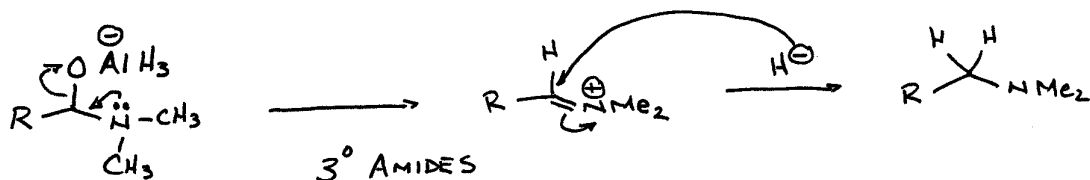
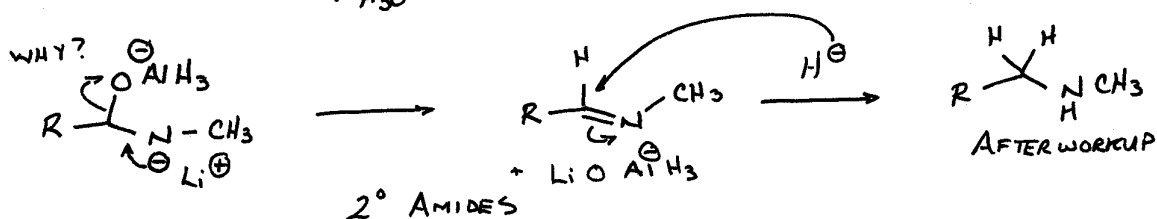
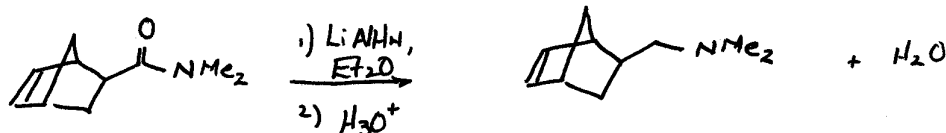


COMPARE

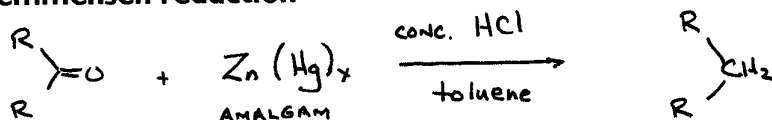


### Carbonyl to Methylene Reductions ( $R_2C=O$ to $R_2CH_2$ )

(March 9-37)

The above reduction methods all reduce ketones/aldehydes, but stop at the alcohol stage. If one wants to go all the way to the alkane stage, there are three direct methods (and several indirect ones). They are:

#### 1) Clemmensen reduction

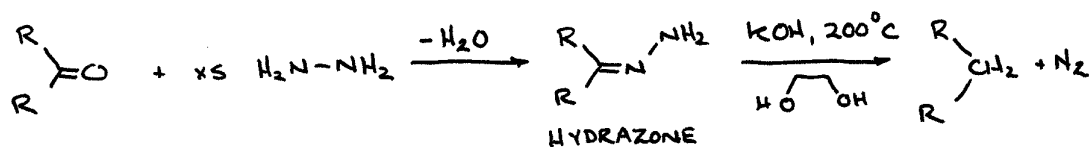


These are very acidic conditions. As a result, this is incompatible with several functional groups. For example:

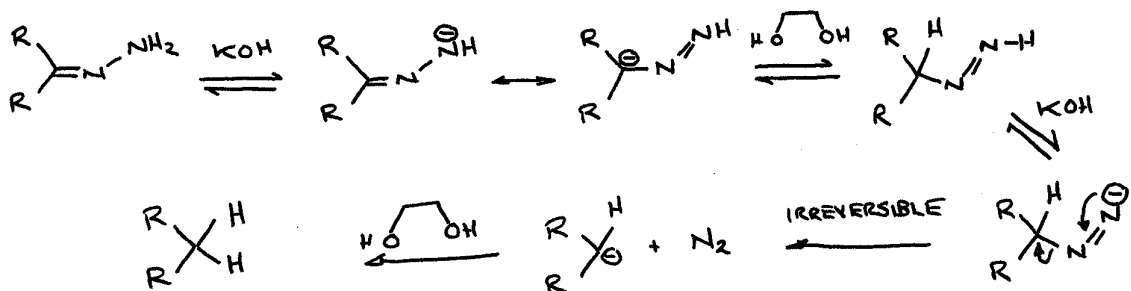
- esters are hydrolyzed to acids under these conditions
- $\beta$ -keto esters are decarboxylated
- alcohols usually eliminate to alkene under these conditions
  - except  $\alpha$ -hydroxy esters (will discuss later)

Although several mechanisms have been proposed, very little is actually known about the mechanism of the Clemmensen reduction. A carbene intermediate is one possibility, and once we look at metal acid reductions, you can probably get an idea of the 1<sup>st</sup> step.

