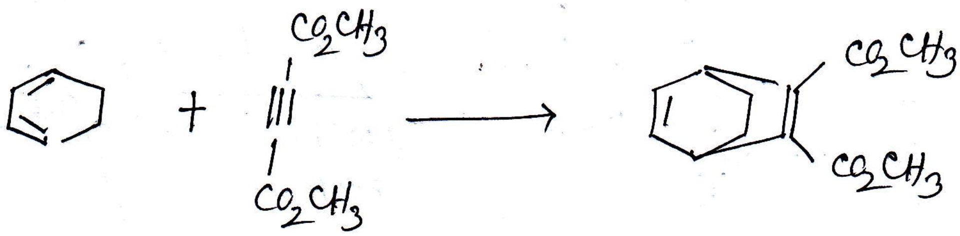
Robinson's Annulation Reaction

Robert Robinson
The Nobel Prize
1947

'Annulation' ⇒ anellus ⇒ little ring
⇓
is a chemical reaction in which a new ring is constructed on a molecule



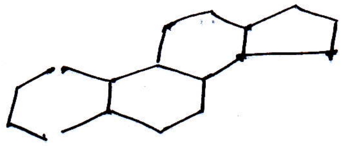
Robinson's Annulation

The sequential process of Michael and aldol reactions leading to a new six-membered ring is known as the Robinson's annulation reaction.

⇓

Application is steroid synthesis

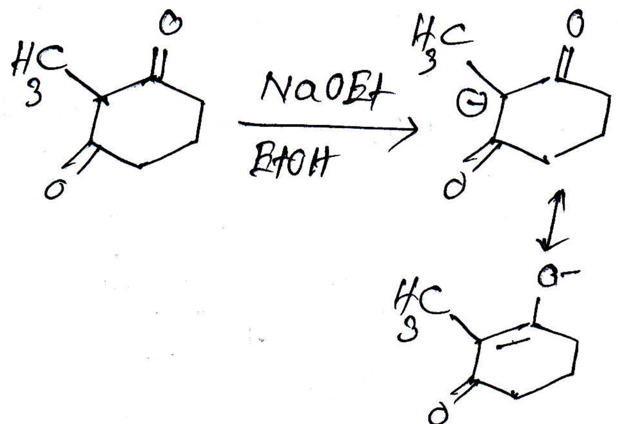
⇓



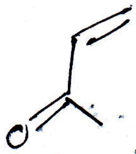
Michael addition + Aldol reaction ⟶ Robinson's annulation

⇓

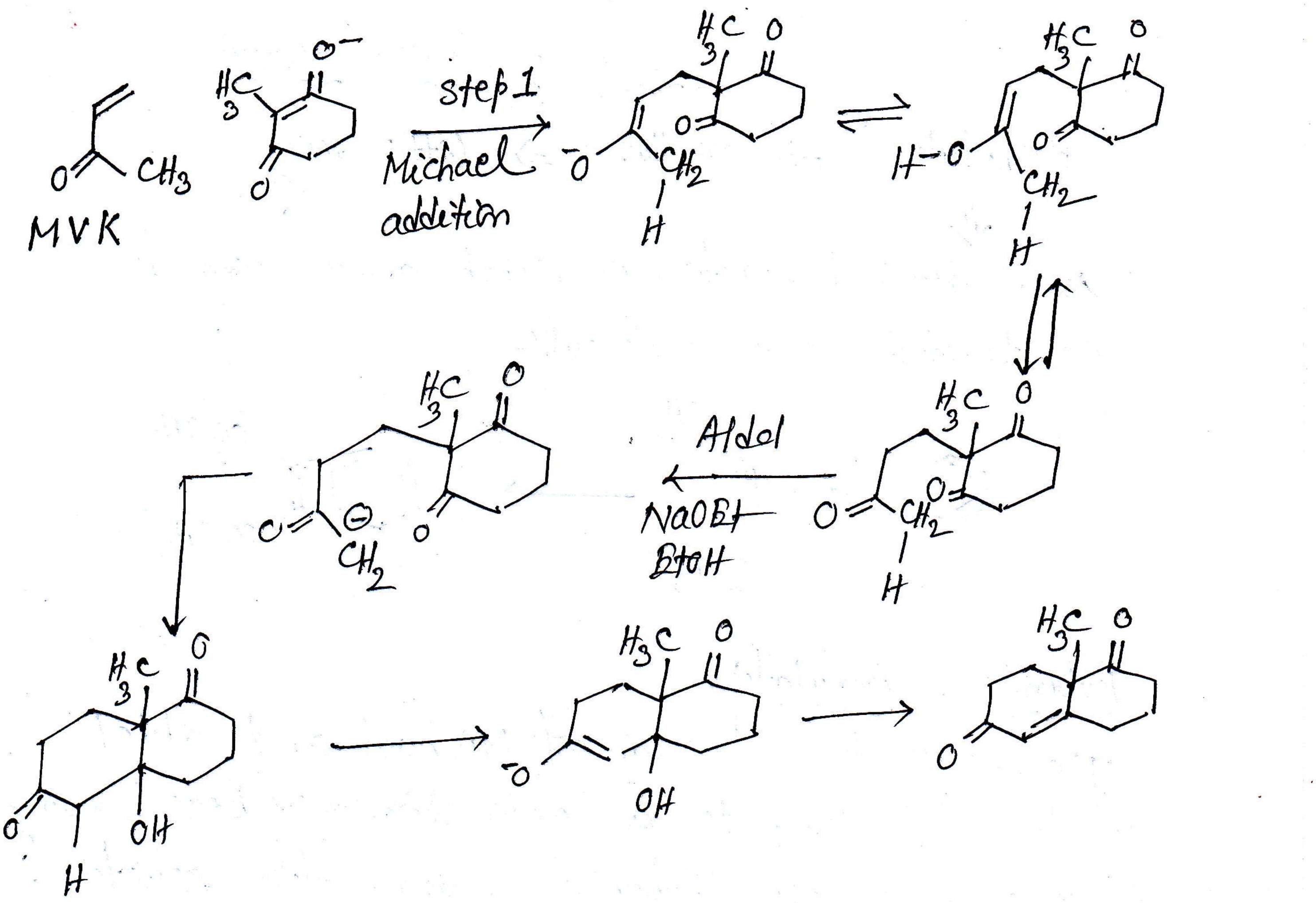
Addition of an enolate to an enone system



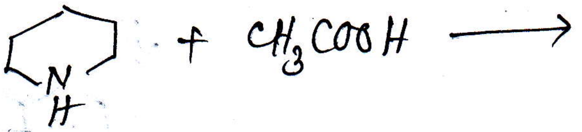
(enolate)



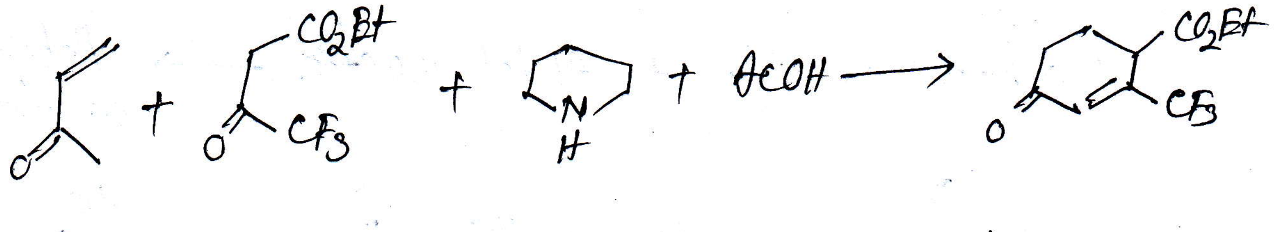
en-one system



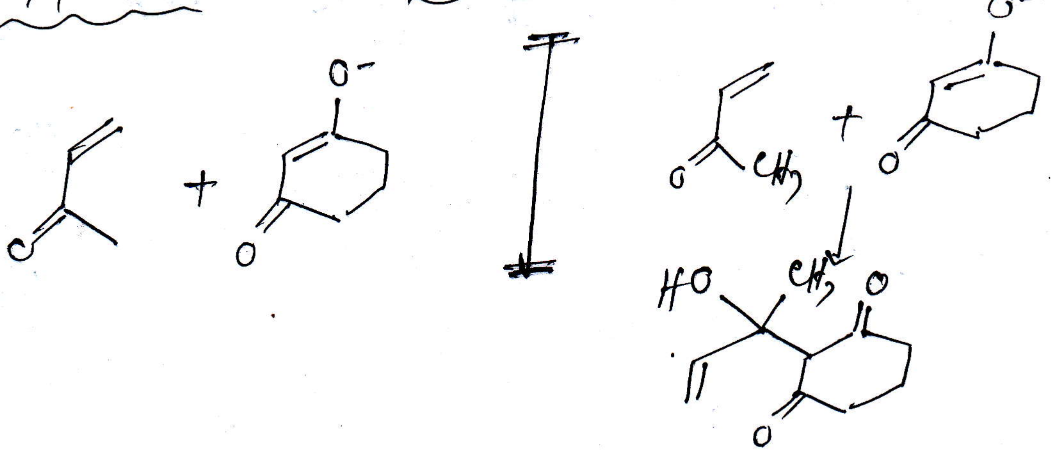
Nature of base ⇒ Weak base is sufficient



buffer system
may be used



Why 1,4-addition instead of 1,2-addition

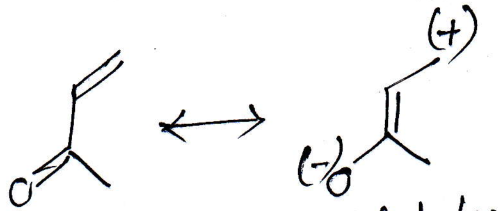


Cause ⇒ SHAB Principle ⇒ Soft-Hard Acid Base

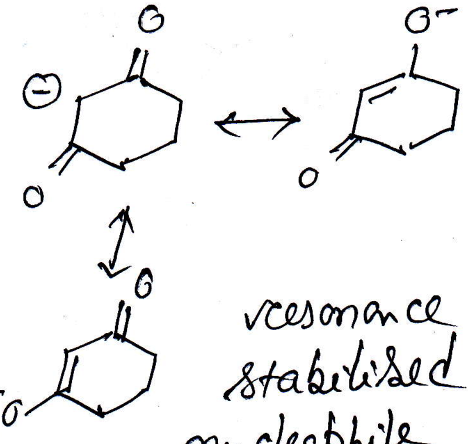
{ Soft acid / Electrophile ⇒ resonance stabilised
{ Hard acid / Electrophile ⇒ non-stabilized (resonance)

Soft base / nucleophile ⇒ resonance stabilised

Hard base / nucleophile ⇒ non-stabilised

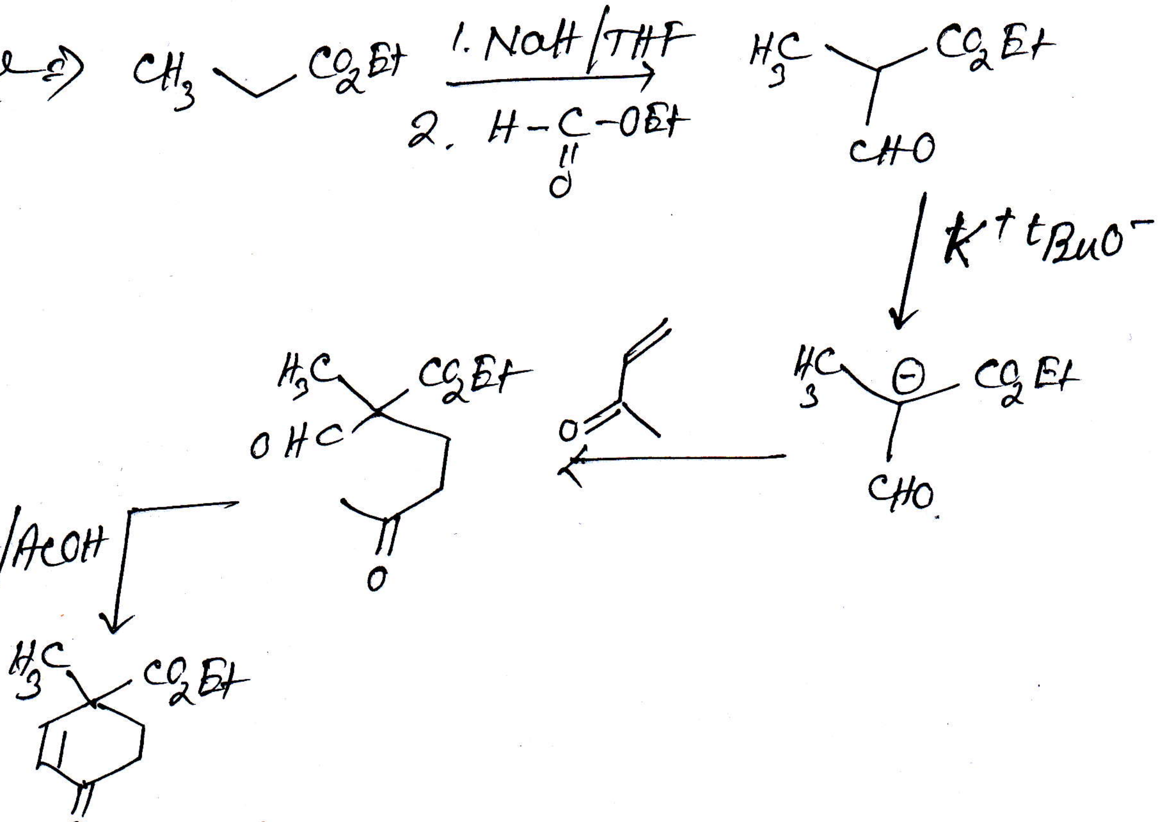


resonance stabilised electrophile



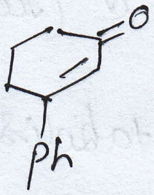
resonance stabilised nucleophile

Example ⇒

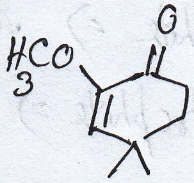


1. How would you synthesize the following compounds using Robinson's annulation method

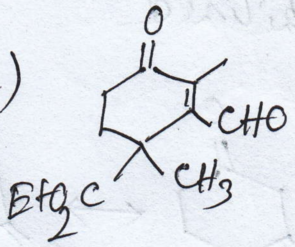
(a)



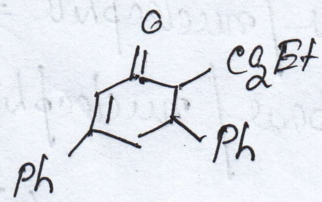
(b)



(c)



(d)

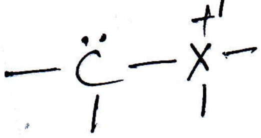


Wittig Reaction

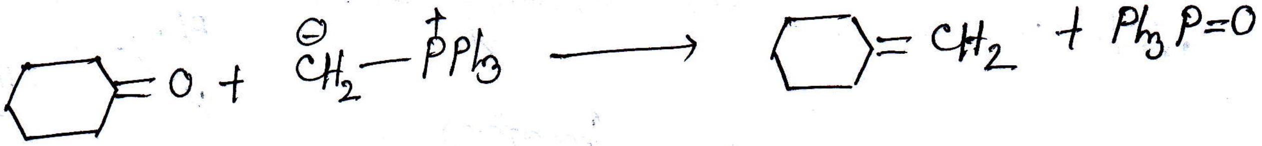
Georg Wittig
The Nobel Prize 1979

Reaction between phosphonium ylide and aldehyde / Ketone to form alkene

ylide ⇒ anionic carbon covalently bonded to a positively charged hetero atom



$X = P, S, N$



Driving force ⇒ P–O bond energy (one of the strongest covalent bond)

How to form ylide ⇒ strong base + phosphonium salt

$\Downarrow$

$CH_3-CH_2CH_2\overset{\ominus}{C}H_2\ Li^+$
n-butyl lithium

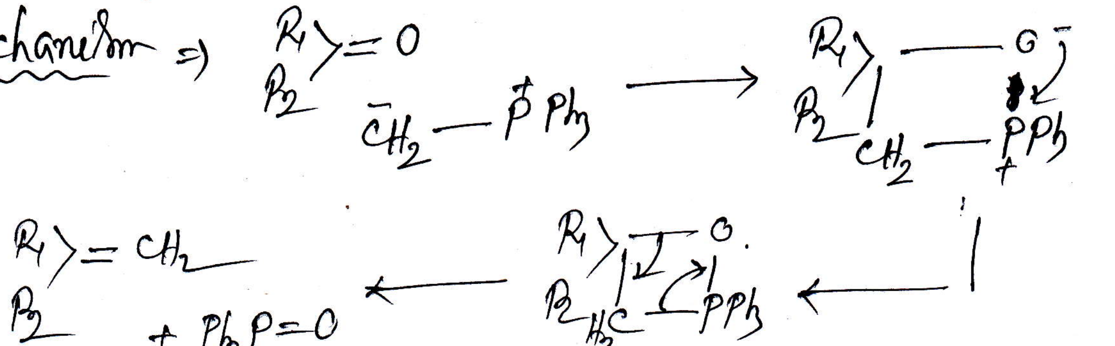
$[Ph_3\overset{+}{P}-CH_3]I^-$

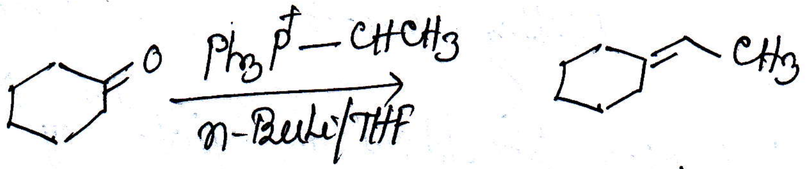
$Ph_3\ddot{P}$ (nucleophile) $+ CH_3-I \longrightarrow Ph_3\overset{+}{P}-CH_2-H$

$\downarrow$ n-$Bu^{\ominus}Li^+$

$Ph_3P=CH_2 \longleftrightarrow Ph_3\overset{+}{P}-\overset{\ominus}{C}H_2$ (ylide)

Mechanism ⇒



Example 

$$\underset{H}{Ph}\!\!>\!=O + Ph_3\overset{+}{P}-\overset{-}{C}HCH_3 \xrightarrow[THF]{n\text{-}BuLi} \underset{H}{Ph}\!\!>\!=\!<\!{}^{CH_3}_{H}$$

(majore)

$$\underset{H}{Ph}\!\!>\!=O + Ph_3\overset{+}{P}-\overset{-}{C}HCO_2Et \longrightarrow \underset{H}{Ph}\!\!>\!=\!\diagdown CO_2Et \text{ (trans)}$$

$$\downarrow LiAlH_4$$

$$\underset{H}{Ph}\!\!>\!=\!\diagdown CH_2OH$$

(trans)

ylide containing electron donating group

⇓

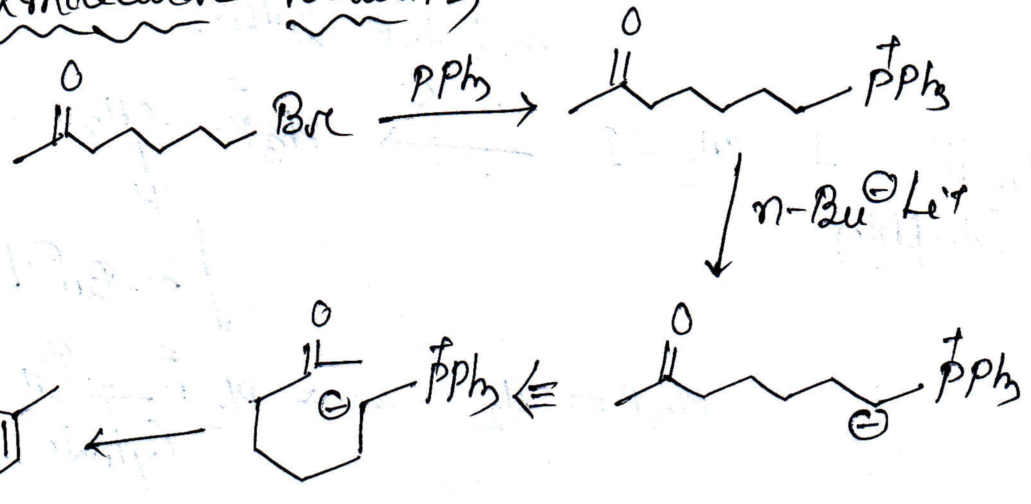
cis-alkene (majore)

ylide containing electron withdrawing group

⇓

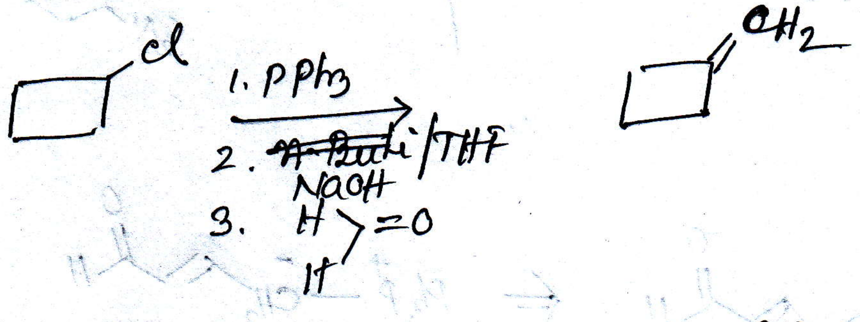
trans-alkene (majore)

Intramolecular version ⇒

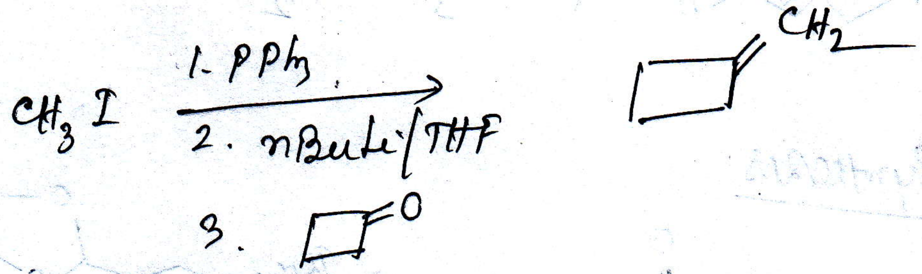


Problem: Which scheme is more efficient?

