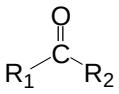
TOPIC 3. ALDEHYDES AND KETONES (Chapters 12 and 16)

OBJECTIVES

1. Describe the synthesis aldehydes and ketones.
2. Describe the carbonyl group and oxidation-reductions reactions associated with alcohols and carbonyl groups.
3. Describe some the addition reactions of aldehydes and ketones in which nucleophiles add to the electrophilic carbonyl.
4. Describe the mechanisms by which carbonyl groups are transformed to alcohols in C-C bond forming reactions.
5. Describe how C-C bonds can be formed by other reactions of organometallic compounds (not involving the formation of alcohols).
6. Use this knowledge to predict the products of reactions and synthesize complex compounds using these procedures.

ALDEHYDES AND KETONES

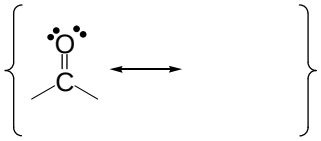
S:12.1; 16.1-3
Prob:16.23



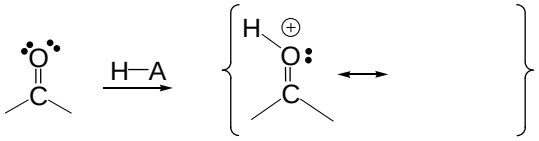
ketone
R_1 or R_2 = alkyl, aryl or alkenyl

aldehyde
R = H, alkyl, aryl or alkenyl

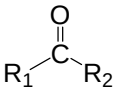
Carbonyls are electrophilic



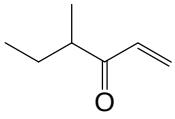
Carbonyls are weakly basic; protonation makes the carbonyl more electrophilic



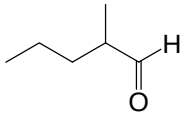
Nomenclature

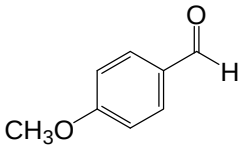


alkane ⇨ #-alkanone
or alkyl alkylketone



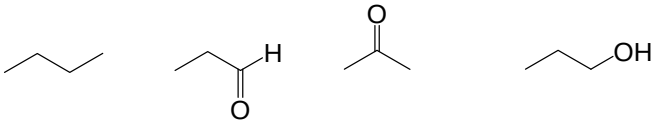
alkane ⇨ alkanal





Physical Properties

The carbonyl group has a permanent dipole moment and is therefore much more polar than a hydrocarbon, but less polar than an alcohol



Boiling point	0°	49°	56°	97°
MW	58	58	58	60
Sol. in water g/100 mL	nil	20	miscible	miscible

OXIDATIONS AND REDUCTIONS IN ORGANIC CHEMISTRY

S:12.2,4
Prob:12.14;16.27,29a,30a,b

Oxidation-Reduction Reactions in Organic Chemistry

Reduction - adding electrons, more hydrogens, less oxygen

Oxidation - removing electrons, less hydrogens, more oxygen

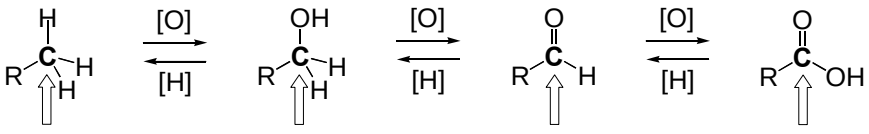
Calculating Oxidation State of Carbon Atoms in Organic Molecules

The oxidation state of a carbon balances the contributions from each of the bonds to its substituents:

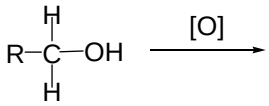
H = +1

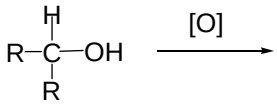
O and other electronegative atoms = -1

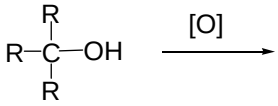
C = 0



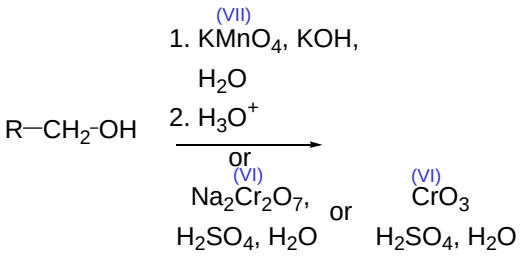
Oxidation of Alcohols (-1 → +1 → +3)

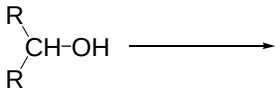


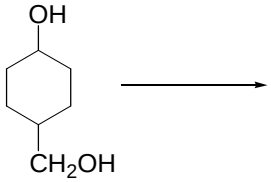




Strong Oxidants



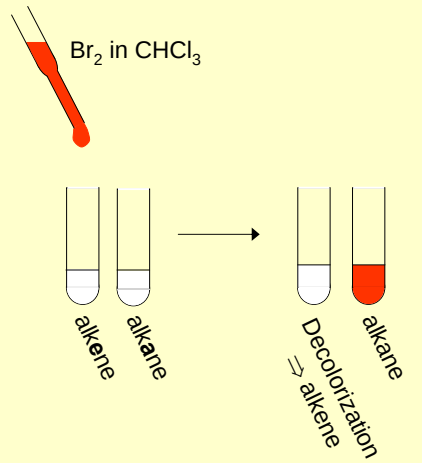




Chemical Tests for Functional Groups

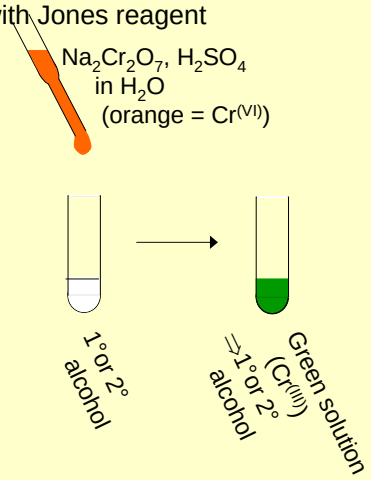
The molecular formula indicates one site of unsaturation. Is it a ring, or an alkene?

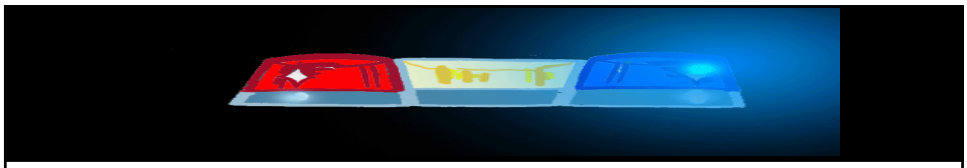
Alkenes decolorize bromine



Infrared spectroscopy indicates the presence of an alcohol (strong, broad absorption at 3500 cm^{-1}). But what type of alcohol is it?

1° and 2° alcohols give a positive test with Jones reagent

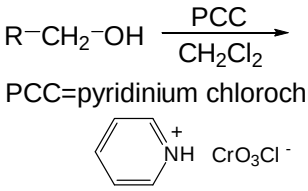




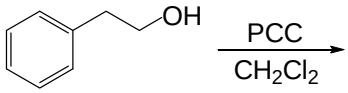
$$2Cr_2O_7^{2-} + 3C_2H_5OH + 16H^+$$

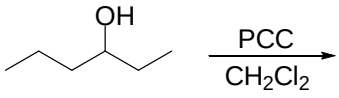
$$4Cr^{3+} + 3CH_3CO_2H + 11H_2O$$

Oxidation of 1° Alcohols with Mild Oxidants



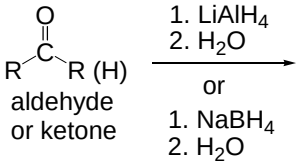
PCC=pyridinium chlorochromate



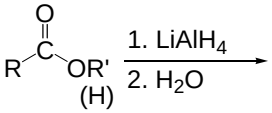


Reduction (+3 → +1 → -1)

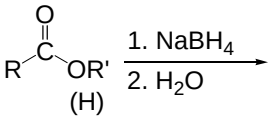
Reduction with $LiAlH_4$ or $NaBH_4$

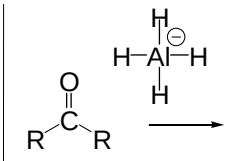


aldehyde
or ketone



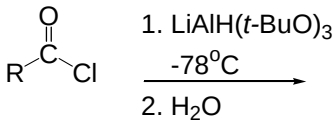
acid or ester



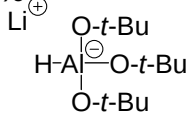


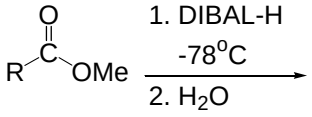
via

Reduction of Carboxylic Acid Derivatives with Mild Reducing Agents

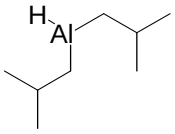


lithium tri(*tert*-butoxy)aluminum hydride $LiAlH(t\text{-}BuO)_3$





diisobutylaluminum hydride DIBAL-H

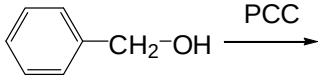


L

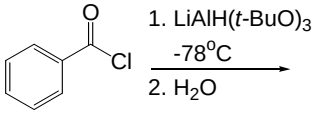
SYNTHESIS OF ALDEHYDES

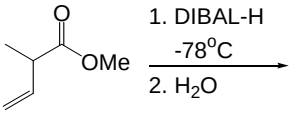
S:16.4

Oxidation of 1° Alcohols



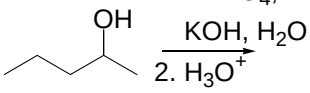
Reduction of Acid Derivatives



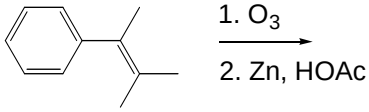


SYNTHESIS OF KETONES

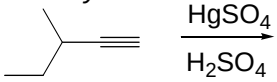
Oxidation of 2° Alcohols



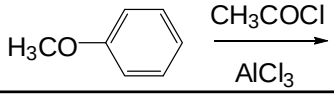
Review: *Ozonolysis of Alkenes*



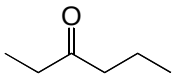
Hydration of Alkynes



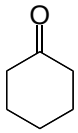
Friedel-Crafts acylation



Problem - Provide a synthesis of 3-hexanone from starting materials with three of fewer carbon atoms.



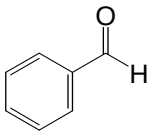
Problem - Provide a synthesis of cyclohexanone from cyclohexane



OXIDATION OF ALDEHYDES AND KETONES

S:16.11,12
Prob:16.24,28,31

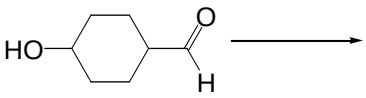
Oxidation of Aldehydes



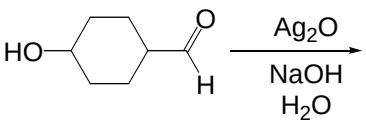
1. $KMnO_4$, KOH, H_2O
2. H_3O^+

or

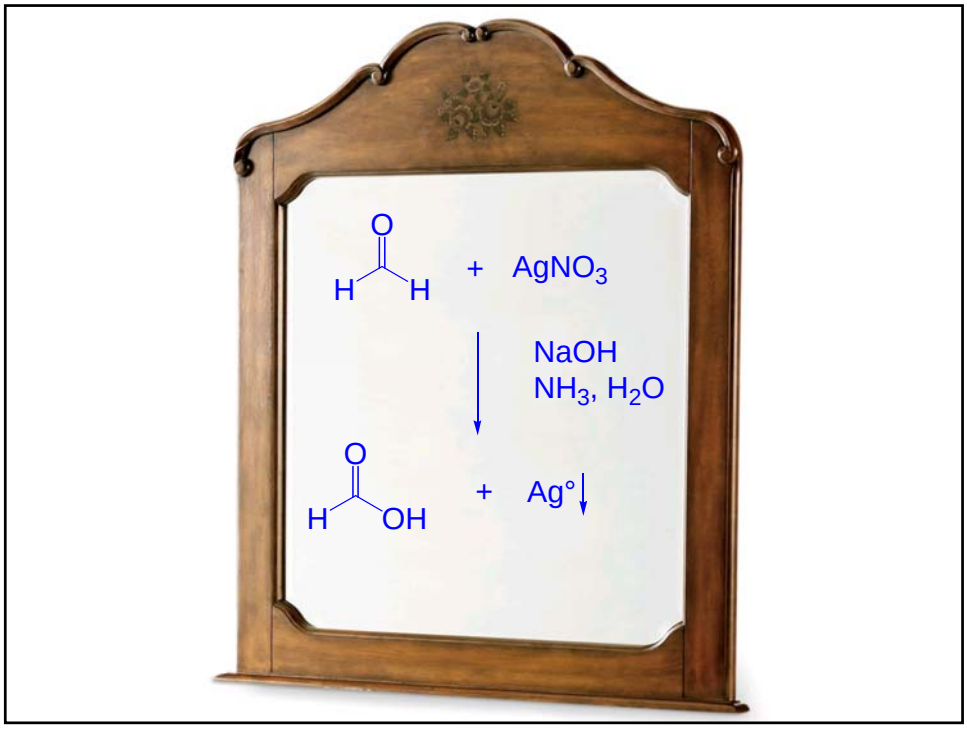
$Na_2Cr_2O_7$, H_2SO_4, H_2O or CrO_3, H_2SO_4, H_2O



Ag_2O is a selective oxidant for aldehydes, avoids use of strong acid or base



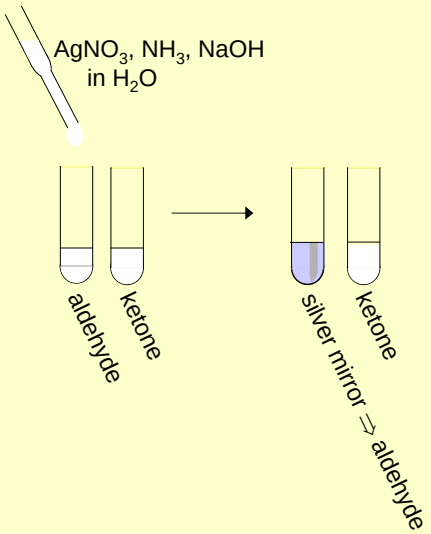
Ag_2O, NaOH, H_2O



CHEMICAL TESTS FOR FUNCTIONAL GROUPS

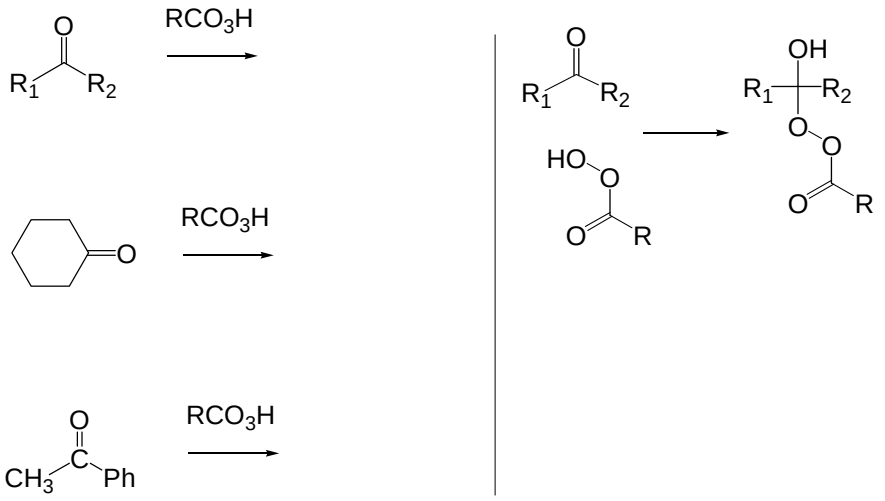
Infrared spectroscopy indicates the presence of an aldehyde or ketone (strong, sharp absorption at ca. 1720 cm^{-1}). Is the compound an aldehyde, or a ketone?

aldehydes give positive Tollen's test (silver mirror)



Oxidation of Ketones

Oxidation with peracids: The Baeyer-Villiger reaction

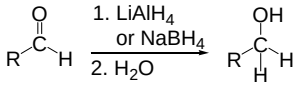


Migratory aptitude: Ph > 3° > 2° > 1° > Me

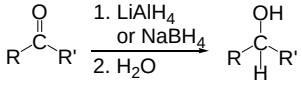
REDUCTION OF ALDEHYDES AND KETONES

S:12.3

Aldehydes



Ketones



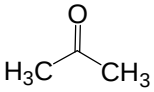
NUCLEOPHILIC ADDITION REACTIONS OF ALDEHYDES AND KETONES

S:16.6
S:12.1B

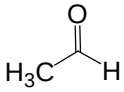
General reaction

: Nu—H ⇌

Examples



HO—H ⇌



$H_3CO—H$ ⇌

? *Prob:16.27,29a,30a,b* ?

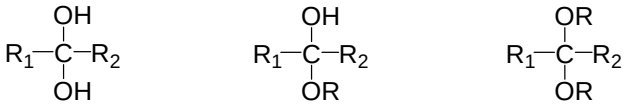
? *Prob: 12.4,14; 16.23* ?

?

OXYGEN NUCLEOPHILES: ADDITION OF WATER AND ALCOHOLS

S:16.7
Prob: 16.48

Structure

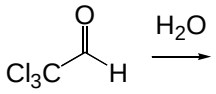


hydrate | hemiacetal | acetal

R_1 or R_2 = H or alkyl

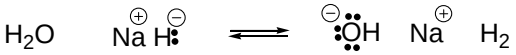
Hydrates

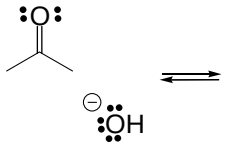
Example



Mechanism of base catalyzed reaction

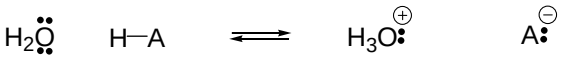
Base catalysis increases the *nucleophilicity* of the *nucleophile*

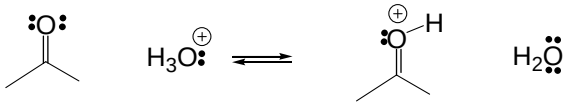


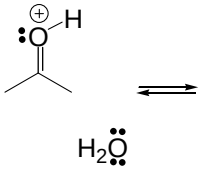


Mechanism of acid catalyzed reaction

Acid catalysis increases the *electrophilicity* of the *electrophile*

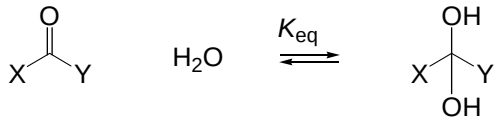






Relative Reactivity (Electrophilicity) of Aldehydes and Ketones

Equilibrium constants for Hydrate Formation

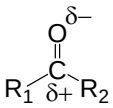


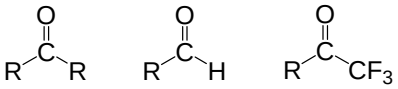
X	Y	K_{eq}	% hydrate at equilibrium
H	H	41	99.96
CH_3	H	1.8×10^{-2}	50
$C(CH_3)_3$	H	4.1×10^{-3}	19
CH_3	CH_3	2.5×10^{-5}	0.14
CF_3	CF_3	22,000	99.9996

Data: 1 M carbonyl compound dissolved in H_2O

Electronic factors

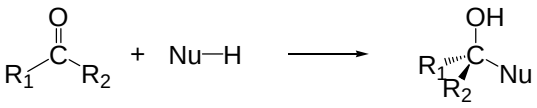
Inductive electron donating groups decrease electrophilicity of carbonyl (and visa versa)





Steric factors

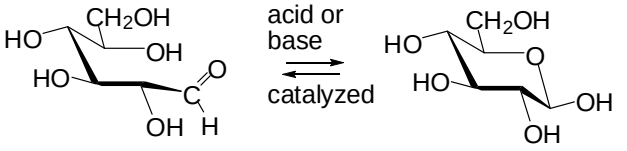
Bulky groups hinder attack of nucleophile and cause steric crowding in product



sp^2, ≈120° *sp*^{3}, ≈109.5°

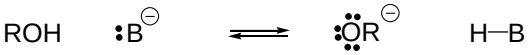
Hemiacetals

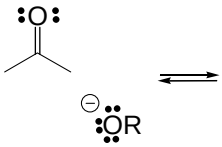
Example: Glucose



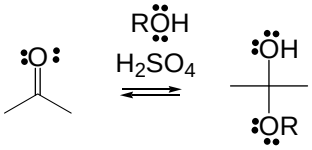
aldehyde form hemiacetal form

Formation: <u>Base</u>-catalyzed reaction





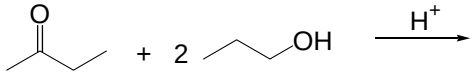
Formation: <u>Acid</u>-catalyzed reaction

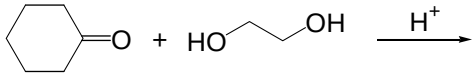


Problem: Draw the mechanism for the acid-catalyzed formation of an hemiacetal (this is analogous to the acid-catalyzed hydration)

Acetals

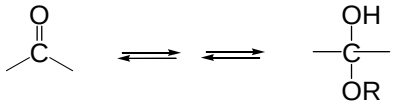
Examples





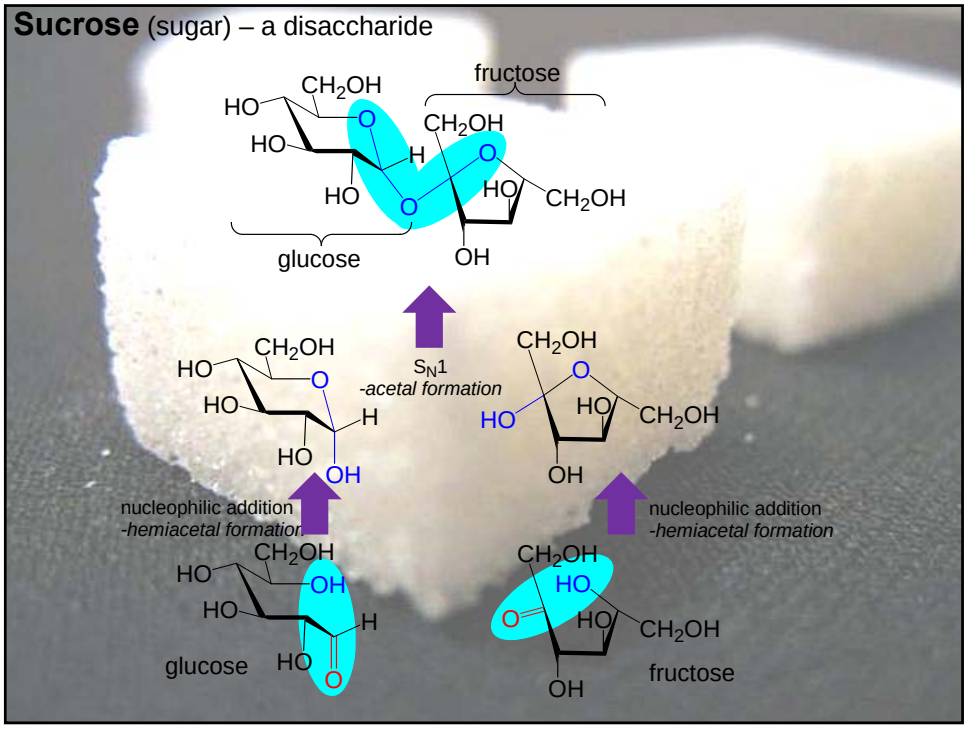
Only formed under acidic conditions

Mechanism for formation of acetals

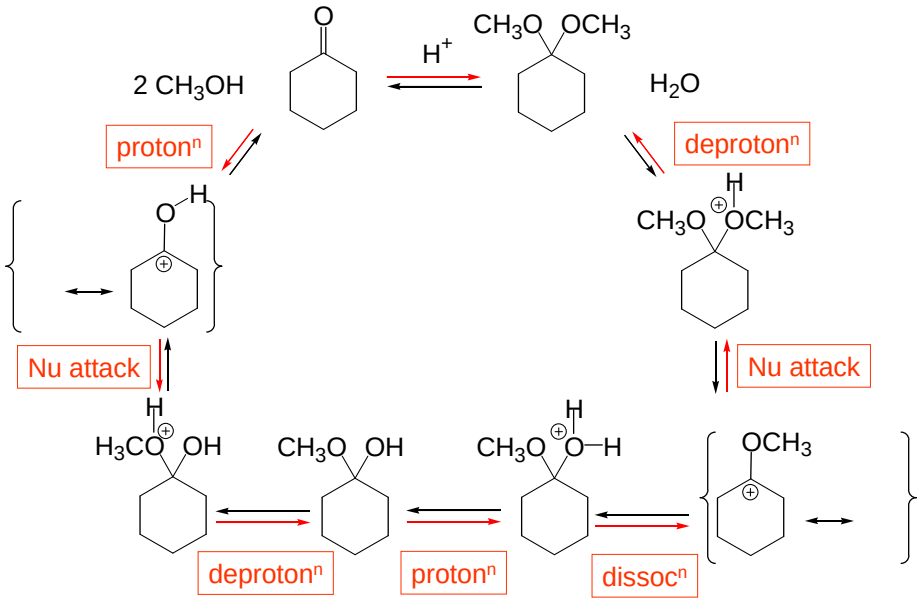


hemiacetal

All steps are reversible – must remove H_2O to drive reaction to completion.

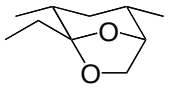


Hydrolysis of Acetals: Mechanism for the REVERSE reaction



Principle of microscopic reversibility: Forward and back reactions take place via the same intermediates and transition states.

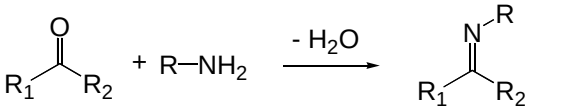
Problem [Solomons 16.46] - Multistriatin is an aggregating pheromone of the European elm bark beetle, the vector of Dutch elm disease. Multistriatin is an acetal. What is the product of hydrolysis of multistriatin formed upon treatment with aqueous acid?



NITROGEN NUCLEOPHILES: ADDITION-ELIMINATION

S:16.8
Prob:16.24

Addition-elimination of 1º Amines

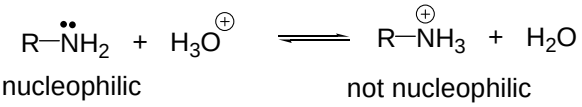


ketone or aldehyde

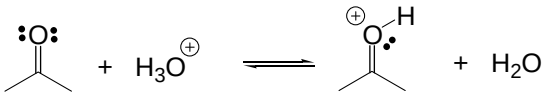
imine - *E* and *Z* isomers possible

Mechanism

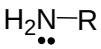
Acid or base catalyzed, but requires careful control of pH

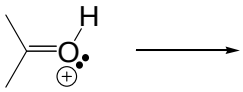


nucleophilic not nucleophilic

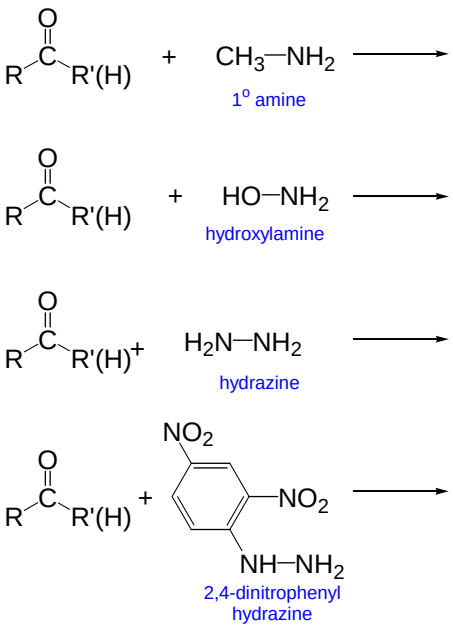


less electrophilic more electrophilic



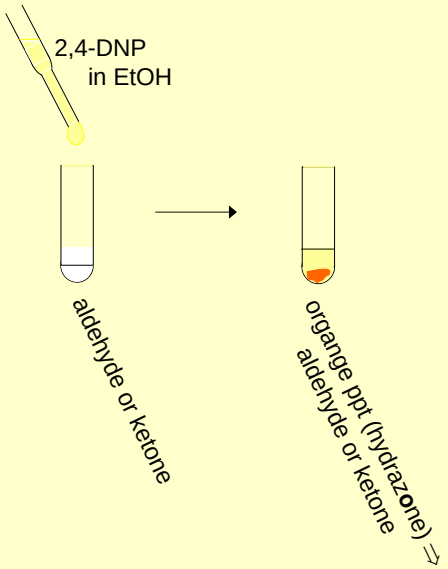


Examples



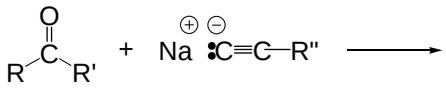
CHEMICAL TESTS FOR FUNCTIONAL GROUPS

Aldehydes and ketones give positive 2,4-DNP test

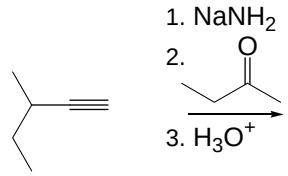


CARBON NUCLEOPHILES: TWO CARBON NUCLEOPHILES WE HAVE SEEN BEFORE

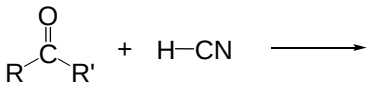
Sodium Acetylides



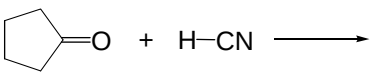
Example



Addition of HCN



Example



ORGANOMETALLIC COMPOUNDS AS NUCLEOPHILES

S:12.5

Organometallic Compounds

Examples:

RMgHal	RLi	RC≡CNa	RZnHal	R_2CuLi
2.5 1.2	2.5 1.0	2.5 1.0	2.5 1.7	2.5 1.8
C-Mg	C-Li	C-Na	C-Zn	C-Cu

Contrast reactivity:

C-O

C-M

C-Br

ORGANOLITHIUM AND ORGANOMAGNESIUM COMPOUNDS

S:12.6

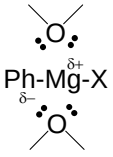
Preparation: Halogen-Metal Exchange

R-X + 2 Li ⟶

R-X + Mg ⟶

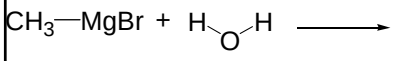
I > Br > Cl >> F

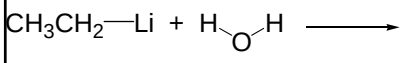
solvent is usually Et_2O or  (THF)

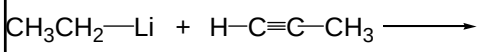


Grignard and Lithium Reagents as Bases

S:12.7
Prob:12.12

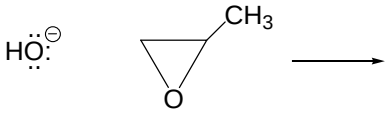




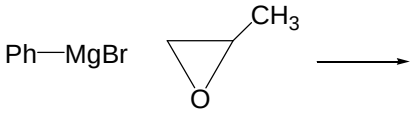


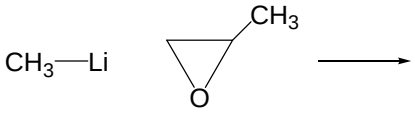
Grignard And Lithium Reagents React with Epoxides

Nucleophilic Ring opening of Epoxides (example from Organic-I)

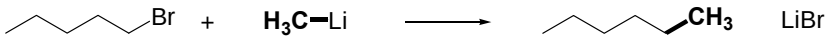


Organometallics as Nucleophiles



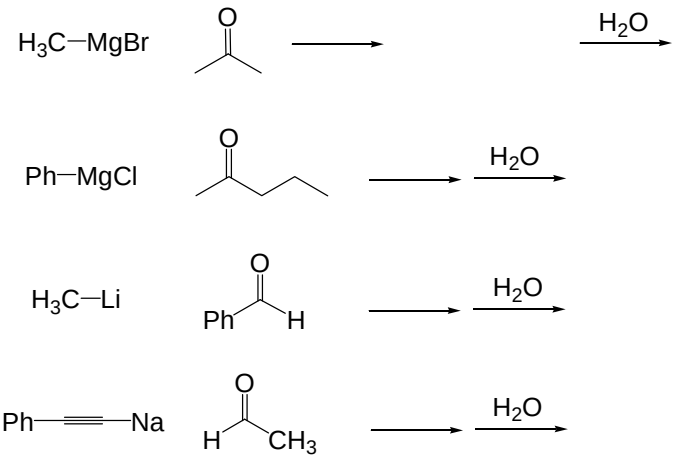


RMgX and RLi do not undergo S_N reactions with alkyl halides

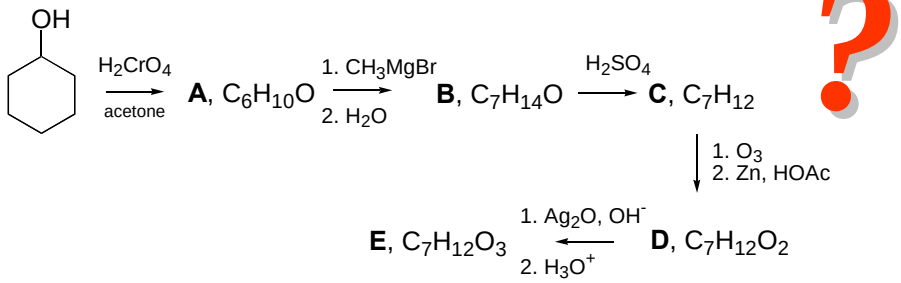


Lithium, Magnesium and Sodium Reagents Add to Carbonyl Groups

S:12.8C-D
Prob:12.12,19,20,21,24

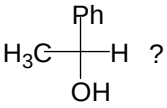


Problem - Identify the structures of compounds **A**-**E** in the following scheme.

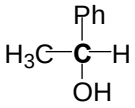


Designing Organic Synthesis: Retroanalysis

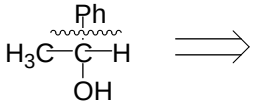
S:12.8A

How would you make  ?

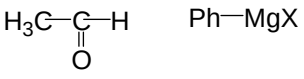
1. Locate the hydroxyl-bearing carbon. This carbon must have been part of the C=O group in the starting material



2. "Disconnect" one of the substituents attached to the carbon bearing the hydroxyl group

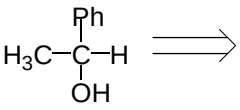


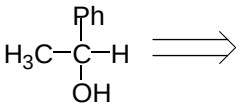
3. These steps reveal the carbonyl-containing substrate and the Grignard (nucleophilic) component



4. Check that you can indeed perform the forward reaction!

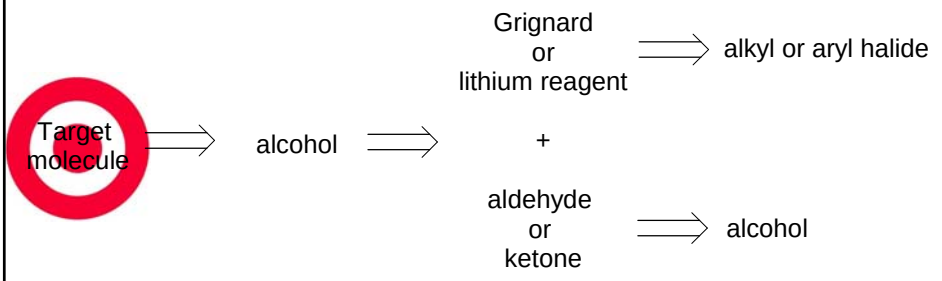
Other ways to disconnect bonds in a Grignard alcohol synthesis





Preparation of Alcohols

1º, 2º and 3º alcohols can all be made by addition of an appropriate carbon nucleophile to an appropriate carbonyl compound (aldehyde or ketone). Accordingly, alcohols are useful synthetic intermediates. When performing a retroanalysis, consider the possibility of making the product from an alcohol, and how this alcohol can be made from smaller molecules using this approach.



Preparation of 1° Alcohols

formaldehyde

1. R-MgBr
2. H_2O

ethylene oxide

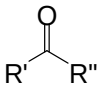
1. R-MgBr
2. H_2O

Preparation of 2° Alcohols

aldehyde

1. R-MgBr
2. H_2O

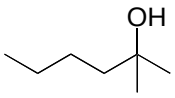
Preparation of 3° Alcohols



ketone

1. R-MgBr
2. H_2O

Problem - Propose a synthesis of 2-methyl-2-hexanol from starting materials with four or fewer carbon atoms

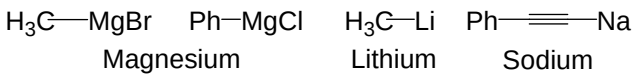


? *Prob:12.12,19,20,21,24* ?

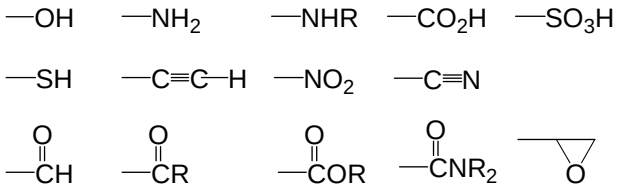
Restrictions on the use of Grignard, Lithium and Sodium Reagents

S:12.8B

Lithium, magnesium and sodium reagents are very reactive as nucleophiles and bases, limiting other functional groups in these reagents



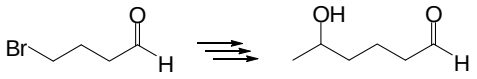
Will react with the following functional groups. This means that we can not prepare them from any starting material containing these funtional groups.



Protecting Groups in Synthesis

S:12.10

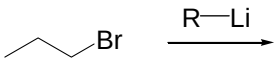
How would you achieve the following transformation?



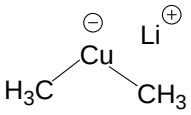
LITHIUM DIAKLYCUPRATES IN COUPLING REACTIONS

S:12.9
Prob:12.17

Problem: Grignard and lithium reagents are strongly basic and promote elimination reactions with alkyl halides, e.g.



Solution: Use dialkylcuprates – they are much less basic, but still nucleophilic



Preparation of cuprates

R-X + 2Li ⟶ RLi + LiX

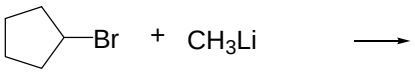
2RLi + CuI ⟶ LiI + R_2CuLi - "Lithium dialkyl cuprate"

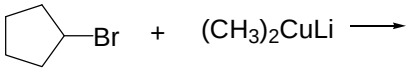
H_3C—Li Cu—I ⟶

R'-X + R_2CuLi ⟶

R'-X: R'=Me, 1°, 2°, vinylic, phenyl
R_2CuCl: R=Me, 1°, 2°, 3°,

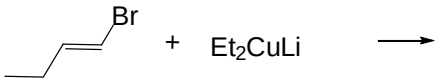
Comparison of reactions of alkyl halides with dialkylcuprates and alkyllithium reagents



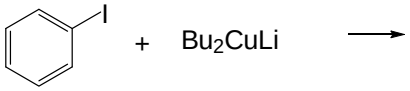


Reactions of cuprates with *sp*^{2} C-halides

Vinyl halides



Aryl halides



? *Prob: 16.32,12.17* ?

?

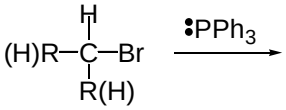
ADDITION OF YLIDES TO ALDEHYDES AND KETONES: THE WITTIG REACTION

S:16.10
Prob:16. 26, 39,50

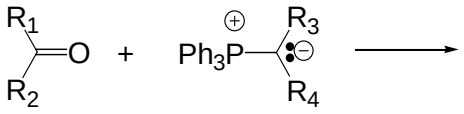
What is an ylide?

carbanion next to a positively charged heteroatom, most often phosphorous

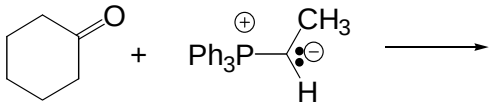
Preparation of phosphonium ylides



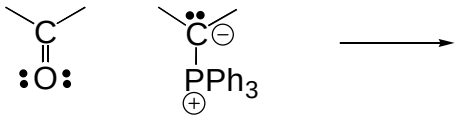
Wittig Reaction: General Reaction



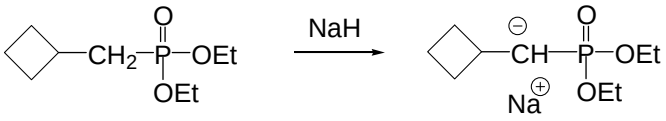
Example

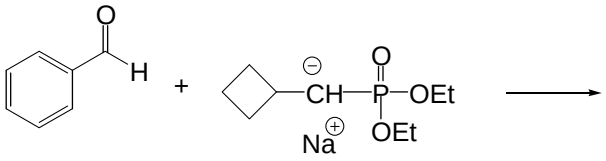


Mechanism of Wittig Reaction



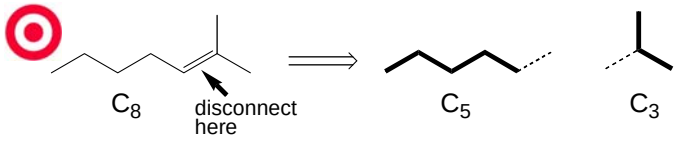
Alternate method - use of a phosphonate ester



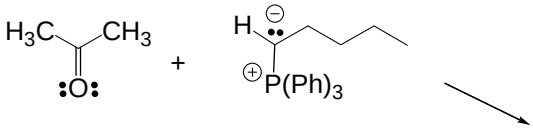


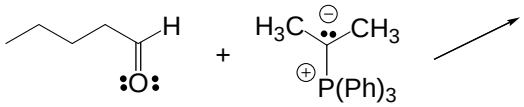
Planning a Wittig Synthesis of an Alkene

There are always two possible routes to make an alkene by Wittig chemistry. How could you make 2-methyl-2-heptene?

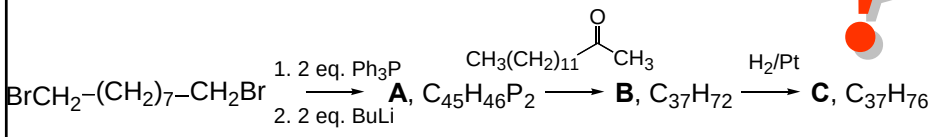


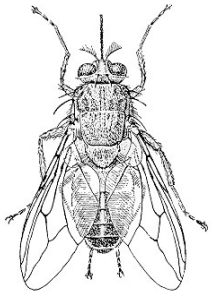
Either C_5 or C_3 can be the carbonyl or ylide





Problem [Solomons 16.39] - The sex attractant of the female tsetse fly can be prepared by the following route. Identify compounds **A**-**C**.





http://entomology.unl.edu/history_bug/gallery/tsetse_drawing.htm

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Other Reactions of Organometallic Reagents (covered later):

$RMgX + CO_2$

RMgX + ester

RMgX + RCN

RCu, R_2CuLi + RCOCl

SPECTROSCOPIC PROPERTIES OF ALDEHYDES AND KETONES

S:16.13
Prob:16.41-44

Compound **A**: contains C, H, Br and O

M^+=184 and 186

positive Tollen's test

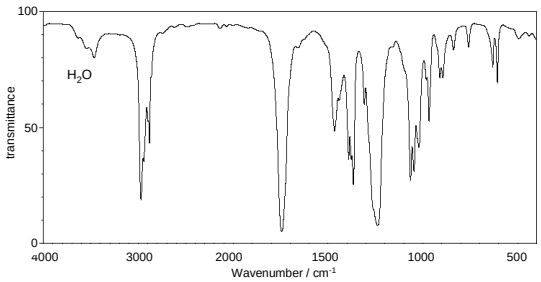
IR 1690 cm^{-1}

^1H NMR singlet at δ 10.1, doublets at 8.1 and 7.5 ppm.

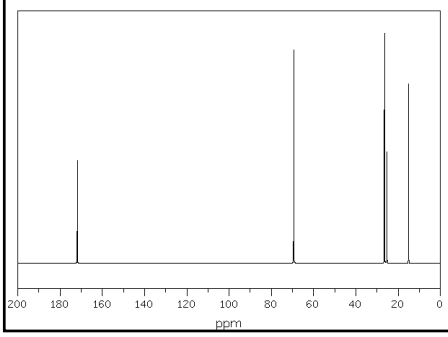
Empirical Formula: $C_5H_{10}O_2$

Mass Spec: M^+ *m/e*= 102

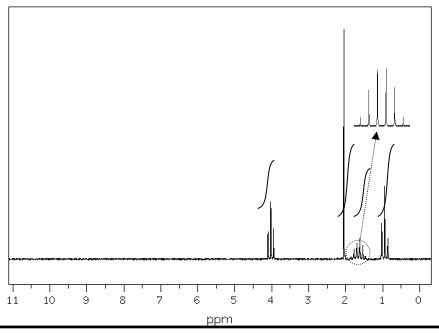
IR



^{13}C NMR



^1H NMR



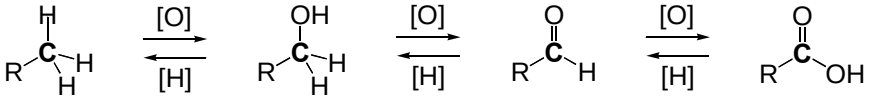
? *Prob: 16.24,26,28,31,39,41-44,50* ?

REVIEW OF CARBONYL CHEMISTRY: REACTIONS AND MULTISTEP SYNTHESIS

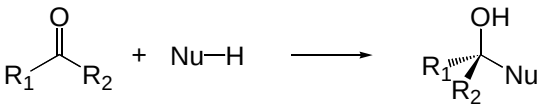
S:16.14
Prob:16.50

Reactions

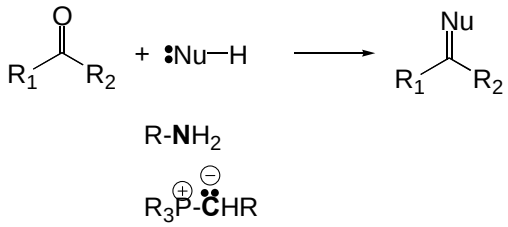
Oxidation and Reduction



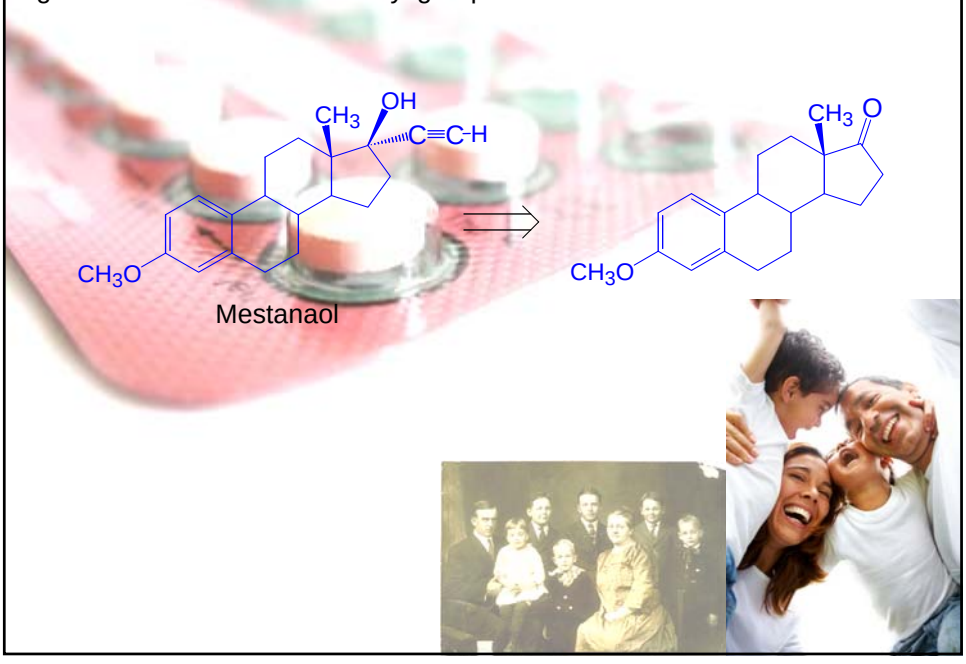
Nucleophilic addition



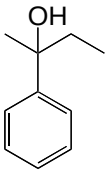
Nucleophilic addition - Elimination



Mestanaol, a component of modern birth control pills, using organometllic addition to carbonyl groups?

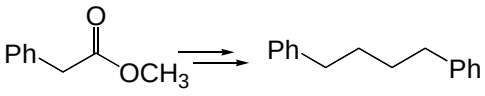


Problem: How could you make 2-phenyl-2-butanol from benzene and any other starting materials with two or fewer carbon atoms.



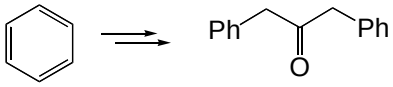
?

Problem: How could you make 1,4-diphenylbutane from $PhCH_2CO_2CH_3$



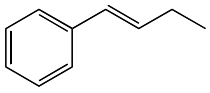
?

Problem: How could you make 1,3-diphenylpropanone from benzene



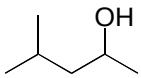
?

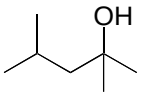
Problem: How could you make 1-phenyl1-butene from benzene?



?

Problem: How could you prepare the following two alcohols from 2-propanol?





TOPIC 3 ON EXAM 3

Types of Questions

- Predict the products obtained from given starting materials,
- Rationalize the outcome of a reaction (i.e., propose a mechanism, draw key intermediates)
- Develop multistep synthetic strategies.

Do the problems in the book; they are great examples of the types of problems on the exam!

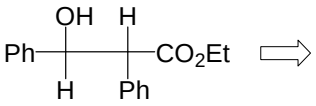
Preparing for Exam 3

- Get up-to-date *NOW!*
- Work as many problems as possible. Do the problems first, then consult the solutions manual.
- Work in groups, discuss chemistry, teach and test each other.
- Do the "Learning Group Problem" at the end of the chapter.

ORGANOZINC COMPOUNDS: THE REFORMATSKY REACTION

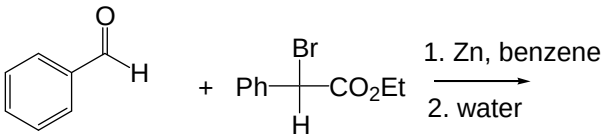
S:16.11
Prob:16.32

Problem: How would you make the following 2° alcohol?



Grignard and lithium reagents react with esters!

Solution: Organozinc reagents do not react with esters



via:

Why are esters less electrophilic than ketones?