



Organic Reaction Mechanism And Reagents



Fundamentals of
organic reaction
mechanisms

The Nobel prize in Chemistry for organic reactions

Few important
organic reactions



Engineering Chemistry: CYC 01
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Syllabus

Chapter-1: Fundamentals of organic reaction mechanisms; Few important reactions and their mechanism along with their applications; Robinson annulation, Hydroboration reaction, Metathesis using Grubb's catalyst and Wittig reaction. Organometallic reagents (Gilman reagents),
3 Lectures



Sir Robert Robinson
The Nobel Prize in Chemistry 1947



Venkatraman Ramakrishnan
The Nobel Prize in Chemistry 2009
Born: 1952, Chidambaram, Tamil Nadu, India
"for studies of the structure and function of the ribosome."



Victor Grignard
The Nobel Prize in Chemistry 1912



The noble prize in chemistry 1979
Herbert C. Brown



Geora Wittig



Photo: U. Montan
Yves Chauvin



The noble prize in chemistry 2005

Robert H. Grubbs

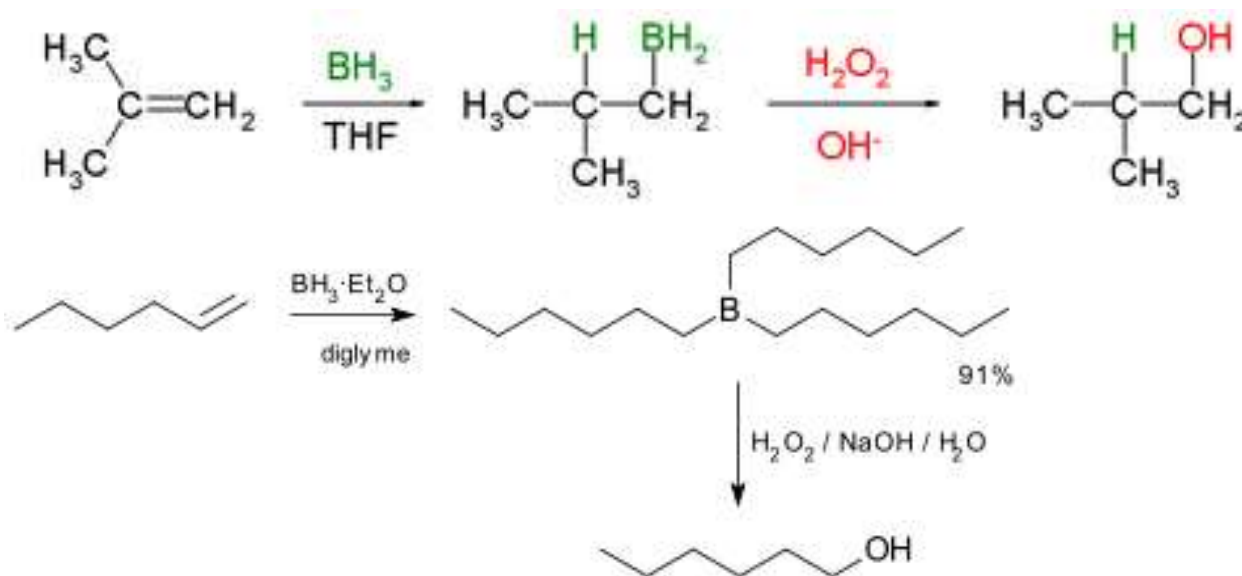


Richard R. Schrock

Hydroboration reaction

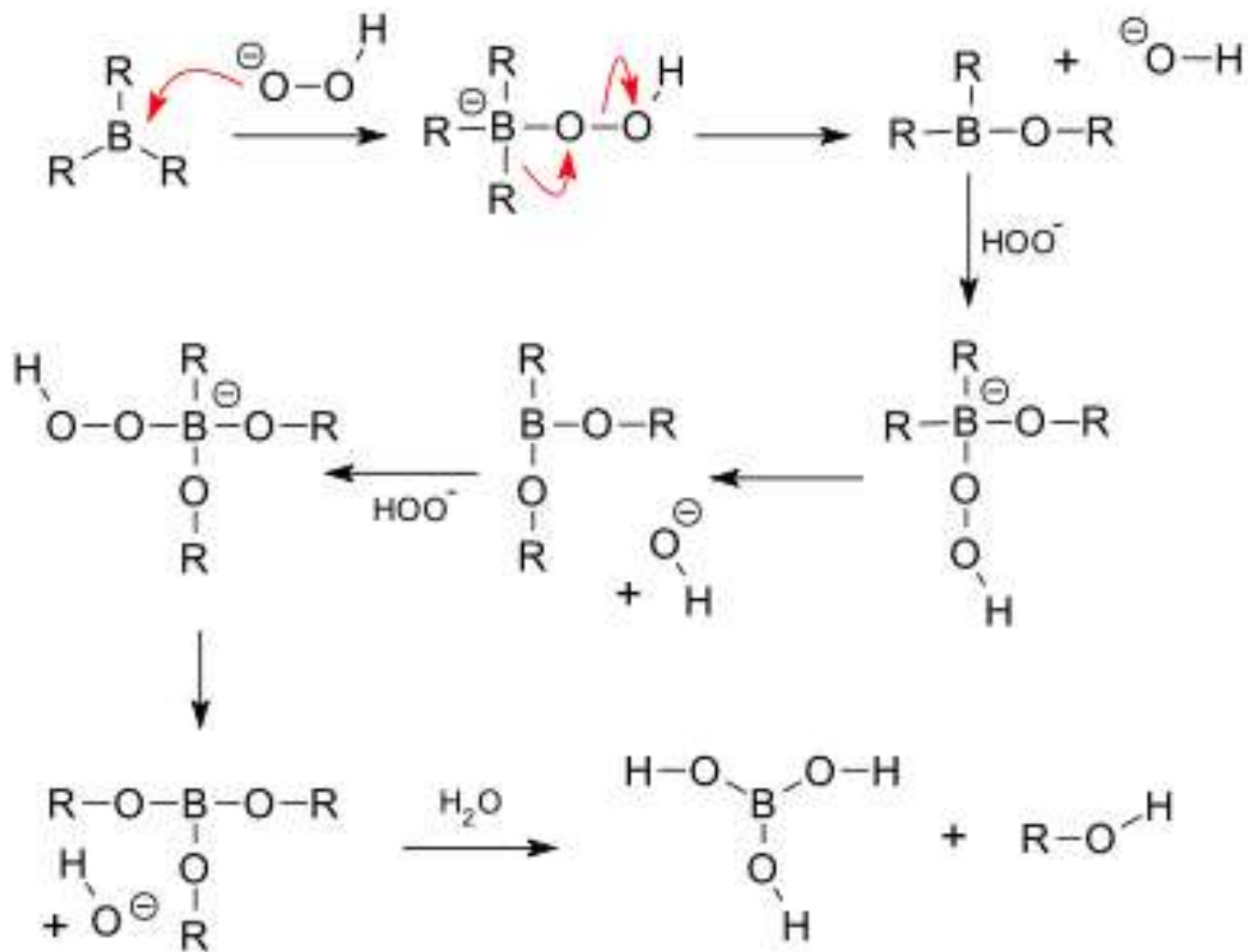
In hydroboration reaction, alkenes are converted to alcohol in a two-step process, first step is syn addition of hydride and dihydroborane to double bond according to anti-Markovnikov rule. Hydroboration-oxidation is an anti-Markovnikov reaction, with the hydroxyl group attaching to the less-substituted carbon. The reaction thus provides a more stereo-specific and regio-selective alternative to other hydration reactions such as acid-catalysed addition and the oxymercuration-demercuration reaction. The reaction was first reported by H. C. Brown in the late 1950s and it was recognized in his receiving the Nobel prize in Chemistry in 1979.

The generalized reaction scheme is as follows,

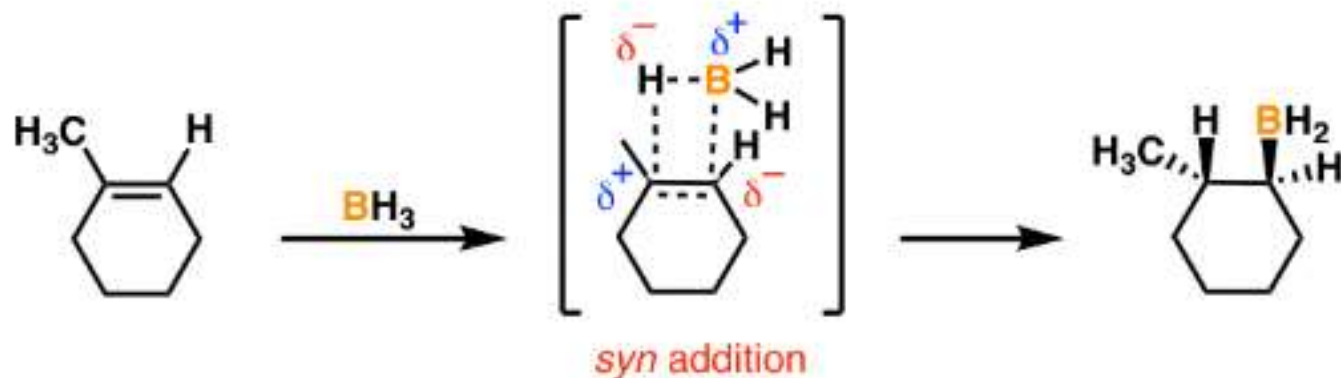


H. C. Brown

Mechanism of Hydroboration reaction:



The Hydroboration Mechanism



- **Concerted transition state**

C-H and C-B bonds are formed at approximately the same time

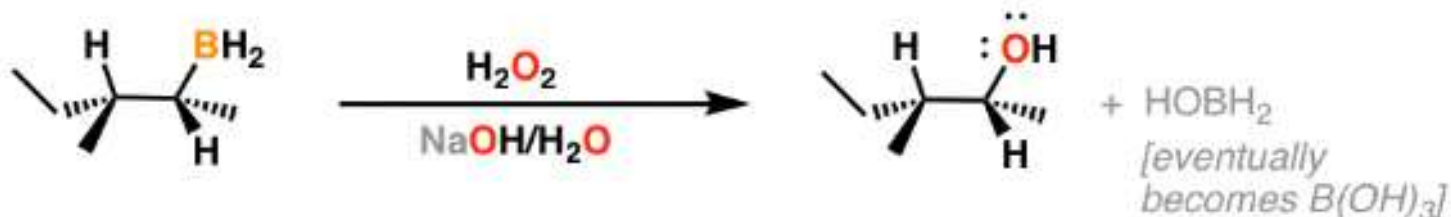
- **'Anti-Markovnikov' Regioselectivity**

The most favored transition state allows the partially negative hydrogen atom to form a bond with the carbon atom best able to bear positive charge (the "most substituted" carbon of the alkene in most cases)

- **'Syn' Stereochemistry**

In this concerted transition state, the C-H and C-B bonds are formed on the same side of the alkene (technical term: "suprafacial")

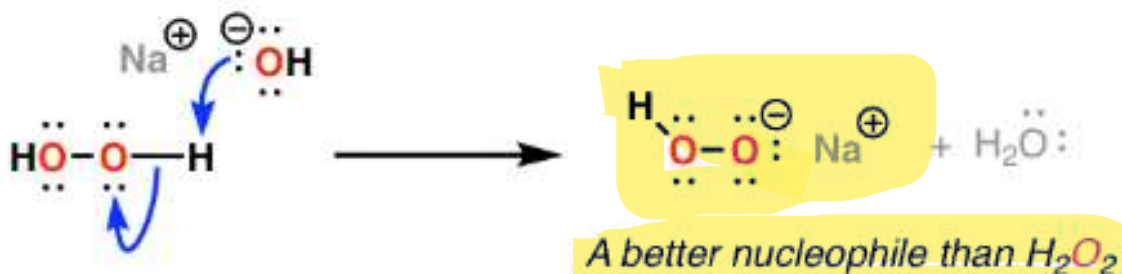
How does the oxidation step work?



- Stereochemistry at carbon is preserved

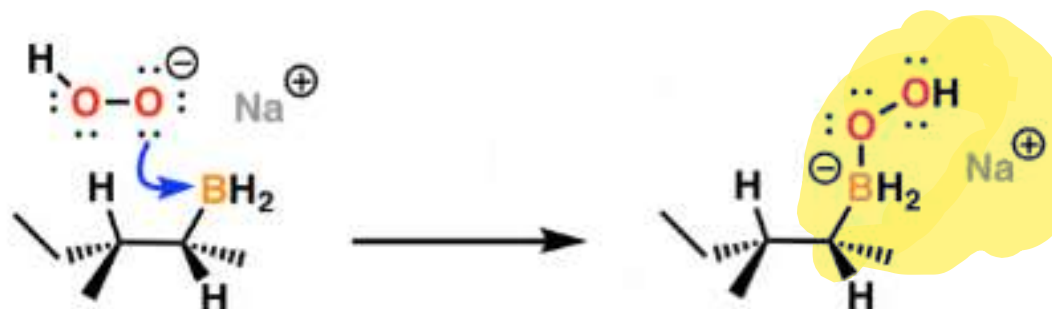
The first step here is deprotonation of hydrogen peroxide to give NaO-OH. Since the conjugate base is a better nucleophile, this speeds up the rate of the subsequent step.

Step 1: Deprotonation of H₂O₂



The next step is a simple Lewis acid-base reaction. The deprotonated peroxide anion then adds to the empty orbital of boron, forming a negatively charged boron species:

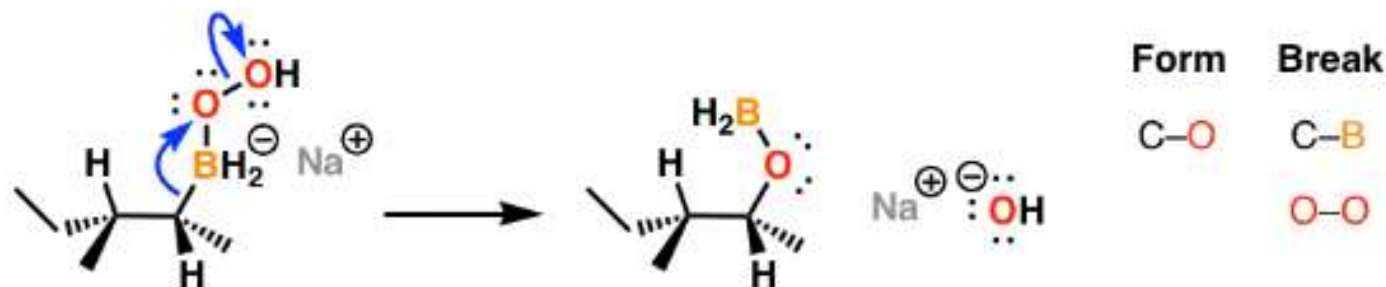
Step 2: attack of peroxide on boron



The next step often gives students difficulty. Here, the pair of electrons in the C–B bond migrates to oxygen, leading to breakage of C–B and formation of C–O, along with rupture of the O–O bond. It's very similar to [1,2-hydride and alkyl shifts we've seen previously](#), except that instead of migrating to the empty p orbital on a carbocation, the electron pair is essentially performing a “[backside attack](#)” on the σ^* orbital of the weak O–O bond.

Note how the charge on boron goes from negative to neutral.

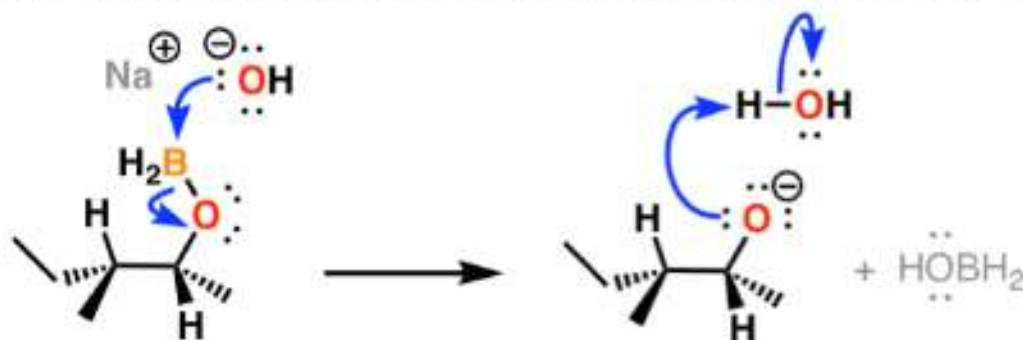
Step 3: Rearrangement



The next step can be written several different ways. Hydroxide ion attacks the empty p orbital of boron, and the O–B bond breaks. Although drawn here as a “concerted” step, where bond formation accompanies bond breakage, it need not be so, since addition of hydroxide to boron does not violate the octet rule.

Finally the negatively charged oxygen is then protonated by water (the solvent).

Step 4: Attack of hydroxide on boron.... and Step 5: protonation of alkoxide



That sums up the key points of the hydroboration reaction.

In the next post, we'll go through some other reactions of alkenes that might not share the *exact* same mechanism as hydroboration, but share a similar pattern of stereochemistry that is also a result of “concerted” reactions.

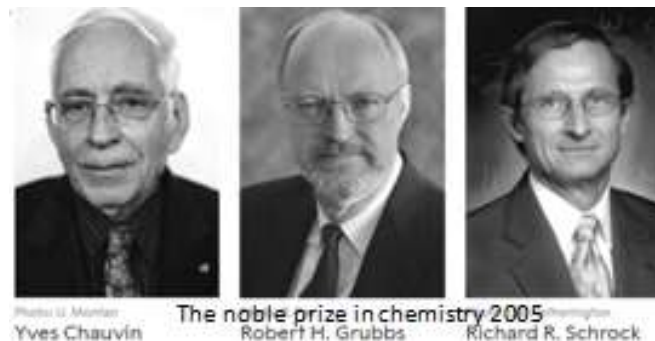
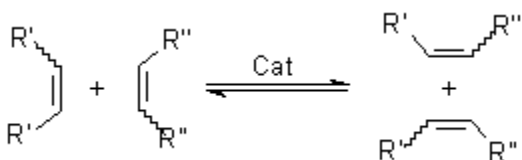
Olefin Metathesis (Grubbs Reaction)

Olefin Metathesis allows the exchange of substituents between different olefins - a transalkylidenation.

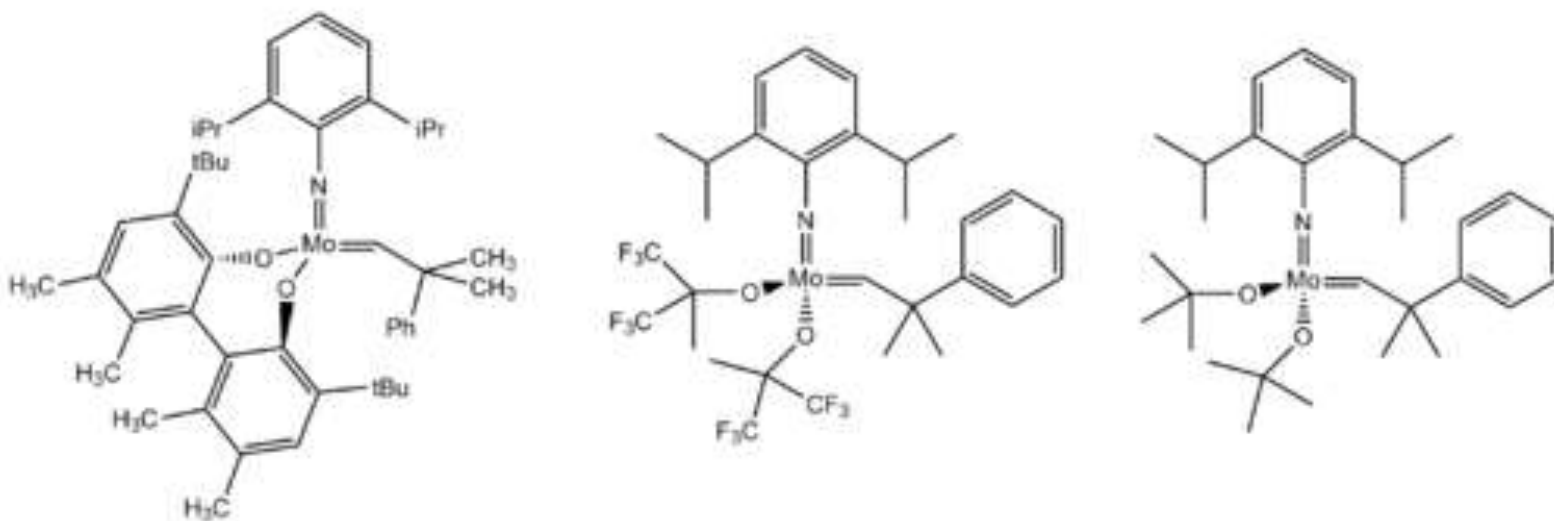
This reaction was first used in petroleum reformation for the synthesis of higher olefins (Shell higher olefin process - SHOP), with nickel catalysts under high pressure and high temperatures. Nowadays, even polyenes with MW > 250,000 are produced industrially in this way.

Synthetically useful, high-yield procedures for lab use include ring closure between terminal vinyl groups, cross-metathesis - the intermolecular reaction of terminal vinyl groups - and ring opening of strained alkenes. When molecules with terminal vinyl groups are used, the equilibrium can be driven by the ready removal of the product ethene from the reaction mixture. Ring opening metathesis can employ an excess of a second alkene (for example ethene), but can also be conducted as a homo- or copolymerization reaction. The driving force in this case is the loss of ring strain.

All of these applications have been made possible by the development of new homogeneous catalysts. Shown below are some of these catalysts, which tolerate more functional groups and are more stable and easy to handle.

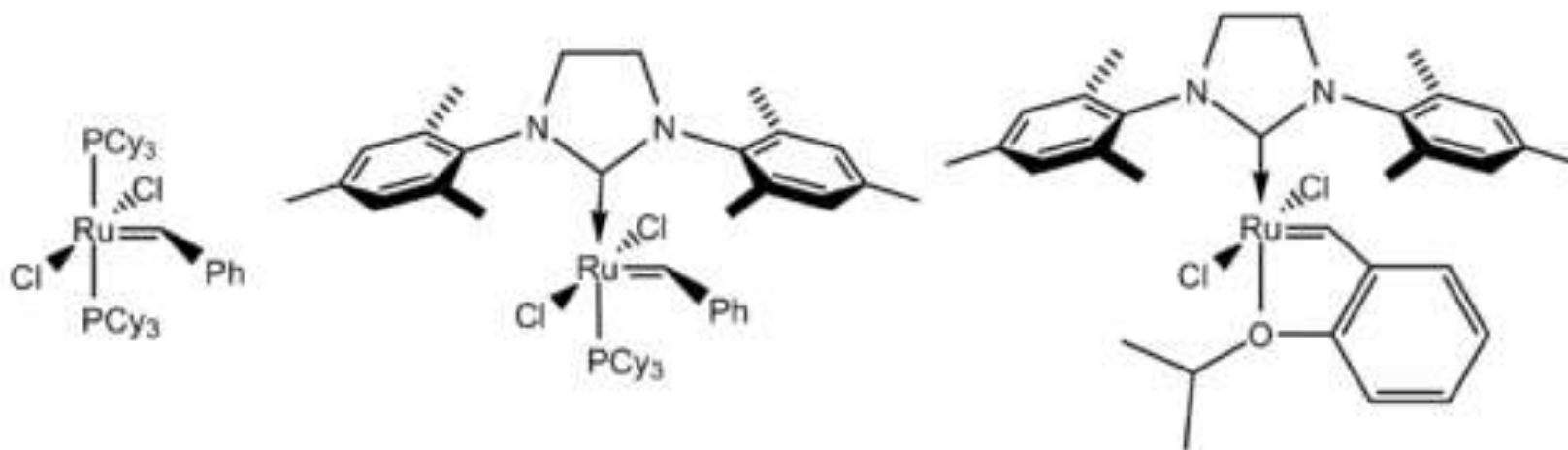


The reaction requires metal catalyst. Most commercially important processes employ heterogeneous catalyst. The heterogeneous catalysts are often prepared by in-situ activation of a metal halides (MCl_x) using organolithium or organotin compounds, e.g. combining MCl_x - $EtAlCl_2$. A typical catalyst support is alumina. Commercial catalysts are often based on molybdenum and ruthenium. Well-defined organometallic compounds have mainly been investigated for small-scale reactions or in academic research. The homogeneous catalysts are often classified as Schrock catalysts and Grubbs catalyst. Schrock catalysts feature molybdenum(VI)- and tungsten(VI)-based centers supported by alkoxide and imido ligands.

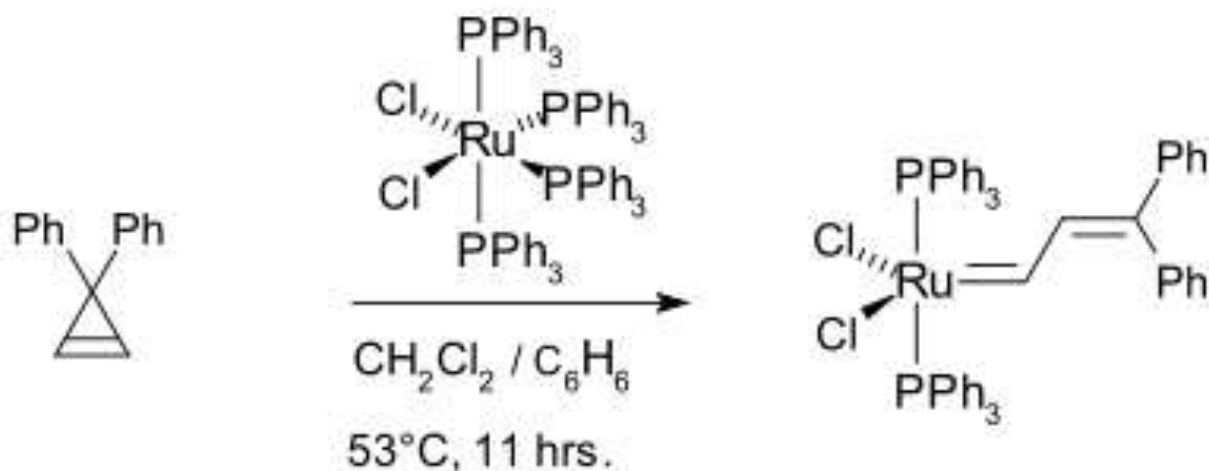


Schrock catalysts

Grubbs catalysts, on the other hand, are ruthenium(II) carbenoid complexes. Many variations of Grubbs catalysts are known. Some have been modified with a chelating isopropoxybenzylidene ligand to form the related Hoveyda-Grubbs catalyst.



Grubbs catalyst



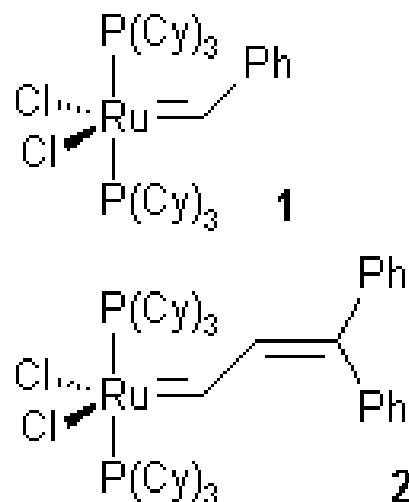
This reaction was first used in petroleum reformation for the synthesis of higher olefins with nickel catalysts under high pressure and high temperatures. Nowadays, even polyenes with MW > 250,000 are produced industrially in this way.

The Schrock catalysts are more active and are useful in the conversion of sterically demanding substrates, while the Grubbs catalysts tolerate a wide variety of functional groups.

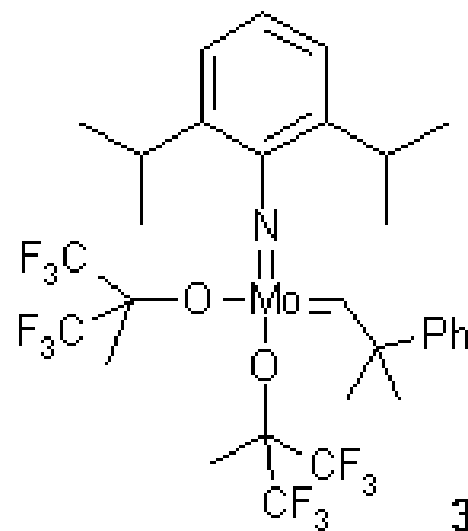


Richard R. Schrock and Robert H. Grubbs at the interview in Stockholm on 6th Dec'2005

Grubbs

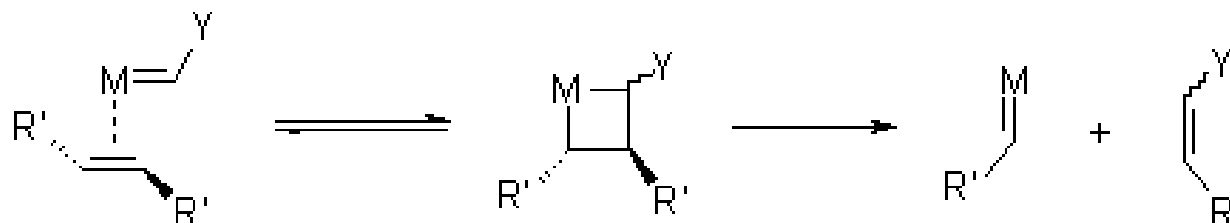


Schrock

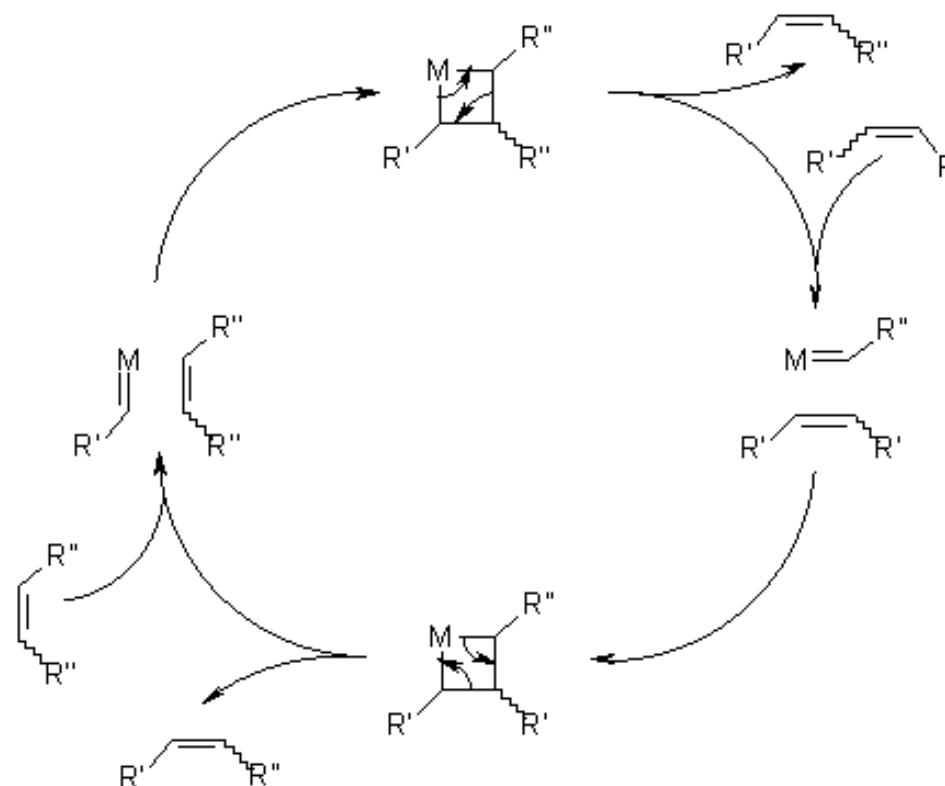


Mechanism of Olefin Metathesis

Initiation:




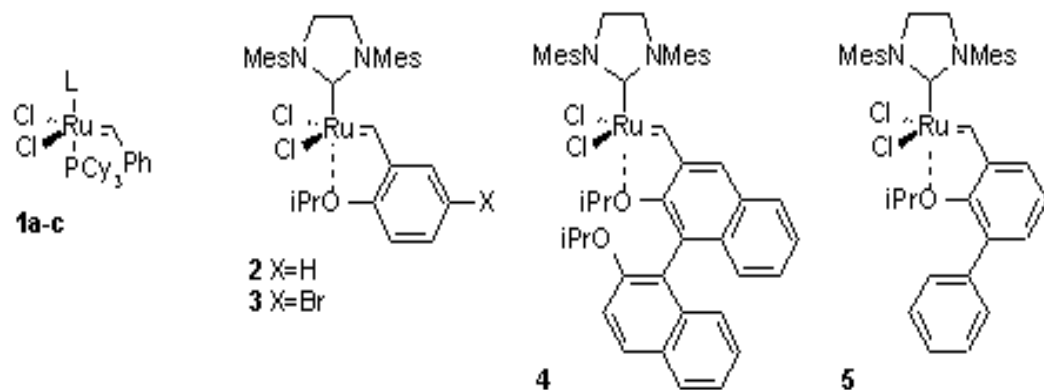
Catalytic Cycle:



Yves Chauvin

The second generation Grubbs catalysts are even more stable and more active than the original versions. Some of these are depicted:

Activity: $2 < \mathbf{1b} < \mathbf{4} < \mathbf{5}$ 



K. Grela, S. Harutyunyan, A. Michrowska, *Angew. Chem. Int. Ed.*, **2002**, *114*, 4038. DOI

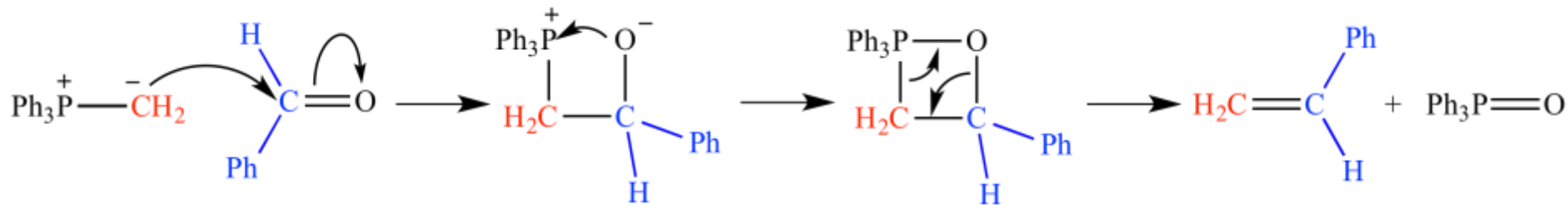
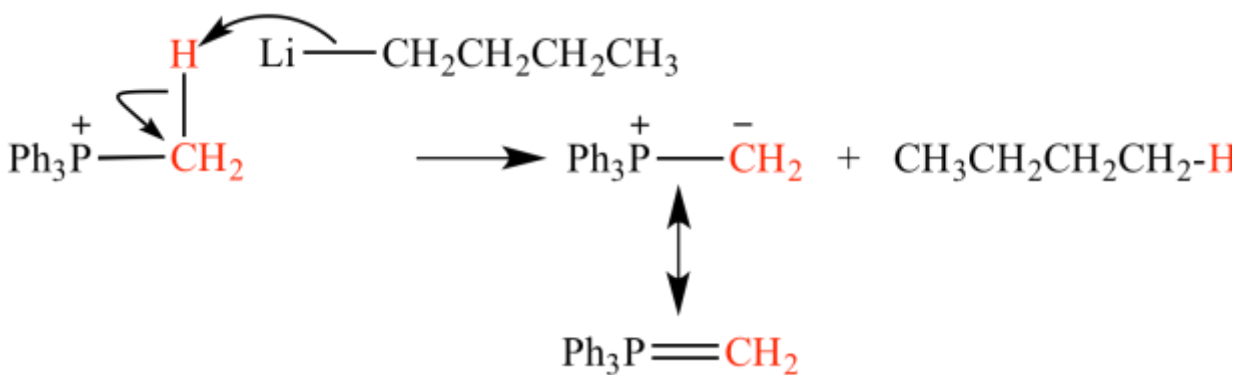


Wittig reaction:

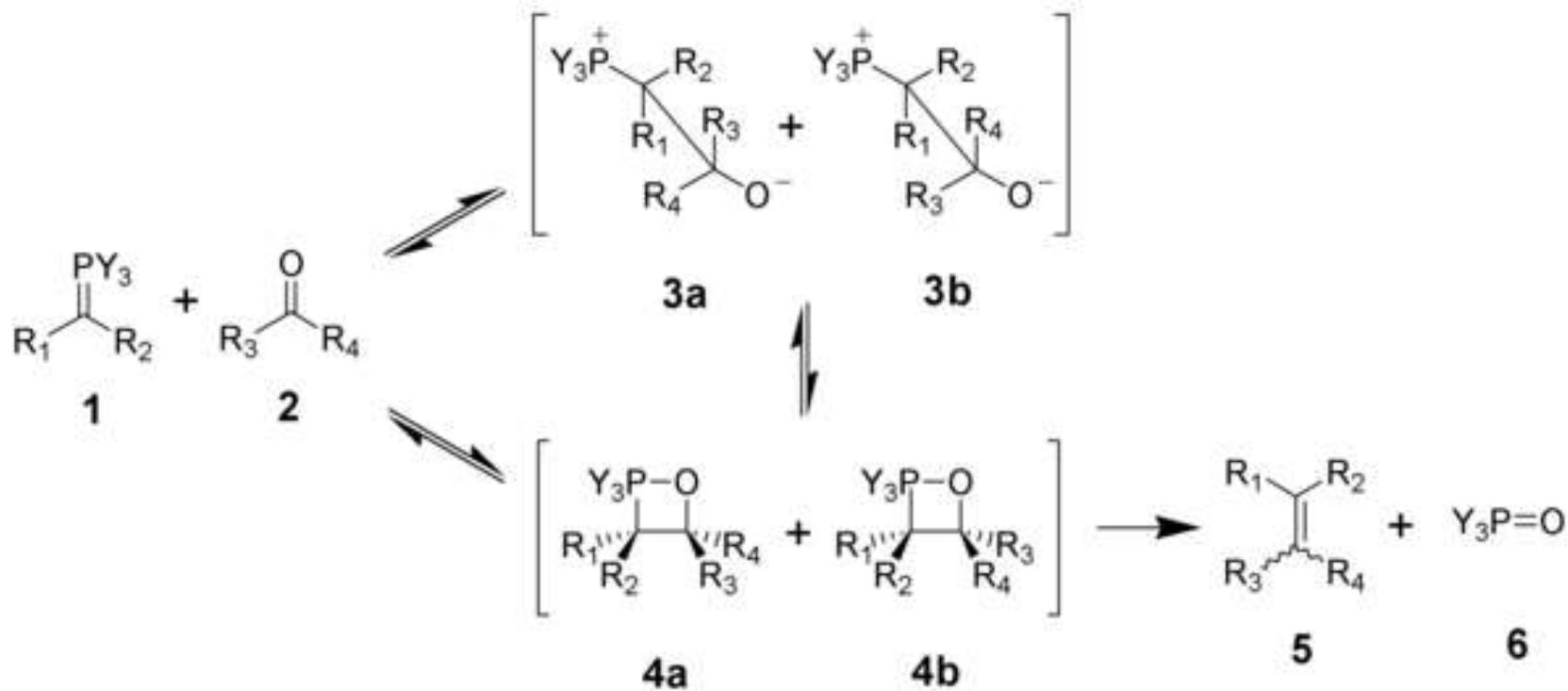
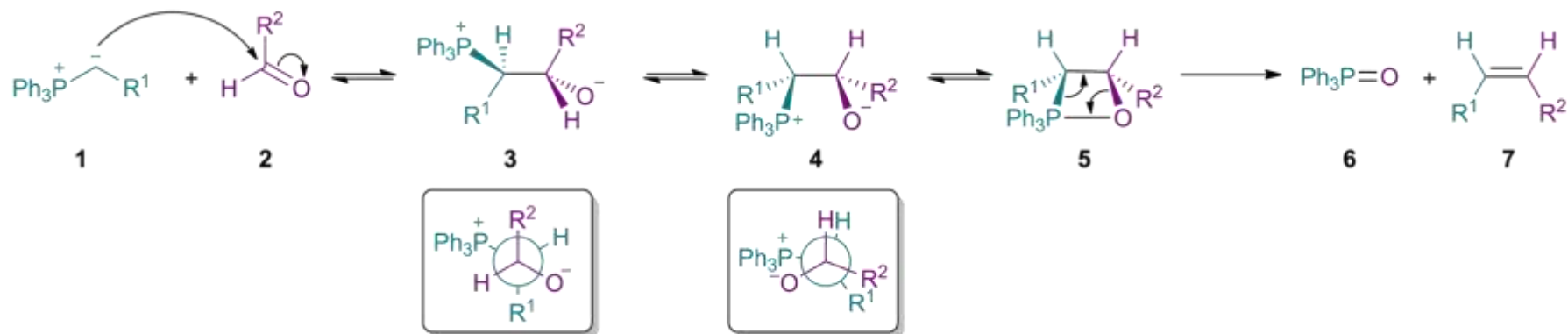
A reaction in which a phosphonium ylide reacts with an aldehyde or ketone to produce an alkene. Shown below is a typical Wittig reaction sequence, with mechanism. S_N2 reaction of triphenylphosphene (Ph₃P) with iodomethane (CH₃I) produces (Ph₃PCH₃⁺I⁻), a phosphonium salt. phosphonium salt deprotonates by butyllithium (CH₃CH₂CH₂CH₂Li) forms methyl-triphenylphosphonium ylide (Ph₃P=CH₂). The phosphoniumylide adds to benzaldehyde to produce styrene, along with triphosphonium oxide (Ph₃P=O) as a bi-product. The four-membered ring intermediate is an oxophosphetane.



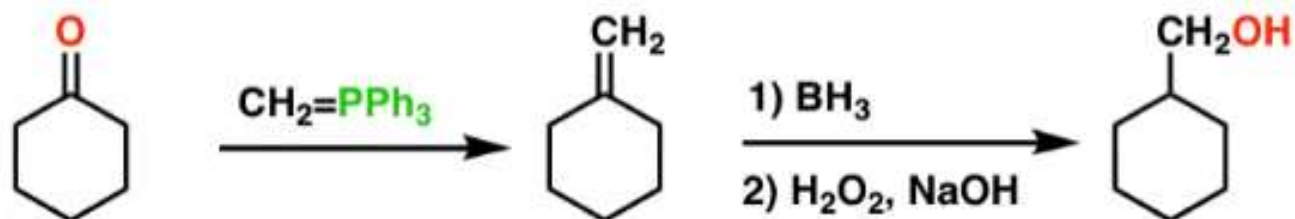
Georg Wittig
The Nobel prize in chemistry in 1979



Stereo-regulated nucleophilic reaction of different steps of Wittig reaction

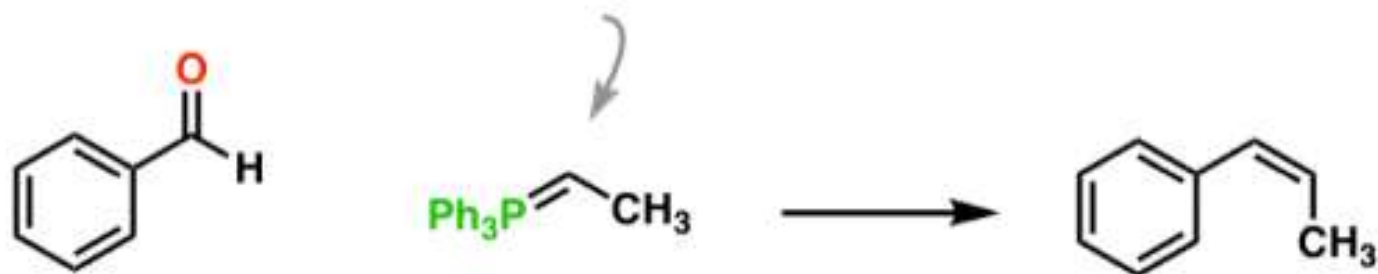


Example in synthesis



What about stereochemistry of the Wittig reaction?

- *Z* products tend to dominate for ylides lacking electron-withdrawing groups
"unstabilized" ylide

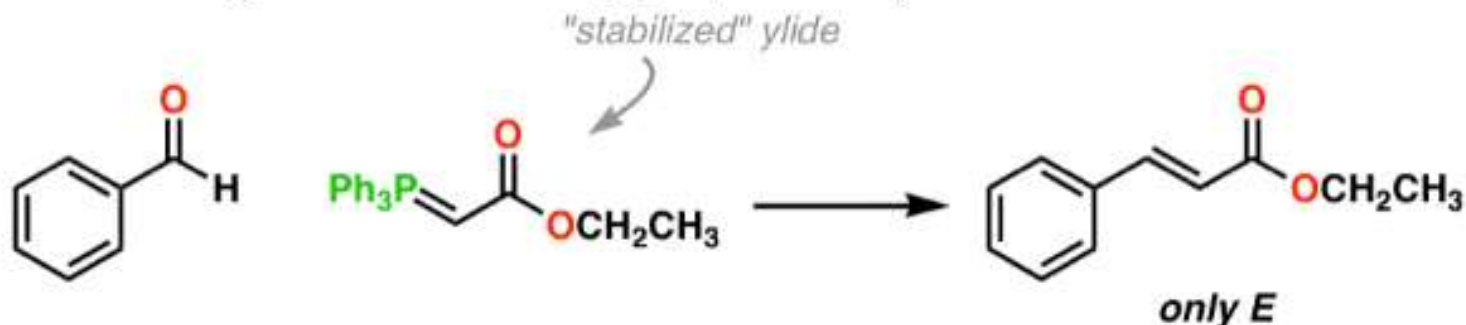


the method in which the ylide is created matters; Na^+ salts give higher *Z:E* ratios than Li^+ salts

Z* : *E
87:13 + $\text{Ph}_3\text{P}=\text{O}$

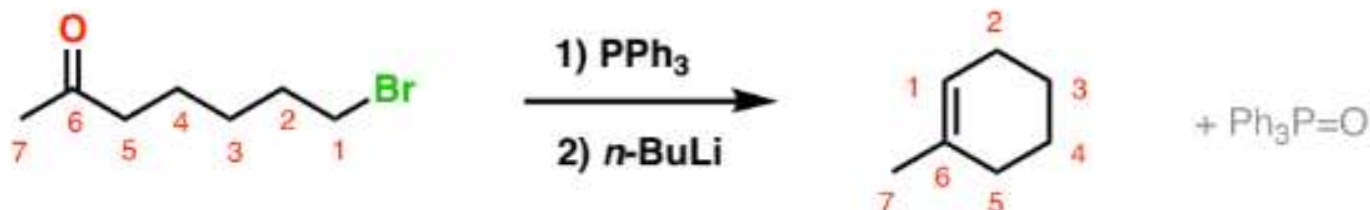
The ratio of the *Z* isomer decreases as electron-withdrawing groups are added to the ylide. These species are called, “stabilized ylides”, as they are less basic (and less reactive).

- Ylides bearing electron-withdrawing groups tend to give *E* alkenes:



This is simple enough and probably enough for most purposes. We don't have time here to get into the excellent [Horner-Emmons-Wadsworth](#) reaction, which bears many similarities to the Wittig, and provides excellent *E:Z* selectivity.

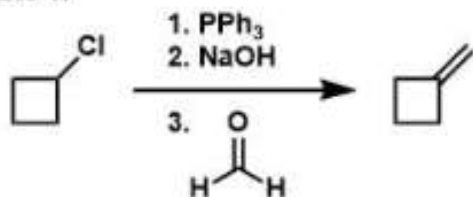
an intramolecular Wittig:



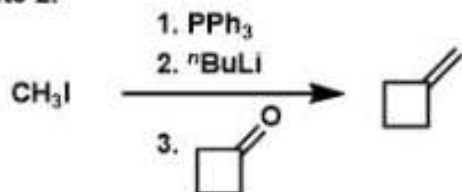
Click to Flip

Two synthetic routes to methylcyclobutane are shown below. Which route is **more efficient**? Explain.

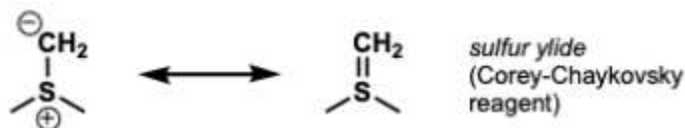
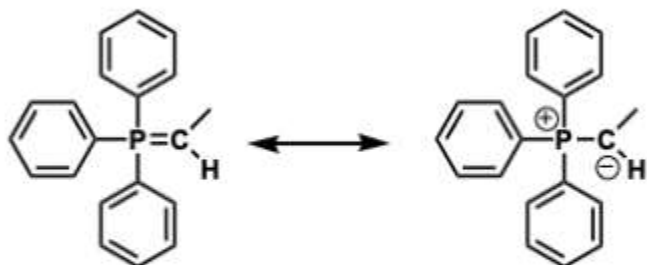
Route 1:



Route 2:

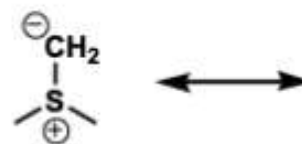
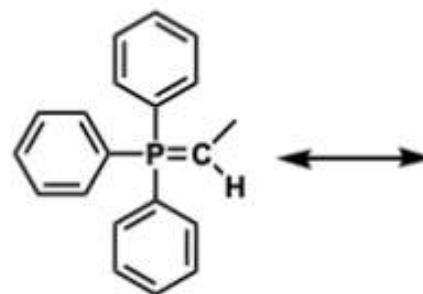


Draw the other major resonance structure for the following compounds.



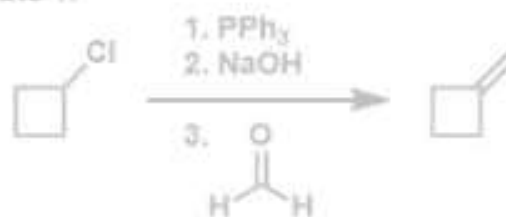
Home work

Draw the other major resonance structure for the following compounds.

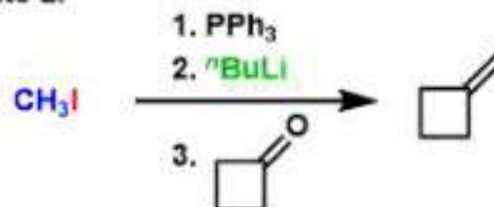


Two synthetic routes to methylcyclobutane are shown below. Which route is **more efficient**? Explain.

Route 1:



Route 2:



- 1) **I⁻ is a better leaving group** compared to Cl^- , so $\text{S}_{\text{N}}2$ with PPh_3 will occur faster.
- 2) **CH_3I is less sterically hindered** compared to cyclobutyl chloride, so $\text{S}_{\text{N}}2$ with PPh_3 will occur faster.
- 2) **$n\text{BuLi}$ is a stronger base** than NaOH , so ylide formation will be much faster.

Home work

[illegible]

$\downarrow \text{H}_3\text{O}^+$
?

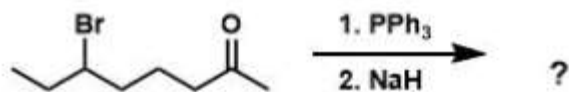
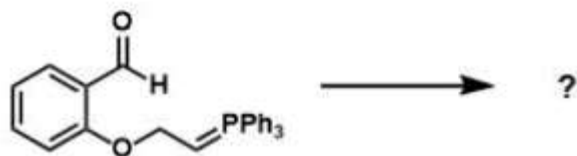
The **acetal protecting group** is needed to mask the aldehyde group - otherwise the ylide would react with itself!

Reaction scheme for the synthesis of 1-(2-methyl-2-octen-1-yl)pyrrolidine:

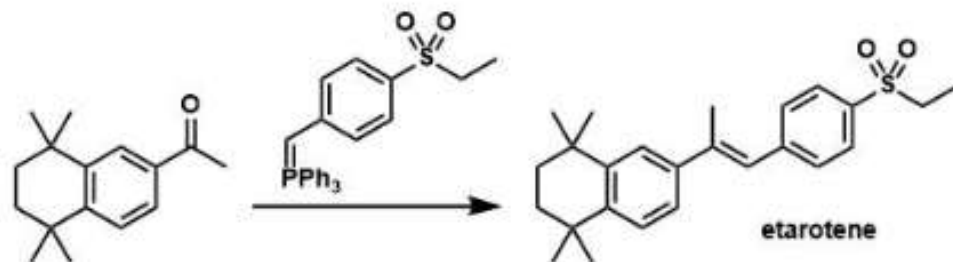
2-octanone reacts with (E)-1-methyl-2-(trimethylphosphoryl)ethene to form (E)-1-(2-methyl-2-octen-1-yl)pyrrolidine.

2-octanone reacts with (E)-1-(cyclohexylmethyl)-2-(trimethylphosphoryl)ethene to form (E)-1-(2-(cyclohexylmethyl)-2-octen-1-yl)pyrrolidine.

Draw the products for the intramolecular Wittig reactions below.

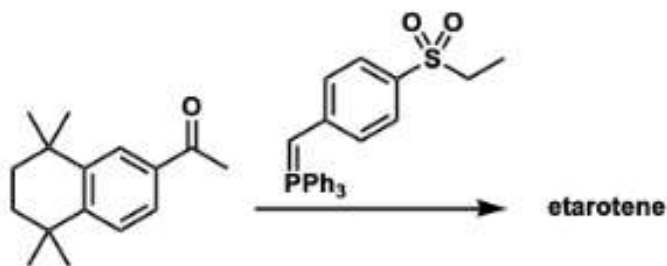


Etarotene is a drug that promotes cell differentiation and potential antitumor activity. The Wittig reaction is used during the final step of its synthesis. **Draw the structure** of etarotene.

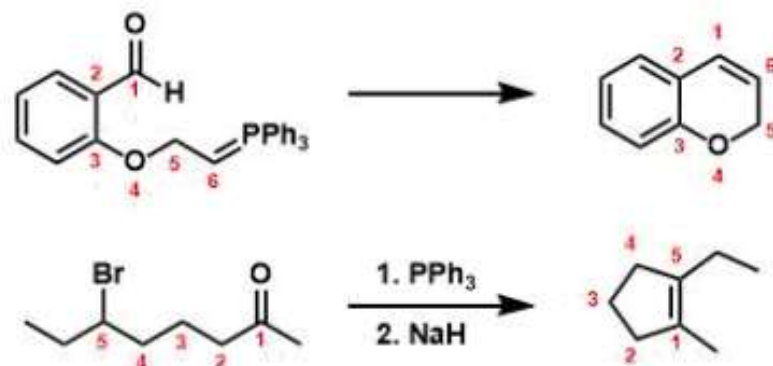


Home work

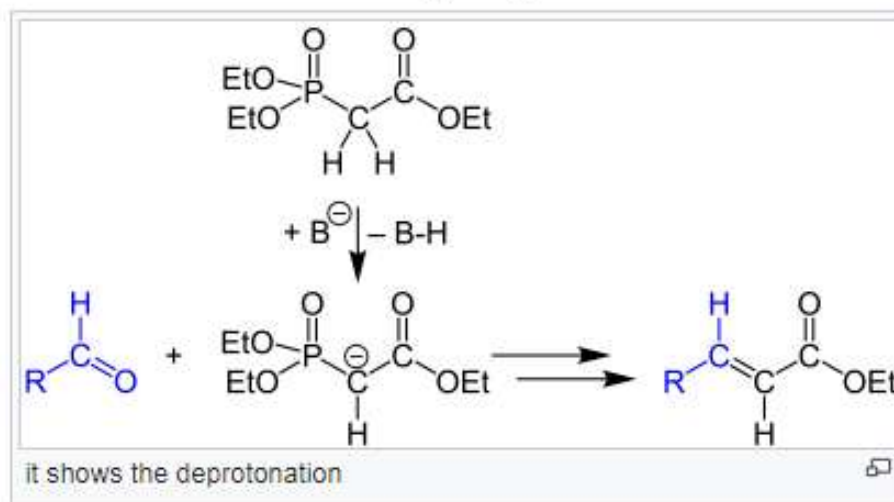
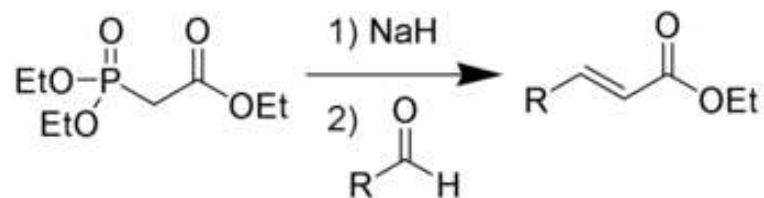
Etarotene is a drug that promotes cell differentiation and potential antitumor activity. The Wittig reaction is used during the final step of its synthesis. **Draw the structure** of etarotene (*hint: the double bond has the E configuratino*)



Draw the products for the intramolecular Wittig reactions below.



The **Horner–Wadsworth–Emmons (HWE) reaction** is a chemical reaction used in organic chemistry of stabilized phosphonate carbanions with aldehydes (or ketones) to produce predominantly E-alkenes.^[1]



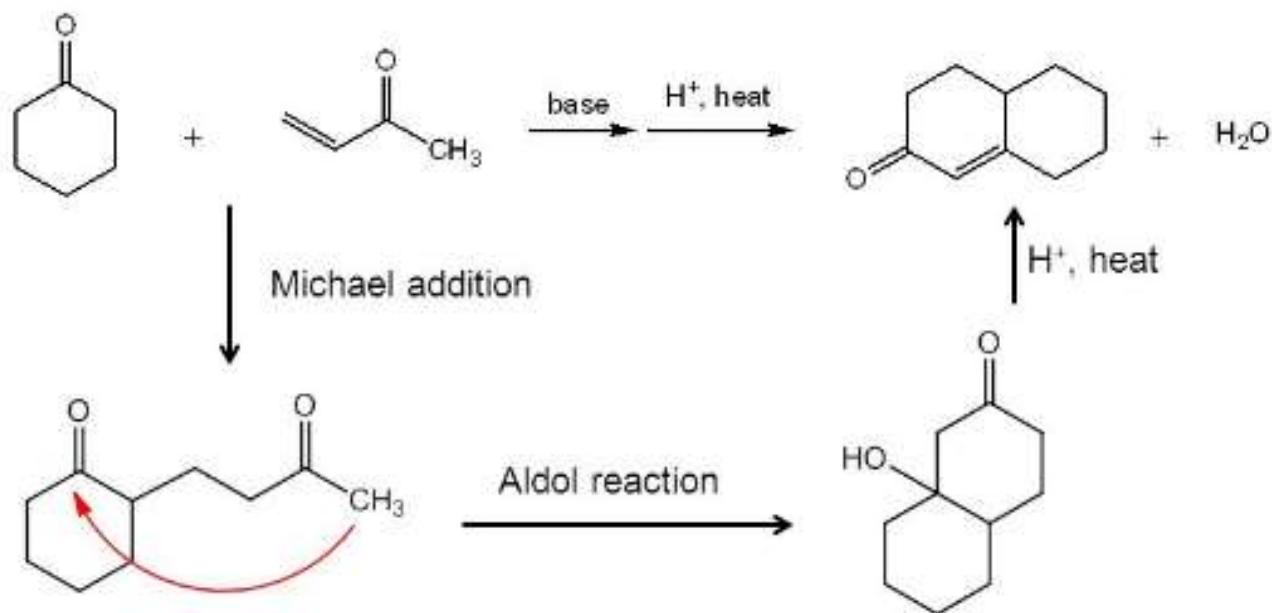
Reference Books:

- (i) A guidebook to mechanism in organic reaction; Peter Sykes, Pearson
- (ii) Organic Chemistry; T. W. Graham Solomon, John Wiley & Sons Inc.



Sir Robert Robinson
The Nobel Prize in Chemistry 1947

Robinson Annulation: Michael Addition Followed by Aldol Condensation

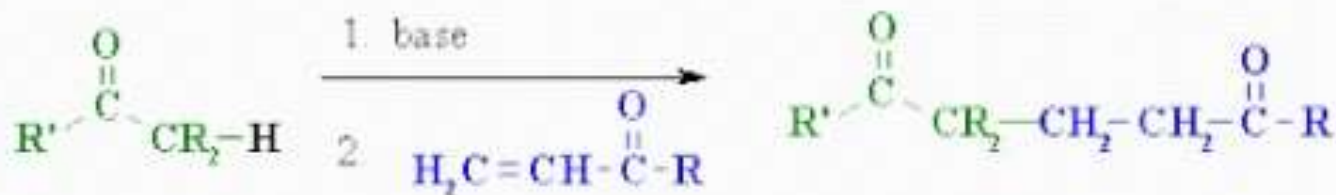




Arthur Michael (1853-1942)

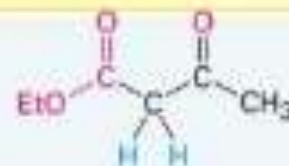
Michael addition

- The Michael reaction or Michael addition is the nucleophilic addition of a carbanion or another nucleophile to an α,β -unsaturated carbonyl compound. It belongs to the larger class of conjugate additions. This is one of the most useful methods for the mild formation of C–C bonds.

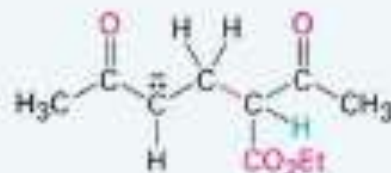
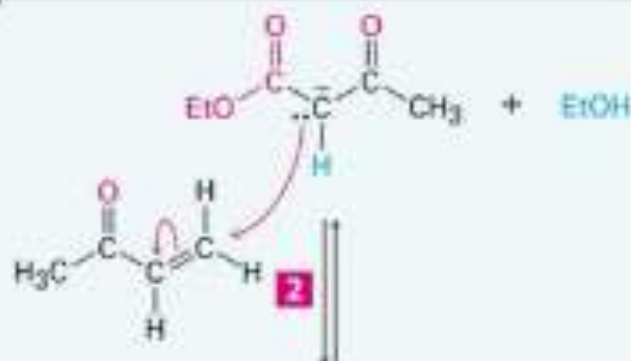


- The α,β -unsaturated compounds undergoing Michael addition is called the Michael acceptor, the nucleophile Michael donor, and the product Michael adduct.

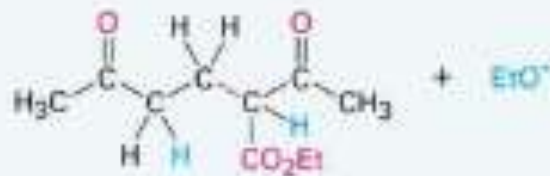
- 1** The base catalyst removes an acidic alpha proton from the starting β -keto ester to generate a stabilized enolate ion nucleophile.



- 2** The nucleophile adds to the α,β -unsaturated ketone electrophile in a Michael reaction to generate a new enolate as product.



- 3** The enolate product abstracts an acidic proton, either from solvent or from starting keto ester, to yield the final addition product.



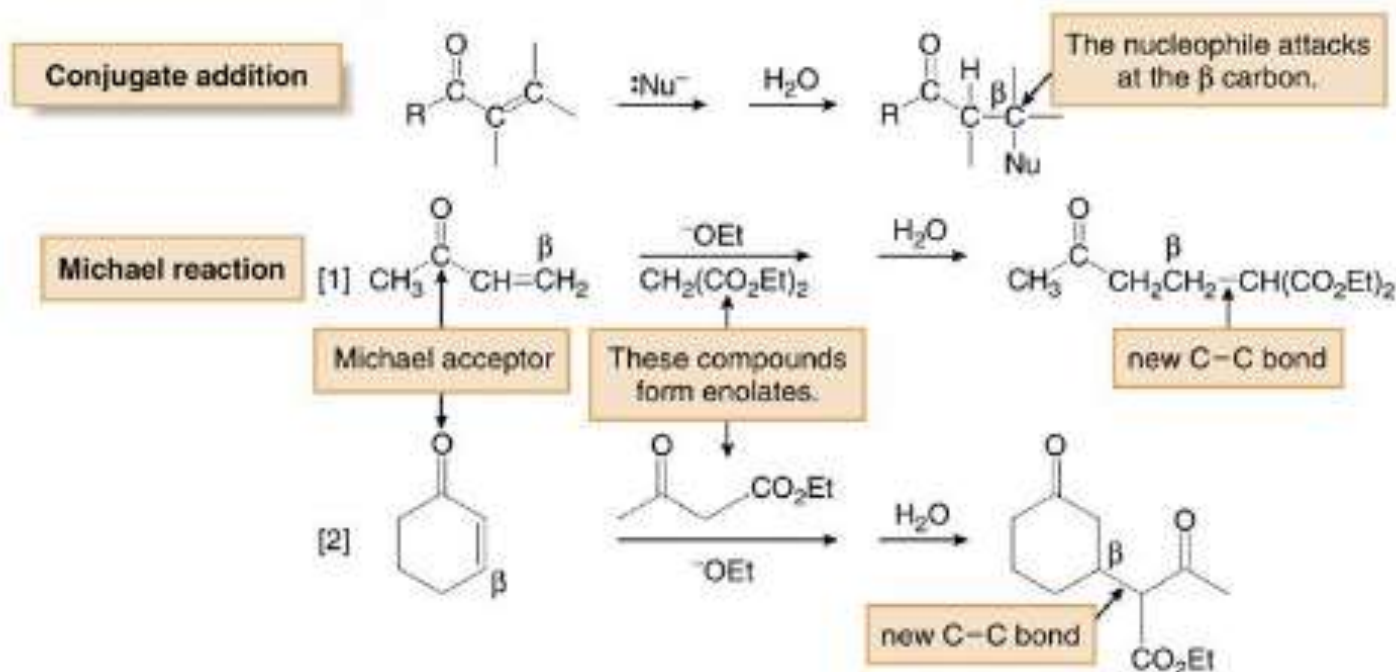


Carbonyl Condensation Reactions

The Michael Reaction

- The Michael reaction involves the conjugate addition (1,4-addition) of a resonance-stabilized enolate to the β carbon of an α,β -unsaturated carbonyl system.

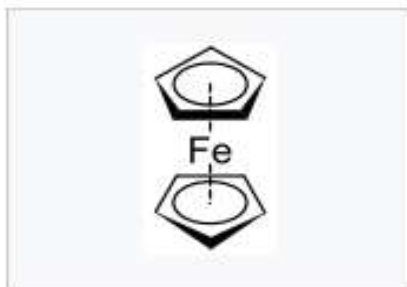
The α,β -unsaturated carbonyl component is often called a **Michael acceptor**.



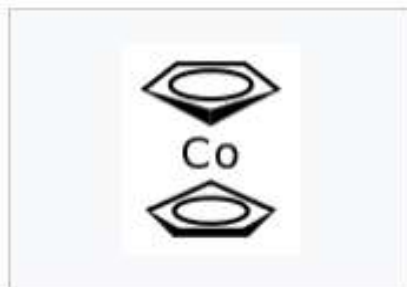
Organometallic compounds

Organometallic compounds are a class of compounds having bonds between one or more metal atoms and one or more carbon atoms of an organyl group. Organometallic compounds are classified by prefixing the metal with organo- (e.g., organopalladium compounds). In addition to the traditional metals and semimetal, elements such as boron, silicon, arsenic, and selenium are considered to form organometallic compounds. Examples are organomagnesium compounds MeMgI (iodo(methyl)magnesium); Et_2Mg (diethylmagnesium); an organolithium BuLi (butyllithium); an organozinc compound $\text{ClZnCH}_2\text{C}(=\text{O})\text{OEt}$ chloro(ethoxycarbonylmethyl)zinc; an organocuprate $\text{Li}^+(\text{CuMe}_2)^-$ (lithium dimethylcuprate); and an organoborane Et_3B (triethylborane).

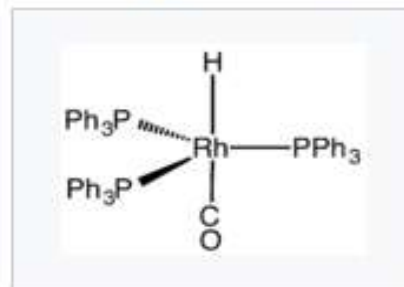
Representative Organometallic Compounds



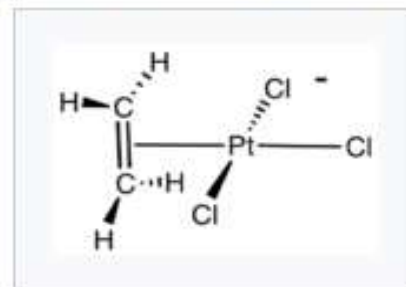
Ferrocene is an archetypal organoiron complex. It is an air-stable, sublimable compound.



Cobaltocene is a structural analogue of ferrocene, but is highly reactive toward air.



Tris(triphenylphosphine)rhodium carbonyl hydride is used in the commercial production of many aldehyde-based fragrances.



Zeise's salt is an example of a transition metal alkene complex.

(Gilman reagents)

A **Gilman reagent** is a lithium and copper (diorganocopper) **reagent** compound, R_2CuLi , where R is an alkyl or aryl. These **reagents** are useful because, unlike related Grignard **reagents** and organolithium **reagents**, they **react** with organic halides to replace the halide group with an R group (the Corey–House **reaction**).

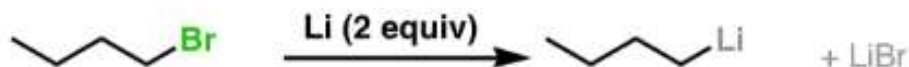
- Alkyl lithium (RLi) forms from RBr and Li metal
- RLi reacts with copper iodide to give lithium dialkylcopper (Gilman reagents)



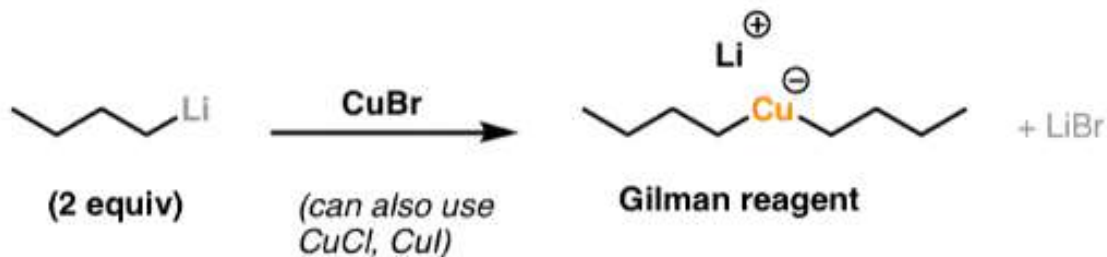
Henry Gilman (1893-1986)

In this post: synthesis of Gilman reagents from alkyl halides

Step 1: formation of organolithium



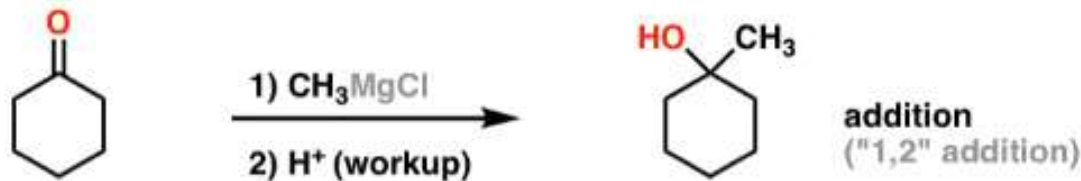
Step 2: formation of organocuprate (Gilman reagent)



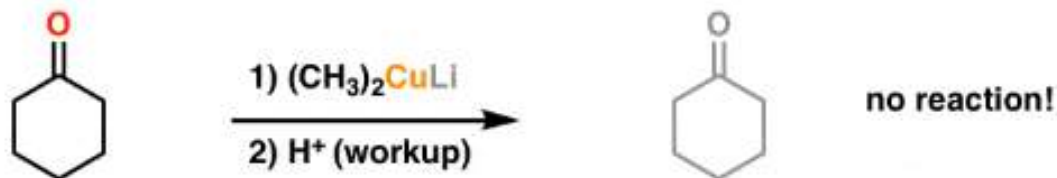
An alternative way of writing the same thing...



Grignard reagents add to ketones (and other carbonyls)...



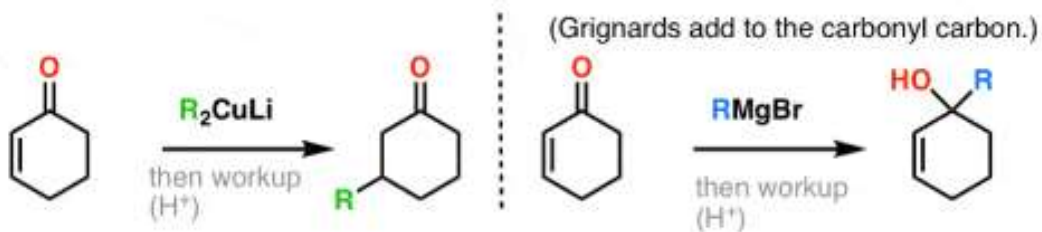
... but Gilman reagents (organocuprates) do **not** !



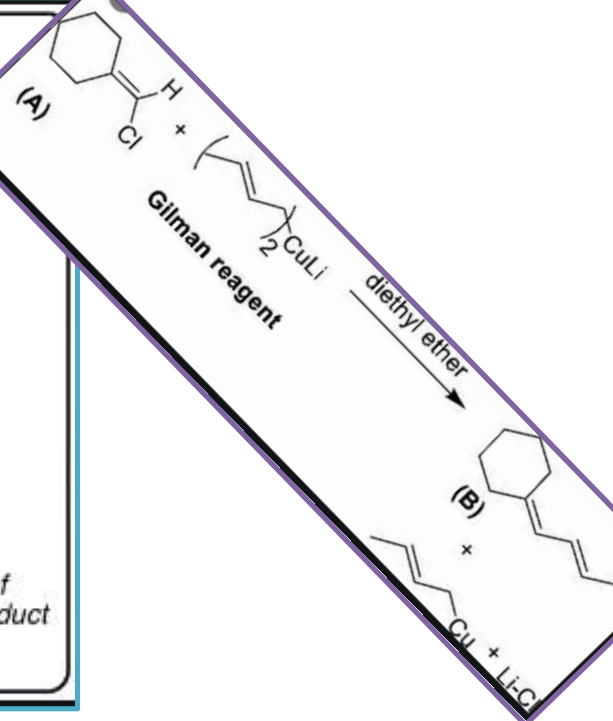
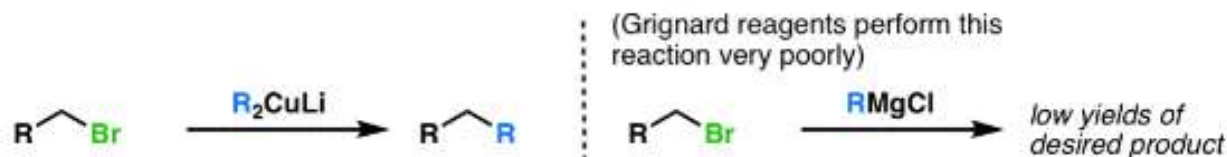
Victor Grignard
The Nobel Prize in Chemistry 1912

