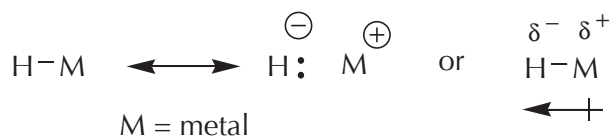


USING HYDROGEN AS A NUCLEOPHILE IN HYDRIDE REDUCTIONS

Like carbon, hydrogen can be used as a nucleophile if it is bonded to a metal in such a way that the electron density balance favors the hydrogen side. A hydrogen atom that carries a net negative charge and bears a pair of unshared electrons is called a **hydride ion**. How much negative charge density resides on hydrogen depends on the difference in electronegativity between hydrogen and the metal it's bonded to.



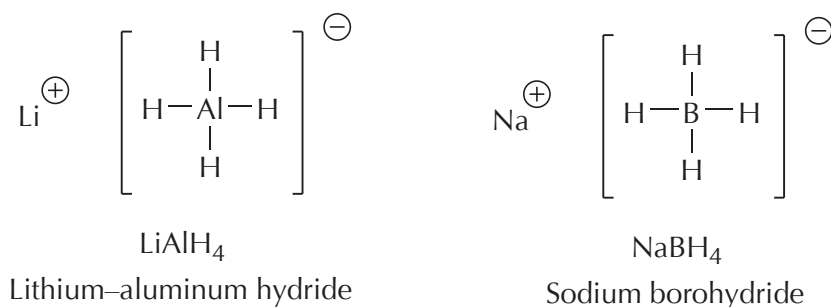
The following table shows the difference in electronegativity between hydrogen and some common metals. Obviously, the greater the difference in electronegativity, the greater the density of negative charge on hydrogen, and the greater the reactivity of the compound as a **hydride delivering agent**.

HYDRIDE DELIVERING AGENT	METAL ELECTRONEGATIVITY	ELECTRONEGATIVITY DIFFERENCE
H-Na (NaH) sodium hydride or H-Li (LiH) lithium hydride	1.0	1.1
H-Ca (CaH ₂) calcium hydride	1.1	1.0
H-Al aluminum hydrides	1.5	0.6
H-B boron hydrides	2.0	0.1

Decreasing
reactivity
↓

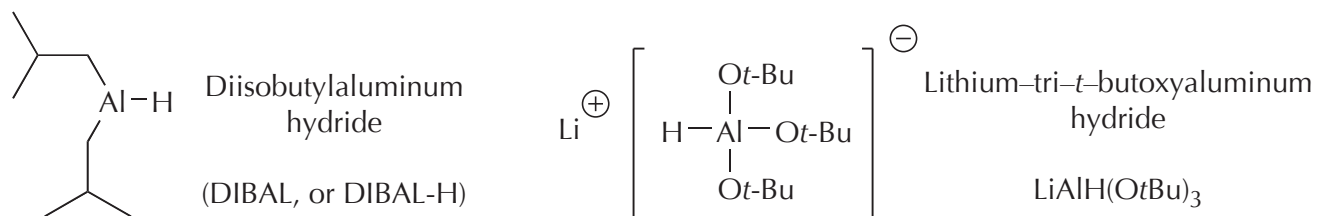
Hydrogen electronegativity is 2.1

For many routine synthetic purposes, sodium and lithium hydrides are simply too reactive, requiring special handling such as inert atmosphere, and careful control of reaction conditions. Calcium hydride is more manageable because it is less reactive, and it is preferred in many reactions. However, many reductions of organic compounds such as carbonyl and carboxyl compounds use aluminum and boron hydride reagents. They are manageable in the laboratory, they are commercially available, and they can be modified to fine-tune their reactivity to various degrees for specific uses. Two of the most widely used hydride reagents in organic synthesis are lithium aluminum hydride, and sodium borohydride, shown below.

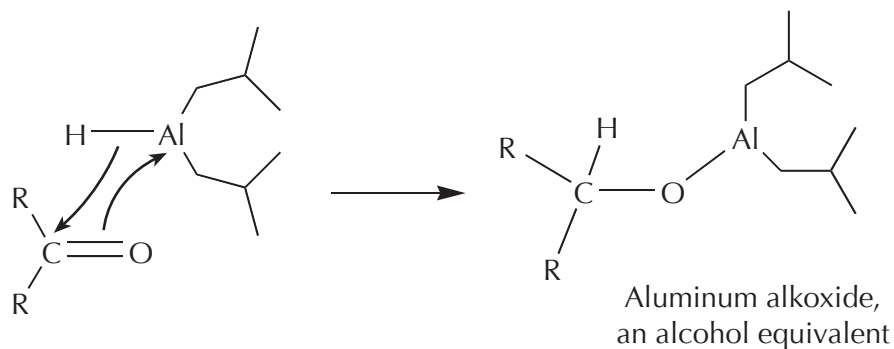


As can be seen from their structure, lithium and sodium are not bonded to hydrogen. They are merely counterions for the negative portion, which is the actual hydride-delivering agent. Second, they are each capable of delivering up to 4 hydride equivalents. Last, we expect sodium borohydride to be less reactive, and therefore more selective, than lithium aluminum hydride. This is in fact the case.

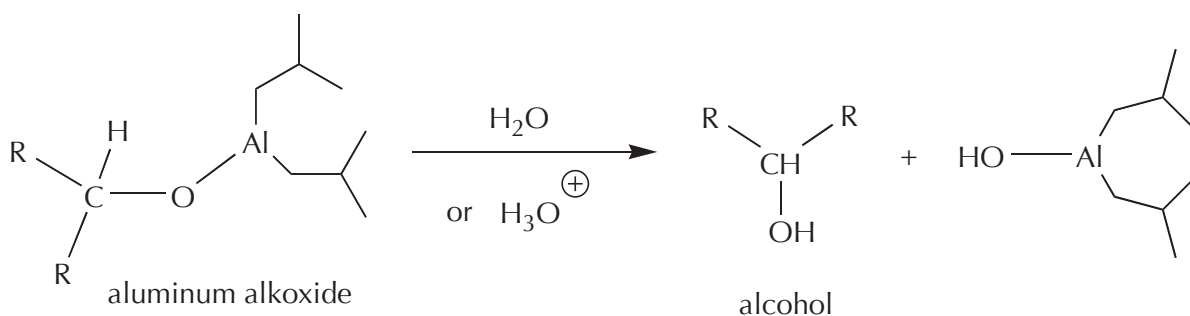
Another way to control the reactivity of these compounds is to replace two hydrogens with bulky alkyl groups, as in the following structures.



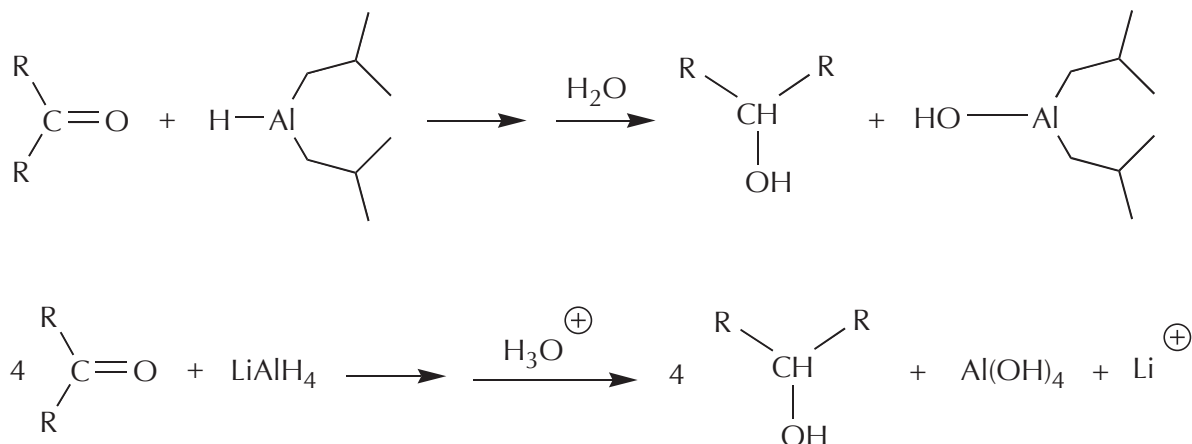
These modifications do two things. The bulky groups prevent fast access of the hydride reagent to the electrophile by a steric effect, and each of them is capable of delivering only one hydride ion instead of four. The mechanism of the hydride attack on a carbonyl carbon shown below demonstrates how these reagents in general work. The hydride-delivering agent must approach the carbonyl carbon until it's close enough to deliver the hydride ion. At the same time, the pi electrons from the C=O bond move to create a new bond to the metal, forming an alkoxide ion as the product, which is an alcohol functional group equivalent.



