Organic Chemistry

Semester-4, CBCS

Course: CEMG CC-4/GE-4

Course taught by: Kaushik Basu, Department of Chemistry, SPCMC, Kolkata
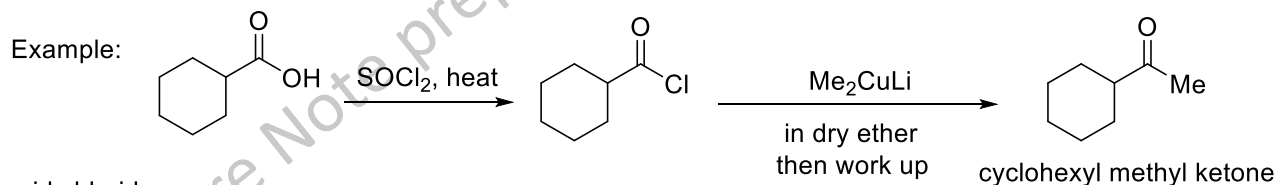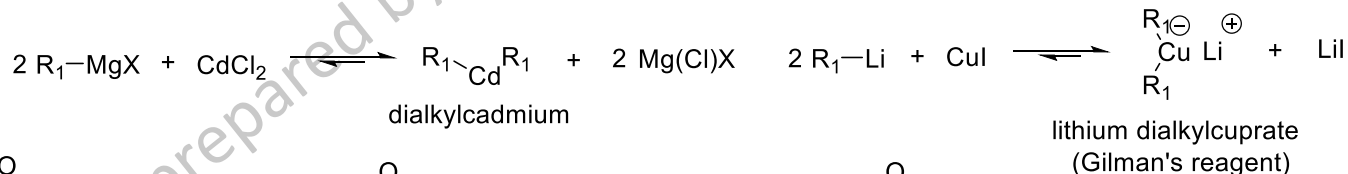
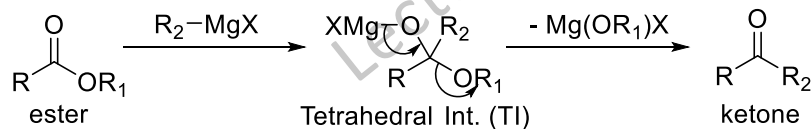email: chiralkaushik@gmail.com

Chemistry of Carbonyl Compounds

Preparation:

A] Using Organometallics and a carboxylic acid derivative:

A carboxylic acid derivative that carries a good LG can react with a GR and affords a ketone
An acid chloride seems to be an ideal choice as it is more reactive than the ketone which is necessary to stop the reaction at ketone stage.

Cl^- is an exellent LG, it is a *v. weak* base
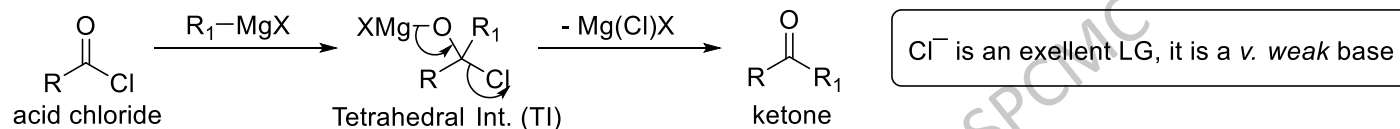
However, GR is extremely reactive, and less selective. So it has a tendency to react with the ketone grenerated *in situ*, leading to tertiary alcohol formation. Thus we need a less reactive and more selective organometallic reagent to synthesise ketone from acid chlorides. Organocoppers and organocadmiums are good choice in this regard. These are less ionic in nature and less reactive than GRs.

χ(Mg) 1.31 < χ(Cd) 1.69 < χ(Cu) 1.9
% ionic character of C-M bond decreases
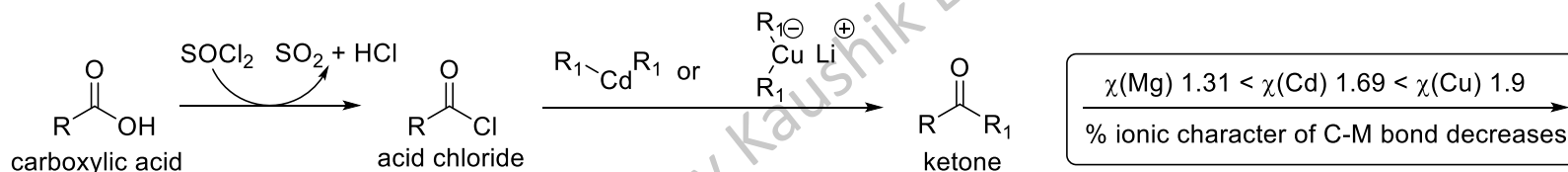
These reagents are prepared from the correpsonding GRs or organolithiums by *transmetallation* reaction.

$2\ R_1-MgX\ +\ CdCl_2 \rightleftharpoons R_1-Cd-R_1\ +\ 2\ Mg(Cl)X$

dialkylcadmium

$2\ R_1-Li\ +\ CuI \rightleftharpoons R_1-Cu-Li^+\ +\ LiI$

lithium dialkylcuprate
(Gilman's reagent)

Example:

cyclohexyl methyl ketone

Using ester in place of acid chlorides:

However, ketone is more electrophilic than ester, thus, the ketone reacts with GR to produce a tertiary alcohol.
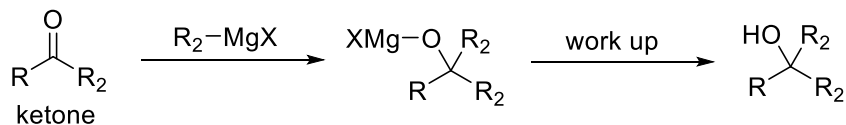
It is very difficult to stop the reaction at ketone stage. For this to happen, GR must never be present in excess during the reaction. This can be done by adding the GR drop wise into the ester taken in ether solvent (the *inverse addition*). The reverse addition must not be done, ever.
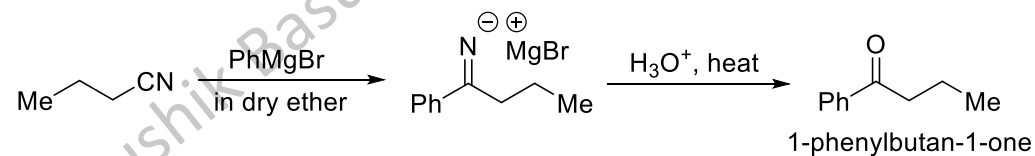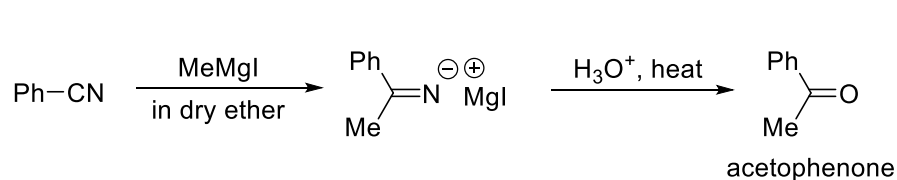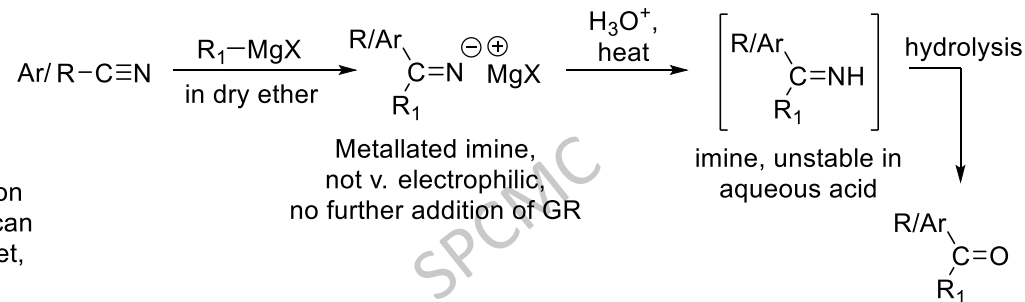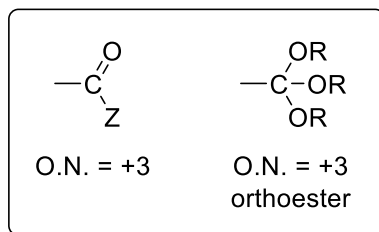
Chemistry of Carbonyl Compounds

Preparation:

B] Using Organometallics and an organocyanide:

$$-\overset{O}{\underset{Z}{C}}- \qquad -C\equiv N$$
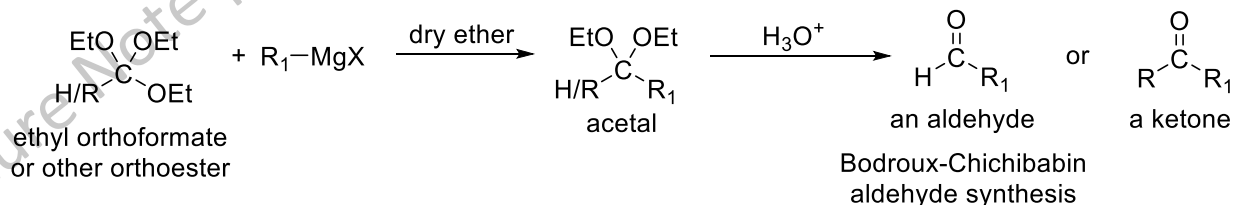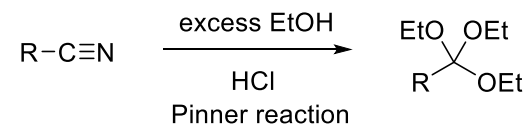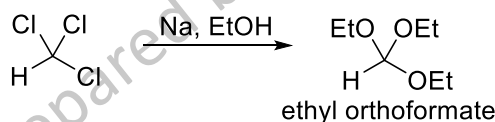
O.N. = +3   O.N. = +3
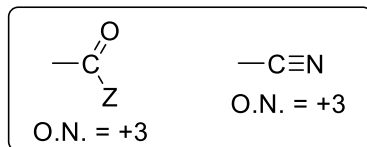
Same O.N. but no LG at all - ideal situation for organomagnesium addition. Nothing can leave, so the first addition is all that we get, in general.
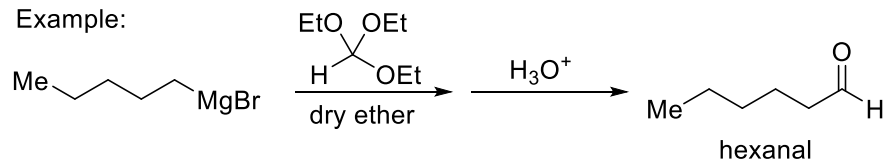
$$Ar/R-C\equiv N \xrightarrow[\text{in dry ether}]{R_1-MgX} \underset{R_1}{\overset{R/Ar}{C}}=N^{\ominus} \overset{\oplus}{MgX} \xrightarrow[\text{heat}]{H_3O^+,} \left[\underset{R_1}{\overset{R/Ar}{C}}=NH\right] \xrightarrow{\text{hydrolysis}} \underset{R_1}{\overset{R/Ar}{C}}=O$$

Metallated imine, not v. electrophilic, no further addition of GR

imine, unstable in aqueous acid

$$Ph-CN \xrightarrow[\text{in dry ether}]{MeMgI} \underset{Me}{\overset{Ph}{C}}=N^{\ominus}\overset{\oplus}{MgI} \xrightarrow[\text{heat}]{H_3O^+,} \underset{Me}{\overset{Ph}{C}}=O$$

acetophenone

$$Me\diagdown\diagup CN \xrightarrow[\text{in dry ether}]{PhMgBr} \underset{Ph}{\overset{N^{\ominus}\overset{\oplus}{MgBr}}{C}}\diagdown Me \xrightarrow[\text{heat}]{H_3O^+,} Ph\overset{O}{\diagdown}\diagup Me$$

1-phenylbutan-1-one

C] Using Organometallics and an orthoester:

$$-\overset{O}{\underset{Z}{C}}- \qquad -\overset{OR}{\underset{OR}{C}}-OR$$

O.N. = +3   O.N. = +3 orthoester

Preparation of orthoesters:

$$\underset{H}{\overset{Cl}{C}}\overset{Cl}{\underset{Cl}{}} \xrightarrow{Na, EtOH} \underset{H}{\overset{EtO}{C}}\overset{OEt}{\underset{OEt}{}}$$

ethyl orthoformate

$$R-C\equiv N \xrightarrow[\text{HCl} \atop \text{Pinner reaction}]{\text{excess EtOH}} \underset{R}{\overset{EtO}{C}}\overset{OEt}{\underset{OEt}{}}$$

$$\underset{H/R}{\overset{EtO}{C}}\overset{OEt}{\underset{OEt}{}} + R_1-MgX \xrightarrow{\text{dry ether}} \underset{H/R}{\overset{EtO}{C}}\overset{OEt}{\underset{R_1}{}} \xrightarrow{H_3O^+} \underset{H}{\overset{O}{C}}-R_1 \quad \text{or} \quad R\overset{O}{\diagup}R_1$$

ethyl orthoformate or other orthoester

acetal

an aldehyde   a ketone

Bodroux-Chichibabin aldehyde synthesis

Example:

$$Me\diagdown\diagup\diagdown MgBr \xrightarrow[\text{dry ether}]{\underset{H}{\overset{EtO}{C}}\overset{OEt}{\underset{OEt}{}}} \xrightarrow{H_3O^+} Me\diagdown\diagup\diagdown\overset{O}{\diagup}H$$

hexanal

Carbonyl group - The Queen of Organic Chemistry:
A source of diverse reactivity.

