PREPARATION OF ALDEHYDES

1. Oxidation of 1° alcohols: $RCH_2OH \rightarrow RCHO$

In general, aldehydes are more easily oxidized than alcohols.

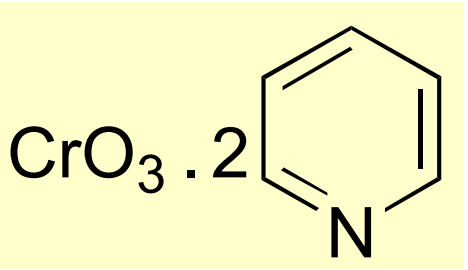
RCHO $\rightarrow$ RCOOH occurs more readily than $RCH_2OH \rightarrow RCHO$.

Therefore, very mild oxidizing agents must by used for the transformation $RCH_2OH \rightarrow RCHO$.

Examples of mild oxidizing agents are:

(a) chromium trioxide-pyridine complex, $CrO_3.2py$;

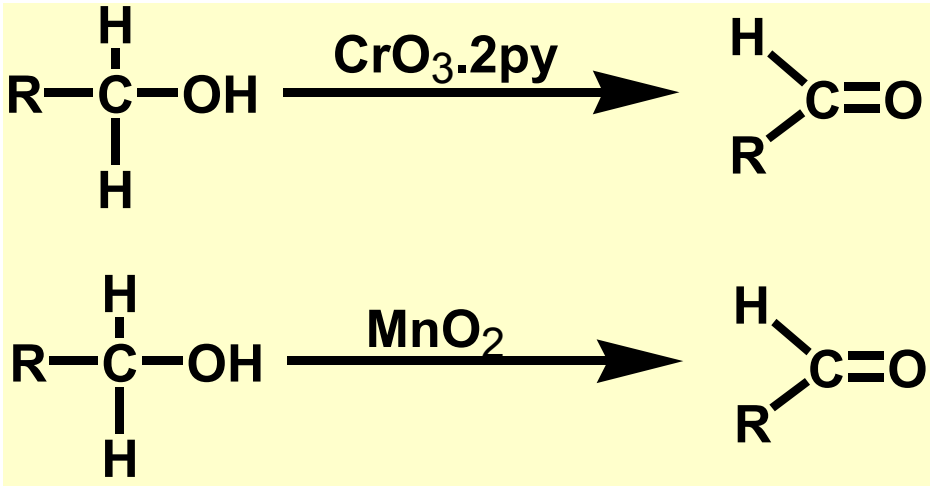
(b) manganese dioxide, MnO_2



PREPARATION OF ALDEHYDES

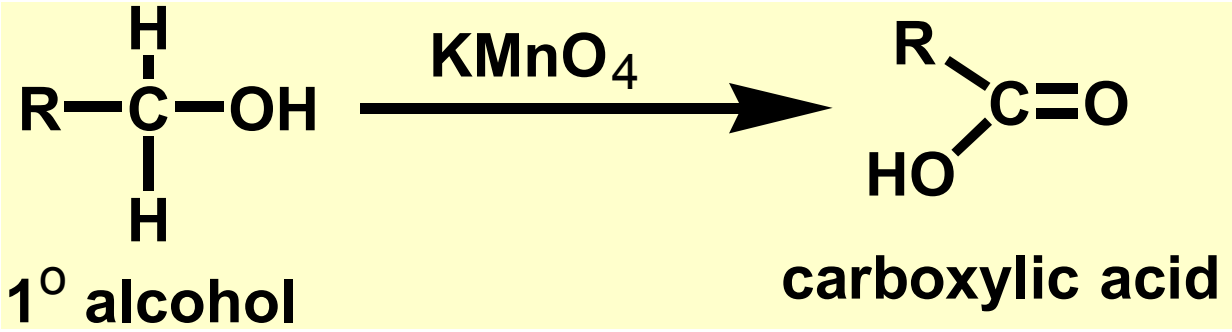
1. Oxidation of 1º alcohols: $RCH_2OH \rightarrow RCHO$

Mild oxidizing agents are used.



You are not required to know the mechanisms of these reactions.

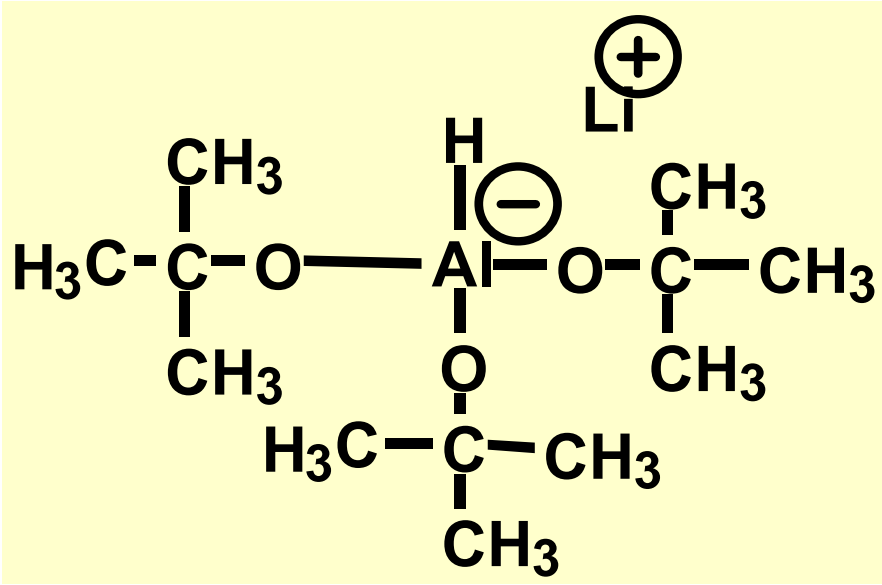
With strong oxidizing agents, e.g. $KMnO_4$, H_2CrO_4, 1º alcohols are oxidized to carboxylic acids.



PREPARATION OF ALDEHYDES

2. Reduction of acyl chlorides: RCOCl → RCHO

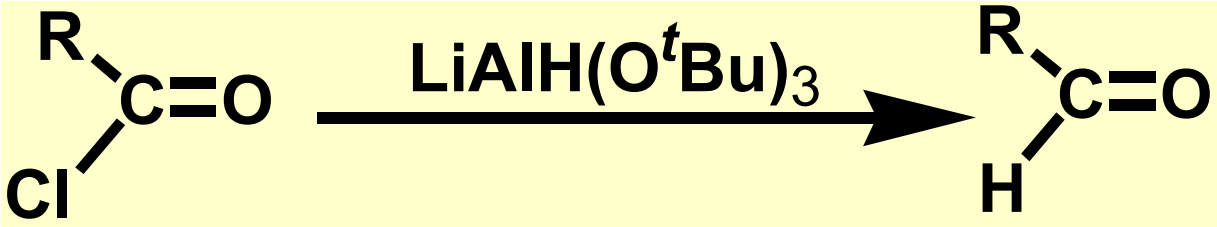
Lithium tri-*t*-butoxyaluminum hydride is often used for this reduction.



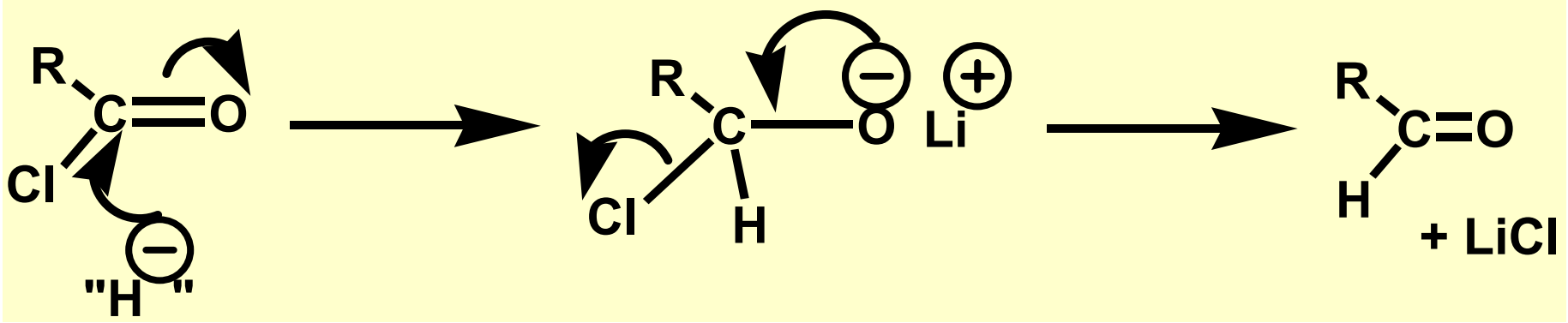
$LiAlH[OC(CH_3)_3]_3$ or $LiAlH(O^tBu)_3$;
this is a mild hydride reducing agent.

