Chemistry of Carbonyl Group

Contents

Chemistry of Carbonyl Group

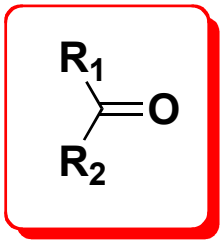
Contents

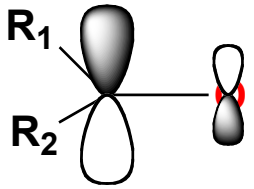
Chemistry of Carbonyl Group

Contents

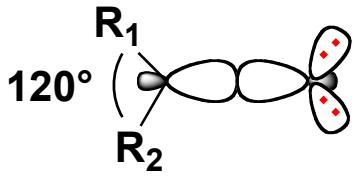
Carbonyl Compounds I: Introduction

Structure of Carbonyl



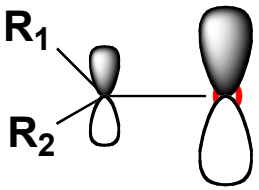


Empty, antibonding π^* orbital



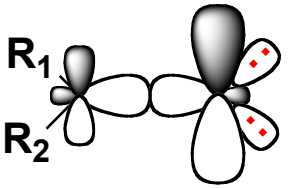
Filled σ orbital

+



Filled π orbital

=

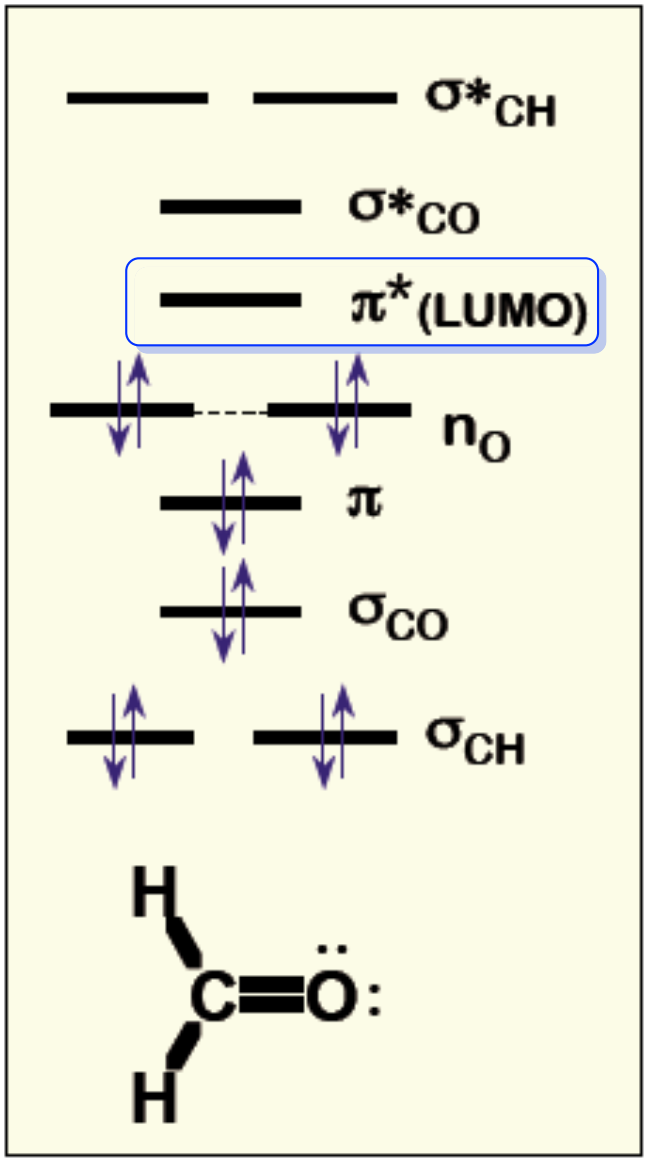


Complete diagram of filled orbitals of C=O bond

C=O has a sp^2 hybridized carbon, so C=O is planar.

C=O group is arguably the most important functional group in organic chemistry

Molecular Orbitals of Formaldehyde



2 σCH 2σ*CH
1σCO 1σ*CO
1πCO 1π*CO
2nO

Structure of Carbonyl

Bond energy (KJ.mol^{-1}): C-O (351); C=O (720)
Bond lengths (Å): C-O (1.43); C=O (1.21)
Electronegativity: C (2.5); O (3.5)

C=O bond is twice as strong as C-O single bond, so why it is so reactive?

Key:

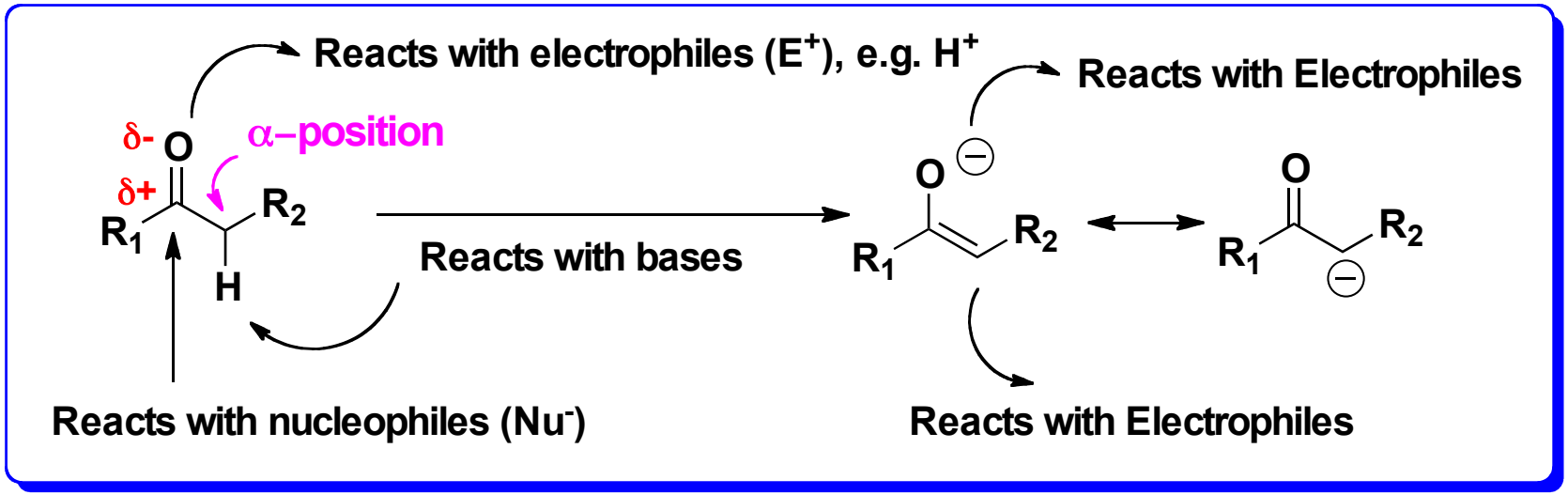
C=O is polarized as oxygen is more electronegative than carbon:

*** in filled π orbital O has a large orbital coefficient than C;**
*** the unfilled π antibonding orbital is skewed in the opposite direction with a large coefficient at the C atom.**

Therefore, There is a partial negative charge on O and a partial positive charge on C. The positively charged carbon atom attracts the negatively charged nucleophiles making the nucleophile addition at the carbon atom of C=O an easy process.

Note: For C=C double bond: Bond energy 614 KJ/mol; Bond length: 1.34 Å
C=C double bond is electron-rich, hence nucleophilic.

Potential Reactivity of Carbonyl Compounds



Three Facts:

The partially positively charged carbonyl carbon acts as an electrophile (reacts with Nu^-).

The negative charged O atom acts as an nucleophile (reacts with E^+). O in C=O is a weak Brønsted base (conjugate acid is a very strong acid), but a strong Lewis base (has two lone pairs)!

The α CH is acidic, deprotonation leading to enolate making the α-CH nucleophilic.

Reminder: pKa of typical Carbonyl compounds

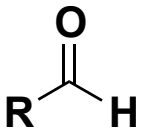
	pKa (H_2O)	pKa (DMSO)
CH_3CHO	~17	
CH_3COCH_3	~17	26.5
CH_3COOCH_3		29.5
CH_3CONEt_2		35
CH_3NO_2	10	17.2
$CH_3COCH_2COCH_3$	9	13.3

	ketone	carboxylic acid	carboxylic ester	amide	phenol
pK_{aH} of carbonyl oxygen	-7	-7	-5	-0.5	-7

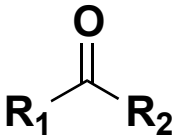
Type of Carbonyl Compounds

Nucleophilic Addition

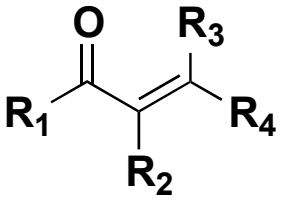
Aldehyde



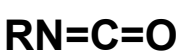
Ketone



Enone

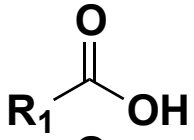


Isocyanate

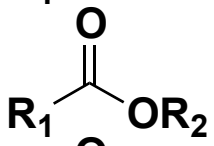


Nucleophilic Substitution (Addition—Elimination)

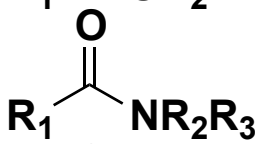
Carboxylic Acid



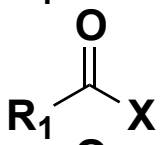
Ester



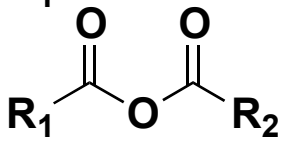
Amide



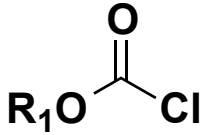
Acyl halide



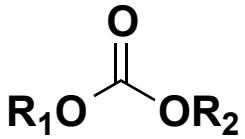
Acyl anhydride



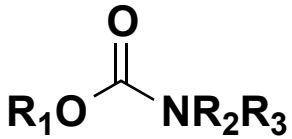
Chloroformate



Carbonate



Carbamate



Factors Control the Rate of Nucleophilic attack on C=O

Magnitude of δ+ on the carbon of C=O: more positive the C is, the faster the nucleophilic addition.

a) Resonance effects: Resonance can increase or decrease the δ+ on the carbon of C=O. In ester and amide, the presence of OR and NR_2 group decrease the δ+ of the C of C=O relative to that of ketone, so esters and amides are less prone to nucleophilic attack relative to ketone.

b) Inductive effects: when considering the reactivity of the same family of carbonyl compounds, the inductive effect needed to be taking into consideration; e.g. the carbonyl of $Cl_3CCOCCl_3$ is more electrophilic than that of H_3CCOCH_3 because of the electron-withdrawing power of the CCl_3 group.

c) Steric Effects: The presence of a large group adjacent to C=O function slows down the nucleophilic attack. Note that the bond angle between R_1 and R_2 in $R_1R_2C=O$ is about 120° . After nucleophilic addition, the angle between R_1 and R_2 is reduced to 109° since carbon became sp3 hybridized, hence more crowded in product.

d) Leaving group: A good leaving group render the carbonyl substitution reaction easier (e.g. acyl chloride is more reactive than ester towards nucleophile.

Chemistry of Aldehydes and Ketones

Why Aldehydes (RCHO) is more reactive than ketone (R^1COR^2) towards nucleophile?

α) **δ+ of C=O: Alkyl group is electron-donating. There are 2 alkyl residues in ketone and only 1 in aldehyde, so δ+ of C=O in aldehyde > δ+ of C=O in ketone, aldehydes are more reactive than ketone.**

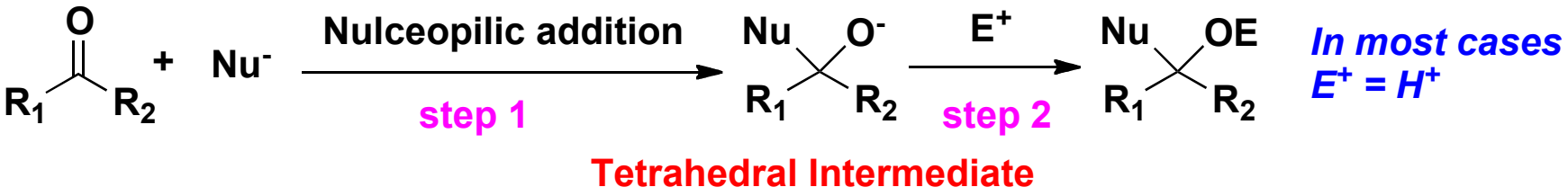
b) **Steric effect: Alkyl is bigger than H, so steric hindrance is more pronounced in ketone than in aldehyde. Therefore, aldehydes are more reactive than ketone**

Important: There are no leaving group present in aldehydes and ketones (cleave of the C-C bond is a high energy process, so addition reaction occurs at the expense of the substitution reaction.

Carbonyl Compounds II: Reversible Nucleophilic Additions

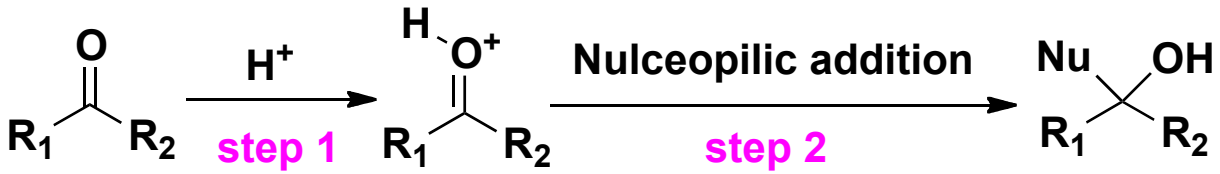
Nucleophilic Addition to Aldehydes and Ketones: Two Possible Mechanistic Pathways

Pathway 1 (under neutral and basic conditions):



Step 1 is rate-limiting step, proton transfer (E^+ = H) is generlly a fast rxn.

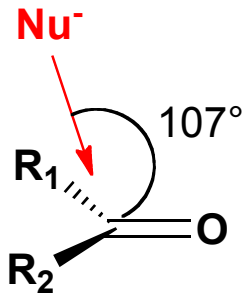
Pathway 2 (under acidic conditions):



- **Carbonyl oxygen is a very weak Brønsted base, strong Brønsted acid is needed to effect the protonation.**
- **Step 2 is the rate rate-limiting step although the protonated C=O is more electrophilic than the non-protonated one.**
- ***Lewis acid can be used instead of H^+ to activate C=O and can be catalytic*.**

Nucleophilic Addition to Aldehydes and Ketones: Burgi-Dunitz Angle

The Bürgi-Dunitz angle describes the angle of attack of a nucleophile at a carbonyl center. The angle was named after Hans-Beat Bürgi and Jack D. Dunitz.



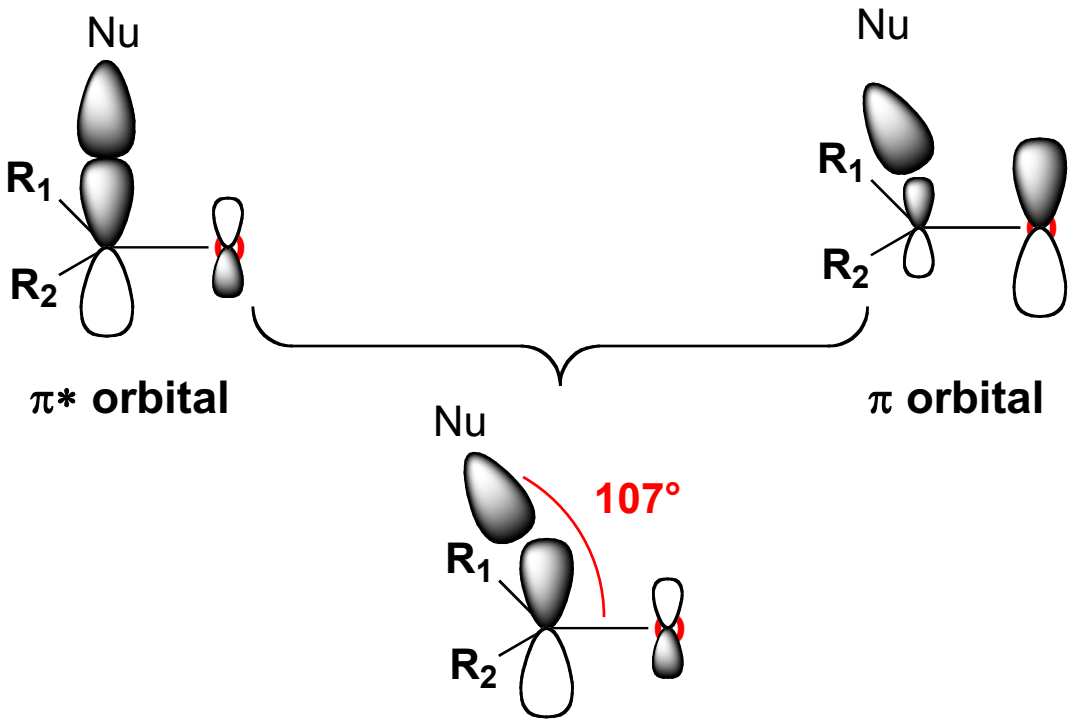
The angle of attack is neither 90° , nor 109° (bond angle of tetrahedral carbon). It is 107° . It allows maximum orbital overlap between HOMO of Nu and LUMO of C=O

Important for understanding the stereochemical outcome of nucleophilic addition (will not be addressed in this course).

Burgi-Dunitz Angle, Why 107°

90° attack, better orbital overlap between lone pair of Nu and π* orbital of C=O

However, this orientation suffer from repulsion from the Filled π orbital



How the Reaction Will be Presented in this Course

a) A General Reaction Scheme

b) Mechanism (Arrow pushing)

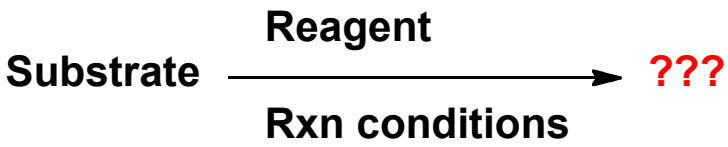
c) Examples

Two Type of Nucleophilic Addition to Carbonyl:
Reversible Addition
Irreversible Additions

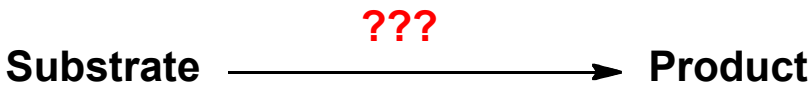
Learning Organic Reactions…by Knowing the Reaction Mechanism

For each reaction type: Understand the electron flow from SM to product
Be able to:

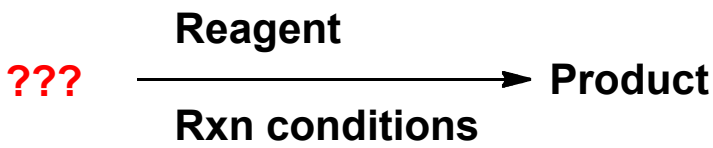
a) **Provide the structure of the products if the the structure of substrates, reagents and reaction conditions are known.**



b) **Provide the reagents and reaction conditions if the structure of the SM and the products are known.**

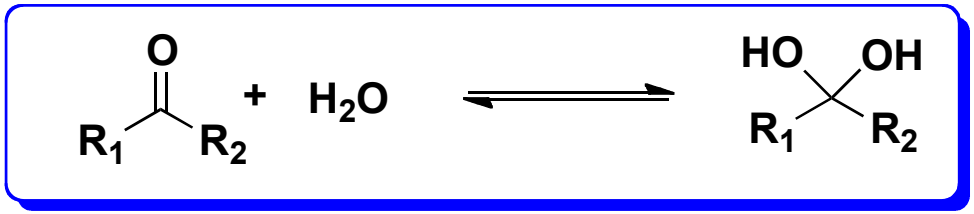


c) **Provide the structure of the SM if the structure of the products, reagents and reaction conditions are known.**

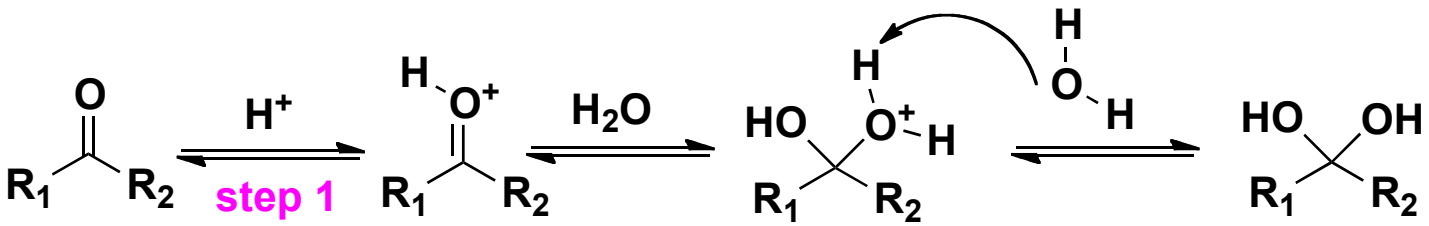


Reversible Addition to Aldehydes and Ketones

Addition of Water Leading to Hydrate



The reaction is generally catalyzed by acid. The mechanism is as follows:



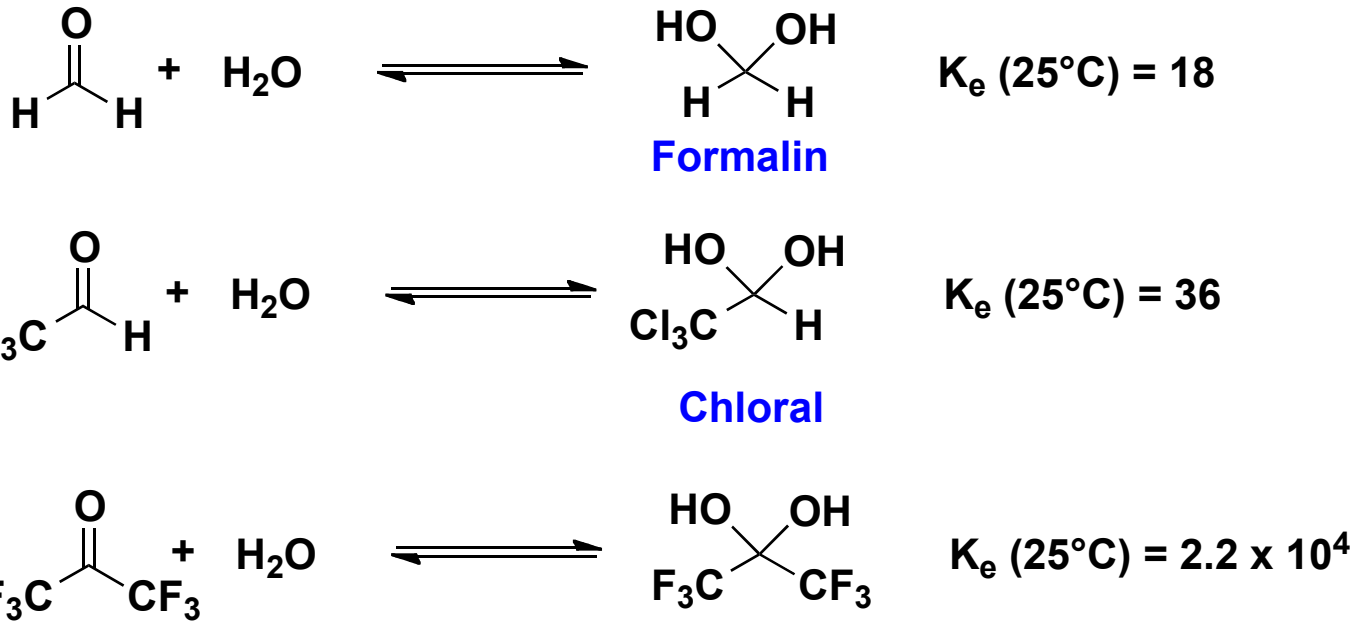
In general, only a small amount of aldehydes and ketones were hydrated.
Ketones are less prone to hydration than aldehyde (why?), e.g.:
K_e of MeCHO = 0.01, K_e of MeCOMe = 1.8 x 10^{-5}.
Hydrate is unstable and generally difficult to isolate.

However, Hydrate can be the main form in water with strongly electrophilic aldehydes (How to render the C=O electrophilic??)

Reversible Addition to Aldehydes and Ketones

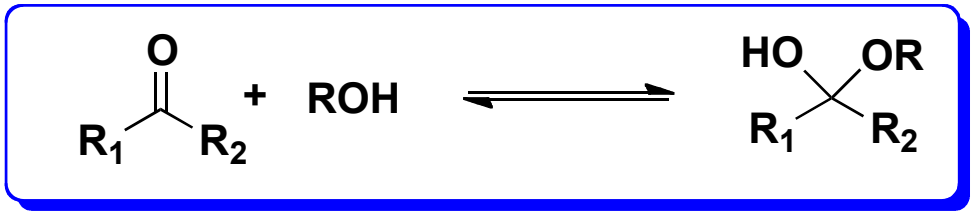
Addition of Water Leading to Hydrate

HCHO, Cl_3CCHO, F_3CCHO, F_3CCOCF_3 exist mainly in its hydrate form.