Route 1



Route 2



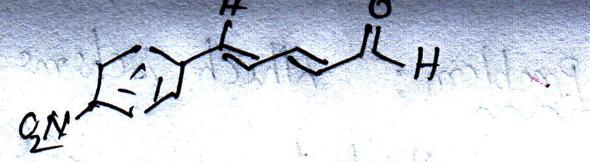
Reasons ⇒

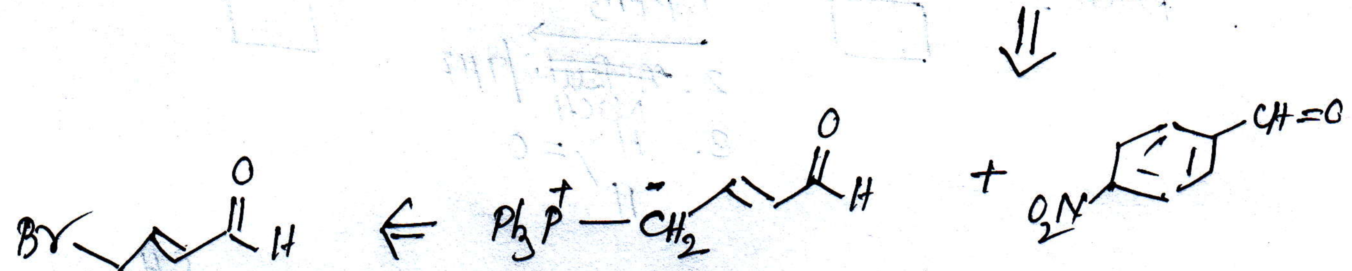
1.

2.

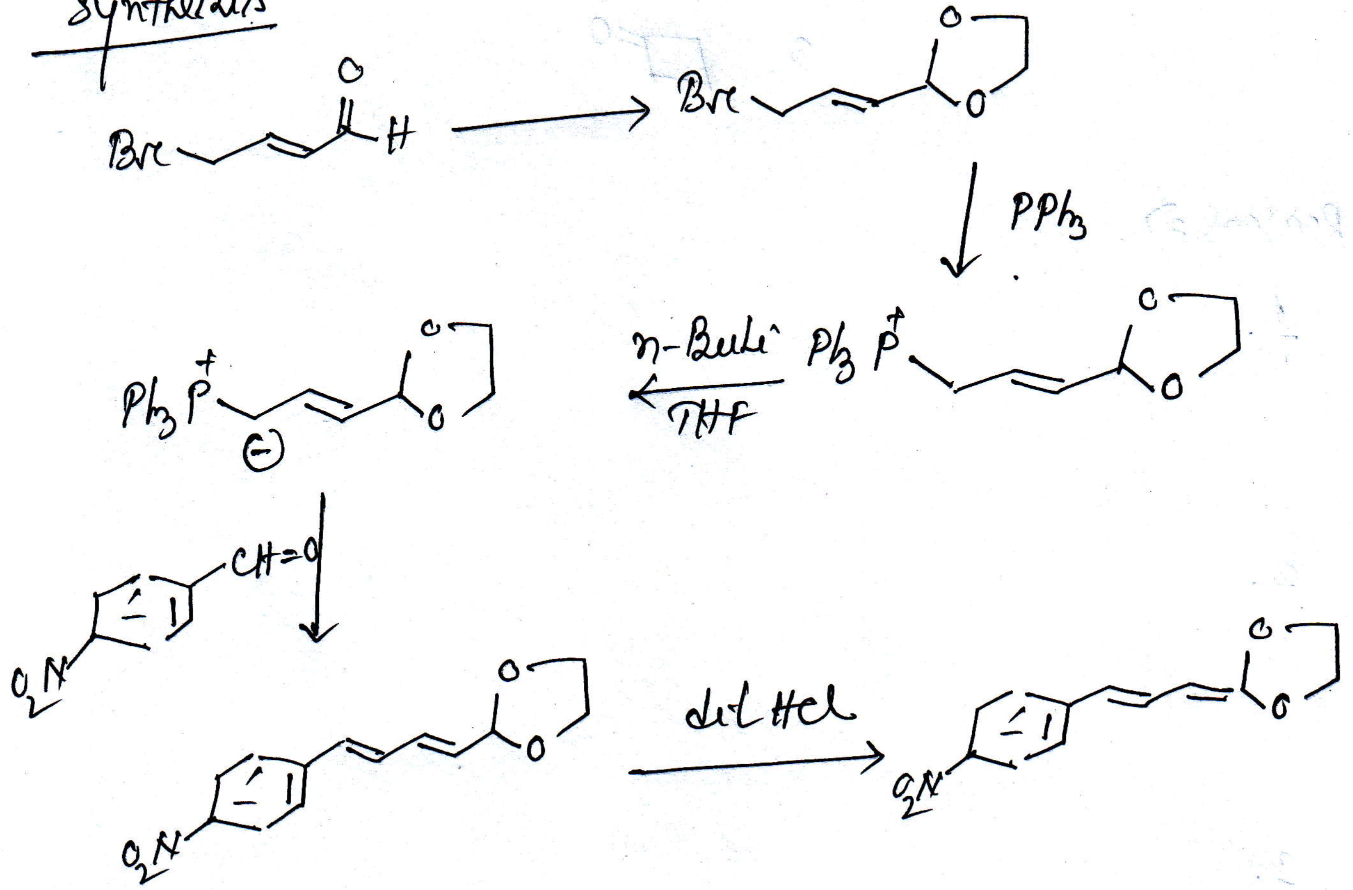
3.

Problem How to Synthesize

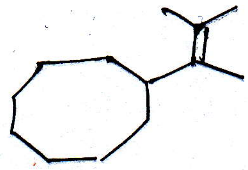


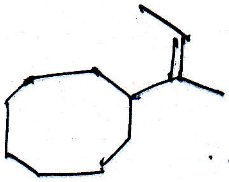


Synthesis

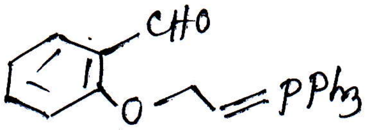


Problem How to make

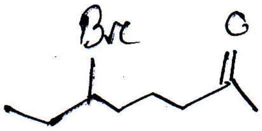




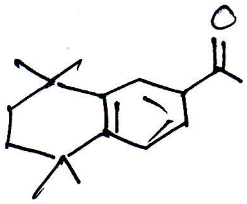
Home work



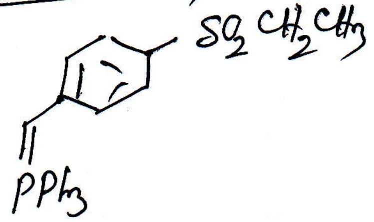
$\longrightarrow$ Product ?