The last step towards formation of the alcohol is then protonation of the alkoxide using water or dilute acid. **As in the case of Grignard reactions, this step is always assumed, and as such it may or may not be shown explicitly.**



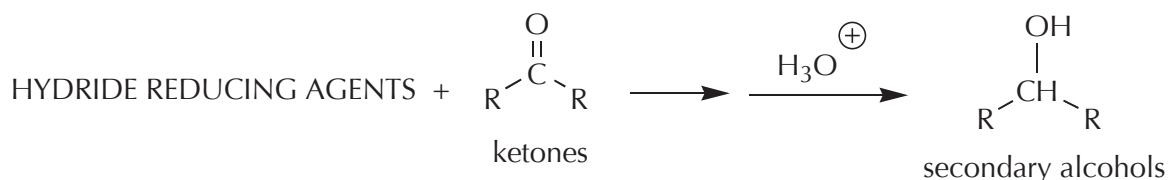
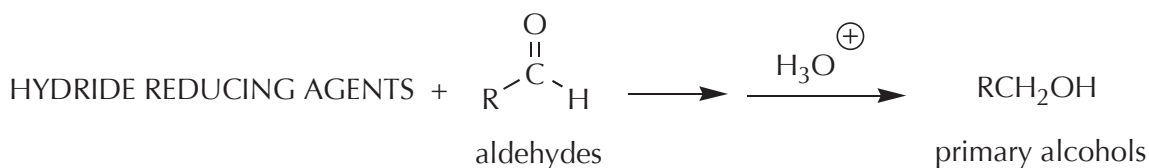
Balanced equations reflect the number of hydride ions delivered for complete reduction:



SYNTHETIC OUTCOMES

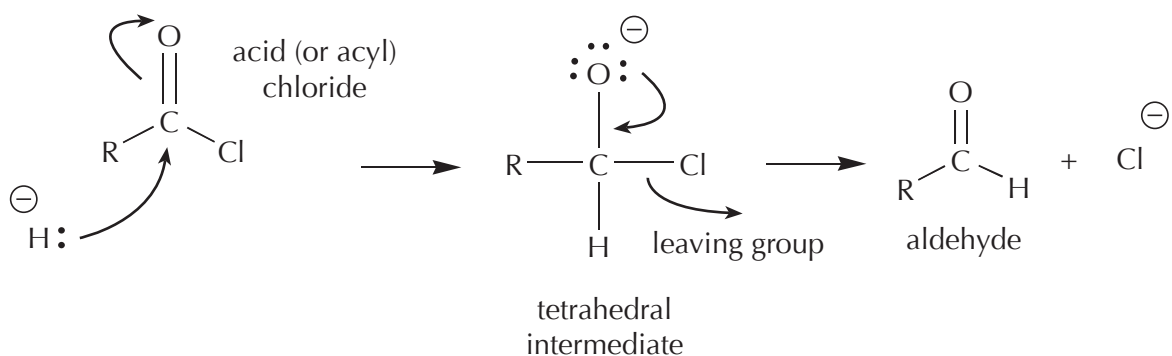
The attack of hydride ions as nucleophiles on electrophilic carbon creates a new C–H bond, **therefore the carbon atom undergoes a reduction** (gain of bonds to hydrogen). Because of this, this type of reactions is commonly referred to as **reductions**, even though the mechanism is a nucleophilic addition. Likewise, the hydride delivering agent is more commonly referred to as a **hydride reducing agent**, or just **reducing agent**.

Unlike the attack of carbon nucleophiles on a carbonyl carbon, the attack of a hydride ion produces no new C–C bonds and therefore there is no expansion of the carbon chain. Consequently, only primary and secondary alcohols can be made by this approach.

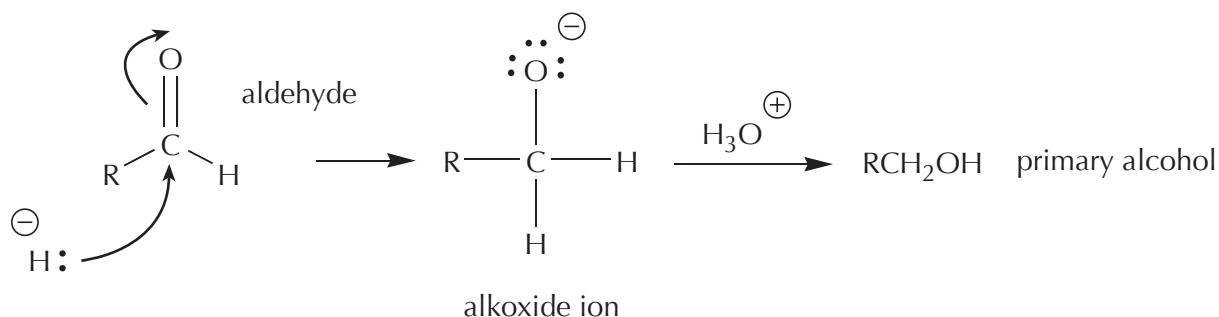


REACTIONS WITH ACID CHLORIDES AND ESTERS

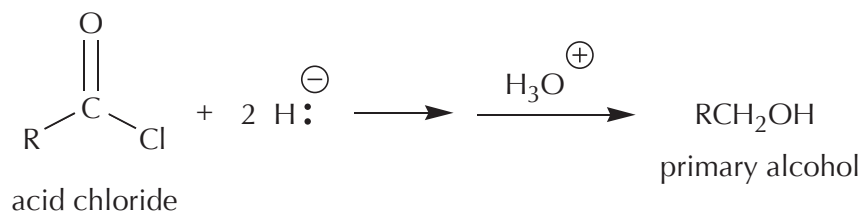
The mechanism of action of hydride reductions on acid chlorides and esters (carboxyl groups) is similar to that taking place with carbonyl compounds, except that acid chlorides and esters have a leaving group (–Cl and –OR). So the reaction does not stop at formation of the alkoxide ion as a tetrahedral intermediate, but keeps going with an internal nucleophilic displacement of the leaving group. The direct outcome of this process is formation of the corresponding carbonyl compound (aldehyde or ketone), which may or may not undergo further reduction to alcohol, depending on the nature of the reagents used and reaction conditions. The following mechanism illustrates this concept. For simplicity, only the hydride ion is shown.



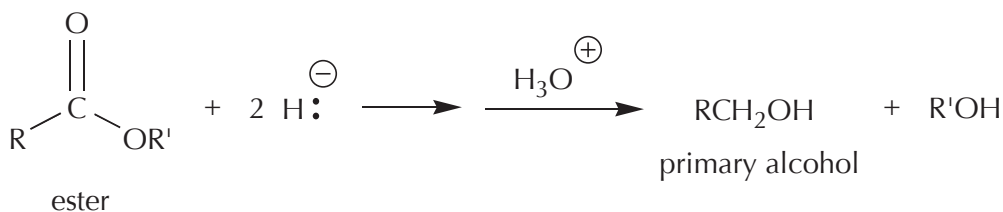
If a full reactivity reducing agent such as LiAlH_4 is used, the reaction does not stop at the aldehyde stage, since the carbonyl carbon of the aldehyde can be attacked by another hydride equivalent. This results in formation of the primary alcohol (after hydrolysis of the alkoxide ion) as the final product.



The net reaction then is:



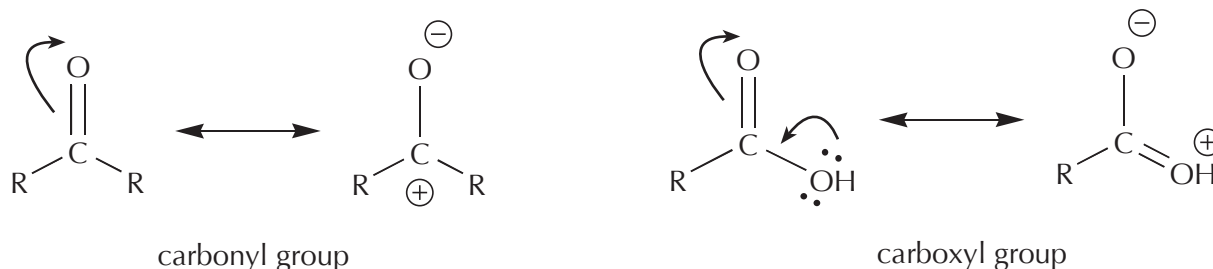
The reaction with an ester is similar, but the leaving group is different ($\text{R}'\text{O}^-$). Can you draw the mechanism that leads to formation of the products shown?



Notice that with both (and all) carboxyl groups, hydride reductions lead to formation of primary alcohols only. There is no possibility of forming secondary alcohols by this method because the carboxyl group is at the end of the carbon chain, or else the chain gets broken so that the carboxyl carbon ends up at the end of a chain in the final product.

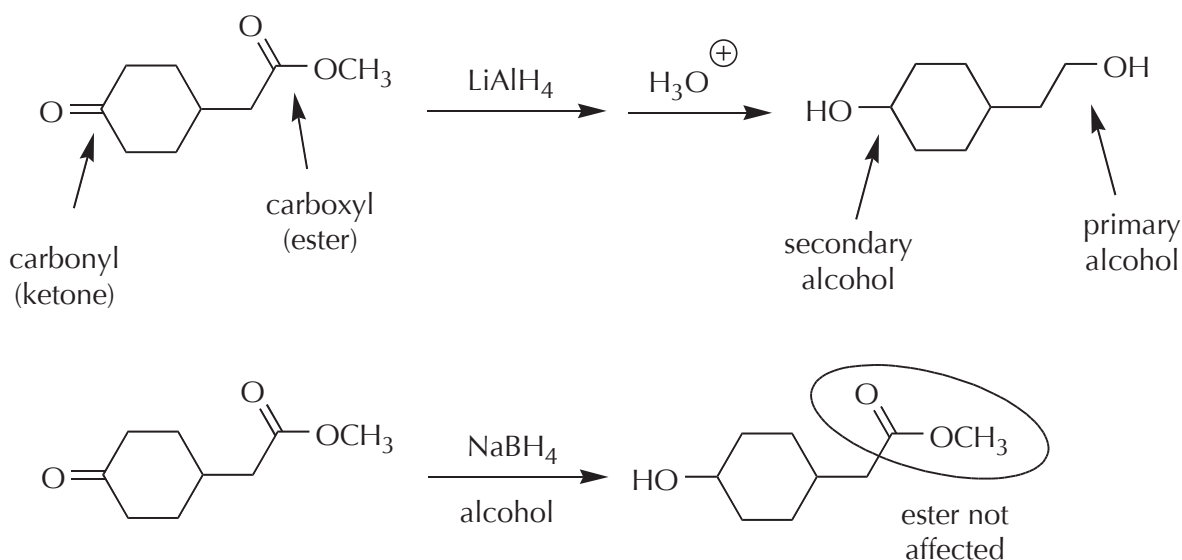
ELECTROPHILICITY OF CARBONYL GROUPS VERSUS CARBOXYL GROUPS

In terms of electrophilic character, carboxyl groups are not as reactive as carbonyl groups. Examination of the resonance structures reveals that the carbonyl carbon bears a higher degree of positive charge than the carboxyl carbon, and is therefore a better (more reactive) electrophile.



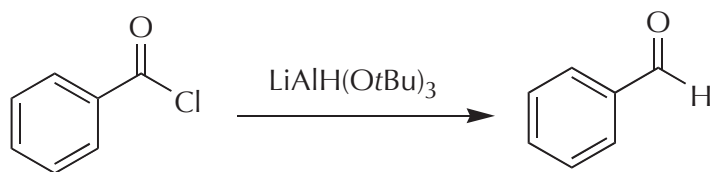
Although the above example uses a carboxylic acid as the instance of carboxyl group, acid chlorides and esters behave similarly. You should be able to draw the resonance structures for both of these groups as well.

