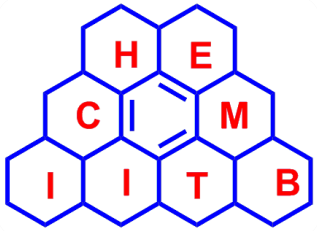
Designing Organic Synthesis



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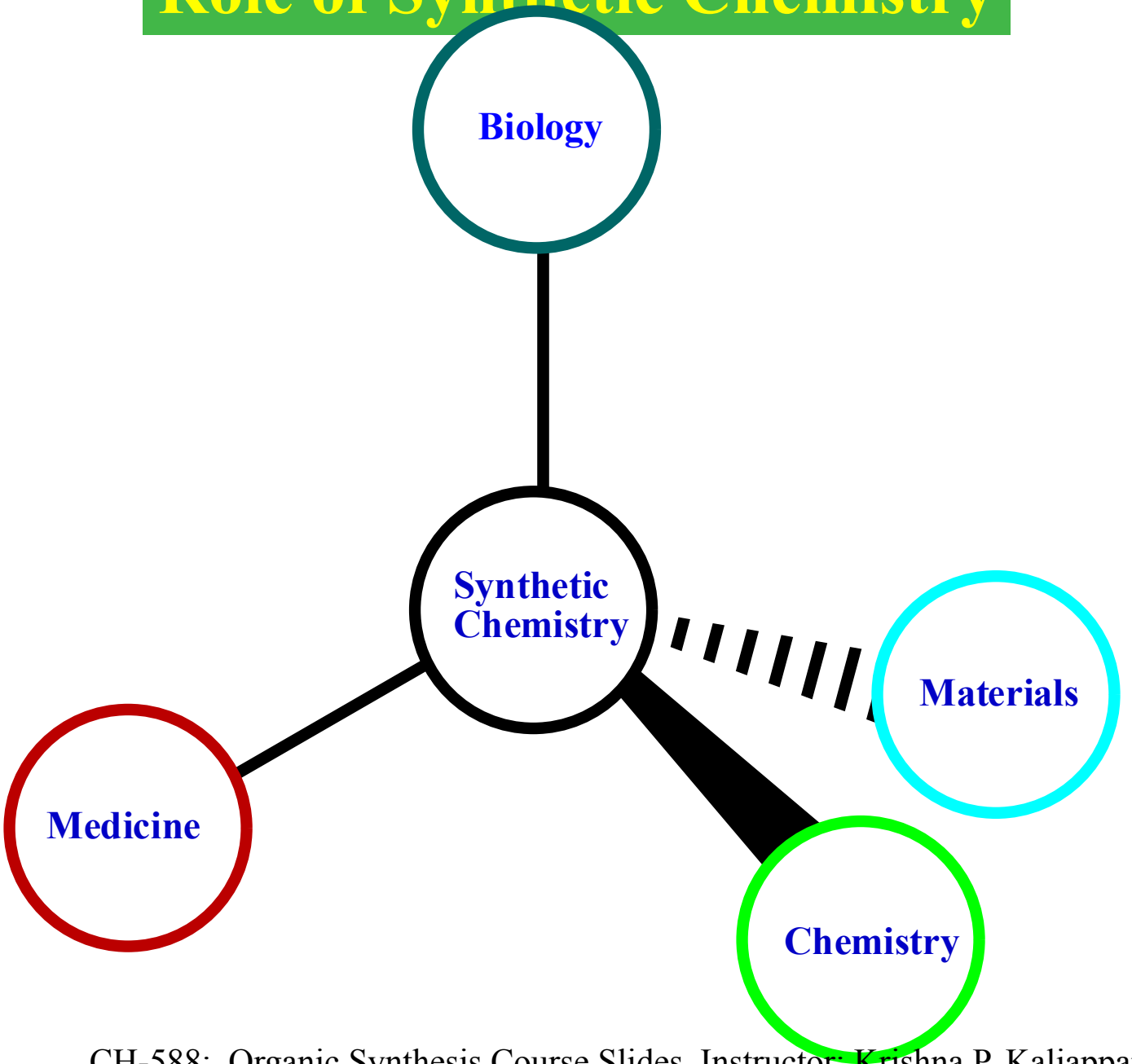
Role of Synthetic Chemistry



Synthesis: An Ever Challenging and Exciting Science

- Introduction
- Technical terms
- Why to do synthesis?
- History of synthesis
- Designing synthetic strategy
- Retrosynthetic analysis
- Practice of total synthesis (analysis and synthesis)
- Linear and convergent synthesis
- Examples

Technical Terms

- **Organic Synthesis-**means the same as synthetic organic chemistry
- **Total Synthesis:** The chemical synthesis of a molecule from a relatively simpler starting materials
- **Semisynthesis:** the synthesis of a given molecule from an advanced precursor related to it
- **Formal Synthesis:** the synthesis of a key intermediate that has been already converted into the target molecule
- **Partial Synthesis:** the synthesis of a portion of the naturral product

Basic Requirements

Knowledge

Creativity

Artistic Taste

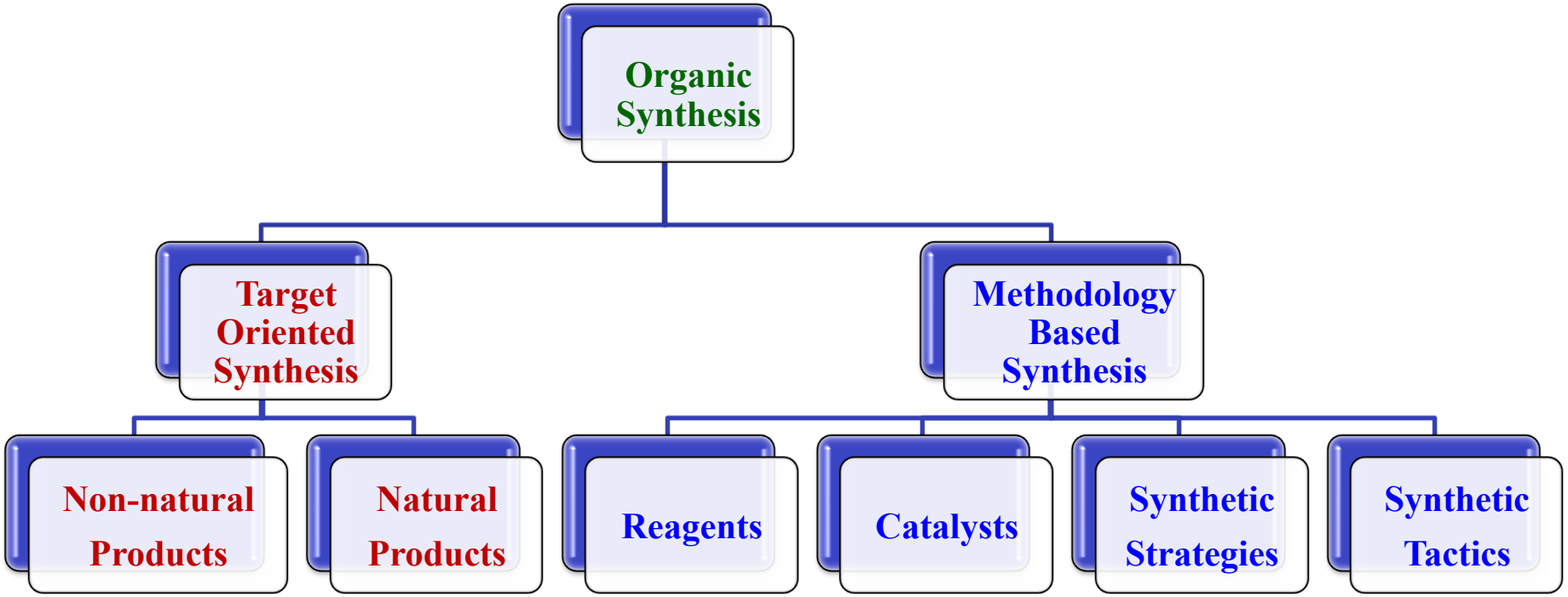
Persistence

Stamina

Experimental Skill

Courage and Character

Organic Synthesis

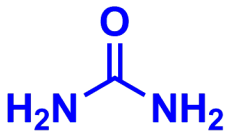


Need for Synthesis

- Food for creativity
- Scientific excitement and satisfaction
- Dual nature as science and art
- In early days, it was used to confirm the structure
- Testing new reagents and catalysts
- Discovery of new chemistry
- Applications in medicine, biology and materials science
- Structural activity relationship
- Application in every day's life

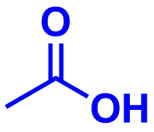
History

- The birth of total synthesis occurred in 19th century
- In 1828, the first synthesis reported was by Wohler on Urea
- In 1845, Kolbe coined the word synthesis
- The most spectacular synthesis of 19th century was Glucose
- Since then there are several outstanding synthesis



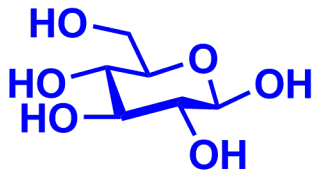
urea

Wohler, 1828



acetic acid

Kolbe, 1845



glucose

Fischer,1890

History

- Simple targets were considered in early days
- Theses simple targets were synthesized by often starting with compounds which are closely related to products
- These became impractical when the targets became more complex
- To tackle this, higher level of intellectual planning and skill are required
- Better understanding of reaction mechanisms
- A working knowledge of reliable reactions
- Proper understanding of stereochemistry and conformational analysis
- Use of new spectroscopic methods
- Introduction of new technique "Retrosynthetic Analysis" helped a lot in achieving the synthesis of complex target molecules

Retrosynthetic Analysis

- Reverse of Synthesis-The process of breaking down the TM into available starting materials by FGI and disconnection

- Disconnection is reverse operation to a reaction: An imaginary cleavage of a bond to break the molecule into starting materials

