

# **CHEM – 750**

## **Advanced Organic synthesis**



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# C-C BOND FORMATION

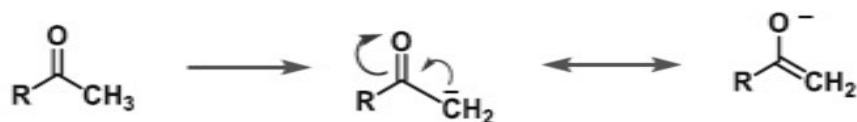
## Carbanion:

By the removal of a proton from a carbon by a Bronsted base.



## Enolate anion:

By the removal of a proton from a carbon alpha to a carbonyl group.

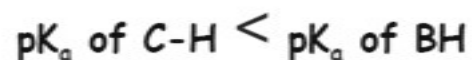


Formation of enolate depends

## Condition:

Acidity of C-H bond,  
Base

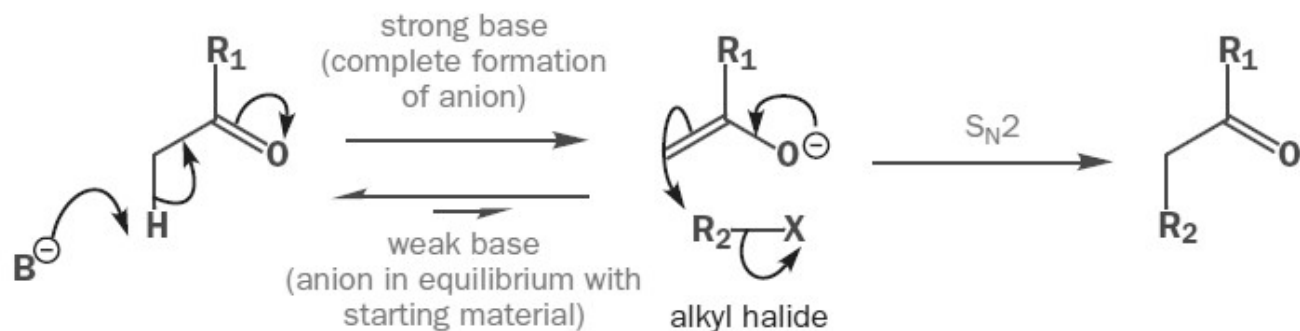
Acidity of C-H bond greater than the acidity of conjugate acid of the base used for deprotonation



The acidity of C-H bond depends on the functional group attached to it.  
The order of acidity,

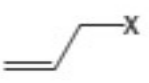
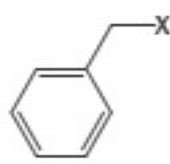

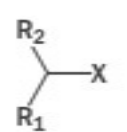
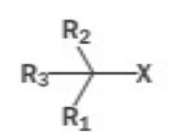


# C-Alkylation



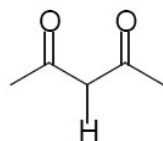
## Factors effecting C-alkylation

- solvent
- base
- cation
- temperature

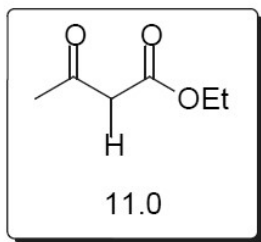
<p>methyl</p> <p>H<sub>3</sub>C—X</p>	<p>allyl</p> <p></p> <p>alkylate very well</p>	<p>benzyl</p> <p></p>	<p>primary alkyls</p> <p></p> <p>alkylate well</p>	<p>secondary alkyls</p> <p></p> <p>alkylate slowly</p>	<p>tertiary alkyls</p> <p></p> <p>do not alkylate</p>
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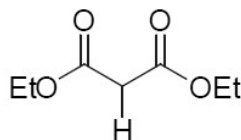
# Some important substrates & Bases



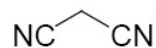
9.0



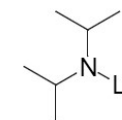
11.0



12.7

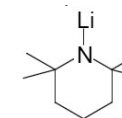


11.2



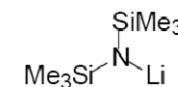
lithium diisopropylamide

LDA



lithium tetramethylpiperide

LTMP



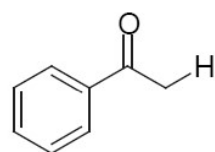
lithium hexamethyldisilazide

LHMDS

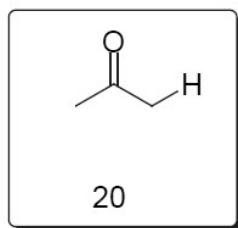
BuLi

Alkoxides

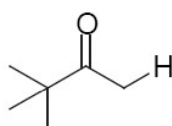
NaH, KH



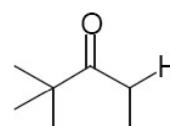
15.8



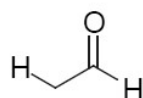
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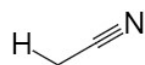
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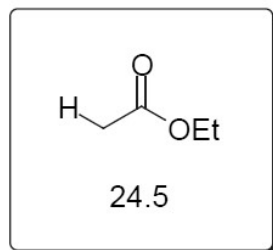
21.3



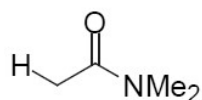
17



25



24.5



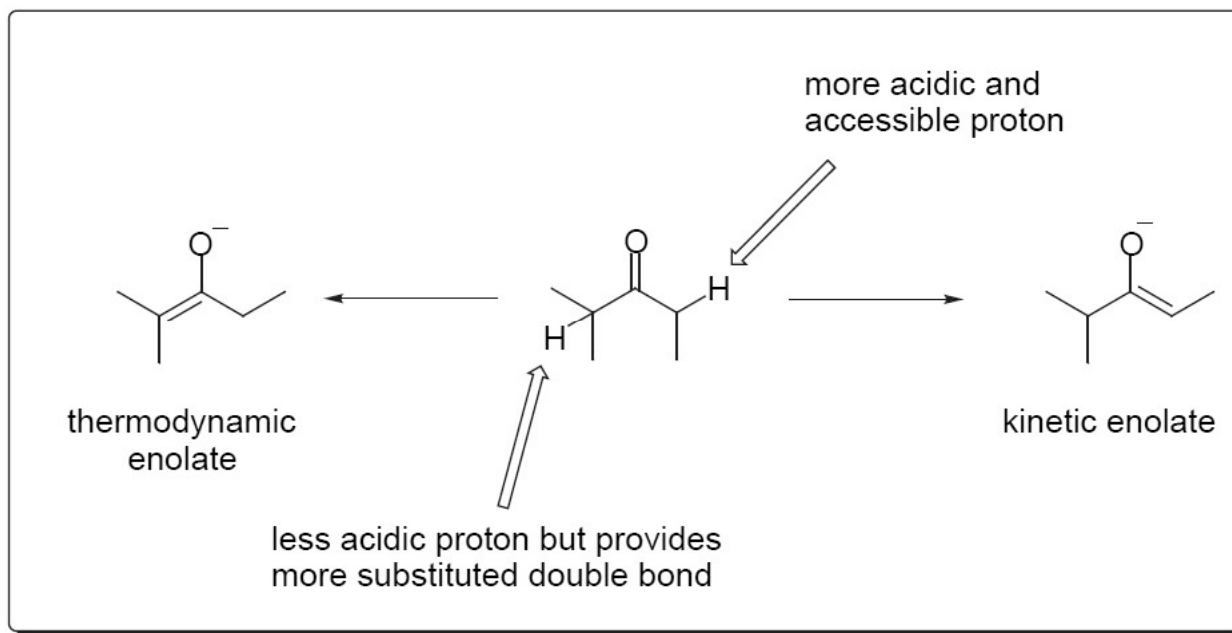
30

**pKa values helps to  
select the base**



# Regioselectivity in Enolate Formation

- Kinetic vs. thermodynamic control



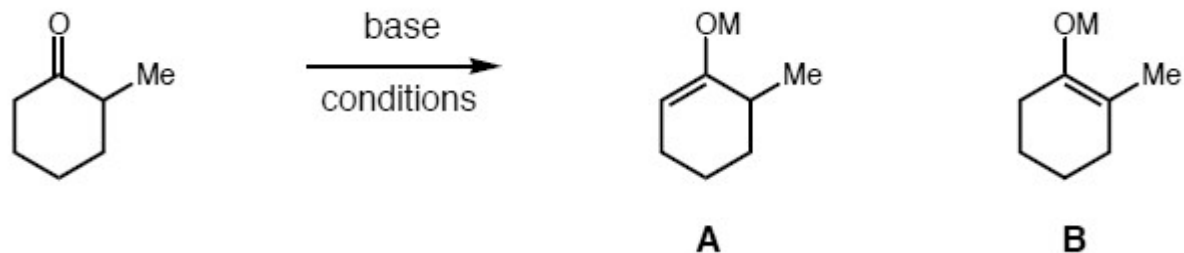


## Regioselectivity in Enolate Formation

factors favouring the formation of the kinetic enolate	factors favouring the formation of the thermodynamic enolate
aprotic solvents e.g. THF, Et <sub>2</sub> O (no acidic proton to encourage the reverse reaction)	protic solvents e.g. ROH which have slightly more acidic protons than the enolate and favour formation of the enol allowing tautomerisation to the ketone ( <i>i.e.</i> the reverse reaction)
strong bases e.g. LDA (which generate a weak conjugate acid (e.g. <sup>i</sup> Pr <sub>2</sub> NH) specifically one which is less acidic than the enolate product).	weaker bases which provide a relatively strong conjugate acid.
oxophilic cations e.g. Li <sup>+</sup>	
low temperature (e.g. < -78 °C)	higher temperature
short reaction times	long reaction times
<i>All these conditions suppress equilibration and ensure the reaction is essentially irreversible.</i>	<i>All these conditions encourage the reverse reaction</i>



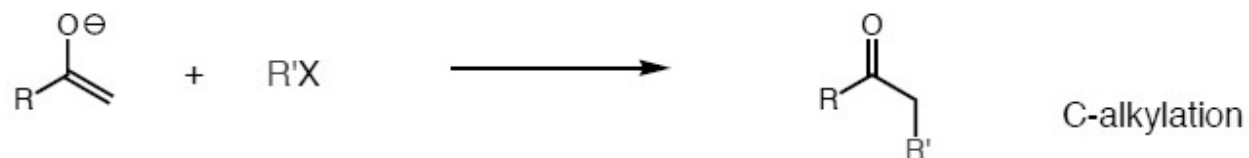
# Kinetic vs. Thermodynamic Control



base	temp	ratio (A/B)	control
$\text{LiN}(i\text{-C}_3\text{H}_7)_2$	0 °C	99:1	kinetic
$\text{KN}(\text{SiMe}_3)_2$	-78 °C	95:5	kinetic
$\text{Ph}_3\text{CLi}$	-78 °C	90:10	kinetic
$\text{Ph}_3\text{CK}$	25 °C	67:33	kinetic
$\text{Ph}_3\text{CK}$	25 °C	38:62	thermodynamic
$\text{NaH}$	25 °C	26:74	thermodynamic
$\text{Ph}_3\text{CLi}$	25 °C	10:90	thermodynamic



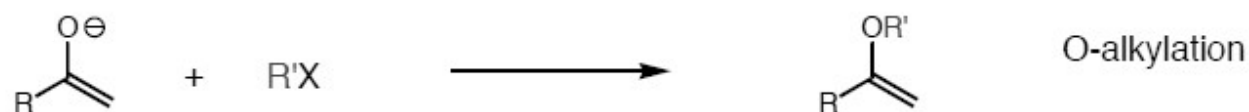
# Enolates: Ambident Nucleophiles



$$E(\text{C}=\text{O} + \text{C}-\text{C}) > E(\text{C}=\text{C} + \text{C}-\text{O})$$

$$745 + 347 \text{ kJ/mol} > (614 + 358) \text{ kJ/mol}$$

$$1097 \text{ kJ/mol} > 972 \text{ kJ/mol}$$



## *O-alkylation (charge control)*

- Predominant with hard leaving groups
- Favored by an early transition state, where charge distribution is the most important factor
- Favored by conditions that afford a dissociated, more reactive enolate
- Prevalent in polar, aprotic solvents
- Metal chelators are effective additives

