CHEMISTRY 365 SYLLABUS

Spring 2016

Organic Chemistry Laboratory II

Classroom: Langseth 307	Office Hours: M/W/F 9-10:30, 1:00-2:00,
Dr. Craig P. Jasperse	Mon 9-10:30, 1:00-2:00
web: http://www.mnstate.edu/jasperse/	Tues 10-11:30
Office: Hagen 407J	Wed 9-10:30, 1:00-2:00
Telephone: 477-2230	Thurs 1:00-2:00
e-mail: jasperse@mnstate.edu	Fri 9-10:30, 1:00-2:00

Required Text and Materials: Room: Langseth 307 (lab)
1) Safety Goggles
2) Lab Manual (print from website, see http://web.mnstate.edu/jasperse/Chem365/Chem365.html)
*note: Avoid printing this from university computers/printers using Firefox.

Lab Schedule: SL307	Tuesday 12-2:50	Wednesday 3-5:50	Thursday, 9-11:50

Date	
Jan 12-14	Cyalume: Chemiluminescence
Jan 19-21	Grignard Reaction, Part 1
Jan 26-28	Grignard Reaction, Part 2
Feb 2-4	Alcohol to Ester; Catalysis; Distillation; NMR
Feb 9-11	Snow-Day Makeup/No Lab
Feb 16-18	Alcohol Unknown (NMR)/Synthesis of Aspirin
Feb 23-25	Wittig Reaction
Mar 1-3	Aldehydes and Ketones Unknown/Derivative
Mar 8-10	Dibenzalacetone by Aldol Condensation
Mar 15-17	No Lab. Spring Break.
Mar 22-24	Multistep Synthesis Module Week One
Mar 29-31	Multistep Synthesis Module Week Two
Apr 5-7	Multistep Synthesis Module Week Three
Apr 12-14	Academic Conference. No Lab (or Snow-Day Makeup Lab)
Apr 19-21	Amine Unknowns
Apr 26-28	Carboxylic Acid Unknown and Titration Catchup, Cleanup, Checkout

Grading Policy:

1. **Attendance**: Laboratory attendance is important! In the event of an absence, you will receive zero points for that experiment. Attending a different session for a given week may be possible upon arrangement.

2. **Individual Lab Scores**: Most experiment will require completion of a lab report, perhaps answers to some questions, and often identification of unknowns. Some of the grade will be based on quality of results, for example successful identification of an unknown, or high yield, or high product purity. Unless notified otherwise lab reports should be completed by the following lab period. For lab reports in which you are required to answer some questions, these will count into the lab report scores.

3. **Write Your Own Lab Report.**   While some experiments may be done with a partner, you should keep your own observations and write your report individually, unless told otherwise.

4. Instructor's **evaluation of your laboratory technique and understanding**: This can contribute up to 20% of the total grade. Expect this to be more a grade-lowering factor than a grade-elevating factor.

Tentatively letter grades will be assigned as follows. There will be some + and – grades.
A   ($\geq$90%)
B   ($\geq$80%)
C   ($\geq$70%)
D   ($\geq$60%)

Safety Notes: Noncompliance may result in dismissal from lab and a zero for the week!
1. Wear safety goggles in the organic laboratory.
2. Dispose of chemical wastes in appropriate containers.
3. The impact of the chemicals used in some of these experiments on unborn babies is not fully known. If you are pregnant or become so, I advise you to drop organic chemistry laboratory.

Course Description
CHEM 365 Organic Chemistry Laboratory II (1 credit)
Purification, synthesis, and identification of organic compounds, and the study of organic reactions.
Prerequisite: Chem 355

Student Learning Outcomes/Course Objectives
Students should master the laboratory techniques required for various synthetic reactions, and for the characterization, identification, and purification of various organic compounds. The ability to identify unknowns, including via use of spectroscopy, is an important outcome goal.

Academic Honesty
Cheating will not be tolerated and will be reported to the Dean of your College and the Vice President for Academic Affairs. It may also be reported to the Student Conduct Committee for further disciplinary action. For a full description of the MSUM Academic Honesty Policy, please see the Student Handbook. (http://wwwmnstate.edu/sthandbook/POLICY/index.htm)

Special Accommodations
Students with disabilities who believe they may need an accommodation in this class are encouraged to contact Greg Toutges, Coordinator of Disability Services at 477-5859 (Voice) or 1-800-627-3529 (MRS/TTY), CMU 114 as soon as possible to ensure that accommodations are implemented in a timely fashion.

# Chemiluminescence: Synthesis of Cyalume and Making it Glow

Intro *Chemiluminescence* is the process whereby light is produced by a chemical reaction. The flashes of the male firefly in quest of a mate is an example of natural chemiluminescence. In this experiment we will make Cyalume, the chemical used in "light sticks." A light stick contains a solution of cyalume containing a trace catalytic amount of a colorizing agent (catalyst). Inside is a sealed vial of aqueous hydrogen peroxide. When you bend the light stick, the hydrogen peroxide vial breaks, the hydrogen peroxide reacts with the cyalume (those are the two stoichiometric reactants), and energy is released. This energy is absorbed/released by the catalytic colorizing agent, resulting in the bright glow of varying color; the same stoichiometric reactants can be used, but when different colorizing catalysts are included, different colors result. Cyalume is an invention of the American Cyanamide Company. In today's experiment, we will make some cyalume, then make up two glow solutions: one will use a commercial colorizer, and the other will use a home-made colorizer that you will synthesize later this semester. (We'll use material that students from previous year made.)

## Nature of the Energy Release and Glow Formation

The chemistry that forms the color glow in a light stick is shown below. A cyalume is a symmetric diester, such as **4**. It reacts with hydrogen peroxide (red oxygens) by oxygen exchange. Trichlorophenol (green) is released as each of the two red oxygens of hydrogen peroxide connect to the two blue carbonyl groups. The 4-memeberd ring "squarate" diester, including the two carbonyls from the original cyalume and the two oxygens from hydrogen peroxide, is unstable due to ring-strain, and fragments to give two molecules of carbon dioxide and energy.
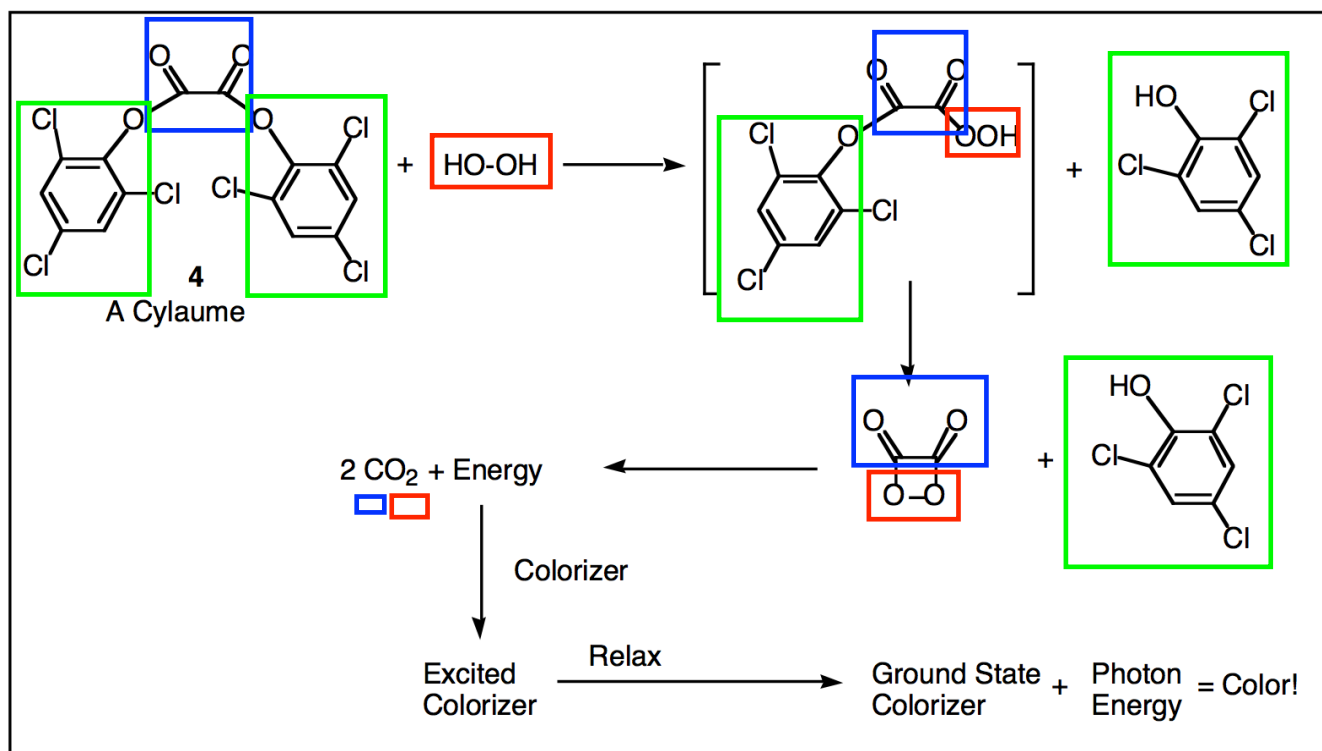
The energy released during the fragmentation "excites" a colorizing molecule that must be present. In other words, an electron in the colorizer gets "excited" from its ground state to an excited state. When it subsequently relaxes back to the ground state, a photon of energy is released. If the energy gap ΔE between the excited state and the ground state is in the visible region of the electromagnetic spectrum, then visible photons of distinctive color are released. This is what causes the bright colors. Since different colorizers have different ΔE, they release photons of different colors.
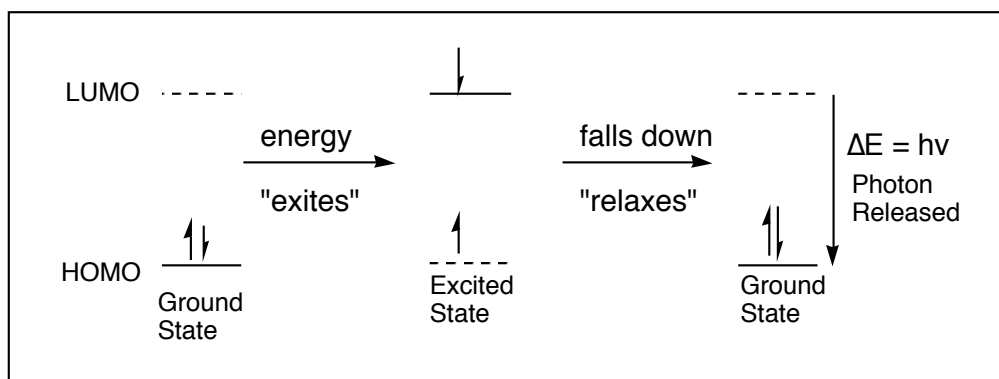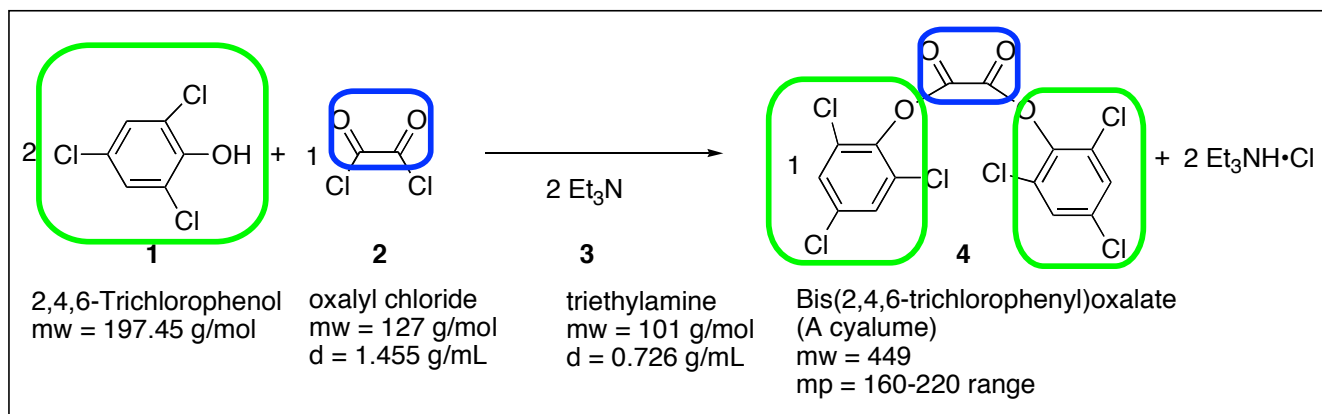
Several things to note about the exitation/relatation process: 1) The energy gap between the HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) determines the photon frequency and the color of the photon released. 2) For most organics, the HOMO-LUMO gap is not in the visible frequency. 3) To have a HOMO-LUMO gap that's in the visible spectrum, extensive conjugation is required. The examples shown below, which are the colorizers we will use, are representative. 4) Only a catalytic amount of colorizer is required. Excitation and relaxation regenerates the original molecule in its ground state, ready to repeat the process.

commercial
colorizer
(purple glow)

homemade
colorizer
(yellow/green flow)
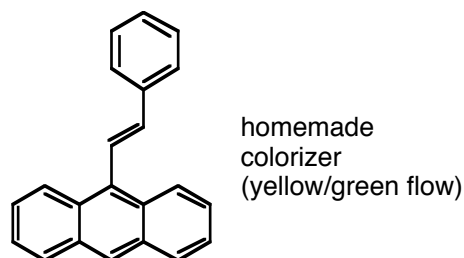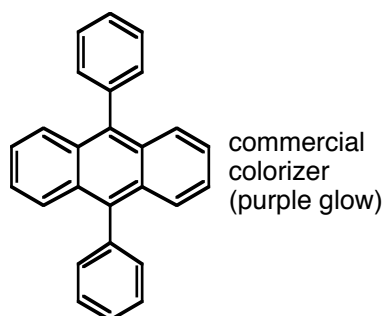
Cyalume Synthesis Overview

The synthetic reaction is shown below. Oxalyl chloride **2** (the blue reactant) is a symmetric acid chloride that is highly electrophilic and is very reactive because of the chloride leaving group. One oxalyl chloride reacts with two molecules of phenol **1** (green chemical) to give the diester **4**, which is a cyalume. (Not all cyalumes have the same 2,4,6-trichloro substitution pattern on the arene rings.) Triethylamine is an amine base which serves to absorb the two HCl's that get produced during formation of the diester.

2,4,6-Trichlorophenol
mw = 197.45 g/mol

oxalyl chloride
mw = 127 g/mol
d = 1.455 g/mL

triethylamine
mw = 101 g/mol
d = 0.726 g/mL

Bis(2,4,6-trichlorophenyl)oxalate
(A cyalume)
mw = 449
mp = 160-220 range

Part I: Cyalume Synthesis Procedure
1. Work with partner
2. Use a 25-mL round-bottomed flask containing a medium-sized stir bar (not the really small "flea" stir-bars, use the next larger one…)
3. Add about 0.790 g of trichlorophenol. (Record to three significant figures.)
4. Add 6 mL of toluene (solvent, bp = 111ºC). (This is solvent, so need not measure precisely.) (Record observations).
5. Add 0.56 mL of triethylamine by syringe, and swirl. (Bring the solution to the dispensing hood, with both partners to watch. Records observations).
6. Bring to other hood where instructor will inject 0.200 mL of oxalyl chloride. Swirl. The oxalyl chloride is a smelly lachrymator (makes you cry), and needs to be measured with a special syringe in the hood. (Both partners come. Record observations.)
7. After swirling your mixture, attach a reflux condenser, and reflux the mixture <u>gently</u> while stirring for 15 minutes on a hot plate/stir plate to complete the reaction. Note: With no heat, the reaction is too slow. But with excess heat, decomposition can occur. You'd like to have it hot enough so that your toluene can barely boil, but you don't want to go to extremes and have it boiling super-crazy.
    *   Set the hot plate heat setting to 6.
    *   Since the hot plate doesn't make very good contact with the flask, that's why the hot plate needs to be set that high. Make sure it's actually contacting the flask.
    *   During the fifteen minutes of heating, you could calculate your moles of each of the three reactants, identify which is limiting, and calculate your theoretical yield. You can also write up much of your report.
8. Cool the mixture well, eventually in ice, and collect the solid (both cyalume and triethylamine hydrochloride salt) with a small Buchner funnel.
    *   Use a bent/curved spatula to try to help drag/scrape as much as possible of your solid material out of the round-bottomed flask.
9. Use about 5 mL of hexane to rinse the flask and rinse the solids in the Buchner funnel. Pour the liquid into the organic waste bottle.
10. Make sure the solid is pretty dry before the next step.
11. Transfer the solid into a beaker, and add 10-12 mL of water. Stir the solution well with a spatula, trying to break up the solid chunks if necessary.
    *   Purpose: The triethylamine hydrochloride, being ionic, should dissolve into the water. The cyalume, being organic, should remain insoluble.
12. Filter using a small Buchner funnel.
13. Rinse with an additional 5-10 mL of water.
14. Transfer the cyalume solid into your smallest beaker. Add 2 mL of toluene.
15. Heat on a hot-plate until the toluene achieves a gentle boil. (Hot-plate setting of maybe 5?) If your sample dissolves completely, you may achieve a normal recrystallization. If it doesn't dissolve completely, just maintain boil for 2-4 minutes, then remove from the heat and let the solution cool, eventually to ice-cold.
    *   Heating a solid that doesn't dissolve completely is called "**<u>digestion</u>**". So long as the crystal has some solubility in the solvent, digestion still allows back-and-forth between solid phase and solution, and can frequently still allow impurities to be released to the solvent. In the current case, if you use more toluene in order to get a true recrystallization, sometimes it's hard to initiate crystal growth, and the loss of product to solvent is frequently very severe.
16. Filter on a Hirsch funnel (your smallest ceramic filtration unit).
17. Rinse with 2-4 mL of hexane (one or two pipets worth..).
18. Aspirate thoroughly.
19. Take mass. (Do this today, don't need to wait.)
20. Take out sample for melting point. (Can wait if you wish, but you can do this today if you want.)

Part II: The Chemiluminescent Reaction

1. The instructor will distributed two vials to each pair of students. Each will have about 3 mg of colorizer, one with the commercial colorizer and the other with the home-made colorizer.
2. Add 5 mL of diethyl phthalate (organic solvent, bp > 298ºC) into each of the two vials.
3. Warm the vials on a hot plate. (The heating is not essential. But the initial glow will be more dramatic if the temperature is hot, resulting in faster reaction.) Don't heat too much; you need to be able to carry the vials. Suggestion: hot-plate setting of 3.5, for five minutes.
4. Bring your vials, with their caps, to the dark room. (Room across the hall.) Both partners come.
5. The instructor will then inject 0.35 mL of 30% hydrogen peroxide/water.
6. Screw the covers back on, shake, and observe the pretty lights!
7. Each partner can take one of the vials home. Show them off to your roommates to show that chemistry is fun! (Woo hoo.) Watch to see how long you can still see them glow. Some students have glow for 2 days or even longer..
8. Eventually it's best to bring the vials back and pour the material out in the waste bottle in the hood. However, if you do drain the liquid in the sink or toilet, that's acceptable also.
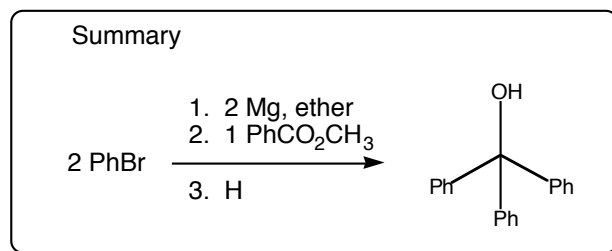
Lab Report

- Write up a standard synthesis lab report for Part I. (Review to make sure you know what the standardz synthesis style lab report should look like. Ask instructor if in doubt.)
  - Hand-written work should be OK.
  - Make sure your first page shows the reaction; lists the chemicals used (actual measured amounts); shows the mole calculations for the trichlorophenol, the oxalyl chloride, and the triethylamine; shows the work unit conversions involved in the mole calculations; identifies which reactant is limiting; and shows the theoretical yield in grams.
  - Normally the procedure can start on a second page.
  - The data/results should come following the procedure, and should include mp, mass yield, and percent yield.
  - No assigned post-lab questions.
- You don't need to write anything up for Part II. That's just for fun!
-

<u>Standard Synthesis Laboratory Report Format (example)</u>: The following layout is standard for a "synthesis reaction" report. Provide the parts and information <u>in the sequence specified</u>.

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!

Summary

2 PhBr → (1. 2 Mg, ether / 2. 1 PhCO$_2$CH$_3$ / 3. H) → product with OH, Ph, Ph, Ph

2. Listing of all <u>Chemicals Used</u>
- 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?
   o First, because it fits in near your mole calculations above.
   o 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.
   o Third, it's nice to know approximately how much material is expected, so you can recognize whether your actual results are reasonable or problematic.
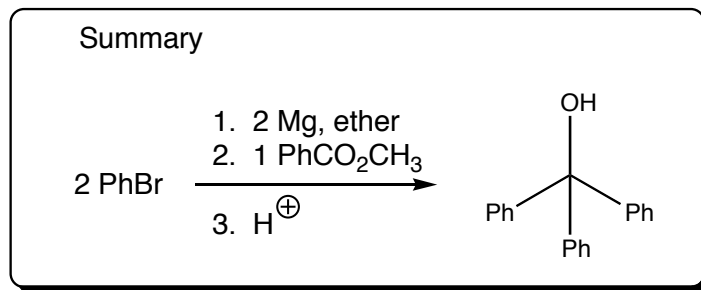
4. Writeup of Actual Procedure.
- For this particular experiment, the "procedure" section will be by far the biggest portion of your report.
- This should be a concise but detailed description of things, including:
   o What you <u>actually did</u> (even if not recommended or not from recipe)
   o All <u>observations</u> should be included. These include <u>all observed changes</u>, such as:
      - Changes in **color**
      - Changes in **solubility** (formation of precipitate or cloudiness…)
      - Changes in **temperature** (like, reaction became hot…)
      - Formation of **bubbles**
   o <u>Time and temperature</u> 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 **<u>past tense</u>**, not **<u>command tense</u>**. (Rather than "Add this", should read "I added this", or "I dropped that…")
   o Use of personal pronouns is accepted in this class. You may use "I" or "we" to simplify writing.

5. Product Analysis
- Any GC, NMR, mp, bp, or TLC information. For this report, mp information must be included. What's required depends on the actual experiment and what data was obtained.
- Final yield and percent yield information.

6. Discussion/Summary. Need not be long, but any conclusions or excuses would go here…
7. Answers to any assigned Questions

Chem 355   Jasperse   Grignard Synthesis of Triphenylmethanol

Summary

$$2 \text{ PhBr} \xrightarrow[\text{3. } H^{\oplus}]{\begin{array}{l}\text{1. } 2 \text{ Mg, ether} \\ \text{2. } 1 \text{ PhCO}_2\text{CH}_3\end{array}} \begin{array}{c}\text{OH} \\ | \\ \text{Ph} - C - \text{Ph} \\ | \\ \text{Ph}\end{array}$$

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.

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

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**.
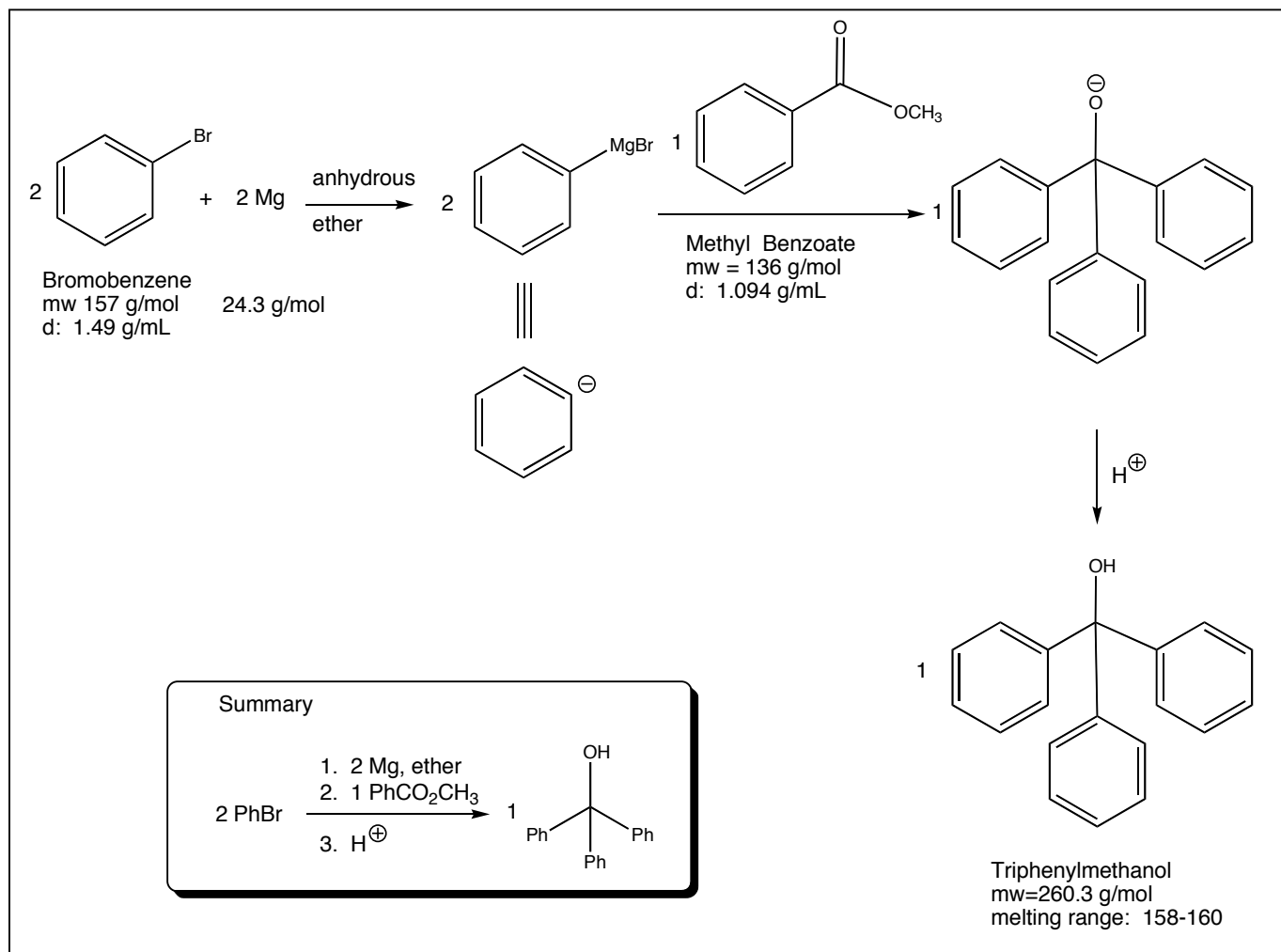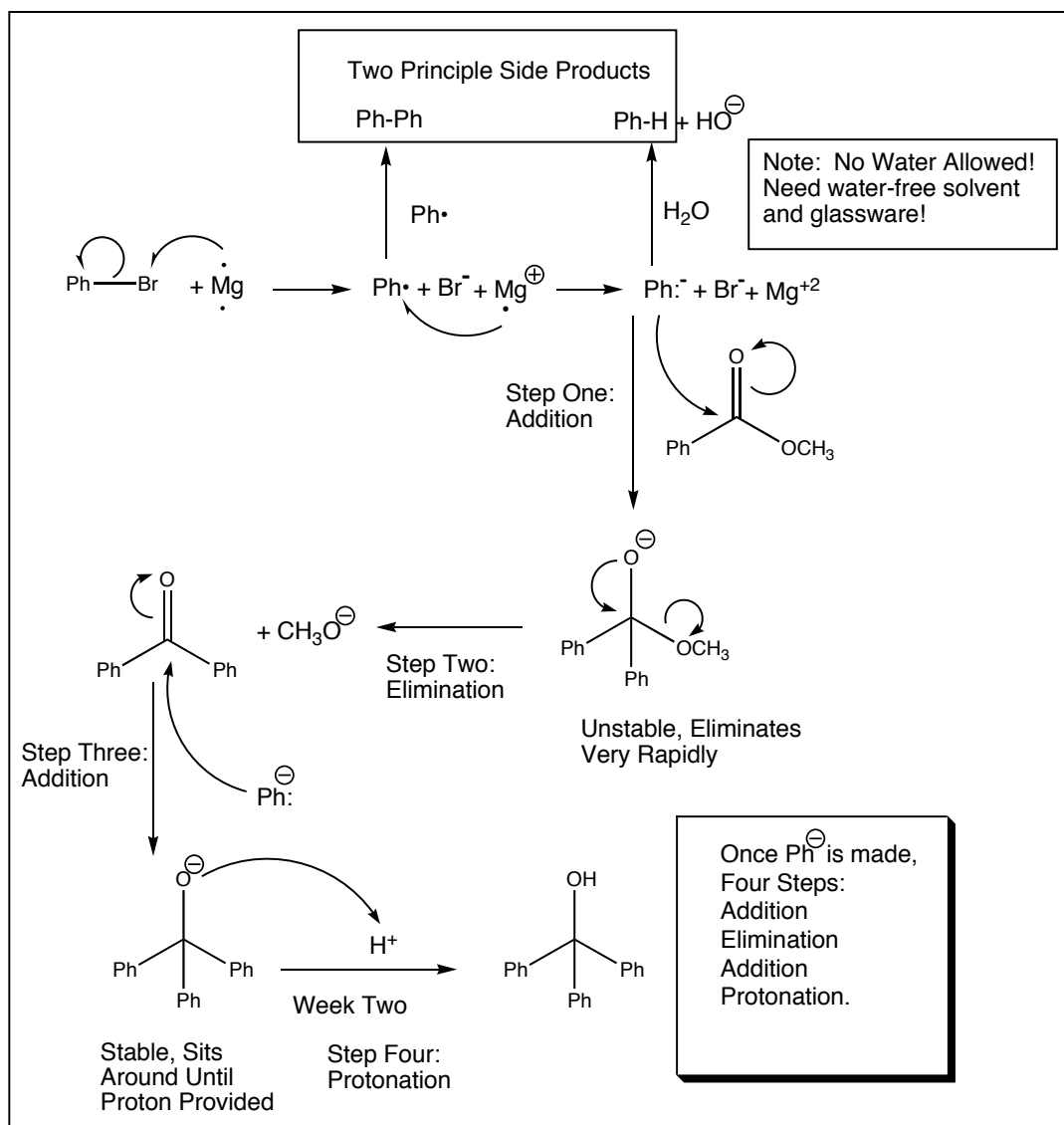
Some of its reactions are shown below.
- **It reacts as a strong base with water or alcohols**.
  - Conversion from less stable R⁻ to more stable HO⁻ or RO⁻ is favorable.
- **It reacts as a strong nucleophile with carbonyl groups aldehydes, ketones, and esters.**
  - Conversion from less stable R⁻ to more stable RO⁻ is favorable, followed by protonation to give alcohols ROH.
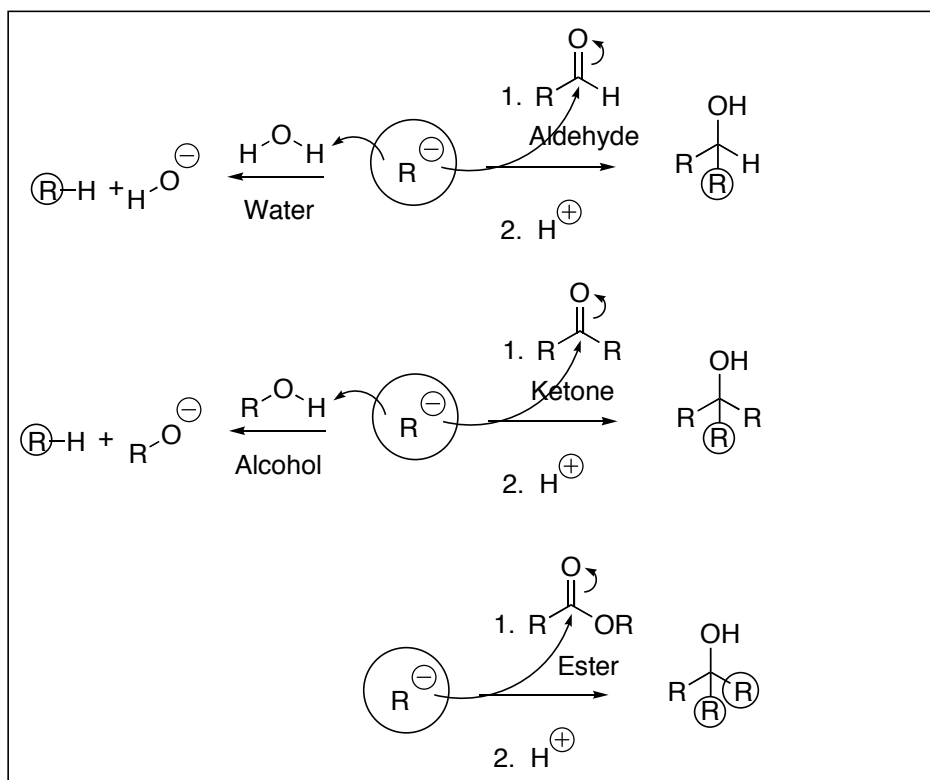
II. Overview of Our Experiment

