

SHIVAJI UNIVERSITY, KOLHAPUR.



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CHOICE BASED CREDIT SYSTEM

Syllabus For

M.Sc. Part -I Chemistry,

Applied Chemistry and Industrial Chemistry

SEMESTER I AND II

(Syllabus to be implemented from June, 2018 onwards.)

Semester – I: Theory and Practical Courses

Theory courses	Paper No.	Title
CH.1.1/APCH1.1/INDCH1.1	I	Inorganic Chemistry.-I
CH.1.2/APCH1.2/INDCH1.2	II	Organic Chemistry.-I
CH1.3/APCH1.3/INDCH1.3	III	Physical Chemistry-I.
CH.1.4/APCH1.4/INDCH1.4	IV	Analytical Chemistry-I.

Practical courses

CHP.1.1/APCHP1.1/INDCHP1.1	PI	Relevant practicals.
CHP.1.2/APCHP1.2/INDCHP1.2	PII	

Semester –II Theory and Practical Courses

Theory courses	Paper No.	Title
CH.2.1/APCH.2.1/INDCH.2.1	V	Inorganic Chemistry.-II
CH.2.2/APCH.2.2/INDCH.2.2	VI	Organic Chemistry.-II
CH.2.3/APCH.2.3/INDCH.2.3	VII	Physical Chemistry-II
CH.2.4/APCH.2.4/INDCH.2.4	VIII	Analytical Chemistry-II

Practical courses

CHP.2.1/APCHP.2.1/INDCHP.2.1	PIII	Relevant practicals.
CHP.2.2/APCHP.2.2/INDCHP.2.2	PIV	

Paper – II, Organic Chemistry-I(CH.1.2/APCH.1.2/INDCH.1.2)

UNIT-I

15L

A) Reaction Mechanism: Structure and Reactivity

8L

Types of reactions, strength of acids and bases. Generation, structure, stability and reactivity of carbenes, arynes, nitrenes and effect of structure on reactivity, resonance and field, steric effects. Thermodynamic and Kinetic requirements, Introduction to Kinetic and Thermodynamic control reaction.

B) Aliphatic Nucleophilic substitutions

7L

The SN₂, SN₁ and SN_i reactions with respects to mechanism and stereochemistry. Nucleophilic substitutions at an allylic, aliphatic trigonal, benzylic, and vinylic carbons. Reactivity effect of substrate structure, effect of attacking nucleophiles, leaving groups and reaction medium. SN reactions at bridge head carbon, competition between SN₁ and SN₂, Ambident nucleophiles, Neighbouring Group Participation.

UNIT-II

15L

A) Introduction to aromaticity in Benzenoid and non – Benzenoid compounds.

7L

Three, four and five membered systems. tropone, tropolone, tropylium salts.

B I] Aromatic Electrophilic Substitutions

8L

Introduction, the arenium ion mechanism, orientation and reactivity in Nitration, Sulphonation, Friedel-Crafts and Halogenation in aromatic systems, energy profile diagrams. The ortho/para ratio, ipso attack, orientation in their ring systems. Diazo-coupling, Vilsmeier-Haak reaction, Von Richter rearrangement

II] Nucleophilic aromatic substitution reactions SN₁, SN₂.

UNIT-III

15L

A) Elimination Reactions

5L

The E1, E2 and E1cB mechanisms. Orientation in Elimination reactions. Hofman versus Saytzeff elimination, Reactivity: effects of substrate structures, attacking base, the leaving group, the nature of medium on elimination reactions. Pyrolytic elimination reactions.

B) Study of following reactions

10L

Mechanism of condensation reaction involving enolates, Benzoin, Stobbe, Robinson annulation, Simon-Smith, Vlhmann, Mc-Murry, Dakin, prins, Wurtz-Fittig reaction,

Hunsdiecker reaction, Pummerer, , Rupe, Gabriel–Colman, Corey-Chaykovsky reaction, Nef reaction, Passerini reaction, Baylis-Hilman reaction, Mitsunobu Reaction.

UNIT-IV

15L

Stereochemistry: Concept of chirality Prochiral relationship, homotopic, enantiotopic and diastereotopic groups and faces. Racemic modifications and their resolution, R and S nomenclature. Conformational analysis : Cyclohexane derivatives, stability and reactivity, Conformational analysis of disubstituted cyclohexanes. Introduction of optical activity in the absence of chiral carbon (spiranes and allenes)

Paper-VI, Organic Chemistry-II (CH.2.2/APCH.2.2/INDCH.2.2)

UNIT-I

15L

A) Study of following rearrangements

5L

Curtius, Lossen, Wittig, Neber, Ortaon, Hofmann-Martius and Demjanov reaction.

B) Photochemistry

10L

Effect of light intensity on the rate of photochemical reactions. Types of photochemical reactions, photochemistry of alkynes, intramolecular reactions of the olefinic bonds, geometrical isomerism, cyclisation reactions, rearrangements of 1,4 and 1,5-dienes, photochemistry of carbonyl compounds, intramolecular reactions of carbonyl compounds saturated cyclic and acyclic α , β -unsaturated compounds, cyclohexadienones, intermolecular cycloaddition reactions, dimerisation and oxitane formation, photochemistry of aromatic compounds, photo fries reactions of anilides, photo fries rearrangements. Singlet molecular oxygen reactions.

UNIT-II

15L

A) Hydroboration

4L

Various hydroborating agents their mechanism and synthetic applications *viz* 9-borabicyclo-[3.3.1]nonane (9-BBN), thexylborane, H B diisoamylborane. (Sia₂BH) BH₃•SMe₂. (BMS), Borane as reducing agent.

B) Enamins

4L

Formation, reactivity and synthetic applications of enamines

C) Oxidation

7L

Applications of oxidizing agents like chromium trioxide, manganese dioxide, Woodward-Prevost hydroxylation, Chloranil, hydrogen peroxide. Swern oxidation. PCC (Corey's reagent), PDC (Cornforth reagent), Baeyer-Villiger oxidation.

UNIT-III

15L

A) Reductions

9L

Study of following reductions- Catalytic hydrogenation using homogeneous and heterogeneous catalysts. Study of following reducing reagents and reactions: Wolff-Kishner, Birch, Sodium cyano borohydride, Sodium in alcohol, Fe in HCl, Adam's catalyst, Lindlar catalyst, TBTH.

B) Protection of functional group

6L

Principle of protection of alcohol, amine, carbonyl and carboxyl groups.

UNIT-IV**15L****A) Study of Organometallic compounds****8L**

Organo-lithium, Use of lithium dialkyl cuprate, their addition to carbonyl and unsaturated carbonyl compounds. Study of coupling reactions *viz* Heck, Suzuki, Stille, Nigishi and Sonogashira coupling.

B) Methodologies in organic synthesis**7L**

Ideas of syntheses and retrones, Functional group transformations and inter conversions of simple functionalities.

REFERENCE BOOKS

1. Modern synthetic reactions-(Benjamin) H. O. House.
2. Reagents in organic synthesis-(John Wiley) Fieser and Fieser
3. Principles of organic synthesis-(Methuen) R. O. C. Norman
4. Hydroboration- S. C. Brown.
5. Advances in Organometallic Chemistry- (A.P.)F. C. A. Stone and R. West.
6. Organic Chemistry (Longman)Vol. I & Vol. II- Finar
7. Oxidation by-(Marcel Dekker) Augustin
8. Advanced Organic chemistry 2nd Ed. R R. Carey and R. J. Sundburg.
9. Tetrahedron reports in organic chemistry- Vol.1, No. 8.
10. Organic Synthesis-(Prentice Hall)R. E. Ireland.
11. Homogeneous Hydrogenation-(J. K.) B. R. James.
12. Comprehensive Organic Chemistry- (Pargamon) Barton and Ollis.
13. Organic reactions- various volumes- R. Adams.
14. Some modern methods of Organic synthesis-(Cambridge) W. Carruthares.
15. Organic chemistry- Jonathan clayden.

Paper-VI: Organic Chemistry-II (CH.2.2)

I. Organo-lithium compounds

II. Organo-copper compounds: Lithium dialkyl cuprate (addition to carbonyl and unsaturated carbonyl compounds).

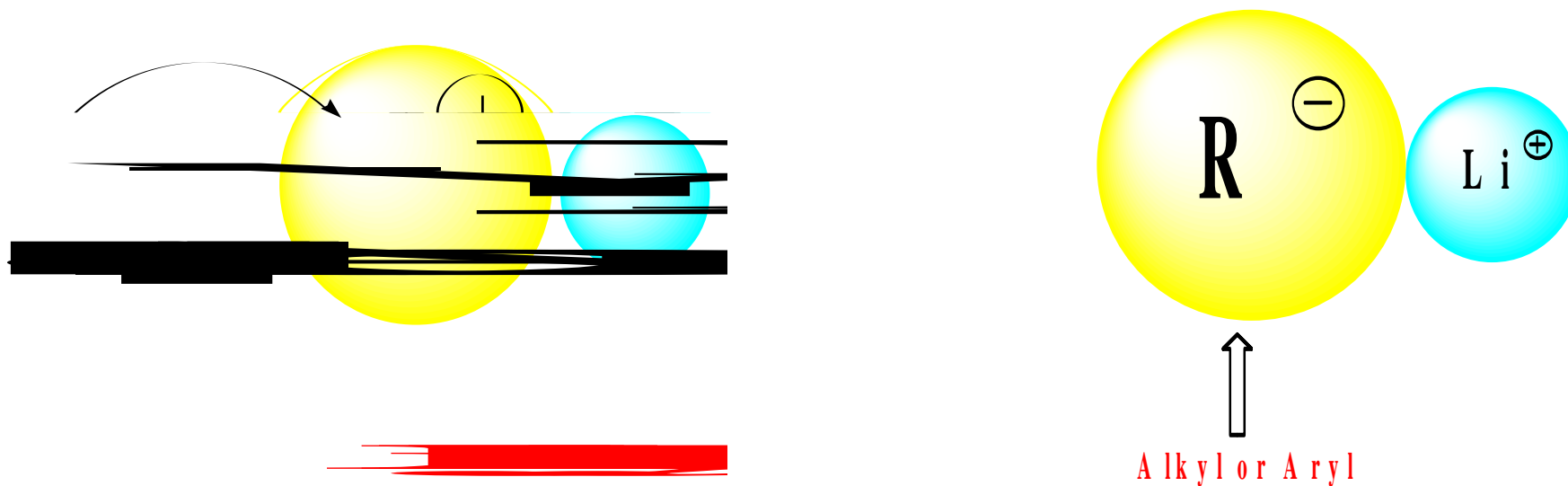
III. Palladium Chemistry:

- 1. Heck cross- coupling reaction**
- 2. Suzuki cross- coupling reaction**
- 3. Stille cross- coupling reaction**
- 4. Nigeshi cross- coupling reaction**
- 5. Sonogashira cross- coupling reaction**

Organo-lithium compounds

Organolithium reagents are organometallic compounds that contain C-Li bonds.

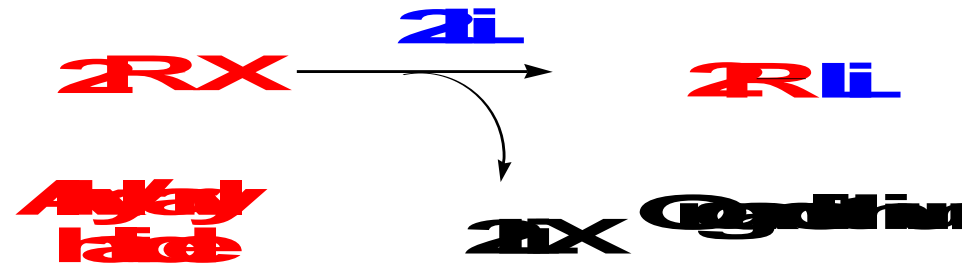
In organic synthesis, these reagents are frequently used to transfer the organic group (R- Alkyl or aryl) to the substrates in synthetic steps.



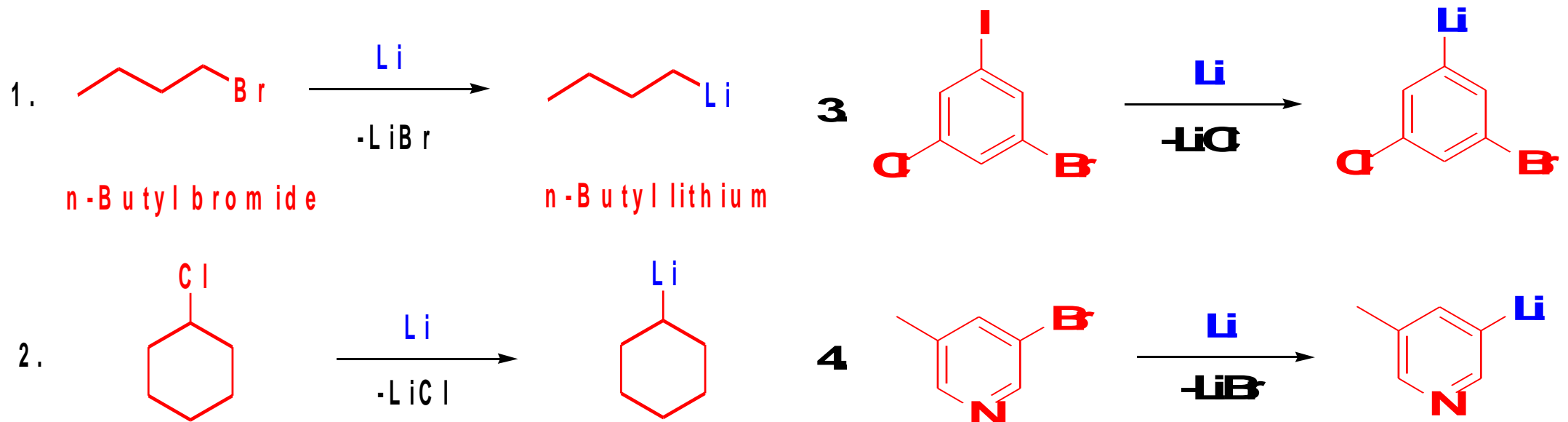
Acts as a strong base/nucleophile
Hence reacts with acid/electrophile

Preparation

Method I: Reaction of organic halides with lithium.

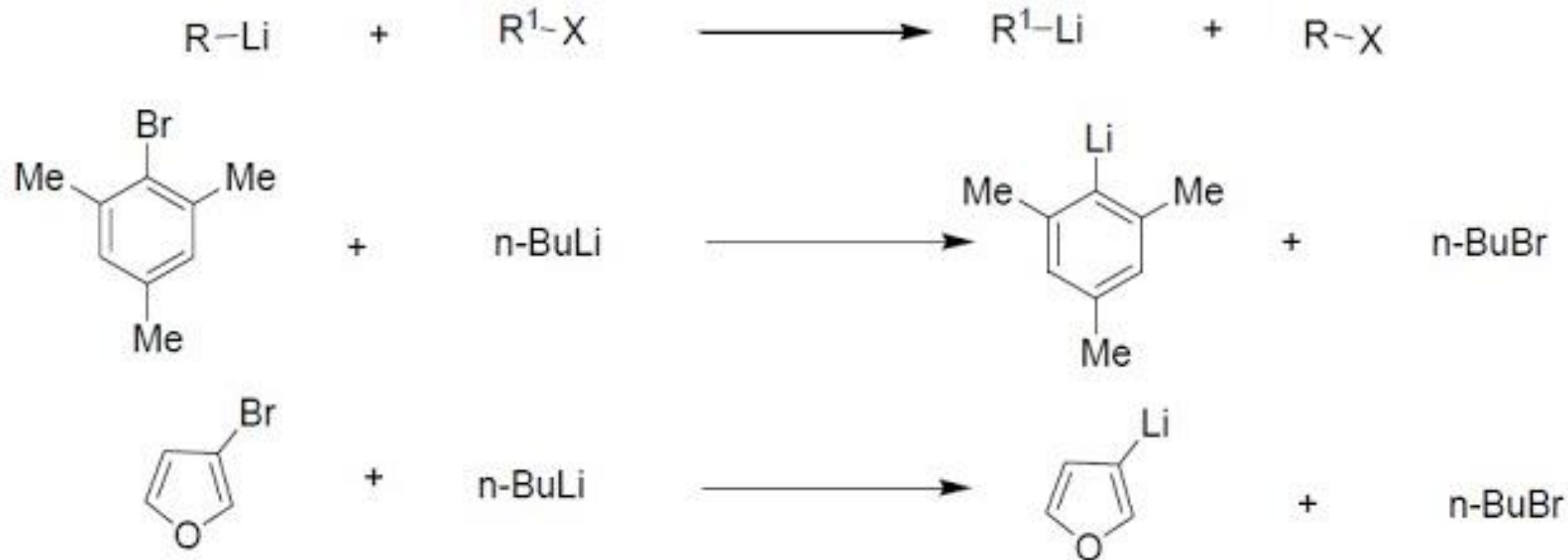


Order of reactivity of organic halides
 $RI > RBr > RCl$.



Preparation

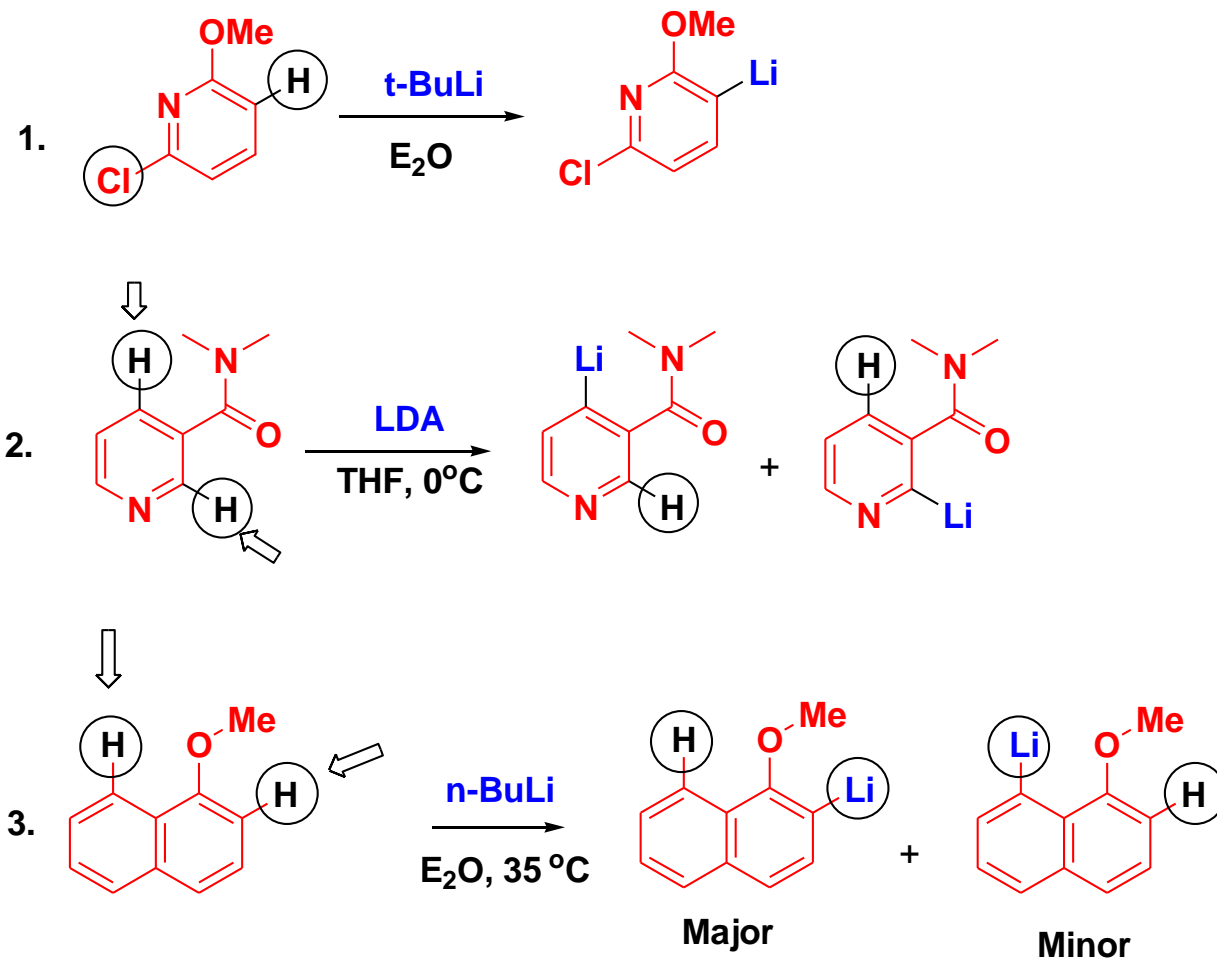
Method II: Metal Halogen Exchange Reaction.



The equilibrium lies to the right, if the organic group is able to accommodate the electron density than the organic species on the left.

Preparation

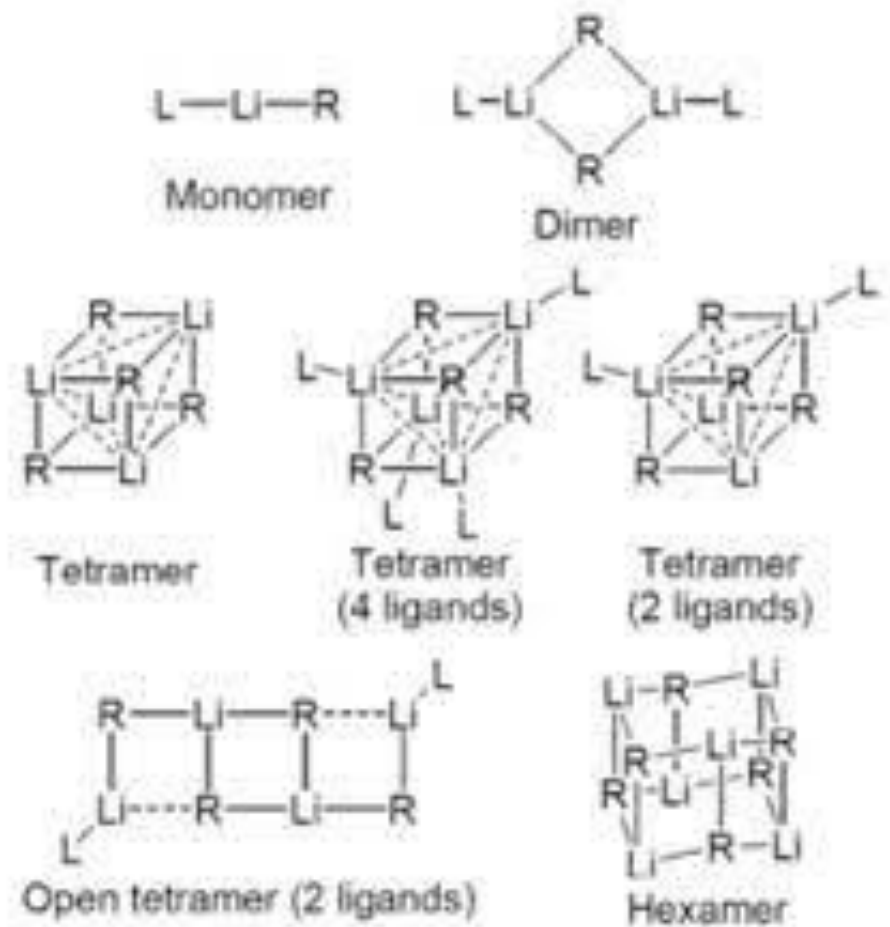
Method III: Ortholithiation



The reactivity ortho-directing groups:

$\text{SO}_2\text{NR}_2 > \text{SO}_2\text{Ar} > \text{CONR}_2 > \text{CONHR} > \text{CSNHR}, \text{CH}_2\text{NR}_2 > \text{OR} > \text{NHR} > \text{SR} > \text{CR}_2\text{O}-$

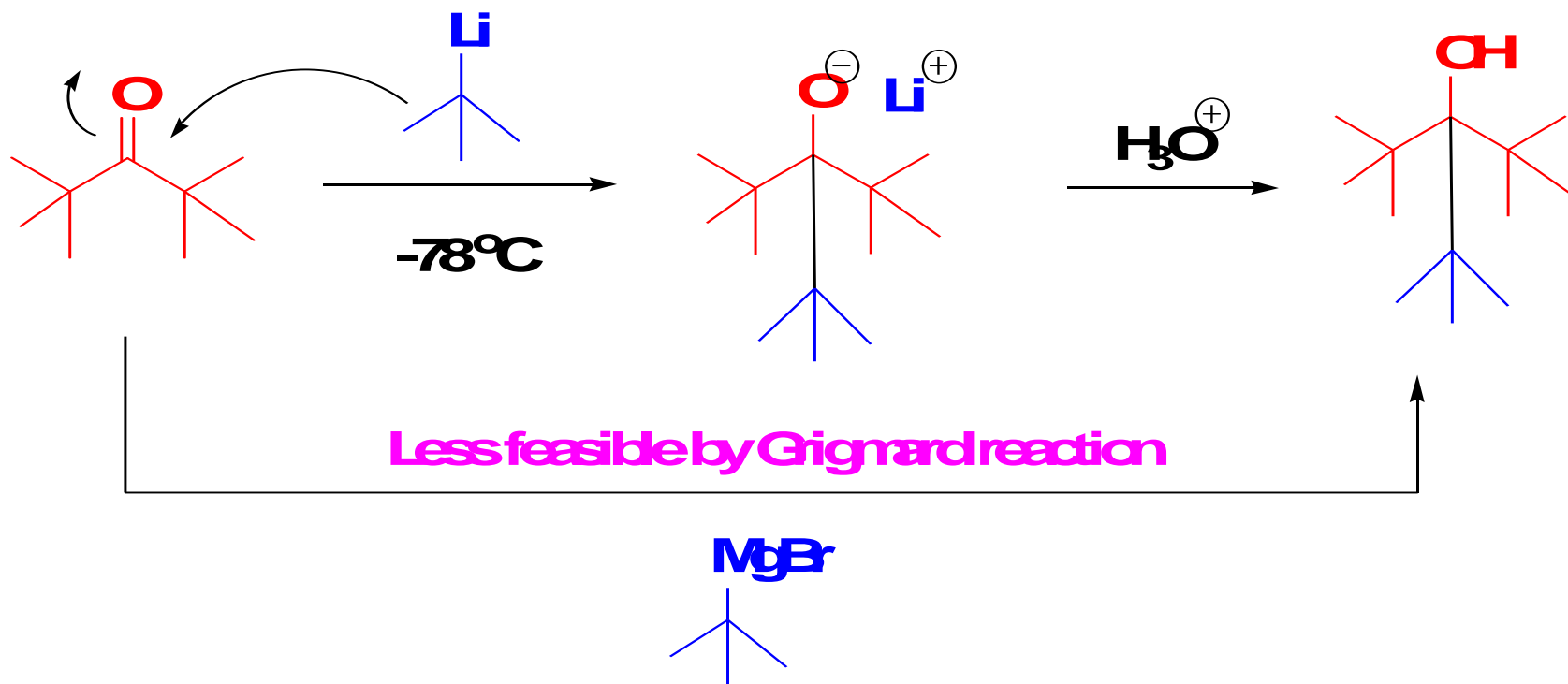
Structures



The structure of organolithium compounds is dominated by their highly oligomeric nature as a result of 3-center 2-electron bridging bonds. In all cases the extent of oligomerization is dependant on the identity of the alkyl (or aryl) group.

Reactions

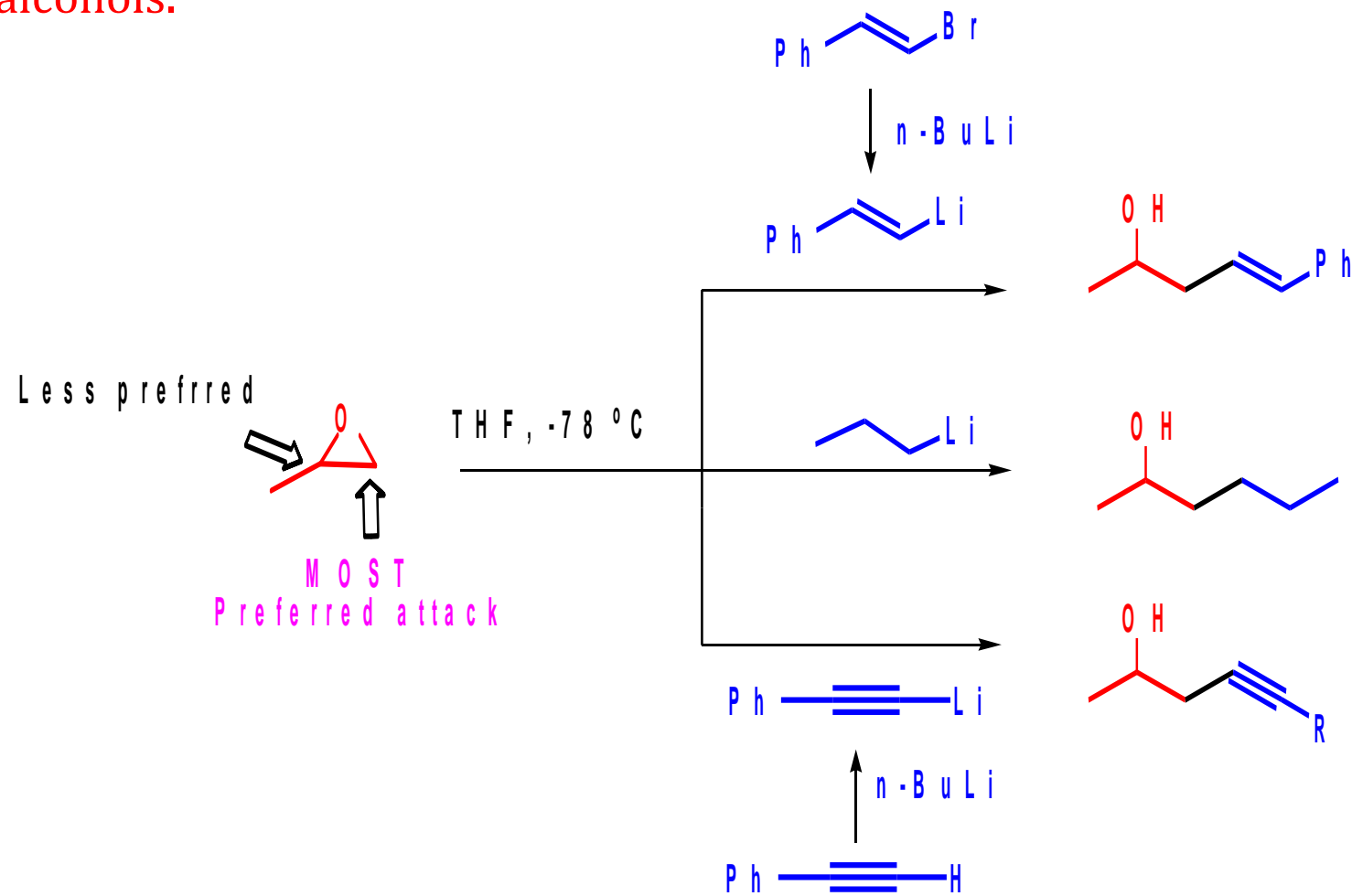
1. Reaction with Carbonyl Compounds: Organolithium reacts with carbonyl compounds as that of the Grignard reagents.



In comparison to Grignard reagents, organolithium reagents are less susceptible to steric factors and reacts with hindered ketones.

Reactions

2. Reactions with Epoxides: Epoxides react with organolithium reagents to give primary alcohols (as in the case of Grignard reagents). Use of unsaturated organolithium reagent gives unsaturated alcohols.

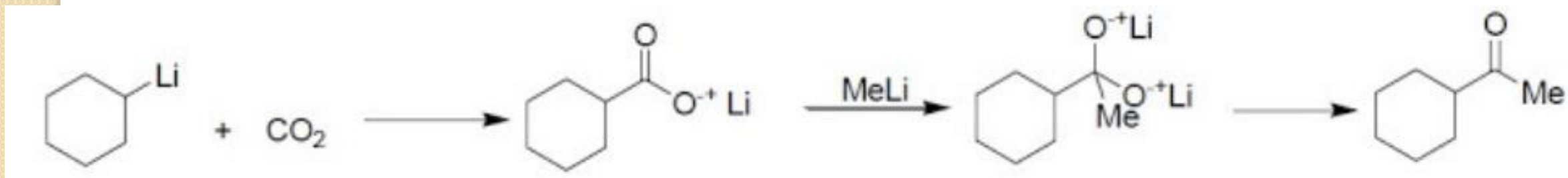


Organolithium preferably attacks on less substituted carbon of epoxides.

Reactions

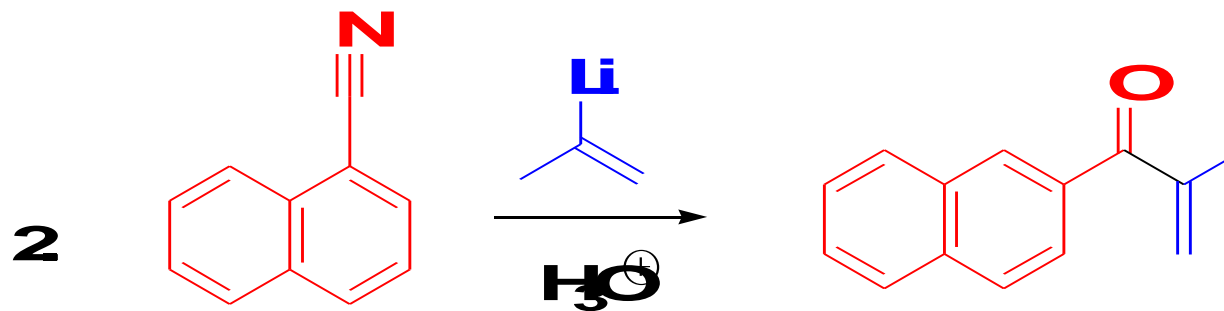
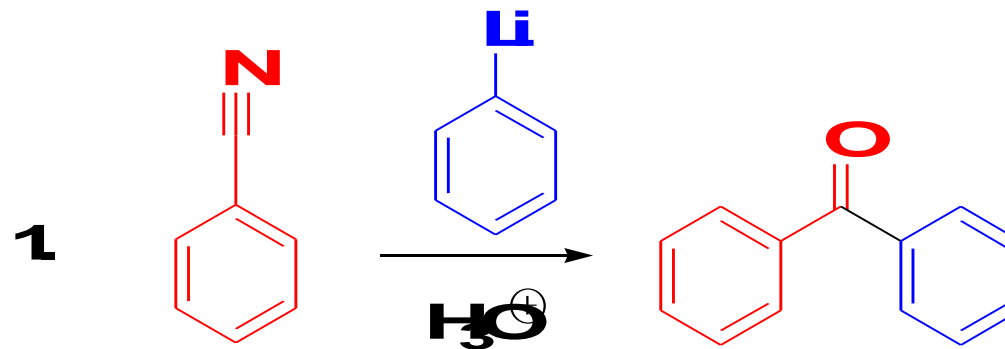
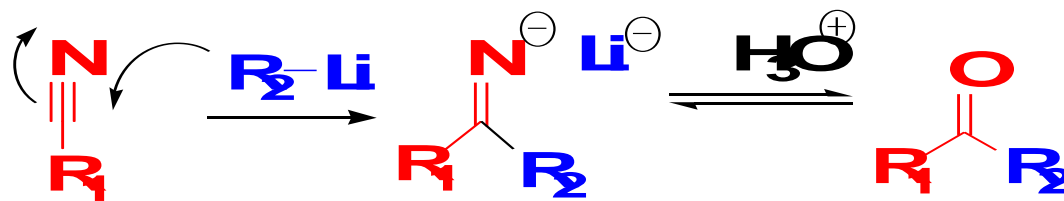
3. Reactions with Carbon Dioxide : A major difference between the reactivity of Grignard reagents and organolithium reagent is observed in their reactivity towards CO₂.

The reaction of Grignard reagents with CO₂ stops at the carboxylate stage, while in case of organolithium reagents, the carboxylate ion formed reacts with another equiv of organolithium to generate a ketone.



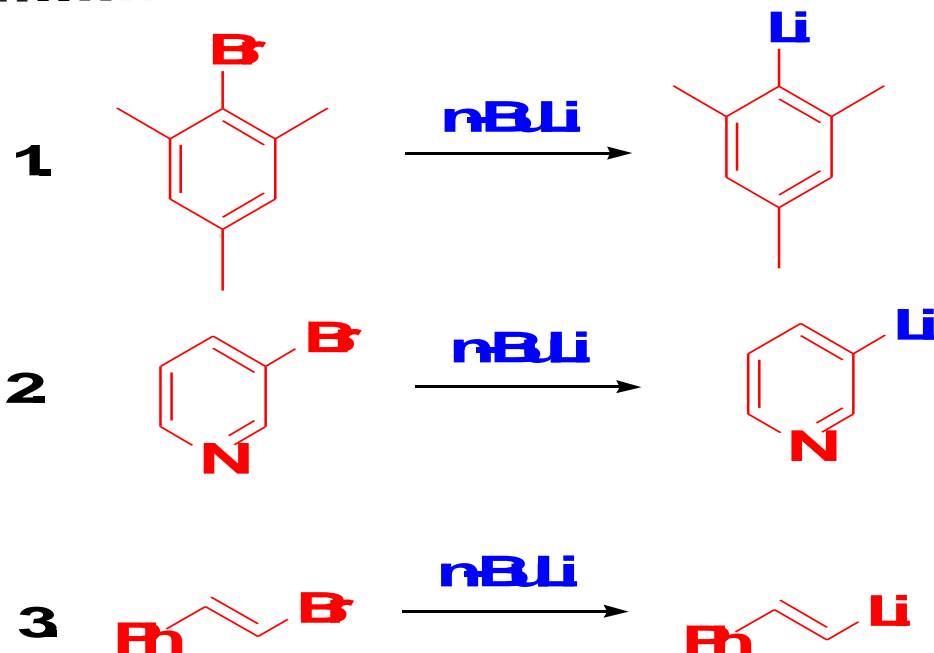
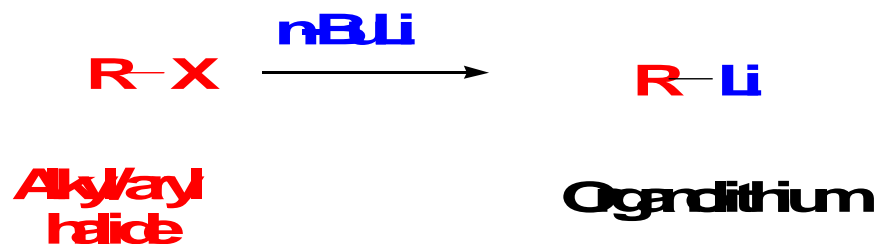
Reactions

4. **Reactions with Alkyl Cyanide** : As in the case of Grignard reagents, the reactions of organolithium reagents with alkyl cyanides give imine salts, which undergo hydrolysis in the presence of water to give



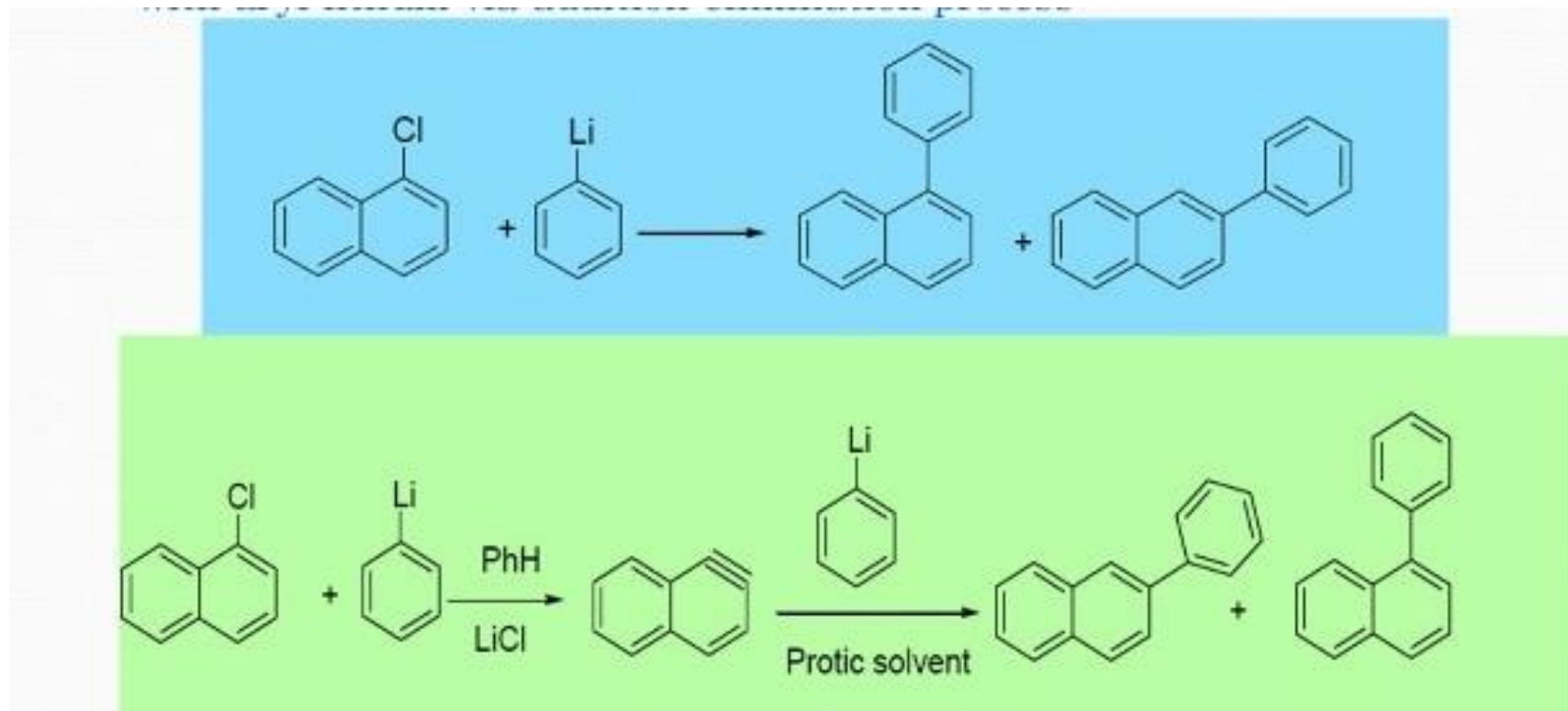
Reactions

5. Electrophilic Displacement : Reaction of an organic halide with an organometallic compound is known as metal halogen exchange reaction is example for electrophilic displacement. This reaction is useful for the synthesis of vinyl- and phenyl lithium



Reactions

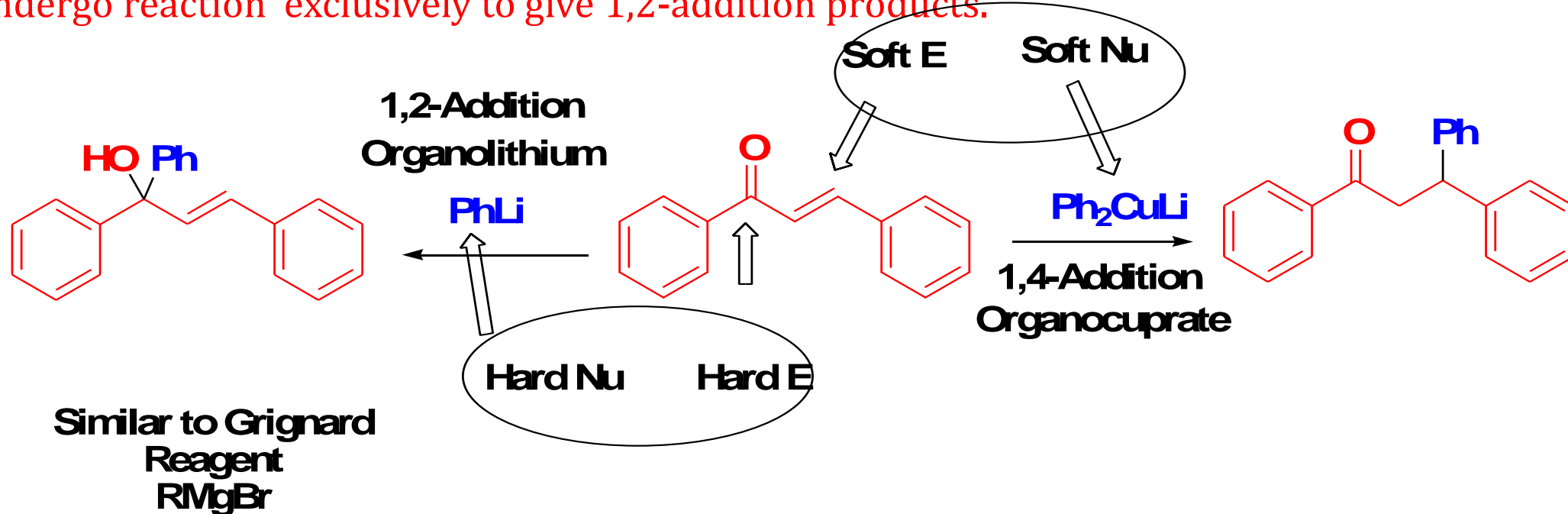
6. Nucleophilic Displacement : Alkyl and aryl halides can be reacted with alkyl and aryl lithium reagents to give hydrocarbons.



1. The reaction of alkyl halides with alkyl lithium takes place by SN2 mechanism.
2. While aryl halides react with aryl lithium via addition-elimination process .

Reactions

7. Reaction with α,β -Unsaturated Carbonyl Compounds : The organolithium reagents undergo reaction exclusively to give 1,2-addition products.



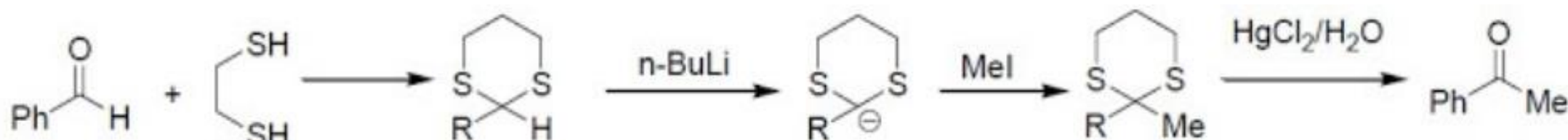
1. Exclusive formation of 1,4-addition product, however, can be achieved using lithium dialkylcuprates .

2. In the case of Grignard reagents, α,β -unsaturated carbonyl compounds undergo reaction either at 1,2- or 1,4-addition depending on the structure of the carbonyl compound. The main reason is steric hinderance.

Reactions

8. Deprotonation

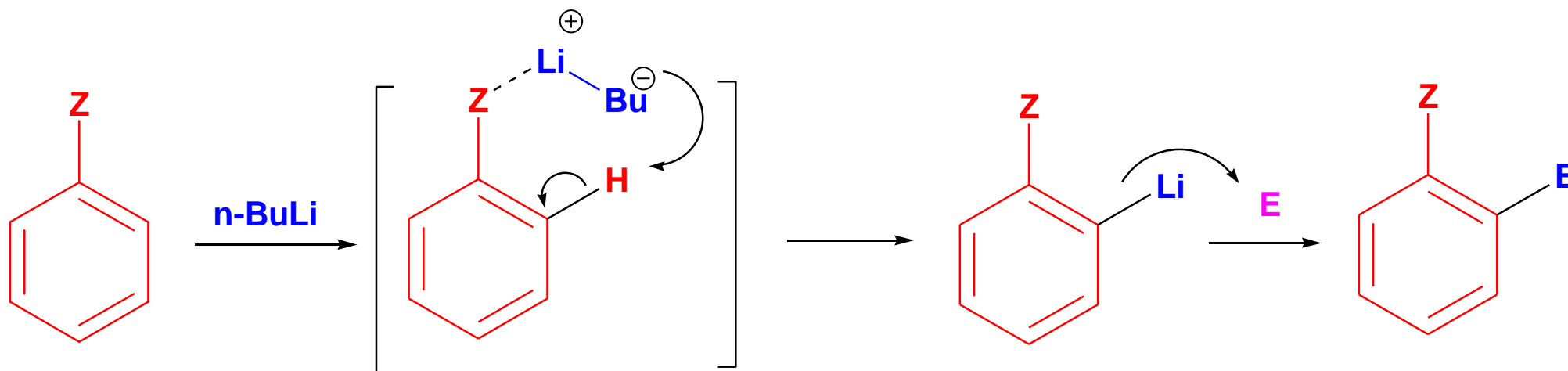
- The basic nature of organolithiums can also be put to good use in achieving **umpolung** at the carbonyl centre of an aldehyde. In this protocol a C=O function is first protected by 1,3-dithiane and then the proton is removed by an organolithium



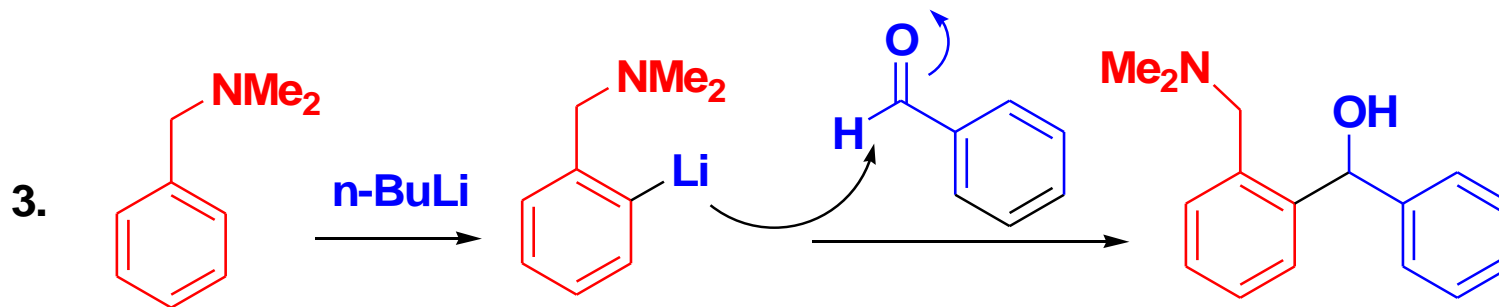
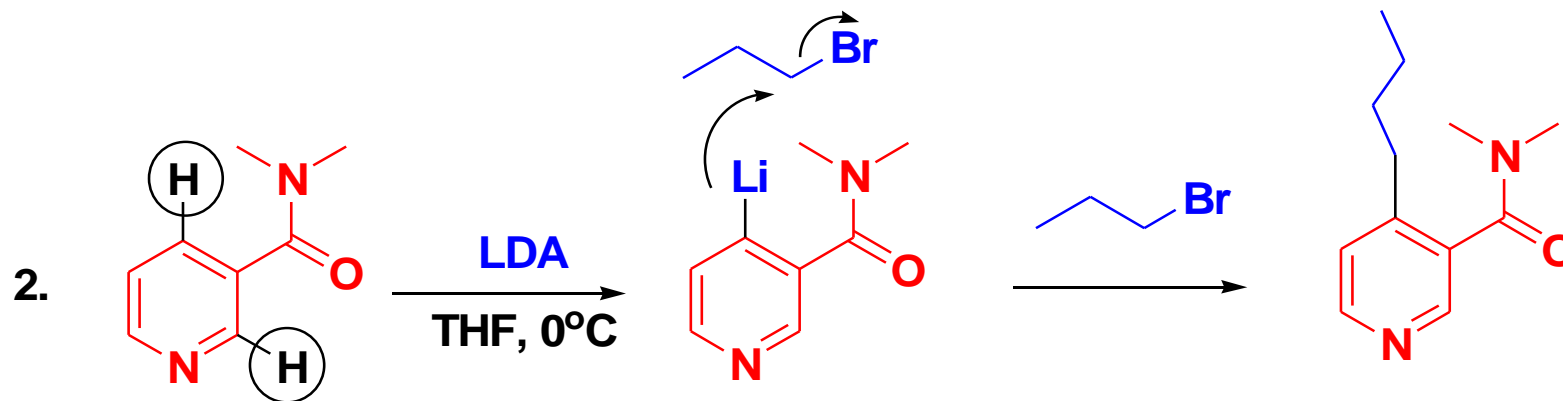
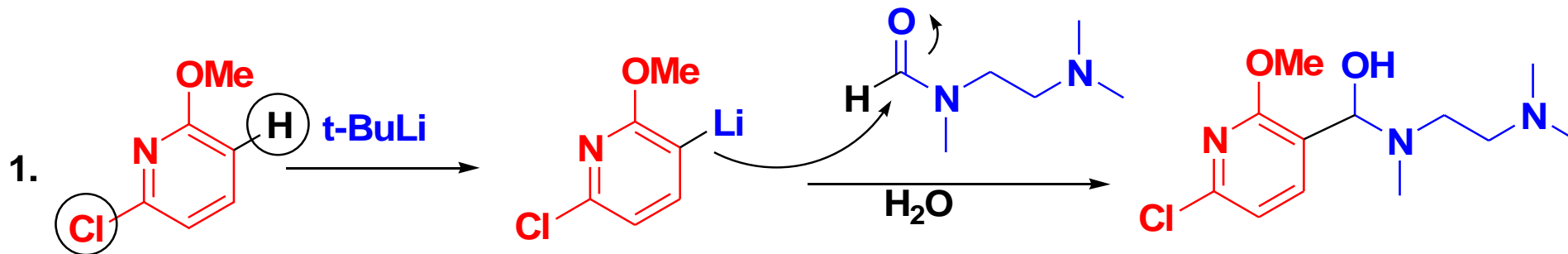
Reactions

9. Directed ortho Lithiation : It is an adaptation of electrophilic aromatic substitution in which electrophiles attach themselves exclusively to the ortho- position of a direct metalation group or DMG through the intermediary of an aryllithium compound.

Mechanism: The interaction between the lithium and the electron-rich directing group favors the lithiation at the ortho position.

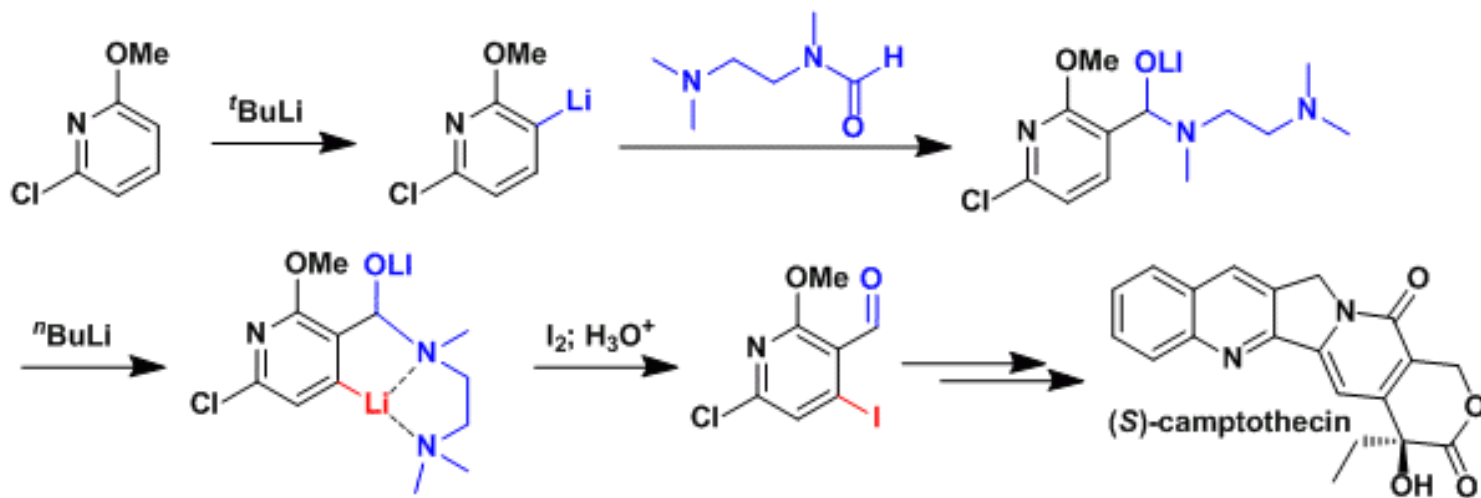
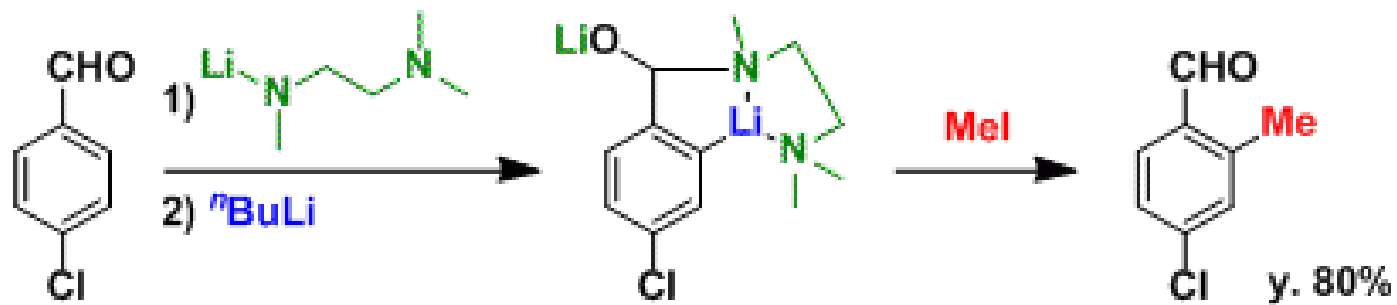


Directed ortho metalation (DoM) is an adaptation of electrophilic aromatic substitution in which electrophiles attach themselves exclusively to the ortho- position of a direct metalation group or DMG through the intermediary of an aryllithium compound.



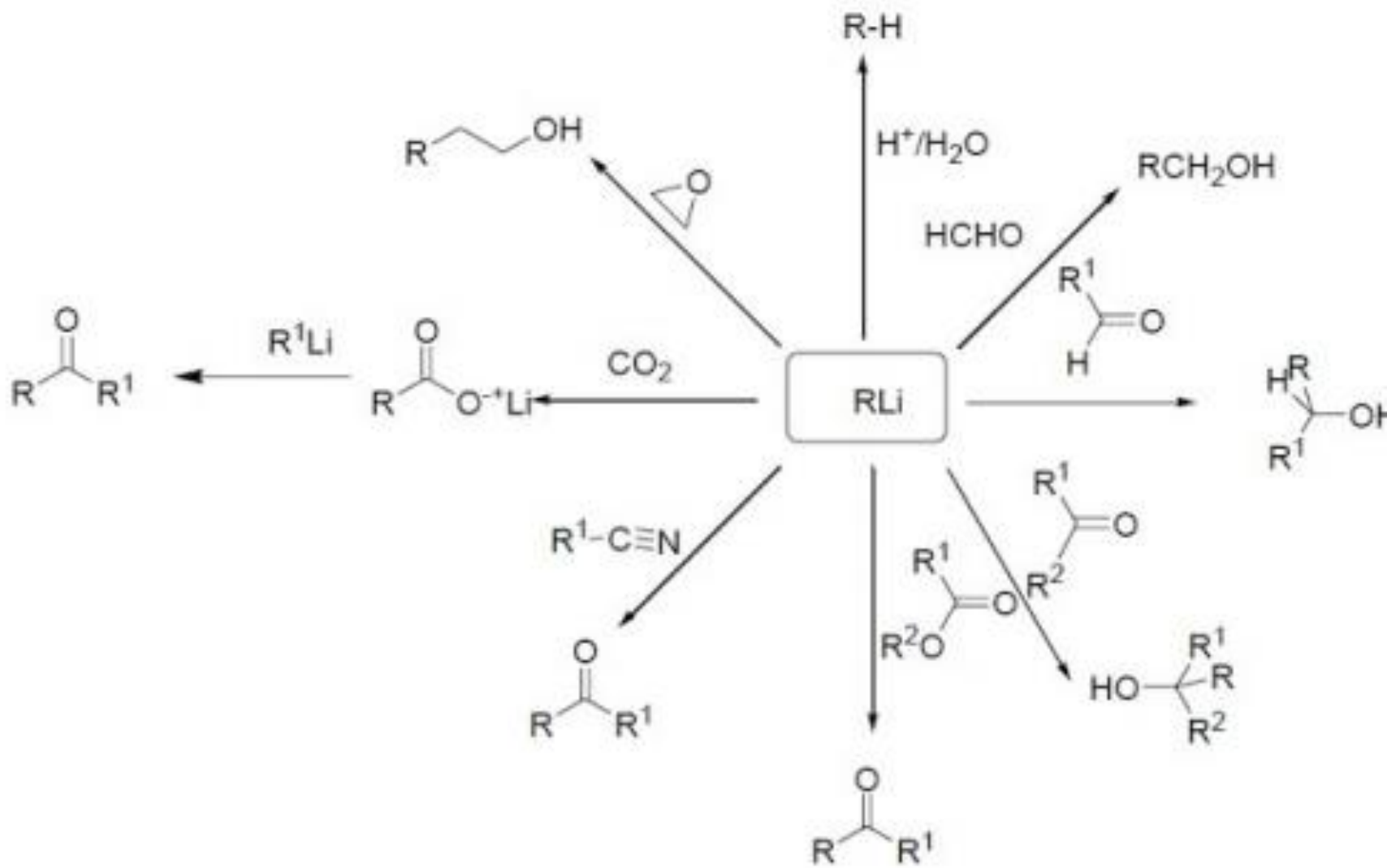
It is useful because the starting material does not need to have a halogen atom. For example, in the case of benzyldimethylamine, the nitrogen atom directs attack of the butyllithium.

Reactions



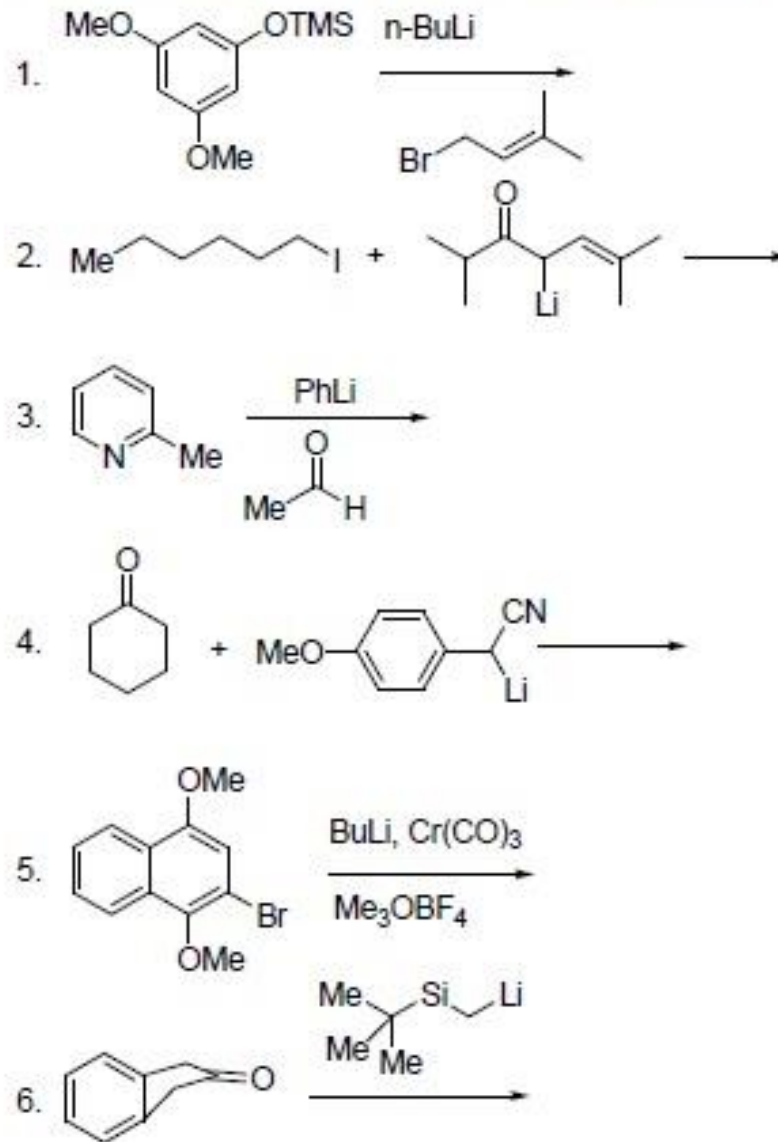
It is useful because the starting material does not need to have a halogen atom. For example, in the case of benzyldimethylamine, the nitrogen atom directs attack of the butyllithium.

Organometallic compounds



Problems

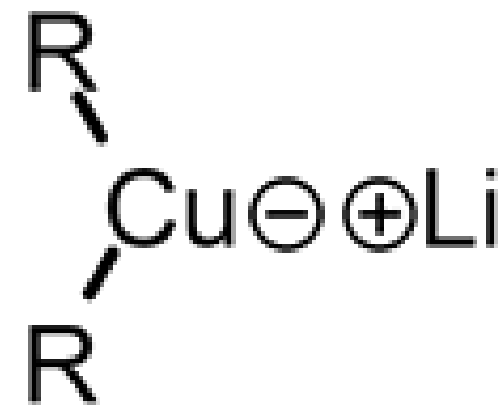
Predict the major products of the following reactions



Organo-copper compounds (Gilman Reagents) Lithium dialkyl cuprates



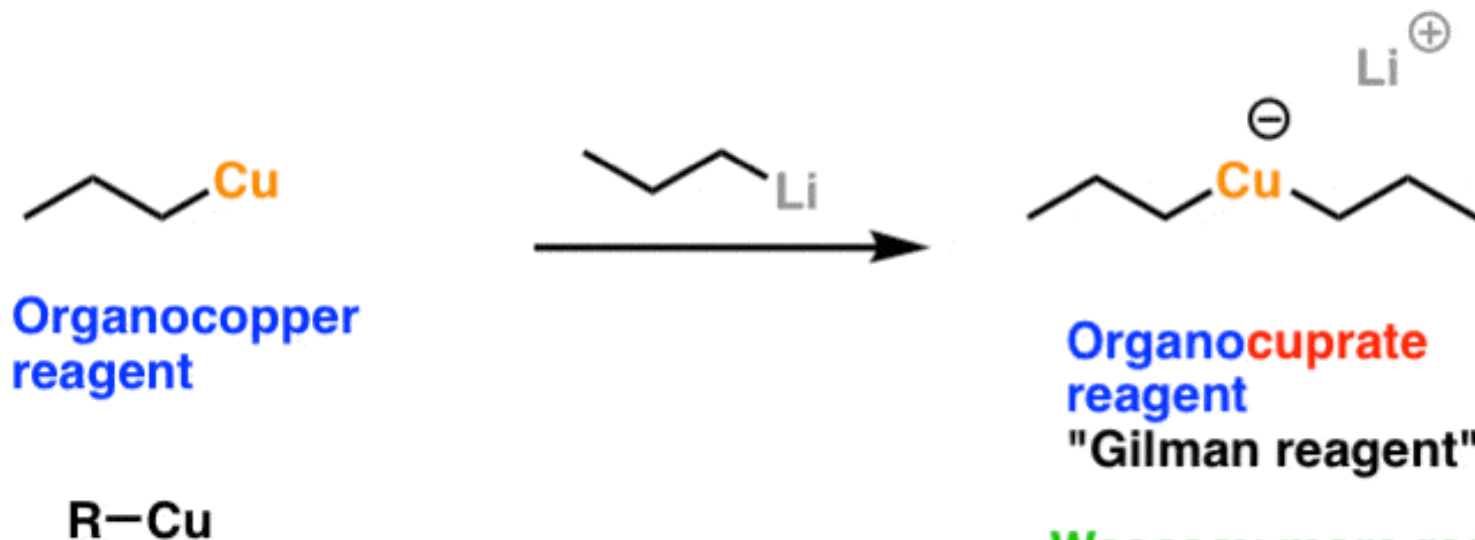
1919: Henry Gilman
"father of organometallic chemistry,"



Addition to carbonyl and unsaturated carbonyl compounds

- Gilman reagents, are useful nucleophiles for conjugate addition as well as SN2 reactions.
- In the 1940's Iowa chemist Henry Gilman discovered that adding one further equivalent of an organolithium reagent to an organocopper compound resulted in an "organocuprate" reagent, with two Cu–C bonds and is also comprised of a positive counter-ion [lithium in this case].

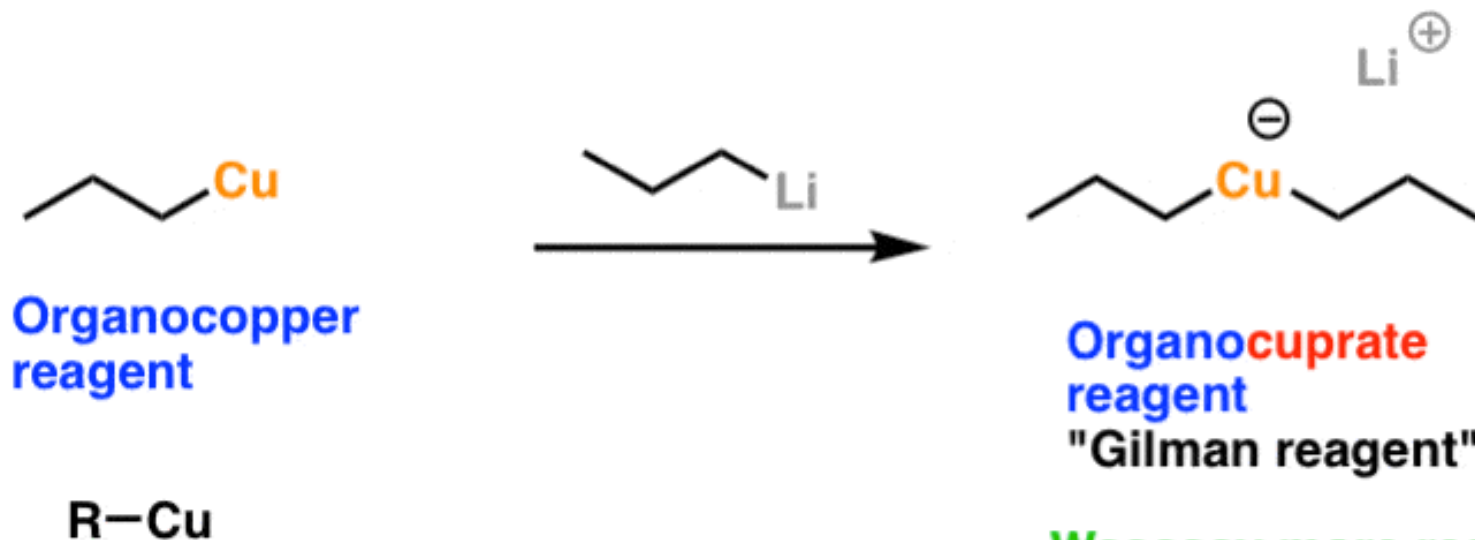
Gilman found that adding a second equivalent of an organolithium (R–Li) to an organocopper reagent makes an "organocuprate" reagent, which is far more reactive (and useful)



Waaaaay more reactive than an organocopper

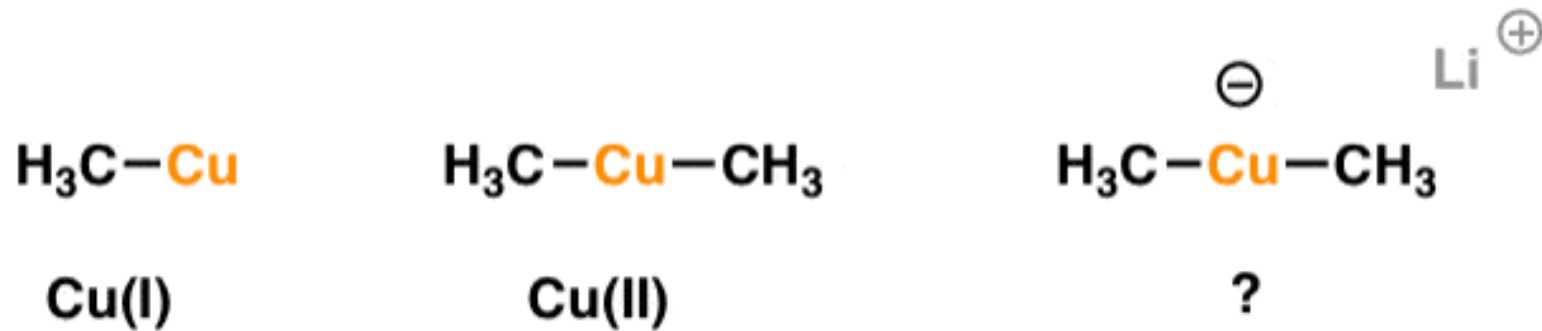
- Note that “-ate” at the end. [e.g. sulfate, nitrate, tosylate] are negatively charged?]
- Organocuprates, with the general formula R_2CuLi , have the same general pattern of reactivity as organocopper reagents, but are much more reactive.
- These compounds are commonly referred to as “Gilman reagents” in ol’ H.G.’s honour.
- Why are they more reactive? We’ll talk about that in the next post.

Gilman found that adding a second equivalent of an organolithium (R–Li) to an organocopper reagent makes an "organocuprate" reagent, which is far more reactive (and useful)



Waaaaay more reactive than an organocopper

Quiz time: what's the oxidation state of copper in a Gilman reagent?



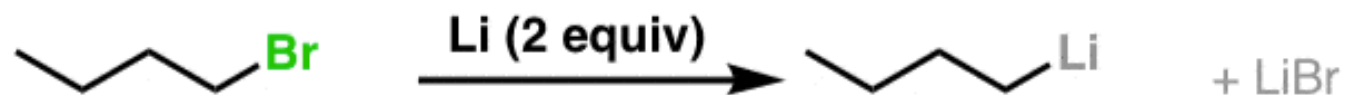
What's the oxidation state?

Bonding between a carbanion R^- with Li^+ is almost purely ionic (note the electronegativity difference of about 1.5) meaning that a significant portion of the bonding interaction is due to electrostatic interactions.

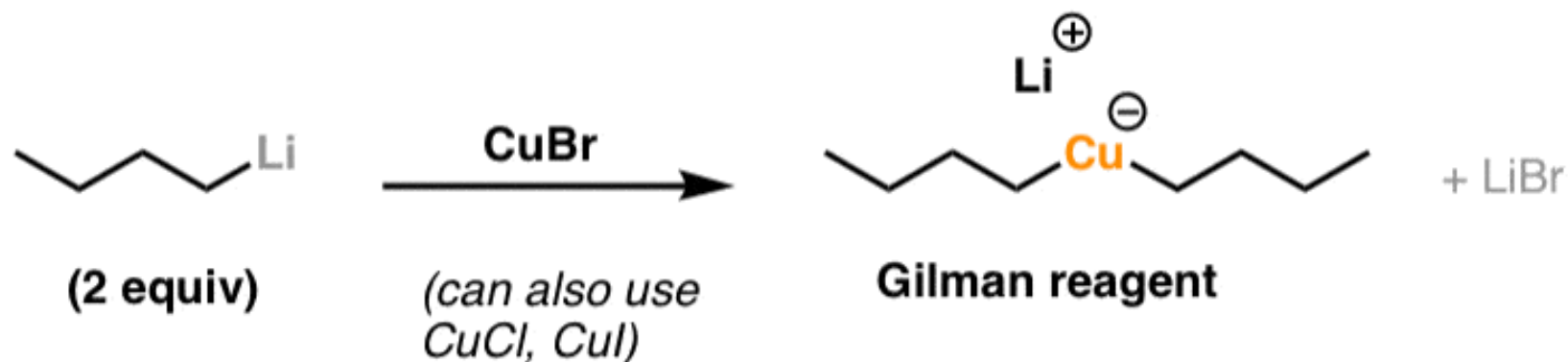
In contrast, bonding between C and Cu is considerably more covalent. There's less of an electronegativity difference (Cu 1.9 vs. C 2.5) and the bonding is better described by metal-carbon bond overlap.

Preparation 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...



Direct formation of an organometallic from the organohalide and that metal [a process we call 'insertion', or "oxidative addition", FYI] is less favored.

Look at copper for instance: the "direct reduction" doesn't work nearly as well as it does for Li and Mg.

I don't mean to imply that it *can't* be done, but it generally requires heat and the addition of extra reagents that influence the oxidation potential of the metal we call "ligands" (not going to get into that now) in order to get this reaction to go.

Copper is one example of a metal where direct reduction doesn't work so well



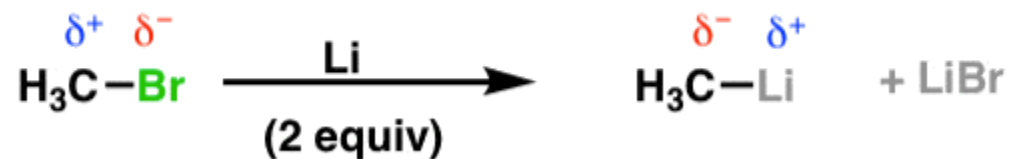
Not nearly as easy a reaction as making a Grignard or organolithium reagent!

Why? Largely because copper has a much lower reduction potential (i.e. is a poorer reducing agent) than lithium or magnesium.

In practice, this reaction *can* be done, but typically needs a lot of heat plus additional reagents("ligands") that we won't get into here

Formation of Organometallics From Alkyl Halides Involves Reduction: Direct Formation Of Organometallics From Metals Like Cu Is Much More Difficult Than For Mg or Li

Recall that formation of an organometallic from an alkyl halide is a *reduction*



Lithium and magnesium are particularly strong reductants, compared to other metals (nickel and copper, for example)

Selected Oxidation potentials for various metals:

	Stronger reducing agent			Weaker oxidizing agent
Li (s)	→	Li ⁺ + e	3.04 V	
Na (s)	→	Na ⁺ + e	2.71 V	
Mg (s)	→	Mg ²⁺ + 2 e	2.36 V	
Al (s)	→	Al ³⁺ + 3 e	1.66 V	
Zn (s)	→	Zn ²⁺ + 2 e	0.76 V	
Fe (s)	→	Fe ²⁺ + 2e	0.45 V	
Ni (s)	→	Ni ²⁺ + 2 e	0.26 V	
Cu (s)	→	Cu ²⁺ + 2e	-0.34 V	Stronger oxidizing agent

↓ Weaker reducing agent

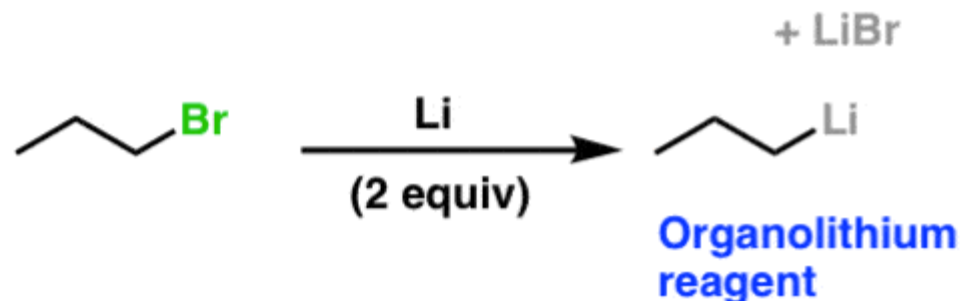
Transmetalation

pre-made organometallic (such as an organolithium or Grignard reagent) where the reduction has already occurred. We can then add a copper (I) salt such as CuBr or CuCl.

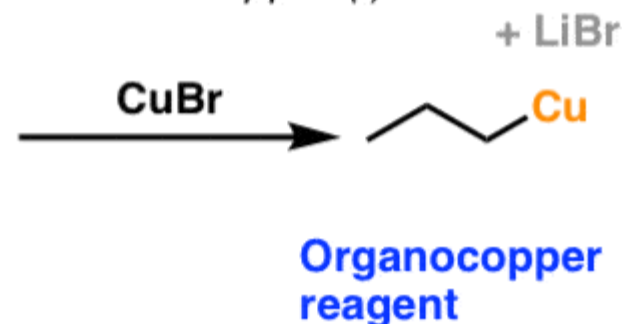
There's a way around this though!

We can start with an organolithium or Grignard (where carbon is already reduced) and *then* exchange the metal

Step 1: Organolithium formation



Step 2: "Transmetalation" with a copper (I) salt

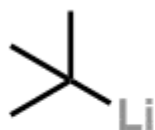


This process is called "Transmetalation"

Can use CuCl, CuBr, CuI

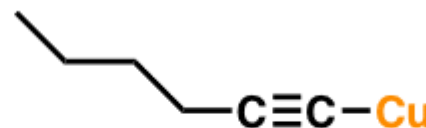
Organocopper Reagents: WAY Less Reactive Than Grignards

In comparison to Grignard and organolithium reagents which are violently destroyed by water (and sometimes air) organocopper reagents are fairly sedate. For instance, there are organocopper reagents that you can leave out in the air without incident, like 1-hexynylcopper.



t-Butyllithium

spontaneously combusts in air



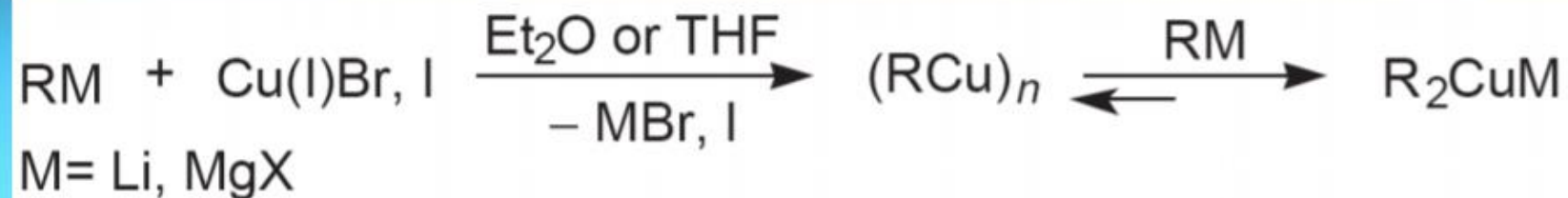
Hexynylcopper

air stable, needs no special handling

Homocuprate reagents

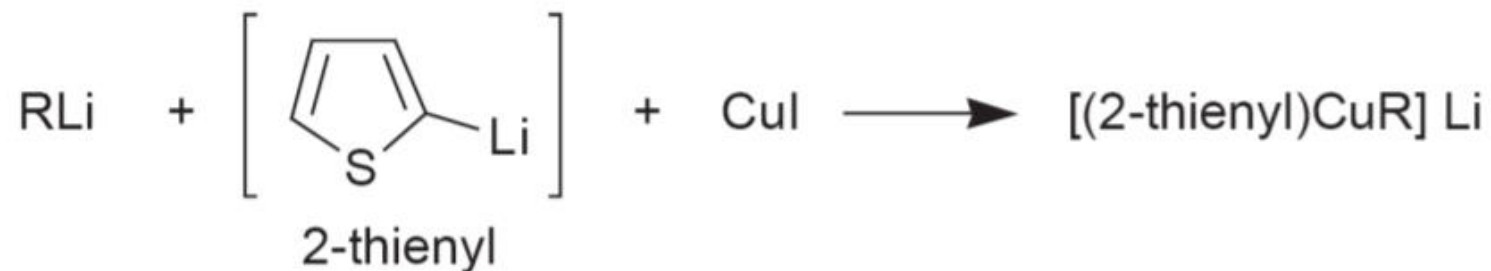
(Gilman reagent: R_2CuLi , R_2CuMgX)

- 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.



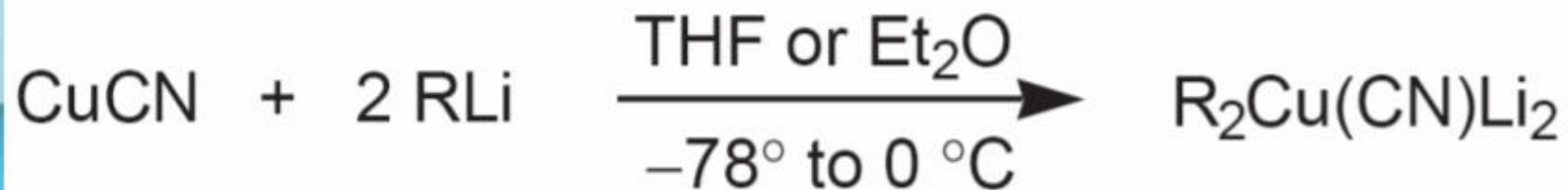
Heterocuprate reagents

- Since only one of the organic groups of homocuprates is usually utilized, a non-transferable group bonded to copper, such as $\text{RC}\equiv\text{C}$, 2-thienyl, PhS , $t\text{-BuO}$, 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.



Higher-order organocuprate reagents (Lipshutz reagents)

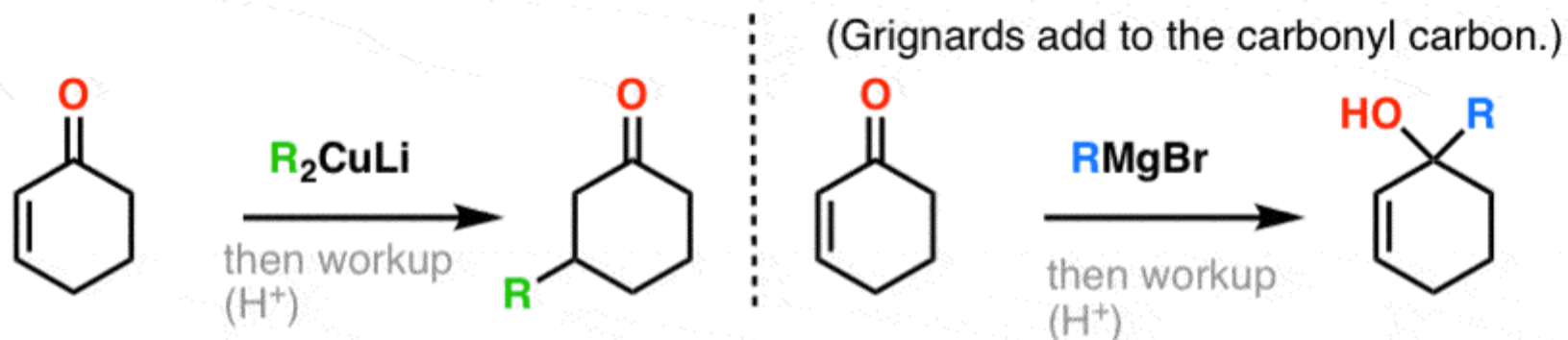
- Cyanocuprates exhibit the reactivity of homocuprates and the thermal stability of heterocuprates.
- readily available by the reaction of $\text{CuC}\equiv\text{N}$ with 2 equivalents of RLi . The cyanocuprates are especially useful for substitution reactions of secondary halides and epoxides.



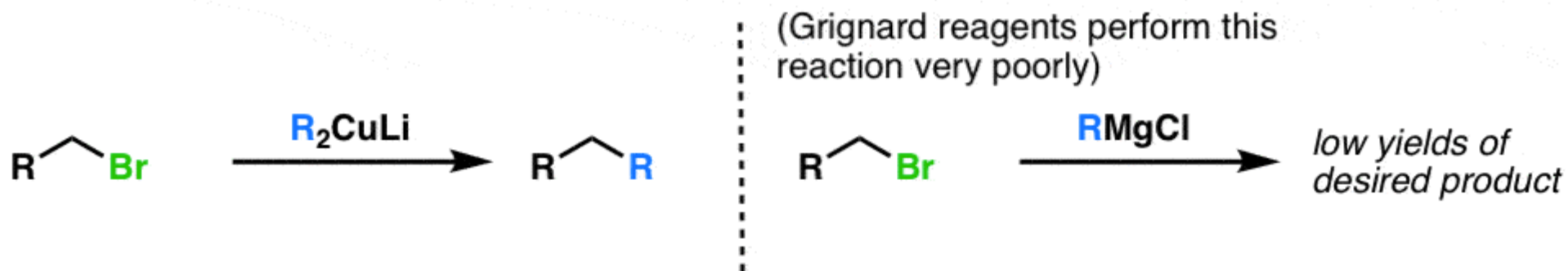
Organocopper Reagents: REactions

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

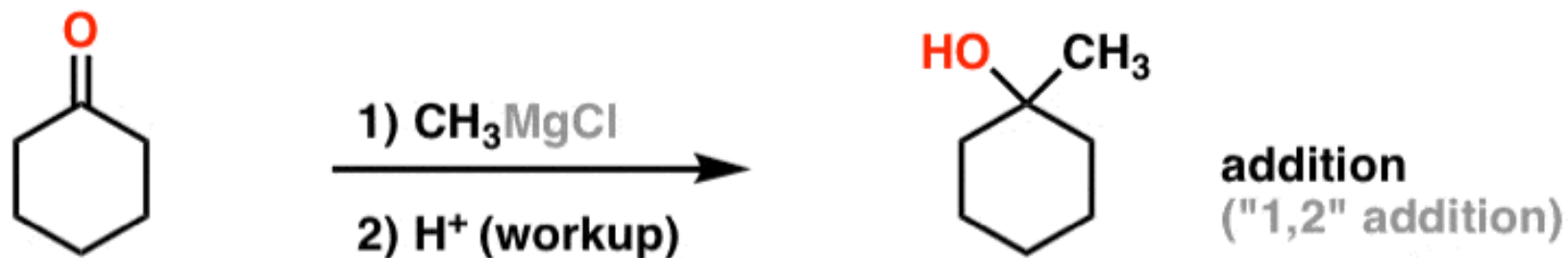


2) Gilman reagents are effective nucleophiles for S_N2 reactions

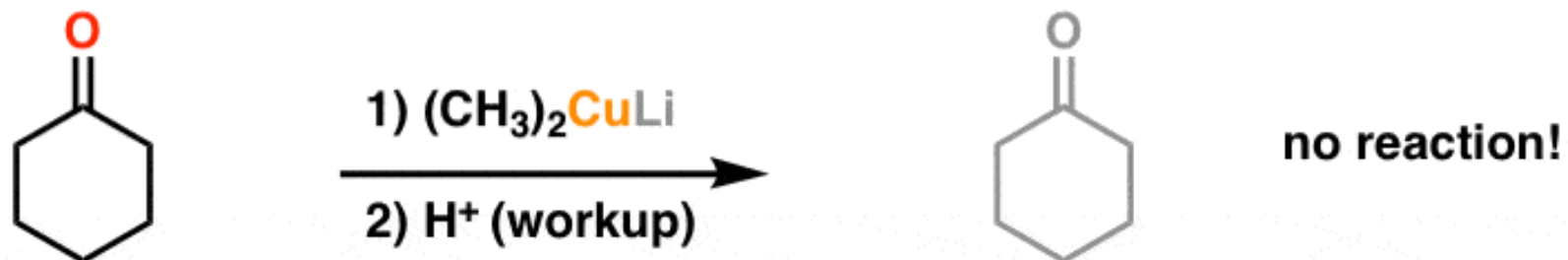


Gilman Reagents vs. Grignard Reagents

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

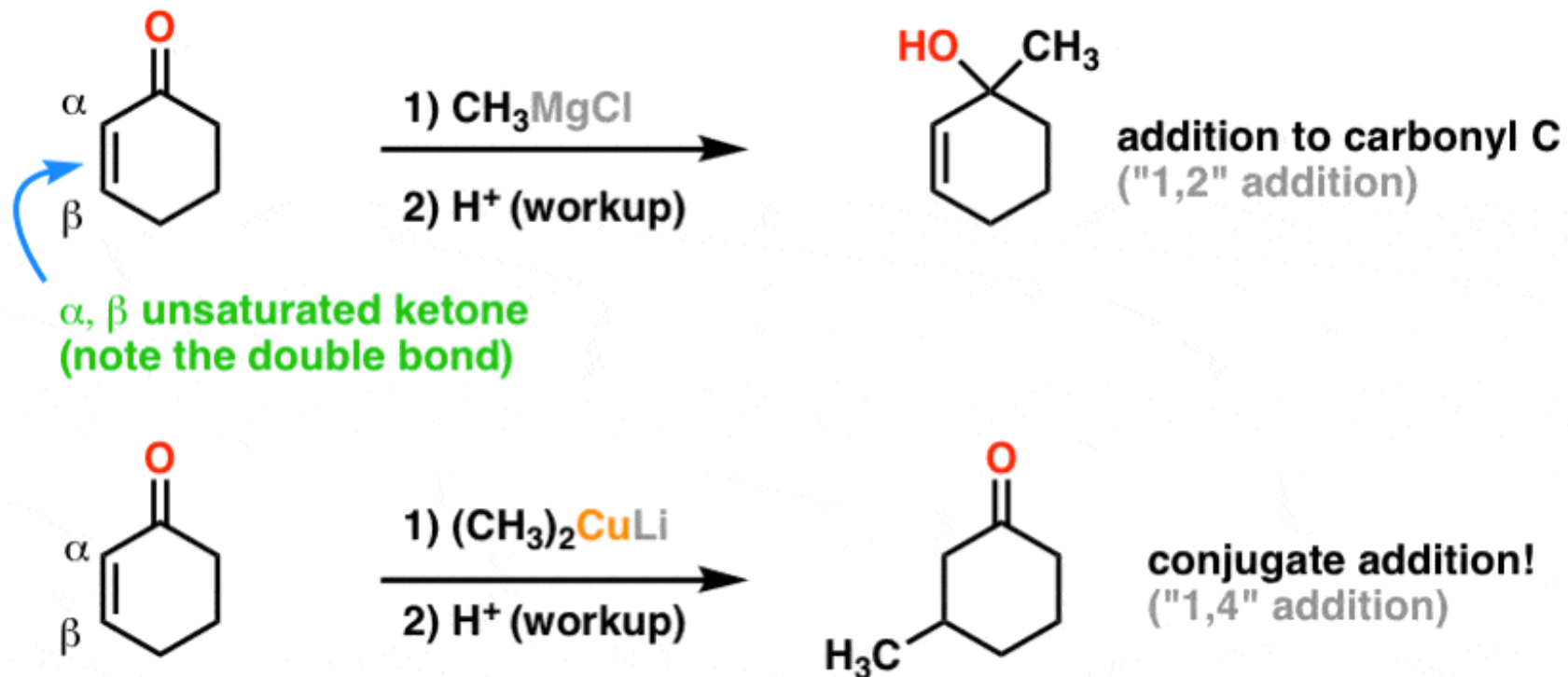


... but Gilman reagents (organocuprates) do **not** !



Let's put a double bond next to the ketone and run

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



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.

Conjugate Addition: A Key Reaction of Gilman Reagents

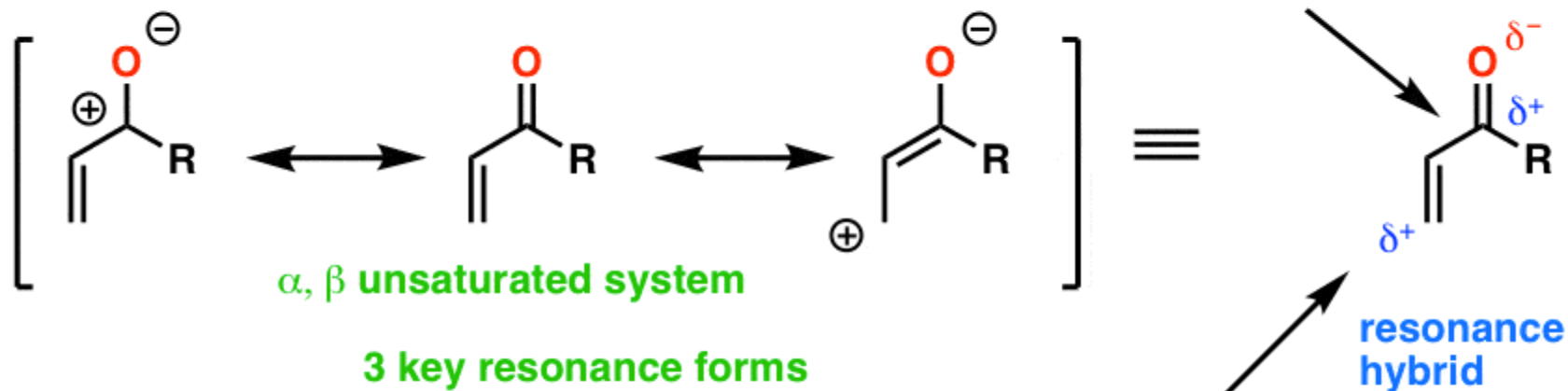
No reaction with "ordinary" alkenes



Wait - why might a nucleophile attack *there*?

Consider the resonance forms

This carbon is electrophilic
(not news to you, hopefully)

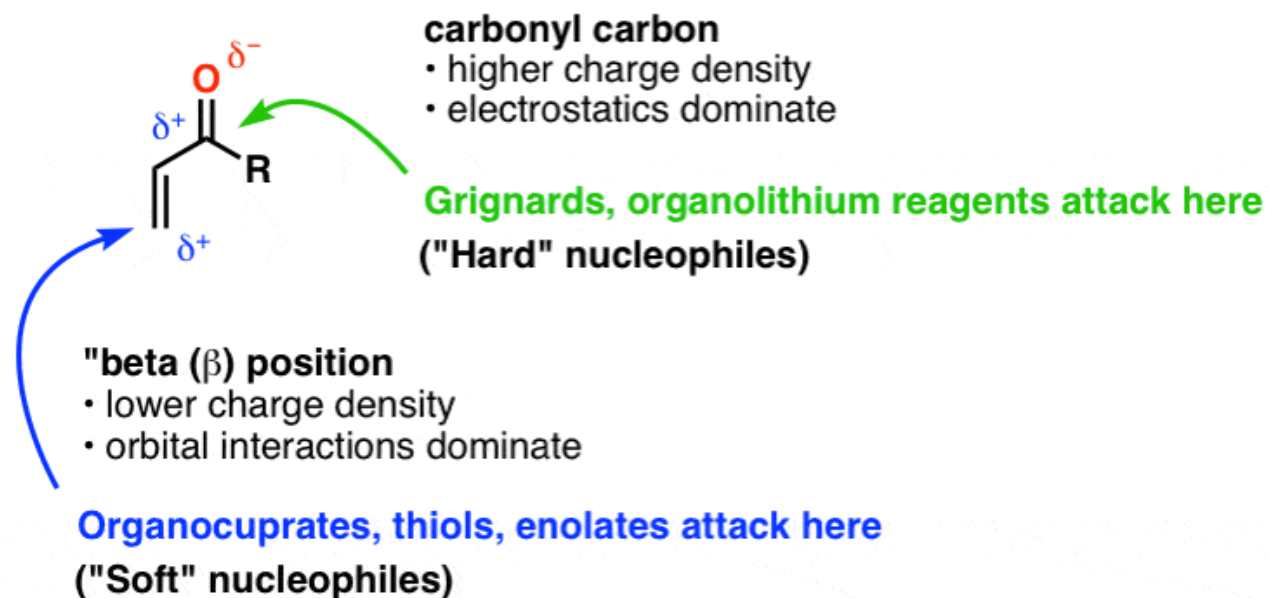


But - this carbon is also electrophilic ! will react with nucleophiles!

How Do You Know Whether "Normal" Addition or "Conjugate" Addition Will Occur?

Grignards add to carbonyls, while organocuprates do conjugate addition. we'd have to go into some molecular orbital theory to get at the key concept of "Hard Soft Acid Base (HSAB) Theory", and at this point, we're not going to cover it.

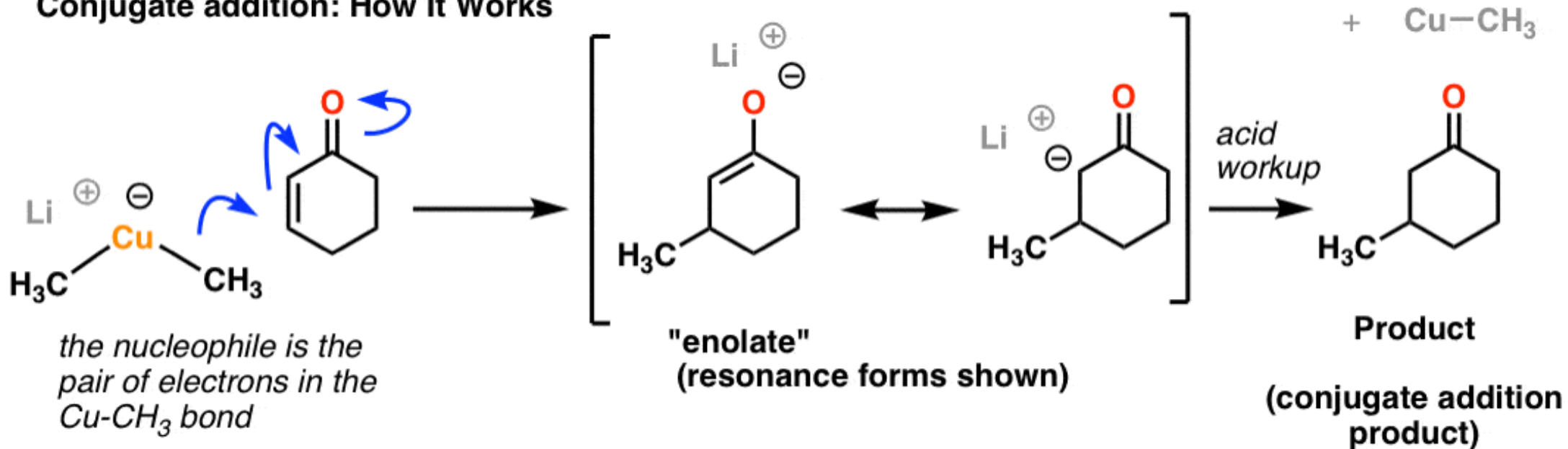
So how can you tell whether a nucleophile will attack at the carbonyl carbon or do a "conjugate" addition ?



A deeper understanding of this isn't possible without more exploration of molecular orbital theory (upper year courses), in particular "Hard-Soft Acid Base Theory" (HSAB)

Conjugate Addition: Mechanism

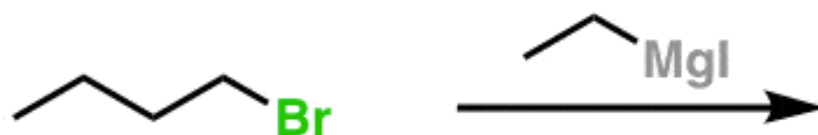
Conjugate addition: How It Works



Gilman Reagents Are Excellent Nucleophiles For S_N2 Reactions

Another difference between Grignards and organocuprates: S_N2 reactions

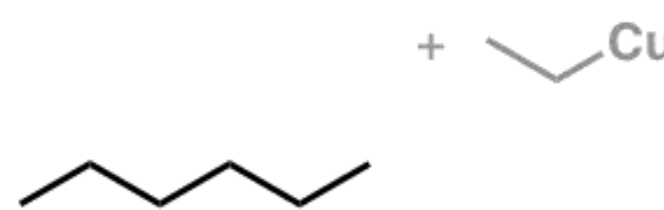
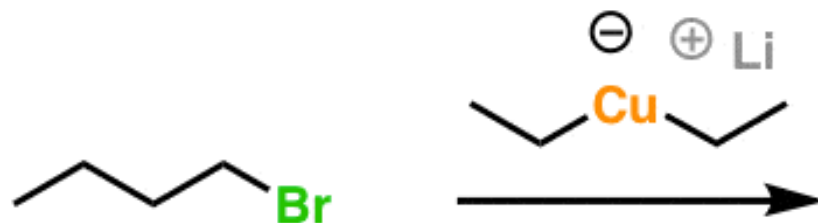
Grignard reagents don't work well for S_N2 reactions!!



no S_N2 reaction

*competing reactions:
deprotonation, reduction*

However, Gilman reagents are effective for this reaction



new C–C bond

Successful S_N2 reaction!

A useful way to make C–C bonds !

Conclusion: Gilman reagents (organocuprates) perform two reactions that Grignard reagents (and organolithiums) do not:

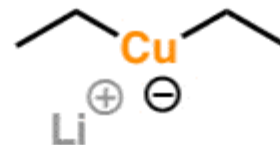
- They perform conjugate additions to α,β unsaturated ketones.
- They are effective nucleophiles for S_N2 reactions.

What would be the better nucleophile? An organocopper reagent or an organocuprate reagent?

Q: What do you think would be the better nucleophile?

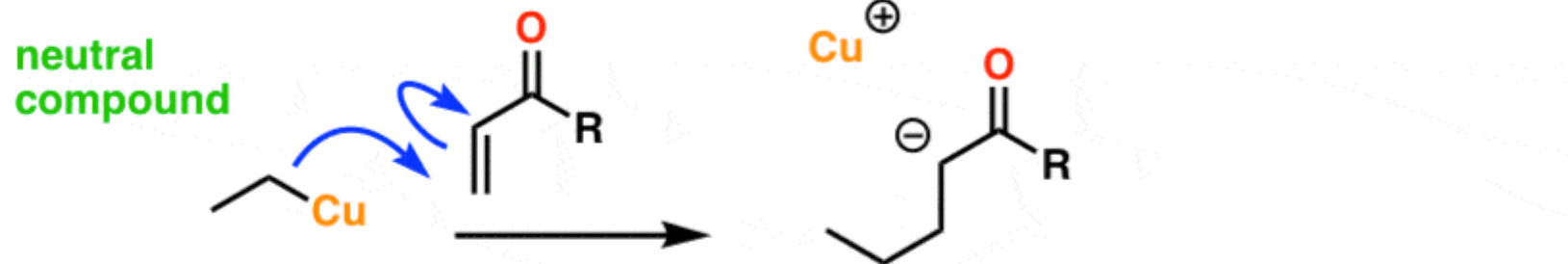


Organocopper reagent

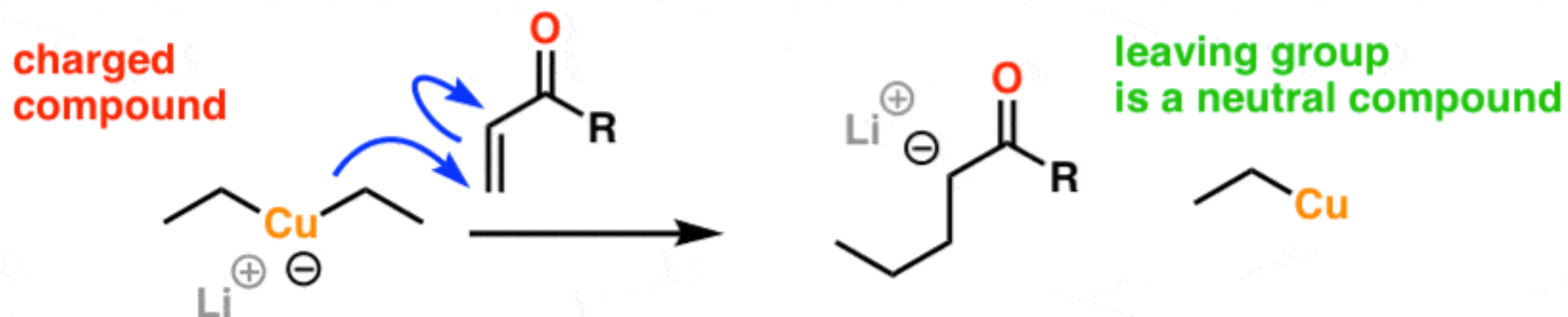


Organocuprate reagent

Think about the leaving group:



Organocopper reagents are neutral, relatively stable compounds, and after they act as nucleophiles Cu^+ remains as the "leaving group"



Organocuprate compounds, by contrast, are charged compounds, relatively unstable, after they act as nucleophiles a relatively stable organocopper reagent remains behind.

When **organocopper** reagents act as nucleophiles, they go from neutral, relatively stable compounds to ionic Cu^+ . Although this is a sweeping generalization, charge minimization is generally associated with greater stability in organic chemistry. We're going from a neutral compound (organocopper) to a charged ion (Cu^+). [I could also add that Cu^+ , being a soft ion, is not very effective in binding to O^- , but that's a pretty advanced point].

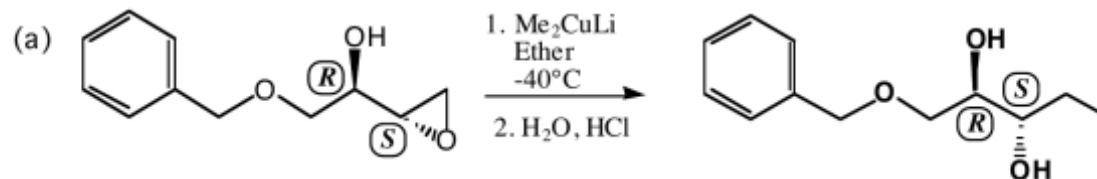
Compare that to **organocuprates**. There, we're starting as a relatively unstable **charged** species, and our final copper product is the **neutral** organocopper reagent. This is definitely downhill in terms of stability. It's reasonable to expect that the organocuprate will be more reactive, and hence be a better nucleophile.

The same principle can be used to explain why NaBH_4 is a better reducing agent than BH_3 , and LiAlH_4 is a better reducing agent than AlH_3 .

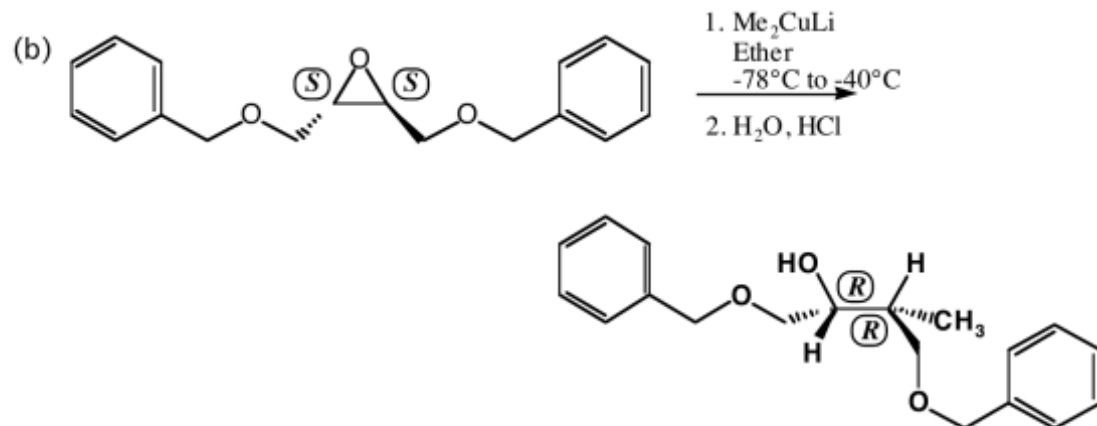
How do Gilman reagents open epoxides?

Reactions in Context

Problem 15.25 The synthesis of carbohydrates can be particularly difficult because of the large number of chiral centers and OH functional groups present. Epoxides can be useful synthetic intermediates in carbohydrate syntheses. Draw the product of the following reactions of a Gilman reagent with each epoxide.

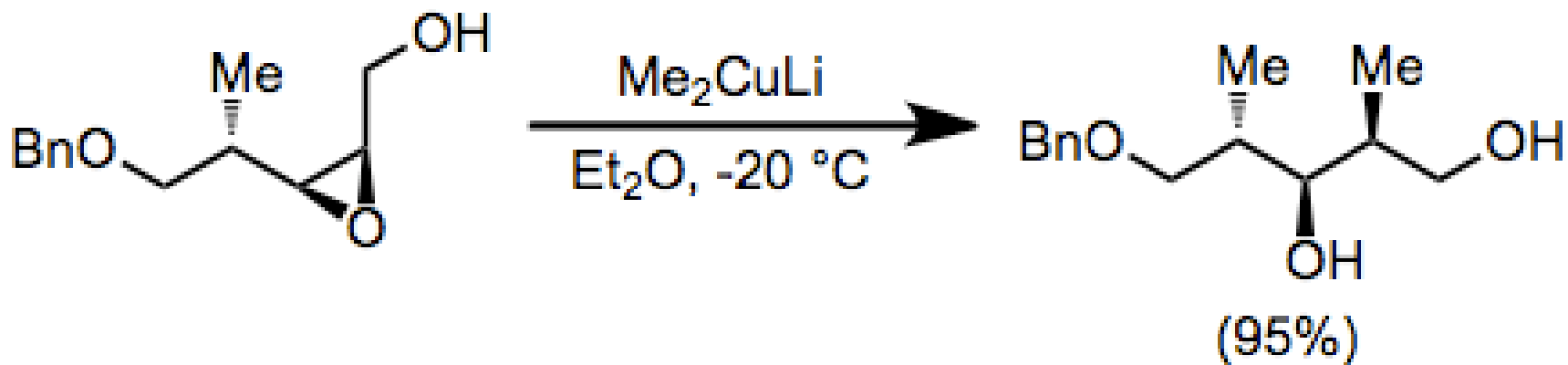
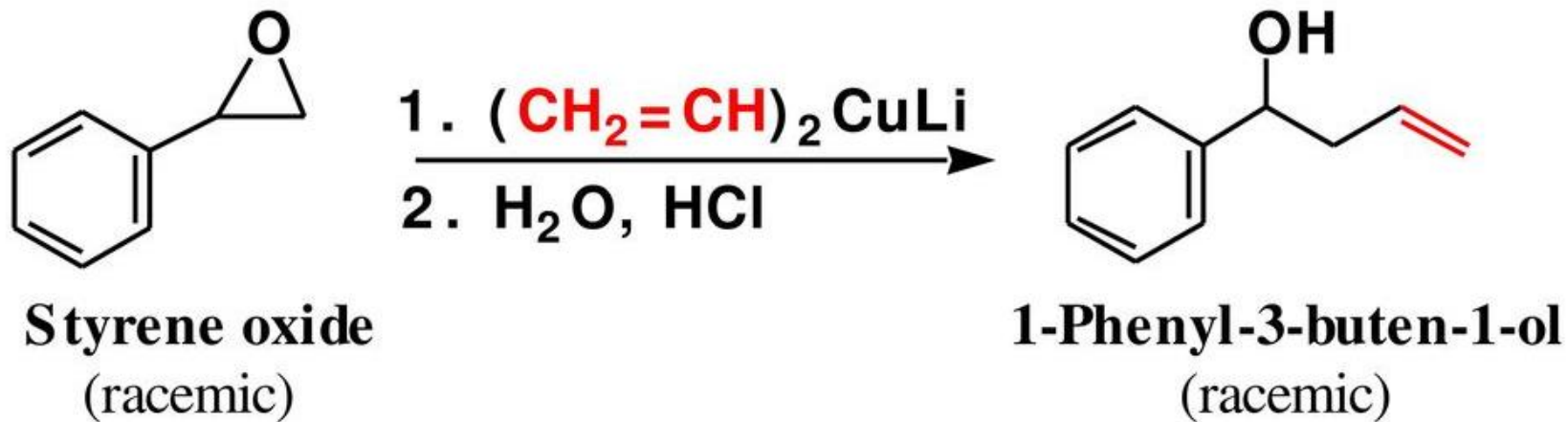


Note in the above reaction that the Gilman reagent reacted with the less-hindered side of the epoxide. Note also that the starting epoxide was a single enantiomer (*R,S*), the stereochemistry of which determines the stereochemistry of the product, which was therefore formed as a single enantiomer.



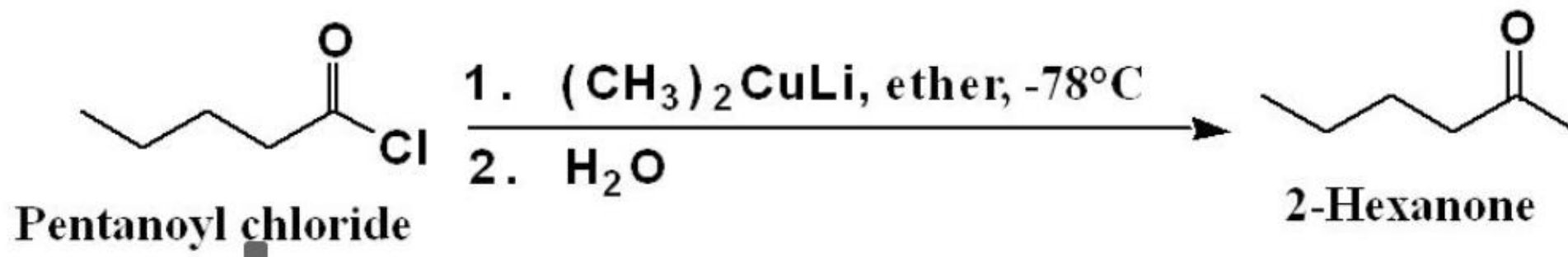
Once again, the starting material is a single enantiomer (*S,S*), the stereochemistry of which determines the stereochemistry of the single enantiomer product.

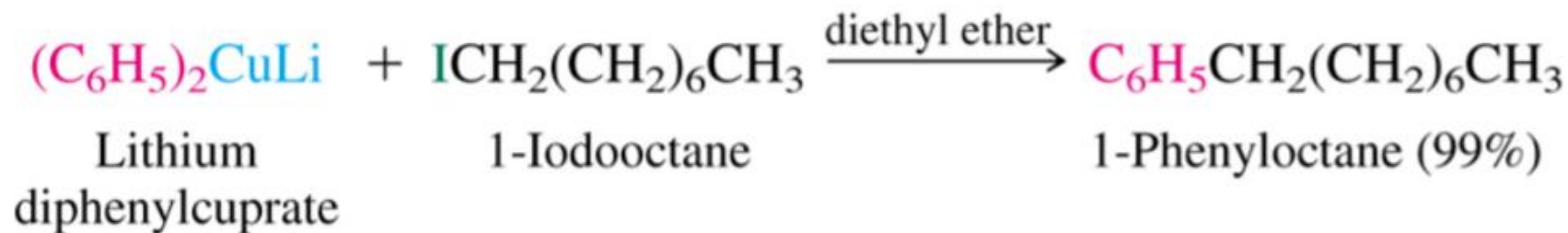
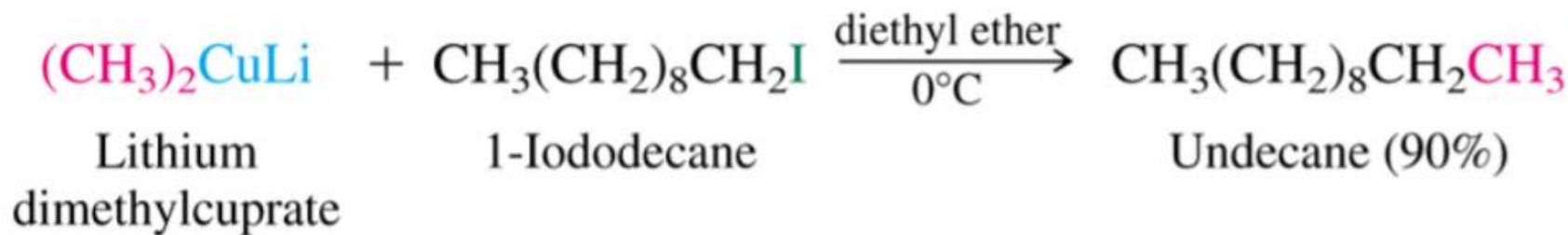
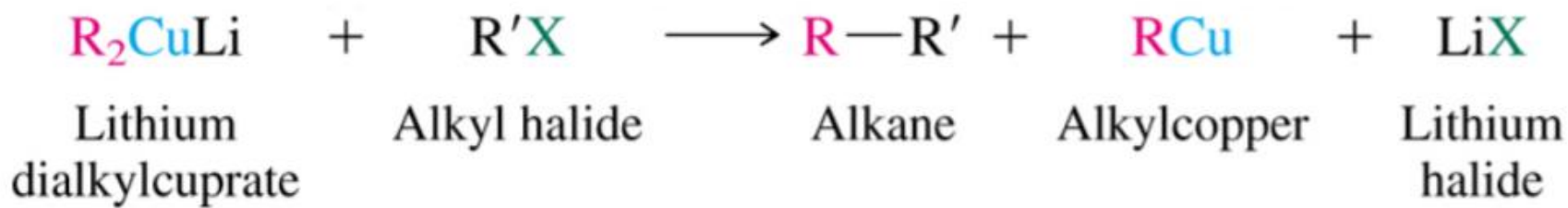
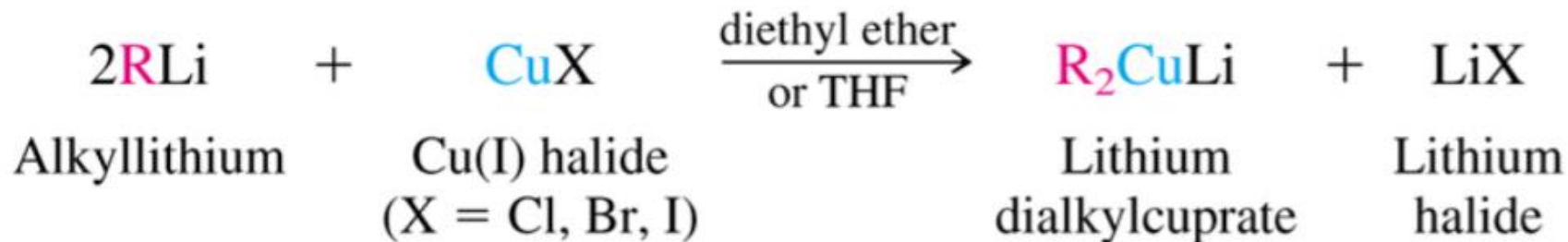
In the first reaction, the reaction doesn't take place at a stereocenter, so there's no way to observe the inversion.



Reactions with Acid Chloride

- Acid chlorides at -78°C react with Gilman reagents to give ketones.
 - Under these conditions, the TCAI is stable, and it is not until acid hydrolysis that the ketone is liberated.



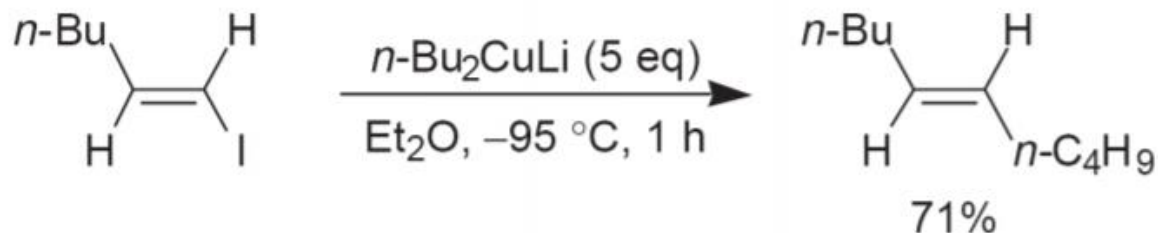


- Use of organocopper reagents offers a very efficient method for coupling of two different carbon moieties.
- Cu is **less electropositive than Li and Mg**, the *C–Cu bond is less polarized than the C–Li and C–Mg bonds*. This difference produces three useful changes in reactivity:
 - organocopper reagents 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: $\text{RCOCl} > \text{RCHO} > \text{tosylates, iodides} > \text{epoxides} > \text{bromides} \gg \text{ketones} > \text{esters} > \text{nitriles}$.
- In reactions with α,β -unsaturated carbonyl compounds, the organocopper reagents **prefer 1,4-addition over 1,2-addition**.

Reaction of Organocuprates

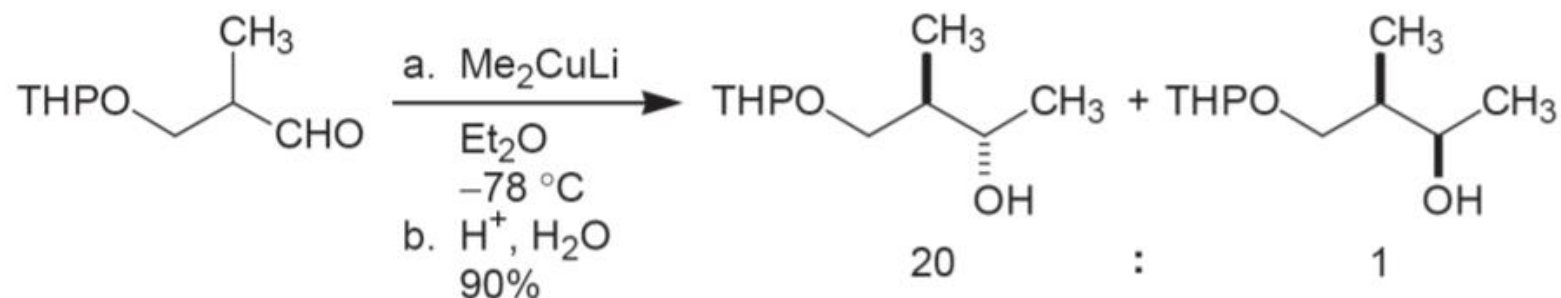
❖ *Reaction of vinyl halides*

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



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

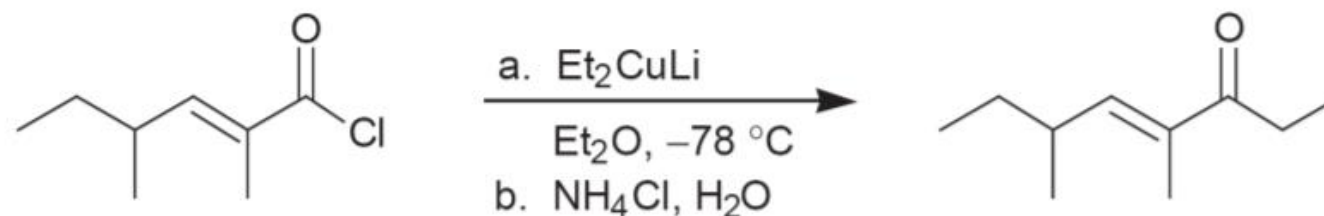
- Organocuprates undergo 1,2-additions to aldehydes, ketones, and imines. Reactions are often **highly diastereoselective**.



