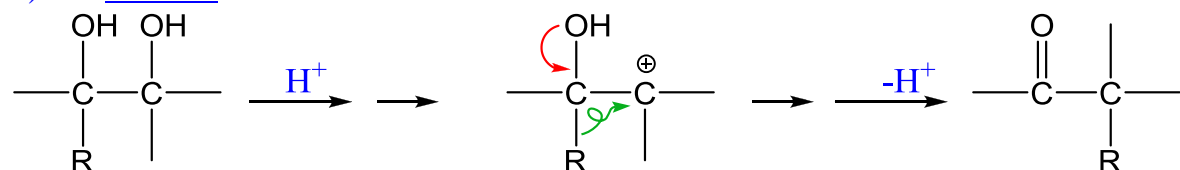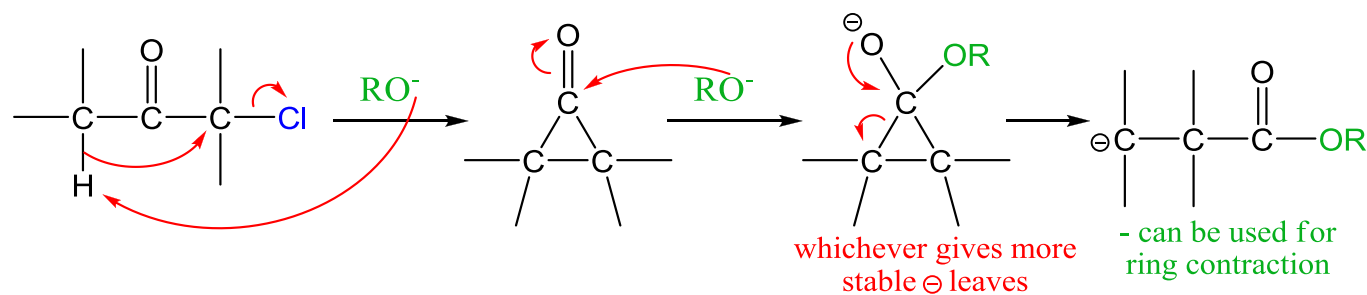Overheads: - Today's Outline
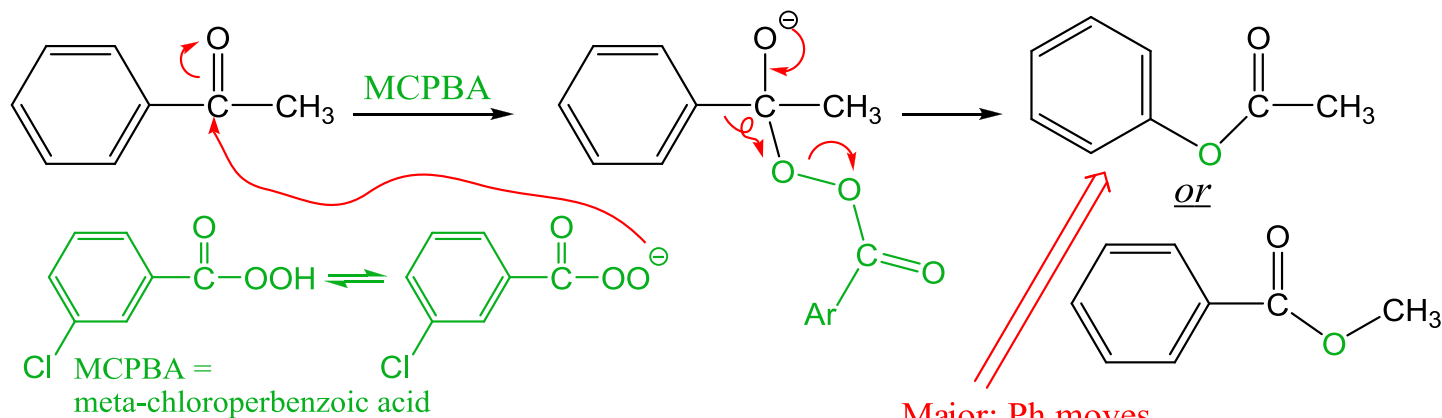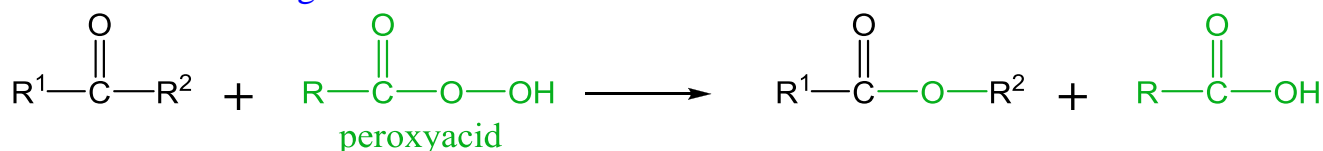
Recap Thursday: Rearrangements

1)   Pinacol

a)   OH leaves to give most stable C+
b)   H > aryl > alkyl (3° > 2° > 1°) ⇨ neighboring group participation

semi-pinacol: $R\text{-}N_2^+$ = LG   → can be used for ring expansion

2)   Favorskii

whichever gives more stable ⊖ leaves

- can be used for ring contraction

3)   Baeyer-Villiger Oxidation

Also involves rearrangement

$$R^1\!-\!\overset{O}{\underset{}{C}}\!-\!R^2 \;+\; R\!-\!\overset{O}{\underset{}{C}}\!-\!O\!-\!OH \longrightarrow R^1\!-\!\overset{O}{\underset{}{C}}\!-\!O\!-\!R^2 \;+\; R\!-\!\overset{O}{\underset{}{C}}\!-\!OH$$

peroxyacid

MCPBA

Cl MCPBA =
   meta-chloroperbenzoic acid

or

Major: Ph moves
more easily than CH_3

Migratory Aptitude (for Baeyer-Villiger)
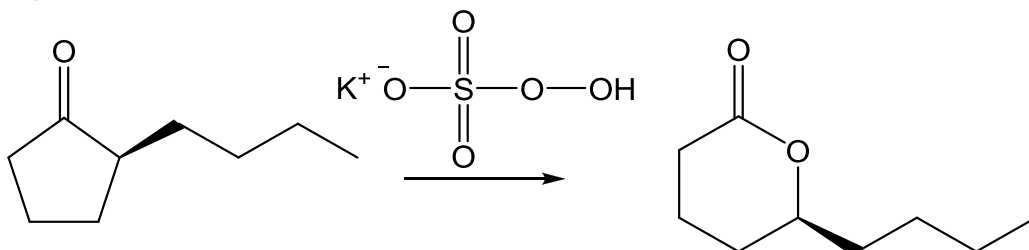   3° > 2° ≈ phenyl > 1° > methyl

Most substituted moves more easily

Good way to <u>oxidize</u> ketone → ester

MCPBA was most common reagent, but it is shock-sensitive and raises health concerns, so price ↑, availability ↓

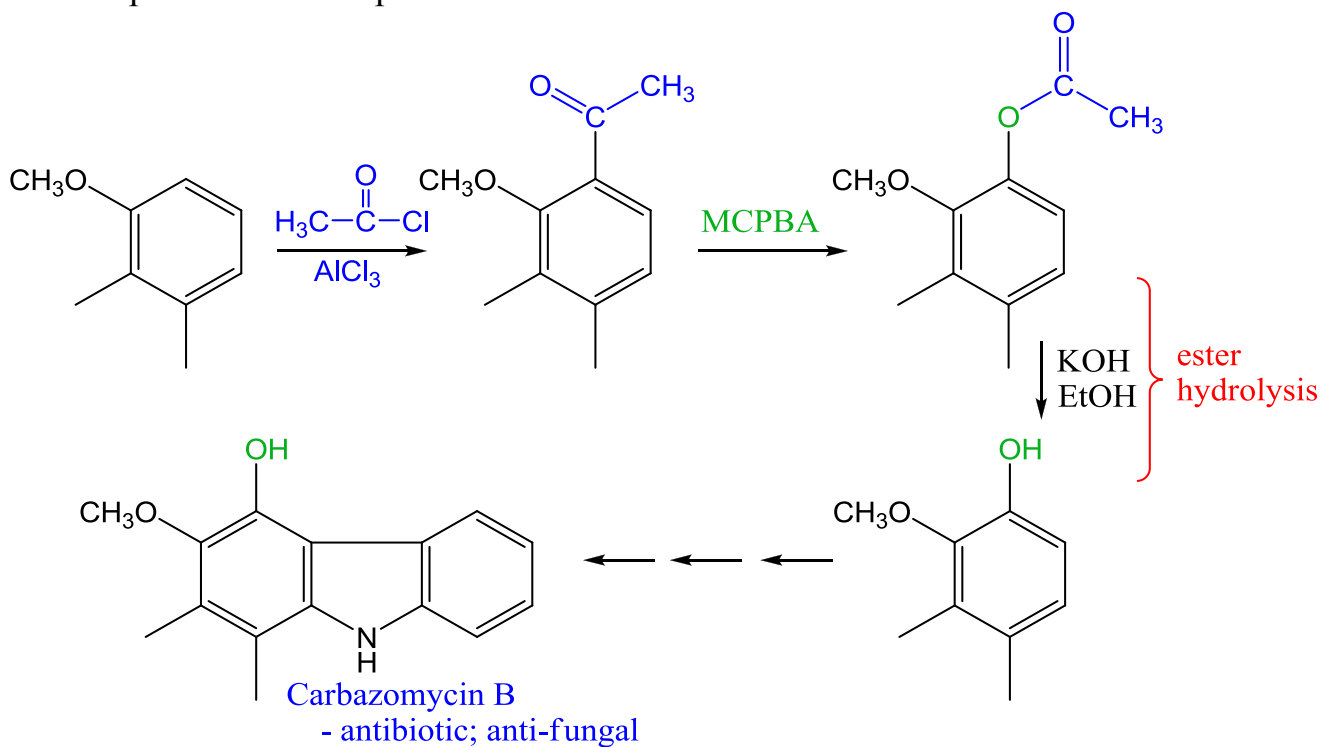Can also use Oxone™ = $KHSO_5$
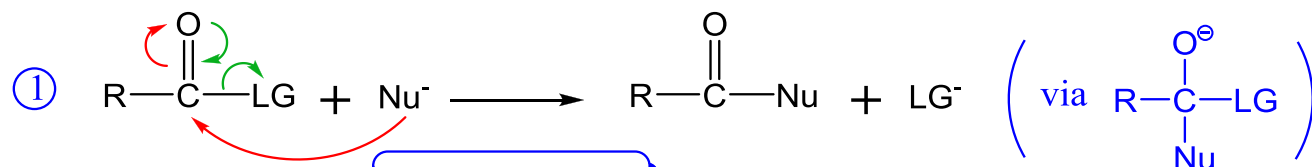
e.g

- most sub. "R" moves

- since concerted, stereochemistry of migrating center is <u>retained</u> (stays the same)
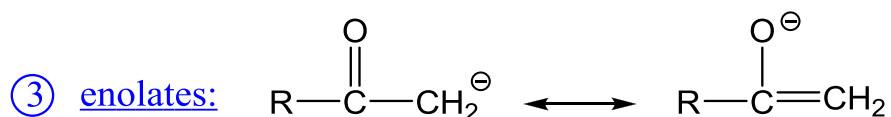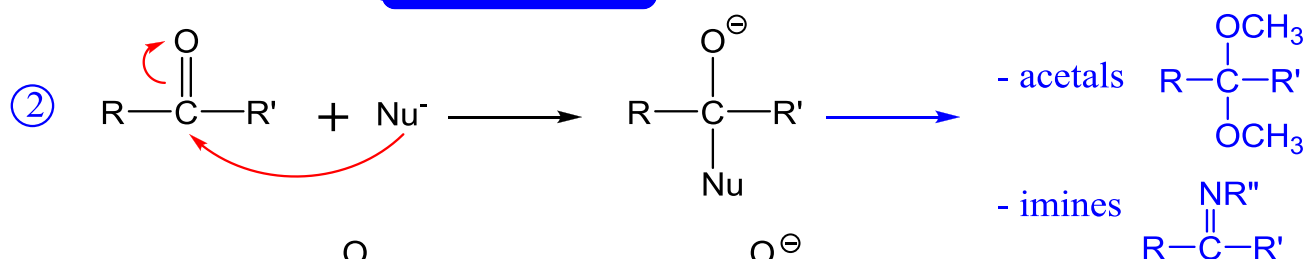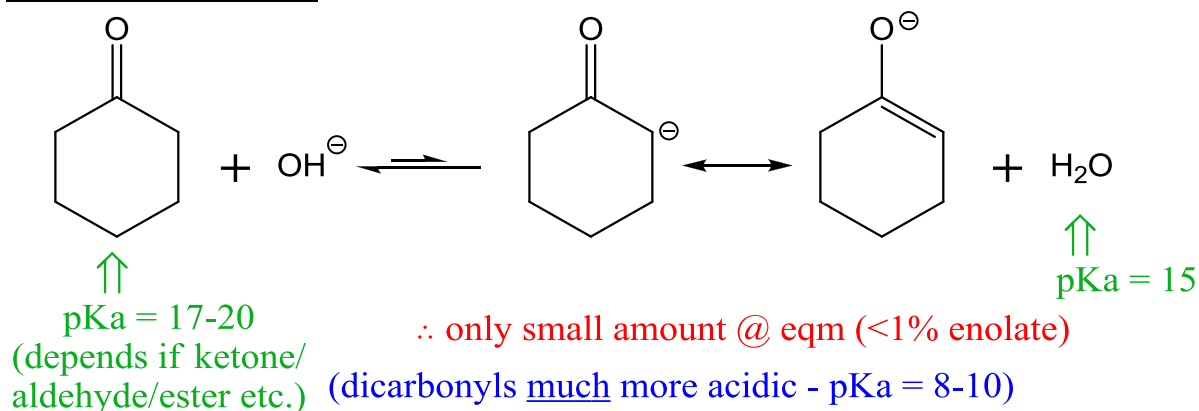
an example from Nola's past: ☺

MCPBA

KOH
EtOH } ester hydrolysis

Carbazomycin B
- antibiotic; anti-fungal

Carbonyl Reactions

① $R-C(=O)-LG$ + Nu^- ⟶ $R-C(=O)-Nu$ + LG^- (via $R-\underset{Nu}{\overset{O^{\ominus}}{\underset{|}{C}}}-LG$)

shortcut used to combine 2 steps

② $R-C(=O)-R'$ + Nu^- ⟶ $R-\underset{Nu}{\overset{O^{\ominus}}{\underset{|}{C}}}-R'$

- acetals $R-\underset{OCH_3}{\overset{OCH_3}{\underset{|}{C}}}-R'$

- imines $R-\overset{NR''}{\underset{\|}{C}}-R'$

③ <u>enolates:</u> $R-\underset{}{\overset{O}{\underset{\|}{C}}}-CH_2^{\ominus}$ ⟷ $R-\overset{O^{\ominus}}{\underset{\|}{C}}=CH_2$

More about Enolates

$+ OH^{\ominus}$ ⇌ ⟷ $+ H_2O$

pKa = 17-20
(depends if ketone/
aldehyde/ester etc.)

∴ only small amount @ eqm (<1% enolate)

(dicarbonyls <u>much</u> more acidic - pKa = 8-10)

pKa = 15

→ to deprotonate <u>completely</u> need stronger base

e.g. $\overset{}{N}-H$ ⟶ $N^{\ominus}$ ∴ <u>much</u> stronger base
   - gives 100% enolate

pKa ~ 35
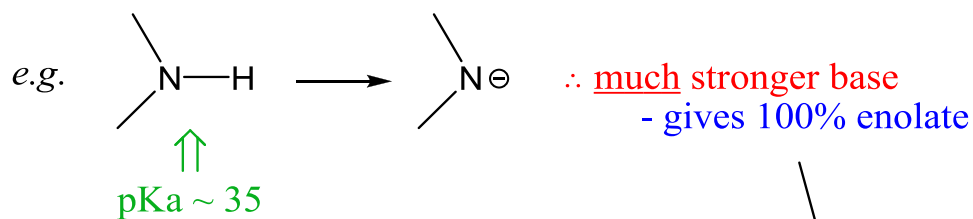
<u>LDA</u> - lithium diisopropylamide = $N^{\ominus} Li^{\oplus}$

amide = $^{\ominus}NR_2$

(not $H_2N-\overset{O}{\underset{\|}{C}}-R$)

bulky R groups
∴ not good Nu^- but <u>great</u> base

R_2NH + BuLi ⟸ pKa ~ 50!
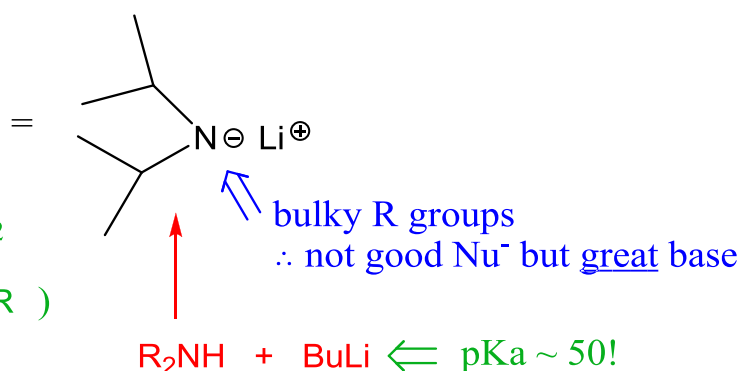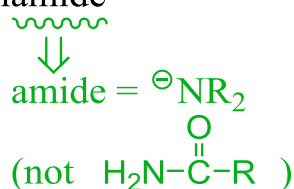
Alkylation of Enolates
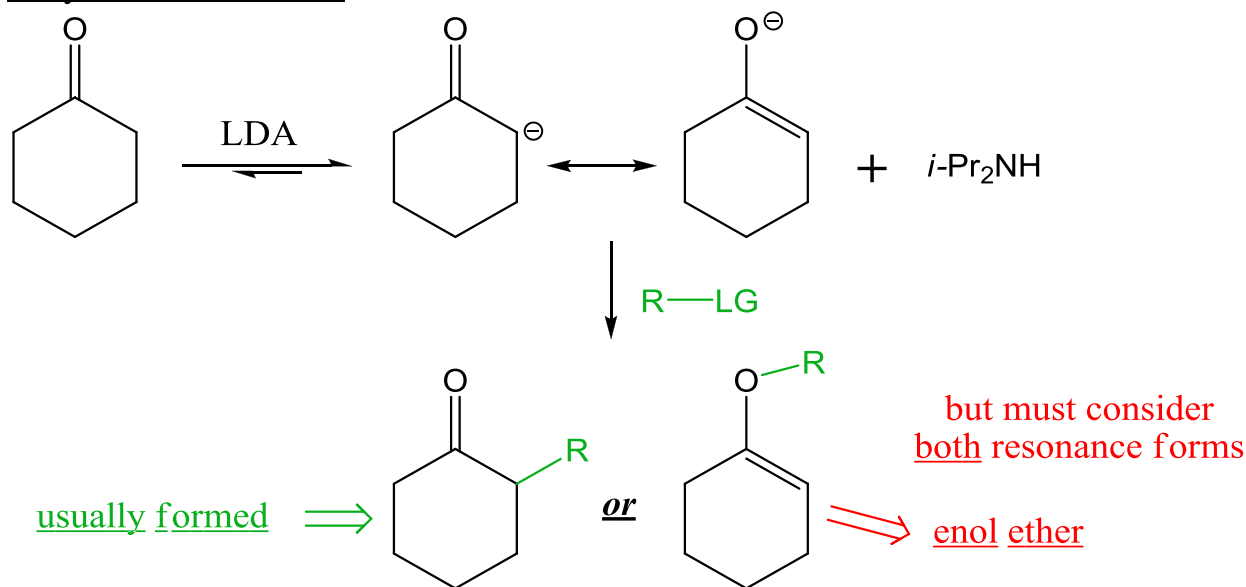
usually formed $\Longrightarrow$ C-alkylation

or

but must consider <u>both</u> resonance forms $\Longrightarrow$ enol ether

O-alkylation

C-alkylation ⇓
favored by enolate close to cation (blocks O)

- Li$^+$ enolate
- less polar solvents (THF, ether)

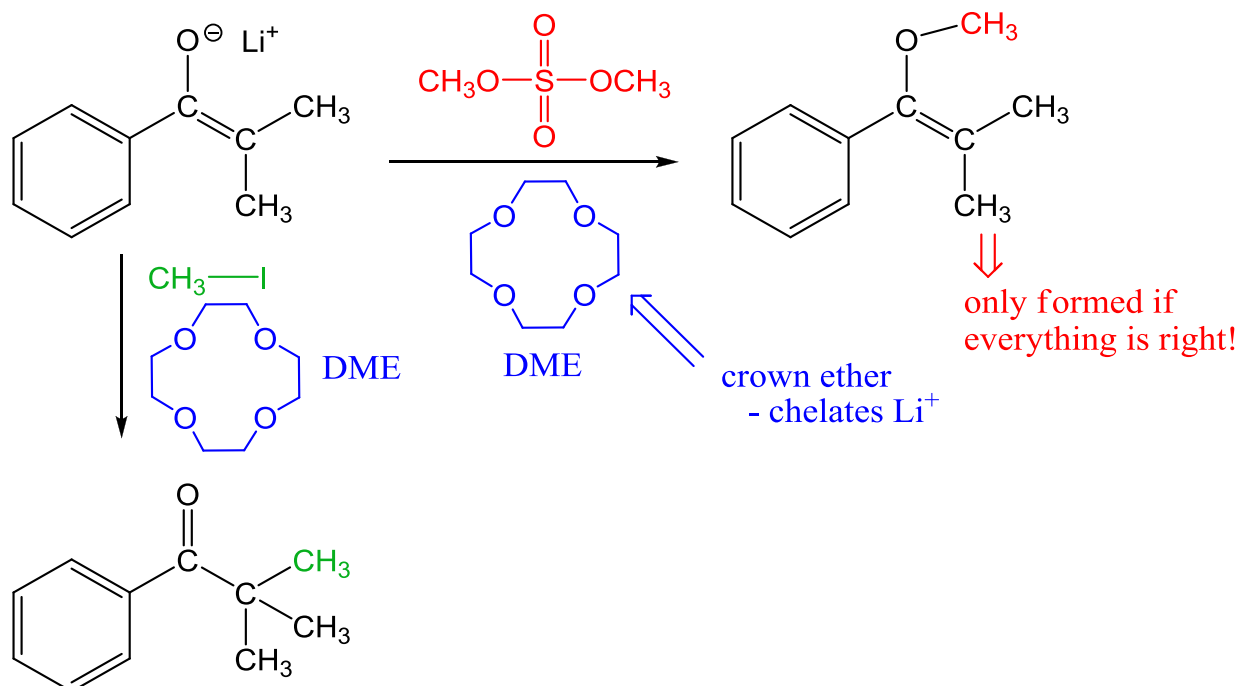- LG = halides <u>always</u> gives <u>C-alkylation</u>

O-alkylation ⇓
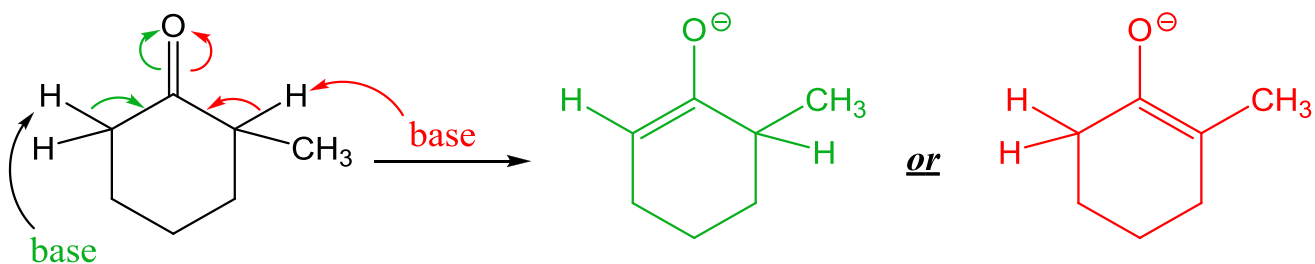favored by "free" enolate (separation of RO$^-$ from M$^+$)

- K$^+$ or Na$^+$ enolate
- <u>very</u> polar solvents
  e.g. DME = H$_3$CO⌒OCH$_3$
  TMEDA = ⌒N⌒N⌒ } chelate the Na$^+$/K$^+$

- LG = sulfonate $^\ominus$O–S(=O)(=O)–R

e.g.

only formed if everything is right!

DME

DME ⟸ crown ether - chelates Li$^+$

CH$_3$—I

What if ketone is unsymmetrical?

more stable enolate?

which H easier to remove?

less hindered
= formed faster

= kinetic enolate

⇓

low temp; bulky base

most sub = most stable

= thermodynamic enolate

⇓

high temp; small base

100% kinetic

$\xrightarrow[\text{-78°C}]{\text{LDA} \atop \text{THF}}$

$\xrightarrow[\text{+25°C}]{\text{KH} \atop \text{THF}}$

100% thermo
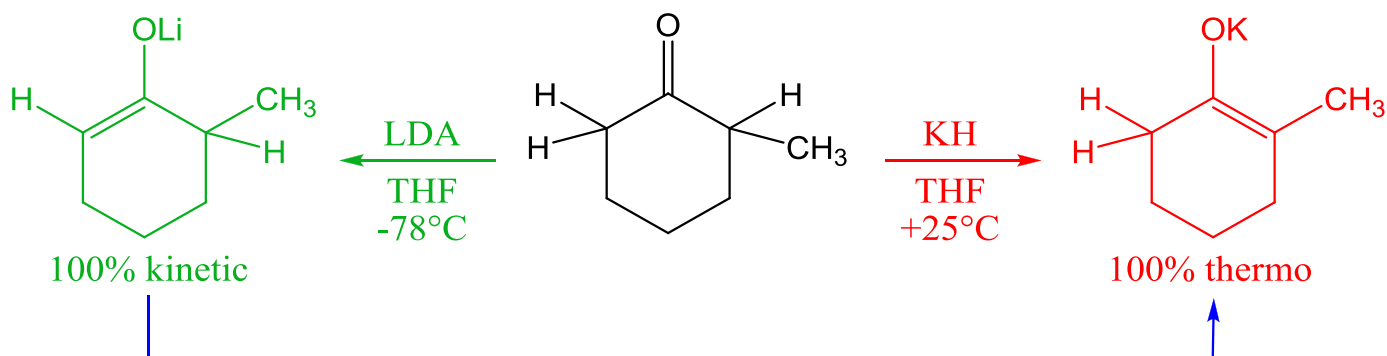
BUT - heat up to 25°C, get equilibrium = thermo!

→ to get kinetic enolate (harder!) need to avoid equilibrium:

- strong, bulky base ⟶ 100% deprotonation (if any ketone left, will get to eq'm)
- cold