Organometallic Chemistry

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organocopper, organozinc

Organocopper compounds

Reviews

- Most seen example: Lithium Dialkylcopper (organocuprate) $[(R)_2Cu]^- Li^+$
- Cuprates are less reactive than organolithium
- R acts as a Nucleophile
- Oxidation state of copper is Cu(I).
- Nucleophile “R” will attack various organic electrophiles.
- Organocuprates are used in cross-coupling reactions to form higher alkanes.

- Cross-Coupling Reaction: coupling of two different alkyls R and R’ to yield a new alkane (R-R’). This type of reaction is used to make new C-C between alkyl groups.

Organocopper Reagents (Gilman Reagent)

$$2RLi + CuX \xrightarrow[\text{or THF}]{\text{diethyl ether}} R_2CuLi + LiX$$

Alkyllithium

Cu(I) halide (X = Cl, Br, I)

Lithium dialkylcuprate

Lithium halide

$$R_2CuLi + R'X \longrightarrow R{-}R' + RCu + LiX$$

Lithium dialkylcuprate

Alkyl halide

Alkane

Alkylcopper

Lithium halide

$$(CH_3)_2CuLi + CH_3(CH_2)_8CH_2I \xrightarrow[0^\circ C]{\text{diethyl ether}} CH_3(CH_2)_8CH_2CH_3$$

Lithium dimethylcuprate

1-Iododecane

Undecane (90%)

$$(C_6H_5)_2CuLi + ICH_2(CH_2)_6CH_3 \xrightarrow{\text{diethyl ether}} C_6H_5CH_2(CH_2)_6CH_3$$

Lithium diphenylcuprate

1-Iodooctane

1-Phenyloctane (99%)

Gilman Limitations

- Methyl and 1° R-X iodides work well
  - elimination occurs with 2° and 3 ° R-X
  - seems to follow S_N2 conditions
- also works for vinyl and aryl halides

Organocopper compounds

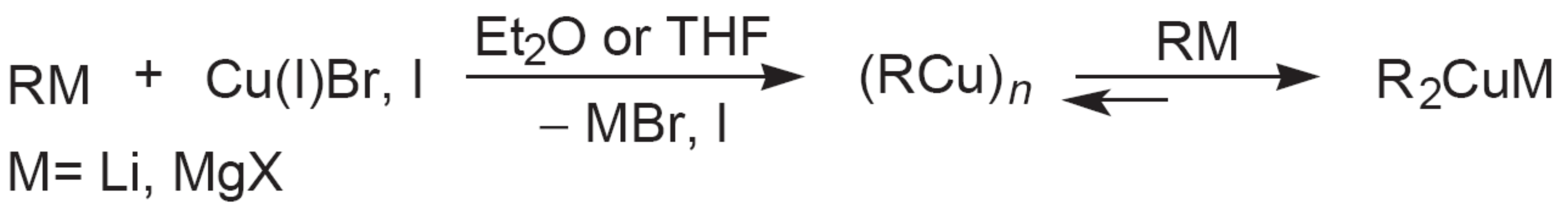
- Use of organocopper reagents offers a very efficient method for coupling of two different carbon moieties.
- Cu is **less electropositive than Li and Mg**, the *C–Cu bond is less polarized than the C–Li and C–Mg bonds*. This difference produces three useful changes in reactivity:
  - organocopper reagents react with **alkyl-**, **alkenyl-**, and **aryl halides** to give *alkylated products*.
  - organocopper reagents: **more selective** and *can be acylated with acid chlorides* without concomitant attack on ketones, alkyl halides, and esters.
  - Relative reactivity: RCOCl > RCHO > tosylates, iodides > epoxides > bromides >> ketones > esters > nitriles.
- In reactions with α,β-unsaturated carbonyl compounds, the organocopper reagents prefer **1,4-addition** over **1,2-addition**.

Preparations

Homocuprate reagents

(**Gilman reagent**: R_2CuLi, R_2CuMgX)

- widely used organocopper reagents.
- prepared by reaction of copper(I) bromide or preferably copper(I) iodide with 2 equivalents of appropriate lithium or Grignard reagents in ether or THF
- The initially formed **$(RCu)_n$** are polymeric and insoluble in Et_2O and THF but dissolve on addition of a second equivalent of RLi or RMgX.
- The resultant organocuprates are thermally labile and thus are prepared at low temperatures.



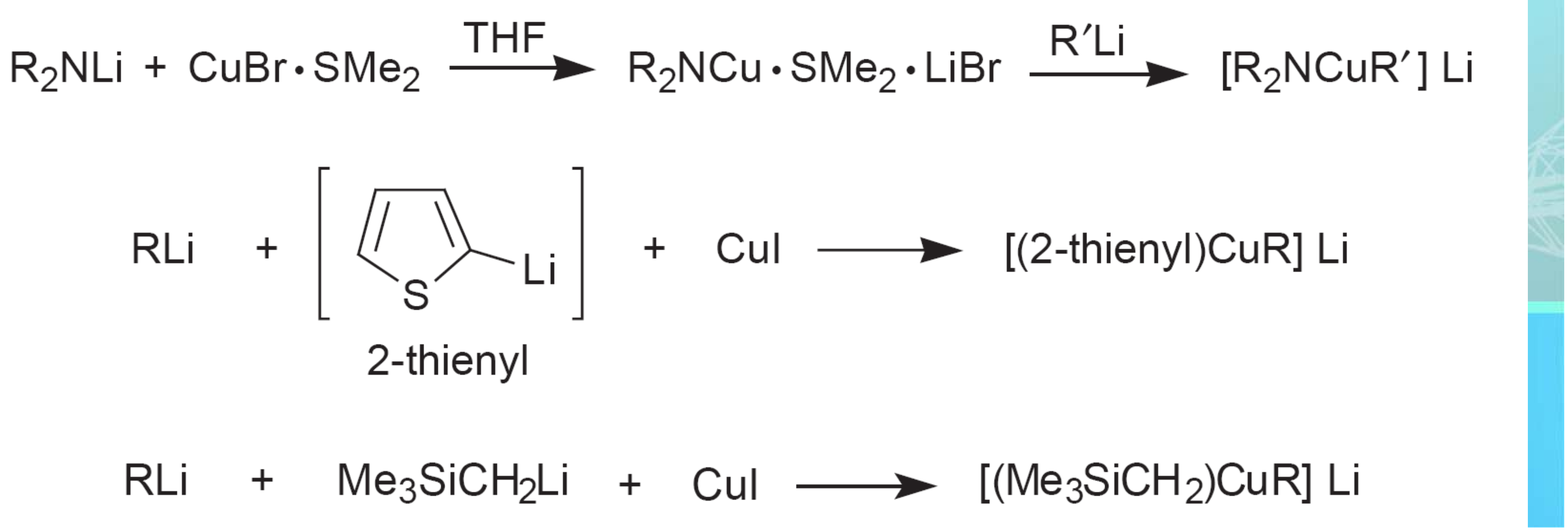
$$\mathrm{RM} + \mathrm{Cu(I)Br,\ I} \xrightarrow[-\ \mathrm{MBr,\ I}]{\mathrm{Et_2O\ or\ THF}} (\mathrm{RCu})_n \overset{\mathrm{RM}}{\rightleftarrows} \mathrm{R_2CuM}$$

M= Li, MgX

Preparations

Heterocuprate reagents

- Since only one of the organic groups of homocuprates is usually utilized, a non-transferable group bonded to copper, such as RC≡C, 2-thienyl, PhS, *t*-BuO, R_2N, Ph_2P, or Me_3SiCH_2, is employed for the preparation of heterocuprate reagents.
- These cuprates are usually thermally more stable (less prone toward β-elimination of Cu–H), and a smaller excess of the reagent may be used.



Preparations

Higher-order organocuprate reagents (Lipshutz reagents)

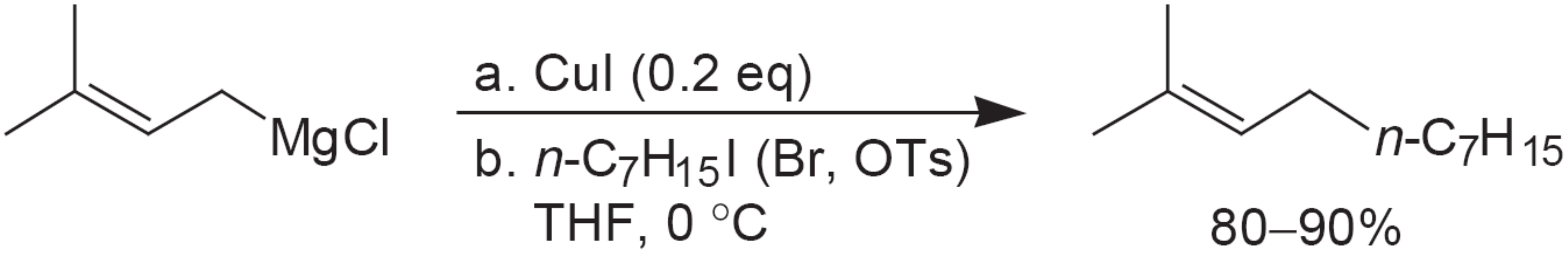
- Cyanocuprates exhibit the reactivity of homocuprates and the thermal stability of heterocuprates.
- readily available by the reaction of CuC≡N with 2 equivalents of RLi. The cyanocuprates are especially useful for substitution reactions of secondary halides and epoxides.

$$\mathrm{CuCN} \quad + \quad 2\ \mathrm{RLi} \quad \xrightarrow[-78^\circ \text{ to } 0\ ^\circ\mathrm{C}]{\text{THF or } \mathrm{Et_2O}} \quad \mathrm{R_2Cu(CN)Li_2}$$

Preparations

Grignard-Copper(I) reagents

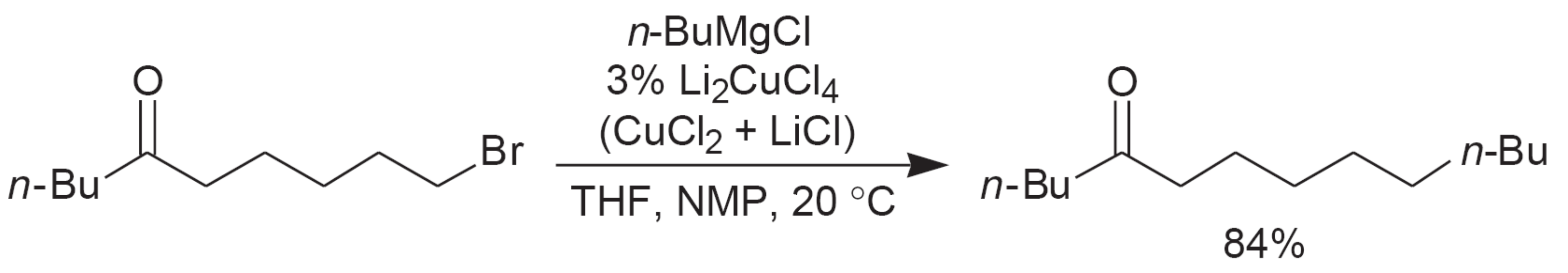
- Copper-catalyzed reactions of RMgX reagents are attractive when compatible with the functionality present in the starting material.
- use of Grignard reagents is often the method of choice since they are readily available and only catalytic amounts of Cu(I) halides are required.



Preparations

Grignard-Copper(I) reagents

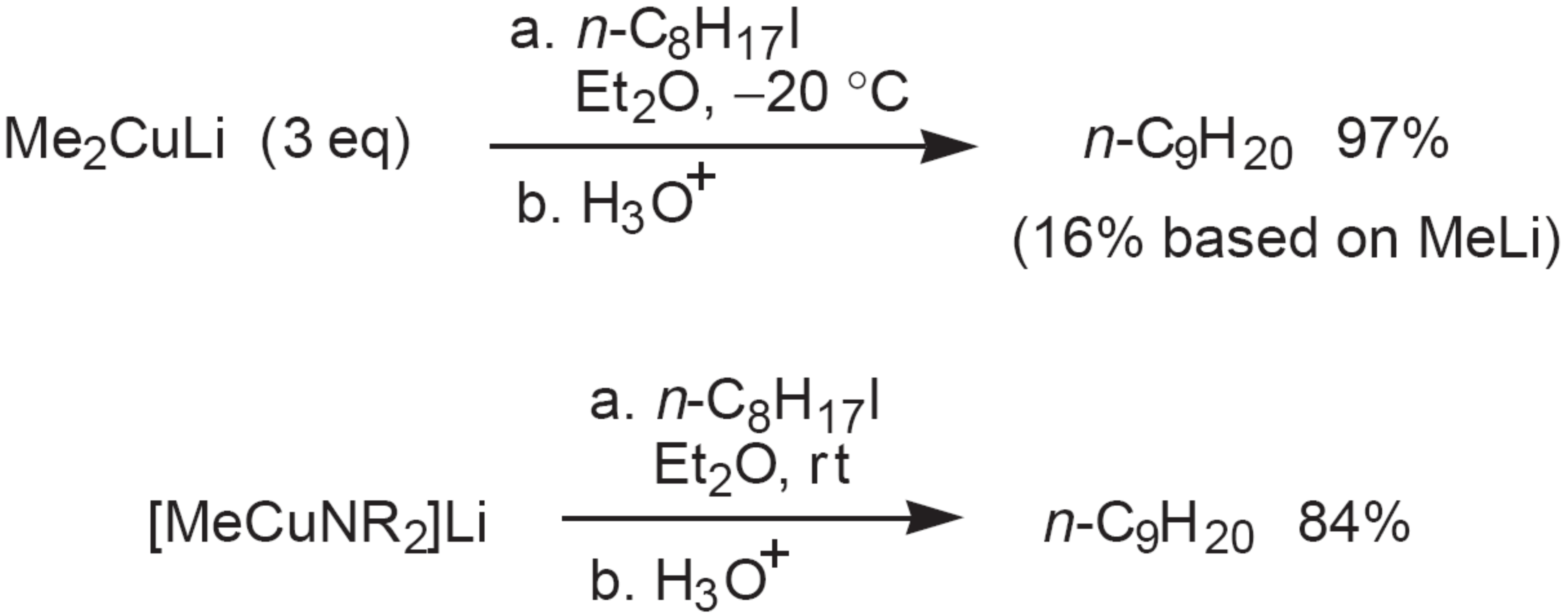
- Cu-catalyzed alkylation of organomagnesium reagents by RBr and RI in the presence of NMP (*N*-methylpyrrolidinone, a nontoxic, polar, aprotic solvent) represents an attractive alternative to the classical cuprate alkylation reaction.
- Only a slight excess of the Grignard reagent is required, and the reaction tolerates keto, ester, amide and nitrile groups. This method is especially suited for large-scale preparations.



Reaction of Organocuprates

❖ *Substitution of alkyl halides*

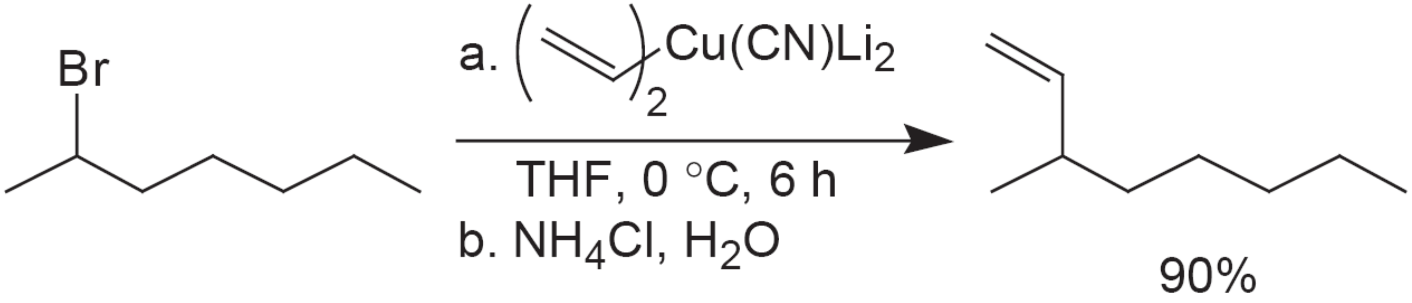
- coupling of a ***primary alkyl iodide*** with an organocuprate is more economical when using a heterocuprate than a homocuprate.



Reaction of Organocuprates

❖ *Substitution of alkyl halides* *(cont'd)*

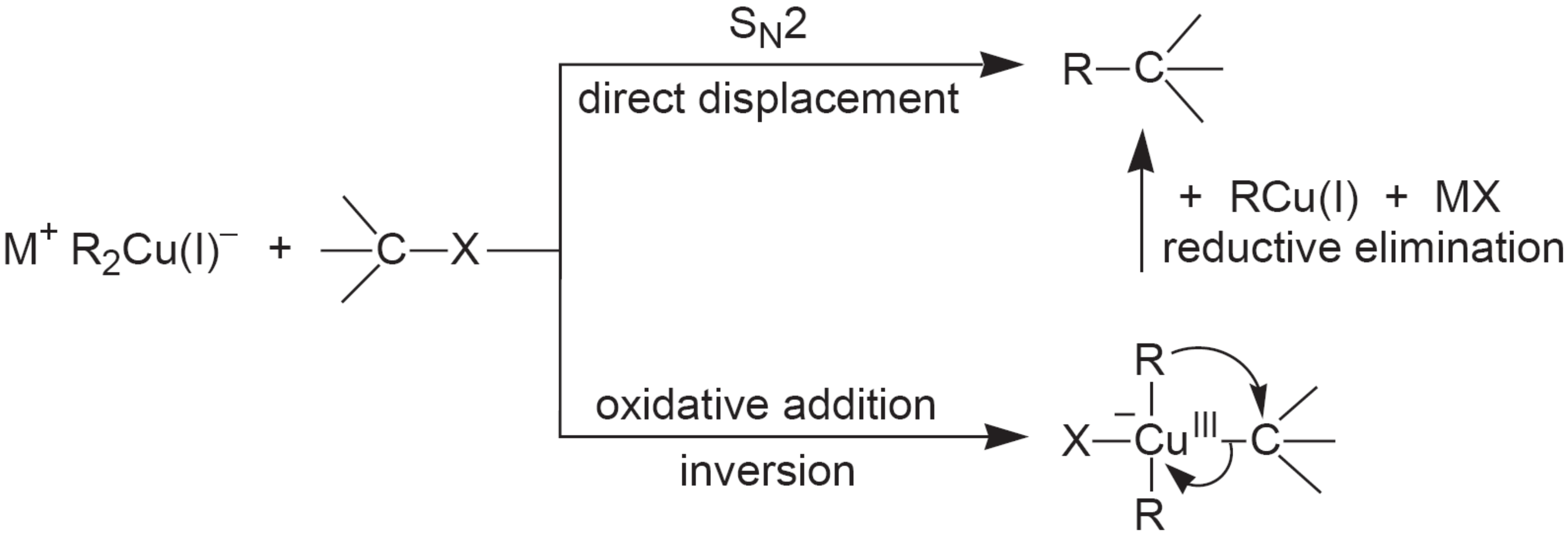
- While homocuprates readily undergo substitution reactions at primary positions, they do not couple well with unactivated secondary halides.
- However, cyanocuprates undergo substitution reactions even at unactivated secondary carbon centers.



Reaction of Organocuprates

❖ *Substitution of alkyl halides* *(cont'd)*

- ❖ mechanism for the substitution reaction is complex, depending on nature of cuprate reagent, substrate, and solvent used.
- reaction may proceed via an S_N2 displacement or via an oxidative addition followed by reductive elimination.



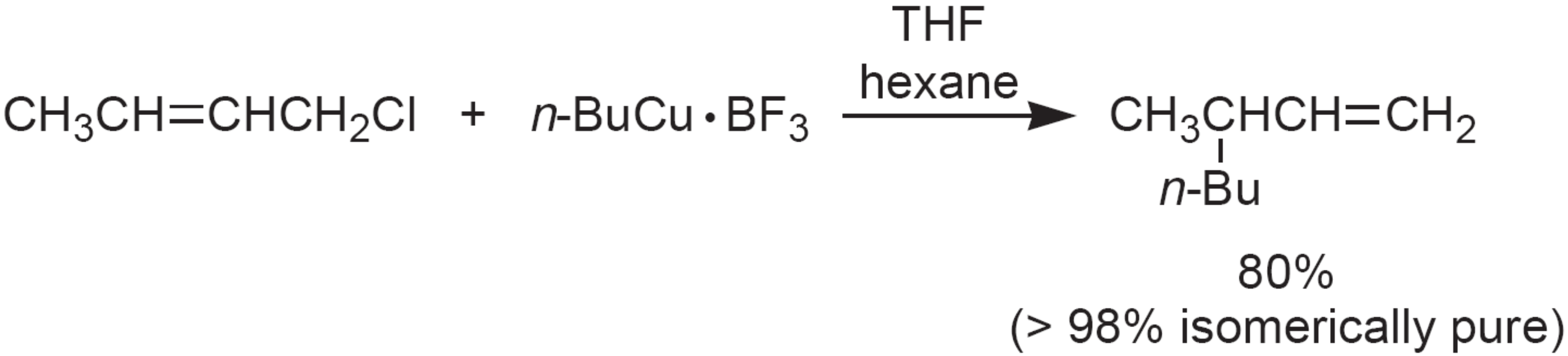
Reaction of Organocuprates

❖ *Substitution of allylic halides*

- Alkylation of allylic halides with organocuprates usually produces mixtures of products due to competing S_N2 and S_N2' reactions.

$$\mathrm{Cu(I)} + n\text{-BuLi (hexane)} \xrightarrow{\text{THF}} \text{“}n\text{-BuCu”} \xrightarrow[-78\ ^\circ\text{C to rt}]{\mathrm{BF_3 \cdot Et_2O}} \text{“}n\text{-BuCu} \cdot \mathrm{BF_3}\text{”}$$

- Substitution with complete allylic rearrangement (S_N2 reaction) is observed with $RCu{\cdot}BF_3$ as the alkylating agent.



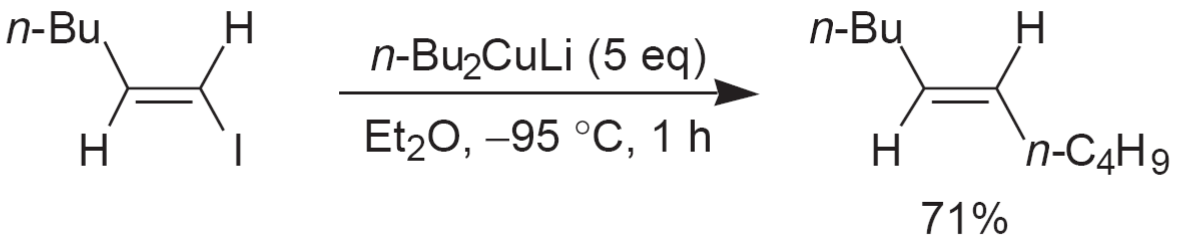
$$\mathrm{CH_3CH{=}CHCH_2Cl} + n\text{-BuCu} \cdot \mathrm{BF_3} \xrightarrow[\text{hexane}]{\text{THF}} \mathrm{CH_3\underset{\displaystyle n\text{-Bu}}{\underset{|}{C}}HCH{=}CH_2}$$

80%
(> 98% isomerically pure)

Reaction of Organocuprates

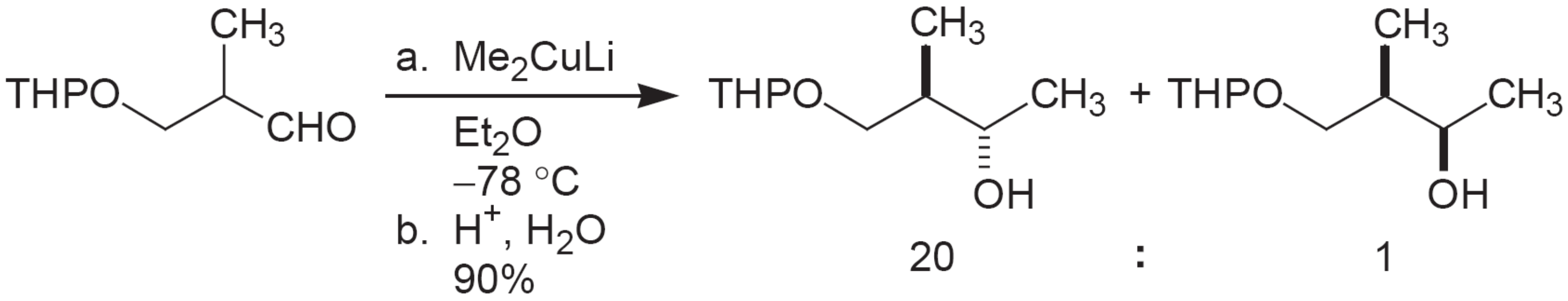
❖ *Reaction of vinyl halides*

- Coupling of alkenyl bromides or iodides with organocuprates proceeds with high stereoselectivity.



❖ *1,2-Addition to aldehydes and ketones*

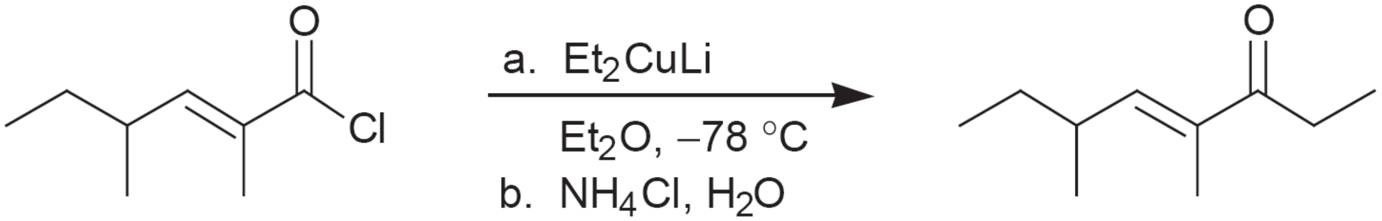
- Organocuprates undergo 1,2-additions to aldehydes, ketones, and imines. Reactions are often highly diastereoselective.



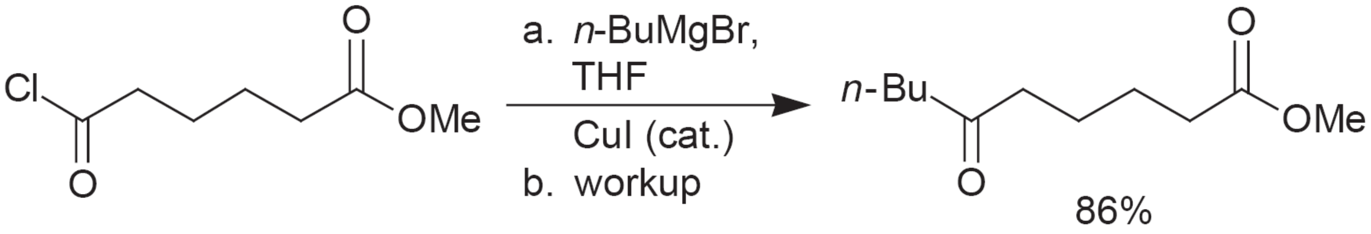
Reaction of Organocuprates

❖ *Acylation*

- reaction of organocopper reagents with acid chlorides affords corresponding ketones in high yields. Retrosynthetically, the reaction amounts to an alkylation of a carboxylic acid.



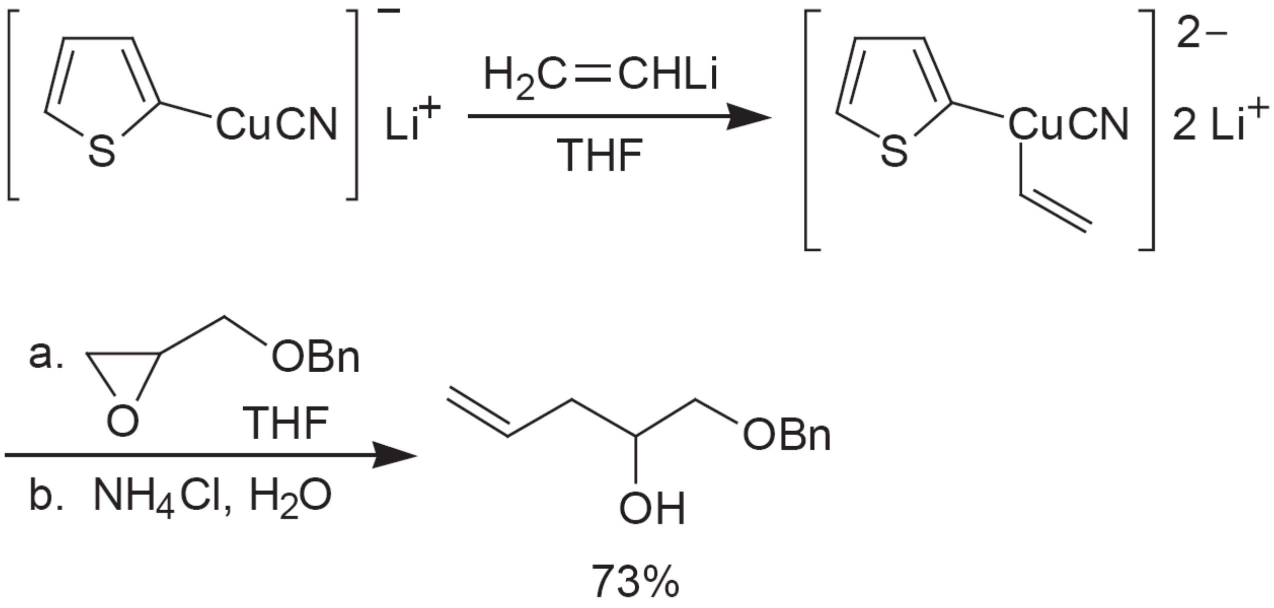
- In the presence of a catalytic amount of CuI, Grignard reagents convert acid chlorides chemoselectively to the corresponding ketones via a transiently formed cuprate reagent, which reacts competitively with the initial Grignard



Reaction of Organocuprates

❖ *Epoxide cleavage reactions*

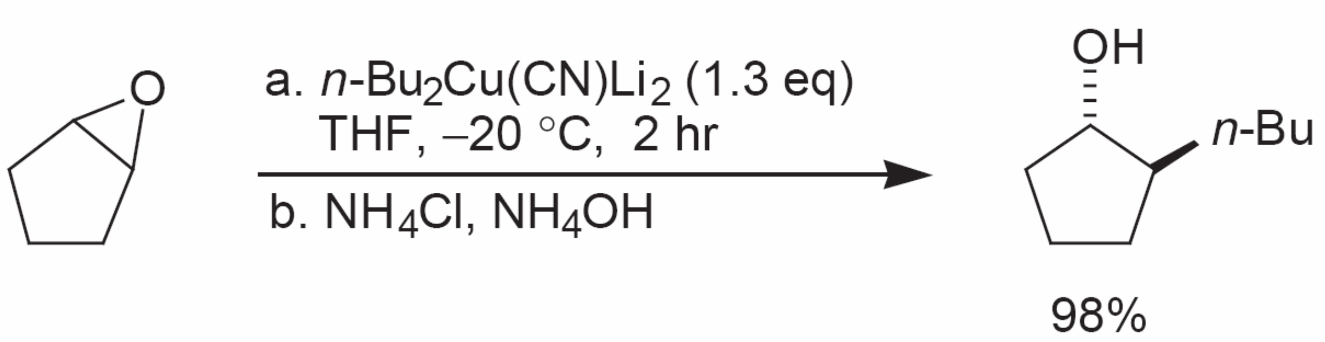
- $R_2Cu(CN)Li_2$ reagents: among the mildest and most efficient reagents available for generating C-C bonds by way of epoxide cleavage using organocopper chemistry.
- nucleophilic addition occurs at the less sterically hindered carbon of the oxirane ring



Reaction of Organocuprates

❖ *Epoxide cleavage reactions* *(cont'd)*

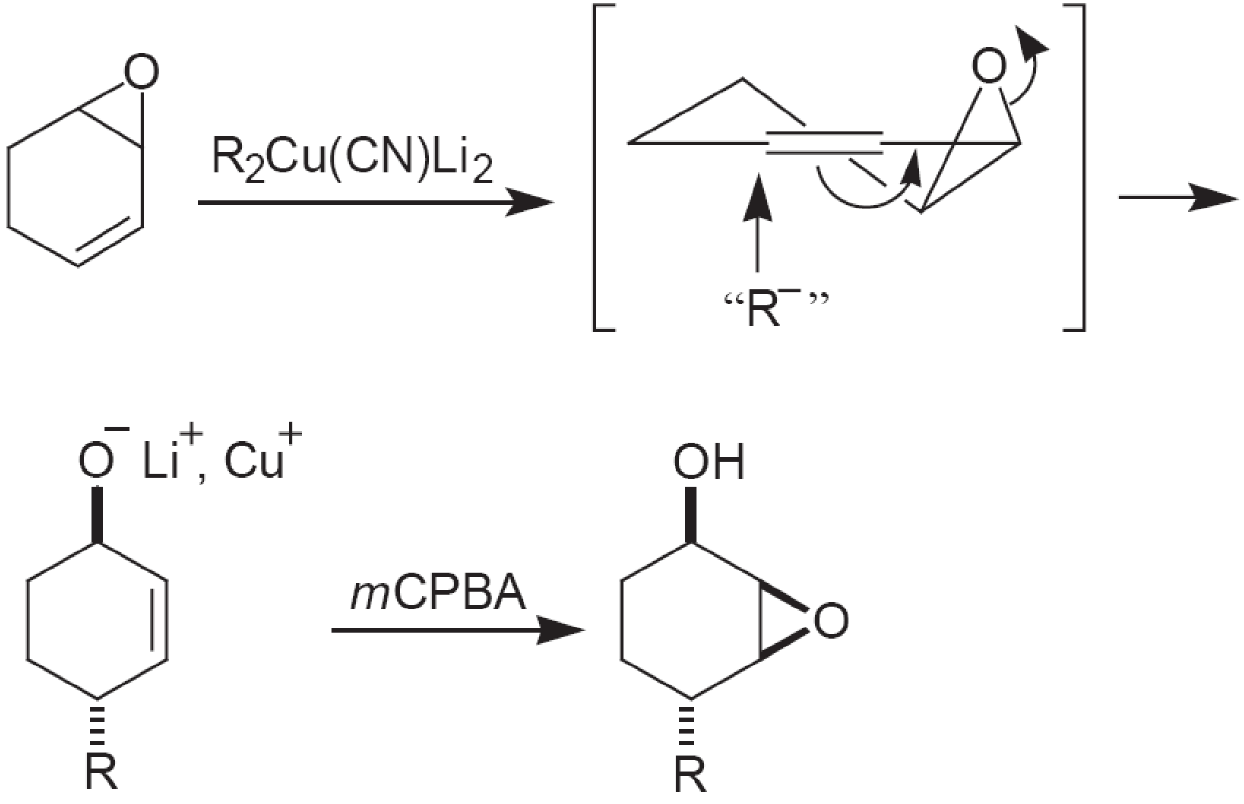
- Stereospecific S_N2 opening of cyclic epoxides with cyanocuprates furnishes, after workup, the *trans*-2-hydroxy-alkylated products.



Reaction of Organocuprates

❖ ***Epoxide cleavage reactions*** *(cont'd)*

- However, the unsaturated epoxide reacts with cyanocuprates via an *anti*-S_N2-type mechanism. Directed epoxidation of the resultant allylic alcoholate produces a hydroxy epoxide containing 4 stereodefined carbon centers.



Reaction of Organocuprates

❖ *Conjugate Addition*

- Conjugate addition is an important C–C bond formation
- Organometallic reagents may add in a 1,2- or 1,4-manner to α,β-unsaturated carbonyl compounds.

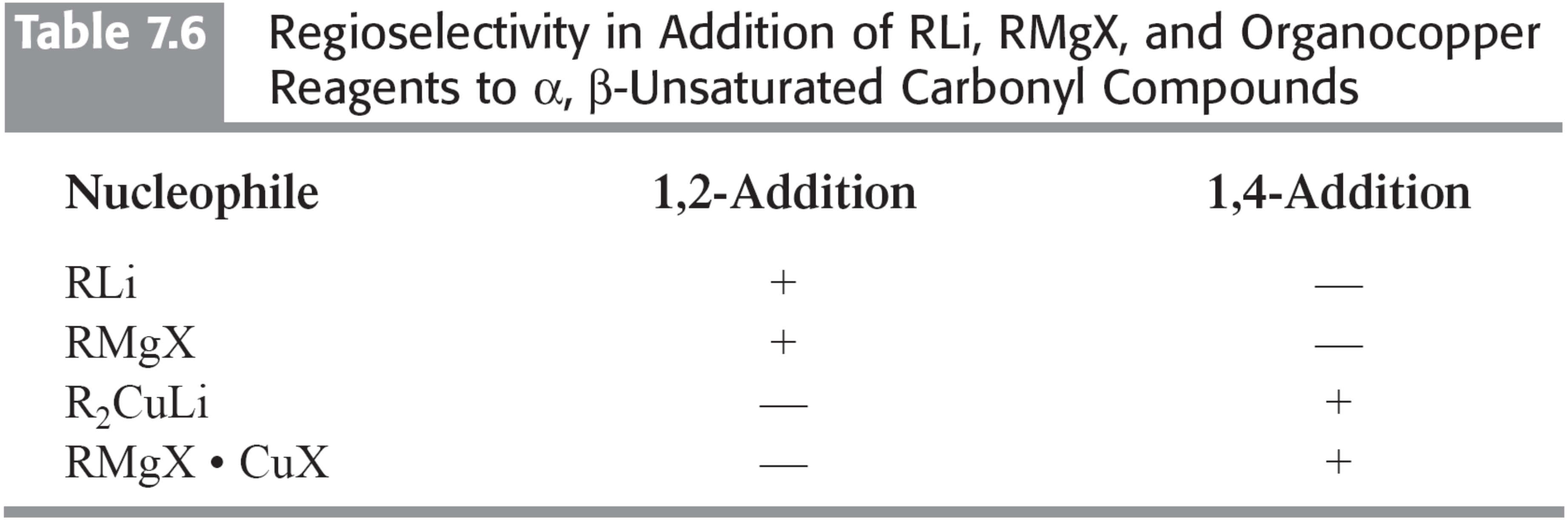


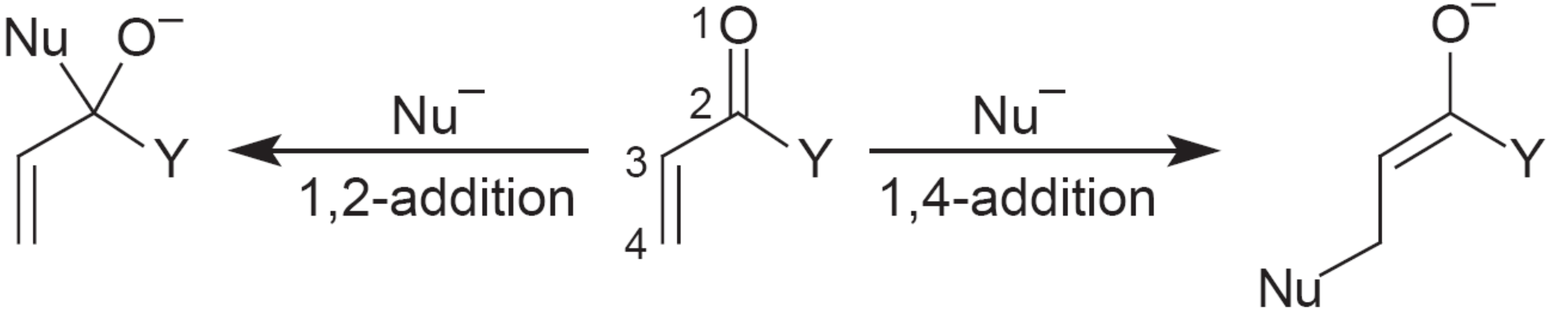
Table 7.6 Regioselectivity in Addition of RLi, RMgX, and Organocopper Reagents to α, β-Unsaturated Carbonyl Compounds

Nucleophile	1,2-Addition	1,4-Addition
RLi	+	—
RMgX	+	—
R_2CuLi	—	+
RMgX • CuX	—	+

Reaction of Organocuprates

❖ *Conjugate Addition* *(cont'd)*

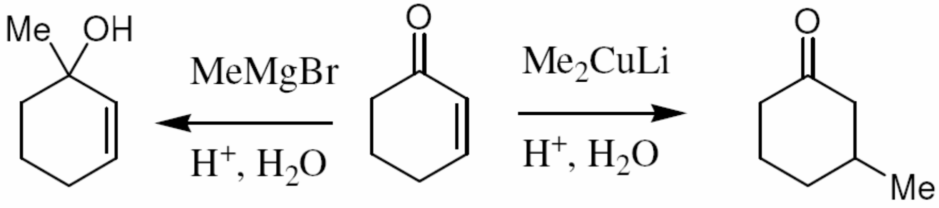
- ***1,4-Addition*** (conjugate addition) is most successful with "**soft**" (relatively nonbasic) nucleophiles such as –C≡N, RNH_2, RNH, RSH, enolates derived from β-dicarbonyl compounds, and organocuprates.
- ***1,2-Addition*** is most successful with "**hard**" (relatively basic) nucleophiles such as hydride, organolithiums, and Grignard



Y = H, R, OR, halogen

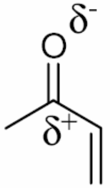
enolate anion

Organometallic - Regioselectivity



$\mathrm{MeMgBr} \equiv \overset{\ominus}{\mathrm{CH}_3}\ \ \overset{\oplus}{\mathrm{MgBr}}$

Electron pair (negative charge)
is held close to the carbon atom:
Hard Nucleophile.

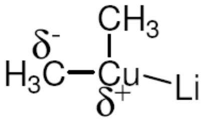


high partial charge
on carbon atom of
carbonyl:
Hard Electrophile

Hard species: carries a charge, or a high partial charge.

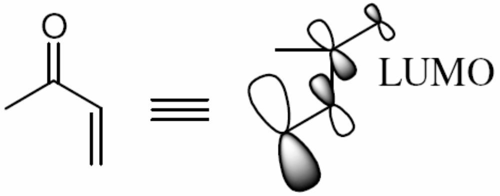
Hard nucleophiles react fastest with hard electrophiles.

$\mathrm{Me_2CuLi} \equiv$



Electron pair is shared between carbon and copper atoms,
only a slight partial charge on carbon atom:
Soft Nucleophile.

Soft nucleophiles react *via* the best FMO interactions.



β-carbon has the
largest co-efficient

Soft species: carries a low partial charge.

Soft nucleophiles react at the alkene.

Reaction of Organocuprates

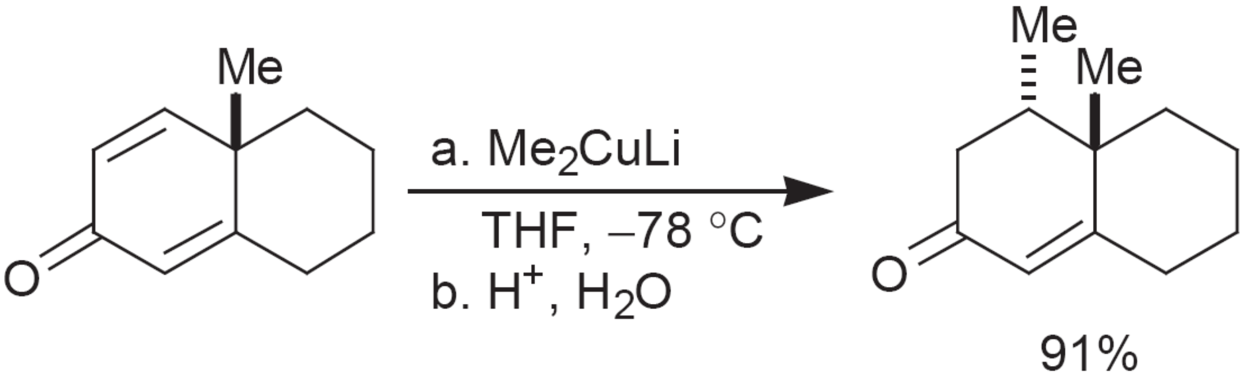
❖ *Conjugate Addition* *(cont'd)*

- organocopper reagents used for conjugate additions to enones are homocuprates,heterocuprates, higher-order cuprates, and Grignard reagents in the presence of catalytic amounts of copper salts (CuX).

- Addition of organocopper reagents to α,β-unsaturated carbonyl compounds (enones and conjugated esters) generates enolates with concomitant introduction of an organic group at the β-position.

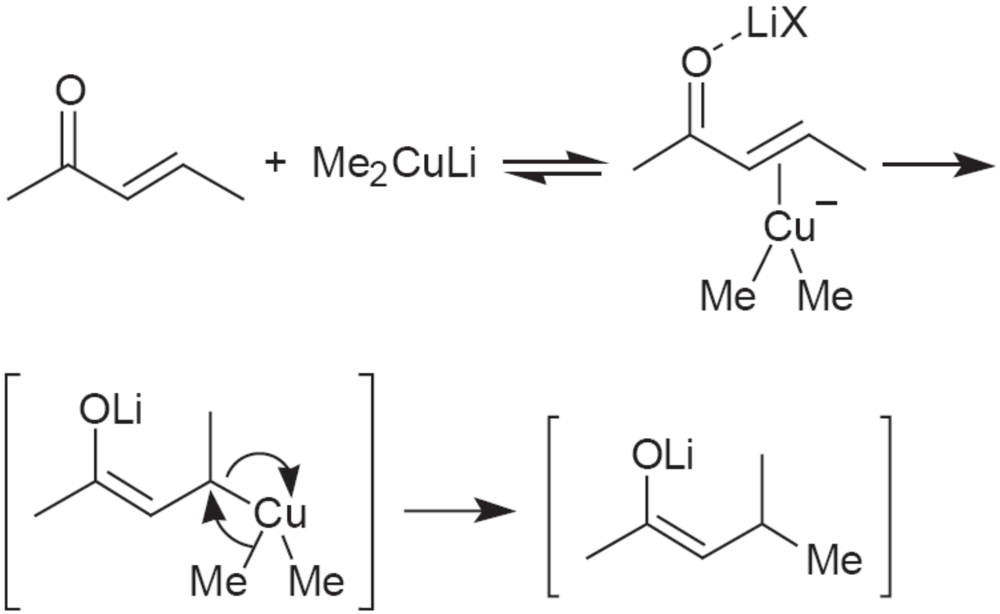
Reaction of Organocuprates

- In bicyclic system below, addition is **chemoselective**, involving the. The reaction is also less hindered double bond of the dienone and **stereoselective** in that introduction of the "Me" group occurs preferentially from the less hindered side of the molecule.



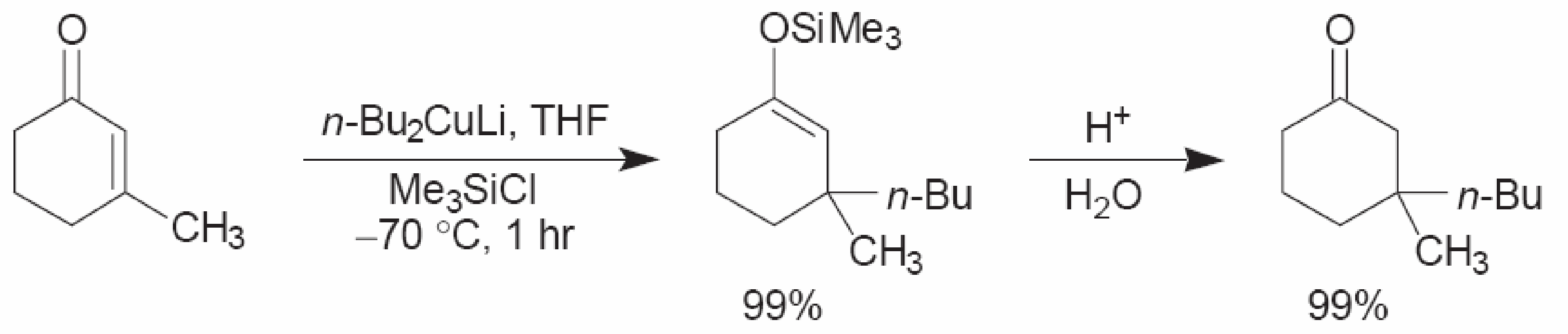
Reaction of Organocuprates

- The mechanistic picture for addition of organocuprates to α,β-unsaturated carbonyl compounds is no less complex than that for substitution reactions.
- On the basis of current information, conjugate addition of lithiocuprates to α, β-unsaturated ketones and esters may proceed via a initial reversible copper(I)-olefin-lithium association, which then undergoes oxidative addition followed by reductive elimination.



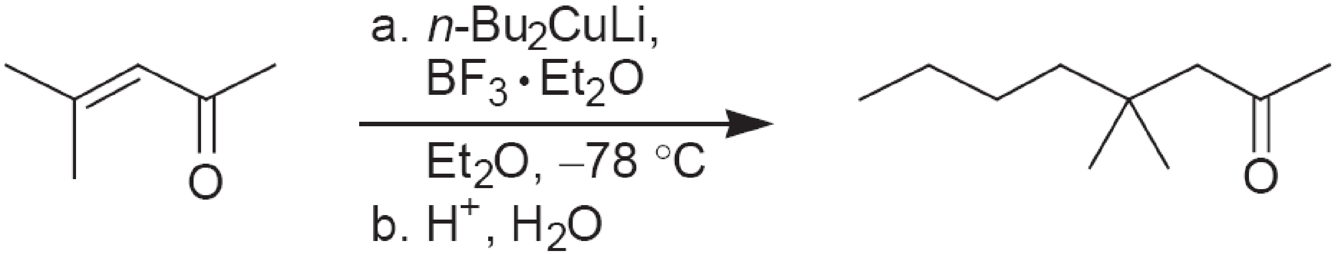
Reaction of Organocuprates

- Conjugate additions of organocopper reagents with large steric requirements and/or when there is steric hindrance at the reaction center of the enone may be difficult.
- Addition of Me_3SiCl accelerates the conjugate additions of copper reagents to such enones, probably by activating the carbonyl group.
- For example, 3-methylcyclohexenone is essentially inert to *n*-Bu_2CuLi at –70 °C in THF.
- However, in the presence of Me_3SiCl the enolate initially formed is trapped to give the β-disubstituted silyl enol ether in 99% yield. Hydrolysis of the silyl enol ether regenerates the carbonyl group.

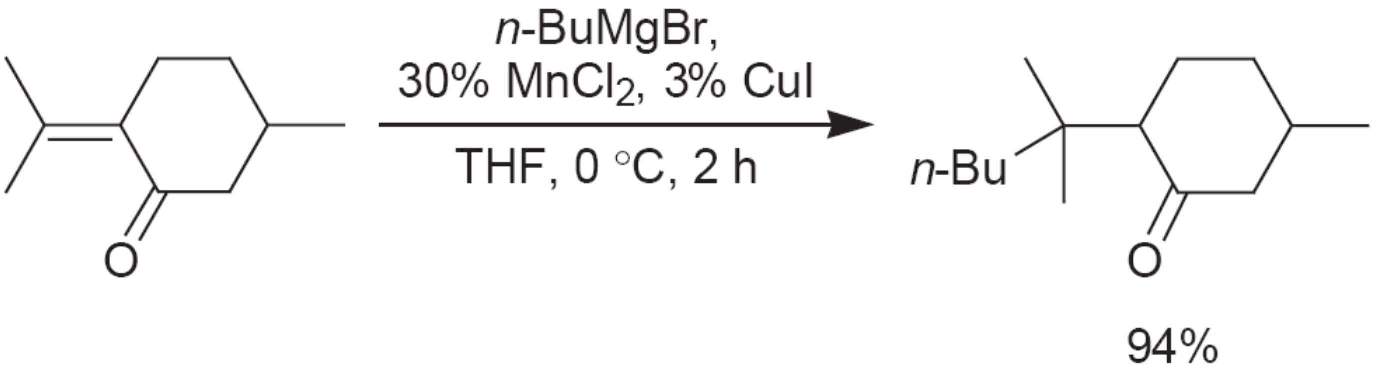


Reaction of Organocuprates

- Reactions of β,β-disubstituted enones with organocuprates are often not very successful because of steric of the C=C.
- In these cases, use of **$R_2CuLi–BF_3 \cdot OEt_2$** often obviates the problem. Possibly, Lewis acid BF_3 further polarizes and activates the ketone by coordination.

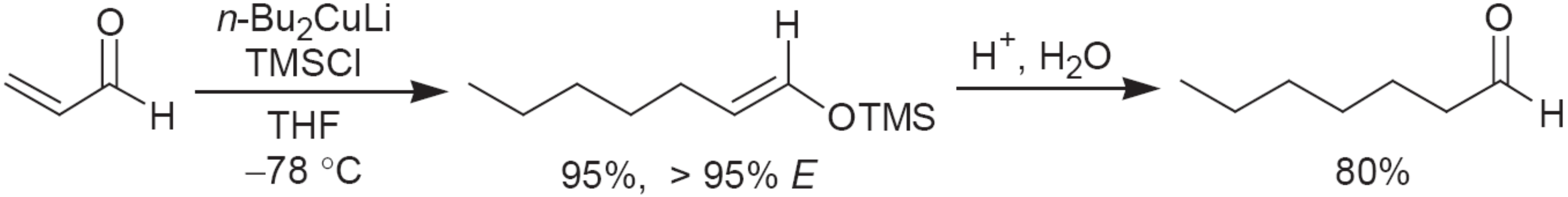


- Grignard reagents in the presence of CuX or a mixture of $MnCl_2$ and CuI undergo 1,4-addition to hindered enones.



Reaction of Organocuprates

- reaction of dialkylcuprates with α,β-unsaturated aldehydes results in the preferential 1,2-addition to the carbonyl group.
- However, in the presence of Me_3SiCl, conjugate addition prevails to furnish, after hydrolysis of the resultant silyl enol ether, the saturated aldehyde.



Reaction of Organocuprates

- Conjugate additions of dialkylcuprates to β-substituted-α,β-unsaturated acids and esters give low yields. Addition of boron trifluoride etherate, BF3·OEt_2, to certain dialkylcuprates and higher-order cuprates enhances their reactivity in Michael additions to conjugated acids and esters.

n-BuCu • BF_3: 52%

n-Bu_2CuLi: < 1%

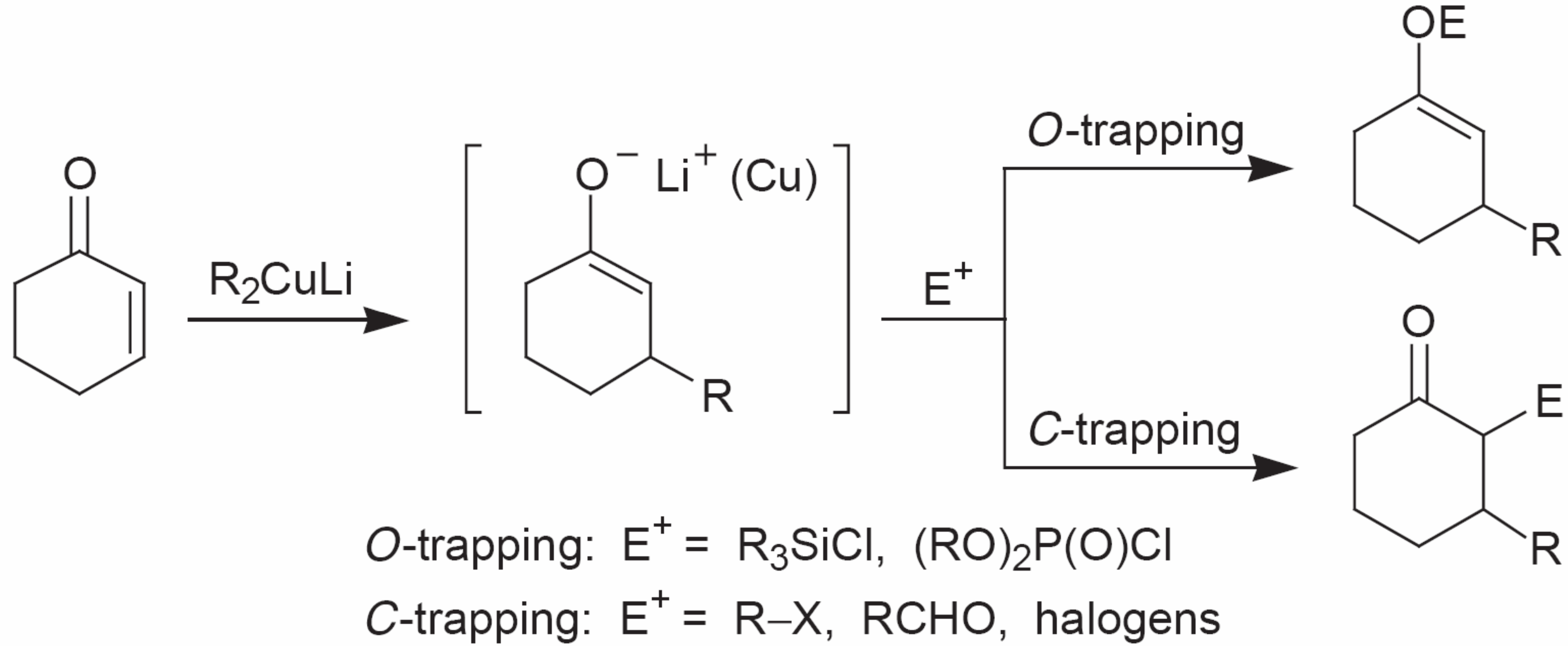
Reaction of Organocuprates

❖ *Tandem 1,4-addition – Enolate Trapping*

- One of the fundamental contributions of **organocopper** chemistry to organic synthesis is the ability to transfer ligands in a 1,4-manner to α,β-unsaturated C=O compounds to produce enolate anions in a ***regioselective*** manner.
- These may be trapped by a variety of electrophiles in ***tandem*-type reactions**.
- The enolates produced from conjugate additions of organocuprates to α, β-unsaturated C=O compounds possess 2 nucleophilic sites, reacting either at the oxygen or the carbon terminus.
- Electrophiles having a high affinity toward oxygen such as chlorosilanes and phosphorochloridates tend to give ***O*-trapping products**, whereas alkyl halides, aldehydes, α-halocarbonyl compounds, and halogens furnish ***C*-trapping products.**

Reaction of Organocuprates

❖ *Tandem 1,4-addition – Enolate Trapping*



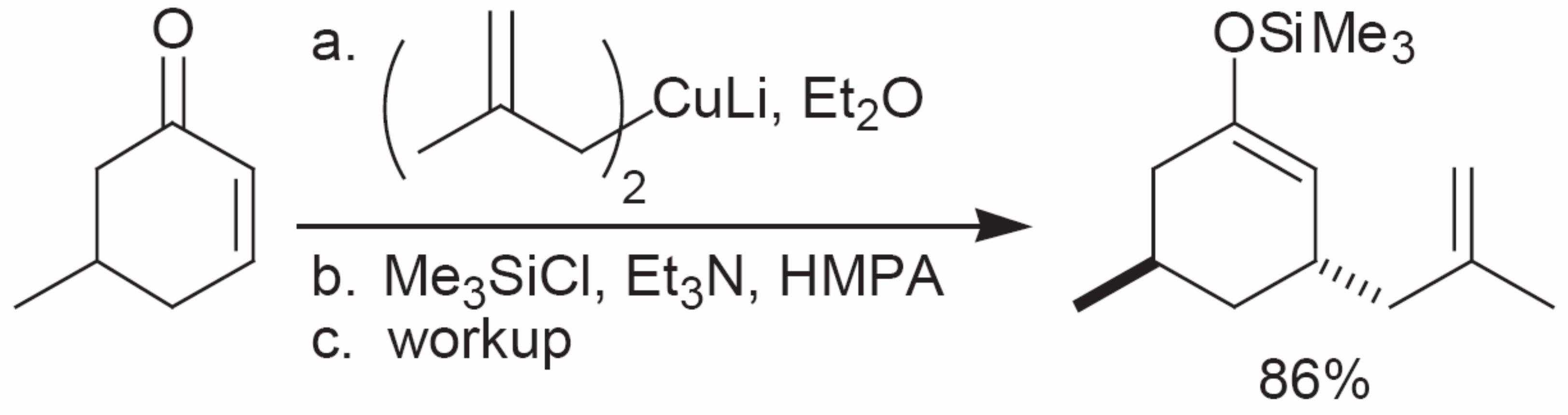
O-trapping: E^+ = R_3SiCl, $(RO)_2P(O)Cl$

C-trapping: E^+ = R–X, RCHO, halogens

Reaction of Organocuprates

❖*O-Trapping.*

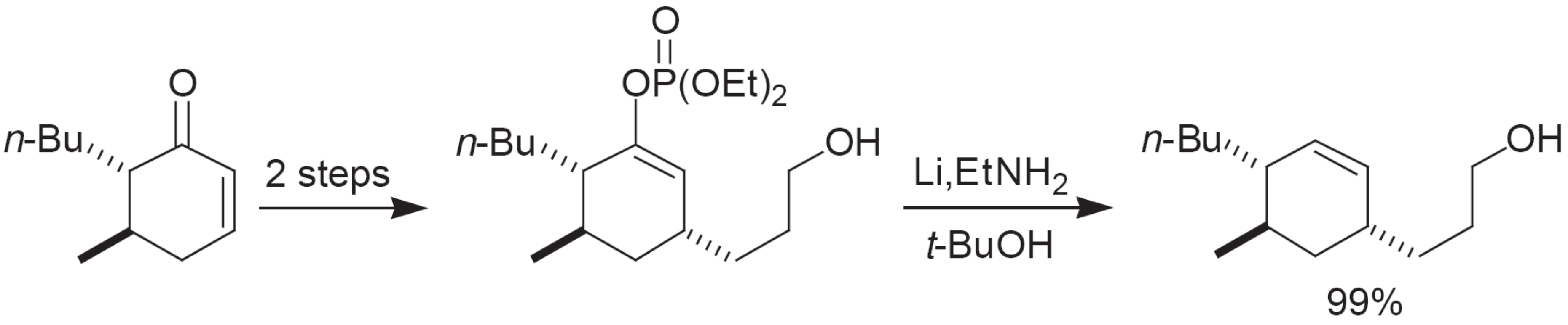
- enolate generated from enone below reacts at O with chlorotrimethylsilane in the presence of triethylamine to produce the trimethylsilyl enol ether.
- **Silyl enol** ethers are valuable intermediates for the preparation of regiodefined enolates.



Reaction of Organocuprates

❖*O-Trapping*

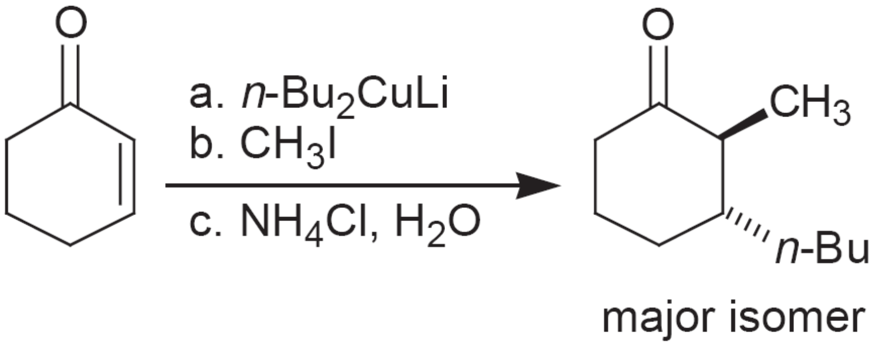
- Treatment of enolates with $(RO)_2P(O)Cl$ also results in *O*-trapping to yield the corresponding enol phosphates.
- Dissolving metal reduction of enol phosphates is useful for the deoxygenation of ketones with concomitant, regiospecific formation of the alkene.



Reaction of Organocuprates

❖*C-Trapping*

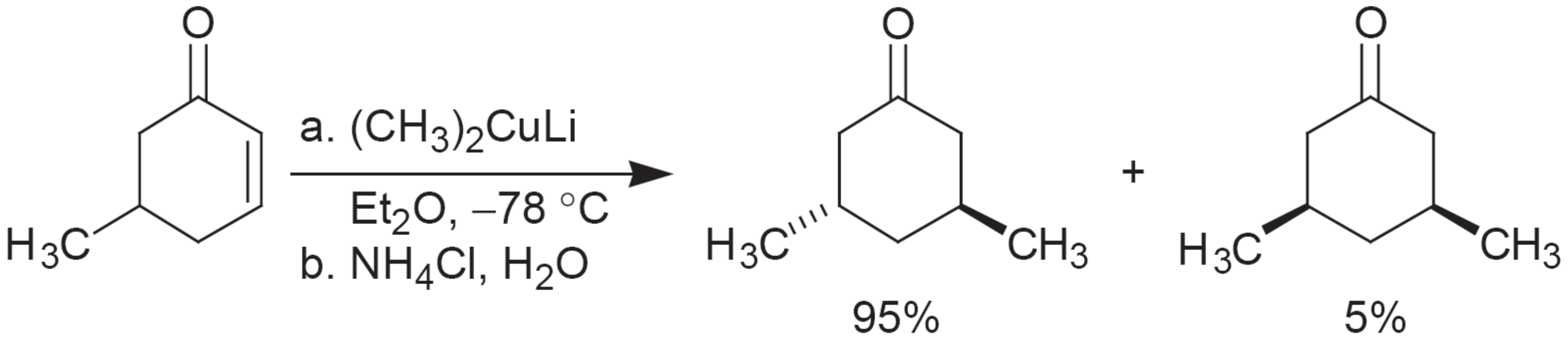
- Alkylation or hydroxyalkylation (i.e., reaction with RCHO) of enolates derived from conjugate addition of organocuprates affords vicinal dialkylated products.
- However, the reaction is confined to **highly reactive alkylating agents** such as methyl, allyl, propargyl, benzyl, and α-halocarbonyl compounds or aldehydes.
- Enolates obtained from conjugate addition of homocuprates or copper-catalyzed Grignard reagents undergo aldol condensation with aldehydes in the presence of ZnCl2 to give stereoisomeric mixtures of aldol products.



Reaction of Organocuprates

❖ *Stereochemistry of 1,4-addition*

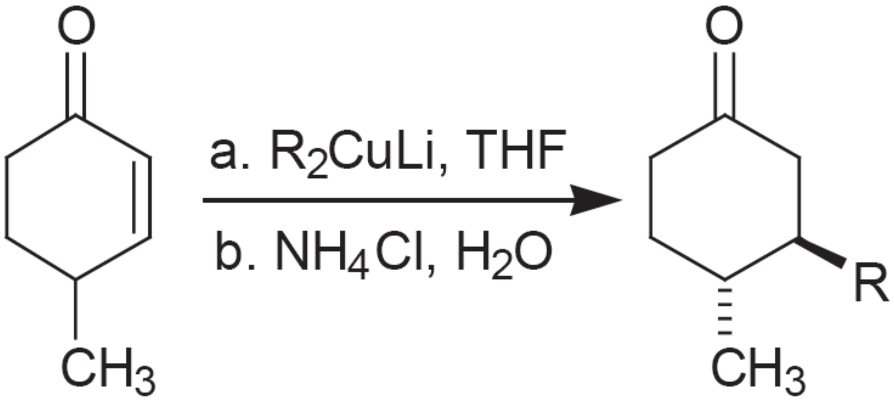
- Factors controlling the stereochemistry of conjugate additions are not well understood.
- Mixtures of isomers are produced, but generally one isomer predominates. Both steric and electronic factors play a role.
- Generally, **Michael-type additions** have **late** and hence **product like —** and **chairlike—transition states.**
- example below, for stereoelectronic reasons antiparallel attack by the nucleophilic “CH_3” is favored over parallel attack.



Reaction of Organocuprates

❖ *Stereochemistry of 1,4-addition*

- Note that the 4-methylcyclohexenone gives preferentially the *trans*-product.
- In this case, the reaction proceeds via a conformation with the Me group being **pseudoaxial** due **to A^{1,2} strain**.

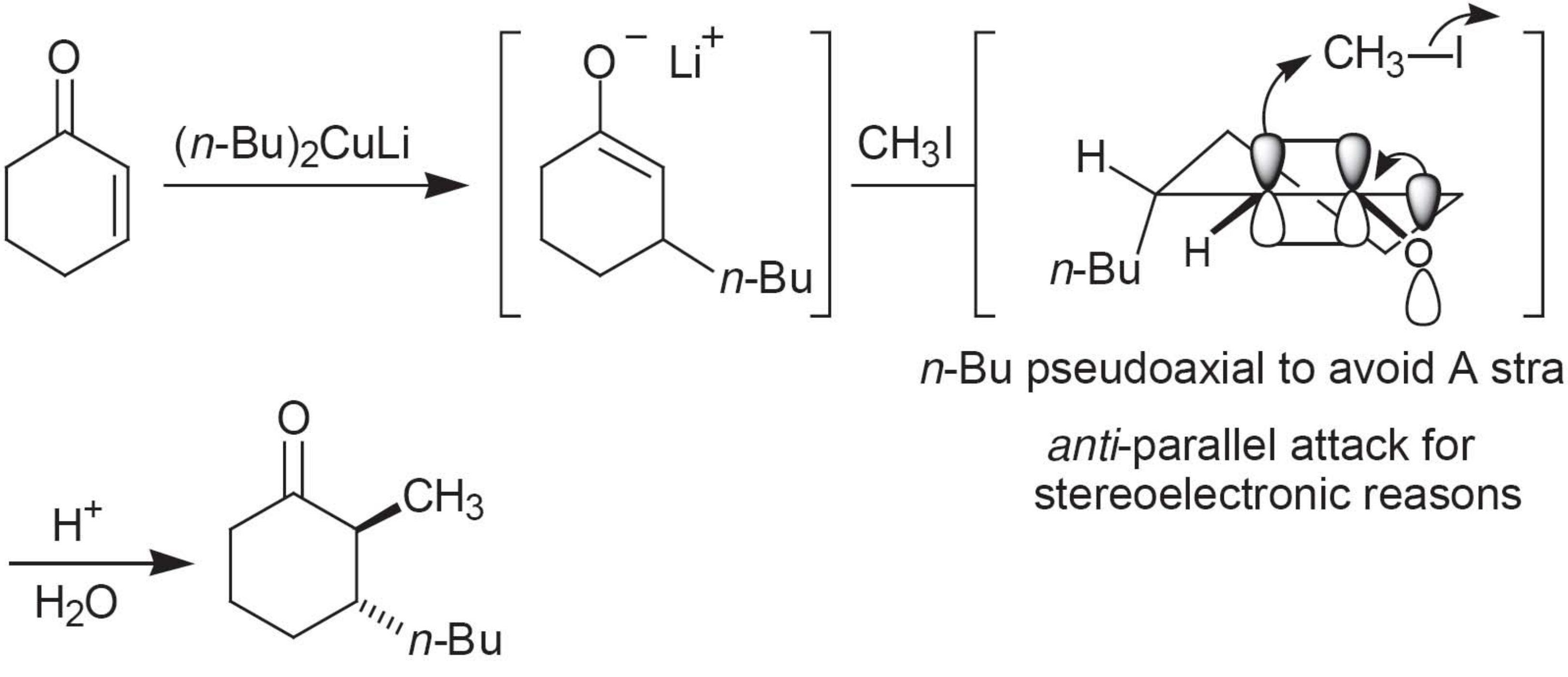


- addition of organocuprates to enones followed by alkylation of resultant enolates generates 2 C-C bonds in a single reaction

Reaction of Organocuprates

❖ *Stereochemistry of 1,4-addition*

- *Alkylation of an enolate* proceeds via an **early**, hence a **reactant-like**, **transition state**.
- Thus, steric factors in the ground state play an important role.



n-Bu pseudoaxial to avoid A strain

anti-parallel attack for stereoelectronic reasons

major isomer

Organozinc compounds

- In contrast to the polar nature of C–Li and C–MgX bonds, the **C–Zn bond is highly covalent** and hence **less reactive**, allowing the preparation of functionalized derivatives.

- The carbon zinc bond is polarized towards carbon due to the differences in electronegativity --- carbon: 2.55 and zinc:1.65

- utilization of organozinc reagents mainly focused around preparation and utilization of functional organozinc compounds in organic syntheses (**Reformatsky reaction**), cyclopropanation (**Simmons-Smith reaction**), and **transmetalations** with transition metals.

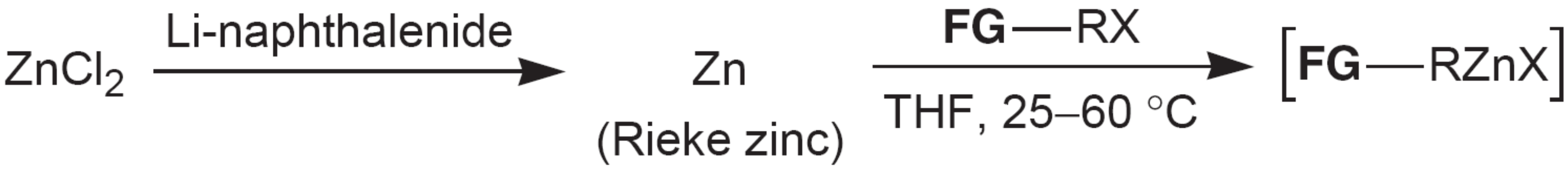
Organozinc reagents

- The first organozinc ever prepared = diethylzinc (Et_2Zn), by Edward Frankland in 1849, was also the first ever compound with a metal to carbon sigma bond.
- Many organozinc compounds are pyrophoric and therefore difficult to handle.
- Organozinc compounds in general are sensitive to oxidation, dissolve in a wide variety of solvents where protic solvents cause decomposition.
- In many reactions they are prepared *in situ*. All reactions require inert atmosphere: N_2 or Ar
- The three main classes of organozincs are: **organozinc halides R-Zn-X** with, **diorganozincs** R-Zn-R, and **lithium zincates or magnesium zincates M^+R3Zn^-** with M = lithium or magnesium

Preparations

Alkylzinc iodides (RZnI)

- Primary and secondary alkylzinc iodides (RZnI) are best prepared by direct insertion of zinc metal (zinc dust activated by 1,2-dibromoethane or chlorotrimethylsilane) into alkyl iodides or by treating alkyl iodides with ***Rieke* zinc**. The zinc insertion can tolorate a lot of functional groups, allowing preparation of polyfunctional organozinc reagents.



$$ZnCl_2 \xrightarrow{\text{Li-naphthalenide}} \underset{\text{(Rieke zinc)}}{Zn} \xrightarrow[\text{THF, 25–60 °C}]{\mathbf{FG}\text{—RX}} \left[\mathbf{FG}\text{—RZnX}\right]$$

R: alkyl, aryl, benzyl, allyl

X: Br, I

FG: CO_2R, enolate, CN, halide, etc.

Preparations

Alkylzinc iodides (RZnI)

- **Rieke metals** are highly reactive metal powders prepared by the methods developed by Reuben D. Rieke.
- Rieke metals are highly reactive because they have high surfaces areas and lack passivating surface oxides.
- The method usually involves reduction of a THF suspension an anhydrous metal chloride with an alkali metal. Typical alkali metals used in this method are potassium, sodium, and lithium.
- For example, the preparation of Rieke magnesium employs potassium as the reductant:

$$MgCl_2 + 2K \rightarrow Mg + 2\,KCl$$

Preparations

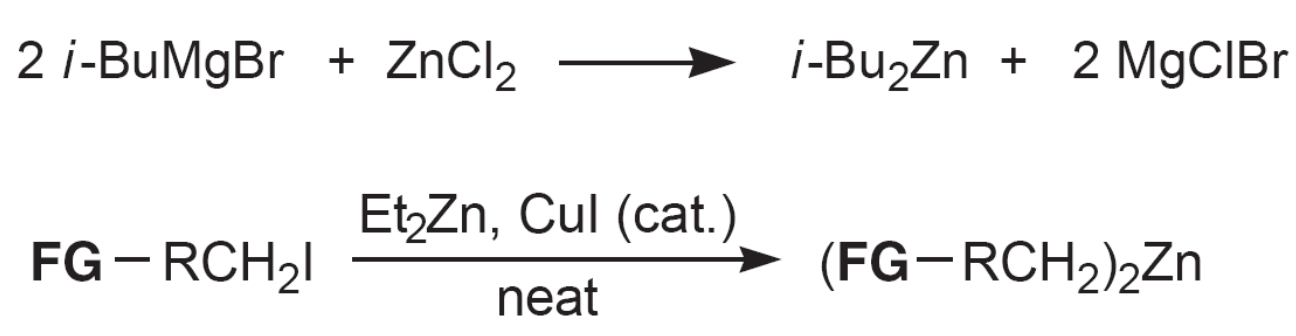
Alkylzinc iodides (RZnI)

- **Rieke metals**
- More recent reports emphasize the use of the less hazardous lithium metal in place of potassium.[2] Among the many metals that have been generated by this method are Mg, Ca, Ti, Fe, Co, Ni, Cu, Zn, In.
- In some cases the reaction is carried out with a catalytic amount of an electron carrier such as biphenyl or naphthalene. The coprecipitated alkali metal chloride is usually not separated from the highly reactive metal, which is generally used *in situ*.

Preparations

Dialkylzinc **(R_2Zn)**

- Unfunctionalized dialkylzincs (R_2Zn) are obtained by transmetalation of zinc halides, such as $ZnCl_2$, with organolithium or Grignard reagents.
- Iodide-zinc exchange reactions catalyzed by CuI provide a practical way for preparing functionalized dialkylzincs.



$$2\ i\text{-BuMgBr} + ZnCl_2 \longrightarrow i\text{-Bu}_2Zn + 2\ MgClBr$$

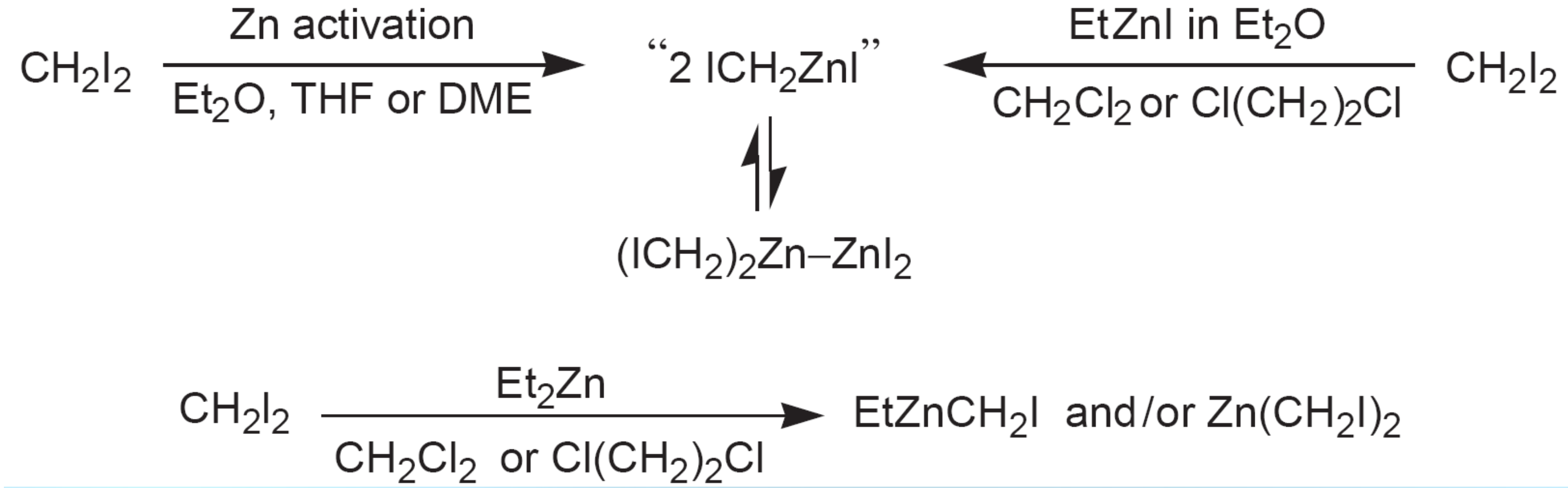
$$\mathbf{FG}-RCH_2I \xrightarrow[\text{neat}]{Et_2Zn,\ CuI\ (cat.)} (\mathbf{FG}-RCH_2)_2Zn$$

- Diorganozincs are always monomeric, the organozinc halides form aggregates through halogen bridges very much like Grignard reagents and also like Grignards they display a Schlenk equilibrium

Preparations

Dialkylzinc **(R_2Zn)**

- oxidative addition of Zn metal to diiodomethane affords an iodomethylzinc iodide, tentatively assigned as **ICH_2ZnI** (**Simmons-Smith reagent**), which is used for cyclopropanation of alkenes.
- Alkyl group exchange between diethylzinc and diiodomethane produces the iodomethyl zinc carbenoid species, tentatively assigned as **$EtZnCH_2I$** (**Furukawa's reagent**).



$$CH_2I_2 \xrightarrow[\text{Et}_2\text{O, THF or DME}]{\text{Zn activation}} \text{“}2\ ICH_2ZnI\text{”} \xleftarrow[CH_2Cl_2 \text{ or } Cl(CH_2)_2Cl]{EtZnI \text{ in } Et_2O} CH_2I_2$$

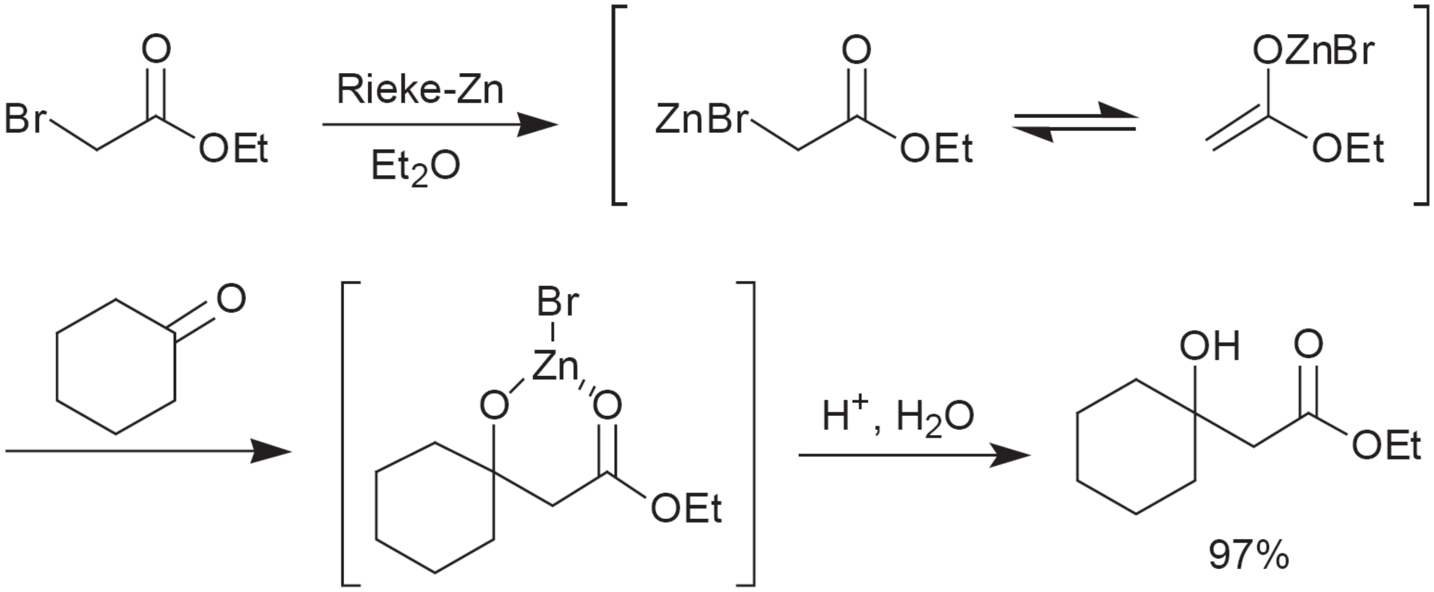
$$\text{“}2\ ICH_2ZnI\text{”} \rightleftharpoons (ICH_2)_2Zn{-}ZnI_2$$

$$CH_2I_2 \xrightarrow[CH_2Cl_2 \text{ or } Cl(CH_2)_2Cl]{Et_2Zn} EtZnCH_2I \text{ and/or } Zn(CH_2I)_2$$

Reaction of Organozinc compounds

❖ *The Reformatsky Reaction*

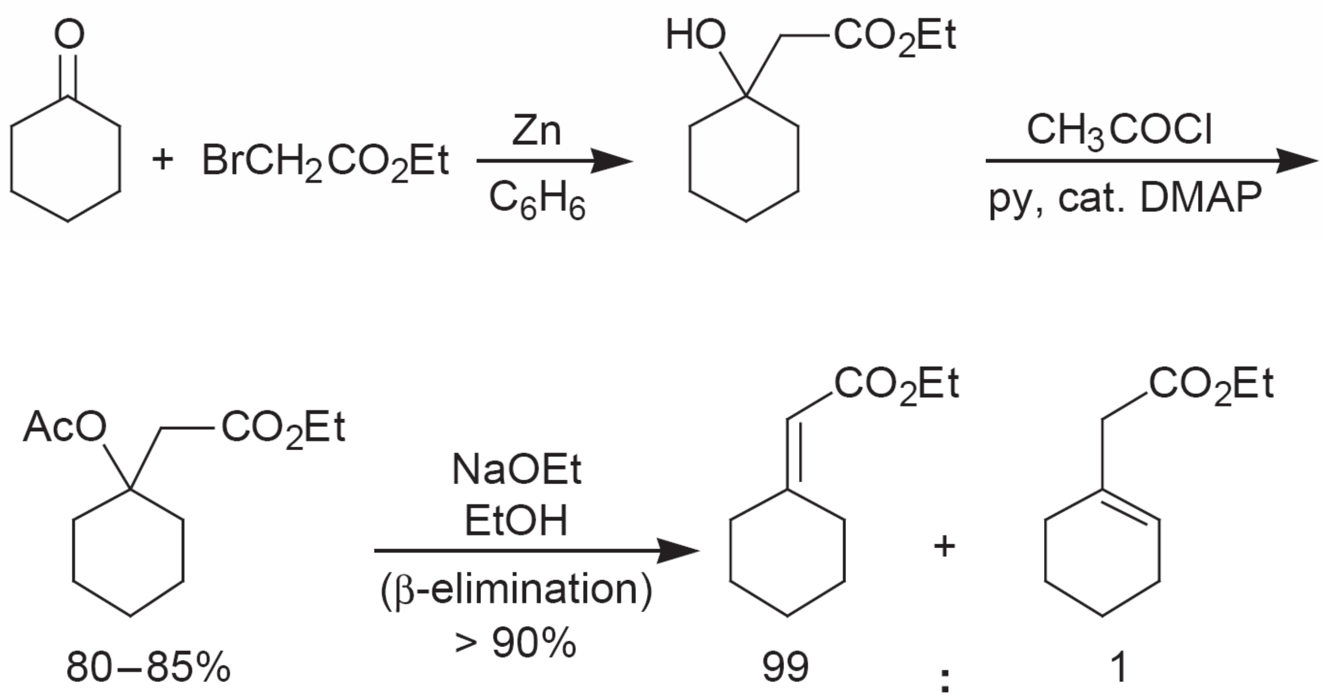
- involves condensation of ester-derived zinc enolates with aldehydes or ketones to give corresponding β-hydroxy esters.
- zinc enolates are generated by addition of an α-haloester in THF, DME, Et_2O, benzene, or toluene to an **activated zinc**, such as a Zn-Cu couple or zinc obtained by reduction of zinc halides with potassium (**Rieke zinc**).



Reaction of Organozinc compounds

❖ *The Reformatsky Reaction*

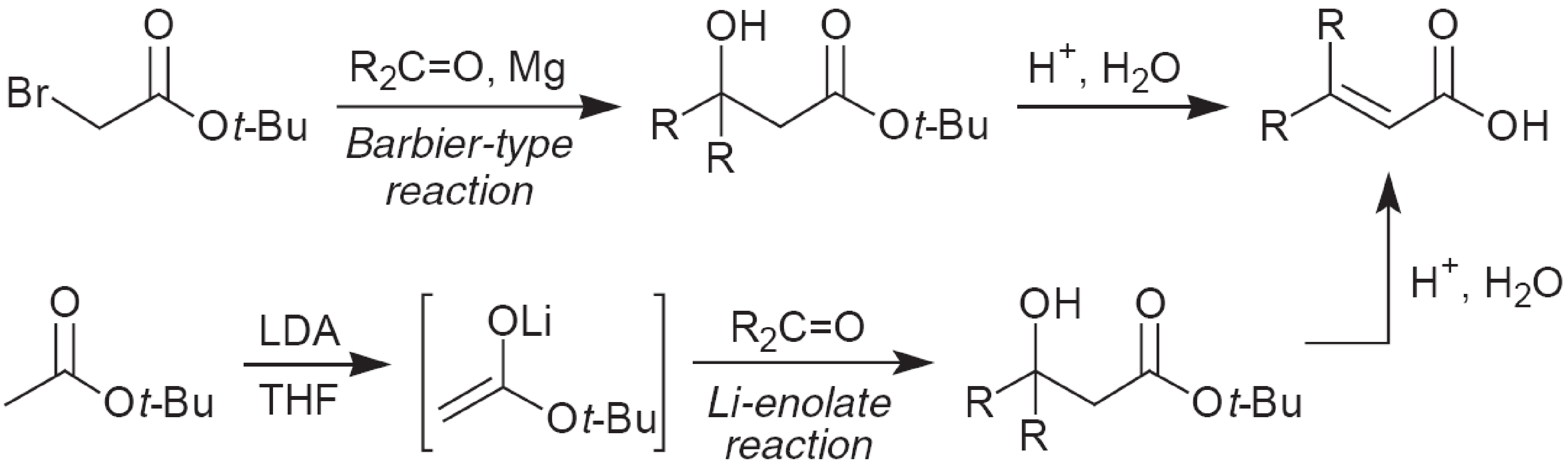
- Important: conversion of β-hydroxy esters to α,β-unsat. esters
- Acid-cat. dehydration gives α,β- + β,γ-unsaturated esters mixture
- However, conversion of the initially formed β-hydroxy esters to their corresponding acetates by treatment with acetyl chloride, followed by base-catalyzed dehydration with NaOEt, produces conjugated esters in high purity.



Reaction of Organozinc compounds

❖ *The Reformatsky Reaction*

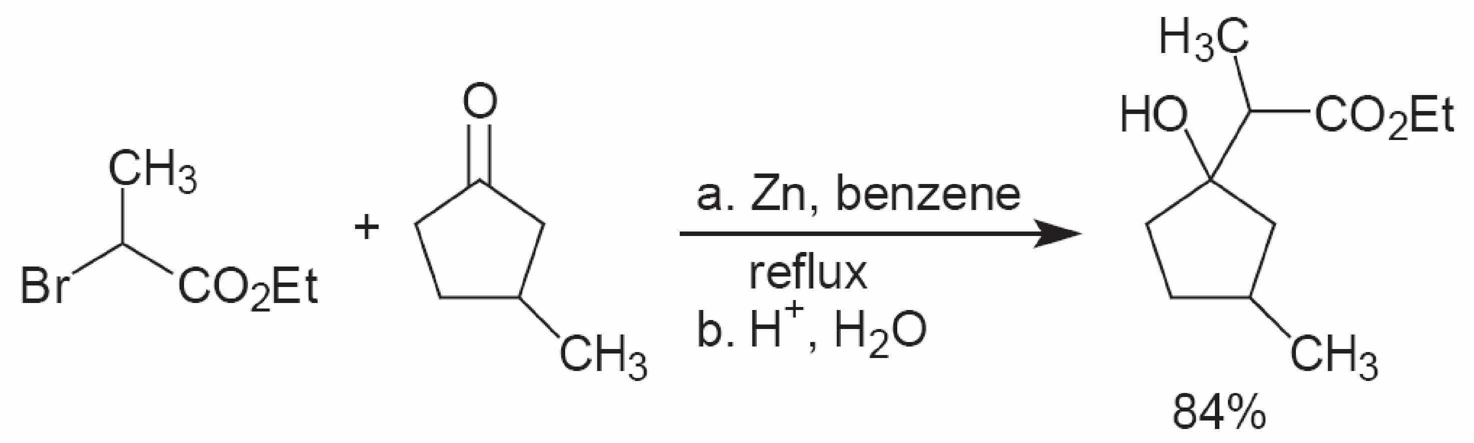
- β-Hydroxy esters and α,β−unsaturated esters may also be prepared either via a single-step ***Barbier-type condensation*** of a *t*-Bu-bromoester with carbonyl compounds in the presence of Mg metal or via a two-step condensation with Li-enolates



Reaction of Organozinc compounds

❖ *The Reformatsky Reaction*

- Reformatsky enolates: different from base-generated enolates since zinc enolates add to highly hindered+to easily enolizable ketones, thus no formation of condensation products.
- No danger of a Claisen-type self-condensation since zinc-enolates do not react with esters but react readily with aldehydes and ketones to furnish **aldol-type products**.

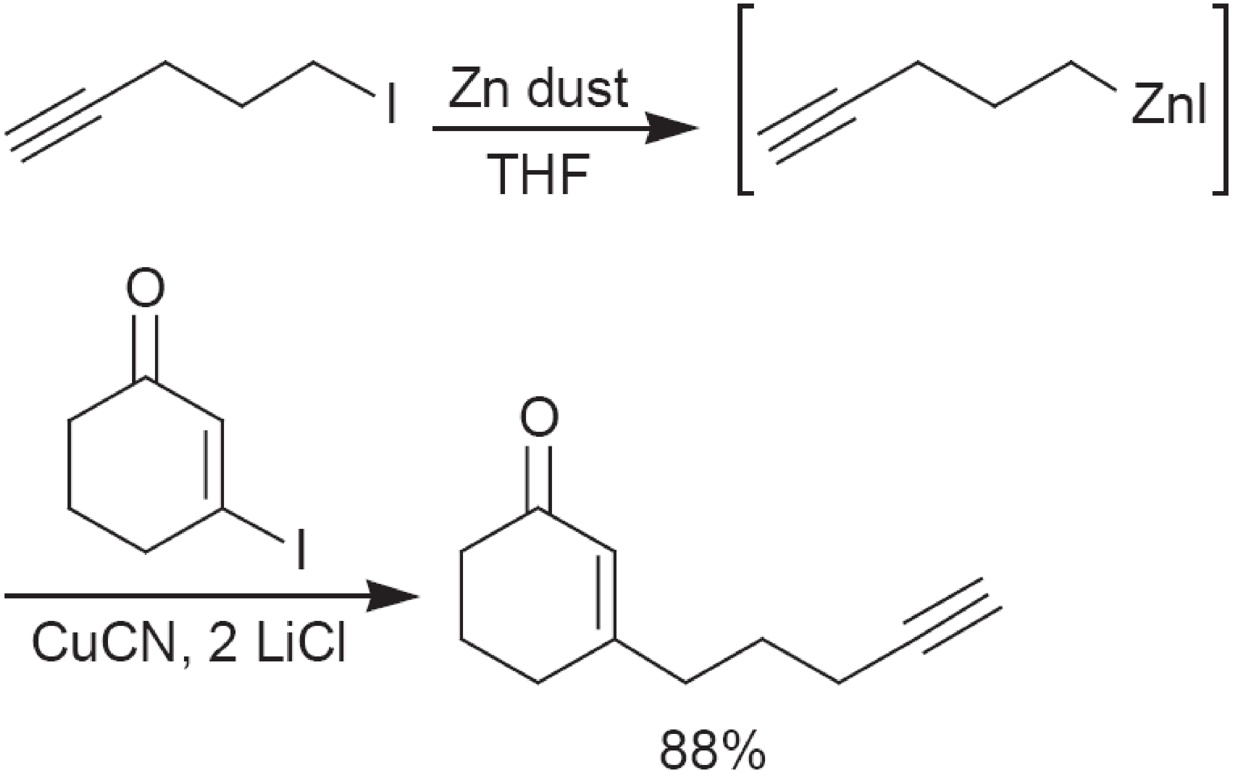


- Enantioselective addition of organozinc to C=O gives chiral alcohols.

Reaction of Organozinc compounds

❖ *Reactions of functionally substituted RZnI*

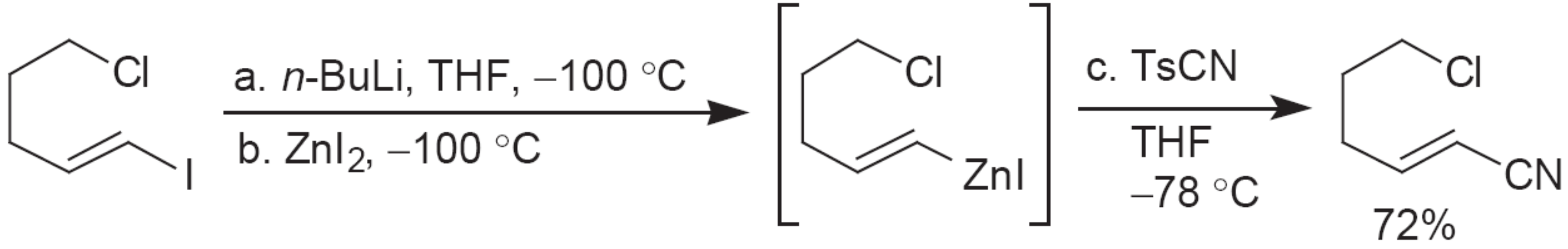
- application of functionally substituted organozincs allows for construction of C-C bonds while circumventing tedious protection-deprotection strategies.

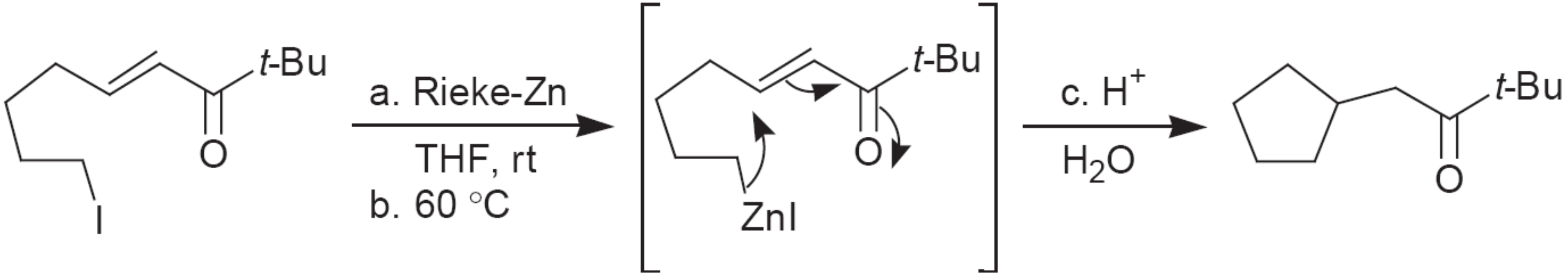


Reaction of Organozinc compounds

❖ *Reactions of functionally substituted RZnI*

- Note that tosyl cyanide reacts with alkenyl or arylzinc reagents to provide α,β-unsaturated alkenyl or aromatic nitriles, respectively



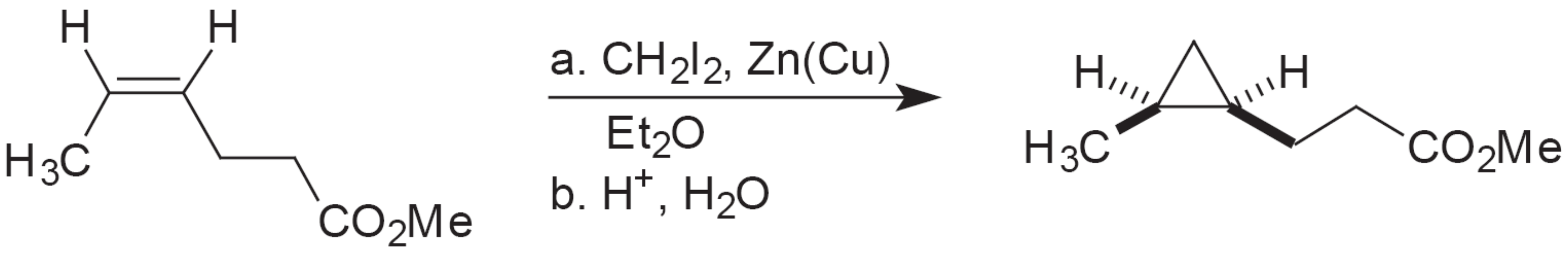


Reaction of Organozinc compounds

Cyclopropanation

- Cyclopropane rings are encountered in many natural products possessing interesting biological activities.
- Cyclopropane moiety represents a useful synthon for further synthetic transformations.
- In 1958, Simmons and Smith reported that treatment of a zinc-copper couple with diiodomethane in ether produces a reagent that adds to alkenes to form cyclopropanes.

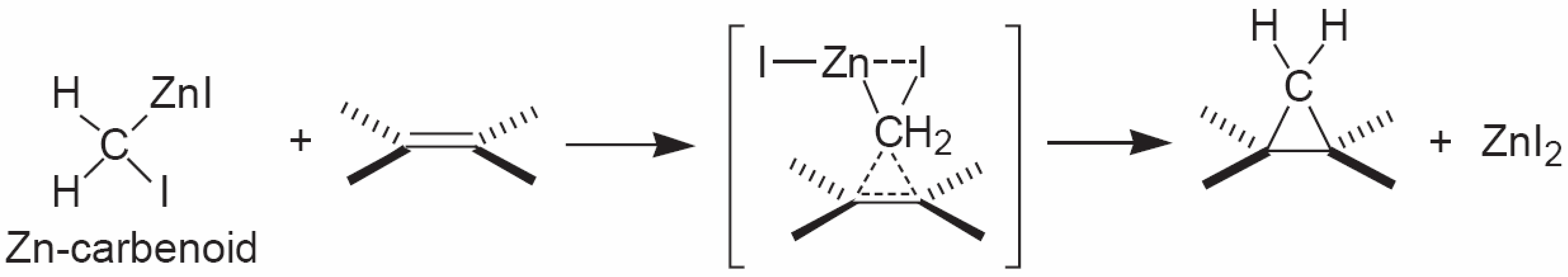
$$CH_2I_2 \quad + \quad Zn(Cu) \xrightarrow[35\ ^\circ C]{Et_2O} ICH_2ZnI$$



Reaction of Organozinc compounds

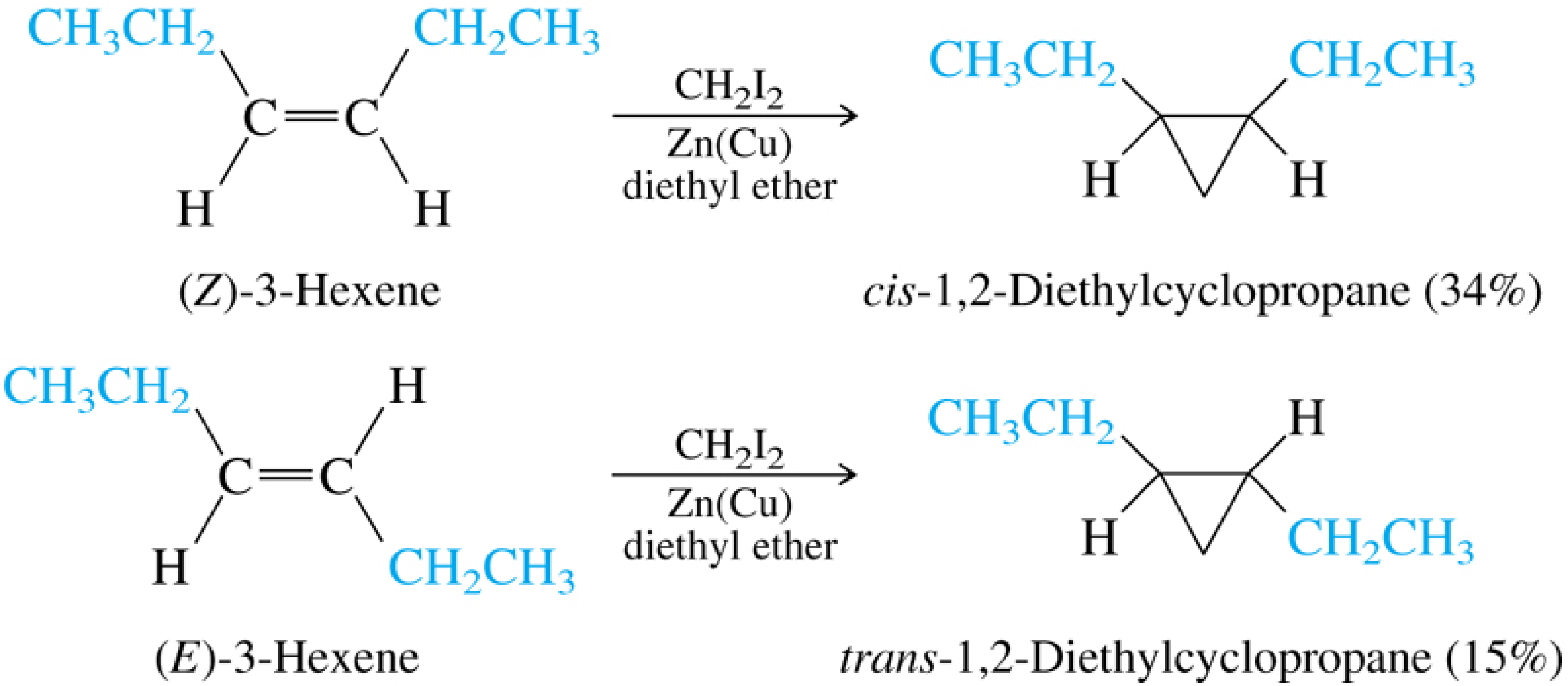
❖ *Cyclopropanation*

- The cyclopropanation reaction of simple alkenes appears to proceed via ***stereospecific syn*-addition** of a **Zn-carbenoid** (carbene-like species) to the double bond without the involvement of a free carbene.



Reaction of Organozinc compounds

- ***stereospecific syn*-addition** of **Zn-carbenoid** to the double bond



Reaction of Organozinc compounds

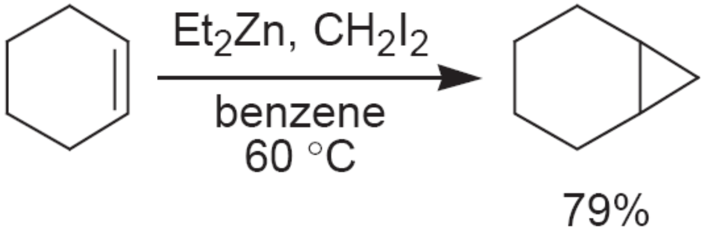
❖ *Cyclopropanation*

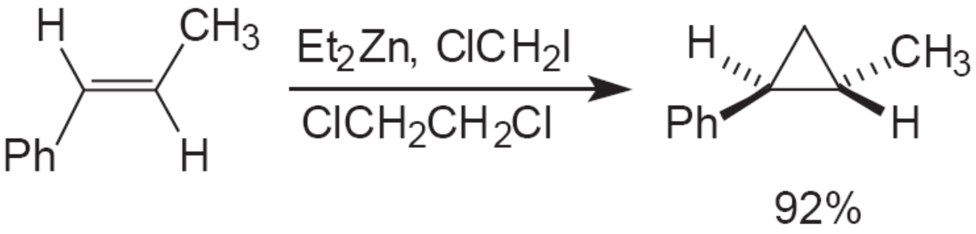
- characteristics:
  - stereospecificity (retention of olefin geometry);
  - tolerance of a variety of functional groups, such as Cl, Br, OH, OR, CO_2R, C=O, and CN;
  - the *syn*-directing effect of hydroxyl and ether functions;
  - chemoselectivity—zinc carbenoids are electrophilic and react chemoselectively with the more nucleophilic double bond in dienes and polyenes.

Reaction of Organozinc compounds

❖ ***Cyclopropanation*** modifications of Simmons-Smith :

- **Furukawa's reagent**, (iodomethyl)zinc derived from diethylzinc and diiodomethane, or its modification using chloroiodomethane instead of diiodomethane, allows more flexibility in the choice of solvent.
- The reagent is homogeneous and the cyclopropanation of olefins can be carried out in noncomplexing solvents, such as dichloromethane or 1,2-dichloroethane, which greatly increase the reactivity of the zinc carbenoids.

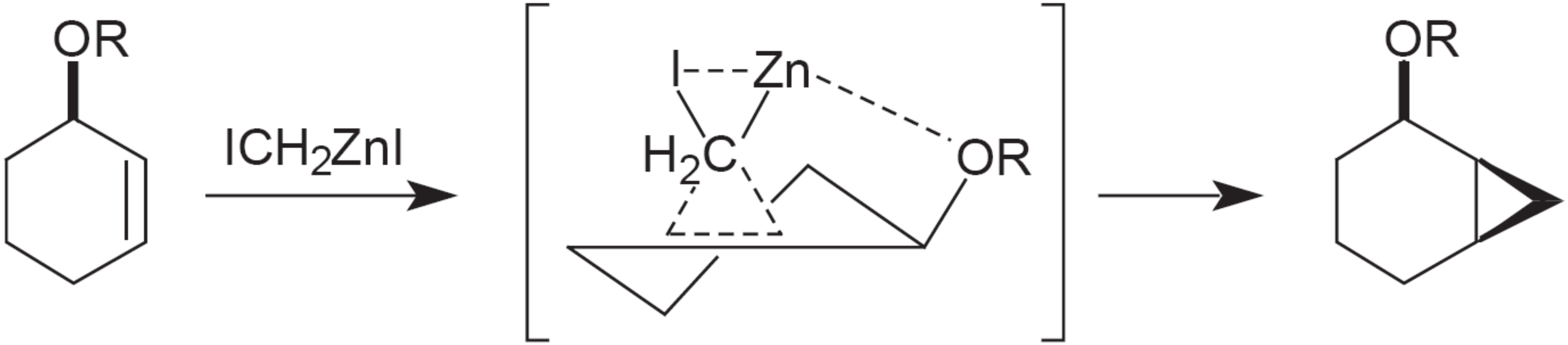




Reaction of Organozinc compounds

❖ *Directed Simmons-Smith Cyclopropanation*

- A particularly interesting aspect of the Simmons-Smith reaction is the ***stereoelectronic control*** exhibited by proximal OH, OR groups, which favor cyclopropanation to occur from the same face of the double bond as the oxy substituents.
- order of decreasing directive effects : OH > OR > C=O



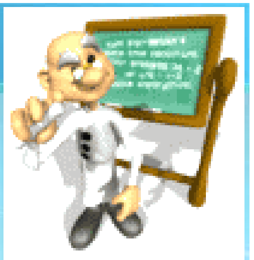
Reaction of Organozinc compounds

❖ *Transmetalation*

- Although the C–Zn bond is rather unreactive toward electrophiles such as aldehydes, ketones, esters, and nitriles, it undergoes transmetalations with many transition metal complexes to furnish new organometallics capable of reacting with a variety of electrophilic substrate.

- See the use in Coupling reactions later in the course.

References - organometallics



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