

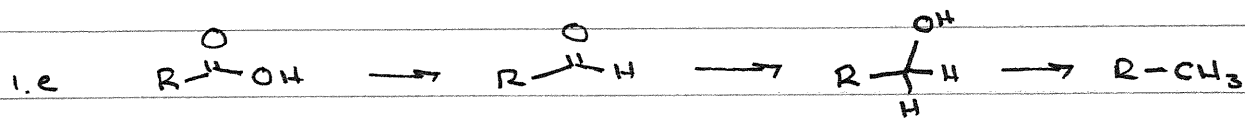
## REDUCTIONS

- UNTIL NOW WE'VE BEEN CONSIDERING CARBON SKELETON CONSTRUCTION

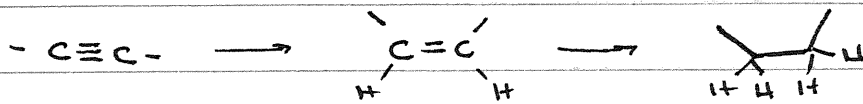
- NOW WISH TO LOOK AT FUNCTIONAL GROUP MODIFICATION  
- 'COMMONEST' - OXIDATION AND REDUCTION

## ORGANIC DEFINITION

REDUCTION - EITHER ADDITION OF H ATOMS OR REMOVAL OF O ATOMS



OR

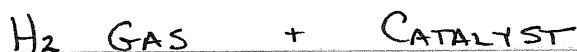


OXIDATION - REVERSE

WE ARE GOING TO ADDRESS REDUCTIONS FROM MOST COVALENT TO MOST IONIC

- SIMPLE MNEMONIC IS THAT V. COVALENT REAGENTS PREFER COVALENT SUBSTRATES, IONIC REAGENTS FAVOUR V. POLARIZED SUBSTRATES

### 1) CATALYTIC HYDROGENATION



CATALYST TENDS TO DICTATE WHICH FUNCTIONAL GROUPS CAN BE REDUCED

- TEND TO BE FINELY DIVIDED METAL POWDERS, OR ONES COATED ON AN INERT SUPPORT

Pd, Pt, Ni (R<sub>2</sub>Ni = RANEY NICKEL), Pd/C  
ON CHARCOAL (OR CARBON)

- SOLUBLE, SMALL MOLECULE CATALYSTS DO EXIST

Cl-Rh(PPh<sub>3</sub>)<sub>3</sub> WILKINSON'S CATALYST

- SOLVENTS - ANYTHING INERT

H<sub>2</sub>O, EtOH, CH<sub>3</sub>-C(=O)-OEt, CH<sub>3</sub>-CO<sub>2</sub>H

- TOUGH ONES CAN BE DONE UNDER HIGH TEMPERATURE AND HIGH P<sub>H<sub>2</sub></sub> - IN A BOMB.

- RELATIVE REACTIVITY OF CATALYSTS

a) 'LOWISH' - USED MOSTLY BECAUSE YOU HAVE THE MOST SELECTIVITY

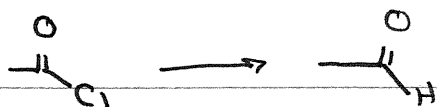
Pd, Pd/C, R<sub>2</sub>Ni, ClRh(PPh<sub>3</sub>)<sub>3</sub>

b) HIGHER - Pt, Ru

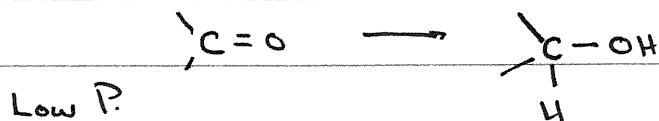
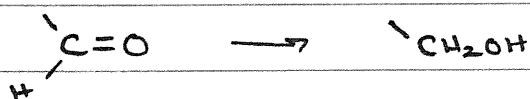
c) HIGHEST - Rh, Ir

HIGHER REACTIVITY CATALYSTS, OR EVEN SOME OF THE LOWISH ONES AT HIGH T, P CAN REDUCE EVEN BENZENES, BUT LET'S GO WITH THE SIMPLE ONES

SIMPEST

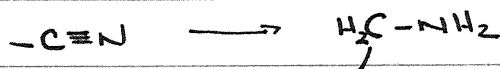


- THERE IS EVEN SOME  
SELECTIVITY WITH ALKENE  
TYPE



HIGH P?

HARDEST

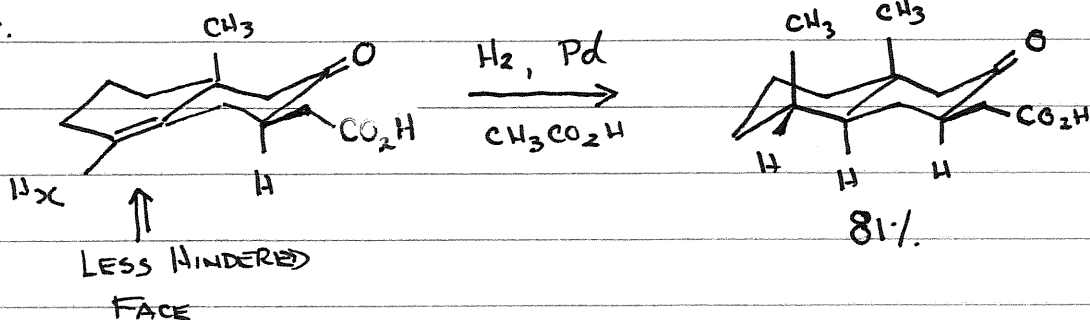


AROMATICS, ESTERS, AMIDES, ACIDS NEED MORE FORCING  
CONDITIONS.

### - CONSIDERATIONS

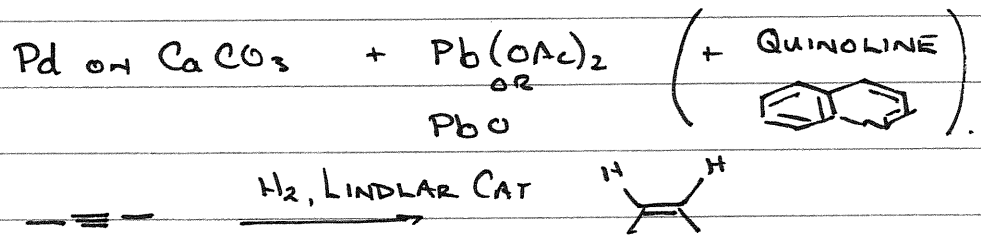
- H ATOMS ADD CIS - FROM THE LESS HINDERED SIDE OF  
ALKENE

i.e.