region of high e-density - nucleophilic

can react with electrophiles

region of e-deficiency - electrophilic

can react with nucleophiles

relatively acidic

base

enolate - ambident nucleophile

can react with electrophiles
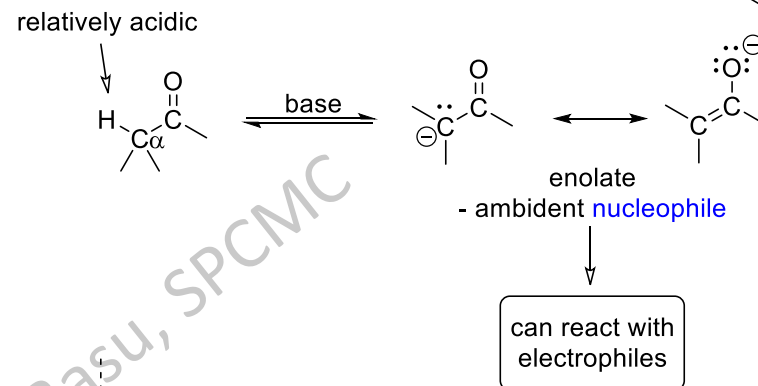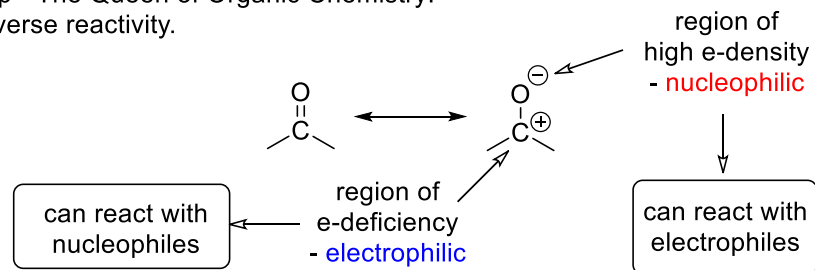
Nucleophilic addition to **polar** C=O

a) Strong nucleophiles:

carbonyl acting as an electrophile

alkoxide intermediate

Carbonyl compounds offer opportunity to form new C-C bonds
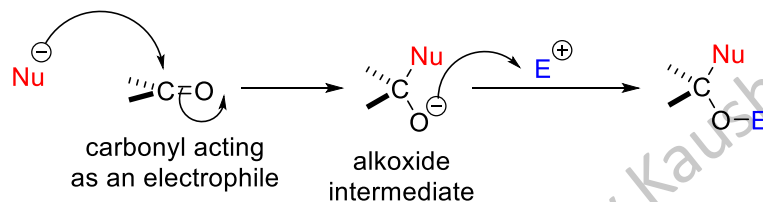
b) Weak nucleophiles:

i) under acid catalysis - activating the C=O:

sp^2, trigonal, planar

(oxocarbenium int)

regenerated

is more electrophilic than

electrophilicity of C=O enhanced by protonation
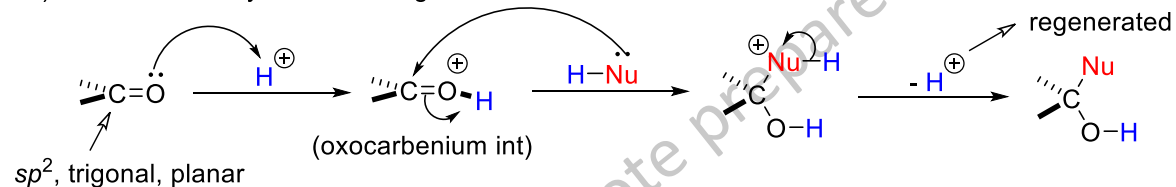
ii) under base catalysis - activating the nucleophile

(base)

B-H + Nu
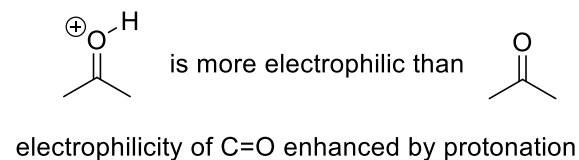
Nu^- is more nucelophilic than H-Nu

nucleophilicity of H-Nu enhanced by deprotonation

regenerated

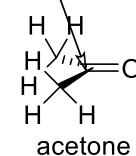Relative reactivity towards nucleophiles: The RDS is the attack of the nucleophile to the carbonyl carbon -

A] Steric effects:

direction of approach

ca. 107°

107°

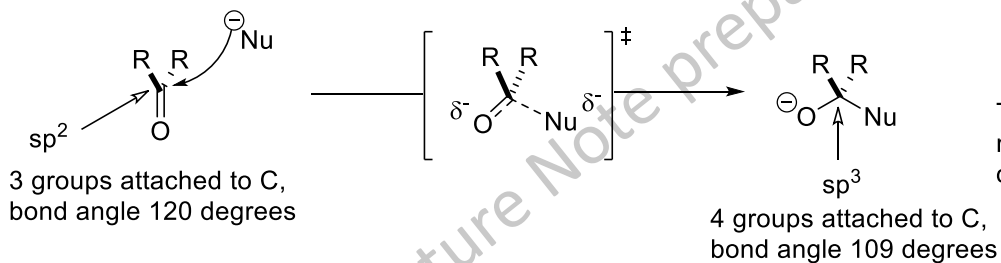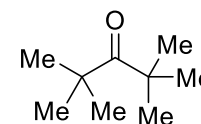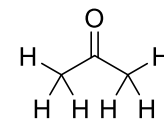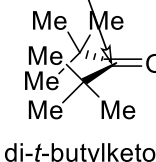nucleophilic attacks
C=O at 107° angle
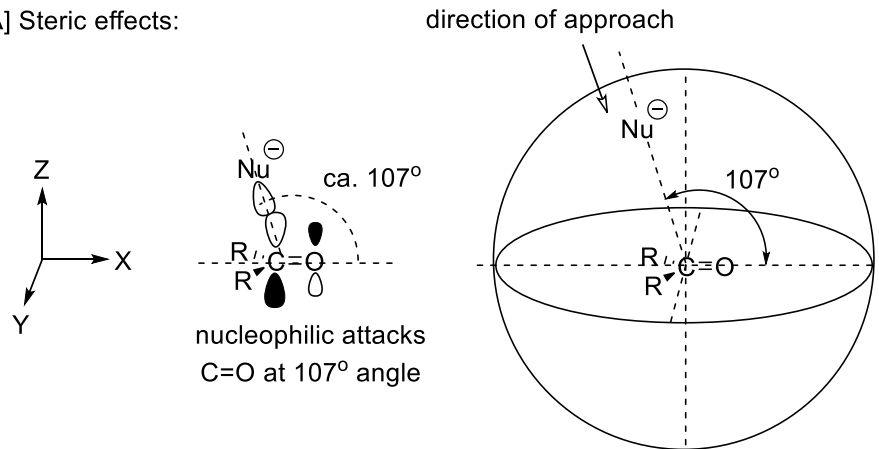
Any other components of the molecule that get in the way of (i.e., that cause steric hindrance to the) incoming nucleophile will significantly diminish the rate of addition.

This implies that as the size of R increases, it becomes increasingly difficult for the nucelophile to approach the carbonyl carbon, rate of reaction decreases.

approach easier

approach difficult

acetone

di-*t*-butylketone

sp²

3 groups attached to C,
bond angle 120 degrees

‡

sp³

4 groups attached to C,
bond angle 109 degrees

Therefore, as the nucelophile adds, the TS and the adduct becomes more crowded than the reactant. Thus, with bulky R groups, the rate of addition is lowered.

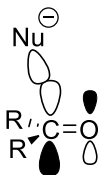Considering this, we expect the following order of reactivity:
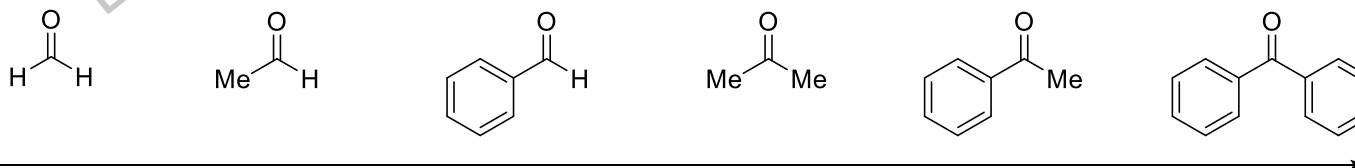
Crowding around the carbonyl carbon increases, reactivity towards nucleophile decreases

Chemistry of Carbonyls: Addition Reactions

Relative reactivity towards nucleophiles: The RDS is the attack of the ncuelophile to the carbonyl carbon -
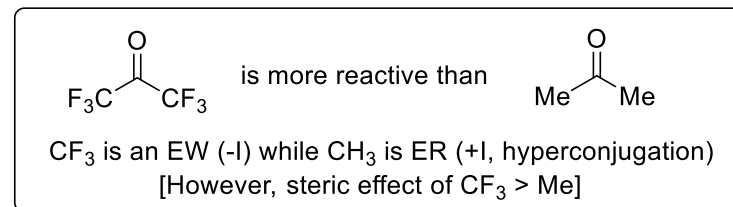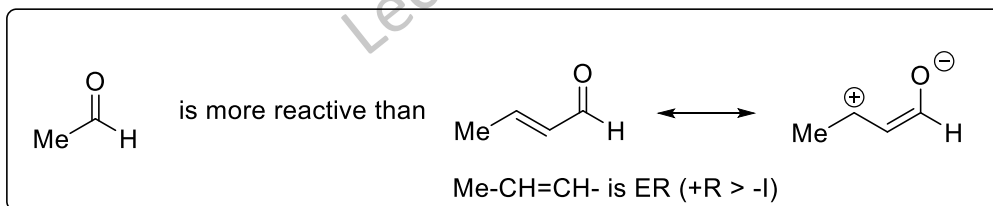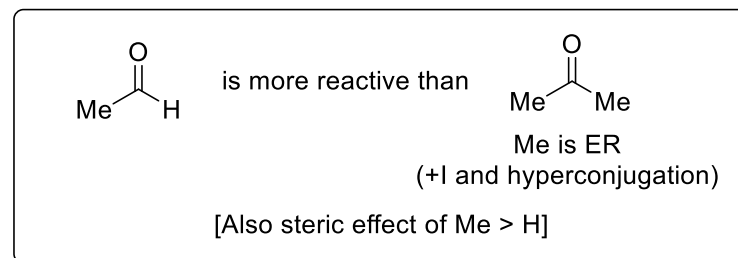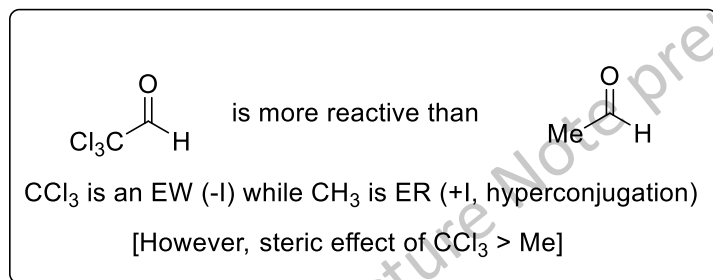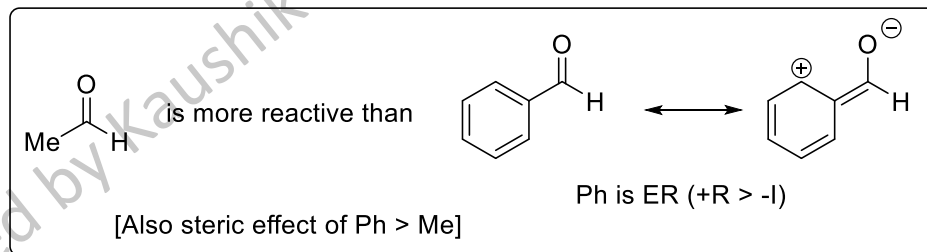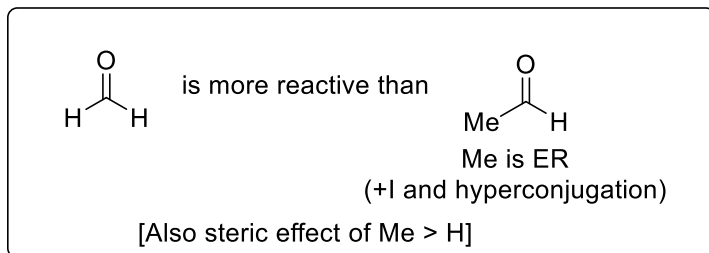
B] Electronic effects:

e-transfer from nucleophile to the carbonyl carbon
- the more e-deficient the carbonyl carbon is, fater is the nucleophilic attack.

In presence of EW substituents on the carbonyl carbon - electrophilicity of carbonyl carbon increases
- reactivity towards nucleophile increases.

