strained or distorted but the reaction has not yet occurred



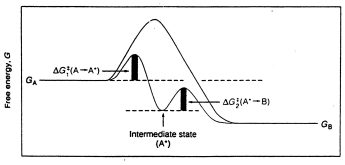
Activation energy

- A catalyst lowers the energy of activation by:
  - Forcing molecules into conformations that favor the reaction
    - i.e. the catalyst may re-orientate molecules
- Change in free energy is identical to uncatalyzed reaction: **the catalyst does not change the thermodynamic equilibrium!**



Activation energy

- Sometimes catalysts cause one large energy barrier to be replaced by two smaller ones
  - Reaction passes through intermediate stage



Catalytic Hydrogenation

- Catalytic Hydrogenation has three components
  - The unsaturated substrate
  - The hydrogen (or hydrogen source)
  - A catalyst
- The reduction reaction is carried out at different temperatures and pressures depending upon the substrate and the activity of the catalyst.

Why Choose Catalytic Hydrogenation?

- Simple work-up
  - Generally clean reactions
- No extra ions or compounds to deal with; just remove solvent.
- Can be done neat.
- Most cost-effective choice for scale-up
- In Process; spent catalyst is usually recoverable for cost savings

Nature of Catalysis

- **Heterogeneous catalysis**
  - Refers to the form of catalysis where the phase of the catalyst differs from that of the reactants.
- **Homogeneous catalysis**
  - Are catalytic reactions where the catalyst is in the same phase as the reactants

Heterogeneous Catalysis

- Heterogeneous catalysis is the alternative to homogeneous catalysis, where the catalysis occurs at the interface of two phases, typically gas-solid.
- The term is used almost exclusively to describe solutions and it is often implies catalysis by organometallic compounds.

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Heterogeneous Catalysis

- One or more of the reactants are ***adsorbed*** on to the surface of the catalyst at ***active sites***.
- There is some sort of interaction between the surface of the catalyst and the reactant molecules which makes them more reactive.
- The reaction happens.
- The product molecules are ***desorbed***.

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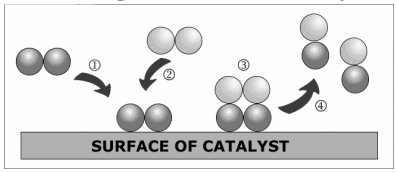
Heterogeneous Catalysis

Heterogeneous Catalysis



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Heterogeneous Catalysis

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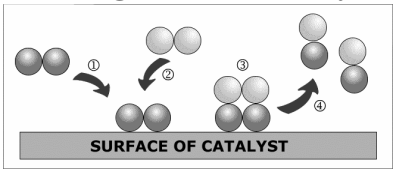

Adsorption (STEP 1)
Incoming species lands on an active site and forms bonds with the catalyst. It may use some of the bonding electrons in the molecules thus weakening them and making a subsequent reaction easier.

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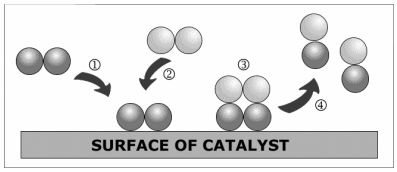
Heterogeneous Catalysis

Heterogeneous Catalysis



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Heterogeneous Catalysis

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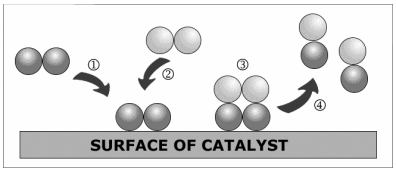

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There is a re-arrangement of electrons and the products are then released from the active sites

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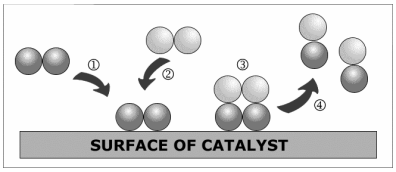
Heterogeneous Catalysis

