

CH 310 N

T TH 2-3:30

LECTURE 8

Textbook Assignment: Chapter 15 Begin

Homework (for credit): POW 4 posted

Today's Topics: Aldehydes & Ketones

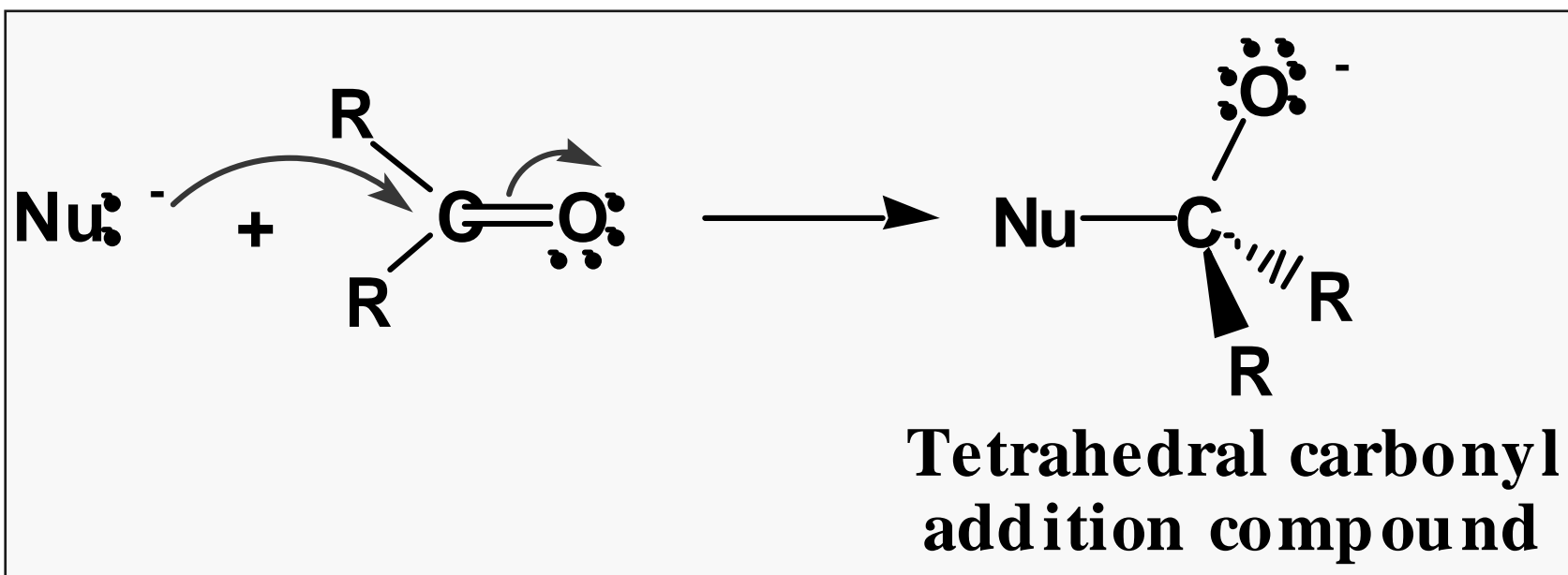
Notice & Announcements:

Exam I: Grading in Progress

Aldehydes And Ketones

Reaction Themes

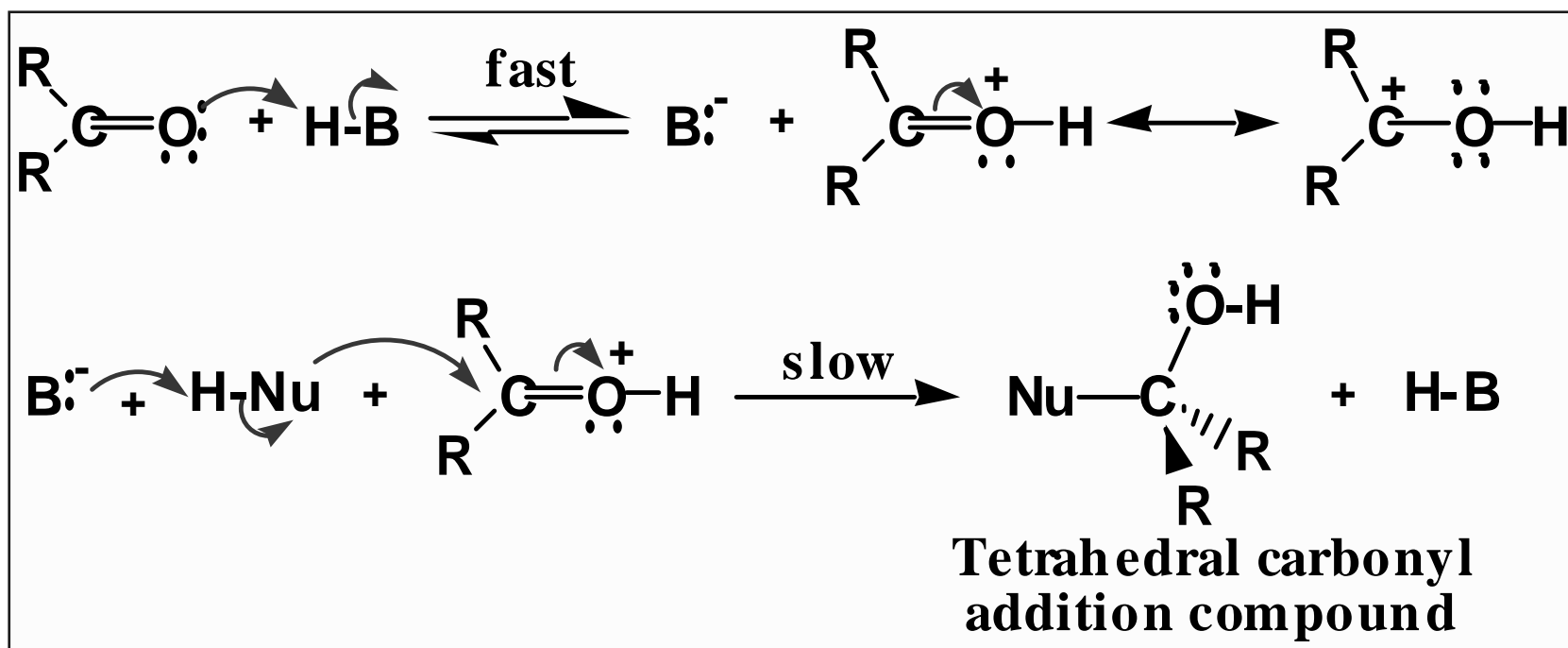
One of the most common reaction themes of a carbonyl group is addition of a nucleophile to form a tetrahedral carbonyl addition compound (intermediate).



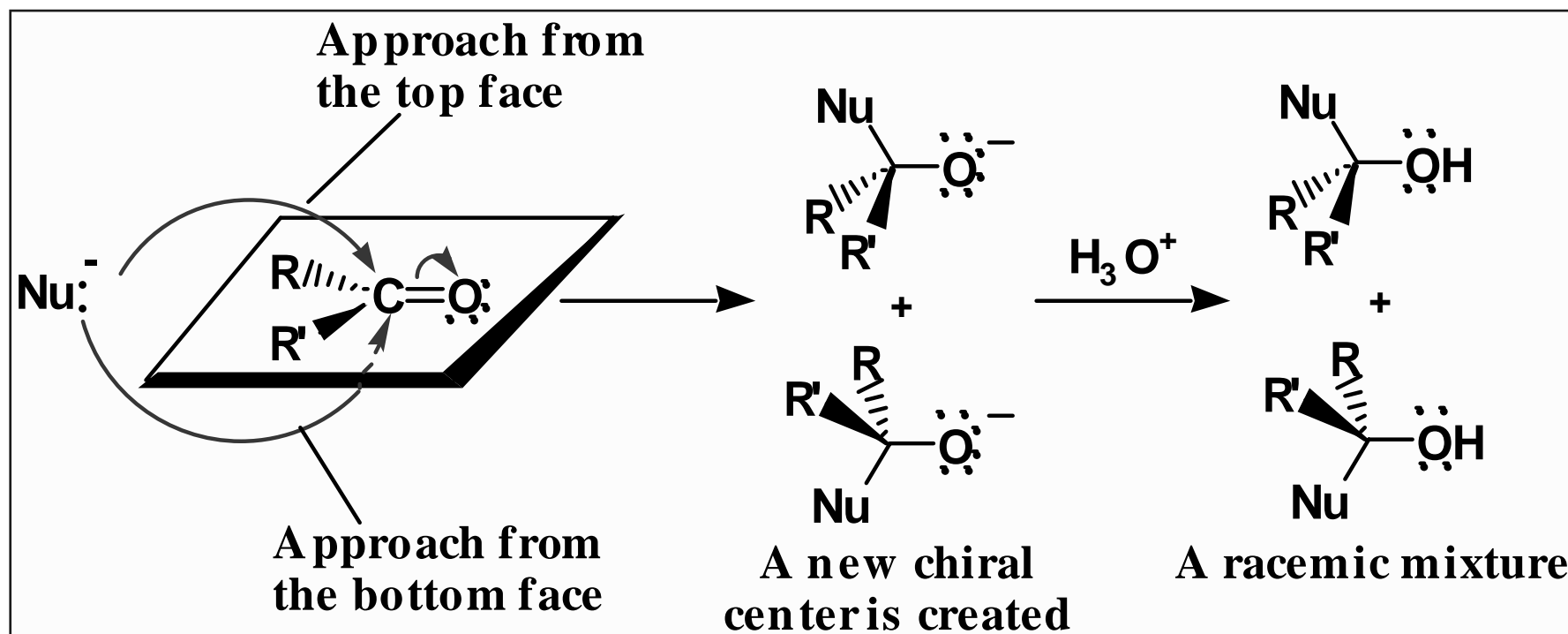
Reaction Themes

A second common theme is reaction with a proton or other Lewis acid to form a resonance-stabilized cation--

- **protonation** increases the electron deficiency of the carbonyl carbon and makes it more reactive toward nucleophiles



- often the tetrahedral product of addition to a carbonyl is a **new chiral center**
- if none of the starting materials is chiral and the reaction takes place in an achiral environment, then enantiomers will be formed as a racemic mixture



Addition of C Nucleophiles

Addition of carbon nucleophiles is one of the most important types of nucleophilic additions to a **C=O** group

- a new **carbon-carbon bond** is formed in the process
- Focus on addition of these carbon nucleophiles:

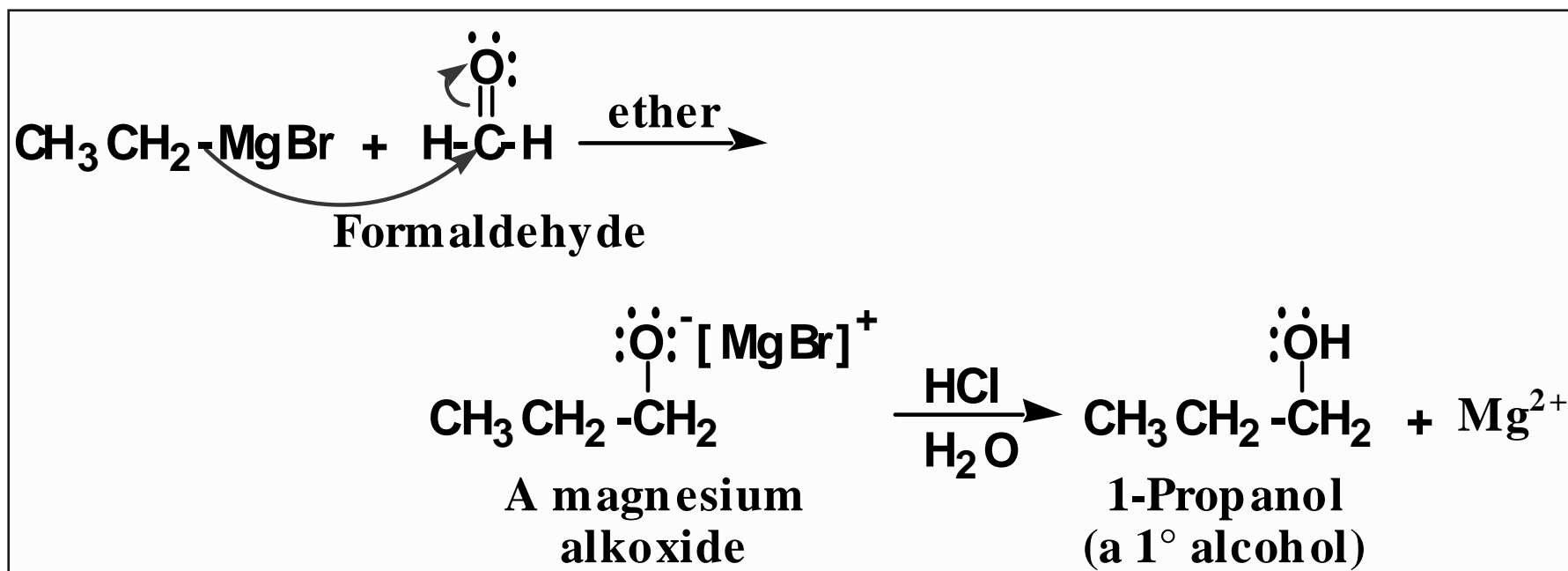
RMgX	RLi	RC≡C: ⁻	⁻:C≡N:
A Grignard reagent	An organolithium reagent	An alkyne anion	Cyanide ion

Grignard Reagents

- Given the difference in electronegativity between carbon and magnesium (2.5 - 1.3), the C-Mg bond is polar covalent, with $C\delta^-$ and $Mg\delta^+$
 - in its reactions, a Grignard reagent behaves as a carbanion
- **Carbanion:** an anion in which carbon has an unshared pair of electrons and bears a negative charge
 - a carbanion is a good nucleophile and adds to the carbonyl group of aldehydes and ketones

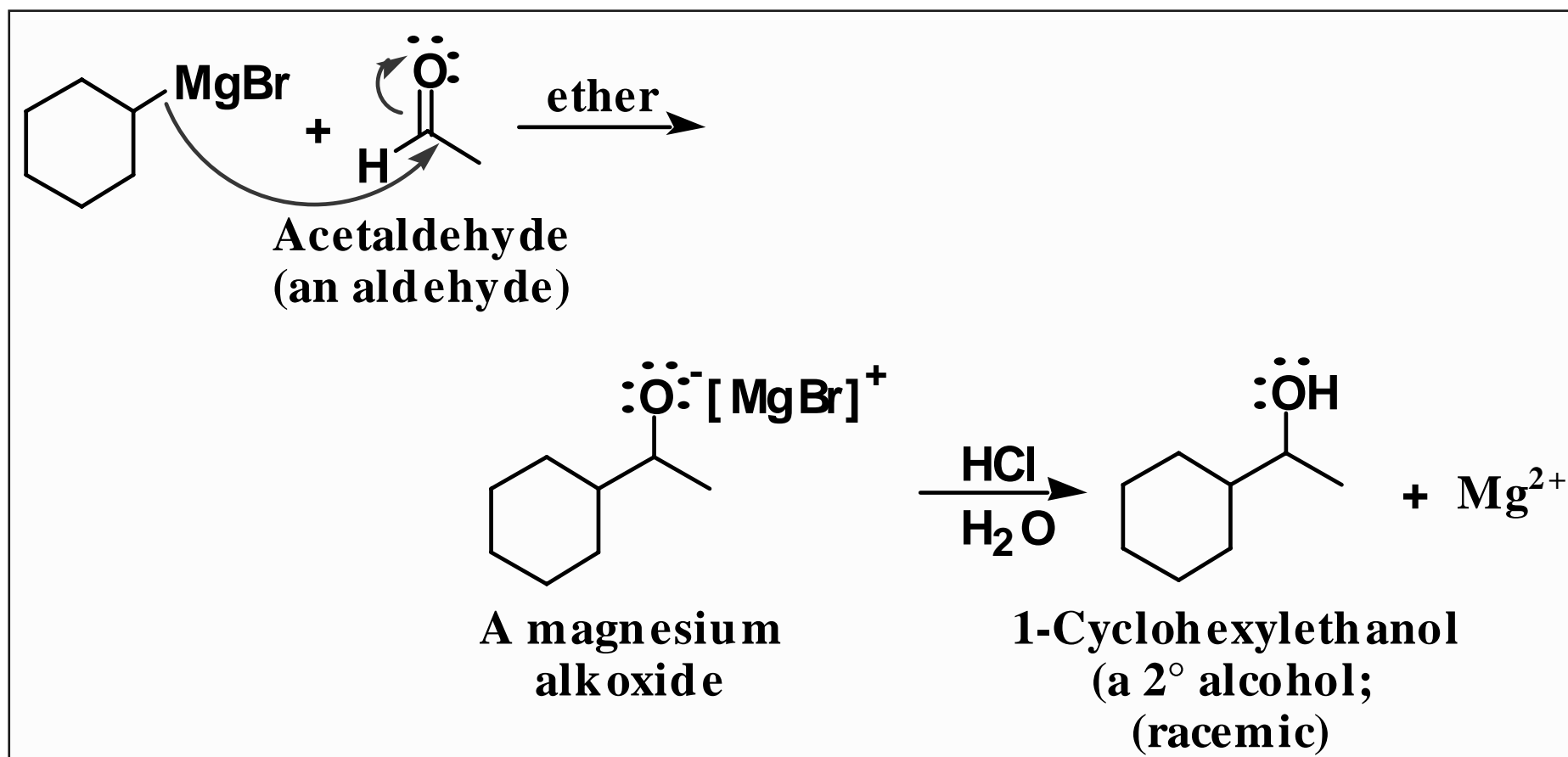
Grignard Reagents

- addition of a Grignard reagent to formaldehyde followed by H_3O^+ gives a 1° alcohol



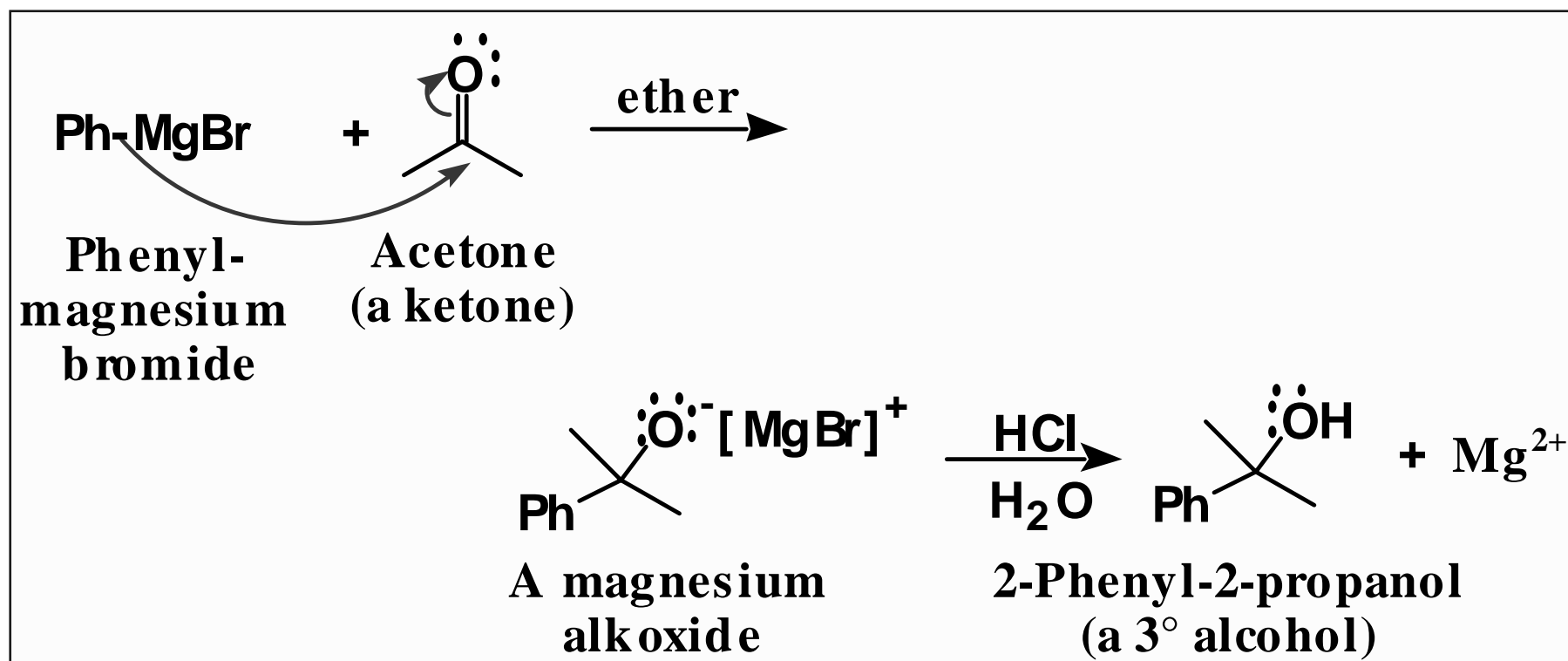
Grignard Reagents

– addition to any other RCHO gives a 2° alcohol

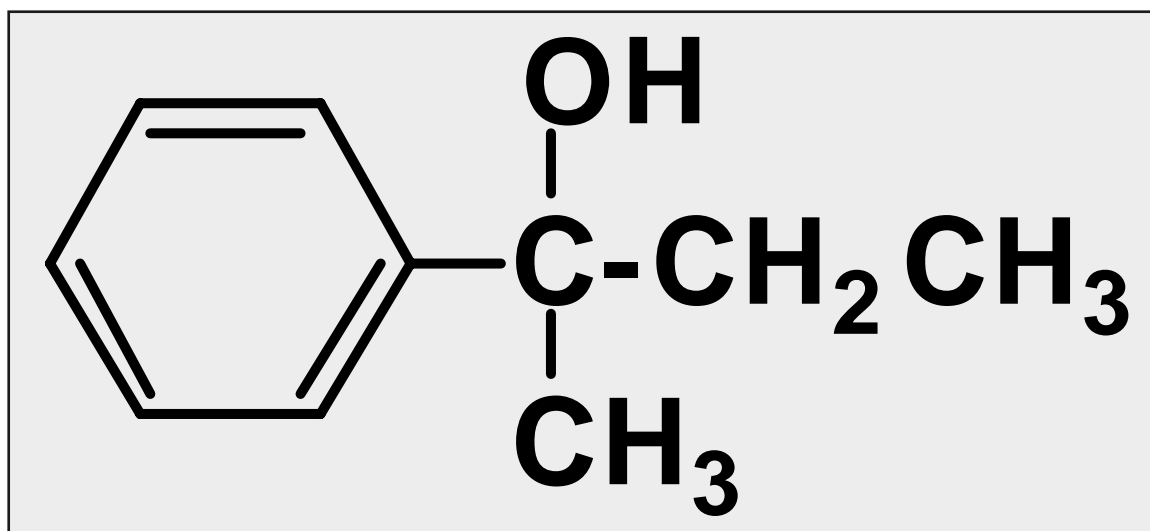


Grignard Reagents

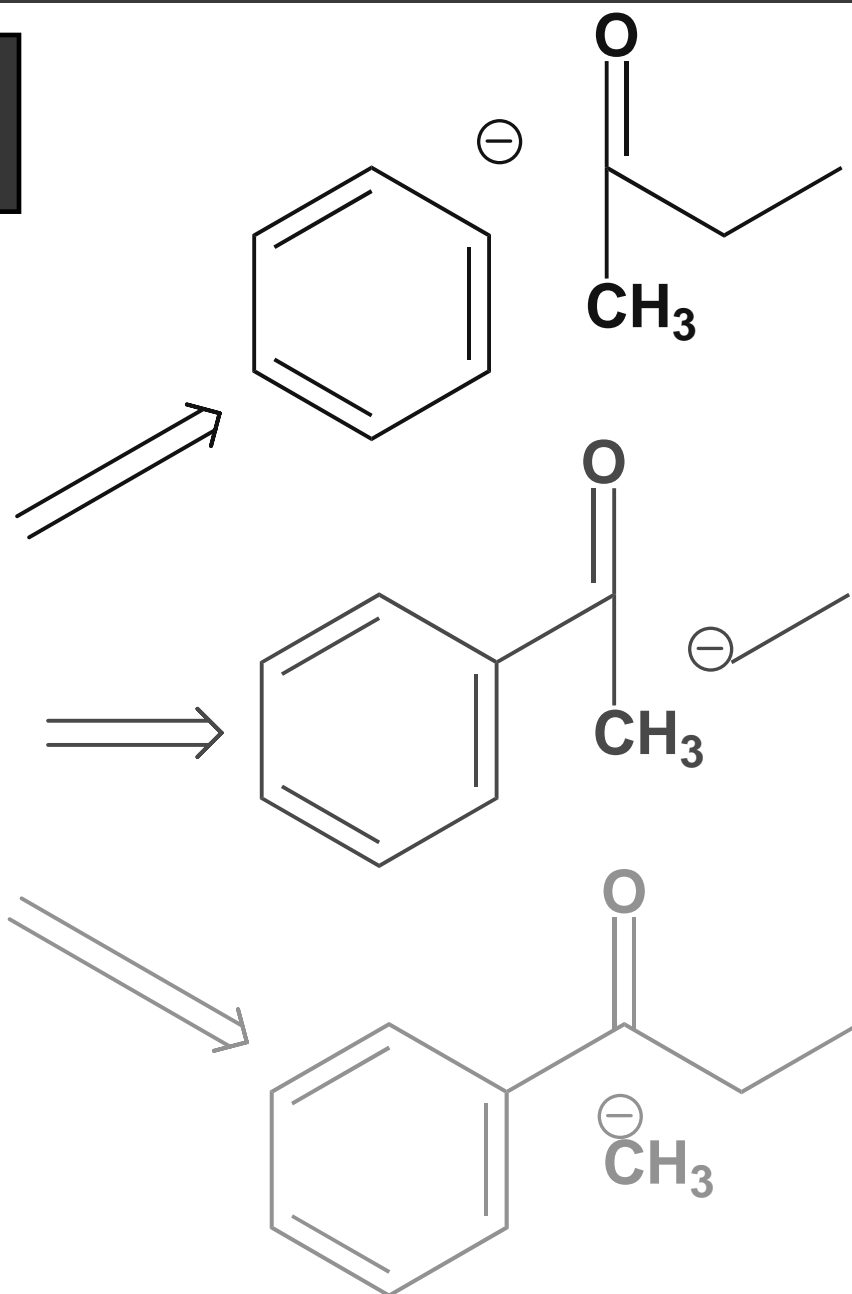
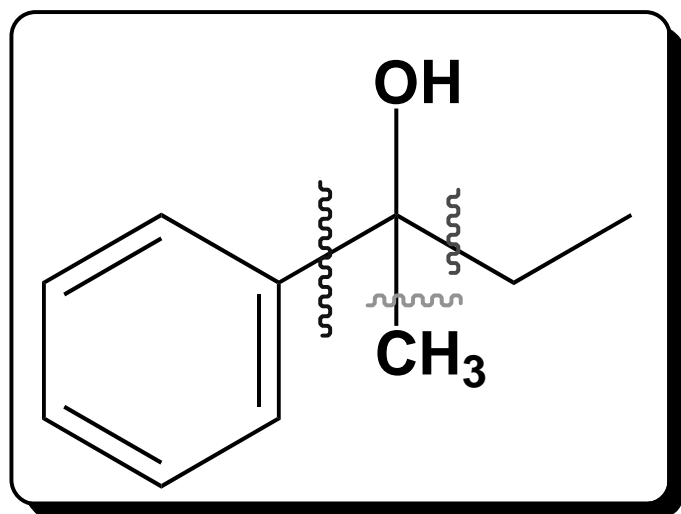
– addition to a ketone gives a 3° alcohol

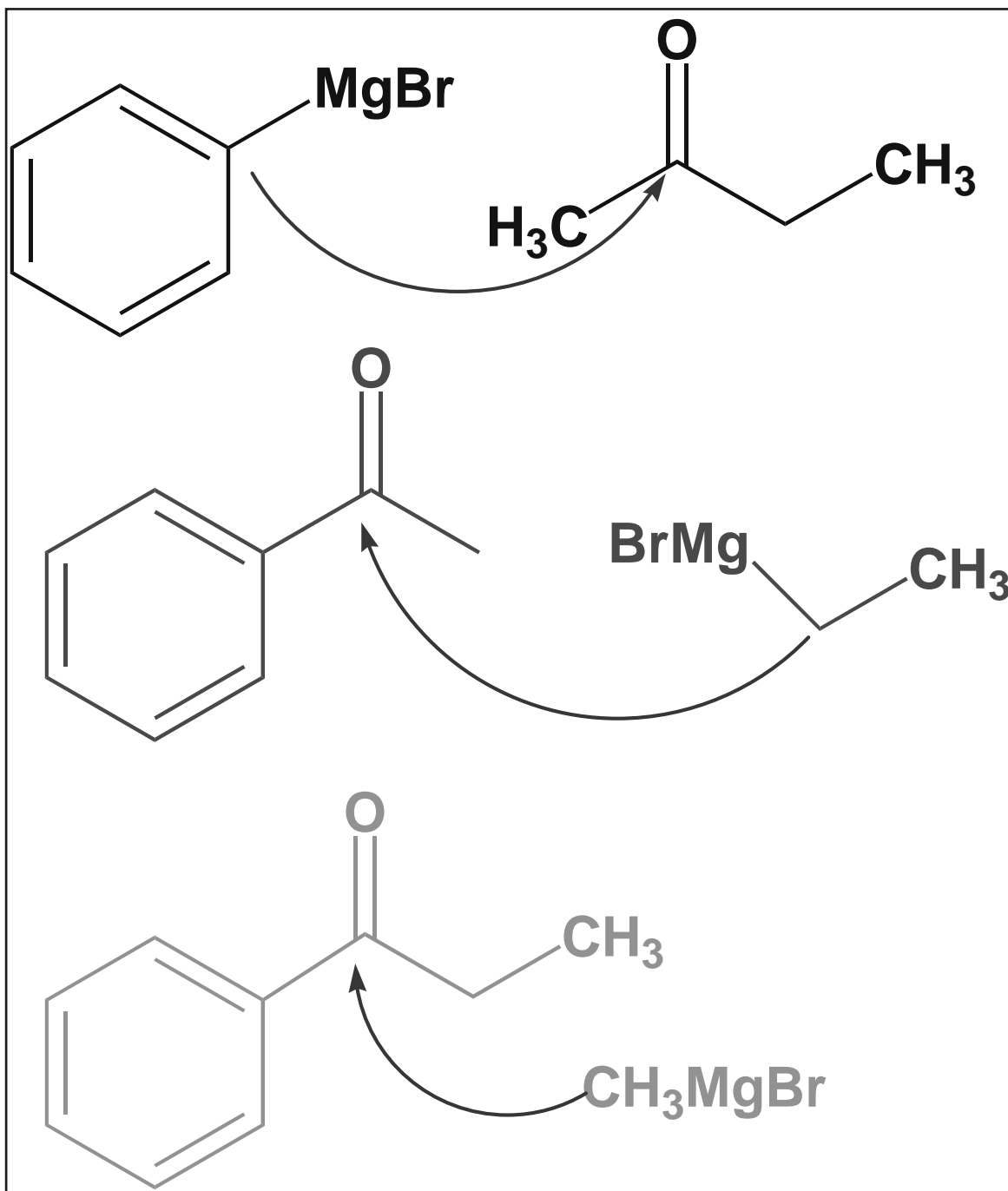


Problem: 2-phenyl-2-butanol can be synthesized by three different combinations of a Grignard reagent and a ketone. Show each combination.

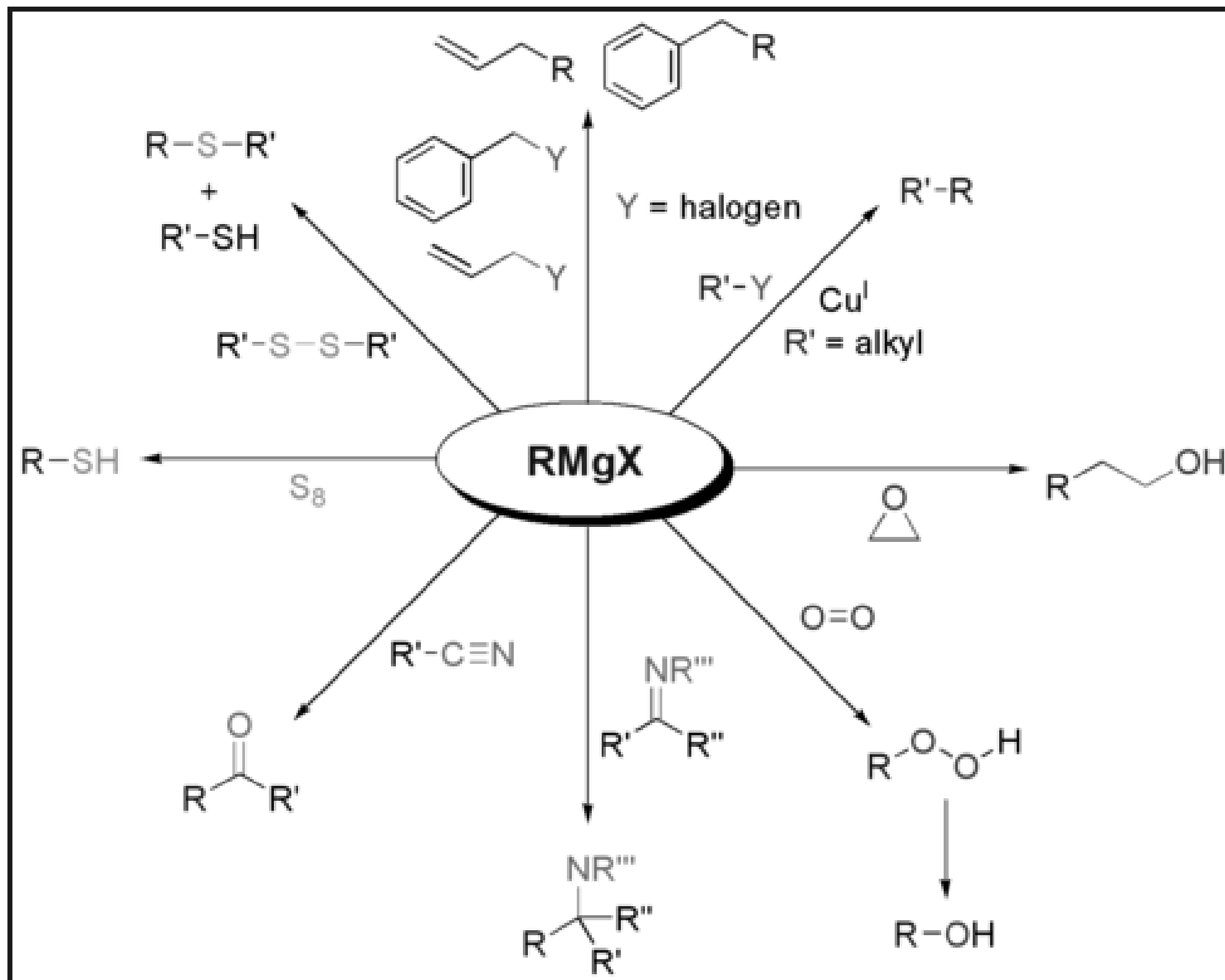


A Simple Retrosynthetic Analysis



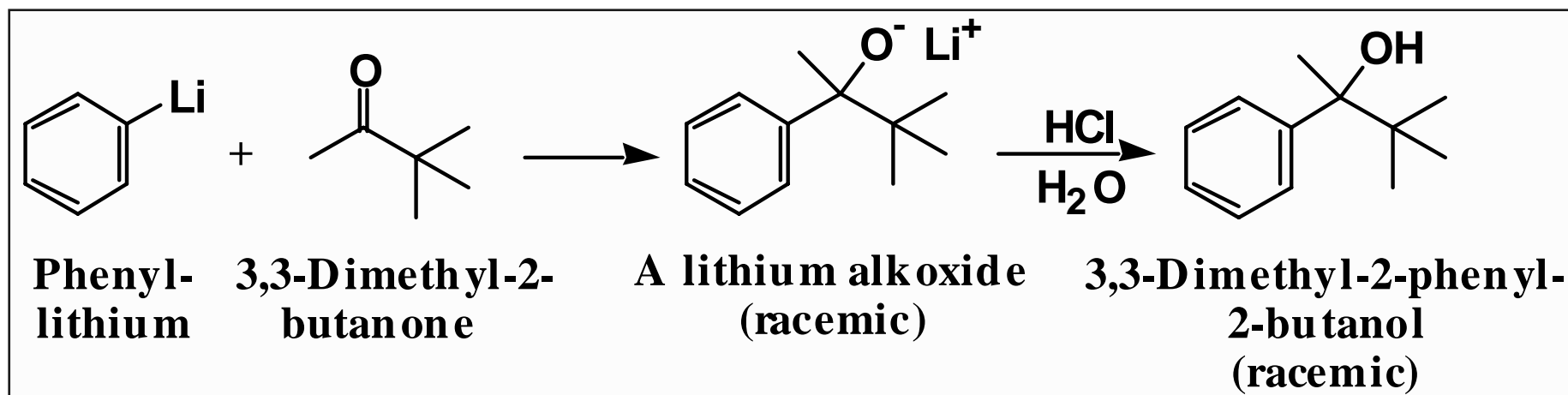


Common Conversions using Grignard Reagents



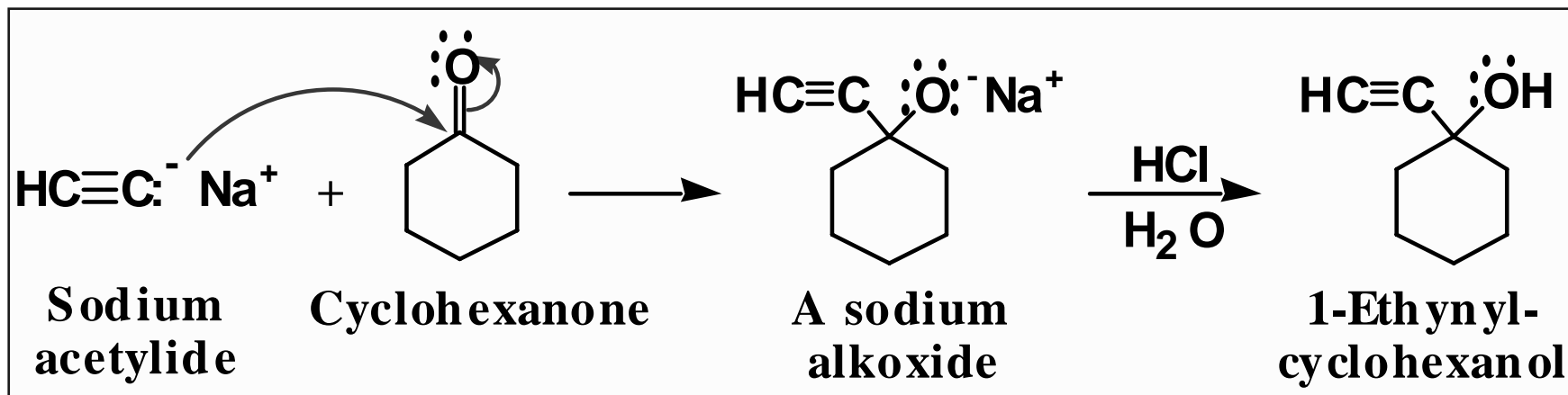
Organolithium Reagents

Organolithium compounds are generally more reactive in C=O addition reactions than RMgX, and typically give higher yields



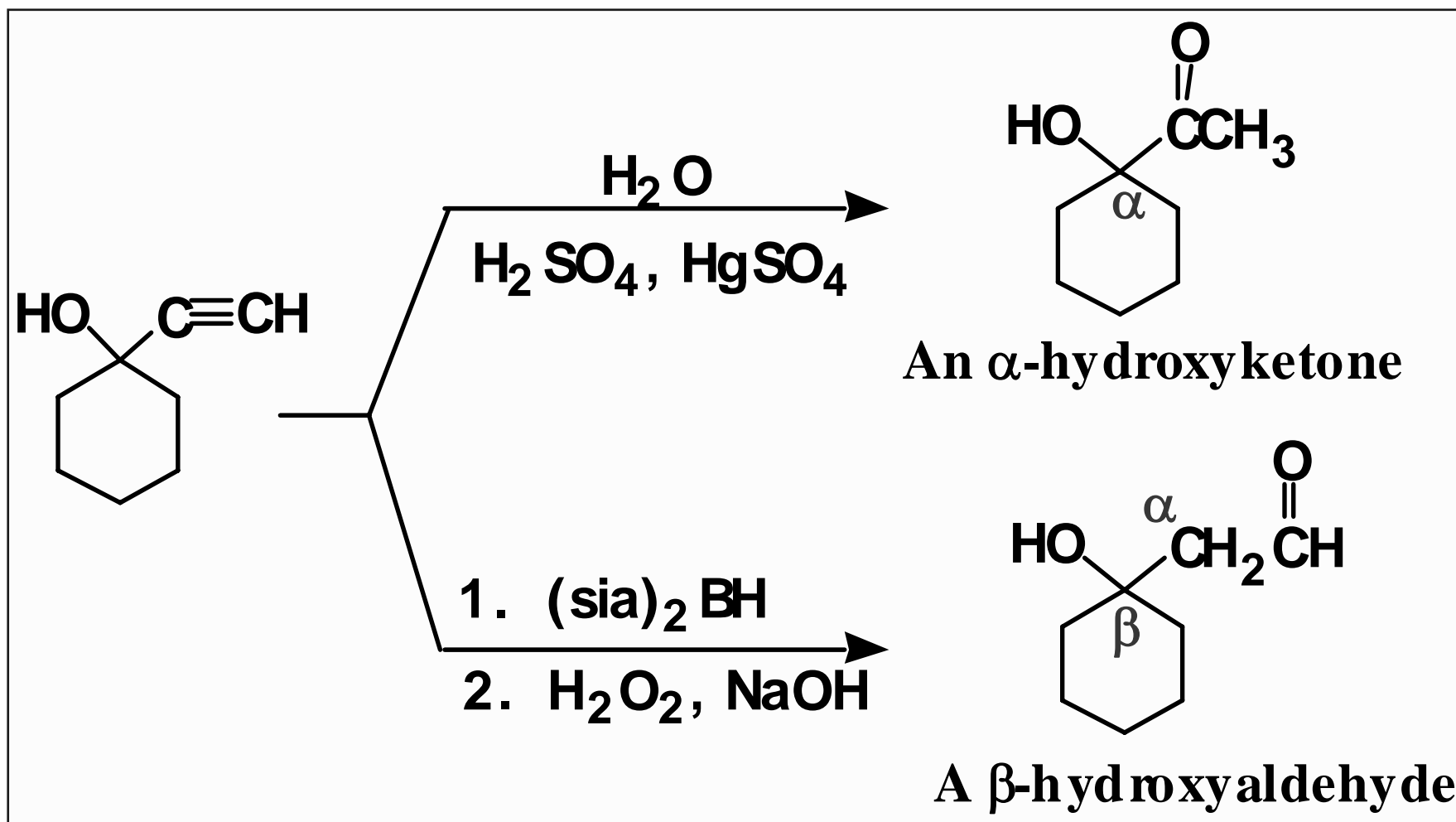
Salts of Terminal Alkynes

- Addition of an alkyne anion followed by H_3O^+ gives an α -acetylenic alcohol
- Note: this is a 2-C homologation