- TM-Target molecule to be synthesized

- FGI-Functional Group Interconversion

- Synthon-Fragments resulting from disconnection

- Synthetic Equivalent-Actual substrates used for the forward synthesis

Practice of Synthesis

It involves two stages

- Analysis
- Synthesis

Analysis

- Select the target molecule
- Identify the functional groups/strategic bonds in the molecule
- Disconnect bonds using known and reliable reaction
- Repeat disconnection as necessary to reach starting materials
- Don't compromise during the planning stage
- Try to use at least one novel disconnection
- Evaluate all pathways and choose the most attractive route

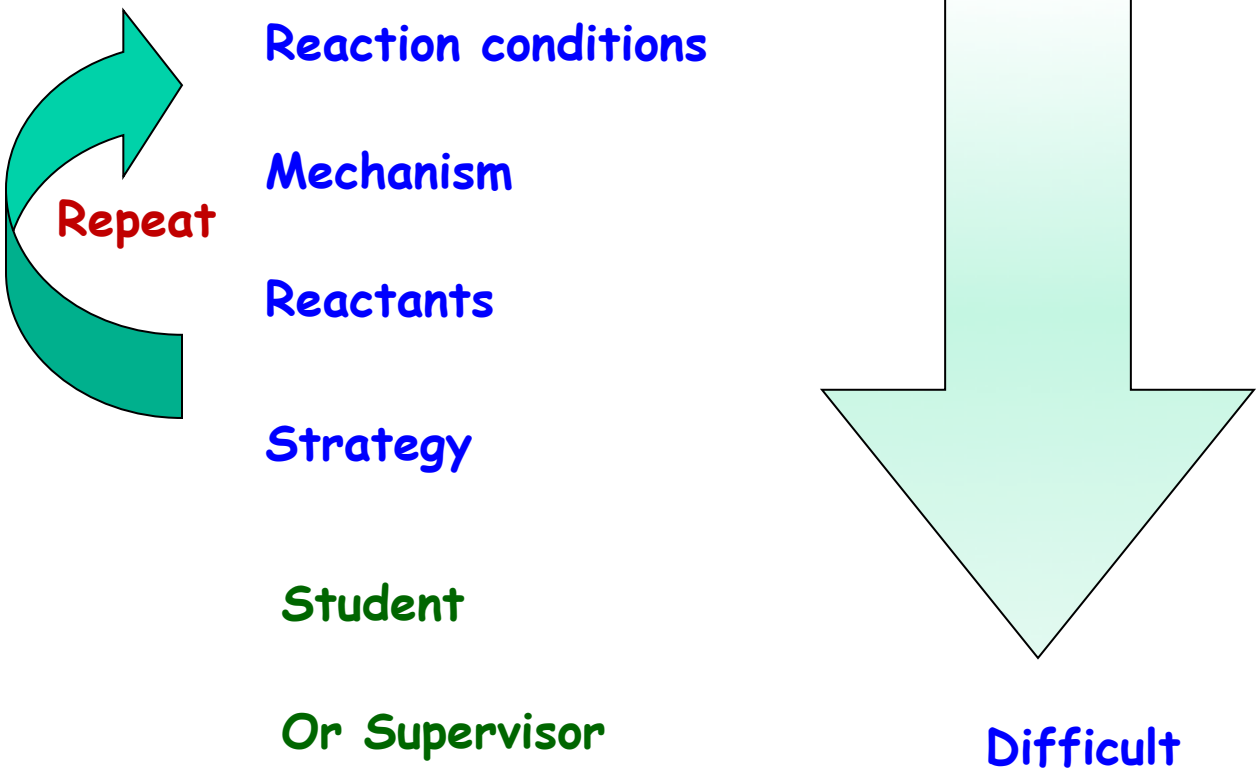
Advantages of Analysis

- This leads to
  - Readily available and inexpensive starting materials
  - Efficient synthetic reactions
  - Practical and convenient conditions
  - Flexibility of modification in case of pitfalls
  - Synthesis of analogues of natural products
  - Quick and elegant route

Design and Execution of Synthesis

- Write all the possible retrosynthetic pathways
- Evaluate all the pathways and go ahead with the most attractive one
- Write the real synthesis with reagents and conditions
- Collect all the relevant literature work
- Procure the required chemicals
- Execute the Synthesis
- Modify the plan according to unexpected failures

Trouble Shooting

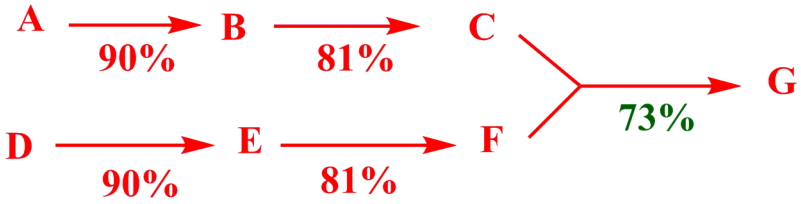


P. A. Wender, Stanford University

Linear and Convergent Synthesis

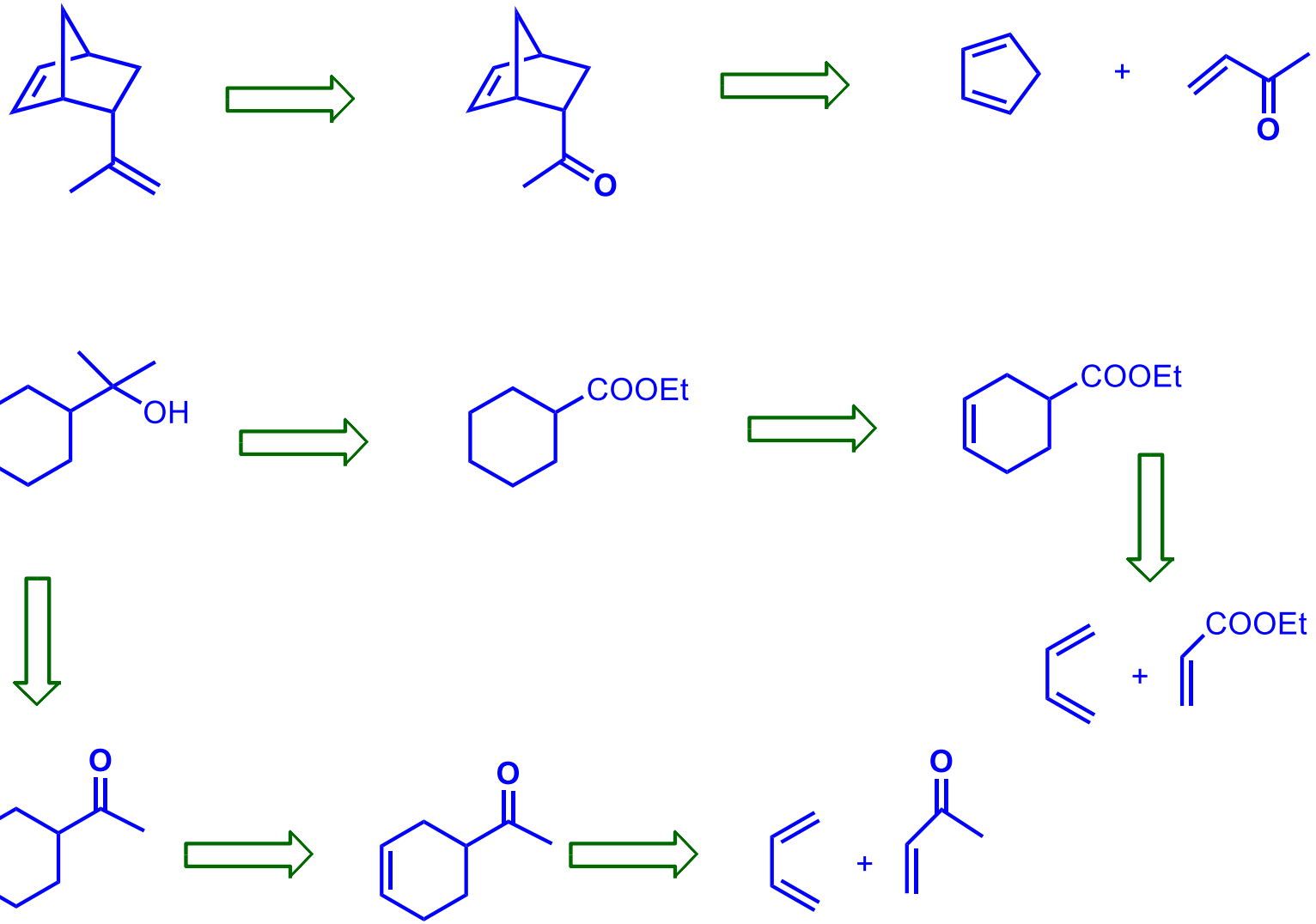
- **Linear synthesis:** Synthesis of target molecule in a linear fashion
- **Convergent synthesis:** Synthesize two or more fragments and couple them in a later stage to obtain the target molecule
- Consider a synthesis that involves 5 steps with a yield of 90% each, then