## *C-alkylation (orbital control)*

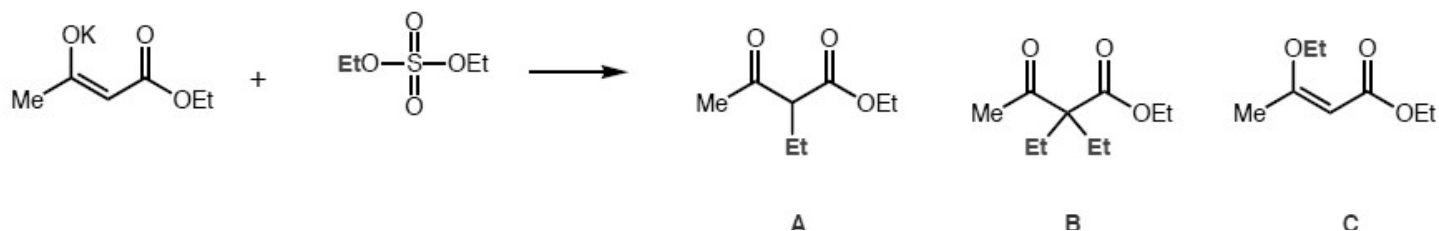
- Predominant with soft leaving groups
- Favored by a later transition state, where partial bond formation is the dominant factor
- More stable than the O-alkylation product
- Favors smaller, harder cations due to tighter coordination
- Prevalent in protic & apolar solvents





## Dissociation vs. clustering of ions

- O-alkylation is prevalent when the enolate is dissociated
- C-alkylation is prevalent where ion clustering occurs

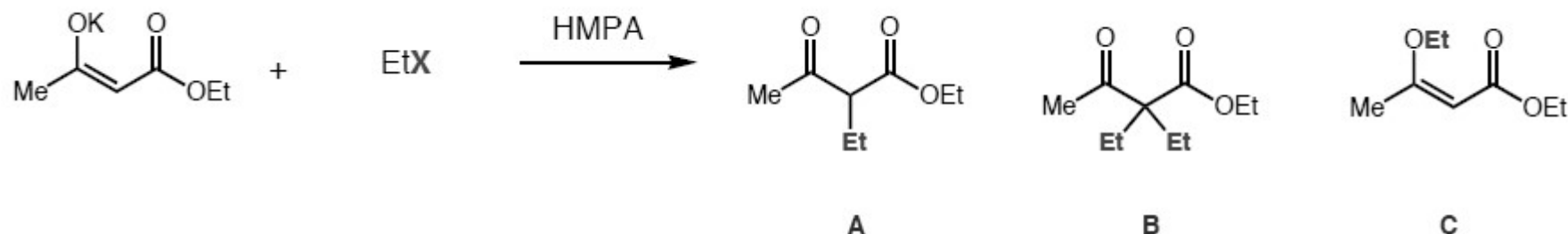


solvent	A	B	C
HMPA	15%	2%	83%
<i>t</i> -BuOH	94%	6%	0%
THF	94%	6%	0%

- HMPA promotes ion dissociation, favoring O-alkylation
- THF promotes ion clustering, favoring C-alkylation
- *t*-BuOH hydrogen-bonds with enolate anion, favoring C-alkylation



## Nature of the Leaving Group



X	A	B	C
OTs	11%	1%	88%
Cl	32%	8%	60%
Br	38%	23%	39%
I	71%	16%	13%

- **Hard**---OTs > Cl > Br > I---**Soft**
- Greater O-alkylation is observed with harder electrophiles
- Greater C-alkylation is observed with softer nucleophiles



## Orbital Overlap (Baldwin's Suggestions)

- For enolate cyclizations, orbital overlap is imperative

