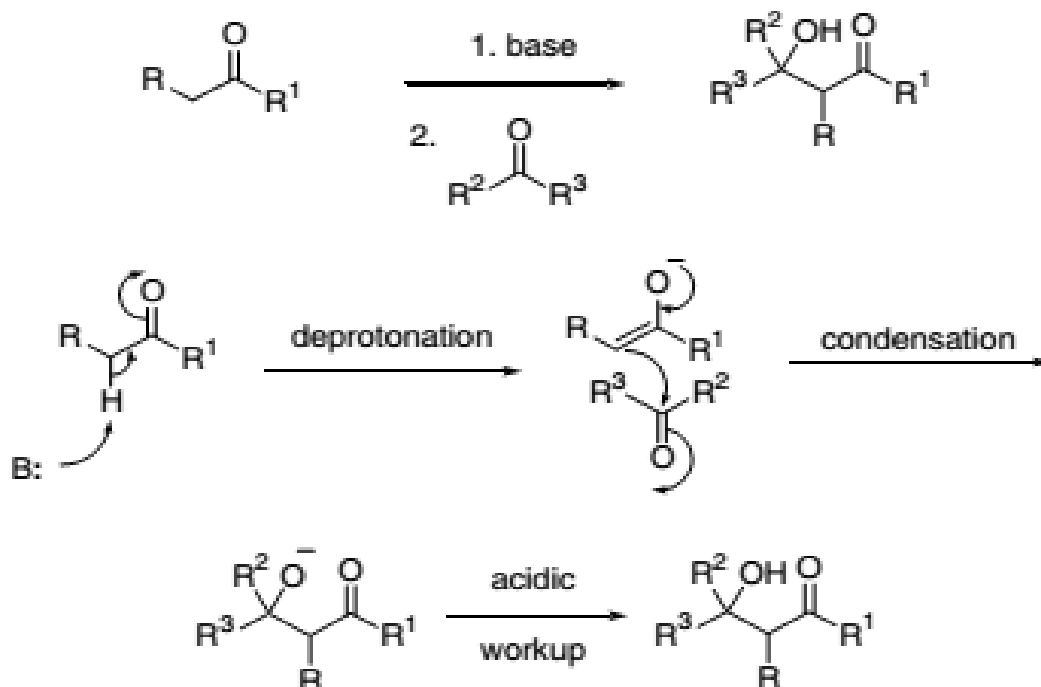


## BS 6<sup>th</sup> Named Reaction ( Active Methylene) CHEM 373

- *Acid and base catalysed aldol condensations. Conditions, mechanism and synthetic applications of the following reactions, Claisen reaction, Claisen – Schmidt reaction, Knoevenagel reaction, Perkin reaction, Reformatsky reaction, Stobbes condensation, Darzen's glycidic ester synthesis, Mannich reaction and Wittig reaction).*

### **Aldol condensation**

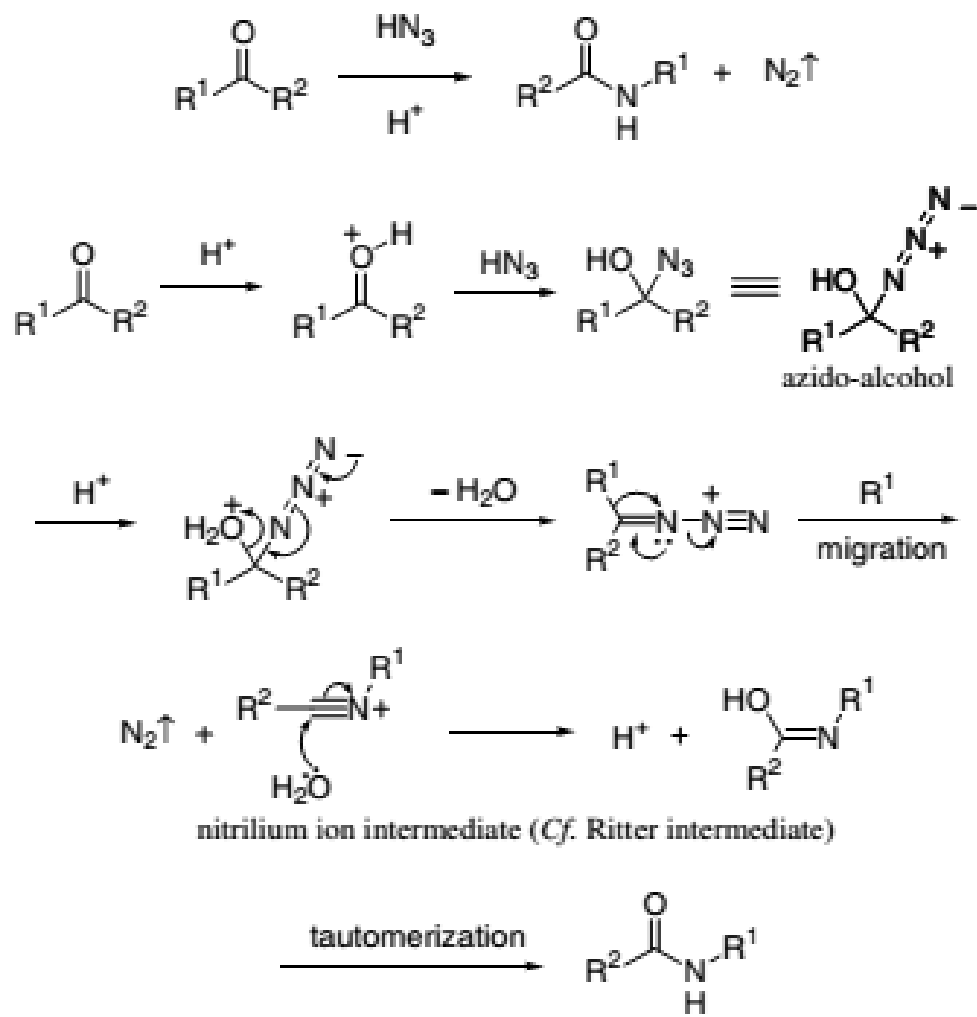
Condensation of a carbonyl with an enolate or an enol. A simple case is addition of an enolate to an aldehyde to afford an alcohol, thus the name **aldol**.



