Advanced Organic Chemistry/ Organic Synthesis – CH 621

Ring Closure – Ring Opening

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Introduction

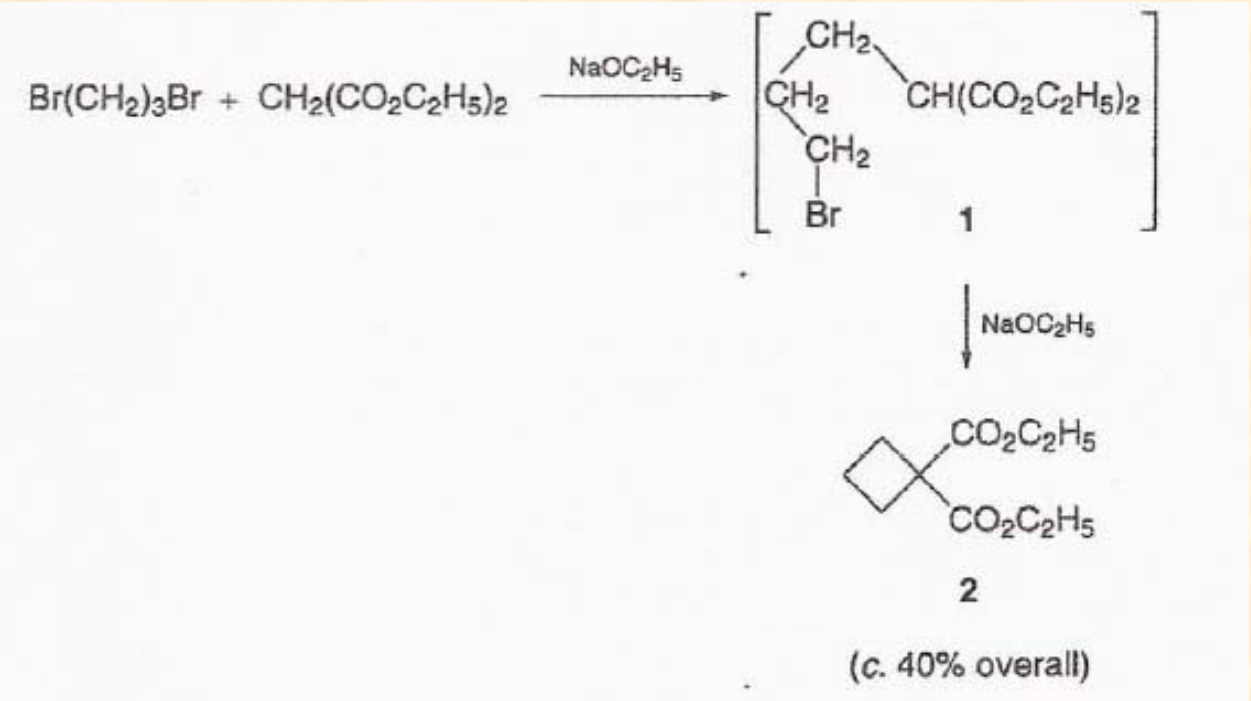
Importance of cyclic compounds

- Intramolecular cyclizations by E^+-Nu^- interactions
- Cycloadditions
- Electrocyclic cyclizations
- Ring Openings

Ring Closure – Intramolecular Cyclizations

Intramolecular cyclization by electrophile–nucleophile interaction

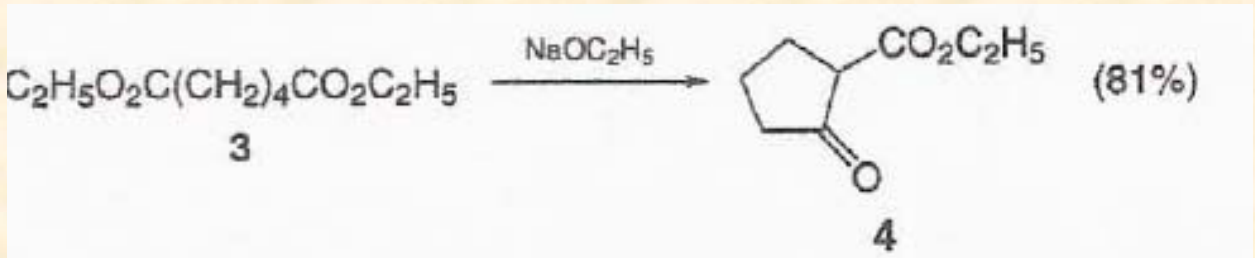
Alkylation



Ring Closure – Intramolecular Cyclizations

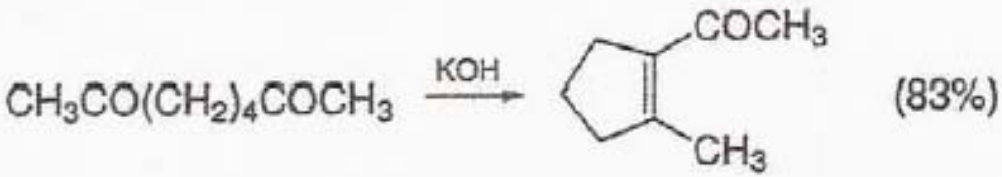
Intramolecular cyclization by electrophile–nucleophile interaction

Acylation



Dieckmann reaction

Condensation

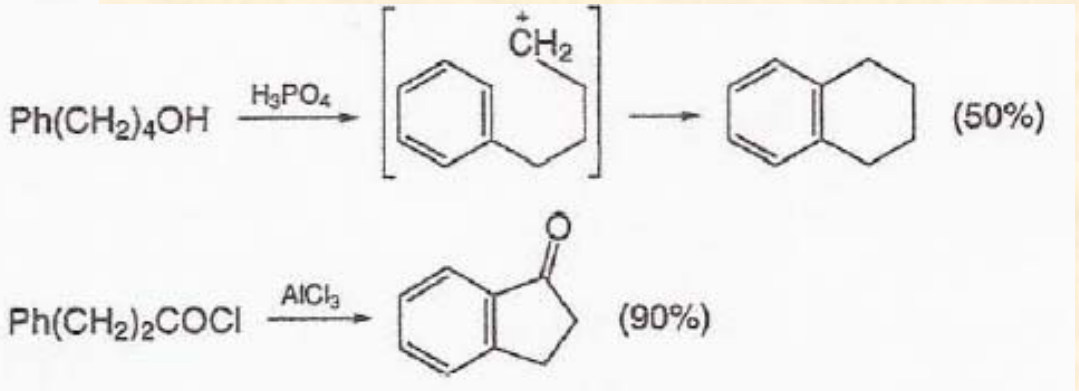


Ring Closure – Intramolecular Cyclizations

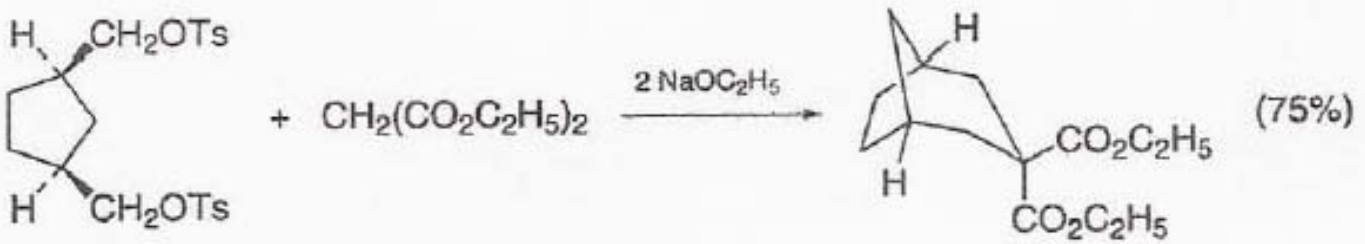
Intramolecular cyclization by electrophile–nucleophile interaction

Synthesis of bicyclic compounds

Electrophilic aromatic substitution



Alkylation

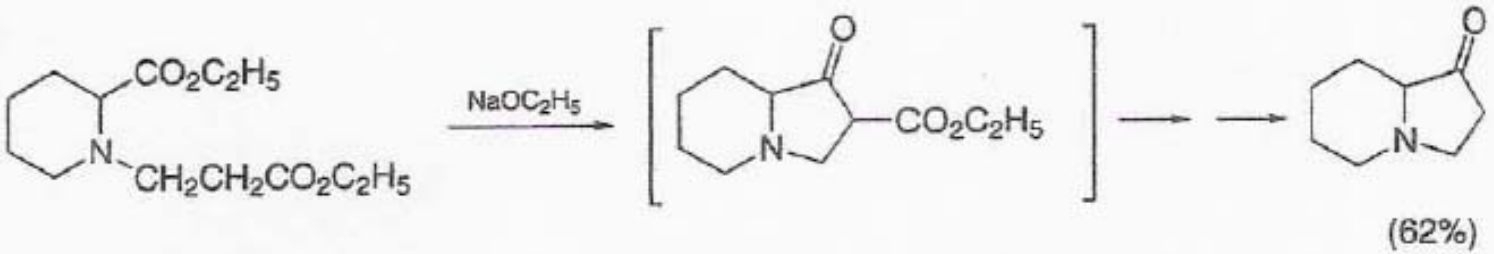


Ring Closure – Intramolecular Cyclizations

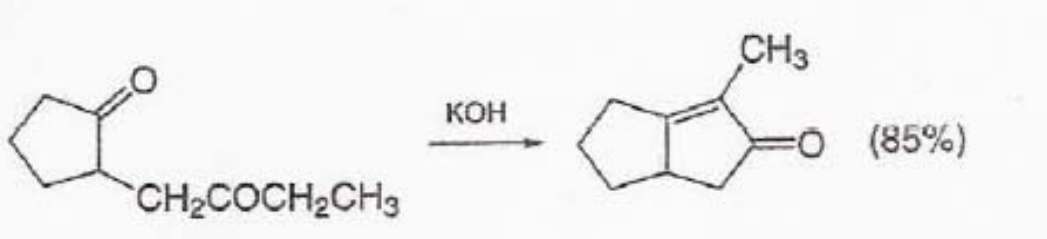
Intramolecular cyclization by electrophile–nucleophile interaction

Synthesis of bicyclic compounds

Acylation

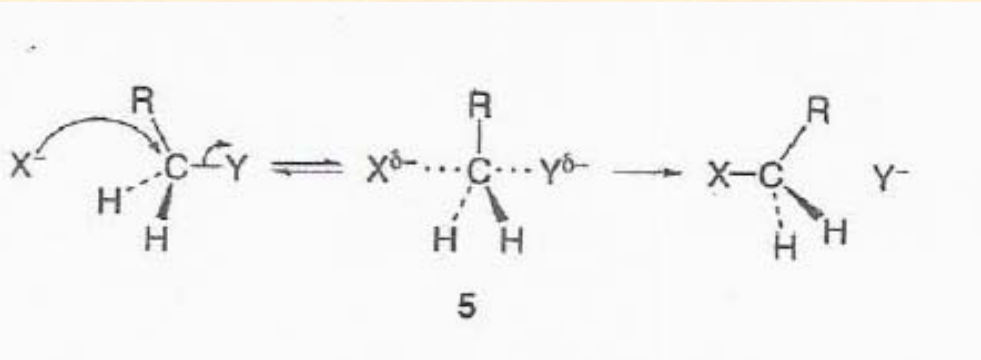


Condensation



Ring Closure – Intramolecular Cyclizations

7.1.2 *Facility of intramolecular ring closure: Baldwin's rules*



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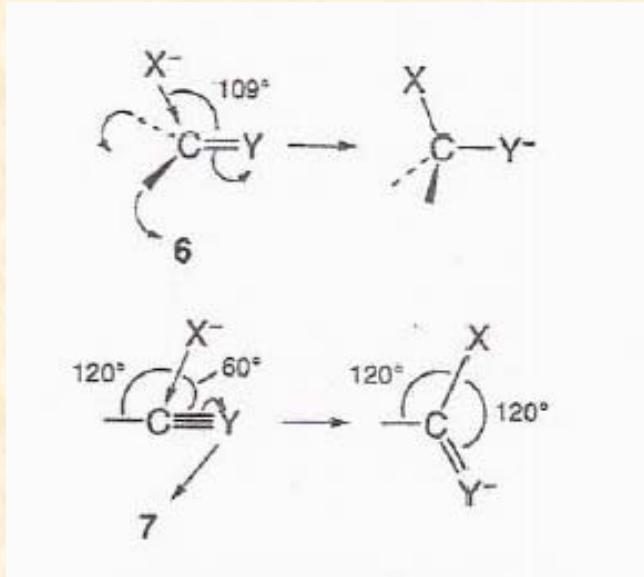


(i) the size of the ring being formed,

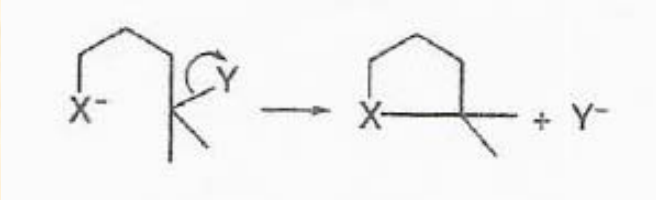
(ii) whether the atom or group Y lies outside the ring being formed or else is part of the ring system,

(iii) whether the electrophilic carbon is tetrahedral, trigonal or digonal

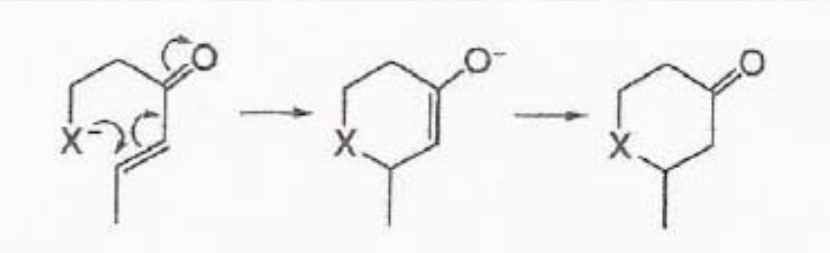
Ring Closure – Intramolecular Cyclizations

7.1.2 *Facility of intramolecular ring closure: Baldwin's rules*

5-*exo-tet* (five-membered ring, Y outside the ring being formed, tetrahedral carbon undergoing substitution)



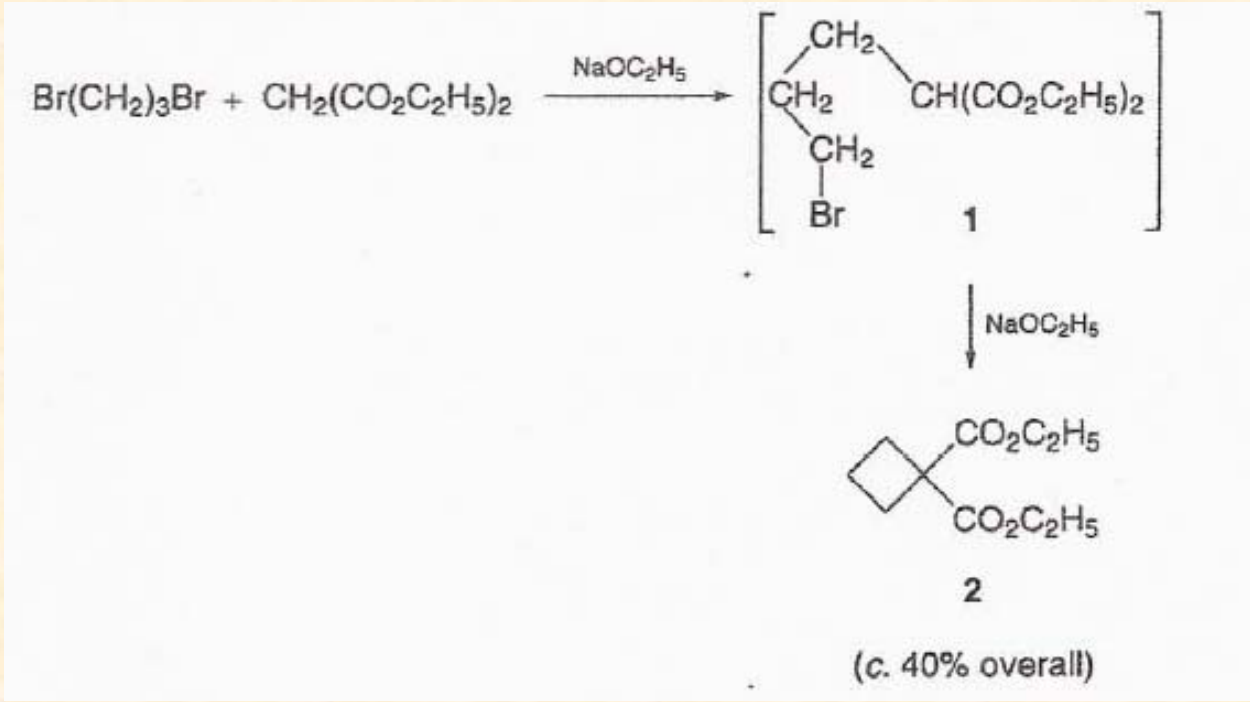
6-*endo-trig* [six-membered ring, Y (= carbon in this case) forming part of the ring, trigonal carbon undergoing addition]



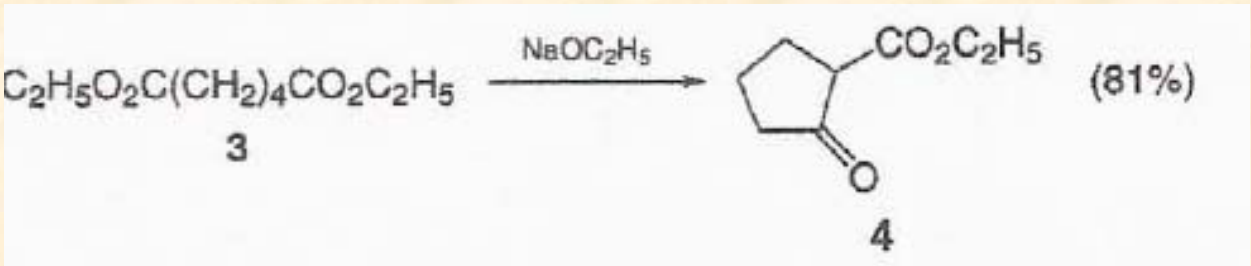
Ring Closure – Intramolecular Cyclizations

7.1.2 *Facility of intramolecular ring closure: Baldwin's rules*

4-exo-tet



5-exo-trig



Ring Closure – Intramolecular Cyclizations

7.1.2 *Facility of intramolecular ring closure: Baldwin's rules*

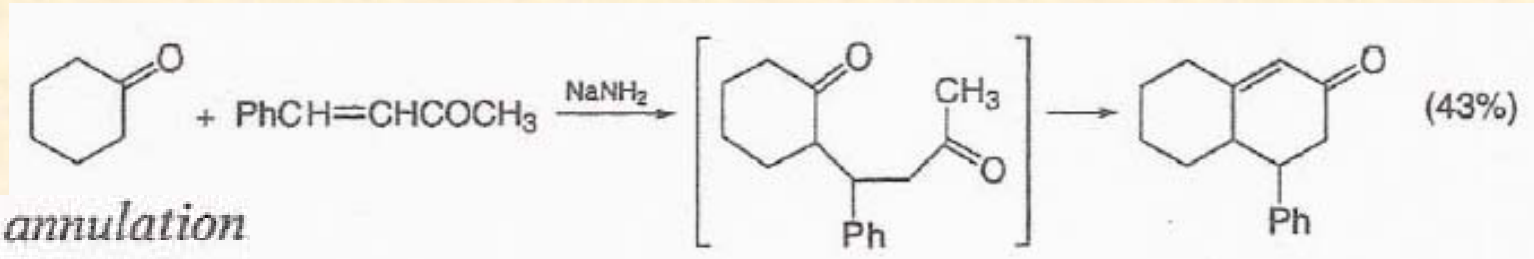
Rule 1 3- to 7-*exo-tet* processes are all favoured; 5- and 6-*endo-tet* processes are disfavoured.[16]

Rule 2 3- to 7-*exo-trig* processes are all favoured; 3- to 5-*endo-trig* processes are disfavoured; 6- and 7-*endo-trig* processes are favoured.