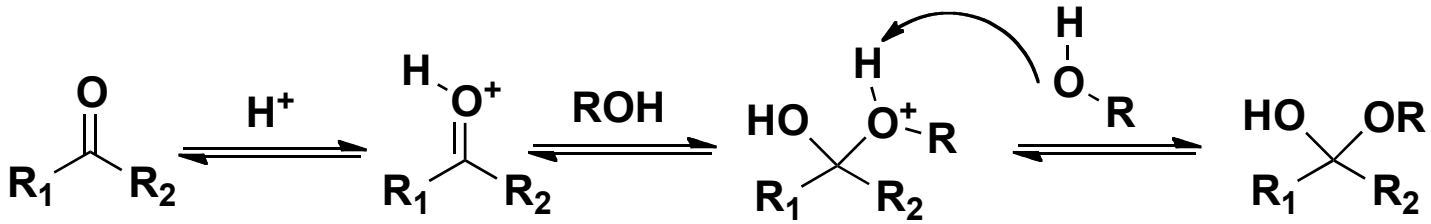


Reversible Addition to Aldehydes and Ketones

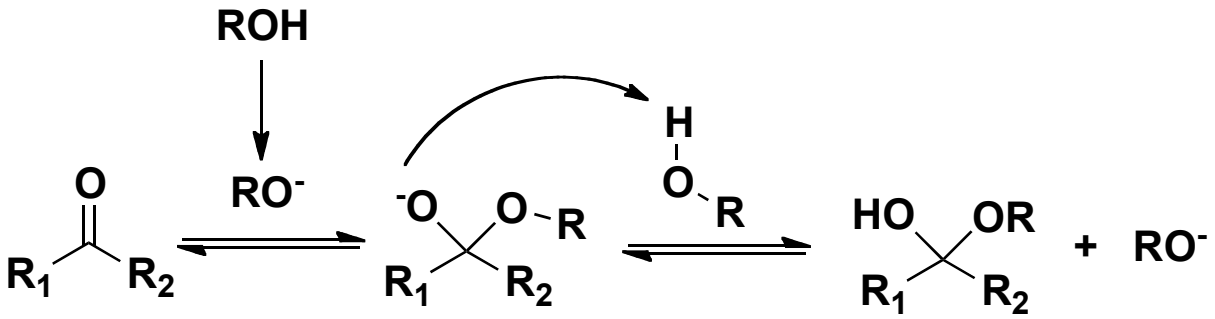
Addition of Alcohol Leading to Hemiacetal



The reaction is generally catalyzed by acid. The mechanism is as follows:



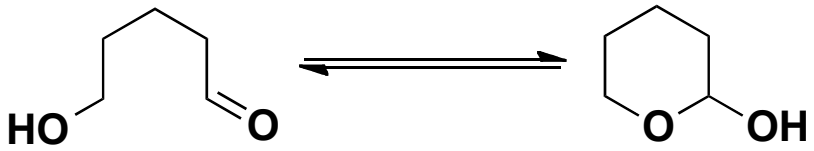
The reaction can also be base catalyzed. The mechanism is as follows:



Reversible Addition to Aldehydes and Ketones

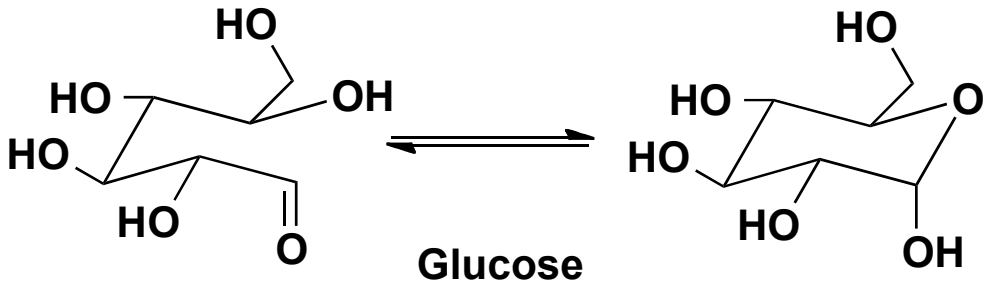
Addition of Alcohol Leading to Hemiacetal

Energy is needed to promote the hemiacetal formation.
The K_e for most of the hemiacetal reaction is less than one, except the formation of 5- and 6-membered cyclic hemiacetal



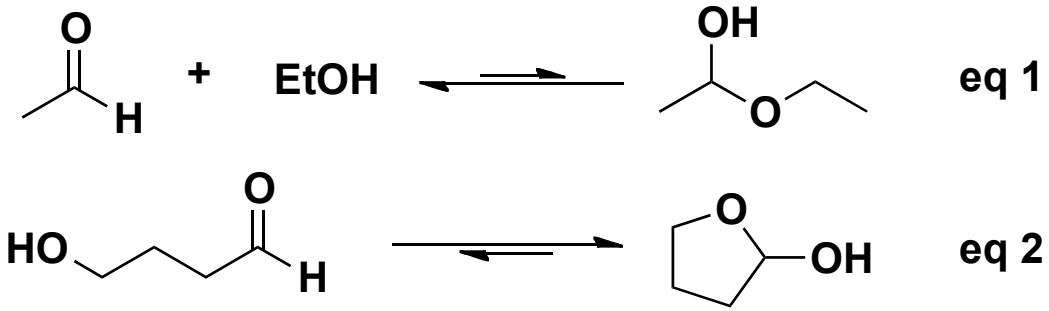
$K_e = 16$

Cyclic hemiacetal exist in nature, e.g. glucose



Why 5- and 6-Membered cyclic acetals are Easy to Form: Entropy vs Enthalpy

Enthalpy change depends on the bond broken and bond formed and is inherent to a given reaction
Entropy can became a dominant factor when one deals with two similar reactions: one intermolecular and the other intramolecular.



The hemi-acetal formation in both equation has similar enthalpy changes. However, eq 1 has tendance to go to the left side, while eq2 moves more to the right, so why?

Both reaction loose entropy, however, the bimolecular reaction (eq 1) loose more entropy than the intramolecular one shown in eq 2).

Note: 5- and 6-membered rings are always easy to form. However, macrocyclization is difficult due to the significant lose of entropy.

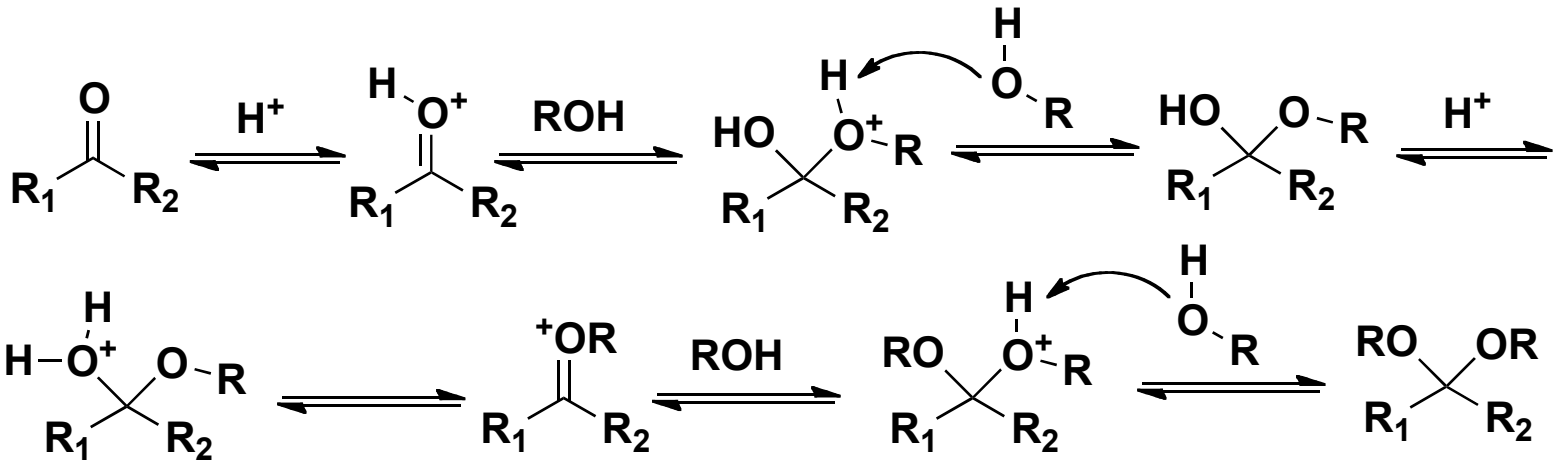
Reversible Addition to Aldehydes and Ketones

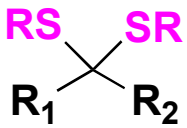
Addition of Alcohol Leading to Acetal (Ketal)

Reaction of 2 equiv of alcohol with aldehydes (or ketones) in the presence of a catalytic amount of acid led to acetal $R_1R_2C(OR)_2$.

Acetal from aldehyde
Ketal form ketone

Mechanism of acid-catalyzed formation of acetal (ketal):

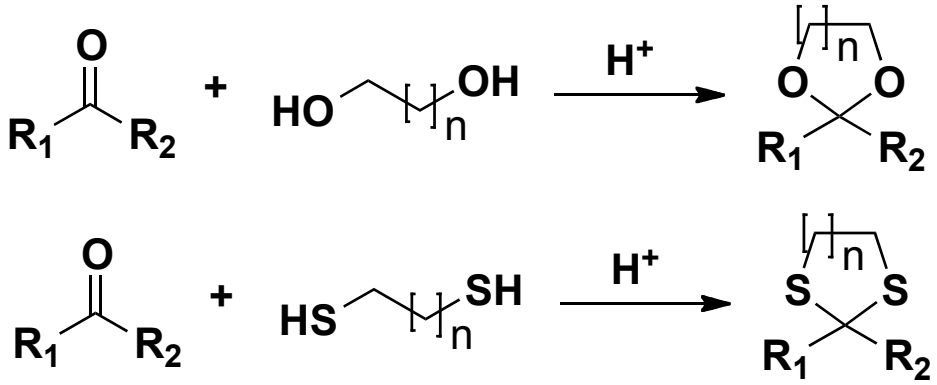




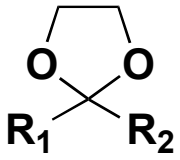
Dithioacetal (Dithioketal) can be formed in similar way.

Reversible Addition to Aldehydes and Ketones

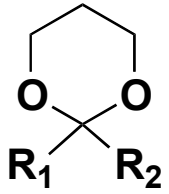
Addition of Diol Leading to Cyclic Acetal (Ketal)



Draw the mechanism of cyclic acetal (cylic ketal) formation.



Dioxolane

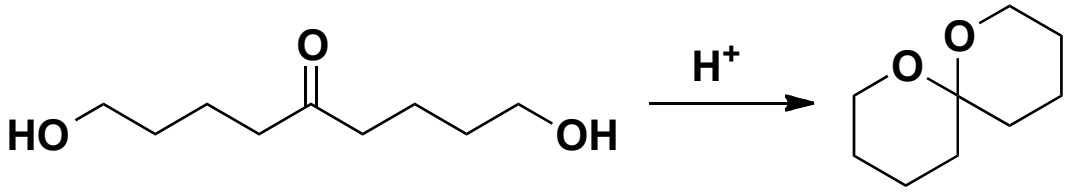


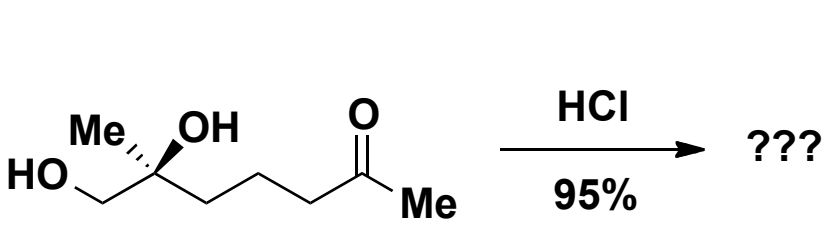
1,3-Dioxane

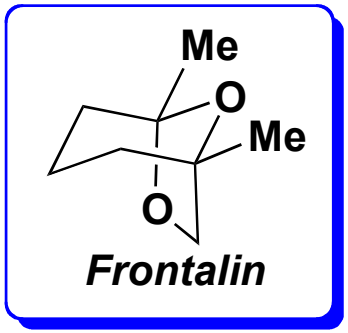
Dioxolanes and dioxanes are very useful protecting group for carbonyl compounds. *The electrophilicity of C=O group disappeared. It is no more reactive towards nucleophiles*.

Acetal (Ketal) Formation in Natural Product Synthesis

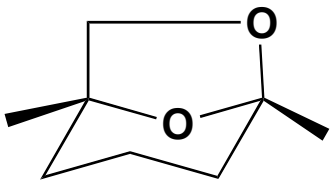
Case of Frontalin



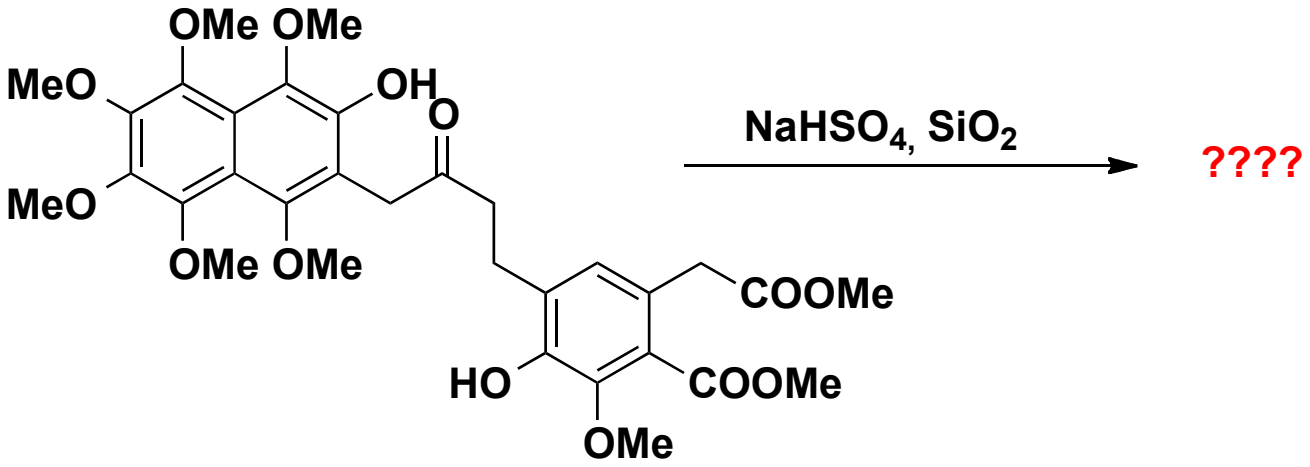




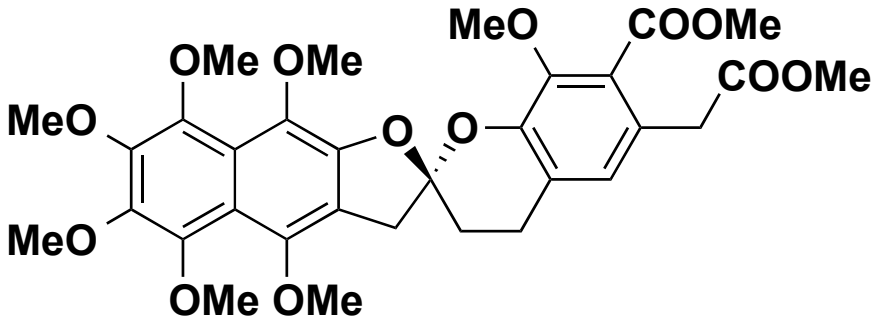
Give the structur of the product and Detail the reaction sequence???



Acetal (Ketal) Formation in Natural Product Synthesis
Phenol can also Participated in Aetalization: Case of Rubromycin

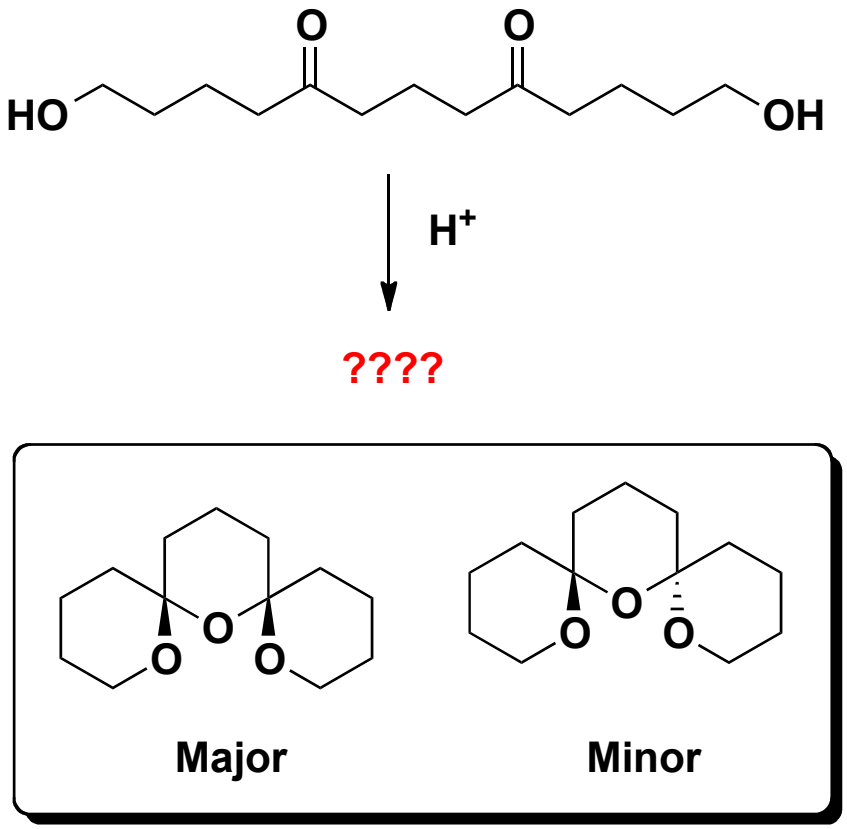


Answer:



Brimble, M. A. *Angew. Chem. Int. Ed*. **2009**, *48*, 7996.

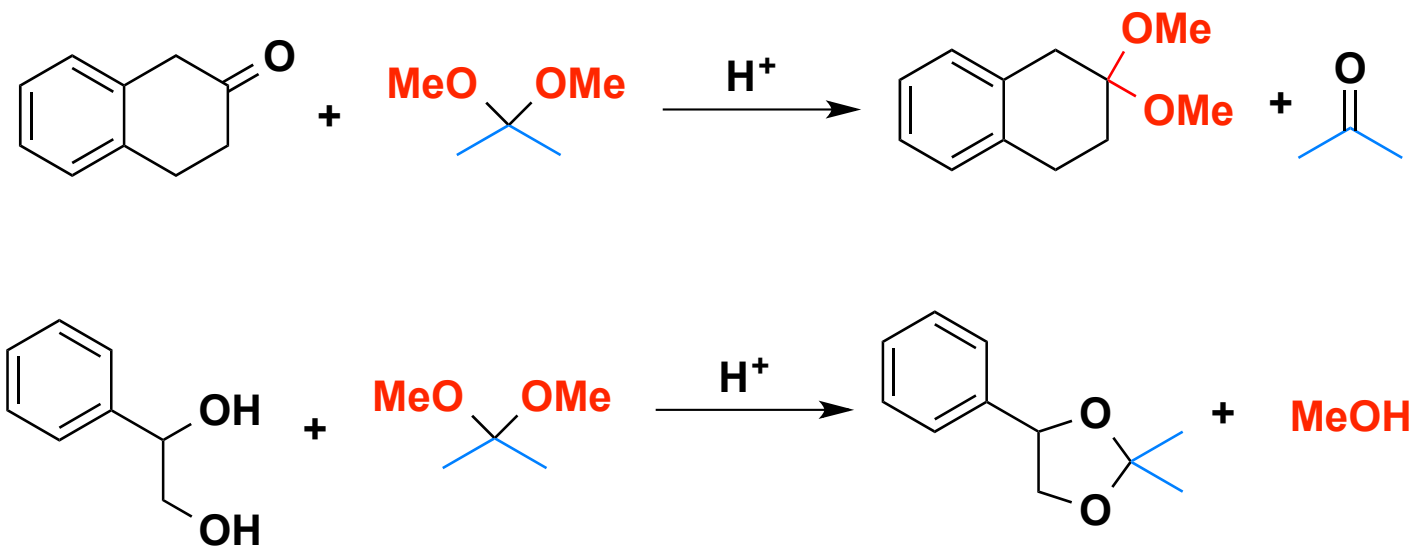
Acetal (Ketal) Formation in Natural Product Synthesis



Do not need to indicate the stereochemistry

McGarvey, G. J. *Tetrahedron Lett*. **1996**, *37*, 5461.

Transacetalization

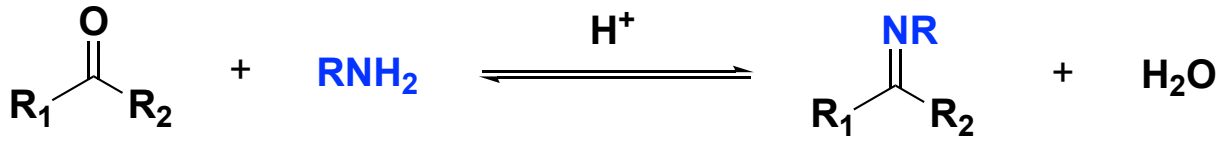


MeO OMe **can act as a donor of methanol or acetone depening on the reaction partner**

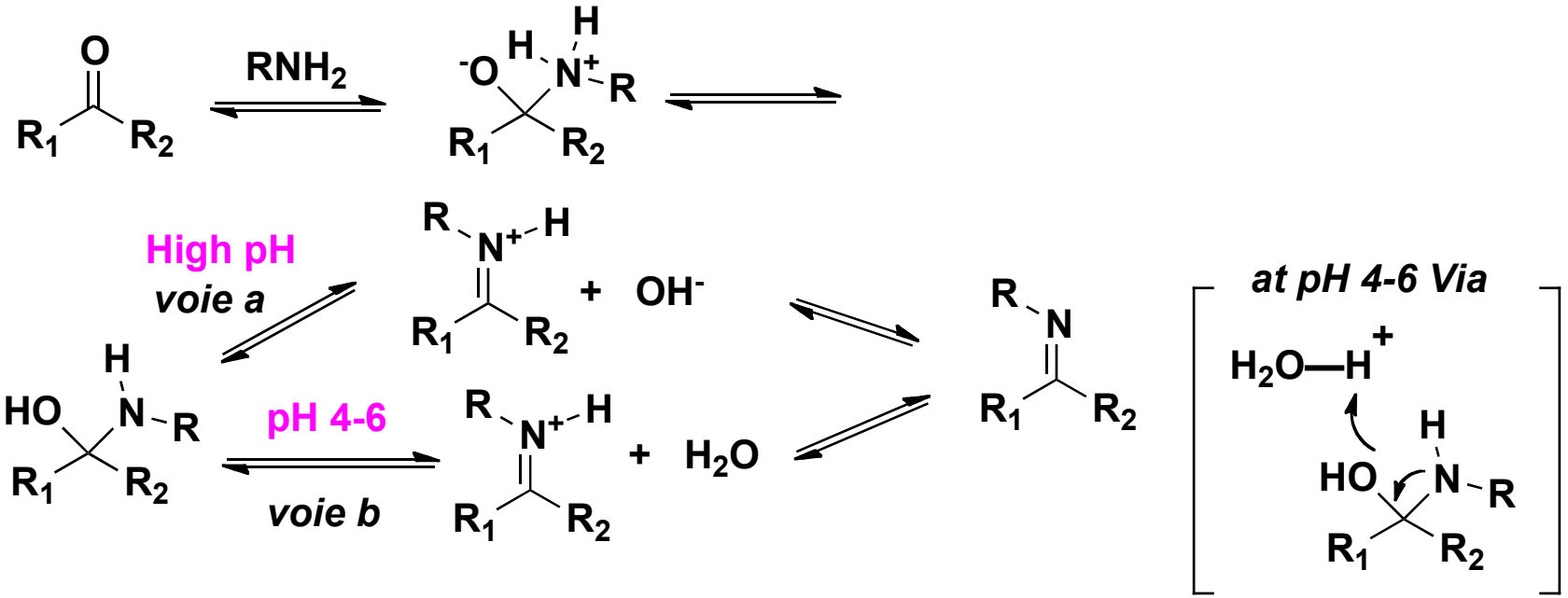
Reversible Addition to Aldehydes and Ketones

Addition of Amine Leading to Imine

When aldehydes and ketones react with primary amines, they produce a class of compounds that contain a carbon—nitrogen double bond called imines, or sometimes Schiff bases (named after chemist Hugo Schiff).



Mechansim:



Note: a) Imine has two possible isomers: *trans* or *cis;*

b) Acid speeds up the water elimination step (voie b). Not the addition step. At the pH range of 4-6, the protonation of ketone cannot take place!