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.

Bromobenzene
mw 157 g/mol   24.3 g/mol
d: 1.49 g/mL

Methyl Benzoate
mw = 136 g/mol
d: 1.094 g/mL

Triphenylmethanol
mw=260.3 g/mol
melting range: 158-160

Summary

2 PhBr $\xrightarrow{\substack{1.\ 2\ Mg,\ ether \\ 2.\ 1\ PhCO_2CH_3 \\ 3.\ H^{\oplus}}}$ 1

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
    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. Use a clamp with metal grips. (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 it's 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 <u>2 grams of magnesium metal</u>. (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 <u>40 mL of ether</u> into the separatory funnel and put stopper back on.
11. Measure out <u>9.0 mL of bromobenzene</u> 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, and stir. 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 <u>without</u> need for crushing, specifically note this in your write-up.
16. 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 15 minutes, the boiling will probably have 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 <u>volume (in mL)</u> it will take to add <u>5.0 grams of liquid methyl benzoate (density = 1.094 g/mL)</u>.
2. Calculate the number of **moles** used for magnesium, bromobenzene, and methyl benzoate.
3. Calculate the **<u>overall theoretical yield</u>** (in grams) for your final product of next week, triphenylmethanol (mw = 260 g/mol).
   - To do this, you must **<u>first identify</u>** 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. <u>Your limiting reactant and theoretical yield should consider only original reactants and final product</u>, 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
1. After the hour is up, let the reaction cool down (an ice-water bath might help).
2. Add <u>15 mL of ether</u> to your separatory funnel. (Stopcock closed).
3. Add <u>5.0 grams of methyl benzoate</u> to your separatory funnel by syringe. (Remember, you calculated this volume in Phase 2….)
4. 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!
5. If everything is added without excessive boiling, try to shake everything up, and give it five minutes or so to continue reacting.
6. If the reaction is still hot, cool it with the ice bath.
7. 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!
8. 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 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.
   - Magnsesium 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 seperatory 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. Prepare a sample for GC-MS analysis. Take out one pipet from your organic phase and place it into a GC-MS vial and submit to the GC-MS queue.

10. Drain the organic layer from the separatory funnel into an Erlenmeyer flask.

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 with (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 Erlenmeyer flask.
   - The size of the flask should be either a 150- or 250-mL flask. (You don't want it to end up much more than half full.)
   - 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. 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 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. Use a capillary to take a droplet from the solvent and put it on the tlc plate in the "post-crystallization solvent" spot E.

22. Filter your crystals with Buchner funnel and aspirator.

23. Rinse with cold ligroin.

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 D.

25. Prepare and submit a sample for GC-MS analysis. Take out one pipet of the solution you made in the previous step (that you used for TLC) and place that solution into a GC-MS vial. Submit to the queue.
    - Comparing the GC of the purified crystals to the crude GC that you took earlier (see step 9?) will enable you to see how much your purity improved as a result of the crystallization process.
    - Based on retention times and/or the mass spectra, you should also be able to evaluate what organic contaminants were present in the crude and/or final product. Use of the mass spec library could be applied here.

26. 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:
        o Is biphenyl present in the crude mix (lane C)? In the purified material (lane D)?
        o Is methyl benzoate present in the crude mix (lane C)? In the purified material (lane D)?
        o Any other side products in the crude (lane C)?
        o Did recrystallization purify the material at all (lane D versus lane C)?
        o Did crystallization get all of the product out of the solvent, or is some left in the solvent (lane E)?

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

28. Get your final mass.

29. 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 postlab 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 postlab 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?)
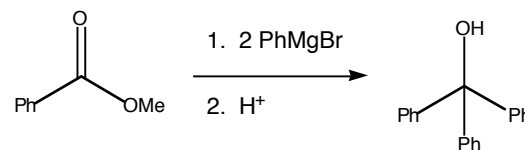
2. Triphenylmethanol can also be prepared by the reaction of PhMgBr with diethylcarbonate $(CH_3CH_2O)_2C=O$, followed by H^+ workup. Draw a detailed, step-by-step mechanism for the following reaction: (on attached sheet?)
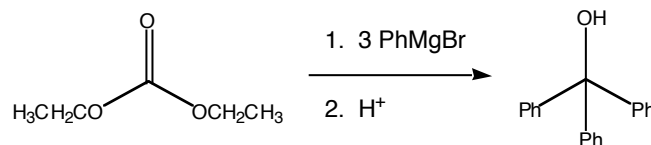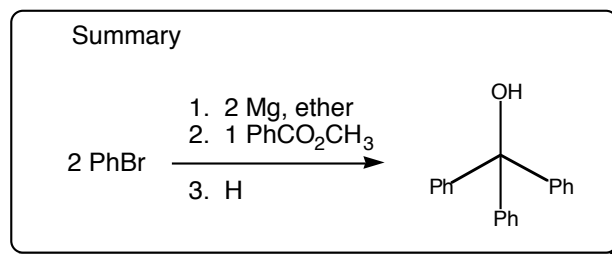

3. If you hadn't bothered to flame-dry your glassware or used a drying tube, what byproduct would have formed?

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.

7.

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!

Summary

2 PhBr →
1. 2 Mg, ether
2. 1 PhCO$_2$CH$_3$
3. H

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?
    o   First, because it fits in near your mole calculations above.
    o   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.
    o   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:
    o   What you actually did (even if not recommended or not from recipe)
    o   All observations should be included. These include all observed changes, such as:
        *   Changes in **color**
        *   Changes in **solubility** (formation of precipitate or cloudiness…)
        *   Changes in **temperature** (like, reaction became hot…)
        *   Formation of **bubbles**
    o   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…")
    o   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, 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 you 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

Basic GC-MS Operation   Compressed Draft 3   For Chem 355/365
Note: The following assumes that the hydrogen and compressed air gases have been turned on; that the machine has been warmed up; that the gc/ms program has been opened; that an appropriate "method" and "sequence" have been selected; and that Jasperse will shut things down.

Sequenced Data Acquisition: Using the Autosampler to Sequence Runs Automatically
Note: this assumes that Jasperse has already prepared and started a "sequence" ("Grignard.." for example, but you are trying to add your sample to the lineup. If you're first in line, get Jasperse to come and help.

1. **Add your sample to the back of the line in the autosampler.**
   • Do NOT leave any open holes (unless the sample belonging in that hole is being sampled.)
   • Filling a "sample-is-in-the-injector-tray" hole will cause a system freeze.

2. **Open "edit sequence" by clicking the "edit" icon on the yellow panel** low on the computer screen.
   • This will open a spreadsheet that you can edit.
   • Add your names in the "name" box that goes with your vial number.
   • **Click OK**. Note: if you don't click "OK", the machine will freeze at the end of the current run. NEVER leave the spreadsheet page open unless somebody behind you is going to close it.
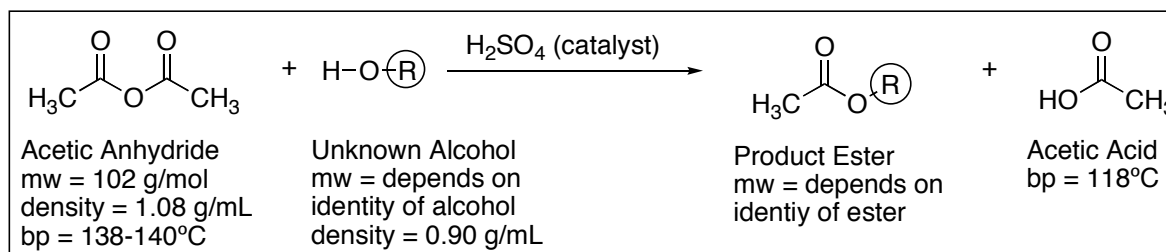
Data Processing/Analysis: Getting and Printing the GC Graph, % Report, and/or Mass Spec.
• Note: data analysis can be done while acquisition is ongoing.
• Note: this assumes that the "**gcms data analysis**" software and appropriate analysis method are opened. In the data analysis page, check on the top blue line to see if it says "Enhanced data analysis-ADEFAULT-RTE.M…", or "Grignards", or something that fits the experiment for the week. If not, check with Jasperse or open it. (ex, Method > Load Method > Yes > ADefault-RTE.M > OK.)

3. **Open a data file** using the left mouse button to double click.
   • Your data file should be within the folder Organic Lab within the Data folder.
   • Data file will have the names "Vial-1" or "Vial-2", so **remember which vial was yours**.

4. **Printing GC Graph, % report, and retention times**: **Click Method>Run Method**
   • Repeat as many times as needed to provide prints for each student in your group.

5. **Printing Mass Specs: Click the 2nd Hammer icon.**
   • Click the 2nd hammer icon as many times as needed to provide prints for each student in group.
   • Note: You don't need to wait for a print to finish before clicking the hammer again. If you've got 5 partners, just click the hammer five times and the prints will come out one by one….

Library Matching: With a data file open (as described in #3 above):

6. **Right mouse double-click on a peak in the top window** to get its individual mass spectrum to appear in the lower window.

7. **Right mouse double-click on the mass spectrum to get a library search results**
   • Note: the library searches aren't perfect and don't always find the very best structure match.

ALCOHOL TO ESTER
Acid-Catalyzed Esterification of an Unknown Alcohol

Acetic Anhydride	**Unknown Alcohol**	**Product Ester**	**Acetic Acid**
mw = 102 g/mol	mw = depends on	mw = depends on	bp = 118°C
density = 1.08 g/mL	identity of alcohol	identiy of ester	
bp = 138-140°C	density = 0.90 g/mL		

Summary: You will be given an unknown alcohol, you will convert it to an ester, and you will identify both the original alcohol and the derived ester using boiling point and H-NMR.

Some Learning Goals:
1. Observe the dramatic impact of acid catalysis
2. Understand the construction of esters
3. Review the distillation process
4. Use NMR combined with boiling point to identify the product ester

Procedure: **NMR of reactant**: Prepare a proton NMR on your starting alcohol by injecting about 0.07 mL into an NMR tube, followed by about 0.8 mL of CDCl3. Submit to the NMR queue. (Instructor: experiment used is "Proton 8".)

Reaction: To a 50-mL round-bottomed flask, add your tiniest stir bar. Take to hood area. Add 7.5 mL of acetic anhydride (via either buret or syringe) and directly add 5.0 mL of an unknown alcohol via syringe. (Measure as precisely as possible. Notice that nothing happens.) Attach a Claisen adapter to the flask. Place a thermometer adapter with a thermometer in the main arm of the Claisen adapter so that the thermometer point is immersed in the liquid (but not so deep that it interferes with the stir bar.) Place a reflux condenser in the side arm of the Claisen adapter. Note that no exotherm or reaction has occurred. Then remove the Claisen adapter and add two drops of concentrated sulfuric acid (may be strong exotherm). Rapidly plug the Claisen adapter (with thermometer and condenser) back into the flask, and magnetically stir the solution while checking the thermometer to see if the temperature jumps. After the internal temperature has reached its maximum, wait an additional 3 minutes before beginning workup.

Workup: Pour the mixture into a separatory funnel, and use a 25-mL ether rinse to aid the transfer. Add some solid ice (around 10g). Extract the acids and unreacted acetic anhydride by adding 20-mL of NaOH solution. Be sure to shake things up vigorously, let settle, and then drain the lower aqueous layer into a beaker. Add another 20-mL of NaOH, shake, settle, and again drain the aqueous layer into the same beaker. Repeat this process a 3rd time. Pour the organic layer into an Erlenmeyer flask and rinse the separatory funnel with an additional 5mL of ether. Dry the ether solution over anhydrous sodium sulfate, then filter the solution (use a long-stemmed funnel with a little glass wool) into a clean, dry, 50- or 100-mL round-bottomed flask.

Distillation: Have three 125-mL Erlenmeyer flasks (**A**, **B**, and **C**) ready, with both **B** and **C** pre-weighed. Distill (simple distillation) the ether and the product, using a heating mantle as heat source. The ether will boil off at relatively low temperature (<95°) and should be collected in flask **A**. After the temperature has hit 100° allow ~5 more drops and then make flask **B** your receiver. If at some point above 100° the temperature appears to be settling into a new plateau, swap in flask **C**. (Not all of you will use the 3rd flask.) Record the "plateau" temperature at which most of your ester boils off.

Analysis: Weigh your product esters in flasks **B** and perhaps **C**. Prepare and submit a GC-MS for **B** and perhaps **C** by adding one drop and diluting with a pipet of ether. Prepare and submit an NMR for **B** and perhaps **C** by filling the skinny end of a long pipet to about 1 inch, shoot that into your tube, and then use 0.8 mL of CDCl3 to dilute/rinse the pipet directly into the NMR tube. Between the bp information about the product ester and the NMR information about the alcohol and/or product ester, determine the structure of both the product ester and the starting alcohol.
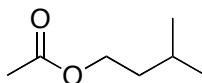
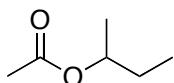Ester Candidates
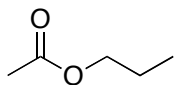
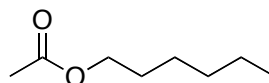Propyl Acetate, 100-105° ± 10°
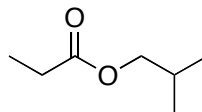
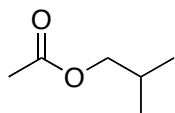Isobutyl Propionate, 132-147°
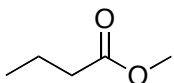
Methyl Butyrate, 100-105° ± 10°
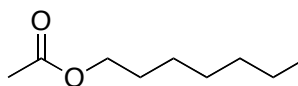
Isopentyl Acetate, 132-147°

s-Butyl Acetate, 112-120°

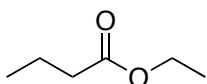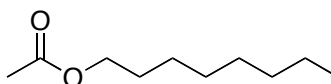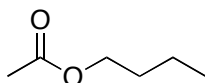Hexyl Acetate, 167-177°
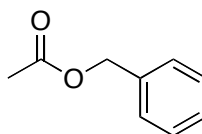
Isobutyl Acetate, 114-120°

Heptyl Acetate, 187-197°

Ethyl Butyrate, 117-125°

Octyl Acetate, 202-220°

Butyl Acetate, 114-126°

Benzyl Acetate, 202-220°

Lab Report: This week, we'll skip the usual procedure writeup. Instead, report or attach:
1. Mass yield of collection **B** and perhaps **C** if you had two different collections.
2. Boiling range of ester
3. H-NMR spectra of starting alcohol.
   - See http://web.mnstate.edu/jasperse/Chem365/H-NMR%20Interp%20Short.doc.pdf for some interpretation tips.
4. H-NMR spectra of product ester(s). (Instructor will use this to help assess product purity)
5. GC chromatogram of your distilled product. Graph/% Report only, not mass specs.
6. Identity of the ester you made. Keys are the boiling point, the NMR(s), and the identity of the acetic anhydride reactant.
7. Identity of the alcohol you began with. (Based on your product ester and/or your NMR.)
8. Calculate the % yield [Note: this depends on your alcohol and ester structures and on their molecular weights. Assume each starting alcohol had a density of 0.90 g/mL (not exactly true, but close enough) for your volume-mass-mole calculation.]
   - tip: To determine the theoretical, yield, you'll need to figure out the molecular weight of both your alcohol and your product ester in order to do mass/mole interconversions.

Student Name:

1. Alcohol Letter:

2. Ester Identity: mw of Ester:

3. Alcohol Identity: mw of Alcohol:

4. GC Retention time for Ester:

5. GC purity for Ester:

(Note: the   GC   ignores   low-boiling
components, so the purity level shown does not
consider   contamination   by   ether,   acetic
anhydride, or acetic acid.)

6. Boiling Range of Ester:

7. Mass Yield of Ester:

8. Theoretical yield: (**show your work**)

9. % Yield:

10. Attach your NMR's, for both starting alcohol and product ester collection **B** and perhaps
    C, or else write the name of the partner to whose report they are attached:

11. Instructor only: does the product ester NMR show good purity?

Basic GC-MS Operation   Compressed Draft 3   For Chem 355 Organic Unknowns Lab
Note: The following assumes that the hydrogen and compressed air gases have been turned on; that the machine has been warmed up; that the gc/ms program has been opened; that an appropriate "method" and "sequence" has been selected; and that Jasperse will shut things down.

Sequenced Data Acquisition: Using the Autosampler to Sequence Runs Automatically
Note: this assumes that Jasperse has already prepared and started a "sequence" ("Chem355 Unknowns..", or "Nitration" or "Grignard.." or "Esters" for example), but you are trying to add your sample to the lineup.

- ## If you're first in line, get Jasperse to come and help.

1. **Add your sample to the back of the line in the autosampler.**
   - Do NOT leave any open holes (unless the sample belonging in that hole is being sampled.)
   - Filling a "sample-is-in-the-injector-tray" hole will cause a system freeze. When the machine tries to put the injection sample back, it will have no place to go.

2. **Open "edit sequence" by clicking the "edit" icon on the yellow panel low on the computer screen.**
   - This will open a spreadsheet that you can edit.
   - Add your names in the "sample" box that goes with your vial number.
   - **Click OK**. Note: if you don't click "OK", the machine will freeze at the end of the current run. NEVER leave the spreadsheet page open unless somebody behind you is going to close it.

Data Processing/Analysis: Getting and Printing the GC Graph, % Report, and/or Mass Spec.
- Note: data analysis can be done while acquisition is ongoing.
- Note: this assumes that the "**gcms data analysis**" software and appropriate analysis method are opened. In the data analysis page, check on the top blue line to see if it says "Enhanced data analysis-ADEFAULT-RTE.M…", or "Grignards", or something that fits the experiment for the week. If not, check with Jasperse or open it. (ex, Method > Load Method > Yes > ADefault-RTE.M > OK.)

8. **Open a data file** using the **left mouse button to double click**.
   - Your data file should be within the folder Organic Lab within the Data folder.
   - Data file will have the names "Vial-1" or "Vial-2", so **remember which vial was yours**.

9. **Printing GC Graph, % report, and retention times**: **Click Method>Run Method**
   - Repeat as many times as needed to provide prints for each student in your group.

10. **Printing Mass Specs: Click the 2nd Hammer icon.**
    - Click the 2nd hammer icon as many times as needed to provide prints for each student in group.
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Library Matching: With a data file open (as described in #3 above):

11. **Right mouse double-click on a peak in the top window** to get its individual mass spectrum to appear in the lower window.

12. **Right mouse double-click on the mass spectrum to get a library search results**
Note: the library searches aren't perfect and don't always find the very best structure match.

User's Guide to NMR: General
- For help, see Dr. Jasperse, Hagen 407J, phone 477-2230   Draft 10/28/15

1. **Add sample to a Spinner/Turbine**

2. **Adjust depth** by placing the turbine into the golden depth finder

3. **Load sample/turbine into autosampler.**
   - Press the round white **Access Request Button** on the panel below the sample trays/doors
   - **Wait until "status" light turns to a solid yellow, and the message panel reads "door unlocked**"

4. **Opening Program on Computer: Usually already open**, and usually to correct "operator"
   - If not open: Operator: Should be your class or research group   Password: none.
   - To switch operator, click **Logout** from submit mode and select the correct operator

5. **"Submit" vs "Spectrometer" modes:** New Study/Submit Queue to submit; Spectrometer to print/view
   - Click "**New Study**" button (lower left) to jump from Spectrometer to Submit mode
   - Click "**Cancel**" button (lower left) to exit Submit queue and go to Spectrometer:

6. **Experiment Selection** (from within Submit mode). Usually preselected for organic labs.
   - If not already in New Sample/submit queue mode, push **New Study** button on lower left
   - **Proton8** is the normal H-NMR experiment, under the "UserStudies" folder
   - For some classes/operators, **Proton8** has been set to open by default, since most NMR's are regular H-NMR's
   - Add experiments as needed from the Experiment Selector.
   - To **edit or delete**: **right click** on experiment and select "Open Experiment" or "Delete Experiment"

7. **3 Step Submission** (assuming the experiment already specified, and still/already in Submit mode).
   a. Fill **Sample Name** (for both computer filing and printout recognition)
   b. **Click Sample Spot**: Click on the button showing your sample site. (Remember/record! ☺)
   c. **Submit**: clicking the red **Submit** button on the lower left side.
   - **Note**: Can repeat this 3-step sequence for new samples/new students, if running same experiment

   - **Comment box**: (can add comments for the paper printout). (Control C to cut and Control K to paste)
     Other submission options of possible use for advanced labs, research, or offsite Concordia users:
     Solvent; **Autoplot** (offsite Concordia users should turn this off); **Email**; **Email Address** (offsite
     Concordia users should set this correctly!☺); **Lock**: (with non-deuterated solvent run unlocked),
     Shim (with non-deuterated solvent run 1H PFG); **Tune**

8. **Opening Completed Samples for Printing and Processing. ("Spectrometer Mode" required)**
   - Must be in "Spectrometer" mode, not "Submit" mode.
   - If in submit mode, "Submit" button will display (lower left). Click "**Cancel**" to exit Submit mode.
   - In "Spectrometer" mode, must have "Zones" map displayed (96 sample nodes show). Click on little
     circle icon (🔲) to the upper left of the spectra-display panel, if zones map not already open.
   a. Right click on sample number
   b. Click "Show Study"
   c. Click on file folder name located on the left
   d. Then **double click** on spectrum you want to view to load it into the spectra-display viewscreen.
   e. Process > **Auto Plot** or **Print**. See next page for more detailed printing and processing instructions.
   - Re-click the little circle icon (🔲) to get back to zone map in order to open other files
   - To return to "Submission" mode in order to run more samples, click "New study"

9. **Logout:** Click **"Logout"** button underneath spectrum-display from Submit Mode.

10. Plotting (when wanting non-automatic plots)
- Must be in the process mode. (Highlight "Process" beneath the spectrum display)
a. Click "**Auto Plot"** or "**Print**" button, way on lower right corner of page.
b. Re-click if you want to print additional copies for the other students
- Note to offline Concordia users: this "plot" command will print to MSUM NMR-room printer. ☺
- For advanced labs or research groups, additional plot preferences are available in the process mode by clicking "**Plot** (Beneath spectrum display, 2nd from bottom underneath "Start")

11. Horizontal Expansions
- With spectrum displayed on screen, use a panel of display icons on the far right.
a. Click on the magnifying glass icon (6th icon down, 🔍)
b. Move your cursor to the left end of the zone you want to expand, then **hold down left mouse button** and slide it to the other end of the zone you want to expand.
- To return to the full display, you can either click on the 3rd icon (✥) or the 5th icon (🔍).
- If the lines aren't tall enough, type "vsadj" (vertical scale adjust) on the command line.

12. Manual Integration: Defining Integrals Yourself (see #13 to also give nice integral numbers)
- With spectrum displayed, must be in the process mode ("Process" beneath the spectrum display)
a. Choose "**Integration**" (Beneath spectrum display towards left, 2nd underneath "Start")
b. Hit "**Clear Integrals**" button (slightly further to the right and lower down from previous button)
c. Hit "**Interactive Resets**" button (immediately above the "clear integrals" button) and define
  1. Move cursor beyond the left end of the signal you want to integrate.
  2. Left-mouse click-and-release
  3. Move the cursor to the right of the signal, and again click-and-release. Everything between the two "clicks" will be integrated.
  4. Repeat this for each area you want to integrate.
d. Click very top cursor icon (▥) to the right of the display screen to regain normal cursor function

13. Setting Nice Integral Numbers (While already in integration mode following steps a-d above**)**
a. Click cursor on one of your integral regions
b. Click "Normalize Area" to" "**Single Peak**" below "Set Integral Area" panel underneath the display
c. Set "integral area" to some nice whole number (1, 2, or 3, depending on your molecule)
d. Click the "set integral value" button
- If it says "cursor is outside of integral region", then reset the cursor on an integral of choice, and re-click the "set integral value" button again.
- Click "**Auto Plot"** (lower right) in order to print.

14. Other Processing Options for Advanced Users/Research Groups/2D-NMR

1. Peak Picking	4. Insets	6. Absolute Concentration Integration
2. Vsadj	5. Arraying spectra	7. 2D NMR processing, including varying the
3. wp=2p sp=2p plot		signal intensity

15. Opening Spectra From the Data Folders
- Click on the Folder icon and find your class or research professor's folder
- Double-click on the folder with your name.
- Double click on the experiment file
- To get the Folder icon to go back up a step, click on the Folder icon again, then click ONCE only on the little icon that shows an arrow up

16. Getting the last sample out and replacing with a Lock Sample (if auto-eject isn't turned on)
a. In "Spectrometer" mode, display "zones" map (⬛)
b. Right click on sample 48 => select "Sample in Magnet" (3rd choice from the bottom) => OK.