Yields of 90% at each stage in a 5-stage linear synthesis

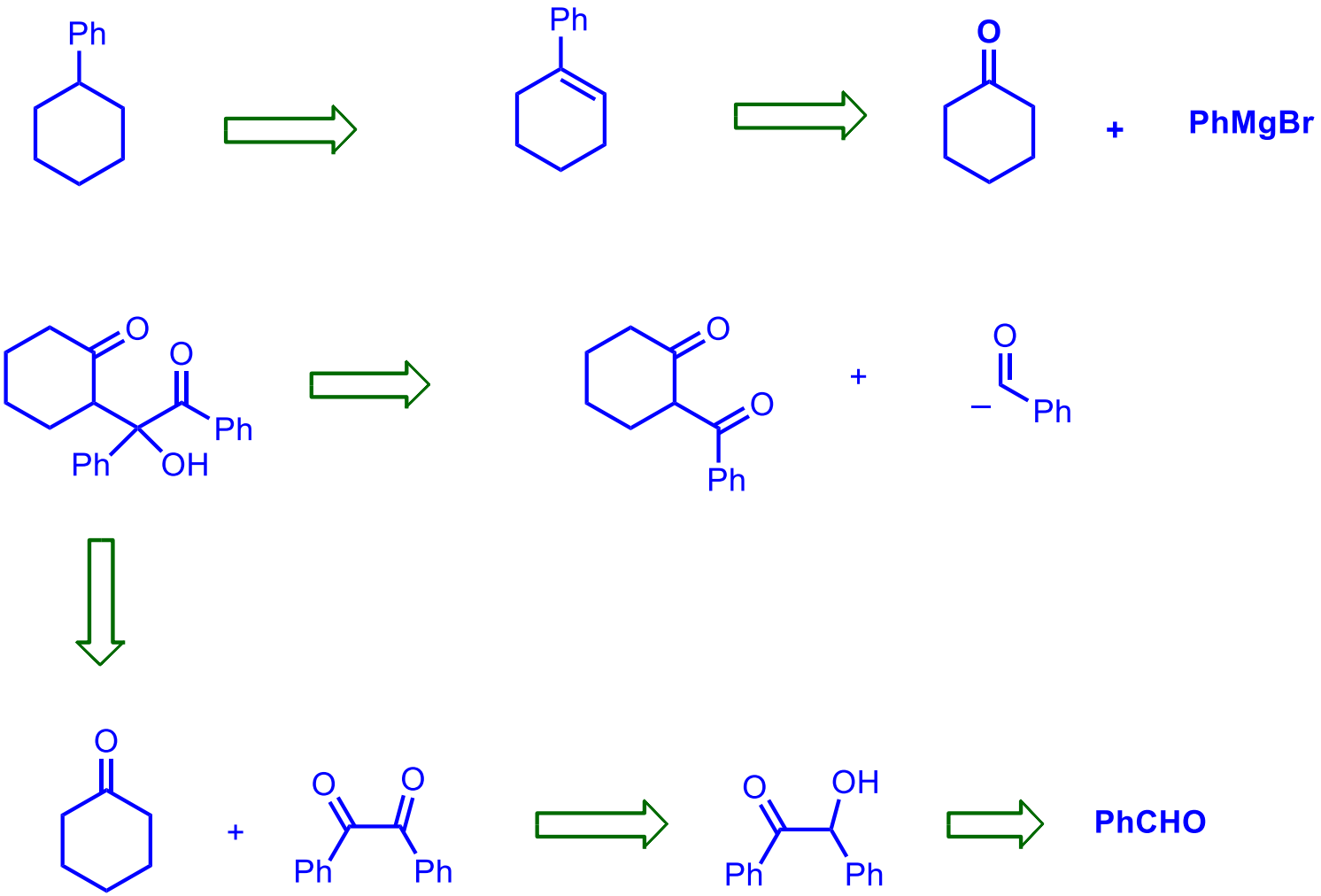


Yields of 90% at each stage in a 5-stage convergent synthesis

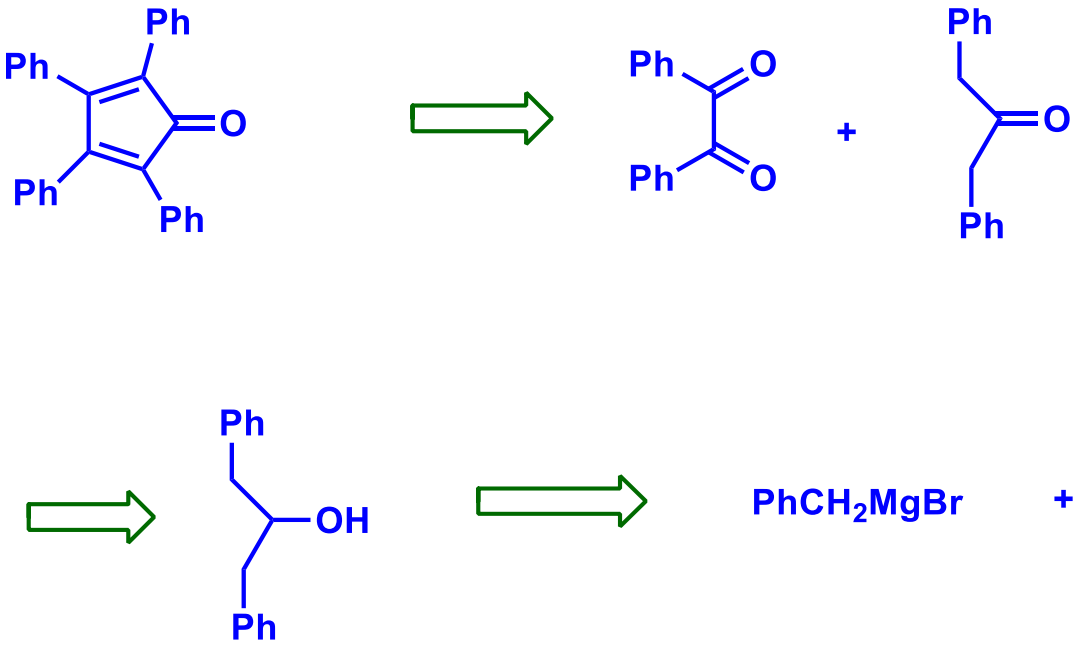
Examples



Examples

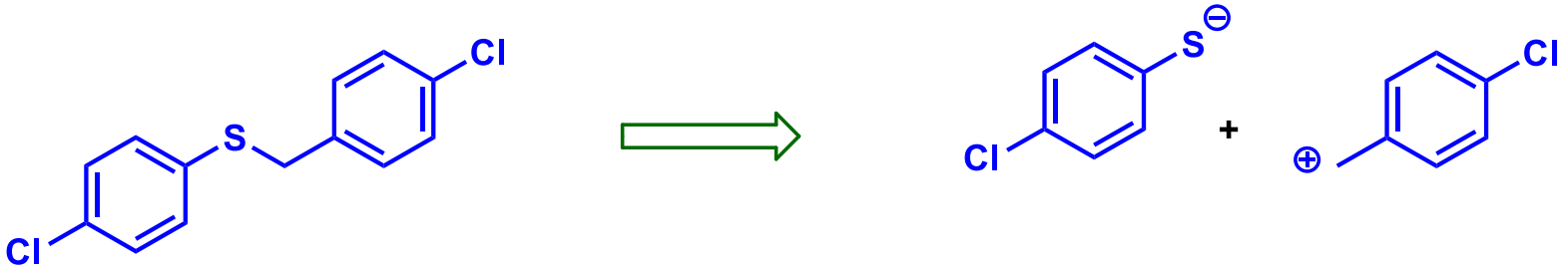


Examples

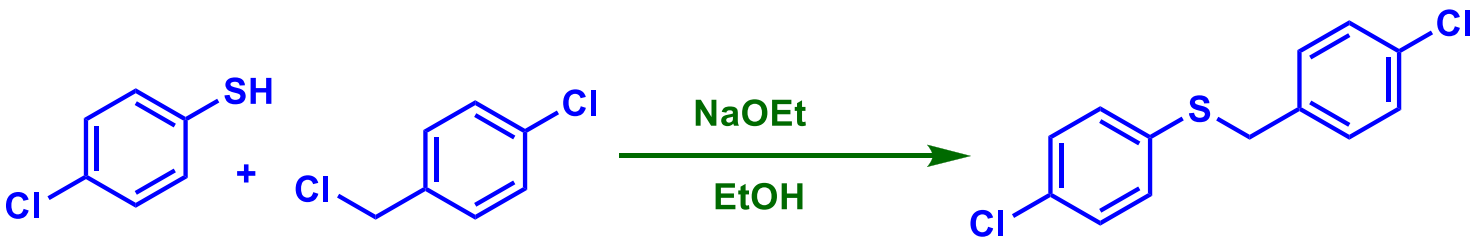


Synthesis of Chlorobenzide

