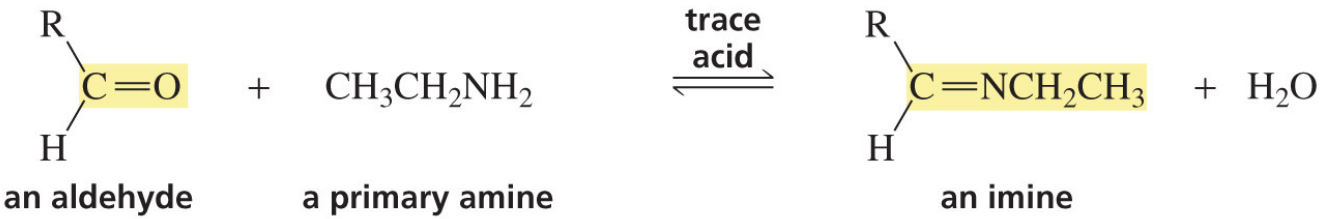
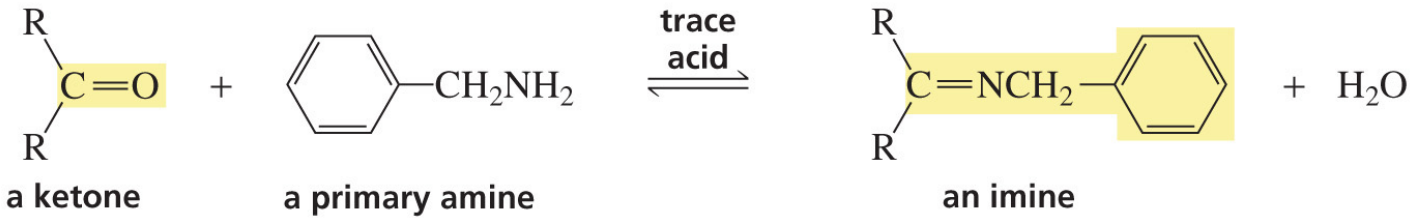
Rxn of A&K with 1° amine

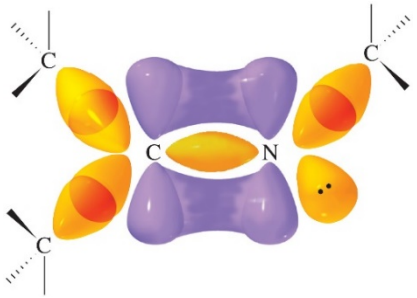
- addition-elimination, not addition
  - how-to-react 2 ~ when N: or O: Nu: sl#9
- rxn w/ 1° amine → imine



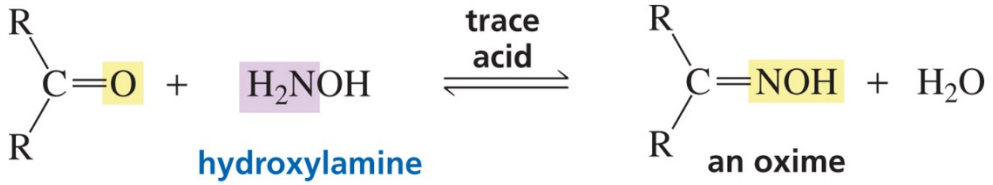


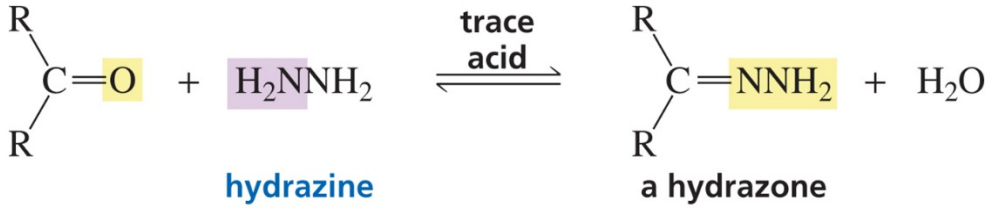
  - acid necessary
    - trace [catalytic amount]? should be controlled. see sl#34

- imine ~ $R_1R_2C{=}N\text{-}R_3$
  - when $R_3 \neq H$ ~ Schiff base



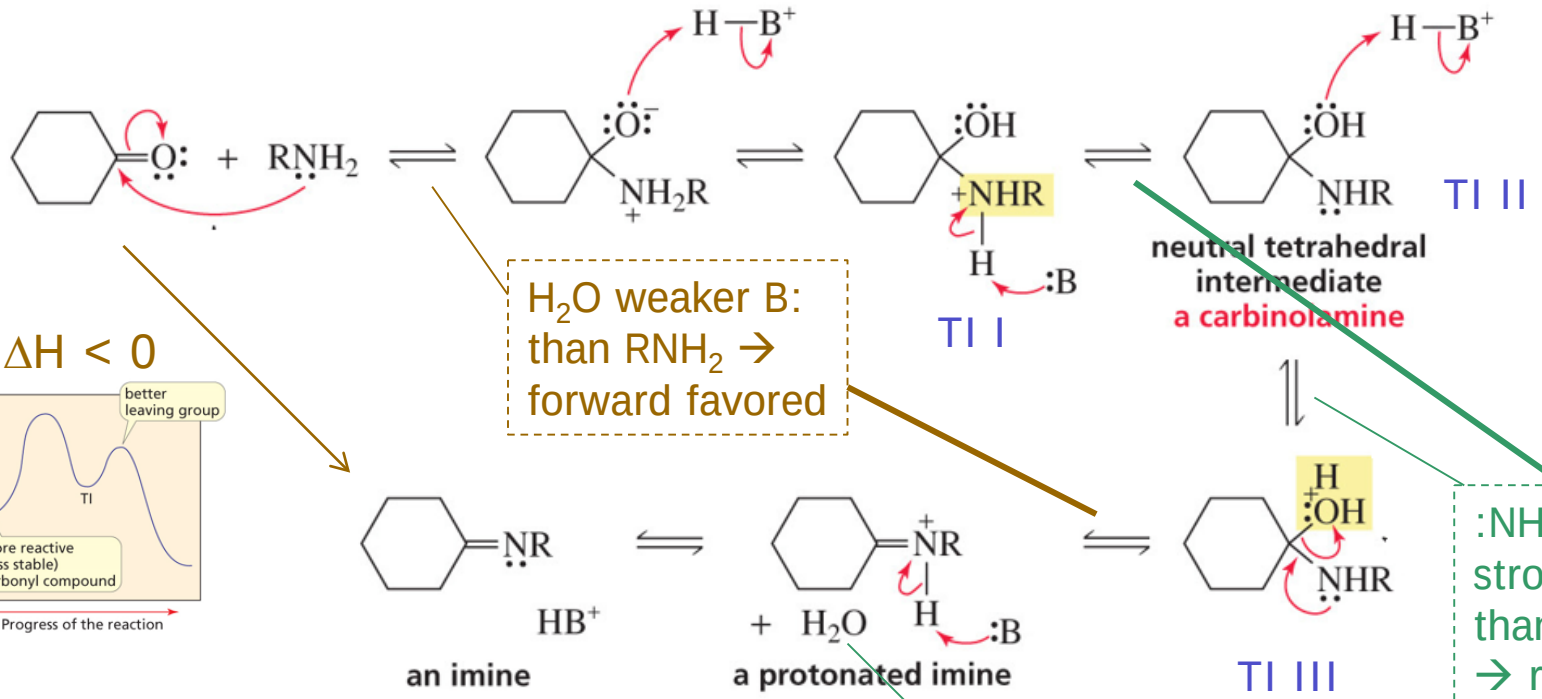
- rxn with amine deriv → imine deriv





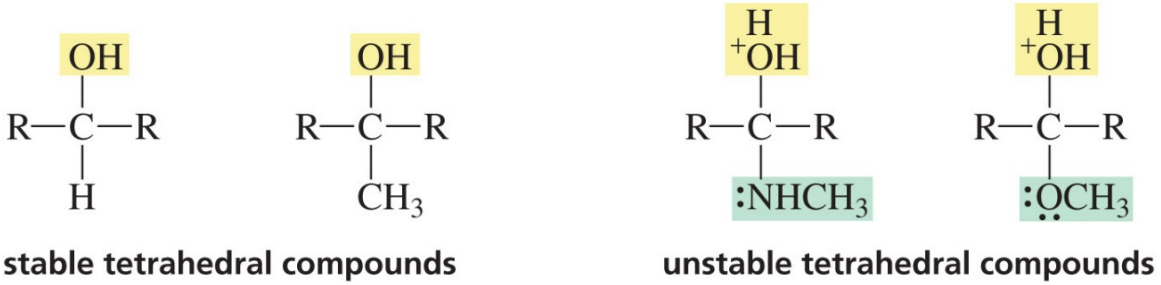
- mechanism

carbinolamine = amine and OH at the same C



- TI's similar to ester or amide hydrolysis ~ <u>not</u> stable
- ΔH < 0 ~ forward favored ~ removal of H_2O to push forward

- add'n-elim'n, not addition ← interm unstable

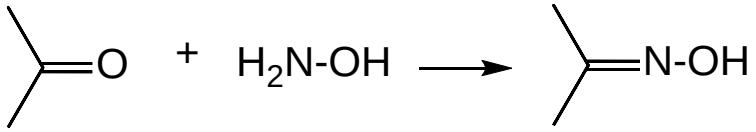


stable tetrahedral compounds

unstable tetrahedral compounds

A comp'd having sp^3 C bonded to two EN atoms is unstable.
N: O: gives e to eliminate protonated H_2O.

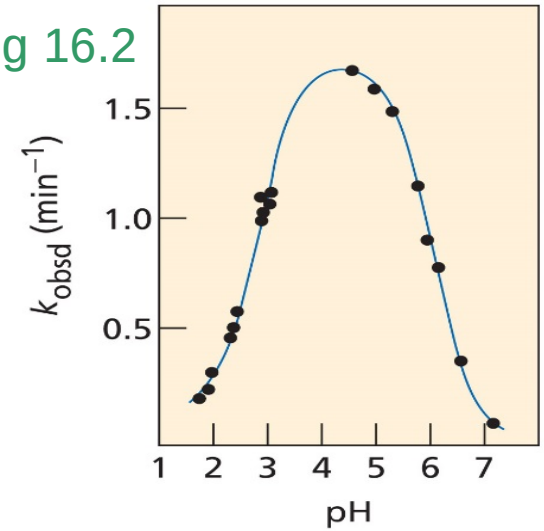
- pH control



pKa of $H_3\overset{\oplus}{N}$-OH = 6.0

  - max rate at pH of 4.5
    - at pH < 4.5 ~ low con'n of -NH_2 (→ -NH_3^+)
    - at pH > 4.5 ~ low conc'n of $^+OH_2$ (TI III)
  - for RNH_2, pH control at? Problem 27–

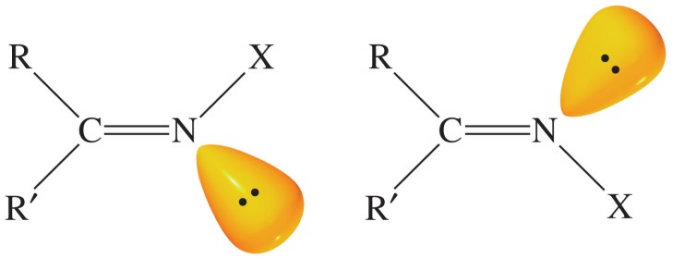
Fig 16.2



- Backward hydrolysis of imine is irreversible.

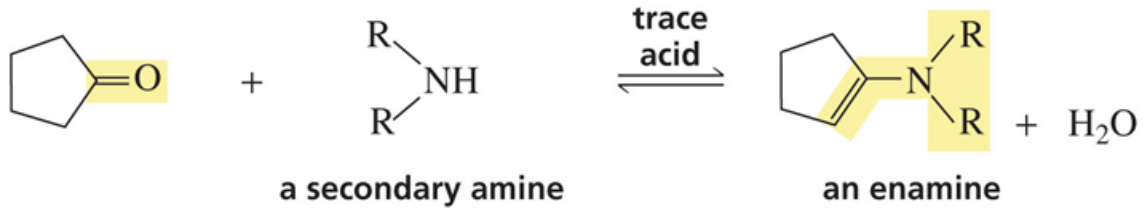
- imine formation
  - unstable TI → N: gives e to eliminate OH_2
    → N^+HR [an acid] formed
    → loses H^+ to be neutralized

- Imines have stereoisomers.
  - Problem 31

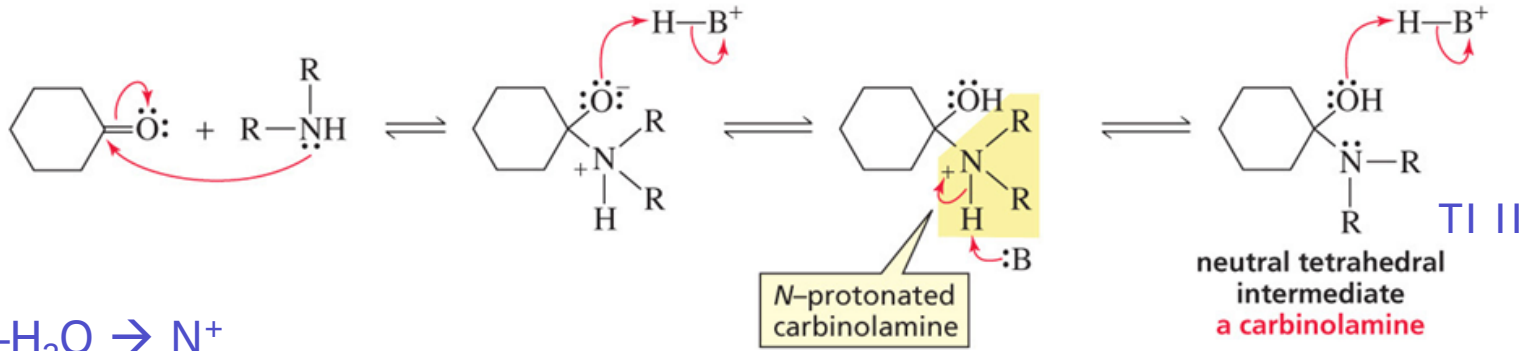


Rxn with 2° amine

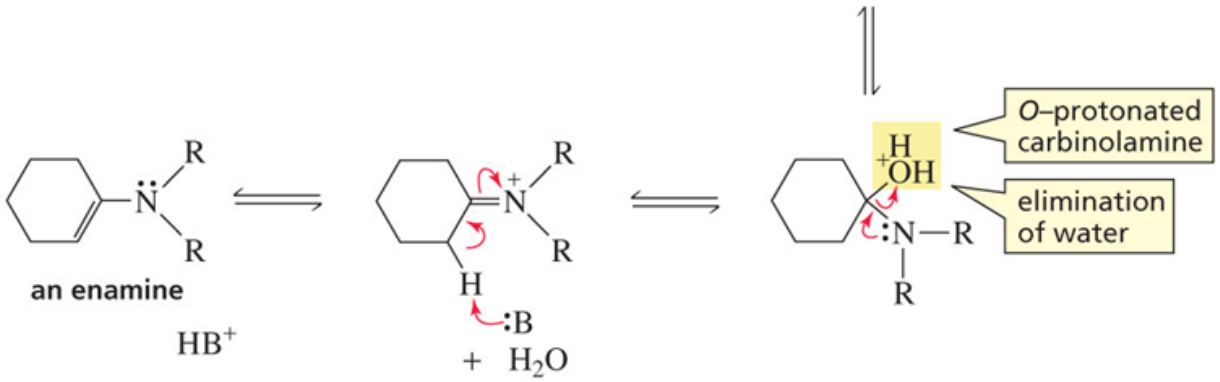
- to produce enamine



  - enamine ~ amine with = ~ α,β-unsat'd 3° amine

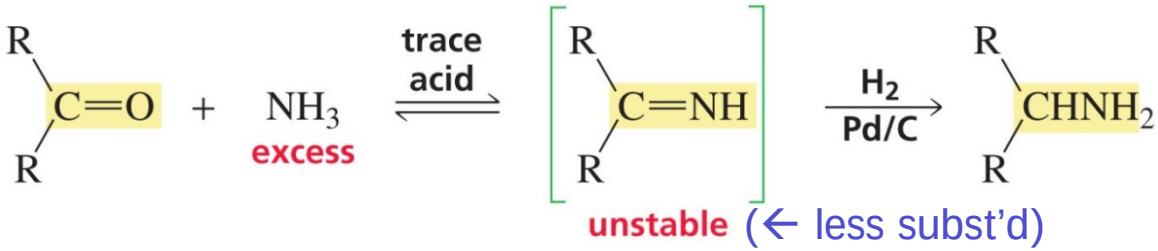


$-H_2O \rightarrow N^+$
To be neutralized,
B: takes H from α-C*
instead of from N
* α-C of carbonyl
* β-C of 3° amine



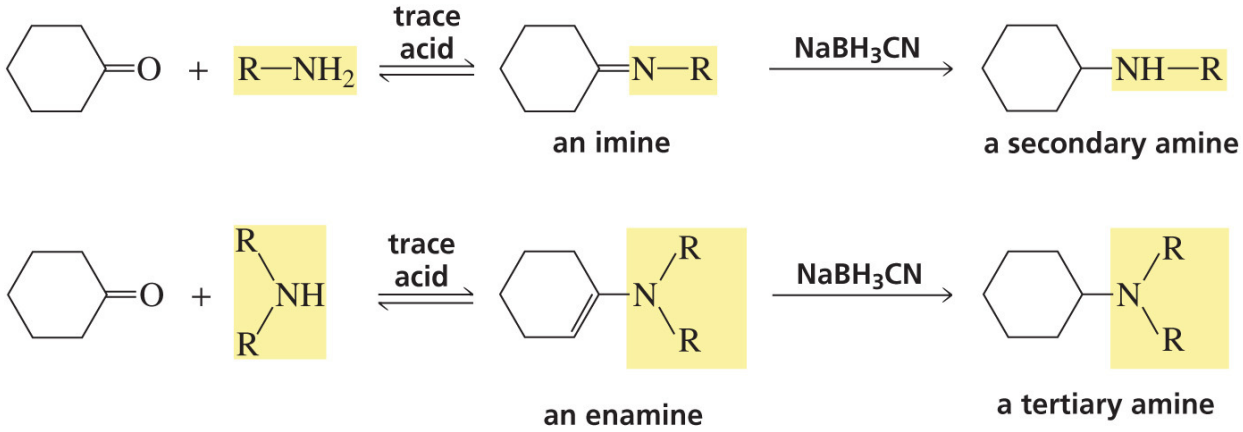
Rxn with NH_3 → reductive amination *Ch 16 #37*

- imine (reduced) to amine (w/ reducing agent)



π bond energy
C=O ~ 380
C=N ~ 320 kJ/mol

  - C=O also reduced? not with Pd (only with Ni) sl#27
  - 1° amine with xs ammonia; why xs? multiple ... Problem 34
  - 2° and 3° amine with 1° and 2° amine, respectively

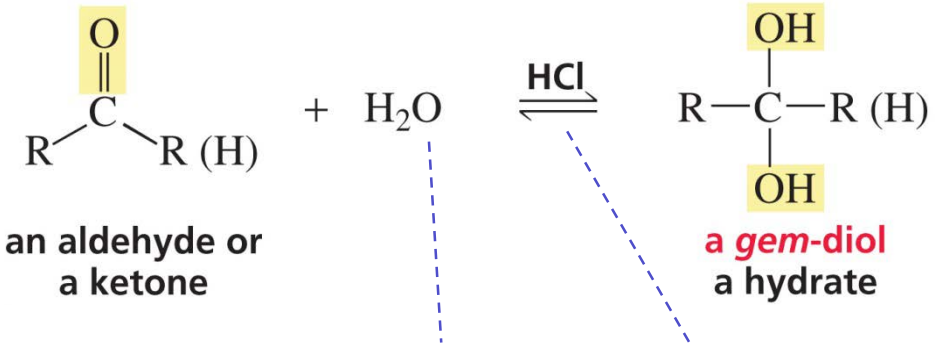


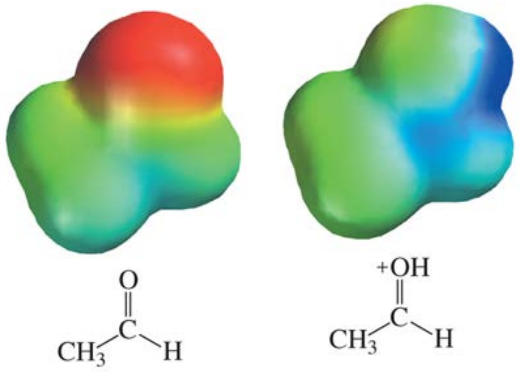
    - $NaBH_3C{\equiv}N$ ~ stable and easy to handle (even with H^+)

