

# Designing Organic Synthesis

## A

### Synthon approach

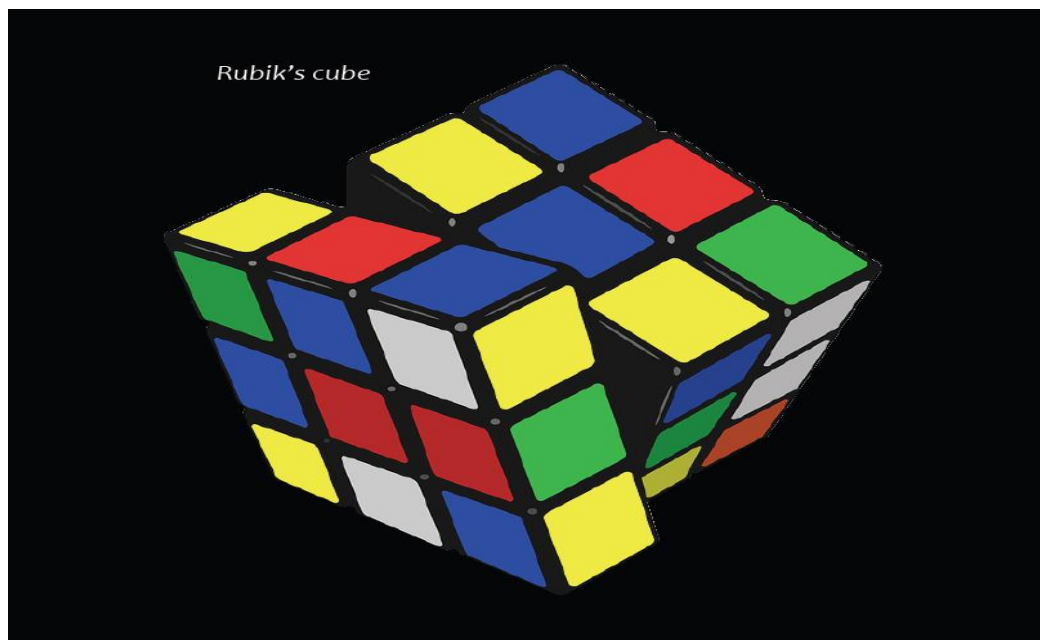
Dr. BRAJA NARAYAN PATRA  
ASSOCIATE PROFESSOR IN CHEMISTRY  
UTKAL UNIVERSITY



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Synthon approach

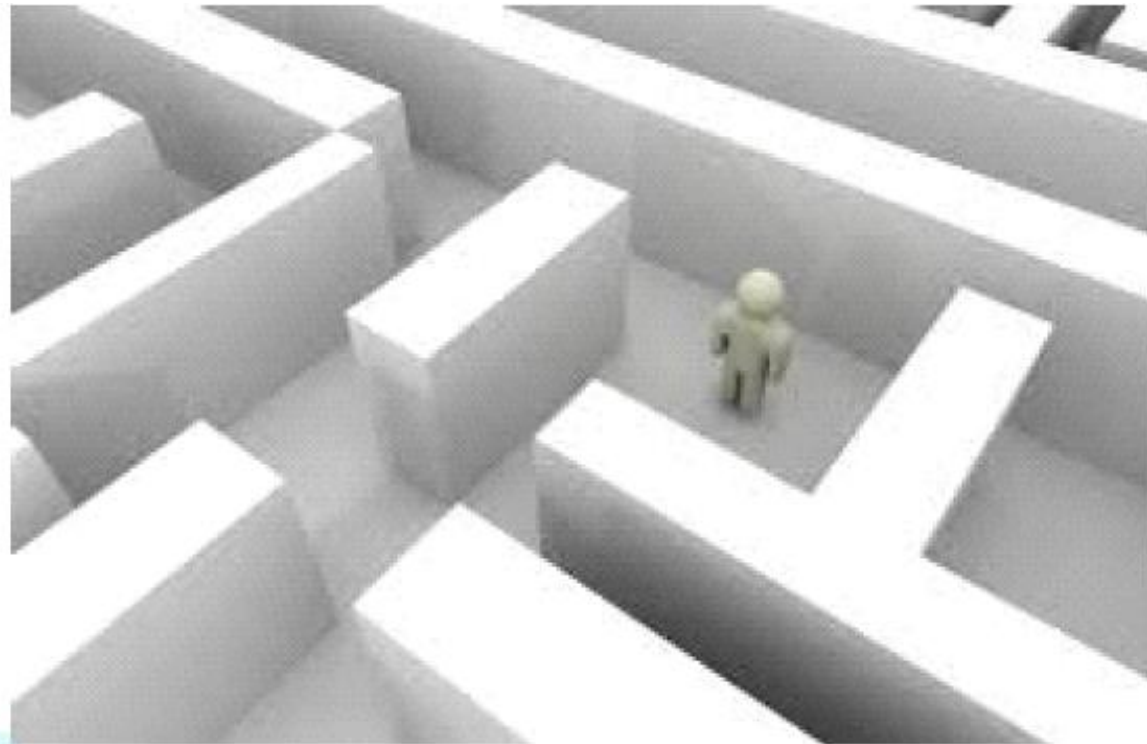




# Planning a journey to unknown



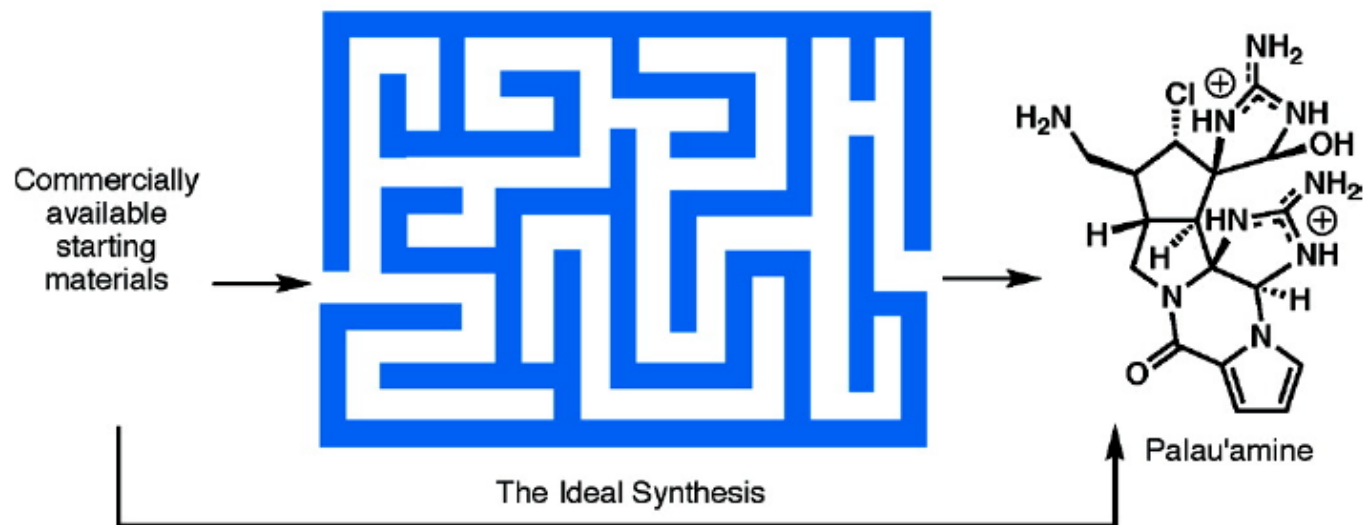
DESTINATION



"I am not lost, I am just wondering"



# Today's Total Synthesis





## ***Environmentally acceptable***

*avoidance of problematic waste (the greenest route)  
avoidance of toxic intermediates (the healthiest route)*

## ***Safe***

*avoidance of risking procedures (the safest route)*

## ***Economically acceptable***

*cost of materials (the cheapest route)  
novelty (the patent route)*

## ***Robust***

*easily scale-up, reproducibility*



## ***Highly efficient***

*Simple, high yield, a few steps  
... sequence of only construction reactions...*

- ... sequence of only construction reactions involving no intermediary refunctionalizations, and leading directly to the target, not only its skeleton but also its correctly placed functionality

*Hendrickson, J. B. J. Am. Chem. Soc. 1975, 97, 5784*



*The exercise of Organic Synthesis requires*

*1. Knowledge of Reactivity (Structure-Mechanism)*

*2. Design ability (Retrosynthetic Analysis)*

*The ultimate goal of Organic Synthesis is to assemble an organic compound (**target**) from readily available starting materials and reagents in the most efficient way.*

*This process usually begins with the design of a synthetic plan (**Strategy**)*



## Strategy ■

*Strategy refers to the general plan to synthesize the TGT*  
*Retrosynthetic arrows should provide a clear idea of the strategy*

## Tactic ■

*Tactical issues deal with the actual execution of the plan*  
*Tactic is closely associated with structure and reactivity*



## LEFT BRAIN

Logic

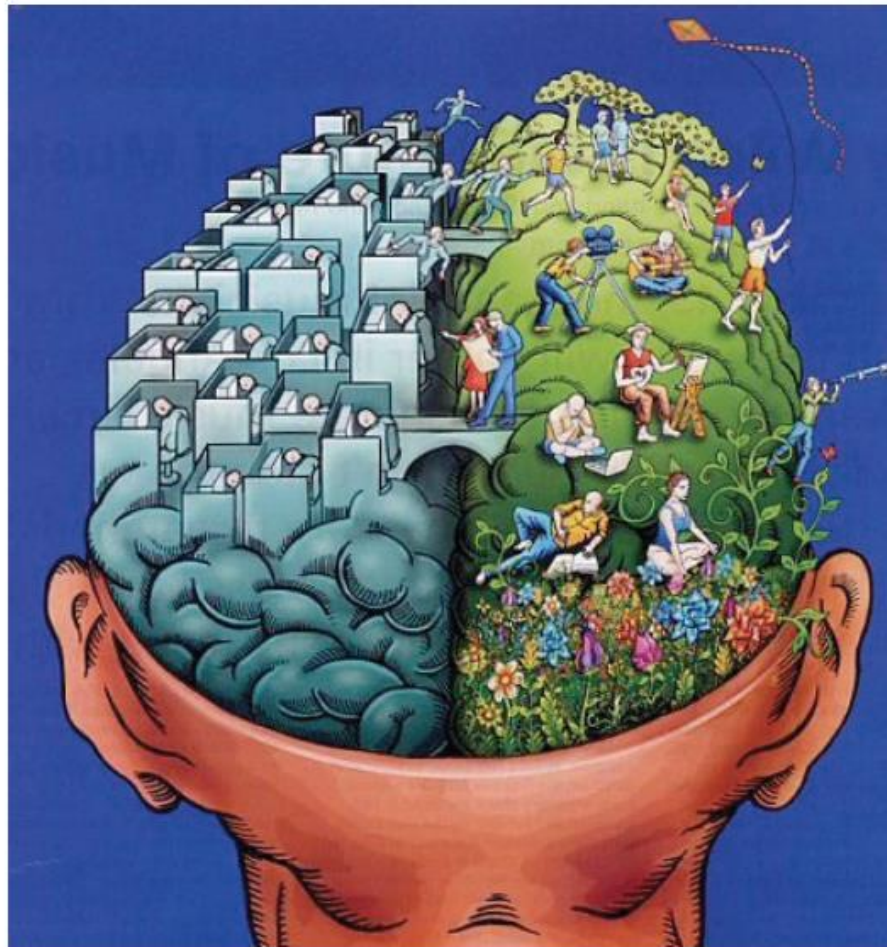
Analysis

Organization

Knowledge /Facts

Detail

Maths & Science



## RIGHT BRAIN

Intuition

Emotion

Spirituality

Belief

Big picture

Art / Music

<http://www.webdesignerdepot.com/2009/>



*Tactic*



*Strategy*





*Is there any standard strategy to analyze any target ?*

*Is there any preferential manner to proceed ?*

*Not exactly,*

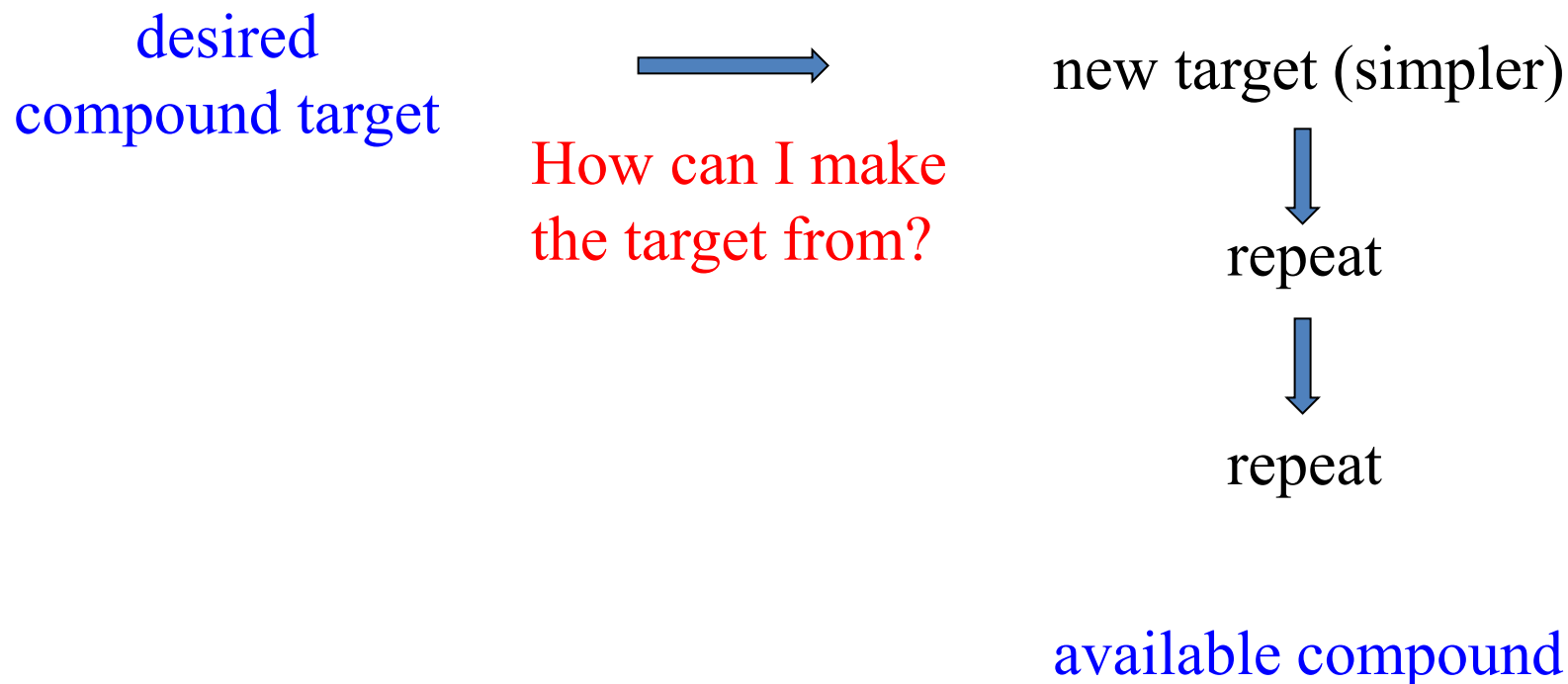
*Freedom, imagination, and risk are common words in synthesis*

*Organic Synthesis is a heuristic and somehow artistic activity  
in which concepts as beauty or elegance often appears*



# The Strategy of Organic Synthesis

Retrosynthetic Analysis: work backwards



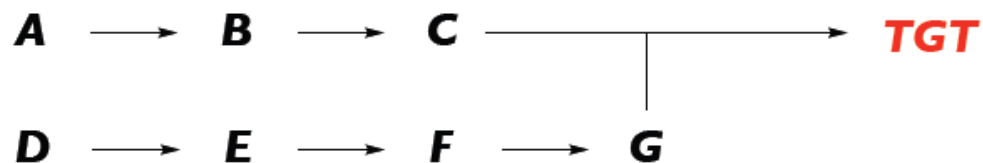


- Number of steps as low as possible (**Step Economy**)
- Number of non-necessary redox steps as low as possible (**Redox Economy**)
- Flexibility, easy scale-up, availability of starting materials, ...
- Avoidance of toxic intermediates, side products, and waste
- Convergent syntheses are used to be better than lineal syntheses

## Lineal Synthesis



### Convergent Synthesis





**Retrosynthesis:** An analytical operation which breaks bonds of complex molecules to the possible starting materials

**Disconnection:** An imaginary bond cleavage corresponding to the reverse of real reaction. This is indicated by wavy line.

**Synthon:** Idealized fragments resulting from a disconnection usually an ions

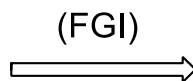
**Synthetic equivalent/Reagent:** A Chemical compound used as equivalent of a Synthonr

**Target Molecule:** Molecule to be synthesized



**Retron:** Each reaction generate a characteristic structural feature in the Product .  
For instance Enone present in product is the result of aldol condensation reaction.  
This substructure (enone) is called retron

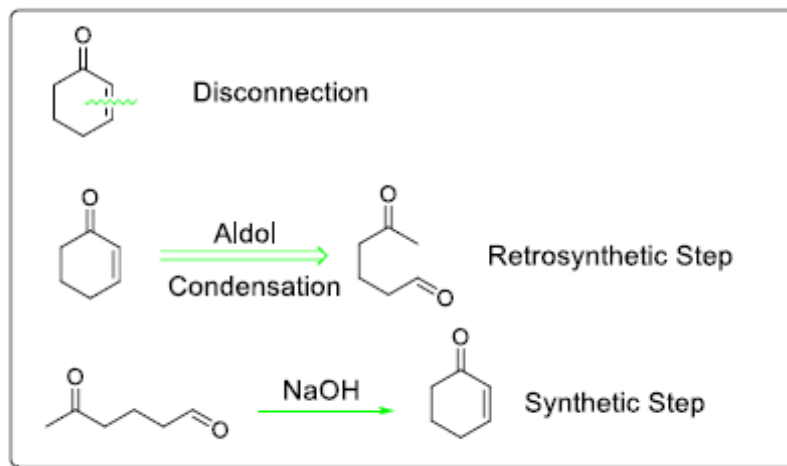
**Functional Group Interconversion (FGI):** The operation of writing one functional group for another so that disconnection become possible





## Symbols of Retrosynthetic Analysis

- A disconnection is represented by a wavy ({} ) line through the bond being disconnected,.
- A retrosynthetic arrow ( $\Rightarrow$ ) represents going from the target molecule “backwards” to simpler molecules (retrons).
- A synthetic arrow ( $\rightarrow$ ) represents going in the forward direction.

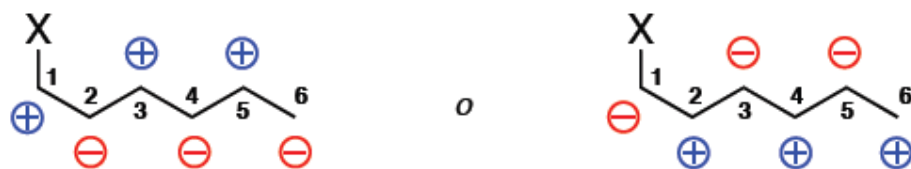




## Based on the relationships between FG

Main ideas:

1. Any TGT is formed by a carbon backbone & FG (heteroatom)
2. The FG (heteroatom) polarizes the carbon backbone
3. Mainly applied to heterolytic mechanisms: nucleophile/electrophile



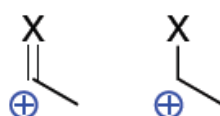
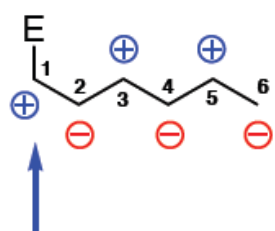
It might be useful to consider the carbon framework of any molecule as an ionic aggregate, whose origin relies on the presence of functional groups.  
The symbol designations, + and -, simply denote potential electrophilic or nucleophilic site reactivity



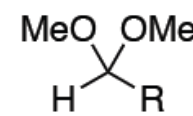
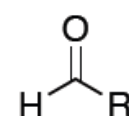
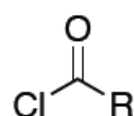
Depending on their nucleophilic / electrophilic role,

synthons can be classified as **electron donors (d)** or **acceptors (a)** and

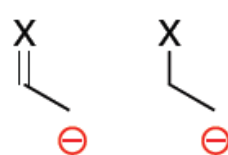
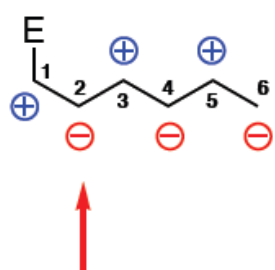
are accordingly numbered with respect to the relative positions of a FG and the reactive carbon atom



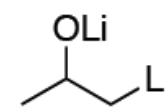
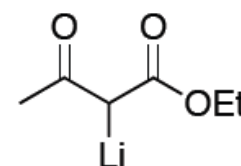
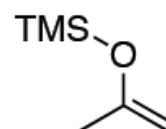
Synthon  $a^1$



Synthetic precursors



Synthon  $d^2$



Synthetic precursors

Therefore, synthons can be  $a^0, a^1, a^2, a^3, \dots$  or  $d^0, d^1, d^2, d^3, \dots$



## Synthons d

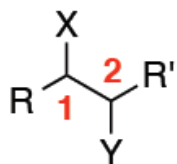
Type	Example	Reacting materials	FG
$d^0$	$\text{MeS}^\ominus$	$\text{MeSH}$	$\text{>C-S-}$
$d^I$	$^\ominus\text{C}\equiv\text{N}$	$\text{KC}\equiv\text{N}$	$-\text{C}\equiv\text{N}$
$d^2$	$^\ominus\text{CH}_2\text{CHO}$	$\text{CH}_3\text{CHO}$	$-\text{CHO}$
$d^3$	$^\ominus\text{C}\equiv\text{C-COOMe}$	$\text{HC}\equiv\text{C-COOMe}$	$-\text{CO}_2\text{Me}$
Alkyl-d	$\text{Me}^\ominus$	$\text{MeLi}$	

## Synthons a

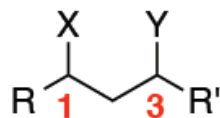
Type	Example	Reacting materials	FG
$a^0$	$^\oplus\text{PMe}_2$	$\text{ClPMe}_2$	$\text{Me}_2\text{P-}$
$a^I$	$\text{>C(OH)}^\oplus$	$\text{>C=O}$	$-\text{CO-}$
$a^2$	$\text{>C(O)}^\oplus$	$\text{Br-CH}_2\text{C(=O)-}$	$-\text{CO-}$
$a^3$	$\text{>C(O}^\ominus\text{)OMe}^\oplus$	$\text{CH}_2=\text{C(OMe)C(=O)-}$	$-\text{CO}_2\text{Me}$
Alkyl-a	$\text{Me}^\oplus$	$\text{MeI}$	



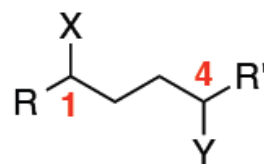
*The relationship between two FG depends on how distant they are ...*



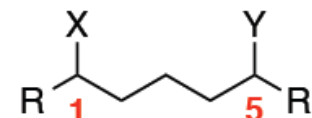
*1,2-Relationship*



*1,3-Relationship*

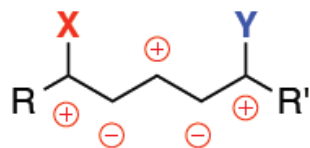


*1,4-Relationship*

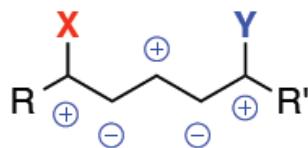


*1,5-Relationship*

*... and the polarization that they impart on the backbone*

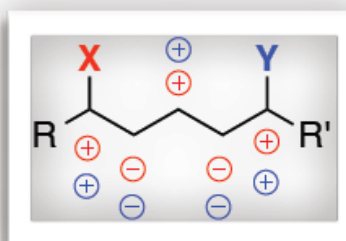


*polar arrangement by X*

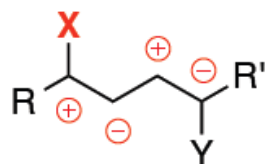


*polar arrangement by Y*

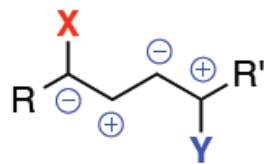
≡



*consonant  
(matched)*

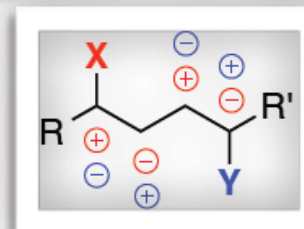


*polar arrangement by X*



*polar arrangement by Y*

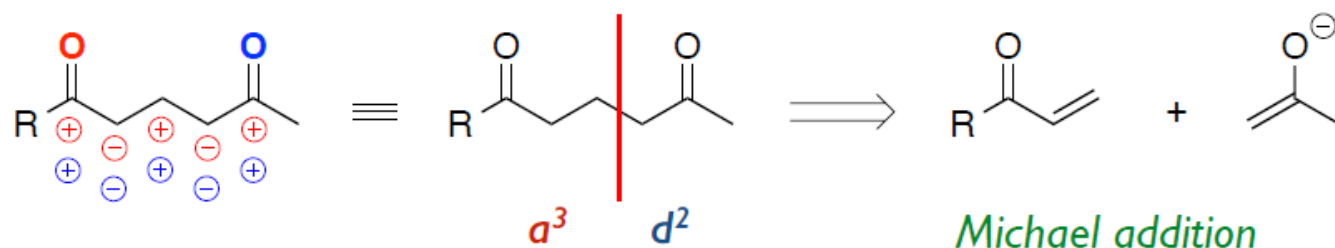
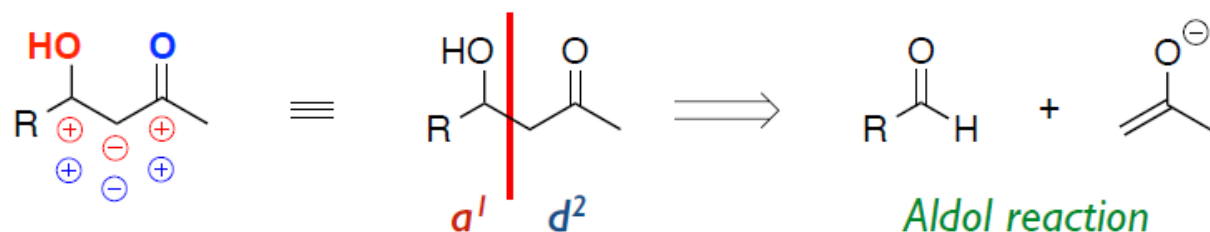
≡



*dissonant  
(mismatched)*



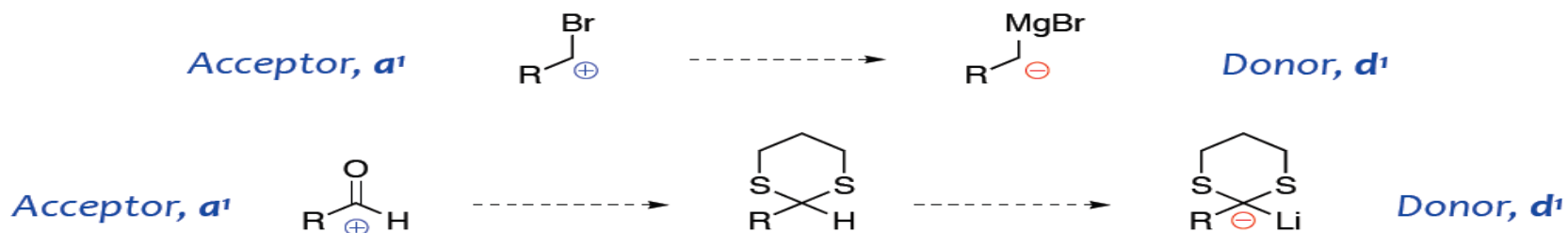
*Consonant (matched) relationships are quite easy to analyze ...*



*Dissonant (mismatched) relationships are much more complicated and usually require the inversion on the polarity (UMPOLUNG) of one of the participants*



**UMPOLUNG** refers to the change of the self-reactivity of a synthon



Seebach, D. *ACIEE* **1969**, 8, 639; **1979**, 18, 239

For a seminal application, see Seebach, D.; Corey, E. J. *JOC* **1975**, 40, 231

**Pay an especial attention to  $a^2$  synthons**

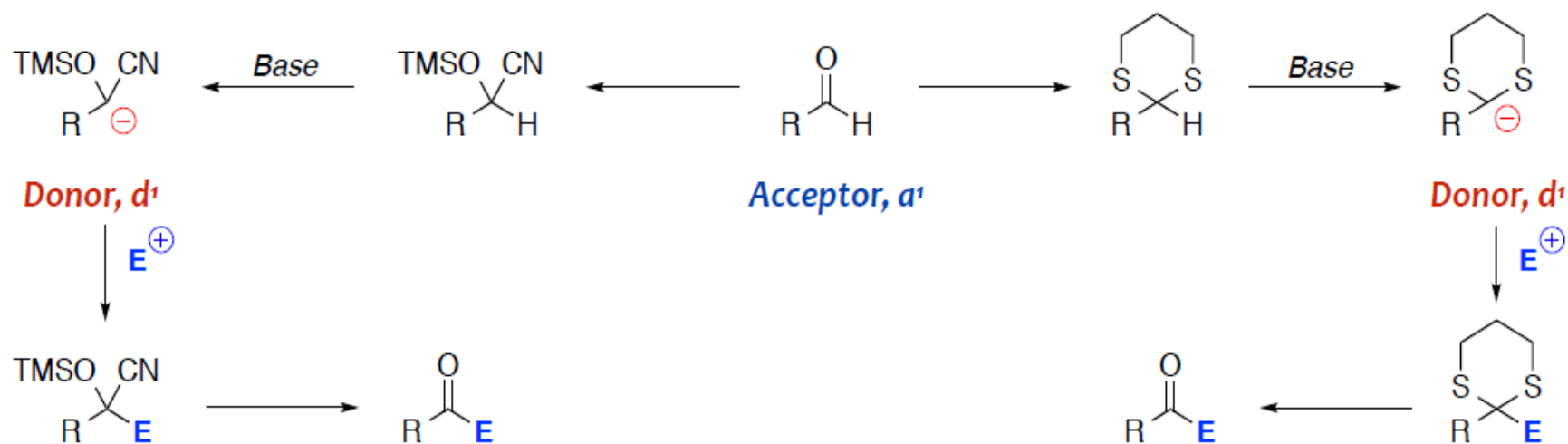


**$a^2$  Synthons**

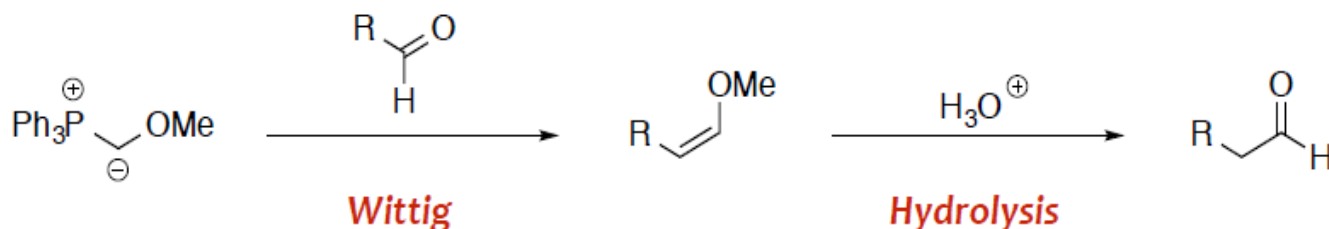


## CARBONYL EQUIVALENTS

refers to modifications on the carbonyl FG that producing an inversion on reactivity



## MASKED CARBONYL COMPOUNDS

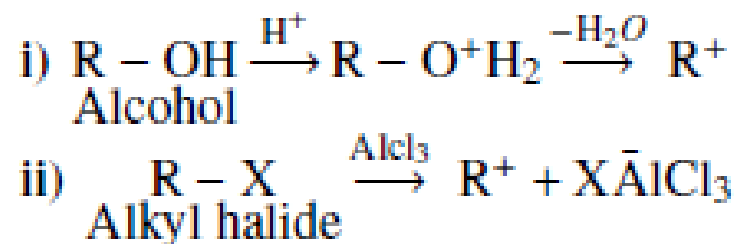




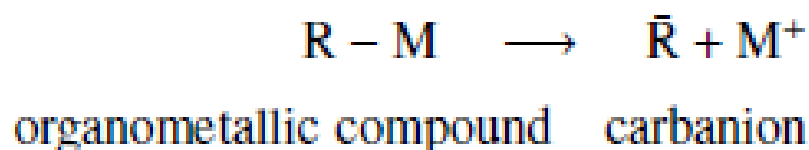


## B) Alkyl ions –

### a) Alkyl cation (carbenium ion)<sup>+</sup>



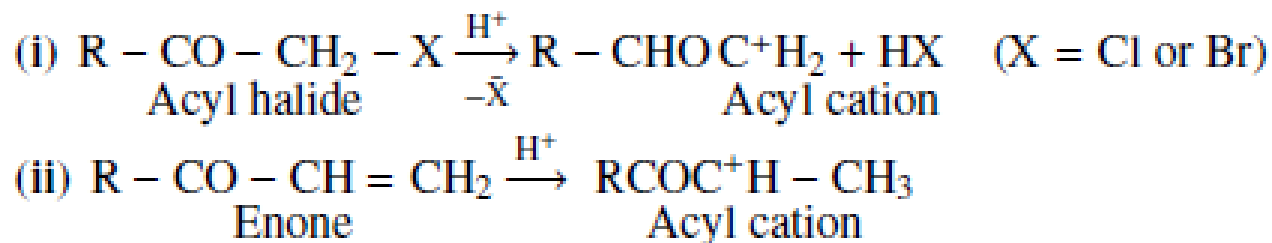
### b) Alkyl anion (carbanion)<sup>-</sup>





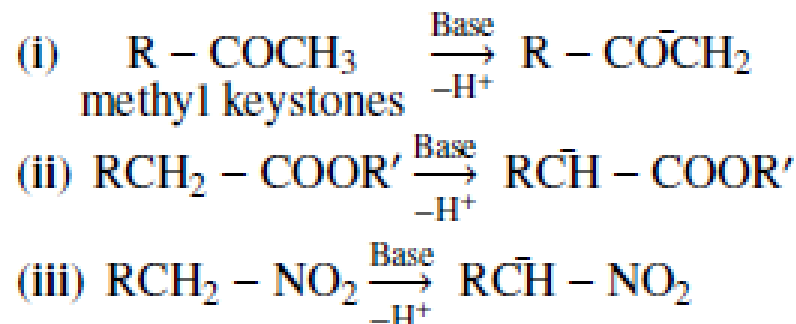
## C) Acyl ions

### a) Acyl cations



### b) Acyl anion

Removal of a proton from a methylene group adjacent to a electron-withdrawing group.

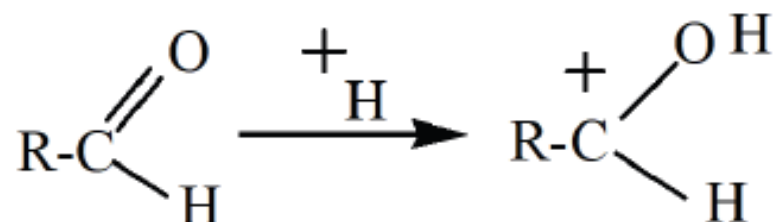




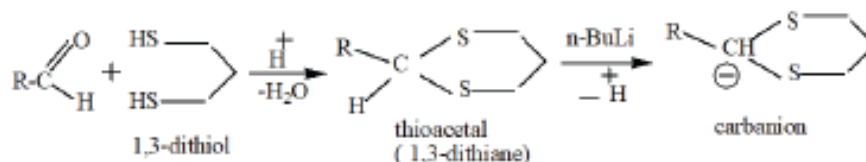
## D) Ethoxy anion

## E) Aldehyde carbonyl as a cation and anion

The aldehyde carbonyl carbon is electron deficient and undergoes nucleophilic attack.



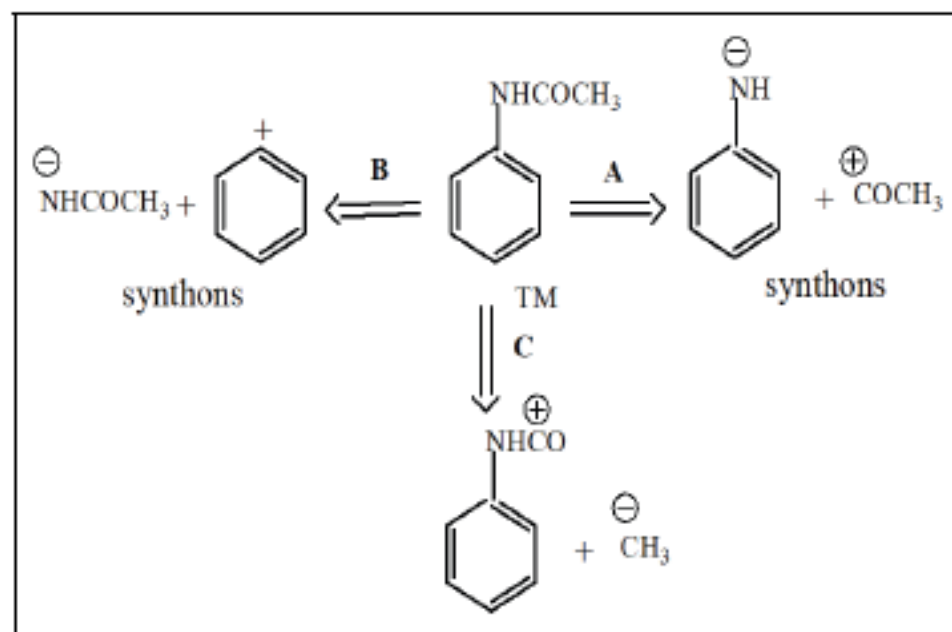
The aldehyde carbonyl carbon can also undergo electrophilic attack when it is converted into an anion. The polarity of the electron – deficient aldehyde carbonyl carbon can be reversed and this is known as ‘umpolung’.



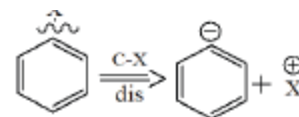
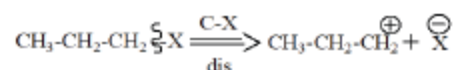


## *Guidelines or Empirical Rules (Heuristics) to a Proper Disconnection*

1) Disconnection should correspond to a known and reliable reaction. So, a thorough knowledge of reactions is necessary (*Figure*



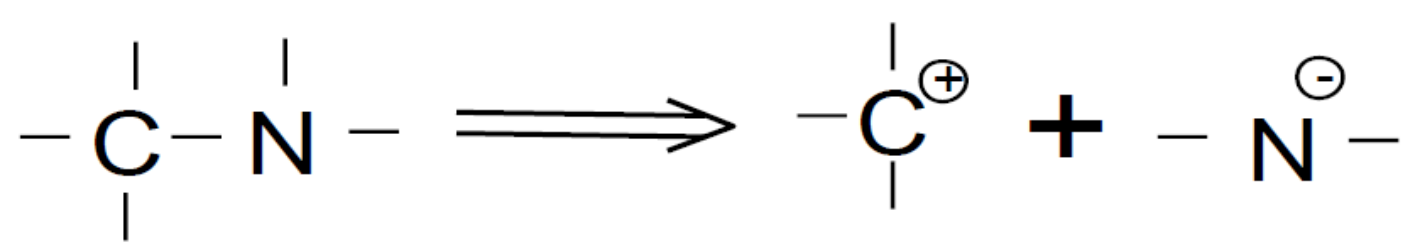
2) Disconnect C-X bond.





**Rule -3**

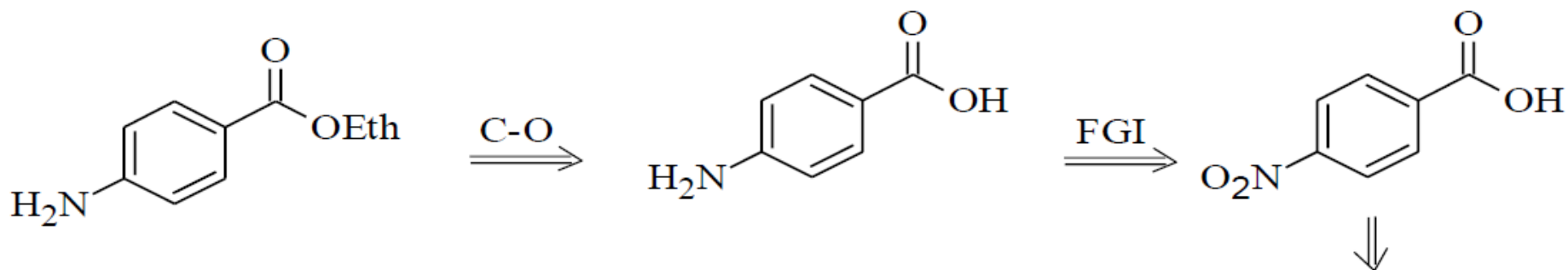
A bond joining a carbon to a hetero atom always broken with the electron pair on hetero atom. e.g



**Rule -3**

Sometimes a disconnection carried out does not generate sufficient stabilised fragments, but such fragments can be obtained by using FGI or by introducing an additional electron withdrawing group and then removing it after synthesis.

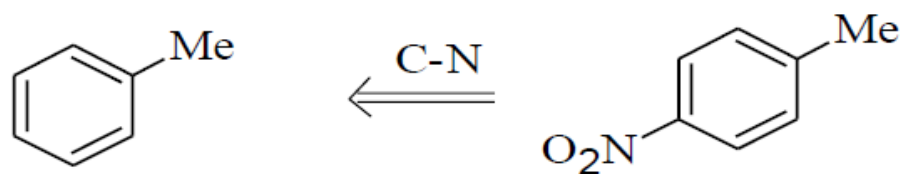




TM

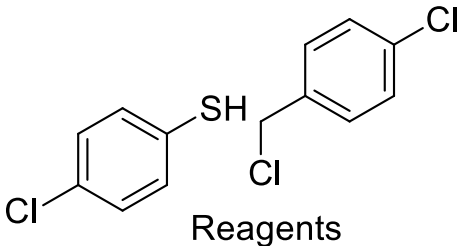
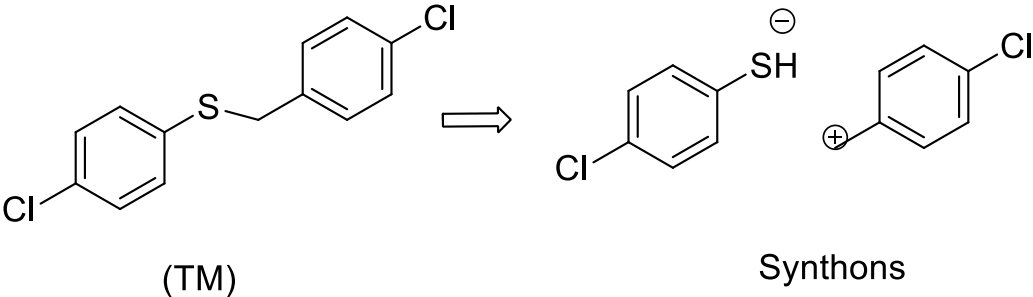
### Benzocaine :

- Toluene is readily available starting material
- Me is activating and ortho-/para- directing
- We know reagents for the synthon  $\text{NO}_2$

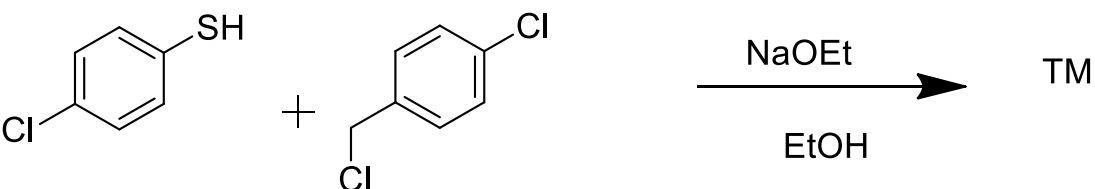




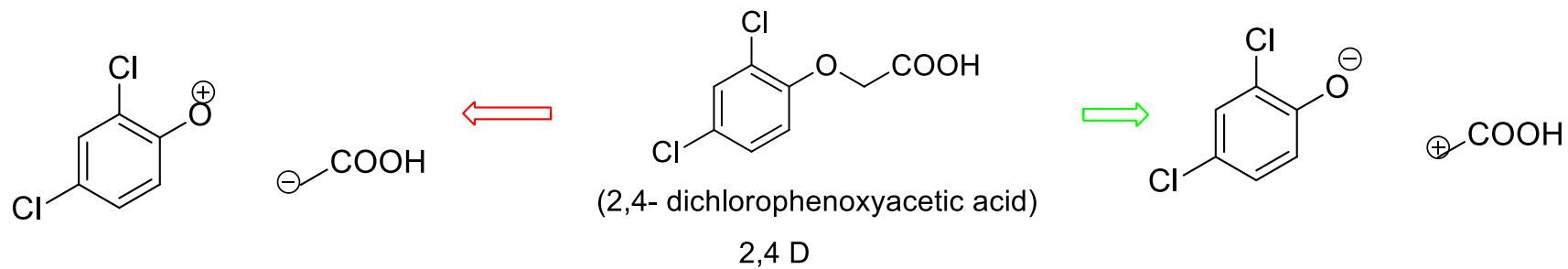
For compound consisting of two parts joined by a heteroatom, disconnect next to hetero atom



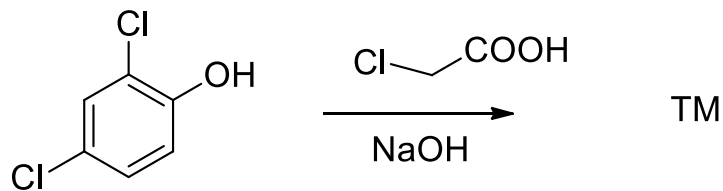
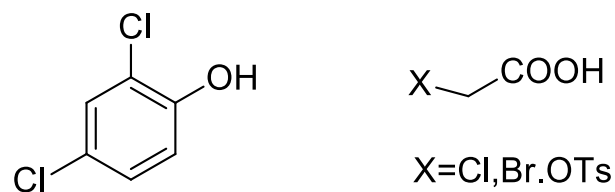
Synthesis







TM









**Target molecule (TGT)**  
*the molecule to be synthesized*

**Retrosynthetic analysis or retrosynthesis**  
*the process of mentally breaking down a molecule into a starting material*

**Disconnection**  
*an imaginary bond cleavage corresponding to a reverse of a real reaction*

**Transform**  
*the exact reverse of a synthetic reaction*

**Retron**  
*structural subunit on the target that enables a transform to operate*

**Synthon**  
*idealized fragment resulting from a disconnection, which is related to possible synthetic operations*

**Umpolung**  
*reversal of normal polarization of a molecule or synthon*

**Reagent**  
*a real chemical compound used as the equivalent of a synthon*



### **Synthesis tree**

*set of all the possible disconnections and synthons leading from the target to the starting materials of a synthesis*

### **Total synthesis**

*the chemical synthesis of a TGT from relatively simple starting materials*

### **Formal total synthesis**

*the chemical synthesis of an intermediate that has already been transformed into the desired target*

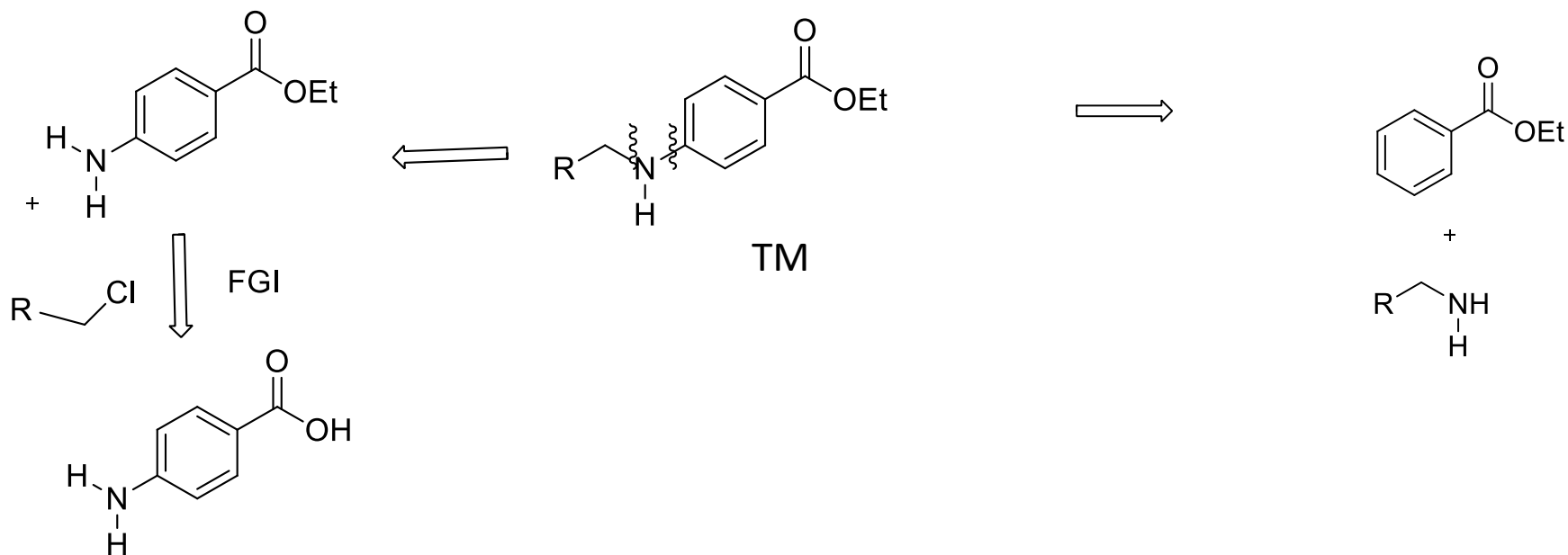
### **Lineal synthesis**

*a synthesis of consecutive steps*

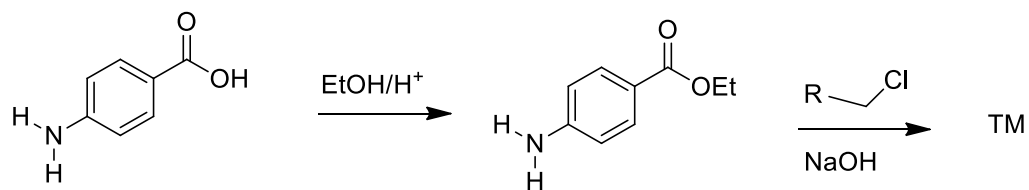
### **Convergent synthesis**

*a synthesis involving the assembly of fragments*





## Synthesis

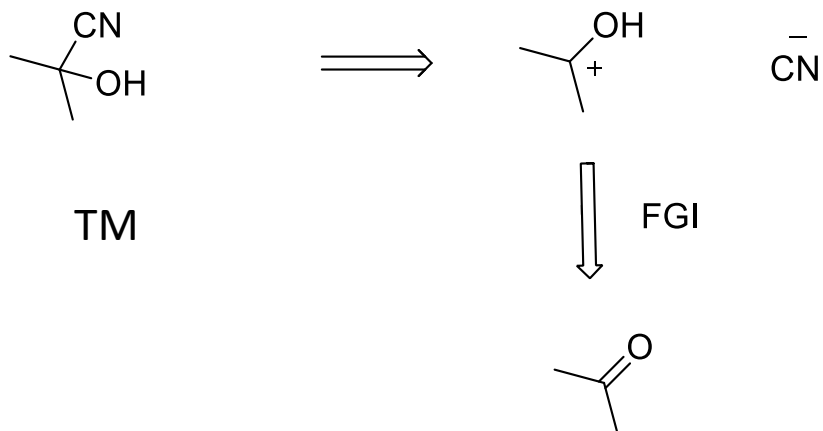




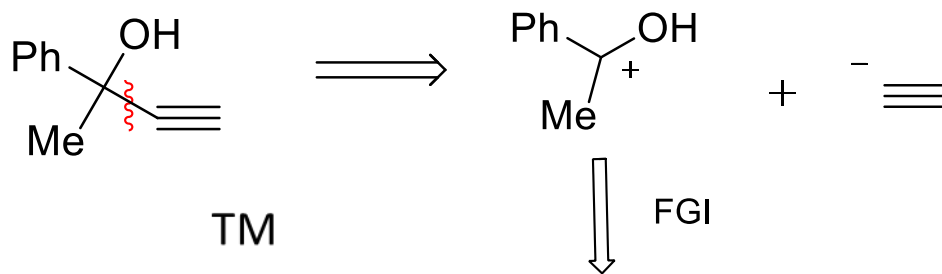
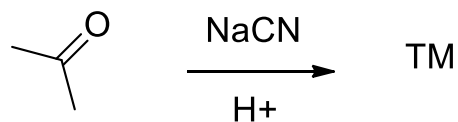




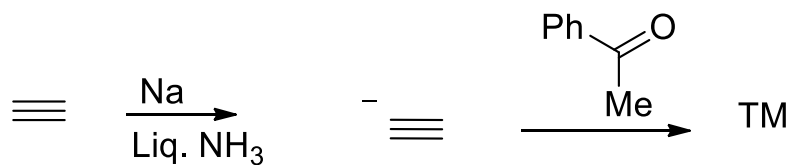
## One group disconnection



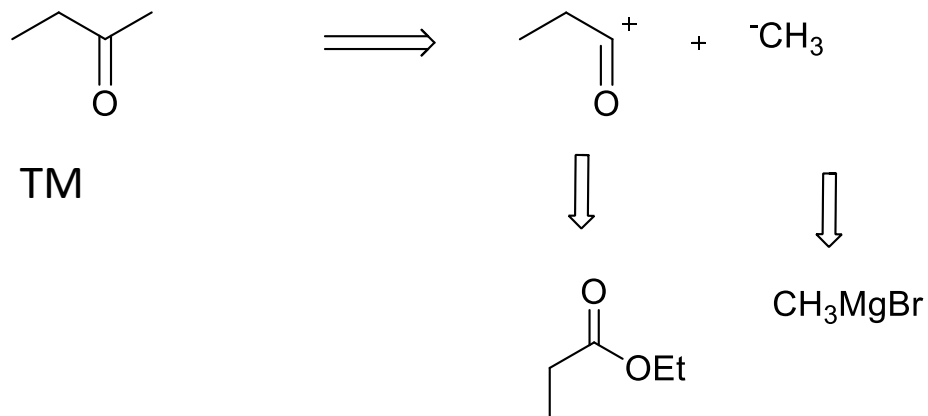
## Synthesis



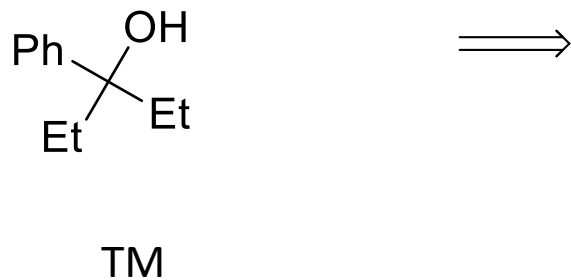
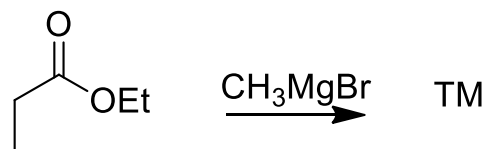
## Synthesis



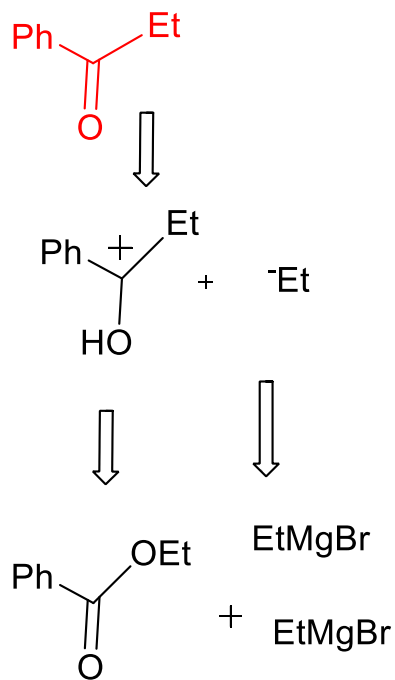
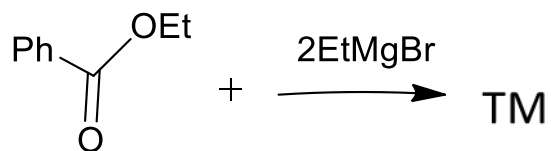




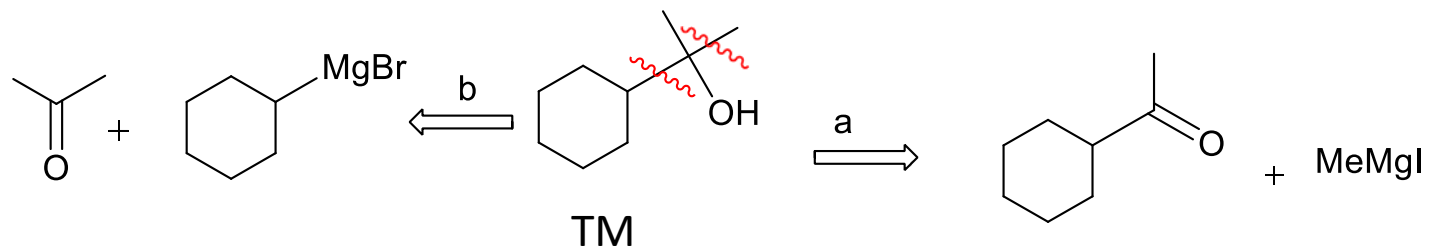
Synthesis



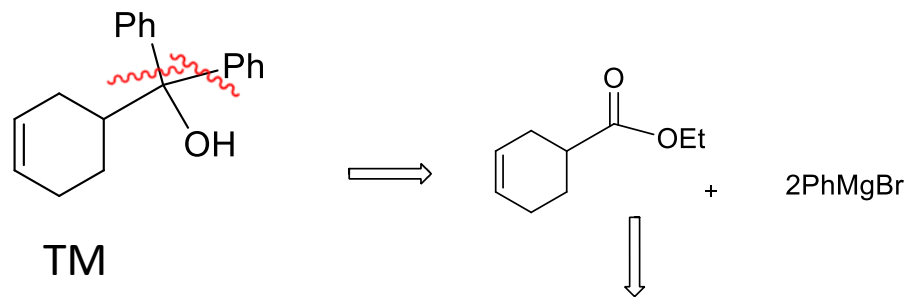
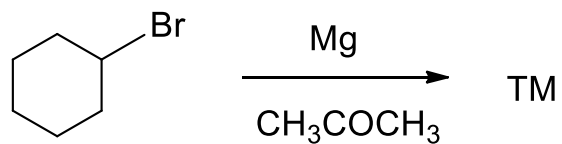
Synthesis



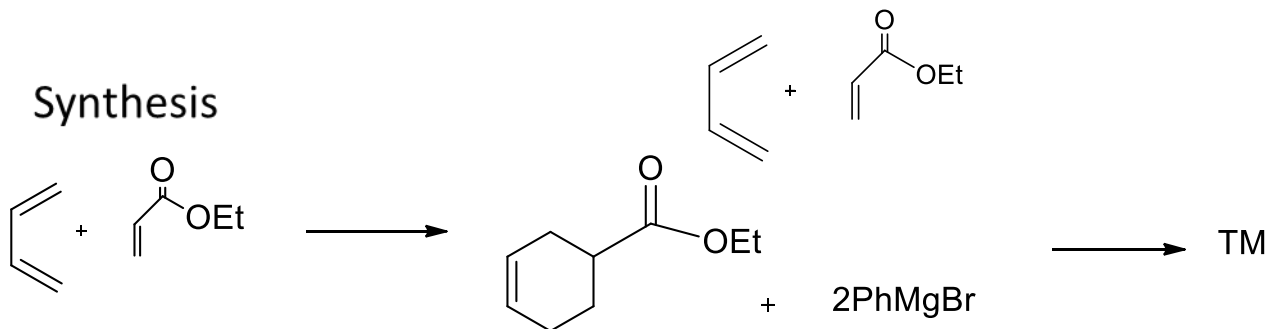




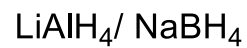
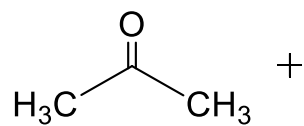
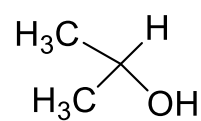
### Synthesis



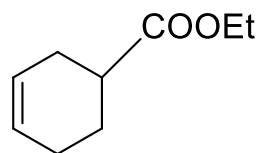
### Synthesis



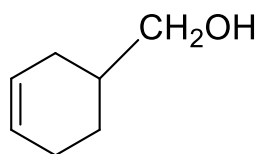




TM

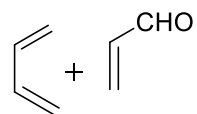
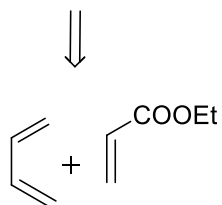
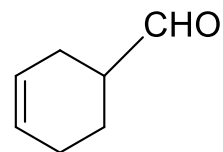


FGI

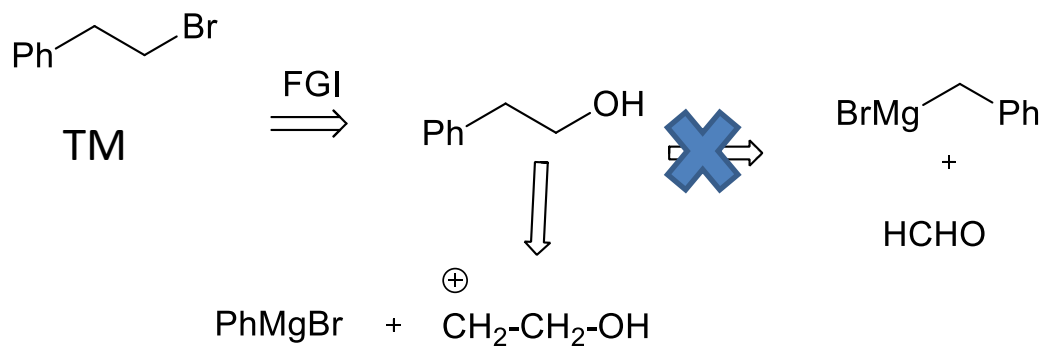
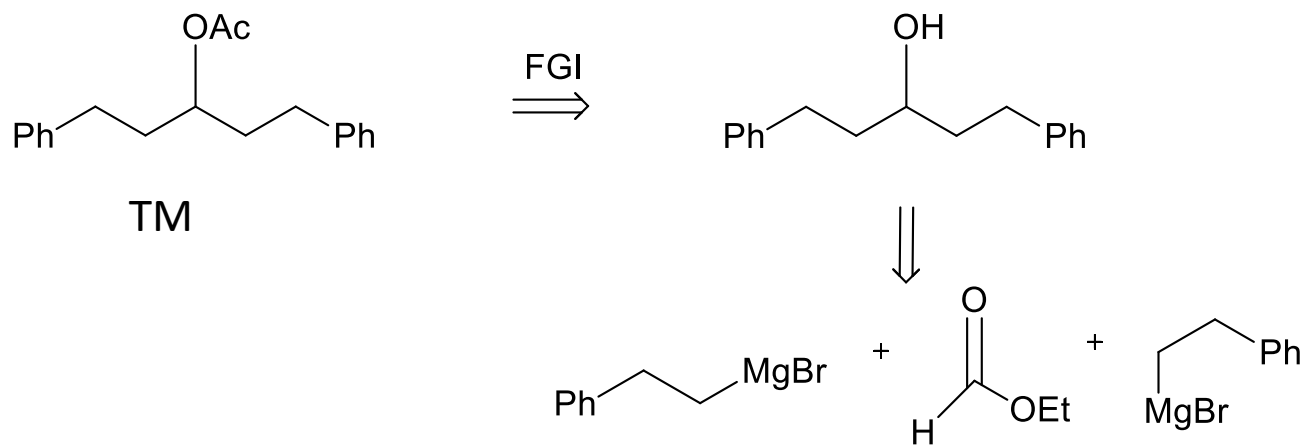