17. **Logout:** Click **"Logout"** button underneath spectrum-display

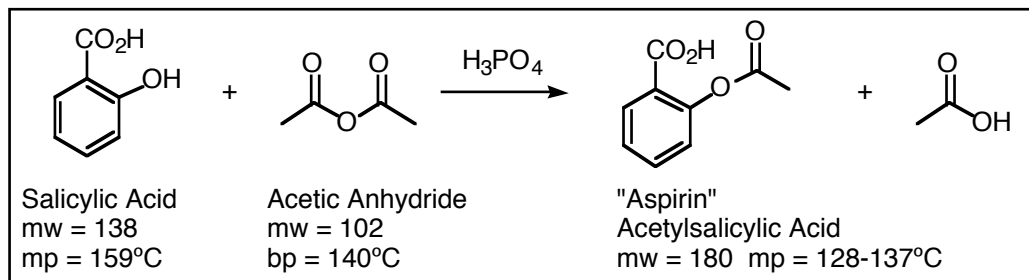## Alcohol Unknowns and Aspirin

Part 1: Microscale Synthesis of Aspirin

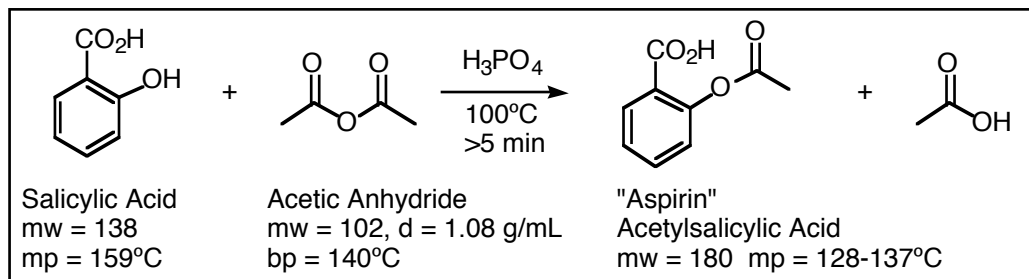| Salicylic Acid | Acetic Anhydride | "Aspirin" |
| mw = 138 | mw = 102 | Acetylsalicylic Acid |
| mp = 159ºC | bp = 140ºC | mw = 180 mp = 128-137ºC |

Intro Aspirin is among the most versatile drugs known to medicine, and is among the oldest (the first known use of an aspirin-like preparation can be traced to ancient Greece…). The starting material salicylic acid is cheap ($30/kg), because it is available by carboxylation of phenol with carbon dioxide. The esterification that we will do today is the same process that is used industrially for commercial aspirin synthesis.

Aspirin is found in more than 100 common medications. It is usually used for one of four reasons: as an analgesic (painkiller), as an antipyretic (fever reducer), as an anti-inflammatory agent, or as an anti-clotting agent. It is a premier drug for reducing fever. As an anti-inflammatory, it has become the most widely effective treatment for arthritis. Patients suffering from arthritis must take so much aspirin (sometimes several grams a day) that gastric problems may result. For this reason aspirin is often combined with a buffering agent.   The ability of aspirin to diminish inflammation occurs because aspirin transfers its acetyl group onto an enzyme; conversion of the enzyme from its amine form to amide form inhibits the synthesis of certain prostaglandins that enhance inflammation.

If aspirin were a new invention, the FDA would place hurdles in the path of its approval. It has an effect on platelets, which play a vital role in blood clotting. In newborn babies and their mothers, this reduction in clotting can lead to bleeding problems. However, this same reduction in clotting has been turned to great advantage. Heart specialists urge potential stroke victims to take aspirin regularly to inhibit clotting in their arteries, and it has been shown that one-half tablet per day will help prevent heart attacks in healthy men. Adult diabetics are routinely advised to take regular aspirin as a preventative measure against heart attacks.

Although aspirin once made up >90% of the commercial pain-killer market, it now faces stiff competition from other analgesics (acetaminophen [Tylenol], ibuprofen [Advil], and naproxen [Aleve]…)

The aspirin you make today is exactly the same chemically as a commercial aspirin except for two things: yours has not met FDA purity standards, but yours is also "undiluted". Commercial aspirin is held together by a binder which makes up most of the mass. Medicines are never the pure chemical. When you take a tablet or a capsule or a liquid dose or an injection of a medicine, the active ingredient usually comprises only a small fraction of the mass. Most of the "stuff" is binder (for a tablet) or solvent. While all aspirins are the same, for many others medicines the dosage of active ingredient varies (children's Tylenol versus adult…)

Salicylic Acid
mw = 138
mp = 159°C

Acetic Anhydride
mw = 102, d = 1.08 g/mL
bp = 140°C

"Aspirin"
Acetylsalicylic Acid
mw = 180 mp = 128-137°C

Procedure

1. Work with partner if you want.
2. Weigh out 0.138 g of salicylic acid (1.0 mmol) and add it to a small test tube
3. Add one small drop of 85% phosphoric acid
4. Add 0.30 mL of acetic anhydride by syringe. This is present in excess, and can be used in part to rinse down any salicylic acid that was stuck on the walls of the tube.
5. Swirl the reactants thoroughly, then heat the mixture in a beaker of boiling water for ≥5 minutes.
6. Remove the test tube from the heat.
7. Add 5 drops of water to the mixture to decompose excess acetic anhydride. (One molecule of acetic anhydride plus one water reacts to give two molecules of acetic acid.)
8. Add about 1 mL (about half of a full pipet) of water and allow the tube to cool slowly to room temperature.
9. Cool in ice-water bath.
10. If crystallization of the product does not occur during the cooling process, try swirling and poking with a boiling stick, and/or add an ice chip and poke some more with the boiling stick. If this still doesn't promote crystal formation, add a second pipet of cold water and poke some more with the boiling stick.
11. Vacuum-filter using a small Hirsch funnel.
12. Rinse the tube and the funnel with a pipet of ice-cold water.
13. Rinse with a second pipet of ice-cold water.
14. Let the crystals dry before getting the yield and taking a melting point.

15. **Lab report on the aspirin**: report the mass recovered, calculate the % yield, and report the melting range. (The melting range is typically rather broad for aspirin because of the carboxylic acid which hydrogen-bonds to the ester.)
    • No procedure writeup required.

Part 2: Analysis of an unknown alcohol.
* A list of alcohol candidates with their boiling points is listed two pages from here
* Conduct the classification tests shown below to try to determine the following:
    o Is alcohol "big" or "little"? (solubility test)
    o Is alcohol "dense" (aromatic) or "non-dense" (alkyl alcohol)? (solubility test)
    o Is alcohol 1°, 2°, or 3°? (NMR, Chromic Acid test, Lucas test)
* Use NMR to identify your specific alcohol
* Use micro-boiling point (hard!) to try to shorten your list of candidates

Classification Tests
1. <u>Water Solubility</u> Test (Helpful, but not always decisive or clear-cut. Useful, but don't depend on it too much?!)
* Add 15 drops of water to a small test tube, and then add 2 drops of alcohol. Shake vigorously. Is it homogeneous or heterogeneous? If heterogeneous, do the droplets float or sink?
* Interpretation:
    a. Alcohols with >6 carbons definitely won't be soluble.
    b. Alcohols with <3 carbons definitely will be soluble.
    c. Alcohols with 3-6 carbons may be borderline, and could go either way. (If you think you're borderline, then adding more water should enable full dissolving. Or adding more drops of alcohol should confirm incomplete solubility)
    d. An insoluble alcohol that sinks is an alcohol that has an aromatic ring present
    e. An insoluble alcohols that floats is probably an alkyl alcohol, although some aromatics are also floaters.
Note: Insoluble doesn't prove ≥6 carbons; it only proves ≥4 carbons. And soluble doesn't prove ≤3 carbons; it only proves ≤5 carbons.

2. <u>Chromic Acid</u> test (Jones Oxidation): positive for 1° or 2° alcohols (or amines)
* Add 15 drops of acetone, 1 drop of alcohol, and then 1 drop of Jones reagent
* A positive test is color change from orange→green/brown within 5 s. The reaction is normally accompanied by formation of a precipitate
* Interpretation: indicates the presence of a 1° or 2° alcohol, or an amine
* Note: The test involves oxidation to a carbonyl product. If the alcohol doesn't have a hydrogen on the hydroxy-bearing carbon, no oxidation is possible. Thus tertiary alcohols don't react, but both primary and secondary do.

3. <u>Lucas Test</u> ($ZnCl_2$/conc. HCl): positive for 3° or 2° alcohols, <u>or for allylic/benzylic 1°</u>
* Add 30 drops of Lucas reagent to small test tube, then add 3-4 drops of alcohol, shake vigorously, and let settle.
* Tertiary alcohols or allylic/benzylic alcohols react immediately to give two layers
* Secondary alcohols react within 2-5 minutes to give a cloudy solution or two layers
* Primary alcohols that are neither benzylic or allylic dissolve. Primary alcohols that are allylic/benzylic react, because they can make carbocations very well.
* Interpretation: if the mixture remains homogeneous after several minutes, you know you have a non-allylic/non-benzylic primary alcohol.
* Note: The test involves the S_N1 conversion of alcohols (acid-water soluble) to alkyl chlorides, which are insoluble.

NMR   Run proton; decoupled carbon; 2-Dimensional H-H; and 2D H-C NMR.
- Add sample by drawing up about 1 inch of your unknown into the skinny part of a long-stemmed pipet, then place the pipet into an NMR tube. (Alternatively, add 2-3 drops of unknown, being sure they are true drops, and not just "bubbles" that are 99% air!)
- Add 0.8-mL of $CDCl_3$ solvent (volumes not critical) directly through the pipet to rinse the sample into the NMR tube.
- Cap the sample and take it to the NMR room (SL 305), get it loaded, and submit into the queue. The experiment is called "H-C-HH-HC" and is under the UserStudies folder. The instructor will presumably have this all ready and queued up.
- Do expansions as appropriate, to clarify splitting. Manual integrations will usually help a lot.
- Zooming and adjusting the scaling on the 2D H-C NMR could help.
- Several challenges may complicate things in the H-NMR:
  1. It will be entirely common in longish alkyl groups that several alkyl H groups will overlap. In 1-octanol, for example, CH2's 3-7 will probably all make a big superimposed lump that integrates for around 10H.
  2. For secondary alcohols, the hydrogens of adjacent CH2 groups end up being non-equivalent; one is cis and one is trans to the OH. So they are different, and end up with possibly different chemical shifts and complicated splittings.
  3. The OH hydrogen can come almost anywhere, and superimposes on other alkyl H's.
  4. The OH hydrogen is often a lumpy shape.
  5. Sometimes the OH doesn't split at all with the C-H hydrogens, but sometimes it does.
  6. On the carbon to which the OH is attached, the hydrogens are sometimes broadened or deformed by the OH hydrogen. So the splitting can be complex. See instructor for consulting.
  7. Aromatic H's commonly overlap into one big 5H lump.

Micro-Boiling Points in the Melting Point Apparatus

A microscale boiling point can be taken in a melting point tube that has an inverted "bell" in it. Add about 5 uL of liquid via syringe and tapping. (Make sure the bell is already in place.) The "bell" is a narrow piece of tubing with the upper end closed off, and should be at least the length of a fingernail. Preparing bells will require some glass-melting/stretching.

Run two samples side-by-side, one containing 1-propanol with a known boiling point of 97ºC, the second with your actual unknown alcohol. Note the original liquid levels at the start.

When a liquid is heated, pre-boiling bubbling will often occur as the air inside the bell heats and expands and gets displaced by sample evaporation. When the boiling point is reached, more rapid bubbling often takes place. Keep heating somewhat beyond the point where you think boiling has occurred, because you may not be experienced enough to distinguish "pre-boiling" bubbles from real boiling bubbles.

In many cases, you won't see nice bubbles. Even so, at or somewhat beyond the boiling point, vaporization should accelerate such that the liquid level will drop. Watch for this.

These boiling points will not be very accurate, especially for an inexperienced user. Don't trust them to be accurate better than to about 10 degrees. While the observed boiling points are imprecise, they still greatly shorten the list of candidates. The instructor will have a list of boiling points; check with instructor to confirm whether you're boiling point is within 10º and is close enough, or whether you need to re-run the micro-boiling point.

Alcohol Candidates

bp	Alcohol
65	Methanol
78	Ethanol (anhydrous)
82	2-propanol (isopropanol)
83	t-butyl alcohol (2-methyl-2-propanol)
97	1-propanol (propyl alcohol)
98	2-butanol (sec-butyl alcohol)
102	2-methyl-2-butanol
108	2-methyl-1-propanol (isobutyl alcohol)
115	3-pentanol
118	1-butanol
119	2-pentanol
129	3-methyl-1-butanol
132	4-methyl-2-pentanol
137	1-pentanol
140	cyclopentanol
140	2-hexanol
157	1-hexanol
160	cyclohexanol
176	1-heptanol
178	2-octanol
185	2-ethyl-1-hexanol
195	1-octanol
204	benzyl alcohol (phenyl methanol)
204	1-phenylethanol (sec-phenethyl alcohol)

Unknown Report Sheet

Unknown Number or Letter: Your Name

Draw your unknown's Structure:

Data Summary
1. Boiling points: measured bp _____   listed bp_____

2. Chemical Tests   _____   Result and probable meaning

a. Water solubility

        If insoluble, did it sink or float?

b. Jones Reagent (Chromic Acid)

c. Lucas Reagent

Comments, if you have any:

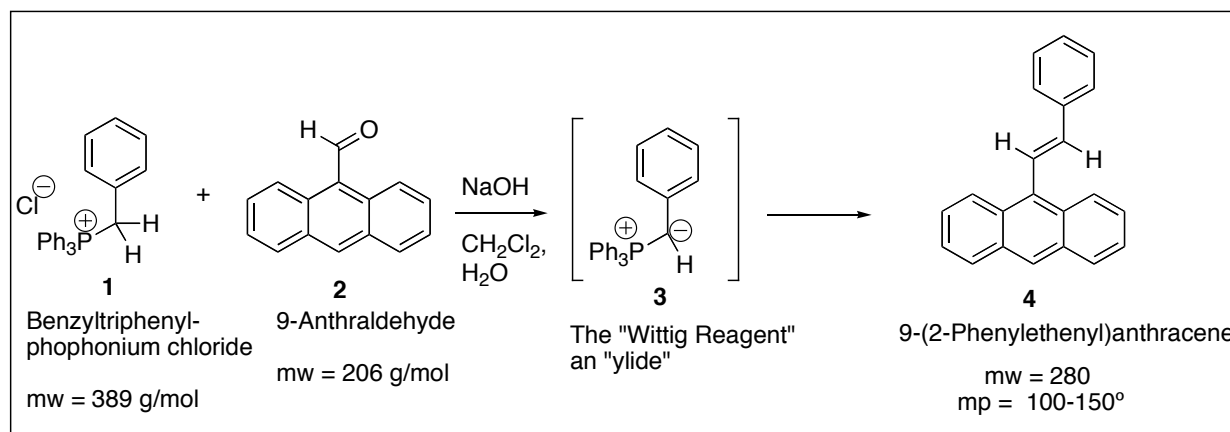3. Attach copies of all four of your NMR spectra.

4. **On the H-NMR spectrum, create a standard summary table of your H-NMR data**, detailing chemical shifts, integrations, and splittings. Draw the structure of your molecule, with identifiers by each carbon (typically a, b, c…). Then on your standard summary table add a column in which you explain which hydrogens (a, b, or c, etc…) are responsible for which signals. Note: if the sample is too concentrated, the splitting may in some cases get broadened and become problematic. The OH may also induce weird splitting, as may cis/trans issues in 2° alcohols. In many cases, some overlapping may occur.

5. **On the carbon spectrum, draw the structure of your molecule, again with identifiers by each carbon (typically a, b, c…)**. Then **next to each line in the carbon spectrum, write the letter a, b, or c etc. which is responsible**.   Using your H-C 2-dimensional NMR will be very helpful for figuring out which carbon is which in the 0-50 zone.

6. Comments (if any).

7. **Remember to attach your aspirin data or write on this sheet somewhere**.

The Wittig
Reaction: Synthesis of Alkenes

1
Benzyltriphenyl-
phophonium chloride

mw = 389 g/mol

2
9-Anthraldehyde

mw = 206 g/mol

3
The "Wittig Reagent"
an "ylide"

4
9-(2-Phenylethenyl)anthracene

mw = 280
mp = 100-150°

Intro   The "Wittig Reaction" is one of the premier methods for the synthesis of alkenes. It uses a carbonyl compound as an electrophile, which is attacked by a "phosphorus ylide" (the "Wittig reagent".) While many other routes to alkenes can proceed via elimination reactions (E1 or E2 reactions from alcohols or alkyl halides, for example), in elimination reactions the carbon skeleton is already pre-assembled. In the Wittig reaction, however, two smaller carbon units are conjoined to make the alkene double bond. Thus molecules of increasing size and complexity can be quickly assembled. In addition, there is no ambiguity regarding the site of the double bond. (In contrast to elimination reactions, which often give mixtures of "more substituted" and "less substituted" structural isomers.) The Wittig reaction is nicely complementary to the aldol condensation, in which carbonyl compounds are attacked not by a phosphorus ylide but by an enolate. Aldol condensations always result in "enones", alkenes with a carbonyl attached. Wittig reactions are more general in that the product carbonyl does not need to have an attached carbonyl. The alkene product **4** that you make today is the one that was used a few weeks ago as the colorizer for the chemiluminscence experiment (it gave the green solution.)

General Wittig Reaction: Synthesis of Alkenes
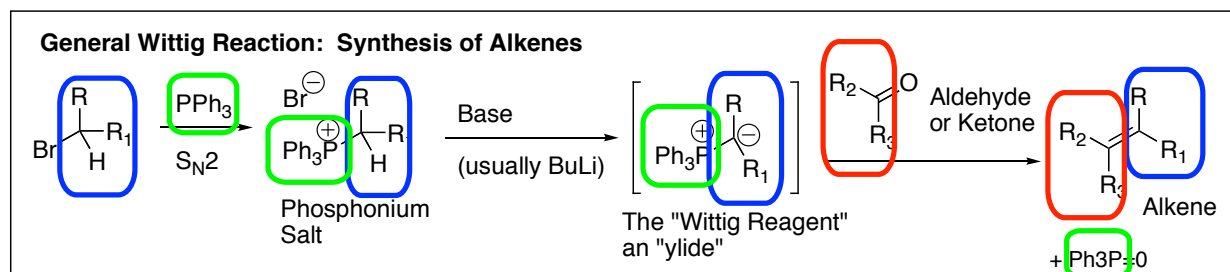
Mechanism

The general mechanism of the Wittig reaction is shown above. The phosphonium ion is deprotonated by base. The positively charged phosphorus atom is a strong electron-withdrawing group, which activates the neighboring carbon atom as a weak acid. For many phosphonium ions, a very strong base (commonly butyl lithium) is required in order to do the deprotonation. The use of such strong base requires moisture-free conditions such as were required for doing the Grignard reaction. In today's experiment, however, very concentrated sodium hydroxide is

Wittig Mechanism
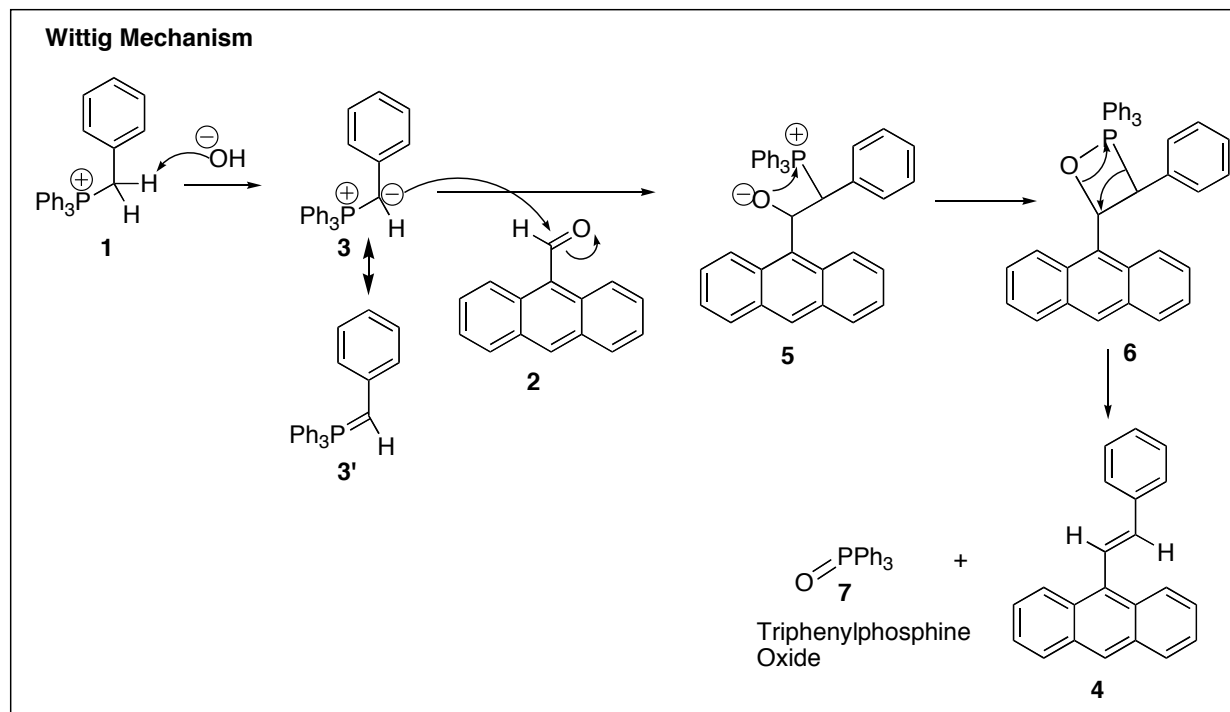
strong enough to do the deprotonation. This is because the carbanion **3** that is produced is stabilized not only by the positive phosphorus, but also by conjugation with the benzene ring. Notice that carbanion **3** has a resonance structure, **3'**, in which it is unnecessary to draw any formal charges. Either resonance structure is reasonable; **3'** has the advantage that it involves no formal charge, and has a double bond to carbon in exactly the same place where the final alkene C=C double bond ends. But **3'** has the disadvantage that it doesn't illustrate why the carbon should be so nucleophilic. In addition, it involves a phosphorus with five bonds. Resonance structure **3** is useful in that it shows why the carbon should be so nucleophilic, and also is consistent with the popular octet rule.

   Once the carbanion/ylide **3** is formed, it is strongly nucleophilic, and attacks carbonyls just like other strong nucleophiles (for example, Grignard reagents…), producing an alkoxide **5**. Alkoxide **5** rapidly closes onto the phosphorus to form the 4-membered ring **6**, which is not very stable. The "betaine" **6**, with its 4-membered ring, rapidly fragments to give the desired alkene **4** and triphenylphosphine oxide **7** as a side product.

   Wittig Reactions and the Phosphine Oxide Side Product 7: This side product is non-trivial to remove. It's too "organic" to wash out into a water layer, and it's too heavy to boil away. In today's experiment, we will remove it based on its polarity and H-bonding ability, in contrast to the non-polar alkene **4**. This separation will be accomplished by recrystallization from a somewhat polar hydrogen-bonding alcohol solvent, but it needs to be done carefully to selectively remove phosphine oxide **7** without losing too much of alkene **4**.

   The Diagnostic Color Changes of Wittig Reactions: One interesting aspect of Wittig reactions that is not well illustrated today is that normally the carbanion/ylides **3** are colored, often intensely so. (Many are a deep, blood red or sometimes grape-juice purple). The product alkene and phosphine oxides are normally not colored, as is normally true of the phosphonium salt and the carbonyl electrophile. Thus you can often monitor Wittig reactions by color: formation of color shows you've made the ylide; disappearance of the color shows that the ylide has reacted and gone on to final products. While you will see some meaningful color changes

today, they won't be as intense or diagnostic, for a couple of reasons. 1) In today's case, the extended conjugation of both the starting anthraldehyde **2** and the product alkene **4** make both of them colored. So whereas normally there is no color at the beginning or the end, only during the ylide middle, today the colors of both the starting aldehyde and the product alkene partially mask the color of the ylide. 2) In today's case, the conjugation of the ylide carbanion with the benzene weakens the color of the ylide. It's not nearly as intense or red as for a non-conjugated ylide. Still, you will be able to see some changes in color as the reaction proceeds. One additional factor to consider is whether the phosphonium salt or the carbonyl is the limiting reactant. If the carbonyl is in surplus, all of the ylide (and it's color) should get consumed. But if the carbonyl is limiting, even after it is fully reacted there may be some residual ylide (and it's color) that survives.

   The Unusual Solvent Combination for Today: Most reactions are conducted in a homogeneous solution, where everything is dissolved and can move around such that reactants can collide. This is difficult to accomplish, however, when you have both strongly hydrophobic reactants (the aldehyde in today's experiment) and strongly hydrophilic reactants (sodium hydroxide). The phosphonium salt is also ionic, and thus also has problems dissolving in organic solvent. Rather than having a homogeneous solvent system that can get these extremely opposite chemicals all into the same solution, today's solvent system will be a mixture of water and dichloromethane. These two are not cosoluble, and will give two separate layers. Thus the ionic hydroxide and the phosphonium salt can go into the water, and the aldehyde and the product alkene can go into the dichloromethane. When the ylide forms, it has no overall charge, and thus can switch phase from the water to the organic phase. (This is called a "Phase Transfer" reaction.) **Note: Phase transfer can only take place at the interface between the two phases. In order to maximize contact between the two phases, it is very important that the mixture be well stirred to provide lots of small droplets and lots of surface area for organic/water contact.**

Wittig Reaction Procedure
1. May work with partner, or may work alone.
2. Place a small (smallest possible) stirring bar in a large test-tube.
3. Set the test-tube into a beaker or Erlenmeyer so that you can stand it on a stir-plate.
4. Weigh out 0.300 g of 9-anthraldehyde **2** and add this to the test tube.
5. Add two pipets of dichloromethane and stir.
   - Note: does the aldehyde dissolve?
   - What color is the solution?
6. Weigh out 0.480 g of benzyltriphenylphosphonium chloride **1** and place it into the test tube.
7. Add 1 pipet of water, using this to try to rinse down any phophonium salt that's stuck on the sides
   - Note: does the salt dissolve?
   - What color is the salt?
   - Is the solution warm to the touch at this point?
8. Stir the mixture vigorously, and then add 0.65 mL of 50% sodium hydroxide solution by syringe.
   - Note: Is the solution warm to the touch at this point?
   - What colors are the layers?
   - Has the salt dissolved yet?
   - Which layer is on top, the aqueous or the organic layer?
9. Stir the solution vigorously for 10 minutes.

10. Workup: Dilute with 3 mL of dichloromethane and 5 mL of water, and pour the mixture into the separatory funnel.
11. Rinse the test tube with another 3 mL of dichloromethane and 3 mL of water and pour this also into the separatory funnel.   Shake it up vigorously, and then allow time to settle.
    • Which layer is on top, the aqueous or the organic layer? If unsure, how could you check?
12. Pour the organic layer into a 50-mL Erlenmeyer.
13. Add an additional 5-mL of dichloromethane to the separatory funnel, and shake vigorously again.
14. Pour the organic layer into the same 50-mL Erlenmeyer that has the other dichloromethane.
15. "Dry" the organic solution with sodium sulfate.
16. Filter the organic solution into a separate 50-mL Erlenmeyer, using a funnel packed with glass wool to filter off the sodium sulfate.
17. Rinse the original Erlenmeyer and the funnel with additional dichloromethane.
18. Add a boiling stick to your organic solution, and then place the Erlenmeyer into a hot-water bath (250-mL beaker?) to boil off the dichloromethane. (Be thorough…)
    • Note: How do you know when to quit? If you know what your theoretical yield is, it will help you realize approximately how much stuff you should expect to have left once the solvent is removed…
19. Remove your Erlenmeyer from the hot water bath.
    • Does anything crystallize?
    • At this point you have at least three or maybe four things present. The desired alkene **4**; the undesired phosphine oxide side product **7**; perhaps some unreacted aldehyde **2**; and perhaps some solvent that hasn't quite all boiled away.
    • Place your material into an ice bath, and scratch it with a boiling stick. If it crystallizes, that confirms that you've done an adequate job of boiling off your dichloromethane. If it doesn't crystallize, you should probably boil some more off.
    • If you don't get rid of your dichloromethane adequately, leftover dichloromethane will keep product dissolved at the end of the recrystallization process, and your yield will be affected.
20. Purify your alkene by recrystallizing from 1-propanol solvent. The concept here is that the triphenylphosphine oxide is more soluble in the propanol than is the alkene product, because the phosphine oxide can use it's oxygen to hydrogen-bond to the solvent, whereas the alkene has no hydrogen-bonding capability.
    • Do you remember the logic and procedure for a recrystallization? If not, try to review!
    • A good starting guess may be about 6 mL, but you may need to improvise as needed. (If it doesn't dissolve even after reaching the boiling point, what should you do?)
    • This recrystallization can be done right in the same 50-mL Erlenmeyer flask.
21. Rinse with a very small amount (2 mL?) of ice-cold propanol. We don't want to add water and make the solvent much "worse" for fear that water will knock the triphenylphosphine oxide out of solution and contaminate the product.
22. Let things dry thoroughly before getting your yield and mp. Once you have your yield, also calculate your % yield.