Heterogeneous Catalysis



ANIMATION

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Heterogeneous Catalysis

Heterogeneous Catalysis

ANIMATION

CATALYTIC ACTION

Alkynes: Hydrogenation Reactions

- Two spatial (stereochemical) aspects of alkene hydrogenation:
  - Syn addition of both H atoms to double bond
  - Hydrogenation is stereoselective, corresponding to addition to less crowded face of double bond

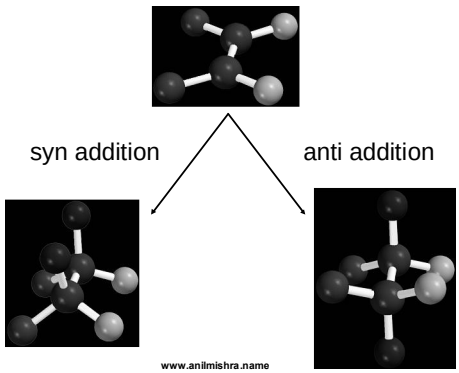
Alkenes: Hydrogenation Reactions

- **Catalytic Hydrogenation is a SYN Addition of H_2**
  - **SYN Addition: Both Atoms Add to Same Side (Face) of pi Bond**
- **Catalyst: Lowers Transition State Energy (Activation Energy)**

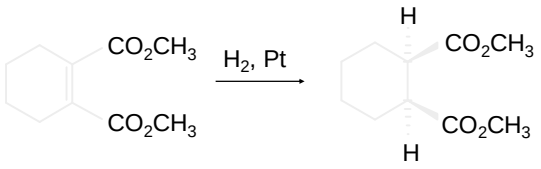
Alkynes: Hydrogenation Reactions

- **Platinum Catalysts Allow Double Addition of H_2 On Alkyne**
  - **Can Also Hydrogenate Once to Generate Alkenes**
  - **Cis and Trans (E and Z) Stereoisomers are Possible**
  - **Can Control Stereochemistry with Catalyst Selection**

Syn-Additon versus Anti-Addition



Example of Syn Addition



(100%)

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Stereoselectivity

- A reaction in which a single starting material can give two or more stereoisomeric products but yields one of them in greater amounts than the other (or even to the exclusion of the other) is said to be **stereoselective**.

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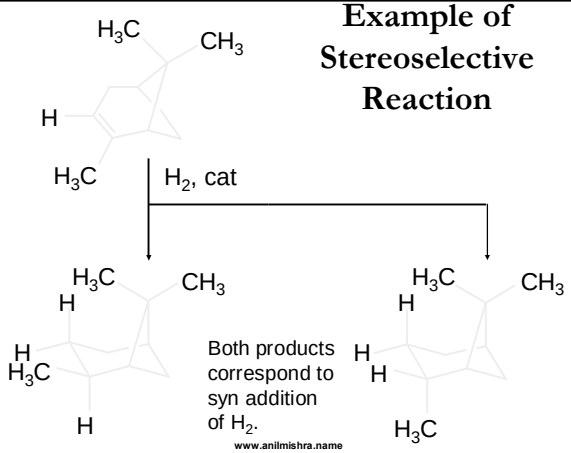
Example of Stereoselective Reaction



Both products correspond to syn addition of H_2.

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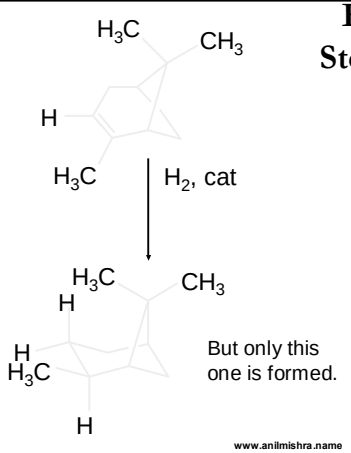
Example of Stereoselective Reaction



But only this one is formed.

