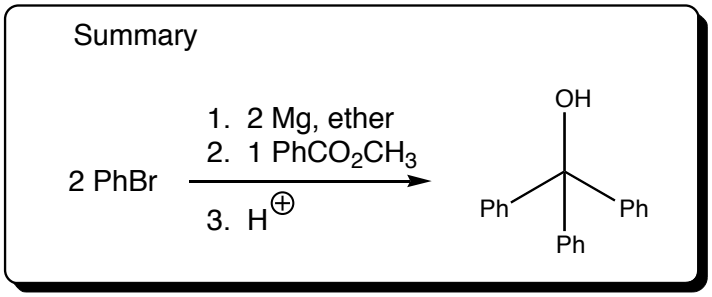
Chem 355 Jasperse Grignard Synthesis of Triphenylmethanol



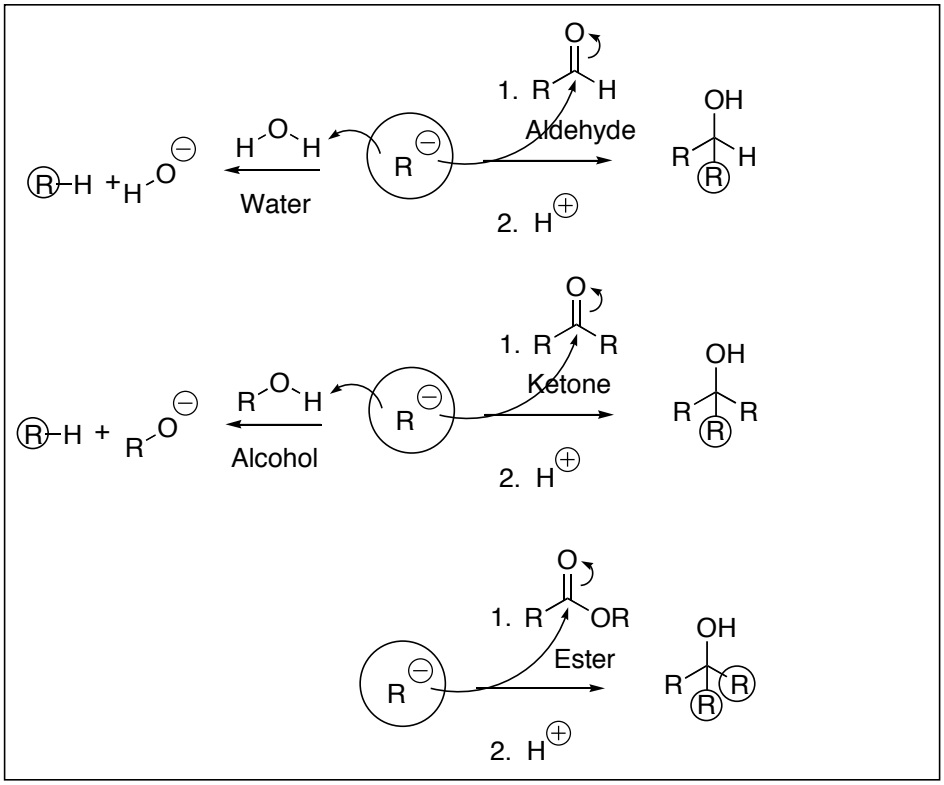
I. Background In 1912 Victor Grignard received the Nobel prize in chemistry for his work on the reaction that bears his name, a carbon-carbon bond-forming reaction by which almost any alcohol may be formed from appropriate alkyl halides and carbonyl compounds. The Grignard reagent RMgBr is easily formed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

$$R\text{-}Br + Mg \rightarrow RMgBr \qquad RMgBr = R^{\ominus} + Mg^{2+} + Br^{\ominus}$$

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

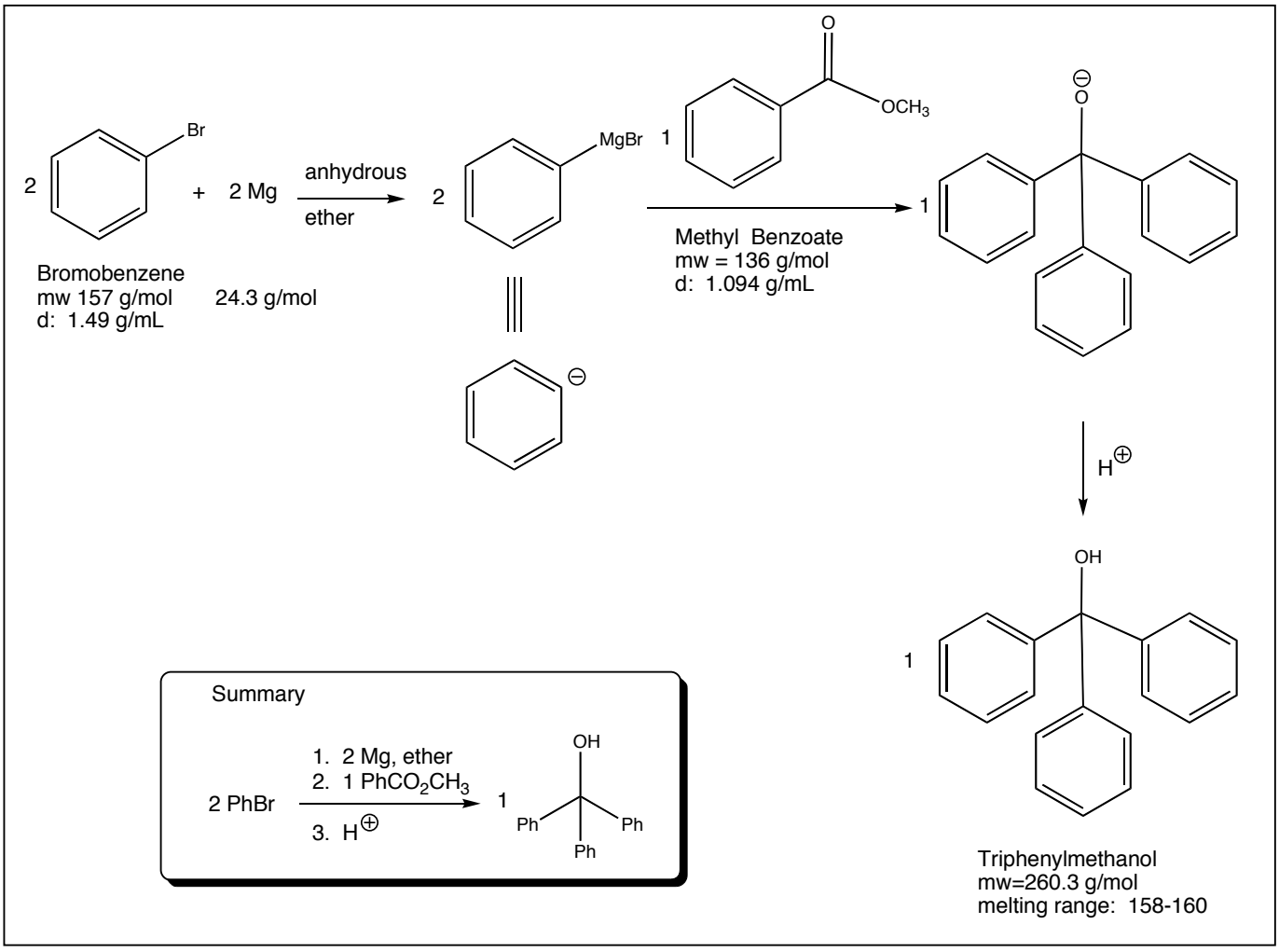
Some of its reactions are shown below.

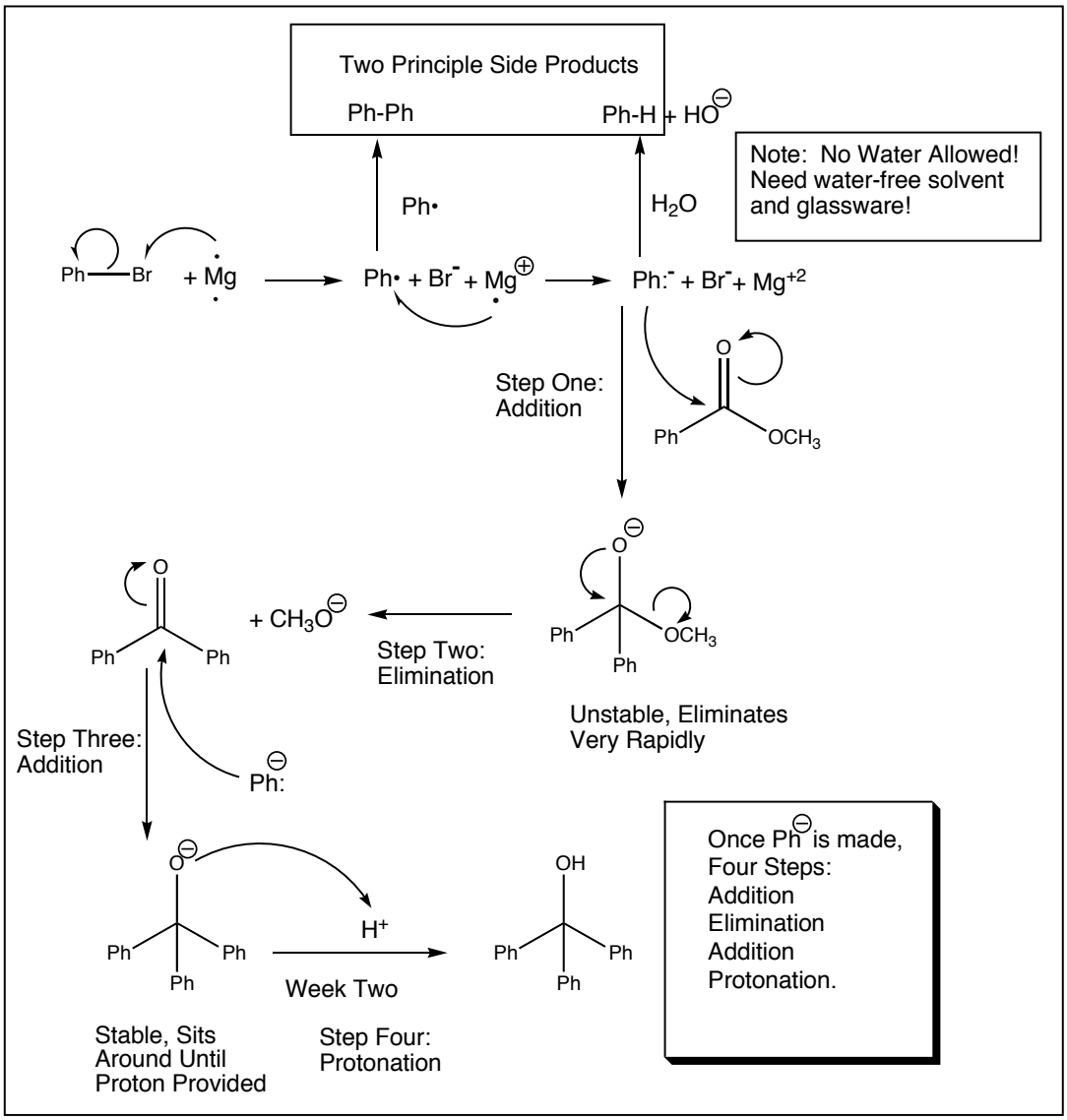
- **It reacts as a strong base with water or alcohols**.
  - Conversion from less stable R^- to more stable HO^- or RO^- is favorable.
- **It reacts as a strong nucleophile with carbonyl groups aldehydes, ketones, and esters.**
  - Conversion from less stable R^- to more stable RO^- is favorable, followed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

1. **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.
2. **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.**
3. **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.
4. **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: (Instructor will have a demo-display set up).
    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

2. Clamp the 250-mL round-bottomed flask to a vertical rod. Use a clamp with metal grips. (Rubber clamps will melt and stink when subjected to Bunsen-burner flame!) Don't add other glassware yet.
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. (Note: do NOT add the stir-bar until after step 16.)
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 briefly, as best you can. (Do not flame-dry the separatory funnel or drying tube.)
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 to at least 3 significant figures.)
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, perhaps using folded weighing paper or weighing boat, 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, and add it to the separatory funnel.
12. If he hasn't already done so, ask the instructor to add one small chip of iodine into the separatory funnel.
13. Drain the bromobenzene/ether/iodine solution into the round-bottomed flask.
    - **The iodine serves two functions.**
        a. **Indicator**. The color will disappear when the magnesium is activated. Until the color goes away, the magnesium won't be able to react with the bromobenzene.
        b. **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. Put a jack with a stir-plate underneath your flask. 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 1-2 minutes, beg the instructor to come over to crush some magnesium. Note: If yours starts without need for crushing, specifically note this in your write-up.
16. With a medium stir bar ready but not in the flask, ask the instructor to come over and 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! ADD A MEDIUM STIR BAR AS SOON AS THE MAGNESIUM IS CRUSHED.

17. The reaction should be so exothermic that it will be self-boiling for some time. Note the position of the "reflux ring". Within 10 minutes, the boiling will probably moderate. Turn the hot-plate heat setting to 5 in order to maintain a good rate of boiling.
18. 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.

1. Calculate what volume (in mL) it will take to add 5.0 grams of liquid methyl benzoate (density = 1.094 g/mL).
2. Calculate the number of **moles** used for magnesium, bromobenzene, and methyl benzoate.
3. 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 of the three reactants (Mg, PhBr, or $PhCO_2CH_3$) 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_3COH could you make? Given your calculated moles of PhBr, how many moles of Ph_3COH could you make? Given your calculated moles of $PhCO_2CH_3$, how many moles of Ph_3COH 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.
4. 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
- The following two steps can be done in advance, during the last ten minutes of your reaction….

1. Add 15 mL of ether to your separatory funnel. (Stopcock closed).
2. Add 5.0 grams of methyl benzoate to your separatory funnel by syringe. (Remember, you calculated this volume in Phase 2….) (Return syringe to the hood! ☺)
3. After the hour is up, let the reaction cool down so that it's not much hotter than room temperature. (Add some ice to a metal pail. Applying an ice bath in the metal pail for one minute might help cool.)
4. While magnetic-stirring, and with the solution in the flask not much hotter than room temperature, drain the ester/ether solution into the round-bottomed flask, slowly so that the reaction doesn't overheat too much. If things start to boil too hard, pause/slow the addition and/or apply the cold bath.
    - Record your observations!
5. After everything is added, keep stirring for an additional 20 minutes, during which time the exotherm and boiling should subside. If the reaction is still hot after 20 minutes, cool it with the ice bath.
6. 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!
7. Using your round-bottomed flask holder, 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 30 mL of ether, 40 grams of ice, and 50mL 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, and use a microspatula to break up the big chunks and to free up the stir-bar. Then use magnetic stirring to try to help dissolve things.

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. ($1\ Mg + 2\ H^+ \rightarrow Mg^{2+} + H_2$ gas)

5. Pour the mixture into your separatory funnel. (The magnesium doesn't need to be totally dissolved…)
   - Note: pour as much of your solution in as can fit. The water layer will settle to the bottom. Drain off some water layer to make more space, so that you can add the rest of your original mixture.

6. Pour an additional 10 mL of sulfuric acid and 30 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. GC #1: Prepare a sample of the "crude" solution for GC-MS analysis. Use a pipet to transfer ~0.2ml of the yellow organic phase into a GC vial, then dilute it with ether to ~1.5mL depth. Submit to the GC-MS queue.

10. Drain the organic layer from the separatory funnel into a 250-mL Erlenmeyer flask.

- You will see some solid product on various surfaces after this. Wherever ether with product went, the ether will evaporate and leave product behind. You can recover this product with additional ether rinse. Fortunately, the theoretical yield is so high that small amounts of lost product don't add up to much.

11. Add about 5 grams of sodium sulfate to "dry" the ether layer. Add additional scoops if there is no dry granular sodium sulfate left, and is instead all clumped up (indicating that there may be too much water for the sodium sulfate to handle).

12. Plug your long-stem funnel with a little glass wool

13. Pour the ether solution through the glass-wool-plugged funnel into a different 250-mL 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.

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 C. (Some capillaries should be on the end bench across from the liquid-dispensing hood). Take droplets from the authentic biphenyl and methyl benzoate bottles in the hood and apply them as well, to spots A and B. Save the plate until you've finished purifying the product, at which point you'll be able to apply your last spots D and E.

16. Add 30 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 might be a good starting guess?

19. Boil the solution down to ~30 mL or so, then add another 30 mL ligroin and again boil down to around 30 mL. (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.)

20. Remove the boiling stick, remove from heat and put a beaker or watch-glass over the top to prevent evaporation, and let cool slowly to grow your crystals, first to room temperature and then to 0ºC.
    - Note: You need to have some solvent left for the impurities to swim in! If it looks like your solvent is less than 25 ml, add additional ligroin and swirl.

21. GC #2: After the mixture has cooled, use a pipet to draw up some of the liquid phase and transfer ~0.3mL into a GC-MS vial then dilute it with ether to ~1.5mL depth. Submit to the GC-MS queue following step 22.

22. Use a capillary to take a droplet from your GC-vial of "mother liquor" solution, and put it on the tlc plate in the "post-crystallization solvent" spot E.

23. Filter your crystals with your medium Buchner funnel (using vacuum as usual).

24. Rinse with 15 mL of cold ligroin. If the crystals still look kind of discolored, perhaps rinse with another 10ml.

25. GC #3: Make a solution of the "pure" product by transferring a few tiny crystals (needn't be very dry) to a GC vial, and add some ether. 3-5 crystals is probably plenty. Then take a capillary and put a droplet of this "purified" solution (it doesn't need to be fully dissolved) onto your tlc plate in the "purified" spot D.
    - The solid probably won't dissolve completely, just take from the solution phase.

