**Syllabus**
**S42 Chemical Synthesis and Reactivity**

**Professors Rachel Narehood Austin and Jen Koviach**
**ST 2004**
**Dana 306 and Dana 219 (afternoons mostly)**

**Required Texts: ACS style guide and Advanced Practical Organic Chemistry**

In this course, you will learn the proper techniques in the following areas:

- Washing glassware
- Drying solvents – proper drying agent for which solvents, storing dried solvents
- Assembling glassware
- Glassware nomenclature
- Performing complex reactions – set up, monitoring, work-up, and purification
- Using Reference books
- Running NMR spectra and reporting peaks
- Running FTIR spectra and reporting peaks
- Operating a schlenk line – gas cylinders, vacuum gauges
- Running GC-MS and reporting peaks
- Using a fume hood
- Basic chemical safety
- Running UV-VIS spectra and reporting peaks
- Running X-ray crystallography and solving crystal structures
- Making conductivity measurements
- Running EPR spectra and reporting peaks

**Time commitments:** You are expected to commit from 9 am until 4 pm Monday through Thursday, and 9 am until noon on Fridays for the five weeks of short term for this course, although we anticipate that you will only spend approximately 25 hours per week in lab. Students must arrive in Dana 300 at 9 am every day unless they have made prior arrangements with the instructors, and return at 4 pm to fulfill lab duties. It is the responsibility of the student to plan his or her work schedule. Judicious time management can make the required work go faster, potentially freeing up some time during the short term. However, it is the student's responsibility to complete all required projects and to turn in all required lab reports.

**Grading:** You will receive a letter grade for your work in this course. That grade will be based on your work in the course and your lab reports. A lab report is required for each of the six experiments. Failure to hand in any of the six required reports will result in failure of the course.

When lab reports are written correctly, the student will receive full credit for the report. The report will be returned to the student ungraded until it is correctly written. Eighty percent of your grade will be based upon your lab reports (your grade for the lab reports will either be an A or an F). The remaining twenty percent of your grade will be based on class participation in group meetings, promptness in arriving to lab each morning, and efforts made in maintaining the laboratory space and equipment.

**Lab reports:** See Chapter 3 in your textbook for a description of the sections of a lab report. A sample lab report is included in this document. Lab reports should consist of a one paragraph abstract that summarizes what was done in the experiment and what was determined. The lab report should include schemes of compounds and reactions where appropriate, and compounds should be numbered. Schemes should be constructed in ChemDraw. The lab report should also consist of a detailed experimental section, written in the third person, past tense, following proper ACS style guidelines with all spectral data reported fully. Finally, where appropriate, the lab report should include a brief results section stating all results obtained. All lab reports must be handed in by the last Thursday of the semester, except for seniors who must have them in by the last Tuesday of the semester.

**Getting help:** We have a TA for the course who should be available to help you out. Jen or Rachel should also be available throughout the day. If you are having a problem, DO NOT address your questions to other staff or faculty members unless it is an emergency. Keep in mind that your classmates may be able to help too.

**Group meetings:** We will meet as a group at **3:00 pm on Thursdays in Dana 219** to discuss the articles you have read and to discuss any challenges students have encountered. We will rotate primary responsibility for leading these meetings through the class. Snacks will be provided.

**Course Schedule:** We have selected six different experiments that span a range of topics and techniques used for synthesizing molecules and characterizing their reactivity. We've put the two easiest syntheses first. However, you may use your own judgment in planning your work. You can do the experiments in the order you want. Also, we are willing to entertain proposals for other projects in lieu of those we've provided. If you want to do another project, you must be able to provide a literature reference that has a complete characterization of the product you intend to make and a full description of how to characterize its reactivity, if relevant. Any student proposals must be given to us for our approval by the first day of the second week of the semester.

**Lab Notebook:** Everything you do in lab should be recorded in your lab notebook. The notebook must be bound (not spiral bound or loose leaf) with numbered pages. Every experiment should start on a new page. See chapter 3 of your textbook for a very good example of a nice layout of a lab notebook.

**Lab responsibilities:** It is your responsibility to wash all your own glassware, to return all chemicals to the place they belong, to use all equipment properly and to leave it in the proper state at the end of the day. We will remind you once if you are not maintaining the lab properly. After the first reminder, further violations will affect your semester grade.

**Student Tasks:** Each week you and your partner will be assigned to a different task in the laboratory. Such assignments are typical of the way that research groups work. They help to share the responsibility of keeping a chemistry lab running smoothly. You and your partner must do your assigned task each day. Failure to discharge your responsibility will result in additional taks being assigned and/or a lowering of the grade. Many of these tasks will require that you come back to lab right at 4pm to make sure things are left appropriately at the end of the day.

Tasks:

1. Balances – make sure that all the balances are spotless at the end of every day
2. Hoods – make sure that the hoods are secured in proper condition at the end of every day. That means that sashes are pulled down, reactions are secured (water hoses are clamped on), flasks are covered (open flasks are not allowed to remain in hoods), excess reagents are put away, rotary evaporator traps are empty, rotary evaporators are turned off, vacuum pumps are turned off (unless otherwise arranged) and traps are emptied and lowered. Make sure that all unnecessary lights in lab are turned off too.
3. Hazardous Waste – check to make sure that hazardous waste logs are being filled in properly and that waste is being disposed of according to our rules. Make sure waste bottles are capped and are inside secondary containers. Fill out the daily inspection sheet. When waste bottles get full, fill out the hazardous waste label properly and give the waste bottle to Lorna or Gary or Mary.
4. Solution duty – make sure that all general laboratory solutions including TLC solvents and dipping solutions are kept stocked. When one runs low, make more.
5. General lab cleanliness – make sure that the lab is kept clean. Tables and benches should not be piled up with stuff.
6. Dishes – every person is responsible for washing his or her own dishes. However the group responsible for dishes will make sure that the base bath and nochromix bath are being treated with respect (nothing should be put in those baths until they have been washed thoroughly with soap and acetone and scrubbed). This group will also keep alconox solutions made up and keep the acetone containers filled. We will have acetone bottles in lab that we will use to refill our wash bottles and when those get low, Lorna or Gary or Mary should be notified. This group is also responsible for making sure that the acetone waste is properly disposed of.

# Laboratory Safety

Chemistry laboratories can be dangerous places. You can get hurt (badly) in lab if you do not work safely. Like many worthwhile technical activities (picture hiking on glaciers), the dangers are greatly minimized if you know how to work properly.

Below we've bulleted a few key safety facts you should always remember. After that we've included more information on some of the technical details of chemical safety. We've also included a handout from the American Chemical Society to help impress upon you the ubiquity with which chemists focus on safety.

1. Safety goggles must be worn at all times.

2. Smoking, eating, or drinking in lab is forbidden.

3. Know the location of the nearest fire extinguisher, safety shower, and eye wash fountain.

4. When a reaction is left alone for extended periods of time (6-8 hours), leave a note next to it indicating important facts for persons working in its vicinity. Condenser hoses should be wired on.

5. Know the physical, chemical, and toxicological properties of the reactants, products, and solvents used in each experiment. As mentioned above, any important safety information should be written in the lab notebook.

6. Know, and follow, proper disposal methods for chemicals.

7. Long hair should be securely fastened; open toed shoes are forbidden. Avoid wearing bulking or dangling clothes. Shorts are forbidden – legs should be covered.

8. Clean up the laboratory before you leave.
9. Wear gloves while handling chemicals; wash your hands thoroughly before leaving the lab.

10. Label chemicals if you pour them into unlabelled flasks.

11. Do not rush; do not take short-cuts. If you rush, at best you will get poor results. At worst, you will be a danger to yourself and those around you.

12. Fume hoods are a chemist's best friend but DO NOT ASSUME that they are always working. Always double check to make sure that a fume hood is sucking air from the room (and not just making loud noises)

13. If you have any questions or concerns about the experiment you are performing, ask the laboratory instructor.

More detail …

Keeping oneself free from injury relies on 1) avoiding risky situations and 2) minimizing risks. Working as a chemist does present risks but being knowledgeable can minimize these risks.

The first thing to do before entering into an unfamiliar work environment is to identify the potential hazards. Every laboratory will have slightly different hazards. In general, we can divide the hazards up into categories—hazards due to chemicals, compressed gases, glassware, and equipment. This lab will examine some of the hazards due to chemicals; background information included will examine the hazards associated with compressed gases.

The single most important thing that you can do to minimize your chance of injury is to be aware of your environment and to avoid doing anything until you are certain that you understand the consequences of your action. Never turn on a knob "to see what will happen." Understand completely what will happen before you turn on the knob.

Chemical hazards can be classified in a number of different ways. Generally strong acids and bases make up two categories. Materials that are highly flammable make up another category. Materials that are air or moisture sensitive make up a fourth category. Materials that are toxic or suspected to have chronic effects, often at low doses make up a fifth and sixth category. It is critical to appreciate that toxicological information is limited. For that reason it is prudent to treat all chemicals as though they are potentially toxic unless there is clear contrary evidence. **In order to safely work with any chemical, you must know the potential hazards of that chemical.**

**Acids**

Acids are corrosive. The potential hazard of a given acid depends on a number of factors including the strength and the concentration of the acid. While formal definitions of acid vary, most definitions incorporate the notion that an acid is either a proton donor (Bronsted acid) or an electron pair acceptor (Lewis acid). Developing an absolute ranking of acid strengths is exceedingly difficult. Strong acids are extremely reactive and readily lose a proton or gain an electron pair. Common examples of strong Bronsted acids that you will investigate are nitric acid ($HNO_3$), sulfuric acid ($H_2SO_4$), and hydrochloric acid (HCl). Examples of strong Lewis acids are $BF_3$•$OEt_2$, Ti(O*i*-Pr)$_4$, and trimethylsilyl triflate (TMSOTf). The proper handling techniques for strong Lewis acids is different than Bronsted acids, and can be found in the section on air and moisture sensitive reagents.

The vast majority of acids are weak and do not readily lose protons or gain electron pairs. Weak acids are commonly used in cooking. For example, vinegar is a 5% (by volume) solution of the weak acid, acetic acid ($CH_3CO_2H$), while citric acid is the weak acid that gives a tangy taste to lemons.

Many acids are used as solutions in water and the acid concentration is described using the term *molarity* (M), which is defined as the number of moles of a substance in a liter of solution. This description can be a bit confusing, however, because strong acids of the same molarity are much more reactive than weak acids of the identical molarity and therefore have greater corrosive effects. To predict the effect of an acid, it is necessary to know both the concentration and the extent to which it dissociates. It is important to remember, however, that the health risk that a given acid poses is not entirely a function of the strength of the acid. HF, for example, is the weakest of the binary halide acids, is extremely toxic. This toxicity is a function of other chemical characteristics of the acid.

**How to work safely with acids**

Because acids are corrosive to skin and clothing, it is most important that they be handled with care and kept off of the skin. If an acid does get on your skin of clothing, immediately flush the area with plenty of water and report the incident to your instructor. Note, however, that when an acid is added to a base or to water, the reaction will generate heat—take precautions! If acid spills on your lab bench, neutralize it with sodium bicarbonate ($NaHCO_3$). Household baking soda is sodium bicarbonate.

Always remember to add acid to water.
Always remember to add acid to base.

**Properties of strong bases**

Bases are the opposite of acids, they are proton acceptors or electron pair donors. Strong bases readily accept protons or donate an electron pair; weak bases are much less reactive. Many students think of a base only as something that contains an -OH group. This is not necessarily the case, however, since lithium hydride (LiH) and ammonia ($NH_3$) are both bases. Very strong bases include *n*-butyl lithium (*n*-BuLi) and diisopropyl amide. These bases should be handled as air/moisture sensitive materials. Common strong bases include sodium hydroxide (NaOH), potassium hydroxide (KOH), and barium hydroxide ($Ba(OH)_2$); most bases are however weak. Common examples of weak bases include ammonia ($NH_3$), which is the base present in dilute solution in household ammonia and sodium bicarbonate ($NaHCO_3$, baking soda). Like acids, the concentration of a base is measured in molarity (M) or, less often, in weight/weight percentage (%w/w). Once again a strong base of a given molarity is much more reactive than a weak base of the same molarity. To predict the property of a base it is necessary to know both the concentration and the proton affinity (for Bronsted bases).

**Oxidizing and Reducing Agents**

Strong oxidizing agents and strong reducing agents are also chemicals that warrant respect. An oxidizing agent is a substance that oxidizes something else; it is itself reduced. Likewise a reducing agent reduces something else; it is itself oxidized in the reaction. Household bleach (Clorox™), which is a dilute solution of sodium hypochorite, NaOCl, is a potent oxidizing agent. As mentioned previously, nitric acid and sulfuric acid are oxidizing acids. Thus, part of their reactivity is due to their ability to oxidize other substances.

**Air and Moisture Sensitive Reagents**

Many chemicals are reactive with oxygen or moisture in the air. Therefore, their exposure to the atmosphere must be minimized. Compounds that are highly air or moisture sensitive are typically handled in a glove box. We will not use any of these compounds. However, compounds such as *n*-BuLi, $Ti(O\textit{i}\text{-}Pr)_4$, and NaH must be treated carefully. Air sensitive liquids are typically sold in Sure-Seal™ bottles, which have a septum underneath the cap. Proper syringe techniques must be used to dispense these chemicals (syringe: pp. 89-90 of your textbook, cannula: pp 79-82 of your textbook). The air sensitive solids you will use may be weighed on the balance and quickly added to a reaction.

**Carcinogens and Other Chronic Toxins**

There are a whole host of chemicals that are potentially very harmful to humans for which no simple demonstration of their toxicity is possible. These are chemicals that generally act at low doses over a long period of time to change the fundamental biochemistry of the organism. While regulations designed to protect human health have spurred a great deal of research into the toxic effects of chemicals, a great deal of uncertainty about low-dose toxicity remains. For this reason, it is prudent to treat all chemicals with care and to minimize exposure to all chemicals. Volatile liquids and gases generally pose a greater health risks because routes of exposure are more available. Modern day chemical fume hoods are designed to limit exposure to safe levels. Still certain substances, e.g. known human carcinogens or viruses, are handled only in specially designed glove boxes. Halogenated organic solvents (e.g. methylene chloride) comprise a class of suspected human carcinogens to which you are likely to be exposed. Carcinogens are chemicals that can either bind directly to DNA, can be metabolized to a compound that can bind directly to DNA, or act in some other way to promote the cancer process once DNA has been altered. Because of the complexity of the human metabolic system, it is extremely difficult to predict how a particular compound will be transformed inside the human body. In addition, there are important differences between humans both in their metabolic systems and in their history of past exposures that make it even more difficult to predict how exposure to a particular compound will affect a particular person. Responses take many years to manifest, further complicating the situation. Therefore, the best laboratory techniques demand that every precaution be taken to minimize exposure to all chemicals, with particular care being given to organic chemicals that are in the liquid or gas phase. Make sure that the hood is sucking air out of the room. We have meters that are available to measure air flow (80-200 $cfmin^{-1}$ is standard). We also generally tape a small strip of kimwipe to the hood sash. If that is not being visible pulled into the hood, stop and investigate!

**Gloves**

Do not assume that putting on a pair of nitrile or latex gloves will protect you from all chemical risks. Gloves are manufactured to resist only certain hazards. Nitrile or latex gloves are generally good as serving as a barrier to common chemicals. However some highly toxic chemicals will quickly penetrate them and they are completely inadequate for strong bases and acids. Some people have allergies to latex gloves and should look for non-latex alternatives. It is also essential that you remove disposal gloves before leaving the lab. Do not touch door knobs or other commonly used parts of the building with gloved hands.

**Material Data Safety Sheets**

Material data safety sheets are required by law to be available to all employees who handle any chemical. They provide detailed information about hazards and chemical properties of substances being handled and should be read before one works with a new chemical for the first time. Do not assume that material data safety sheets are completely comprehensive. Not all chemical risks are known. Prudent practices are always warranted.

**Compressed gas cylinder**

A typical compressed gas tank comes with an on-off valve (main valve), a gas outlet device, and a safety seal or an emergency pressure release fitting that looks like a nut. Never tamper with this safety seal. The seal is designed so that if the pressure inside the tank exceeds the limit of the cylinder capacity, the seal will rupture, preventing explosion. Note that gas cylinders containing flammable gases such as $H_2$, CO, or methane come with special fittings having left handed threads. The connector for these gases can be recognized by V-shaped marking on the edges of the hexagonal nut. These unusual features help the users of these gases recognize that they must adopt utmost caution in the use of these potentially dangerous materials.

When using a large gas cylinder, always fasten the cylinder with a strap to a cylinder support, tightly secured to an edge of a working table. Never work with an improperly secured cylinder.

The main valve on a cylinder acts as an on-off valve, which when opened allows the gas to rush out from the cylinder. Note that the main valve does not provide a mechanism for the control of the pressure and flow rate of the gas. In order to control the pressure and flow rate of the gas, it is advisable to use some sort of gas control device, such as a pressure regulator. Depending on the nature of the work, one can use two kinds of regulators—a needle valve regulator or a single, two-stage pressure regulator.

A needle valve regulator is the least expensive type and provides for manual control of the gas flow. The needle valve is attached to the main cylinder valve. Such regulators are used only when the system to be flushed has an unobstructed outlet for the gas flow. Since needle valves do not control the pressure, their use in closed systems cannot be recommended. In the case of a compressed gas cylinder (e.g. with CO, $N_2$, and Ar which do not exist as liquids under high pressure), a needle valve cannot maintain a constant flow of the gas, because as the gas is used up, the pressure in the cylinder will gradually drop, resulting in a slow change of the outlet pressure of the gas. A continuous adjustment of the gas flow rate would be necessary.

In order to maintain $N_2$ or Ar flows, a good pressure regulator, which controls the pressure as well as the flow rate, must be used. There are two basic types of pressure regulators: two stage and single stage. Most pressure regulators incorporate two pressure gauges to monitor the pressures. If you stand facing the cylinders on the regulator, the right-hand side gauge is used for monitoring the cylinder gas pressure; the left hand side gauge is used for setting and adjusting the outlet pressure. Note that neither the regulator nor the gauges control the flow rate of the gases; flow rate is controlled by a needle valve situated at the outlet end of the pressure regulator.

The two-stage pressure regulator reduced the pressure in two steps prior to delivery. In the first stage, the high-pressure gas is automatically adjusted to a preset intermediate pressure range. In the second stage of the control system, the desired pressure is manually adjusted. The two-stage regulators are used when precise control of the pressure as well as of the flow rate is needed.

Single stage regulators have the same functions as the two-stage regulators. They regulate the pressure of the gas as well as the flow rate in one step, using a single diaphragm. Periodic adjustment of the pressure must be made to compensate for the decreasing pressure in the cylinder as the gas is continuously used up.

When a very dry and oxygen free environment is needed, additional pre-purification of a commercial gas is often necessary. Supporting copper or MnO are the most convenient solid oxygen scavengers used for removing oxygen from the commercial gas. Molecular sieves 4 or 5 Å (Linde type) are efficient desiccants for removing water. The inert gas from the needle valve outlet is passed through a desiccant column packed with molecular sieves, followed by a column containing the oxygen scavengers and finally through another column of molecular sieves.

A cylinder should never be emptied completely. When the pressure regulator reads approximately 25 psig or 2-atm of pressure, close the main valve, remove the pressure regulator, recap the head of the cylinder, and return it to the supplier for refilling. If the cylinder cannot be dispatched immediately for refilling, put an “empty” sign tag around the neck of the cylinder, and store it, belted securely, until its return.

**Examine a gas cylinder with a regulator in the lab. Be certain that you can identify the on/off valve, the regulator, the needle valve, the side gauge, the harness that holds the cylinder in place.**

# Waste Disposal Policies

Bates College Department of Chemistry strictly adheres to waste handling policies designed to keep us into full compliance with all EPA and OSHA guidelines. It is essential that these policies are followed. If you have any questions about them, please ask.

All hazardous waste must be stored in appropriate, sealed containers. Each container must be labeled with the words “Hazardous waste” and must be stored in a secondary waste containment vessel. Because much of the hazardous wastes we generate are volatile, waste accumulation areas are located in the fume hoods in each research and teaching lab. Generally, hazardous waste is separated into three types. These are: organic halogenated waste (any organic waste with any halogenated solvent. If you generate waste that has both methylene chloride and hexanes, for example, it must be placed in this container); organic non-halogenated waste; aqueous waste. Incompatible wastes such as strong acids and bases or strong oxidizing and reducing agents may not be stored together. Please ask if you have any questions about whether two wastes are incompatible or not. A record must be kept of everything that is placed in the hazardous waste container. These logs must be quite specific as to what is being placed in the container. Simply saying “aqueous waste” is not sufficient.

Here are a couple of common violations to be aware of. Liquid wastes must be kept capped. The fines for failure to cap wastes are quite high so remember to put the top back on the waste container after you use it. Liquid wastes need to be in the primary waste container and not spilled into the secondary container. Records need to be well maintained. Secondary containment needs to be in place at all times. Acetone is considered a hazardous waste and must be disposed of in hazardous waste containers.

**Weekly Planner**

Fill this out each week and give to us so we (and you) can know what you are planning to do each week. PLAN AHEAD!!!! Be sure you have all glassware clean and dry and all solvents distilled so you can begin your reaction when you intend to. Don't forget to order any chemicals you might need in advance – chemicals generally take 1-3 days to reach us. THINK AHEAD!!!!!!

| | MONDAY | TUESDAY | WEDNESDAY | THURSDAY | FRIDAY |
|---|---|---|---|---|---|
| **AM** | | | | | |
| **PM** | | | | | |

# Performing Reactions or experiments

Review chapters nine and ten of your textbook for a description of the general procedures for performing reactions. Read chapter 16 (Troubleshooting) which will help tell you what to avoid while performing reactions. Before performing an experiment, read the entire procedure. Make sure that you understand the entire procedure before beginning the experiment.

You must be able to answer all of the following questions before beginning:

procedure: Do you understand the entire procedure?

glassware: What size glassware should you use? Do you have all of the necessary glassware? Does it need to be oven dried before use?

other equipment: What other equipment do you need to use for the reaction? Do you need to dry other equipment (don't forget a stir bar!)

anhydrous/non-anhydrous conditions: Do you need to take special precautions to avoid moisture? Many reactions must be performed under an inert atmosphere ($N_2$ or Ar) with oven dried glassware.

reagents: Are all of the reagents available? Is each reagent a liquid or a solid? How much will you add? Do you need to take special precautions with any of the reagents?

solvent: Does your solvent need to be anhydrous? If so, can you buy it anhydrous or do you need to purify it before using it? If you need to distill the solvent, what will you distill it from (a list of drying agents for specific solvents is in chapter 5.4 or appendix 1 of your textbook) How much will you use?

temperature: Do you need to reflux or heat your reaction to a certain temperature? Do you need to cool your reaction to a certain temperature? A list of the temperatures of common slushes is found on page 162-163 of your textbook.

monitoring: How will you know when the reaction is complete?

quench/work-up: How will you quench the reaction? Do you need to take special precautions while quenching? How will you work up the reaction?

purification: How do you know if you need to purify the product? If you need to purify it, how will you do it?

characterization: What methods are necessary to characterize the product? Do any instruments need to be calibrated beforehand? Are there any other preparations necessary before a piece of equipment can be used (e.g. turned on, gassed ordered, buffers made, sample chambers prepared)?