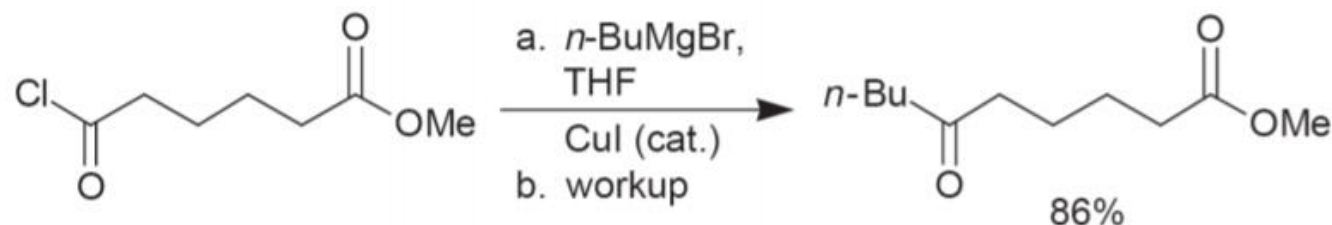
Reaction of Organocuprates

❖ Acylation

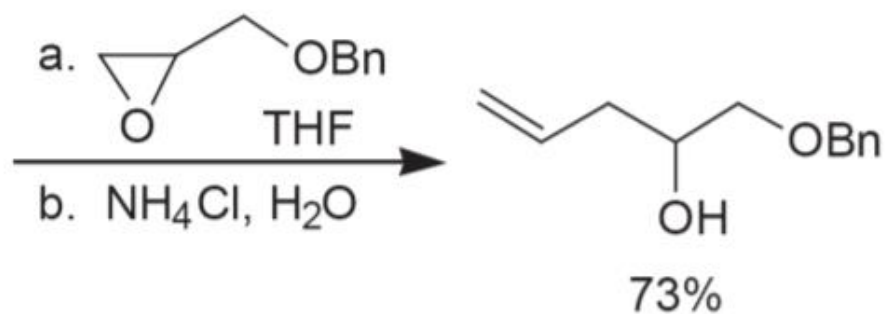
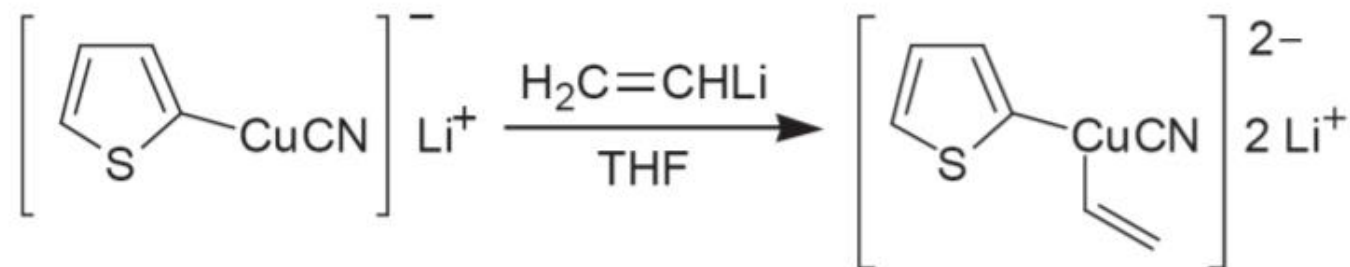
- reaction of organocopper reagents with acid chlorides affords corresponding ketones in high yields. Retrosynthetically, the reaction amounts to an alkylation of a carboxylic acid.



- 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

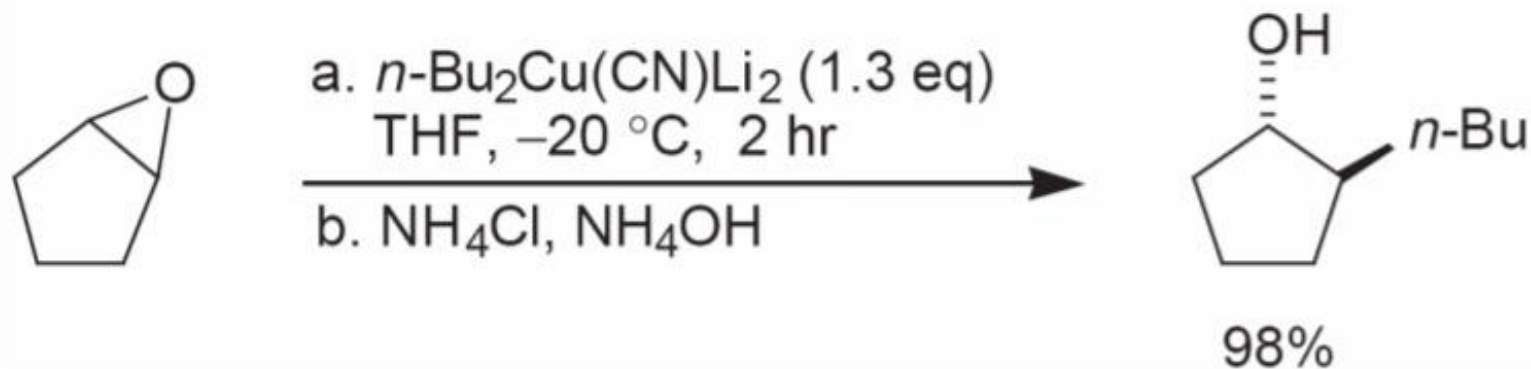


- $R_2Cu(CN)Li_2$ reagents: among the mildest and most efficient reagents available for generating C-C bonds by way of epoxide cleavage using organocopper chemistry.
- nucleophilic addition occurs at the less sterically hindered carbon of the oxirane ring



❖ Epoxide cleavage reactions (cont'd)

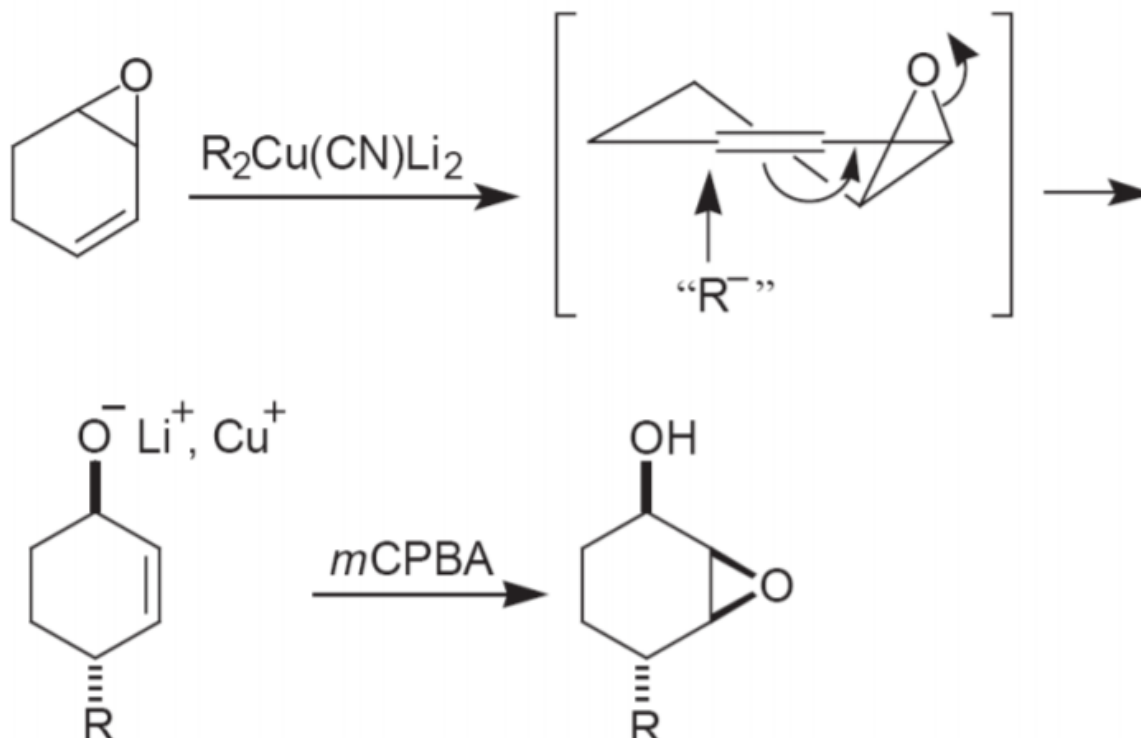
- Stereospecific S_N2 opening of cyclic epoxides with cyanocuprates furnishes, after workup, the *trans*-2-hydroxy-alkylated products.



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

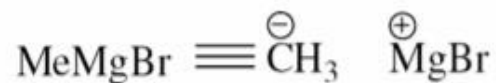
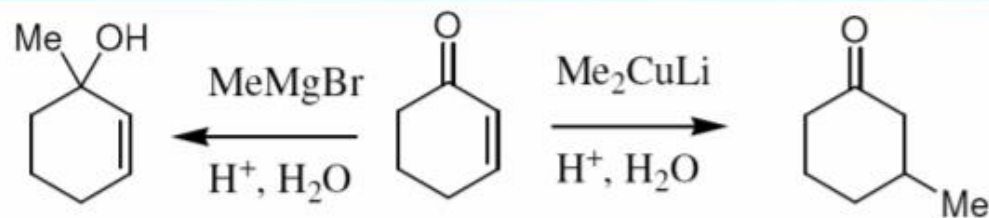
❖ Conjugate Addition

- 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.

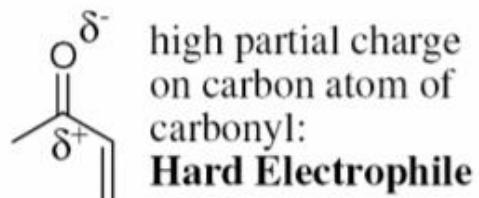
Table 7.6 Regioselectivity in Addition of RLi, RMgX, and Organocopper Reagents to α,β -Unsaturated Carbonyl Compounds

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

Organometallic - Regioselectivity



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



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

Hard nucleophiles react fastest with hard electrophiles.



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

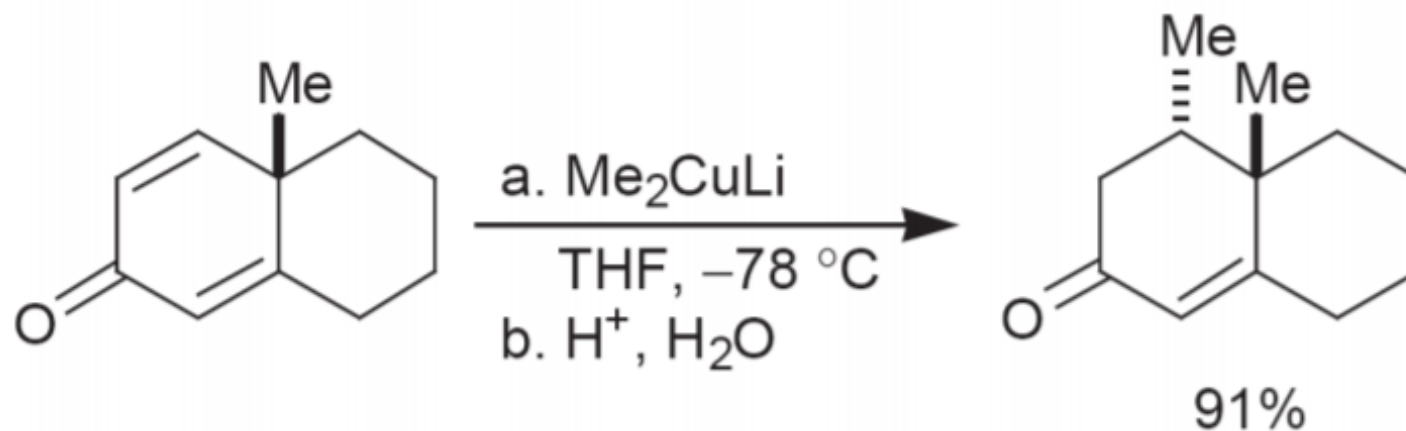
Soft nucleophiles react *via* the best FMO interactions.



Soft species: carries a low partial charge.

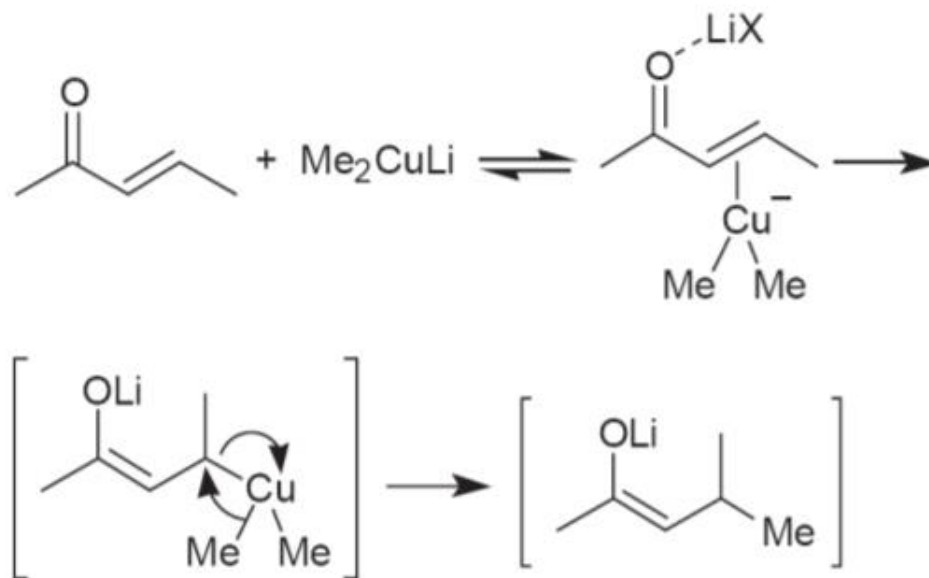
Soft nucleophiles react at the alkene.

In bicyclic system below, addition is **chemoselective**, involving the **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.



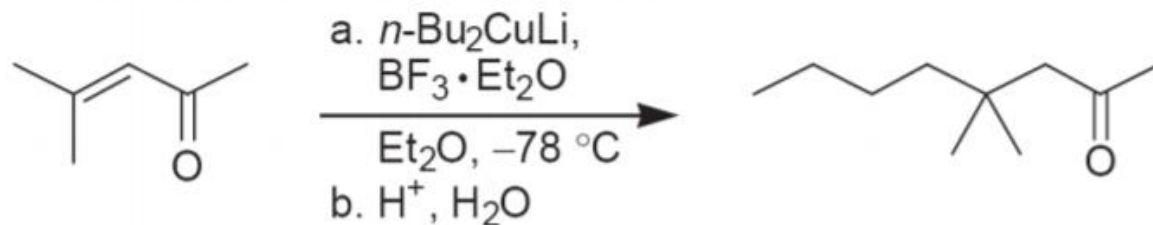
Reaction of Organocuprates

- 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 an initial reversible **copper(I)-olefin-lithium association**, which then undergoes **oxidative addition followed by reductive elimination**.

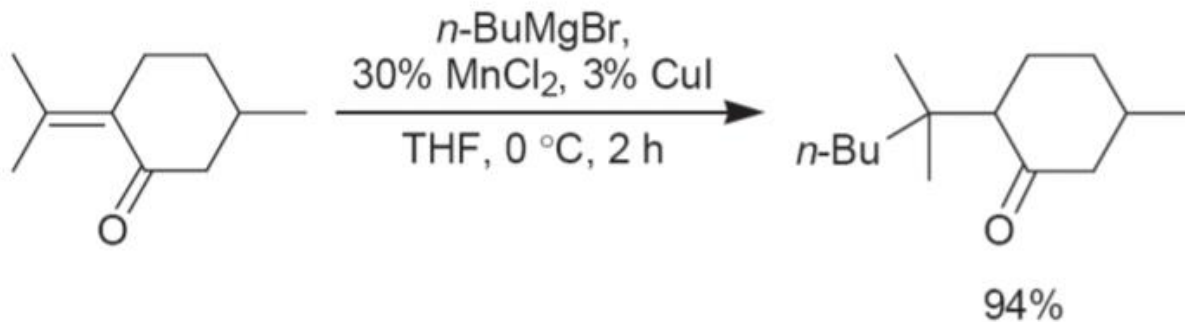


Reaction of Organocuprates

- 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.

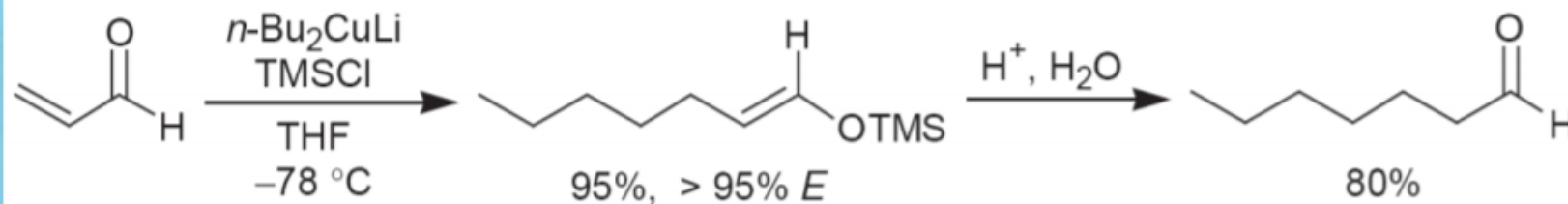


- Grignard reagents in the presence of CuX or a mixture of $MnCl_2$ and CuI undergo 1,4-addition to hindered enones.



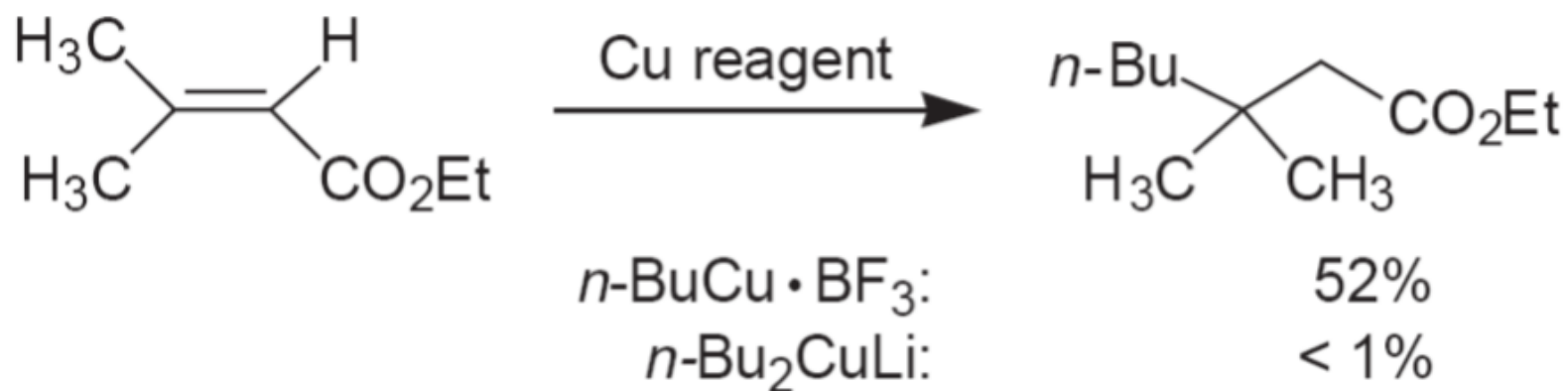
Reaction of Organocuprates

- 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

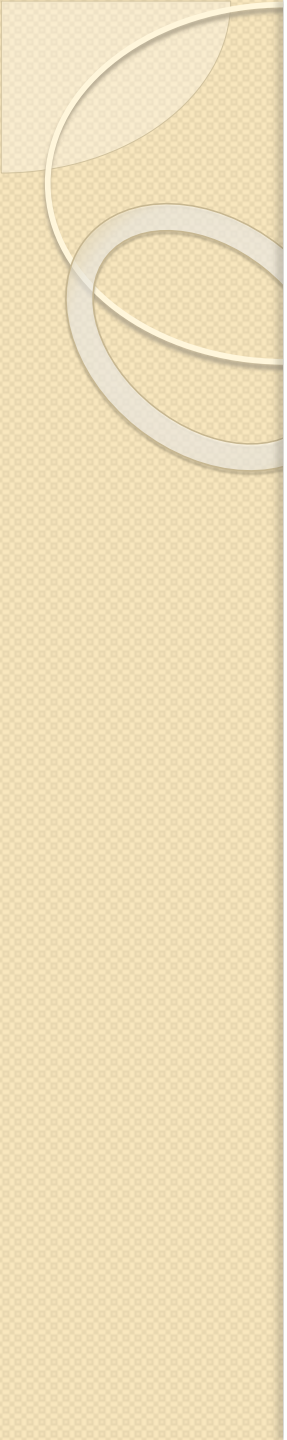
- Conjugate additions of dialkylcuprates to β -substituted- α,β -unsaturated acids and esters give low yields. Addition of boron trifluoride etherate, $\text{BF}_3 \cdot \text{OEt}_2$, to certain dialkylcuprates and higher-order cuprates enhances their reactivity in Michael additions to conjugated acids and esters.



Reaction of Organocuprates

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

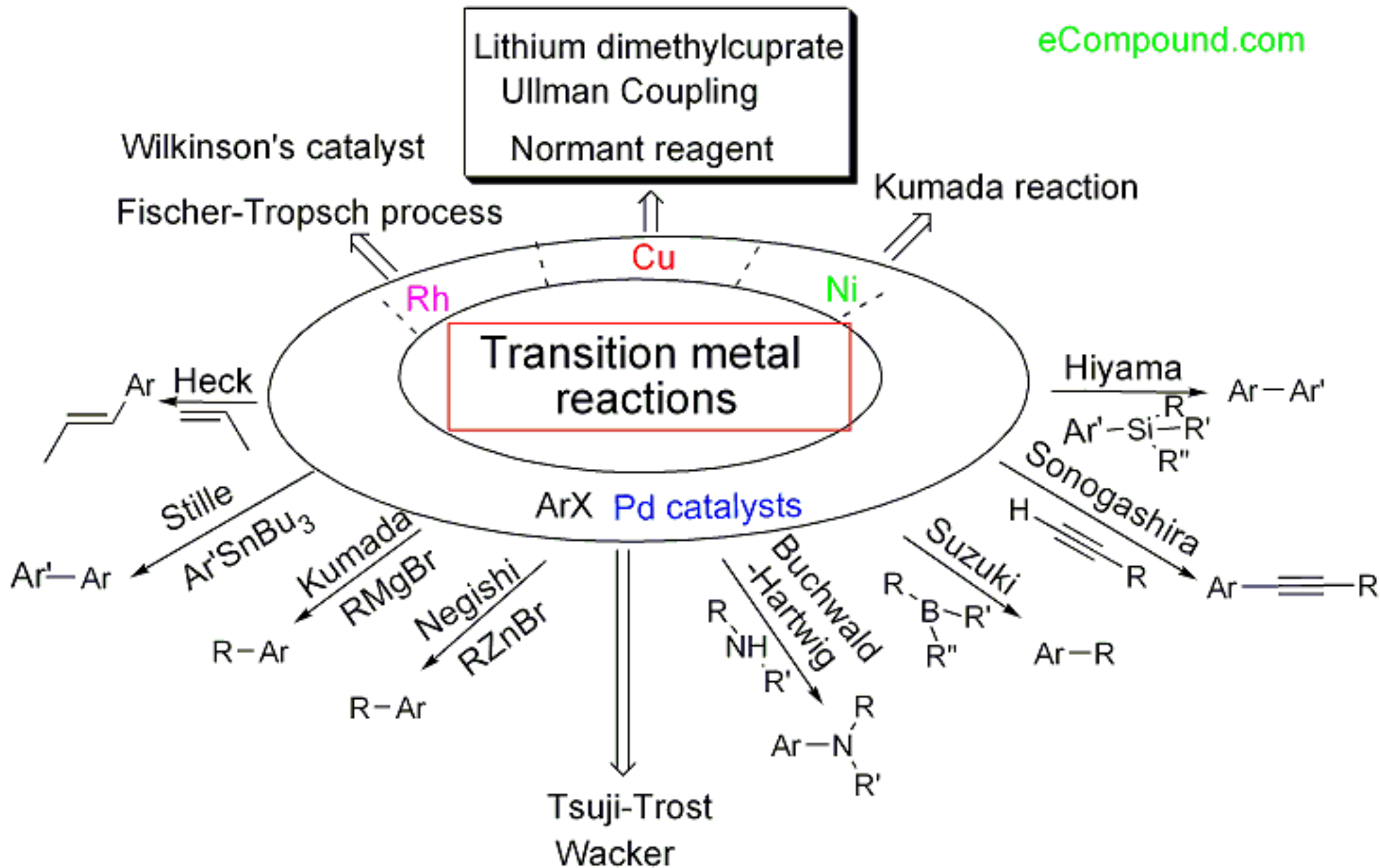
- One of the fundamental contributions of **organocopper** chemistry to organic synthesis is the ability to **transfer ligands in a 1,4-manner** to **α,β -unsaturated C=O** compounds to produce enolate anions in a **regioselective** manner.
- These may be trapped by a variety of electrophiles in **tandem-type 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**.

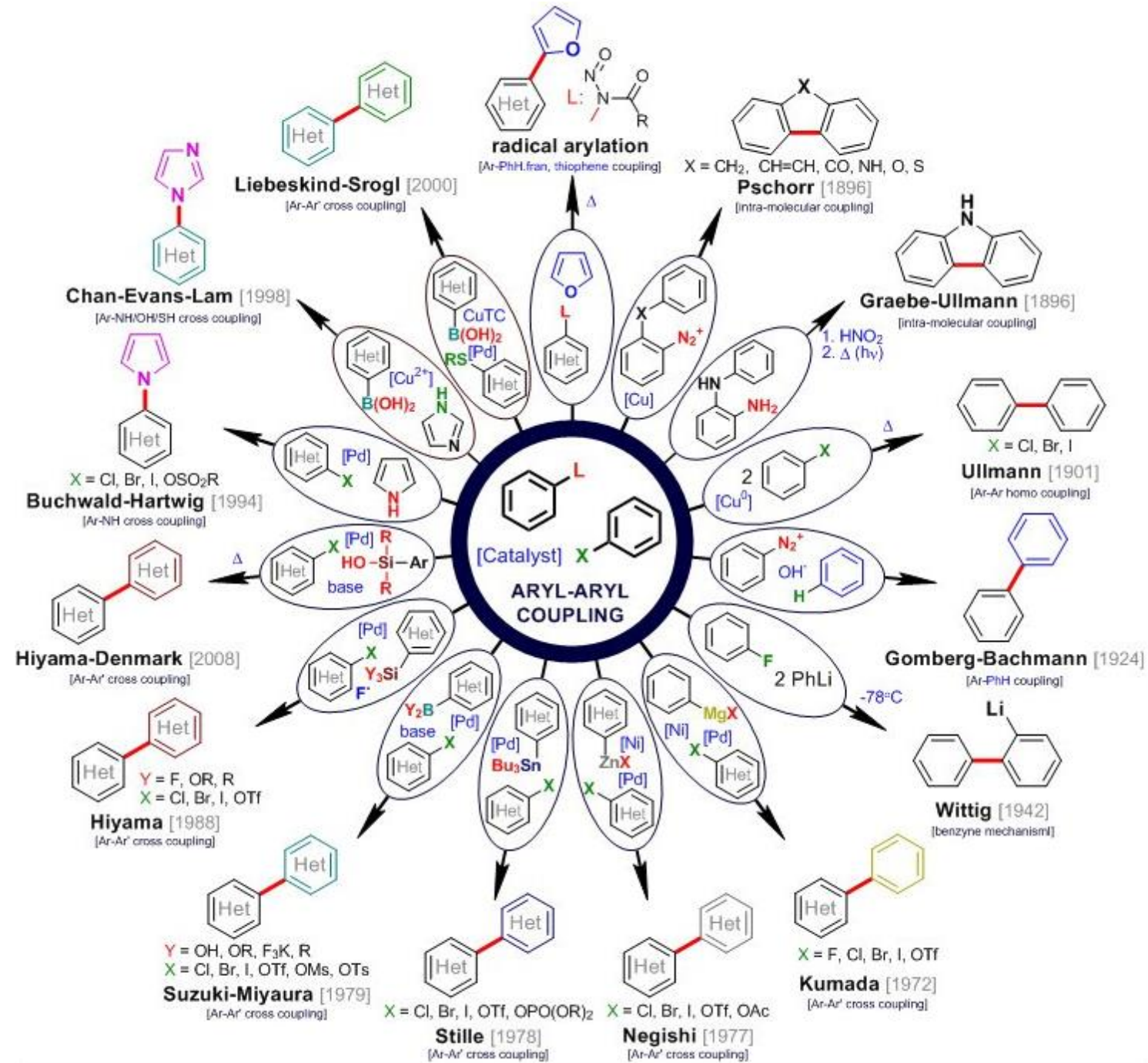


Paper-VI: Organic Chemistry-II (CH.2.2)

Palladium Chemistry

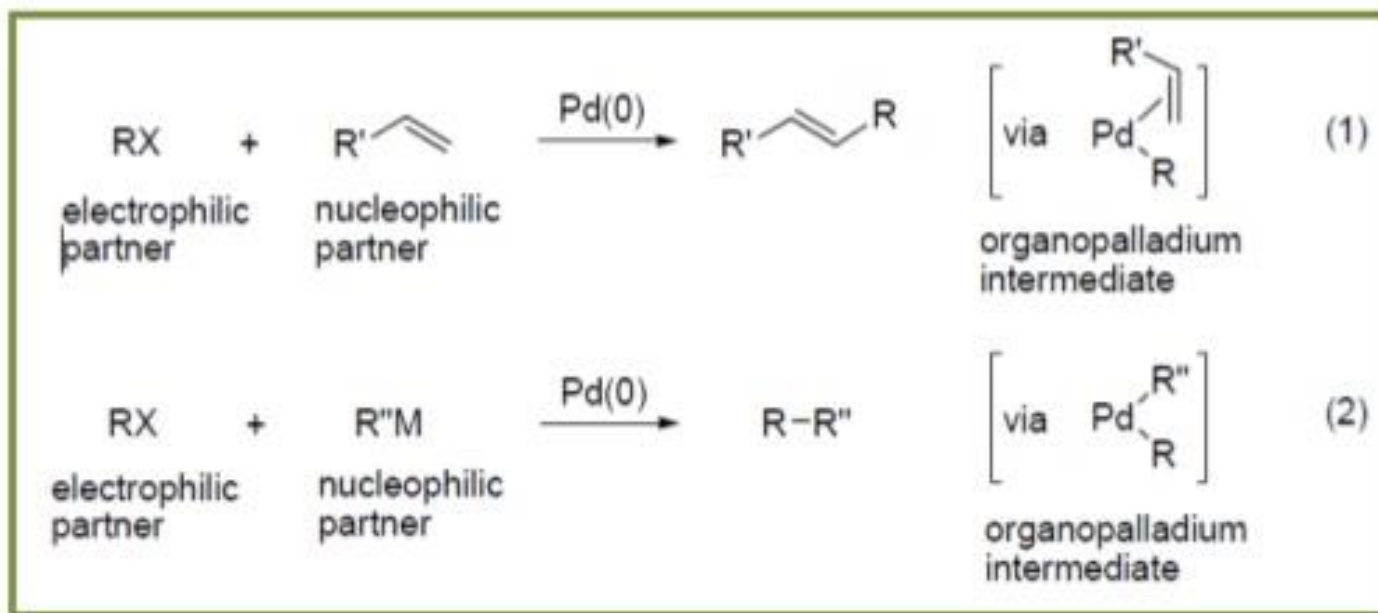
1. Heck cross- coupling reaction
2. Suzuki cross- coupling reaction
3. Stille cross- coupling reaction
4. Nigeshi cross- coupling reaction
5. Sonogashira cross- coupling reaction





What are C-C cross coupling reactions?

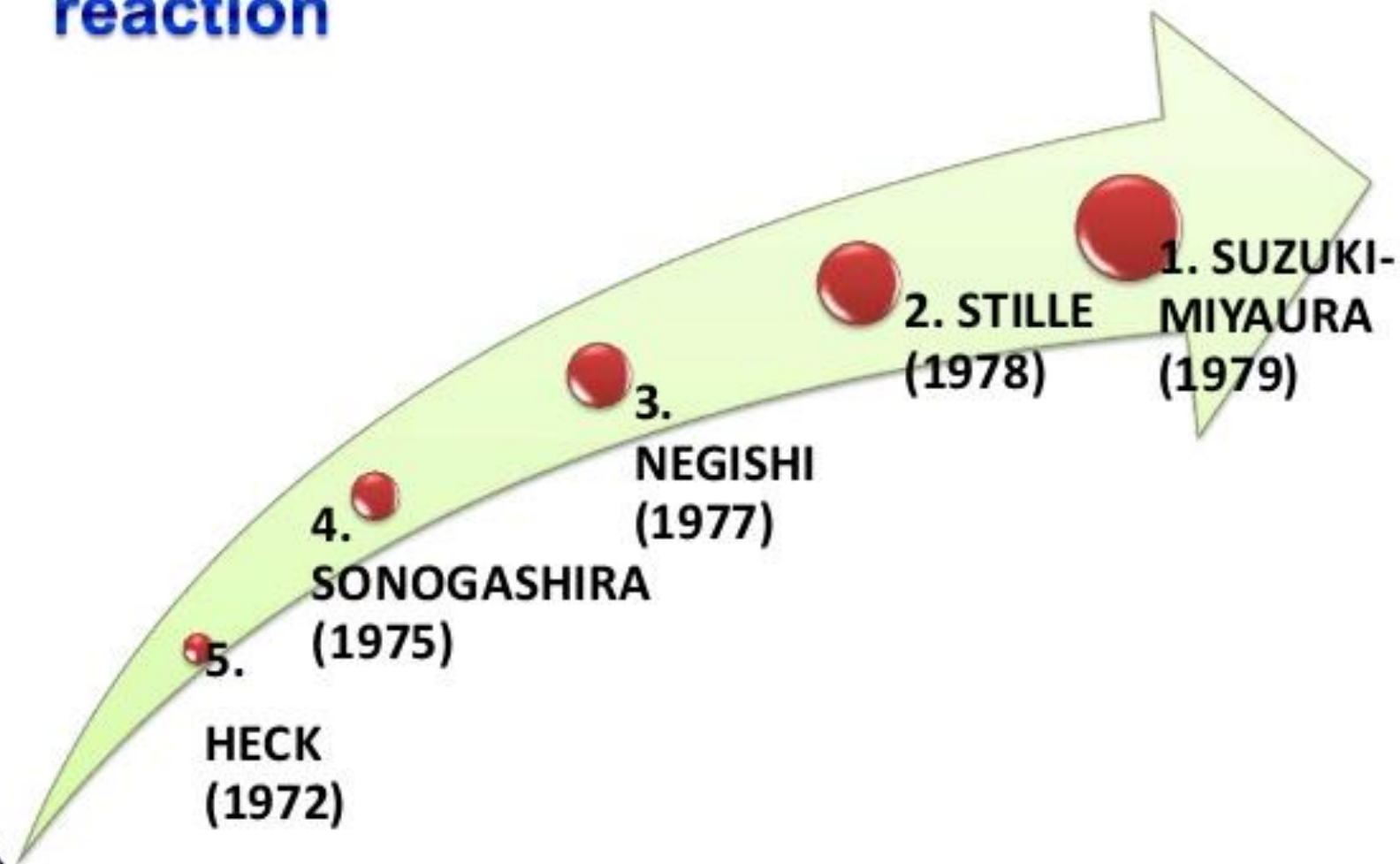
The C-C bond formation between an organic electrophile (RX) and a nucleophile (Organometallic R'M or R'-C=C) in the presence of a transition metal catalyst, usually Pd (even Cu, Ni, Fe etc. are also used).

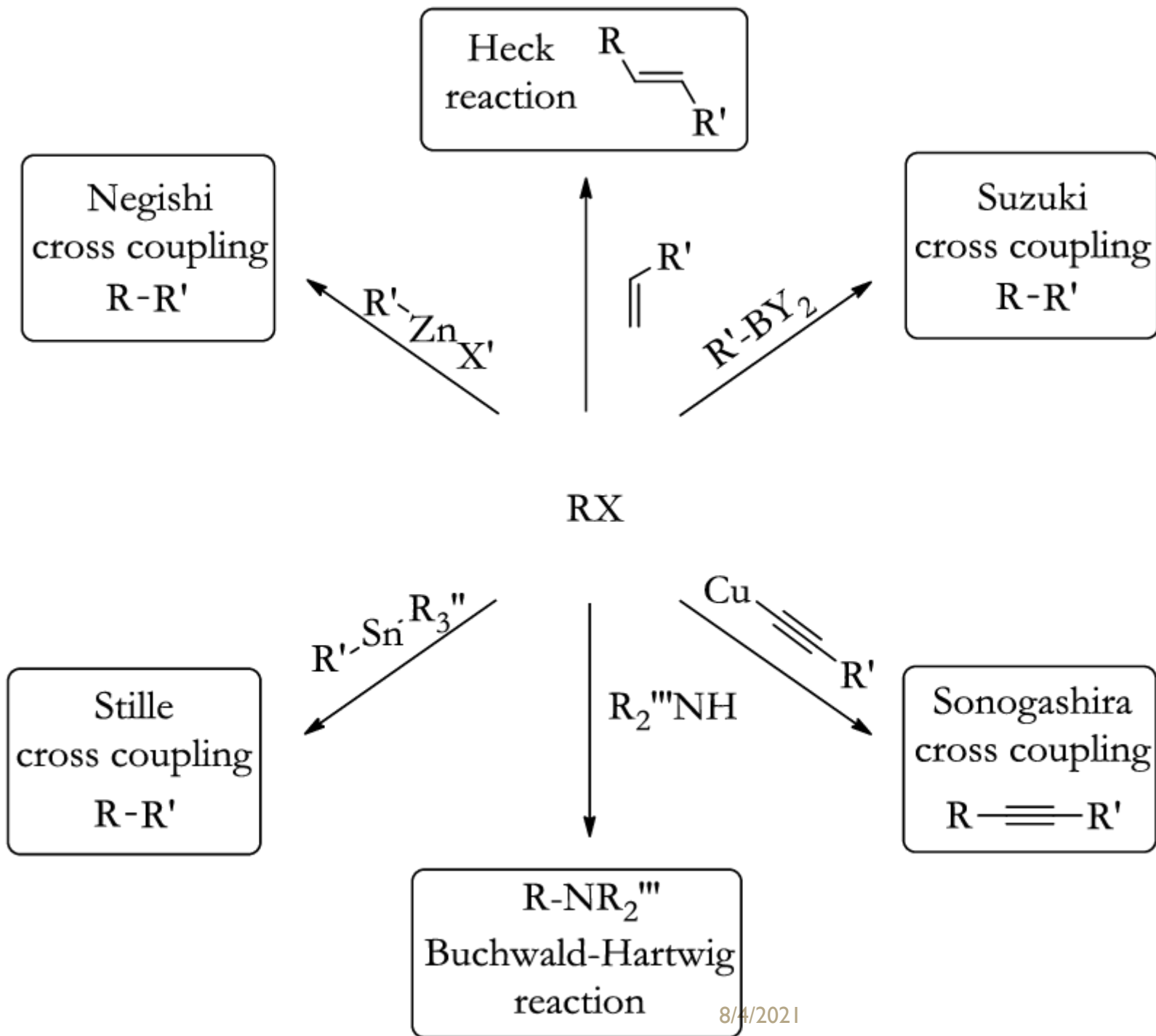


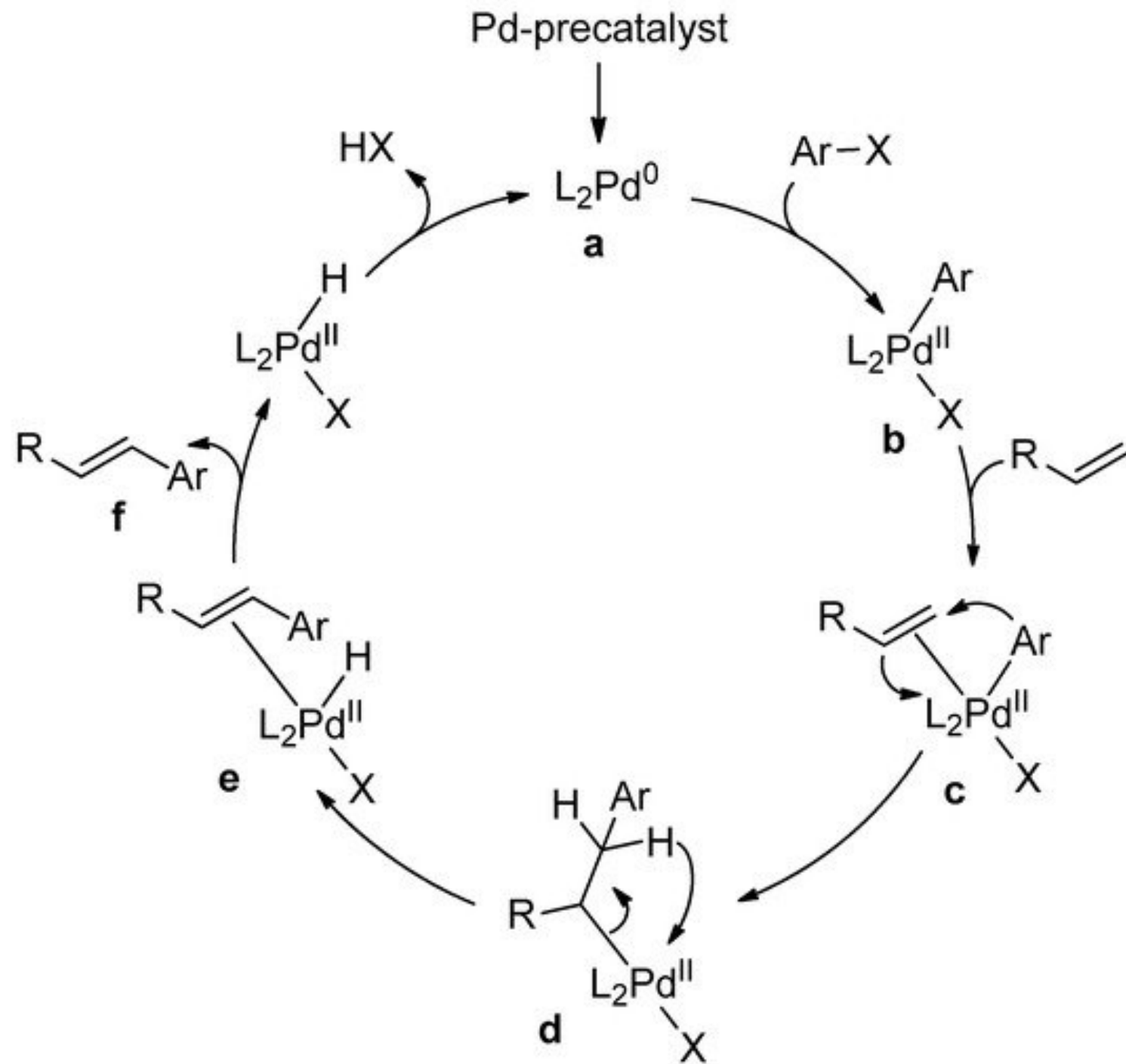
Why Palladium?

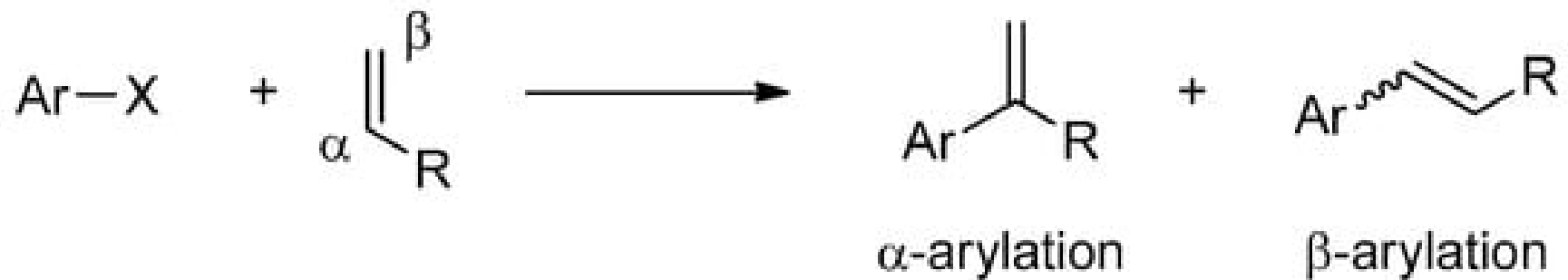
- Palladium is a *d*-block transition metal.
- Pd favours the formation of tetrahedral d^{10} and square planar d^8 complexes of low oxidation states (0 and II respectively).
- This feature **affords Pd good electron-donating and electron-accepting capabilities**, allowing fine-tuning by altering the electronic properties of its ligands.
- Pd may easily participate in concerted processes due to its **closely lying HOMO and LUMO energies**.
- Pd complexes tend to be less sensitive to oxygen and are less toxic.

These are the five main reactions which are related to C-C cross coupling reaction

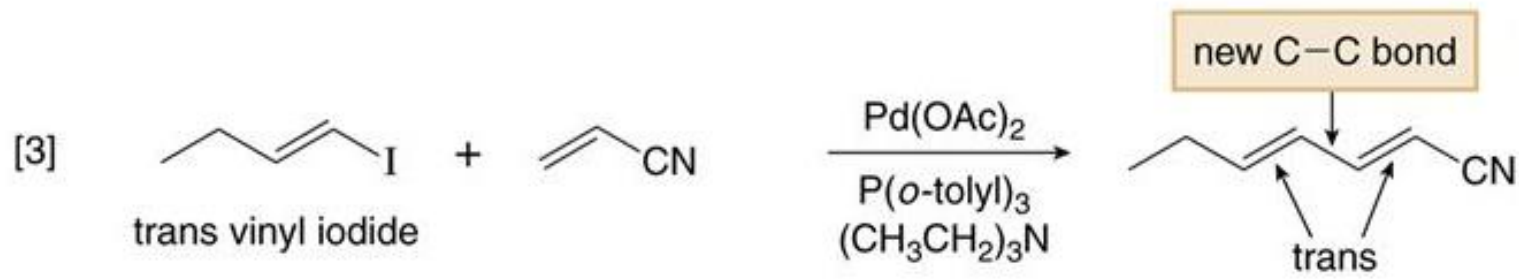
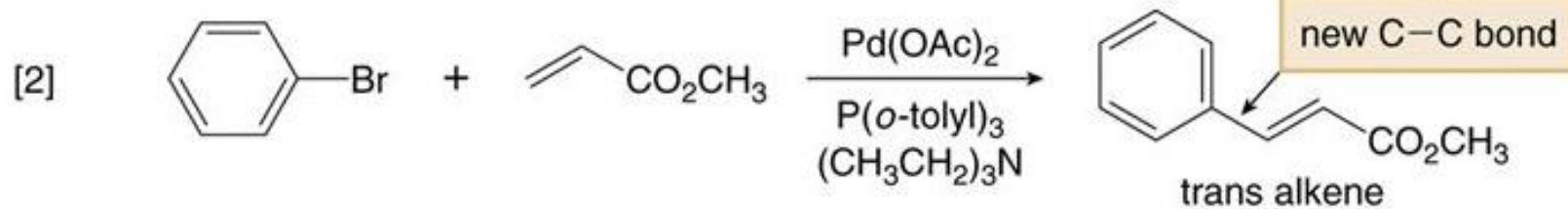
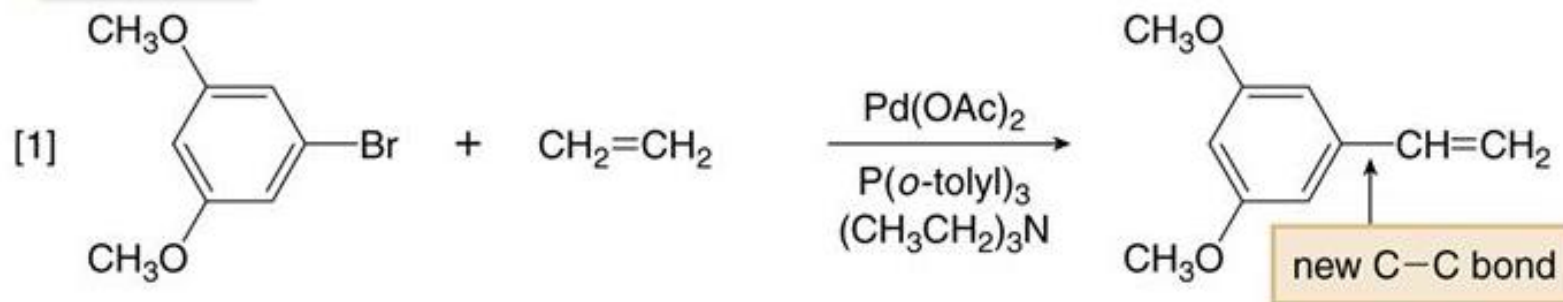




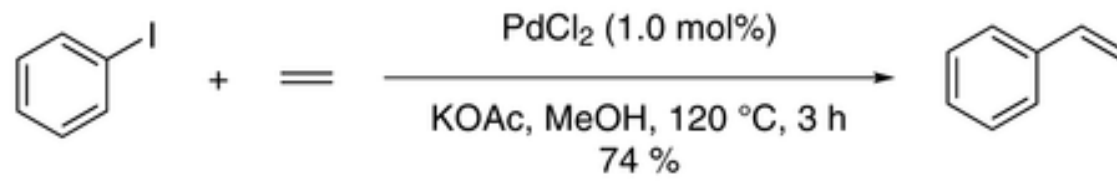




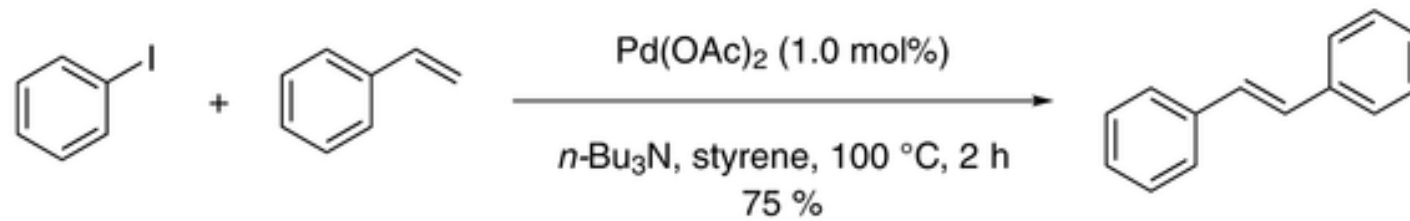
Examples



Mizoroki 1971



Heck 1972



Importance of C-C coupling reactions

The Nobel Prize was awarded jointly to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for Palladium-catalyzed C-C cross coupling reaction in 2010.



Prof. Richard F. Heck



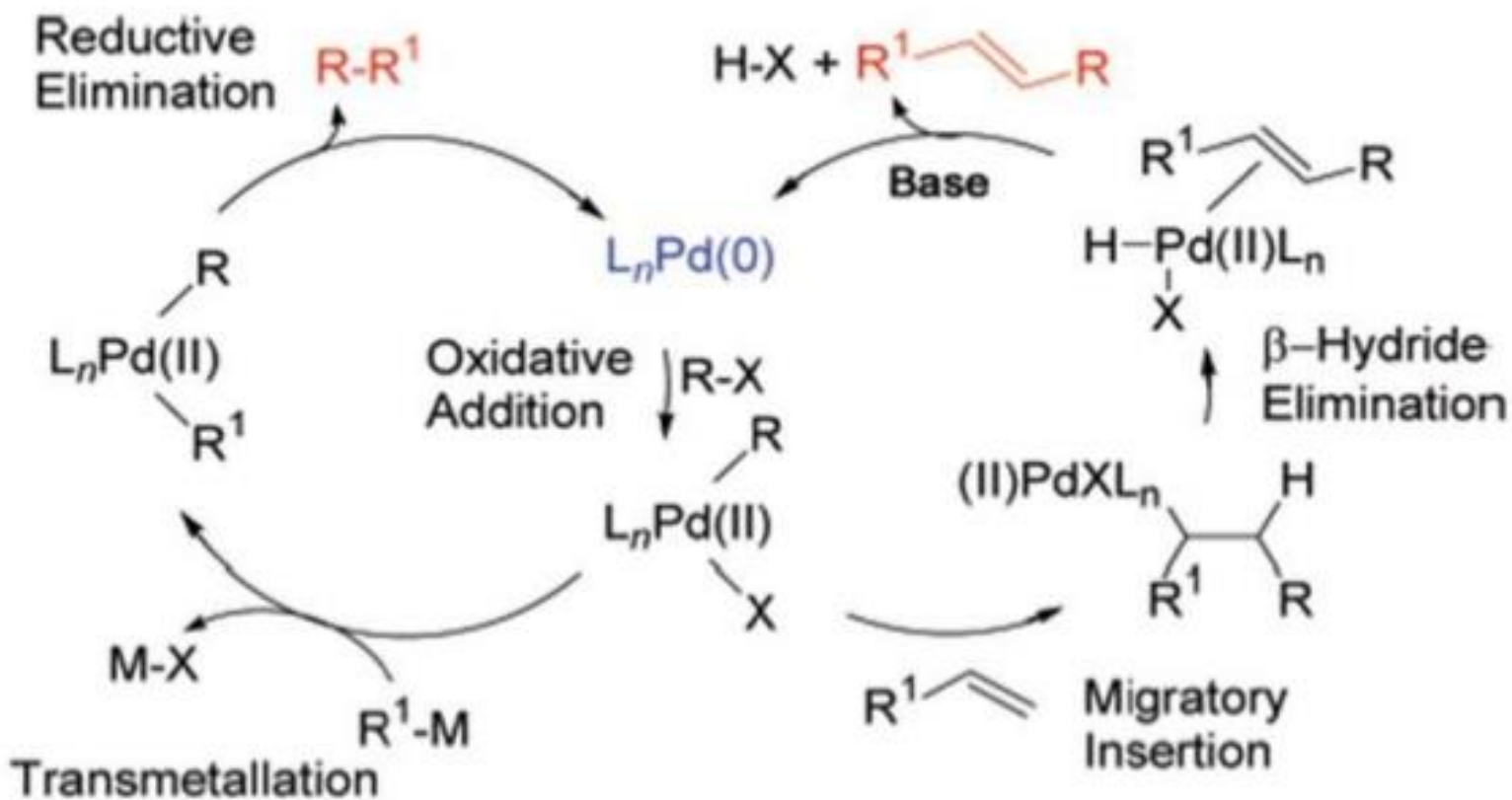
Prof. Ei-ichi Negishi



Prof. Akira Suzuki

1. Importance of chemical processes in the pharmaceutical and industries.
2. The key steps in building complex molecules from simple precursors.

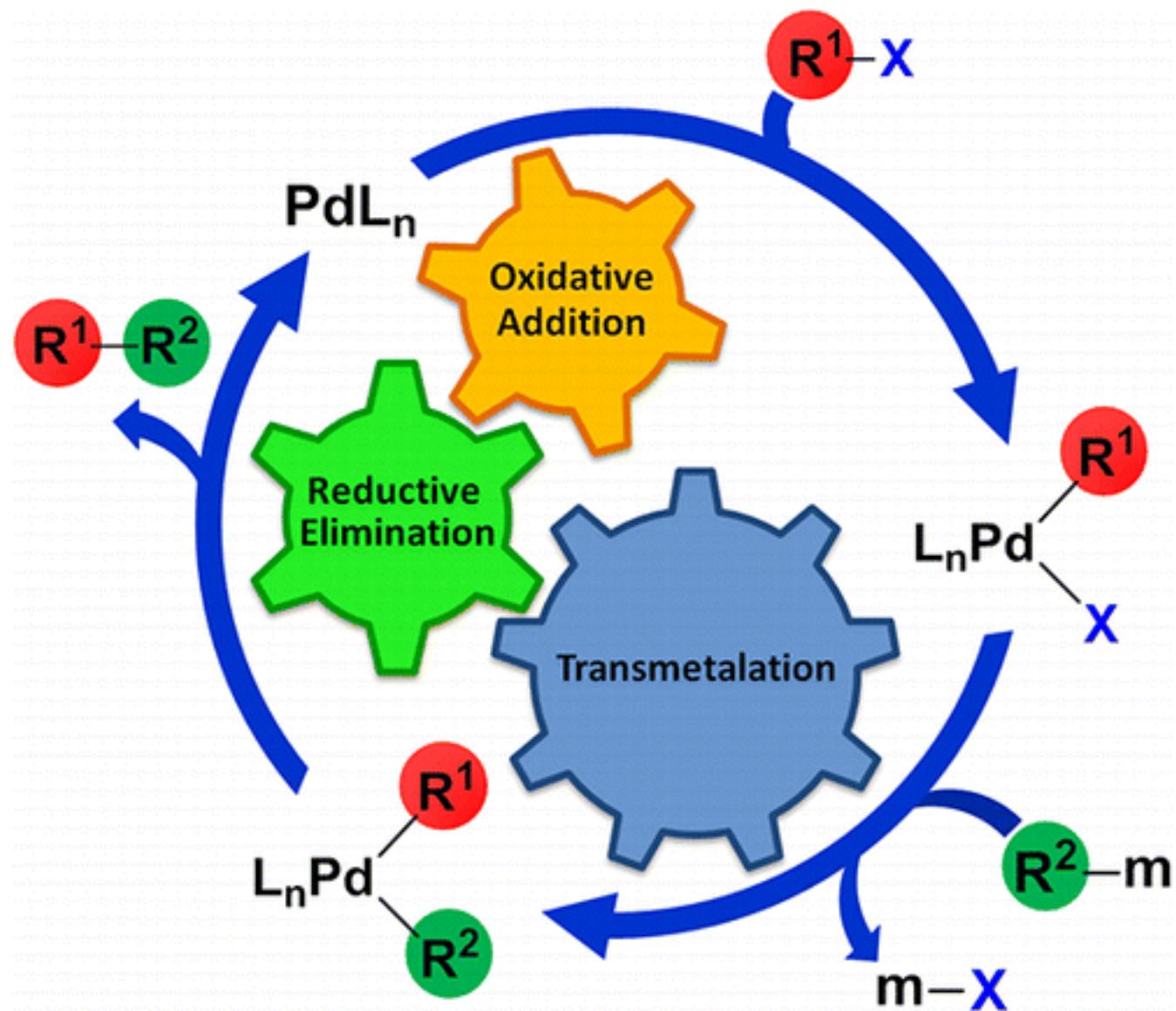
General Mechanism of C-C cross coupling reactions.



Negishi - R^1-M = Organozinc compound
 Stille - R^1-M = Organotin compound
 Suzuki - R^1-M = Organoborane compound

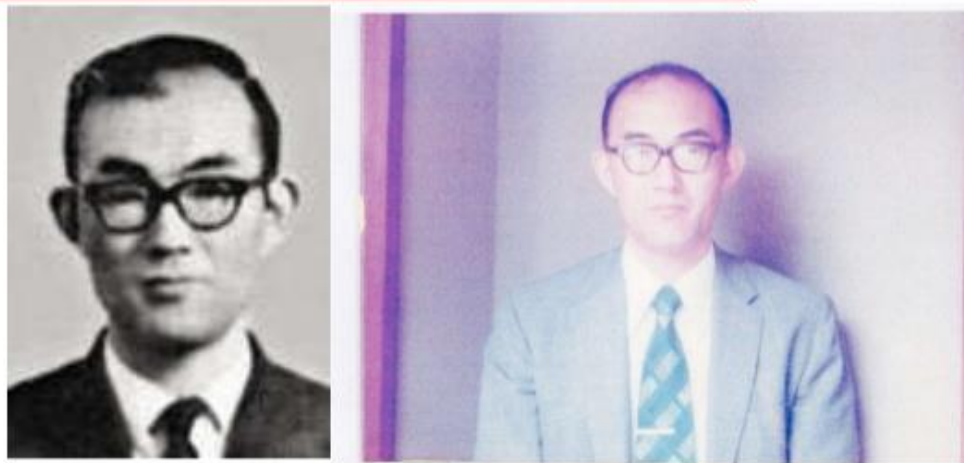
Heck-Mizoroki

Mechanism of Coupling Reactions



1. Heck cross- coupling reaction Or Mizoroki-Heck olefination

Tsutomu Mizoroki



Heck, improved Mizoroki's reaction conditions to make the process more practical (J. Org. Chem. **1972**, 37, 2320).

Mizoroki published one more report on the topic (Bull. Chem. Soc. Jpn. **1973**, 46, 1505) before succumbing to pancreatic cancer at the age of 47, in 1980.

By then, chemists were already starting to give the reaction a name.

18



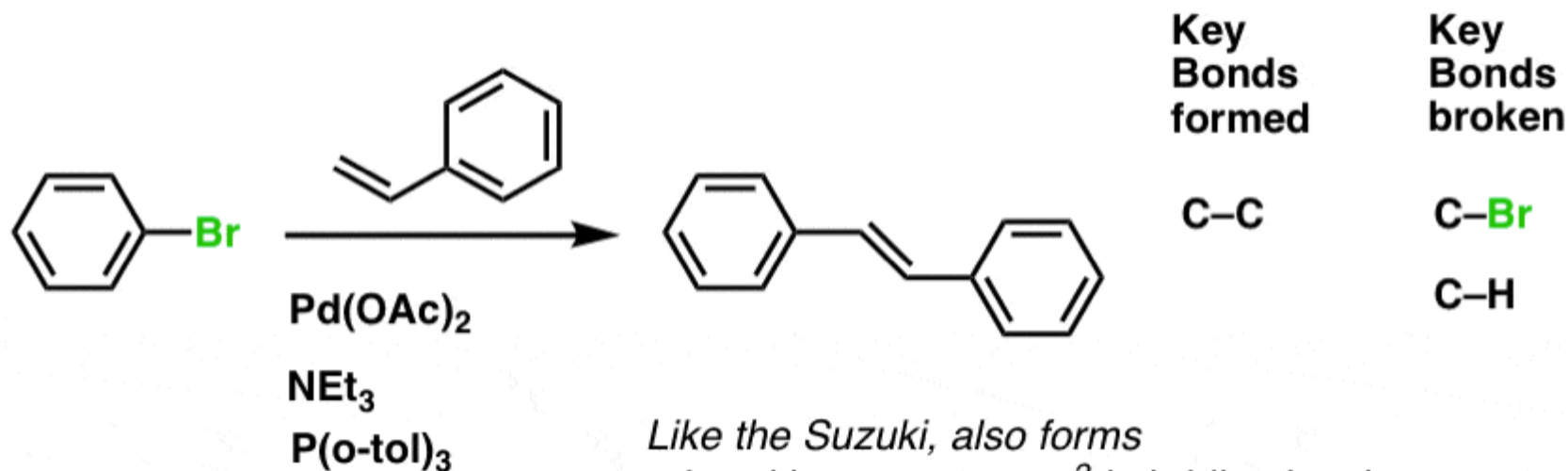
Heck:
"Unfortunately, Mizoroki died quite young, before he could do much chemistry with palladium,". "Maybe if he'd lived, it might've been called the Mizoroki reaction instead."

21

Mizoroki-Heck olefination/coupling reactions

In its most basic form, the Heck olefination is the palladium catalyzed coupling of an aryl halide and an olefin to afford an aryl alkene. The first example of such a reaction was discovered in 1971 by Mizoroki.

Heck Reaction - another Pd-catalyzed C–C bond forming reaction



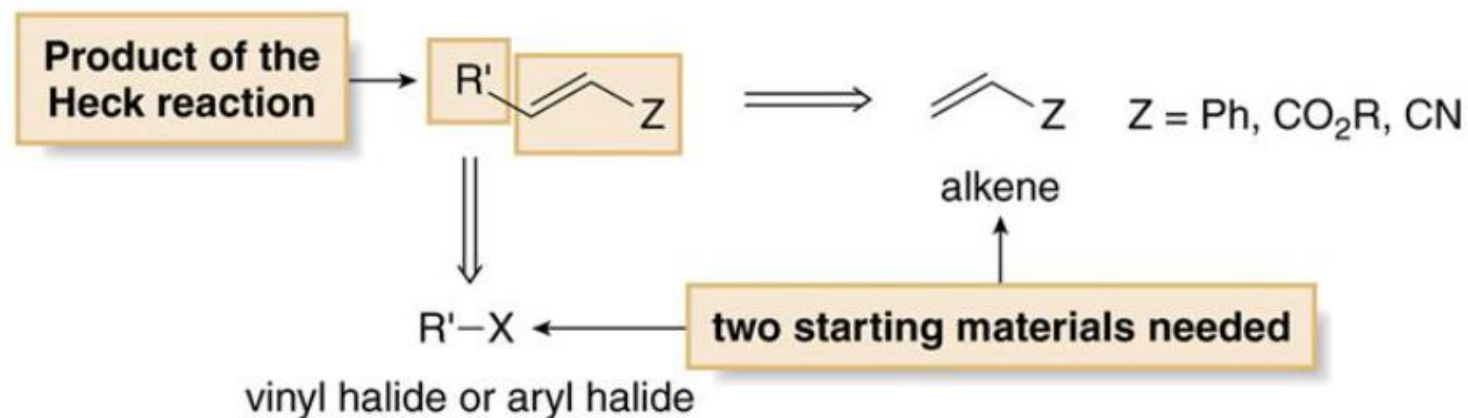
Like the Suzuki, also forms a bond between two sp^2 hybridized carbons

Examples

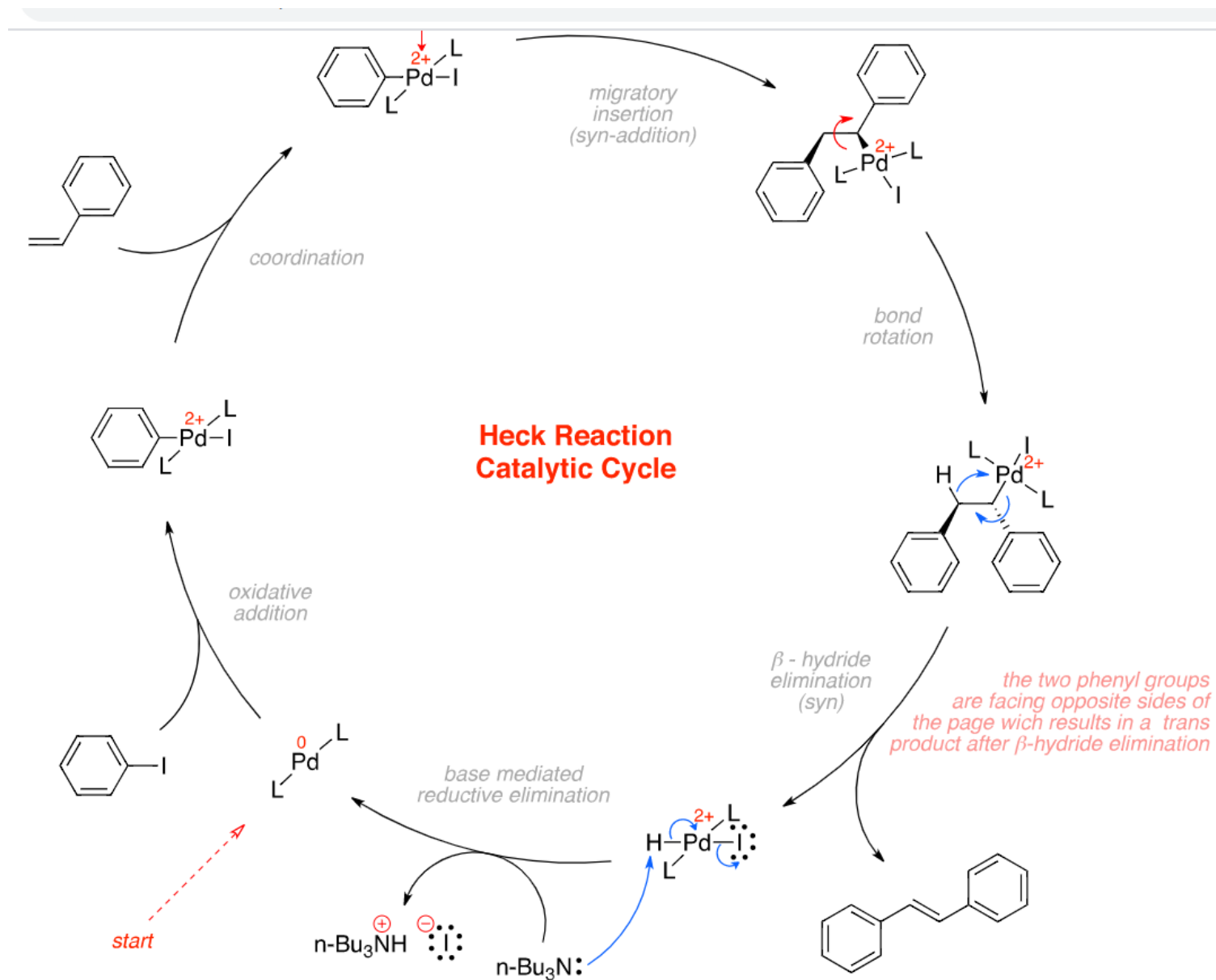
Using the Heck Reaction in Synthesis

- To use the Heck reaction in synthesis, you must determine what alkene and what organic halide are needed to prepare a given compound.
- To work backwards, locate the double bond with the aryl, COOR, or CN substituent, and break the molecule into two components at the end of the C=C not bonded to one of these substituents.

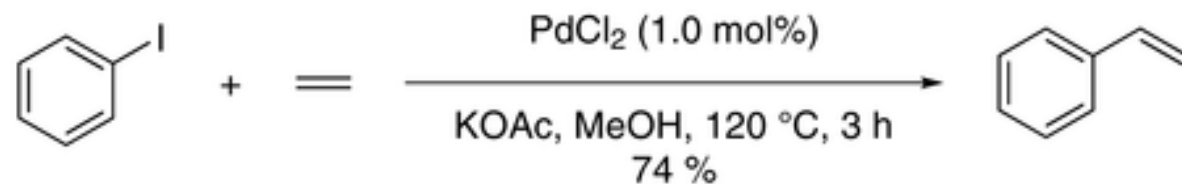
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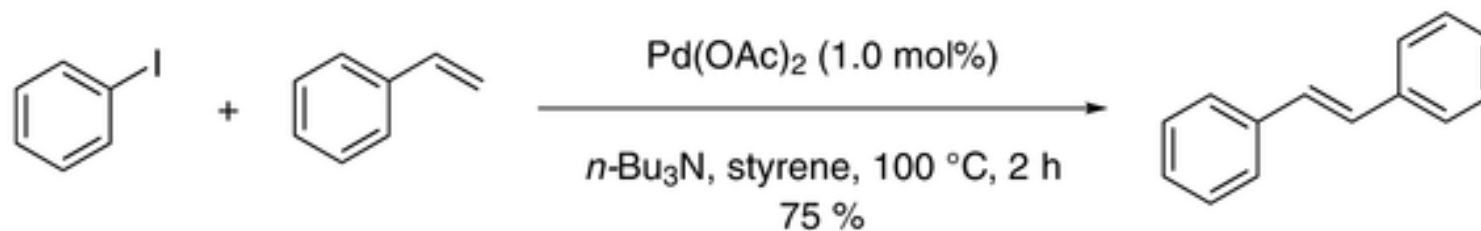
Mechanism



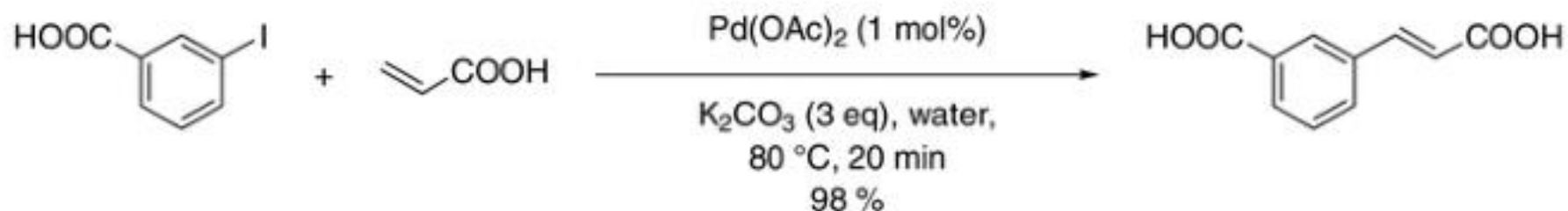
Mizoroki 1971



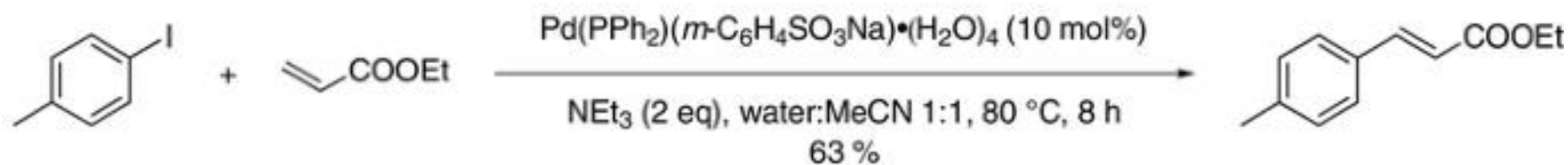
Heck 1972

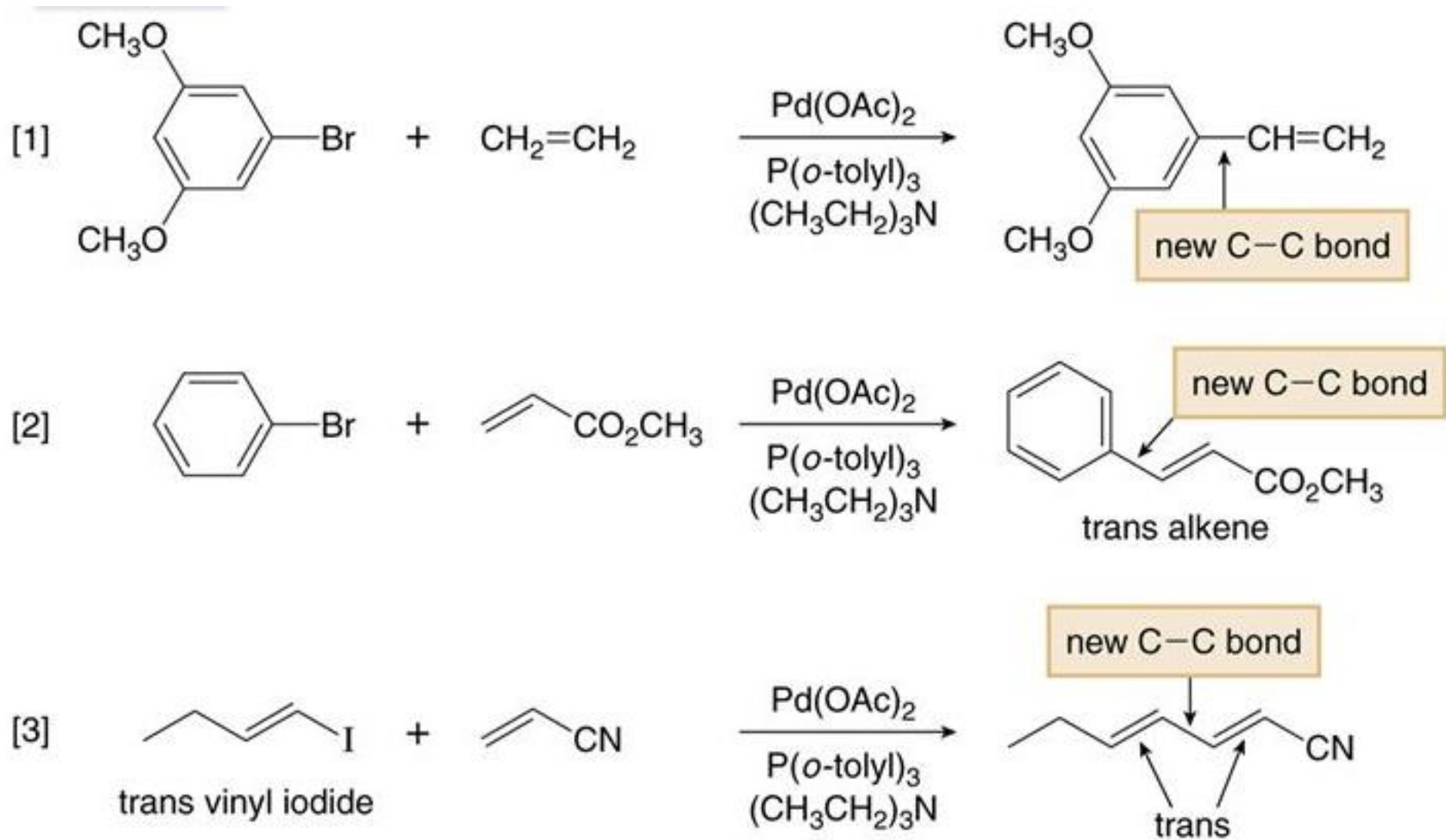


Beletskaya 1988



Calabrese 1990





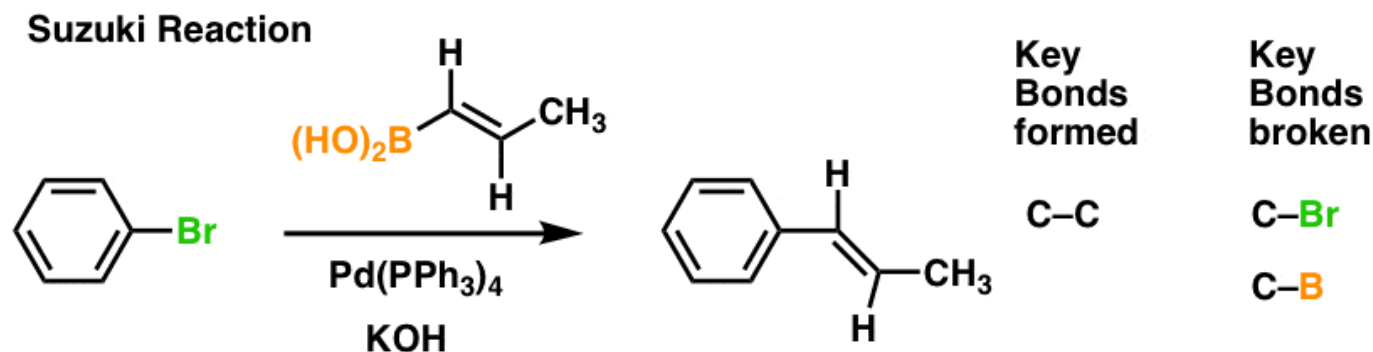
The Suzuki-Miyaura Reaction

NOBEL PRIZE

Professor Emeritus Akira Suzuki, 2010

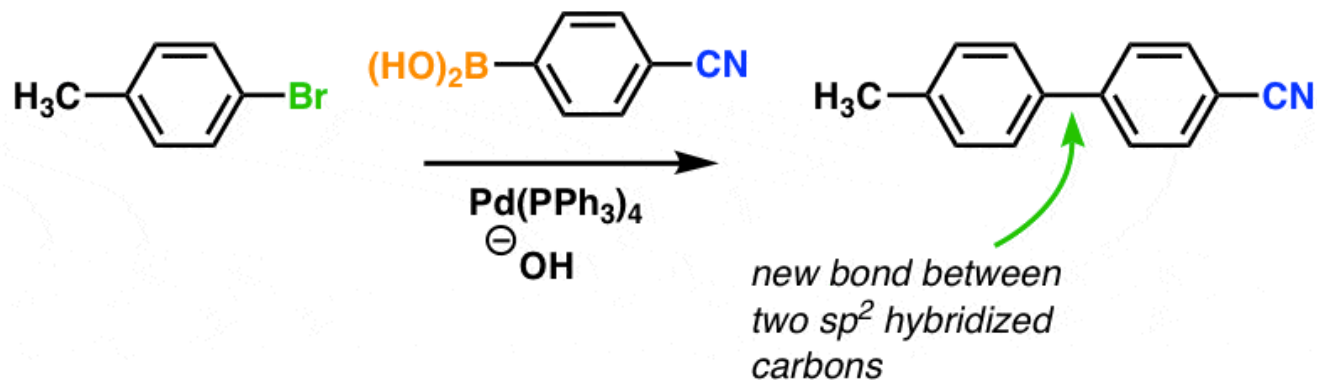


Reaction: The Suzuki reaction is a Pd-catalyzed reaction for forming a new C-C bond between an alkenyl or aryl **halide** (Br, Cl, or I or OTf) and an alkenyl or aryl **boronic acid** R-B(OH)₂ in presence of base such as K₂CO₃, NaOH or organic base such as triethylamine.

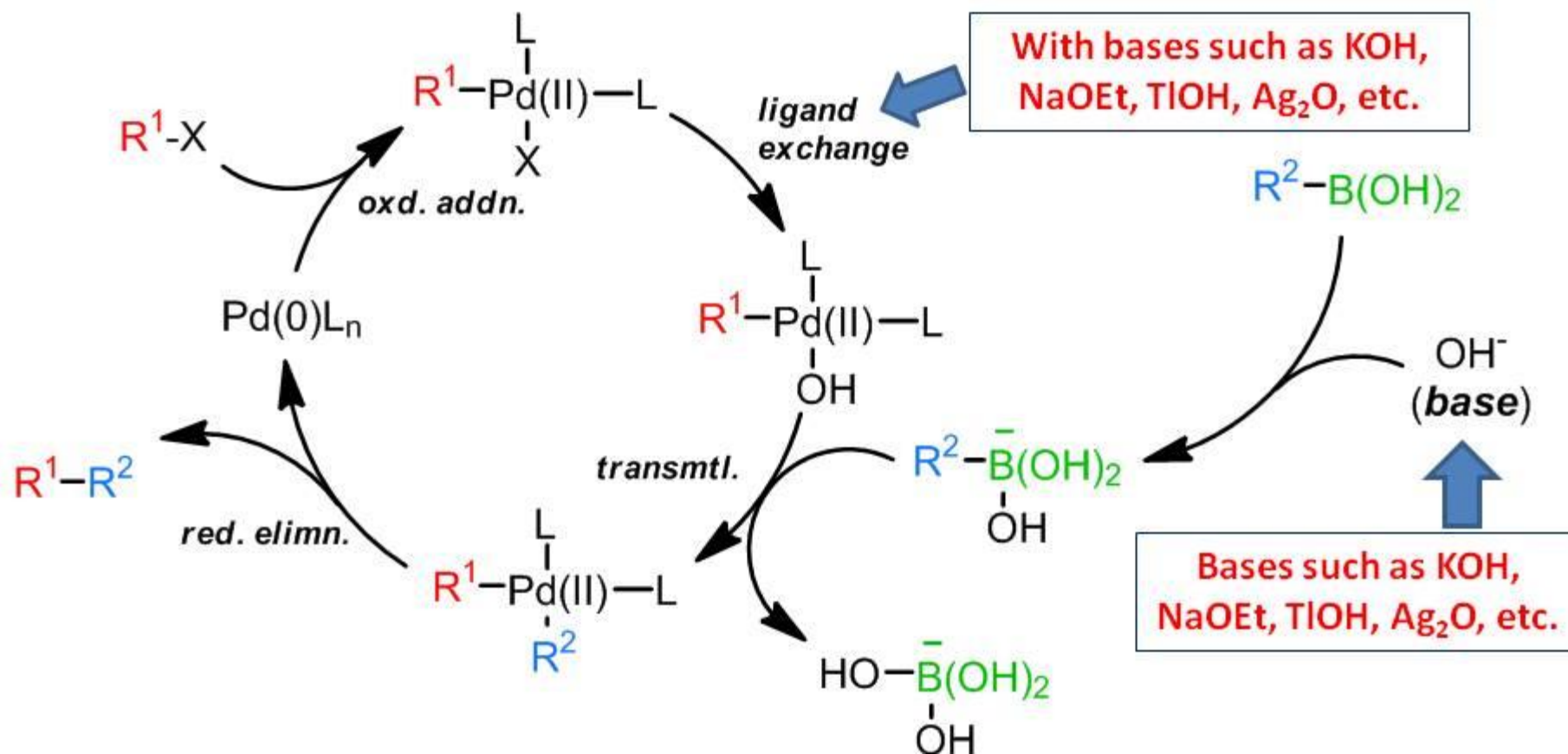
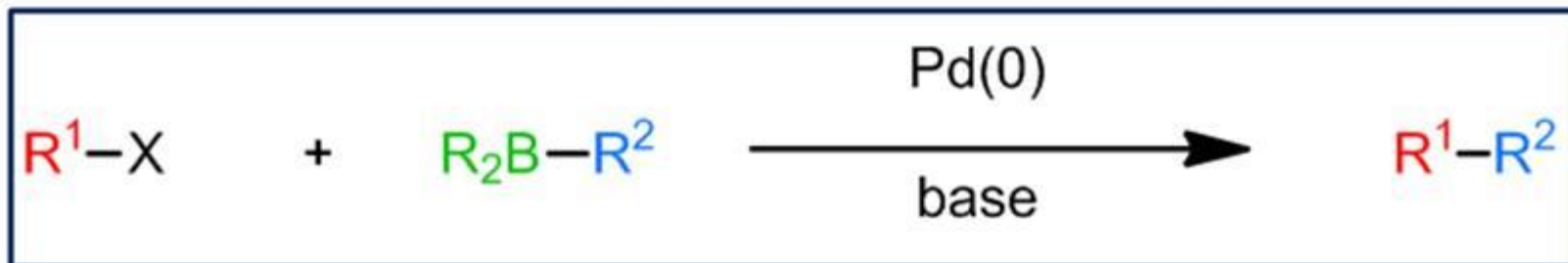


Generally used to couple together two sp^2 -hybridized carbons

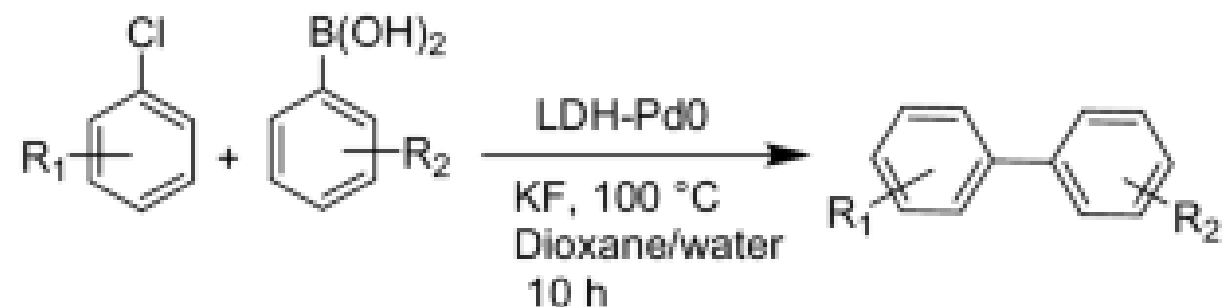
Another example:



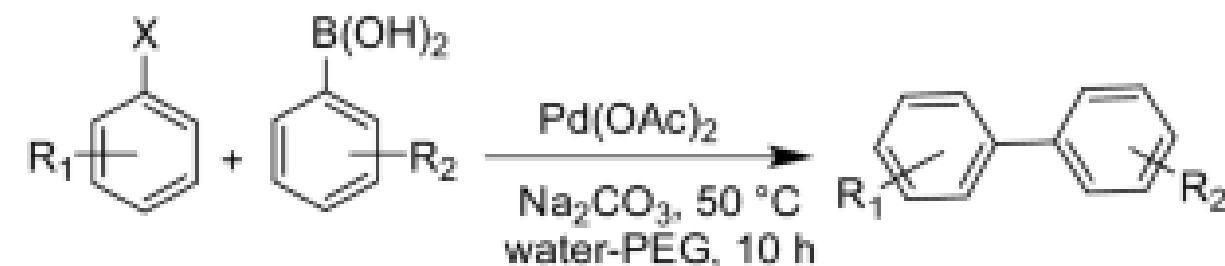
Suzuki-Miyaura Reaction mechanism:



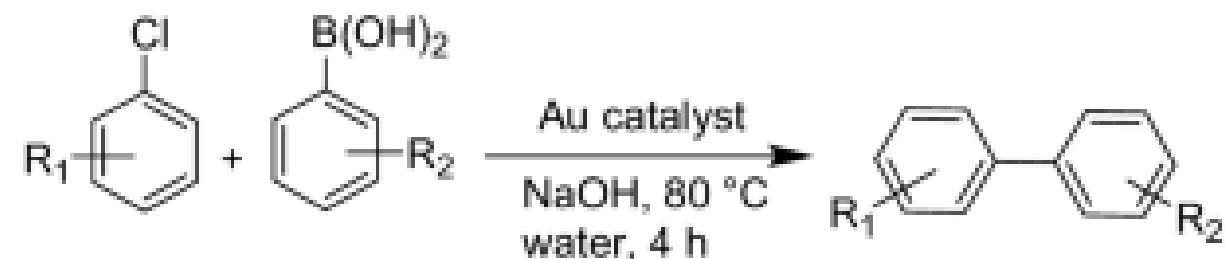
- i. Suzuki coupling reaction of chloroarenes using LDH-Pd0
B. M. Choudhary et al.



- ii. Phosphine-Free palladium acetate catalyzed Suzuki reaction in water Y. Zhang et al.



- iii. Suzuki coupling reaction of chloroarenes using gold nanoparticles R. Guo et al.

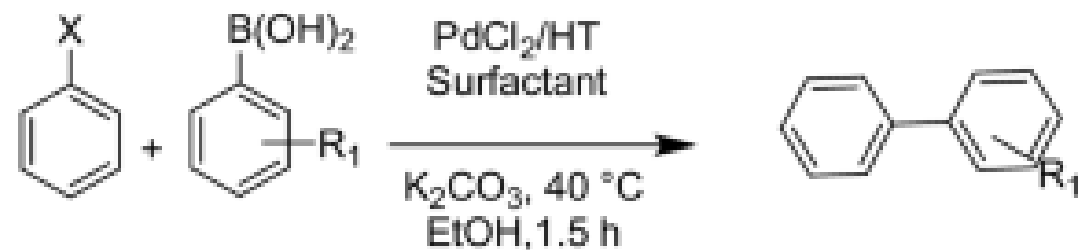


iv. Palladium-catalyzed, ligand-free Suzuki reaction in water

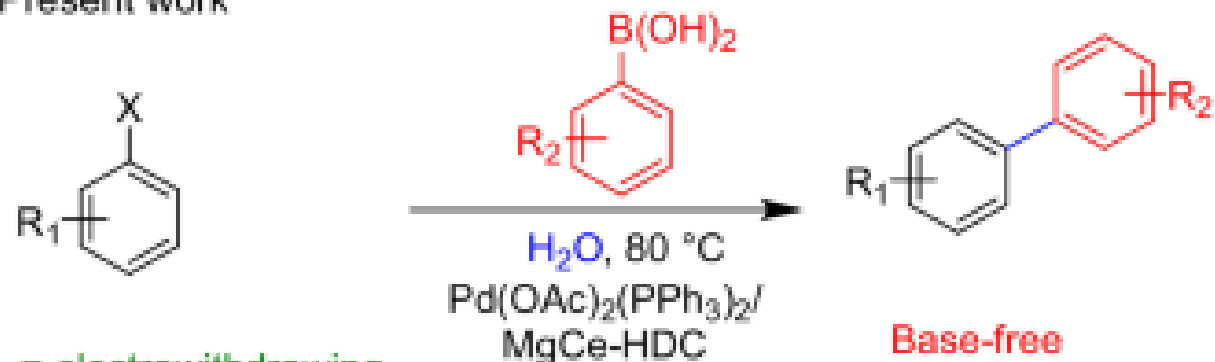
K. B. Sharpless and Biao Jiang et al.



v. Suzuki-Miyaura coupling reaction using hydrotalcite-supported palladium catalyst Kohki Ebitani et al.



vi. Present work



R_1 = electrowithdrawing,
electrodonating

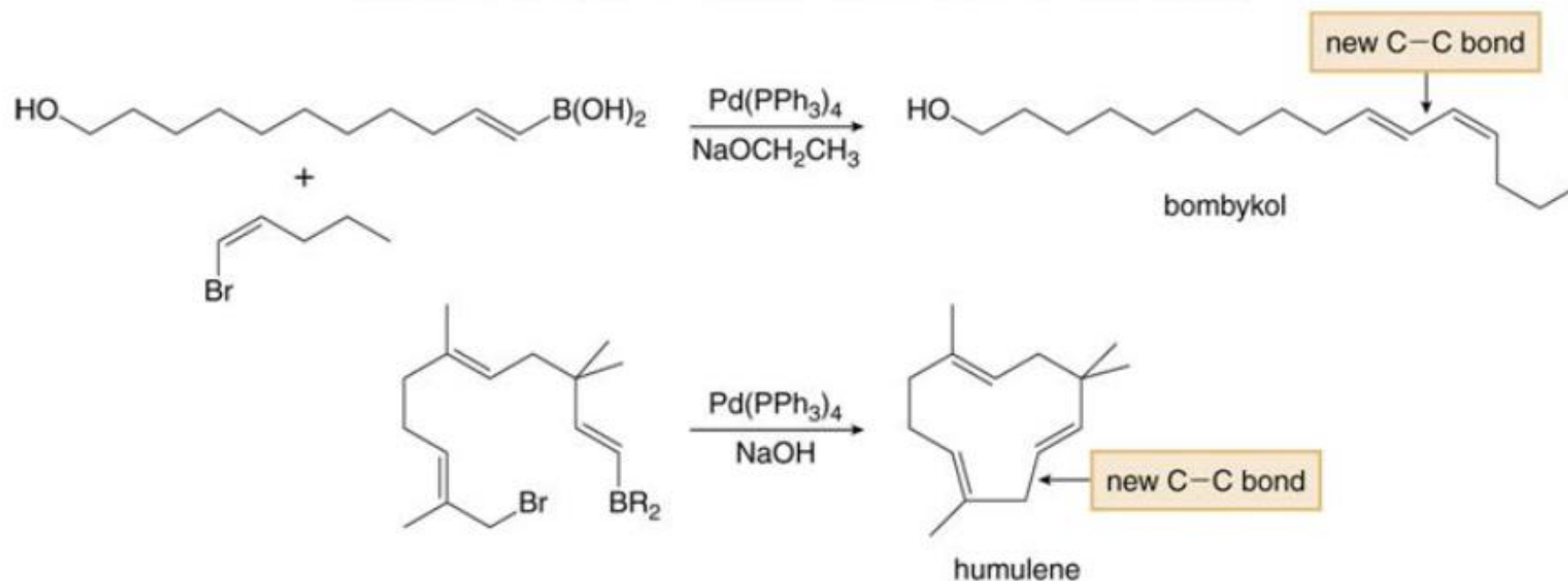
X = Br, I

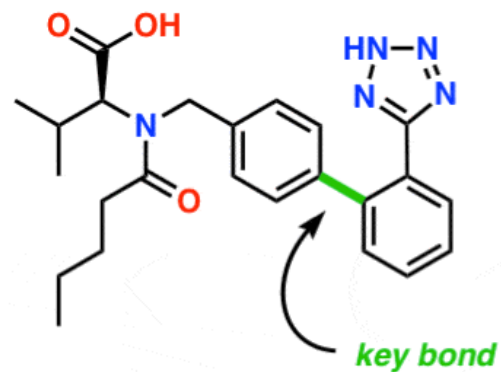
Base-free
35 examples
Yields of up to 90 %

- The Suzuki reaction was a key step in the synthesis of bombykol, the sex pheromone of the female silkworm moth.
- The synthesis of humulene illustrates that an intramolecular Suzuki reaction can form a ring.

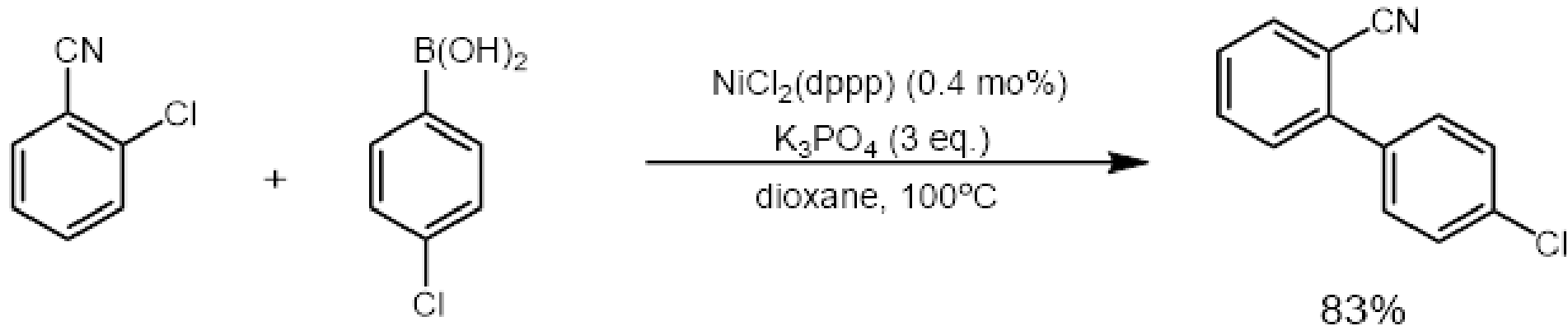
Figure 26.2

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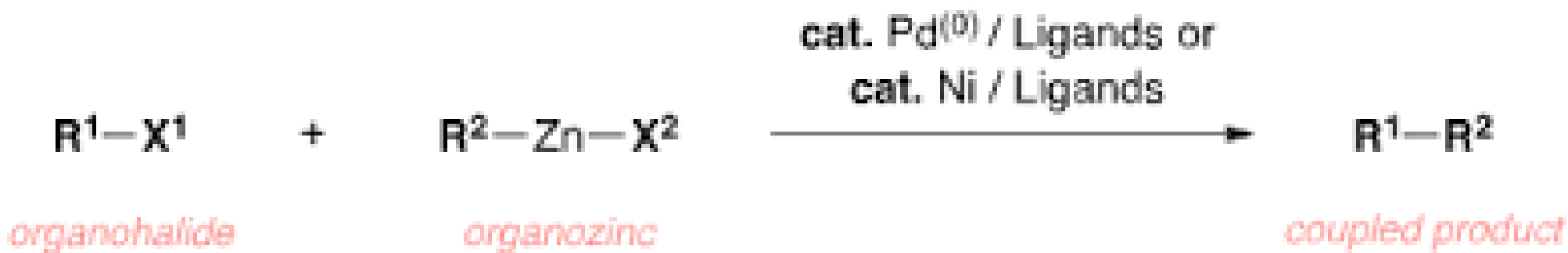


Valsartan
(antihypertensive drug)



Negishi cross-coupling Reaction



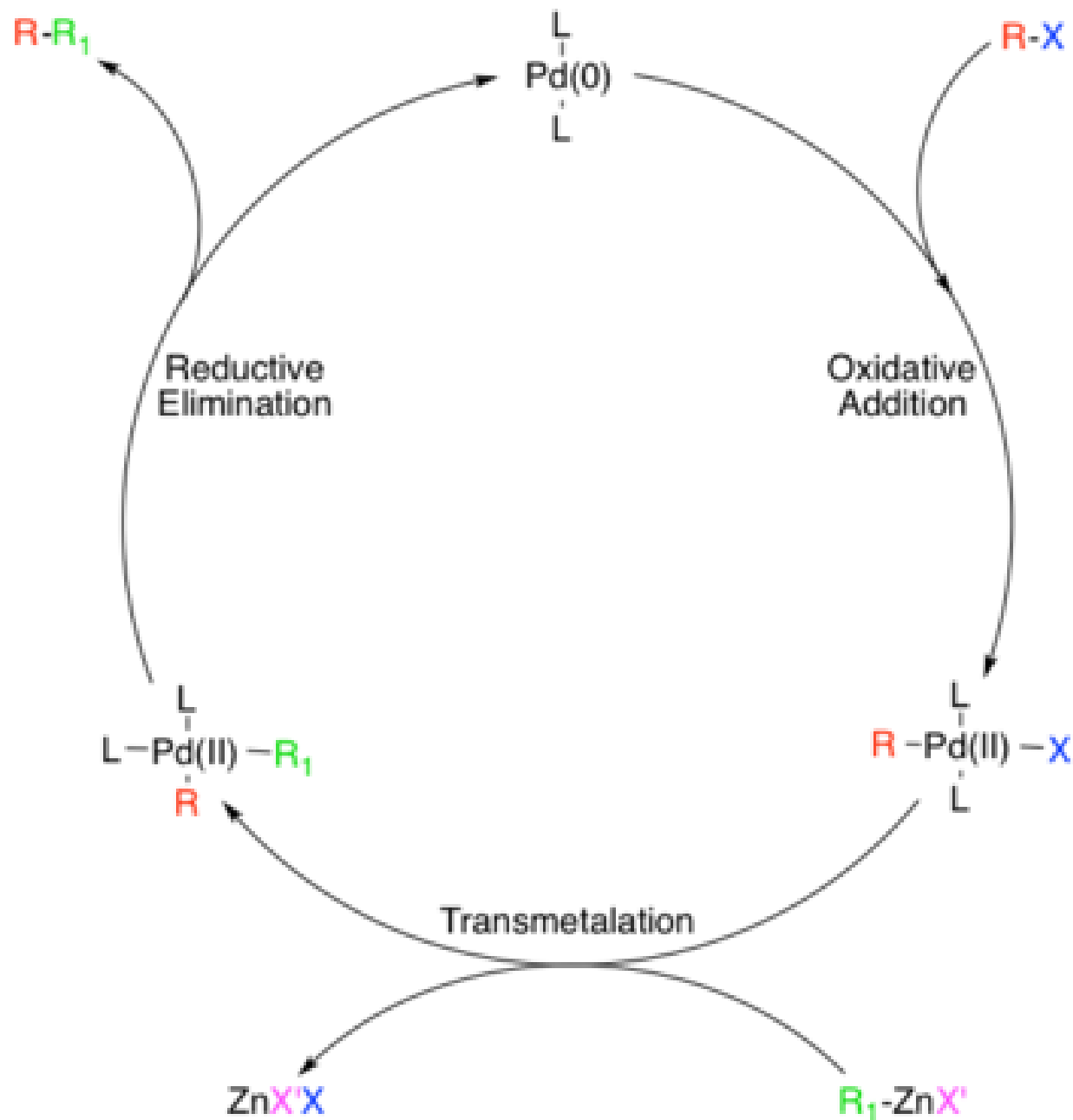


R^1 = aryl, alkenyl, alkynyl, acyl, ...

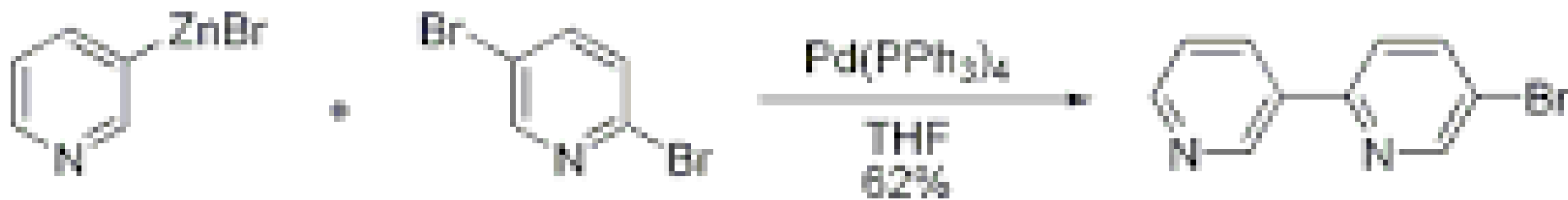
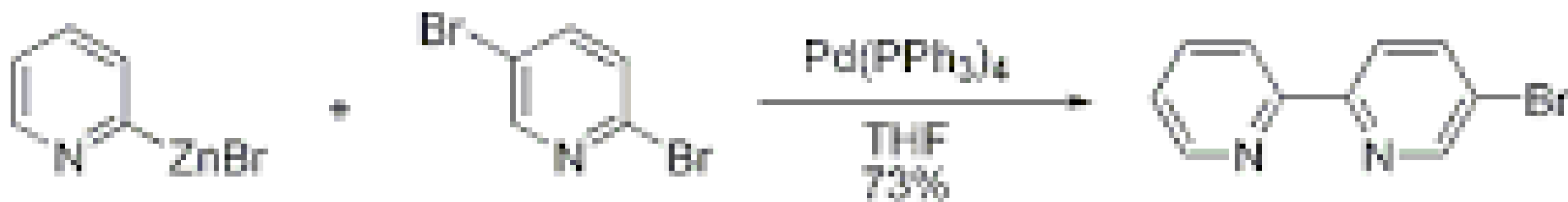
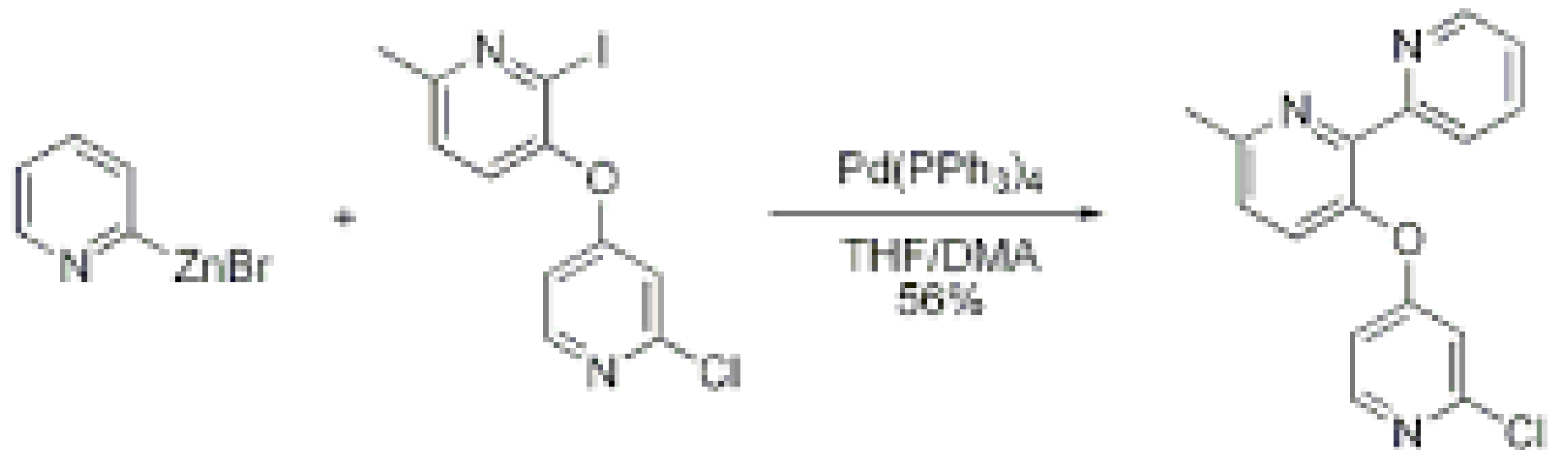
X^1 = Cl, Br, I, OTf, OAc

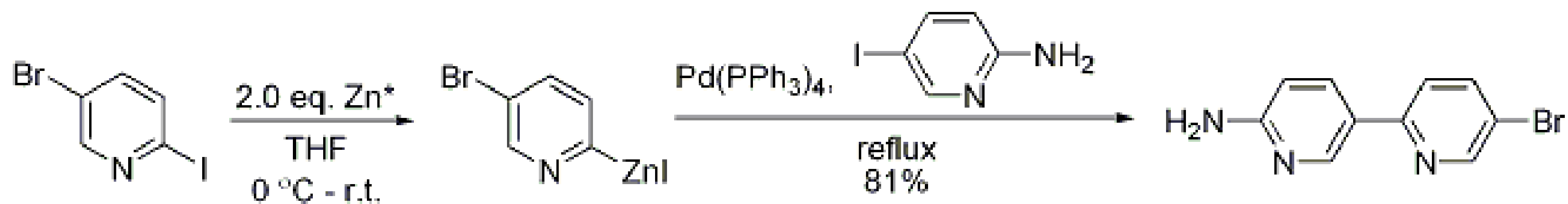
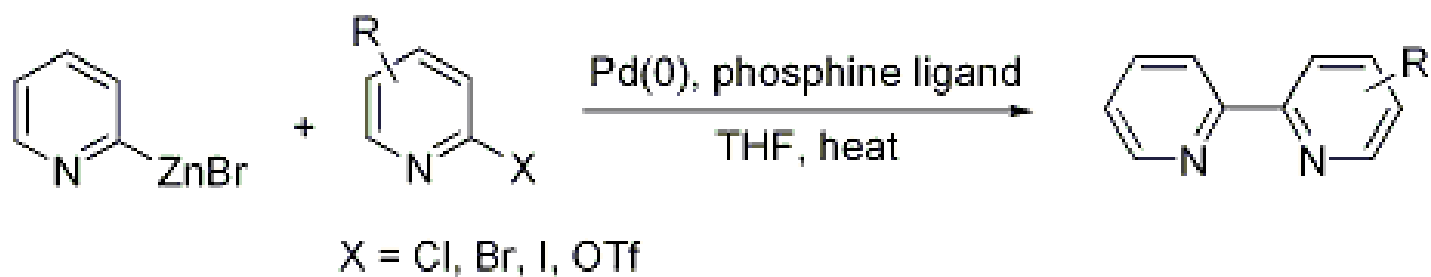
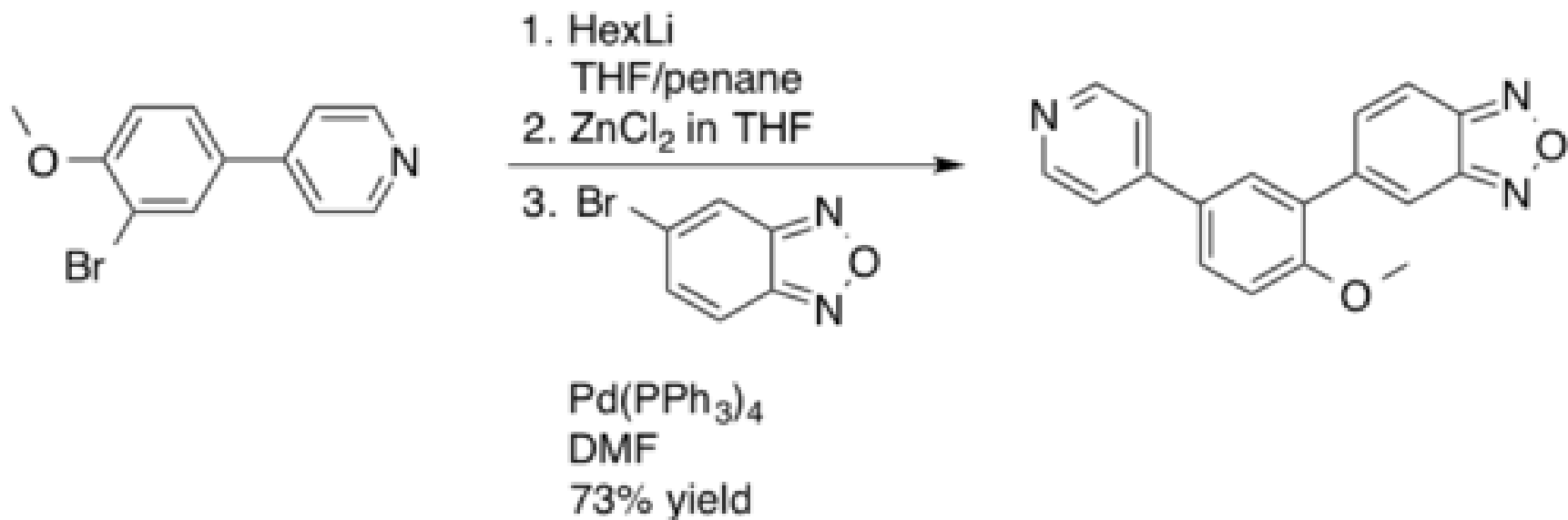
R^2 = aryl, alkenyl, allyl, benzyl, ...

X^2 = Cl, Br, I

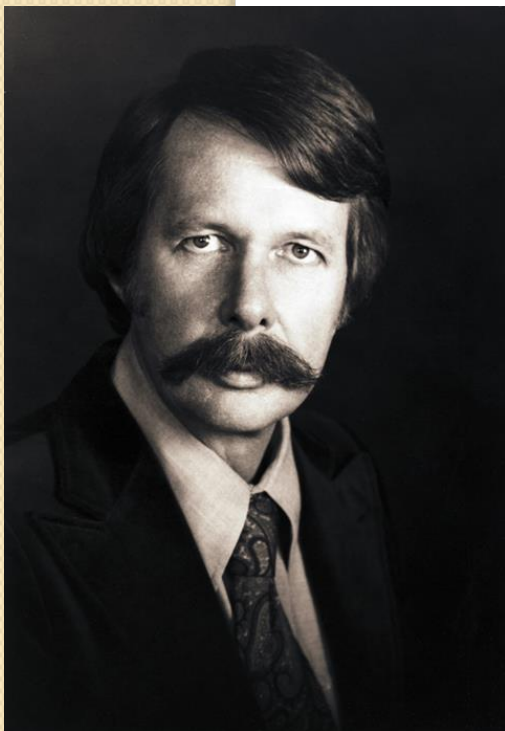
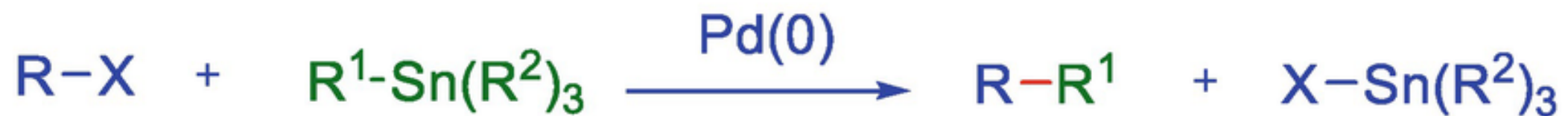


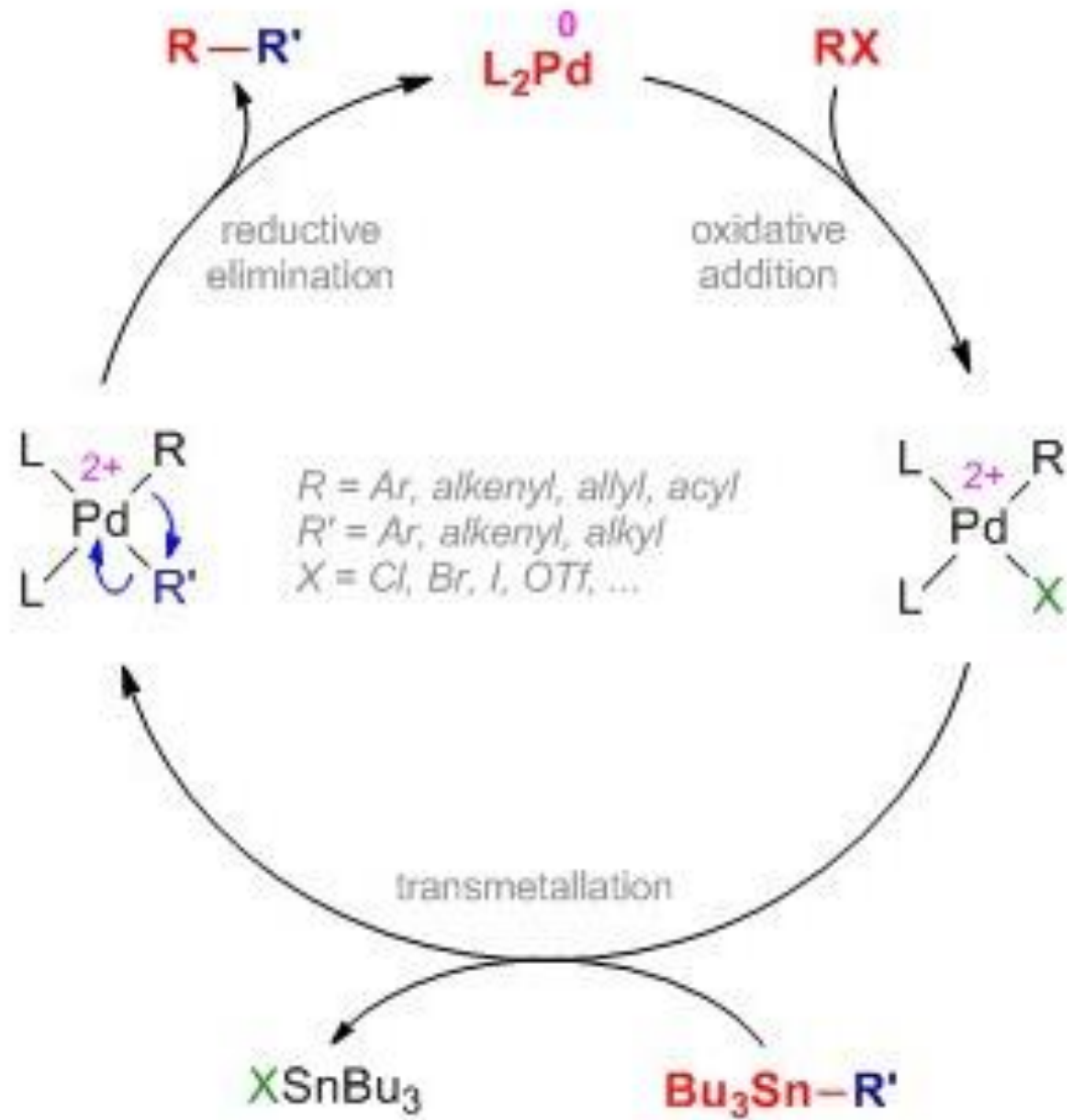
R = aryl, alkenyl, propargyl, acyl
R₁ = aryl, alkenyl, allyl, benzyl, homoallyl, homopropargyl
X = I, Br, Cl, OTf, OAc
X' = I, Br, Cl
L = ligand

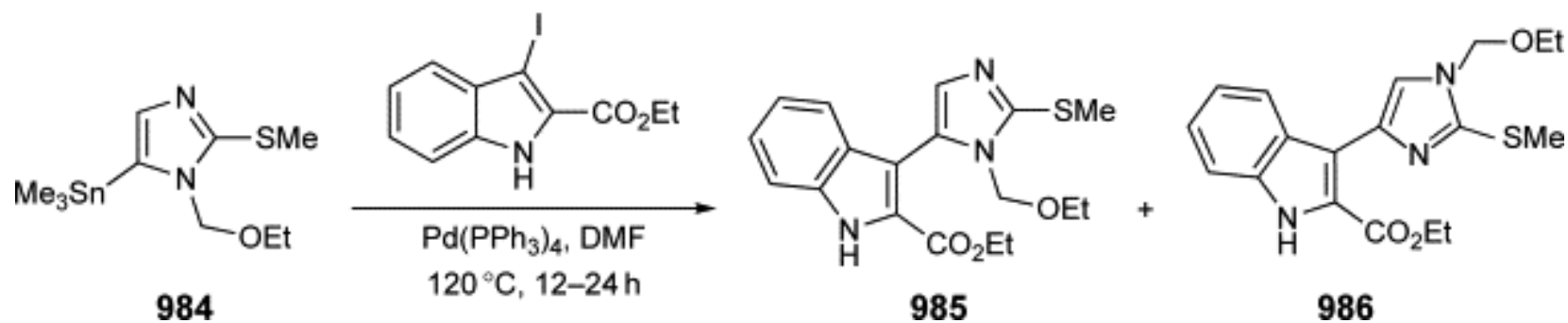
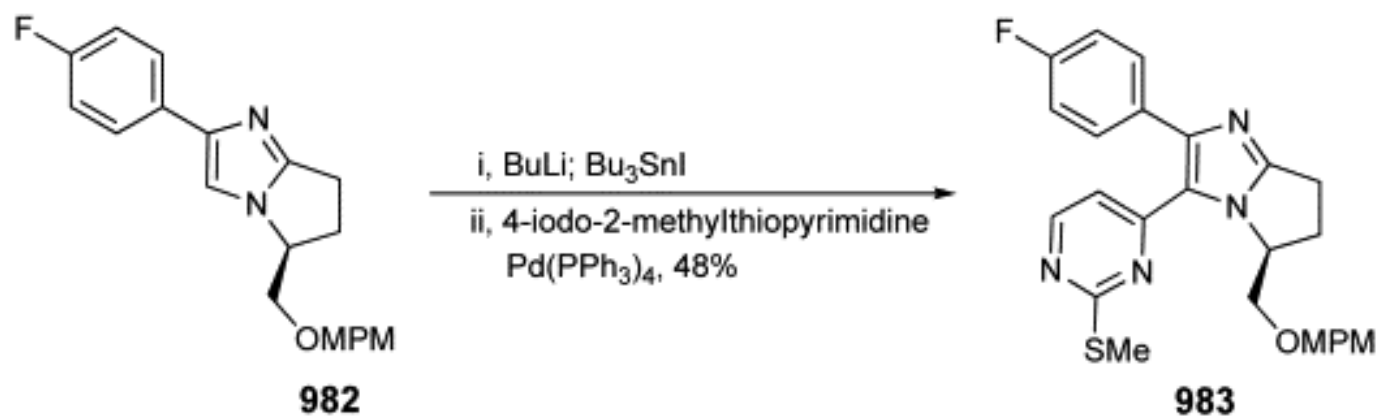
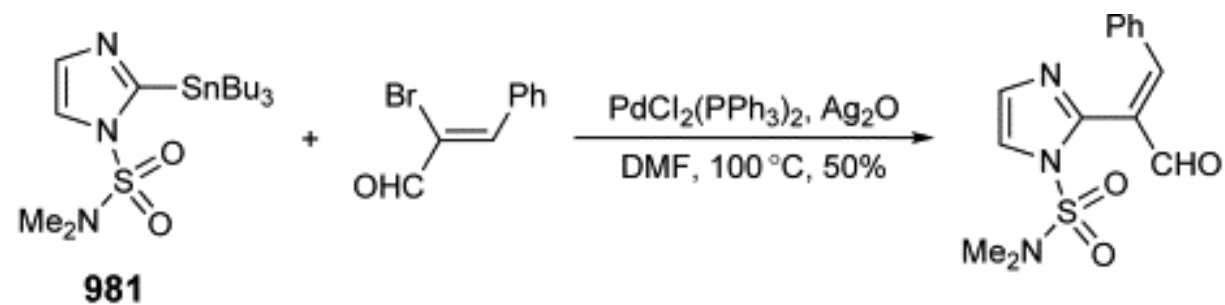


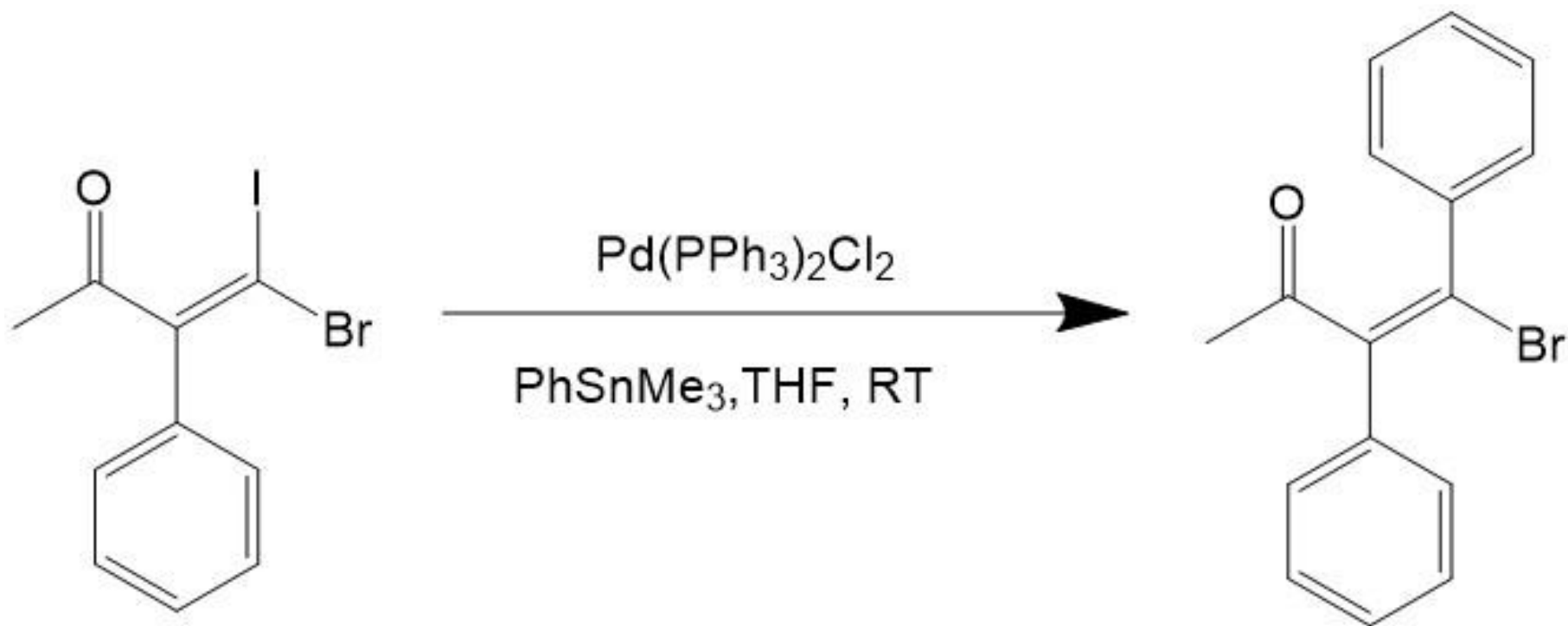
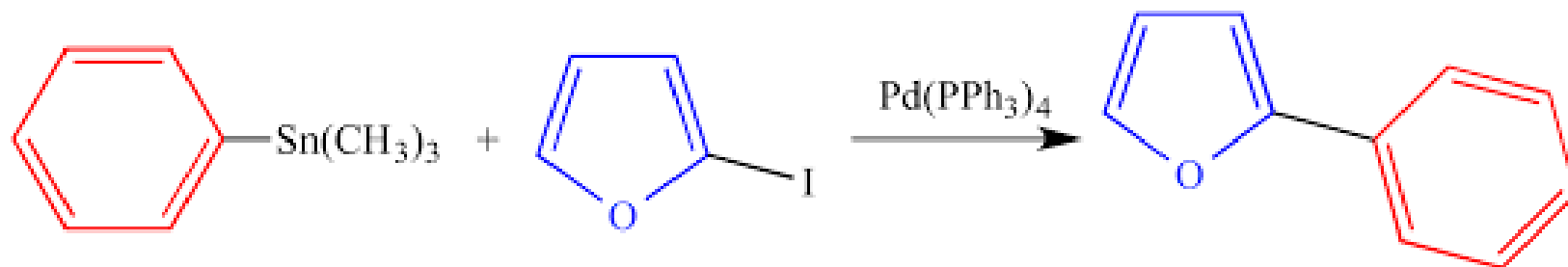


Stille cross-coupling Reaction

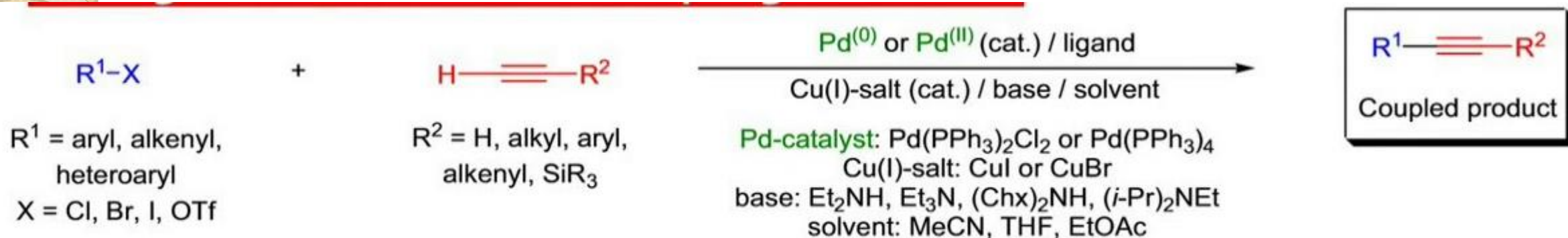








Sonogashira cross-coupling Reaction



Kenkichi Sonogashira



- **Discovery :-** In 1975, K. Sonogashira
- **The general features :**
- the coupling can usually be conducted at or slightly above room temperature, and this is a major advantage.
- the copper(I) salt can be the commercially available CuI or CuBr and are usually applied in 0.5-5 mol% with respect to the halide or alkyne

