University of Zagreb
Faculty of Chemical Engineering and Technology
Study programme Chemical and Environmental Technology

SYNTHESIS CONTROL- CHEMOSELECTIVITY, STEREOSELECTIVITY AND REGIOSELECTIVITY

Prof. Marijana Hranjec, PhD

Academic year 2024/2025

ORGANIC SYNTHESIS

Well planned organic synthesis include:

- ❖starting from readily available and commercially acceptable reactants
- ❖use of efficient and selective reactions
- ❖avoiding extreme and hazardous reactants and reaction conditions
- ❖flexibility - to have plan B if plan A fails
- ❖very good knowledge of organic reactions and mechanisms
- ❖adaptability
- ❖commercially acceptable total synthetic route with respect to environmental criteria - "green chemistry„
- ❖innovation and creativity

Selectivity - the efficiency of the synthetic pathway

1. **CHEMOSELECTIVITY** - reaction of only one functional group in relation to all existing functional groups in the structure of the molecule
2. **REGIOSELECTIVITY** - formation of only one regioisomer in relation to all possible regioisomers
3. **STEREOSELECTIVITY** - formation of one stereoisomer - diastereoselectivity and enantioselectivity

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CHEMOSELECTIVITY

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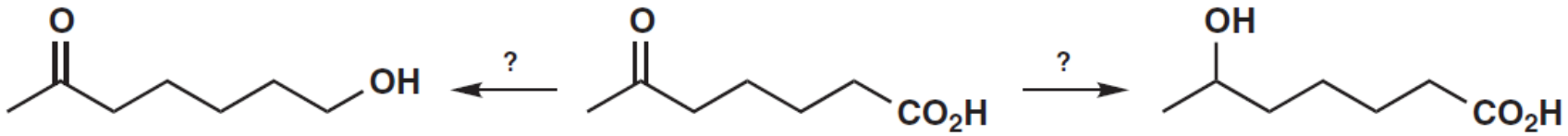
CHEMOSELECTIVITY

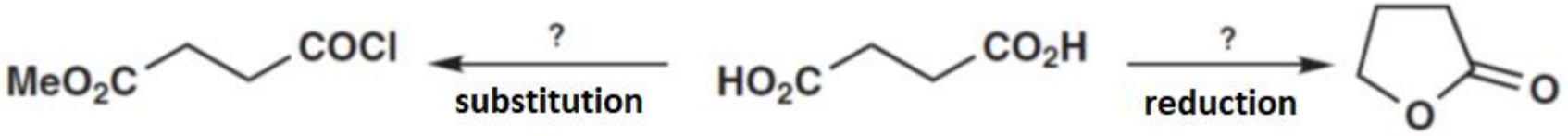
- it is the clearest and simplest way to control the synthesis from existing ones
- selectivity between individual functional groups in the structure of a molecule
- the selectivity of a molecule to different chemical reagents

Selectivity between functional groups includes:

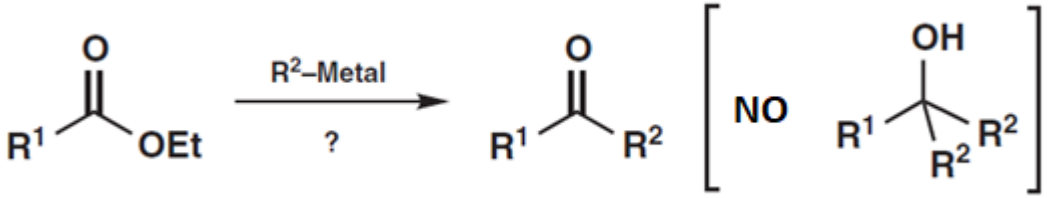
- reaction of only one functional group in relation to all existing in the structure of the molecule



- selective reaction of one of several identical functional groups in the structure of the molecule

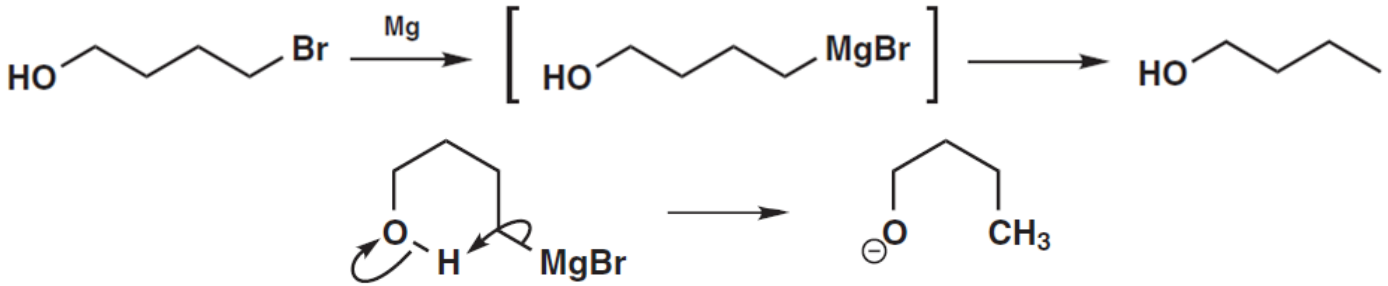


- a selective reaction of a functional group that can itself react with a given reagent

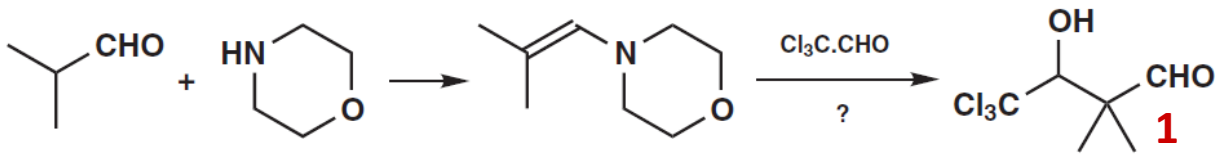


CHEMOSELECTIVITY

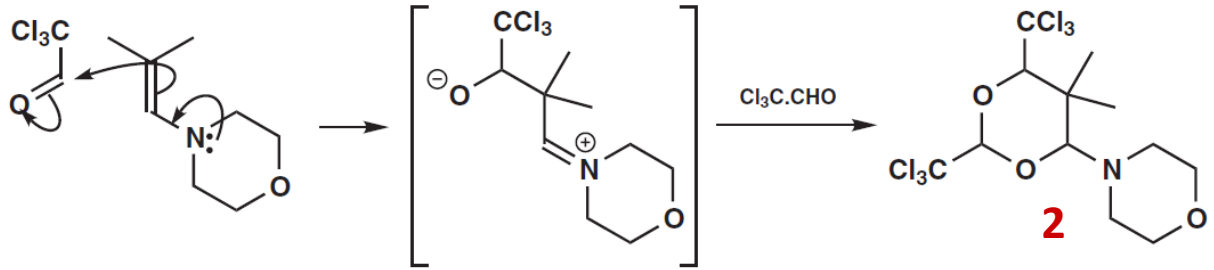
- highly selective and specific reagents
- their use must only take place for the reaction for which they are intended
- they have to satisfy the following conditions:
  - ✓ they must not react with themselves



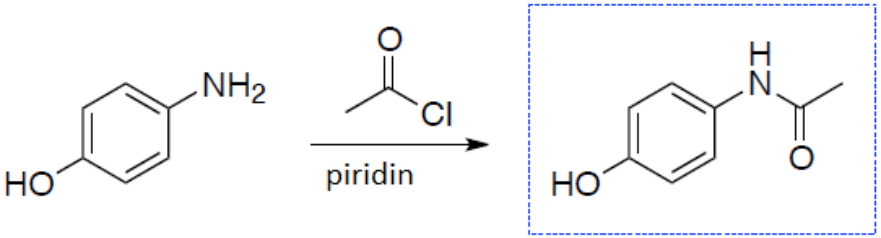
- they must not react with a FG other than the one for which they are intended
- they must not react with the product
- the reaction of aldehydes and chlorals, via enamine, should be a simple synthetic route for the preparation of aldols

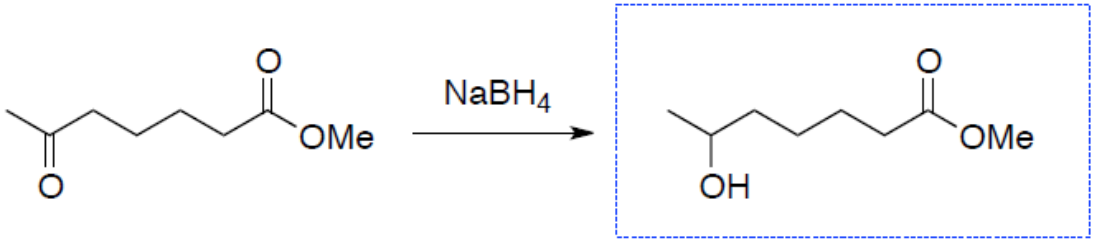


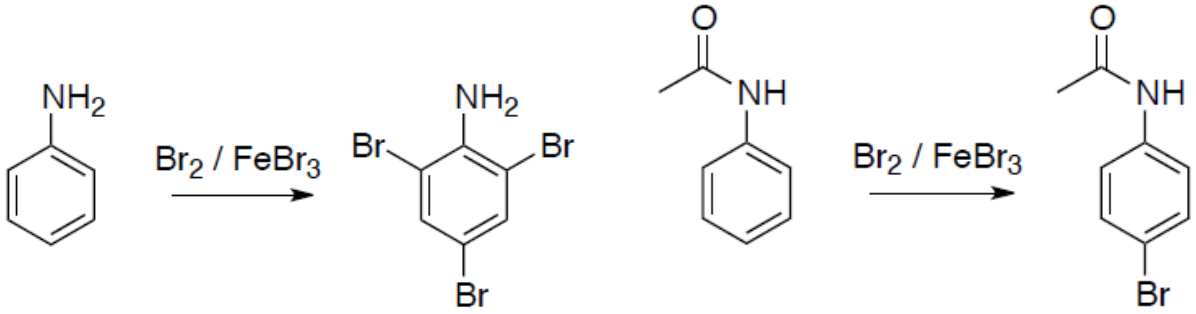
- enamine is reacted with chloral, except aldol 1 and adduct 2 in a ratio of 2: 1

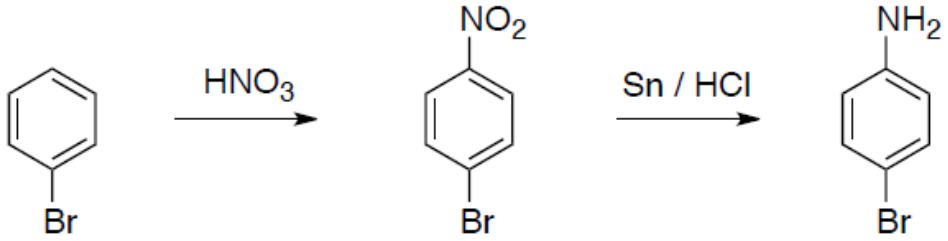


CHEMOSELECTIVE REACTIONS

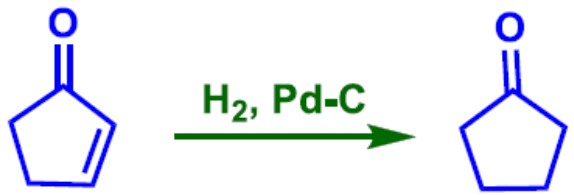


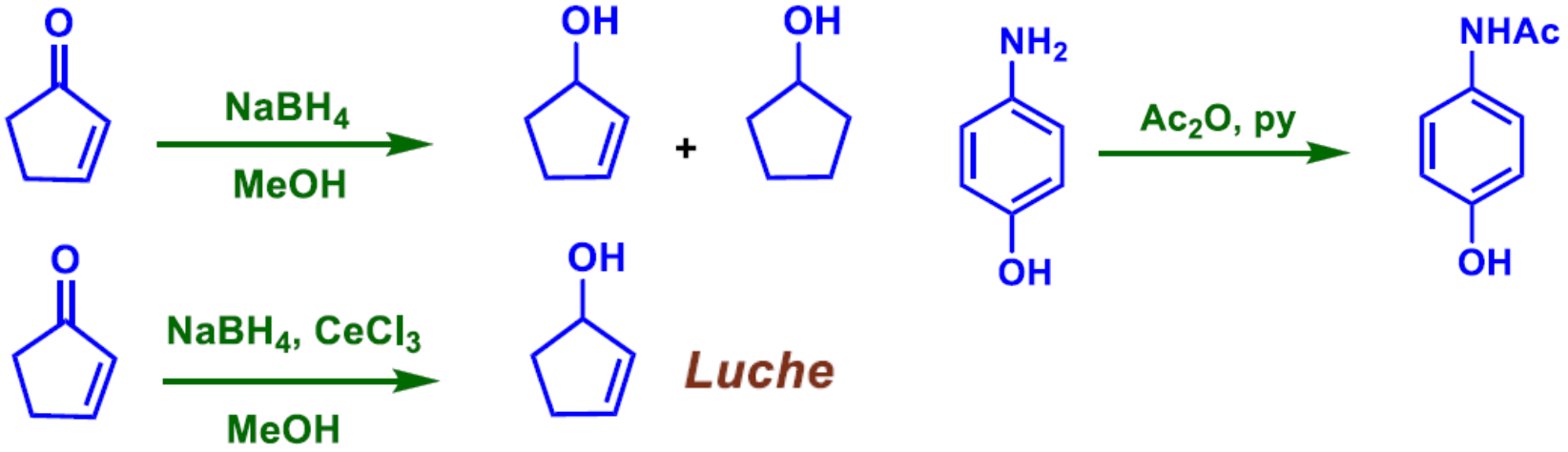


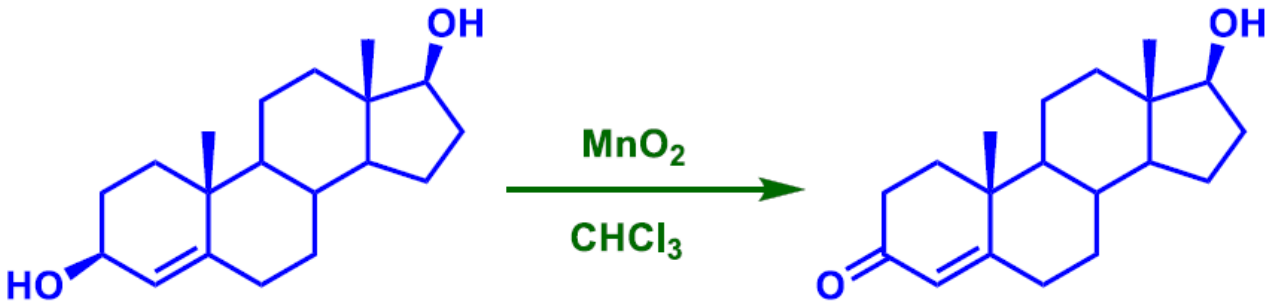




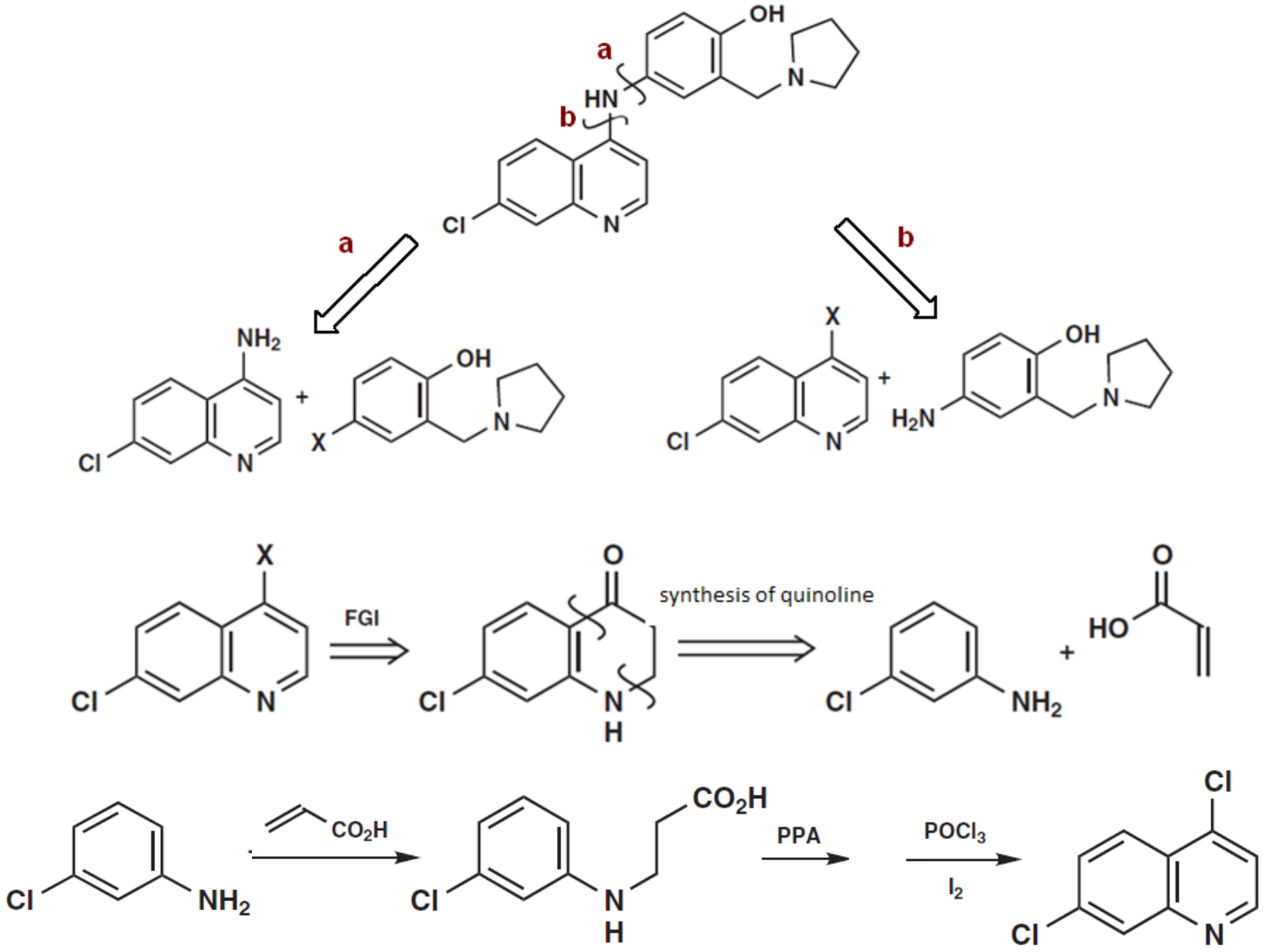
CHEMOSELECTIVE REACTIONS



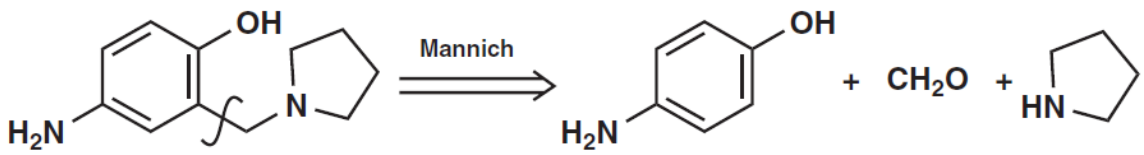




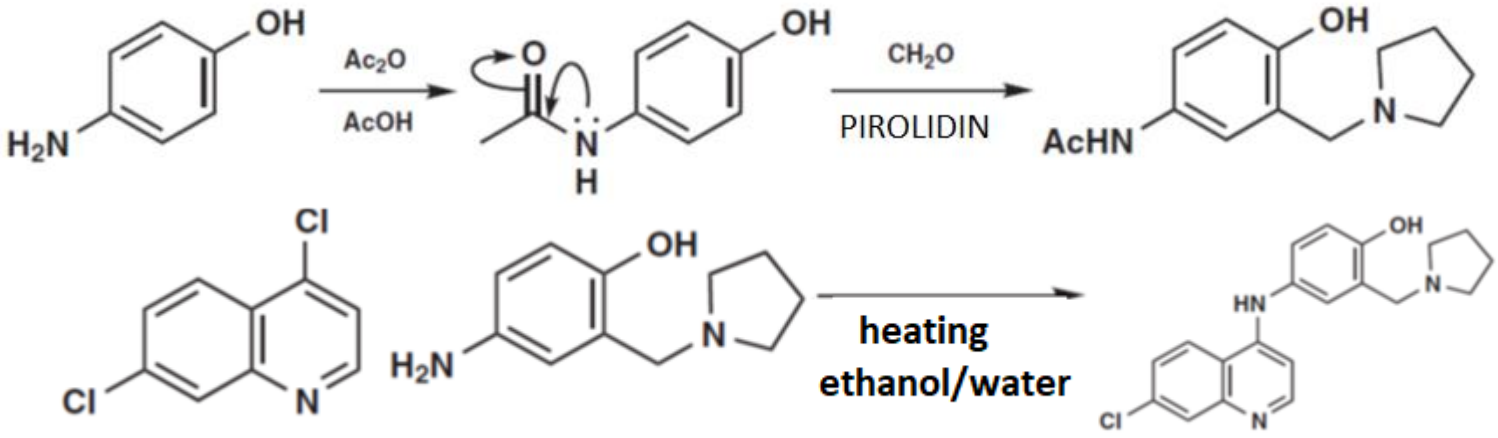
CHEMOSELECTIVE REACTIONS



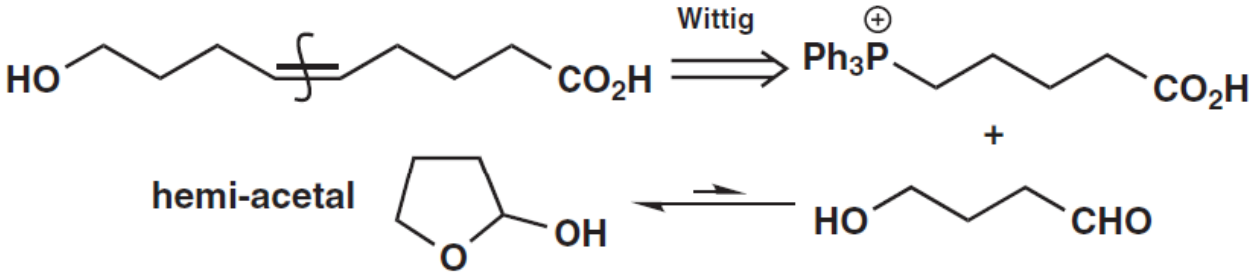
EXAMPLES – WITH PROTECTIVE GROUP



Protection of amino group:



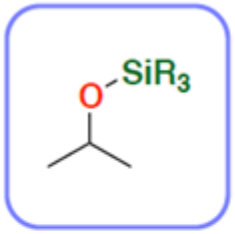
EXAMPLES – WITHOUT PROTECTIVE GROUP



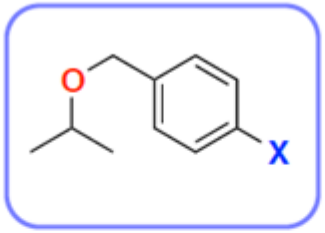
Protective groups

Protection for alcohols:

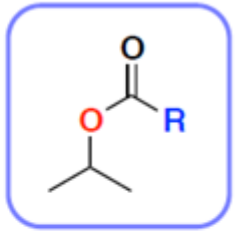
silyl-ethers



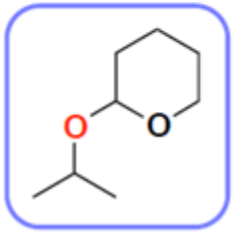
benzyl-ethers



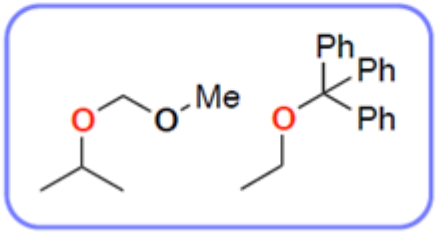
esters/carbonates



acetales



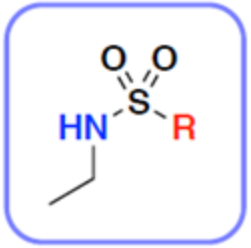
ethers



Protection for amines:

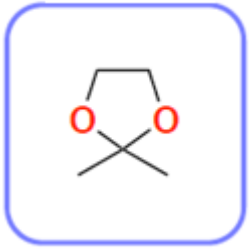
carbamates

sulfonamides



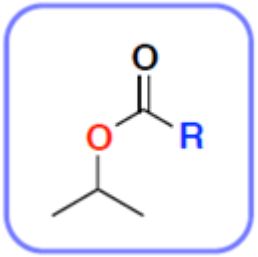
Protection for carbinoles:

acetales



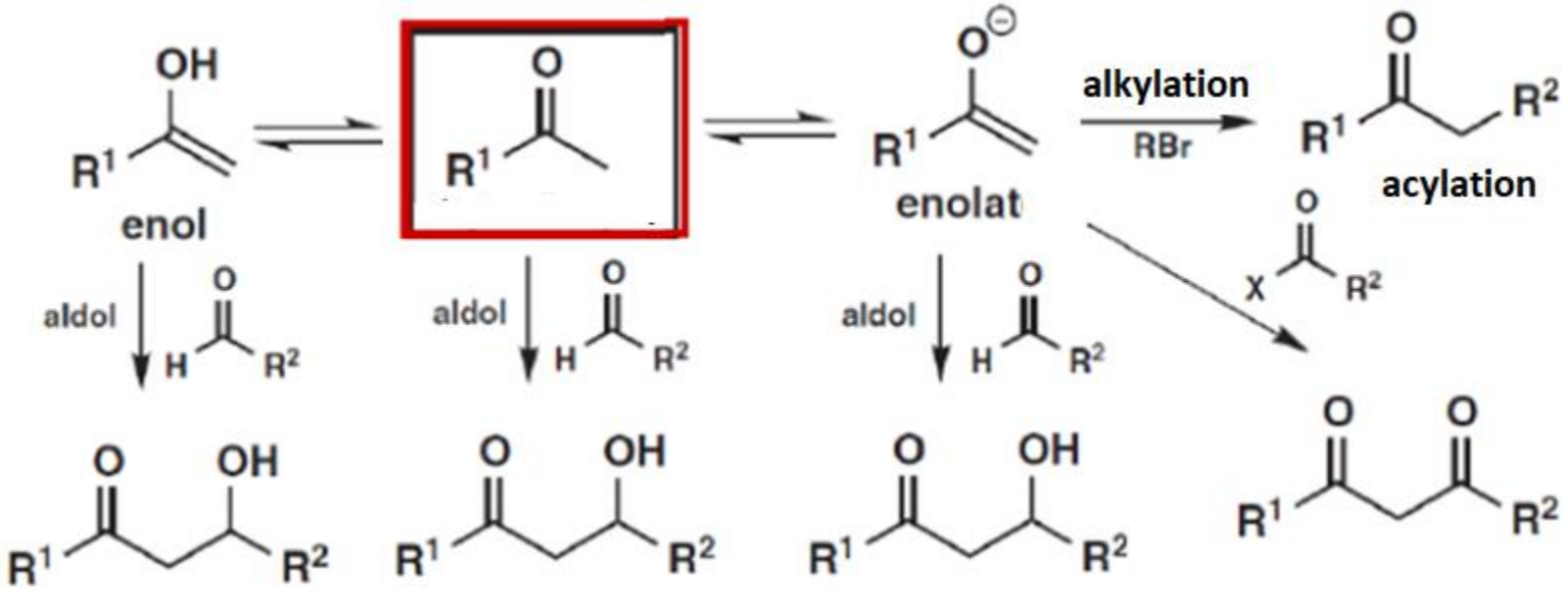
Protection for carboxylic compounds:

esters/carbonates

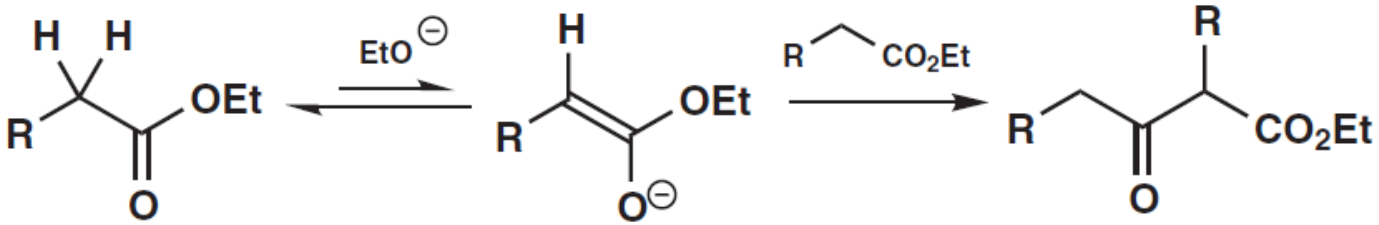


ENOLES AND ENOLATES

❖ the problem of chemoselectivity occurs in the reactions of molecules with similar functional groups - especially in enols and enolate anions

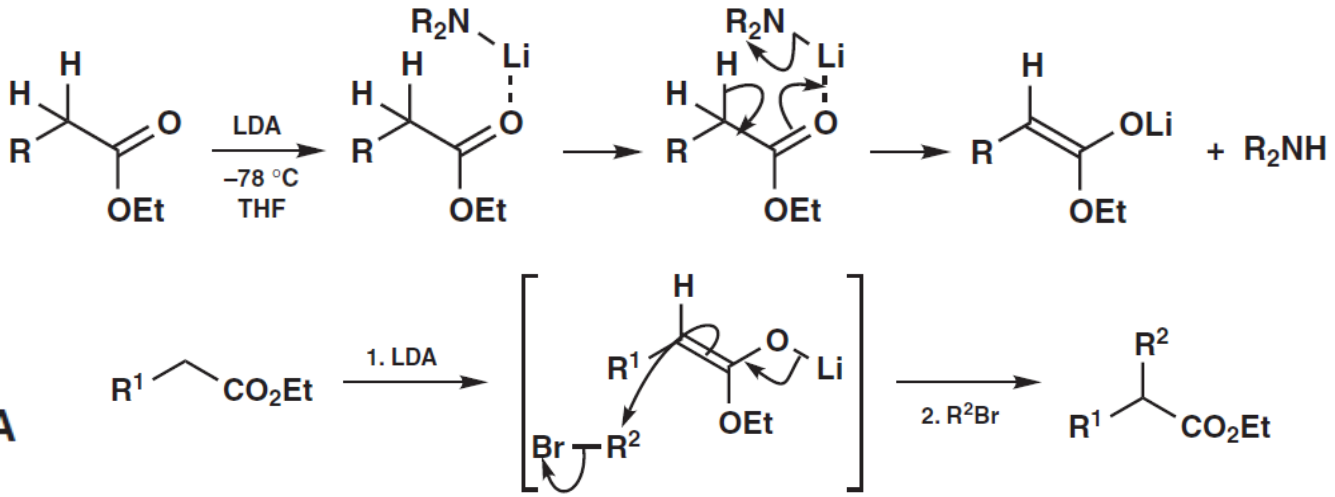


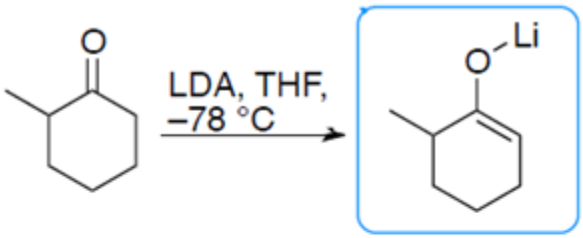
EXAMPLE – alkylation of esters



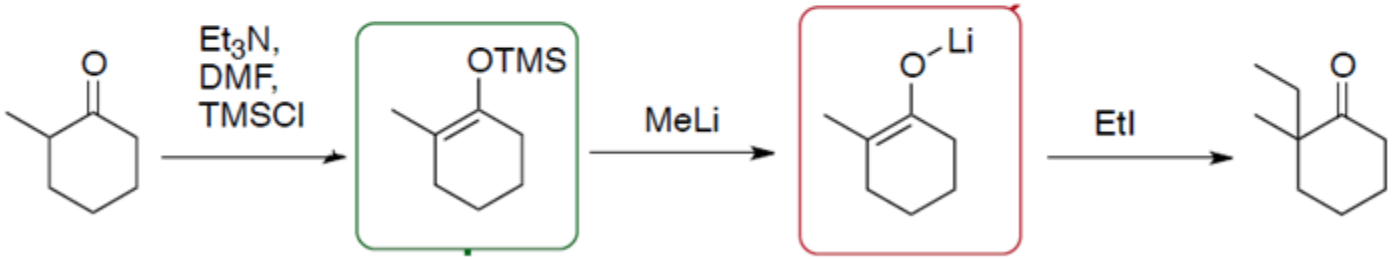
ENOLES AND ENOLATES

Preparation of lithium enolates:





kinetic enolate

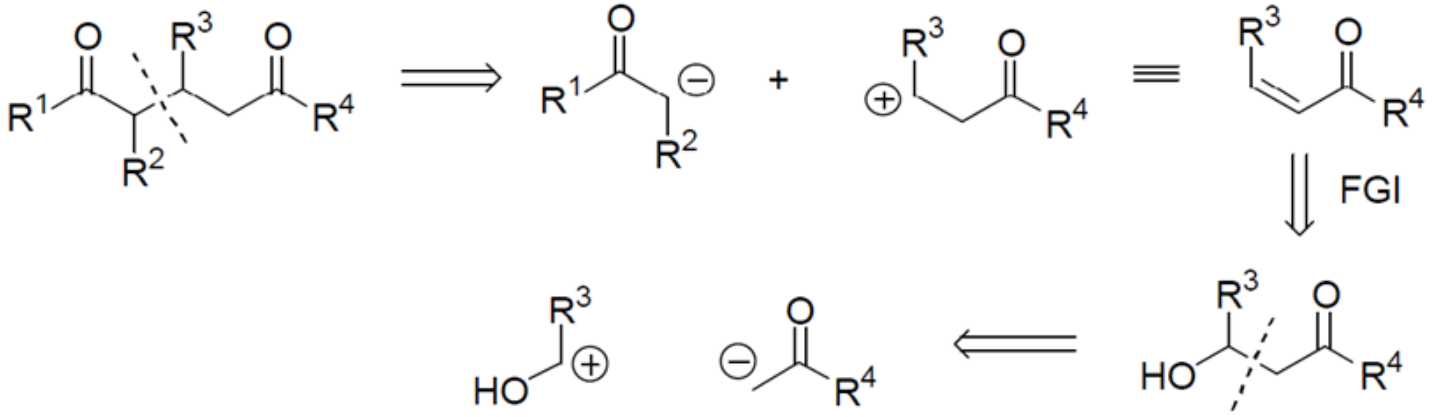


silyl-enole-ether

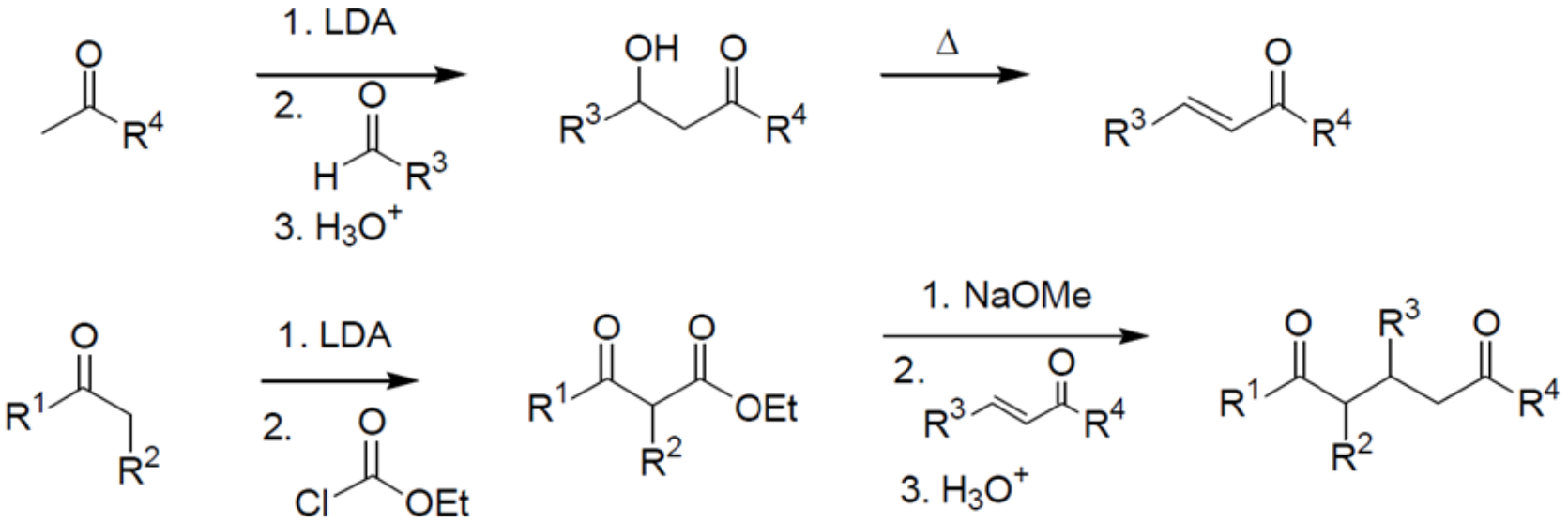
thermodinamic enolate

EXAMPLE – TWO FUNCTIONAL GROUPS

Retrosynthesis:

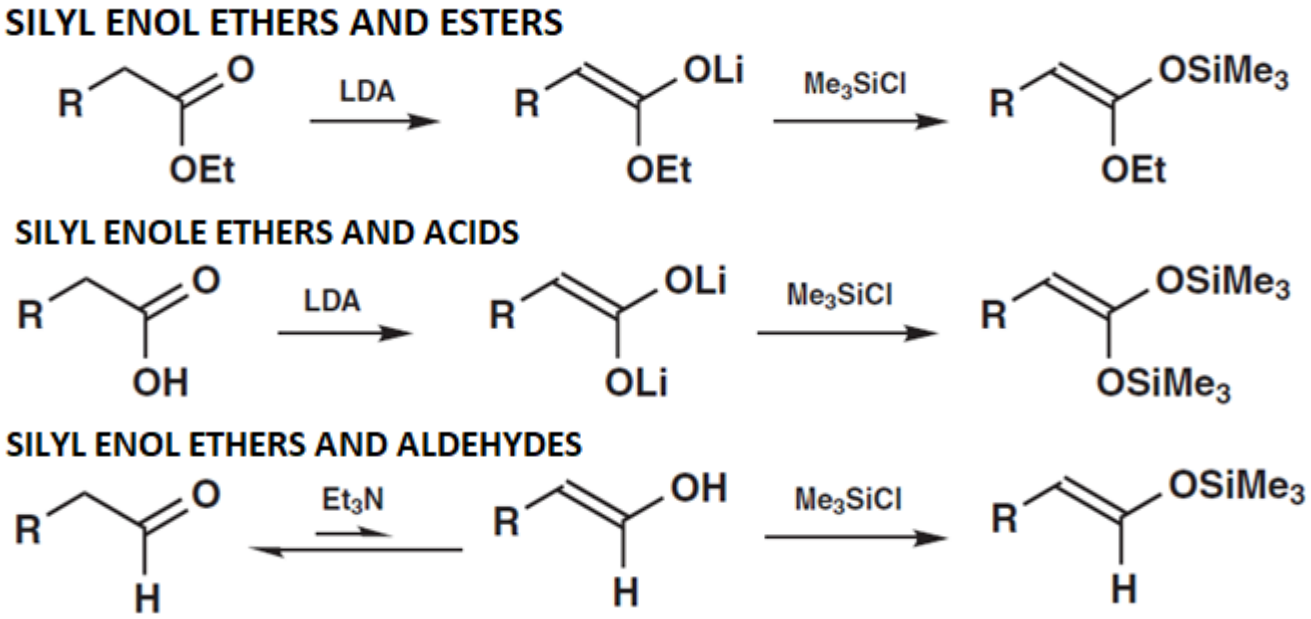


Sinthesis:

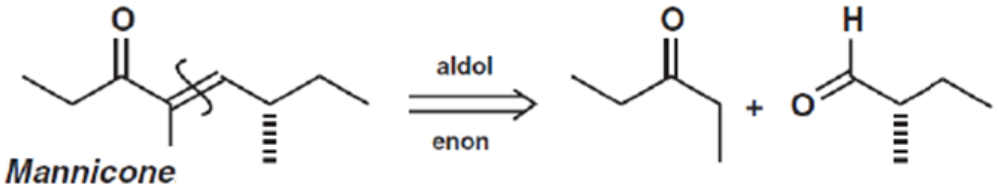


SILYL ENOL ETHERS

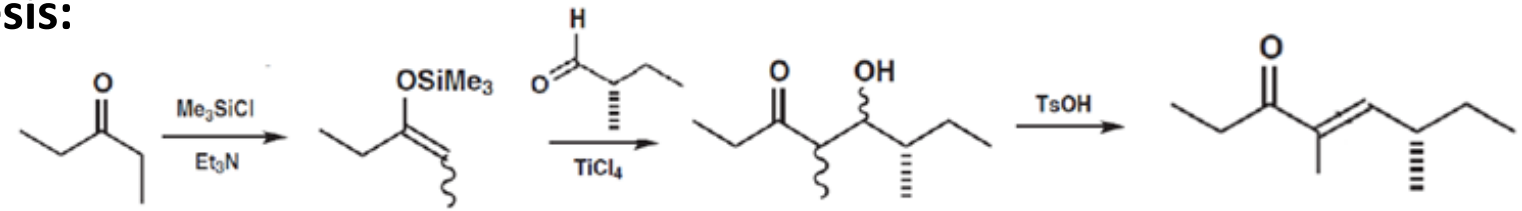
❖ are prepared from lithium enolate esters and carboxylic acids or under mild conditions with a tertiary amine; the Si atom is a very good electrophile and reacts very quickly with the oxygen atom of enolate



Retrosynthesis



Synthesis:



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REGIOSELECTIVITY

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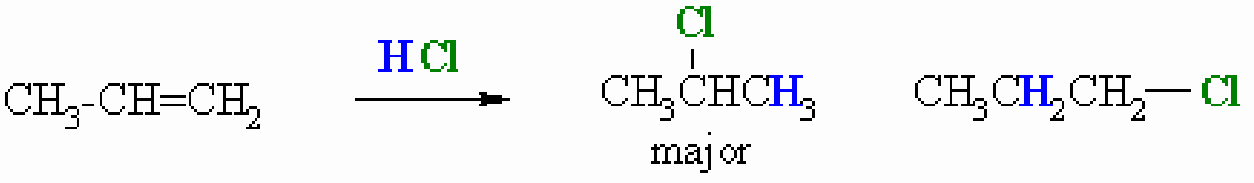
REGIOSELECTIVITY

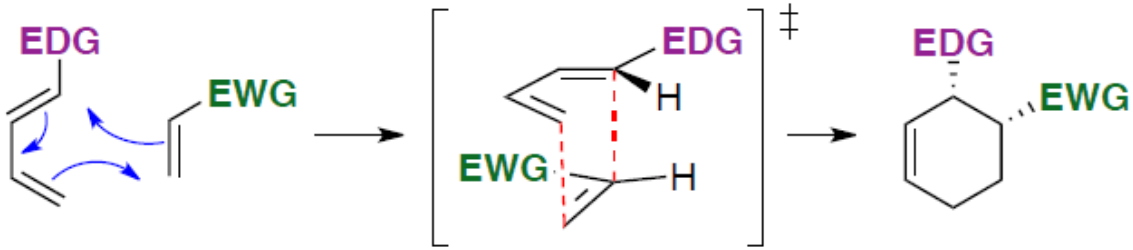
❖ **regioselectivity** - controlling different aspects of a functional group - how to conduct a reaction to react to a specific part of a functional group

❖ the formation of one regioisomer is favoured over all possible ones

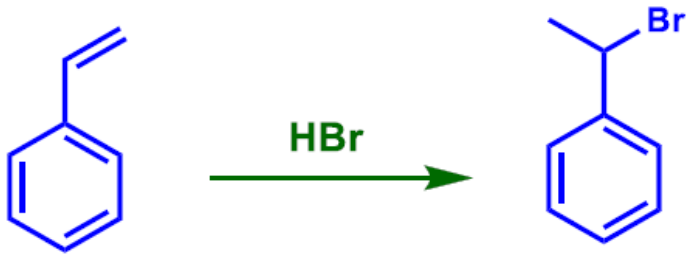


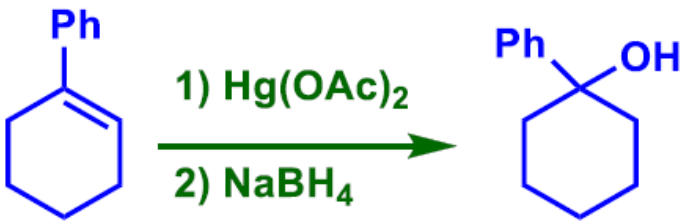
❖ **regiospecific reaction** - only one product is formed

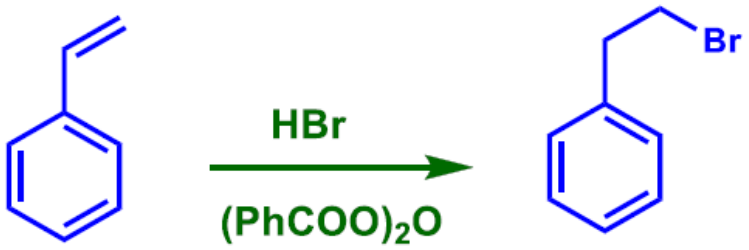
❖ there are several elements for regioselective control, e.g. groups blocking a specific active site or region of a molecule, activating groups or control achieved by proper selection of reaction conditions



EXAMPLES

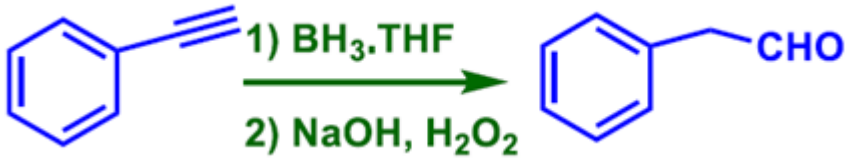




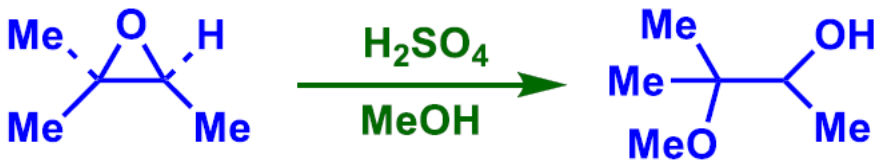


Markovnikov and anti-Markovnikov adition

oxymercuration and hydroboration



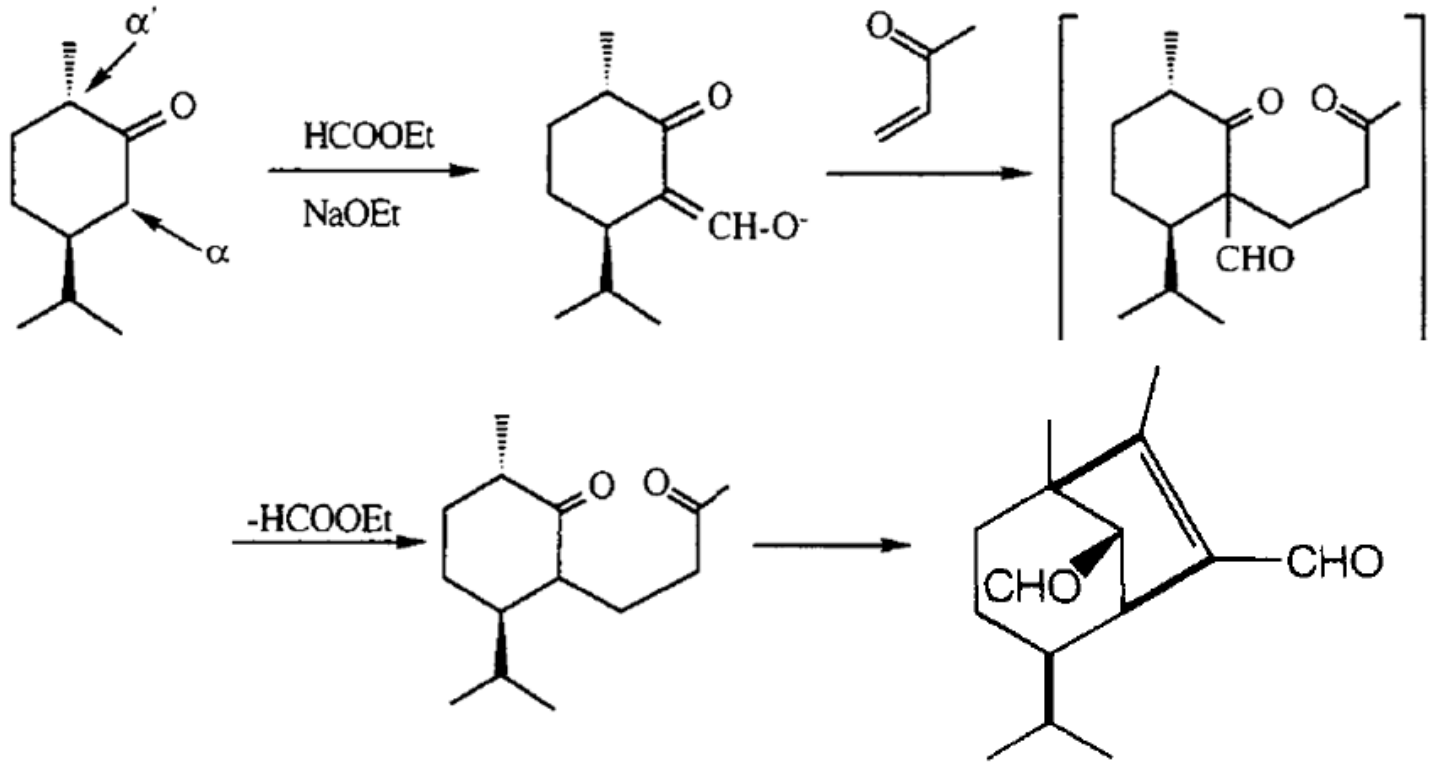
hydrogenation of alkyne



epoxy ring opening

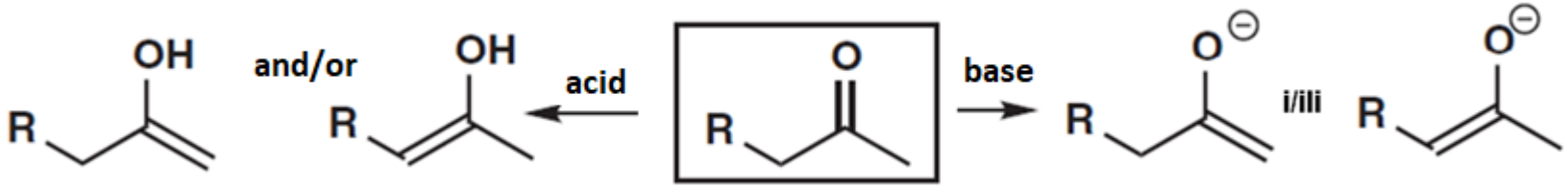
EXAMPLE – ACTIVATING GROUP

❖ the α-position is activated by the introduction of a formyl group



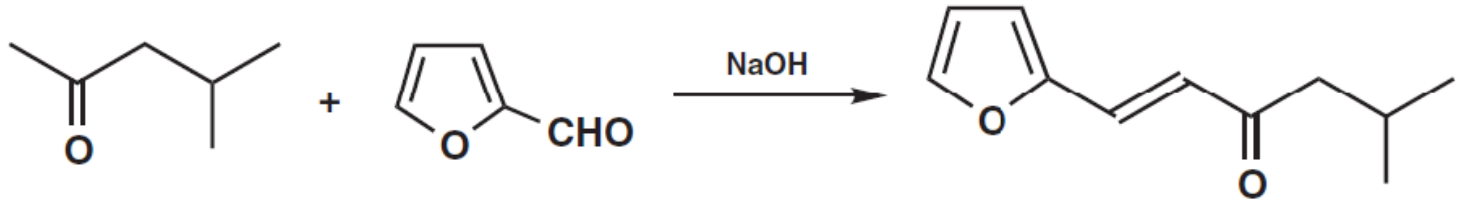
Regioselectivity in enols and enolates

- **aldol reactions** - enol or enolate of one carbonyl compound reacts with another carbonyl compound

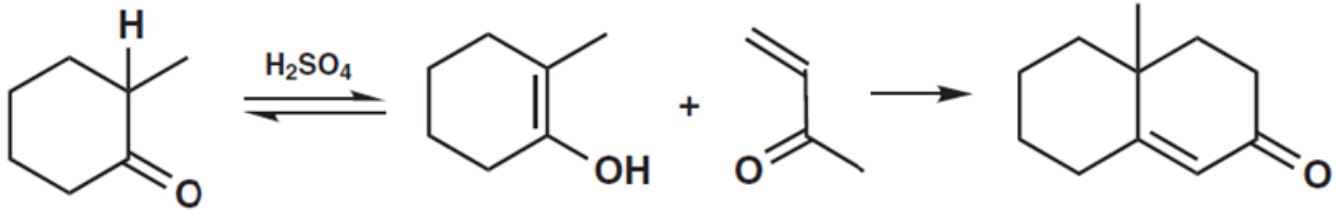


Regioselectivity controlled by reaction conditions

- methyl group is more acidic due to weak electron donor character of alkyl group - kinetic control

