10. Aldeidi e Chetoni

(1) Reattività dei composti carbonilici.

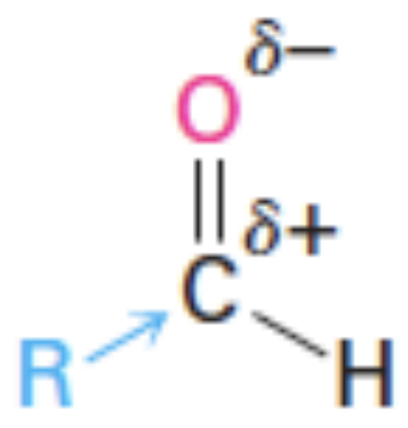
(2) Addizione di nucleofili forti e deboli al carbonio carbonilico.

(3) Formazione di immine ed enammine.

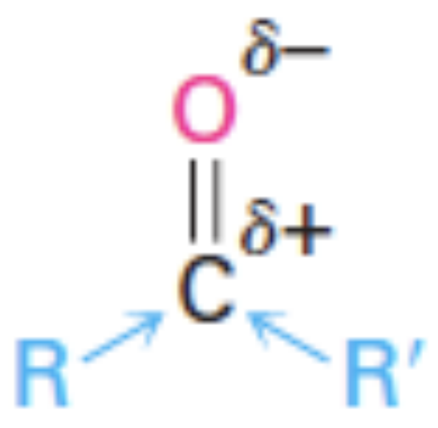
(4) Formazione di acetali e emiacetali come gruppi protettori del gruppo carbonilico.

(5) Reazione di Wittig.

(6) ~~Addizione nucleofilica ad aldeidi e chetoni alfa,beta-insaturi in presenza di nucleofili deboli (addizione-1,4 coniugata) e forti (addizione-1,2 diretta).~~



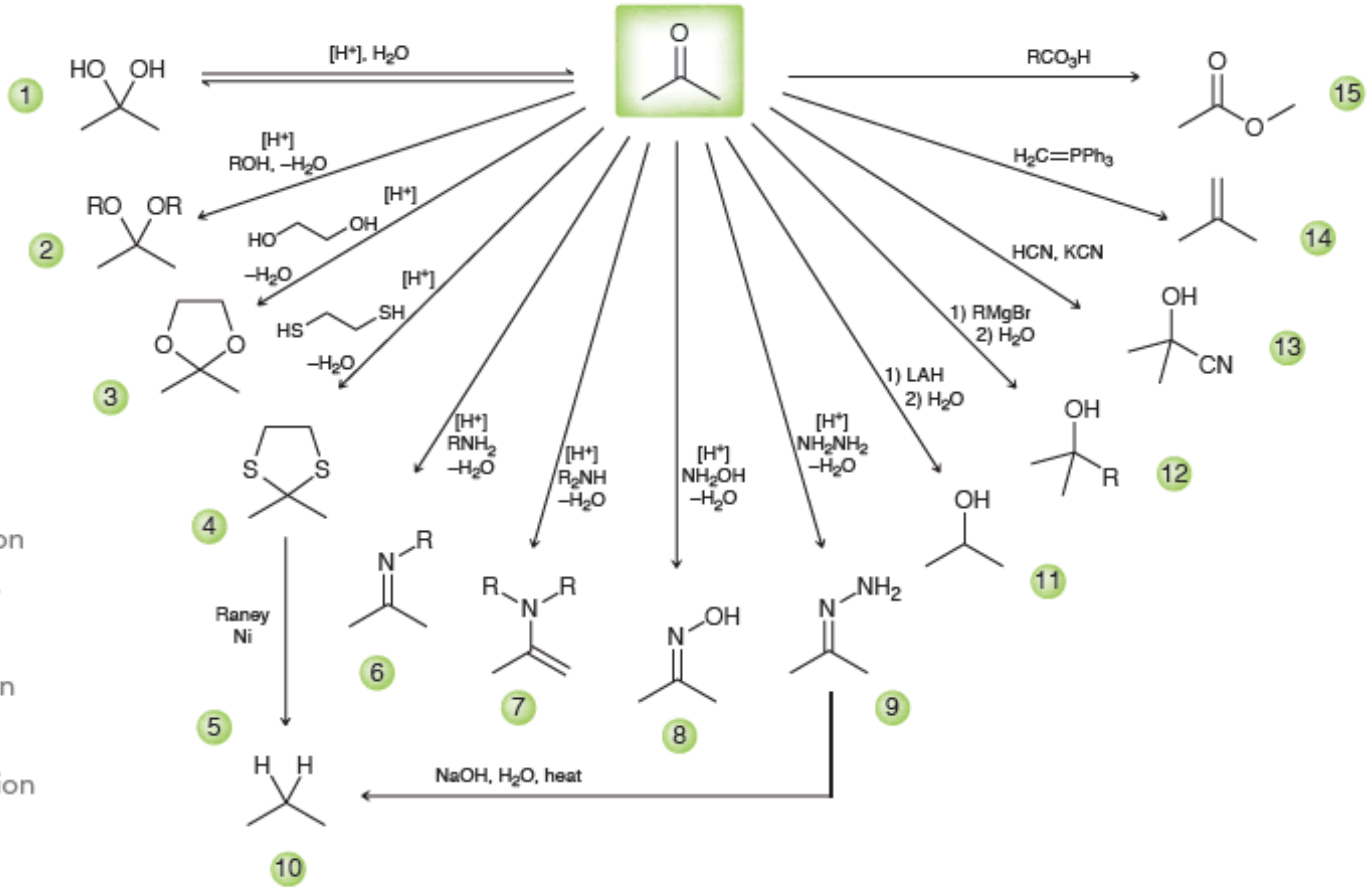
Aldehyde
(less stabilization of δ+, more reactive)



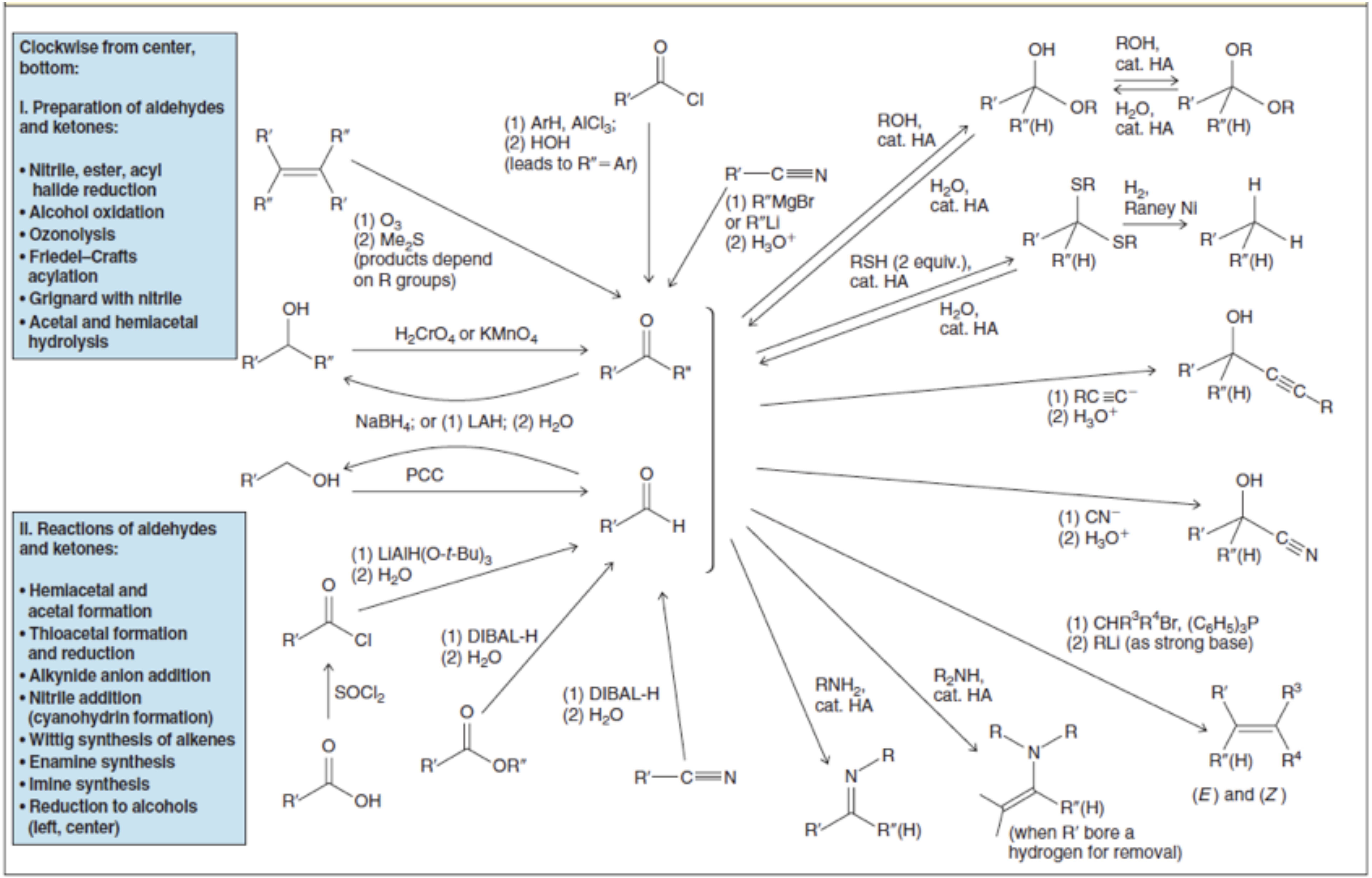
Ketone
(more stabilization of δ+, less reactive)

Revisione delle reazioni di aldeidi e chetoni

1. Hydrate Formation
2. Acetal Formation
3. Cyclic Acetal Formation
4. Cyclic Thioacetal Formation
5. Desulfurization
6. Imine Formation
7. Enamine Formation
8. Oxime Formation
9. Hydrazone Formation
10. Wolff-Kishner Reduction
11. Reduction of a Ketone
12. Grignard Reaction
13. Cyanohydrin Formation
14. Wittig Reaction
15. Baeyer-Villiger Oxidation



Connessioni sintetiche tra aldeidi, chetoni e altri gruppi funzionali



Clockwise from center, bottom:

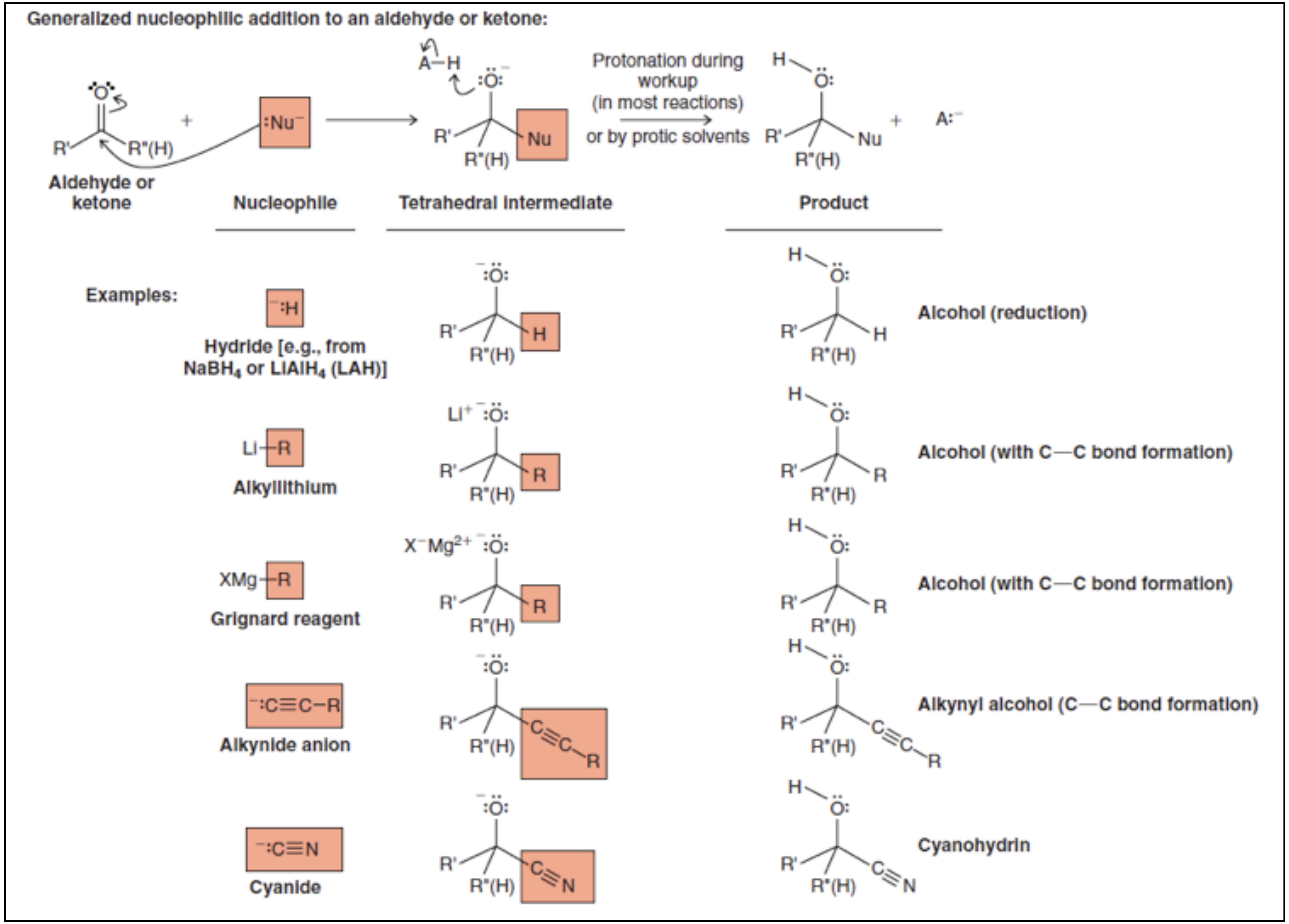
I. Preparation of aldehydes and ketones:

- Nitrile, ester, acyl halide reduction
- Alcohol oxidation
- Ozonolysis
- Friedel–Crafts acylation
- Grignard with nitrile
- Acetal and hemiacetal hydrolysis

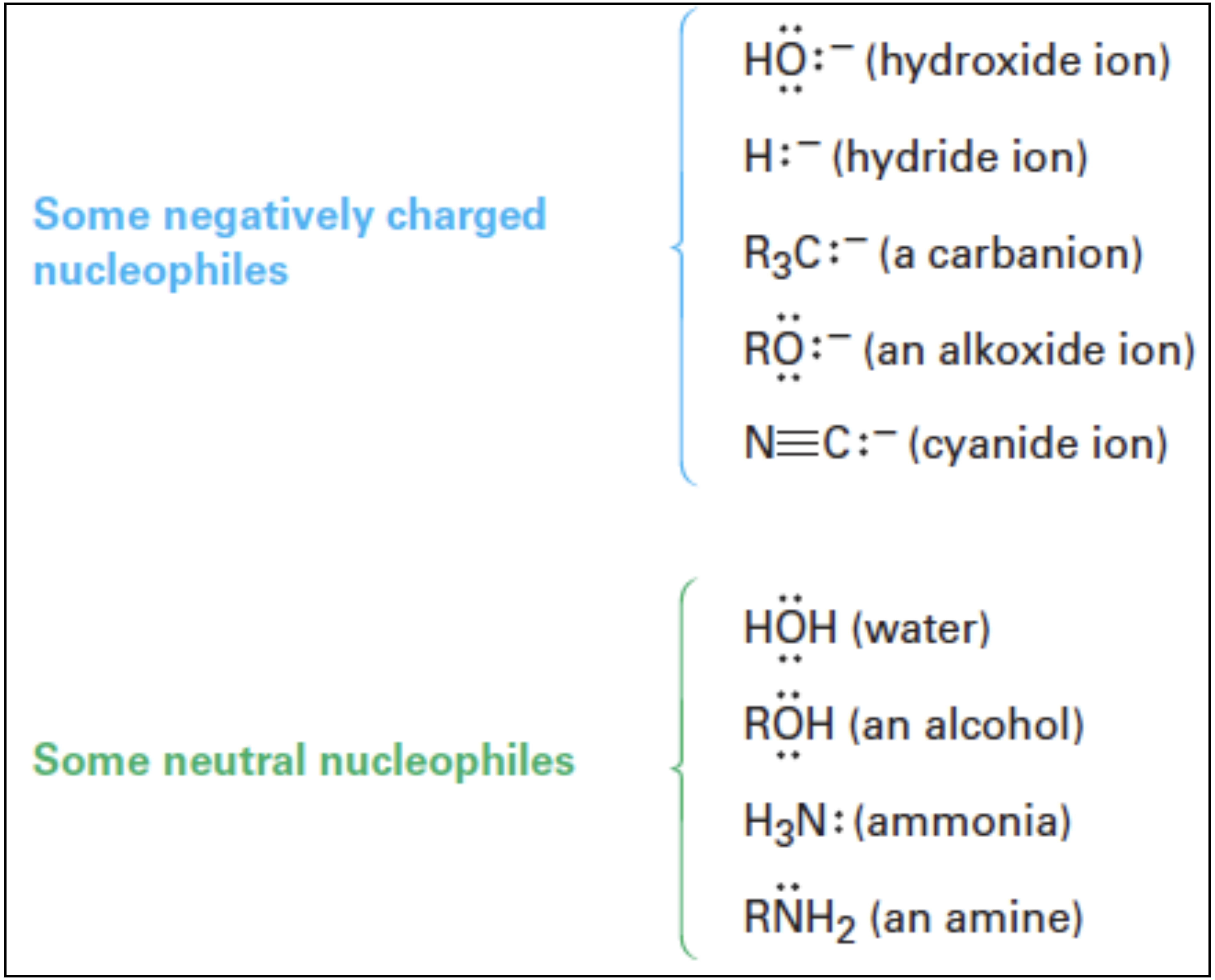
II. Reactions of aldehydes and ketones:

- Hemiacetal and acetal formation
- Thioacetal formation and reduction
- Alkynide anion addition
- Nitrile addition (cyanohydrin formation)
- Wittig synthesis of alkenes
- Enamine synthesis
- Imine synthesis
- Reduction to alcohols (left, center)

Reazione generale: Addizione nucleofila di aldeidi e chetoni in condizioni basiche



Addizione nucleofila di aldeidi e chetoni con Nucleofili forti e Deboli



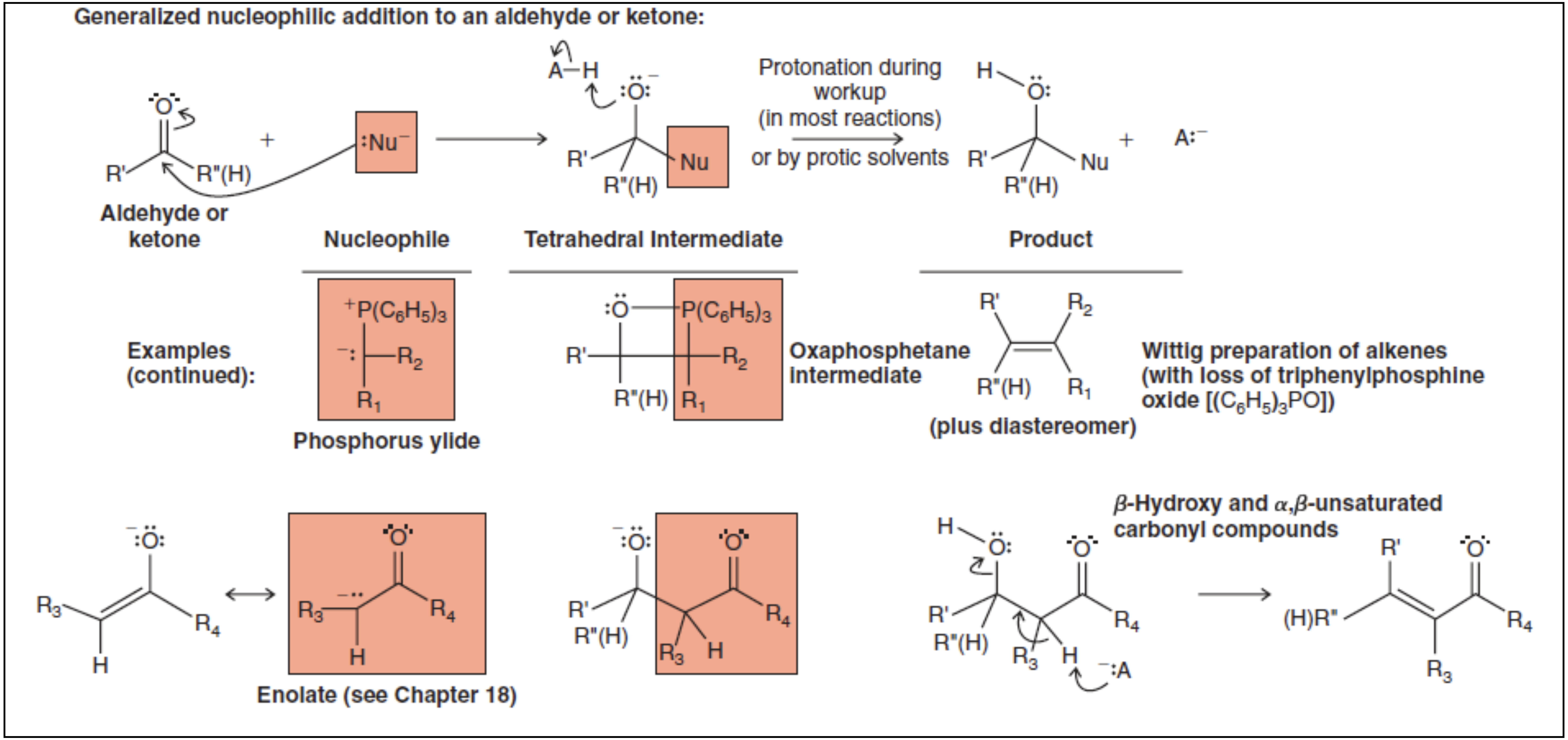
Some negatively charged nucleophiles

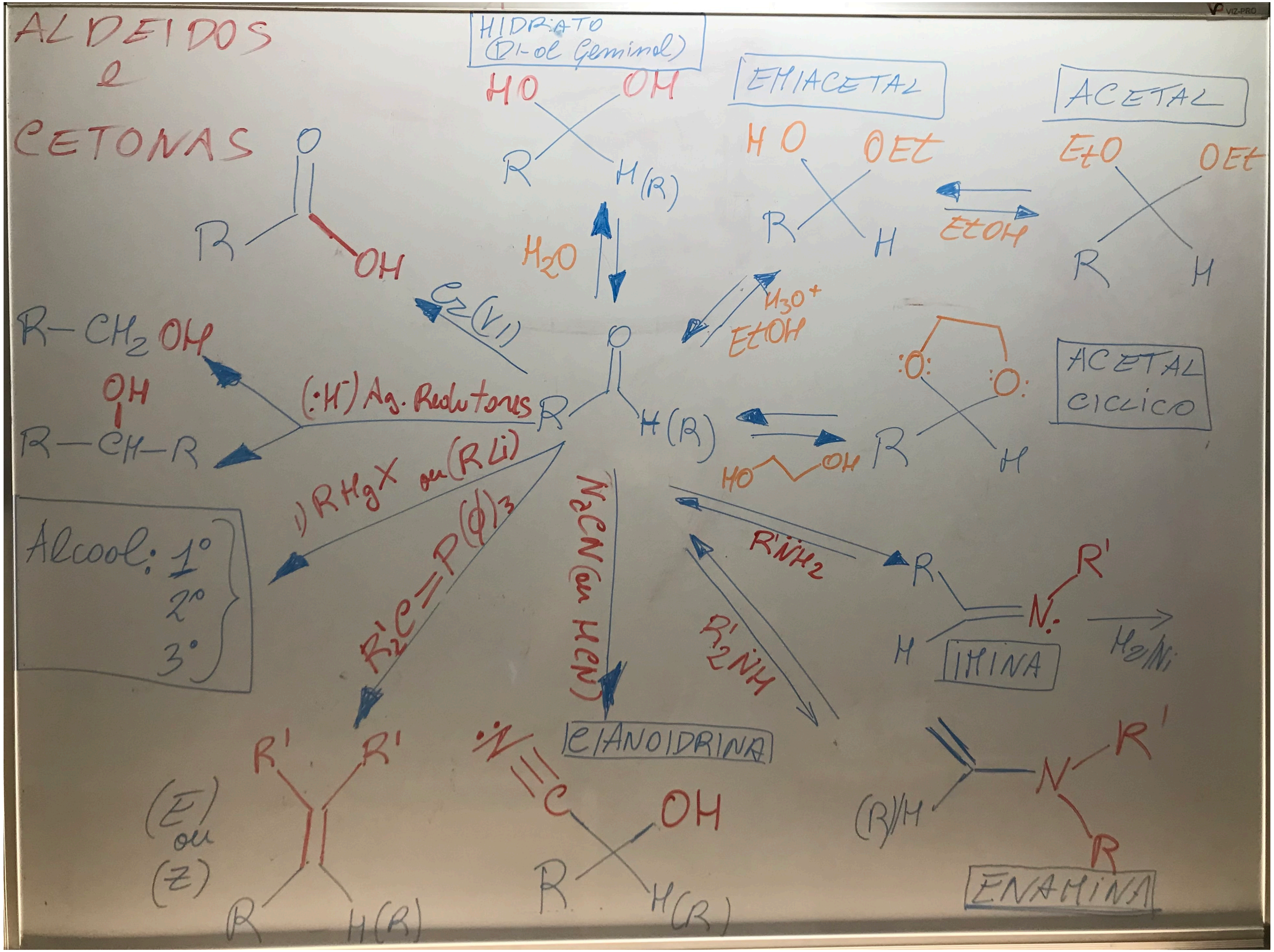
- $H\ddot{\underset{..}{O}}{:}^{-}$ (hydroxide ion)
- $H{:}^{-}$ (hydride ion)
- $R_3C{:}^{-}$ (a carbanion)
- $R\ddot{\underset{..}{O}}{:}^{-}$ (an alkoxide ion)
- $N{\equiv}C{:}^{-}$ (cyanide ion)

Some neutral nucleophiles

- $H\ddot{\underset{..}{O}}H$ (water)
- $R\ddot{\underset{..}{O}}H$ (an alcohol)
- $H_3N{:}$ (ammonia)
- $R\ddot{N}H_2$ (an amine)

Generalized nucleophilic addition to an aldehyde or ketone:




ALDEIDOS
e
CETONAS
HIDRATO
(DI-ol Geminal)
HO OH
R H(R)
H2O
EMIACETAL
HO OEt
R H
EtOH
ACETAL
EtO OEt
R H
H3O+
EtOH
O
R OH
Cr(VI)
R–CH2OH
OH
R–CH–R
(:H⁻) Ag. Redutores
1) RMgX ou (RLi)
Alcool: 1°
2°
3°
O
R H(R)
:O: :O:
R H
HO OH
ACETAL ciclico
R'2C=P(ϕ)3
N≡C(ou HCN)
R'NH2
R
N R'
H
IMINA
H2/Ni
R'2NH
R'
(E)
ou
(Z)
R' R'
R H(R)
:N≡C OH
R H(R)
CIANOIDRINA
R'
N
(R)/H
R
ENAMINA

✓ Gruppo carbonilico, C=O

- Aldeidi e chetoni
- Acidi carbossilici
- Derivati funzionali degli acidi carbossilici
- Enolati


$H\overset{\overset{:O:}{\|}}{C}H$

Metanale
(Formaldeide)


$CH_3\overset{\overset{:O:}{\|}}{C}H$

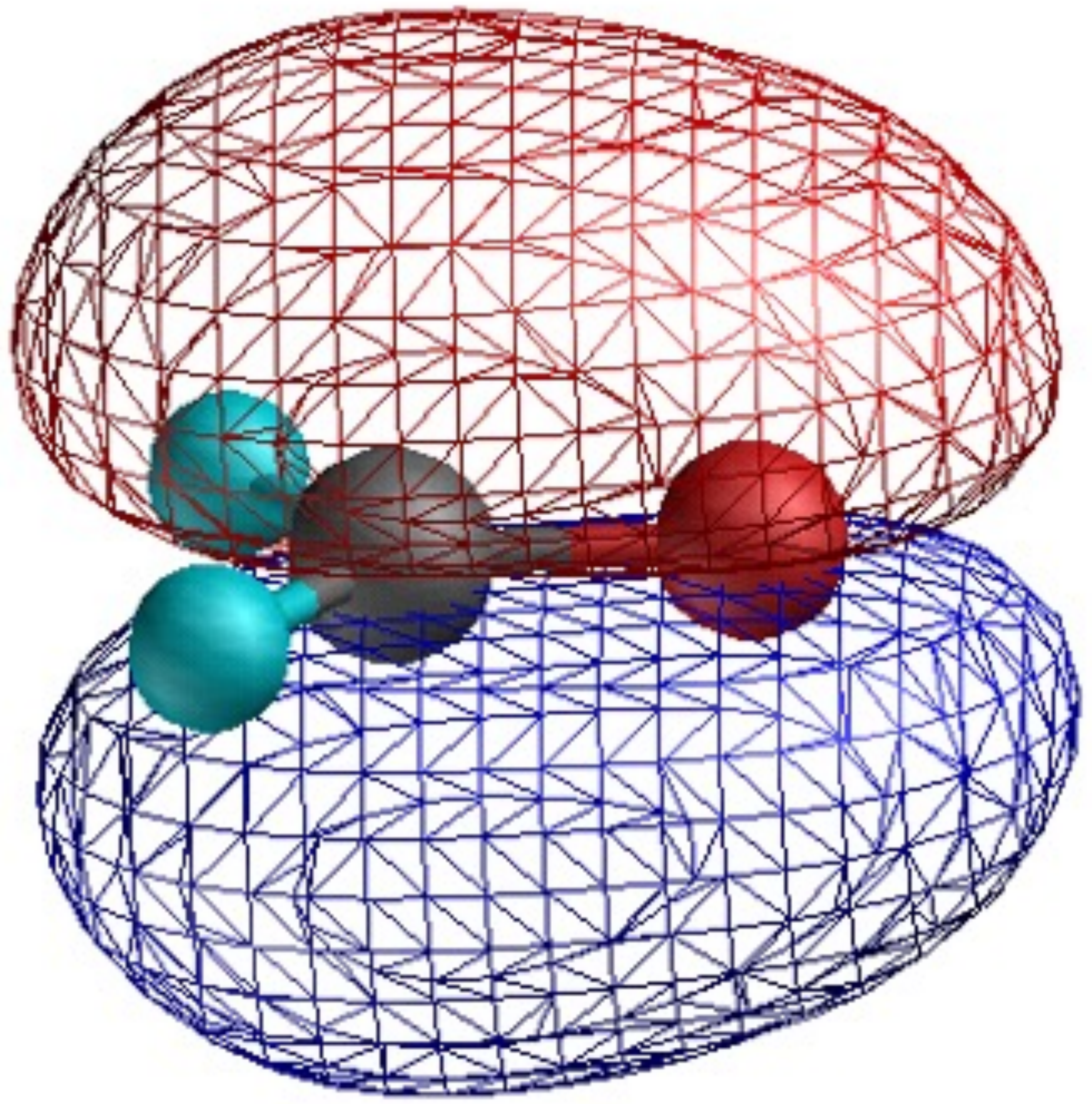
Etanale
(Acetaldeide)


$CH_3\overset{\overset{:O:}{\|}}{C}CH_3$

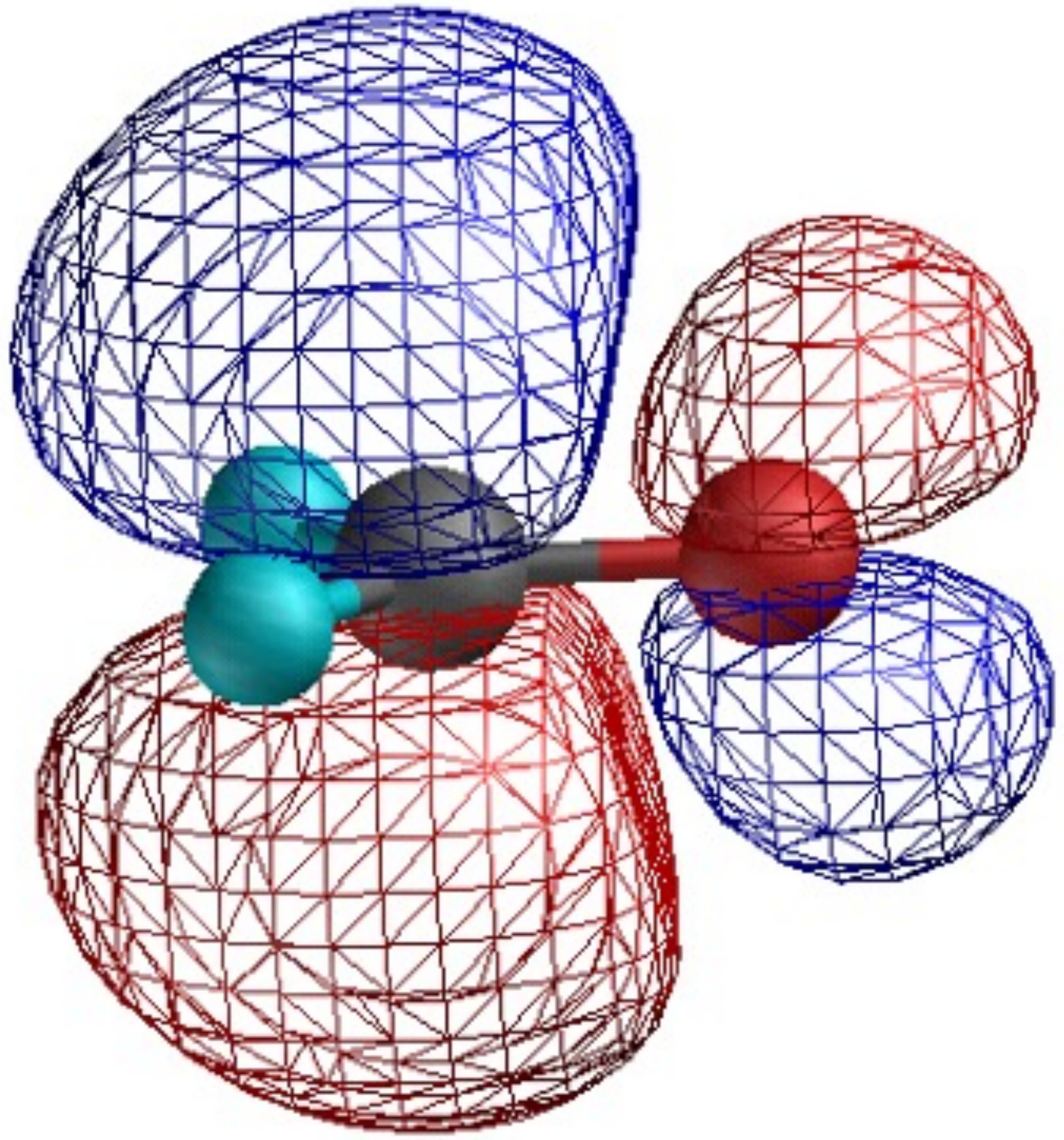
Propanone
(Acetone)

- $C=O$
- Un legame sigma (sovrapposizione di orbitali sp^2) e un legame pi greco (sovrapposizione di orbitali paralleli $2p$)
- Es.: formaldeide:

Orbitale π



Orbitale π*



Nomenclatura: aldeidi

✓ IUPAC:

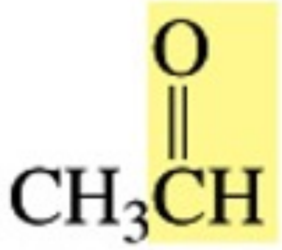
- La catena base è la più lunga che contiene il gruppo funzionale
- Cambiano il suffisso -o dell’alcano in -ale
- Aldeidi insature: l’infisso -an- diventa -en-
- Per molecole cicliche ove -CHO è legato all’anello si usa il suffisso –carbaldeide

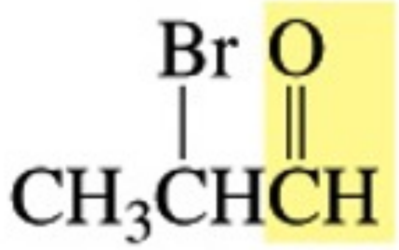
✓ Comune

- for an aldehyde, the common name is derived from the common name of the corresponding carboxylic acid

Nomenclatura: aldeidi

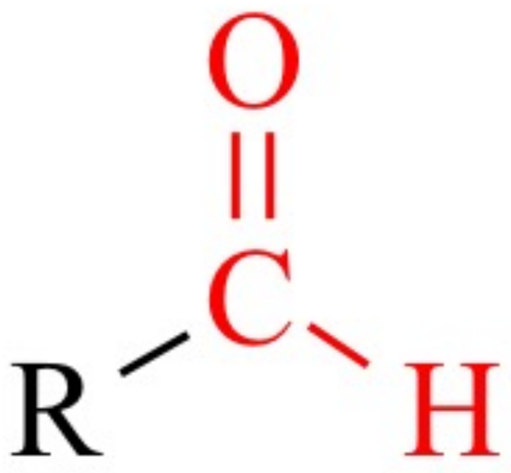

$\overset{O}{\overset{\|}{HCH}}$


$CH_3\overset{O}{\overset{\|}{C}}H$


$CH_3\overset{Br}{\overset{|}{C}}H\overset{O}{\overset{\|}{C}}H$

systematic name: methanal — ethanal — 2-bromopropanal

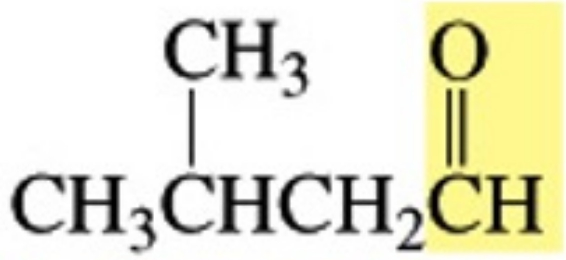
common name: formaldehyde — acetaldehyde — α-bromopropionaldehyde

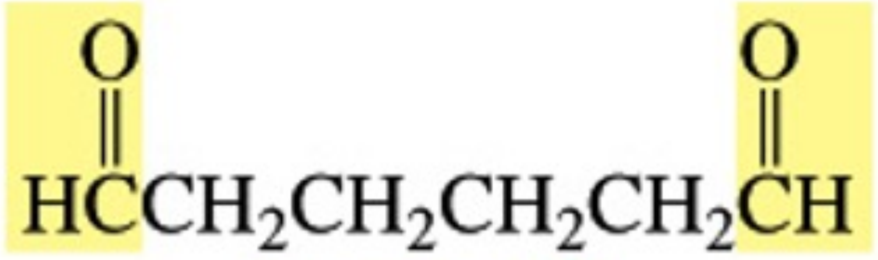


$R-CHO$

[R = R, Ar, H]


$CH_3\overset{Cl}{\overset{|}{C}}HCH_2\overset{O}{\overset{\|}{C}}H$

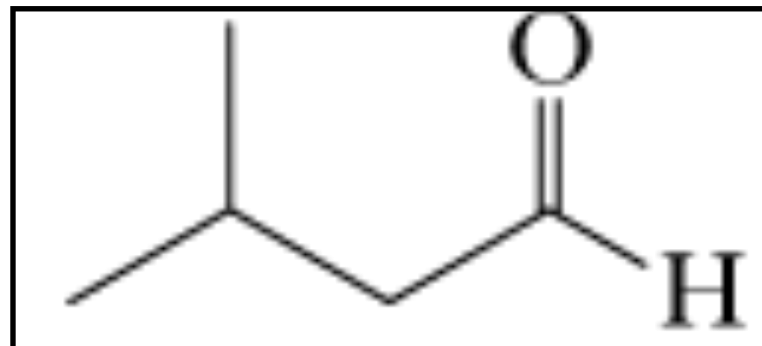

$CH_3\overset{CH_3}{\overset{|}{C}}HCH_2\overset{O}{\overset{\|}{C}}H$


$H\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}H$

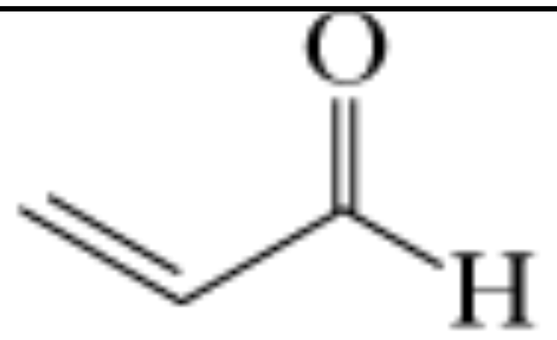
systematic name: 3-chlorobutanal — 3-methylbutanal — hexanedial

common name: β-chlorobutyraldehyde — isovaleraldehyde

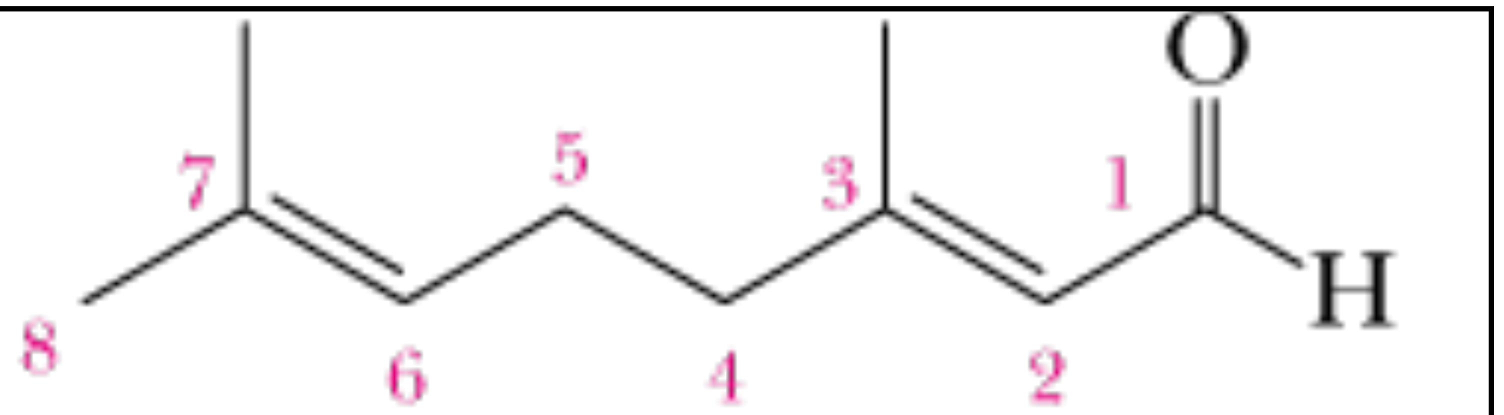
A. Nomenclatura IUPAC



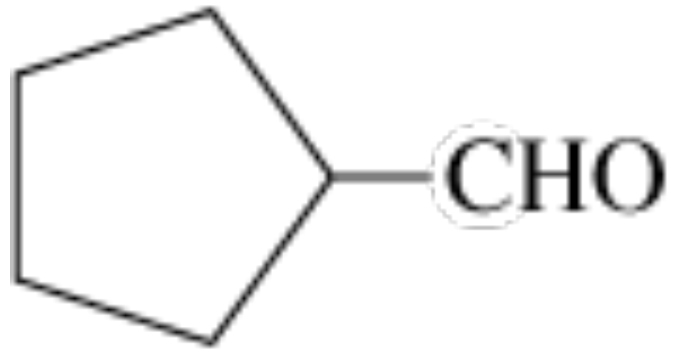
3-Metilbutanale



2-Propenale
(Acroleina)

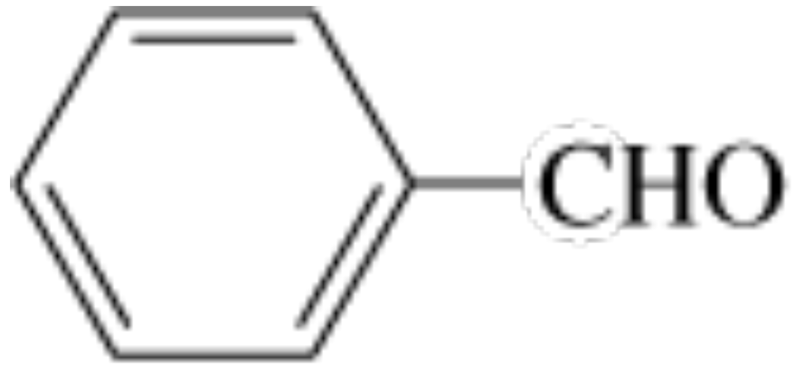


(2*E*)-3,7-Dimetil-2,6-ottadienale
(Geraniale)

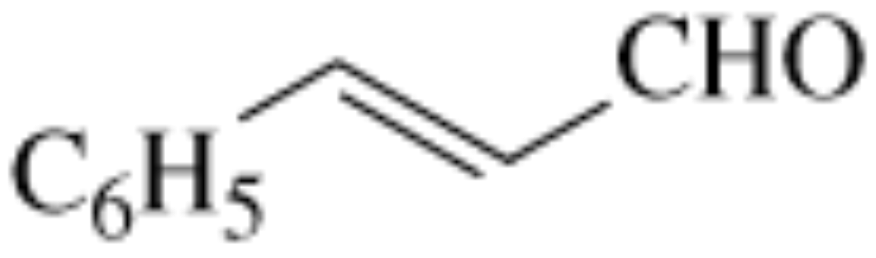


Ciclopentan-carbaldeide

***trans*-4-Idrossi-cicloesancarbaldeide**



Benzaldeide



***trans*-3-Fenil-2-propenale**
(Cinnamaldeide)

Nomenclatura: chetoni

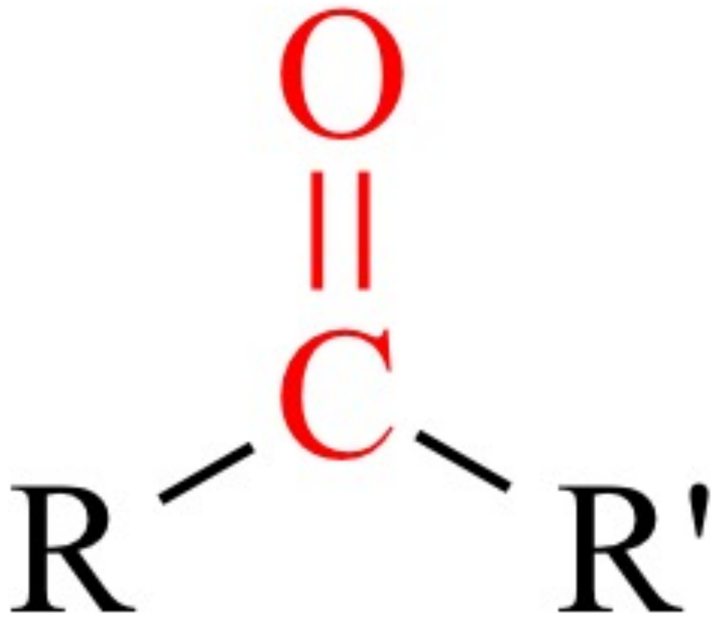
✓ IUPAC

- Catena principale: la più lunga che contiene il carbonile
- Il suffisso -o diventa -one
- La catena si nulera dalla estremità che porta ad attribuire il numero più piccolo al C(=O)

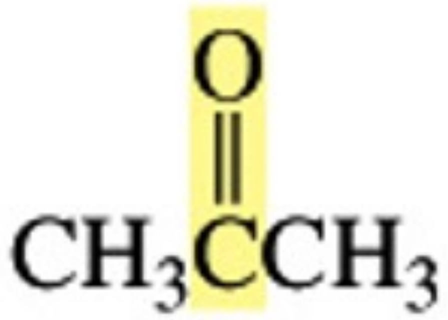
✓ Comune

- for a ketone, name the two alkyl or aryl groups bonded to the carbonyl carbon and add the word ketone

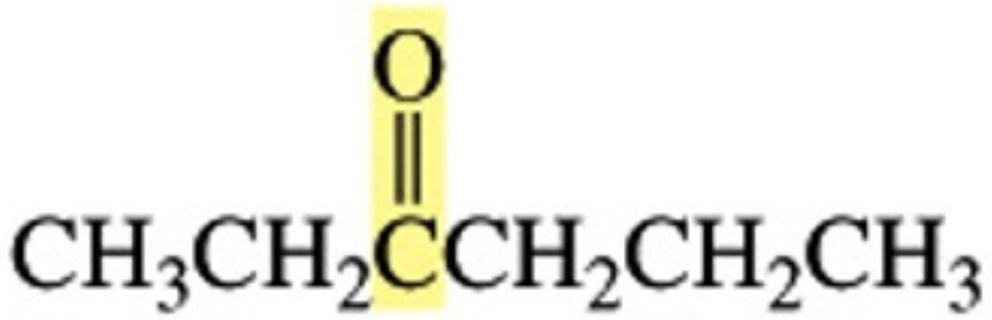
Nomenclatura: chetoni



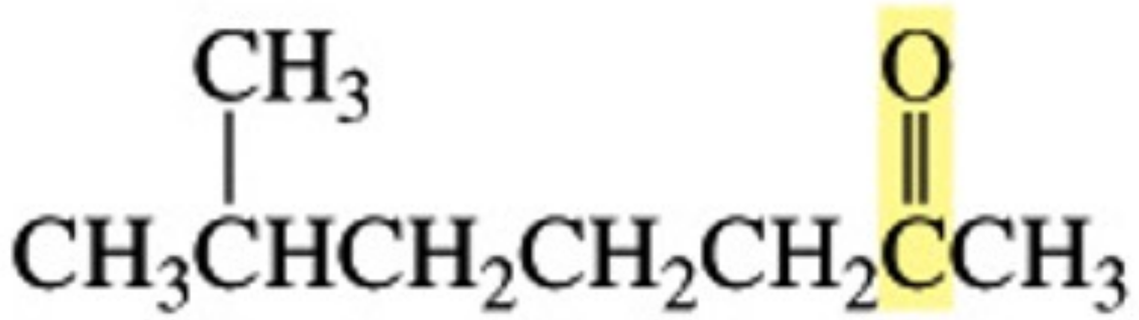
[R, R' = R, Ar]



$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_3$$

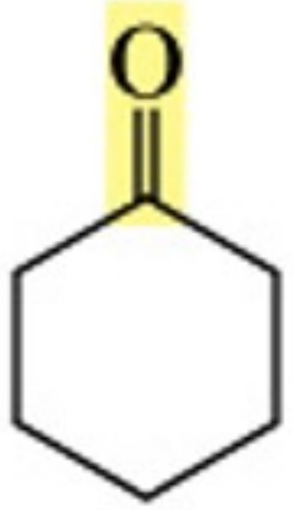


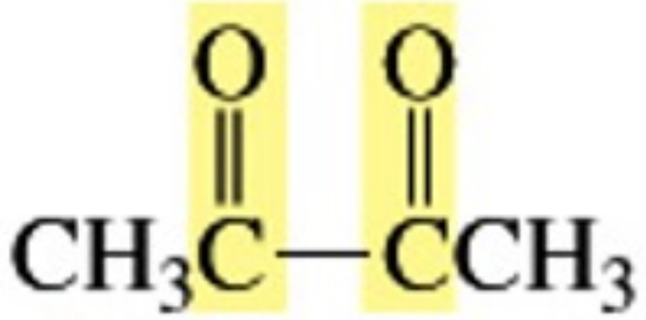
$$CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}CH_2CH_2CH_3$$



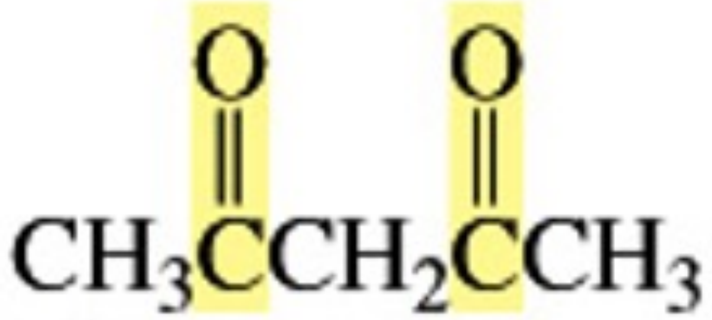
$$CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2CH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}CH_3$$

systematic name:	propanone	3-hexanone	6-methyl-2-heptanone
common name:	acetone		
derived name:	dimethyl ketone	ethyl propyl ketone	isohexyl methyl ketone

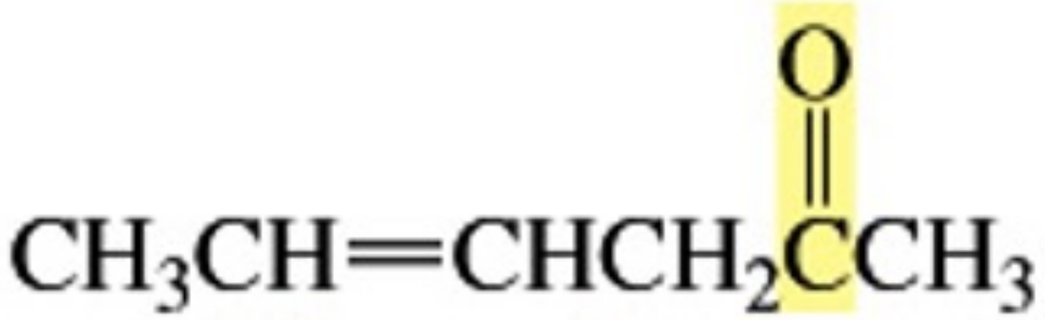




$CH_3\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}CH_3$

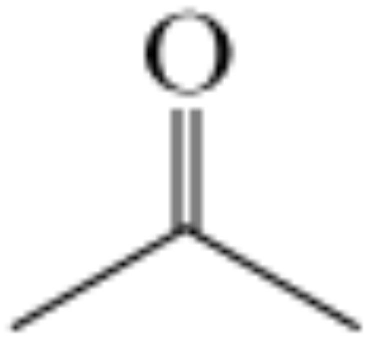


$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$

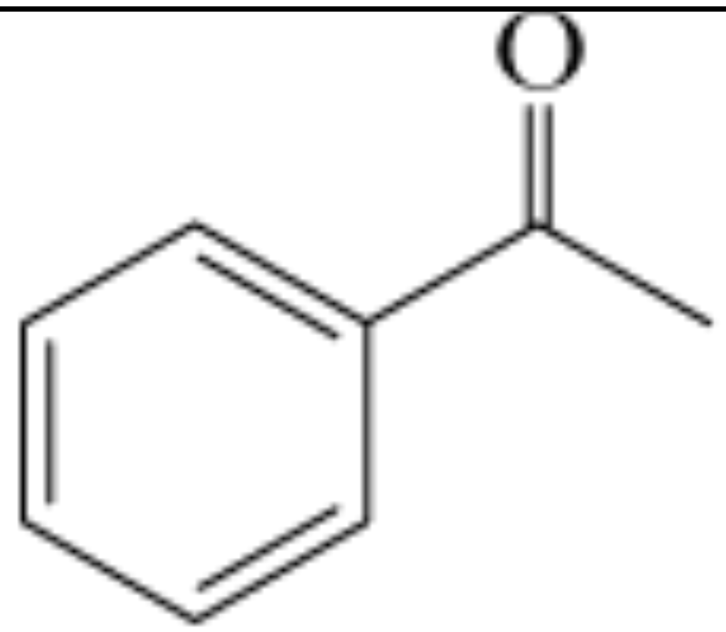


$CH_3CH{=}CHCH_2\overset{O}{\overset{\|}{C}}CH_3$

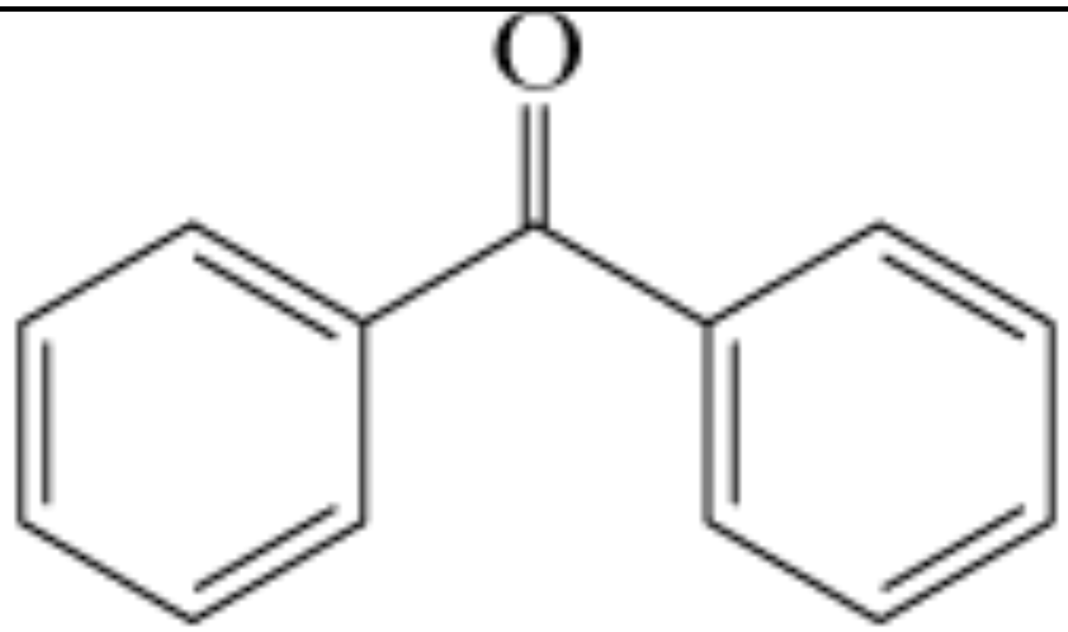
systematic name:	**cyclohexanone**	**butanedione**	**2,4-pentanedione**	**4-hexen-2-one**
common name:			**acetylacetone**	



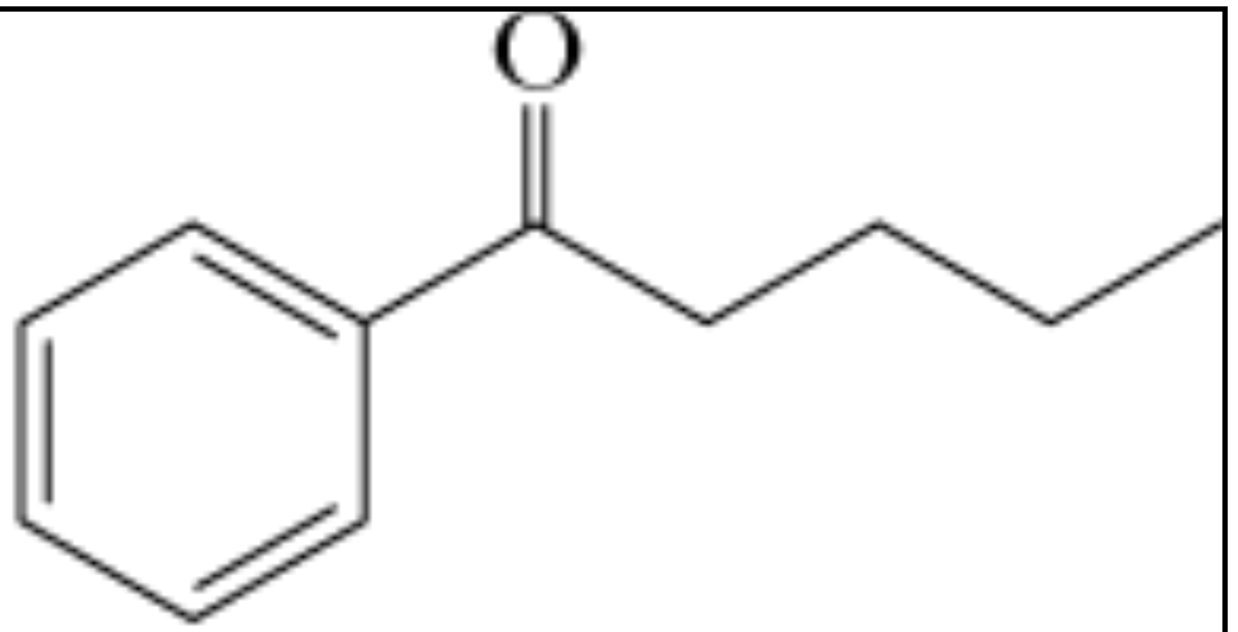
Propanone (Acetone)



Acetofenone



Benzofenone



1-Fenil-1-pentanone

Nella denominazione di composti che contengono più di un gruppo funzionale che può essere indicato da un suffisso, il sistema IUPAC ha stabilito un ordine di priorità dei gruppi funzionali. L'ordine di priorità dei gruppi funzionali che abbiamo studiato finora è riportato nella Tabella

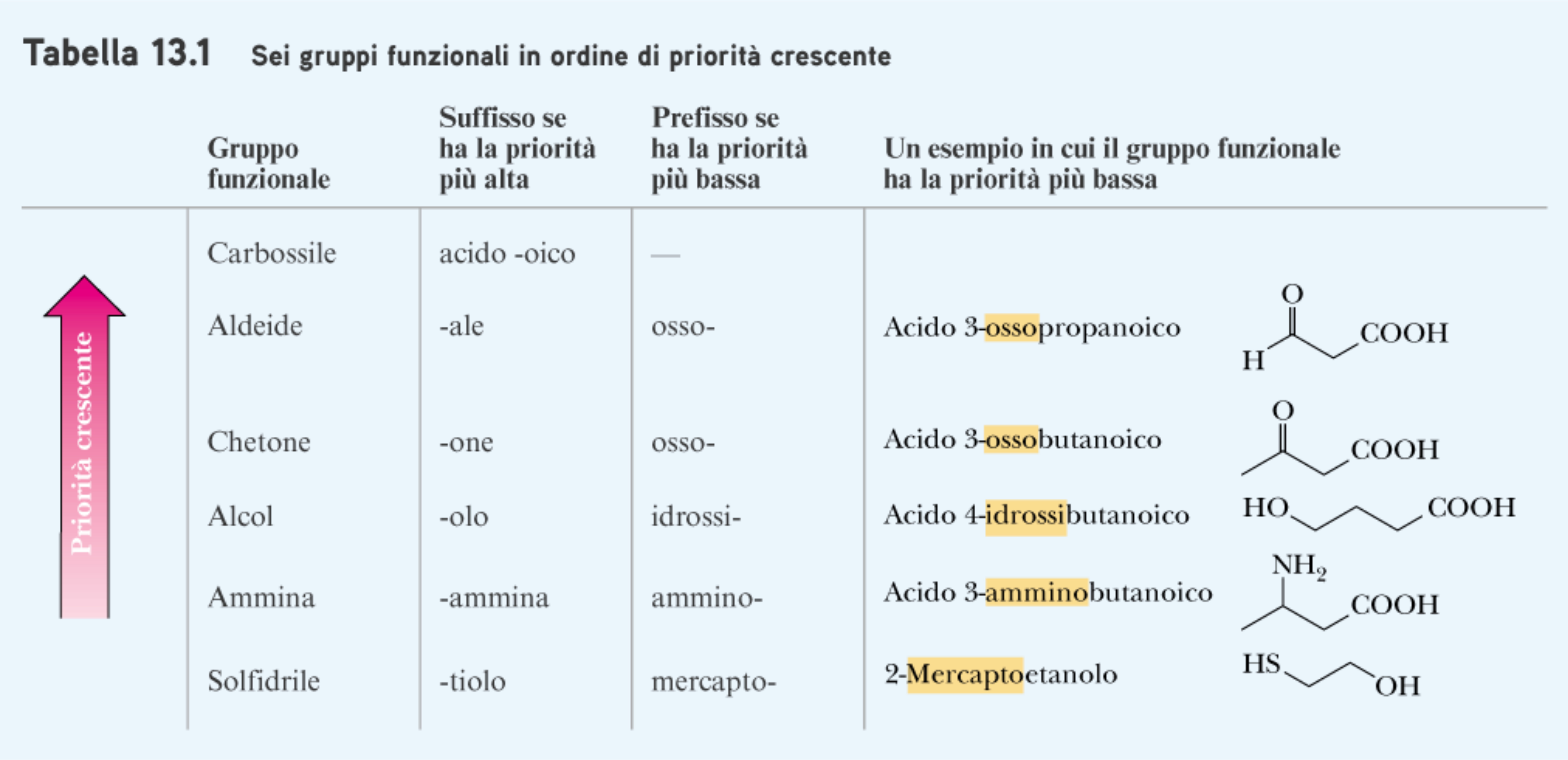


Tabella 13.1 Sei gruppi funzionali in ordine di priorità crescente

Gruppo funzionale	Suffisso se ha la priorità più alta	Prefisso se ha la priorità più bassa	Un esempio in cui il gruppo funzionale ha la priorità più bassa
Carbossile	acido -oico	—	
Aldeide	-ale	osso-	Acido 3-ossopropanoico
Chetone	-one	osso-	Acido 3-ossobutanoico
Alcol	-olo	idrossi-	Acido 4-idrossibutanoico
Ammina	-ammina	ammino-	Acido 3-amminobutanoico
Solfidrile	-tiolo	mercapto-	2-Mercaptoetanolo

PRIORIDADE CRESCENTE

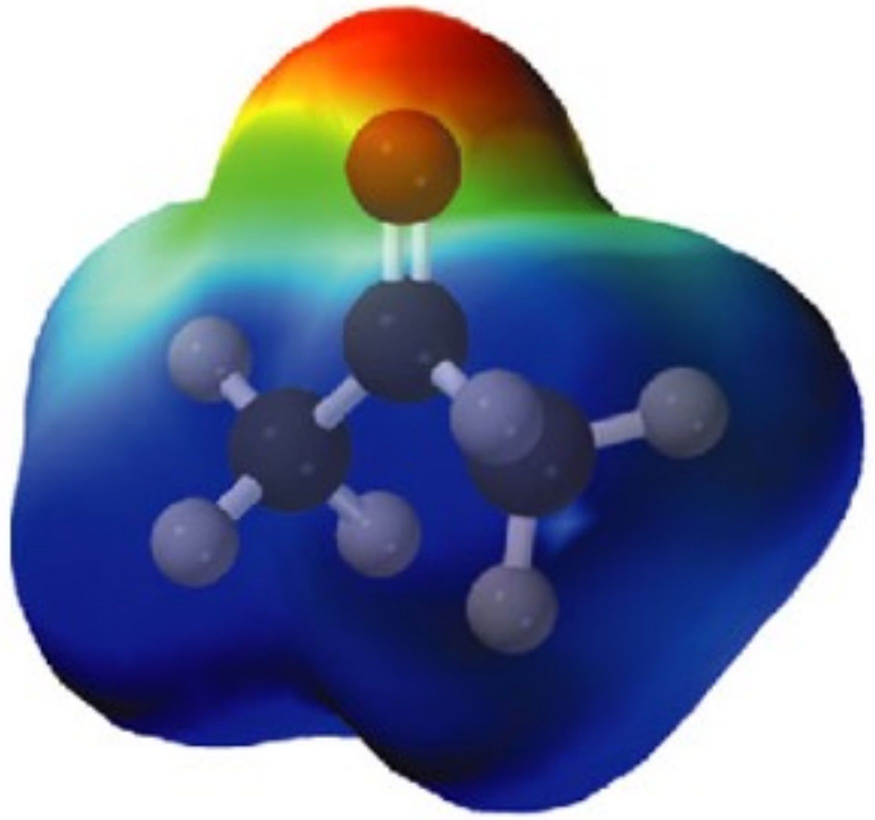
Função	Sufixo	Prefixo (no caso da função não ser considerada a principal)
Ácido carboxílico	oico	-
Aldeído	al	oxo ou formil
Cetona	ona	oxo
Álcool	ol	hidróxi
Amina	amina	amino
Haleto orgânico	-	nome do elemento

Proprietà fisiche

- ✓ L'ossigeno è più elettronegativo del carbonio (3.5 vs 2.5) e pertanto il gruppo C=O è polare (e polarizzabile)

Polarity of a carbonyl group

More important contributing structure



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- ✓ interazioni dipolo-dipolo:
  - they have higher boiling points and are more soluble in water than nonpolar compounds of comparable molecular weight

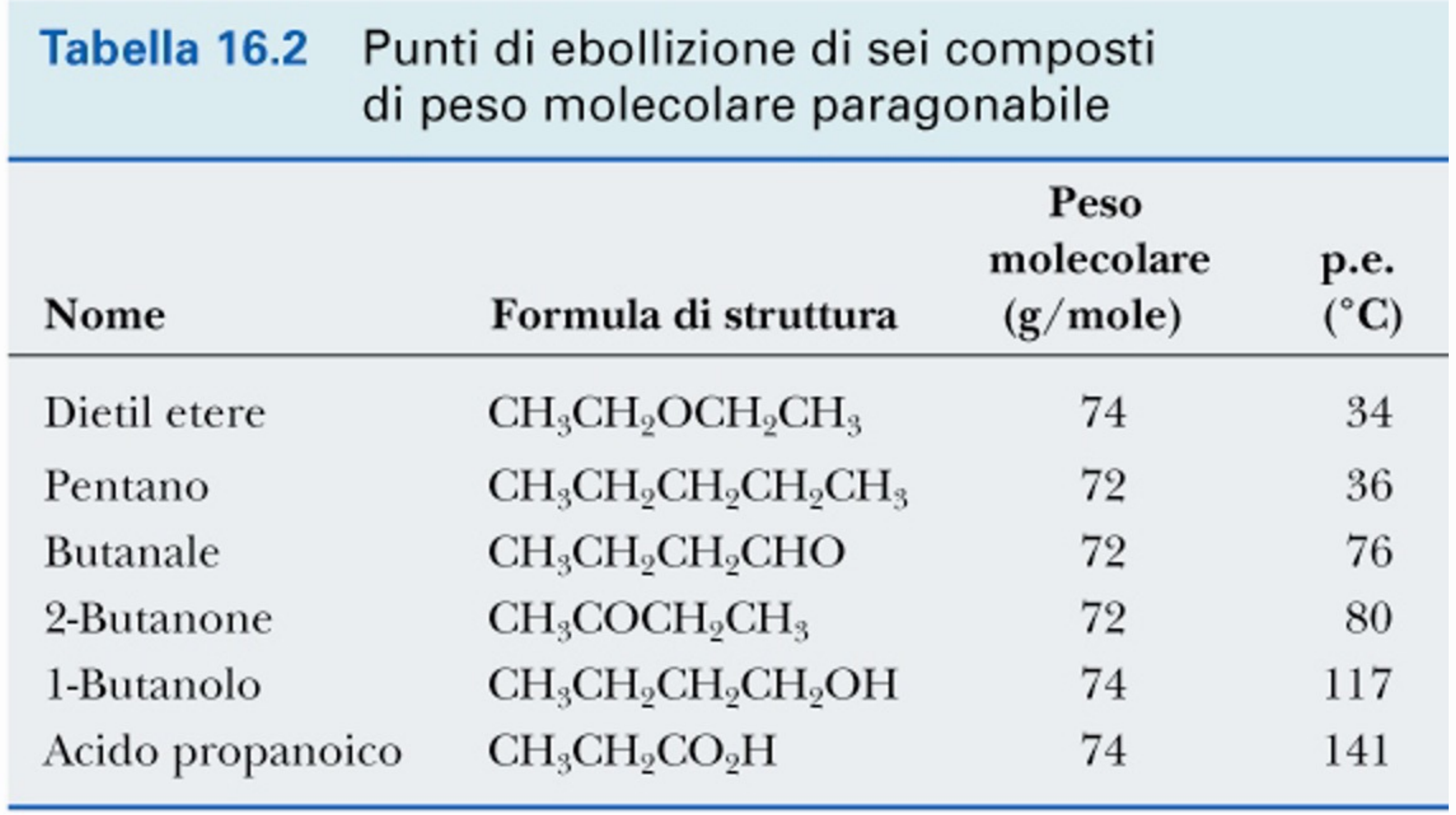


Tabella 16.2 Punti di ebollizione di sei composti di peso molecolare paragonabile

Nome	Formula di struttura	Peso molecolare (g/mole)	p.e. (°C)
Dietil etere	$CH_3CH_2OCH_2CH_3$	74	34
Pentano	$CH_3CH_2CH_2CH_2CH_3$	72	36
Butanale	$CH_3CH_2CH_2CHO$	72	76
2-Butanone	$CH_3COCH_2CH_3$	72	80
1-Butanolo	$CH_3CH_2CH_2CH_2OH$	74	117
Acido propanoico	$CH_3CH_2CO_2H$	74	141

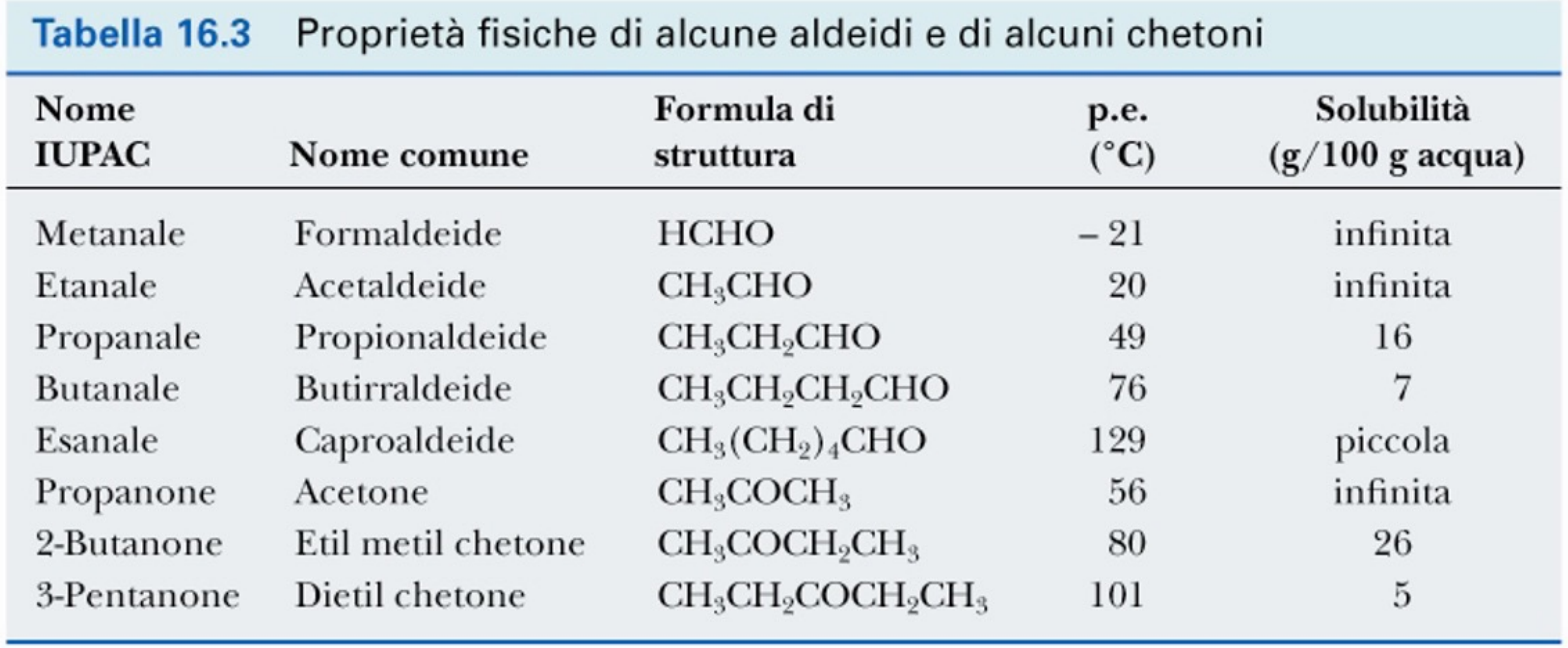
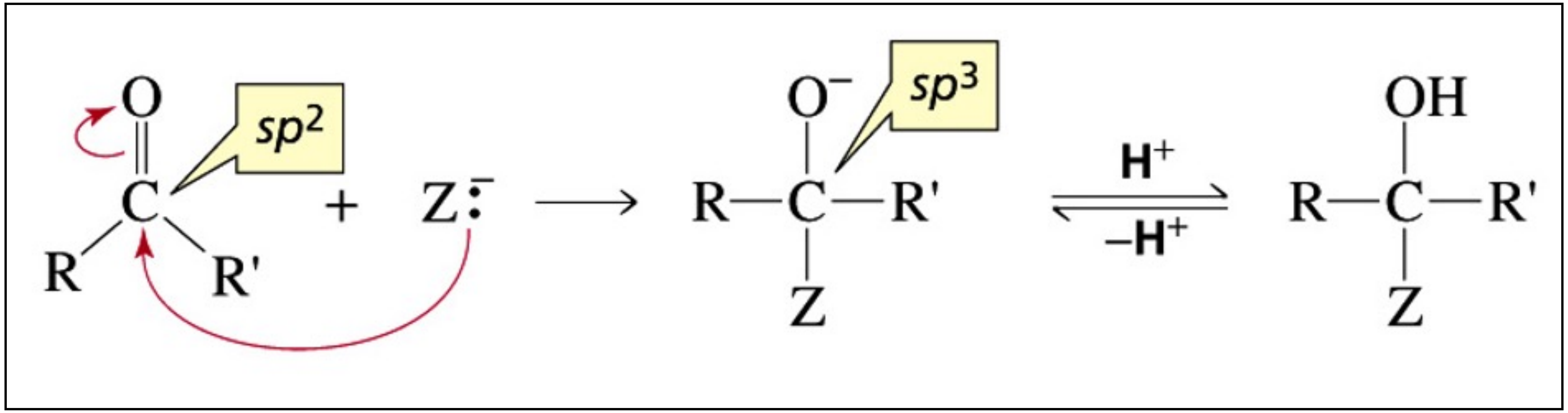


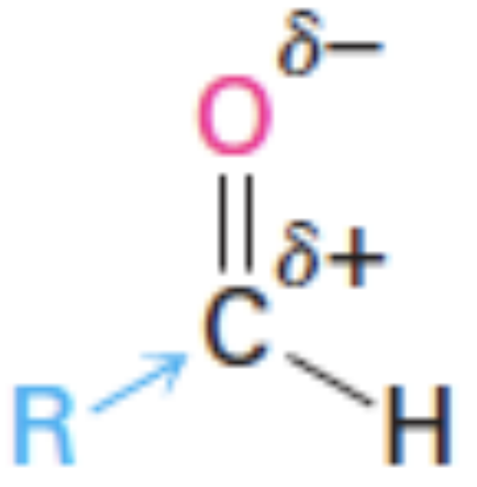
Tabella 16.3 Proprietà fisiche di alcune aldeidi e di alcuni chetoni

Nome IUPAC	Nome comune	Formula di struttura	p.e. (°C)	Solubilità (g/100 g acqua)
Metanale	Formaldeide	HCHO	– 21	infinita
Etanale	Acetaldeide	CH_3CHO	20	infinita
Propanale	Propionaldeide	CH_3CH_2CHO	49	16
Butanale	Butirraldeide	$CH_3CH_2CH_2CHO$	76	7
Esanale	Caproaldeide	$CH_3(CH_2)_4CHO$	129	piccola
Propanone	Acetone	CH_3COCH_3	56	infinita
2-Butanone	Etil metil chetone	$CH_3COCH_2CH_3$	80	26
3-Pentanone	Dietil chetone	$CH_3CH_2COCH_2CH_3$	101	5

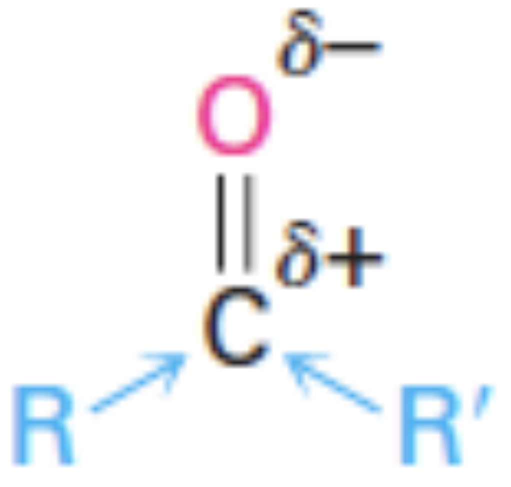
Reattività: ADDIZIONI NUCLEOFILE ACILICHE

Addizione nucleofila al gruppo carbonile: addizione al doppio legame C=O



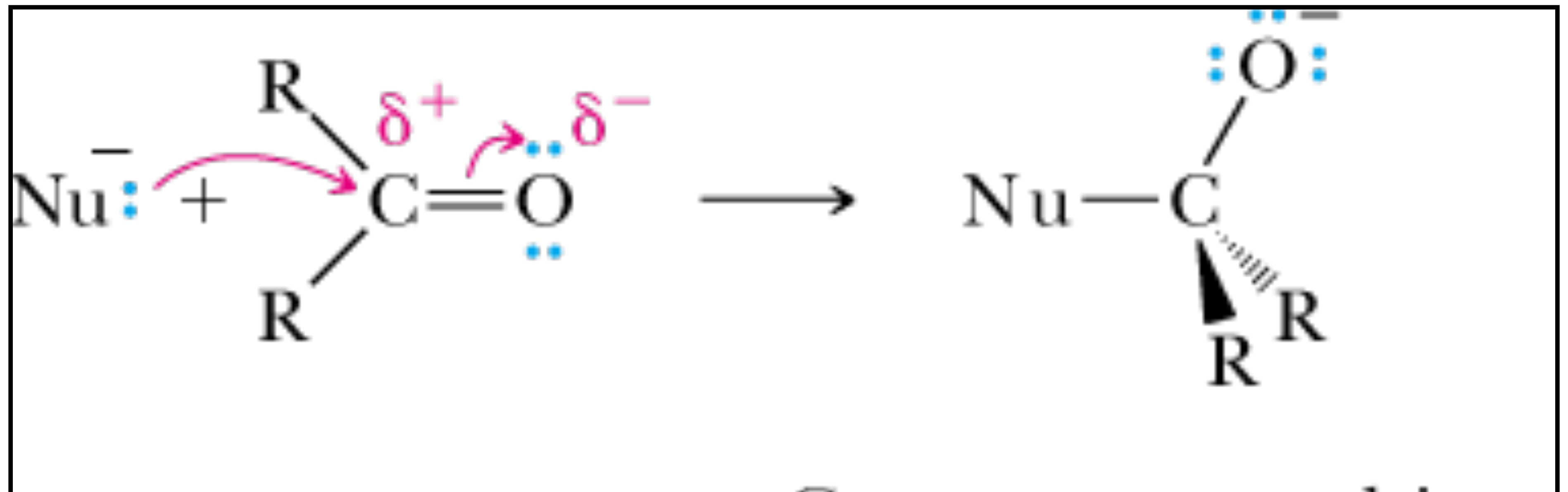


Aldehyde
(less stabilization of δ+, more reactive)

