

Basic Concepts Recap:

Nucleophiles and Electrophiles

- **nucleophiles** are neutral or anionic species that donate high energy electrons from a filled orbital (HOMO) to an electrophile
- **electrophiles** are neutral or cationic species with low energy vacant or anti-bonding orbitals (LUMO) that can accept electrons

Curved Arrows

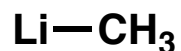
- organic chemists use curved arrows to show reaction mechanisms and demonstrate resonance structures
- curved arrows indicate the flow of electrons

Organic Acids and Bases

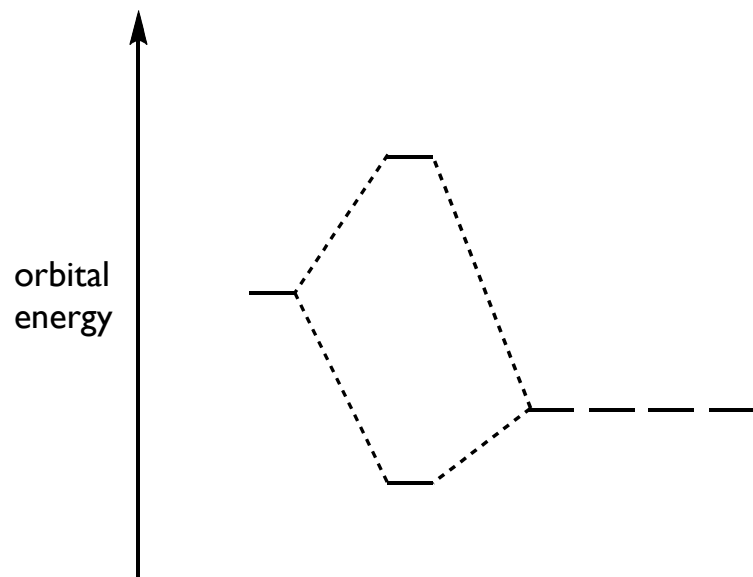
- Strong acids have weak conjugate bases; strong bases have weak conjugate acids
- When intuiting the “acidity” of a proton, consider the stability of the conjugate base
- Important factors: delocalization of charge (resonance stabilization), hybridization of carbon, inductive effects of electronegative atoms

Organometallic Reagents: Carbon Nucleophiles

Organometallic reagents: a carbon is bound to a more electropositive metal, resulting in a polar covalent bond with substantial negative charge on carbon. When $M = \text{Mg}$ or Li , these reagents behave as “carbanions”



MO considerations:



How to Make Organometallic Reagents

Grignard reagents (organomagnesium reagents):

François Auguste Victor Grignard

- shared the Nobel Prize in chemistry with Paul Sabatier in 1912

"for the discovery of the so-called Grignard reagent, which in recent years has greatly advanced the progress of organic chemistry"

http://nobelprize.org/nobel_prizes/chemistry/laureates/1912/grignard-bio.html

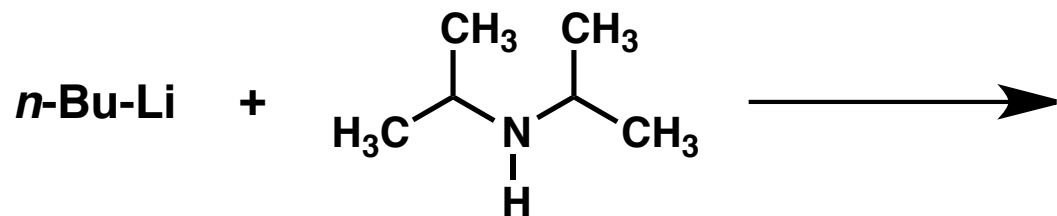
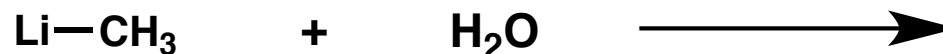


How to Make Organometallic Reagents

Organolithiums:

Organometallic Reagents are Strong Bases

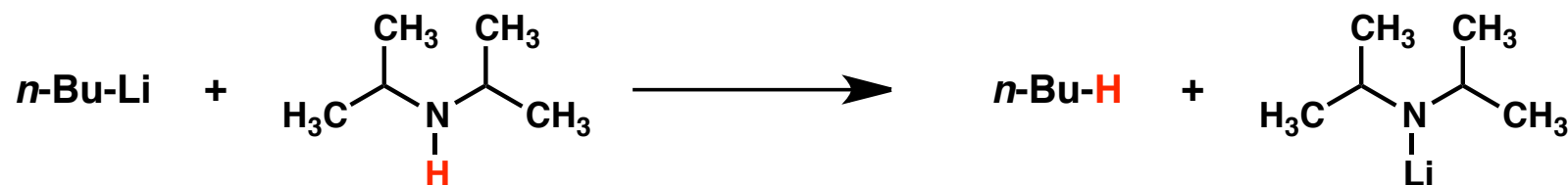
Organometallic reagents will deprotonate acidic protons



Remember: a **base can deprotonate acids** with **pK_a values** that are **lower** than its **conjugate acid**.

Organometallic Reagents are Strong Bases

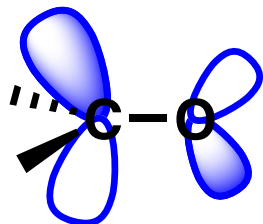
In terms of pK_a and equilibrium constants:



remember: a base can deprotonate acids with pK_a values that are lower than it's conjugate acid.

Organometallic Reagents Add to Carbonyls

Remember, carbonyls are electrophilic at carbon:

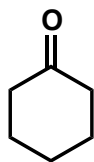
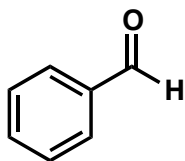


A general mechanism for organometallic addition to carbonyl:

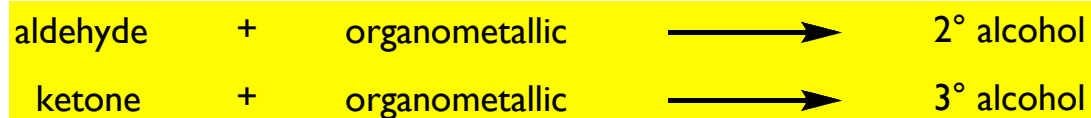
Organometallic Reagents Add to Carbonyls

Organometallic reagents are nucleophilic at carbon

- addition of organometallic reagents to carbonyls form C–C bonds
- “work-up” step typically involves addition of aqueous acid



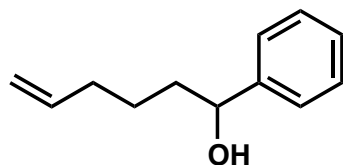
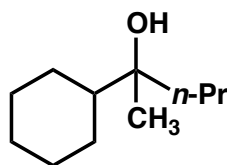
General reactions:



Thinking Backwards: Retrosynthesis

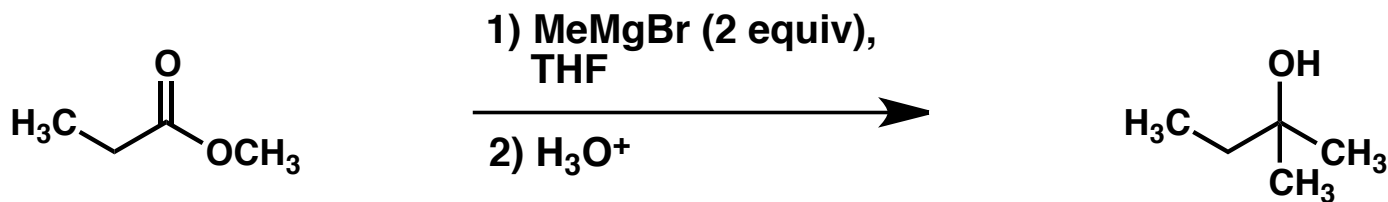
We now know how to make C–C bonds. We can design syntheses of carbinols.

- it can be helpful to think backwards (**retrosynthetically**)



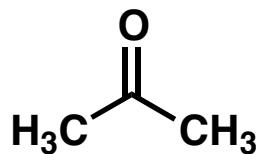
Addition of Organometallics to Esters:

Esters undergo **double-addition** of organometallic reagents

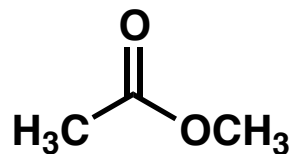


Why Are Ketones More Electrophilic than Esters?

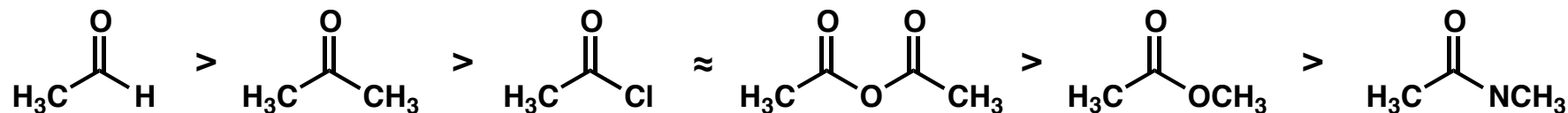
Can use **resonance structures** to rationalize reactivity trend:



vs.

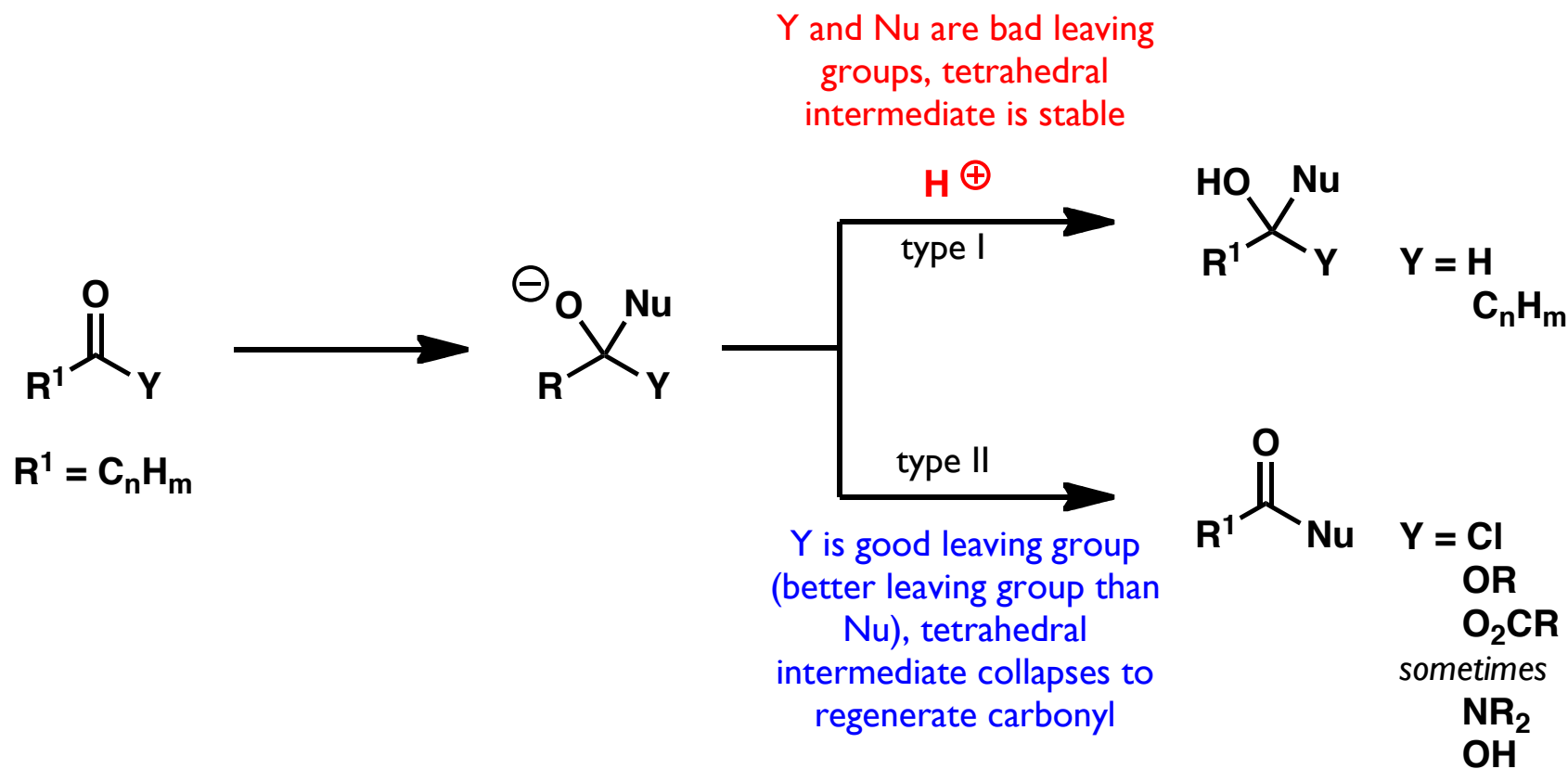


Trend in carbonyl electrophilicity:



Divergent Reactivity in Carbonyl Addition Reactions

All carbonyl addition reactions can roughly be divided into two categories:

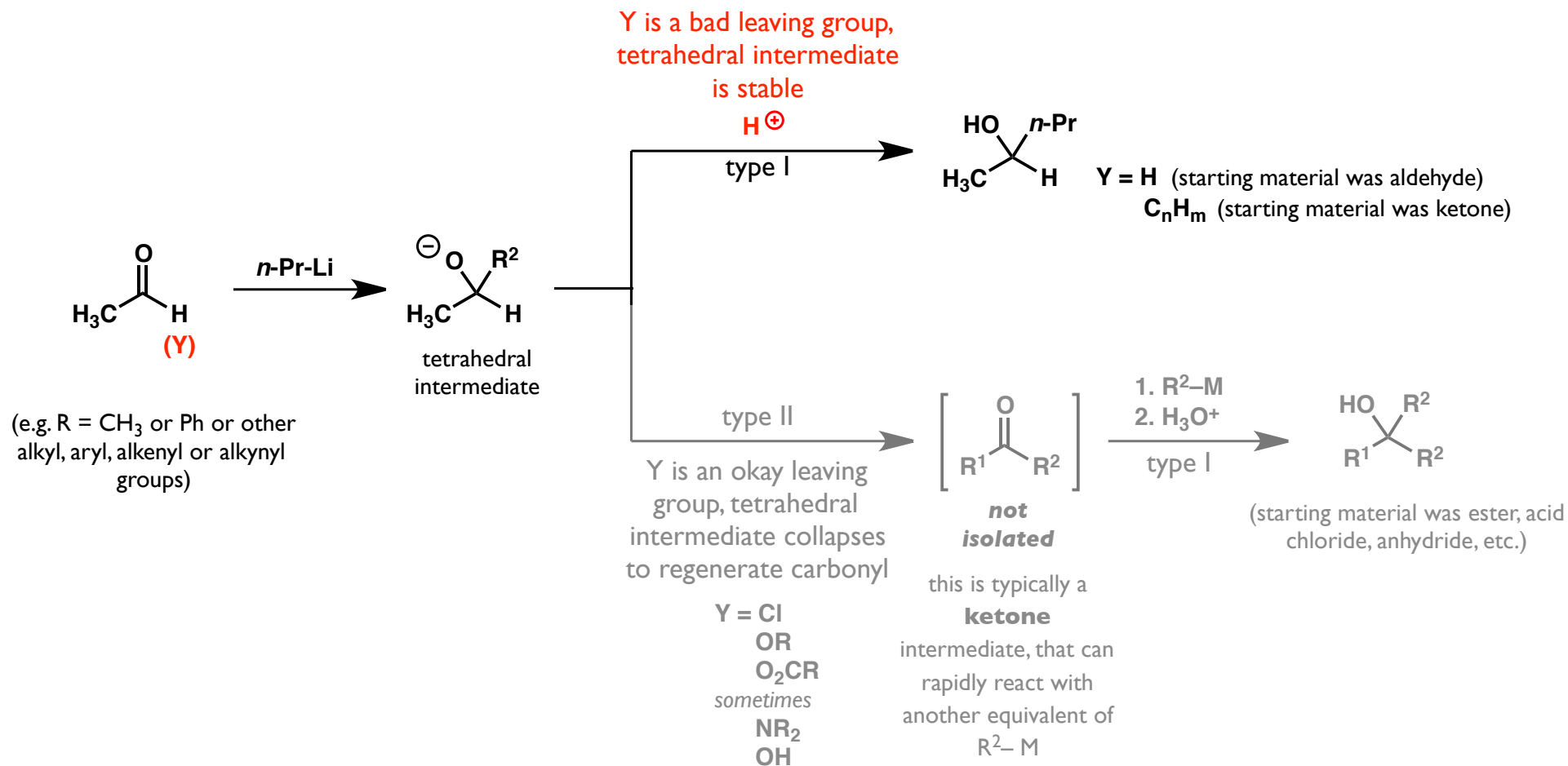


the fate of carbonyl additions depends on *both*:

- the nature of the carbonyl electrophile
- the nature of the nucleophile

Divergent Reactivity in Carbonyl Addition Reactions

Let's consider Type I additions first:



Divergent Reactivity in Carbonyl Addition Reactions

Now let's consider Type II additions:

