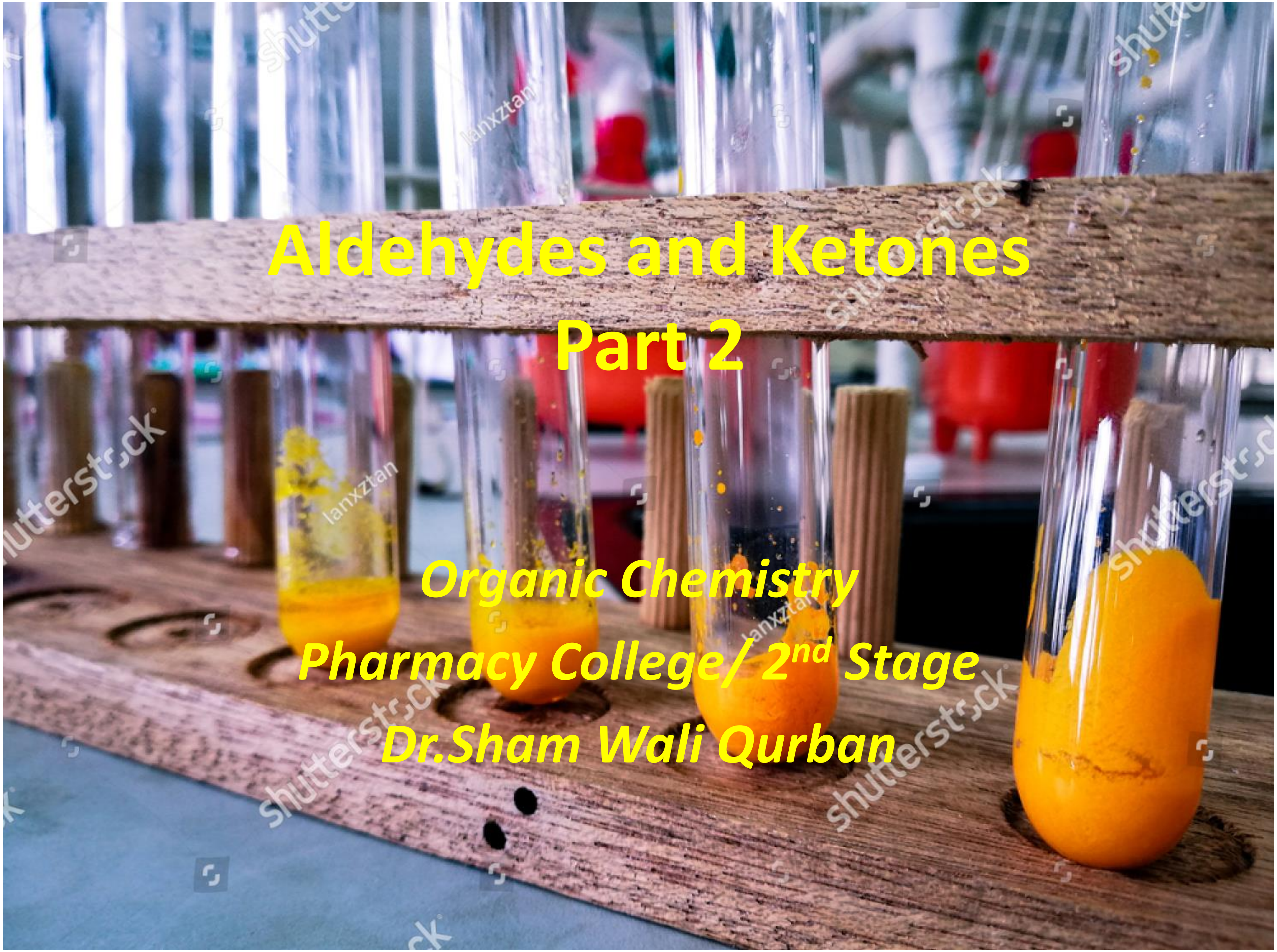


Aldehydes and Ketones

Part 2

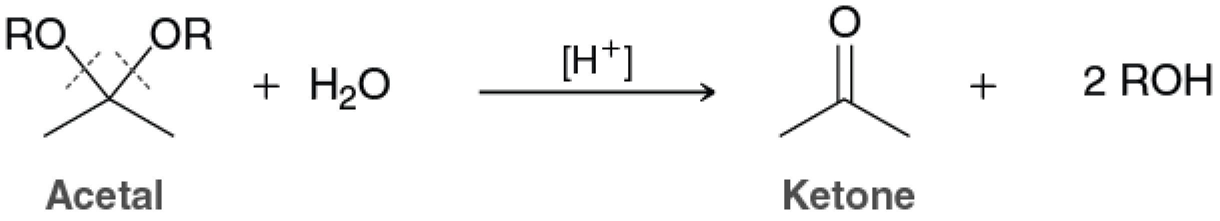
Organic Chemistry

Pharmacy College/ 2nd Stage

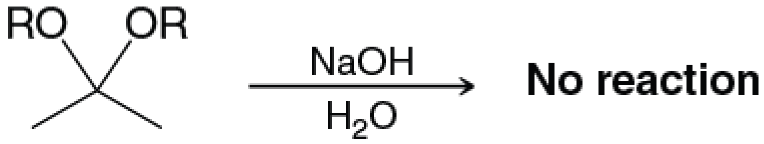
Dr.Sham Wali Qurban

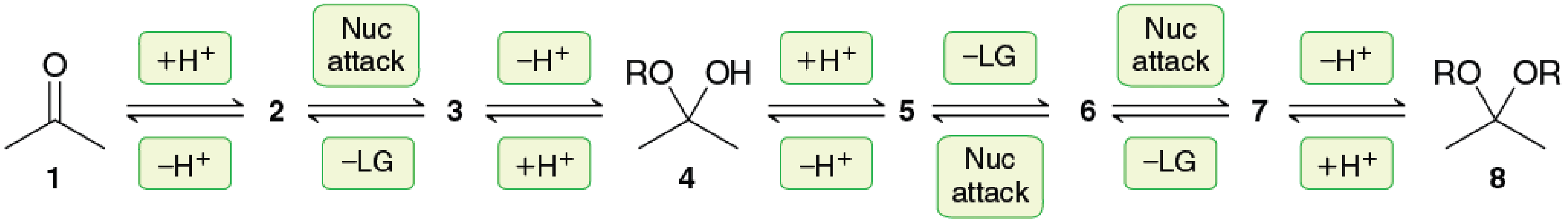
19.7 Hydrolysis of Acetals, Imines, and Enamines

The treatment of an acetal with aqueous acid affords the corresponding aldehyde or ketone:

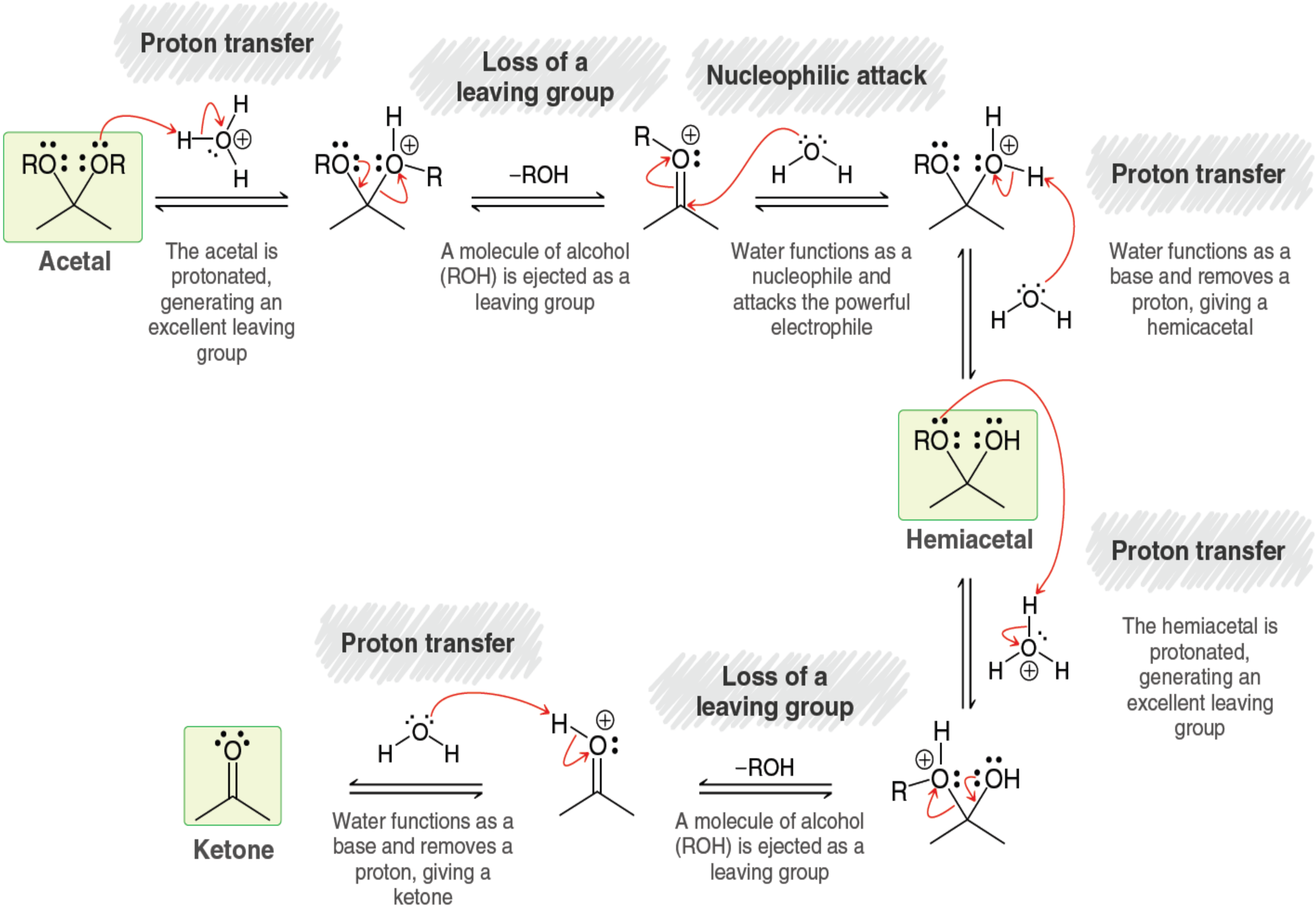


This process is called a hydrolysis reaction





MECHANISM 19.9 HYDROLYSIS OF ACETALS



Acetal

Proton transfer

The acetal is protonated, generating an excellent leaving group

Loss of a leaving group

A molecule of alcohol (ROH) is ejected as a leaving group

Nucleophilic attack

Water functions as a nucleophile and attacks the powerful electrophile

Proton transfer

Water functions as a base and removes a proton, giving a hemicacetal

Hemiacetal

Proton transfer

The hemiacetal is protonated, generating an excellent leaving group

Loss of a leaving group

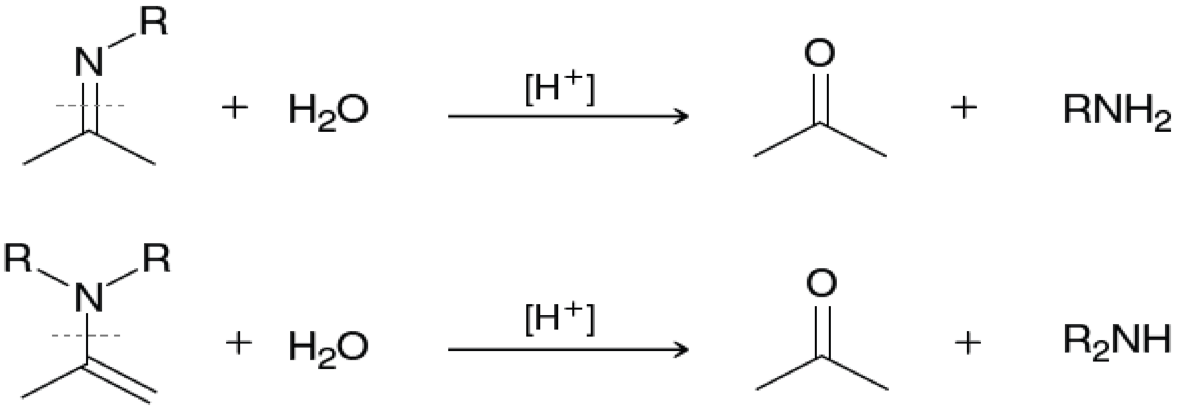
A molecule of alcohol (ROH) is ejected as a leaving group

Proton transfer

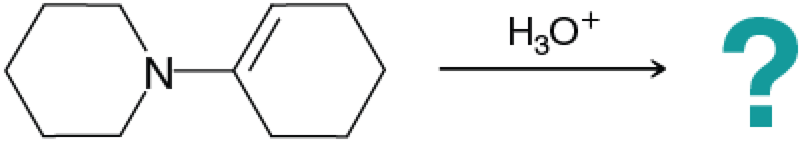
Water functions as a base and removes a proton, giving a ketone

Ketone

Imines and enamines also undergo hydrolysis when treated with aqueous acid, and the red wavy lines (below) indicate the bonds that undergo cleavage:

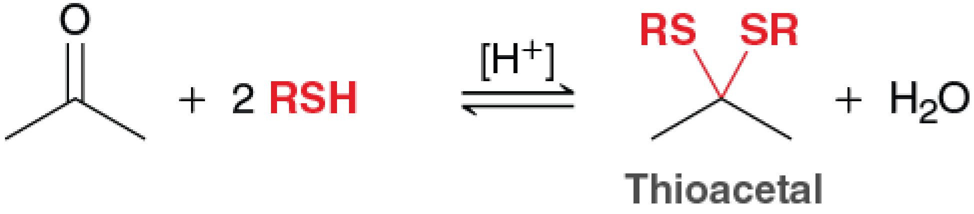


19.5 drawing the products of a hydrolysis reaction

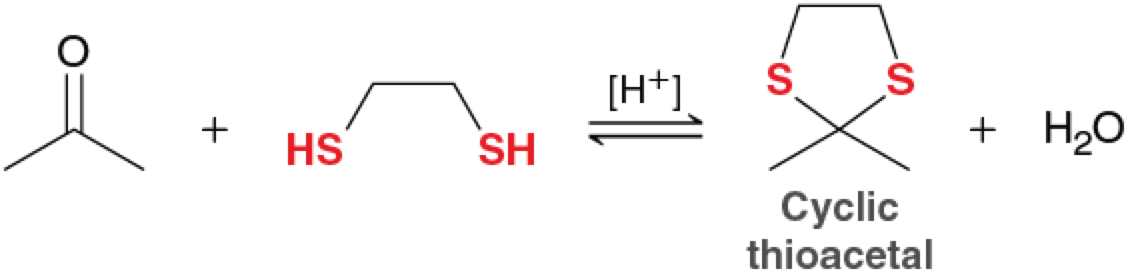


19.8 Sulfur Nucleophiles

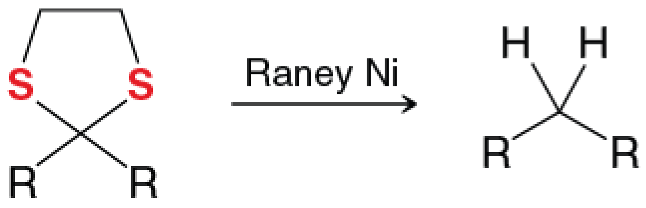
In acidic conditions, an aldehyde or ketone will react with two equivalents of a thiol to form a **thioacetal**:



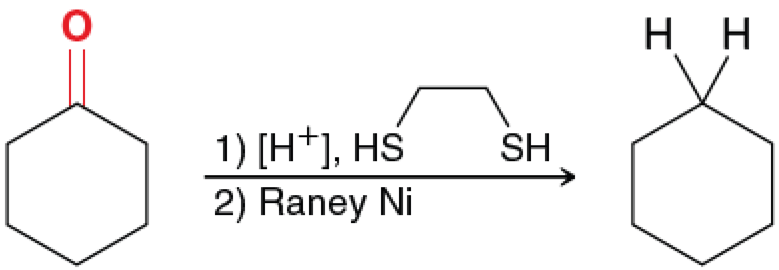
This transformation proceeds via a mechanism that is directly analogous to acetal formation, with sulfur atoms taking the place of oxygen atoms. If a compound with two SH groups is used, a cyclic thioacetal is formed:



When treated with Raney nickel, thioacetals undergo **desulfurization**, yielding an alkane:



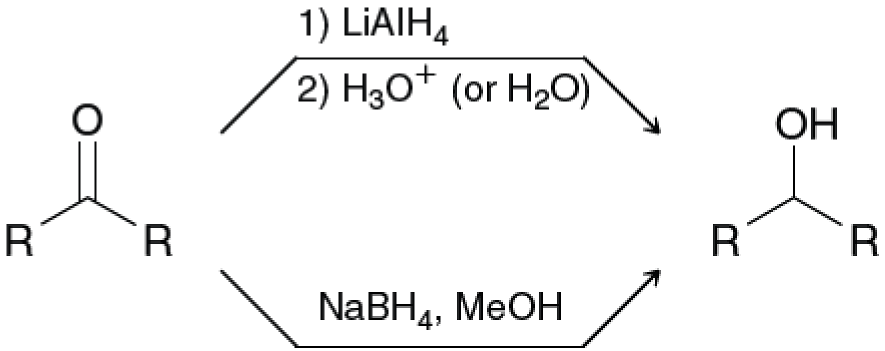
The reactions above provide us with another two- step method for the reduction of a ketone:



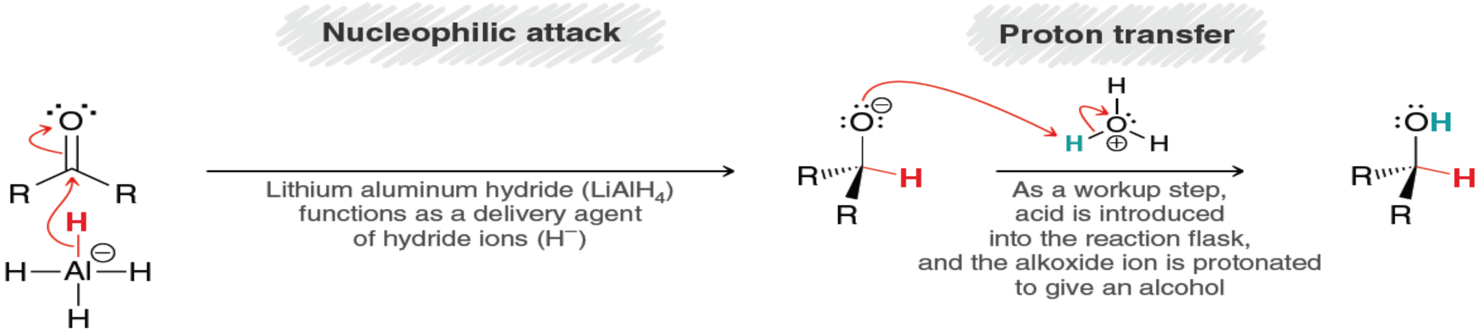
This method involves formation of the thioacetal followed by desulfurization with Raney nickel.

19.9 Hydrogen Nucleophiles

When treated with a hydride reducing agent, such as lithium aluminum hydride ($LiAlH_4$) or sodium borohydride ($NaBH_4$), aldehydes and ketones are reduced to alcohols:

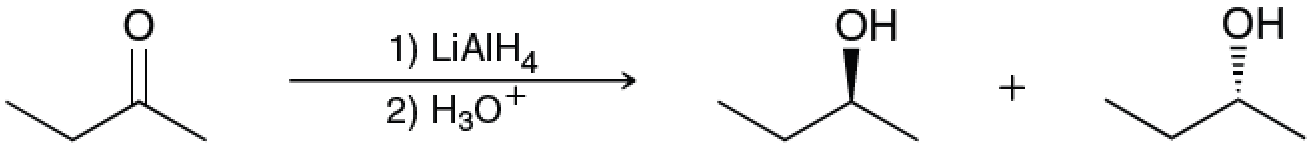


MECHANISM 19.10 THE REDUCTION OF KETONES OR ALDEHYDES WITH HYDRIDE AGENTS



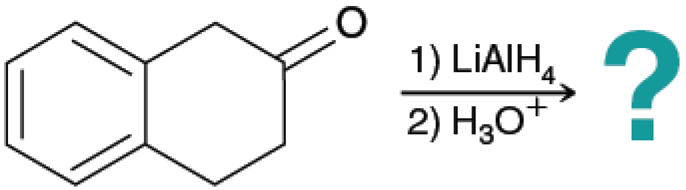
Lithium aluminum hydride ($LiAlH_4$) functions as a delivery agent of hydride ions (H^-)

As a workup step, acid is introduced into the reaction flask, and the alkoxide ion is protonated to give an alcohol when an unsymmetrical ketone is reduced with a hydride reducing agent, such as **LiAlH$_4$ or NaBH$_4$**, a new chiral center is generated, and a pair of stereoisomers is obtained.



Racemic mixture

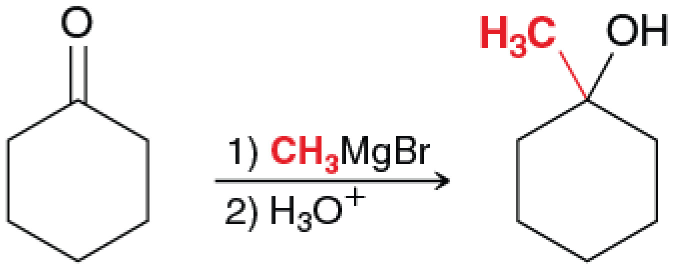
19.28 Predict the major product(s) for each of the following reactions:

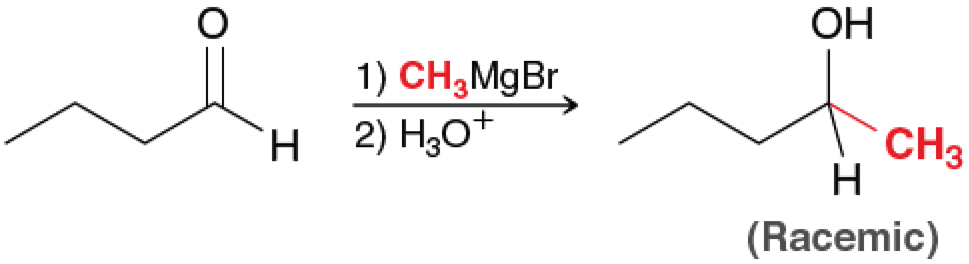


19.10 Carbon Nucleophiles

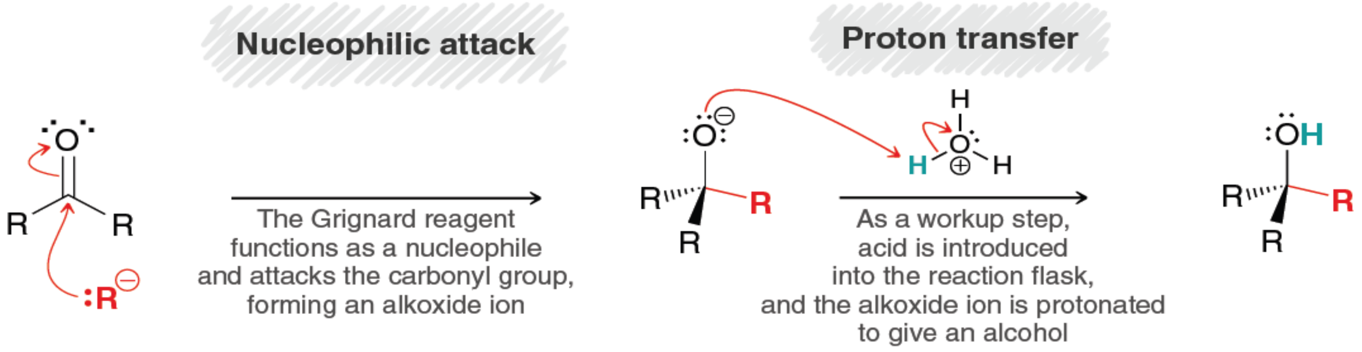
Grignard Reagents

When treated with a Grignard reagent, aldehydes and ketones are converted into alcohols, accompanied by the formation of a new C-C bond:





MECHANISM 19.11 THE REACTION BETWEEN A GRIGNARD REAGENT AND A KETONE OR ALDEHYDE



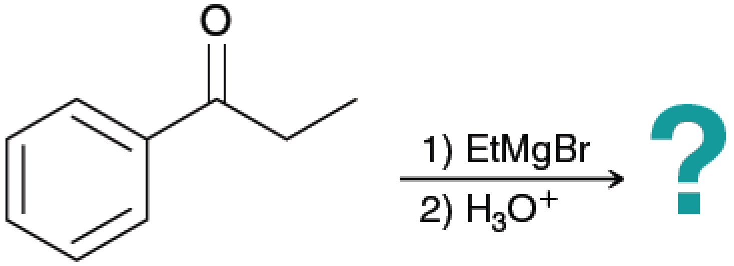
Nucleophilic attack

The Grignard reagent functions as a nucleophile and attacks the carbonyl group, forming an alkoxide ion

Proton transfer

As a workup step, acid is introduced into the reaction flask, and the alkoxide ion is protonated to give an alcohol

19.30 Predict the major product(s) for each of the following:



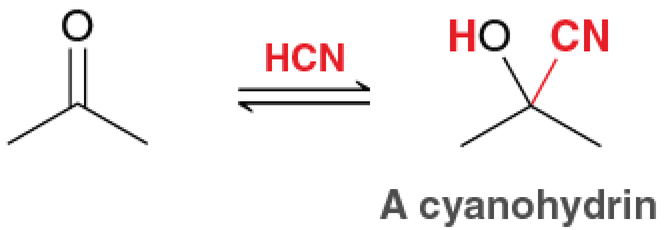
1) EtMgBr

2) H_3O^+

?

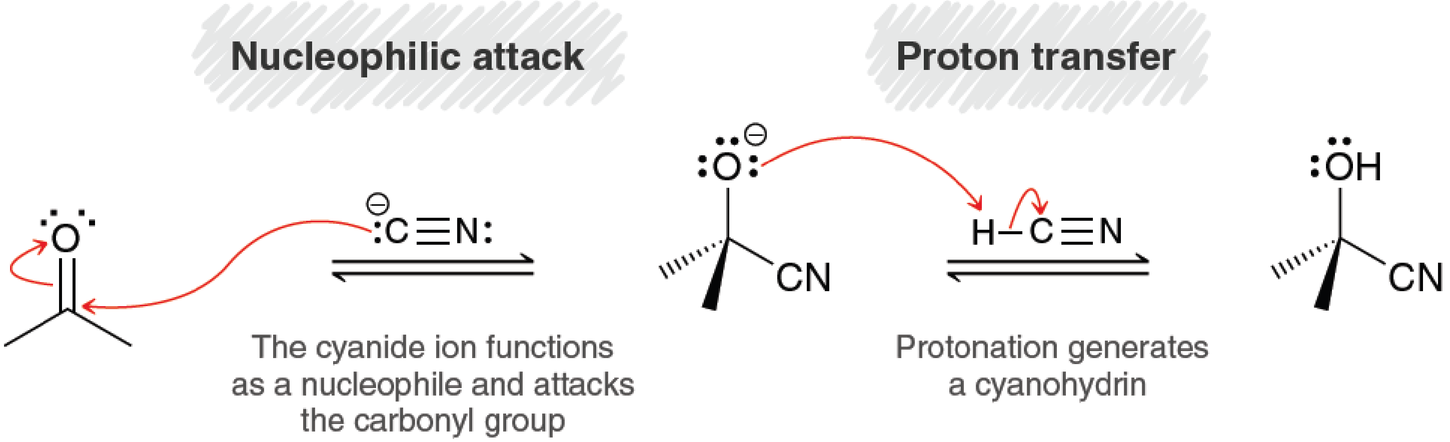
Cyanohydrin Formation

When treated with hydrogen cyanide (**HCN**), aldehydes and ketones are converted into **cyanohydrins**, which are characterized by the presence of a cyano group and a hydroxyl group connected to the same carbon atom:



This reaction was studied extensively by Arthur Lapworth (University of Manchester) and was found to occur **more rapidly in mildly basic conditions.**

MECHANISM 19.12 CYANOHYDRIN FORMATION



Nucleophilic attack

The cyanide ion functions as a nucleophile and attacks the carbonyl group

Proton transfer

Protonation generates a cyanohydrin

Rather than using a catalytic amount of base to form cyanide ions, the reaction can simply be performed in a mixture of HCN and cyanide ions (from KCN).

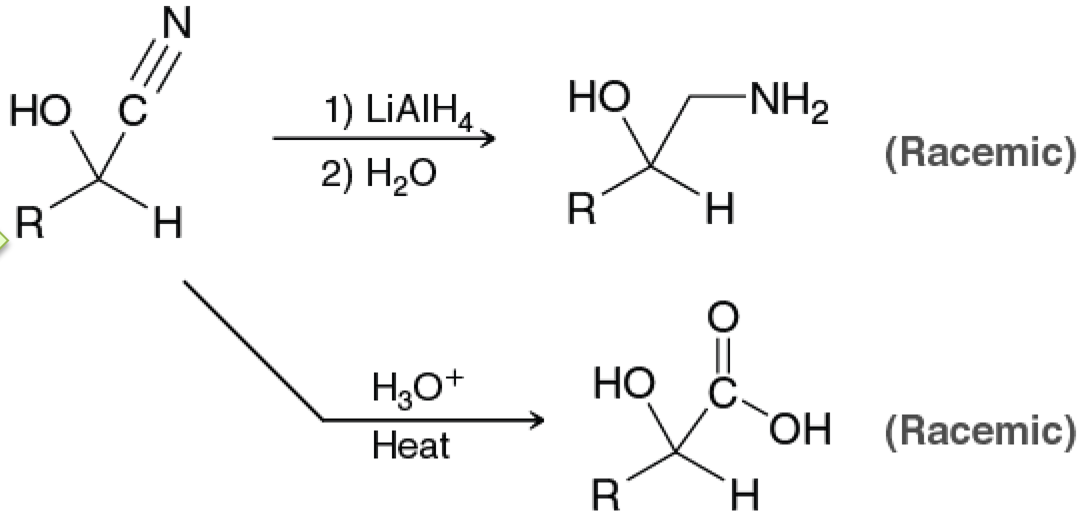
78%

(Racemic)

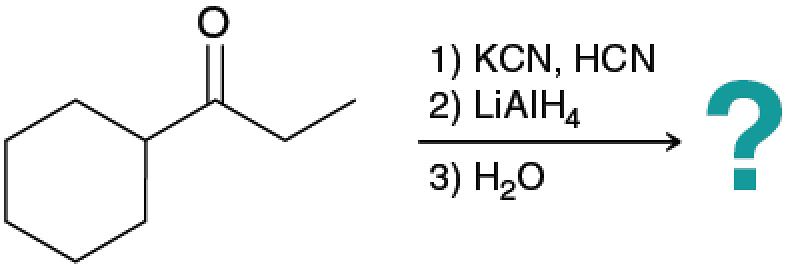
88%

HCN is a liquid at room temperature and is extremely hazardous to handle because it is highly toxic and volatile (**b.p. = 26°C**). To avoid the dangers associated with handling HCN, cyanohydrins can also be prepared by treating a ketone or aldehyde with potassium cyanide and an alternate source of protons, such as HCl:

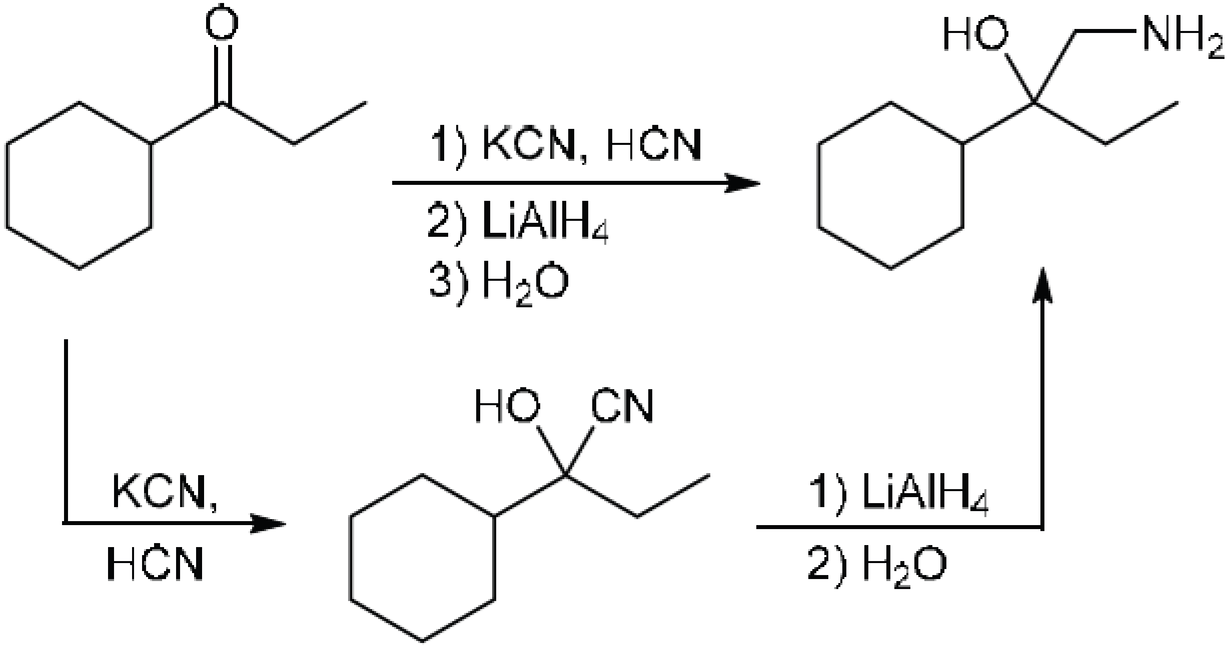
Cyanohydrins are useful in syntheses, because the cyano group can be further treated to yield a range of products.



19.32 Predict the major product for each of the following reaction sequences:

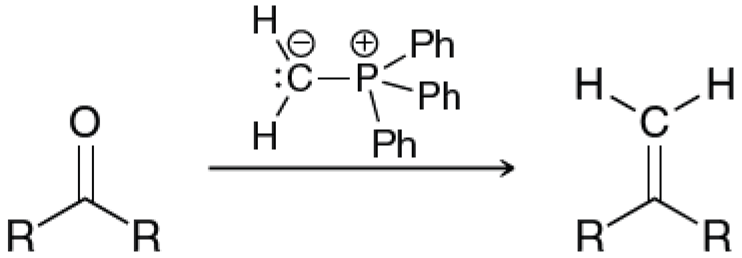


Solution

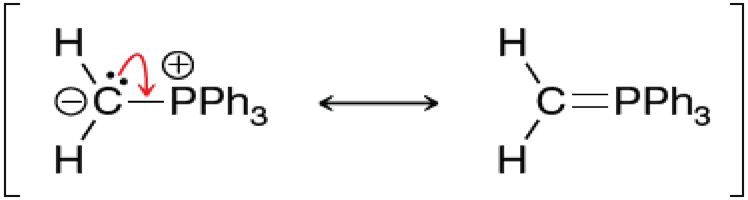


Wittig Reactions

Georg Wittig, a German chemist, was awarded the 1979 Nobel Prize in Chemistry for his work with phosphorus compounds and his discovery of a reaction with enormous synthetic utility. This reaction is called the **Wittig reaction** (pronounced Vittig):

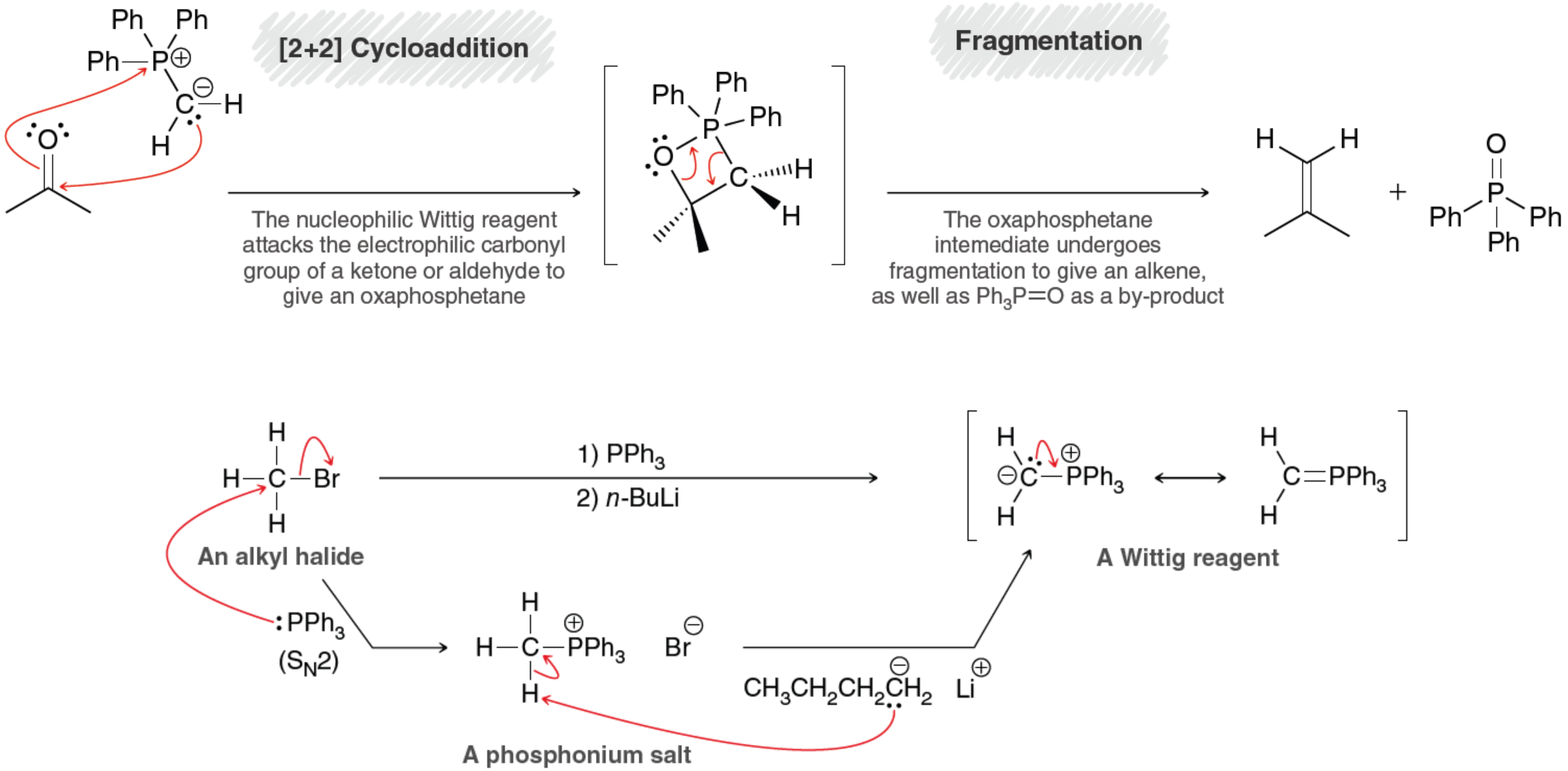


Because it forms an alkene product, this reaction is also known as the Wittig olefination reaction (the term “olefin” was once commonly used for unsaturated compounds such as alkenes).