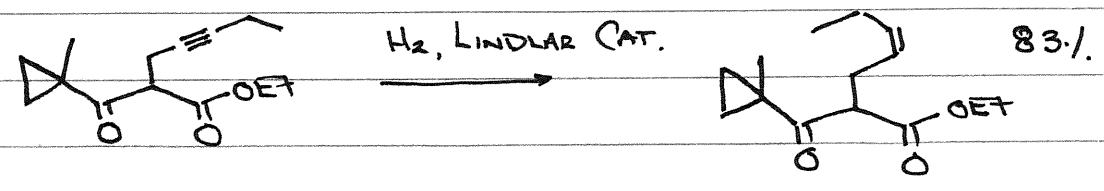


- SPECIFICALLY FOR ALKYNES

- ALKYNES AND ALKENES ARE CLOSE IN REACTIVITY, SO A SPECIALIZED, POISONED, CATALYST IS USED FOR SELECTIVE ALKYNE REDUCTION - LINDLAR CATALYST

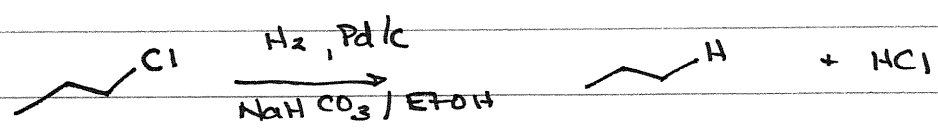


BEST WAY TO INTRODUCE A CIS-DISUBST. ALKENE



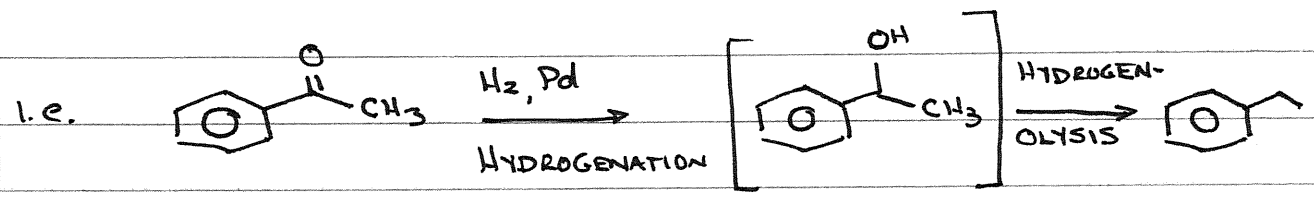
- COMPETING RXN - HYDROGENOLYSIS

- CLEAVAGE OF A C-X SINGLE BOND



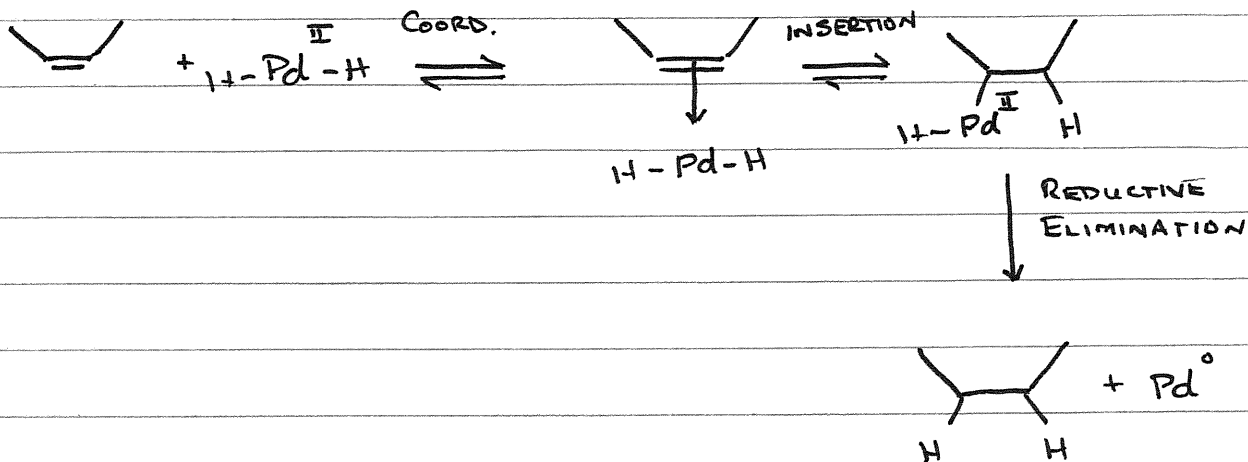
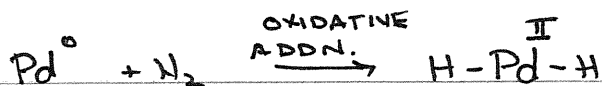
- CAN BE A NUISANCE OR CAN BE USEFUL

- SHOWS UP MOST WHEN X = REALLY GOOD LEAVING GROUP OR IN BENZYLIC SUBSTRATES.

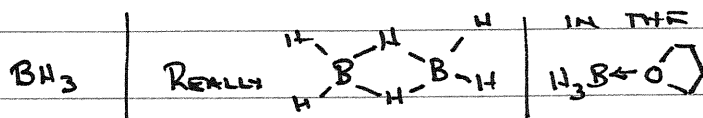


MECHANISM? - I'M TAKING SOME ARTISTIC LICENSE HERE, SINCE IT'S USUALLY ON A Pd SURFACE

- I'M EXTRAPOLATING TO SINGLE MOLECULES



## 2) HYDROBORATION

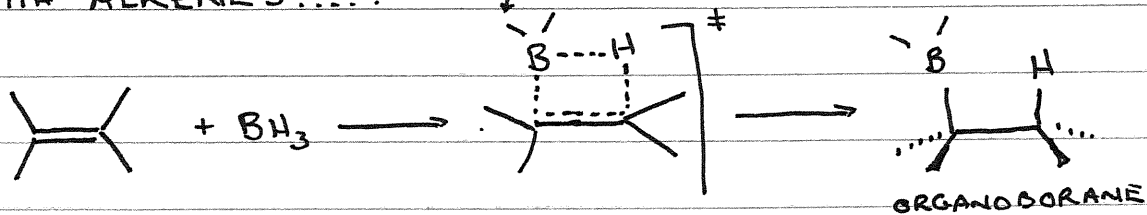


- HAVE NOW MOVED TO POLAR COVALENT REAGENT

$$\overset{\delta+}{\text{H}}\text{B}^{\delta-}-\text{H}$$

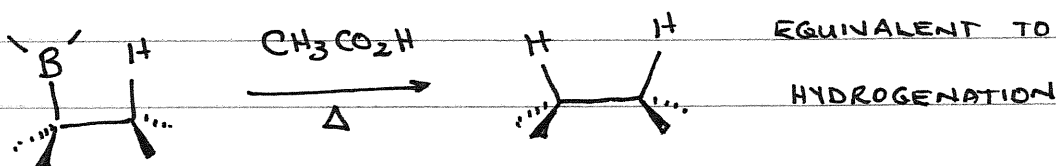
- FUNCTIONAL GROUP SELECTIVITY PATTERNS ARE SIMILAR TO CATALYTIC HYDROGENATION, WITH ONE HUGE EXCEPTION

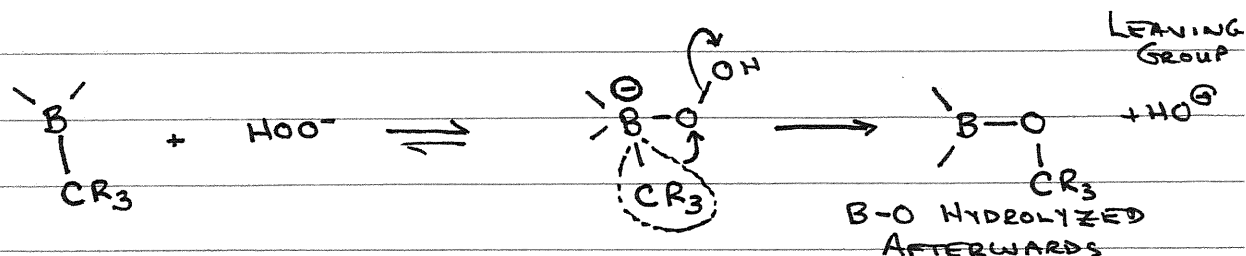
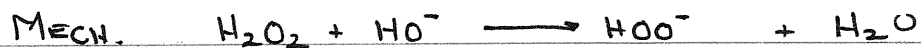
- WITH ALKENES.....



DON'T NORMALLY ISOLATE, BUT USUALLY

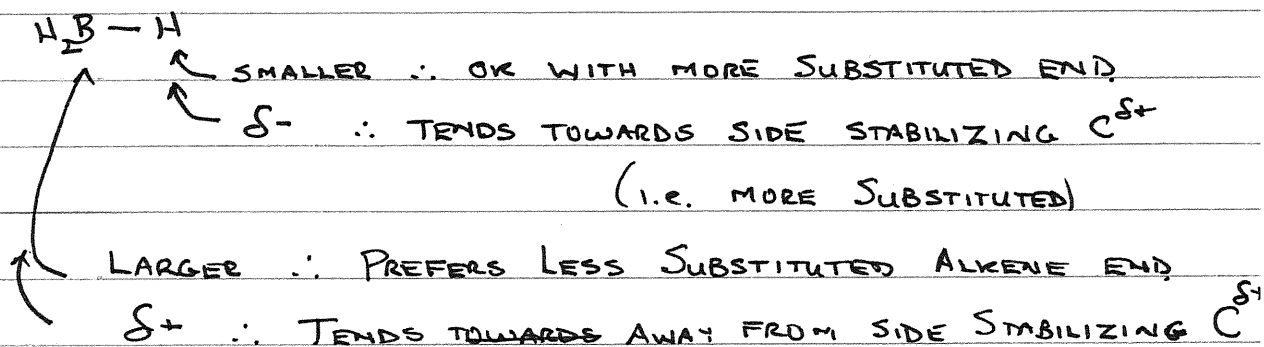
DO.....



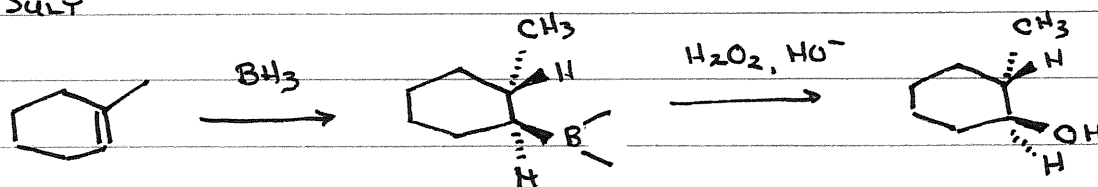


- FIRST HINT OF OUR NUCLEOPHILIC REARRANGEMENTS, AT END OF COURSE

RECALL: ADDN REGIOCHEMISTRY IS UNUSUAL, TOO



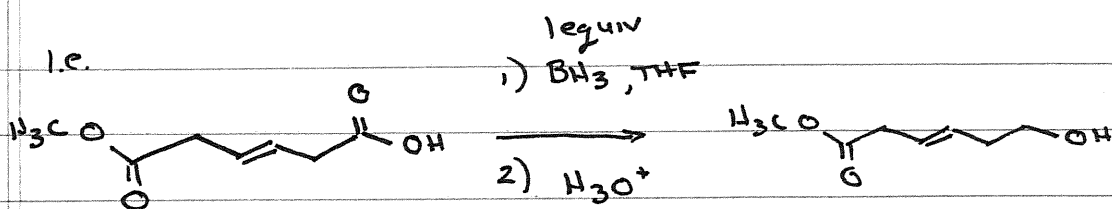
RESULT



OFTEN CALLED  
'ANTI-MARKOVNIKOV'

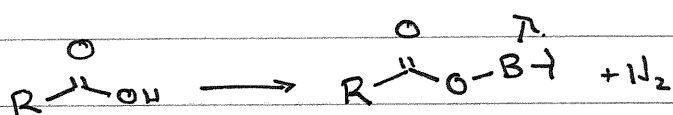
- NOW, THAT FUNCTIONAL GROUP SELECTIVITY REVERSAL  
- NORMALLY, CARBOXYLIC ACIDS ARE NEAR OR AT THE BOTTOM OF GROUPS THAT CAN BE REDUCED

- WITH HYDROBORATION, THEY ARE THE VERY EASIEST THINGS



WHY ARE ACIDS SO FAST ?