The difference in reactivity between the two groups means that the carbonyl group can be reduced with both high reactivity reducing agents such as lithium aluminum hydride, and less reactive agents such as sodium borohydride. The carboxyl group, on the other hand, will respond only to lithium aluminum hydride and will not be affected by sodium borohydride. This is illustrated by the following example.



REDUCTION OF CARBOXYL GROUPS TO ALDEHYDES USING MODIFIED HYDRIDE REAGENTS

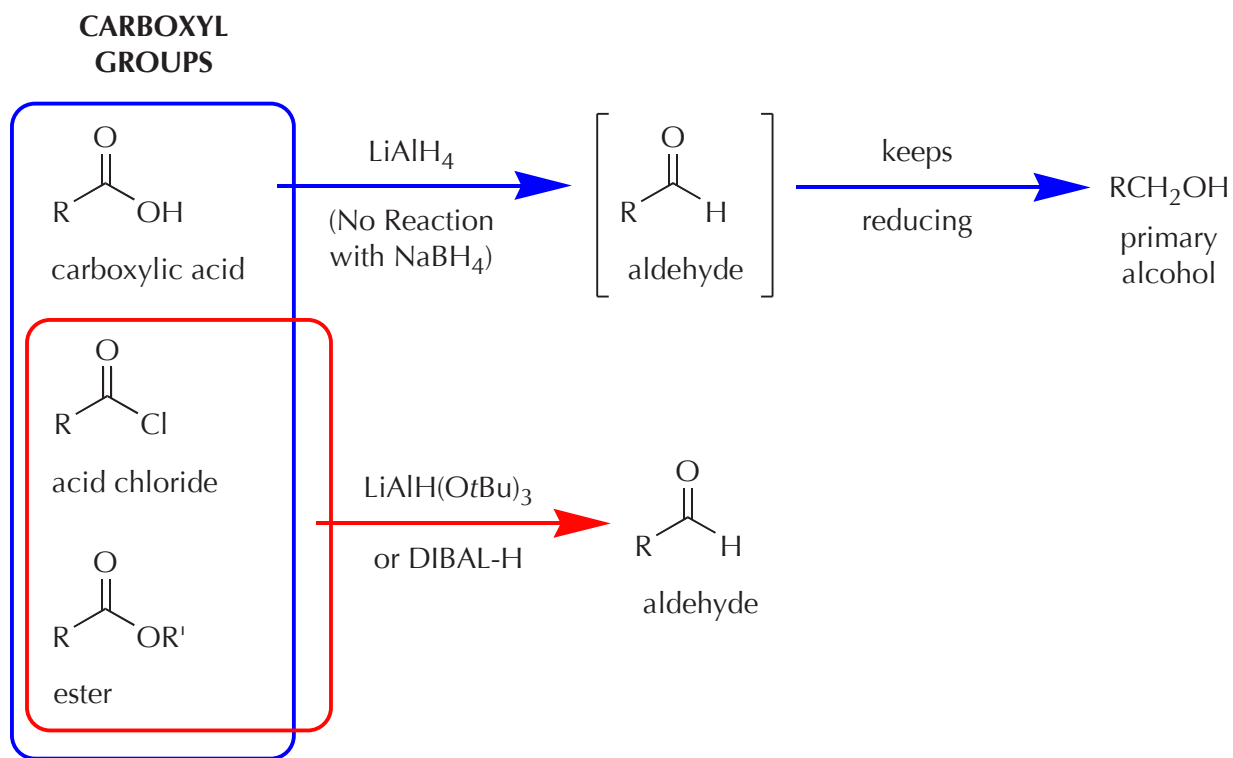
It was stated before that carboxyl groups get reduced all the way to primary alcohols when full reactivity reducing agents are used. The mechanism of reduction goes through an aldehyde stage, but it cannot stop there because the aldehyde gets further reduced to alcohol. So the question is, can we stop at the aldehyde stage by using modified hydride reagents that have bulky groups in the structure and are capable of delivering only one hydride per equivalent. The answer is yes, because those reactions are slower and we can control the number of hydride ions delivered, so that by limiting this parameter we prevent the aldehyde from undergoing further reduction. Such reductions can be accomplished using DIBAL-H or LiAlH(OtBu)₃.