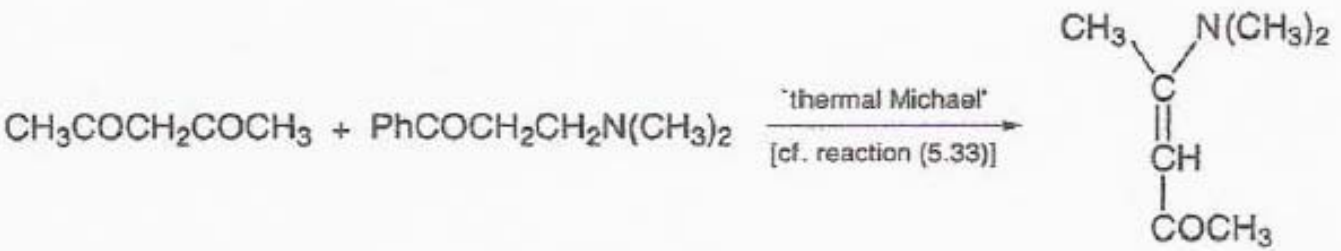
Rule 3 3- and 4-*exo-dig* processes are disfavoured; 5- to 7-*exo-dig* processes are favoured; 3- to 7-*endo-dig* processes are favoured.

Ring Closure – Intramolecular Cyclizations

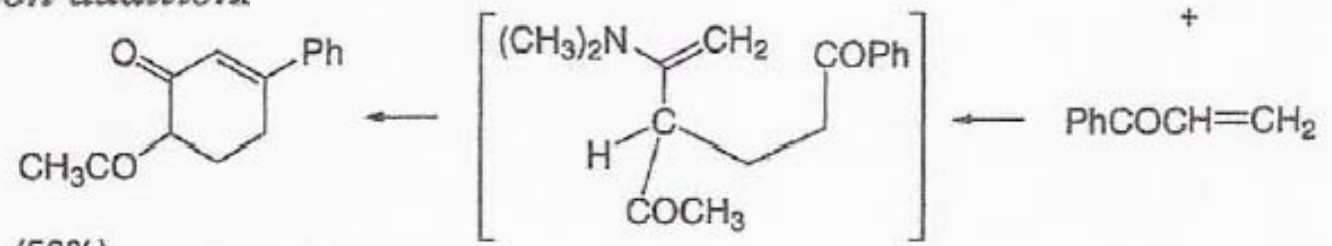
7.1.3 *Michael addition in ring-closure processes*



Robinson annulation

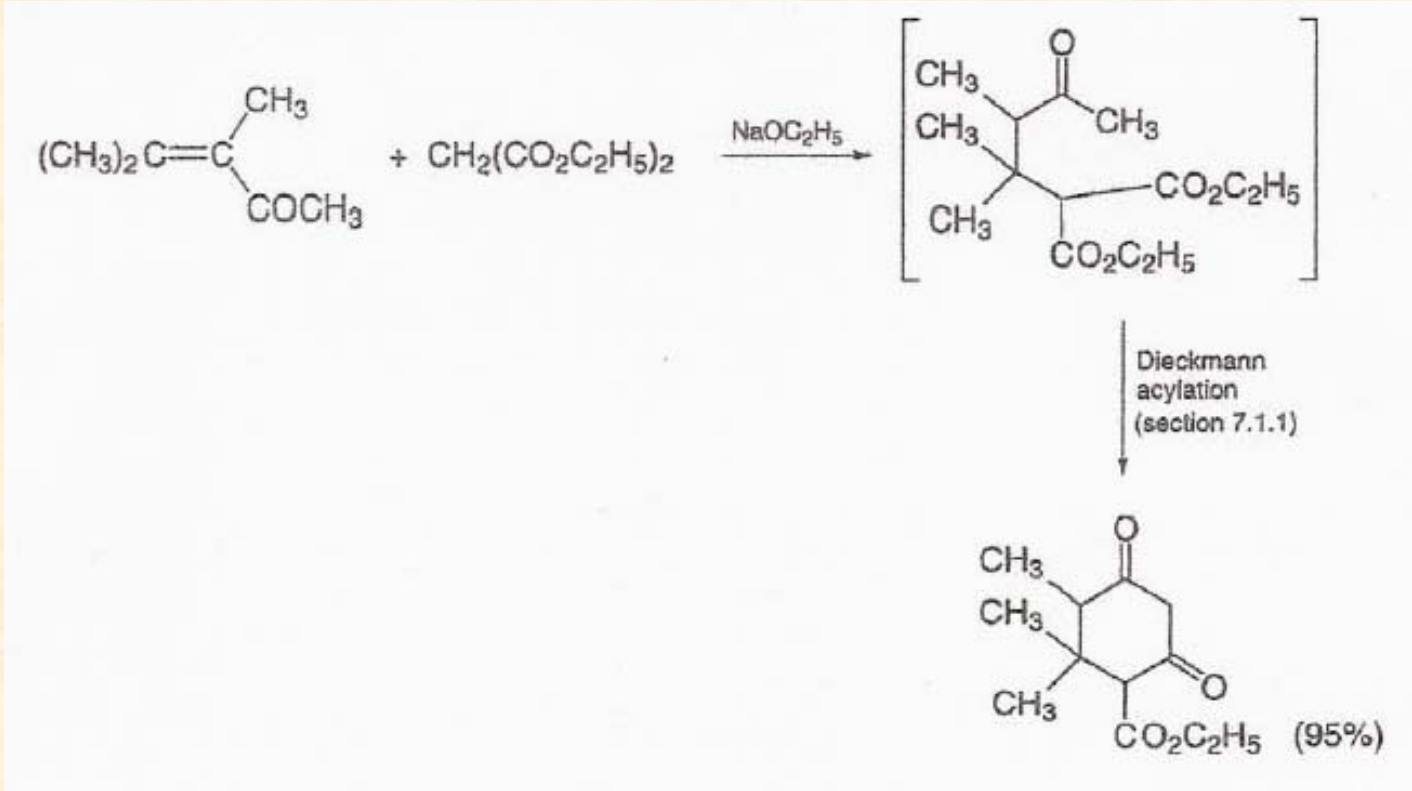


Michael–Robinson addition



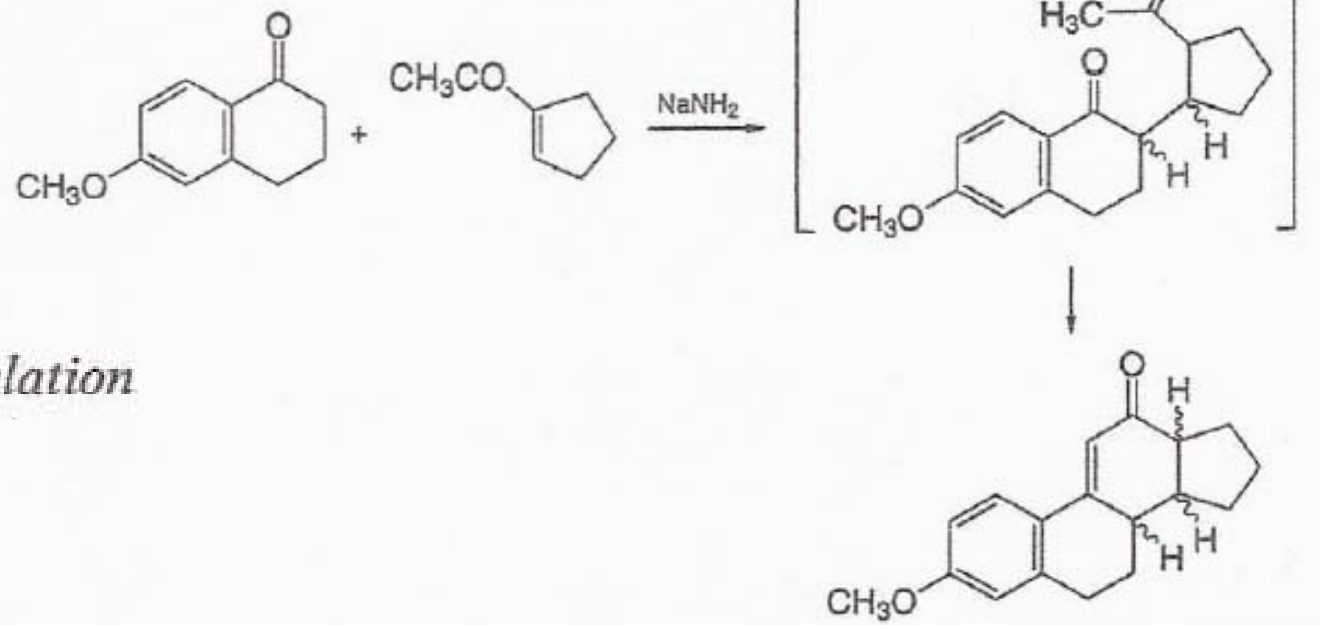
Ring Closure – Intramolecular Cyclizations

7.1.3 *Michael addition in ring-closure processes*



Ring Closure – Intramolecular Cyclizations

7.1.3 *Michael addition in ring-closure processes*



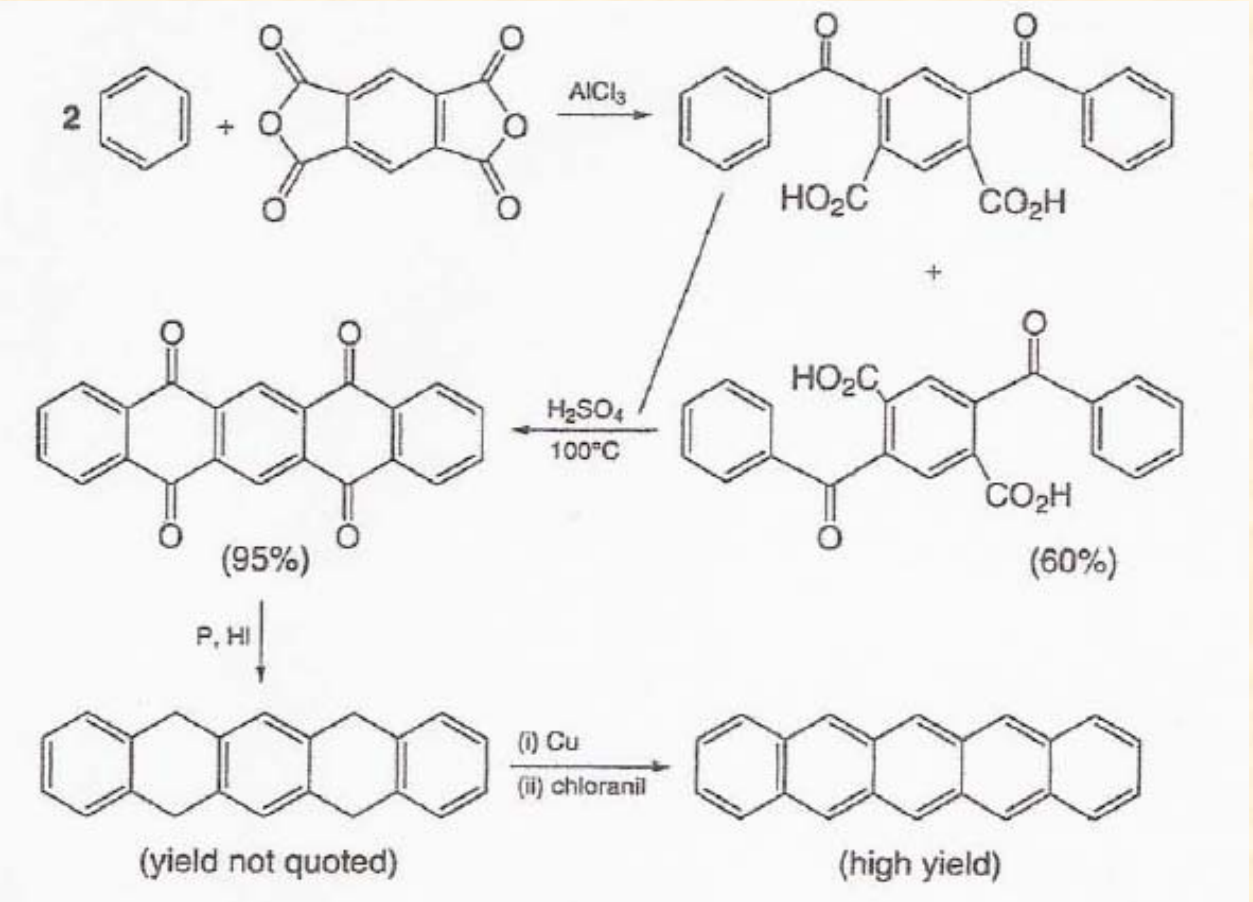
(44%: mixture of diastereoisomers)

Robinson annulation

Ring Closure – Intramolecular Cyclizations

7.1.4 Cyclization leading to aromatic and heteroaromatic rings

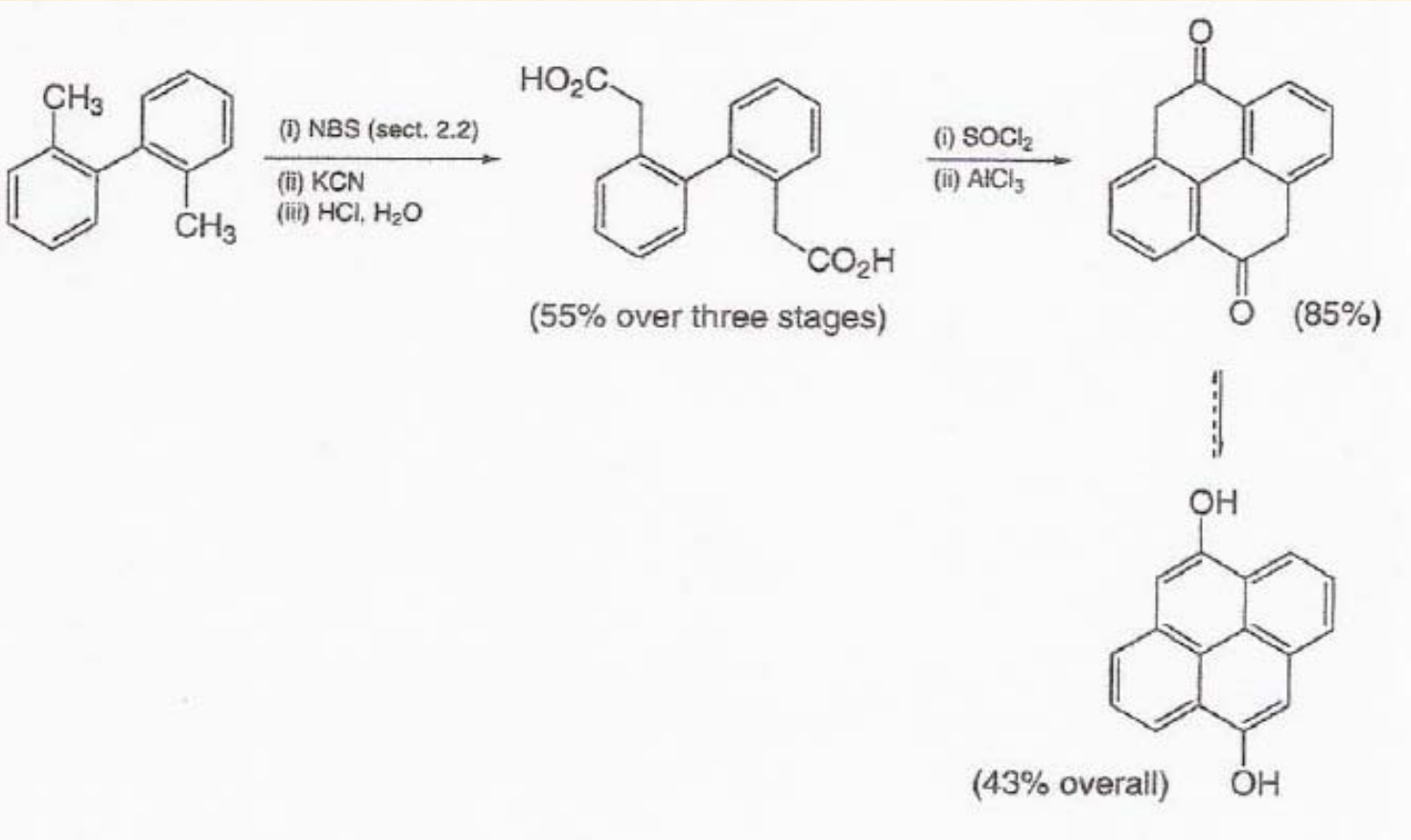
7.1.4.1 Carbocyclic rings



Ring Closure – Intramolecular Cyclizations

7.1.4 Cyclization leading to aromatic and heteroaromatic rings

7.1.4.1 Carbocyclic rings

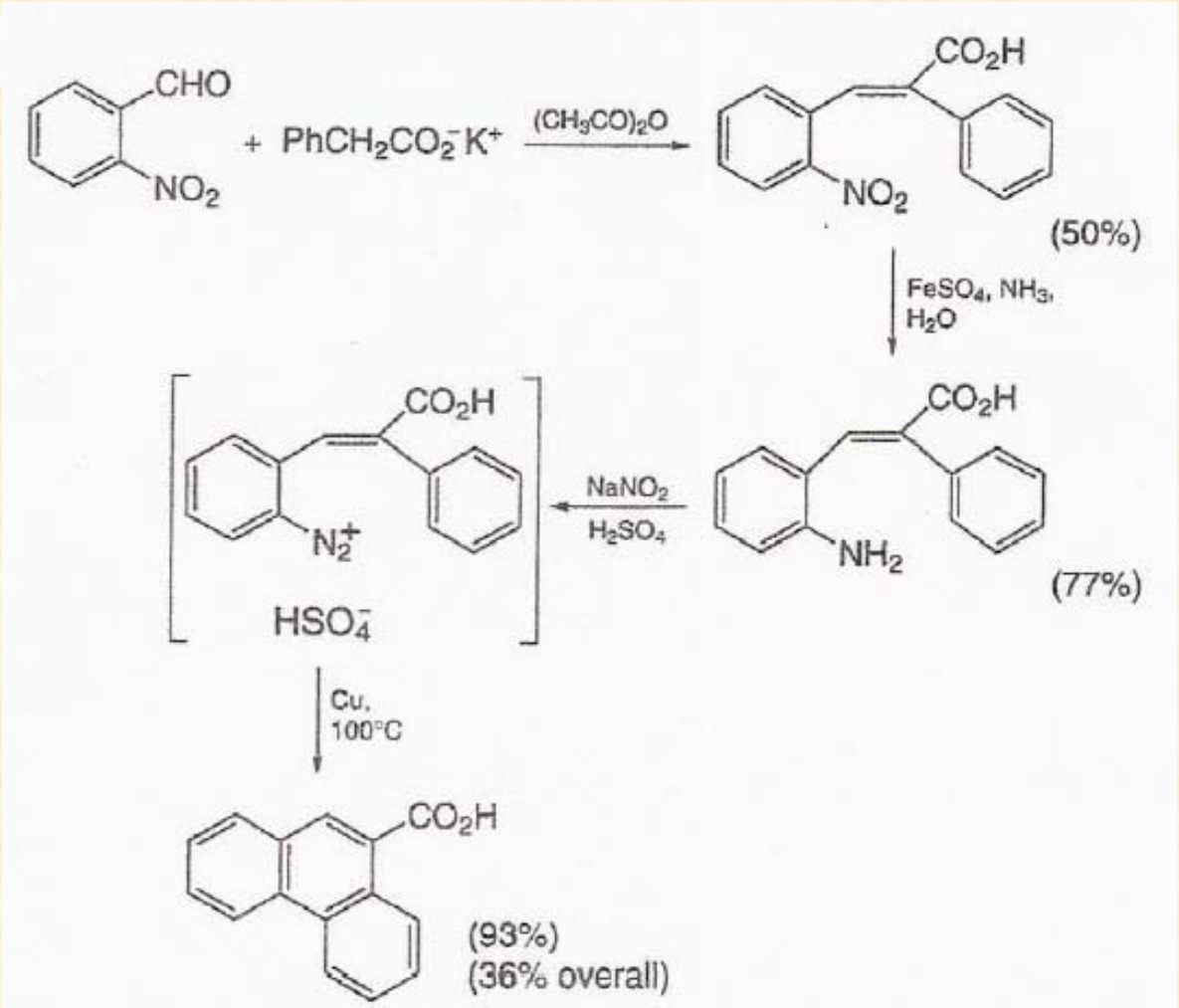


Ring Closure – Intramolecular Cyclizations

7.1.4 Cyclization leading to aromatic and heteroaromatic rings

7.1.4.1 Carbocyclic rings

Pschorr reaction



Ring Closure – Intramolecular Cyclizations

7.1.4.2 Heterocyclic rings

(i) in the synthesis of a monocyclic compound, the ring-closure step very often (although by no means always) involves carbon–heteroatom bond formation;