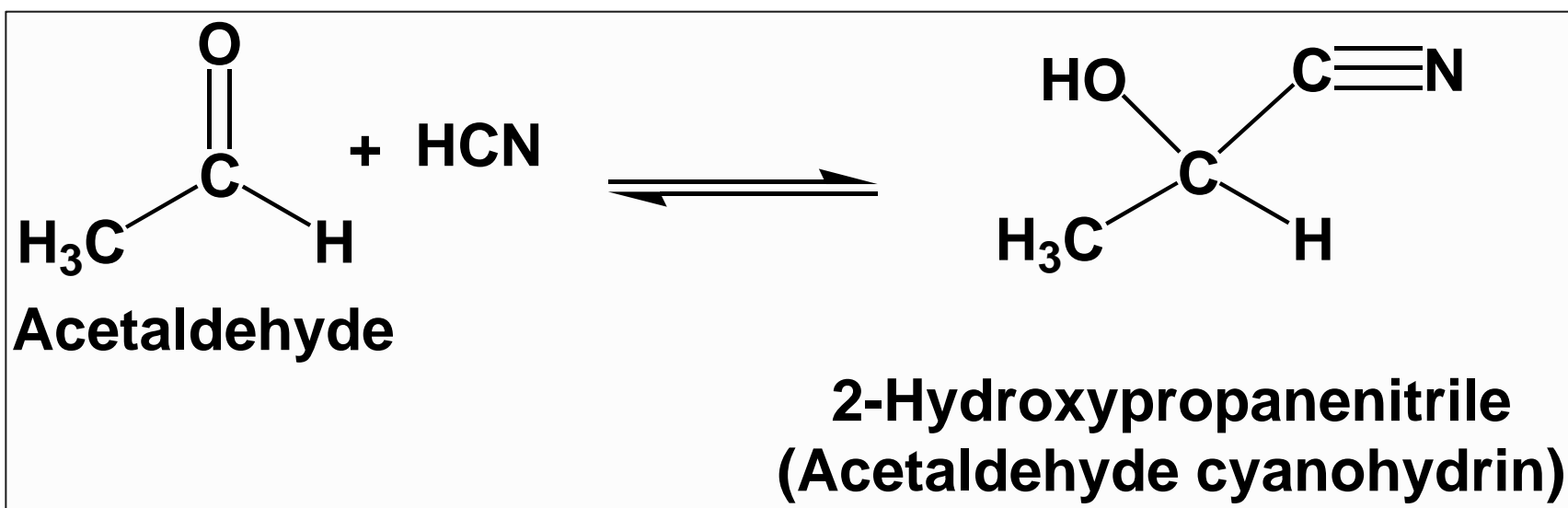
Homologation is a term used for extending a carbon chain

Oxidation of Terminal Alkynes



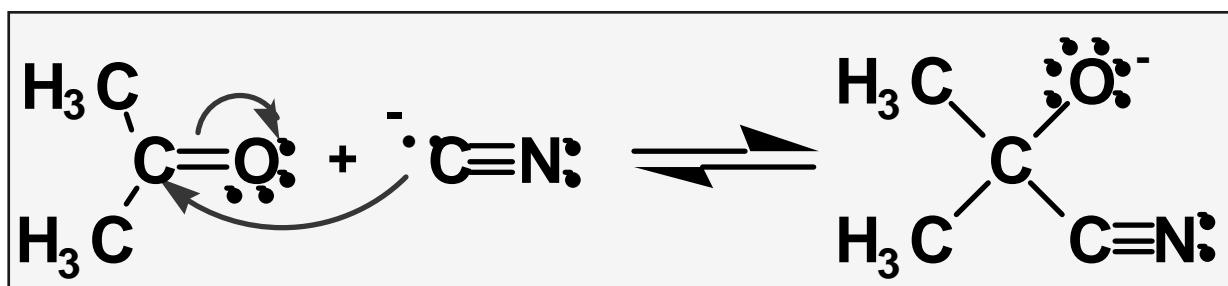
Addition of HCN

- HCN adds to the C=O group of an aldehyde or ketone to give a cyanohydrin
- Cyanohydrin: a molecule containing an -OH group and a -CN group bonded to the same carbon

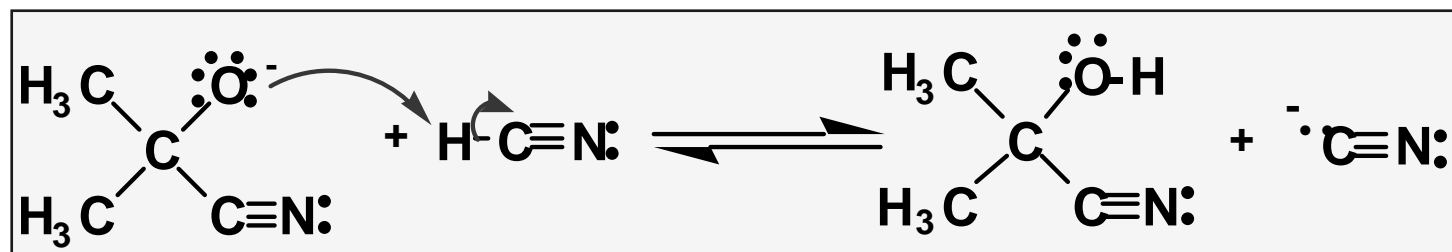


Addition of HCN

- Mechanism of cyanohydrin formation
 - Step 1: nucleophilic addition of cyanide to the carbonyl carbon



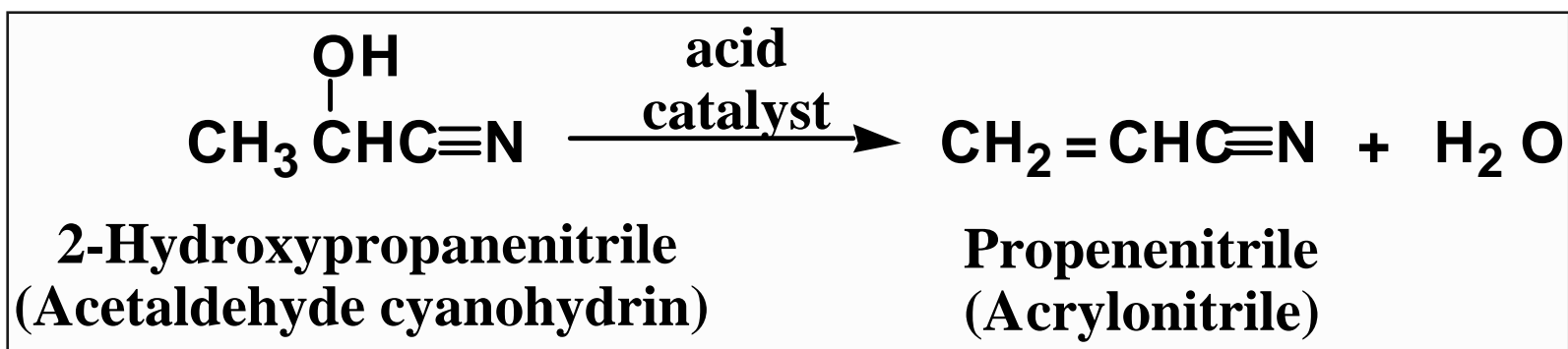
- Step 2: proton transfer from HCN gives the cyanohydrin and regenerates cyanide ion



Cyanohydrins

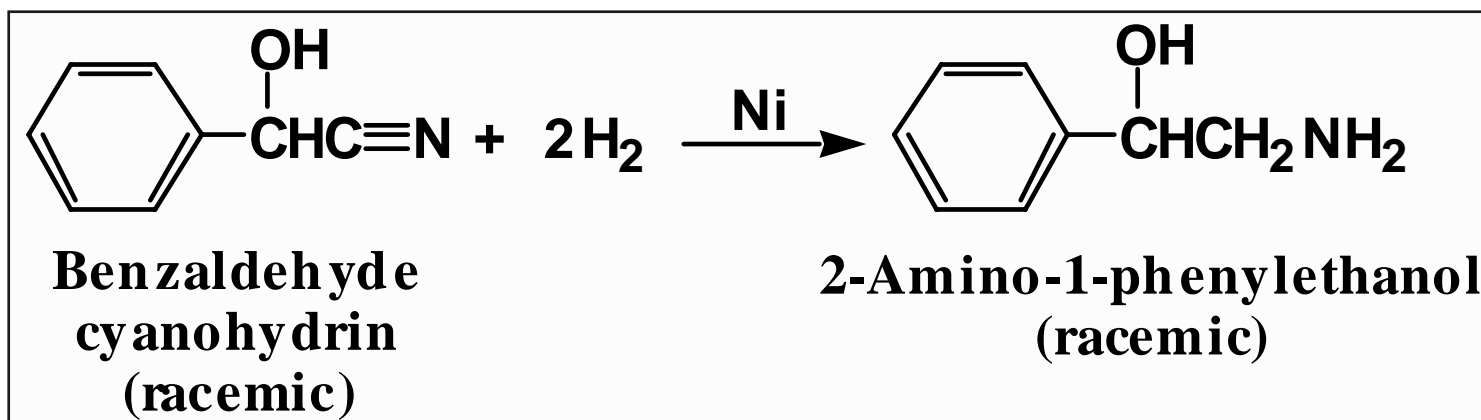
- The value of cyanohydrins
 - acid-catalyzed dehydration of alcohol gives an alkene

Monomer for polymers



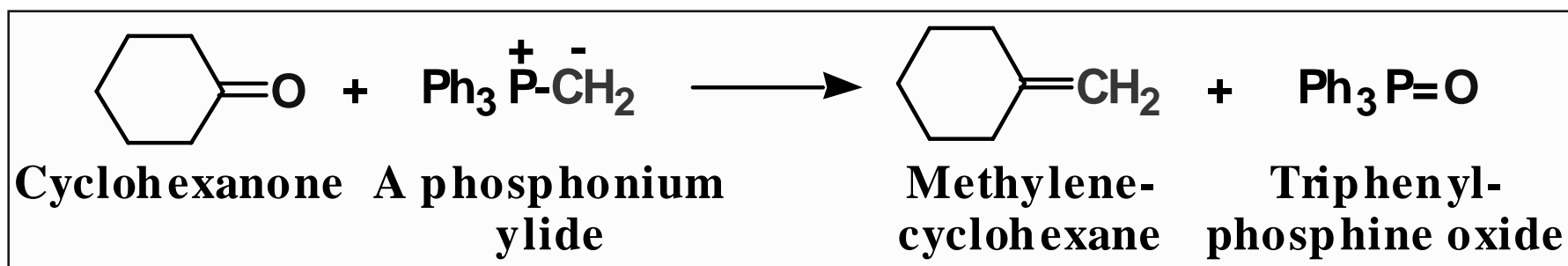
Cyanohydrins

- catalytic reduction of the cyano group gives a 1° amine

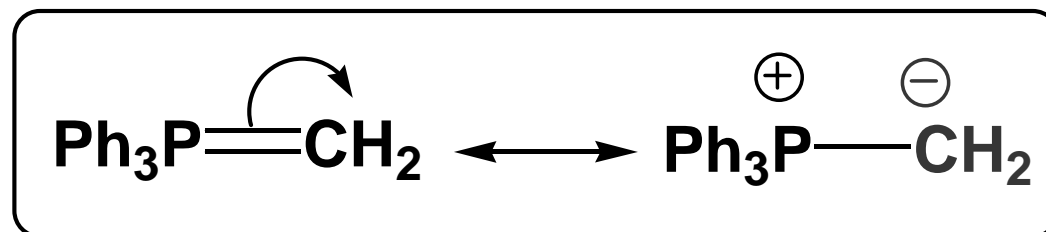


Wittig Reaction

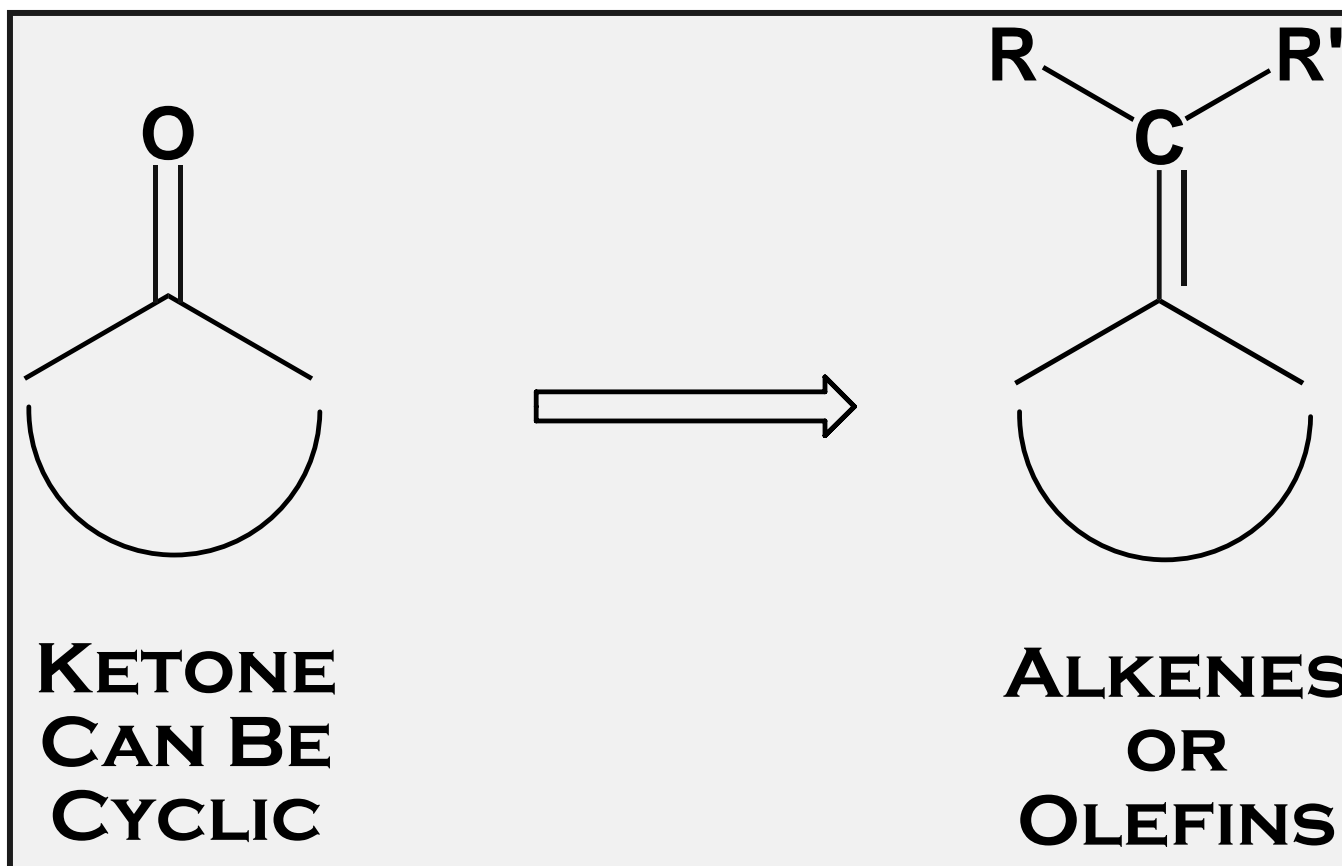
The Wittig reaction is a very versatile synthetic method for the synthesis of alkenes (olefins) from aldehydes and ketones



Ylides are reagents (or reactive intermediates) which have adjacent charges:



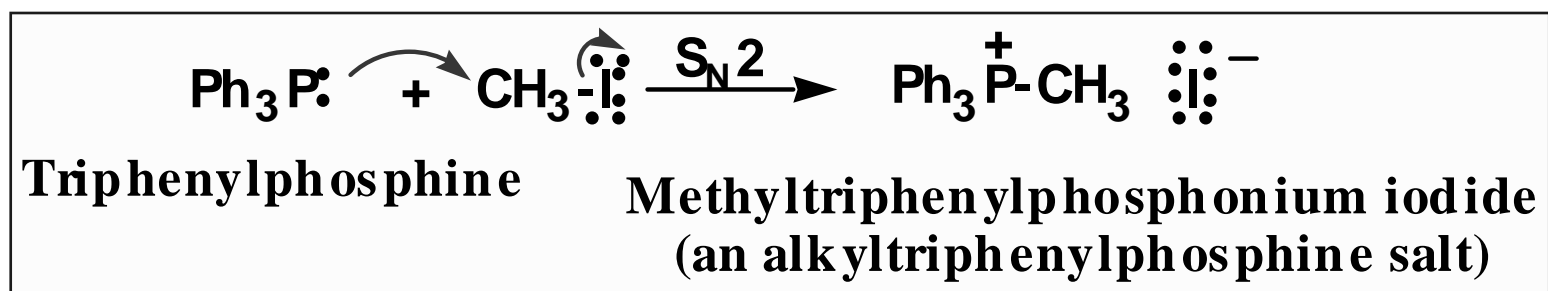
Overall Synthetic Transformation of Wittig Reagents & Its Variations



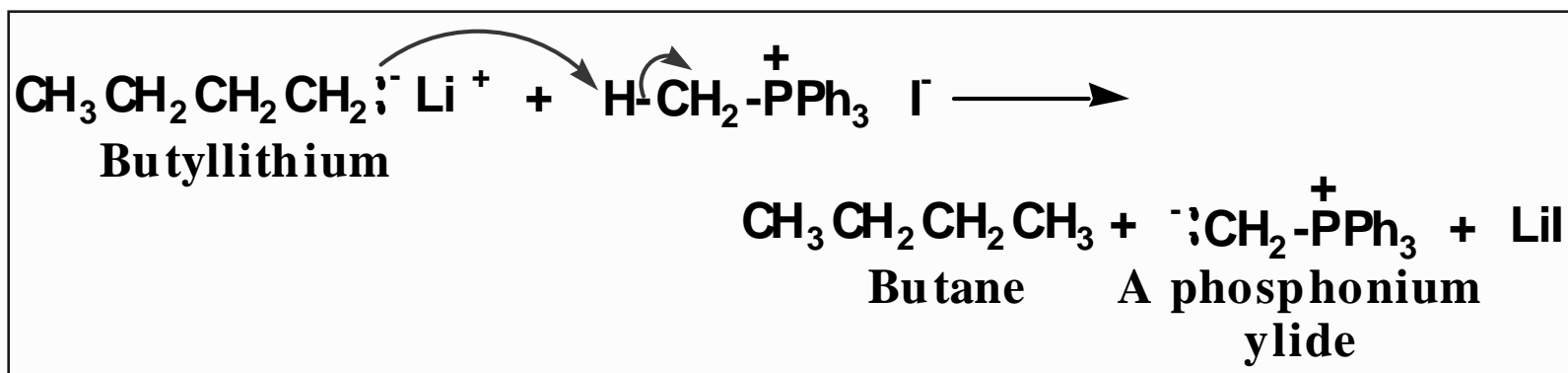
Phosphonium ylides

Phosphonium ylides are formed in two steps:

Step 1: nucleophilic displacement of iodine by triphenylphosphine



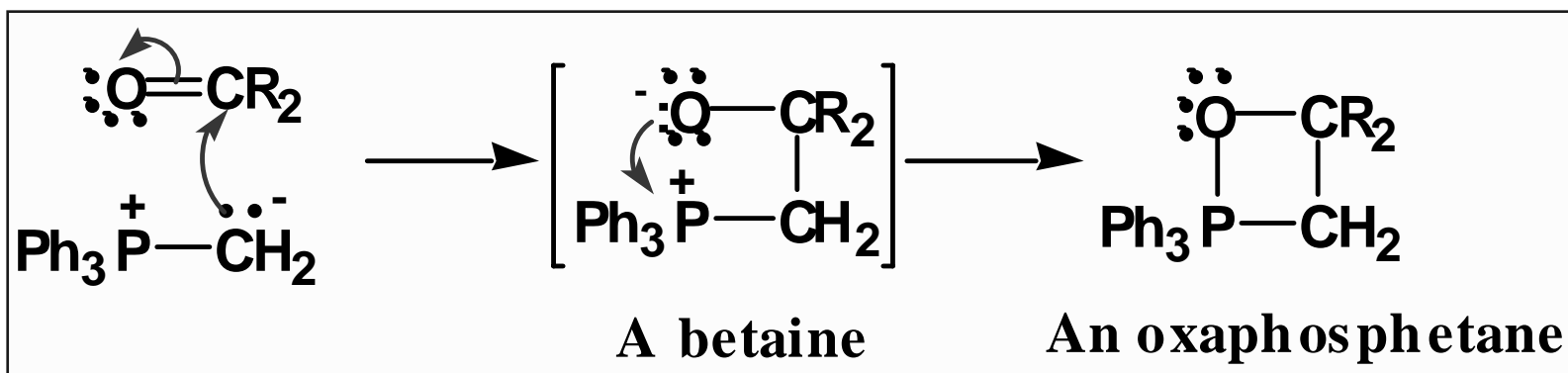
Step 2: treatment of the phosphonium salt with a very strong base, most commonly BuLi, NaH, or NaNH₂



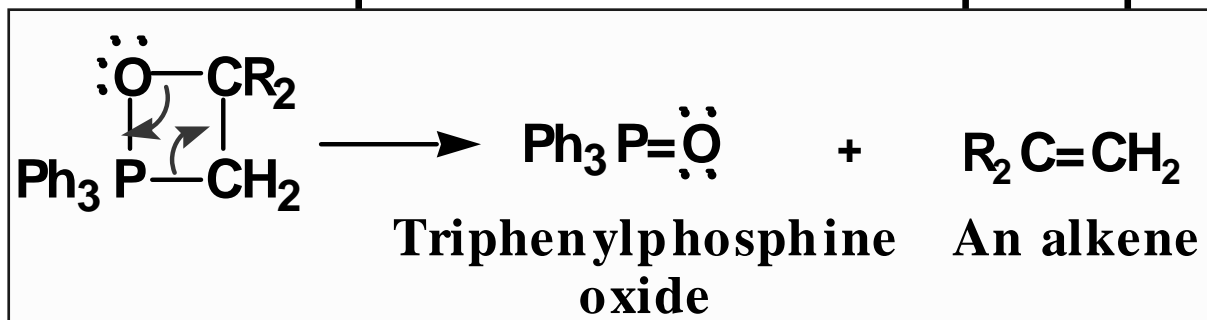
Wittig Reaction

Phosphonium ylides react with the C=O group of an aldehyde or ketone to give an alkene

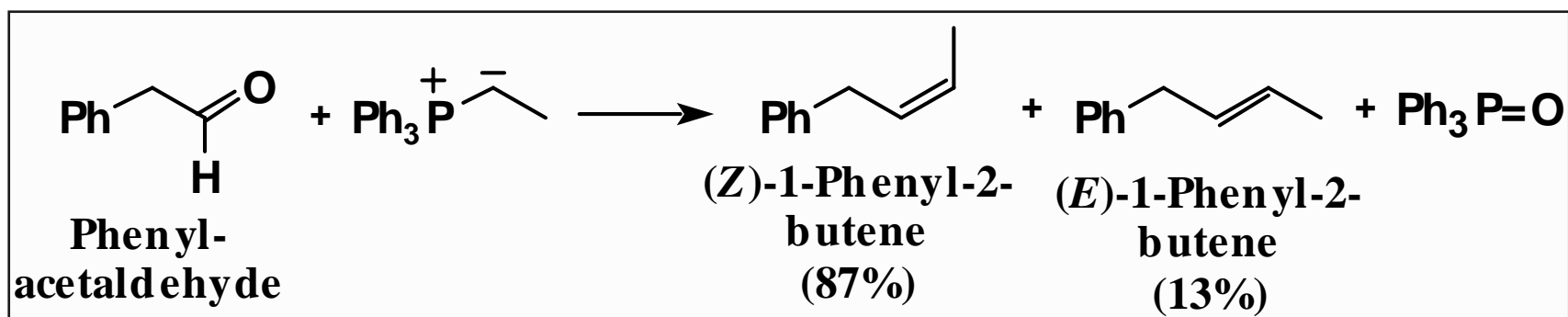
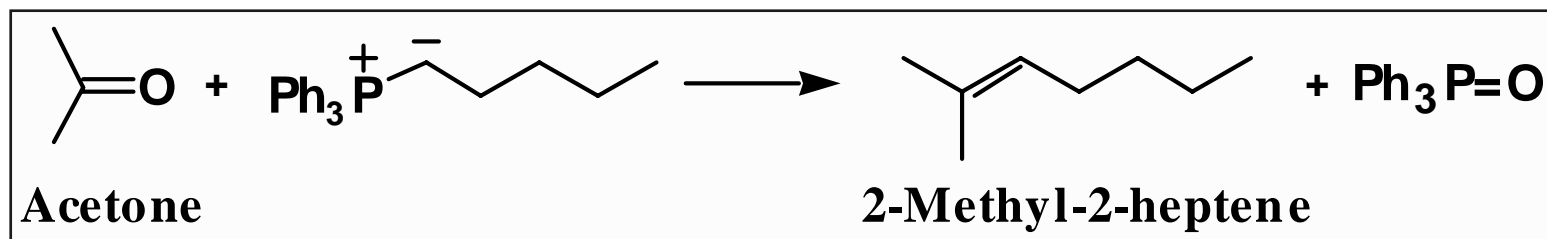
Step 1: nucleophilic addition of the ylide to the electrophilic carbonyl carbon



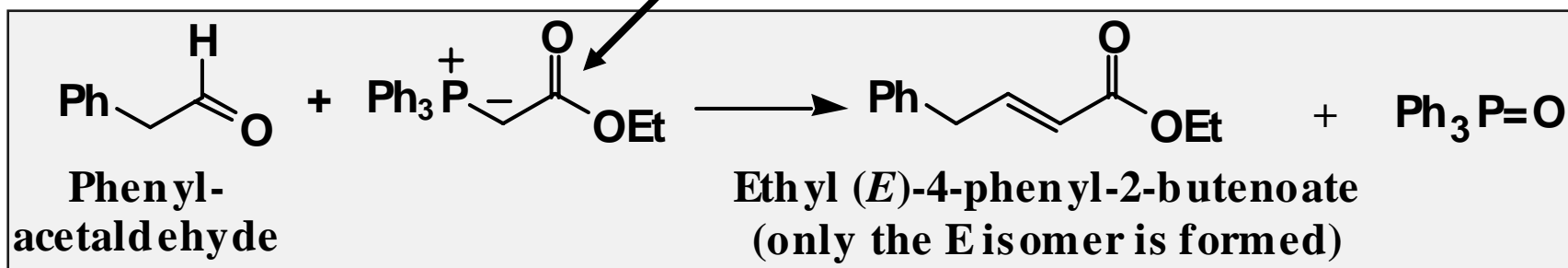
Step 2: decomposition of the oxaphosphetane



Wittig Reaction

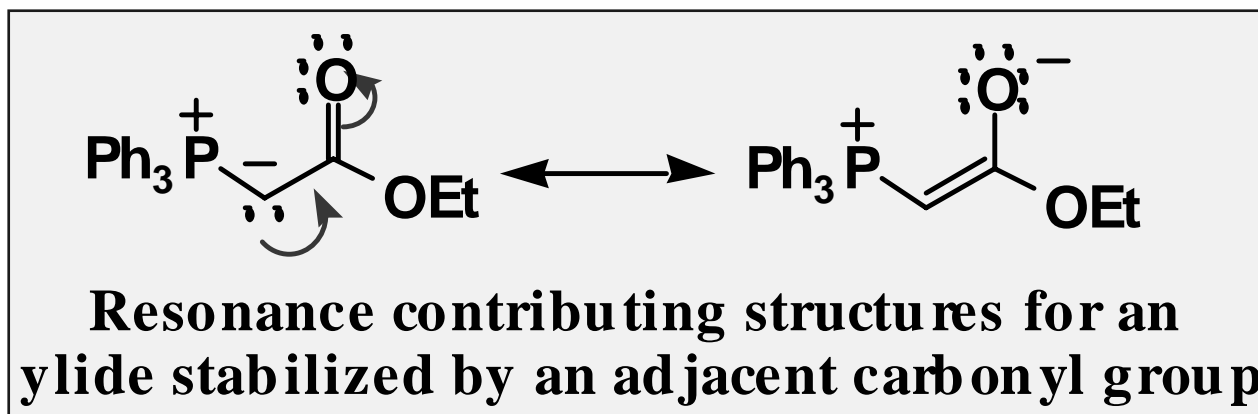


Resonance stabilized Wittig reagent:



Wittig Reaction

- some Wittig reactions are *Z* selective, others are *E* selective
- Wittig reagents with an anion-stabilizing group, such as a carbonyl group, adjacent to the negative charge are generally *E* selective

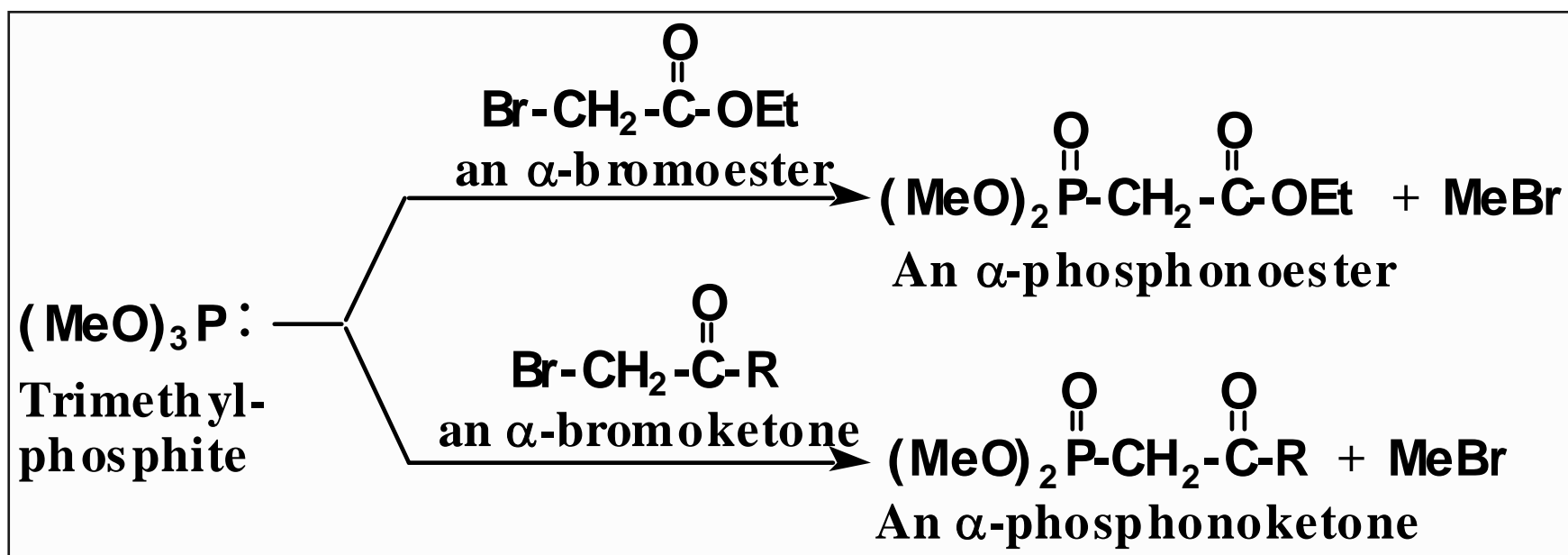


- Wittig reagents without an anion-stabilizing group are generally *Z* selective (cis)