PREPARATION OF ALDEHYDES

2. Reduction of acyl chlorides .



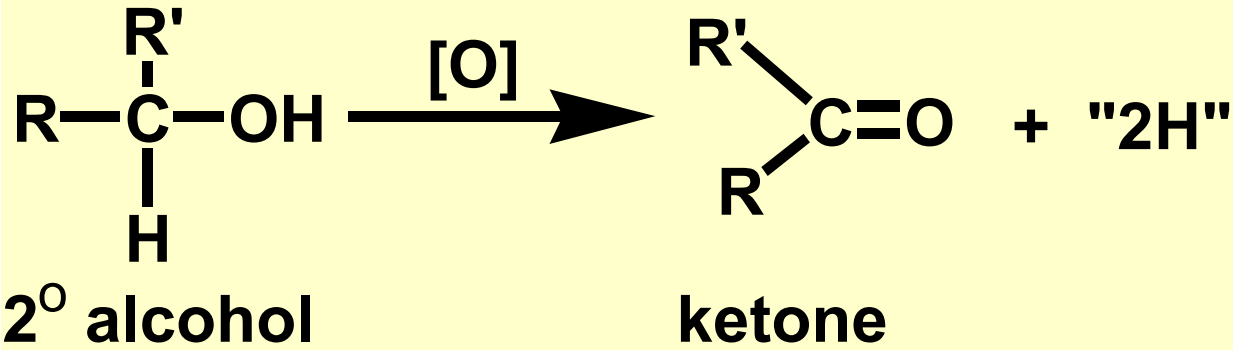
A partial, simplified mechanism for this reaction:



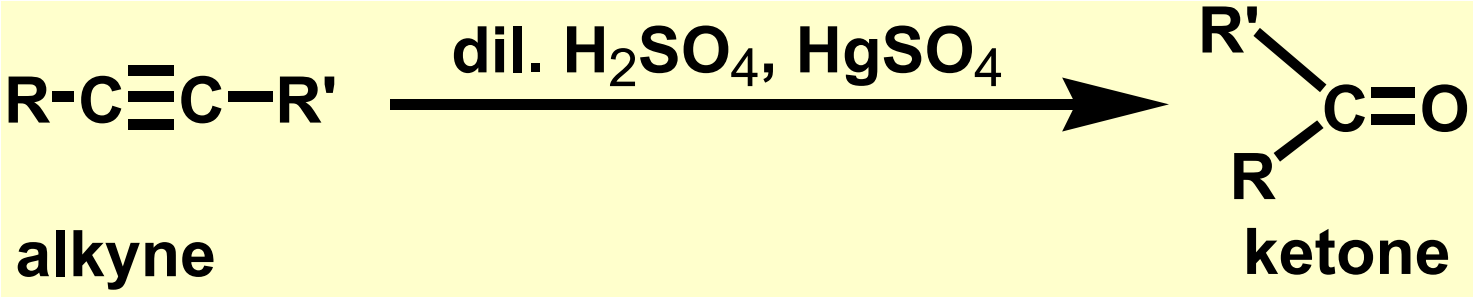
PREPARATION OF CARBONYL COMPOUNDS

B. Preparation of ketones

1. Oxidation of 2^{o} alcohols yields ketones.



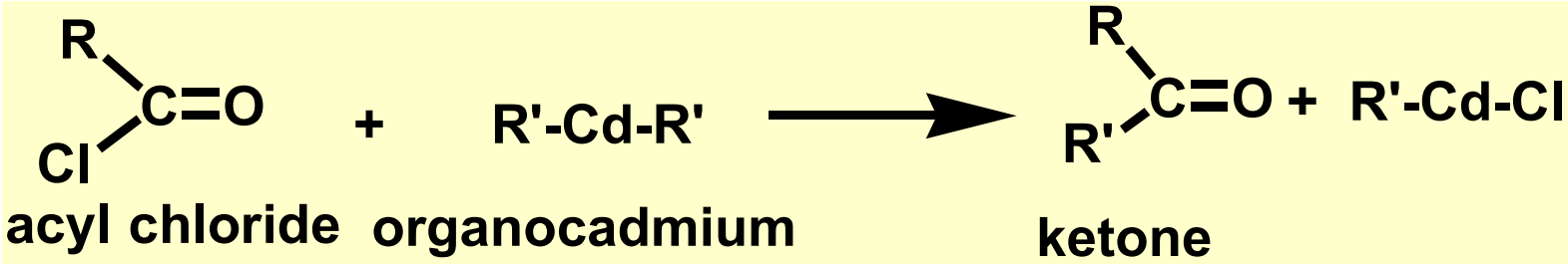
2. Ketones are formed by addition of H_2O to alkynes



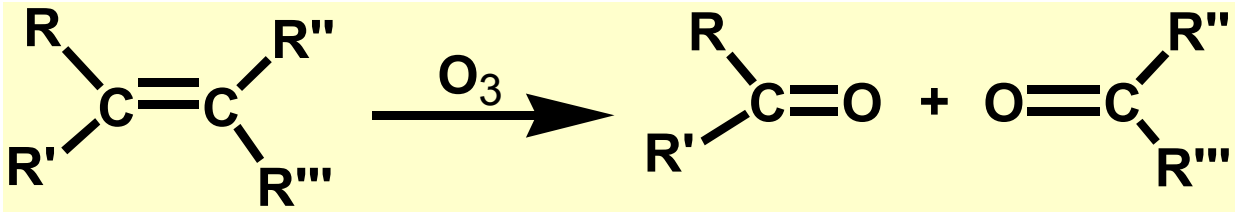
PREPARATION OF CARBONYL COMPOUNDS

B. Preparation of ketones

3. Replacement of chloride in acyl chlorides by nucleophilic alkyl groups of organocadmium compounds or lithium dialkylcuprates produces ketones

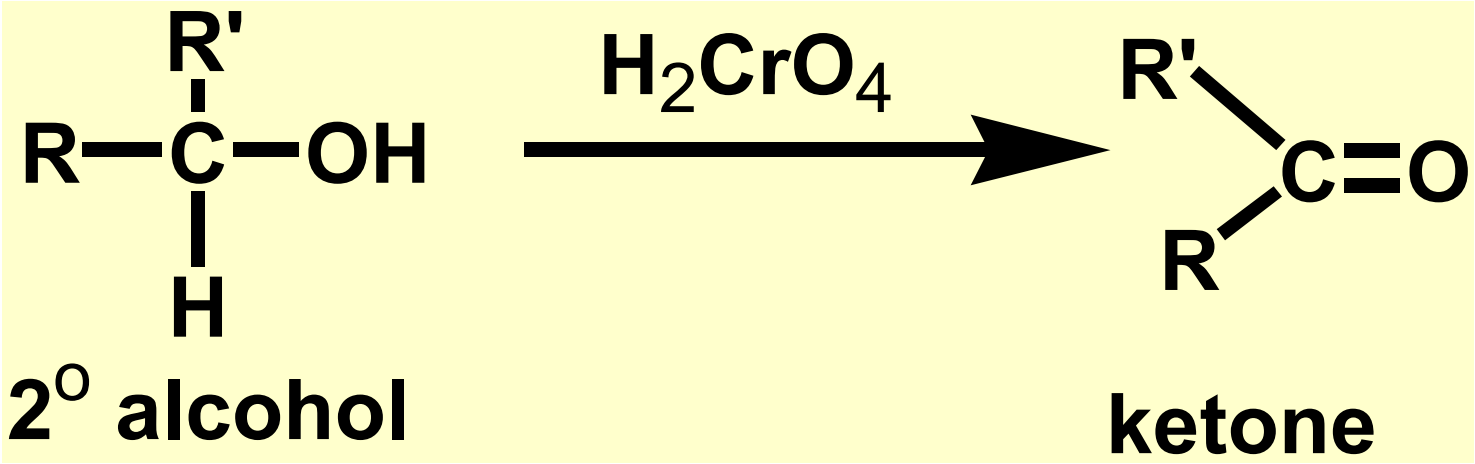


4. Ozonlysis of geminally substituted alkenes yields ketones.



PREPARATION OF KETONES

1. Oxidation of 2° alcohols



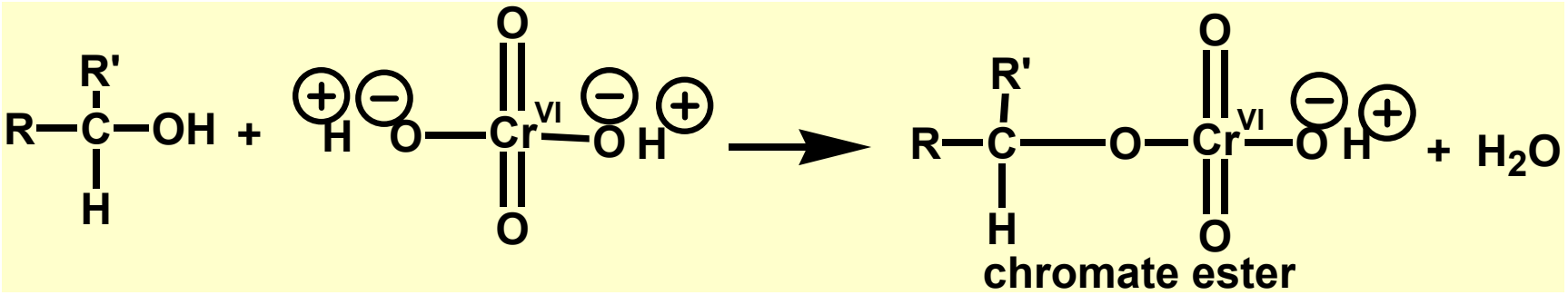
The most commonly used reagent for this oxidation is H_2CrO_4, chromic acid (Jones reagent), prepared from CrO_3 and H_2SO_4; in H_2CrO_4 , chromium is in the + 6 oxidation state.

PREPARATION OF KETONES

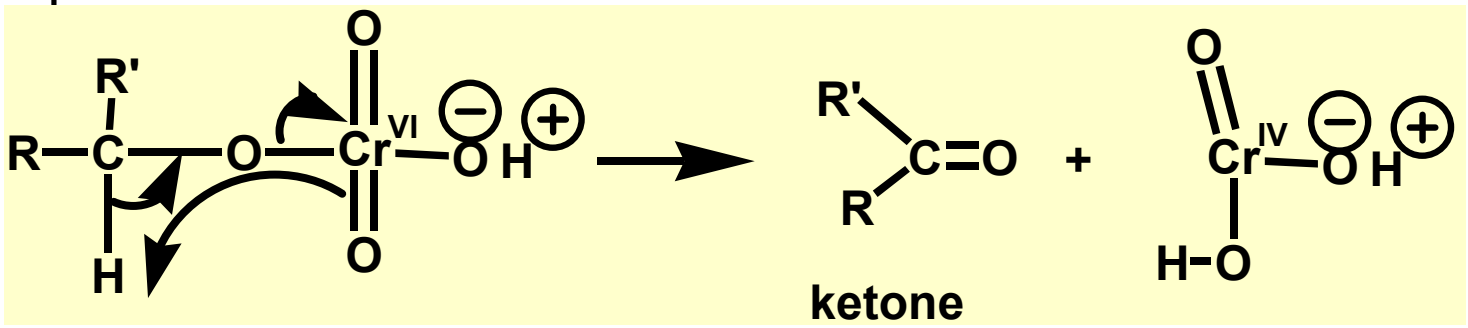
1. Oxidation of 2º alcohols with Jones reagent, H_2CrO_4

Key steps in the partial mechanism for this oxidation are:

(a) formation of a chromate ester from the alcohol and H_2CrO_4;



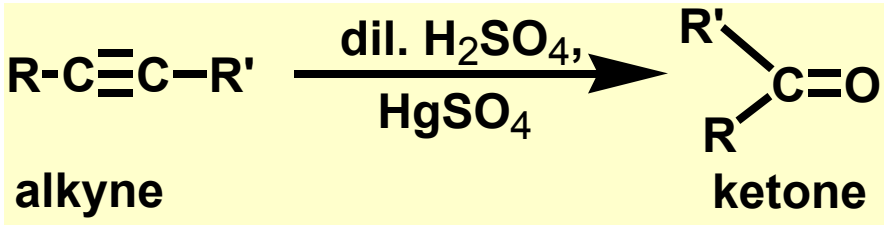
(b) decomposition of the chromate ester



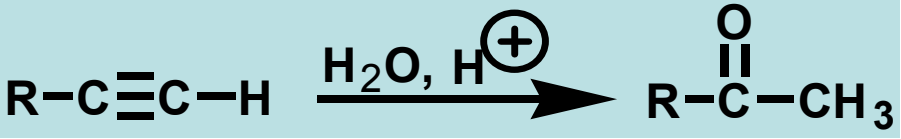
Cr (III) is eventually formed, and the color of the reaction mixture changes from orange to green.

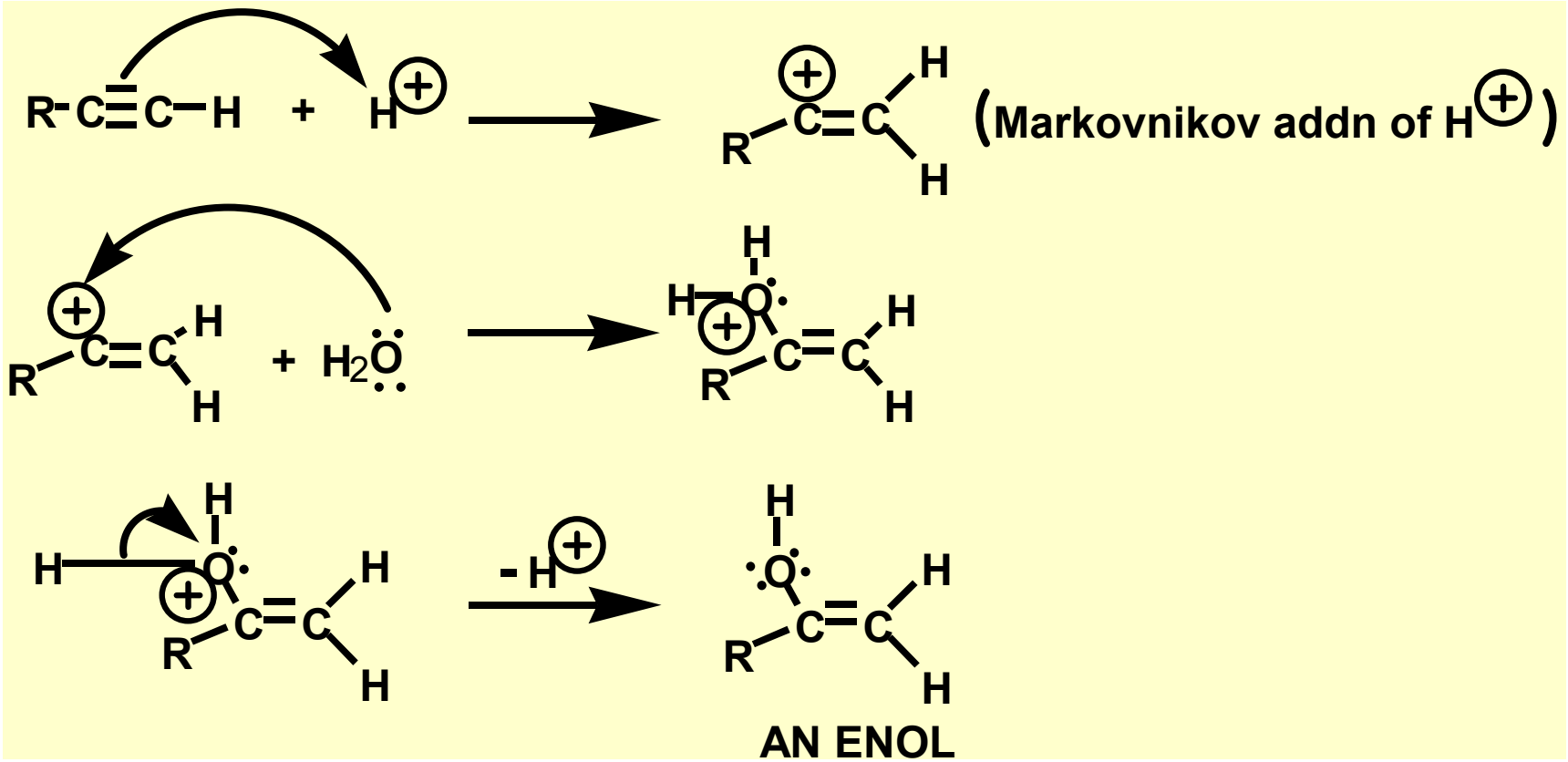
PREPARATION OF KETONES

2. Hydration of alkynes



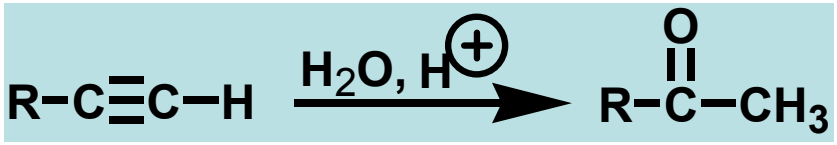
Let R' = H, so the alkyne is terminal:

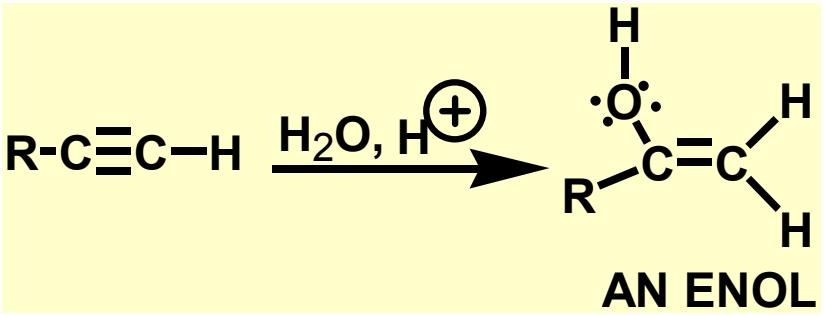




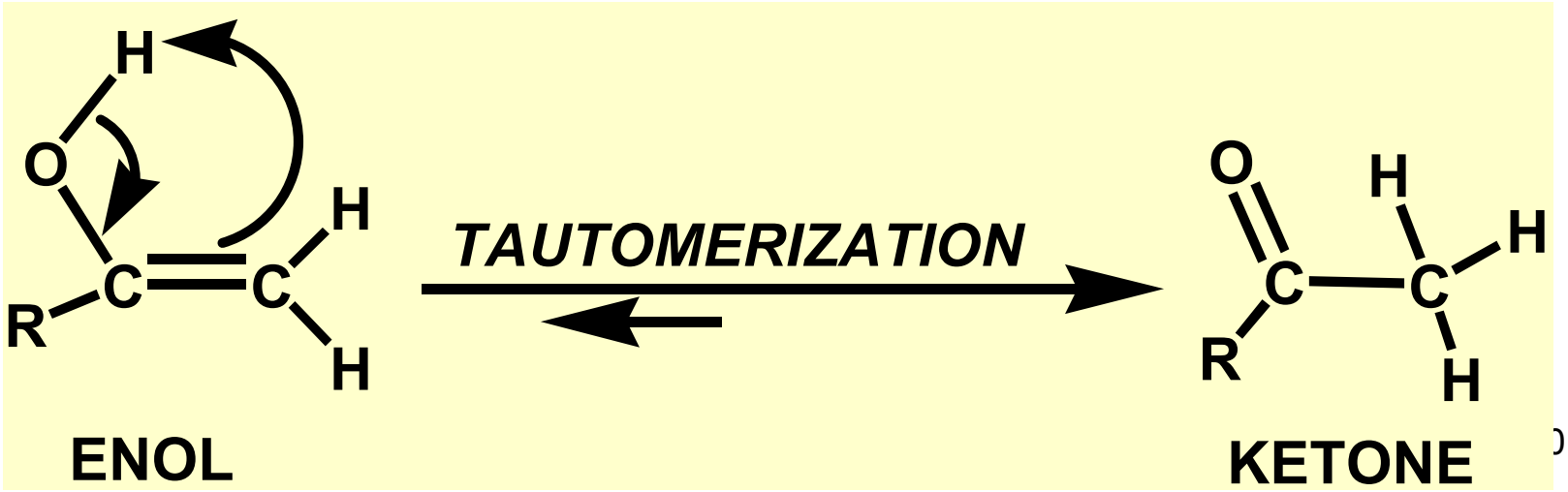
PREPARATION OF KETONES

2. Hydration of alkynes





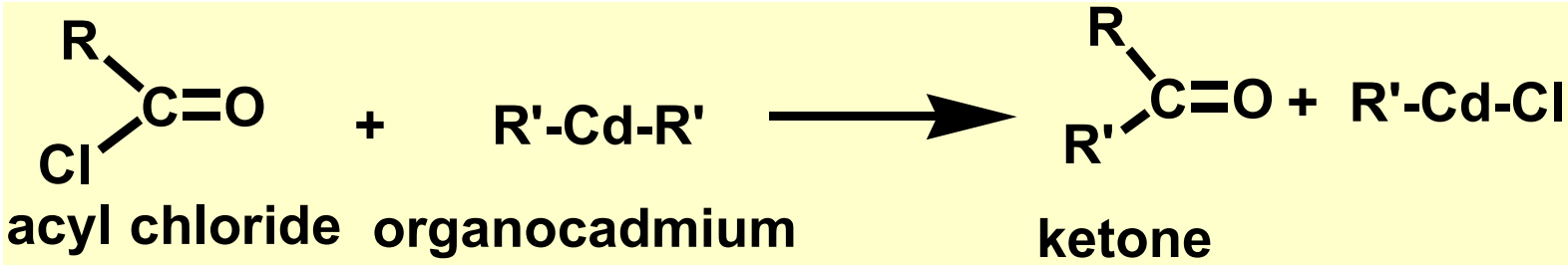
An ***enol*** is a ***tautomer*** of a ketone. Tautomers are isomers which differs only in the location of a hydrogen atom.



