

# **Woerpel Group Survival Manual**

**04/11/03**

## Notes on Personal Safety

- A copy of the UCI Environmental Health and Safety Chemical Hygiene Plan is located in a white binder in the clean room above the small food refrigerator. Use it as a resource for specific safety, chemical storage, and procedural information. Everyone should peruse it at least once, and a periodic refresher wouldn't hurt.
- Although we often avoid wearing the proper protective equipment, it is *strongly* advisable to do so. The level of personal protection employed should be commensurate with the hazards involved. Safety glasses with side shields are the norm, but they will not adequately protect you from liquids or flying objects coming at you from an oblique angle. Double or even triple-gloving is common when working with particularly toxic or caustic reagents.
- Because of the potential for situations to escape our control, it is imperative that any extremely hazardous procedure be carried out with the utmost care according to well-established and practiced methods. For this reason, one should NEVER work alone. If no one is in your lab, go next door or across the hall and make them aware of your presence. Check up on one another periodically. Exercise common sense at all times. A weary or distracted mind leads to mistakes.
- Be cognizant of the safety-related items in your lab and in other labs near you. Familiarize yourself with the contents of our first aid kits in case you ever need to use them. Replace items immediately upon usage so they may be available in the future. There are eye-wash stations in every sink and attached to both safety showers in our hallway (located outside room 5004 and across the hall between rooms 5012 and 5024). Kits are available for common chemical spills and for mercury spills. Know their location, their contents, and how to use them.
- **\*KEY\***: Older students are ALWAYS available for consultation on any lab matter and especially with issues of safety. No one is ever unapproachable.

## Notes on Group Safety:

### Chemical Waste:

- Proper labeling, handling, and storage of chemical waste is crucial. Labeling has been made simpler due to recent adoption of the one label per bottle protocol. Each label must list the exact date when the waste was first generated. Waste carboys (5 gal) must always reside in secondary containment bins, and we will eventually have a large flammable cabinet explicitly for storage of these containers. Small (4 L) bottles of liquid waste stored in the fume hood or bench top must also have secondary containment and be capped when not in use (this is the most forgotten rule). Extremely hazardous waste (e.g. chromium, tin, lead) cannot be kept longer than 9 months. Accumulation of group chemicals in fume hoods or on bench tops is discouraged.

Avoid pouring anything down the drain you wouldn't store in your refrigerator. Polluting the environment in this fashion and, likewise, consciously permitting hazardous liquids to evaporate in the fume hoods, is illegal. Throwing chemicals or needles into the trash is strictly prohibited. Utilize the solid waste and sharps containers, respectively, for these materials. Be conscious of where waste goes when it is disposed of improperly.

#### Compressed Gas Cylinders:

- ALL cylinders must be secured with chains in a wall-mounted bracket unless they are currently being moved to a place where they eventually will be chained. We are in the process of maximizing the amount of wall-brackets/chains in the hall closets. Excess cylinders cannot merely be buttressed against chained ones or against walls. If we do not have a bracket to accommodate a cylinder, we should not have that cylinder. Cylinders only become dangerous when they are punctured or if the top is removed. These situations are most likely to occur when a cylinder falls, which is most apt to happen when it is not properly chained (*vide supra*).

#### Cleanliness:

- Keeping personal and common work areas clean and uncluttered is beneficial to the work environment. In addition, general cleanliness decreases the amount of potential safety hazards. We can be cited by the EPA for operating in an excessively cluttered or dirty workspace. Periodically police your area and others' as well.

#### Security:

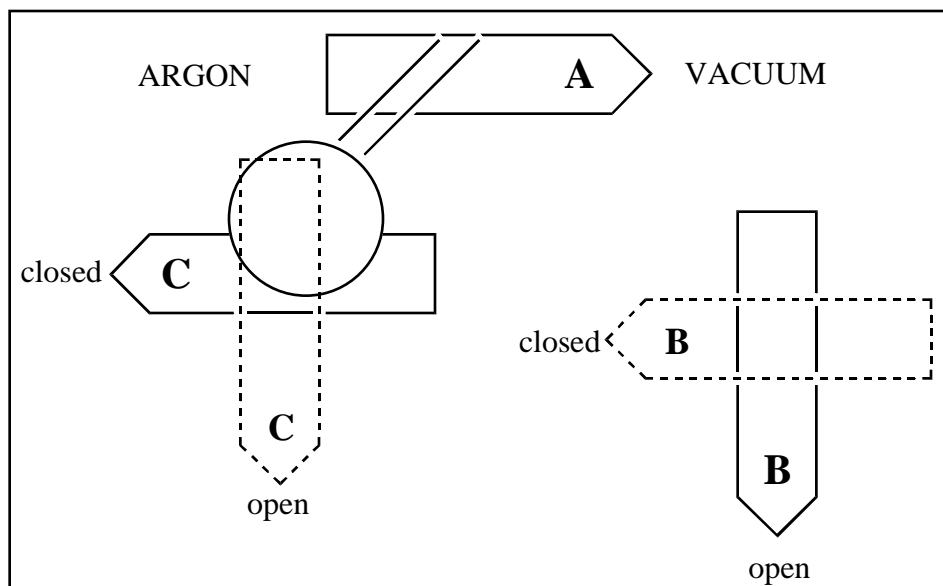
It should be common sense, but maintain vigilance for suspicious persons or activities operating in and around the lab and building. Persons who would not ordinarily belong in a research lab should immediately identify themselves. Even EPA officials cannot enter the labs without EH&S accompaniment.

#### Other:

Technically speaking, bicycles are not to be kept in the research labs because they are a trip hazard and may block a potential escape route. We may be cited for disregarding this minor issue.

As safety-related issues arise, feel free to ask any colleague, the safety coordinator (who, if applicable, can relay a message to the pertinent party), Rama Singh (the PS safety coordinator, [rpsingh@uci.edu](mailto:rpsingh@uci.edu), office in the stockroom), or Keith.

## How to use the solvent system:



You should find the solvent bulb in one of the two possible resting states.

**Resting State (Empty):** Both stopcocks on the bulb should be screwed shut. Valve **A** is on vacuum, valve **B** is open, and valve **C** is closed. To remove solvent when the bulb is in this resting state, close valve **B** to place the bulb under static vacuum, turn valve **A** to argon, then follow steps **5-8**.

**Resting State (Full):** Both stopcocks on the bulb should be screwed shut. Valve **A** is on argon, valve **B** is open, and valve **C** is closed.

If you want to use the solvent already in the bulb, simply unscrew the top stopcock fully (*do not let your needle scrape against the side of the stopcock*), insert your needle, remove solvent, and put the bulb back in the appropriate resting state.

If you do not want to use the solvent in the bulb, open the bottom stopcock and blow out the solvent into the discard bottle. Close the lower stopcock and follow steps **1-8**.

1. Evacuate the solvent bulb by turning valve **A** to vacuum. Wait until the pump stops pulling.
2. Refill the solvent bulb with argon by turning valve **A** to argon.
3. Repeat the evacuation/ backfill procedure (steps **1-2**) two more times.
4. Evacuate the solvent bulb once more by turning valve **A** to vacuum. Once the pump has stopped pulling, close valve **B** to place the bulb under static vacuum, then turn valve **A** to argon.
5. If using methylene chloride, open the valve on the bottom of the left methylene chloride column.
6. Open valve **C** and pull down solvent. Once enough solvent has been collected, close valve **C** to stop solvent flow.

7. Open valve **B** to place solvent bulb under argon. Unscrew the top stopcock fully (do not let your needle scrape against the side of the stopcock), insert your needle, remove solvent, and put the bulb back in the appropriate resting state.
8. If using methylene chloride, close valve on left methylene chloride column.

If you leave solvent in the bulb, please record the time and date of collection on the white board to minimize waste.

If you need to collect a large amount of solvent you may clamp a round-bottomed flask with a 24/40 joint to the ground-glass joint at the bottom of the solvent bulb. Open the lower stopcock and then follow steps **1-8**.

**Notes:**

- **These solvents are expensive so try not to remove more than you need.**
- **DO NOT place valve A on vacuum while valve C is open or solvent is in the bulb.**
- **Please contact Sarah if septa are decomposing or if a solvent is empty (or any other problems).**

## How to use the Solvent Stills

Location of stills:

- (1) *i*-Pr<sub>2</sub>NH and Et<sub>3</sub>N are located in 5004
- (2) hexanes, benzene, and acetonitrile are located in 5024

Before turning on the still:

1. Make sure that the stills are under a positive N<sub>2</sub> or Ar atmosphere.
2. Make sure there is an adequate enough solvent for your usage. If the solvent level is low notify the still-person to refill the still.
3. So people are aware that you are using a still please place a tag or sign with your name on it on the still.

Bringing up the stills:

1. Turn up the variac to the setting indicated on it for filling the stills.
2. Allow the solvent to reflux and rinse down the sides of the receiving bulb.
3. Once the bulb has been completely rinsed close the valve and begin to collect solvent.  
**DO NOT REFLUX TO DRYNESS!**
4. Upon collection of the desired amount of solvent turn down the variac to the resting setting indicated on it.
5. Allow the solvent to cool before taking it up in a syringe. *Use proper syringe technique!!!*
6. Once complete drop the solvent.