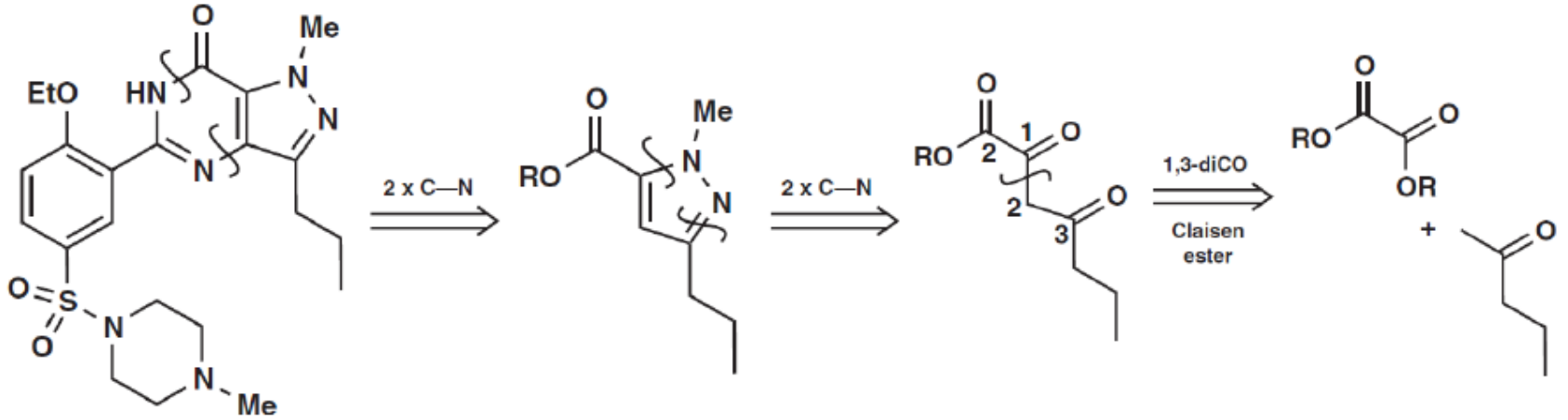


- thermodynamic control - Robinson's annealing



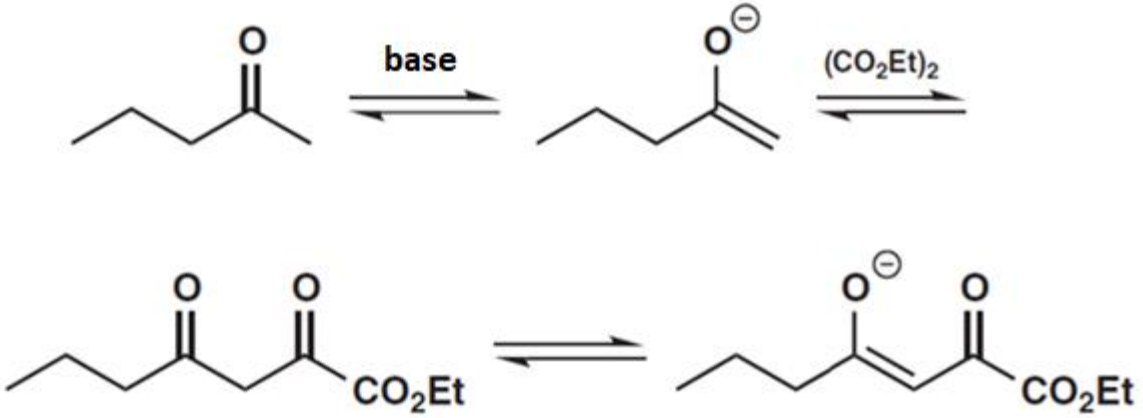
Example

Retrosynthesis:



Sildenafil (Viagra™)

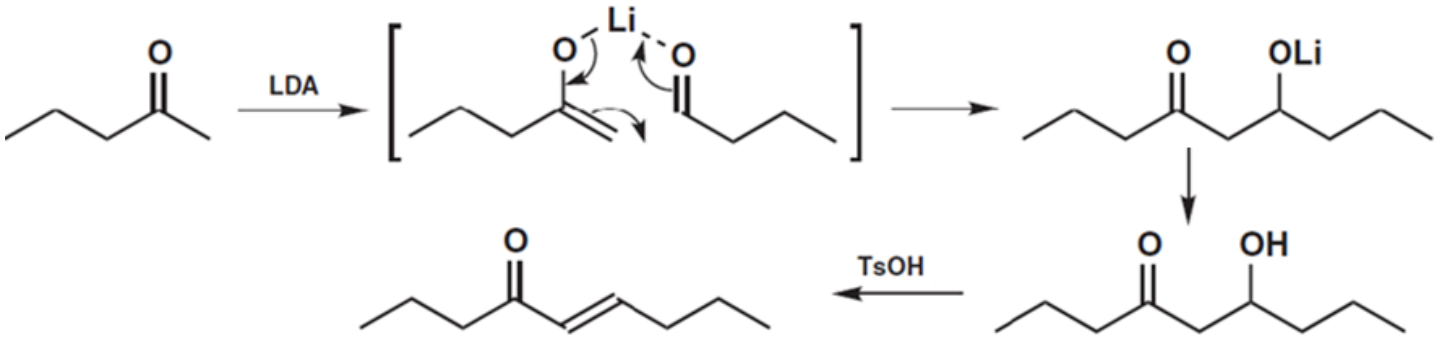
Synthesis:



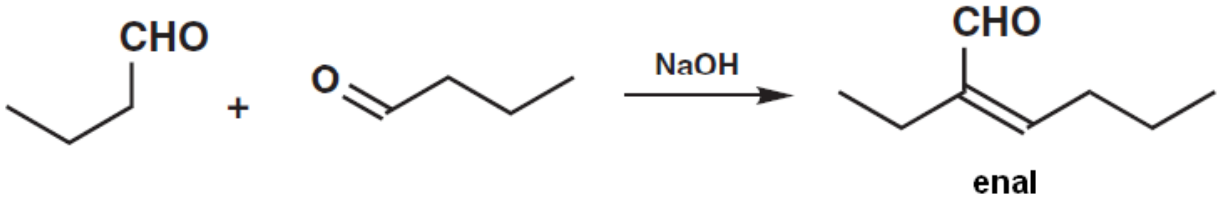
Regioselective aldol reactions

Aldol reactions with specific enol equivalents

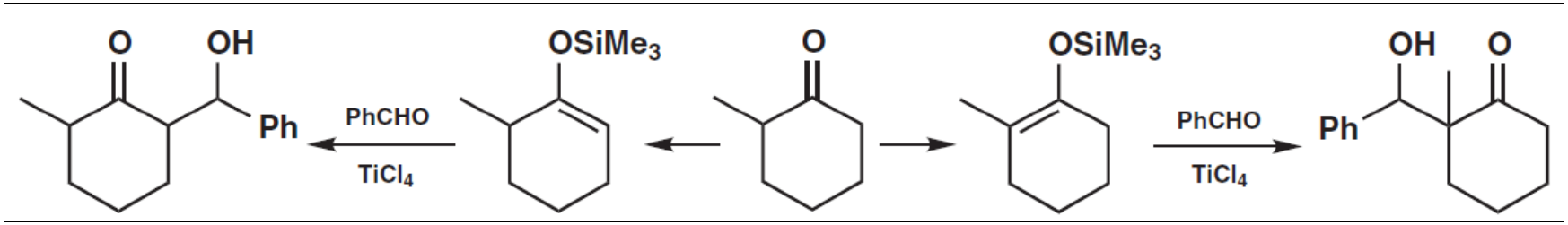
❖ lithium enolates can be used directly in aldol reactions



❖ by the traditional method with NaOH an enal will be formed

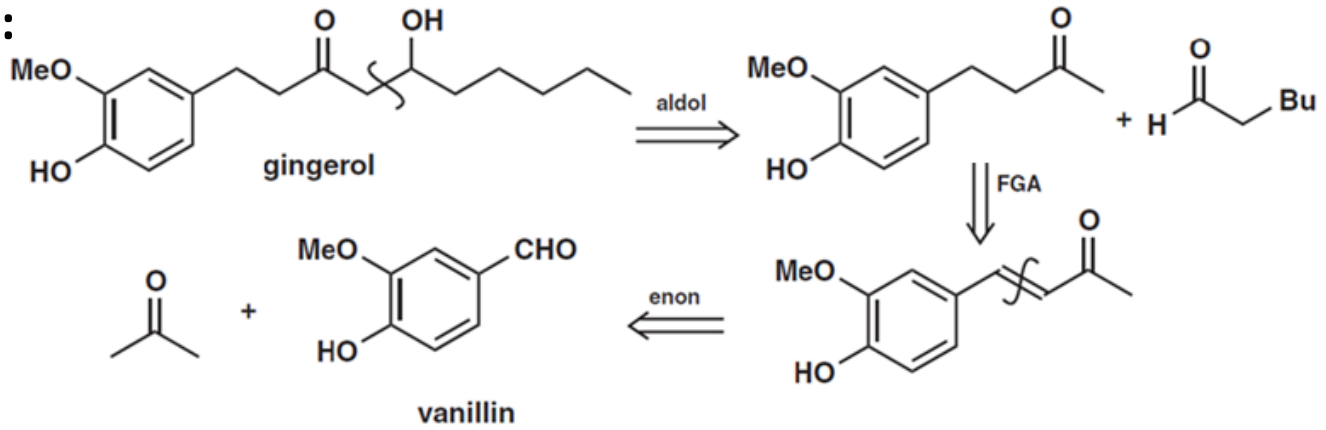


Aldol reactions catalyzed by Lewis acids

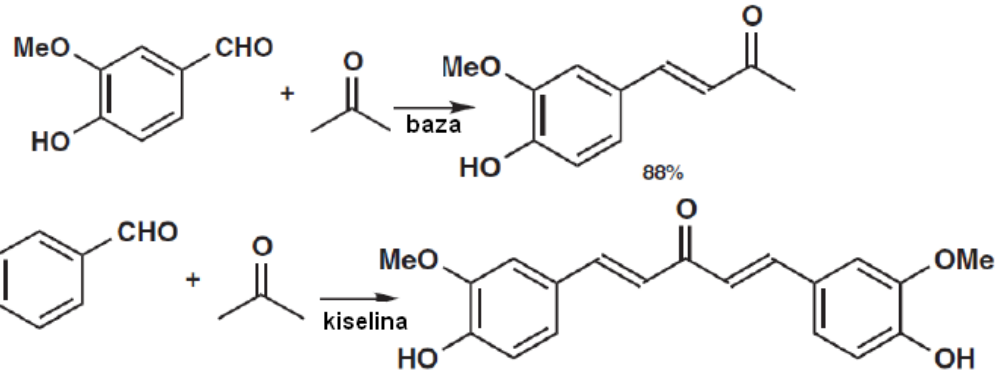


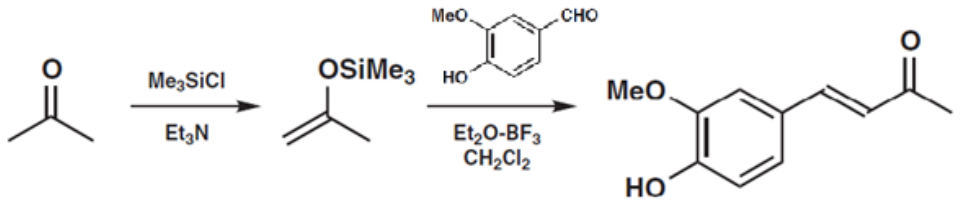
Example

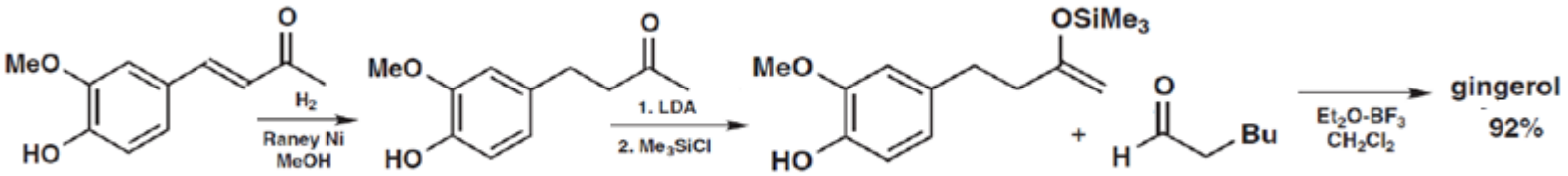
Retrosynthesis:



Synthesis:





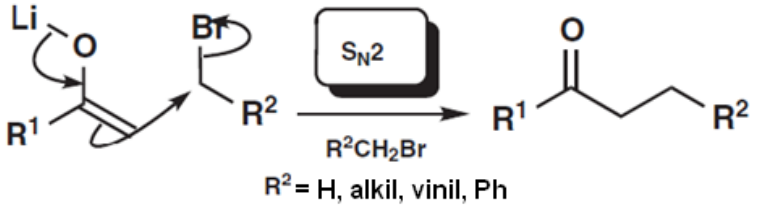


Reaction on a C or O atom?

- enols, enolates and their equivalents have two nucleophilic sides, the corresponding carbon atom or heteroatom (O, Li, Si)

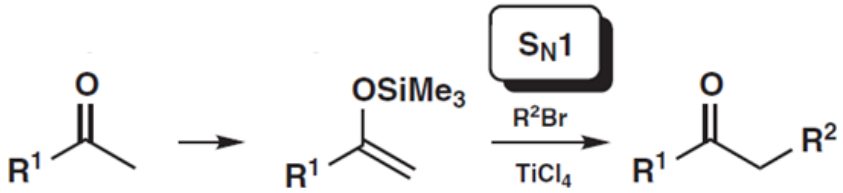
Alkylation on a carbon atom

- C-alkylation with lithium enolates



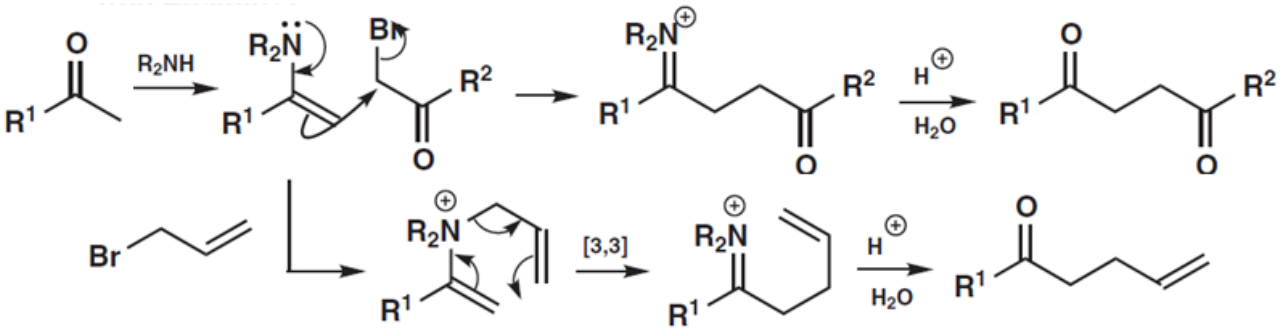
R² = H, alkil, vinil, Ph

- C-alkylation with silyl-enol ethers



R² = t-alkil, alil, benzil

- C-alkylation with enamines
  - enamines react with α-halocarbonyl compounds to give 1,4-dicarbonyl products and with allyl halides by reacting N atoms to give γ, δ-unsaturated ketones



University of Zagreb
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Study programme Chemical and Environmental Technology

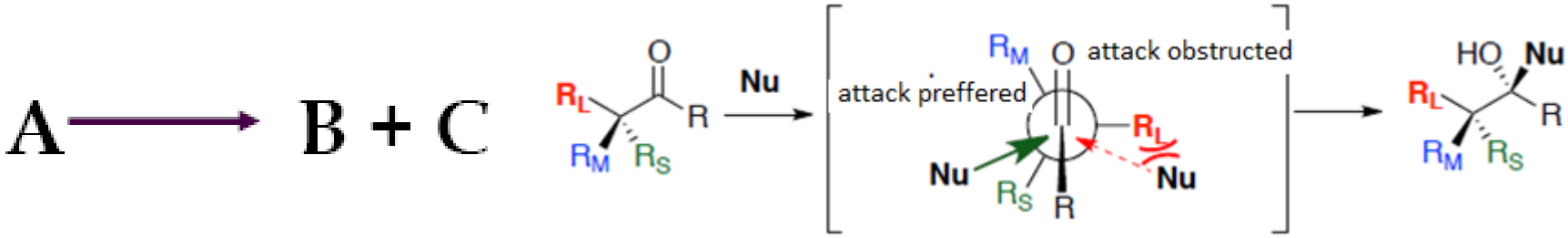
STEREOSELECTIVITY

Prof. Marijana Hranjec, PhD

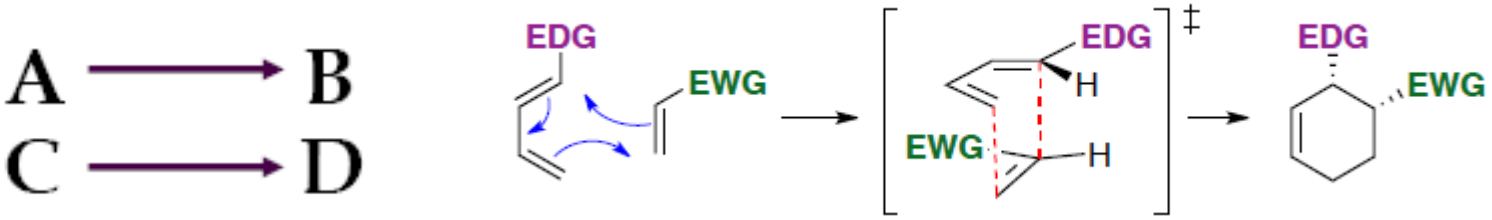
Academic year 2024/2025

INTRODUCTION

- **STEREOSELECTIVITY -** at first view it is the easiest to understand
- control of stereochemistry, more precisely “new” stereochemistry
- in many chemical reactions that lead to the formation of new C-C and C = C bonds and increase the molecular structure, a "new" stereochemistry appears
- very important in modern organic chemistry
- **stereoselective reactions -** one or mostly one stereoisomer is formed



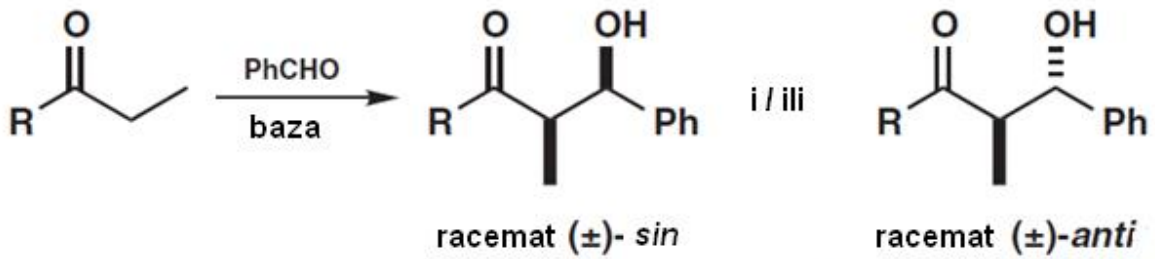
- **stereospecific reactions** - different stereoisomers of the starting compound give different stereoisomeric products; only one stereochemical outcome is possible



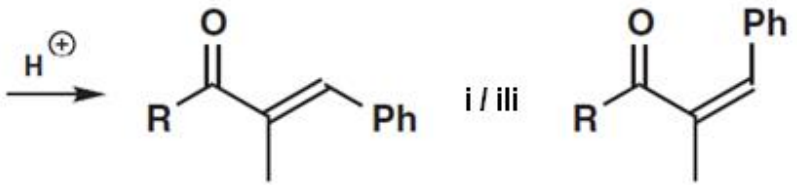
STEREOCHEMISTRY OF ALDOL REACTIONS

Stereochemical control: syn, anti, E and Z

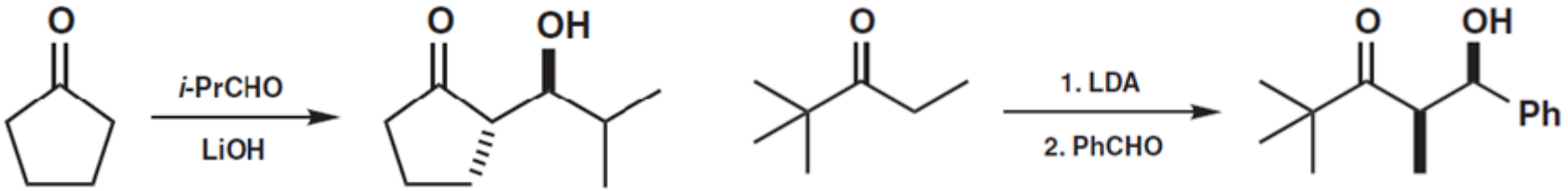
- aldol reactions usually give rise to new stereogenic centers



