

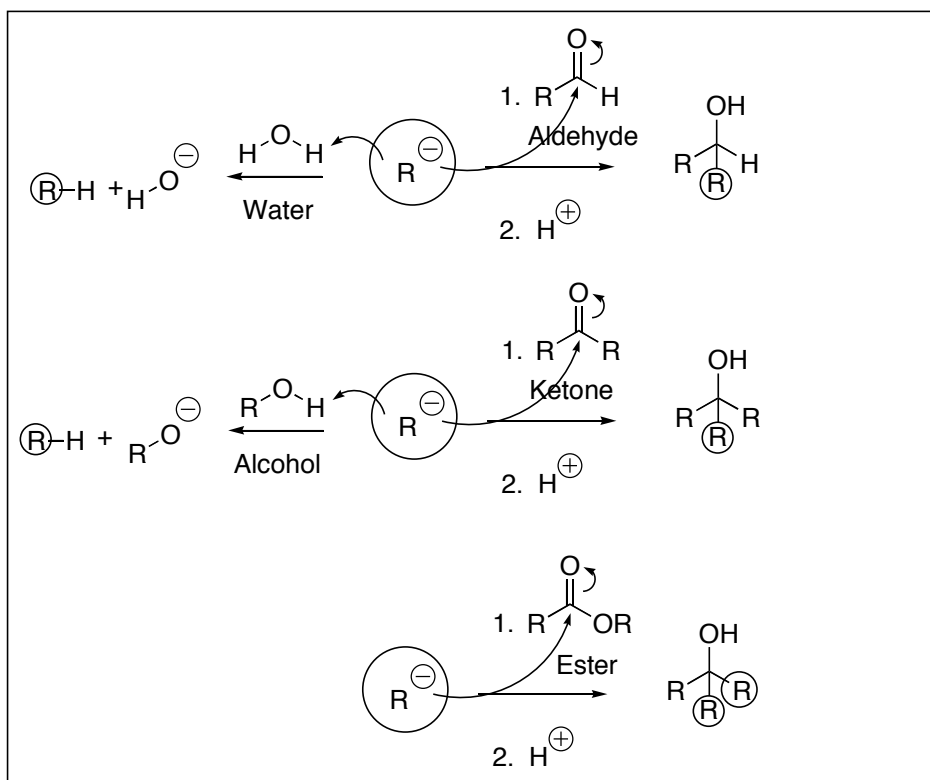
**I. Background** In 1912 Victor Grignard received the Nobel prize in chemistry for his work on the reaction that bears his name, a carbon-carbon bond-forming reaction by which almost any alcohol may be formed from appropriate alkyl halides and carbonyl compounds. The Grignard reagent  $\text{RMgBr}$  is easily formed by redox reaction of an alkyl halide with magnesium metal in anhydrous diethyl ether solvent.



The Grignard reagent **can be viewed as an ionic species consisting of carbanion  $\text{R}^-$** , with a  $\text{Mg}^{2+}$  counterion and an additional  $\text{Br}^-$  counterion. **The carbanion  $\text{R}^-$  is very reactive, and functions both as an extremely strong base and an extremely strong nucleophile.**

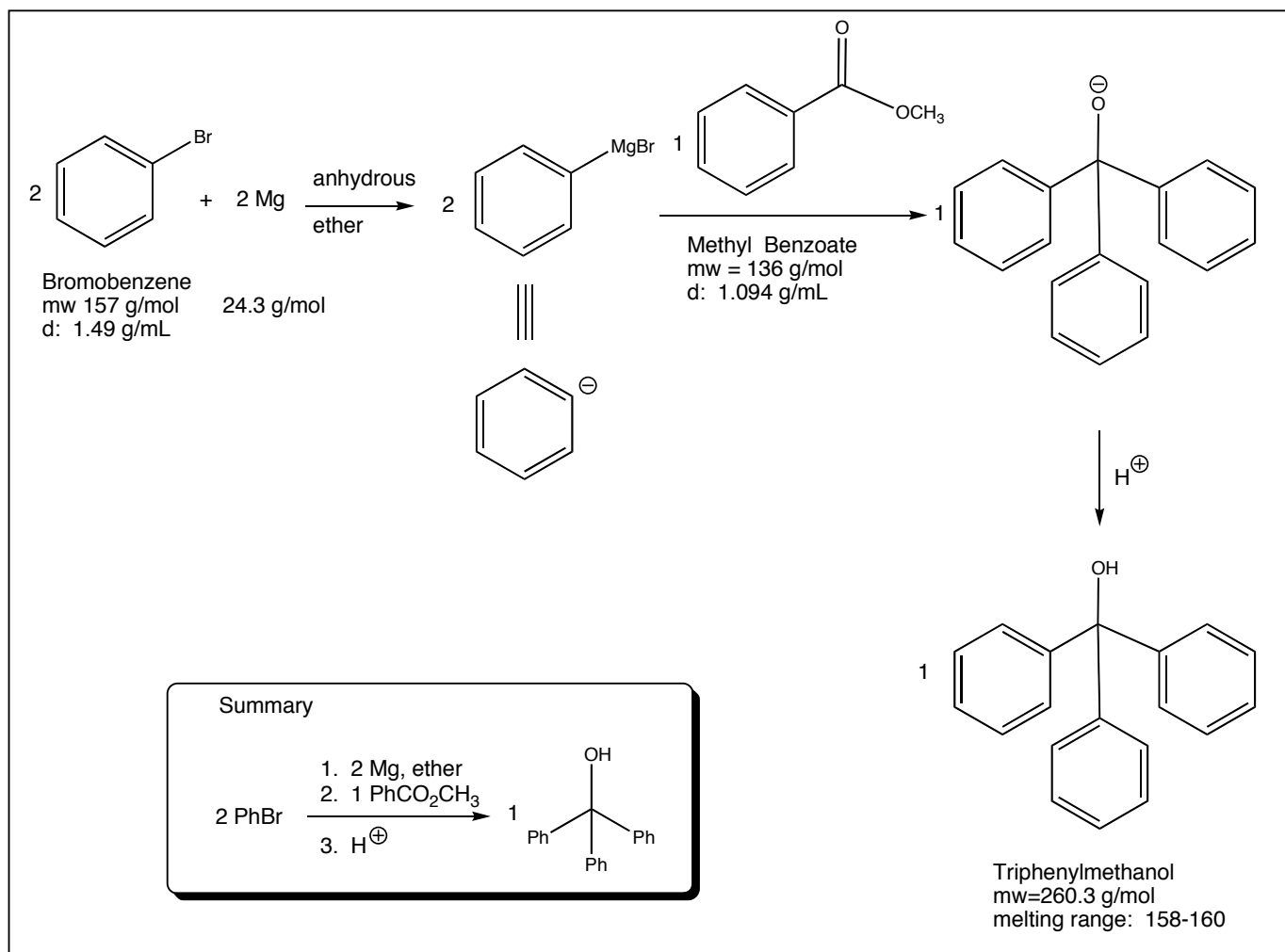
Some of its reactions are shown below.

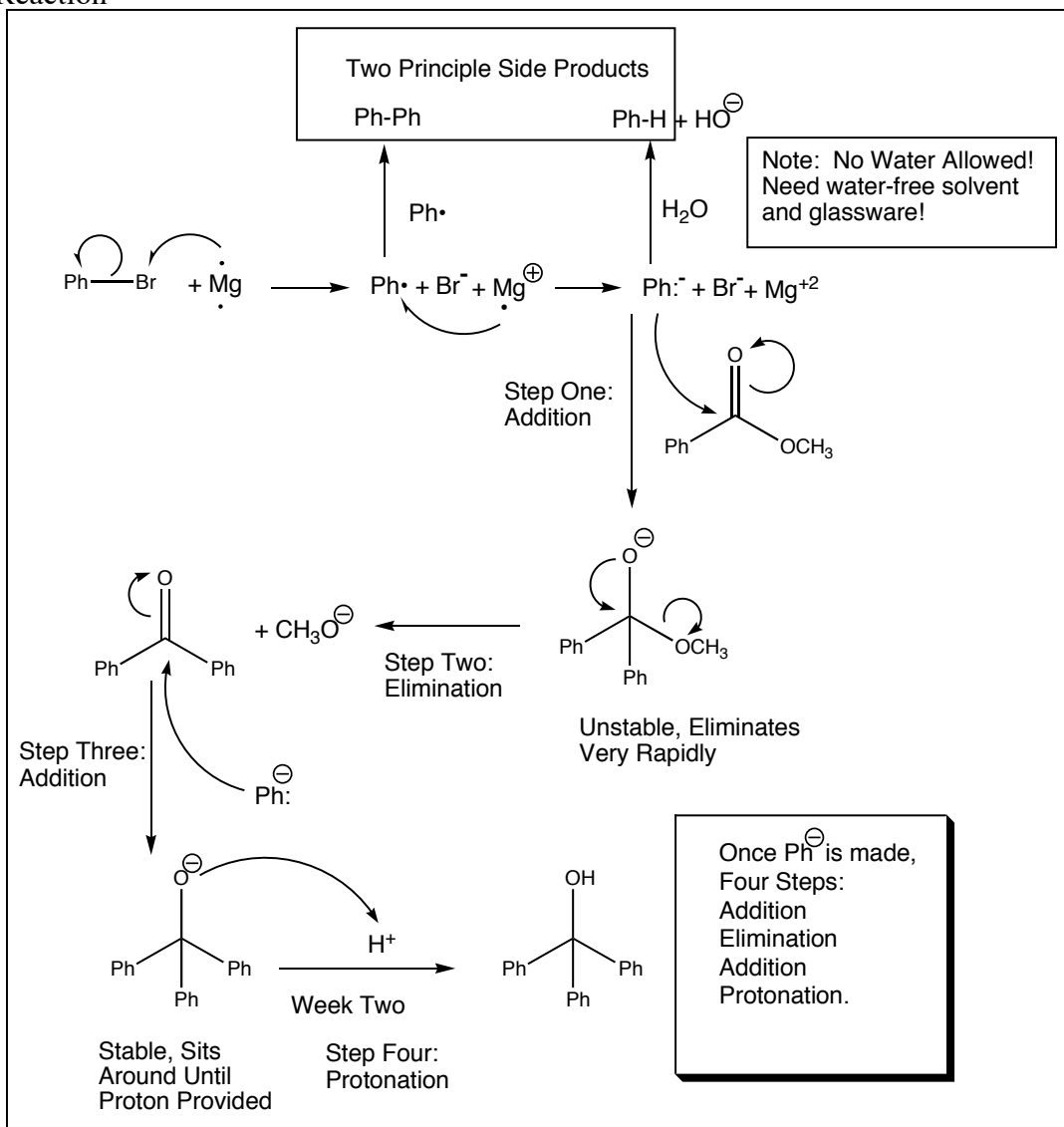
- **It reacts as a strong base with water or alcohols.**
  - Conversion from less stable  $\text{R}^-$  to more stable  $\text{HO}^-$  or  $\text{RO}^-$  is favorable.
- **It reacts as a strong nucleophile with carbonyl groups aldehydes, ketones, and esters.**
  - Conversion from less stable  $\text{R}^-$  to more stable  $\text{RO}^-$  is favorable, followed by protonation to give alcohols  $\text{ROH}$ .



**II. Overview of Our Experiment**

Our experiment is shown below. During week one we will generate the Grignard reagent (step one) and react it with the ester (step two). During the second week we will neutralize the alkoxide (step three), isolate the alcohol, purify the alcohol by recrystallization, and do product analysis.





**The overall mechanism** is illustrated above. The carbanion is generated by electron transfer from magnesium metal. The reactive carbanion then attacks electrophilic carbonyl to give an anionic intermediate (step one). This unstable intermediate rapidly eliminates a methoxide anion (step two). The resulting ketone is attacked again (step three). The resulting anion waits patiently until next laboratory period, at which time acid will be added to protonate the anion (step four).

**Byproducts and Potential Problems** There are two main byproducts and three problems.

- The first side product is biphenyl, Ph-Ph**, which is formed in competition with the Grignard reagent PhMgBr. Following initial electron transfer, the phenyl radical Ph• can either accept another electron leading to the desired carbanion, or combine with another phenyl radical to make biphenyl.
- The second side product is benzene (Ph-H), resulting from protonation of the carbanion.** The carbanion is supremely basic, so if there is any water in the solvent or in the glassware, or if moist air is allowed to enter the reaction mixture, some of the carbanion will be protonated. **Great care is thus required to ensure “dry”, water-free conditions.**
- The third problem is getting the magnesium to actually do the electron transfers!** Pure magnesium is an active metal, so active that any magnesium that has been exposed to air is inevitably coated with a film of magnesium oxide on its surface. This oxide film blocks the bromobenzene from actually contacting active magnesium, and thus prevents the requisite electron transfer. **For a Grignard reaction to work, it is necessary that fresh active magnesium be exposed.** Otherwise no electron transfer from magnesium to bromobenzene can take place, no carbanion can be formed, and no reaction proceeds. We will use two techniques, iodine activation and physical crushing, to activate our magnesium.
- The fourth problem is unreacted starting material.** (Could be the Ph-Br, the Mg, and/or the ester).

### III. Procedure: Week One

Note: All equipment and reagents must be dry!

#### **Phase 1: Preparing the Grignard Reagent**

1. Dig out the following pieces of glassware:
  - a. 250-mL round-bottomed flask
  - b. "Claisen" two-branched connecting adapter (piece #9 in your kit)
  - c. reflux condenser (piece #12 in your kit)
  - d. separatory funnel with stopper
  - e. drying tube packed with calcium chloride
  - f. stick the drying tube into the rubber end of the thermometer adapter
2. Clamp the 250-mL round-bottomed flask to a vertical rod. If possible, use a clamp with grips that are either pure metal or else have non-flammable white coating rather than gray rubber coating. (Rubber clamps will melt and stink when subjected to Bunsen-burner flame!)
3. Light your Bunsen burner and pass the flame over the flask until there is no more steam visible on the surface of the glass.
4. As soon as the steam is gone from the flask, add the Claisen adapter to the flask and flame dry it as well
5. As soon as the steam is gone from both the flask and the adapter, add the reflux condenser to the flask, and flame dry as best you can.
6. While everything is still hot, attach the drying tube into the top of the reflux condenser, add the separatory funnel with its stopper on into the other arm of the Claisen adapter.
  - **At this point, the interior should be entirely closed from wet air getting in. The separatory funnel blocks out one side, and any air coming in through the column must pass through the drying tube.**
7. Weigh out about 2 grams of magnesium metal. (Record weight)
8. When the glassware is cool enough to handle, add tubing to the condenser so that you can run a slow stream of tap water through the condenser. Reassemble the array as quickly as possible.
9. When the glassware is cool enough to handle, lift out the condenser and pour in the magnesium, then replace the condenser as soon as possible.
10. Pour 40 mL of ether into the separatory funnel and put stopper back on.
11. Measure out 9.0 mL of bromobenzene in a graduated cylinder. Record the volume as accurately as possible.
12. Ask the instructor to add one small chip of iodine into the separatory funnel. (The iodine can be added directly to the round-bottomed flask, or to the separatory funnel before the ether is added).
13. Drain the bromobenzene/ether/iodine solution into the round-bottomed flask.
  - **The iodine serves two functions.**
    - a. The first is as an **indicator**. The color will disappear when the magnesium is activated and is able to do redox chemistry with bromobenzene.
    - b. The second is as an **activator**. Iodine is sometimes able to chemically "clean" the surface of the magnesium so that fresh, active magnesium is exposed so that it can do redox chemistry with bromobenzene. However, it doesn't often work!
  - **Make a mental picture of how much magnesium you have to begin with, so you can remember later on for comparison.**
14. If the redox chemistry of the Grignard reaction initiates, the iodine color will go away, the solution will begin to get hot, there will be some bubbling, and things may become slightly cloudy.
15. If there is no indication of reaction after two minutes, beg the instructor to come over to crush some magnesium. Note: If yours starts without need for crushing, specifically note this in your writeup.
16. The instructor will use a glass rod to try to crush some of the pieces of magnesium firmly against the bottom of the flask. This will expose fresh, active magnesium that should be able to initiate the redox chemistry and the formation of the Grignard reagent. Trying to crush very very hard magnesium pieces inside a glass flask is dangerous, though; it's easily possible to punch a hole in the glass. So if somebody is going to poke a hole in your flask, let it be the instructor so he can take the blame rather than doing it yourself!

- The reaction should be so exothermic that it will be self-boiling for some time. If the rate of boiling subsides, apply a heating mantel (connected to the Variac, not directly to the wall outlet) and apply heat to maintain a good rate of boiling. A power setting of 20-25 is good; do not exceed 25.
- Maintain boiling for one hour.
  - Note: notice how the reflux condenser works. The bottom flask can be boiling hot (which facilitates maximum reaction rate), but the condenser enables you to liquify and recycle all of the boiling solvent.**
  - Keep good procedural and observational notes of everything that you see and do!**

### Phase 2: Things to do during the Grignard Hour...

Once the reaction is clearly going, prepare for Phase 3, in which you will add the methyl benzoate ester electrophile to the carbanion that you are making. And do the calculations that you will eventually need to include in your report.

- Calculate what volume (in mL) it will take to add 5.0 grams of liquid methyl benzoate (density = 1.094 g/mL).
- Calculate the number of **moles** used for magnesium, bromobenzene, and methyl benzoate.
- Calculate the **overall theoretical yield** (in grams) for your final product of next week, triphenylmethanol (mw = 260 g/mol).
  - To do this, you must **first identify** which if the three reactants (Mg, PhBr, or PhCO<sub>2</sub>CH<sub>3</sub>) is the **limiting reactant**
  - To do this, you must factor in the overall stoichiometry, which is not all 1:1:1:1. (Given your calculated moles of Mg, how many moles of Ph<sub>3</sub>COH could you make? Given your calculated moles of PhBr, how many moles of Ph<sub>3</sub>COH could you make? Given your calculated moles of PhCO<sub>2</sub>CH<sub>3</sub>, how many moles of Ph<sub>3</sub>COH could you make?)
  - In calculating theoretical yield for a multistep reaction, theoretically every step will be perfect. (We know otherwise, but we're talking theoretical yield here...) Thus you don't need to calculate or measure quantities for any intermediates. Your limiting reactant and theoretical yield should consider only original reactants and final product, all things which are easily quantified.
- After the Grignard solution has reacted for one hour, check to see how much magnesium is left. Any qualitative estimate of about how much is left? (None? 10%? 50%?)
  - What implications might this have on your possible yield? Is it necessary for all of your magnesium to have reacted completely in order to get 100% yield? Or could you get 100% yield even if some of your magnesium remains unreacted?

### Phase 3: Reacting the Grignard Reagent with the Methyl Benzoate

- After the hour is up, let the reaction cool down (an ice-water bath might help).
- Add 15 mL of ether to your separatory funnel. (Stopcock closed).
- Add 5.0 grams of methyl benzoate to your separatory funnel by syringe. (Remember, you calculated this volume in Phase 2....)
- Remove the cold bath (if you have one on), then drain the ester/ether solution into the round-bottomed flask, slowly so that the reaction doesn't overheat to much. Try to shake the solution around as much as possible (hard to do when it's clamped!) If things start to boil hard, reapply the cold bath.
  - Record your observations!
- If everything is added without excessive boiling, try to shake everything up, and give it five minutes or so to continue reacting.
- If the reaction is still hot, cool it with the ice bath.
- Remove all the glassware from the top of the round-bottomed flask, and stuff in a rubber stopper.
  - Note: it is essential that the solution isn't hot when you do this. If it is, then when it cools it will create a vacuum and suck the stopper in...)
  - Note: it is essential that the vigorous exothermic reaction is done before you stopper the flask. Otherwise if stirring or further reaction generates enough heat, it will cause the ether to boil and blow the stopper off!
- Stash the round-bottomed flask with the chemicals and the stopper into a secure spot in your drawer, and wait till next lab to finish!

**IV. Procedure: Week Two**

1. Record your observations for what your mixture looks like at this point.
2. Remove the stopper, and add about 40 grams of ice and 50 mL of 2M sulfuric acid
  - The acid will react exothermically with both the anion and unreacted magnesium. The ice is there simply to absorb the heat.
3. Swirl well to promote hydrolysis and break the solid clumps. Use a spatula to break up the chunks.
4. In the process, three things should happen:
  - The anion should be protonated, giving the neutral organic alcohol product. This should partition into the organic ether layer.
  - Magnesium salts should be ionic, so they should partition into the aqueous layer.
  - Unreacted leftover magnesium metal will react with the acid to give molecular hydrogen. That's what causes the bubbling. ( $1 \text{ Mg} + 2 \text{ H}^+ \rightarrow \text{Mg}^{2+} + \text{H}_2 \text{ gas}$ )
5. Pour the mixture into your separatory funnel. (The magnesium doesn't need to be totally dissolved...)
6. Pour an additional 10 mL of sulfuric acid and 10 mL of ether into your flask, swirl to try to dissolve up anything left on the walls, and pour into the separatory funnel. (These need not be measured, just pour some in approximately.)
7. Drain off the bottom aqueous layer into a beaker.
8. Add another 20 mL of sulfuric acid into the separatory funnel, shake it up, and drain off the aqueous layer again. Pour the combined aqueous layers into the aqueous waste bottle in the hood.
9. Drain the organic layer from the separatory funnel into an Erlenmeyer flask.
10. Add about 5 grams of sodium sulfate to "dry" the ether layer. Add additional scoops if the sodium sulfate is all clumped up (indicating that there may be too much water for the sodium sulfate to handle).
11. Plug your long-stem funnel with a little glass wool
12. Pour the ether solution through the glass-wool plugged funnel into a different Erlenmeyer flask. The wool should be sufficient to filter off the solid sodium sulfate, and only allow the solution to get into the flask. Rinse your original flask and the sodium sulfate with an additional portion of ether.
  - At this point, your solution should be free of water and of magnesium salts. Other than the ether solvent itself, you should have nothing but the desired product and organic contaminants.
13. Prepare a sample for GC-MS analysis. Take out one pipet, and add it to your 25-mL beaker. Add a solvent (ether or acetone or whatever organic solvent is available in the hood) to dilute to 10 mL. Take one pipet of this diluted mixture into your 10-mL Erlenmeyer, and dilute this to almost 10 mL. Take one pipet of this diluted solution and place it into a GC-MS vial. Label it. You can save it and run it later (you'll need to run another one later anyways.)
14. Make a TLC plate with five pencil marks for five tracks ready:
  - a. Authentic biphenyl
  - b. Authentic methyl benzoate
  - c. Crude mixture
  - d. Purified mixture
  - e. Post-crystallization solvent
15. Take a capillary droplet from your mixture, and put it on the "crude mixture" spot. Take droplets from the authentic biphenyl and methyl benzoate bottles in the hood and apply them as well. Save the plate until you've finished purifying the product, at which point you'll be able to apply your last spot.
16. Add 25 mL of "ligroin" solvent (all hydrocarbons, mostly hexanes, but not pure) to your ether solution. The product is more soluble in ether than in hydrocarbons, so you are essentially adding some "bad solvent" to facilitate a mixed solvent recrystallization.

17. Add a boiling stick to your organic solution
18. Now heat your solution on a hot plate. A power setting around 5 or 6 might be a good starting guess?
19. Boil the solution down to 20-25 mL or so. (Crystals may start to form before this, depending on your yield. But if you stop boiling as soon as the first crystals form, you'll still have too much solvent and will get a low yield.) Add another 20 mL ligroin and again boil down to around 20-25 mL.
20. Remove from heat, and let cool slowly to grow your crystals, first to room temperature and then to 0°C.
21. Filter your crystals with Buchner funnel and aspirator.
22. Rinse with cold solvent. (What to use?)
23. Take a droplet from the solvent and put it on the tlc plate in the "post-crystallization solvent" spot
24. Take about 0.2 grams of your crystals (needn't be bone dry) and dissolve in 3 mL of ether. Then take a capillary and put a droplet of this purified material onto your tlc plate in the "purified" spot.
25. Prepare a sample for GC-MS analysis. Take out one pipet of the solution you made in the previous step, and add it to your 25-mL beaker. Add a solvent (ether or acetone or whatever organic solvent is available in the hood) to dilute to 10 mL. Take one pipet of this diluted mixture into your 10-mL Erlenmeyer, and dilute this to almost 10 mL. Take one pipet of this diluted solution and place it into a GC-MS vial. Label it.
26. You can run this GC-MS and the "crude" GC-MS. You will be able to evaluate the purity of your sample, and compare it to the purity you had prior to crystallization. You should also be able to use the library to perhaps evaluate what contaminants were present prior to purification and what contaminants perhaps remained after crystallization.
27. Run the tlc in designated solvent (10% ethyl acetate/hexane?), and analyze by UV and the "dip" solution.
  - Mark down the results, with the following questions in mind:
    - Is biphenyl present in the crude mix? In the purified material?
    - Is methyl benzoate present in the crude mix? In the purified material?
    - Any other side products in the crude?
    - Did recrystallization purify the material at all?
    - Did crystallization get all of the product out of the solvent?
28. Take a melting range on your final product. (Should melt above 150°, so heat accordingly)
29. Get your final mass.

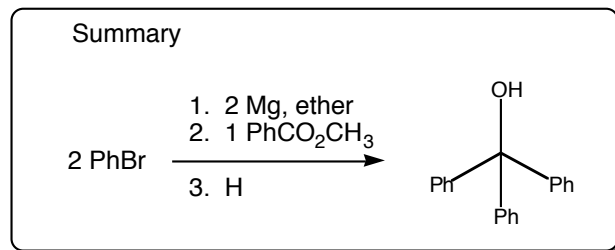


## Grignard Reaction

Lab Report Requirements and Format: The following layout is standard for a “synthesis reaction” report. Provide the parts and information in the sequence specified.

## 1. Title = Reaction Summary

For an organic reaction, there is no point in having a Worded Title: The chemical reaction is the best title summary of what you did!

2. Listing of all Chemicals Used

- This should include all chemicals used, including solvents.
- For each chemical, you should include the actual quantity used and measured. For example, with the methyl benzoate you measured a volume by syringe, rather than by weighing on a balance. So you should list the volume you actually used rather than just the weight.
- If a person was later to repeat your experiment, they should be able to look at this list and know all the chemicals they'd need to have on hand and in what quantities, in order to complete the experiment.
- In some cases, there may be considerable roundoff (you needn't keep precise record of the quantity of solvent that was used, for example, or of sodium sulfate drying agent...)
- For reactants that might possibly be limiting reactants and might possibly factor into calculation of the theoretical yield, however, you must include more than just the quantity of chemical used. You should also include a conversion from what you measured into the number of moles used.

## 3. Calculation of Theoretical Yield

- Specify which chemical is the limiting reactant
- Given moles of limiting reactant, calculate theoretical moles of product
- Given moles of product, calculate theoretical grams of product.
- Note: Why do this so early in report?
  - First, because it fits in near your mole calculations above.
  - Second, if calculated in advance, as with most research, you know which chemical is limiting and thus must be measured most carefully, but you also know which are in excess and thus need not be measured with equal precision.
  - Third, it's nice to know approximately how much material is expected, so you can recognize whether your actual results are reasonable or way off.

## 4. Writeup of Actual Procedure.

- For this particular experiment, the “procedure” section will be by far the biggest portion of your report.
- This should be a concise but detailed description of things, including:
  - What you actually did (even if not recommended or not from recipe)
  - All observations should be included. These include all observed changes, such as:
    - Changes in **color**
    - Changes in **solubility** (formation of precipitate or cloudiness...)
    - Formation of **bubbles**
    - Changes in **temperature** (like, reaction became hot...)
  - Time and temperature details:
    - Whenever you heat something or cool something, the procedure should specify
    - Specify times. Whether you boiled for 5 minutes or 5 hours matters!
- Writing details: As a record of what actually happened, the report must be written in past tense, not command tense. (Rather than “Add this”, should read “I added this”, or “I dropped that...”)
- Use of personal pronouns is accepted in this class. (Teachers in other classes may have different requirements). But you are not obligated to avoid references to “I” or “we” in this class.

## 5. Product Analysis

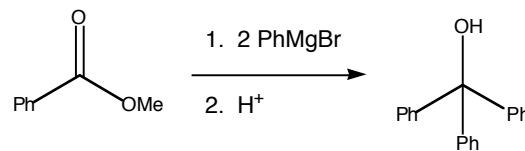
- Any NMR, mp, bp, TLC information, and GC-MS. For this report, mp, gc-ms, and TLC information must be included.
- Final yield and percent yield information. (include detailed TLC picture and interpretation...)

## 6. Discussion/Summary. Need not be long, but any conclusions or excuses would go here...

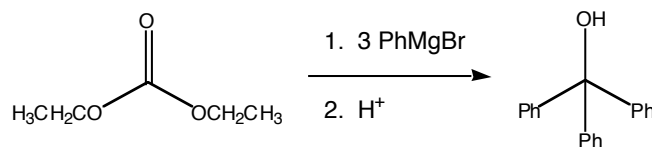
## 7. Answers to any assigned Questions

## Assigned Questions, Grignard Lab

1. Draw a detailed, step-by-step mechanism for the reaction you actually did: (on attached sheet?)



2. Triphenylmethanol can also be prepared by the reaction of PhMgBr with diethylcarbonate (CH<sub>3</sub>CH<sub>2</sub>O)<sub>2</sub>C=O, followed by H<sup>+</sup> workup. Draw a detailed, step-by-step mechanism for the following reaction: (on attached sheet?)



3. If you hadn't bothered to flame-dry your glassware or used a drying tube, what byproduct would have formed?
4. If the methyl benzoate you used had been wet (contained water), what byproduct would have formed? (Note: the answer for this problem may or may not be the same as for previous problem.)
5. Your yield was considerably less than 100%. Discuss where you think things might have come up short. You may wish to differentiate reaction things (reasons or evidence that you didn't have complete chemical conversion) versus isolation things (reasons or evidence that you didn't isolate all of the product that was actually made chemically). (It's possible that your TLC may support or disprove some possible explanations.)
6. Given the quantities of chemicals used in this recipe, one could conceivably have gotten a 100% chemical yield without having completely reacted all of the magnesium, or without having completely reacted all of the bromobenzene. But it would not have been possible to get 100% chemical yield if the methyl benzoate didn't react completely. Explain.