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CHEMISTRY 365 SYLLABUS

Spring 2025

Organic Chemistry Laboratory II

Classroom: Langseth 307 Dr. Craig P. Jasperse web: http://www.mnstate.edu/jasperse/ Office: Hagen 407J Telephone: 477-2230 e-mail: jasperse@mnstate.edu	Office Hours: M-W-F 9-10:30; M-T-W-H-F 1-2:30 But much afternoon time is available, too

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 Location: Langseth 307	Thursday, 1:30-4:20

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Grading Policy:

1. **Attendance**: Laboratory attendance is important! In the event of an absence, you will receive zero points for that experiment.
   - There are two weeks that I've scheduled to accommodate makeup labs.
   - In case of other COVID-quarantine necessitated makeup labs, contact Dr. Jasperse.

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 perhaps 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/A-	(≥90%)
B-/B/B+	(≥80%)
C-/C/C+	(≥70%)
D-/D/D+	(≥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)

Safety & Procedural Information

MSUM Sexual Violence Policy: Acts of sexual violence are intolerable. MSUM expects all members of the campus community to act in a manner that does not infringe on the rights of others. We are committed to eliminating all acts of sexual violence.

MSUM faculty and staff are concerned about the well-being and development of our students. We are obligated to share information with the MSUM Title IX Coordinator in certain situations to help ensure that the students' safety and welfare is being addressed, consistent with the requirements of the law. These disclosures include but are not limited to reports of sexual assault, relationship violence, and stalking.
If you have experienced or know someone who has experienced sexual violence, services and resources are available. You may also choose to file a report. For further information, contact Lynn Peterson, Title IX Coordinator, petrsnly@mnstate.edu; 218-477-2967, or Ashley Atteberry, Director of Student Conduct & Resolution, ashley.atteberry@mnstate.edu 218-477-2174; both located in Flora Frick 153. Additional information is available online mnstate.edu/titleix.

Bias Incident Statement: A bias incident is an act of bigotry, harassment, or intimidation that is motivated in whole or in part by bias based on an individual's or group's actual or perceived race, color, creed, religion, national origin, sex, gender, age, marital status, disability, public assistance status, veteran status, sexual orientation, or familial status. If you are a student who has experienced or witnessed a hate or bias incident, we want to address the incident and provide you with resources. Contact the Campus Diversity Officer, Jered Pigeon (jered.pigeon@mnstate.edu, 218-477-2047, 114 CMU) or the Dean of Students, Kara Gravley-Stack (kara.gravleystack@mnstate.edu, 218-477-4222, 153 Flora Frick Hall). Additional information is available at: https://www2.mnstate.edu/oscar/.

Student Grievance/Complaint Process: This general procedure is applicable only to those administrative actions for which no special grievance procedure has been established. Special procedures have been established for certain academic (e.g., graduation, grades), student conduct, discrimination/harassment, and employment related matters. Students desiring to appeal actions or procedures of University administrative offices must meet with the following officials, continuing up the hierarchy as necessary to resolve the issues.

Academic Affairs
1. Department Chair of the academic discipline in which the problem arose
2. Dean of that college discipline
3. Provost and Senior Vice President for Academic Affairs
4. President

Administrative Affairs
1. Director of specific area
2. Vice President for Administrative Affairs
3. President

Student Affairs
1. Director of specific area
2. Vice President for Student Affairs
3. President

This process can also be found in the Policies and Procedures section of the Student Handbook (p. 12) (mnstate.edu/student-handbook/).

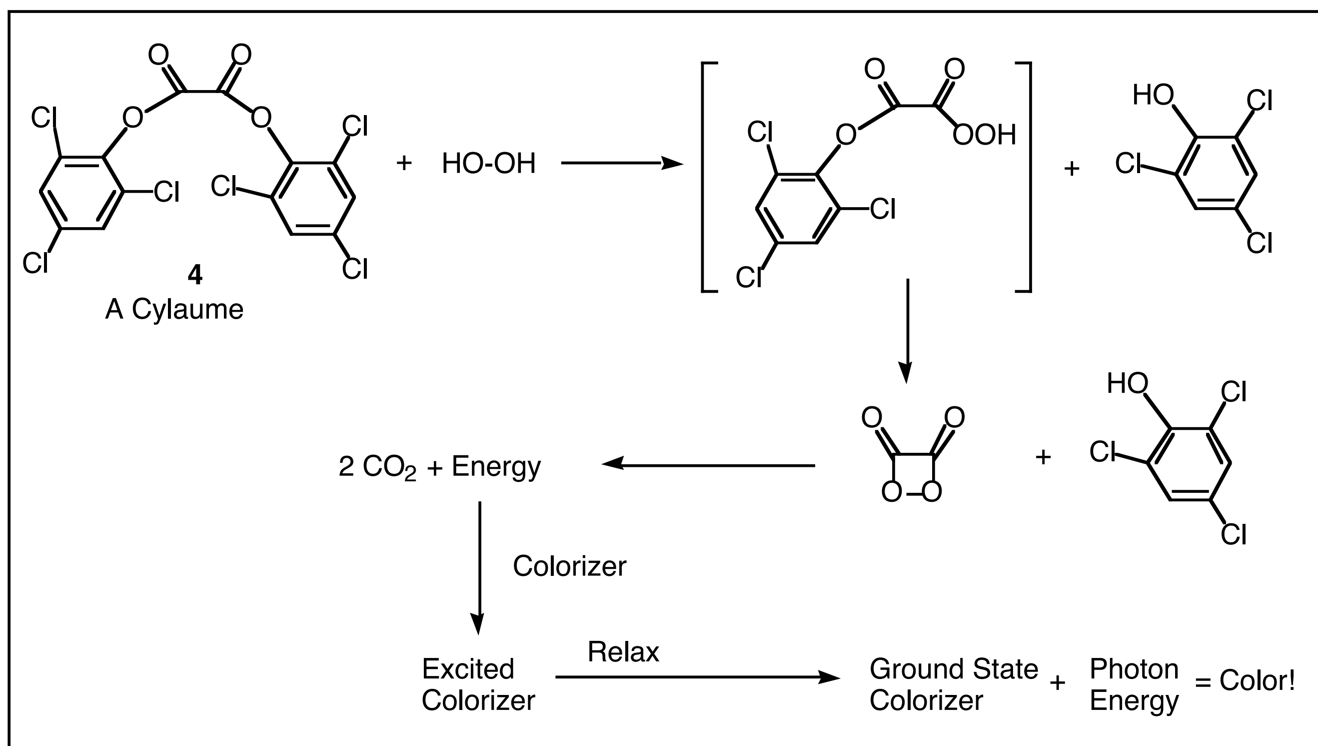
Building Emergency Plans: Whether taking your courses online, hybrid, Hyflex, or face-to-face, you may find yourself on campus at some point, so best to be prepared and aware. Building floor plans showing emergency exit routes, fire extinguisher locations and fire alarm pull stations are conspicuously located in classrooms, labs, conference rooms, departmental main offices and residence halls. The Emergency Preparedness Guides (flip style booklets) are located with the maps. Please review the floor plans as well as the guide so you know how to respond in an emergency to help protect yourself and others. If you have questions, please contact Ryan Nelson, Director of Public Safety, at ryan.neslon@mnstate.edu or 218-477-5869. (mnstate.edu/public-safety/).

Chemiluminescence: Synthesis of Cyalume and Making it Glow

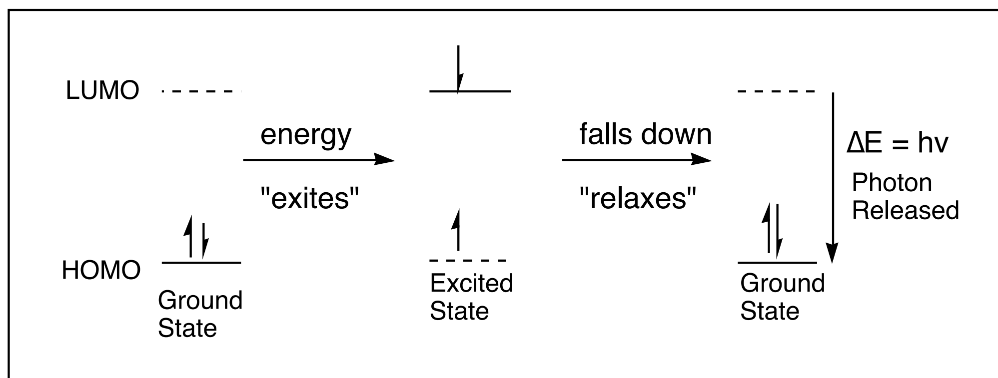
Intro *Chemiluminescence* is the process whereby light is produced by a chemical reaction. The flashes of the male firefly in quest of a mate is an example of natural chemiluminescence. In this experiment we will make Cyalume, the chemical used in "light sticks." A light stick contains a solution of 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

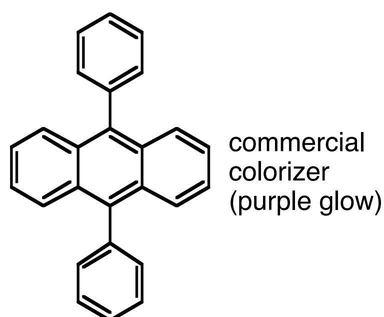
The chemistry that forms the color glow in a light stick is shown below. A cyalume is a symmetric diester, such as **4**. It reacts with hydrogen peroxide (red oxygens) by oxygen exchange. Trichlorophenol (green) is released as each of the two red oxygens of hydrogen peroxide connect to the two blue 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.

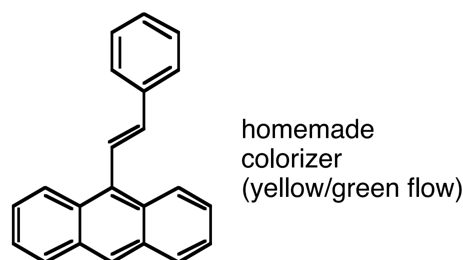


The energy released during the fragmentation "excites" a colorizing molecule that must be present. In other words, an electron in the colorizer gets "excited" from its ground state to an excited state. When it subsequently relaxes back to the ground state, a photon of energy is released. If the energy 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.



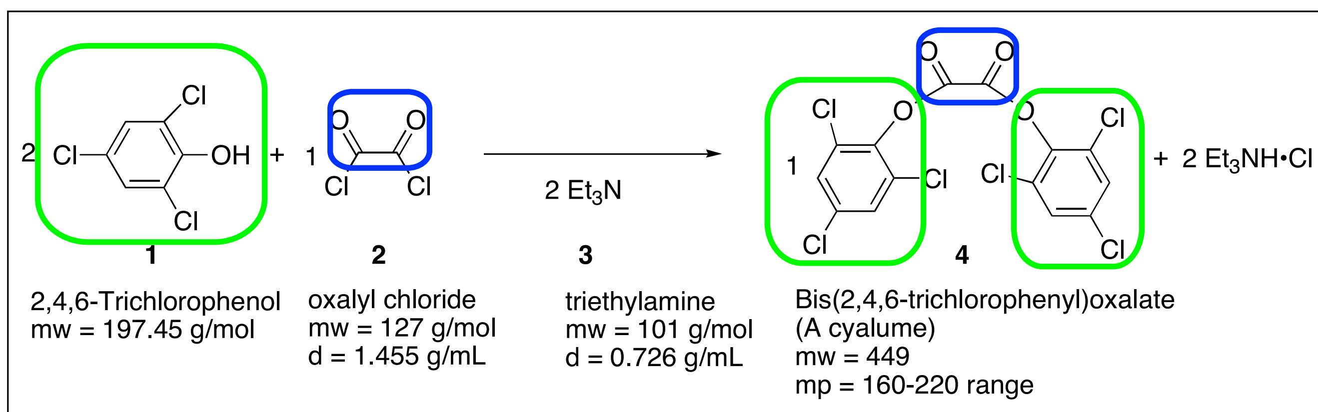
Several things to note about the exitation/relatation process: 1) The energy gap between the HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) determines the photon frequency and the color of the photon released. 2) For most organics, the HOMO-LUMO gap is not in 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.





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.



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. Record 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 gently 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 and vacuum.
   - 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 4?) Maintain a gentle boil for 2-4 minutes (record observations, for example whether there are brown particles left, or whether it all dissolves….), then remove from the heat and let the solution cool, eventually to ice-cold.
    - Heating a solid that doesn't dissolve completely is called "**digestion**". 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 (smallest ceramic filtration unit). (You'll need to "mold" your 42.5mm filter paper.)
17. Rinse with 2-4 mL of hexane (one or two pipets worth..).
18. Vacuum thoroughly. (10 minutes should be good.)
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

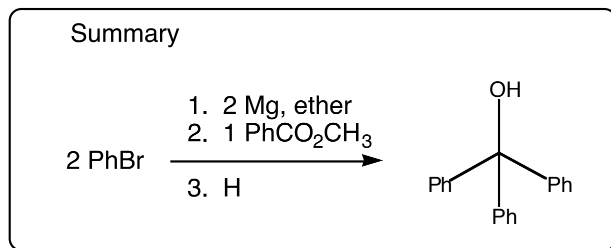
1. The instructor will distributed two vials to each pair of students. Each will have about 3 mg of colorizer, one with the commercial colorizer and the other with the home-made colorizer.
2. Add 0.1g (or more) of cylaume to each vial.
    - 0.1 grams should be enough to get a good glow
    - Excess can be donated to Dr. Jasperse's cyalume jar in the acetone/waste hood
    - I can use your student-prepared cyalume for school demonstrations
    - If you have a good yield, you could also put in >0.1g of cyalume into each of your vials. Probably the reaction will glow longer if you put in more cyalume fuel.
3. Add 5 mL of diethyl phthalate (organic solvent, bp > 298ºC) into each of the two vials.
4. 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.
5. Bring your vials, with their caps, to the dark room. (Room across the hall.) Both partners come.
6. The instructor will then inject 0.35 mL of 30% hydrogen peroxide/water.
7. Screw the covers back on, shake, and observe the pretty lights!
8. 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..
9. 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 standard 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!



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.

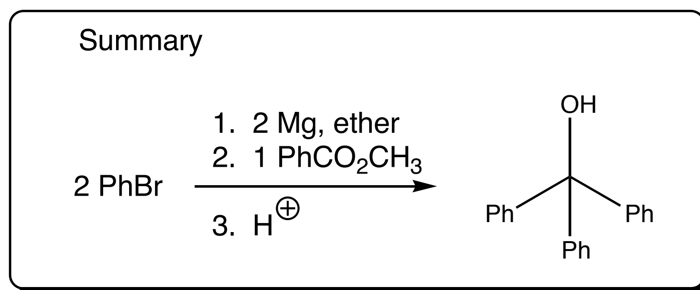
3. Calculation of Theoretical Yield
- Specify which chemical is the limiting reactant
- Given moles of limiting reactant, calculate theoretical moles of product
- Given moles of product, calculate theoretical grams of product.
- Note: Why do this so early in report?
  - First, because it fits in near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

4. Writeup of Actual Procedure.
- For this particular experiment, the "procedure" section will be by far the biggest portion of your report.
- This should be a concise but detailed description of things, including:
  - What you <u>actually did</u> (even if not recommended or not from recipe)
  - 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**
  - <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…")
  - 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



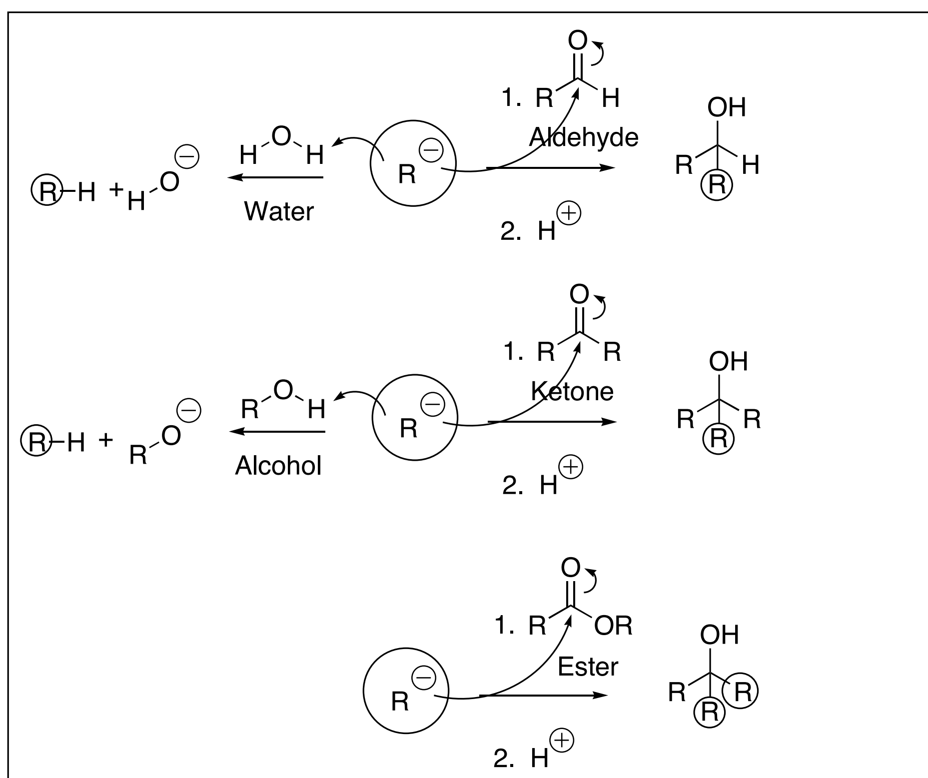
I. Background In 1912 Victor Grignard received the Nobel prize in chemistry for his work on the reaction that bears his name, a carbon-carbon bond-forming reaction by which almost any alcohol may be formed from appropriate alkyl halides and carbonyl compounds. The Grignard reagent RMgBr is easily formed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

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

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**.

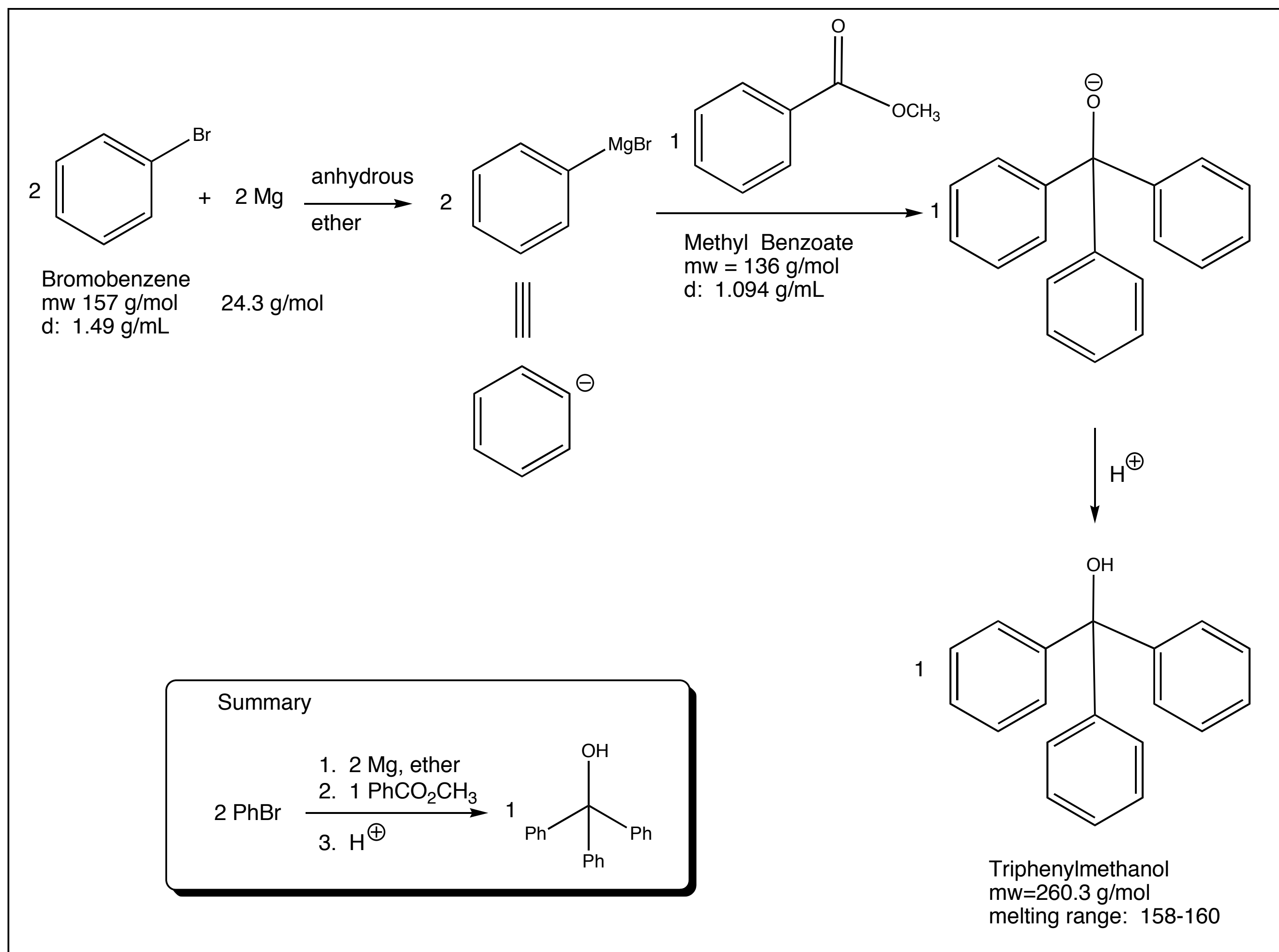
Some of its reactions are shown below.

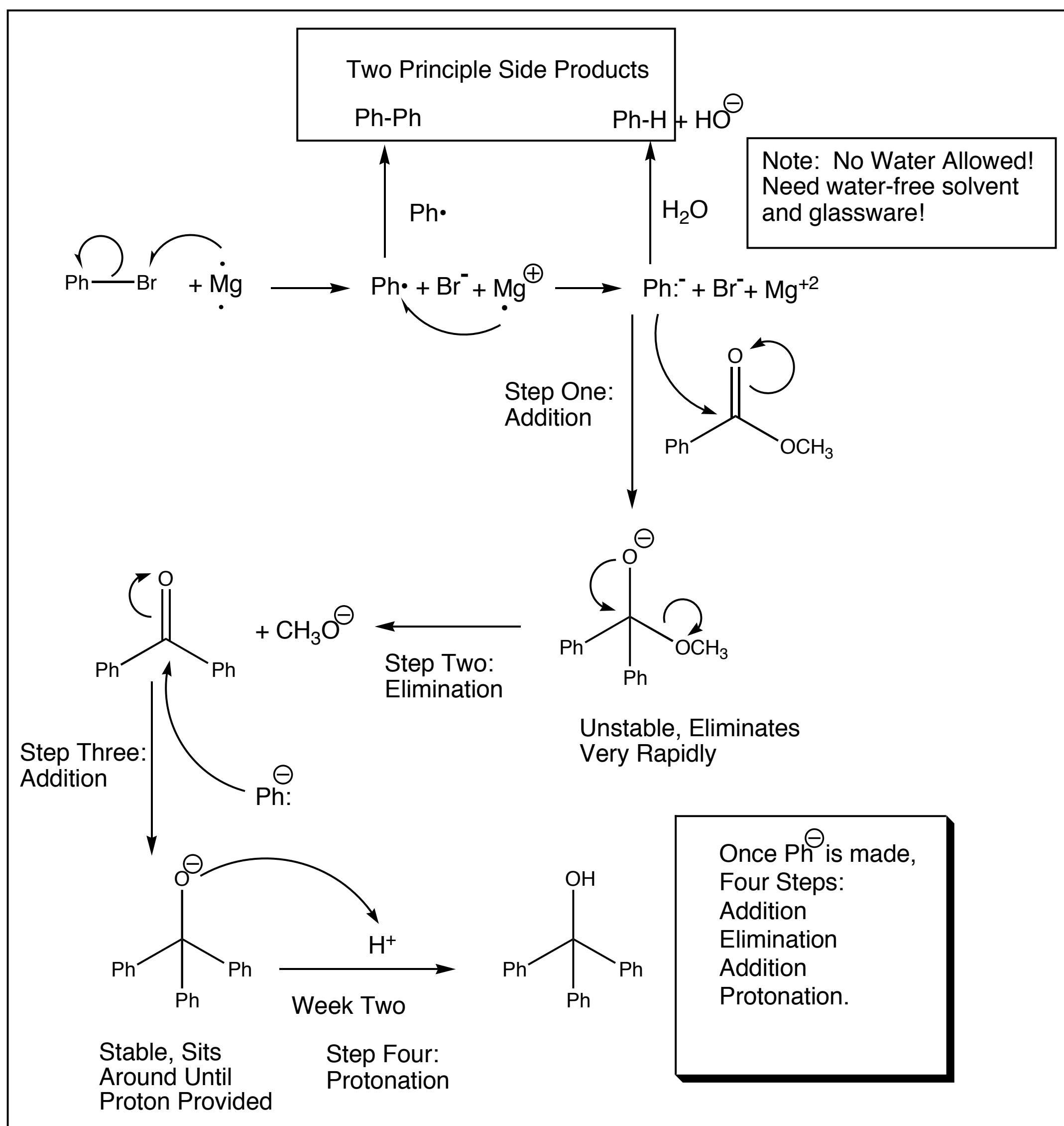
- **It reacts as a strong base with water or alcohols**.
  - Conversion from less stable R^- to more stable HO^- or RO^- is favorable.
- **It reacts as a strong nucleophile with carbonyl groups aldehydes, ketones, and esters.**
  - Conversion from less stable R^- to more stable RO^- is favorable, followed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





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

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

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

III. Procedure: Week One

Note: All equipment and reagents must be dry!

Phase 1: Preparing the Grignard Reagent

1. Dig out the following pieces of glassware: (Instructor will have a demo-display set up).
    a. 250-mL round-bottomed flask
    b. "Claisen" two-branched connecting adapter (piece #9 in your kit)
    c. reflux condenser (piece #12 in your kit)
    d. separatory funnel with stopper
    e. drying tube packed with calcium chloride

2. Clamp the 250-mL round-bottomed flask to a vertical rod. Use a clamp with metal grips. (Rubber clamps will melt and stink when subjected to Bunsen-burner flame!) Don't add other glassware yet.
3. Light your Bunsen burner and pass the flame over the flask until there is no more steam visible on the surface of the glass.
4. As soon as the steam is gone from the flask, add the Claisen adapter to the flask and flame dry it as well. (Note: do NOT add the stir-bar until after step 16.)
5. As soon as the steam is gone from both the flask and the adapter, add the reflux condenser to the flask, and flame dry briefly, as best you can. (Do not flame-dry the separatory funnel or drying tube.)
6. While everything is still hot, attach the drying tube into the top of the reflux condenser, add the separatory funnel with its stopper on into the other arm of the Claisen adapter.
    - **At this point, the interior should be entirely closed from wet air getting in. The separatory funnel blocks out one side, and any air coming in through the column must pass through the drying tube.**
7. Weigh out about 2 grams of magnesium metal. (Record weight to at least 3 significant figures.)
8. When the glassware is cool enough to handle, add tubing to the condenser so that you can run a slow stream of tap water through the condenser. Reassemble the array as quickly as possible.
9. When the glassware is cool enough to handle, lift out the condenser and pour in the magnesium, perhaps using folded weighing paper or weighing boat, then replace the condenser as soon as possible.
10. Pour 40 mL of ether into the separatory funnel and put stopper back on.
11. Measure out 9.0 mL of bromobenzene in a graduated cylinder, and add it to the separatory funnel.
12. If he hasn't already done so, ask the instructor to add one small chip of iodine into the separatory funnel.
13. Drain the bromobenzene/ether/iodine solution into the round-bottomed flask.
    - **The iodine serves two functions.**
        a. **Indicator**. The color will disappear when the magnesium is activated. Until the color goes away, the magnesium won't be able to react with the bromobenzene.
        b. **Activator**. Iodine is sometimes able to chemically "clean" the surface of the magnesium so that fresh, active magnesium is exposed so that it can do redox chemistry with bromobenzene. However, it doesn't often work!
    - **Make a mental picture of how much magnesium you have to begin with, so you can remember later on for comparison.**
14. Put a jack with a stir-plate underneath your flask. If the redox chemistry of the Grignard reaction initiates, the iodine color will go away, the solution will begin to get hot, there will be some bubbling, and things may become slightly cloudy.
15. If there is no indication of reaction after 1-2 minutes, beg the instructor to come over to crush some magnesium. Note: If yours starts without need for crushing, specifically note this in your write-up.
16. With a medium stir bar ready but not in the flask, ask the instructor to come over and use a glass rod to try to crush some of the pieces of magnesium firmly against the bottom of the flask. This will expose fresh, active magnesium that should be able to initiate the redox chemistry and the formation of the Grignard reagent. Trying to crush very very hard magnesium pieces inside a glass flask is dangerous, though; it's easily possible to punch a hole in the glass. So if somebody is going to poke a hole in your flask, let it be the instructor so he can take the blame! ADD A MEDIUM STIR BAR AS SOON AS THE MAGNESIUM IS CRUSHED.

17. The reaction should be so exothermic that it will be self-boiling for some time. Note the position of the "reflux ring". Within 10 minutes, the boiling will probably moderate. Turn the hot-plate heat setting to 5 in order to maintain a good rate of boiling.
18. Maintain boiling for one hour.
    - **Note: notice how the reflux condenser works. The bottom flask can be boiling hot (which facilitates maximum reaction rate), but the condenser enables you to liquify and recycle all of the boiling solvent.**
    - **Keep good procedural and observational notes of everything that you see and do!**

Phase 2: Things to do during the Grignard Hour…
Once the reaction is clearly going, prepare for Phase 3, in which you will add the methyl benzoate ester electrophile to the carbanion that you are making. And do the calculations that you will eventually need to include in your report.

1. Calculate what volume (in mL) it will take to add 5.0 grams of liquid methyl benzoate (density = 1.094 g/mL).
2. Calculate the number of **moles** used for magnesium, bromobenzene, and methyl benzoate.
3. Calculate the **overall theoretical yield** (in grams) for your final product of next week, triphenylmethanol (mw = 260 g/mol).
    - To do this, you must **first identify** which of the three reactants (Mg, PhBr, or $PhCO_2CH_3$) is the **limiting reactant**
    - To do this, you must factor in the overall stoichiometry, which is not all 1:1:1:1. (Given your calculated moles of Mg, how many moles of Ph_3COH could you make? Given your calculated moles of PhBr, how many moles of Ph_3COH could you make? Given your calculated moles of $PhCO_2CH_3$, how many moles of Ph_3COH could you make?)
    - In calculating theoretical yield for a multistep reaction, theoretically every step will be perfect. (We know otherwise, but we're talking theoretical yield here…) Thus you don't need to calculate or measure quantities for any intermediates. Your limiting reactant and theoretical yield should consider only original reactants and final product, all things which are easily quantified.
4. After the Grignard solution has reacted for one hour, check to see how much magnesium is left. Any qualitative estimate of about how much is left? (None? 10%? 50%?)
    - What implications might this have on your possible yield? Is it necessary for all of your magnesium to have reacted completely in order to get 100% yield? Or could you get 100% yield even if some of your magnesium remains unreacted?

Phase 3: Reacting the Grignard Reagent with the Methyl Benzoate

- The following two steps can be done in advance, during the last ten minutes of your reaction….

1. Add 15 mL of ether to your separatory funnel. (Stopcock closed).
2. Add 5.0 grams of methyl benzoate to your separatory funnel by syringe. (Remember, you calculated this volume in Phase 2….) (Return syringe to the hood! ☺)
3. After the hour is up, let the reaction cool down so that it's not much hotter than room temperature. (Add some ice to a metal pail. Applying an ice bath in the metal pail for one minute might help cool.)
4. While magnetic-stirring, and with the solution in the flask not much hotter than room temperature, drain the ester/ether solution into the round-bottomed flask, slowly so that the reaction doesn't overheat too much. If things start to boil too hard, pause/slow the addition and/or apply the cold bath.
    - Record your observations!
5. After everything is added, keep stirring for an additional 20 minutes, during which time the exotherm and boiling should subside. If the reaction is still hot after 20 minutes, cool it with the ice bath.
6. Remove all the glassware from the top of the round-bottomed flask, and stuff in a rubber stopper.
    - Note: it is essential that the solution isn't hot when you do this. If it is, then when it cools it will create a vacuum and suck the stopper in…)
    - Note: it is essential that the vigorous exothermic reaction is done before you stopper the flask. Otherwise if stirring or further reaction generates enough heat, it will cause the ether to boil and blow the stopper off!
7. Using your round-bottomed flask holder, stash the round-bottomed flask with the chemicals and the stopper into a secure spot in your drawer, and wait till next lab to finish!

IV. Procedure: Week Two

1. Record your observations for what your mixture looks like at this point.

2. Remove the stopper, and add about 30 mL of ether, 40 grams of ice, and 50mL of 2M sulfuric acid
   - The acid will react exothermically with both the anion and unreacted magnesium. The ice is there simply to absorb the heat.

3. Swirl, and use a microspatula to break up the big chunks and to free up the stir-bar. Then use magnetic stirring to try to help dissolve things.

4. In the process, three things should happen:
   - The anion should be protonated, giving the neutral organic alcohol product. This should partition into the organic ether layer.
   - Magnesium salts should be ionic, so they should partition into the aqueous layer.
   - Unreacted leftover magnesium metal will react with the acid to give molecular hydrogen. That's what causes the bubbling. ($1\ Mg + 2\ H^+ \rightarrow Mg^{2+} + H_2$ gas)

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

6. Pour an additional 10 mL of sulfuric acid and 30 mL of ether into your flask, swirl to try to dissolve up anything left on the walls, and pour into the separatory funnel. (These need not be measured, just pour some in approximately.)

7. Drain off the bottom aqueous layer into a beaker.

8. Add another 20 mL of sulfuric acid into the separatory funnel, shake it up, and drain off the aqueous layer again. Pour the combined aqueous layers into the aqueous waste bottle in the hood.

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

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

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

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

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

13. Pour the ether solution through the glass-wool-plugged funnel into a different 250-mL Erlenmeyer flask.
    - The wool should be sufficient to filter off the solid sodium sulfate, and only allow the solution to get into the flask.
    - Rinse your original flask and the sodium sulfate with an additional portion of ether.
    - At this point, your solution should be free of water and of magnesium salts. Other than the ether solvent itself, you should have nothing but the desired product and organic contaminants.

14. Make a TLC plate with five pencil marks for five tracks ready:
    a. Authentic biphenyl b. Authentic methyl benzoate c. Crude mixture
    d. Purified mixture e. Post-crystallization solvent

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

16. Add 30 mL of "ligroin" solvent (all hydrocarbons, mostly hexanes, but not pure) to your ether solution. The product is more soluble in ether than in hydrocarbons, so you are essentially adding some "bad solvent" to facilitate a mixed solvent recrystallization.

17. Add a boiling stick to your organic solution

18. Now heat your solution on a hot plate. A power setting around 5 might be a good starting guess?

19. Boil the solution down to ~30 mL or so, then add another 30 mL ligroin and again boil down to around 30 mL. (Crystals may start to form before this, depending on your yield. But if you stop boiling as soon as the first crystals form, you'll still have too much solvent and will get a low yield.)

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

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

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

23. Filter your crystals with your medium Buchner funnel (using vacuum as usual). Rinse with 15 mL of cold ligroin.

24. Transfer crystals to a beaker with a stir bar, add 15 mL of ligroin and 5 mL of diethyl ether, and stir vigorously for 5 minutes. Filter again, and vacuum dry.

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

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

27. Run the tlc in designated solvent (5% ethyl acetate/hexane), and analyze by UV and the "dip" solution.
    - Mark down the results, with the following questions in mind:
        - Is biphenyl present in the crude mix (lane C)? In the purified material (lane D)?
        - Is methyl benzoate present in the crude mix (lane C)? In the purified material (lane D)?
        - Any other side products in the crude (lane C)?
        - Did recrystallization purify the material (lane D versus lane C)?
        - Did most impurities in crude lane C end up in the crystal (lane D) or the solvent (lane E)?

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

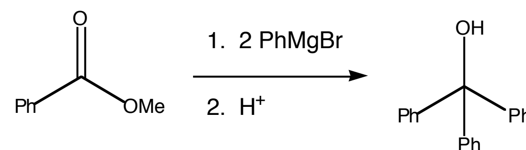
29. Get your final mass.

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

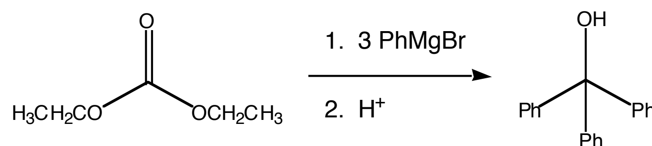
- The assigned post-lab questions are on the following page. You can perhaps answer some or all of them on the page, or else answer some or all of them on attached sheet(s) of paper.
- This two-week lab and two-week lab report will count for 20 rather than 10 points.
- For this report (and this report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

Assigned Questions, Grignard Lab

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



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



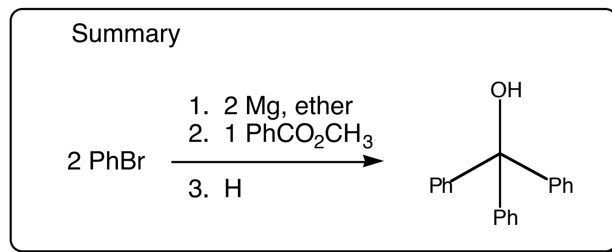
3. If you hadn't bothered to flame-dry your glassware or used a drying tube, what byproduct would have formed?

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

5. Your yield was considerably less than 100%. Discuss where you think things might have come up short. You may wish to differentiate reaction things (reasons or evidence that you didn't have complete chemical conversion) versus isolation things (reasons or evidence that you didn't isolate all of the product that was actually made chemically). (Your GC data should inform your answer.)

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.

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



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

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

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

4. Writeup of Actual Procedure.
- For this particular experiment, the "procedure" section will be by far the biggest portion of your report.
- This should be a concise but detailed description of things, including:
  - What you actually did (even if not recommended or not from recipe)
  - All observations should be included. These include all observed changes, such as:
    - i. Changes in **color**
    - ii. Changes in **solubility** (formation of precipitate or cloudiness…)
    - iii. Changes in **temperature** (like, reaction became hot…)
    - iv. Formation of **bubbles**
  - Time and temperature details:
    - v. Whenever you heat something or cool something, the procedure should specify
    - vi. Specify times. Whether you boiled for 5 minutes or 5 hours matters!
- Writing details: As a record of what actually happened, the report must be written in **<u>past tense</u>**, not **<u>command tense</u>**. (Rather than "Add this", should read "I added this", or "I dropped that…")
  - Use of personal pronouns is accepted in this class. You may use "I" or "we" to simplify writing.

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

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

7. Answers to any assigned Questions

Basic GC-MS Operation Compressed Draft 4 For Chem 355 Organic Unknowns Lab

Note: The following assumes the gc/ms program has been opened and warmed up; that an appropriate "method" and "sequence" have been selected; and that Jasperse will turn things off.

Sequenced Data Acquisition: Using the Autosampler to Sequence Runs Automatically

Note: this assumes that Jasperse has already prepared a "sequence", but you are trying to add your sample to the lineup.

- If you're first in line, get Jasperse to come and help. Or hit "OK" and "Run Sequence".

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 and is in the injector tray.)
   - 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 high 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: Data files are in a Data Folder, usually open on the left. Or, you can click "Data Analysis from the yellow panel on top of the GC software field.

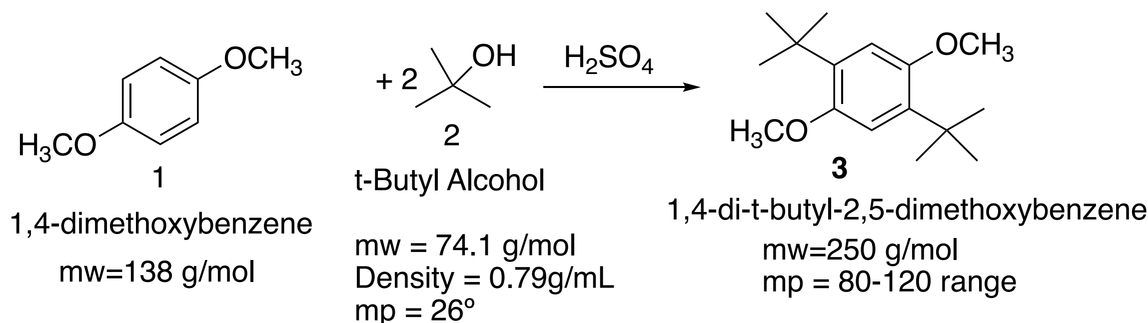
3. **Open a data file: double click** with the **left mouse button** to.
   - Data file will have the names "Vial-1" or "Vial-2", so **remember which vial was yours**.
   - Your data files should be within an Organic Lab folder.

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 5th Hammer button.**
   - Click the 5th hammer button 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….

Friedel-Crafts Alkylation of 1,4-Dimethoxybenzene



General Issues with Electrophilic Aromatic Substitution Reactions

1. **Polysubstitution**

   Aromatic substitutions always involve the issue of how many substitutions will occur. Will reaction stop after one substitution? Will it proceed to give a second substitution? Will it proceed further to give a third substitution? In today's experiment the reaction does not stop after a single substitution, but proceeds on to a second. However, it does basically stop after the second substitution and does not proceed appreciably to a third or fourth substitution. Influential factors are electronic and steric:

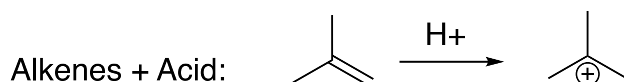
- Electronics: are new substituents electron donating or electron withdrawing? Will they stabilize or destabilize the cation involved in subsequent substitutions? As a result will they activate or deactivate toward subsequent substitution?
- Steric: are new substituents large enough to obstruct further substitution?

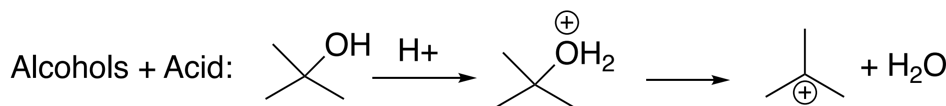
2. **Position of Substitution: Ortho, Meta, or Para To a Pre-existing Substituent?**

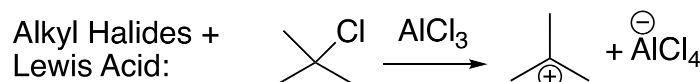
   Relative to a pre-existing substituent (or several of them…), will a new substitution occur ortho, meta, or para? Electronic and steric factors are again influential. In today's experiment, for example, after the first t-butyl group is attached, why does the second t-butyl group go where it does?

3. **Generation of the Electrophile**

   All electrophilic aromatic substitution reaction mechanisms require a strong electrophile, usually cationic. In today's experiment, the active electrophile is the t-butyl cation. For a general alkylation, in which an alkyl cation is required, there are several alternate precursors. Ours will use the alcohol, which under protonation can lose water and produce the 3° carbocation which can then add to the aromatic ring.







Reaction Procedure:

1. Weigh out 1.50 g of 1,4-dimethoxybenzene and place in a 125-mL Erlenmeyer flask containing a stir bar.
   - Note: For calculations, this will be the limiting reagent.
2. Measure out 3.10 mL of warm t-butyl alcohol into a syringe, and inject into the Erlenmeyer flask. (Note: t-butanol freezes at 26ºC, so it's best to handle it somewhat warm so it stays liquid. If it has much chance to cool off, it may solidify and complicate delivery.)
   - Note: This is a substantial surplus of t-butanol. There is lots more than two equivalents relative to the aromatic substrate.
   - So, for theoretical yield calculations, this is NOT a factor for limiting reagent.
   - This also means that there must be some reason why substitution quits after adding two t-butyl groups, and for some reason will NOT add a third t-butyl group.
3. Measure out 5 mL of acetic acid from a buret. You can deliver this directly into your Erlenmeyer, or else drain it into a small flask/beaker and pour it in. Acetic acid is smelly, so delivering it directly in the hood is a good way to reduce smells in the lab. If you do transfer via a small flask/beaker, rinse that out pretty quickly in the hood so that the lab doesn't smell too much like vinegar.
4. Cool the Erlenmeyer flask in an ice-water bath on a stir plate, and adjust to get steady stirring.
5. Drain 10 mL of concentrated sulfuric acid from a buret into your separatory funnel. Note 1: Make sure the stopcock on your separatory funnel is not open! Note 2: Sulfuric acid is a very strong acid; you do not want any to touch your skin or clothes.
6. Position your separatory funnel above your Erlenmeyer flask, and then drop in the sulfuric acid <u>very slowly</u>, drop by drop, over a period of 5-7 minutes into the continuously stirred solution. Keep the Erlenmeyer flask in an ice-water bath throughout.
7. After addition of the sulfuric acid is complete, remove the cold bath and continue stirring at room temperature for 20 minutes to allow completion of the reaction.
8. During this 20-minute wait, rinse the separatory funnel with the residual sulfuric acid with tap-water. You can drain into the sink. This is also a good time to write up your lab report, including stoichiometry calculations, procedure and observations, and post-lab questions.

Isolation of the Crude Product:

9. Add some ice to the Erlenmeyer flask to dilute the sulfuric acid, swirling the flask as you do so. (One of the functions of the ice is to absorb some of the heat that is produced when sulfuric acid and water mix.) Then add ice-cold water to a total volume of 75 mL or more, swirling vigorously as you add.
10. Use a scoopula or micro-spatula to swirl and stir the mixture for at least two minutes.
11. At this point, you should have a lot of crystal that formed. Because the desired product has so many carbons, it has very low solubility in water, so adding all the water basically crashes most of the the product from solution.
12. Filter the solution using a Buchner funnel.
13. Rinse thoroughly with another 70 mL of ice-cold water. (The function of the water is to make sure all the sulfuric acid, acetic acid, and t-butanol is washed away from the product.)
14. Take the Buchner funnel off of the filter flask, and pour the water down the drain. Then reattach the Buchner funnel.
15. Rinse with a 5-mL portion of ice-cold methanol
16. Rinse again with a second 5-mL portion of ice-cold methanol. (The methanol washes away some organic impurity and also functions to remove much of the water.)
17. Measure your crude mass
18. Save a small portion of the crystals for a crude melting point.

Recrystallization of the Crude Product:

19. The main batch of crystals should be purified by recrystallization. Use methanol as your main solvent. Use your experience in recrystallization in order to figure out how to do this. Remember, you want to dissolve the solid in a minimum of hot solvent. So, if your solvent is boiling hot and your crystals still won't dissolve, what should you do? Add more solvent! Conversely if you think you have too much/too good solvent, what should you do? Either boil some off, or add some water (one drop at a time) to reduce the solubility and approach saturation. (Mixed solvent technique).
20. Use your experience to guide your filtration and washing of the crystals.
21. Pour the methanol from the filter flask into the alcohol waste container in the hood.
22. Let the crystals vacuum dry for at least 8-10 minutes before getting mass yield and taking melting point. When you take your melting point of the recrystallized material, also take a melting point of the crude material in order to compare so you can see whether recrystallizing actually helped.
23. Take a H-NMR of the product. To run an NMR on a solid, stab the tube into the crystal, like you do to get some solid into a melting point tube. Remember that for an H-NMR of a liquid you put in one or two drops; so, try to put in enough solid that would be comparable to a drop of liquid. Note: Students routinely put in too little solid! Remember that most of the space in a solid crystal is just air. So, compared to a drop of liquid you'd like to have 5 times as much volume of a solid. If your tube is maybe $1/10^{th}$ full, that will be good for this week. Dilute to about 1/3 depth with D-chloroform. Note: The NMR is for instructor's grading purposes, just to see how clean your material is. You don't need to explain it in your lab report.

Caution: Safety Note: Concentrated sulfuric acid is very potent and will dissolve you, your clothes, your papers, or anything else it touches! Avoid pouring; try to use burets/pipets exclusively, or as much as possible. Rinse your glassware thoroughly with water after usage. Acetic acid is smelly, so avoid exposing this outside of the hood.

Cleanup: If an aqueous acid waste bottle is out, put your original solution (following filtration) into that. If not, dilute the original solution with water, neutralize with sodium carbonate (expect it to fizz!), and pour down the drain.

Pour the methanol from the recrystallization into the organic waste container.

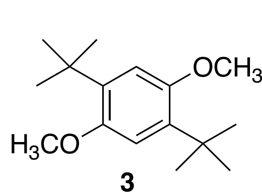
Lab Report:

Standard synthesis lab report format. Data must include the crude and recrystallized melting points; the crude and purified mass yield and percent yield; and the H-NMR.

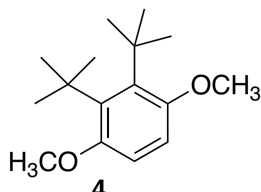
Questions:

1. Draw a detailed mechanism for the formation of t-butyl-2,5-dimethoxybenzene. (In other words, for the first alkylation, but not the second…).
   (draw this on the back side or on a different sheet).

2. The actual dialkylation product is 1,4-di-t-butyl-2,5-dimethoxybenzene. Why is this isomer preferred rather than the alternative isomer 1,2-di-t-butyl-3,6-dimethoxybenzene?

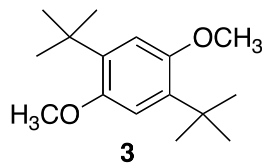


Does Form.

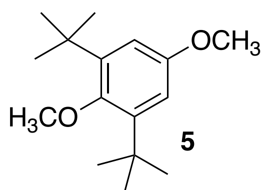


Doesn't form. Why?

3. The actual dialkylation product is 1,4-di-t-butyl-2,5-dimethoxybenzene. Why is this isomer preferred rather than the alternative isomer 1,3-di-t-butyl-2,5-dimethoxybenzene?



Does Form.



Doesn't form. Why?

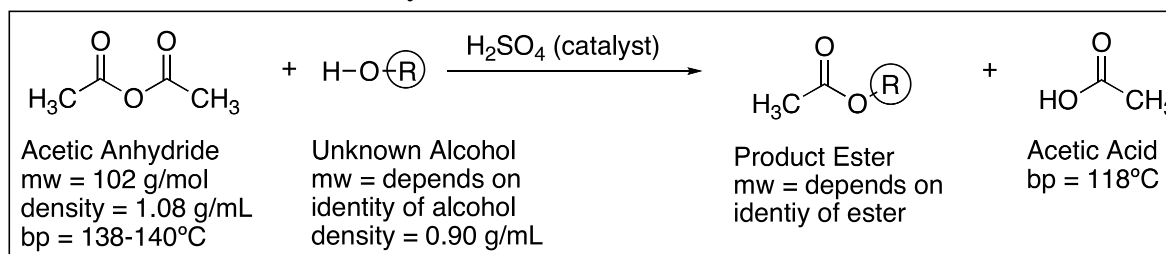
4. From your actual calculations, how many moles of t-butyl alcohol did you use, and how many moles of 1,4-dimethoxybenzene did you use? [The major product involves only two moles of t-butyl alcohol adding per mole of 1,4-dimethoxybenzene. The following questions relate to why you added more than one, but not more than two…]

5. Why do you think you <u>did not</u> stop after just a single alkylation? In other words, why were you able to add two t-butyls, not just one?

6. Why do you think you <u>did</u> stop after two alkylations? In other words, why were you able to add two t-butyls, but did not continue on to add a third t-butyl group at least to some of your molecules, even though there was still a lot of t-butyl alcohol left at the end?

7. You used t-butanol and acid to generate the t-butyl cation used to form 1,4-di-t-butyl-2,5-dimethoxybenzene. Suggest two organic precursors other than t-butanol that could be used as precursors for t-butyl cation?

ALCOHOL TO ESTER
Acid-Catalyzed Esterification of an Unknown Alcohol



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. Run your proton NMR as time permits. The instructor will probably have a take-your-turn-on-NMR-list on the whiteboard. (Instructor: experiment used is "Proton 8".)

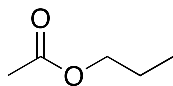
Reaction: To a 50-mL round-bottomed flask, add your tiniest stir bar. Take to hood area. Add 7.5 mL of acetic anhydride via buret (or perhaps syringe), and directly add 5.0 mL of an unknown alcohol via syringe. (Measure as precisely as possible. Notice that nothing happens.) Back in hood, attach a Claisen 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) directly into the stirring solution. 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. **IF** the temperature doesn't climb to ≥50º, contact the instructor, and/or try adding an additional drop of sulfuric acid. After the internal temperature has reached its maximum, wait an additional ≥3 minutes before beginning workup.