Lab Report: Standard synthesis style lab report. Be sure to include detailed observations on some of the things that happened. For product, include yield, mp, and % yield.

Questions: None assigned.

Carbonyl Unknowns

Overview:
You will receive a carbonyl compound as an unknown. It can be either an aldehyde or a ketone, and may or may not contain an aromatic ring. Your job will be to identify your carbonyl compound. Several pieces of information will be useful:
- Water solubility tests (big or small? Aromatic or not?)
- Boiling point of starting material (try at least once)
- The melting point of the derivative (required)
- NMR information on the starting material. (H and C-decoupled)

Classifying Tests

1. <u>Water Solubility</u> Test (Helpful, but not always decisive or clear-cut. Use, but don't depend on it too much?!)
   - Add 15 drops of water to a small test tube, and then add 2 drops of sample. Shake vigorously. Is it homogeneous or heterogeneous? If heterogeneous, do the droplets float or sink?
   - Interpretation:
     a. Carbonyls with <4 carbons always dissolve
     b. Carbonyls with >6 carbons never dissolve
     c. Carbonyls with 4-6 C's, borderline; may dissolve or may not. Sometimes adding some more water will dissolve, if doesn't initially.
     d. An insoluble carbonyl that sinks has an aromatic ring present for sure
     e. An insoluble carbonyl that floats is probably nonaromatic, although some aromatics are also floaters.

2. Summary of chemical tests related to carbonyls, not all of which we will do, but which you should know to answer questions
   - 2,4-dinitrophenylhydrazine test: positive for aldehydes or ketones.
   - Tollens' test: Positive for Aldehydes, not for Ketones. Similar to Schiff's test, but more famous (good) but more expensive (bad) (Note: we'll tell by H-NMR. Shift at ~9-10ppm proves aldehyde.)
   - Iodoform Test: Positive for Methyl Ketones (CH_3COR). (This is also pretty easy to see by H-NMR, since you get a 3H singlet in the 2's.)
   - Br_2/CH_2Cl_2 test: Positive for Alkenes (to distinguish C=C from C=O double bonds)

3. NMR: Prepare a sample by drawing up about 1 inch of your unknown into the skinny part of a long-stemmed pipet, then place the pipet into an NMR tube. (Alternatively, add 2-3 drops of unknown, being sure they are true drops, and not just "bubbles" that are 99% air!). Add 0.8 mL of CDCl3 directly through the pipet to rinse the sample into the NMR tube. Get it into the NMR queue and run the experiment called "H8-C64" in the UserStudies folder.
   - Aldehydes are easily distinguished from ketones by H-NMR. The aldehyde hydrogen, which is attached to the carbonyl carbon, shows up in the 9-10.5ppm chemical shift area. Ketones will show no such signal in that area.
   - Aromatic hydrogens ortho to a carbonyl are typically pushed downfield, toward 8 ppm. This is because a carbonyl group is a strong electron withdrawer, so it makes the ortho carbons more electron poor, which "deshields" the ortho hydrogens.

Derivative: Making a 2,4-DNP Derivative of Your Aldehyde or Ketone

Put 4 pipets of 2,4-DNP solution into a large test tube, add a stirring bar, and add 30 drops of your unknown to the well-stirred solution. After 5 minutes, cool, add 2 pipets of cold water, filter, wash with cold water, and wash with a small amount (three pipets) of cold ethanol. Aspirate thoroughly, and hopefully get a crude mp. Recrystallize (or "digest") from absolute ethanol, using a 125-mL Erlenmeyer.   Make a starting guess of 4 mL ethanol, then once the mixture reaches boiling improvise/adjust appropriately depending on what you see. If you have both some hot ethanol and perhaps also some hot water prepared, that may make it faster/easier to make rapid adjustments to your solvent. (If you add cold ethanol or water, the response is complicated by the change in temperature.)

In some cases, it takes a lot of ethanol to get the crystals dissolved. The amount of ethanol required will vary from one unknown to another; saturated alkyl ones usually dissolve easily, the longer the alkyl chains the easier.   Aromatic aldehydes/ketones are often much harder to dissolve and require a lot of ethanol, or else simply will never dissolve completely. If you have added 50 mL of ethanol to your boiling solution and the solid has still not dissolved completely, then just let it boil for another five minutes and then take it off from the heat and allow cooling to proceed. In this case ("digestion"), simply boiling the mixture for a while enables the impurities to get free, even if not all of the crystal is completely dissolved at any one time.

Disposal: Into DNP waste container.
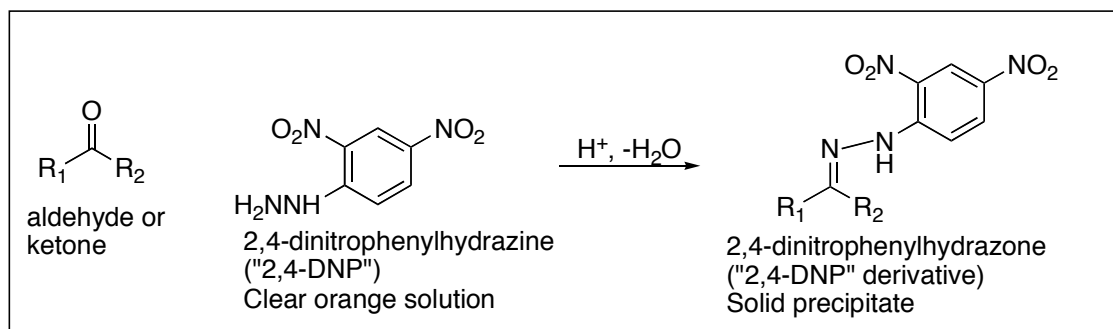
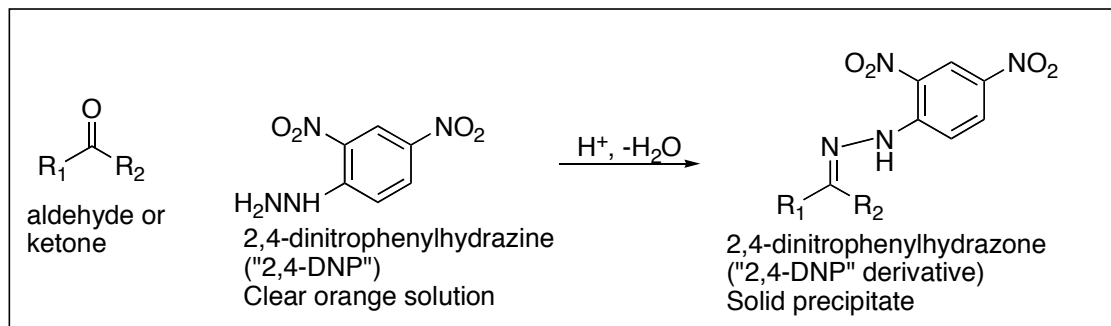**Chemical Derivatives: General Considerations/Purpose**

A classic way to help identify a material is to convert it into a crystalline derivative. This is particularly valuable if the initial chemical is a liquid or is impure. We've seen that although melting points are easy to measure, boiling points are not. By converting a liquid (or impure) sample for which a meaningful bp/mp is not easy to obtain into a crystalline solid, we can get useful melting points.

Unfortunately the usefulness of a solid's melting point is dependent on having very pure solids. Your product must be purified well and dried well if it's melting range is expected to have any accuracy. Thus your success in making and using solid derivatives for identification purposes will hinge on your purification skills.

Lists of derivatives with their characteristic melting points are widely available. These are useful even if the melting point or boiling point of the starting material is available. Often several candidates may fit into the mp/bp of the starting unknown. But by having both a value for the starting material as well as the derivative, resolution is often possible.

SOME CHEMICAL TESTS TO KNOW

2,4-Dinitrophenylhydrazone ("DNP") Test: Specific for Aldehydes or Ketones (but not esters, acids, or amides)

aldehyde or ketone

2,4-dinitrophenylhydrazine ("2,4-DNP")
Clear orange solution

2,4-dinitrophenylhydrazone ("2,4-DNP" derivative)
Solid precipitate

The "DNP" test is positive for both aldehydes and ketones, but not for alkenes or esters/acids/amides.   This is representative of how $H_2N\text{-}Z$ reagents react with aldehydes or ketones to eliminate water and make "imines", with a C=N-Z bond. In the chemical test, the DNP reagent is soluble; if a derivative forms, it precipitates from solution. So the formation of a precipitate is what you watch for. The DNP-derivatives tend to be highly crystalline because of the extended conjugation; from the carbonyl carbon through the two nitrogens through the ring through the two nitro attachments, all the atoms are flat and sp^2. The color of the precipitate is often informative; saturated carbonyl compounds tend to give yellow derivatives, while unsaturated aldehydes or ketones tend to give red or orange derivatives. The experiment is excellent as a chemical test, when you don't know if you have an aldehyde or ketone. But it is also excellent as a way to make a solid derivative which can be purified by recrystallization and whose melting point can be taken. The melting points of many DNP derivatives are known and listed.

Tollens Test: Specific for Aldehydes. Positive for Aldehydes Only.
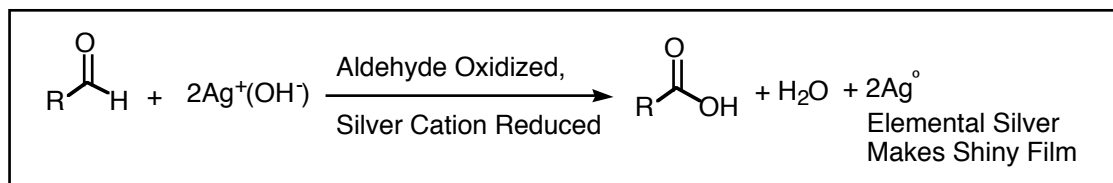
A classic alternative to the Schiff's test fo aldehydes is the the Tollens Test. Tollens reagent is a soluble AgOH solution. [Actually $Ag(NH_3)_2OH$]. When mixed with an aldehyde, the aldehyde carbon is oxidized to a carboxylic acid, and the Ag(I) cation is reduced to elemental Ag(0). The elemental silver films out on the surface of the test tube in which the test is conducted, and a "silver mirror" can be observed. This reaction has historic importance. For centuries during the middle ages this was the process used to make mirrors. (These silver mirrors were less clear than modern mirrors). This silver coating process was also used to apply a silver coating to any object. We will not use this test in lab because the Schiff's test is cheaper and easier. Test tubes used for Tollen's test must be thrown away, and the silver reagent is somewhat expensive.

Iodoform Test: Specific for Methyl Ketones (CH$_3$COR)
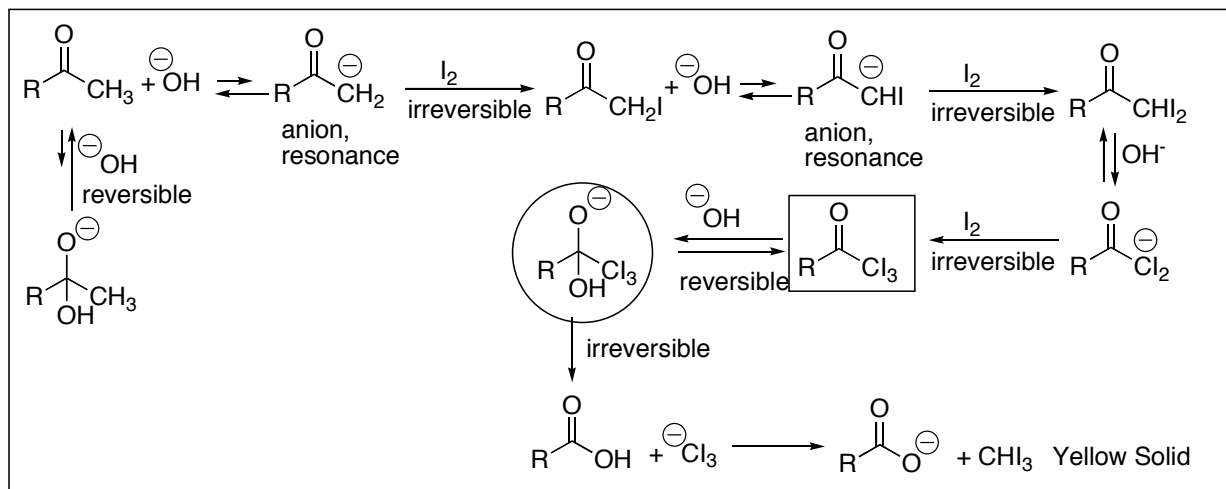
Methyl ketones can be distinguished from other ketones by the iodoform test. The methyl ketone is treated with iodine in an NaOH/water solution. Methyl ketones produce a yellow solid called "iodoform", other ketones or aldehydes do not. The mechanism is shown below, and is somewhat complex. Deprotonation of the methyl ketone hydrogen gives a resonance-stabilized anion, which attacks iodine. Once the first iodine is installed, the remaining methyl hydrogens become even more acidic and get deprotonated followed by iodination in rapid sequence to generate the tri-iodo RCOCI$_3$ species (in box). Hydroxide routinely adds to carbonyls, but normally this addition is reversible, non-productive, and insignificant. However, hydroxide addition to the RCOCI$_3$ is productive; in this case, the anion (in circle) can eliminate the $^-$CI$_3$ anion. This is a decent leaving group because the three electron-withdrawing iodo groups stabilize the anion. This elimination is also irreversible, so by LeChatelier's principle all of the chemicals drain off through this pathway. Following elimination, the $^-$CI$_3$ anion picks up a proton to make iodoform, CHI$_3$, which is a yellow crystalline solid. The formation of this yellow solid is a "positive" test; if no yellow solid forms, the test is "negative". Ketones other than methyl ketones are unable to get to the RCOCI$_3$ species (in box), are unable to undergo the fragmentation that the circled anion undergoes, and are unable to make the solid iodoform.

Br$_2$ Test: Specific for Alkenes (Not Ketones or Aldehydes)

Bromine is a routine test for alkenes. (Although a mono-substituted alkene is shown in the picture, di-, tri- and tetra-substituted alkenes also react with bromine.) Bromine adds to alkenes but not to carbonyl compounds (or to ordinary arenas).   The
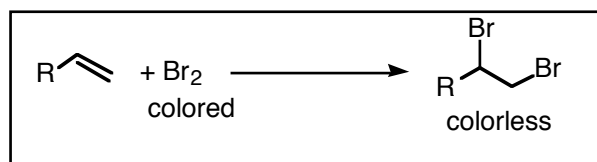
nature of the test is to add a few drops of bromine, which is strongly colored, to an excess of an organic sample. If the color disappears, it means the bromine reacted and therefore that the organic unknown contains an alkene. If the color persists, it means the bromine did not react, and therefore that no alkene is present in the organic unknown.