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### Schmidt reaction

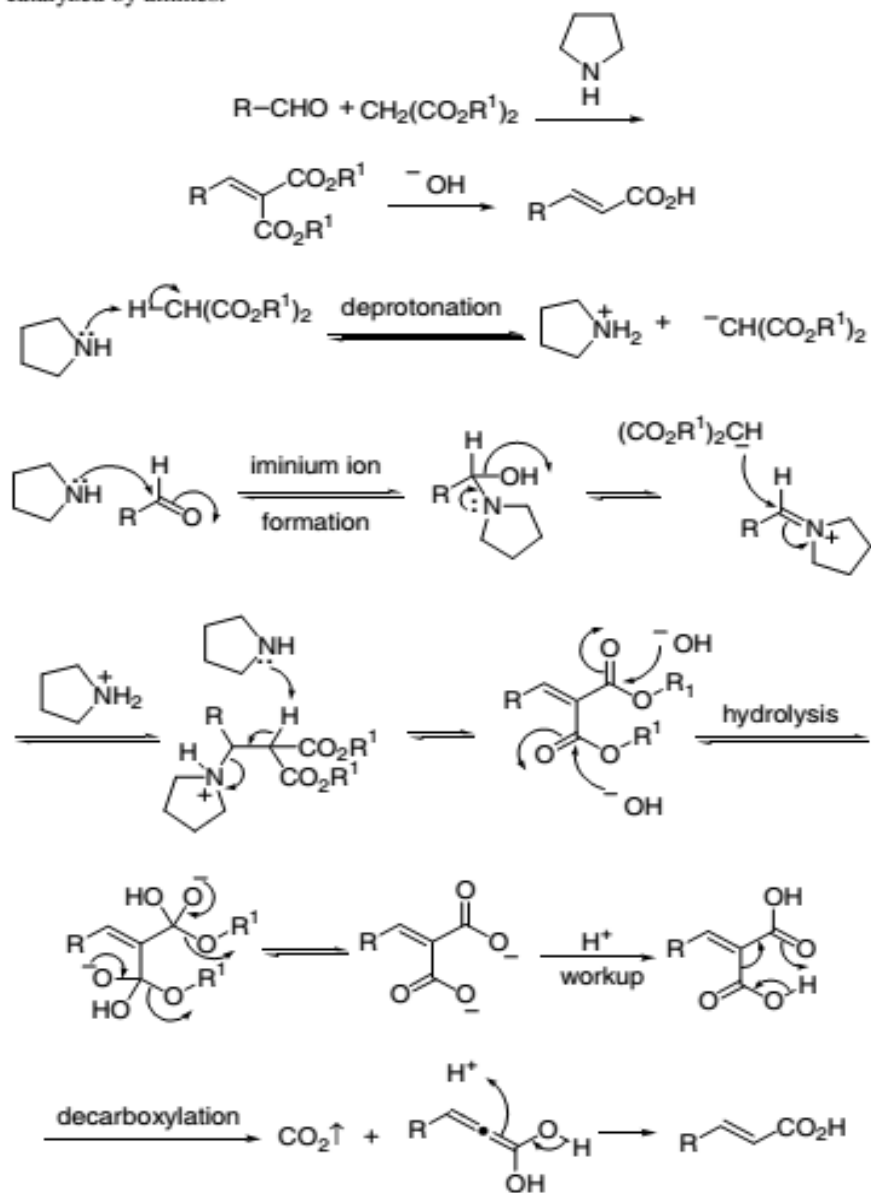
Conversion of ketones to amides using  $\text{HN}_3$  (hydrazoic acid).



