## Organometallic compounds

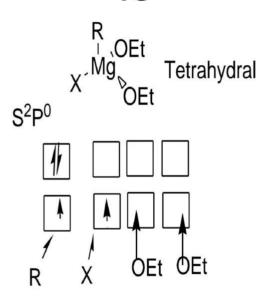
- Compounds that contain metal-carbon bonds, R-M: R= alkyl, aryl gr; M= Mg, Li, Na, Cu, Zn etc.
- Provide nucleophilic carbon atom, utilize for new C-C bond formation
- Can be treated as R-M = R<sup>-</sup>M<sup>+</sup>
- reagent can be formulated as RMgX or R2Mg.
- Grignard

### Laboratory preparation of Grignard reagent

Br + Mg 
$$\xrightarrow{\text{ether}}$$
 MgBr  
Br + Mg  $\xrightarrow{\text{ether}}$  MgBr  
 $R-X$  + Mg  $\xrightarrow{\text{ether}}$  R-MgX  $\xrightarrow{\text{O}_2 \& H_2O}$  free condition cat.  $I_2$  and 1,2-dibromoethane  $R=1^0, 2^0, 3^0, \text{ aryl}$ 

## Structu

re



## Mechanis

m:

$$R-X + Mg \longrightarrow R-X^{-} + Mg^{+}$$

$$R-X^{-} \longrightarrow R^{+} + \chi^{-}$$

$$R^{+} + Mg^{+} \longrightarrow RMg^{+}$$

$$RMg^{+} + \chi^{-} \longrightarrow RMgX$$

## Reactivi ty

Reactivity

l>Br>Cl>>F Low bond energy toward iodide

Alkyl halide>Vinyl or aryl halides

Reactive Groups

Reactive functional group: aldehyde, ketone, ester, amides, halides, nitrile

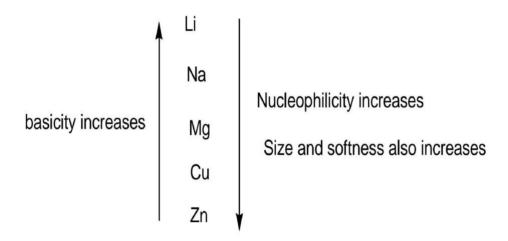
**Acidic** 

hydrogen>>aldehyde>keto>ester>nitrile>a mide

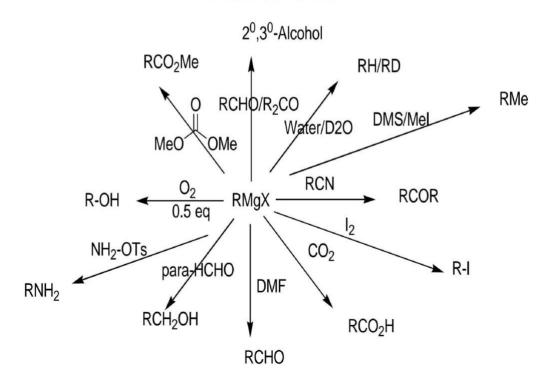
# Temperature dependent Grignard preparation

## Basicity vs Nucleophilicity

Basicity vs Nucleophilicity of organometalic reagent



## **Common Reactions**



# Usefull reagents

triethyl orthoformate/ triethoxymethane: protected ethylformate

$$N$$
 +  $N$  MgCl  $N$  Keto

Secondary amine preparation

## Abnormal behaviour/side reaction

Q. Between i and ii which one favor? explain.

# Intramolecular reaction

# SN2-type reaction

# 1,2-vs1,4-addition

Hindered group at 2-position allow to addition at 4-position

## Temperature control reaction

# Sensitive Grignard reagent preparation

#### Halogen-Magnesium exchange reaction

$$R = CN, NO_2, CO_2Et$$

$$X = Br, I$$

$$R = CN, NO_2, CO_2Et$$

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$$R = CN, NO_2, CO_2Et$$

#### Magnesium enolate formation

O OMgBr

$$X = Br/VCI$$

CI + (CH<sub>3</sub>)<sub>2</sub>CHMgBr

-30°C

CI

MgBr

Compedition between aryl iodide and benzyl chloride if use Mg metal

## Proble

### m

? PhCHO (2 eq) PhMgBr PhCHO (1 eq) ?

PhOHO CO<sub>2</sub>Et PhMgBr ?

PhMgBr ?

PhMgBr ?

PhMgBr ?

$$CH_3CH=CHCOR + CH_3MgBr \rightarrow ? [R = Et, i-Pr, t-Bu]$$

?

$$C_2H_2$$
?

 $C_2H_2$ 
?

 $C_2H_2$ 
?

 $C_3H_2$ 
PhCH<sub>2</sub>CN
?

 $C_3H_2$ 
?

 $C_3H_2$ 
PhCH<sub>2</sub>CN
?

## **Organolithium compounds**

## Laboratory preparation of Li reagent

$$RX + 2Li \xrightarrow{0^{0}C} R-Li + LiX$$

$$RI>RBr>RCI$$

$$MeI + 2Li \xrightarrow{0^{0}C} Me-Li + LiX$$

$$RI>RBr>RCI$$

$$Me-Li + LiX$$

$$RI>RBr>RCI$$

$$R-Li + LiX$$

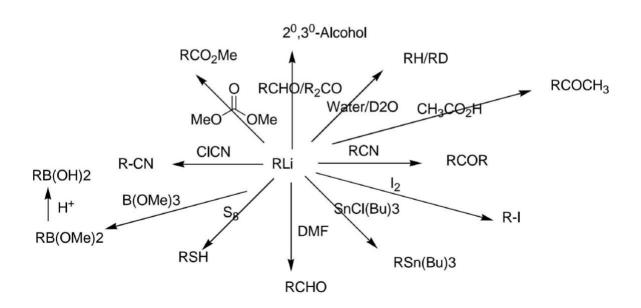
hydrocarbon solvent: hexamers

in ether : tetramers

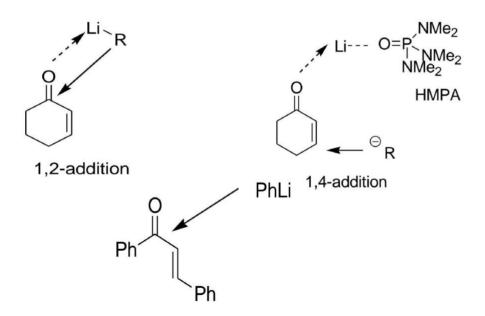
chelating solvent: monomer

TMEDA, HMPA

### Halogen-Metal exchange or metallation or Lithiation



## 1,2-addition vs 1,4-addition



Highly reactive RLi usually react 1,2-addition but addition of HMPA favor 1,4-addition

### Snthesis of ketone from carboxylic acid

RLi 
$$CO2$$
  $R o O-Li$   $RLi$   $H_3O+$   $R o O$ 

$$CH_3CO_2H o CH_3 o C$$

#### Amide to nitrile

#### Copper reagent

Use of organocopper reagents offers a very efficient method for coupling of two different carbon moieties. Since copper is less electropositive than lithium and magnesium, the C-Cu bond is less polarized than the C-Li and C-Mg bonds.

Organocopper complexes (RCu)

Lower-order cuprates (R, CuLi, also known as Gilmanreagents

Lower-order cyanocuprates (RCu(CN)Li)

Higher-order cyanocuprates (R<sub>2</sub>Cu(CN)Li<sub>2</sub>)

The organocopper reagents are 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

#### **Preparation**

Step 1: formation of organolithium

Step 2: formation of organocuprate (Gilman reagent)

An alternative way of writing the same thing...

### SN2 & SN2' type reaction

Same side attack of Nu to LG

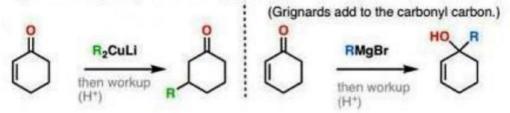
$$\begin{array}{c} H \\ C = C \\ CH_3 \end{array} + \underbrace{(CH_3CH_2)_2CuLi} \quad \xrightarrow{\text{ether}} \quad \begin{array}{c} H \\ H_3C \end{array} C = C \\ CH_3 \\ + CH_3Cu \\ + CH$$

- When a Gilman reagent reacts with an alkyl halide (except F<sup>-</sup>) one of the alkyl groups replaces the halide
- Alkyl groups can substitute halogens attached to alkene or aromatic C with Gilman reagent; impossible with S<sub>N</sub>1 or S<sub>N</sub>2 reaction
- Mechanism unknown, probably radical

#### Only 1,4-addition

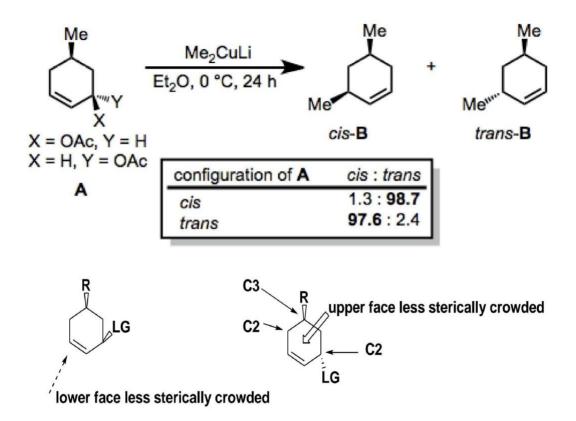
Summary: Gilman reagents (organocuprates) contrast with Grignard (and organolithium reagents) in two important ways:

#### 1) Gilman reagents perform "conjugate addition" to $\alpha$ , $\beta$ unsaturated ketones



#### 2) Gilman reagents are effective nucleophiles for S<sub>N</sub>2 reactions

### 1,4-di keto synthesis



### Organo zinc reagent

### **Preparation**

### Reaction

### **Reformatsky reaction**

#### **Blaise** reaction

$$R_1-CN \xrightarrow{ \begin{array}{c} Zn \ (1.5 \ equiv) \\ BrCH_2CO_2Et \\ \hline (1.5 \ equiv) \\ \hline THF, \ reflux, \ 1 \ h \\ >98\% \ conv. \end{array}} \begin{array}{c} Br \\ Zn \\ HN & O \\ \hline R_1 & OEt \\ \end{array} \begin{array}{c} NH_2 \ O \\ \hline R_1 & OEt \\ \end{array}$$

#### 4-amino unsaturated ester

### LDA preparation & use

#### Selective mono-lithiation at low temperature in presence of heavy atom

Regioselectivity: Coordination effect of CO2<sup>-</sup> group less stable anion, more reactive attack fast

CO<sub>2</sub>H

#### Alkynyl lithium reagents undergo exo-cyclisation to cycloalkylidine isomer

Br 
$$(CH_2)_3CH_3$$
  $(CH_2)_3CH_3$  Exo-product  $SP^2$  vs  $SP^3$  anion stability

### Solvent dependent lithiation at different temperature

At low T, for simple hydrocarbon halide with no functional gr, highly insoluble in THF but in benzene it is soluble at rt or higher T

Coordinating solvent like THF required low T BUT non coordinating solvent benzene, can be done in high T

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$$\begin{array}{c} & & & \\$$

L = Large gr or coordinating gr

Prepare using suitable Grignard reagent.

Prepare from iodobenzene

CI 
$$\frac{\text{a. } \text{Et}_2\text{CuLi}}{\text{Et}_2\text{O}, -78 \, ^{\circ}\text{C}}$$

$$\text{b. } \text{NH}_4\text{CI, H}_2\text{O}$$

$$\frac{\text{1. BuLi, ether, } -90 \, ^{\circ}\text{C}}{\text{2. MnI}_2, -50 \, ^{\circ}\text{C}}$$

$$\frac{\text{CI}}{\text{2. mod } -20 \, ^{\circ}\text{C to r.t.}}$$

CI

70%

OOO Mg, THF
DIBAH (1 mol%)
EtBr (5 mol%)

$$<20$$
 °C, high yields

MgBr

(1)

MgBr

(2)

(3)