Summary: Gilman reagents (organocuprates) contrast with Grignard (and organolithium reagents) in two important ways:

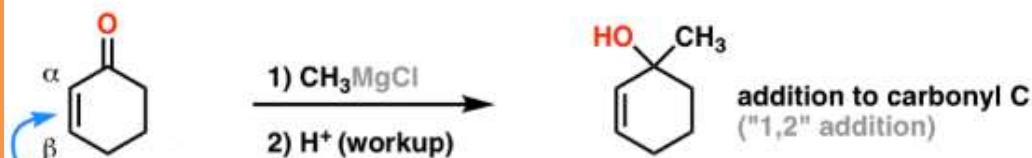
1) Gilman reagents perform "conjugate addition" to α, β unsaturated ketones



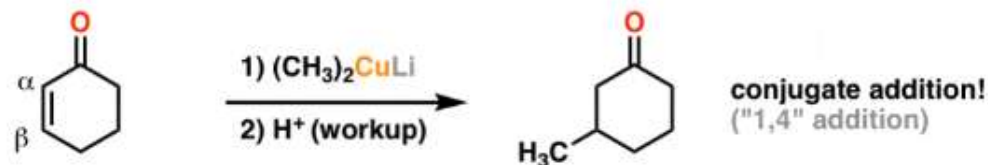
2) Gilman reagents are effective nucleophiles for $\text{S}_\text{N}2$ reactions



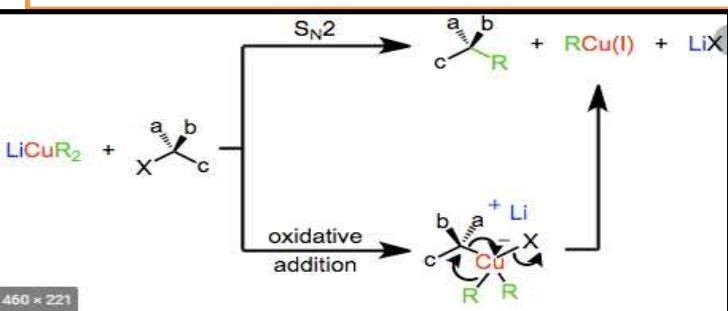
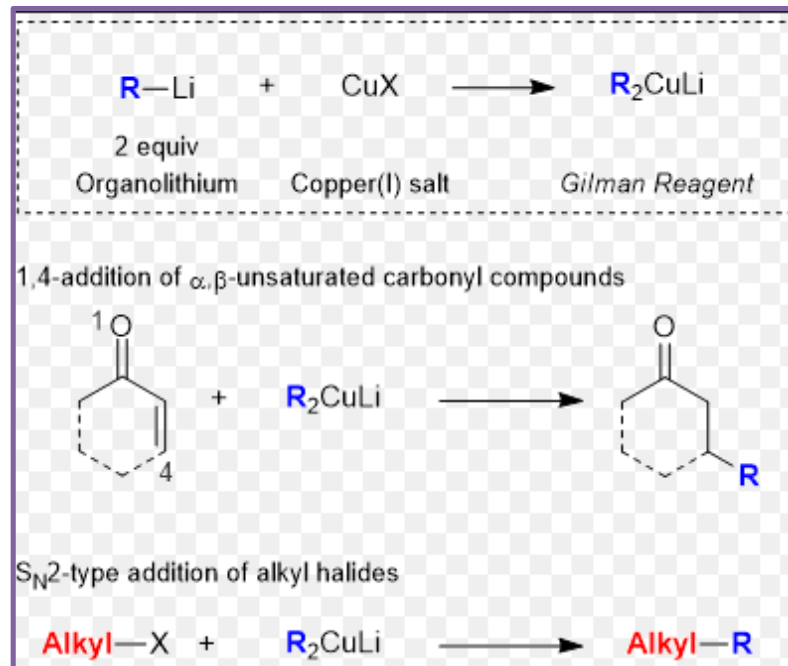
Even more interesting: contrast their reactivity with α, β unsaturated ketones



α, β unsaturated ketone
(note the double bond)



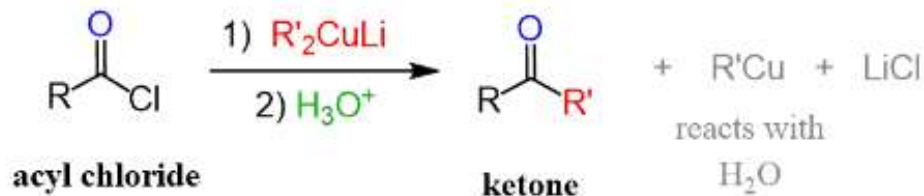
the carbon directly adjacent to a carbonyl is referred to as the "alpha" (α) carbon. the next carbon along is the "beta" (β) carbon, then the "gamma" (γ) and so on.



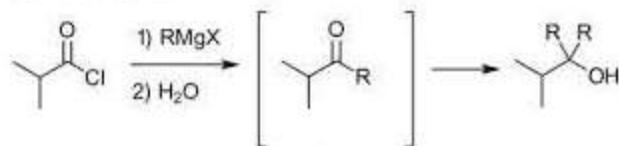
The reaction of acid chlorides with Grignard reagents produces a 3° alcohol.



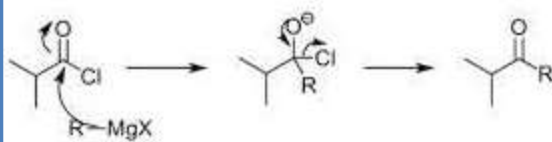
The reaction of acid chlorides with lithium dialkylcuprates produces ketones.

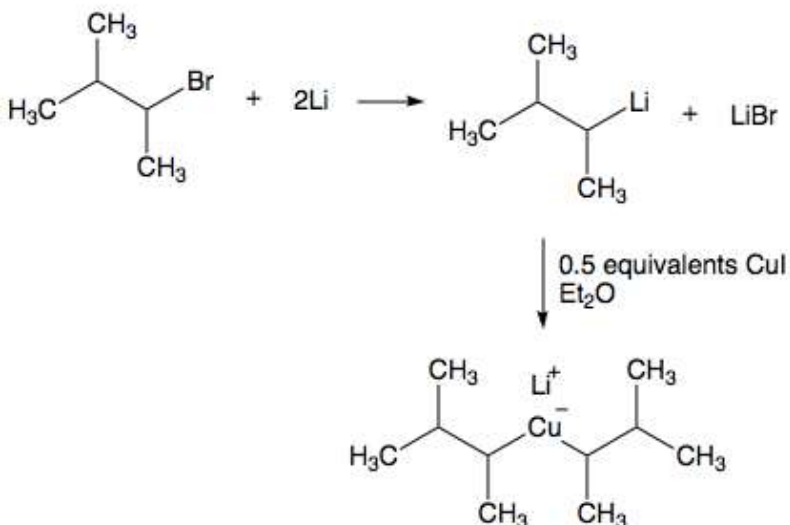


Grignard reagents

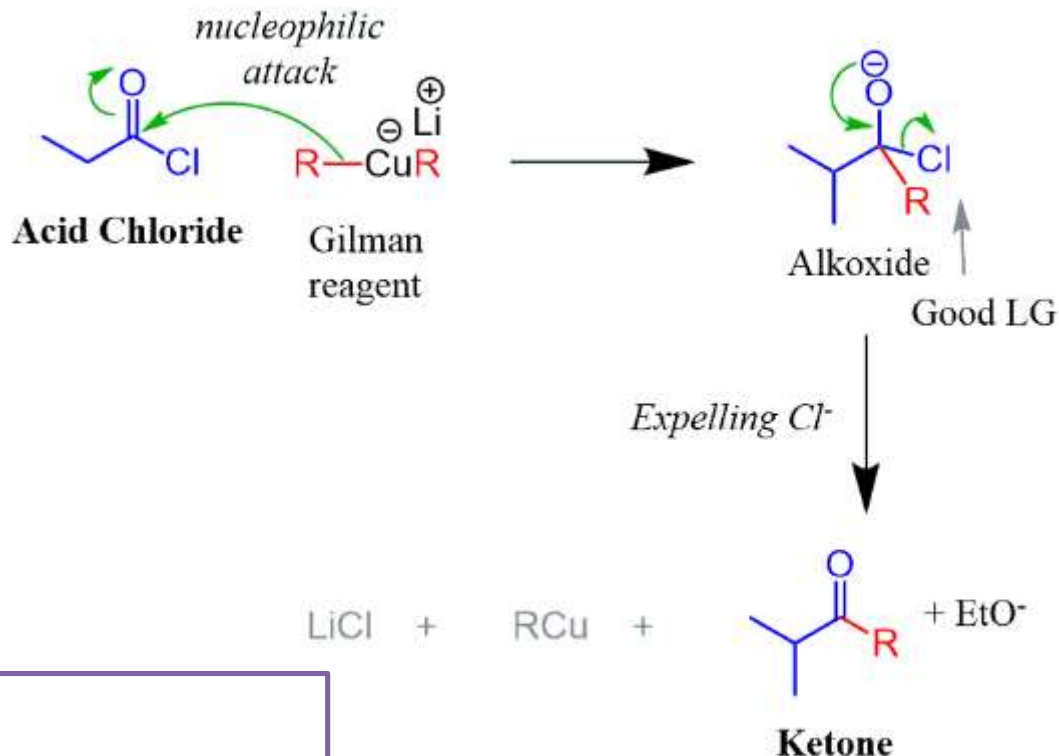


Ketones are less reactive, but Grignard reagents are less selective



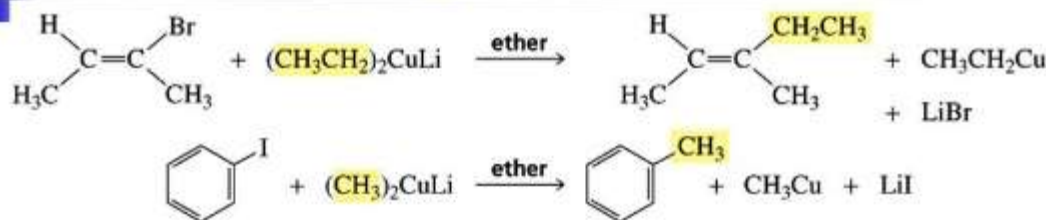


Synthesis, uses and application of Gilman reagent



Can no longer be attacked by R₂CuLi

Gilman Reagents



- When a Gilman reagent reacts with an alkyl halide (except F⁻) one of the alkyl groups replaces the halide
- Alkyl groups can substitute halogens attached to alkene or aromatic C with Gilman reagent; impossible with S_N1 or S_N2 reaction
- Mechanism unknown, probably radical

-:End:-

Thank you!



Next PPT on Spectroscopy
is coming soon.

N. B.: For any doubt, constructive criticism
and suggestions or any correction to improve
the power point would be most welcome. PPT
is prepared within short time for the interest
of B. Tech. students.
Own hand photography in Canary Island, Spain: SCM