PREPARATION OF KETONES

3. Replacement of chloride in acyl chlorides by nucleophilic alkyl groups of (a) organocadmium compounds or
   (b) lithium dialkylcuprates.

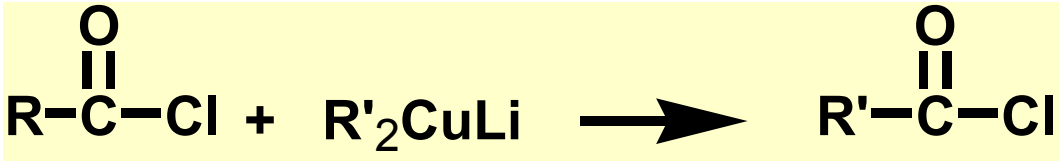
(a) Acyl chlorides + organocadmiums



Organocadmiums are prepared from Grignard reagents
(Cd is less electropositive than Mg)

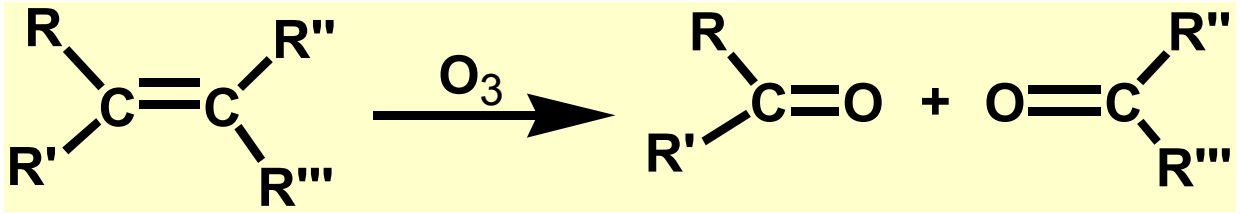
$2R'MgCl + CdCl_2 \rightarrow R'_2Cd + 2MgCl_2$

(b) Acyl chlorides + lithium dialkylcuprates

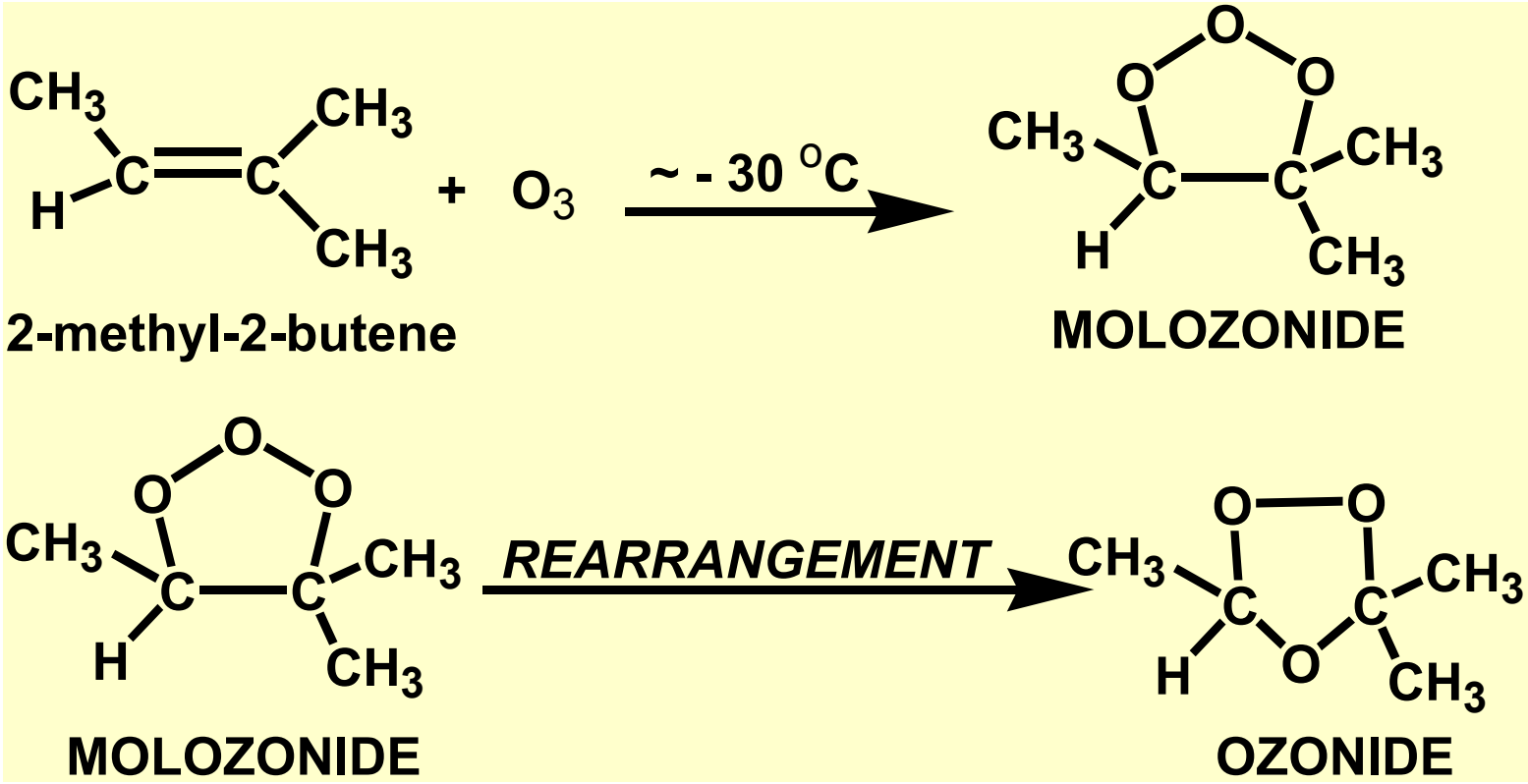


PREPARATION OF KETONES

4. Ozonlysis of geminally substituted alkenes

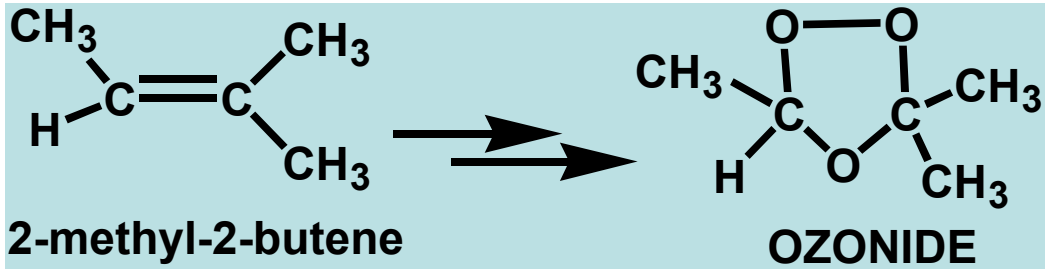


Ozonlolysis is cleavage by ozone

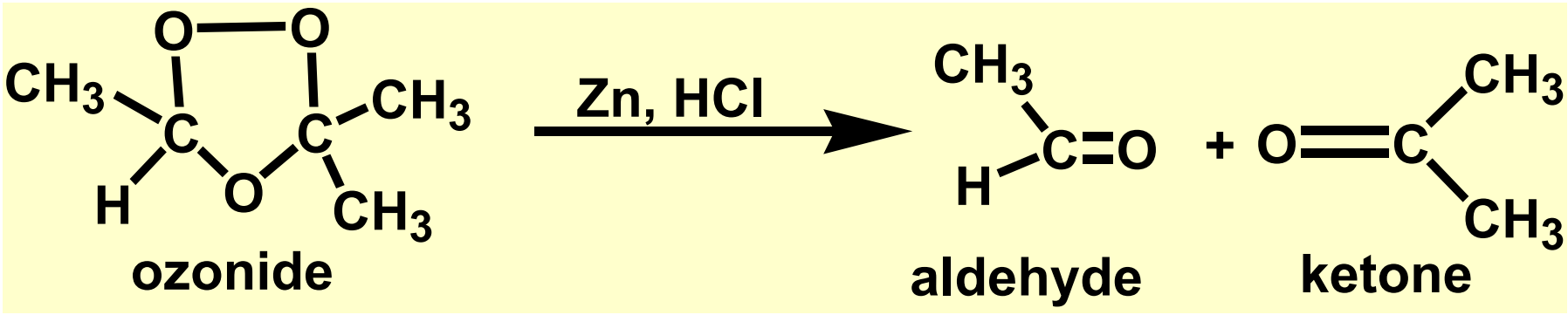


PREPARATION OF KETONES

4. Ozonlysis of geminally substituted alkenes



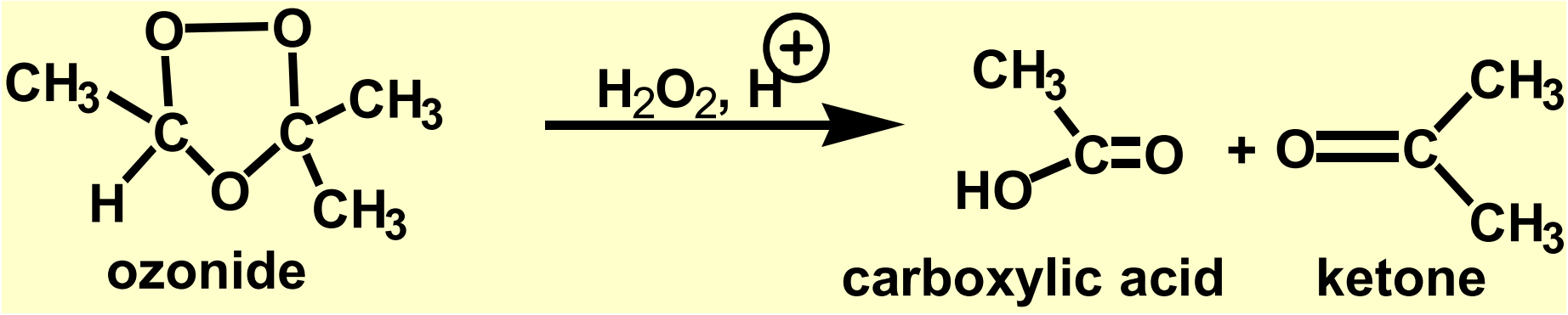
(a) Reductive workup of the ozonolysis reaction



When one of the substituents of the alkene is H, reductive workup of the ozonloysis yields an aldehyde functional group at that carbon.