Reversible Addition to Aldehydes and Ketones

Addition of Amine Leading to Imine

Formation of imine requires acid catalyst. The acidity (pH) of the reaction media influence the reaction rate and the reaction outcome.
Optimum pH range: from 4 to 6. Outside this range, the reaction slow down significantly.
At high pH, reaction went through voie a generating two charged species from a neutral amino alcohol (hemiaminal), hence it is a high energy process (*in general, reaction requires high energy when the number of charged species increases from reactants to products*).

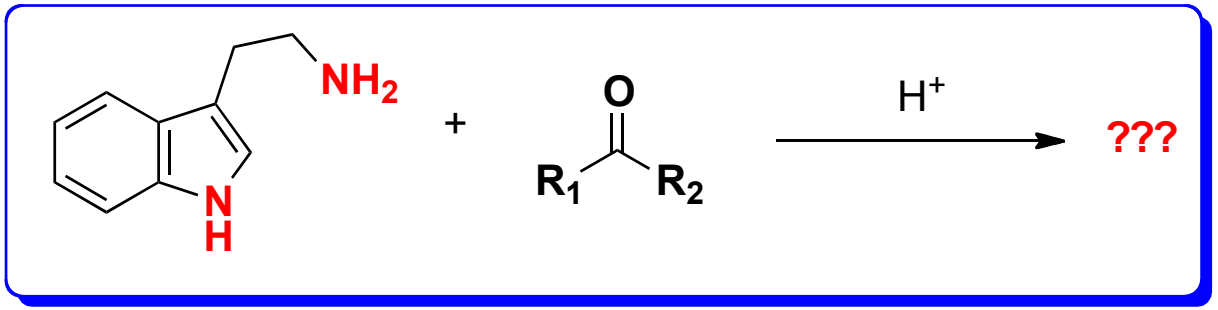
At pH between 4 to 6, the solution contains sufficient protons to "protonate" the —OH group. The —OH group then leaves as water (voie b). The reaction requires less energy in this case, the reaction goes faster than voie a.

At low pH, the amine RNH_2 is protonated to RNH_3^+. It is no more nucleophilic as the lone-pair electron of nitrogen is no more available to attack the carbonyl.

Note: Imines are generally not very stable and frequently generated in situ during the reaction. However, imines derived from anilines are easily isolable.

Hydrolysis of imines to alhedydes, Write the mechanism

Imine Formation: Chemoselective issue



Pictet-Spengler reaction

Addition of Other Nucleophilic Nitrogen Compound to Carbonyl

Nucleophiles	Products
NH_2OH (hydroxylamine)	$R_1R_2C{=}NOH$ (Oxime)
NH_2NH_2 (hydrazine)	$R_1R_2C{=}NNH_2$ (Hydrazone)
$PhNHNH_2$	$R_1R_2C{=}NNHPh$ (Phenylhydrazone)

Mechanism: similar to imine formation

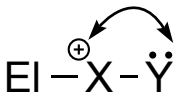
Draw the mechanism of the formation of hydrazone

Note:

Oxime and hydrazone are much more stable than imine;
Oxime and hydrazone have two possible isomers: *trans* or *cis*

Alpha-Effect: Enhanced reactivity of nuclophiles due to the presence of an Adjacent atom with a lone-pair electron

Destabilization of the ground state hence high energy and more nucleophilic



Stabilization of partial charge of transition state reduing hence the activation energy

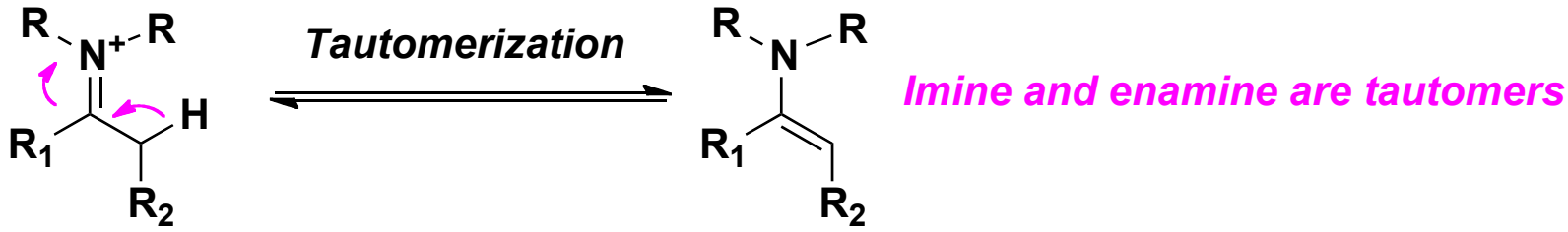
Reversible Addition to Aldehydes and Ketones

Addition of Secondary Amine Leading to Enamine

Secondary amines (R_2NH) react as nucleophiles with ketones and aldehydes to form a group of compounds called enamines. The structure of enamines differs from imines in that they contain a carbon—carbon double bond.

The reaction starts as the nucleophile reacts with the carbonyl group to form the intermediate carbinolamine. Next, the carbinolamine dehydrates to form iminium Because the nitrogen has no hydrogens, an adjacent carbon atom loses a hydrogen. The deprotonation results in the isomerization of a double bond.

Enamines are very useful reaction intermediates. The β-carbon of enamines is nucleophilic (like β-carbon of enol).

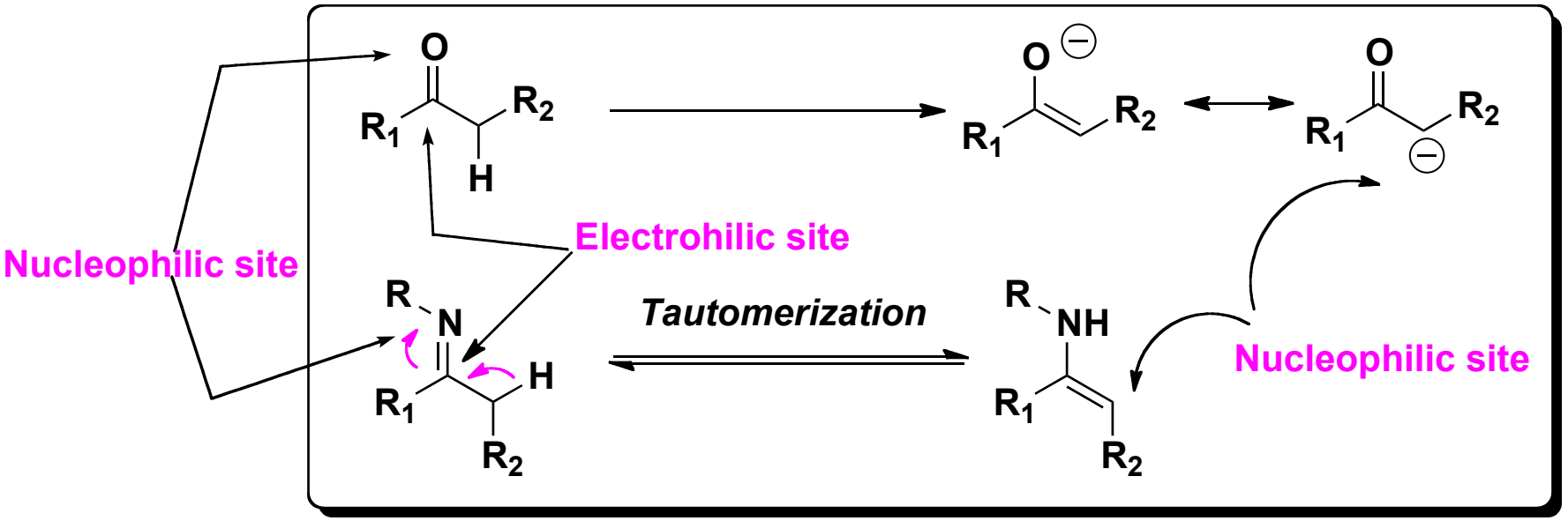


Imminium salt **Enamine**

Imine and enamine are tautomers

Note: Enamine, like imine, has two possible isomers: *trans* or *cis*

Imines *vs* Aldehydes and Ketones

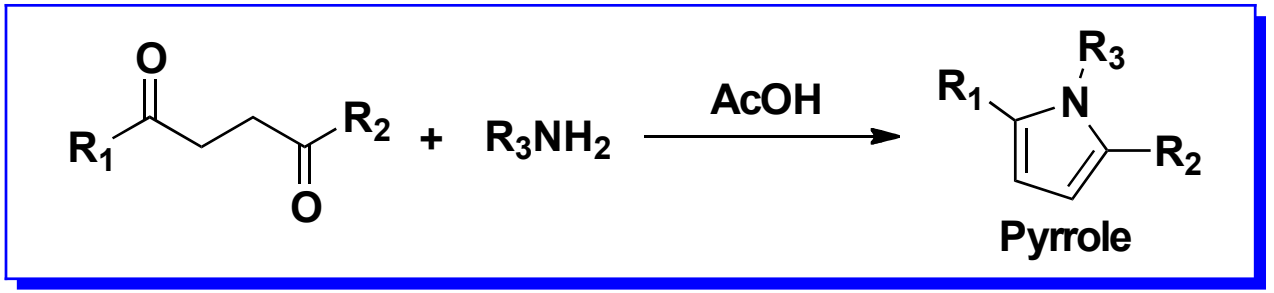


Imine is more basic than carbonyl oxygen, is thus easily protonated under mild acidic conditions. The protonated form, called iminium salt is more electrophilic than the non-protonated carbonyl.

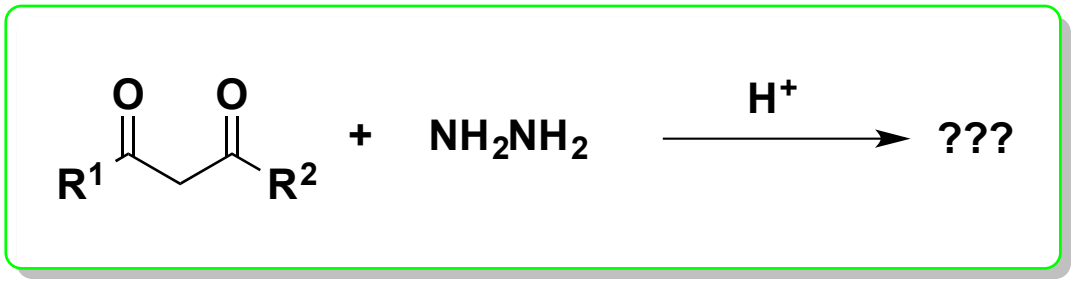
There are Lewis acids that can selectively activate carbonyl (oxophilic) or imine (azophilic) towards the nucleophilic addition.

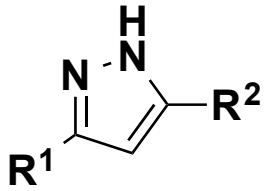
Heterocycle Synthesis

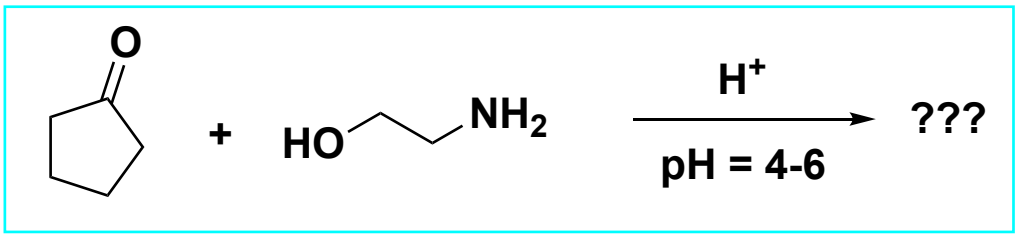
Draw the reaction mechanism (The Paal-Knorr pyrrole synthesis)



Give the structure of the product and Draw the reaction mechanism



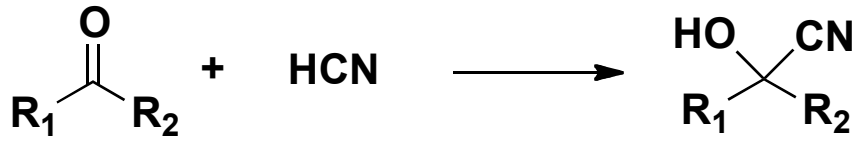




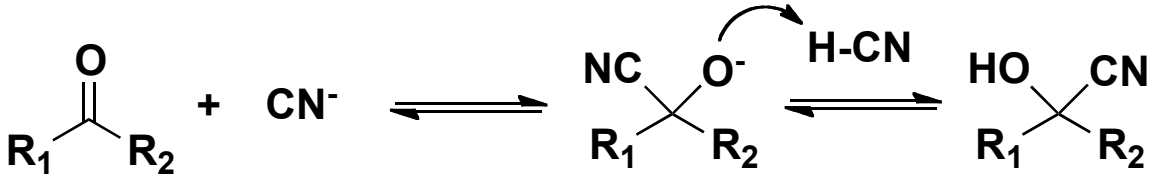
Reversible Addition to Aldehydes and Ketones

Addition of Cyanide Leading to Cyanohydrine

Addition of HCN to carbonyl affords 2-hydroxy alkylnitrile, called cyanohydrine



Mechanism:



HCN is a very weak acid. In aqueous solution, the concentration of cyanide is low and the addition to C=O is relatively slow.
pKa of HCN: 9.3; pKa of aliphatic alcohol: about 16. So the 2nd step, the proton transfer from HCN to alkoxide, would be easy.

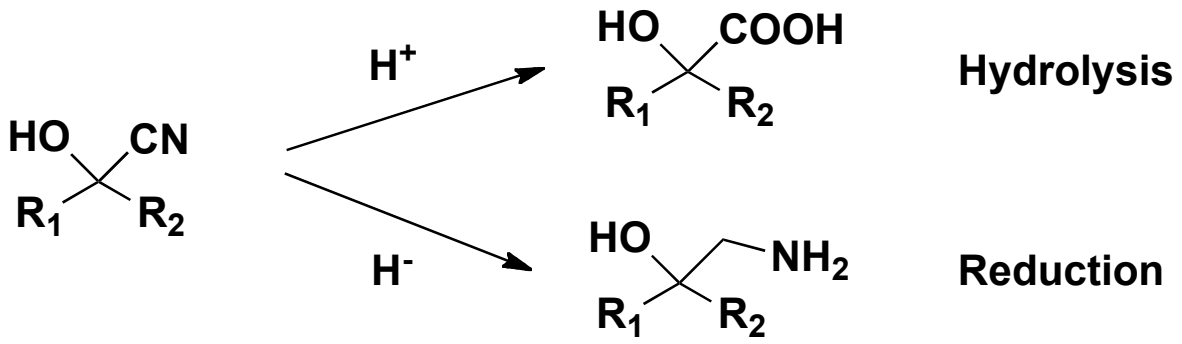
The reaction is reversible as cyanide is a good leaving group.
Cyanohydrines derived from aldehydes is much more stable than those derived from ketone (Why? just by considering the bond angle and difference in steric hindrance between carbonyl compound (sp_2) and cyanohydrine (sp_3).

Note: *HCN is a colorless, highly toxic liquid that boils at 26° C.* It is miscible in water. The aqueous solution is called hydrocyanic acid.

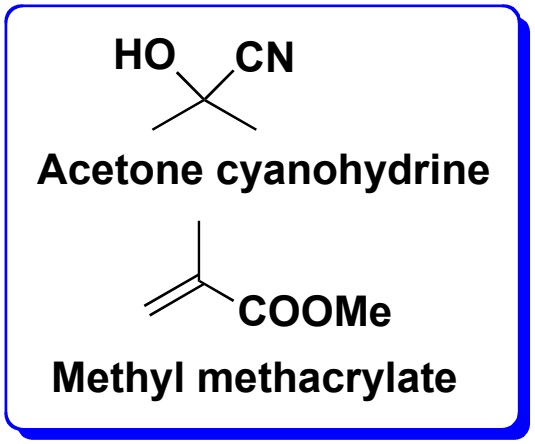
Reversible Addition to Aldehydes and Ketones

Addition of Cyanide Leading to Cyanohydrine

Cyanohydrines are useful precursors of α-hydroxyacid,1,2-amino alcohol etc



Hydrolysis of nitrile to carbocylic acid, Mechanism???



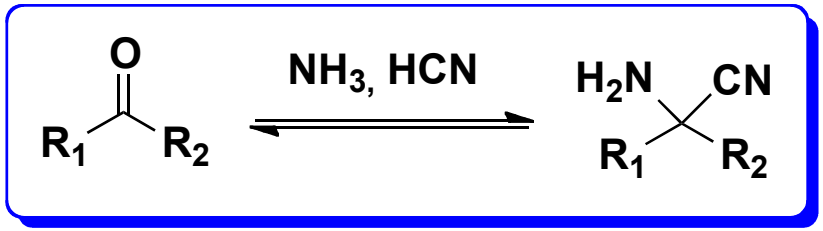
Precursor of methyl methacrylate (ACH route, industrial process), an important monomer in polymer chemistry.
Poly(methyl methacrylate) (PMMA) is a transparent thermoplastic, used as a light or shatter-resistant alternative to glass.

In academic lab, used as a donor of cyanide.
Advantage: slow release of cyanide.

Abbreviation: ACH = Acetone Cyanohydrine

Reversible Addition to Aldehydes and Ketones

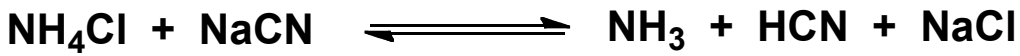
Strecker reaction: Synthesis of α-aminonitrile



Draw a detailed mechanism, analyse the possible competitive side reactions and analyze the outcome from kinetic/thermodynamic view point.

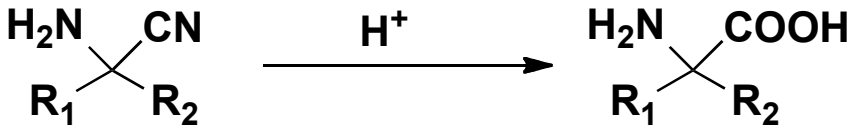
The Strecker reaction is the very first example of Multicomponent reaction

An easy way to generate NH_3 and HCN in situ:

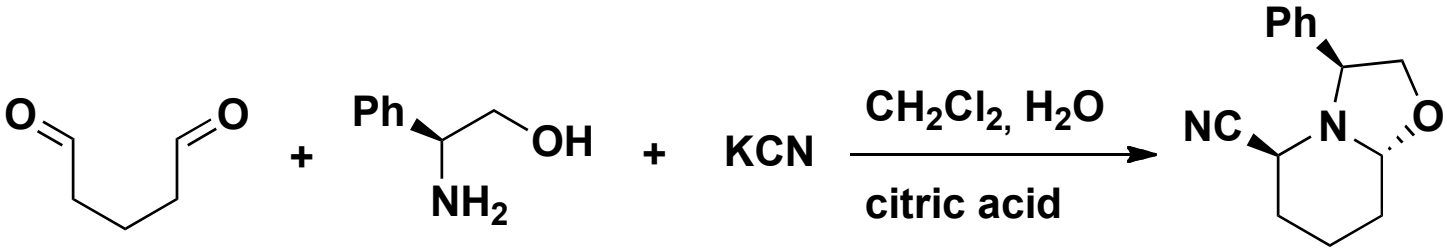


pKaH of NH_4^+: 9.24; pka of HCN: 9.3, so K_e approach to 1

α-amino nitrile is extremely useful in organic synthesis. One prominent example is its conversion to α-amino acid.



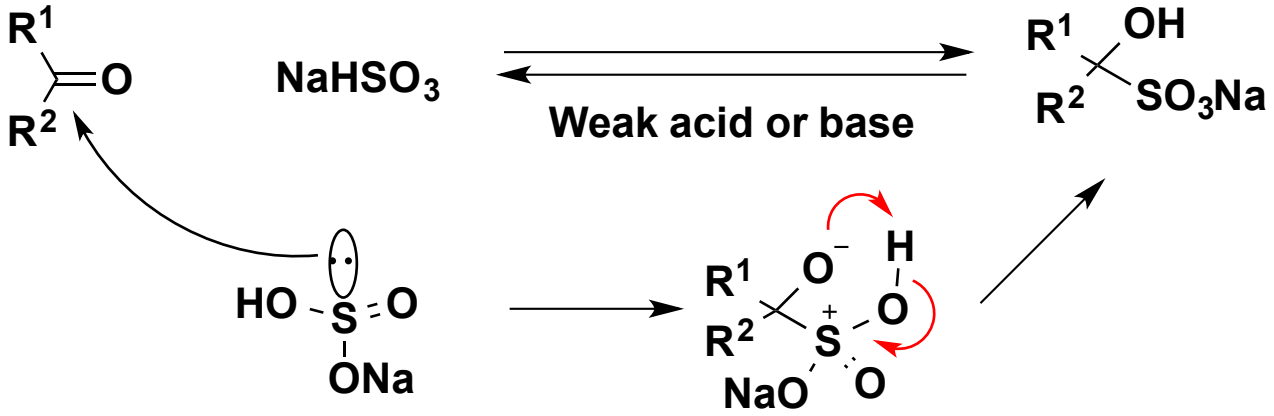
α-Aminonitrile and α-Aminoether



Draw a detailed reaction mechanism????
Need to combine all the chemistry you've just learnt

Reversible Addition to Aldehydes and Ketones

Bisulfite (Hydrogensulfite) addition compounds

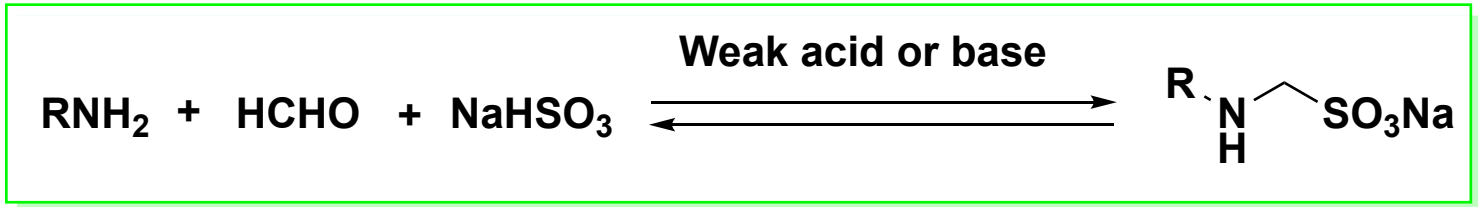


Application

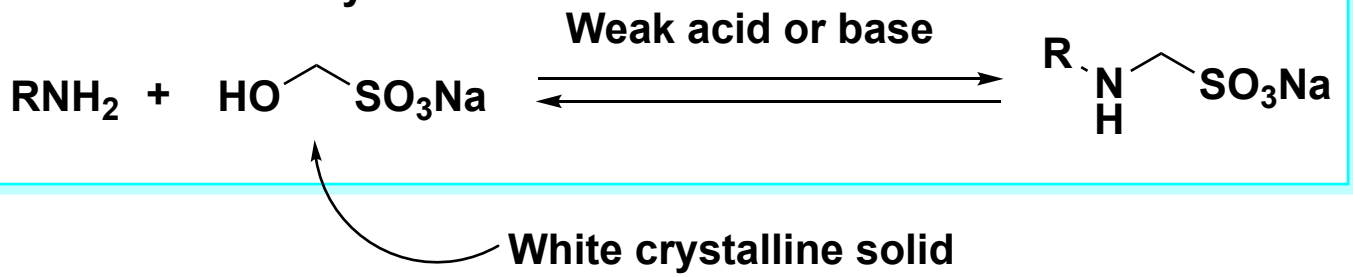
Bisulfite (Hydrogensulfite) addition compounds are crystalline compound (and easily crystallized). It was used for isolating or purifying aldehydes. Bisulfite (Hydrogensulfite) addition compounds gave back to aldehyde under slightly basic ($NaHCO_3$) or acidic conditions.

Reversible Addition to Aldehydes and Ketones

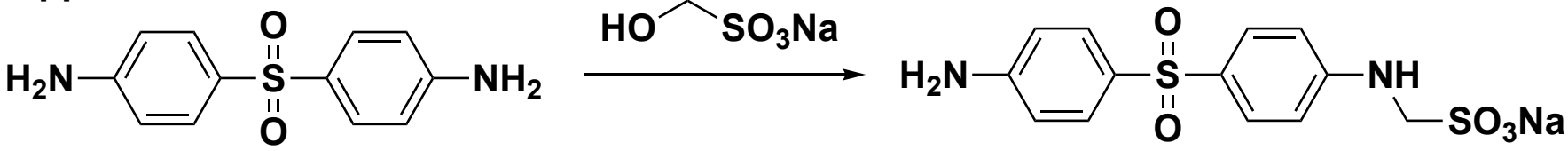
Bisulfite (Hydrogensulfite) addition to Imines



More conveniently:



Application:

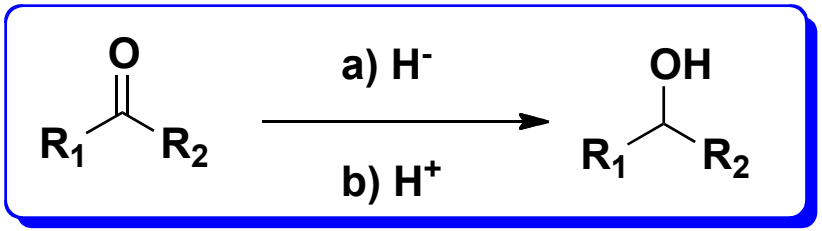


Dapsone: Anti-leprosy drug
Problem: Insolube in water

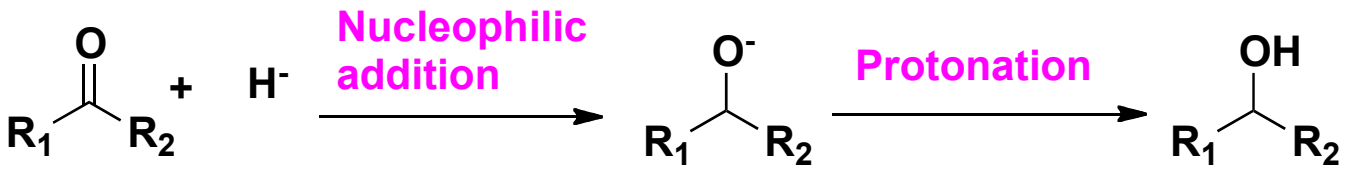
Water soluble, a Pro-drug

Carbonyl Compounds III: Irreversible Nucleophilc Additions

Reduction of Aldehydes and Ketones with Hydride



Mechanism:



Overall, one C-H bond and one O-H bond are formed. Reduction of aldehydes give primary alcohols, while reduction of ketones produce secondary alchols.

Two common reducing agents:

a) **lithium aluminum hydride ($LiAlH_4$, often abbreviated to LAH). It is very stronger reducing agent displaying thus low chemoselectivity. It is sensitive to moisture and reacts violently with H_2O to generate H_2 and heat (and consequently fire). Thereore it should be handled with care.**

b) **Sodium borohydride ($NaBH_4$). It is much milder reducing agent, showing better chemoselectivity. The reduction often performed in aqueous alcohol.**

Reactivity Order and Why

Reactivity: $LiAlH_4$ > $LiBH_4$ > $NaBH_4$ > $NaBH_3CN$

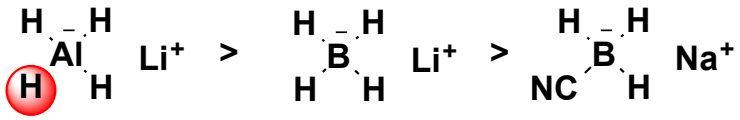
Why?

a) Electronegativity B: 2.04, Al: 1.61. B pulls electron stronger than Al, electron density of hydride in $LiBH_4$ is less than that of $LiAlH_4$; $LiBH_4$ is a weaker reducing agent than $LiAlH_4$.

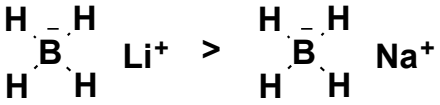
b) Li coordinates to carbonyl striongerly than Na, activates carbonyl better than Na, therefore $LiBH_4$ is a stronger reducing agent than $NaBH_4$

c) Cyanide is electron-withdrawing group, it renders the electron density of hydride in $NaBH_3CN$ even lower than that of $NaBH_4$, therefore less reactive.

Electron density of H

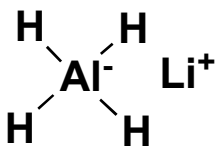


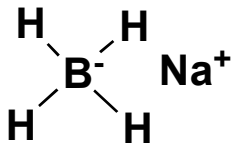
Lewis acidity of reducing agent:



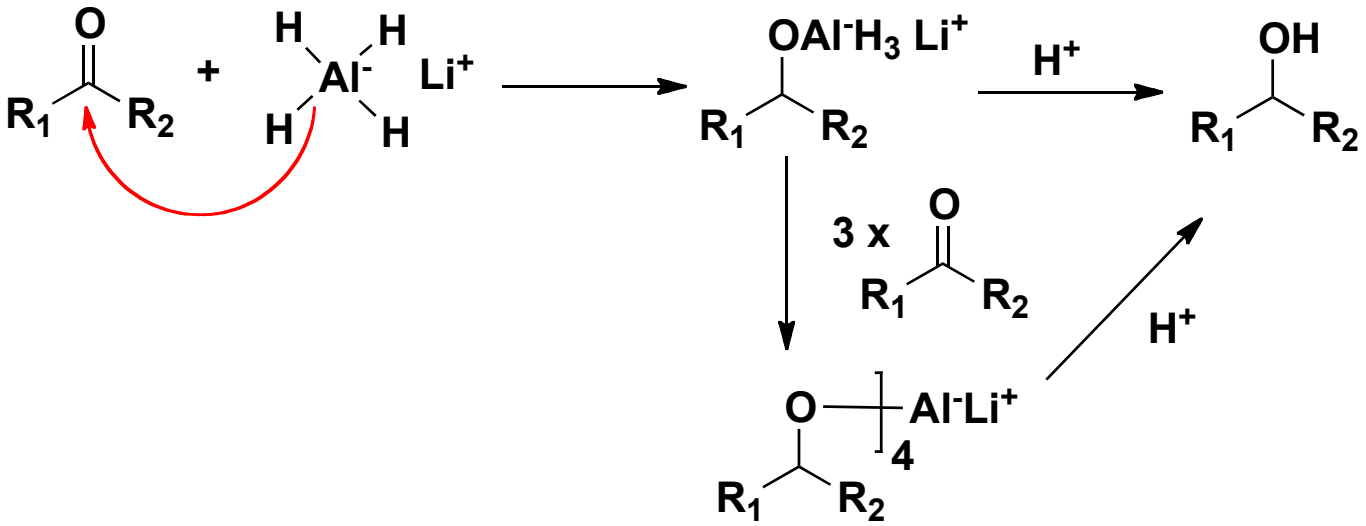
Reduction of Aldehydes and Ketones with Hydride

Structure of LAH and $NaBH_4$:





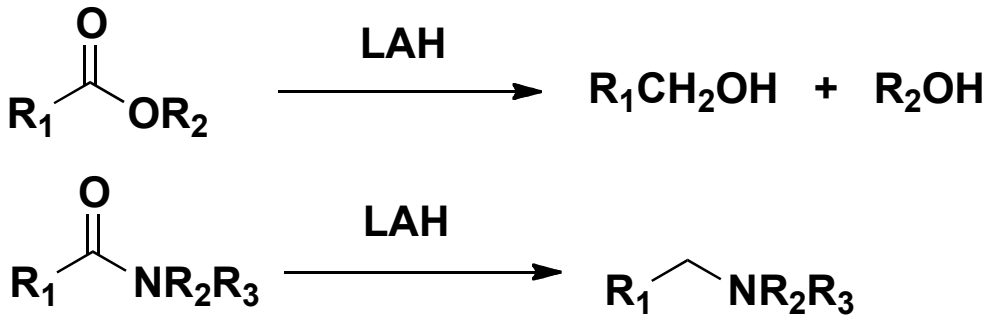
Mechanism of reduction with LAH:



Theoretically, 1 mol of LAH can reduce 4 mol of aldehyde or ketone
Note: a) the negative charge in Al doesn't mean that there is a lone pair on Al, one can not draw an arrow coming out of this charge to form a new bond
b) *NaH is not a reducing agent*. The 1s orbital is too small to interact with carbon's 2p orbital. *It mainly serve as a base* to interact with the σ* orbital of H-X (X could be any atom) bond. With $NaBH_4$ as reducing agent, it is the B-H σ orbital (HOMO) that interacts with the LUMO of the C=O.

Reduction of Esters, amides and with Hydride

Esters are reduced to primary alcohols by LAH
Amides are reduced to amines by LAH



Two mol of hydrides (H^-) is required to convert esters to alcohols.
Two mol of hydrides (H^-) is required to convert amides to amines.
Draw the mechanism of the reduction

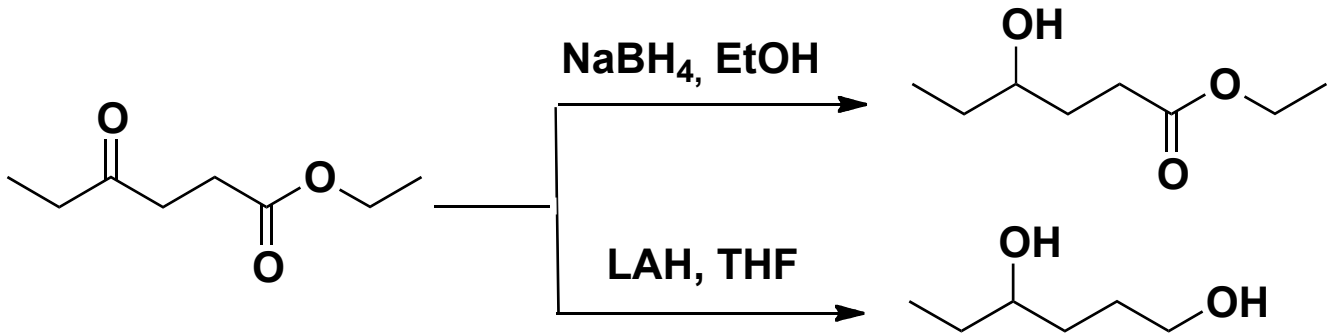
$NaBH_4$ DO NOT reduce esters and amides (*Reminder: the cabonyl of esters and amides are less reactive than that of aldehydes and ketones, why?*)

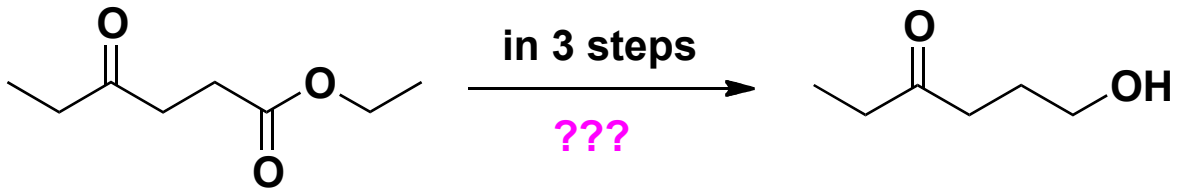
Reduction of Carbonyls with Hydride

Reminder: chemoselectivity refers to the relative reactivity of one functional group over the others.

$LiAlH_4$: **Can reduce aldehyde, ketone, carboxylic acid, ester, amide etc…**
Anhydrous tetrahydrofurane (THF), diethyl ether are frequently used as reaction solvent

$NaBH_4$: **Can *chemoselectively* reduce aldehyde and ketone in the presence of carboxylic acid, ester and amide etc…**
Aqueous ethanol is frequently used as reaction solvent.

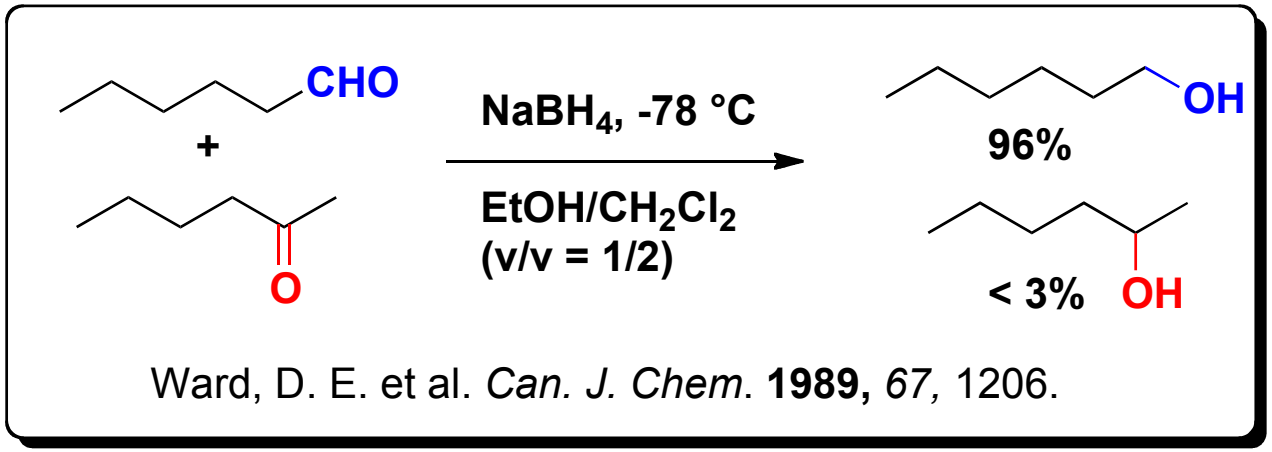




Hint: LAH DO NOT reduce ketal.

Chemoselective Reduction of Aldehyde in the Presence of Ketone

$NaBH_4$ reduces both aldehydes and ketones when the reaction is performed in EtOH at room temperature.
By performing the reduction in a solvent mixture EtOH-CH_2Cl_2 at -78 ° C, chemoselective reduction of aldehyde in the presence of ketone is possible.



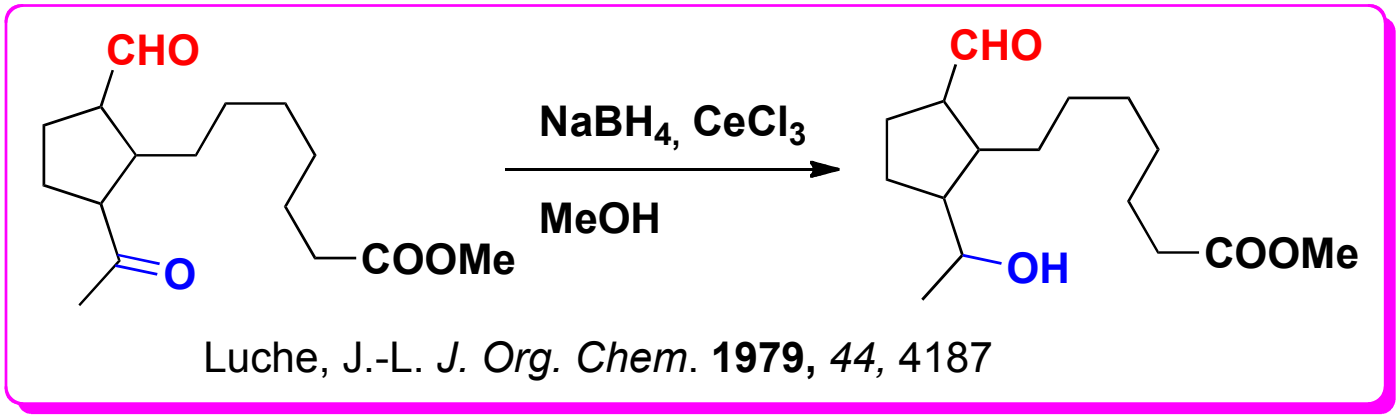
Ward, D. E. et al. *Can. J. Chem.* **1989,** *67,* 1206.

How to make a cooling bath at -78 ° C: *acetone + dry ice.*

Note: Solvent is an important parameter that needed to be considered when conducting a chemical transformation

Chemoselective Reduction of Ketone in the Presence of Aldehyde: Luche Reduction

Luche Reduction: combined use of $NaBH_4$ and $CeCl_3$. Used for chemoselective reduction of Ketone in the presence of aldehyde, and reduction of α,β-unsaturated ketone in the presence of non-conjugated ketone.



Luche, J.-L. *J. Org. Chem.* **1979,** *44,* 4187

What is special with the couple: $NaBH_4$—$CeCl_3$:

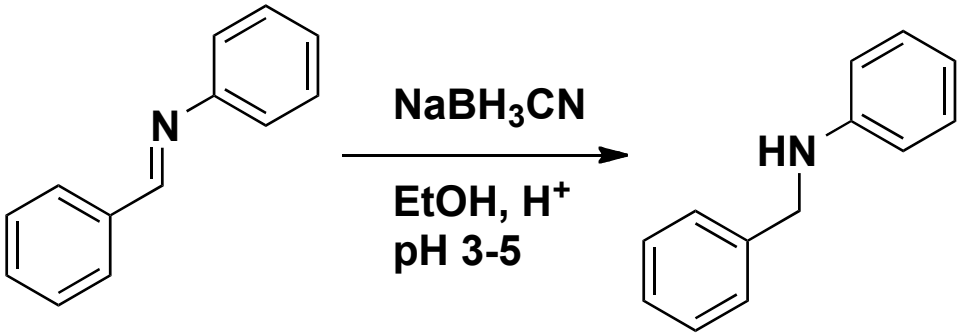
a) **$CeCl_3$ is a highy oxophilic Lewis acid that can catalyze the reaction of MeOH (or H_2O) with aldehyde leading to dimethyl acetal (or hydrate) which is stable towards hydride. Aldehyde is unmasked during work-up.**

b) **$CeCl_3$ is capable of catalyzing the methanolysis of sodium borohydride. The resulting reagents, various sodium methoxyborohydrides [$NaB(OMe)_nH_{4-n}$], are harder reducing agents (*according to HSAB principles*) and therefore effect an 1,2-reduction of enone with higher selectivity.**

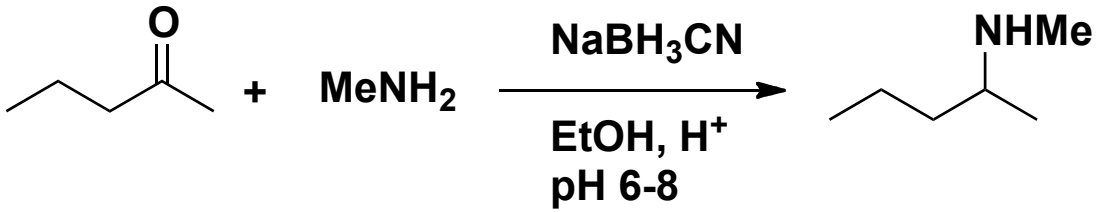
c) **$CeCl_3$ coordinates also to the oxygen of MeOH making the proton of MeOH more acidic, accelerating therefore the proton transfer to metal alkoxide.**

Reduction of Imines with Hydride: Reductive amination of carbonyl compounds

$NaBH_3CN$ and $NaBH(OAc)_3$ are milder reducing agent than $NaBH_4$, especially useful for reducing imines to amines.



Most of the aliphatic imines are too unstable to be isolated
***Solution*: one pot conversion of aldehydes/ketones to amines**

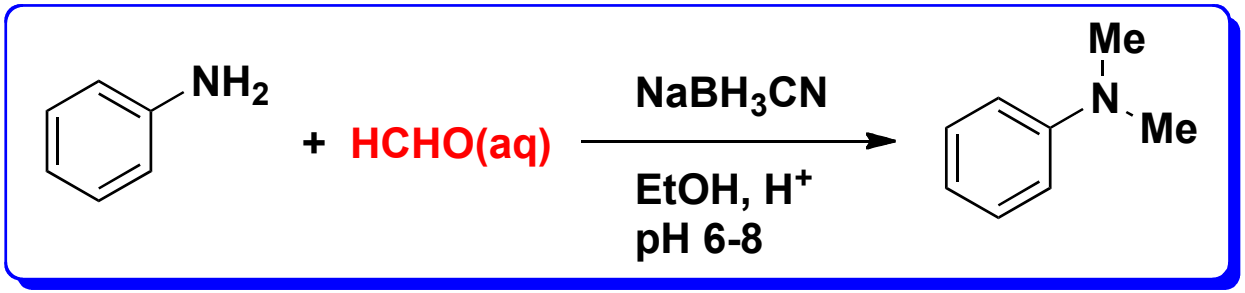


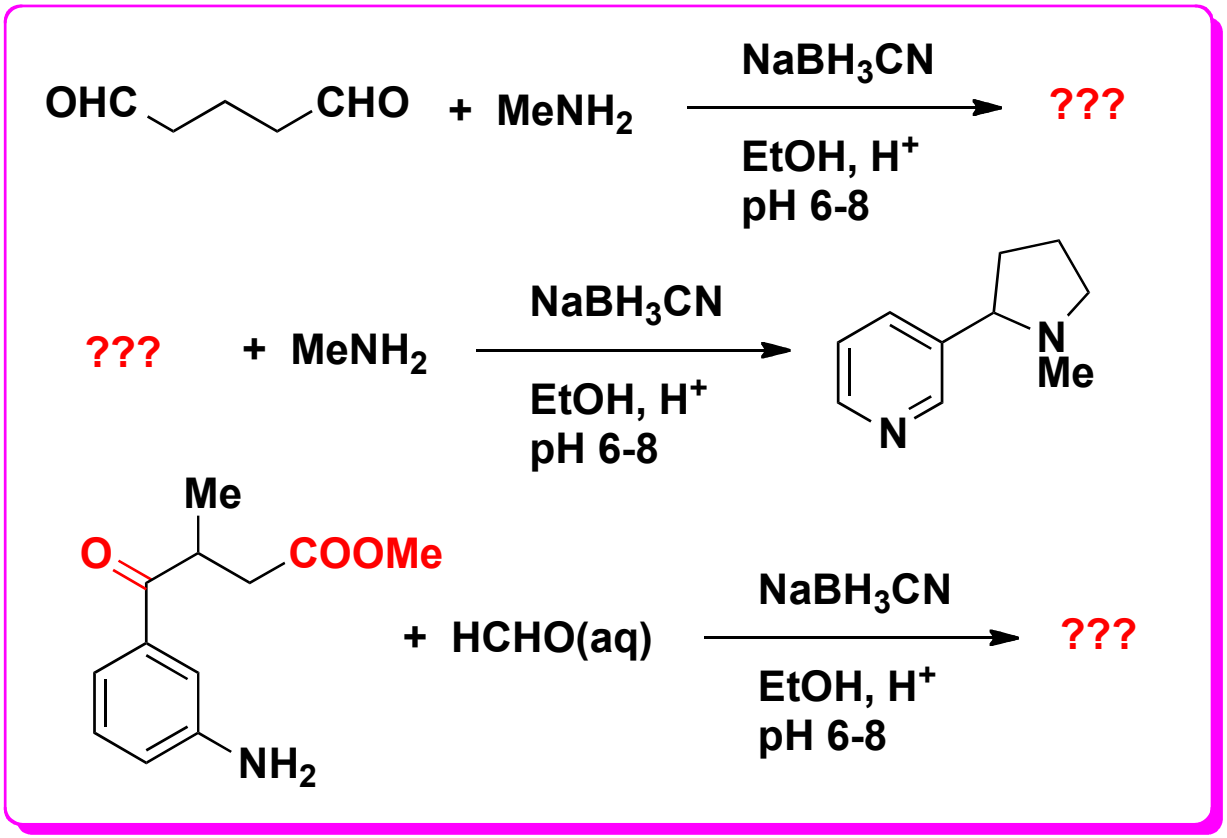
Draw a detailed mechanism, analyze the possible competitive side reactions

Note: At pH 3-5, $NaBH_3CN$ reduces also aldehydes and ketones to the corresponding alcohol

