

### Reduction

1. Please rank the following reducing agents in order of reactivity:  $\text{LiAlH}_4$ ,  $\text{LiBH}_4$ ,  $\text{NaBH}_4$ . Explain your answer.

We need to consider:

1) **The cation.**

Both lithium and sodium act as Lewis acids and coordinate to the oxygen atom of the carbonyl group. This increases the amount of positive charge density on the carbonyl carbon, rendering it more electrophilic. Lithium is a stronger Lewis acid than sodium, making  $\text{LiBH}_4$  a stronger reducing agent than  $\text{NaBH}_4$ , i.e.  $\text{LiBH}_4 > \text{NaBH}_4$ .

2) The **electronegativity** of the atom at the centre of the anion.

The more electronegative the atom is, the less electron density will be on the hydrides; the less electron density on the hydrides, the less able they are to act as nucleophiles to reduce the carbonyl, i.e.  $\text{LiAlH}_4 > \text{LiBH}_4$ . (In other words: Because aluminium is less electronegative than boron, the Al-H bond ( $\Delta E = 0.6$ ) in  $\text{LiAlH}_4$  is more polar than the B-H bond ( $\Delta E = 0.16$ ) in  $\text{LiBH}_4$ , making  $\text{LiAlH}_4$  a stronger reducing agent.)

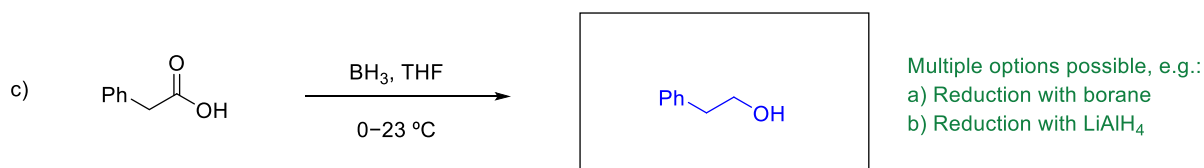
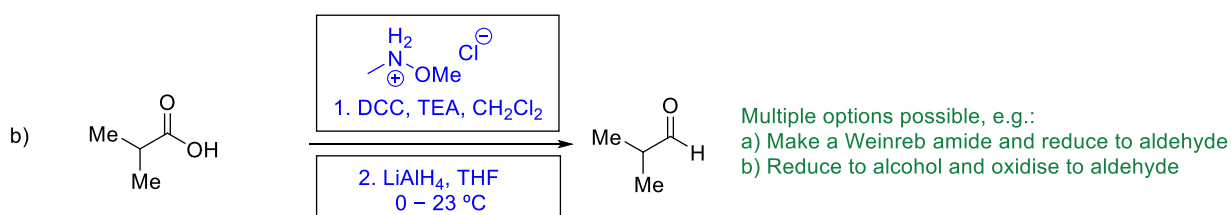
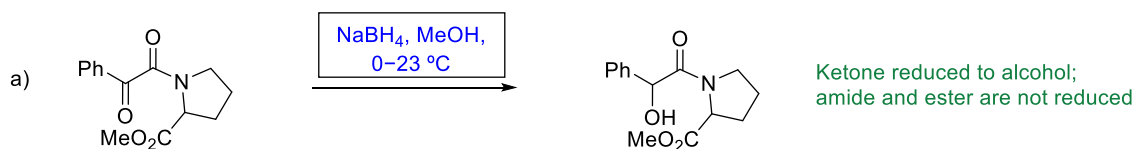
Pauling electronegativity of H is 2.20

Pauling electronegativity of Al is 1.61

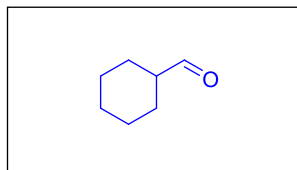
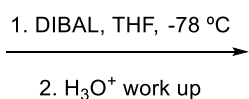
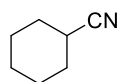
Pauling electronegativity of B is 2.04

The two factors combined give the following order in reactivity:  $\text{LiAlH}_4 > \text{LiBH}_4 > \text{NaBH}_4$

2. Provide suitable reagents, reaction conditions and products for the following transformations. Include the mechanism for parts c), d), f). (*For mechanisms see below*)