$\xrightarrow[2.\ NaH]{1.\ PPh_3}$ Product ?



$\longrightarrow$ Product ?



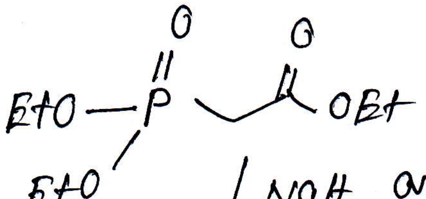
Horner, Wadsworth and Emmons modification

Aim $\Rightarrow$ i) to make stabilized ylide

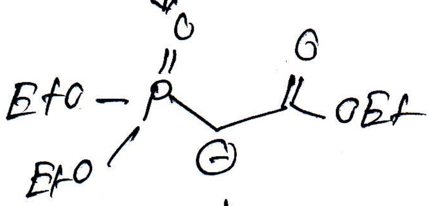
$\hookrightarrow$ to make E-alkene

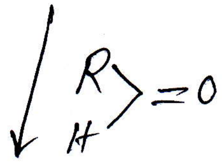
ii) to make the by-product water soluble

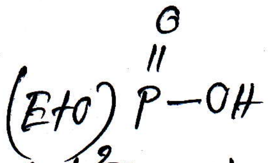
$Ph_3P=O$
soluble in organic solvent



$\downarrow$ NaH or BuLi

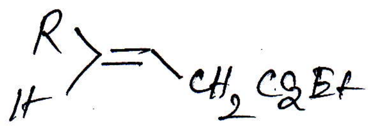






Soluble in water
(seperated by solvent extraction)

+



Gilman Reagent ← Henry Gilman

Organometallic reagent ⇒ Lithium and copper reagent

⇓

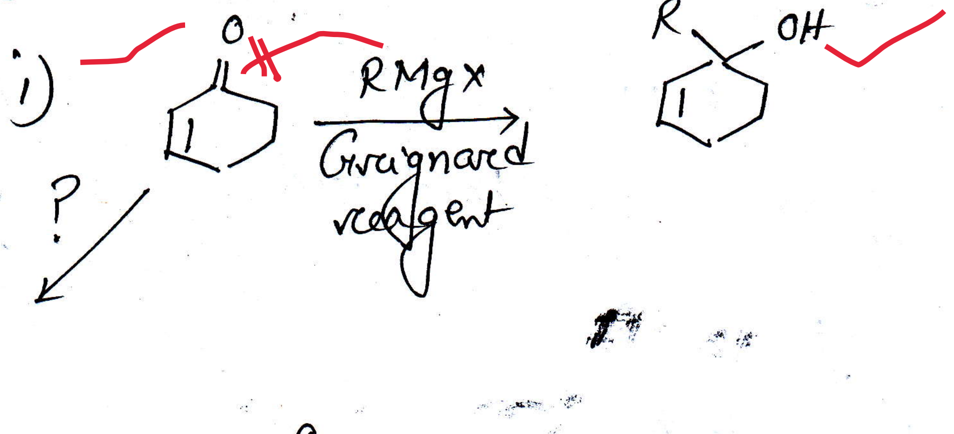
diorgano copper

R_2CuLi

$(CH_3)_2CuLi$

Lithium dimethyl cuprate

Importance :

i) 

ii)

$$CH_3-\overset{O}{\overset{\|}{C}}-OH \xrightarrow{?} CH_3-\overset{O}{\overset{\|}{C}}-CH_3$$

$$CH_3-\overset{O}{\overset{\|}{C}}-OH \longrightarrow CH_3-\overset{O}{\overset{\|}{C}}-Cl \xrightarrow{CH_3MgX} CH_3-\underset{CH_3}{\underset{|}{\overset{OH}{\overset{|}{C}}}}-CH_3$$

$$CH_3-\overset{O}{\overset{\|}{C}}-Cl \longrightarrow CH_3-\underset{CH_3}{\underset{|}{\overset{O^-}{\overset{|}{C}}}}-Cl \longrightarrow CH_3-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow{CH_3MgX} CH_3-\underset{CH_3}{\underset{|}{\overset{OH}{\overset{|}{C}}}}-CH_3$$

iii)

$$CH_3-\underset{Br}{\underset{|}{CH}}-CH_2CH_3 \xrightarrow{?} CH_3-\underset{CH_3}{\underset{|}{CH}}-CH_2CH_3$$

$$CH_3-\underset{Br}{\underset{|}{CH}}-CH_2CH_3 \xrightarrow{CH_3MgX} CH_3-CH=CH-CH_3$$

Synthesis ⇒ $CH_3-Br \xrightarrow[\text{2 equiv.}]{\text{Li metal}} CH_3Li + LiBr$

$2\,CH_3Li \xrightarrow{CuBr} [CH_3-Cu-CH_3]Li^{+} + LiBr$

Gilman reagent

Difference between Grignard and Gilman reagent

$R\,Mg\,X$ → hard acid (Mg); hard base (R)