Chlorobenzide-used to kill mites and ticks

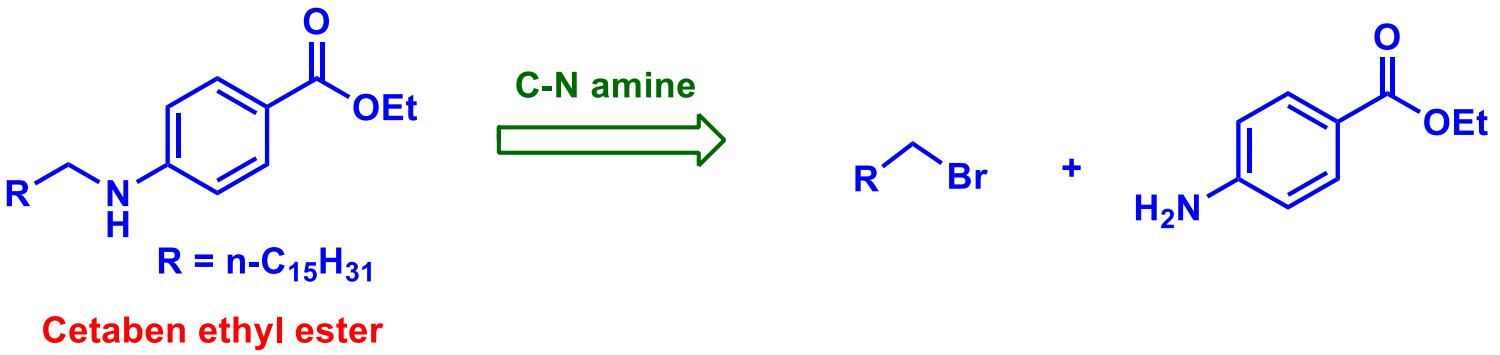


Chlorobenzide



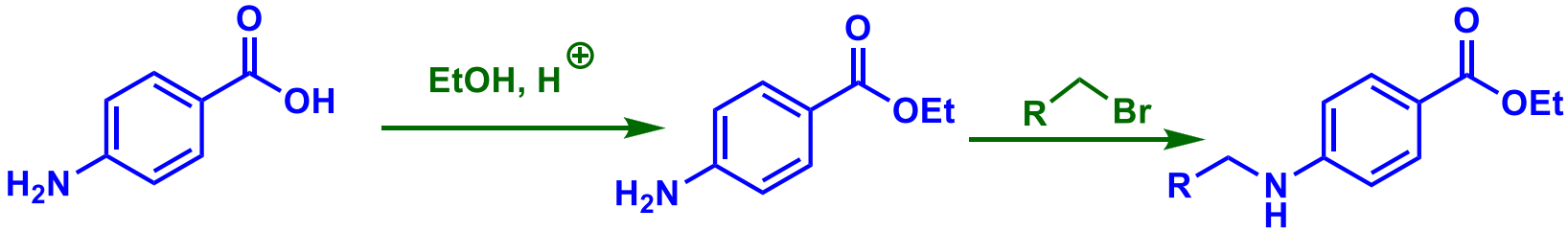
Synthesis of Cetaben ethyl ester

Cetaben ethyl ester-used to lower blood lipid levels



R = n-$C_{15}H_{31}$

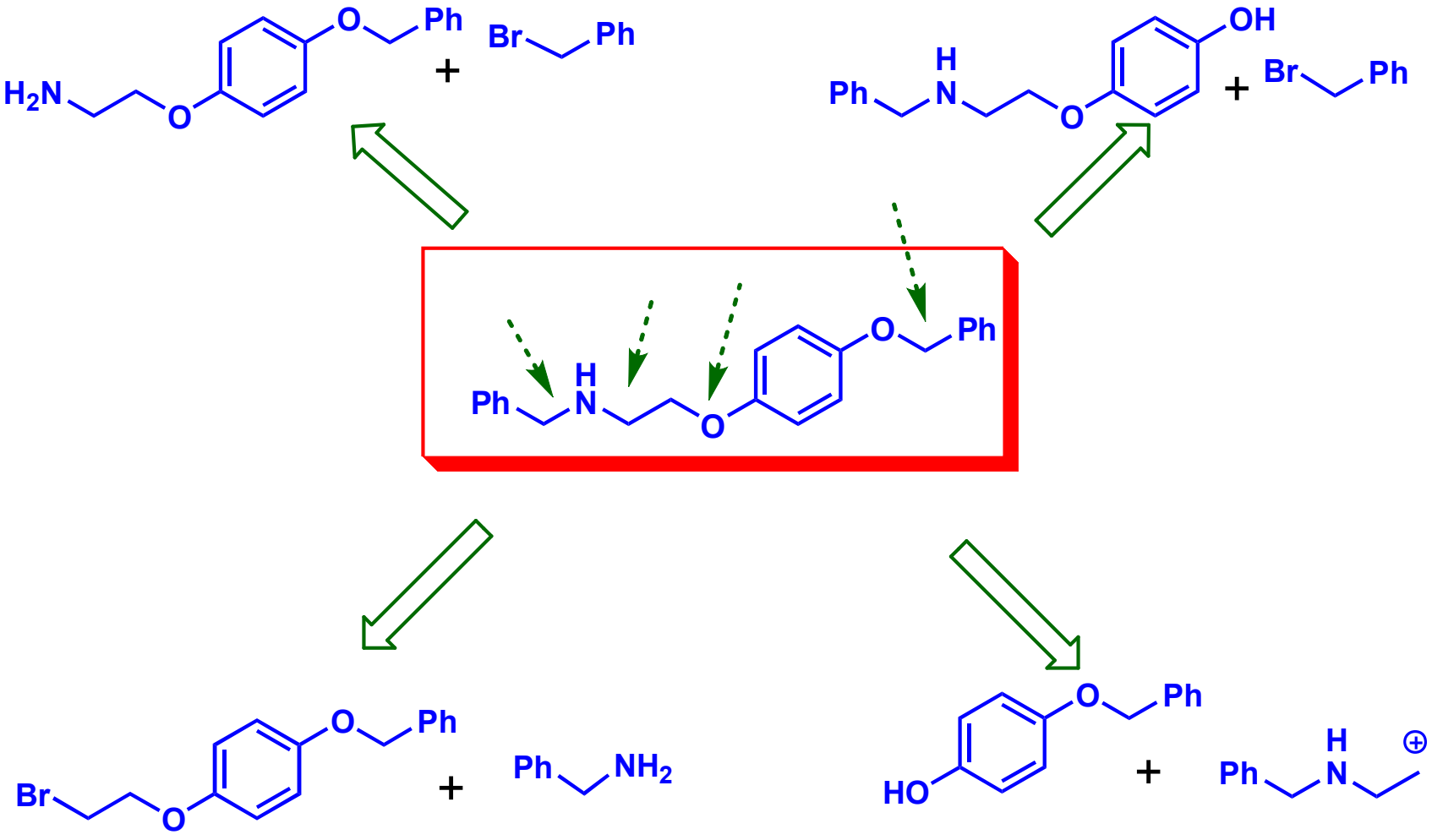
Cetaben ethyl ester



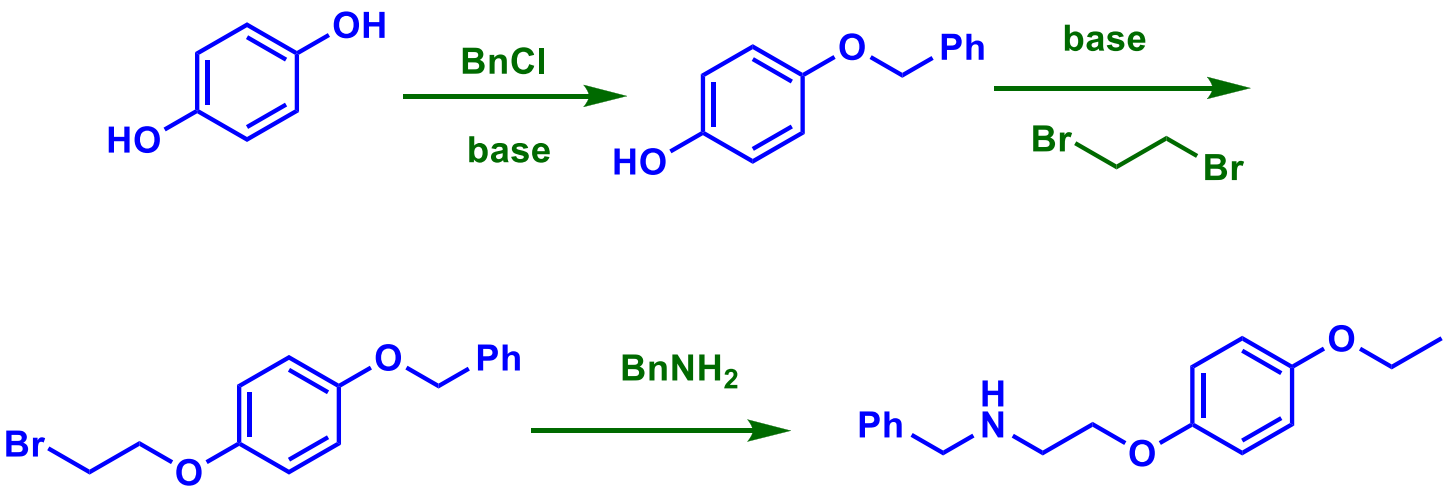
R = n-$C_{15}H_{31}$

Synthesis