In presence of ER substituents on the carbonyl carbon - electrophilicity of the carbonyl carbon decreases
- reactivity towards nucleophile decreases.

For the same nucleophile:

is more reactive than

Me is ER
(+I and hyperconjugation)

[Also steric effect of Me > H]

is more reactive than

Ph is ER (+R > -I)

[Also steric effect of Ph > Me]

is more reactive than

CCl_3 is an EW (-I) while CH_3 is ER (+I, hyperconjugation)

[However, steric effect of CCl_3 > Me]

is more reactive than

Me is ER
(+I and hyperconjugation)

[Also steric effect of Me > H]

is more reactive than

Me-CH=CH- is ER (+R > -I)

is more reactive than

CF_3 is an EW (-I) while CH_3 is ER (+I, hyperconjugation)
[However, steric effect of CF_3 > Me]

Addition of hydrogen cyanide: Formation of cyanohydrin:

Generally done with a cyanide salt and an aq. acid:

$$\text{(ketone)} \xrightarrow[\text{r.t.}]{\text{NaCN, } H_2SO_4\text{*, } H_2O} \text{NC} \quad \text{OH}$$

[* acid is added dropwise throughout the reaction]

Mechanism:

$$N\equiv C^\ominus + \text{(C=O)} \xrightarrow[\textit{slow}, \text{RDS}]{\begin{array}{c}\text{nucleophilic}\\\text{addition}\end{array}} \text{NC} \quad O^\ominus$$

(linear shape, good nucleophile)

cB of cyanohydrin
- tetrahedral geometry

$$\xrightarrow[\text{protonation}]{H-O^\oplus(H)(H)} \text{NC} \quad \text{OH} + \text{(H}_2\text{O)}$$

$$\text{NC} \quad O^\ominus \text{ (C)} \quad \text{is more basic than} \quad N\equiv C^\ominus$$
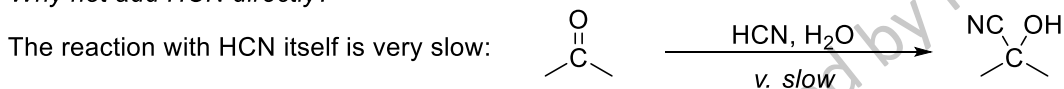
pK_{aH} 13 $\qquad\qquad$ pK_{aH} 9
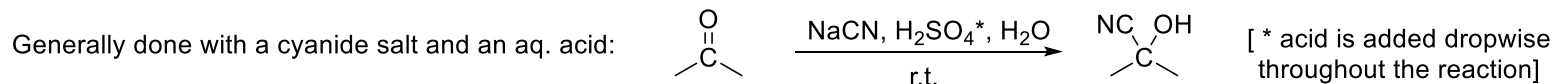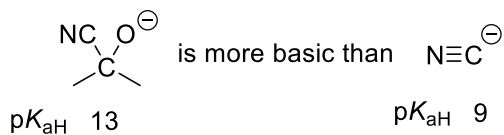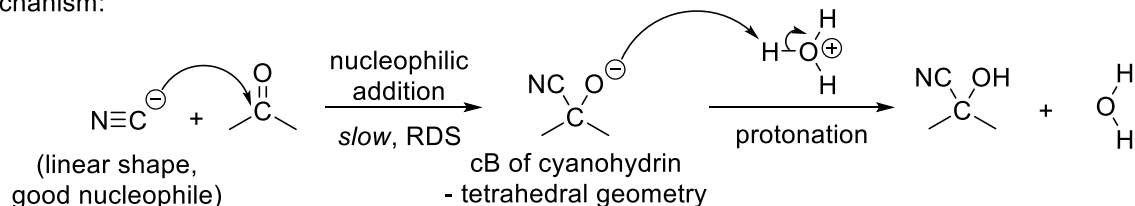
So the cB of cyanohydrin gets prefenrentially protonated as the acid is slowly added to the medium. We cannot add the acid completely at the beginning of the reaction, that would protonate the cyanide leading to loss of nucleophilicity and generation of deadly HCN.
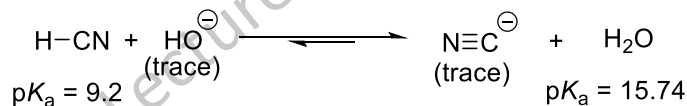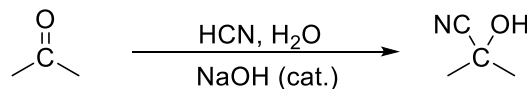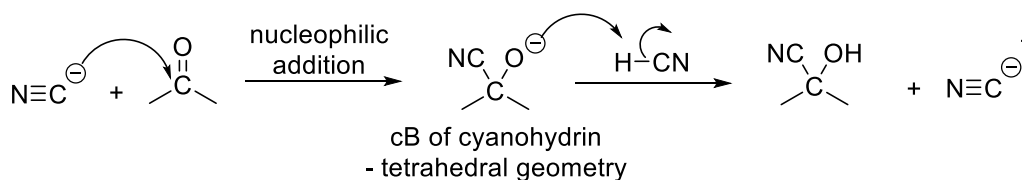
Why not add HCN directly?

The reaction with HCN itself is very slow:

$$\text{(C=O)} \xrightarrow[\textit{v. slow}]{\text{HCN, } H_2O} \text{NC} \quad \text{OH}$$

Why?

HCN is a weak acid, it does not dissociate enough generate cyanide in aq. med. for rapid reaction.

$$H-CN + H_2O \rightleftharpoons N\equiv C^\ominus + H-O^\oplus(H)(H)$$

$pK_a = 9.2$ $\qquad\qquad\qquad\qquad$ $pK_a = -1.54$
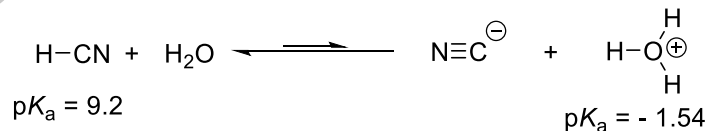
Adding a catalytic amount of alkali improves the rate dramatically:

$$\text{(C=O)} \xrightarrow[\text{NaOH (cat.)}]{\text{HCN, } H_2O} \text{NC} \quad \text{OH}$$

$$H-CN + HO^\ominus \text{(trace)} \rightleftharpoons N\equiv C^\ominus \text{(trace)} + H_2O$$