#### 2) Wolff-Kischner Reduction (the Huang-Minlon modification)

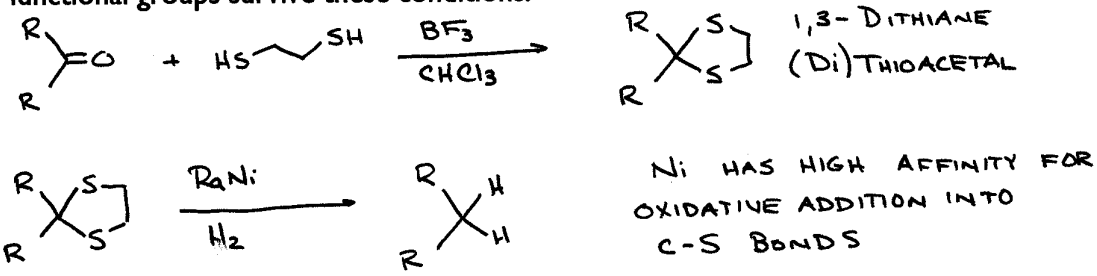


In contrast, the Wolff-Kischner reduction is very basic, and its mechanism is more easily understood. In general, more functional groups can take these conditions than the Clemmensen. What is involved here is a hydrazone, which is sort of a type of imine.



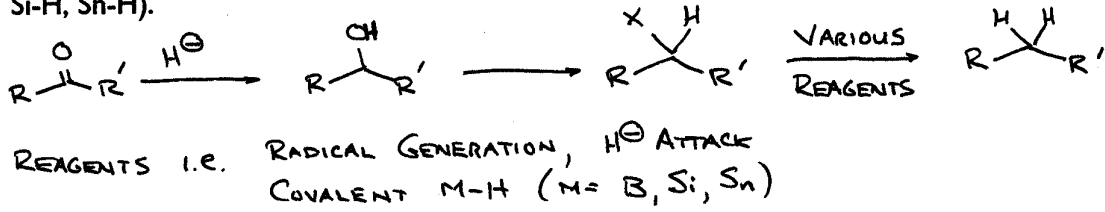
### 3) Thioacetal Route (1,3-Dithiane) (March 4-36)

This route involves forming a sulphur based acetal (1,3-dithiane, or thioacetal) from the ketone. These can act as protecting groups, much like acetals, with at least one major difference: C-S bonds are highly susceptible to hydrogenolysis, particularly with Ni catalysts. The overall result is a two-step reduction, but the conditions are very mild, so many functional groups survive these conditions.



#### Other routes

There are several other multiple step methods for the R<sub>2</sub>C=O to RCH<sub>2</sub> transformation. We won't go through them here, except to say that they usually involve reduction of the carbonyl to an alcohol, conversion of the alcohol into a leaving group, and removal of that leaving group by radical methods, hydride attack, or with covalent M-H (B-H, Si-H, Sn-H).



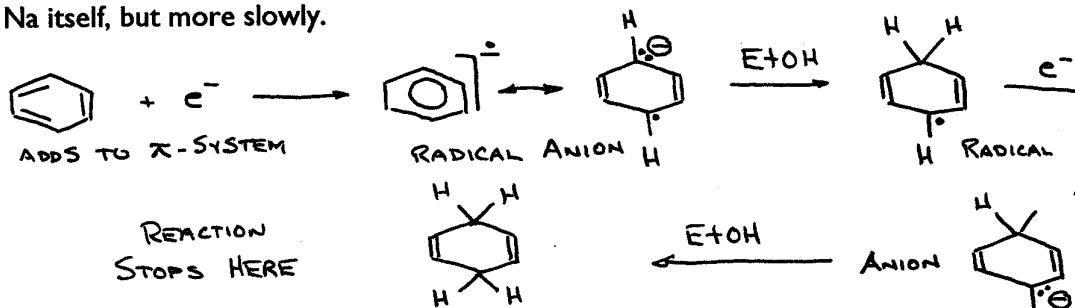
#### Dissolving Metal reductions

There are several types of reduction which result from electrons donated from very electropositive metals, such as Li, Na, K, Ca. These normally add to π-systems, initially to give radical anions, and ultimately reduction. They tend to do reductions not so easy for any of the other methods we've looked at so far, and so they are useful.

## Birch Reduction

(MARCH 5-10)

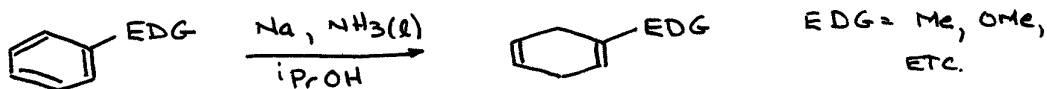
Na metal (most common) or Li metal dissolves in liquid  $\text{NH}_3$  (at  $-33^\circ\text{C}$ ) to give a blue solution. This solution is comprised of  $\text{Na}^+$  + an electron ( $e^-$ ) solvated by the  $\text{NH}_3$ . With aromatic compounds, this electron adds to the  $\pi$ -system. An alcohol such as EtOH or *i*PrOH is present to protonate the anionic intermediates formed; the alcohol does react with Na itself, but more slowly.



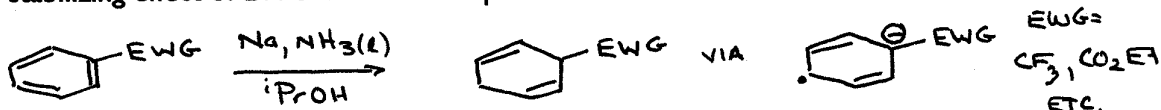
The product is always a non-conjugated cyclohexadiene.

**Regiochemistry:** This is highly predictable, depending upon whether the existing substituent is electron donating (+I, +M) or electron withdrawing (-I, -M).

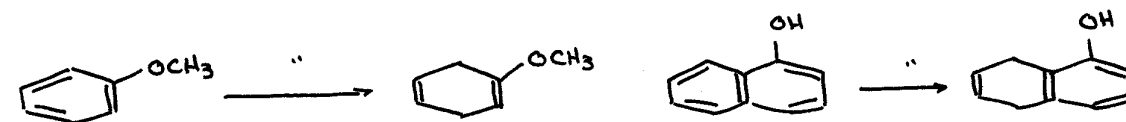
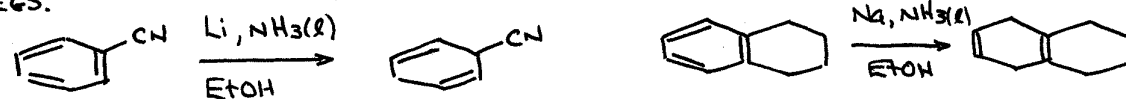
If R is electron donating, the R group ends up on an  $\text{sp}^2$  hybridized C



If R is electron withdrawing, the R group ends up on an  $\text{sp}^3$  hybridized C, due to the stabilizing effect of EWG on the anion portion of the radical anion.

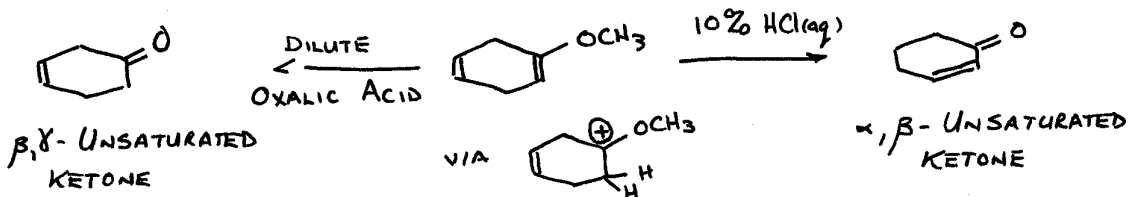


EGS.