Rxn of A&K with water

- O Nu:
- forming hydrate* [gem-diol = geminal diol]

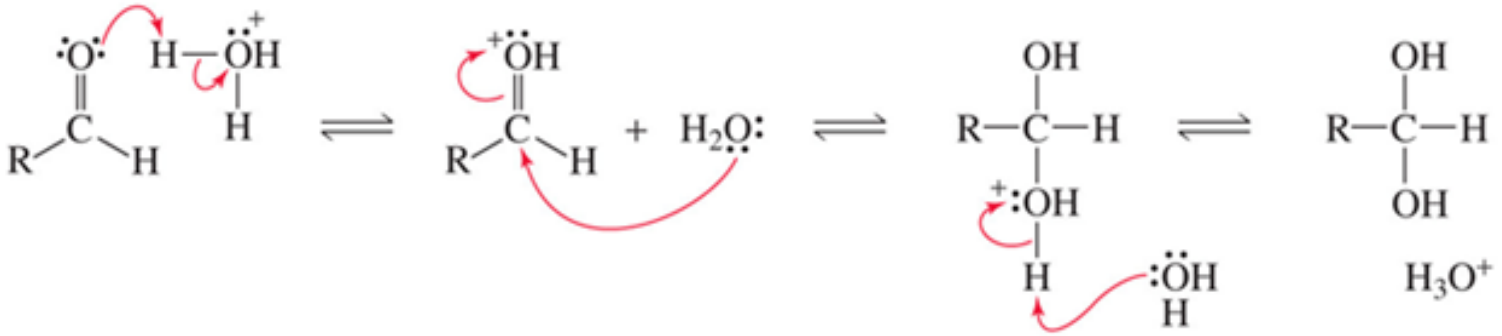
hydrate [水化物]
in a narrow sense
in inorg chem?





poorer Nu: than N: ~ need (acid) catalyst

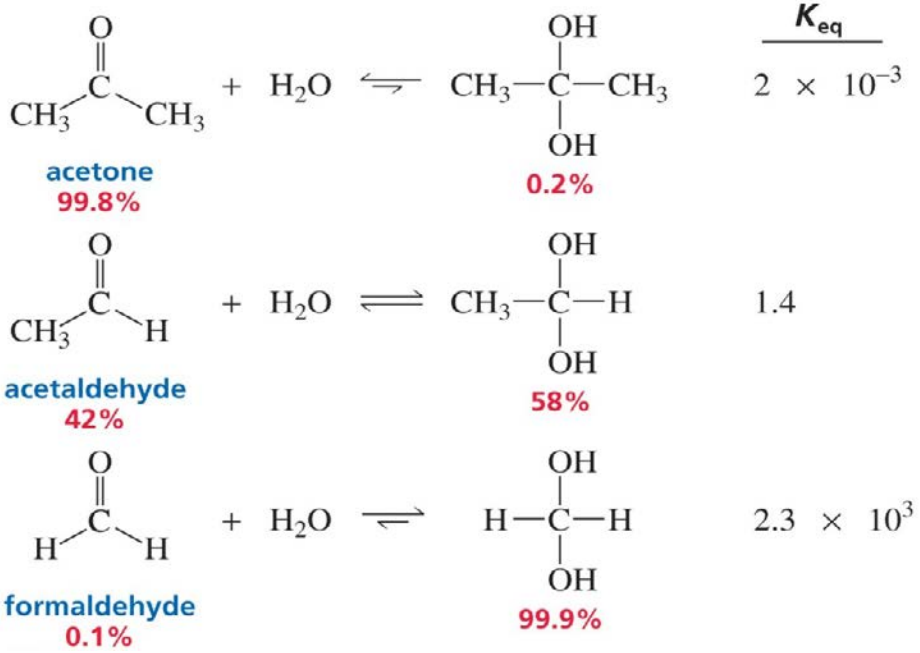
- mechanism



- ⁻OH-catalized? yes. Problem 36

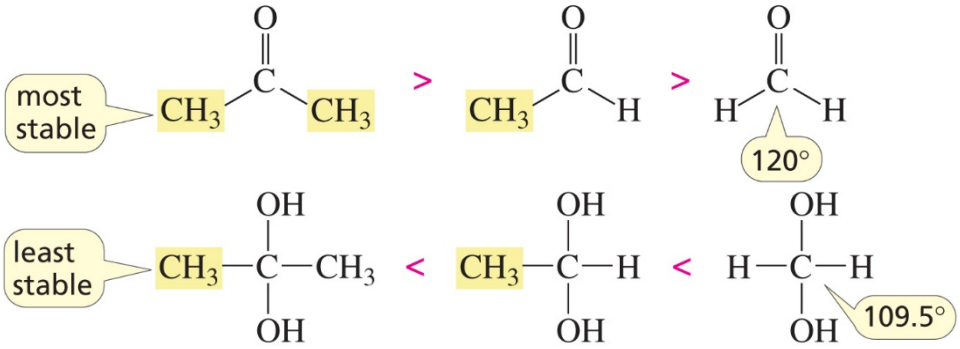
lose H^+ from O^+ to be neutral

- reactivity and stability (of reactant and product)



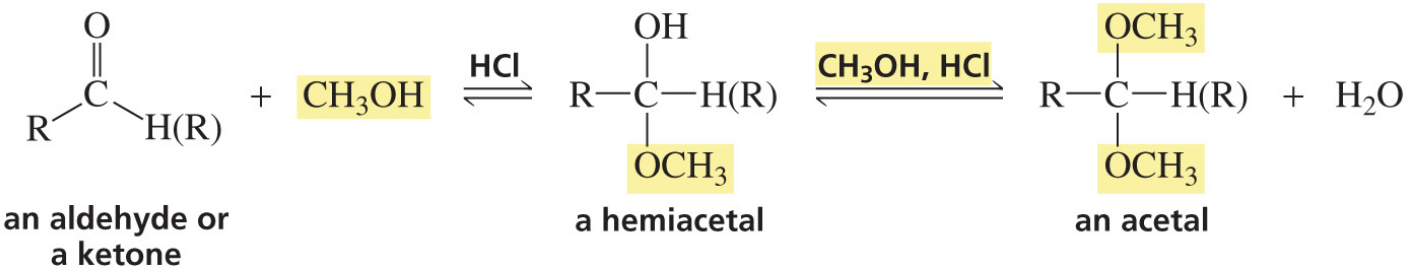
"*Generally speaking*, a comp'd having sp^3 C bonded to two EN atoms is unstable". p730 and p781

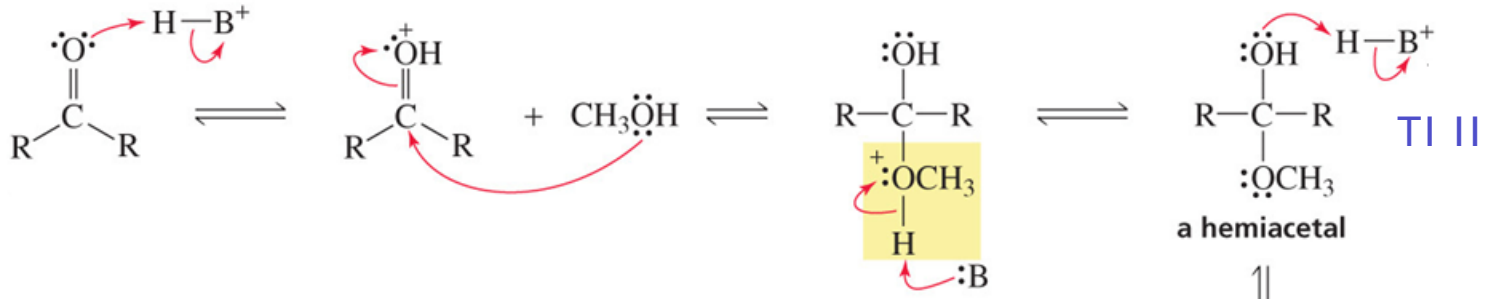
- why?

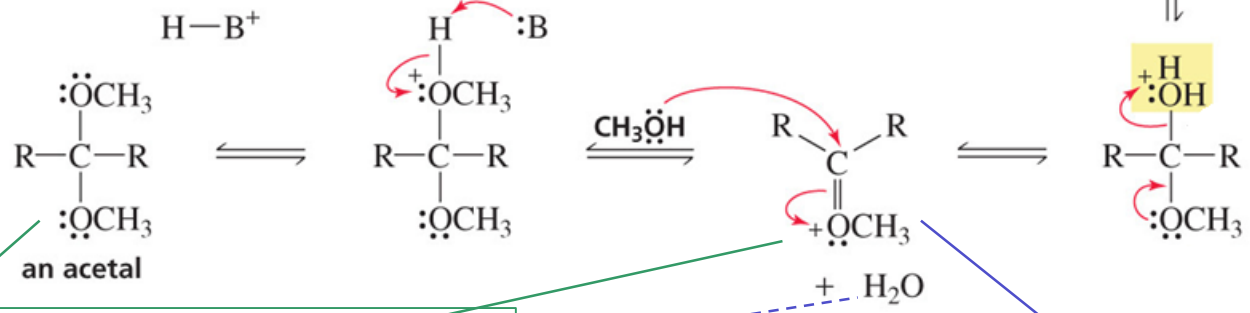


Rxn with ROH

- to hemiacetal to acetal [≈ hemiketal to ketal] $R_2C(OR')_2$



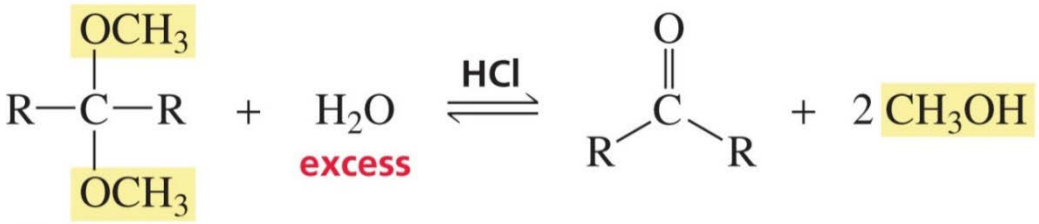




- unstable but more stable than O^+
- can be isolated when H_2O removed

O^+ neutralized by adding another OR

- Acetal can be hydrolyzed back to aldehyde or ketone.
  - in the presence of acid



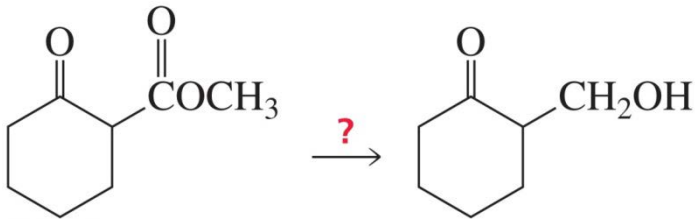
  - reversible
    - for N Nu:, it was <u>not</u> reversible ~ $RN^{+}H_3$

Comparison of mechanisms for

- addition of C or H Nu:
  - RMgX, acetylide, cyanide
  - hydride
- formation of imine, enamine, hydrate, and acetal
  - N or O Nu: adds to C
  - water leaves → forming N^+ or O^+
  - neutralized by
    - losing proton from N^+
    - losing proton from α-C
    - losing proton from O^+
    - losing proton from 2nd-added ROH

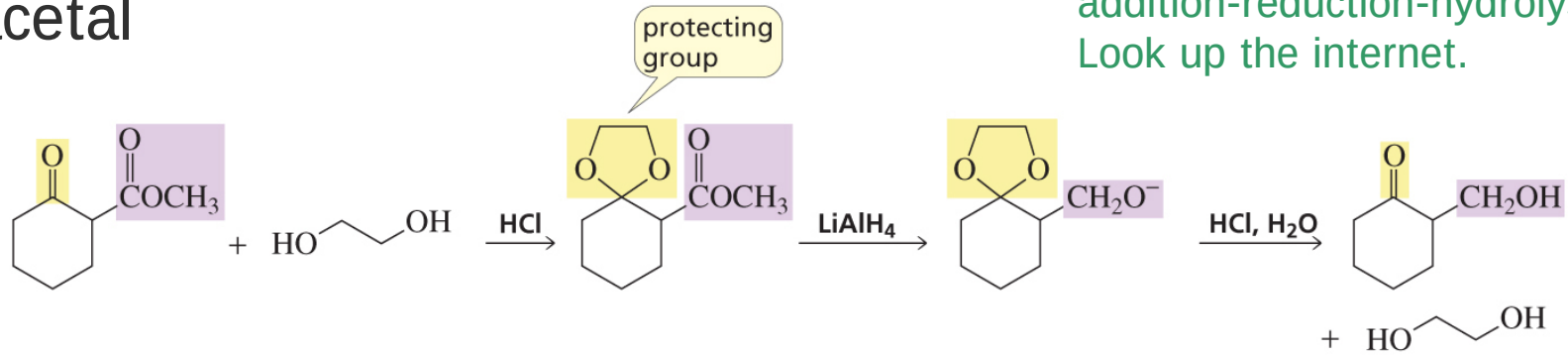
Protecting groups

- what for?



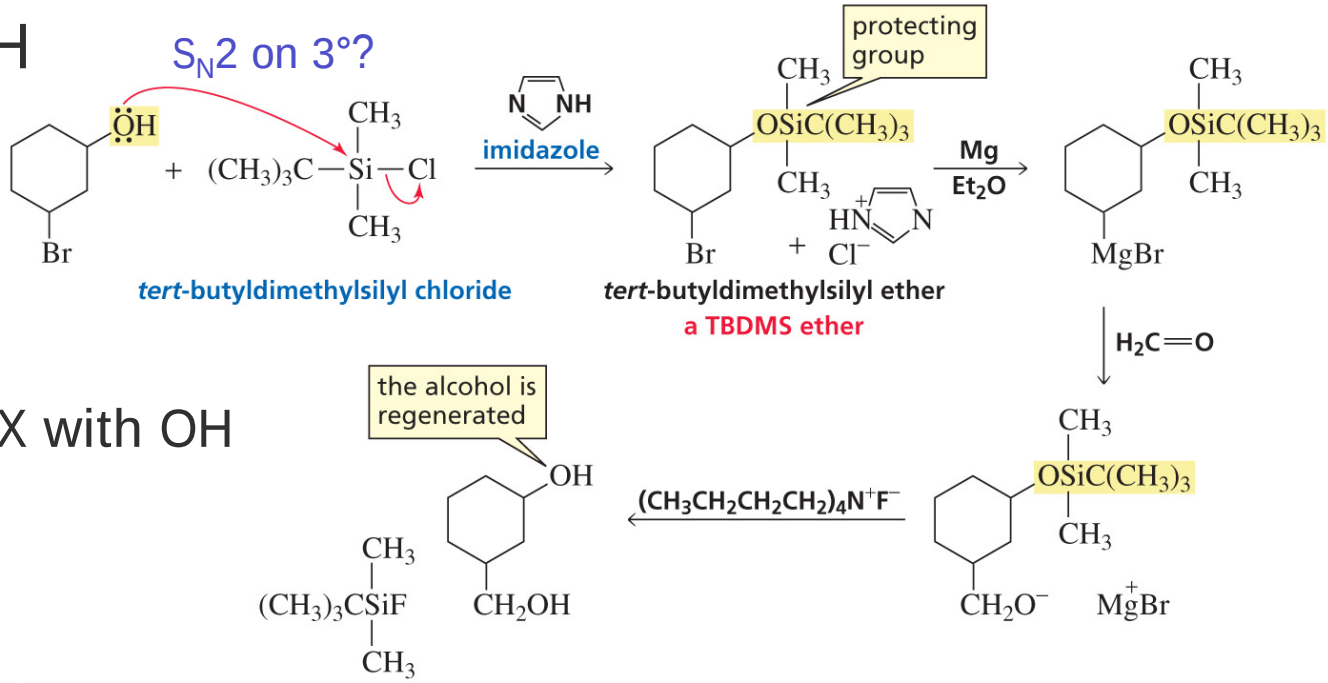
  - reducing ester without reducing (more reactive) keto group
  - Chemoselection cannot afford. ← reactivity, mechanism
- protection-reaction-deprotection
- acetal

mechanisms?
addition-reduction-hydrolysis
Look up the internet.



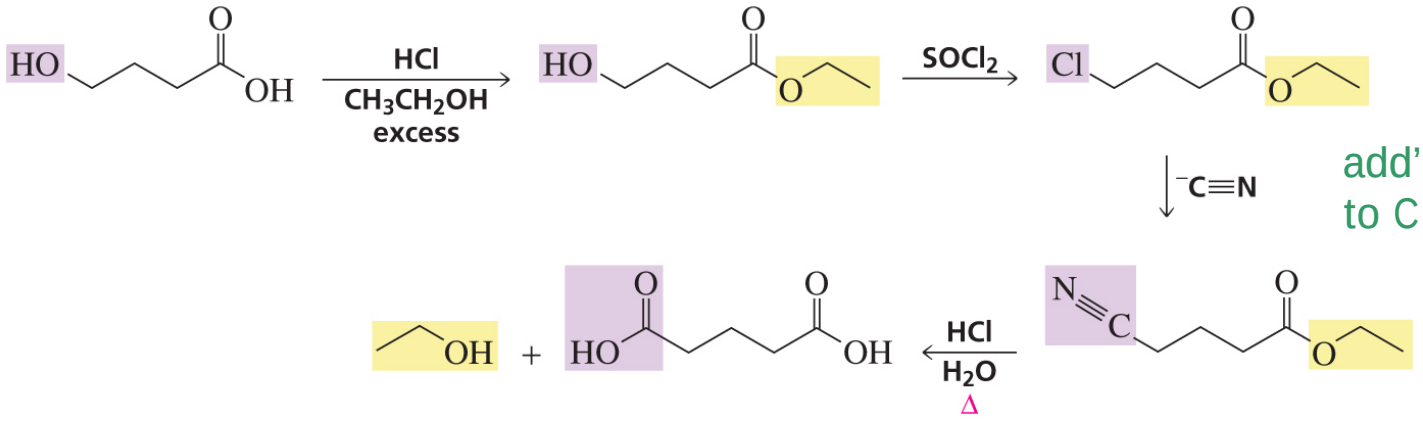
(Cyclic) acetal is a good protecting group.

- protecting OH



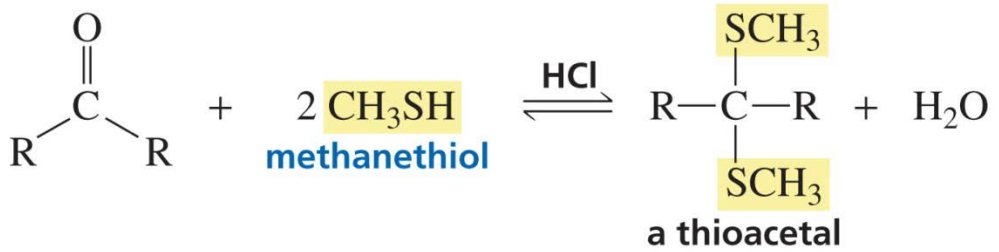
  - why? RMgX with OH

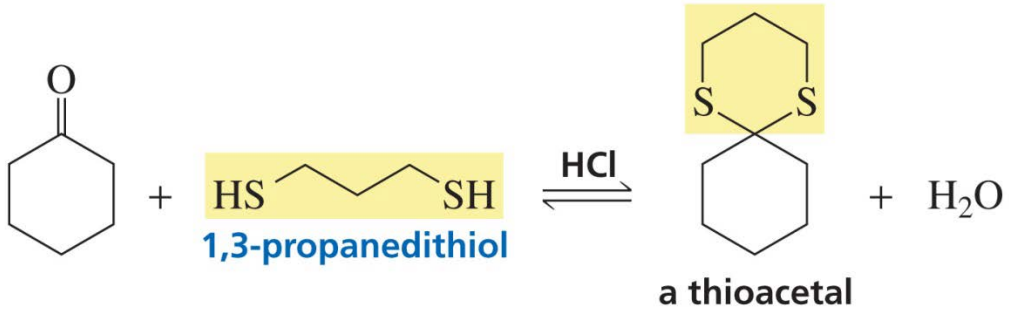
- protecting OH of RCOOH



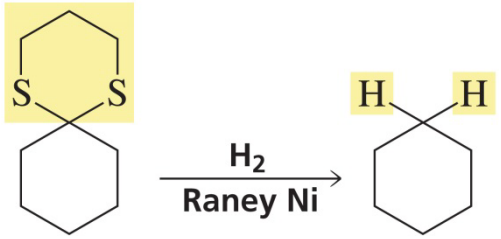
Addition of S Nu:

- to thioacetal





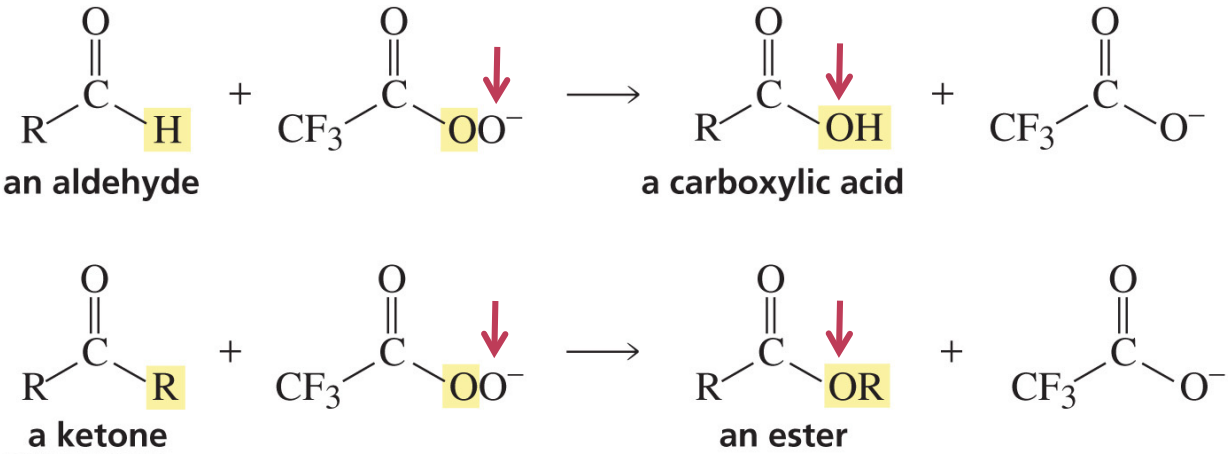
- thioacetal desulfurized



- The sequence enables C=O to CH_2.

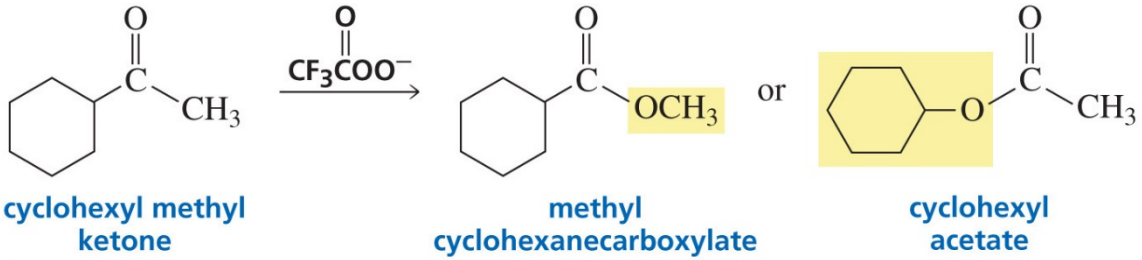
Rxn of A&K with peroxyacid

- Baeyer-Villiger oxidation
  - extra O of peroxyacid inserted betw C(=O) and R [H]

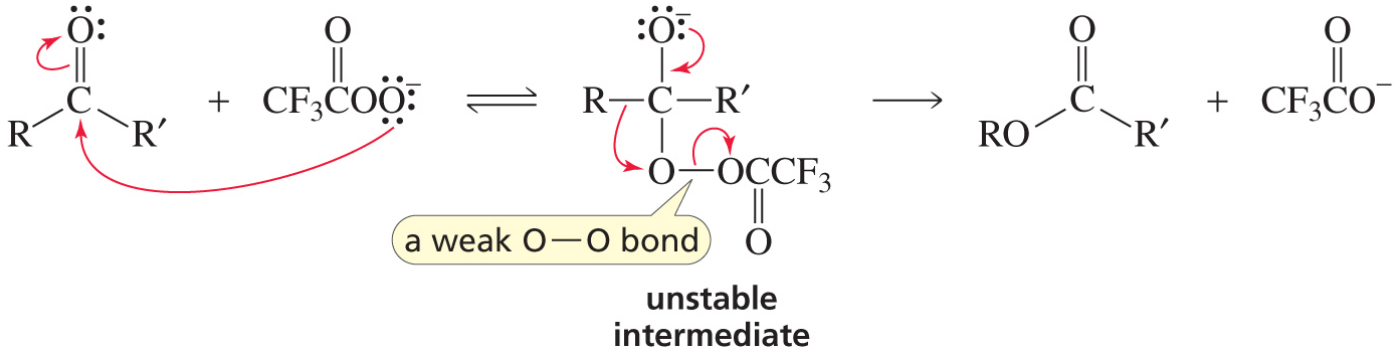


peroxyacid addition to = → epoxide §6.10 p293

- which R? or both? see mechanism.



- mechanism



  - addition of (extra) O:, then
  - breakage of O–O and migration of R

just like 1,2-shift in C^+ rearrangement

    - tendency of shift

most likely to migrate — H > *tert*-alkyl > *sec*-alkyl ~ phenyl > primary alkyl > methyl — least likely to migrate

    - Problem 47
    - b. aldehyde always to RCOOH

Wittig rxn

- synthesis of C=C from C=O using ylide
  - ylide
    - comp'd with opposite charges on covalent-bonded adjacent atoms of complete octets
    - usually betw P^+, N^+, S^+ and $C:^-$
    - resonance to 'ylene'
  - Wittig rxn ~ interchange of =O and =C

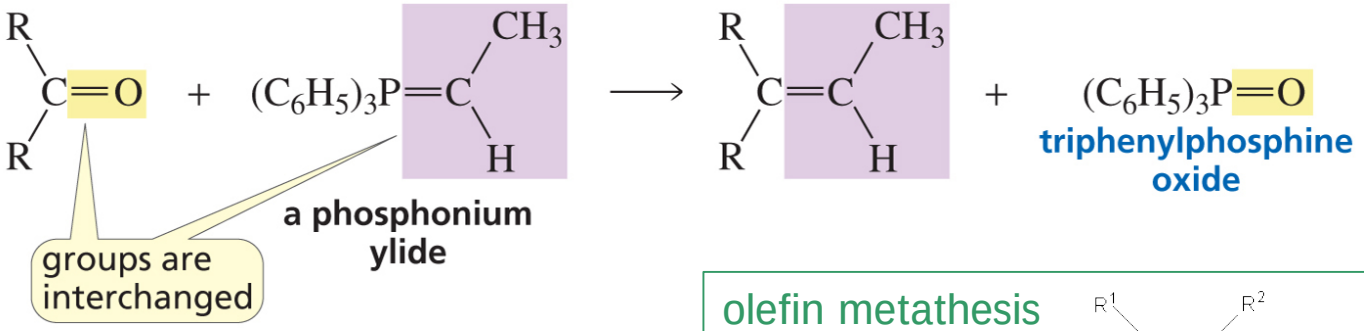
The Nobel Prize in Chemistry 1979

Herbert C. Brown
Prize share: 1/2

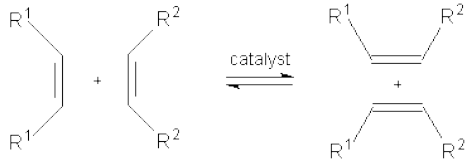
Georg Wittig
Prize share: 1/2

$(C_6H_5)_3\overset{+}{P}—\overset{\cdot\cdot}{\underset{\cdot\cdot}{C}}HR \longleftrightarrow (C_6H_5)_3P{=}CHR$

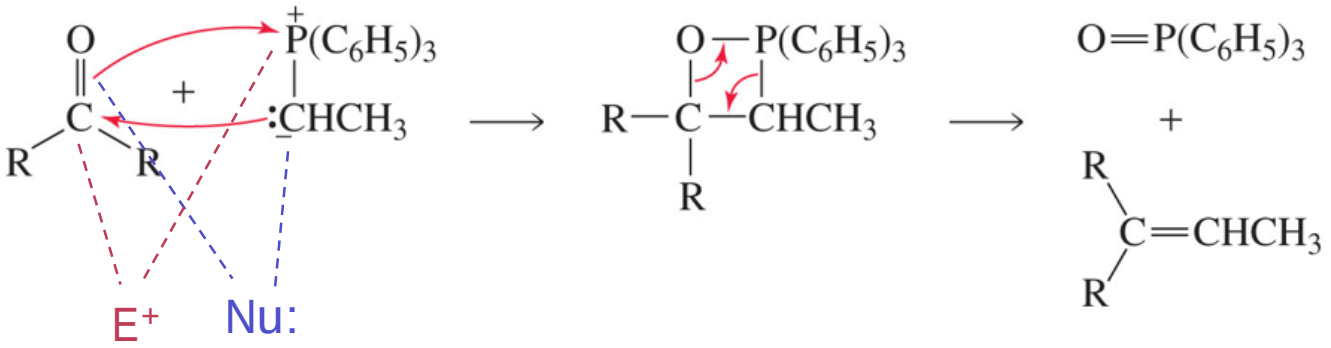
a phosphonium ylide



olefin metathesis
§11.5

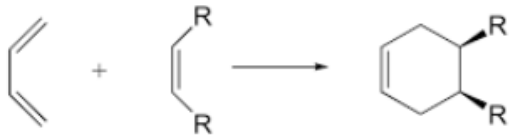


- mechanism ~ [2+2] cycloaddition

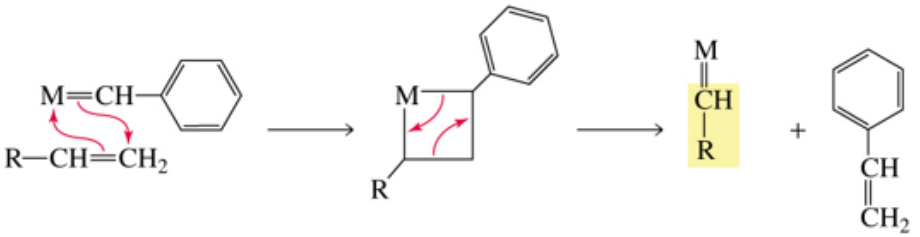


ylide is a C Nu:.

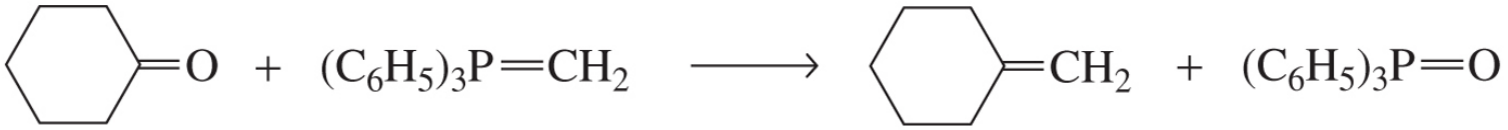
Diels-Alder rxn ~
[4+2] cycloaddition
§8.14



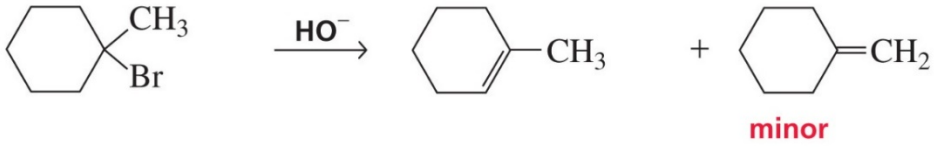
OM ~
[2+2] cycloaddition
§11.5



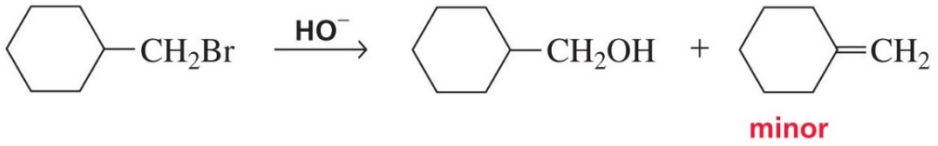
- Wittig rxn is the best way for terminal alkene (w/ $Ph_3P{=}CH_2$).



  - other methods? minor product.

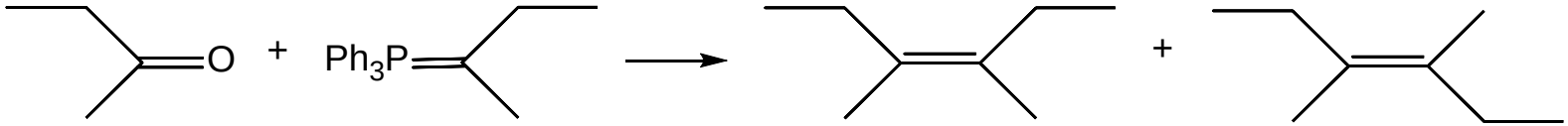


E2, Zaitsev

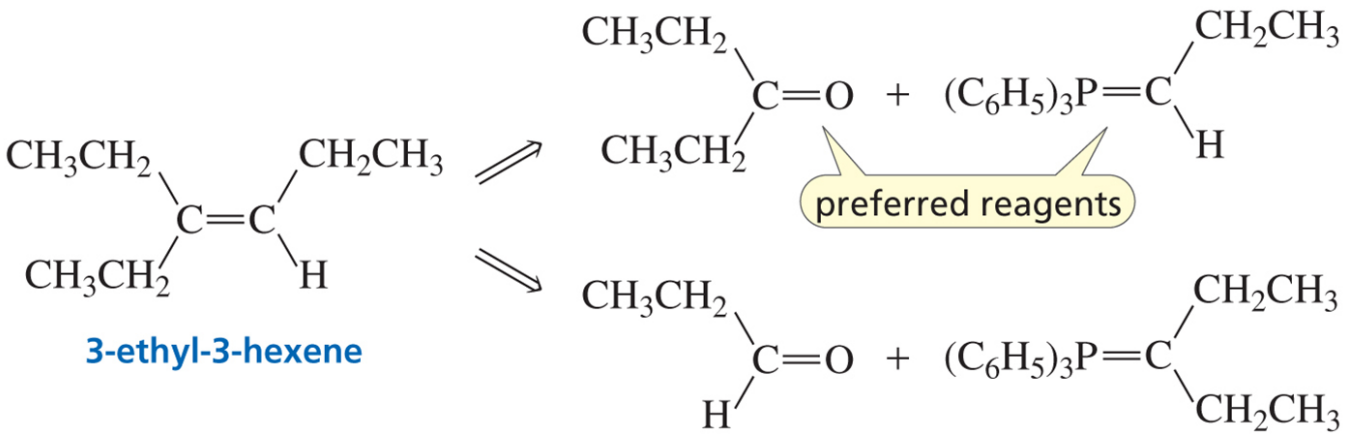


E2 < S_N2

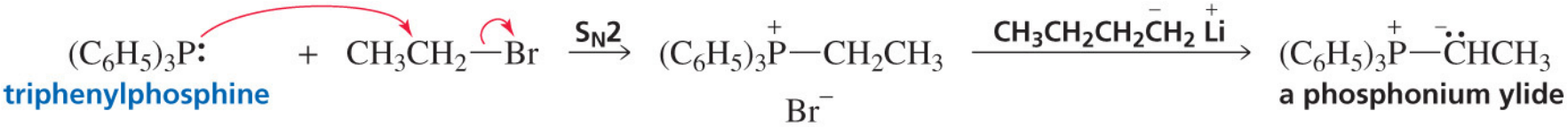
- not stereoselective in internal alkene



- preferred route? ← preferred ylide synthesis



- ylide from S_N2 of RX, followed by – H^+ by BuLi

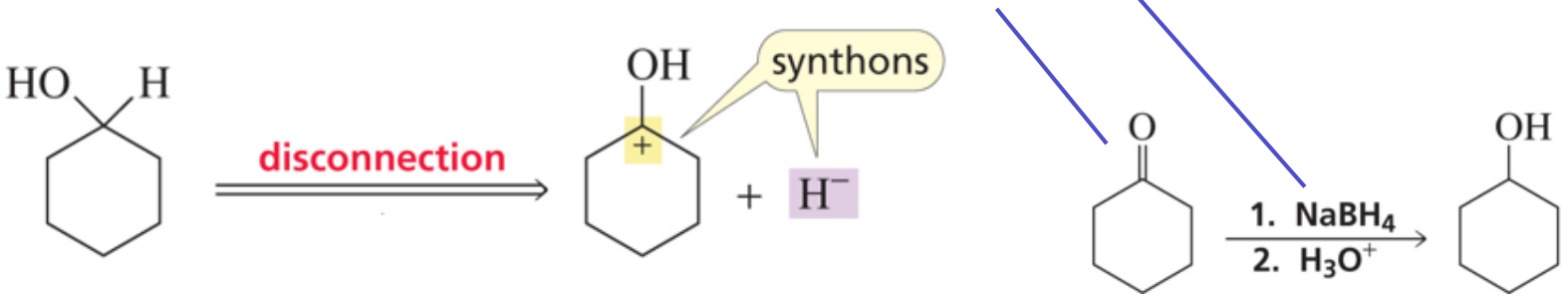


In retrosynthetic analysis...

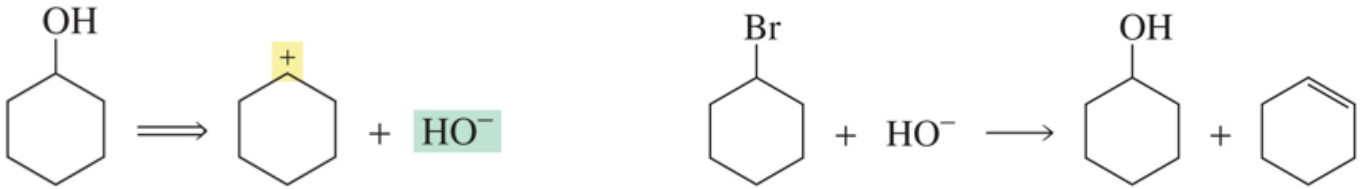
retrosynthetic analysis

target molecule ⟹ Y ⟹ X ⟹ W ⟹ starting materials

- disconnection, synthon, synthetic equivalent

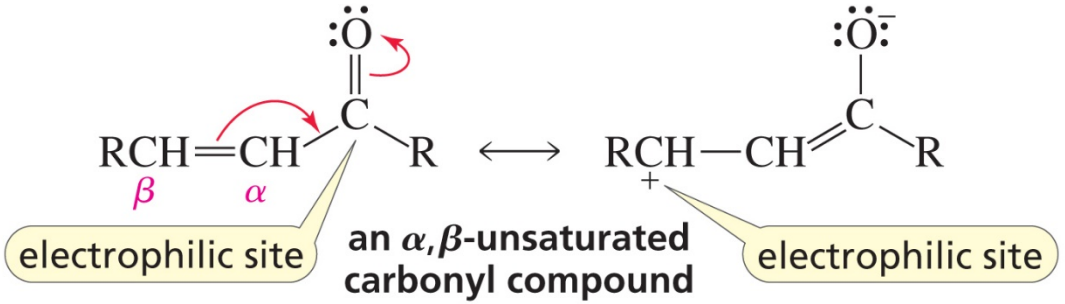


  - synthon ~ (idealized) fragment
  - synthetic equivalent ~ source of synthon (actually used)
- disconnection legitimate?