## Operating Instructions to the HP6850 GC and autosampler

**Resting state:** All gases turned off at tank valve with *Shutdown* method chosen.

The last person to leave at night is responsible for shutting down the GC if samples are not currently running.

**Ready State:** All gases (hydrogen, helium, and air) turned on at tank valve with the appropriate method chosen. Green box at the left-hand side of the screen will indicate “ready”.

**Sign Up:** Sign up for use in GC logbook, record # samples and any problems encountered. Communicate with previous user to ensure availability of GC.

**Sample preparation:** Use vials made available for the GC. (The vials from the stockroom do not fit!) Filter your material (1mg/mL) through a silica plug (celite or basic alumina also ok) eluting with EtOAc or diethyl ether. Column fractions can be used as samples as long as the solvent is appropriate. **NO HALOGENATED SOLVENTS ARE TO BE INJECTED IN THE GC!**

**Select Appropriate Method:** click on *OVEN*. Edit times and temperature. Please do not edit other parts of the method without consulting the GC manager.

### For single sample:

1. choose single sample button
2. *Run control*      *sample info*
3. Enter Operator name: keith  
Subdirectory: KAW  
File Name: kawII36.D  
Location: Vial 9  
Sample Name: kaw-II-36  
Comment: reaction at 2h
4. When information is filled in, click *Run Method* or *OK*, then *Start*

### For sequence of samples:

1. choose sequence button
2. *Sequence*      *Load Sequence*  
Choose appropriate sequence (Ex: KAW\_GC.S)
3. *Sequence*      *Sequence Parameters*
4. Enter Operator Name: keith  
Subdirectory: KAW
5. *Sequence*      *Sequence Table*
6. Enter Information:

Location	Sample Name	Method Name	Inj/Location	Sample Type
Vial 8	Kaw-II-36fr1	Kwoerpel	1	sample

7. To enter more samples, click *Append Line* to create new line. Fill in information as described in #6.
8. When table is complete, click *Run Sequence* or *OK*, then *Start*

## “Old GC” HP5890 Operating Instructions

### • Why use the HP5890?

**It contains a column more suited for more polar compounds. If non-adequate separation is seen with the HP 6850, try the HP5890.**

NO HALOGENATED SOLVENTS ARE TO BE INJECTED IN THE GC!!! This means you must rotavap your NMR samples and re-dissolve if necessary! This will contribute to longer detector life and better performance from the ignitor coil.

### RESTING STATE

**Injector:** ON 250 °C

**Detector:** ON 200 °C

**Oven:** ON 100 °C

**Gases:** ALL OFF on GC panel

H<sub>2</sub> and Air are OFF at tank

**He is ON at tank**

This allows the column to be flushed with a continuous, yet minute flow of He to keep the column clean.

### STARTUP

- 1) Turn on H<sub>2</sub> and Air at tank valves and on GC panel.
- 2) Turn detector temperature up to 275 °C and let gases flow through the column 5–10 minutes.
- 3) Ignite detector
  - a) get signal reading: Push SIG1, A, ENTER, SIG1 on GC panel (should read zero or nearly so)
  - b) push ignite button and hold flame above the detector. A pop should be heard followed by an increase in the signal. Check ignition by holding a pipette or vial above detector – condensation should be observed. If GC does not light after a few attempts, ask the GC manager to adjust the flow rates and/or clean the detector.
- 4) Turn AUX GAS on at GC panel.
- 5) Turn oven up to 250 °C at GC panel for 20–30 minutes. Signal should read ~ 3, but less than 5–6 without fluctuation. Then turn the oven down to your desired temperature at GC panel.

### METHOD

On GC panel:

- 1) Push INIT TEMP button, type in starting temperature, then ENTER
- 2) Push INIT TIME, type in holding time at starting temperature, then ENTER
- 3) For a ramp, push RATE, enter # for degrees per minute, then ENTER. Otherwise, type in 0 deg/min, then ENTER
- 4) Push FINAL TEMP, type in ending temperature, then ENTER
- 5) Push FINAL TIME, type in holding time at final temperature, then ENTER

## INJECTION

- 1) Zero detector by pressing ZERO and ENTER
- 2) Flush syringe with your sample three times
- 3) Use syringe to inject roughly 1.0  $\mu\text{L}$  of sample and simultaneously press START button.  
Be careful to not bend needle!
- 4) Flush syringe with EtOAc three times.

## SHUTDOWN

Return GC to resting state described above and sign the LOGBOOK. Remember to report any GAS CYLINDER SHORTAGES to the GC manager.

## Glove-box Standard Operating Procedure

### General Use:

1. **Antechamber:** Normal Materials (glassware, plastic, metals)  
To bring items into the box, be sure inner door is closed:
  - (1) Fill the antechamber with  $\text{N}_2$  by changing the black valve from “evacuate” to “ $\text{N}_2$ -fill.”
  - (2) Remove the outer door by unscrewing the door. Place your materials into the antechamber and replace the outer door.
  - (3) Place the valve to evacuate and allow the pump to pull the antechamber down to  $<100$  mTorr. Partially refill the antechamber with  $\text{N}_2$ . (Repeat the process 4-5 times)
  - (4) Refill the antechamber with  $\text{N}_2$  and the materials can be brought into the box using the inner door of the antechamber.
  - (5) After you are done, place the materials in the antechamber (if it was never open to outside), close inner door, open outer door and remove items. Replace door and always leave the valve on “evacuate”.
2. **Antechamber:** Other Materials (solids, liquids...)
  - (1) With solids and liquids, a closed system under ambient pressure must never be used when pumping something into the box through the antechamber.
  - (2) The system must either be vented (i.e. vial containing solid has septa with a needle in it, or a round bottom fitted with a frit) or completely under vacuum (i.e. a liquid that has undergone three freeze, pump, thaw cycles).
  - (3) Paper products are porous and require special handling, such as being pumped on in the antechamber overnight, prior to use (never bring in cork rings, paper towels or other paper products).
3. **Use of Gloves:**
  - (1) Never use gloves with bare hands if a ring, watch or bracelet is worn. Cotton gloves can be used to cover rings.
  - (2) When using liquids, it is recommended that secondary gloves are worn over the box gloves.
  - (3) Take extreme caution when handling sharp objects.
4. **Common Protocols:**
  - (1) When using solids, always clean the area with tape, Kim Wipes will only push the solids around.

- (2) Any trash that is generated should be placed in the zip-lock bag or in the glass-waste can (unless a volatile liquid is on the item, then it must be brought out of the glove box).
  - (3) Leave the glove box the way in which you found it.
5. **Precautions taken with volatile (bp < 200 °C) liquids:**
- (1) Prior to using volatile liquids, the circulator must be turned off (be sure red light on the control panel is not lit).
  - (2) When finished with the box, purge the system by turning the yellow handle at the top of the box to a 45° angle.
  - (3) Allow the box to purge at least 5 minutes (if volatile liquids were used for a short time) and typically 10-15 minutes if the circulator was off for 30–120 minutes.
  - (4) After purging is complete, press the “circulation” button, a question on the screen will tell you to “continue with ins.”, you must press the “ins” button to turn the circulator on.
- If there are any problems, please notify Tim or Tom immediately!**

### **Instructions to use Perkin-Elmer 1600 FTIR**

1. To turn on the IR simply turn the knob that is located behind the IR counterclockwise.
2. Press **Enter**
3. Press **Backg** followed by **Scan** to identify background scanning.
4. From the screen, press *4* initiate background scanning.
5. Once background scanning has completed at the bottom right of the screen under *scan* it should read *Ready*.
6. Lift the lid to the left of the IR screen and place your sample in the slot.
7. Press **Scan**
8. From the screen press *16* to initiate scanning of your sample.
9. Once the scanning is complete, the bottom right hand corner of the screen, under *scan*, should read *Ready*.
10. Your spectra will come up on the screen.
11. To mark peaks:
  1. Press **Shift** and **Peaks** simultaneously to introduce cursor onto the screen.
  2. Using the arrows will allow you to move around.
  3. Stop at the peak that you wish to label and press **Shift** and **Mark** simultaneously.
  4. Repeat steps 2 and 3 as many times as necessary.
  5. Press **Shift** and **Peaks** to remove the cursor from the screen.
12. Turn on plotter and follow the directions to the right on the plotter. Replace step 5 with: Press **Plot**.
13. Once done plotting remove the pen from the carousel of the plotter and CAP IT!!!!
14. Turn off plotter, remove your sample, and dim the monitor screen by turning the knob on the back of the IR counterclockwise.
15. Finally, sign your name, PI, date, and the # of samples you took an IR of on the notebook right next to the plotter.

## HPLC Varian Prostar instructions

Before use, all solvents must be filtered and sonicated. Use solvents “for HPLC”-only. Make sure that there is enough solvent in both bottles before pumping, so that no air gets into the pumps.

Injection is manual! Before injecting the sample the injector should be in the LOAD position. Flush it with solvent several times before and after injecting.