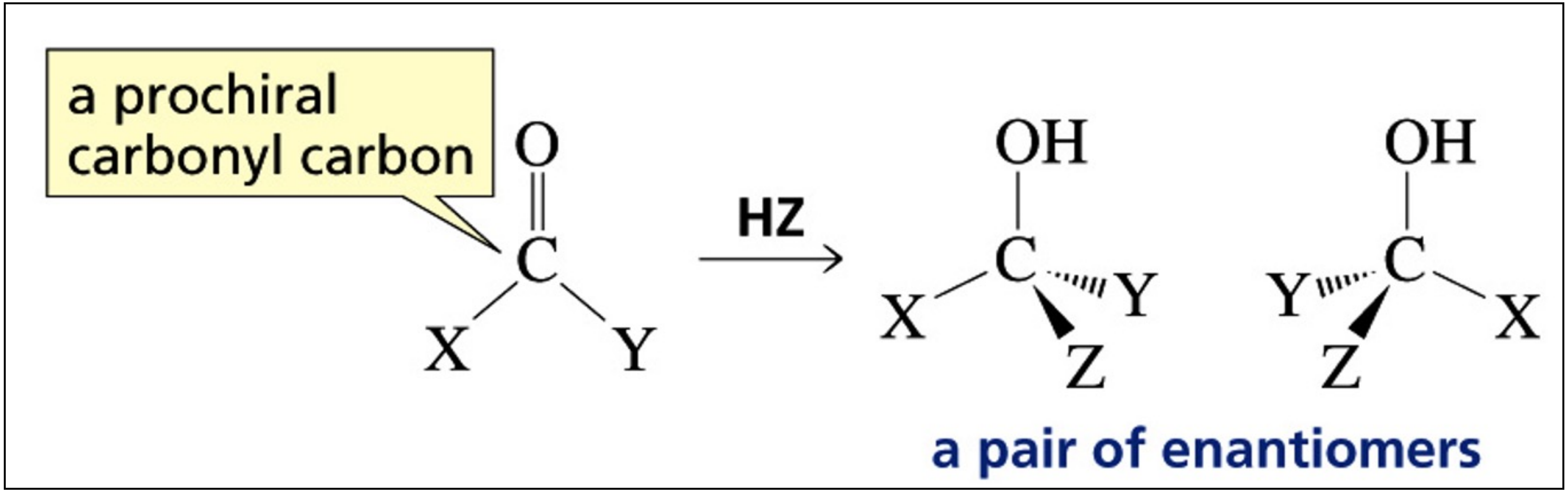


Ketone
(more stabilization of δ+, less reactive)

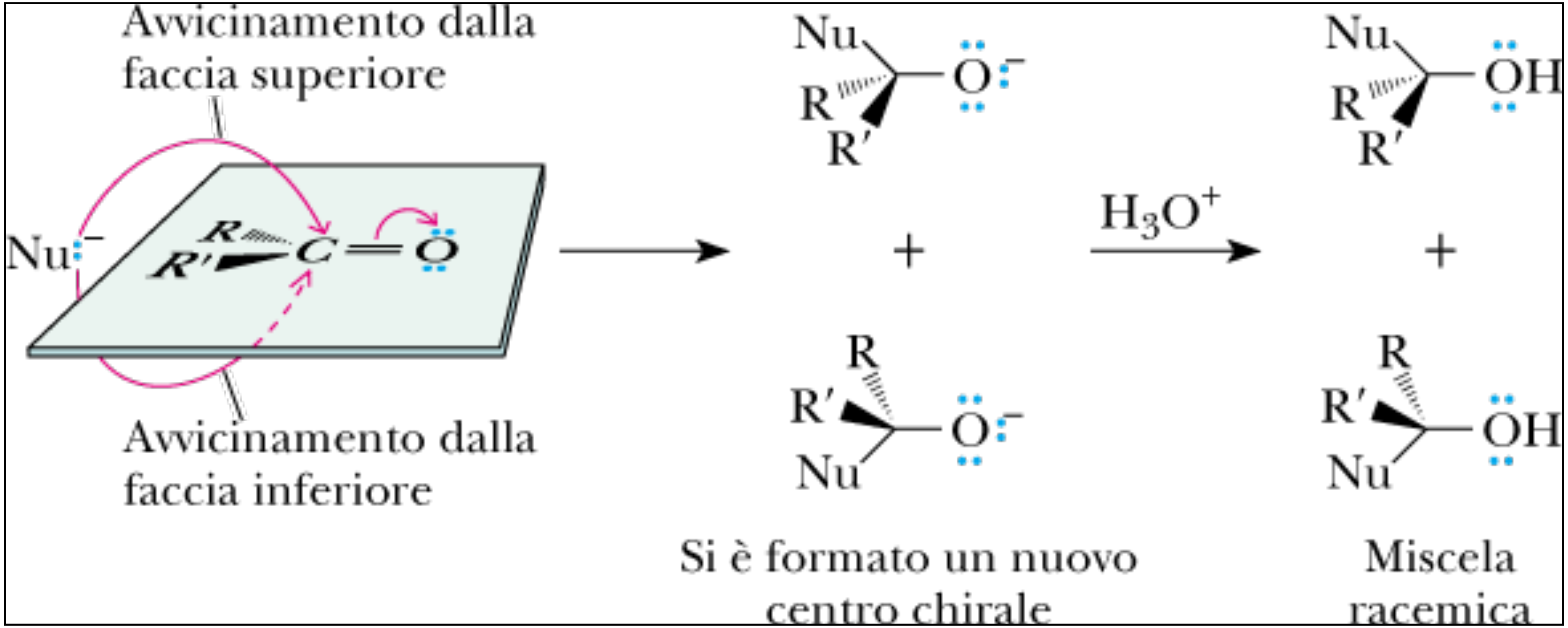
STEREOCHIMICA DELL'ADDIZIONE NUCLEOFILA



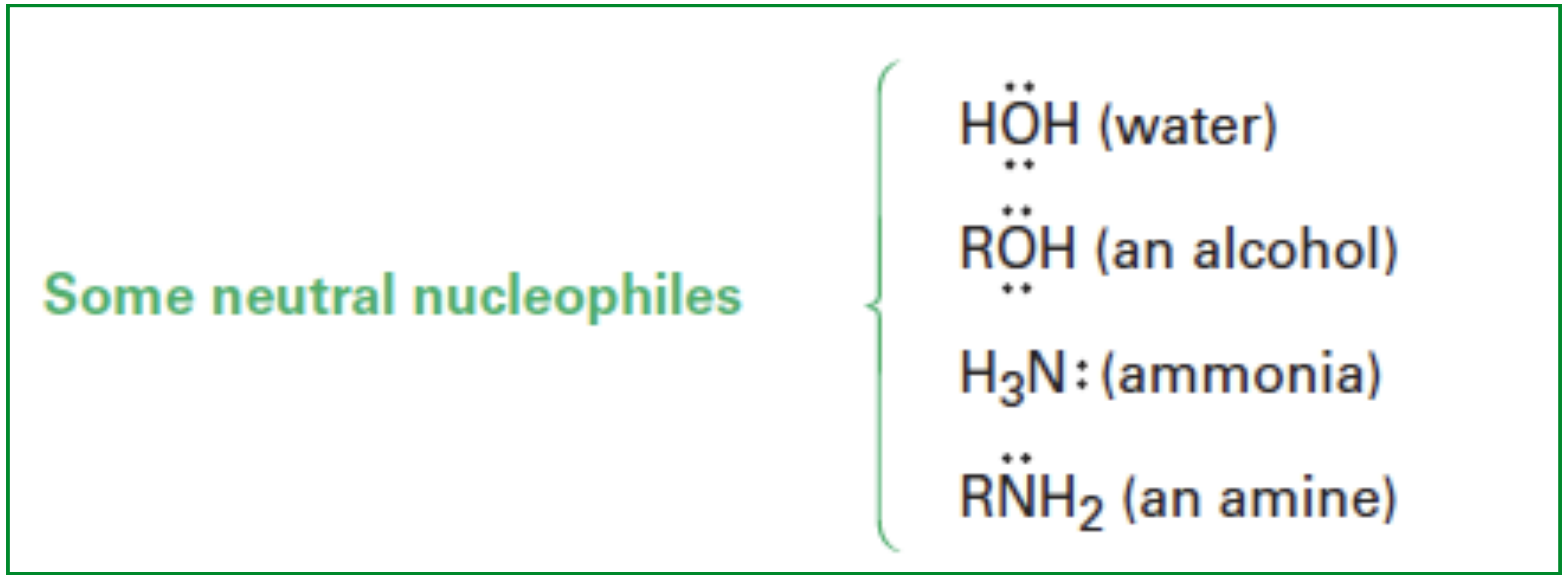
Composto tetraedrico
di addizione al carbonile



STEREOCHIMICA DELL'ADDIZIONE NUCLEOFILA

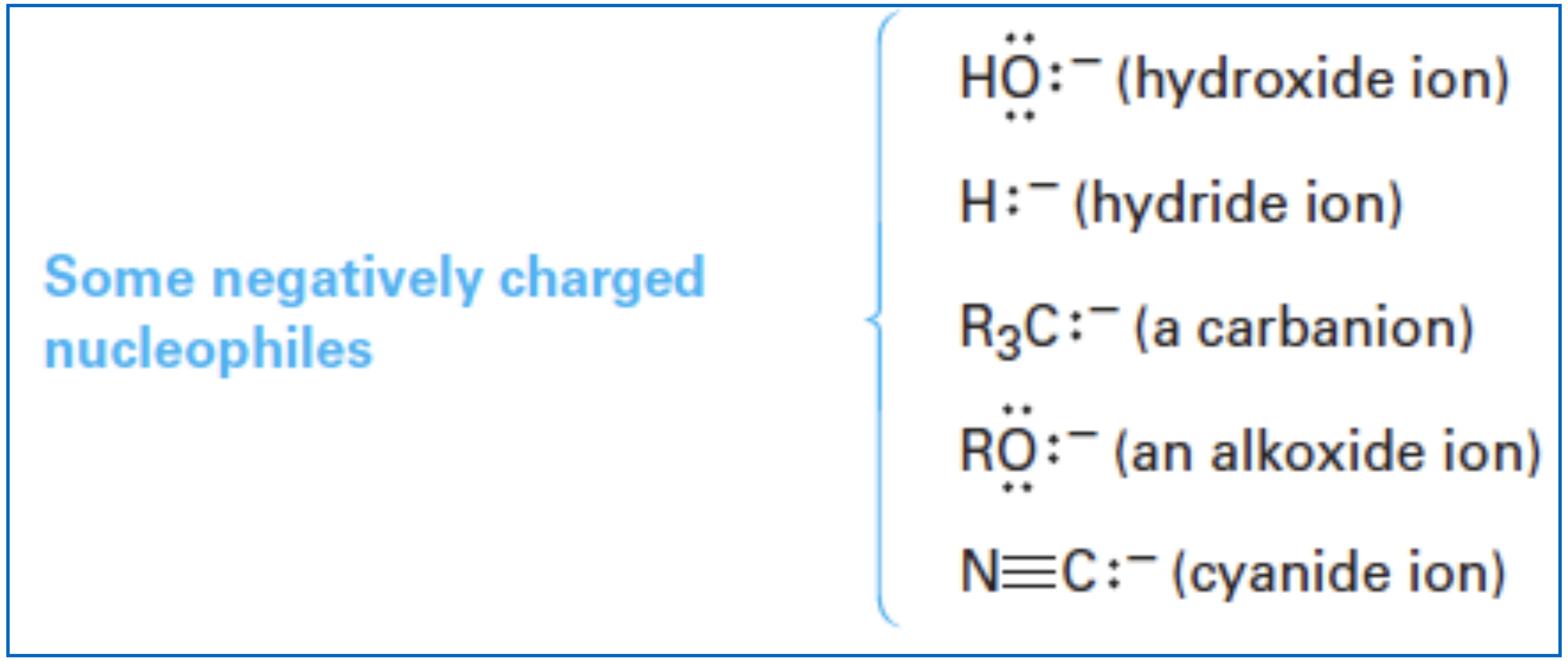


Addizione nucleofila al gruppo carbonile di Aldeidi e Chetoni



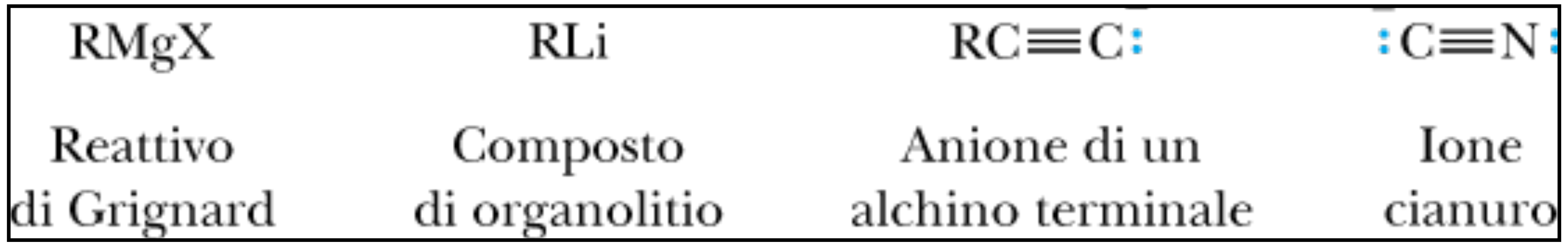
Some neutral nucleophiles

- $\mathrm{H\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}H}$ (water)
- $\mathrm{R\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}H}$ (an alcohol)
- $\mathrm{H_3N{:}}$ (ammonia)
- $\mathrm{R\overset{\cdot\cdot}{N}H_2}$ (an amine)



Some negatively charged nucleophiles

- $\mathrm{H\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}{:}^-}$ (hydroxide ion)
- $\mathrm{H{:}^-}$ (hydride ion)
- $\mathrm{R_3C{:}^-}$ (a carbanion)
- $\mathrm{R\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}{:}^-}$ (an alkoxide ion)
- $\mathrm{N{\equiv}C{:}^-}$ (cyanide ion)



RMgX	RLi	$\mathrm{RC{\equiv}C{:}^-}$	$\mathrm{^-{:}C{\equiv}N{:}}$
Reattivo di Grignard	Composto di organolitio	Anione di un alchino terminale	Ione cianuro

Addizione nucleofila al gruppo carbonile di Aldeidi e Chetoni

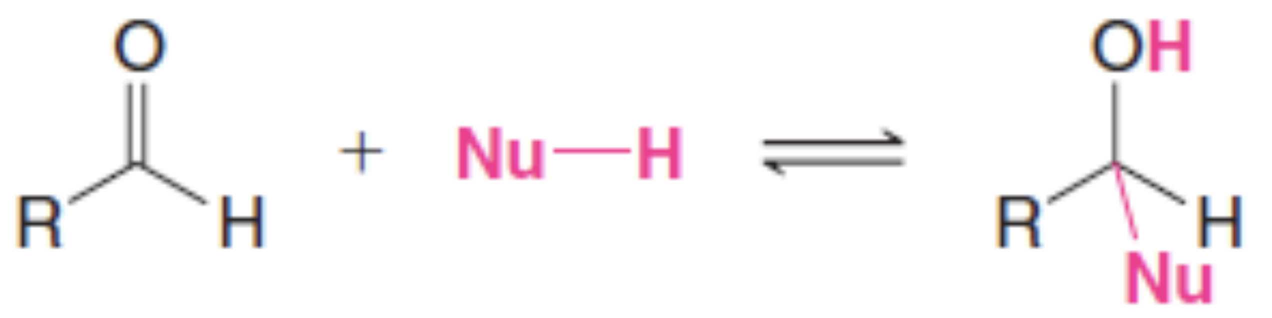
Some neutral nucleophiles

- $H\ddot{O}H$ (water)
- $R\ddot{O}H$ (an alcohol)
- $H_3N:$ (ammonia)
- $R\ddot{N}H_2$ (an amine)

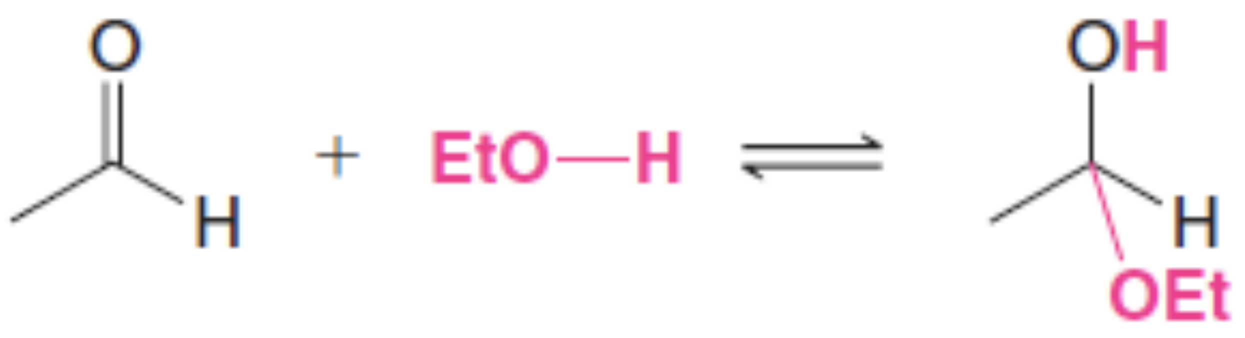
Some negatively charged nucleophiles

- $H\ddot{O}:^-$ (hydroxide ion)
- $H:^-$ (hydride ion)
- $R_3C:^-$ (a carbanion)
- $R\ddot{O}:^-$ (an alkoxide ion)
- $N{\equiv}C:^-$ (cyanide ion)

General Reaction

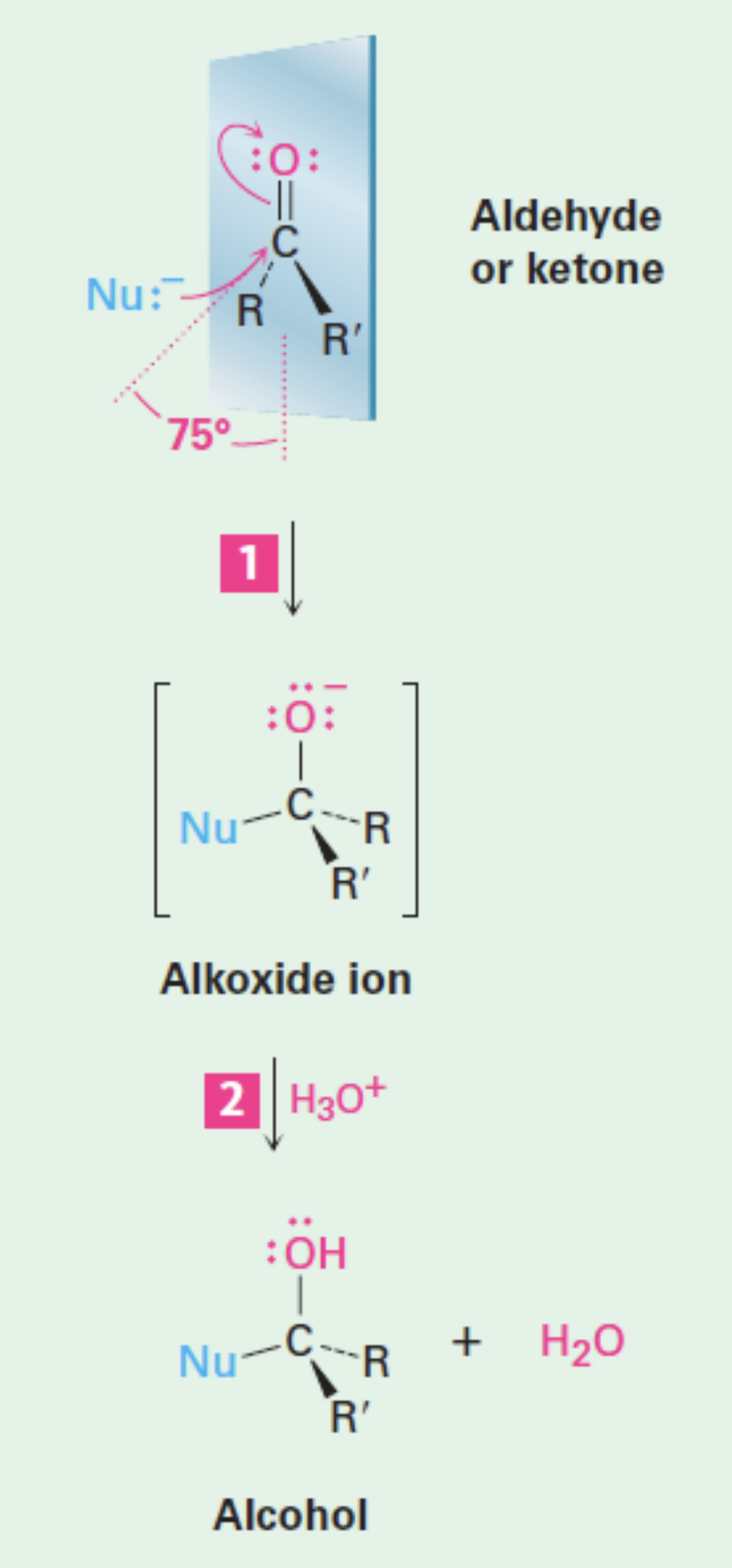


Specific Examples



A hemiacetal
(see Section 16.7)

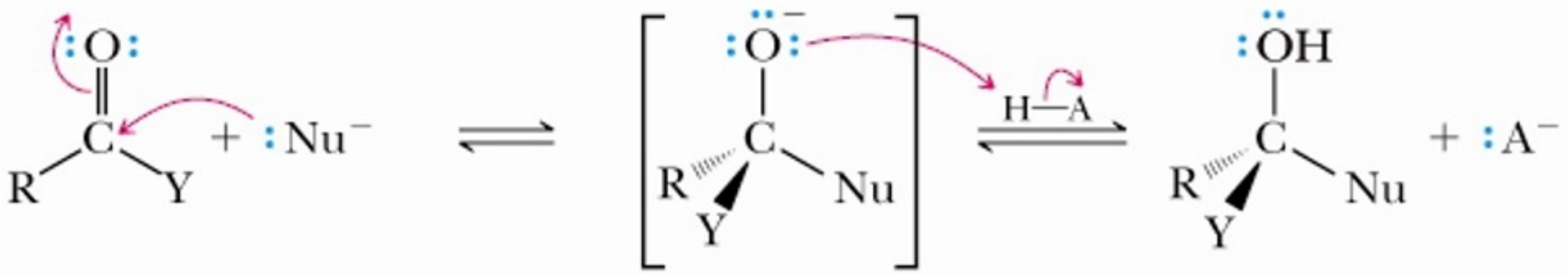
A cyanohydrin
(see Section 16.9)



Reattività:

Addizione nucleofila al gruppo carbonile: base catalizzata e acido catalizzata

Addizione nucleofila (condizioni basiche):

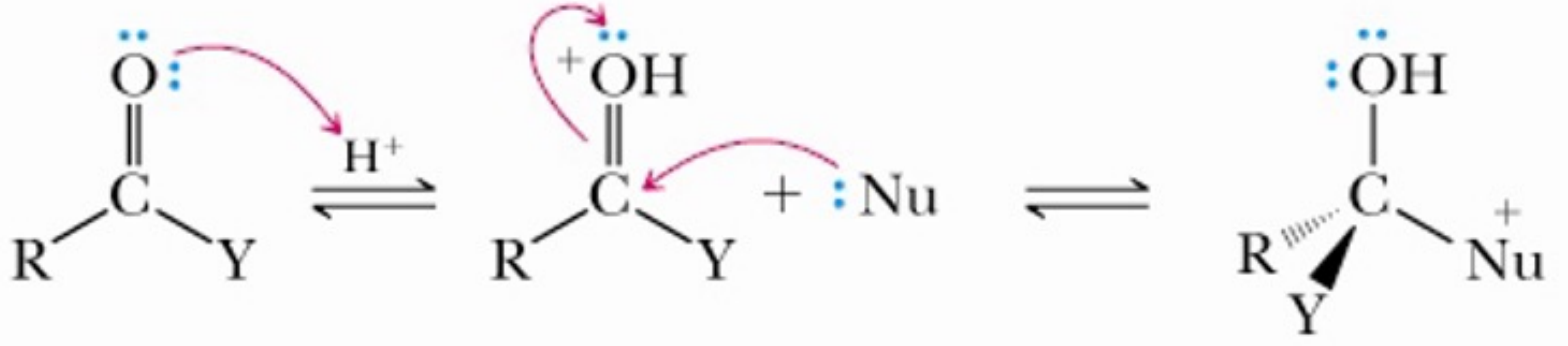


Un derivato di un acido carbossilico

Intermedio tetraedrico di addizione al carbonile

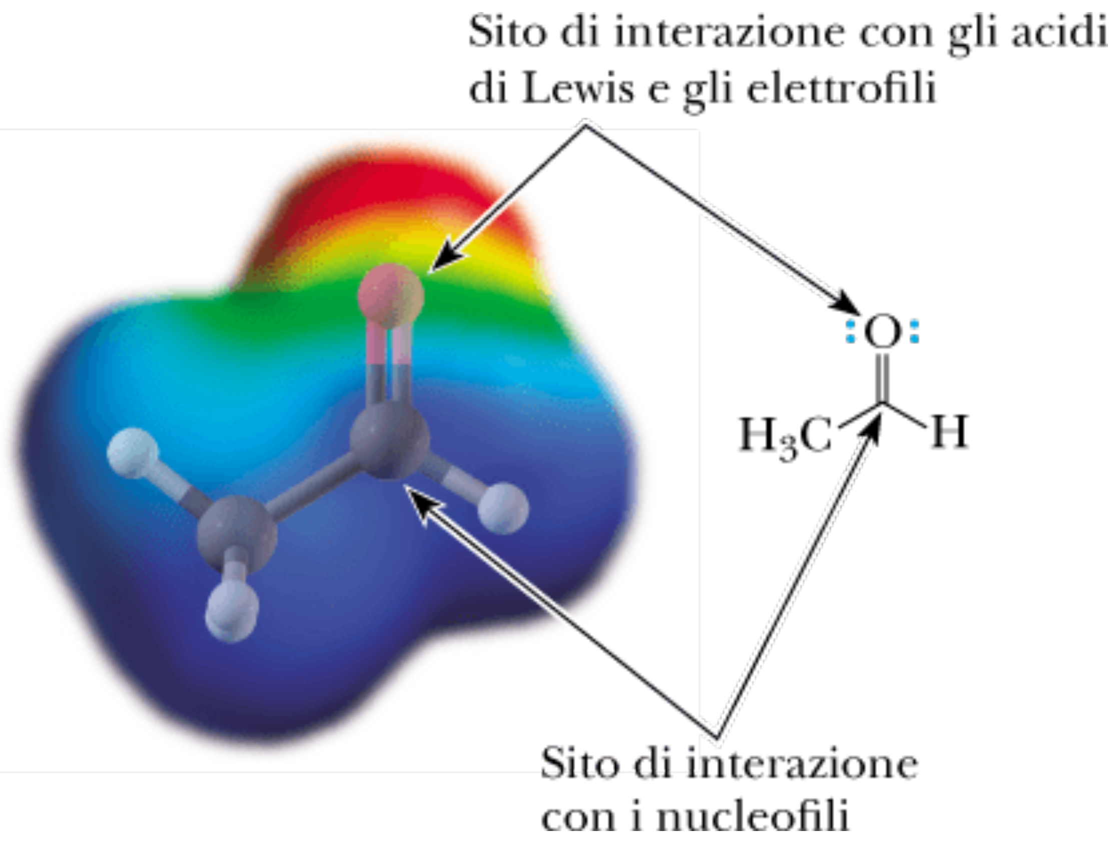
Prodotto di addizione

Addizione nucleofila (condizioni acide):

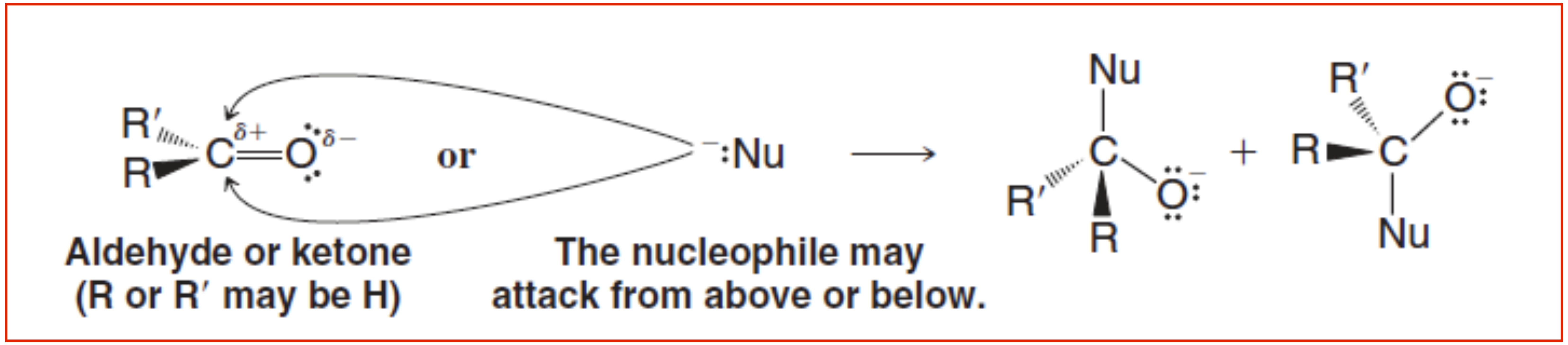


Un derivato di un acido carbossilico

Intermedio tetraedrico di addizione al carbonile

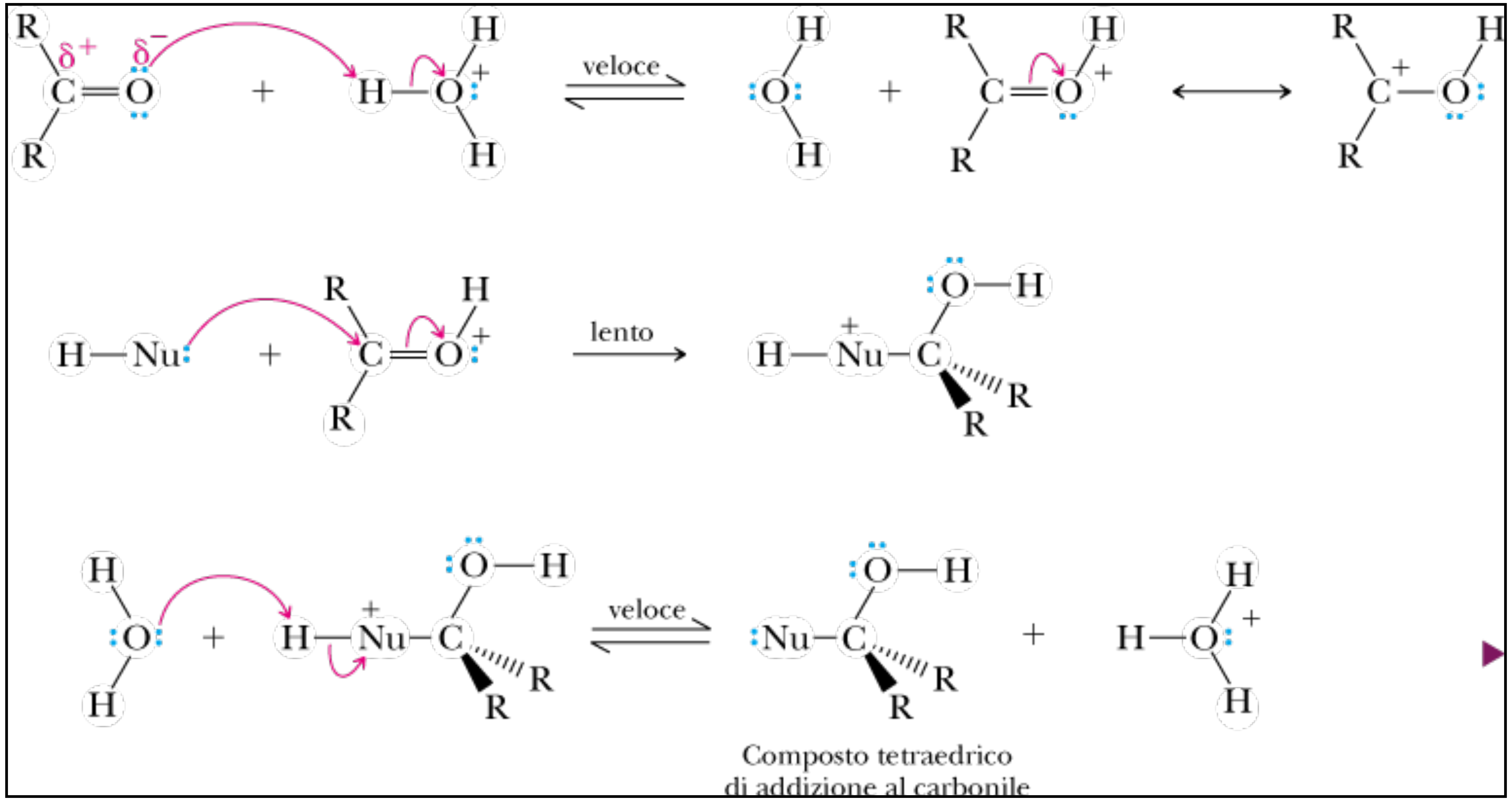


STEREOCHIMICA DELL'ADDIZIONE NUCLEOFILA



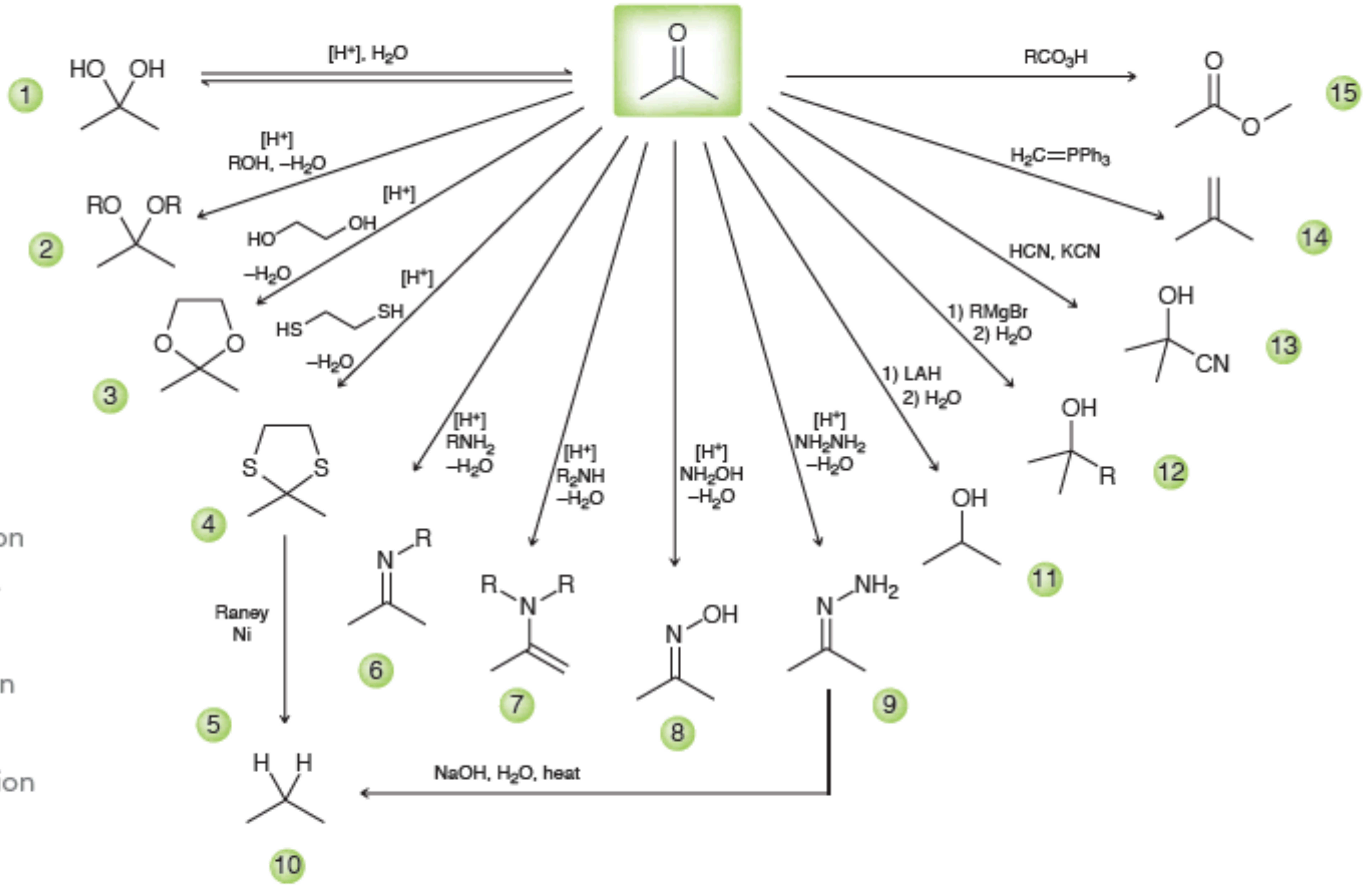
Aldehyde or ketone
(R or R′ may be H)

The nucleophile may
attack from above or below.

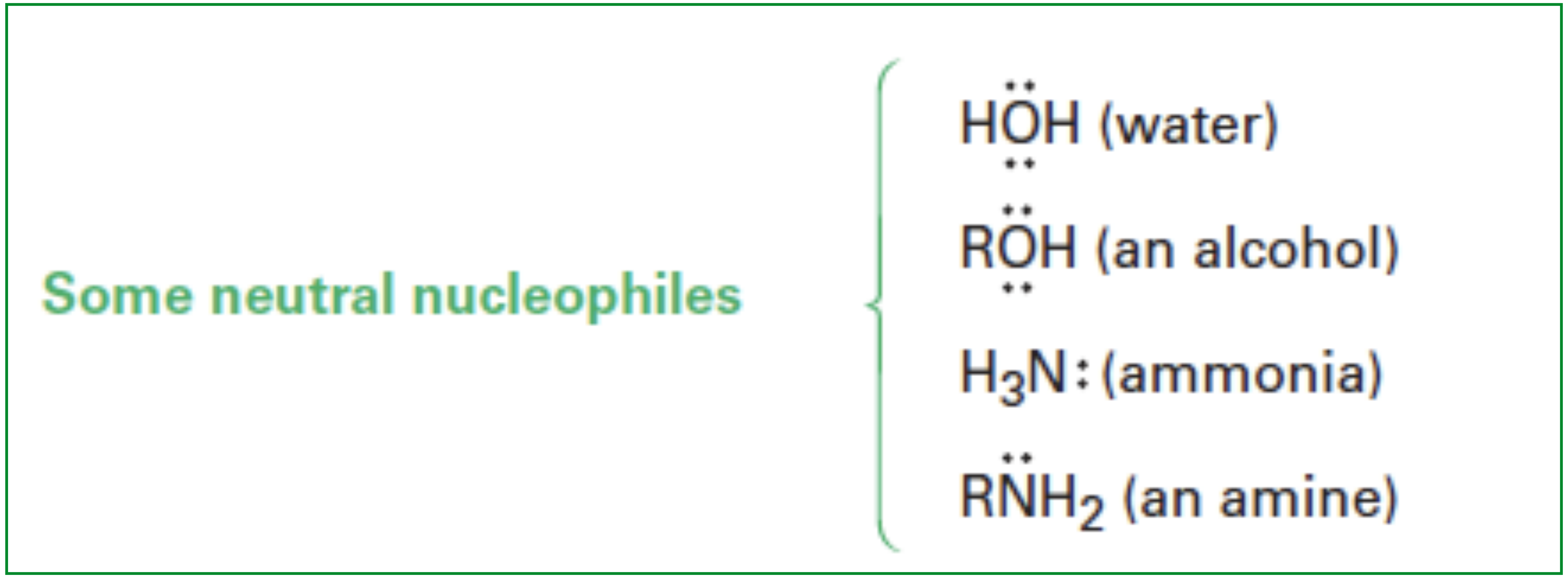


Composto tetraedrico
di addizione al carbonile

1. Hydrate Formation
2. Acetal Formation
3. Cyclic Acetal Formation
4. Cyclic Thioacetal Formation
5. Desulfurization
6. Imine Formation
7. Enamine Formation
8. Oxime Formation
9. Hydrazone Formation
10. Wolff-Kishner Reduction
11. Reduction of a Ketone
12. Grignard Reaction
13. Cyanohydrin Formation
14. Wittig Reaction
15. Baeyer-Villiger Oxidation



Reazioni di addizione nucleofila al gruppo carbonile
Con un nucleofilo debole (neutro)



Some neutral nucleophiles

$H\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}H$ (water)

$R\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}H$ (an alcohol)

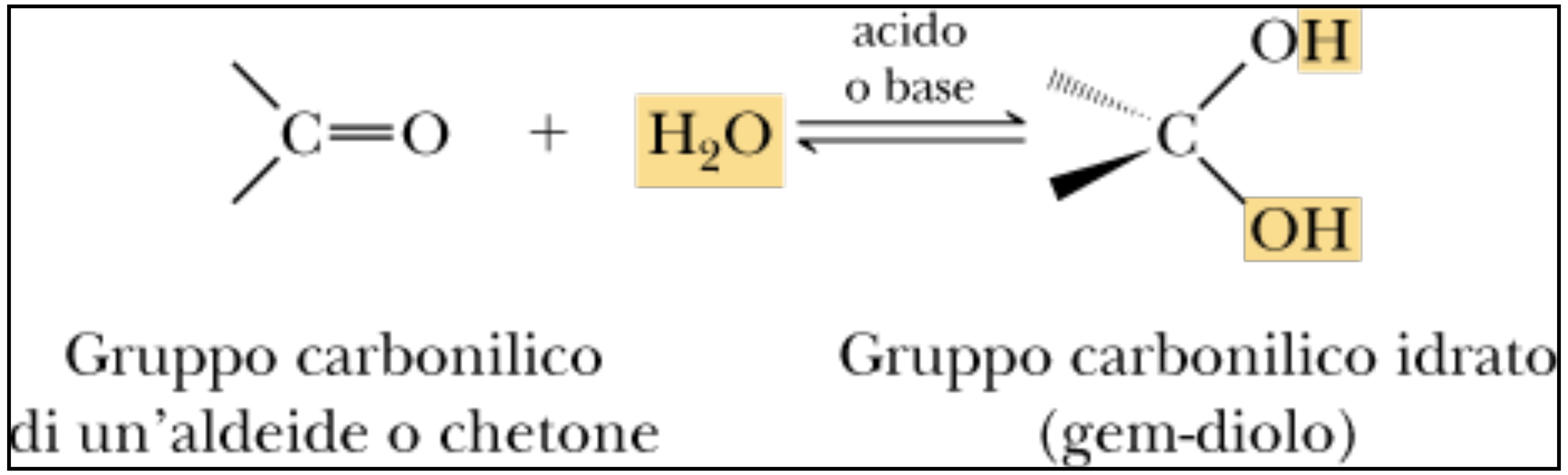
$H_3N\!:$ (ammonia)

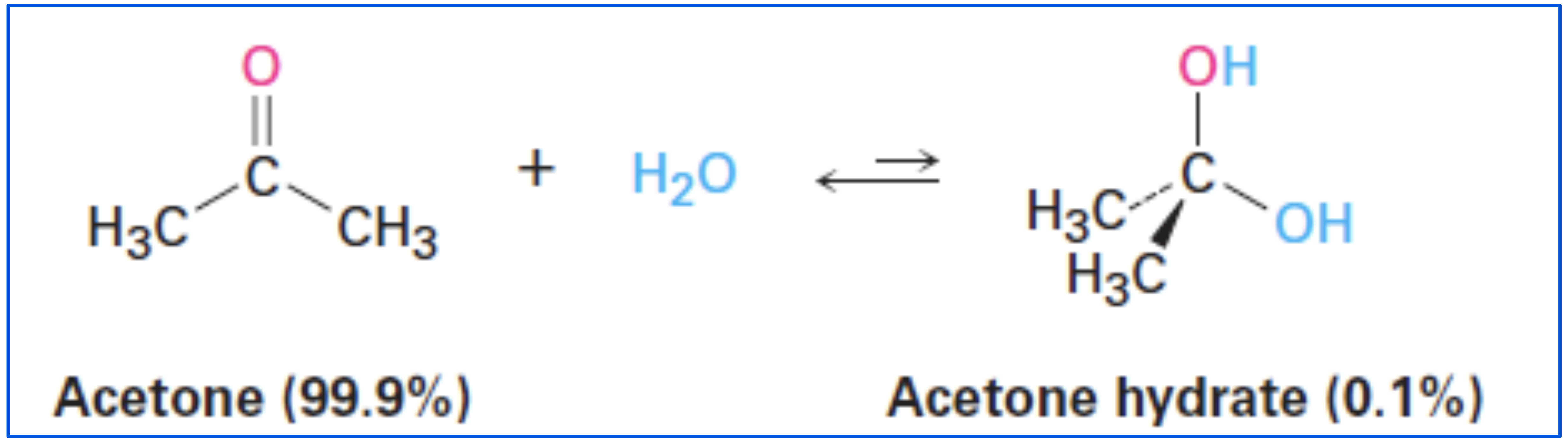
$R\overset{\cdot\cdot}{N}H_2$ (an amine)

1) Aggiunta di acqua (idratazione): Di-ol geminale
2) Aggiunta di alcoli: emiacetali e acetali
3) Aggiunta di ammine: immine ed enamine

(1) ADDIZIONE di H_2O: idratazione , Formazione di Carbonili idrati

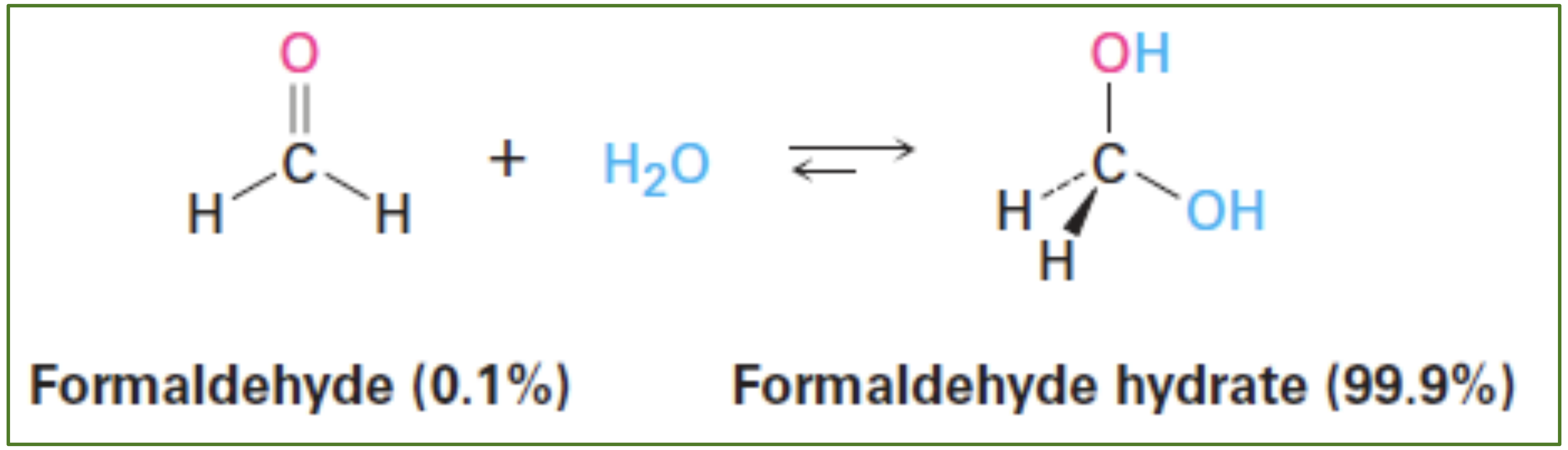
Idrati di aldeidi 1,1-dioli (gem-Dios) derivanti da un'aggiunta nucleofila di acqua al gruppo carbonile dell'aldeide





Acetone (99.9%)

Acetone hydrate (0.1%)

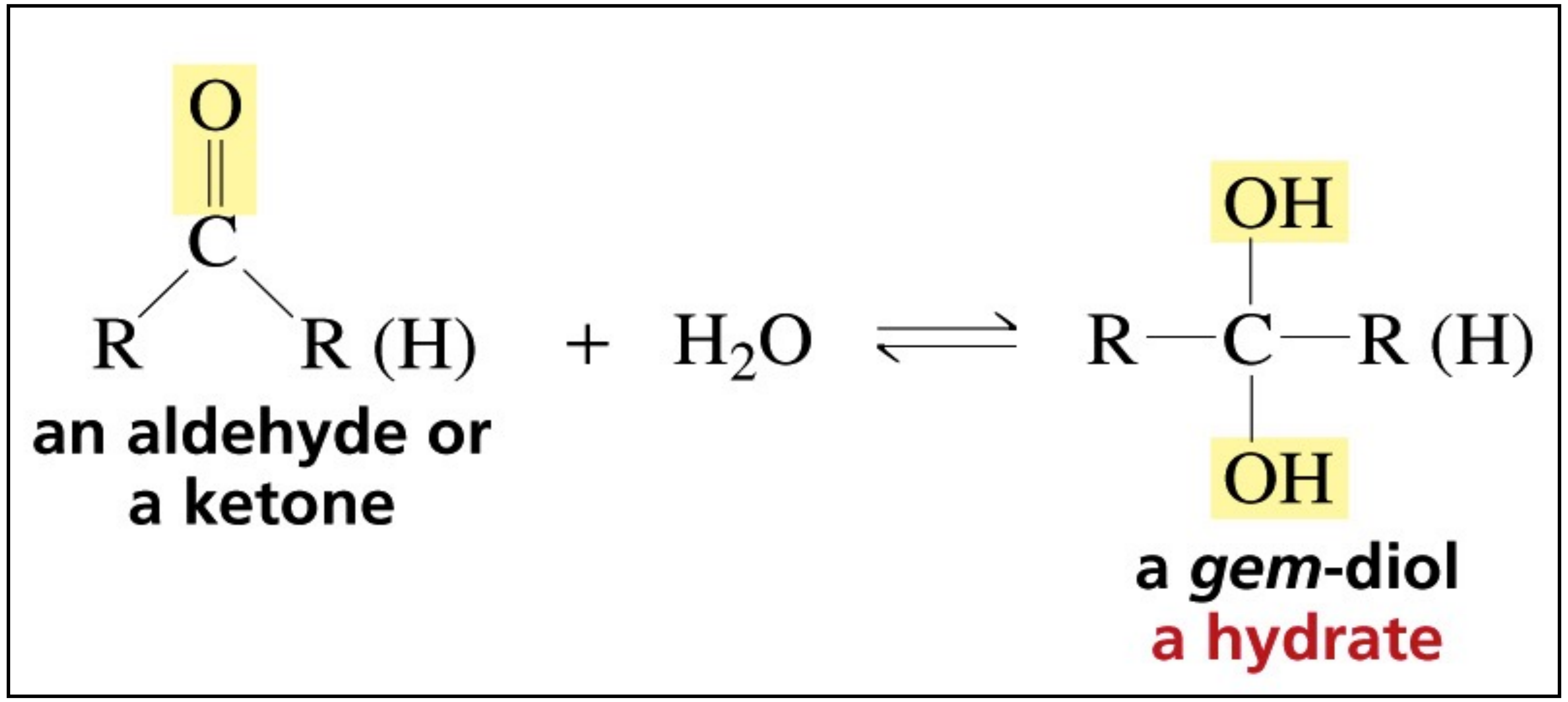


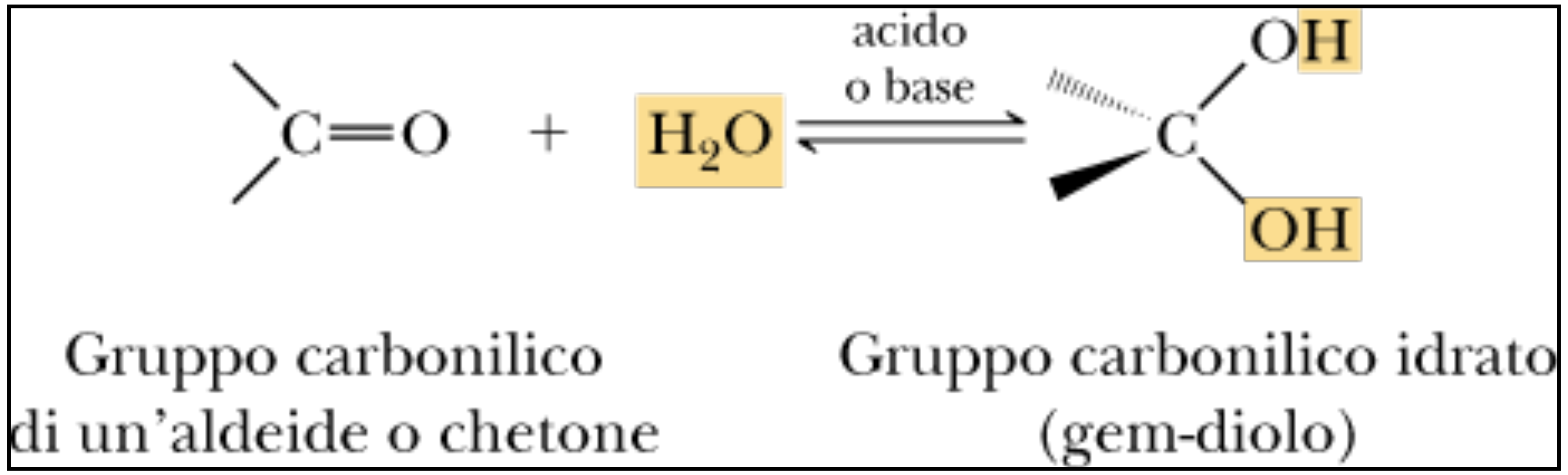
Formaldehyde (0.1%)

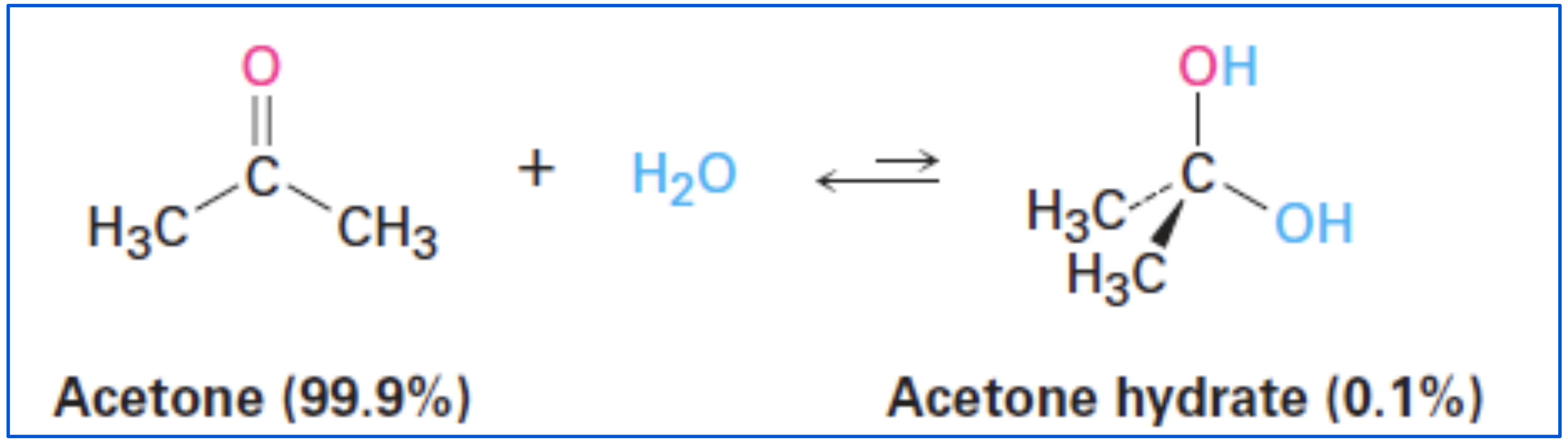
Formaldehyde hydrate (99.9%)

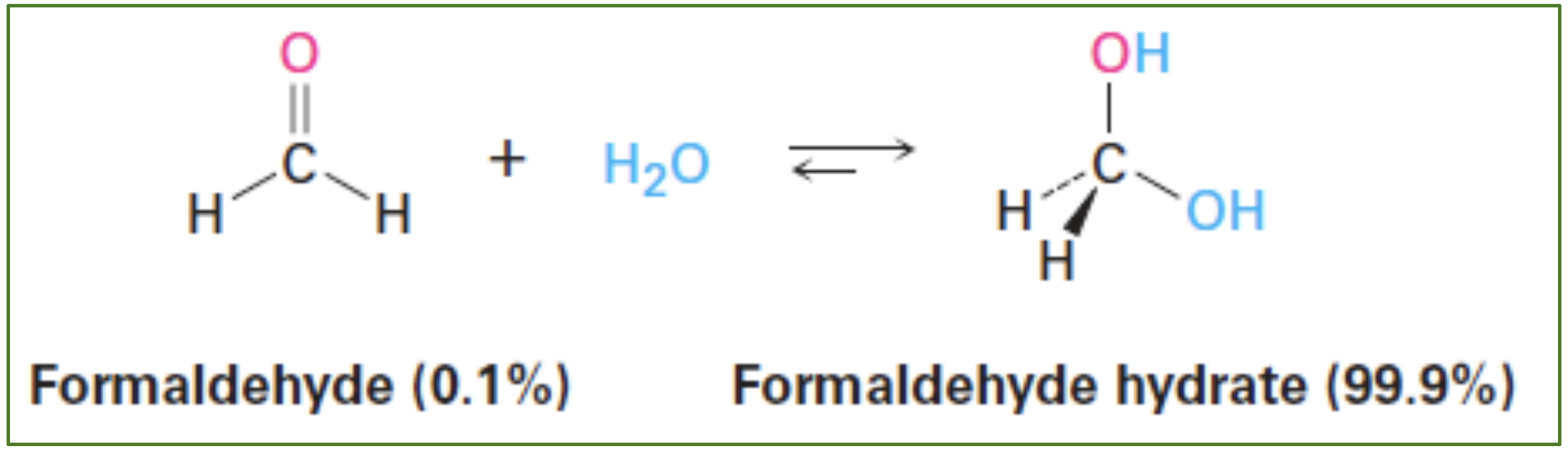
(1) ADDIZIONE di H_2O: idratazione , Formazione di Carbonili idrati

Idrati di aldeidi 1,1-dioli (gem-Dios) derivanti da un'aggiunta nucleofila di acqua al gruppo carbonile dell'aldeide

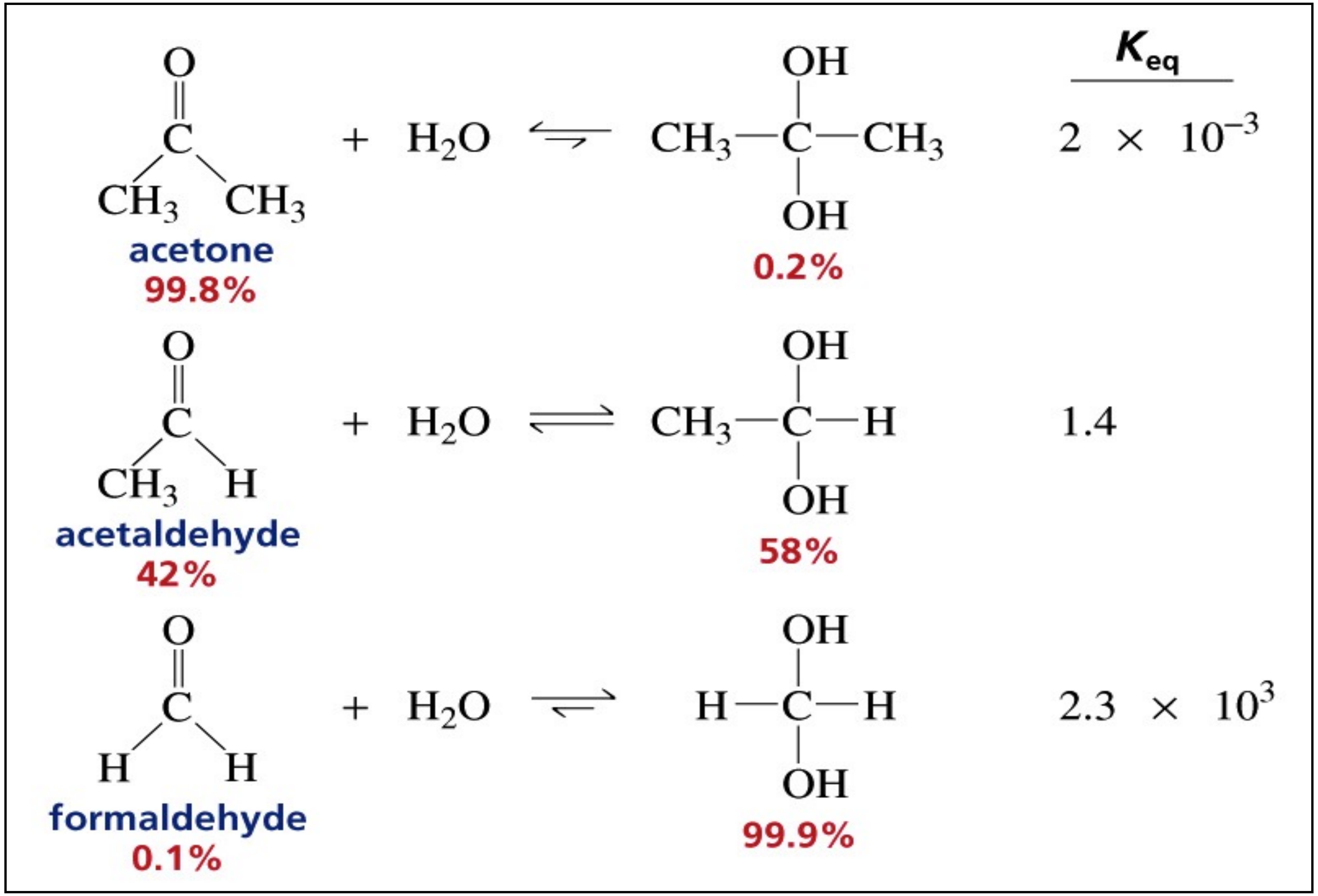






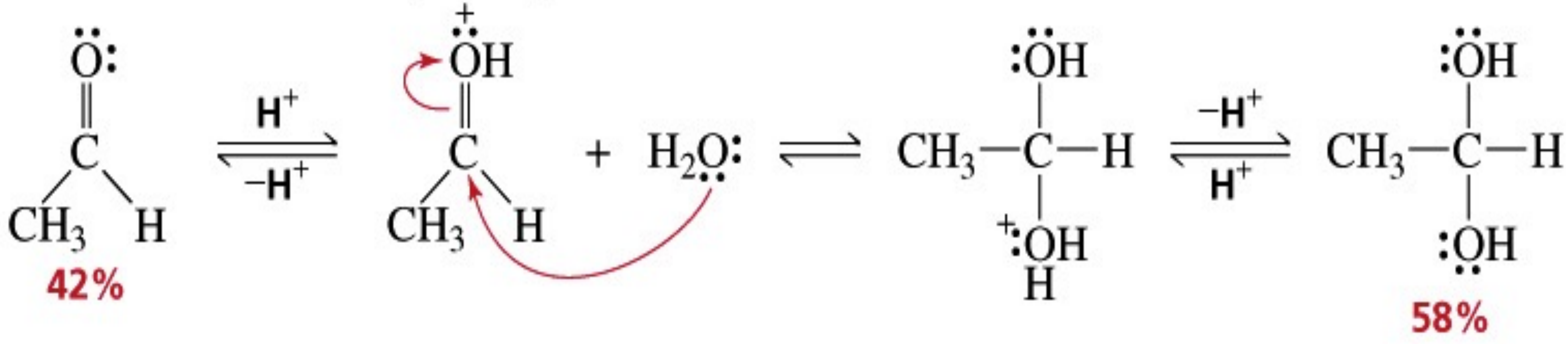


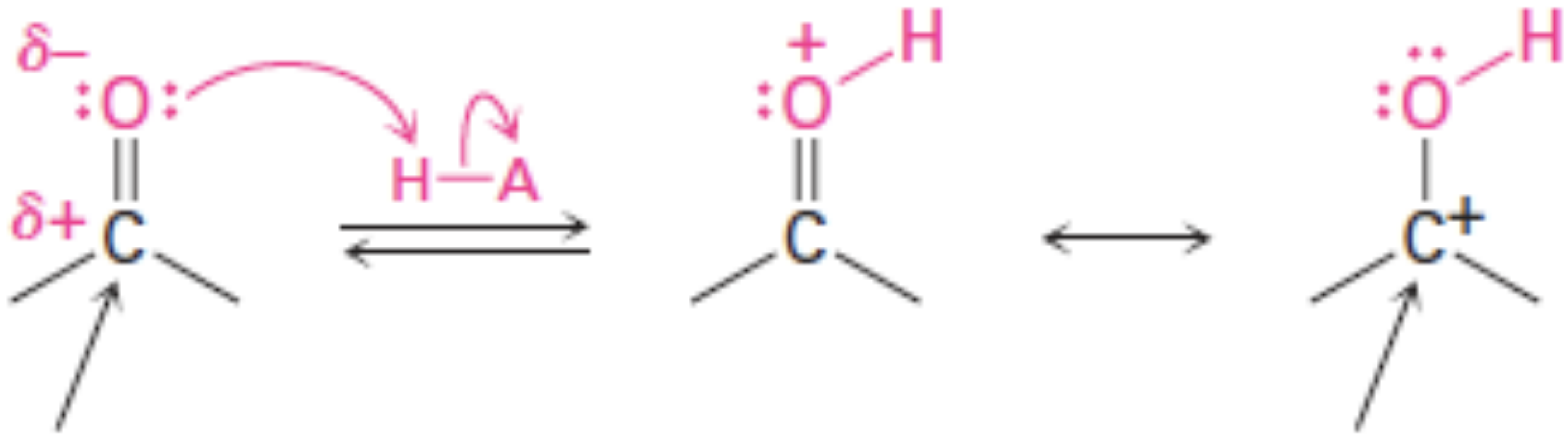
L'equilibrio in presenza di acqua: Il chetone è svantaggiato



(1) Addizione di H_2O: Meccanismo di idratazione catalizzata dall'acido

mechanism for acid-catalyzed hydrate formation

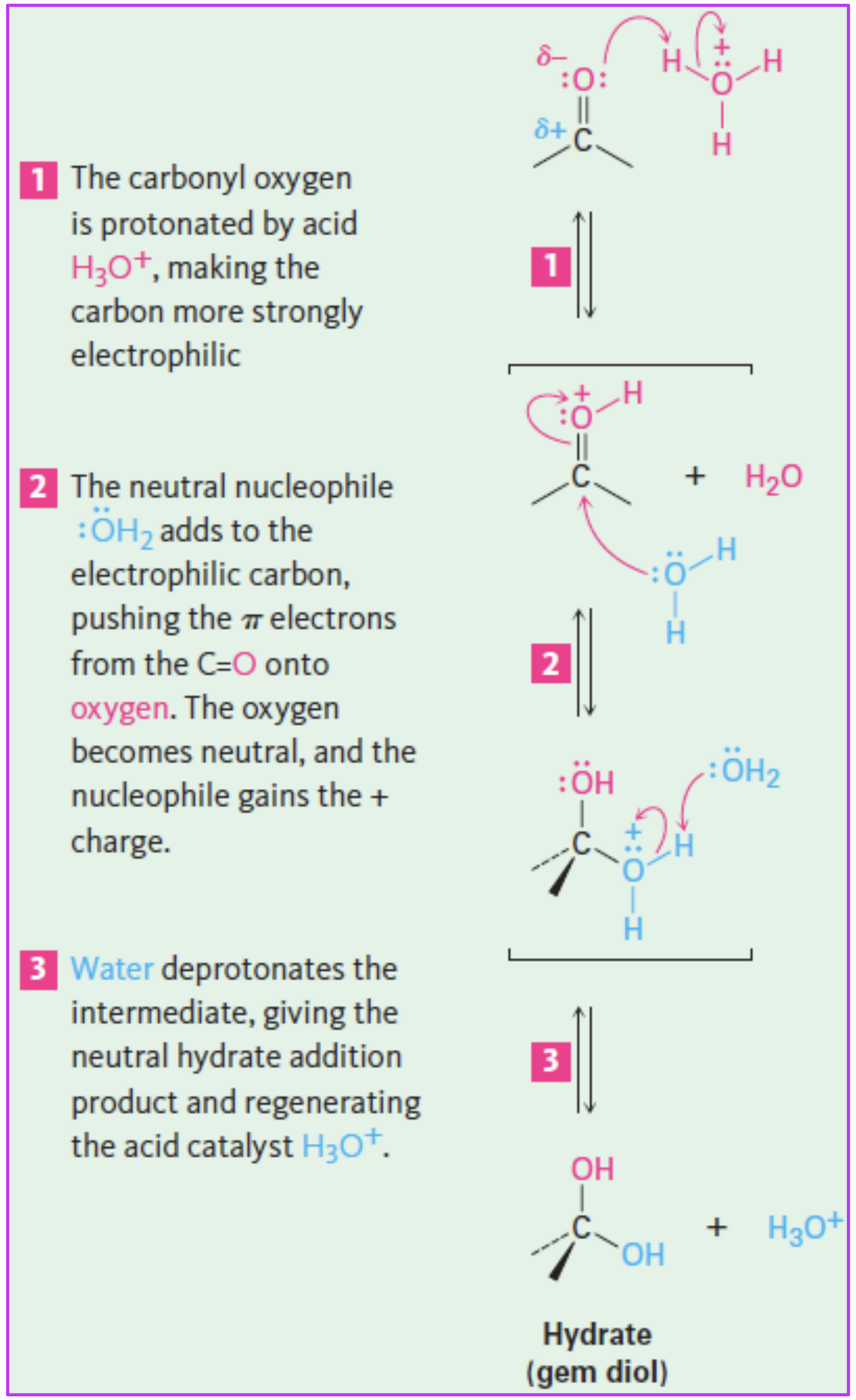




A neutral carbonyl group is moderately electrophilic because of the polarity of the C–O bond.

A protonated carbonyl group is strongly electrophilic because of the positive charge on carbon.

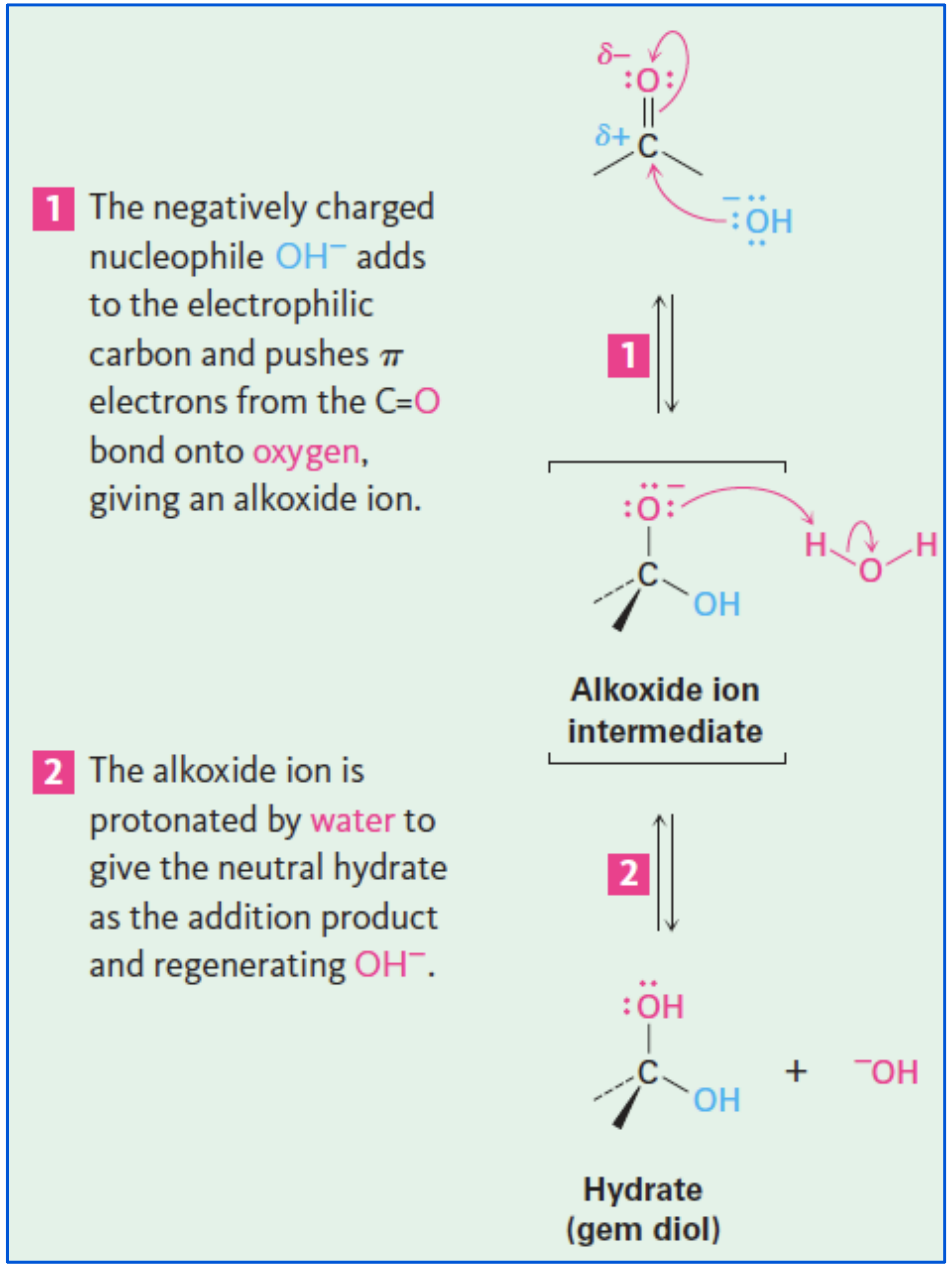
(1) Addizione di H_2O: Meccanismo di idratazione catalizzata da un acido o da una base



1 The carbonyl oxygen is protonated by acid H_3O^+, making the carbon more strongly electrophilic

2 The neutral nucleophile $:\ddot{O}H_2$ adds to the electrophilic carbon, pushing the π electrons from the C=O onto oxygen. The oxygen becomes neutral, and the nucleophile gains the + charge.

3 Water deprotonates the intermediate, giving the neutral hydrate addition product and regenerating the acid catalyst H_3O^+.

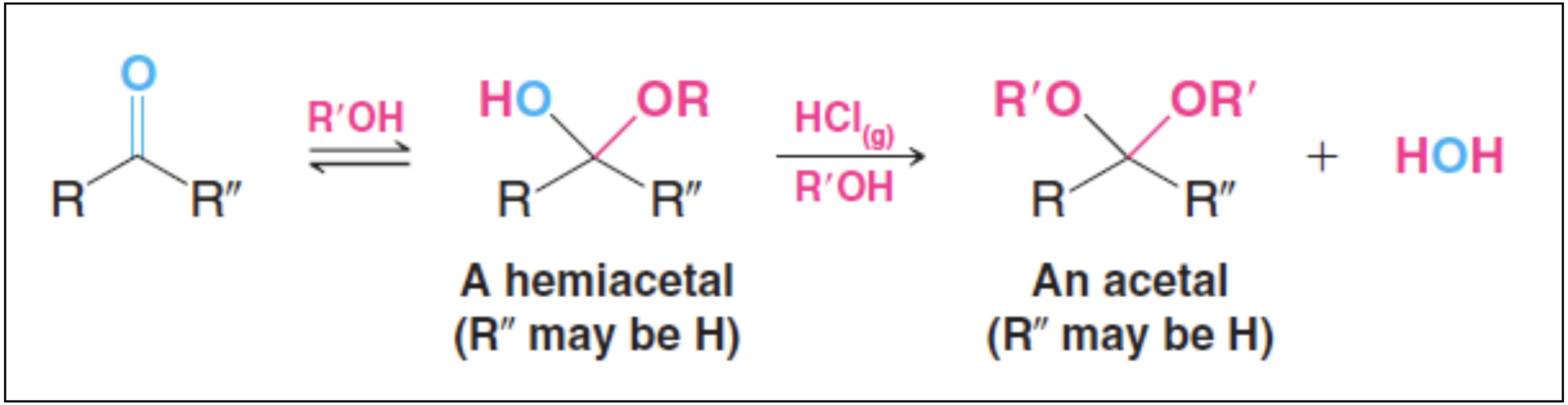


1 The negatively charged nucleophile OH^- adds to the electrophilic carbon and pushes π electrons from the C=O bond onto oxygen, giving an alkoxide ion.

2 The alkoxide ion is protonated by water to give the neutral hydrate as the addition product and regenerating OH^-.

(2) Addizione nucleofila degli alcoli al gruppo carbonile: Formazione di emiacetali e acetali

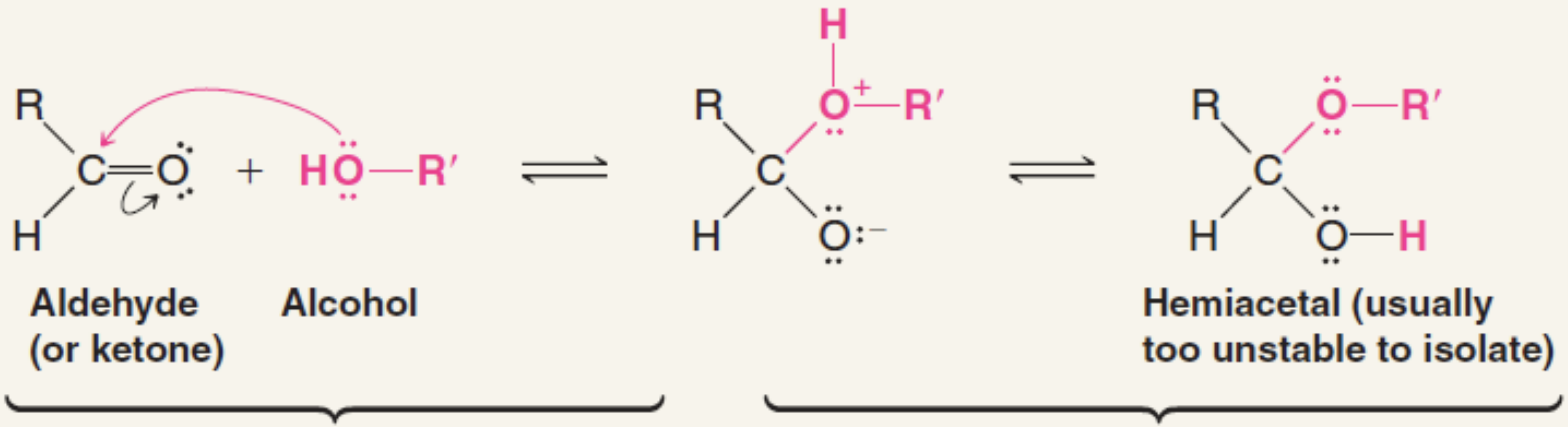
Gli aldeidi e i chetoni reagiscono reversibilmente con due equivalenti di un alcol in presenza di un catalizzatore acido per formare acetali



-Gli emiacetali hanno un gruppo -OH e un gruppo -OR legato allo stesso atomo di carbonio.

-Un acetale ha due gruppi -OR legati allo stesso atomo di C.

(2) Addizione nucleofila degli alcoli al gruppo carbonile: Formazione di emiacetali



Aldehyde (or ketone)

Alcohol

Hemiacetal (usually too unstable to isolate)

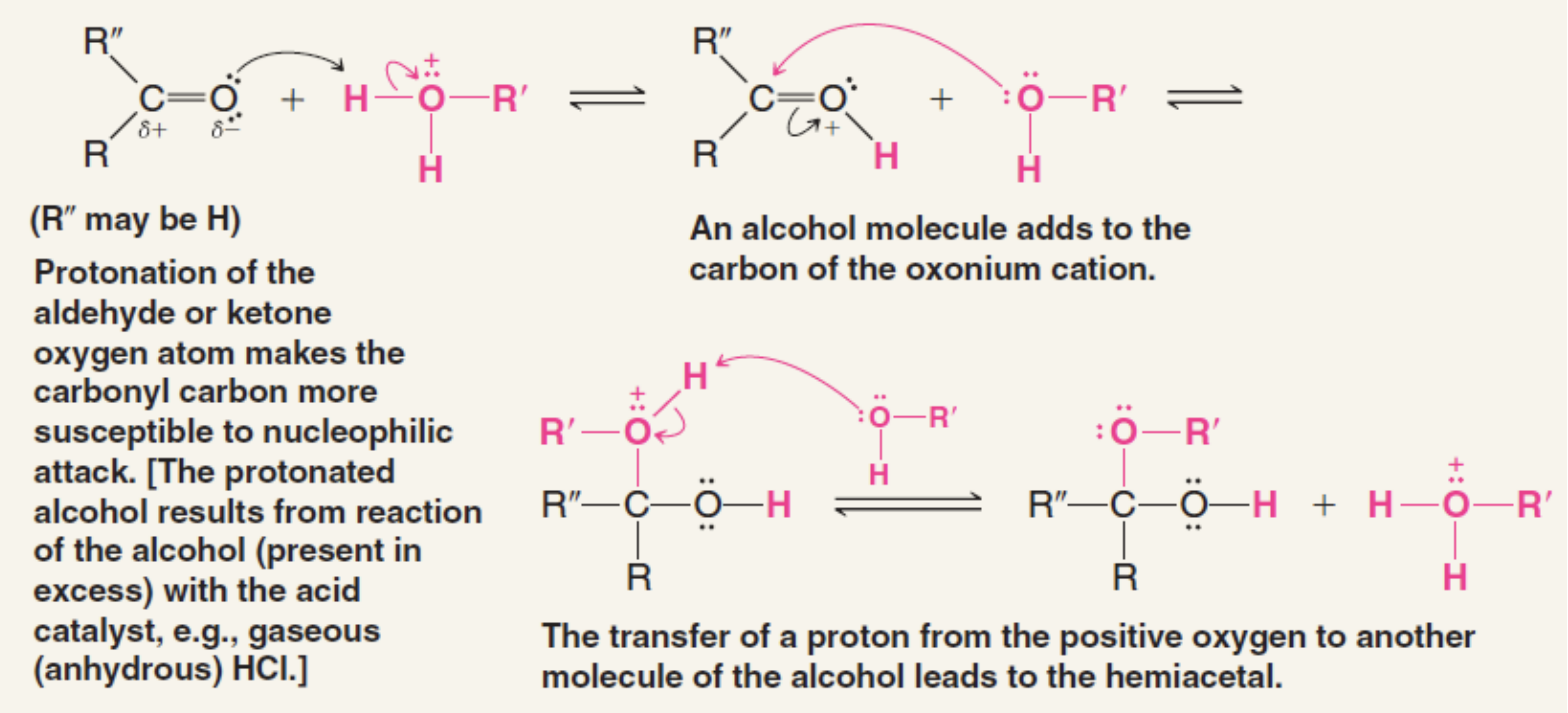
In this step the alcohol attacks the carbonyl carbon.

In two intermolecular steps, a proton is removed from the positive oxygen and a proton is gained at the negative oxygen.

Formazione di emiacetali:

Gli alcoli sono nucleofili deboli che si addizionano Ad aldeidi e chetoni lentamente, in condizioni neutre.

(2) Addizione nucleofila degli alcoli al gruppo carbonile: Formazione di emiacetali catalizzata da acidi



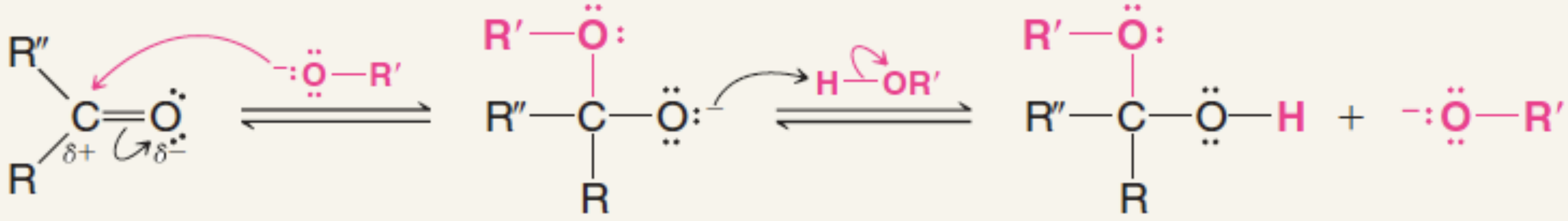
(R″ may be H)

Protonation of the aldehyde or ketone oxygen atom makes the carbonyl carbon more susceptible to nucleophilic attack. [The protonated alcohol results from reaction of the alcohol (present in excess) with the acid catalyst, e.g., gaseous (anhydrous) HCl.]

An alcohol molecule adds to the carbon of the oxonium cation.