Aldehyde/Ketone Candidates

Bp of Starting Carbonyl	Unknown	mp of 2,4-DNP Derivative
48	propanal	148
56	acetone	126
63	2-methylpropanal	187(183)
75	butanal	123
80	2-butanone	117
91	3-methylbutanal	123
92	2-methylbutanal	120
100	2-pentanone	143
102	3-pentanone	156
103	pentanal	107(98)
115	4-methyl-2-pentanone	95
128	5-hexen-2-one	108
129	4-methyl-3-penten-2-one	205
131	cyclopentanone	146
131	hexanal	104(107)
145	4-heptanone	75
145	5-methyl-2-hexanone	95
146	2-heptanone	63-68 *
147	3-heptanone	81
153	heptanal	108
156	cyclohexanone	162
169	3-methylcyclohexanone	155
173	2-octanone	58
179	benzaldehyde (PhCHO)	237
200	o-methylbenzaldehyde	194
204	p-methylbenzaldehyde	234
202	ethanoylbenzene	244
216	1-phenyl-2-propanone	156
217	(2-methylpropanoyl)benzene	163
218	propanoylbenzene	191-198 *
226	p-methylacetophenone	258
232	butanoylbenzene	191
235	4-phenyl-2-butanone	127
248	p-methoxybenzaldehyde	253

Name:

Lab Report Requirements: No procedure or yield information required. Fill out the unknown report sheet. Attach your NMRs. (Must take at least one of H-NMR or C-NMR, or both.) Answer the following questions.

Questions:

1. What is the purpose of making derivatives of liquid unknowns?

2. Using a chemical test or tests, how could you distinguish between 3-pentanone and pentanal?

3. Using a chemical test or tests, how could you distinguish between 3-pentanone and 2-pentanone?

4. Using a chemical test or tests, how could you distinguish between 3-pentanone and 4-penten-1-ol?

5. Draw a possible structure for a molecule C_5H_8O that gives a positive tollens' test and does not react with Br_2/CH_2Cl_2?

6. Draw the structure of a compound C_5H_8O that reacts with 2,4-dinitrophenylhydrazine, decolorizes bromine in dichloromethane, but does not give a positive iodoform test.

7. Draw two structural isomers for $C_5H_{10}O$ that would both give positive iodoform tests?

8. Draw a possible structure for C_4H_8O that would <u>not</u> give a positive dinitrophenylhydrazone test?

Unknown Report Sheet-Carbonyls   Name

Your unknown Letter/Number:

Draw the structure for your unknown:

1. Physical Examination of Starting Material

a) Physical State_____ b) Color_____ c) Odor_____

2. Solubility Tests on Starting Material

Solubility in Water: _____   If Insoluble, Does it Float or Sink?

        Conclusion:

3. Boiling point:

4. Derivative: observed mp   literature mp
Crude (if possible):
Recrystallized

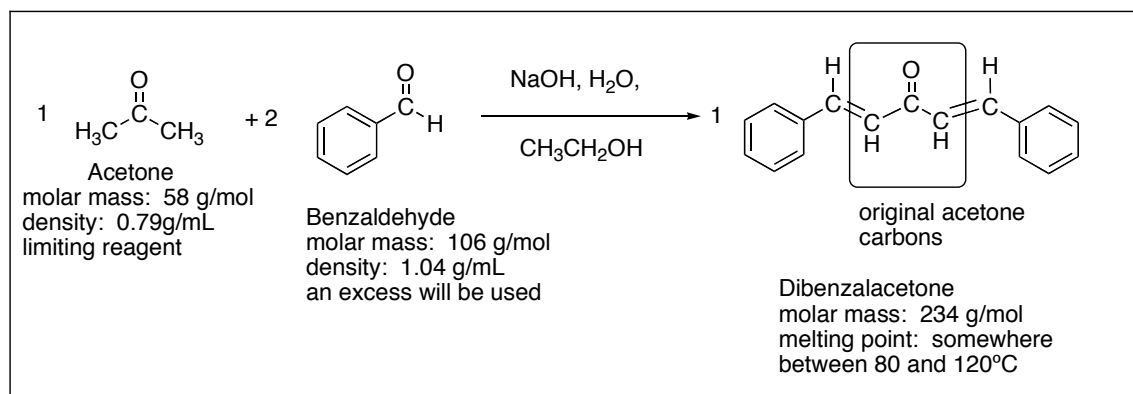5. H-NMR (attach, with assignments/interpretation.)
    - **On the proton spectrum, create a standard summary table of your H-NMR data, detailing chemical shifts, integrations, and splittings.**
    - Draw the structure of your molecule, with identifiers by each carbon (a, b, c…).
    - Then on your standard summary table add a column in which you explain which hydrogens (a, b, or c, etc…) are responsible for which signals. Note: if the sample is too concentrated, the splitting may in some cases get broadened and become problematic.

6. C-NMR (attach, with assignments/interpretation)
    - Draw the structure of your molecule, with identifiers by each carbon (a, b, c…).
    - Draw letters next to carbon lines that can be assigned.
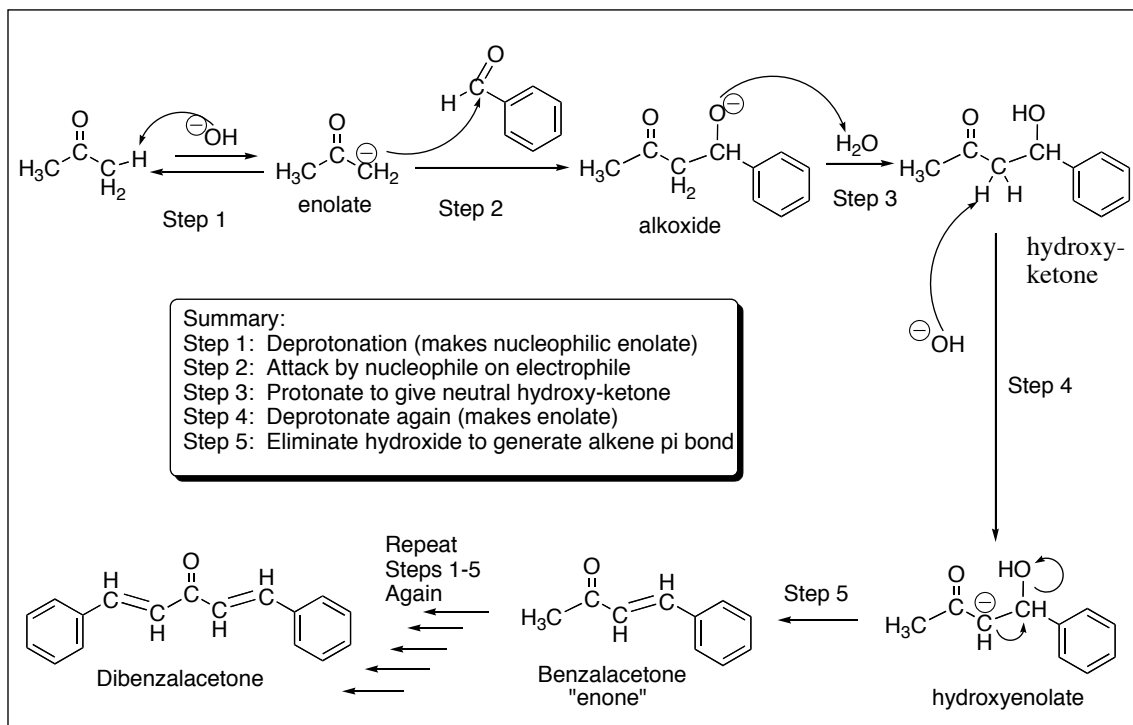   - Without a C-H 2D NMR, you may not be able to assign all of your lines.)

7. Comments, difficulties, complaints, etc.

ALDOL SYNTHESIS of DIBENZALACETONE, AN ORGANIC SUN SCREEN

1 Acetone
molar mass: 58 g/mol
density: 0.79g/mL
limiting reagent

+ 2 Benzaldehyde
molar mass: 106 g/mol
density: 1.04 g/mL
an excess will be used

NaOH, H_2O, CH_3CH_2OH

1 original acetone carbons

Dibenzalacetone
molar mass: 234 g/mol
melting point: somewhere between 80 and 120°C

Overview: The reaction of an aldehyde with a ketone employing sodium hydroxide as the base is an example of a mixed aldol condensation reaction. You will do a double mixed-aldol condensation reaction between acetone and benzaldehyde. Acetone has α-hydrogens (on both sides) and thus can be deprotonated to give a nucleophilic enolate anion. The aldehyde carbonyl is much more electrophilic than that of a ketone, and therefore reacts rapidly with the enolate. The alkoxide produced is protonated by solvent, giving a β-hydroxyketone, which undergoes base-catalyzed dehydration.   The elimination process is particularly fast in this case because the alkene is stabilized by conjugation to not only the carbonyl but also the benzene. In today's experiment you will use excess benzaldehyde, such that the aldol condensation can occur on both sides of the ketone.

Mechanism for Aldol Condensation

Step 1
enolate
Step 2
alkoxide
Step 3
hydroxy-ketone

Summary:
Step 1: Deprotonation (makes nucleophilic enolate)
Step 2: Attack by nucleophile on electrophile
Step 3: Protonate to give neutral hydroxy-ketone
Step 4: Deprotonate again (makes enolate)
Step 5: Eliminate hydroxide to generate alkene pi bond

Step 4

Repeat Steps 1-5 Again

Dibenzalacetone

Benzalacetone "enone"

Step 5

hydroxyenolate

Procedure:

Calculations

1. Calculate the volume required to produce 0.0125 mol of acetone.
2. Calculate the volume of 2.2 "equivalents" of benzaldehyde. (In other words, 2.2 times as many moles of benzaldehyde as of acetone.) Note: the equation involves a simple 2:1 stoichiometry.
*   By using an actual 2.2:1 ratio, it ensures that the benzaldehyde is surplus and that the acetone is limiting. This is helpful for several reasons:
    a. **Aldehyde oxidation**. Aldehydes are often impure, because oxidation to carboxylic acid is fairly facile. By using 2.2 equivalents of benzaldehyde, then even if 10% of the benzaldehyde is corrupt <u>we ensure that we still have enough to fully react with the acetone</u>.
    b. **Reaction Time**. By having an excess of benzaldehyde, <u>it makes it easier for the reaction to go to completion</u>. Otherwise late in the reaction there isn't much benzaldehyde left to react, so the reaction slows down a lot. By intentionally putting in some extra, it maintains at least a minimal concentration of electrophilic benzaldehyde till the very end, such that getting 100% conversion of isn't so hard and doesn't take so long.
    c. **Ease of Product Purification**: **Disubstitution versus monosubstitution**. Enabling complete conversion greatly simplifies purification. If complete conversion does not occur, either because benzaldehyde runs out or because insufficient time is used, the desired "disubstitution" product "dibenzalacetone", in which two benzaldehydes have been incorporated, is contaminated by "benzalacetone", the "monosubstitution" product in which only one benzaldehyde has been incorporated. Since the mono- and disubstituted products aren't that different, it's not that easy to remove the undesired side-product from the main desired product. But if you just make sure the reaction goes all the way to the desired product, then you don't need to worry about it!

Doing the Reaction:

1. Use a 125-mL Erlenmeyer flask with a magnetic stirring bar.
2. Add 50 mL of the NaOH-Ethanol-Water solution mixture.
3. Place the solution on the magnetic stirrer and adjust the stirring dial to get a nice, even stirring action.
4. To this add the calculated amount of benzaldehyde by syringe
5. Add the calculated amount of acetone by syringe, last. (The acetone should go in last, after the benzaldehyde electrophile is already available. If the acetone goes in first, it could do aldol condensation on itself, in which enolate anions just attack neutral acetone carbonyls. Ketone carbonyls aren't competitive with aldehyde carbonyls as electrophiles, but if there are no aldehydes available, ketones are better than nothing!)
6. Watch the solution carefully, with a watch, at the beginning of the reaction, so that you can keep good observational records.
    *   How long does it take for the solution to turn yellow? Given that all the reactants are colorless, what does the yellow color mean?
    *   How long does it take for the solution to become cloudy, and for solid to then accumulate?
7. Let the solution stir for 30 minutes. (Calculate, write report, do theoretical yield, etc.)
8. Add 20 mL of water, and then filter the mixture
9. Pour the filtrate into the waste container.

10. Wash the crystals three times with 50-mL of water each time.
    * The product is so organic that it has essentially no solubility in water. Water washes are no threat to your yield.
    * The initial product is contaminated by sodium hydroxide. The extensive water washes removes all traces of sodium hydroxide.
11. If the crystals are still pretty wet, press them drier by pressing a filter paper on top to absorb water.
12. Weight the crude product; remove a small crystal for a crude melting point that you can run later; and take a spatula tip and prepare a sample for GC. (Ethanol or acetone can be used as solvent; the solution should be concentrated enough to be noticeably yellow.) Get your sample into the GC queue as rapidly as possible.
13. Purify the bulk of your crystals by recrystallizing from ethanol, or ethanol perhaps spiked by water as needed.
14. Rinse the crystals with an appropriate rinse solvent. (What might that be?)
15. Dry thoroughly.
16. Take yield, mp, prepare and run a GC on the purified material, and calculate the % yield.

Lab Report:
Standard synthesis lab report. Yield, % yield, and mp's of crude and recrystallized products.

Questions:
1. How would you modify the experiment in order to make benzalacetone, $PhCH=CHCOCH_3$ instead of dibenzalacetone $PhCH=CHCOCH=CHPh$?

2. What ingredients would you use if you wanted to make benzalacetophenone, $PhCH=CHCOPh$?

Miscellaneous Notes
o Does the benzaldehyde smell familiar? It's found in almond, almond paste, and is familiar from cherries and vanilla. Lots of cookies and bars have this smell.
o Acetone has many uses, including as a paint and varnish remover; as a fingernail polish remover, and as a solvent in many varnishes, rubber cements, lacquers, etc. It is also a natural metabolic byproduct found in the body in limited quantity. Elevated quantities are symptomatic of metabolic disorders, such as uncontrolled diabetes.

o Q: The formation of the yellow color shows that a new chemical is forming, very quickly. The formation of the cloudiness and the insoluble solid also indicates that something is forming that wasn't present at first. Actually, the yellow color and the solid are one and the same. But how come the solid doesn't appear instantly, as fast as the yellow color?
o A: This is the result of solubility chemistry. The solvent has the ability to dissolve a limited quantity of the product. Product is forming continuously, right from the start; but it takes a minute or so until there is enough product formed to hit the solubility-saturation threshold. Any further product exceeds the solvent's ability to hold it, and thus comes out as insoluble solid. At first this insoluble stuff looks to the eye as if it is just milky cloudiness. But soon enough it look like solid crystalline material.