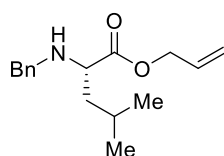
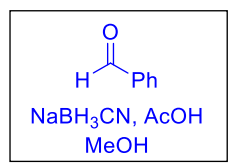
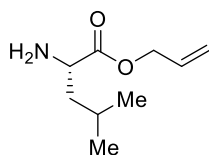


d)



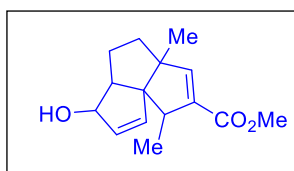
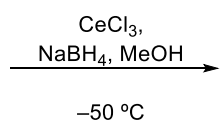
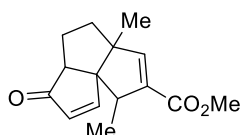
Reduction of nitrile to imine followed by imine hydrolysis

e)



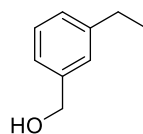
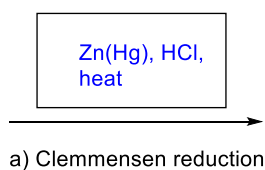
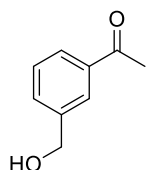
**Reductive amination;**  
Formation of iminium ion, which is then reduced to amine (aldehyde is not reduced with NaBH<sub>3</sub>CN)

f)



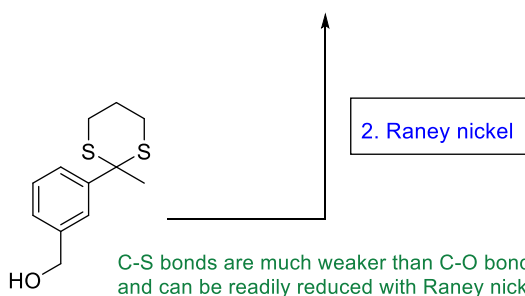
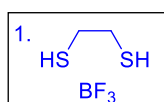
**Luche reduction:**  
Selective reduction of  $\alpha,\beta$ -unsaturated ketones to alcohol in presence of a Lewis acid. Esters, aldehydes and non-conjugated ketones are not reduced.

g)



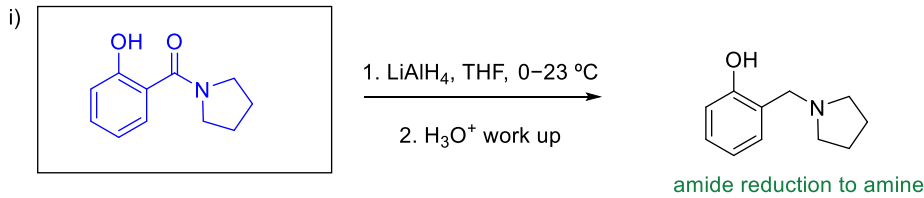
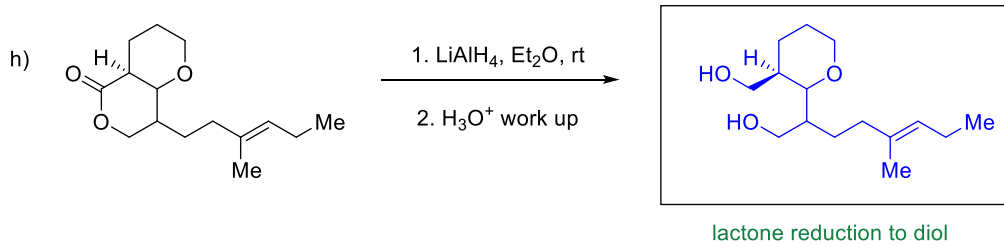
Multiple options possible:  
a) Clemmensen reduction  
b) Mozingo reduction  
c) Wolff-Kishner reduction (see lecture: N<sub>2</sub>H<sub>4</sub>, KOH,  $\Delta$ T)

