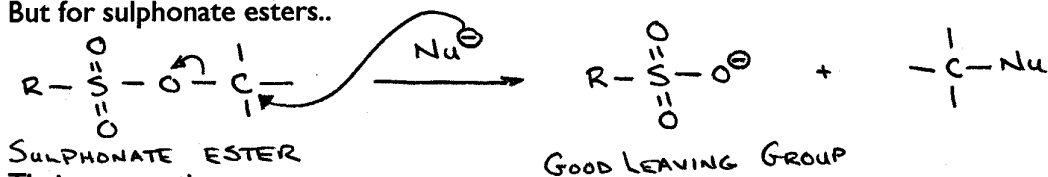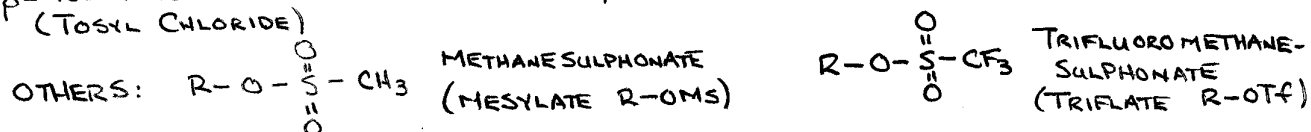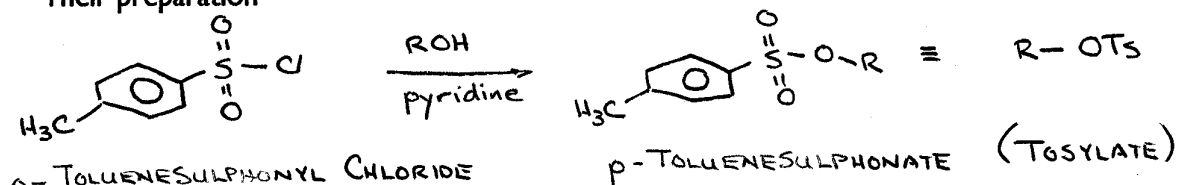There, one gets addition, not S_N2 attack. Attack at sp^3 carbon *is* known, but is much less common. But for sulphonate esters..

SULPHONATE ESTER

GOOD LEAVING GROUP

Their preparation

p-TOLUENESULPHONYL CHLORIDE
(TOSYL CHLORIDE)

p-TOLUENESULPHONATE (TOSYLATE)

OTHERS: $R-O-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-CH_3$ METHANE SULPHONATE
(MESYLATE R-OMS)

$R-O-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-CF_3$ TRIFLUORO METHANE-SULPHONATE
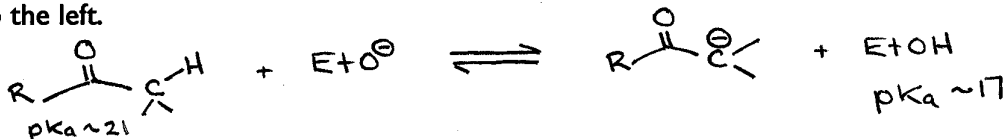(TRIFLATE R-OTf)

These are roughly equivalent to bromide as a leaving group, and they can be used interchangeably.

Nature of Base

   In the deprotonation of a ketone (or ester) by a base like alkoxide, the equilibrium lays well to the left.

As a result, you will have a high concentration of EtO⁻, which is nucleophilic, at any one time. As a result, you have two potential nucleophiles (enolate, ethoxide), and can get ethoxylation of the R-X.
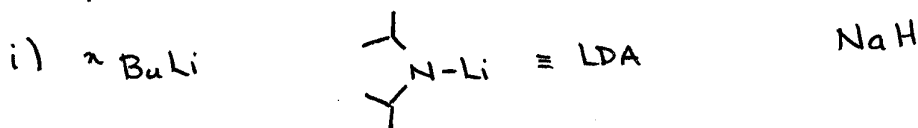
$$R-X \; + \; EtO^{\ominus} \; \longrightarrow \; R-OEt \; + \; X^{\ominus}$$
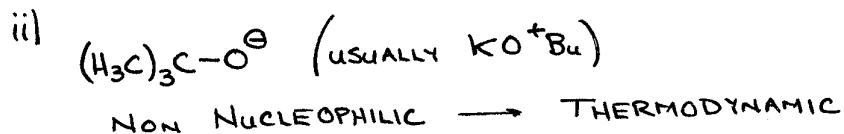
This does not happen with aldol type reactions.
One can do two things to remedy this.
i)   Use a stronger base
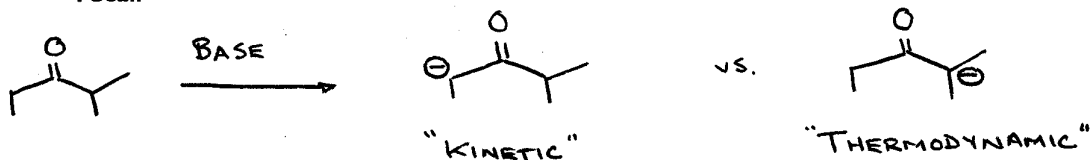ii)   Use a non-nucleophilic base.

The possibilities are

i) $\sim BuLi$ $\underset{\diagdown}{\overset{\diagup}{N}}-Li \equiv LDA$ NaH

   'IRREVERSIBLE' DEPROTONATION IN APROTIC SOLVENTS → KINETIC

ii) $(H_3C)_3C-O^{\ominus}$ (usually KO^+Bu)

   NON NUCLEOPHILIC ⟶ THERMODYNAMIC

Nature of Anion

-recall

"KINETIC"   vs.   "THERMODYNAMIC"
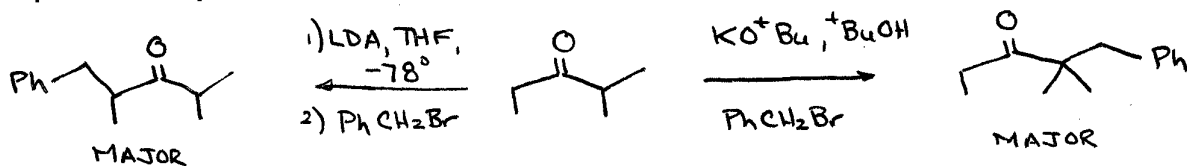
If the reaction is run under kinetic conditions (strong base, no excess ketone, aprotic solvent), the less substituted product is obtained.

If the reaction is run under thermodynamic conditions, the more substituted product will be formed predominantly. **Therefore,**