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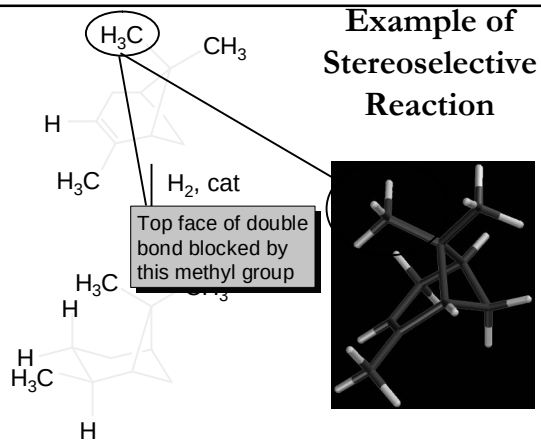
Example of Stereoselective Reaction



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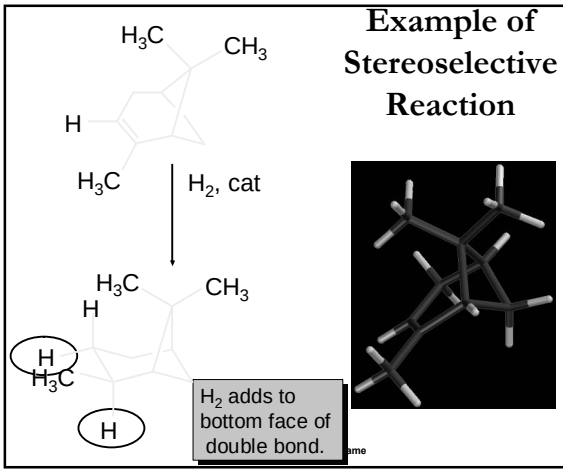

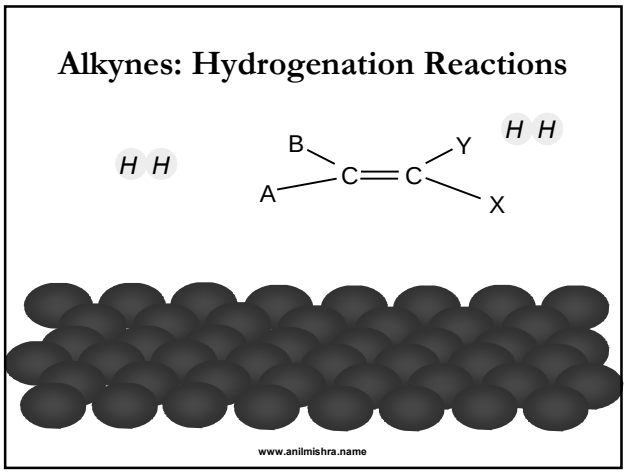
Alkynes: Hydrogenation Reactions
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H H
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C
C
X
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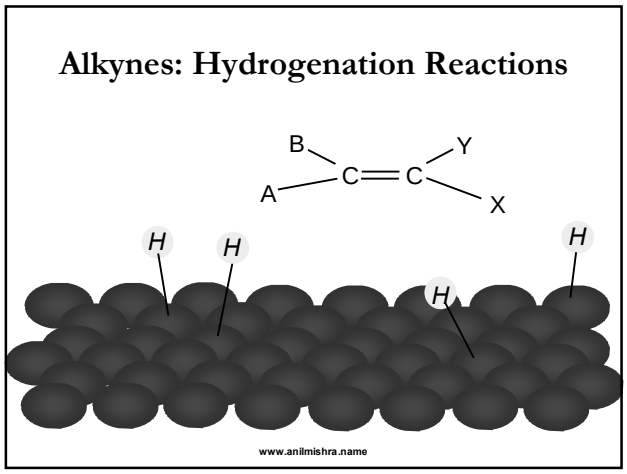
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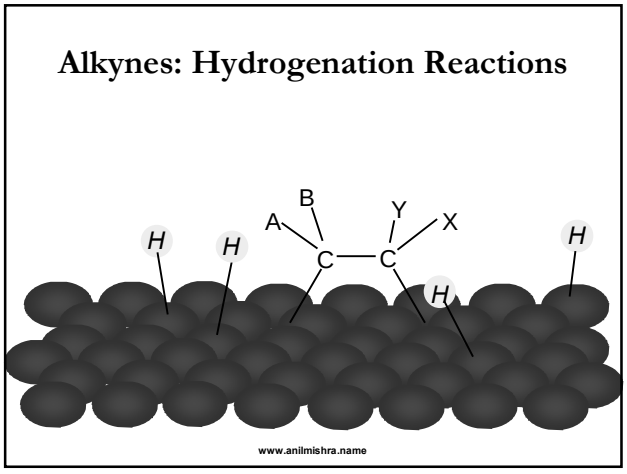
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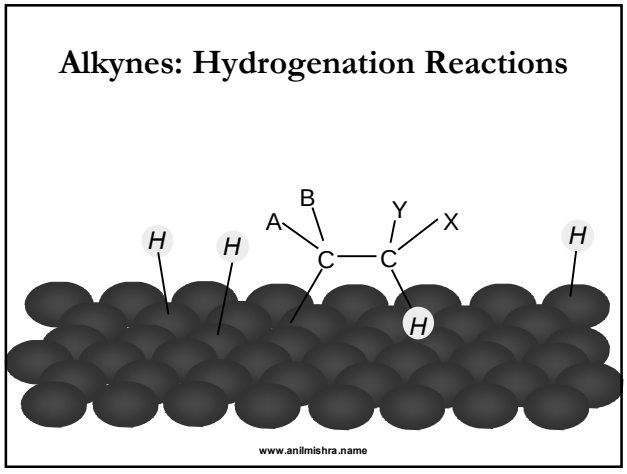
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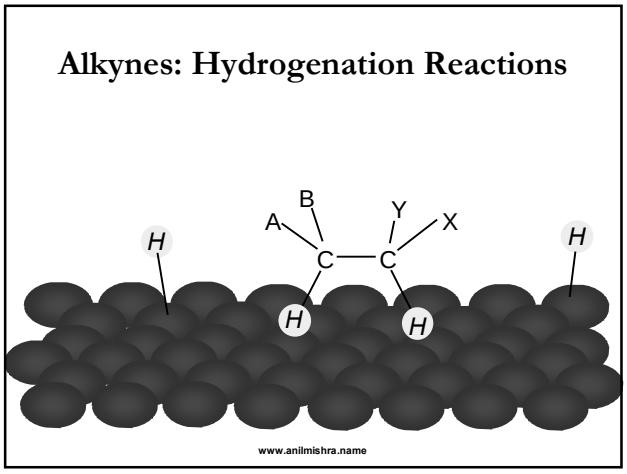
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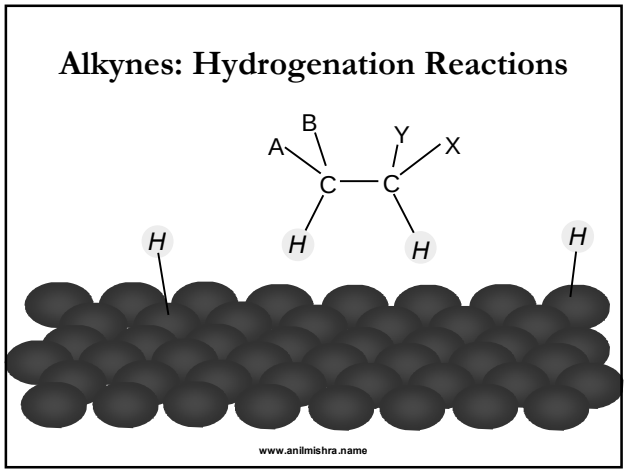
Alkynes: Hydrogenation Reactions
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Metal Catalysts

- Metals like platinum and nickel make good catalysts because they adsorb strongly enough to hold and activate the reactants, but not so strongly that the products can't break away.