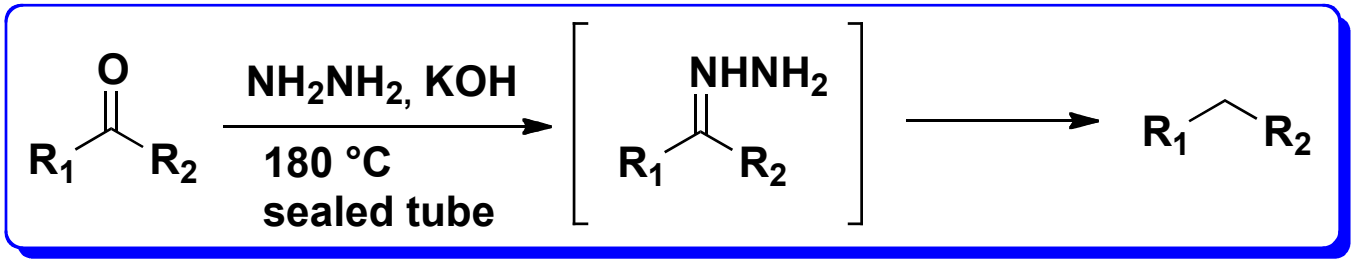
C. F. Lane, *Synthesis*, 1975, 135-146

Reduction of Imines with Hydride: Reductive Amination of Carbonyl compounds

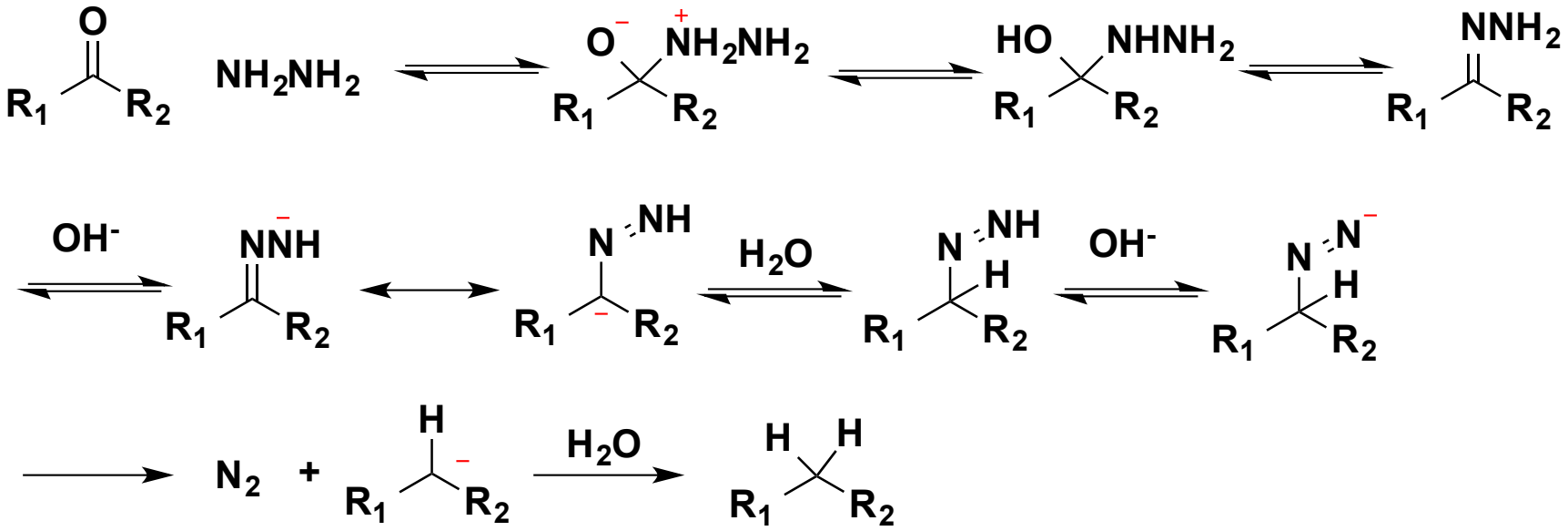




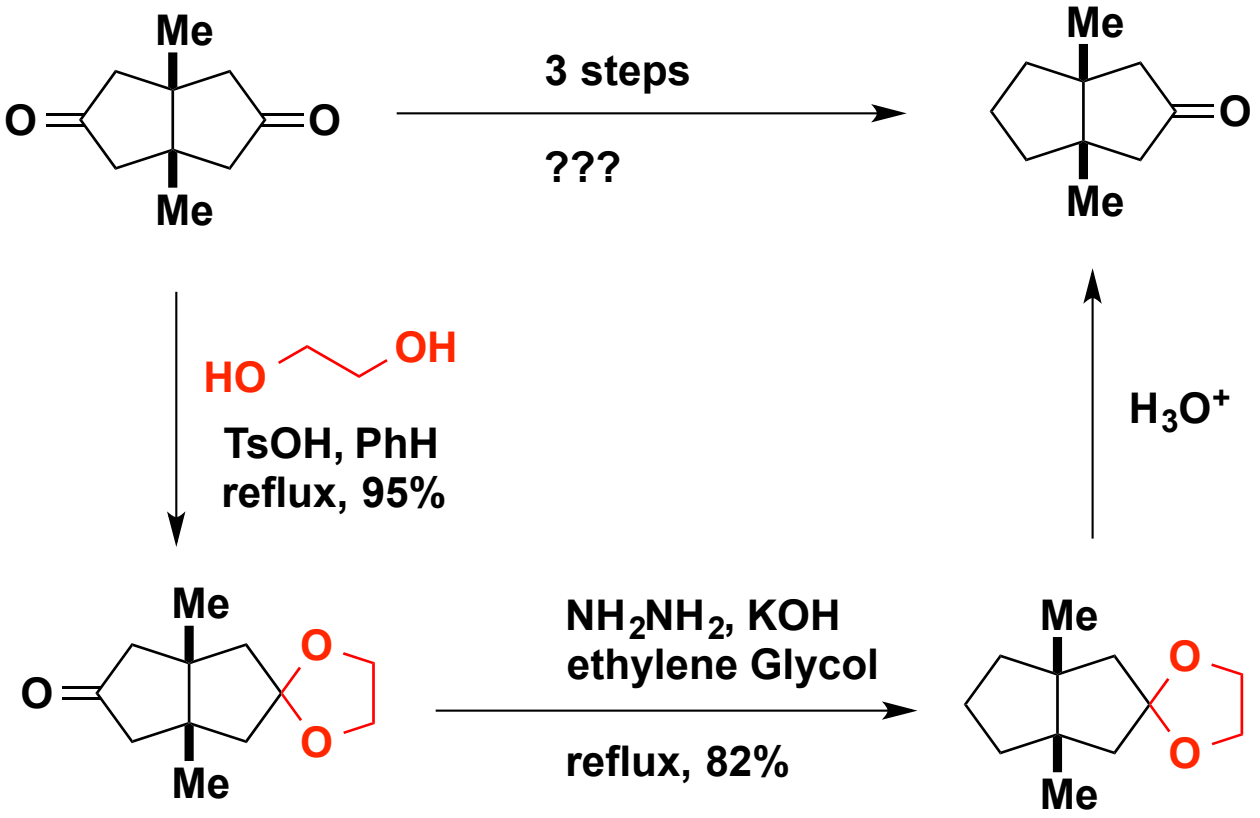
Reduction of Carbonyl to alkane: Wolff-Kishner-Huang Reduction



Mechanism

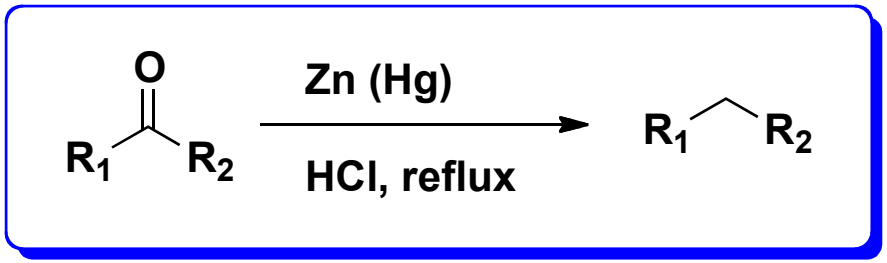


Applicable only to base-stable compounds.
Otherwise using Clemmensen reduction



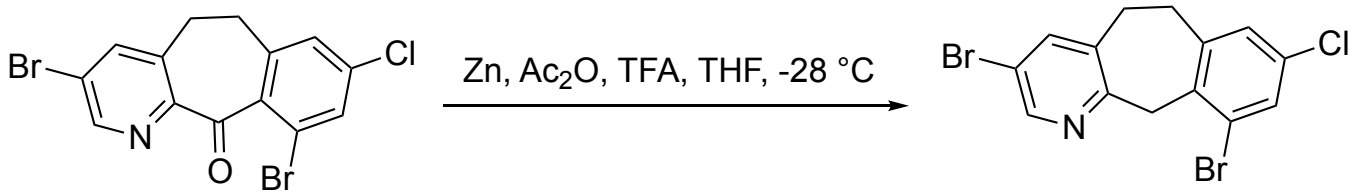
Paquette, L. A. *J. Org. Chem*. **1979**, *44*, 3731.

Reduction of Carbonyl to alkane: Clemmensen Reduction



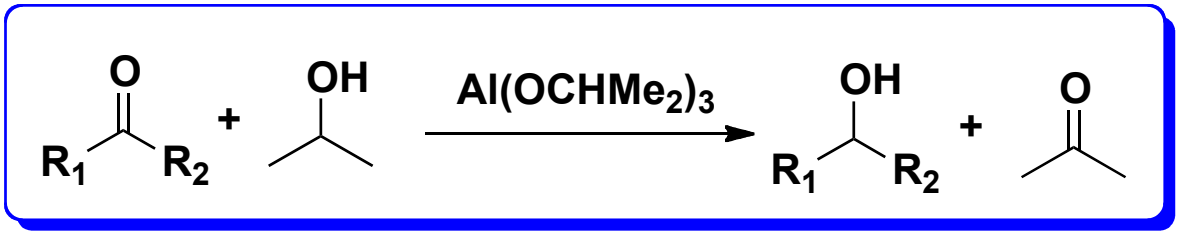
The reduction takes place at the surface of the zinc catalyst. In this reaction, alcohols are not postulated as intermediates, because subjection of the corresponding alcohols to these same reaction conditions does not lead to alkanes. The reaction most probably went through the single electron transfer process.

Modification: Perform the reaction in organic solvent under following conditions: Zn, Ac_2O, TFA, THF. Reaction occurred at below room temperature. For example:

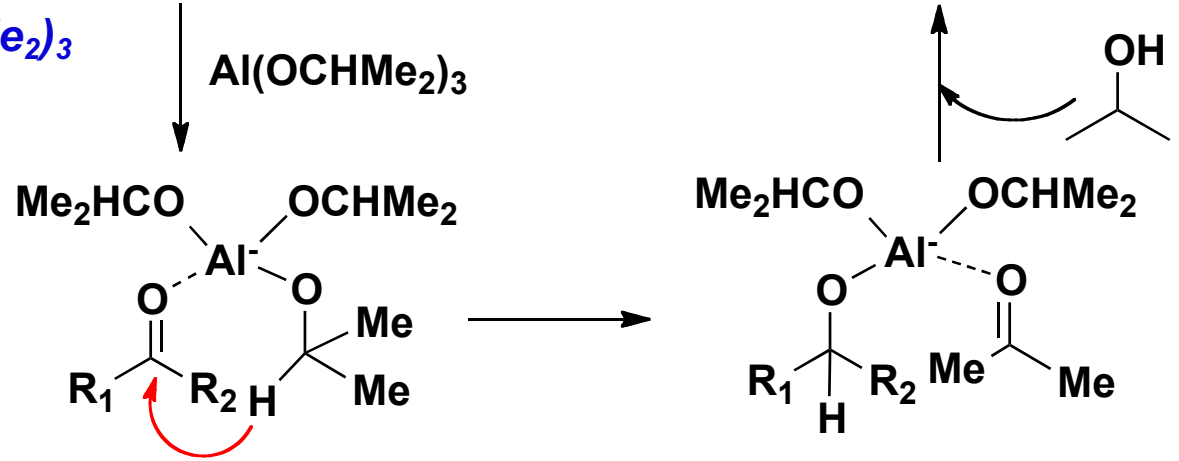


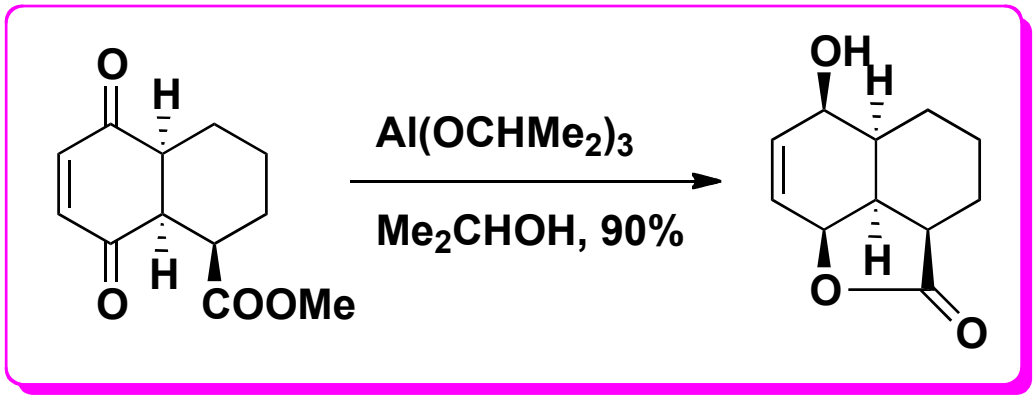
Applicable only to Acid-stable compounds. It is thus complementary to Wolff-Kishner-Huang Reduction.

Reduction of Carbonyls: The Meerwein-Ponndorf-Verley Reaction (MPV Reaction)

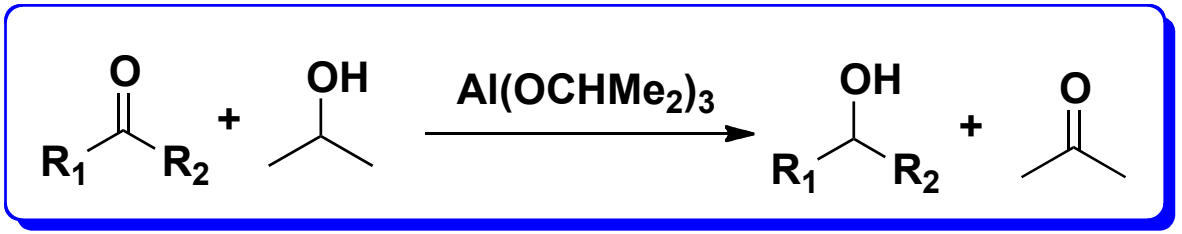


Note: $Al(OCHMe_2)_3$ is a Lewis acid

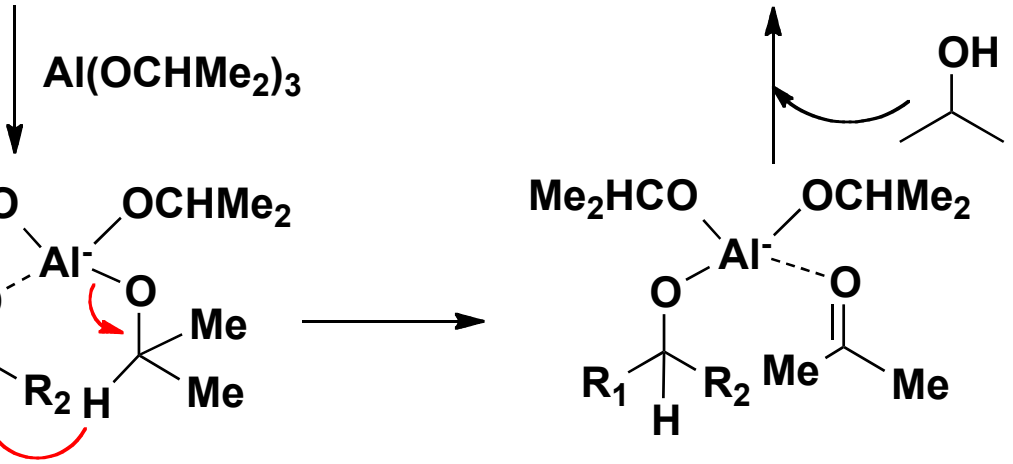


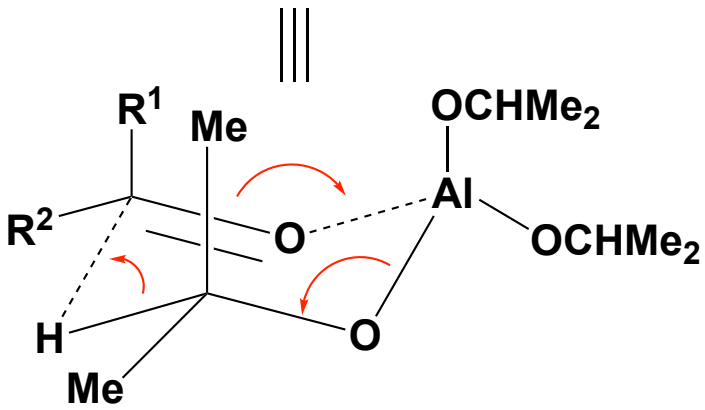


The Meerwein-Ponndorf-Verley Reaction (MPV Reaction): Zimmerman-Traxler chair-like TS



Note: $Al(OCHMe_2)_3$ is a Lewis acid





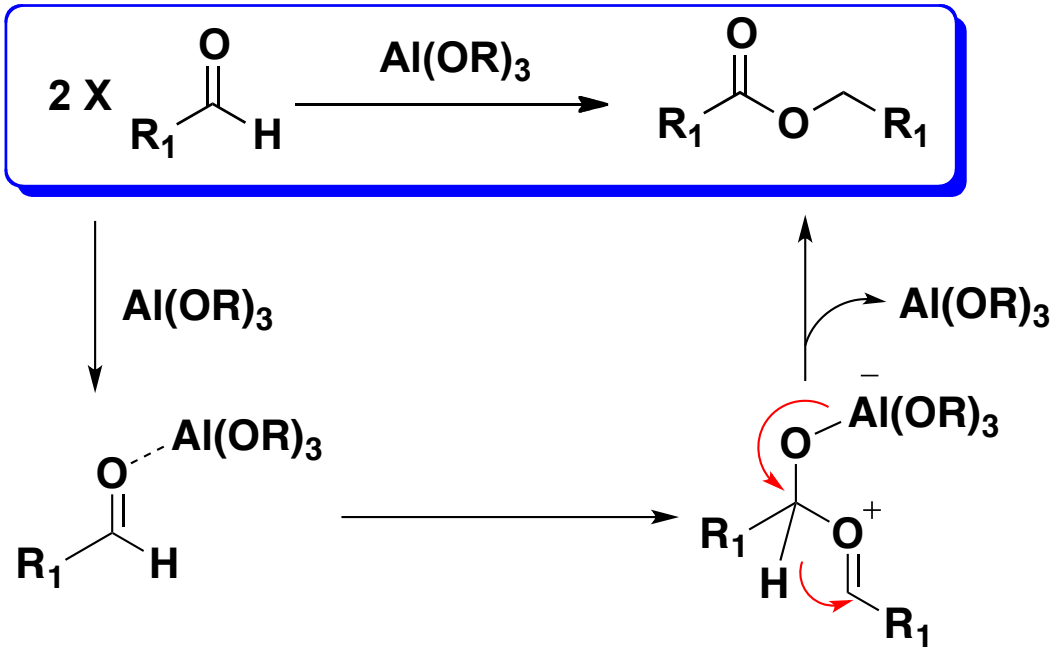
Note: the MPV reaction is reversible. The reverse reaction is known as Oppenauer oxidation

Zimmerman-Traxler chair-like TS

Redox reaction of Aldehydes: The Tishchenko Reaction

The Tishchenko Reaction is a disproportionation reaction that allows the preparation of esters from two equivalents of an aldehyde. It was also called Tischenko-Claisen reaction as Claisen was the first to observe this reaction.

Initially proposed mechansim:

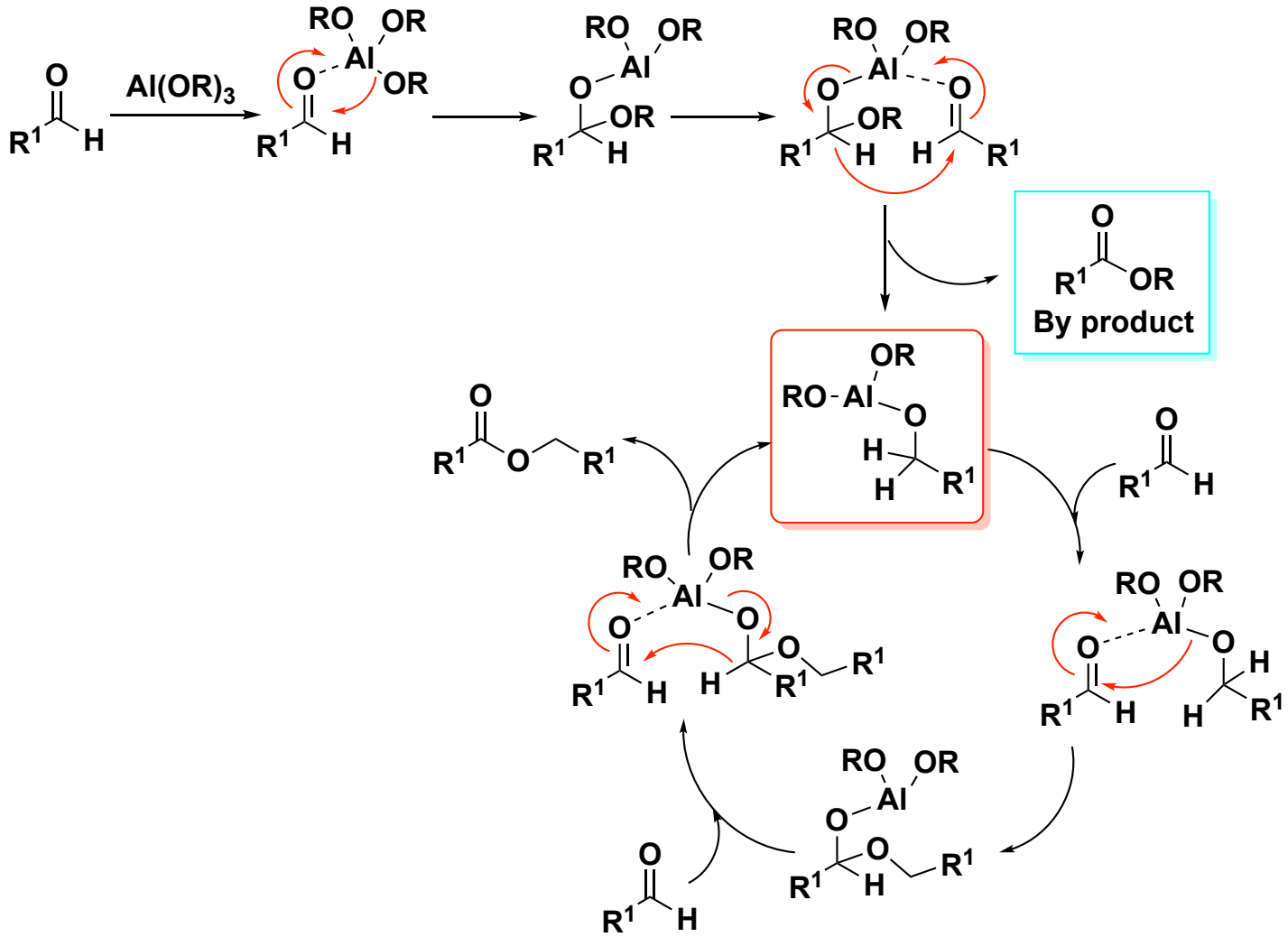


Note: In above mechanism, the oxygen of C=O of one aldehyde was proposed to act as nucleophile to attack the carbon of another C=O function. However, The mechanism of the reaction is much more complex than it was shown. Depending on the nature of the R group in $Al(OR)_3$, other mechanistic pathway is possible (Ogata, Y. Kawasaki, A. Tetrahedron 1969, *25*, 929.)

Many other Lewis acids, especially lanthanoid salts, are effective to promote this reaction.

Redox reaction of Aldehydes: The Tishchenko Reaction

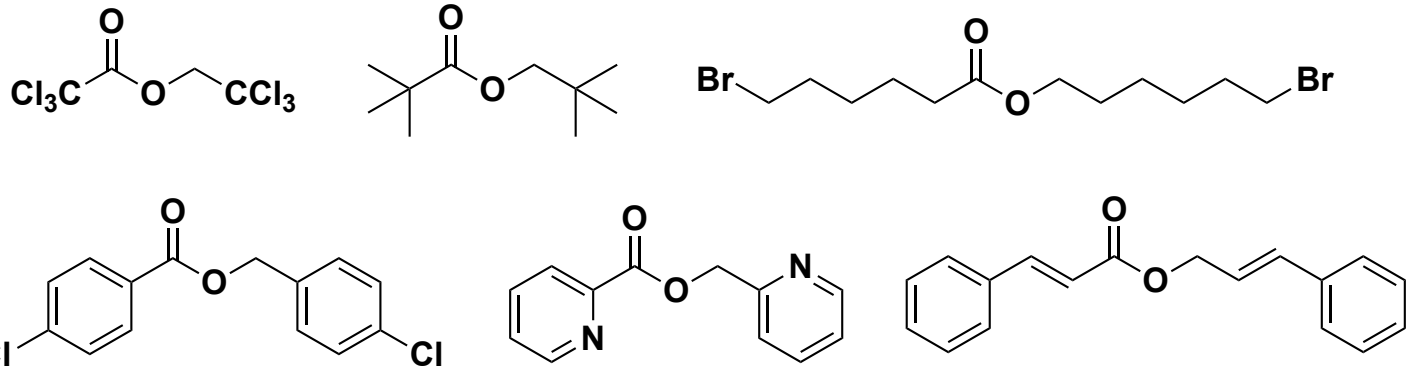
Accepted Mechanism:



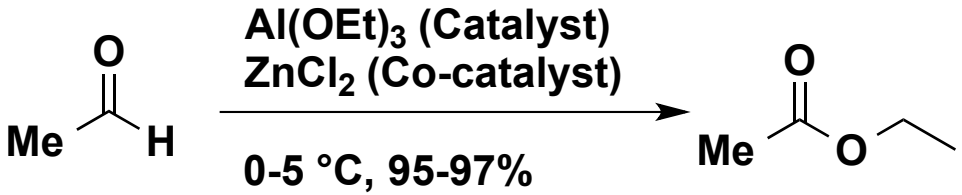
Koskinen, A.M. P. *Recent Res. Develp. Org. Chem.* **2001**, *5*, 225-255.

