

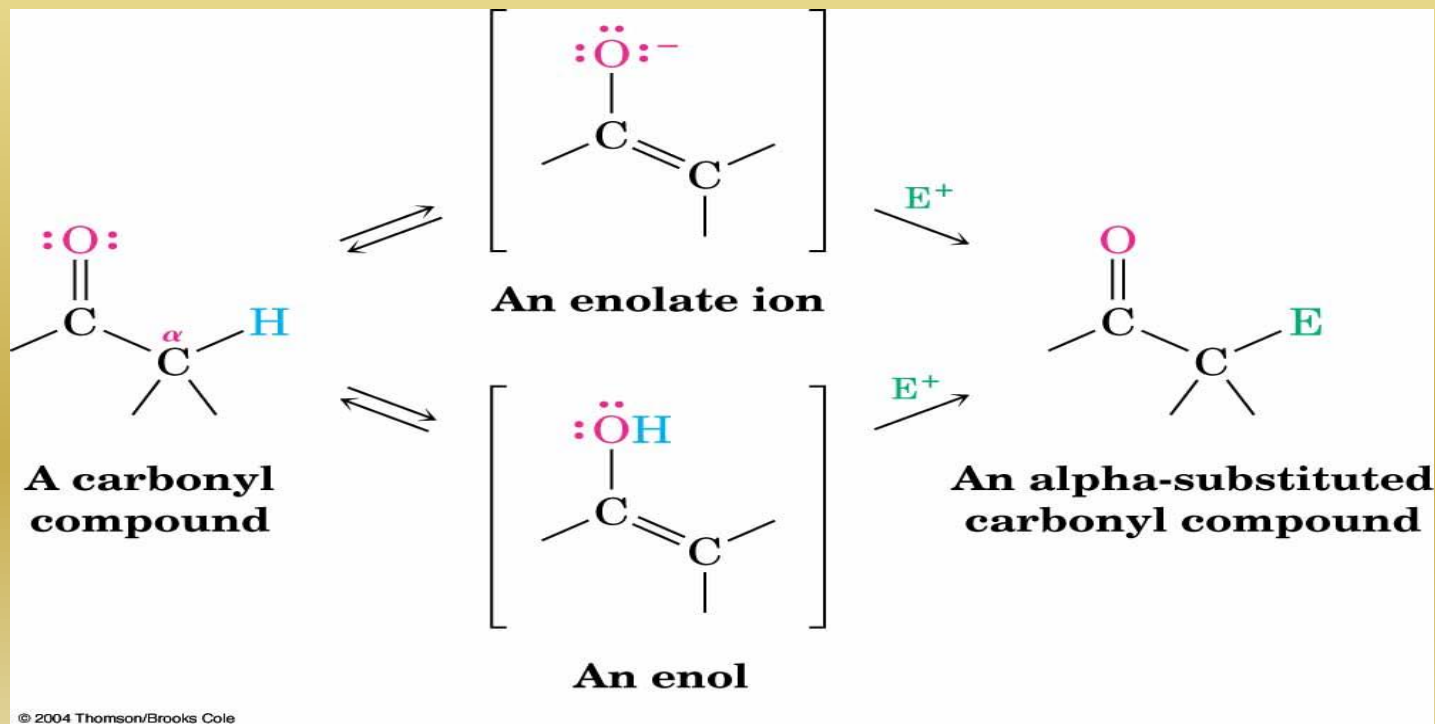


Carbonyl Alpha-Substitution Reactions

Based on McMurry's *Organic Chemistry*, 7th edition By
Jalal Hasan Mohammed 2014-2015

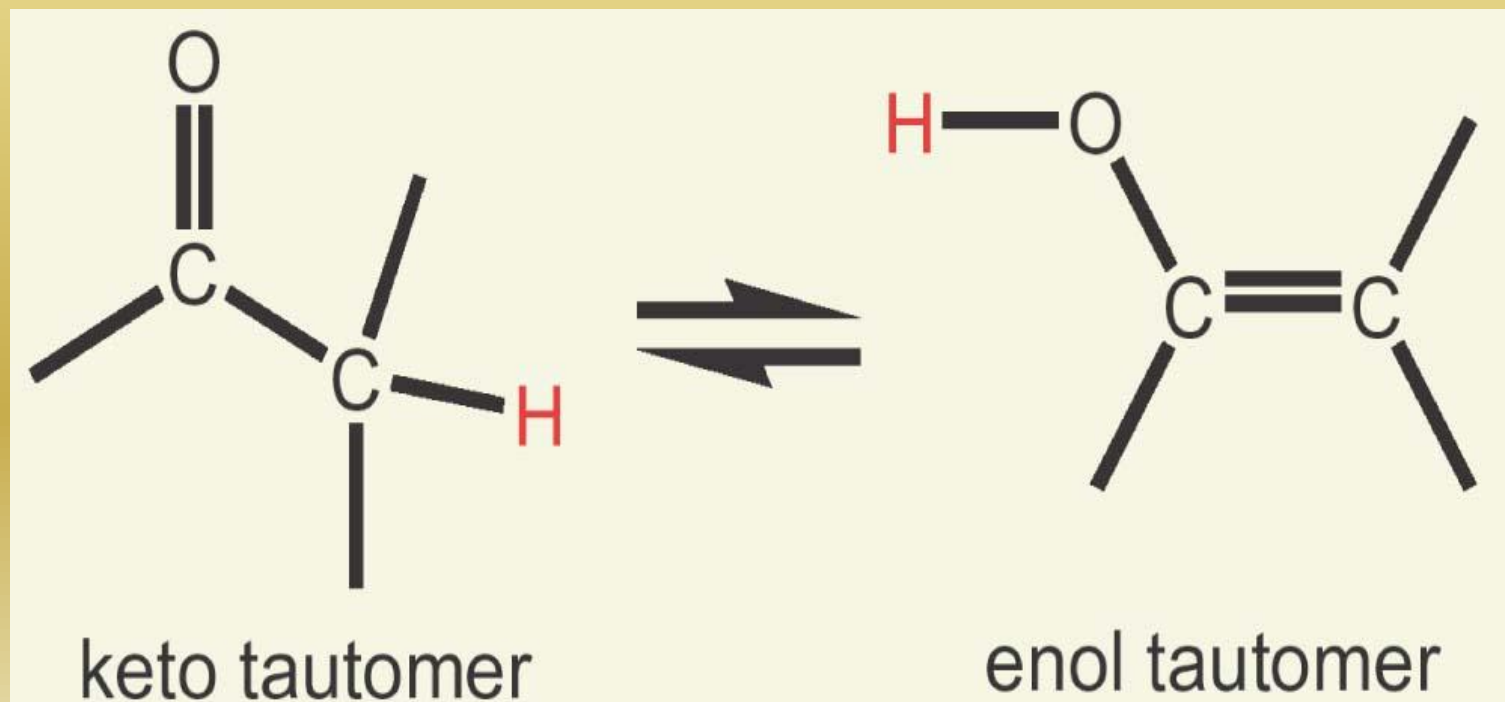
The α Position

- The carbon next to the carbonyl group is designated as being in the α position
- Electrophilic substitution occurs at this position through either an *enol* or *enolate ion*



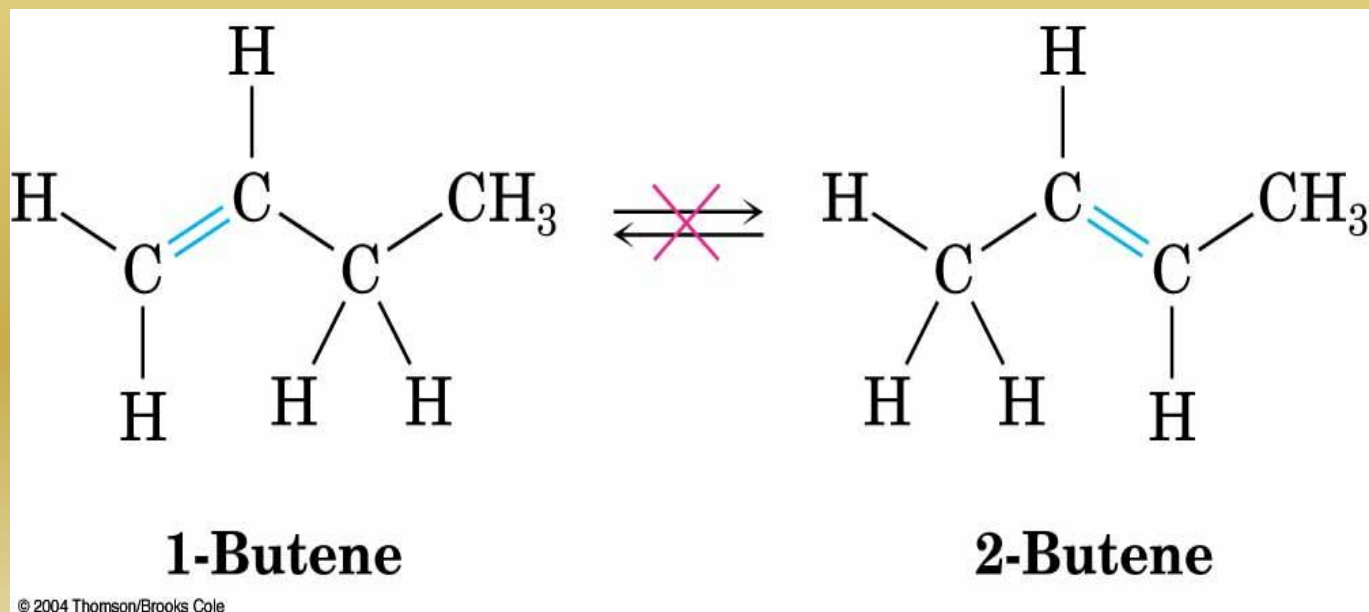
Keto–Enol Tautomerism

- A carbonyl compound with a hydrogen atom on its α carbon rapidly equilibrates with its corresponding enol
- Compounds that differ only by the position of a moveable proton are called tautomers



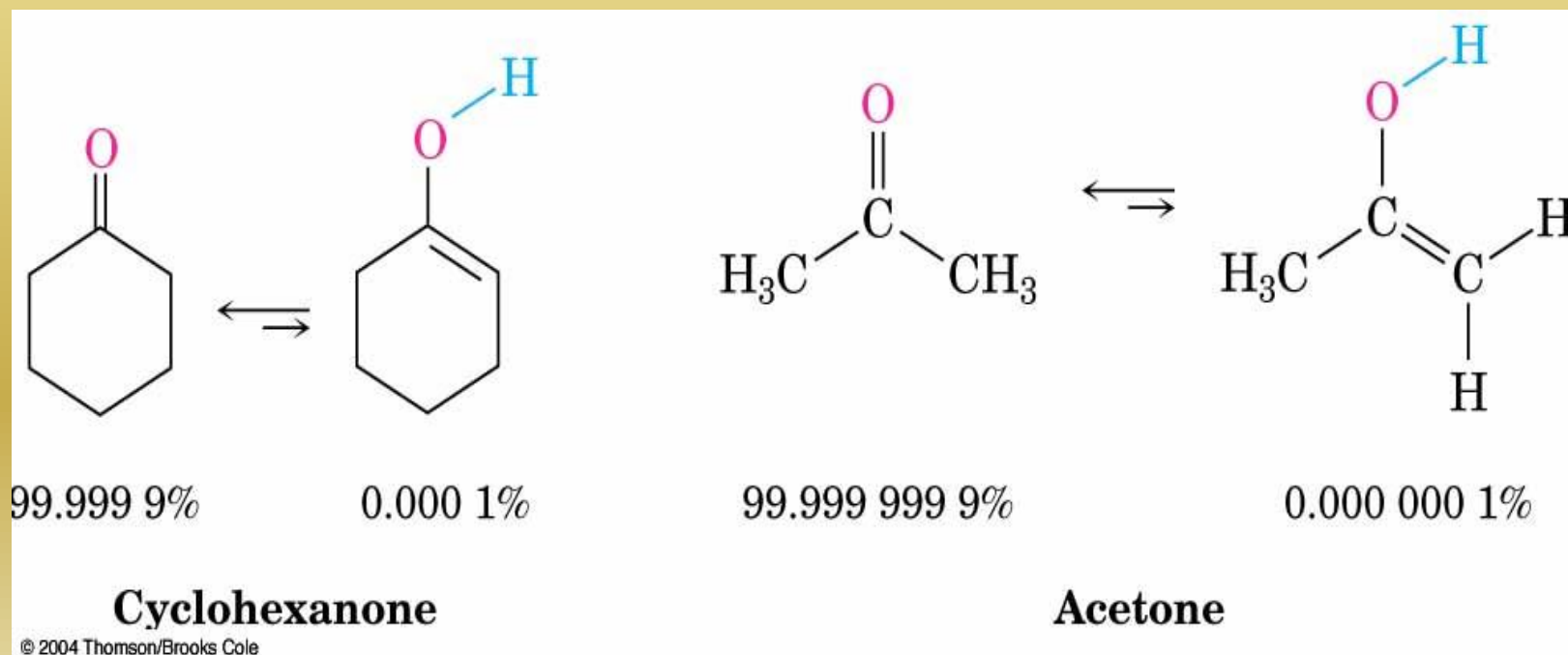
Tautomers Are Not Resonance Forms

- Tautomers are structural isomers
- Resonance forms are representations of contributors to a single structure
- Tautomers interconvert rapidly while ordinary isomers do not



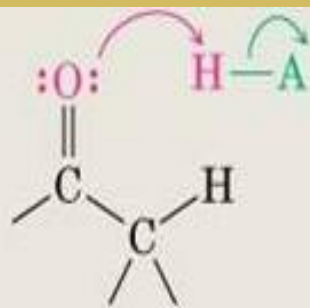
Enols

- The enol tautomer is usually present to a very small extent and cannot be isolated
- However, since it is formed rapidly, it can serve as a reaction intermediate

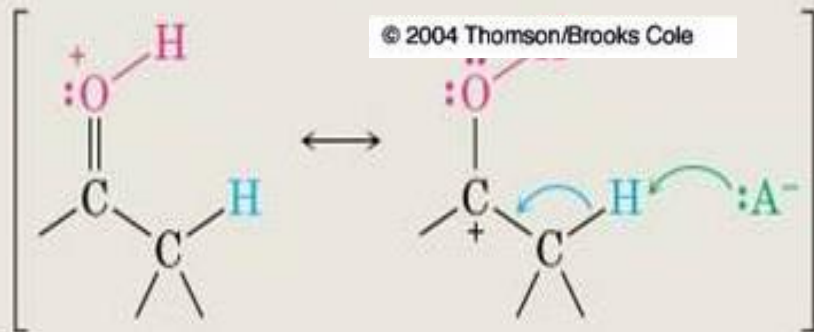


Acid Catalysis of Enolization

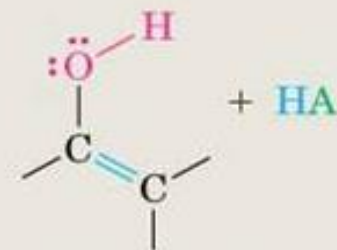
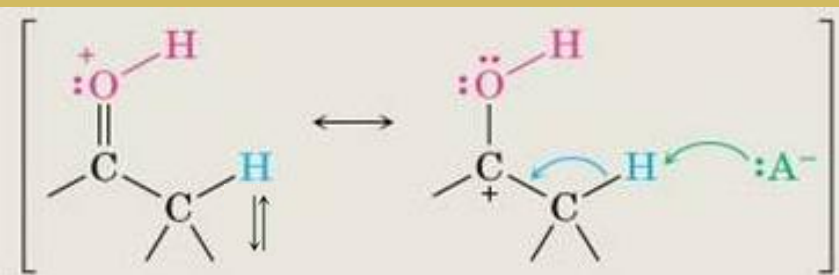
- Brønsted acids catalyze keto-enol tautomerization by protonating the carbonyl and activating the α protons



Keto tautomer

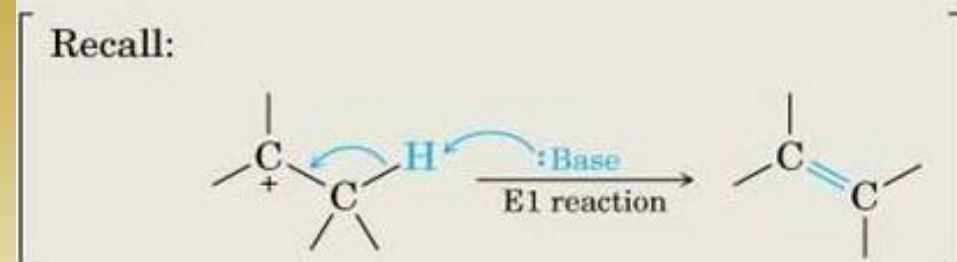


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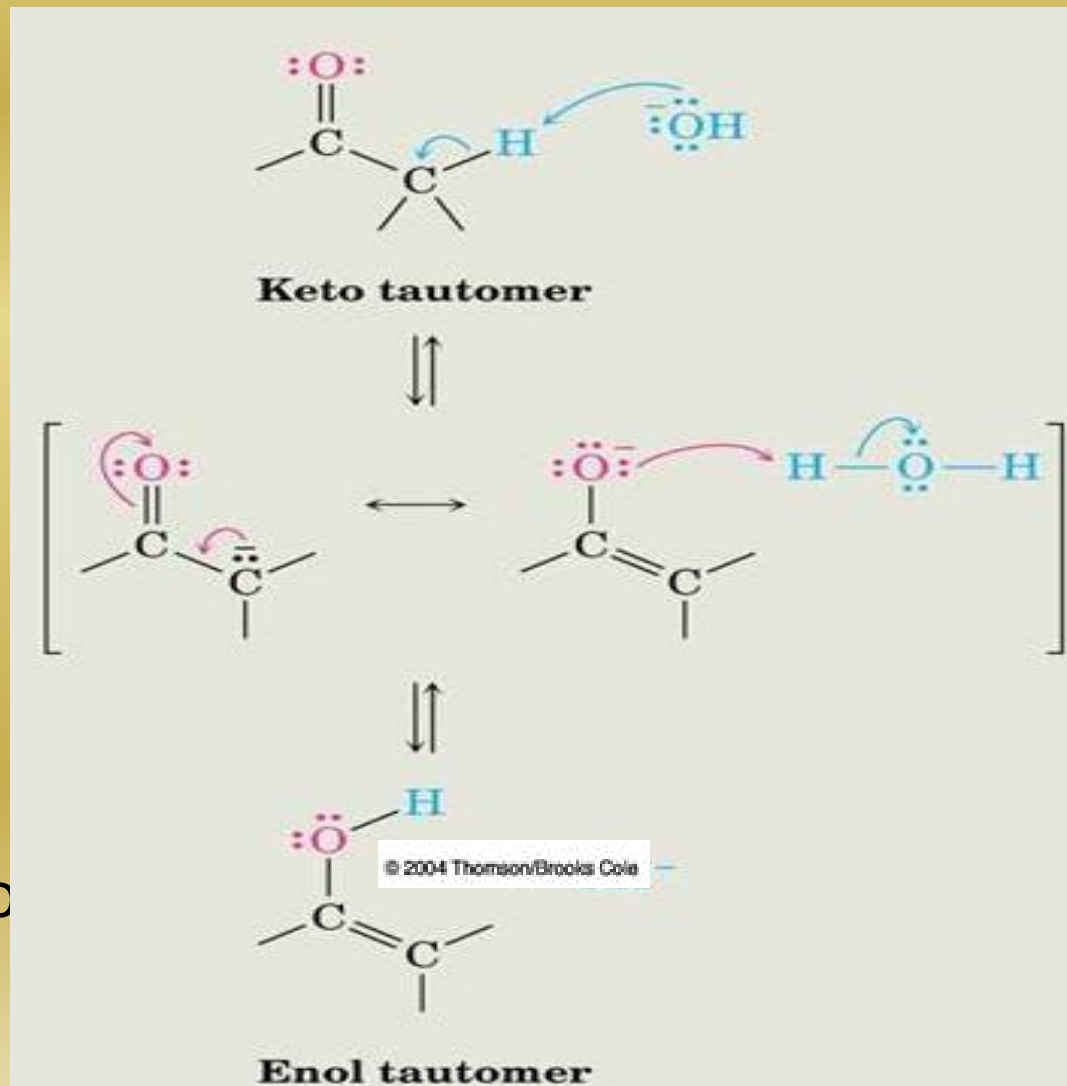
Enol tautomer

Recall:



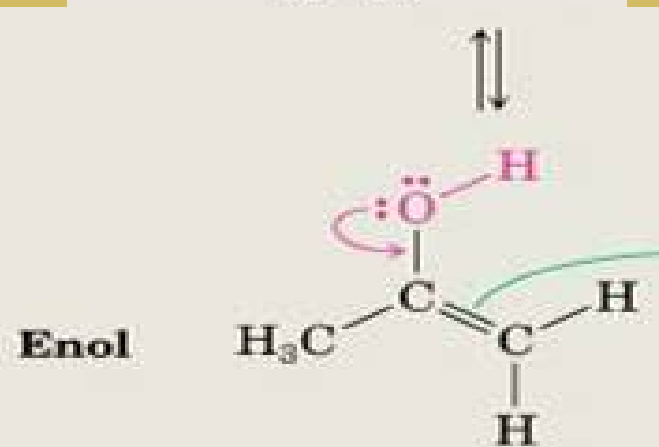
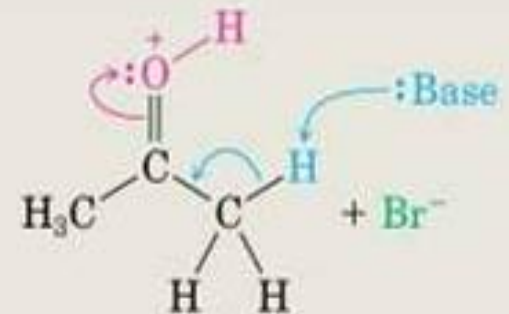
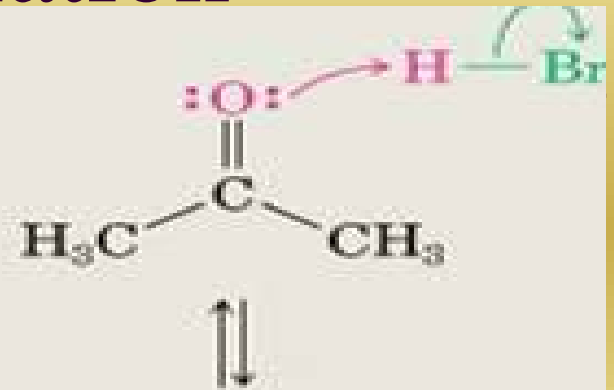
Base Catalysis of Enolization

- Brønsted bases catalyze keto-enol tautomerization
- The hydrogens on the α carbon are weakly acidic and transfer to water is slow
- In the reverse direction there is also a barrier to the addition of the proton from water to enolate carbon



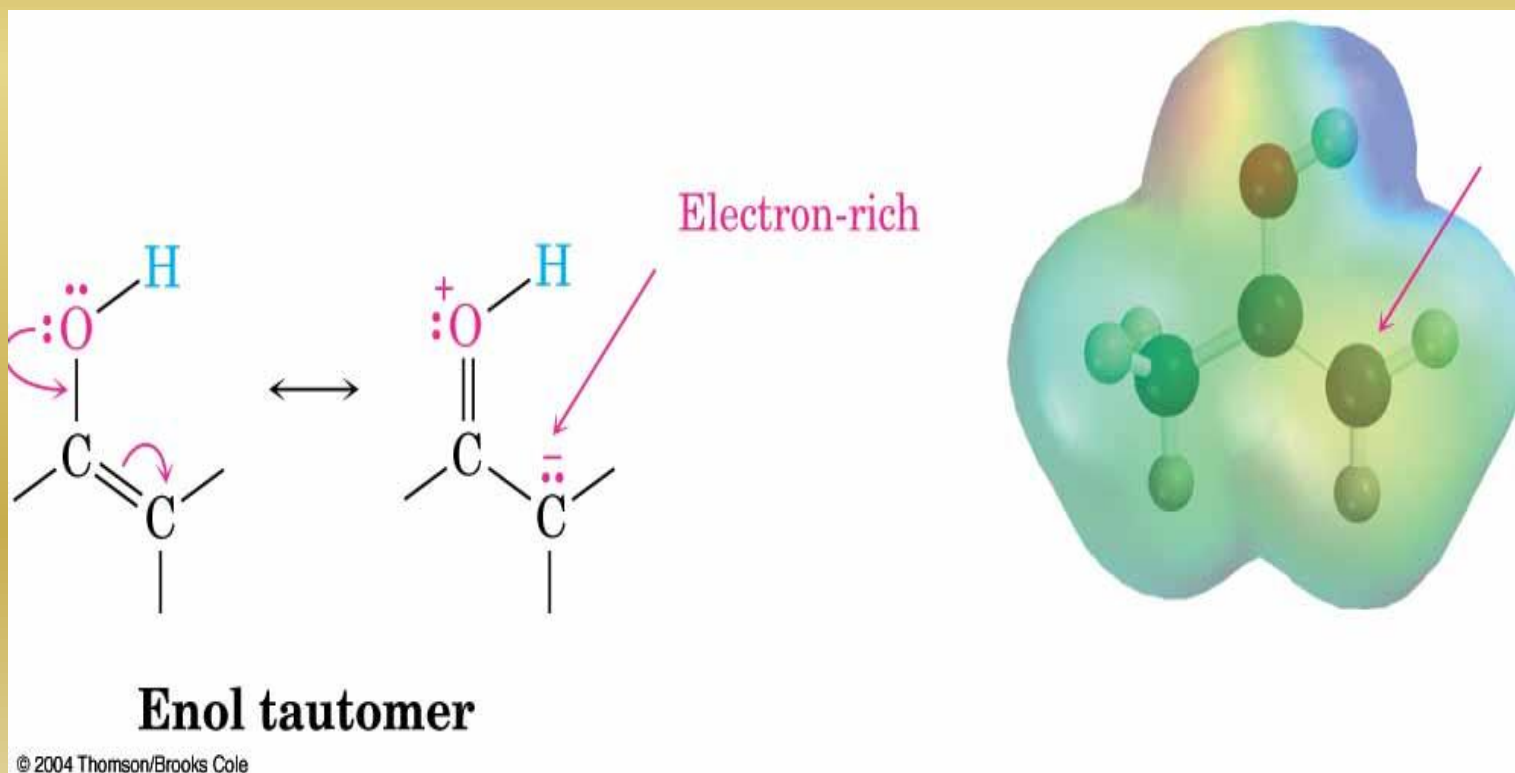
Acid Catalyzed Enolization

- The addition of a proton to the carbonyl oxygen makes the α C-H more acidic, reducing the barrier to the enol
- The enol then can react with another electrophile



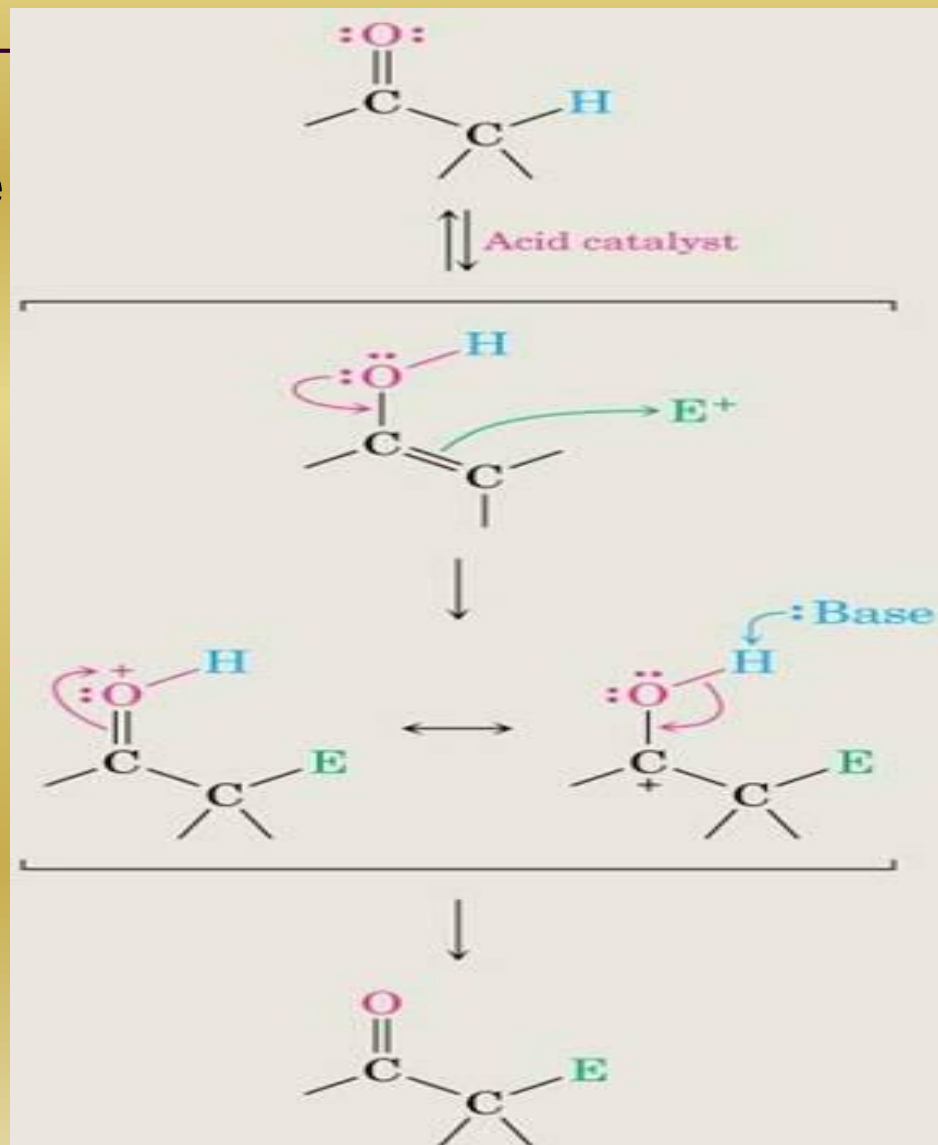
22.2 Reactivity of Enols: The Mechanism of Alpha-Substitution Reactions

- Enols behave as nucleophiles and react with electrophiles because the double bonds are electron-rich compared to alkenes



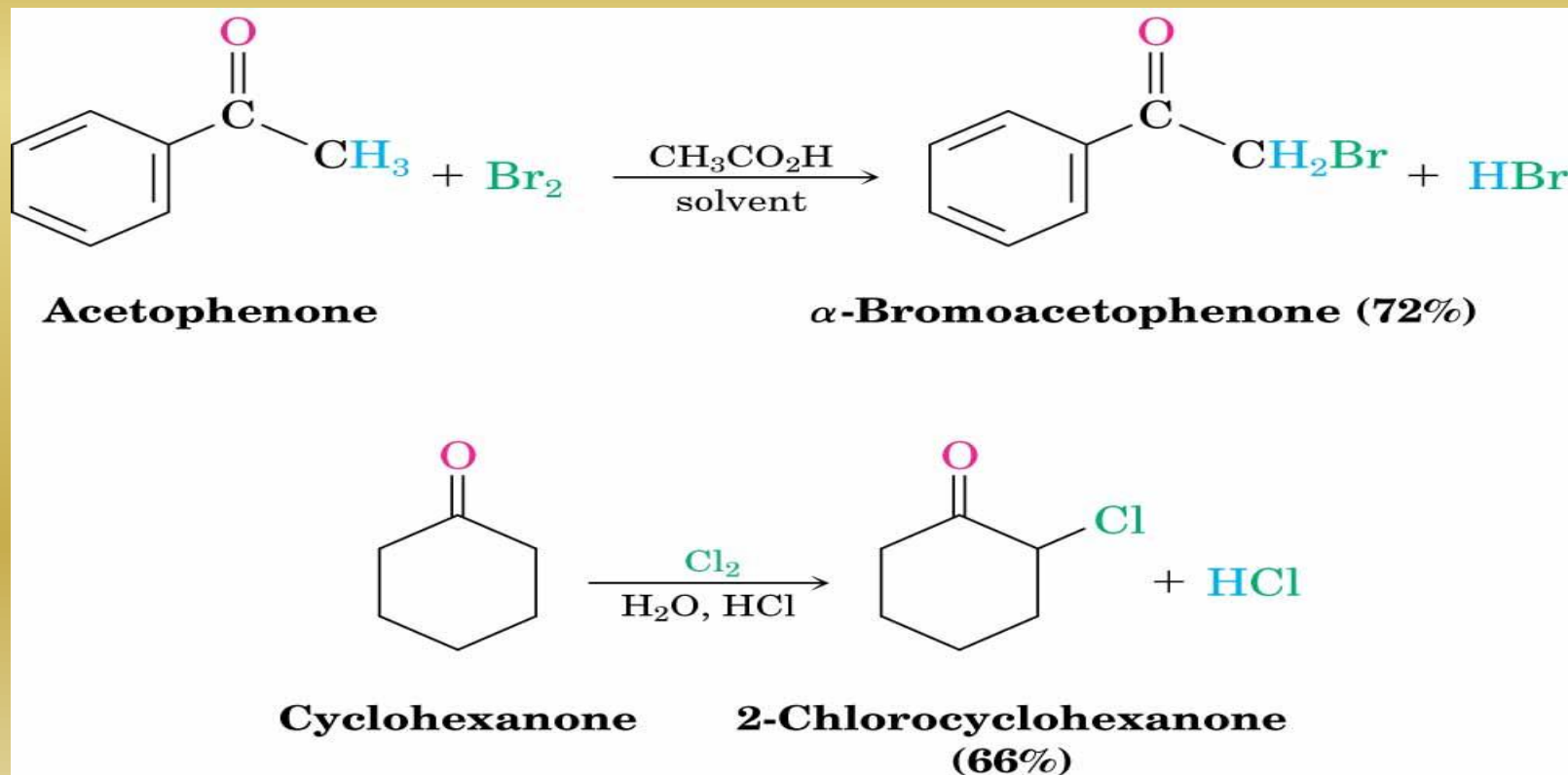
General Mechanism of Addition to Enols

- When an *enol* reacts with an electrophile the intermediate cation immediately loses the —OH proton to give a substituted carbonyl compound



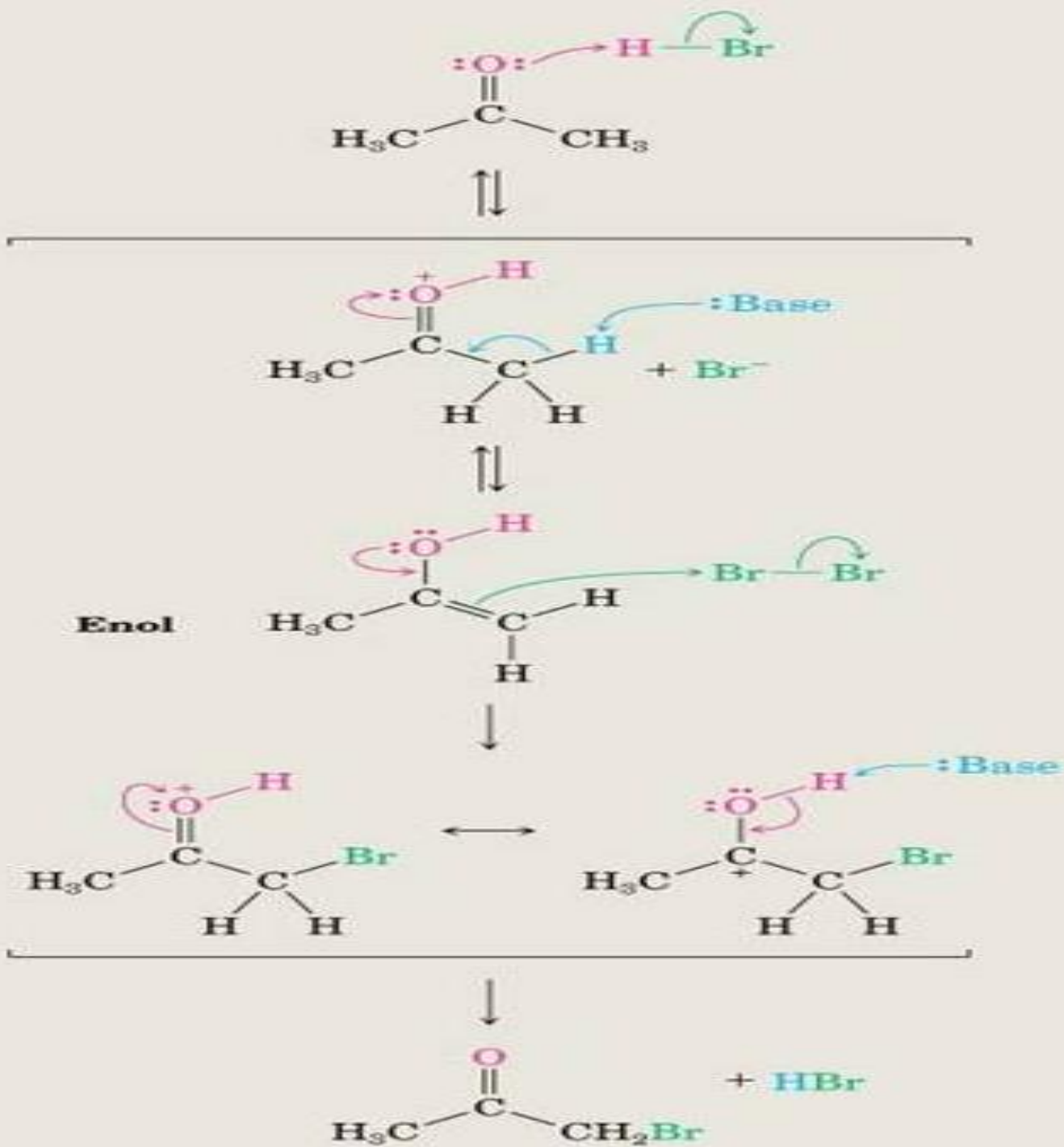
22.3 Alpha Halogenation of Aldehydes and Ketones

- Aldehydes and ketones can be halogenated at their α positions by reaction with Cl_2 , Br_2 , or I_2 in acidic solution



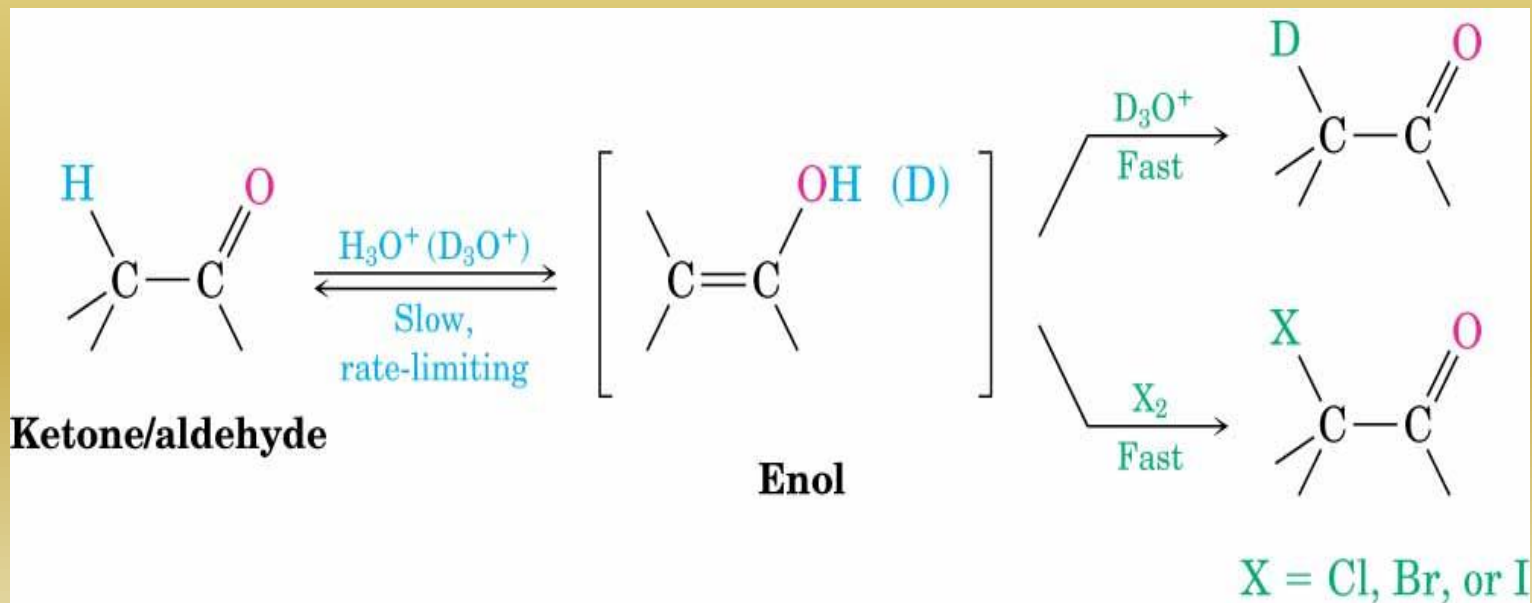
Mechanism of Electrophilic Substitution

- The enol tautomer reacts with an electrophile
- The keto tautomer loses a proton



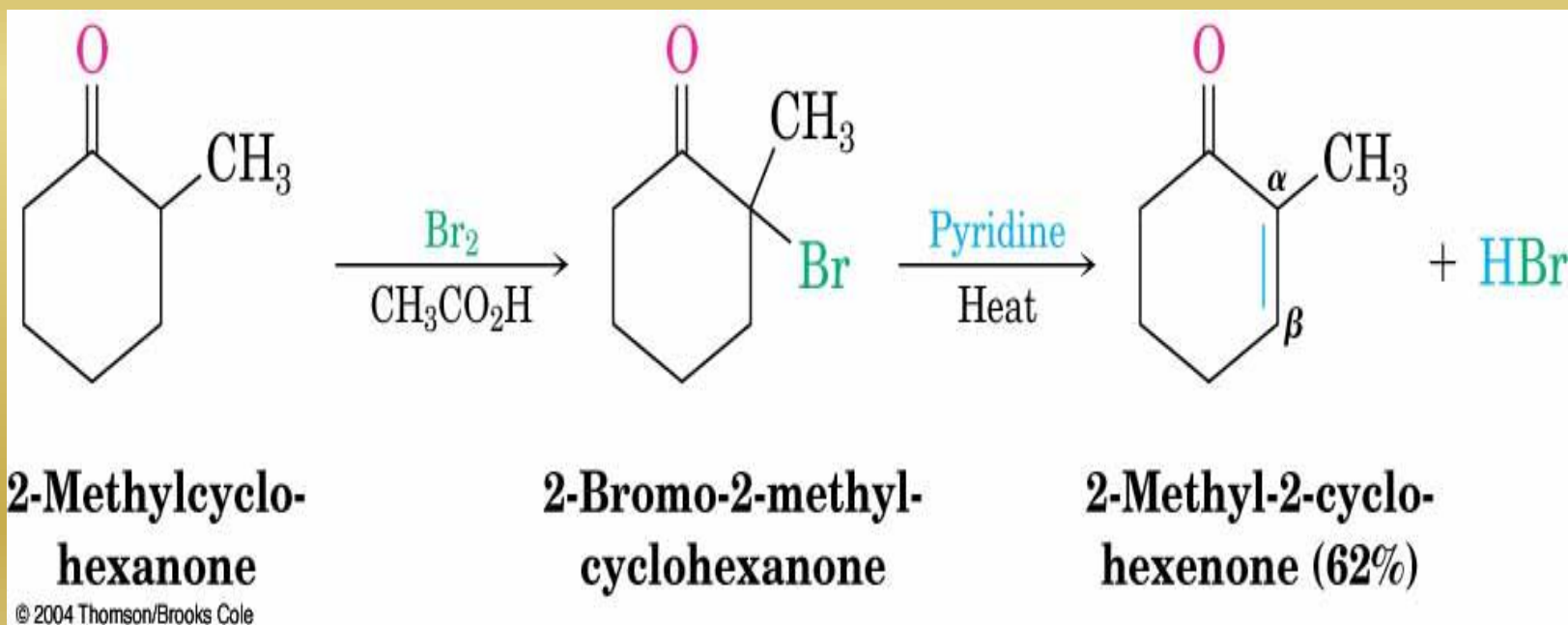
Evidence for the Rate-Limiting Enol Formation

- The rate of halogenation is independent of the halogen's identity and concentration
- In D_3O^+ the α H's are replaced by D's at the same rate as halogenation
- This because the barrier to formation of the enol goes through the highest energy transition state in the mechanism



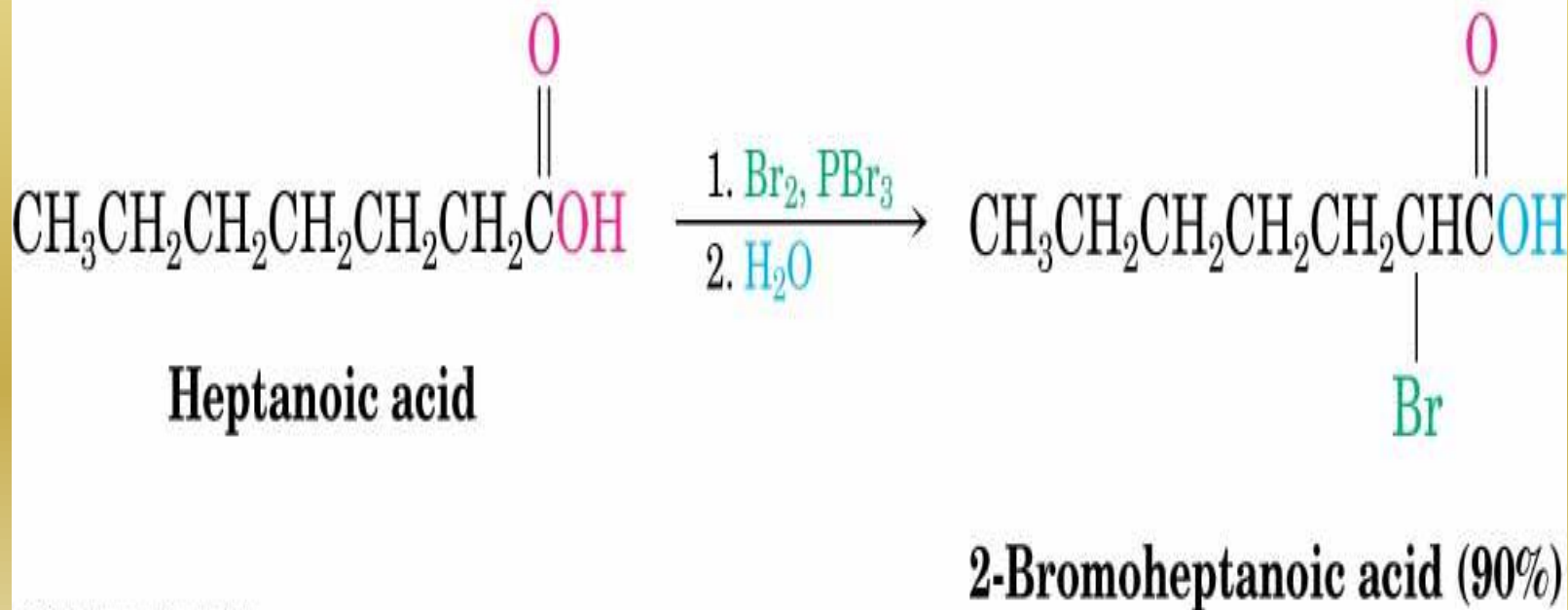
Elimination Reactions of α -Bromoketones

- α -Bromo ketones can be dehydrobrominated by base treatment to yield α,β -unsaturated ketones



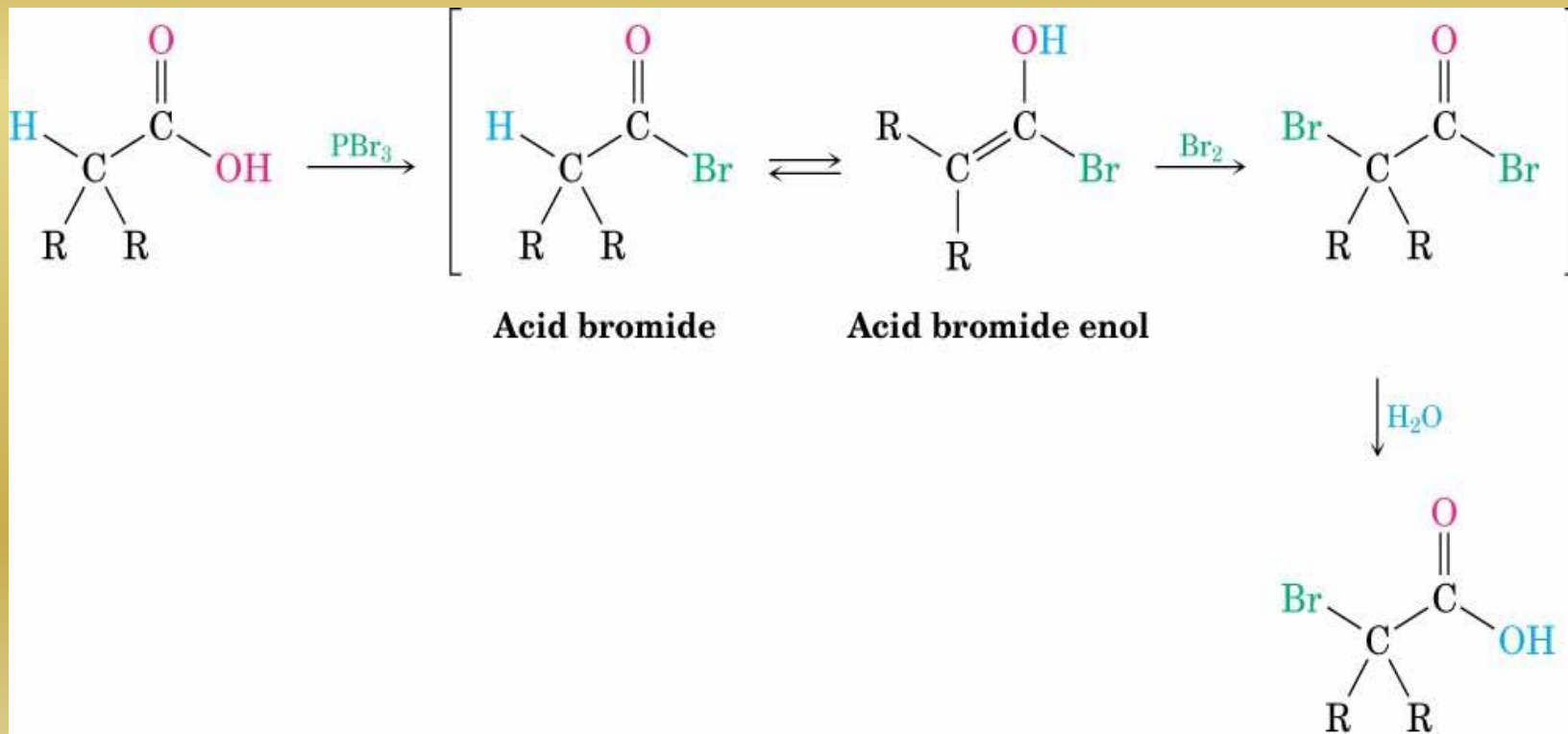
Alpha Bromination of Carboxylic Acids: The Hell–Volhard–Zelinskii Reaction

- Carboxylic acids do not react with Br_2 (Unlike aldehydes and ketones)
- They are brominated by a mixture of Br_2 and PBr_3 (Hell–Volhard–Zelinskii reaction)



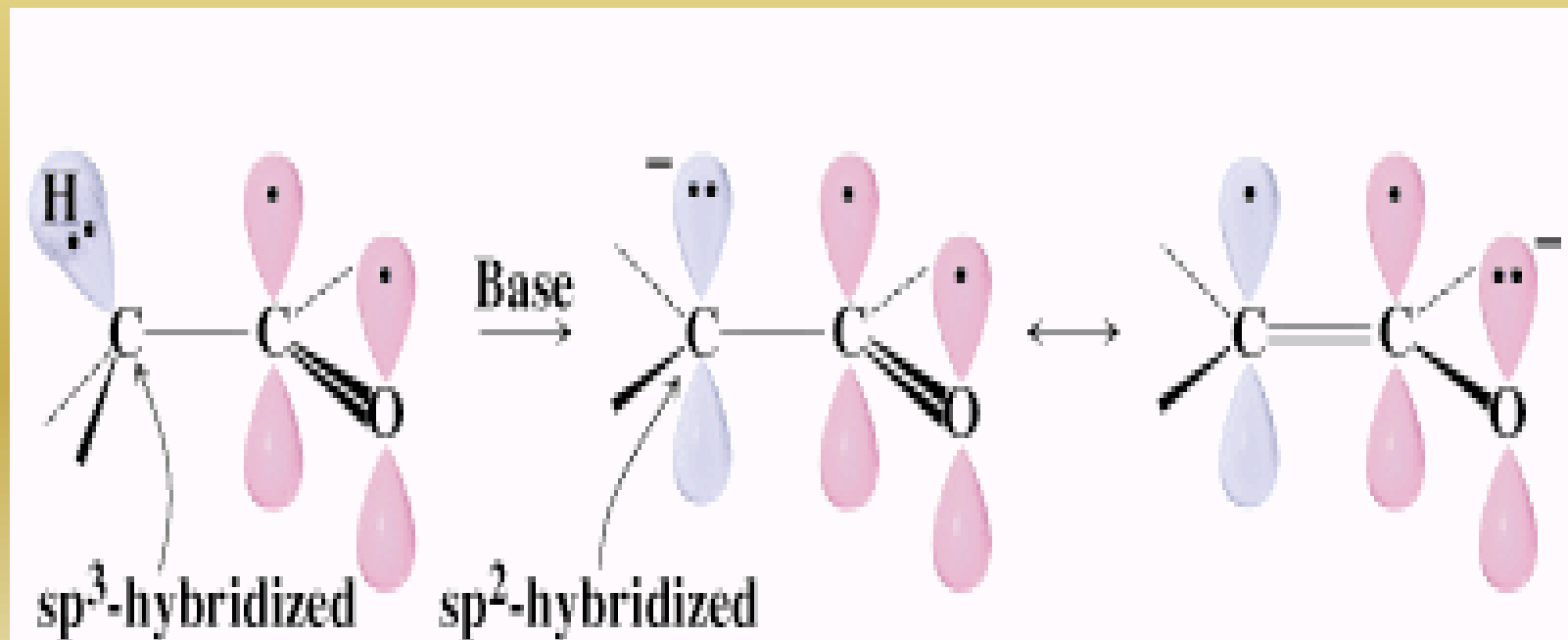
Mechanism of Bromination

- PBr_3 converts $-\text{COOH}$ to $-\text{COBr}$, which can enolize and add Br_2



22.5 Acidity of Alpha Hydrogen Atoms: Enolate Ion Formation

- Carbonyl compounds can act as weak acids (pK_a of acetone = 19.3; pK_a of ethane = 60)
- The conjugate base of a ketone or aldehyde is an enolate ion - the negative charge is delocalized onto oxygen

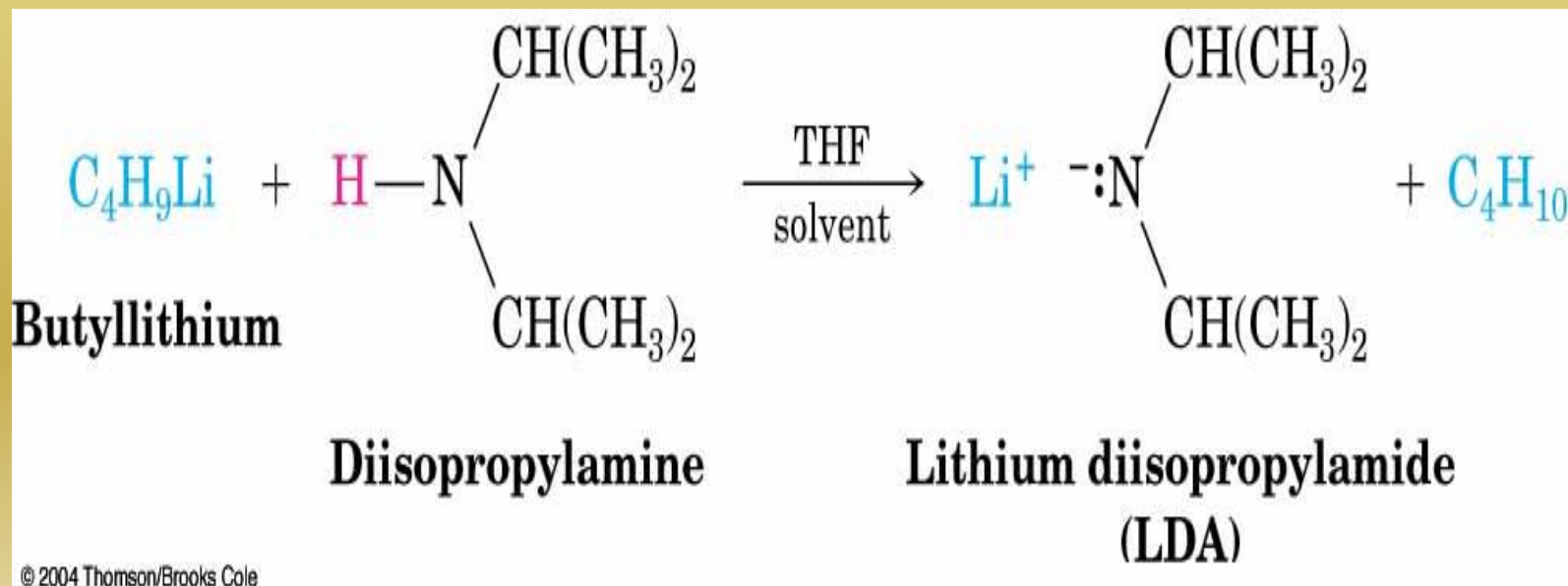


Reagents for Enolate Formation

- Ketones are weaker acids than the OH of alcohols so a more powerful base than an alkoxide is needed to form the enolate
- Sodium hydride (NaH) or lithium diisopropylamide [LiN(*i*-C₃H₇)₂] are strong enough to form the enolate

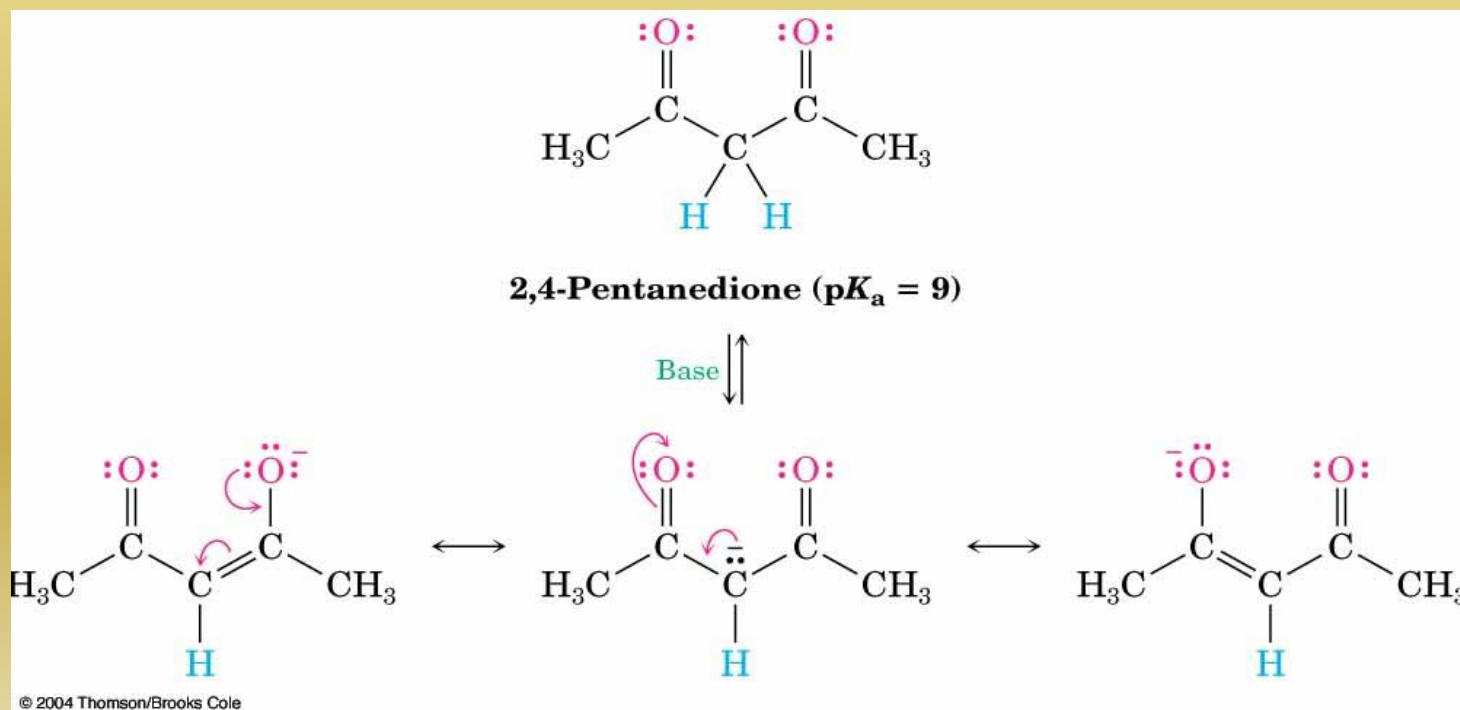
Lithium Diisopropylamide (LDA)

- LDA is from butyllithium (BuLi) and diisopropylamine ($pK_a \approx 40$)
- Soluble in organic solvents and effective at low temperature with many compounds (see Table 22.1)
- Not nucleophilic



β -Dicarbonyls Are More Acidic

- When a hydrogen atom is flanked by two carbonyl groups, its acidity is enhanced (Table 22.1)
- Negative charge of enolate delocalizes over both carbonyl groups

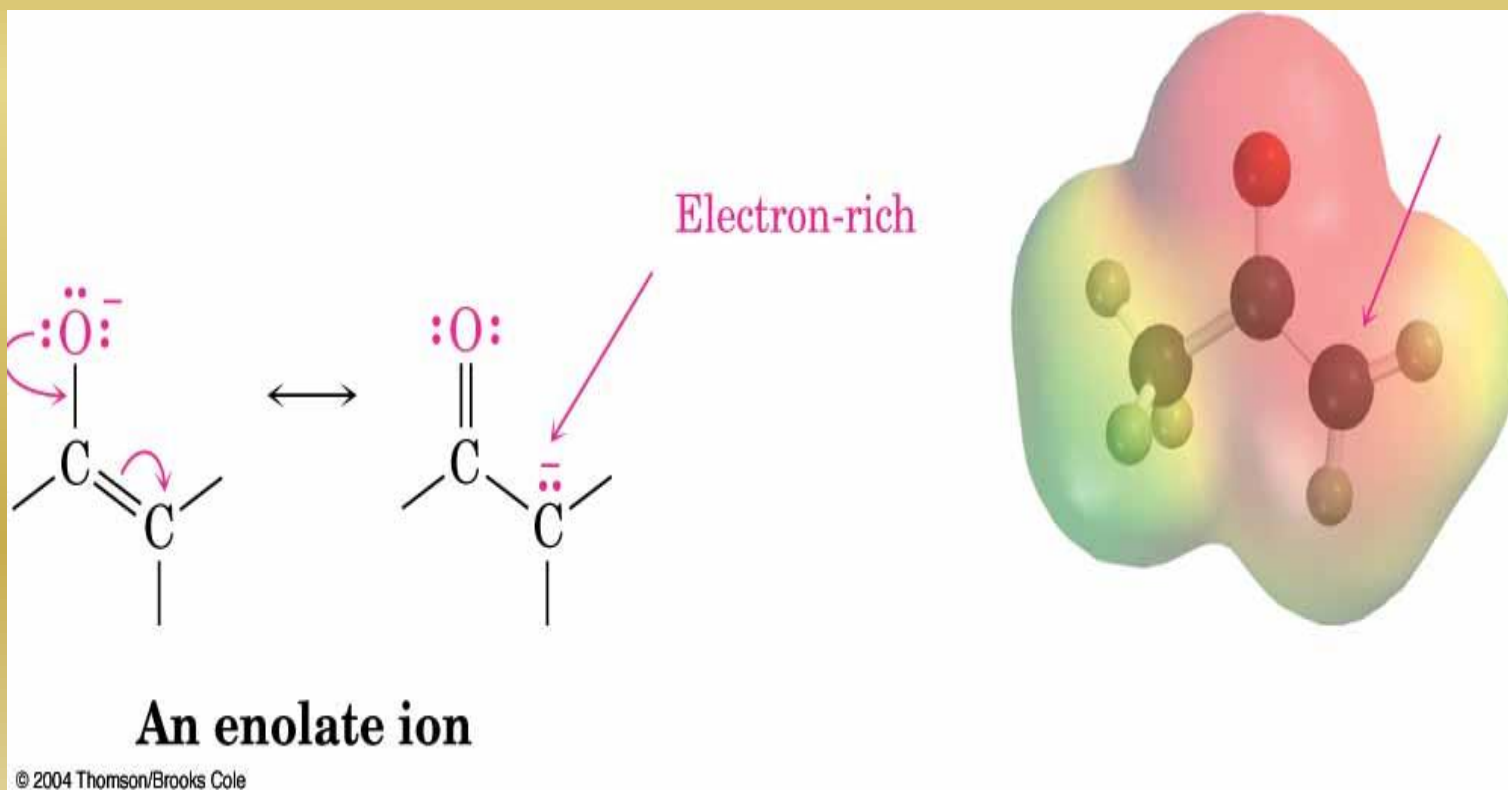


Acidities of Organic Compounds

Compound type	Compound	pK _a
Carboxylic acid	CH ₃ COOH	5
1,3-Diketone	CH ₂ (COCH ₃) ₂	9
1,3-Keto ester	CH ₃ COCH ₂ CO ₂ C ₂ H ₅	11
1,3-Dinitrile	CH ₂ (CN) ₂	–
1,3-Diester	CH ₂ (CO ₂ C ₂ H ₅) ₂	13
Alcohol	CH ₃ CH ₂ OH	16
Acid chloride	CH ₃ COCl	16
Aldehyde	CH ₃ CHO	17
Ketone	CH ₃ COCH ₃	19
Ester	CH ₃ CO ₂ C ₂ H ₅	25
Nitrile	CH ₃ CN	25
Dialkymide	CH ₃ CON(CH ₃) ₂	30
Ammonia	NH ₃	36
Dialkylamine	HN(i-C ₃ H ₇) ₂	40
Alkyne	HC≡CH	25
Alekene	CH ₂ =CH ₂	44
Alkane	CH ₃ CH ₃	60

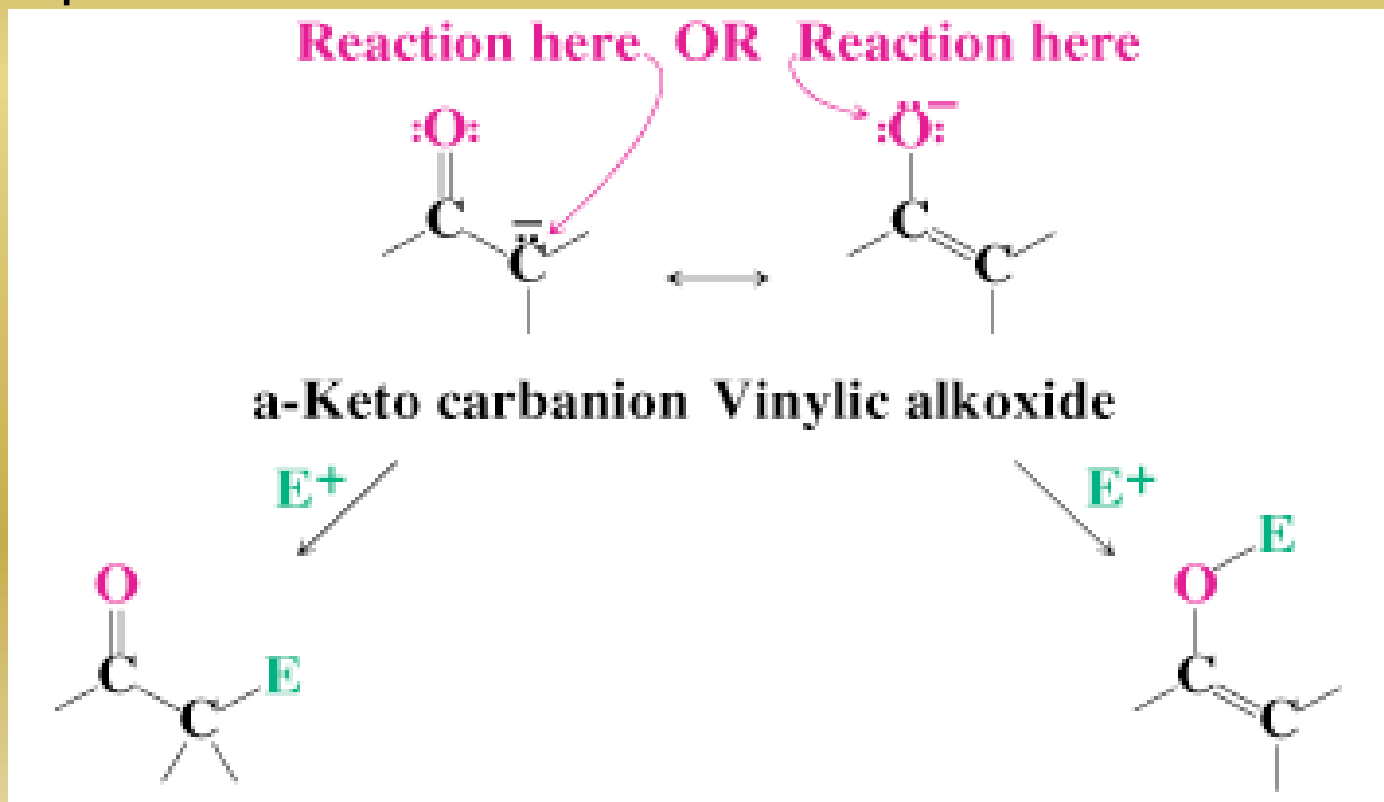
Reactivity of Enolate Ions

- The carbon atom of an enolate ion is electron-rich and highly reactive toward electrophiles (enols are not as reactive)



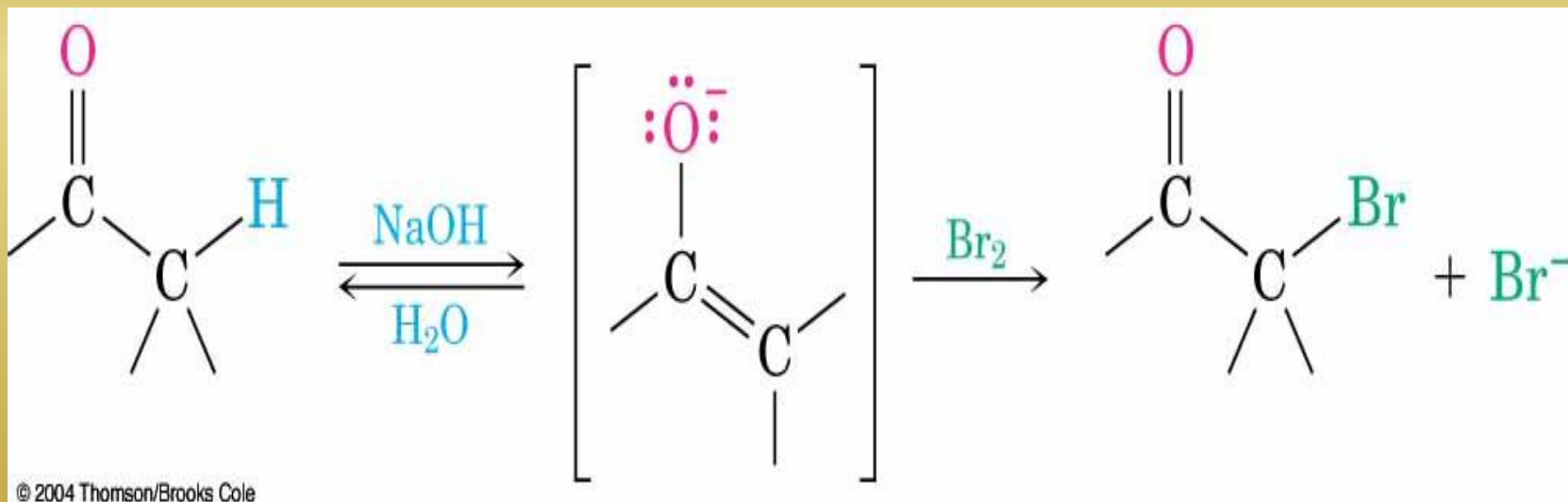
Two Reactions Sites on Enolates

- Reaction on oxygen yields an enol derivative
- Reaction on carbon yields an α -substituted carbonyl compound