# BS 6<sup>th</sup> Named Reaction ( Active Methylene) CHEM 373

## Knoevenagel condensation

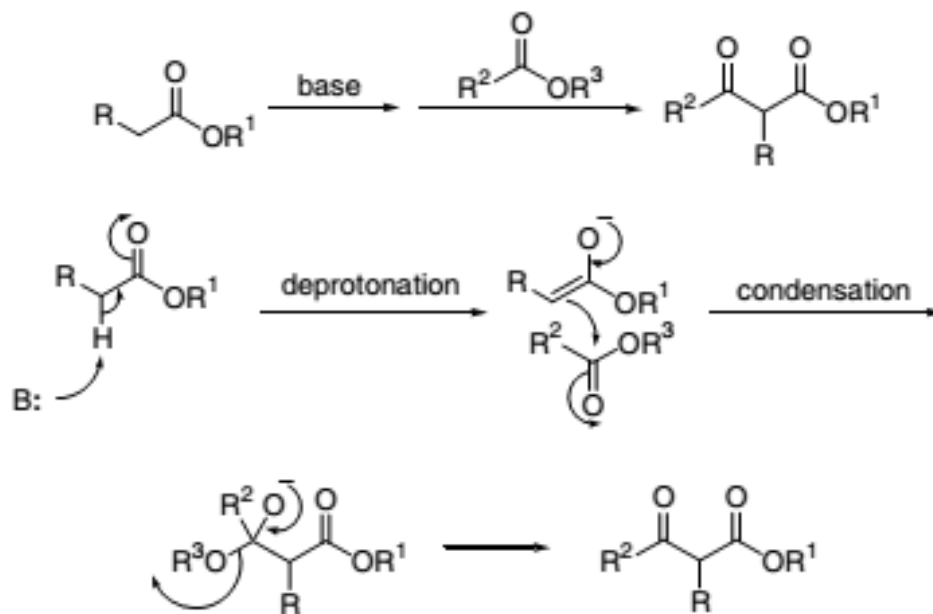
Condensation between carbonyl compounds and activated methylene compounds catalyzed by amines.



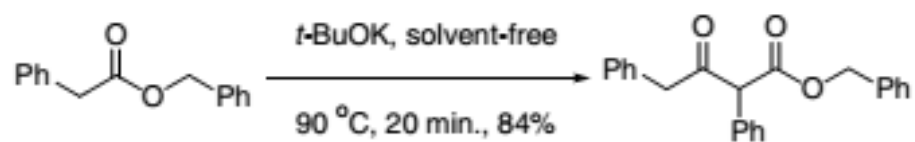
# BS 6<sup>th</sup> Named Reaction ( Active Methylene) CHEM 373

## Claisen condensation

Base-catalyzed condensation of esters to afford  $\beta$ -keto esters.



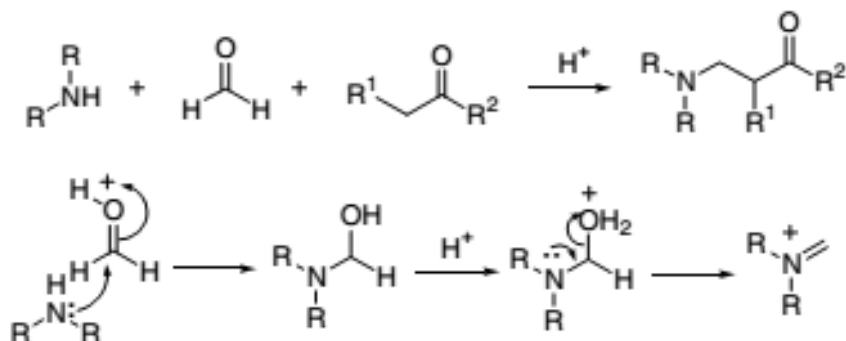
### Example 1<sup>9</sup>



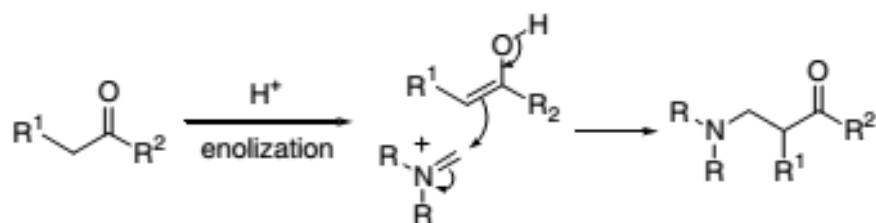
# BS 6<sup>th</sup> Named Reaction ( Active Methylene) CHEM 373

## Mannich reaction

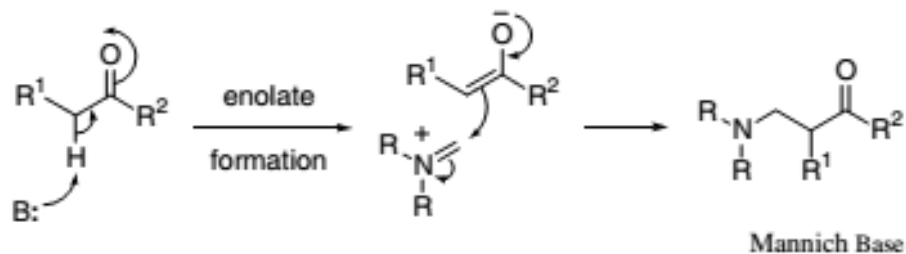
Three-component aminomethylation from amine, formaldehyde and a compound with an acidic methylene moiety.



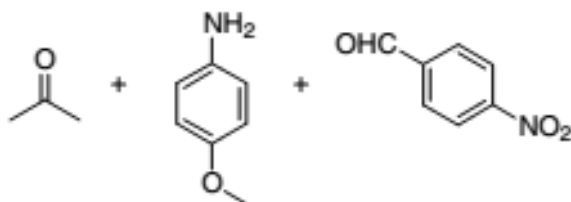
When R = H, the <sup>+</sup>Me<sub>2</sub>N=CH<sub>2</sub> salt is known as **Eschenmoser's salt**



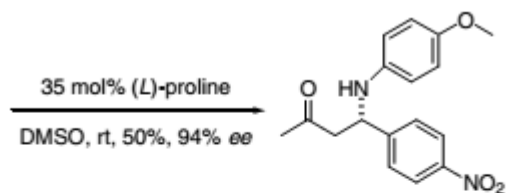
The Mannich reaction can also operate under basic conditions:



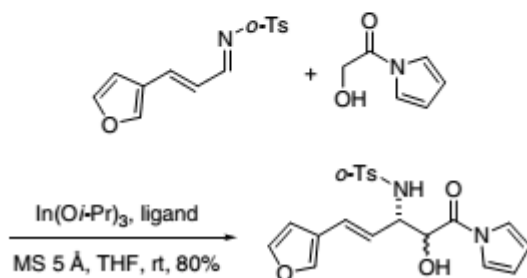
Example 1, asymmetric Mannich reaction<sup>4</sup>



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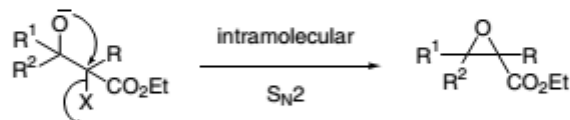
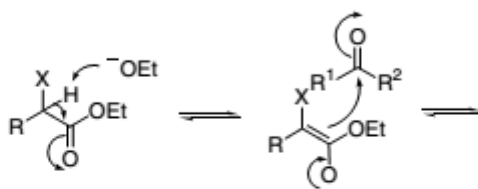
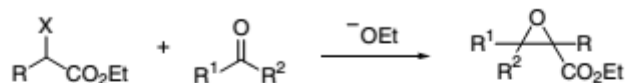


Example 2, asymmetric aza-Mannich reaction<sup>13</sup>

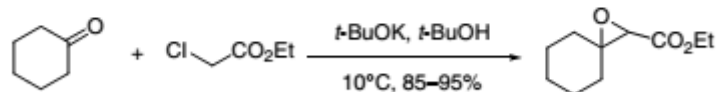


## Darzens glycidic ester condensation

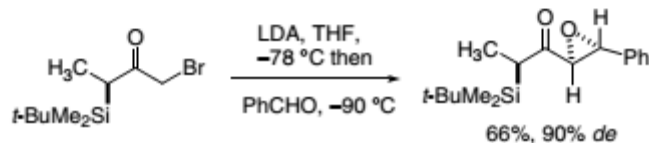
$\alpha,\beta$ -Epoxy esters (glycidic esters) from base-catalyzed condensation of  $\alpha$ -haloesters with carbonyl compounds.



Example 1<sup>4</sup>



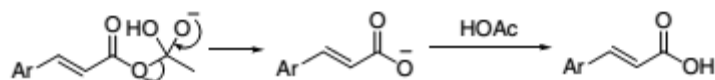
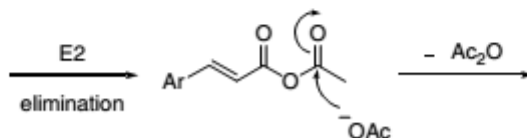
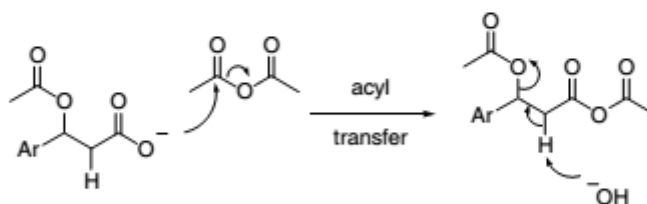
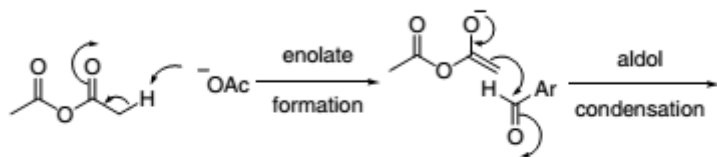
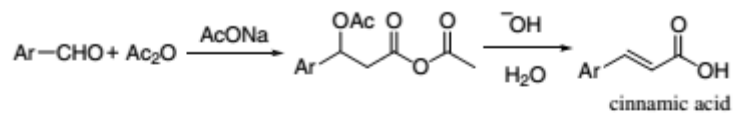
Example 2<sup>9</sup>



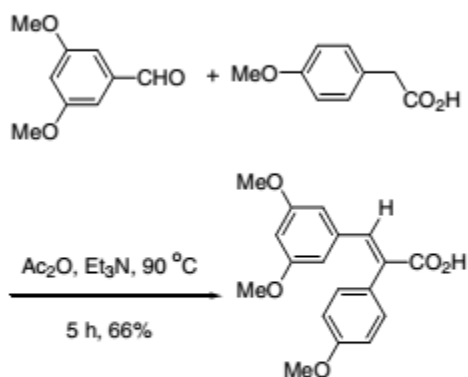
# BS 6<sup>th</sup> Named Reaction ( Active Methylene) CHEM 373

## Perkin reaction

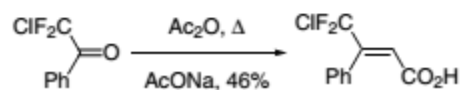
Cinnamic acid synthesis from aryl aldehyde and acetic anhydride.



### Example 1<sup>9</sup>



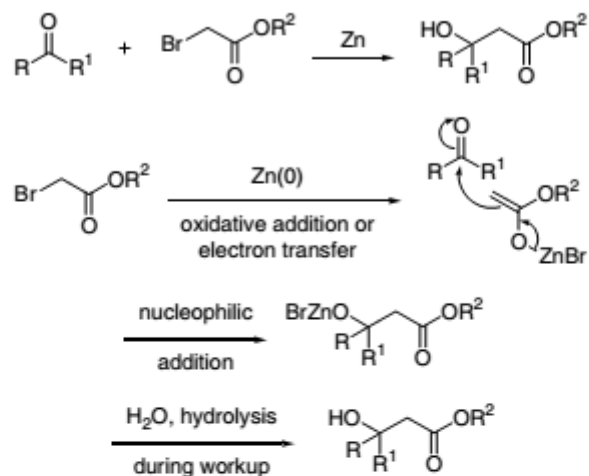
### Example 2<sup>10</sup>



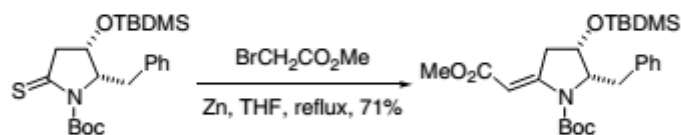
# BS 6<sup>th</sup> Named Reaction ( Active Methylene) CHEM 373

## Reformatsky reaction

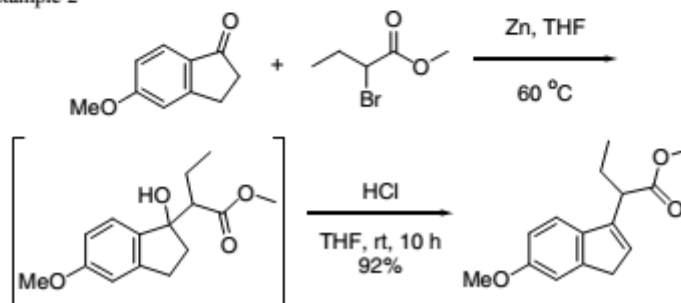
Nucleophilic addition of organozinc reagents generated from  $\alpha$ -haloesters to carbonyls.



Example 1<sup>5</sup>



Example 2<sup>11</sup>

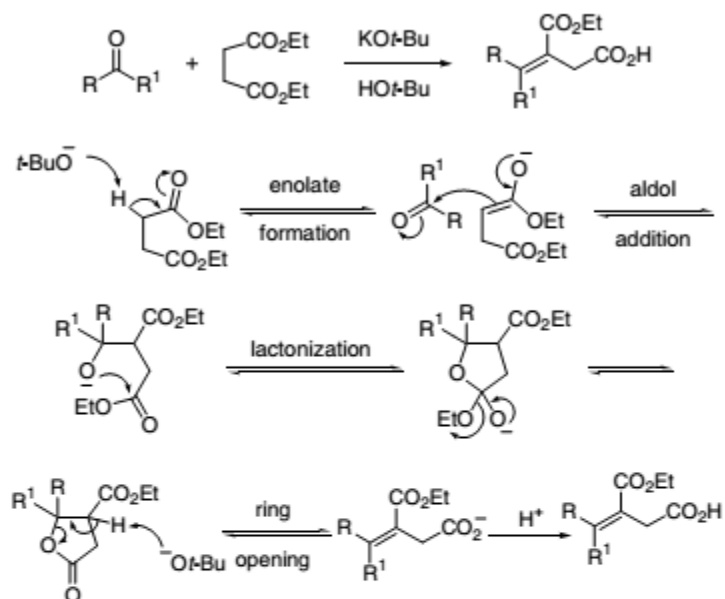




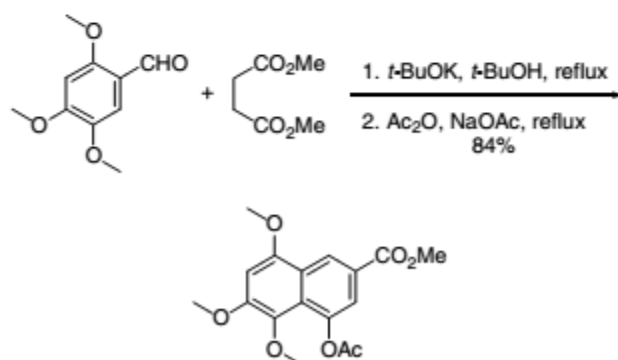
# BS 6<sup>th</sup> Named Reaction ( Active Methylene) CHEM 373

## Stobbe condensation

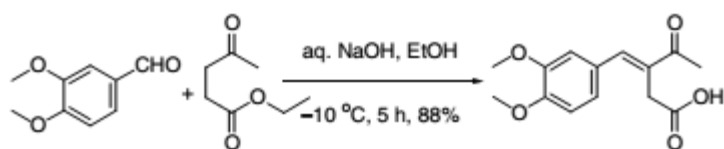
Condensation of diethyl succinate and its derivatives with carbonyl compounds in the presence of a base.



Example 1<sup>12</sup>



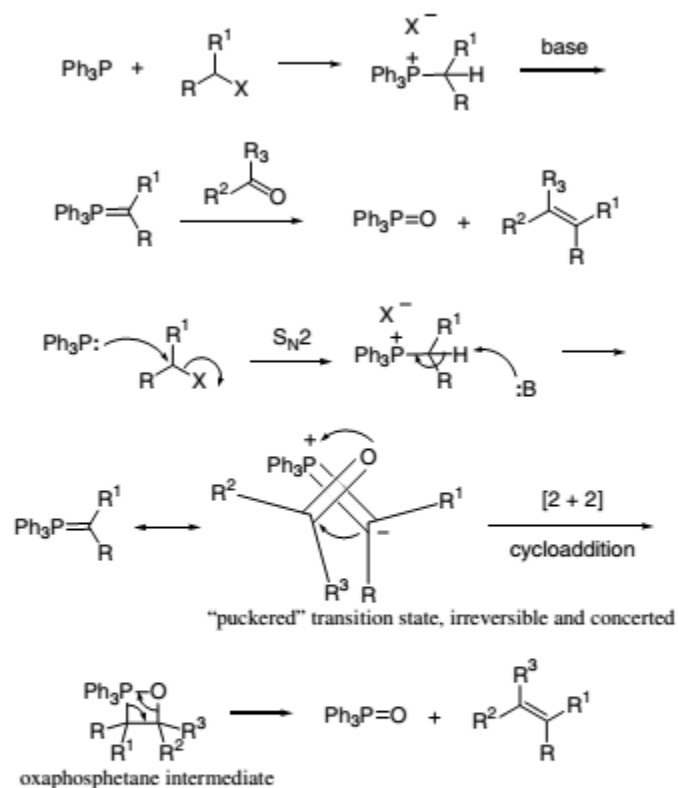
Example 2<sup>13</sup>



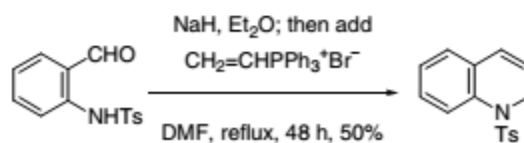
# BS 6<sup>th</sup> Named Reaction ( Active Methylene) CHEM 373

## Wittig reaction

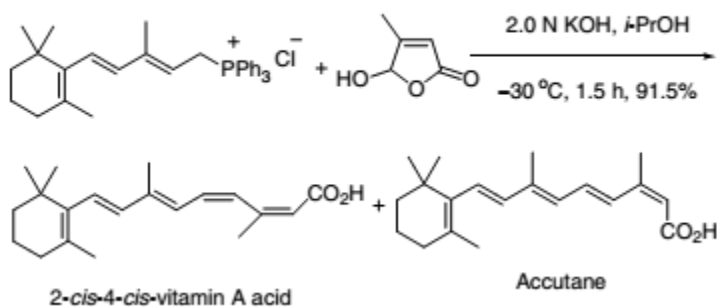
Olefination of carbonyls using phosphorus ylides.



Example 1<sup>3</sup>



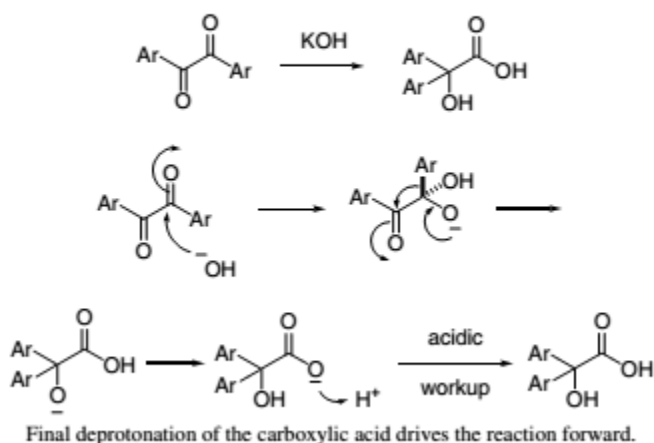
Example 2<sup>4</sup>



# BS 6<sup>th</sup> Named Reaction ( Active Methylene) CHEM 373

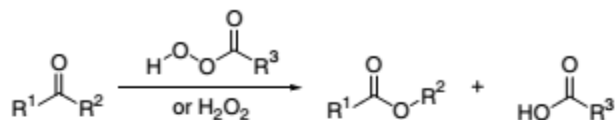
## Benzilic acid rearrangement

Rearrangement of benzil to benzylic acid *via* aryl migration.



## Baeyer-Villiger oxidation

General scheme:



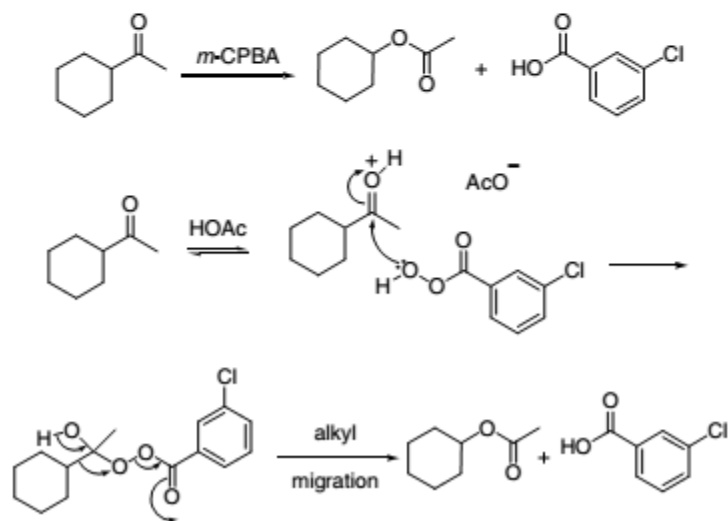
The most electron-rich alkyl group (more substituted carbon) migrates first. The general migration order:

tertiary alkyl > cyclohexyl > secondary alkyl > benzyl > phenyl > primary alkyl > methyl >> H.

For substituted aryls:

*p*-MeO-Ar > *p*-Me-Ar > *p*-Cl-Ar > *p*-Br-Ar > *p*-MeOAr > *p*-O<sub>2</sub>N-Ar

Example 1:

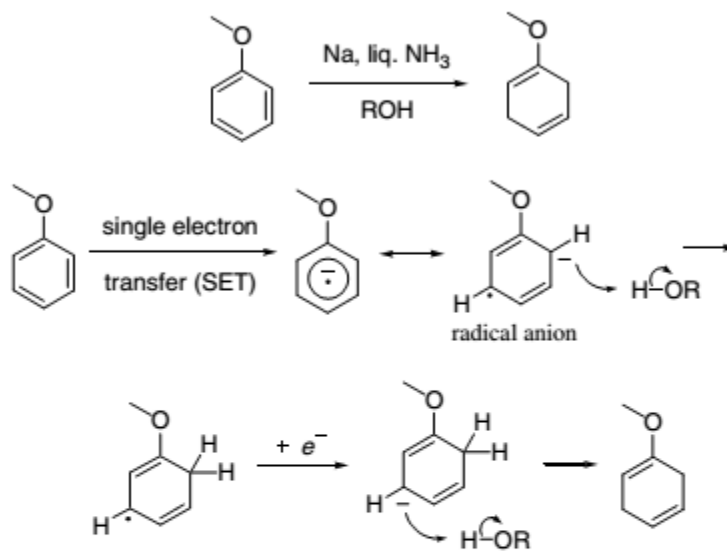


# BS 6<sup>th</sup> Named Reaction ( Active Methylene) CHEM 373

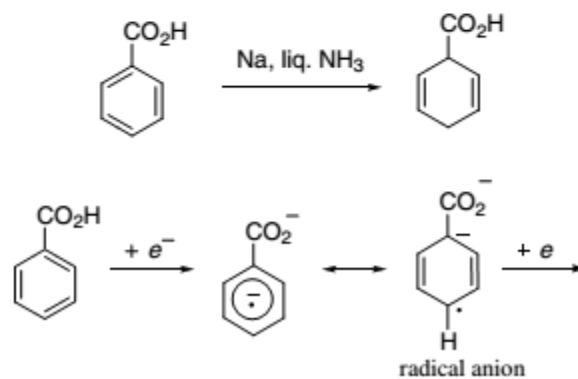
## Birch reduction

The Birch reduction is the 1,4-reduction of aromatics to their corresponding cyclohexadienes by alkali metals (Li, K, Na) dissolved in liquid ammonia in the presence of an alcohol.

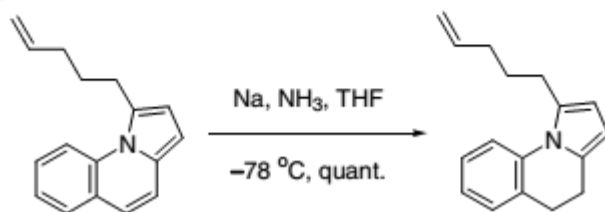
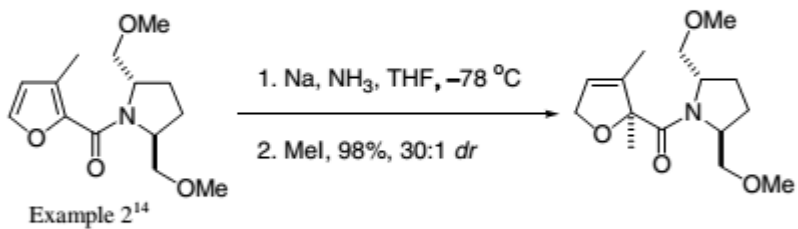
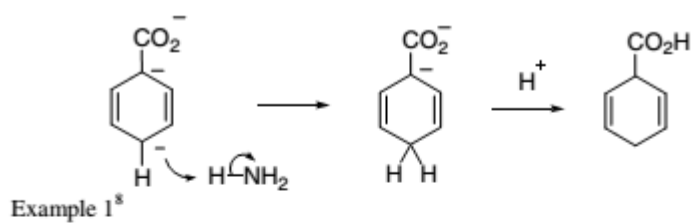
### Benzene ring bearing an electron-donating substituent:



### Benzene ring with an electron-withdrawing substituent:



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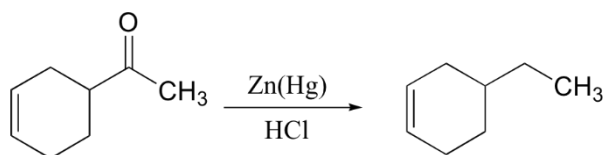


## BS 6<sup>th</sup> Named Reaction ( Active Methylene) CHEM 373

### Reduction of carbonyl carbons to methylene

There are two principle methods for reducing the carbonyl group of a ketone to a simple methylene (CH<sub>2</sub>) carbon. The mechanism for the **Clemmensen reduction** is not well understood, but you will be asked to propose a mechanism for the **Wolff-Kishner reduction**

#### The Clemmensen reduction:



#### Wolff-Kishner reduction