TM

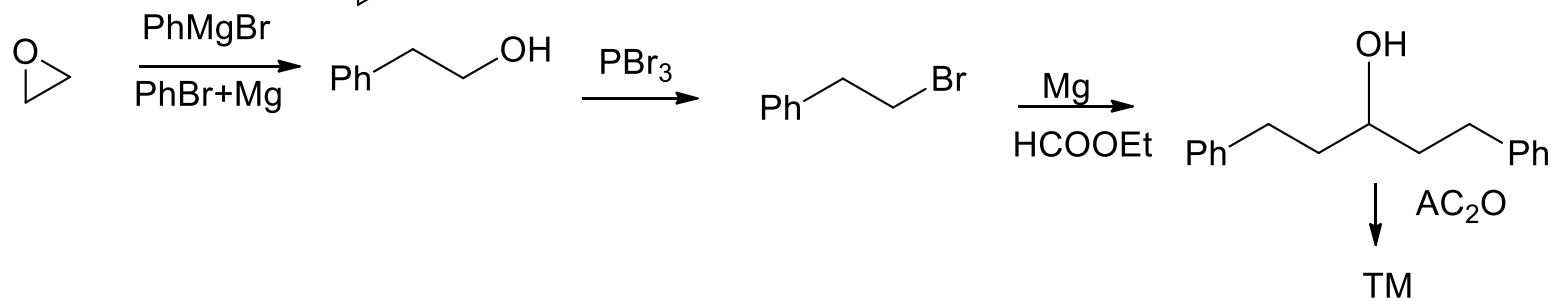
FGI



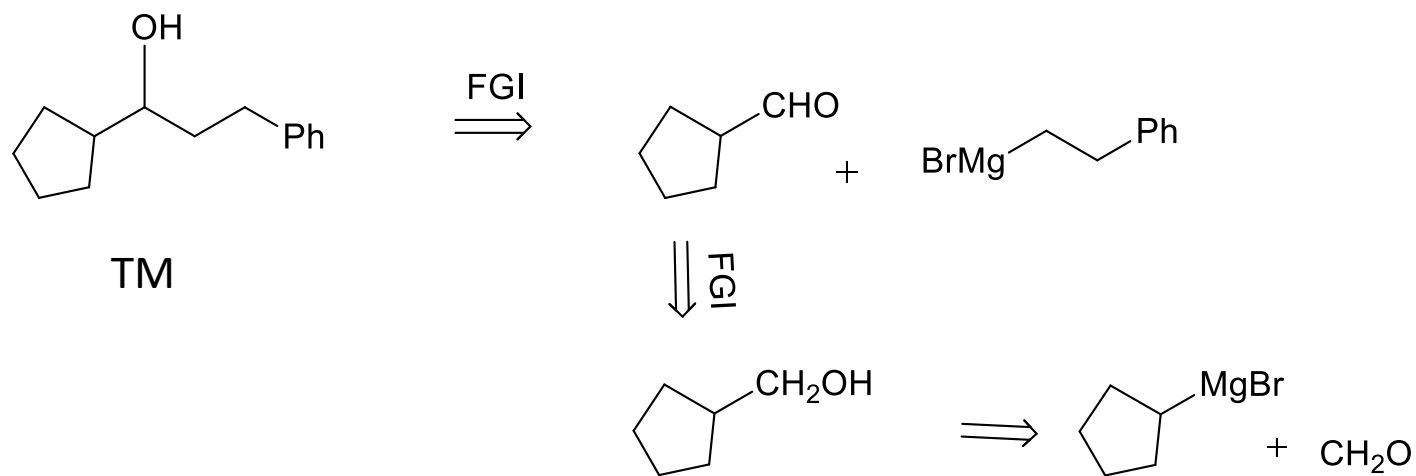




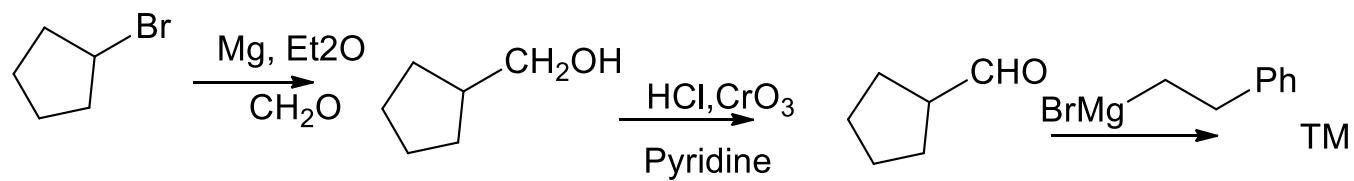
Synthesis



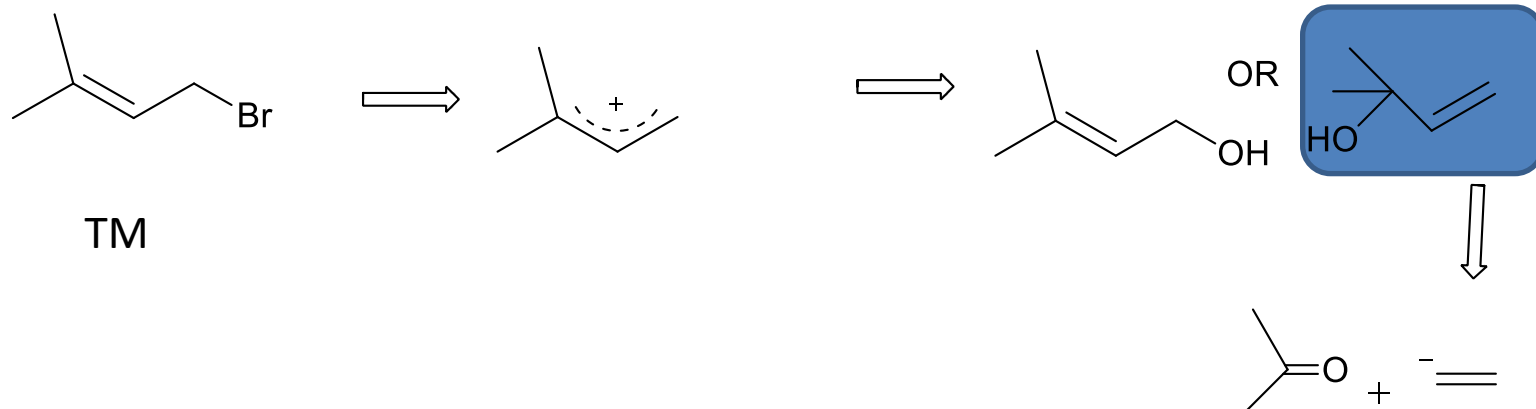




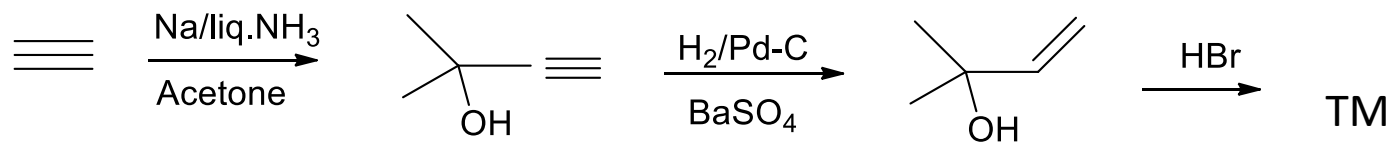
## Synthesis



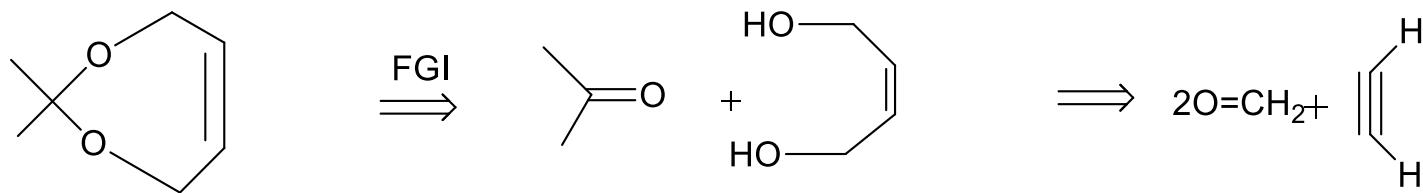




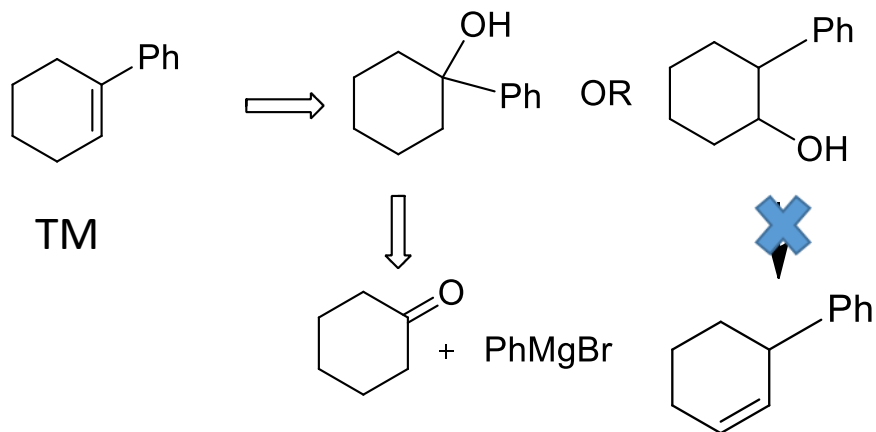
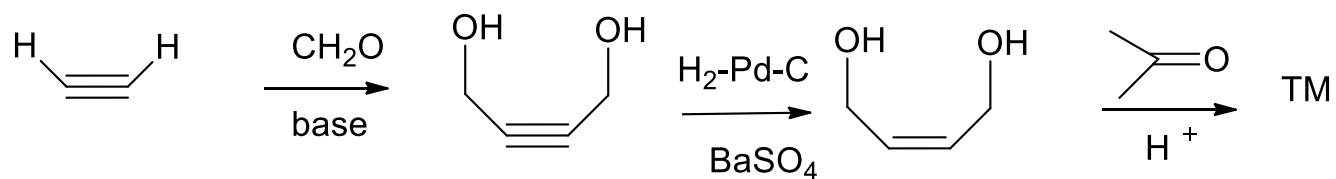
Synthesis





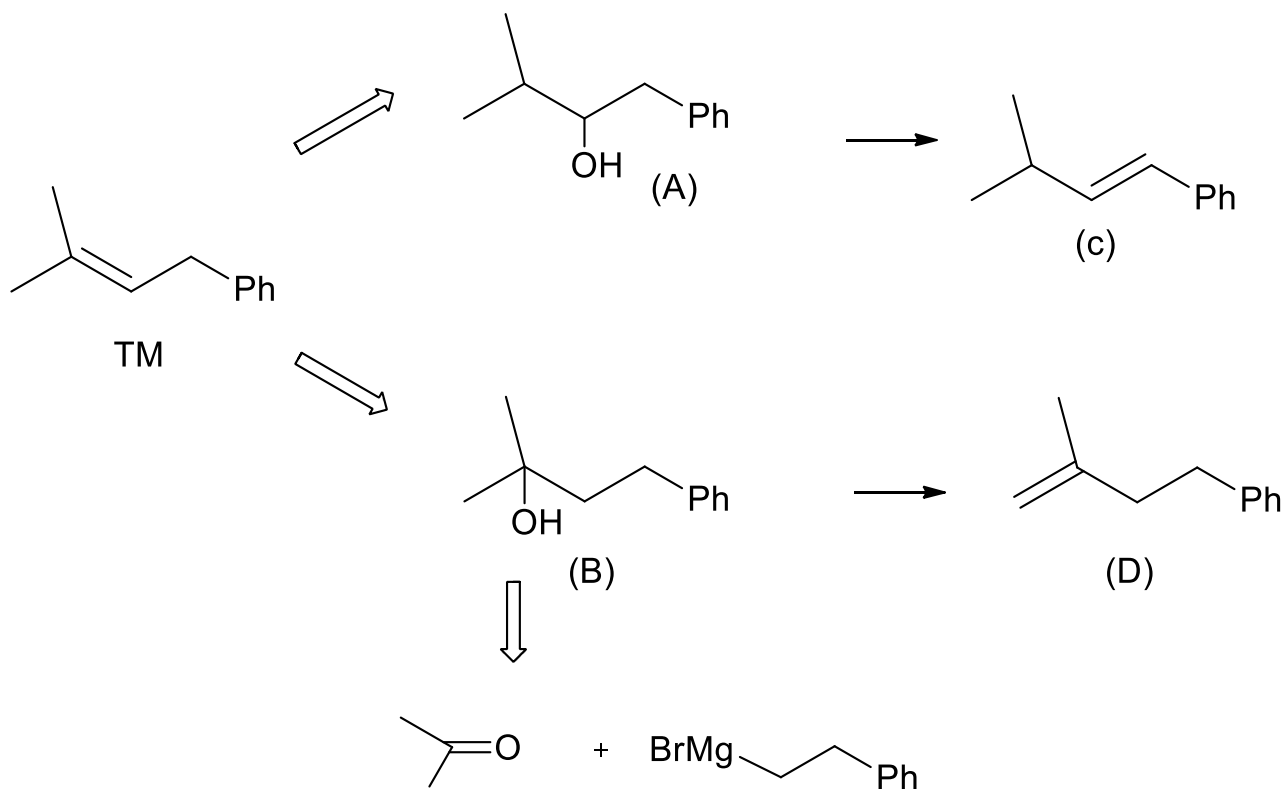


TM

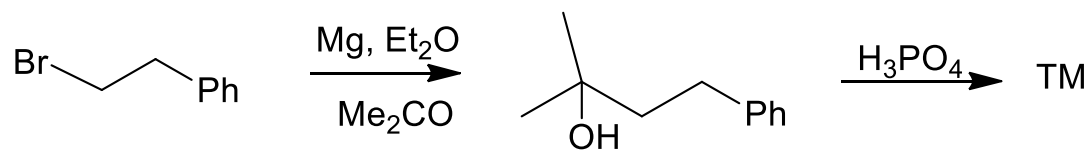


TM

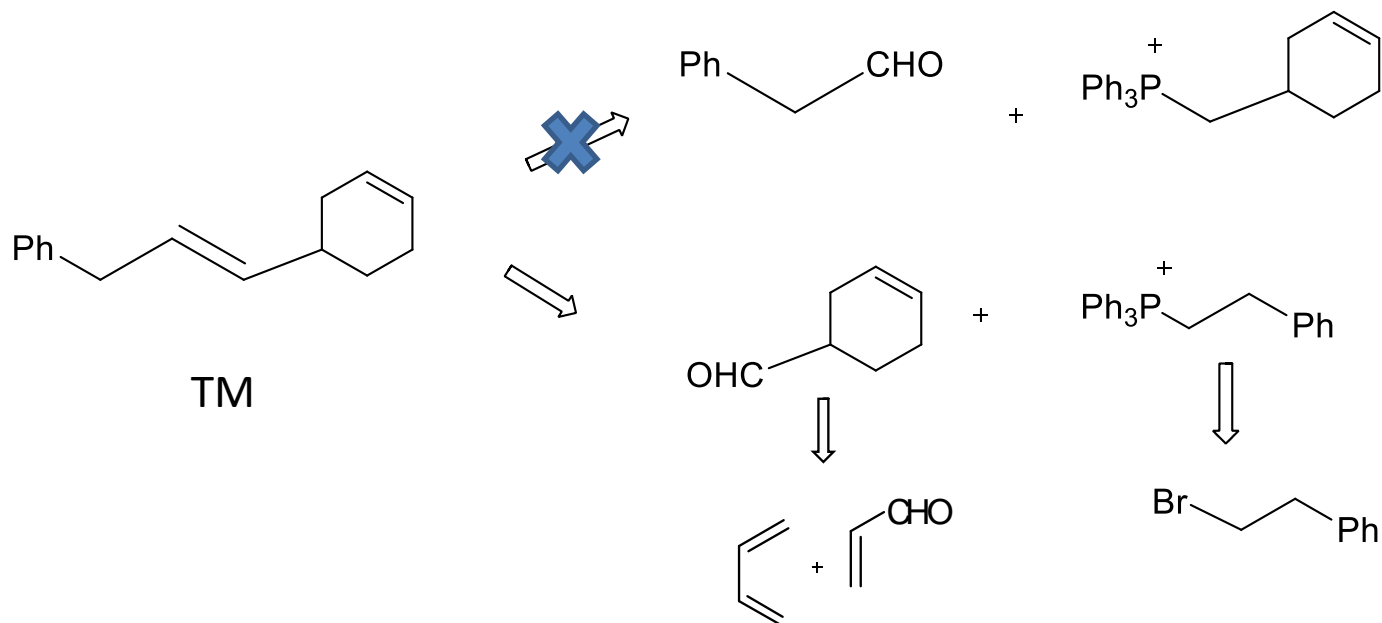
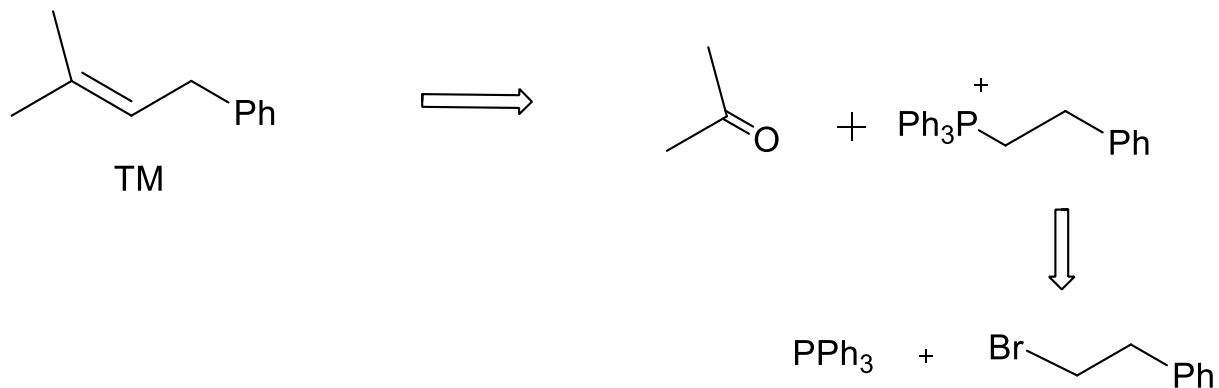




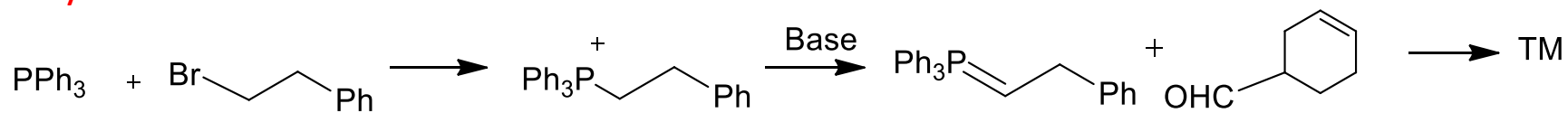
## Synthesis



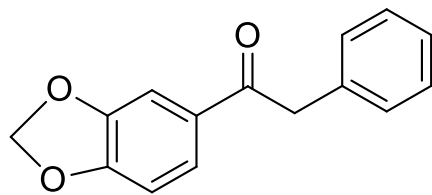




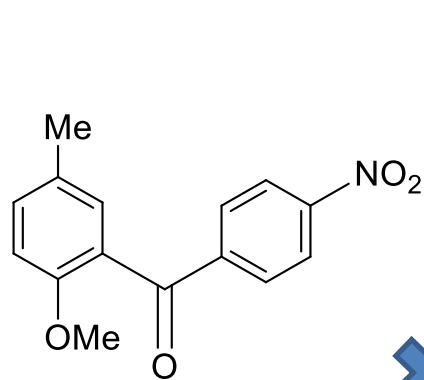
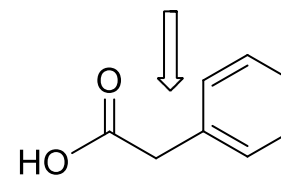
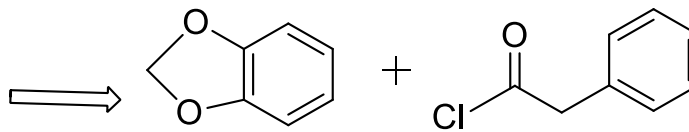
## Synthesis



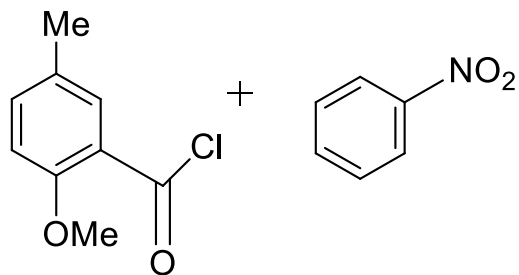
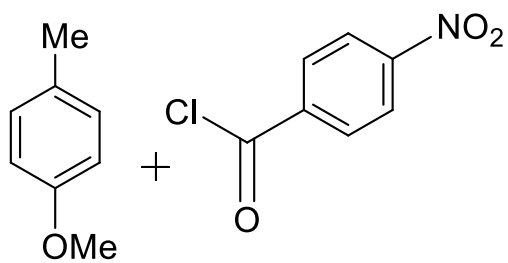
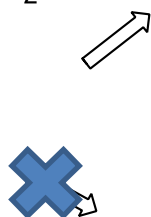




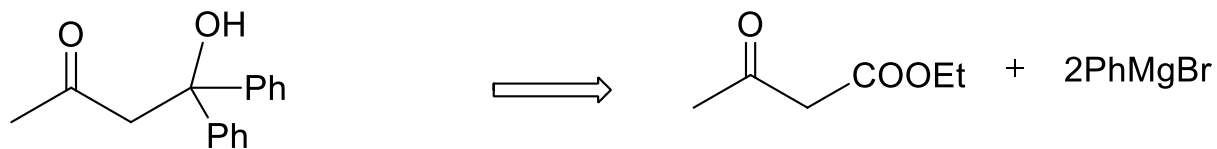
TM



TM

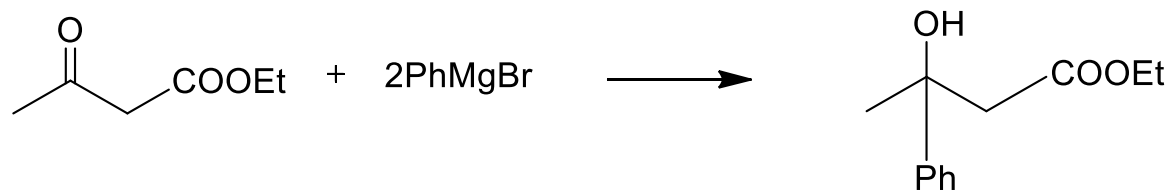




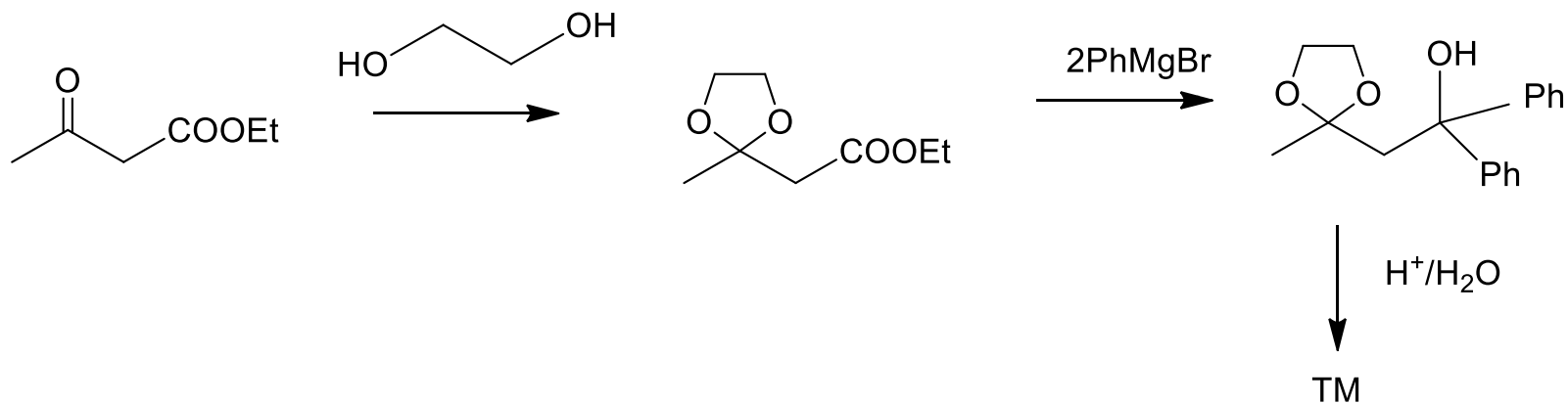


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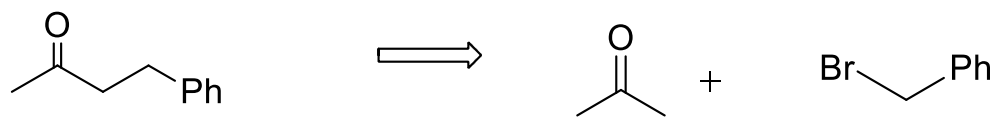
Synthesis



Synthesis

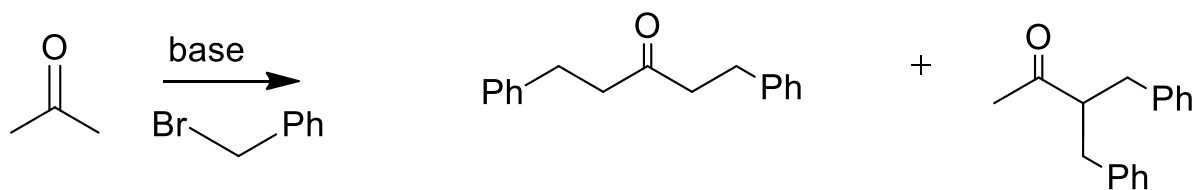




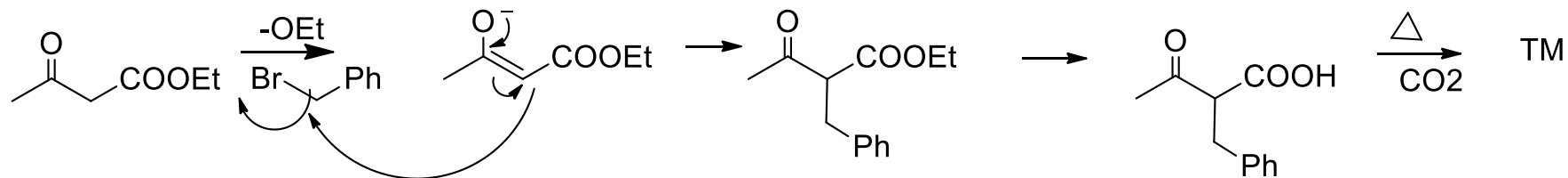


TM

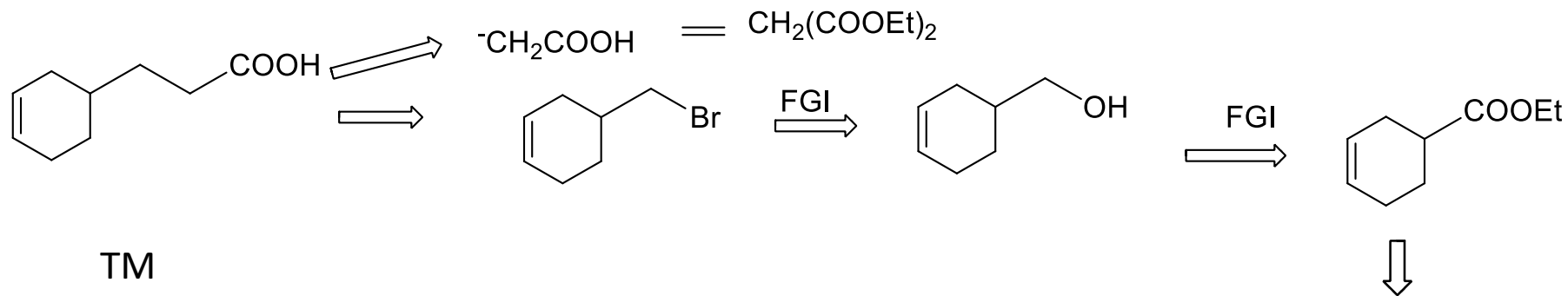
## Synthesis



## Synthesis

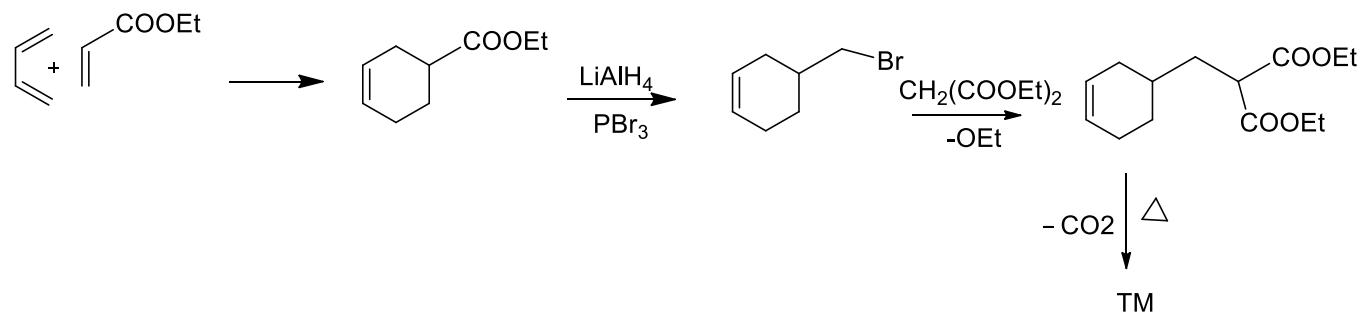




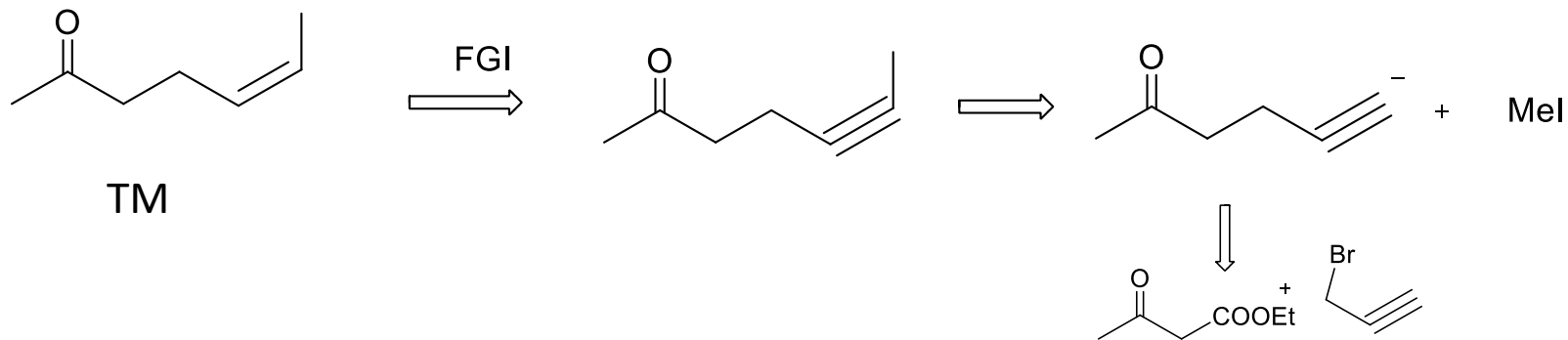


TM

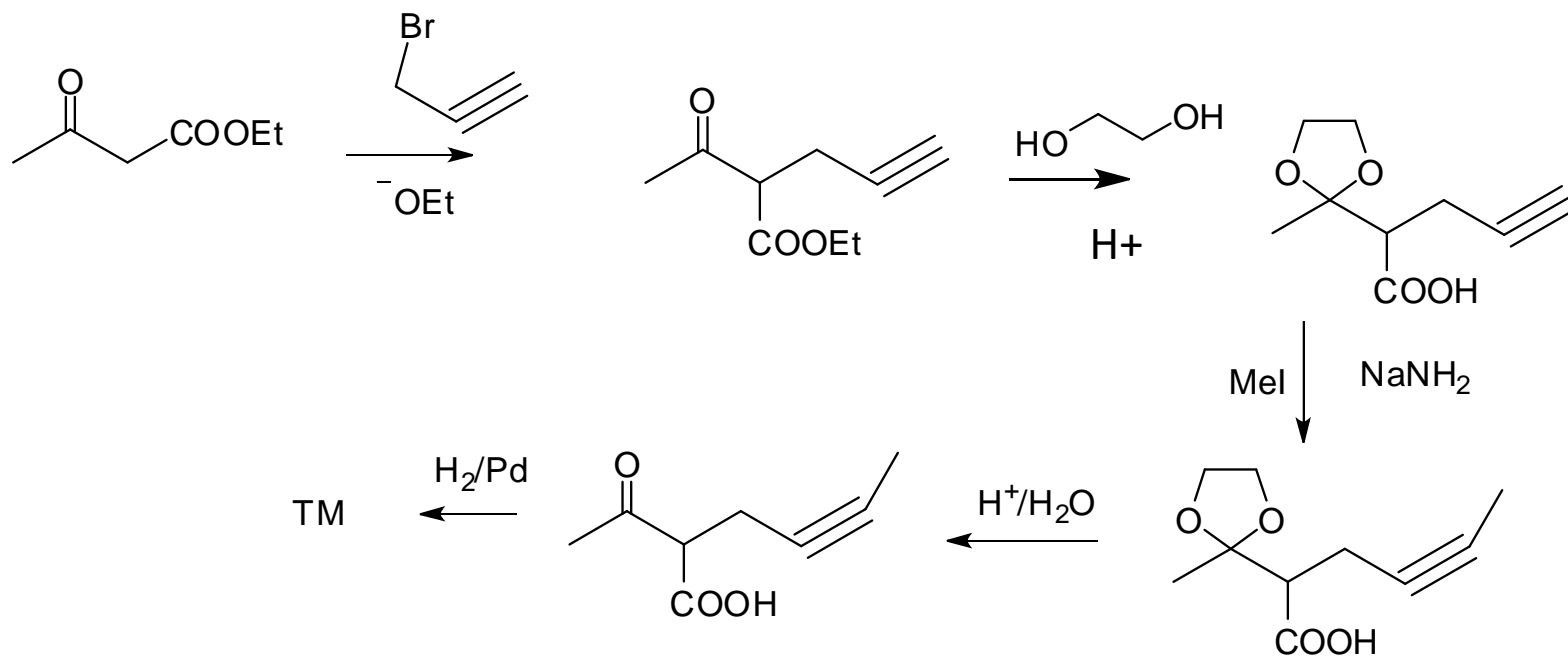
Synthesis



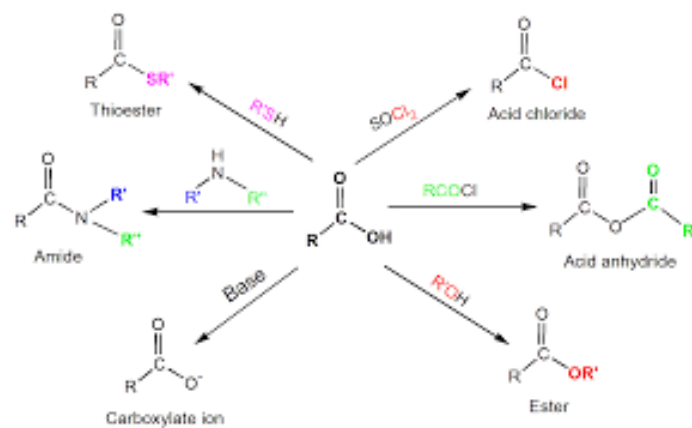
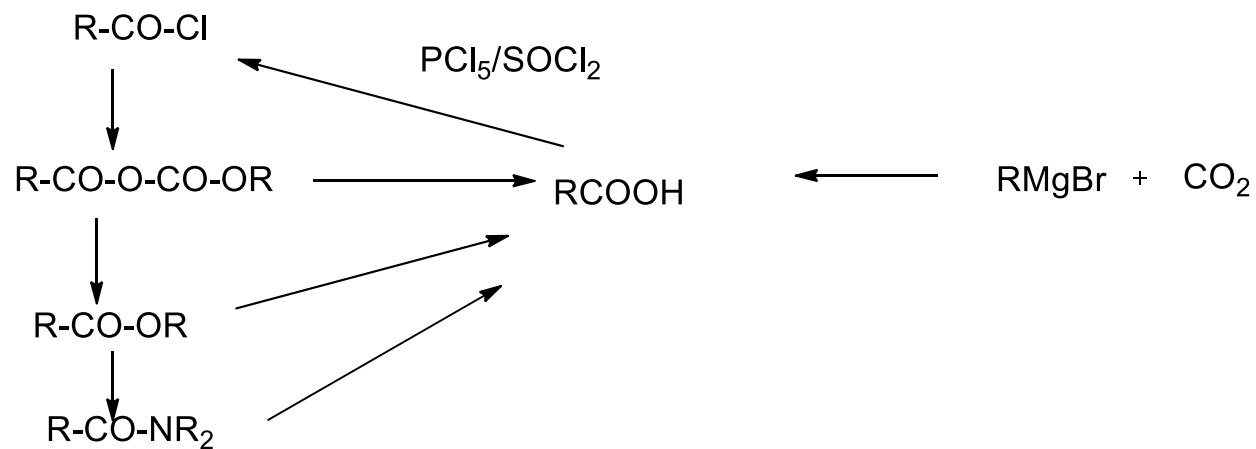




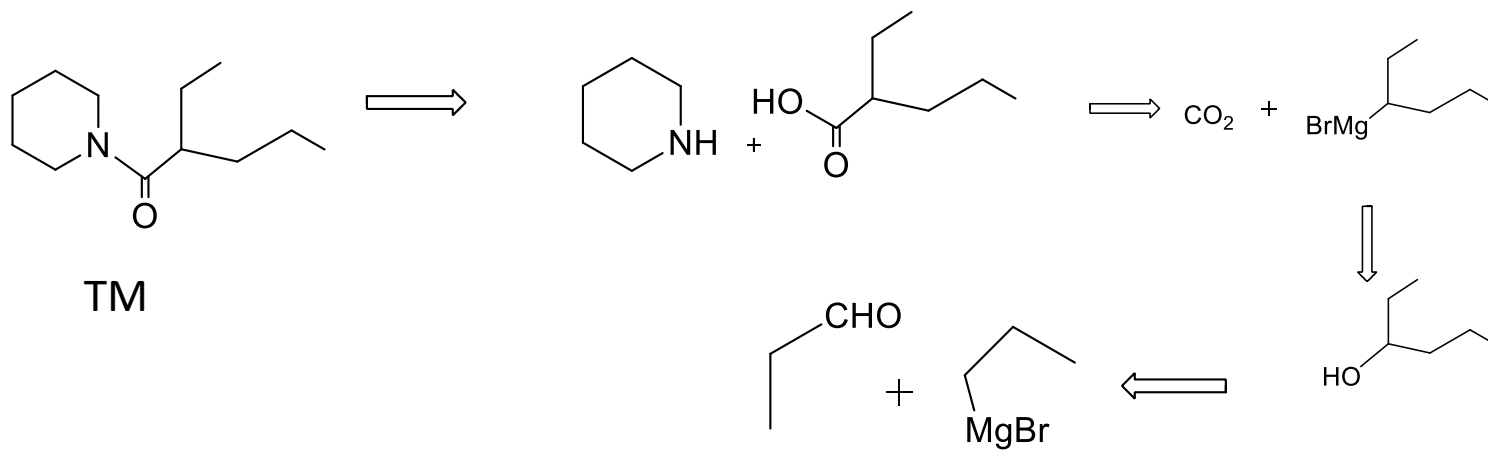
## Synthesis



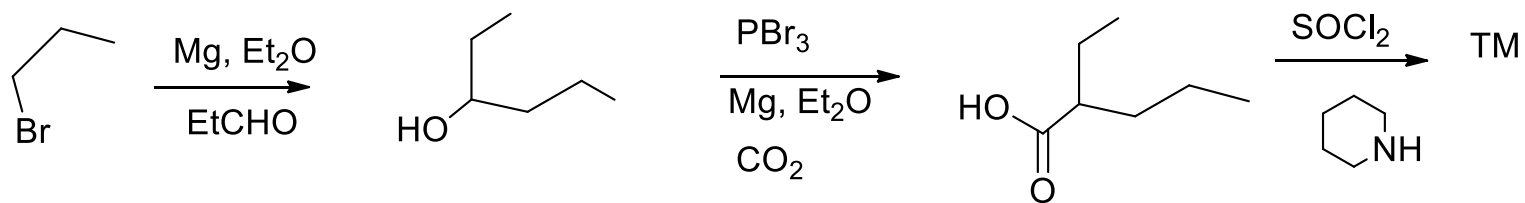




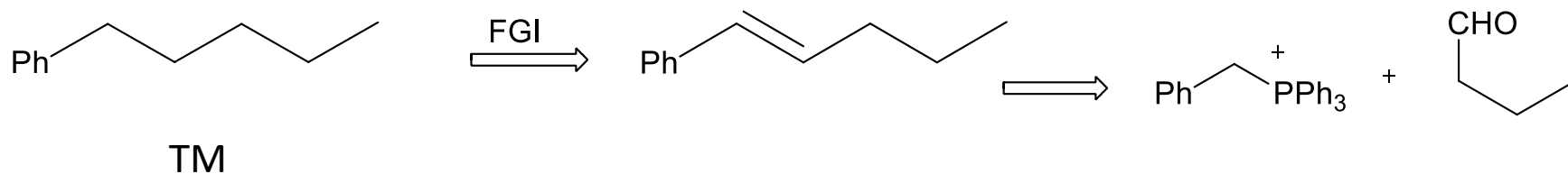
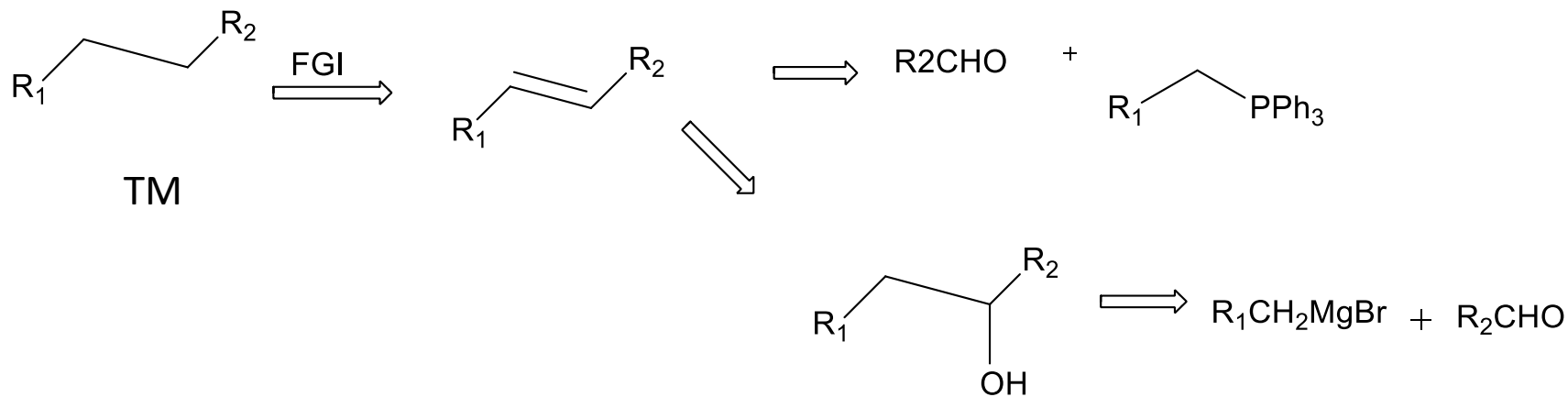




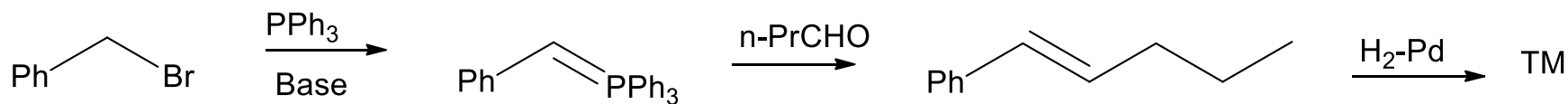
## Synthesis





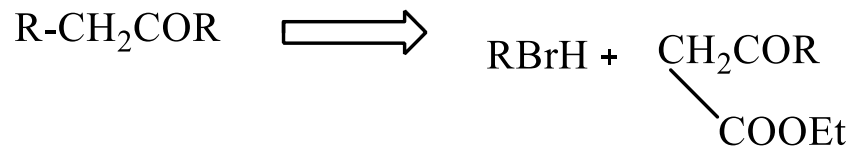
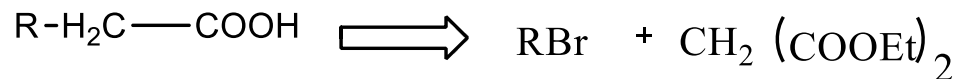
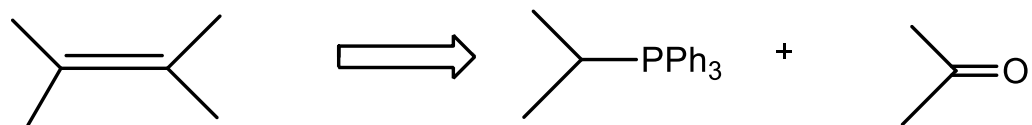
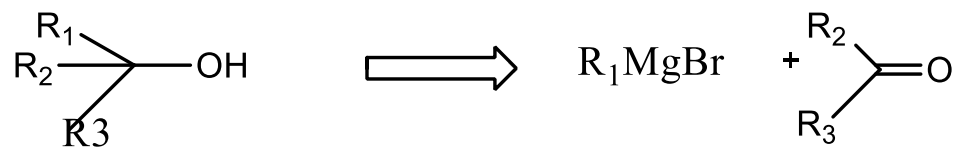


## Synthesis

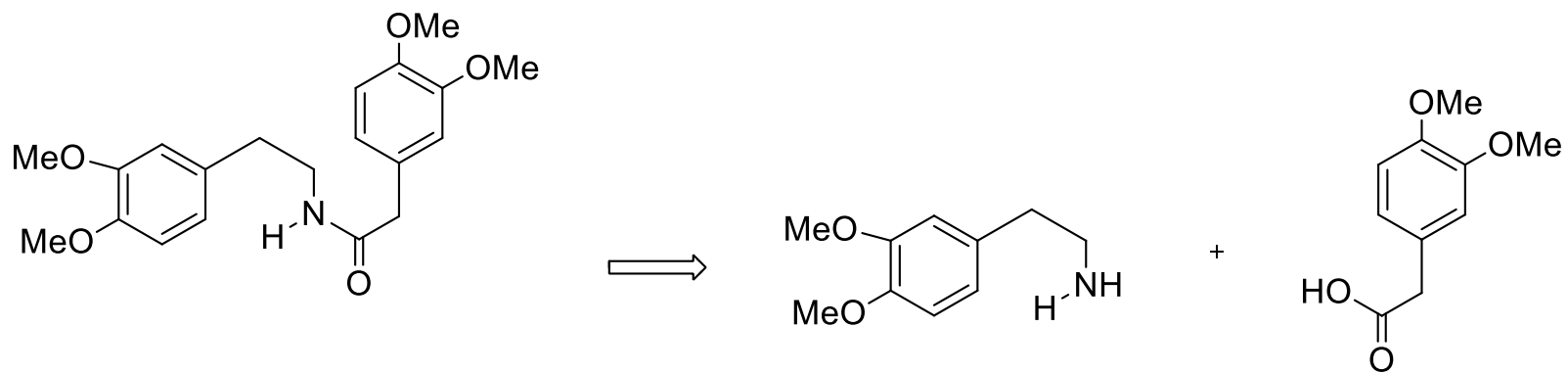




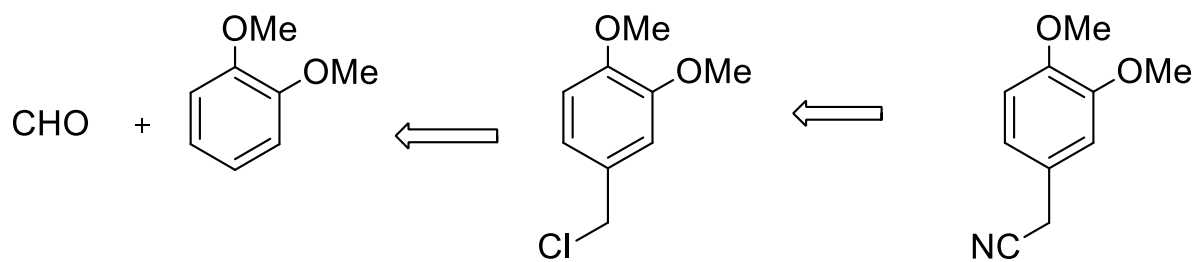
## SUMMARY







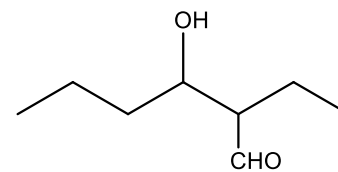
TM



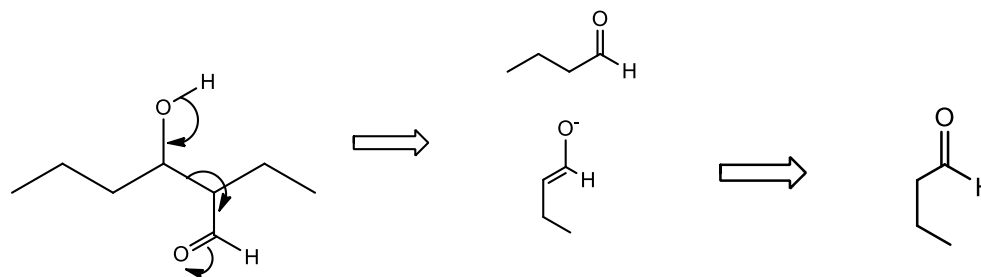


## Two group disconnection

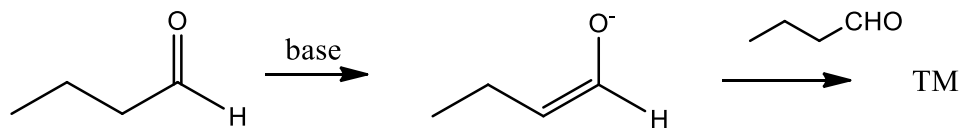
$\beta$ -Hydroxy carbonyl compound



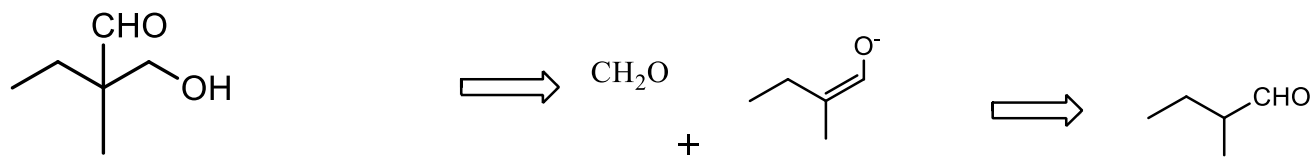
TM



## Synthesis

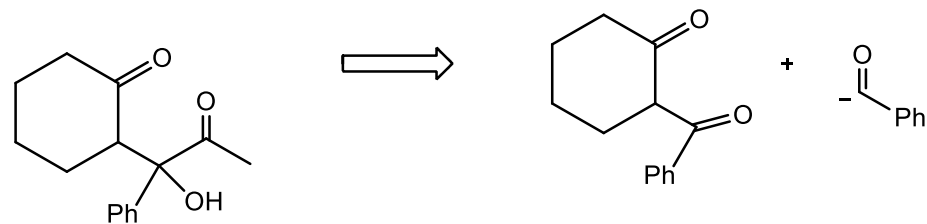
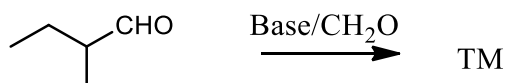




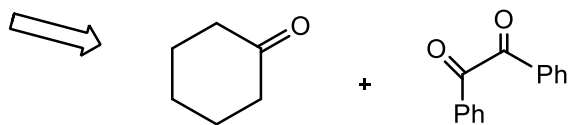


TM

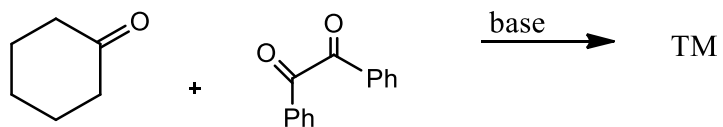
Synthesis



TM

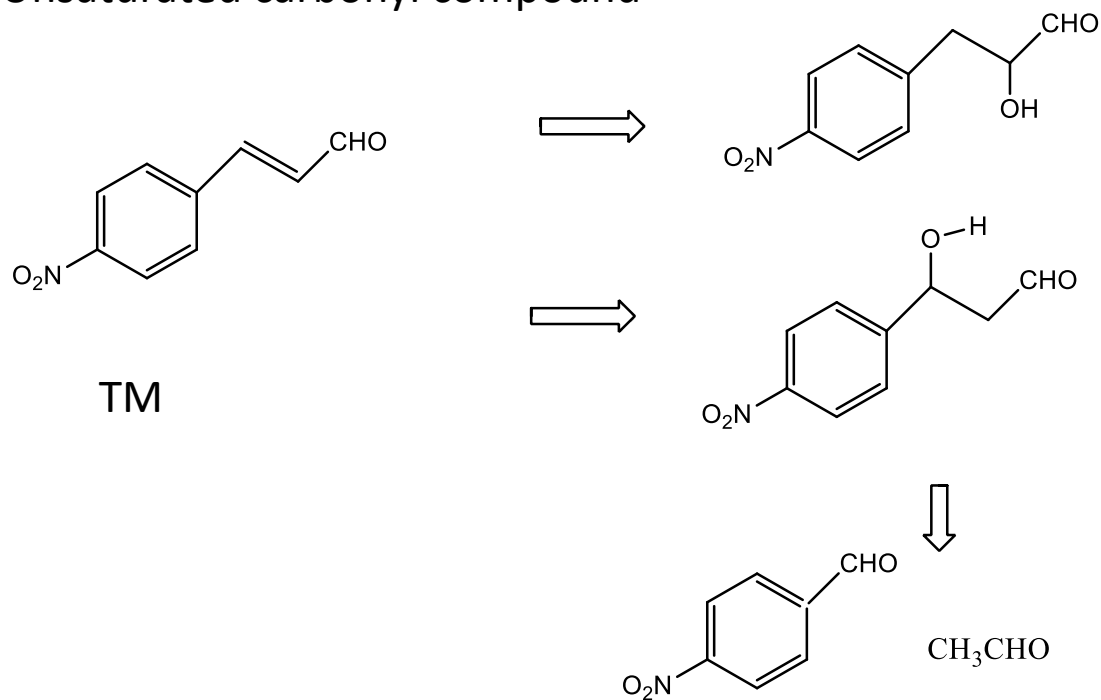


Synthesis

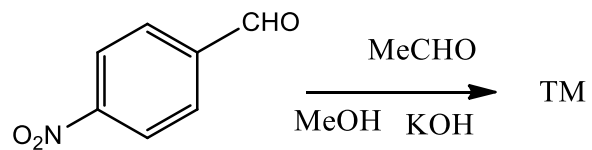




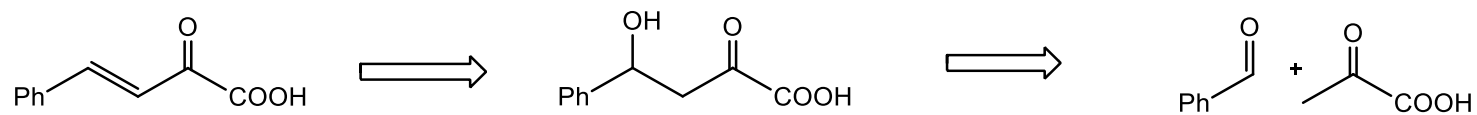
## $\alpha$ , $\beta$ -Unsaturated carbonyl compound



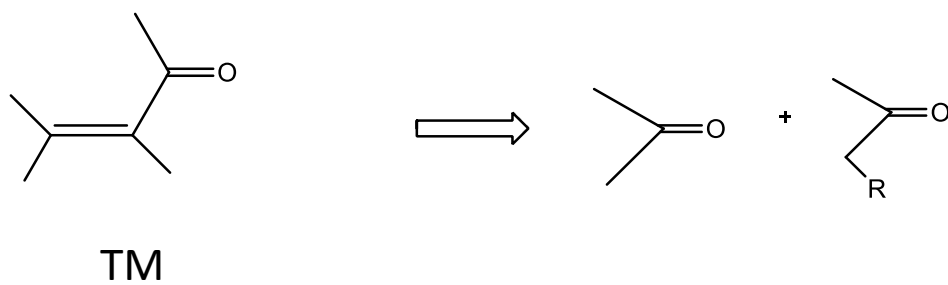
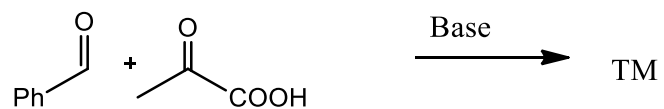
## Synthesis



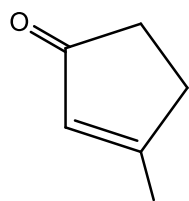




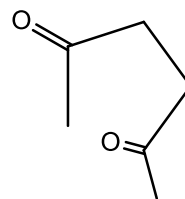
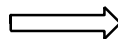
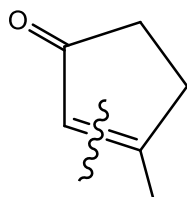
## Synthesis



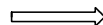
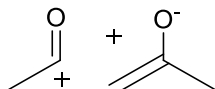
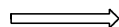
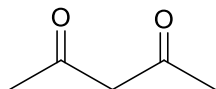




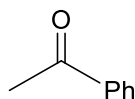
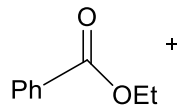
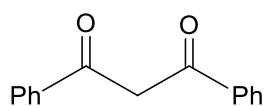
TM



1,3 –Dicarbonyl compounds

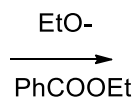
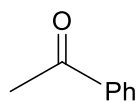


TM



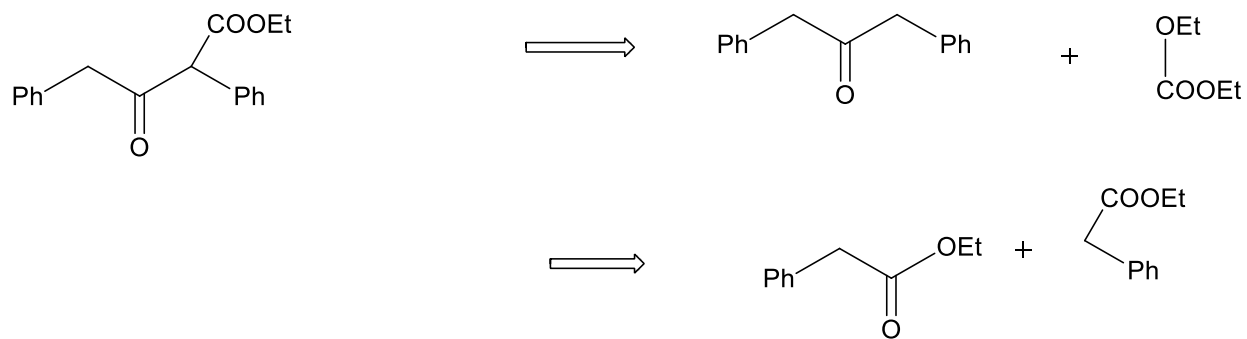
TM

Synthesis

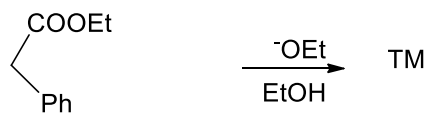


TM

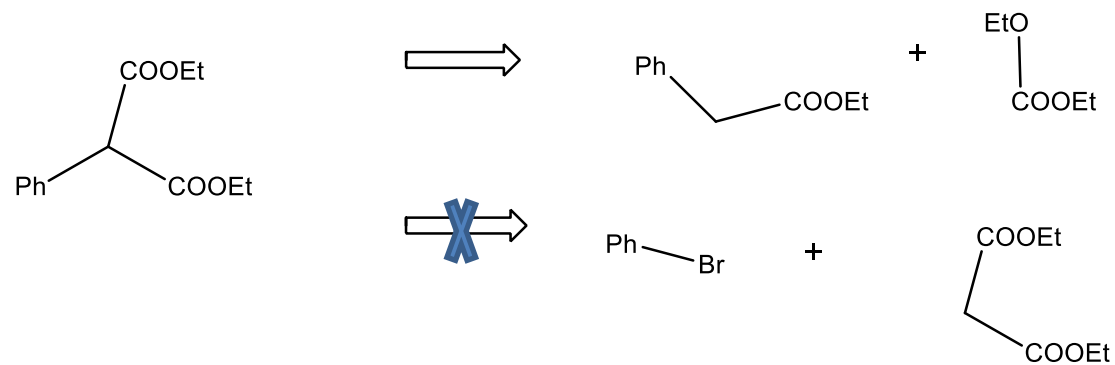




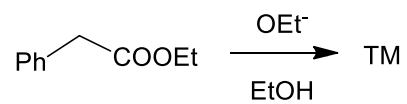
synthesis



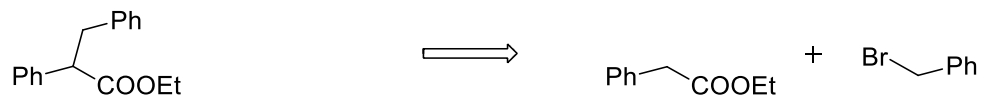




## Synthesis

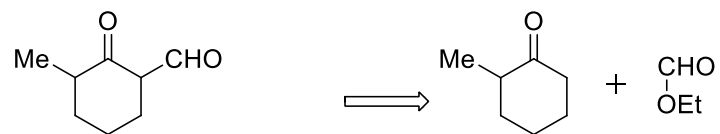






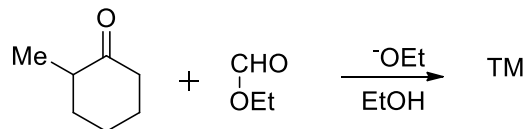
TM

## Synthesis

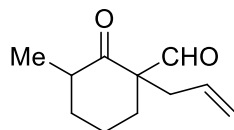


TM

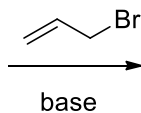
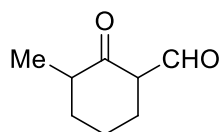
## Synthesis



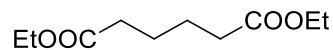
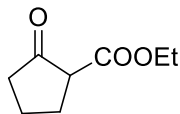




Synthesis TM

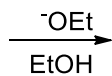
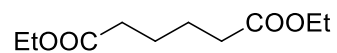


TM



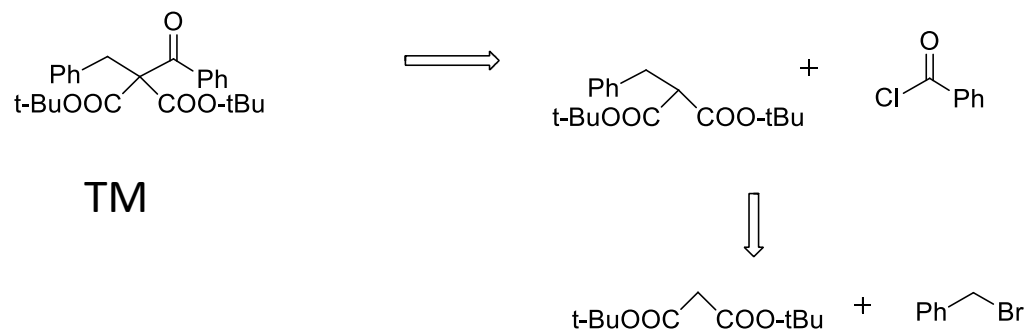
TM

Synthesis

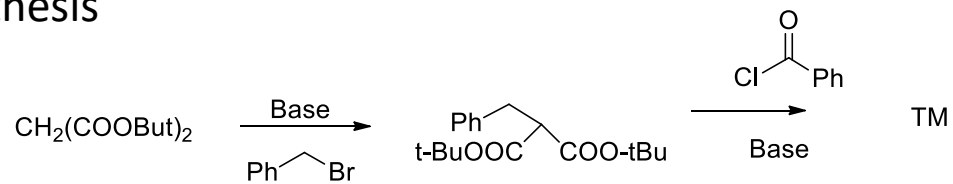


TM

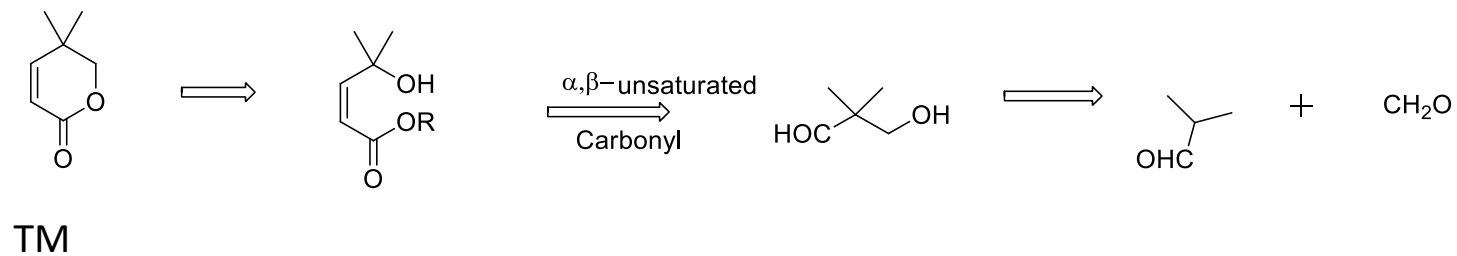




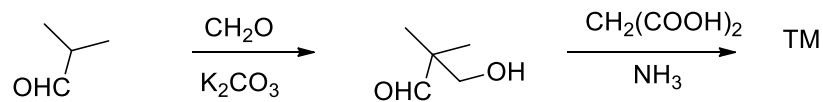
## Synthesis



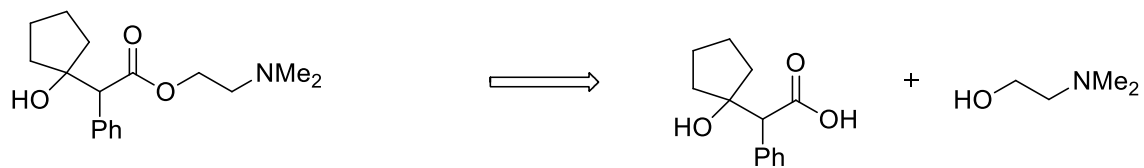




synthesis







TM

## Synthesis