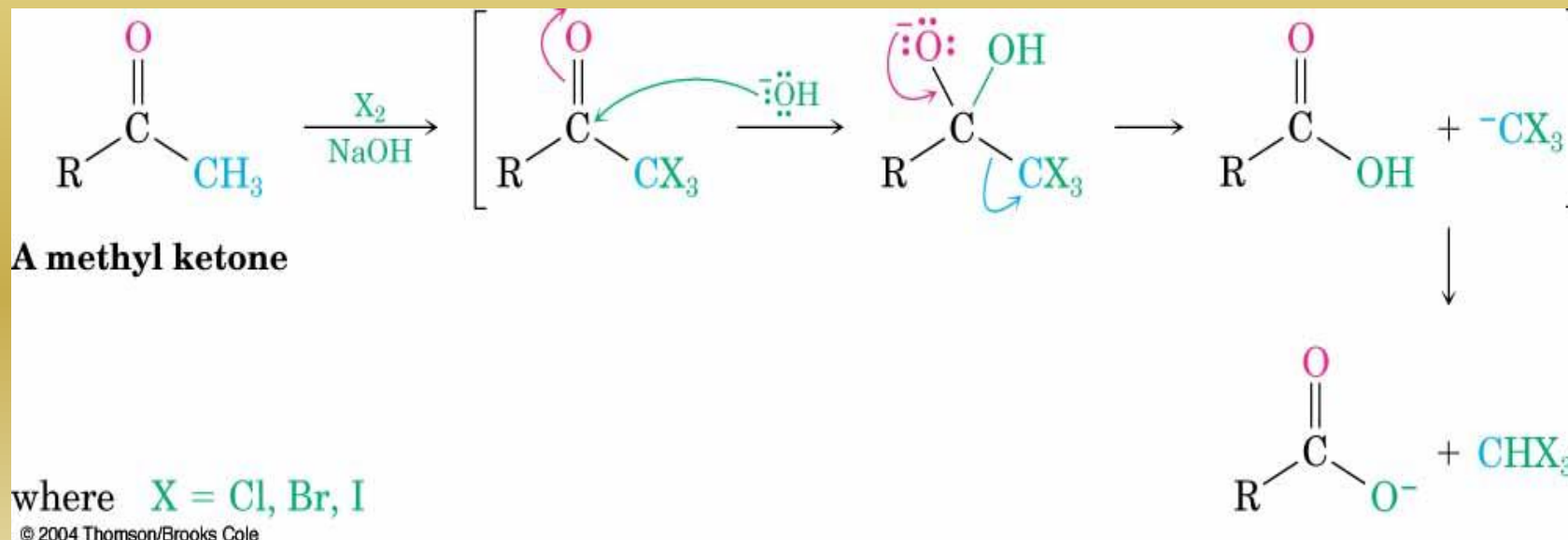
22.7 Halogenation of Enolate Ions: The Haloform Reaction

- Base-promoted reaction occurs through an enolate ion intermediate



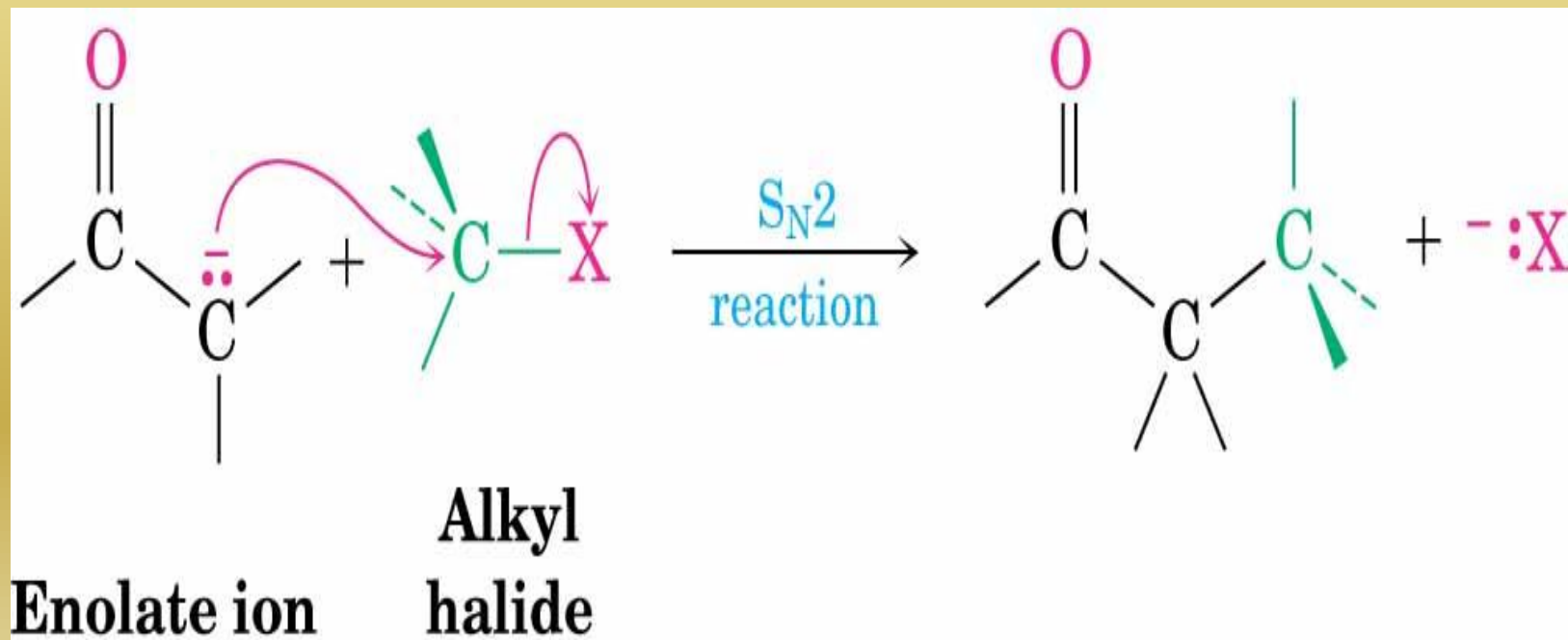
Further Reaction: Cleavage

- Monohalogenated products are themselves rapidly turned into enolate ions and further halogenated until the trihalo compound is formed from a methyl ketone
- The product is cleaved by hydroxide with CX_3 as a leaving group



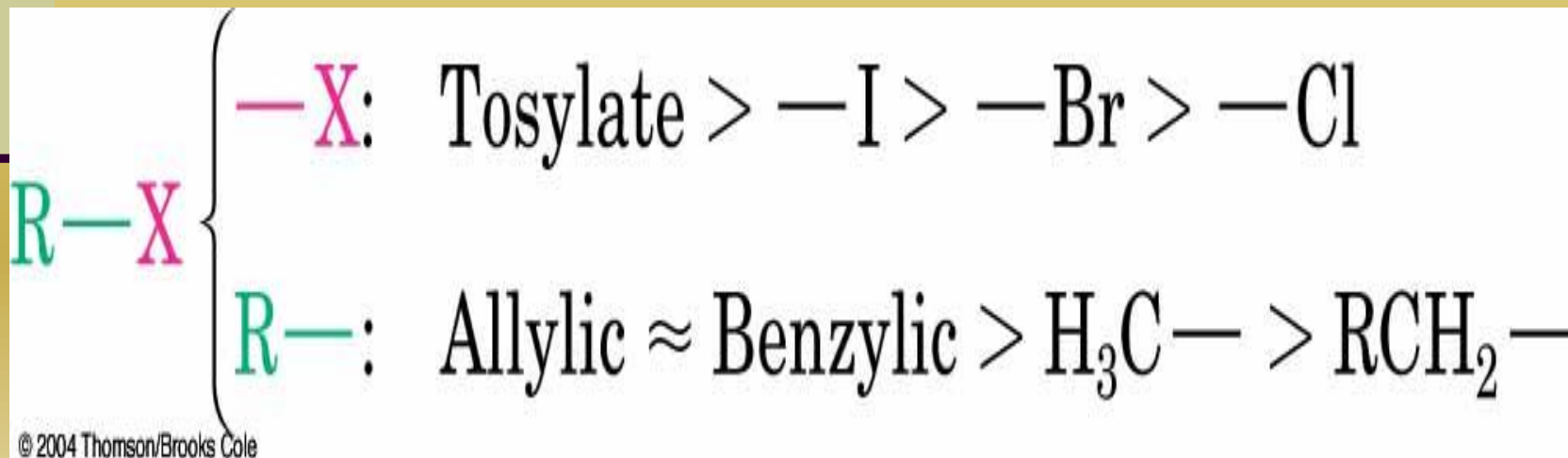
Alkylation of Enolate Ions

- Alkylation occurs when the nucleophilic enolate ion reacts with the electrophilic alkyl halide or tosylate and displaces the leaving group



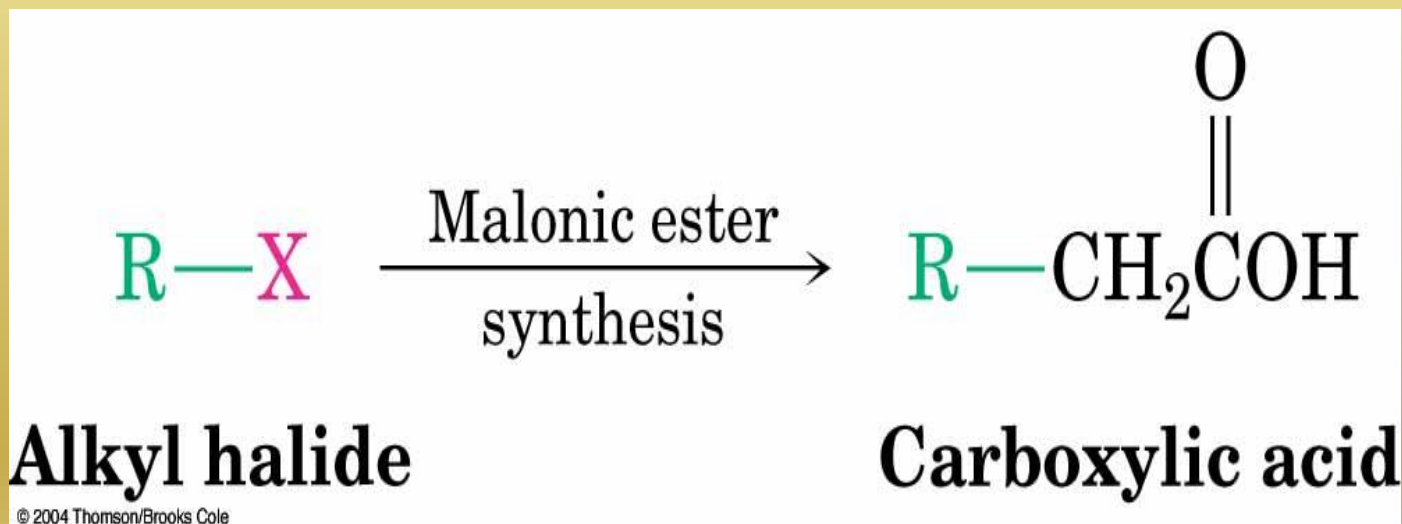
Constraints on Enolate Alkylation

- S_N2 reaction:, the leaving group X can be chloride, bromide, iodide, or tosylate
- R should be primary or methyl and preferably should be allylic or benzylic
- Secondary halides react poorly, and tertiary halides don't react at all because of competing elimination



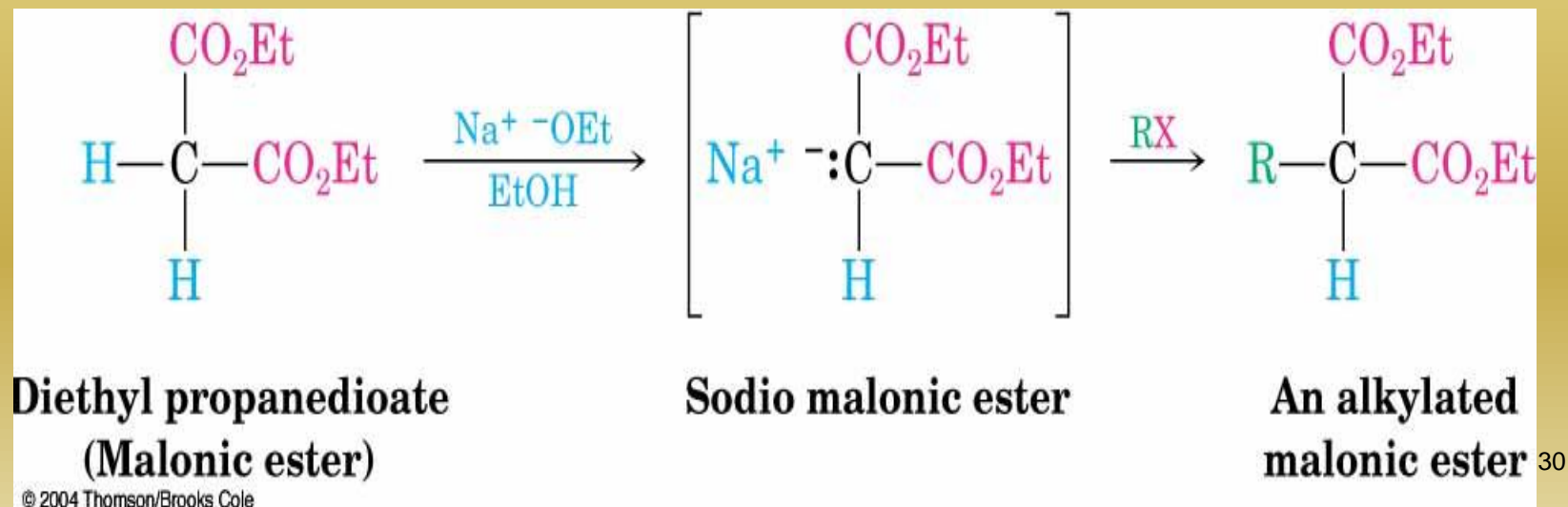
The Malonic Ester Synthesis

- For preparing a carboxylic acid from an alkyl halide while lengthening the carbon chain by two atoms



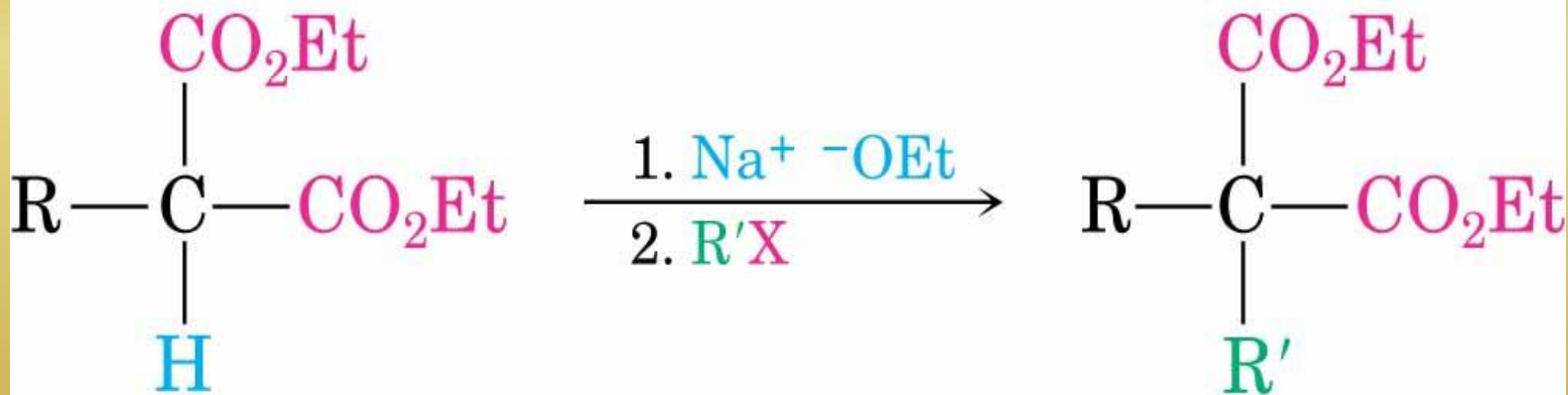
Formation of Enolate and Alkylation

- Malonic ester (diethyl propanedioate) is easily converted into its enolate ion by reaction with sodium ethoxide in ethanol
- The enolate is a good nucleophile that reacts rapidly with an alkyl halide to give an α -substituted malonic ester



Dialkylation

- The product has an acidic α -hydrogen, allowing the alkylation process to be repeated

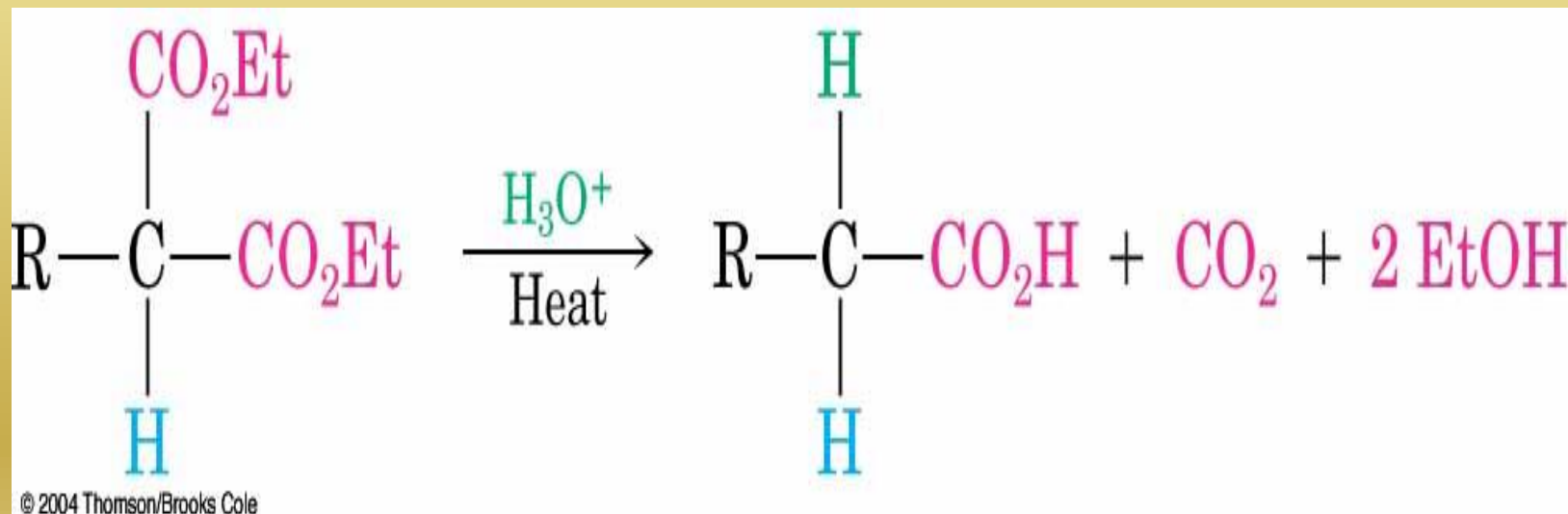


**An alkylated
malonic ester**

**A dialkylated
malonic ester**

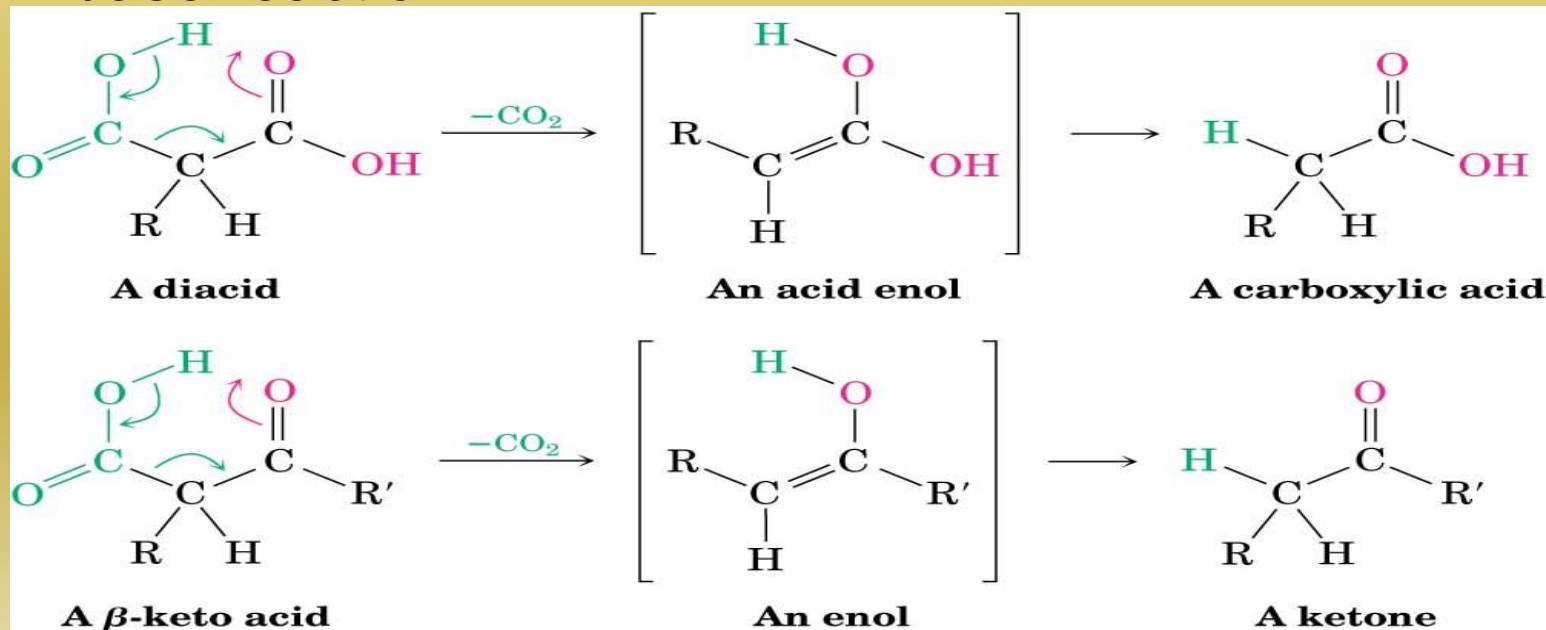
Hydrolysis and Decarboxylation

- The malonic ester derivative hydrolyzes in acid and loses CO₂ (“decarboxylation”) to yield a substituted monoacid



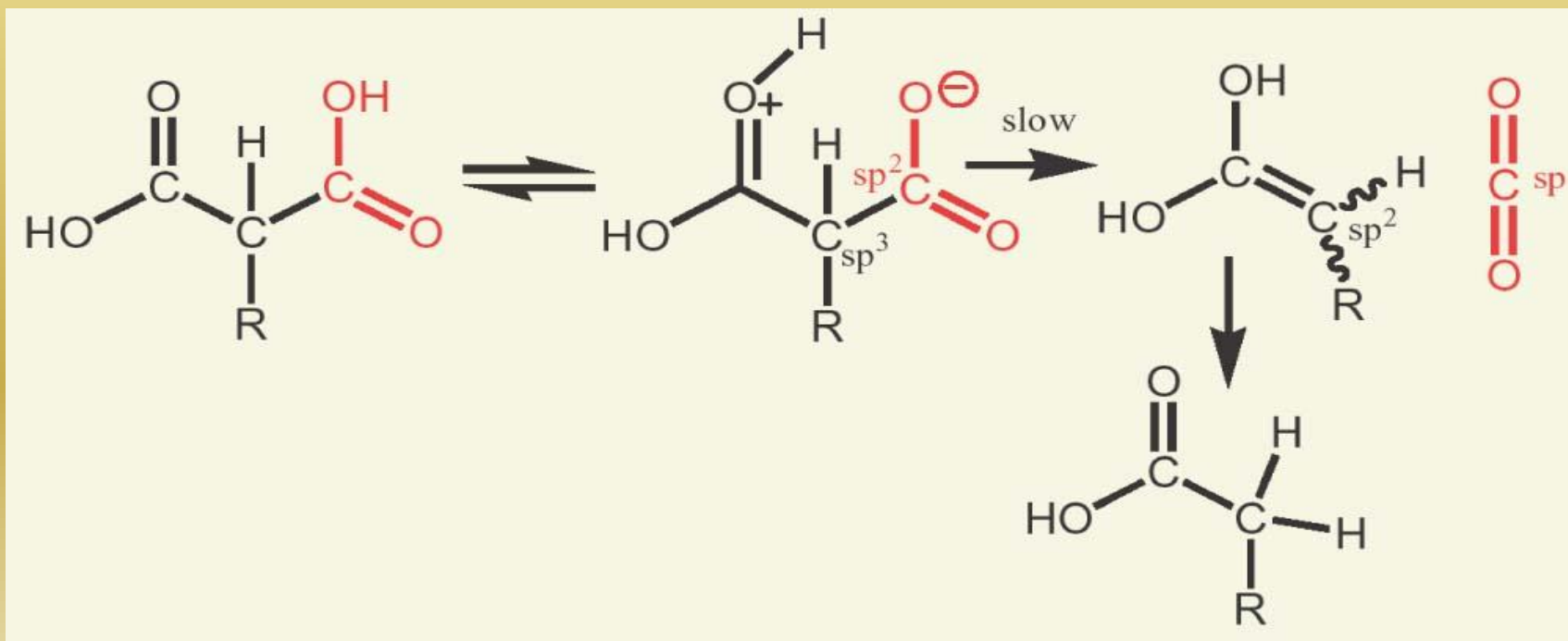
Decarboxylation of β -Ketoacids

- Decarboxylation requires a carbonyl group two atoms away from the $\text{—CO}_2\text{H}$
- The second carbonyl permit delocalization of the resulting enol
- The reaction can be rationalized by an internal acid-base reaction



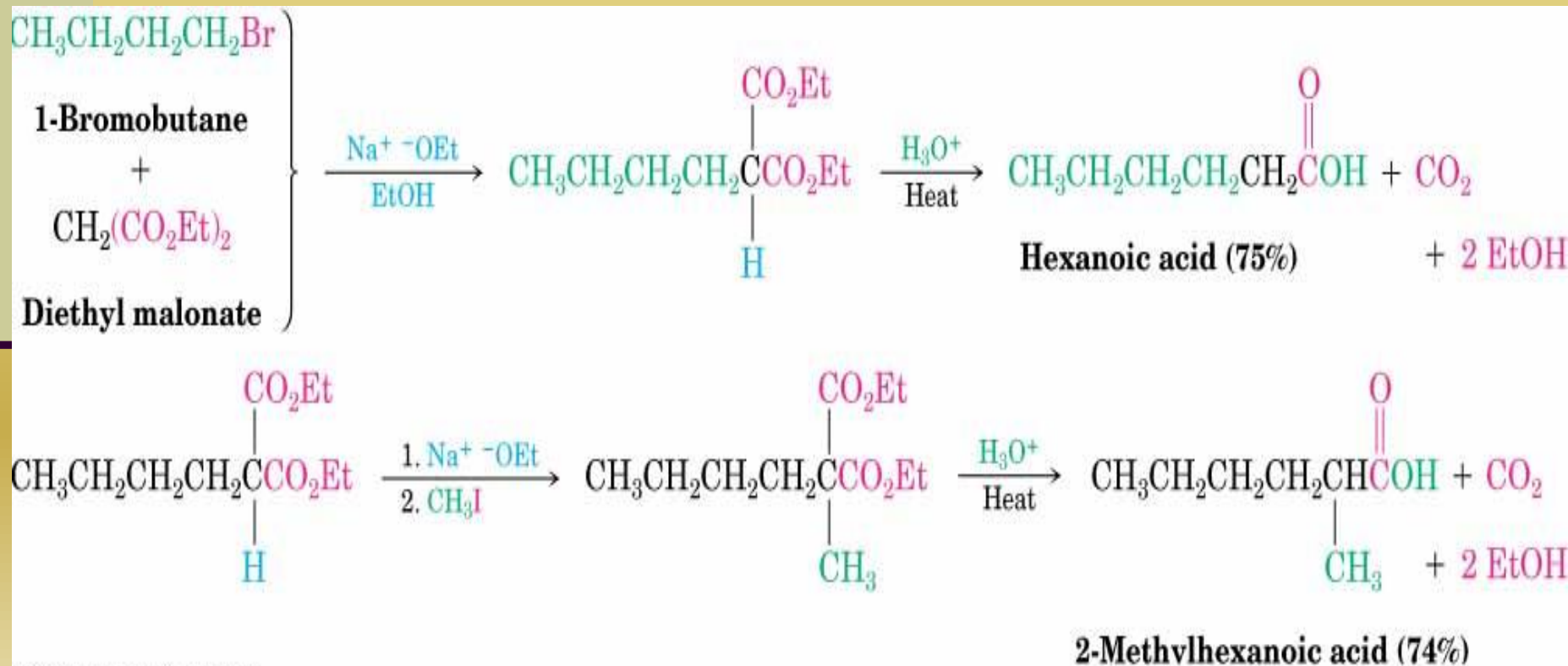
Decarboxylation Involves Changes in Hybridization

- The reaction involves formation of a zwitterionic tautomer
- The carboxylate C is sp^2 and becomes sp in CO_2
- The α -C goes from sp^3 to sp^2 in the key step



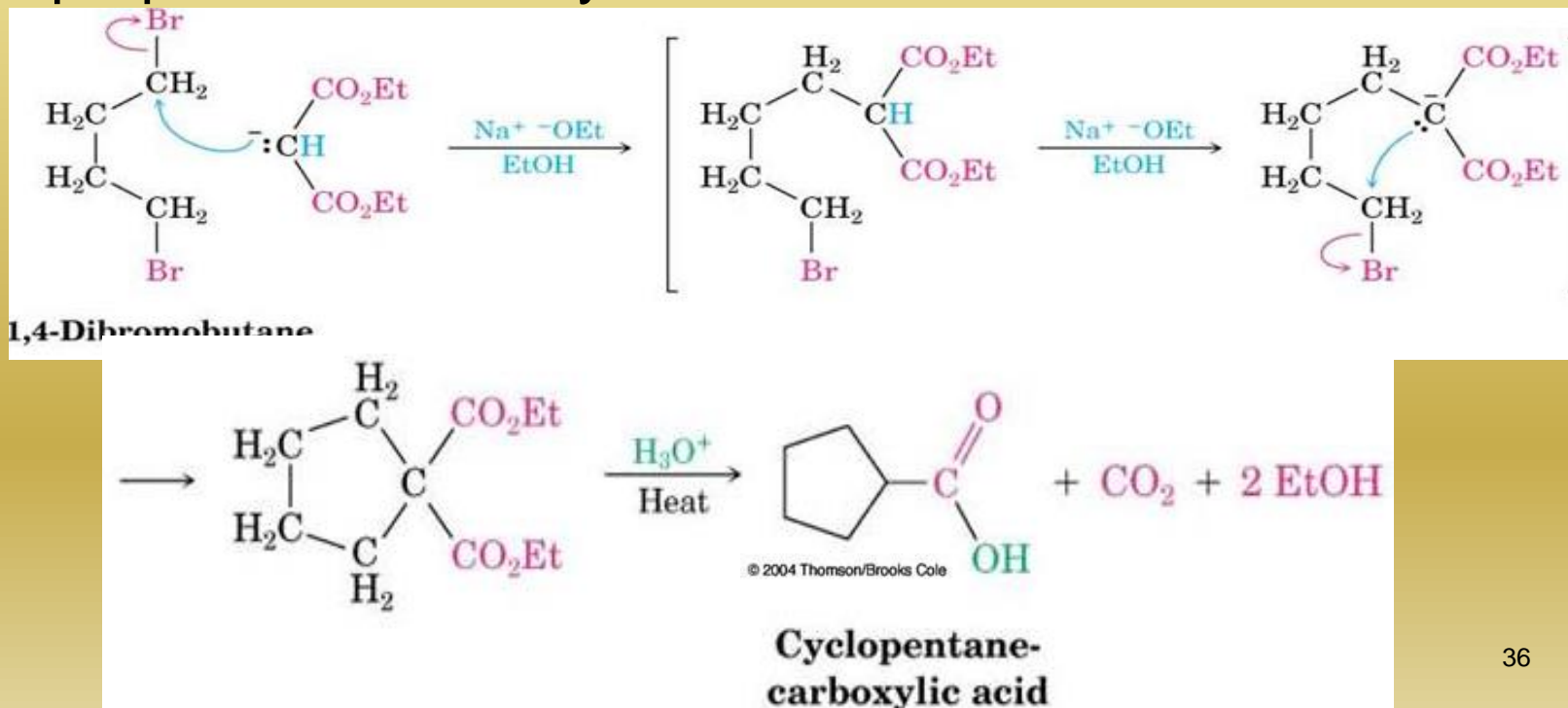
Reminder of Overall Conversion

- The malonic ester synthesis converts an alkyl halide into a carboxylic acid while lengthening the carbon chain by two atoms



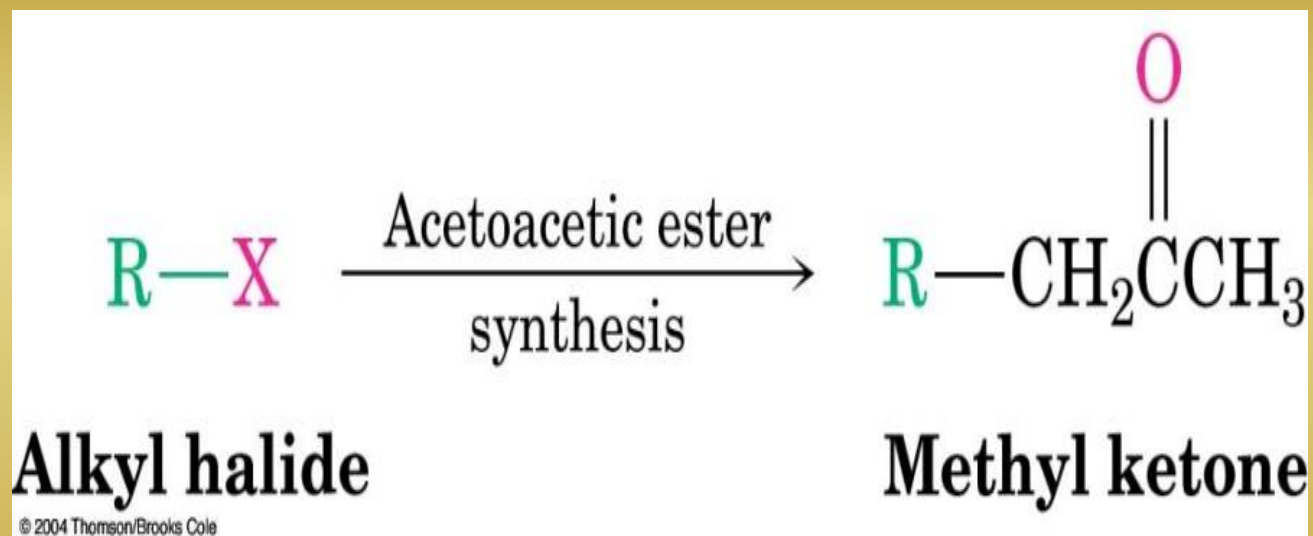
Preparation Cycloalkane Carboxylic Acids

- 1,4-dibromobutane reacts twice, giving a cyclic product
- Three-, four-, five-, and six-membered rings can be prepared in this way



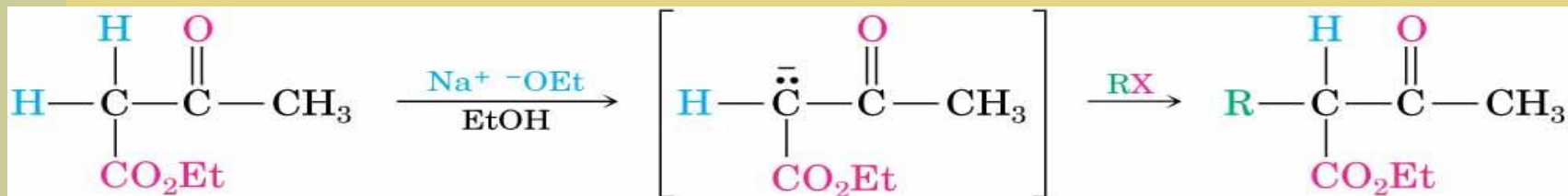
The Acetoacetic Ester Synthesis

- Overall: converts an alkyl halide into a methyl ketone



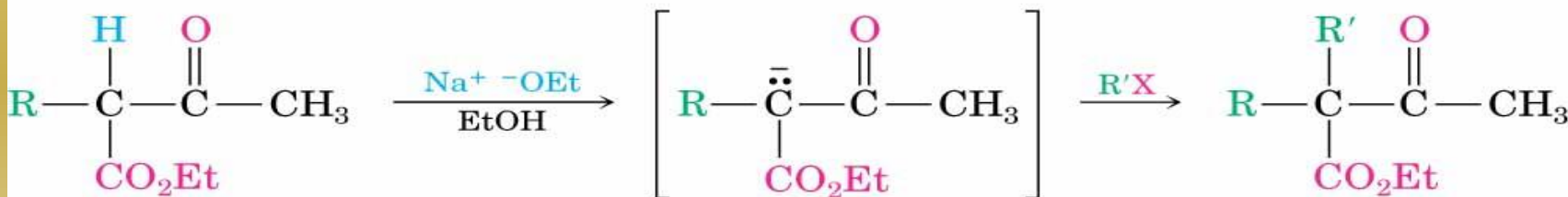
Acetoacetic Ester (Ethyl Acetoacetate)

- α carbon is flanked by two carbonyl groups, so it readily becomes an enolate ion
- This which can be alkylated by an alkyl halide and also can react with a second alkyl halide



Acetoacetic ester

A monoalkylated acetoacetic ester

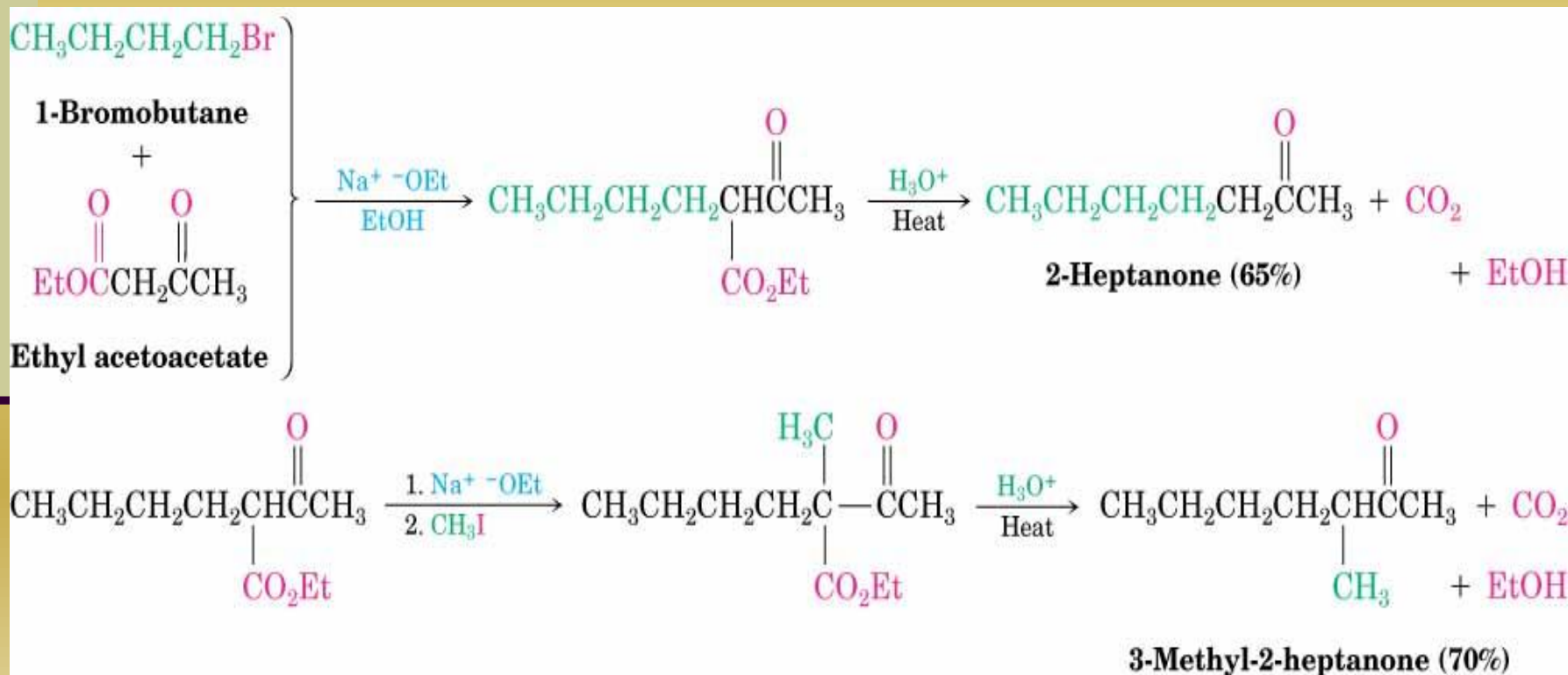


A monoalkylated acetoacetic ester

A dialkylated acetoacetic ester

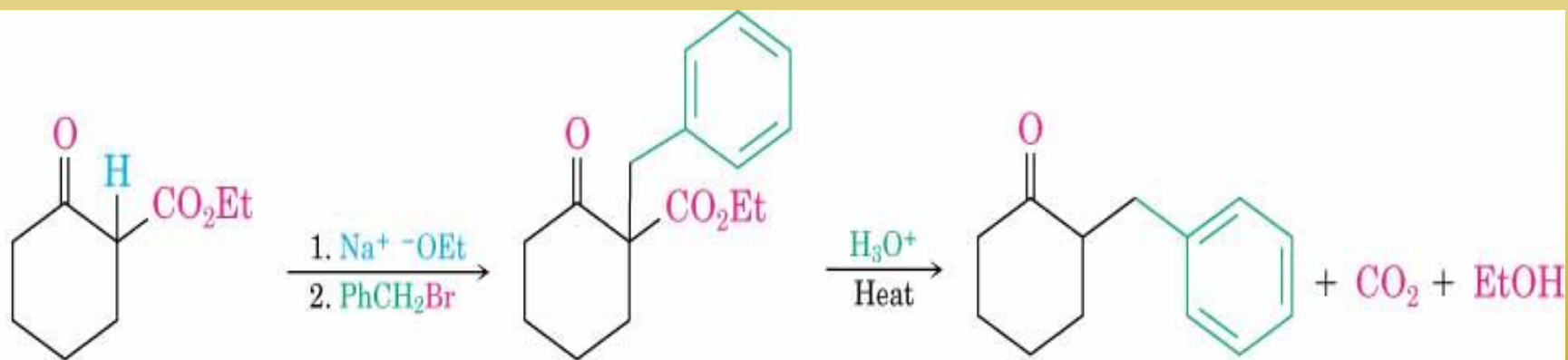
Decarboxylation of Acetoacetic Acid

- β-Ketoacid from hydrolysis of ester undergoes decarboxylation to yield a ketone via the enol



Generalization: β -Keto Esters

- The sequence: enolate ion formation, alkylation, hydrolysis/decarboxylation is applicable to β -keto esters in general
- Cyclic β -keto esters give 2-substituted cyclohexanones



Ethyl 2-oxocyclohexane-
carboxylate

(a cyclic β -keto ester)

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2-Benzylcyclohexanone
(77%)