Before exposing the column to the solvent, you need to make sure that there is no air coming out of the pumps.

Depending on the column and solvent used, the instrument can serve as both normal and reverse phase HPLC. However, some of the columns tolerate only certain solvents and can be destroyed by even very small amounts of other ones. It is therefore imperative that you know what solvent the person before you used, and if necessary, to flush the pumps for extended periods of time.

Pumps are labeled A and B; If you are changing the solvents make sure that the more polar one goes to pump A.

To turn on the HPLC:

1. Turn on the detector and both pumps (on the instrument itself)
2. Attach the column you wish to use
3. Choose HPLC-data acquisition on apple menu
4. Under DATA, select SHOW DATA TRACE (window shows up).
5. Under CONTROL, select SELECT PUMPS (window shows up).
6. Under CONTROL, select MANUAL CONTROL (window shows up). Here you can set the wavelength, flow, and solvent ratio.
7. Under SYSTEM, select SYSTEM STATUS. This will allow you see the actuals during the run.
8. On MANUAL CONTROL window, set the solvent ratio (only % pump B is shown).
9. Type in the flow (warning: by setting the flow, you are setting the pressure, too. Make sure that the pressure/flow you use is in the allowed range of the column; otherwise, both pumps and the column can be destroyed)
10. To start the pumps, press START RAMP button. Before than, make sure that the solvent is not going through the column, but through the ‘outside’ loop. That is achieved by loosening the black knob on the side of the instrument (the first time you use the HPLC ask somebody who knows how to use it to show you).
11. Let solvents flow until there are no more air bubbles coming out of the pumps. Then, you can tighten the black knob mentioned in 9., so that the solvents go through the column. Again, make sure that the pressure you are using is ok.
12. Press START ACQUISITION on the MANUAL CONTROL window.
13. Let solvents flow for ~30 min or until the base line on the data trace window is flat. Then hit STOP ACQUISITION in the manual control window.
14. Injection: Use the flat needle syringes provided. Make a solution of your sample (for analytical columns, optimal concentration is 1 mg/ml; for preparative, it depends on the column, and it can be a lot higher). Inject your sample into the injection loop. Then, turn the loop into the INJECT position and hit START ACQUISITION.
15. When your run is done, hit STOP ACQUISITION and then print your chromatograph. Monitor the pressure during the run and write it down in the log book.

16. You may want to let the solvents go for additional time to rinse the column.
17. Sign the log book and rinse the injection loop.

## **How to Perform Routine Computer tasks on the Apple G4 Computer:**

### **Burning a CD-R/CD-RW**

1. Put a blank CD-R/CD-RW in the CD-RW drive of “Woerpel G4”.
2. Type in a name for the disk
3. Select the format type. Use the default setting. The other settings are for audio CD’s or MP3’s.
4. Drag the desired files onto the CD-R/CD-RW disk. **Be careful not to exceed the storage space on the disk!**
5. From the Finder, click on the “Special” drop down window
6. Click on “Burn CD.”
7. Click “Burn.” **Make certain that you have copied *all* of the desired files to the disk. This IS the point of no return!!**
8. When you are finished, the disk should eject. Label the disk and case.

Congratulations, you have successfully backed up your information.

### **Using the HP Precision Scan Pro<sup>®</sup>**

#### **• *When Scanning from the Platen Glass***

1. Place document on the platen glass
2. Use the “up-down” arrow key on the scanner to select the file type/location to which you would like to scan (Microsoft Word, Adobe Photoshop, Acrobat Reader, printer, etc.)
3. Hit the “scan” button (picture of the scanner) **Ignore the other buttons**
4. Remove your document from the glass

Using this method you can only scan one document per file (I believe). If you have multiple documents per file use the following:

#### **• *When Scanning from the Automatic Document Feeder***

1. Place your documents text up with the top of the document heading into the document feeder. **25 page limit!!!**
2. Open up “HP Precisionscan Pro” software from the Apple Menu:Scanning dropdown window
3. Select the desired output type from the drop down window (grayscale, black and white, etc.)  
**DO NOT ADJUST THE RECOMMENDED OUTPUT RESOLUTION!!!!**
4. Select the “Scan To” tab
5. Select the Image type you wish to scan to (Word, Photoshop, Acrobat Reader, etc.)
6. Click “Scan”
7. When the last page in the feeder has run through re-load the feeder to scan more images into the current document and press “Scan” or press “Done.”
8. Your file will be in Macintosh HD:HP Scanning Software:Scanner Output

Alternatively, you can carry out steps 1-3 and then select the “Save” option. Select the file type you wish to save as (typically PDF), and you can then select the desired saving location. Steps 6-7 are the same.

### **Printing Transparencies from the HP4100dtn Printer**

You can print your group meeting transparencies directly from the printer in the clean room. **HOWEVER**, you must follow the following guidelines:

- Use only the HP LaserJet monochrome transparencies (92296T)
- Print only from the manual feed tray (Tray 1)
- Print only 1-3 transparencies at one time, and then allow the printer to rest a minute. Printing too many transparencies at one time can cause the printer to heat up and **MELT THE TRANSPARENCIES ONTO THE ROLLERS!!**
- Make sure you **TURN OFF** the duplexing option when you print transparencies. **DO NOT** have the printer set to print on both sides. This probably won't be a problem for ChemDraw, but it will be for PowerPoint.
- Transparencies can be found in the bottom drawer of the large filing cabinet in the clean room.

These policies are adapted from are adapted from *Organic Synthesis* and from Professor James Nowick's instructions to students.

The following is a description of the information that should be included in experimental procedures describing the synthesis of compounds. These guidelines are adapted from *Organic Synthesis* and are to be followed in writing notebook entries, quarterly reports, written reports for the advancement to candidacy ("orals"), doctoral dissertations, and experimental procedures for publication. The objective in writing preparative procedures is to provide a "recipe" by which others who are less experienced than yourself (e.g., students with a good laboratory course backgrounds who are just beginning research) could reproduce your synthesis. Use abbreviations that can be deciphered easily.

The following details should be included:

1. Quantities of reagents and solvents used
2. How quickly key reactants was added
3. Times and temperatures used
4. How the crude product was isolated. Include the mass of the material. To write an experimental, you will need to include volumes of solvents/solutions used in workup.
5. How the product was purified
6. The yield, both mass and percent.
7. A description of the purified material color, phase (oil, solid, etc.).
8. Characterization of the material (that is, what spectral and analytical data did you acquire?).
9. any unusual apparatus apparatus

For this information to be included in written reports, it must be included in your notebook. In addition to all of the details described above, a good notebook entry should include:

1. a heading (e.g., an equation)
2. the date
3. a table of reagents (MW, mass, equivalents, density, volume, and source/sample number as well as purification, drying, etc.)
4. relevant references to other notebook pages and the published literature
5. detailed observations
6. drawings of TLC plates
7. GC traces should be photoreduced and taped into the notebook
8.  $^1\text{H}$  NMR spectra of crude products
9. numbers should be assigned to spectra. Your designation should include your initials, notebook number, page number, and some indication whether the spectrum is the first, second, etc. on the page (I designate(d) my data as KAW-III-38A for  $^1\text{H}$  NMR's,  $^{13}\text{C}$ -KAW-III-38B for the  $^{13}\text{C}$  NMR, etc., the "A" and "B" indicating that something was the first or second spectrum for that page; I must confess I never took more than 26 spectra per page!)
10. concise description of spectra (e.g., " $^1\text{H}$  NMR shows desired product contaminated with 5% starting material")
11. conclusions and suggestions for future experiments (e.g., "rerun at lower temperature" or the more informal "went to tar")

12. elemental analysis forms should be taped into the notebook with relevant page references

## General Procedure for Performing a Reaction

When carrying out an experiment, the following should be performed except for special circumstances.

1. Literature or personal precedent should be considered. (For example, if you figured out that the ethyl derivative was hydrolyzed at 22°C, try the methyl case at 22°C.)
2. Make sure you have all the reagents before you get too far.
3. Decide on a reasonable scale for the experiment. For most reactions, about 1 mmol ( $\pm 0.1$  mmol) is good for a first try, if you have enough material. Otherwise, decide scale accordingly. If the starting materials are cheap (<\$0.50/g) and the reaction seems sure to work, consider running the reaction on a few grams.
4. Make the time to set it up and to work it up. You can purify the product later if the reaction works. *Don't let reactions sit around... they aren't wine.*
5. Distill reagents and solvents.
6. Get the reaction going.
7. Make sure you have an NMR and a TLC of your starting material: you will have to know how it *changed* during the course of the reaction. Save a TLC sample.
8. TLC reaction right after you get it started. Maybe it is already done.
9. Write the reaction up in your notebook with the weights you actually used.
10. **Monitor the reaction by TLC.** *The only exception is when starting materials or products decompose in air or on TLC.*
11. When reaction is over by TLC, work it up. Again, consider literature or personal precedent.
12. **GET A CRUDE <sup>1</sup>H NMR.** Assign peaks to starting materials, products, reagents, etc. *No exceptions.* How else do you know what happened?
13. Purify by flash chromatography, recrystallization, distillation, sublimation, etc.
14. Get <sup>1</sup>H NMR's of major fractions from your purification and assign peaks.
15. **Get yields.**
16. Write up notebook.
17. Catalogue NMR's.
18. Wash your glassware. Clean up.