Wittig reagent

MECHANISM 19.13 THE WITTIG REACTION



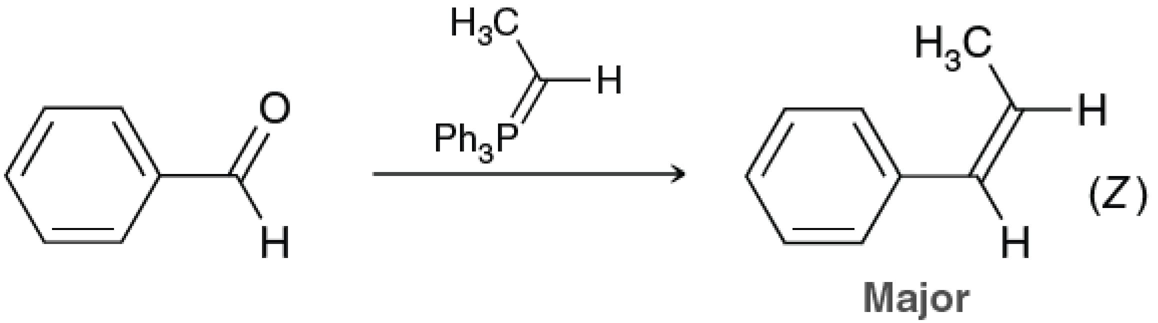
The nucleophilic Wittig reagent attacks the electrophilic carbonyl group of a ketone or aldehyde to give an oxaphosphetane

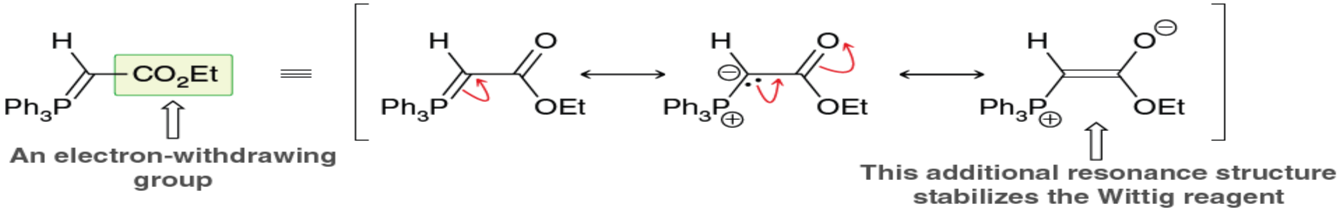
The oxaphosphetane intemediate undergoes fragmentation to give an alkene, as well as $Ph_3P{=}O$ as a by-product

Since the first step is an S_N2 process, the regular restrictions of S_N2 processes apply. Specifically, primary alkyl halides will react more readily than secondary alkyl halides, and tertiary alkyl halides cannot be used.

A variety of strong bases can be used to deprotonate the phosphonium salt intermediate, including **NaH, $NaNH_2$, and PhLi**.

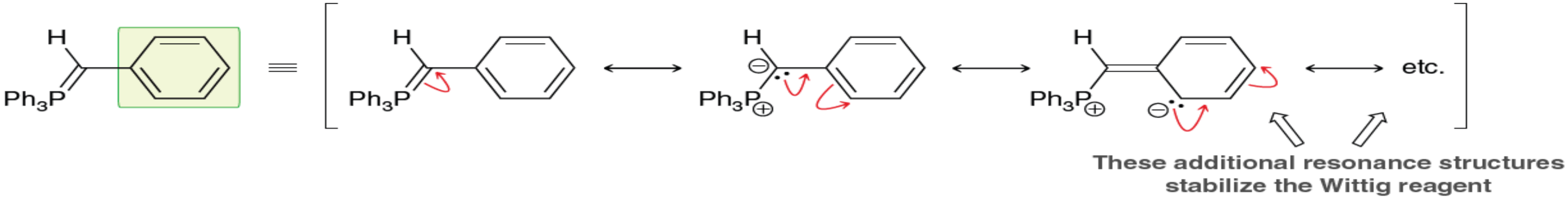
The Wittig reaction is useful for preparing **mono-, di-, or tri**substituted alkenes. **Tetra**substituted alkenes are more difficult to prepare due to **steric hindrance in the transition states.**



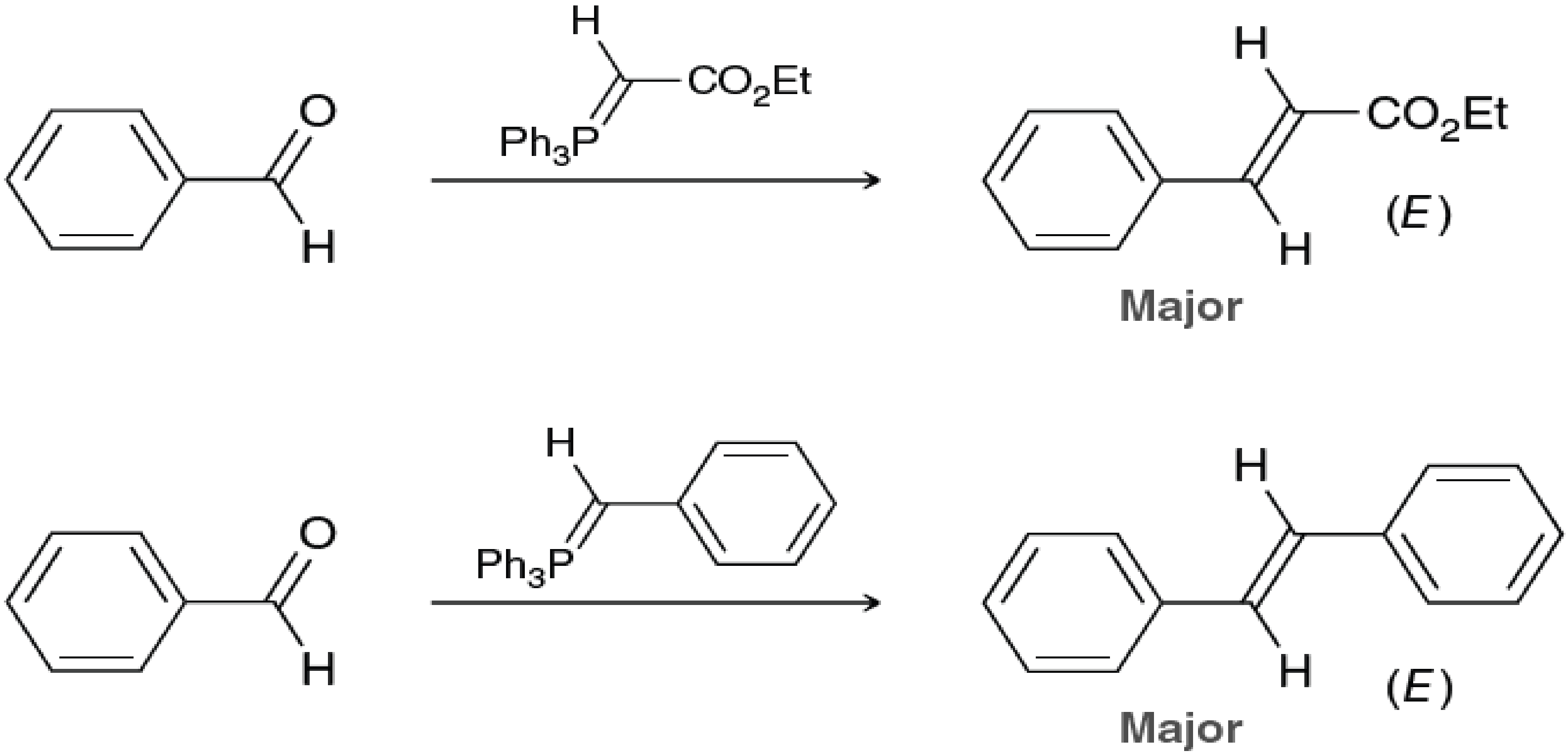


An electron-withdrawing group

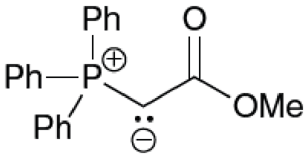
This additional resonance structure stabilizes the Wittig reagent



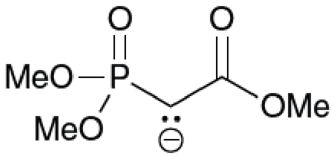
These additional resonance structures stabilize the Wittig reagent


O
H
H
CO_2Et
Ph_3P
H
CO_2Et
H
(*E*)
Major
O
H
H
Ph_3P
H
H
(*E*)
Major

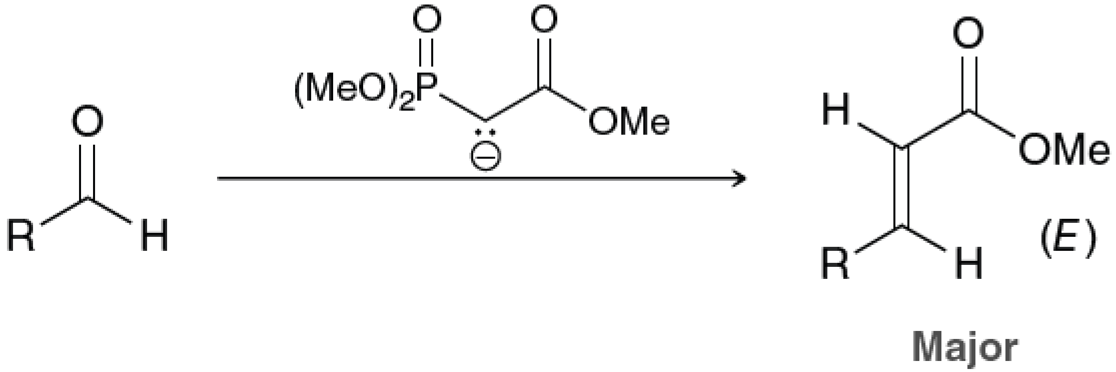
Many variations of the Wittig reaction are also commonly used. For example, in **the Horner–Wadsworth– Emmons reaction (or HWE reaction),** a phosphonate ester carbanion reagent (HWE reagent) is used instead of a stabilized Wittig reagent, although these reagents are very similar in structure:



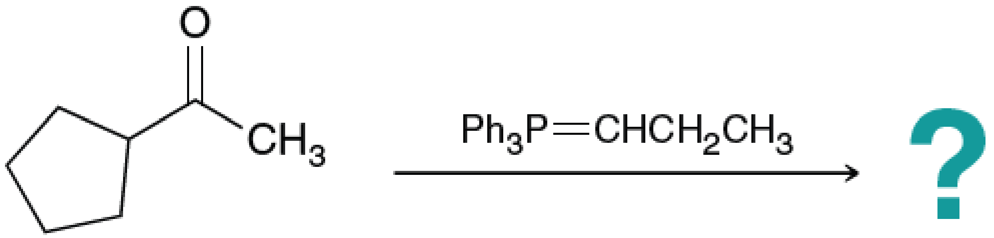
A stabilized Wittig reagent
(resonance-stabilized by ester group)

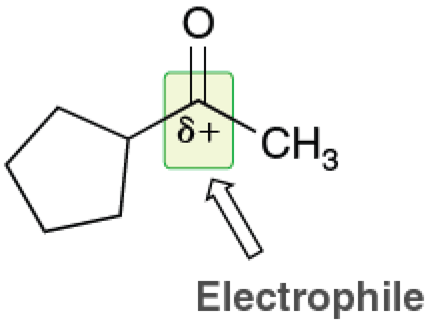


HWE reagent
(a resonance-stabilized phosphonate ester carbanion)

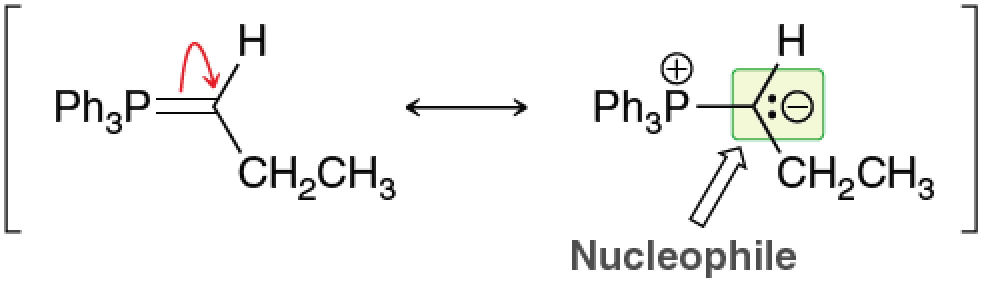


19.6 predicting the major product of a wittig or hwe reaction

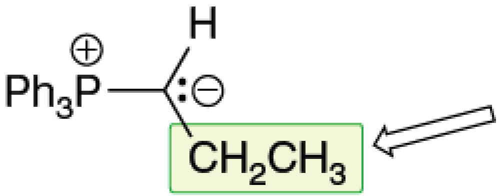




Electrophile

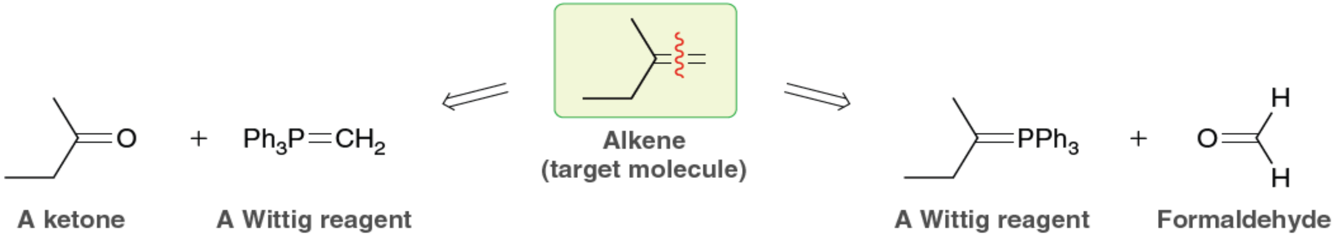


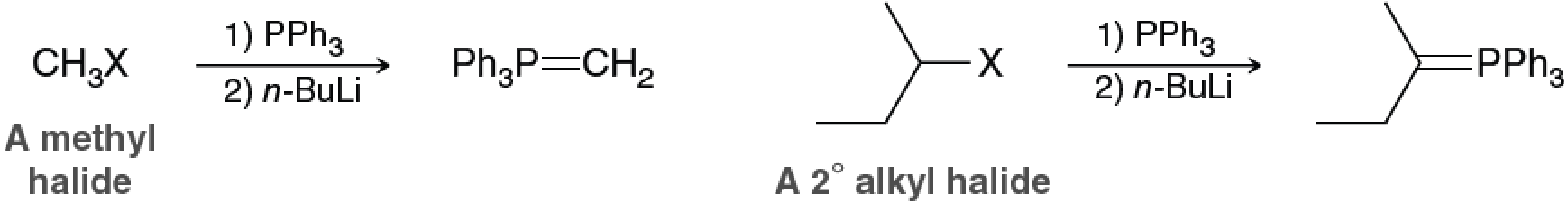
Nucleophile

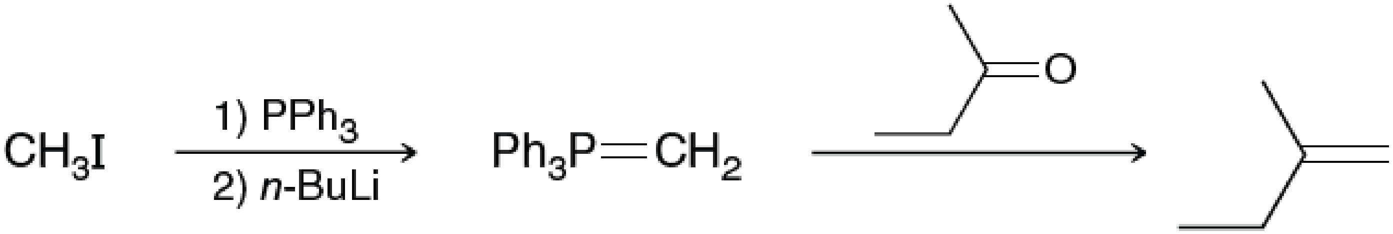


This group does not stabilize the carbanion

When an alkene is made via a Wittig or HWE reaction, a retrosynthetic analysis will always reveal two possibilities to consider, as illustrated in the following case:

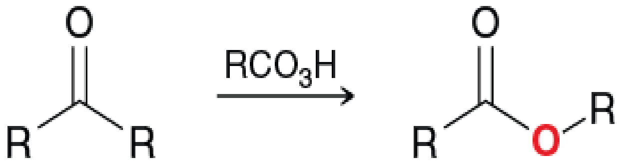




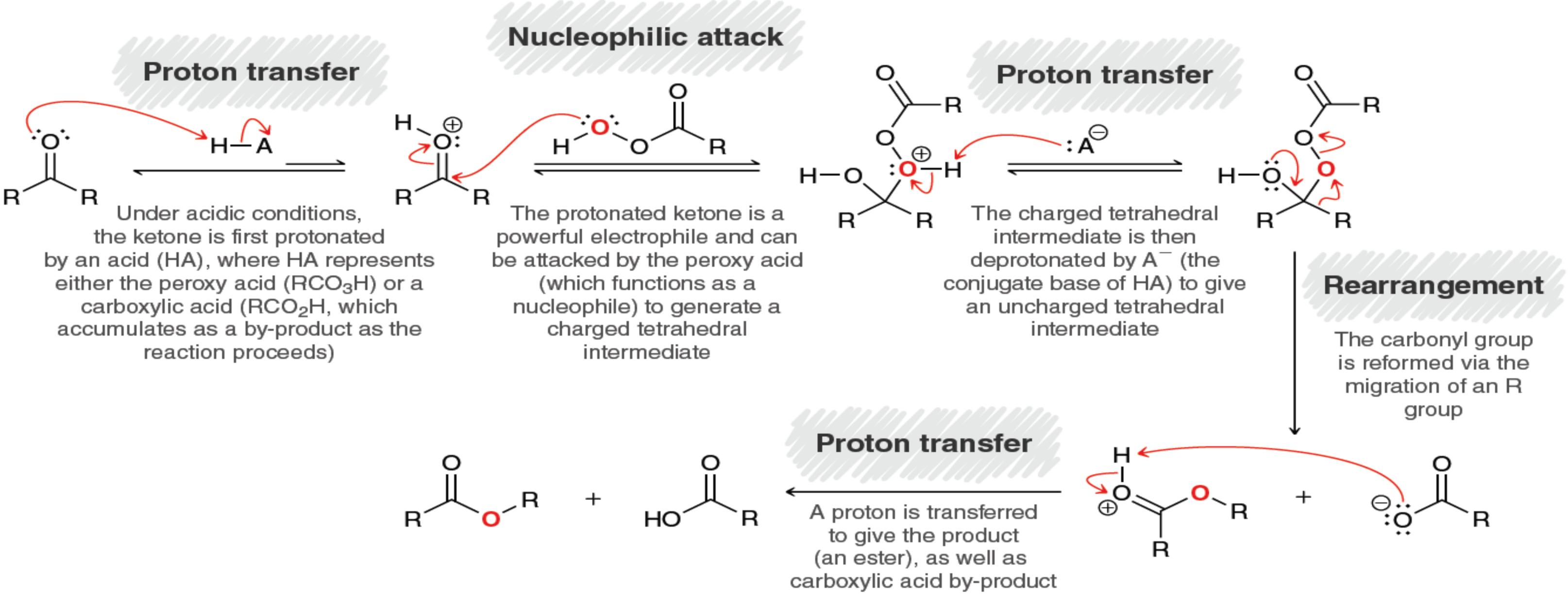


19.11 Baeyer– Villiger Oxidation of Aldehydes and Ketones

When treated with a peroxy acid, ketones can be converted into esters via the insertion of an oxygen atom.



MECHANISM 19.14 THE BAEYER–VILLIGER OXIDATION



Proton transfer

Under acidic conditions, the ketone is first protonated by an acid (HA), where HA represents either the peroxy acid (RCO_3H) or a carboxylic acid (RCO_2H, which accumulates as a by-product as the reaction proceeds)

Nucleophilic attack

The protonated ketone is a powerful electrophile and can be attacked by the peroxy acid (which functions as a nucleophile) to generate a charged tetrahedral intermediate

Proton transfer

The charged tetrahedral intermediate is then deprotonated by A^- (the conjugate base of HA) to give an uncharged tetrahedral intermediate

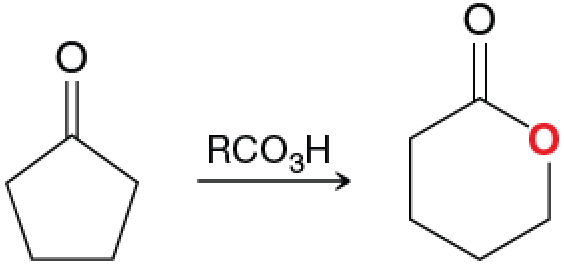
Rearrangement

The carbonyl group is reformed via the migration of an R group

Proton transfer

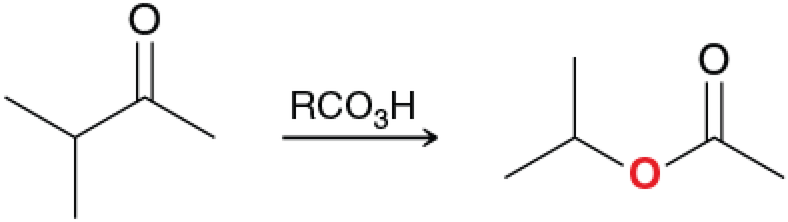
A proton is transferred to give the product (an ester), as well as carboxylic acid by-product

In much the same way, treatment of a cyclic ketone with a peroxy acid yields a cyclic ester, or **lactone**.



A lactone

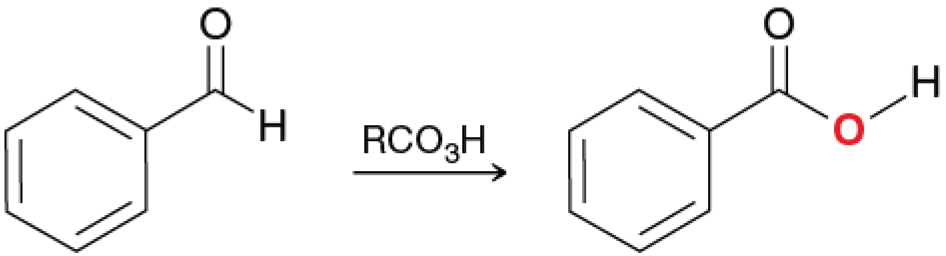
When an **unsymmetrical ketone** is treated with a peroxy acid, formation of the ester is regioselective; for example:



The isopropyl group migrates more rapidly than the methyl group during the rearrangement step of the mechanism

The migration rates of different groups, or **migratory aptitude**, can be summarized as follows:

H > 3° > 2°, Ph > 1° > methyl



19.39 Predict the major product of each reaction below: