CHM 203 Organic Chemistry-II

Unit-4: Formation of Carbon-Carbon Bonds via Organometallic Reagents

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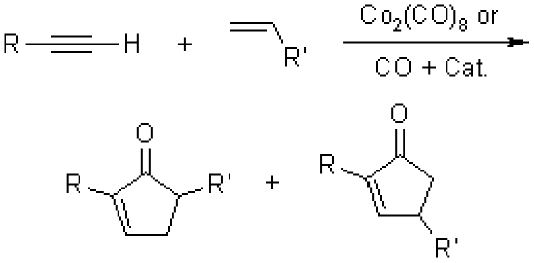
Organometallic Chemistry

- Transition metals extend the range of organic reactions.
- Some of the most exciting reactions are based on transition metals.

For Example:

Heck Reaction: The Pd-catalyzed arylation or alkenylation.

Pauson Khand Reaction:[2+2+1] cycloaddition of an alkyne, an alkene and carbon monoxide.



Simple guide to the stability of transition metal complexes: 18 electron rule

The rule states that thermodynamically stable transition metal organometallic compounds are formed when the sum of the metal d electrons and the electrons conventionally considered as being supplied by the surrounding ligands equals 18.

Example:

Tetrakis(triphenylphosphine)-palladium (0): $Pd(PPh_3)_4$

Pd (0) is the most widely used in homogeneous catalysis:

- Widely used both in industrial and academic laboratories.
- Variety of reactions can be catalyzed together with the range of functional groups tolerated.
- Excellent chemo- and regioselectivity.
- Most synthesis of big organic molecules now involve palladium chemistry in one or more key steps.
- One of the benefits of the Heck reaction is its outstanding trans selectivity.

Choice of Pd Complexes:

$Pd(PPh_3)_4$

$Pd_2(dba)_3$ [dba: dibenzylidene acetone]

$PdCl_2$ [exists as a polymer, relatively insoluble in most organic solvents]

$(PhCN)_2PdCl_2$

$(MeCN)_2PdCl_2$

Basic Chemistry of Pd: dominated by two oxidation states

Pd (0):

1. Normally electron rich nucleophilic species
2. Prone to oxidation, ligand association, insertion and oxidative coupling reactions.
3. Will undergo oxidative addition with suitable substrates such as halides and triflates.

Pd (II):

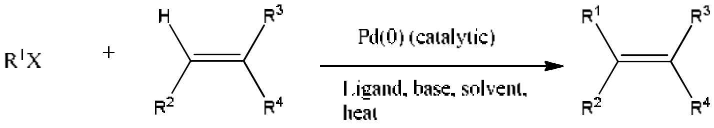
Electrophilic and undergo ligand association and reductive coupling reactions.

Basis of Pd Chemistry:

1. Oxidative addition
2. Transmetalation
3. Reductive elimination

Heck Reaction (Mizoroki-Heck reaction):

Couples an alkene with a halide or triflate (OSO_2CF_3) to form a new alkene.



R^1 = aryl, benzyl, vinyl (alkenyl), alkyl (no beta hydrogens).

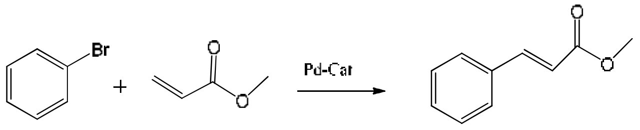
R^2, R^3, R^4 = alkyl, aryl, alkenyl.

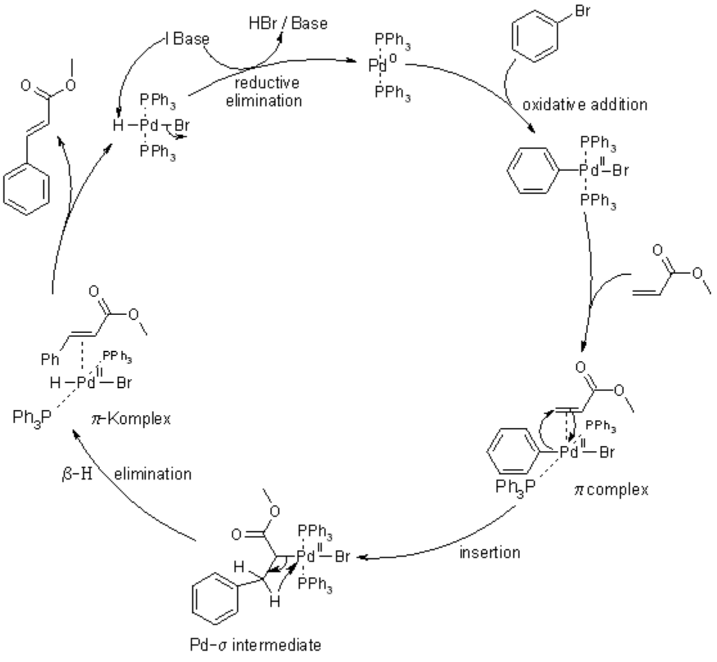
X = Cl, Br, I, OTf, OTs, N_2^+

Ligand = trialkylphosphines, triarylphosphines, chiral phosphines.

Base = *sec*- or *tert*-amine, KOAc, NaOAc, $NaHCO_3$.

Heck Reaction and Mechanism:





Examples:

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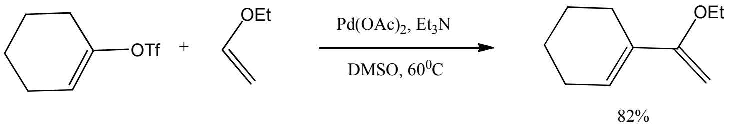
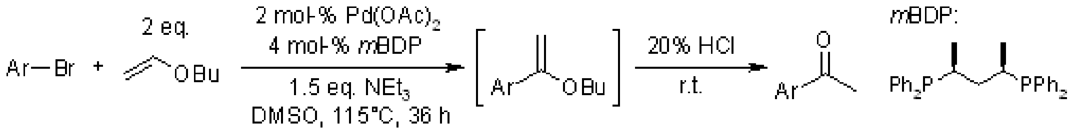
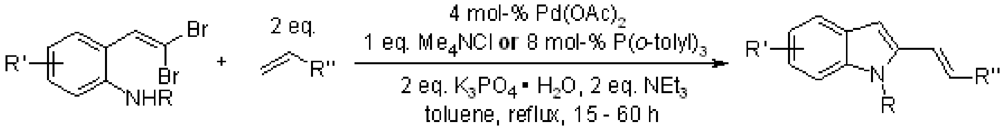


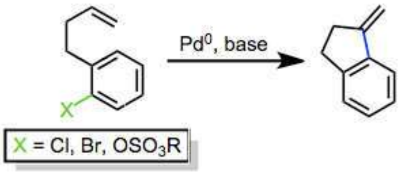
2. *J. Org. Chem.*, **2006**, *71*, 7467-7470.

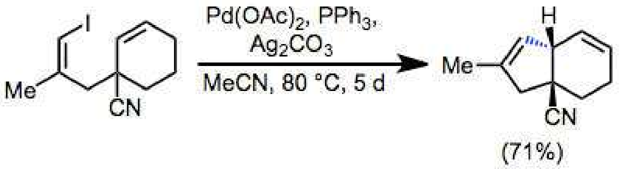


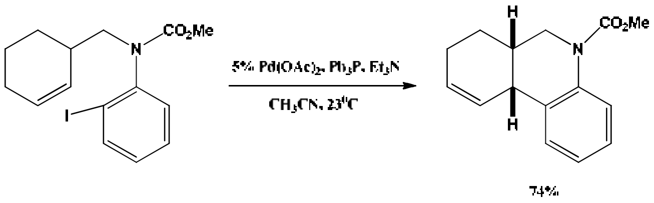
3. *Org. Lett.*, **2006**, *8*, 4203-4206.



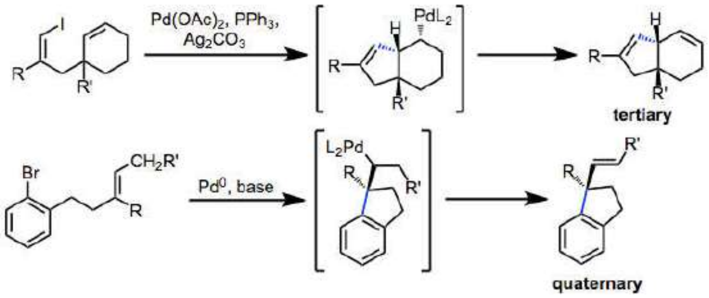
Intramolecular Heck Reaction:

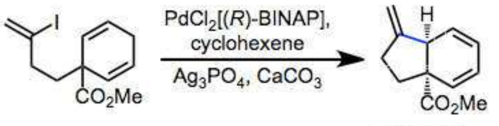






Establishing Tertiary or Quaternary Stereocenters:





(72%) 86% ee

Suzuki Coupling/ Suzuki–Miyaura reaction:

- Pd-catalyzed cross coupling between organoboronic acid and halides.
- Widely used to synthesize poly-olefins, styrenes, and substituted biphenyls.

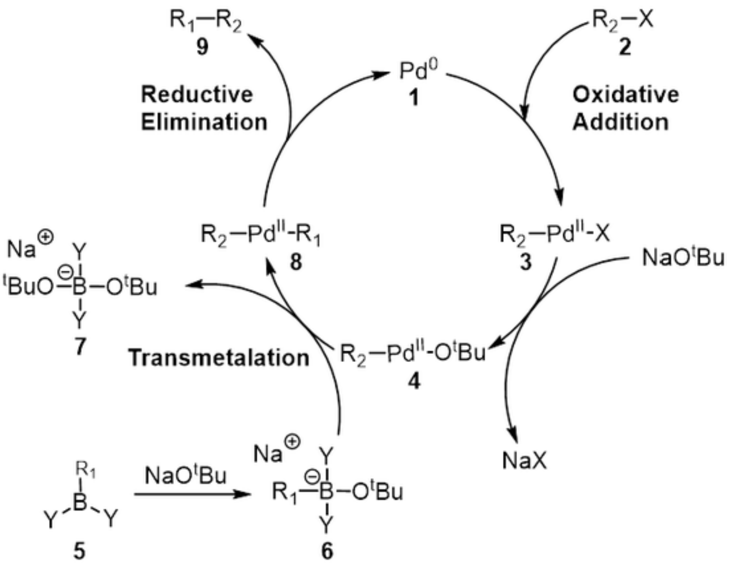
$$R^1{-}B(R)_2 \quad + \quad R^2{-}X \xrightarrow[\text{base, ligand}]{\text{Pd (0) (catalytic)}} \underset{\text{Coupled product}}{R^1{-}R^2} \quad + \quad X{-}B(R)_2$$

R^1 = alkyl, allyl, alkenyl, alkynyl, aryl
R = alkyl, OH, O-alkyl
R^2 = alkenyl, aryl, alkyl
X = Cl, Br, I, OTf, OPO(OR)$_2$ (enol phosphate)
Base = Na_2CO_3, $Ba(OH)_2$, K_3PO_4, Cs_2CO_3, K_2CO_3, TiOH, KF, CsF, Bu_4NF, NaOH, $M^+(^-O$-alkyl)

Reaction Mechanism: Involves 4 Steps

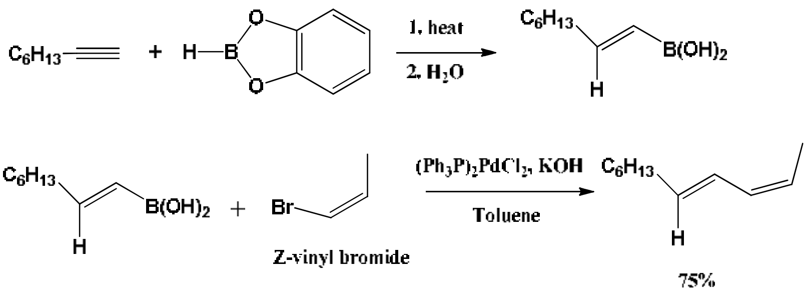
1. Oxidative addition of palladium catalyst **1** to the halide **2** to form the organopalladium species **3**.
2. Reaction (metathesis) of **3**with baseto give intermediate **4.**
3. Transmetalation of **4**with the boron-atecomplex **6** (by reaction of the boronic acid **5** with base) to formthe organopalladium species **8**.
4. Reductive elimination of the desired product **9** along with restoration of the original palladium catalyst **1** which completes the catalyticcycle.

Trialkyl borate (R_3B-OR) could be considered as being more nucleophilic and then more reactive towards the palladium complex present in the transmetalation step.

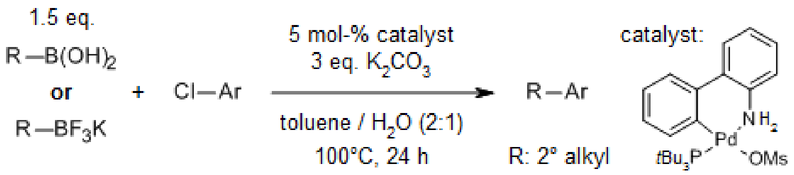


Examples:

1.

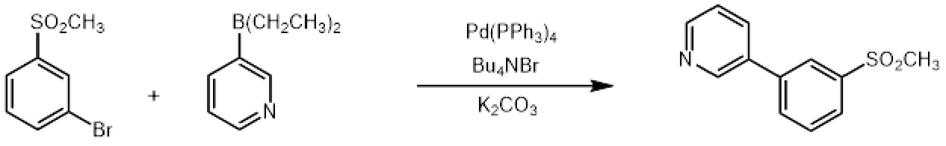


2. *J. Am. Chem. Soc.*, **2014**, *136*, 14027-14030.



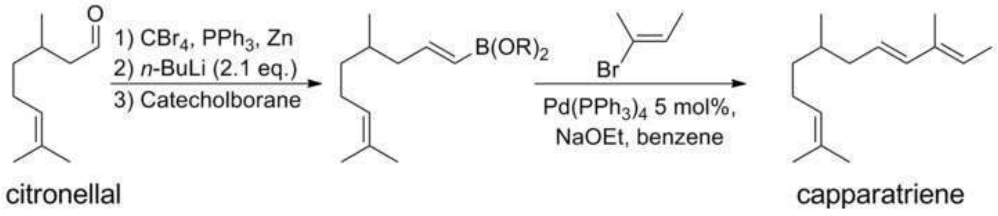
Industrial application

Coupling of 3-pyridylborane and 1-bromo-3-(methylsulfonyl)benzene to form an intermediate that is used in the synthesis of a potential central nervous system agent.

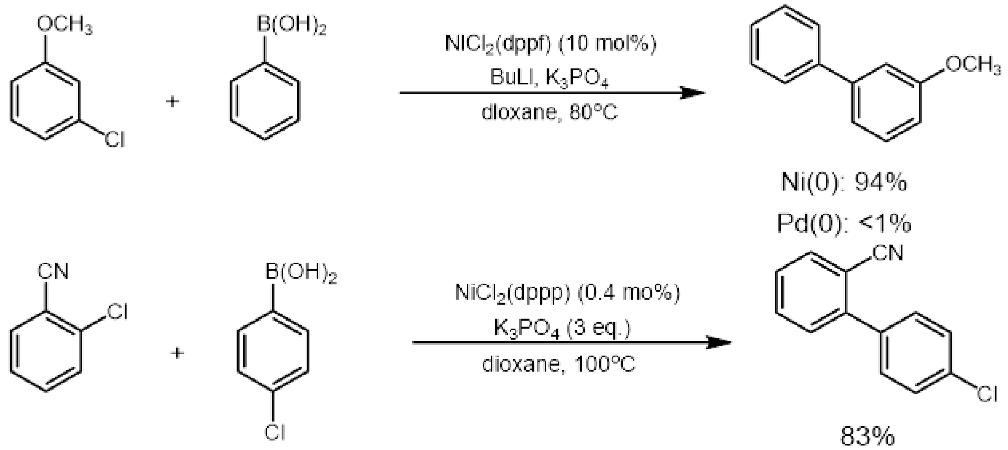


Synthetic applications:

Used a citronellal derivative for the synthesis of caparratriene, a natural product that is highly active against leukemia.



Variations: Metal Catalysts

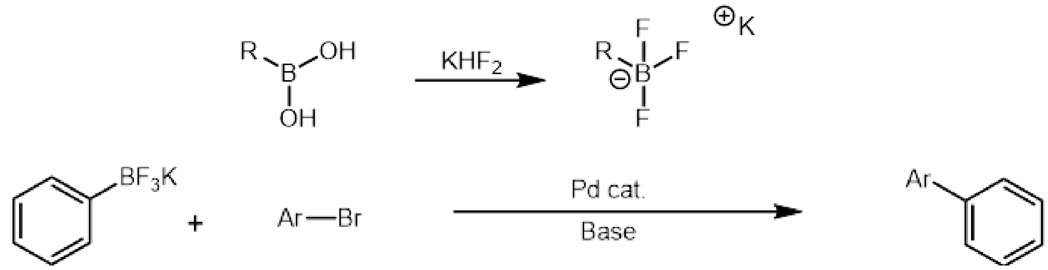


Organoboranes

Aryl boronic acids: comparatively cheaper than other organoboranes and commercially available.

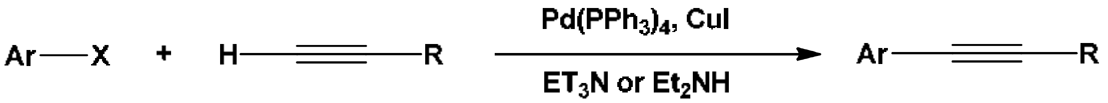
Aryltrifluoroborate salts:

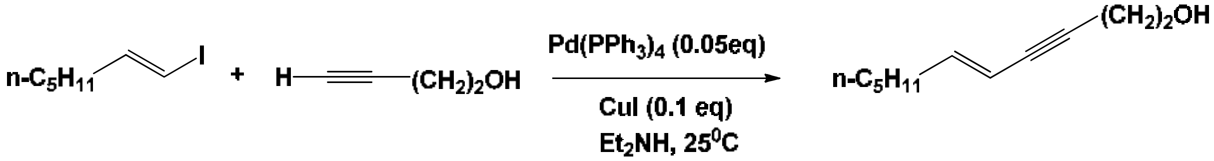
1. less prone to protodeboronation compared to aryl boronic acids.
2. can be formed from boronic acids by the treatment with potassium hydrogen fluoride .

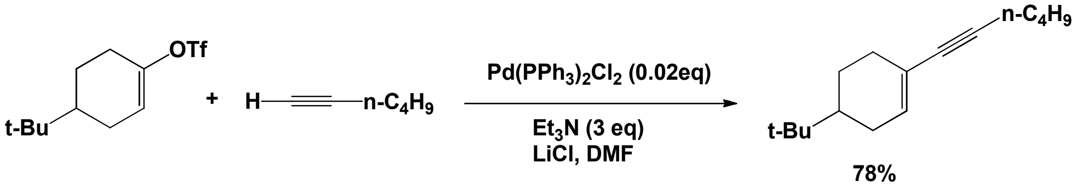


Sonogashira Coupling: (1975, K. Sonogashira& co-workers)
(Catalytic version of the Castro-Stephans reaction)

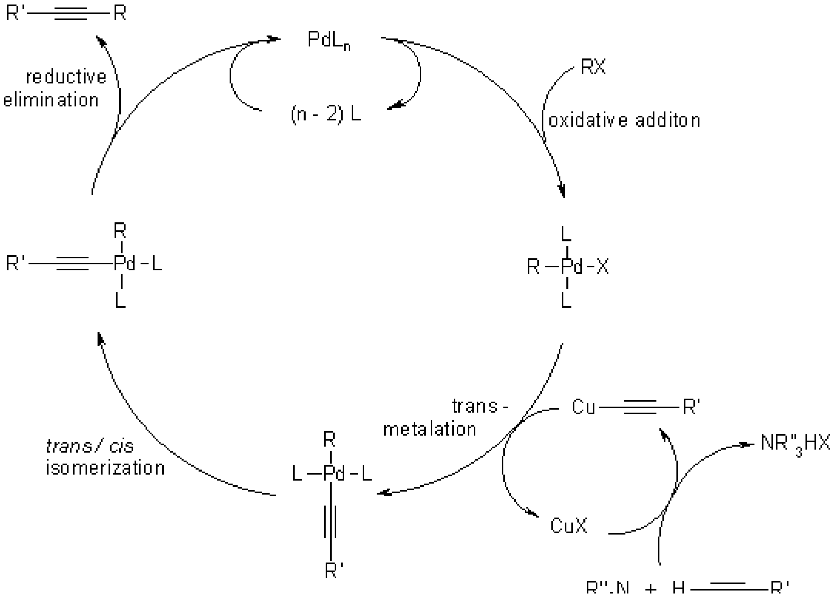
- Coupling of terminal alkynes with aryl or vinyl halides.
- Use of Pd (0) complex as catalyst.
- Use of copper iodide as co-catalyst.
- Performed in the presence of base.
- Mild conditions, frequently RT.







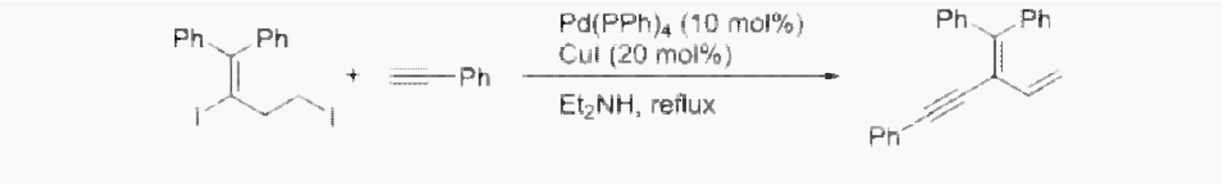
Mechanism:



Applications in Synthesis:

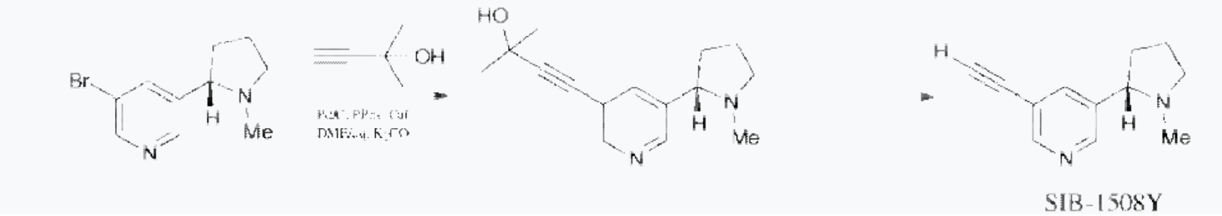
Enynes and enediynes

Synthesis of alk-2-ynylbuta-1,3-dienes from the cross-coupling of a diiodide and phenylacetylene, as shown below.

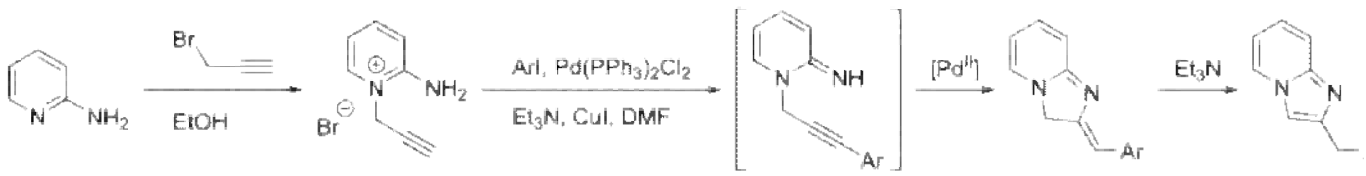


Pharmaceuticals

Synthesis of SIB-1508Y (commonly known as Altinicline) has potential in the treatment of Parkinson's disease, Alzheimer's disease, etc.



Synthesis of imidazopyridine derivatives



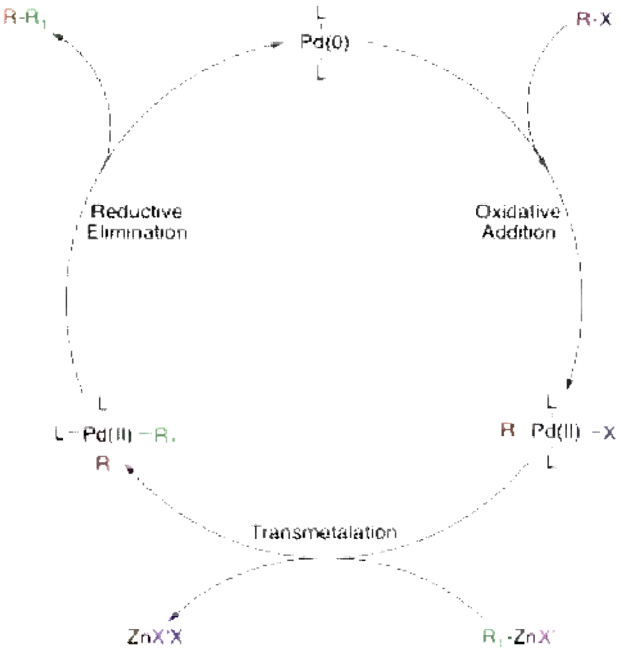
Negishi Coupling (1977):

- Couples organic halides or triflates with organozinc compounds, forming unsymmetrical biaryls(c-c) in good yields.
- Palladium (0)speciesis generally utilized as the metal catalyst (higher yield and and higher functional group tolerance), though nickel is sometimes used.
- Allows the coupling of sp^3, sp^2, and sp carbons, which make it somewhat unusual among the Palladium-catalyzed coupling reactions.
- Organozincs are moisture and air sensitive (less robust conditions: must be performed in an oxygen and water free environment). However, organozincs are more reactive than both organostannanes and organoborates which correlates to faster reaction times.

$$RX \;+\; R'ZnX \xrightarrow[Cl_2Pd(PPh_3)_2 \;+\; 2(i\text{-}Bu)_2AlH]{Ni(PPh_3)_4 \quad \text{or}} R\text{-}R'$$

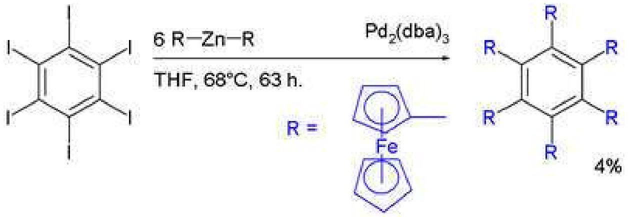
R = alkenyl, aryl, allyl, benzyl, propargyl
R' = akenyl, aryl, alkynyl, alkyl, benzyl, allyl

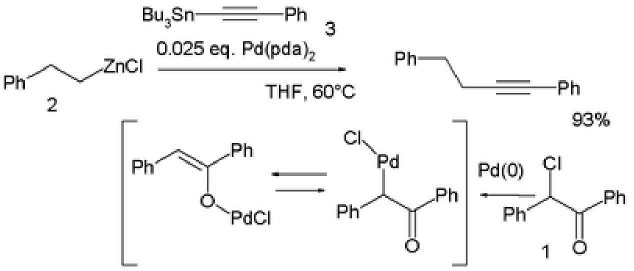
Mechanism:



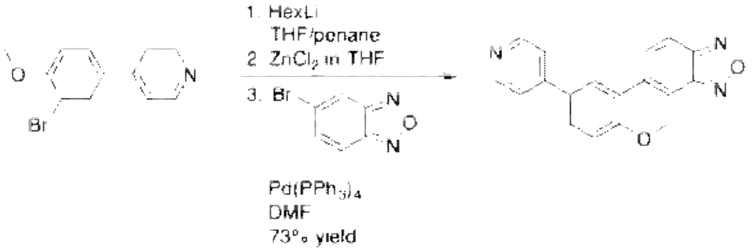
R = aryl, alkenyl, propargyl, acyl
R_1 = aryl, alkenyl, allyl, benzyl, homoallyl, homopropargyl
X = I, Br, Cl, OTf, OAc
X' = I, Br, Cl
L= ligand

Scope:

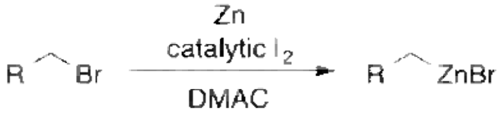




Industrial application: Benzodioxazole synthetic intermediate



Alkylzinc reagents: can be accessed from the corresponding alkyl bromides using iodine in dimethylacetamide (DMAC). The catalytic I_2 serves to activate the zinc towards nucleophilic addition.



Aryl zincs can be synthesized using mild reaction conditions via a Grignard like intermediate.

Organozinc Reagents

- C–Zn bond is highly covalent and hence less reactive, allowing the prepn of functionalized derivatives.
- Centered around the preparation and utilization of functional organic compounds in organic syntheses.

Preparation of Organozinc Compounds:

Alkylzinc Iodides:

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

Rieke metals — highly reactive metals prepared by the methods developed by R. D. Rieke.

- usually prepared by a reduction of a THF suspension of an anhydrous metal chloride with an alkali metal (K, Na & Li).
- highly reactive because they have high surface area and lack surface oxides which retard rx.

R: alkyl, aryl, benzyl, allyl

X: Br, I

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

Dialkylzincs

$$2\ i\text{-}BuMgBr + ZnCl_2 \longrightarrow i\text{-}Bu_2Zn + 2\ MgClBr$$

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

Zinc Carbenoids (carbene-like species)

$$CH_2I_2 \xrightarrow[Et_2O,\ \text{THF or DME}]{\text{Zn activation}} \text{“}\underline{2\ ICH_2ZnI}\text{”} \rightleftharpoons (ICH_2)_2Zn-ZnI_2$$

↓

Simmons-Smith reagent used for cyclopropanation of alkenes.

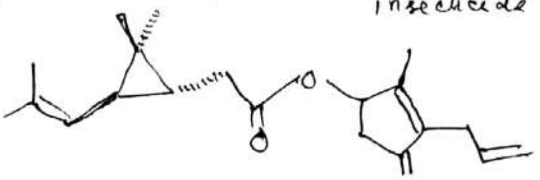
$$CH_2I_2 \xrightarrow[CH_2Cl_2\ \text{or}\ Cl(CH_2)_2Cl]{Et_2Zn} EtZnCH_2I \text{ and/or } Zn(CH_2I)_2$$

↓

Furukawa's reagent

Cyclopropanation

Cyclopropane rings — in many natural pdts such as pyrethrin - a natural insecticide

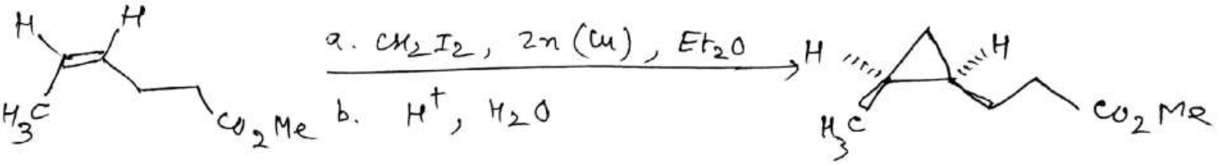


Pyrethrin

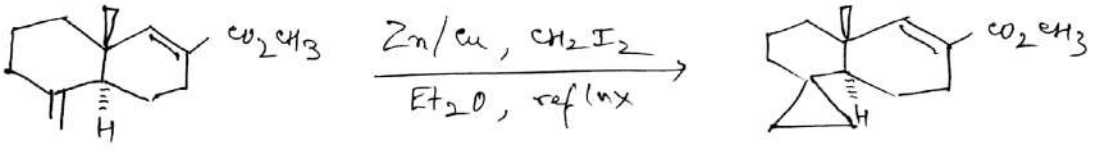
1958 : Simmons & Smith

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

diiodomethane   zinc-copper couple



- stereospecific syn-addition of a Zn-carbenoid (carbene-like species) to the double bond without the involvement of a free carb

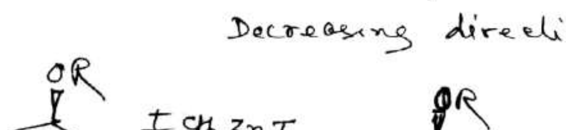


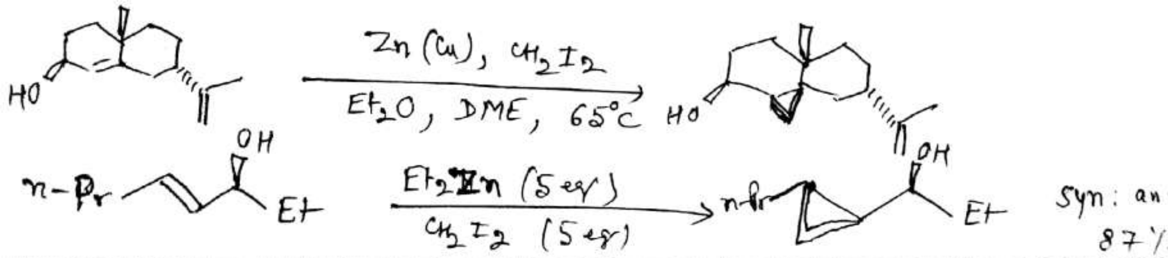
chemoselectivity — zinc carbenoids are electrophilic and react chemoselectively with the more nucleophilic double bond in dienes and polyenes.

Directed Simmons - Smith cyclopropanation

- stereoelectronic control exhibited by proximal OH, OR groups which favour cyclopropanation to occur from the same face of the double bond as the oxy substituents

Decreasing directive effects : OH > OR > C=O





syn : anti > 100 : 1
87 %

organocopper ①

Organocopper Reagents

- Offer a very efficient method for coupling of two different carbon moieties.
- Three useful changes in reactivity, since Cu is less electropositive than ~~Li~~ Li and Mg.

(i) • The organocopper reagents react with alkyl-, alkenyl- and aryl halides to give alkylated products.

(ii) • The organocopper reagents are more selective and can be acylated with acid chlorides without concommitant attack on ketones, alkyl halides and esters.

(iii) In rx with α, β- unsaturated carbonyl compounds, the organocoppe reagents prefer 1,4- over 1,2 - addition.

Prepn of Organocuprates

Homocuprate Reagents

(Gilman Reagents : R_2CuLi, R_2CuMgX,
- thermally labile and thus are ~~prepd~~ prepd at low temp.

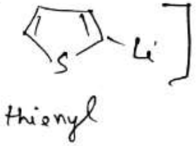
$$RM + Cu(I)Br, I \xrightarrow[-MBr,\ I]{Et_2O \text{ or } THF} (RCu)_n \overset{RM}{\rightleftarrows} R_2CuM$$

M = Li, MgX

Heterocuprate Reagents

- thermally more stable.

$$R_2NLi + CuBr.SMe_2 \xrightarrow{THF} R_2NCu.SMe_2.LiBr \xrightarrow{R'Li} [R_2NCuR']Li$$

R Li + [] + CuI ⟶ [(2-thienyl)CuR] Li

2-thienyl

$$RLi + Me_3SiCH_2Li + CuI \longrightarrow [(Me_3SiCH_2)CuR]Li$$

Reactions of organocuprates

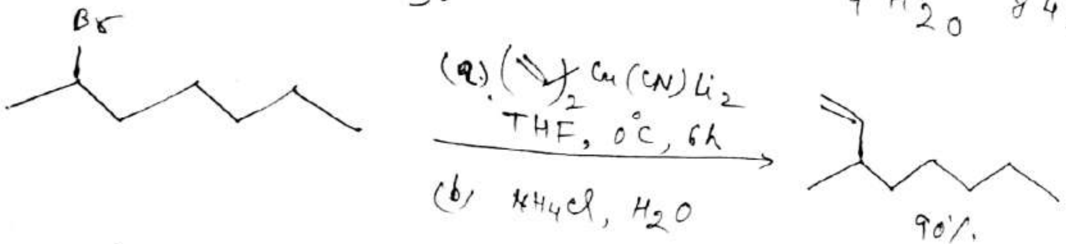
Substitution of alkyl halides

$$Me_2CuLi\ (3\ eq) \xrightarrow[b.\ H_3O^+]{a.\ n-C_8H_{17}I,\ Et_2O,\ -20^\circ C} n-C_9H_{20}\quad 97\%$$

(11% based on MeLi

$$[MeCuNR_2]Li \xrightarrow[b.\ H_3O^+]{a.\ n-C_8H_{17}I,\ Et_2O,\ rt} n-C_9H_{20}\quad 84\%$$

✓



90%.

Mech: via a SN2 displacement or via an oxidative addition ~~follo~~ followed by reductive elimination.

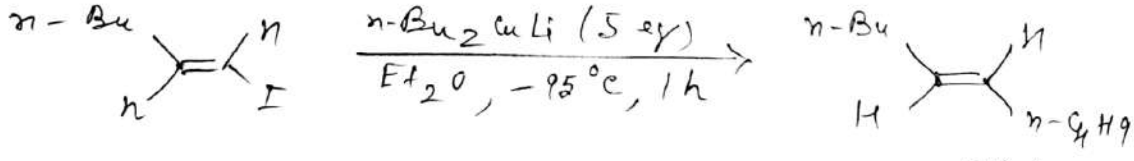
Substitution of Allylic halides

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

$$CH_3CH=CHCH_2Cl + n-BuCu\cdot BF_3 \xrightarrow{THF-hexane} CH_3-\underset{\substack{|\\ n-Bu}}{CH}CH=CH_2$$

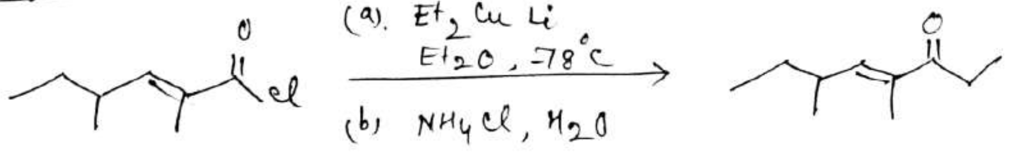
80%.
(>98% isomerically pure

Rx with Vinyl Halides



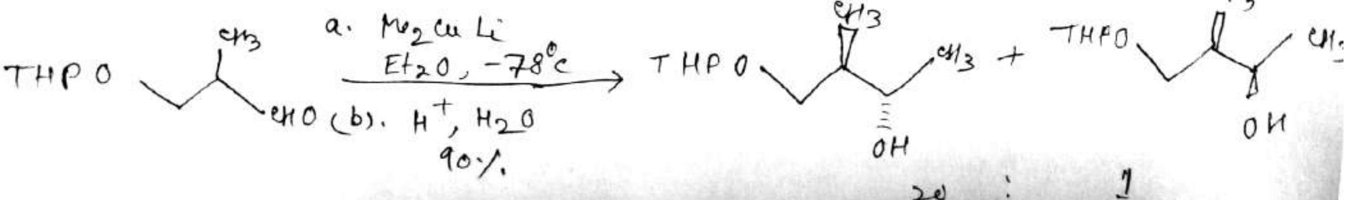
71%.

Acylation



✓ 1,2-Additions to Aldehydes and Ketones and imines

- often highly diastereoselective



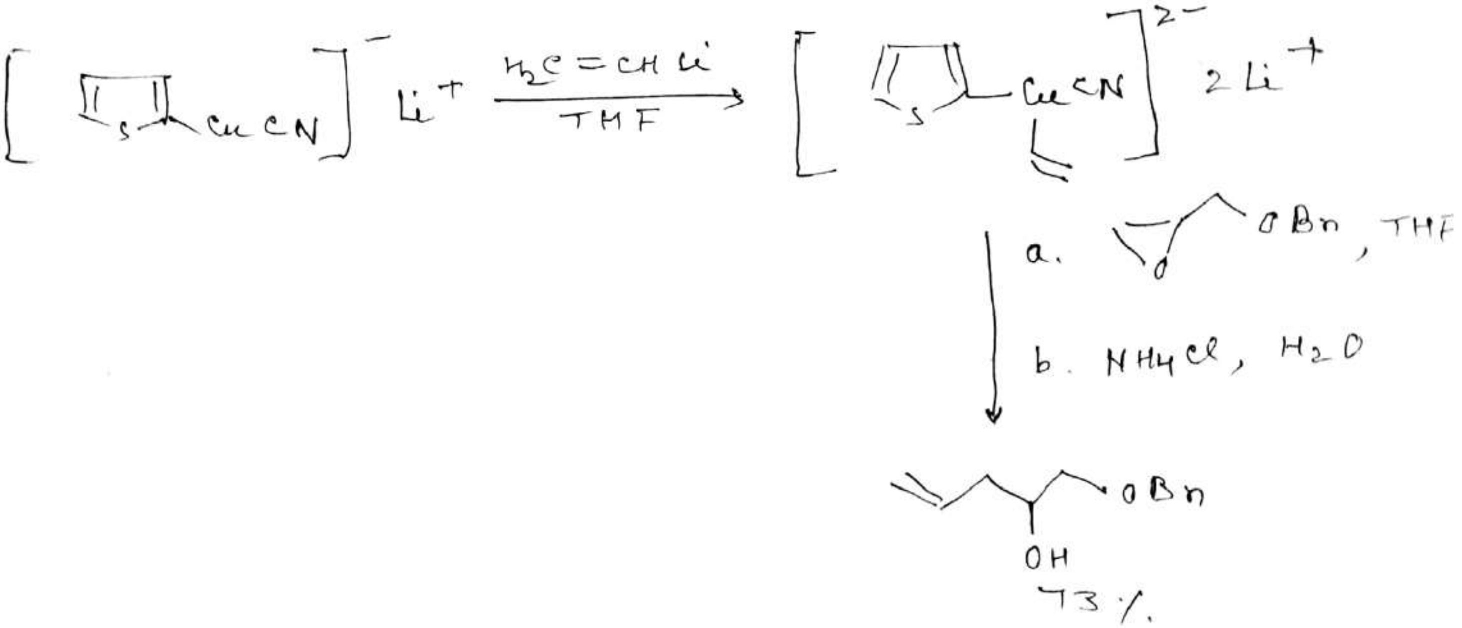
90%.