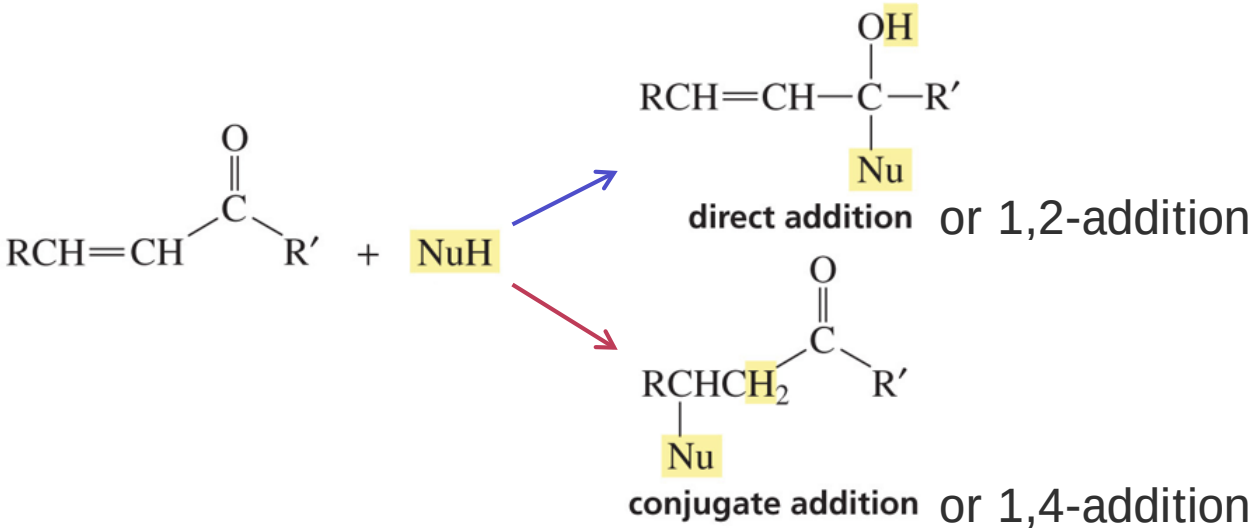


Addition to α,β-unsat'd A&K

- two e-philic C's



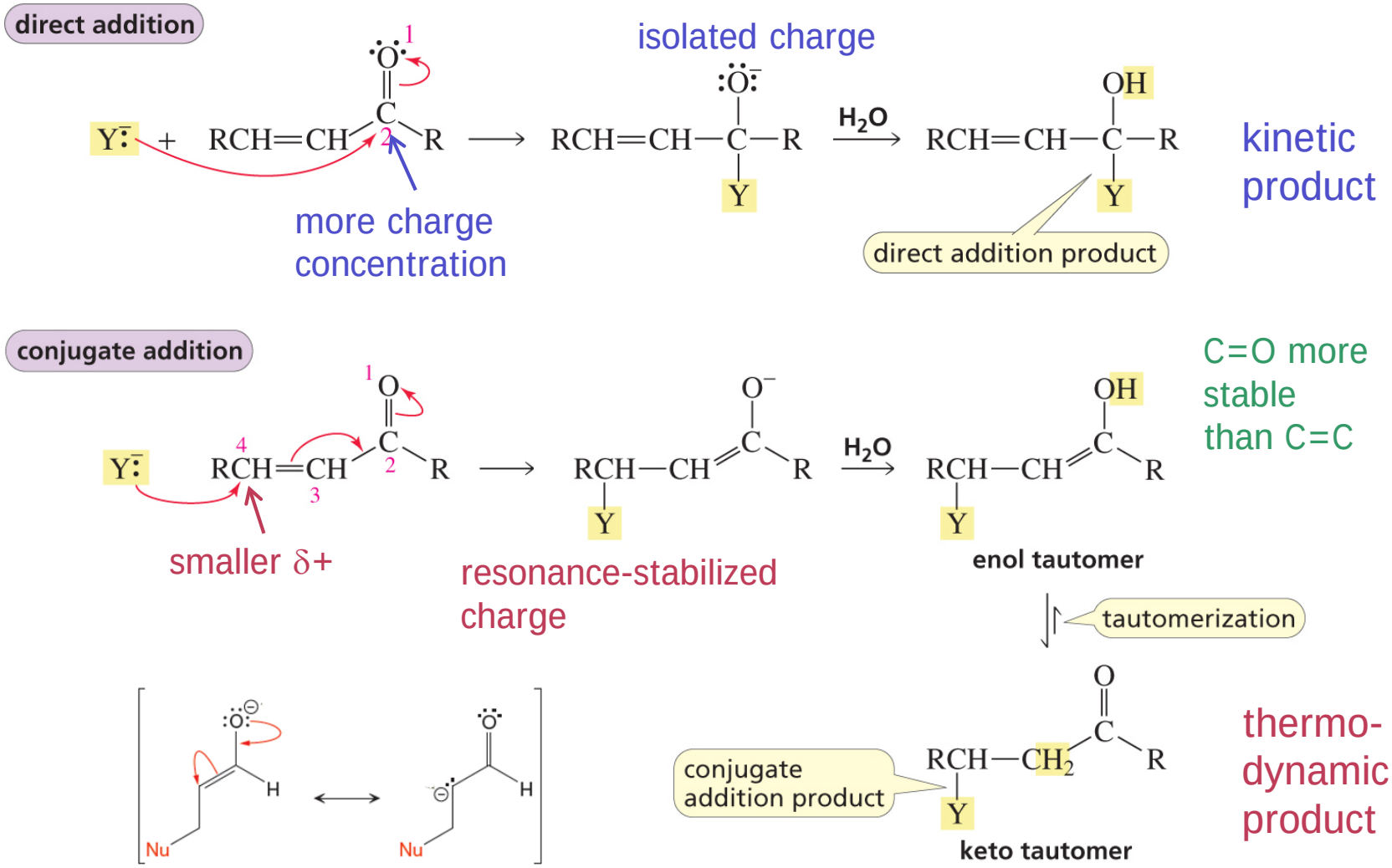
- direct and conjugate addition of Nu:

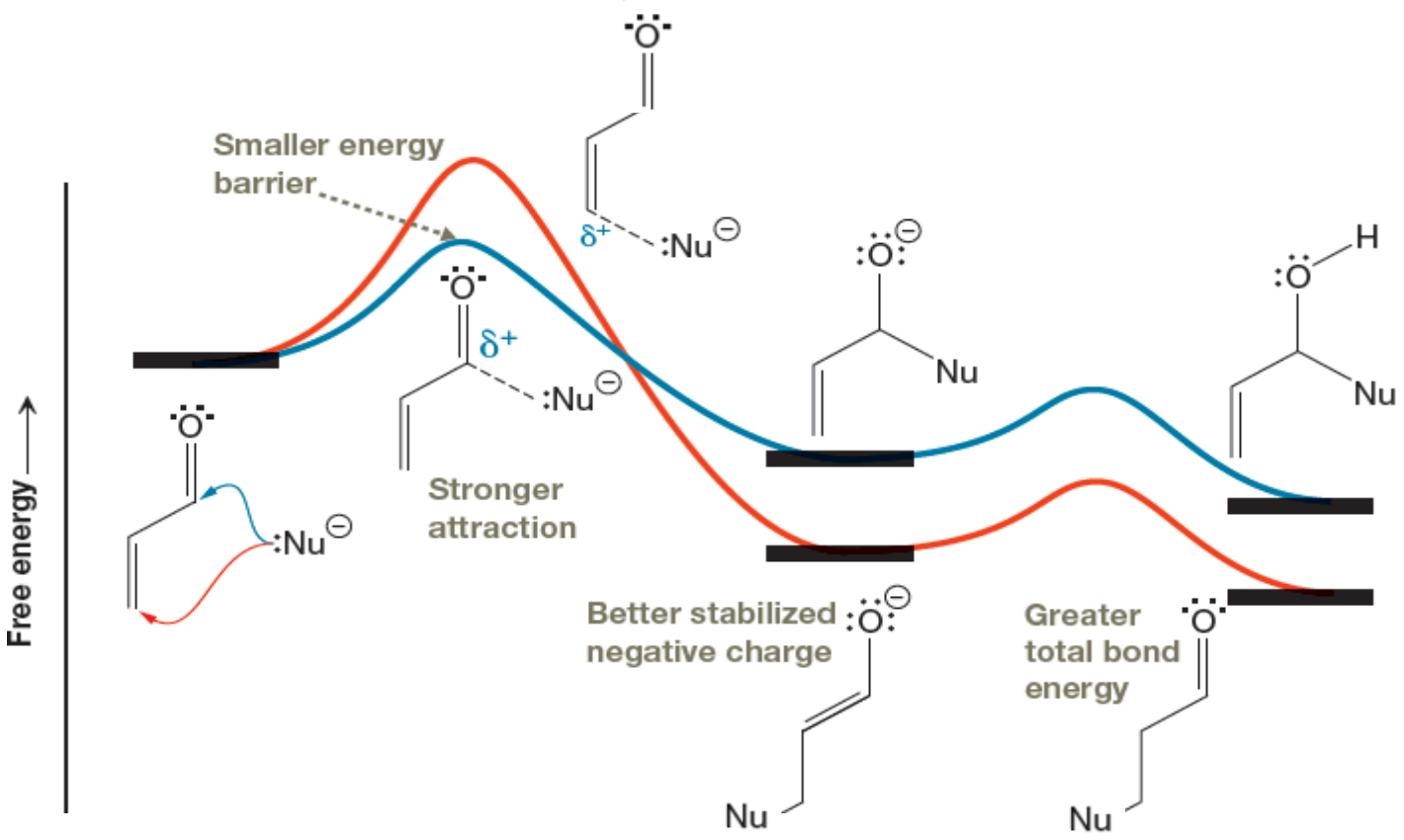


kinetic vs thermodynamic control

See §8.13 1,2- vs 1,4 addition to 1,3-diene

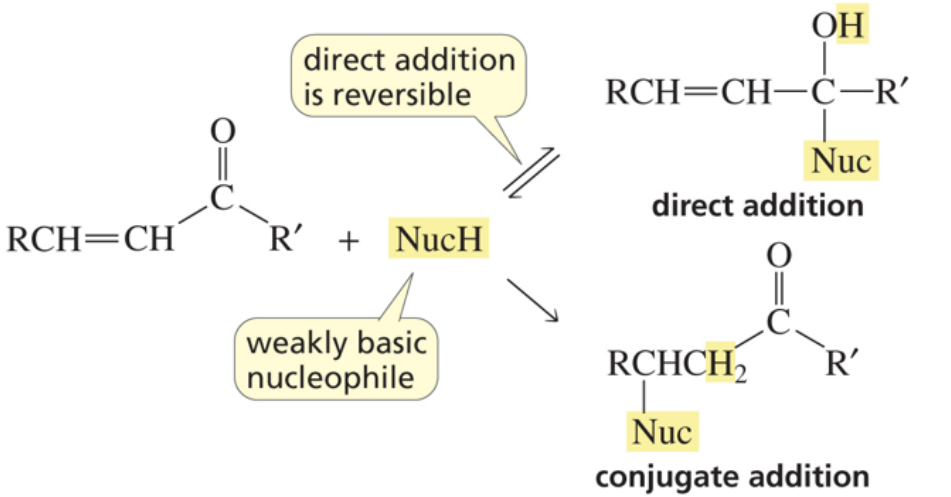
- direct → kinetic and conjugate → thermodynamic



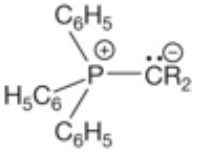
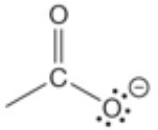
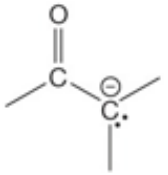


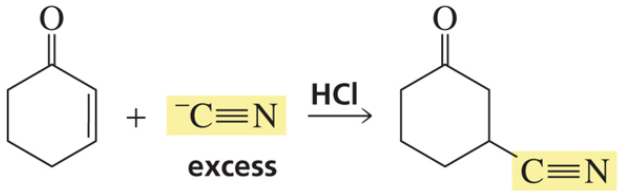
- Kinetic vs thermo control depends on
  - nucleophilicity of Nu:, reactivity of carbonyl,
  - steric effect, and hardness of Nu:.