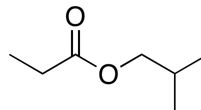
Workup: Pour the mixture into a separatory funnel, and use a 25-mL ether rinse to aid the transfer. Add some solid ice (around 15-20g). Extract the acids and unreacted acetic anhydride by adding 20-mL of NaOH solution. Be sure to shake things up vigorously, let settle, and then drain the lower aqueous layer into a beaker. Add a little more ice, 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. Add a tiny stir bar.

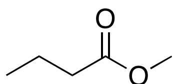
Distillation: Have two 125-mL Erlenmeyer flasks (**A** and **B**) ready, with **B** pre-weighed. Distill (simple distillation) the ether and then the product. The ether will boil off at relatively low temperature (<95˚) and should be collected in flask **A**. After the temperature has surpassed 100˚ allow 7 more drops, then switch to flask **B** to collect the ester. (The 5 drops rinse off ether still in the condenser). For samples C,D,E some glass-wool insulation will be needed, get instructor. Record the "plateau" temperature at which most of your ester boils off. Remove the heat/jack/hot-plate as soon as high-boiling ester stops dripping steadily. (Don't boil dry; heat too long causes insoluble black material to "burn" onto the flask.)

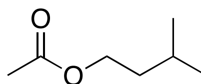
Analysis: Weigh your product ester in flask **B**. Prepare and submit an NMR for **B** by filling the skinny end of a long pipet to about 1-2cm, shoot that into your tube, rest the pipet inside the NMR tube, and then use 0.8 mL of CDCl3 to dilute/rinse through the pipet directly into the NMR tube. Between 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.

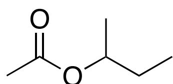
Ester Candidates

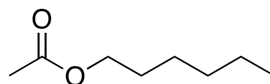

Propyl Acetate, 100-105° ± 10°

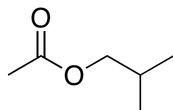

Isobutyl Propionate, 132-147°

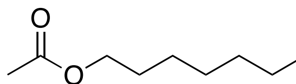

Methyl Butyrate, 100-105° ± 10°

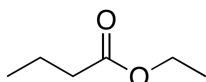

Isopentyl Acetate, 132-147°

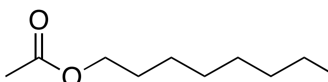

s-Butyl Acetate, 112-120°

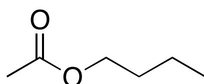

Hexyl Acetate, 167-177°

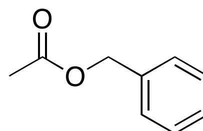

Isobutyl Acetate, 114-120°


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**.
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. **Identity of the ester you made**. Key clues are the boiling point, the NMR(s), and the identity of the acetic anhydride reactant.
6. Identity of the alcohol you began with. (Based on your product ester and/or your NMR.)
7. 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 for your volume-mass-mole calculation. (This is not exactly true, but close enough, and simplifies.)
   - 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: (picture, don't need name) mw of Ester:

- You can quickly calculate the molecular weight by summing up the masses of the carbons (12 g/mol), hydrogens (1 g/mol) and oxygens (16 g/mol)

3. Alcohol Identity: (picture, don't need name) mw of Alcohol:

4. Observed Boiling Range of Your Ester:

5. Mass Yield of Ester:

6. Theoretical yield: (show your work)

7. % Yield:

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

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

Basic GC-MS Operation Compressed Draft 4 For Chem 355 Organic Unknowns Lab

Note: The following assumes the gc/ms program has been opened and warmed up; that an appropriate "method" and "sequence" have been selected; and that Jasperse will turn things off.

Sequenced Data Acquisition: Using the Autosampler to Sequence Runs Automatically

Note: this assumes that Jasperse has already prepared a "sequence", but you are trying to add your sample to the lineup.

- If you're first in line, get Jasperse to come and help. Or hit "OK" and "Run Sequence".

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 and is in the injector tray.)
   - 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 high 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: Data files are in a Data Folder, usually open on the left. Or, you can click "Data Analysis from the yellow panel on top of the GC software field.

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

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.

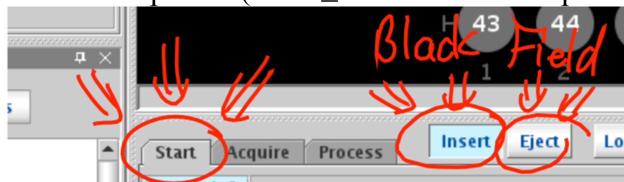
5. **Printing Mass Specs: Click the 5th Hammer button.**
   - Click the 5th hammer button as many times as needed to provide prints for each student in group.

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.

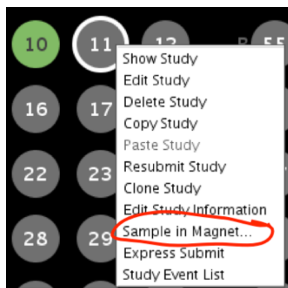
<u>User's Guide to NMR, 2025 Without Autosampler</u>: Draft 2/1/2022. Help: Dr. Jasperse, Hagen 407J, 477-2230

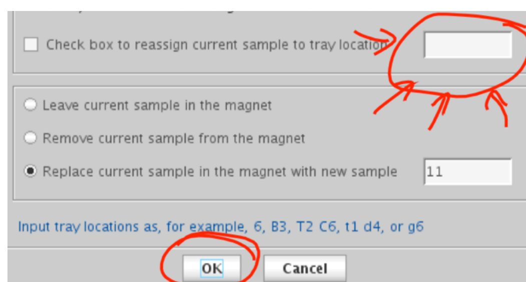
1. Prepare sample in lab; add sample to sample-holder; adjust sample depth using golden depth finder

2. Eject/Insert (Sample Exchange):
   a. Hit "eject" button (below black field) to eject existing sample. (If not visible, click "start" button to make it so)
   b. Manually lift out sample-in-sample-holder combination from the probe (place it in a box)
   c. Place your sample-in-sample-holder into the probe
   d. Hit "insert" button on the computer. (Wait ≥5 seconds before proceeding with step 3a).

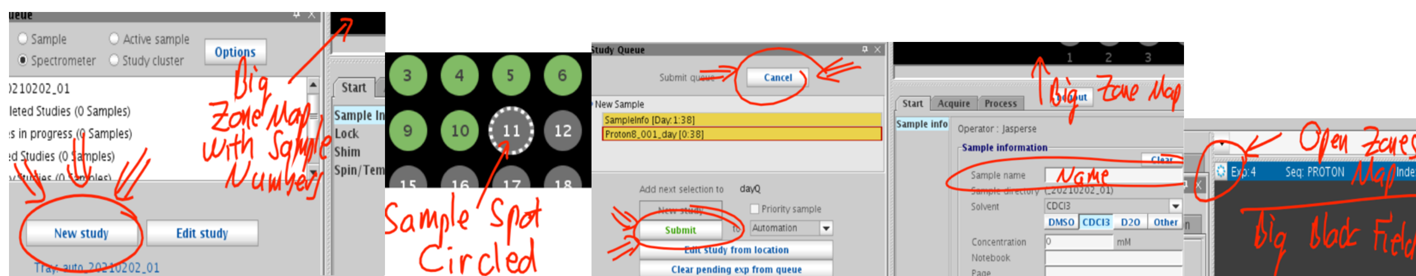


3. Spot Assignment: (Each sample needs to be assigned a sample spot number)
   a. Right-click on the lowest-numbered gray spot number in the zones map. (A pulldown will appear)
   b. Select "Sample in Magnet" (3rd <u>line from the bottom</u> of the pulldown);
   c. Enter your spot number into the upper field. (Remember your spot number)
   d. Hit <u>OK</u>.





4. NMR-Experiment Submission:
   a. Click "New Study" button in lower left. (A yellow experiment file-name will appear).
   b. The default experiment is "Proton-8"; for something different select from panel on upper left.
   c. Left-mouse single-click on your sample spot. (A white circle will appear around the sample spot)
   d. Enter student name(s) into Sample Name field, which is underneath the black field
   e. Submit: click the green "Submit" button on the lower left side. (your sample spot should turn color)
   f. Hit "Cancel" to leave submit-sample mode.
      a. Don't forget to do this. If you do, it will cause problems for both you and the ensuing user.
      b. The yellow experiment file-name will disappear; unfortunately the zones map will too.
   g. Re-open "zones" map: Click on little circle icon ( ) to the upper left of the big gray/black panel, and the zones map with all the sample spot numbers should re-open.
      - Note: An experiment should take about 7 minutes.
      - There should be an automatic one-page printout upon completion.



5. **Printing an extra copy** of spectrum (in case you have a partner)

- Must be in zones-map display. If not, click on little circle icon ( )upper left of the spectra-display panel.

a. Right click on sample number, and a pulldown will appear
b. Click "Show Study"
c. **Double click** on green "PROTON_01" file that will appear in the lower left-hand area. (below your name)
    a. Your spectrum should now appear in the display field, where the zones-map appeared before
d. Click "Process" button underneath the spectrum display field. ("Start" was highlighted previously)
e. Click blue-text-on-white-background "Print" button on lower right to print another copy.

6. Horizontal Expansions

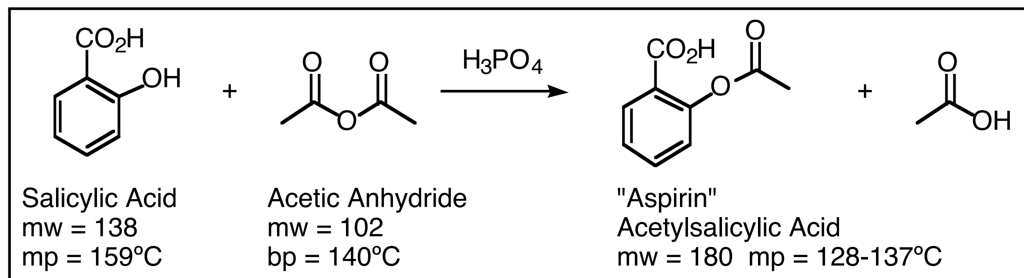
a. Steps 5a-d above describe how to get your spectrum loaded into the display field.
b. With spectrum displayed on screen, use a panel of display icons on the far upper right
c. Click on the magnifying glass icon (6th icon down,)
d. Move your cursor to the left end of the zone you want to expand, then **hold down left mouse button** and slide it to the other end of the zone you want to expand, then release the button.
    a. To return to the full display, you can either click on the 3rd icon ( ) or the 5th icon ( ).
e. Click blue-text-on-white-background "Print" button on lower right to print a copy. (Twice for 2 copies)

7. Exiting so that NMR is Ready for the Next user

a. Click "Start" button underneath the spectrum display field. ("Process" was highlighted previously)
b. Re-open "zones" map: Click on little circle icon ( ) to the upper left of the big gray/black panel, and the zones map with all the sample spot numbers should re-open.

Alcohol Unknowns and Aspirin

Part 1: Microscale Synthesis of Aspirin



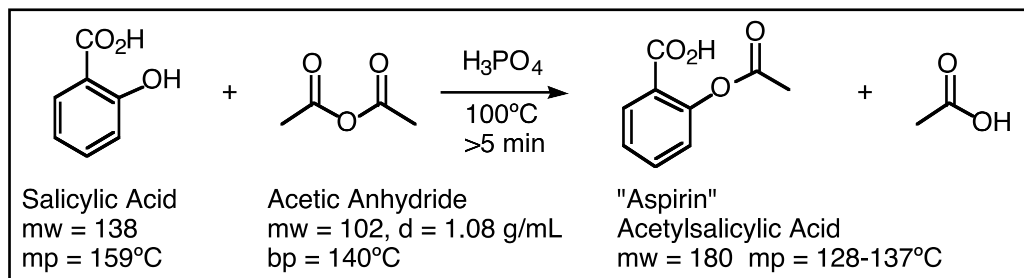
Intro Aspirin is among the most versatile drugs known to medicine, and is among the oldest (the first known use of an aspirin-like preparation can be traced to ancient Greece…). The starting material salicylic acid is cheap (~$50/kg), because it is available by carboxylation of phenol with carbon dioxide. 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, and 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 most aspirins are the same (other than “baby aspirin”, for many others medicines the dosage of active ingredient varies (children’s Tylenol versus adult…)



Procedure

1. Work with partner if you want.
2. Fill a 50-mL beaker with hot water, and begin heating on a hot plate. (Hot plate setting of ~5?). The goal is to get the water hot enough to approach a gentle boil.
3. Weigh out 0.138 g of salicylic acid (1.0 mmol) and add it to a small test tube
4. Add one small drop of 85% phosphoric acid
5. 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.
6. Swirl the reactants thoroughly; then heat the mixture in a beaker of boiling water for ≥5 minutes.
7. Remove the test tube from the heat.
8. Add about 1 pipet of water, carefully (a few drops) at first then faster, 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, into which is molded a water-dampened (to make it limp and flexible) filter paper. (The size that is fitted and would lay perfectly flat on your smaller Buchner 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. (Water doesn't evaporate/dry very fast, so you'd probably like it to be vacuuming for at least 15 minutes, or longer if you're busy with other work anyway.)

15. **Lab report on the aspirin**. Report the:
    - mass recovered,
    - calculate the % yield, and
    - report the melting range.
        - Note: The melting range is typically rather broad for aspirin because of the carboxylic acid which hydrogen-bonds to the ester.
        - No procedure writeup required.
        - The data can be reported either on the bottom or on the back-side of your alcohol-unknown sheet.

Part 2: Analysis of an unknown alcohol.

- A list of alcohol candidates with their boiling points is listed two pages after this.
- Conduct classification tests shown below to try to determine the following:
    - Is alcohol "big" or "little"? (solubility test)
    - Is alcohol "dense" (aromatic) or "non-dense" (alkyl alcohol)? (solubility test)
    - 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. Water Solubility 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. Stir vigorously. Is it homogeneous or heterogeneous? If heterogeneous, do the droplets float or sink?
- Interpretation:
    a. **Big alcohols**: Alcohols with >6 carbons definitely **won't be soluble**.
    b. **Small alcohols**: Alcohols with <3 carbons definitely **will be soluble**.
    c. **Borderline**: Alcohols with 3-6 carbons may be borderline, and **could go either way**.
    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.

Practical Interpretation: Insoluble doesn't prove ≥6 carbons; it only proves ≥3 carbons. And soluble doesn't prove ≤3 carbons; it only proves ≤6 carbons.

- If you think you're **borderline**, then adding more water should enable full dissolving. Or adding more drops of alcohol should confirm incomplete solubility

2. Chromic Acid 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/ugly within 5 seconds. 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 hydroxyl-bearing carbon, no oxidation is possible. Thus tertiary alcohols don't react, but both primary and secondary do.

3. Lucas Test ($ZnCl_2$/conc. HCl): positive for 3º or 2º alcohols, or for allylic/benzylic 1º

- Add 30 drops of Lucas reagent to small test tube, then add 3-4 drops of alcohol, stir really vigorously with a boiling stick, and let settle.
- **Tertiary alcohols or allylic/benzylic alcohols** react pretty **quickly** to give **two layers**
- **Secondary alcohols** react within **<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; 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.
- Add 0.8-mL of $CDCl_3$ solvent (volumes not critical) **directly through the same pipet into the NMR tube** to rinse the sample into the NMR tube.
- Cap and shake the sample and take it to the NMR room (SL 305) and run the NMR as time permits. (The professor will probably keep a taking-turns-on-NMR list on the whiteboard.) The experiment is probably called "H_C_HC" and is under the "355-365" folder. The instructor will presumably have this all ready and queued up.
- Upon completion, do expansions as appropriate to both H-NMR (to clarify splitting) and the 2D HC-NMR. Manual integrations on the H-NMR may often help. Zooming and adjusting the scaling on the 2D H-C NMR could also help. If available, consultating from instructor may help.
- The 2D H-C NMR is invaluable for identifying each carbon. Consult with instructor.
- Several challenges may complicate interpretation of the H-NMR:
  1. In **longish alkyl** groups, several alkyl CH_2 groups will often overlap. In 1-octanol, for example, CH_2's 3-7 will probably all make a big superimposed lump that integrates for around 10H.
  2. For secondary alcohols, CH_2 groups adjacent to the OH-bearing-carbon often show the 2 H's as non-equivalent; one H is cis, the other H is trans to the OH. Due to this cis/trans nonequivalence, the two H's may end up with possibly different chemical shifts and much-complicated splittings.
  3. The OH hydrogen can come almost anywhere, and may superimposes on other alkyl H's.
  4. The OH hydrogen is often/usually (but not always) a lumpy shape.
  5. Often the OH doesn't split at all with the C-H hydrogens, but sometimes it does to variable extent.
  6. On the carbon to which the OH is attached, the hydrogens are sometimes broadened or deformed by the OH hydrogen. So splitting can be complex. Consult with instructor.
  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. A "bell" is a narrow piece of glass tubing, narrow enough to fit inside a melting point tube. A bell must have its upper end closed off, and should be at least the length of a fingernail.

Make six "bells" by glass melting/stretching/sealing/breaking (we'll make extras for later.) Bring a 50-mL Erlenmeyer with 6 regular empty melting-point tubes (into which the bells will be placed) to the bell-making station. The instructor will train you how to make the bells. (Scary and fun!)

Prepare two boiling point samples, **one** a control containing **1-propanol** with a known boiling point of ~90-95ºC; the **second** with your **actual unknown** alcohol. Bring your unknown alcohol and your tubes-with-bells to the loading area (on center table). For each tube, use a syringe to add about 5 uL of either the propanol or unknown sample; try to tap or drop such that the liquid settles to the bottom.

Run the two samples side-by-side (propanol in one tube, unknown in the other.) **Carefully note the original liquid levels at the start**. (**Noticing that it drops later is key clue that boiling has occurred**.)

When a liquid is heated, **pre-boiling bubbling** will usually occur as the air inside the bell heats and expands and gets displaced by sample evaporation. When the **real boiling point** is reached, more **rapid bubbling often takes place, but not always**; **in many cases, though, you won't see nice bubbles**. **What will always reliably happen**, though, is that at or somewhat beyond the boiling point, the **liquid level will drop, as liquid vaporizes and goes up the tube**. **This liquid-level-drop is a more reliable indicator, since it happens whether or not bubbling occurs**. 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.

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

3. Attach copies of all three of your NMR spectra, with interpretation details (see below).

4. **On the H-NMR spectrum, create a 4-column STANDARD SUMMARY REPORT of your ACTUAL H-NMR data, detailing chemical shifts, integrations, and splittings, and source**. Chemical **shifts** need to be specified to at least the **nearest 0.1 ppm**. Draw the structure of your molecule, with **identifiers** by each carbon (typically a, b, c… or 1, 2, 3…). Then on your standard summary table include a "source" column in which you show which hydrogens (CH_2-1 or CH_2-b, or CH_3-6 or CH_3-a, or whatever) are responsible for each 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 2º alcohols. In many cases, some overlapping may occur. Consult with instructor if you have questions!

5. **On the carbon spectrum, draw the structure of your molecule, again with identifiers by each carbon (typically a, b, c… or 1,2,3)**. 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.

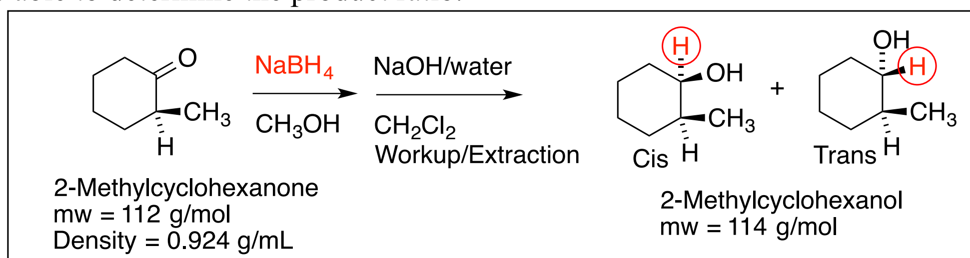
6. Comments (if any).

7. **Remember to attach your aspirin data, (including showing calculations), or write on this sheet somewhere (or on the backside)**.

$NaBH_4$ Reduction of 2-Methylcyclohexanone.
Use of H-NMR Integration for Analysis of Isomeric Product Ratios

BACKGROUND Hydrogen-NMR is useful for analyzing pure samples, and one of the pieces of information is the **integration** of hydrogen signal sets. Integration of hydrogen signal sets measures the signal areas, and these areas are proportional to the number of hydrogens causing the particular signals. Thus in a pure compound, a 3:2 integral ratio would be observed for a CH_3 signal set versus a CH_2 signal set.

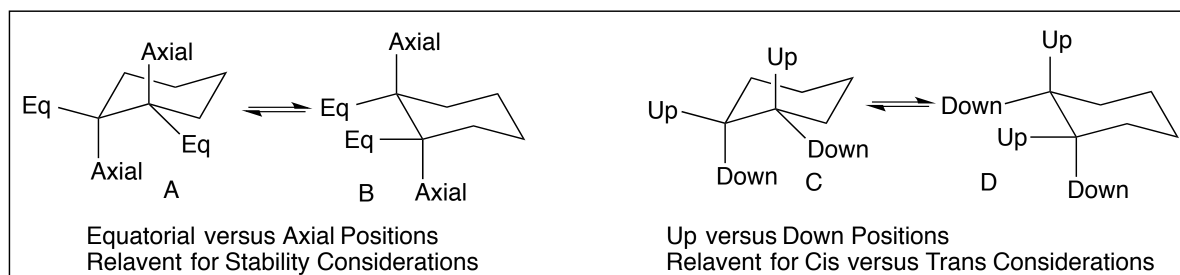
In today's experiment, we will apply integration in a related but different way: to measure the ratio of two **different products formed in a single reaction mixture**. The chemical experiment will be a standard $NaBH_4$ reduction of a ketone to produce alcohol. Due to the chirality of the starting ketone, two diastereotopic cis/trans alcohols are produced. Attack of the hydride from the back face, trans to the methyl group, produces the cis product alcohol. Attack of the hydride from the front face, in which the hydride approaches cis to the methyl group, produces the trans alcohol. The labeled hydrogens on the oxygen-bearing carbons of the alcohol products give NMR signals with different chemical shifts. By integrating the sizes of their signals, we will be able to determine the product ratio.



Chair Conformations and NMR Interpretation Summary: How do we know which product is cis and which is trans?

We know that a substituted cyclohexane ring has two chair conformations of unequal energy.

- To review some of the considerations regarding cyclohexane chairs, you might review the pre-lab video.
- You might also wish to review some Organic I notes about cyclohexane chairs, and/or the video discussing them:
  - Notes: http://web.mnstate.edu/jasperse/Chem365/Cyclohexane%20Chairs%20Review.pdf
  - Video: https://mediaspace.minnstate.edu/media/Cyclohexane+Chairs+and+Cis-Trans+Diastereomers/0_qmuhyoez



- You will want to draw both chairs for the cis isomer, and identify which is the more stable.
- You will then want to draw both chairs for the trans, and identify which of those is more stable.
- You will want to determine which is better overall, the best chair conformation for the cis isomer or the best chair conformation for the trans isomer.

- In the "best cis", you'll want to identify whether the "feature hydrogen" on the hydroxyl carbon is axial or equatorial.

- Several reminders for cyclohexane chair conformations:
    1. When a chair flips, a substituent that was equatorial in the first figure will be axial in the second, while a substituent that is axial in the first will be equatorial in the second. See figures **A** and **B** in the figure.
    2. The most stable chairs have larger-than-hydrogen substituents equatorial. Thus, between the cis and the trans diastereomers, the one in which both the methyl and the hydroxyl are equatorial will be the more stable of the two.
    3. A methyl group is larger than a hydroxyl group. So in the cis/trans conformation in which both can't be equatorial at the same time, the preferred conformation will keep the methyl group equatorial while placing the hydroxyl group axial.
    4. In terms of cis-trans assignment, remember that "**cis**" would involve having both the methyl and the hydroxyl substituents relatively "**up**", whereas "trans" would have one of the methyl/hydroxyl groups "up" and the other "down" (see figures **C** and **D**.)
- **By comparing the best cis chair with the best trans chair, you should be able to recognize which of the two products is more stable overall, cis or trans**.
- **By looking at your models/drawings, you should also be able to recognize whether the best cis chair has an axial or equatorial "feature H" (the hydrogen attached to the oxygen bearing carbon, which will give a signal in the 3's.)**
- **Likewise you can determine whether the trans isomer should have its "feature H" equatorial or axial. (It will be axial in one of the isomers and equatorial in the other.)**

NMR Facts: **An axial hydrogen has a chemical shift further to the right ("upfield", lower number) relative to otherwise analogous equatorial hydrogens** in an H-NMR spectrum.

- The reason for this is that an axial hydrogen is more crowded, and closer to electron clouds around other atoms. The greater crowding/proximity to electron clouds causes the upfield shift.
- Remember that the C-H hydrogen on an oxygen-bearing carbon appear in the 3's. So the "feature H" in both the cis and the trans diastereomers should appear in the 3's.
- The methanol CH3 group also shows up in the 3's. Hopefully the concentration process will remove most or all of the methyl signal, but perhaps check with instructor.

Application: Your drawing/model-building should tell you whether the axial "feature H" correlates to the cis or trans product.

- By integrating the axial (upfield) to equatorial (downfield) signals in the 3's, you will thus be measuring the ratio of the two isomers.

"Thermodynamic Product-Stablity Control" versus "Kinetic Control"

When the same starting material can give two different products, we say that the reaction is either under "product stability" control or under "kinetic control". "Product stability" control usually applies, because factors that stabilize the product often stabilize the transition state as well. But this is not always true: sometimes steric crowding can destabilize a transition state without destabilizing a product. If a reaction does not preferentially produce the most stable product, then the reaction is said to be under "kinetic control" rather than product stability control. In today's experiment, might the methyl group obstruct the front face and thus destabilize the transition state leading to the trans product?

Experimental Procedure

1. To a large test tube, add a teensy stir bar, and add 4 mL (or two full pipet squirts) of methanol
2. Add 0.9 mL of 2-methylcyclohexanone.
   - Use density and molecular weight information to calculate how many moles are involved
   - density = 0.924 g/mL
   - mw = 112 g/mol)
3. Prepare an ice-water bath in your 150-mL beaker
4. Place the test tube into the ice-water bath, place it on your stir plate, and stir
5. Weigh out 0.15 g of $NaBH_4$ (mw = 38 g/mol)
6. Carefully add the $NaBH_4$ to the test-tube. (The $NaBH_4$ is in excess, so if some sticks on the walls of the tube, it isn't a problem).
7. Stir the mixture for five minutes, then after the vigorous bubbling subsides, remove ice-water bath and stir the test-tube mixture at room temperature for 20 minutes.
8. Clamp your smallest iron ring to a vertical rod, and insert your separatory funnel
9. Pour your test tube solution into the separatory funnel
10. Rinse test tube with an additional 8mL of dichloromethane and add this to the separatory funnel
11. Rinse test tube with ~15 mL of tap water, and add to the sep funnel.
12. Then add two full pipets of 3 M sodium hydroxide solution (purpose: to decompose the borate salts and move them into the aqueous phase)
13. Shake the mixture, then let it settle
    - Question: which layer is organic and which is aqueous? If in doubt, add 10 more mL of additional water and watch to see which layer it falls into, and which layer grows!
14. Drain the dichloromethane layer into a 50-mL Erlenmeyer flask
15. Wash the aqueous layer in the sep funnel with an additional 5 mL of dichloromethane, let it settle, and drain the organic layer into the Erlenmeyer flask.
16. Repeat step 14 again; use another 5 mL of dichloromethane to extract any remaining product out of the water layer.
    - Notes: In today's lab, we are doing three dichloromethane extractions to try to get all of the organic product out of the water layer. Being an alcohol, the product has hydrogen-bonding capacity and non-trivial solubility in water. So, if we had just done a single separation, an unnecessarily large amount of product would remain dissolved in the water layer.
    - When doing repeat extractions, it is practical to have the "extracting" solvent be the heavier, denser liquid that sinks to the bottom of the separatory funnel. Thus we are using dichloromethane rather than ether, because relative to water dichloromethane sinks but ether floats.
17. Add a large scoop of anhydrous sodium sulfate to the Erlenmeyer flask to "dry" your organic solvent. If the sodium sulfate all clumps, add more until at least some does not clump up.
18. Add a small stir-bar to a 50-mL round-bottomed flask
19. Pre-weigh the combined flask-plus-stirbar, then clamp it.
20. Take your long stem funnel and push a little glass wool into the neck.
21. Pour the organic solution from the Erlenmeyer through the funnel into the round-bottomed flask. The wool should be sufficient to filter off the solid sodium sulfate, and only allow the solution to get into the flask.
22. Rinse the Erlenmeyer with additional dichloromethane, and pour the rinse through the funnel into the round-bottomed flask.
23. At this point, there should be only CH_2Cl_2, methanol, and alcohol products in your flask.

24. Concentrate the organic solution by rotary evaporation. Be sure the aspirator power is on; that the top air valve is closed; and that you have an adapter for a good glass seal. Make sure that the spinner is also turned on.
25. If the rotovap is too busy, you could do the concentration in your hood, using your vacuum adapter. If so, make sure you have your stir-bar stirring vigorously, and that you very gradually/carefully open your vacuum. You may wish to have the instructor come over to help. It may also provide some extra precaution to include a dry reflux condenser to prevent boil-over.
26. Once the sample has concentrated to a residual oil, (shouldn't take 10 minutes), re-dilute with an additional 10-mL of dichloromethane, then re-concentrate again. The purpose here is to help ensure that all of the methanol distills away.
27. Weigh the flask and calculate your mass yield.
28. Prepare and run an NMR.

Model Building (Optional.)

1. Build a model of both cis and trans 2-methylcyclohexanol.
2. Either chair-flip both, or else build both flip-forms of each
3. For the cis isomer,
    a. which chair-flip conformation is more stable?
    b. In the more stable cis chair, is the "feature hydrogen" axial or equatorial?
4. For the trans isomer,
    a. which chair is more stable?
    b. In the more stable trans chair, is the "feature hydrogen" axial or equatorial?
5. Which is more stable overall, the best cis chair or the best trans chair?

Name:

Sodium Borohydride Lab Report

1. Use Standard Synthesis Format:
    a. Illustrate the Chemical Reaction
    b. Summarize the Chemicals Used
        - Include mole Calculation for 2-methylcyclohexanone. (Assume $NaBH_4$ is excess.)
    c. Calculate the theoretical yield
    d. Write up the procedure, **including observations**
    e. Analysis:
        - Include actual yield, and
        - percent yield
        - Attach NMR

2. Take H-NMR
    - Print full spectrum, with integrals for the two diagnostic signal sets in the 3's.
    - Solvent Notes:
        - CH2Cl2 solvent, if not evaporated completely, will give a singlet at 5.3;
        - and methanol, if not completely extracted/evaporated will give a singlet around 3.5.

3. Discussion/interpretation
    - Draw both cis chairs
      -Identify the better of the two
      –is the "feature" H axial or equatorial?

    - Draw both trans chairs
      -Identify the better of the two
      –is the "feature" H axial or equatorial?

    - Would the cis chair or the trans chair be most stable overall?

    - From the NMR integration and chemical shifts, determine the trans/cis ratio.

    - Was the major product formed via "product-stability control" (the most stable product is formed preferentially) or "kinetic control" (for some steric reason, the fastest reaction/lowest transition state did not lead to the most stable product)?

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:

- NMR information on the starting material. (H, C-decoupled, and 2D HC-NMR)
- 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)

Classifying Tests

1. Water Solubility 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. Stir vigorously. Is it homogeneous or heterogeneous? If heterogeneous, do the droplets float or sink?
   - Interpretation: **Insoluble proves ≥3 carbons. Soluble proves ≤6 carbons.**
     a. **Small**: Carbonyls with <4 carbons always **dissolve**
     b. **Big**: Carbonyls with >6 carbons **never dissolve**
     c. **Borderline**: 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, (we'll only do 2,4-DNP), but which you should know to answer post-lab questions
   - 2,4-dinitrophenylhydrazine (**DNP**) 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. Add 0.8 mL of CDCl3 directly through the pipet to rinse the sample into the NMR tube. Cap it, shake it, and set it into the NMR queue and run the experiment called "H_C_HC" in the 355-365 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.

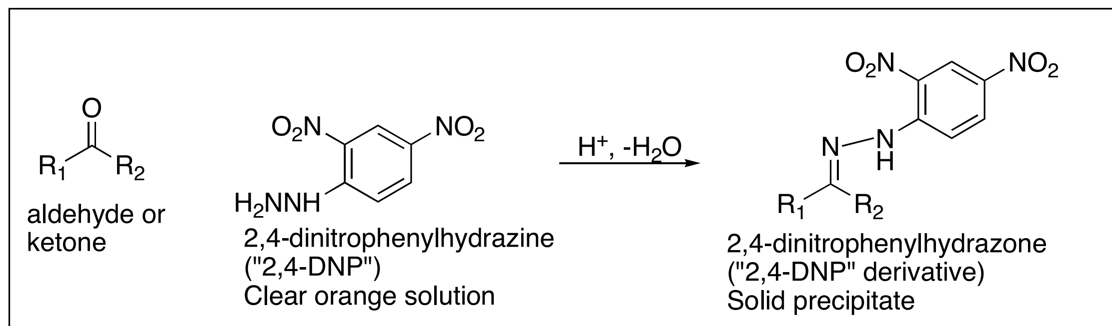
Derivative: Making a 2,4-DNP Derivative of Your Aldehyde or Ketone

Put 4 pipets of 2,4-DNP solution into a large test tube, add a stirring bar, begin very strong stirring, and add 30 drops of your unknown to the well-stirred solution. After 2 minutes, cool, add 2 pipets of cold water, stir, filter, wash with cold water, and wash with a small amount (three pipets) of cold ethanol. Vacuum for a while (5 minutes is probably plenty), and if possible prepare a crude mp sample. (Melt it later, not now. You may need a metal wire "ramrod" to push sticky material to the bottom of a tube. If it's too sticky to get in, don't worry about it.)

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. Prewarm some water in a half-filled 400-mL beaker. (Hot-plate ~6? Would like the bath to be ~80-90º.) If you also **prepare some hot ethanol**, 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 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

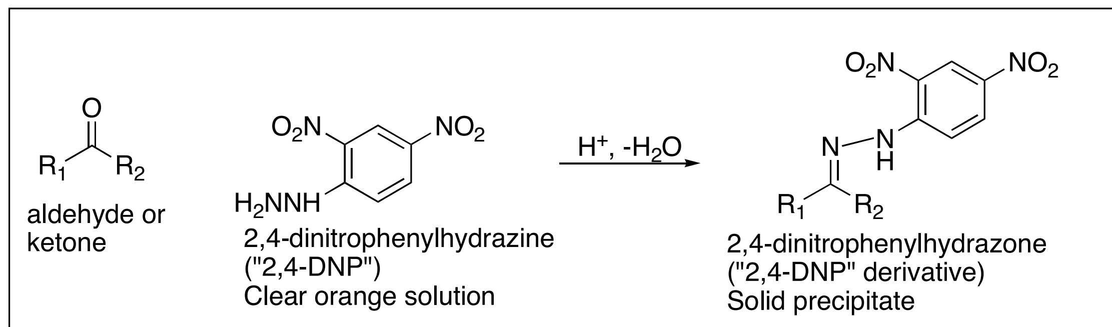
A classic way to help identify a material is to convert it into a crystalline derivative. This is particularly valuable if the initial chemical is a liquid or is impure. We've seen that although melting points are easy to measure, boiling points are not. **By converting a liquid (or impure) sample (for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

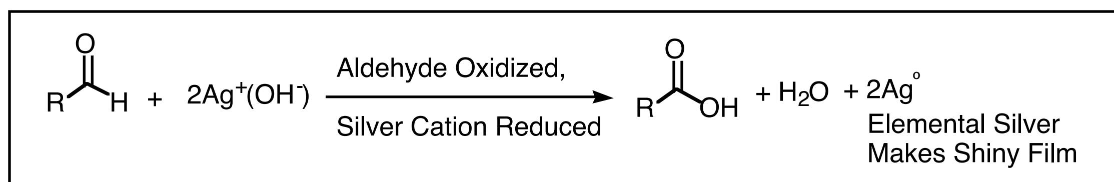
SOME CHEMICAL TESTS TO KNOW

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



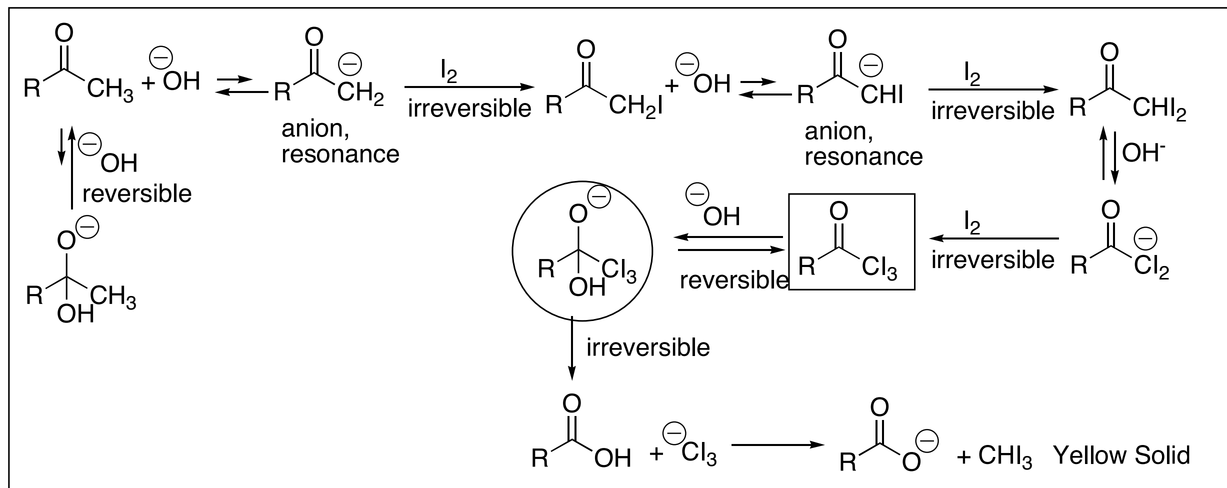
The "DNP" test is positive for both aldehydes and ketones, but not for alkenes or esters/acids/amides. This is representative of how H_2N-Z reagents react with aldehydes or ketones to eliminate water and make "imines", with a C=N-Z bond. In the chemical test, the DNP reagent is soluble; if a derivative 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.



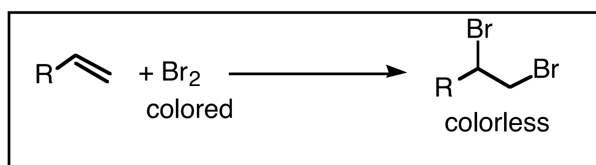
A classic alternative to the Schiff's test fo aldehydes is the the Tollens Test. Tollens reagent is a soluble AgOH solution. [Actually $Ag(NH_3)_2OH$]. When mixed with an aldehyde, the aldehyde carbon is oxidized to a carboxylic acid, and the Ag(I) cation is reduced to elemental Ag(0). The elemental 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_3COR)



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:

<u>Lab Report Requirements:</u> 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.

<u>Questions</u>:

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. Solubility Tests on Starting Material

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

Conclusion:

2. Boiling point:

3. Derivative: observed mp literature mp (see p41)

Crude (if possible):

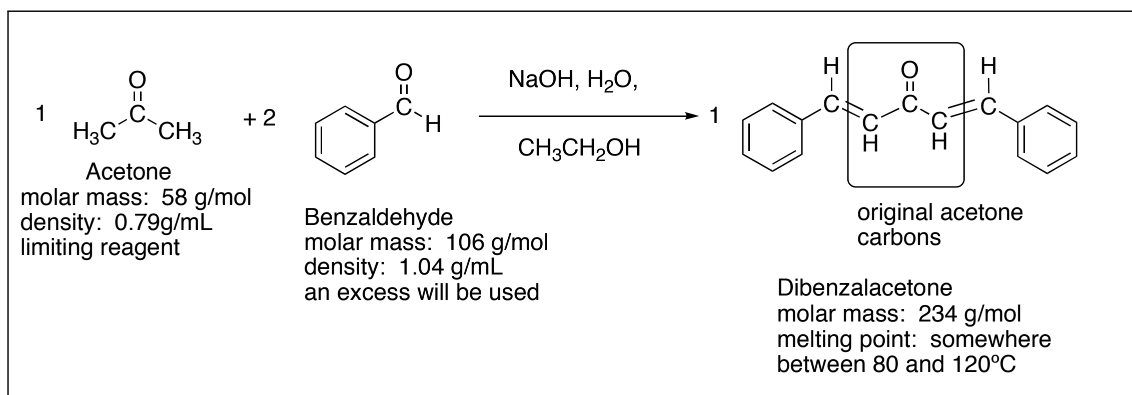
Recrystallized

4. H-NMR (attach, with assignments/interpretation.)
   - **On the proton spectrum, create a STANDARD 4-column SUMMARY REPORT of your ACTUAL H-NMR data, detailing chemical shifts, integrations, and splittings, and "source".**
   - Chemical shifts need to be specified to at least the nearest 0.1 ppm
   - Draw the structure of your molecule, with identifiers by each carbon (a, b, c…).
   - Then on your standard summary table add a "source" 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.

5. 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.
     - The C-H 2D NMR will help you to be able to assign all of your lines.)

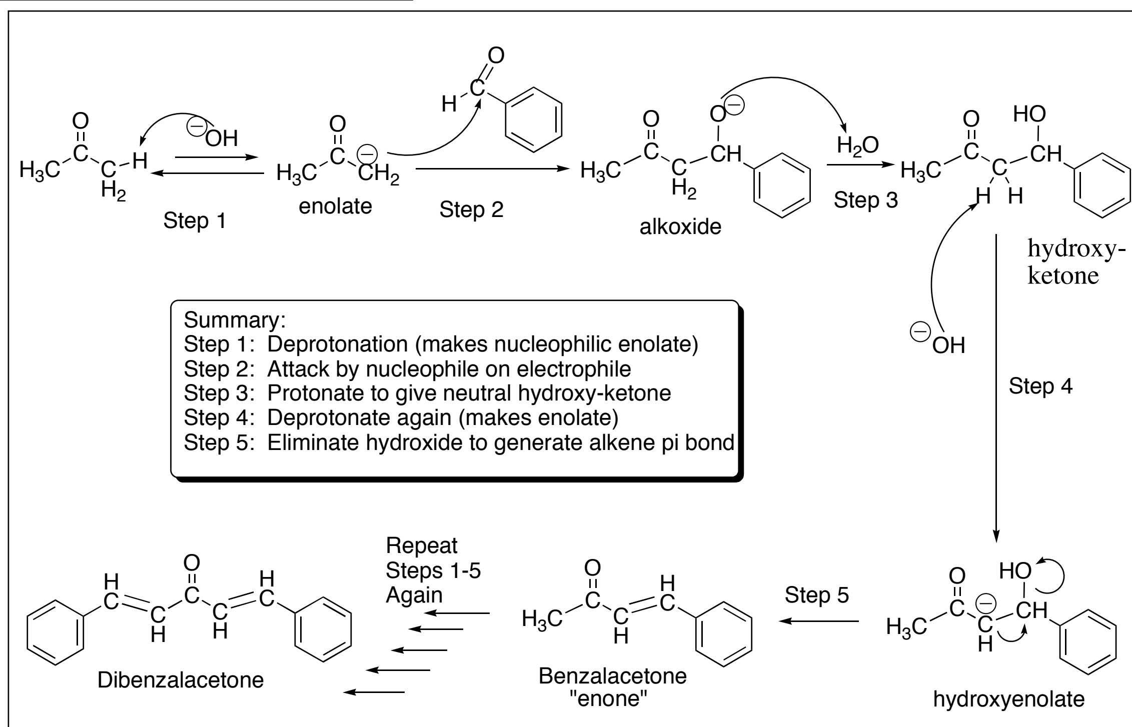
6. Comments, difficulties, complaints, etc.

ALDOL SYNTHESIS of DIBENZALACETONE, AN ORGANIC SUN SCREEN



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



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 we ensure that we still have enough to fully react with the acetone.
  b. **Reaction Time**. By having an excess of benzaldehyde, it makes it easier for the reaction to go to completion. 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 your largest, longest magnetic stirring bar.
2. Add 50 mL of the NaOH-Ethanol-Water solution mixture. (This was premixed for you.)
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. Weigh the crude product, and remove a small crystal for a crude melting point that you can run later. Note: your yield may be >>100%, due to residual water. That's OK, you're going to recrystallize again anyway.
13. Prepare a hot water bath (400-mL beaker, hot-plate ~5). Having somebody in your hood (or adjacent) heat some ethanol, in case one of you needs it, is advisable, too.
14. Purify the bulk of your crystals by recrystallizing from ethanol, using a 125-mL Erlenmeyer inside your hot-water bath. A reasonable starting guess is to add ~4mL ethanol/gram product, and heat it up. Improvise if needed once hot, depending on what you see. (You can add more hot ethanol to increase solubility, or hot water to reduce solubility.) Note: The product has a low melting point, so it's easy to think you've dissolved it when actually you've only melted it. Note: the water bath provides even heating and avoids overheating on the hot-plate surface.
15. After cooling, rinse the crystals with an appropriate rinse solvent. (What might that be?)
16. Dry thoroughly.
17. Take yield and mp, 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?

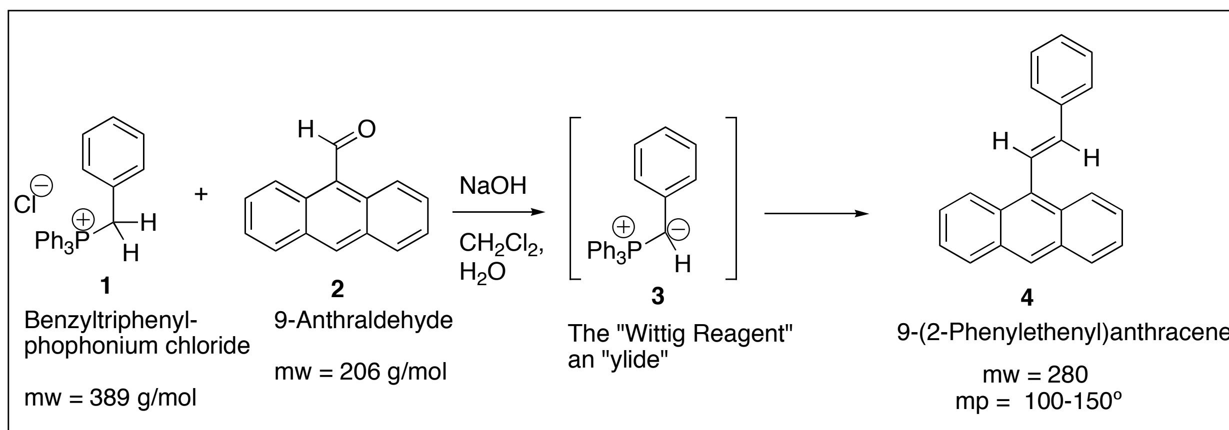
2. What ingredients would you use if you wanted to make benzalacetophenone, PhCH=CHCOPh?

Miscellaneous Notes

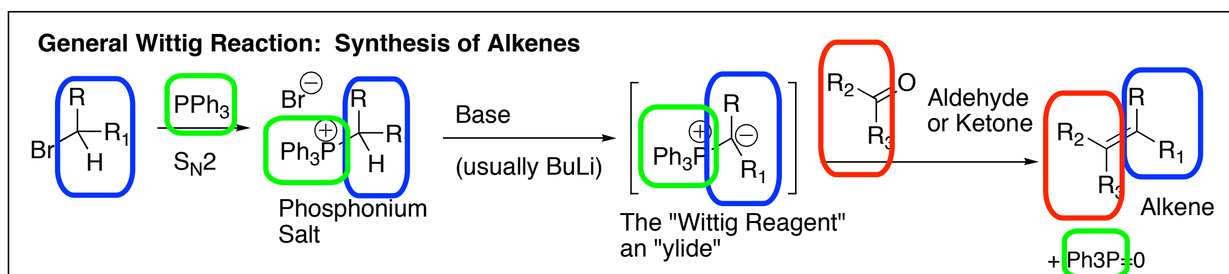
- Does the benzaldehyde smell familiar? It's found in almond, almond paste, and is familiar from cherries and vanilla. Lots of cookies and bars have this smell.
- Acetone has many uses, including as a paint and varnish remover; as a fingernail polish remover, and as a solvent in many varnishes, rubber 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.

- 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?
- 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.

The Wittig
Reaction: Synthesis of Alkenes

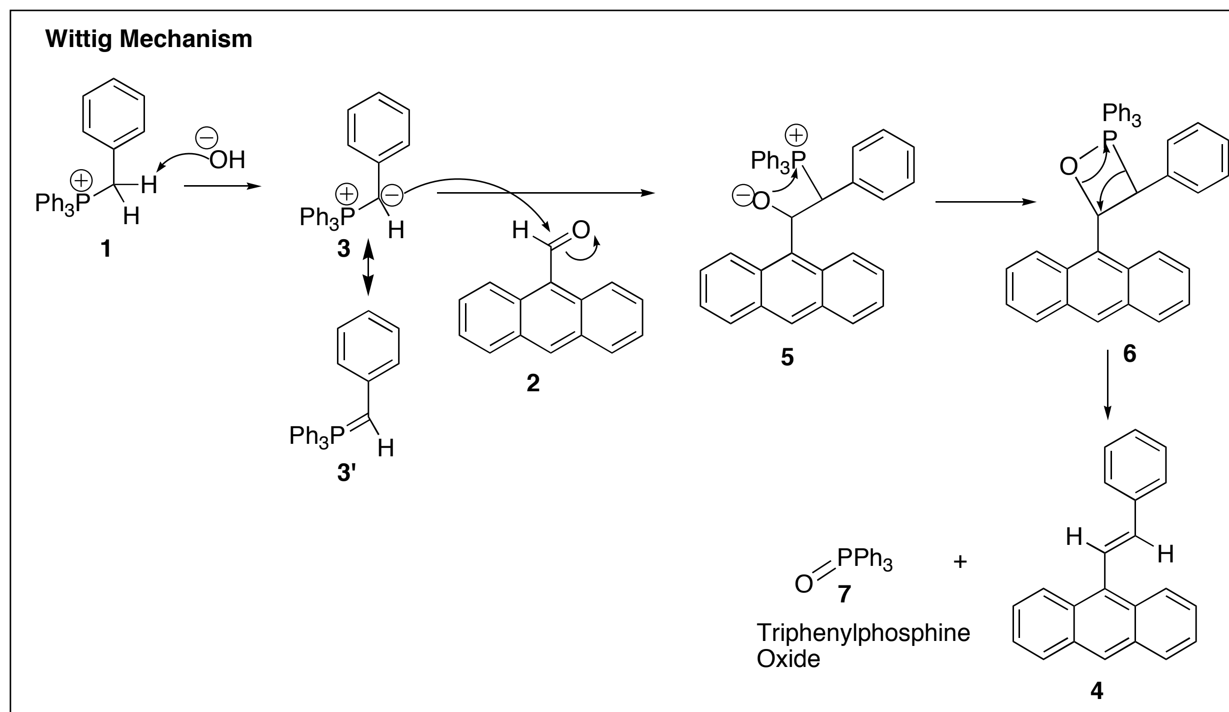


Intro The "Wittig Reaction" is one of the premier methods for the synthesis of alkenes. It uses a carbonyl compound as an electrophile, which is attacked by a "phosphorus ylide" (the "Wittig reagent".) While many other routes to alkenes can proceed via elimination reactions (E1 or E2 reactions from alcohols 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.)



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



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 125-mL Erlenmeyer so that you can stand it on a stir-plate. (Or clamp.)
4. Weigh out ~0.300 g of 9-anthraldehyde **2** and add this to the test tube. (Record exact mass)
5. Add three pipets of dichloromethane and stir. (Squeeze the bulb, draw up what you get, ~1mL)
    - 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?
    - Which layer is on top, the aqueous or the organic layer?
9. Stir the solution vigorously for 10 minutes.
10. Workup: Dilute with 5 mL of dichloromethane and 12 mL of water, and pour the mixture into the separatory funnel. Add 20 more mL of water to the separatory funnel
11. Rinse the test tube with another 3 mL of dichloromethane and 12 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?
12. Pour the organic layer into a 125-mL Erlenmeyer. (Adding a long-stemmed funnel may help.)

13. Add an additional 8-mL of dichloromethane to the separatory funnel, and shake vigorously again. (Any yellow color is product, so where yellow is, more CH_2Cl_2 rinse might be good….)
14. Pour the organic layer into the same 125-mL Erlenmeyer that has the other dichloromethane.
15. "Dry" the organic solution with sodium sulfate.
16. At this point or sooner, get a 400-mL beaker ~1/3 filled with hot water in it, and warm on hot plate. Maybe target ~55° water bath; with the hot-plate around 5, maybe?)
17. Filter the organic solution into a separate ground-glass-neck125-mL Erlenmeyer, using a long-stemmed funnel lightly-plugged with glass wool to filter off the sodium sulfate.
18. Rinse the original Erlenmeyer and the funnel (anything yellow) with additional dichloromethane.
19. Add a boiling stick to your organic solution, and then place the Erlenmeyer into the warm-water bath to boil off the dichloromethane. (Be thorough…. Once it's boiled down some, you can turn up the hot plate to a higher temperature to facilitate a faster boil-off. No point in wasting lots of time boiling the solvent off if we can do it faster. But, we don't it to go crazy and go boiling over the top, either.)
    - 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…
20. Once the solvent is pretty much gone, remove from hot bath, add a vacuum adaptor, turn on vacuum, and continue under vacuum for 2 minutes to remove any last traces of CH_2Cl_2.
21. Remove your Erlenmeyer from the hot water bath.
    - Does anything crystallize?
    - At this point you have at least two things present: the desired alkene **4** and the undesired phosphine oxide side product **7**. If you also have some CH_2Cl_2 solvent that hasn't quite all boiled away, that will reduce your eventual yield and prevent crystallization.
    - 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. (Jasperse has a quick way.)
    - 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 compromised.
22. Purify your alkene by recrystallizing from 1-propanol solvent. (The water bath can now be boiling hot, so turn up your hot-plate setting to ~5.) 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 its 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.
    - This recrystallization can be done right in the same 125-mL Erlenmeyer flask.
23. After Buchner funnel filtration, rinse with a very small amount (2-4 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.
24. Let things dry thoroughly before getting your yield and mp. (Vacuum for at least 10 minutes.) Once you have your mass, also calculate your % yield. (Don't expect a very high yield. The solvent good enough to host all of the triphenylphosphine oxide also hosted much product.)

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.

Research Module Weeks One and Two:

A Writeup for the Research Module Will be Shared Later, and Can be Printed Independently of the Main Manual.

Amine Unknowns

Overview:

You will receive an amine as an unknown. Your job will be to both identify your compound and prepare a derivative. Several pieces of information will be useful:

- Water solubility tests (big or small? Aromatic or not?)
- Solubility in acid-water. (Many basic amines ionize and dissolve in acid-water.)
- Boiling point or melting point of starting material.
- The melting point of the derivative.
- H-NMR information on the starting material.

Classifying Tests

1. Water Solubility Test (Helpful, but not always decisive or clear-cut.)

- Add 15 drops of water to a small test tube, and then add 2 drops or a spatula tip of sample. Stir vigorously. Is it homogeneous or heterogeneous? If heterogeneous, do the droplets float or sink?
- **Interpretation**:
    a. **Small**: Amines with <6 carbons always dissolve.
    b. **Big**: Amines with >10 carbons have ≤5% solubility (never dissolve)
    c. **Borderline**: Amines with 6-9 C's may or may not dissolve.
        a. Amines are more soluble than alcohols; no 7-carbon alcohols would dissolve.
        b. Water solubility depends on basicity. Amines in which the nitrogen lone pair is sp^3 hybridized tend to dissolve much better than if the lone-pair is p.
        c. For basic sp^3-hybridized amines, the solution may takes on a cloudy look when they dissolve. This is due to the basicity and the formation of ammonium hydroxide.

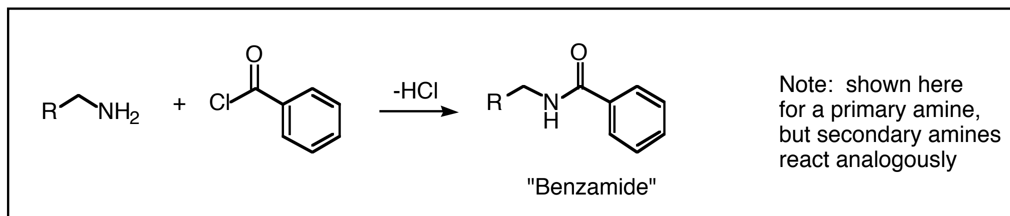
2. HCl/Water Solubility Test
    - Same procedure as above, except use a large test tube, use acid-water (HCl-solution in dispensing hood), add a stir-bar, and use 25 drops of acid-water instead of 15. Use magnetic stirring.
    - Interpretation: Most amines with normal basicity will be protonated and become soluble. If you had a sample that didn't dissolve in water, but does dissolve easily in acid-water, it is likely to be an amine. Caution: solid amines sometimes take a while to ionize and dissolve, and amines in which the nitrogen is conjugated and has the nitrogen lone-pair in a p orbital may be relatively nonbasic and may not dissolve.

3. Amines Smell Variably Rancid. Liquids with sp^3 lone pairs smell worse than solids (less volatile).

4. Many Amines are Solids

5. **NMR**:
    - Splitting: The N-H hydrogens in an amine experience hydrogen bonding. So like alcohol hydrogens, they tend to be a little broad and normally don't participate in splitting.
    - NH or NH2 signals can integrate for 1H or 2H, and typically show in the 1-3 ppm range.
    - Chemical shift: hydrogens on a nitrogen-bearing carbon are not moved as far as when the carbon is oxygenated, but more than when it's allylic. Typically the additivity factor is about 1.5 ppm, and for a typical CH2 group connected to an amine nitrogen, the CH2 group would show up around 2.7 ppm.
    - On an aniline (ArNH2), the hydrogens ortho to the nitrogen are typically pushed upfield, into the 6 ppm window. This is because an amino group is a strong electron donor, so it makes the ortho carbons more electron rich and "shields" the ortho hydrogen, pushing them upfield.

Derivatives: Benzamide Derivatives



1. Place a small stir-bar and 2 mL of aqueous sodium hydroxide solution into a large test tube.
   a. ~1M is good. (≥3M NaOH/H2O may weaken the filter paper).
2. Add the amine, about 15 drops if it's a liquid, about 0.20 g if it's a solid.
3. Stir the solution vigorously, and add about 15 drops of benzoyl chloride.
4. Stir vigorously for 5 minutes.
5. Then acidify with aqueous HCl (this helps the amide to crystallize), while continuing to stir vigorously. (Use pH paper to confirm that the pH is lower than 7. This can be done by touching a boiling stick into the mixture, then touching it onto a strip of pH-paper. An acidic solution should turn the paper red.) There is no risk in making it too acidic.
6. Cool on ice for one minute.
7. Filter the lumpy product through a Buchner funnel, using vacuum. **Pulverize/crush any chunks**.
   - If material is chunky, transfer to a small weighing boat. Place a second empty boat on top, and then grind down on the top boat to crush/grind/pulverize the solid material between the two boats. Then return the material to your Buchner funnel.
   - Chunks/blocks are a problem because contaminants (either amine or benzoyl chloride derivatives) may be entrapped and may not have any exposure/contact with the subsequent acid-water or base-water rinses that are intended to ionize and extract those impurities.
8. Wash repeatedly: with 2 x 10 mL of cold water, then 2 x 10 mL of HCl/water (to wash off unreacted amine).
9. **Recrystallize**, perhaps adding ethanol or water as necessary. A suggested starting point is 3mL of ethanol and 10 drops of water. But the solubilities will vary greatly from unknown to unknown, so you need to make whatever adjustments are appropriate for your particular sample. You shouldn't need these anymore, but several recrystallization reminders (read):

- Use a small Erlenmeyer (25 or 50-mL), not a beaker, to reduce solvent evaporation.
- Make all your adjustment decisions while the solution is boiling hot.
- Heating your Erlenmeyer in a hot-water beaker (150-mL) is convenient, to provide more even heating and to avoid overheating on the hot-plate surface.
- You and your hood partner should also warm up some ethanol in case you need to add some
- Other than when you're just starting, don't add cold solvents.
- During cooling, cover flask to avoid evaporation of the hot solvent.
- If no crystals form even after slowly cooling and then icing, try adding ice chip(s).
- If after chilling you seem to have no solvent, add some cold ethanol. You need solvent for the impurities to have a place to swim!
- Your rinse solvent should be similar to what you think your actual solvent blend is. But avoid water if possible so that your crystals will dry better.

Micro-Boiling Points in the Melting Point Apparatus (if you have a liquid unknown)

A microscale boiling point can be taken in a melting point tube that has an inverted "bell" in it. Add about 7 uL of liquid via syringe and tapping. 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, the liquid level should begin to drop (slowly at first, more rapidly the more "above" the boiling point you are.) Sometimes more rapid bubbling often takes place, but not always. 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. And in some cases, you’ll never see 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.

Amine Candidates

Bp of Starting Amines (Liquids)	Unknown	mp of Benzamide Derivative
48	Propylamine	84
55	Diethylamine	42
78	Butylamine	42
159	Dibutylamine (Bu_2NH)	oil
182-185	Benzylamine ($PhCH_2NH_2$)	105
184	Aniline	163
185	$PhCH(CH_3)NH_2$	120
196	N-Methylaniline ($PhNHCH_3$)	63
200	2-Methylaniline	144
204	3-Methylaniline	125
208	2-Chloroaniline	99
210	2-Ethylaniline	147
216	2,6-Dimethylaniline	168
218	2,4-Dimethylaniline	192
218	2,5-Dimethylaniline	140
225	2-Methoxyaniline	60
230	3-Chloroaniline	120

Mp of Starting Amines (Solids)	Unknown	mp of Benzamide Derivative
35-38	$PhCH_2NHPh$	107
41-48	4-methylaniline	158
49-51	2,5-dichloroaniline	120
52-55	Diphenylamine (Ph_2NH)	180
57-60	4-methoxyaniline	158
57-60	2-aminopyridine	165
58-66	4-bromooaniline	204
71-73	2-Nitroaniline	110
112-114	3-nitroaniline	157
115-116	4-methyl-2-nitroaniline	148
138-140	2-methoxy-4-Nitroaniline	149
148-149	4-Nitroaniline	199

Note: amines are hydrophilic, and tend to absorb some water from the air. Some of the starting amines may also have trace isomeric impurities. The result of moisture and/or impurities means that some of the starting materials may have melting points that are a little bit depressed.

Unknown Report Sheet-Amines

Unknown No. Name

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?

Solubility in HCl/Water: __________________

3. Boiling point or melting point for starting material: "Literature" value: (list, previous page)

4. Recrystallized Derivative

observed mp literature mp

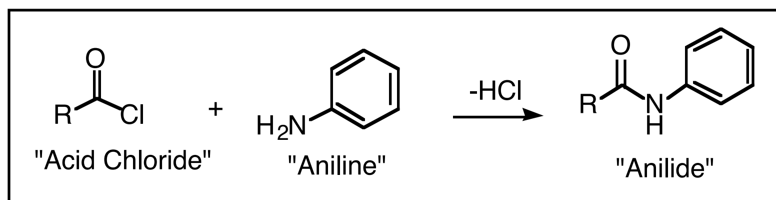
5. H-NMR (attach, with assignments/interpretation.)
   - **On the proton spectrum, create a standard 4-column summary table of your H-NMR data, detailing chemical shifts, integrations, and splittings, and "source" hydrogens.**
   - Draw the structure of your molecule, with identifiers by each carbon (a, b, c…).
   - Then on your standard summary table include a column in which you explain which "source" 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.
   - **Aromatic** H's: Do analyze aromatic H's for solid samples. For liquid samples with aromatics, the aromatic H's will have overlapping so won't be useful to detail.

6. What is My Actual Unknown? (Letter, Structure and Drawing of structure)

7. Comments, difficulties, complaints, etc..

CARBOXYLIC ACID UNKNOWN

A. Anilide Derivative



Place 10 drops (or 0.10 grams, if it's a solid) of the acid chloride into a large test tube. Add a stir bar, and add 1 pipet of ether. To this solution add 20 drops of aniline, dropwise (may spatter if you add it all at once) and stir for 1 minutes if it's not already solid. The primary precipitate that forms is the aniline hydrochloride salt. If your reaction is so exothermic that the ether boils away and you end up with an unstirrable solid, then add another pipet of ether.

After the one minutes is up, add 2 pipets of aqueous NaOH, and continue stirring for an additional two minutes. If some precipitate remains it is the derivative itself.

Use a long pipet to remove the aqueous layer from the bottom of the test tube. (Any unreacted acid chloride should be removed by the basic water.)

Then add 2 pipets of aqueous HCl, and stir vigorously.

Use a long pipet to remove the aqueous layer. (The aniline should be removed in the process.) Cool your solution in an ice-bath for at least a minute.

If you have a significant amount of precipitate at this point, it is the desired derivative. If so, then filter directly over a Hirsch funnel, after which you'll recrystallize the sample.

- However, if you *don't* have a significant amount of precipitate, call instructor over and/or skip down to the instructions in bold.

Assuming you did have a significant amount of precipitate, Recrystallize the crude derivative from ethanol. Ideal volumes will vary depending on your unknown, but a suggested starting point is 2mL of ethanol and 10 drops of water. But the solubilities will vary greatly from unknown to unknown, so you need to make whatever adjustments are appropriate for your particular sample. You shouldn't need these anymore, but several recrystallization reminders:

- Use a small Erlenmeyer, not a beaker, to reduce solvent evaporation.
- Make all your adjustment decisions while the solution is boiling hot.
- Heating your Erlenmeyer in a hot-water beaker is convenient, to provide more even heating than if you just stand it on a hot plate, and to avoid overheating on the hot-plate surface.
- You and your hood partner should also warm up some ethanol in case you need to add some
- Other than when you're just starting, never add cold solvents.
- During cooling, cover the flask to avoid evaporation of the hot solvent.
- Supersaturation is quite common. If you think you're at 50% water, probably stop and cool and see whether crystals will form.
- If no crystals form even after slowly cooling and then icing, try adding ice chip(s).
- Your rinse solvent should be very similar to what you think your actual solvent blend is.

If following the acid wash you do not have a precipitate (or don't have very much precipitate), then much/all of the derivative is dissolved in the ether. Add a boiling stick and heat your test-tube to boil off the ether, either with a heat gun or in a hot-water bath. place it in an ice-bath. (Maybe consult with the instructor for fast help.) The residue will probably then crystallize. If not, try to add an ice chip and scrape it with a rough stick. Whether it

actually crystallized or not, just recrystallize right in the large test tube. Start with around 1 mL of water. Heat it up in a hot water bath, and add as much hot ethanol as it takes to just barely get the product to just barely dissolve. Cool slowly, and perhaps stimulate crystal formation with an ice chip if necessary. Then harvest your crystals. Your wash solvent should probably be at least 50% water.

C. Titration/Neutralization Equivalence→Molecular Weight Determination

Weigh, as accurately as possible, around 200 mg (0.200g) of your acid into a 125 mL Erlenmeyer flask. Use the balance nearest the acetone-hood. (You want 3-4 significant figures after the decimal for this, so the other balances are unacceptable.) Pre-tare the flask, then add sample directly into the flask and record the mass to avoid inaccuracy. (Adding to a boat, recording, and then pouring into Erlenmeyer will introduce error.) Whether you have 200 mg or 220 or 180 doesn't matter, so long as you know exactly what your original mass is. Dissolve your material in around 25 mL of ethanol. [Logic: It is vital that the solution be homogeneous, so you need ethanol to keep it dissolved. But the indicator needs water to work right.] Add 2 drops of phenolphthalein indicator solution. Titrate the solution with _______ M NaOH. (Copy the concentration down from the bottle!)

Summary of titration logic: Molecular weight (or "formula weight", FW) is the ratio of mass per mole. Having weighed your acid, you know the mass very precisely; but how do you know how many moles? By titrating against the precisely standardized base! From the precisely known volume of base and the molarity of the base, you can determine the # of moles of base used. Since the mole/mole stoichiometry is 1 mole of base per 1 mole of acid, the # of moles of base tells the # of moles of acid. Knowing mass of acid and moles of acid, the ratio gives you the formula weight.

Note: Do your titration once, and check the molecular weight value with me. If you get within 5 g/mol, I'll tell you and you won't need to repeat. If you don't get within 5 g/mol, then you'll need to do it again. (Normally several repeats for reproducibility would be in order.)

Molecular weight calculations like this are not perfectly reliable (even if you calculate right!). In general an error of up to five grams/mole is acceptable. Logical reasons for errors are shown below:

- Reason 1: If you don't see the color change right away and "overshoot" the amount of NaOH added, you will have added more moles of NaOH than necessary. The calculation assumes that the number of moles of acid is exactly the same as the number of moles of NaOH added; but if you overshoot the NaOH, this won't actually be true. Your moles of acid will actually be slightly less than the number of moles of base. So when you are dividing mass of acid by moles of acid, you will have a slightly exaggerated number for the denominator. This will result in an underestimation of the grams/mole ratio, and will underestimate the actual molecular weight.
- Reason 2: Not all of the acids are perfectly pure. For example, if the solid sample is only 95% pure, this will cause an error in the calculation! Since acids are somewhat hydrophilic, it's not uncommon for acids to be somewhat wet and to give somewhat exaggerated molecular weight numbers.
-

Example of Molecular Weight Calculation:

Measured data:

- Weight of acid: 0.2015 g
- Molarity of NaOH: 0.1005 M
- Volume of NaOH to reach the titration end-point: 14.50 mL

Mathematical Calculation of Molecular Weight:

- Moles of NaOH $= (14.50 mL)\left(\frac{1L}{1000 mL}\right)\left(\frac{.1005 mol}{1L}\right)$ = 0.001457 mol NaOH
- Moles of acid = moles of base = 0.001457 mol acid

- Molecular weight of acid = $\dfrac{0.2015g}{0.001457mol}$ =138.3 g/mol

B. Melting Point/Boiling Point

If your carboxylic acid is a solid, take its melting point. If it is a liquid, take its micro-boiling point.

E. NMR ^{1}H will be useful. Don't bother with a ^{13}C NMR, since solubility will probably be too low to get anything worthwhile. The OH hydrogen is often very broad, due to H-bonding, sometimes so broad that you won't see it at all.

- 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.
- A carboxylic acid hydrogen will normally be invisible, so don't look for it. They are so broadened by hydrogen-bonding that they often just blend into the baseline. Even if you could see them, they appear down at 11-14 ppm, which is off-scale from our plots.
- Some solid carboxylic acids will have low solubility in CDCl3. If your sample is not completely soluble, you can run it anyway. But sometimes when there isn't that much sample dissolved, background lines from components in the CDCl3 solvent can be misinterpreted for real sample lines. The two most common candidates are a line at 0.00 ppm (tetramethylsilane) and a singlet at 7.26 (CHCl3). These two components are always present when you use CDCl3 solvent, but their height in a printed spectrum looks much taller relative to other signals if the real sample is very dilute versus if the real sample is more concentrated.

Carboxylic Acid Candidates

Liquid Acid Unknowns	bp of Acid	mw of Acid (g/mol)	mp of Anilide Derivative
Ethanoic Acid	118	60	47
Propanoic Acid	141	74	103
Butanoic Acid	162	88	95
Pentanoic Acid	185	102	63
2,2-Dichloroethanoic Acid	194	129	118
Hexanoic Acid	202	116	95
Octanoic Acid	237	140	57

Solid Acid Unknowns	mp of Acid	mw of Acid (g/mol)	mp of Anilide Derivative
Decanoic Acid	31-32	164	70
Bromoethanoic Acid	47-49	139	131
3-Phenylpropanoic Acid	47-49	150	92-98
2,2,2-Trichloroethanoic Acid	54-58	163.4	97
2-Chloroethanoic Acid	61-62	94.5	137
2-Butenoic Acid ($CH_3CH{=}CHCO_2H$)	71-73	86	118
2-Phenylethanoic Acid	76-79	136	118
3-Methylbenzoic Acid	108-110	136	126
Benzoic Acid	122-123	122	163
2-Benzoylbenzoic Acid ($PhCOC_6H_4CO_2H$)	127-128	226	195
Cinnamic Acid ($PhCH{=}CHCO_2H$)	133-135	148	153
2-Chlorobenzoic Acid	138-142	156.5	118
3-Nitrobenzoic Acid	140-142	167	155
2,2-Diphenylethanoic Acid	147-149	212	180
2-Bromobenzoic Acid	150	201	141
2,2-Dimethylpropanoic Acid	163-164	102	127
3,4-Dimethoxybenzoic Acid	179-182	182	154
4-Methylbenzoic Acid	180-182	136	145
4-Methoxybenzoic Acid	182-185	152	169-171
3-Hydroxybenzoic Acid	201-203	138	157
3,5-Dinitrobenzoic Acid	203-206	212	234
4-Nitrobenzoic Acid	239-241	167	211-217

- Note: Carboxylic acids are hydrophilic, and tend to absorb some water from the air. Some of the starting amines may also have trace isomeric impurities. The result of moisture and/or impurities means that some of the starting materials may have melting points that are a little bit depressed.

Unknown Report Sheet- **Carboxylic Acid**

Unknown No. Name

1. Physical Examination of Starting Material

   a) Physical State________________ b) Color_________________

2. Solubility Tests on Starting Material

Solvent:	Water	If Insoluble in Water, Does it Float or Sink?	Aq NaOH	Aq NaHCO
Solubility:	_______	___________________	________	__________

3. Melting point or boiling point for starting material: List value:

4. What is the approximate molecular weight (mw) of my sample, based on my titration?

   ____________ g/mol. (Attach a separate sheet that details your weights, calculation!)
   *Beware of ridiculous significant figures.

5. Derivative

	observed mp	literature mp
Crude (optional)		
Recrystallized		

6. H-NMR (attach, with assignments/interpretation. Do analyze aromatic H's)

- **On the proton spectrum, create a standard 4-column summary table of your H-NMR data, detailing chemical shifts, integrations, and splittings, and "source".**
- Draw the structure of your molecule, with identifiers by each carbon (a, b, c…).
- Then on your standard summary table add a "source" 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.
- Do analyze aromatic H's for solid samples. For liquid samples with aromatics, the aromatic H's will have overlapping so won't be useful to detail.

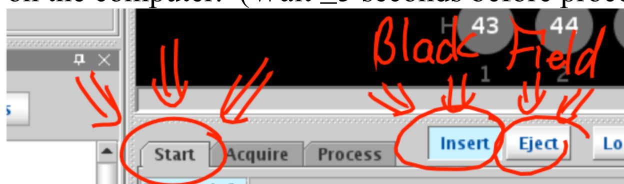
7. What is My Actual Unknown? (Letter and Draw Structure)

8. Comments, difficulties, complaints, etc..

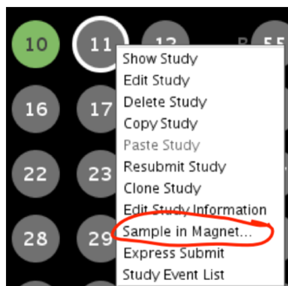
User's Guide to NMR, 2021 Without Autosampler: Draft 11/4/2025. Help: Dr. Jasperse, Hagen 407J, 477-2230

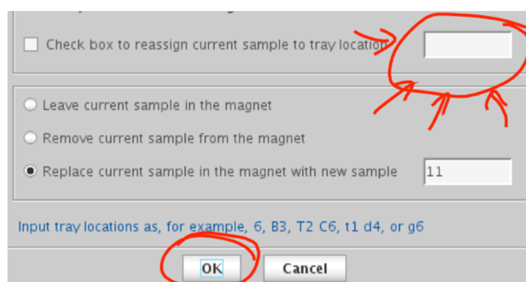
1. Prepare sample in lab; add sample to sample-holder; adjust sample depth using golden depth finder

2. Eject/Insert (Sample Exchange):
   a. Hit "eject" button (below black field) to eject existing sample. (If not visible, click "start" button to make it so)
   b. Manually lift out sample-in-sample-holder combination from the probe (place it in a box)
   c. Place your sample-in-sample-holder into the probe
   d. Hit "insert" button on the computer. (Wait ≥5 seconds before proceeding with step 3a).

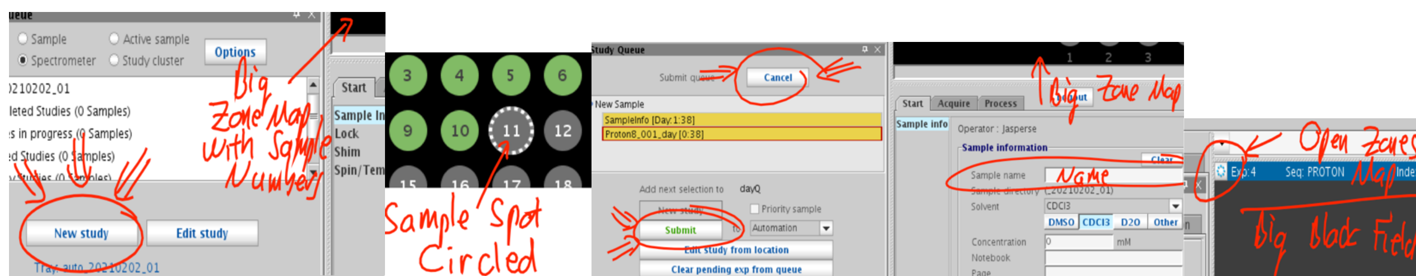


3. Spot Assignment: (Each sample needs to be assigned a sample spot number)
   a. Right-click on the lowest-numbered gray spot number in the zones map. (A pulldown will appear)
   b. Select "Sample in Magnet" (3rd line from the bottom of the pulldown);
   c. Enter your spot number into the upper field. (Remember your spot number)
   d. Hit OK.



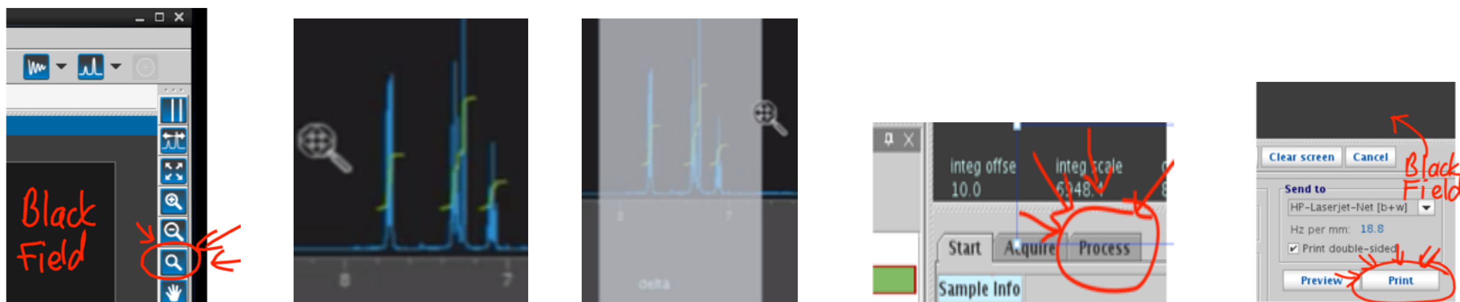


4. NMR-Experiment Submission:
   e. Click "New Study" button in lower left. (A yellow experiment file-name will appear).
   f. The default experiment is "Proton-8"; for something different select from panel on upper left.
   g. Left-mouse single-click on your sample spot. (A white circle will appear around the sample spot)
   h. Enter student name(s) into Sample Name field, which is underneath the black field
   i. Submit: click the green "Submit" button on the lower left side. (your sample spot should turn color)
   j. Hit "Cancel" to leave submit-sample mode.
      a. Don't forget to do this. If you do, it will cause problems for both you and the ensuing user.
      b. The yellow experiment file-name will disappear; unfortunately the zones map will too.
   k. Re-open "zones" map: Click on little circle icon ( ) to the upper left of the big gray/black panel, and the zones map with all the sample spot numbers should re-open.
      - Note: An experiment should take about 7 minutes.
      - There should be an automatic one-page printout upon completion.



5. **Printing an extra copy** of spectrum (in case you have a partner)
   - Must be in zones-map display. If not, click on little circle icon ( )upper left of the spectra-display panel.
   a. Right click on sample number, and a pulldown will appear
   b. Click "Show Study"
   c. **Double click** on green "PROTON_01" file that will appear in the lower left-hand area. (below your name)
      a. Your spectrum should now appear in the display field, where the zones-map appeared before
   d. Click "Process" button underneath the spectrum display field. ("Start" was highlighted previously)
   e. Click blue-text-on-white-background "Print" button on lower right to print another copy.

6. **Horizontal Expansions**
   a. Steps 5a-d above describe how to get your spectrum loaded into the display field.
   b. With spectrum displayed on screen, use a panel of display icons on the far upper right
   c. Click on the magnifying glass icon (6th icon down,)
   d. 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, then release the button.
      a. To return to the full display, you can either click on the 3rd icon ( ) or the 5th icon ( ).
   f. Click blue-text-on-white-background "Print" button on lower right to print a copy. (Twice for 2 copies)



7. **Exiting so that NMR is Ready for the Next user**
   a. Click "Start" button underneath the spectrum display field. ("Process" was highlighted previously)
   b. Re-open "zones" map: Click on little circle icon ( ) to the upper left of the big gray/black panel, and the zones map with all the sample spot numbers should re-open.

Summary of 1H-NMR Interpretation

I. Number of Signal Sets
II. "Chemical Shifts" of the Signal Sets

9's (9.0-10.0) — **Aldehyde** sp^2 hybridized C-H's

7's (6.5-8.4) — **Aromatic** sp^2 hybridized C-H's

5's (4.8-6.8) — **Alkene** sp^2 hybridized C-H's

3's (2.8-4.5) — **Oxygenated** or **Halogenated** sp^3 hybridized C-H's (halogenated and nitrogenated alkyl C-H's will also come in this window, although no candidates for today's lab). Oxygenated sp^3–carbons are routinely present for the following functional groups that contain oxygen single bonds:
- a. **alcohols**,
- b. **ethers**, or
- c. **esters**

2's (1.8-2.8) — **Allylic** sp^3 hybridized C-H's (sp^3 hybridized C-H's that has a double bond attached to the sp^3 hybridized C). Allylic signals routinely appear when one of the following double-bonded functional groups is present:
- d. **carbonyls**, (ketones, esters, aldehydes, acids, amides)
- e. **alkenes**, or
- f. **aromatics**

1's (0.7-2.0) — sp^3 hybridized C-H's, with **no attached Functional Groups**
- g. **Note:** Many molecules with non-functional alkyl portions will give a lot of signal in this area.

0-12 (anywhere!) — **Alcohol/Acid** O-H hydrogens (N-H hydrogens likewise)
- h. **alcohols**,
- i. **carboxylic acids**

1. Check each of the zones. Each one gives you a yes or no answer about the presence of absence of the featured group.
2. End-Check: Check that the functional groups indicated by your chemical shift information match with the structure you believe you actually have! If not, structure needs correction!
3. The regions are somewhat approximate, and have some spillover.
4. For multi-functional complex molecules, there are more complex ways for a C-H to come in some of the above window. For example, an sp^3-hybridized C-H with two attached oxygens can come in the 5's, or an sp^3-hybridized C-H that is doubly allylic can come in the 3's. In other words, the impact of functional groups is roughly additive.

III. Integration These **must be simple whole-number ratios** (2:1, 3:1, 3:2, etc..)

IV. Splitting
- ❑ **N-1 Rule: N lines ⇒ N-1 neighbor H's** (H's directly attached to carbons attached to the C-H group causing the signal)
  - The N-1 Rule is useful when working from spectrum to actual structure
- ❑ **N+1 Rule: N neighbor H's ⇒ N+1 lines**
  - The N+1 Rule is useful when working from structure to actual spectrum

Note: OH hydrogens don't participate in splitting (normally)

Summary of C13-NMR Interpretation

1. **Count how many lines** you have. **This will tell you how many types of carbons** you have. (Symmetry equivalent carbons can at times cause the number of lines to be less than the number of carbons in your structure.)
   a. Each "unique"carbon gives a separate line.
   b. Symmetry duplicates give the same line.
   c. If there are more carbons in your formula than there are lines in your spectrum, it means you have symmetry.

2. **Check diagnostic frequency windows** ("chemical shift windows") of the lines **to provide yes-or-no answers regarding the presence or absence of key functional groups** in your molecule.

220-160	C=O carbonyl carbons, sp^2 hybridized
160-100	C alkene or aromatic carbons, sp^2 hybridized
100-50	C-O oxygen-bearing carbons, single bonds only, sp^3 hybridized
50-0	C alkyl carbons, no oxygens attached, sp^3 hybridized

3. **Use DEPT and/or Coupled C13 NMR to Differentiate C, CH, CH2, and CH3 carbons**.

Type of C	Name	DEPT-135	Coupled C13
CH_3	Methyl	Up	Quartert (q)
CH_2	Methylene	Down	Triplet (t)
CH	Methane	Up	Doublet (d)
C (no attached hydrogens)	Quaternary	Absent	Singlet (s)

4. **Aromatics, Symmetry, and C-13 Signals**. Most aromatics have symmetry, and both the number of aromatic lines and the splitting of the aromatic lines can be indicative of the substitution pattern on a benzene. Mono- and para-disubstituted benzenes have symmetry.

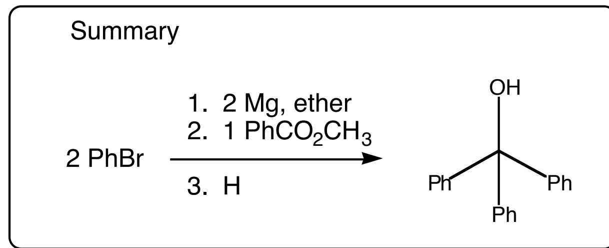
4 lines	s, d, d, d	Monosubstituted benzene. (Has symmetry)
4 lines	s, s, d, d	Para-disubstituted benzene. (Has symmetry)
6 lines	s, s, d, d, d, d	Ortho- or meta-disubstituted benzene. (Has no symmetry)

5. **Signal Height/Size**
   a. Carbons without any attached H's are short. This is common for carbonyls (aldehydes are the only carbonyl carbons that have hydrogens attached) and for substituted carbons in a benzene ring.
   b. Symmetry duplication multiplies signal height (if you have two copies of a carbon, the line will probably be taller than normal!)

Standard Synthesis Laboratory Report Format: The following layout is standard for a "synthesis reaction" report. Provide the parts and information in the sequence specified.

1. Title = Reaction Summary

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



2. Listing of all Chemicals Used

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

3. Calculation of Theoretical Yield

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

4. Writeup of Actual Procedure.

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

5. Product Analysis

- Any NMR, mp, bp, TLC information. For this report, mp and TLC information must be included.
- 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

Basic GC-MS Operation Compressed Draft 4 For Chem 355 Organic Unknowns Lab

Note: The following assumes the gc/ms program has been opened and warmed up; that an appropriate "method" and "sequence" have been selected; and that Jasperse will turn things off.

Sequenced Data Acquisition: Using the Autosampler to Sequence Runs Automatically

Note: this assumes that Jasperse has already prepared a "sequence", but you are trying to add your sample to the lineup.

- If you're first in line, get Jasperse to come and help. Or hit "OK" and "Run Sequence".

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 and is in the injector tray.)
    - 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 high 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: Data files are in a Data Folder, usually open on the left. Or, you can click "Data Analysis from the yellow panel on top of the GC software field.

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

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 5th Hammer button.**
    - Click the 5th hammer button 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….