- A PARTIAL ANSWER



BORON ACTS AS (-M)

EWG FOR O ATOM

∴ MAKES IT V. EWG IN

TOTAL

∴ CARBONYL VERY REACTIVE

3) HYDRIDE ION  $\text{M}^+ \text{H}^-$  - VERY NUCLEOPHILIC

So  $\text{C}=\text{O}$  ATTACKED VERY READILY, WHEREAS  
 $\text{C}=\text{C}$  IS ANYWHERE FROM LOW REACTIVITY TO  
 ABSOLUTELY INERT.

- INVERSE TO CATALYTIC HYDROGENATION

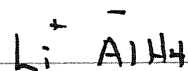
- NaH / KH ? NO. THEY ARE JUST TOO GOOD AS  
 BASES TO BE USED AS NUCLEOPHILES

- THE MOST COMMON ONES



SODIUM BOROHYDRIDE

MILDER, MORE SELECTIVE



LITHIUM ALUMINUM HYDRIDE

MORE REACTIVE, NOT SELECTIVE

- CAN ACTUALLY BE USED IN  
 ALCOHOL SOLVENTS, EVEN  $\text{H}_2\text{O}$

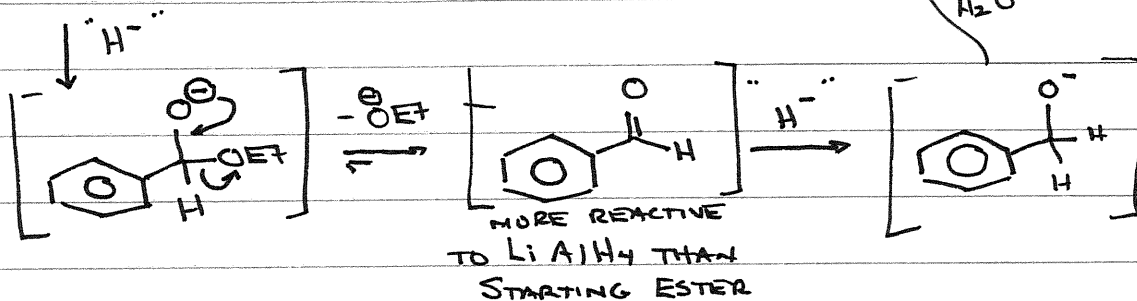
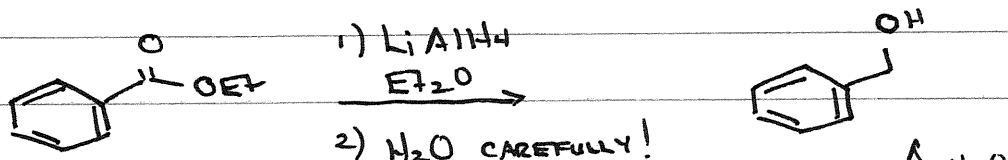
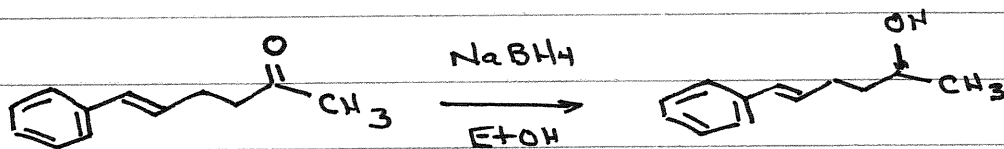
- MUST BE USED IN NON-  
 PROTIC SOLVENTS THF,  $\text{Et}_2\text{O}$

NaBH<sub>4</sub>

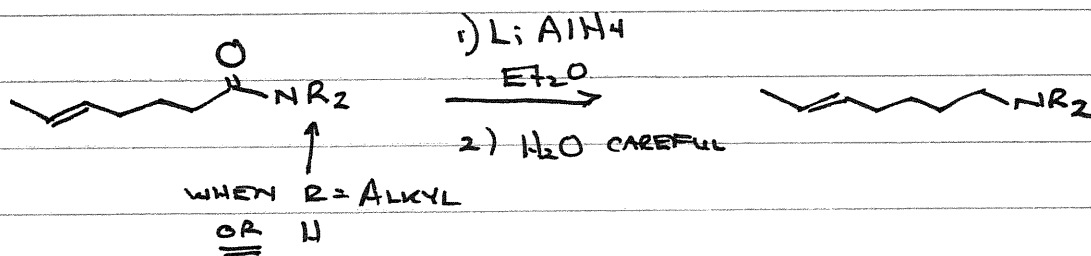
REACTS WITH ALDEHYDES > KETONES > ALL ELSE

LiAlH<sub>4</sub> - ALL CARBONYLS ... EVEN CARBOXYLIC ACID  
(ALBEIT A BIT MORE SLOWLY)