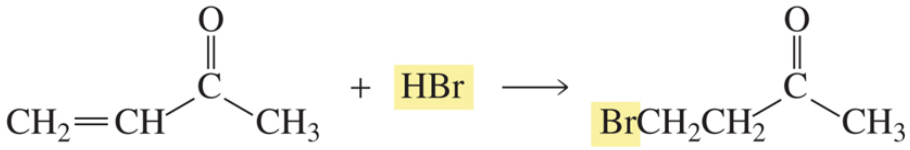
- nucleophilicity of Nu:
  - weak Nu:
    - like N, O, X, S, and C≡N
    - direct add'n reversible → thermo control



higher E
unstable
good L

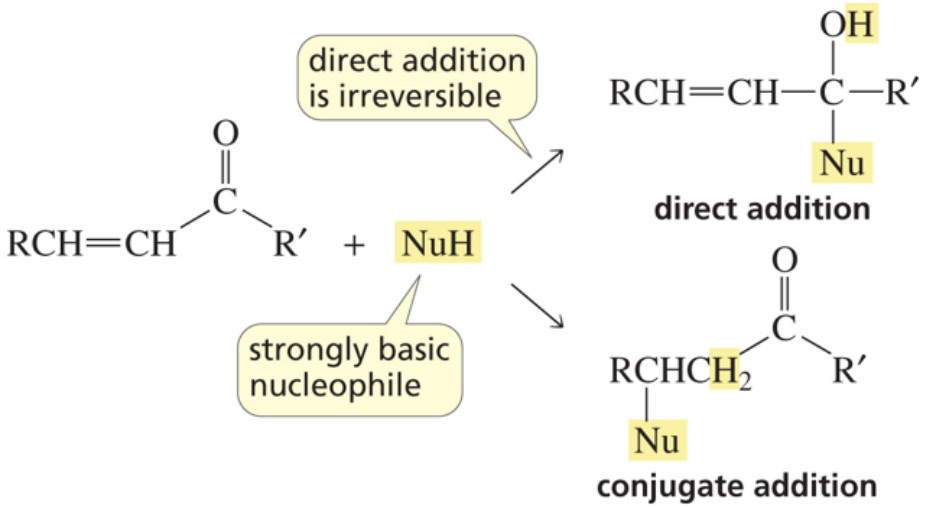
Nucleophiles That Add *Reversibly*	Nucleophiles That Add *Irreversibly*
$HO^{\ominus}$, $RO^{\ominus}$	R—MgBr ($R^{\ominus}$)
$H_2N^{\ominus}$, $R_2N^{\ominus}$	R—Li ($R^{\ominus}$)
$Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$	
	$LiAlH_4$ ($H^{\ominus}$)
$N{\equiv}C^{\ominus}$	$NaBH_4$ ($H^{\ominus}$)
	$^{-}$:C≡CR



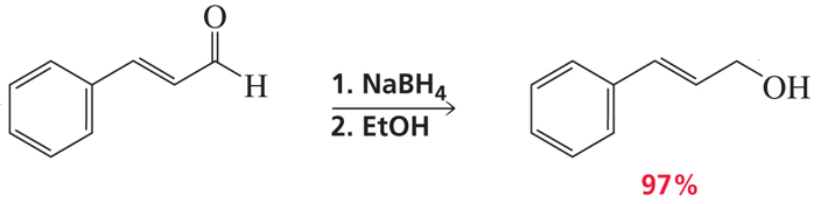


Markovnikov?

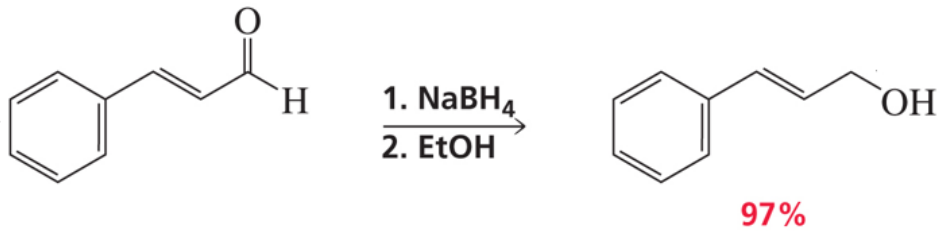
- nucleophilicity of Nu (cont'd)
  - strong Nu:
    - like C and H Nu:
    - both irreversible → kinetic control

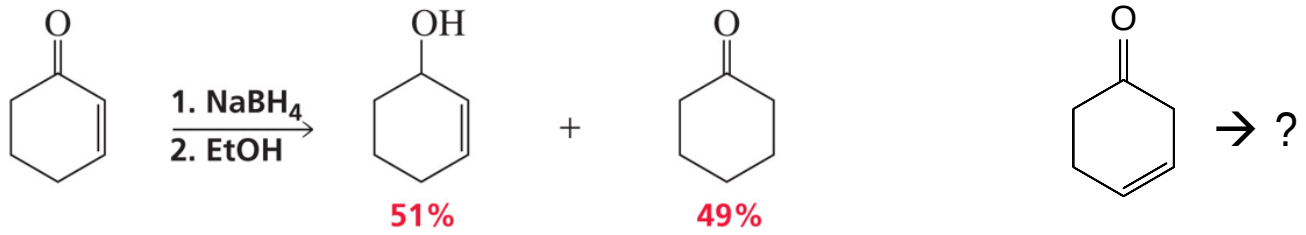


Nu: does not leave.



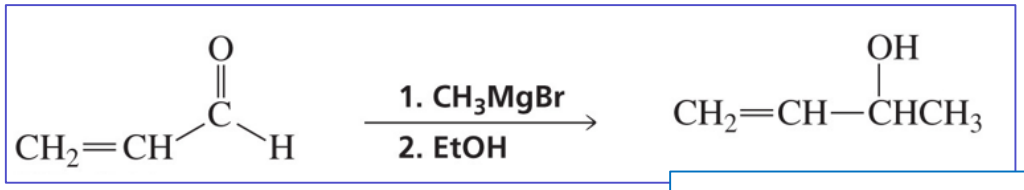
- reactivity of C=O comp'd



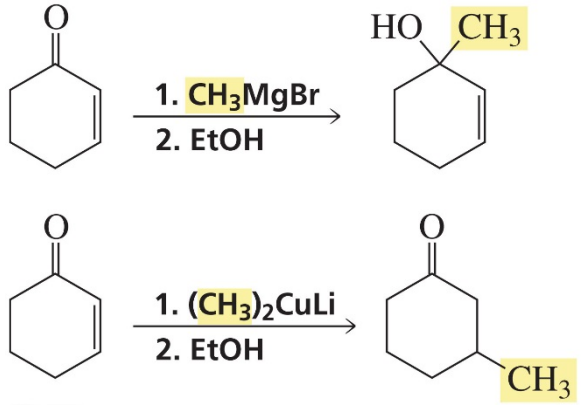


  - (Carbonyl C of) ketone is less reactive.

- steric effect



- hardness of Nu:
  - hard Nu: ~ small with more charge [polarized]

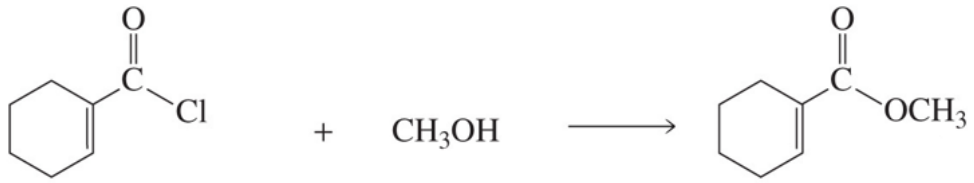


EN(Mg) = 1.2
EN(Cu) = 1.8

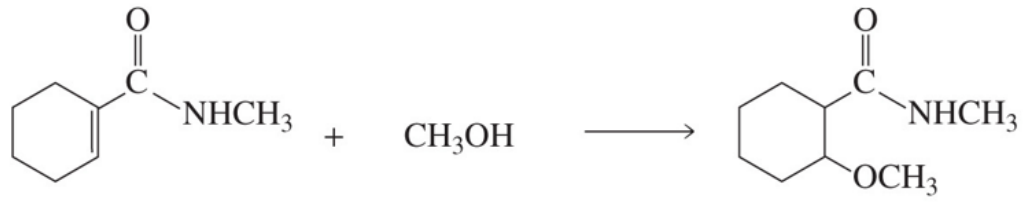
Is R of Gilman reagent a Nu:? maybe yes and maybe no

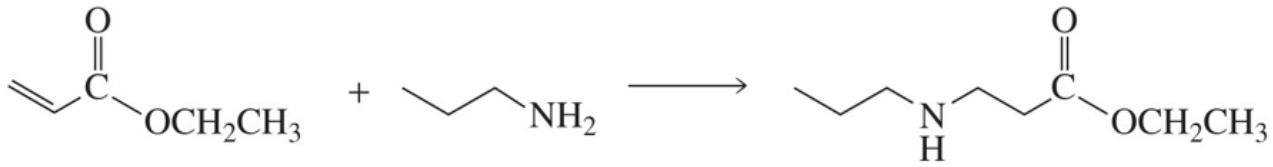
Addition to α,β-unsat'd RCOOH deriv *Ch 16 #60*

- either nu-philic add'n-elimin'n or conjugate add'n
- (reactive) RCOX (and AA) ~ add'n-elimin'n
  - no direct add'n ← good leaving group

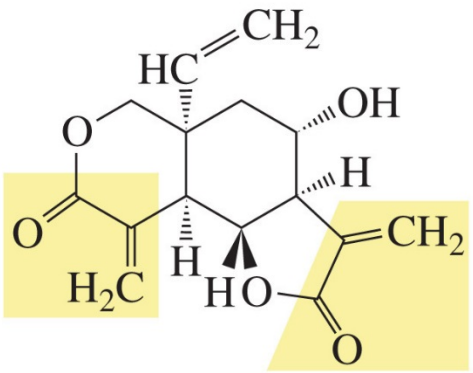


- (less reactive) others ~ conj add'n

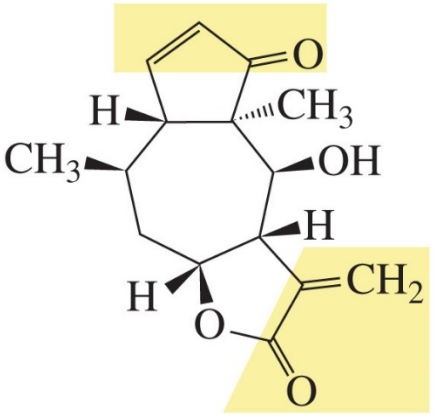




- anticancer drug



vernolepin



helenalin