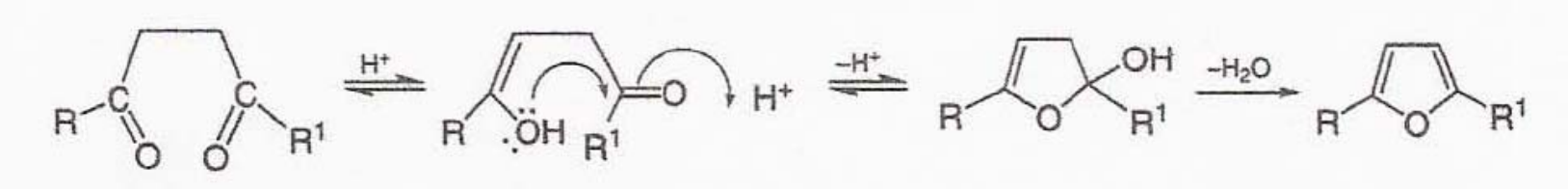
(ii) if the system contains two adjacent heteroatoms, it is unusual for the ring-closure step to involve heteroatom–heteroatom bond formation

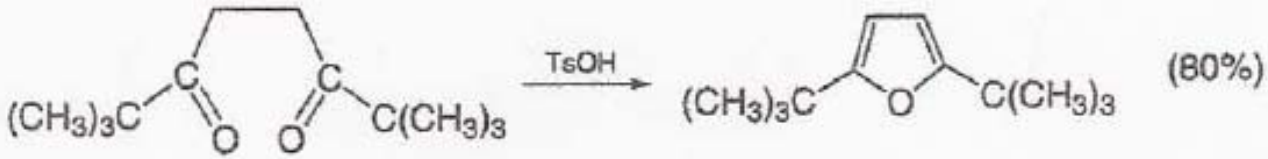
(iii) if the target molecule is bicyclic, with the heterocyclic ring fused to a benzene ring, the starting compound is almost invariably a preformed benzene derivative.

Ring Closure – Intramolecular Cyclizations

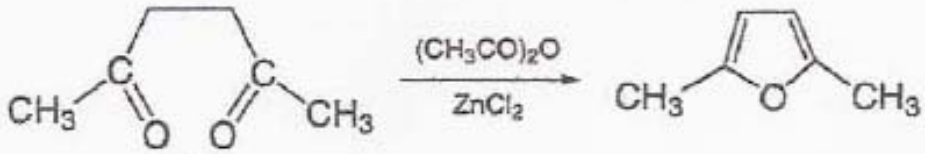
7.1.4.2 *Heterocyclic rings*

Monocyclic compounds



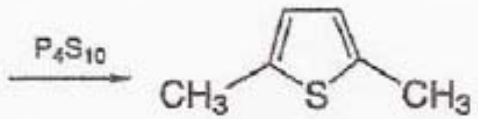
1. 

(80%)

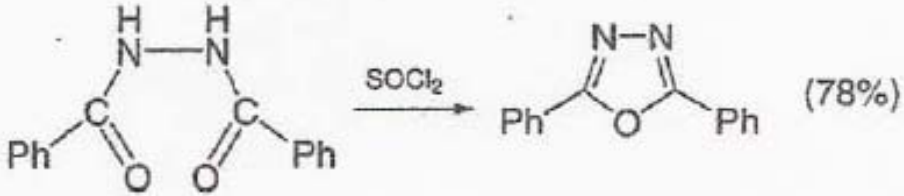
2. 

(62%)

8

3. **8** 

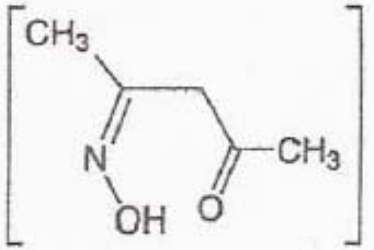
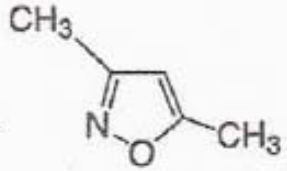
(50%)

4. 

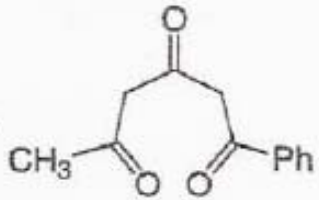
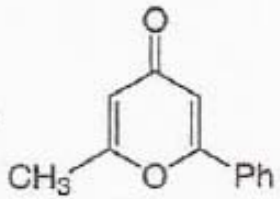
(78%)

Ring Closure – Intramolecular Cyclizations

Monocyclic compounds

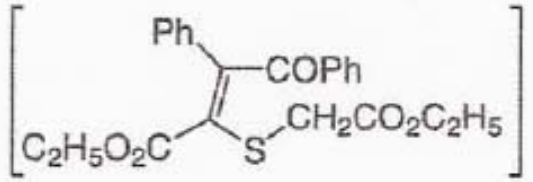
5. $CH_3COCH_2COCH_3 + H_2NOH \xrightarrow{HCl}$  

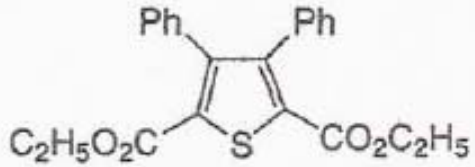
(62%)

6. $CH_3COCH_2COCH_3 \xrightarrow[\text{(ii) } PhCO_2CH_3 \text{ (Claisen acylation; section 5.2.2)}]{\text{(i) } 2KNH_2 \text{ [cf. reaction (5.3)]}}$  $\xrightarrow{H_2SO_4}$ 

(53%) (60%)

(32% overall)

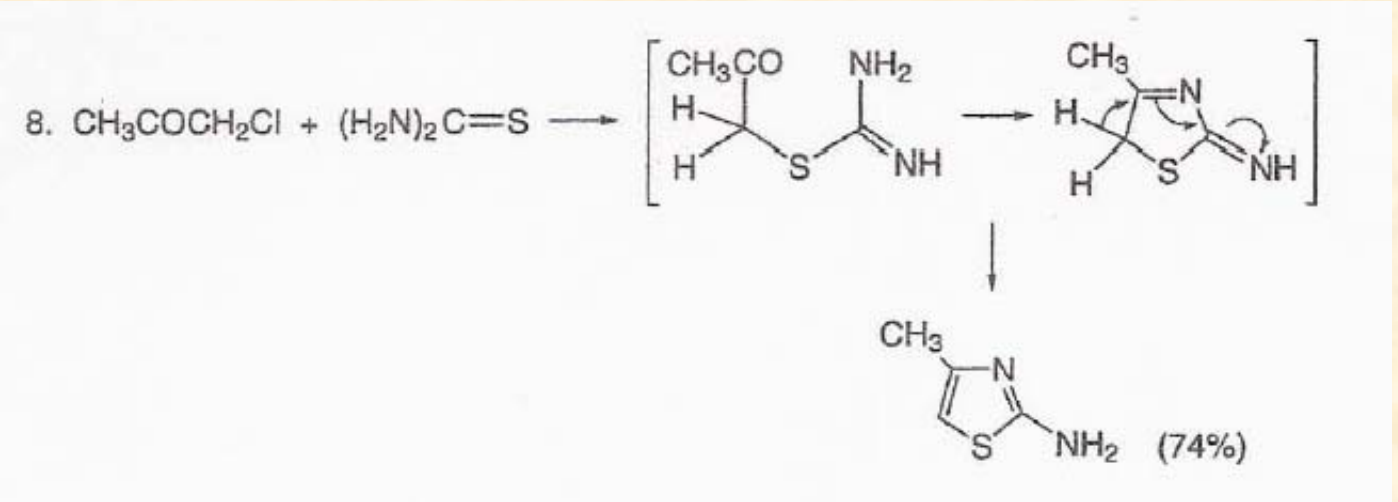
7. $PhCOCOPh + S(CH_2CO_2C_2H_5)_2 \xrightarrow{(CH_3)_3COK}$ 

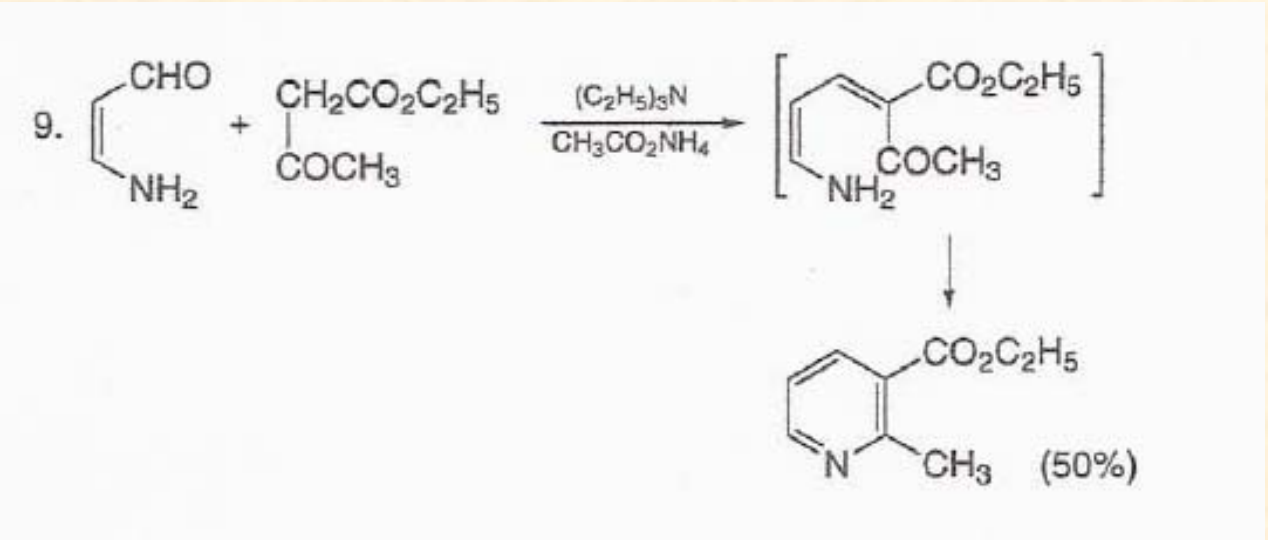


(75%)

Ring Closure – Intramolecular Cyclizations

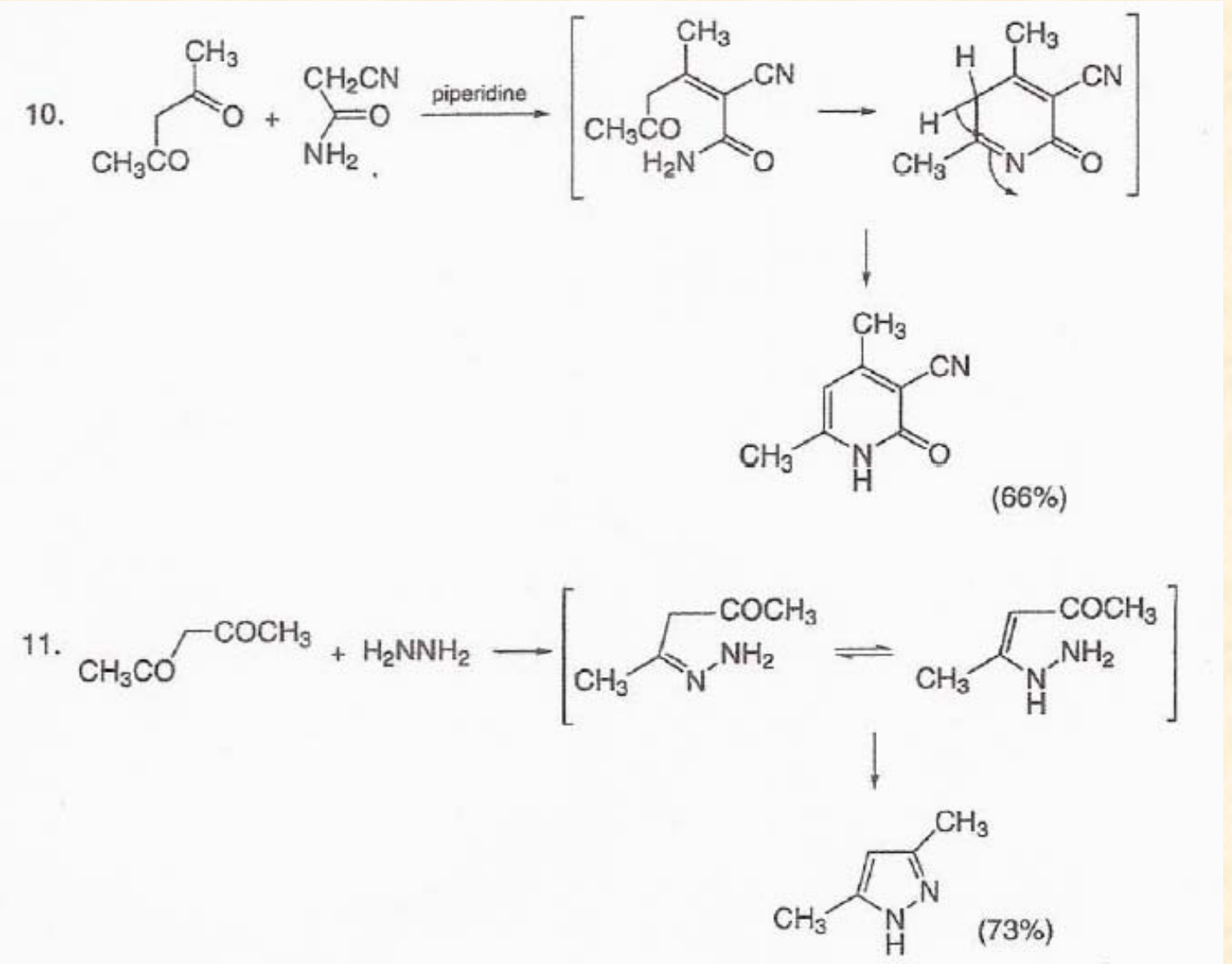
Monocyclic compounds





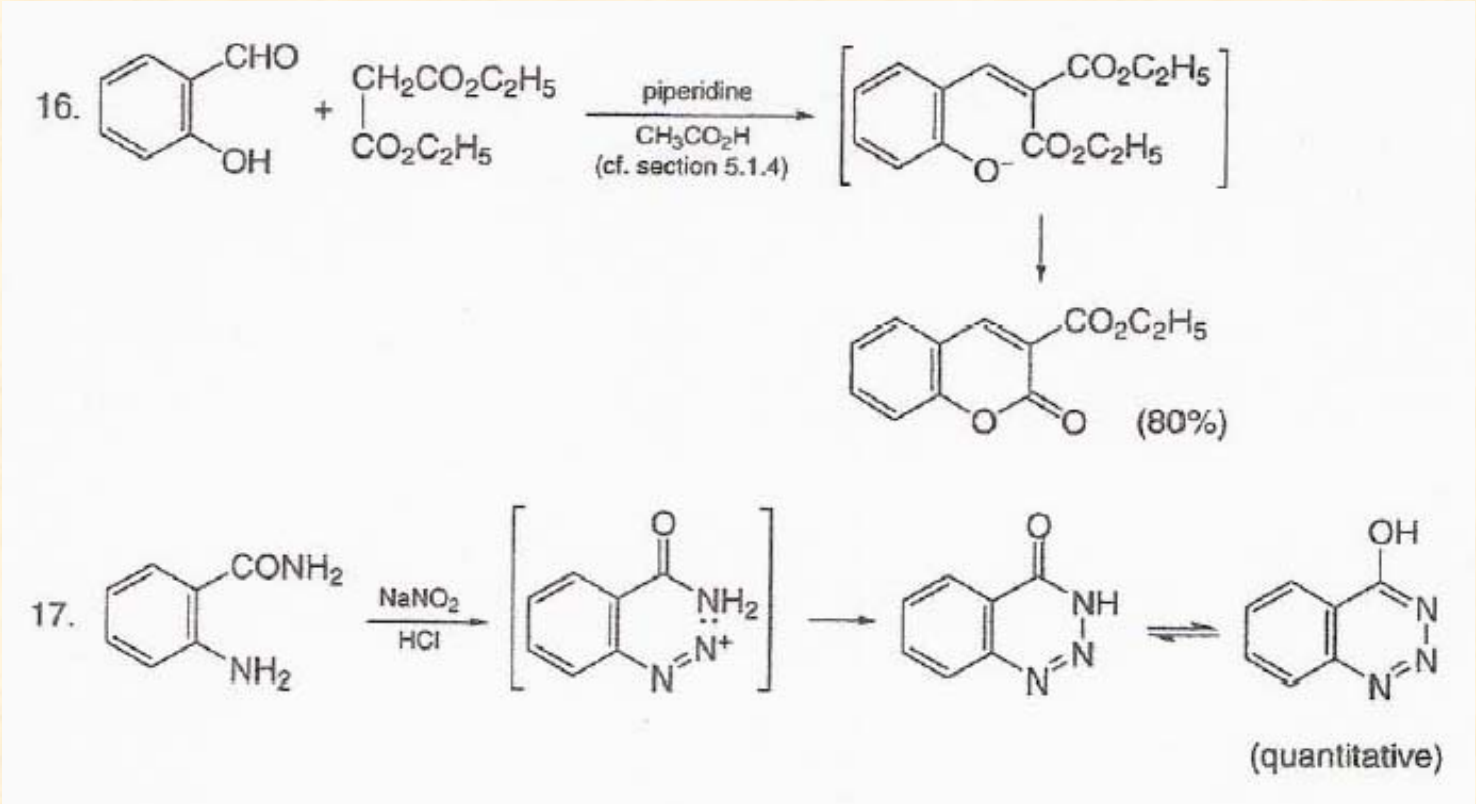
Ring Closure – Intramolecular Cyclizations

Monocyclic compounds



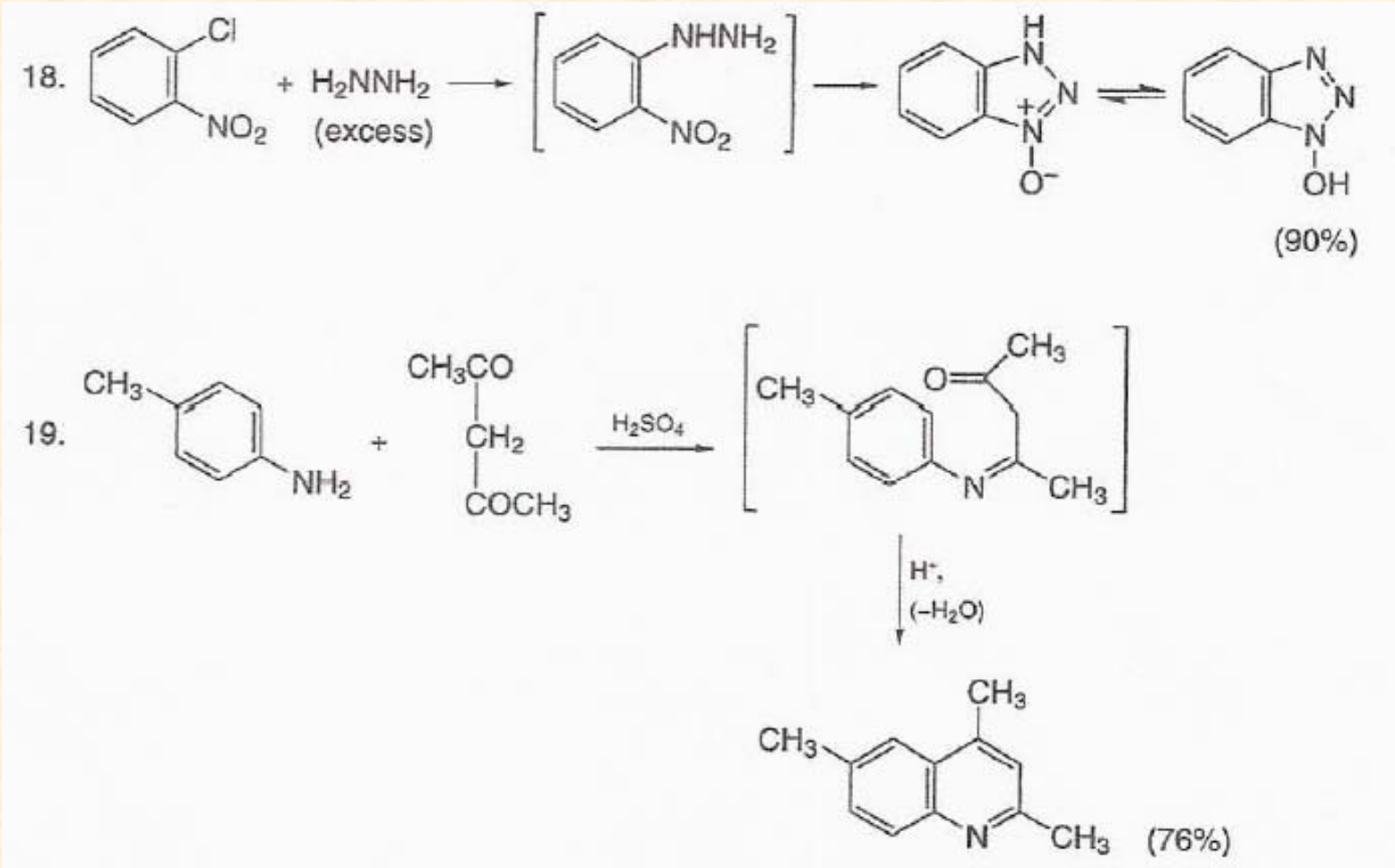
Ring Closure – Intramolecular Cyclizations

Benzofused Compounds



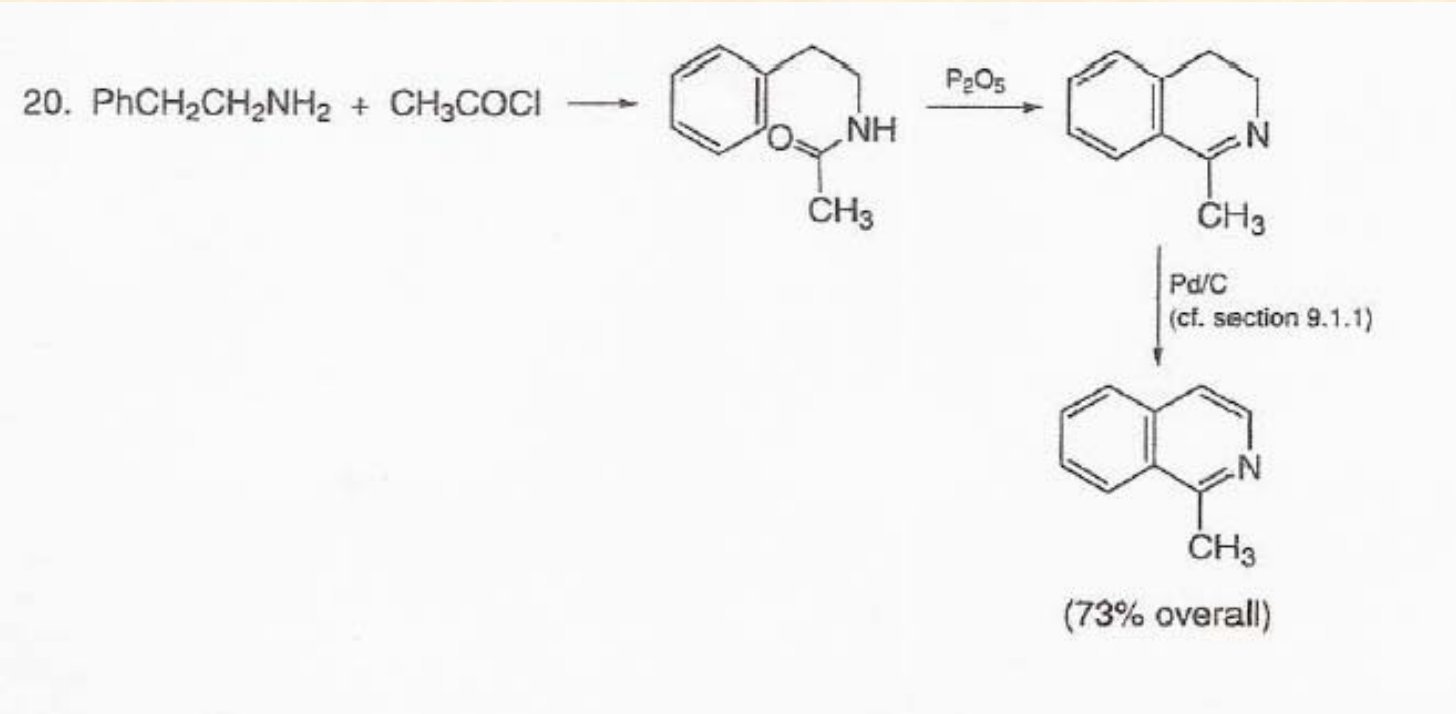
Ring Closure – Intramolecular Cyclizations

Benzofused Compounds



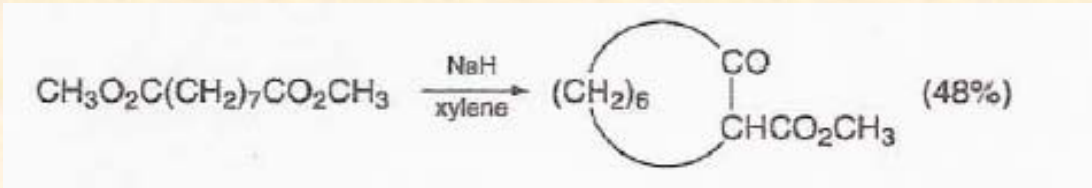
Ring Closure – Intramolecular Cyclizations

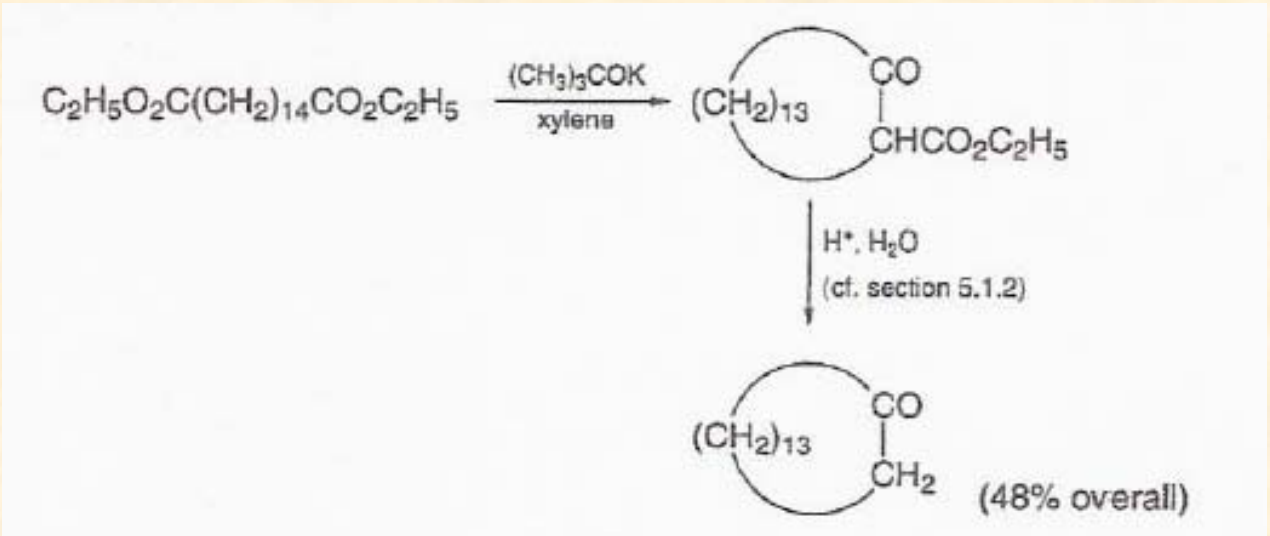
Benzofused Compounds



Ring Closure – Intramolecular Cyclizations

7.1.5 *Formation of medium and large rings*

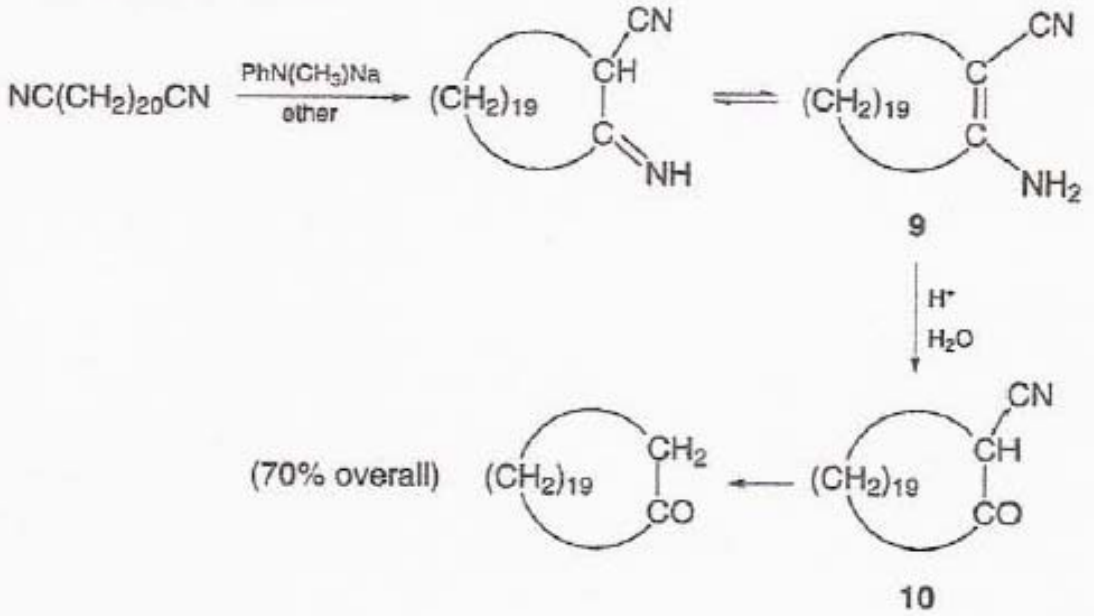


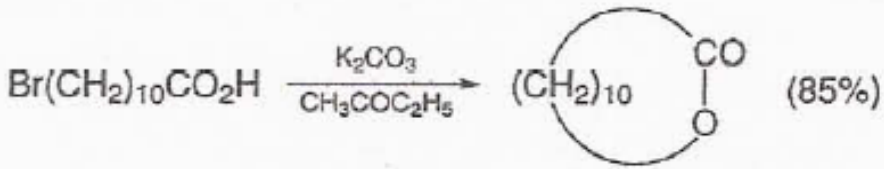


Ring Closure – Intramolecular Cyclizations

7.1.5 Formation of medium and large rings

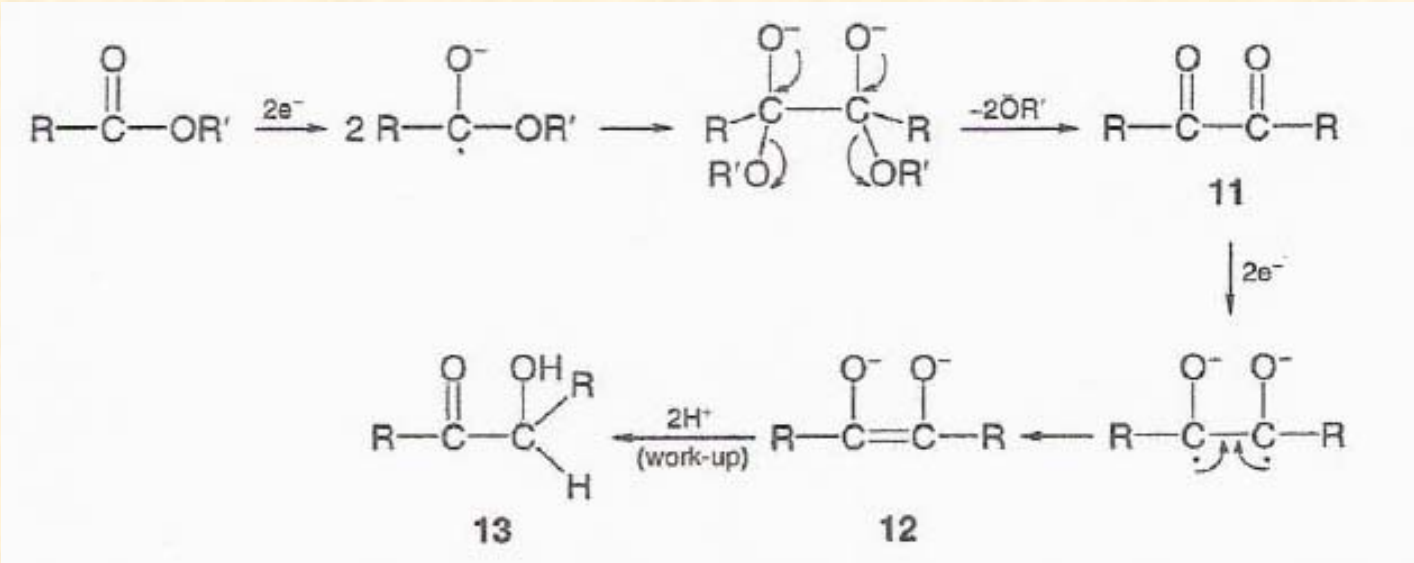
Thorpe–Ziegler reaction

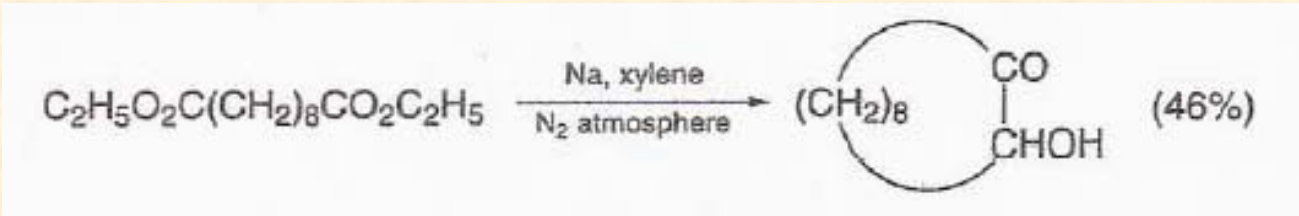


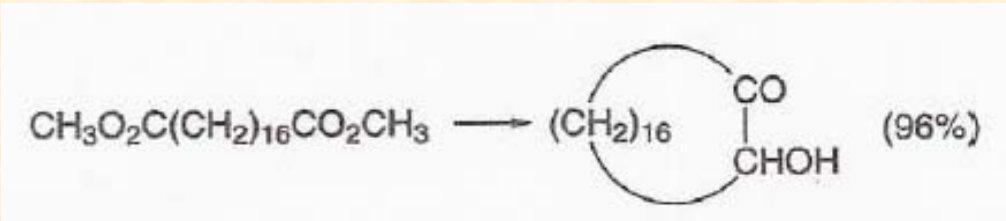


Ring Closure – Intramolecular Cyclizations

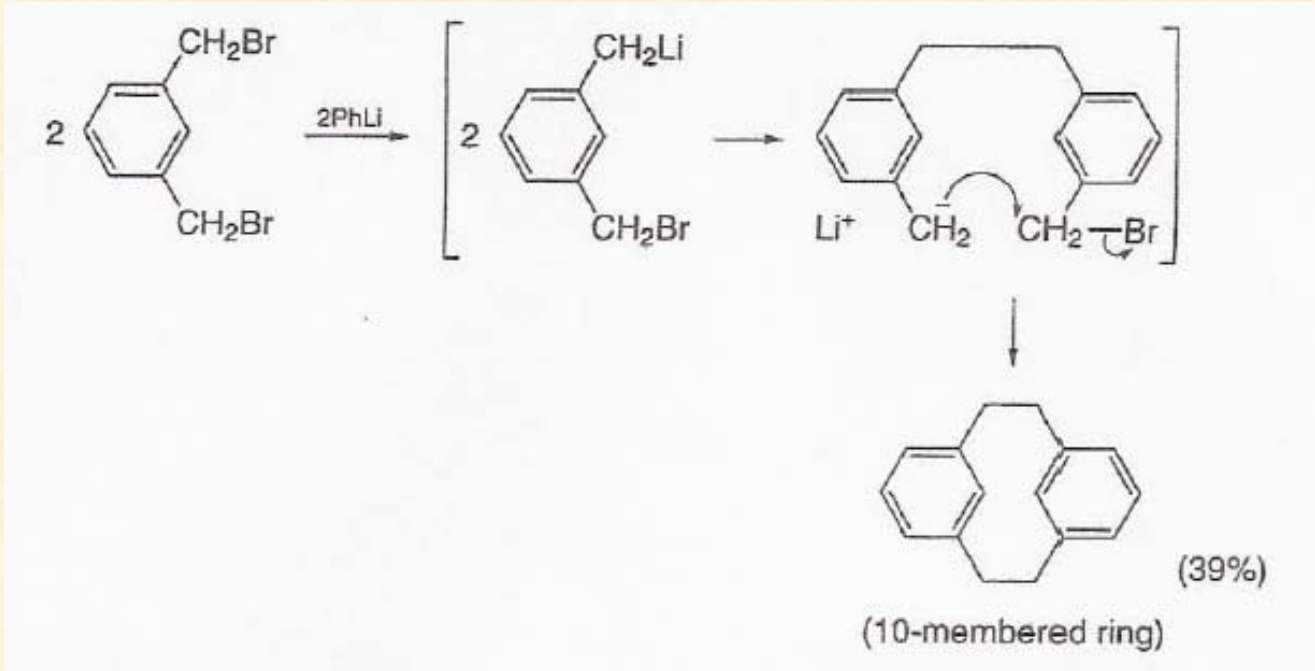
acyloin reaction

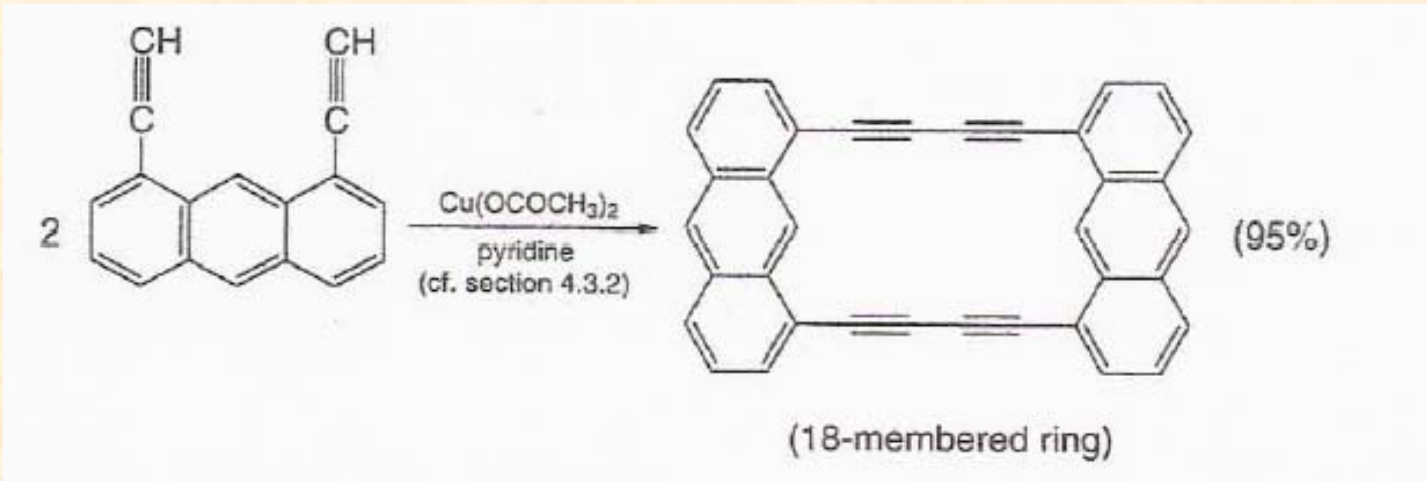




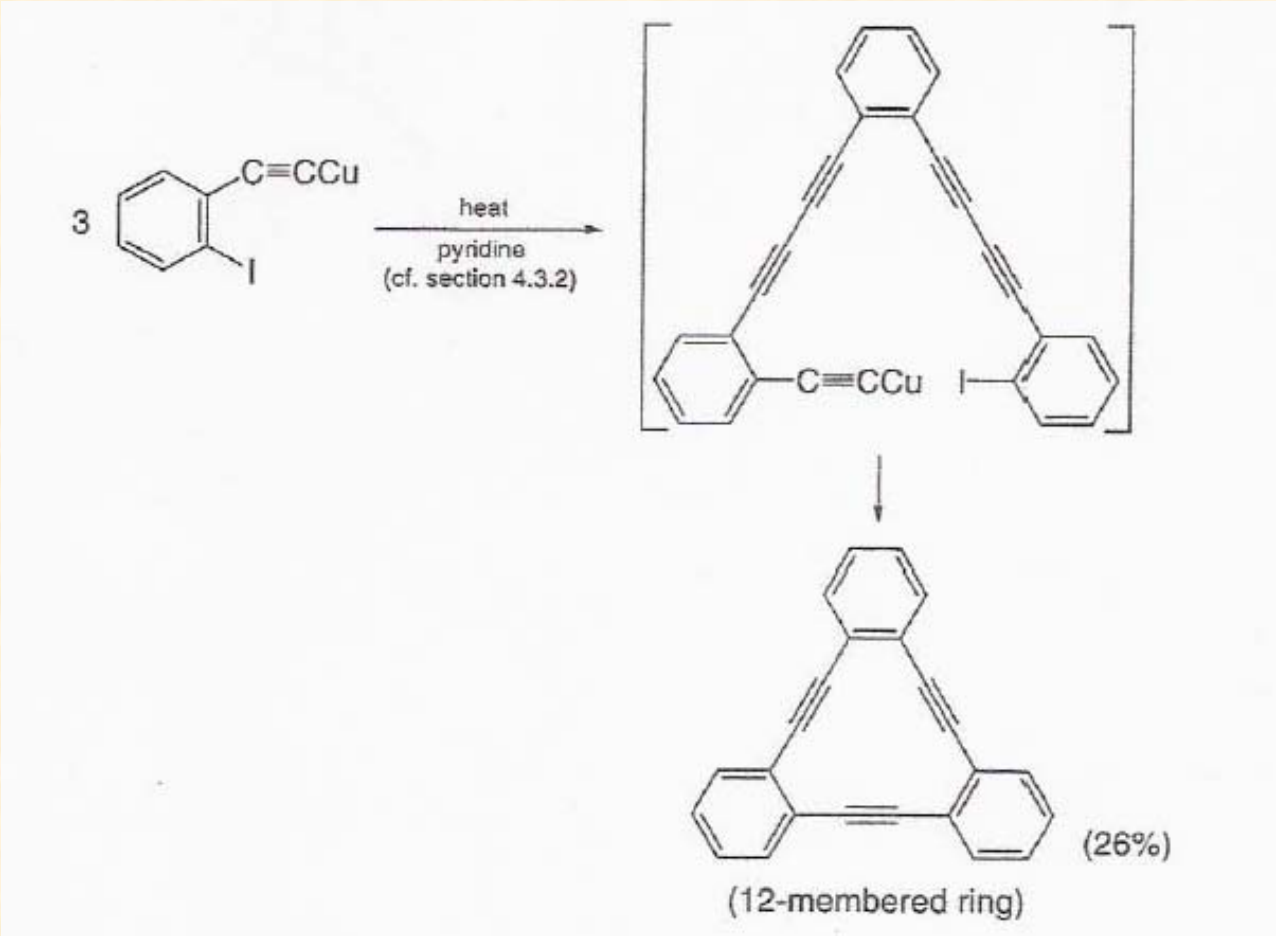


Ring Closure – Intramolecular Cyclizations



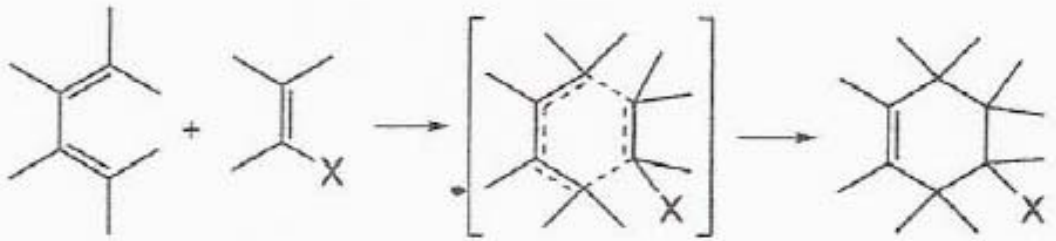


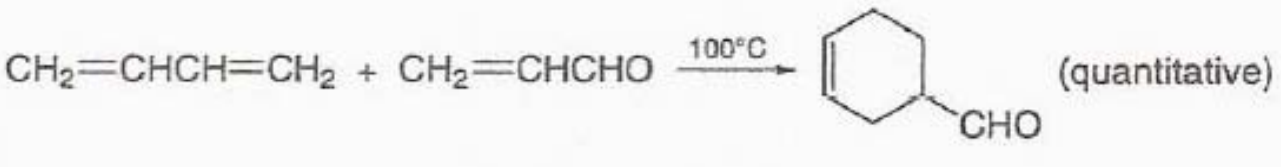
Ring Closure – Intramolecular Cyclizations



