Chemistry 304B, Spring 1999 **Lecture Notes 17**

Review and summary:

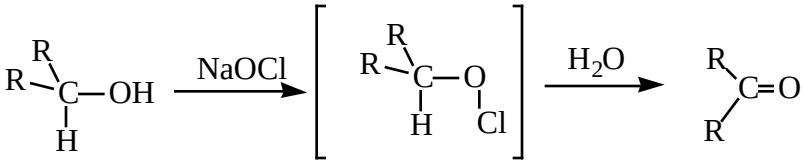
Oxygen and nitrogen nucleophiles react reversibly with aldehydes and ketones. Equilibrium constant depends on a number of steric and electronic features. Acid (always) and base (sometimes) can accelerate the processes. Protons equilibrate among all O and N atoms in a mixture, activating each site.

Carbon nucleophiles, in the form of organometallic reagents, can be generated by several methods and are associated with an electropositive metal [Li, Mg, Zn, Al, etc]. Varying degrees of "extra" electron density on the carbon, depending on how electropositive is the metal. They add to carbonyl groups fast and irreversibly, generating an alcohol.

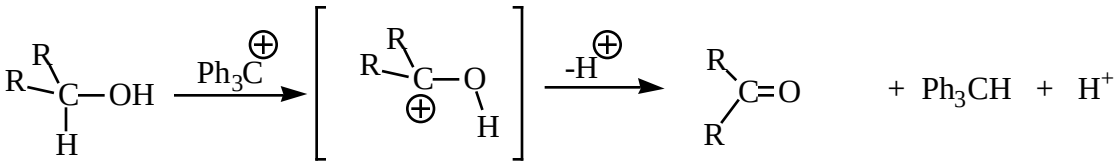
Hydride nucleophiles are available as metal hydrides ($LiAlH_4$, and $NaBH_4$ are the prototype cases). Add H^- to a carbonyl group, generating an alcohol.

Alcohols can be oxidized to give aldehydes and ketone. Two stragegies:

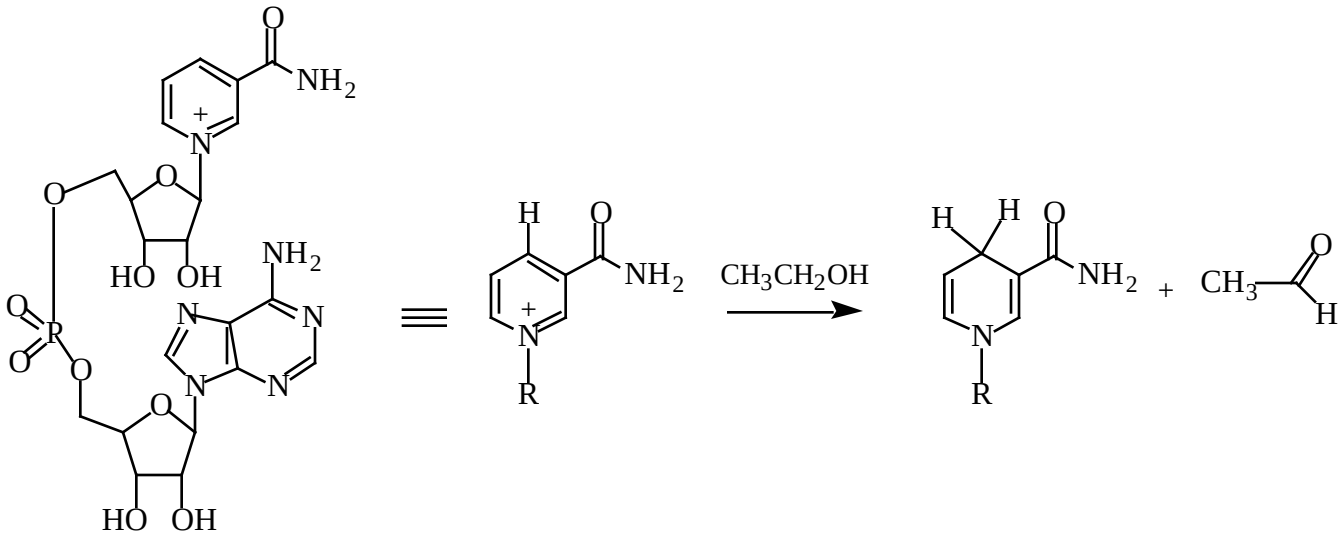
(a) put leaving group at the oxygen and carry out an E2.



