Lesson V.1. Introduction to Organometallics and Metal Hydrides

Lesson V.1.1 The Need for Nucleophilic Carbon

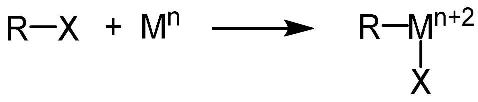
Most of the reactions we have seen up to this point in the course involve breaking a carbon–heteroatom bond and forming another carbon–heteroatom bond or a π bond. Very few reactions that we have seen involve forming a new carbon–carbon σ-bond. Notable exceptions are the Friedel-Crafts alkylation/acylation reactions (Lesson IV.7) or S_N2 reactions using a cyanide ($N{\equiv}C^-$) or acetylide ($H{-}C{\equiv}C^-$) anion as the nucleophile (Lesson III.16, OC1 Primer).

Remember that an *sp*-hybridized C – like the negatively-charged C in cyanide or acetylide – is much more electronegative than an sp^3-hybridized C (Lesson I.10, OC1 Primer), so an *sp*-hybridized C is better able to stabilize a negative charge. Having access to an anion with a negative charge on an sp^3-hybridized C would allow us to make new bonds to C without having triple bonds.

The lower stability of an sp^3-hybridized-C anion makes them harder to prepare and handle than the *sp*-hybridized-C anions. Ideally, we could access the desired nucleophiles as salts having an ionic bond between an sp^3-C and a metal like Li, Na, or Mg. Molecules having a metal–carbon bond are called **organometallic compounds**. Organometallic compounds are versatile sources for a wide range of carbon-centered nucleophiles. We will briefly assess how several important organometallic species are made and used in the following lessons.

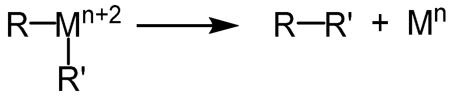
Lesson V.1.2 Oxidative Addition, Reductive Elimination and Transmetallation

One way that organometallic salts are formed is by **oxidative addition**. In the oxidative addition reaction, the metal oxidation state increases by "X" when "X" new groups (groups attached to metals are often called **ligands**) attach to the metal (X is 1 or 2 for reactions in this book). Many of the oxidative addition reactions we will encounter in this course will be the addition of a carbon–halogen bond across a metal (breaking a carbon–halogen bond and forming a metal–carbon and a metal–halogen bond):



$$\mathrm{R{-}X + M^{n} \longrightarrow R{-}\underset{\displaystyle X}{\underset{|}{M}}{}^{n+2}}$$

The reverse of oxidative addition is called **reductive elimination**. In reductive elimination, two anionic ligands come off of the metal and the metal oxidation state goes down by two. Many of the reductive elimination reactions we will encounter will involve the formation of a new C–C bond:



$$\mathrm{R{-}\underset{\displaystyle R'}{\underset{|}{M}}{}^{n+2} \longrightarrow R{-}R' + M^{n}}$$

Similar to how carbon can undergo nucleophilic substitution reactions, a metal can undergo **ligand exchange reactions**, in which one or more ligands on the metal are substituted by one or more new ligands. If one of the anionic ligands undergoing exchange has a C bound to the metal (i.e., R = a hydrocarbon ligand), then the reaction is classified as a **transmetallation** reaction. A transmetallation reaction has the general form:

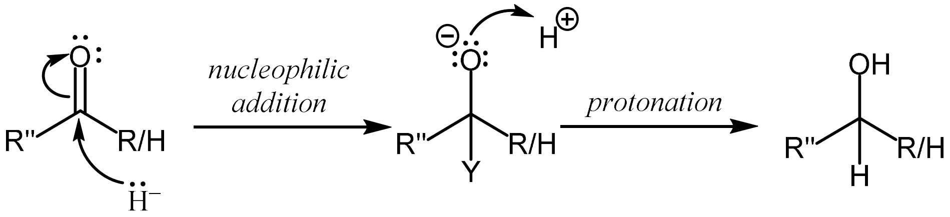
$$M–X + M'–R \rightarrow M–R + M'–X$$

Ligand exchange reactions, particularly transmetallation, occur in most of the stoichiometric and catalytic chemical reactions of organometallic complexes with organic compounds, so it is absolutely essential for the student to understand these reactions.

Lesson V.1.3 The Need for Nucleophilic Hydrogen

We have now seen how organometallic compounds could be useful for preparing new C–C bonds. In a similar fashion, sources of nucleophilic hydrogen could be useful to make new C–H bonds. Anionic hydrogen, H^{-}, called a **hydride** anion, is extremely unstable and reactive. This is because H is the smallest atom, and we know that larger atoms are better at stabilizing negative charge (Lesson I.10, OC1 Primer).

One especially useful application of hydride nucleophiles is nucleophilic addition of hydride to a carbonyl. If nucleophilic addition is followed by protonation of the O, an alcohol will result:



For arrow-pushing mechanisms using metal hydrides, **the reactive species is often abbreviated as “H⁻”** (as in the above example), but we will see that there are several possible sources of nucleophilic H, and they do react differently than this simplification might make it appear.

Lesson V.1.4. Sources of Hydride: $NaBH_4$ and $LiAlH_4$

Metal–hydride complexes – often simply called **metal hydrides** – can be easy to make for some metals simply by combining the elemental metal with hydrogen gas (e.g., $Na + \frac{1}{2} H_2 \rightarrow NaH$). In the metal hydrides, the hydrogen has a substantial δ^{-} charge, so many metal hydrides will spontaneously decompose upon exposure to the moisture in air, to yield hydrogen gas and a lot of heat, often catching fire. This is why ***handling many metal hydrides is dangerous and requires special training***.

The more polar the metal–hydrogen bond, the more reactive the metal hydride generally is. One common hydride source used by chemists is **sodium borohydride ($NaBH_4$)**. Boron has an electronegativity value (E.N. = 2.04) that is lower than, but still very close to, the value for hydrogen (E.N. = 2.2). As a result, a boron–hydrogen bond will still be polarized ($B^{\delta+}–H^{\delta-}$), but it will not be as reactive as, say Na–H or Mg–H bonds. Because it is so easy to handle, $NaBH_4$ is one of the most-widely used metal hydrides in organic synthesis. The borohydride anion BH_4^- features a tetrahedral B-atom at the center connected to 4 H-atoms, all of which carry a δ^- charge that render them nucleophilic.

Some groups are less reactive to nucleophilic addition than others, so some are not reactive enough to react with $NaBH_4$. For this reason, chemists developed **lithium aluminum hydride** ($LiAlH_4$, sometimes abbreviated as **LAH**). This compound is similar to sodium borohydride, but has more polar Al–H bonds instead of B–H bonds, making it more reactive. LAH is reactive enough to facilitate nucleophilic addition to all of the carbonyl functional groups discussed in this text, as we will see in Part VI of this Primer.

Lesson V.2. Preparation of Organolithium, Grignard and Gilman Reagents

Lesson V.2.1 Synthesis of Organolithium Reagents

A compound having a C–Li bond is called an **organolithium reagent**. Organolithium reagents can be prepared by a variety of methods. One approach is to react an alkyl halide (R–X) with 2 equivalents of Li metal:

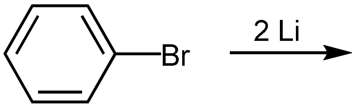
$$R{-}X + 2\,Li \longrightarrow R{-}Li + LiX$$

This route involves oxidative addition because each Li oxidation state increases from 0 to +1.

One significant safety concern for organolithium reagents is that they are **pyrophoric**, meaning that they can spontaneously catch fire upon exposure to air. They are also very water sensitive and react exothermically with humidity in the air or in a reaction solvent. For these reasons, *organolithium reagents must be used under rigorously air- and water-free conditions by specially–trained individuals only*. **For arrow-pushing mechanisms using organolithium reagents, the reactive species is often abbreviated as “R⁻”.**

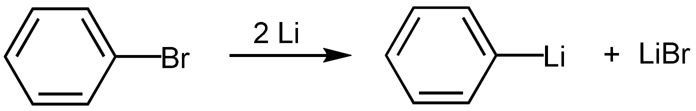
Example IV.2.1

Write a balanced equation for the reaction shown below. How could you abbreviate the nucleophile produced when the organic product is added to solution?

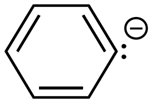


Solution IV.2.1

One lithium atom will oxidatively add to the benzene ring to form phenyl lithium. The other Li atom will form a salt with the Br:



The nucleophilic part of phenyl lithium could be abbreviated:



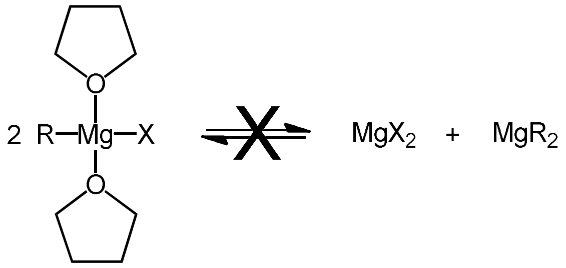
Lesson V.2.2 Synthesis of Grignard Reagents

Organomagnesium reagents, more commonly known as **Grignard reagents (R–Mg–X)**, are safer to handle than are organolithium reagents, but are still highly reactive with air and water and must be handled with care. Grignard reagents are prepared by the oxidative addition of Mg to R–X:

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

An interesting property of Grignard reagents is that they can exist as multiple species in solution in equilibrium with each other: 2 R–Mg–X $\rightleftharpoons$ MgX_2 + MgR_2. For Grignard reagents, this process is termed the **Schlenk equilibrium** and is strongly dependent on the solvent used in the preparation of the Grignard. The Schlenk equilibrium could be a problem because when you do a chemical reaction you want one well-defined species, otherwise you might get more than one reaction happening at once, giving a mixture of products. Fortunately, if an ether solvent such as Et_2O is used, the Grignard reagent actually ends up having solvent molecules bound to the Mg center via their oxygen atoms, stopping the Schlenk equilibrium:

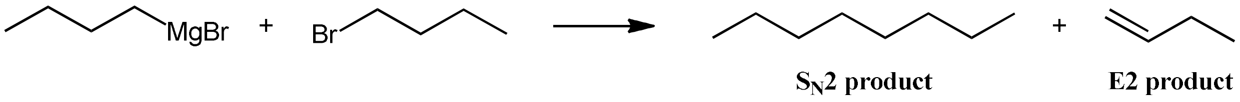
$$2\ \mathrm{R{-}Mg{-}X} \rightleftharpoons \mathrm{X{-}Mg{-}X} \ + \ \mathrm{R{-}Mg{-}R}$$



For arrow-pushing mechanisms using Grignard reagents, the reactive species is often abbreviated as “R⁻”.

Lesson V.2.3 The Limitations of Organolithium and Grignard Reagents

Organolithium and Grignard reagents are strong bases as well as good nucleophiles. Carbon centers that have three or more alkyl branches are the exception; they are too bulky to be good nucleophiles, but are still strong bases. We know that reagents that are both strong bases and good nucleophiles can produce mixtures of S_N2 and E2 products with some substrates (Lesson II.10, OC1 Primer). For example, reaction of ^{n}BuMgBr with 1-bromobutane produces some octane, but also substantial amounts of the E2 product 1-butene:



For this reason, scientists sought to develop other sources of nucleophilic carbon that are less basic. One of the most successful classes of less basic C nucleophile sources are the **Gilman reagents ($LiCuR_2$)**.

Lesson V.2.4 Synthesis of Gilman Reagents

Whereas organolithium and Grignard reagents can be prepared by direct reaction of alkyl halides with Li or Mg metal, this approach does not work with Cu metal. To circumvent this problem, the standard approach to making a Gilman reagent is to use an organolithium or Grignard reagent as the C ligand source and to transfer the ligands to copper by transmetallation. This is typically achieved by reacting the organolithium with CuBr or CuI:

Preparing Gilman Reagents form Organolithium Reagents:

$$2\,RLi \quad + \quad CuX \quad \longrightarrow \quad \underbrace{LiCuR_2}_{\boxed{\begin{array}{c} Li^{\oplus}\,[R{-}Cu{-}R]^{\ominus} \\ \textbf{\textit{Gilman Reagent}} \end{array}}} \quad + \quad Li{-}X$$

In subsequent lessons, we will examine the reactivity of the Gilman reagents with various organic functional groups**.**

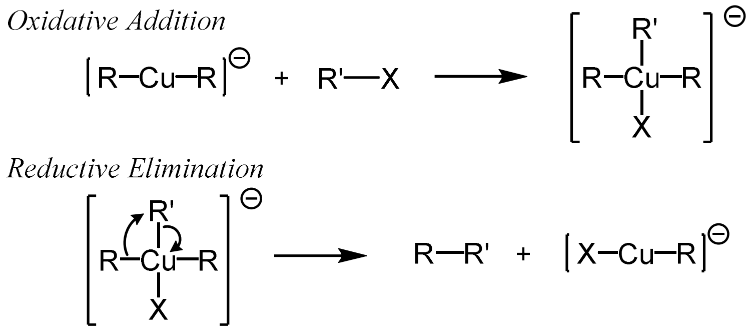
Lesson V.3. Reaction of Organometallics/Metal Hydrides with RX and Epoxides

Lesson V.3.1. Reaction of Organometallics with Carbon–Halogen Bonds

As we discussed in Lesson V.2, the basicity of organolithium or Grignard reagents often causes mixtures of S_N2, E2, and other products with alkyl halides. In contrast, the less basic **Gilman reagents provide an effective and general method for substituting a C–X bond with a C–R bond**:

$$\underset{\textit{Gilman Reagent}}{LiCuR_2} + R'{-}X \longrightarrow R{-}R' + Li\left[X{-}Cu{-}R\right]$$

In contrast to S_N2 reactions (which can only substitute on *sp*^{3}-hybridized C), substitutions using **Gilman reagents work on *sp*^{3}, *sp*^{2} *and sp*-hybridized carbon atoms**. This is because the mechanism of Gilman substitution is different from the S_N2 mechanism. The reaction involves oxidative addition of R'–X to Cu, then reductive elimination of the R–R' product:

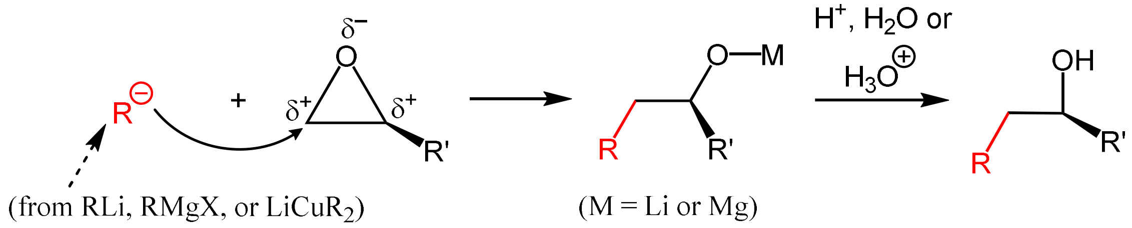


Both oxidative addition and reductive elimination are concerted, so **stereochemistry at both R groups is retained**. Impressively, this reaction works with R'–X substrates spanning a remarkable variety of R' groups (alkyl, alkenyl, alkynyl, and aryl) and halides (X = Cl, Br, or I).

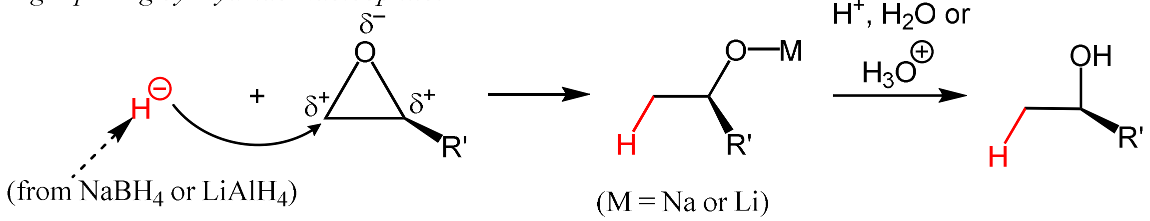
Lesson V.3.2 Reactions with Epoxides

We saw in Lesson II.15 that nucleophiles can cause ring-opening of epoxides. We also saw that when nucleophilic attack occurs in the absence of an acid, the nucleophile preferentially attacks the less-substituted side of the ring. Organometallics and metal hydrides are basic nucleophiles, so they can also be used to ring open epoxides by an S_N2-like attack on the less substituted side of the ring. In fact, we can treat *all* of the organometallic reagents we have discussed (organolithium, Grignard and Gilman reagents) as R^-, and the metal hydrides ($NaBH_4$ and $LiAlH_4$) as H^- nucleophiles following the pattern we have seen for other basic nucleophiles:

Ring-Opening by Organometallic Nucleophile:



Ring-Opening by Hydride Nucleophile:



The acidic workup is needed to protonate the O to give a neutral alcohol product.

Lesson VI.5. Addition of Organometallics/Metal Hydrides to Aldehydes/Ketones

VI.5.1 Aldehydes and Ketones Undergo Reaction Type A

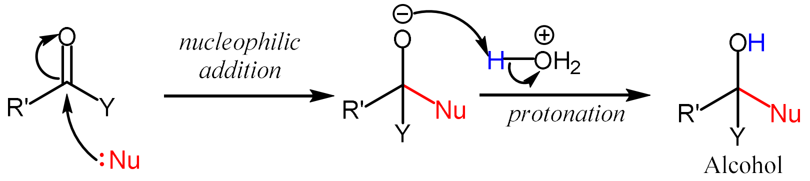
Aldehydes and ketones undergo reaction type A with hydride or C-based nucleophiles. Recall from Lesson VI.3 that Type A reactions involve two steps:

1. nucleophilic addition of an anionic carbon or hydrogen

2. protonation of the anionic oxygen produced by this addition

The general mechanism is as follows:

Carbonyl Reaction Type A

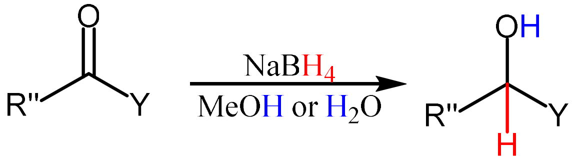


Y = alkyl or aryl (ketones)
or H (aldehydes)

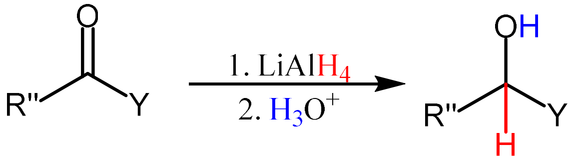
Nu: = hydride or carbanion, including
alkyl, acetylide, or cyanide anions

The nucleophiles for this type of reactions bear negative charge on either a carbon (R^-, provided by an organometallic reagent, an acetylide or cyanide anion) or a hydrogen (H^-, provided by a metal hydride). The reactions exhibiting this type of behavior are summarized here in the following figure:

Addition of $NaBH_4$ or $LiAlH_4$:

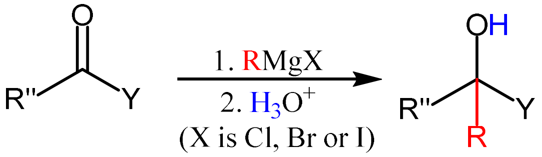


If Y is H, then the product is 1° alcohol
If Y is R', then the product is 2° alcohol



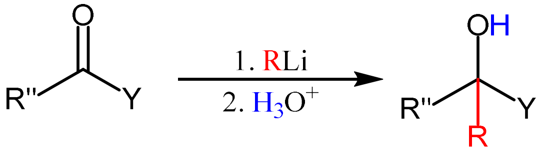
If Y is H, then the product is 1° alcohol
If Y is R', then the product is 2° alcohol

Addition of Grignard Reagent:



If Y is H, then the product is 2° alcohol
If Y is R', then the product is 3° alcohol

Addition of Organolithium Reagent:

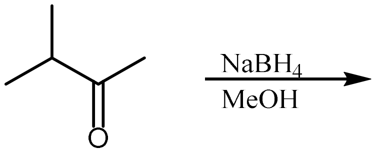


If Y is H, then the product is 2° alcohol
If Y is R', then the product is 3° alcohol

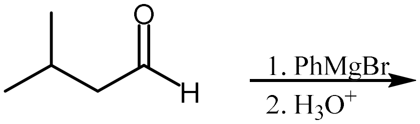
Example VI.5.1

Draw and provide the IUPAC name for the major product for each of the following reactions:

Reaction 1



Reaction 2



Solution VI.5.1

Each reaction above is Type A: 1) nucleophile attack to break the C–O π-bond, then 2) protonation to yield the alcohol products. For Reaction 1, the nucleophile is a H⁻ (from $NaBH_4$) and for Reaction 2 the nucleophile is a Ph⁻ (from PhMgBr). Note that each product contains a chiral center (marked by *), but because each starting material is achiral, the product will be a racemate: