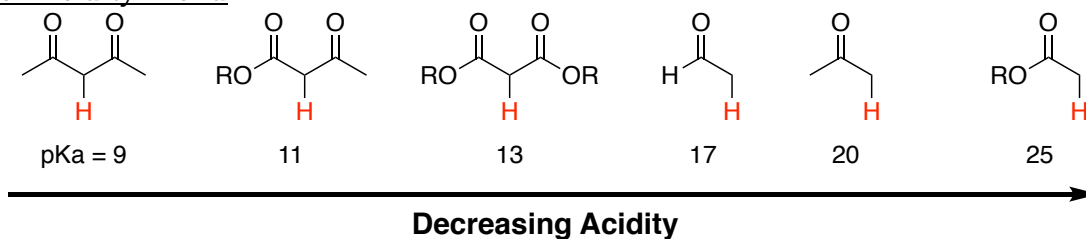
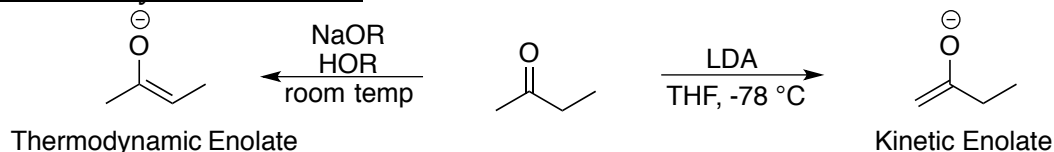


## Chapter 22 Reaction Summary Carbonyl Alpha Substitution Reactions

### Alpha Proton Acidity Trend



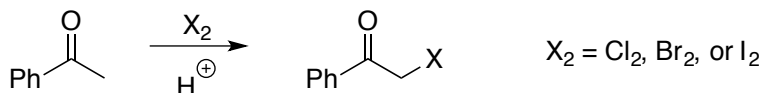
### Kinetic Versus Thermodynamic Enolates



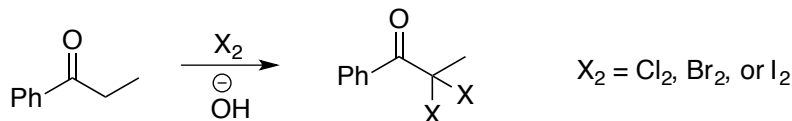
- Thermodynamic Enolate
  - Contains the more substituted double bond.
  - Favored with an alkoxide base at room temperature or higher.
  - Overall the more stable enolate.
- Kinetic Enolate
  - Contains the less substituted double bond.
  - Favored with a strong base such as LDA at lower temperatures.
  - The fastest formed, but least stable enolate.

### Halogenation at the Alpha Carbon

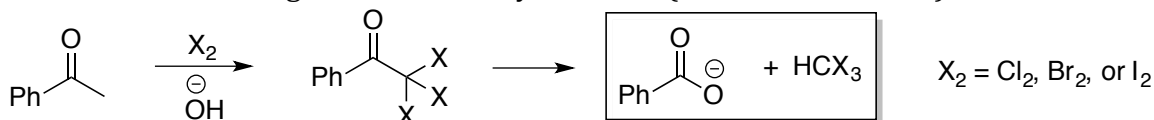
- Acidic Conditions



- Under acidic conditions, **mono**-halogenation occurs.
  - The most commonly used acid is acetic acid ( $\text{CH}_3\text{COOH}$ ), but other acids like HCl and HBr work also.
  - The mechanism of this reaction proceeds via an enol intermediate.
- Basic Conditions

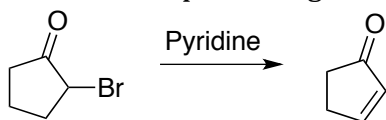


- Under basic conditions, polyhalogenation occurs replacing all of the alpha protons with halogens.
  - The mechanism of this reaction proceeds via an enolate intermediate.
- Base-Promoted Halogenation of Methyl Ketones (Haloform Reaction)



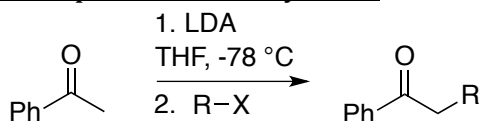
- Under basic conditions, methyl ketones will get tri-halogenated making this carbon a good leaving group. Hydroxide attacks the carbonyl resulting in the loss of  $\text{CX}_3^-$ , which subsequently takes the proton from the  $\text{RCOOH}$  to yield haloform ( $\text{HCX}_3$ ).

## Elimination of Alpha-Halogens to Form $\alpha,\beta$ -Unsaturated Carbonyl Compounds



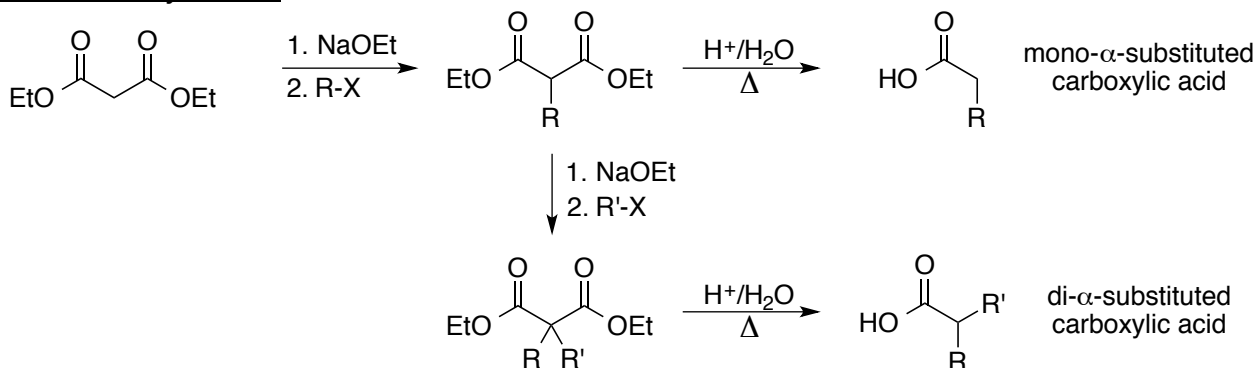
- A halogen  $\alpha$  to a carbonyl can be eliminated using a weak base such as pyridine or  $\text{Li}_2\text{CO}_3$ .

## Direct Alpha Carbon Alkylation



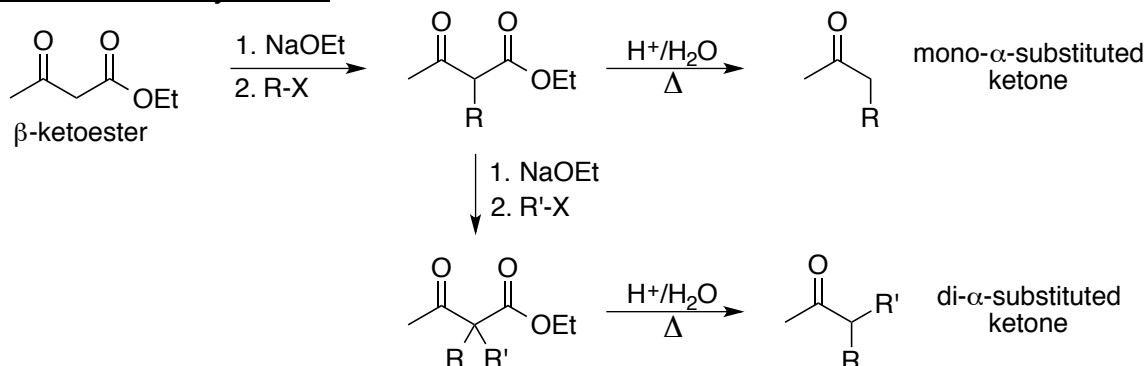
- This reaction allows you to put one or more R-groups on the  $\alpha$ -carbon.
- LDA is the most common base used in the direct alkylation reactions, but alkoxide base can be used if a thermodynamic enolate is desired.
- The alkyl halide used must be methyl or primary because the reaction follows an  $\text{S}_{\text{N}}2$  mechanism.

## Malonic Ester Synthesis



- Diethyl malonate is the starting material used in this reaction.
- The acidic alpha protons can be substituted by one or two R-groups.
- Hydrolysis and decarboxylation yields an  $\alpha$ -substituted carboxylic acid.

## Acetoacetic Ester Synthesis



- This reaction is identical to the malonic ester synthesis except a  $\beta$ -ketoester starting material is used (rather than a diester).
- The product of this reaction is a ketone with one or two R groups at the  $\alpha$ -carbon.