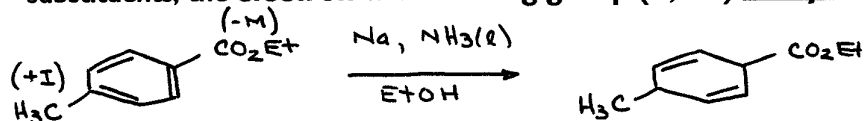
↑ LESS  $e^-$  RICH RING  
 $\therefore$  REDUCED FASTER

The product of reductions of aromatic ethers are particularly useful enol ethers, since these are readily hydrolyzed into ketones. Depending upon the strength of the acid used for this hydrolysis, one can get the conjugated ketone or the non-conjugated one.



### Competition?

In many cases there will be >1 substituent on the arene being reduced. If both substituents are directing the reduction into the same place, then there is no ambiguity in the product formed. If however, there is an electron withdrawing group and electron donating group as existing substituents, the **electron withdrawing group (-I, -M) always controls the process.**



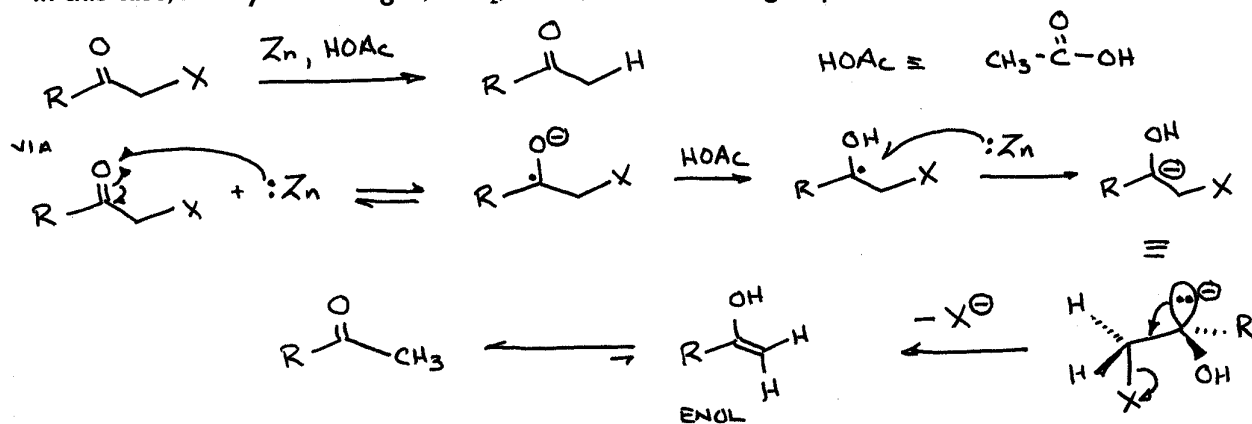
This is a particularly useful reaction. Just recall how tough reduction of arenes was by catalytic hydrogenation. The Birch reduction, on the other hand, is very easy and selective; many functional groups (OH, O<sup>-</sup>, CO<sub>2</sub>H, CO<sub>2</sub>R, NH<sub>2</sub>, and *non-conjugated* alkenes) are stable to these conditions.

Benzylic alcohols, however, are often reduced, as are ketones.