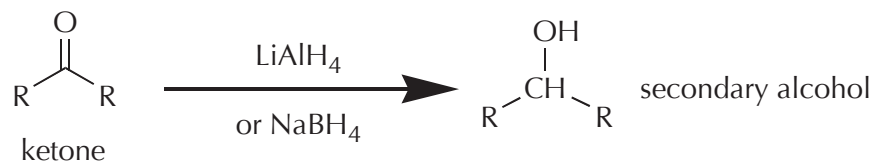
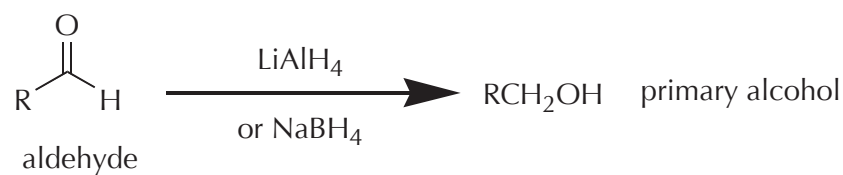
SEE NEXT PAGE FOR A SUMMARY OF REDUCTIONS OF CARBONYL AND CARBOXYL GROUPS

HYDRIDE REDUCTIONS OF CARBONYL AND CARBOXYL GROUPS CHART

All reactions with LiAlH_4 assume treatment with water or dilute acid as the last step.

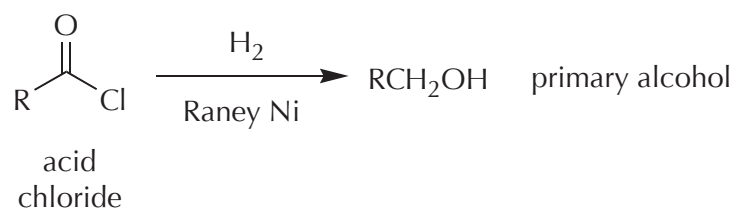
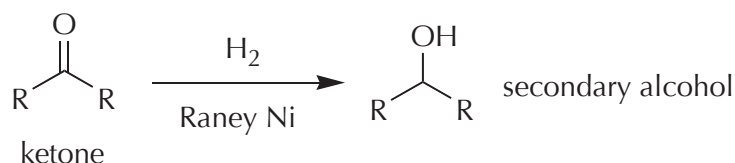
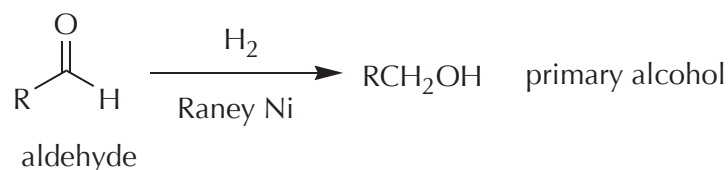


CARBONYL GROUPS

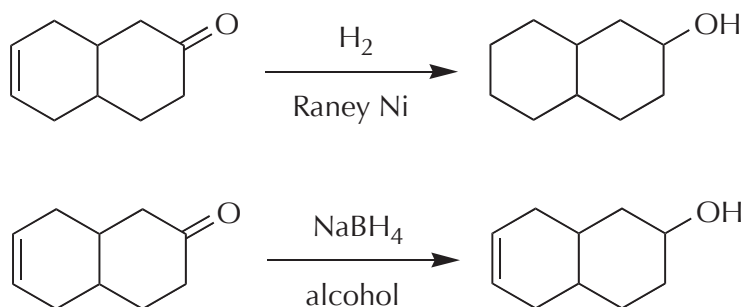


REDUCTION OF CARBONYL COMPOUNDS AND ACID CHLORIDES THROUGH CATALYTIC HYDROGENATION

Another way to reduce carbonyl groups and acid chlorides is through the catalytic addition of hydrogen. Just like the C=C bond, the C=O bond is capable of adding one mole of hydrogen. The catalyst typically used to accomplish this is called **Raney Nickel**.

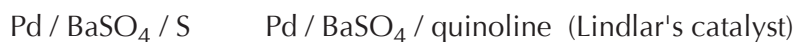


If there are any C=C bonds present in the molecule, obviously they will also take up hydrogen. If selective reduction of the carbonyl group is desired, use NaBH₄ instead.

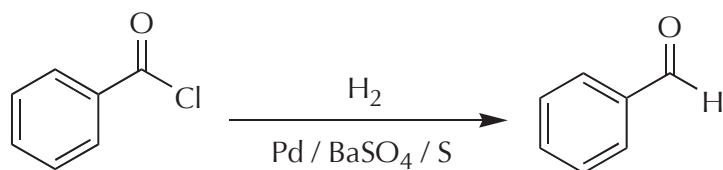


As with the case of hydride reductions, the above reactions also go through the aldehyde stage, but cannot stop due to the high reactivity of the H_2 /catalyst mixture. However, just as was the case in the addition of hydrogen to triple bonds, the process can be stopped at the aldehyde stage by the use of a reduced reactivity version of the H_2 /catalyst mixture. This is accomplished by the addition of a "poison," just as it was done with alkynes to stop at the alkene stage. It turns out that Lindlar's catalyst works in this case as well.

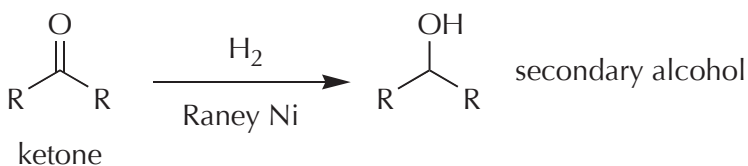
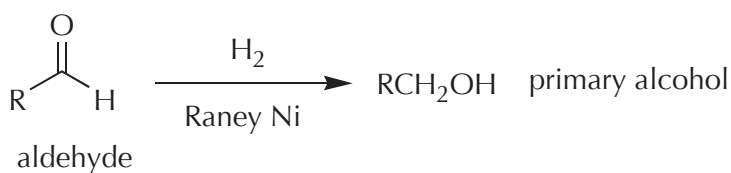
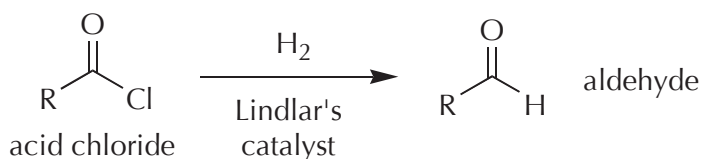
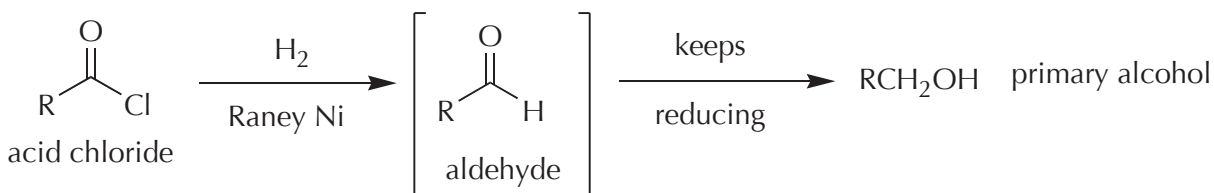
"Poisoned" catalysts for hydrogenation



EXAMPLE:



CATALYTIC HYDROGENATION OF CARBONYL GROUPS AND ACID CHLORIDES



SUMMARY OF METHODS TO SYNTHESIZE ALCOHOLS FROM CARBONYL COMPOUNDS

- 1. TREATMENT OF CARBONYL COMPOUNDS WITH CARBON NUCLEOPHILES SUCH AS GRIGNARD REAGENTS.** Excellent method for the synthesis of primary, secondary, and tertiary alcohols with high degree of specificity.
- 2. TREATMENT OF CARBONYL COMPOUNDS WITH HYDRIDE REDUCING AGENTS.** Good method for synthesizing primary or secondary alcohols with the same number of carbons as the starting material.
- 3. CATALYTIC HYDROGENATION OF CARBONYL COMPOUNDS.** Same applications as number 2 above, but will also reduce pi bonds to alkanes if they are present.