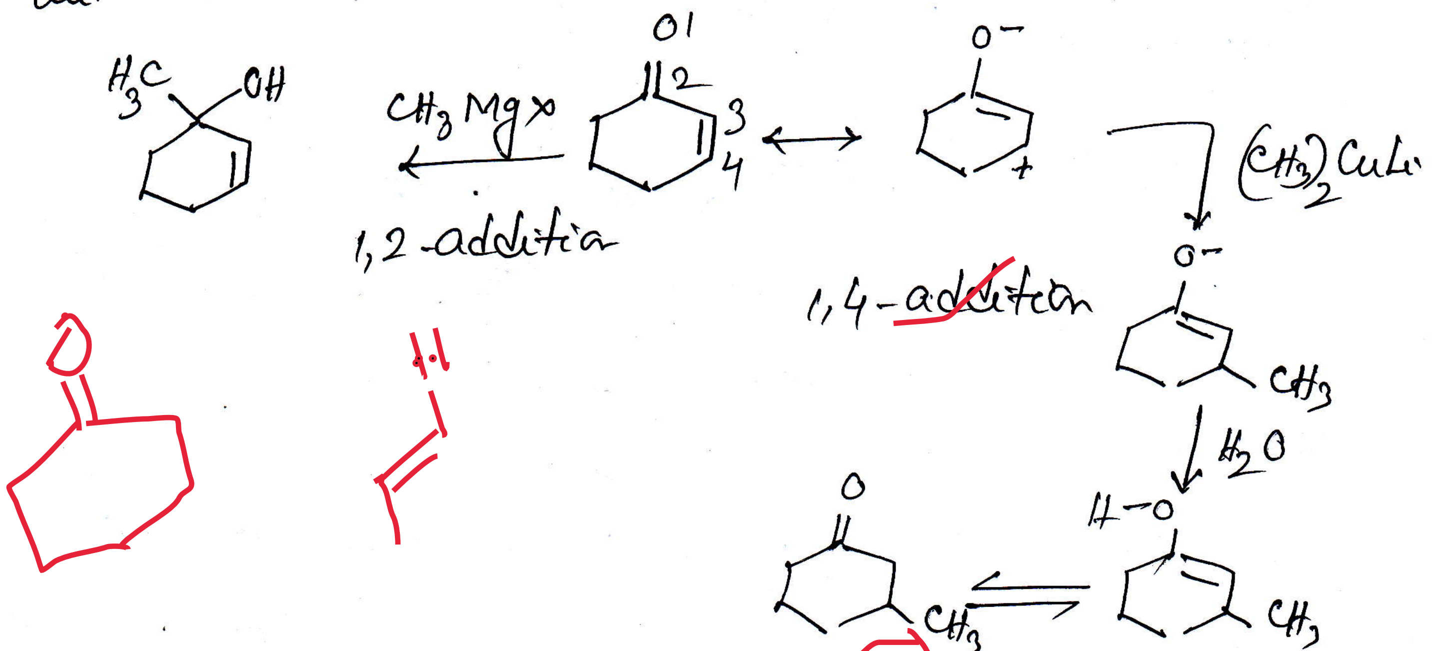
⇓

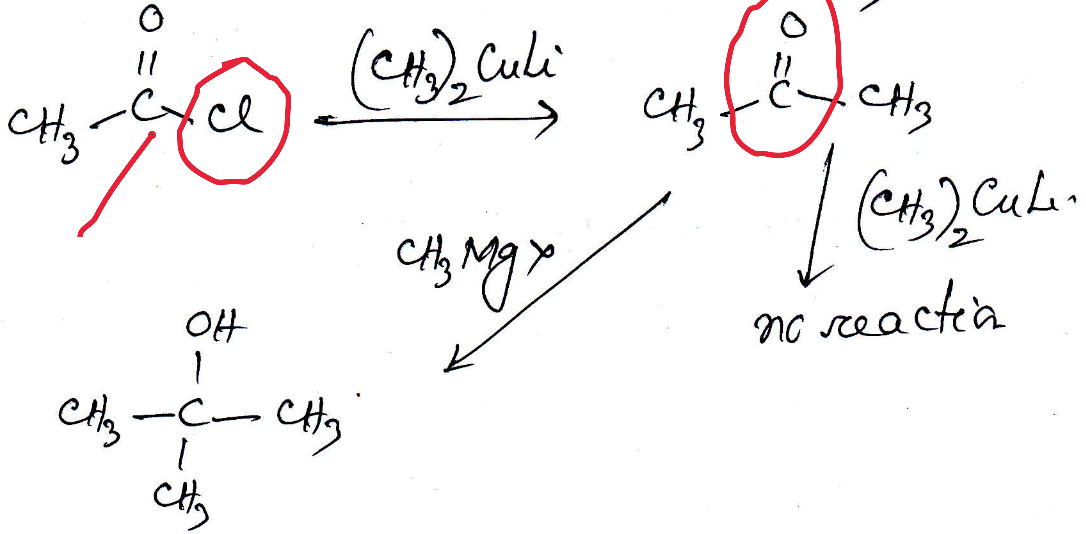
Prefers to bind with hard acid

$[R-\overset{I}{Cu}-R]Li$ → soft acid (Cu); soft base (R)

⇓

Prefers to bind with soft acid





$$CH_3-\underset{}{\overset{Br}{CH}}-CH_2-CH_3 \xrightarrow{CH_3MgBr} CH_3-\overset{Br}{CH}-\underset{H}{CH}-CH_3 \quad H \leftarrow \overset{-}{C}H_3\overset{+}{Mg}Br$$

$$\downarrow$$

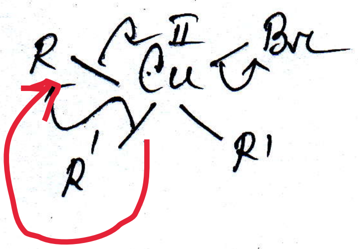
$$H_3C-CH=CH-CH_3$$

? S_N2 ↓ $(CH_3)_2CuLi$

$$CH_3-\underset{CH_3}{CH}-CH_2-CH_3$$

<u>mechanism</u> ⇒ addition - elimination

$$R-Br \xrightarrow{(R')_2\overset{I}{Cu}Li}$$

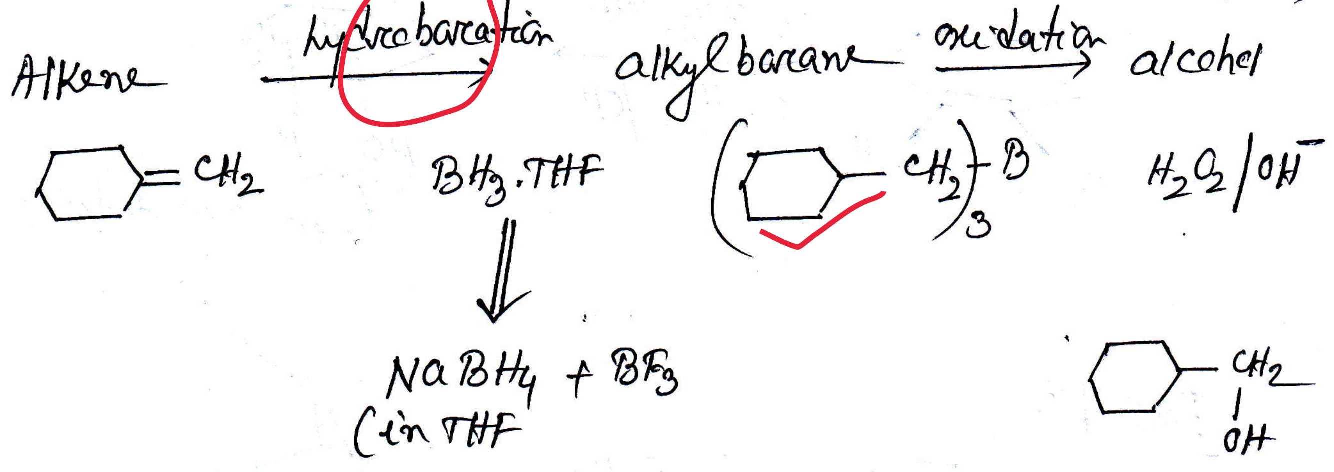


$$\rightarrow R-R'$$

$+ \; Cu(I)$

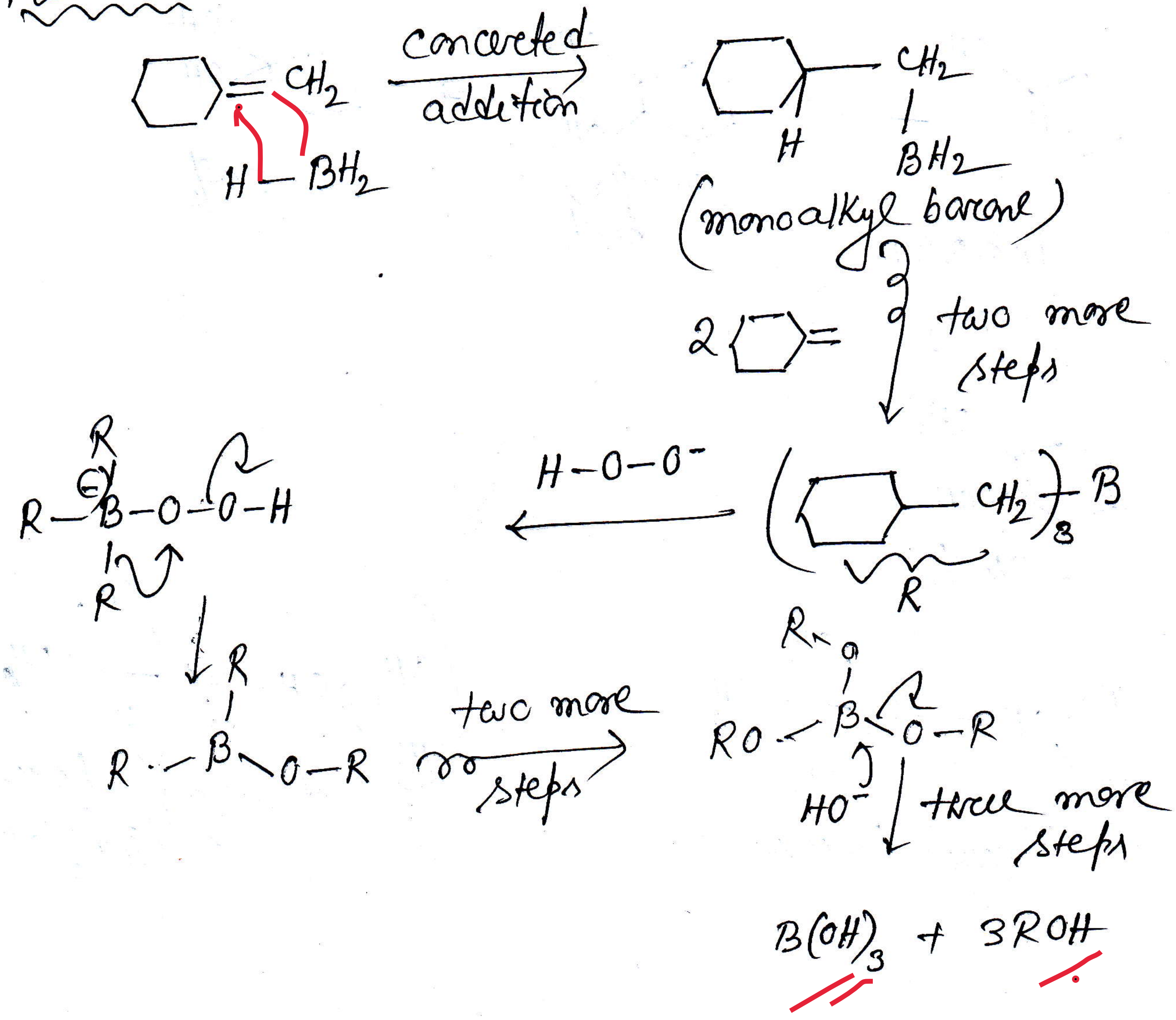
Hydroboration oxidation

H.C. Brown 1950
The Nobel Prize (1979)

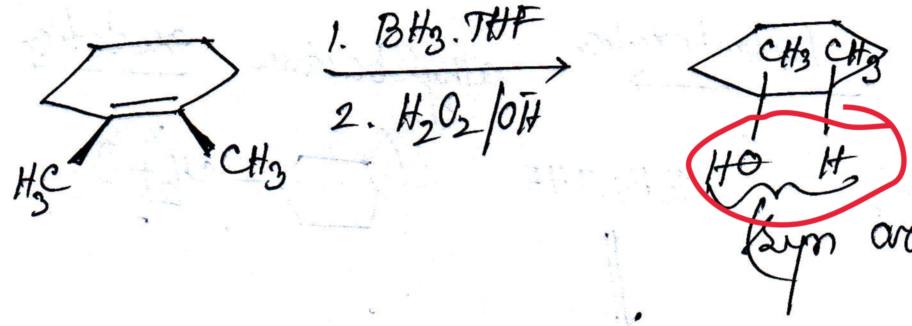


Regioselective reaction. => Anti Markovnikov addition

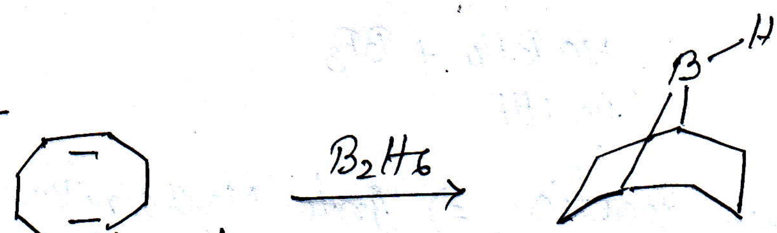
Mechanism



stereochemistry of addition => 'Syn' addition

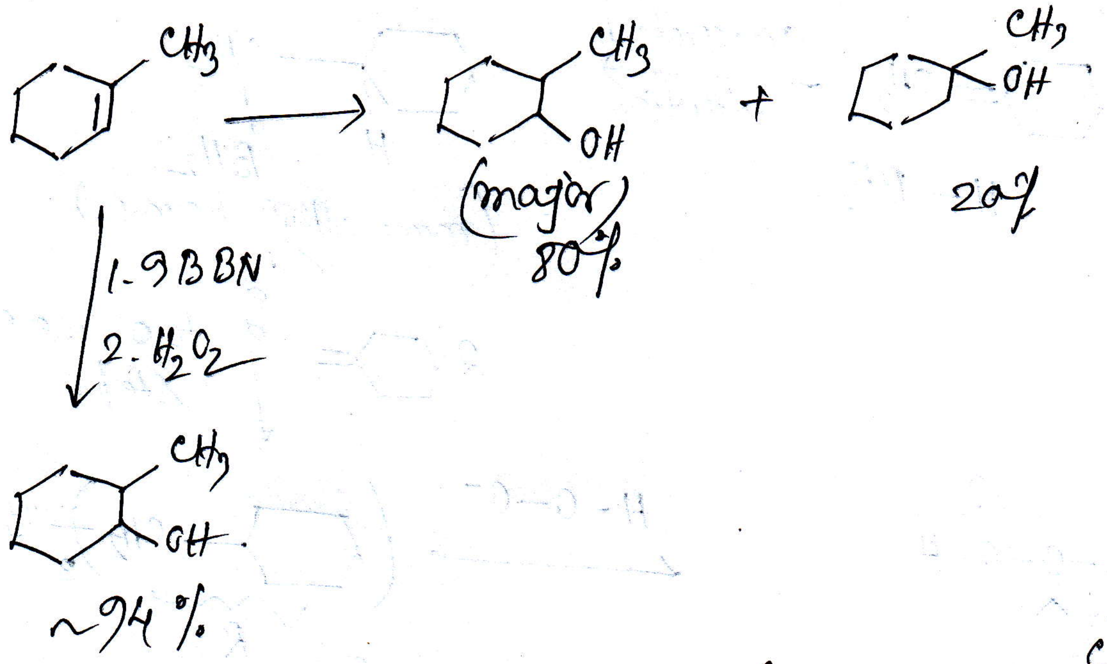


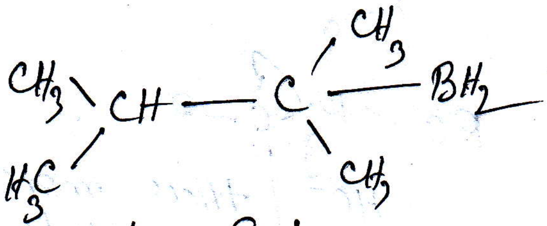
Examples



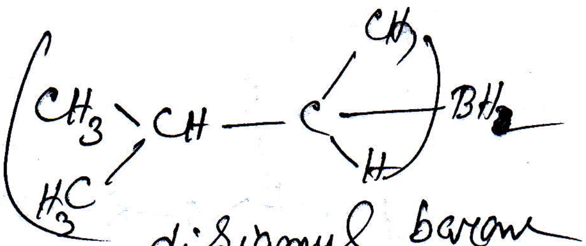
cycloocta-1,5-diene

9-Bora bicyclo [3.3.1] nonane (9BBN)





thexyl borane



disiamyl borane

$(Sia)_2BH$

Olefin Metathesis

⇓

exchange of substituents between olefins

$$R_1R_1C=CR_1R_1 + R_2R_2C=CR_2R_2 \xrightarrow{\text{catalyst}} 2\ R_1R_1C=CR_2R_2$$