20 : 1

Epoxide cleavage Reactions

$R_2Cu(CN)Li_2$ — among the mildest and most efficient reagents available for C–C bond generation by epoxide cleavage.

— nucleophilic addition occurs at the less sterically hindered C of the oxirane ring.



Conjugate Addition

Organometallic reagents may add in a 1,2- or 1,4- manner to α, β-unsaturated carbonyl compds.

Regioselectivity in addition ~~of~~ RLi, RMgX and organocopper reag to α, β-unsaturated Carbonyl compounds.

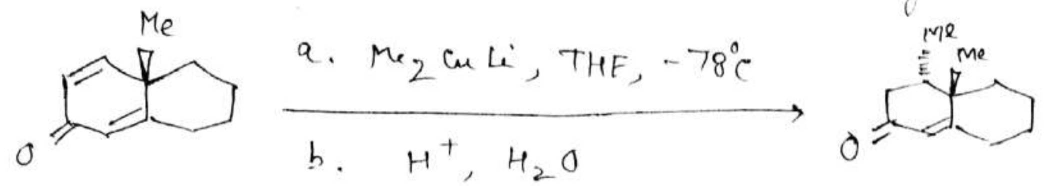
Nucleophile	1,2-Addition	1,4-Addition
R Li	+	−
RMgX	+	−
R_2CuLi	−	+
RMgX · CuX	−	+

1,4-Addition — with 'soft' (relatively nonbasic) nucleophiles such as CN^-, RNH_2, RSH, enolates derived from β-dicarbonyl compounds and organocuprates.

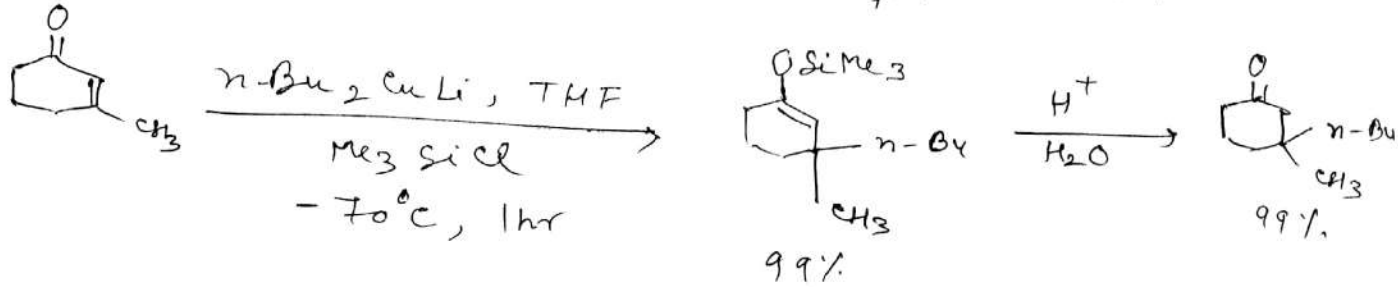
1,2-Addition — with 'hard' (relatively basic) nucleophiles such as hydrid organolithiums and Grignard reagents.

organocupper reagent

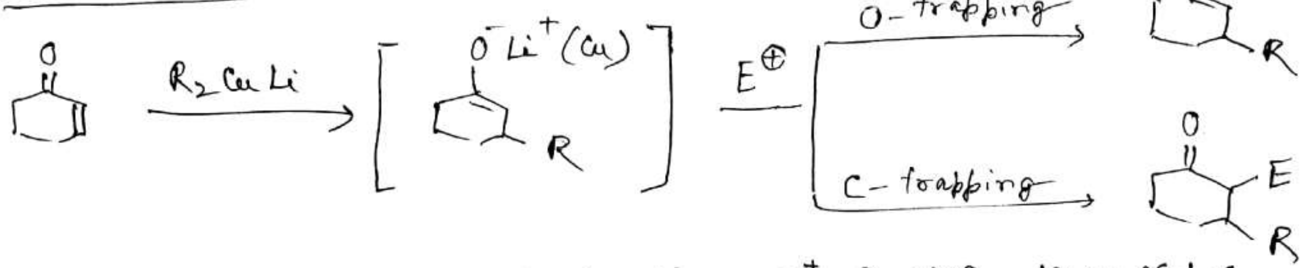
✓



Addition — chemoselective involving the less hindered double bond of the dienone.
— also stereoselective ("Me" from the less hindered side of the molecule).



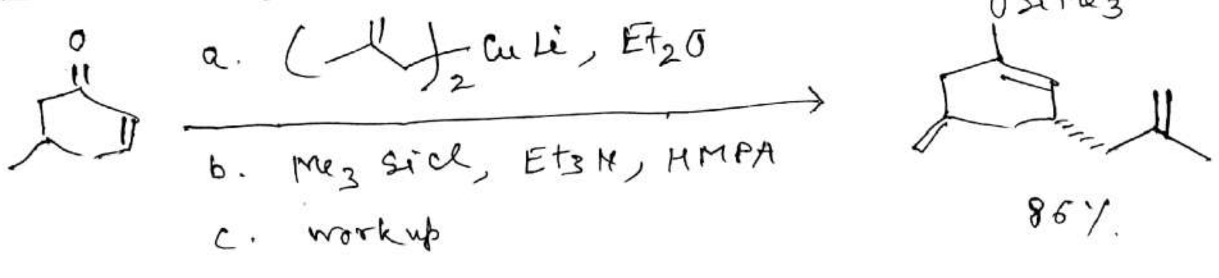
Tandem 1,4-Addition – Enolate Trapping



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

C-trapping: $E^+ = R-X$, RCHO, halogens

O-Trapping



C-Trapping