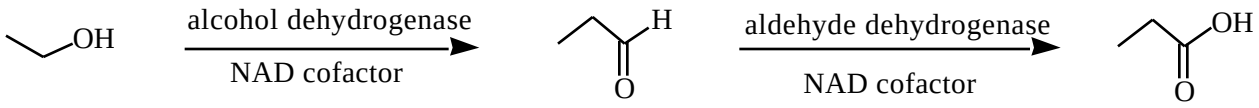
(b) OR remove hydride (H^-) from the carbon by reaction with a strong electrophile such as Ph_3C^+,



Nature's oxidizing agent: NAD



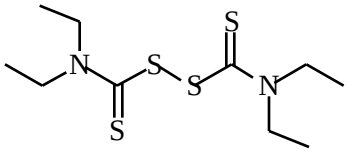
nicotinamide adenosine dinucleotide



Acetaldehyde is reactive and toxic--"intense flushing, nausea, dizziness, throbbing headaches.."

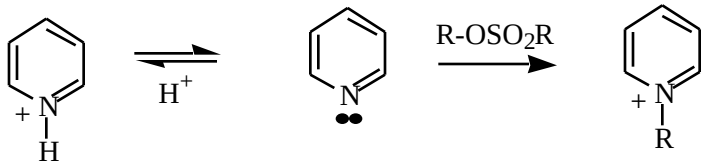
Genetic deficiency: alcohol intolerance

Anatbuse: Inhibits the enzyme *aldehyde dehydrogenase*

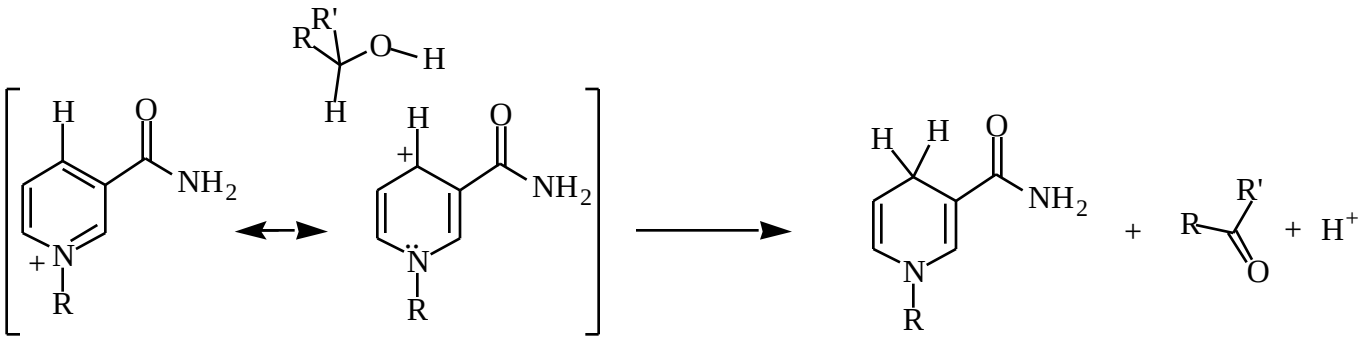


Alcohol dehydrogenase also works on MeOH → formaldehyde (very toxic)
Antidote for MeOH poisoning?

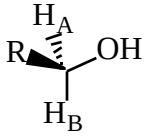
Bio-oxidation mechanism: consider the pyridinium ion:



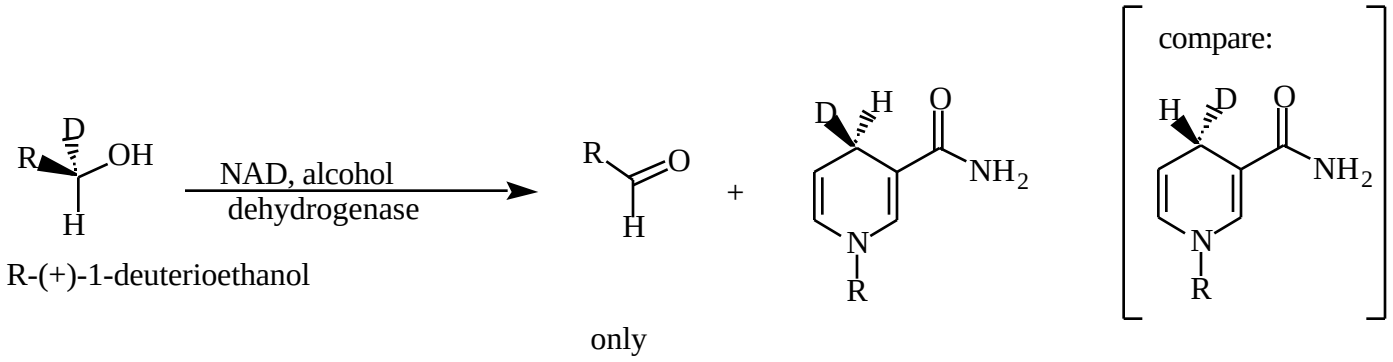
pyridinium ion



SUBTLE STEREOCHEMICAL POINT:



Any difference between H_A and H_B ? Only in an asymmetric environment (e.g., enzyme)



R-(+)-1-deuterioethanol

only

The protons H_A and H_B are NOT **chemically** equivalent.
Connectively equivalent (connected to the same other atoms)

Connectively non-equivalent groups are likely to have different chemical reactivity under any conditions.

Chemically non-equivalent groups are different only in the presence of an asymmetric environment

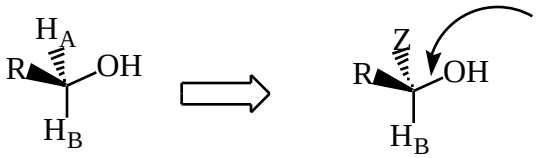
a. stereogenic center in the same molecule
b. asymmetric catalyst (e.g., enzyme)

Test: replace (mentally) one H with another group. Is the product asymmetric?
Non-superimposable mirror images?

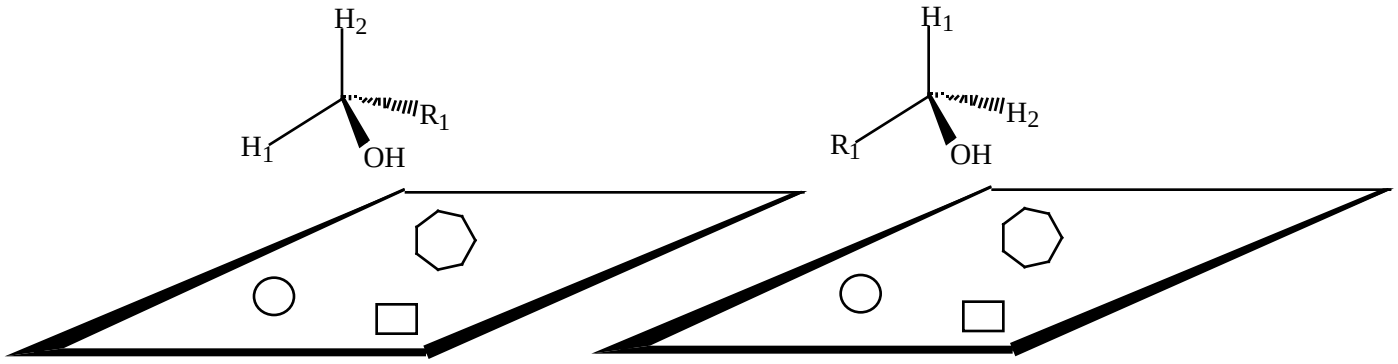
If not, then the H's in question are **homotopic**--chemically equivalent.

If generate new non-superimposable pairs,

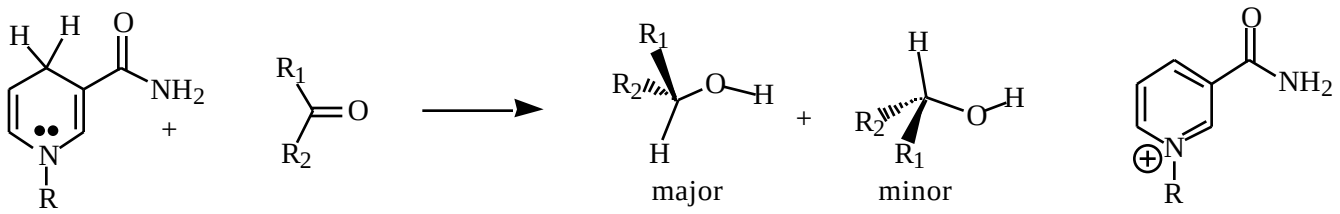
a. if enantiomers (mirror images), then the original H's were **enantiotopic**
b. if diastereoisomers, then the original H's were **diastereotopic.**