ICI-D714-Potential Anti-obesity Drug

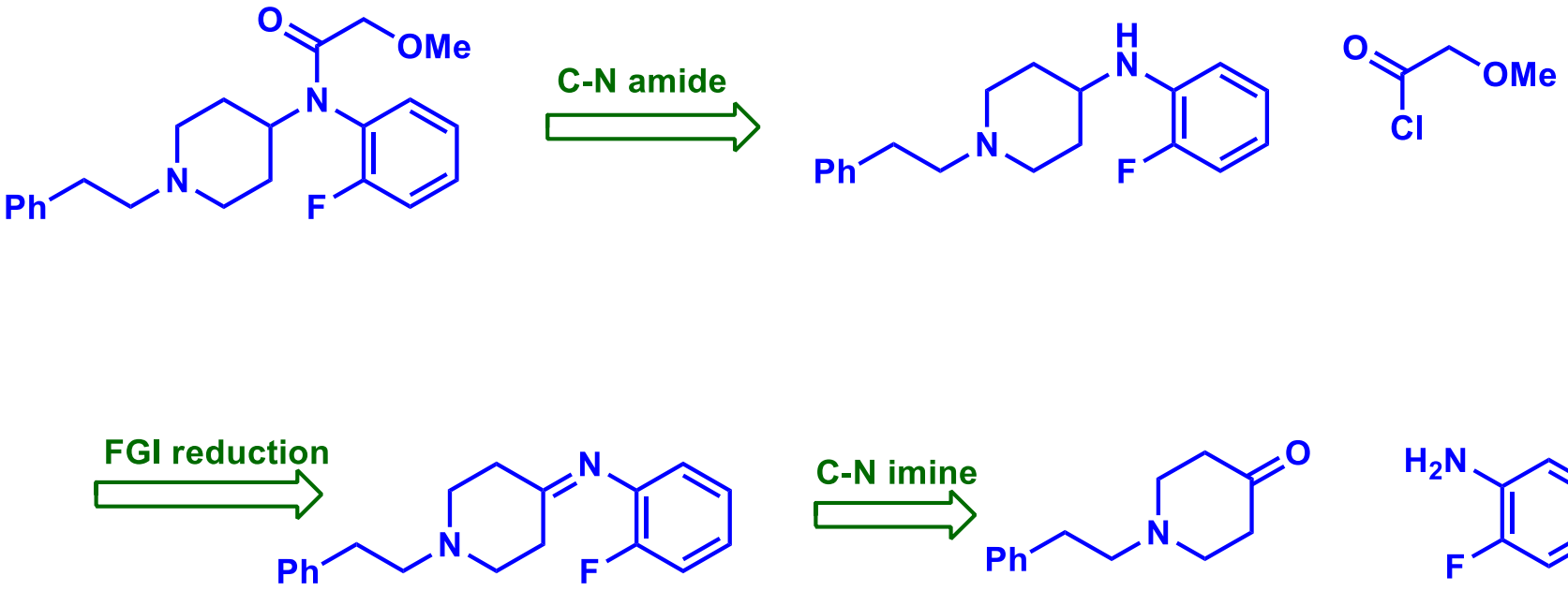


Synthesis

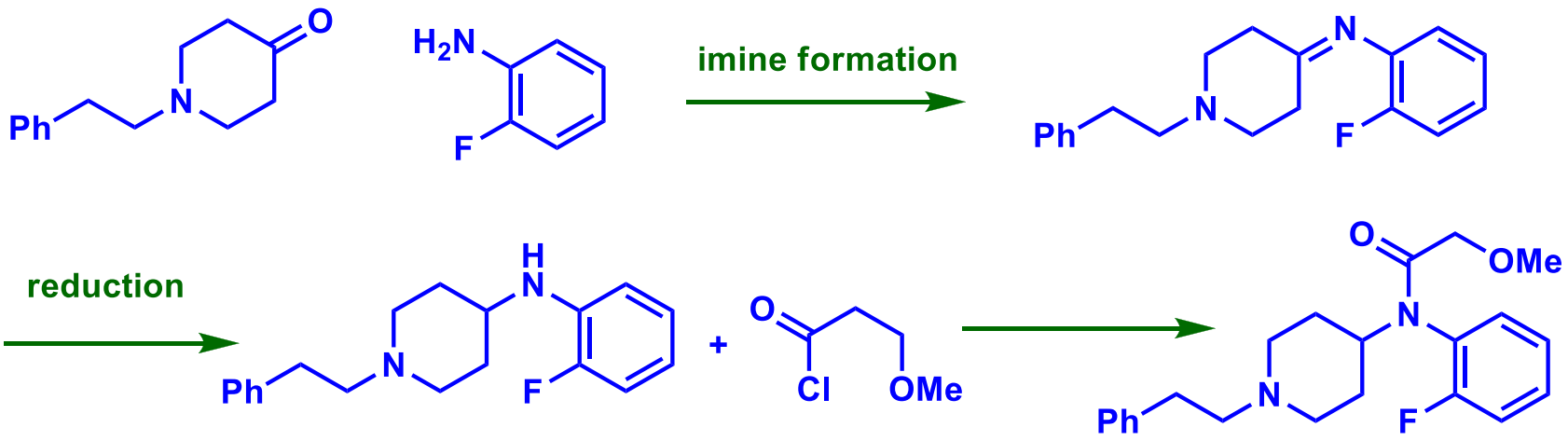


Synthesis of Ocfentanil

Ocfentanil-opioid painkiller



Synthesis


Ph
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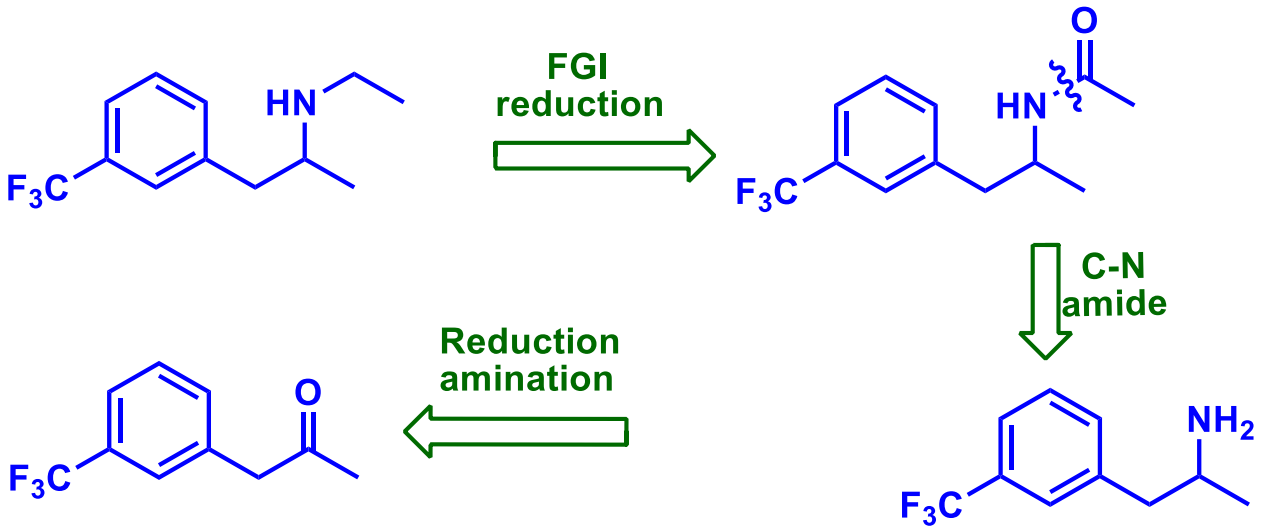
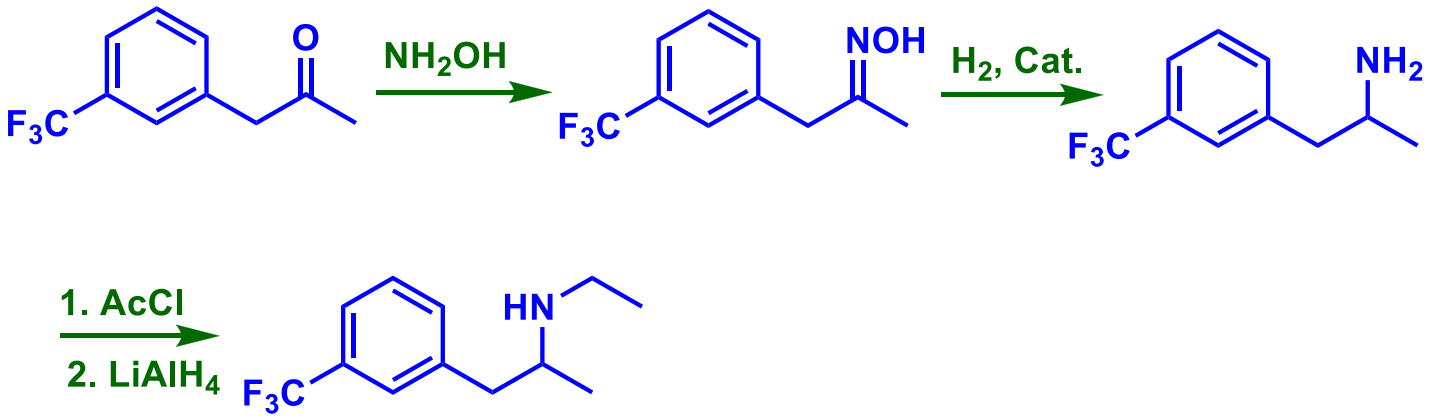
Synthesis of Fenfluoramine