Importance ⇒ i) Reformation of higher alkenes in Petroleum industry

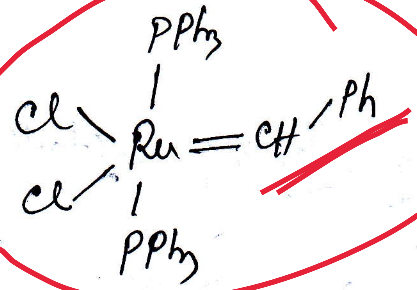
$M_w \approx 250\,000$

ii) High yield reaction

iii) Ring formation (RCM) and Ring opening (ROM) possible

iv) catalysts are stable

Catalyst ⇒ metallo-carbenoids.

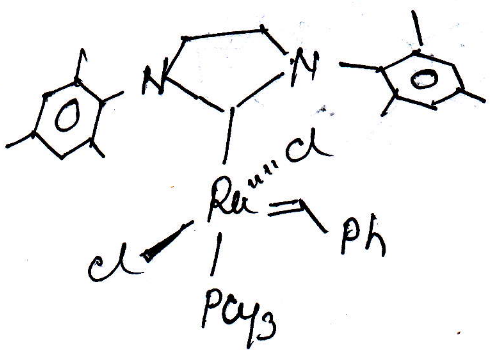


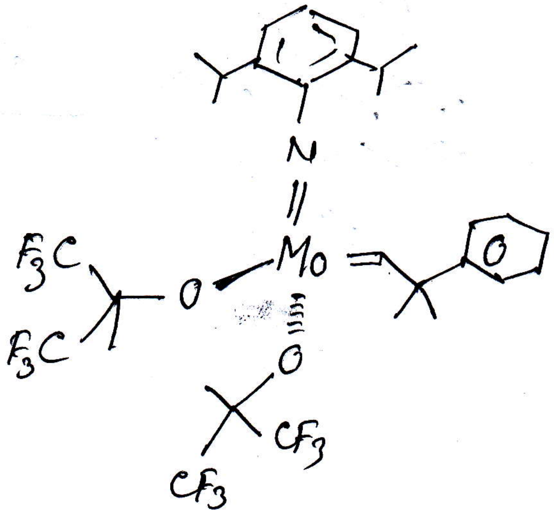
:CH

metal atom/ion ⇒ Ru(II), Mo(VI)

Ru(II) → Grubbs catalyst

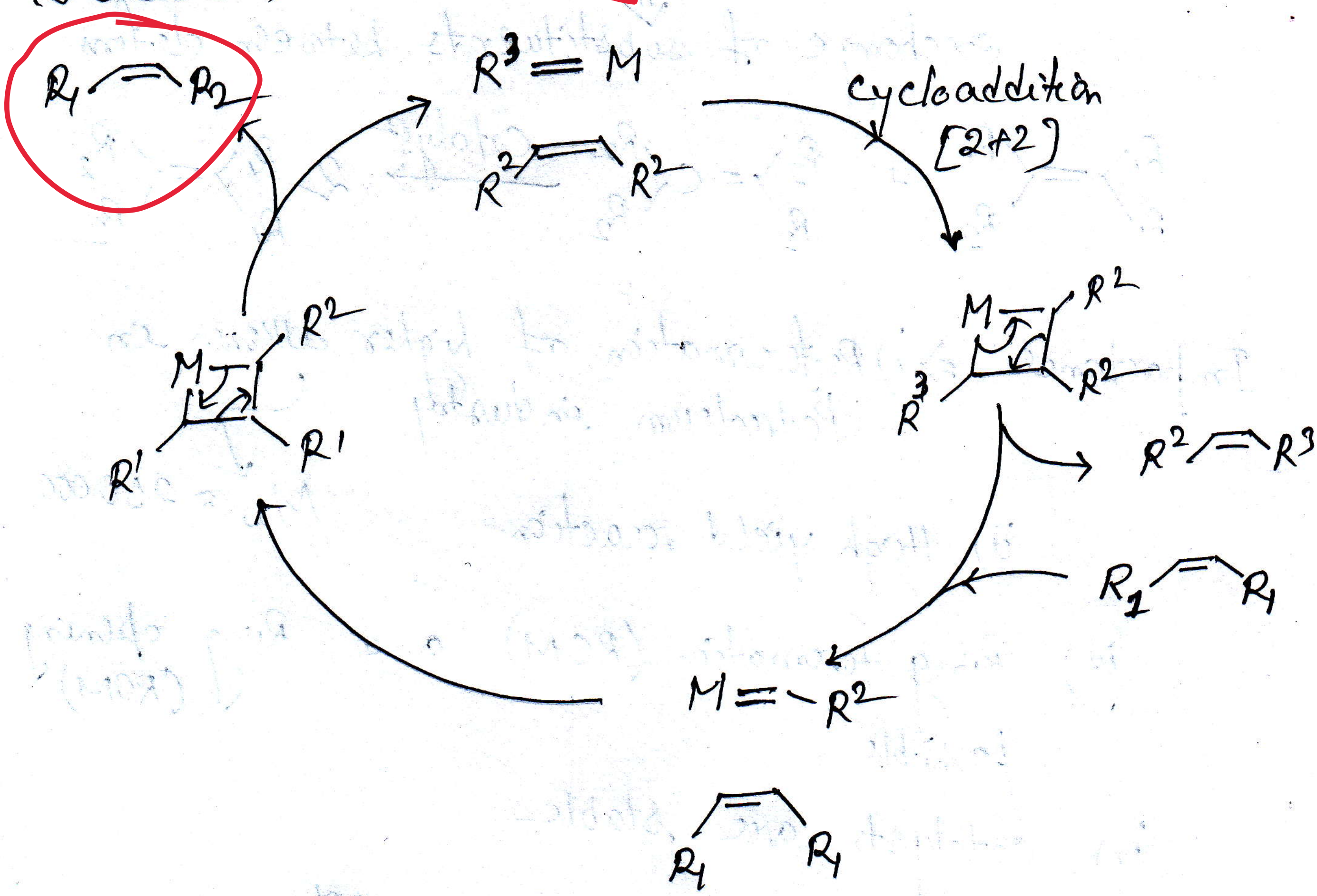
Mo(VI) → Schrock catalyst





Cy ⇒ 

mechanism ⇒



Ring closing metathesis (RCM)