

## Constructing Carbon Frameworks

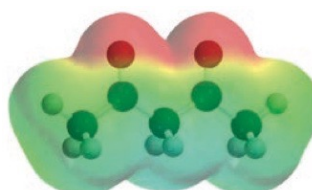
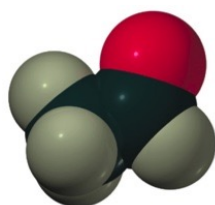
*(More Chemistry of Carbonyl Compounds)*

**Lecturer: Prof. Nigel T Lucas**

*nigel.lucas@otago.ac.nz*

*Room 3n10*

*Ph: 479 5377*



### Syllabus 1

#### 1 Electron Rich Carbon (6<sup>th</sup> Ed, Ch 11; 7<sup>th</sup> Ed, Ch 12; 8<sup>th</sup> Ed, Ch 11)

- Metal-hydrogen exchange
- Metal-halogen exchange

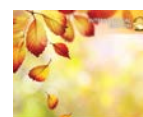
#### 2 Reactions of Organometallic Compounds

(6<sup>th</sup> Ed, Ch 11,18; 7<sup>th</sup> Ed, Ch 12,17; 8<sup>th</sup> Ed, Ch 11,16)

- Organolithium and organomagnesium compounds
  - Basic reactions, nucleophilic reactions
- Organocopper compounds
  - Alkylation, acylation, conjugate addition

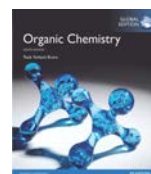
#### 3 Reactions of Enolates (6<sup>th</sup> Ed, Ch 19; 7<sup>th</sup> Ed, Ch 18; 8<sup>th</sup> Ed, Ch 17)

- Alkyl halides
  - 1,3-Dicarbonyl enolates (malonic ester, acetoacetic ester syntheses)
- Carbonyls
  - Aldehydes and ketones (aldol reaction/condensation)
  - Esters (Claisen condensation)



Organic Chemistry  
Seventh Edition  
T. L. Bruice

Bruice  
7<sup>th</sup> Edition



Bruice  
8<sup>th</sup> Edition

## Syllabus 2

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### 4 Electron Rich Carbons with Attached Heteroatoms

(6<sup>th</sup> Ed, Ch 18; 7<sup>th</sup> Ed, Ch 17; 8<sup>th</sup> Ed, Ch 16)

- General considerations
- Sulfur ylids
  - Preparation, reactions, mechanisms
- Phosphorus ylids
  - Preparation
  - Wittig reaction
  - Stereochemistry, mechanism, phosphonates
  - Applications

### 5 Summary

- General synthesis problems
- Examination discussion

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## 1.1 Introduction

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A vast majority of organic compounds can be considered as an arrangement of carbon atoms ('framework') containing various functional groups (e.g. OH, Cl).

An important aspect in considering the synthesis of organic compounds is to be able to use methods for creating the carbon skeleton by **forming carbon–carbon** bonds.

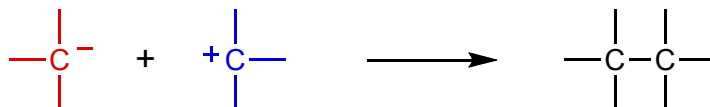
This type of bond formation, in particular using **carbonyl-containing reactants**, is the central focus of this CHEM 202 module.

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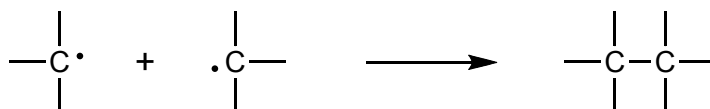
## 1.2 How can you create a C–C?

Combine reactive species:

**Charged (polar)**



**Uncharged** (e.g. radicals, concerted reactions)

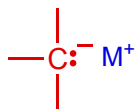


This module will focus on the first (i.e. charged) approach to C–C bond formation

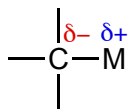
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## 1.3 Electron Rich Carbon

Can be an ionic species where the carbon system contains a full negative charge (i.e. **carbanion**), or a carbon in a polar covalent bonding array (i.e.  $\delta^-$ ):



**carbanion**



**polar covalent**

Carbanions are:

- quite *reactive*, prepared and reacted without delay
- usually associated with very *electropositive metal* cations (Na<sup>+</sup>, K<sup>+</sup>) to achieve electroneutrality
- can be *stabilised* by attaching *electron-withdrawing groups* which delocalise the charge

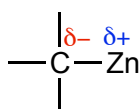
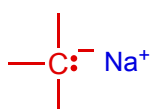
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### 1.3 Electron Rich Carbon

Electron rich carbons which do not have stabilising substitution, are often associated with metals which are less electropositive

- are able to reduce the negative charge on carbon by partial covalent bond formation (Li, Mg, Hg, Zn, B):

carbon (C)	2.5
sodium (Na)	0.9
mercury (Hg)	1.5
zinc (Zn)	1.7



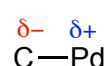
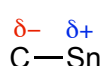
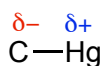
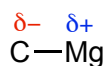
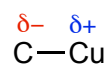
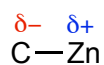
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### 1.3 Electron Rich Carbon – Other Organometallics

The Electronegativities of Some of the Elements <sup>a</sup>															
IA	IIA							IB	IIB	IIIA	IVA	VA	VIA	VIIA	
H 2.1															
Li 1.0	Be 1.5									B 2.0	C 2.5	N 3.0	O 3.5	F 4.0	
Na 0.9	Mg 1.2									Al 1.5	Si 1.8	P 2.1	S 2.5	Cl 3.0	
K 0.8	Ca 1.0	Co 1.7	Ni 1.7	Cu 1.8	Zn 1.7	Ga 1.8	Ge 2.0							Br 2.8	
		Rh 2.4	Pd 2.4	Ag 1.8	Cd 1.5			Sn 1.7							I 2.5
						Hg 1.5			Pb 1.6						

<sup>a</sup>From the scale devised by Linus Pauling

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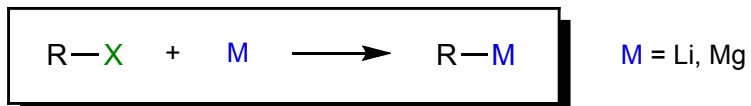


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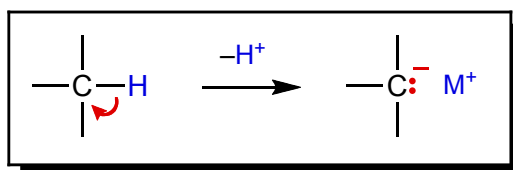
### 1.3 Preparation of Electron Rich Carbons

How do you prepare electron rich carbon?

➤ **metal-halogen exchange**



➤ **metal-hydrogen exchange**



- use a base to remove  $\text{H}^+$
- the C-H bond must be easy to cleave  
→ implies that the substrate must be **acidic**

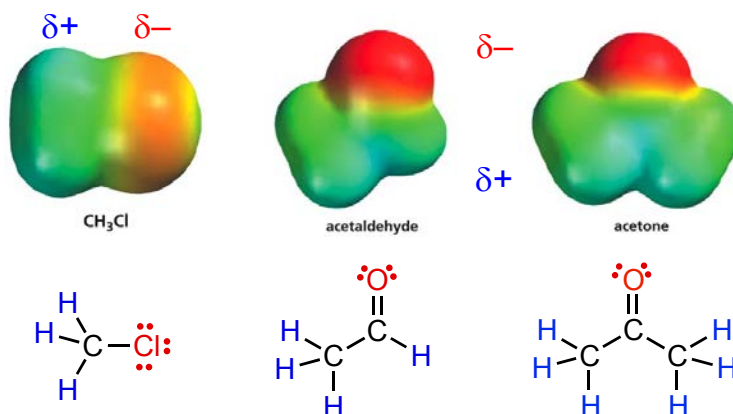
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### 1.4 Electron Poor Carbon

Electron poor carbons are:

- often part of a neutral molecule
- classified as electrophiles

Typical examples are alkyl halides ( $\text{R}-\text{X}$ ), carbonyls ( $>\text{C}=\text{O}$ )



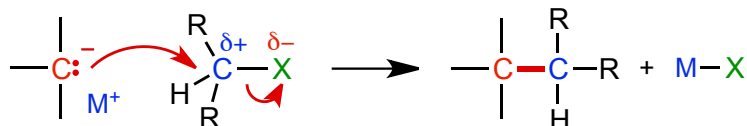
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## 1.5 Combination of Electron Rich & Poor Carbons

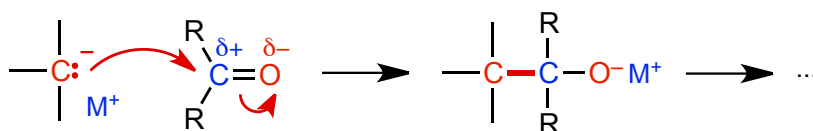
The most common method for making carbon–carbon bonds is to create a reactive, electron rich carbon system

- usually associated with a metal (i.e. organometallic)
- reacted with a wide range of electrophiles

### Alkylation

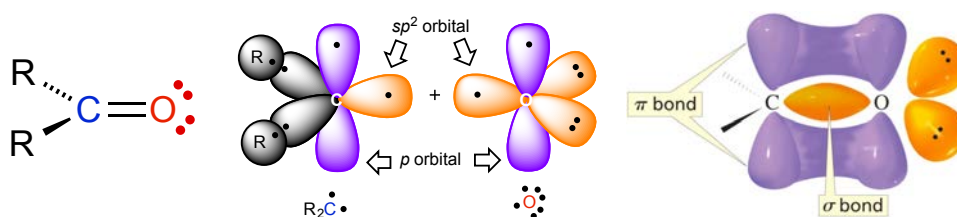


### Hydroxyalkylation

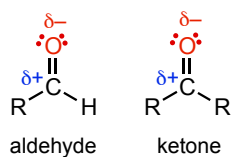


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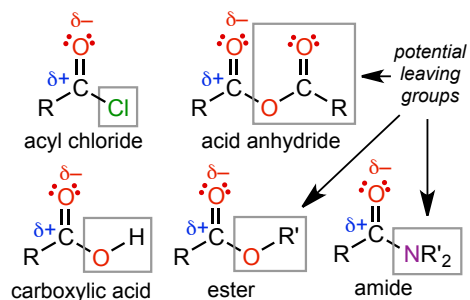
## Revision: Carbonyl Compounds



With a **very poor** leaving group:  
(R = alkyl, aryl)



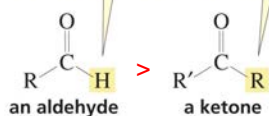
With a **better** leaving group:



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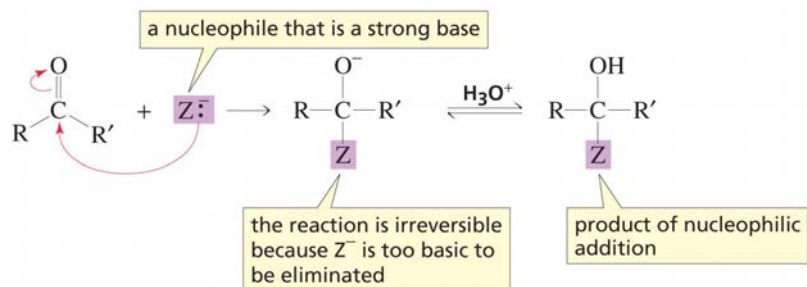
## Revision: Carbonyl Compounds with Poor Leaving Groups

carbonyl compounds with groups that cannot be replaced by a nucleophile



reactivity

Aldehydes and ketones undergo nucleophilic **addition**:



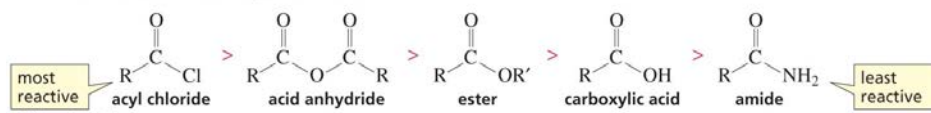
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## Revision: Carbonyl Compounds with Good Leaving Groups

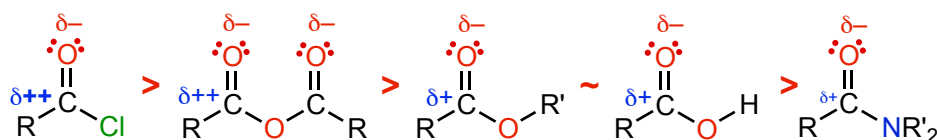
Nature of the substituents influences  $\delta^+$  on the carbonyl carbon.

- More electron withdrawing  $\rightarrow$  more reactive with nucleophiles

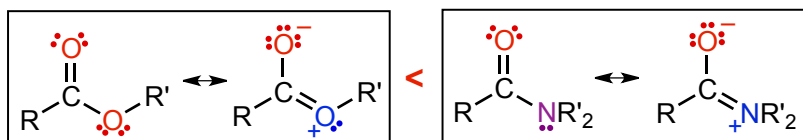
relative reactivities of carboxylic acid derivatives



Inductive effects:



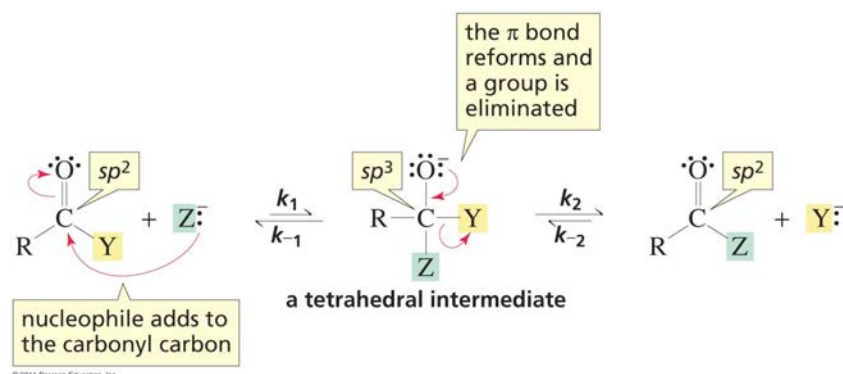
Mesomeric (resonance) effects:



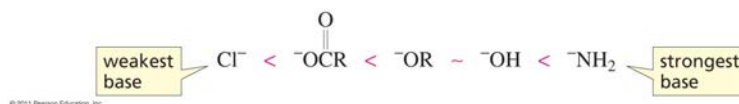
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## Revision: Carbonyl Compounds with Good Leaving Groups

Carboxylic acid derivatives undergo nucleophilic (acyl) **substitution**:



relative basicities of the leaving groups



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## 2.1 Organometallic Compounds

- where there is considerable ion association (or polar covalent bonding), the nett negative charge on the organic (R) component of RM is substantially reduced.



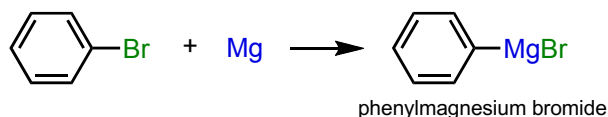
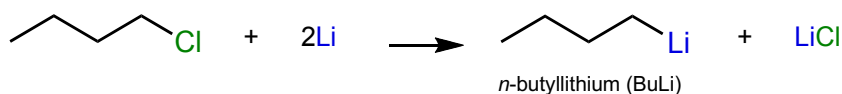
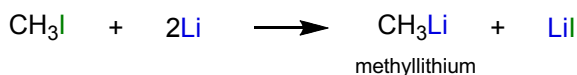
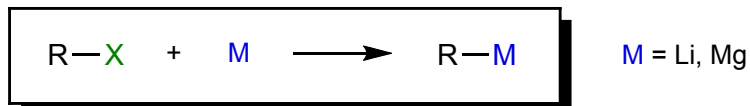
- arrangement can be achieved by using less electropositive metals (e.g. Li, Mg, Cu) and thus organometallic compounds (RM), where R is a simple alkyl or aryl group without any additional anion stabilising groups, can be prepared and used for synthesis.
- typically, they exist as a mixture of clusters  $(RM)_n$  in solution in a dynamic equilibrium which is sensitive to temperature and solvent.
  - despite these complications, organometallics of this type are very useful for organic synthesis and for the purposes of simply understanding reactions, can be usefully considered as RM.

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## 2.2 Synthesis of Electron Rich Carbons

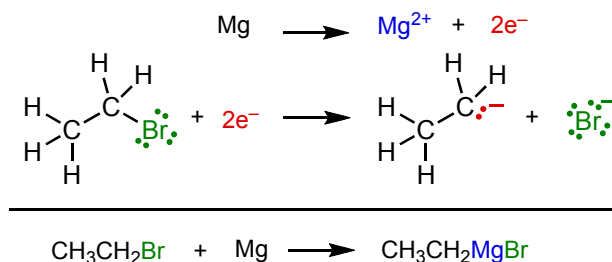
The preparation organometallic compounds with (very) electron rich carbons can be by **metal–halogen exchange**.



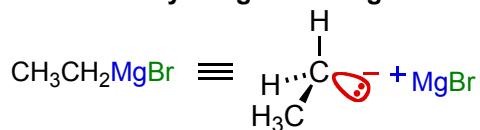
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## 2.2 Metal–Halogen Exchange: Grignard reagents

Organomagnesiums are known as **Grignard reagents** (after the discoverer of these compounds). The Grignard reaction is a redox process.



### Alkyl Grignard Reagents



filled  $sp^3$  hybridised orbital  
tetrahedral geometry at  $\text{C}^-$

### Aryl Grignard Reagents

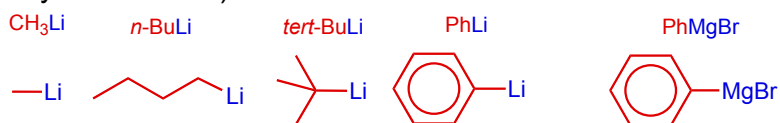


filled  $sp^2$  hybridised orbital  
trigonal planar geometry at  $\text{C}^-$

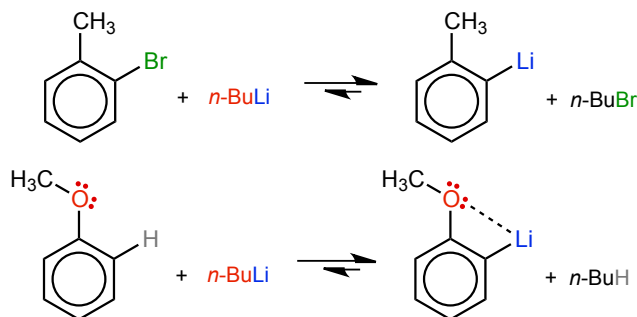
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## 2.3 Common Organolithium/-magnesiums (RM)

Some important organometallic reagents are commercially available (usually as solutions):



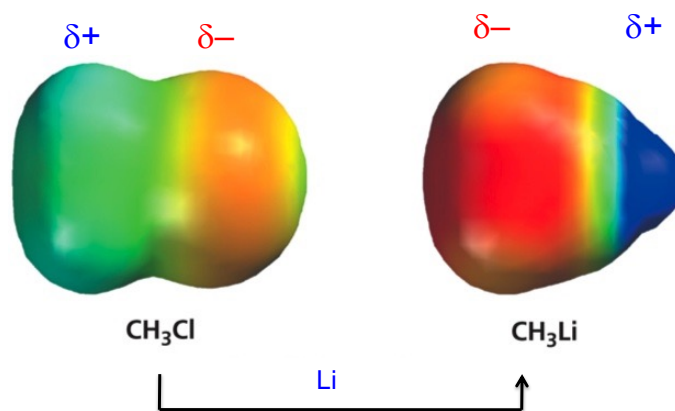
More complex compounds are obtained by *metal-halogen exchange*, *metal-hydrogen exchange* or *transmetallation*, e.g.