PREPARATION OF KETONES

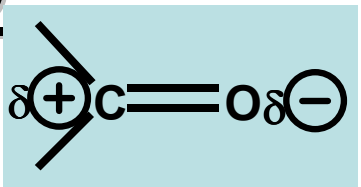
(b) Oxidative workup of the ozonolysis reaction



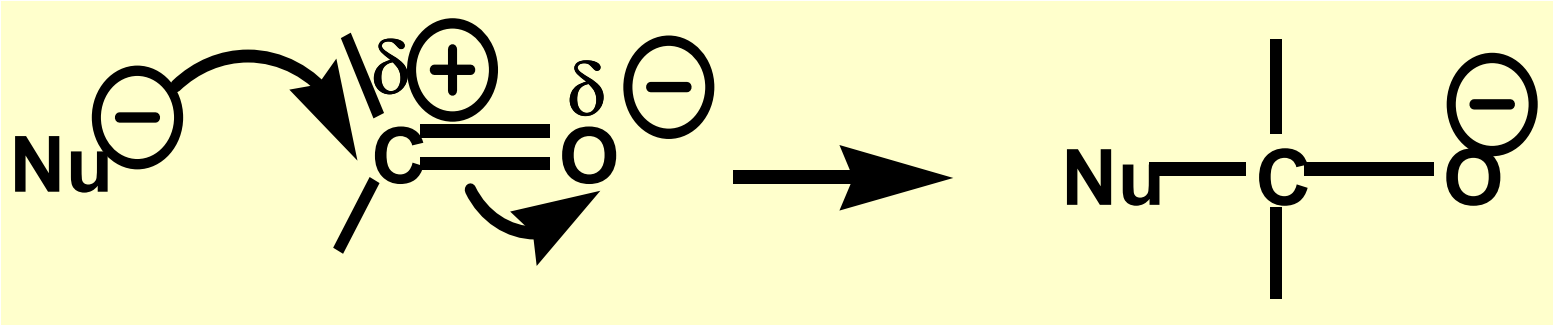
When one of the substituents of the alkene is H, oxidative workup of the ozonloysis yields a carboxyl group at that carbon.

Alkene carbons which bear two alkyl groups always become ketone carbonyls on ozonolysis.

NUCLEOPHILIC ADDITION TO ALDEHYDES & KETONES



Carbonyl ***carbons are electrophilic*** and are susceptible to attack by nucleophiles under neutral and basic conditions.

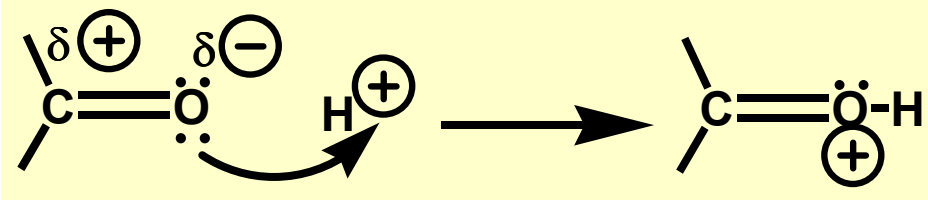


The addition of Grignard reagents to carbonyl compounds is an example of this type of reaction.

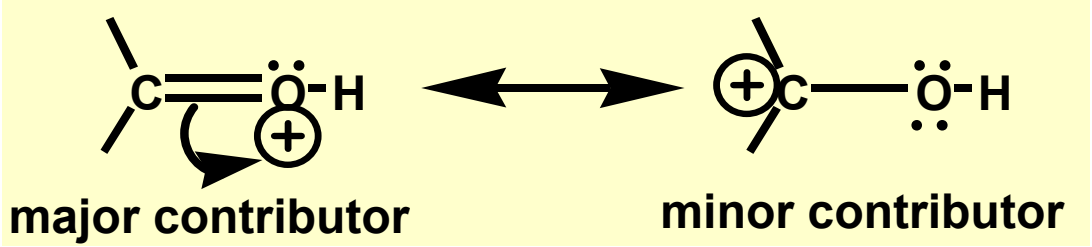
Carbonyl ***oxygens are nucleophilic*** are can be attacked by electrophiles, usually $H^{\oplus}$.

NUCLEOPHILIC ADDITION TO ALDEHYDES & KETONES

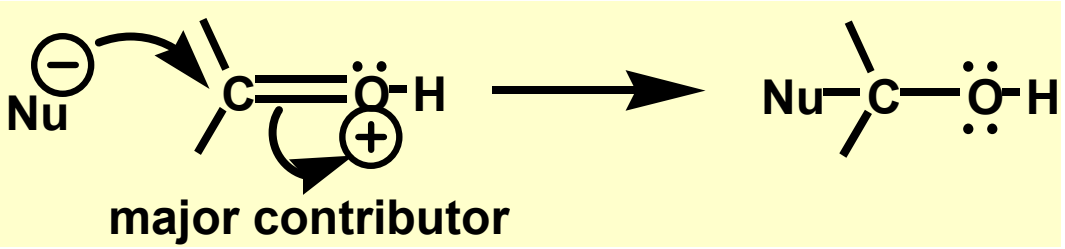
The carbonyl oxygen is nucleophilic, so under acidic conditions:



The protonated carbonyl is a hybrid of two resonance forms:

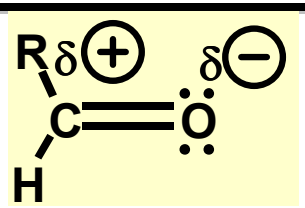
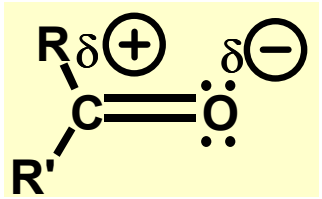


The major contributor is subject to nucleophilic attack as shown:



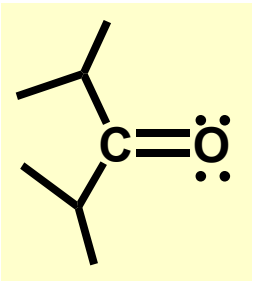
NUCLEOPHILIC ADDITION TO CARBONYL CARBON ∴ OCCURS UNDER BASIC-NEUTRAL CONDITIONS *AND* UNDER ACIDIC CONDITIONS

ALDEHYDES VS. KETONES
STABILITY AND REACTIVITY

Aldehydes  are more reactive and less stable than ketones  for two reasons.

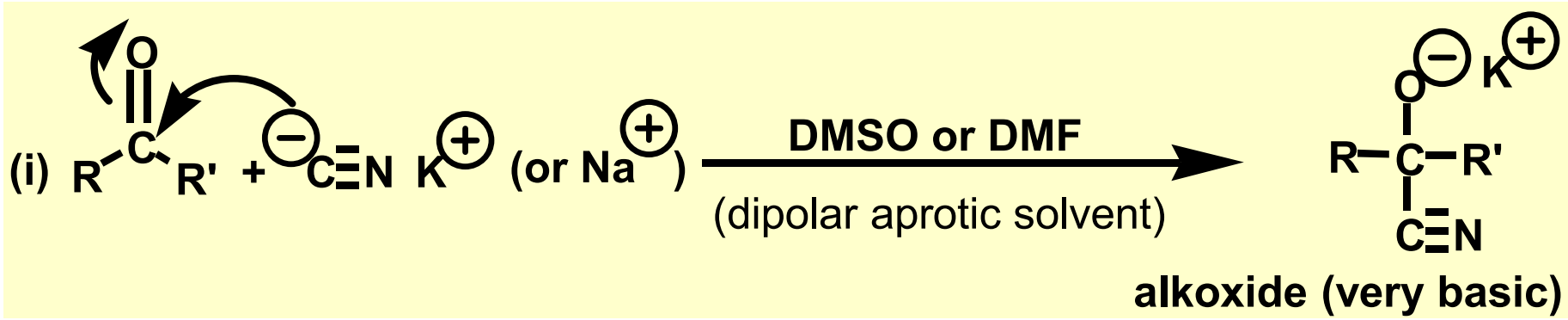
1. In ketones, the $\delta^{\oplus}$ on the carbonyl carbon is stabilized by the electron clouds associated with two alkyl groups.

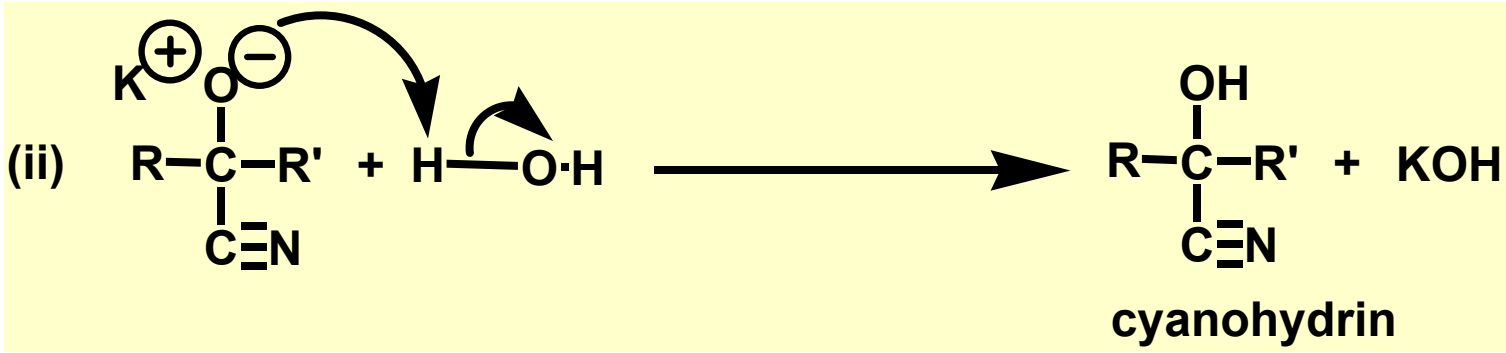
2. The carbonyl group in aldehydes is more sterically accessible than the carbonyl group in ketones. Some ketones, e.g. diisopropyl ketone, are very sterically hindered.



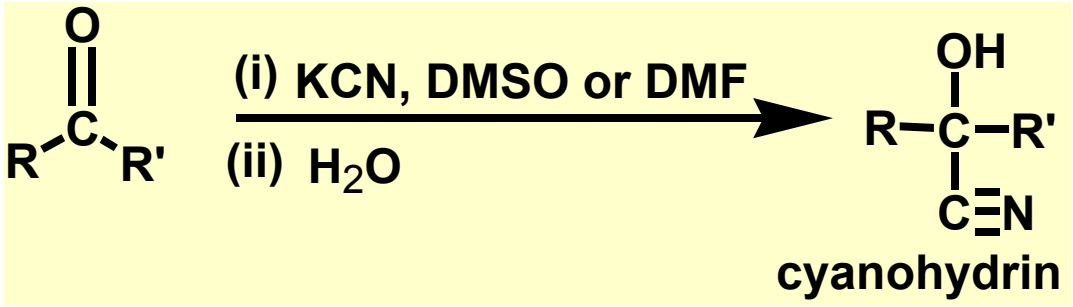
EXAMPLES OF NUCLEOPHILIC ADDITION TO ALDEHYDES & KETONES

1. **Addition of HCN** (neutral-basic conditions). $CN^{\ominus}$ is a very good nucleophile (**ionic nucleophile**). The use of the actual compound HCN is not experimentally feasible, as it is a lethal gas, bp 26 °C. Addition of the elements of HCN to a C=O group is effected in two stages, as follows.

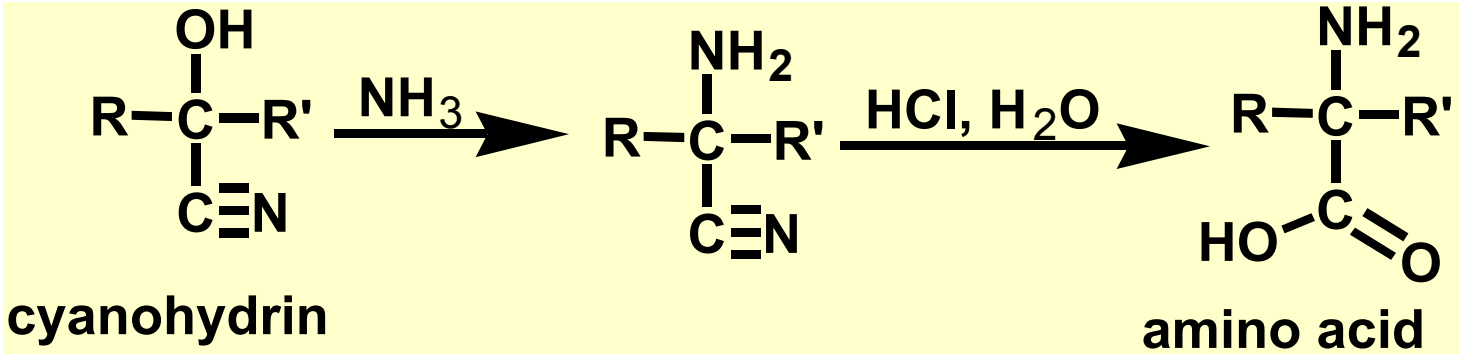




ADDITION OF HCN TO ALDEHYDES & KETONES

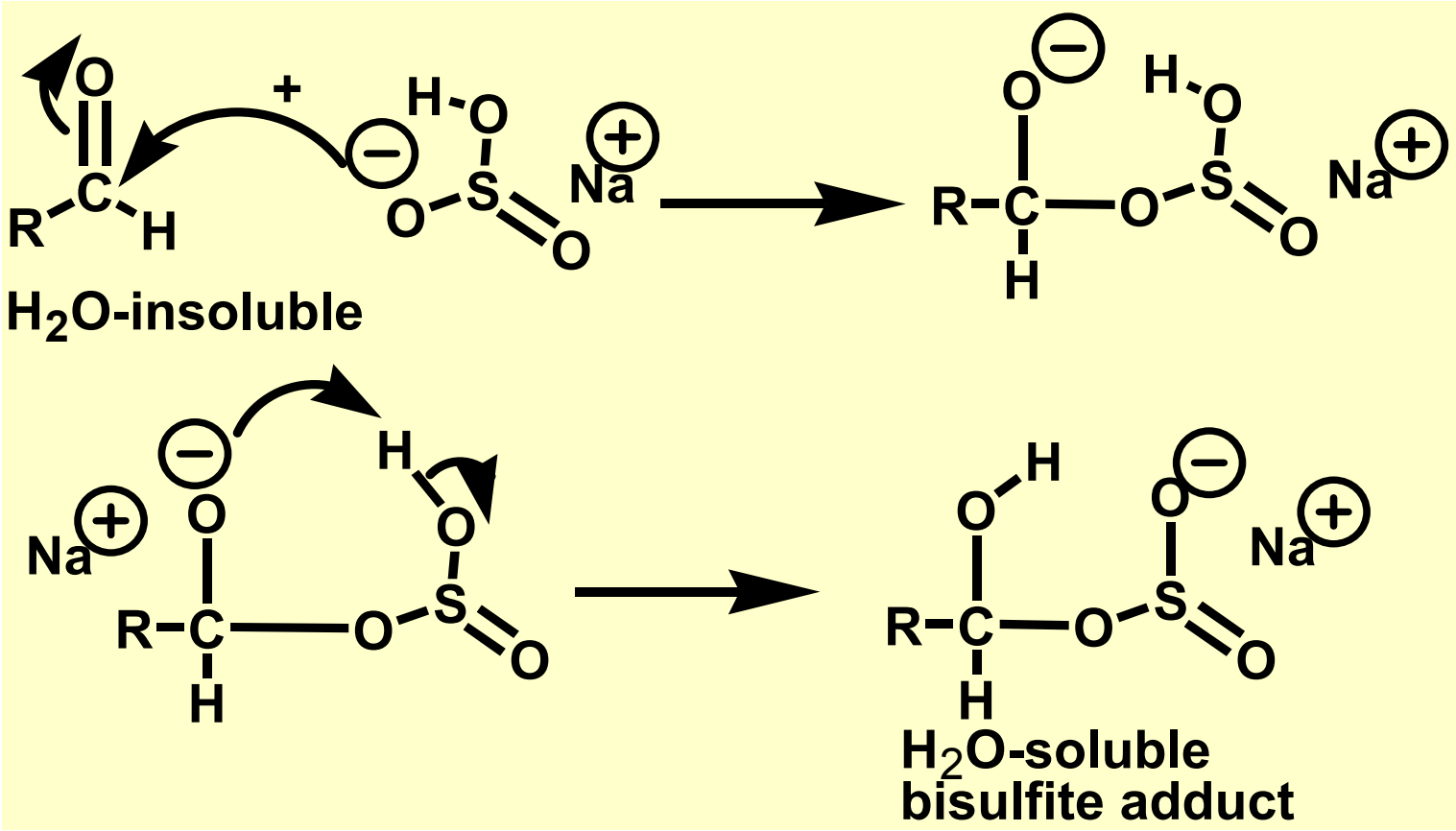


Cyanohydrins are useful synthetic intermediates. On treatment with ammonia, the OH group is converted to an NH_2 group, and the nitrile (CN) group can be hydrolyzed to a carboxyl group.

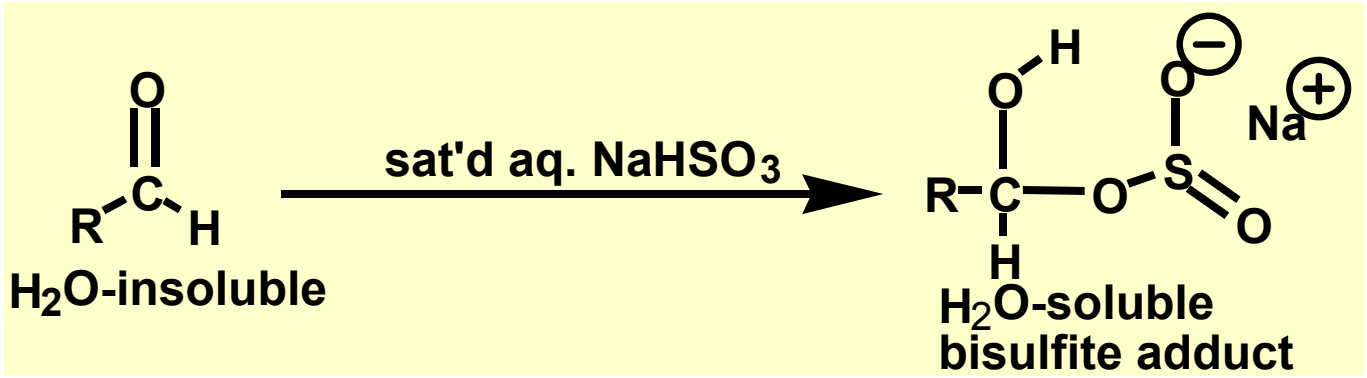


EXAMPLES OF NUCLEOPHILIC ADDITION TO ALDEHYDES & KETONES

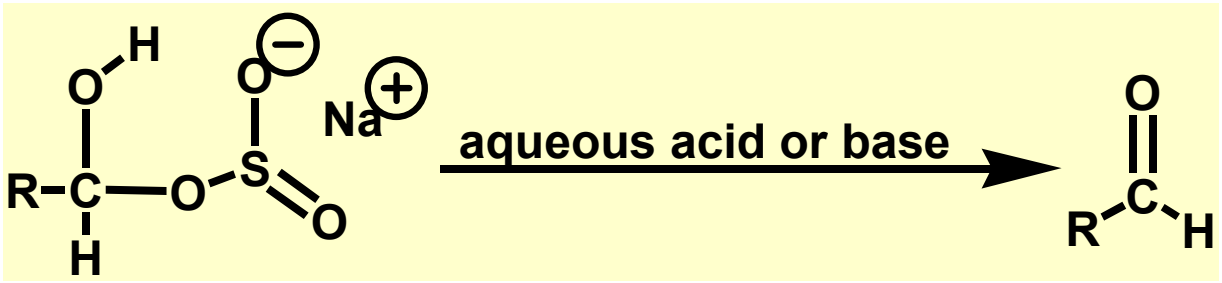
2. **Addition of bisulfite** (saturated aqueous sodium or potassium bisulfite, $NaHSO_3$ or $KHSO_3$, solution) Aldehydes and methyl ketones only, undergo this reaction.$HSO_3^{\ominus}$ is an **ionic nucleophile.**



ADDITION OF $NaHSO_3$ TO ALDEHYDES & METHYL KETONES



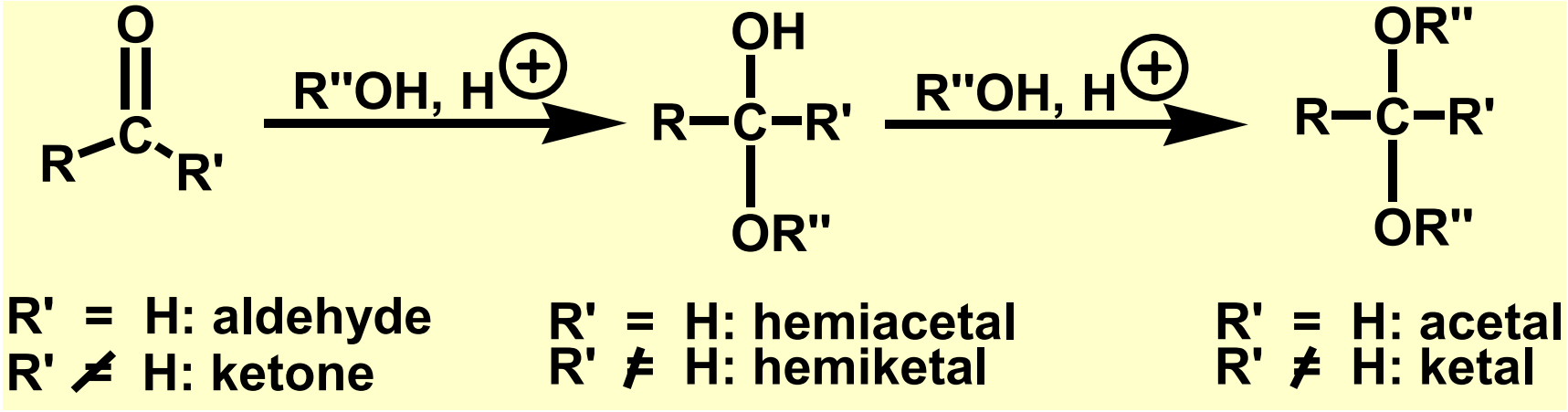
The bisulfite adduct can be hydrolyzed back to the carbonyl compound.



This two-step sequence is sometimes used to separate aldehydes or ketones from mixtures with other H_2O-insoluble compounds.

EXAMPLES OF NUCLEOPHILIC ADDITION TO ALDEHYDES & KETONES

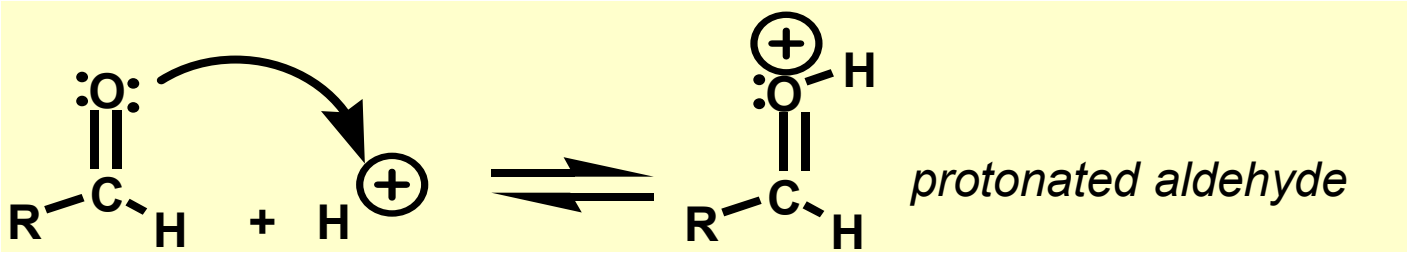
3. **Addition of alcohols;** this is a typical acid-catalyzed nucleophilic addition.



In the next two slides the mechanism of the addition of two equivalents of an alcohol (R′OH) to an aldehyde (RCHO), under acidic conditions, is shown.A **hemiacetal** is first formed, and the final product is an **acetal**.

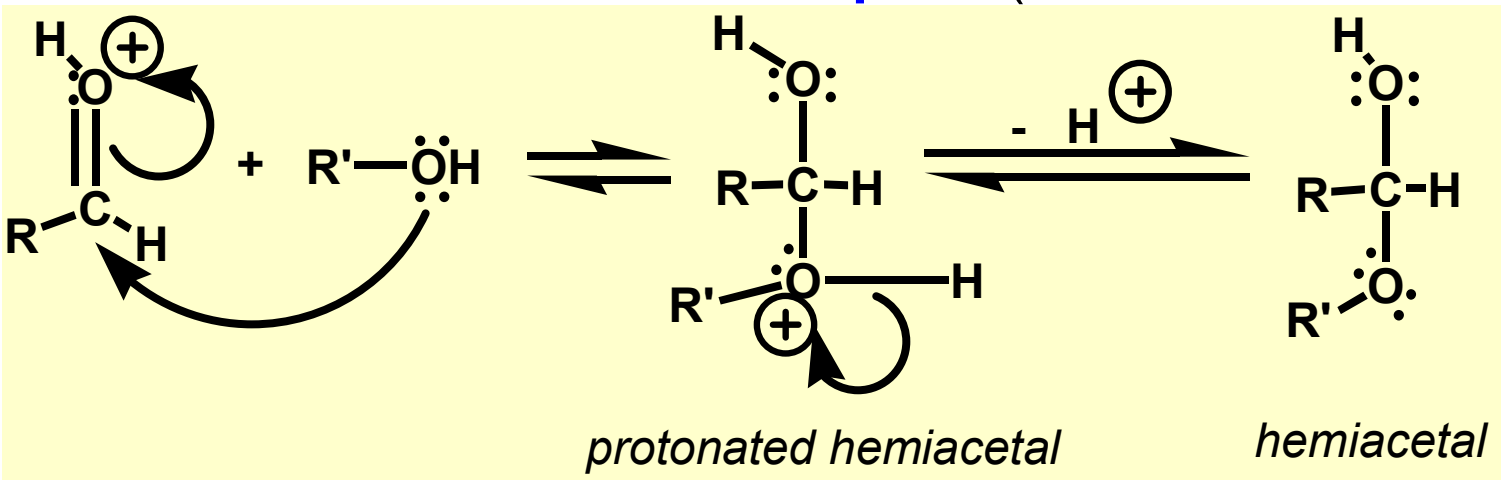
ACID-*CATALYZED* NUCLEOPHILIC ADDITION OF AN ALCOHOL TO AN ALDEHYDE → ACETAL

(a) Protonation of the aldehyde.



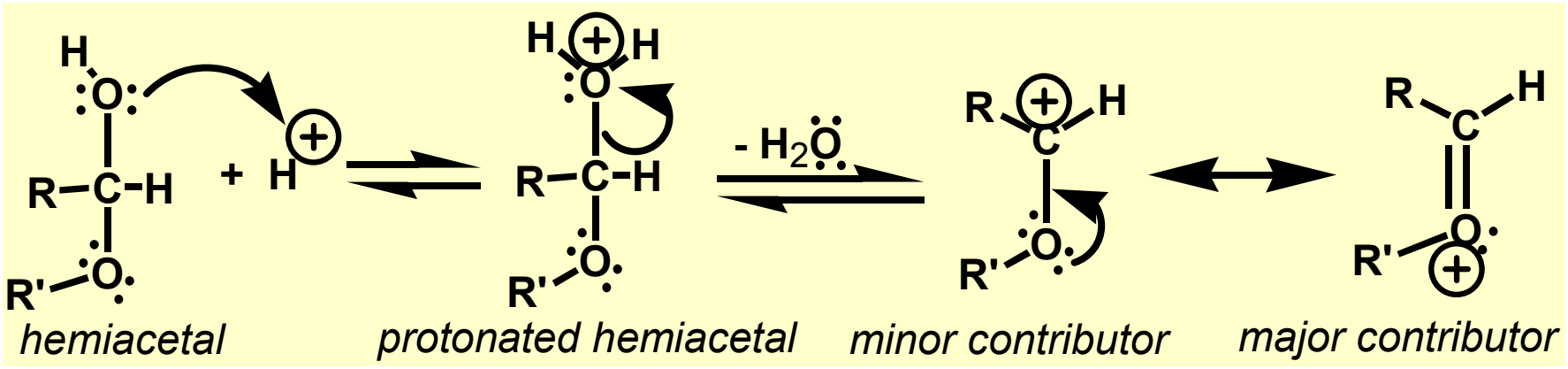
(b) Nucleophilic addition of the alcohol to the protonated aldehyde and loss of a proton from the addition product.

The alcohol is a **molecular nucleophile** (*RECALL TUTORIAL #2!!)*

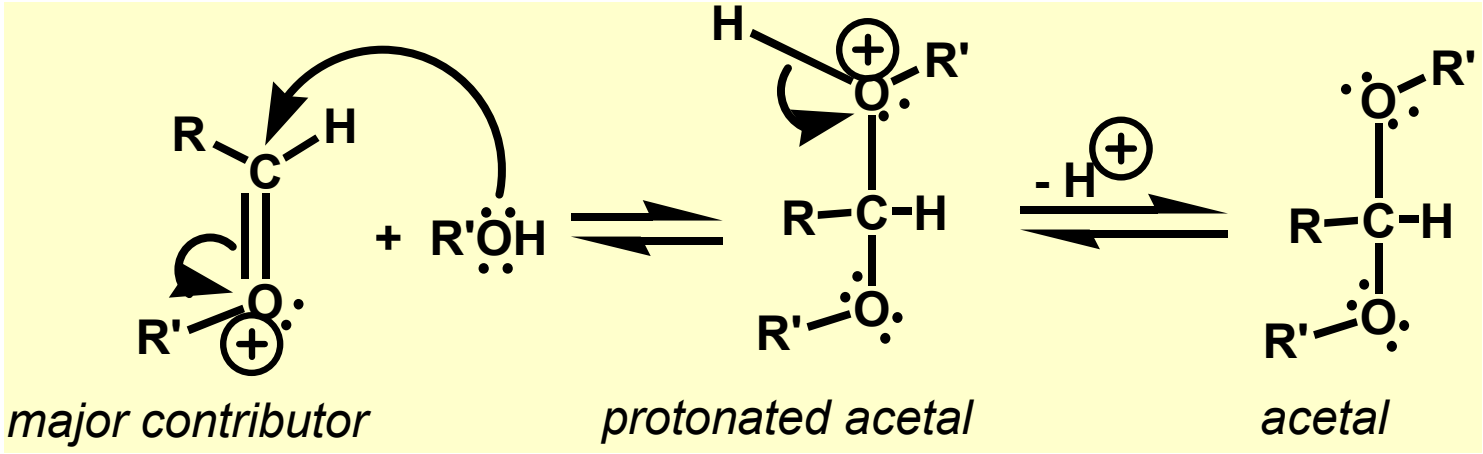


ACID-*CATALYZED* NUCLEOPHILIC ADDITION OF AN ALCOHOL TO AN ALDEHYDE →ACETAL

(c) Protonation of the OH of the hemiacetal and loss of H_2O

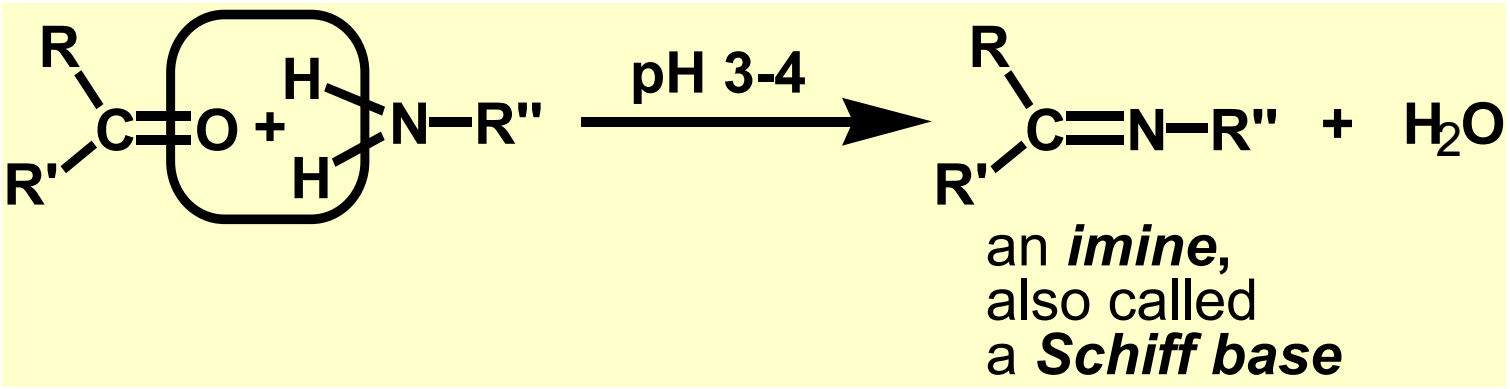


(d) **Nucleophilic addition of a second equivalent of the alcohol** to the major contributor and loss of a proton from the addition product.



EXAMPLES OF NUCLEOPHILIC ADDITION TO ALDEHYDES & KETONES

4. Addition of ammonia and primary amines

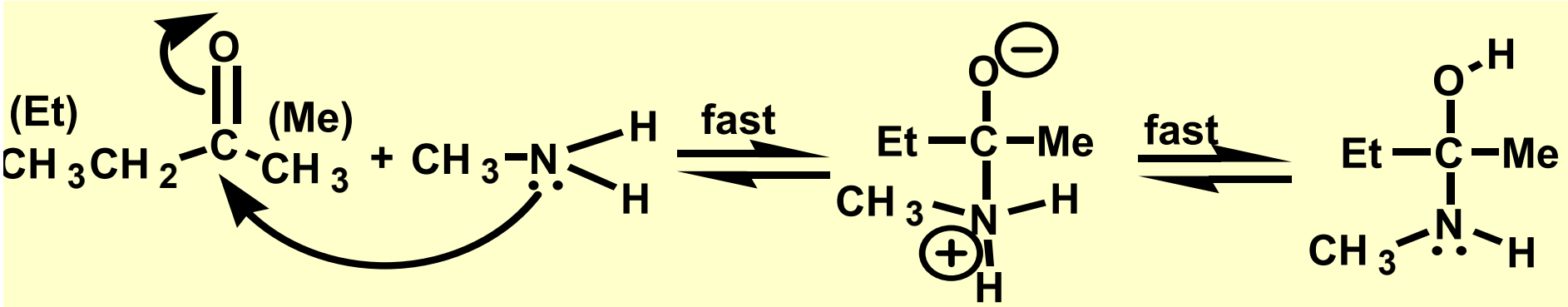


This reaction can be regarded as a condensation between the ***carbonyl compound*** and ***ammonia*** or the amine to form an ***imine*** or ***Schiff base***, with the extrusion of a molecule of ***water***.

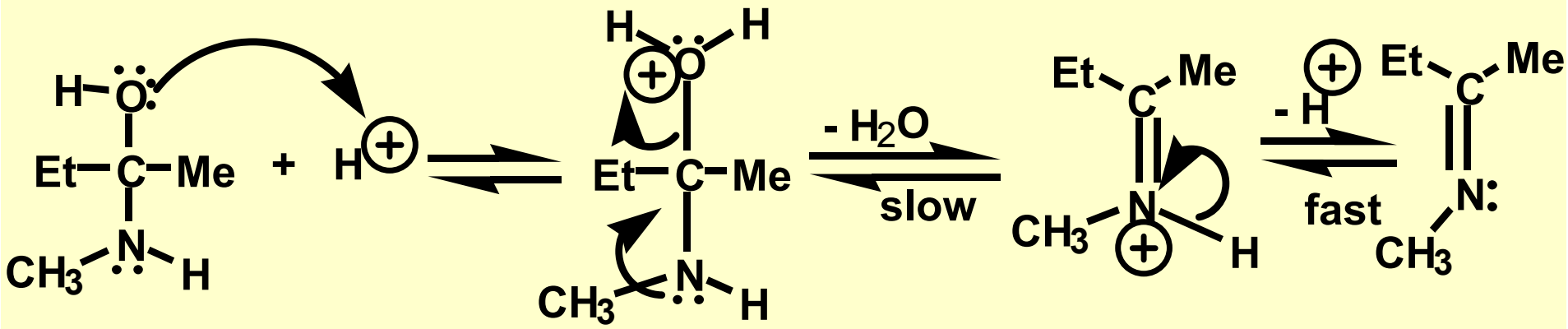
Mechanistically, the process entails nucleophilic addition of ammonia or the amine (molecular nucleophiles) to the electrophilic carbon of the carbonyl group.

ADDITION OF NH_3 AND 1° AMINES TO ALDEHYDES & KETONES: The mechanism of the reaction between butanone and methylamine

(a) Nucleophilic addition of the amine (a molecular nucleophile) to the carbonyl compound followed by a proton shift within the initial adduct.

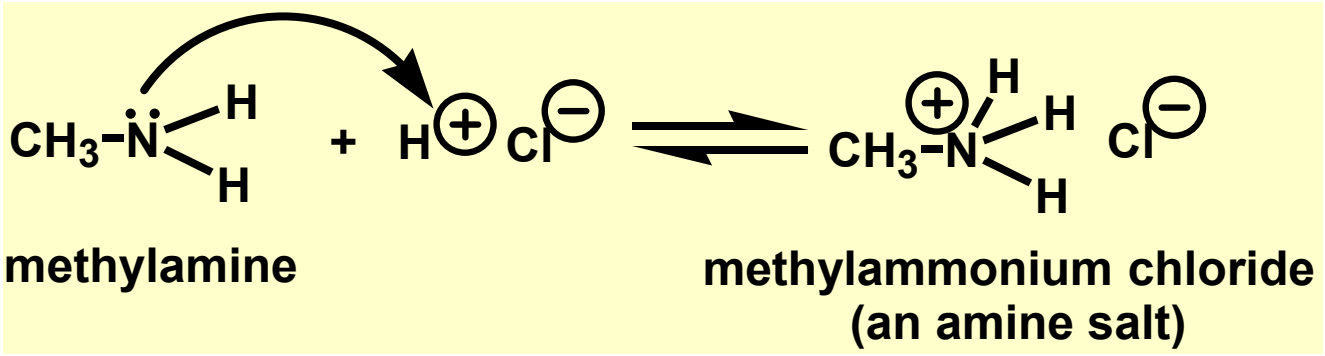


(b) Protonation of the addition product on oxygen, followed by loss of H_2O, then deprotonation to yield the ***IMINE*** or ***SCHIFF BASE***.



ADDITION OF NH_3 AND 1° AMINES TO ALDEHYDES & KETONES

Amines are basic compounds, and are protonated by acid,e.g.



methylamine

methylammonium chloride (an amine salt)

The mechanism shown on the previous slide for the formation of the Schiff base requires the presence of unprotonated amine for step (a) ***and*** acid for step (b).

HOW IS THIS POSSIBLE IN THE SAME REACTION MIXTURE?

*The pH of the reaction mixture is maintained between 3 and 4. At these pH's there are high enough concentrations of unprotonated amine (the molecular nucleophile for the addition step (a)) **and** acid to catalyze the dehydration step (b).*