$pK_a = 9.2$ $\qquad\qquad$ $pK_a = 15.74$

goes on to attack the next C=O, steady supply of cyanide ensured

$$N\equiv C^\ominus + \text{(C=O)} \xrightarrow{\begin{array}{c}\text{nucleophilic}\\\text{addition}\end{array}} \text{NC} \quad O^\ominus \xrightarrow{H-CN} \text{NC} \quad \text{OH} + N\equiv C^\ominus$$

cB of cyanohydrin
- tetrahedral geometry

Lecture Note prepared by Kaustik Basu, SPCMC

Addition of $NaHSO_3$: Formation of bisulfite adducts

Sodium bisulfite ($NaHSO_3$) adds to aldehydes and some ketones to give what is usually known as a bisulfite addition compound. Most aldehydes, methyl ketones, and unhindered cyclic ketones respond favourably when treated with a concentrated aq. solution of $NaHSO_3$.
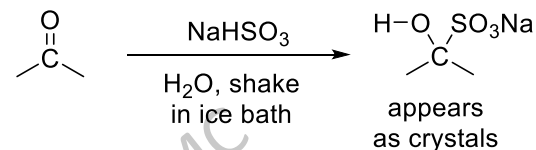
Mechanism:
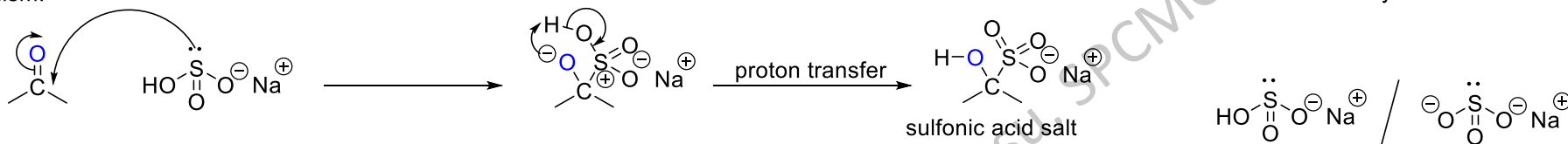
The nucleophile could very well be the sulfite ion, which is more nucleophilic than the bisulfite:

sulfonic acid salt
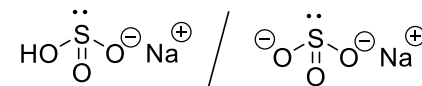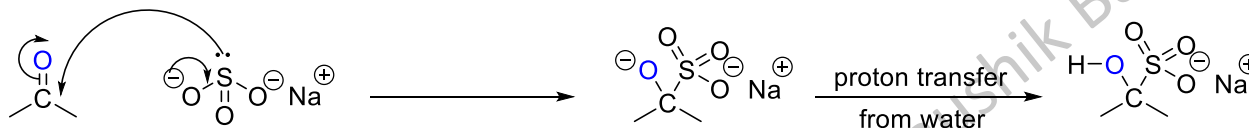
S-end more nucleophilic than the O⁻, the former is the more polarizable centre.

Sulfite / bisulfite ions are potent nucleophile that attack the carbonyl groups of most aldehydes and many unhindered ketones readily, and they are already present as anions in the medium - the addition reaction thus requires *no acid or base catalysis*.
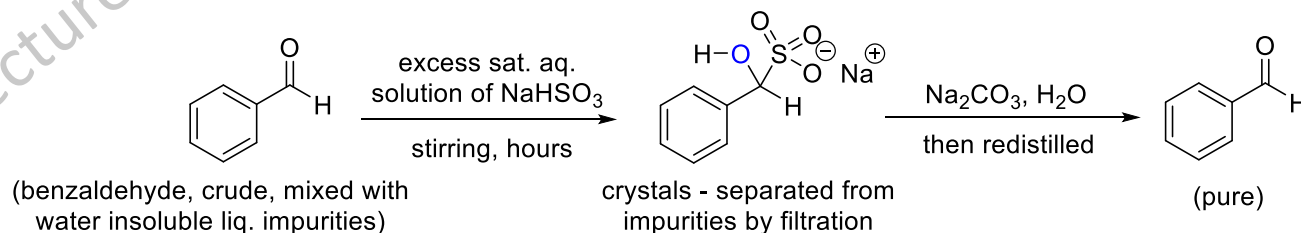
The addition reaction is reversible, the bisulfite adducts decompose to parent carbonyls when taken in dilute acid or base:
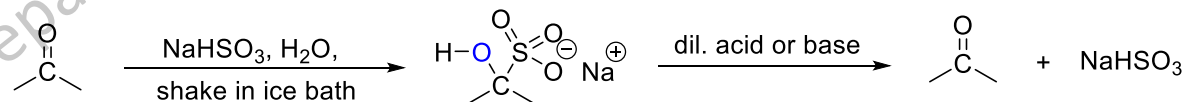
bisulfite adduct, salt - soluble in water, but on cooling appears as crystals

Using the reversibility:

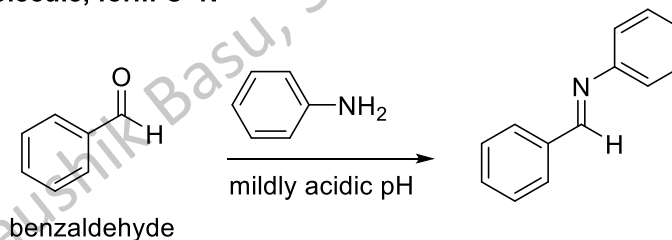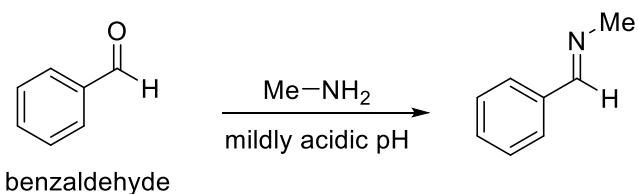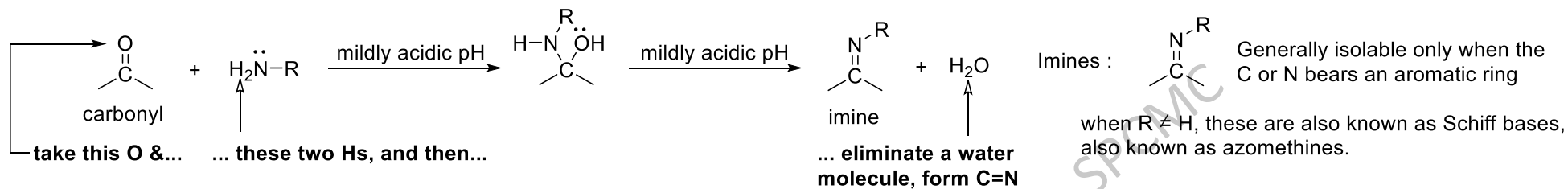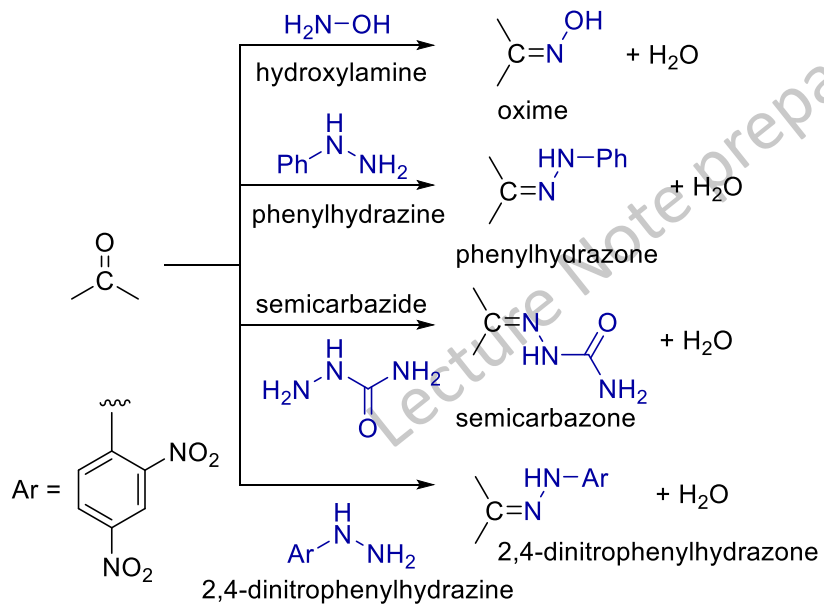1. Purification of liquid aldehydes/ketones:

(benzaldehyde, crude, mixed with water insoluble liq. impurities)

crystals - separated from impurities by filtration

(pure)

Lecture Note prepared by Kaushik Basu, SPCMC

Chemistry of Carbonyls: Nucleophilic substitution at carbonyl carbon with the loss of carbonyl O

Reaction of nitrogen nucleophiles:

Primary amines react with carbonyl compound under acid-catalysed condition to produce imines (C=N bonds)

carbonyl

take this O &...   ... these two Hs, and then...

... eliminate a water molecule, form C=N

imine

Imines :

Generally isolable only when the C or N bears an aromatic ring

when R ≠ H, these are also known as Schiff bases, also known as azomethines.

benzaldehyde

$Me-NH_2$

mildly acidic pH

benzaldehyde

$-NH_2$

mildly acidic pH

Reactions with derivatives of ammonia: Isolable imine derivatives

H_2N-OH
hydroxylamine

$C=N$ OH $+ H_2O$
oxime

Ph $\overset{H}{N}$ NH_2
phenylhydrazine

$C=N$ HN—Ph $+ H_2O$
phenylhydrazone

semicarbazide

H_2N-N NH_2
               O

$C=N$ HN O NH$_2$ $+ H_2O$
semicarbazone

$Ar =$

NO_2

NO_2

Ar $\overset{H}{N}$ NH_2
2,4-dinitrophenylhydrazine

$C=N$ HN—Ar $+ H_2O$
2,4-dinitrophenylhydrazone

These ammonia derivatives are unusually nucleophilic:

H_2N-OH
(N less env than O, more nucleophilic)

Ph $\overset{H}{N}$ NH_2
(N is conjugated with Ph, less nucleophilic than N)

H_2N N H NH_2
               O
(The two N are conjugated with C=O, less nucleophilic than N)

Reason for stability:

The addition product is resonace-stabilized

Chemistry of Carbonyls: Nucleophilic substitution at carbonyl carbon with the loss of carbonyl O
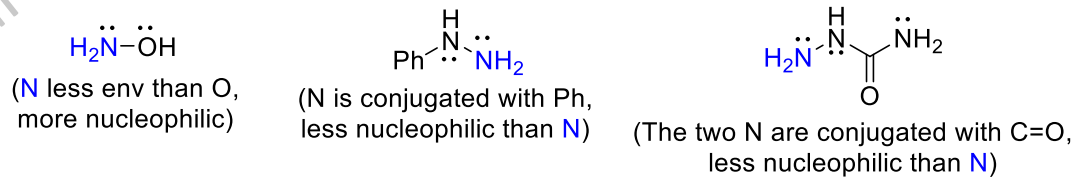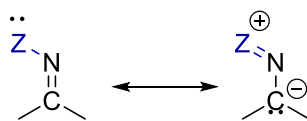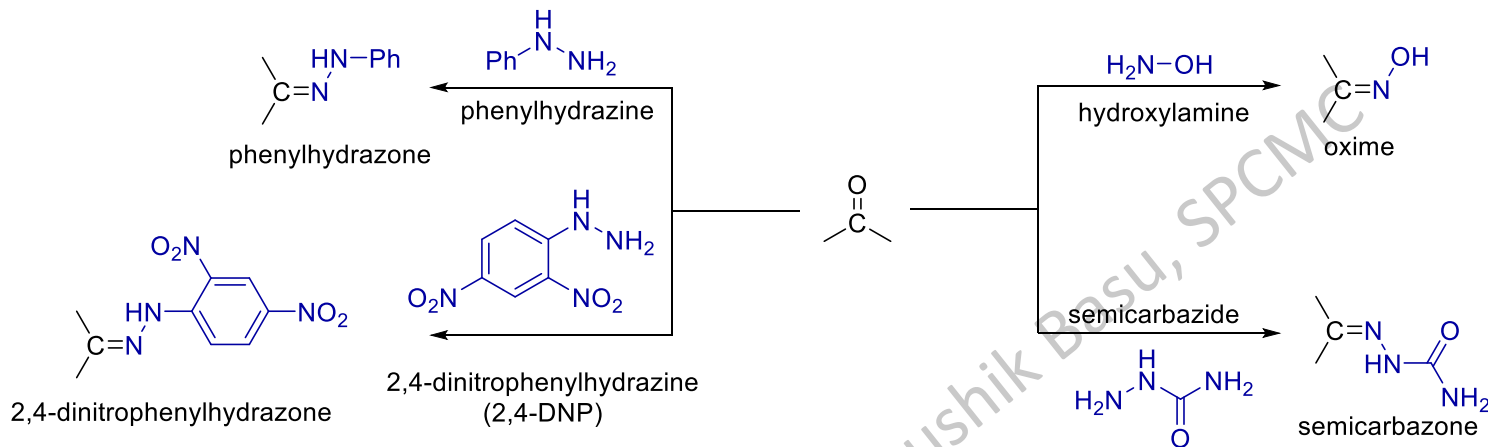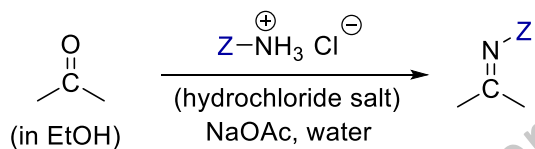
Reaction of nitrogen nucleophiles:

Reactions with derivatives of ammonia: Isolable imine derivatives


phenylhydrazine

phenylhydrazone

2,4-dinitrophenylhydrazone

2,4-dinitrophenylhydrazine (2,4-DNP)

hydroxylamine

oxime

semicarbazide

semicarbazone

Method of preparation: oximes, semicarbazones and phenylhydazones:

$Z-NH_3^{\oplus}$ $Cl^{\ominus}$
(hydrochloride salt)
NaOAc, water

(in EtOH)

NaOAc is a salt of weak acid AcOH, and strong base NaOH, it liberates the ZNH_2 from its hydrochloride salt *in situ*

2,4-DNP derivatives:

cat. H_2SO_4, EtOH
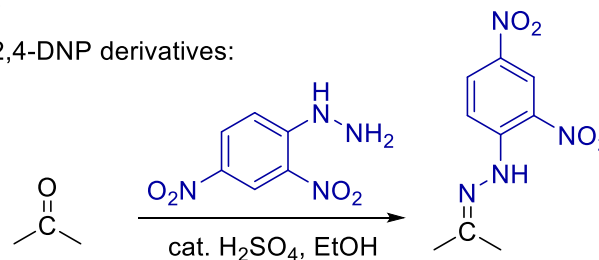
These derivatives are generally crystalline with sharp m.p.s & can be used in identifying unknown organic samples:

Suppose you have been given a liquid that could be either A or B, two isomeric enones.

How can you identify which is it?

The boiling points of these compounds are too similar for an unambiguous identification.

Yet the melting point of either a 2,4-DNP derivative or a semicarbazone of A and B are widely different.

So you can simply prepapre a 2,4-DNP derivative of the liquid sample, isolate it, and check the melting point to see with which 2,4-DNP derivative it tallies.
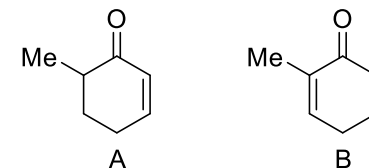
	A	B
B. P. (°C)	69-71	69-70
Semicarbazone, M. P. (°C)	177-178	207-208
2,4-DNP dev., M. P. (°C)	162-164	207-208

**Chemistry of Carbonyl: Fehling's Solution and Tollens' Reagent: Oxidation**

Fehling's solution is an alkaline solution containing cupric tartrate complex. Fehling's is always prepared fresh in the laboratory. It is made initially as two separate solutions, known as Fehling's A and Fehling's B. Fehling's A is a blue aqueous solution of copper(II) sulfate, while Fehling's B is a clear and colorless solution of aqueous potassium sodium tartrate (also known as Rochelle salt) and a strong alkali (commonly sodium hydroxide).Equal volumes of the two mixtures are mixed to get the final Fehling's Solution, which has a deep blue colour.
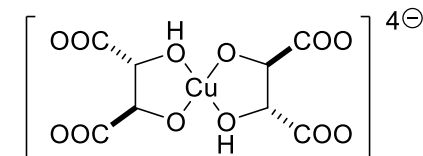
Tollens' Reagent is an alkaline solution containing $Ag(NH_3)_2^+$. This reagent must be freshly prepared in the laboratory. One common preparation involves two steps. First a few drops of dilute sodium hydroxide are added to some aqueous silver nitrate which cause a brown precipitate to appear, that of Ag_2O:

$$2\ AgNO_3 + 2\ NaOH \longrightarrow Ag_2O\ (s) + 2\ NaNO_3 + H_2O$$

To this is added sufficient aqueous ammonia dissolve the brown soild. The resulting solution contains $[Ag(NH_3)_2]^+$ complexes in the mixture, which is the main component of Tollens' Reagent. Sodium hydroxide is reformed:
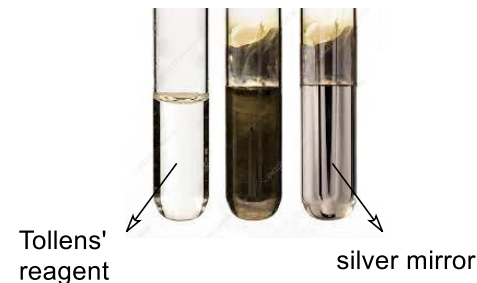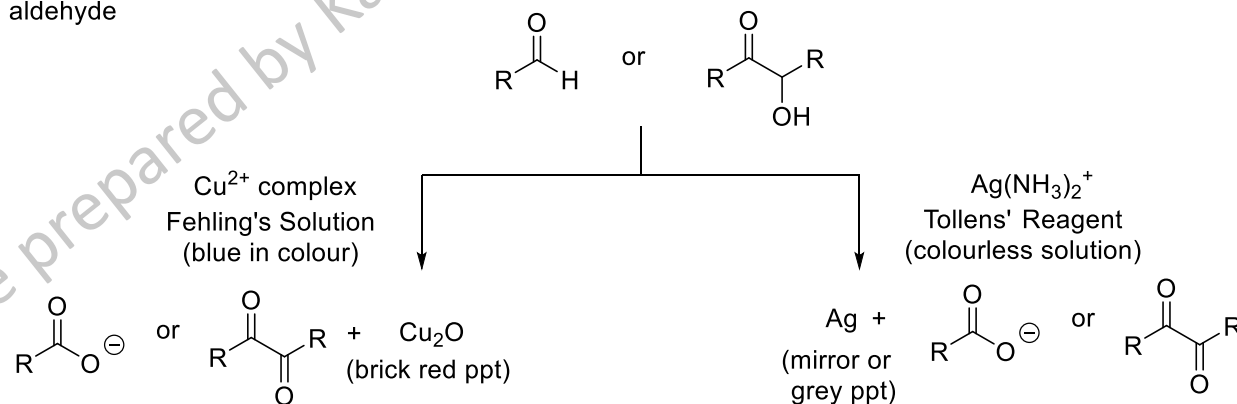
$$Ag_2O\ (s) + 4\ NH_3 + 2\ NaNO_3 + H_2O \longrightarrow 2\ [Ag(NH_3)_2]NO_3 + 2\ NaOH$$
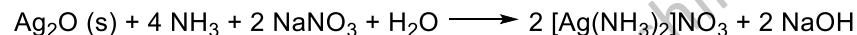
These reagents, Fehling's and Tollens', can oxidise an aldehyde or an α-hydroxyketone

image taken form: https://microbiologyinfo.com/

Blue Cu(II)

colour change with addition of an increasing amount of aldehyde

Cu^{2+} complex
Fehling's Solution
(blue in colour)

$Ag(NH_3)_2^+$
Tollens' Reagent
(colourless solution)

Ag +
(mirror or grey ppt)

+ Cu_2O
(brick red ppt)

Tollens' reagent

silver mirror

In each case, the change is vivid. Thus these reagents are used for the qualitative detection of an aldehyde or a-hydroxyketone.

(10)