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## 2.4 Electron Rich from Electron Poor Carbons

Compare the electrostatic potential maps of an alkyl halide and alkyllithium:



Note the reversal of polarity (*umpolung*)

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## 2.5 Reaction Conditions

Usually the electron rich carbon systems are quite reactive. Avoid:

- air
  - water
  - high temperatures
- Operate under an **inert atmosphere** (argon or nitrogen)

### Common solvents

diethyl ether	Et <sub>2</sub> O
tetrahydrofuran	THF
toluene	

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## 2.6 Properties of Organolithium and –magnesiums

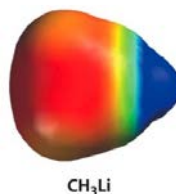
Organolithium (RLi) and –magnesium (RMgX) compounds are surprisingly soluble in non-polar organic solvents, e.g. ether, THF, hexane.

NMR chemical shifts reflect the high electron density on the R moiety:



<sup>1</sup>H NMR: δ

<sup>13</sup>C NMR: δ



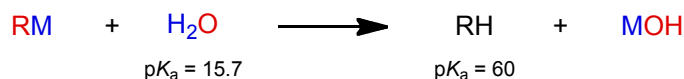
RLi compounds are usually more reactive than RMgX, but for many reactions they are comparable.

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## 2.7 Reactions of Organometallics (RM) – Basic

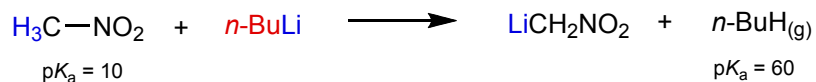
Organolithium and Grignard reagents are usually very **basic** (irreversible) and **nucleophilic**.

### I. Basic Reactions



*Keep away from water!*

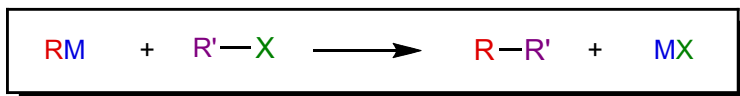
*tert*-BuLi is very reactive and is pyrophoric (spontaneously combusts in air)



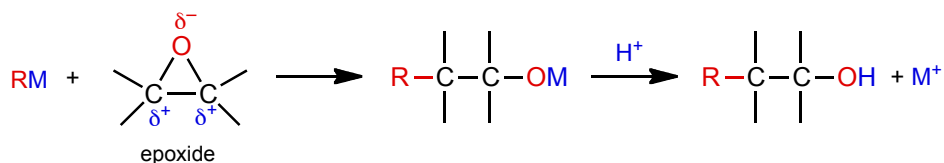
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## 2.8 Reactions of Organometallics (RM) – Nucleophilic 1

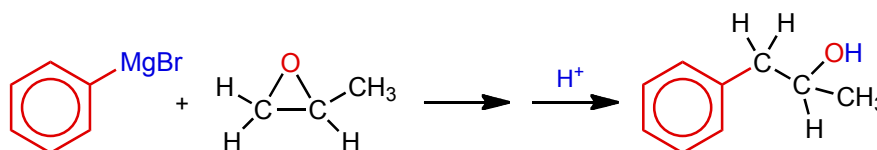
### II. Nucleophilic Reactions



Not very efficient with alkyl halides. Better yields using epoxides.



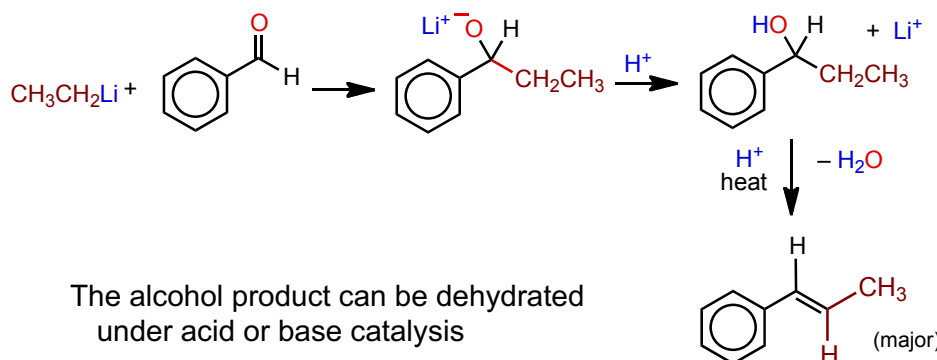
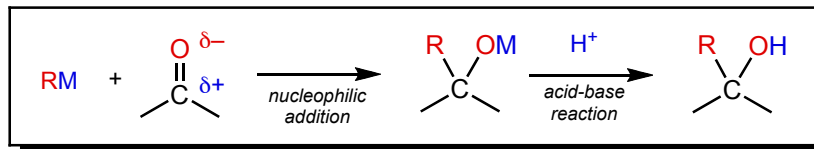
S<sub>N</sub>2 reactivity profile (methyl > 1° > 2° >> 3°):



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## 2.8 Reactions of Organometallics (RM) – Nucleophilic 2

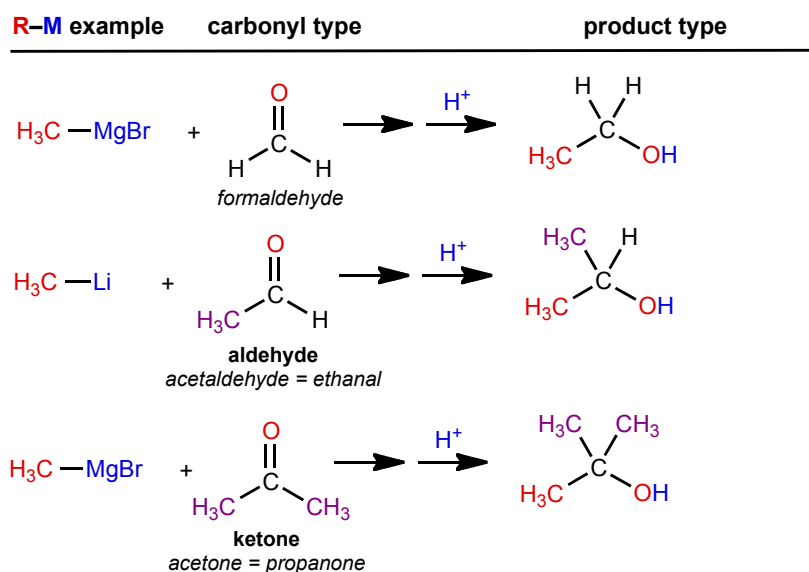
Organolithium and Grignard reagents **add** to the carbonyl of aldehydes and ketones. Acidic work-up of the addition product gives an alcohol



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## 2.8 Reactions of Organometallics (RM) – Nucleophilic 2

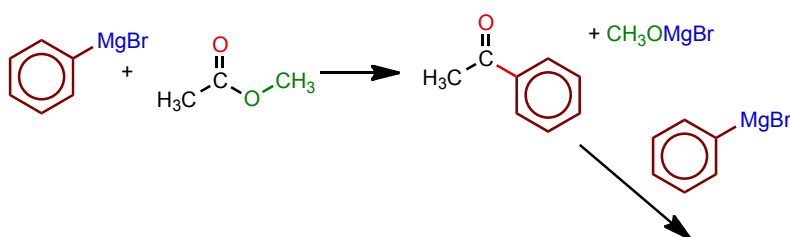
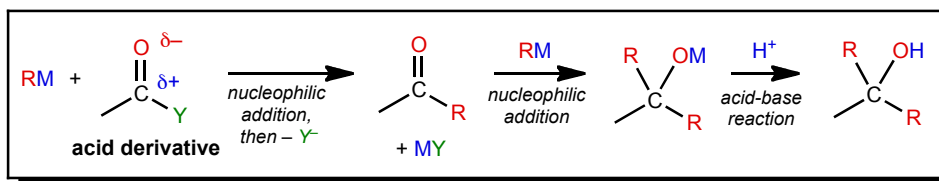
Nucleophilic addition gives access to primary (1°), secondary (2°) and tertiary (3°) alcohols :



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## 2.8 Reactions of Organometallics (RM) – Nucleophilic 3

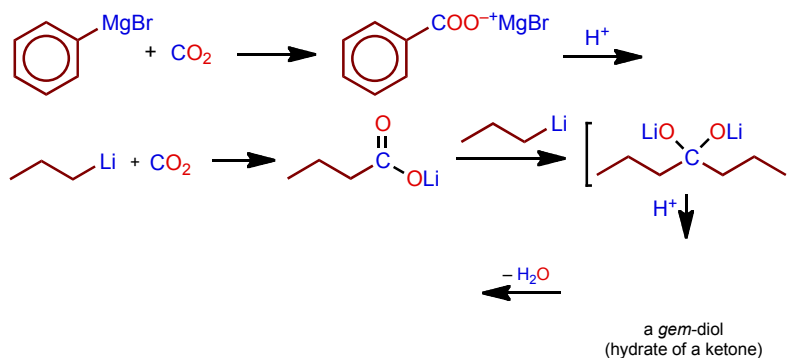
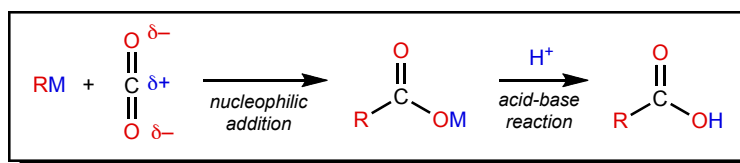
Organolithium and Grignard reagents also participate in nucleophilic acyl **substitution** with carboxylic acid derivatives. The ketone formed can react with a second equivalent of RM (addition).



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## 2.8 Reactions of Organometallics (RM) – Nucleophilic 4

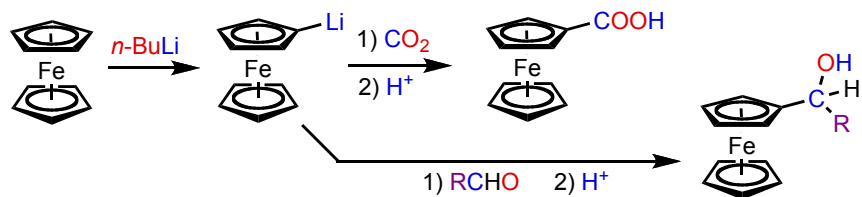
RM reagents react similarly with the carbon atom of  $\text{CO}_2$  to give upon acidification, a **carboxylic acid**. Note that the carbon chain has increased in length by one carbon.