racemat (±)- *sin* racemat (±)-*anti*

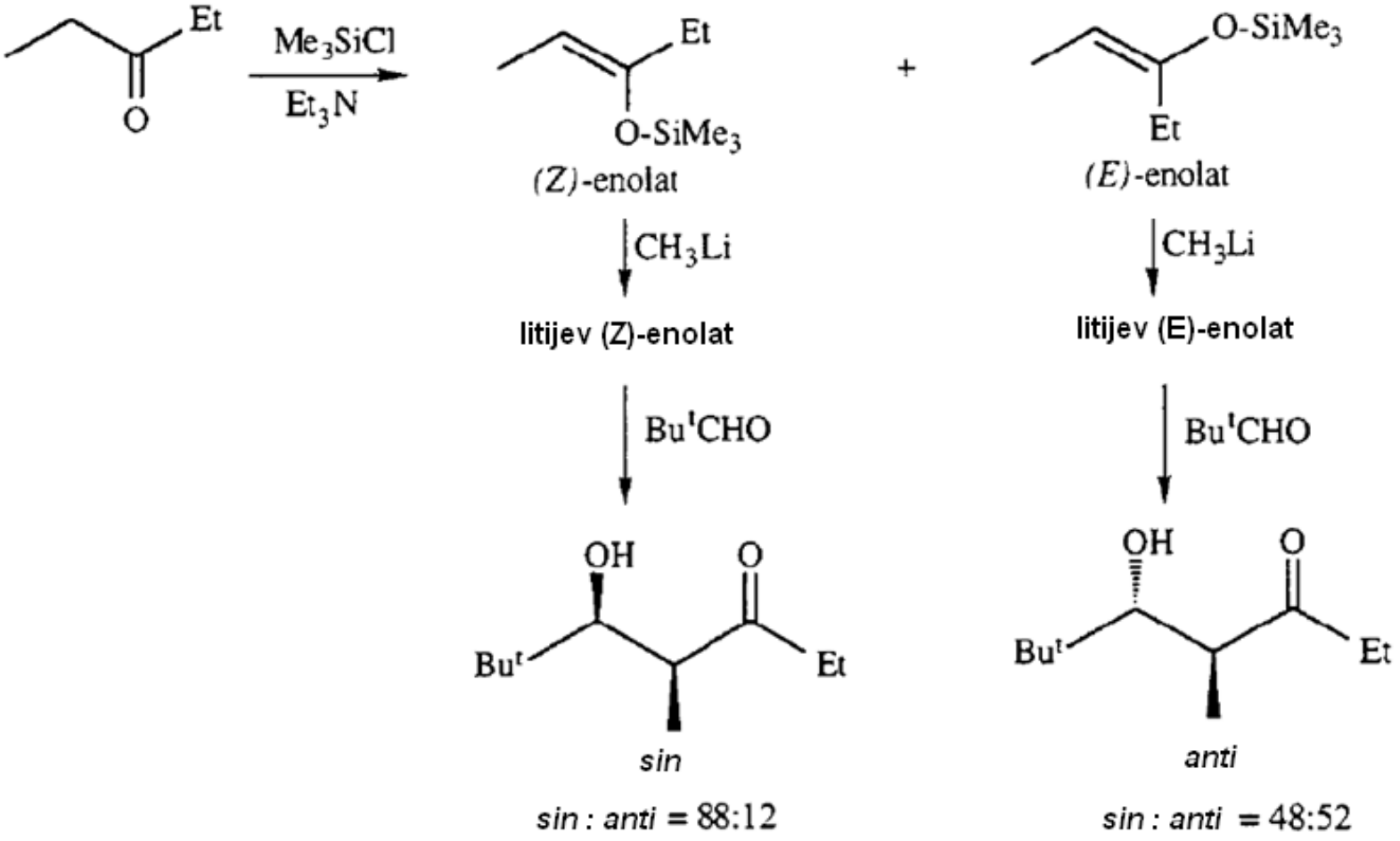


E- *Z*-



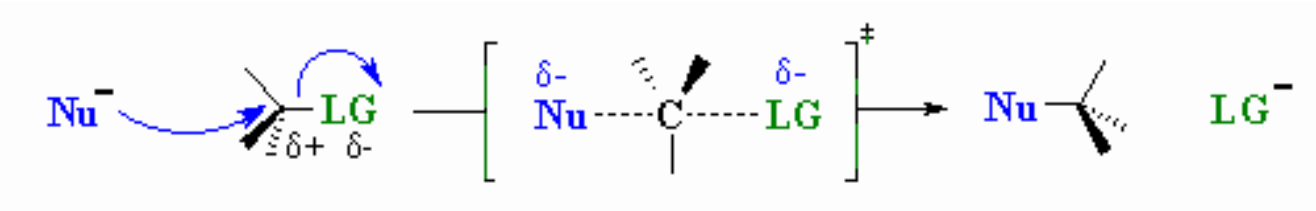
anti- *sin*-

STEREOCHEMISTRY OF ALDOL REACTIONS

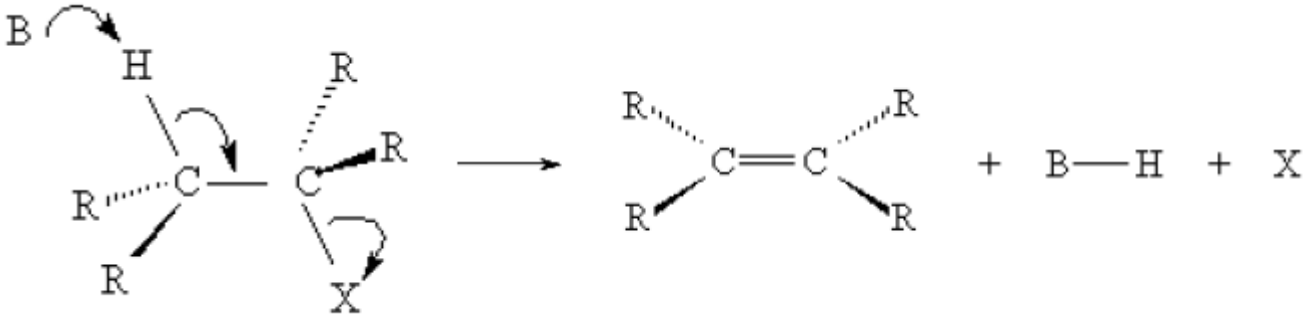


OVERVIEW OF STEREOSPECIFIC REACTIONS

1. S_N2-substitution - inversion at the chiral center

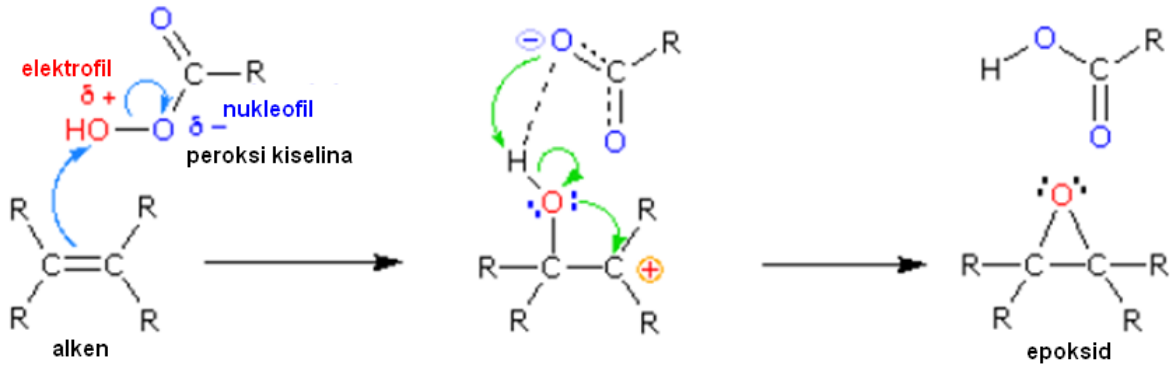


2. E2-eliminations - antiperiplanar position H and X



3. Electrophilic additions to alkenes

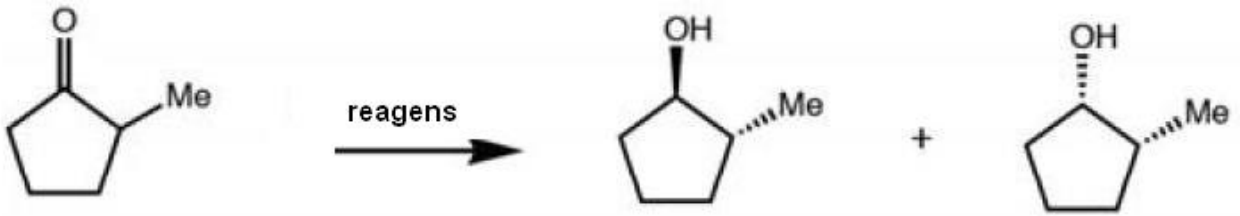
- ✓ **bromination – *trans* addition**
- ✓ **epoxidation – *cis* addition**
- ✓ **hidroxylation – *cis* addition (OsO_4)**
- ✓ ***trans*-addition (R-COOH, H_2O**
- ✓ **hidrogenation – *cis* addition**
- ✓ **partitions - an inversion on the atom where the group migrates**



OVERVIEW OF STEREOSPECIFIC REACTIONS

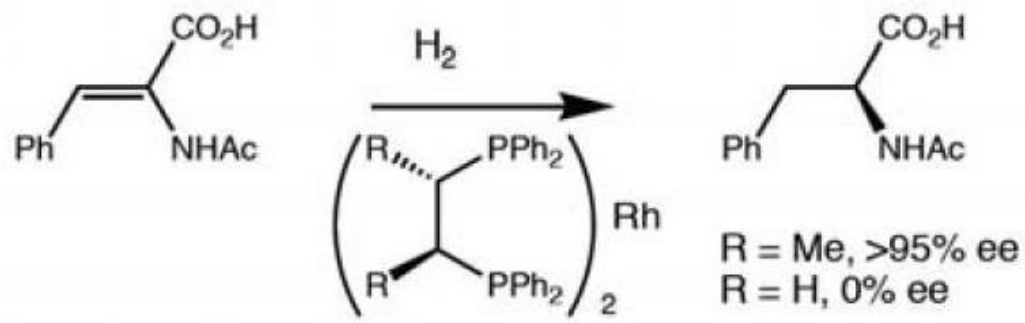
- give substantially one enantiomer of a possible two or one diastereoisomer of several possible diastereoisomers
- the most favourable path can be selected - kinetic control or the most stable product - thermodynamic control

diastereoselective reaction

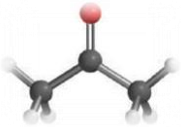


reagens	*trans/cis*
$NaBH_4$	74/26
$LiEt_3BH$	2/98

enantioselective reaction



Learning outcomes of the teaching unit



- ✓ understand the basic concepts related to selectivity
- ✓ understand the concept of chemoselectivity
- ✓ understand the notion of stereoselectivity
- ✓ understand the notion of regioselectivity
- ✓ be able to assess what selectivity is at stake
- ✓ to know the stereospecific reactions