1) LDA, THF, −78°
2) $Ph CH_2 Br$

MAJOR
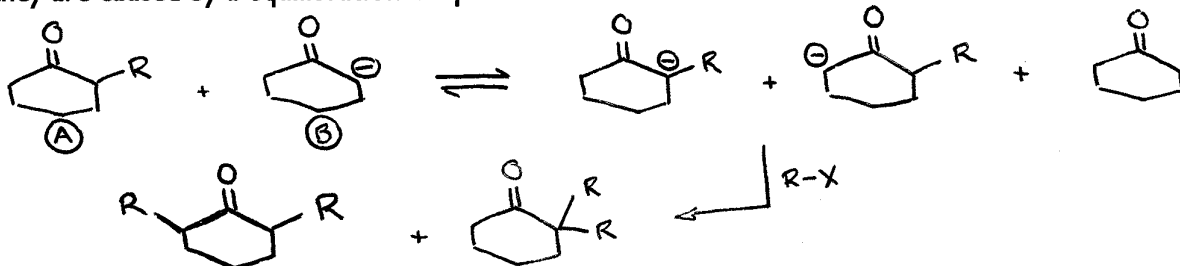
KO^+Bu, ^+BuOH

$PhCH_2Br$

MAJOR

Polyalkylation

If you do a simple alkylation of several enolates (especially the ones derived from cycloalkanones), there is an additional complication.
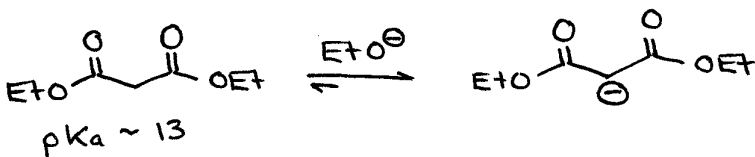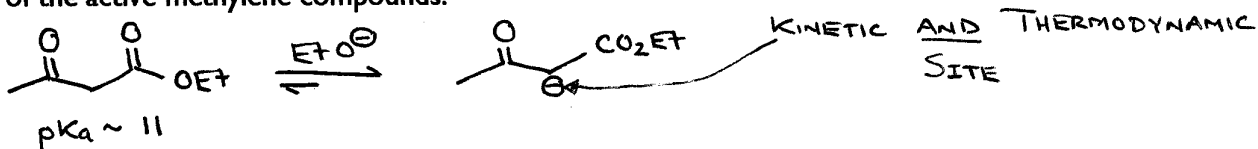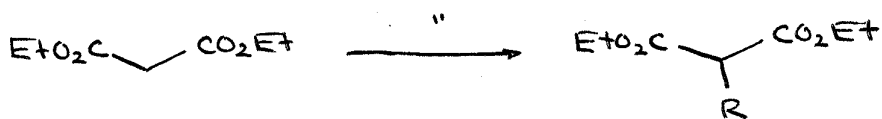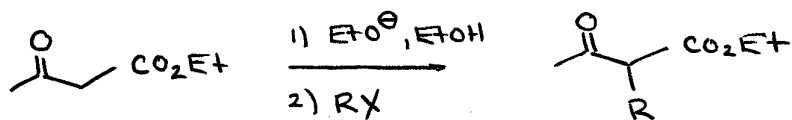

+ MORE
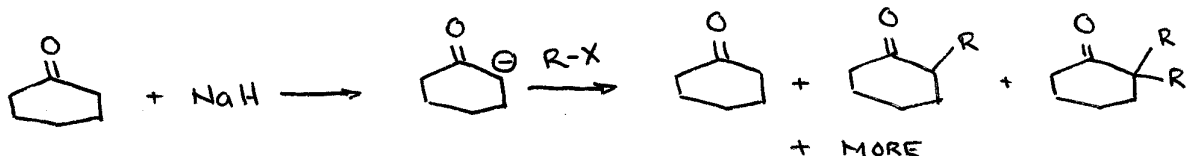
This is called **polyalkylation**. These closely related products are obviously difficult to separate; they are caused by a equilibration of species **A** and **B**.
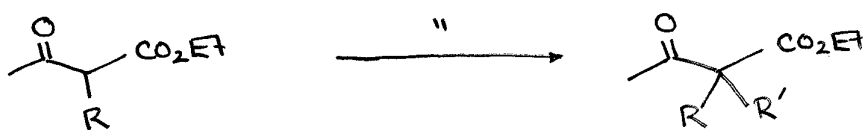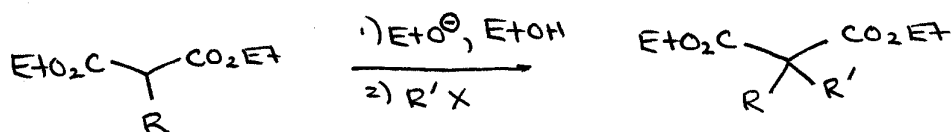

- ALKYLATION SLOW RELATIVE TO PROTON EXCHANGE

Solutions

-One of the most common solutions is to go to active methylene compounds. Alkoxide bases are now strong enough to give essential complete enolate formation, due to the high acidity of the active methylene compounds.
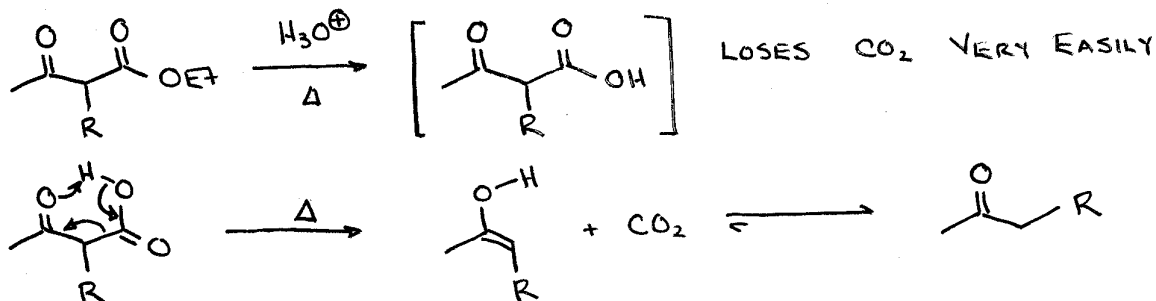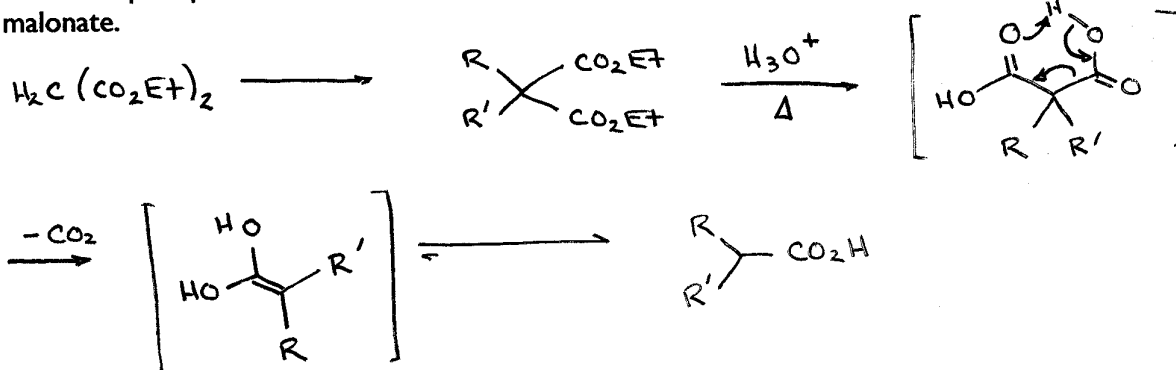

KINETIC AND THERMODYNAMIC SITE

$pKa \sim 11$

$pKa \sim 13$

O
‖
CH₃—C—CH₂—CO₂Et →(1) EtO⁻, EtOH 2) RX)→ $\begin{matrix} O \\ \| \end{matrix}$ CH₃—C—CH(R)—CO₂Et

EtO₂C—CH₂—CO₂Et →(")→ EtO₂C—CH(R)—CO₂Et

NOTE: BOTH CPDS. STILL HAVE VERY ACIDIC PROTONS ∴ CAN REPEAT

EtO₂C—CH(R)—CO₂Et →(1) EtO⁻, EtOH 2) R'X)→ EtO₂C—C(R)(R')—CO₂Et

$\begin{matrix} O \\ \| \end{matrix}$ CH₃—C—CH(R)—CO₂Et →(")→ $\begin{matrix} O \\ \| \end{matrix}$ CH₃—C—C(R)(R')—CO₂Et

The first alkylation is much faster than the 2ⁿᵈ one in these cases, and no sign of polyalkylation can be found. Fortunately, one can now get rid of the extra ester.

$\begin{matrix} O & O \\ \| & \| \end{matrix}$ CH₃—C—CH(R)—C—OEt →($H_3O^⊕$, Δ)→ [$\begin{matrix} O & O \\ \| & \| \end{matrix}$ CH₃—C—CH(R)—C—OH]   LOSES CO_2 VERY EASILY

[six-membered cyclic transition state] →(Δ)→ enol (C=C with O—H) + CO_2 ⇌ $\begin{matrix} O \\ \| \end{matrix}$ CH₃—C—CH₂—R

This 2 step sequence often works much better than the one step procedure. Now using diethyl malonate.

$H_2C(CO_2Et)_2$ → (R)(R')C(CO₂Et)₂ →(H_3O^+, Δ)→ [cyclic: HO—C(R)(R')—C(=O)O···H—O]

→(−CO_2)→ [HO—C(=C(R))—... (R') enol form] ⇌ (R)(R')CH—CO₂H

Looks like the alkylation of CH_3CO_2H. Note, you actually get the _acid_ here; if you want the ester, you must re-esterify it.

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In general, any time you have a product looking like it comes from acetone by alkylation (i.e., a methyl ketone), it is better to go by the acetoacetic ester route. And........

In general, any time you have a product looking like it comes from acetic acid by alkylation, it is better to go by the diethyl malonate route.