A Variant of the Wittig Reagent

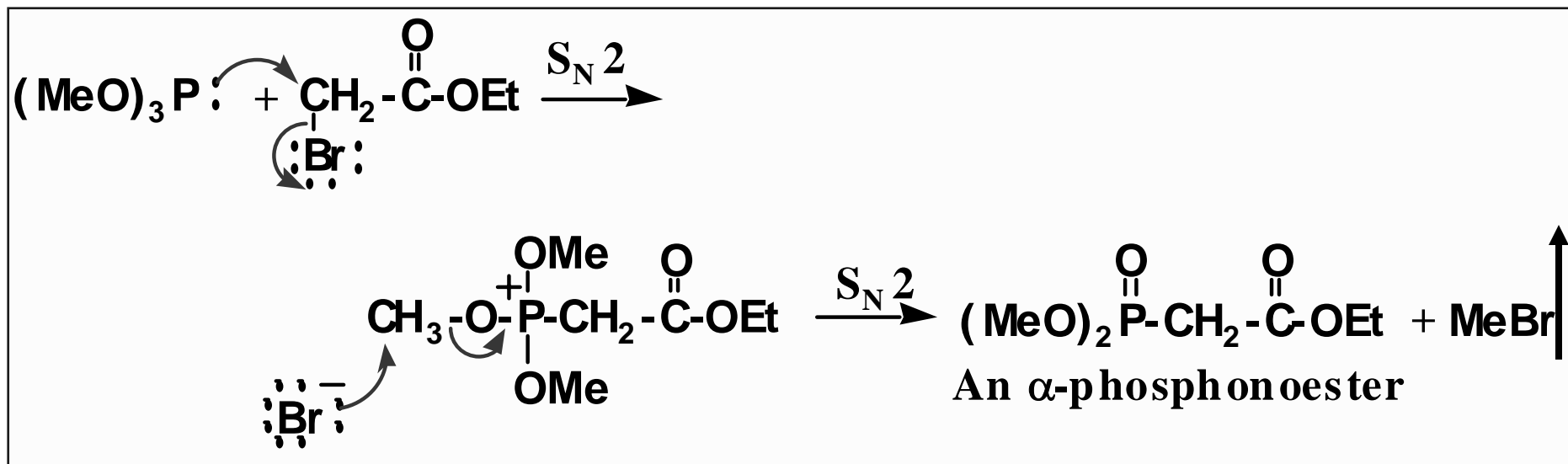
Horner-Emmons-Wadsworth modification

– uses a **phosphonoester**



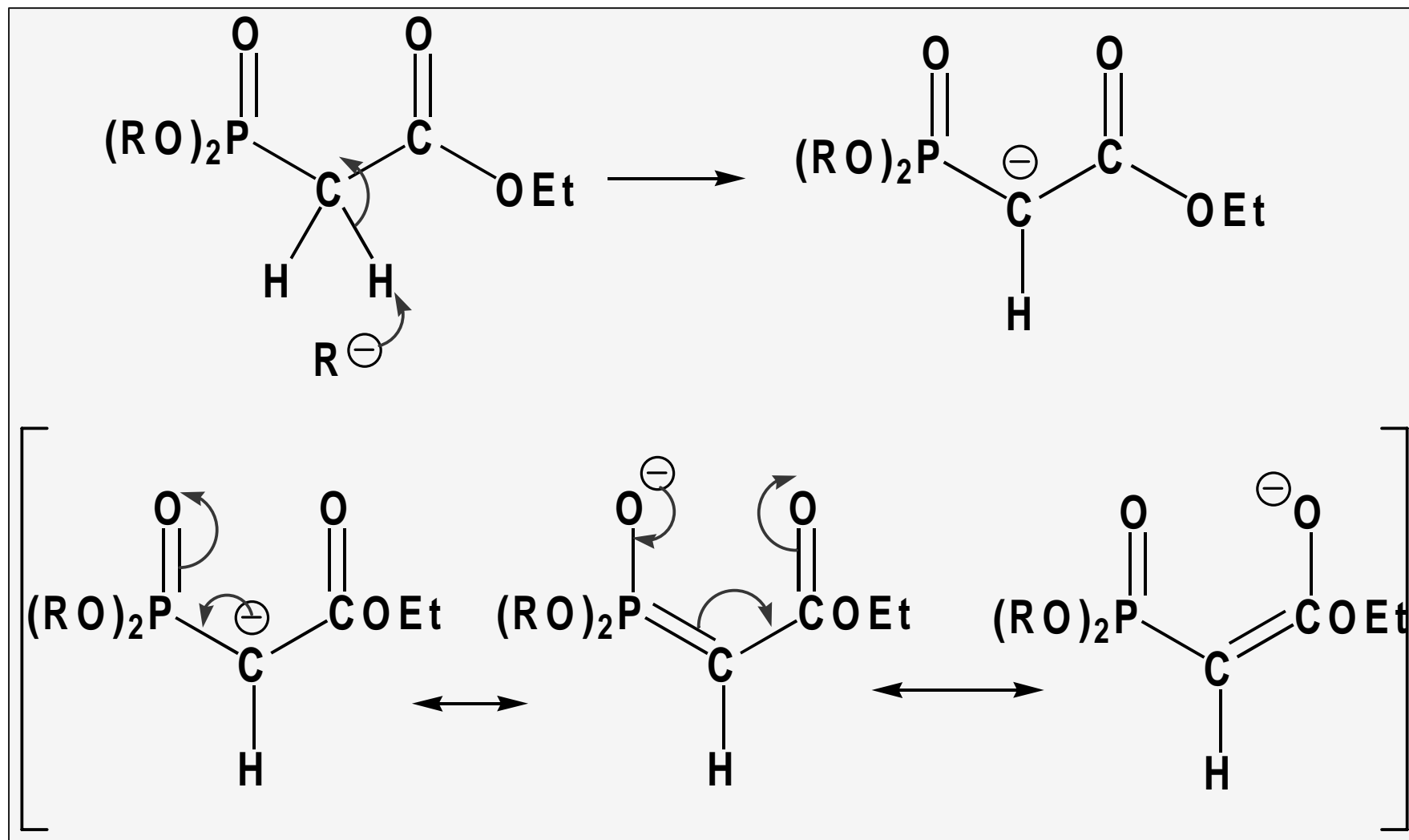
These reagents are usually isolated.

– phosphonoesters are prepared by successive S_N2 reactions



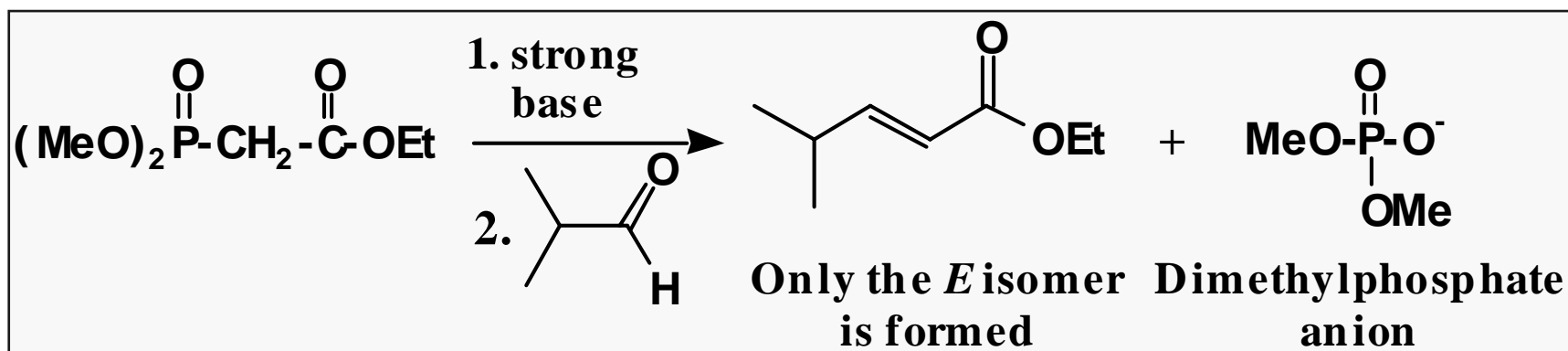
Very exothermic as MeBr is boiled from the reaction mixture

Resonance Stabilization:

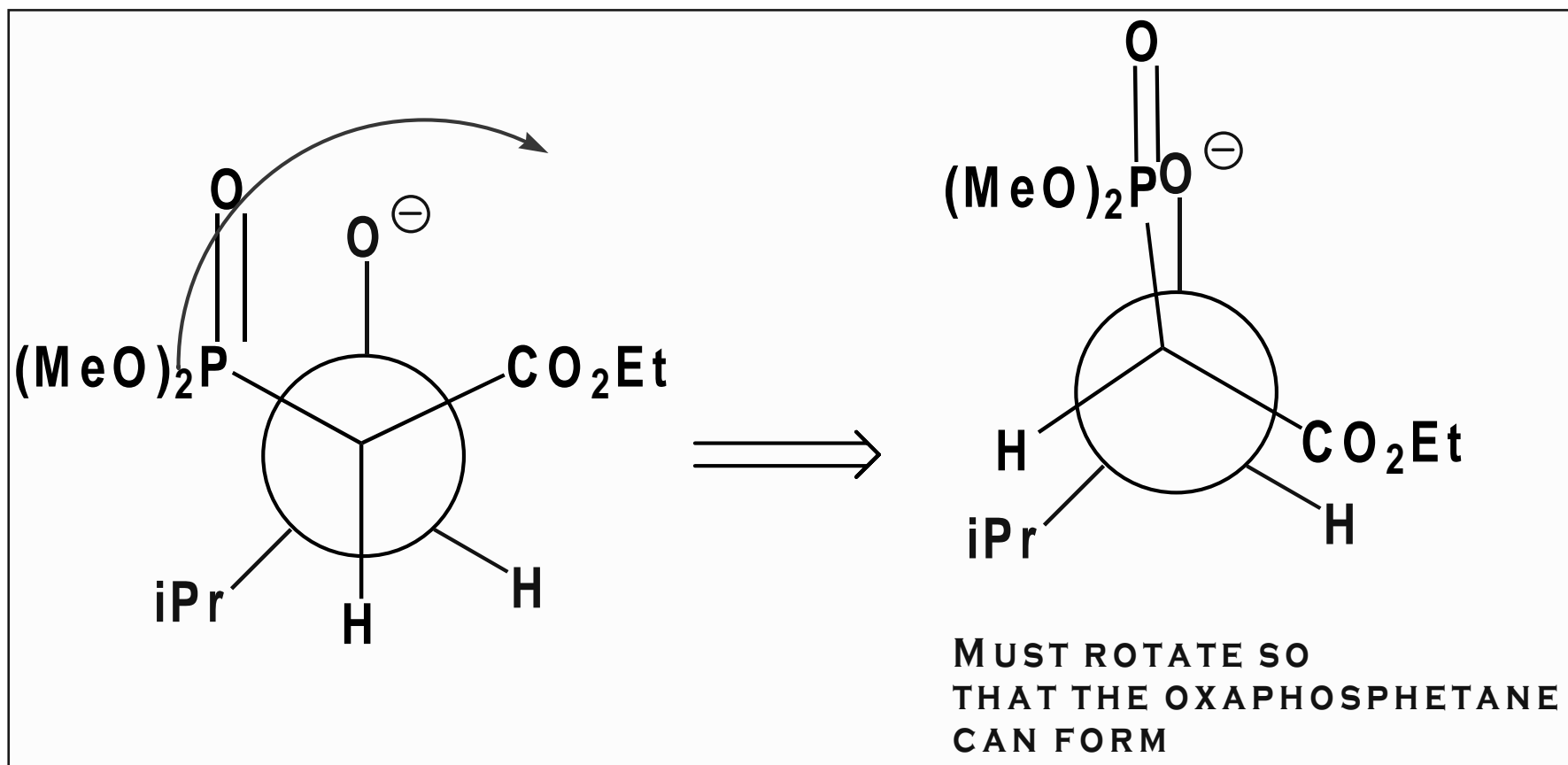


The Use of Phosphonoesters

1. treatment of a phosphonoester with a strong base followed by an aldehyde or ketone gives an alkene
2. a particular value of using a phosphonoester-stabilized anion is that they are almost exclusively *E* selective



Why do Stabilized Horner-Emmons-Wadsworth Reagents give the E olefin?



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