

**EXPERIMENT 2:****The Grignard Reaction: Synthesis of 1,2-diphenyl-1,2-propanediol via a Diastereoselective Reaction.**

**Relevant sections in the text:** Fox & Whitesell, 3<sup>rd</sup> Ed. pg. 400-404, 615-618

*The experiment is based on a procedure reported by J. A. Ciaccio, R. P. Bravo, A. L. Drahus, J. B. Biggins, R. V. Concepcion and D. Cabrera, Department of Chemistry, Fordham University.*

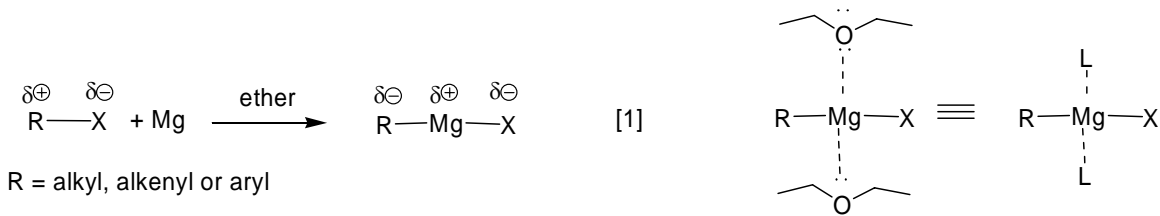
*Thanks to Barbora Bajtos, a former 283g student, who reviewed this laboratory.*

**General Concepts**

The reactions involved in the synthesis of complex organic molecules can commonly be categorized into either *functional group interconversions* or *skeleton building reactions*. The latter category, primarily those involving carbon-carbon bond formations, is most important in anabolic organic synthesis. The various reactions involved in the creation of large molecules from simple starting materials are quite limited in number. One of the most fundamental carbon forming bond reactions is the Grignard reaction.

The Grignard reaction involves an organomagnesium halide compound known as the Grignard reagent. It is formed by the interaction of an alkyl or aryl halide and metallic magnesium in ether solvents. The Grignard reagent is one of several organometallic reagents utilized in organic synthesis; others have been (or will be) discussed in lecture in Chapter 8. The Grignard reagent is particularly important due to its significant nucleophilic character and addition to the carbonyl group. The highly polarized carbon-metal bond is utilized extensively in the expansion of carbon skeletons since the carbon has considerable carbanion character.

The formation of the Grignard reagent occurs at the surface of the Mg metal. The metal is oxidized and the organohalide is reduced to the halide ion and a highly polarized carbon-metal bond with the magnesium.

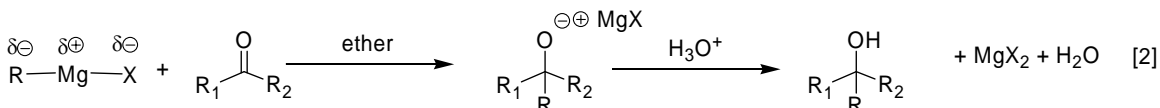


This highly polarized Grignard reagent essentially stops the reaction since it forms an insoluble metallic surface in most non-polar organic solvents. Protic solvents

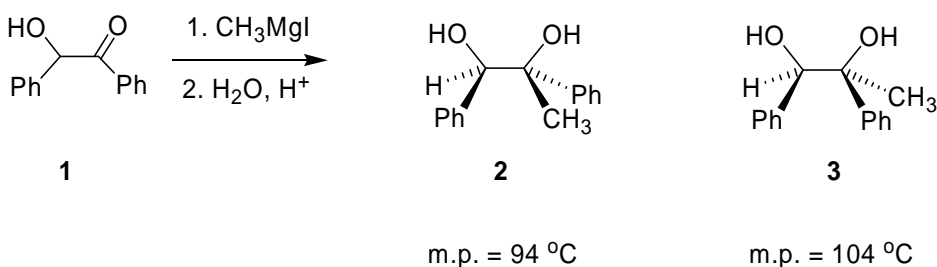
can not be used to solubilize the material because the Grignard reagent, while being an excellent nucleophile, is highly basic. Ether is used to support the reaction, being a relatively polar but aprotic solvent. Magnesium, existing as divalent and electron deficient, forms the Grignard reagent as the ether acts as a Lewis acid, coordinating to the Mg and solubilizing it (see Eq.1).

Grignard reagents react with a variety of carbonyl groups and epoxides to give several functional groups such as reaction with formaldehyde gives 1° alcohols, with other aldehydes it yields 2° alcohols, and with ketones it yields 3° alcohols. Reaction with esters give 3° alcohols, with acyl halides it yields a ketone, with carbon dioxide, carboxylic acids to name some of the transformations.

This particular experiment involves the formation of methylmagnesium iodide and the addition of the ketone benzoin (2-hydroxy-1,2-diphenylethanone), **1**. The alkoxide ion intermediate is formed when the Grignard reagent reacts with a ketone, but is transformed into a tertiary alcohol upon treatment with dilute acid (Eq.2).



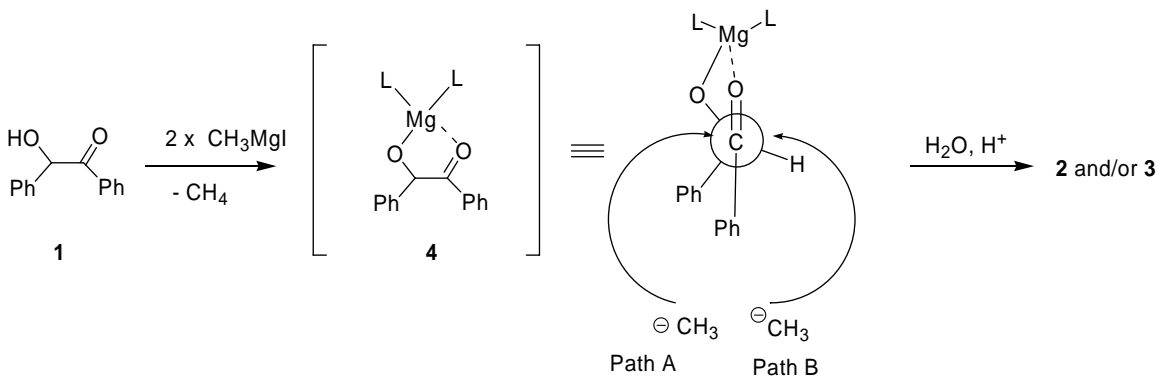
Chiral ketone reactions however produce two diastereomers since the Grignard reagent attacks from either face of the  $\pi$  system of the carbonyl group. The racemic R/S-benzoin (**1**) with  $\text{H}_3\text{CMgI}$  produces the two diastereomers of 1,2-diphenyl-1,2-propanediol, as seen in scheme 1 below.



Scheme 1

The reaction is highly diastereoselective, which means the Grignard reagent prefers to attack one face of the carbonyl over the other. A single diastereomer will be isolated in this experiment, which will be easily identified due to the differing melting points of each. After determining which diastereomer is preferred, you will propose an explanation.

The acidic alcohol group on benzoin causes the  $\text{H}_3\text{CMgI}$  to primarily act as a base, and the resulting conjugated base forms a magnesium complex (**4**). In addition to the formation of this complex, methane gas may be liberated. Note any observation during the laboratory of gas evolution. The diastereoselectivity is associated to the fact that the complex (**4**) is attacked by another equivalent of  $\text{H}_3\text{CMgI}$  as a nucleophile, but prefers one face over the other. This preference should be discussed after determining which diastereomer is the major product.



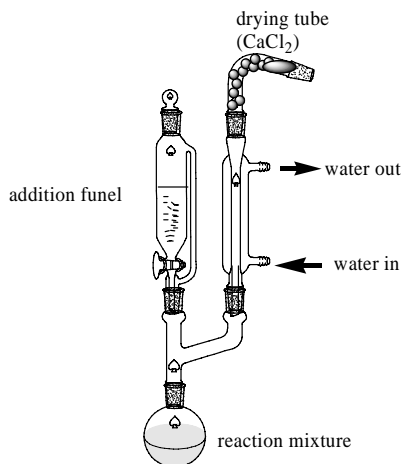
### Experimental Procedure

**\*Note\*:** It is essential that all glassware is clean and DRY since only a trace of water will destroy the Grignard reagent. After completion of the experiment rinse all glassware with acetone and place the addition funnel and round bottom in the oven for the next group.

**\*Hazards\*:** Always work in the fumehood. If transporting anything outside of the hood, be sure it is stoppered. Diethyl ether is highly volatile and HIGHLY FLAMMABLE. Use the sand bath and heating mantle as you did in experiment 1. Be sure your hood does not have any ether in it before using your hot plates. Caution: Iodomethane is a suspected carcinogen, so avoid skin contact with its ether solution. WEAR GLOVES when performing the first part of the experiment.

### Part A: Preparation of Methylmagnesium Iodide

- Transfer 580 mg (0.58g) of magnesium turning (= x mmol) into a small labeled beaker and place in the oven for 10 minutes.
- Prepare a clean and dry 250 mL round bottom flask (DO NOT wash glassware the day of the experiment!) with a small stir bar and sand bath placed on top of a heating mantle. Attach a dry



Claisen adapter equipped with an addition funnel and reflux condenser. To the reflux condenser attach a  $\text{CaCl}_2$  drying tube (the set-up is similar to that shown in the picture). Let it cool.

- Obtain your Mg turnings, crush well with a spatula and add to the round bottom. Let this cool.
- Transfer 24 mL (24 mmol) of a 1.0 M solution of methyl iodide ( $\text{CH}_3\text{I}$ ) in anhydrous diethyl ether to the addition funnel. Add just enough of it to the reaction flask to cover the Mg turnings.
- Stir the suspension. If the reaction does not proceed spontaneously try warming it using the palms of your hand and the reaction should start spontaneously. Be careful not to touch the flask without checking to see if the reaction has started, since you don't want the reaction to proceed too quickly. If your reaction does not start ask your TA for help.
- Add the rest of the contents of the addition funnel over 15 minutes and in small portions once your reaction has begun. The slow addition lessens the formation of ethane, a by-product. (Explain where and why would this form.)
- After all of the  $\text{CH}_3\text{I}$  solution has been added, the mixture should be brought to a gentle reflux while stirring until the Mg metal has completely reacted (~30 minutes). The Grignard reagent is a cloudy gray/white or a brownish colour.

### Part B: Grignard Reaction with $\text{H}_3\text{C}\text{MgI}$ and Benzoin

#### (i) Synthesis of 1,2-diphenyl-1,2-propanediol

- Cool the ethereal  $\text{CH}_3\text{MgI}$  in an ice-water bath. After cooling, dissolve 1.0 g of (+/-) Benzoin – a racemic mixture of the R and S stereoisomers- (4.72 mmol) in ca. 20 mL anhydrous dichloromethane ( $\text{CH}_2\text{Cl}_2$ ) and then add this *dropwise* from the addition funnel over several minutes with stirring.
- The solution will froth due to evolution of methane. (Explain where the methane comes from)
- Remove the ice-water bath and bring the mixture to reflux for another 30 minutes.
- Cool the flask to room temperature in a water bath, then slowly add 50 mL of a 10%  $\text{H}_2\text{SO}_4$  solution into the flask through the addition funnel while stirring.
- Pour the entire contents of the flask into a 250 mL separatory funnel and separate the two layers. Keep the organic phase in an Erlenmeyer flask and then extract the aqueous layer twice with 20 mL of diethyl ether. Take the combined organic layers

and dry them over anhydrous  $\text{MgSO}_4$ , and then gravity filter the organic phase into a *pre-weighed* round bottom flask.

- Concentrate the contents by removing the diethyl ether on a rotary evaporator. The remaining contents should appear as amber colored oil that will solidify upon cooling.
- Determine the weight of the crude product. Save a small portion of crude to obtain a melting point and to perform a TLC. (read experiment 1 from Chem 273a to review )
- Store the rest of the crude product either by itself (preferred) or in a minimum amount of petroleum ether in a clean labeled test tube until the next week. **Do not store in ether! Petroleum ether is *not* really an ether, it is a mixture of hydrocarbons!**
- For the TLC, dissolve some of the crude product set aside earlier in a bit of  $\text{CH}_2\text{Cl}_2$  and spot it on the TLC plate. Run benzoin (dissolved in  $\text{CH}_2\text{Cl}_2$ ) in a separate lane on the same TLC plate. Eluet using 2:1 petroleum ether: ethyl acetate as the solvent mixture. Visualize your TLC by dipping your eluted plate into 20% phosphomolybdic acid stain and drying using a heat gun.
- Determine and report the  $R_f$  values of benzoin and the product(s). Any unreacted benzoin should be observed in the TLC of the crude product. (Draw images of the TLC plate in your lab book so that you can report it accurately in your write-up)

**(ii) Purification of 1,2-diphenyl-1,2-propanediol**

- Recrystallize the crude solid using a minimum amount of hot, high boiling petroleum ether in a 250 mL Erlenmeyer flask (ca. 5-10 mL for every 100 mg of crude product). Decant the mother liquor away from any undissolved solid (if there is any). Allow the flask to cool naturally to form crystals.
- Collect the crystals by vacuum filtration and, when dry, check the melting point and do a TLC analysis with benzoin as the second spot.
- Repeat the recrystallization at least one more time, or until you reach a constant and sharp melting point (you may want to add a small amount of decolorizing charcoal). Repeat a TLC of the final purified product, where no unreacted benzoin should appear.
- Submit a sample of your final crystals to your TA who will check your melting point. Each recrystallization will cause your product yield to diminish, so do not be concerned.

Record your crude yield and recovery yield (and m.p.) after each recrystallization. Obtain and characterize the  $^{13}\text{C}$ ,  $^1\text{H}$  NMR, IR and mass spectra of the product and starting material (the spectra will be provided to you).

**Formal Report Discussion:**

Write-up a formal report as outlined in the material provided to you at the start of term. In addition to reporting the yields (crude and purified), the TLC analysis, melting points, and characterization of the spectra be sure to include:

- Identification and chiral assignment of the two possible diastereomers **2** and **3** (assign R and S; remember each diastereomer is made as its pair of enantiomers).
- Identify the major diastereomer (product **2** or **3**?) in your product from your recrystallization and melting point data.
- Discuss the TLC and spectroscopic data.
- Draw a mechanism that accounts for the diastereoselectivity, and explain.

Your report should be no more than 5 type-written pages + spectra.