The Tishchenko Reaction: Scope and Industrial Application

Scope: **Aliphatic aldeydes, aromatic aldehydes, heteroaromatic aldehydes are accepted substrates. See below the structures of the product:**



Industrial Application

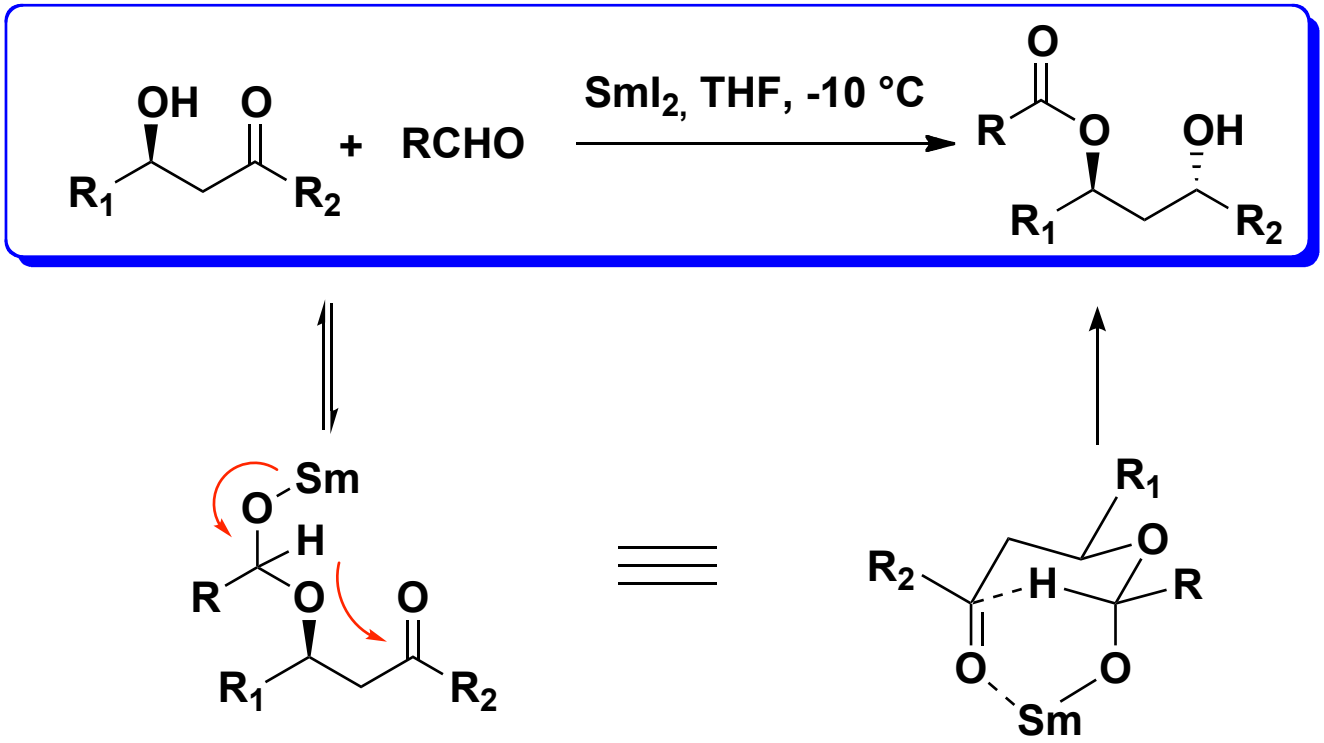


Ethyl acetate production: 500 000 tons per year by Tishchenko reaction

Another major industrial route: Esterification of acetic acid by ethanol

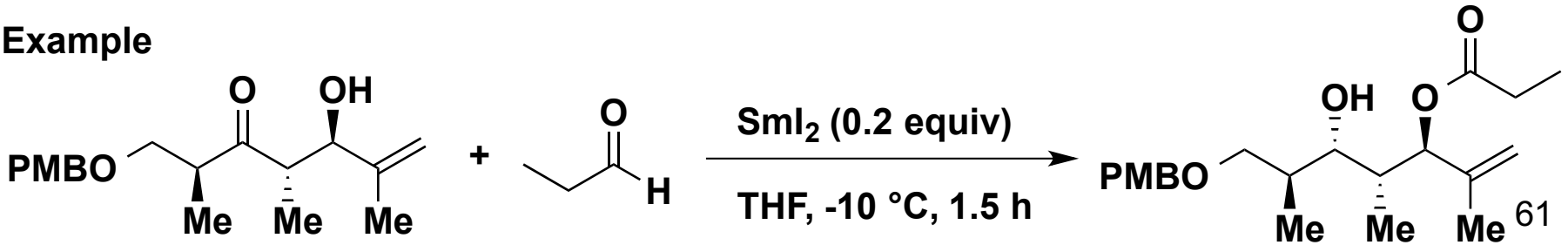
Redox reaction of Aldehydes: The Evans-Tishchenko Reaction

Reduction of β-hydroxy ketone to *anti*-1,3-diol with high level of stereocontrol; Two hydroxy groups are differentiated as one was protected as an ester after the reaction



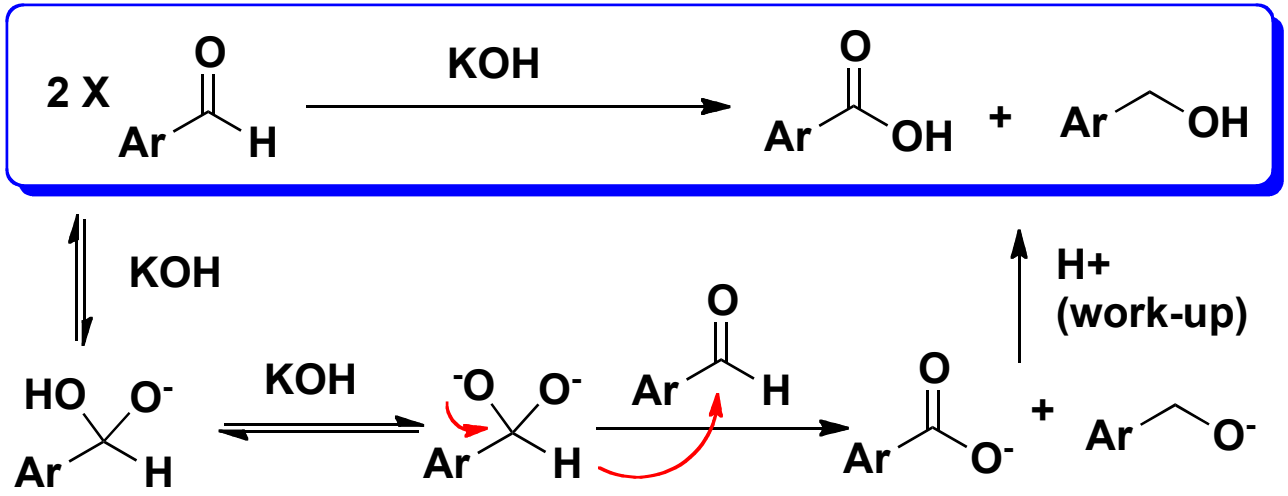
Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1990**, *112*, 6447-6449.

Example

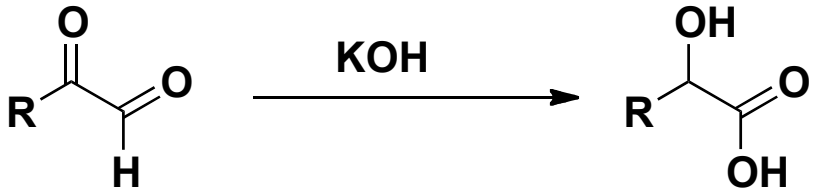


Redox reaction of Aldehydes: The Cannizzaro Reaction

The Cannizzaro reaction: The redox disproportionation of non-enolizable aldehydes to carboxylic acids and alcohols in the presence of concentrated base.



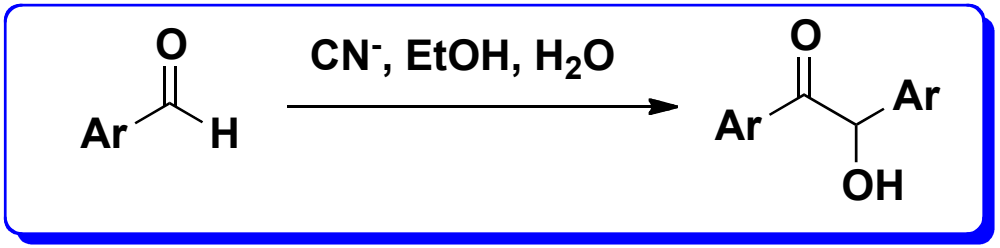
Interesting variant: α-Keto aldehydes undergo an intramolecular disproportionation to afford α-hydroxy acid in excellent yields



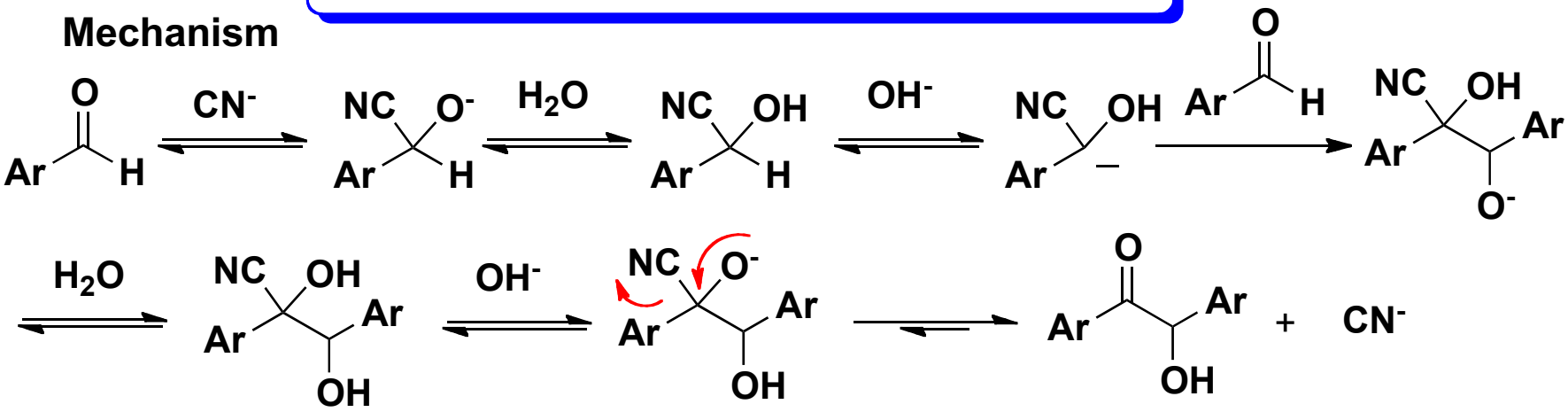
Note: The Canizzaro reaction is not very often used in nowadays' synthesis. But one should keep it in mind as a source of possible side reaction when aldehydes are treated under basic conditions.

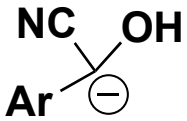
Redox Reaction of Aldehydes: Benzoin Reaction

Benzoin reaction: Conversion of aromatic aldehydes to α-hydroxyketone.
Works only with aromatic aldehydes.

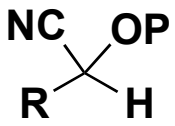


Mechanism





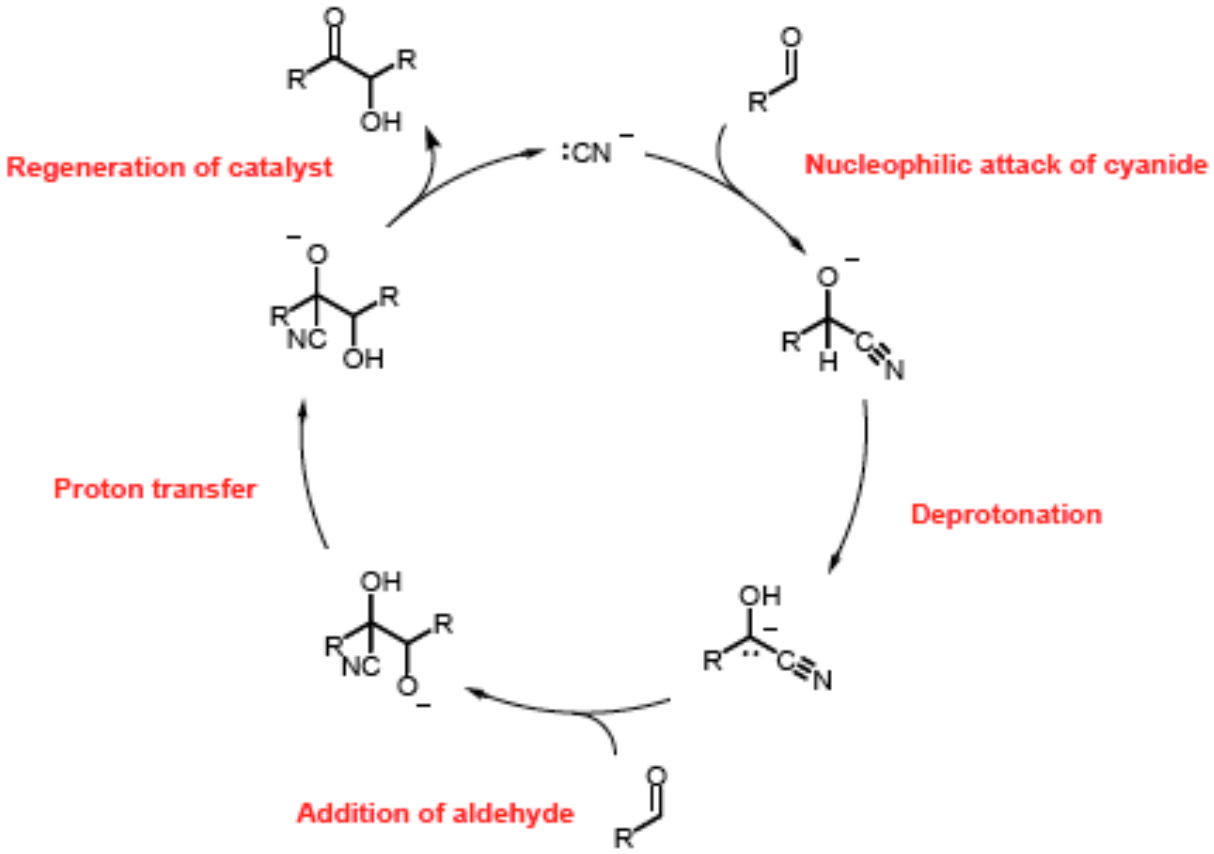
Ar = Phenyl, write all the contributing resonance form to explain why this anion is easily formed.
Note: that cyanide can also conjugate with the anion.



The α-proton of protected α-cyanohydrine can be deprotonated with a strong base. The resulting anion is a very useful synthon that react with a variety of electrophile (not the topics of this courses).
α-cyanohydrine is the « Unpolung » of carbonyl group

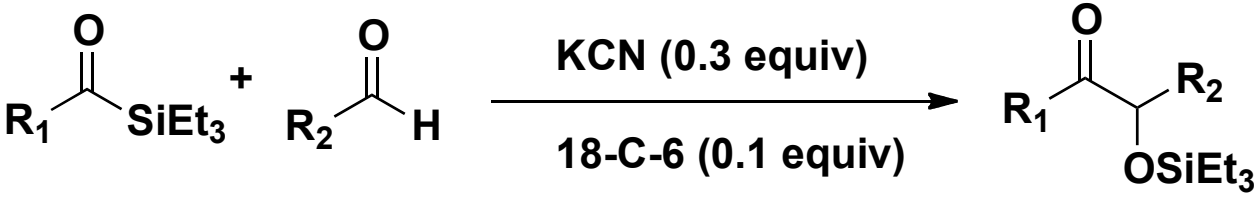
Redox Reaction of Aldehydes: Benzoin Reaction

Benzoin reaction can be performed in the presence of a catalytic amount of CN^-.
One way to write a mechanism of a catalytic process is to make it circular.



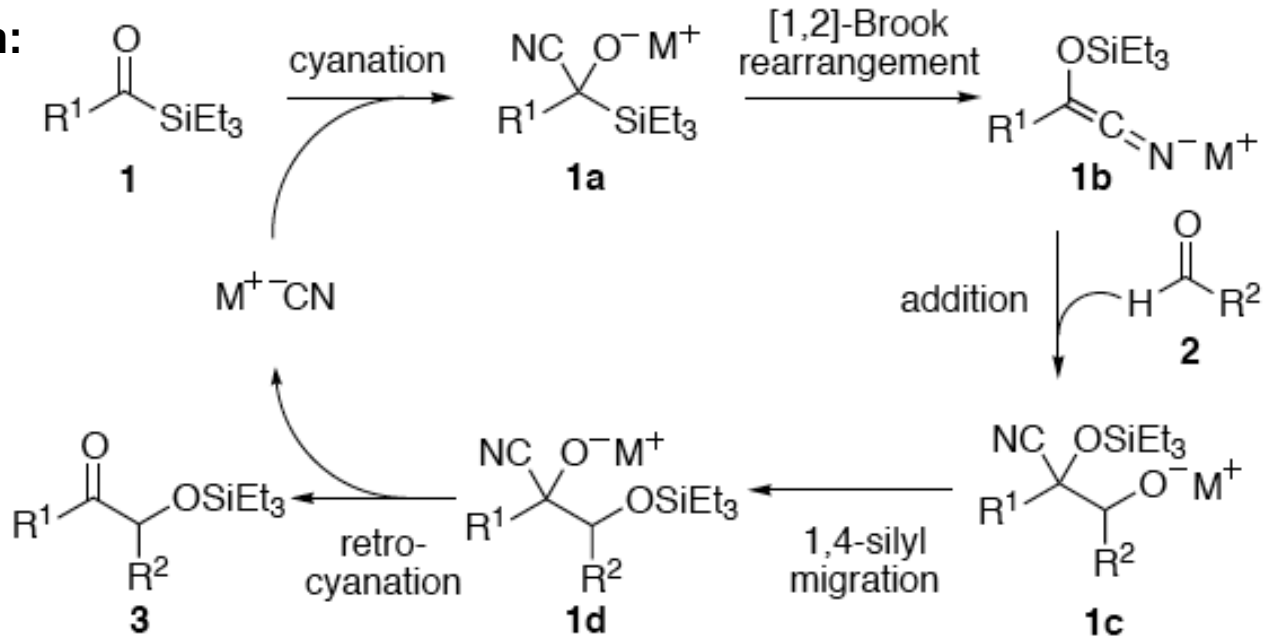
Redox Reaction of Aldehydes: Cross Benzoin Reaction

Under classic benzoin reaction conditions, 4 possible α-hydroxyketones (two homo, two cross coupled) will be produced and selectivity is generally low. Solution: Using silyl ketone as a latent cyanohydrine anion equivalent.



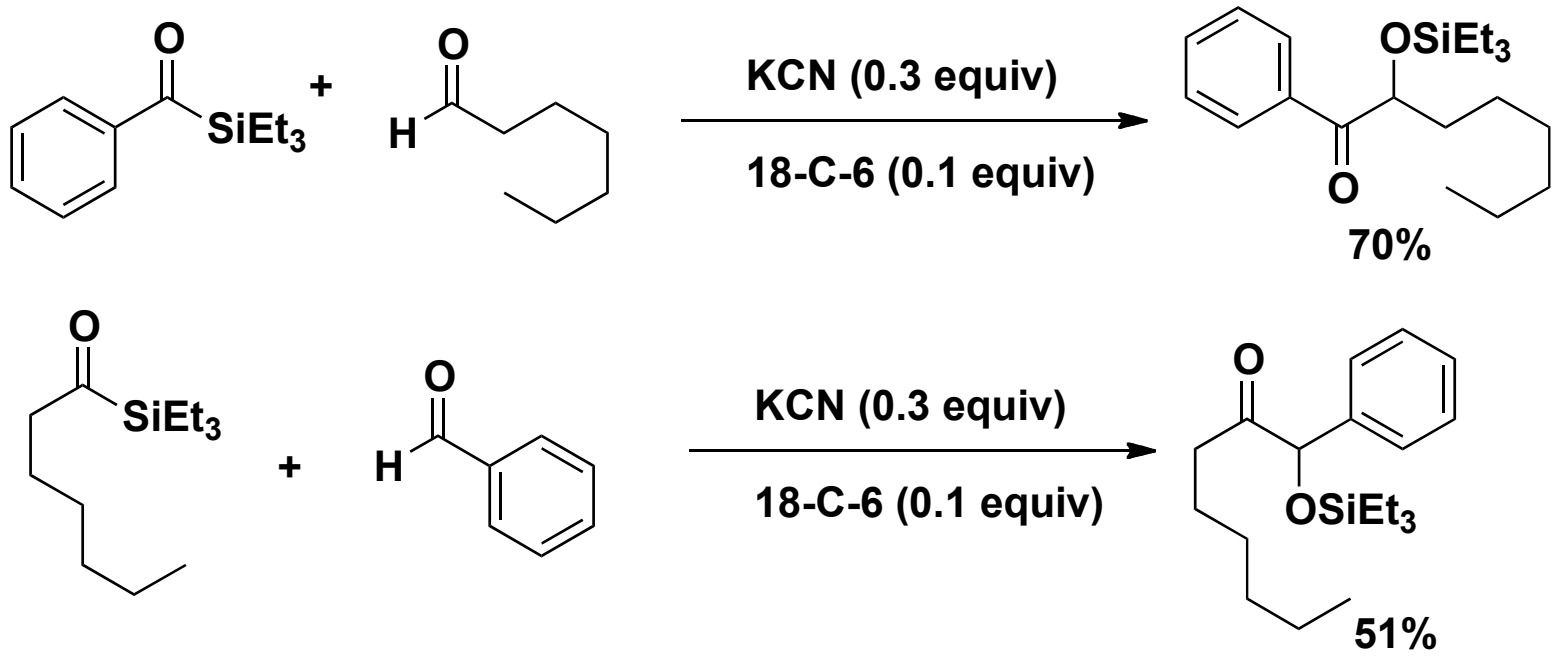
Johnson, J. S. *Angew. Chem. Int. Ed*. **2003,** *42,* 2534-2536.

Mechanism:



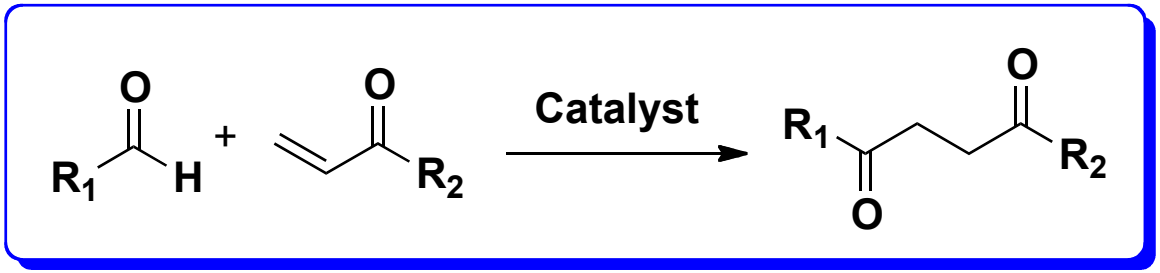
Redox Reaction of Aldehydes: Cross Benzoin Reaction

Examples:

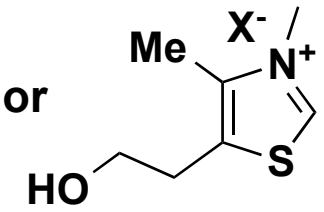


Stetter Reaction

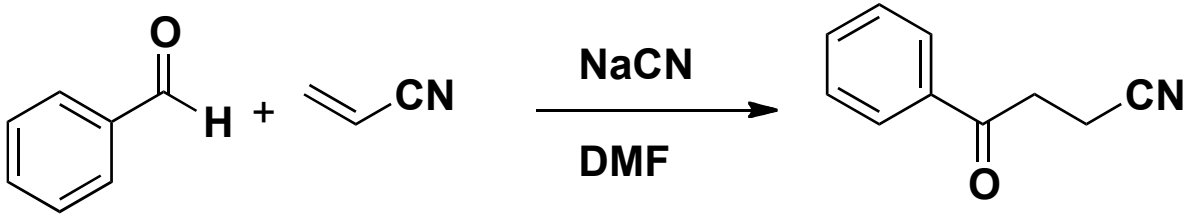
The Stetter Reaction is a 1,4-addition (conjugate addition) of an aldehyde to an a,β-unsaturated compound, catalyzed by cyanide or a thiazolium salt. This reaction competes with the corresponding 1,2-addition, which is the Benzoin condensation. However, the initial steps of the Benzoin-Condensation is reversible, and since the Stetter Reaction leads to more stable adducts, the main product will be that derived from 1,4-addition.