Platinum

- Platinum(IV) oxide, PtO_2, also known as Adams' catalyst, is a black powder that is soluble in KOH solutions and concentrated acids.
- Wide variety of reductions, including hydrogenation and hydrogenolysis, depending upon conditions; most are mild
- Poisoned by amines and sulfur

Platinum cont'd

- If PtO_2 is pre-treated with HOAc or MeOH wash, can reduce benzene rings readily.
- PtO_2 not selective between double and triple C-C bonds.
- Many variants of Pt/C, each with its own selectivity.

Palladium

- Many forms of palladium on support available, each with its own selectivity
- Less than half the cost of platinum
- Gives both hydrogenation and hydrogenolysis
- Most reductions under mild conditions
- Subject to poisoning with sulfur, amines, and lead.

Rhodium

- Expensive (~Pt), but very versatile.
- Best for reductions of aromatic systems (incl. heterocycles) under mild conditions sans acid
- Reduces C=C, nitro, and carbonyls; most reducible groups
- Aromatic vs carbonyl selectivity can be controlled by pH and nearby groups

Just what are Raney metals?

- An alloy of the metal and aluminum is made by melting them together a certain proportions.
- The aluminum is dissolved away using sodium hydroxide solution
- The remaining metal from the alloy "domains" become particles with high surface area and are charged with hydrogen.

$$2Ni—Al + 2OH^{\ominus} + 2H_2O \longrightarrow 2Ni + 2AlO_2^{\ominus} + 3H_2$$

Just what are Raney metals?

- It is extremely flammable in air and must be handled wet with water
- Commercially available, but best if prepared just before use.

Nickel

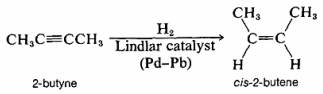
- Mostly used as Raney Nickel
- Very subject to loss of activity within two weeks of preparation, especially W-6 and W-7
- Only modest temperatures and pressures needed
- Can selectively reduce aromatic rings
- Above 100 °C reaction may get out of hand
- Reduces esters, ketones, nitriles

Catalyst Inhibitors and Poisons

- Normally, it is not possible to stop the hydrogenation of an alkyne at the alkene stage, but if the catalyst is suitably deactivated, addition to the triple bond can be achieved without further addition occurring to the resulting double bond.

Catalyst Inhibitors and Poisons

- The preferred catalyst for selective hydrogenation of alkynes is palladium partially "poisoned" with a lead salt (Lindlar catalyst).
- This catalyst shows little affinity for adsorbing alkenes and hence is ineffective in bringing about hydrogenation to the alkane stage:



Catalyst Inhibitors and Poisons

- Inhibitors diminish the rate , but the effect can be reversed by washing it away.
- Poisons exert an appreciable inhibitory effect when present in small amounts.
- Both can be used to fine-tune the selectivity of a catalyst.

Catalyst Inhibitors and Poisons

- Metals and metals Salts
  - Mg, Ni Co have no effect on $PdCl_2$ reductions.
  - Al, Fe, Cu, Zn, Ag, Sn, Pb, Hg, Cr their oxides and carbonates inhibit Palladium.
  - Pt reductions inhibited by Al, Co, Bi.
  - Pt Reductions increased by Fe, Cu Zn, Ag, Pb
  - Raney nickel completely inhibited by mercuric chloride, but 50% inhibited by Ag_2SO_4

Catalyst Inhibitors and Poisons

- Halogen-Containing Compounds
  - Halide ions inhibit Ni, sometimes Pt, Pd:
  - I^- >> Br^- > Cl^- > F^- in a concentration-dependent manner.
  - Corresponding acids just as potent, if anhydrous.

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Catalyst Inhibitors and Poisons

- Halogen-Containing Compounds
  - Non-ionizable organic halides often do not inhibit Pt and Pd, except when directly bonded to the region of reduction
    - e.g. aromatic halides reduced to cyclohexane halides
  - Potent inhibitors (Ni): carbon tet, chloroform, chloral hydrate, trichloroethanol, di- and trichloroacetic acid, alkyl chloride, benzyl chloride, and acetyl chloride.

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