Ring Closure – Cycloadditions

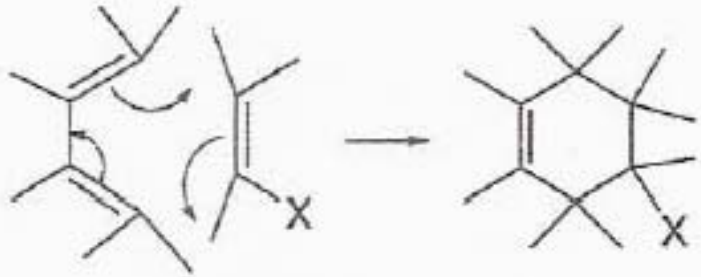
Cycloaddition





pericyclic or *symmetry controlled* reactions

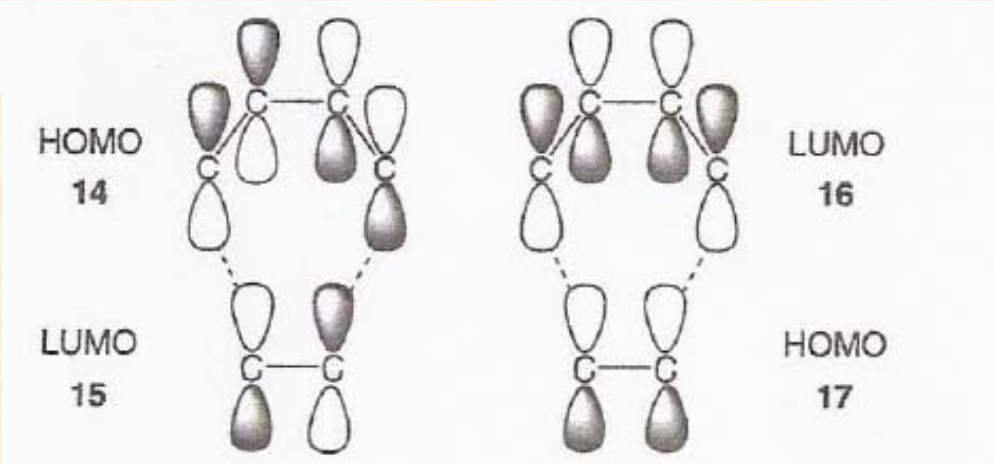
frontier orbitals

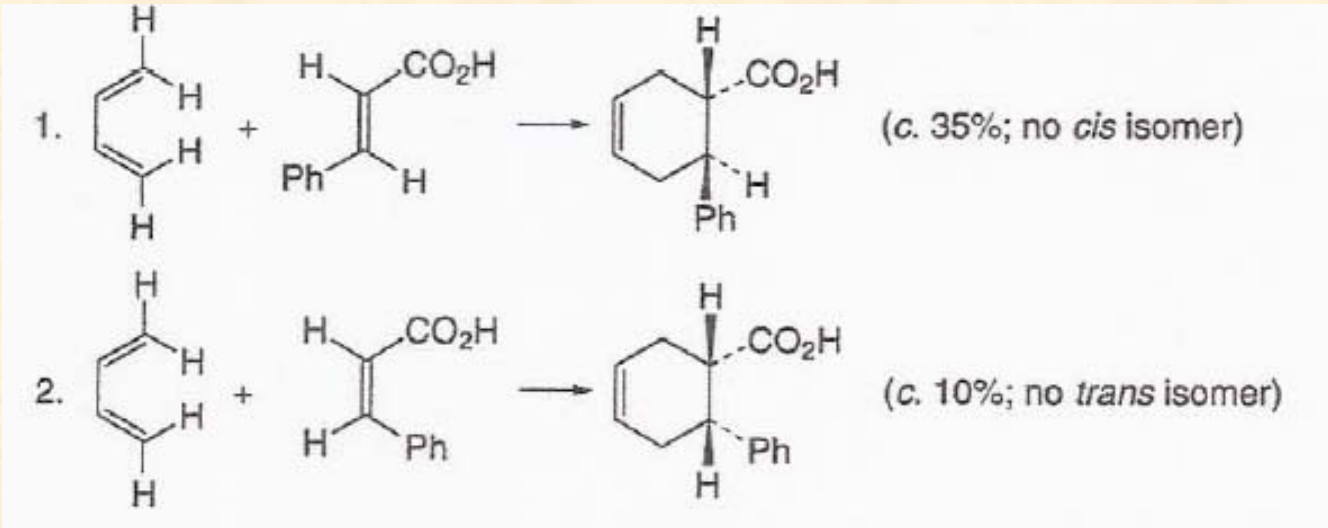


Ring Closure – Cycloadditions

7.2.1 The Diels–Alder reaction

Suprafacial vs. antarafacial additions

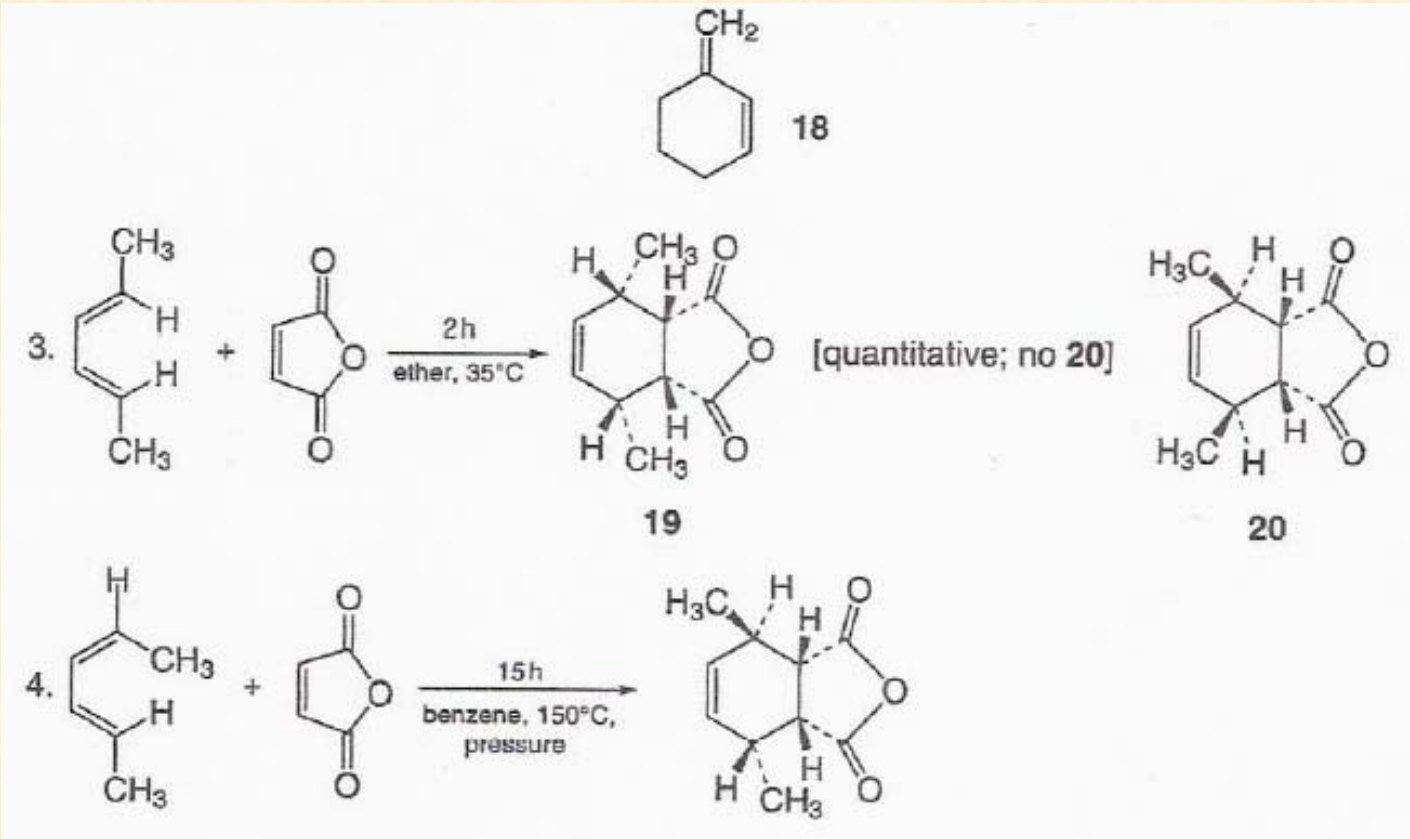




Ring Closure – Cycloadditions

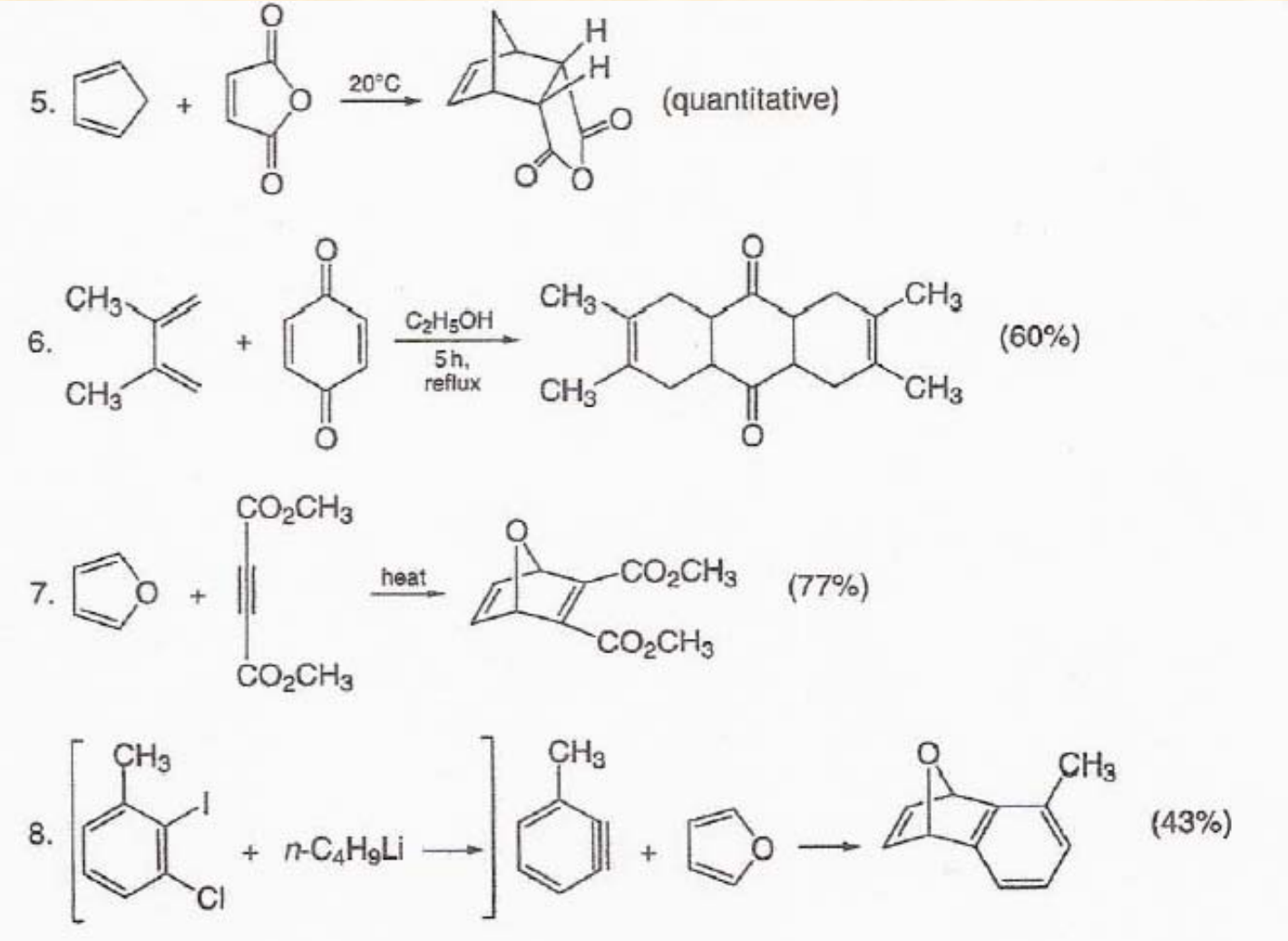
7.2.1 The Diels–Alder reaction

cisoid conformation *transoid* conformation



Ring Closure – Cycloadditions

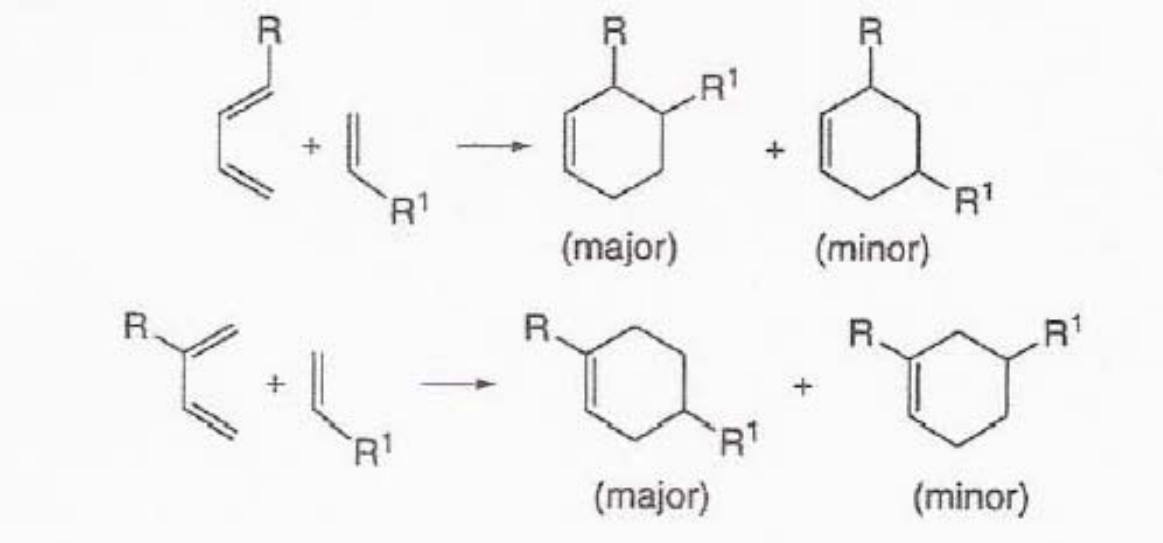
7.2.1 The Diels–Alder reaction



Ring Closure – Cycloadditions

7.2.1 *The Diels–Alder reaction*

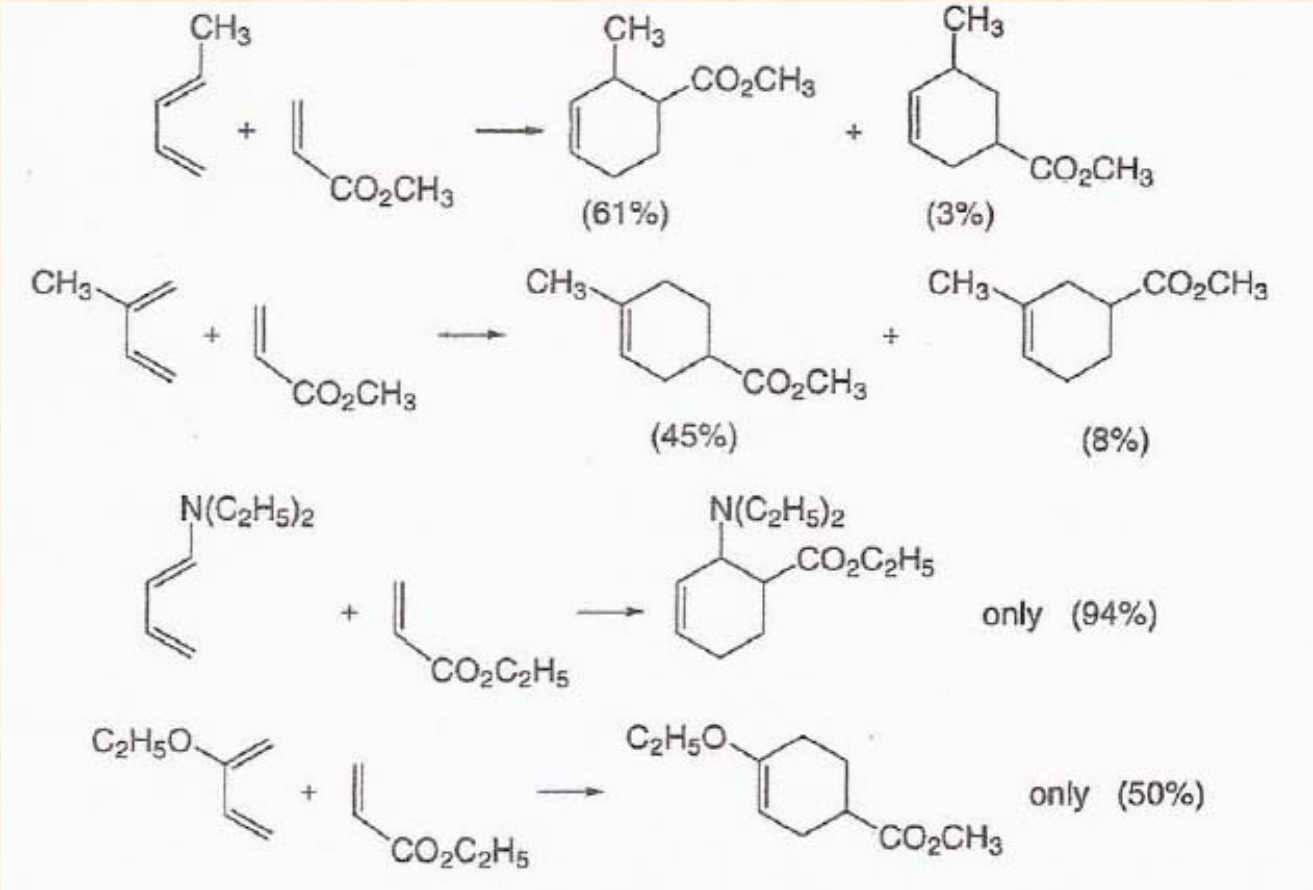
If the diene and dienophile are both unsymmetrical



Ring Closure – Cycloadditions

7.2.1 *The Diels–Alder reaction*

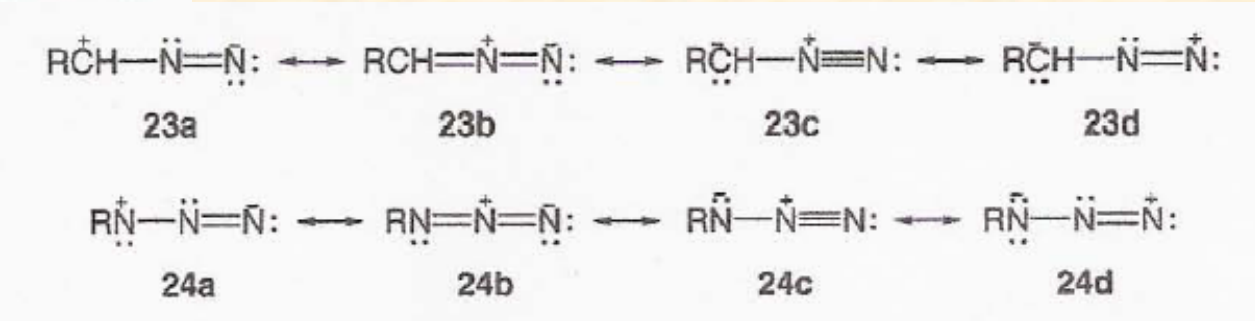
If the diene and dienophile are both unsymmetrical

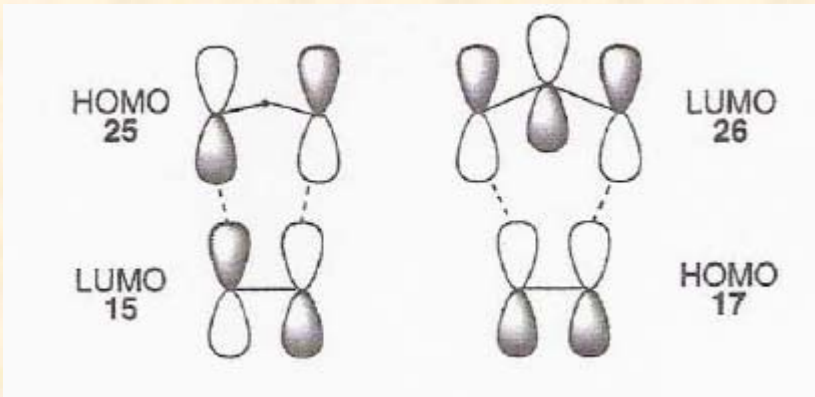


Ring Closure – Cycloadditions

7.2.2 1,3-Dipolar cycloaddition

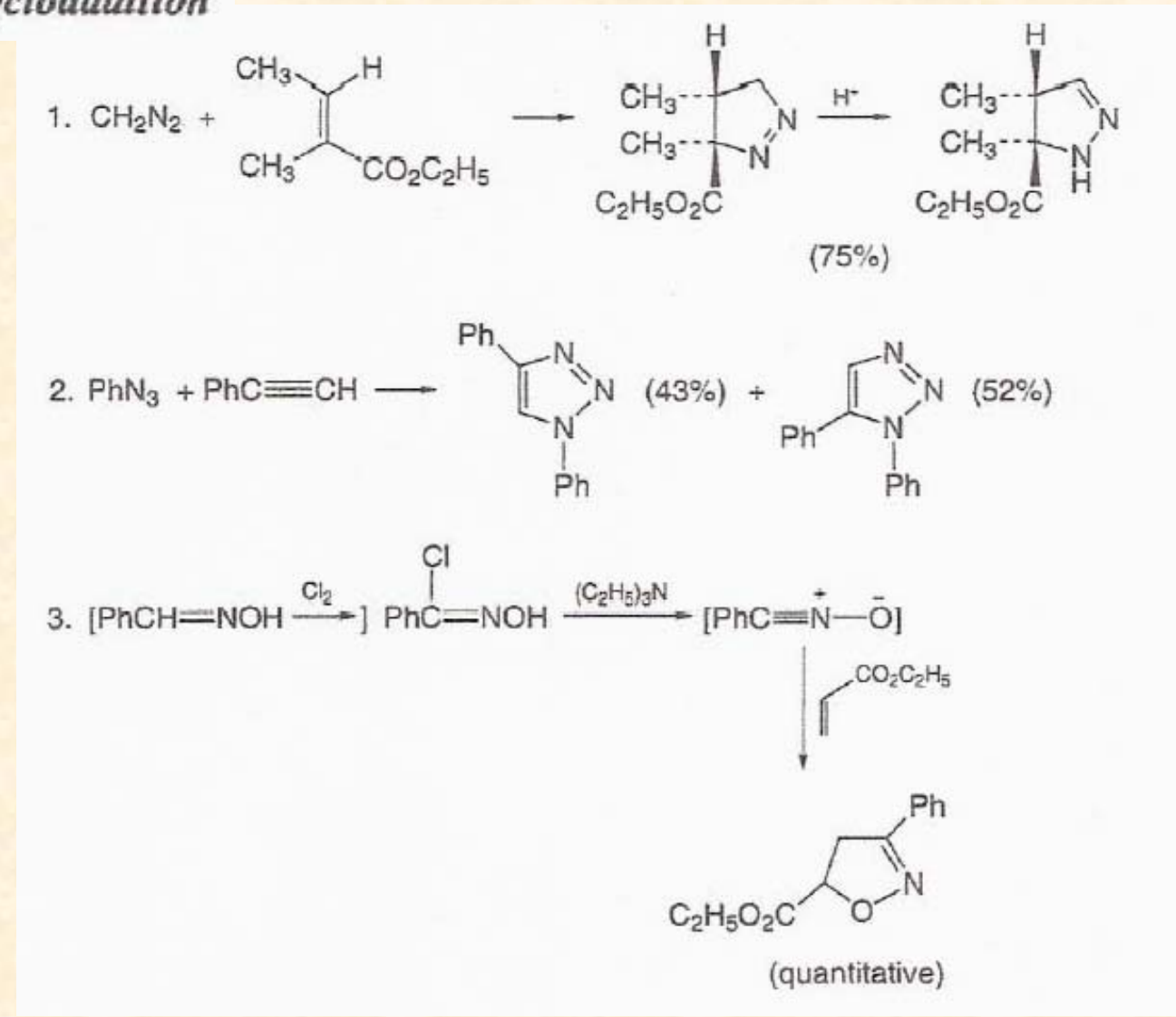
$[4\pi + 2\pi]$ *1,3-dipole*





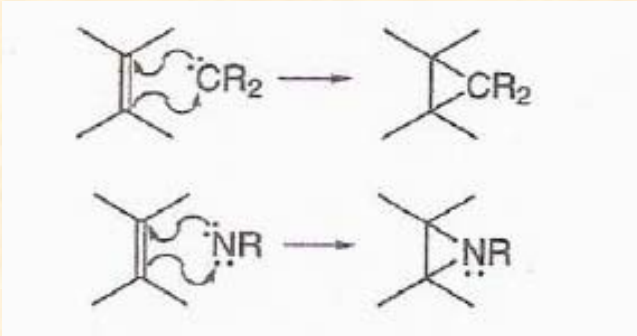
Ring Closure – Cycloadditions

7.2.2 1,3-Dipolar cycloaddition



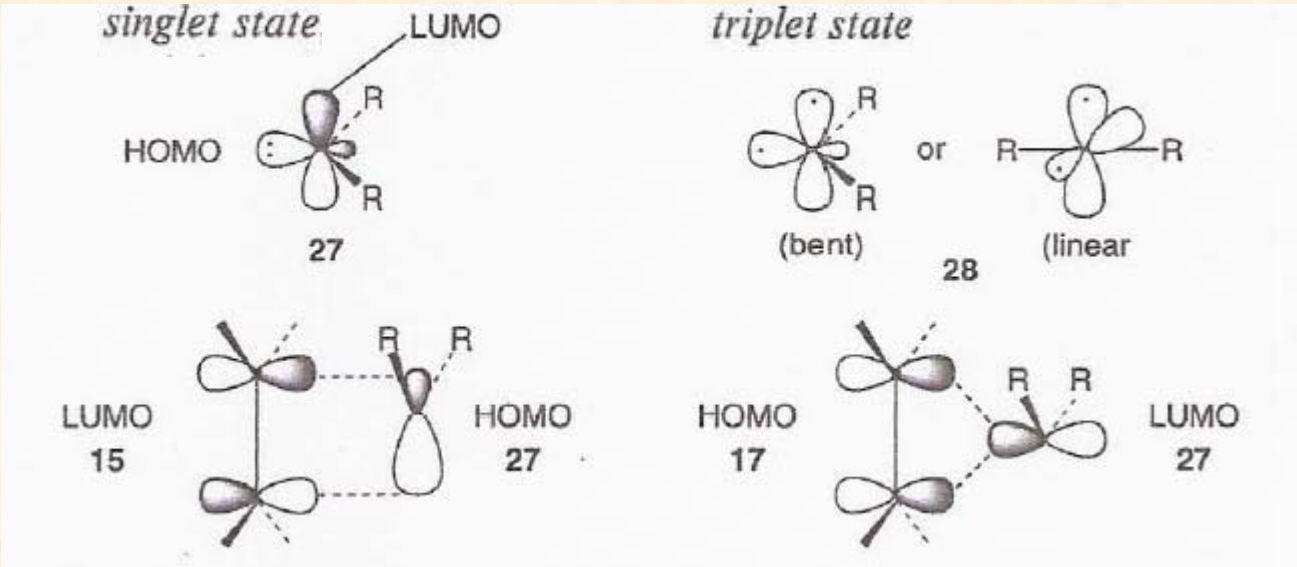
Ring Closure – Cycloadditions

7.2.3 *Addition of carbenes and nitrenes to alkenes*



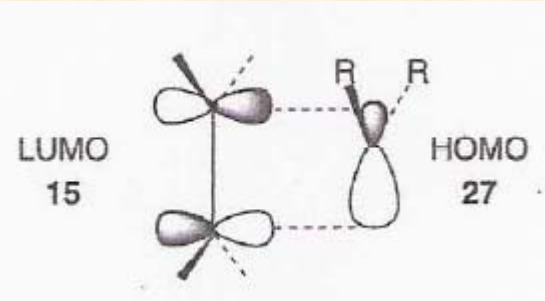
[2 + 2]-cycloaddition

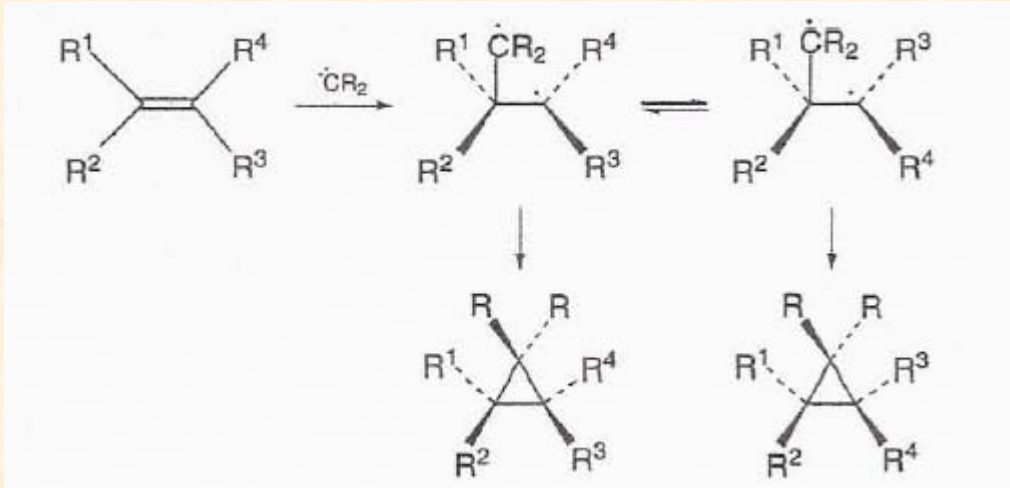
Radical, not concertic



Ring Closure – Cycloadditions

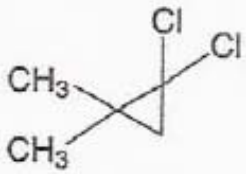
7.2.3 *Addition of carbenes and nitrenes to alkenes*

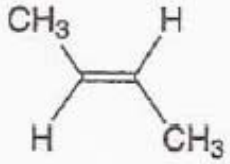
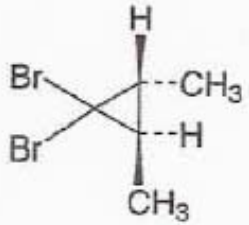


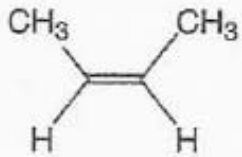
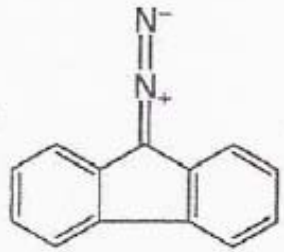
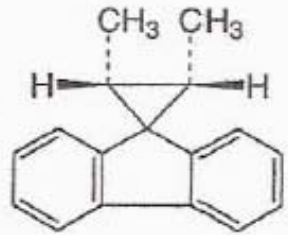
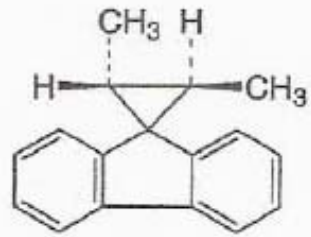


Ring Closure – Cycloadditions

7.2.3 *Addition of carbenes and nitrenes to alkenes*

1. $(CH_3)_2C{=}CH_2 \xrightarrow[NaOCH_3]{Cl_3CCO_2C_2H_5}$  (65%)

2.  $\xrightarrow[(CH_3)_3COK]{CHBr_3}$  (68%)

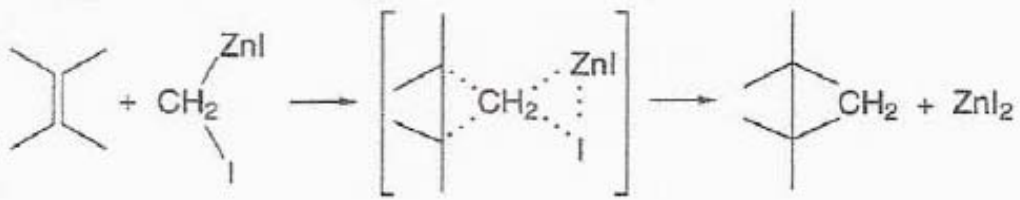
3.  +  $\xrightarrow{h\nu}$  + 

29 **30**

(*c.* 50%; **29** : **30** = 66 : 34)

Simmons–Smith reaction

$CH_2I_2 + Zn \longrightarrow ICH_2ZnI$



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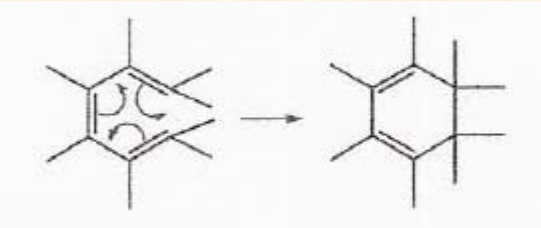
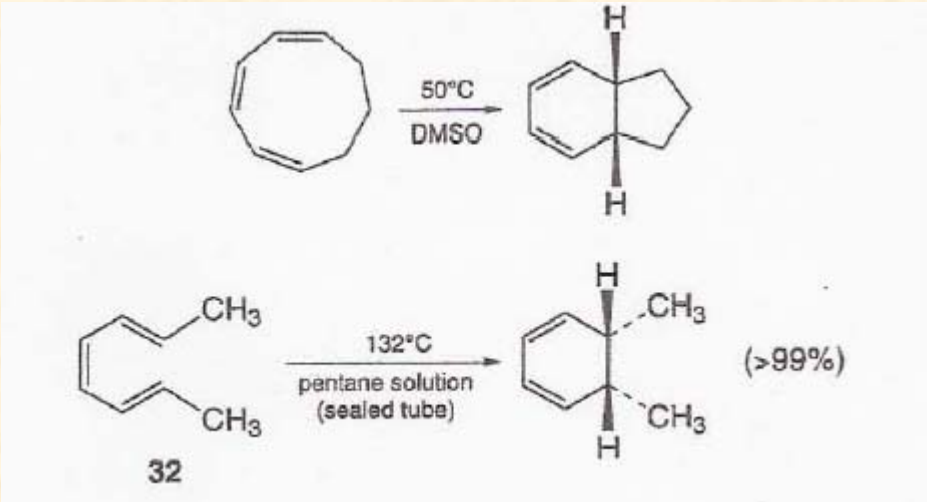
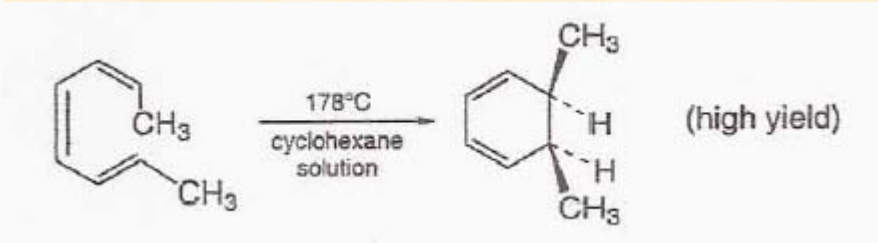
Ring Closure – Cycloadditions

Electrocyclic ring closure



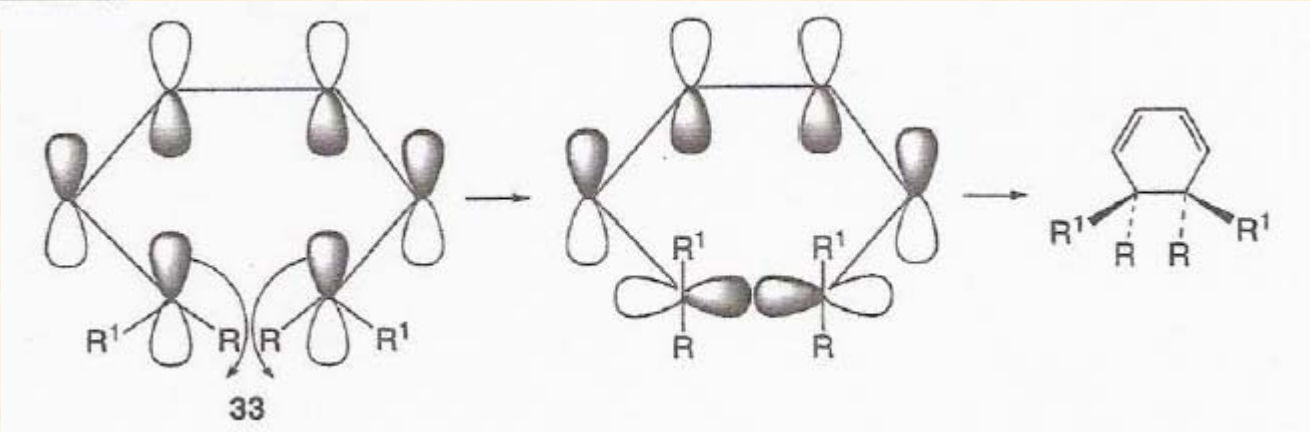




Ring Closure – Cycloadditions

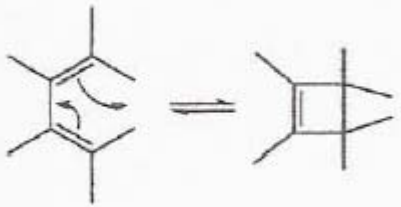
Electrocyclic ring closure

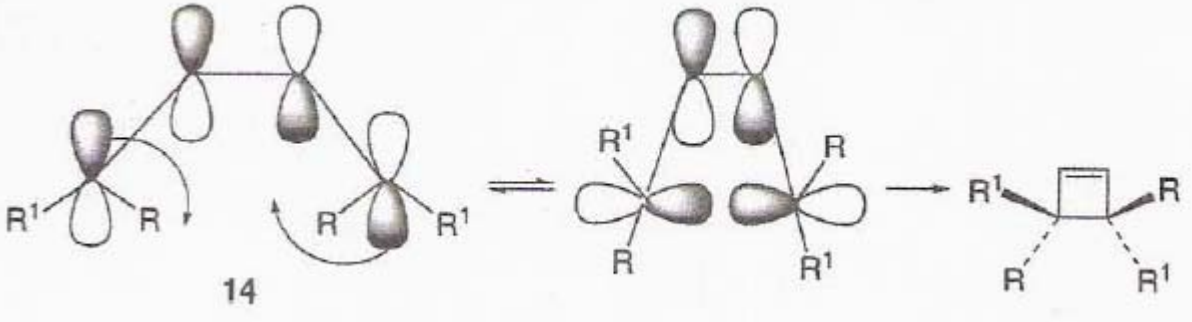
disrotatory process



33

conrotatory process





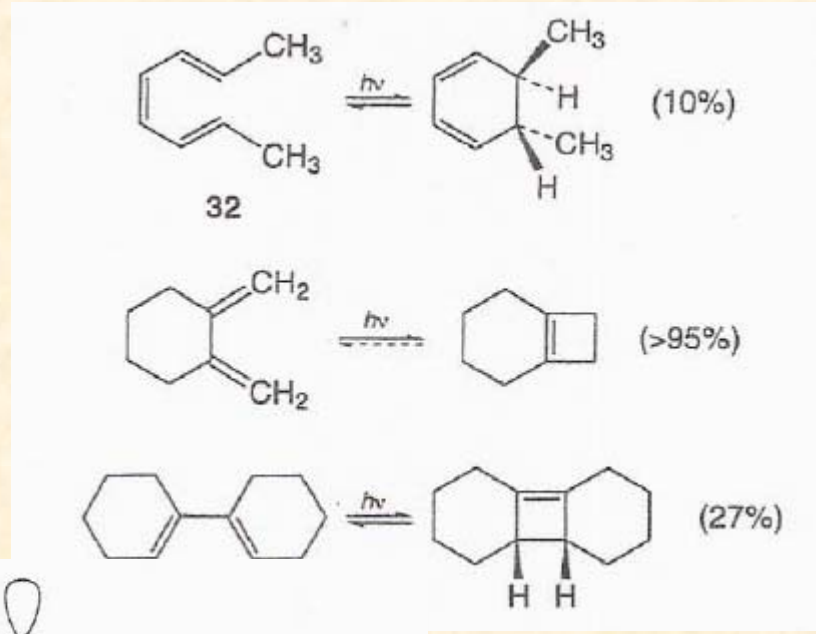
14

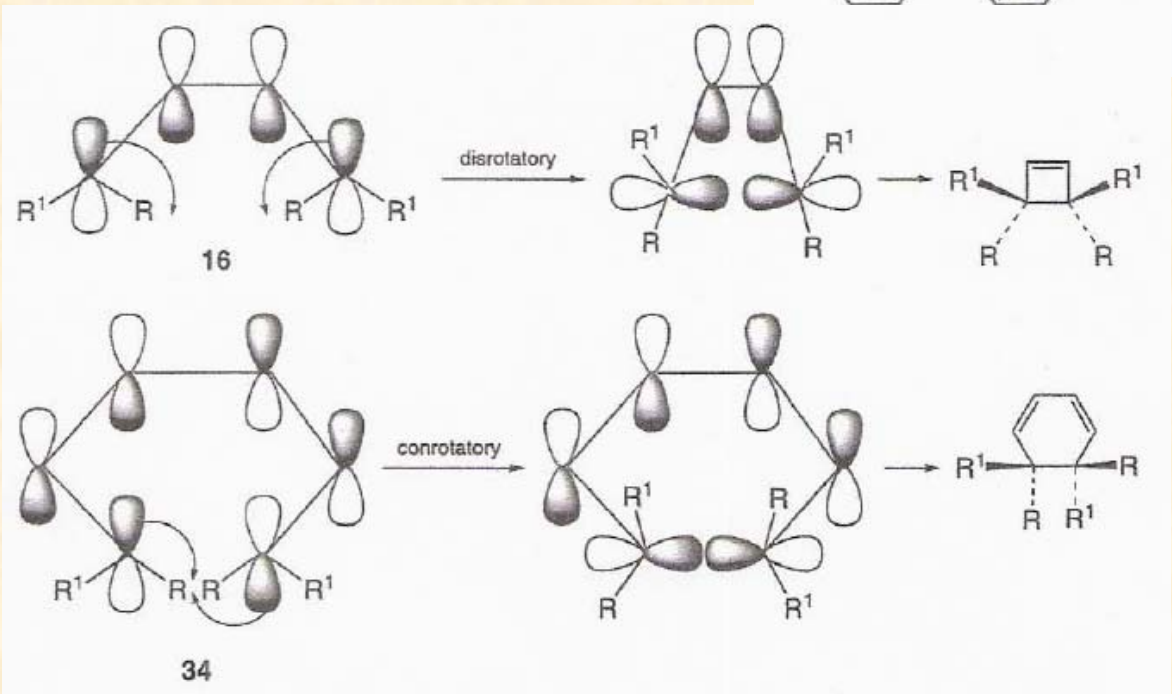
Ring Closure – Cycloadditions

Electrocyclic ring closure

photochemical

opposite



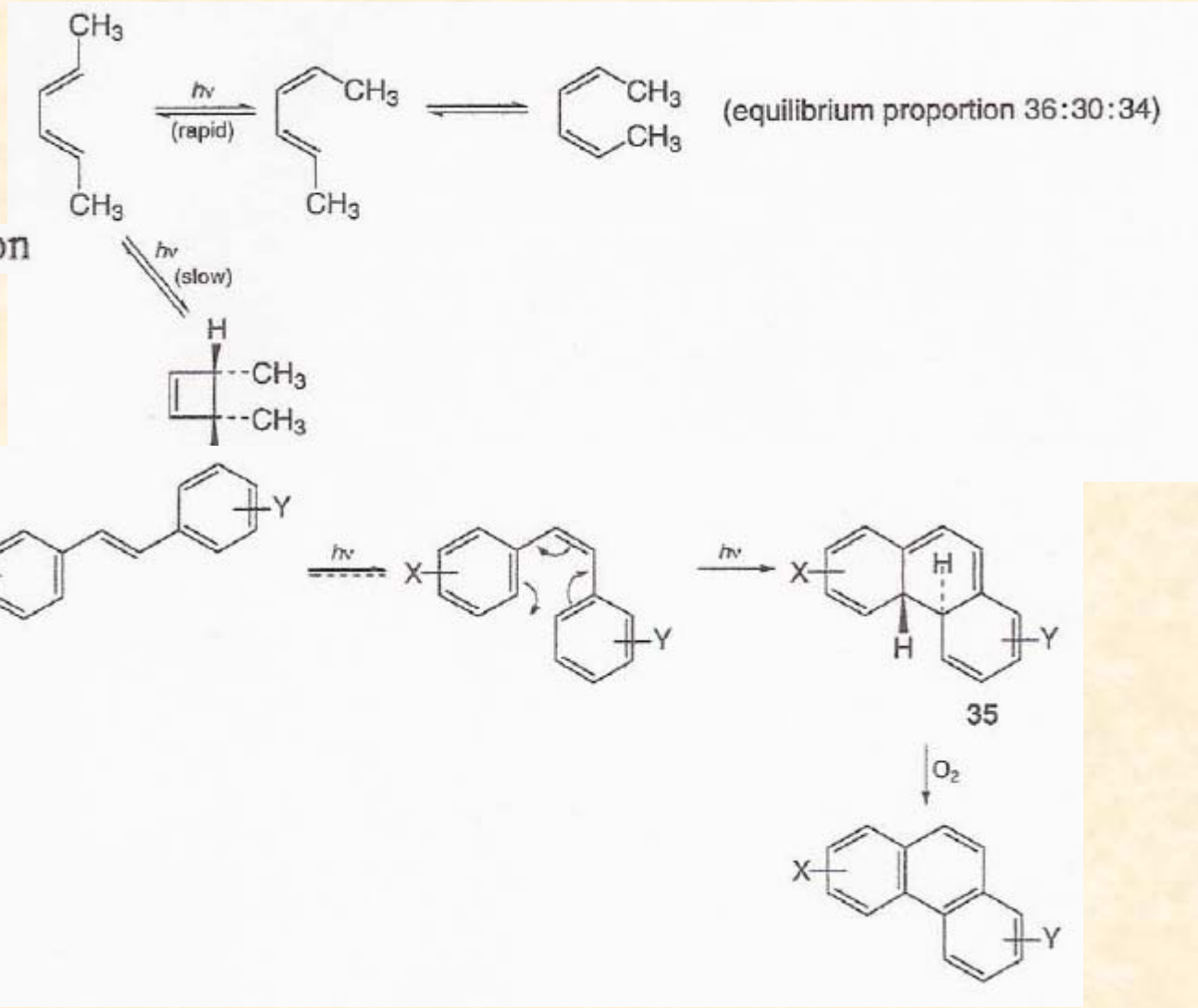


Ring Closure – Cycloadditions

Electrocyclic ring closure

photochemical

$E \rightarrow Z$ isomerization



Ring Opening

Ring opening

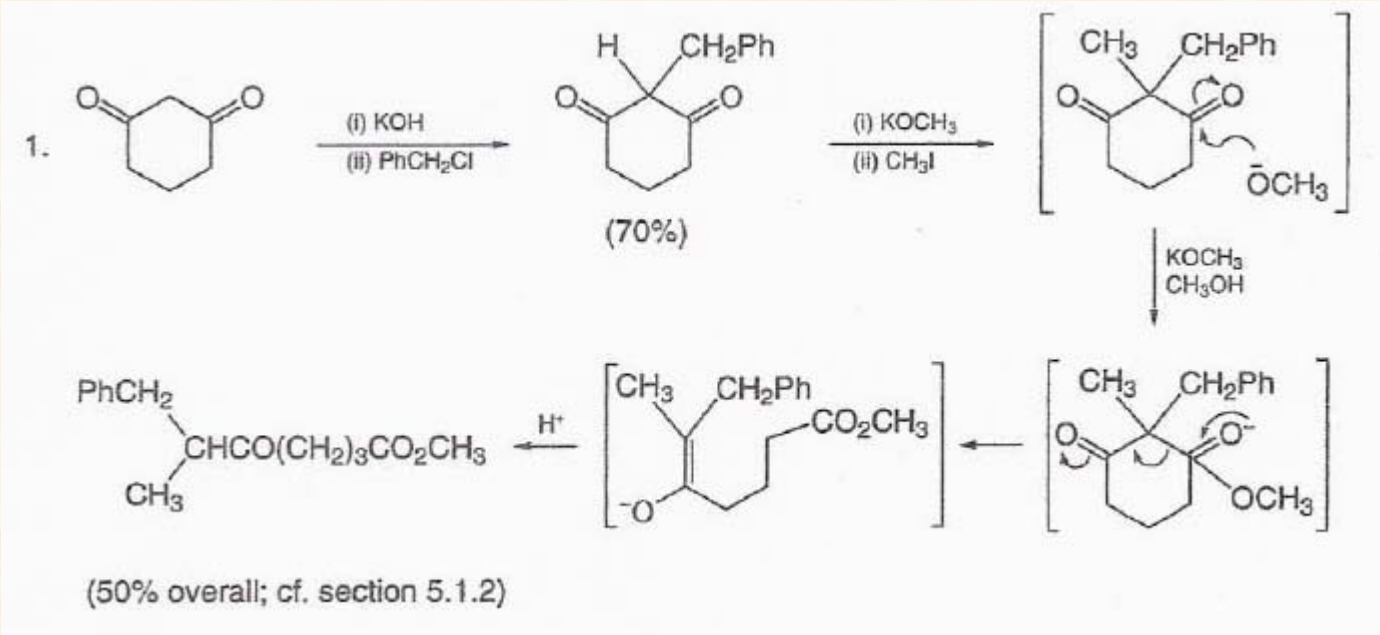
the two main synthetic uses of ring opening

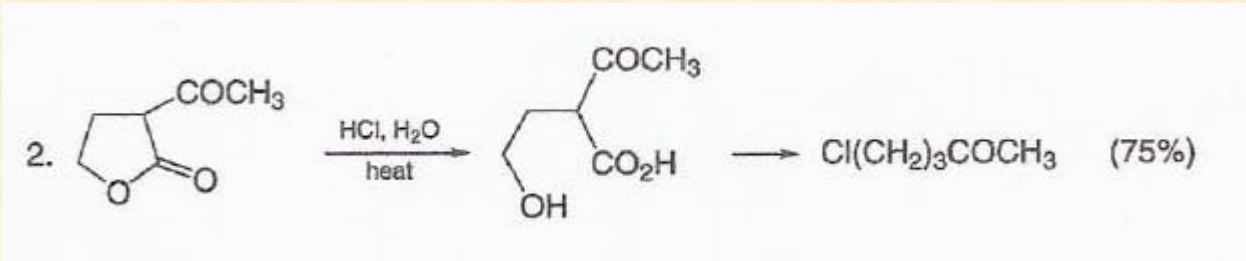
(i) the atoms at either end of the bond which is broken will bear functional groups in the ring-opened product; ring opening may thus provide a route to difunctional molecules in which the functional groups are separated by several other atoms;

(ii) in a bi- or polycyclic molecule, cleavage of a bond which is common to two rings may lead to a medium- or large-ring molecule that is otherwise difficult to prepare.