26. GC #3: Submit your "pure" GC vial to the GC-MS queue.
    - Upon completion, comparing the GC of the purified crystals to the "crude" and "mother liquor" GC's that you took earlier will let you see how much your purity improved as a result of the crystallization process; how some product remained dissolved in the "mother liquor"; and how impurities predominantly remained in the "mother liquor".
    - Based on retention times and comparison to the GC-with-labelled-peaks the instructor gave you, you should be able to identify whether you had biphenyl or methyl benzoate in your crude mix.
    - The GC's will need to be attached in your lab report, and what conclusions or observations can be made from them will need to be discussed in your lab report.

27. Run the tlc in designated solvent (5% 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 (lane C)? In the purified material (lane D)?
        - Is methyl benzoate present in the crude mix (lane C)? In the purified material (lane D)?
        - Any other side products in the crude (lane C)?
        - Did recrystallization purify the material (lane D versus lane C)?
        - Did most impurities in crude lane C end up in the crystal (lane D) or the solvent (lane E)?

28. Take a melting range on your final product. (Should melt above 150º, so heat accordingly)

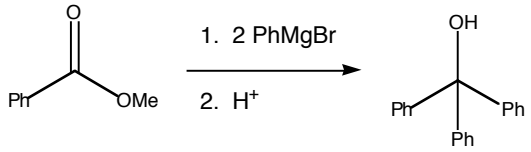
29. Get your final mass.

30. Lab Report: Write a "standard synthesis-style" lab report. A summary of what a standard synthesis-style lab report should look like is described in more detail a few pages after this. This must include calculations, observations, results, and analysis, in addition to answers to the assigned post-lab questions.

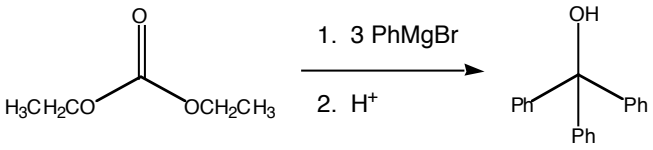
- The assigned post-lab questions are on the following page. You can perhaps answer some or all of them on the page, or else answer some or all of them on attached sheet(s) of paper.
- This two-week lab and two-week lab report will count for 20 rather than 10 points.
- For this report (and this report only!), you may submit a "team" report with your partner, if you wish. If so, each student should attach answers to the post-lab questions. Many of you may find it easier to just write your own individual lab report. So team versus individual, whichever you prefer!

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 $(CH_3CH_2O)_2C{=}O$, followed by H^+ 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?

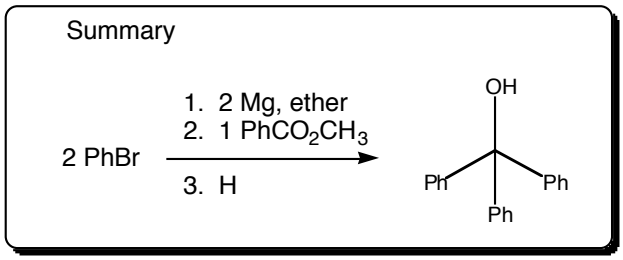
4. If the methyl benzoate you used had been wet (contained water), what byproduct would have formed? (Note: the answer for this problem may or may not be the same as for previous problem.)

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.

Standard Synthesis Laboratory Report 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.
- For reactants that might possibly be limiting reactants and might possibly factor into calculation of the theoretical yield, 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.
- 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…)
- 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.

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 problematic.

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:
        i. Changes in **color**
        ii. Changes in **solubility** (formation of precipitate or cloudiness…)
        iii. Changes in **temperature** (like, reaction became hot…)
        iv. Formation of **bubbles**
    - Time and temperature details:
        v. Whenever you heat something or cool something, the procedure should specify
        vi. 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. You may use "I" or "we" to simplify writing.

5. Product Analysis
- Any NMR, mp, bp, gc/ms, TLC information. For this report: Crude vs recrystallized mp; crude vs recrystallized GC/MS, and TLC information.
- Crude and Final yield and percent yield information.

6. Discussion/Summary. This will need to be significant for the Grignard lab. What do GC and TLC data indicate about purity prior to recrystallization? After? Was the crude material pure? Was all of the methyl benzoate converted to product? Was biphenyl formed as a side product? Were there additional side products? Did the recrystallization clean things up well? Was some of the product lost to the recrystallization solvent? Why did your yield decrease from crude to recrystallized, and what are key reasons why you didn't get 100% yield? (These are just some suggested ideas to deal with.)

7. Answers to any assigned Questions