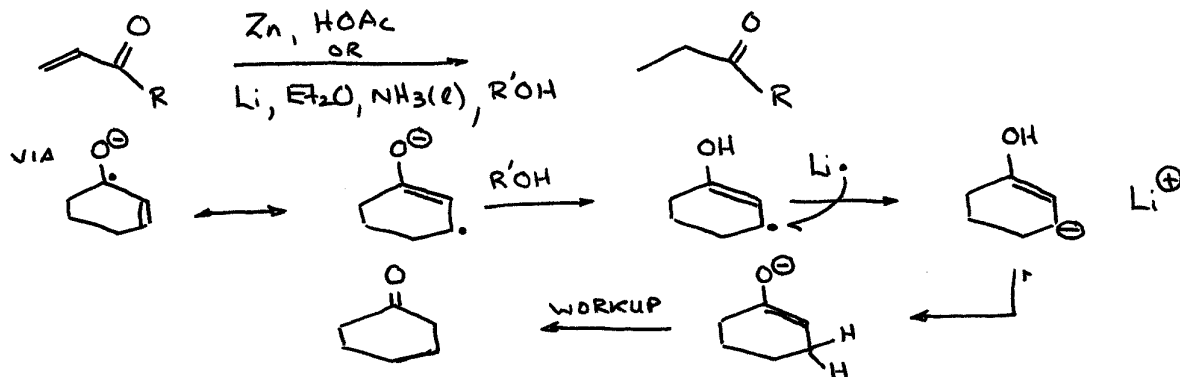
### 3) Metal Acid Reduction

If there is a reasonable leaving group (X) which is a substituent  $\alpha$ -to a ketone, it can also be reduced by a dissolving metal type reduction. In this case, the reagent involved is normally Zn metal in acetic acid (AcOH). These can be thought of as a much weaker version of the Clemmensen reduction, so this probably gives a good idea of how the Clemmensen starts.

In this case, X may be a halogen, -NR<sub>2</sub>, -OAc, or even -OH group.



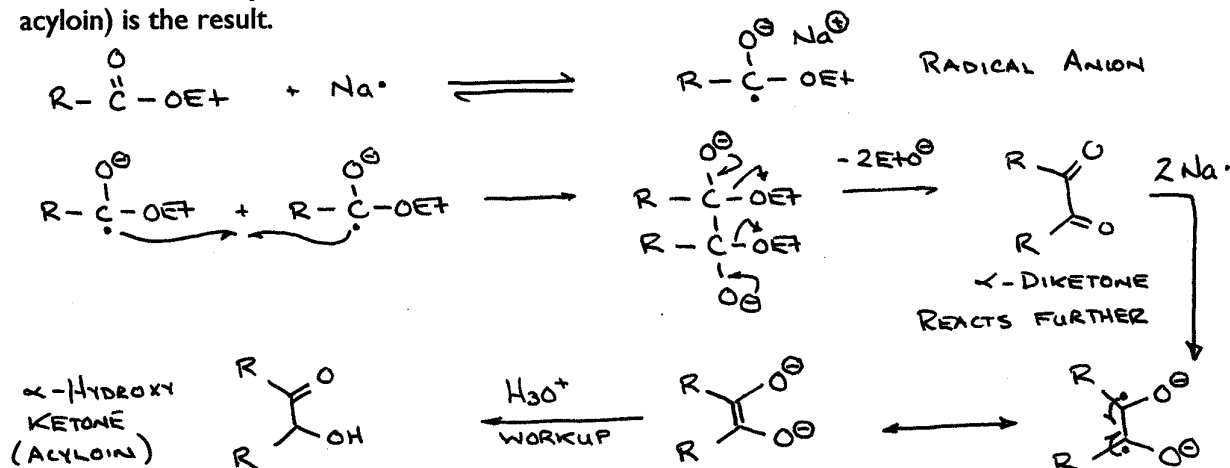
These conditions will also reduce  $\alpha,\beta$ -unsaturated carbonyls to the saturated carbonyls by a related mechanism. Birch-type conditions also work in these cases.



The  $\alpha$ -X group (and the  $\alpha,\beta$ -C=C) are much more readily reduced than the C=O itself, so the reaction stops at the ketone stage. Obviously, then, these types of substituents wouldn't stand up to the Clemmensen reduction

#### 4) Acyloin Condensation

Under the conditions just discussed above, esters are normally inert. If you push it a little, however, Na metal (or K) will transfer an electron to the  $\pi$ -system of the ester. In the absence of a proton source (so there is no alcohol added here), the radical portion of the radical anion will dimerize, forming a C-C bond. This gives an  $\alpha$ -diketone, which is unstable to the reaction conditions, and is further reduced by Na. Ultimately upon addition of water, an  $\alpha$ -hydroxy ketone (trivial name: acyloin) is the result.



The solvent here must be aprotic, due to the reasons discussed above. This can be  $Et_2O$  or THF or benzene, or one can go to toluene or xylene (dimethyl benzene) if one needs the higher boiling point (usually higher molecular weight cases).

This is an excellent way to dimerize two molecules of the same ester. Crossed acyloins, on the other hand, don't normally work well. The most useful application of the acyloin, though, is for cyclization reactions of diesters (i.e., intramolecular reactions). Not only is this excellent for forming rings of conventional size, but even medium and unusually large rings close relatively well by the acyloin, since the C-C bond forming reaction isn't reversible. In fact, the 1<sup>st</sup> reported catenane synthesis (one ring looped through another) was accomplished using an acyloin condensation for the ring closing step.

