SANFORD GROUP WELCOME KIT

Version 4.0

Guidelines, Procedures, & Requirements

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1. Laboratory Safety

1.1. General Considerations

1.1.1. Lab goggles/ glasses **MUST** be worn at all times while working in the lab! This is extremely important because even things that seem pretty common and safe (e.g., using the rotovap) involve placing glassware under reduced pressure, which can lead to implosions.

1.1.2. Do not wear gloves or your lab coat at your desk or in the group room.

1.1.3. Gloves can and should be reused if they are not contaminated. Just carefully remove them and place on your bench for reuse. Unless you are using highly toxic reagents (in which case you should throw out gloves after any chance of contamination – *see toxicity hazards section*), you should not have to use more than 2-3 pairs of gloves a day. Do not wash gloves with organic solvents (latex and nitrile gloves are permeable to acetone).

1.1.4. Know where all eyewashes are located in each lab.

1.1.5. Know where all safety showers are located in each lab.

1.1.6. Know where all fire extinguishers are located in the lab, what kind they are, and what they can be used for.

1.1.7. Nothing should be stored on the lab floors! Keep the floors free of anything other than lab stools and the 10 L LN_2 dewar.

1.1.8. Try not to work alone (especially late at night) in the lab (computer work is okay). This is particulary true if you are doing a large scale-up, running reactions with very reactive materials (*i.e.*, strong oxidants or reductapts, G

glass stopcock off, which may result in a cut to your hand. Remember rubber tubing is cheap, and it is meant to be cut when necessary.

1.3. Common Explosion Hazards

1.3.1. Oxidants in combination with organics can lead to violent exotherms/explosions. Before disposing of large amounts, think of what it may react with and when in doubt place in a separate waste container. Oxidants (*e.g.,* bleach, Cr^{VI} and Mn^{VII} salts, hypervalent iodine reagents, H_2O_2, etc) should be placed in separate waste from organic reagents/solvents.

1.3.2. Oxidizing acids (*e.g.*, nitric acid and aqua regia) can react extremely violently with organics (especially acetone), and the resulting explosions/release of corrosive solutions can lead to serious injury. Acids should *always* be stored in a **separate location** from organic chemicals. Additionally, waste bottles for acids should be clearly marked and placed in a **separate location** from organic waste. This will prevent mistakenly pouring acid waste in with organics (which is the most common cause of this type of explosion). **Aqua regia should not be used by students who have not be trained by the group safety officers on proper precautions for usage and disposal.**

1.3.3. Perchlorate salts can explode without warning, especially when concentrated in the presence of organics (once again, ClO_4^- is a strong oxidant!). Always use a blast shield when concentrating mixtures containing these salts and avoid the use of the ClO_4^- counter anion whenever possible.

1.3.4. Metallic lithium should **never** be placed in N_2 filled dry boxes or under a nitrogen atmosphere on your line. A violent and highly exothermic reaction will result from spontaneous "Li_3N" formation.

1.3.5. Remember that something as common as flash chromatography columns are run under high pressure and can crack/explode unexpectedly.

1.3.6. The condensation of liquid O_2, liquid N_2 and solid Ar in traps on your vacuum line can lead to explosions. *See the vacuum line safety section for further details*.

1.4. Toxicity Hazards

- Thallium salts (*e.g.,* TlOEt).
- Alkyl mercury salts (*e.g.,* $HgMe_2$).
- Tin reagents (especially tetra-alkyl or tri-alkyl aryl Sn compounds).
- Alkylating agents (*e.g.,* MeI).

1.4.1. Exercise extreme caution when using these reagents!! Clean up spills in your hood and in public areas (balances, dry boxes, etc) immediately using appropriate procedures, and dispose of cleaning supplies/gloves in solid waste containers beneath the hood (to avoid fume inhalation).

1.4.2. Dispose of gloves (in solid waste container beneath the hood) whenever you may have come in contact with these reagents.

1.4.3. If any of these compounds are used in the dry box, be sure to (i) use a secondary pair of gloves so as not to contaminate the main gloves, (ii) dispose of all contaminated waste in a separate Ziploc bag before removing it from the box, and (iii) purge the box after the use of these compounds (and before opening the antechamber).

1.4.4. For specific instructions on how to wash glassware that has contacted these reagents, speak with Melanie directly.

1.5. Disposal of Pyrrophoric Materials

1.5.1 Pyrrophoric materials from commercial sources (*e.g,* alkyl lithium reagents, Grignard reagents) that are still in their bottles can be given to chemistry waste disposal (Laurie) without quenching if they are still in their bottles. This is the safest way to dispose of these reagents.

1.5.2 If you are quenching pyrophoric materials before disposal, you should do so with *EXTREME caution!* Remember that one mistake can be catastrophic and literally burn down the lab and injure a large number of your colleagues (and yourself!). The following general procedure should be followed – *WHEN IN DOUBT CONSULT MELANIE OR THE GROUP SAFETY OFFICERS – Tom Lyons and Kara Stowers – before doing anything like this!*

a) **Locate the appropriate fire extinguisher in the lab before starting this procedure *and be sure that you know how to use it.* Do not be complacent.** Fires can result even if you have done the same procedure 99 times before. **PLEASE NOTE THAT A SPECIAL FIRE EXTINGUISHER IS REQUIRED FOR FIRES INVOLVING PYROPHORIC MATERIALS!! Know the proper fire extinguisher – this could literally be a matter of life and death!**

b) Clear your hood **and the area around it** of all flammable solvents (wash bottles, flasks containing solvent, solvent bottles, etc). These can catch on fire very easily and turn a small containable fire into an extremely dangerous fire.

c) Clear your hood and **the area around it** of any paper materials – this includes Kimwipes, paper towels, etc. Again, these can catch fire easily and turn a small fire into an uncontainable one.

d) Place the flask containing the material to be quenched into a secondary container. This is important because if your flask breaks (which can easily can happen from vigorous stirring) the pyrophoric material will be contained.

e) Suspend the pyrophoric material in hexanes or some other inert solvent if there is not solvent in there already.

f) Fit the flask with a ***large*** reflux condenser (and put the N_2 inlet on the top of this). This serves two purposes – (i) it provides additional headspace for when H_2 gas is generated in the quenching process and (ii) limits exotherms in the quenching process by allowing for the solvent to reflux (thereby cooling the mixture).

g) Fit the condenser on the flask containing the material to be quenched with a N_2 inlet and a vent. *An N_2 atmosphere is important for safely quenching these materials because fires are caused by the highly exothermic reaction of H_2 with O_2 in the presence of heat and a flammable solvent.* Without O_2 a fire is unlikely – although dangerous exotherms can occur which can explode your flask and/or make the pyrophoric materials shoot out uncontrolably, *so be sure to have adequate ventilation and ADD THE QUENCHING AGENT EXTREMELY SLOWLY!!!*

h) Add MeOH to this mixture ***SLOWLY*** over the course of hours/days. When in doubt about the proper rate of addition, go slower.

i) Keep in mind that metals (Na, K, Na/K) get an oxide coating around them in the quenching process. As a result, there may still be some metal present even after several hours/days stirring in the presence of MeOH. After several days, it is usually safe to add H_2O slowly to quench the final material. But again, use caution – and do not do this until there are not noticeable large chunks of metal present.

2. Vacuum Line Procedure—Using the Vacuum Line

You will receive thorough training on vacuum line technique by Melanie and/or a trained group member before using your line. However, remember that many of the techniques

involved can be confusing, and the consequences of making a mistake can be very dangerous as well as costly. Therefore, if you are ever in doubt about how to do something, please be sure to ask Melanie before proceeding.

2.1. The following are references that contain a lot of useful information on almost all aspects for Schlenk and high vacuum technique (i) **Experimental Organometallic Chemistry**, Andrea L. Wayda and Marcetta Y. Darensbourg, Eds., American Chemical Society: Washington DC, 1987. (ii) **The Manipulation of Air Sensitive Compounds**, D. F. Shriver, Robert E. Krieger Publishing House: Malabar, FL, 1982.

2.2. Argon is a solid and N_2 is a liquid at LN_2 temperature (–195^{o}C). Therefore, it is extremely dangerous to p

2.9.4. If not being used, the traps should be taken down at the end of the day, and the remaining LN_2 should be returned to the group 10 L dewar.

2.9.5. Before putting traps back up, be sure that they are completely free of solvent (if necessary place them in the oven for 15-30 minutes before proceeding).

2.10. Pumps and Pump Oil

2.10.1. Pump oil should be changed three times a year – in December, April, and August. This will typically coincide with group clean up days (*see group clean up section*). It is your responsibility to keep your pump clean (by avoiding contamination with solvents) and to change your pump oil on a regular basis. Remember, a clean pump will work smoother, longer, and most importantly it will pump down faster.

2.10.2. For problems with your pump (poor pump performance, leaking, strange noises, etc), immediately shut it down and talk to Melanie in order to diagnose the problem.

2.10.3. Familiarize yourself with your pump by reading the operating manual. This will be extremely helpful when it comes time to change your pump oil.

3. Cleaning Glassware

***Note**: Although it may not seem that important, cleaning glassware is one of the most important tasks that you will do in lab – contaminated glassware (along with contaminated solvents) are the two biggest causes of reactions going bad!*

3.1. General Group Glassware

3.1.1. Rinse out flask into organic waste to remove organic material by washing with a H_2O-miscible organic solvent like acetone, MeOH, or THF, depending on solubility.

3.1.2. Thoroughly clean grease off of all joints with hexanes and a Kimwipe.

3.1.3. Scrub both the interior and exterior of the flask vigorously with a washing brush and soap/warm water to remove salts and remaining residues.

3.1.4. Glass and Teflon stopcocks should be removed from joints before cleaning. They are easily damaged by small particles such as salts and the stopcock bore tends to hold up liquids.

3.1.5. Rinse flask with warm water (at least 2-3 times) and with distilled water (at least 2-3 times) to remove all soap/residues.

3.1.6. Finally, rinse with a small amount of acetone and place on the drying racks.

3.1.7. If glassware remains visibly dirty after this procedure **DO NOT** leave it one the drying rack for someone else to take and use!! ASK Melanie about the best way to get it clean – this will usually entail either placing it in the base bath and/or washing with strong acid (*e.g.* conc. H_2SO_4, HNO_3) to remove residual metal salts.

3.2. Frits

3.2.1. Rinse your frit with solvents in which the solids on it are soluble. Typically this would involve MeOH followed by acetone then EtOAc then CH_2Cl_2. Then, turn the frit upside-down and rinse with these solvents a second time.

3.2.2. Note that aqeous washes (*i.e.,* those with bleach/water/acid/etc) are sometimes necessary to remove toxic reagents like Sn and/or other reagents that are soluble in these media. However, these washings need to be separated from the organic washings, and disposed of separately (*see waste section*). Also, washes with H_2O and/or aqueous solutions should be followed by copious rinsing with MeOH before the introduction of immiscible organics like CH_2Cl_2 or hexanes.

3.2.3 If residue remains (especially metal-based residue) it can often be removed by placing 50% conc. HCl and 50% MeOH in the frit and allowing it to drip through slowly, followed by rinses with HCl, H_2O and MeOH.

3.2.4 If *any* particulate matter remains on the frit and/or it is not completely white, you should place it in one of the bucket in for cleaning with piranha solution (conc. H_2SO_4/H_2O_2) or aqua regia (HCl/HNO_3). However, YOU MUST COMPLETELY REMOVE ORGANIC SOLVENTS from the frit before subjecting it to piranha solution or aqua regia (highly oxidizing!). So, rinse the frits with MeOH followed by copious water before placing them in the bucket

3.3. NMR Tubes

3.3.1. Rinse the contents of your NMR tubes into organic (or aqueous) waste (depending of the contents of the tube).

3.3.2. Rinse tubes at least one to two more times with a wash bottle into your waste before using the NMR tube cleaner. These steps are important to avoid excessive contamination of the NMR tube cleaner with everyone's samples.

3.3.3. Note that you should never stick the tip of a wash bottle into an NMR tube to wash it out. This will inevitably lead to breaking the end off the tube. Instead, always hold the bottle several cm away from the end of the tube to spray the solvent in.

3.3.4. If solids/precipitated metals remain in the tube at this point, clean it out with some solvent (typically acetone) and a pipe cleaner.

3.3.5. Use the NMR tube washer to finish cleaning the tube. Typical solvent rinses might involve MeOH followed by acetone, then EtOAc then CH_2Cl_2.

3.3.6. Note again that aqueous washings (*i.e.,* those with bleach/water/acid/etc) are sometimes necessary to remove toxic reagents like Sn and/or when the reagents used in NMR experiments are soluble in these media. However, these washings need to be separated from the organic washings, and disposed of appropriately (*see waste section*). Also, washes with H_2O and/or aqueous solutions should be followed by copious rinsing with MeOH before the introduction of immiscible organics like CH_2Cl_2 or hexanes.

3.3.7. Place NMR tubes flat in the oven to dry. However *do not* leave them in the oven for more than ~6-8 hrs (after which they should be placed in a dessicator for storage). Leaving the NMR tubes in the oven for longer than this can lead to warping, which may cause problems with spinning, shimming and/or result in breakage in the NMR instruments.

3.4. Syringes/Needles

3.4.1. **ALL** syringes need to be cleaned directly after use! This prevents them seizing up or clogging (often irreversibly) with dried out residues. Additionally, these expensive pieces of glassware are in limited supply and are shared between many co-workers.

3.4.2. Clean gas-tight syringes by rinsing them 2-3 times with 3-4 different solvents. Typically this would include MeOH, acetone, EtOAc, and CH_2Cl_2.

3.4.3. Gas tight syringes should be placed in the oven after cleaning *without their plungers* for 3-4 hrs. Longer times in the oven can lead to cracking and/or damage to the syringe. They should then be placed in a dessicator. Plungers should be wiped off and placed directly into a dessicator after cleaning. This prevents irreversible expansion/contraction of the plunger from repeated heating/cooling cycles.

3.4.4. Non-disposable needles should be rinsed thoroughly using the aspirator vacuum needle cleaner with appropriate solvents (depending on what you used, typically MeOH followed by acetone then EtOAc then CH_2Cl_2 followed again by acetone).

3.4.5. Once again, note that aqueous washing of both gas tight syringes and needles (*i.e.,* those with bleach/water/acid/etc) are sometimes necessary to remove toxic reagents like Sn and/or when the reagents used are soluble in these media. However, these washings need to be separated from the organic washings, and disposed of appropriately (*see waste section*). Additionally, washes with H_2O and/or aqueous solutions should be followed by rinsing with copious MeOH before the introduction of immiscible organics like CH_2Cl_2 or hexanes.

4. Glove Box

4.1.1. You must be checked out by **Andrew Higgs** or **Nick Ball** on the glove box before using this piece of equipment. She will give you a handout with general procedures and rules for the use of this instrument.

5. Dri-Solv System

5.1. Dispensing solvent into group solvent bulbs (you should be trained by **Matt Remy** before using this system):

5.1.1. Attach flask to your vacuum line (***use only Teflon – Krytox – grease***). Evacuate bulb completely (<10 mbar) and refill with N_2. Repeat 3 times. On final cycle leave the flask under vacuum, and close Teflon stopcock.

5.1.2. Attach bulb to solvent system. Evacuate and refill the head space (between Teflon stopcock and 24/40 adapter) 3 times (by turning the valve to "evacuate" followed by "refill"). You should evacuate for ~ 30 s per cycle. On final cycle leave head space under vacuum and turn valve to "closed" position.

5.1.3. To dispense solvent, open solvent valve (upper valve) to "open" position

5.1.4. Use the metering valve (the one that turns) to dispense solvent carefully into flask.

5.1.5. When complete, close metering valve and solvent valve, and then close Teflon stopcock on your flask.

5.1.6. Use "refill" valve to refill line with N_2 and remove your closed flask.

5.1.7. Flush line with N_2 for ~ 1 minute to remove most residual solvent.

5.1.8. Cap the line with a yellow plug.

5.1.9. Fill the trap (on the left of the system) with dry ice/i-PrOH, and evacuate using "evacuate" valve.

5.1.10. After 5 min of evacuation turn "evacuate" valve to "closed".

5.1.11. If any solvent has condensed in the trap, close off the pump and vent the system (using the three-way valve hanging next to the pump). Allow trap to warm and then empty contents. Then place system under vacuum again.

5.2 Dispensing solvent into round bottom flasks/reaction vessels:

5.2.1 If you reaction requires dry solvent, but is not extremely sensitive, you can dispense directly into the round bottom flask. In this case, simply place the flask below the spigot, and turn on the solvent flow.

5.2.2 When solvent dispensing is complete, purge out the line with N_2 (using "refill" valve) for ~ 1 min. Then carry out steps 5.1.7 to 5.1.11 above.

6. GC/GCMS and HPLC

6.1. Everyone must be trained by **Lopa Desai** or **Joy Racowski** before using the GC and by **Tom Lyosn** before using the GCMS.

6.2. Everyone must be trained by **Kami Hull** or **Kara Stowers** before using the HPLC.

7. Triannual Group Cleanup

7.1 More in progress.

8. Lab Notebooks

8.1. Maintaining a clear, well organized, and up-to-date lab notebook is critical for (a) keeping track of your experiments for your thesis, (b) any publications/ patents that you will write and (c) enabling future generations of students to reproduce your work.

8.2. General instructions for keeping a lab notebook are as follows.

8.3. Skip 3-4 pages in the beginning for the Table of Contents and update the TOC regularly (monthly, at least).

8.4. Use only non-erasable ink in your notebook.

8.5. Write the reaction/experiment clearly at the top of each page. If you are following a published procedure, indicate the reference from which the procedure was obtained.

8.6. Make a table including each reagent, it's molecular weight, the measured quantity – g (or mL), mol, and eq – used in the reaction, and the commercial source/purity of the reagent.

8.7. Write a detailed experimental, including the rate/order/time/temperature of addition of each reagent and solvent, and, where appropriate, any color changes that take place during the reaction. Also, detail all work up procedures and TLC data (where appropriate) for the reaction.

8.8. Be sure to weigh the product and determine the % yield for all reactions!!

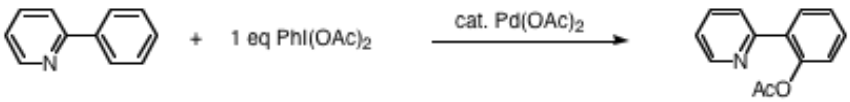
8.9. NMR spectra should be saved and labeled according to the notebook number, page, and sample they refer to. For example, 1mss23.007 would refer to Melanie S. Sanford notebook #1, p. 23, sample #7.

8.10. Everyone is responsible for backing up their data on Zip disks or CD's.

8.11. A sample lab notebook page is shown below.

9. Sample Notebook Page

Date: 9/14/2004



Chemical	Source	Mol. Weight	mmol (Eq)	Amount
$Pd(OAc)_2$	Pressure	224 g/mol	0.064 (0.05 eq)	14 mg
2-phenylpyridine	Aldrich	155.20 g/mol	1.29 (1 eq)	200 mg
$PhI(OAc)_2$	Acros	322.10 g/mol	1.29 (1 eq)	415 mg
AcOH (solvent)	Fisher			8 mL

Procedure

• $Pd(OAc)_2$, $PhI(OAc)_2$ and 8-methylquinoline were placed in a 20 mL vial in that order. Acetic acid (8 mL) was added. Mixture is a clear suspension with yellow solids at bottom of vial.

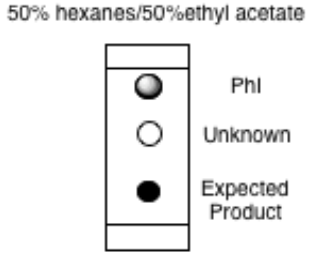
• Placed in oil bath at 100ºC and heated for 1 hr. After 5 min, color changes to black.

• Removed vial from bath and allowed to stand at 5 min at room temperature. Opened and removed ~10 mL for GC analysis.

• GC (GC1, mss short method) shows 8% starting material (retention time 4 min) and 80% of a new peak at 6 min. Other unidentified peaks were observed at 7 and 9 min (5% each). **GC labeled 1mss27.001**. (Notebook 1, mss, page 27, 1st spectrum obtained)

• Rotovapped vial to dryness. Some of the material bumped into the rotovap trap. Recovered material by rinsing the trap with acetone (3 x 5 mL). Some remained stuck in the rotovap trap.

• Dissolved reaction mixture in methylene chloride. Ran TLC's in 40%/60% and 50%/50% and 60%/40% hexanes/ethyl acetate. Optimal conditions were 50%/50% hexanes/ethyl acetate (product rf ~ 0.2).



• Mistakenly dropped vial on bench and spilled approximately 1/4 of material. Yield is expected to be low as a result.

• Rotovapped to dryness and redissolved in 50% hexanes/50% ethyl acetate

• Loaded onto silica column (50 g silica, wet-packed in 50%/50% hexanes/ethyl acetate), and collected 100 fractions. Every other fraction was TLCed and fractions 7-9, 11-14, and 32-47 (each of the three spots were

collected and rotovapped to dryness. Obtained 114 mg of fractions 7-9, 10 mg of fractions 11-14 and 212 mg of fractions 32-47.

• GC's of each set of fractions were obtained: Fractions 7-9: 1mss27.002; Fractions 11-14: 1mss27.003; and Fractions 32-47: 1mss27.004. Each appears to be pure.

• ^{1}H NMR spectra of each fraction was obtained in $CHCl_3$. Fractions 7-9: 1mss27.005; Fractions 11-14: 1mss27.006; and Fractions 32-47: 1mss27.007.

Conclusions from ^{1}H NMR and GC analysis:

Fractions 7-9 are iodobenzene with some other solvent impurities.
Fractions 11-14 contain aromatic and aliphatic peaks. Need to do more analysis to figure out what this is.
Fractions 32-47 are the expected product. No solvent is present.

Molecular weight of product:	213.2 g/mol
Amount Expected:	275 mg
Amount Obtained:	212 mg
% Yield:	77% yield

10. General

9.1. Please notify Melanie if you will be out of town for one working day or more.

9.2. Weekly group meetings will be held at 7 pm on Thursday nights – please notify Melanie if you cannot attend for any reason.

9.3. It is important to keep up on the current literature in organic and organometallic chemistry – particularly as it relates to your project. Additionally, you will periodically be asked to choose a paper from the current literature to present in group meeting. The following are journals that you should read each week and are appropriate sources for group meeting papers:

J. Am. Chem. Soc.
Organometallics
Org. Lett.
J. Org. Chem.
Angew. Chem., Int. Ed.

*Note that reading the literature is critical not only to learn more about your project/area of research but also to get you prepared for upcoming seminar speakers, proposal writing, orals, local and national ACS meetings, cumes, writing your own papers, and ultimately getting a job!

9.4. General tips for reading the chemical literature:

9.4.1. You cannot expect to read everything.

9.4.2. Try to read papers that are (i) the most interesting to you and (ii) the most relevant to your and the group's research projects.

9.4.3. No one has time to read the entire text of every article. Read the abstract and introduction and then try to discern the major point of the paper from the Figures and Schemes. If you find something especially interesting or unclear consult the text for further details. Keep in mind when writing your own papers that these are the sections that are usually the most read.

9.4.4. Whenever possible, discuss with others what you have read! This will solidify your general knowledge as well as improve your understanding of what you have read.

9.4.5. Take particular note of papers that describe selective reactions. These are the most useful in synthetic chemistry and the most difficult to find by traditional searching techniques.

9.4.6. Keep an eye out for molecules that could be assembled using the methodology that you are developing. This will be helpful for those of you who are interested in applying methodology in total synthesis, as well as for writing proposals.

9.5. Other journals to keep an eye on (monthly) are:

Tetrahedron Letters
Tetrahedron
JCS, Perkin 1
JCS, Dalton Transactions
Chem. Comm.
Chem, Reviews
Acc. Chem. Res.
Synlett

9.6. <u>Expectations for rotation students:</u> As a rotation student, you should plan to work at least 20 hrs per week in lab. (A typical division of labor would be ~20 hr/week for classes, ~20 hr/week on teaching and ~20 hr/week in lab). Although this time may be somewhat broken up between days, night, weekends, weekdays, etc, it should hopefully give you enough time in lab to get a substantial

amount accomplished during your rotation. Obviously, the more that you work above and beyond these hours, the more you will be able to accomplish over the semester. At the end of the semester, you will present a group meeting presentation on your research. Also, in addition to the fact that I'll be around lab helping out much of the time, we will each have formal meetings every week to discuss your week's accomplishments/next weeks plans for research.