



**Advanced Organic Chemistry/
Organic Synthesis – CH 621**

**C-C Bond Formation through
Carbanions**

Bela Torok

Department of Chemistry

University of Massachusetts Boston

Boston, MA

C-C bond formation through carbanions



Stability of carbanions

- Carbanions stabilized by two $-M$ groups
- Carbanions stabilized by one $-M$ group
- Carbanions stabilized by P or S
- Nucleophilic acylations
- Alkene, arene, heteroarene nucleophiles

C-C bond formation through carbanions

Carbanions stabilized by two $-M$ groups



1

(1 $pK_a \approx 4$)



2

(2 $pK_a \approx 9$)



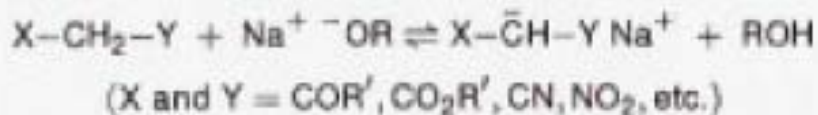
3

pK_a values of c. 13

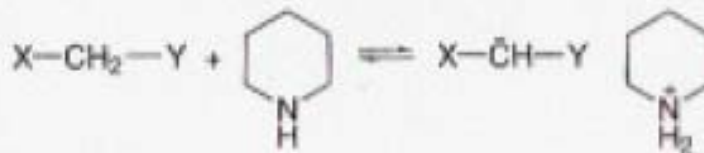


4

(i) These compounds are deprotonated

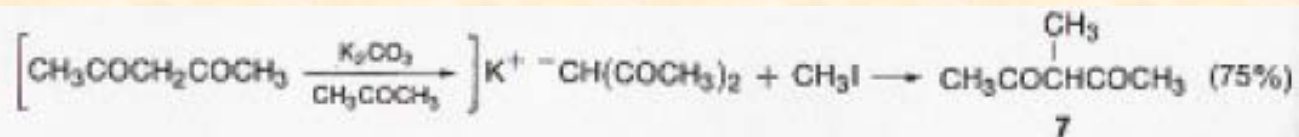
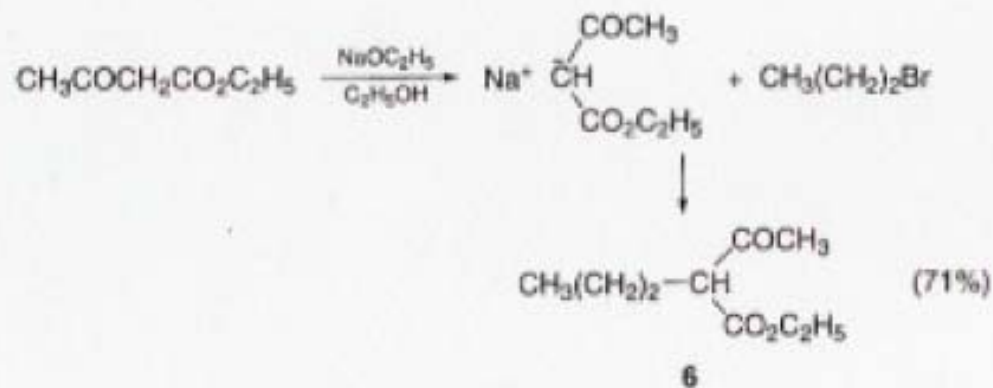
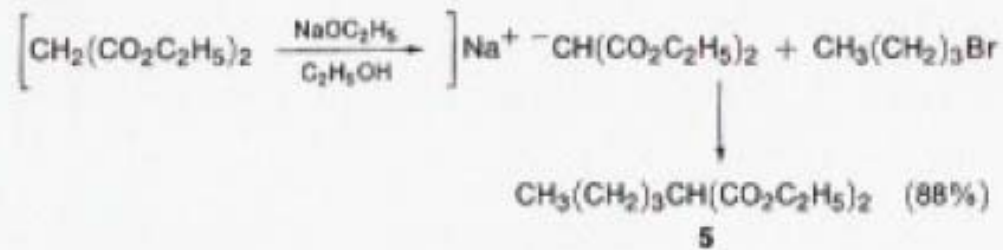


(ii) These compounds are also deprotonated, if not completely then at least to a significant extent, by organic bases such as piperidine ($pK_a \approx 11$):



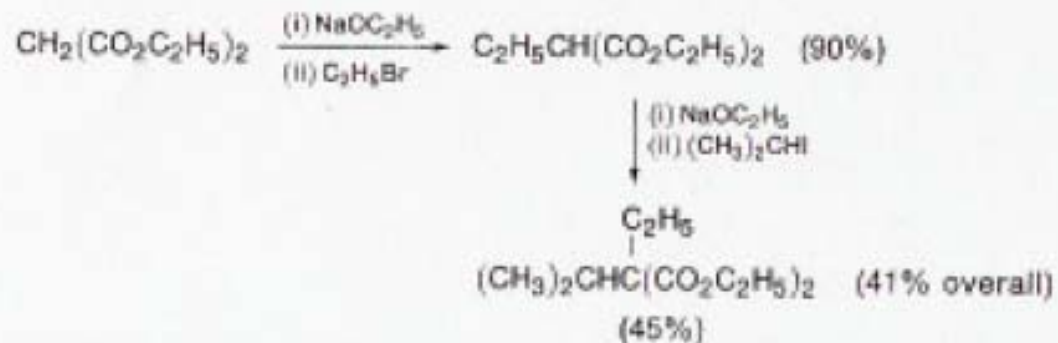
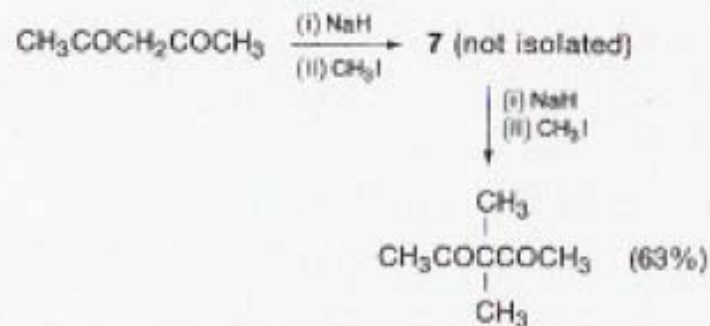
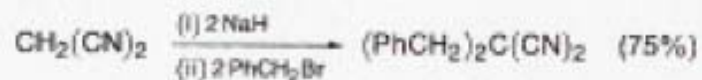
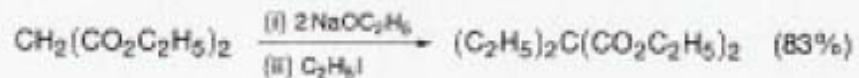
C-C bond formation through carbanions

5.1.1 Alkylation



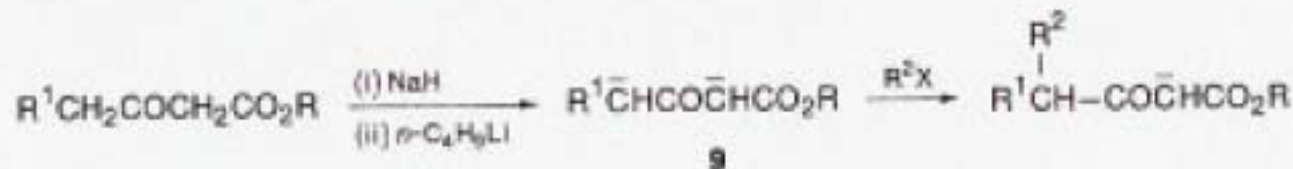
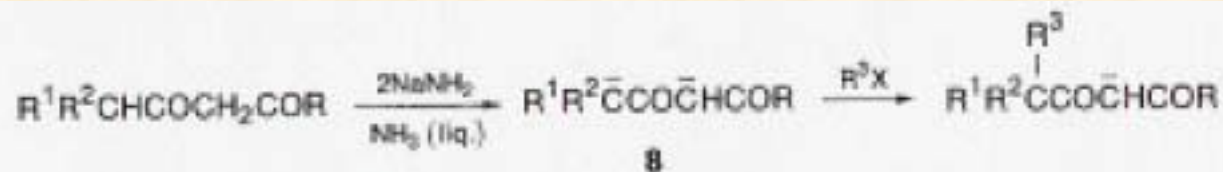
C-C bond formation through carbanions

5.1.1 Alkylation



C-C bond formation through carbanions

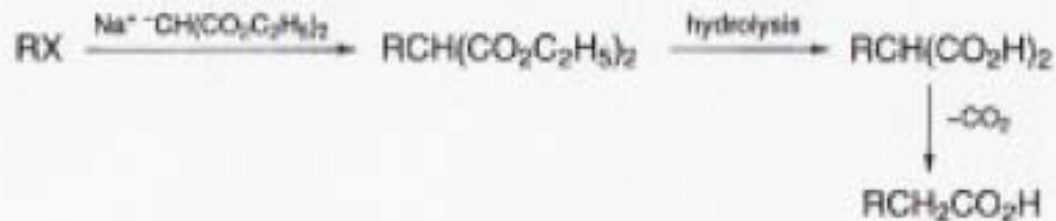
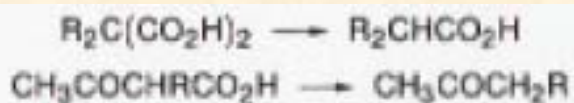
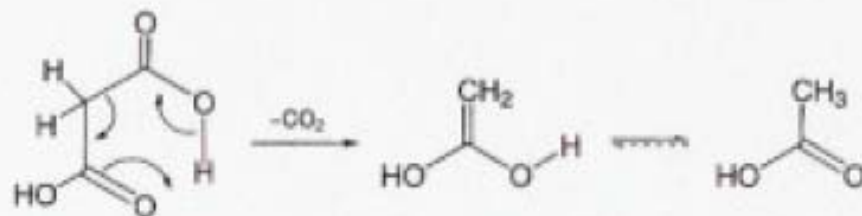
5.1.1 Alkylation



ambident nucleophiles

C-C bond formation through carbanions

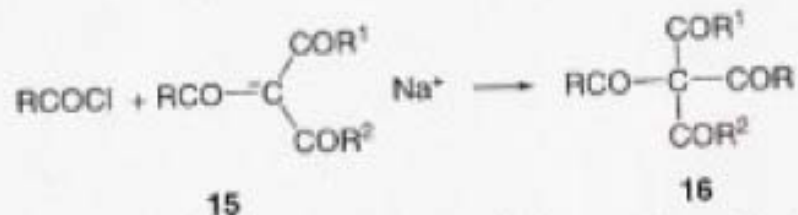
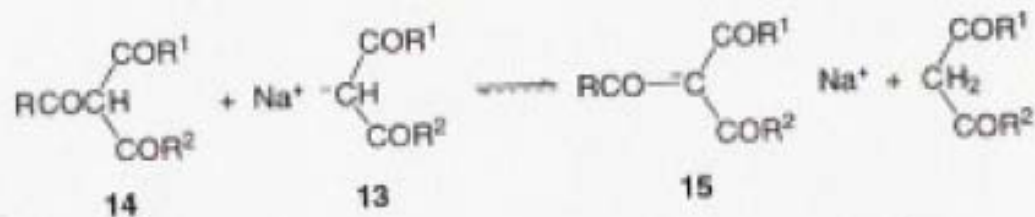
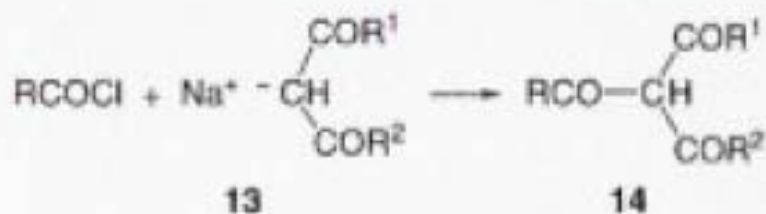
5.1.2 Hydrolysis of the alkylated products: a route to carboxylic acids and ketones



C-C bond formation through carbanions

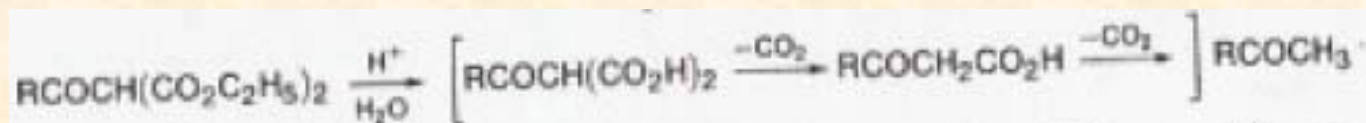
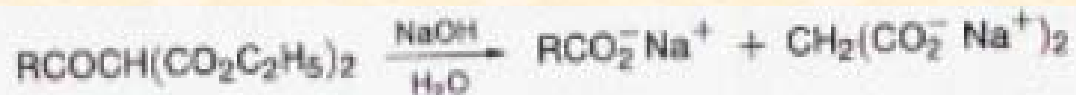
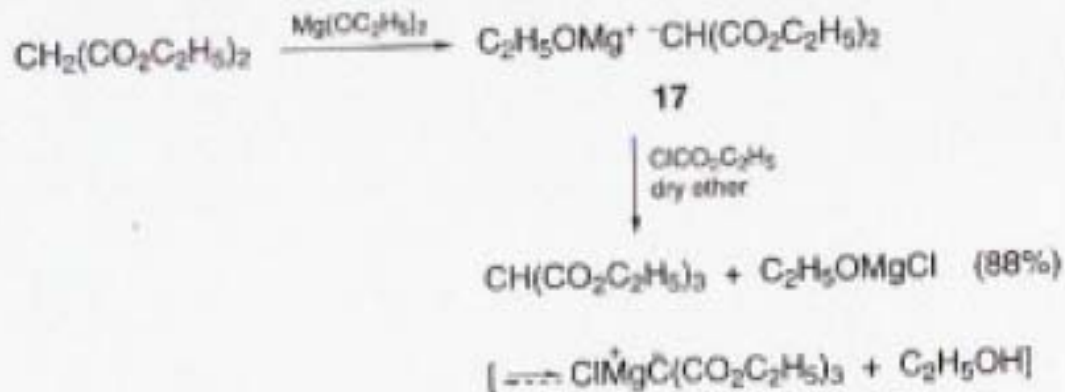
5.1.3 Acylation

acylation products of the type $\text{RCOCH} \begin{matrix} \text{COR}^1 \\ \text{COR}^2 \end{matrix}$ are strongly acidic



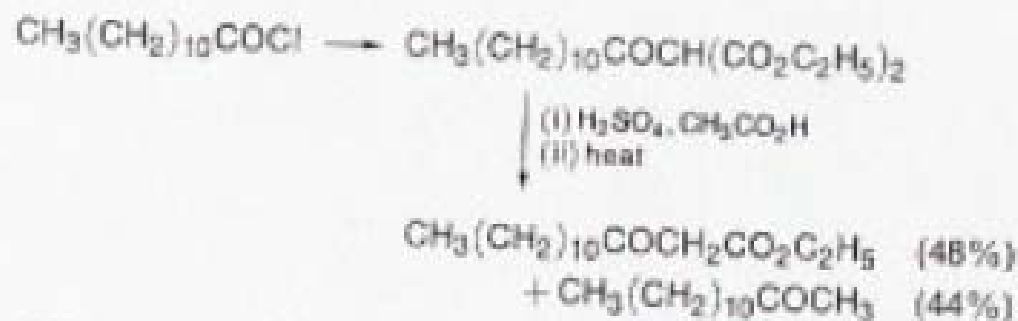
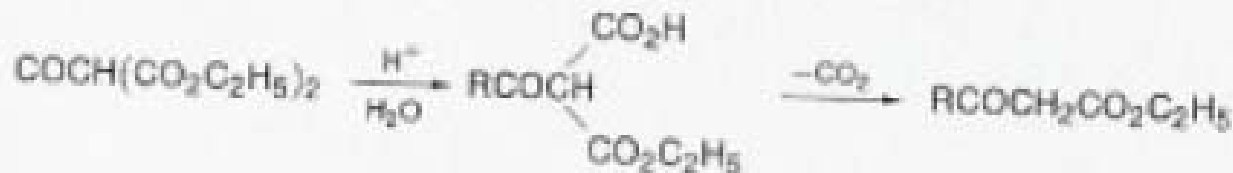
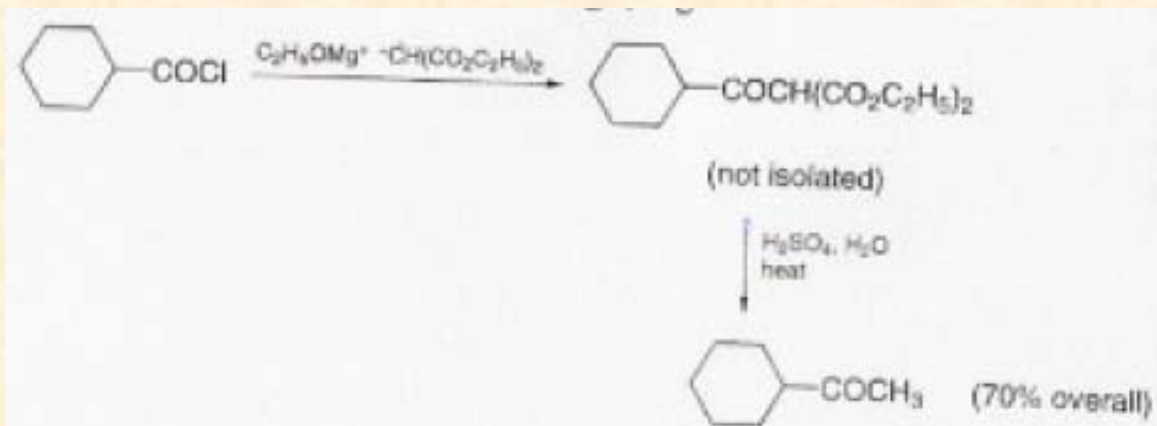
C-C bond formation through carbanions

5.1.3 Acylation



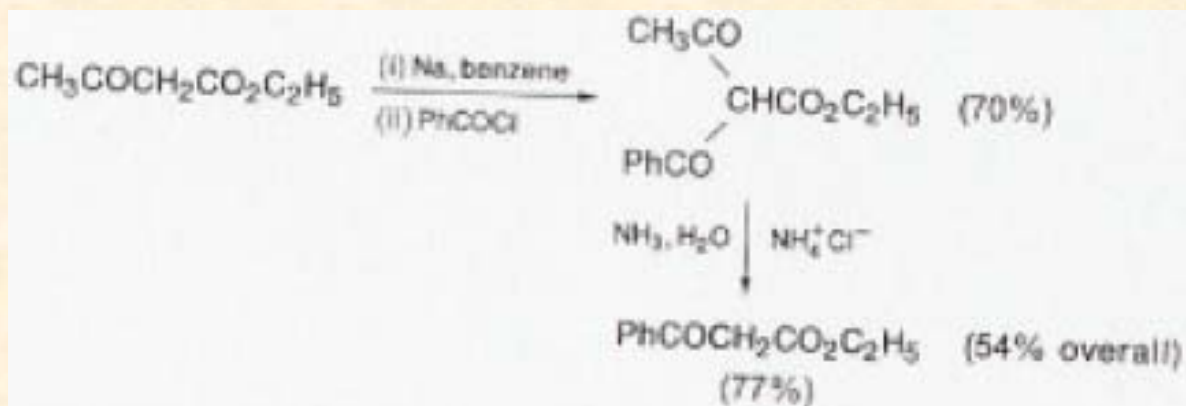
C-C bond formation through carbanions

5.1.3 Acylation



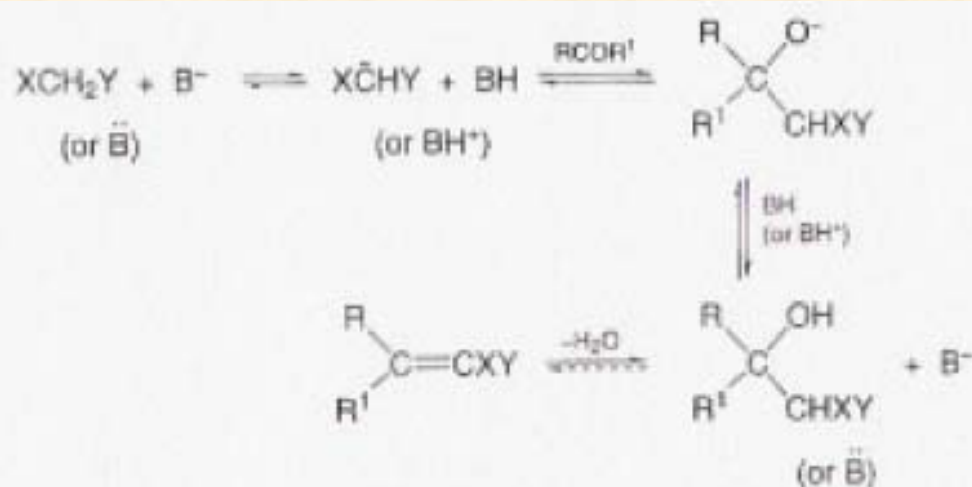
C-C bond formation through carbanions

5.1.3 Acylation



C-C bond formation through carbanions

5.1.4 Condensation reactions



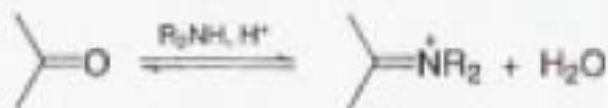
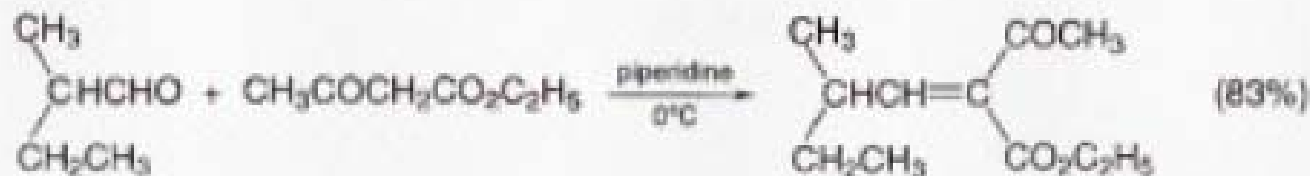
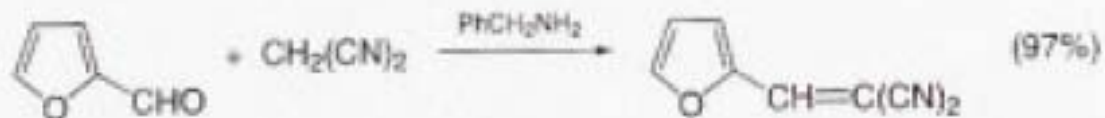
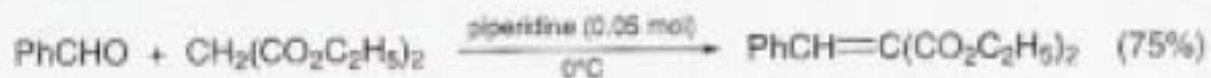
overall stoichiometry



C-C bond formation through carbanions

5.1.4 Condensation reactions

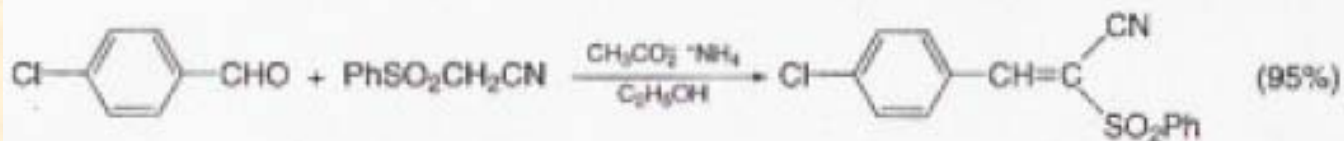
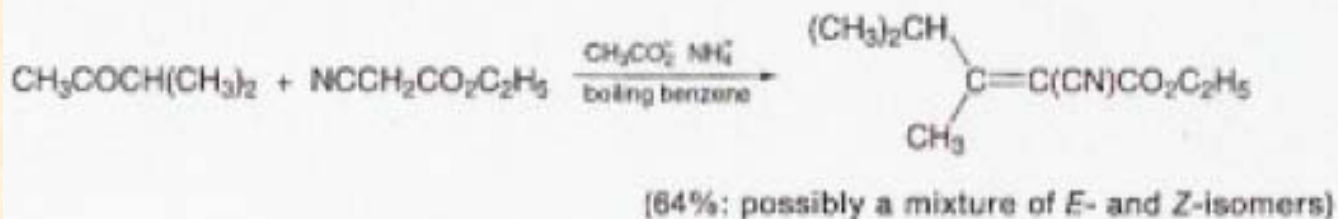
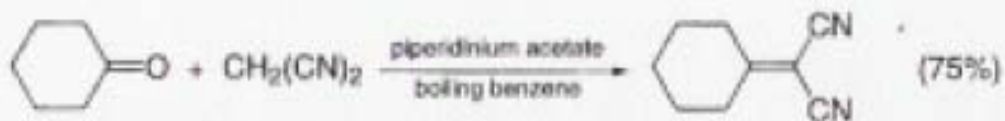
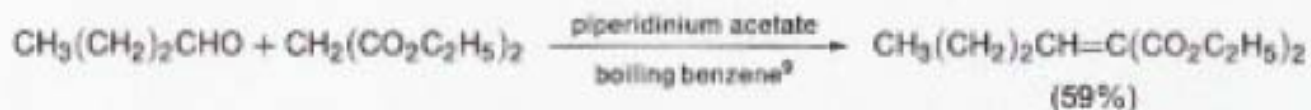
Knoevenagel condensation



C-C bond formation through carbanions

5.1.4 Condensation reactions

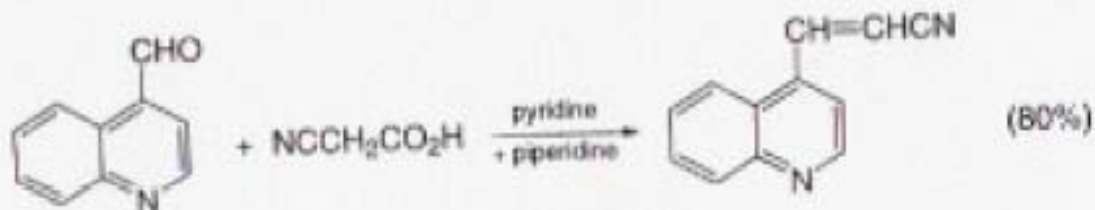
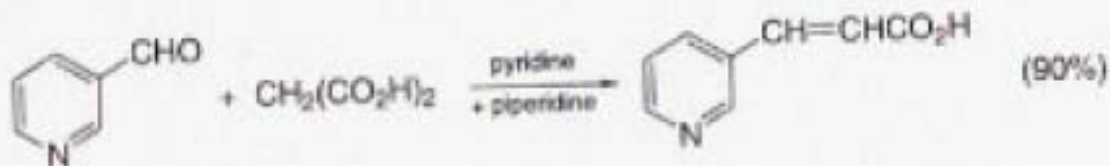
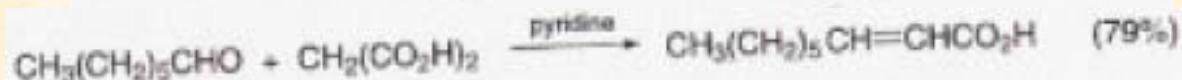
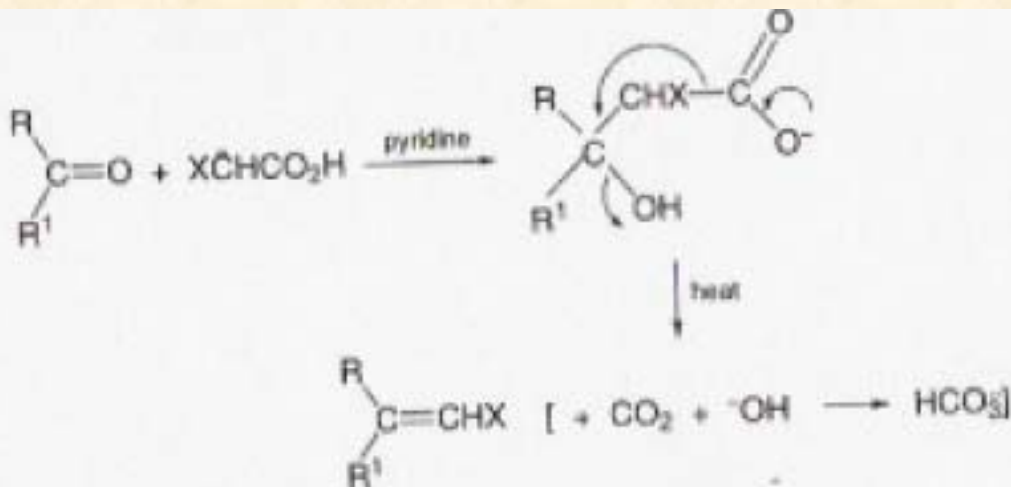
Knoevenagel condensation



C-C bond formation through carbanions

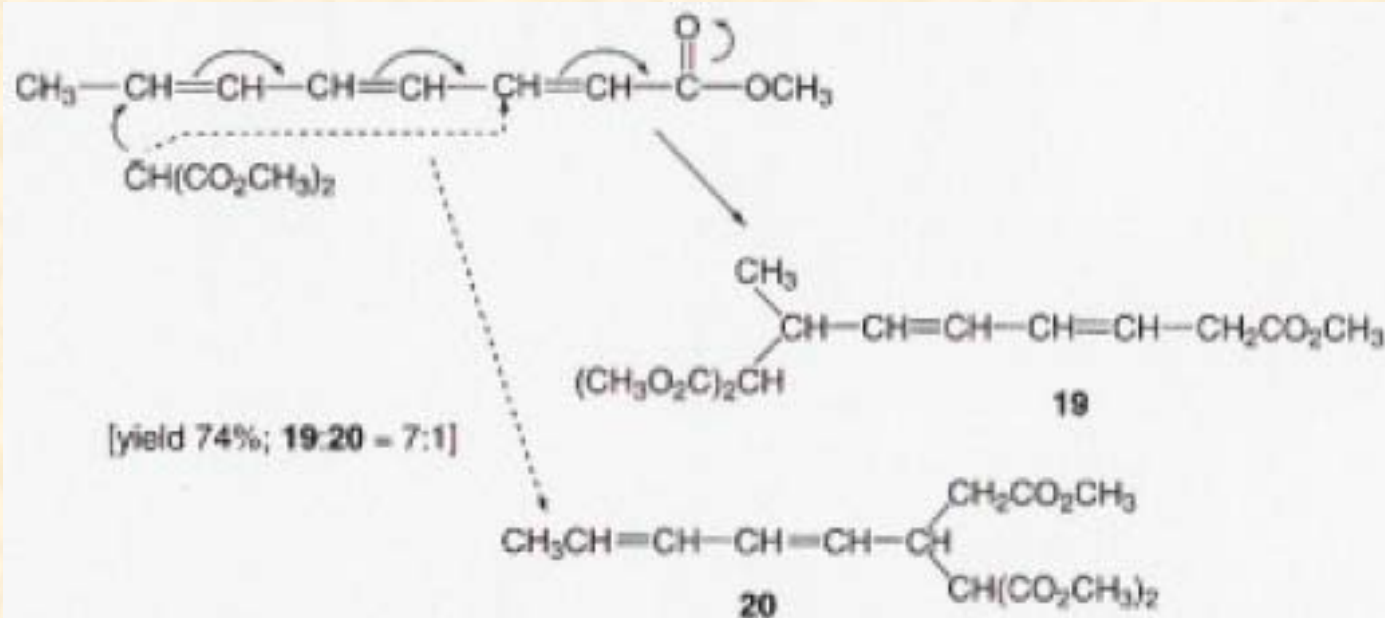
5.1.4 Condensation reactions

Doebner condensation



C-C bond formation through carbanions

5.1.5 Reactions with $\text{>C}=\overset{\overset{|}{|}}{\text{C}}-\overset{\overset{|}{|}}{\text{C}}=\text{O}$ and related systems: the Michael reaction



C-C bond formation through carbanions



Carbanions stabilized by one $-M$ group

Moderate acidity: pK_a

RCH_2X or R_2CHX (X being a $-M$ group)

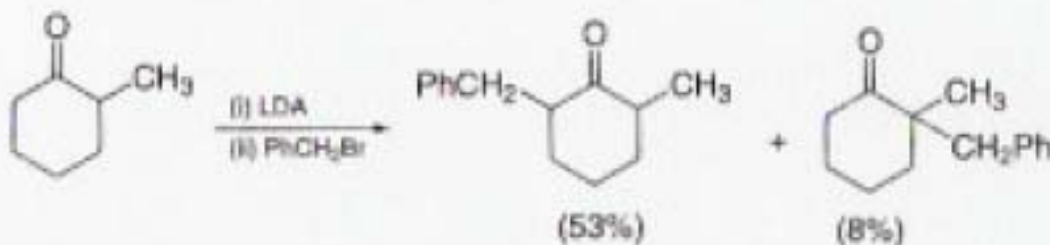
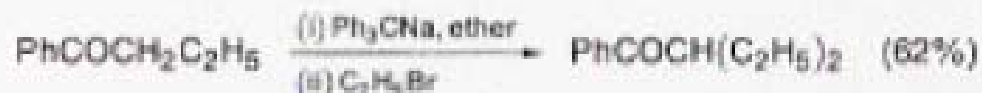
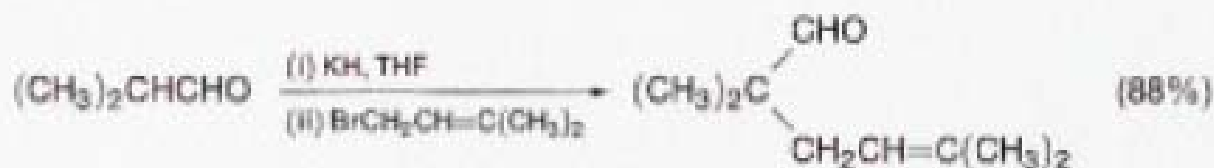
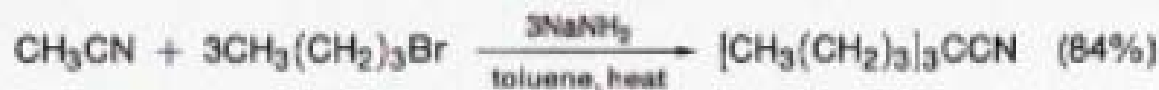
9-10 nitromethane

19-27 others

Equilibrium concentration of the carbanion

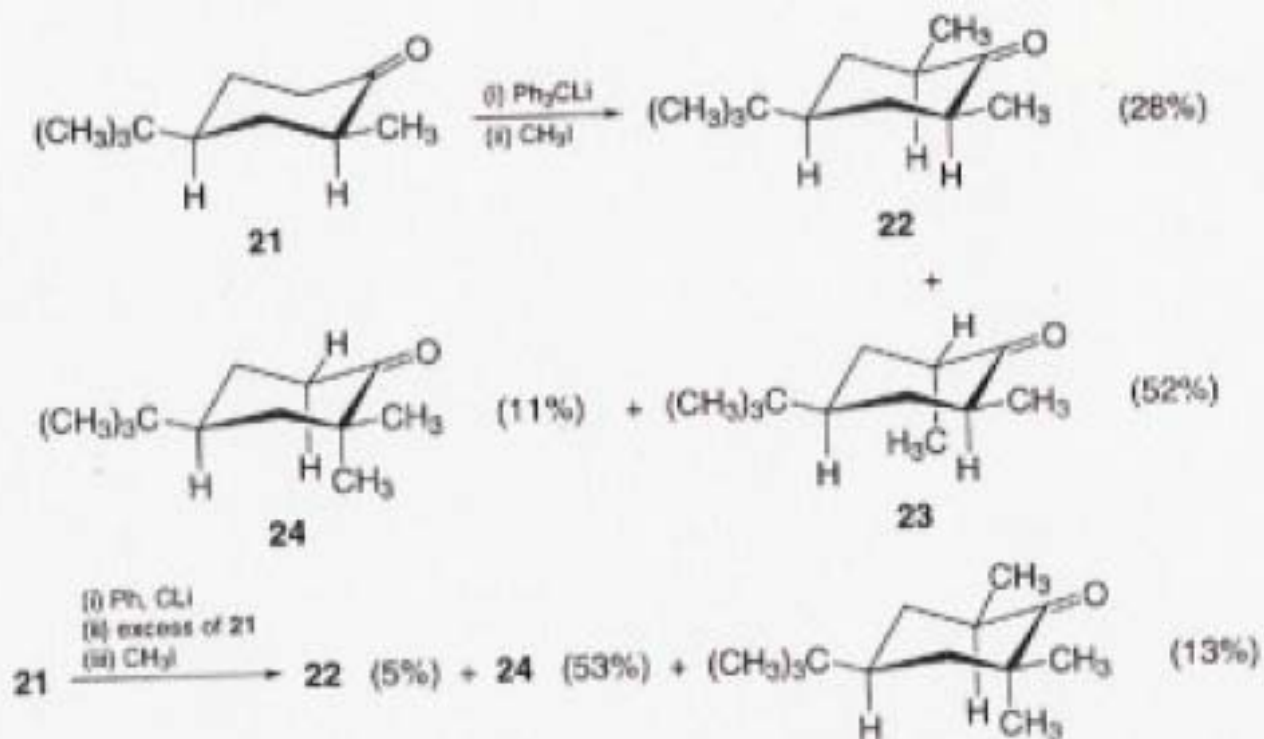
C-C bond formation through carbanions

5.2.1 Alkylation



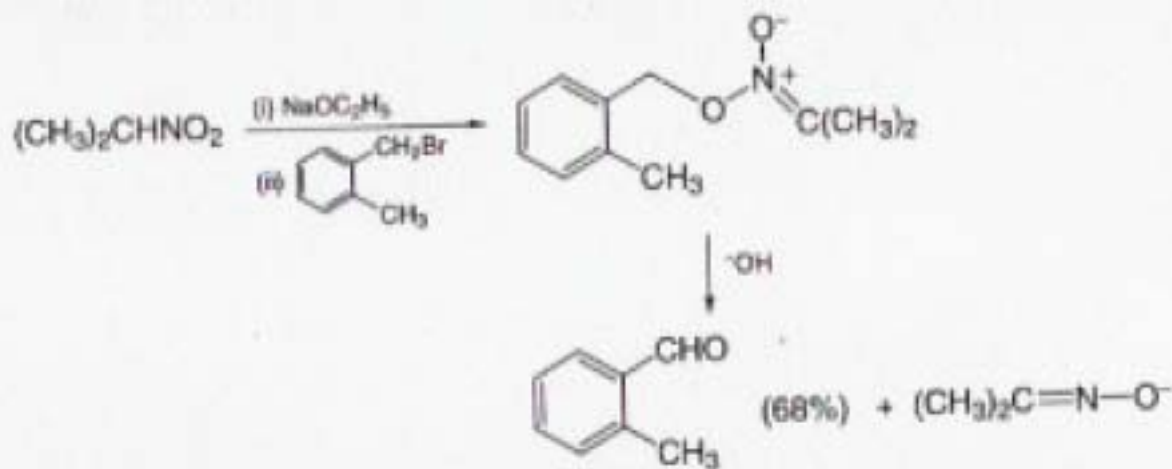
C-C bond formation through carbanions

5.2.1 Alkylation



C-C bond formation through carbanions

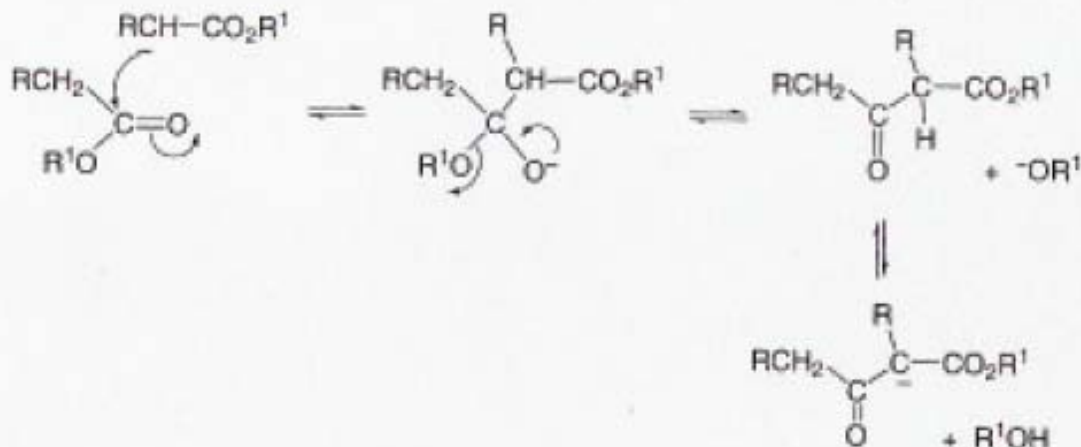
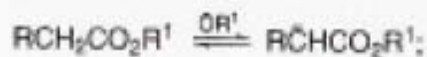
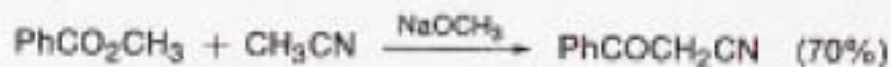
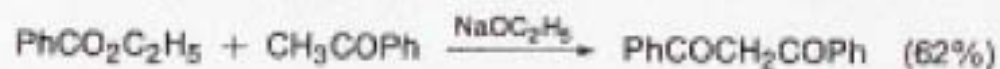
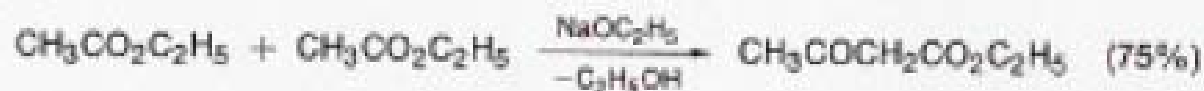
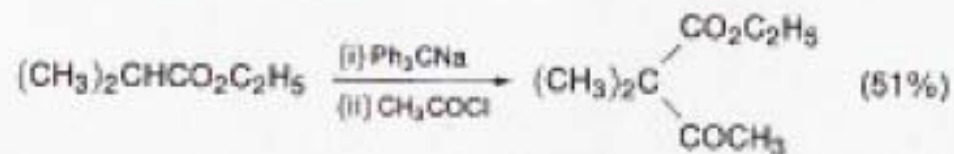
5.2.1 Alkylation



C-C bond formation through carbanions

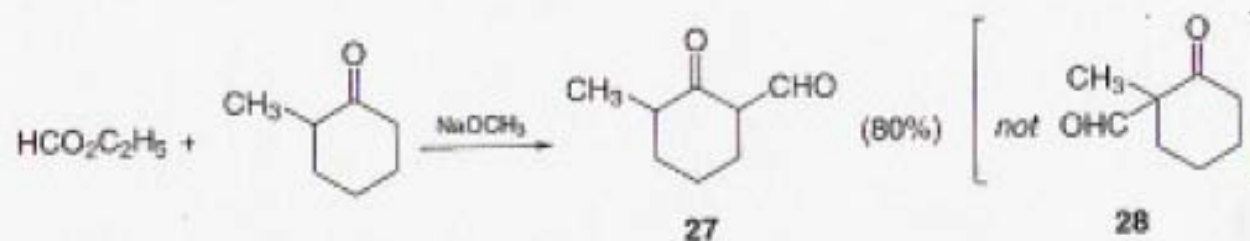
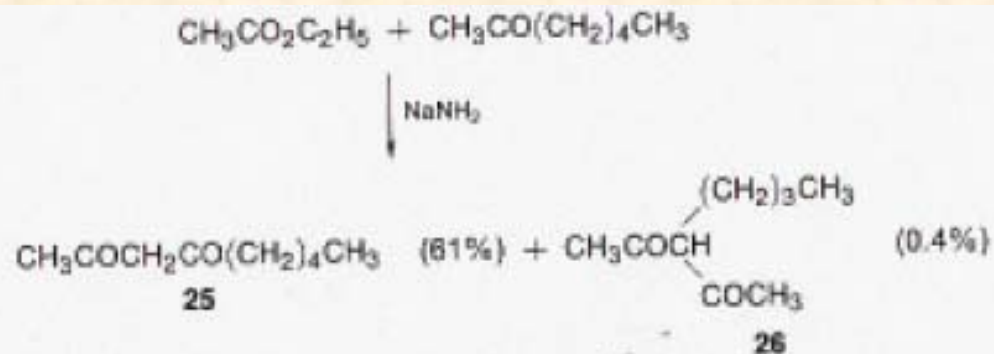
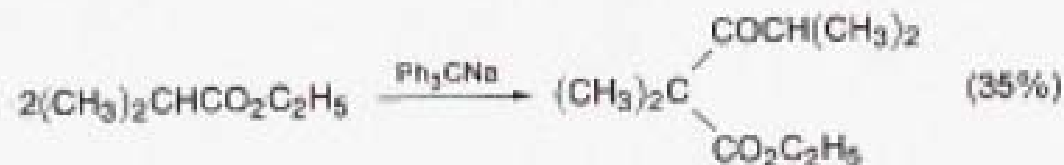
5.2.2 Acylation

Claisen ester condensation



C-C bond formation through carbanions

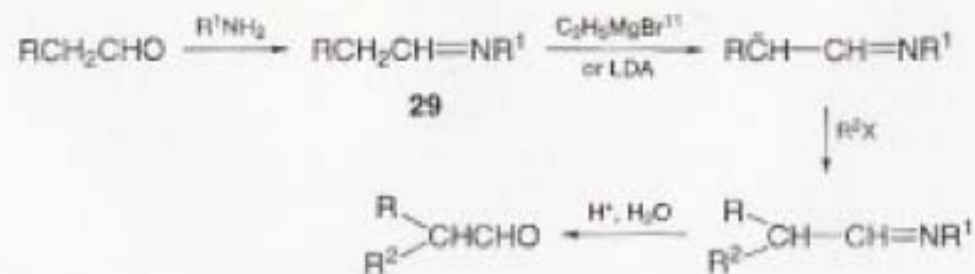
5.2.2 Acylation



C-C bond formation through carbanions

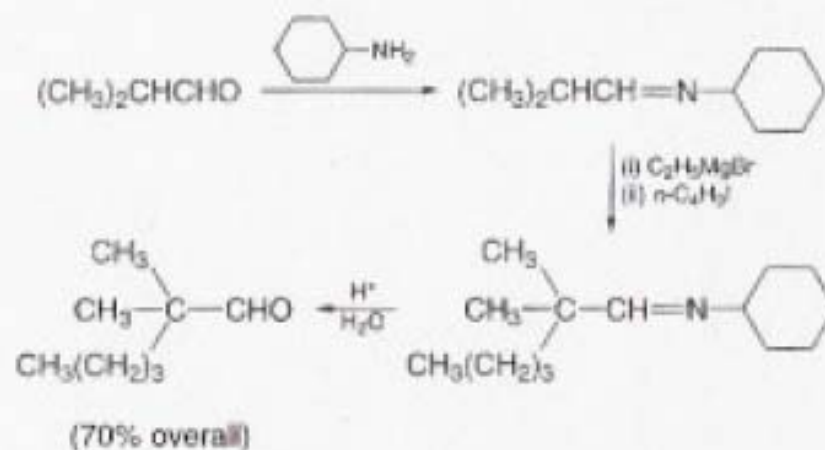
5.2.3 Indirect routes to α -alkylated aldehydes and ketones

Routes to α -alkylated aldehydes



[R¹ = (CH₃)₃C, (CH₃)₂N, cyclohexyl]

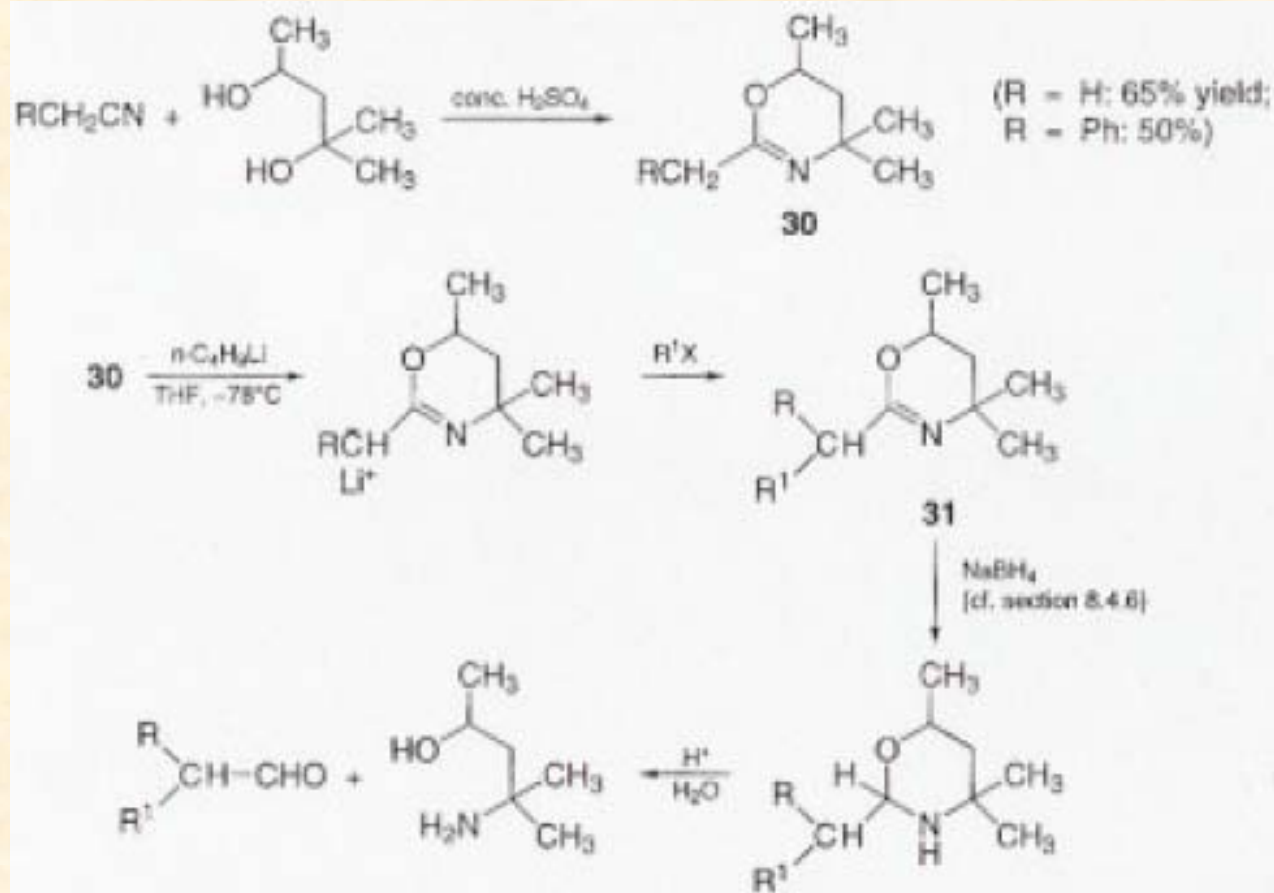
e.g.



C-C bond formation through carbanions

5.2.3 Indirect routes to α -alkylated aldehydes and ketones

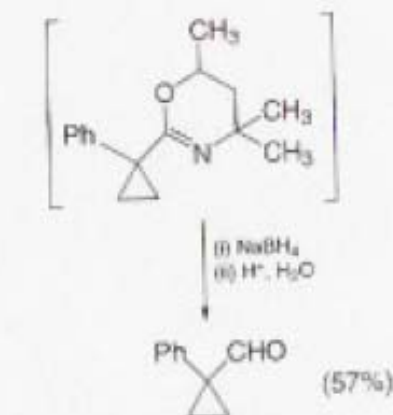
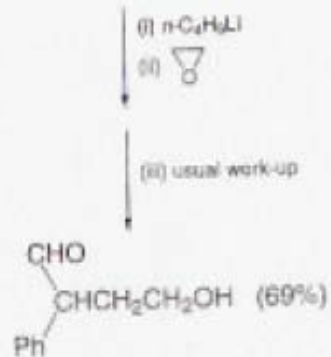
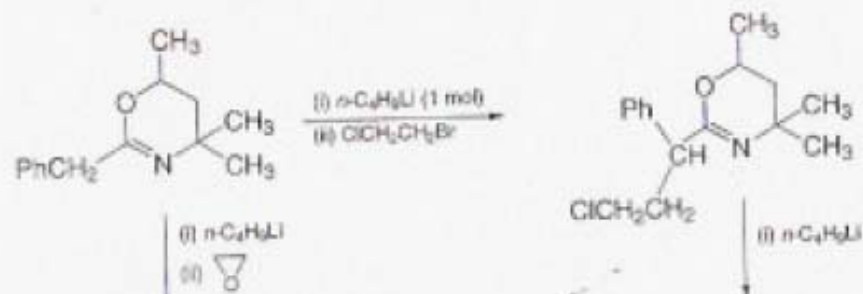
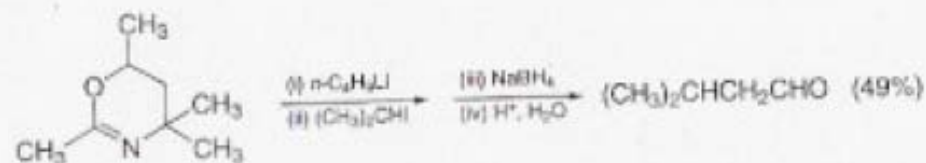
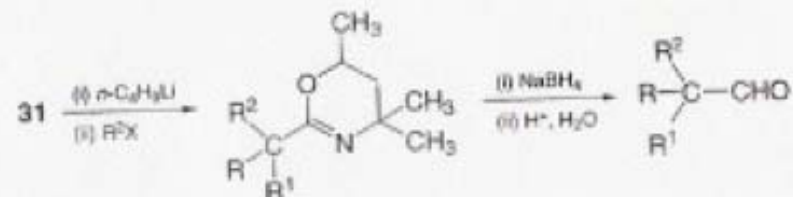
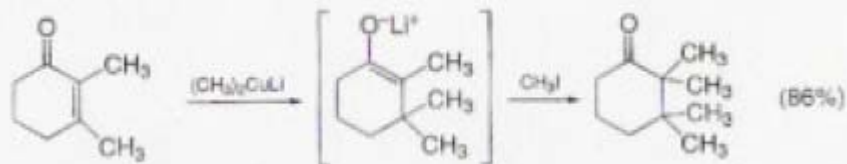
Routes to α -alkylated aldehydes



C-C bond formation through carbanions

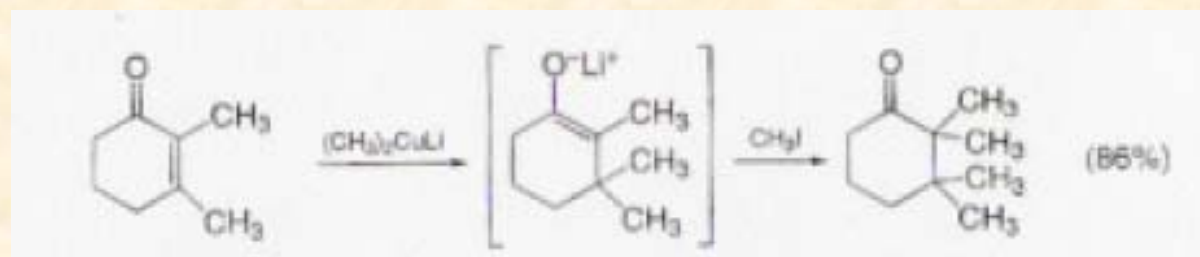
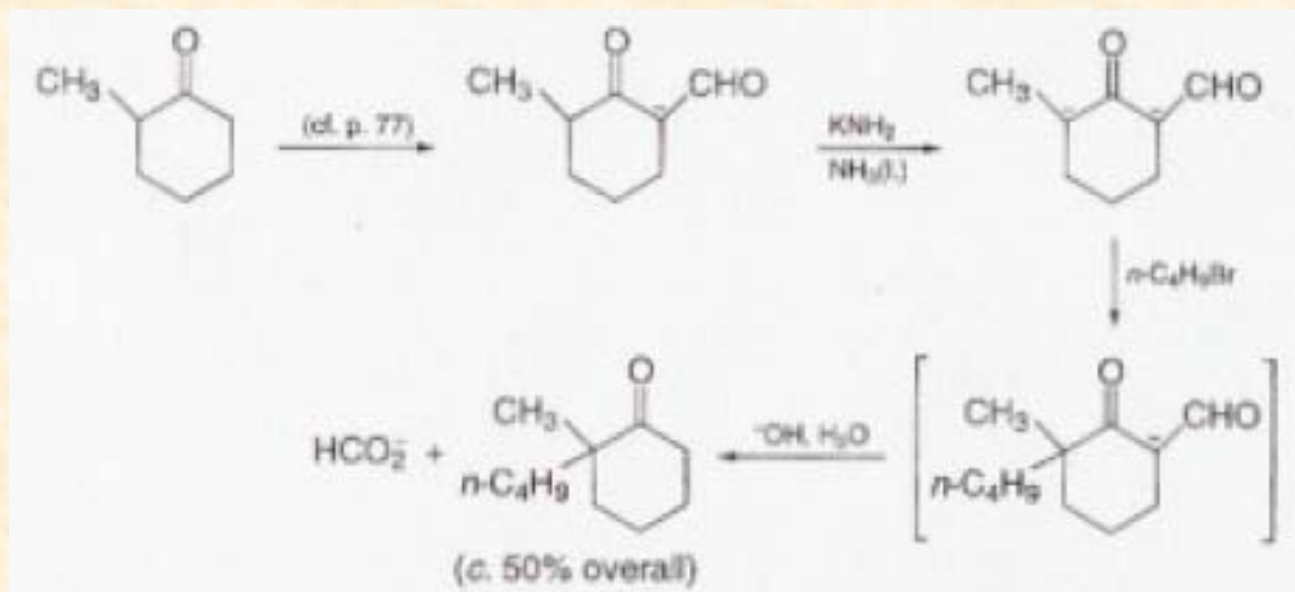
5.2.3 Indirect routes to α -alkylated aldehydes and ketones

Routes to α -alkylated aldehydes



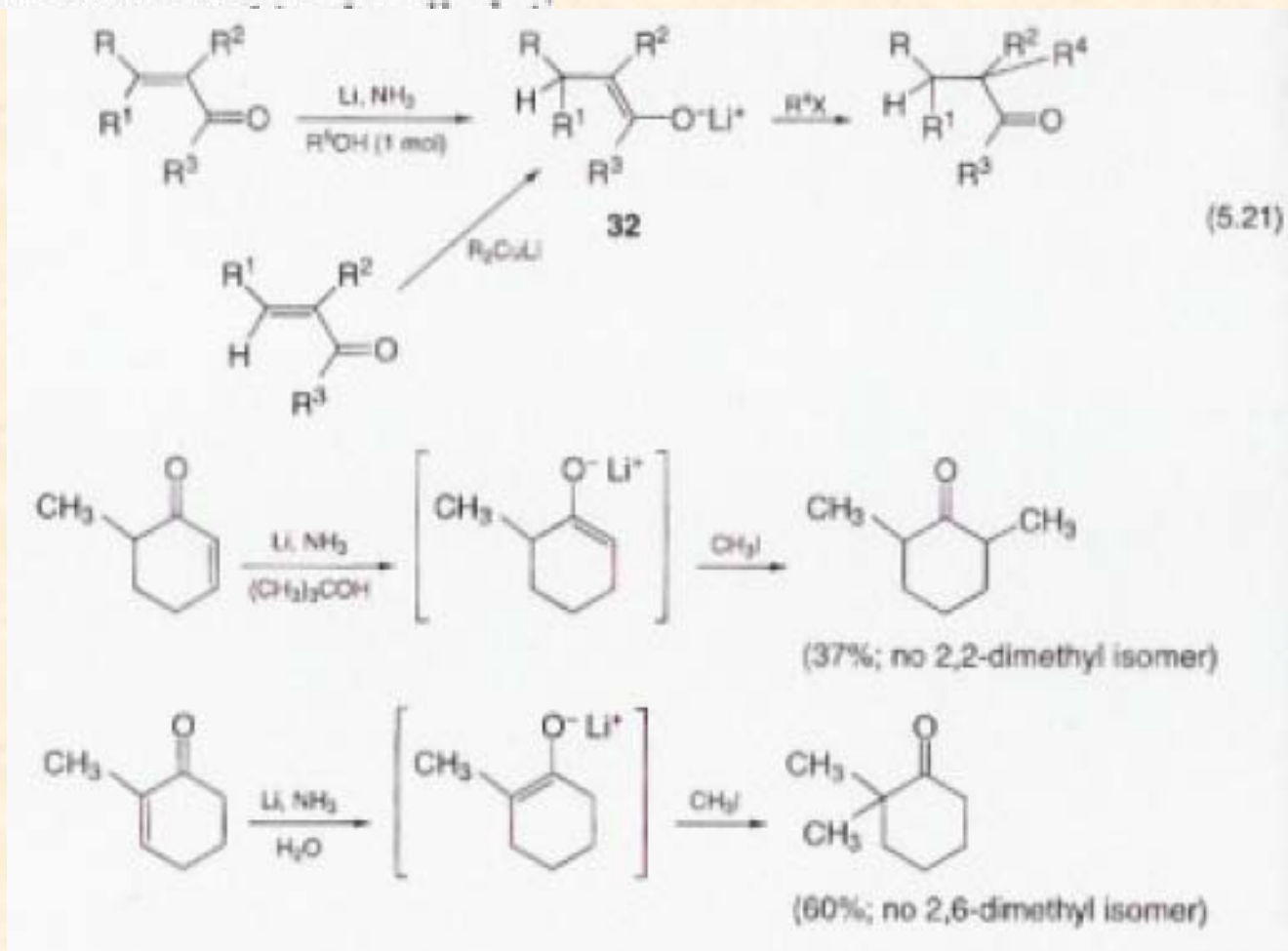
C-C bond formation through carbanions

Routes to α -alkylated ketones: 'specific enolates'



C-C bond formation through carbanions

Routes to α -alkylated ketones: 'specific enolates'

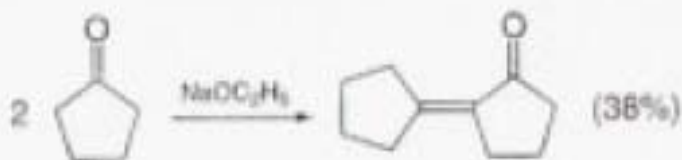
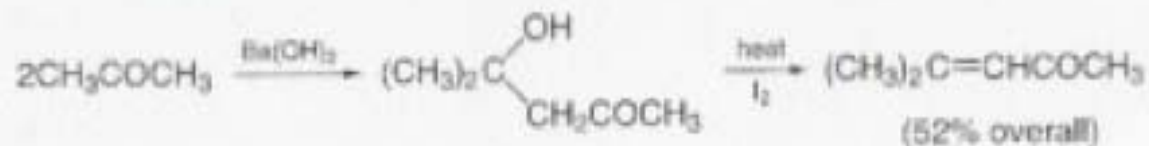
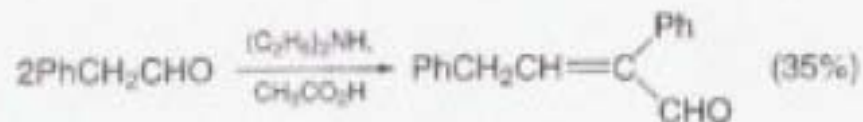
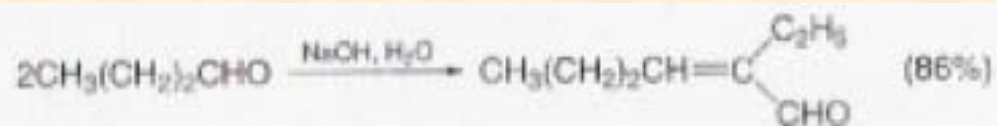
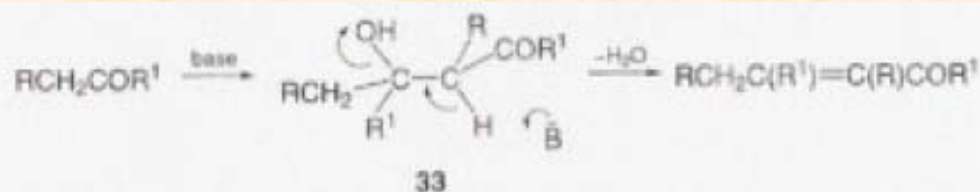


C-C bond formation through carbanions

5.2.4 Condensation reactions¹

5.2.4.1 Self-condensation of aldehydes and ketones

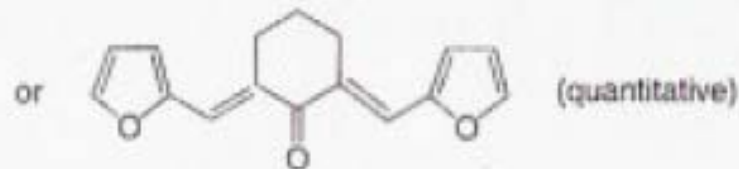
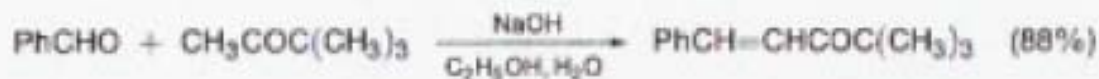
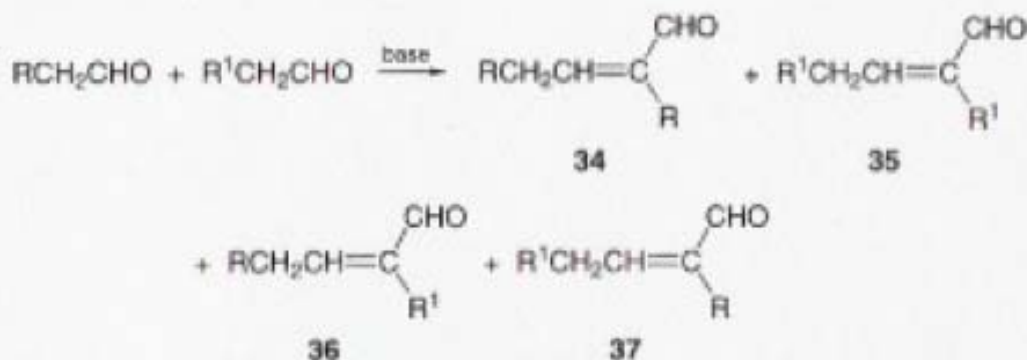
aldol condensation



C-C bond formation through carbanions

5.2.4 Condensation reactions

5.2.4.2 Mixed condensations

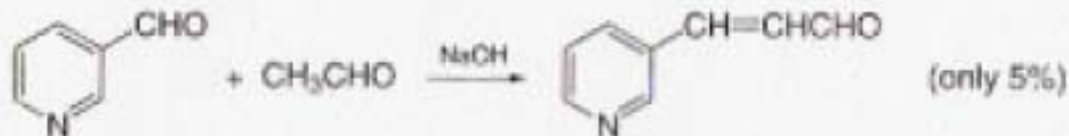
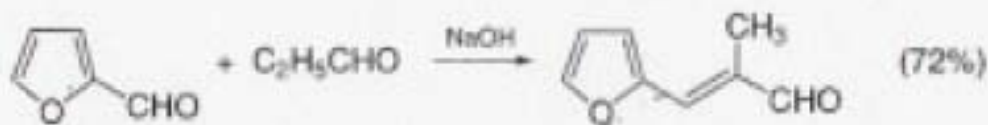
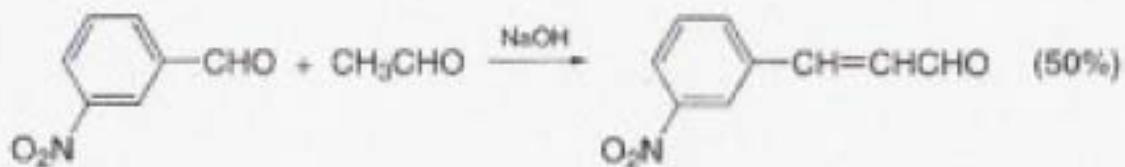
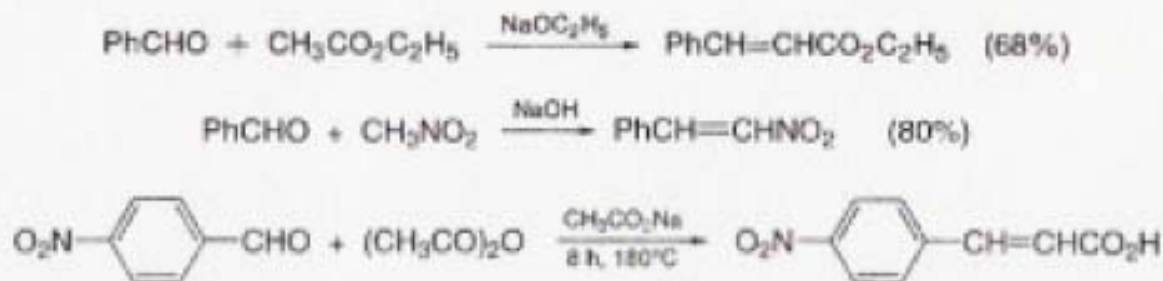


(depending on proportions of reactants)

C-C bond formation through carbanions

5.2.4 Condensation reactions

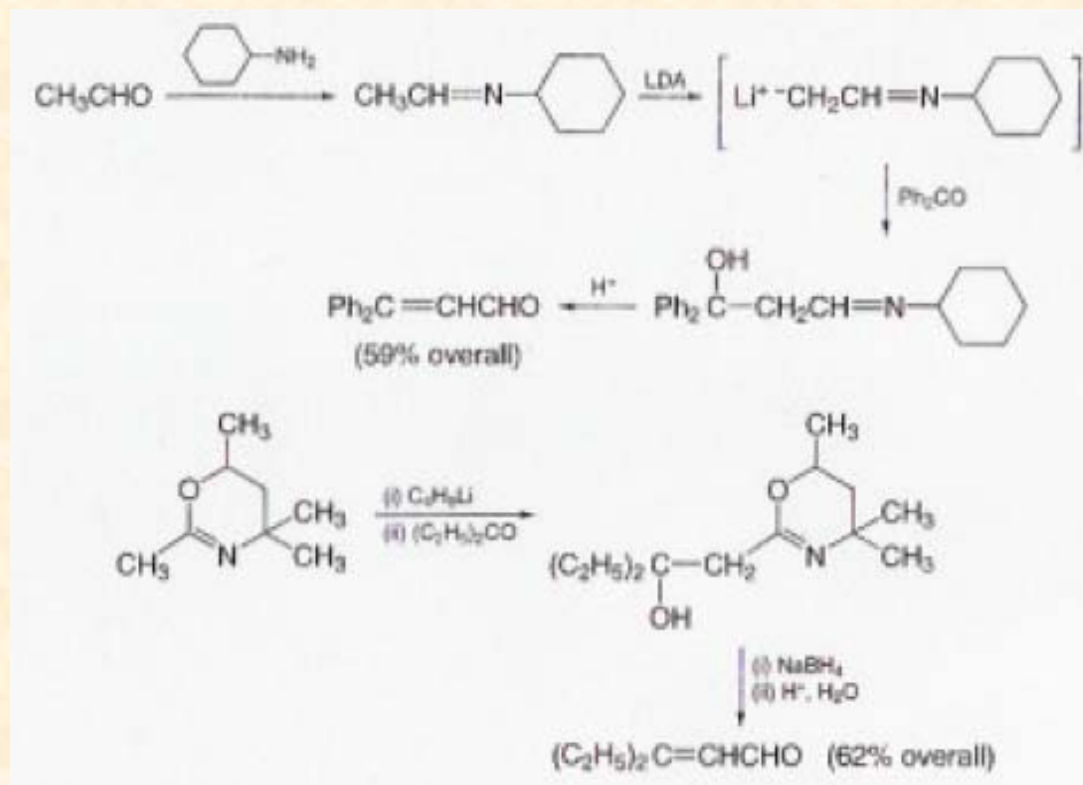
5.2.4.2 Mixed condensations



C-C bond formation through carbanions

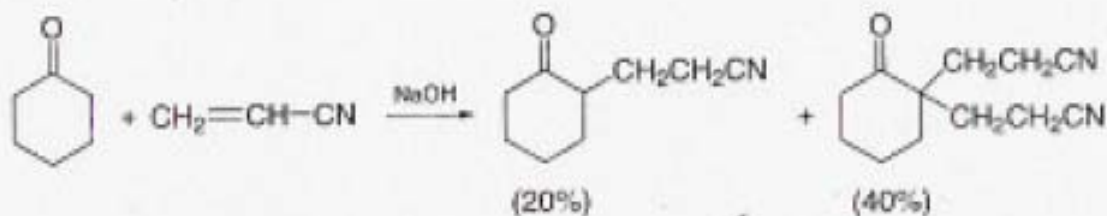
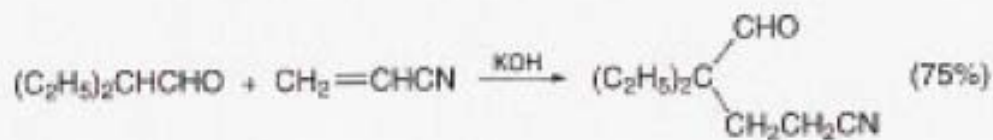
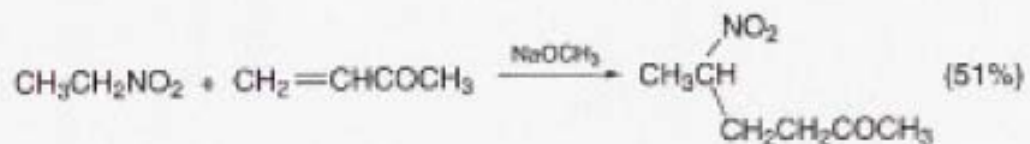
5.2.4 Condensation reactions

5.2.4.2 Mixed condensations



C-C bond formation through carbanions

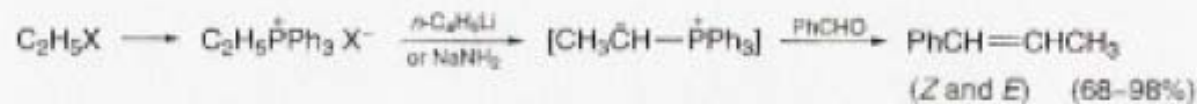
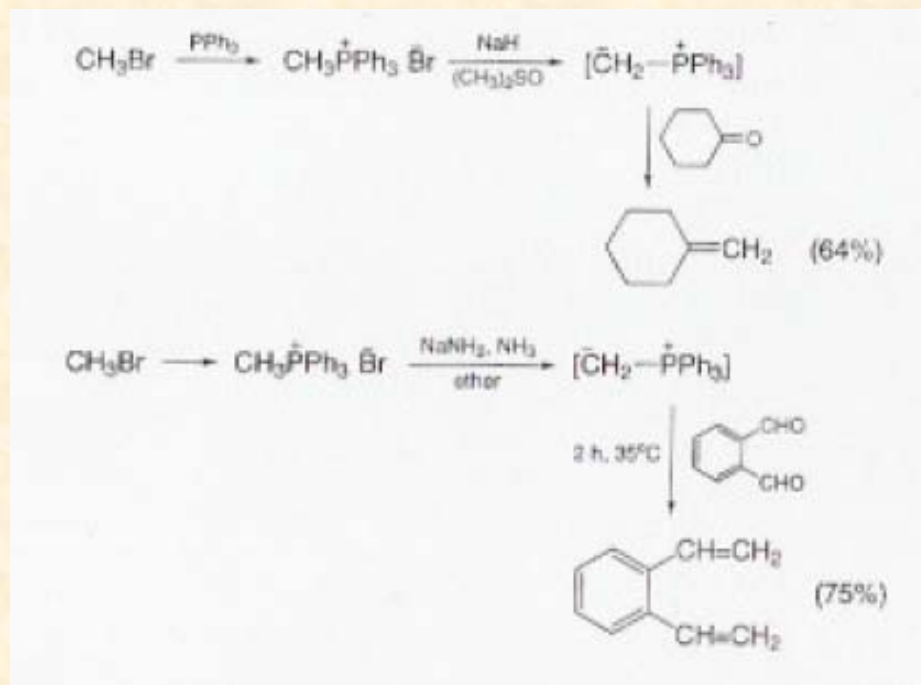
5.2.5 Michael reactions



C-C bond formation through carbanions

5.3.1 The Wittig reaction

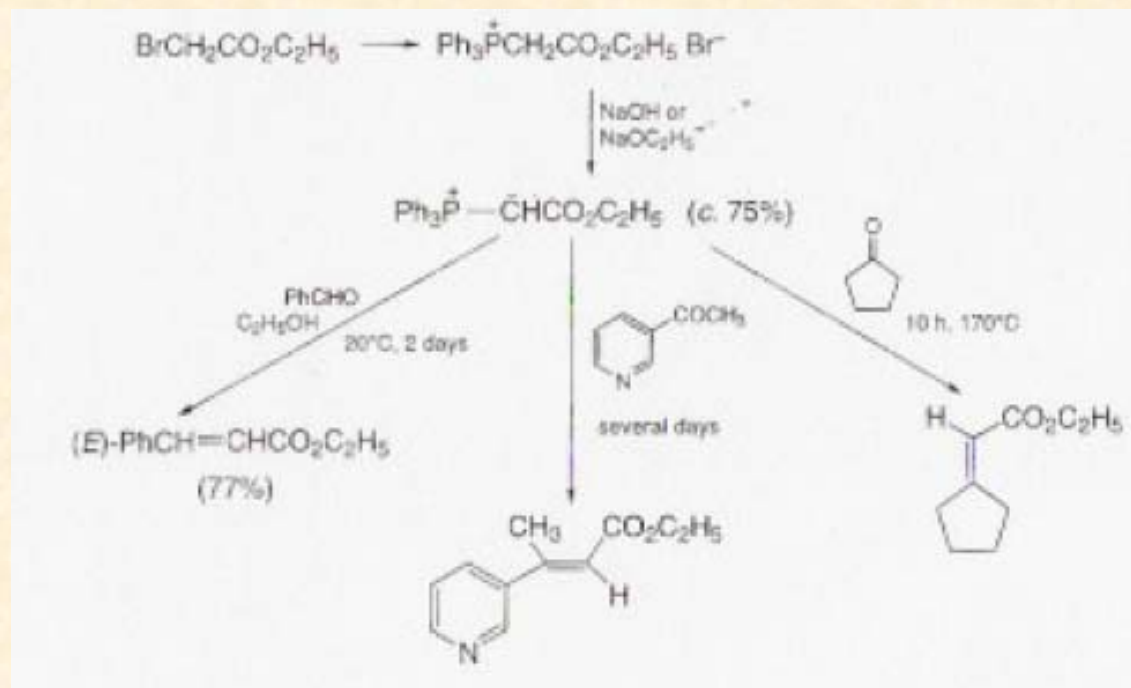
5.3.1.1 Non-stabilized ylides



C-C bond formation through carbanions

5.3.1 The Wittig reaction

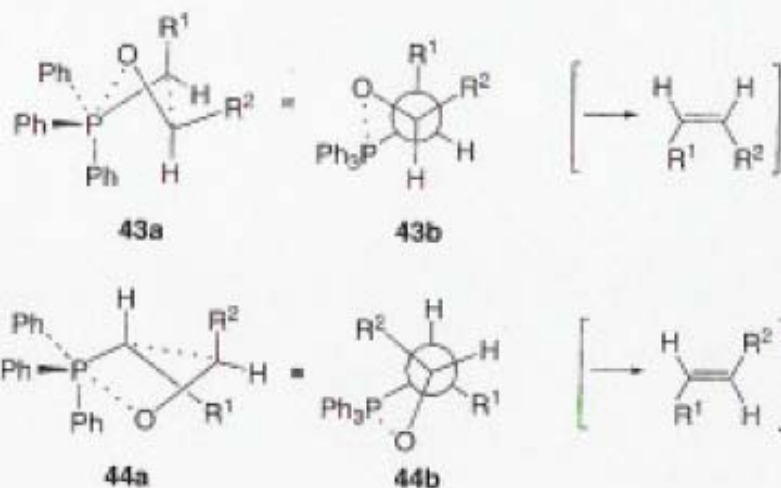
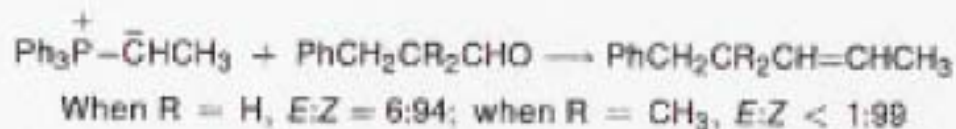
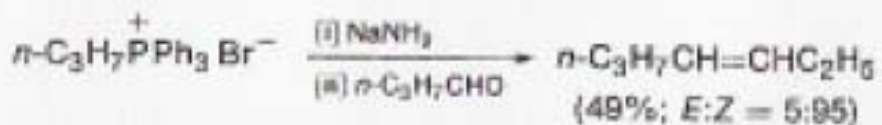
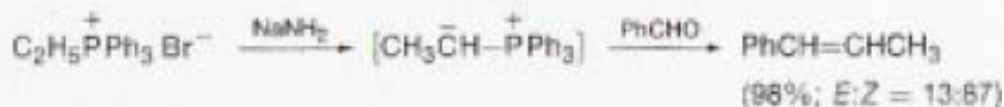
5.3.1.2 Stabilized ylides



C-C bond formation through carbanions

5.3.1 The Wittig reaction

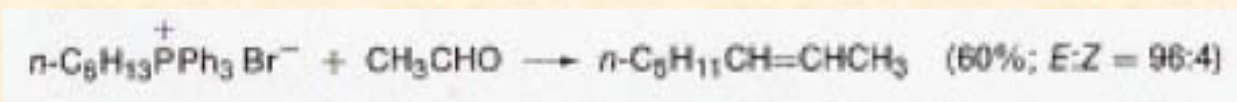
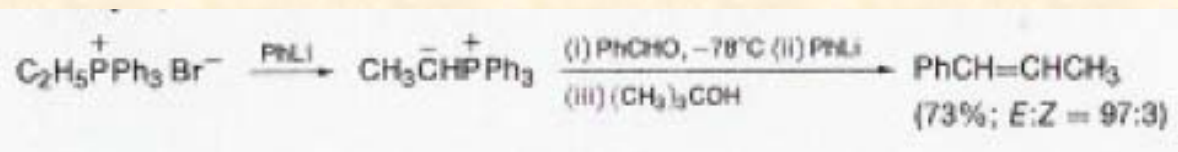
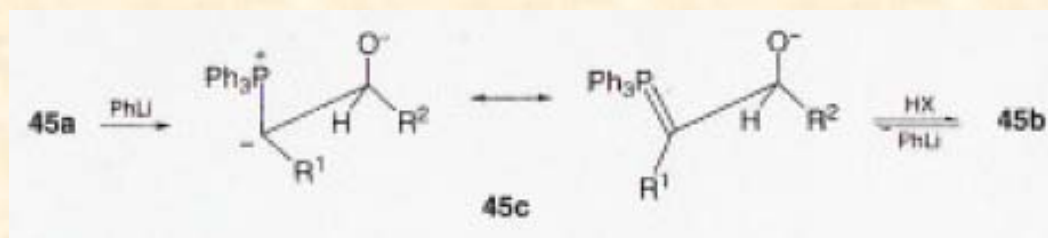
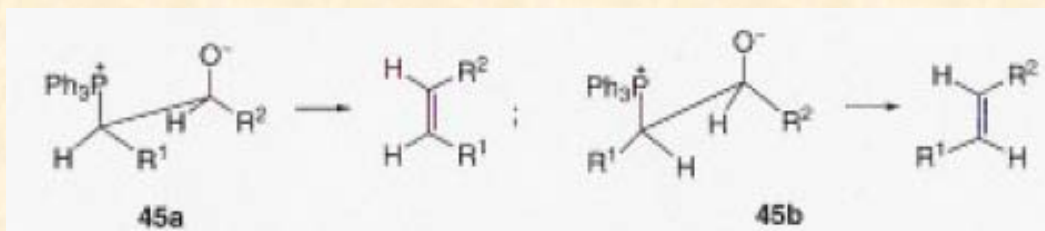
5.3.1.3 Steric control in the Wittig reaction



C-C bond formation through carbanions

5.3.1 The Wittig reaction

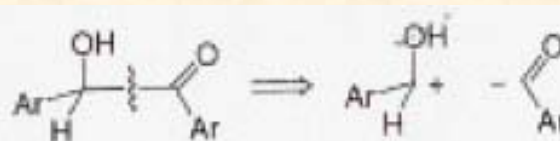
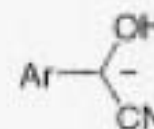
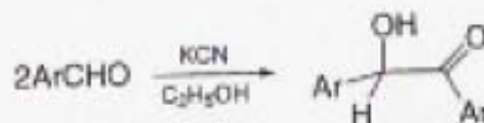
5.3.1.3 Steric control in the Wittig reaction



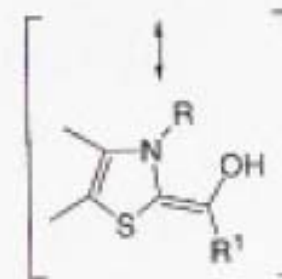
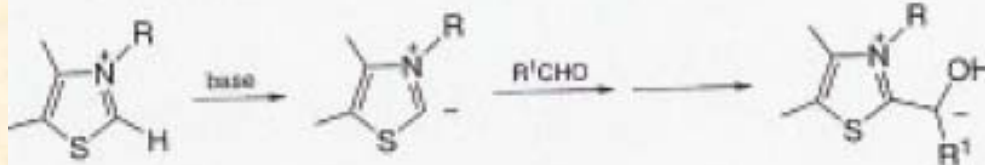
C-C bond formation through carbanions

Nucleophilic acylation

5.4.1 The benzoin reaction

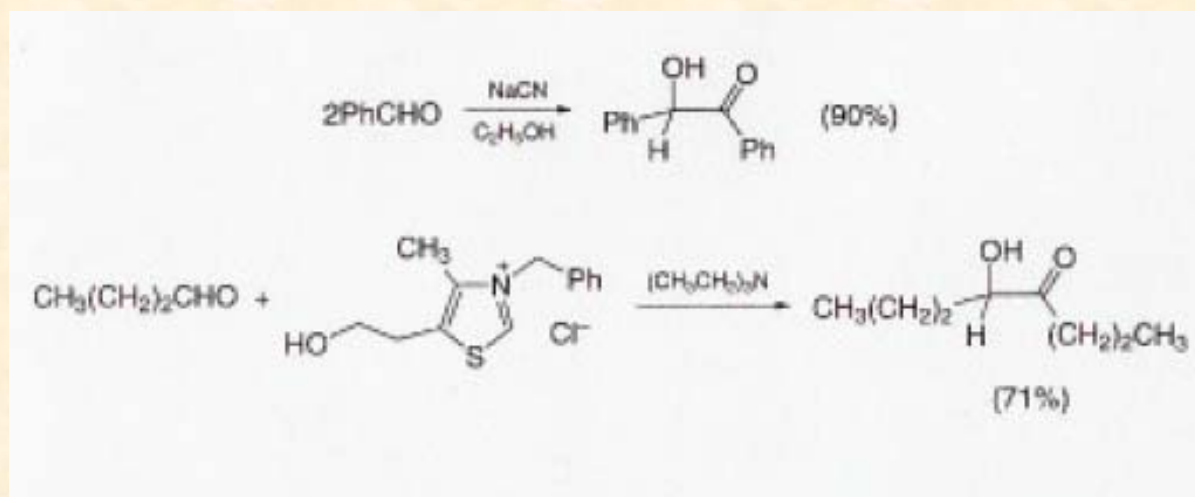


Umpolung.



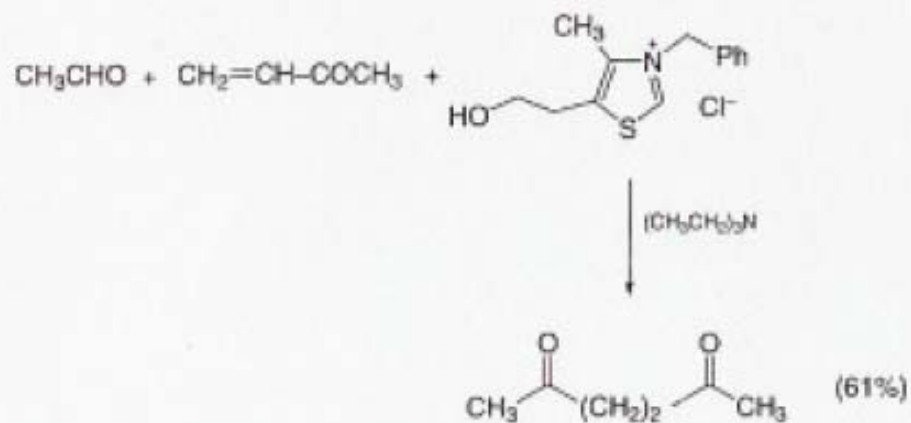
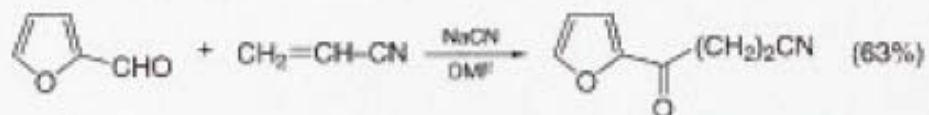
C-C bond formation through carbanions

5.4.1 The benzoin reaction



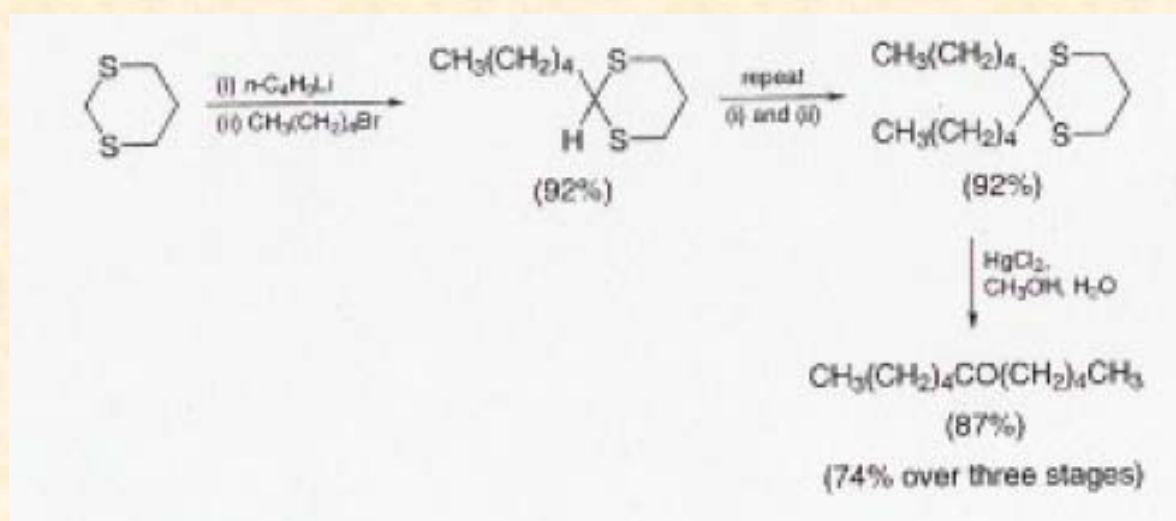
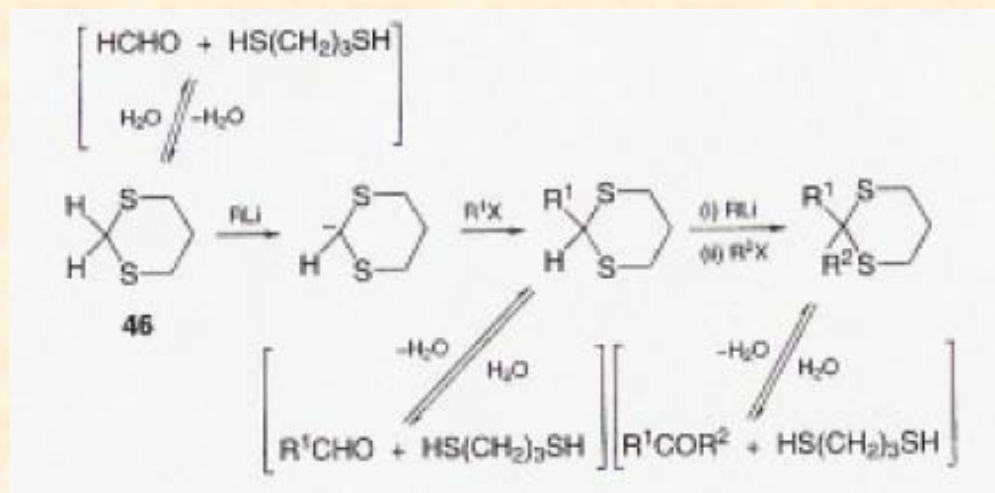
C-C bond formation through carbanions

5.4.2 Conjugate addition (the Stetter reaction)



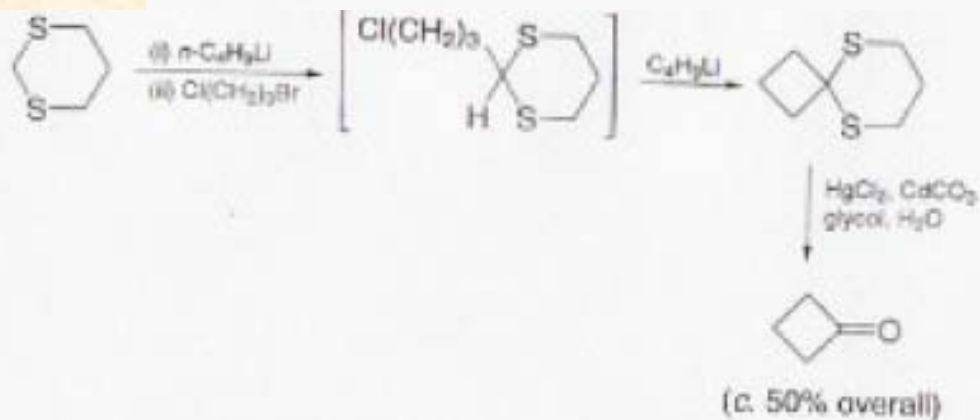
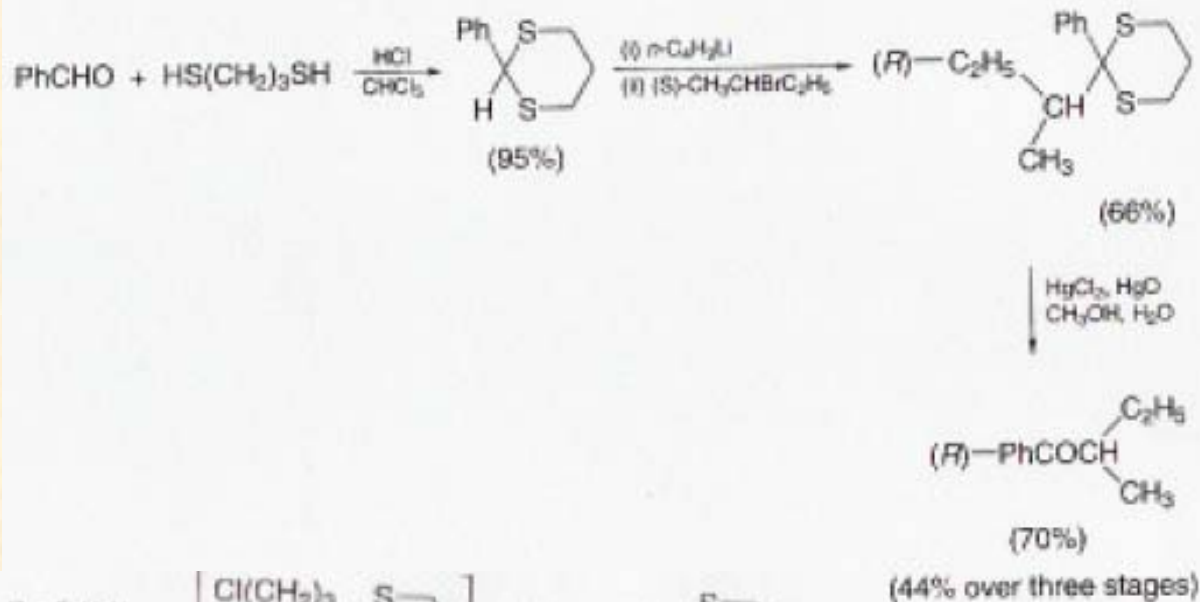
C-C bond formation through carbanions

5.4.3 1,3-Dithianes and 1,3,5-trithianes



C-C bond formation through carbanions

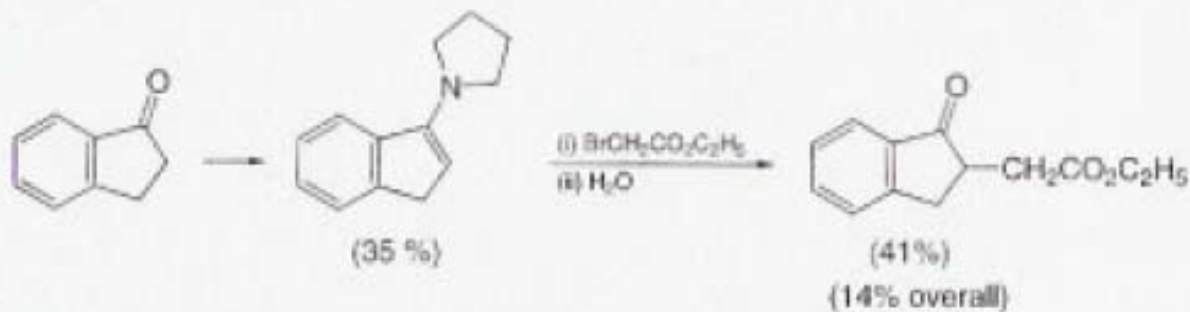
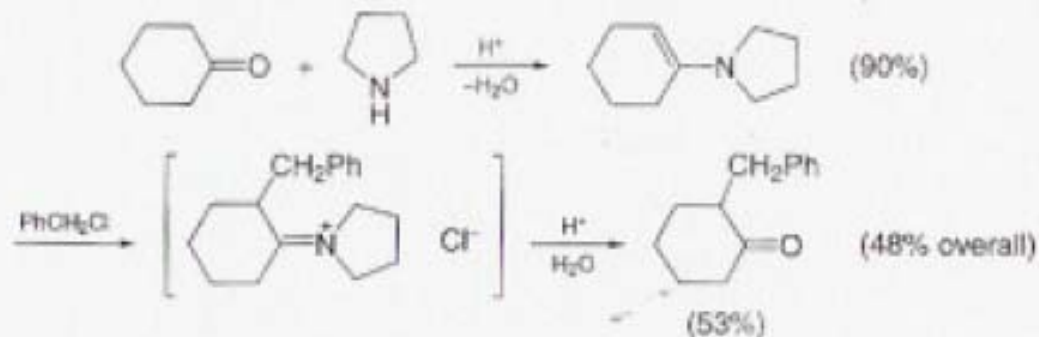
5.4.3 1,3-Dithianes and 1,3,5-trithianes



C-C bond formation through carbanions

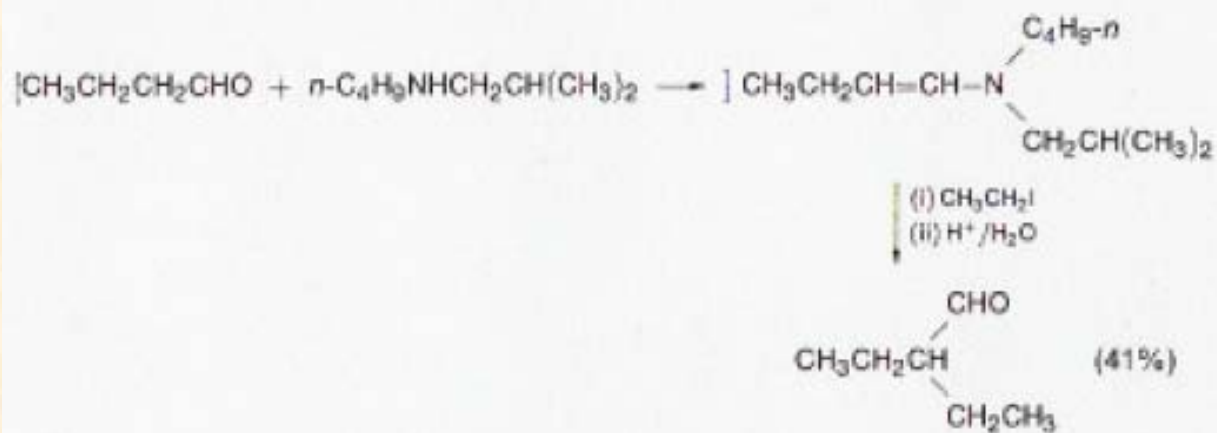
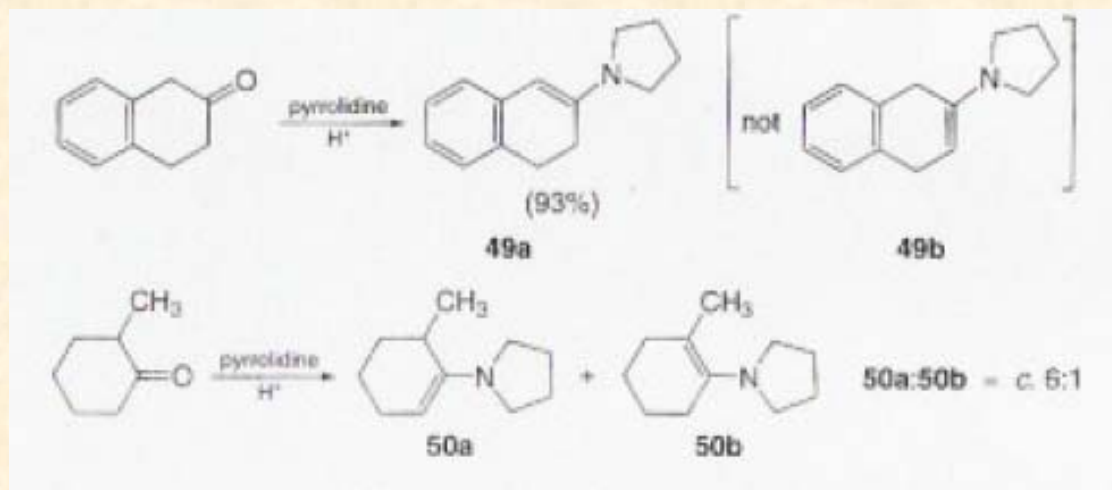
Alkene, arene and heteroarene nucleophiles

5.5.1 Alkylation



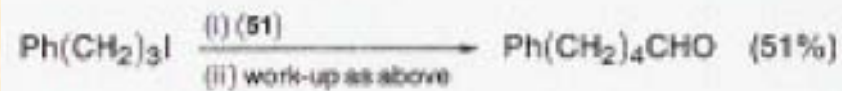
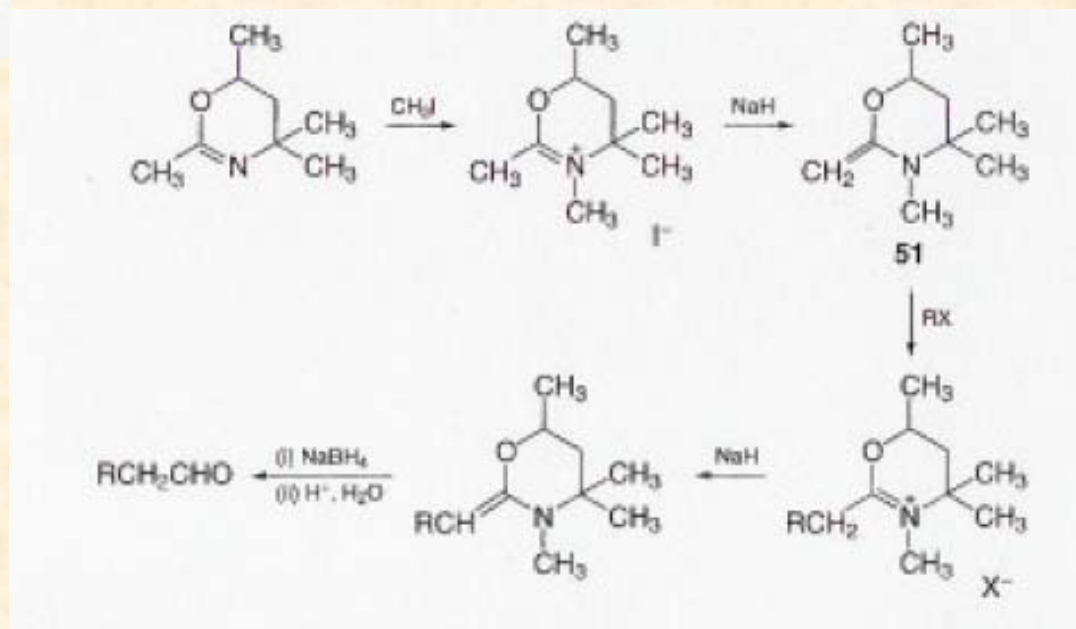
C-C bond formation through carbanions

5.5.1 Alkylation



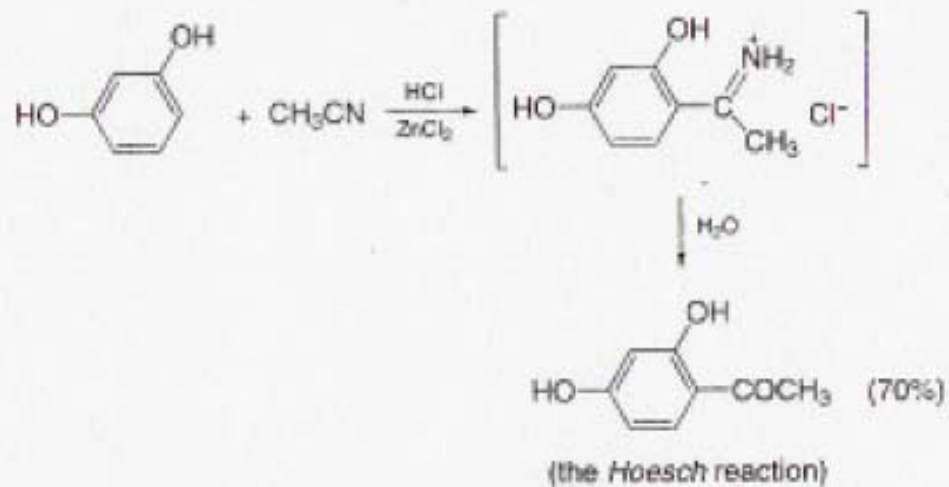
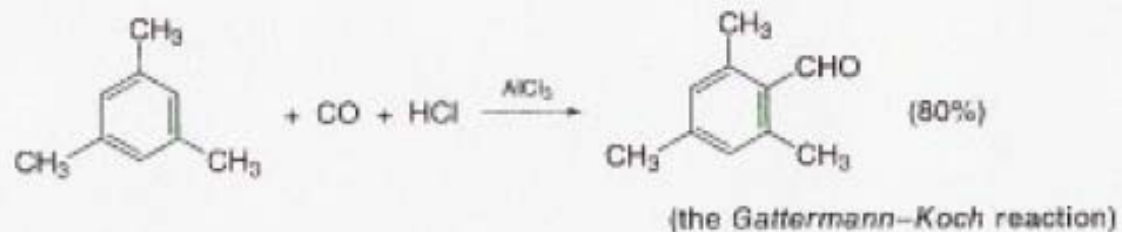
C-C bond formation through carbanions

5.5.1 Alkylation



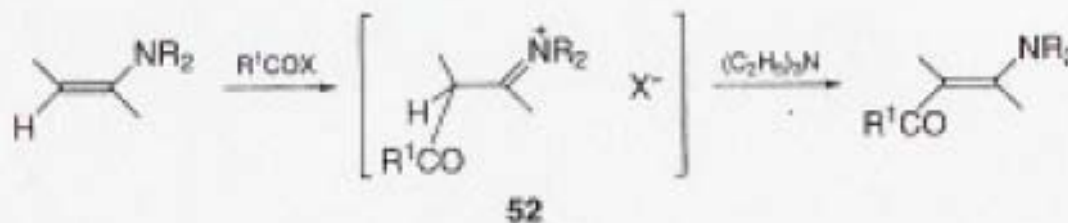
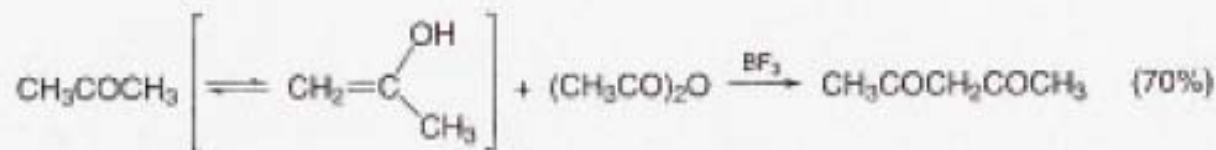
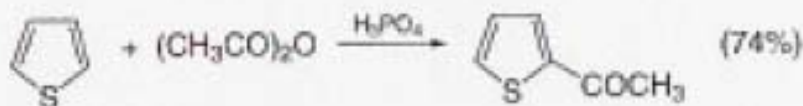
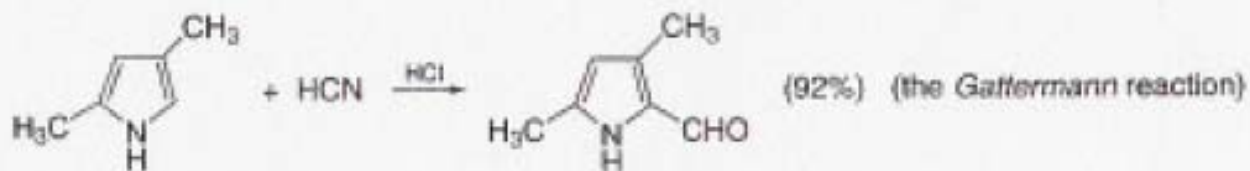
C-C bond formation through carbanions

5.5.2 Acylation



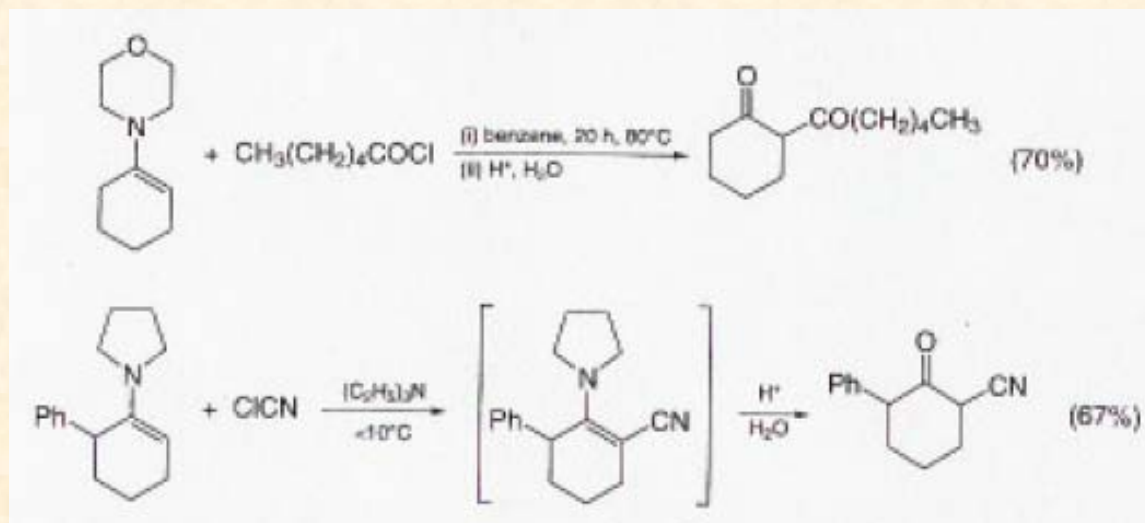
C-C bond formation through carbanions

5.5.2 Acylation

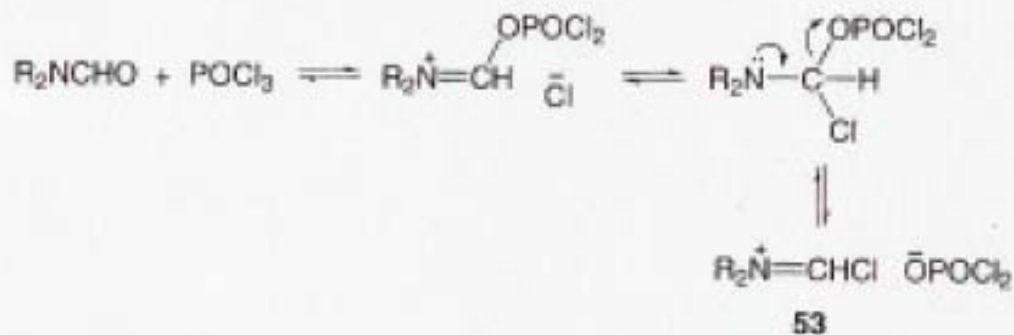


C-C bond formation through carbanions

5.5.2 Acylation



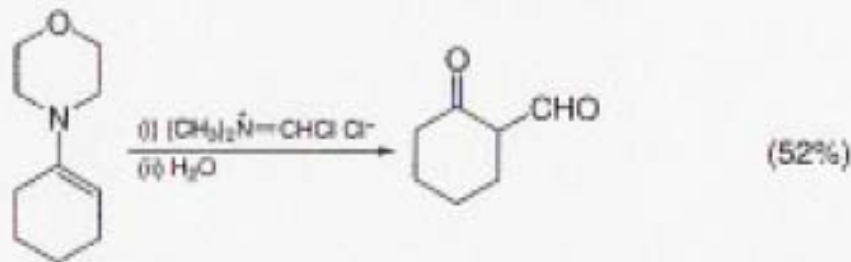
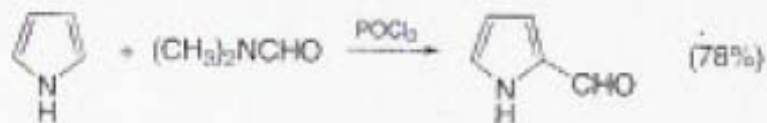
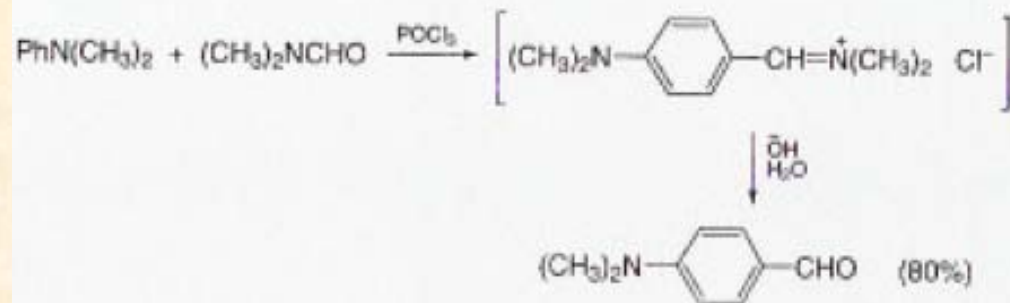
Wilsmeier-Haack-Arnold
reaction



C-C bond formation through carbanions

5.5.2 Acylation

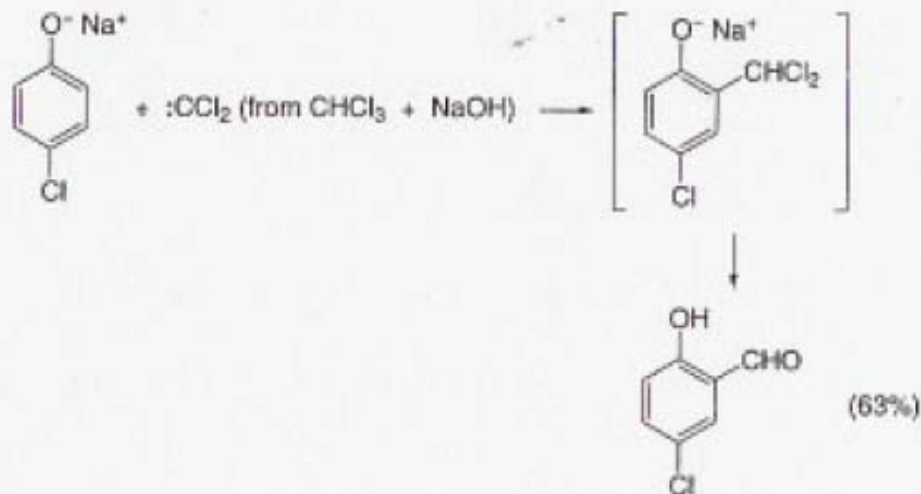
Wilsmeier-Haack- reaction



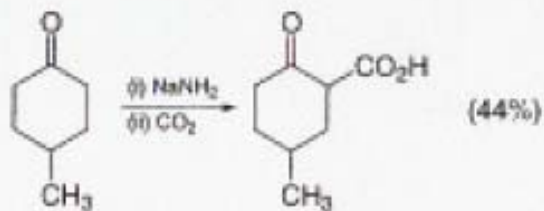
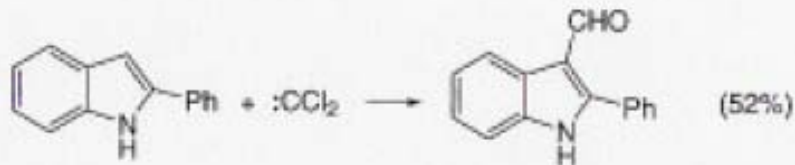
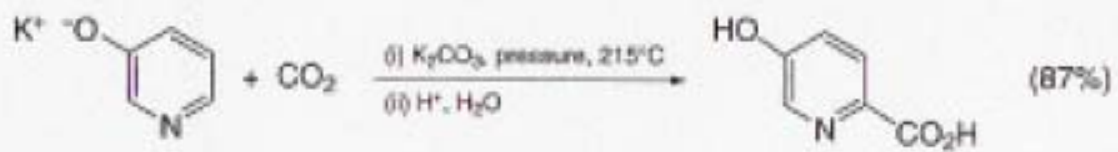
C-C bond formation through carbanions

5.5.2 Acylation

Reimer-Tiemann reaction

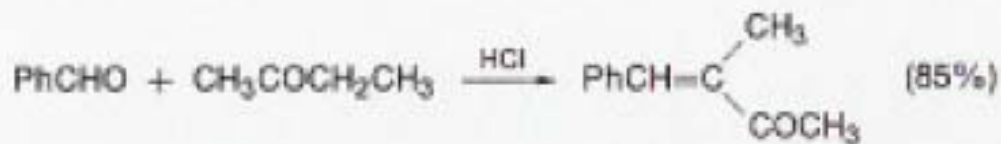
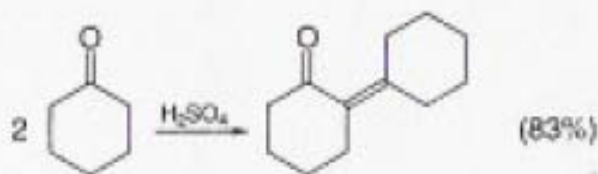
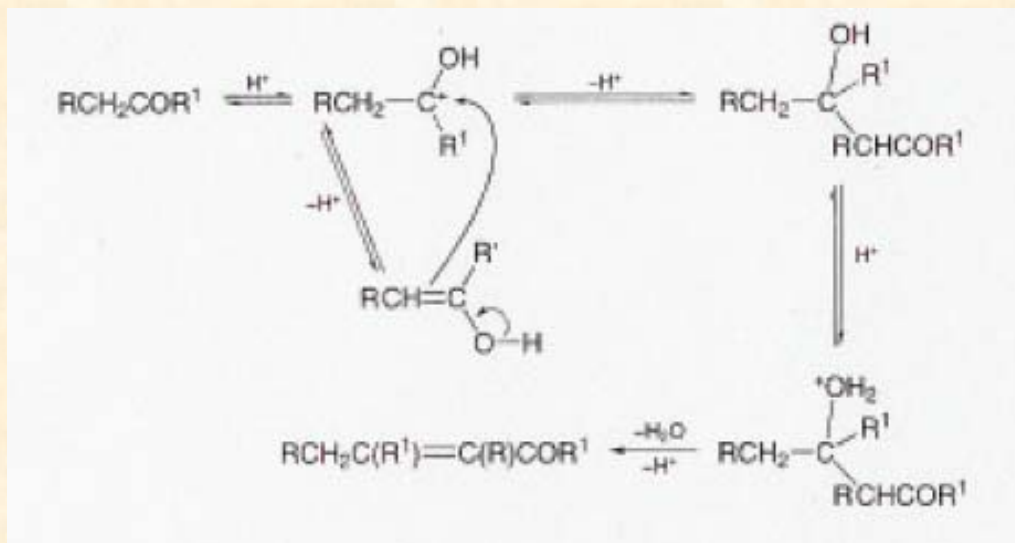


Kolbe-Schmitt reaction



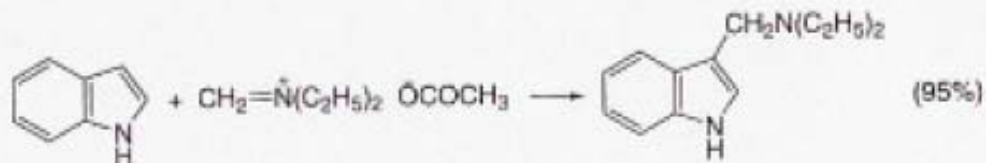
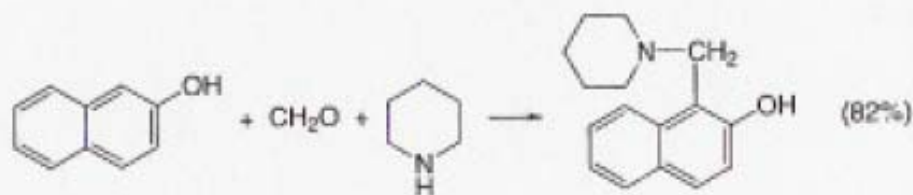
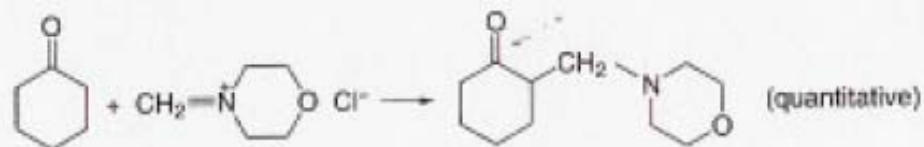
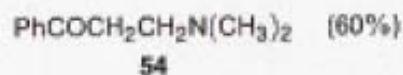
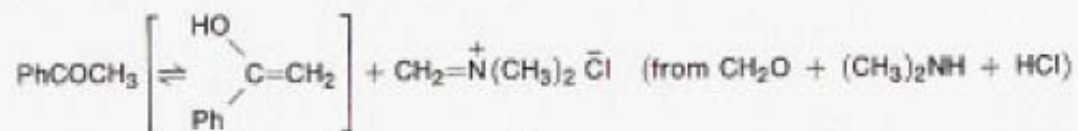
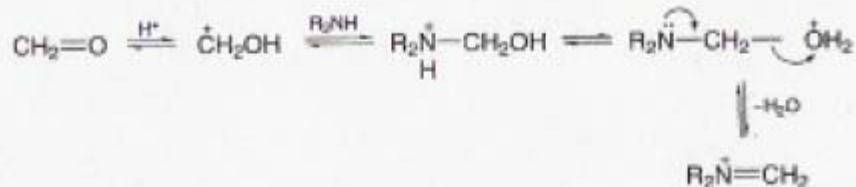
C-C bond formation through carbanions

5.5.3 Addition and condensation reactions with carbonyl and related compounds



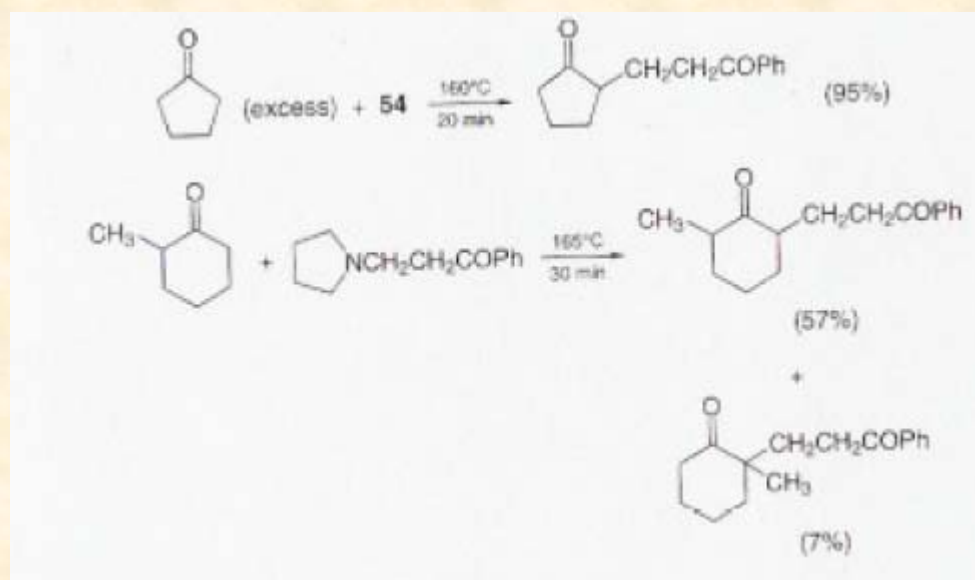
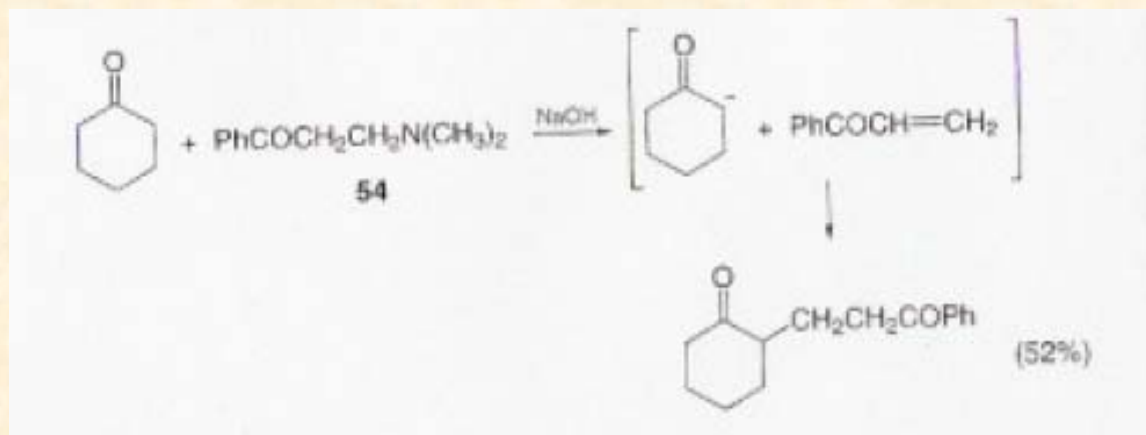
C-C bond formation through carbanions

Mannich
reaction



C-C bond formation through carbanions

Mannich reaction

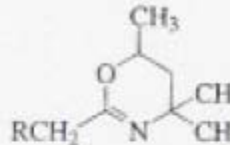

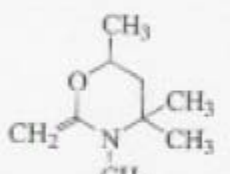


Summary

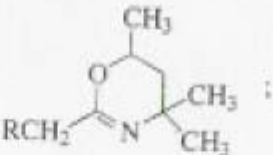
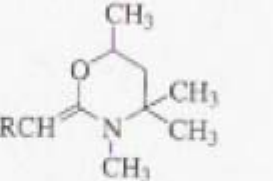
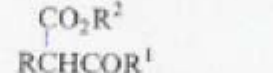
Table 5.1 Disconnections for some products formed from stabilized carbanions and related species

Section number	Product	Synthons		Synthetic equivalents	
		Electrophilic	Nucleophilic	Electrophilic	Nucleophilic
5.1.1 (pp. 61–64)	$\text{RCH}(\text{CO}_2\text{R}^1)_2$	$\Rightarrow \text{R}^+$	$\bar{\text{C}}\text{H}(\text{CO}_2\text{R}^1)_2$	RX (halide)	$\text{CH}_2(\text{CO}_2\text{R}^1)_2$
5.1.1	$\begin{array}{c} \text{CO}_2\text{R}^2 \\ \\ \text{RCH} \\ \\ \text{COR}^1 \end{array}$	$\Rightarrow \text{R}^+$	$\begin{array}{c} \text{CO}_2\text{R}^2 \\ \\ \bar{\text{C}}\text{H} \\ \\ \text{COR}^1 \end{array}$	RX (halide)	$\begin{array}{c} \text{CO}_2\text{R}^2 \\ \\ \text{CH}_2 \\ \\ \text{COR}^1 \end{array}$
5.1.1 (pp. 62–64)	$\text{RCH}_2\text{COCH}_2\text{COR}^1$	$\Rightarrow \text{R}^+$	$\bar{\text{C}}\text{H}_2\text{COCH}_2\text{COR}^1$	RX (halide)	$\text{CH}_3\text{COCH}_2\text{CO}$
5.1.2 reaction (5.4)	$\text{RCH}_2\text{CO}_2\text{H}$	$\Rightarrow \text{R}^+$	$\bar{\text{C}}\text{H}_2\text{CO}_2\text{H}$	RX (halide)	$\text{CH}_2(\text{CO}_2\text{R}^1)_2$
5.1.2 reaction (5.5)	RCH_2COR^1	$\Rightarrow \text{R}^+$	$\bar{\text{C}}\text{H}_2\text{COR}^1$	RX (halide)	$\begin{array}{c} \text{CO}_2\text{R}^2 \\ \\ \text{CH}_2 \\ \\ \text{COR}^1 \end{array}$
5.1.3 reaction (5.8)	$\begin{array}{c} \text{COR}^1 \\ \\ \text{RCOCH} \\ \\ \text{COR}^2 \end{array}$	$\Rightarrow \text{RCO}^+$	$\begin{array}{c} \text{COR}^1 \\ \\ \bar{\text{C}}\text{H} \\ \\ \text{COR}^2 \end{array}$	RCOCl	$\begin{array}{c} \text{COR}^1 \\ \\ \text{CH}_2 \\ \\ \text{COR}^2 \end{array}$
reaction (5.11)	$\begin{array}{c} \text{COR}^2 \\ \\ \text{RCOCH}_2\text{CO}_2\text{R}^1 \\ \\ \text{COR}^2 \end{array}$	$\Rightarrow \text{RCO}^+$	$\bar{\text{C}}\text{H}_2\text{CO}_2\text{R}^1$	RCOCl	$\begin{array}{c} \text{COR}^2 \\ \\ \text{CH}_2(\text{CO}_2\text{R}^1)_2 \end{array}$
5.1.5 reaction (5.15)	$\begin{array}{c} \text{R}_2\text{C}-\text{CH} \\ \quad \\ \text{CH}(\text{COR}^3)_2 \quad \text{R}^1 \end{array}$	$\Rightarrow \text{R}_2\text{C}^+-\text{CHR}^1-\text{COR}^2$	$\bar{\text{C}}\text{H}(\text{COR}^3)_2$	$\text{R}_2\text{C}=\text{CR}^1-\text{COR}^2$	$\text{CH}_2(\text{COR}^3)_2$
5.2.1 (pp. 73–75) also 5.2.3.2	$\text{RR}^1\text{CHCOR}^2$ (CN)	$\Rightarrow \text{R}^+$	$\text{R}^1\bar{\text{C}}\text{H}\text{COR}^2$ (CN)	RX	$\text{R}^1\text{CH}_2\text{COR}^2$ (CN)

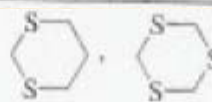

Summary

5.2.2 (pp. 75–77)	$\text{RCOCHR}^1\text{CO}_2\text{R}^2$	$\Rightarrow \text{RCO}^+$	$\text{R}^1\bar{\text{C}}\text{HCO}_2\text{R}^2$	RCO_2R^2	$\text{R}^1\text{CH}_2\text{CO}_2\text{R}^2$
5.2.3.1 reaction (5.17)	RR^2CHCHO	$\Rightarrow (\text{R}^2)^+$	$\text{R}\bar{\text{C}}\text{HCHO}$	R^2X	$\text{RCH}_2\text{CH}=\text{NR}^1$
5.2.3.1 reaction (5.19)	RR^1CHCHO	$\Rightarrow (\text{R}^1)^+$	$\text{R}\bar{\text{C}}\text{HCHO}$	R^1X	
5.4.3 reaction (5.25)	R^1COR^2	$\Rightarrow (\text{R}^2)^+$	$\text{R}^1\bar{\text{C}}\text{O}$	R^2X	
5.5.1 (pp. 95–96)	$\text{RR}^1\text{CHCOR}^2$	$\Rightarrow \text{R}^+$	$\text{R}^1\bar{\text{C}}\text{HCOR}^2$	RX	$\text{R}^1\text{CH}=\overset{\text{R}^2}{\text{C}}-\text{NR}_2^3$
5.5.1 reaction (5.26)	RCH_2CHO	$\Rightarrow \text{R}^+$	$\bar{\text{C}}\text{H}_2\text{CHO}$	RX	
5.5.2 (pp. 96–99)	$\begin{array}{c} \text{COR}^1 \\ \diagdown \\ \text{RCH} \\ \diagup \\ \text{COR}^2 \end{array}$	$\Rightarrow \text{R}^1\text{CO}^+$	$\text{R}\bar{\text{C}}\text{HCOR}^2$	R^1COCl	$\text{RCH}=\overset{\text{R}^2}{\text{C}}-\text{NR}_2^3$
5.5.3 (pp. 100–103)	$\text{RCOCH}_2\text{CH}_2\overset{\text{R}^1}{\text{C}}\text{HCOR}^2$	$\Rightarrow \text{RCOCH}_2\text{CH}_2^+$	$\text{R}^1\bar{\text{C}}\text{HCOR}^2$	$\text{RCOCH}_2\text{CH}_2\text{NR}_2^3$	$\text{R}^1\text{CH}_2\text{COR}^2$

Summary

Synthon	Synthetic equivalents	For example(s), see page(s)
(a) <i>Nucleophilic synthons</i>		
4. $\text{R}\bar{\text{C}}\text{HCHO}$	RCH_2CHO ; $\text{RCH}_2\text{CH}=\text{NR}^1$;  	74, 77-9, 81-4, 96
5. $\text{R}\bar{\text{C}}\text{HCO}\text{R}^1$	RCH_2COR^1 ; $\text{RCH}=\text{C}\begin{matrix} \text{R}^1 \\ \text{NR}_2^2 \end{matrix}$; 	64-8, 73-7, 79-82, 94-103
6. $\text{R}\bar{\text{C}}\text{HCO}_2\text{H}$	$\text{RCH}_2\text{CO}_2\text{R}^1$; $\text{RCH}(\text{CO}_2\text{H})_2$; $\text{RCH}(\text{CO}_2\text{R}^1)_2$	65-8, 70-3
7. $\text{R}\bar{\text{C}}\text{HCO}_2\text{R}^1$	$\text{RCH}_2\text{CO}_2\text{R}^1$; $\text{RCH}(\text{CO}_2\text{R}^1)_2$; $\text{RCH}=\text{C}\begin{matrix} \text{O}^- + \text{ZnBr} \\ \text{OR}^1 \end{matrix}$ (section 4.2.2)	46-7, 65-7, 73, 76-7, 83-4
8. $\text{R}\bar{\text{C}}\text{HCN}$	RCH_2CH ; RCHCN	71, 73, 76
9. $\text{R}\bar{\text{C}}\text{HCOCH}_2\text{COR}^1$	$\text{RCH}_2\text{COCH}_2\text{COR}^1$	63, 80

Summary

Synthon	Synthetic equivalents	For example(s), see page(s)
10. $\bar{C}HO$		92-4
11. $R\bar{C}O$		92-4
12. $R\bar{C}(COR^1)_2$, $R\bar{C}(CO_2R^1)_2$, etc.	$RCH(COR^1)_2$, $RCH(CO_2R^1)_2$, etc.	60-73 77, 80, 96-9
(b) <i>Electrophilic synthons</i>		
6. $\bar{C}HO$	HCO_2R ; $HCONR_2$; $CH(OR)_3$; $ClCH=NR_2 X^-$	
12. $\bar{C}H_2CH_2COR$	$CH_2=CHCOR$; $R_3N^+CH_2CH_2COR$; $R_3N^+CH_2CH_2COR X^-$	71-3, 84-8, 101-3
13. $\bar{C}HCl_2$	$CHCl_3$ (via $:CCl_2$)	99