Fenfluoramine-Neuroactive drug

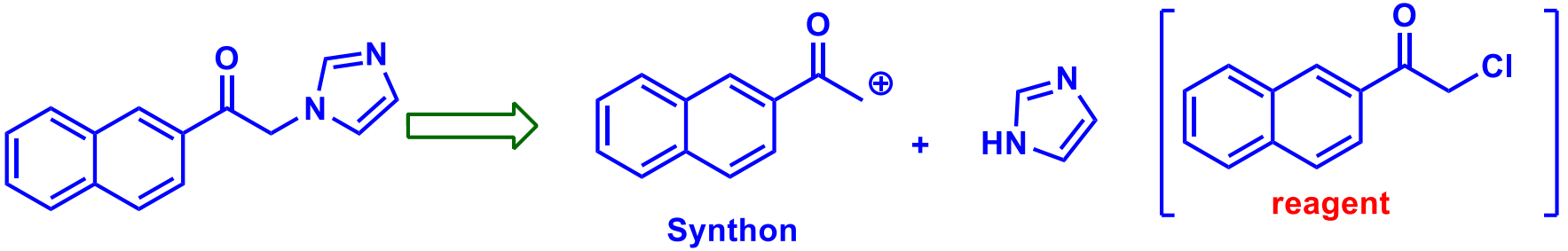


Synthesis

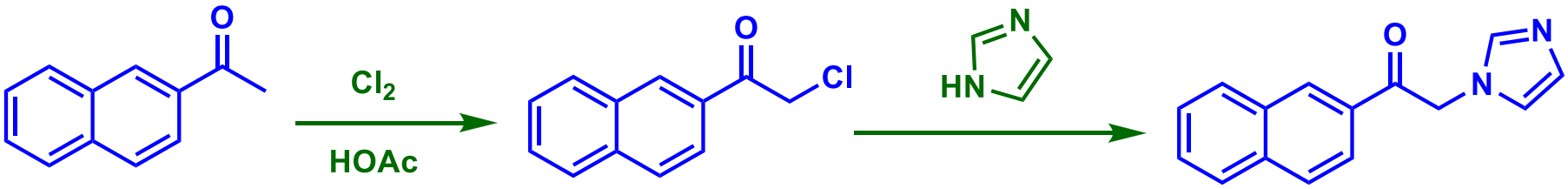


Synthesis of Nafimidone

Nafimidone-Antiparasitic drug

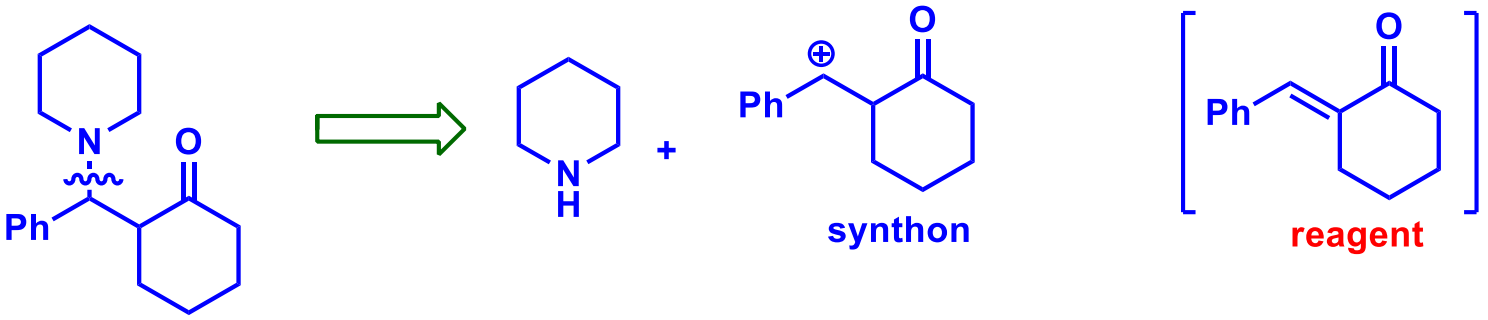


Synthesis

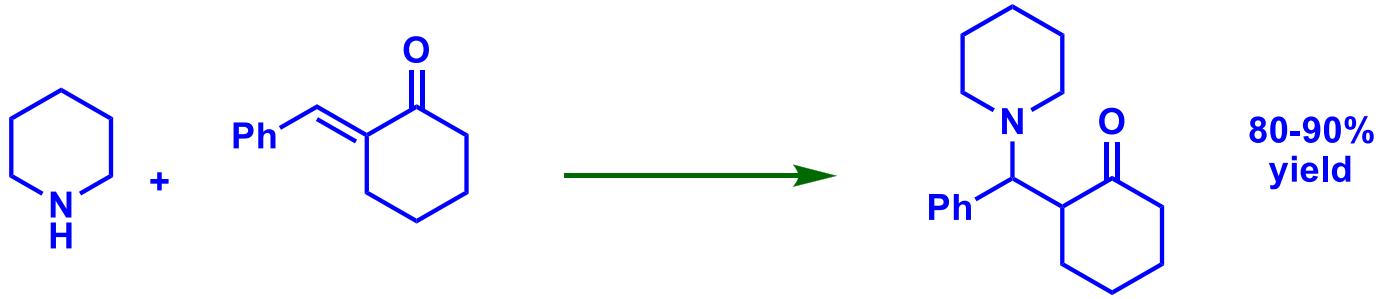


Synthesis of Atropine Mimic

Atropine mimic

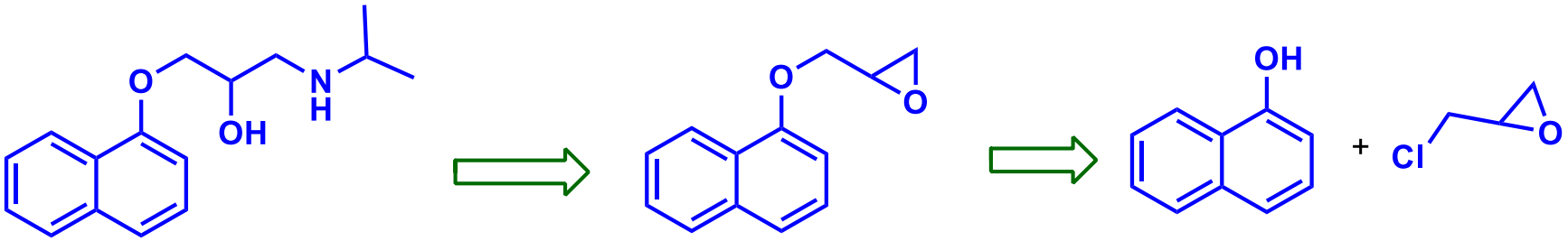


Synthesis

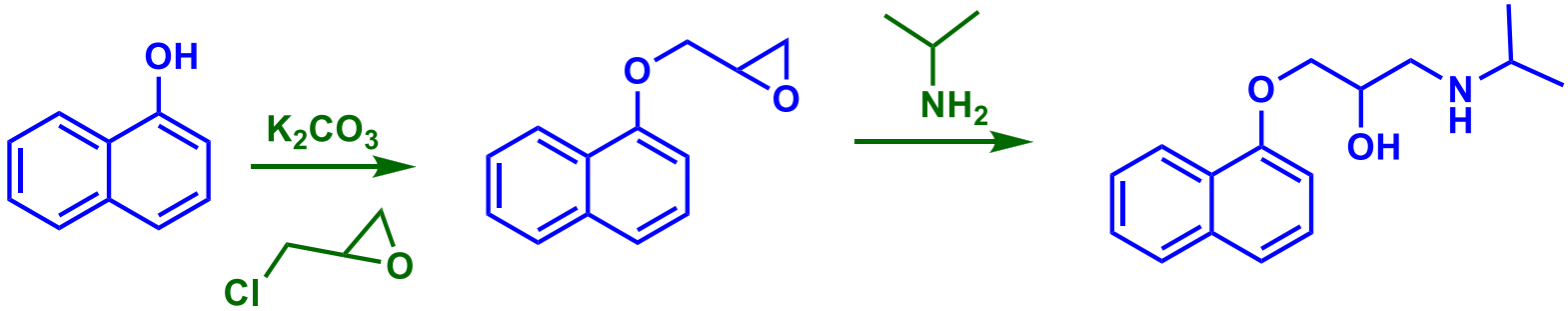


Synthesis of Propranolol

Propranolol-Beta-Blocker, reduces blood pressure

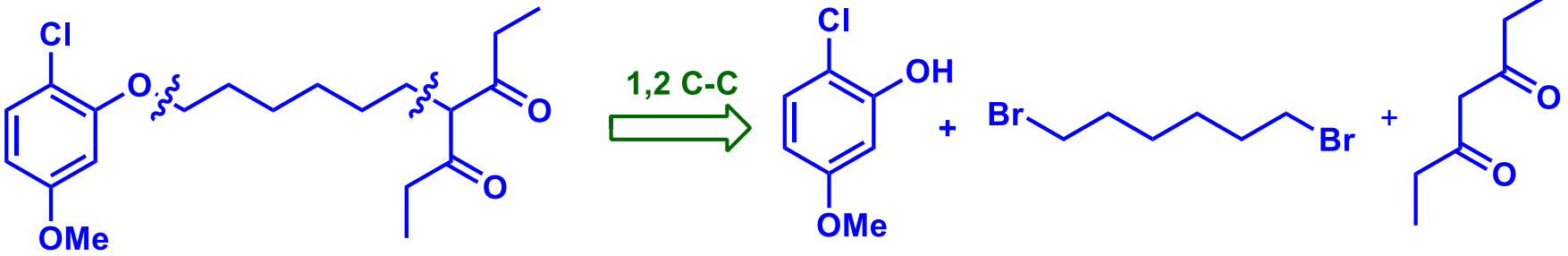


Synthesis

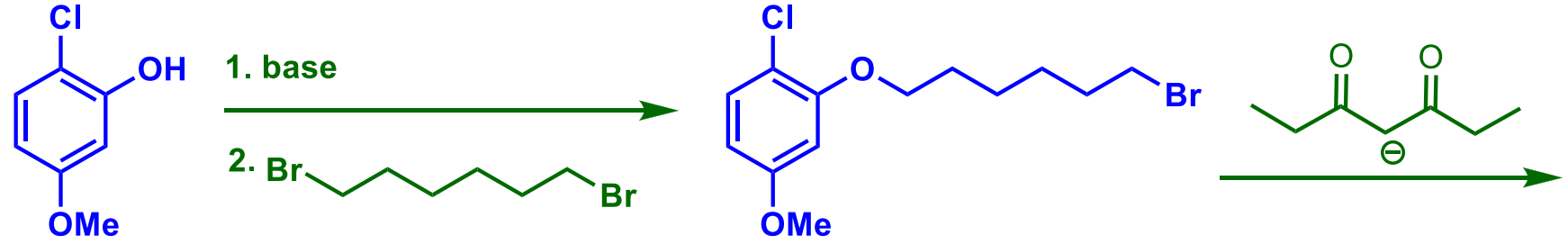


Synthesis of Arildone

Arildone-prevents polio and herpes simplex viruses from 'unwrapping' their DNA



Synthesis

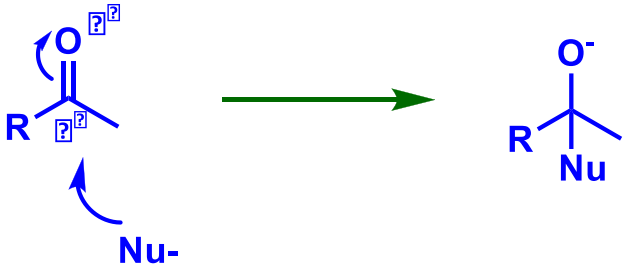


Umpolung

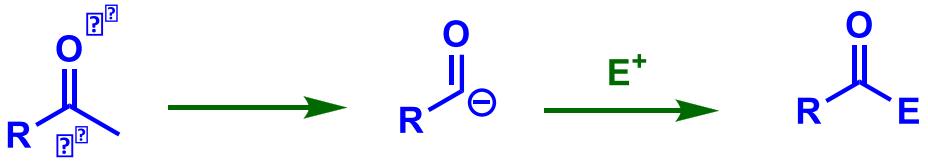
- means reversal of polarity

- Carbon atom of the carbonyl group is electrophilic in nature and susceptible to nucleophilic attack
- A reversal of the positive polarity of the carbonyl group to formyl or acyl anion is called Umpolung process.

Traditional Nucleophilic Addition to a Carbonyl Group



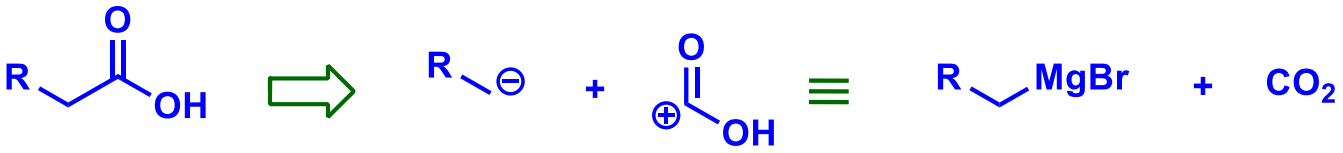
Umpolung Approach (E^+ = electrophile)



Example

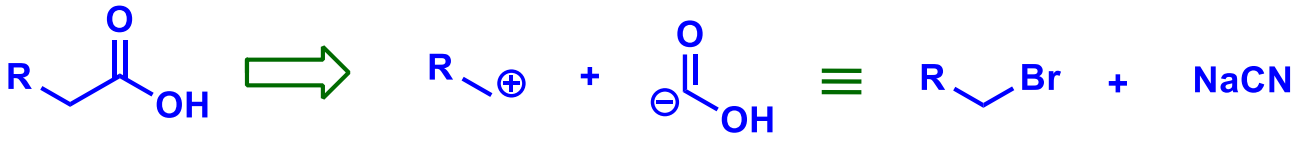
Carboxylic acids could be made by the addition of a Grignard reagent to carbon dioxide

Traditional approach to carboxylic acid

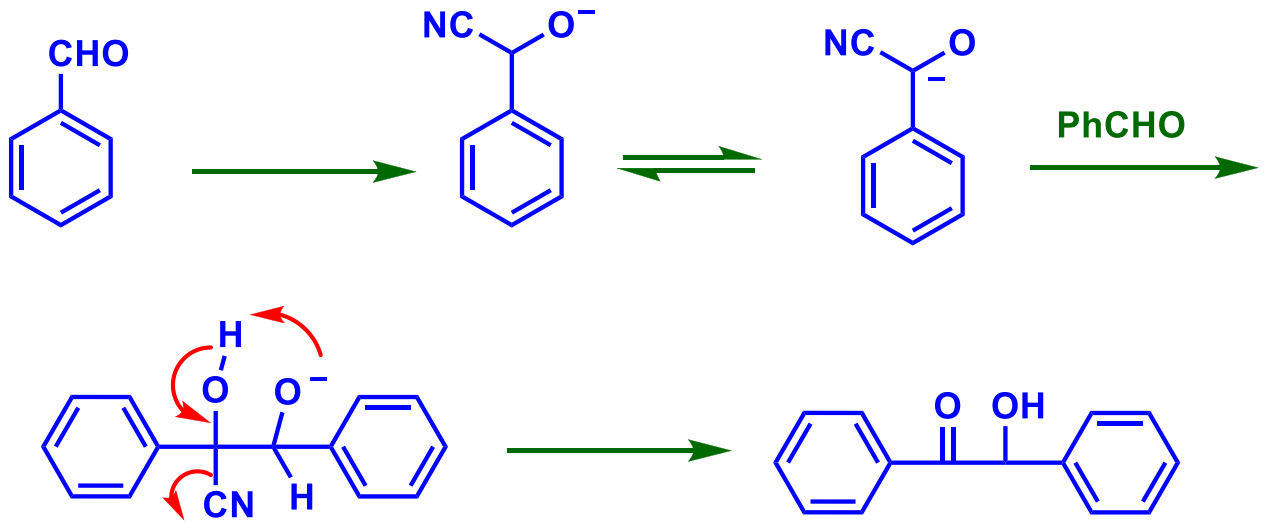


carboxylic acids can also make by nucleophilic displacement of halides by cyanides followed by hydrolysis. This is a classical example of Umpolung process.