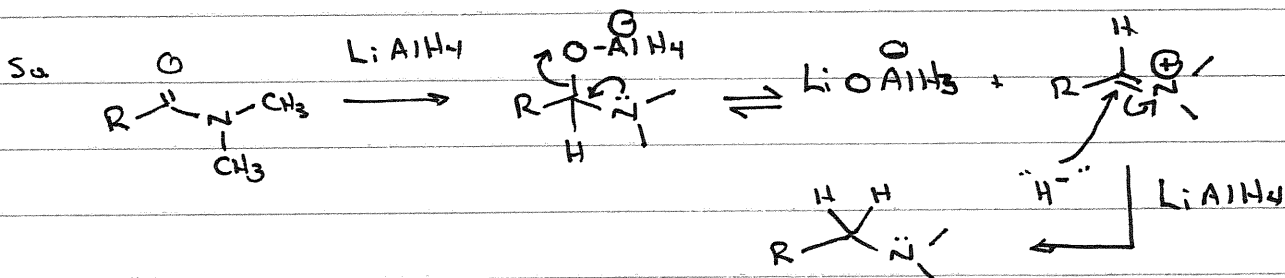
SOME EXAMPLES



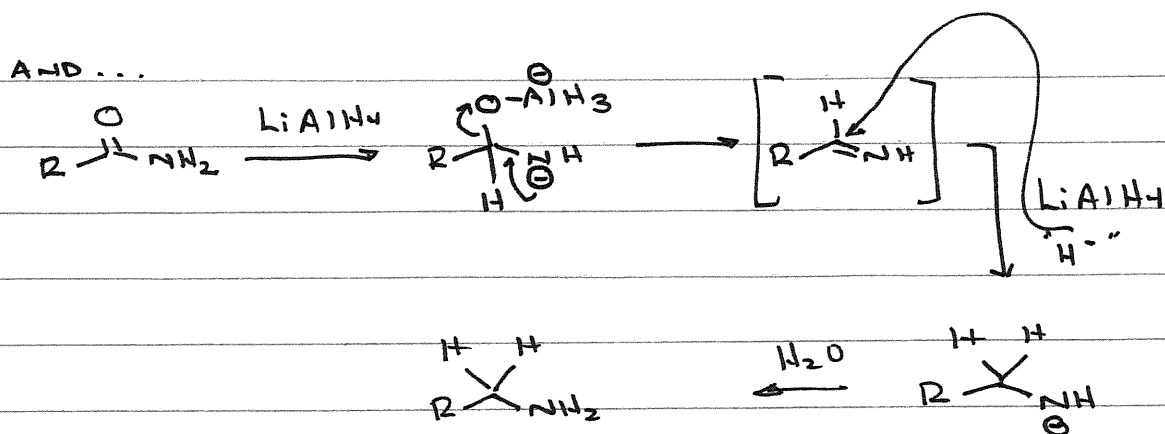
A NON-OBVIOUS ONE



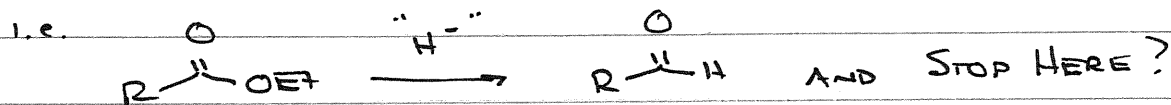
WHY? - THIS MAY REQUIRE SOME SUSPENDING OF DISBELIEF, BUT  $\ominus\text{O-AlH}_3$  IS A "GOOD ENOUGH" LEAVING GROUP.





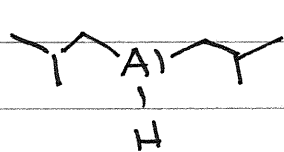


CAN WE OVERCOME THE ESTER "OVERREDUCTION" LIKE WE COULD FOR THE ADDITION OF  $\text{RLi}$ ,  $\text{RMgBr}$



## 2 SOLUTIONS.

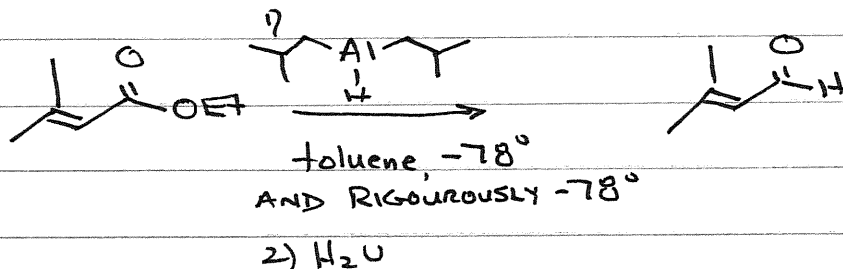
1) IN MANY CASES, WITH A SPECIALTY REDUCTANT DIBAL-H



DIISOBUTYLALUMINUM HYDRIDE

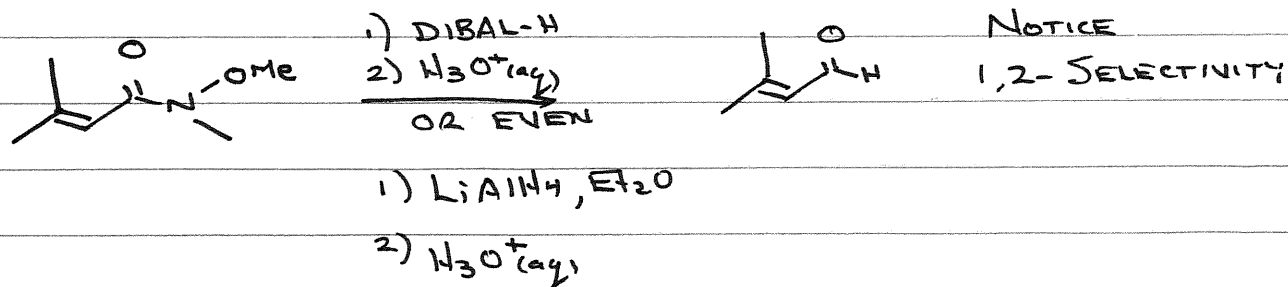
- AND CAREFUL CONTROL OF LOW TEMP. ( $-78^\circ$ ) AND A NON-POLAR SOLVENT

THE TETRAHEDRAL INTERMEDIATE HANGS TOGETHER LONG ENOUGH TO STOP AT 1 REDUCTION



- IF T GETS TOO HIGH, OVERREDUCTION TO ALCOHOL OCCURS

2) THE WEINERB AMIDES WORK BEAUTIFULLY HERE, TOO.



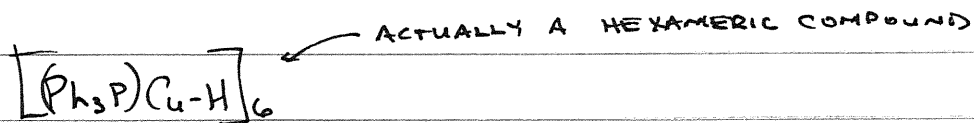
1,2-VS 1,4-??

- "HYDRIDE" SOURCES, INCLUDING DIBAL-H, HAVE A 1,2-ADDN PREFERENCE

- IN SOME CASES, THE ADDITION OF  $\text{CeCl}_3$  IS NEEDED TO GIVE COMPLETE 1,2-SELECTIVITY  
( $\text{NaBH}_4 + \text{CeCl}_3$  IS CALLED LUCHE REAGENT.)

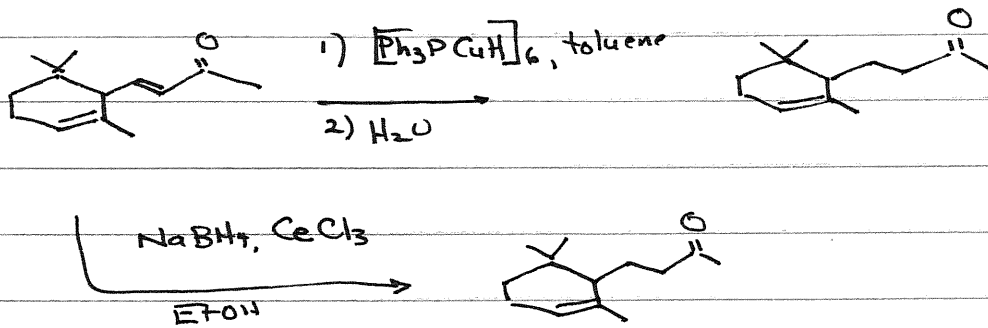
AND IF YOU WANT 1,4- WITH A HYDRIDE TYPE REAGENT?

- THERE IS ONE HYDRIDE SOURCE THAT IS AN ORGANOCOPPER



- REACTS IN A CONJUGATE (1,4-) ADDITION MODE WITH

$\alpha,\beta$ -UNSAT. KETONES, ALDEHYDES, ESTERS

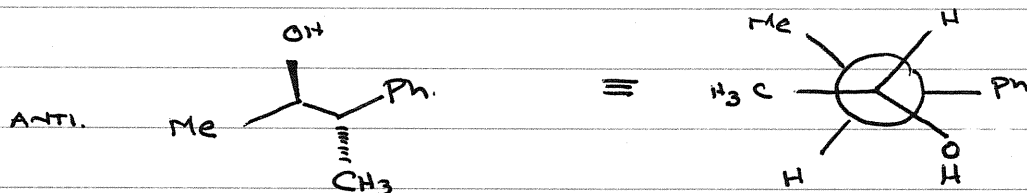
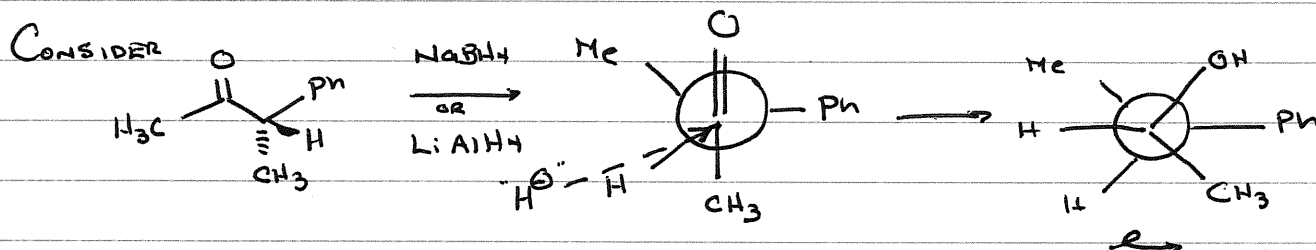
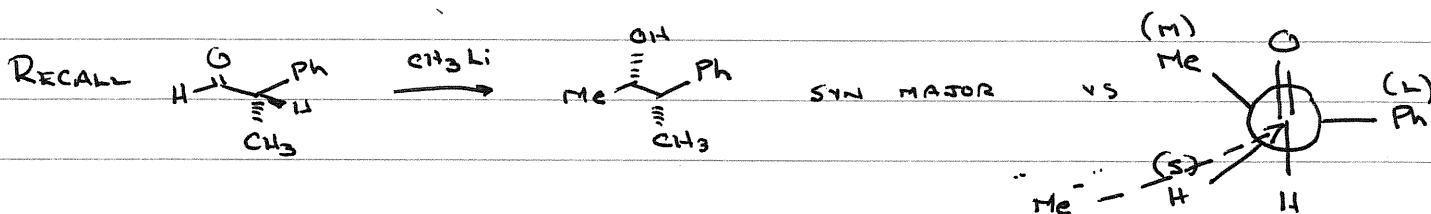


# STEREOCHEMISTRY IN HYDRIDE REDUCTIONS

- THIS RULES WE DISCUSSED BEFORE ON THE STEREOCHEMISTRY OF ORGANO-METALLIC ADDNS TO ALDEHYDES AND KETONES ALSO APPLIES TO "H<sup>-</sup>" NUCLEOPHILES

i.e. FELKIN-AHN, CRAM CHELATE, AXIAL/EQ. ADD TO CYCLOHEXANONES

- THIS CAN BE V. ADVANTAGEOUS,



∴ IF SWITCH FROM - ALDEHYDE S.M. W R<sup>-</sup> NUCLEOPHILE TO...  
R<sup>-</sup> KETONE W "H<sup>-</sup>" NUCLEOPHILE,  
ONE GETS THE OPPOSITE DIASTEREOMER. - GENERAL RULE