Furthermore, in acetoacetic esters, the other methyl group (not towards the ester) also has significant (albeit less) acidity. It can be deprotonated by a second equivalent of a strong base, and this second anionic is even more reactive to alkylation.
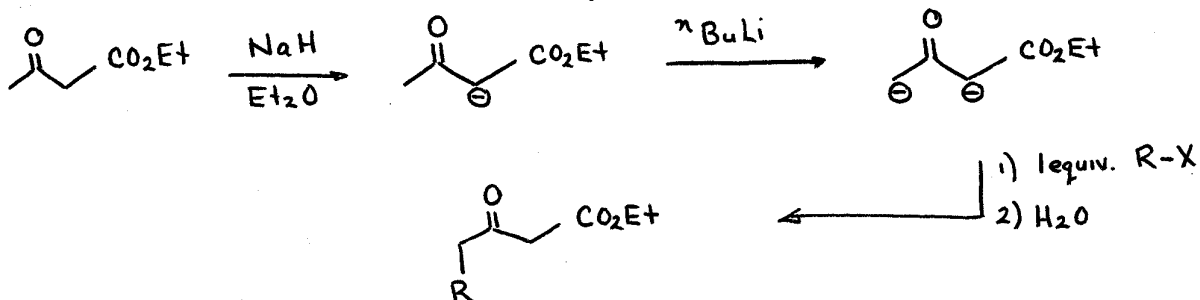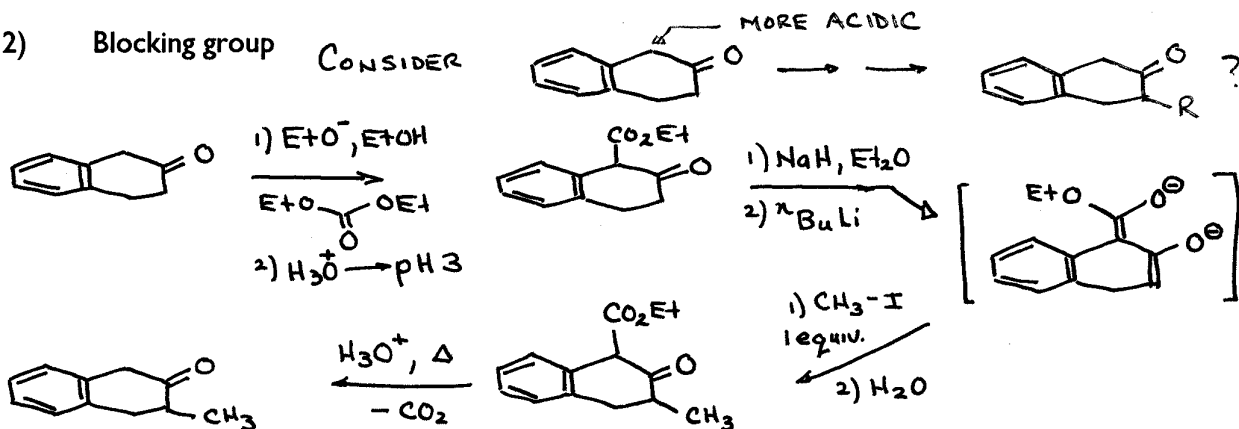

So these a excellent for the regioselective substitution of ketones, these active methylene groups can both be used as an activating and a blocking group.
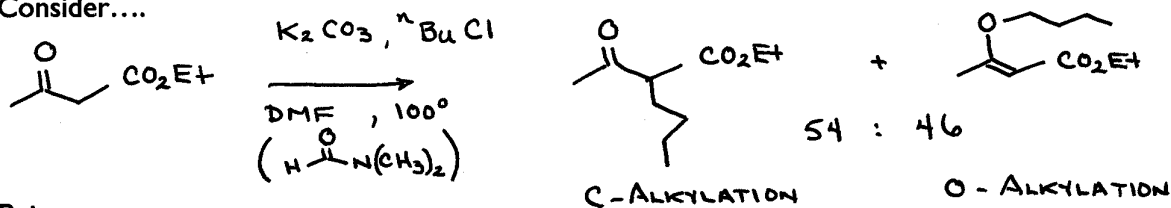
1)   Activating group
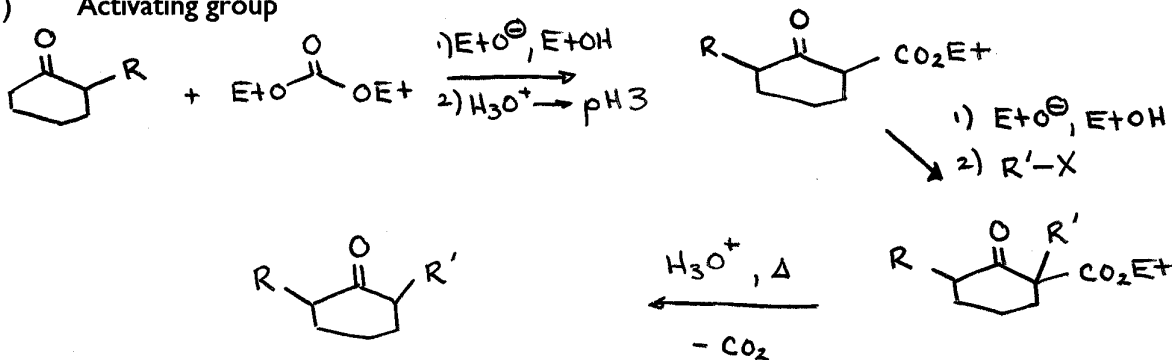
2)   Blocking group

By now, it looks as if β-keto esters are absolutely foolproof, but it is in these cases that **the O-versus C- alkylation** 'problem' raises its head.
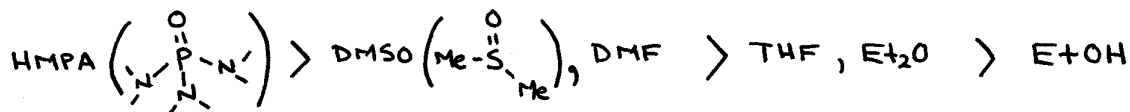
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Consider....

Points

    i)   This is particularly significant for active methylene compounds

    ii)   This is dependent on the cation $R_4N^+ > K^+ > Na^+ > Li^+ > BrMg^+$

   iii)   This is 'worse' for electrophiles which are 'hard acids' (by the Pearson definition)
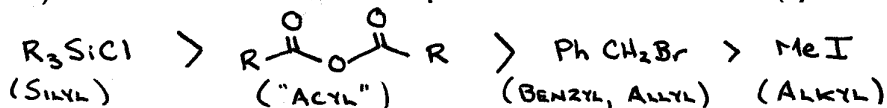

    iv)   This is 'worse' in highly cation coordinating solvents

    v)   If one has an equilibrium based situation, C-alkylation is thermodynamic (except for $E^+ = R_3SiCl$)

Enamines   (SEE MARCH 2-19)

    Another solution to polyalkylation involves the preparation of enamines and their use as enolate equivalents
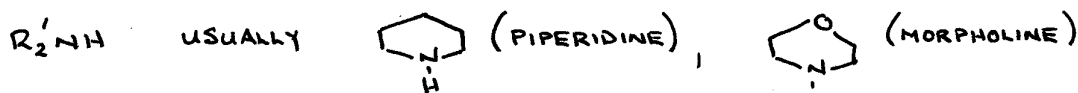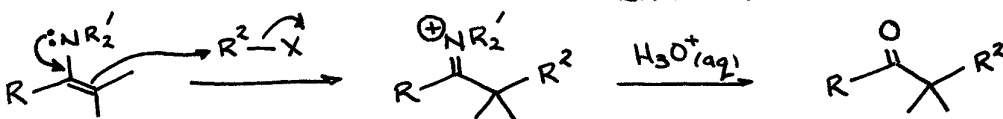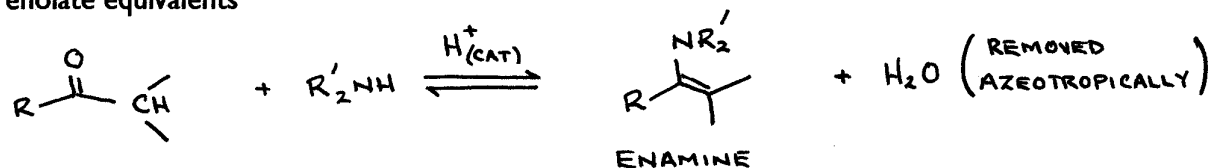
Advantages i)   No added base required

             ii)   Polyalkylation minimal or none

             iii)   Regiochemistry is unusual
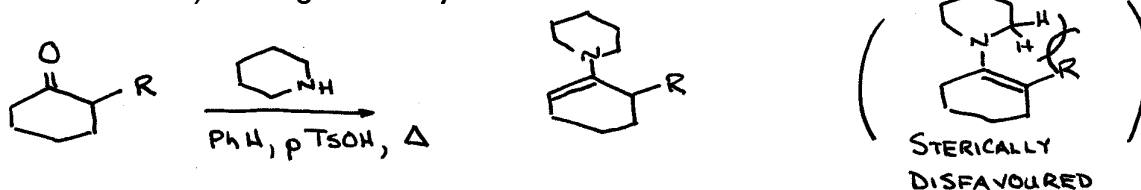
Therefore, alkylation occurs on the less substituted position, generally.