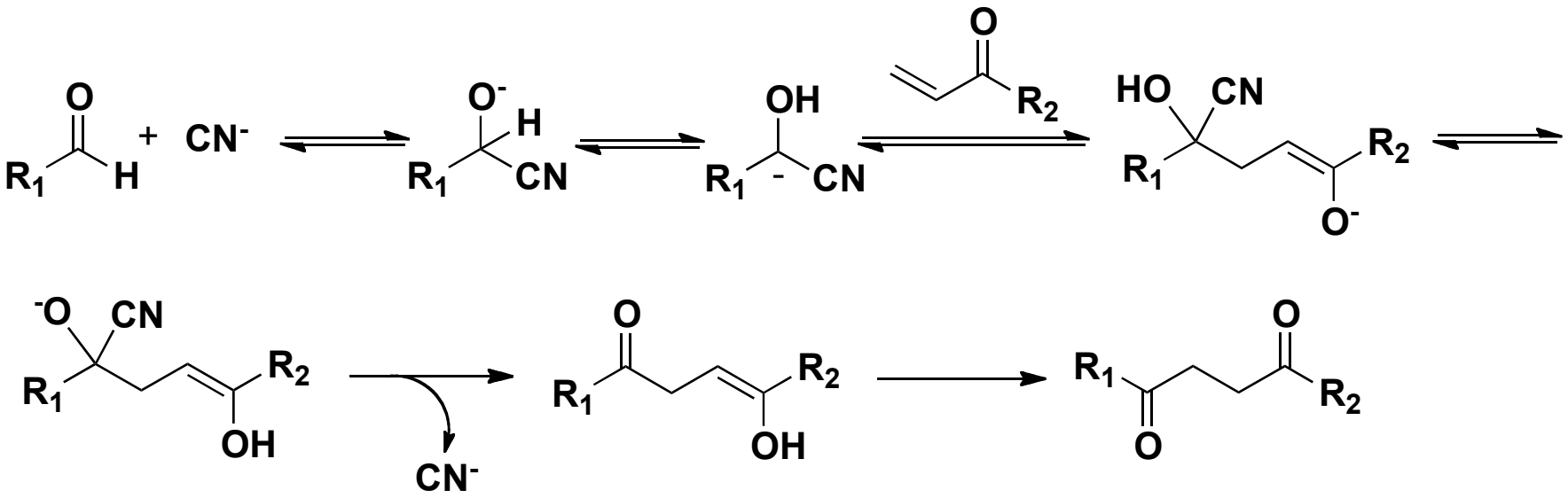
Catalyst: KCN **or**

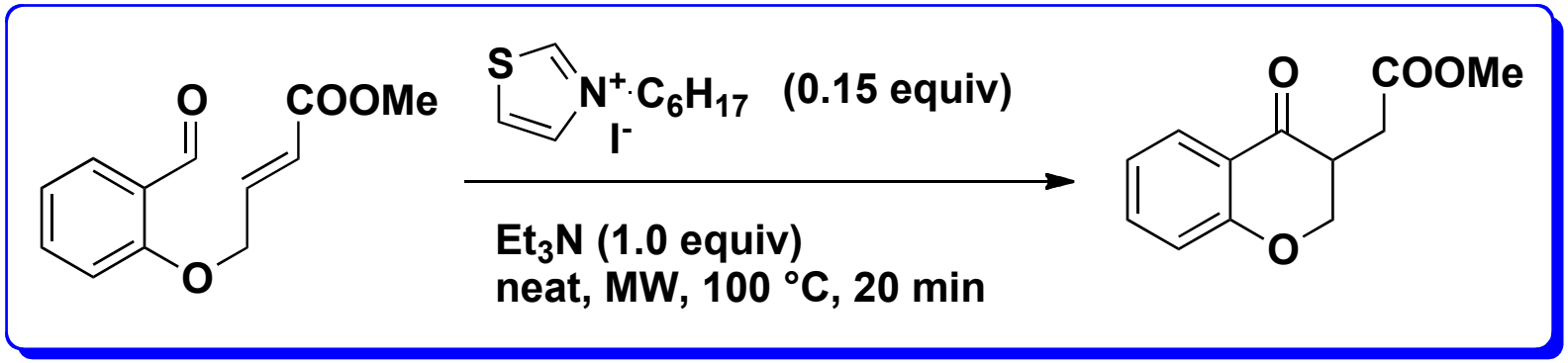


Thiazolium



Stetter Reaction: Mechanism

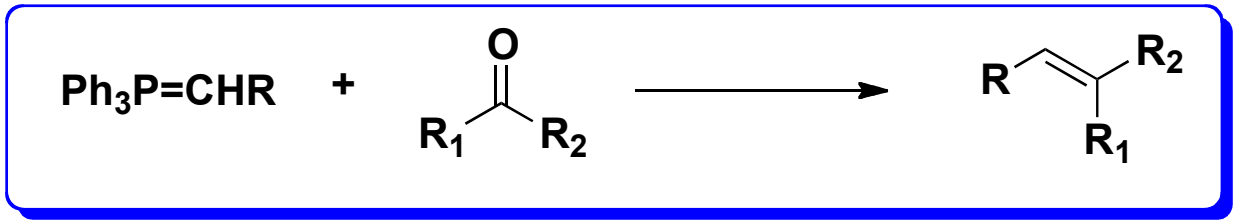




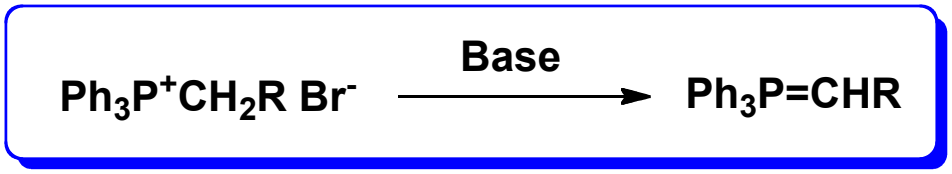
Carbonyl Compounds V:
Wittig Reaction and Its Variants

Reaction of Aldehydes and Ketones: Wittig Reaction

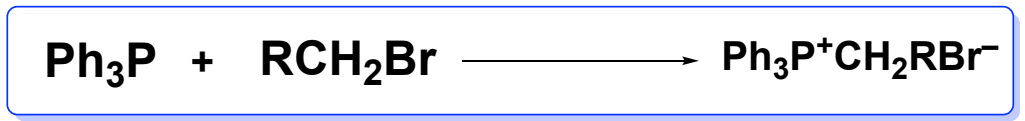
Wittig reaction: reactin of aldehyde with phosphonium ylide leading to olefin. Discovered in 1954 by George Wittig for which he was awarded Nobel prize in 1979



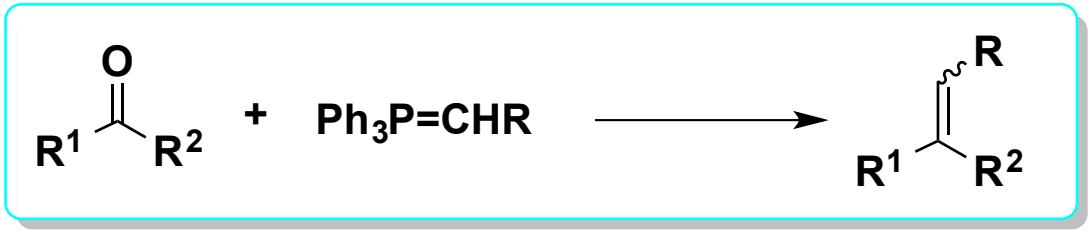
Phosphonium ylide can be generated in situ from phosphonium salt in the presence of a base.



Phosphonium salt is easily prepared by simply mixing a phosphine with an alkylbromide (a S_N2 reaction).



Wittig Reaction



Total Position Selectivity:

The double bond replaces the original aldehyde or ketone function.

E- and Z-stereoselectivity:

can be readily controlled through careful selection of the phosphorus reagent and reaction conditions

Phosphonium ylide: "classic Wittig ylide"
Phophonate anion: "Horner-Wadsworth-Emmons reaction
Phospine oxide anion "Horner-Wittig reaction

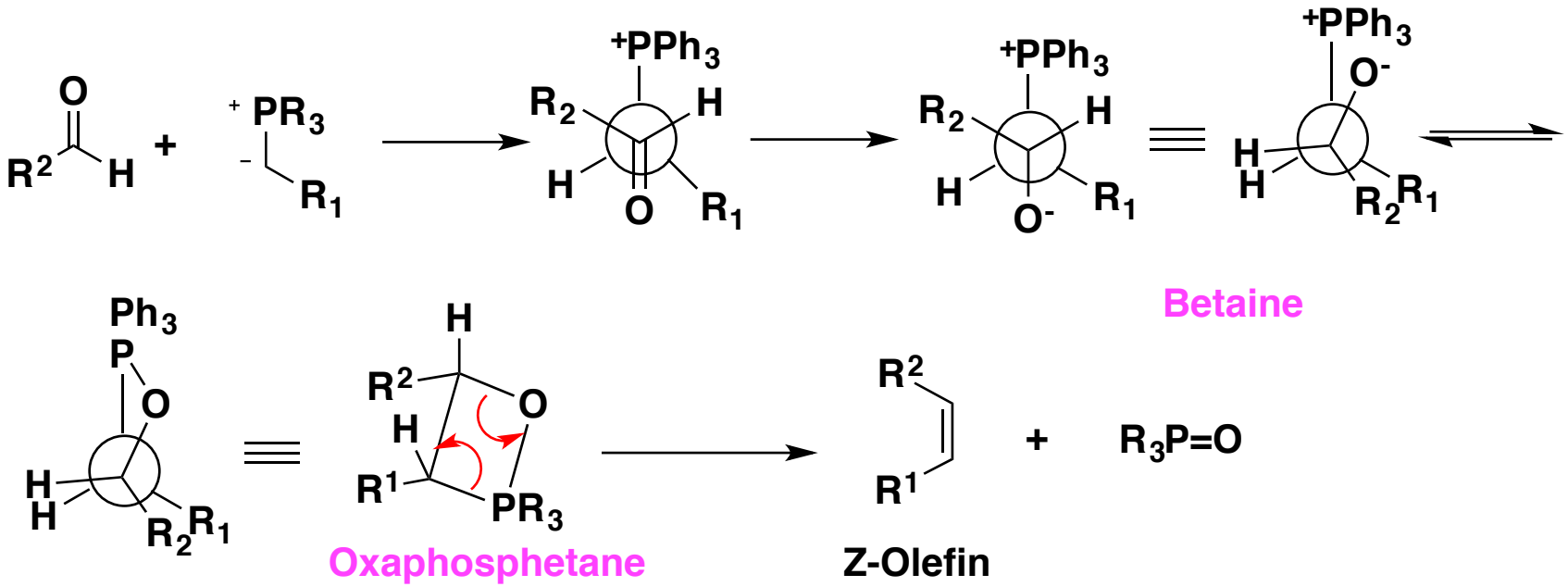
Ylides are neutral molecules but have positively and negatively charged centers on adjacent atoms that are connected by a σ bond.

i) **Non-stabilized ylides: The ylides with *electron donating groups* on negatively charged carbon. They are less stable and more reactive (eg R = Alkyl)**
ii) **Stabilized ylides: The ylides with *electron withdrawing groups* adjacent to the negatively charged carbon. They are more stable (eg R = COOMe)**

In general:

**** The unstabilized ylides react faster and lead to (Z)-alkenes.***
**** The stabilized ylides react slowly and lead to (E)-alkenes.***

Wittig Reaction: Mechanism



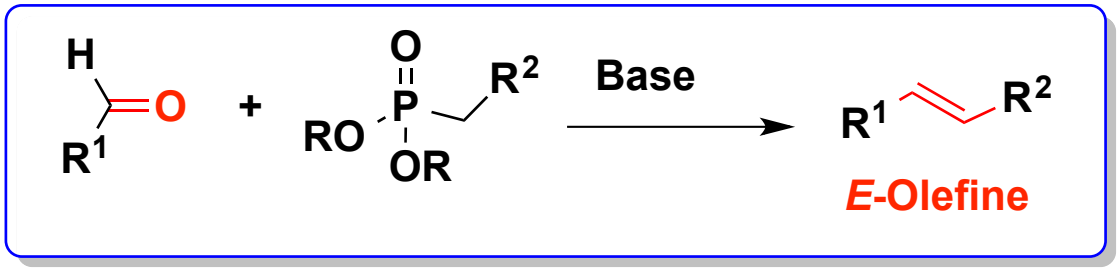
The ylide acts as a nucleophile adding to the carbonyl carbon. The resulting alkoxide oxygen adds to the phosphorus in an intramolecular fashion leading to a four-membered ring, called oxaphosphetane. This ring fragments (*Syn* elimination) to produce the alkene and the triphenylphosphine oxide.

***Z*-Olefine is a kinetic product.**

The Wittig reaction works well with aldehydes. It can also be used with ketones, but the *Z*/E selectivity is generally difficult to control.

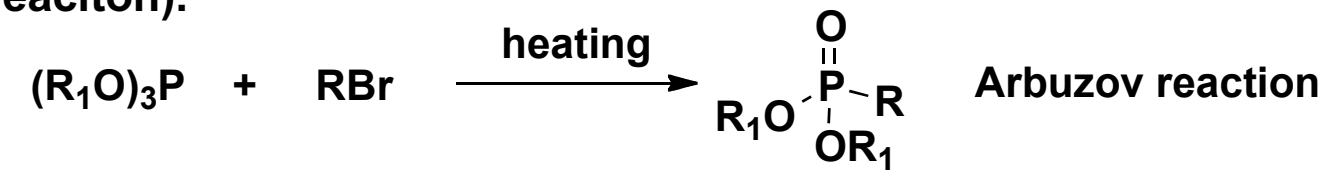
The Horner-Wadsworth-Emmons Reaction

The reaction of a phosphonate-stabilized carbanion with a carbonyl compound is called Horner–Wadsworth–Emmons reaction (HWE).



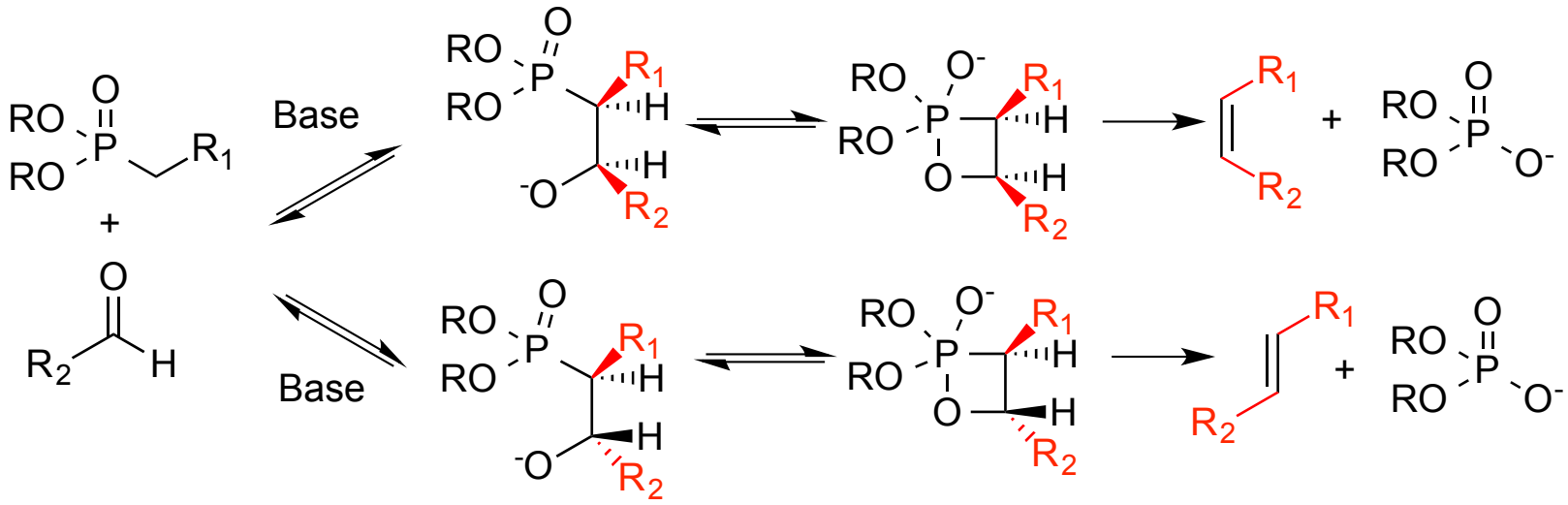
Stabilized ylide R_3P=CHCOOMe is significantly less reactive due to the anion stabilizing effect of the ester function. Phosphonate anion $(RO)_2P(O)CH^-COOR$ is more reactive than R_3P=CHCOOMe toward the carbonyl function.

The phosphonate can be prepared by reaction of trialkyl phophite with alkyl halide (Arbuzov reaciton).



***E-selectivity*: The HWE reaction between phosphonates and aldehydes generally affords the E-olefine.**

The Horner-Wadsworth-Emmons Reaction: Mechanism

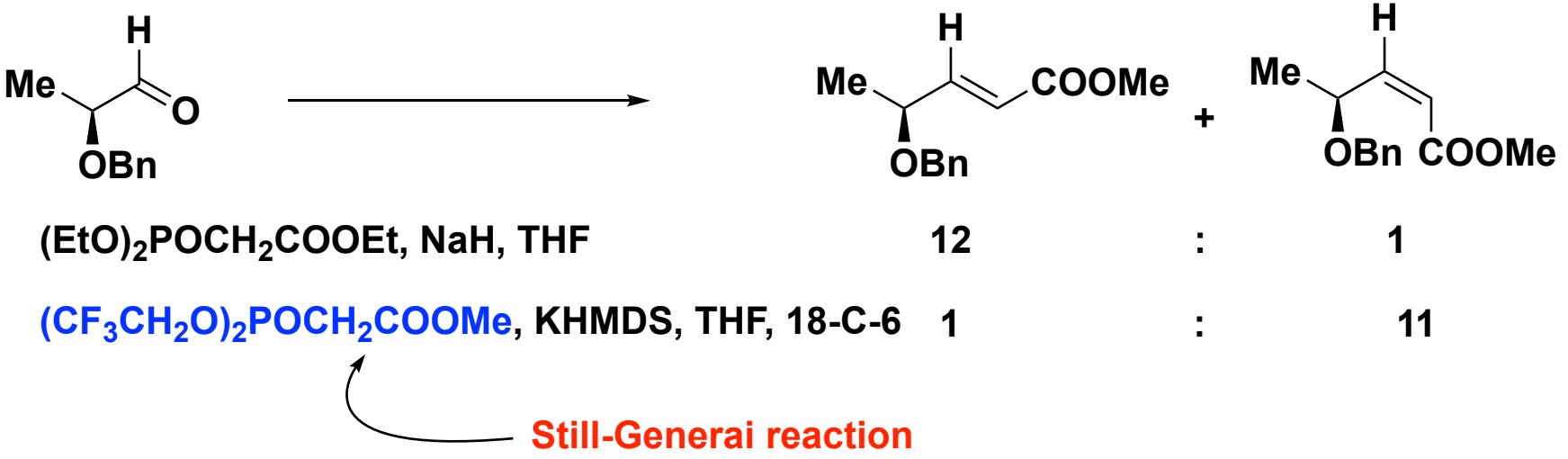


The nucleophilic addition of phosphonate anion to carbonyl carbon is reversible leading to thermodynamically more stable *E*-alkene.
However, many factors including the structure of phosphonate and aldehydes, reaction conditions etc can influence the stereochemical outcome of the HWE reaction.

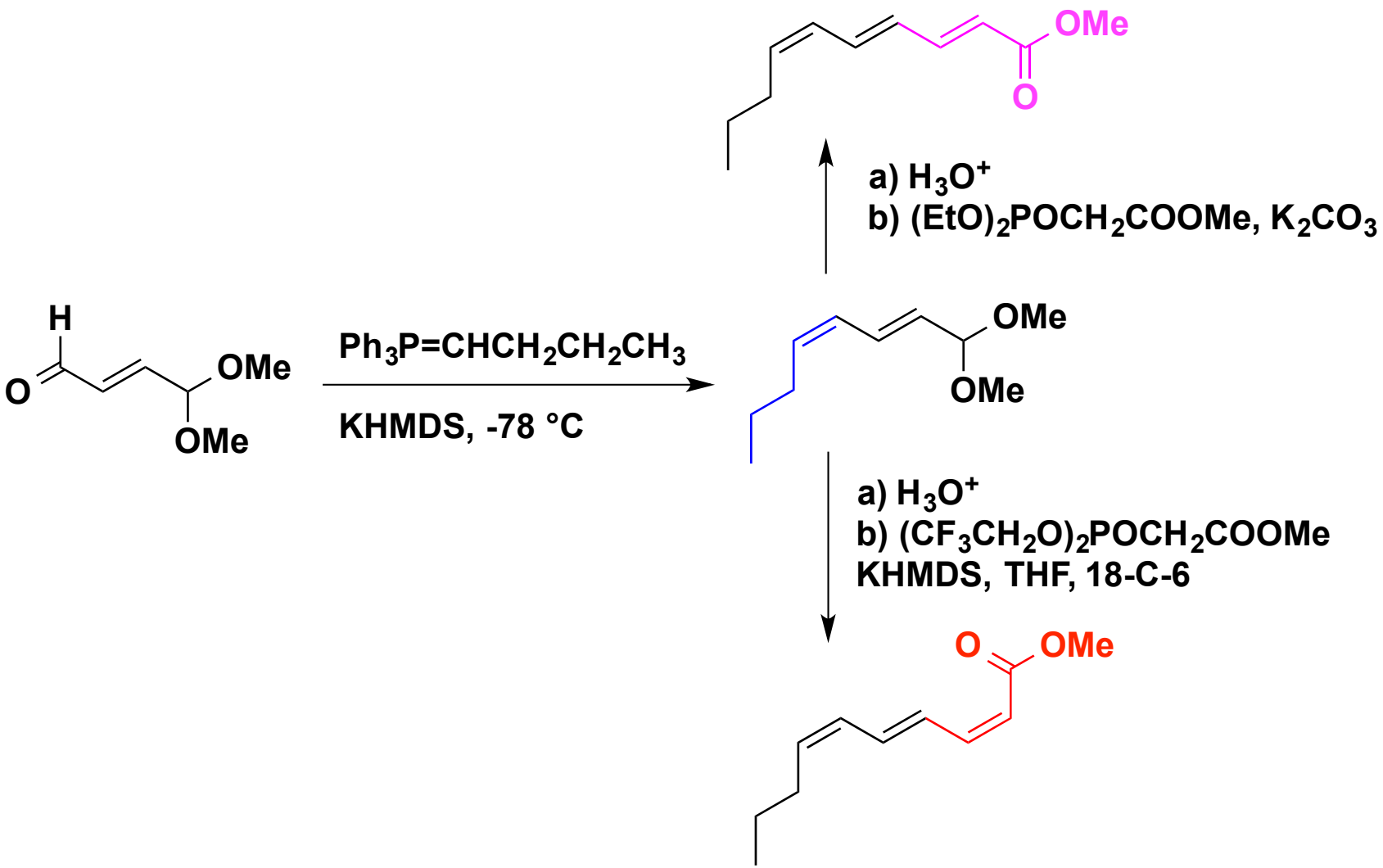
The phosphorus byproducts are water-soluble and hence readily separated from the desired product.

Still-Gennari Modification of the HWE reaction

Reaction of (2,2,2-trifluoroethyl)phosphonate with aldehydes afford Z-alkene as a major product.



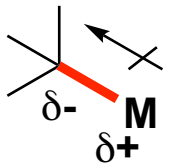
Stereoselective Construction of Polyenes



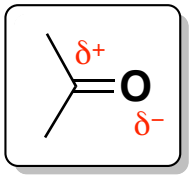
Carbonyl Compounds VI:
Nucleophilic Addition of Organometallics

Organometallic Reagents

Organometallic reagents (R-M) contain a carbon-metal bond.
Li, Mg, Cu, Zn, and Ce are the most common metals used.



Having a polarized C-M bond
***Electronegativity*:**
C: 2.55
Li: 0.98; Mg: 1.30; Zn: 1.65; Cu: 1.90; Sn: 1.96; Ce: 1.12



General structure of Organometallics:

R-Li; RMgX; $R_2Cu^-Li^+$; R_2Zn

In all these organometallics, carbon attached to metal bears formerly negative charge.

The more polar the C-M bond, the more reactive the organometallic reagents.
However, the Lewis acidity of metals needs to be taken into consideration when one considers the reactivity and selectivity of a given organometallic.

Organometallic Reagents

The more polar the C-M bond, the more reactive the organometallics. Li and Mg are more electron-positive than Cu, so RLi (organolithium), RMgX (organomagnesium) are more reactive than R_2CuLi (Organocuprate). RMgX is also called Grignard reagent, named after its inventor. Victor Grignard was awarded Nobel Prize in 1912 for this discovery.

Organometallic reagents are strong bases that readily abstract a proton from acidic protons (water, alcohol, amide NH etc…) to form hydrocarbons. Since acid-base reaction is much faster than the nucleophilic addition, an excess of organometallic is required when carbonyl substrates contain an acidic proton.

RLi and RMgX are pyrophoric (burn spontaneously upon exposure to air). They are commercially available in solution form.

Reactions involving organometallic reagents are generally performed in inert atmosphere and under anhydrous conditions.

Preparation of Organometallic Reagents

* Organolithium and Grignard reagents are typically prepared by reaction of an alkyl Halide with the corresponding metal.

Metal-halogen exchange

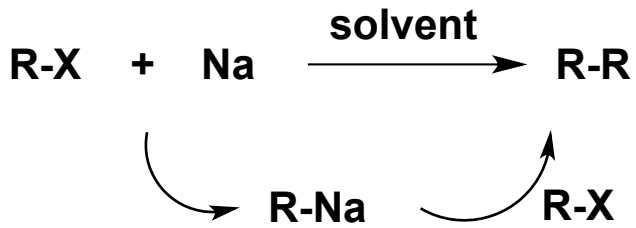
Insertion of Mg into R-X bond

Acid-base reaction

Organolithium exists as hexamer, tetramer, dimer or monomer depending on the solvent in which they were prepared and the natural of the R group.

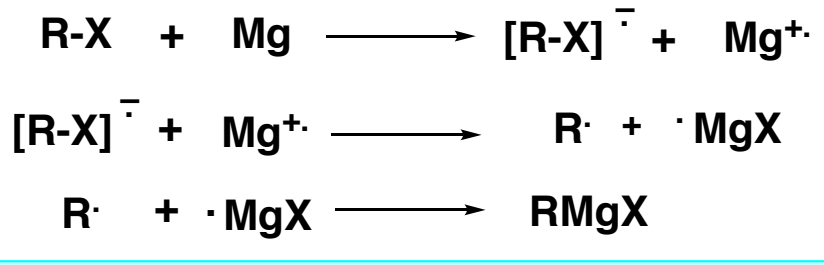
* Organocuprates are prepared by reaction of RLi with Cu(I) salt.

Note: Reaction of sodium with RX affords R-R. The reaction is called Wurtz reaction

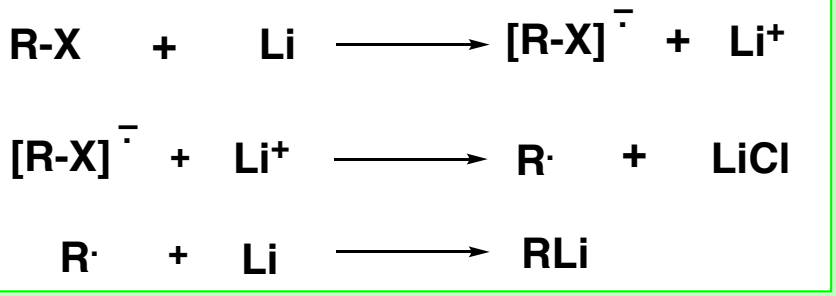


Formation of Grignard and Organolithium reagents: Simplifed Mechanism

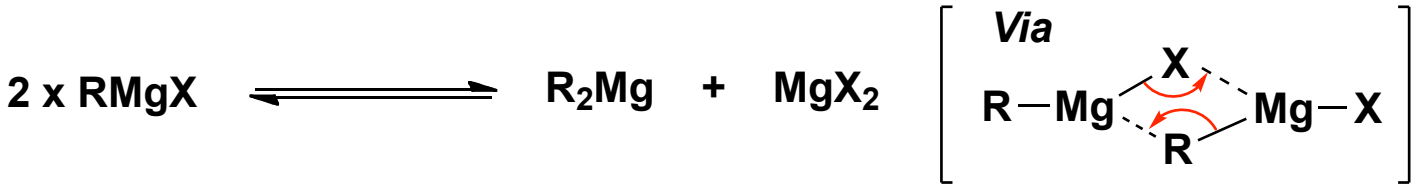
Formation of Grignard



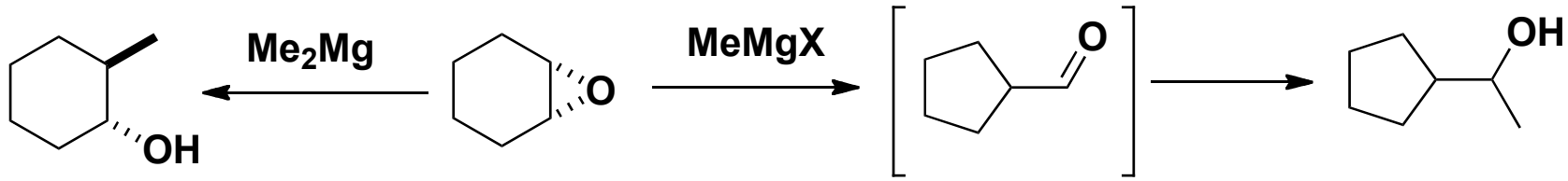
Formation of Organolithium



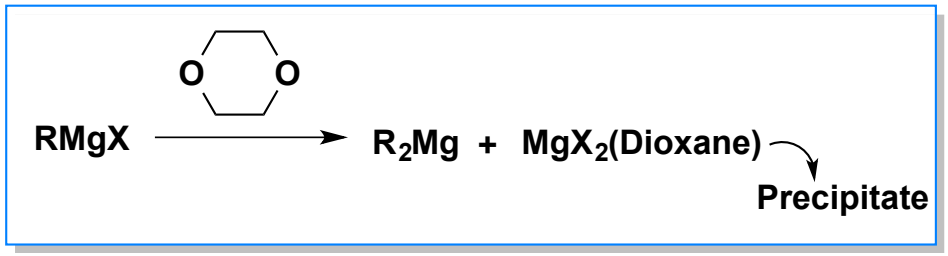
Schlenk Equilibrium



Since magnesium halides are moderate Lewis acids, their presence in solution may influence the outcome of certain chemical reactions. One example of this perturbation is the reaction of cyclohexene oxide with methylmagnesium bromide, as shown on the right in the following equation. Magnesium bromide rearranges the epoxide to cyclopentanecarbaldehyde, which then adds the Grignard reagent in an expected manner. The dimethylmagnesium, on the other hand, simply open the epoxide ring in a S_N2 manner.

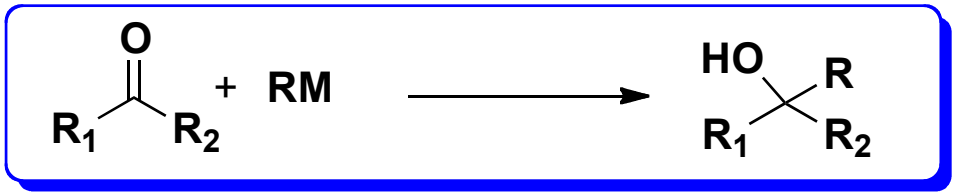


In dioxane, the equilibrium is shifted to R_2Mg because MgX_2 form a polymeric complex with solvent that precipitates.



Diethyl ether, Tetrahydrofuran are frequently used solvent for Grignard. Dioxane is not.

Addition of Organometallic Reagents to Carbonyl



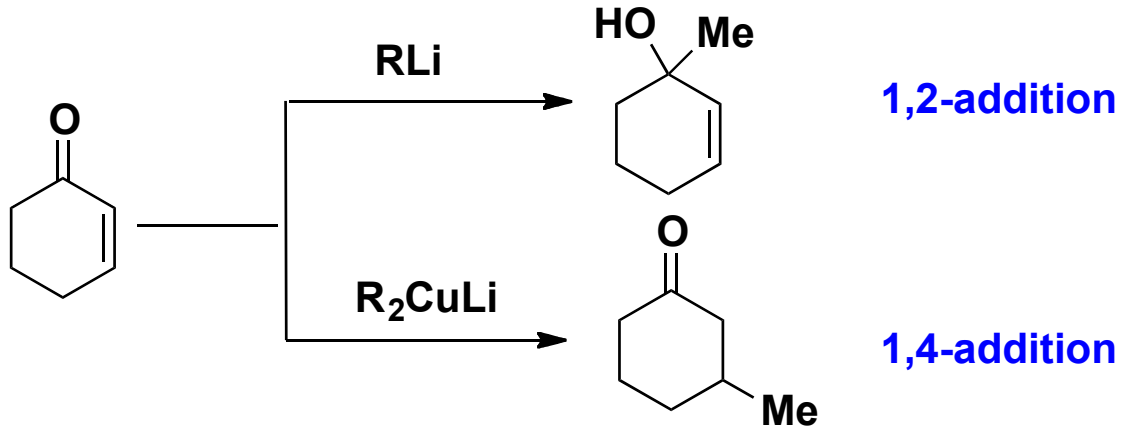
This reaction follows the general mechanism for nucleophilic addition—that is, nucleophilic attack by a carbanion followed by protonation of the resulting alkoxide.

Addition of oranometallic to formaldehyde affords primary alcohol
Addition of oranometallic to aldehyde affords secondary alcohol
Addition of oranometallic to ketone affords tertiary alcohol

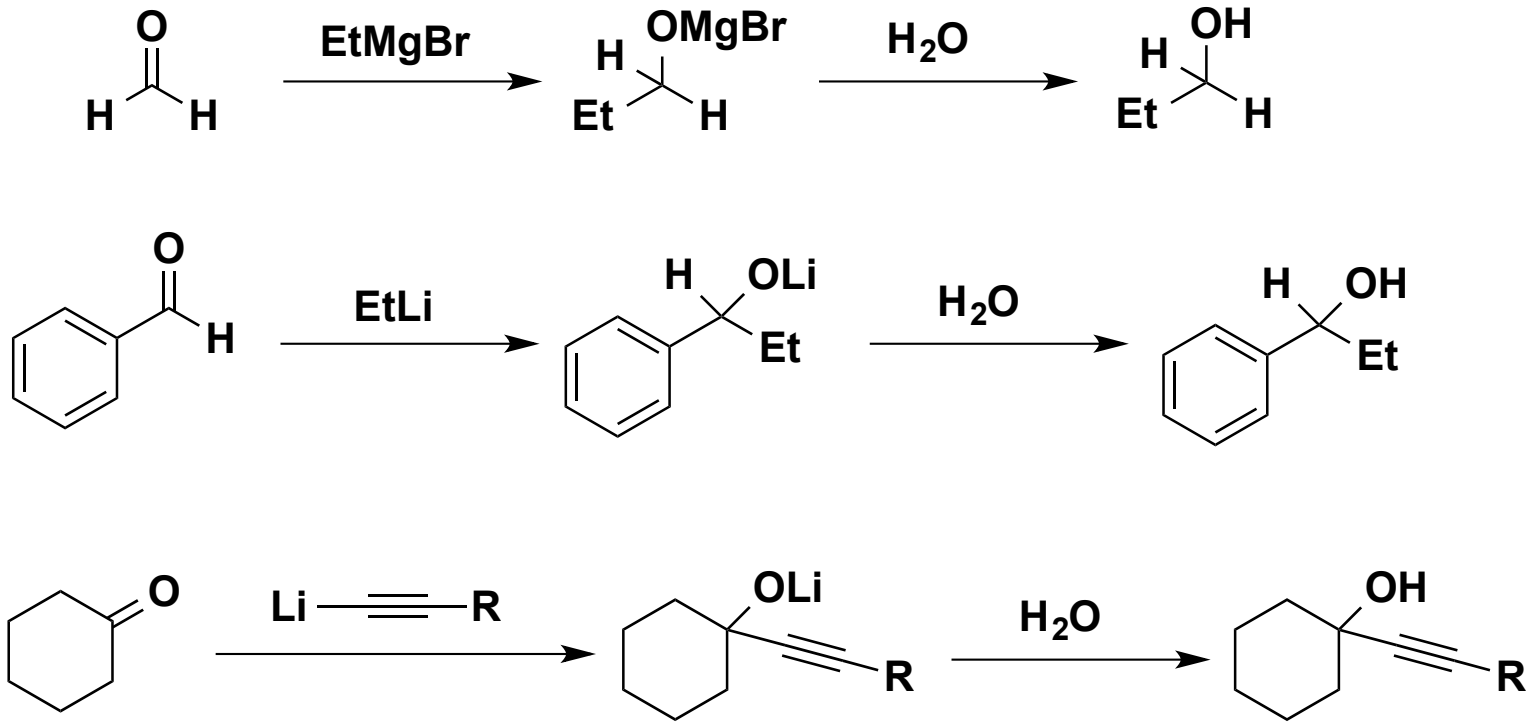
With α,β-unsaurated ketone:

RLi and RMgX prefer 1,2-addition leading to allylic alcohol

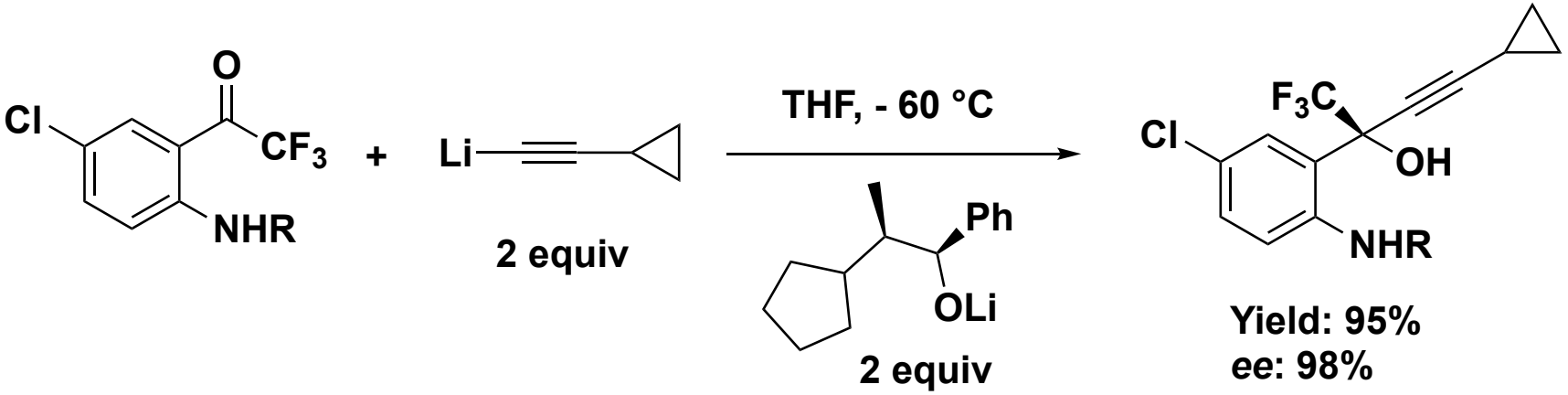
R_2CuLi (Gilman reagent) prefers 1,4-addition leading to β-functionalized saturated ketone

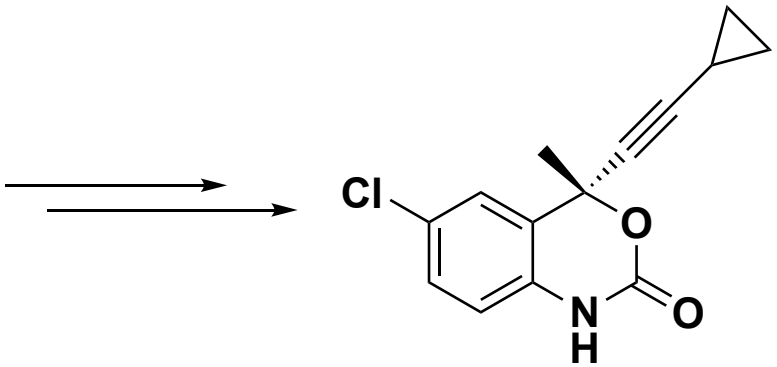


Addition of Organometallic Reagents to Carbonyl: Examples

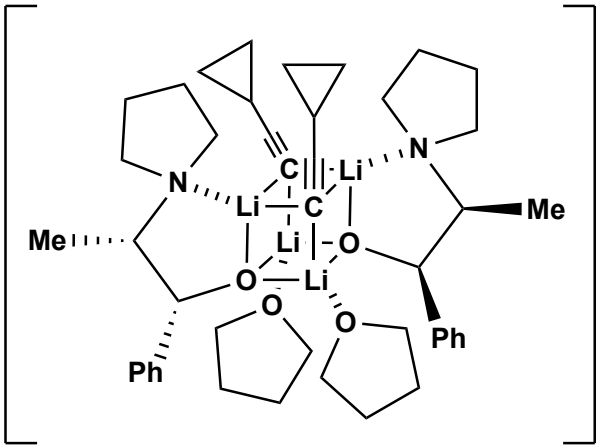


Synthesis of Efavirenz





Efavirenz, Anti-HIV drug

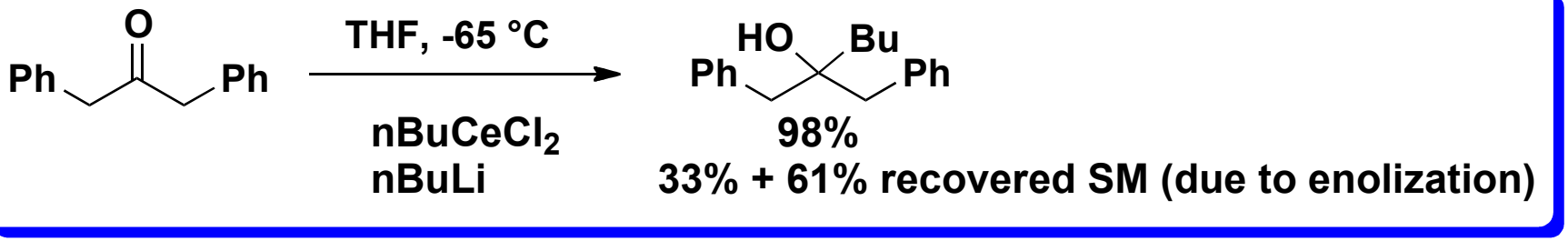


Addition of Organometallic Reagents to Carbonyl

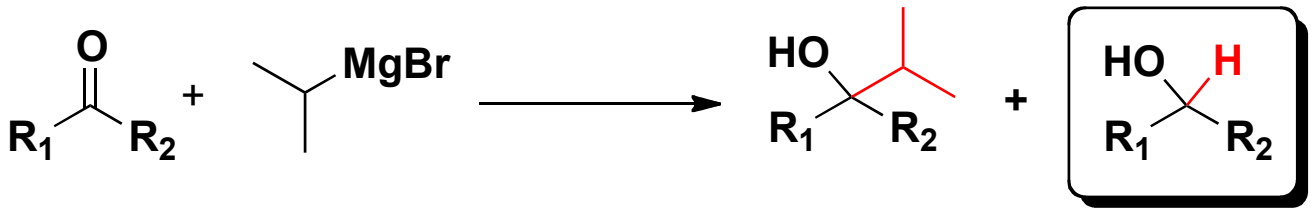
Two competitive side reactions:

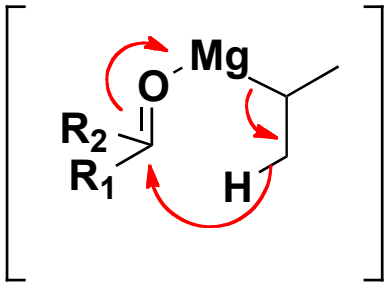
*** Grignard reagent acts as a base leading to enolate.**

In this case, using organocerium reagents $RCeCl_2$, prepared in situ from RMgX (or RLi) and $CeCl_3$, could solve the problem.



*** Grignard reagent acts as a reducing agent. This happens with hindered substrates or reagents.**

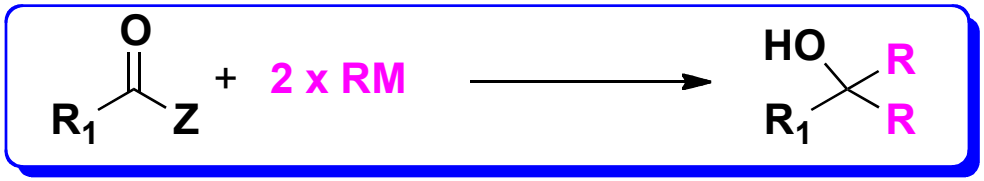




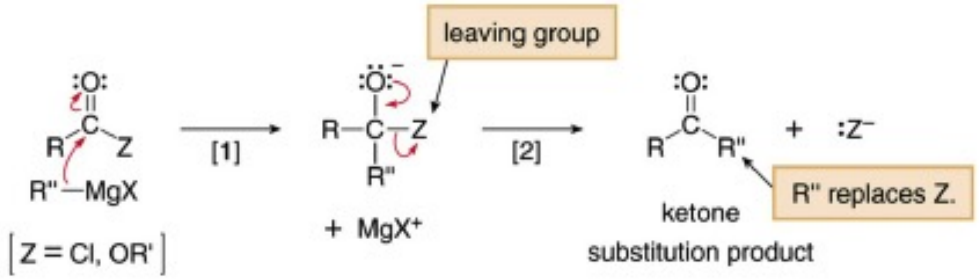
Reminder: the Meerwein-Ponndorf-Verley reaction

Addition of Organometallic Reagents to Ester and acyl chloride

Both esters and acid chlorides form tertiary alcohols when treated with two equivalents of either Grignard or organolithium reagents.

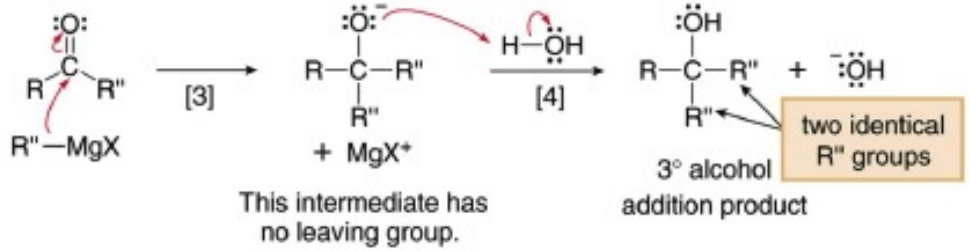


Part [1] Nucleophilic substitution forms a ketone.



- **Nucleophilic attack of (R")⁻** (from R"MgX) in Step [1] forms a tetrahedral intermediate with a leaving group Z.
- In Step [2], the π bond is re-formed and **Z⁻ comes off.** The overall result of the addition of (R")⁻ and elimination of Z⁻ is the substitution of R" for Z.
- Because the product of Part [1] is a ketone, it can react with a second equivalent of R"MgX to form an alcohol by nucleophilic addition in Part [2].

Part [2] Nucleophilic addition forms a 3° alcohol.



- **Nucleophilic attack of (R")⁻** (from R"MgX) in Step [3] forms an alkoxide.
- **Protonation of the alkoxide** by H_2O in Step [4] forms a 3° alcohol.

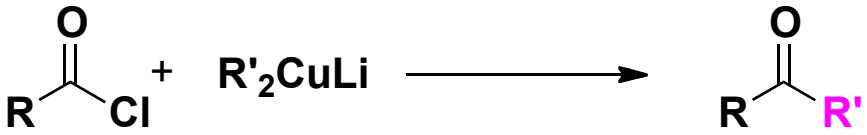
Note: Ketone is more electrophilic than ester

From acyl chloride to Ketone with Organocuprate

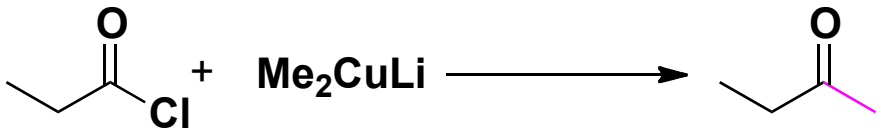
To form a ketone from a carboxylic acid derivative, a less reactive organometallic reagent—namely an organocuprate is needed.

Acid chlorides react with R'_2CuLi to give a ketone as the product. On the other hand, esters are not reactive enough to react with R'_2CuLi.

General Reaction

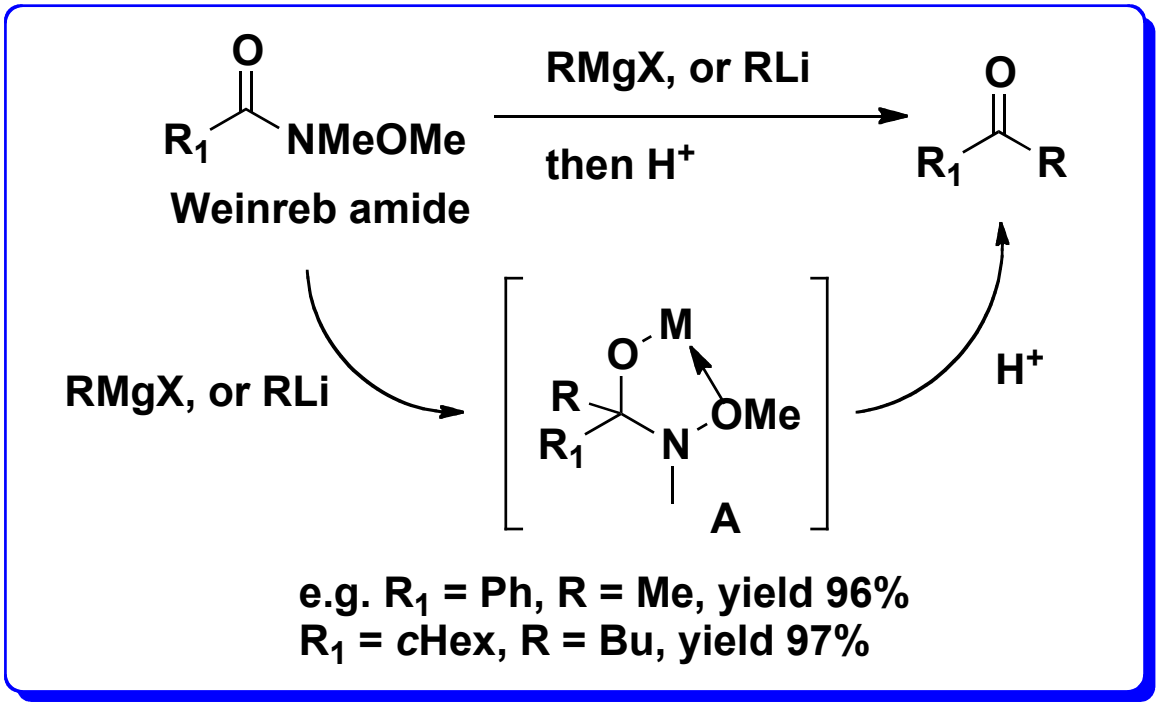


Example



Note: Acyl chloride is more reactive than ketone

From Weinreb Amide to Ketone



Why the reaction stop at the ketone level?

Intermediate A is stable thanks to the formation of a chelate. It did not undergo the fragmentation untill aqueous work up.

Similarly, the Weinreb amide can be reduced to aldehyde.