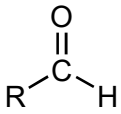
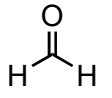
California State Polytechnic University, Pomona
Organic Chemistry II, CHM 3150, Dr. Laurie S. Starkey
Chapter 19 (Klein): Aldehydes & Ketones

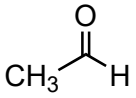
I) Nomenclature (19.1, 19.2)

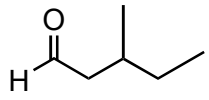
Try SkillBuilder 19.1

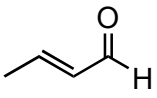
Aldehydes (RCHO) 

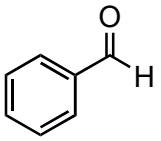
parent: alkanal (C=O is always C#1)

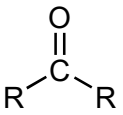

methanal (formaldehyde)


ethanal (acetaldehyde)

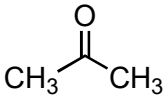

3-methylpentanal

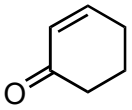

(*E*)-2-butenal

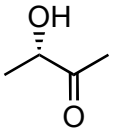

benzaldehyde (common)
IUPAC:

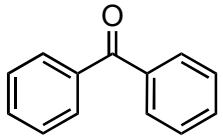
Ketones (RCOR) 

parent: #-alkanone
(C=O gets lowest possible #)


2-propanone (acetone)

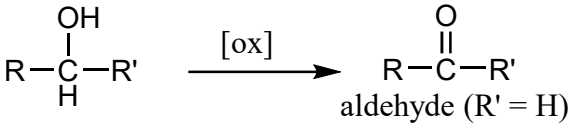

2-cyclohexen-1-one


(*S*)-3-hydroxy-2-butanone
(ketone is higher priority FG)

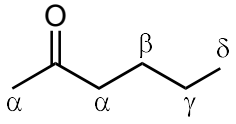

benzophenone (common)
IUPAC:

II) Preparation/Synthesis of Aldehydes & Ketones (19.3)

a) Oxidation of alcohols (12.10)

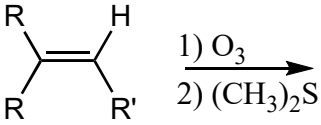


aldehyde (R' = H)
or ketone

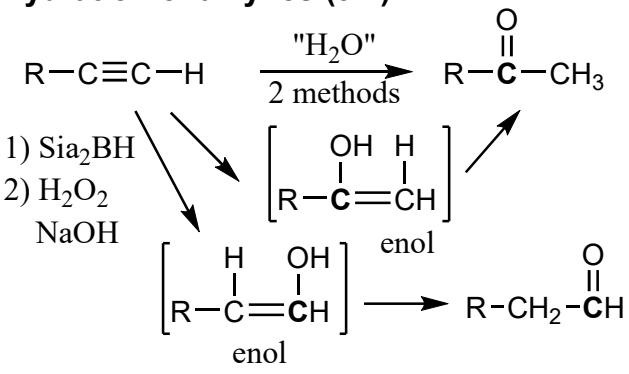


α, β, γ indicates relative position
(α means "next to" carbonyl)

b) Ozonolysis of alkenes (8.12)



c) Hydration of alkynes (9.7)



III) Reactions with Nucleophiles (Nu:) (19.4)
- A) Hydride (12.4, 19.9)
- B) Carbon Nu: (19.10)
  - 1) NaCN and NaC≡CR
  - 2) Organometallic reagents (RMgBr, RLi)
  - 3) Wittig reaction (& HWE)
- C) Oxygen Nu: (19.5) & hydrolysis (19.7)
- D) Nitrogen Nu: (19.6)

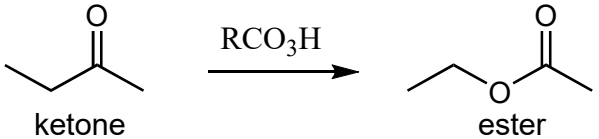
IV) Oxidation and Reductions (19.8, 19.9)

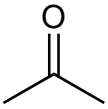
V) Applications of Acetals
- A) carbohydrates (24.5)
- B) protective groups (19.5, 12.7)

VI) Synthesis strategies (19.12)

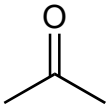
Read on your own: 19.13 (IR/NMR Spectroscopy)

Skip section 19.11 (Baeyer-Villiger Oxidation):



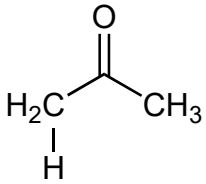


resonance



inductive effects

Reactivity

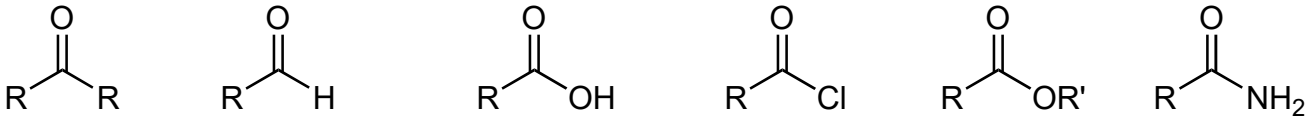


** C=O is very strong and stable functional group

BDE (kcal/mol) C-O 79 C=O <160?

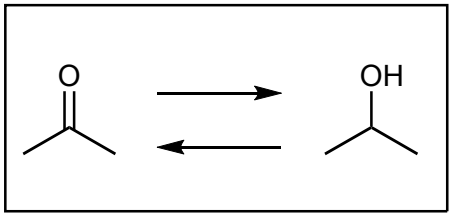
** formation of C=O can be a driving force for a reaction

Carbonyl-containing functional groups:



III) Reactions with Nucleophiles (Nu:) (19.4)

A) Hydride (12.4)



$LiAlH_4$ - lithium aluminum hydride (LAH)
$NaBH_4$ - sodium borohydride
} both are sources of hydride

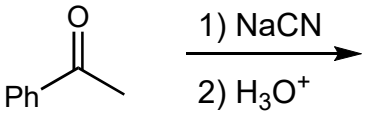
this is described as a(n) reduction / oxidation reaction

B) Carbon Nu: (makes C–C bonds!)

1) Carbanions: $R^{\ominus}Na^{\oplus}$

Acetylide anion

Cyanide anion



a "cyanohydrin"

-- reaction is reversible (NC^- ok LG)

-- RCN (nitrile) $\xrightarrow{H_3O^+}$ RCO_2H (Ch. 20)

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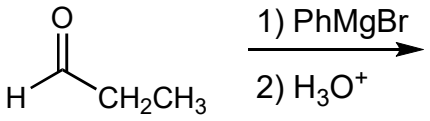
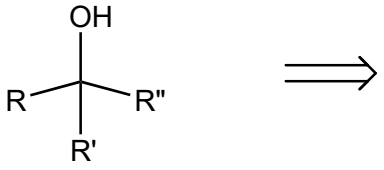
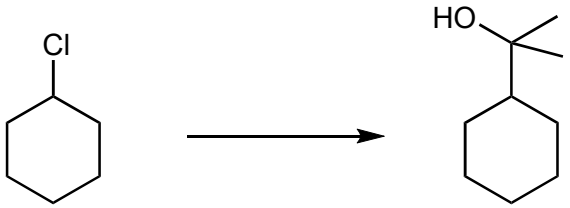
2) Organometallic reagents (RMgX, RLi) (12.6)



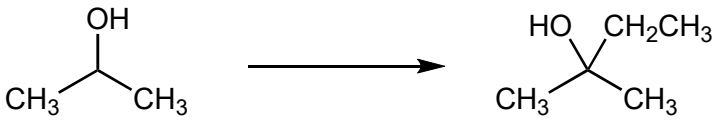
Retrosynthesis of alcohols **Ketone + Grignard ⟶ Alcohol**



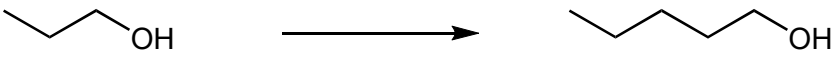
Example: Transform



Example: Transform



Example: Transform *(4th example: see p 19-9)*



SkillBuilders 12.5 & 13.7

III) Reactions with Nucleophiles (Nu:)

B) Carbon Nu: (19.10)

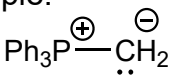
3) Wittig Reaction

(pronounced "Vittig")

Use of Wittig reagent:
reacts with aldehydes & ketones

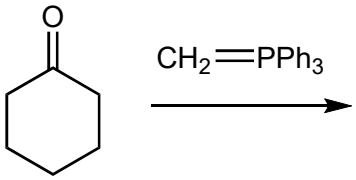
Wittig Reagent -
a resonance-stabilized carbanion (Nu:)

Example:

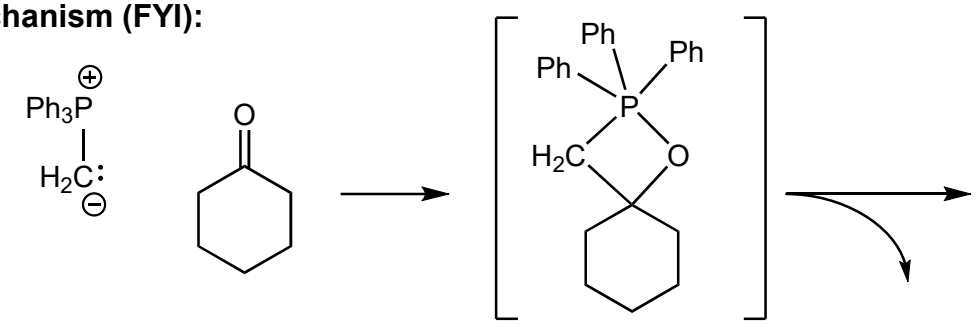


a phosphonium ylide (+/- charges)

Example:



Mechanism (FYI):



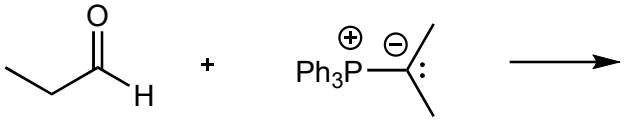
oxaphosphetane intermediate
(falls apart)

Preparation of Wittig reagent: two steps from an alkyl halide (RX)

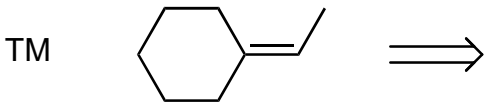
Nu: E^+

BuLi = $CH_3CH_2CH_2CH_2Li$
Butyllithium is a strong base

Predict the major product:



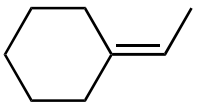
Wittig Retrosynthesis

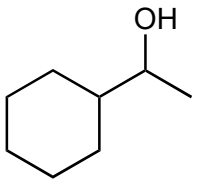
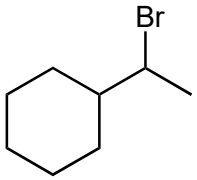
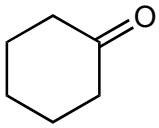
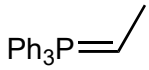


Synthesis:

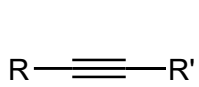
Try SkillBuilder 19.6

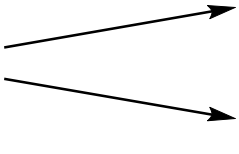
Summary: Synthesis of Alkenes

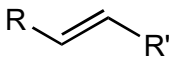
Target Molecule: 

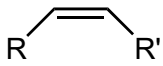
Starting Material	Reagents	Mechanism
alcohol (ROH) 	conc. H_2SO_4, heat (dehydration)	**E1** -- Carbocation can rearrange -- Gives most stable alkene (Zaistev)
alkyl halide (RX) 	NaOH, heat (*t*-BuOK gives Hofmann regio.)	**E2** -- Anti elimination -- Gives most stable alkene (Zaistev) (bulky base = less hindered H = less subt'd alkene, Hofmann)
ketone or aldehyde 	Ph_3P= 	**Wittig** -- Alkene replaces C=O -- Great regiocontrol -- Ideal for synthesis

Also:


alkyne




trans alkene

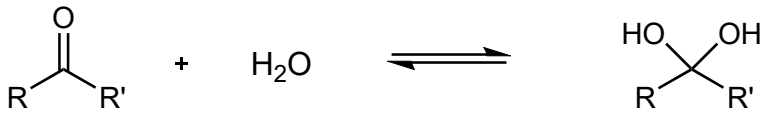

cis alkene

Mechanism: N/A
(reduction rxn)

III) Reactions with Nucleophiles (Nu:)

C) Oxygen Nu: (19.5)

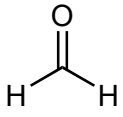
1) addition of water → hydrate


a ket/ald

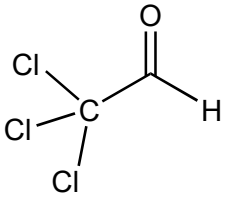
a hydrate

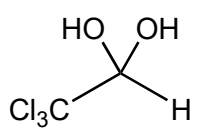
exceptions:

a) Formaldehyde is 99% hydrate in aqueous solution



b) Hydrate is favored if there is a δ^+ center near carbonyl


chloral



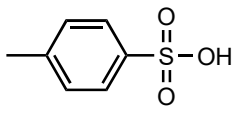
chloral hydrate
- more stable (less δ+)
- can be isolated
- “Mickey Finn” knockout drops

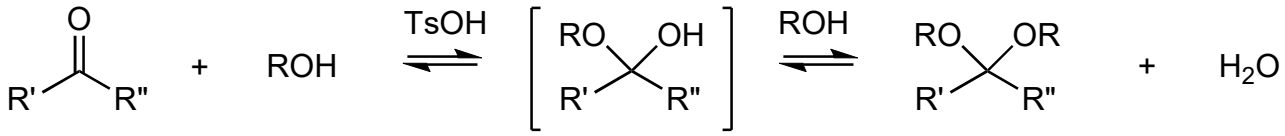
III) Reactions with Nucleophiles (Nu:)

C) Oxygen Nu: (19.5)

2) addition of ROH → acetal

TsOH = tosic acid (catalyst)
* like H_2SO_4
* soluble in organic solvents

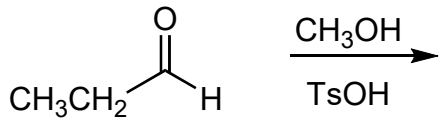




ald/ketone alcohol acetal

H_3O^+ causes reverse reaction (19.7)

Predict:

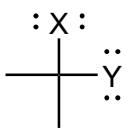


Mechanism: - acid catalyzed so first step:
- only neutral or negative / positive charges

Try SkillBuilder 19.2

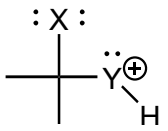
What is a CTI? **C**harged **T**etrahedral **I**ntermediate

Tetrahedral Intermediate
- sp^3 carbon
- at least two groups have lone pair(s)

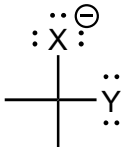


***Charged* Tetrahedral Intermediate**
- sp^3 carbon, two groups have lone pair(s)
- one group has a charge (+ or –)
- can collapse! (push-pull)

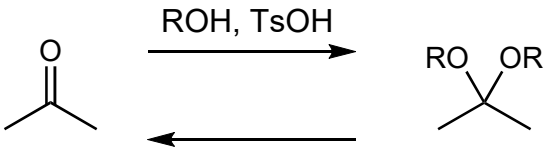
acid-catalyzed



base-catalyzed

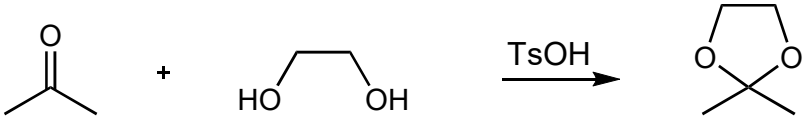


Acetal Summary



formation of acetal adds ___ equivalents of alcohol

Cyclic Acetals

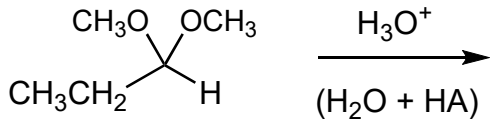


what makes this an acetal?

use a *diol* (both equiv. of ROH in same molecule) to make a cyclic acetal

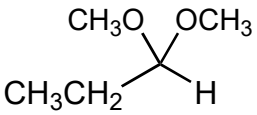
---

Hydrolysis of an Acetal: Regenerates Carbonyl (19.7)



acetal hydrolysis regenerates C=O
is this an oxidation reaction?

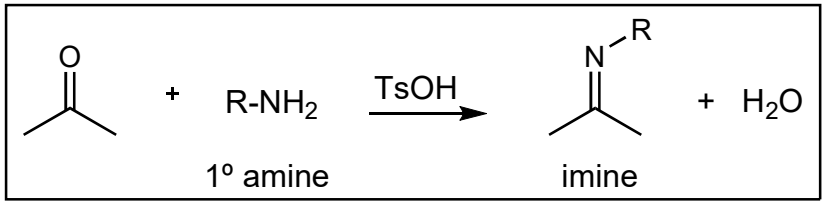
Mechanism: exact reverse of acetal formation (theory of microscopic reversibility)



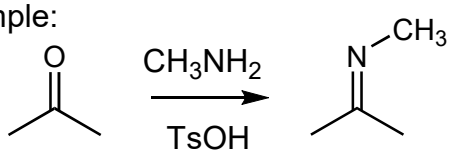
III) Reactions with Nucleophiles (Nu:)

D) Nitrogen Nu: (19.6)

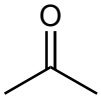
1) Reaction with NH_3 or RNH_2
(ammonia or a primary/1º amine)



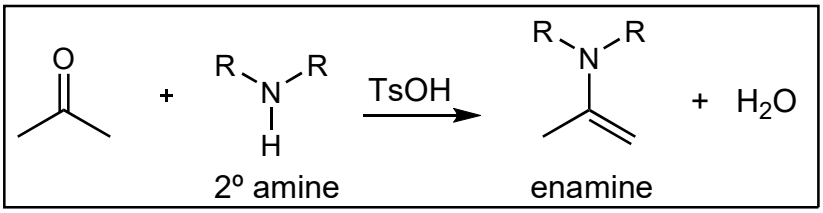
Example:



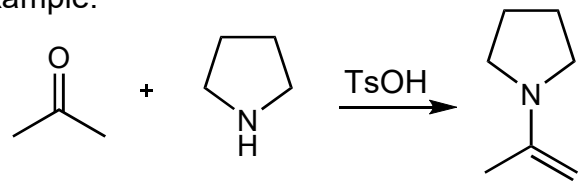
Mechanism* (***SkillBuilder 19.3***) **varies from textbook - either mechanism is okay!*



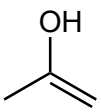
2) Reaction with R_2NH
(a secondary/2º amine)



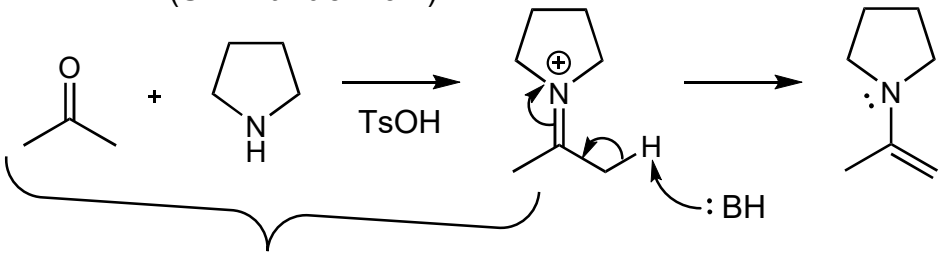
Example:



Note similarity of enAMINE to enOL structure



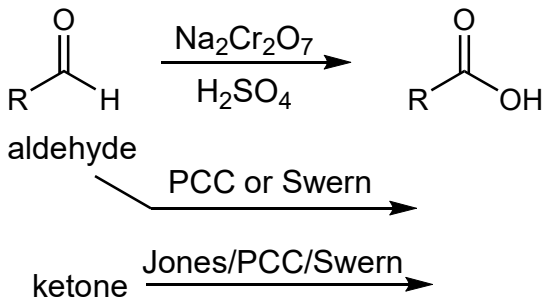
Mechanism (***SkillBuilder 19.4***)



formation of iminium ion, as above.... ...followed by deprotonation

Like acetals, imines and enamines undergo hydrolysis with H_3O^+ (19.7). ***Try SkillBuilder 19.5***

Aldehydes can be oxidized to carboxylic acids



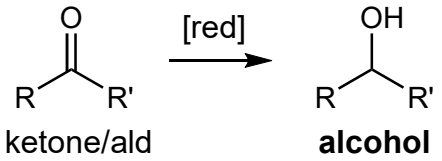
Other RCHO Oxidizing Agents:

Tollens' silver mirror test ($Ag^+ \rightarrow Ag°$)

Carbohydrates with an aldehyde group are referred to as "reducing sugars" because they can be oxidized

- Benedict's Test (red/brown precipitate)
- Fehling's Solution ($Cu^{2+} \rightarrow Cu^+$)

Reduction of aldehydes and ketones (19.8, 19.9)



1) $LiAlH_4$; 2) H_3O^+

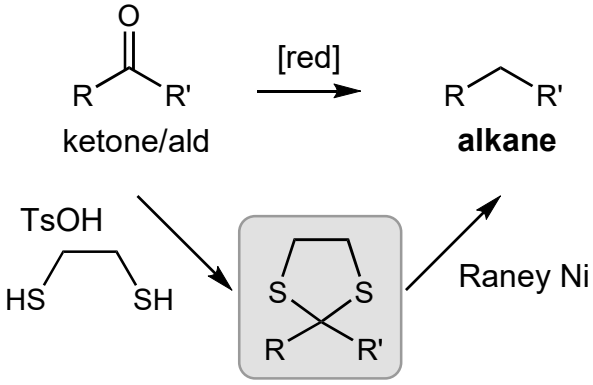
or

$NaBH_4$, MeOH

or

Raney nickel (Ni-H_2)

- catalytic hydrogenation of C=O
- reduces alkenes/alkynes also



Clemmenson Reduction

$Zn(Hg)$, HCl, H_2O

or

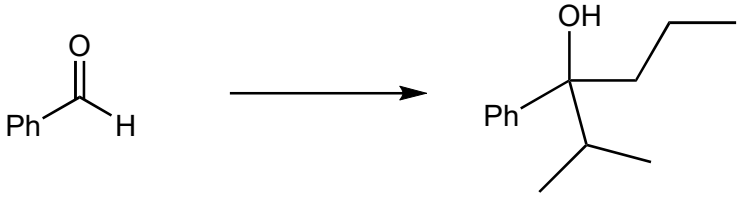
Wolff-Kishner Reduction

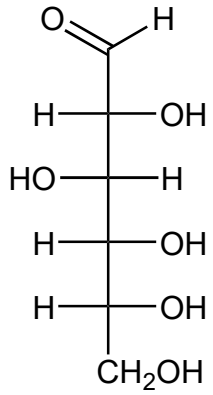
1) NH_2NH_2; 2) KOH, heat

or

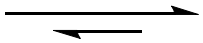
Raney Ni (Ni-H_2) reduction of thioacetal (19.8)

Example: Transform

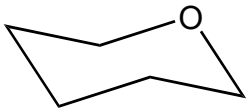




D-glucose
(an aldose)

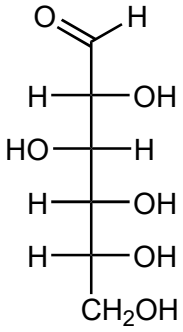


predominantly in cyclic form in solution



D-glucopyranose

Formation of a 5-membered ring (furanose form)

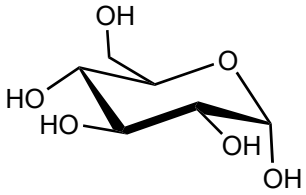


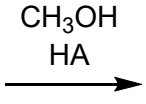
D-glucose

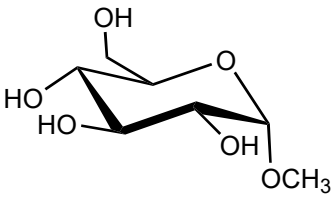
D-glucofuranose

6- to 5-membered ring mech? See page 19-14

Reactions of glucose: acetal formation

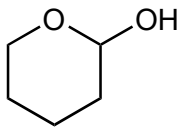


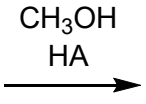


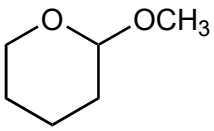


methyl-α-D-glucoside

Mechanism for formation of glycosidic bond:



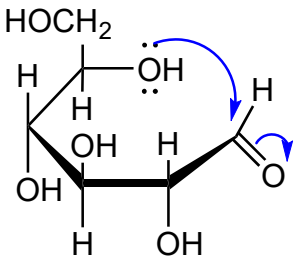




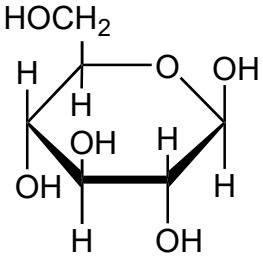
hemiacetal

acetal

alternate POV:

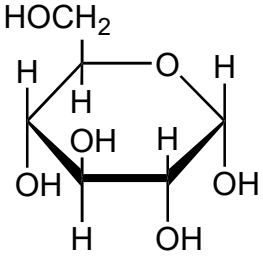


D-glucose



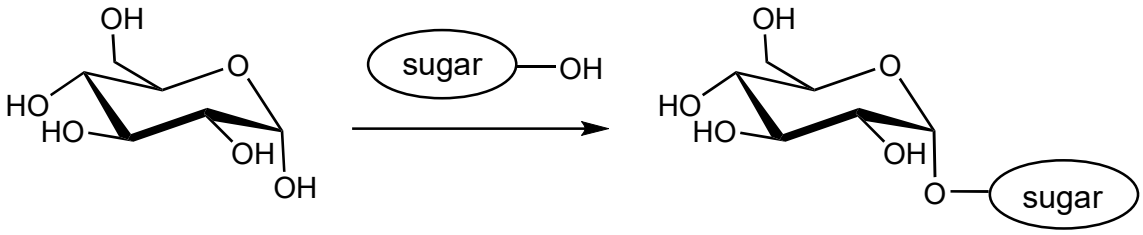
β-D-glucopyranose
(Haworth projection)

+

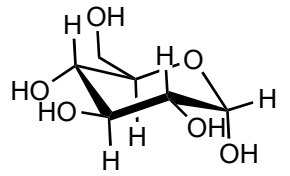


α-D-glucopyranose

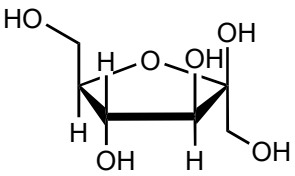
Link two sugars to make a disaccharide, and continue links to make polysaccharides.



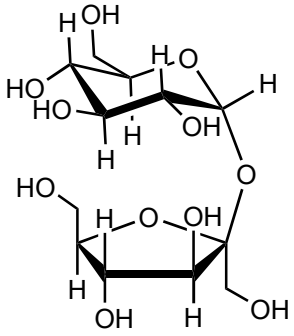
Formation of Disaccharides (24.7)



D-glucose

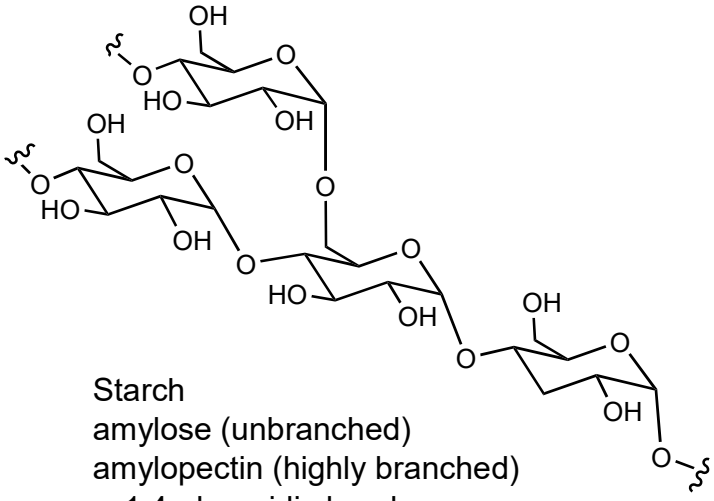


D-fructose



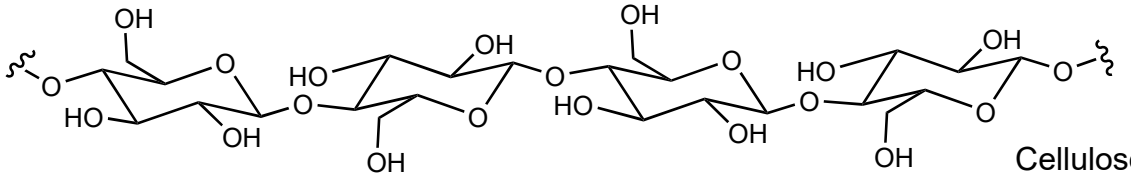
sucrose
(a disaccharide)

Polysaccharides (24.8)



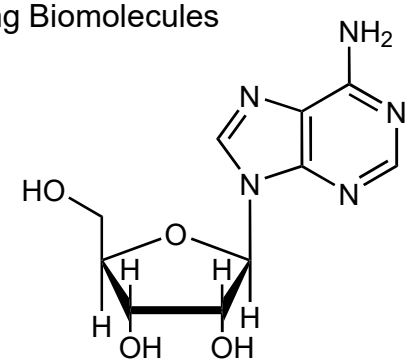
Starch
amylose (unbranched)
amylopectin (highly branched)
α-1,4-glycosidic bonds
water-soluble, digestible by animals

Polysaccharides (24.8)

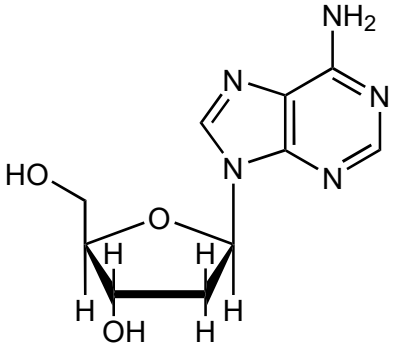


Cellulose
β-1,4-glycosidic bonds
rigid, insoluble, not digestible

Other Sugar-Containing Biomolecules (24.10)



ribonucleoside
(RNA)

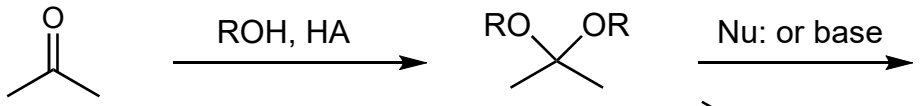


deoxyribonucleoside
(DNA)

V) Application of Acetals

B) Protective Groups (19.5, 12.7)

** Protective group strategy: hide carbonyl, do reaction elsewhere on molecule, regenerate C=O

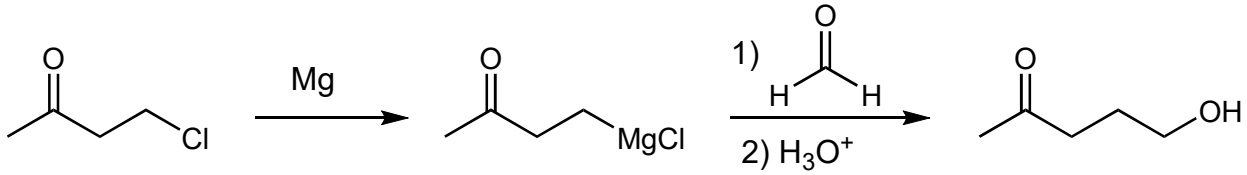


* C=O is an Electrophile
  (due to C=O resonance)
* has acidic α protons

* not an E^+
  (no LG or C=O)
* no acidic α protons

hydrolysis is only acetal reaction
(acetal is unstable to acidic conditions)

What happens when the following synthesis is attempted?

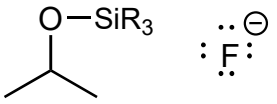


** Can also protect alcohols (hide the acidic OH proton) (12.7)

silyl ether

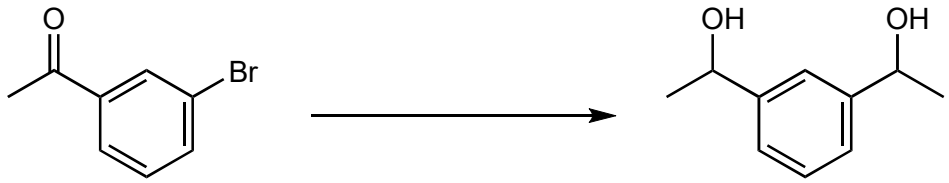
$Bu_4N^+ F^-$
(TBAF)

Fluoride removes silyl ether protective groups

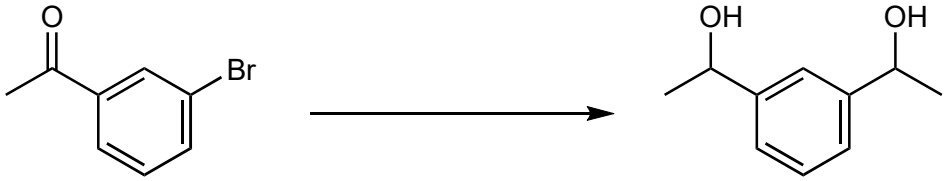


TMS = trimethylsilyl
TES = triethylsilyl
TBS = t-butyldimethylsilyl
TiPS = t-butylisopropylsilyl

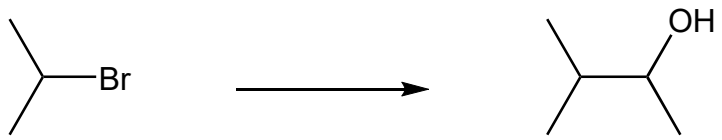
Example: Transform

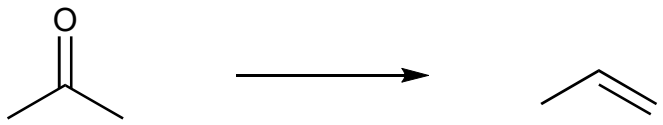


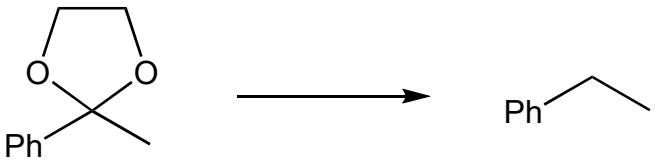
Example: Transform (Alternate Route)



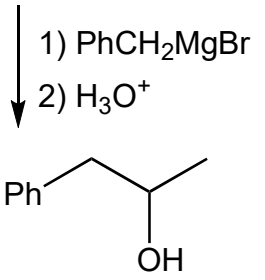
Transform examples (provide reagents necessary to convert starting material to desired product







Provide missing starting material:



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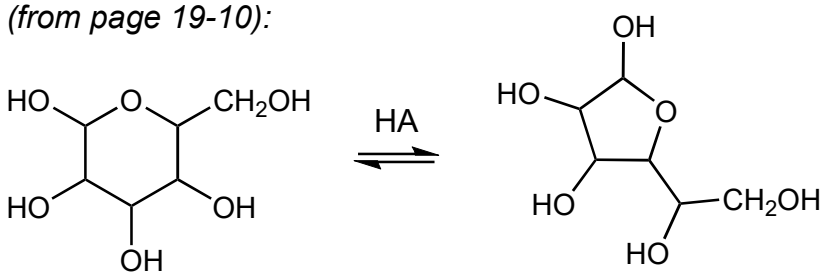
propose a mechanism *(from page 19-10):*



Organic Chemistry II CHM 3150, Dr. Laurie S. Starkey, Cal Poly Pomona

Chapter 19 Summary (Klein): Aldehydes & Ketones

I. Introduction to the reactivity of the carbonyl (19.1)
   a) C=O carbon is electrophilic (δ^+) and reacts with nucleophiles
   b) C=O oxygen is δ^- and can be protonated
   c) α-hydrogens are acidic (covered in Chapter 21)

II. Nomenclature (19.1, 19.2): alkan**al** or #-alkan**one** (C=O is highest priority F.G.) ***SkillBuilder 19.1***

III. Preparation of ketones & aldehydes: a review (19.3)
   a) oxidation of alcohols (12.10)
   b) ozonolysis of alkenes (8.12)
   c) hydration of alkynes (9.7)

IV. Reactions with nucleophiles; all add to δ^+ carbonyl carbon (19.4)
   a) Hydride Nu: (12.4, 19.9)
      i) $LiAlH_4$ or $NaBH_4$ as sources of hydride, "$H:^-$"
      ii) a reduction reaction that gives an alcohol product
   b) Carbon Nu: makes C–C bonds!! (19.10)
      i) NaC≡N and NaC≡CH carbanions give alcohol products
      ii) organometallic reagents (12.6)
         A) Grignard (RMgX) and organolithium (RLi) reagents
         B) use in synthesis, consider retrosynthesis of alcohols ***SkillBuilders 12.5 & 13.7***
      iii) Wittig reaction
         A) Wittig reagent prepared from alkyl halide (Ph_3P, then base)
         B) Wittig reagent reacts with carbonyl to give C=C double bond
      i) use in synthesis, consider retrosynthesis of alkenes ***SkillBuilder 19.6***
   c) Oxygen Nu: (19.5)
      i) addition of H_2O gives hydrate (only formaldehyde, compounds like chloral)
      ii) addition of ROH gives acetal (TsOH is acid catalyst) ***SkillBuilder 19.2***
         A) mechanism for acetal formation (via tetrahedral intermediates)
         B) mechanism for acetal hydrolysis (reverse of formation) (19.7) ***SkillBuilder 19.5***
   d) Nitrogen Nu: (19.6)
      i) addition of 1° amines (RNH_2) give imines (mechanism) ***SkillBuilder 19.3***
      ii) addition of 2° amines (R_2NH) give enamines (mechanism) ***SkillBuilder 19.4***
      iii) enamines & imines can also be hydrolyzed (H_3O^+) to regenerate C=O (19.7)

V. Oxidations of aldehydes to carboxylic acids
   a) RCHO → RCO_2H (ox. agent: metals, $Na_2Cr_2O_7$ or $KMnO_4$) (ketones N/R)

VI. Reductions of aldehydes and ketones (19.8, 19.9)
   a) to alcohol with LAH or Raney Nickel (Ni-H_2)
   b) to alkane
      i) Clemmenson (Zn-Hg, HCl, H_2O)
      ii) Wolff-Kishner (N_2H_4 to make imine, followed by NaOH/heat)
      iii) via thioacetal ($HSCH_2CH_2SH$, followed by Raney Ni) (19.9)

VII. Applications of acetals
   a) Carbohydrates as examples of cyclic hemiacetals (24.5)
   b) Protective Groups in organic synthesis to hide carbonyls and alcohols (12.7, 19.5)
      i) Synthesis strategies (19.12) ***SkillBuilder 19.7***

SKIP section 19.11 (Baeyer-Villiger Oxidation)
READ on your own section 19.13 (IR/NMR Spectroscopy)