Ring Opening

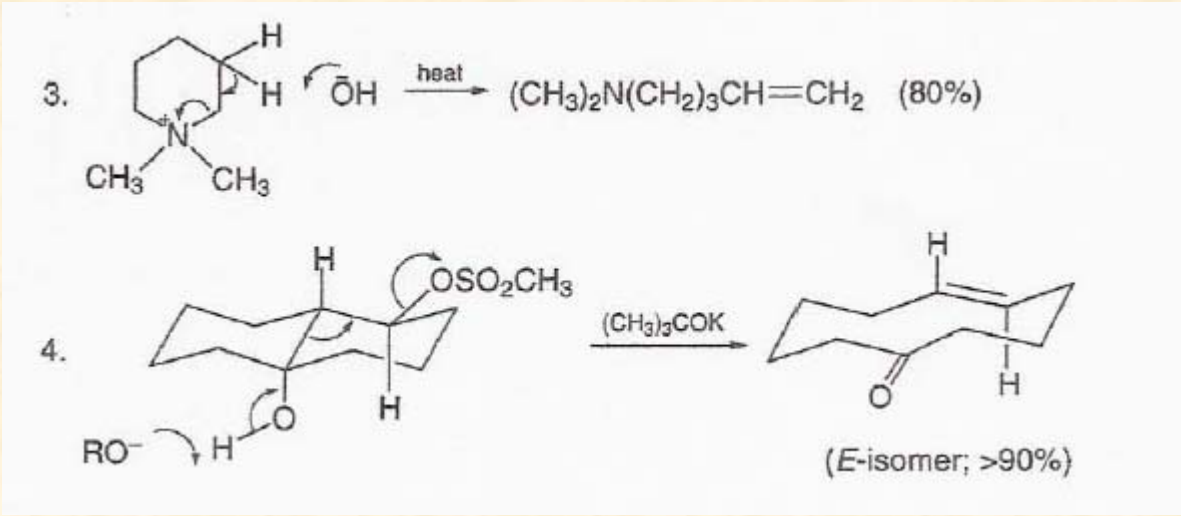
7.4.1 *Hydrolysis, solvolysis and other electrophile–nucleophile interactions*





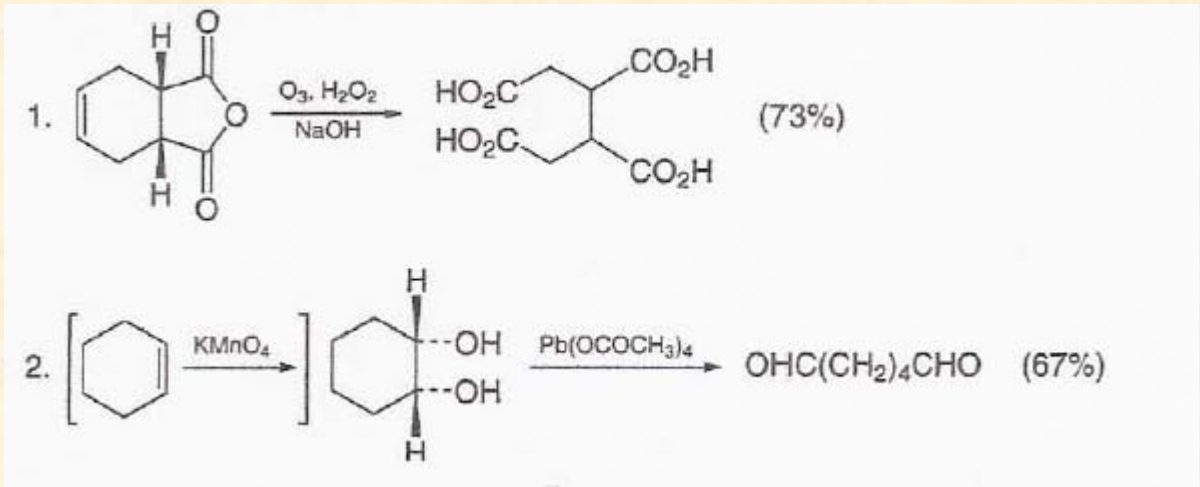
Ring Opening

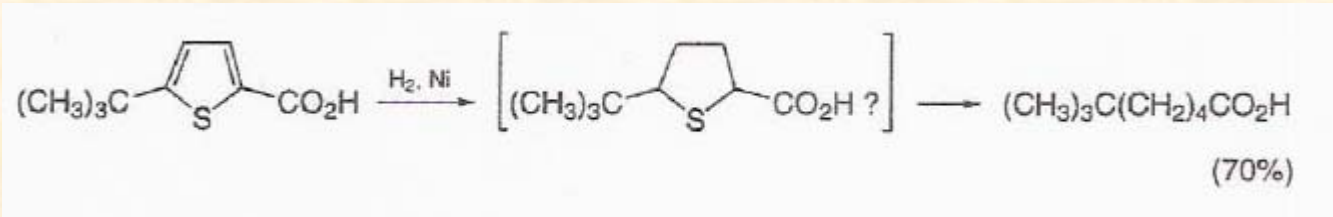
7.4.1 *Hydrolysis, solvolysis and other electrophile–nucleophile interactions*



Ring Opening

7.4.2 *Oxidative and reductive ring opening*

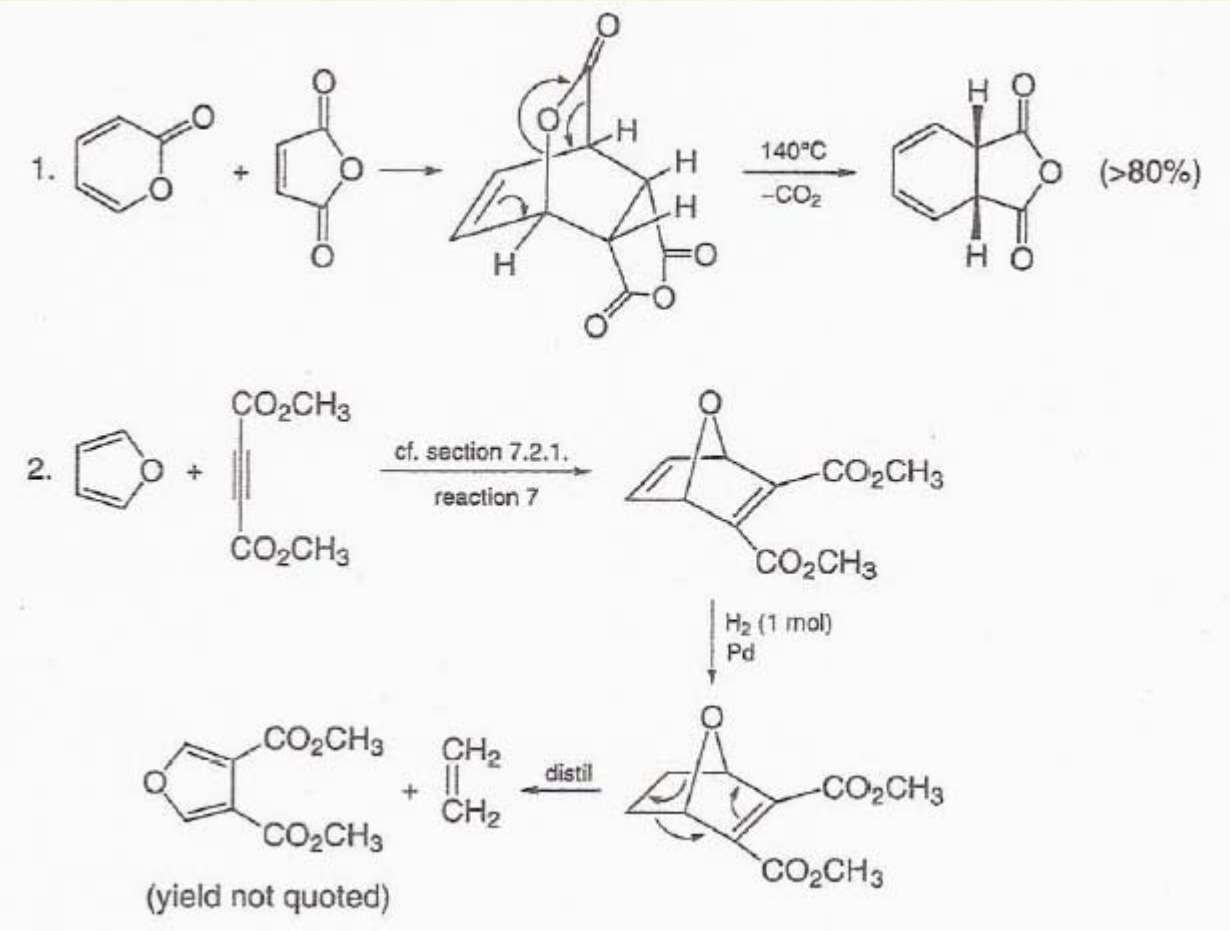




Ring Opening

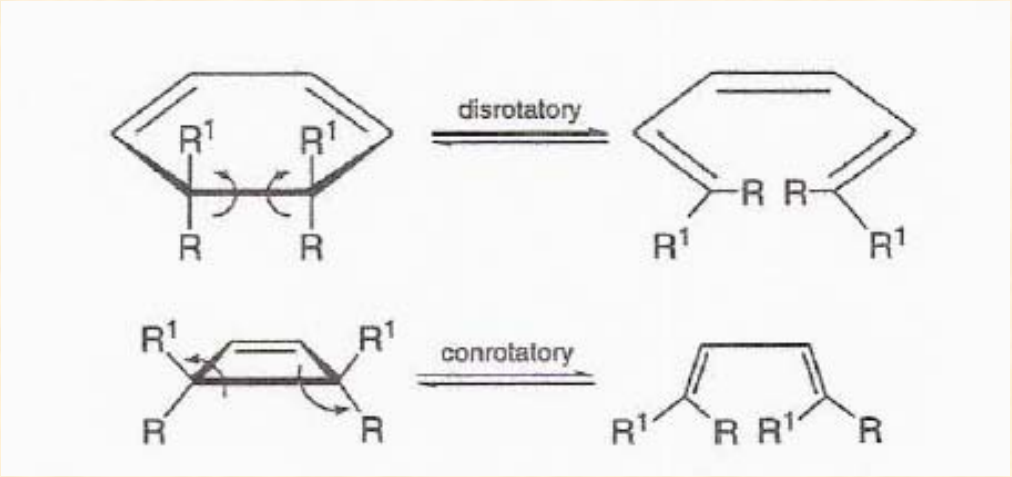
7.4.3 Pericyclic ring opening

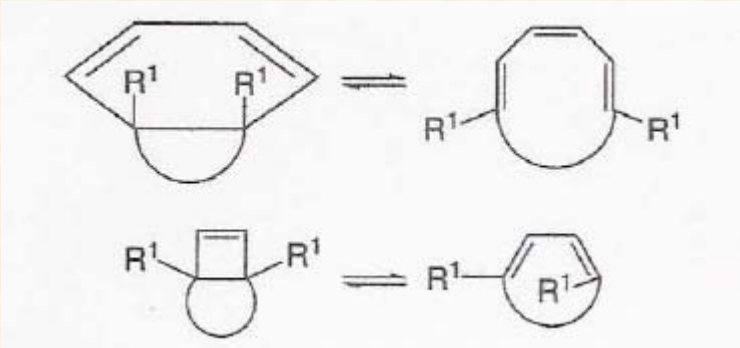
retro-Diels–Alder reaction

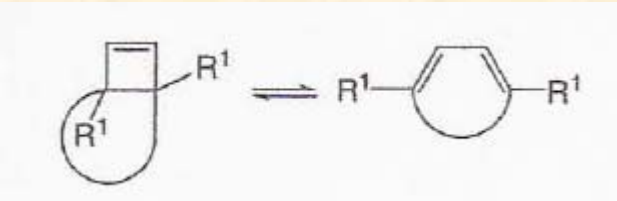


Ring Opening

Electrocyclic ring opening

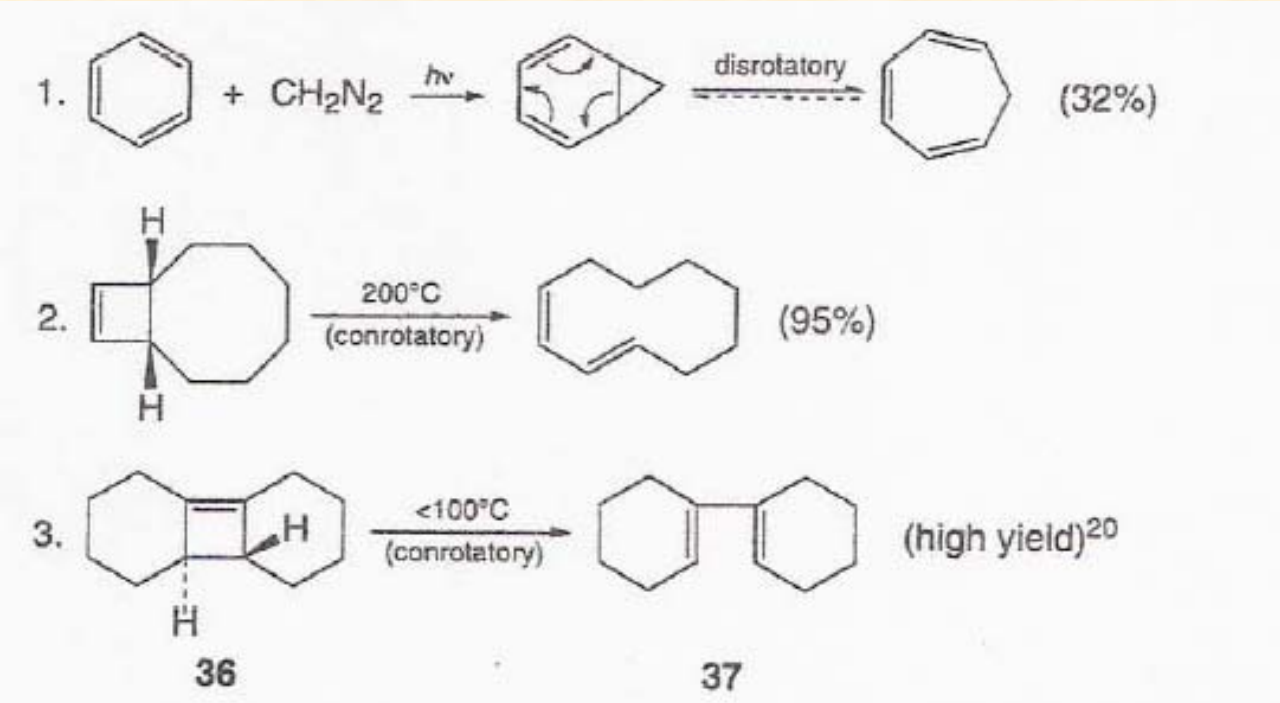






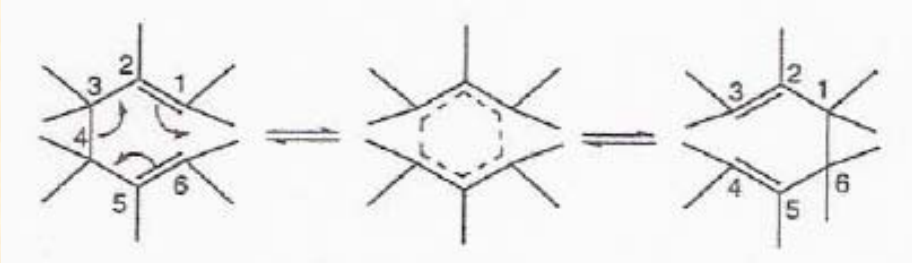
Ring Opening

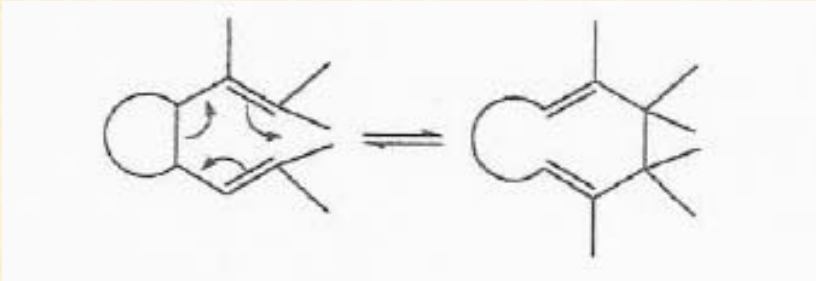
Electrocyclic ring opening



Ring Opening

Cope rearrangement





Ring Opening

Cope rearrangement