به نام خدا

دانشگاه گیلان

روشهای سنتز مواد آلی

1

References:

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Synthesis

(from the Greek word synthesis [***Suntithenai***] = [***Sun****(together) +* ***tithenai****(to put)*]= the process of putting together)

Synthetic chemistry

- synthetic organic chemistry
- synthetic inorganic chemistry

is the science of constructing molecules from atoms and/or (usually) simpler molecules.

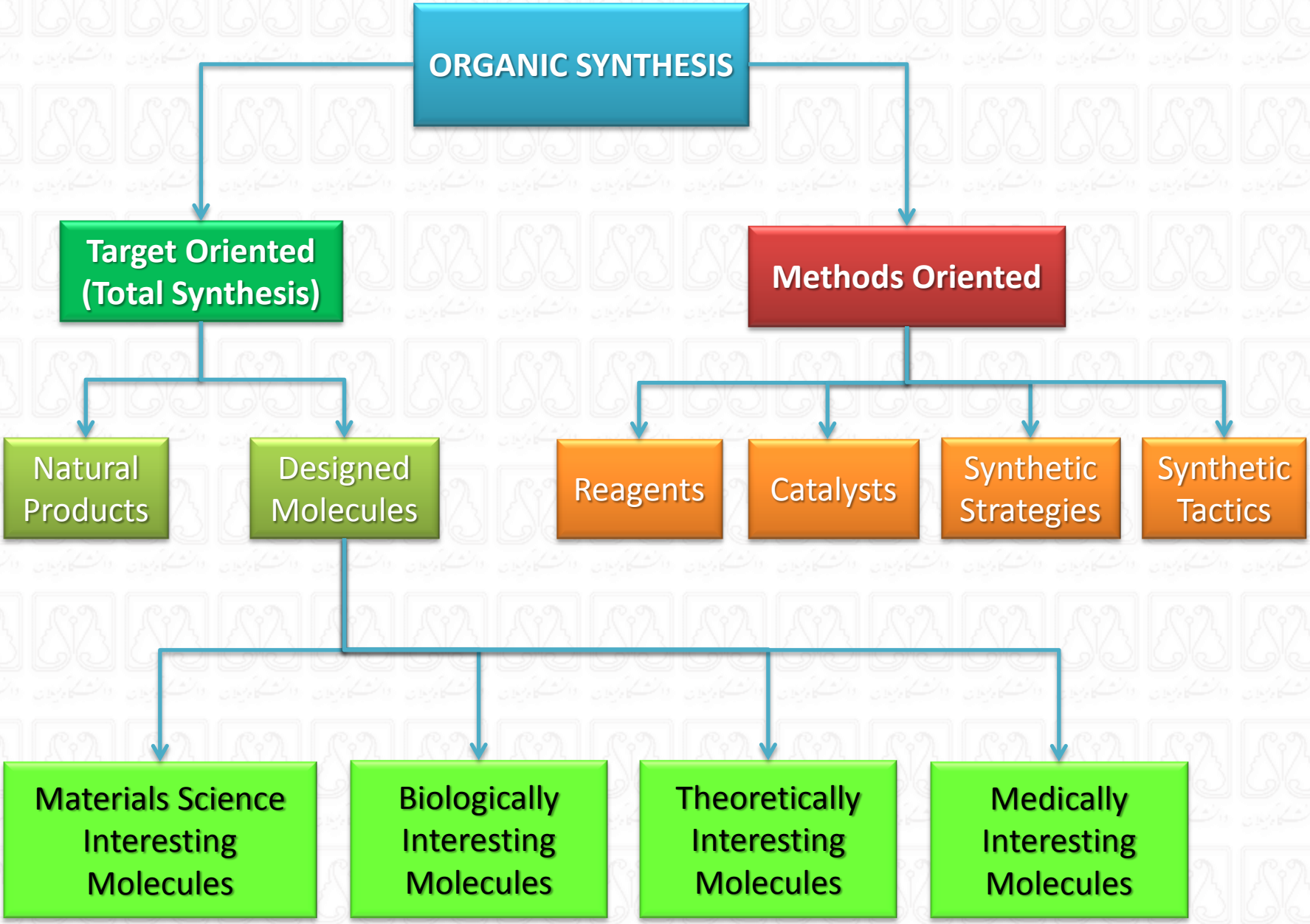
organic synthesis

synthetic organic chemistry

science of synthetic chemistry

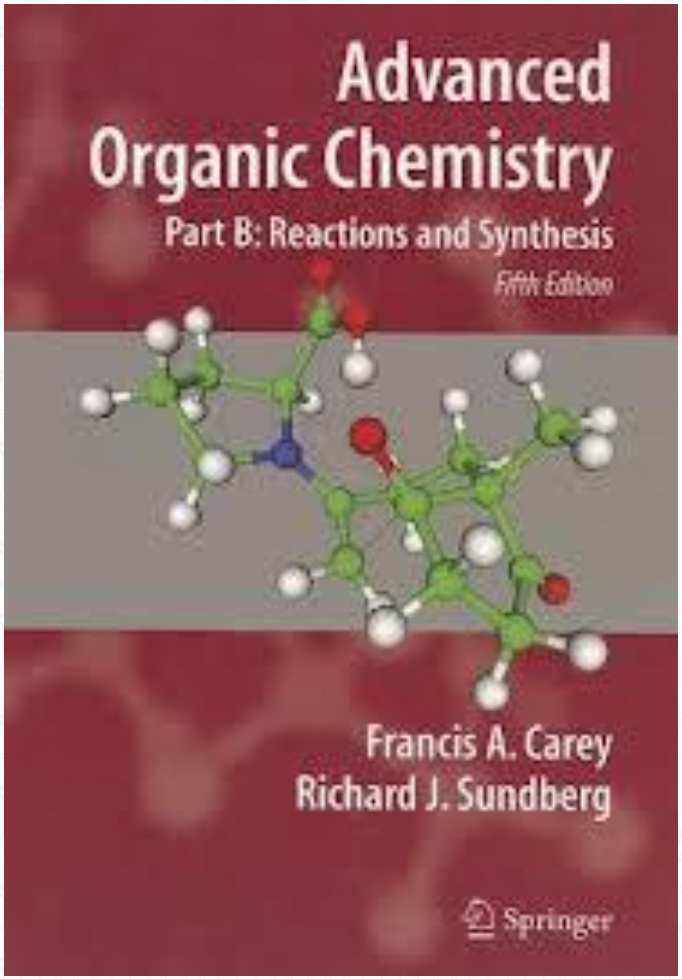
chemical synthesis is the process by which a particular molecule is synthesized in the laboratory.

total synthesis is the chemical synthesis of a molecule, usually a natural product, from relatively simple starting materials


ORGANIC SYNTHESIS
Target Oriented (Total Synthesis)
Methods Oriented
Natural Products
Designed Molecules
Reagents
Catalysts
Synthetic Strategies
Synthetic Tactics
Materials Science Interesting Molecules
Biologically Interesting Molecules
Theoretically Interesting Molecules
Medically Interesting Molecules

ORGANIC SYNTHESIS

1. **Design of synthesis**
   a. Initial consideration in synthesis design
      - Carbon skeleton
      - Functional skeleton
   b. The retro-synthetic approach
   c. Starting materials
   d. Yield and reaction specificity
2. **Constraction reactions**
   a. Half-reactions and recognition patterns
   b. Annelation reactions
   c. Fragmentation reactions
3. **Functional group interconversions**
   a. Altering functional groups
   b. Removing functional groups
   c. Selectivity
   d. Protecting groups
4. **Stereochemistry**



Advanced Organic Chemistry

FIFTH EDITION

Part B: Reactions and Synthesis

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Charlottesville, Virginia

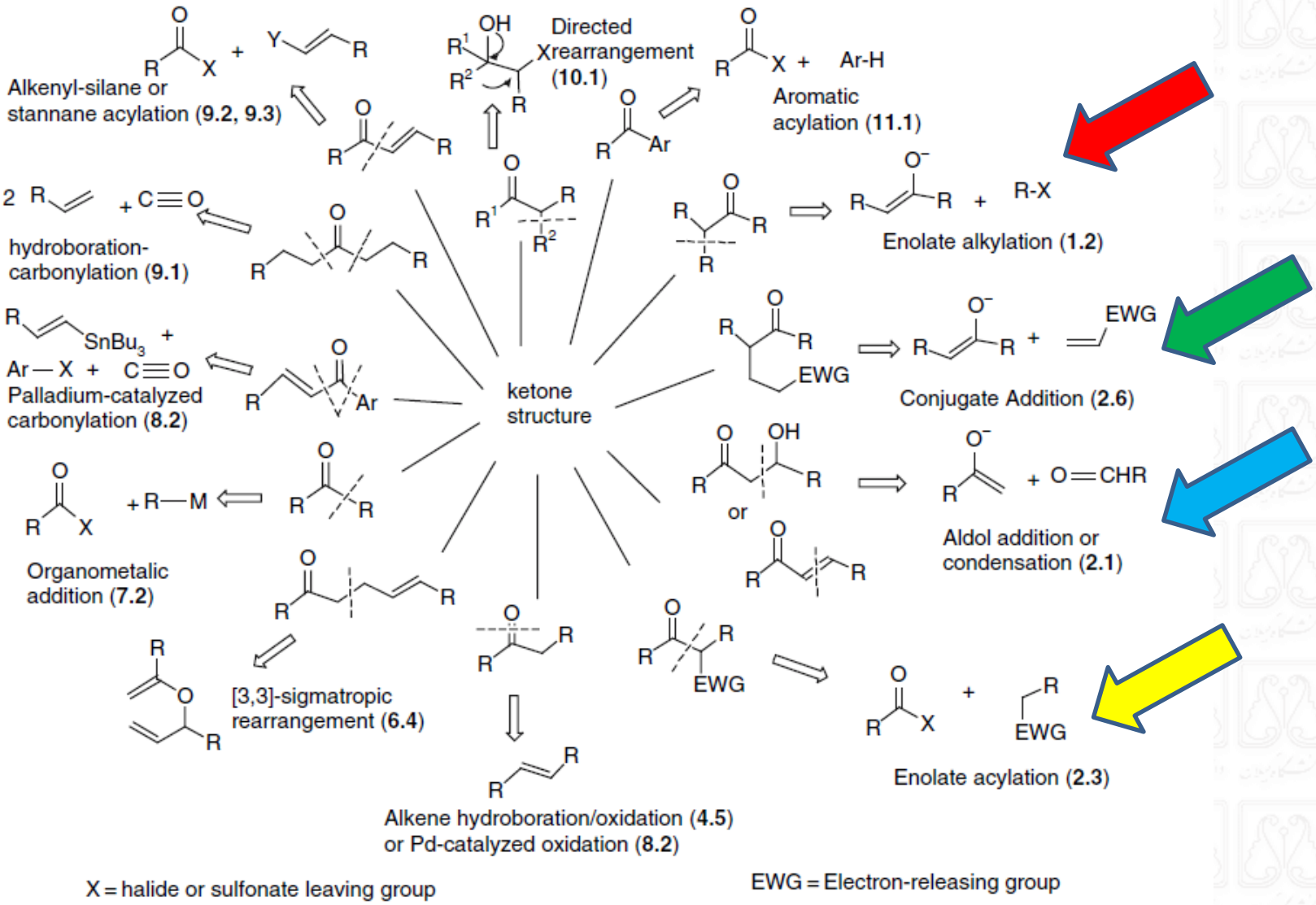
Springer

The focus of Part B is on the closely interrelated topics of *reactions* and *synthesis*.

We want to be able to answer questions such as:

- What transformation does a reaction achieve?
- What is the mechanism of the reaction?
- What reagents and reaction conditions are typically used?
- What substances can catalyze the reaction?
- How sensitive is the reaction to other functional groups and the steric environment?
- What factors control the stereoselectivity of the reaction?
- Under what conditions is the reaction enantioselective?

For example, in the course of learning about the reactions in Chapter 1 to 12, we will encounter a number of ways of making ketones, as outlined in the scheme that follows.



Part B emphasizes the most important reactions used in organic synthesis. The material is organized by reaction type.

Chapters 1 and 2 discuss the alkylation, conjugate addition and carbonyl addition/condensation reactions of enolates and other carbon nucleophiles.

1

Alkylation of Enolates and Other Carbon Nucleophiles

Chapter 1. Alkylation of Enolates and Other Carbon Nucleophiles

Introduction

1.1. Generation and Properties of Enolates and Other Stabilized Carbanions

1.1.1. Generation of Enolates by Deprotonation

1.1.2. Regioselectivity and Stereoselectivity in Enolate Formation from Ketone and Esters

1.1.3. Other Means of Generating Enolates

1.1.4. Solvent Effects on Enolate Structure and Reactivity

1.2. Alkylation of Enolates

1.2.1. Alkylation of Highly Stabilized Enolates

1.2.2. Alkylation of Ketone Enolates

1.2.3. Alkylation of Aldehydes, Esters, Carboxylic Acids, Amides, and Nitriles

1.2.4. Generation and Alkylation of Dianions

1.2.5. Intramolecular Alkylation of Enolates

1.2.6. Control of Enantioselectivity in Alkylation Reactions

1.3. The Nitrogen Analogs of Enols and Enolates: Enamines and Imine Anions

Introduction

- **C-C bond formation** is the basis for the construction of the molecular framework of organic molecules by synthesis.

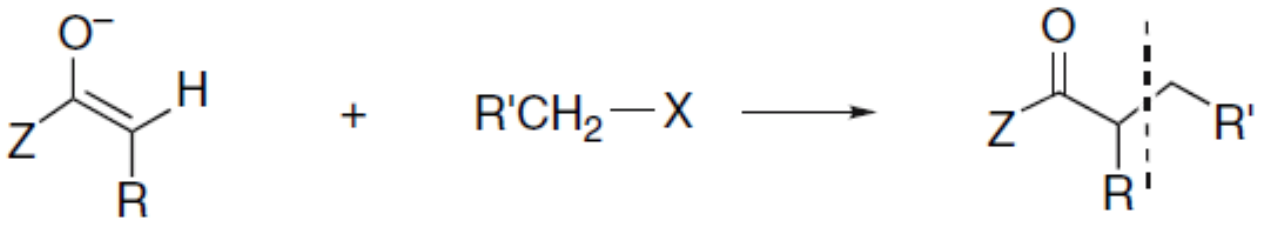
- One of the fundamental processes for C-C bond formation is a reaction **between a nucleophilic and an electrophilic carbon**.

- Reactions of C-nucleophile(*enolates*, *imine anions*, and *enamines*) with *alkylating agents*.

Crucial Factor for C-C bond formation by S_N2 reaction

- (1) the condition for generation of the carbon nucleophile
- (2) the effect of the reaction conditions on the structure and reactivity of the nucleophile
- (3) the **regio- and stereoselectivity** of the alkylation reaction

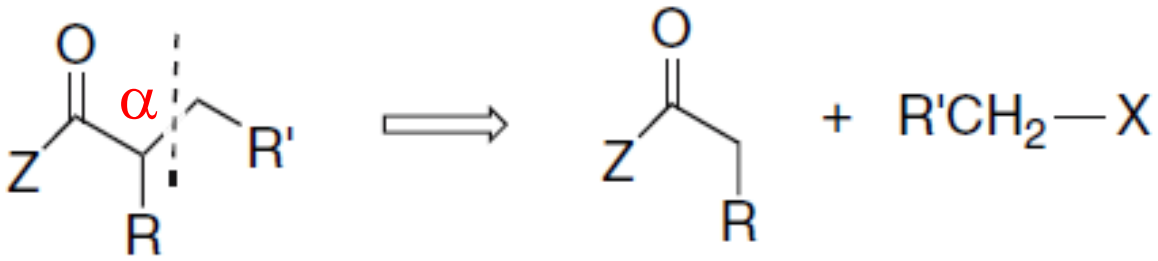
The reaction can be applied to various carbonyl compounds, including ketones, esters, and amides.



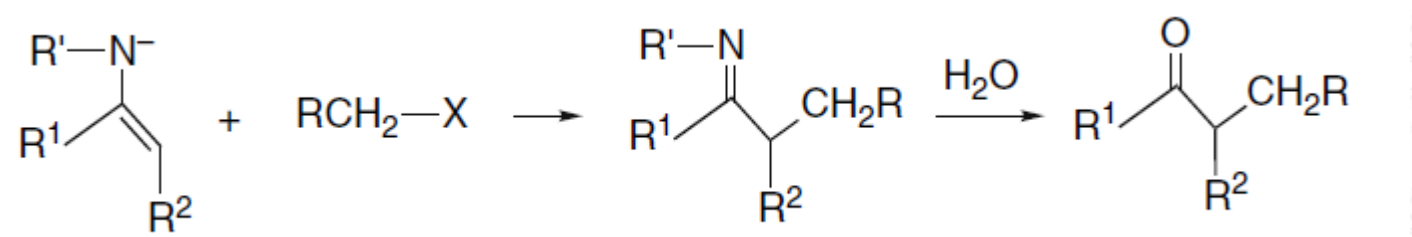
Z = R, RO, R_2N enolate alkylation

Ketones esters amides

In the retrosynthetic sense, the disconnection is between the α-carbon and a potential alkylating agent.



The alkylated imines can be hydrolyzed to the corresponding ketone



imine anion

imine

Either enolate or imine anions can be used to introduce alkyl α-substituents to a carbonyl group.

1.1. Generation and Properties of Enolates and Other Stabilized Carbanions

1.1.1. Generation of Enolates by Deprotonation

- In the present chapter we relate the properties and reactivity of carbanions stabilized by carbonyl and other EWG substituents to their application as nucleophiles in synthesis
- there is a fundamental relationship between the stabilizing functional group and the acidity of the C–H groups, as illustrated by **the pK data**

1) pK data ⇨ the stability and reactivity of carbanions.

(The acidity of the reactant determines which bases can be used for generation of the anion.)

2) distinction between

kinetic or thermodynamic control

of enolate formation by deprotonation

⇨ which determines the enolate composition.

Generation of an enolate or other stabilized carbanion by deprotonation

- under conditions in which the enolate is *in equilibrium* with its conjugate acid or under which the reactant is *completely converted* to its conjugate base

(The key determinant is the amount and strength of the base)

- The base must be derived from a substantially weaker acid than the reactant.
- Or the reagent must be a stronger base than the anion of the reactant.
- Most current procedures for alkylation of enolates and other carbanions involve complete conversion to the anion.

- The **solvent** and other **coordinating or chelating additives** also have strong effects on the structure and reactivity of carbanions formed by deprotonation.

strongest acids

water and are appropriate for hydroxylic solvents.

Table 1.1. Approximate pK Values from Some Compounds with Carbanion Stabilizing Groups and Some Common Bases[a]

Compound	pK_{ROH}	pK_{DMSO}	Base	pK_{ROH}	pK_{DMSO}
$O_2NCH_2NO_2$	3.6		$CH_3CO_2^-$	4.2	11.6
$CH_3COCH_2NO_2$	5.1				
$CH_3CH_2NO_2$	8.6	16.7	HCO_3^-	6.5	
$CH_3COCH_2COCH_3$	9				
$PhCOCH_2COCH_3$	9.6		PhO^-	9.9	16.4
CH_3NO_2	10.2	17.2			
$CH_3COCH_2CO_2C_2H_5$	10.7	14.2	CO_3^{2-}	10.2	
$NCCH_2CN$	11.2	11.0	$(C_2H_5)_3N$	10.7	
$PhCH_2NO_2$		12.3	$(CH_3CH_2)_2NH$	11	
$CH_2(SO_2CH_3)_2$	12.2	14.4			
$CH_2(CO_2C_2H_5)_2$	12.7	16.4			
Cyclopentadiene	15		CH_3O^-	15.5	29.0
$PhSCH_2COCH_3$		18.7	HO^-	15.7	31.4
$CH_3CH_2CH(CO_2C_2H_5)_2$	15		$C_2H_5O^-$	15.9	29.8
$PhSCH_2CN$		20.8	$(CH_3)_2CHO^-$		30.3
$(PhCH_2)_2SO_2$		23.9	$(CH_3)_3CO^-$	19	32.2
$PhCOCH_3$	15.8	24.7			
$PhCH_2COCH_3$	19.9				
CH_3COCH_3	20	26.5			
$CH_3CH_2COCH_2CH_3$		27.1			
Fluorene	20.5	22.6			
$PhSO_2CH_3$		29.0			
$PhCH_2SOCH_3$	29.0		$[(CH_3)_3Si]_2N^-$	30[b]	
CH_3CN	25	31.3			
Ph_2CH_2		32.2			
Ph_3CH	33	30.6	NH_2^-	35	41
			$CH_3SOCH_2^-$	35	35.1
			$(CH_3CH_2)_2N^-$	36	
$PhCH_3$		43			
CH_4		56			

a. From F. G. Bordwell, *Acc. Chem. Res.*, **21**, 456 (1988).
b. In THF; R. R. Fraser and T. S. Mansour, *J. Org. Chem.*, **49**, 3442 (1984).

strongest bases

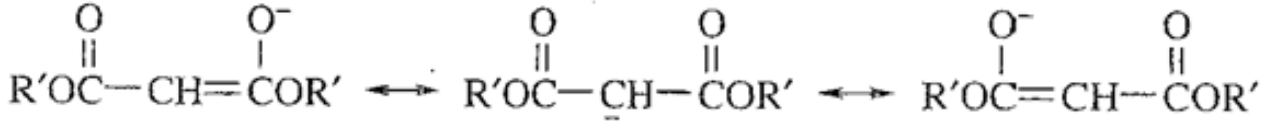
Ability to stablize carbanion:

$$NO_2 > COR > CN \sim CO_2R > SO_2R > SOR > Ph \sim SR > H > R.$$

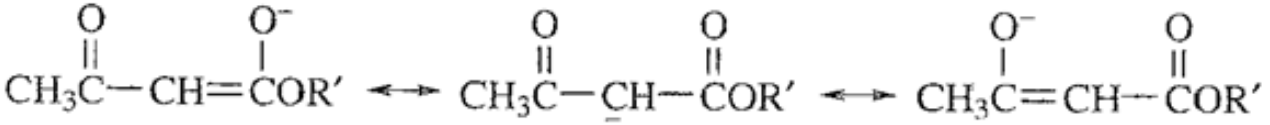
1 Enolate of ketone

2 Enolate of ester

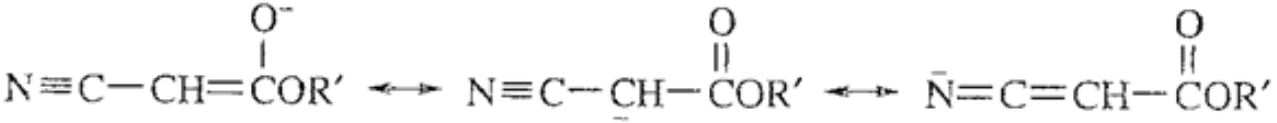
3 Malonic ester anion



4 Acetoacetic ester anion



5 Cyanoacetic ester anion



sodium or potassium alkoxides

1960

aprotic solvents THF

1- **lithium di-isopropylamide (LDA)**

2- anions of hexaalkyldisilylamines, especially **hexamethyldisilazan (LiHMDS, NaHMDS, and KHMDS).**

3- **lithium tetramethylpiperidide (LiTMP)**

4- **amide anion $^{-}NH_2$**

5- **conjugate base of DMSO ("dimsyl" anion)**

6- **triphenylmethyl anion**

7- **Sodium and potassium hydride NaH and KH**

For a carbon acid C−H and a base B−H,

$$K_{a_{(C-H)}} = \frac{[C^-][H^+]}{[C-H]} \text{ and } K_{a_{(B-H)}} = \frac{[B^-][H^+]}{[B-H]}$$

for the reaction

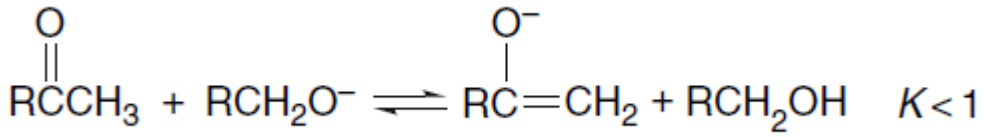
$$C-H + B^- \rightleftharpoons B-H + C^-$$

at equilibrium

$$\frac{K_{a_{(C-H)}}[C-H]}{[C^-]} = \frac{K_{a_{(B-H)}}[B-H]}{[B^-]}$$

$$K = \frac{[B-H][C^-]}{[C-H][B^-]} = \frac{K_{a_{(C-H)}}}{K_{a_{(B-H)}}}$$

By comparing the approximate p*K* values of the bases with those of the carbon acid of interest, it is possible to estimate the position of the acid-base equilibrium for a given reactant-base combination

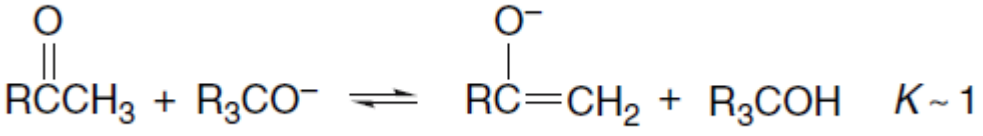


alkyl ketone

primary alkoxide ion

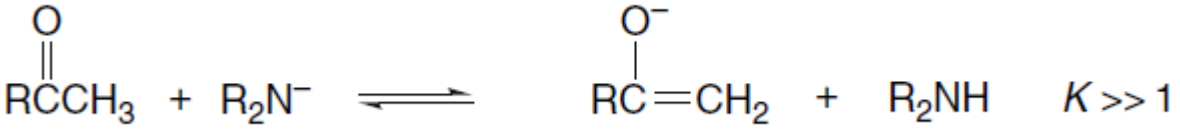
R= CH_3 p*K*= 20 p*K*= 16

convert only a fraction of a ketone to its anion



R= CH_3 p*K*= 20 tertiary alkoxide p*K*= 19

more favorable equilibrium will be established

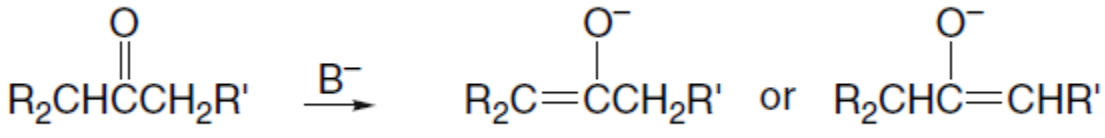


R= CH_3 p*K*= 20 amide bases R = $(CH_3)_2CH$ p*K*= 36

complete formation of the enolate occurs

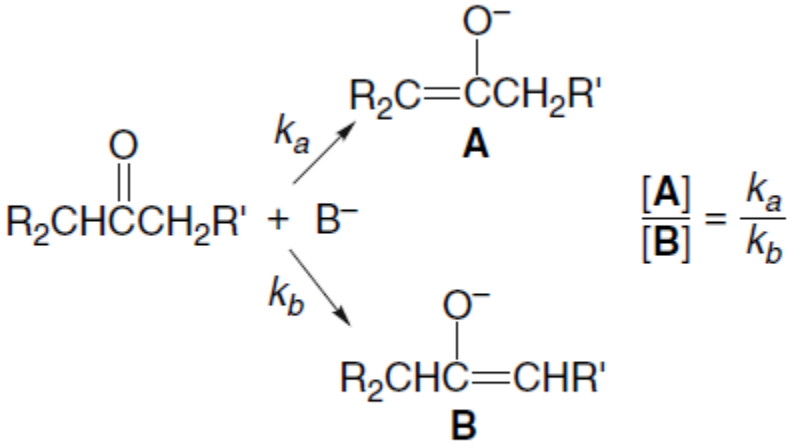
1.1.2. Regioselectivity and Stereoselectivity in Enolate Formation from Ketones and Esters

Deprotonation of carbonyl compound



unsymmetrical dialkyl ketone

two *regioisomeric* enolates



Kinetic control of isomeric enolate composition

By adjusting the conditions of enolate formation, it is possible to establish either kinetic or thermodynamic control.

Conditions for ***kinetic control*** *of enolate formation are those in which deprotonation is:*

- rapid,

- quantitative,

- and irreversible

This requirement is met ***experimentally*** *by using:*

- a very strong base such as LDA or LiHMDS

- in an aprotic solvent

- in the absence of excess ketone.

Lithium *is a better counterion than sodium or potassium for regioselective generation of the* ***kinetic enolate****,*
as it maintains a tighter coordination at oxygen and reduces the rate of proton exchange.

Use of an ***aprotic solvent*** *is essential*
because protic solvents permit enolate equilibration by reversible protonation-deprotonation,
which gives rise to the ***thermodynamically controlled*** *enolate composition.*

Excess ketone *also catalyzes the equilibration by proton exchange.*

*Conditions of **kinetic control** usually favor formation of the less substituted enolate, especially for methyl ketones.*

The main reason for this result is that

removal of a less hindered hydrogen is faster, for steric reasons, than removal of a more hindered hydrogen.

Steric factors in ketone deprotonation are accentuated by using bulky bases