## CHELATION CONTROL.

- COUNTERION TO TWO COMMON REAGENTS ARE Li<sup>+</sup> AND Na<sup>+</sup>

∴ NOT METALS PRONE TO PARTICIPATE IN CHELATION CONTROL

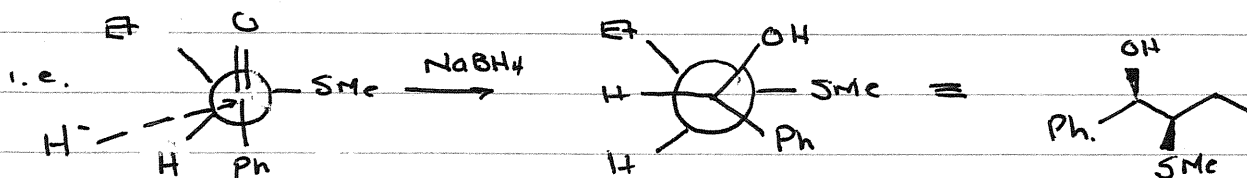
SO HOW DO WE GET THIS TO OCCUR IF WE WANT IT

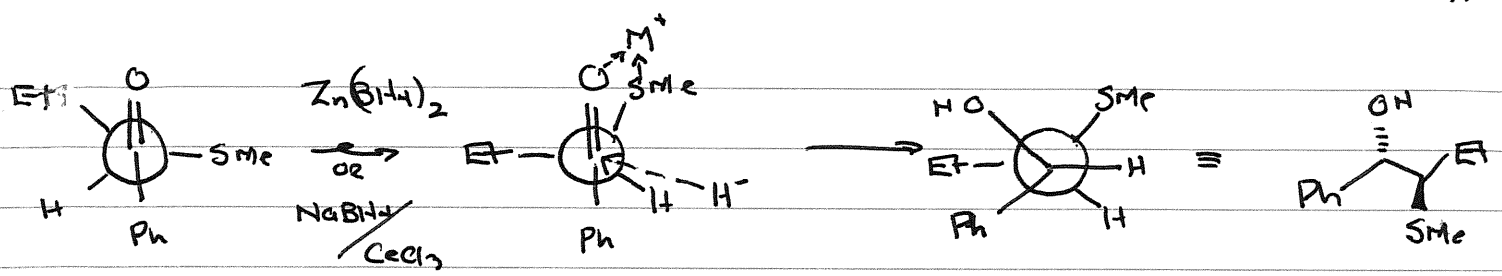
1) LUCHE REAGENT CeCl<sub>3</sub> + NaBH<sub>4</sub>

Zn<sup>2+</sup>, Ce<sup>3+</sup> DO PARTICIPATE

2) Zn(BH<sub>4</sub>)<sub>2</sub>

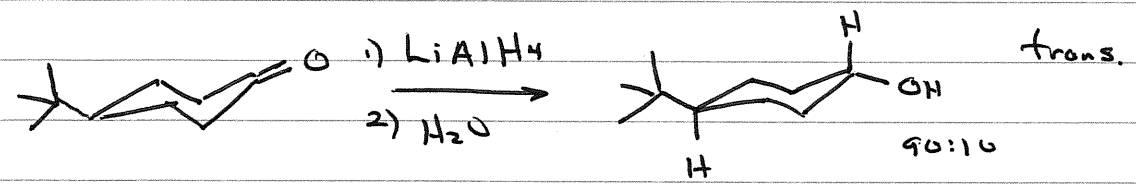
IN CHELATION





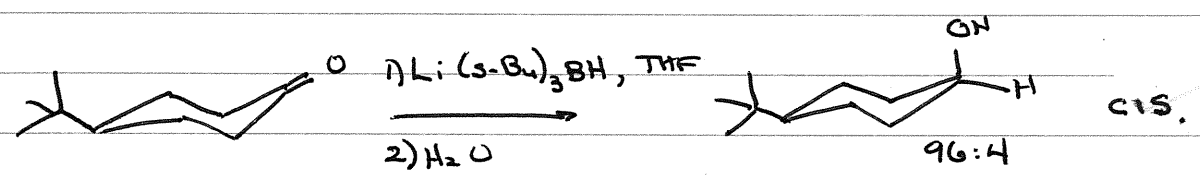
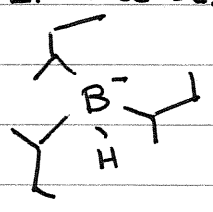
### ATTACK ON CYCLOHEXANONES.

$H^-$  IS AS SMALL AS YOU CAN GET.  $\therefore$  AXIAL ATTACK



How would you GET EQUATORIAL ATTACK

$Li^+ (sec-Bu)_3BH^-$  LITHIUM TRI-SEC-BUTYL BOROHYDRIDE  
 (LITHIUM SELECTRIDE).



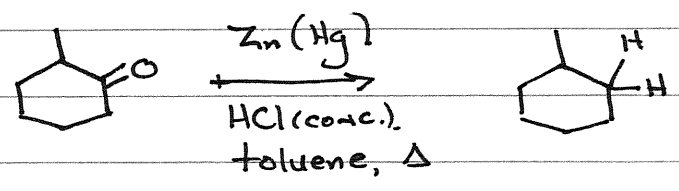
# REDUCTION OF CARBONYLS $\Rightarrow$ CH<sub>2</sub>

## -3 GENERAL METHODS

- 1 V. ACIDIC
  - 1 V. BASIC
  - 1 'HYDROGENATION LIKE'
- } EACH HAS SITUATIONS WHERE IT'S A PROBLEM

### 1) CLEMMENSEN

- V. ACIDIC - USES Zn-MERCURY AMALGAM IN ACID

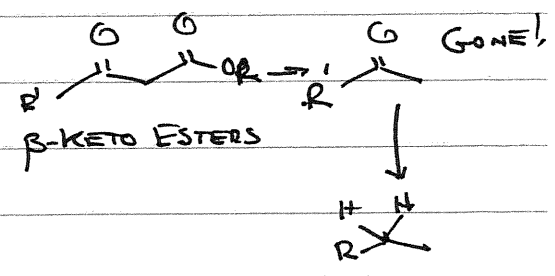
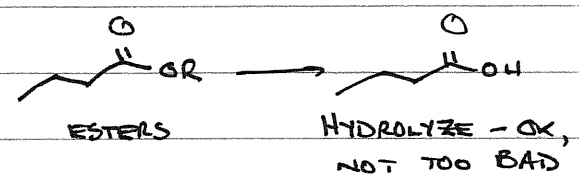
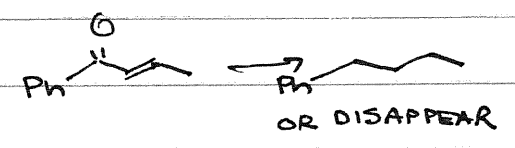
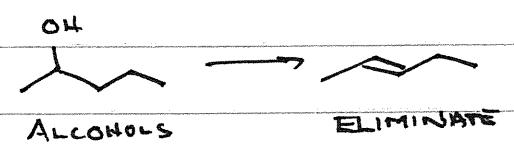
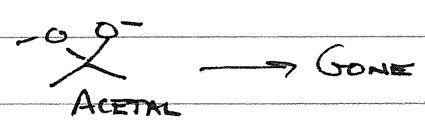


MECH. NOT WELL UNDERSTOOD - RADICAL INTERMEDIATES PROBABLE

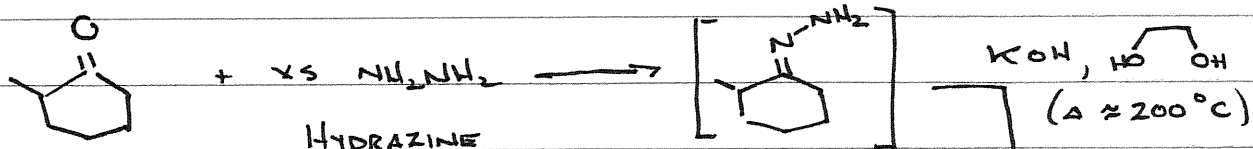
- ZINC CARBENE POSSIBLE

- MAY GIVE A SPECULATIVE ANSWER ONCE WE GET TO DISSOLVING METAL REDUCTIONS.

SINCE IT'S SO ACIDIC, SEVERAL GROUPS DON'T SURVIVE



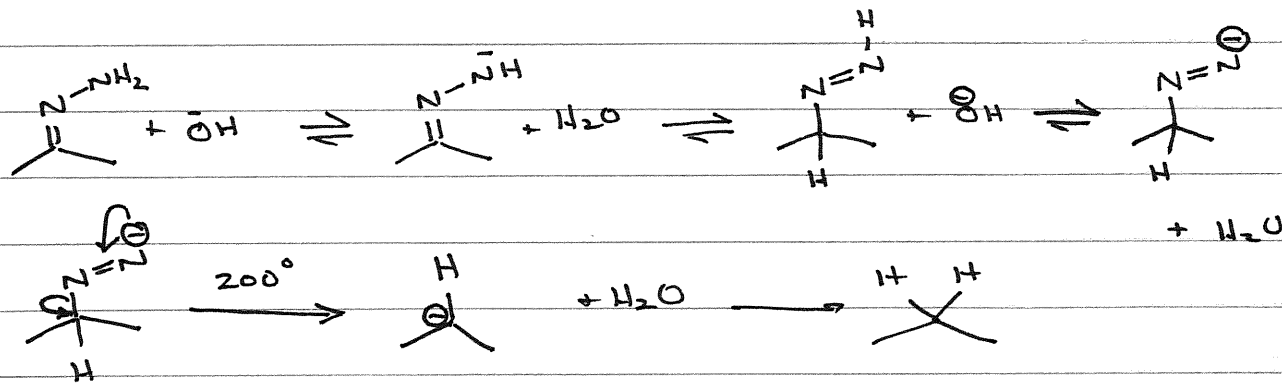
2) WOLFF-KISHNER (HUANG-MINLON MODIFICATION)



NOTE: NEW MODIFICATION  
 $KO^+Bu$  IN DMSO GOES AT  $r^+$

CAN ISOLATE  
 OR CHOOSE  
 NOT TO

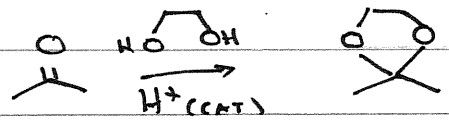
MECH. IS UNDERSTANDABLE HERE



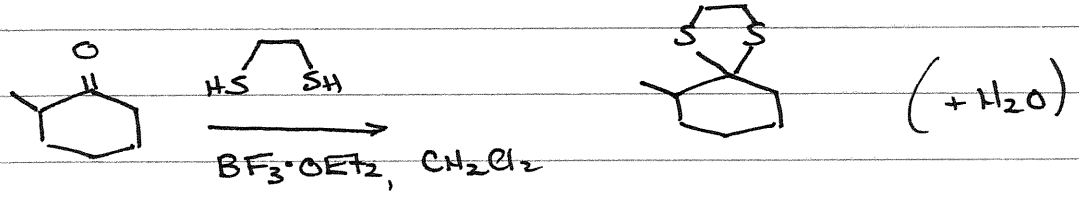
- FUNCTION GROUP TOLERANCE NOT GREAT  
 ESTERS, AMIDES HYDROLYZE, HALOGENS, CYANOS,  
 NITRO GROUP REACTION
- ISOLATED ALCOHOLS, ACETALS PROBABLY ARE OK
- MAYBE SLIGHTLY LESS BAD THAN CLEMMENSEN

3) DITHIOACETAL ROUTE (1,3-DITHIANE) - MOZINGO REDUCTION

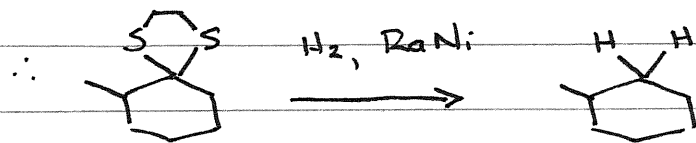
- RECALL ACETALS



- DITHIOACETALS ARE MADE SIMILARLY, EXCEPT USUALLY IT'S  
 A LEWIS ACID



DITHIOACETALS ARE V. SIMILAR TO ACETALS, EXCEPT THE C-S BOND HAS A HIGH PROPENSITY FOR HYDROGENOLYSIS WHEN Ni IS USED AS CATALYST



- MUCH Milder THAN OTHER TWO REDUCTIONS
- THERE ARE EVEN REPORTED CASES WHERE ALKENES SURVIVE

NOTE: AT THIS POINT, YOU CAN EVEN PROBABLY MAKE UP YOUR OWN METHOD.

- GENERAL APPROACH