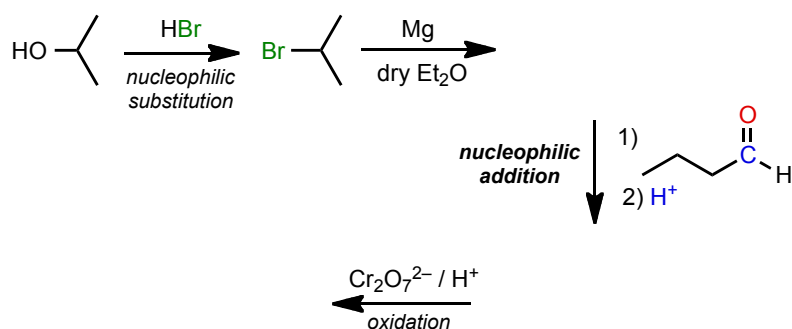
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## 2.8 Reactions of Organometallics (RM) – Examples

- the cyclopentadienyl ring of ferrocene can be lithiated



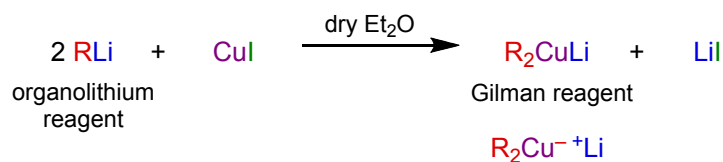
- synthesis of an ant alarm pheromone



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## 2.9 Organocopper Compounds – Preparation

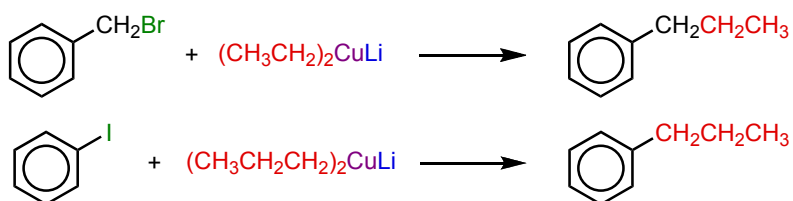
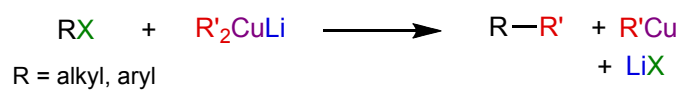
Organocopper reagents (organocuprates) can be prepared by reaction of an organolithium reagent with copper(I) iodide in diethyl ether (or THF).



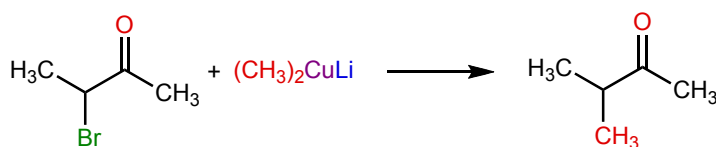
- very useful to synthetic chemists as they are a *complementary* reagent to  $\text{RLi}$  /  $\text{RMgX}$
- are less basic than  $\text{RLi}$  /  $\text{RMgX}$
- react selectively with alkyl and aryl halides, but *not with saturated carbonyls*

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## 2.9 Organocopper Compounds – Alkylation



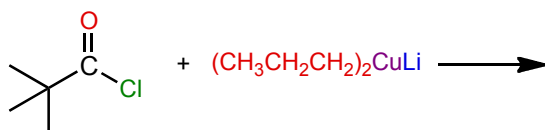
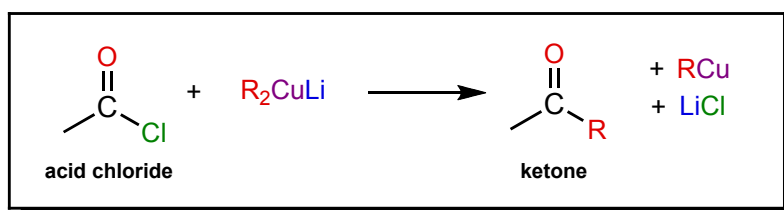
Organocopper reagents can replace halogens in compounds that contain carbonyl groups (compare to organolithiums, Grignard → addition to C=O)



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## 2.9 Organocopper Compounds – Acylation

Carboxylic acid chlorides can react with organocopper reagents in a nucleophilic acyl substitution reaction:

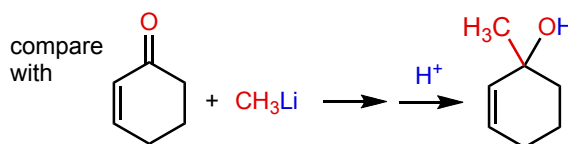
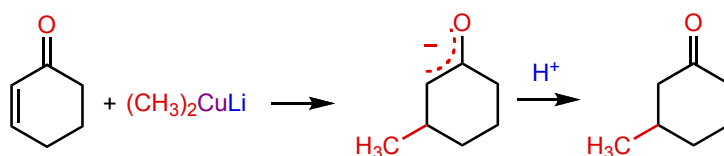
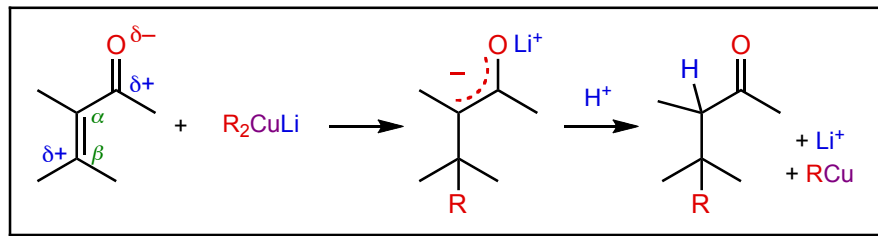


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## 2.9 Organocopper Compounds – Conjugate Addition

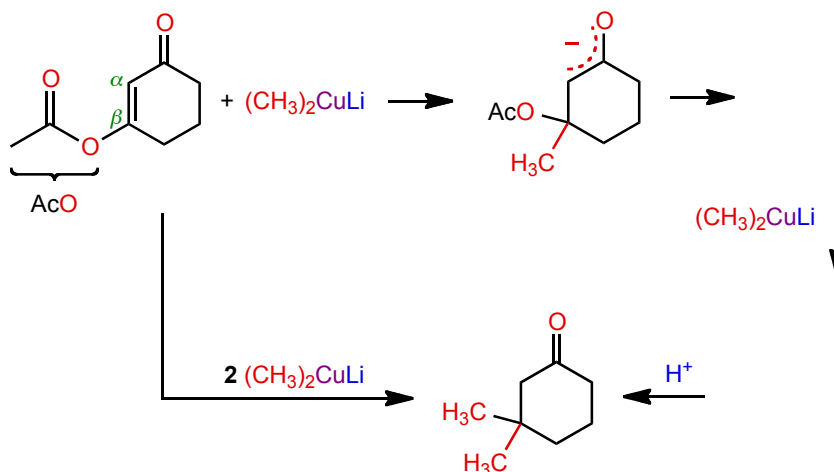
Many copper-containing organometallic compounds add to  $\alpha,\beta$ -unsaturated ketones in smooth 1,4-additions.



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## 2.9 Organocopper Compounds – Conjugate Addition

When there is a good leaving group in the  $\beta$ -position of an enone, nucleophilic **substitution** can occur. This can be followed by **1,4-addition** of another equivalent of  $R_2CuLi$ .

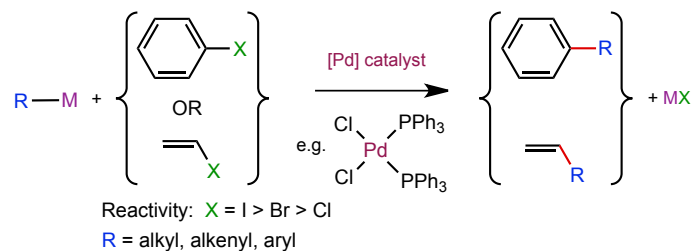


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## 2.10 Other Organometallics – Pd-catalysed Coupling

In recent years, many new methods using transition metals to carry out coupling reactions have been developed; those that involve organopalladium intermediates are the most heavily studied.

- Pd is used *catalytically* not stoichiometrically (typically 1-5 mol% Pd)
- catalytic use has economic and environmental advantages
- the most common general process is Pd-mediated cross-coupling with aryl/alkenyl **halides**, forming a new C–C bond.



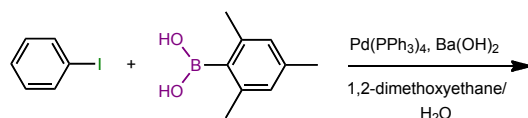
$R-SnR_3$	$R-B(OR)_2$	$R-ZnX$	$R-MgX$	$R-SiR_3$	$RC\equiv C-Cu$	$\begin{matrix} H & R' \\ & \backslash / \\ & C=C \\ & / \backslash \\ H & R' \end{matrix}$
Stille	Suzuki	Negishi	Kumada	Hiyama	Sonogashira	Heck

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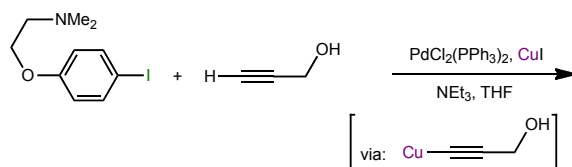
## 2.10 Other Organometallics – Pd-catalysed Coupling

- examples of Pd-catalysed couplings:

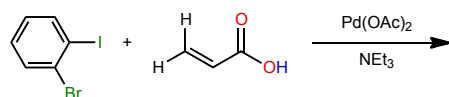
- **Suzuki coupling** (via a boronic acid)



- **Sonogashira coupling** (via a copper acetylide from terminal alkyne)



- **Heck coupling** (alkene)



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