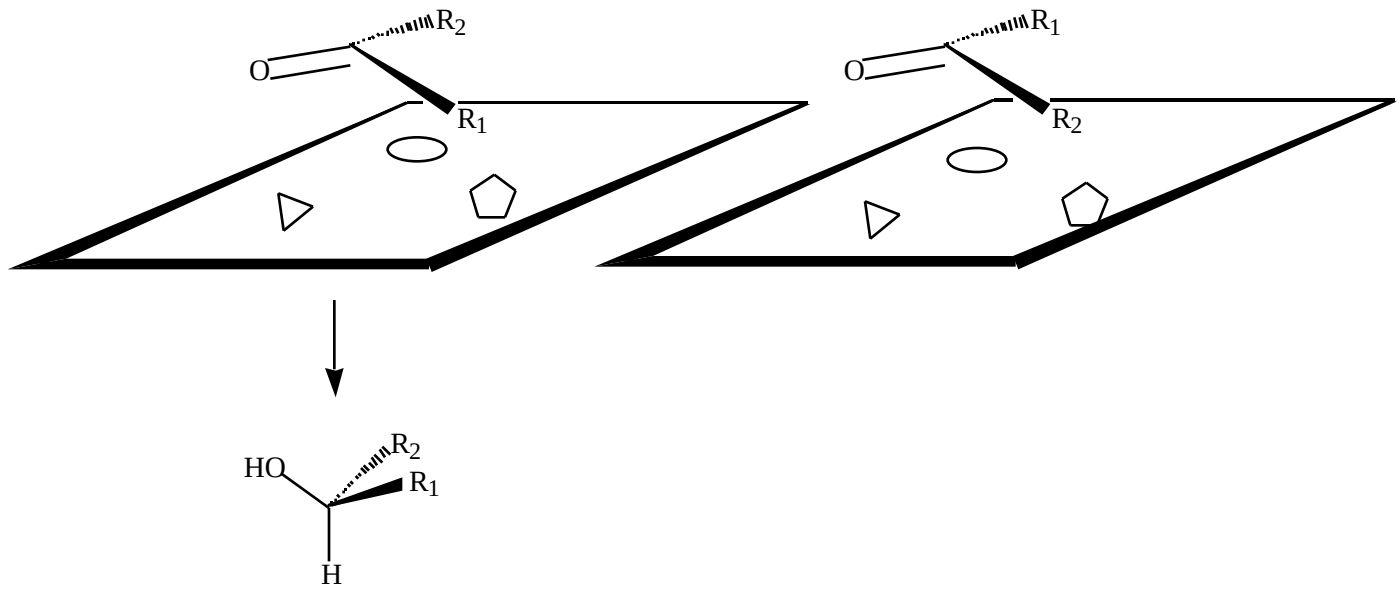
H_a and H_B are **enantiotopic**



As usual, biological reactions can go both directions: **NADH is an effective ketone reducing agent:**



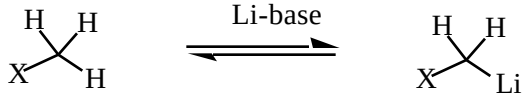
How does it achieve selective addition?



STABILIZED CARBANIONS:

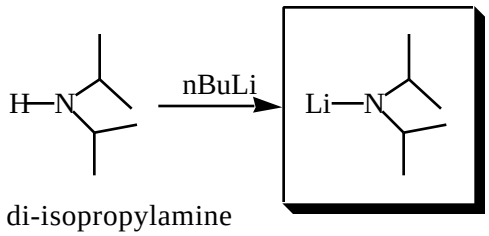
recall:

Now: Replace H with other groups that can stabilize a (-) charge.



X = NR_2, OR not stabilized
X = SR → pK_a ca 40
X = SO_2R → pK_a ca 30
X = NO_2 → pK_a ca 11
X = C(=O)R → pK_a ca 18-22

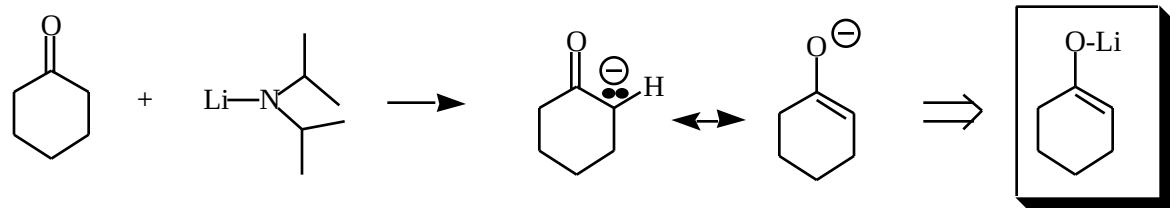
Typical base: n-Butyl-Li (very strong base and good nucleophile; adds to ketones)



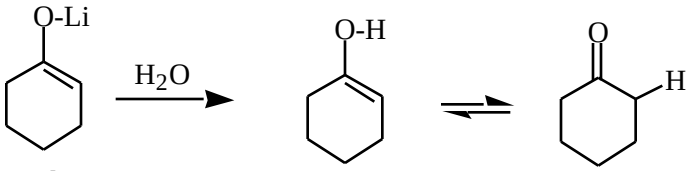
di-isopropylamine

lithium diisopropyl amide

strong base and non-nucleophilic



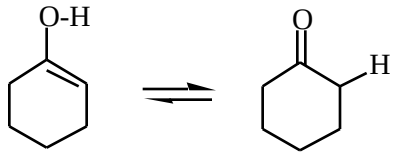
pKa 20 [pKa ca 35] resonance and inductive (dipole) stabilization predominant form



enolate anion enol keto

Which is more stable???
[exam 1...]

Analogy with the allyl anion.



enol keto

Favors the ketone, but low barries, rapid equilibration
Accelerated by acid and base. How?