- ❑ 19. If the product is a new compound, get: mp, IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR (DEPT or HMQC if compound is structurally complex or assignment isn't clear), MS (low res, high res),  $[\alpha]$  (if optically active), and elemental analysis.
- ❑ 20. If compound isn't fully characterized with yield and full experimental, it cannot be reported in a thesis or in the literature.

## Silica Gel Chromatography Information

*Copyright: E. Vedejs U of Michigan*

This material summarizes the most important preparative separation methods: preparative layer chromatography (PLC) and flash chromatography (FC). It is important to learn both of these techniques. Neither one is well suited for all of the following tasks: (1) isolation of pure samples, (2) determination of material balance, (3) determination of yield, (4) product recovery of several gram scale.

FC requires less preparative time (PLC plates require 2-3 days to dry). It is often a very useful way to obtain at least some pure material in cases where the total yield is not critical. FC also has the advantage to remove the worst polar contaminants from a mixture (by plug filtration through a layer of cheaper silica gel) prior to using the good column. However, FC demands constant attention during the separation, and it is seldom done with sufficient care to achieve total separations. Although there is no inherent reason why total separations could not be achieved by FC, the amount of time and level of skill required to do this on a column is higher. For difficult separations, each repeat separation requires the same constant monitoring, and many fractions have to be collected to minimize the risk of overlapping sections.

The PLC technique requires the same skill level for any separation, and total separation (i.e., no overlapping fractions) is achieved by reducing plate loading. This advantage is especially important when it is necessary to establish the upper limit for isolated yield from a given reaction. Although there are a few "tricks" that must be learned to achieved maximum resolution, there are some major advantages: (1) whenever two components are separated by 0.1 Rf or more, they can be completely separated by PLC; (2) the Rf values will translate directly from an analytical plate to a well-made prep plate; there is no guess work regarding fractions if the zones can be visualized; (3) separations require minimum monitoring once the optimum solvent system is known; no further optimization is necessary for subsequent repeat separations. Using FC, a similar level of control is possible if (1) the column is uniform, (2) the solvent system has been optimized to give Rf 0.3 for the desired zone, (3) the column is adjusted for different loading by changing the diameter (*not* length!!). If these precautions are taken and the instructions provided by Still *et al.* (attached) are followed carefully, the desired material will elute predictably.

Successful FC requires high quality solvents because more solvent is needed to elute a column than to develop a plate and to extract individual zones. We have experienced few if any problems using the solvents at UM, but technical grade solvents cannot be trusted. They usually contain non-volatile residues due to polymerization of unsaturated impurities, air oxidation, and other contaminants. If high purity solvents are stored for a long time after air exposure, they too can become contaminated. "Purified" samples from FC that show extraneous NMR signals due to solvent residues are not adequate for characterization purposes or for the calculation of yield

unless the % contamination can be determined and reported. Unless such samples can be recrystallized, distilled, or carefully PLC'd or HPLC'd after FC, the data will not be acceptable for publication or for thesis purposes, especially in cases where the exact mass will be used to establish the molecular formula. MS data can be misleading for a variety of reasons (a tiny impurity can produce the "molecular ion"), so sample quality is especially important and the same level of purity is needed as for samples that give satisfactory elemental analyses. Samples that show ANY extra unknown peaks in the NMR spectrum are automatically suspect.

PLC also has inherent limitations. The technique is laborious than FC if material has to be purified on several gram scale. No more than ca. 200 mg (Rf difference > 0.25) or 50 mg (Rf difference ca. 0.1) can be separated on one 8" × 2 mm plate. PLC can also be difficult if the mixture is not UV active. However, PLC is superior for sample characterization and for the determination of yield because it minimizes solvent use, and routinely allows for total separation of the mixture.

It is important to learn both techniques and to know when each one is appropriate. FC can be used whenever fast access to reasonable pure material is desired, especially for reactions done on a gram scale or larger. PLC can be used to obtain a reliable optimum yield of a reaction that is being optimized. For this purpose, the reaction can be done on ca. 100 mg scale or less, depending on the difficulty of separation. If the best yields require working on a larger scale, then the reaction is diluted to a known volume, and an appropriate aliquot is taken for PLC separation. The overall isolated yield is then calculated. Remember that the isolated yield is the % recovery of pure material, or an estimate based on recovery adjusted for the % of a *known* impurity. There is no deception involved if you separate 1/10 of the reaction by PLC and report the overall yield based on 10x the recovery from one PLC plate because the procedure will report isolation by PLC. Anyone who wants to use 10 plates will be able to reproduce the reported result. Yields based on FC or PLC can be deceptive unless there is a way to assay solvent residues. Another misleading practice is to determine product ratio by NMR, and then to calculate the "yield" from the weight of mixed fractions or crude product. This is unacceptable because there is no way to isolate this "yield", and often there is no information about what impurities really are. It would be misleading to report the yield of a mixture without reporting the yield of the separated material that was used for characterization. Yield results for FC must identify the weight and purity of all fractions that are used in the yield calculation. Furthermore, the experimental procedure **MUST** identify the number and volume of all fractions, and must indicate which fractions contain which products. Otherwise, there is no way for someone to reproduce the isolation method unless you use the same conditions each time (optimized Rf value, column height, use of solvent combination for elution). Gradient chromatography is notoriously difficult to reproduce because it is seldom described with sufficient detail. DO NOT use gradient unless you have to; it will be easier to write up your results if you stick to the recommended procedure below, and separations will be easily predictable.

PLC is superior to FC for the purification of samples for characterization, but analytically pure samples may require a second, small scale (ca. 10-20 mg) separation using the minimum of silica gel and reliable solvents. Semi-prep HPLC can also be used. Regardless of the separation method, solids must always be recrystallized to a good melting point from a specified solvent and distillable liquids should always be distilled prior to HRMS analysis.

### **Analytical TLC**

**DIMENSIONS:** Recommended plate size: 2.5" (6-7 cm) vertical; horizontal depends on the number of spots; 1/4" per spot is ample room. Shorter plates will not do well with difficult

mixtures; longer ones are OK for really tough separations but after ca. 6", they begin to suffer from diffusion because of the excessive development time.

**SOLVENT SYSTEM AND TRICKS:** Most common for neutral organics: 5-25% ether/hexanes; 5-25% acetone:hexanes helps sharpen up O-H or amide N-H containing spots. The three component system 1-5:1:1 hexane:ether:dichloromethane can have remarkable properties, sometimes resulting in inverted relative R<sub>f</sub> values compared to the simpler two-component systems, especially with multifunctional molecules. Many poly functional unsaturated compounds can also benefit from benzene or halocarbon based systems. Always optimize the solvent system for a difficult separations. The differences can be amazing, and they are in no way predictable or rationable.

Avoid methanol or ethanol! These solvents will extract binder from the silica gel. Depending on the co-solvent and the care taken to equilibrate the developing chamber with the phase, polar solvents such as the alcohols may create an artificial solvent front where the polar solvent stops climbing the plate, with unpredictable consequences for the separation. IF you need a polar solvent, try isopropanol or THF.

Basic amines do not run well on silica gel (a weak acid!) unless they are sterically hindered. Buffering the silica gel with NH<sub>4</sub>OH during plate preparation, or addition of a drop of aqueous NH<sub>4</sub>OH to the developing chamber can help minimize the "tailing" of amines. Aqueous NH<sub>4</sub>OH can be used in the homogeneous system with isopropanol as co-solvent for polar amines. If an organic solvent has to be used to achieve R<sub>f</sub> = 0.3, then separation of an aqueous phase can be controlled by adding anhydrous sodium sulfate to the solvent+ammonia mixture. Enough ammonia will remain dissolved in the organic phase to help improve spot shape.

Tailing is often seen with other polar compounds such as phenols or carboxylic acids. This problem can usually be controlled by tinkering with solvent systems: (add H-bond acceptors like acetone), but buffering with acids may be necessary in extreme cases. Whatever you do, remember that TLC depends on multiple equilibration events. The solvent reservoir, silica gel, and air space in the developing chamber must all be in equilibrium, and this will take time for non-volatile solvents such as alcohols or acetonitrile. If you don't allow enough time for the chamber to equilibrate, the less volatile solvents will not be distributed evenly on the plate due to differences in the extent of evaporation, and the results will be unpredictable. Mixtures containing highly polar components may also produce false solvent fronts, resulting for what amounts to chromatographic separation of the solvent mixture.

**OPTIMUM TECHNIQUE:** Until you are experienced spot 2-3 concentrations of each sample to find the one that does not "tail" due to overloading. A good solvent system will give nearly a circular zone from a "spot" if the plate is not overloaded. Always spot "knowns" along with the mixture being assayed. Include starting material, expected product(s), and a sample of the crude product from various attempts or from parallel experiments. Side-by-side comparisons are always important for revealing subtle differences. Never trust R<sub>f</sub> values alone to identify spots. When optimizing a reaction, do several reactions at the same time so that side-by-side comparisons are easier. Place a strip of filter paper along the wall of the developing chamber to help speed up equilibration of liquid and vapor phases. For difficult separations, optimize the solvent system and adjust polarity (i.e. vary % hexane) until the R<sub>f</sub> of the most important zones is >0.1 and <0.4 if possible. This will permit multiple (up to three) developments to maximize separation if necessary.

**VISUALIZATION:** Always check for UV-visible and for iodine-absorbing spots. Place enough iodine in a covered beaker to produce visible vapors (a thin layer of crystals is all it

takes!). Nearly all organics absorb more  $I_2$  than silica gel alone, resulting in a brown spot. Some halides, amides, and certain very polar compounds will resist the iodine. These show up as white spots against a pale brown background. Other, more specialized developing methods are available in the form of spray reagents. Many of these are specific for functional groups. Check any chromatography book for recipes. For preparative work, UV-invisible zones can also be detected by dusting the plate with  $I_2$ -saturated silica gel to mark the surface of the plate. UV markers can also be added to provide reference points for scraping zones. Aromatics such as fluorenone, chalcone, anthracene, benzil, etc., are convenient additives because they are easily visible in milligram quantities. Choose one that has a convenient  $R_f$  value to run ahead or behind the zone of interest.

**TLC MONITORING OF REACTION MIXTURES:** The ideal conditions for typical reactions will usually result in detectable changes in the starting material vs. product ratios over a time scale of tens of minutes to several hours. Always monitor reactions by TLC as often as necessary to determine how fast the reaction is under a given set of conditions. This is an important part of the optimization process. Avoid “overnight reactions” unless you know that they really need that much time. Frequent TLC monitoring early in the optimization process ensures that transient intermediates or sensitive products will not be missed. If you monitor low temperature reactions, remember that the act of spotting will warm up the reactants and will accelerate the reaction. Unless you can first quench the reaction, this type of monitoring may be misleading and could lead to a dangerous situation (premature warming of an incomplete reaction can result in an exotherm).

### **Preparative Layer Chromatography (PLC).**

**TLC AS A STARTING POINT FOR PLC:** Any mixture that can be separated on a 3-4” analytical plate can be separated on a preparative plate. The solvent system for typical preparative separations can be the same as for the analytical plate if the separation is easy ( $R_f$  differences of 0.15 or more), provided that the zone of interest has polarity (perhaps from 10% ether-hexane to 5% ether-hexane so that multiple developments are possible. In this situation, the plate is developed once to resolve the least polar zones. These are scraped off using careful razor blade technique. The remaining undamaged silica layer is dried with a gentle stream of air until the back of the plate appears “dry” (ca. 2 min. is enough), and the remaining zones are developed again, this time only as far as the scraped zone. This technique will maximize the separation of the nonpolar as well as polar zones and can be repeated as many as three times for tough mixtures. The only difference between analytical and preparative work is that equilibration of the solvent chamber takes more time for the preparative work. It is best to avoid relatively polar, non-volatile solvents in PLC to minimize the equilibration problem.

**SAMPLE APPLICATION:** Use the prepTLC applicator (first time ask someone to demonstrate); dissolve your sample in 0.5-1mL of  $CH_2Cl_2$ , transfer the solution with a pipette into the apparatus (CAREFUL). After the application rinse your flask and using the same pipette transfer the solution to the application apparatus and apply it to the plate. Things to look out for: Do not tilt the apparatus too much, otherwise your solution might spill out, or the needle can come out, making the application zone too wide. Manual application using a supported straight edge guide and a pipette drawn out to a capillary is also possible with practice (use a non-volatile solvent like  $CCl_4$  for this; very fast and easy once you learn).

**DEVELOPMENT:** If the application was perfect, you may want to pre-develop the plate 2-3 times to sharpen the origin zone. Extreme problems can be handled by developing the plate just past the applied zone using a more polar solvent system than you plan for chromatography,

drying the plate (gentle air hose flow), and repeating the process until the zone looks uniform. This sharpens the zone because the lower edge will “run” longer than the front of the zone. If the application was successful and the separation is expected to be easy ( $R_f$  differences of  $>0.2$ ), then the predevelopment is not necessary. For difficult separations (difference in  $R_f$  values of 0.05 to 0.15), 1-2 predevelopments using the same solvent system as for the optimum separation is recommended to sharpen zones. The ultimate separations may require predevelopment, as well as one or two redevelopments. Each time, the plate must be taken out of the developing chamber and dried before the next development can be performed. As already mentioned, the optimized solvent system will be the one that moves the desired zone at  $R_f$  0.2-0.3 and that produces round spots on the TLC with no tailing or streaking.

Since prep plates run longer than analytical plates, somewhat more diffusion of zones will occur. There will be also more time for the decomposition of sensitive compounds. It is a good idea to check the stability of your mixture using the two-dimensional TLC test (spot mixture at the corner of a square analytical plate and develop in one direction; dry and store for an arbitrary “decomposition time”; then, develop the plate at a direction perpendicular to the original direction; if the sample is stable on silica gel, there will be no streaking in the second development, no residue at the second origin, and spots will fall along a diagonal of the plate). If the stability of your compound is in question, try to minimize the development time. Remember that a 4”x 8” analytical plate can hold ca. 5-10 mg of mixture. These can be developed in 10 minutes, minimizing contact time. Samples that decompose on prep plates (sensitive acetals, TMS ethers, etc.) can often be purified this way for characterization purposes.

**VISUALIZATION:** See comments under TLC for the most important methods. For prep work, it is often possible to see zones of UV-invisible compounds by watching from behind the plate as the solvent dries. Zones that contain significant amounts of organics absorbed on the silica gel will stay wet longer than areas that contain no absorbed material, and the front of the zone will be most distinct. This will not work for small quantities, and the zone will not be visible for more than a few seconds as the solvent evaporates. Be ready with a sharpie to mark the outline of the zone on the back of the plate.

**EXTRACTION ZONES:** Use a safety razor to scrape the silica gel onto glassine weighing paper or a smooth piece of aluminum foil. Crush lumps with a spatula and place the powder in a **COARSE POROSITY** sintered glass filter funnel that contains a layer of ca. 3 mm  $MgSO_4$  and tap it into a uniform column. Pressed into place with a glass rod or filter packed as a slurry under aspirator vacuum. The filter should be ca. 1 cm in diameter for PLC Zones for a 8” plate, and the filter should be connected to ca. 5-10 cm of 1 cm tubing to allow ample room for the silica gel and solvent. Pour the powder into the filter on top of the  $MgSO_4$  and tap it into a uniform column. For 90% of typical organic mixtures, ether is the ideal extraction solvent. Add ether slowly enough to be continuously absorbed by the silica gel. Once the silica gel is wetted through, apply a little more ether at the top and gently apply air pressure or gentle aspirator vacuum. A typical zone from one plate can easily be extracted with 4-5 mL ether if the silica gel is crushed to a powder and forced into the filter (air pressure or glass rod) to avoid channels. Use a tared 10 mL or 25 mL flask as the receiver so that recording the weight after evaporation is easy. Evaporate the ether. In case any microdroplets of water (always present in the silica gel!) made it through the  $MgSO_4$ , azeotropic removal of the water will occur when the residue is freed of ether residues by evaporation of 1-2 mL  $CCl_4$  or  $CDCl_3$ , prior to NMR analysis. However, you should be careful to weigh the sample before this is done. An accurate weight will be more difficult after NMR analysis since NMR solvents are non-volatile.

Most plates can be used twice if the mixture being developed is not too messy. Plan to develop the plate 2/3 of the way if the separation is not too difficult. The top can then be used for a second separation. Non-Polar material that climbs with the solvent front will run faster than your mixture when the plate is inverted and used a second time.

**GENERAL COMMENTS ABOUT SILICA GEL SEPARATIONS:** The size of a zone on a column or plate is limited by the amount of silica gel needed to absorb the organic material. A zone containing ca. 30-40 mg of material on a well made 1.5 mm plate can be as narrow as 0.5". The width of the zone will increase in proportion to weight, and a 100 mg zone will take up 1-1.5". If the silica layer is uneven, there will be variations in zone width. This will also happen for overloaded plates (150-250 mg per 8" plate is the limit). Dark streaks that slowly fade in the course of development indicate initial overloading. The same factors apply to columns, and zone dimensions are sensitive to column packing. Uneven packing causes channels in the column and a non-uniform front. As with plates, the volume and polarity of the solvent used to apply the mixture to the silica column will also influence zone width.

Beginners often become convinced that their product is absorbed tightly on the silica gel and use huge amounts of solvent trying to extract or elute the "missing" material. Most of the time, the problem is that crude reaction mixtures contain residual solvent that "disappears" during the separation process. Highly polar sideproducts also tend to "disappear" because they stick to the origin. However, there is no way that a zone will migrate with 20% ether/hexane, but will refuse to extract with straight ether. Probably 95% of typical organic materials will do nothing irreversible with silica gel. If a spot migrates on an analytical plate, but seems to disappear on a column or a prep plate, try the two-dimensional test for decomposition. If that isn't the problem, then the next most likely source is "pilot error".

All silica based separation methods are fundamentally the same. Claims of large differences and advantages for specific devices and techniques can usually be traced back to individuals who learn one method well and don't look carefully at the alternatives. Particle size is important for resolution and convenient speed of elution. Best results require using silica gel of uniform size optimized by the manufacturers specifically for FC (controlled to avoid fine particles that cause too much back pressure) or for PLC (inorganic binder added for mechanical stability of the dried silica layer).

## Characterization of New Compounds

August, 2001

These policies are adapted from the *Journal of Organic Chemistry* and from Professor James Nowick's instructions to students.

Full characterization of new compounds (those not previously reported in the published literature) is required for publication in journals such as the *Journal of the American Chemical Society* and the *Journal of Organic Chemistry*. You will need this data as well for the second year written exam, the advancement to candidacy exam ("orals"), and your dissertation. The goal of characterization is to establish both the structure and the degree of purity of a compound. One piece of advice: characterize compounds as soon as you first prepare and purify them. Delaying characterization can lead to unsatisfying months of simply running flash columns and getting combustion analyses. Since the requirements for characterization will affect your advancement to candidacy, doctoral dissertation, publication of papers, and timely departure from the group, you cannot get around characterization.

The following is taken from the Journal of Organic Chemistry Instructions to Authors regarding characterization (they chose to bold certain sentences, which has been preserved):

**“Characterization. For all known compounds, the source of the material or references to the utilized literature preparation method and published characterization data must be provided.** Spectral data should be presented only if it augments or updates the previously published data.

For all **new compounds that appear as title compounds in the Experimental Section of Articles and Notes, adequate evidence to establish identity AND degree of purity (see below) must be provided.** This can be presented in the body of the manuscript, in which case it will appear in the printed version of the Journal. Alternatively, it can appear as Supporting Information. For Articles that report the preparation of large numbers of new compounds, authors should be selective in presenting spectral data for the printed version of the Journal. In most cases, a listing of <sup>1</sup>H and <sup>13</sup>C NMR resonances will suffice. NMR peak assignments should not be given in the printed version of the Journal unless they are derived from definitive experiments such as isotopic labeling, DEPT, or two-dimensional NMR experiments. If desired, a full listing of NMR data, accompanied by subjective peak assignments, may be included in the Supporting Information. Full lists of infrared absorptions and mass spectral fragmentations should not be presented in the printed version of the Journal. List only those infrared absorptions that are diagnostic for important functional groups and only those mass spectral fragments that are diagnostic for a particular skeleton. Authors may supply high resolution mass spectral (HRMS) data as an additional criterion of compound identity. Additional spectral and characterization data may be published as Supporting Information.

In general, **evidence of the degree of purity of each new compound should include elemental analyses for carbon and hydrogen, and nitrogen if present.** Acceptable error limits for combustion analytical data are (0.4%. **For some compounds, combustion analysis is not feasible. At the author's discretion, an 8.5- x 11-in. photocopy of the proton or carbon NMR spectrum will fulfill the requirement.** Photocopied spectra should be of sufficient contrast that they will, in turn, photograph well and must each be labeled with the compound number and structure. They will be published as Supporting Information. See Supporting Information below for requirements. **For some kinds of work, indicators of purity other than**

**NMR spectra and elemental analysis are more appropriate.** Distillation followed by gas chromatography, column chromatography followed by HPLC, and gel electrophoresis are acceptable as evidence of purity in these cases. The purpose of this requirement is to allow a reader who repeats a preparation to determine that the procedure has resulted in the expected product of the expected purity. **Note that HRMS data cannot serve as a criterion of compound purity in lieu of elemental analysis."**

The characterization of any compound will include the following.

**Melting Point.** (solids only) Provides evidence of purity. Melting points are required for all solids.

**Infrared Spectroscopy (IR).** Critical to establishing functional groups present in your compounds. Make sure to record the state of the sample (e.g., thin film, solution in  $\text{CHCl}_3$ , KBr pellet, nujol mull, etc.). List major peaks, particularly ones of characteristic functional groups. For publication, most lists are about a half-dozen or so peaks.

**$^1\text{H}$  NMR Spectroscopy ( $^1\text{H}$  NMR).** Critical to establishing both structure and purity of compounds. Make sure to record the solvent and field strength (e.g., 300 MHz,  $\text{CDCl}_3$ ). Chemical shifts should be reported to hundredths of a ppm. Integrals should be calculated and rounded to the nearest integer. Most integrals are accurate to within 5 - 10%. If the integral is particularly important (such as a ratio of compounds), you will need to obtain integrals from a one-pulse spectrum. Peak printouts should be obtained to facilitate calculation of coupling constants. Coupling constants are reported in Hz and should be rounded to the nearest tenth of a Hz. A photocopy of the  $^1\text{H}$  NMR spectrum of each new compound must be included in second year written exams, the advancement to candidacy exam ("orals"), and your dissertation. *Never alter the spectrum or integrals with pen or white-out, as this constitutes an act of scientific fraud.*

**$^{13}\text{C}$  NMR Spectroscopy ( $^{13}\text{C}$  NMR).** Make sure to record the *solvent and field strength* (e.g., 75 MHz,  $\text{CDCl}_3$ ). (Remember, the field strength for  $^{13}\text{C}$  NMR is approximately one quarter that of  $^1\text{H}$  NMR.) Chemical shifts should be reported to tenths of a ppm, and any coupling data (say to a heteroatom such as  $^2\text{H}$  or  $^{31}\text{P}$ ) must be noted. All signals should be present; if you have overlapping signals, you must take the spectrum in a different solvent.

**High-Resolution Mass Spectrometry (HRMS).** Provides evidence for the molecular weight and elemental composition of a compound, but provides no indication of purity. Calculated and observed weights should be reported to four decimal places. Make sure to use "exact masses" (atomic masses of main isotopes) in calculating molecular weights. Experimental and calculated masses must match within 5 ppm (0.0015 amu on a compound with molecular weight 300).

**Elemental Analysis.** A time-honored technique that provides evidence for both purity and molecular formula. Samples should be sent to Atlantic Microlabs as soon as materials of high purity are obtained. In general, it is a good idea to place samples under high vacuum overnight prior to submission to ensure that samples contain no traces of solvent. Special care should be taken with viscous oils, as it is difficult to remove all traces of solvent from these samples. Note that small traces of chlorinated solvents generally will introduce larger deviations in analyses than small traces of non-chlorinated solvents. Acceptable error limits for elemental analyses are  $\pm 0.4\%$ . The analytical labs' results are generally precise to within about  $\pm 0.1\%$ , so if your sample does not give an acceptable analysis, further purification is probably required.

**Optical Rotation.** (enantiomerically enriched compounds only) This technique provides evidence of purity. All enantiomerically enriched compounds should be analyzed by optical rotation. This technique is easy and quick.

**Gas Chromatography Data.** Periodically, you will wish to report GC data for product ratios, such as diastereomer ratios. The GC provides response ratios between peaks as determined by the detector (in our case, flame ionization); it does not provide product ratios. If you know that two peaks have the same molecular formula, then the response ratios correlate quite well with actual product ratios. If the compounds have different formulas, the ratio is irrelevant and will need to be calibrated (calibration is relatively easy if you have clean samples of both materials). Ratios obtained by GC must be in agreement with ratios obtained by NMR methods. In order to call a minor peak in the GC trace a minor "isomer," either an authentic sample of that isomer must be made, or GCMS will be required to assign that peak's structure. Keep copies of GC traces from which product ratios are determined; the dynamic range should be such that small amounts of minor products (under 2-3%) are registered by the detector and integrator. All traces used to obtain product ratios will be submitted with manuscripts.

**Yields.** You will need yields on all reactions for which you wish to write an experimental. These yields should be on preparative scale (>100 mg in most cases), and must be for pure materials (as determined by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopies, GC, etc.).

**Regarding Unstable and Known Compounds:** Unstable intermediates may be characterized less rigorously (e.g., crude  $^1\text{H}$  NMR, IR), provided that a subsequent product is isolated, purified, and fully characterized. Compounds that are observed in small quantities as interesting side-products may also be characterized less rigorously (e.g.,  $^1\text{H}$  NMR, IR, HRMS), but if you are going to spend much time discussing a compound it should be fully characterized. In some cases, it may be appropriate to purify only a small portion of an intermediate to a high level of purity (e.g., an intermediate in a large-scale multistep synthesis.) In such cases, you should indicate this in the experimental procedure and provide characterization data for the analytical sample (e.g., "An analytical sample was purified by column chromatography on silica gel to afford a colorless oil: IR ...;  $^1\text{H}$  NMR ...;  $^{13}\text{C}$  NMR ...; HRMS ...; Anal...."). Compounds that are known and fully characterized in the literature may also be characterized less rigorously ( $^1\text{H}$  NMR, and  $^{13}\text{C}$  NMR are sufficient, but IR and MS can be obtained easily, so should be performed; elemental analysis is not required).

### Some Tips for Writing Manuscripts

A worthwhile guide to writing would take about 100 pages. Mercifully, Strunk and White have written just such a guide: *Elements of Style* (an outstanding investment if you happen to be at a bookstore). Believe it or not, computer grammar checkers are quite good, so I would try that first. They are imperfect, however, so I have compiled a few reminders for you. These topics tend to be the same ones I notice with every paper or grant I read:

1. **Paragraphs and Thesis statements.** Paragraphs are units that include related sentences. Paragraphs have thesis statements that indicate how the sentences are related. These sentences are the first sentence of every paragraph. For example, you might have a series of sentences that describe important NMR data such as hydrogen bonding or a variable-temperature NMR experiment. These sentences should flow logically from one to the next

and not jump around. One might use the following thesis sentence: “Variable temperature NMR experiments provided important information about the hydrogen bonding pattern of compound **11**.”

2. **Verb tense.** You should not switch verb tense in the middle of a paper. Usually past tense is preferred, although sometimes present is more appropriate.
3. **Subject/verb agreement.** Check to make sure subjects and verbs are either both singular (“Amide 6 was crystallized”) or both plural (“Amides 6 and 8 were crystallized”). Be aware that sometimes the subject defines a collection but is itself singular (“A mixture of amides **6** and **8** was crystallized” with “mixture” as the subject).
4. **Extraneous words.** Words such as “surprisingly,” “interestingly,” “much to our delight,” and “in the event” add little to text. “Very” also adds little to a qualifier... just think, would you trump “very” with “oh so very” or, more simply, “very very?”
5. **Colloquial expressions.** The above words are colloquial as well, but some other colloquial expressions are better rendered more formal. For example, “The ester was reacted with the amine” sounds fine in the laboratory, but this level of informality is not appropriate for a report. The word “treated” can often be substituted for “reacted” and therefore papers can be made more formal rather easily. Be aware, though, that sometimes you can overuse the same sentence structure, so change it up a bit.
6. **Contractions.** Contractions aren’t (I mean, “are not”) appropriate for formal writing.
7. **Imprecise subjects of sentences.** “This” cannot serve as the subject of a sentence. Although it can serve as a noun, it is not a precise one. Specifying what “this” is can be much better: the expressions “this phenomenon,” “this compound,” or “this experiment” can serve as subjects of sentences.
8. **Weak sentence constructions.** A few common sentence constructions are believed to be weak because the infinitive “to be” must be employed as the verb. For example, sentences starting with “There is...” or “There are...” need no other verbs. Consider the following:

“There are no examples of silacyclopropanes used as synthetic intermediates.”  
compared with:

“Silacyclopropanes have not been employed as synthetic intermediates.”

The second sentence has a more active verb and is thus a “stronger” sentence.

9. **Qualification.** Do not have gradations of yield like high/good/satisfactory/moderate/modest/poor. Calling something “high yield” or “poor yield” is descriptive, but one person’s “modest” is another’s “poor.” The same idea applies to selectivities, etc.
10. **Numbers.** Numbers less than or equal to twelve are normally written out (whereas 13 and higher are not).
11. **Experimental data.** In figures, put only the most important experimental details. Too much information will only serve to hide key data. You will find that a description of reagents is sufficient, and the details of solvent and temperature are not critical. Do not include too much experimental detail in the text of a paper, either. Save the details like how much solvent, etc. for the experimental section.

## Tips for simplifying the writing process:

1. Make a full sentence outline. For an example, please see the attached outline. A full sentence outline will force you to see the big picture and make decisions about your material. What you will see emerge is the thesis statements for the paragraphs of your paper.
2. Draw the equations, figures, and schemes. They should follow from the outline. If you wanted to draw it but it is not in the outline, either put it in the outline because it is important, or do not draw a figure for it. Between the figures and the outline, your point should come across clearly.
3. Go ahead and write a first draft. Pay particular attention to what you want to say, not how you say it. That will come later. Try and get everything into the paper that must be there. Extraneous material can be edited out later. Do not feel bad if the first draft is not Shakespeare.
4. Now give the manuscript a first edit. Think about every paragraph. Does it have a thesis statement? Does each paragraph follow a theme? Is the flow logical if you only read the first sentence of each paragraph? At this stage, you should be focusing in on content and whether the overall flow of the paragraph is good. Wording comes later.
5. When you are happy that the paper flows properly, go through each sentence. First, fix the spelling. Second, try the grammar checker. It will flag gross mistakes so you do not have to parade your Neanderthal writing in front of others. Does each sentence hold together by itself? Does it fit within the paragraph, following the previous sentence leading into the next one?
6. Give your paper to a colleague, preferably one who is not too knowledgeable about their work. Have them read it critically, both noting its good parts and its bad ones. Take their comments into consideration when you revise. By the way, pride of authorship is an ugly thing. So is a vindictive reader.
7. A final note: Someone once told me, "There is no paper that does not improve upon shortening." We have all heard, "Brevity is the soul of wit," and "A picture is worth a thousand words." I (KAW take these comments to heart when I write. Finally, I try desperately to avoid R. B. Woodward's blistering criticism, "You write like a truck driver talks."

## Sample Full-sentence Outline

for W. S. Palmer, K. A. Woerpel, *Organometallics* **1997**, *16*, 1097-1099.

### I. Introduction

A. Metal-mediated reactions of silirenes[Seyferth, 1977 #64; Seyferth, 1984 #60; Seyferth, 1985 #24] and alkylidenesiliranes[Ando, 1986 #85; Saso, 1989 #16; Saso, 1988 #58] with alkynes result in extrusion of a silylene unit or an insertion reaction. Although mechanisms have been postulated which explain these products, little experimental support has been reported. No applications of these reactions to siliranes have been reported, and no stereochemical information has been obtained to date, largely because of difficulties in making siliranes.

B. We reasoned that the mechanisms of these reactions of three-membered silanes could be evaluated if they could be extended to siliranes bearing stereochemical markers. In this way,

the stereochemical outcome of the reactions could be determined and the mechanisms either supported or refuted. We have used Boudjouk's stable siliranes (1,1-di-*tert*-butyl-2,3-dimethylsilirane **1**) to address similar issues regarding insertion reactions of carbonyl compounds.[Bodnar, 1995 #2]

C. We have discovered that stable siliranes 1,1-di-*tert*-butyl-2,3-dimethylsilirane **1** in fact undergo insertion reactions and silole synthesis with stereospecific retention of configuration at the carbon atom. We can also comment on oxidative addition reactions of metals into C-Si bonds as well as on the specific reactions of siliranes. Silylene intermediates may be implicated but are not required.

## II. Reaction with a variety of alkynes

A. Reactions with a variety of terminal alkynes provides silole products. The product is obtained with high regioselectivity favoring materials with the alkene substituent away from the bulky silyl group. In some cases, particularly with the *cis* silirane, insertion products are sometimes obtained as well. With diynes, we observe formation of oligosiloles as well as macrotetrasiloles. The regiochemistry of the insertion product is also high. Control experiments indicate that palladium is necessary. Modification of reaction conditions does not lead to more insertion product.

B. The stereochemical course of these reactions is worthy of note. The insertion reaction proceeds stereospecifically with retention of configuration, although the low extent of insertion with *trans* **1** does not allow for a more detailed analysis than presented here. The stereochemistry with respect to liberated alkene is also stereospecific retention. Both processes have the same stereochemical outcome.

C. The regiochemistry with respect to substituents on the silirane ring is interesting. It gives the product of addition at the least hindered position, in contrast to our observations of reactions with aldehydes and alcohols.

D. When no alkyne was added, we see slow conversion to the rearranged product.

## III. Mechanism analysis

The proposed mechanisms for these transformations involves oxidative addition. Our data indicates it proceeds with stereospecific retention of configuration of stereochemistry at the carbon atom. This intermediate can partition in one of three ways, leading to silole, silacyclopentene, and silane. Considering the interest in the stereochemical aspects of extrusion from other small heterocycles such as epoxides, aziridines, and episulfides (carbenes?), we can contribute that silylene extrusion proceeds with retention of configuration. The mechanism supported by our data is shown in the scheme. This logical proposal was suggested by other authors many years ago, but the stereochemical experiments reported provide additional support.

## IV. Conclusion

In conclusion, palladium-mediated reactions of siliranes have been demonstrated to proceed with stereospecific retention of configuration. Our data points at the formation of palladasilacyclobutanes. Further experiments will be directed at transferring silylene units to other functionalaties.

## Writing Experimentals

### Symbols, Punctuation, and Formatting for Experimental Data

**This section has been adapted from a handout by Professor Scott Rychnovsky**

**Note:** The key strokes involve an older version of Microsoft Word for Macintosh, so if your symbols do not look ideal, you will need to figure out which are the best keystrokes for your word processing program

Temperature: 65 °C

Temperature: -78 °C

Selectivity: 98:2

Yield: 95%

Joining names: Horner–Emmons reaction

A melting point: mp = 65–67 °C

A weight: 73 mg or 0.073 g

A volume: 35 mL of water

Hours: 7 h

Micromoles: 13.2 μmol

Compound Formulas: BF<sub>3</sub>·OEt<sub>2</sub>

NMR Format: 7.25 (s, 1H)

Coupling: (dd, *J* = 6.7, 10.0, 1H)

1.7–1.4 (m, 3 H)

<sup>1</sup>H NMR Data: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 7.20–7.35 (m, 5H), 5.05 (d, *J* = 2.9, 1H), 4.24 (dq, *J* = 6.4, 2.0, 1H),

If overlapping data, use the following:

1.08 (s, 9H and m, 1H)

<sup>13</sup>C NMR Data: <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) 143.3, 128.0, 126.9,

Rotation: [α]<sub>D</sub><sup>25</sup> +12.1° (*c* 0.91, CHCl<sub>3</sub>); : a in Symbol font, *c* italicized, space after it.

MS:

HRMS (CI/isobutane) *m/z* calcd for C<sub>19</sub>H<sub>33</sub>O<sub>2</sub>Si (M + H)<sup>+</sup> 321.2250, found 321.2249. Space around '+' (or '-'). Space after italic m, and before italic z. '/' not italicized. '+' is superscript. If the ion is an M<sup>+</sup>, then use (M<sup>+</sup>) with the "+" as superscript in the parentheses. Also, if you have lost a *t*-Bu group for example, use (M - C<sub>4</sub>H<sub>9</sub>)<sup>+</sup> with the fragment listed as its molecular formula

Note punctuation. Calcd has no period.

Analysis:

Anal. Calcd for C<sub>19</sub>H<sub>32</sub>O<sub>2</sub>Si: C, 71.18; H, 10.08. Found: C, 70.97; H, 9.98.

Naming: (2*R*,3*S*)-Dimethyl...

'*R*' and '*S*' are italicized and always put in parentheses. Use no spaces in a name. Only numbers and italicized words have dashes around them.

Volumes: 3 x 10 mL

"x" is "x" in Helvetica font

degree sign: SHIFT+OPTION+8

minus = en dash: OPTION+hyphen (without space)

no space before and after ':'; normalized to 100 (use spaces in ChemDraw figures, though, because the 75% reduction makes the numbers microscopic

no space between number and '%'; no decimals

en dash: OPTION+hyphen

use en dash and degree sign. Add spaces around '=' and after the number but not around the en dash.

Space after number.

use small m, capital L, then "of" before the solvent

space before "h", same symbol for singular and plural

μ: OPTION+m; μ: m in Symbol font.

' ' character: SHIFT+OPTION+9 or

: d in Symbol font

Italicize *J*. Spaces around '=', no space in the integration. "Hz" does not need to be written, as the general experimental has this in it.

Use en dash for a range of values.

(-)-Roxaticin

*N*-methylmorpholine *N*-oxide

(*E*)-2-butene.

*tert*-butyl alcohol

15:85 – 20:80 EtOAc:hexanes

>94% ee

References

example: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

*Tetrahedron Lett.* **1980**, *21*, 100–104.

*Tetrahedron Lett.* **1979**, 100–104. (No volume number before 1980)

The formatting of references may be handled by EndNote, a commonly used program for managing bibliographic information.

### Miscellaneous Symbols:

hyphen '-'

en dash '–'

em dash '—'

Line return (not a new paragraph)

heat: ' '

Triple bond '≡'

Words that should not be abbreviated: saturated, quantitative, aqueous, powdered,

Nouns that take singular verbs: grams, milligrams, equivalents, number, mixture,

Useful abbreviations: h (hour(s)), min (minutes), equiv (equivalents), eq (equation), mmol (millimoles), calcd (calculated)

### Numbering:

Scheme 1, 2, 3...

Figure 1, 2, 3 ...

eq 1, 2, 3 ...

Table 1, 2, 3 ...

### Abbreviations:

For a complete list of standard abbreviations, see: *J. Org. Chem.* **2001**, *66*, 24A.

### Miscellaneous Words:

to describe “rotovapping”: “concentrated *in vacuo*”

Celite (capitalized)

one-pot

overalkylate

transmetalation

“reflux” is not a verb: “heated at reflux” is the more accurate description

Use en dash for minus sign, separate name fragments with a hyphen (no line break)

Italicize atom symbols in a chemical name.

Italicize '*E*' and '*Z*'.

italicize *tert*, *sec*

Spaces around '-' (en dash) but not “:”

No space between '>' or '%' and number. Space between '%' and 'ee'.

A space but no punctuation before '*J.*' and '**1969**'.

**The following text is a sample experimental in JOC format (we thank Dr. J. H. Smitrovich for assembling this experimental).** Please note the grammar used to describe the procedure and the format for reporting characterization data.

**(1*R*\*,2*S*\*,3*R*\*)-1-Phenyl-2-methyl-1,3-butanediol (2).** To a cooled (0 °C) solution of *tert*-butylhydroperoxide (0.207 g, 2.30 mmol, 90%) in 1.3 mL of DMF was added CsOH·H<sub>2</sub>O (0.331 g, 1.97 mmol). After the mixture was allowed to warm to 25 °C, a solution of oxasilacyclopentane **1** (0.050 g, 0.164 mmol) in 0.8 mL of DMF was added dropwise by syringe. After 10 min, *n*-Bu<sub>4</sub>NF (0.214 g, 0.82 mmol, hydrate, lyophilized from benzene) was added. The reaction mixture was heated at 75 °C for 8 h. After the mixture was cooled to 25 °C, Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> was added, and the solvent was removed *in vacuo*. The resultant oily solid was partitioned between 5 mL of H<sub>2</sub>O and 10 mL of Et<sub>2</sub>O. The layers were separated, and the aqueous layer was extracted with 2 × 10 mL of Et<sub>2</sub>O. The combined organic layers were washed with 10 × 1 mL of H<sub>2</sub>O and 5 mL of brine, dried (MgSO<sub>4</sub>), and concentrated *in vacuo* to afford 0.057 g of a yellow oil. The oil was purified by flash chromatography (25:75 – 35:65 EtOAc:hexanes) to yield the product as a colorless oil (0.019 g, 64%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 7.20-7.35 (m, 5H), 5.05 (d, *J* = 2.9, 1H), 4.24 (dq, *J* = 6.4, 2.0, 1H), 3.85 (br s, 1H), 3.4 (br s, 1H), 1.71 (m, 1H), 1.23 (d, *J* = 6.5, 3H), 0.83 (d, *J* = 7.2, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) 143.3, 128.0, 126.9, 125.6, 78.4, 72.0, 44.9, 21.4, 4.0; IR (thin film) 3355, 2975, 1380, 1199, 974, 742 cm<sup>-1</sup>; HRMS (CI/isobutane) *m/z* calcd for C<sub>19</sub>H<sub>33</sub>O<sub>2</sub>Si (M + H)<sup>+</sup> 321.2250, found 321.2249. Anal. Calcd for C<sub>19</sub>H<sub>32</sub>O<sub>2</sub>Si: C, 71.18; H, 10.08. Found: C, 70.97; H, 9.98.

## Tips for Proofreading Experimentals

1. All experimentals should be consistent. Keep in mind, though, that they should all be consistent *and* correct.
2. Significant figures must be considered. If a weight or volume is only precise to two significant figures, then no calculation using that number can be more precise than to two significant figures.
3. Several abbreviations, punctuations, etc. can be inadvertently incorrect. Check things like “mL” instead of its smaller relative “ml”... stuff like that.
4. Solids must have melting points.
5. Optically pure materials must have optical rotations.
6. Check the IR for key functional groups that the compound should have. Only a half dozen or so important frequencies should be listed.
7. Does the phase (solid or liquid) of the IR match the reported phase?
8. Make sure that the spectral data is in the correct order and is consistent experimental to experimental.
9. Check <sup>1</sup>H NMR spectra for the proper number of hydrogens. Make sure integrations are listed for every peak, and that all data is presented consistently.
10. Consider the <sup>1</sup>H NMR spectral data. Is it consistent with the structure?
11. Check agreement of coupling data with the proposed structure. Coupling constants must appear twice, naturally.
12. Check <sup>13</sup>C NMR for the proper number of carbons. Is the spectrum consistent with the structure?
13. Make sure the HRMS passes. Double-check the format. Is the ionization method indicated?
14. Check the elemental analysis to make sure it passed ( $\pm 0.4\%$ ). Make sure the format is correct and that the molecular formula is consistent with the HRMS.
15. If there are compounds with the same molecular formula (such as diastereomers), most of the data between the two ought to be similar (but not identical). Check the relation, because then you can catch mistakes in both at the same time.
16. Make sure compound numbers agree with the text.

**One way to proceed with proofreading:** Examine one particular type of data for all of the experimentals (the assembly-line method). I start at combustion analyses, and make sure the format is right for every compound and that they all pass. This way, the correct format for this data is always fresh in my mind. Then I proceed onto the HRMS and stuff like that. Then I do the IR, <sup>1</sup>H, and <sup>13</sup>C NMR spectra together for each compound, since at that point I am thinking more intensely about structure and functional groups