The transfer of a proton from the positive oxygen to another molecule of the alcohol leads to the hemiacetal.

(2) Addizione nucleofila degli alcoli al gruppo carbonile: Formazione di emiacetali catalizzata da basi

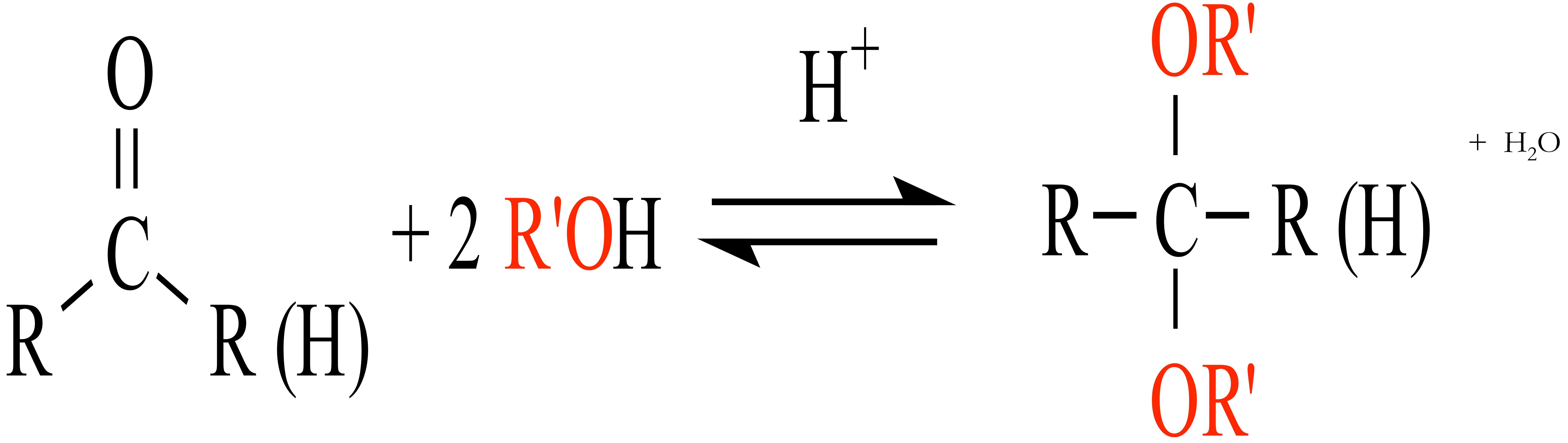


(R″ may be H)

An alkoxide anion acting as a nucleophile attacks the carbonyl carbon atom. An electron pair shifts onto the oxygen atom, producing a new alkoxide anion.

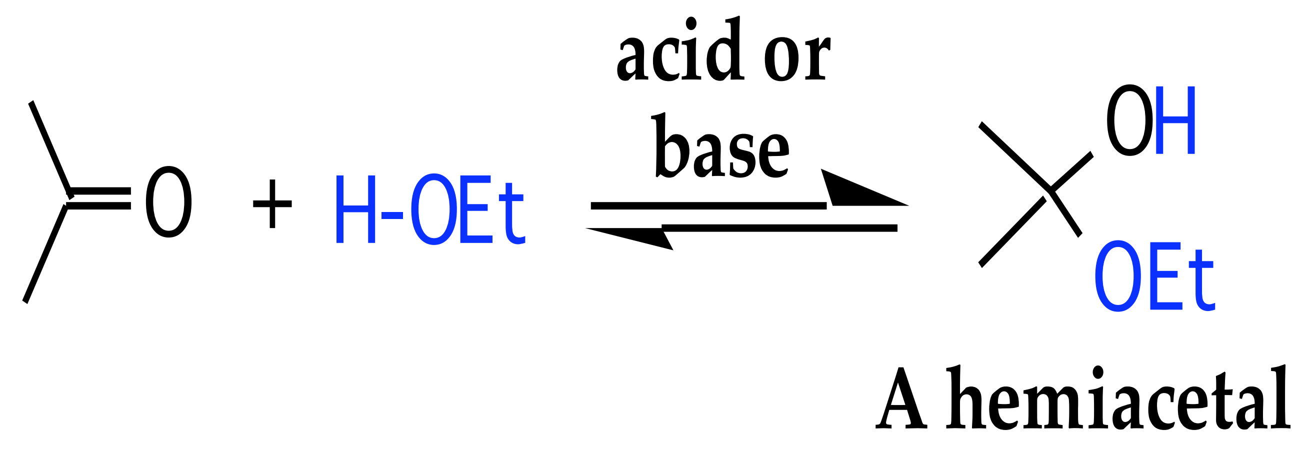
The alkoxide anion abstracts a proton from an alcohol molecule to produce the hemiacetal and regenerates an alkoxide anion.

(2) Addizione nucleofila degli alcoli al gruppo carbonile: Formazione di acetali

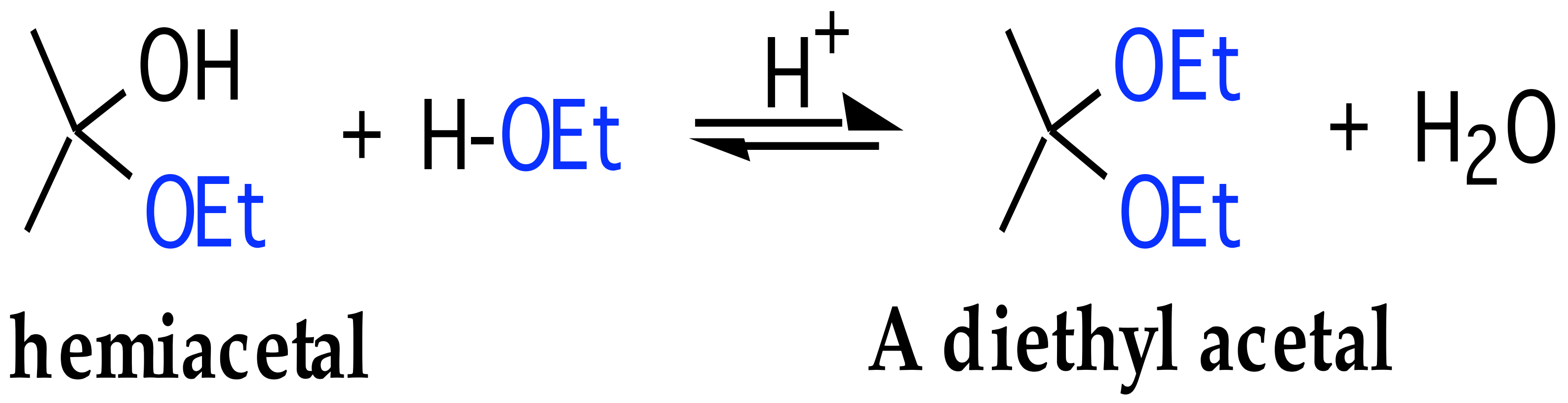


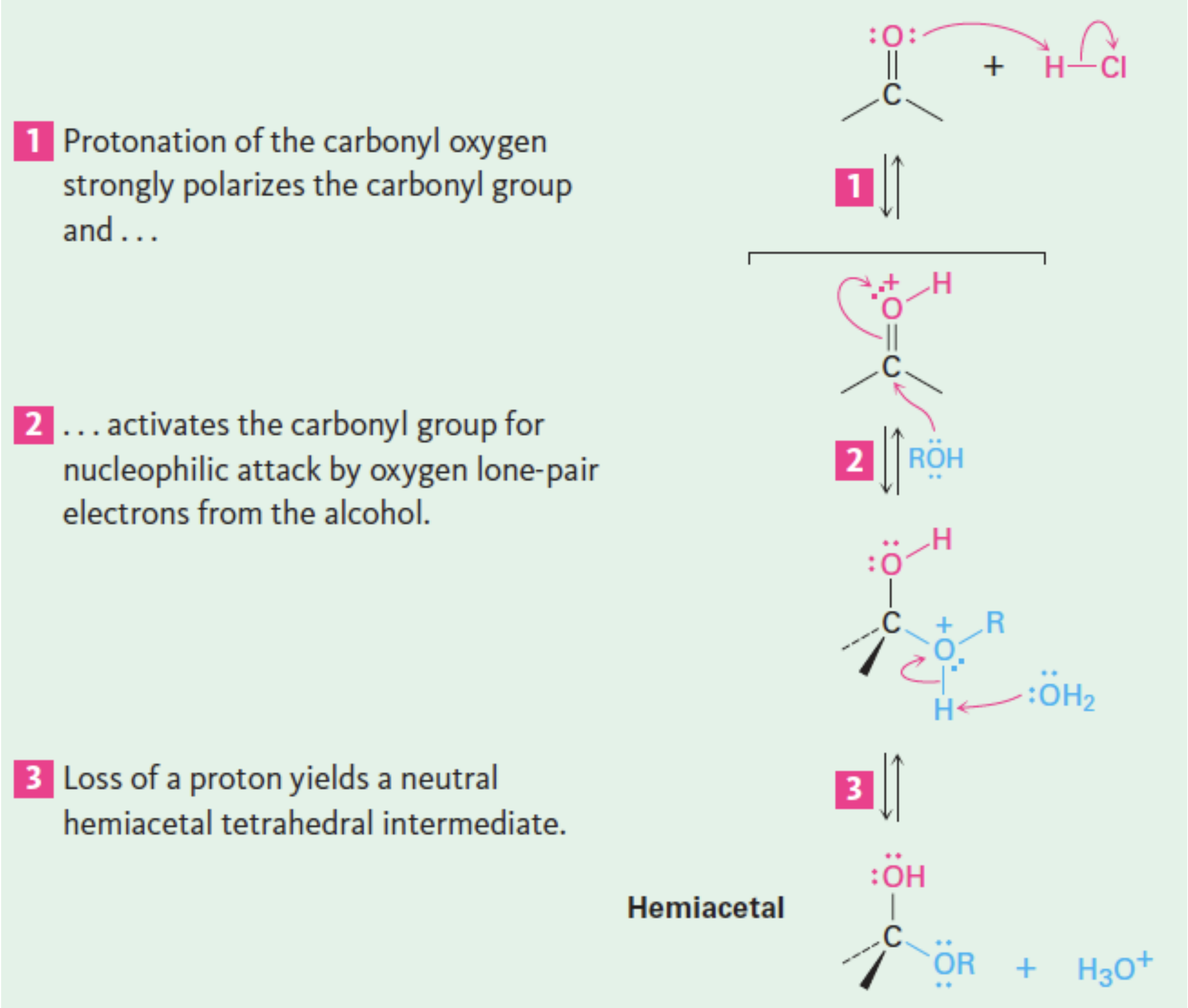
(2) Addizione nucleofila degli alcoli al gruppo carbonile: Formazione di acetali

1° STADIO:



2° STADIO:

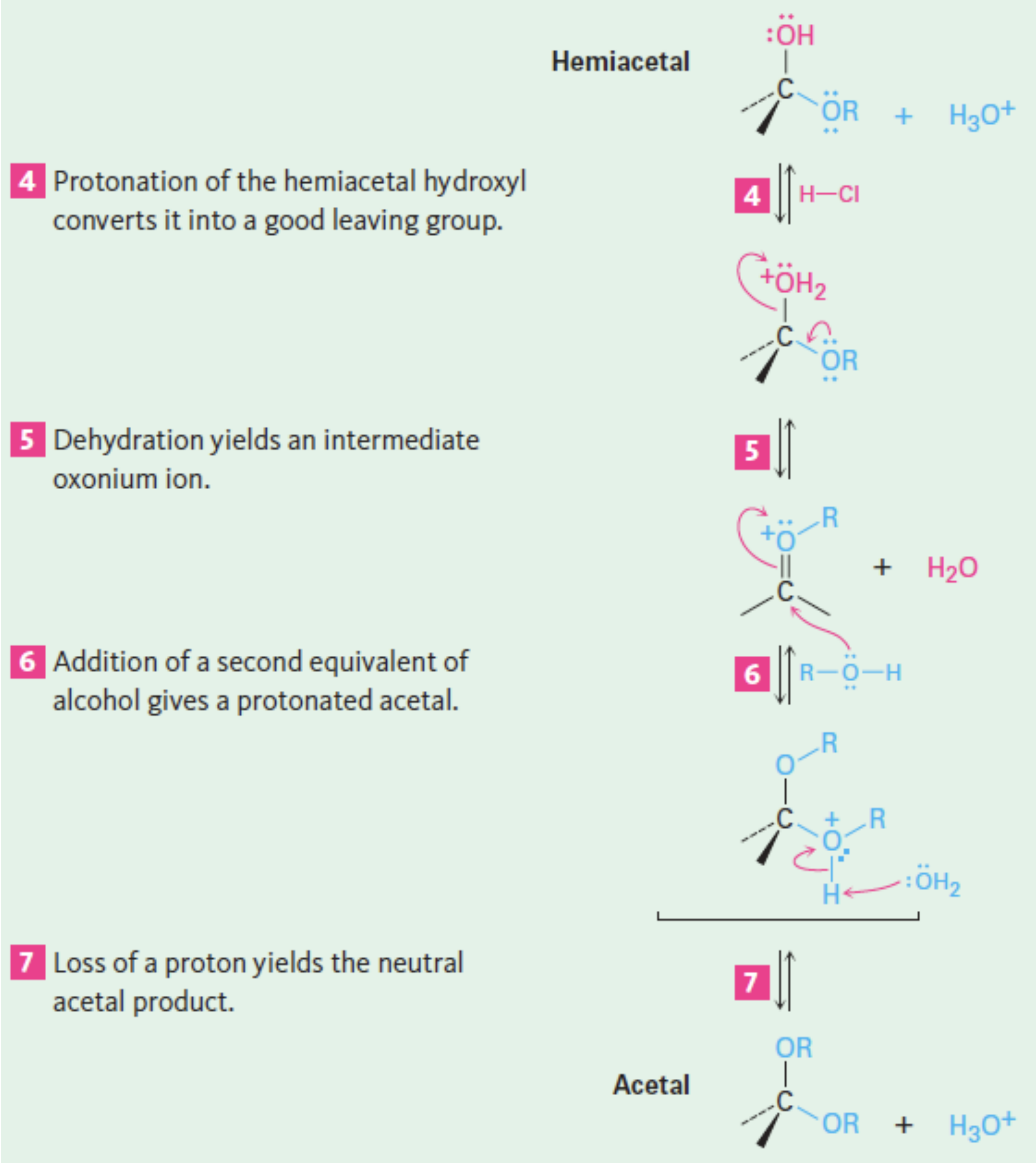




1 Protonation of the carbonyl oxygen strongly polarizes the carbonyl group and . . .

2 . . . activates the carbonyl group for nucleophilic attack by oxygen lone-pair electrons from the alcohol.

3 Loss of a proton yields a neutral hemiacetal tetrahedral intermediate.



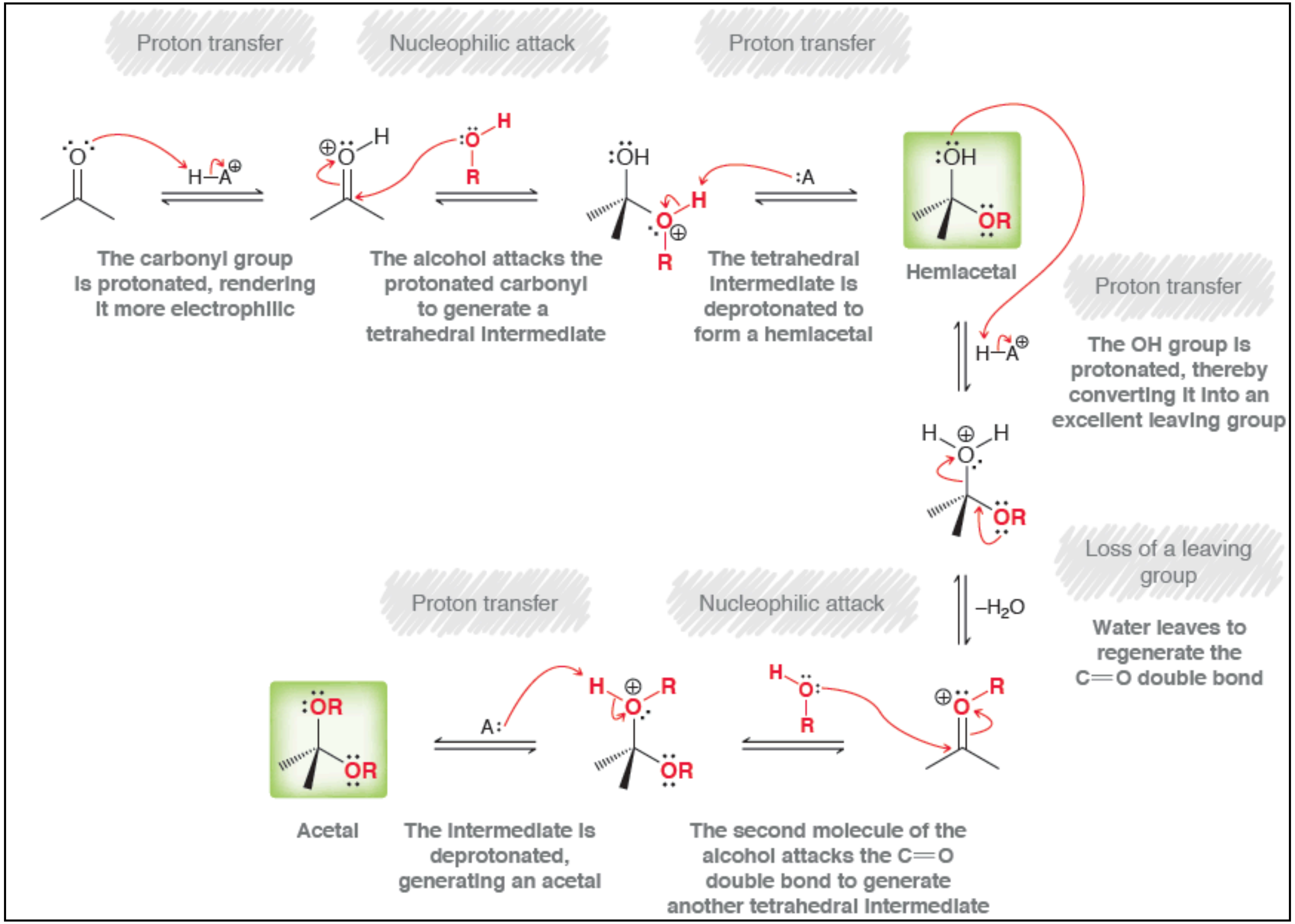
4 Protonation of the hemiacetal hydroxyl converts it into a good leaving group.

5 Dehydration yields an intermediate oxonium ion.

6 Addition of a second equivalent of alcohol gives a protonated acetal.

7 Loss of a proton yields the neutral acetal product.

(2) Meccanismo per Formazione di acetali in ambiente acido



Proton transfer

The carbonyl group is protonated, rendering it more electrophilic

Nucleophilic attack

The alcohol attacks the protonated carbonyl to generate a tetrahedral intermediate

Proton transfer

The tetrahedral intermediate is deprotonated to form a hemiacetal

Proton transfer

The OH group is protonated, thereby converting it into an excellent leaving group

Loss of a leaving group

Water leaves to regenerate the C═O double bond

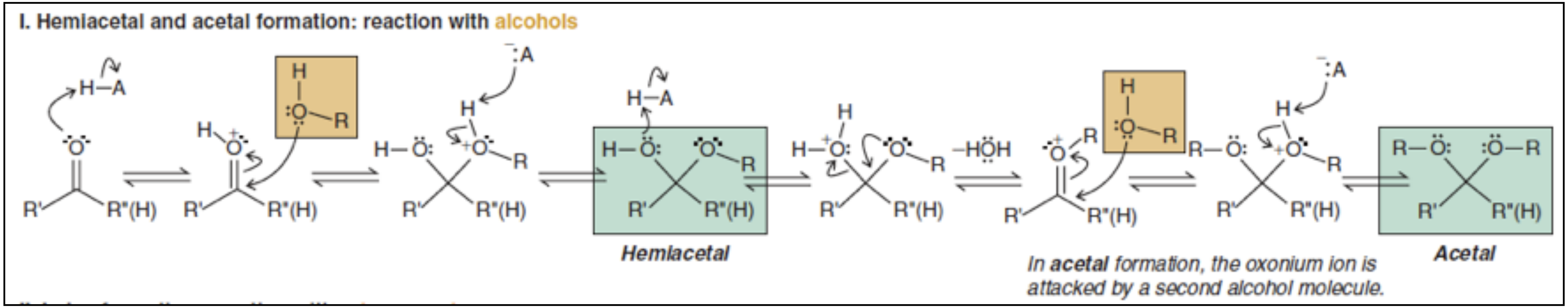
Nucleophilic attack

The second molecule of the alcohol attacks the C═O double bond to generate another tetrahedral intermediate

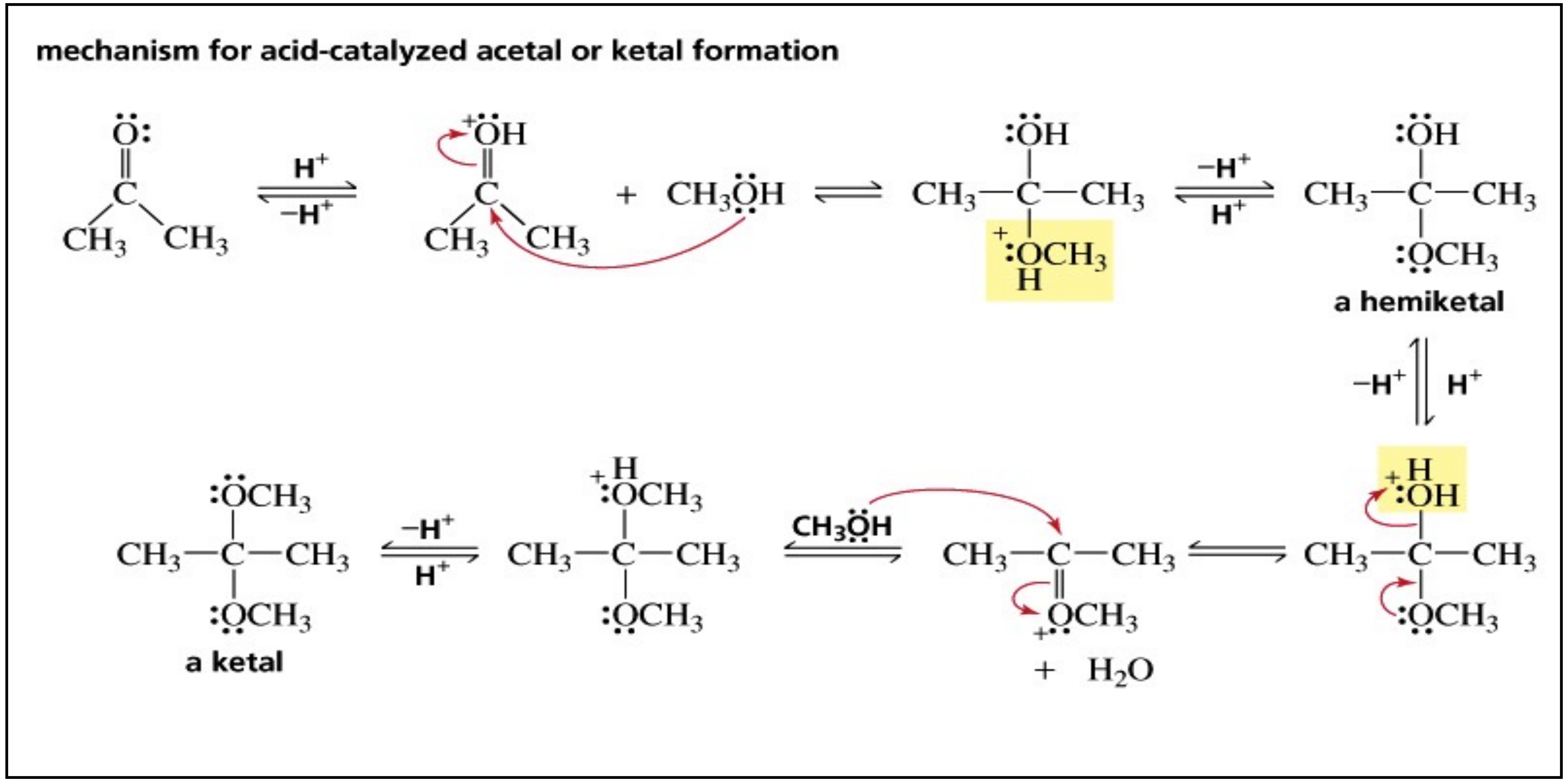
Proton transfer

The intermediate is deprotonated, generating an acetal

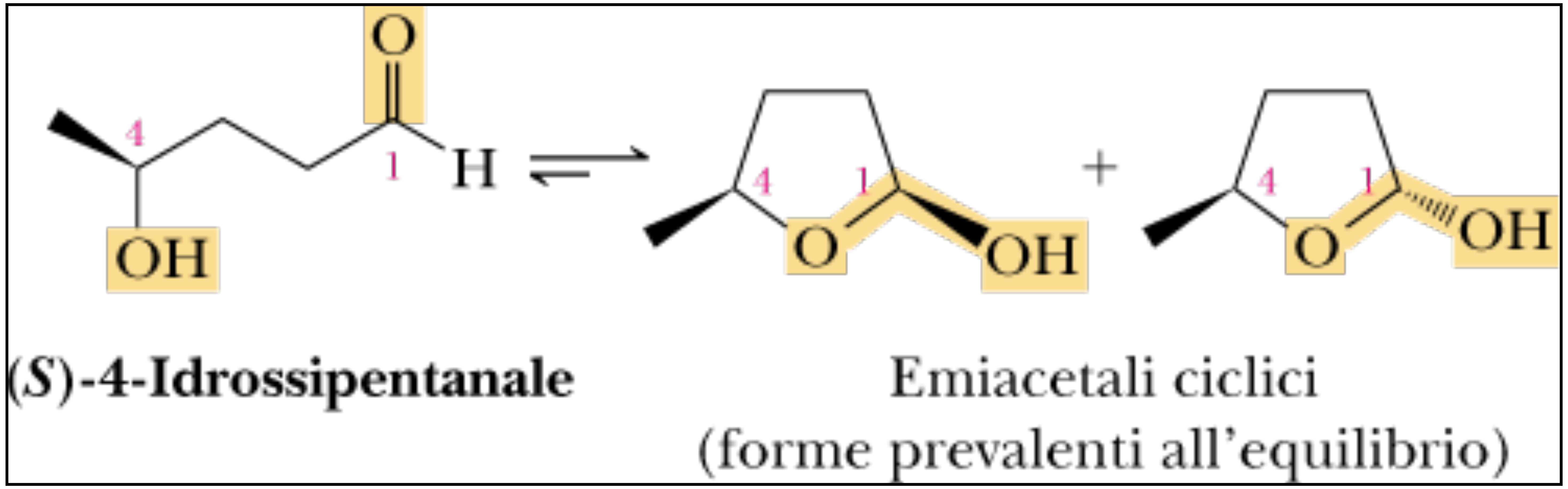
(2) Meccanismo per Formazione di acetali in ambiente acido

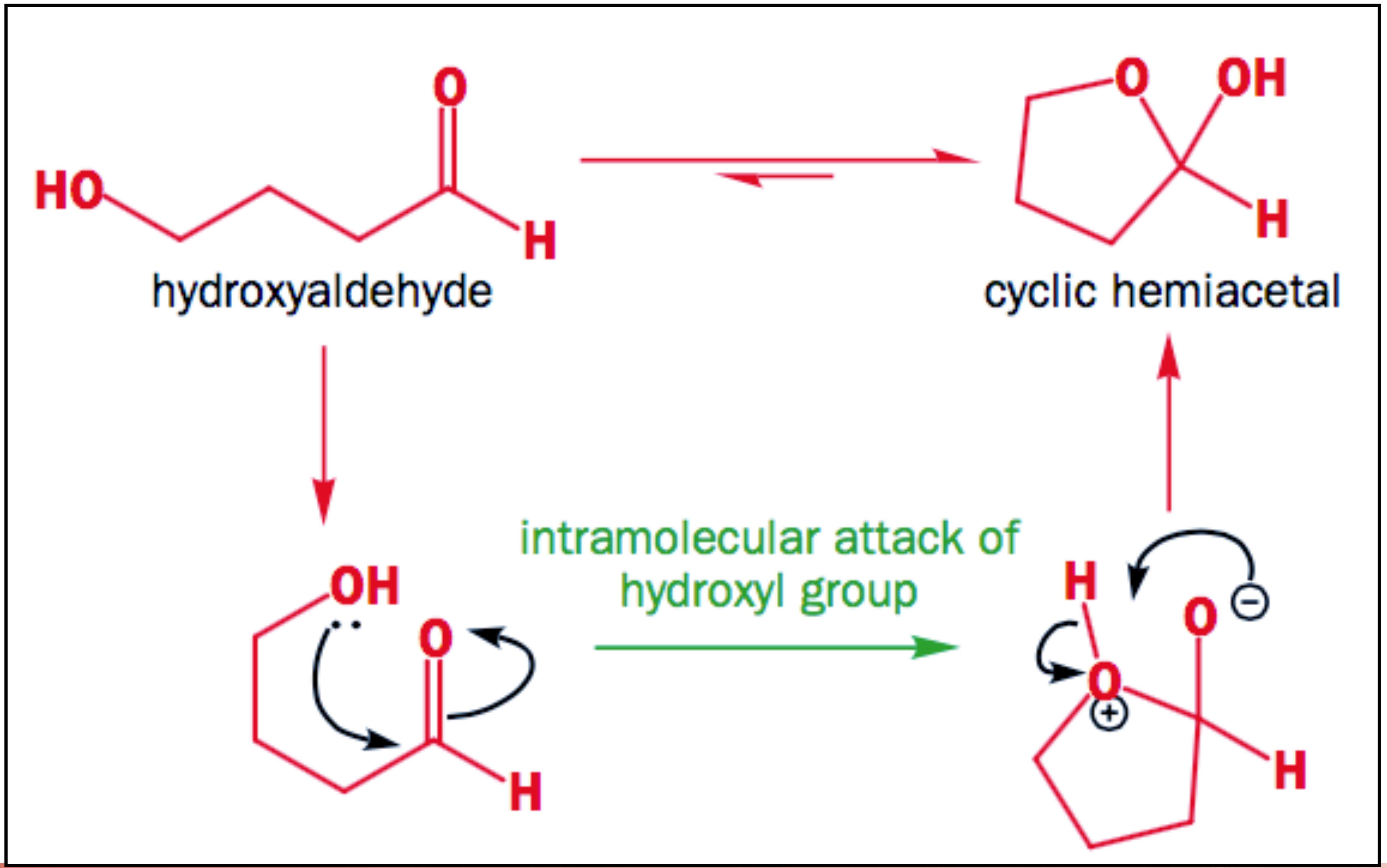

I. Hemiacetal and acetal formation: reaction with alcohols

In acetal formation, the oxonium ion is attacked by a second alcohol molecule.

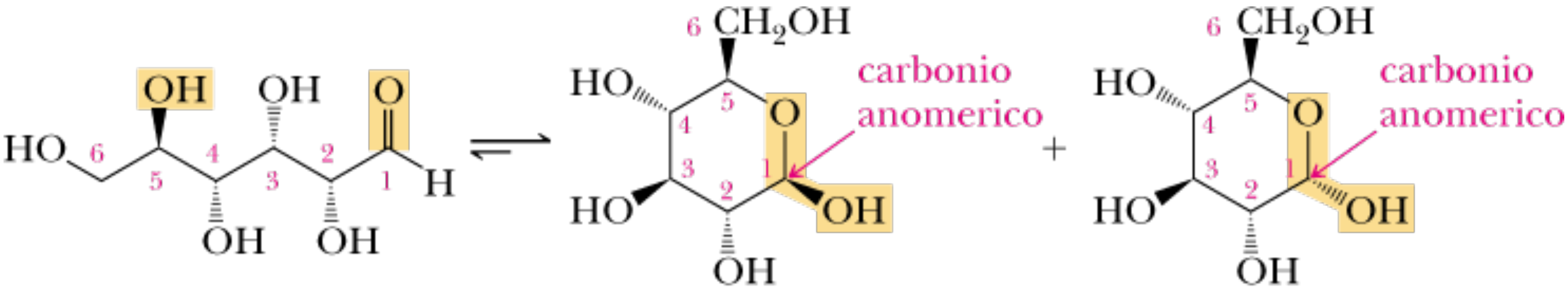

mechanism for acid-catalyzed acetal or ketal formation

(2) Meccanismo per Formazione di emiacetali ciclici a 5 atomi





(2) Meccanismo per Formazione di emiacetali ciclici a 6 atomi

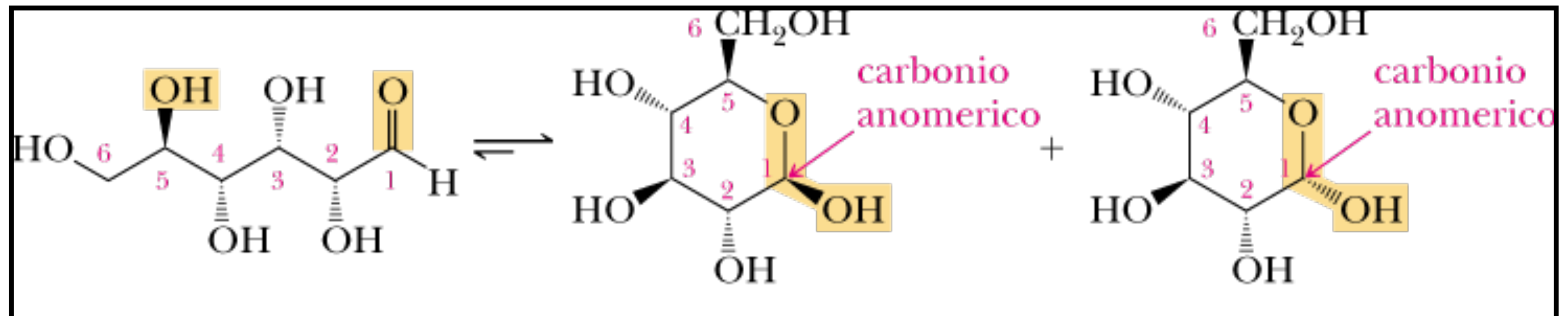


D-Glucosio
(forma a catena aperta)

Anomero β del D-glucosio
emiacetalico ciclico
(prevalente all'equilibrio)

Anomero α del D-glucosio
emiacetalico ciclico

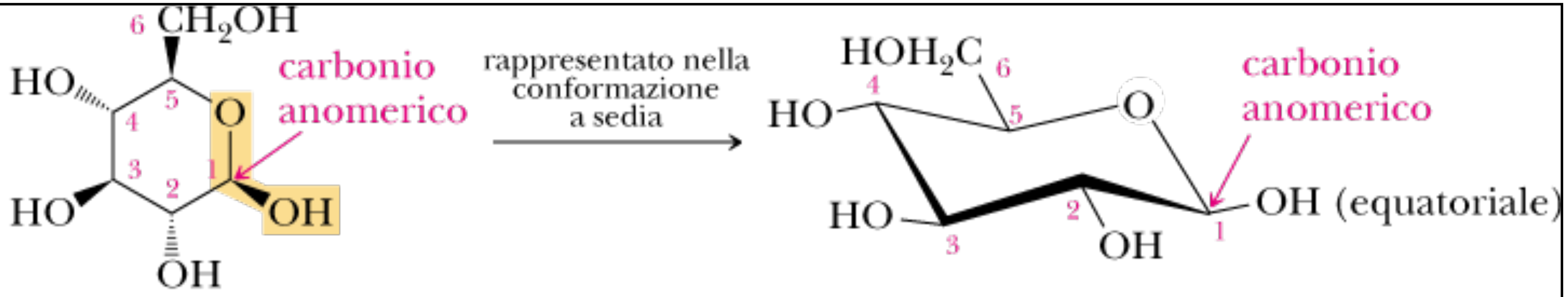
(2) Meccanismo per Formazione di emiacetali ciclici a 6 atomi



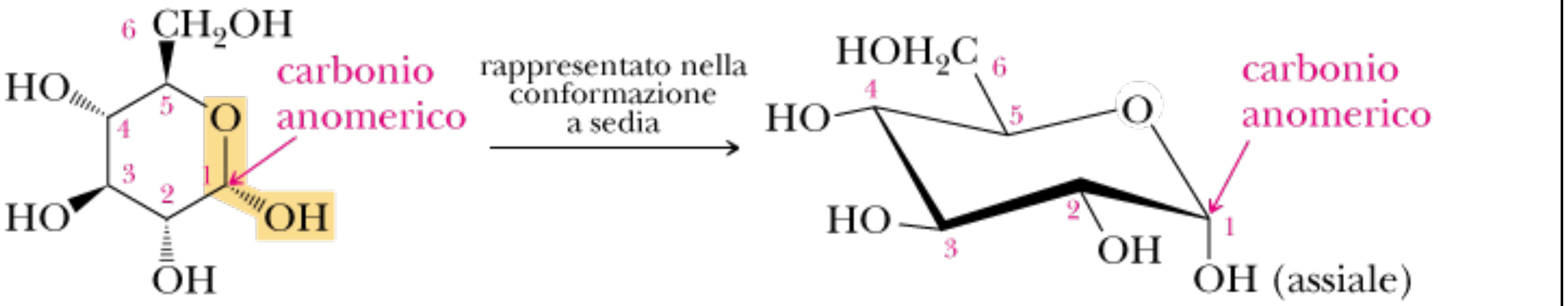
D-Glucosio (forma a catena aperta)

Anomero β del D-glucosio emiacetalico ciclico (prevalente all'equilibrio)

Anomero α del D-glucosio emiacetalico ciclico

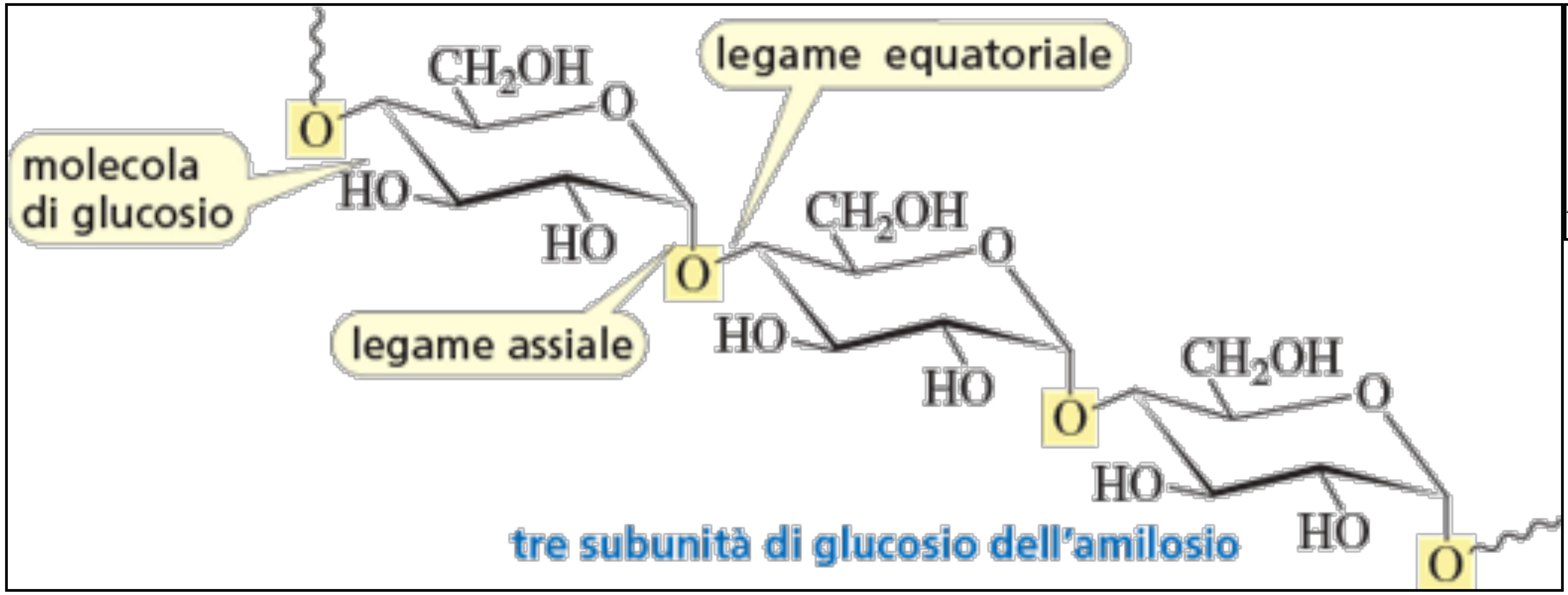


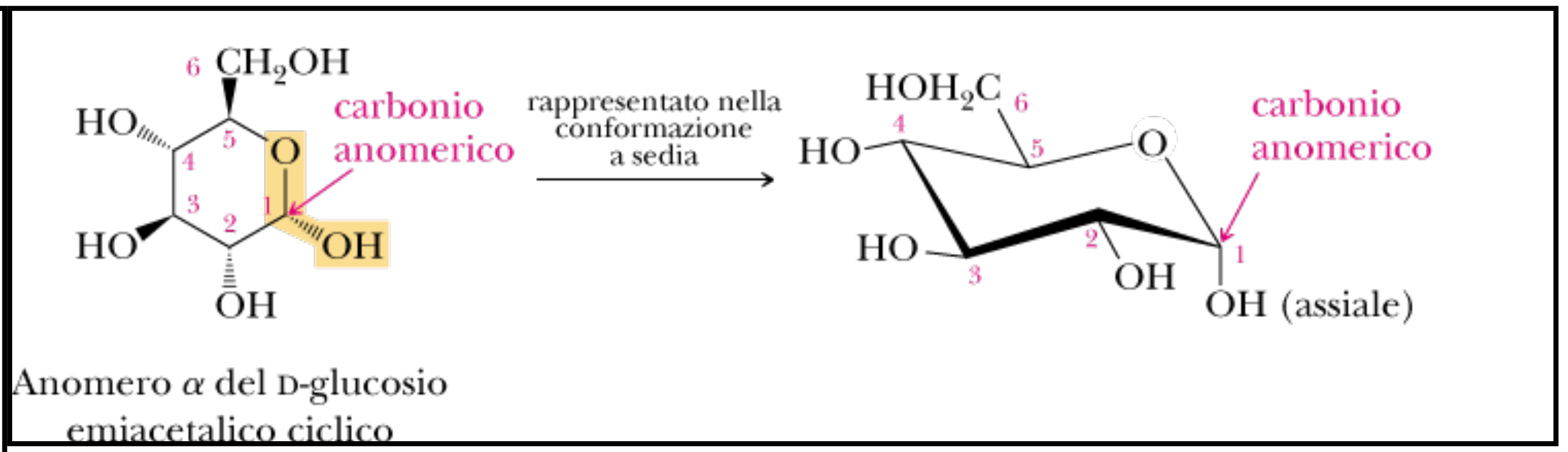
Anomero β del D-glucosio emiacetalico ciclico



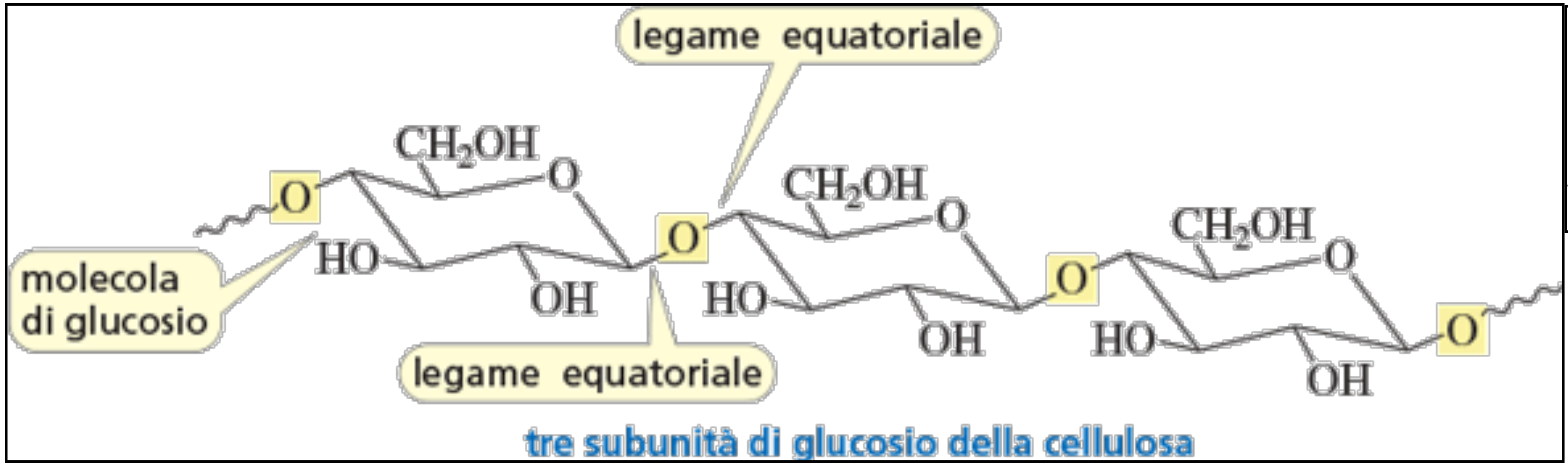
Anomero α del D-glucosio emiacetalico ciclico

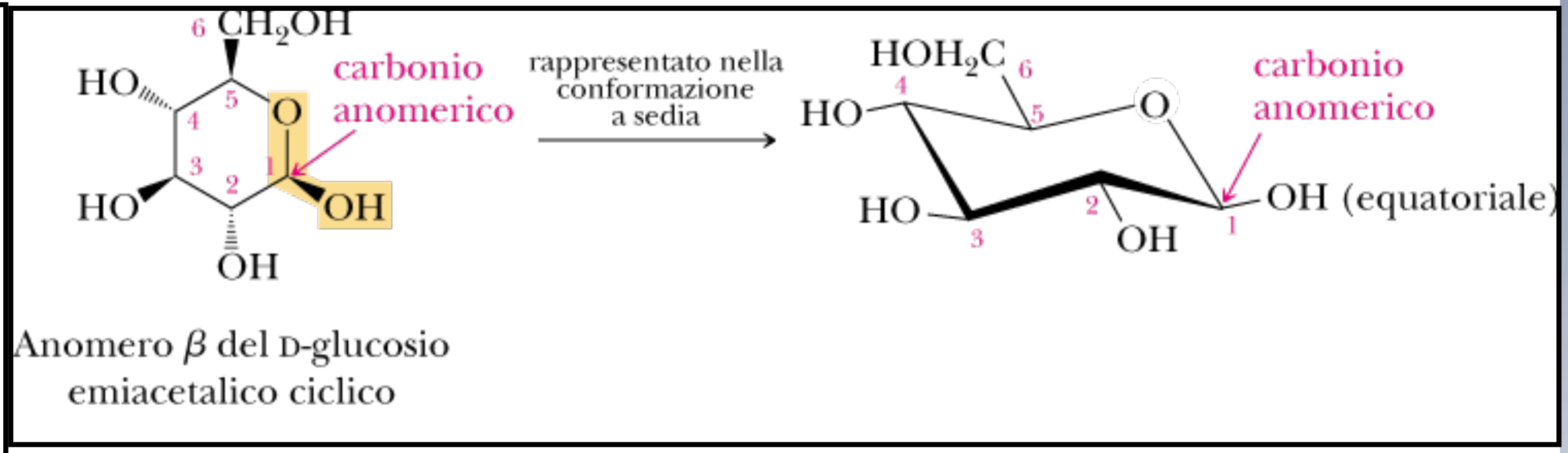
(2) alfa-glucosio nell'amilosio e beta-glucosio nella cellulosa





Anomero α del D-glucosio emiacetalico ciclico

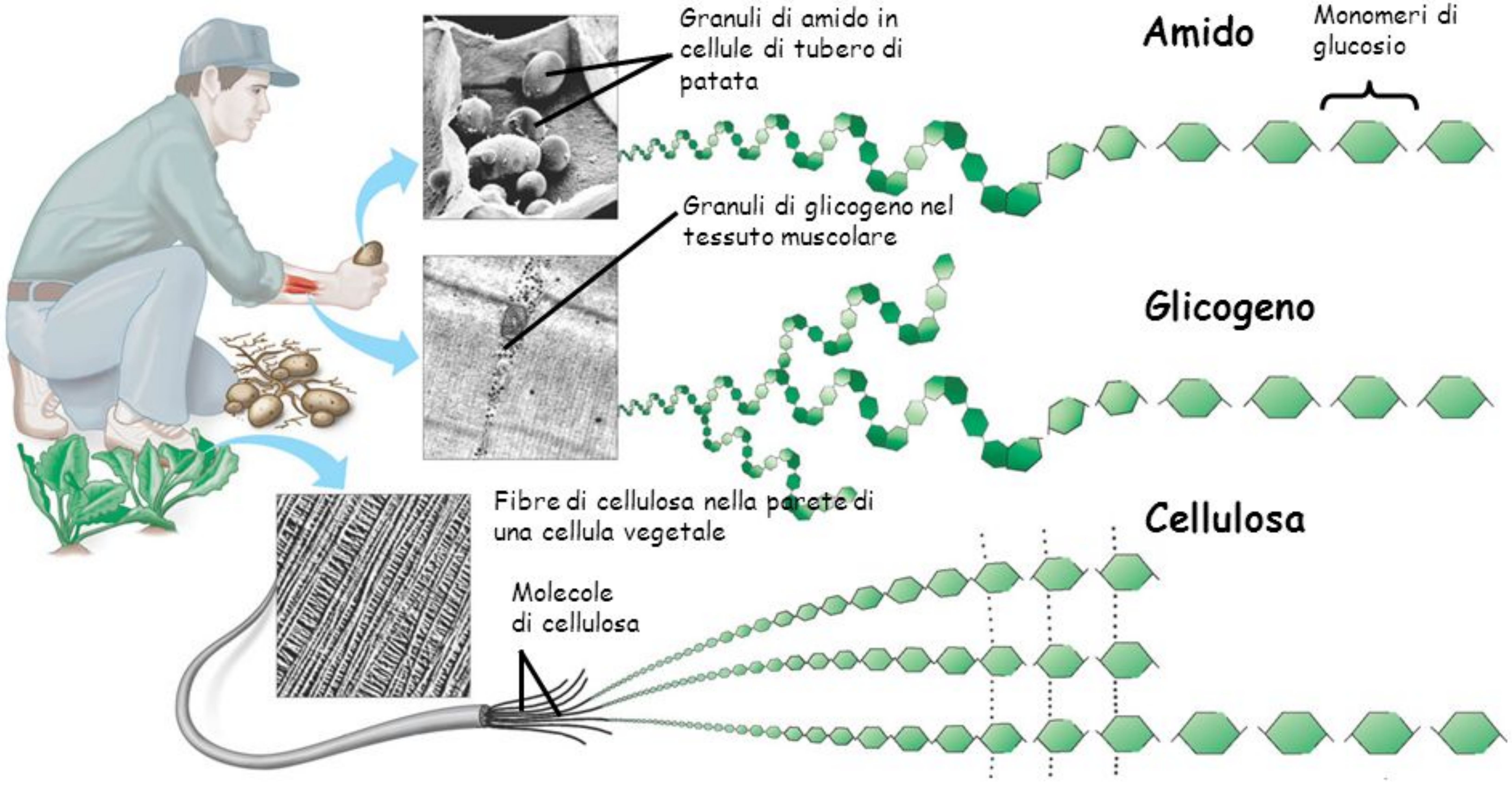


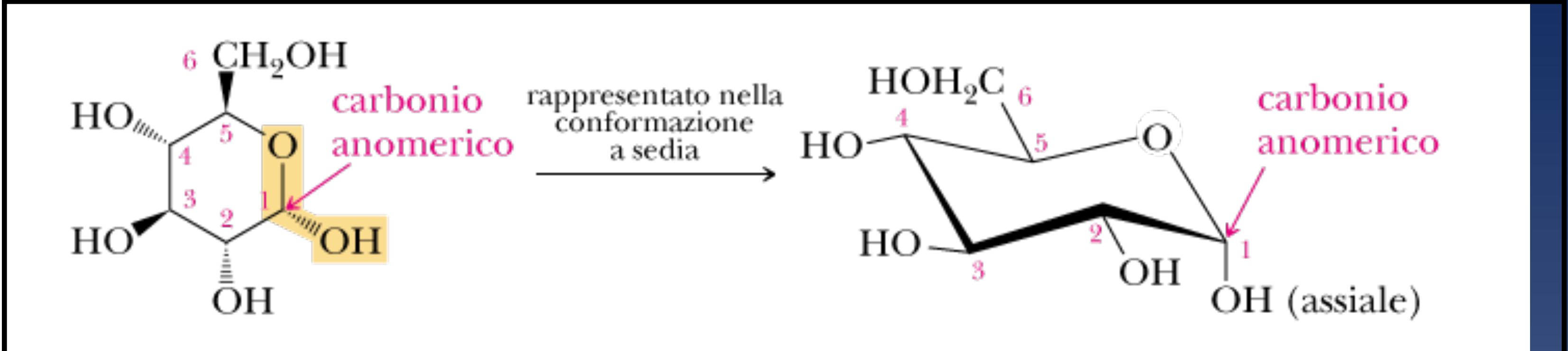


Anomero β del D-glucosio emiacetalico ciclico

I polisaccaridi di interesse biologico

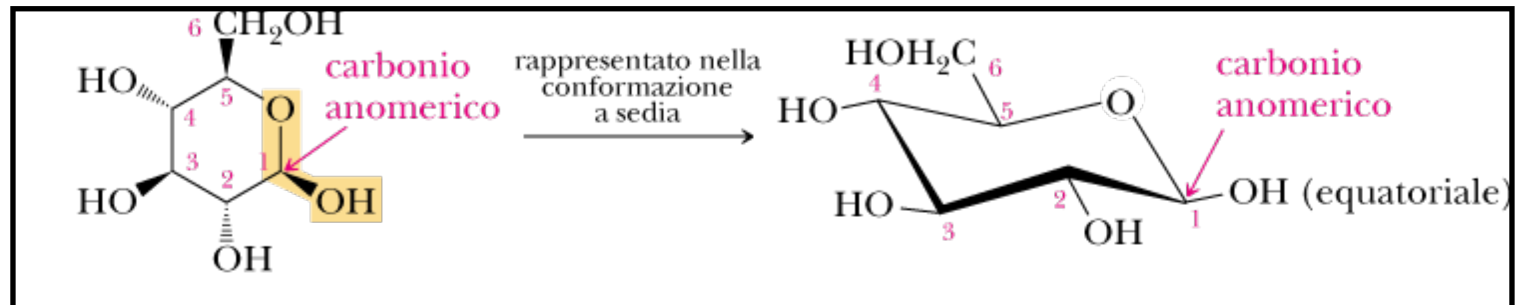
L'**amido** e il **glicogeno** immagazzinano zuccheri di riserva
La **cellulosa** si trova nelle pareti delle cellule vegetali





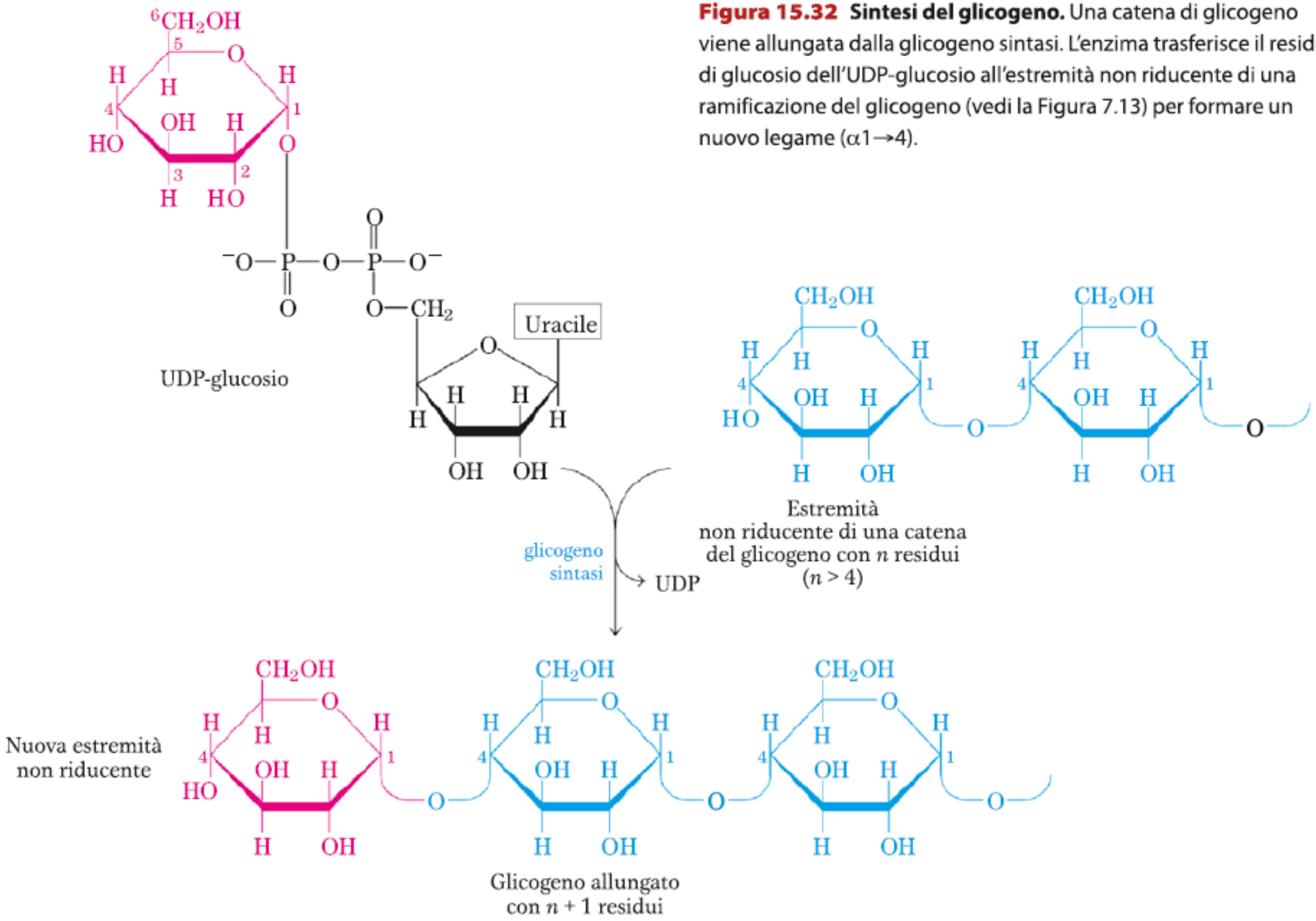
Anomero *α* del D-glucosio emiacetalico ciclico

Illustrazione 3D dell amido, biomolecola elicoidale dell'amilosio,

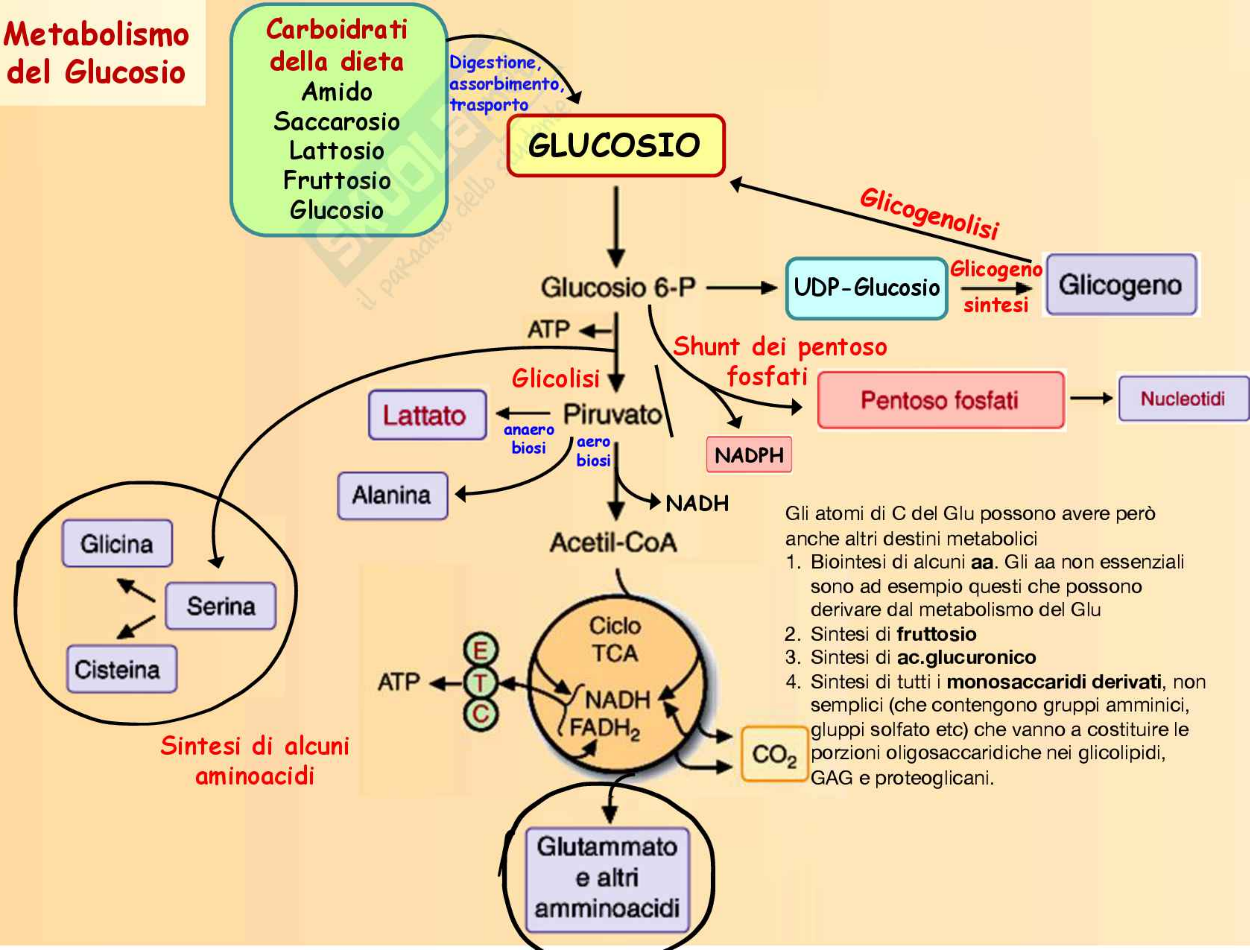


Anomero *β* del D-glucosio emiacetalico ciclico

Figura 15.32 **Sintesi del glicogeno.** Una catena di glicogeno viene allungata dalla glicogeno sintasi. L'enzima trasferisce il residuo di glucosio dell'UDP-glucosio all'estremità non riducente di una ramificazione del glicogeno (vedi la Figura 7.13) per formare un nuovo legame (α1→4).



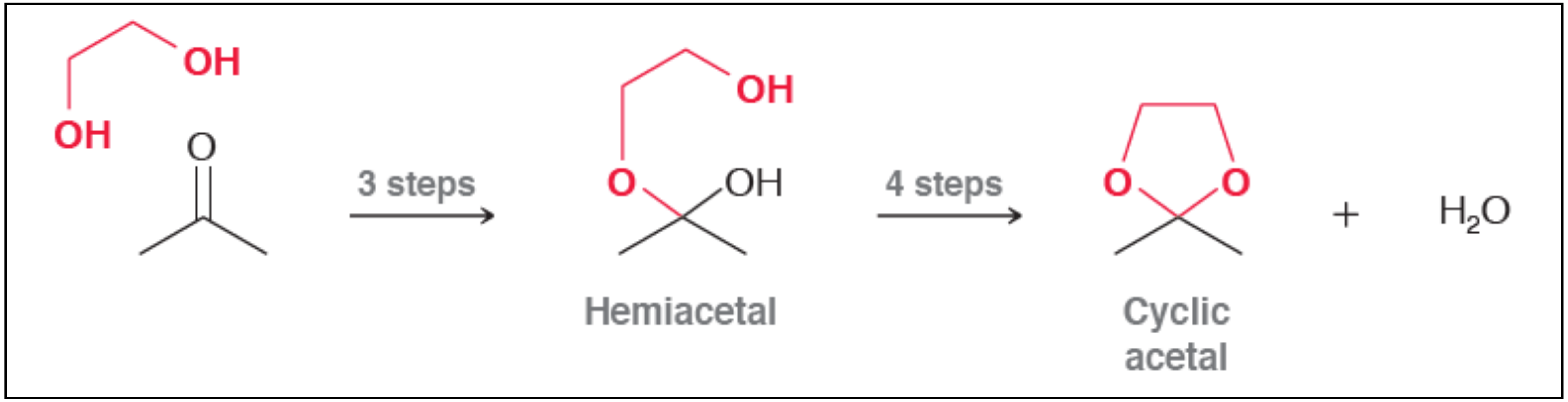
Metabolismo del Glucosio

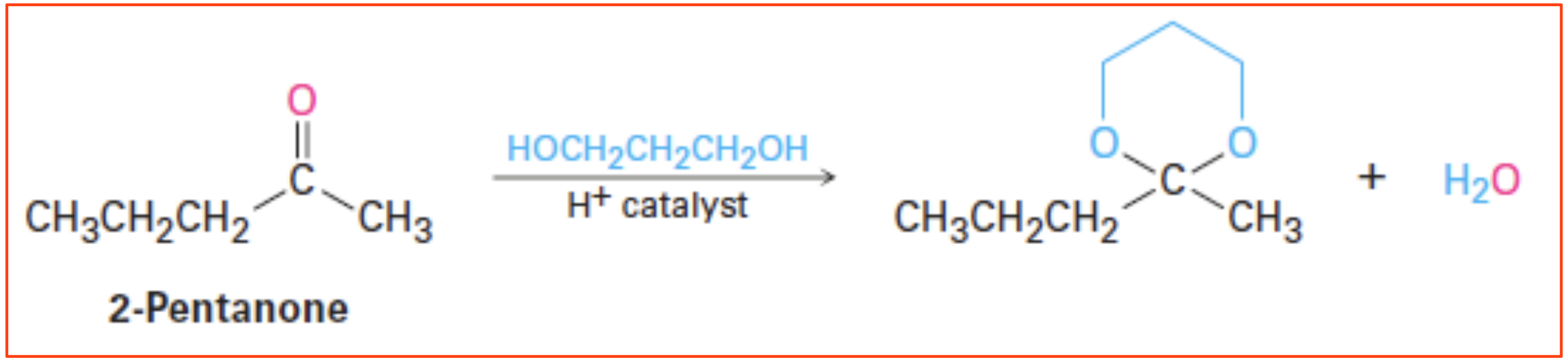


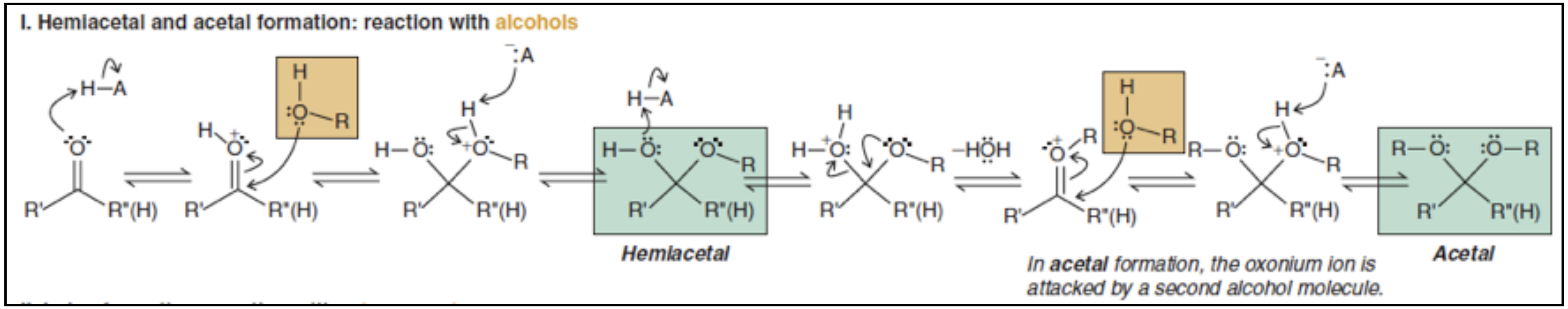
Gli atomi di C del Glu possono avere però anche altri destini metabolici

1. Biointesi di alcuni **aa**. Gli aa non essenziali sono ad esempio questi che possono derivare dal metabolismo del Glu
2. Sintesi di **fruttosio**
3. Sintesi di **ac.glucuronico**
4. Sintesi di tutti i **monosaccaridi derivati**, non semplici (che contengono gruppi amminici, gluppi solfato etc) che vanno a costituire le porzioni oligosaccaridiche nei glicolipidi, GAG e proteoglicani.

(2) Addizione nucleofila degli alcoli al gruppo carbonile: Formazione di acetali ciclico



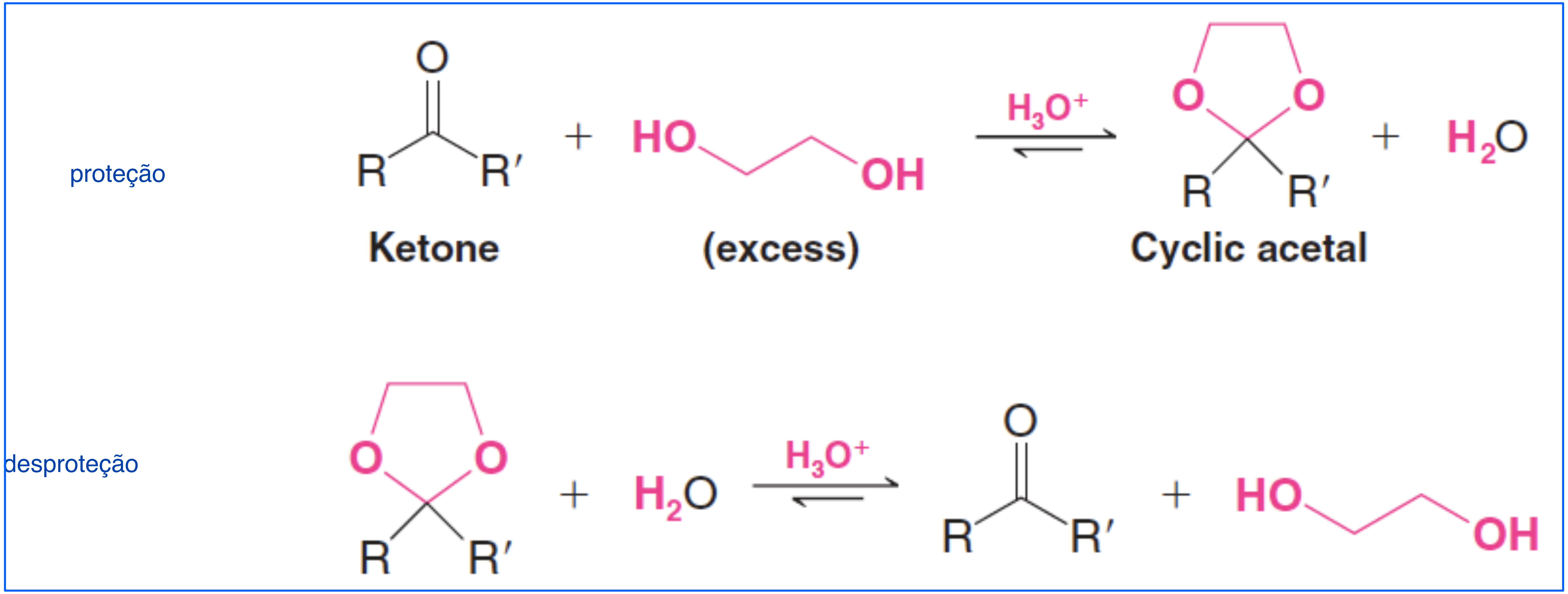



I. Hemiacetal and acetal formation: reaction with alcohols

*In **acetal** formation, the oxonium ion is attacked by a second alcohol molecule.*

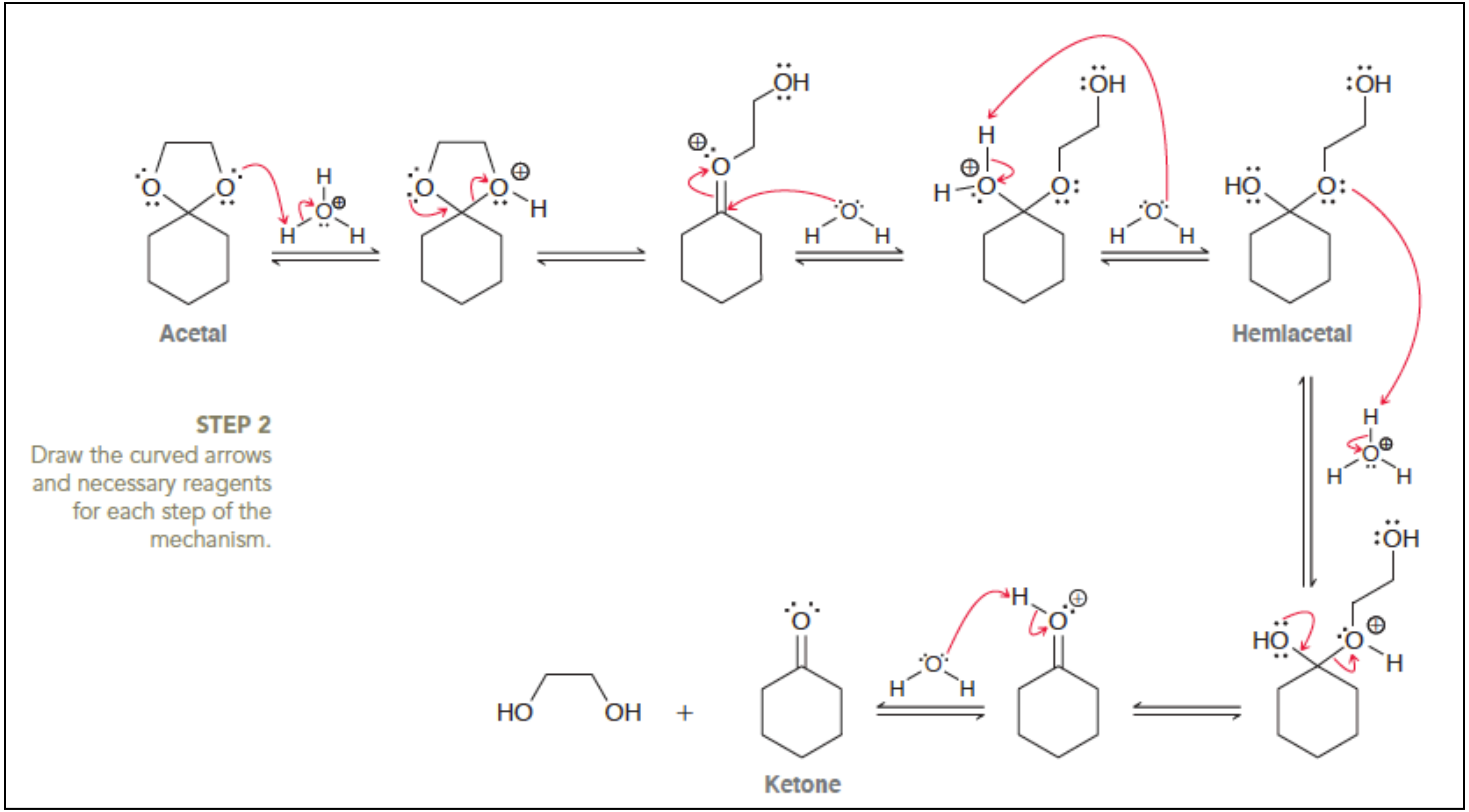
Acetali come gruppi di protezione del gruppo carbonile

Sebbene gli acetali siano idrolizzabili in aldeidi e chetoni in un ambiente acido acquoso, sono stabili nelle soluzioni di base.



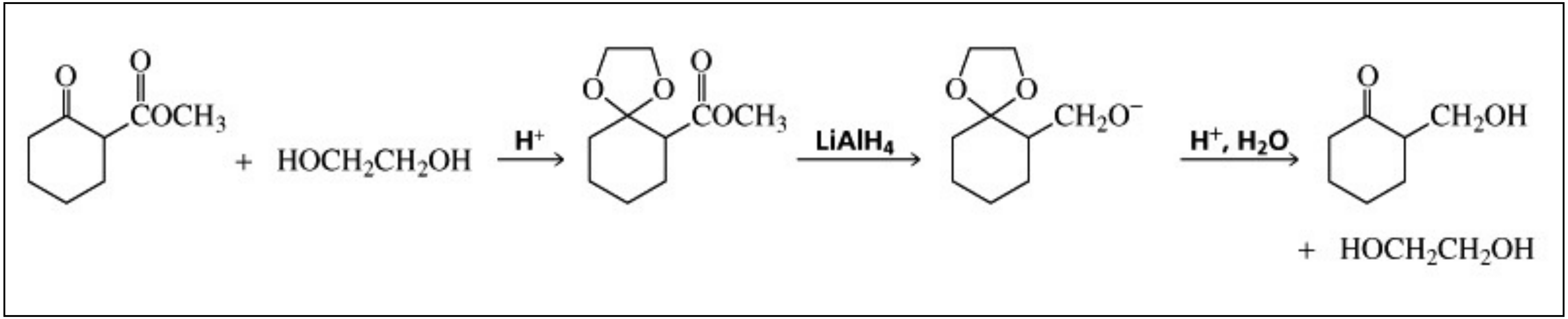
Gli acetali sono usati come gruppi protettori in un ambiente basico o nucleofilo

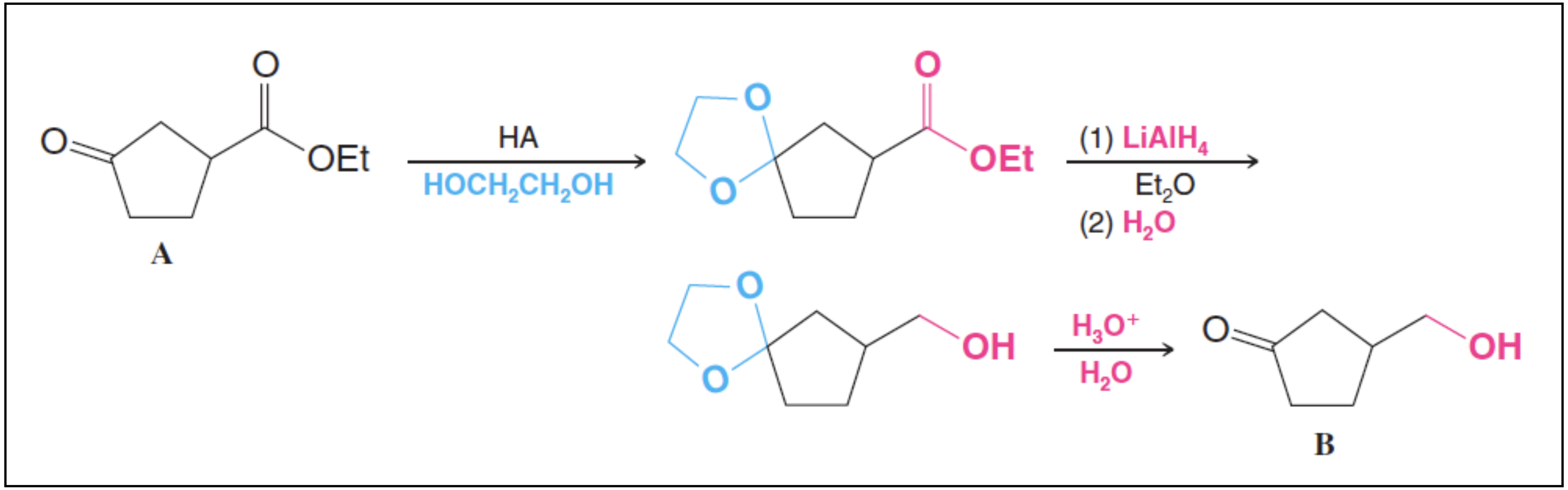
Idrolisi degli ACETALI in ambiente acido



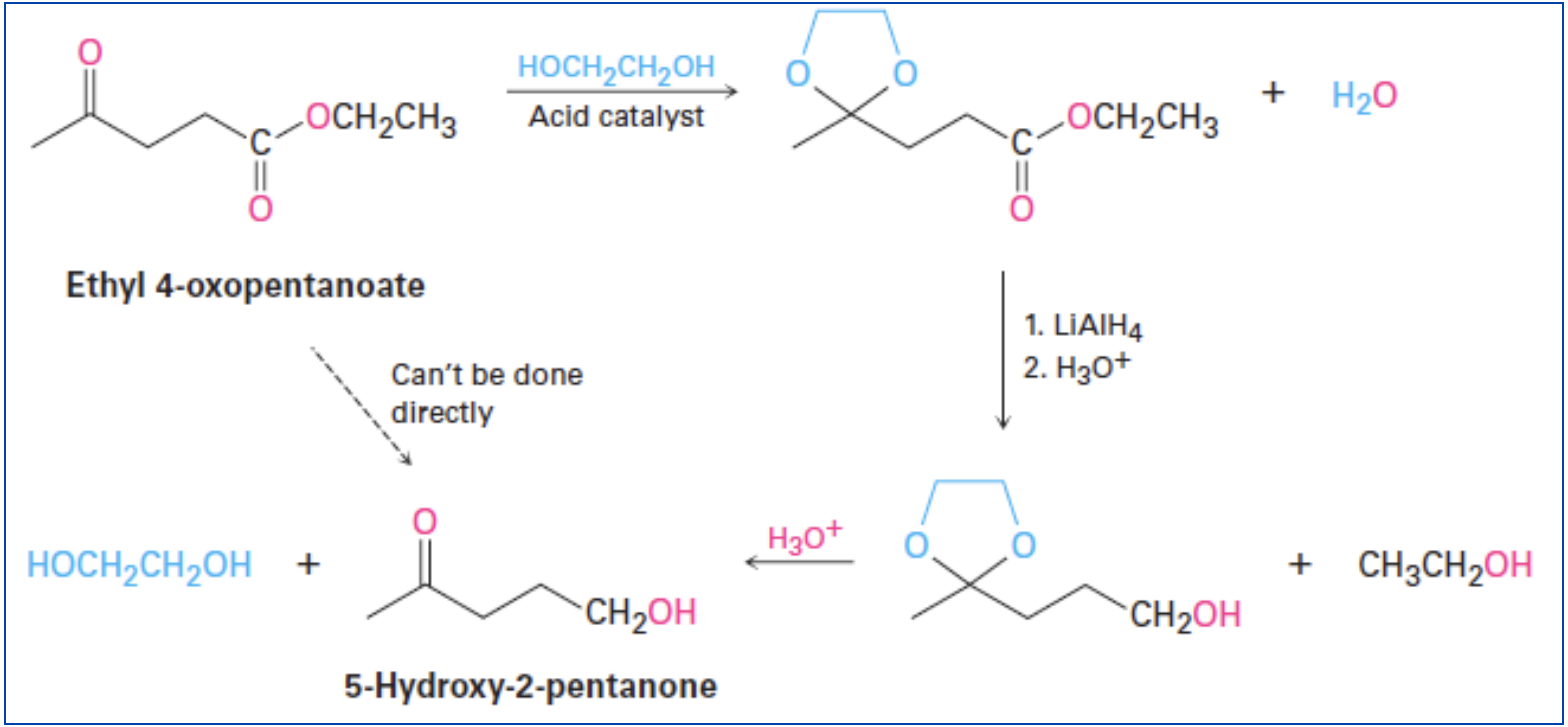
STEP 2
Draw the curved arrows and necessary reagents for each step of the mechanism.

Acetali come gruppi protettori degli aldeidi e chetoni in soluzioni basiche

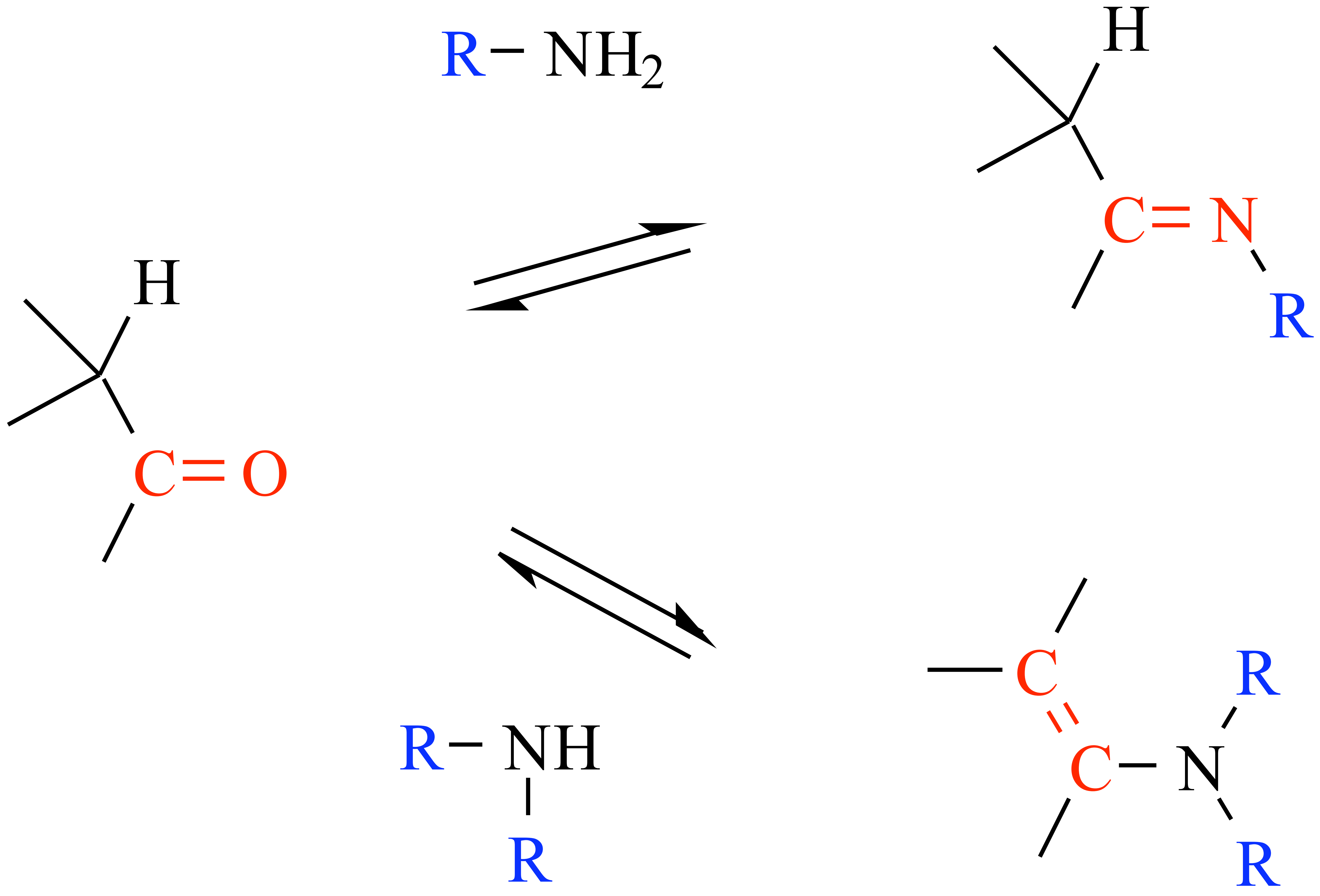




Acetali come gruppi protettori degli aldeidi e chetoni in soluzioni basiche



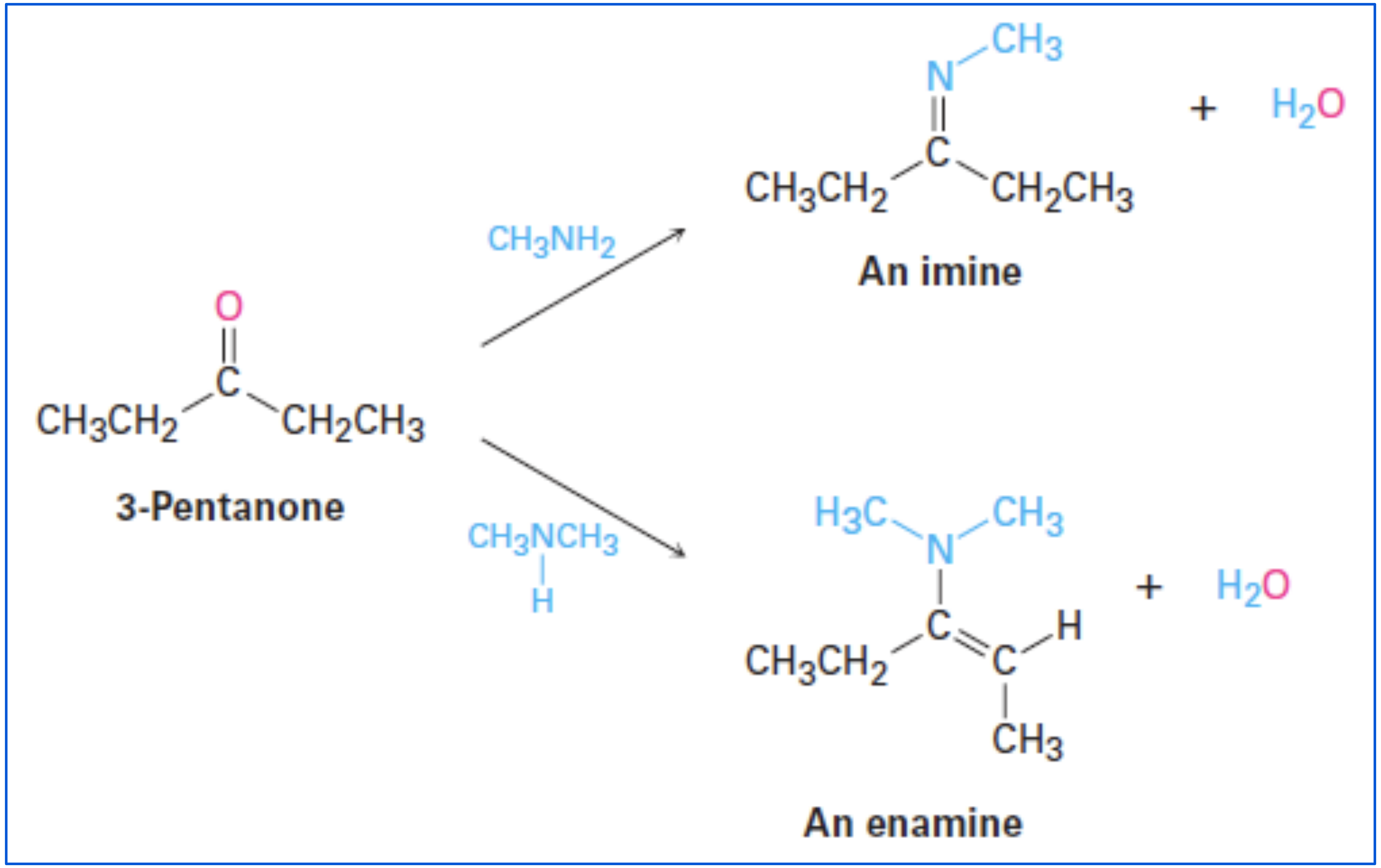
3) addizione Nucleofilica di ammine: Formazione di Immine e Enammine



IMMINA
Doppio legame
C=N

ENAMMINA
Doppio legame
C=C

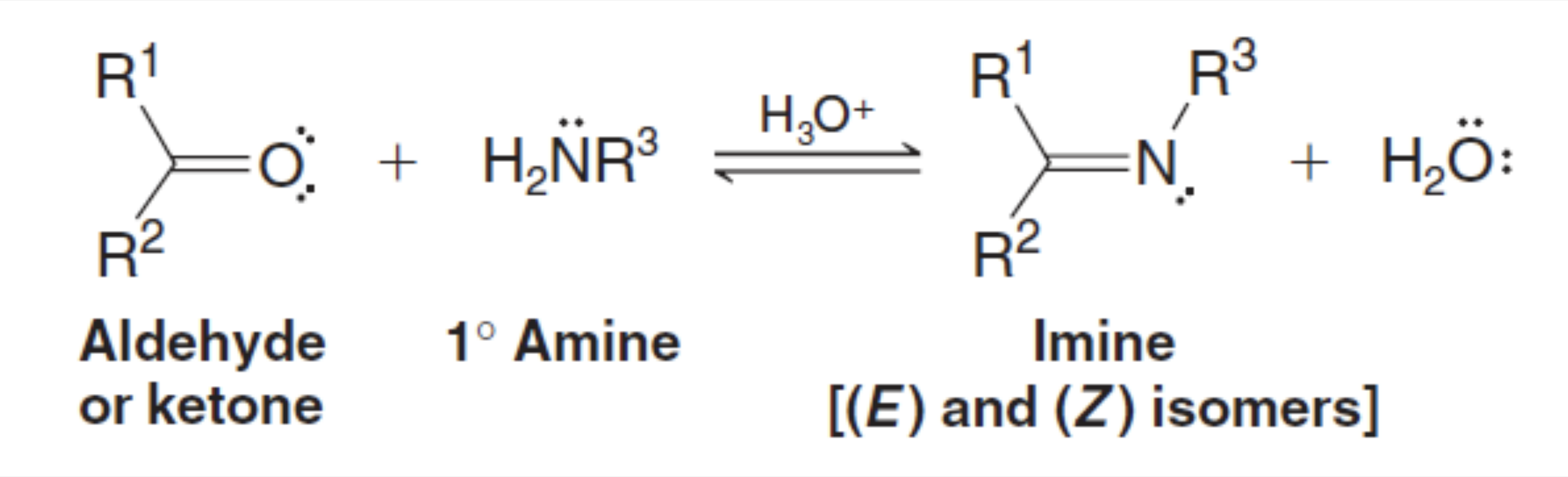
3) addizione Nucleofilica di ammine: Formazione di Immine e Enammine



3-Pentanone

An imine

An enamine

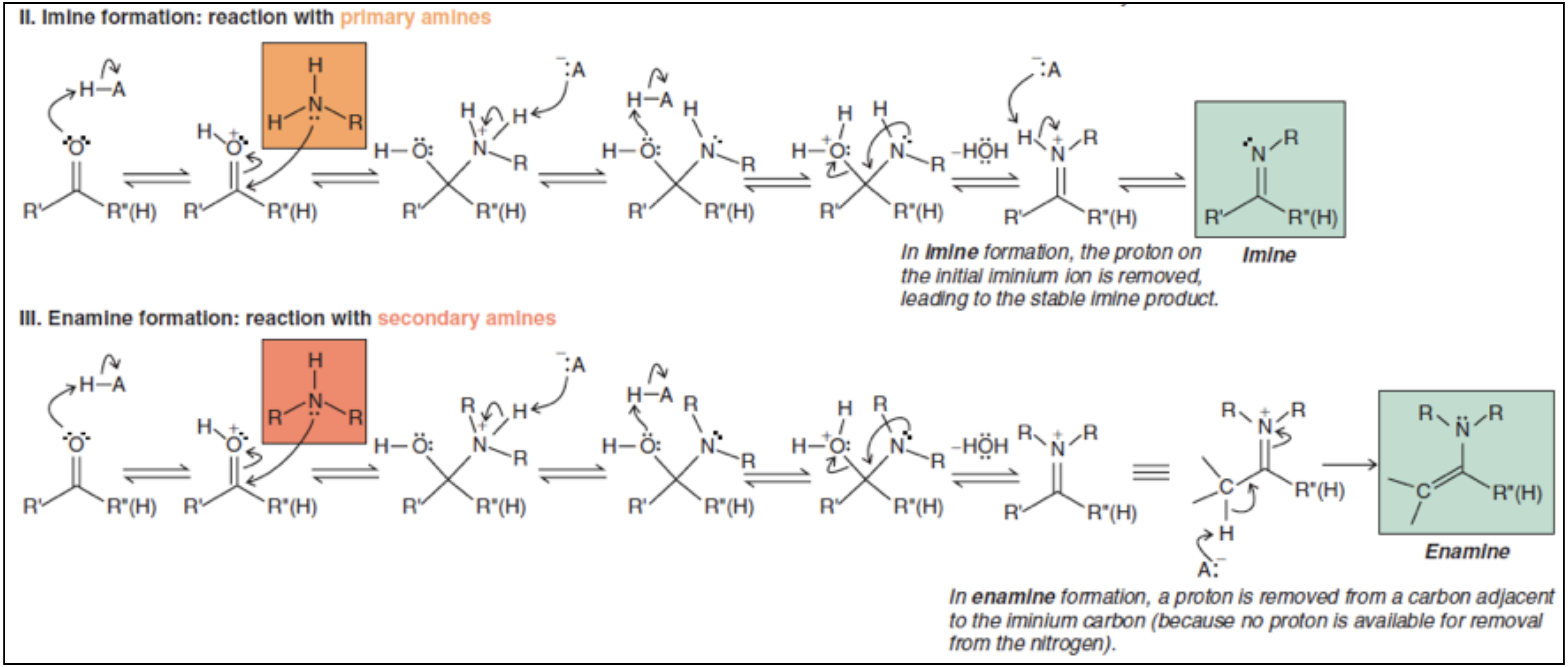


Aldehyde or ketone

1° Amine

Imine [(*E*) and (*Z*) isomers]

3) MECCANISMO addizione Nucleofilica di ammine: Formazione di Immine e Enammine

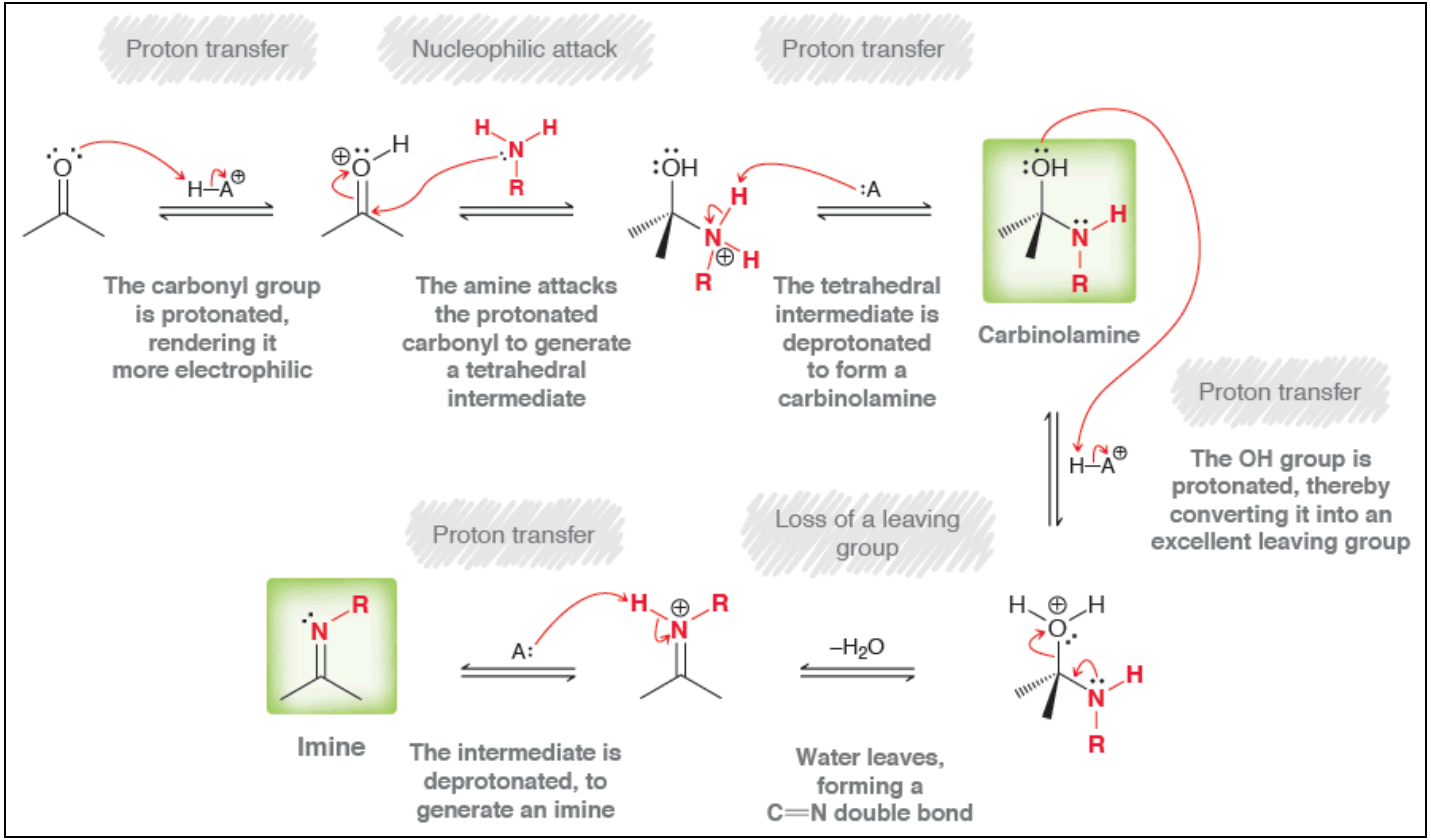

II. Imine formation: reaction with primary amines

In **imine** formation, the proton on the initial iminium ion is removed, leading to the stable imine product.

III. Enamine formation: reaction with secondary amines

In **enamine** formation, a proton is removed from a carbon adjacent to the iminium carbon (because no proton is available for removal from the nitrogen).

3) MECCANISMO addizione Nucleofilica di ammine: Formazione di Immine



Proton transfer

The carbonyl group is protonated, rendering it more electrophilic

Nucleophilic attack

The amine attacks the protonated carbonyl to generate a tetrahedral intermediate

Proton transfer

The tetrahedral intermediate is deprotonated to form a carbinolamine

Carbinolamine

Proton transfer

The OH group is protonated, thereby converting it into an excellent leaving group

Loss of a leaving group

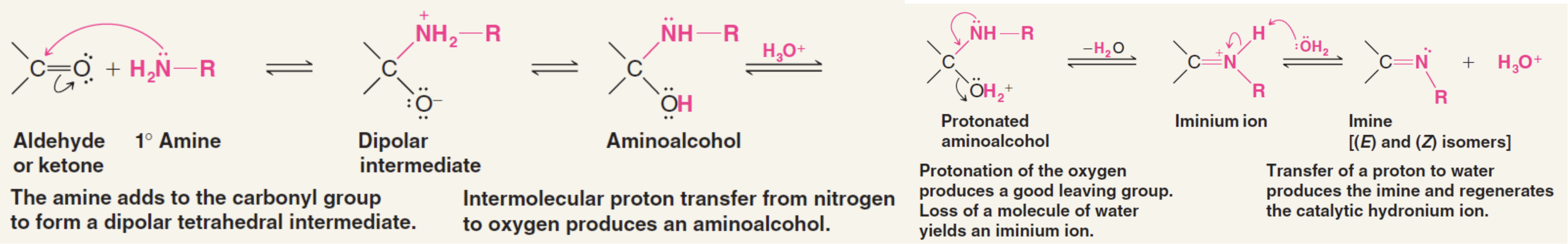
Water leaves, forming a C═N double bond

Proton transfer

The intermediate is deprotonated, to generate an imine

Imine

3) MECCANISMO addizione Nucleofilica di ammine: Formazione di Immine (miscela di isomeri E e Z)



Aldehyde or ketone

1° Amine

Dipolar intermediate

Aminoalcohol

Protonated aminoalcohol

Iminium ion

Imine [(*E*) and (*Z*) isomers]

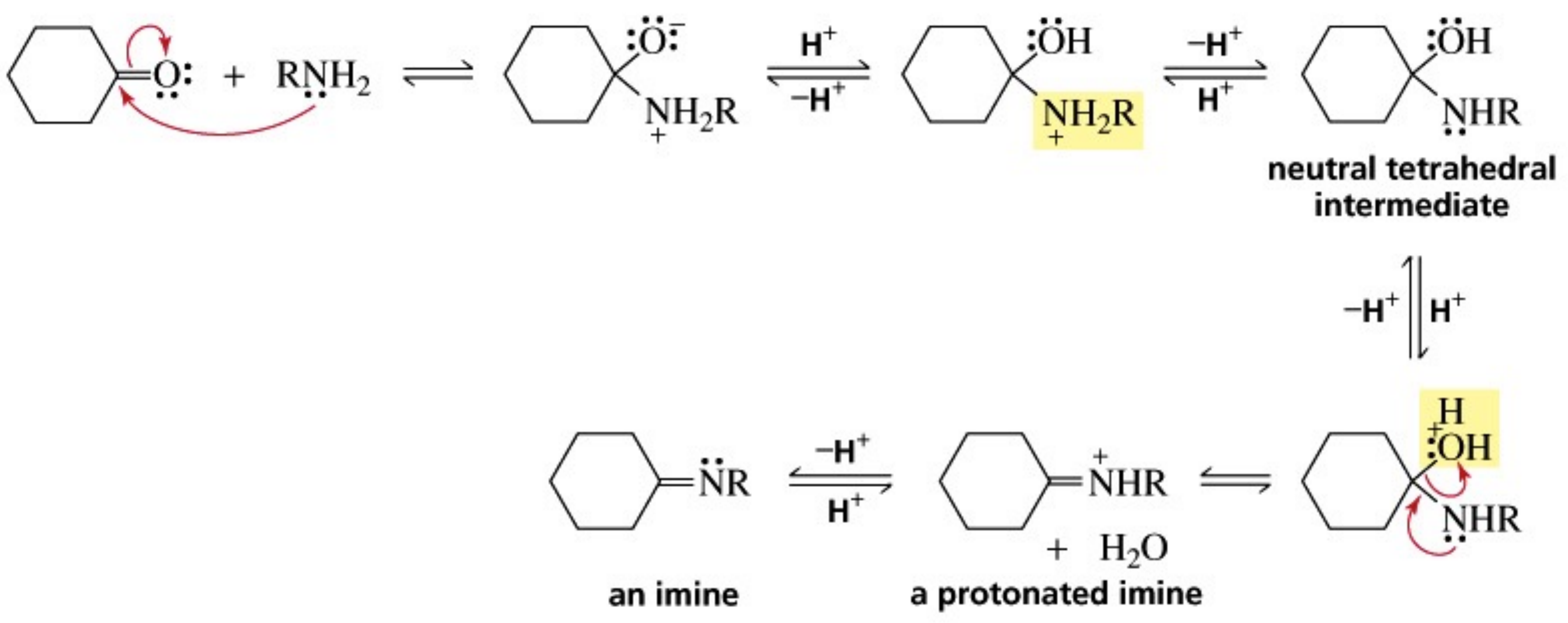
The amine adds to the carbonyl group to form a dipolar tetrahedral intermediate.

Intermolecular proton transfer from nitrogen to oxygen produces an aminoalcohol.

Protonation of the oxygen produces a good leaving group. Loss of a molecule of water yields an iminium ion.

Transfer of a proton to water produces the imine and regenerates the catalytic hydronium ion.

mechanism for imine formation

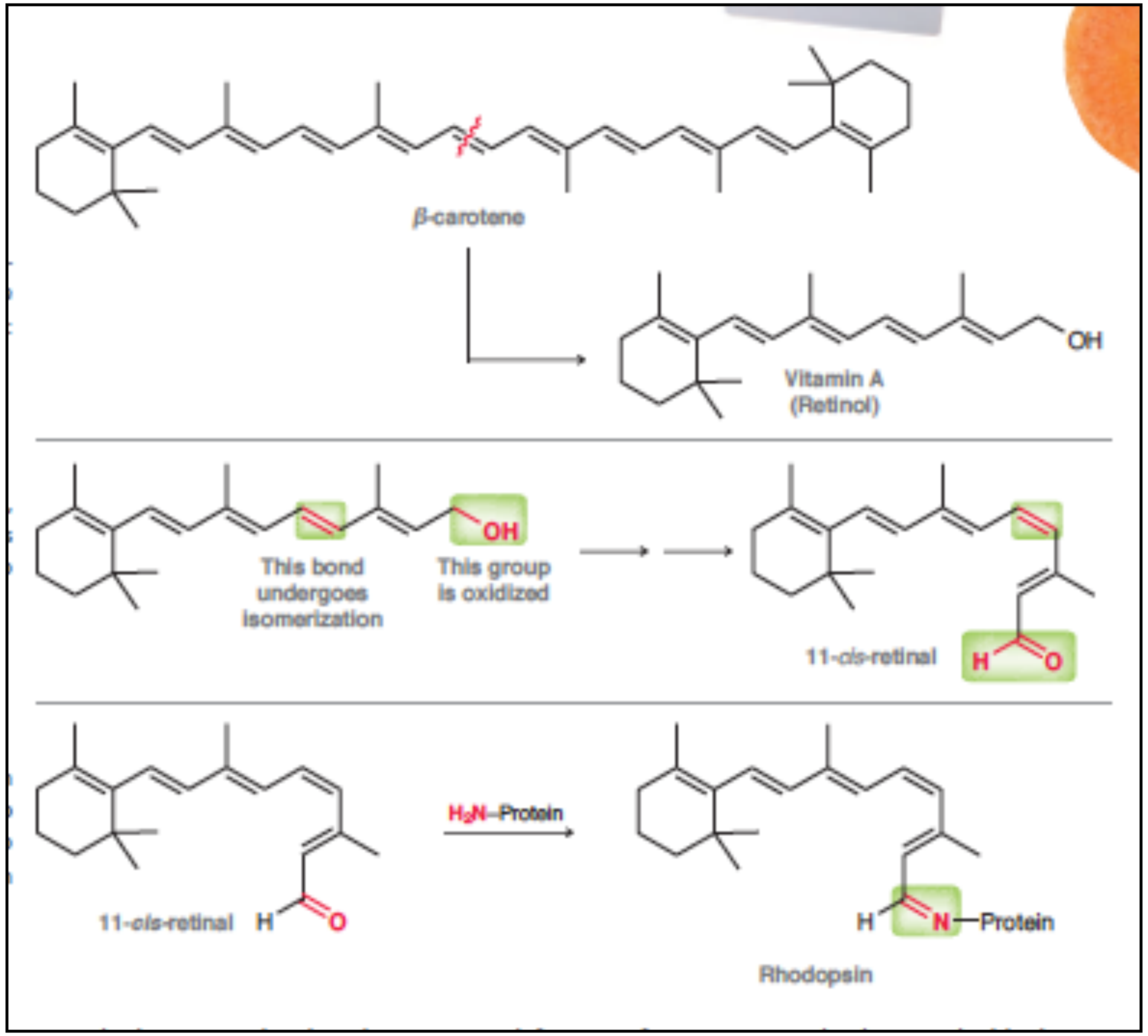


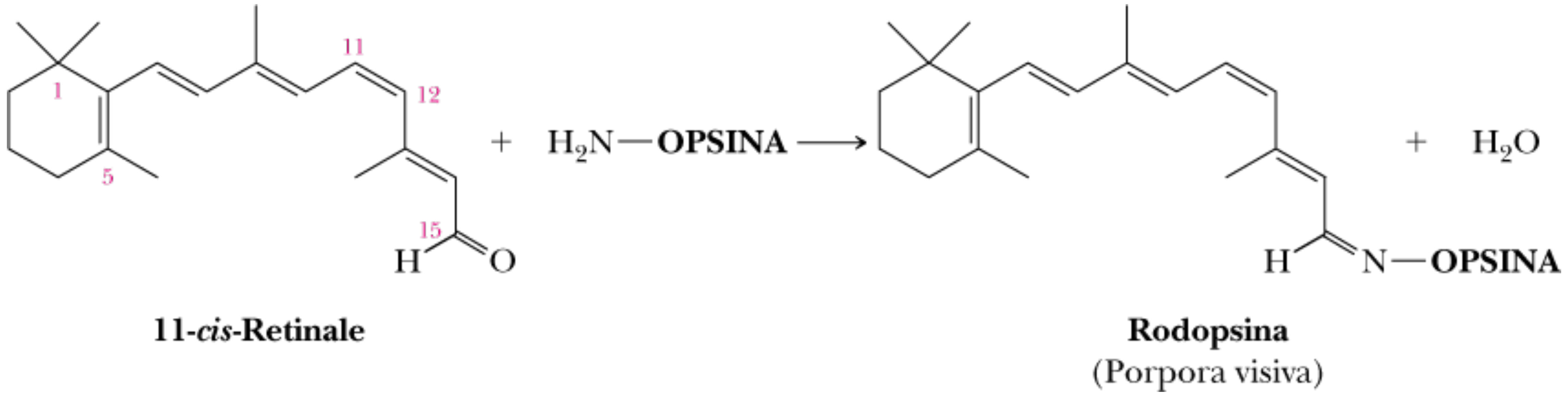
neutral tetrahedral intermediate

an imine

a protonated imine

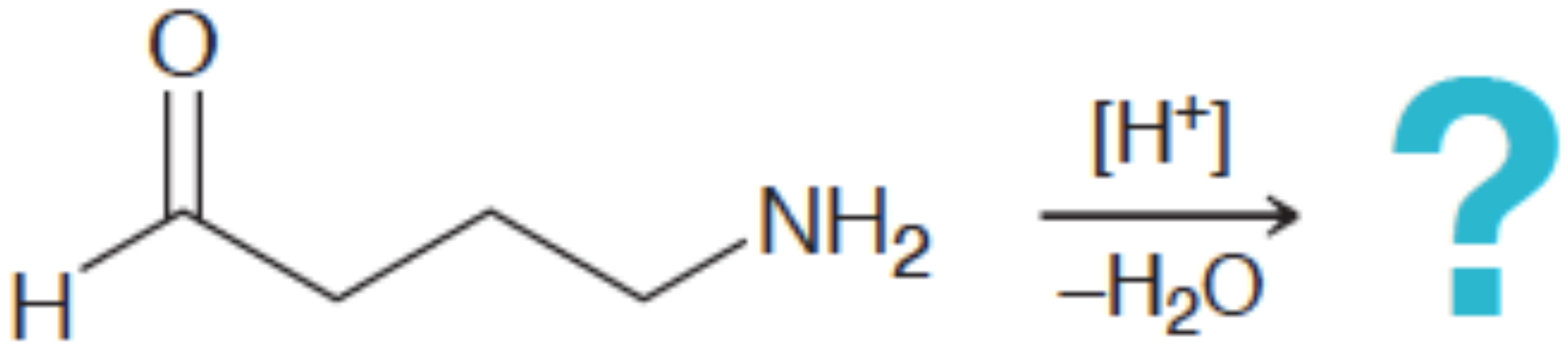
Beta-carotene e la vista



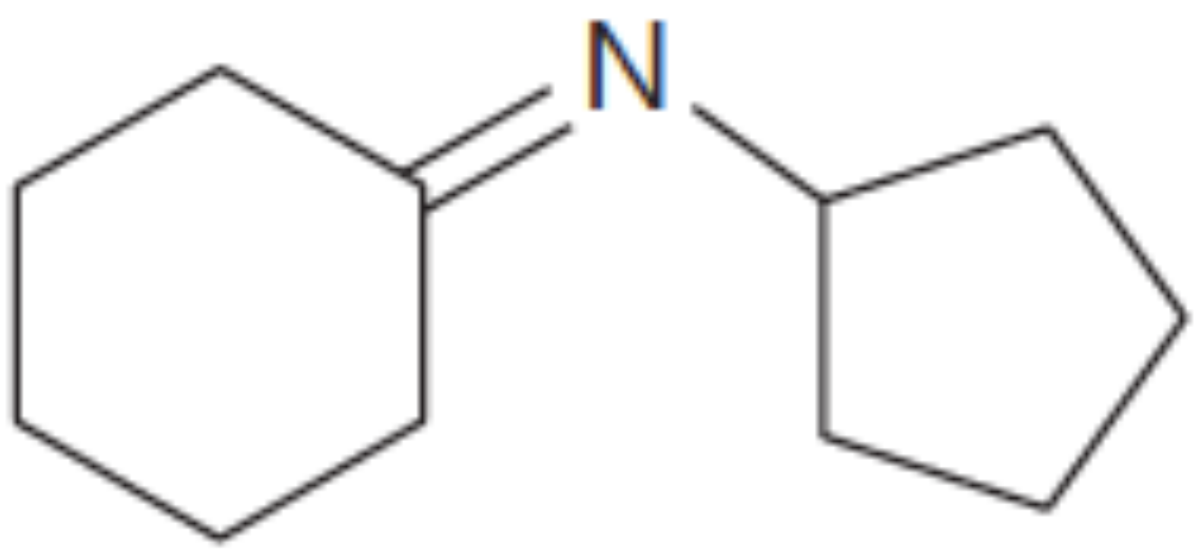


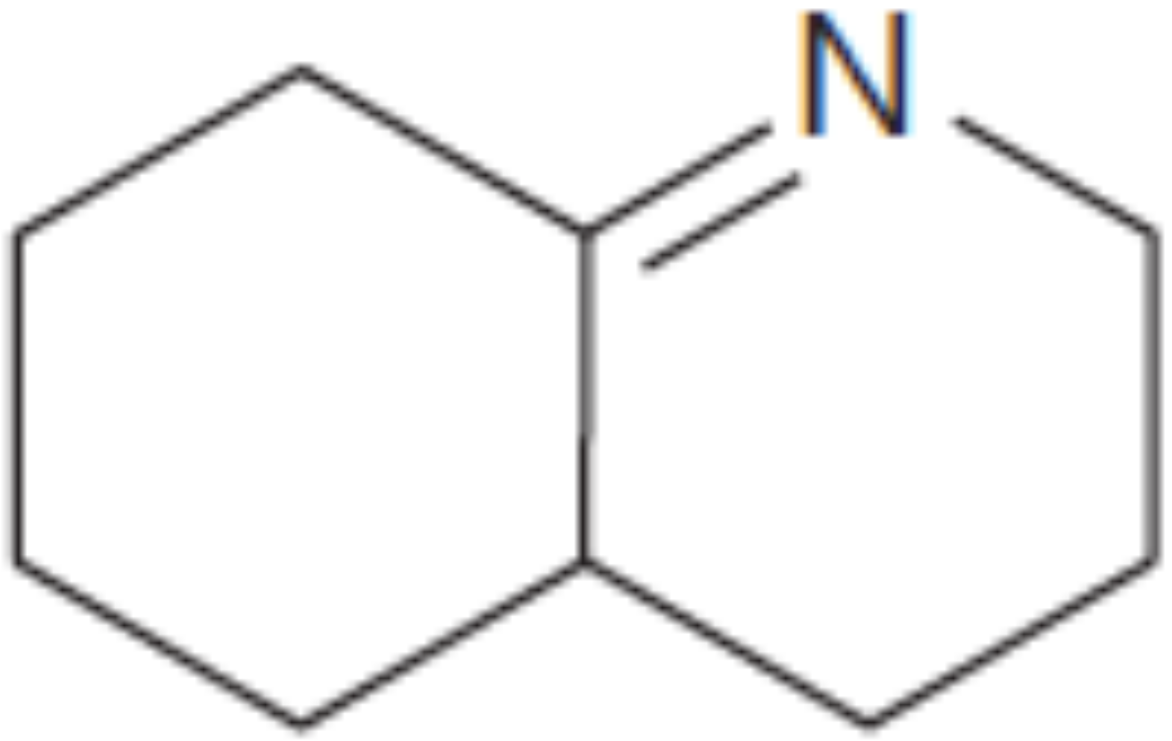
L’assorbimento di fotoni da parte della rodopsina provoca una isomerizzazione da cis a trans del doppio legame sul carbonio 11, con conseguente cambiamento della conformazione molecolare, che determina la generazione di un impulso nervoso, responsabile della visione nei mammiferi.

PROBLEMA: Prevedere il prodotto principale della seguente reazione intramolecolare

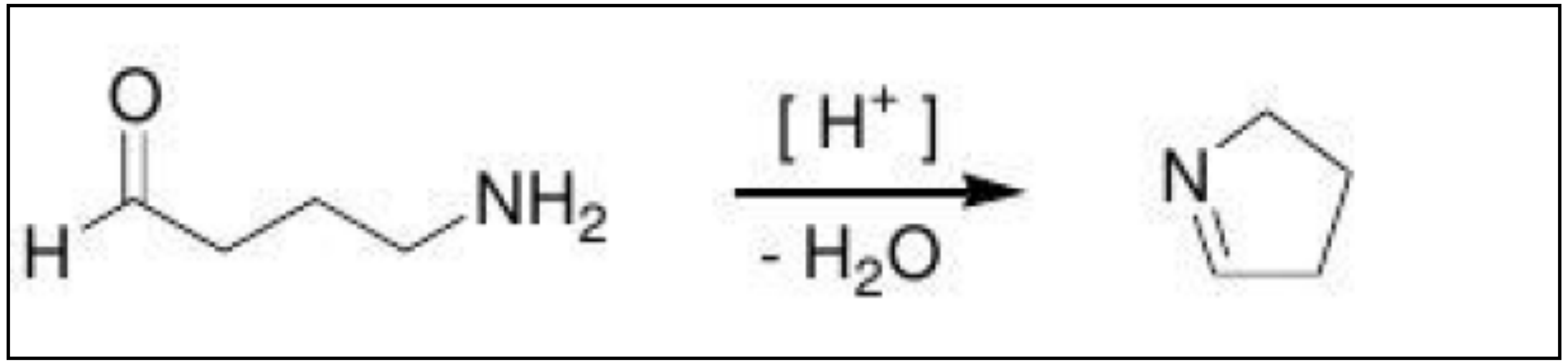


PROBLEMA: Indica i reagenti che useresti per ottenere ciascuna delle seguenti imine.

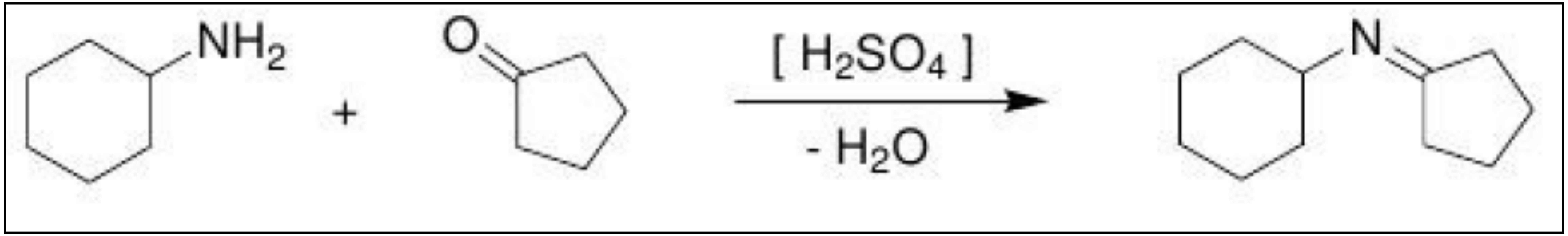


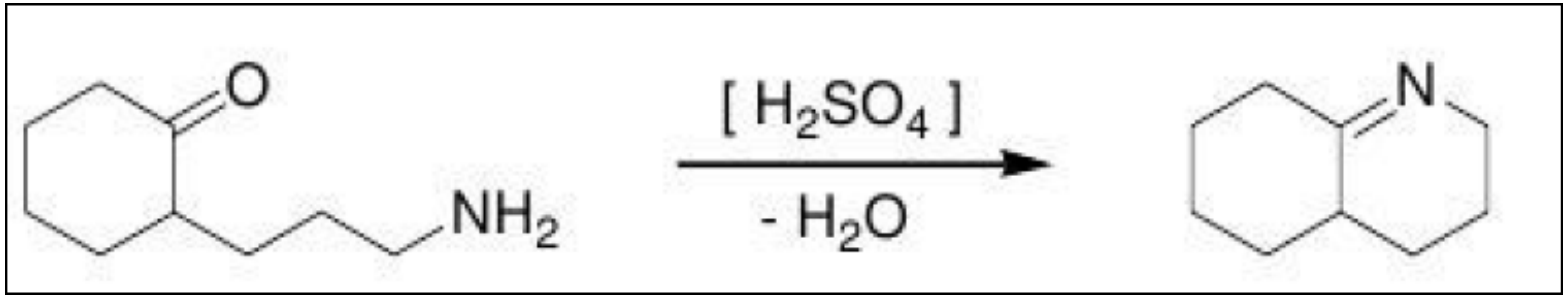


PROBLEMA: Prevedere il prodotto principale della seguente reazione intramolecolare

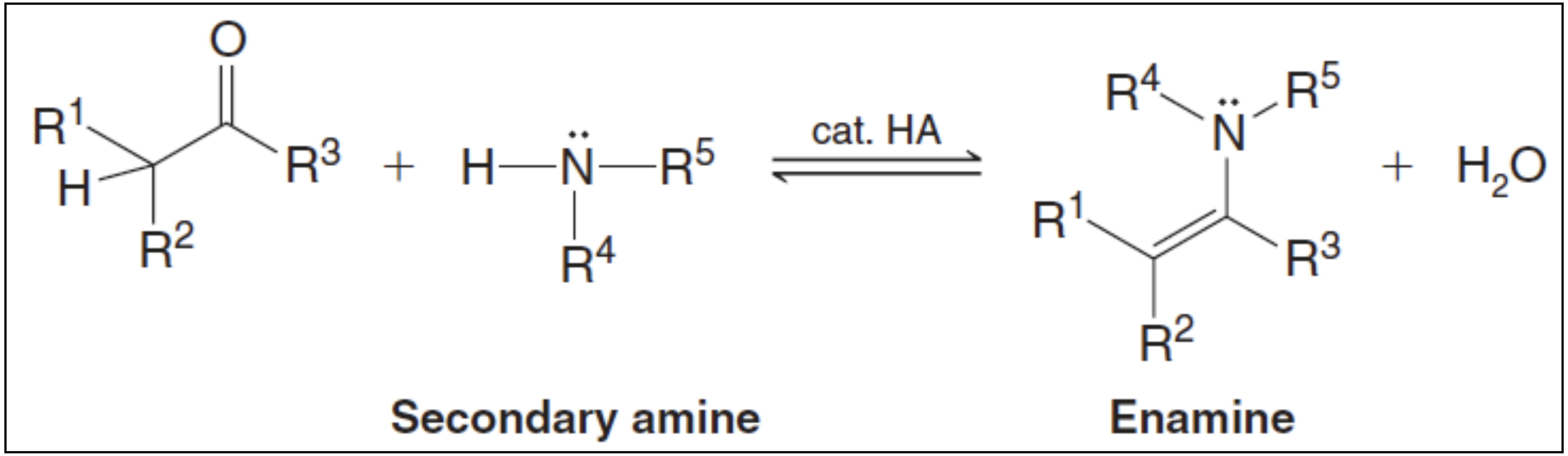


PROBLEMA: Indica i reagenti che useresti per ottenere ciascuna delle seguenti imine.





3) addizione Nucleofilica di ammine: Formazione di Enammine



Aldeidi e chetoni reagiscono. Con ammine secondarie per forme ENAMINE

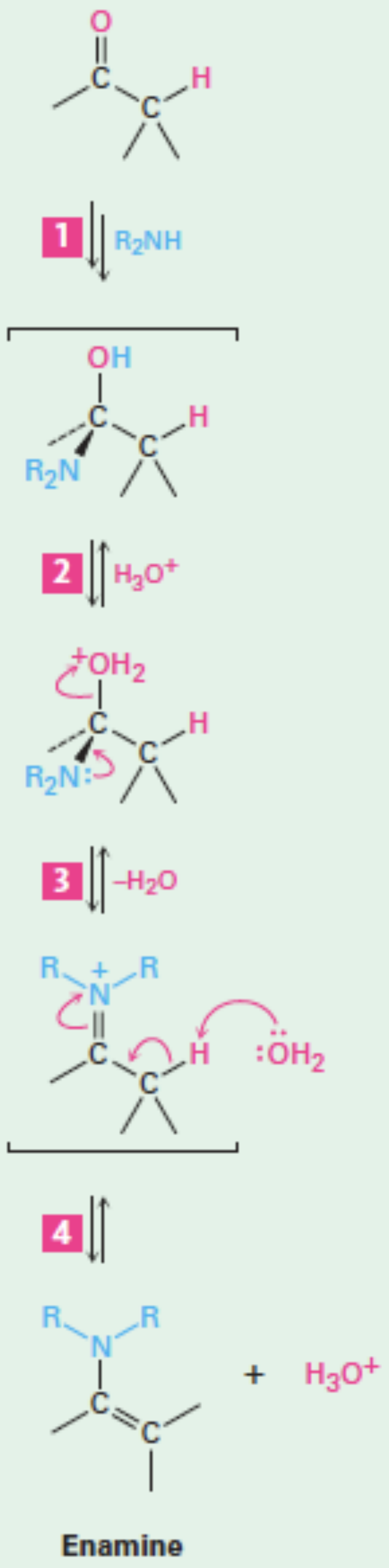
3) MECCANISMO: addizione Nucleofilica di ammine per la Formazione di Enammine

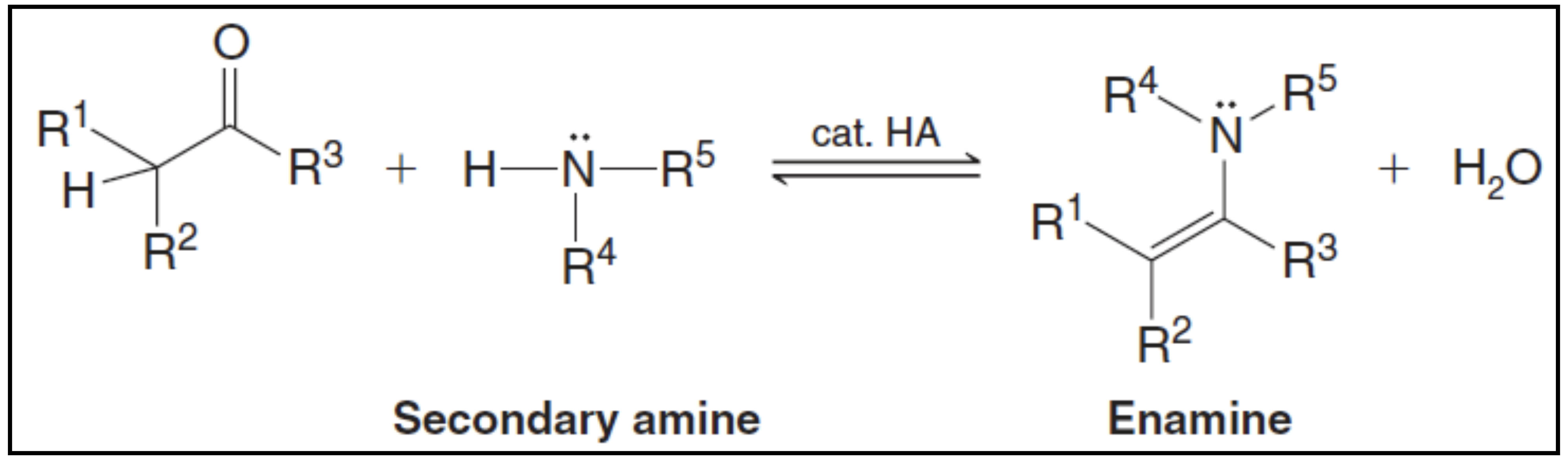
1 Nucleophilic addition of a secondary amine to the ketone or aldehyde, followed by proton transfer from nitrogen to oxygen, yields an intermediate carbinolamine in the normal way.

2 Protonation of the hydroxyl by acid catalyst converts it into a better leaving group.

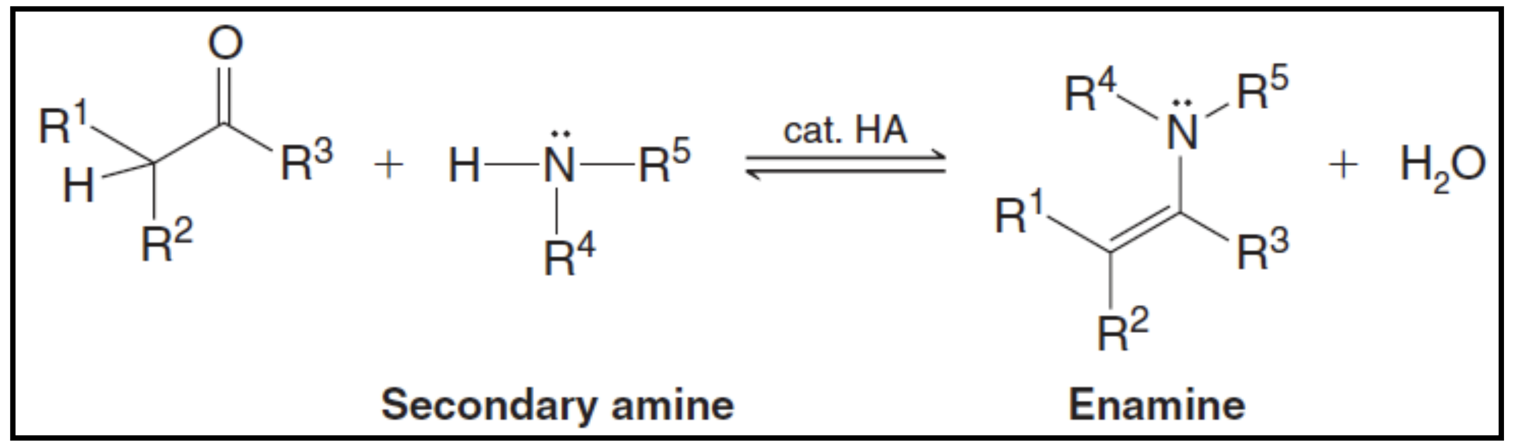
3 Elimination of water by the lone-pair electrons on nitrogen then yields an intermediate iminium ion.

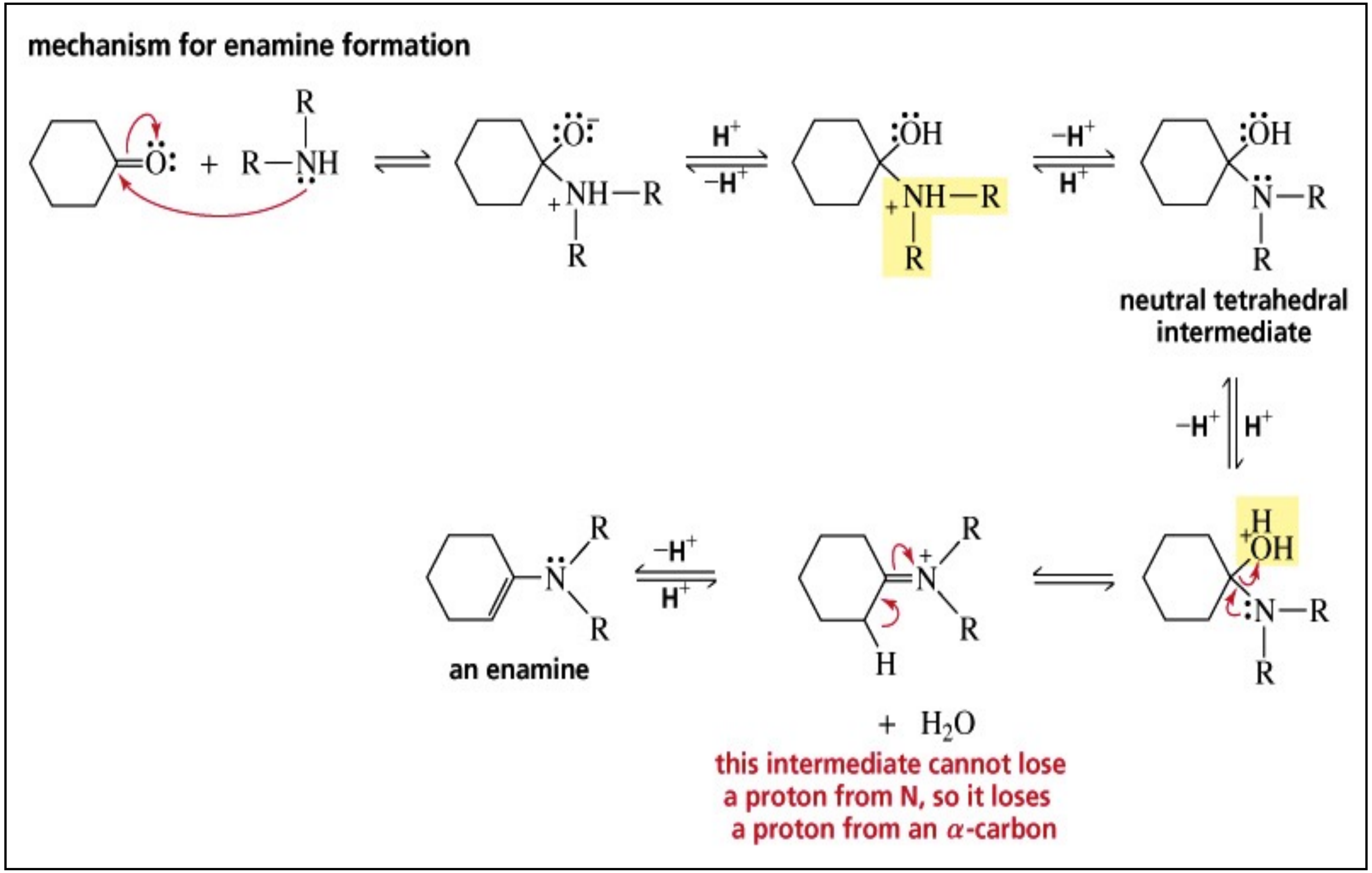
4 Loss of a proton from the alpha carbon atom yields the enamine product and regenerates the acid catalyst.





3) MECCANISMO: addizione Nucleofilica di ammine per la Formazione di Enammine



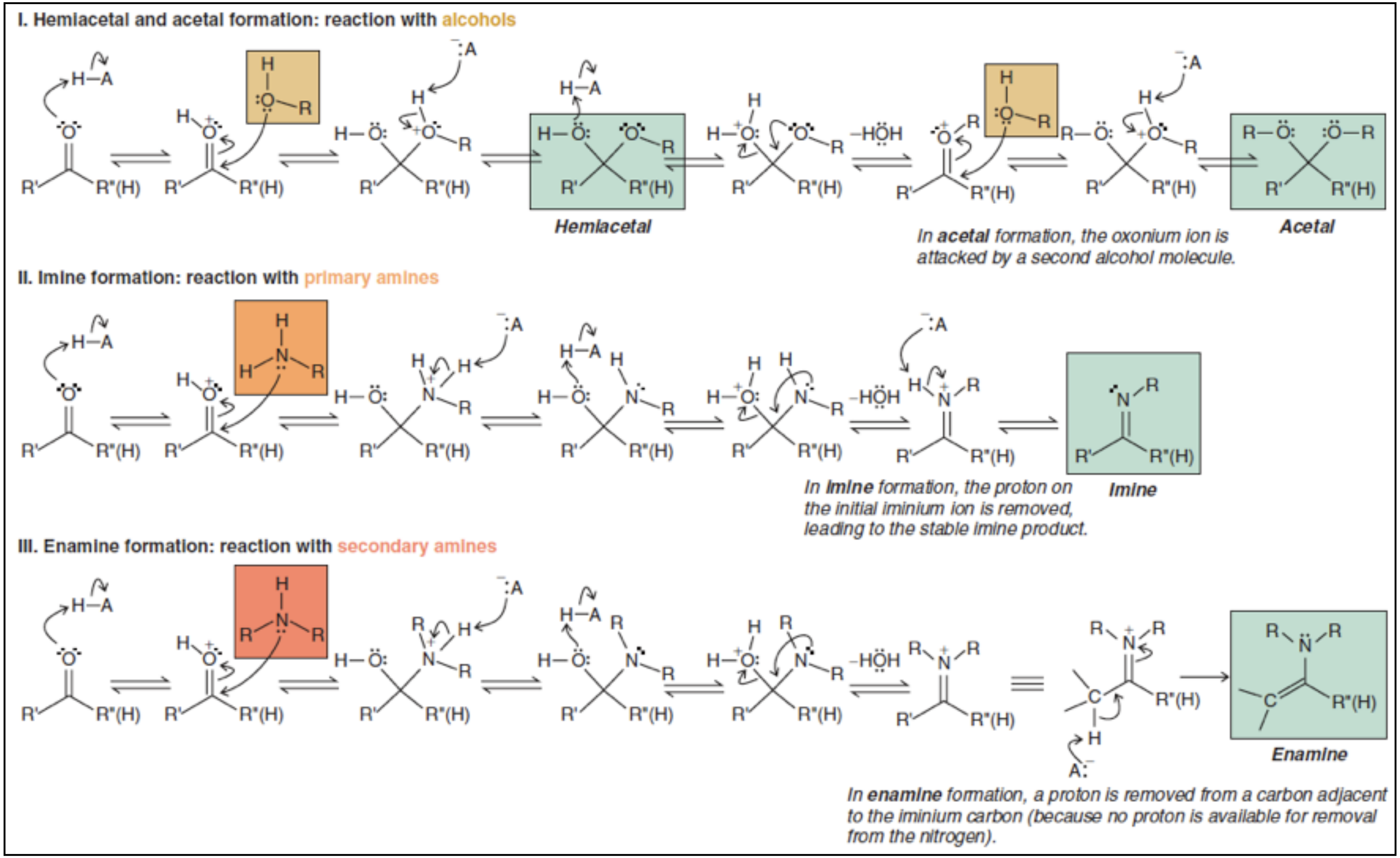

mechanism for enamine formation

neutral tetrahedral intermediate

an enamine

this intermediate cannot lose a proton from N, so it loses a proton from an α-carbon

3) MECCANISMi per la formazione di Emiacetali, Acetali, Immine ed enammine



I. Hemiacetal and acetal formation: reaction with alcohols

*In **acetal** formation, the oxonium ion is attacked by a second alcohol molecule.*

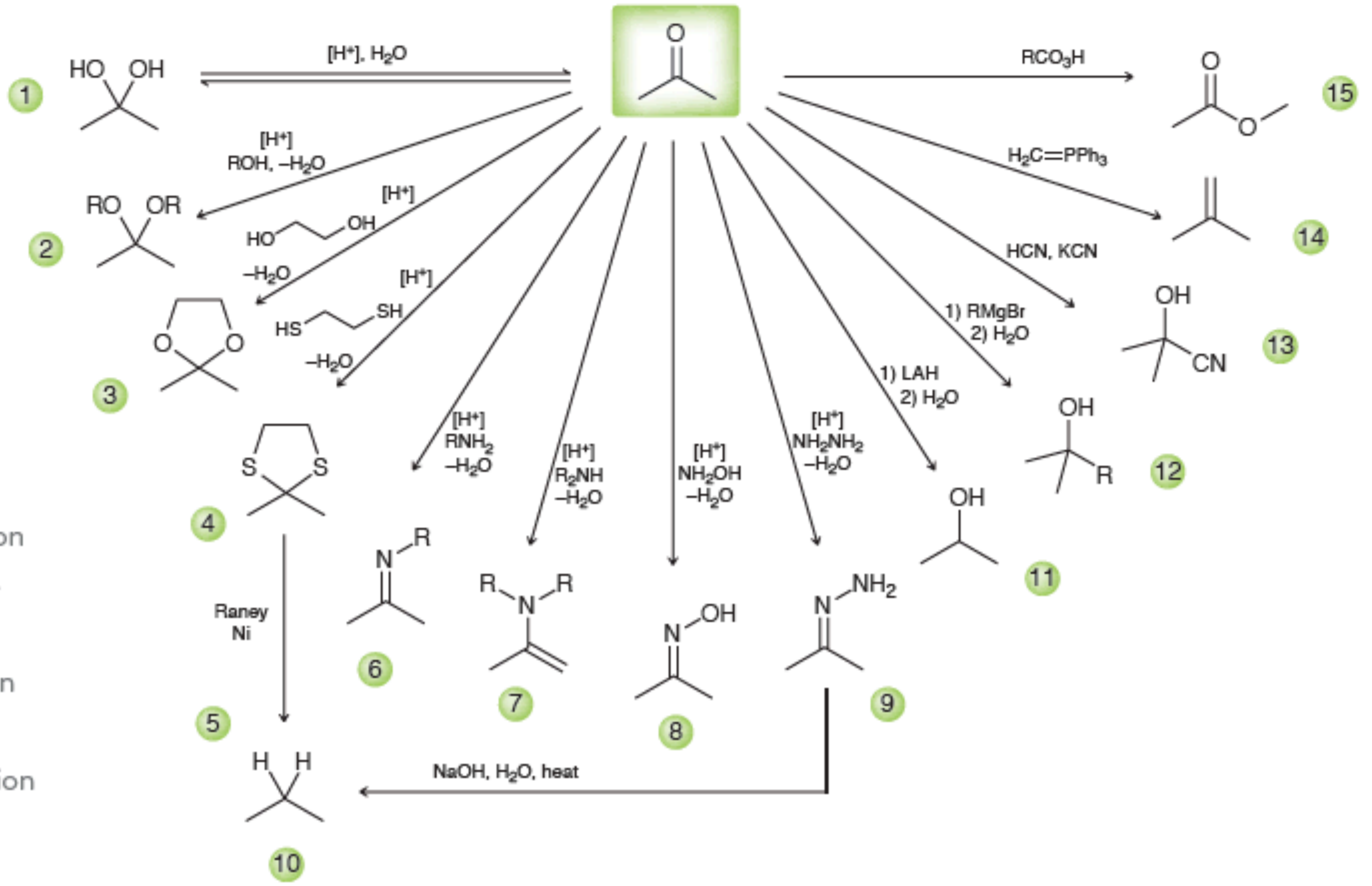
II. Imine formation: reaction with primary amines

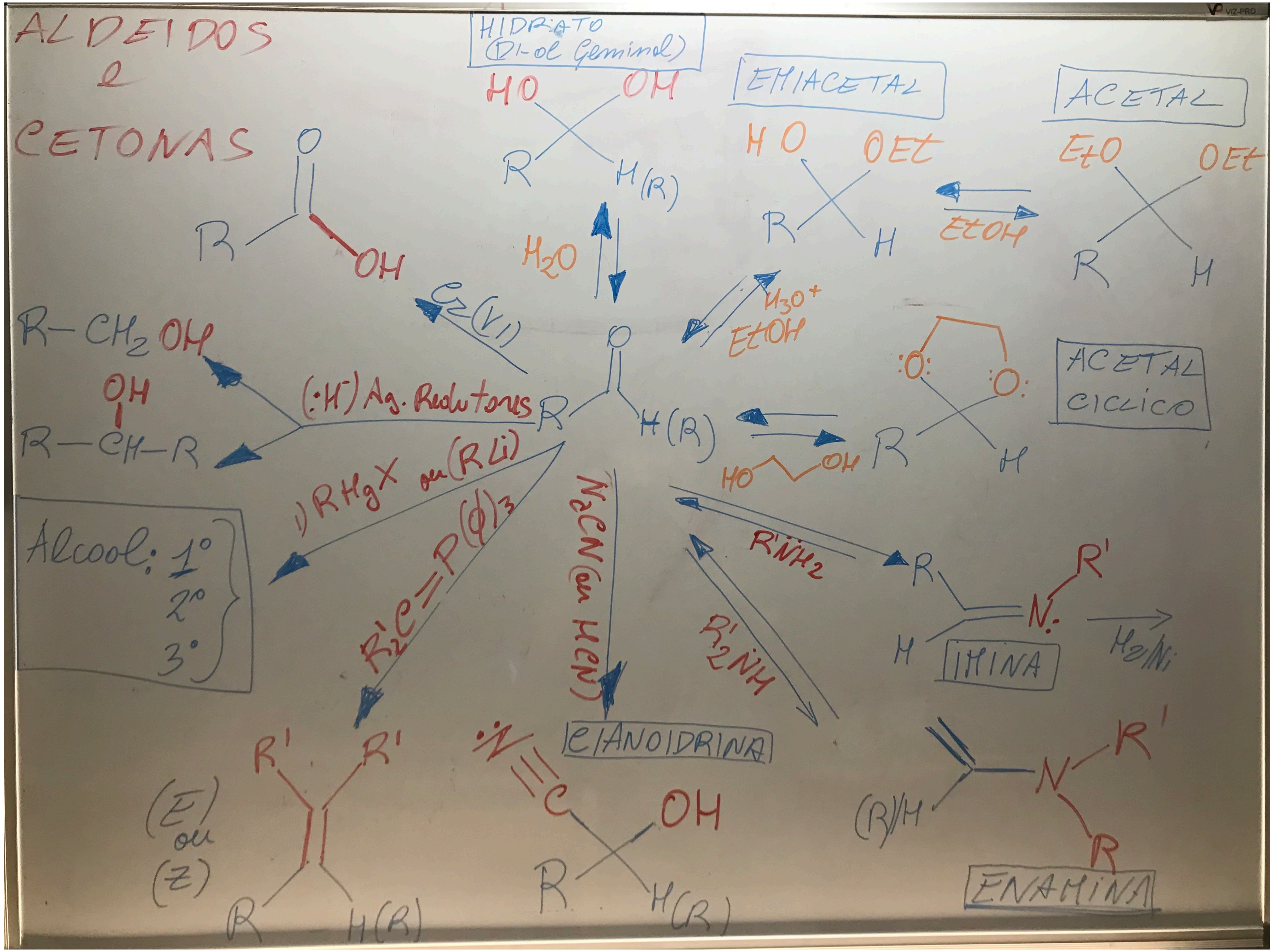
*In **imine** formation, the proton on the initial iminium ion is removed, leading to the stable imine product.*

III. Enamine formation: reaction with secondary amines

*In **enamine** formation, a proton is removed from a carbon adjacent to the iminium carbon (because no proton is available for removal from the nitrogen).*

1. Hydrate Formation
2. Acetal Formation
3. Cyclic Acetal Formation
4. Cyclic Thioacetal Formation
5. Desulfurization
6. Imine Formation
7. Enamine Formation
8. Oxime Formation
9. Hydrazone Formation
10. Wolff-Kishner Reduction
11. Reduction of a Ketone
12. Grignard Reaction
13. Cyanohydrin Formation
14. Wittig Reaction
15. Baeyer-Villiger Oxidation

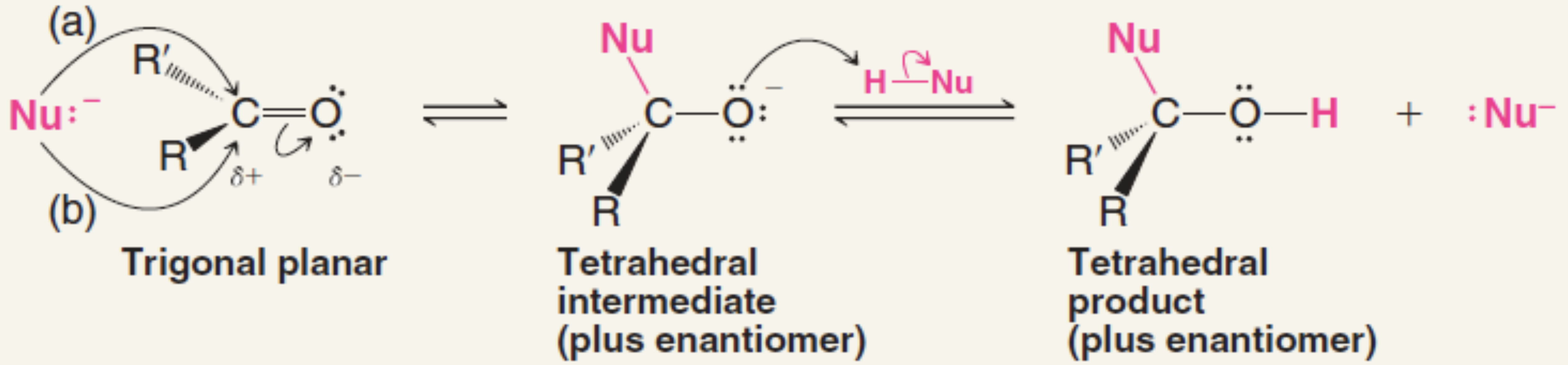



ALDEIDOS
e
CETONAS
HIDRATO
(Di-ol Geminal)
HO OH
R H(R)
H2O
EMIACETAL
HO OEt
R H
EtOH
ACETAL
EtO OEt
R H
H3O+
EtOH
ACETAL
CICLICO
:O: :O:
R H
HO OH
O
R OH
Cr(VI)
O
R H(R)
R—CH2OH
OH
R—CH—R
(:H⁻) Ag. Redutores
1) RMgX ou (RLi)
Alcool: 1°
2°
3°
R'2C=P(ϕ)3
N2CN (ou HCN)
R'NH2
R'2NH
R
N:
R'
H
IMINA
H2/Ni
(R)/H
N
R'
R
ENAMINA
R' R'
(E)
ou
(Z)
R H(R)
:N≡C OH
R H(R)
CIANOIDRINA

Reazioni di addizione nucleofila al gruppo carbonile
Con un nucleofilo FORTE (Carico negativamente)

Some negatively charged nucleophiles

- $H\ddot{\underset{..}{O}}:^-$ (hydroxide ion)
- $H:^-$ (hydride ion)
- $R_3C:^-$ (a carbanion)
- $R\ddot{\underset{..}{O}}:^-$ (an alkoxide ion)
- $N{\equiv}C:^-$ (cyanide ion)



In this step the nucleophile forms a bond to the carbon by donating an electron pair to the top or bottom face of the carbonyl group [path (a) or (b)]. An electron pair shifts out to the oxygen.

In the second step the alkoxide oxygen, because it is strongly basic, removes a proton from H—Nu or some other acid.

Reazioni di addizione nucleofila al gruppo carbonile
Con un nucleofilo FORTE (Carico negativamente)

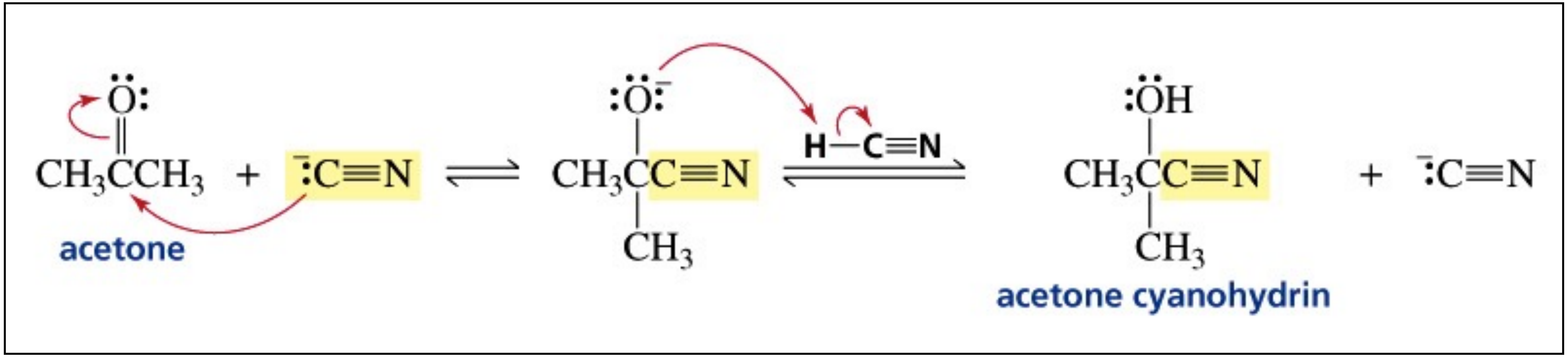
4) Reazione con cianuro di idrogeno, acido cianidrico (HCN) o NaCN

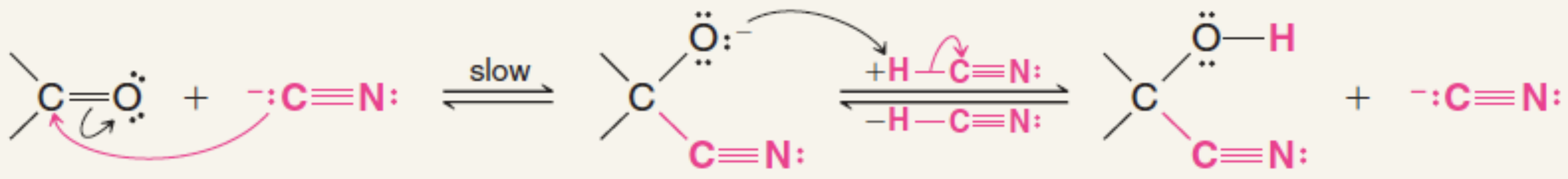
5) Reazione di Wittig: $R_2C{=}P(Ph)_3$

6) Aggiunta di un reagente Grignard: RMgX o RLi

7) Reazione dell'anione acetiluro (base coniugata dell'acetilene): $RCC{:}^- \ Na^+$

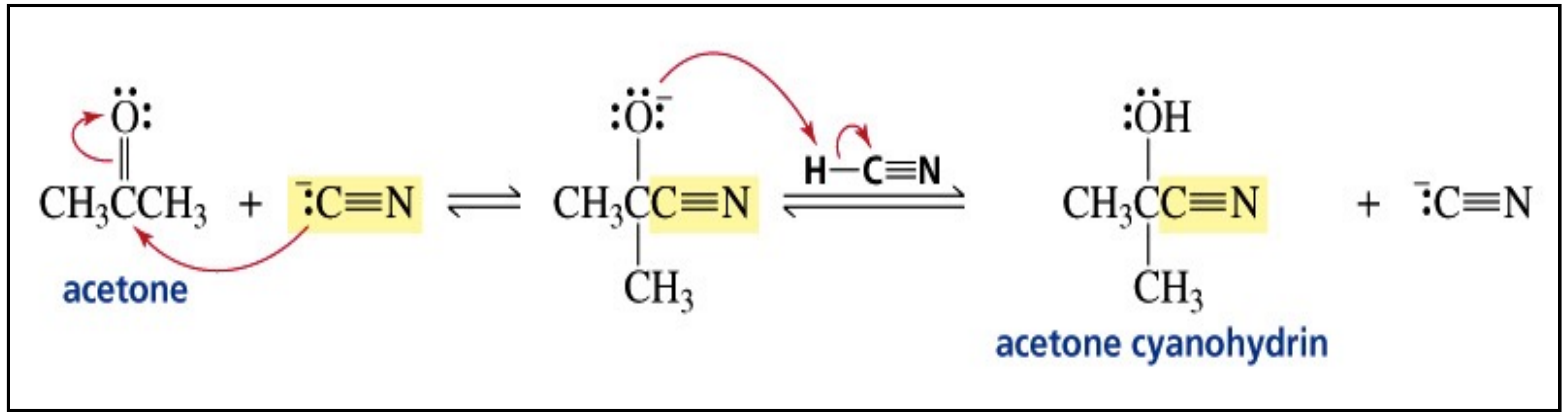
FORMAZIONE DELLA CIANOIDRINA



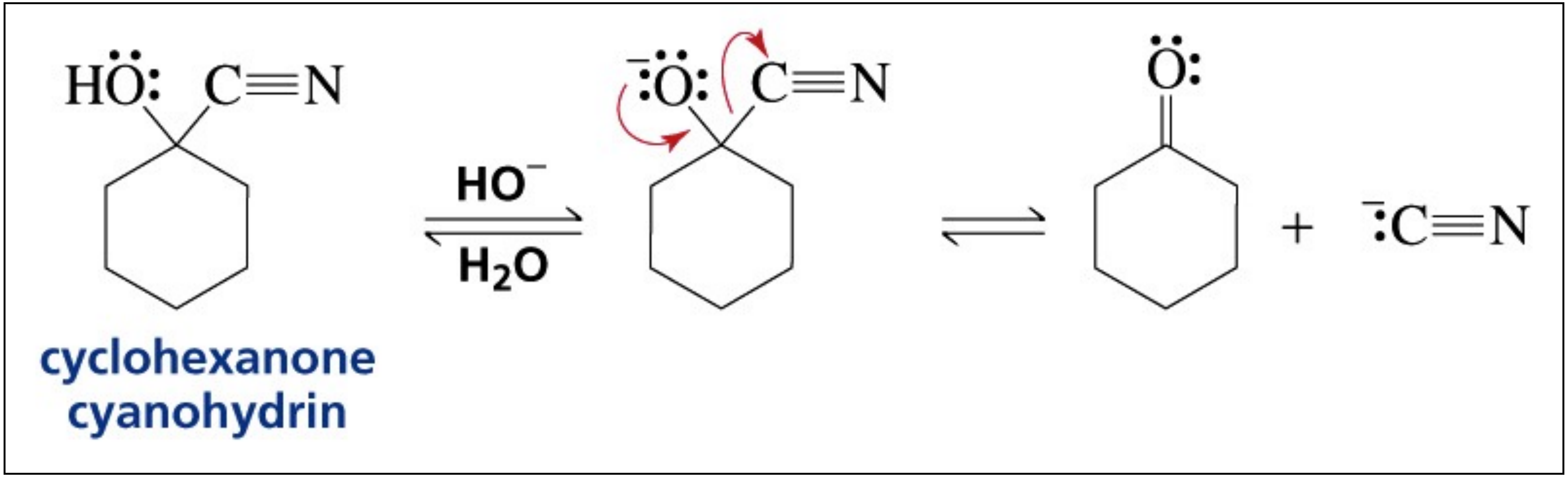


Great care must be taken when working with hydrogen cyanide due to its high toxicity and volatility. Reactions involving HCN must be conducted in an efficient fume hood.

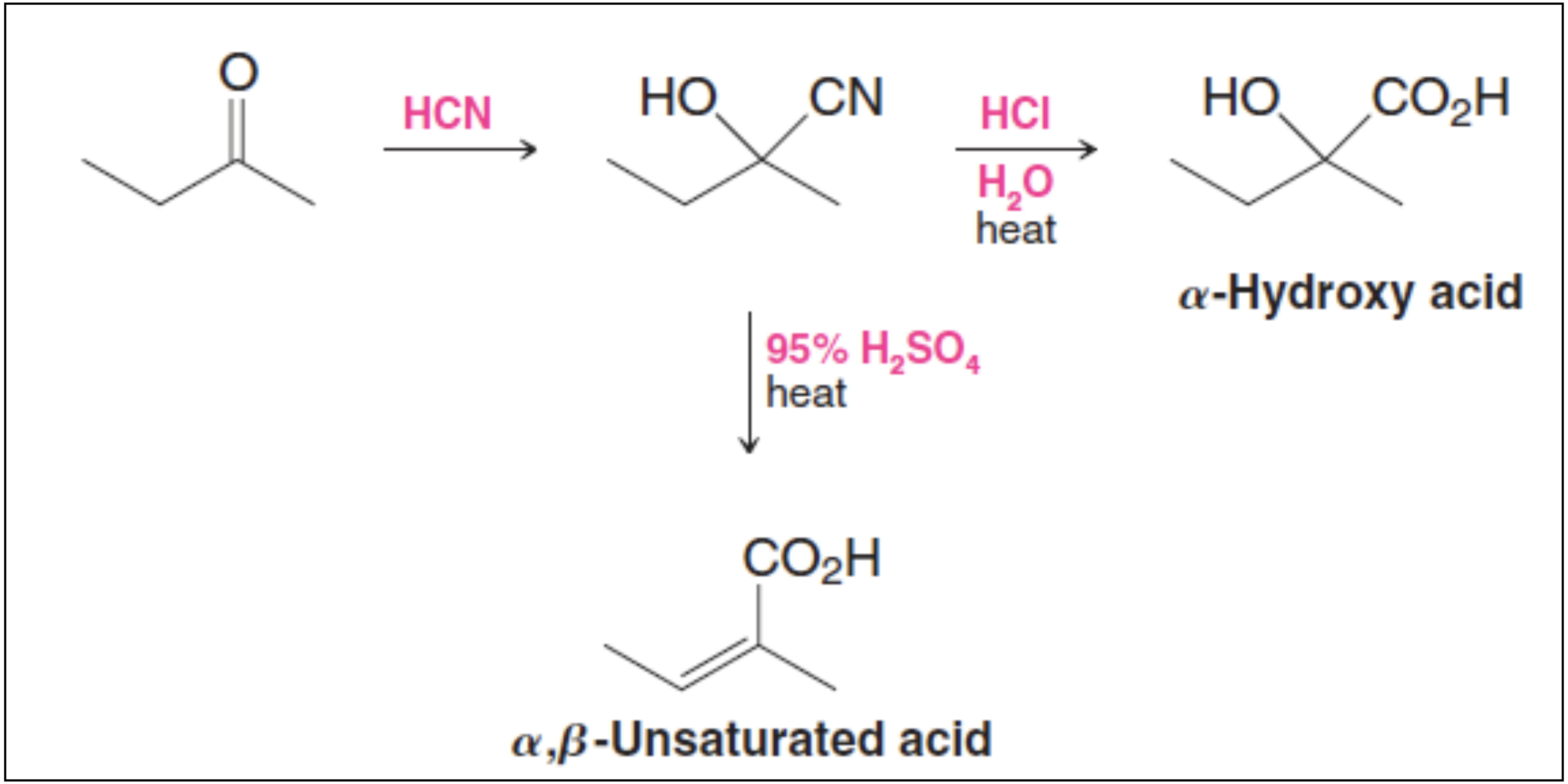
FORMAZIONE DELLA CIANOIDRINA



In un ambiente basico , una cianidrina viene trasformata in un composto carbonilico

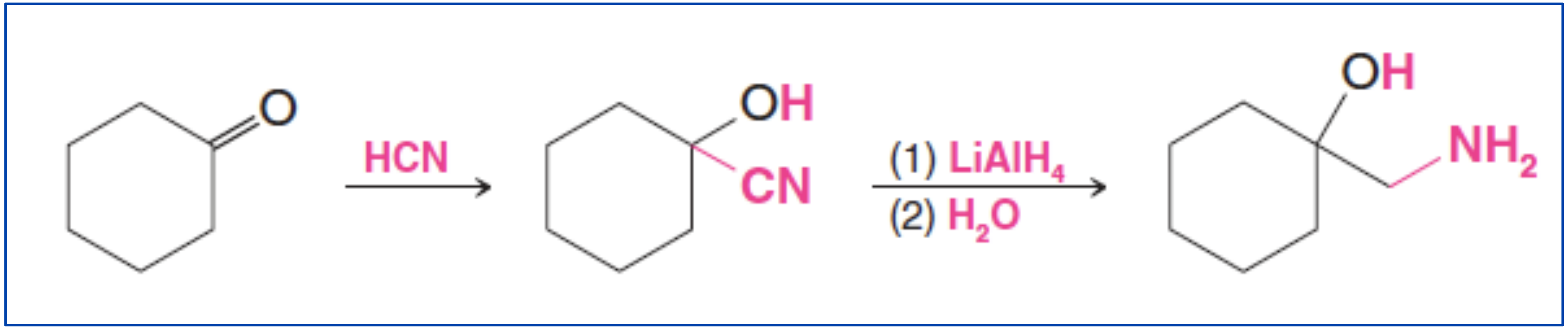


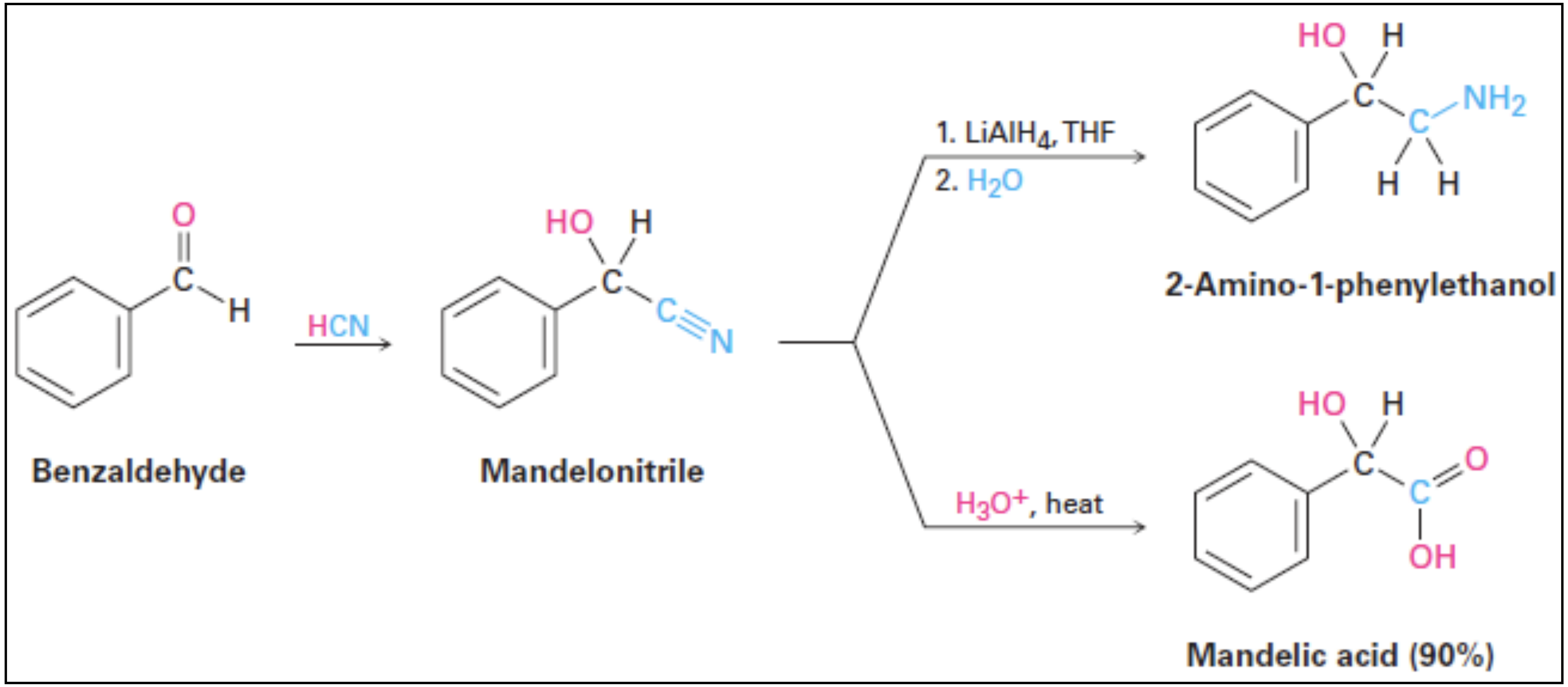
FORMAZIONE DELLA CIANOIDRINA E TRASFORMAZIONE DELLA CIANOIDRINA
Reazione con cianuro di idrogeno (HCN) o NaCN: ADDIZIONE NUCLEOFILA DI HCN
L'IDROLISI ACIDA DELLA CIANOIDRINA PERMETTE LA FORMAZIONE DI ALFA-IDROSSI ACIDI E ALFA-BETA-INSATURI



FORMAZIONE DELLA CIANOIDRINA E TRASFORMAZIONE DELLA CIANOIDRINA

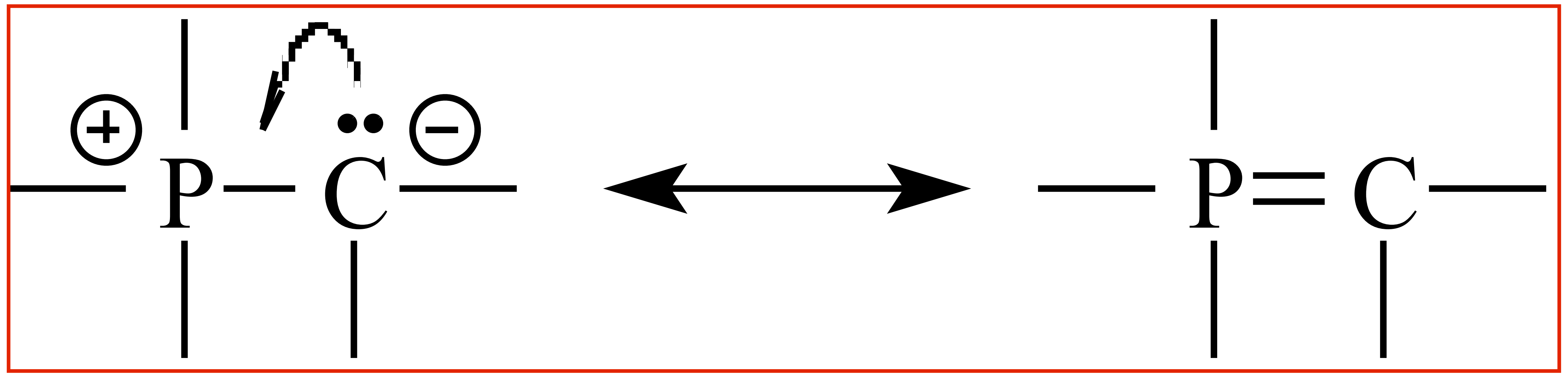
Riduzione della cianoidrina con Litio Alluminio idruro (LAH) per fornire beta-amminoalcoli

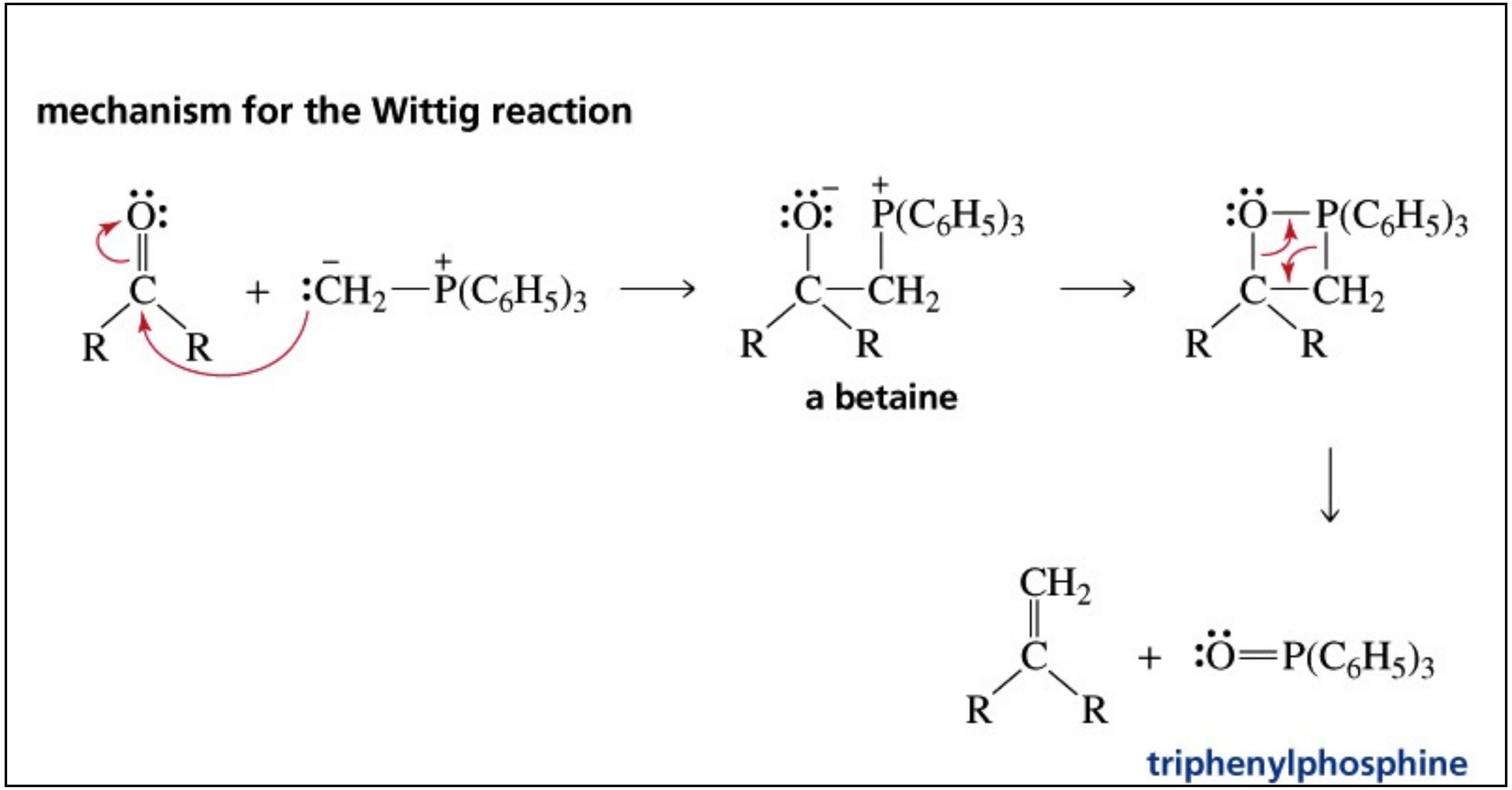




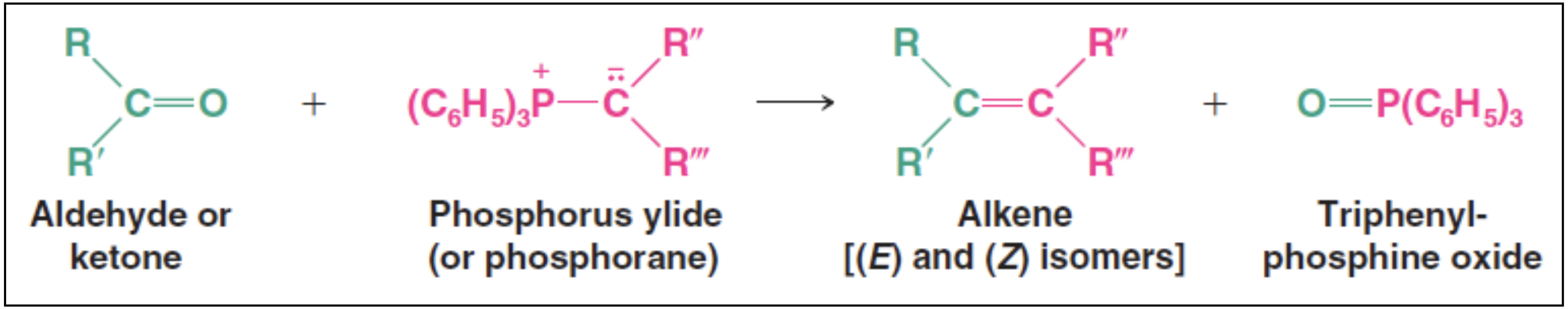
(5) Reazione di Wittig: Addizione nucleofila di ileto i fosforo $R_2C=P(C_6H_5)_3$

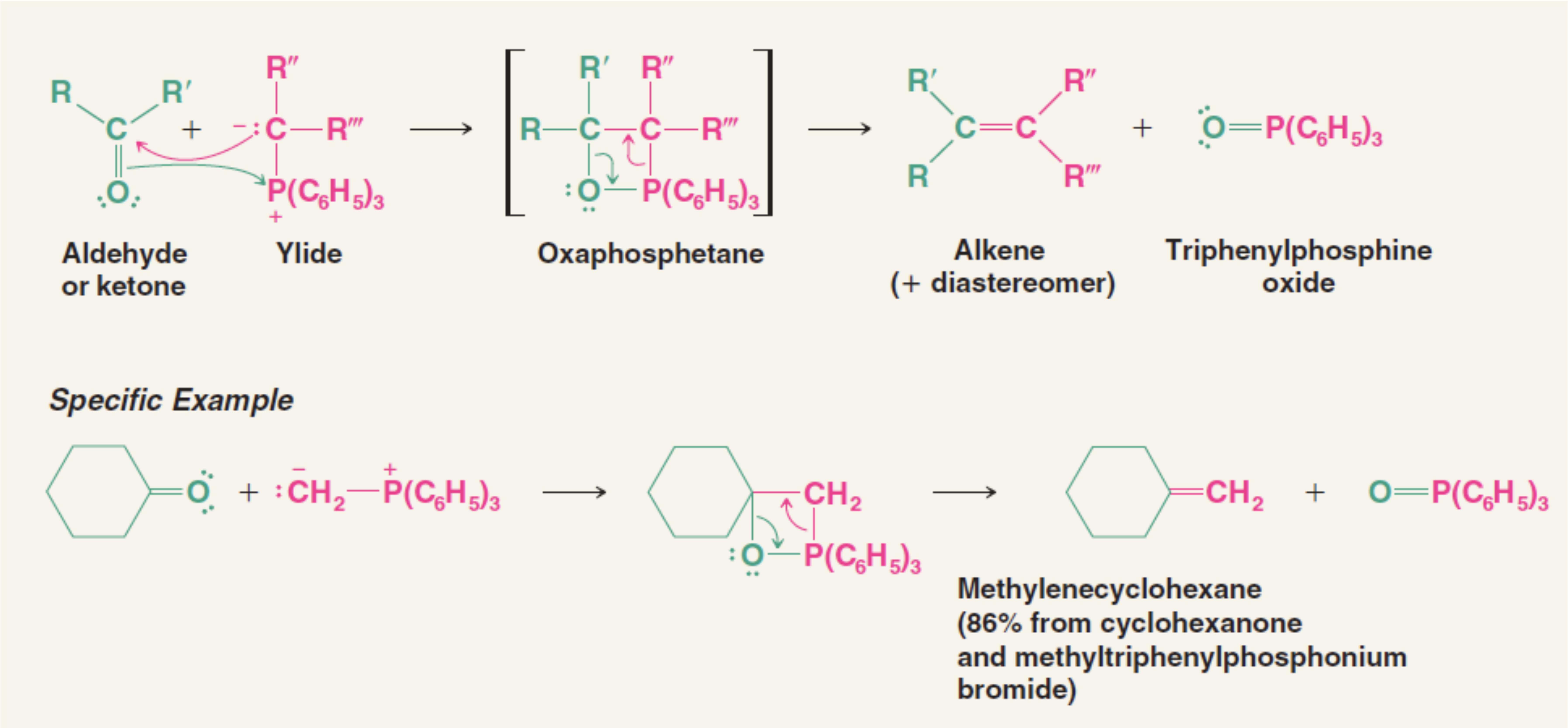
Un ilide è un composto dipolare neutro



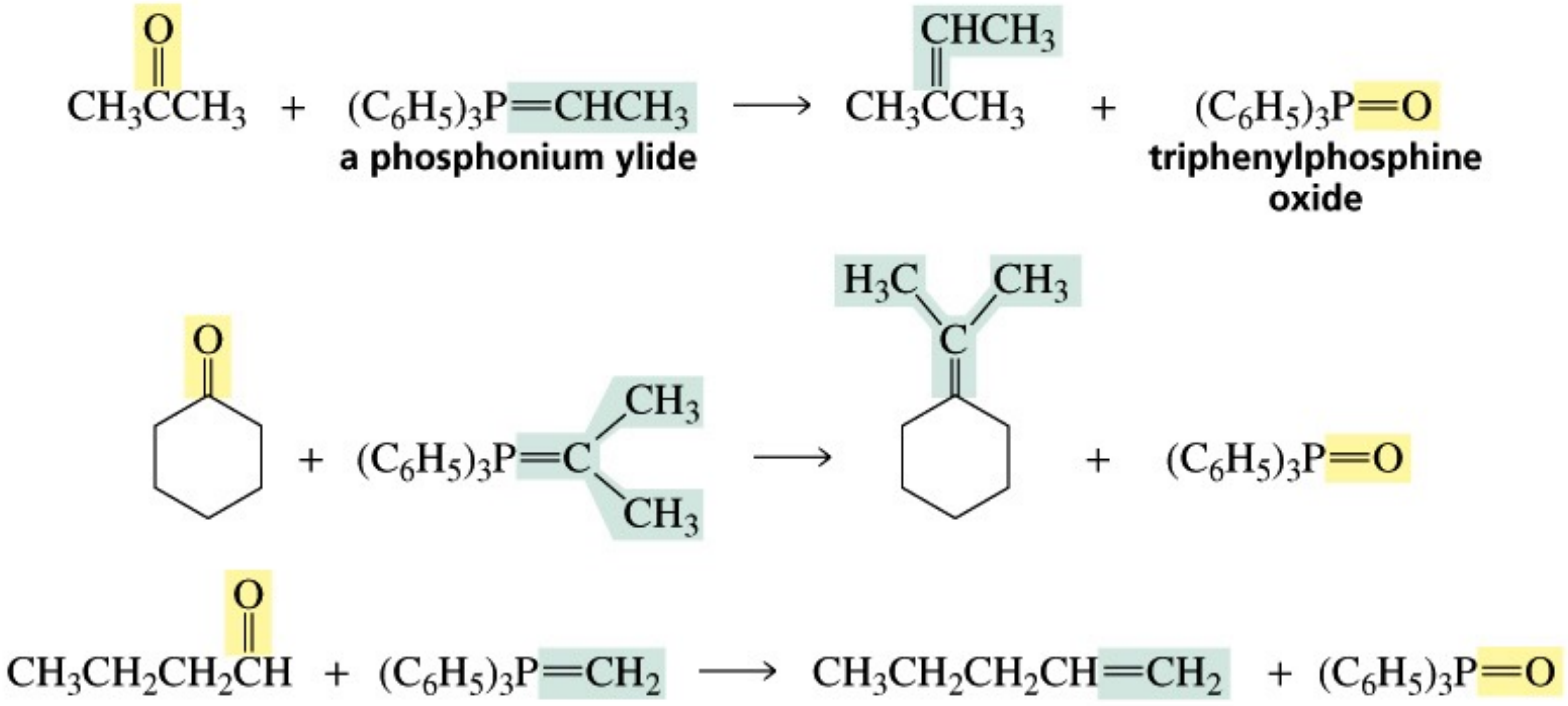


(5) Reazione di Wittig: aldeidi e chetoni reagiscono con le ilidi del fosforo per produrre alcheni e ossido di trifenil fosfina

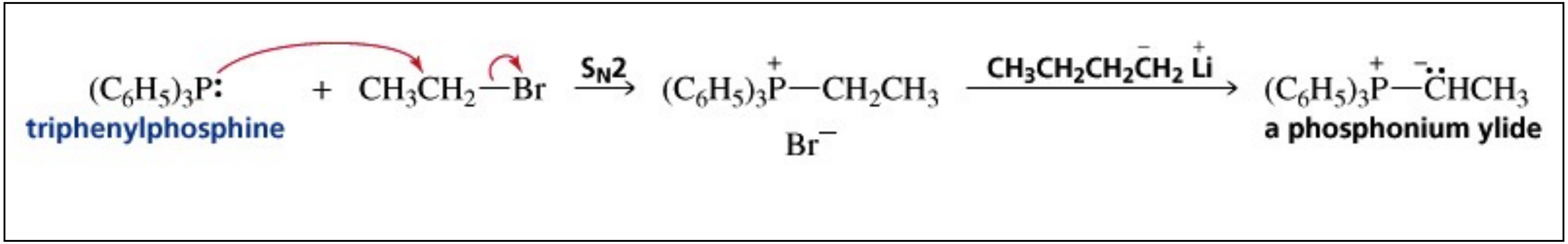




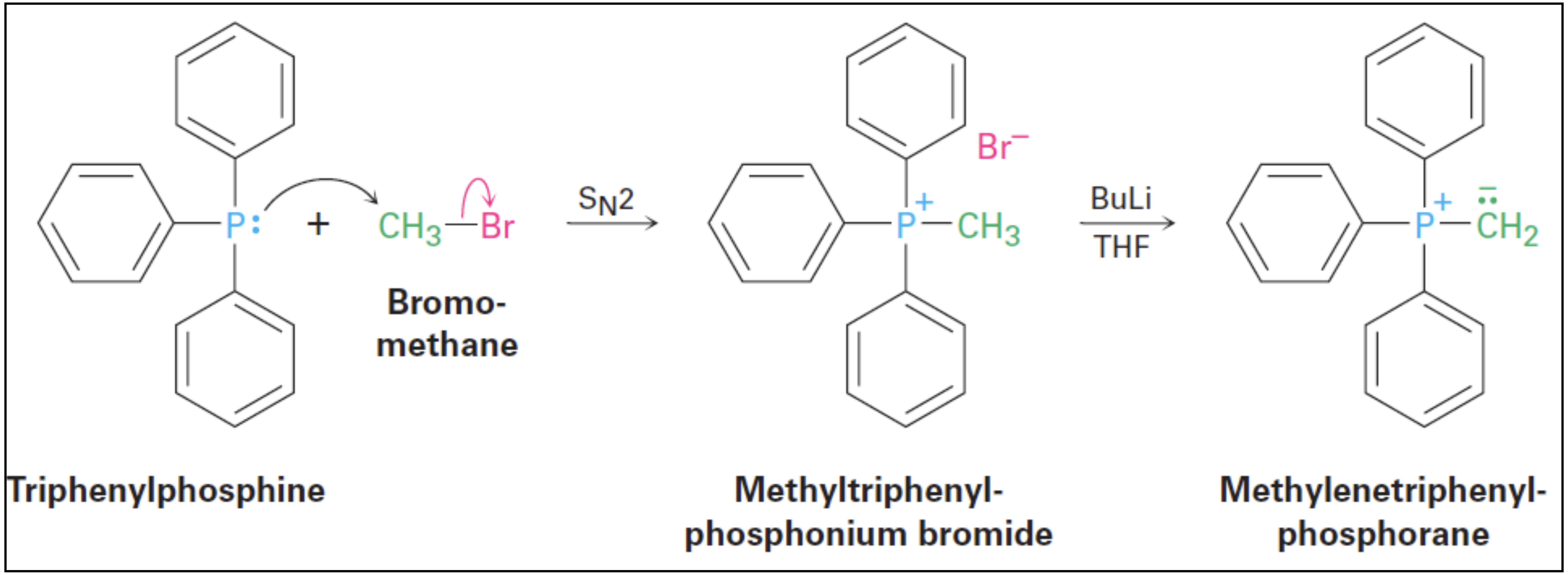
(5) Reazione di Wittig: aldeidi e chetoni reagiscono con le ilidi del fosforo per produrre alcheni e ossido di trifenil fosfina



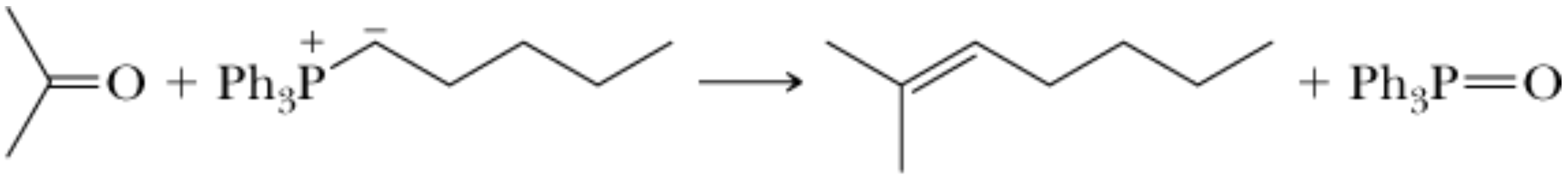
Preparazione degli ilidi di fosforo:
Sono facilmente preparati da trifenil fosfine e alogenuri alchilici primari o secondari



$$(C_6H_5)_3P\!: + CH_3CH_2{-}Br \xrightarrow{S_N2} (C_6H_5)_3\overset{+}{P}{-}CH_2CH_3\ Br^- \xrightarrow{CH_3CH_2CH_2\overset{-}{C}H_2\ \overset{+}{Li}} (C_6H_5)_3\overset{+}{P}{-}\overset{-}{\ddot{C}}HCH_3$$

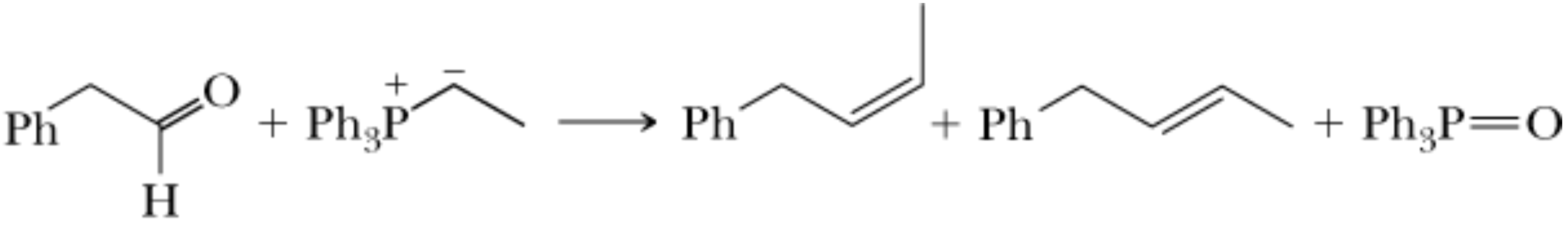


ESEMPI: sintesi di alcheni attraverso la reazione di Wittig



Acetone

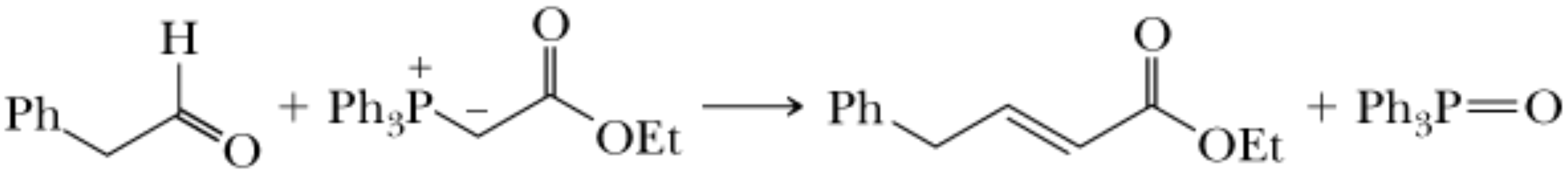
2-Metil-2-eptene



Fenilacetaldeide

(*Z*)-1-Fenil-2-butene
(87%)

(*E*)-1-Fenil-2-butene
(13%)

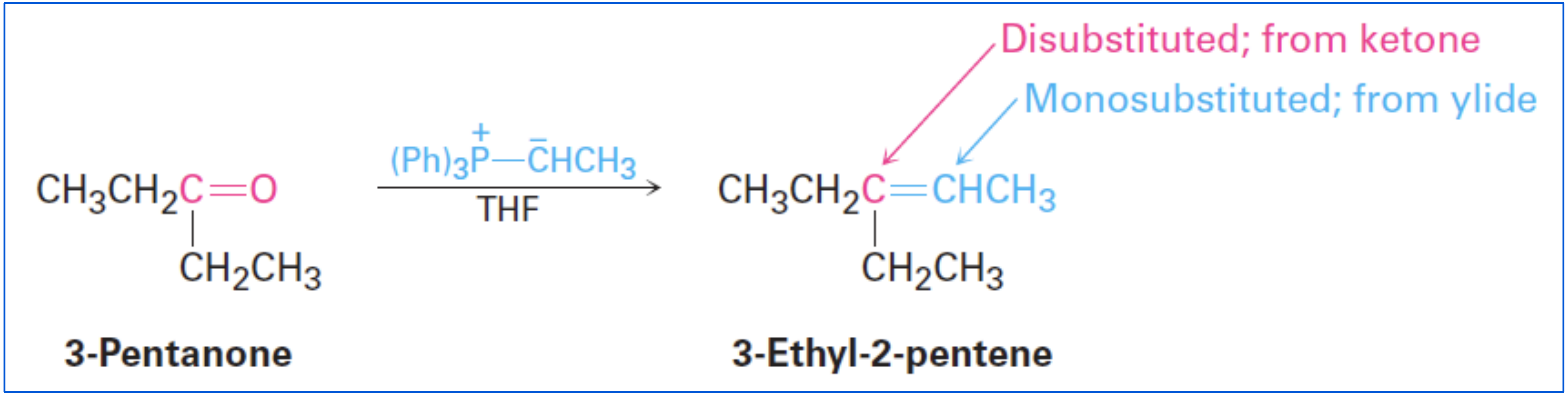


Fenilacetaldeide

(*E*)-4-Fenil-2-butenoato di etile
(solo l'isomero *E*)

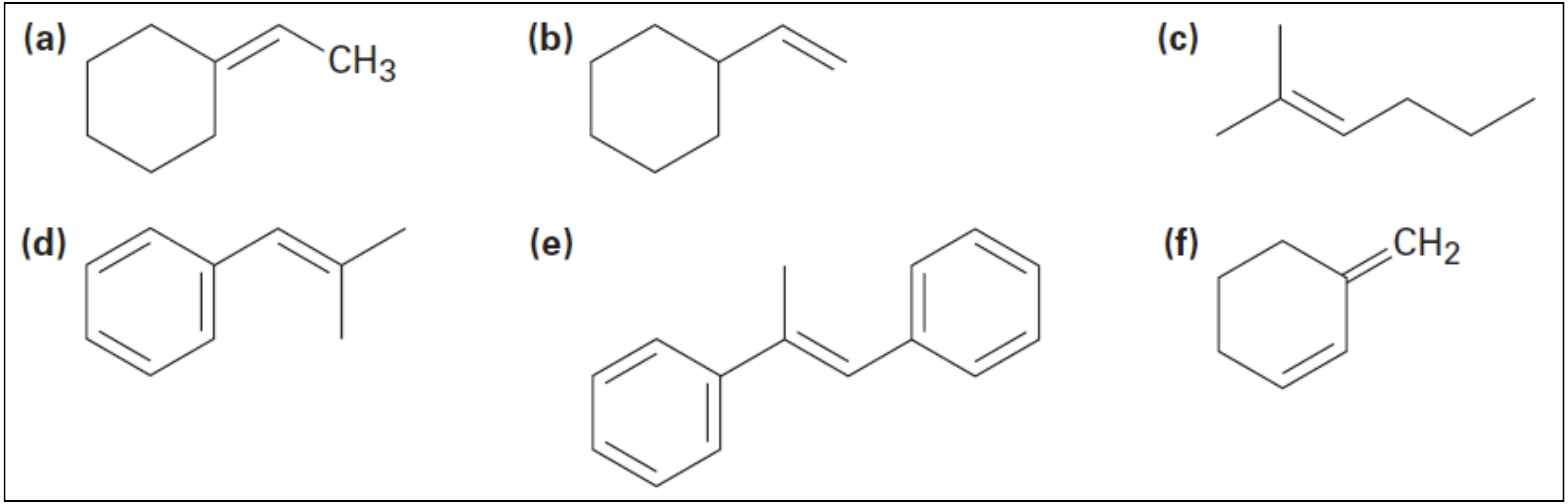
- **Problema: Sintetizzare gli alcheni usando una reazione di Wittig .**
- **Quale composto di carbonile e quale ileto di fosforo puoi usare per preparare 3-etil-2-pentene?**

- **Problema: Sintetizzare gli alcheni usando una reazione di Wittig .**
- **Quale composto di carbonile e quale ileto di fosforo puoi usare per preparare 3-etil-2-pentene?**



- **Problema: Sintetizzare gli alcheni usando una reazione di Wittig.**

- **Quale composto di carbonile e quale ileto di fosforo dovresti usare per preparare ciascuno dei seguenti composti?**

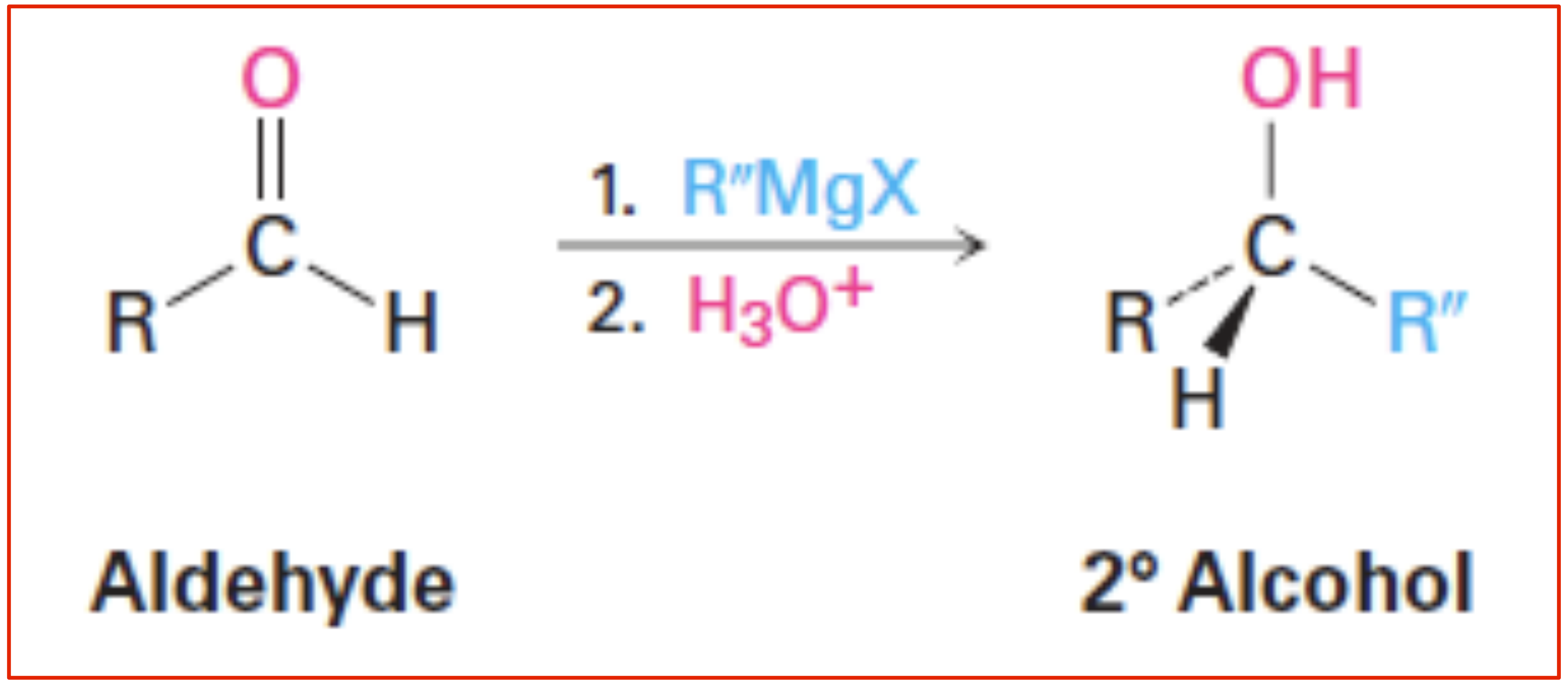


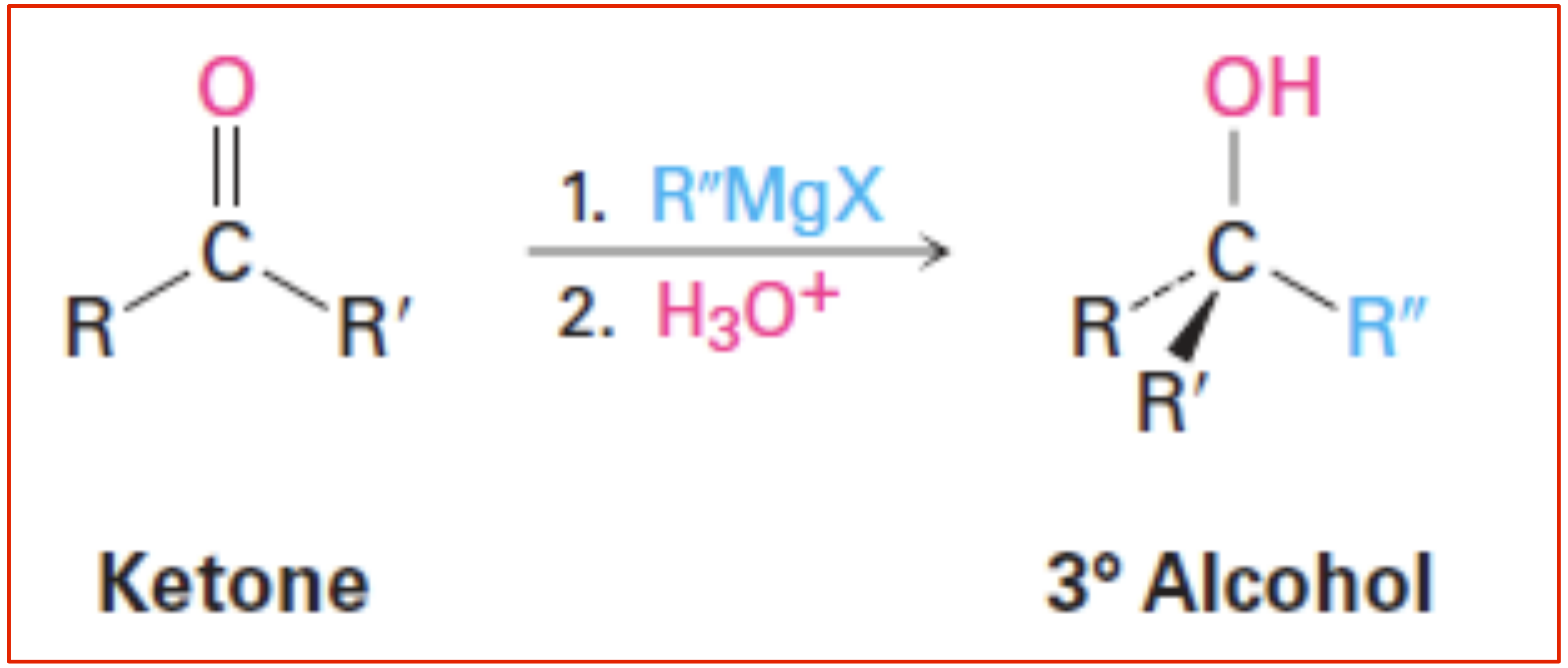
(6) Addizione nucleofila dei reagenti di Grignard:

$$CH_3CH_2Br \xrightarrow[Et_2O]{Mg} CH_3CH_2MgBr$$

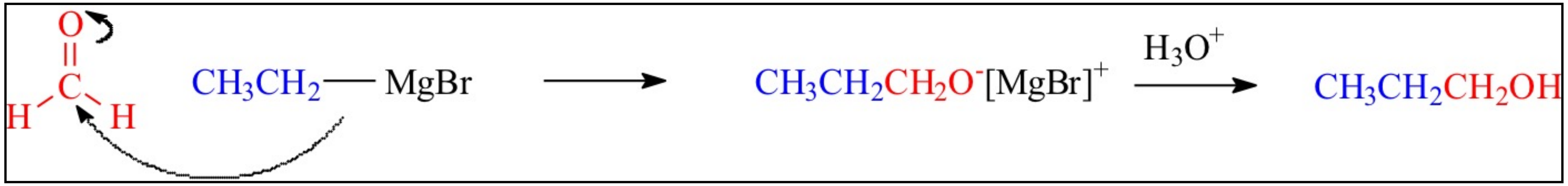
CH_3CH_2MgBr reacts as if it were $CH_3\overset{-}{\ddot{C}}H_2 \quad \overset{+}{Mg}Br$

Formazione di alcoli

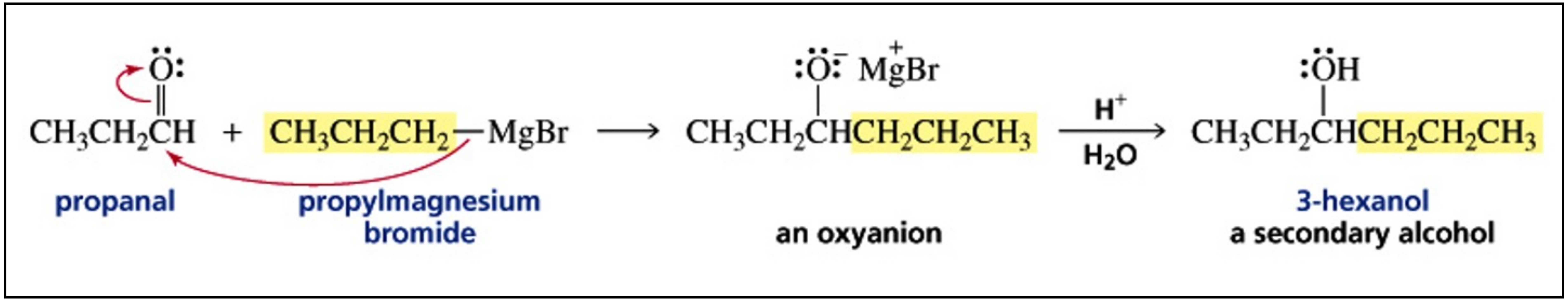




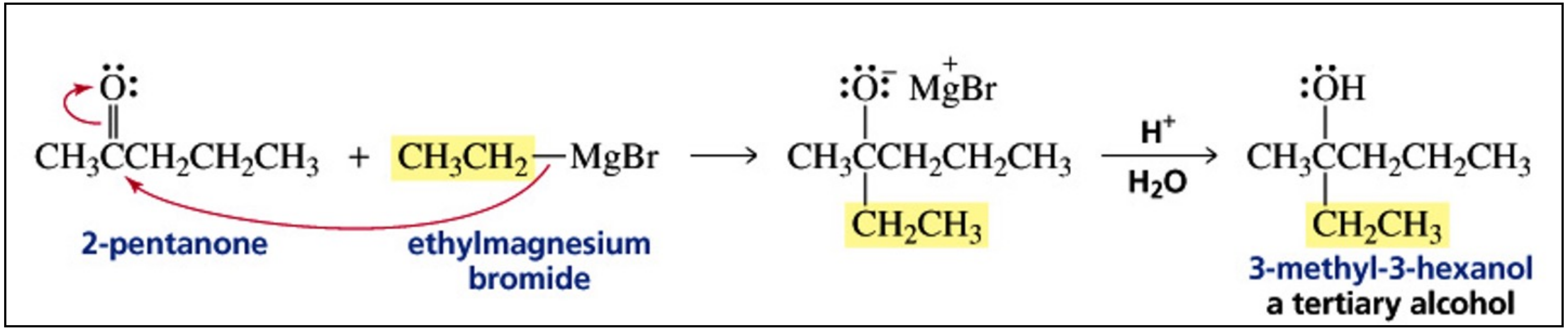
(6) Meccanismo dell'aggiunta nucleofilica di RMgX al gruppo carbonile, seguita dalla protonazione di un alcossido intermedio, producendo un alcol



$$H_2C{=}O + CH_3CH_2{-}MgBr \longrightarrow CH_3CH_2CH_2O^-[MgBr]^+ \xrightarrow{H_3O^+} CH_3CH_2CH_2OH$$

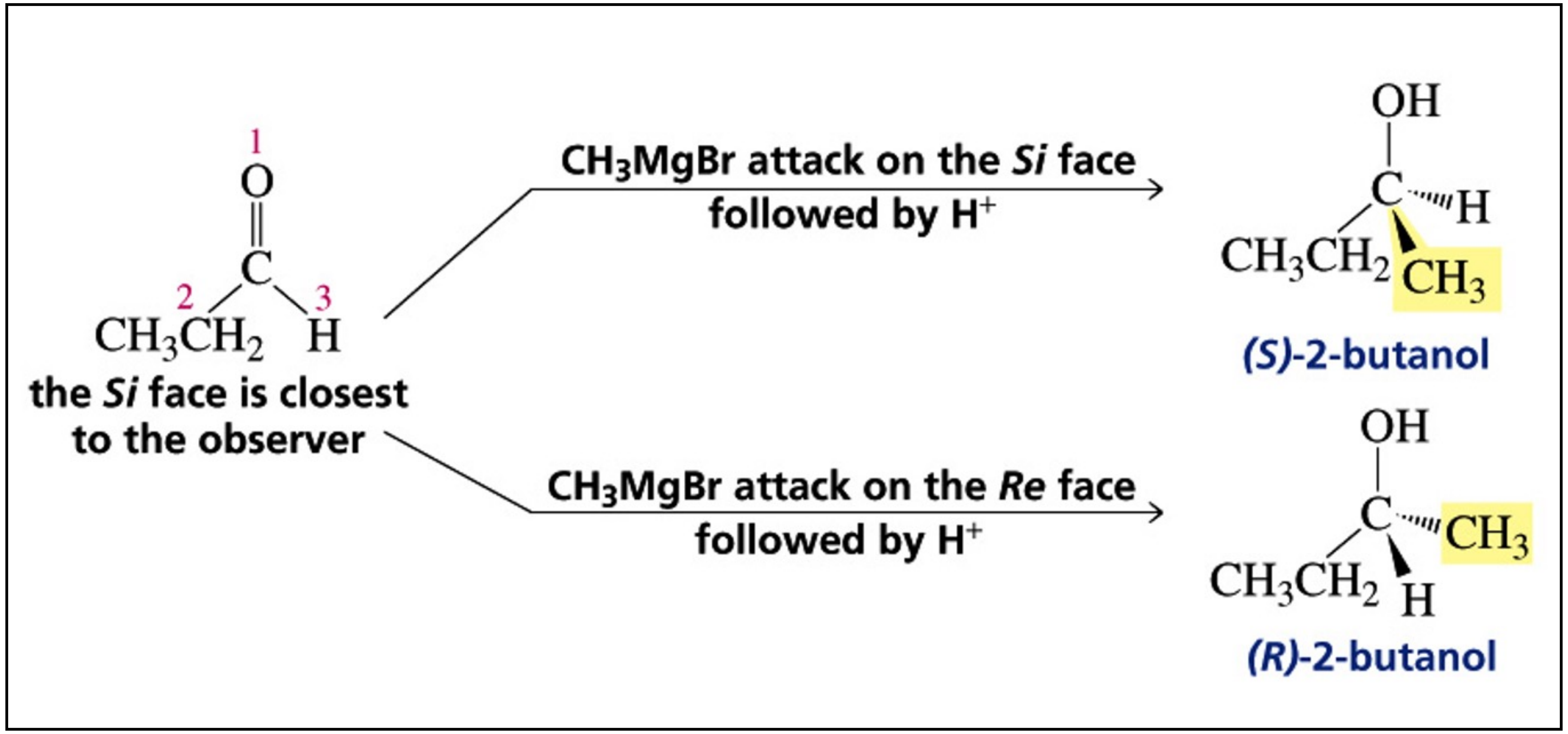


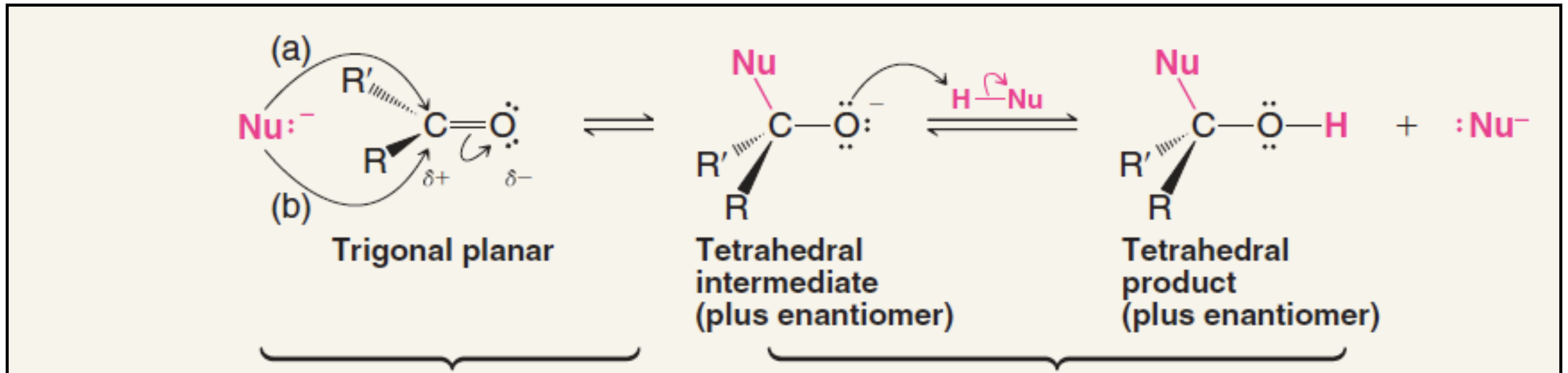
$$CH_3CH_2\overset{\overset{\ddot{O}:}{\|}}{C}H + CH_3CH_2CH_2{-}MgBr \longrightarrow CH_3CH_2\overset{\overset{:\ddot{O}:^- \ \overset{+}{Mg}Br}{|}}{C}HCH_2CH_2CH_3 \xrightarrow[H_2O]{H^+} CH_3CH_2\overset{\overset{:\ddot{O}H}{|}}{C}HCH_2CH_2CH_3$$



$$CH_3\overset{\overset{\ddot{O}:}{\|}}{C}CH_2CH_2CH_3 + CH_3CH_2{-}MgBr \longrightarrow CH_3\underset{\underset{CH_2CH_3}{|}}{\overset{\overset{:\ddot{O}:^- \ \overset{+}{Mg}Br}{|}}{C}}CH_2CH_2CH_3 \xrightarrow[H_2O]{H^+} CH_3\underset{\underset{CH_2CH_3}{|}}{\overset{\overset{:\ddot{O}H}{|}}{C}}CH_2CH_2CH_3$$

(6) Stereochimica dell'addizione nucleofila di RMgX al gruppo carbonile

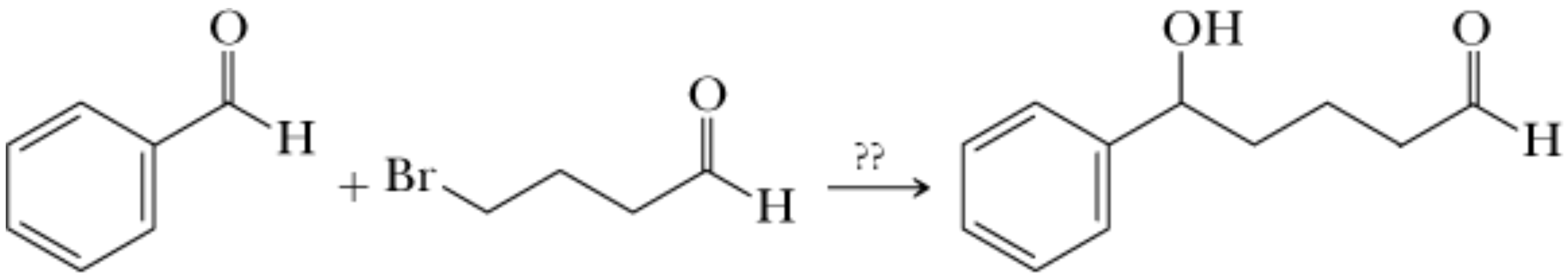




In this step the nucleophile forms a bond to the carbon by donating an electron pair to the top or bottom face of the carbonyl group [path (a) or (b)]. An electron pair shifts out to the oxygen.

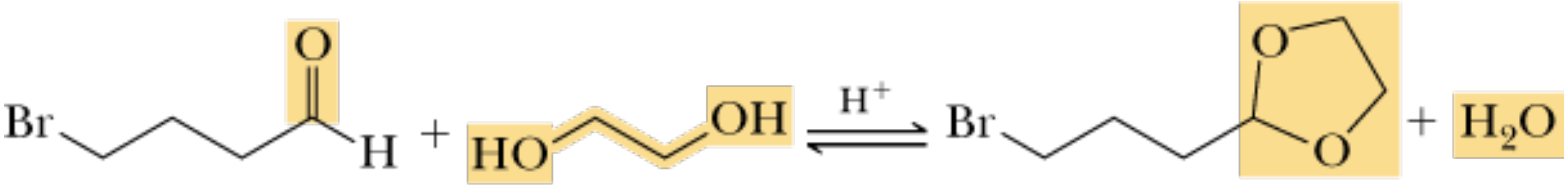
In the second step the alkoxide oxygen, because it is strongly basic, removes a proton from H—Nu or some other acid.

Acetali come gruppi protettori del carbonile

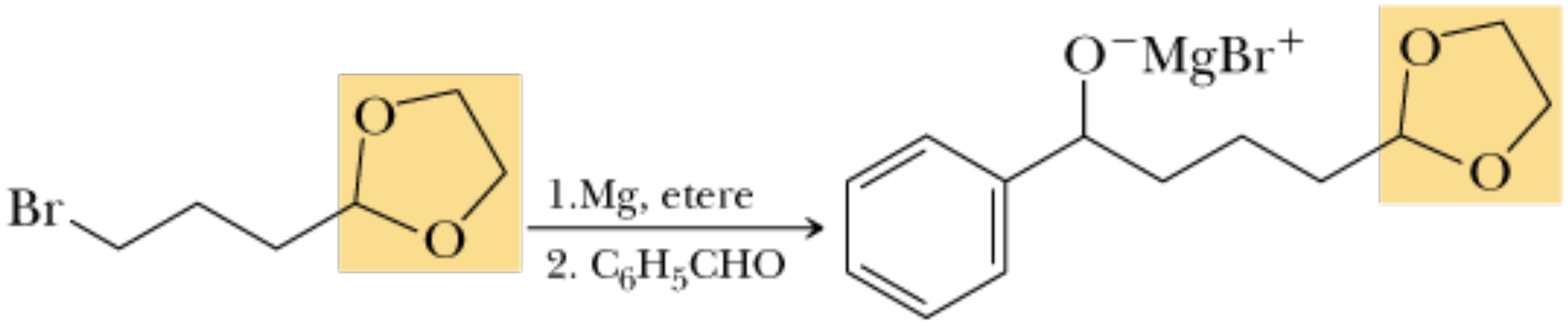


Benzaldeide **4-Bromobutanale** **5-Idrossi-5-fenilpentanale**
(miscela racemica)

Acetali come gruppi protettori del carbonile

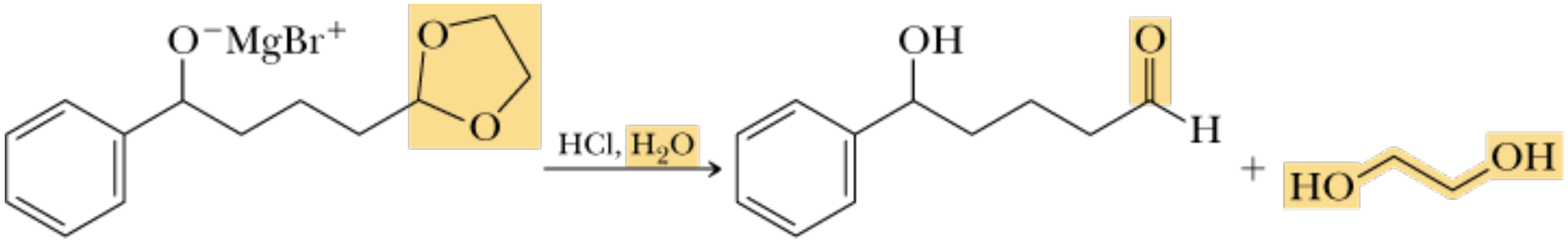


Acetale ciclico



Acetale ciclico

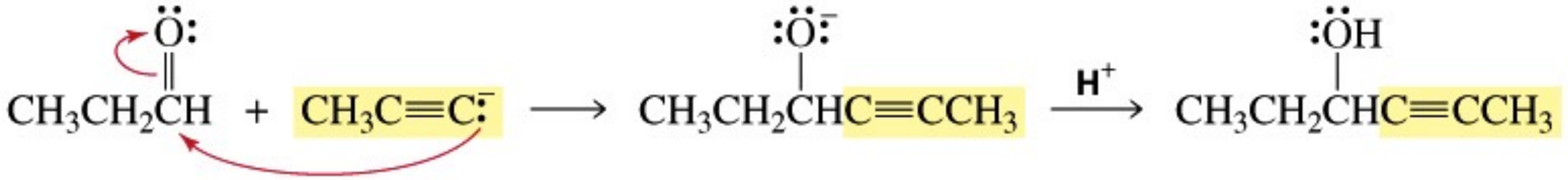
Alcossido di magnesio chirale
(miscela racemica)



5-Idrossi-5-fenilpentanale
(miscela racemica)

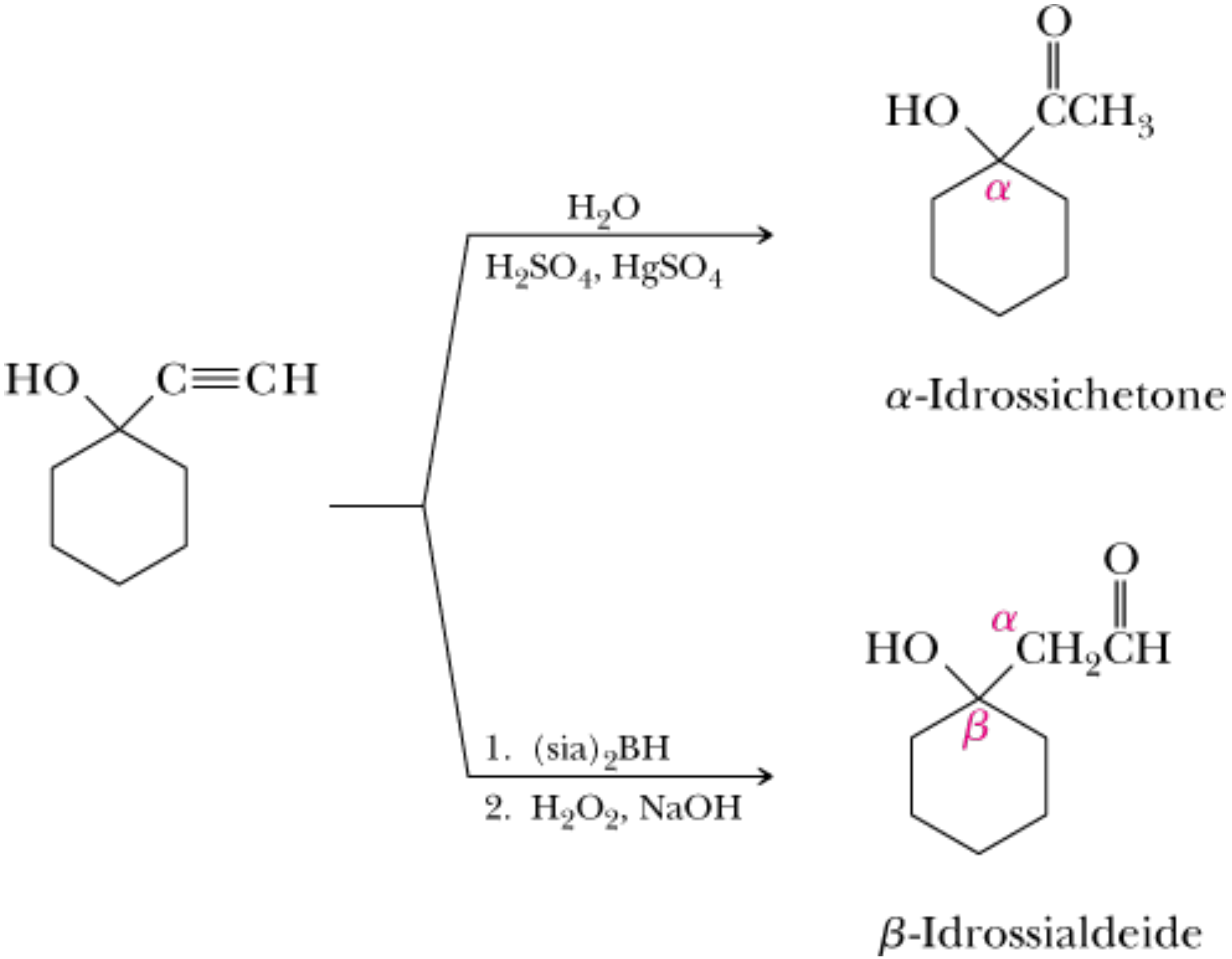
7) Reazione dell'anione acetiluro (base coniugata dell'acetilene): RCC:$^-$ Na$^+$

$$CH_3C{\equiv}CH \xrightarrow[NH_3]{NaNH_2} CH_3C{\equiv}C{:}^-$$

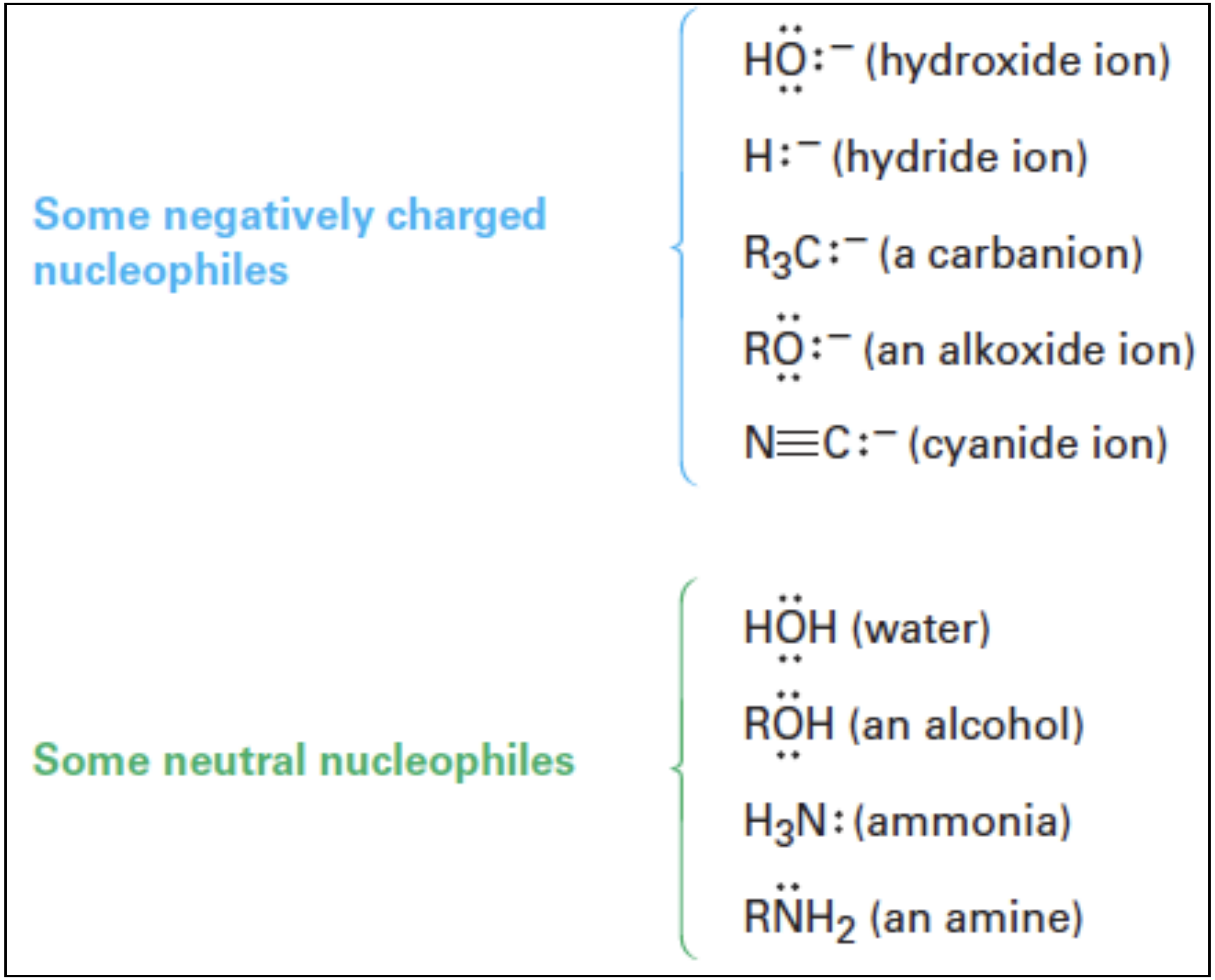


$$CH_3CH_2\overset{\overset{\ddot{O}:}{\|}}{C}H + CH_3C{\equiv}C{:}^- \longrightarrow CH_3CH_2\overset{\overset{:\ddot{O}:^-}{|}}{C}HC{\equiv}CCH_3 \xrightarrow{H^+} CH_3CH_2\overset{\overset{:\ddot{O}H}{|}}{C}HC{\equiv}CCH_3$$

7) Reazione dell'anione acetiluro (base coniugata dell'acetilene): RCC:$^-$ Na$^+$



Reazioni di addizione nucleofila di aldeidi e chetoni

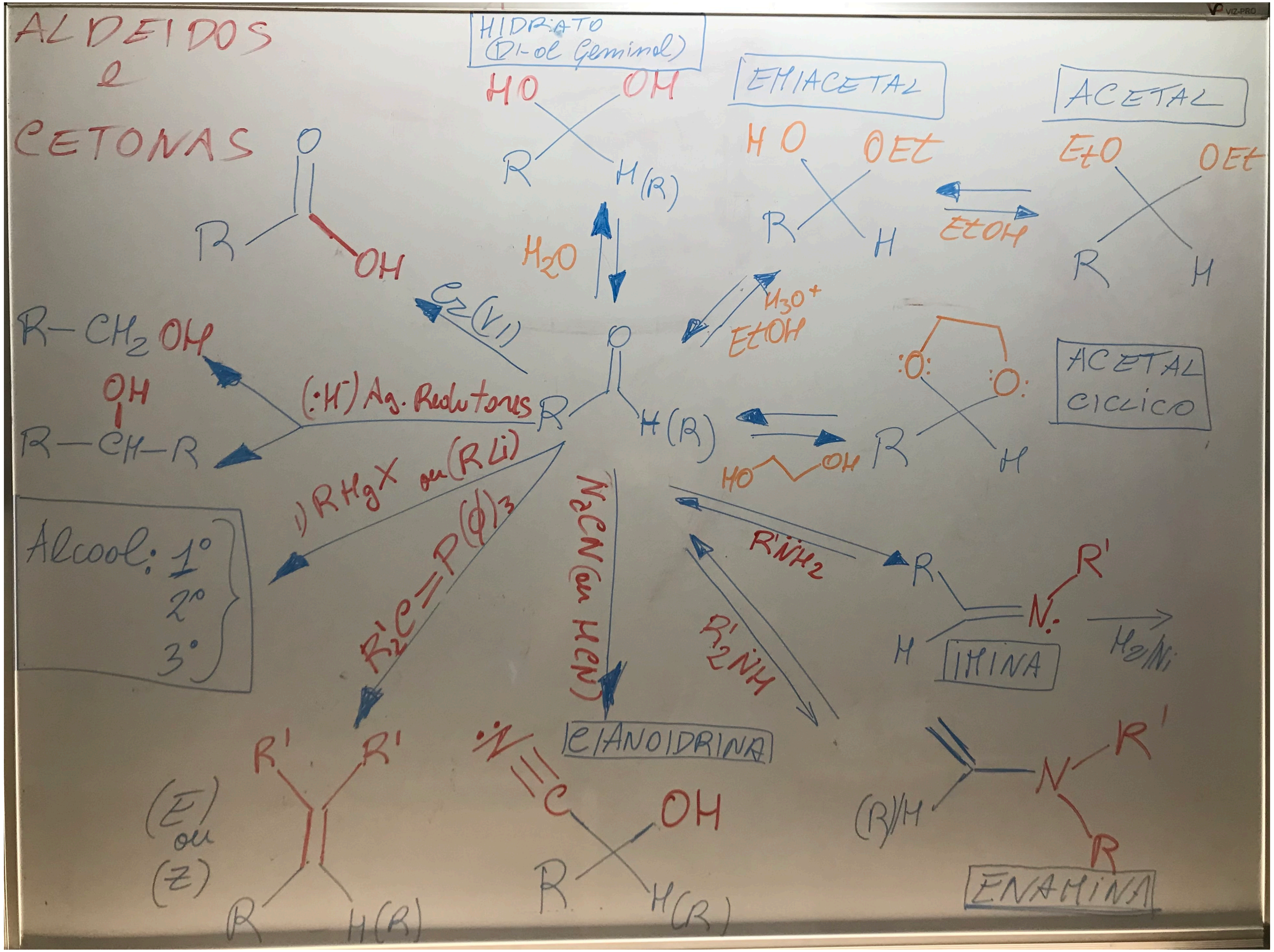


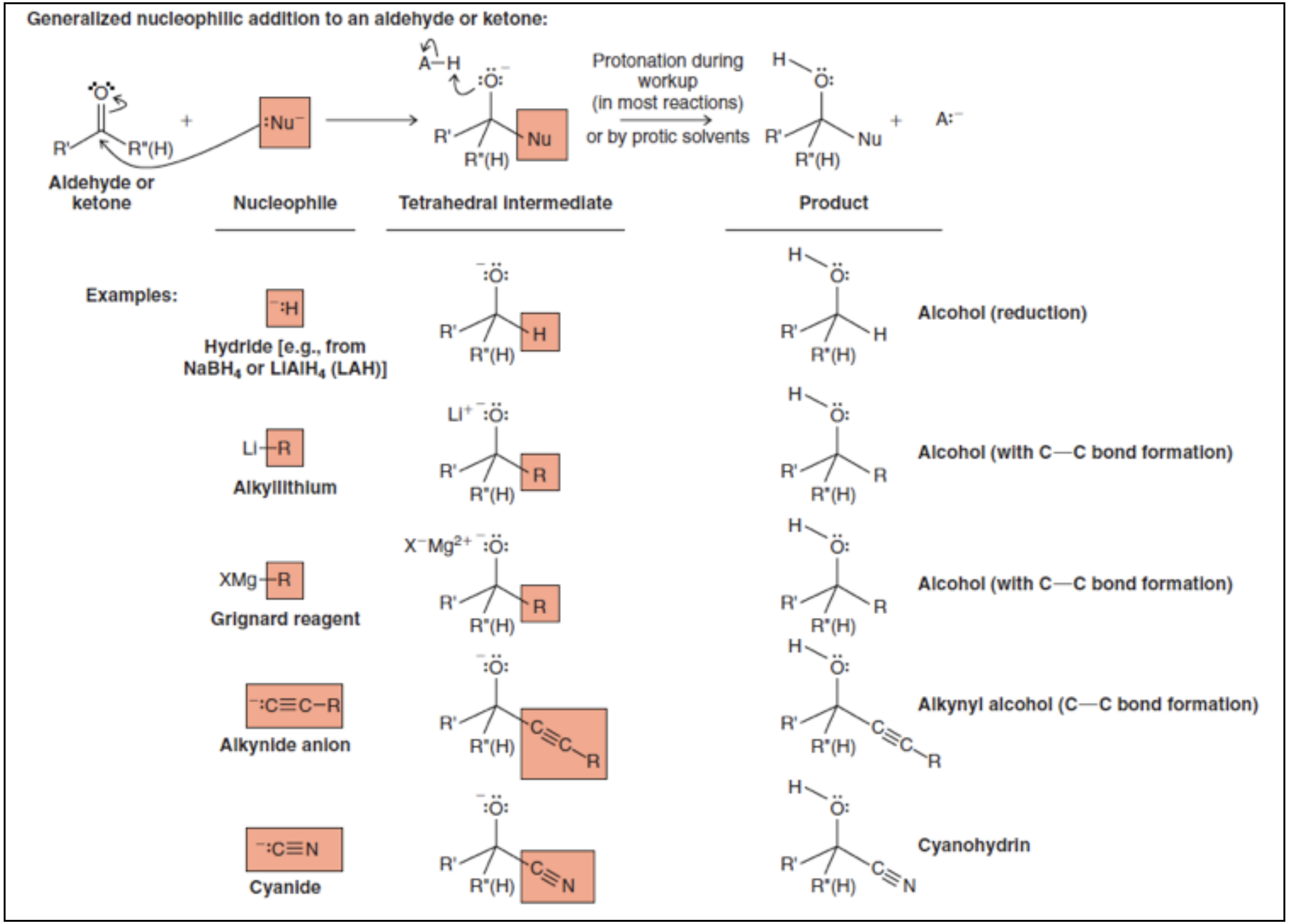
Some negatively charged nucleophiles

- $H\underset{\cdot\cdot}{\ddot{O}}:^-$ (hydroxide ion)
- $H:^-$ (hydride ion)
- $R_3C:^-$ (a carbanion)
- $R\underset{\cdot\cdot}{\ddot{O}}:^-$ (an alkoxide ion)
- $N{\equiv}C:^-$ (cyanide ion)

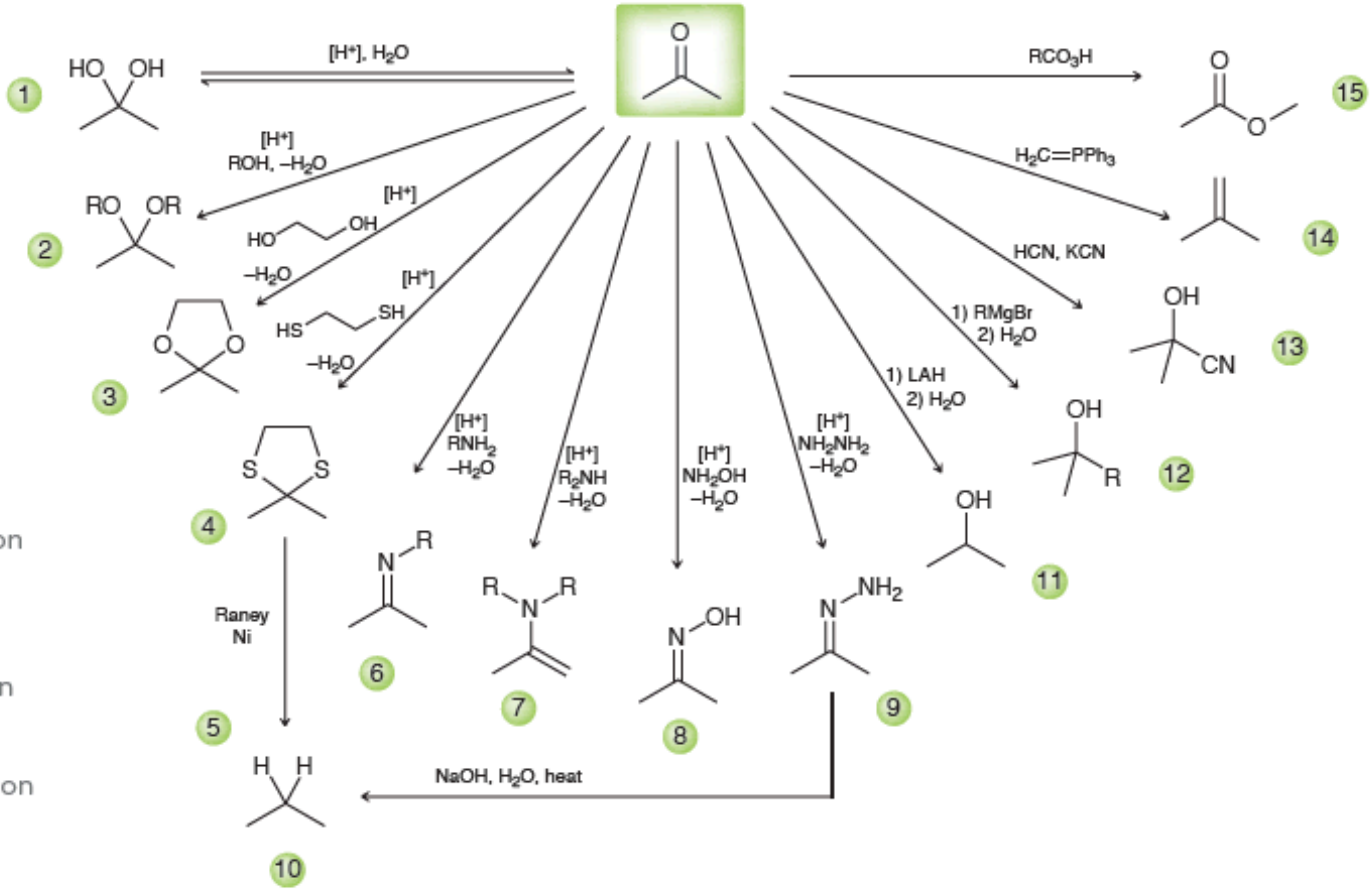
Some neutral nucleophiles

- $H\underset{\cdot\cdot}{\ddot{O}}H$ (water)
- $R\underset{\cdot\cdot}{\ddot{O}}H$ (an alcohol)
- $H_3N:$ (ammonia)
- $R\ddot{N}H_2$ (an amine)


ALDEIDOS
e
CETONAS
HIDRATO
(Di-ol Geminal)
HO OH
R H(R)
H2O
EMIACETAL
HO OEt
R H
EtOH
ACETAL
EtO OEt
R H
H3O+
EtOH
O
R H(R)
R OH
Cr(VI)
R—CH2OH
OH
R—CH—R
(:H⁻) Ag. Redutores
1) RMgX ou (RLi)
Alcool: 1°
2°
3°
R'2C=P(ϕ)3
(E)
ou
(Z)
R' R'
R H(R)
NaCN (ou HCN)
CIANOIDRINA
:N≡C OH
R H(R)
:O: :O:
R H
HO OH
ACETAL
CICLICO
R'NH2
R N:
R'
H
IMINA
H2/Ni
R'2NH
(R)/H N R'
R
ENAMINA


Generalized nucleophilic addition to an aldehyde or ketone:
Aldehyde or ketone
Nucleophile
Tetrahedral intermediate
Protonation during workup (in most reactions)
or by protic solvents
Product
Examples:
Hydride [e.g., from NaBH4 or LiAlH4 (LAH)]
Alkyllithium
Grignard reagent
Alkynide anion
Cyanide
Alcohol (reduction)
Alcohol (with C—C bond formation)
Alcohol (with C—C bond formation)
Alkynyl alcohol (C—C bond formation)
Cyanohydrin

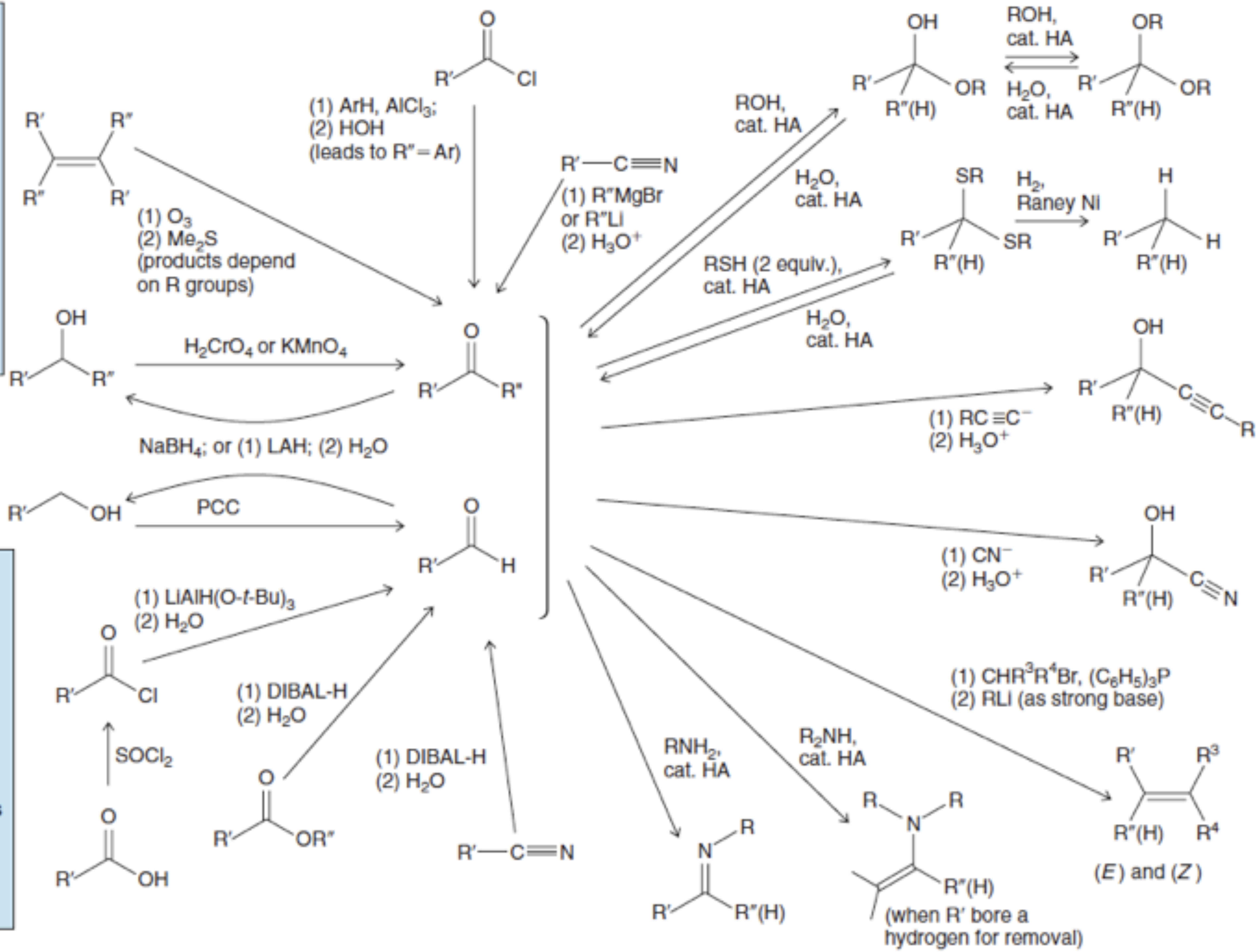
1. Hydrate Formation
2. Acetal Formation
3. Cyclic Acetal Formation
4. Cyclic Thioacetal Formation
5. Desulfurization
6. Imine Formation
7. Enamine Formation
8. Oxime Formation
9. Hydrazone Formation
10. Wolff-Kishner Reduction
11. Reduction of a Ketone
12. Grignard Reaction
13. Cyanohydrin Formation
14. Wittig Reaction
15. Baeyer-Villiger Oxidation



Clockwise from center, bottom:

I. Preparation of aldehydes and ketones:

- **Nitrile, ester, acyl halide reduction**
- **Alcohol oxidation**
- **Ozonolysis**
- **Friedel–Crafts acylation**
- **Grignard with nitrile**
- **Acetal and hemiacetal hydrolysis**



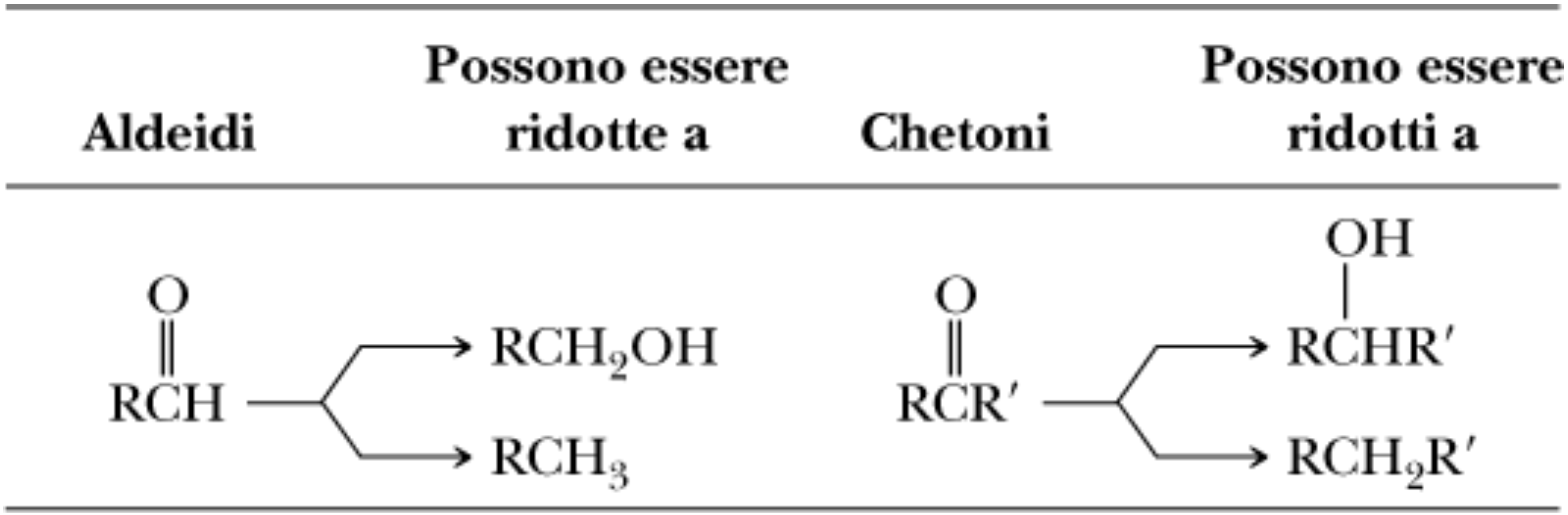
II. Reactions of aldehydes and ketones:

- **Hemiacetal and acetal formation**
- **Thioacetal formation and reduction**
- **Alkynide anion addition**
- **Nitrile addition (cyanohydrin formation)**
- **Wittig synthesis of alkenes**
- **Enamine synthesis**
- **Imine synthesis**
- **Reduction to alcohols (left, center)**

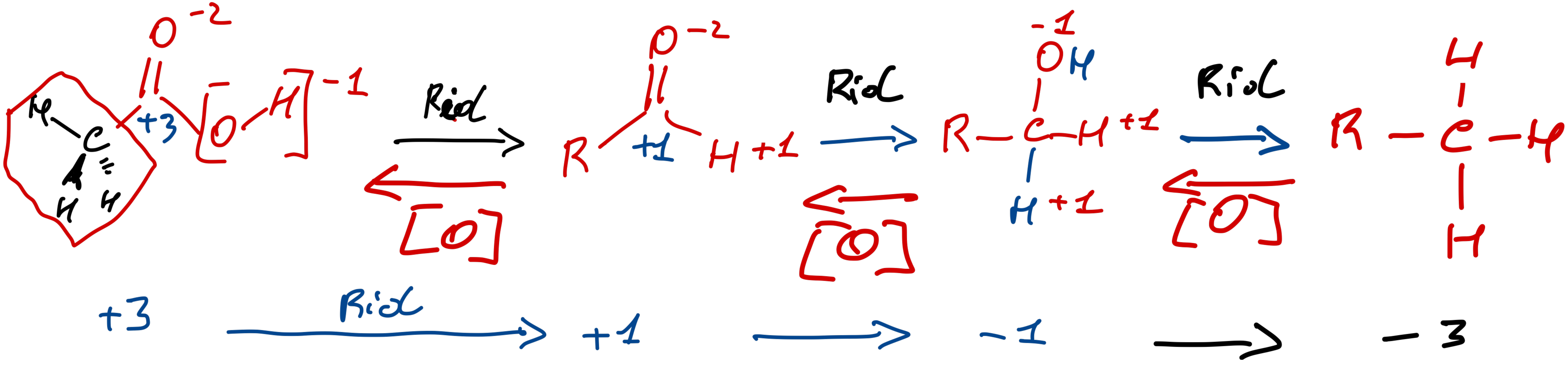
Preparazione

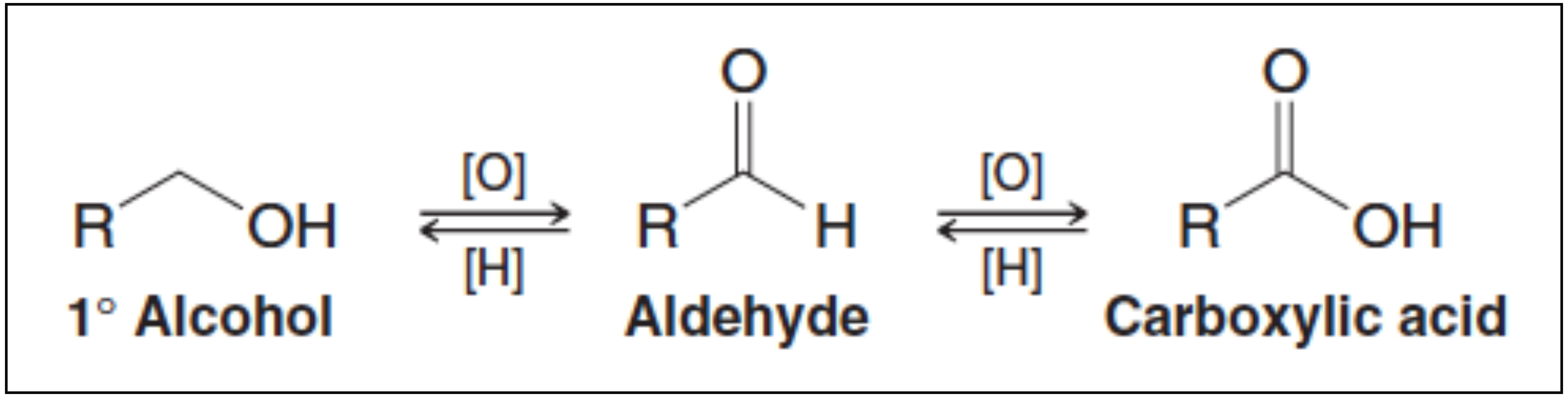
Di aldeidi e chetoni

Riduzione e ossidazione di aldeidi e chetoni

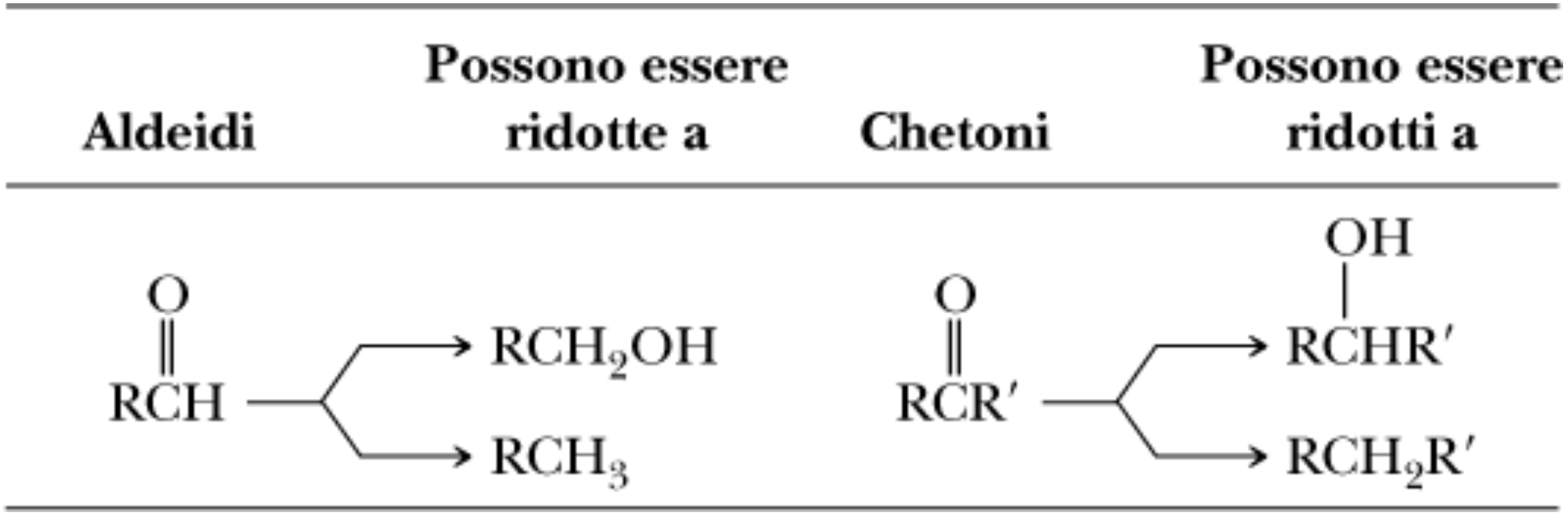


Aldeidi	Possono essere ridotte a	Chetoni	Possono essere ridotti a
$\mathrm{R\overset{\overset{O}{\|}}{C}H}$	$\mathrm{RCH_2OH}$ $\mathrm{RCH_3}$	$\mathrm{R\overset{\overset{O}{\|}}{C}R'}$	$\mathrm{R\overset{\overset{OH}{\vert}}{C}HR'}$ $\mathrm{RCH_2R'}$

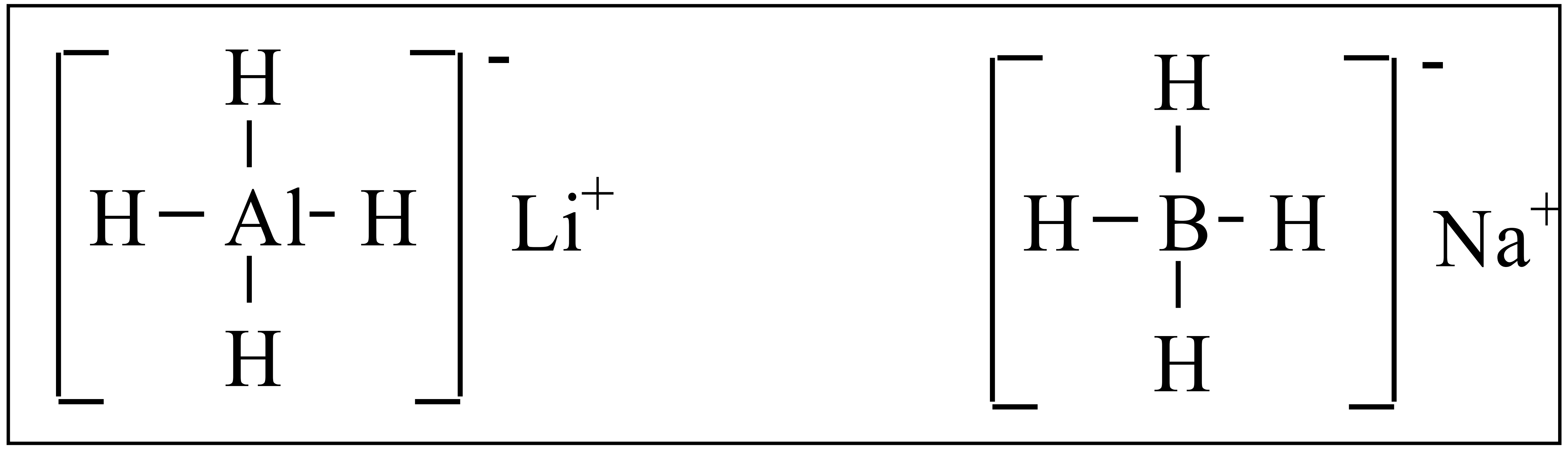

O -2
+3
[O-H] -1
Rid
[O]
O -2
R
+1
H +1
Rid
[O]
-1
OH
R-C-H +1
H +1
Rid
[O]
R-C-H
H
H
+3
Rid
+1
-1
-3


R
OH
[O]
[H]
O
R
H
[O]
[H]
O
R
OH
1° Alcohol
Aldehyde
Carboxylic acid

Riduzione con ione idruro (H:$^-$)



Aldeidi	Possono essere ridotte a	Chetoni	Possono essere ridotti a
$R\overset{O}{\overset{\parallel}{C}}H$	RCH_2OH RCH_3	$R\overset{O}{\overset{\parallel}{C}}R'$	$R\overset{OH}{\overset{\vert}{C}}HR'$ RCH_2R'



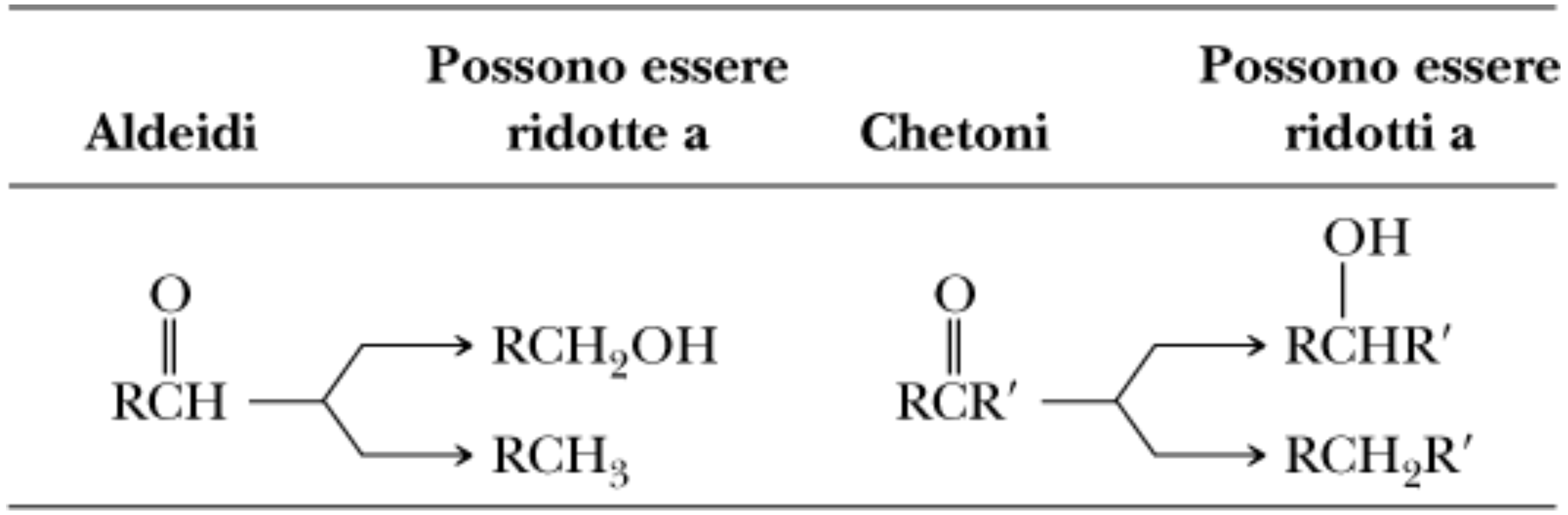
$\left[H-\overset{H}{\underset{H}{Al}}-H\right]^- Li^+$ $\left[H-\overset{H}{\underset{H}{B}}-H\right]^- Na^+$

✓$NaBH_4$ (**Sodio Boro Idruro**) e

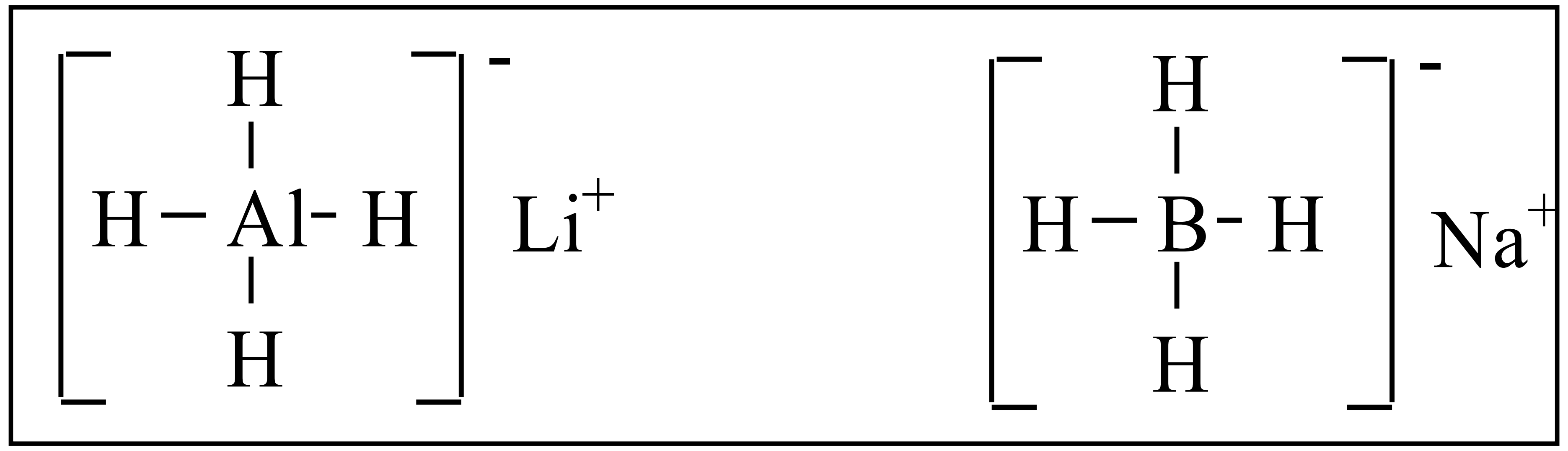
✓$LiAlH_4$ (**Litio Aluminio Idruro**, LAH)

- Fonte di ioni idruro H:$^-$,
- eccelente nucleofilo

Riduzione con ione idruro (H:$^-$)



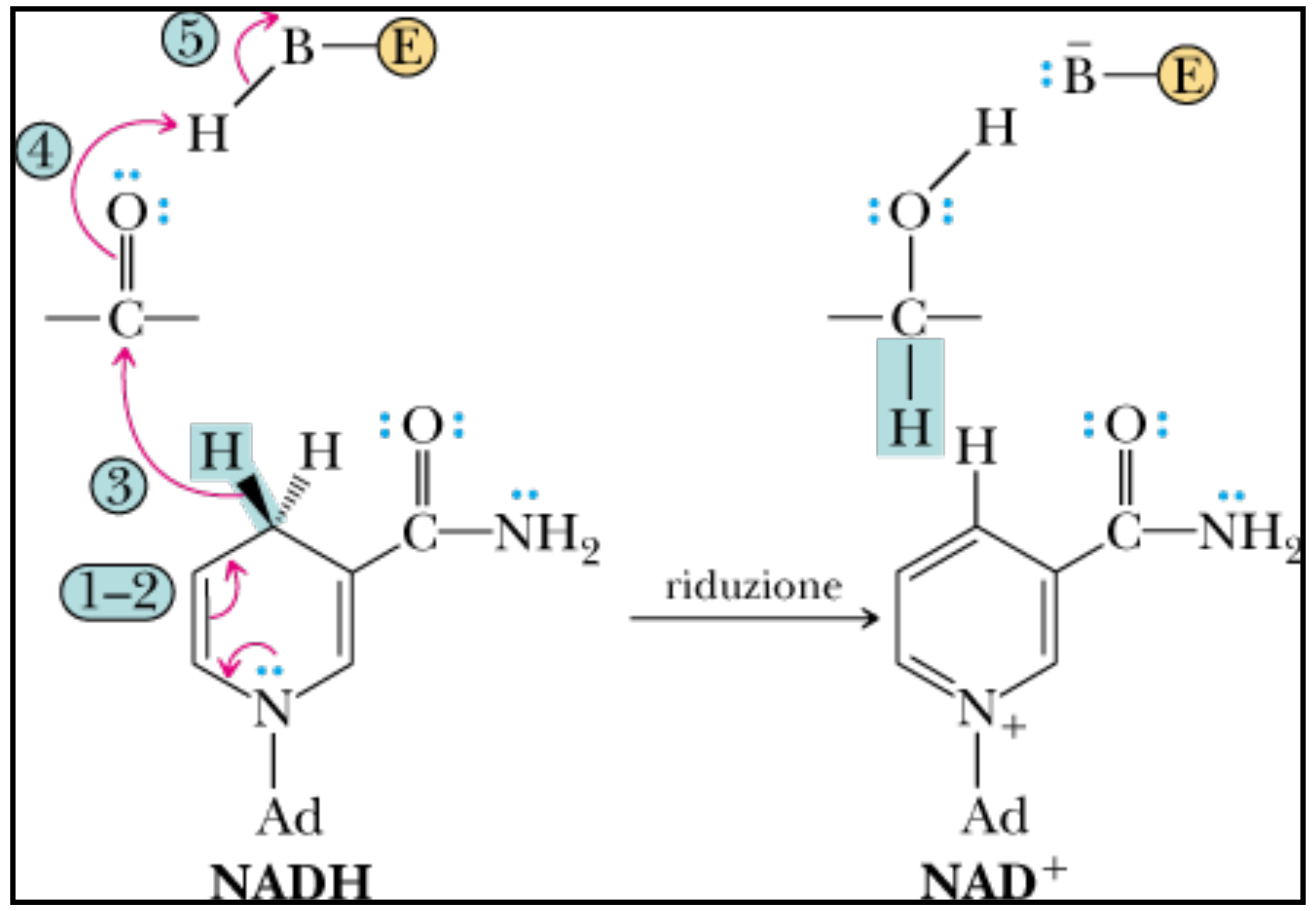
Aldeidi	Possono essere ridotte a	Chetoni	Possono essere ridotti a
$R\overset{O}{\overset{\|}{C}}H$	RCH_2OH RCH_3	$R\overset{O}{\overset{\|}{C}}R'$	$R\underset{}{\overset{OH}{\overset{\mid}{C}}}HR'$ RCH_2R'



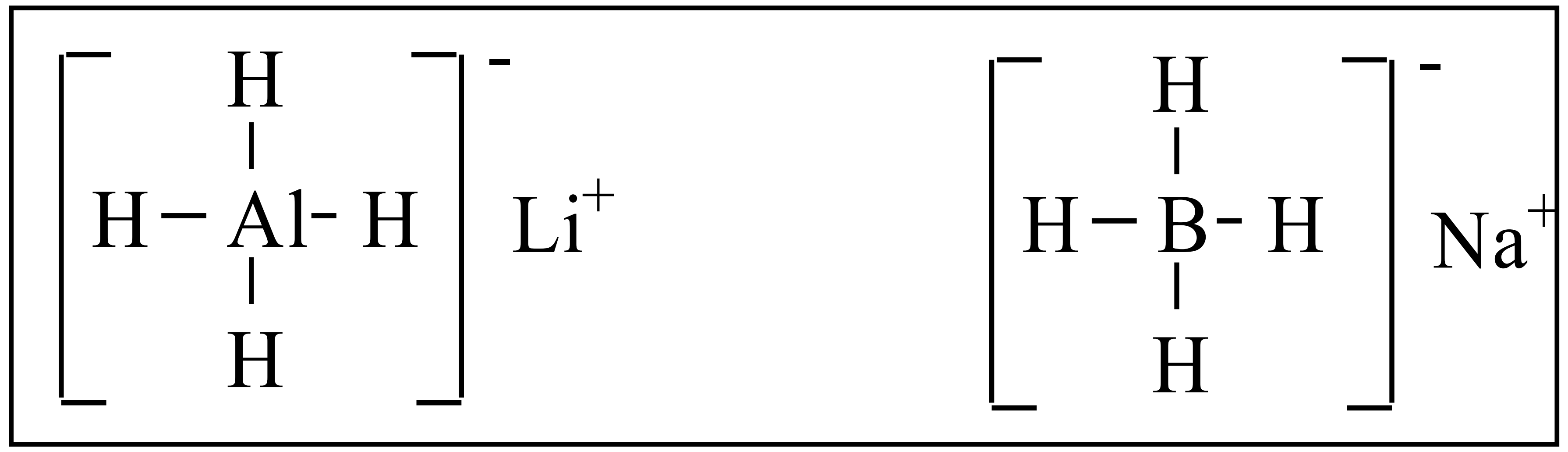
$$\left[\mathrm{H-\overset{\displaystyle H}{\underset{\displaystyle H}{Al}}-H}\right]^{-} \mathrm{Li^+} \qquad \left[\mathrm{H-\overset{\displaystyle H}{\underset{\displaystyle H}{B}}-H}\right]^{-} \mathrm{Na^+}$$

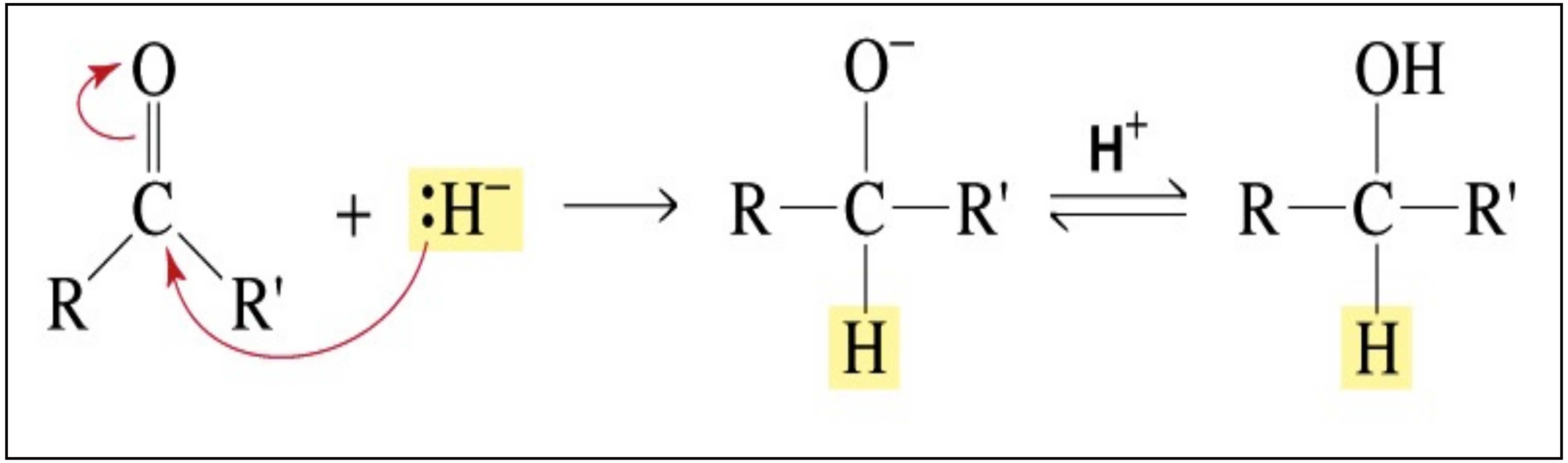
$$CH_3-\overset{O}{\overset{\|}{C}}-H + NADH + H_3O^+ \xrightarrow{\text{alcol deidrogenasi}} CH_3CH_2OH + NAD^+ + H_2O$$

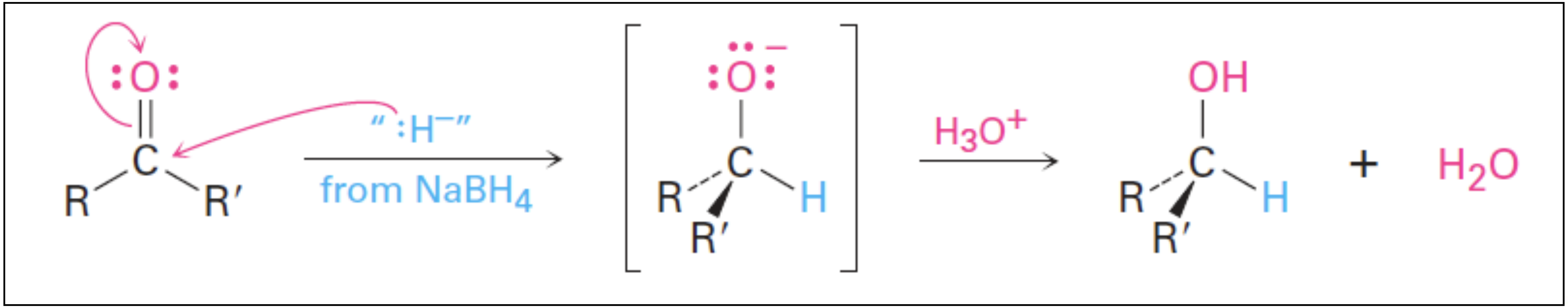
Acetaldeide **Etanolo**



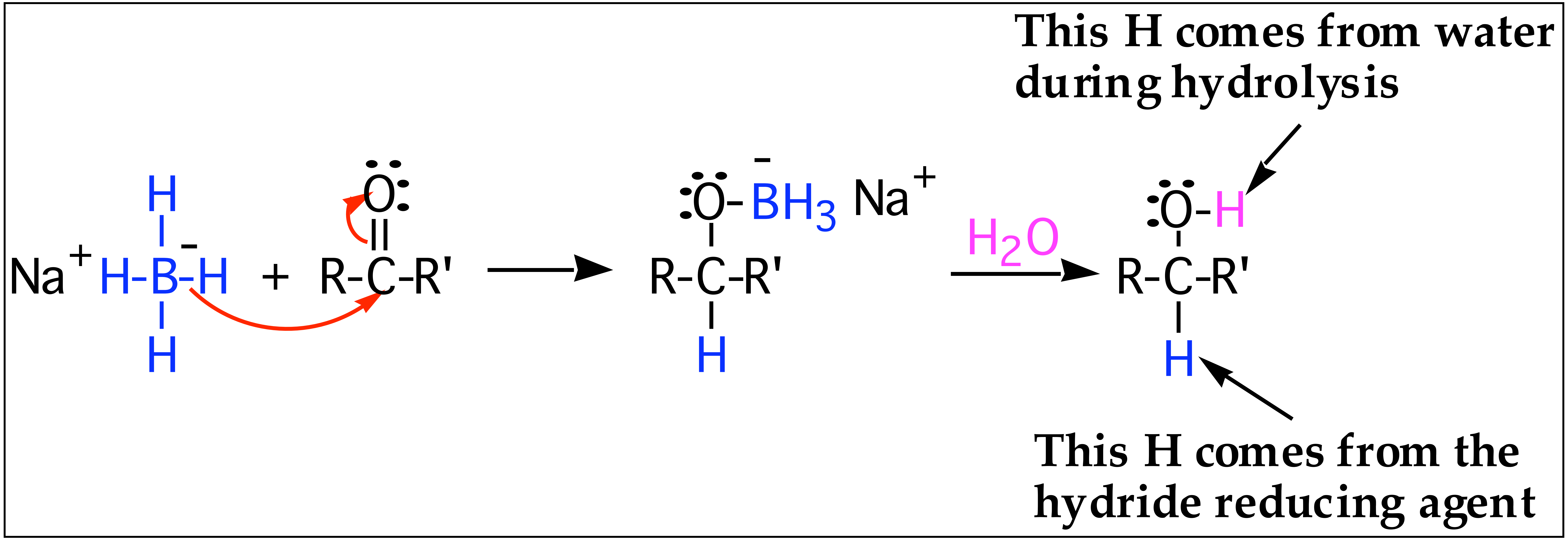
Riduzione con ione idruro (H:$^{-}$)







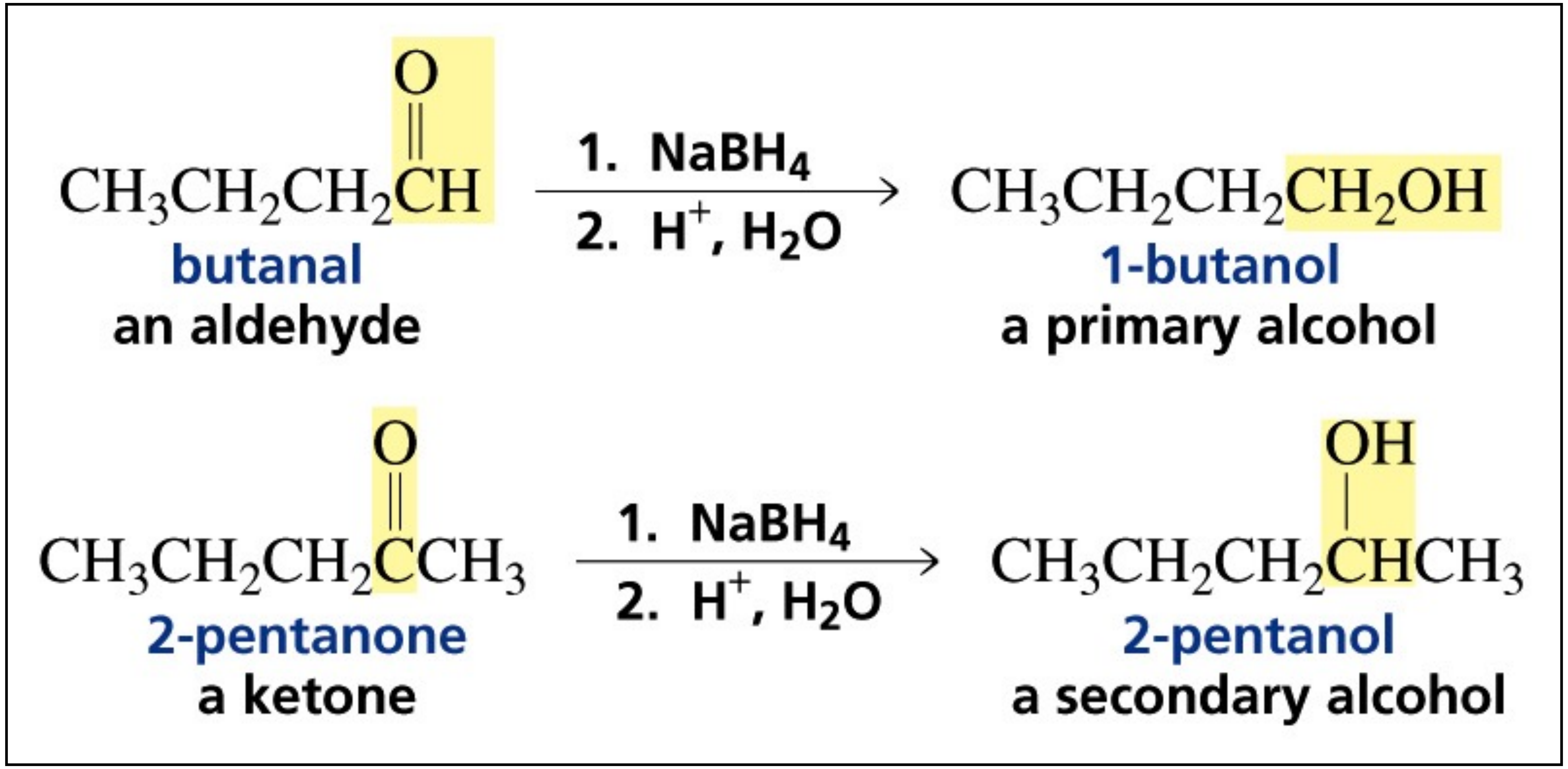
Meccanismo di Riduzione del $NaBH_4$ fonte di ($H:^-$)



This H comes from water during hydrolysis

This H comes from the hydride reducing agent

Riduzione con NaBH₄ fonte di (H:⁻)



$$CH_3CH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}H \xrightarrow[2.\ H^+,\ H_2O]{1.\ NaBH_4} CH_3CH_2CH_2CH_2OH$$

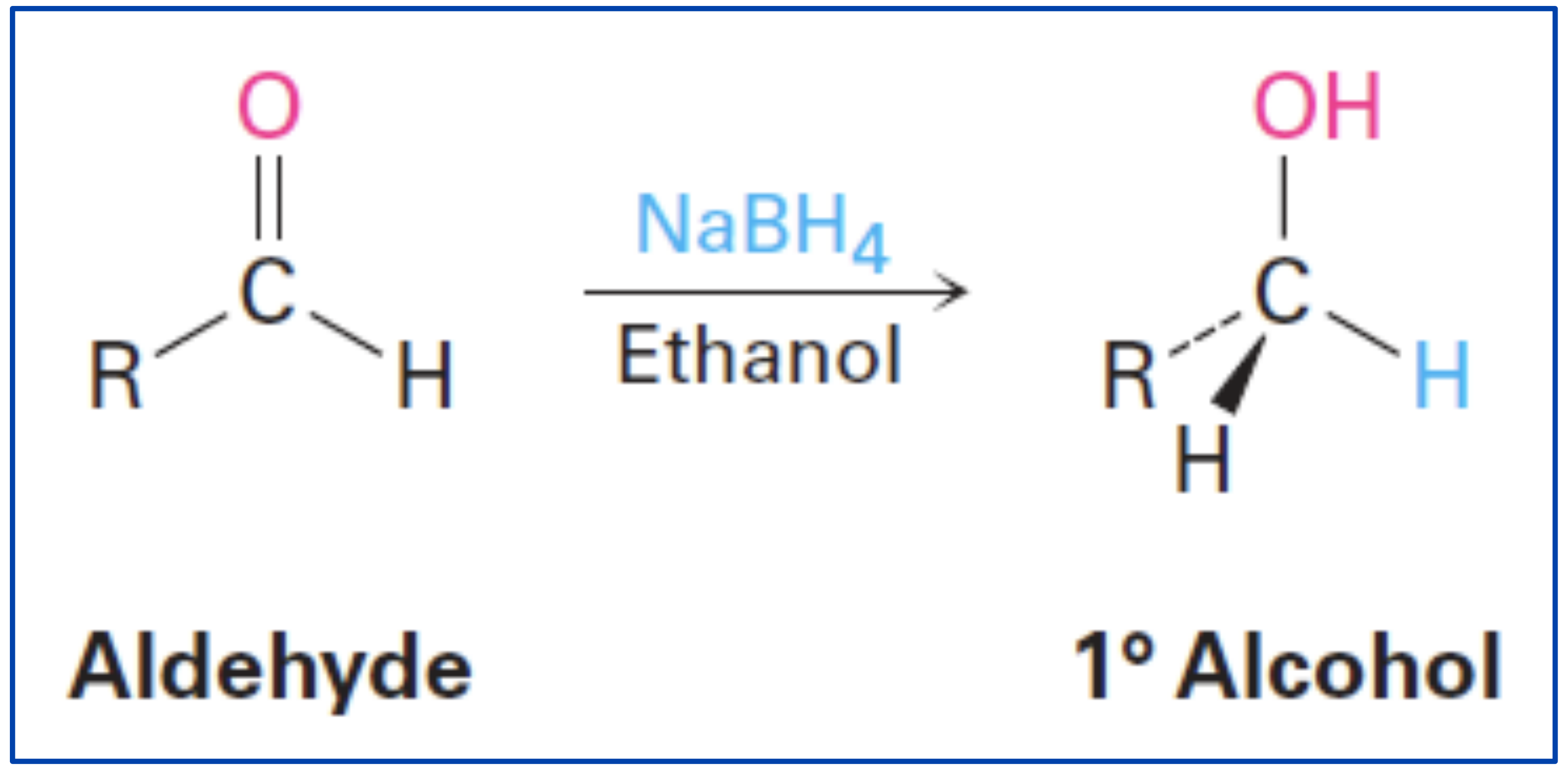
butanal
an aldehyde

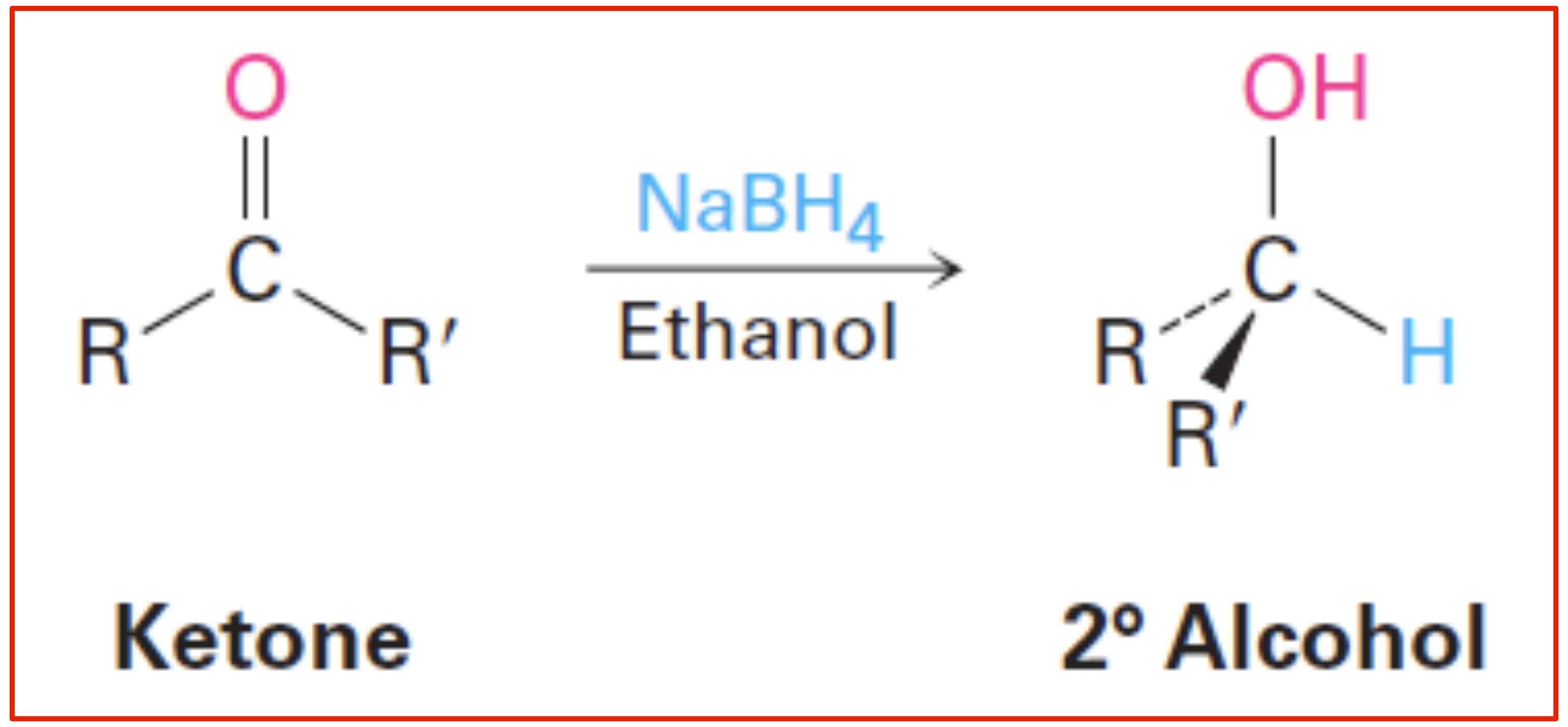
1-butanol
a primary alcohol

$$CH_3CH_2CH_2\overset{\overset{\displaystyle O}{\|}}{C}CH_3 \xrightarrow[2.\ H^+,\ H_2O]{1.\ NaBH_4} CH_3CH_2CH_2\overset{\overset{\displaystyle OH}{|}}{C}HCH_3$$

2-pentanone
a ketone

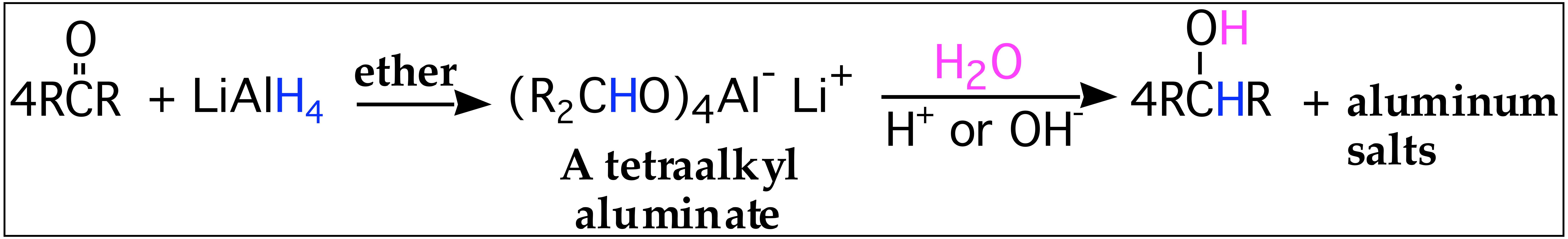
2-pentanol
a secondary alcohol





Riduzione dei chetoni con $LiAlH_4$ fonte di ($H:^-$)

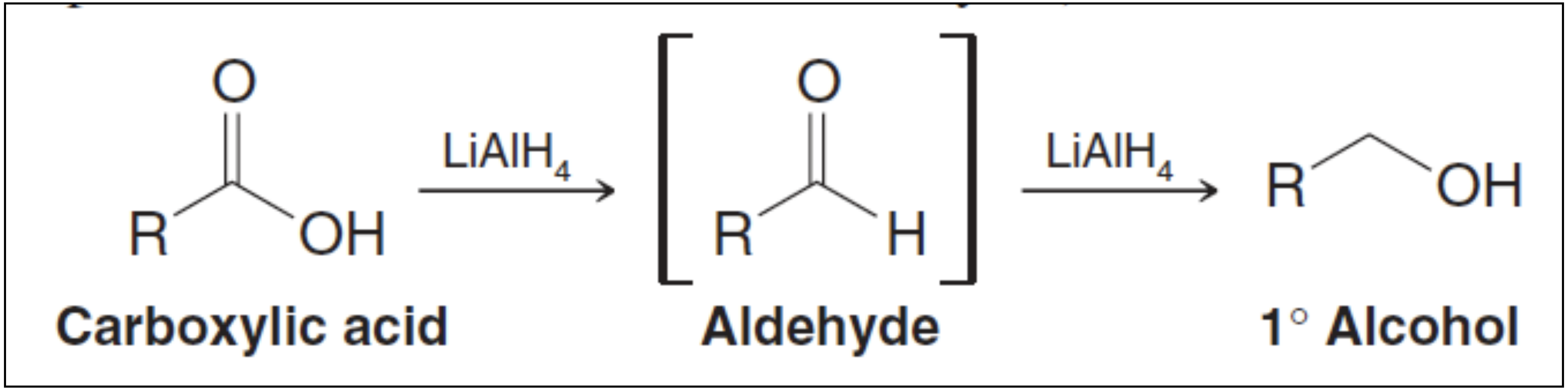
- A differenza di $NaBH_4$, $LiAlH_4$ reagisce violentemente con acqua, alcol e altri solventi protici
- La riduzione deve avvenire in etere

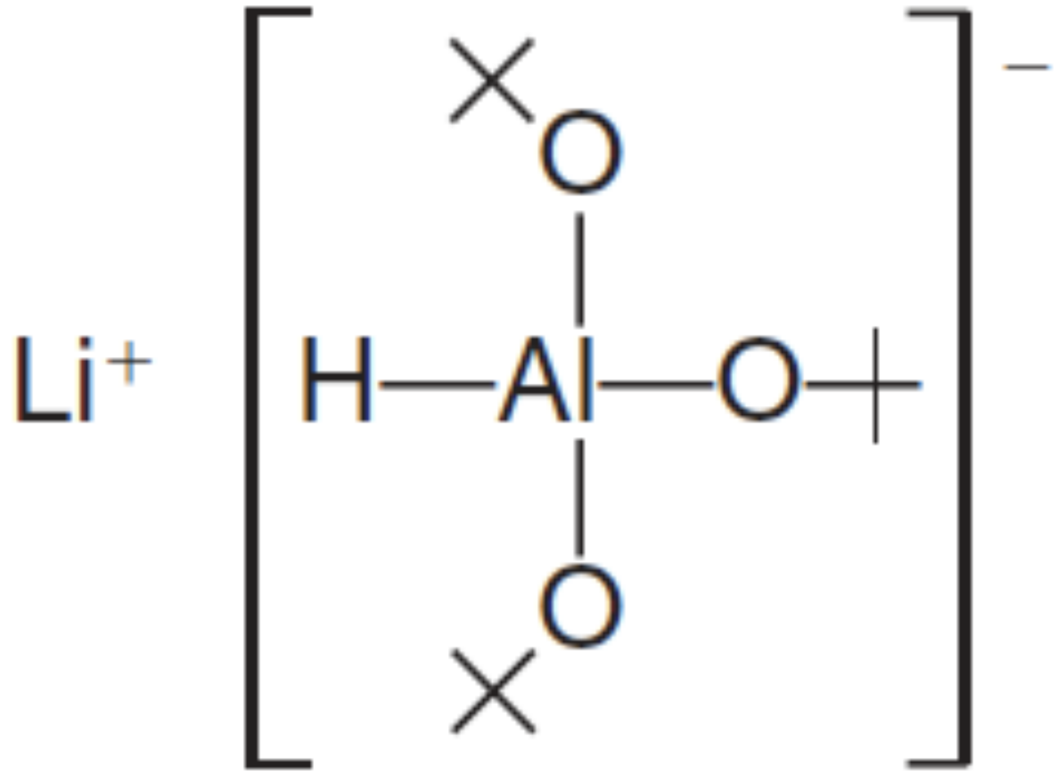


$$4R\overset{O}{\overset{\|}{C}}R + LiAlH_4 \xrightarrow{\text{ether}} (R_2CHO)_4Al^- \, Li^+ \xrightarrow[H^+ \text{ or } OH^-]{H_2O} 4R\overset{OH}{\overset{|}{C}}HR + \text{aluminum salts}$$

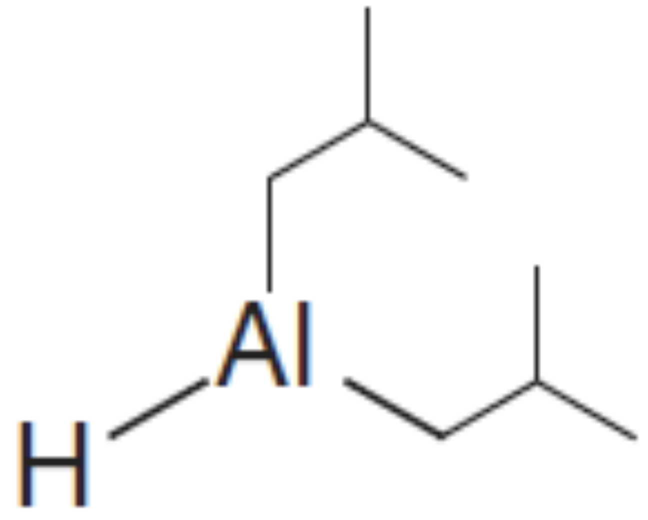
A tetraalkyl aluminate

Riduzione degli acidi carbossilici e aldeidi con $LiAlH_4$ fonte di ($H:^-$)

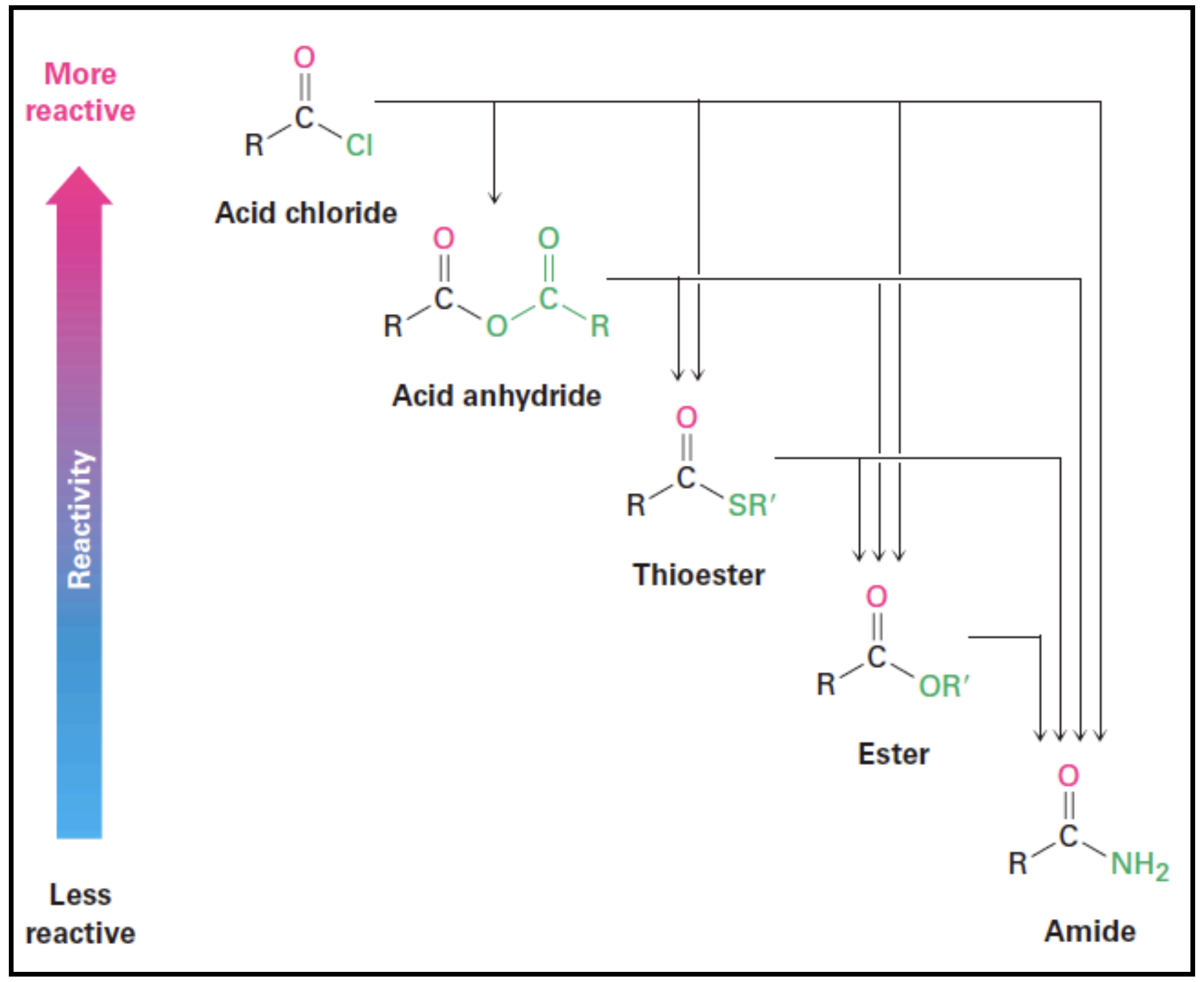




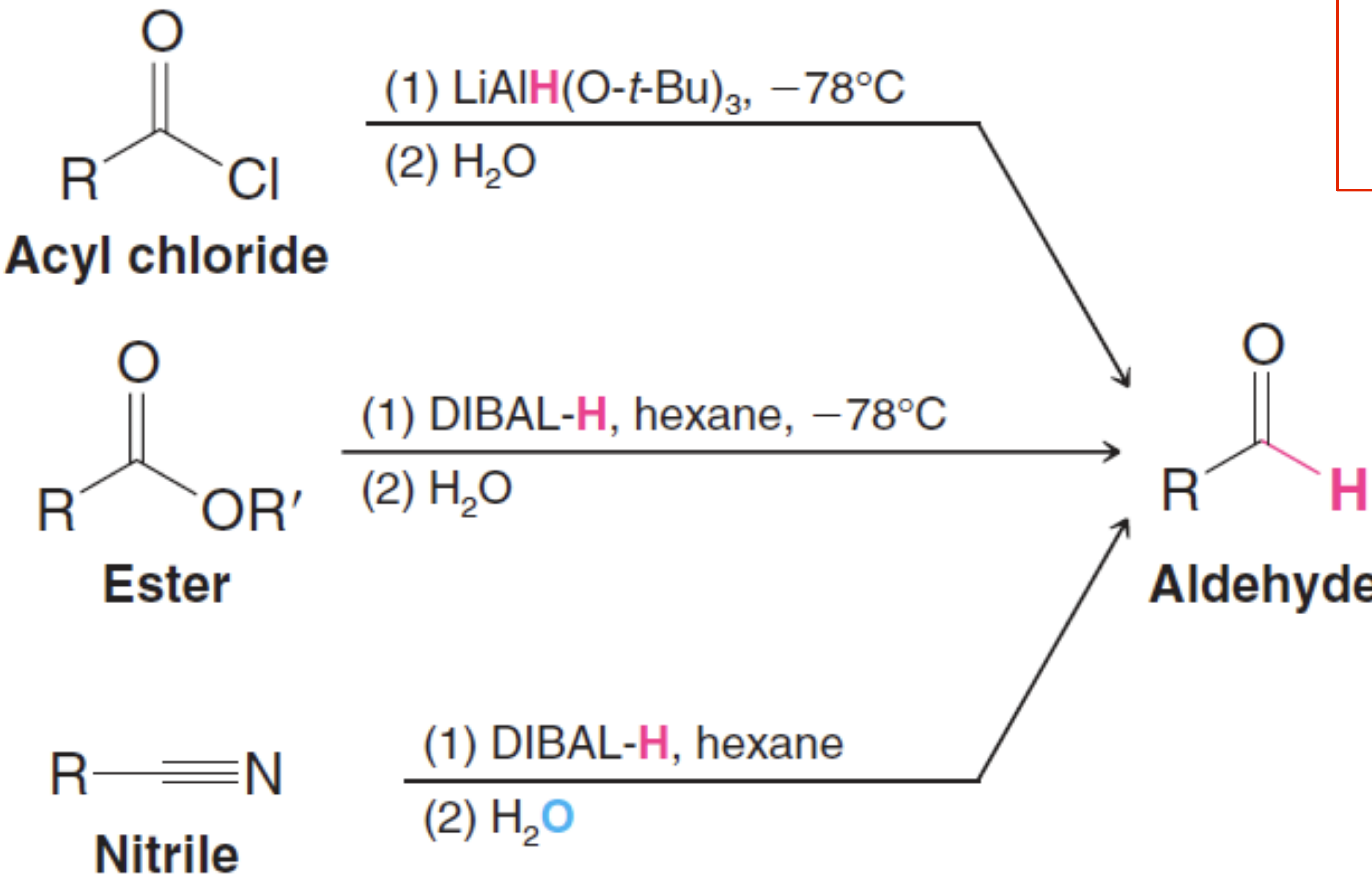
Lithium tri-*tert*-butoxy-aluminum hydride

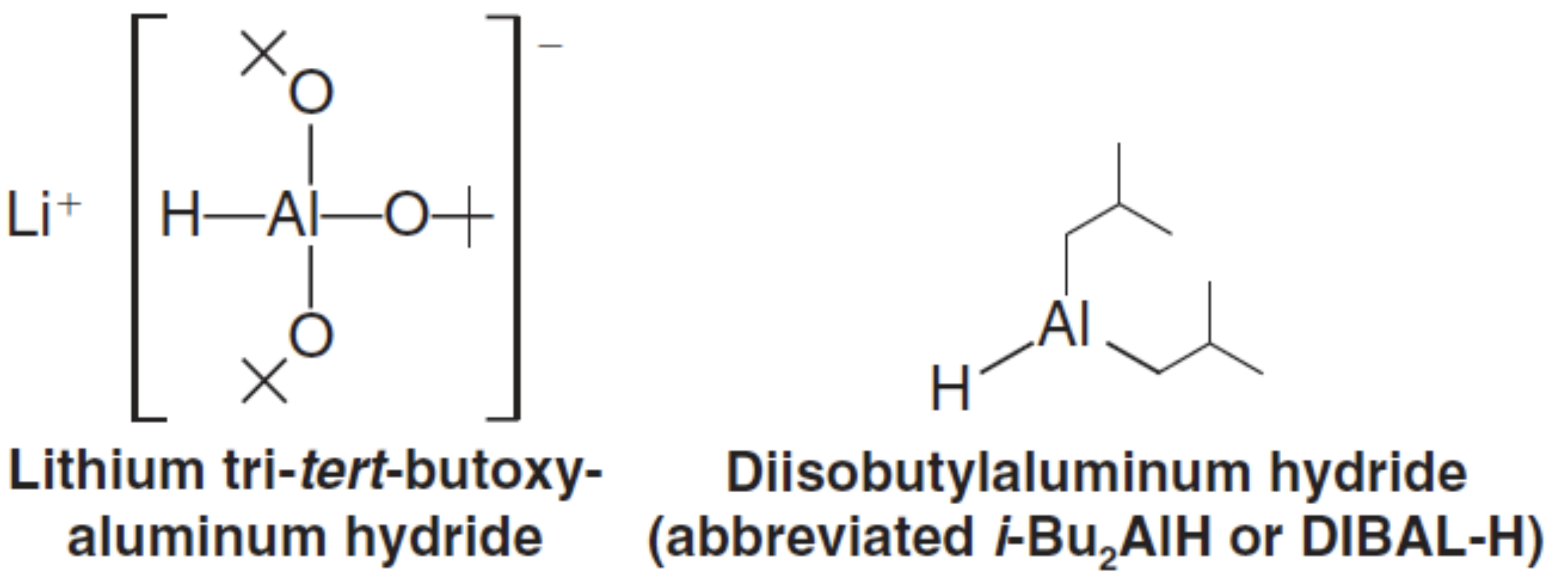


Diisobutylaluminum hydride (abbreviated *i*-Bu_2AlH or DIBAL-H)

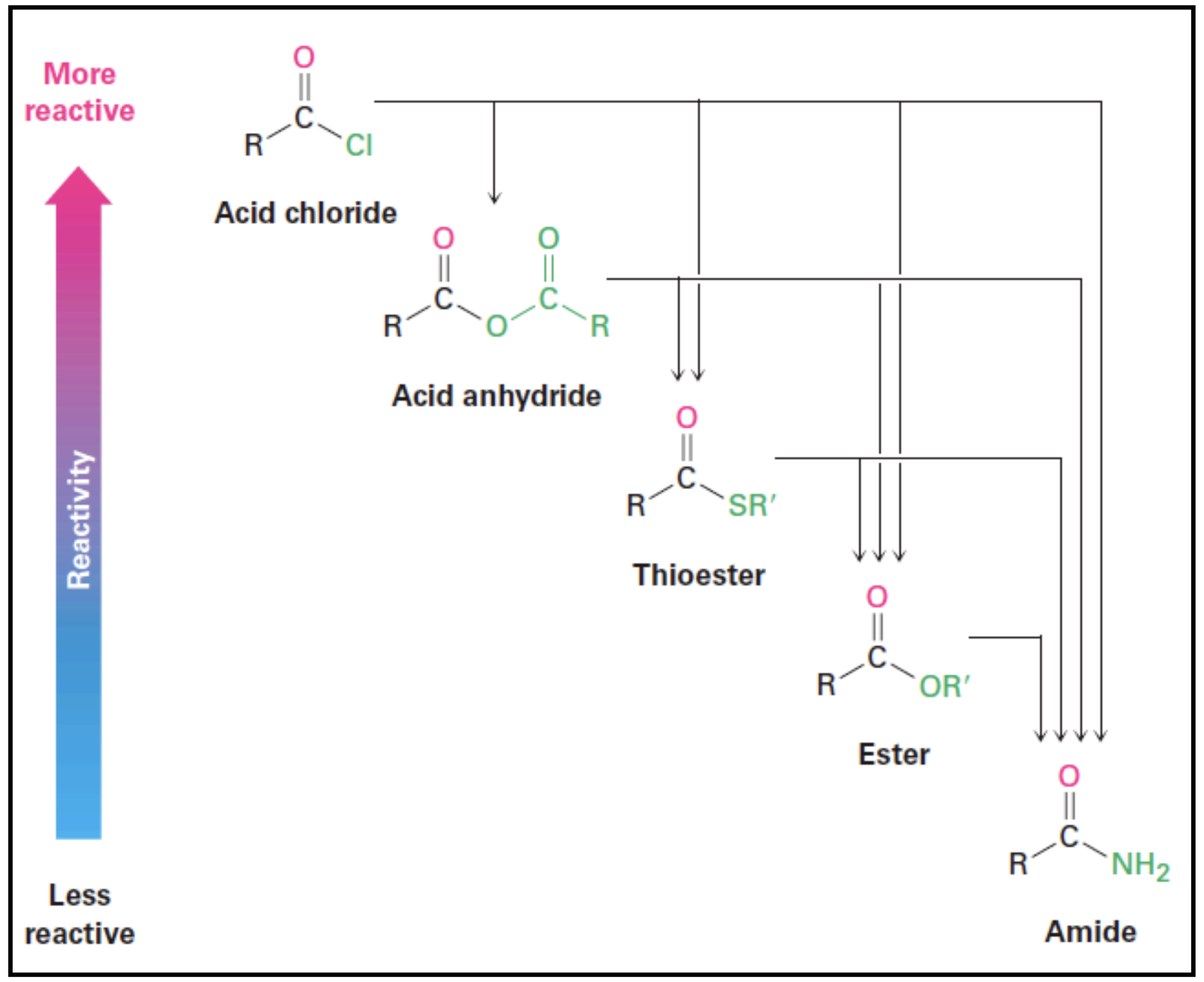


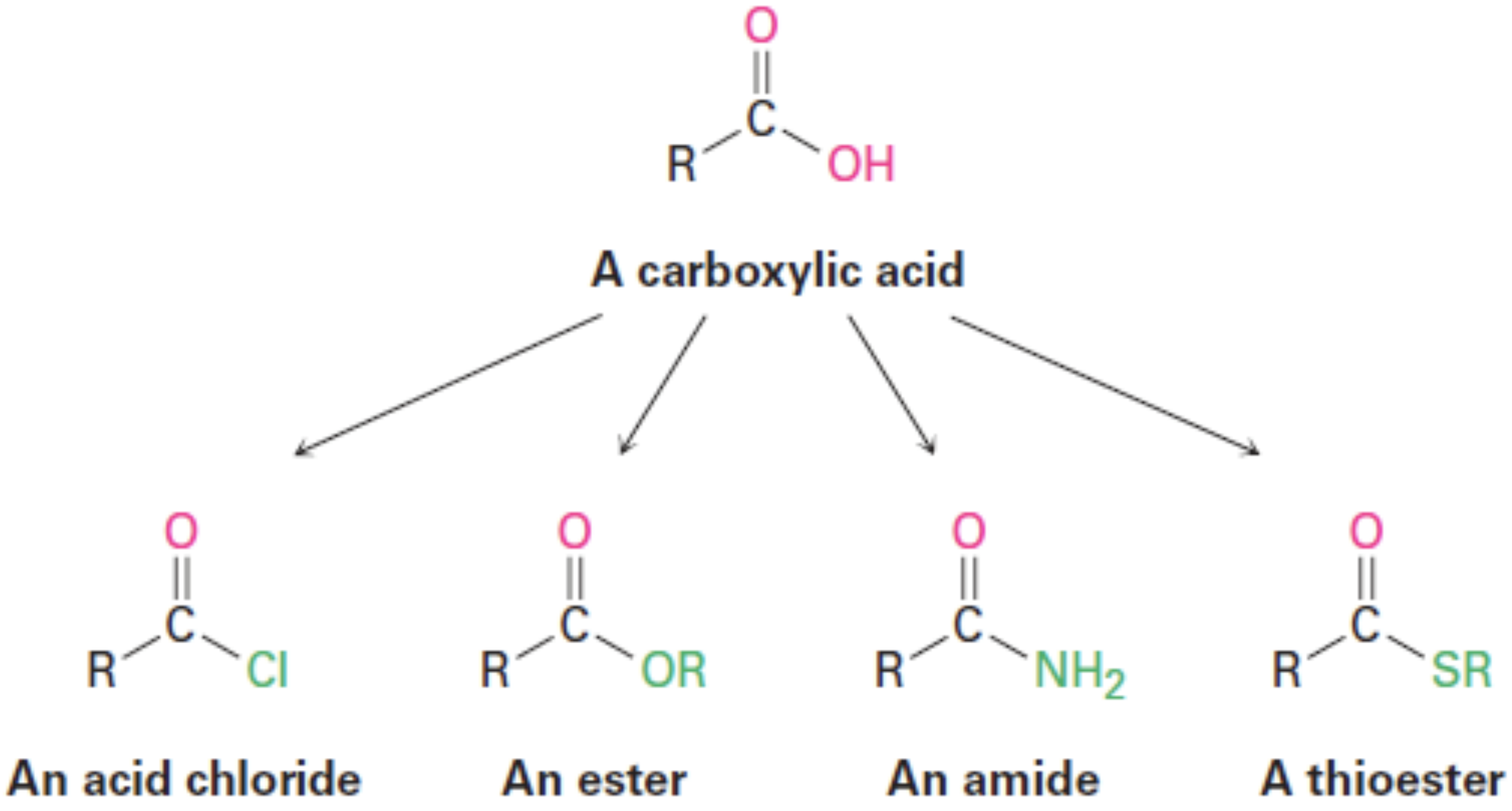
Formazioni delle delle aldeidi con riduttori deboli (DIBAL) in presenza di cloruro acilico, estere e nitrile.

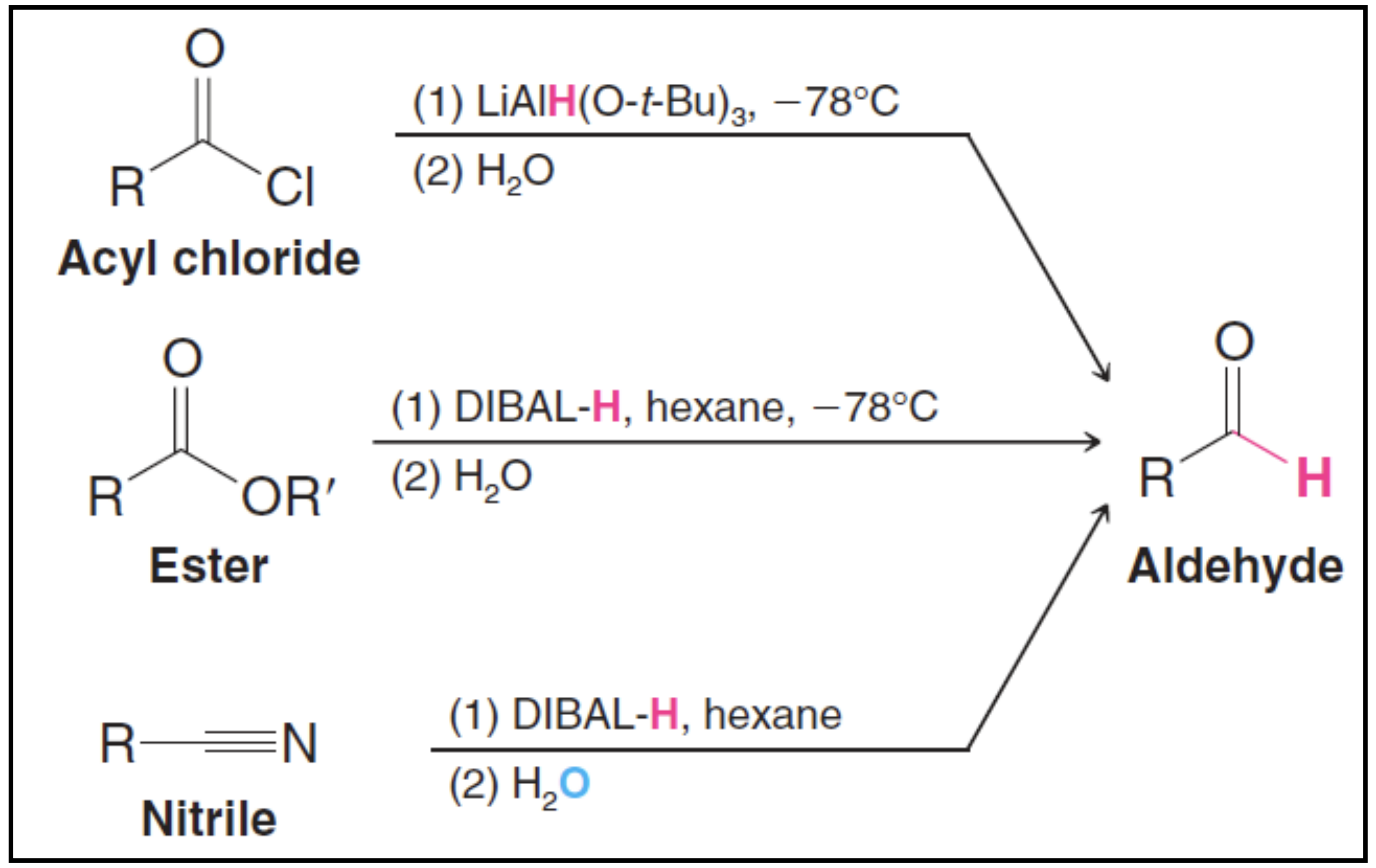


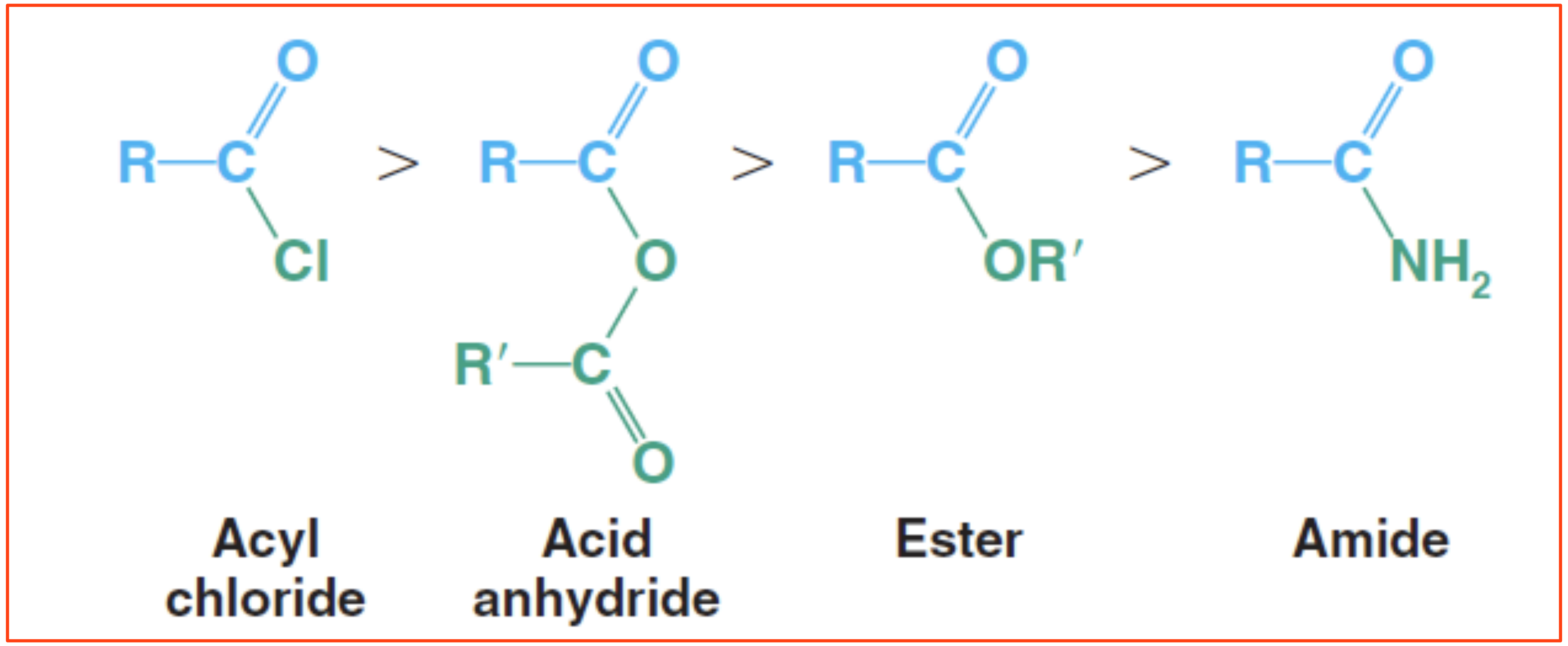


Derivati dell'acido carbossilico

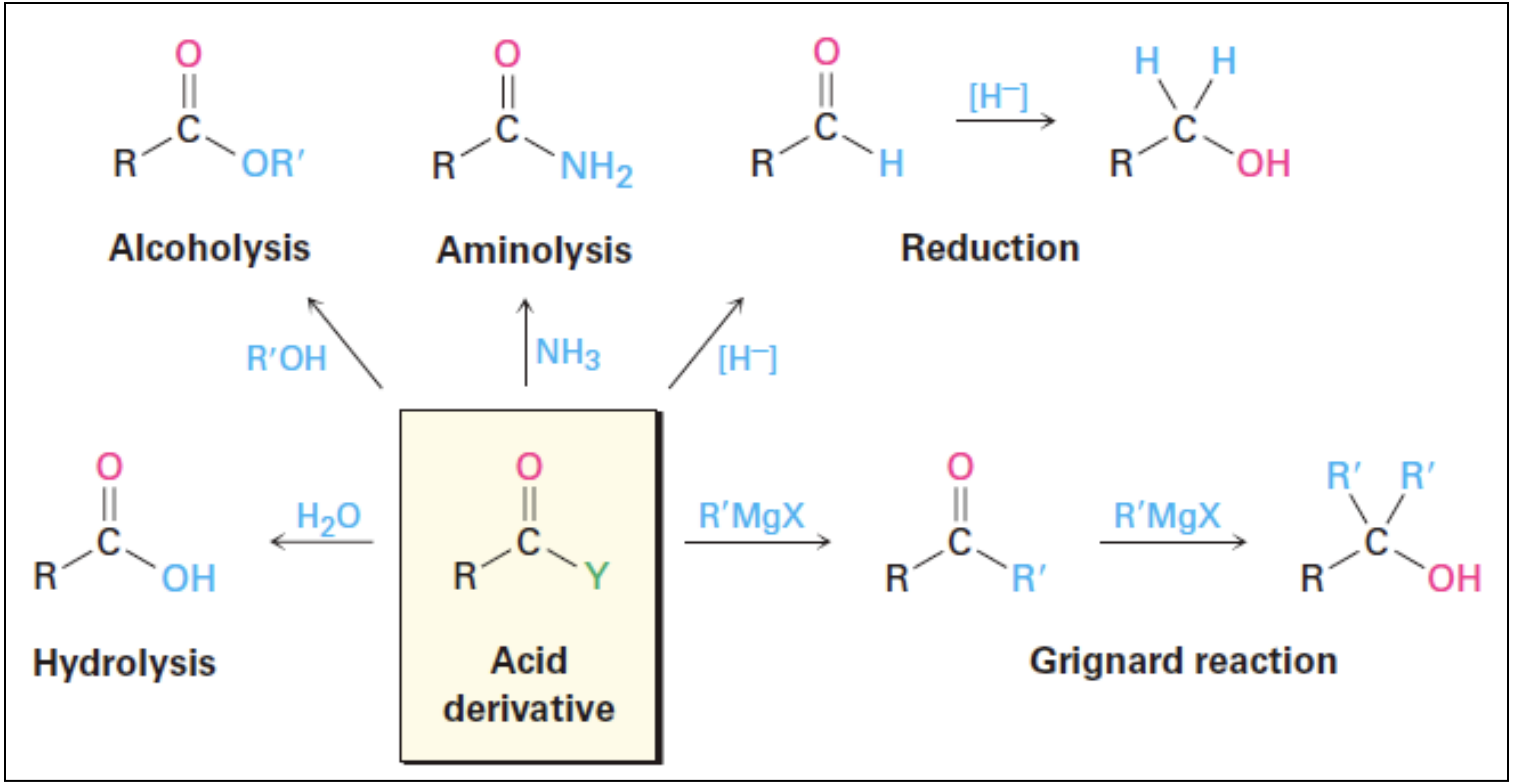




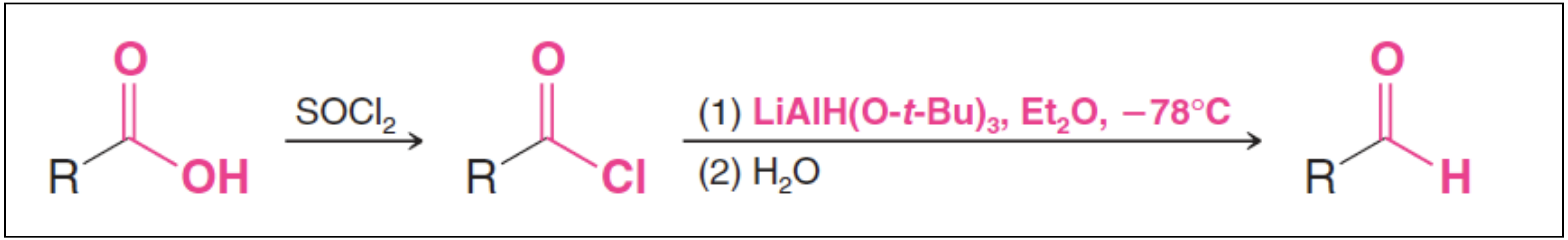


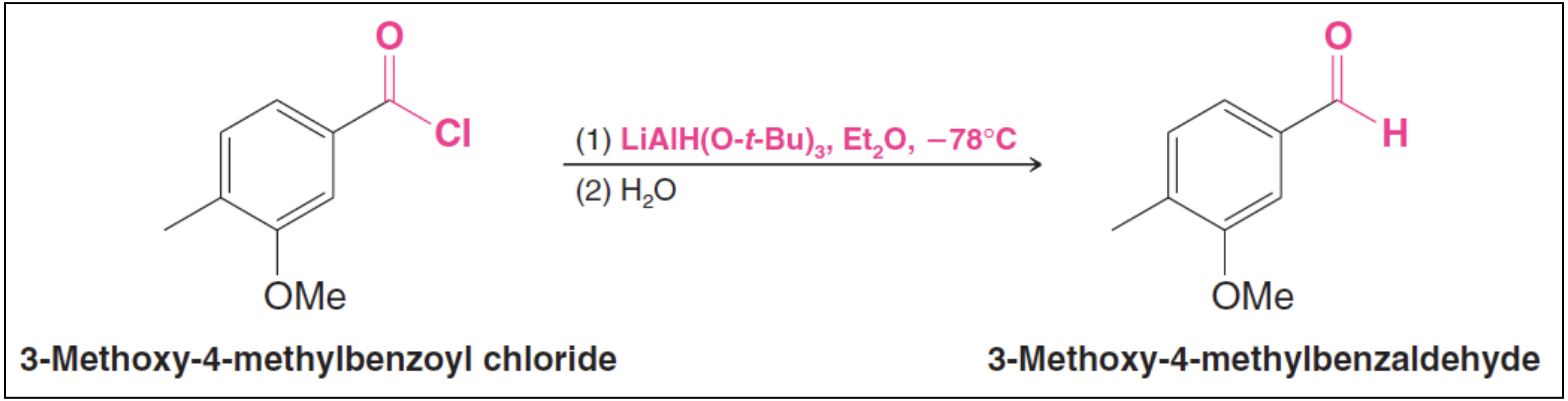


Addizione-eliminazione al carbonio acilico



Sintesi di aldeidi da acidi e derivati carbossilici (Cloruro acilico)

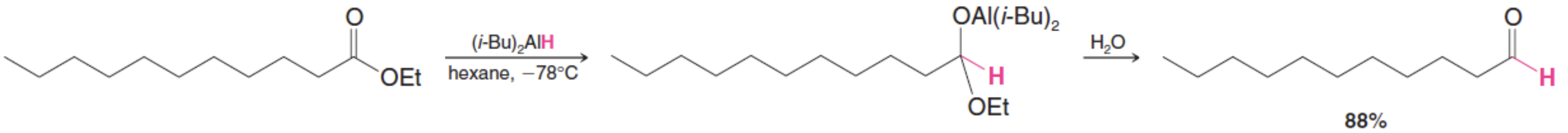


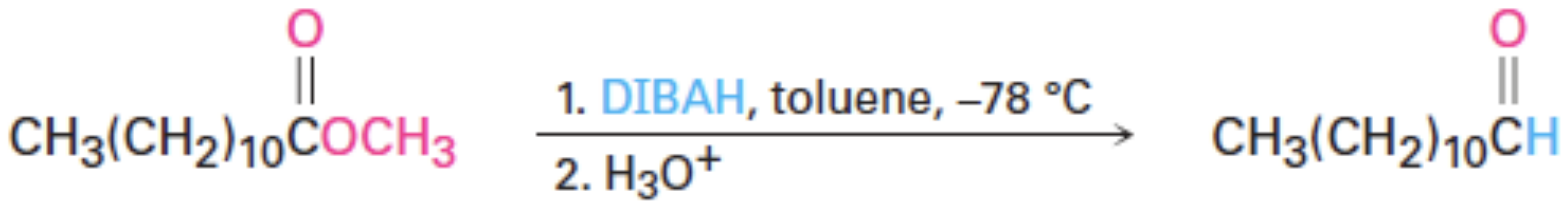


3-Methoxy-4-methylbenzoyl chloride

3-Methoxy-4-methylbenzaldehyde

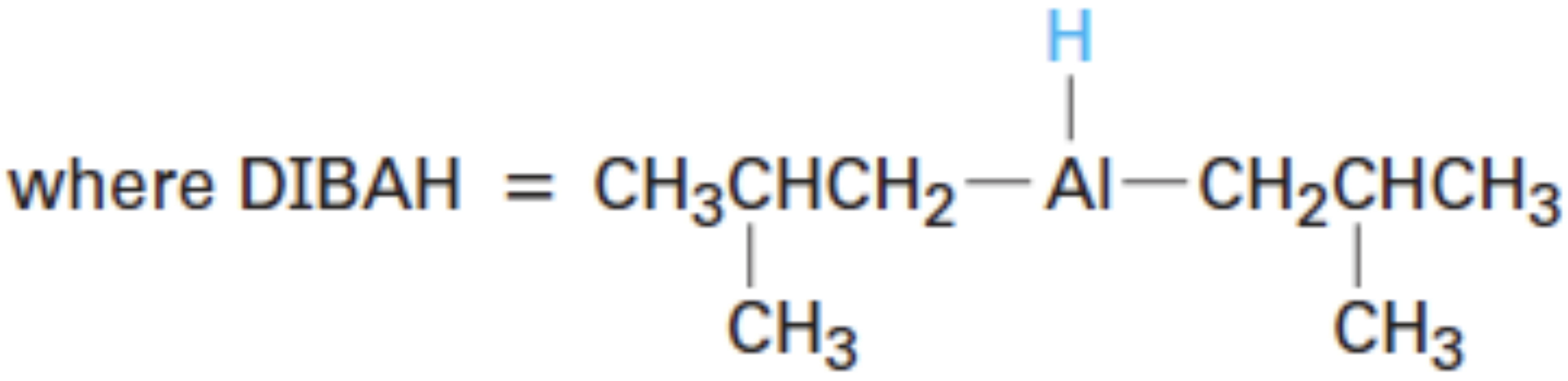
Sintesi di aldeidi da acidi e derivati carbossilici (Esteri)





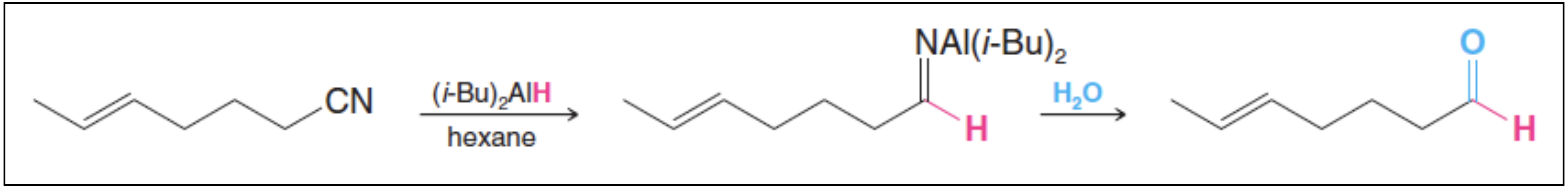
$$CH_3(CH_2)_{10}\overset{O}{\overset{\|}{C}}OCH_3 \xrightarrow[2.\ H_3O^+]{1.\ \text{DIBAH, toluene, –78 °C}} CH_3(CH_2)_{10}\overset{O}{\overset{\|}{C}}H$$

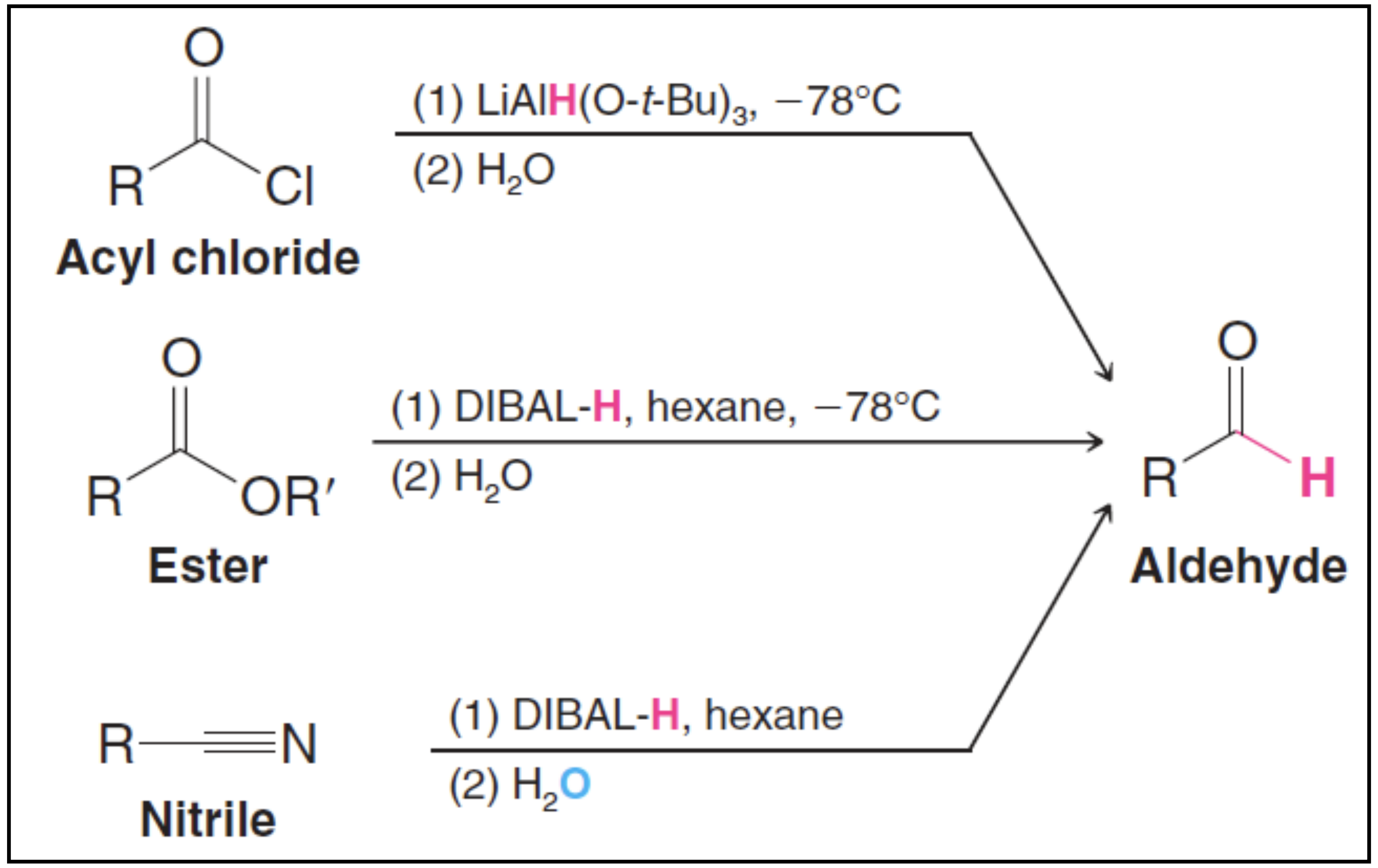
Methyl dodecanoate **Dodecanal (88%)**



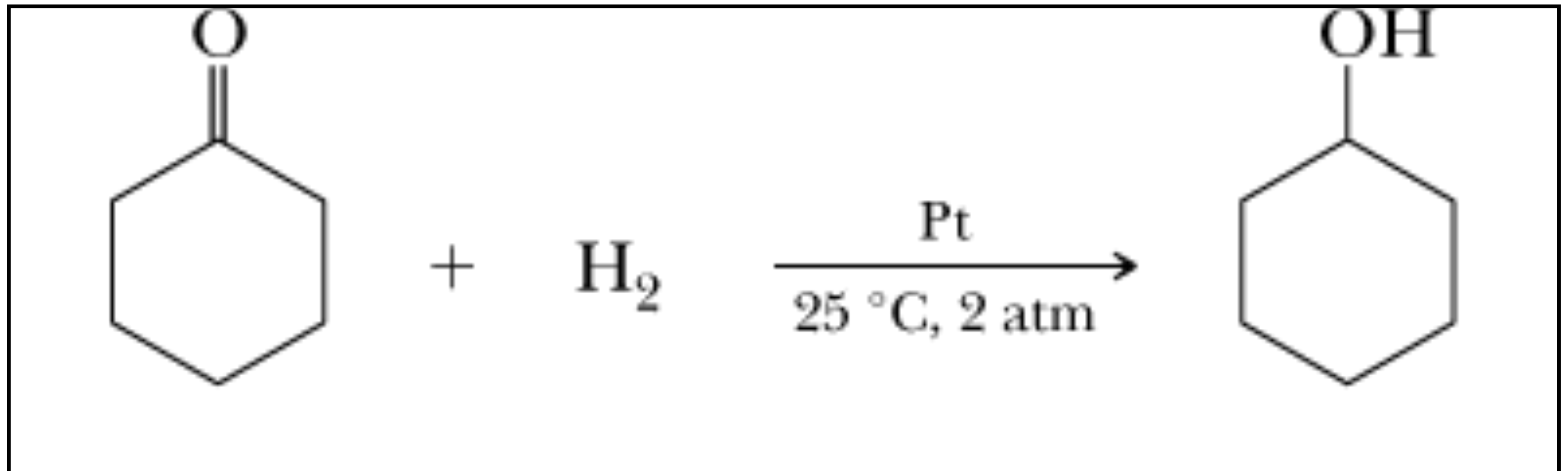
$$\text{where DIBAH} = CH_3\underset{\underset{CH_3}{|}}{C}HCH_2{-}\overset{\overset{H}{|}}{Al}{-}CH_2\underset{\underset{CH_3}{|}}{C}HCH_3$$

Sintesi di aldeidi da acidi e derivati carbossilici (Nitrili)

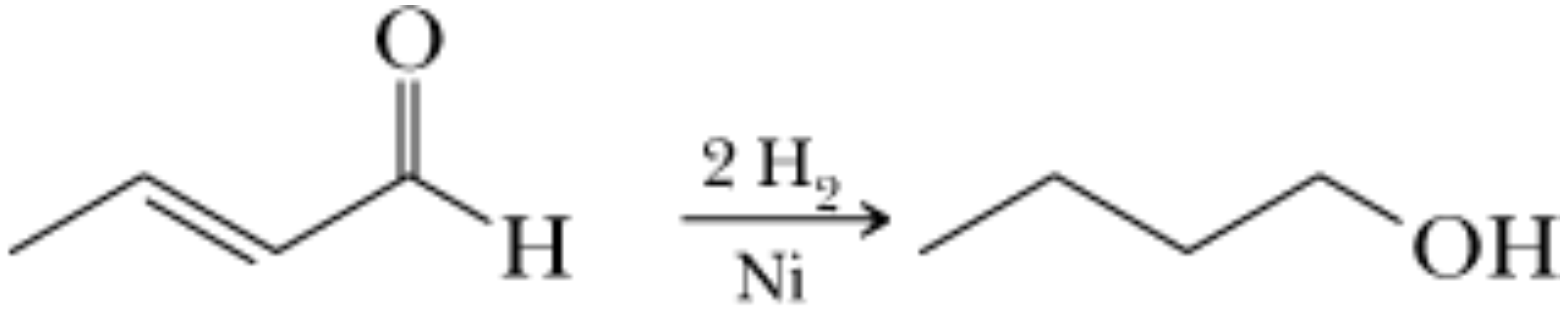




B. Riduzione catalitica



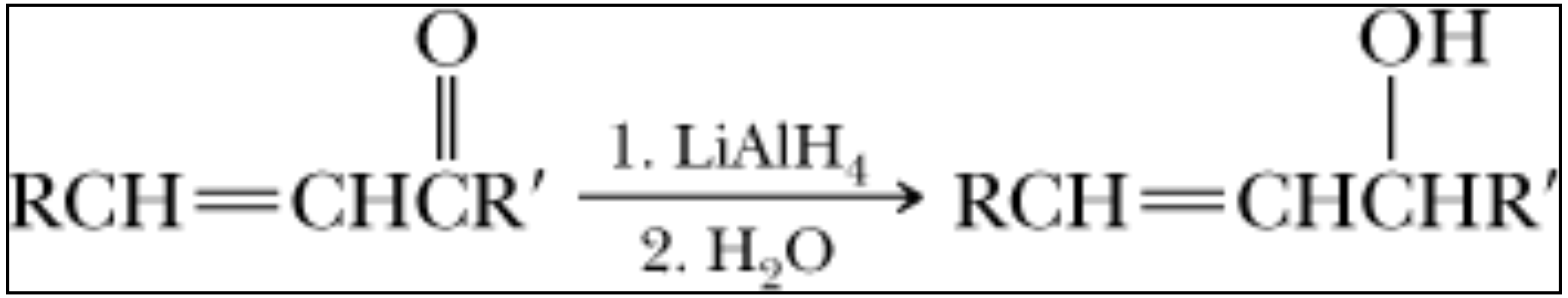
Cicloesanone **Cicloesanolo**



***trans*-2-Butenale**
(Crotonaldeide)

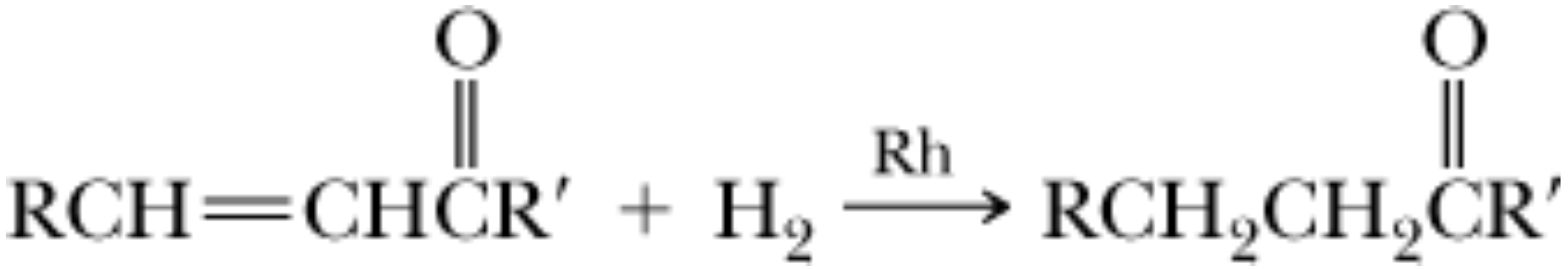
1-Butanolo

C. Riduzione selettiva



$$\mathrm{RCH{=}CH\overset{O}{\overset{\|}{C}}R' \xrightarrow[2.\ H_2O]{1.\ LiAlH_4} RCH{=}CH\overset{OH}{\overset{|}{C}}HR'}$$

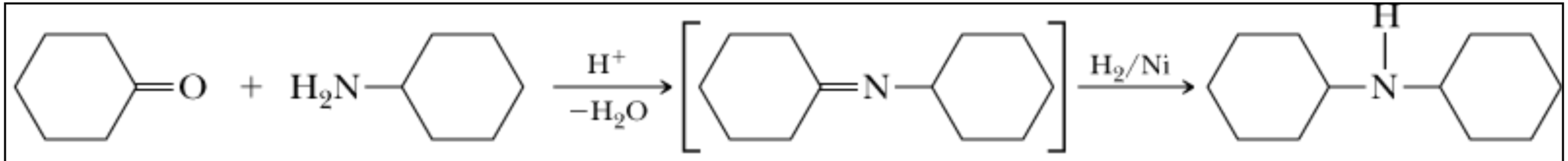
Utilizzando gli idruri metallici è possibile ridurre il gruppo carbonilico di un’aldeide o di un chetone senza ridurre i legami presenti nella stessa molecola. Gli idruri metallici, come LiAlH4 e NaBH4, sono reagenti nucleofili. I gruppi funzionali che non sono elettrofili, come i legami negli alcheni, non reagiscono.



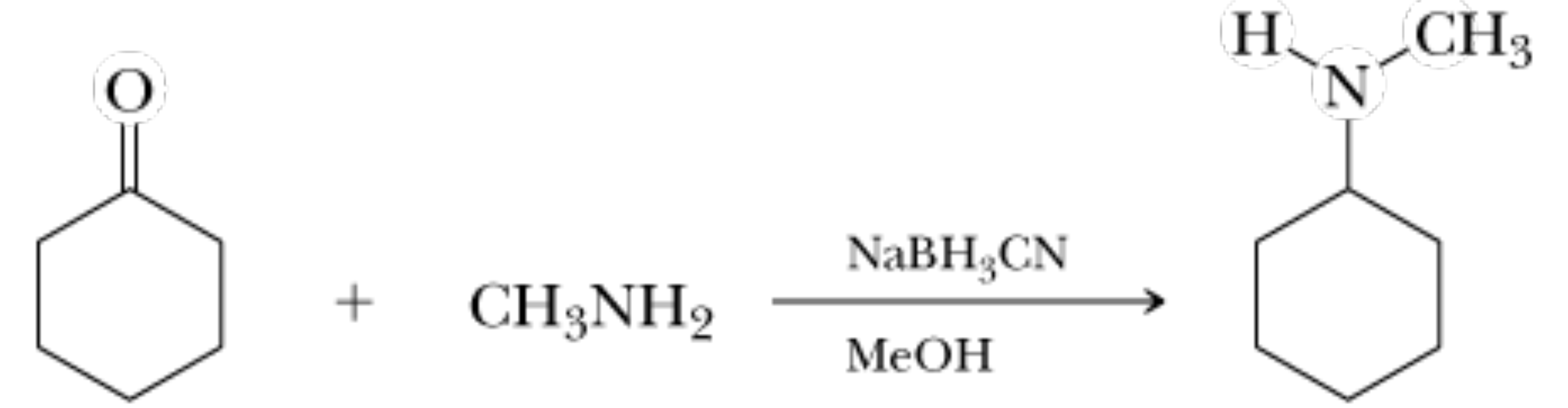
$$\mathrm{RCH{=}CH\overset{O}{\overset{\|}{C}}R' + H_2 \xrightarrow{Rh} RCH_2CH_2\overset{O}{\overset{\|}{C}}R'}$$

la riduzione selettiva del doppio legame carbonio-carbonio in presenza di un gruppo carbonilico, impiegando rodio su polvere di carbone come catalizzatore.

D. Amminazione riduttiva



Cicloesanone **Cicloesilammina** (Immina intermedia) **Dicicloesilammina**

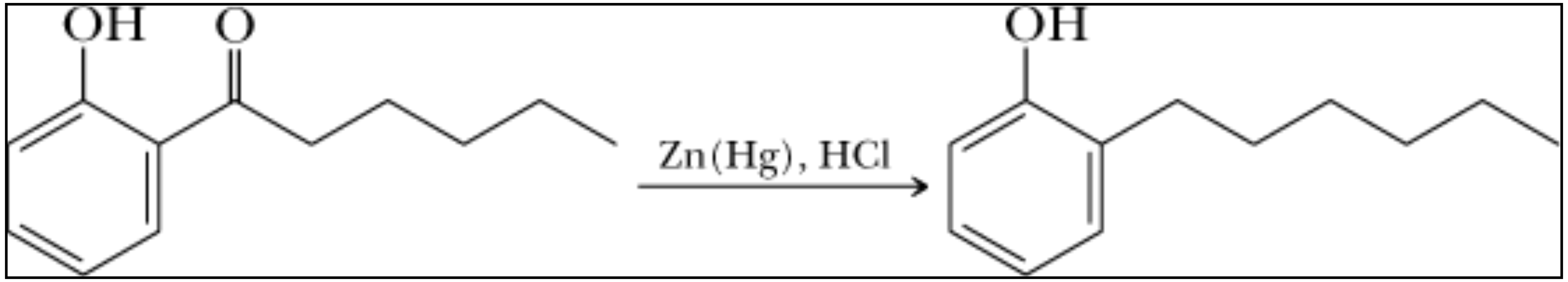


Cicloesanone ***N*-Metilcicloesilammina**

È anche possibile svolgere l’amminazione riduttiva in un solo passaggio utilizzando un agente riducente che non sia abbastanza potente da ridurre l’aldeide o chetone, ma che sia abbastanza forte da ridurre l’immina prodotta (che è più facile da ridurre). L’agente riducente utilizzato di solito è il cianoboroidruro di sodio, NaBH3CN

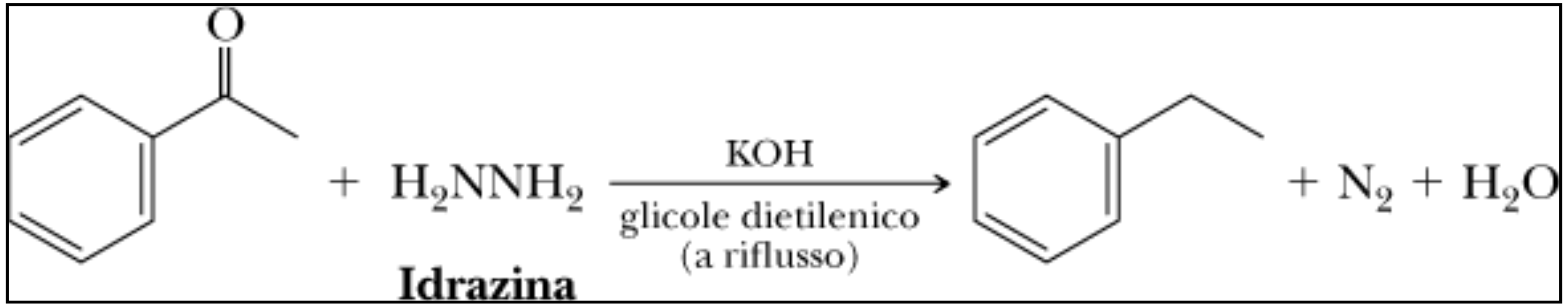
E. Riduzione di un gruppo carbonilico a gruppo metilenico

Riduzione di Clemmensen



Sono disponibili diversi metodi per ridurre il gruppo carbonilico di un'aldeide o di un chetone a gruppo metilenico (—CH2—). Uno dei primi metodi scoperti consiste nel far bollire a riflusso l'aldeide o il chetone con amalgama di Zn (ossia zinco con uno strato superficiale di mercurio) in HCl concentrato.

riduzione di Wolff-Kishner,



La riduzione di Wolff-Kishner, scoperta indipendentemente da N. Kishner nel 1911 e da L. Wolff nel 1912, e riportata pochi mesi dopo la scoperta di Clemmensen, è un metodo alternativo per ridurre un gruppo carbonilico a gruppo metilenico. In questa riduzione, una miscela di aldeide o chetone, idrazina e idrossido di potassio concentrato viene fatta bollire a riflusso in un solvente altobollente come il glicole dietilenico (p.e. 245 °C).

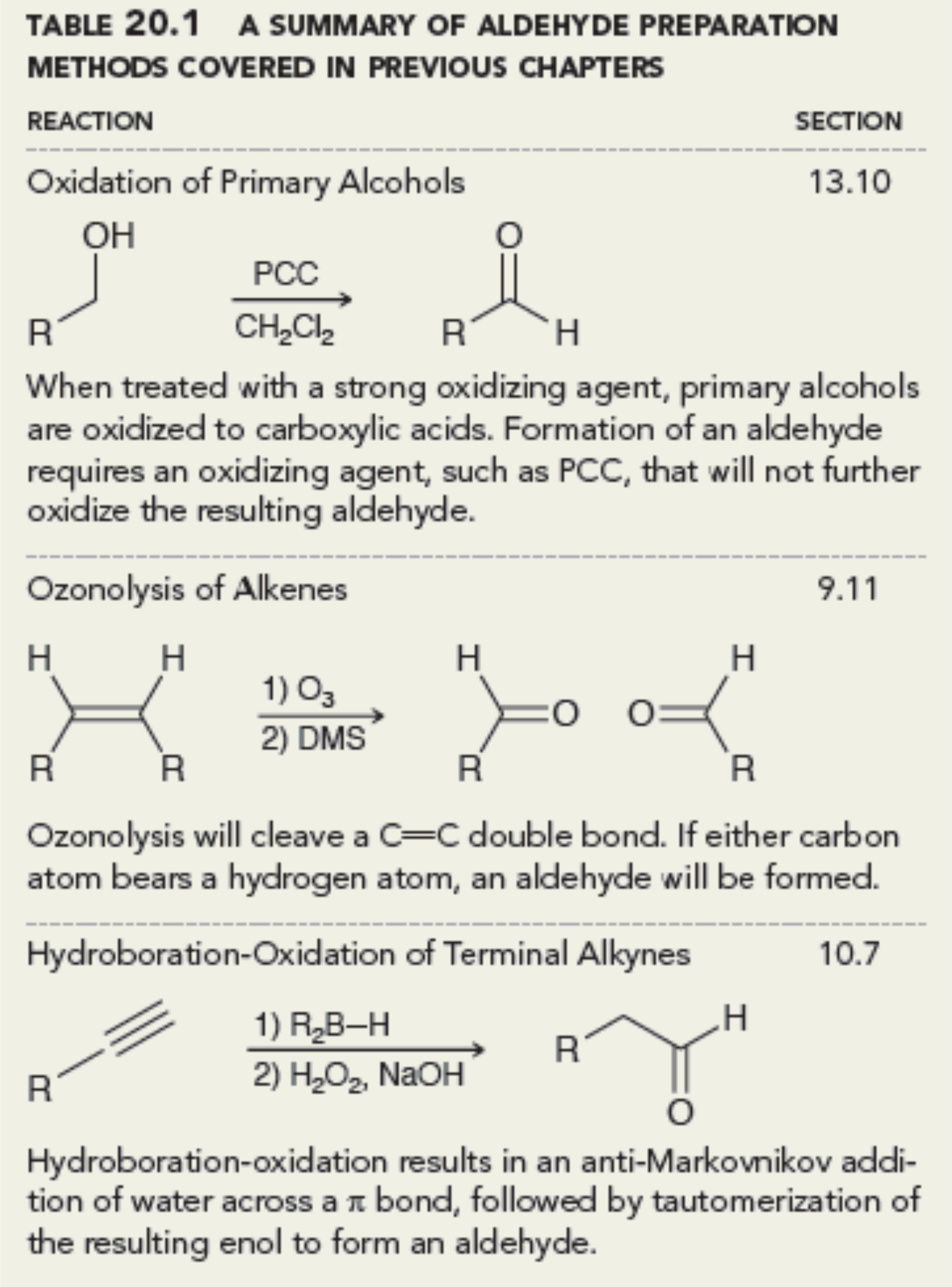


TABLE 20.1 A SUMMARY OF ALDEHYDE PREPARATION METHODS COVERED IN PREVIOUS CHAPTERS

REACTION	SECTION
Oxidation of Primary Alcohols $\xrightarrow[\text{CH}_2\text{Cl}_2]{\text{PCC}}$ When treated with a strong oxidizing agent, primary alcohols are oxidized to carboxylic acids. Formation of an aldehyde requires an oxidizing agent, such as PCC, that will not further oxidize the resulting aldehyde.	13.10
Ozonolysis of Alkenes $\xrightarrow[\text{2) DMS}]{\text{1) O}_3}$ Ozonolysis will cleave a C═C double bond. If either carbon atom bears a hydrogen atom, an aldehyde will be formed.	9.11
Hydroboration-Oxidation of Terminal Alkynes $\xrightarrow[\text{2) H}_2\text{O}_2\text{, NaOH}]{\text{1) R}_2\text{B–H}}$ Hydroboration-oxidation results in an anti-Markovnikov addition of water across a π bond, followed by tautomerization of the resulting enol to form an aldehyde.	10.7

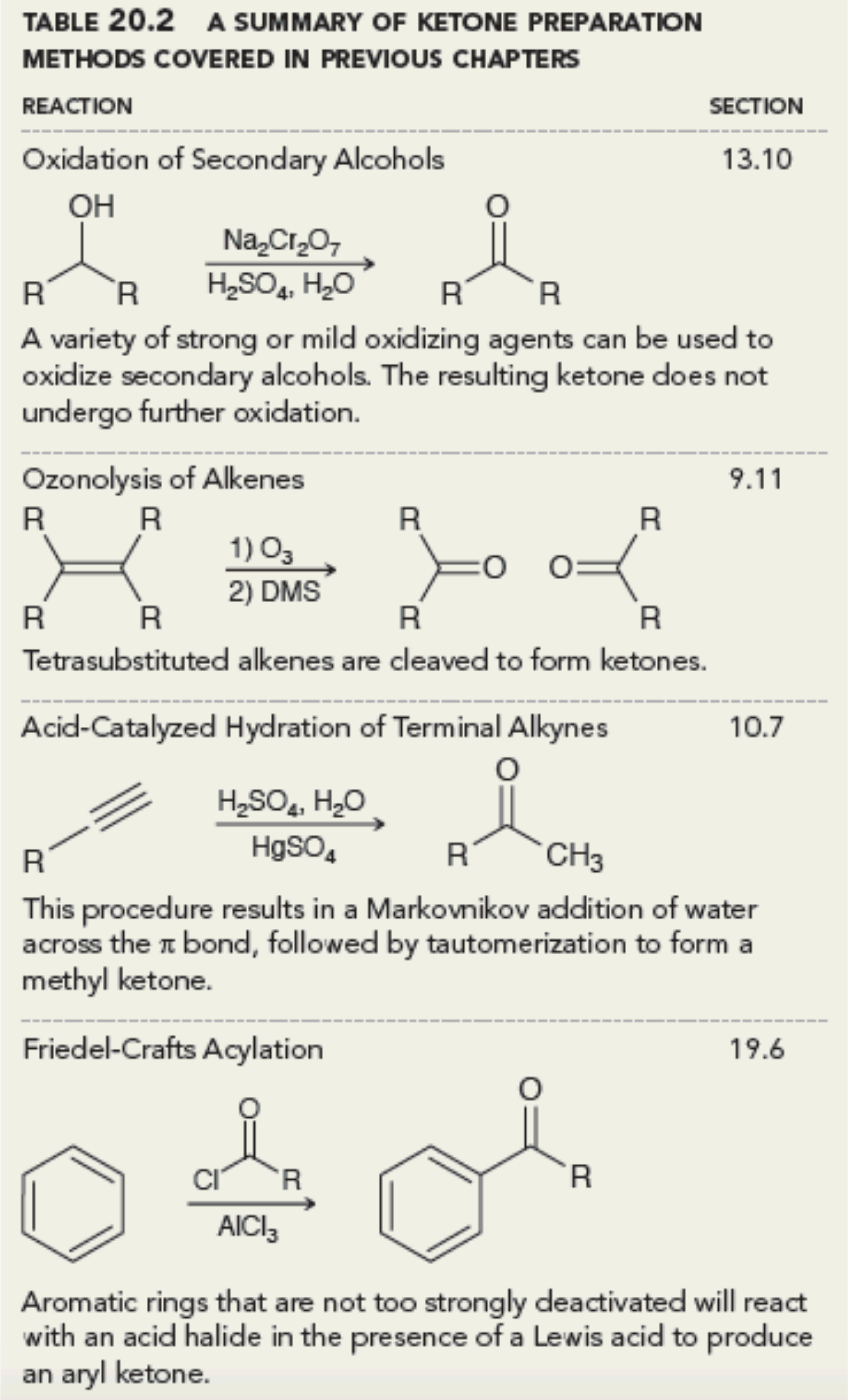
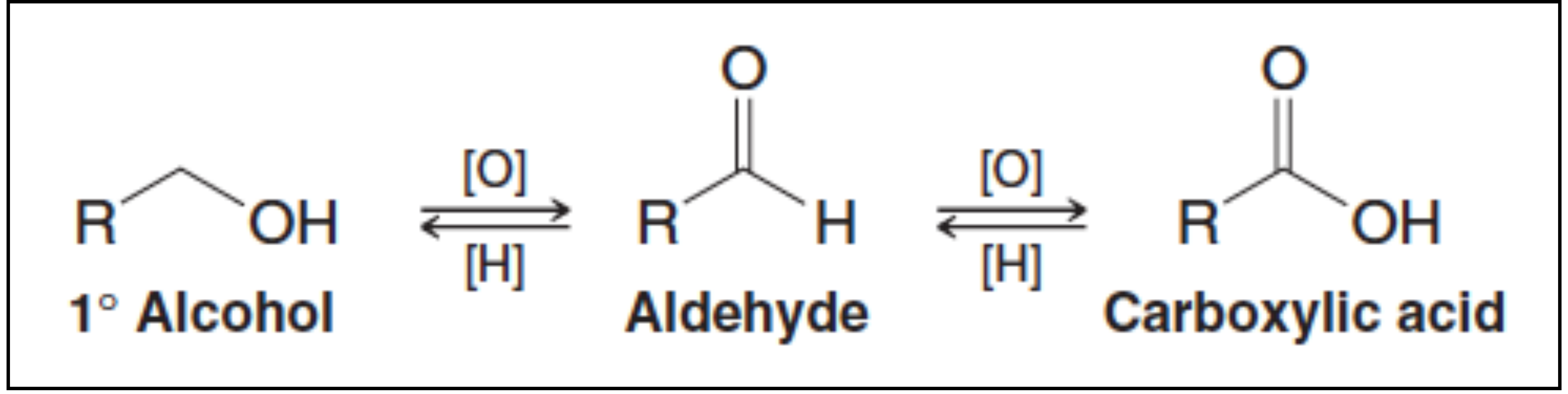
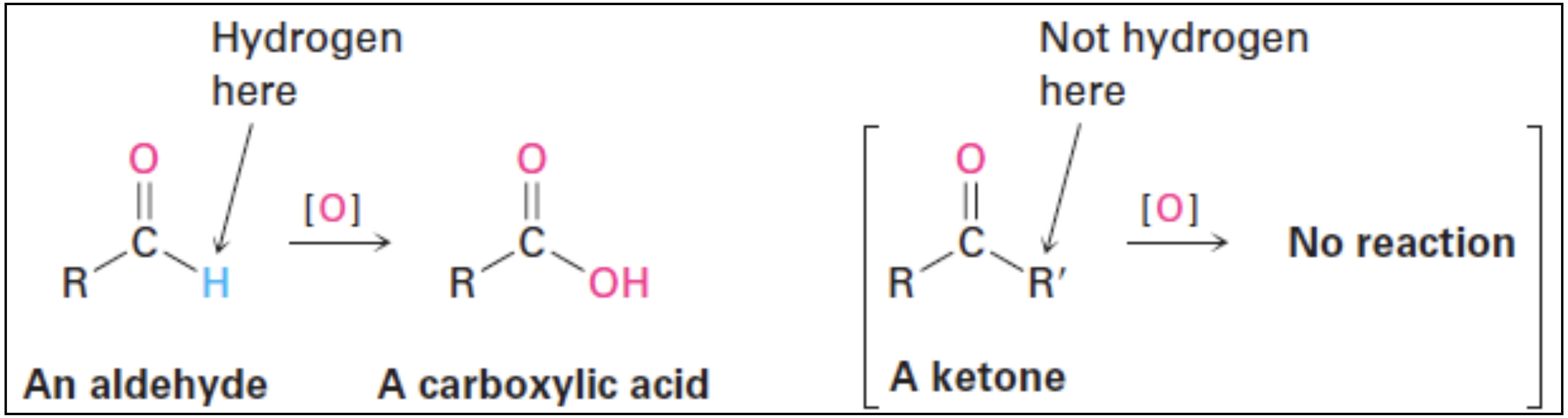


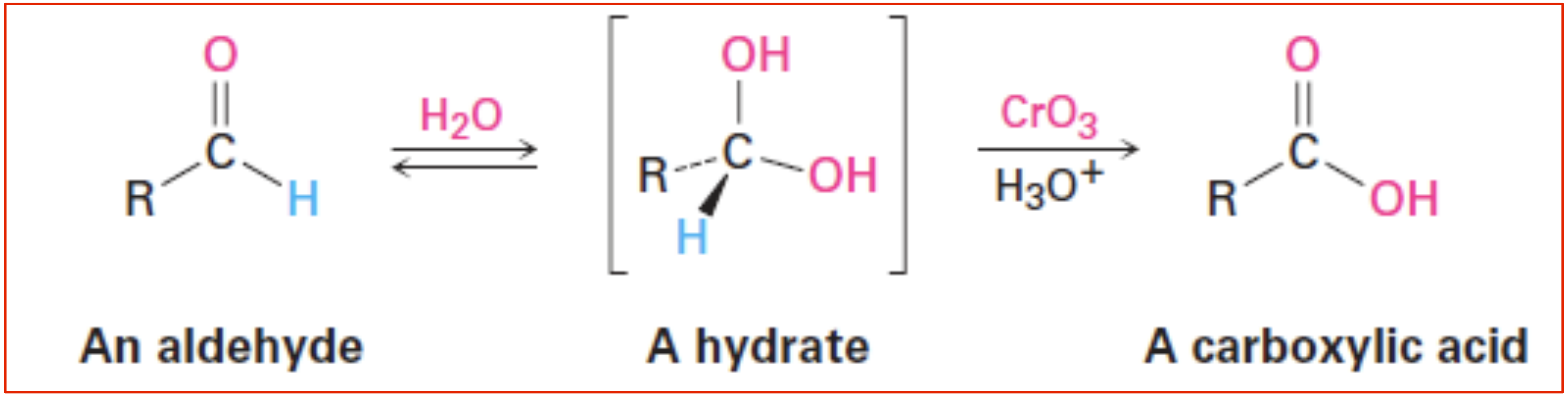
TABLE 20.2 A SUMMARY OF KETONE PREPARATION METHODS COVERED IN PREVIOUS CHAPTERS

REACTION	SECTION
Oxidation of Secondary Alcohols $\xrightarrow[\text{H}_2\text{SO}_4\text{, H}_2\text{O}]{\text{Na}_2\text{Cr}_2\text{O}_7}$ A variety of strong or mild oxidizing agents can be used to oxidize secondary alcohols. The resulting ketone does not undergo further oxidation.	13.10
Ozonolysis of Alkenes $\xrightarrow[\text{2) DMS}]{\text{1) O}_3}$ Tetrasubstituted alkenes are cleaved to form ketones.	9.11
Acid-Catalyzed Hydration of Terminal Alkynes $\xrightarrow[\text{HgSO}_4]{\text{H}_2\text{SO}_4\text{, H}_2\text{O}}$ This procedure results in a Markovnikov addition of water across the π bond, followed by tautomerization to form a methyl ketone.	10.7
Friedel-Crafts Acylation $\xrightarrow{\text{AlCl}_3}$ Aromatic rings that are not too strongly deactivated will react with an acid halide in the presence of a Lewis acid to produce an aryl ketone.	19.6

Ossidazione delle aldeidi

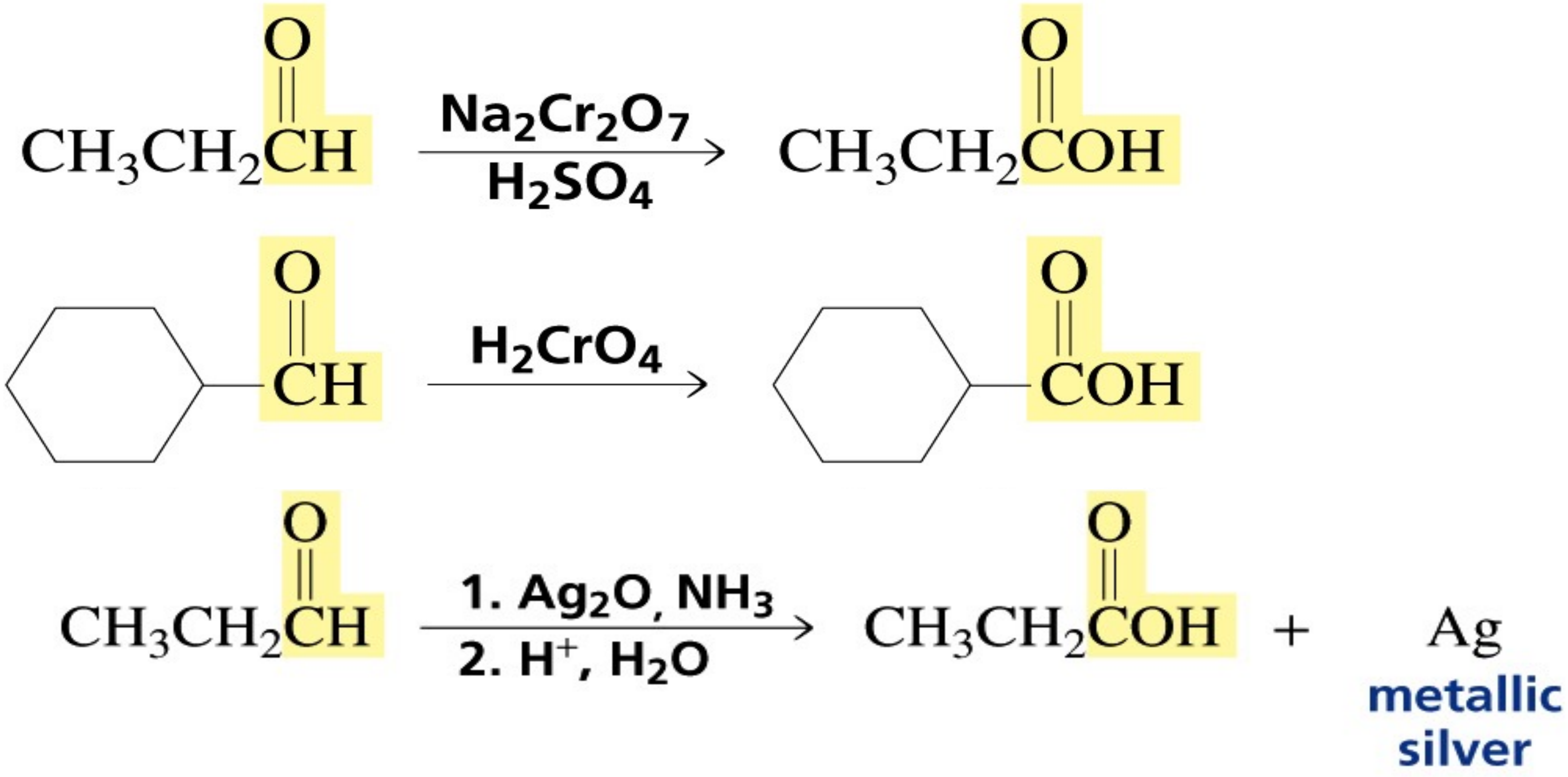






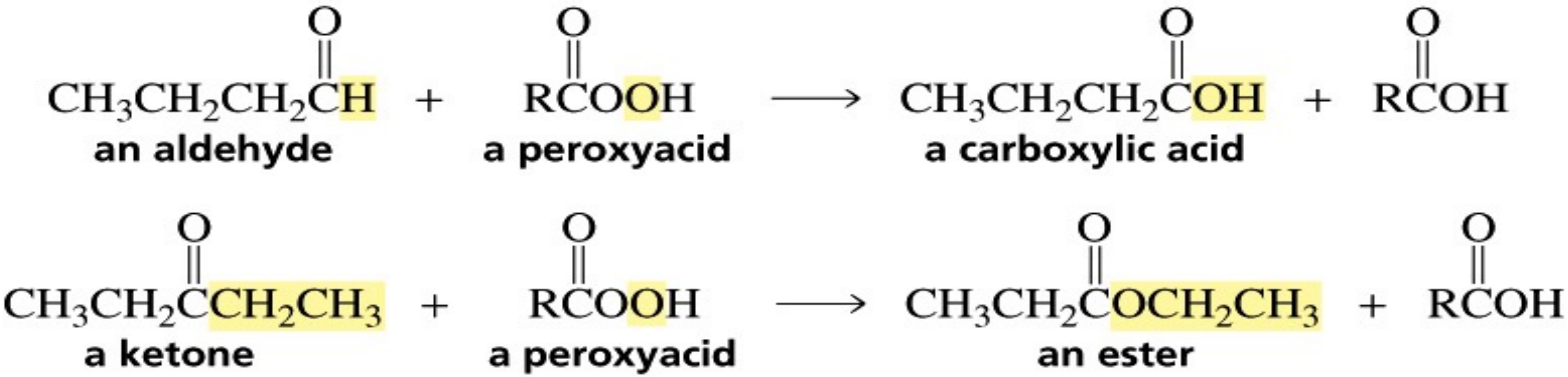
Ossidazione degli aldeidi in acidi carbossilici

✓ Gli aldeidi sono ossidati da Cr(VI) o Ag(I) ad acidi carbossilici



Ossidazione di aldeidi e chetoni in acidi carbossilici

- ✓ Ossidazione i Bayer-Villiger

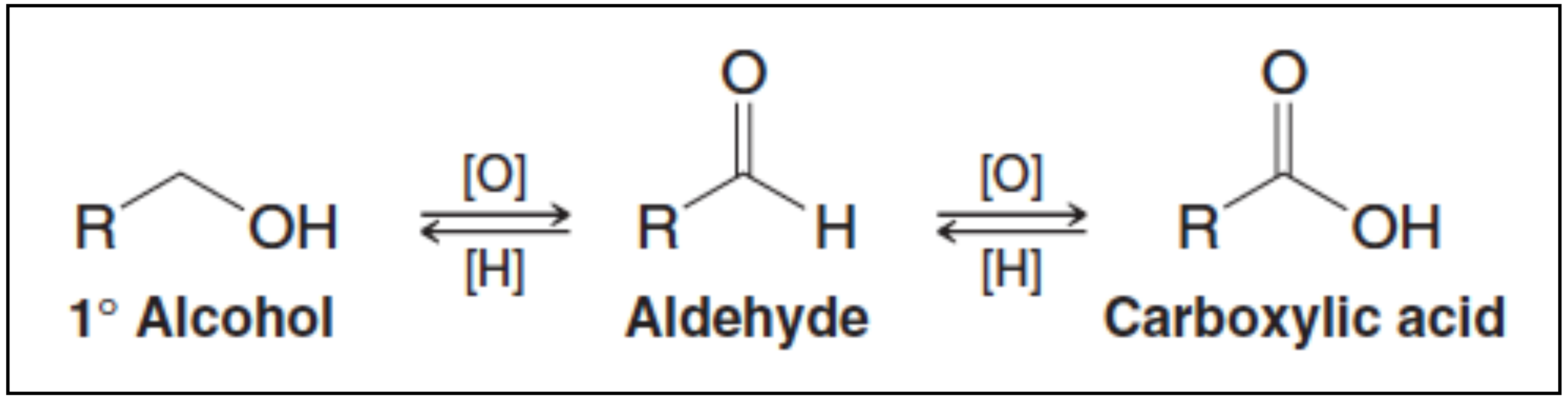


$$\mathrm{CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}H} + \mathrm{R\overset{\overset{O}{\|}}{C}OOH} \longrightarrow \mathrm{CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}OH} + \mathrm{R\overset{\overset{O}{\|}}{C}OH}$$

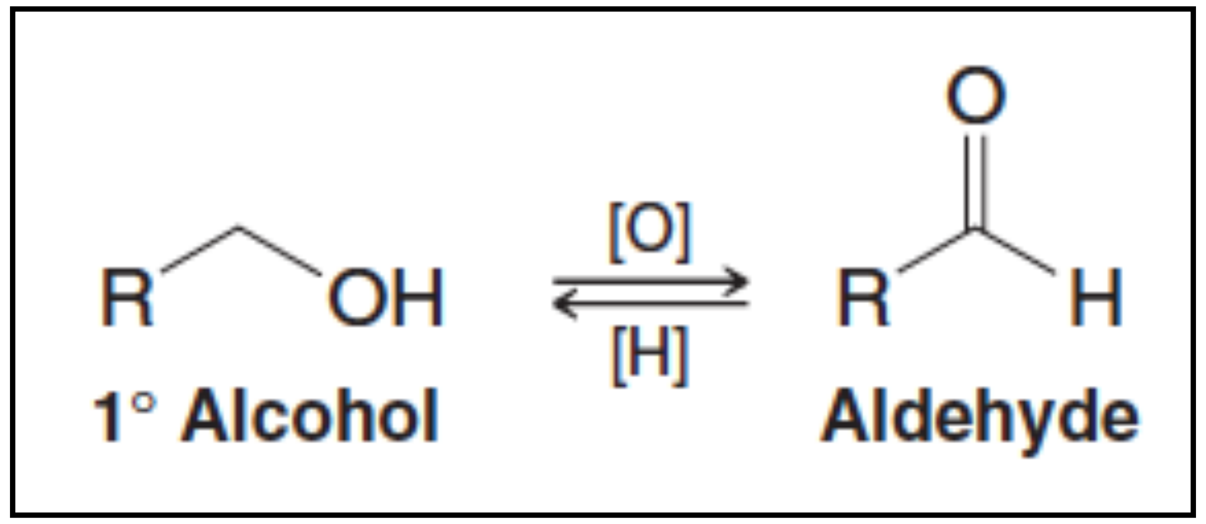
an aldehyde — a peroxyacid — a carboxylic acid

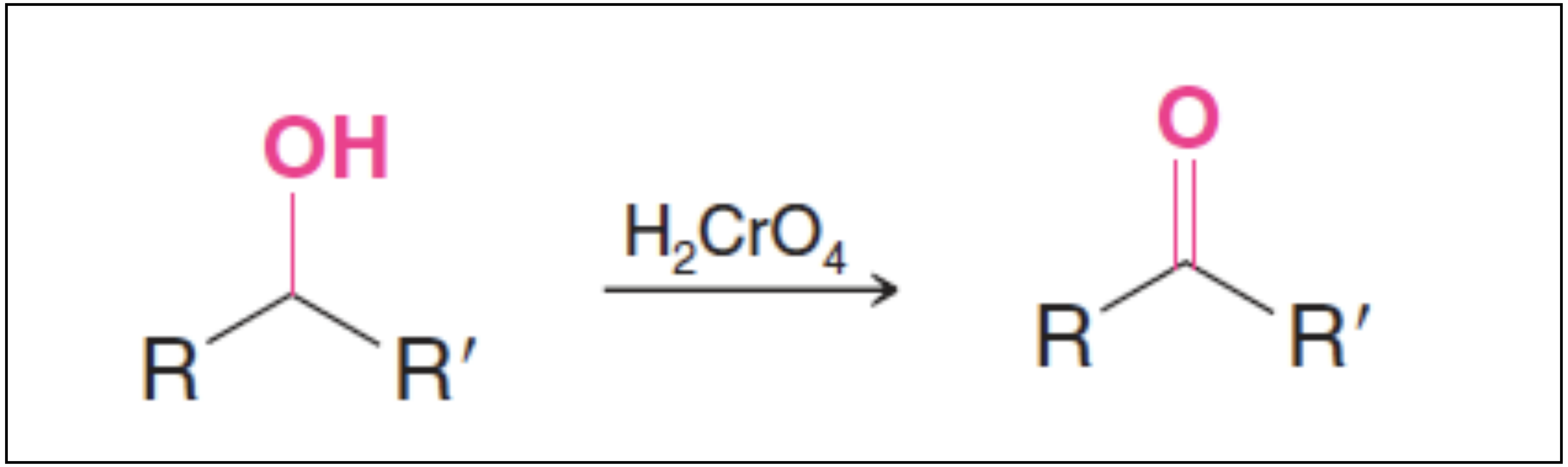
$$\mathrm{CH_3CH_2\overset{\overset{O}{\|}}{C}CH_2CH_3} + \mathrm{R\overset{\overset{O}{\|}}{C}OOH} \longrightarrow \mathrm{CH_3CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3} + \mathrm{R\overset{\overset{O}{\|}}{C}OH}$$

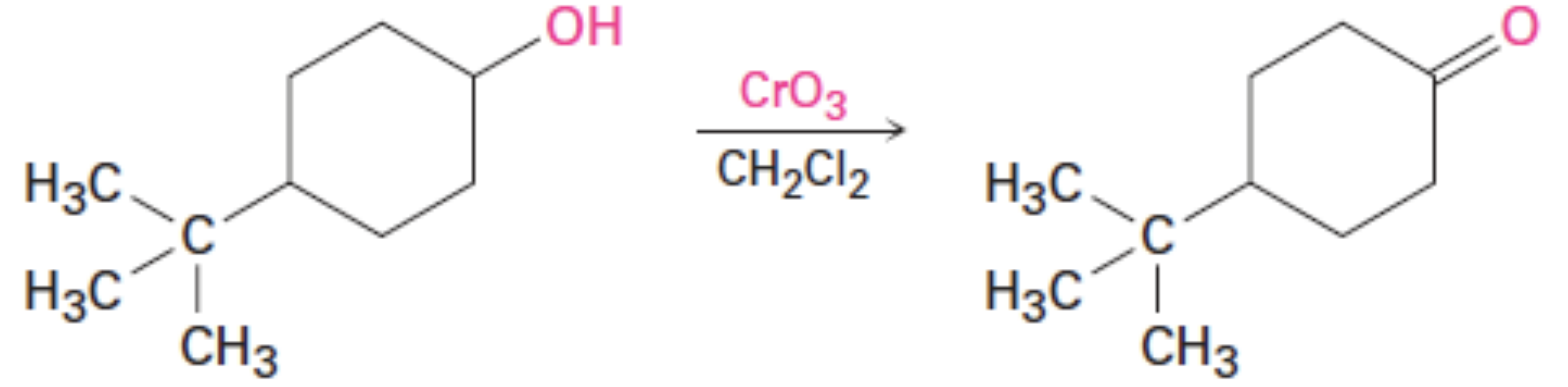
a ketone — a peroxyacid — an ester



Ossidazione dei chetoni ad alcoli secondari

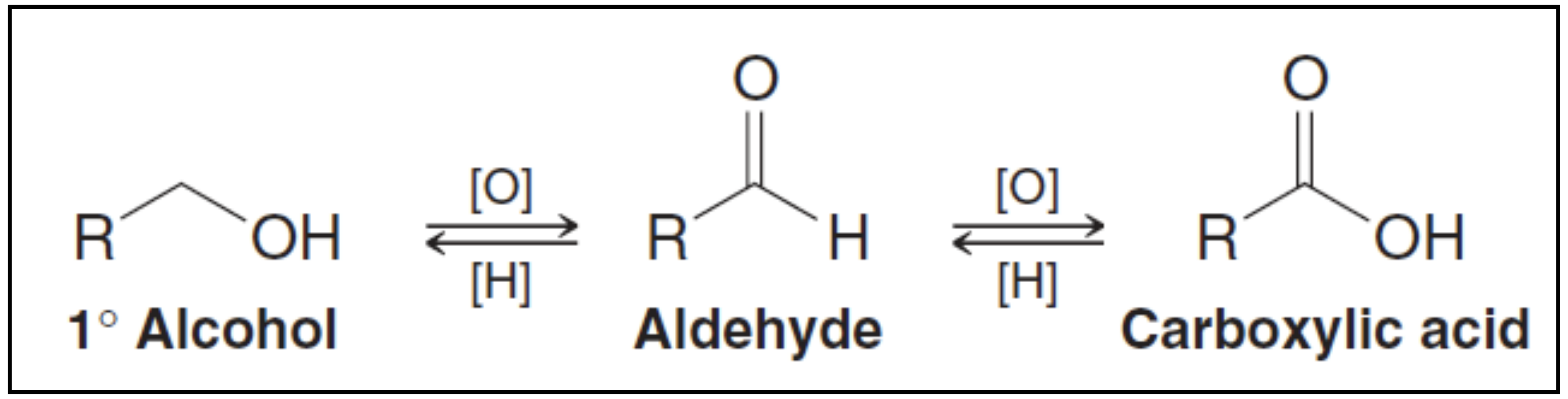


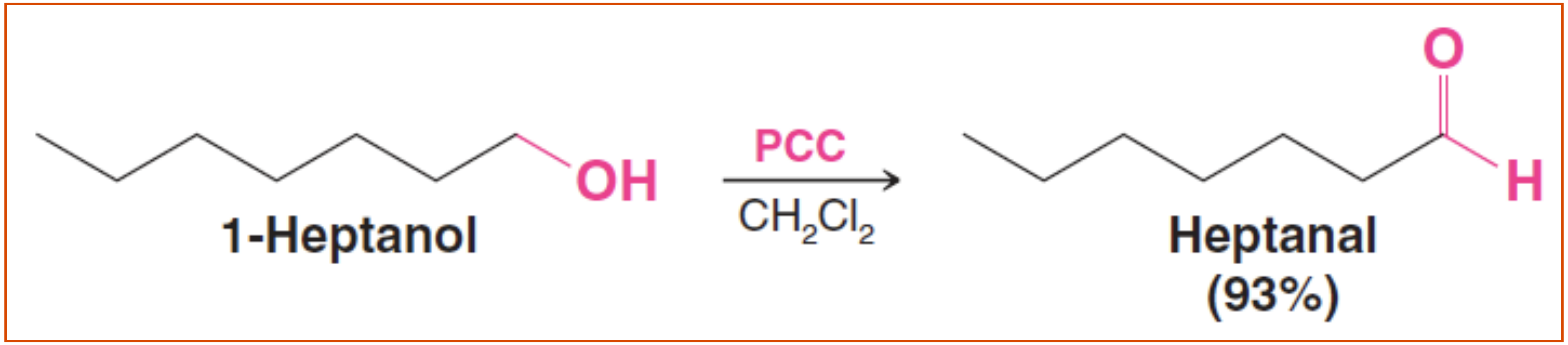


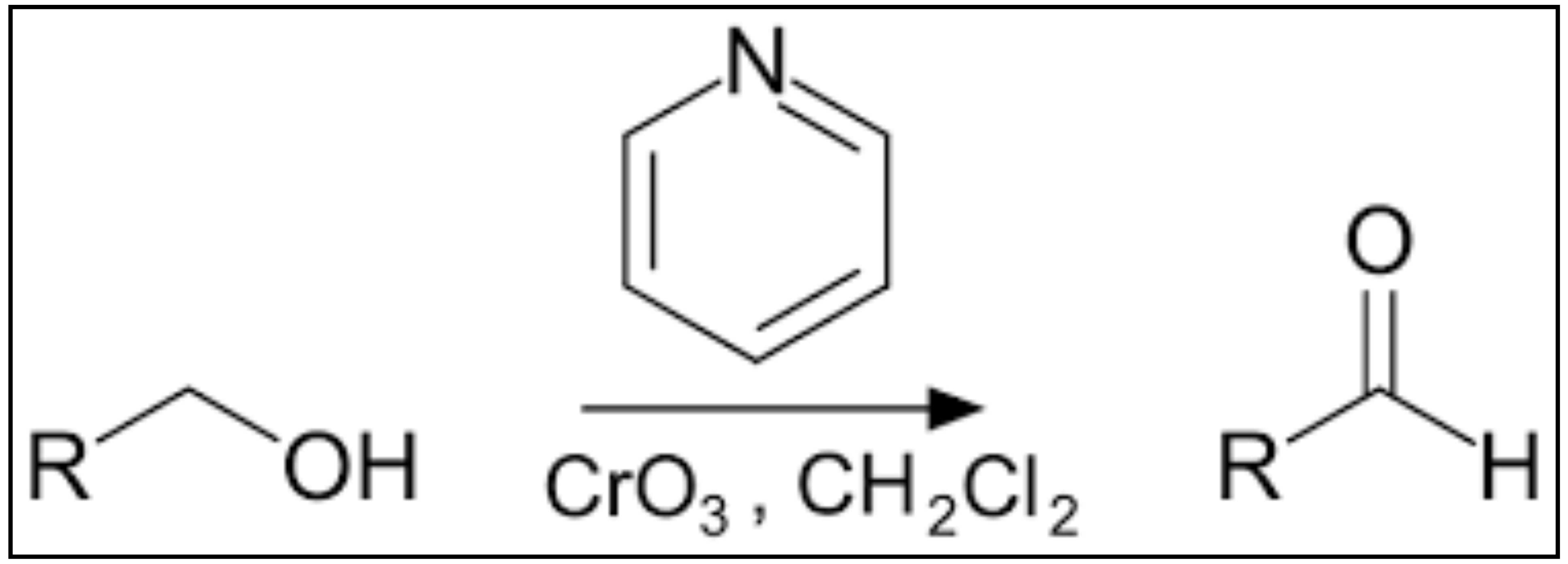


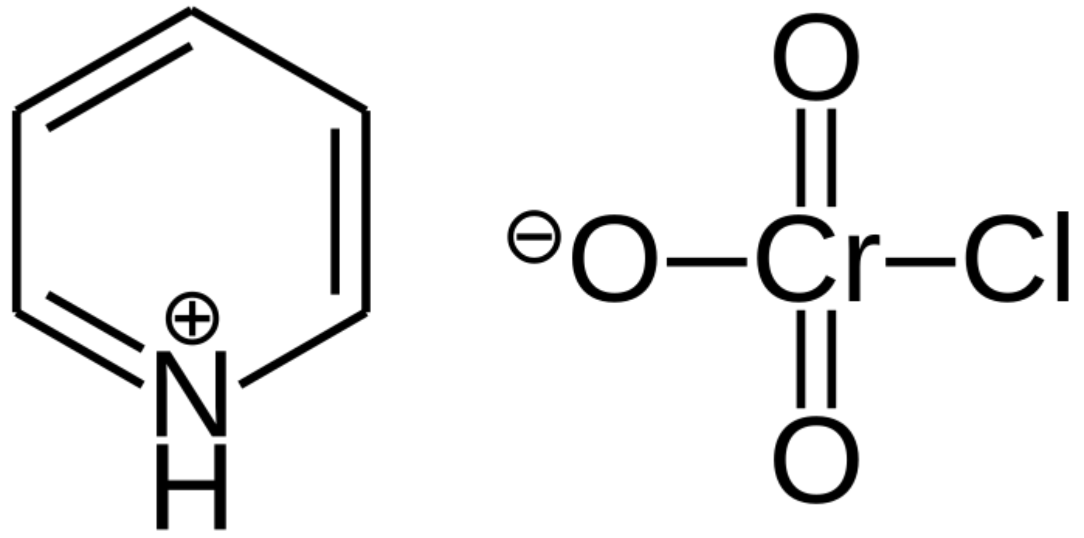
4-*tert*-Butylcyclohexanol **4-*tert*-Butylcyclohexanone (90%)**

Ossidazione delle aldeidi ad alcoli primari



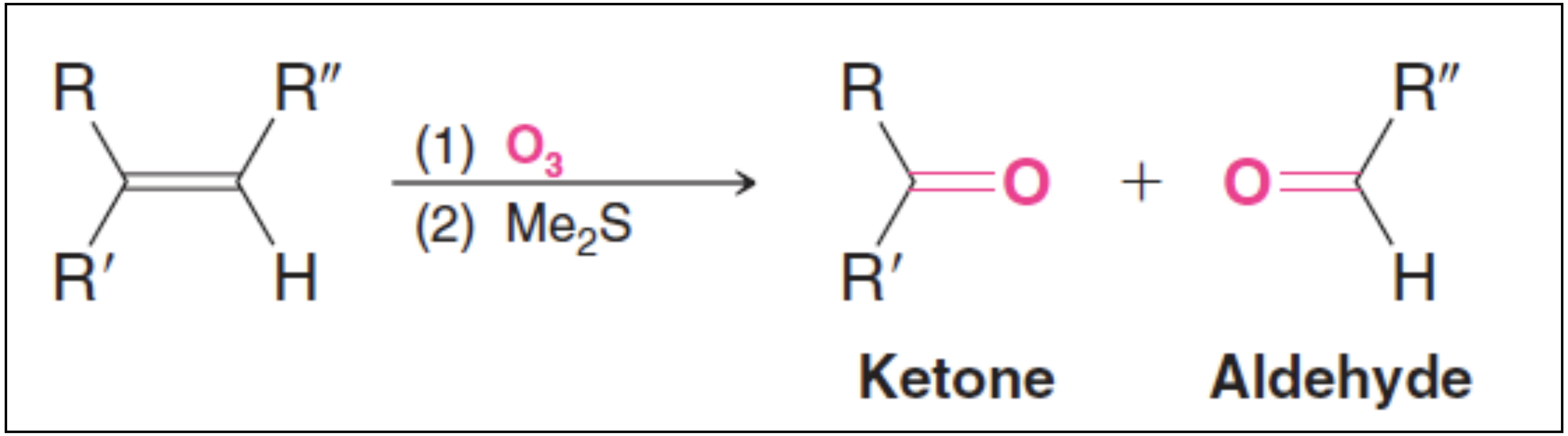


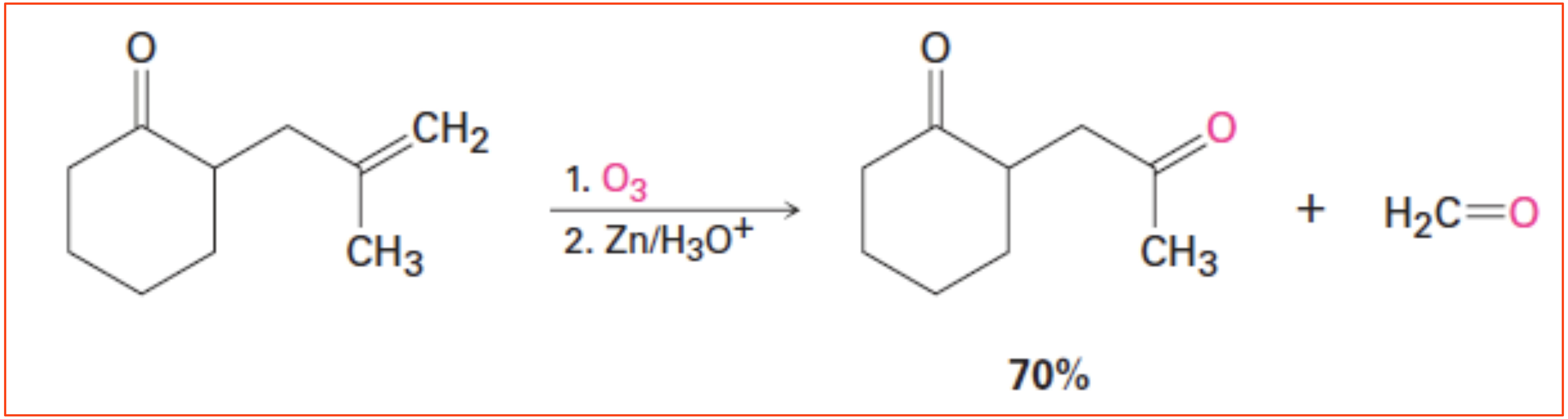




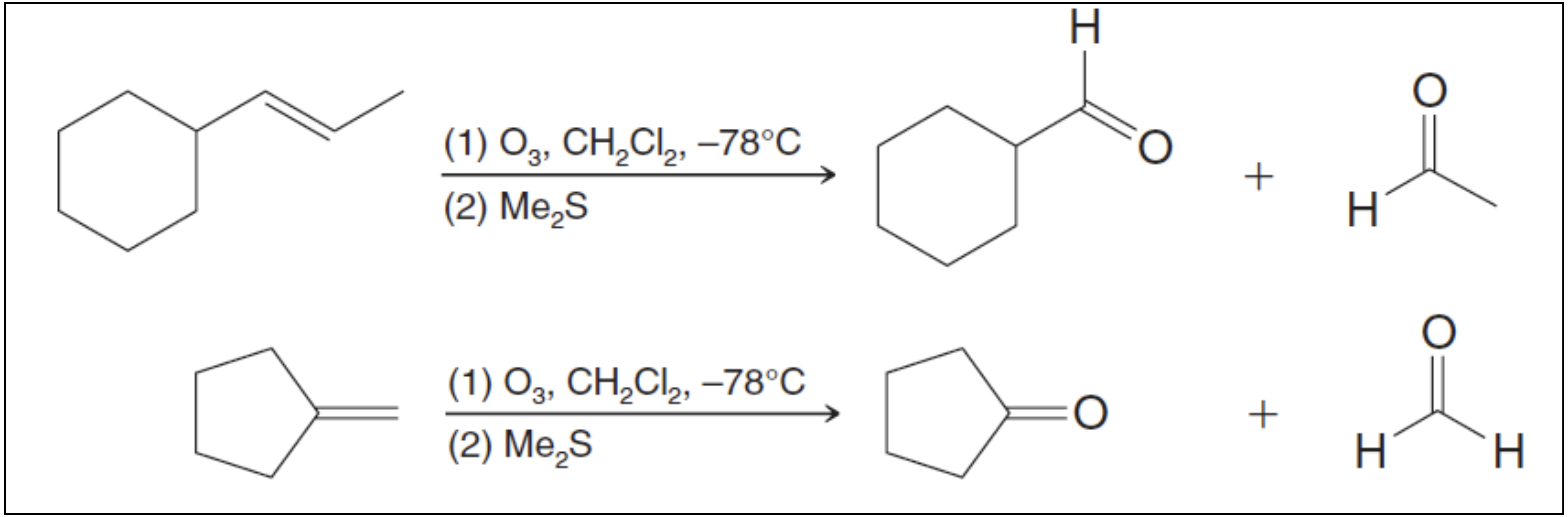
PCC = clorocromato di piridinio

Sintesi di aldeidi e chetoni
Ozonolisi degli alcheni

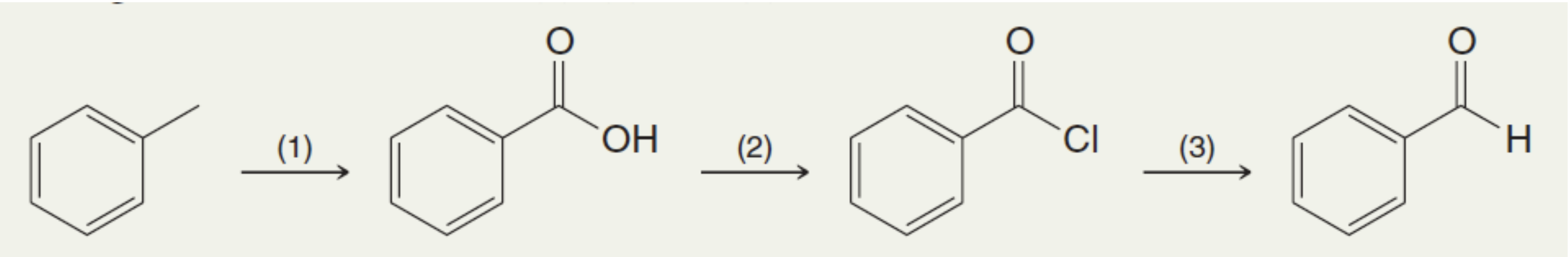




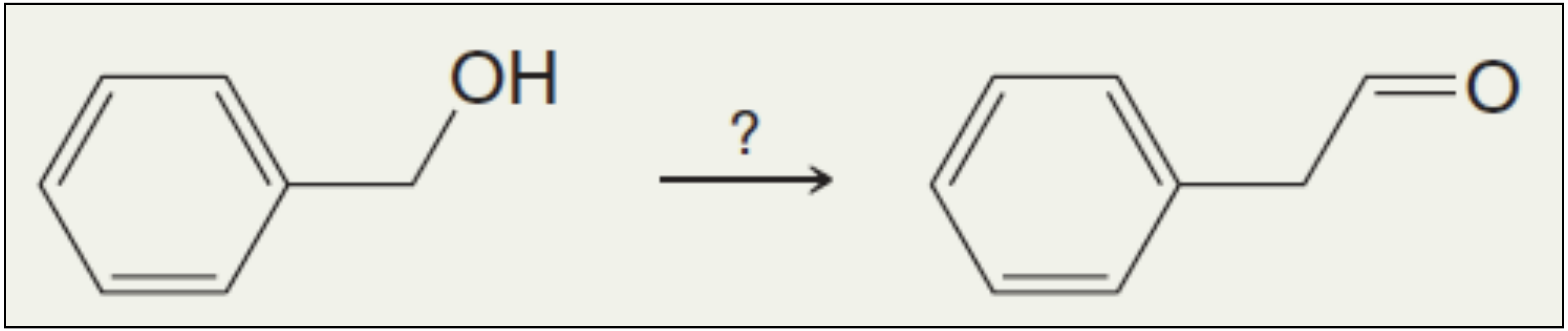
Sintesi di aldeidi e chetoni
Ozonolisi degli alcheni



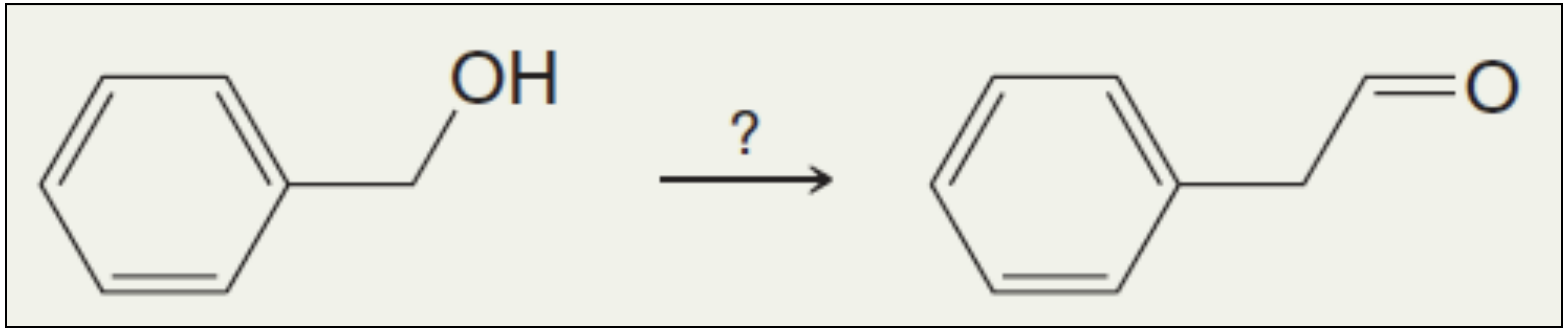
ESERCIZIO: FORNIRE i REAGENTI PER LE SEGUENTI TRASFORMAZIONI

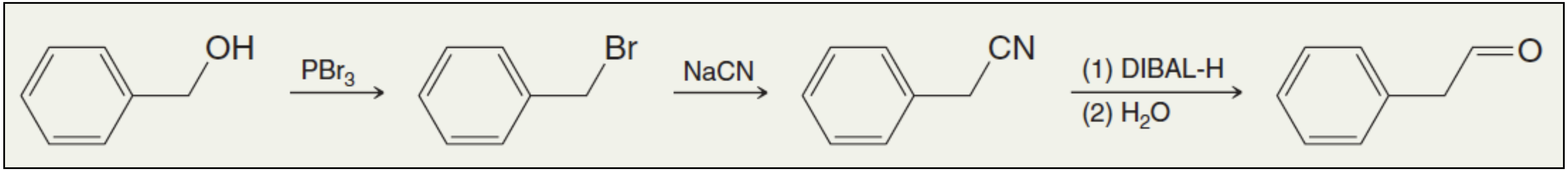


ESERCIZIO: PARTENDO DALL'ALCOL BENZILICO , PROPONETE UNA SINTESI PER IL FENILETANO

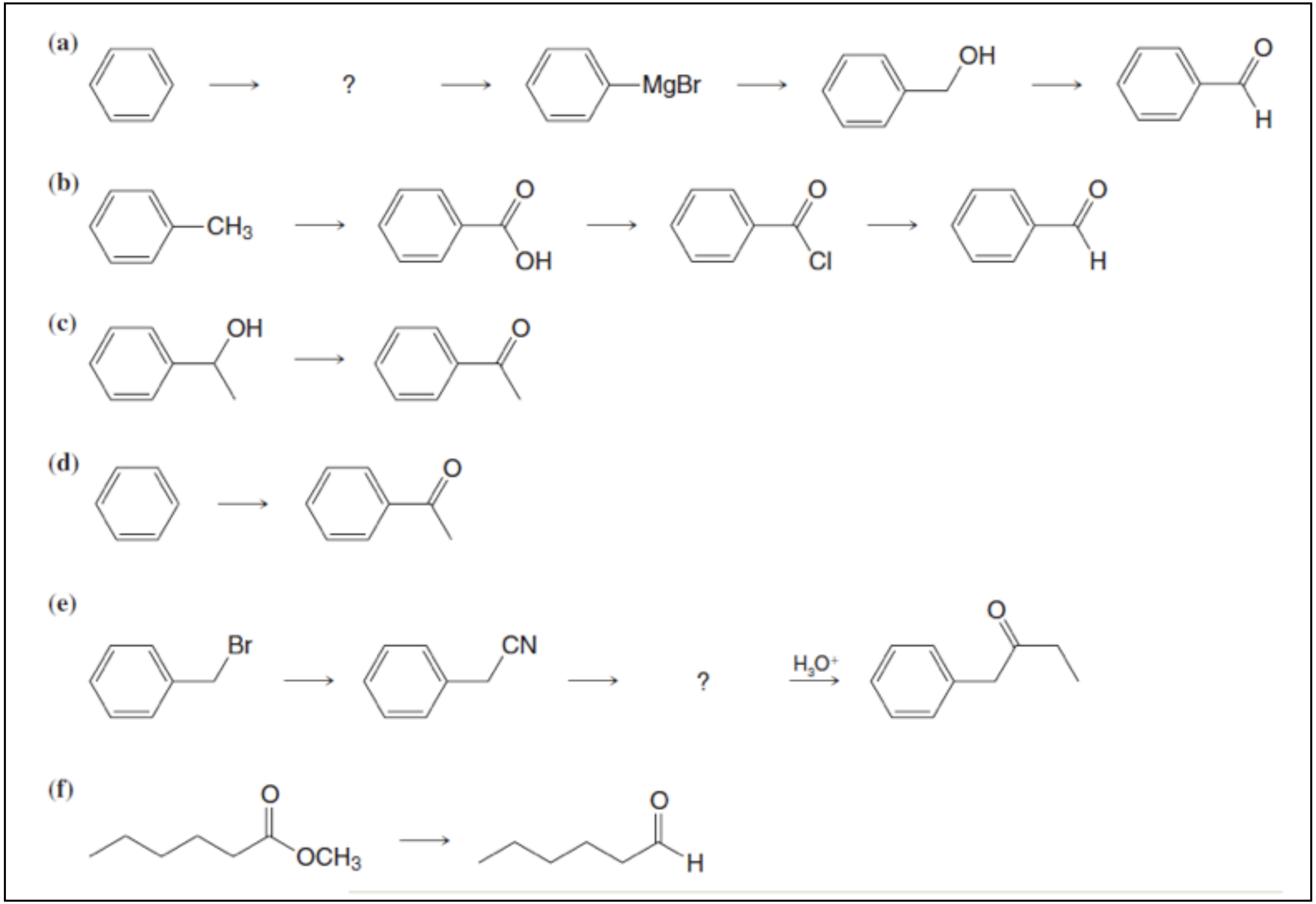


ESERCIZIO: PARTENDO DALL'ALCOL BENZILICO , PROPONETE UNA SINTESI PER IL FENILETANO

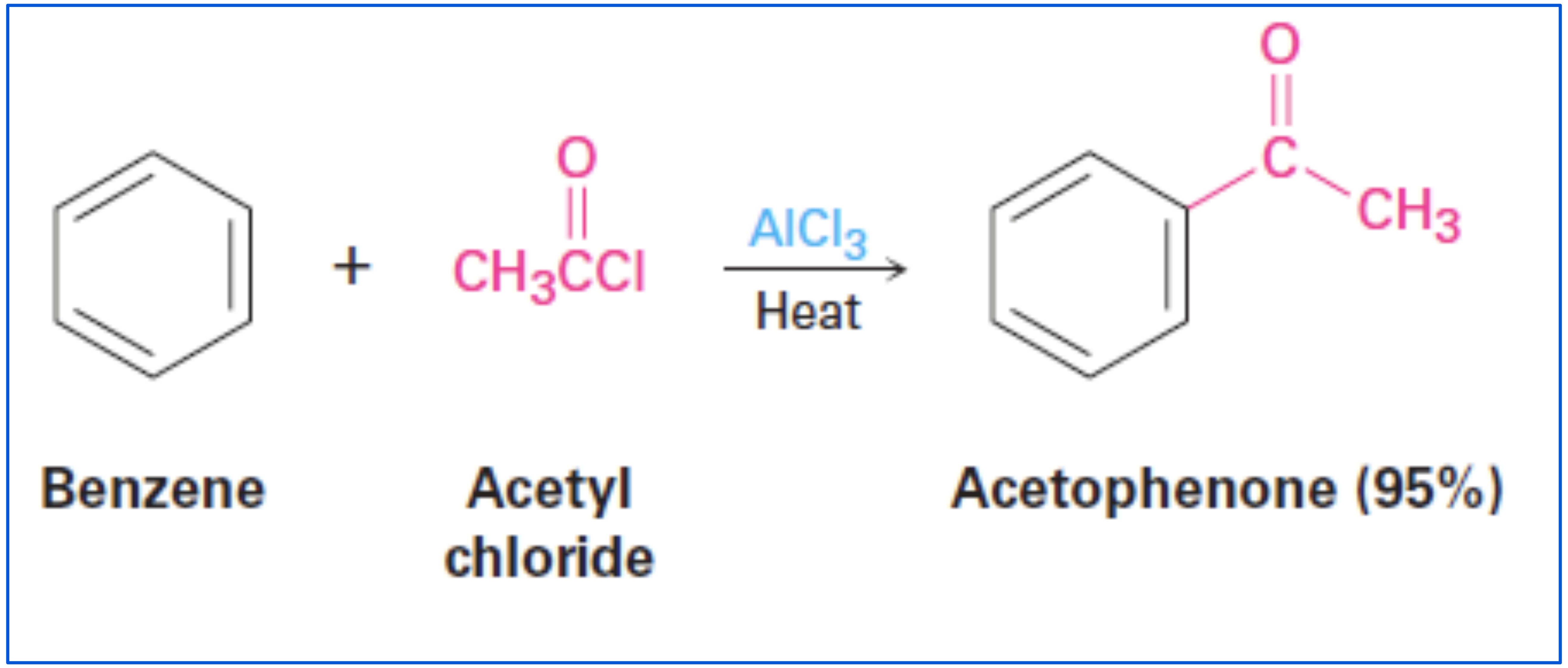


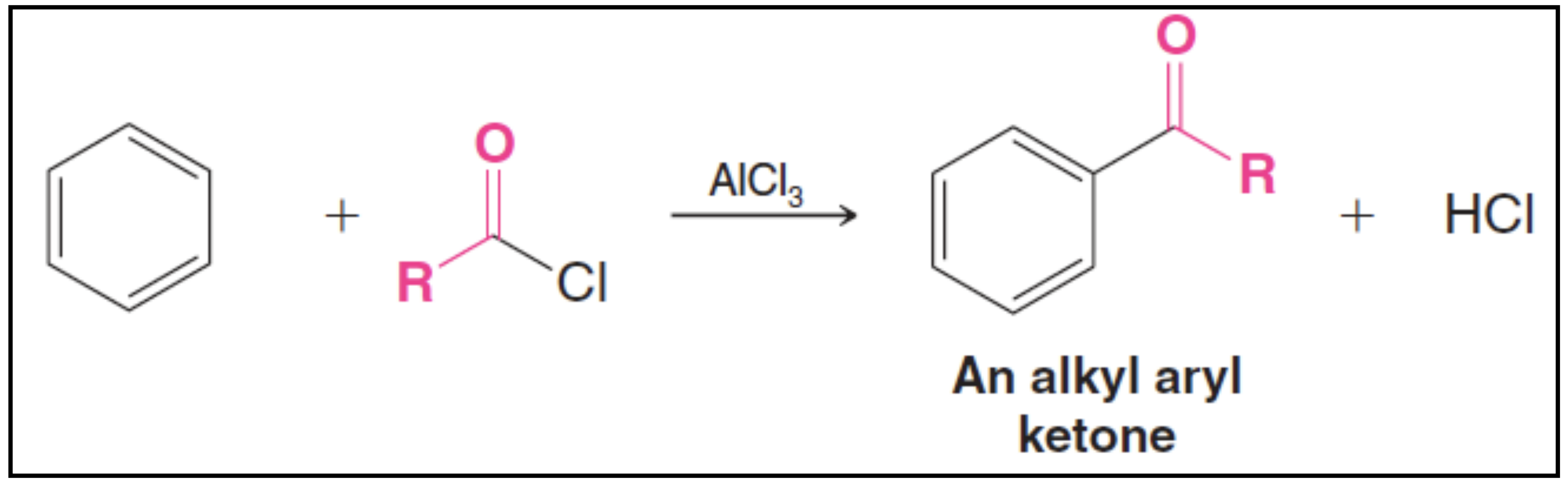


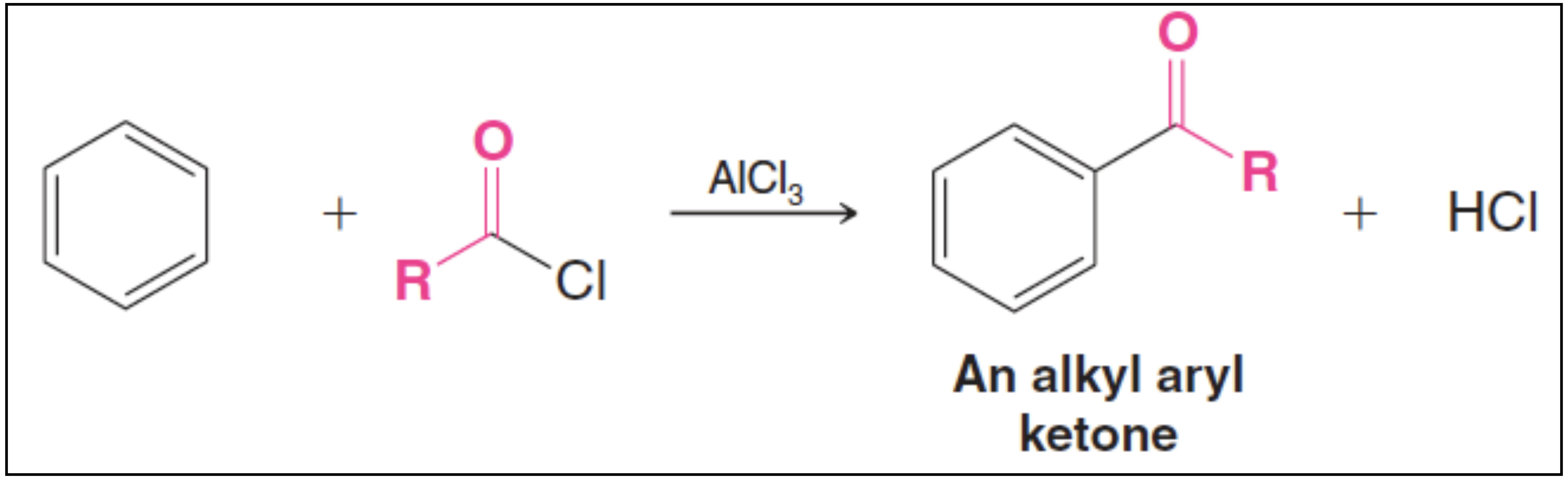
Problema: fornire i reagenti e indicare gli intermediari per ciascuna delle seguenti sintesi



Sintesi dei chetoni a partire dai benzeni: REAZIONI DI FRIEDEL CRAFT

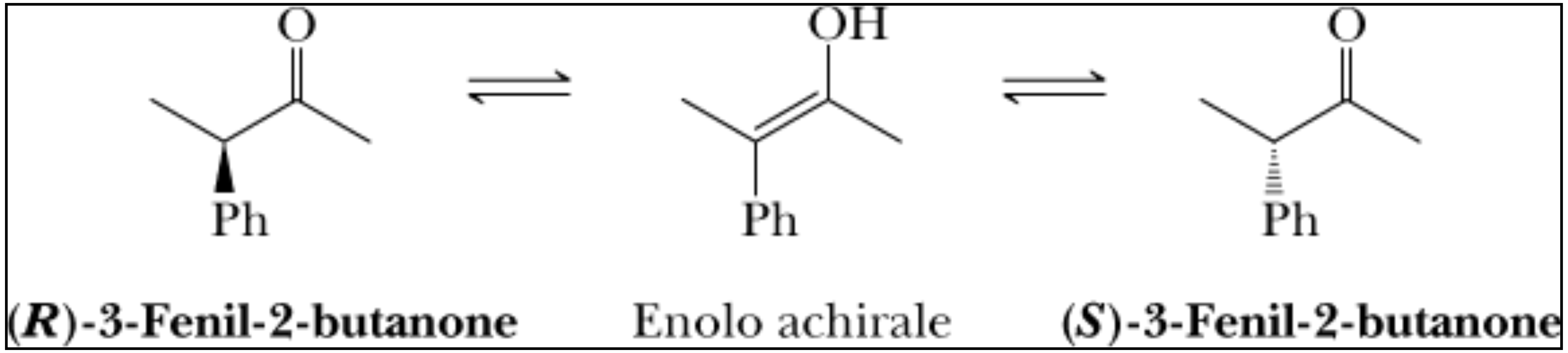






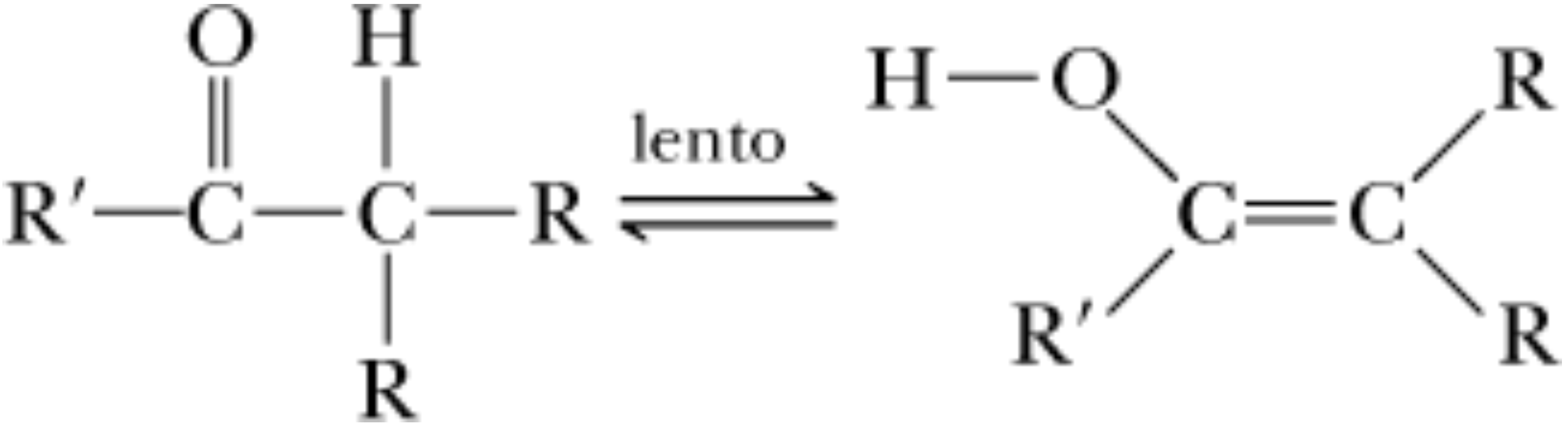
Reazioni al carbonio α

A. Racemizzazione


(***R***)**-3-Fenil-2-butanone** Enolo achirale (***S***)**-3-Fenil-2-butanone**

Quando il 3-fenil-2-butanone in forma enantiomericamente pura (R o S) è sciolto in etanolo, al passare del tempo non si ha alcuna variazione dell'attività ottica della soluzione. Tuttavia, se si aggiunge un acido (per esempio, HCl acquoso o gassoso) o una base (per esempio, etossido di sodio) in piccola quantità, l'attività ottica della soluzione comincia a diminuire e gradualmente sparisce. Quando il 3-fenil-2-butanone viene isolato da questa soluzione, si trova che esso è una miscela racemica

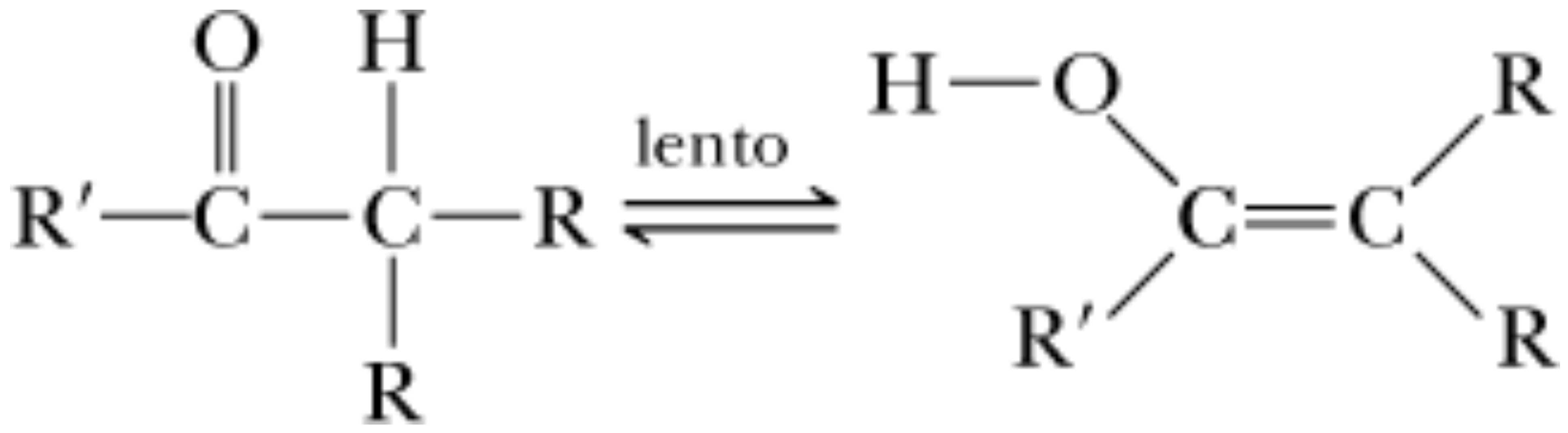
Tautomeria cheto-enolica

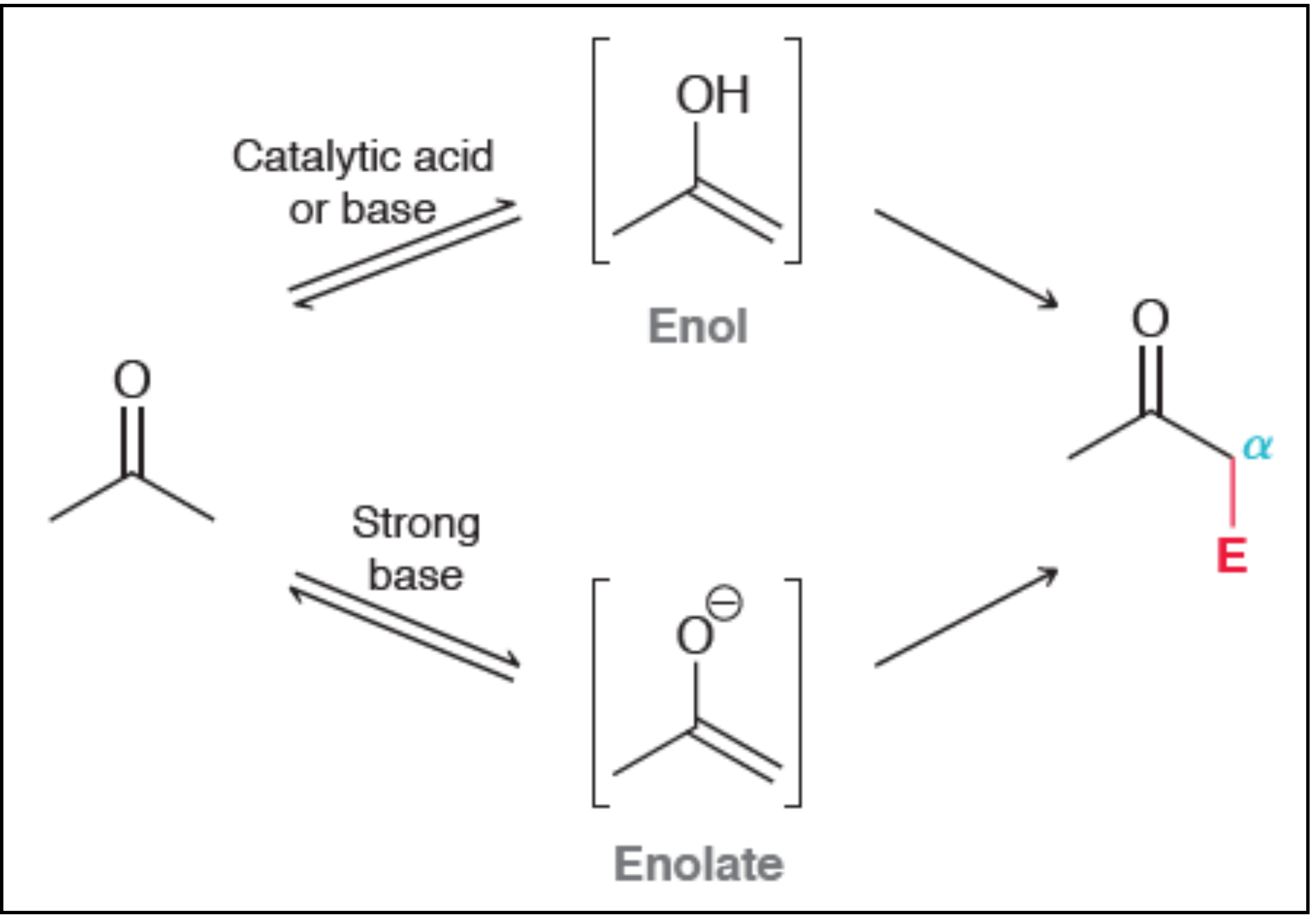


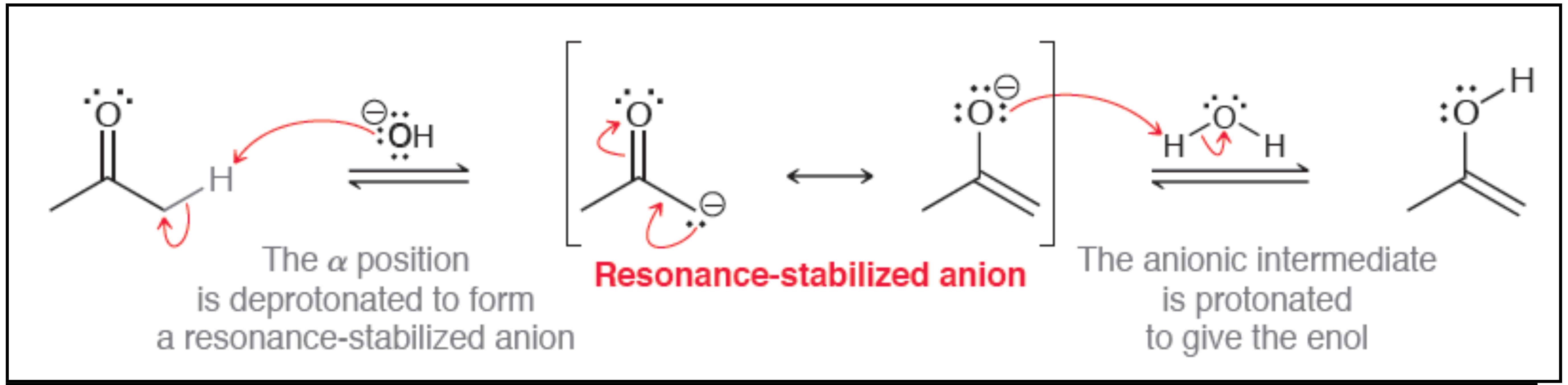
Reazioni al carbonio α

A. Racemizzazione

Tautomeria cheto-enolica

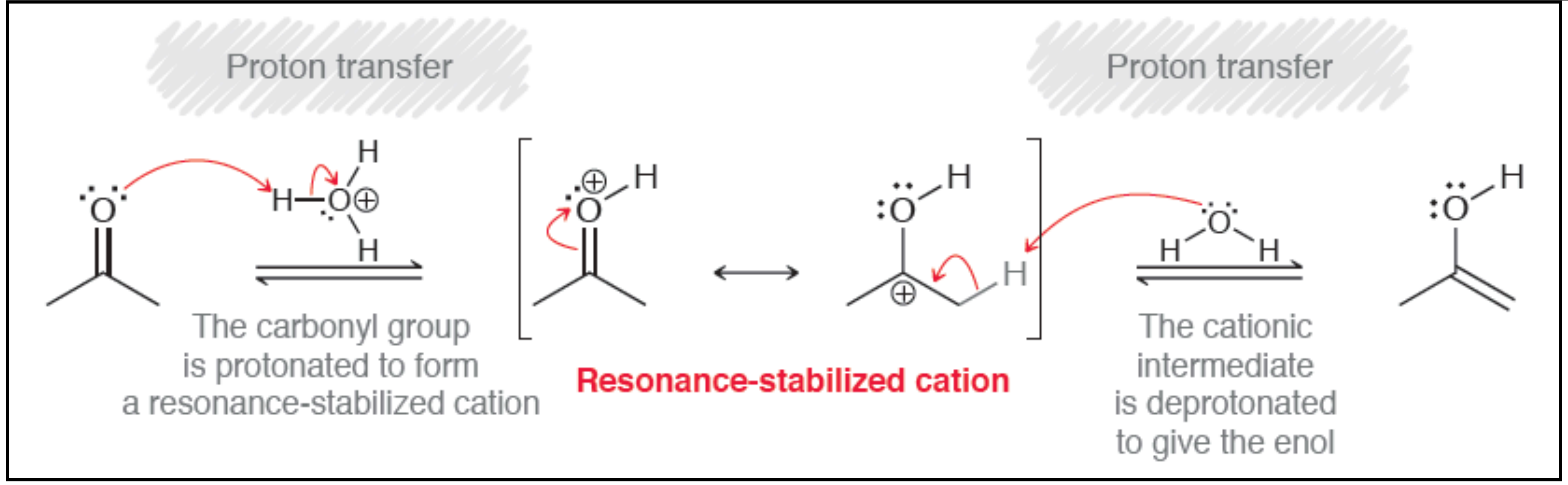






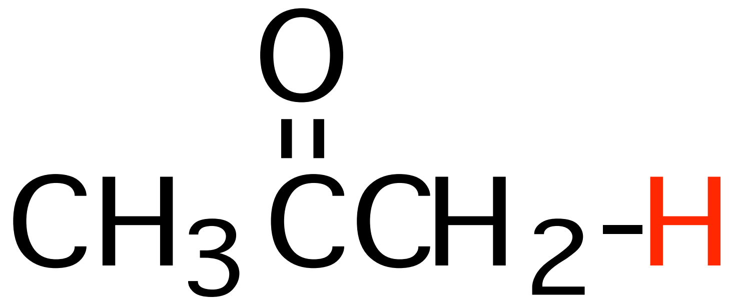
The α position is deprotonated to form a resonance-stabilized anion

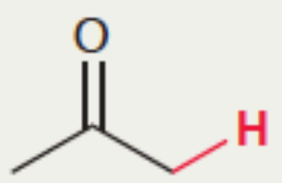
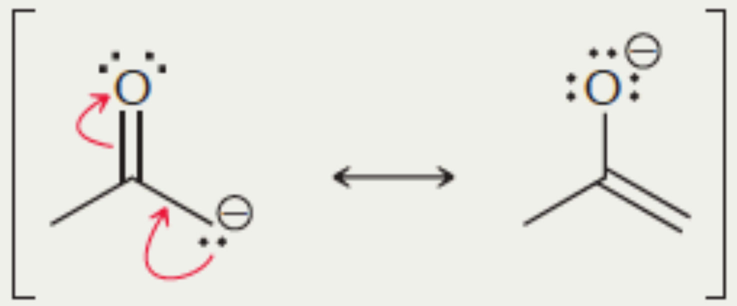
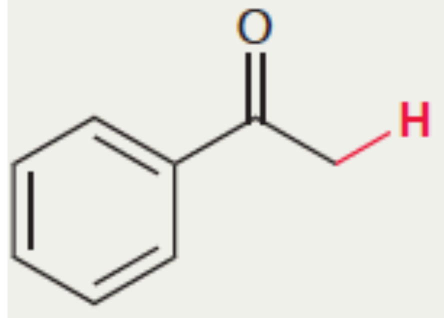
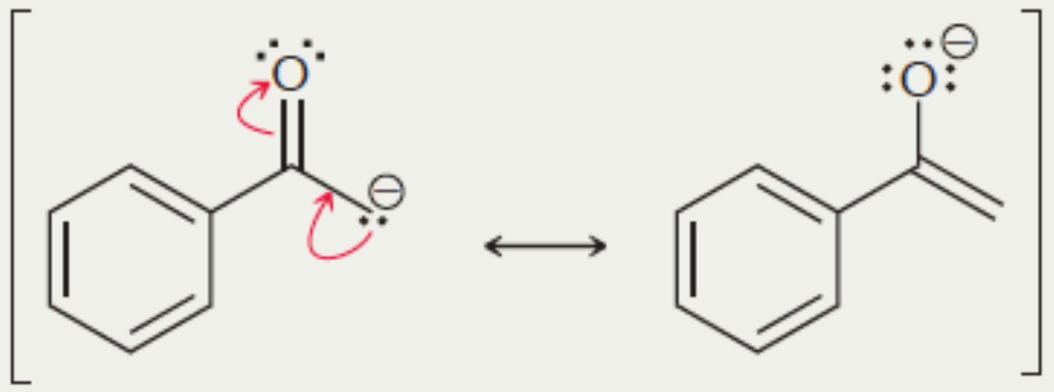
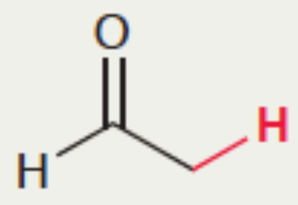
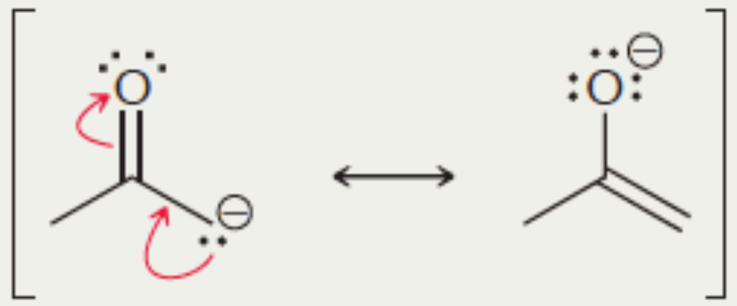
The anionic intermediate is protonated to give the enol

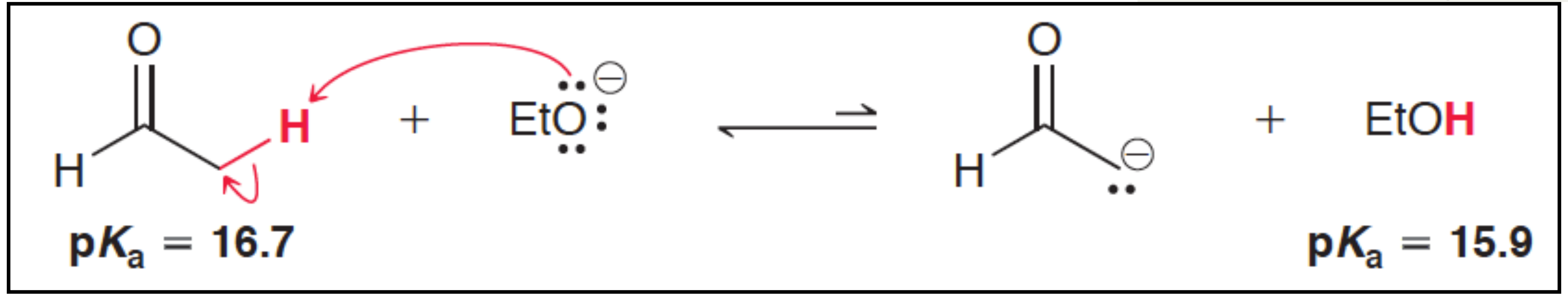


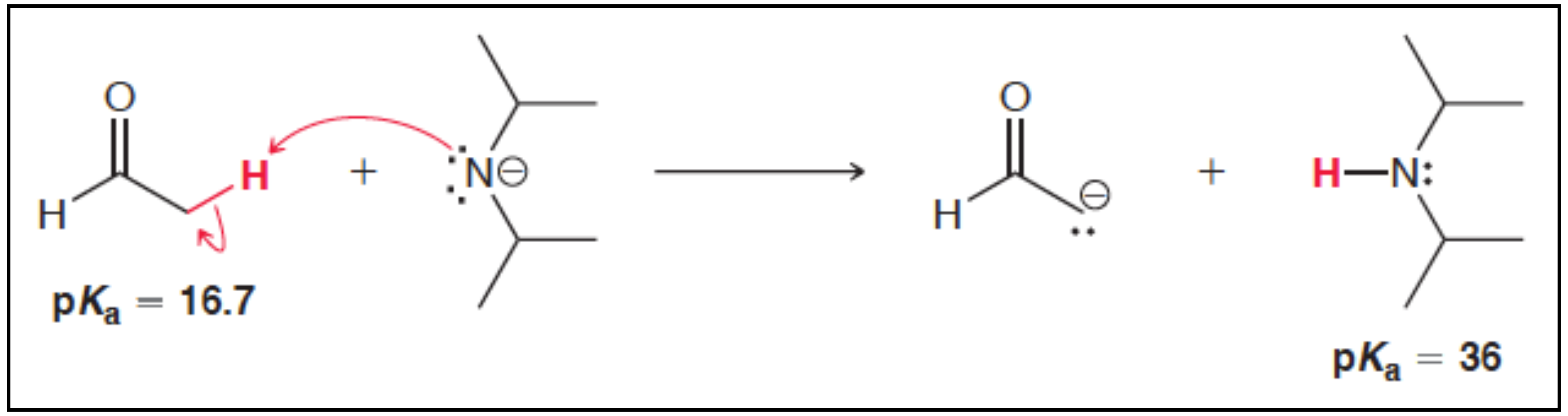
The carbonyl group is protonated to form a resonance-stabilized cation

The cationic intermediate is deprotonated to give the enol

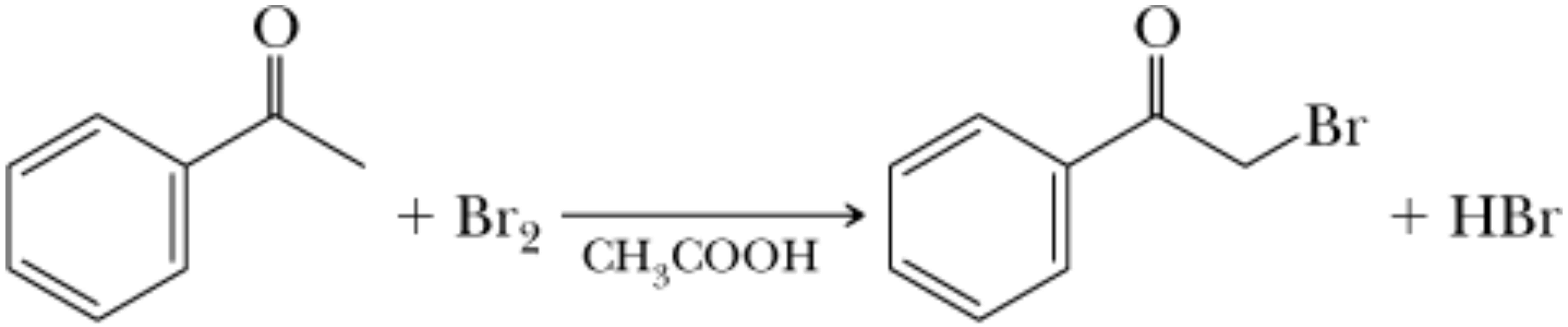
Type of Bond	pKa
CH_3CH_2O-H	16
 $CH_3\overset{O}{\overset{\|}{C}}CH_2$-H	20
$CH_3C\equiv C$-H	25
$CH_2=CH$-H	44
CH_3CH_2-H	51

Compound	pK_a	Enolate
 Acetone	19.2	
 Acetophenone	18.3	
 Acetaldehyde	16.7	





C. α-Alogenazione

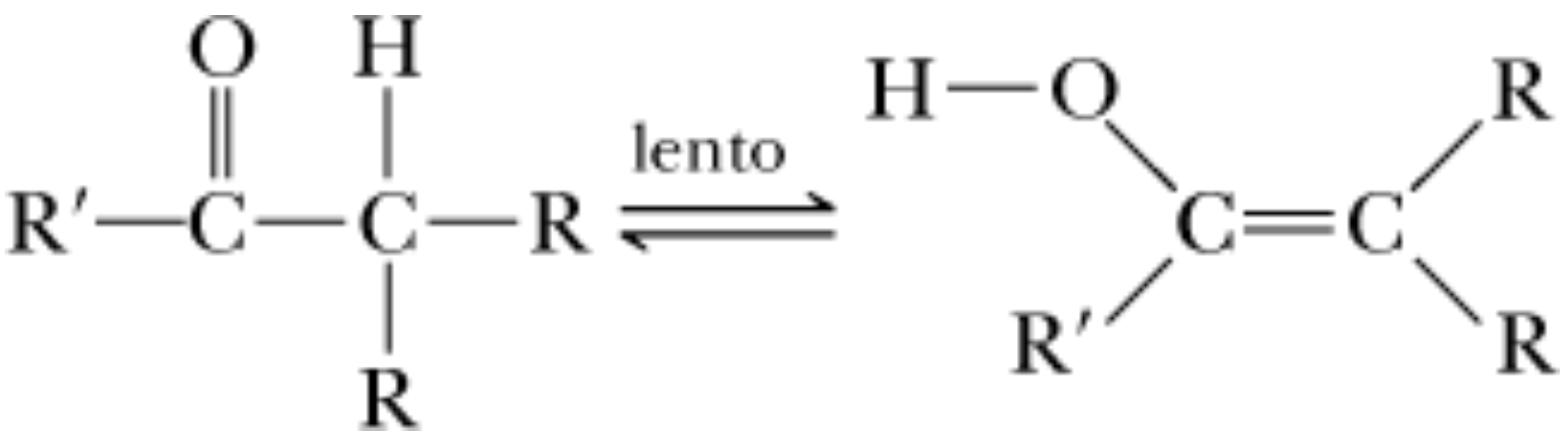


Acetofenone α-Bromoacetofenone

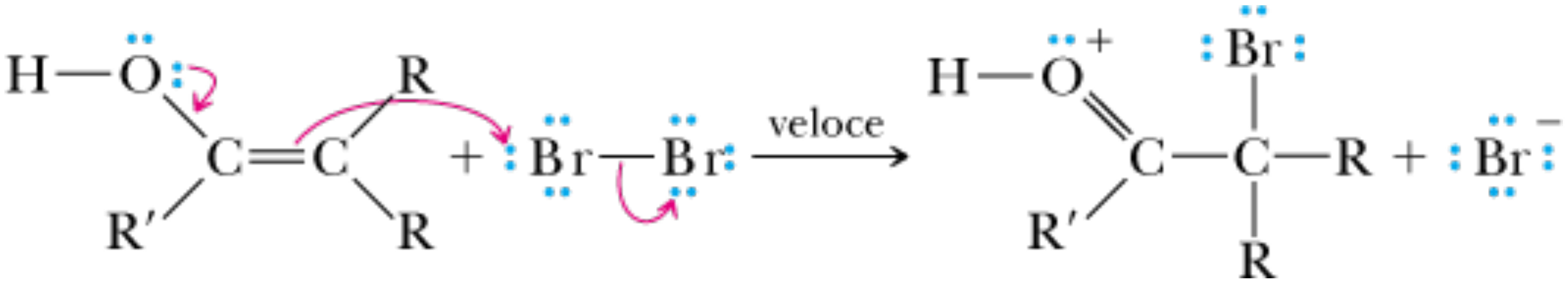
Type of Bond	pK_a
CH_3CH_2O-H	16
$CH_3\overset{O}{\overset{\|}{C}}CH_2$-H	20
$CH_3C{\equiv}C$-H	25
$CH_2{=}CH$-H	44
CH_3CH_2-H	51

α-Alogenazione acido-catalizzata di un chetone

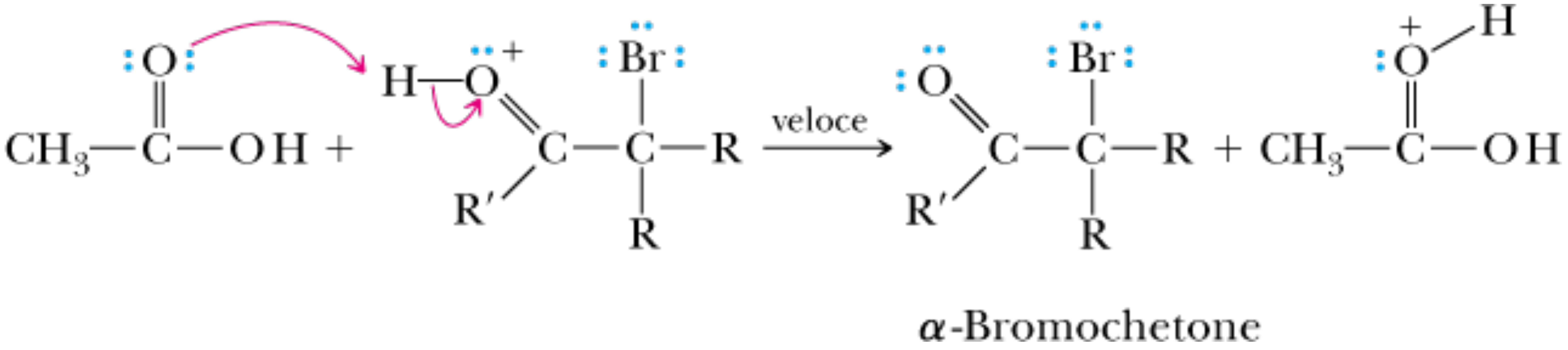
Stadio 1 Tautomeria cheto-enolica. La tautomeria cheto-enolica acido-catalizzata dà un enolo.



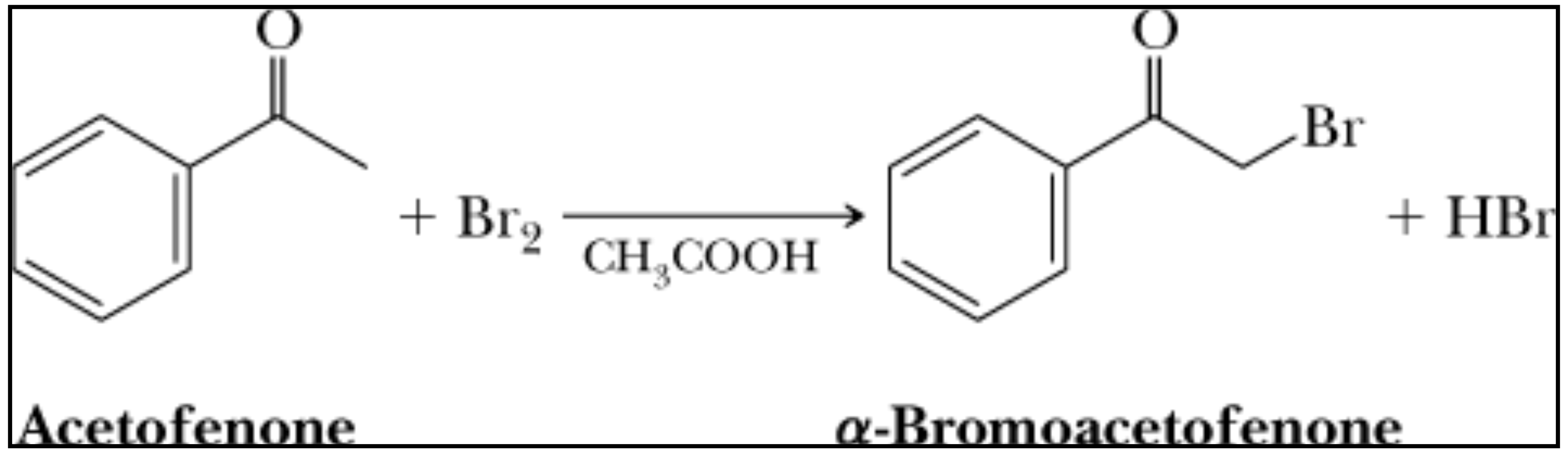
Stadio 2 Formazione di un nuovo legame tra un nucleofilo (legame π) e un elettrofilo



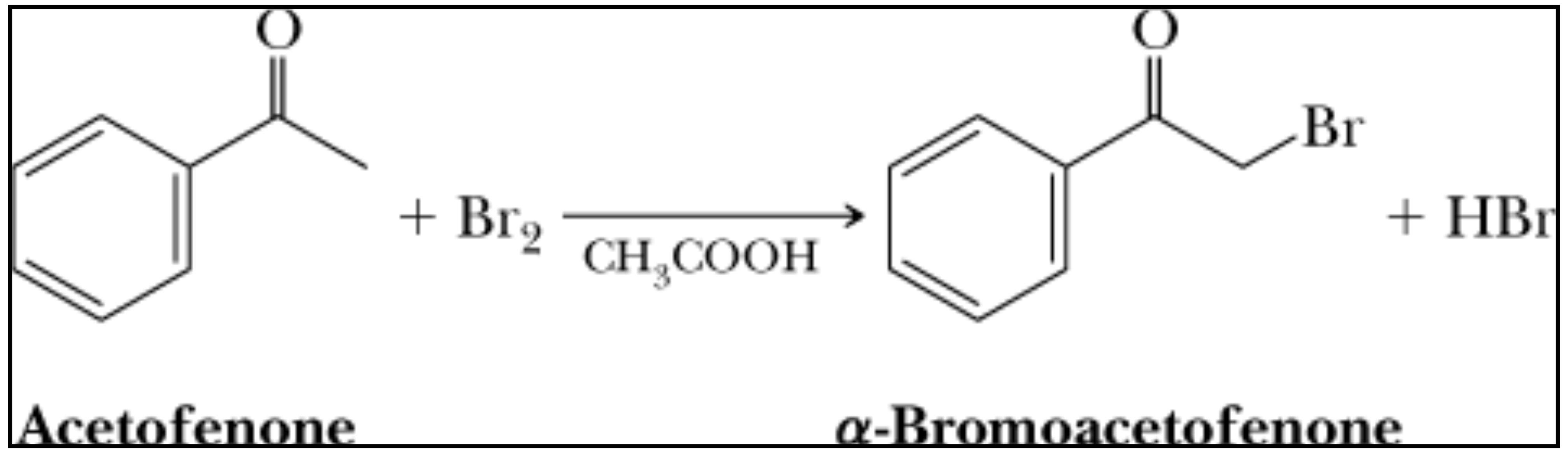
Stadio 3 Rimozione di un protone. Il trasferimento di un protone a una base dà l'α-alogenochetone.

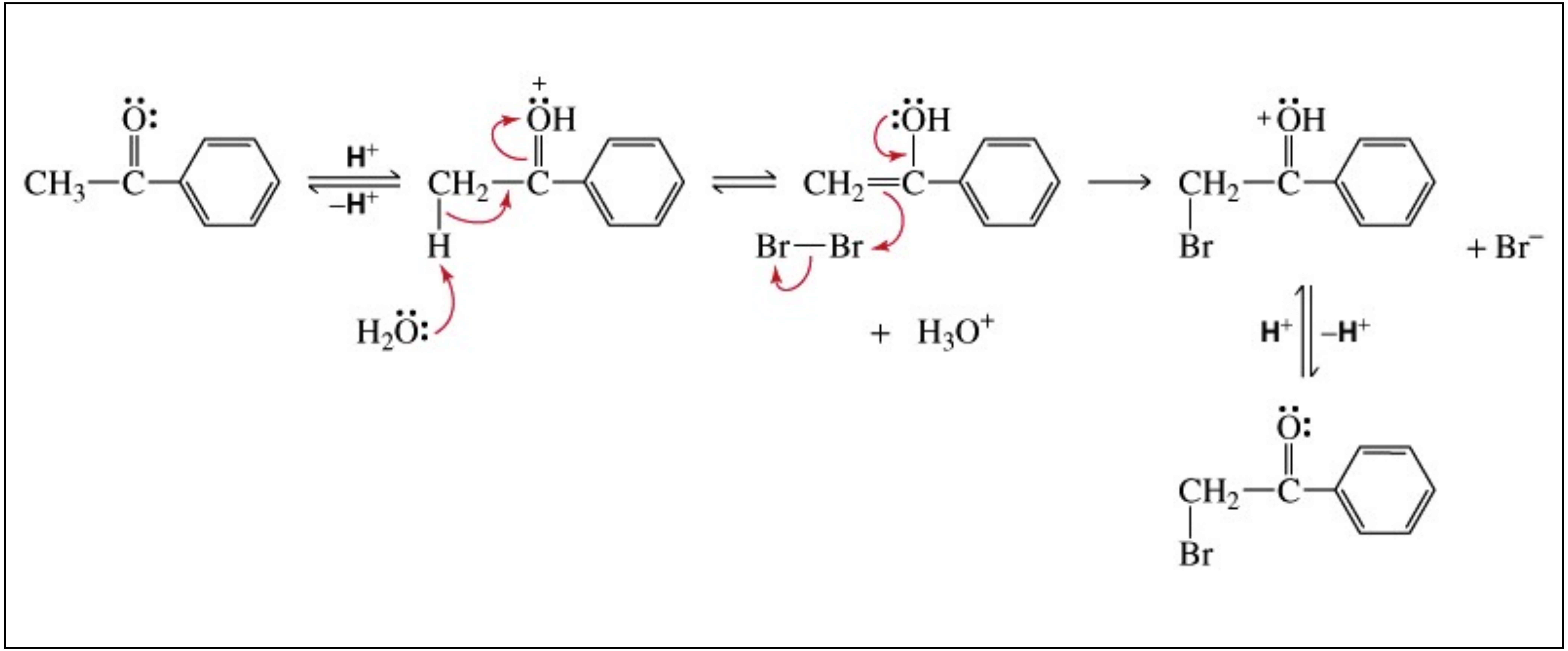


α-Alogenazione

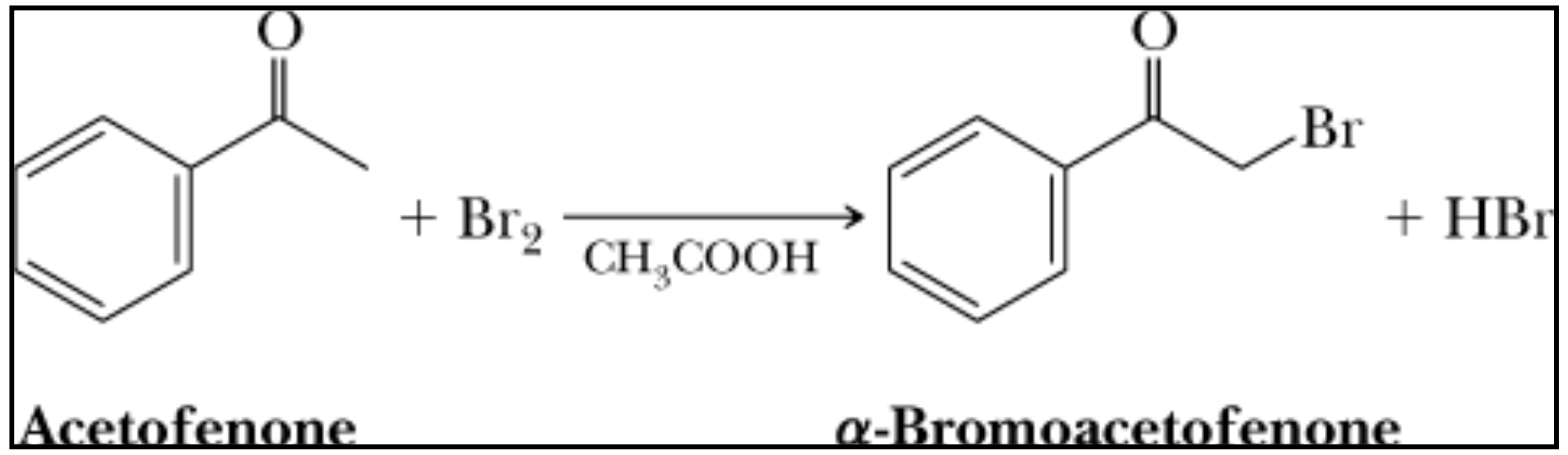


α-Alogenazione

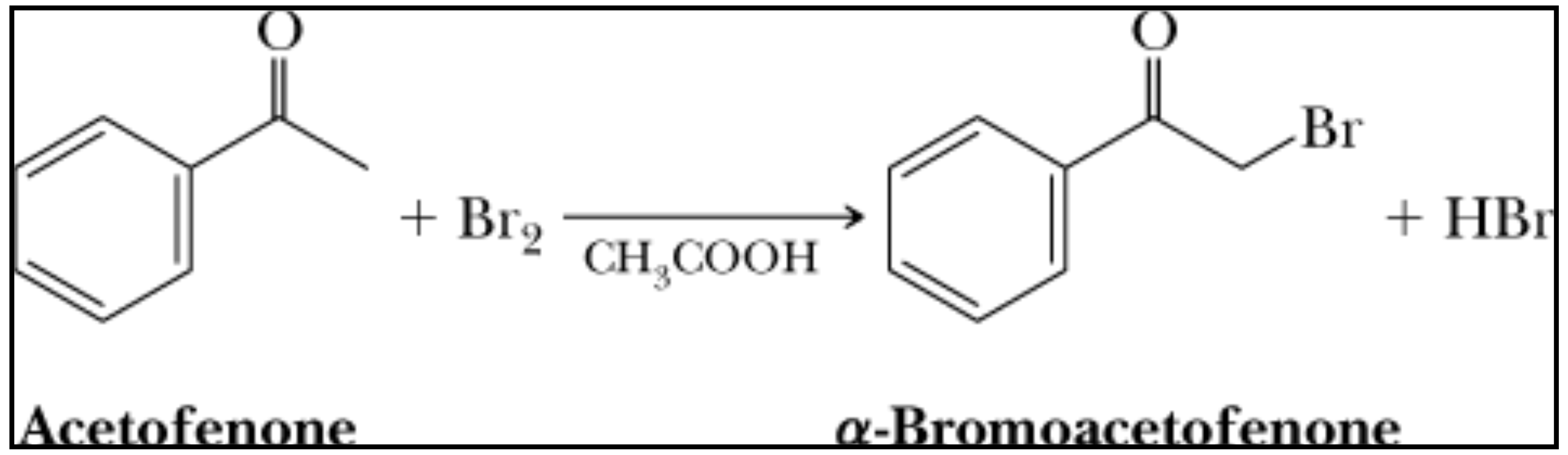


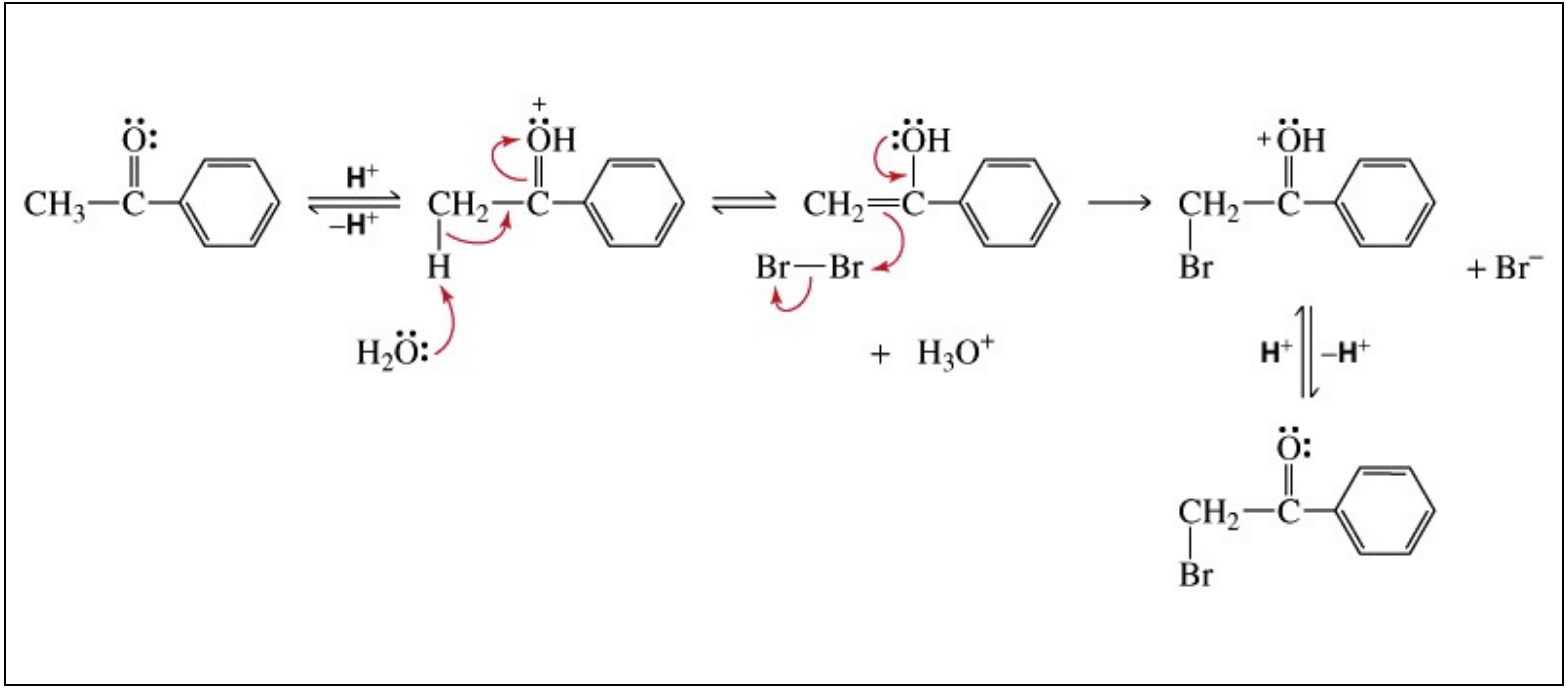


α-Alogenazione

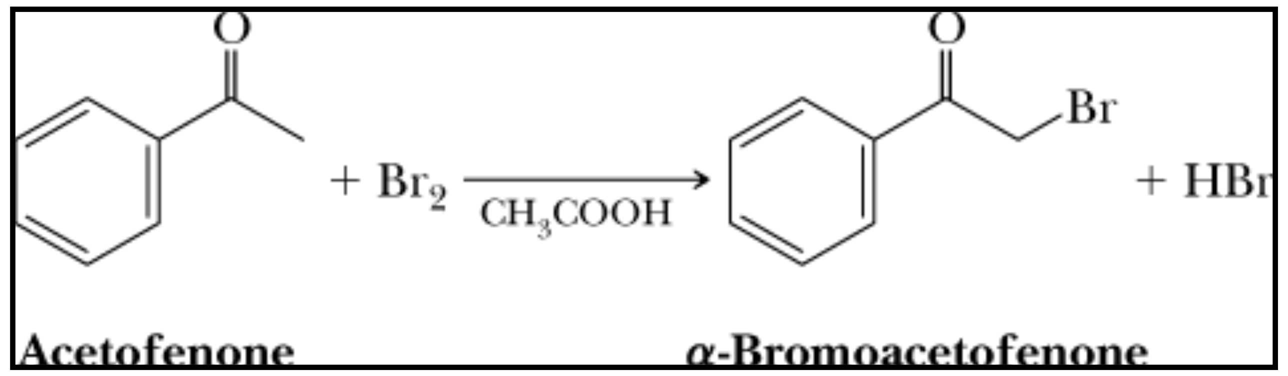


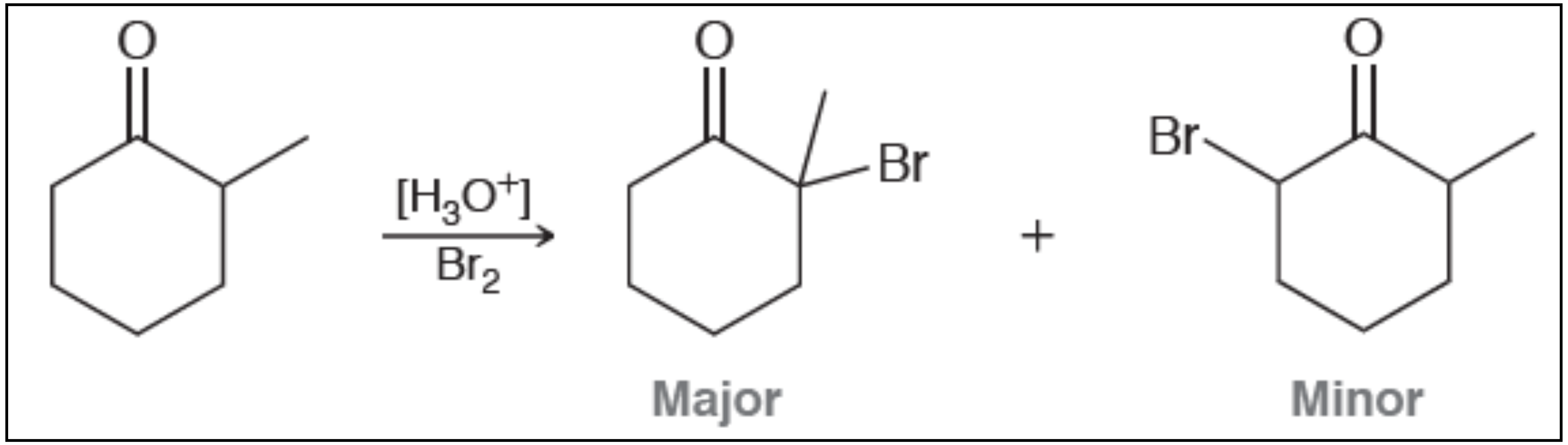
α-Alogenazione

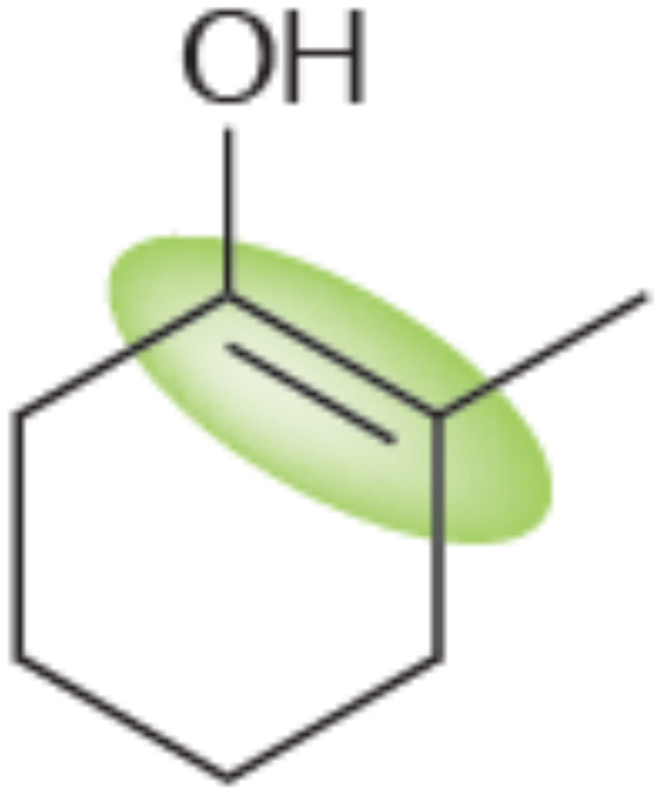




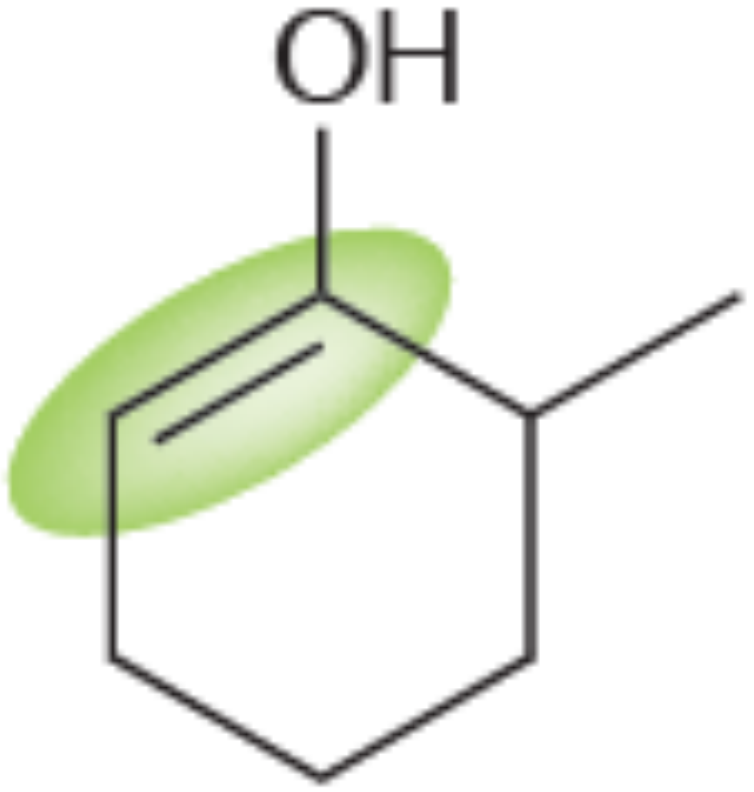
α-Alogenazione - Bromurazione Regioselettiva





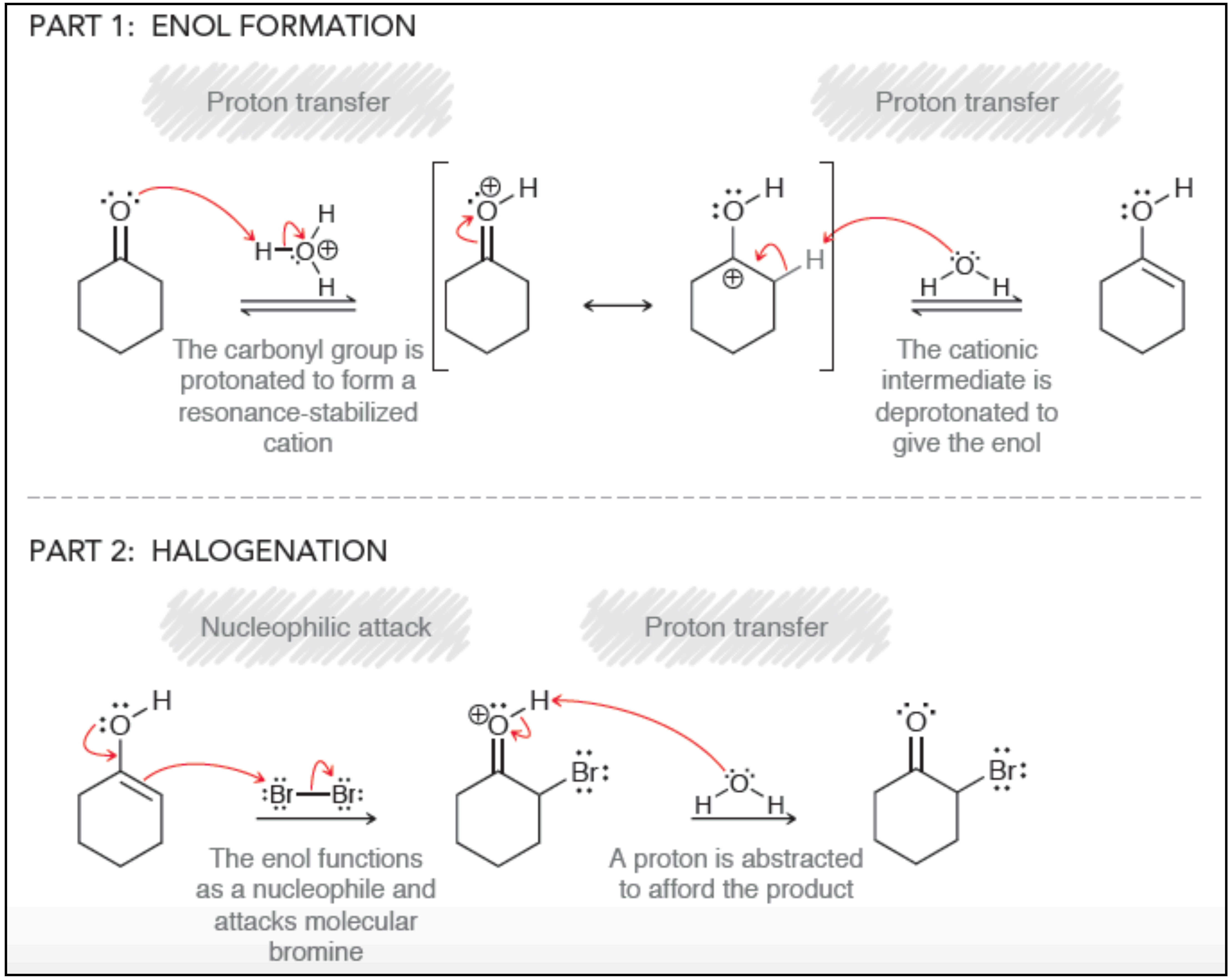


More substituted (more stable)



Less substituted (less stable)

α-Alogenazione - Bromurazione Regioselettiva



PART 1: ENOL FORMATION

Proton transfer

The carbonyl group is protonated to form a resonance-stabilized cation

Proton transfer

The cationic intermediate is deprotonated to give the enol

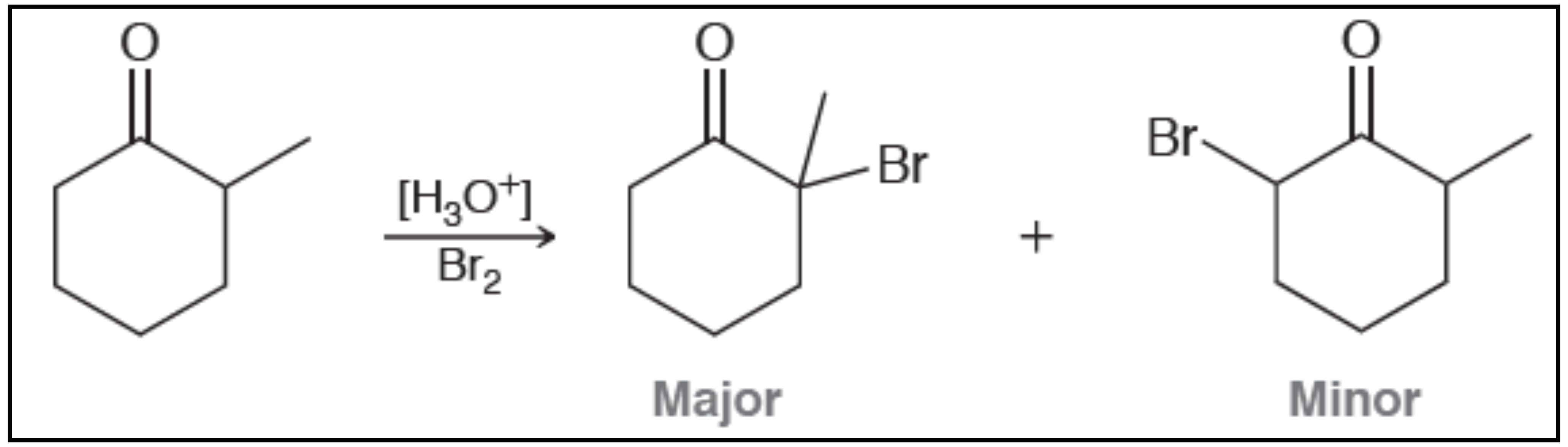
PART 2: HALOGENATION

Nucleophilic attack

The enol functions as a nucleophile and attacks molecular bromine

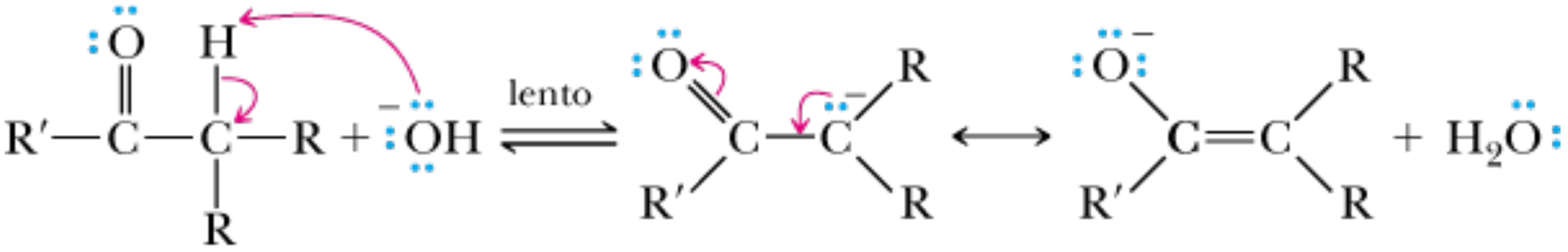
Proton transfer

A proton is abstracted to afford the product



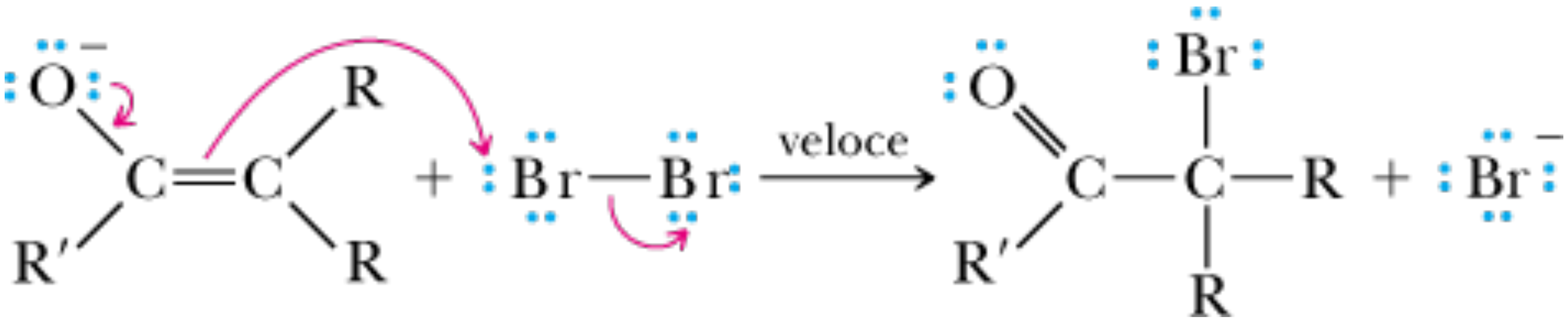
α-Alogenazione di un chetone promossa da una base

Stadio 1 Rimozione di un protone. Il trasferimento di un protone da un carbonio α alla base dà un anione enolato stabilizzato per risonanza.

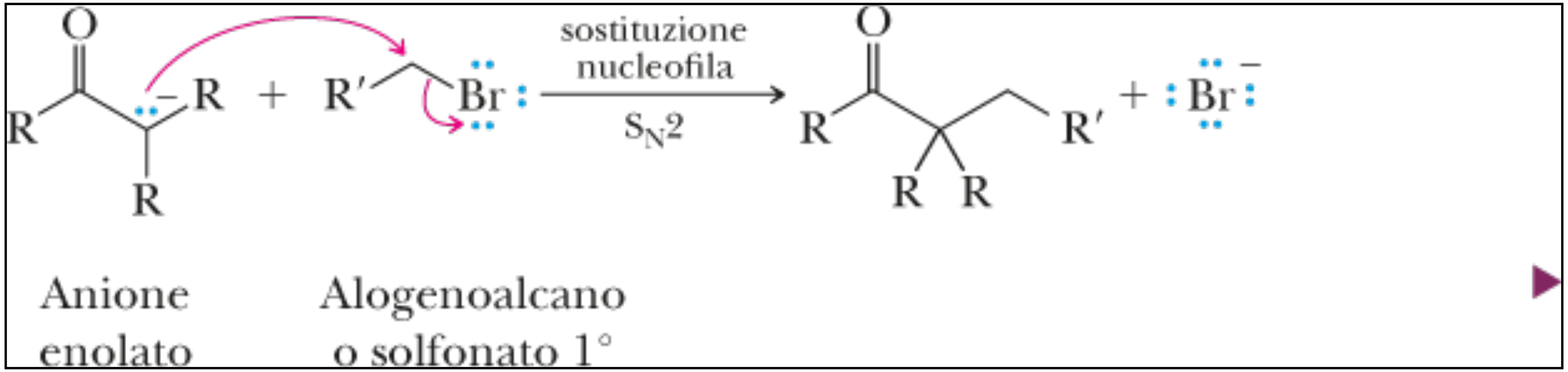


Anione enolato stabilizzato per risonanza

Stadio 2 Formazione di un nuovo legame tra un nucleofilo (legame p) e un elettrofilo

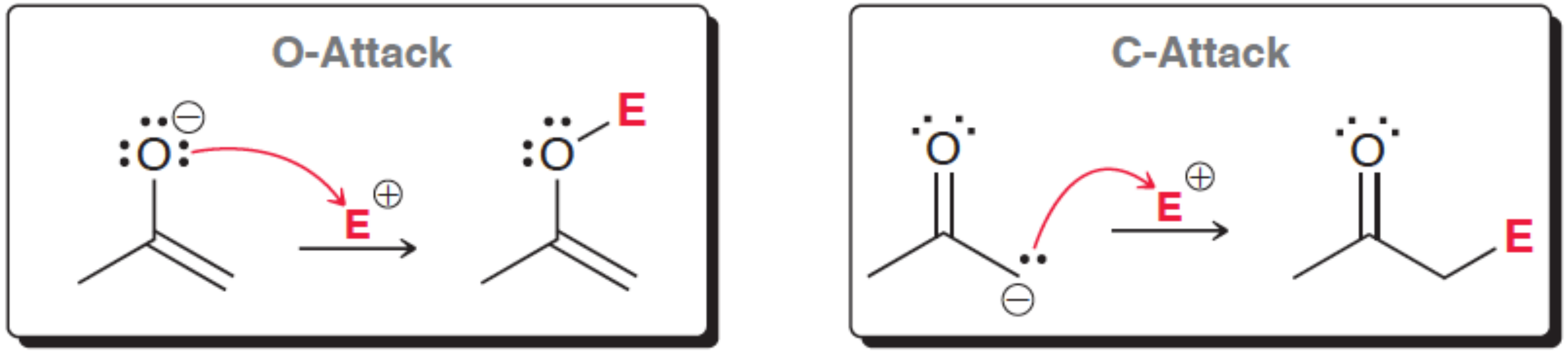


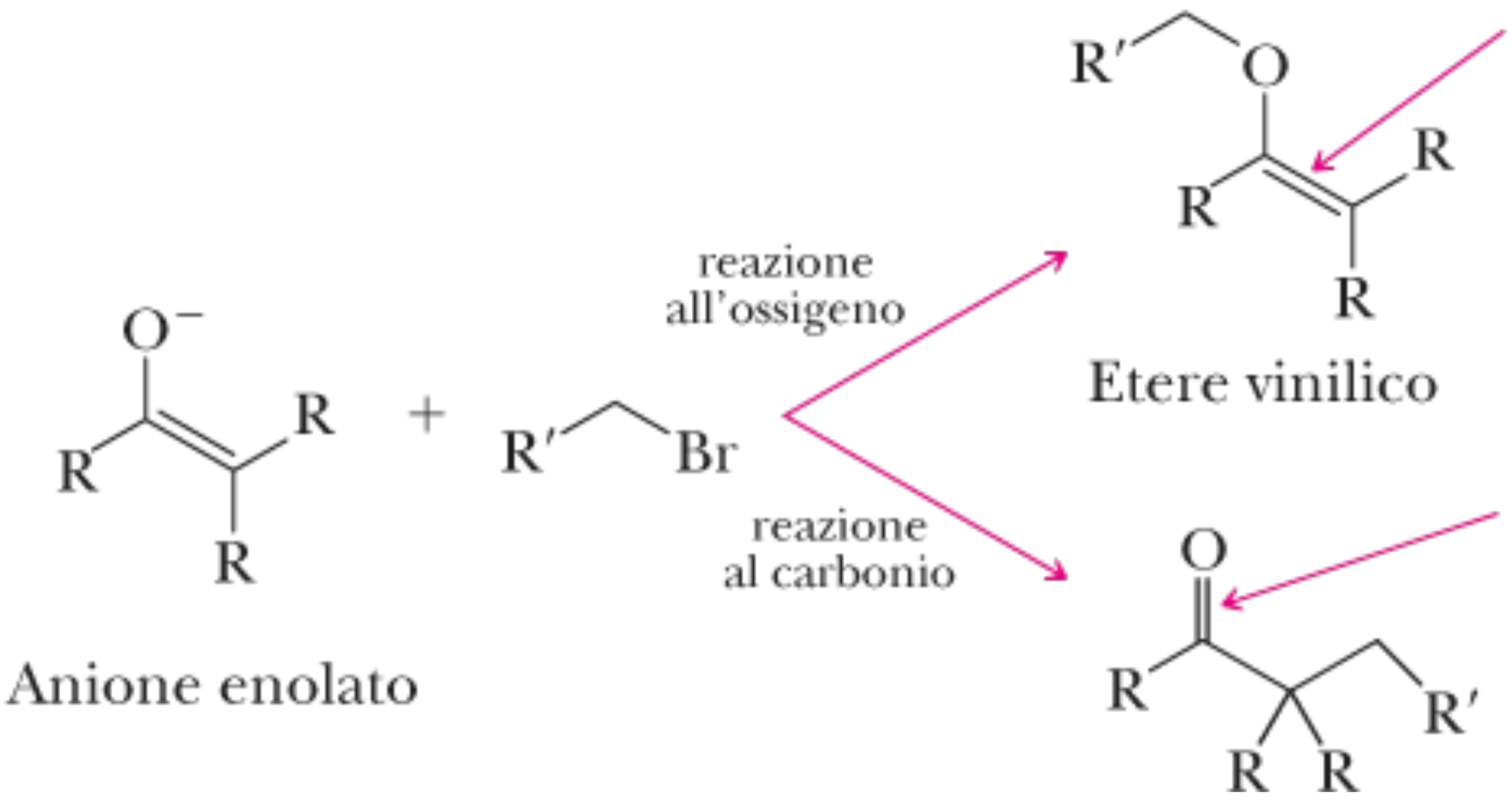
Formazione dello ione enolato cinetico e termodinamico. Alchilazione del carbonio alfa base catalizzata.



Gli anioni enolato sono importanti per la sintesi poiché reagiscono al carbonio per formare nuovi legami carbonio-carbonio in due tipi di reazioni. In primo luogo, essi agiscono da nucleofili nelle reazioni di sostituzione nucleofila SN2, come illustrato nella seguente reazione generale.

Formazione dello ione enolato cinetico e termodinamico. Alchilazione del carbonio alfa base catalizzata.

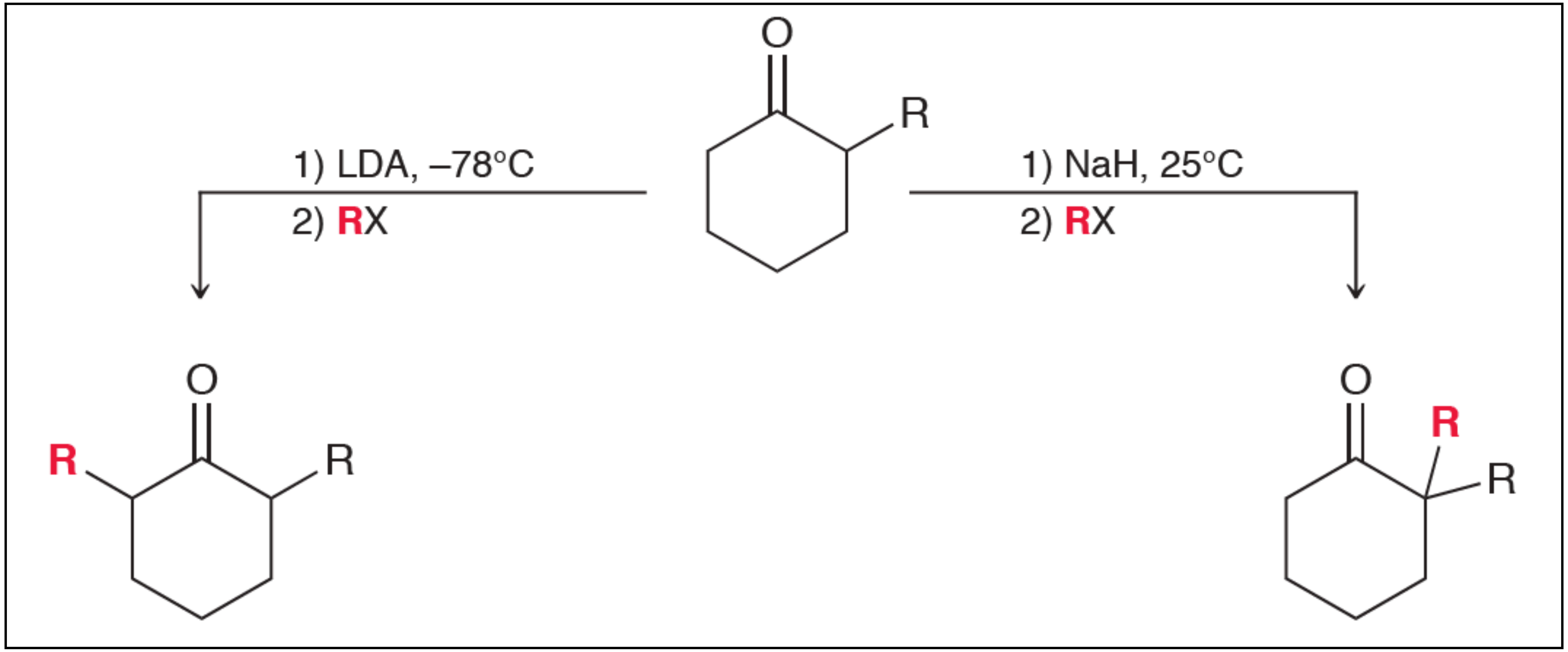




questo prodotto ha un legame C=C di tipo π, quindi è meno stabile

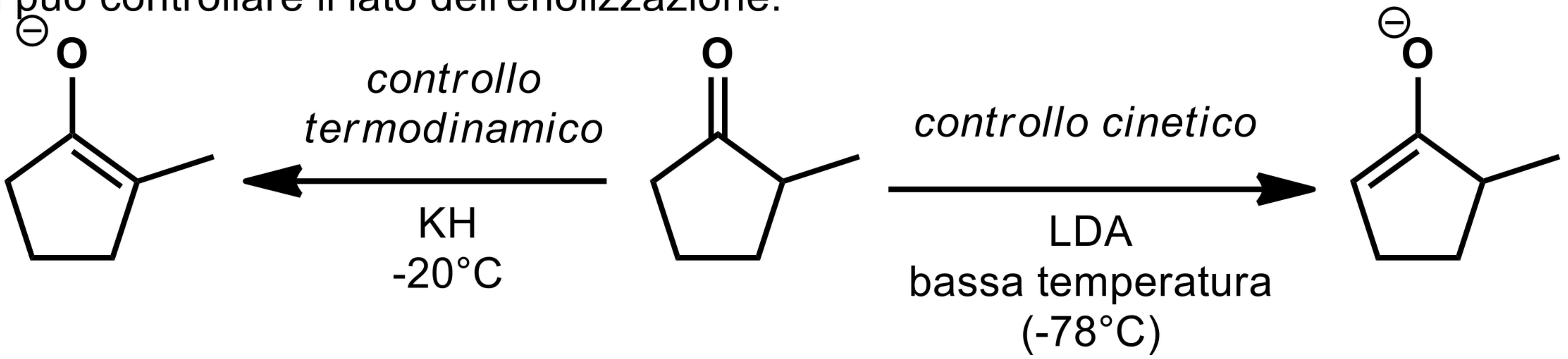
questo prodotto ha un legame C=O di tipo π, quindi è più stabile

Formazione dello ione enolato cinetico e termodinamico. Alchilazione del carbonio alfa base catalizzata.



Con chetoni asimmetrici si può controllare il lato dell'enolizzazione:

l'enolato più ingombrato è più stabile perché in generale i doppi legami più sostituiti sono più stabili



l'attacco dell'LDA sul lato meno ingombrato è più veloce

10. Aldeidi e Chetoni

(1) Reattività dei composti carbonilici.

(2) Addizione di nucleofili forti e deboli al carbonio carbonilico.

(3) Formazione di immine ed enammine.

(4) Formazione di acetali e emiacetali come gruppi protettori del gruppo carbonilico.

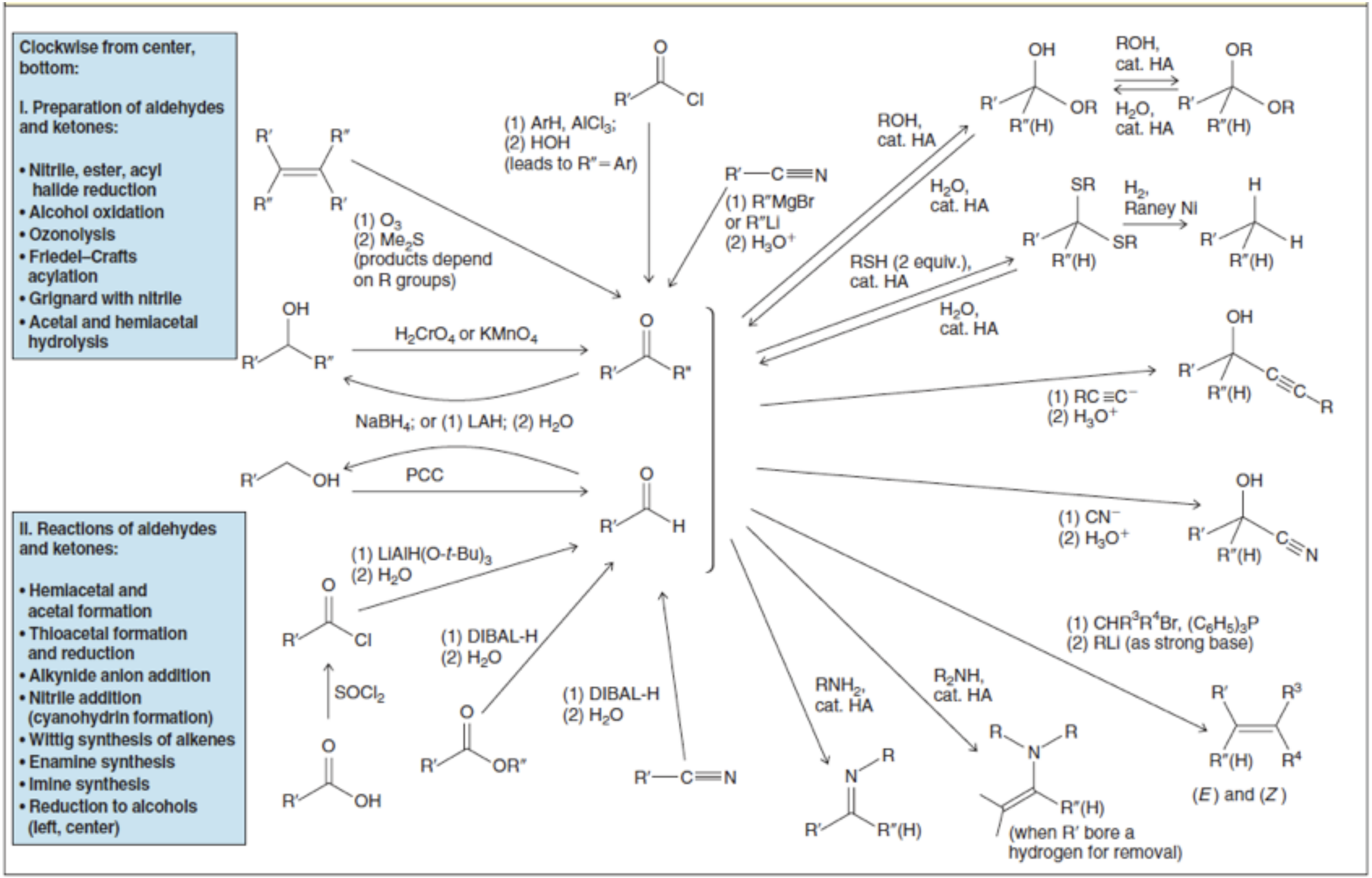
(5) Reazione di Wittig.

(6) Acidità dell’idrogeno alfa di derivati carbonilici.

(7) Tautomeria cheto-enolica. Alogenazione del carbonio alfa di aldeidi e chetoni.

(8) Formazione dello ione enolato cinetico e termodinamico.

(9) Alchilazione del carbonio alfa base catalizzata.



Clockwise from center, bottom:

I. Preparation of aldehydes and ketones:

- **Nitrile, ester, acyl halide reduction**
- **Alcohol oxidation**
- **Ozonolysis**
- **Friedel–Crafts acylation**
- **Grignard with nitrile**
- **Acetal and hemiacetal hydrolysis**

II. Reactions of aldehydes and ketones:

- **Hemiacetal and acetal formation**
- **Thioacetal formation and reduction**
- **Alkynide anion addition**
- **Nitrile addition (cyanohydrin formation)**
- **Wittig synthesis of alkenes**
- **Enamine synthesis**
- **Imine synthesis**
- **Reduction to alcohols (left, center)**