b) Mozingo reduction

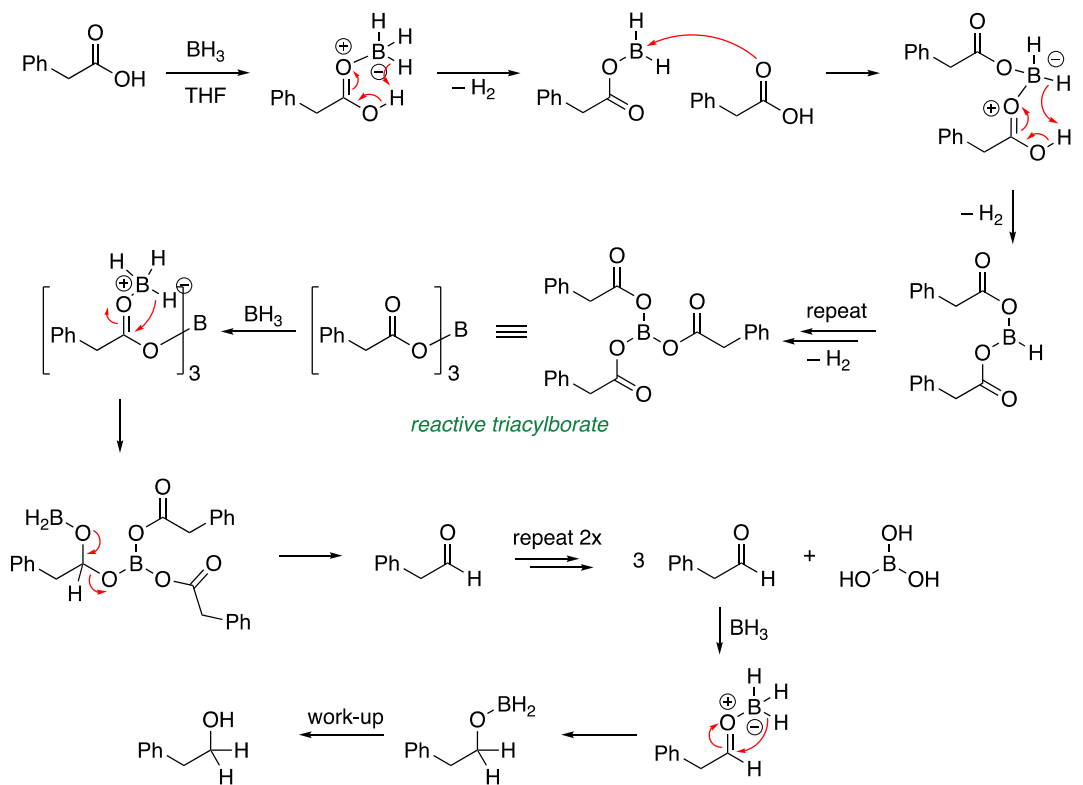
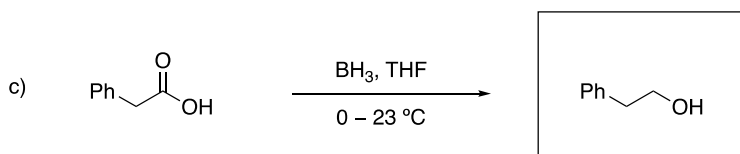


2. Raney nickel

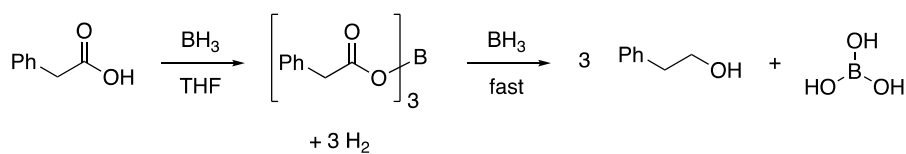
C-S bonds are much weaker than C-O bonds and can be readily reduced with Raney nickel



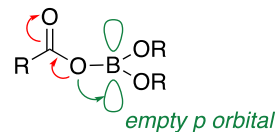
**Mechanisms:**



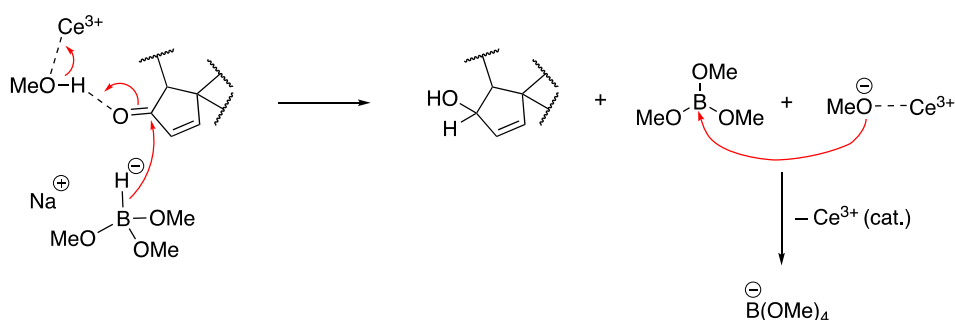
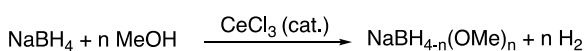
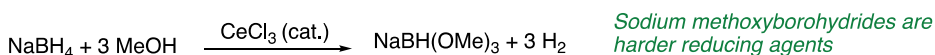
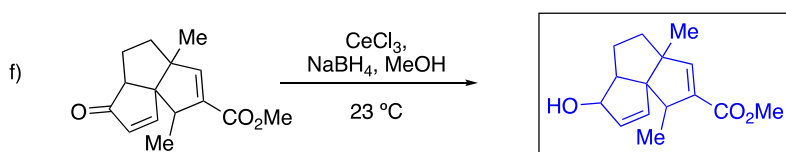
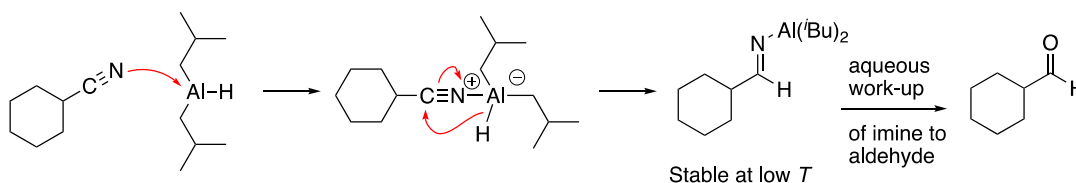
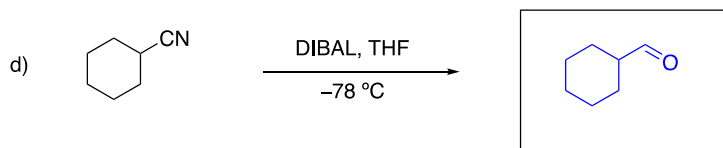
Overall:



- Borane reacts with  $\text{RCO}_2\text{H}$  to form triacylborates with evolution of hydrogen gas.
- Triacylborates = 'boron esters'.
- Esters are usually less electrophilic than ketones, but these boron esters are much more reactive.
- Oxygen next to boron has to share its electrons (lone pair) between the carbonyl group and the boron's empty p orbital.
- See Clayden 2<sup>nd</sup> Ed., Chapter 23, page 532 to find out more.



Note: The mechanism can be shortened. No need to show the same steps three times. This is just a complete stepwise mechanism to help you follow the reaction.

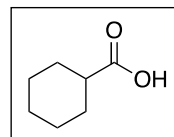


- The Luche reduction is an organic reaction used to convert an  $\alpha,\beta$ -unsaturated ketone to an allylic alcohol using cerium trichloride, sodium borohydride, and an alcohol solvent.
- The role of the cerium is to coordinate to the alcohol, making its proton more acidic, which allows for it to be abstracted by the carbonyl oxygen of the ketone starting material.
- In other words,  $\text{Ce}^{3+}$  facilitates H-bonding of solvent to carbonyl group in order to activate the carbonyl group making the carbon of  $\text{C}=\text{O}$  more electrophilic.  $\text{Ce}^{3+}$  can also directly coordinate to the carbonyl oxygen, activating the  $\text{C}=\text{O}$ . Hence, 1,2-reduction is observed.

- The  $\text{NaBH}_4$  starting reagent also reacts with the cerium activated alcohol to form a series of alkoxyborohydrides and these "hard reagents" result in the 1,2-hydride attack on the protonated carbonyl to give the final allylic alcohol product
- $\text{BH}_4^-$  is a soft reagent and would favour 1,4-addition, but  $\text{NaBH}(\text{OMe})_3$  is hard and reacts preferentially via 1,2-addition.
- The  $\text{Ce}^{3+}$  activated carbonyl group is a hard acid and  $\text{NaBH}(\text{OMe})_3$  is a hard base  $\rightarrow$  HSAB concept (the hard alkoxyborohydride reacts with the hard ketone).
- Esters are not reduced with  $\text{NaBH}_4$ .

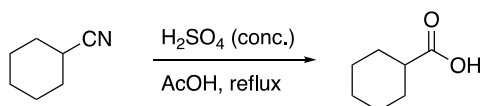
3. How would you make the following molecules?

a) Provide 3 different ways to make this carboxylic acid:

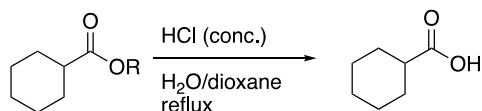


Possible ways to make a **carboxylic acid**:

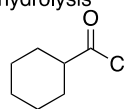
1) Nitrile hydrolysis



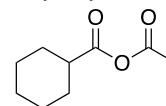
2) Ester hydrolysis



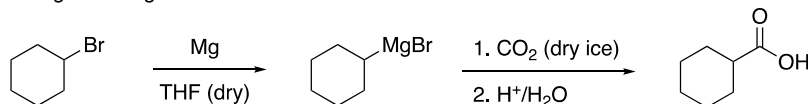
Or acyl chloride hydrolysis



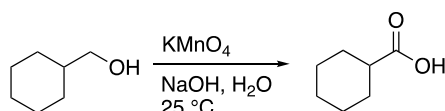
Or anhydride hydrolysis



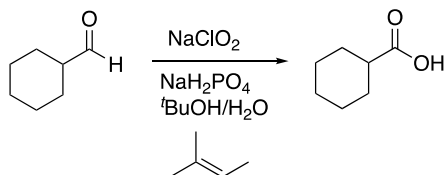
3) Via Grignard reagent



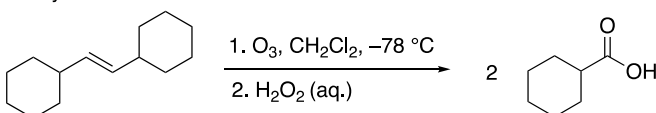
4) Oxidation of alcohol



5) Pinnick oxidation

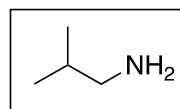


6) Ozonolysis

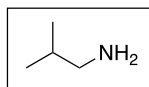


+ any other good example

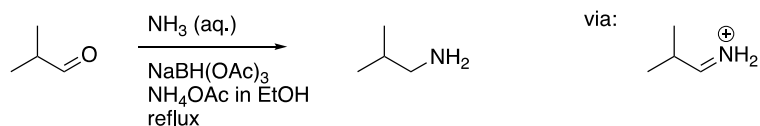
b) Provide 3 different ways to make this amine:



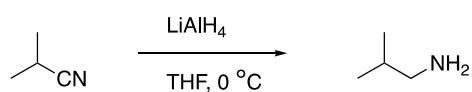
Possible ways to make an **amine**:



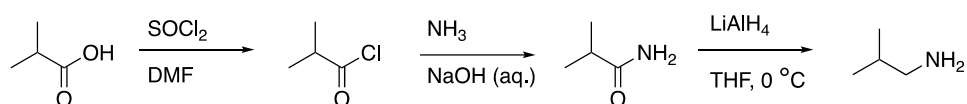
1) Reductive amination



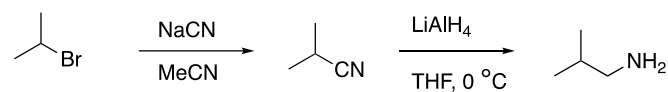
2) Cyano group (nitrile) reduction



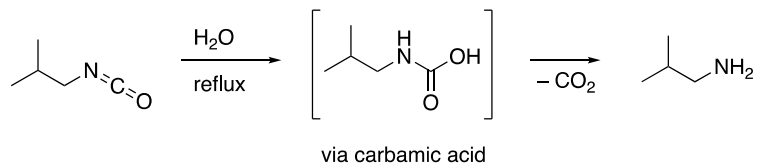
3) Carboxylic acid – acyl chloride – amide – amine



4) Alkyl bromide – nitrile – amine



5) From isocyanate



+ any other good example

4. Provide the product and the reaction mechanism for the following reaction.