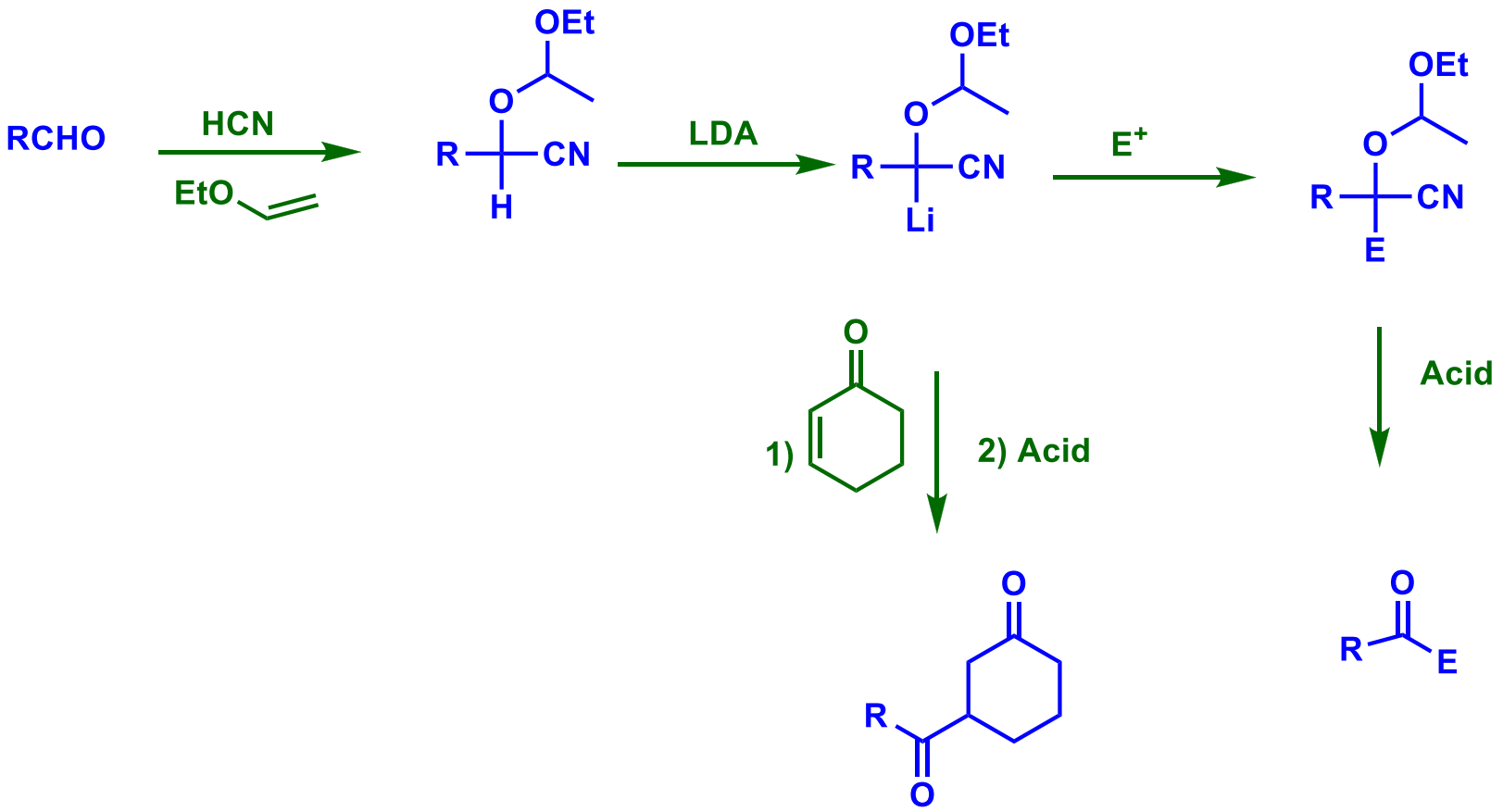
Umpolung approach to carboxylic acid



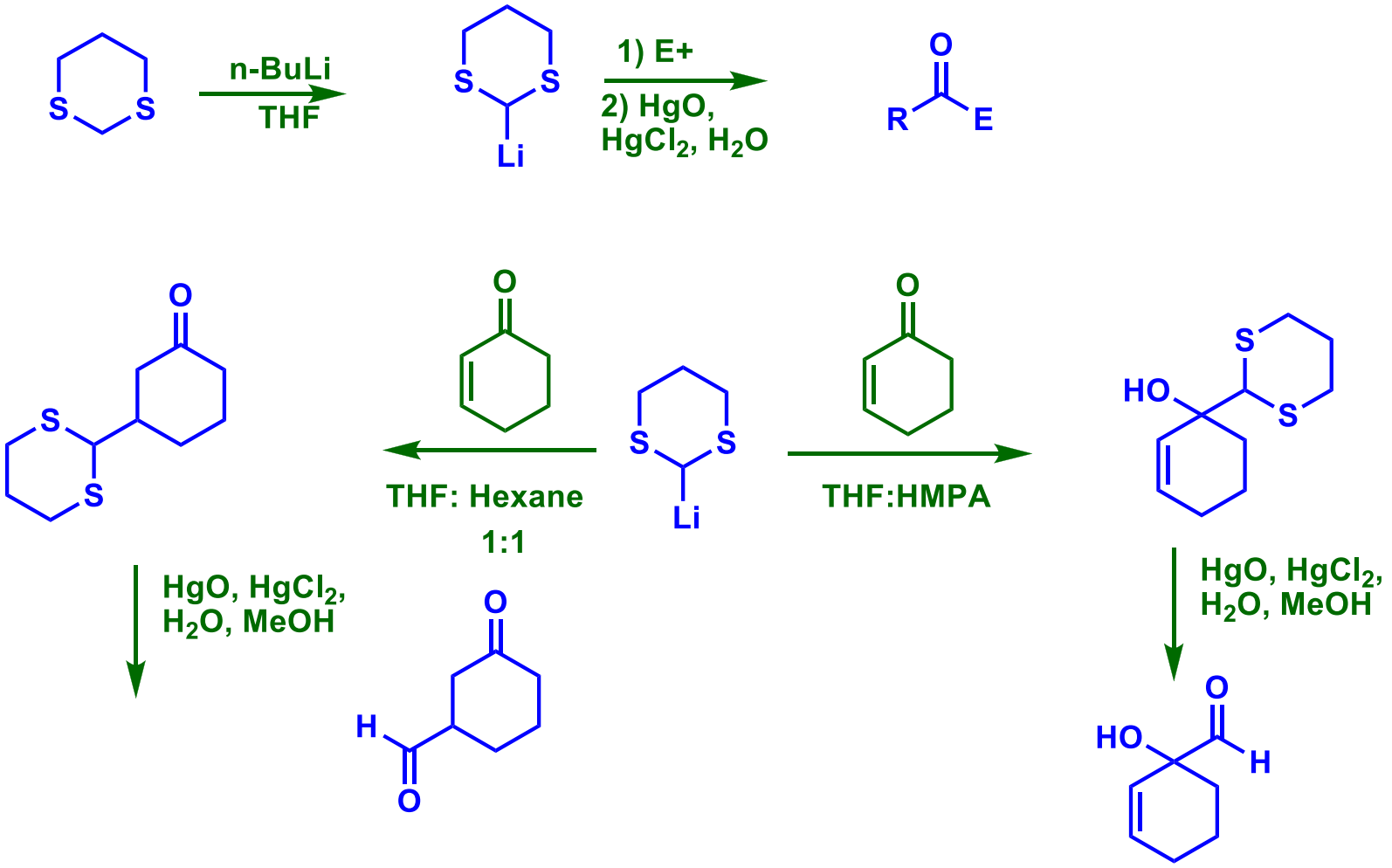
Acyl anion derived from cyanohydrins



Acyl anion derived from cyanohydrins



Acyl anion derived from 1,3-dithianes



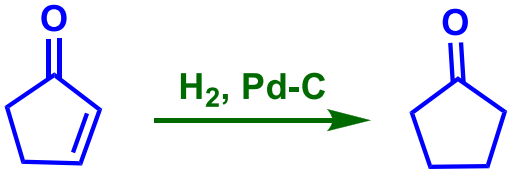
SELECTIVITY

- Chemoselectivity
- Regioselectivity
- Stereoselectivity

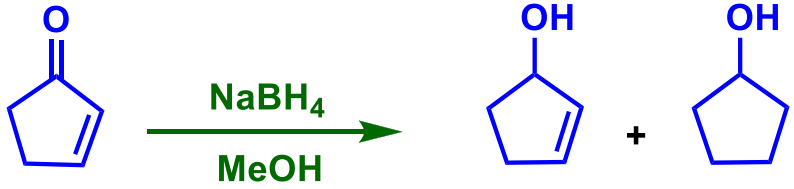
Chemoselectivity

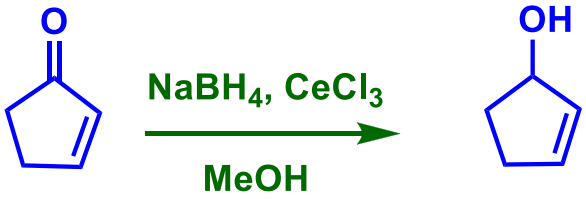
-preferential reactivity of one functional group (FG) over another

Chemoselective reduction of C=C over C=O



Chemoselective reduction of C=O over C=C

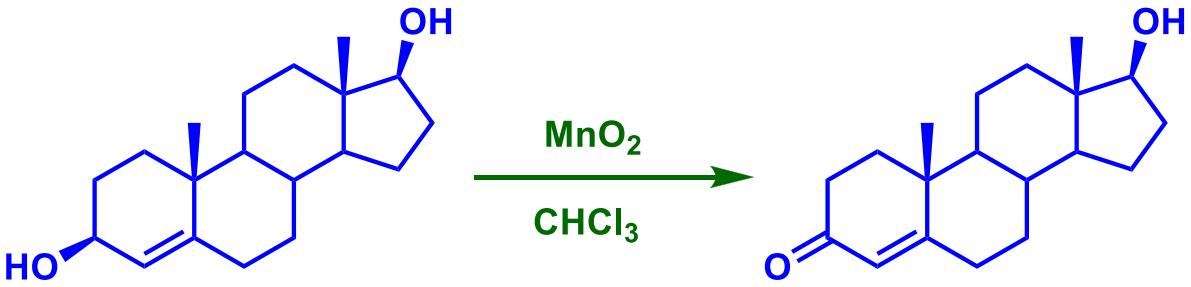




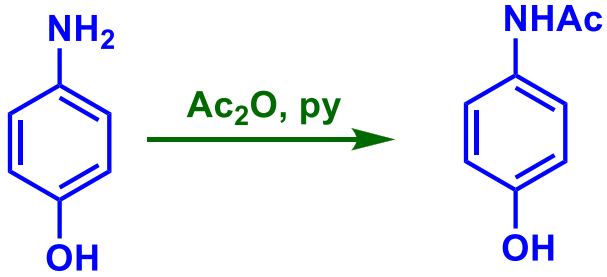
Luche reduction

Examples

Chemoselective oxidation of allylic alcohols over other alcohols



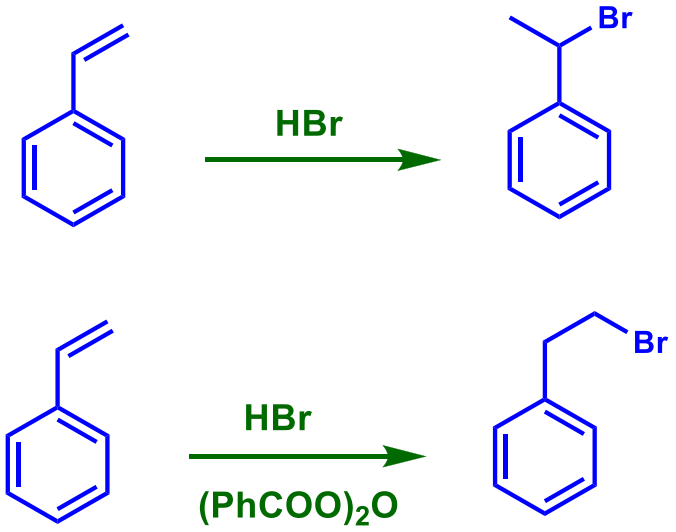
Chemoselective acetylation of amines over phenols



Regioselectivity

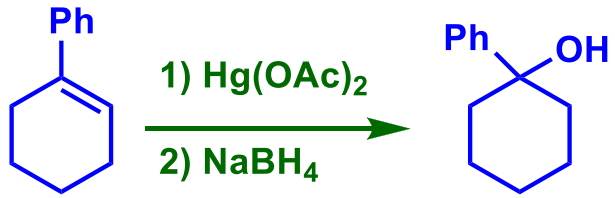
Preferential reactivity of one site over the other site of the same functional group

Addition of HBr to alkenes



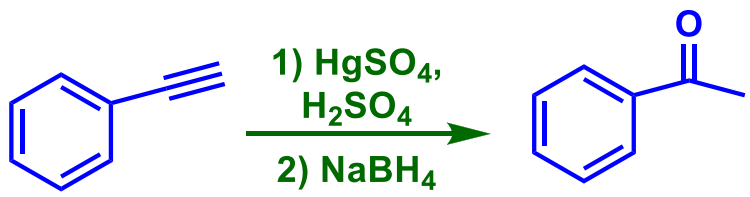
Examples

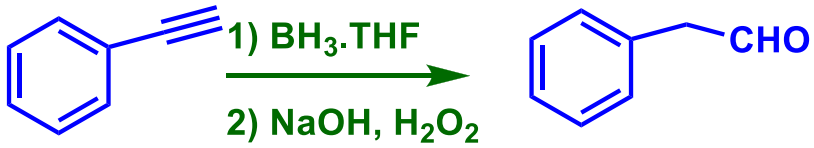
Hydration of alkenes (Oxymercuration and Hydroboration)



Examples

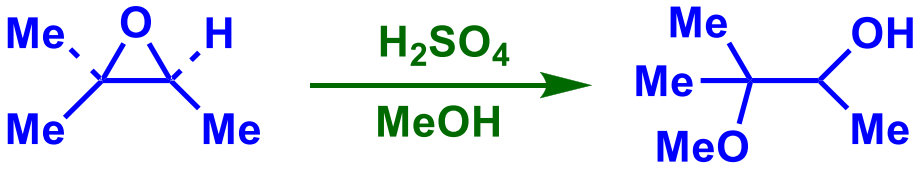
Hydration of alkynes

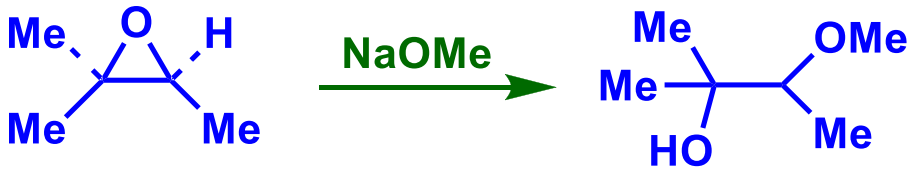




Examples

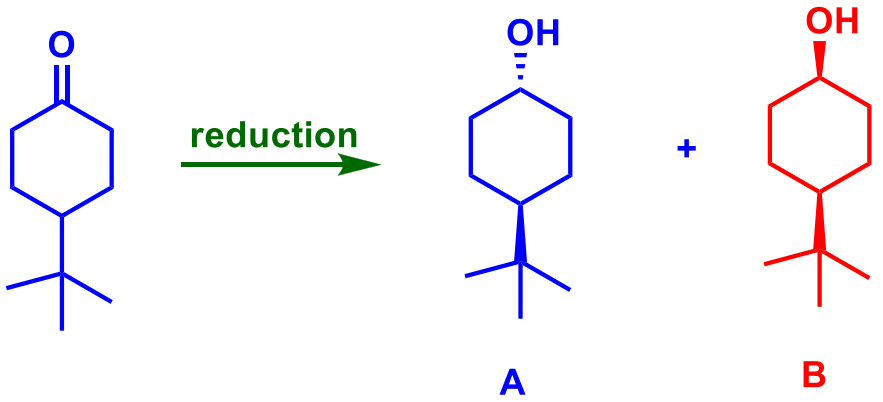
Epoxide opening

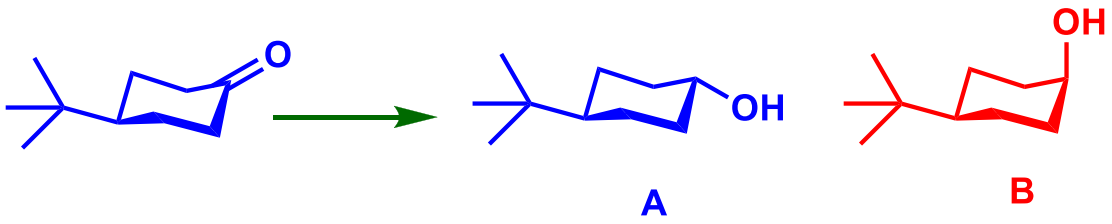




Stereoselectivity

Predominant (or exclusive) formation of one of several possible stereoisomeric products





LAH, $NaBH_4$ affords predominantly *A* and bulky reducing agents like $LiAlH(OBu\text{-}t)_3$ gives predominantly B.