

Guide To Synthetic Chemistry

Keske Research Group

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Introduction

The purpose of this document is to provide a resource for the proper execution of laboratory techniques in synthetic chemistry. Whenever attempting a technique you are unfamiliar with, please refer to another member of the research group or directly to Professor Keske.

Safety

Personal Protective Equipment (PPE)

Within the lab setting, lab coats, and glasses must be worn at all times. Lab coats need to be worn closed. Nitrile gloves are also provided in different sizes. When working at a fumehood, these should also be worn.

Gloves

The importance of gloves can not be overstated, while their protectiveness is often over-implied. Gloves will prevent your skin coming in contact with many hazardous substances. However, they are not perfect as they can rip and are inherently porous. Things will go through nitrile gloves. ***If you spill a hazardous chemical on your gloved hands, you should remove, discard and replace your glove.***

Gloves are typically taken off and re-worn in the lab setting if they are not dirty or damaged. It is very common for workers in a lab to leave the lab and remove their gloves and put them in their lab coat pocket for future use.

You should always wash your hands after you take a pair of gloves off.

Gloves protect your hands from many things in the lab. As a result, your gloves may have hazardous substances on them which can transfer to other objects such as door handles. As such, ***gloves should only be worn in the lab. Do not wear gloves in the hallways, or anywhere else in the chemistry building.*** When you leave the lab, you should take off your gloves and washed your hands.

The Michael Jackson rule: If you are carrying something that requires a gloved hand such as a chemical you are transporting, only wear one glove in the hallway. This will leave your other hand available for opening doors. Alternatively, use the cart or other secondary container to transport the object in question.

Lab Coats

Lab coats should always be worn when working with anything hazardous in the lab. Your lab coat will protect yourself and your clothing from hazards in the lab. You WILL develop stains on your lab coat. Those stains otherwise would have been on your clothes or yourself. You additionally run the risk of carrying any spilled chemicals on your lab coat with you when you leave the lab. Similarly to gloves, they should be removed when leaving the lab.

Safety Specs

You must wear something over your eyes in the lab at all times. If you wear prescription glasses, you should wear over-glasses on top of your glasses.

Do not wear contact lenses in the lab. The solvents we work with in the lab can dissolve/melt contact lenses. Seriously. **Wear something to protect your eyes.**

Food and Drink

Do not eat or drink in the lab at any time for any reason. Do not bring food or drink into the lab for any reason. Use the fridge in the Chemistry Commons to store your food. Leave drinks outside the lab. As awesome as it would be to drink coffee while running a column, don't do it.

Similarly, do not throw out food waste in the lab. It gives the wrong image and may suggest that you are eating in the lab to any cleaning staff. Use the garbage bins in the hallway.

Transporting Liquids

When we pick chemicals up from science stores, or borrow things from other labs, it is common to carry chemicals with us in the hallways of the Chemistry Building. As chemicals typically come in glass containers, it is possible that you can break the container during transit. If a bottle breaks in the lab, it is relatively contained, when a bottle breaks in a hallway it is typically much worse. As a result, it is safest to use secondary containers when transporting chemicals. This is especially true of large solvent bottles (Winchesters). When using carts, ensure they have a raised lip to prevent bottles from sliding off.

Introduction to Organic Synthesis

General Considerations

There are different phases of each synthesis:

1. Synthesis
2. Workup
3. Purification
4. Characterization
5. Write up

There is often not just one way to do something. As a result, this document is not intended to be treated as a mandatory technique list. But instead should hopefully inform and establish confidence within the lab setting.

In general, reactions should never be attempted before:

- A preliminary search has been performed using a resource such as Reaxys.
- All required reagents have been located in the lab
- All safety protocols are considered
- You have planned out the procedure
- You have enough time to finish what is needed
- The experiment should be written out in your lab book

Flasks should be filled **no more** than halfway, and ideally less. If a reaction requires 25 mL of solvent, it is advisable to run this reaction in a 100 mL round bottom flask. The size of the stir bar chosen should reflect the size of the flask chosen.

All reactions should be run in the fumehood (where possible). Flasks should be clamped securely to retort stands. Culture tubes should either be secured in heating blocks or otherwise secured to retort stands.

Reactions can be heated with silicone oil baths, or heating blocks. Never use water baths for heating, and never heat the reaction directly on the hot plate. **CAUTION:** Always ensure that the temperature probe from the hot plate is placed in the oil bath or heating block.

Flasks should not be left open to air. If a reaction is run under an atmosphere of air, it is still recommended to seal the flask with a septum and use a needle to vent the reaction or attach a vacuum adapter. This is primarily to avoid contamination of your reaction by unwanted things falling in, and to avoid solvent evaporation in the fumehood.

All compounds that are synthesized require extensive drying before characterizing them. This typically requires drying under high vacuum, or extended drying on the drying line. Failure to do this will result in inflated yields, and NMR spectra displaying mostly solvents which are not appropriate for publication.

General Techniques and Equipment

Drying Glassware

Glassware is notoriously hydrophilic in nature and holds onto water from the atmosphere. In synthetic chemistry, this is a big problem as the small amount of water that lingers on the glassware can cause sensitive reactions to fail or suffer from low yields. As a result, where appropriate all glassware is pre-dried before use.

Oven: Glassware such as flasks should be placed in the laboratory oven for no less than one hour to ensure that it is dry before use. Be careful retrieving the glassware from the oven – use tweezers or the oven mitts. Use of the oven requires planning to ensure that you pre-emptively put the glassware in the oven before you need it. **CAUTION** – plastic of any sort (such as taps on Schlenk flasks or stop cocks) should be removed before being placed in the oven. They can melt or be deformed/damaged.

After glassware is removed from the oven, it should be placed under vacuum to cool down. This is most conveniently done by use of the drying line (*vide infra*). This will ensure that no unwanted air or moisture collects in the flask during cool down.

Alternatively, you can dry glassware as needed in a hurry by using a blow torch (see below). While this is more hazardous, it is very convenient and requires mere seconds to dry glassware. Caution should be taken with this, and if you are unsure how to properly use a blowtorch, do not attempt it.

Drying Glassware with a Blowtorch

The easiest and most effective way to dry glassware (most likely a round bottom flask) with a blowtorch is to seal the flask with a rubber septum and place the flask under vacuum on the drying line utilizing a needle adapter. This is important as when you start to dry the glassware with the blow torch, the vacuum will remove the water vapour from the flask as you produce it.

CAUTION: Before you start this process, ensure that there is nothing flammable near by. Ensure you are not clamping your flask with something that could melt. The blow torch is very hot, and your flask will not be the only thing that is exposed to the flame.

Once the flask is under vacuum, use the blowtorch to coat the entire surface of the glassware with flame. You should see water condensation appearing and disappearing as you do this. Once you see no more condensation (likely less than 5 seconds), you are done.

Leave the glassware to cool to room temperature under vacuum before you use it for anything. This will likely take 5-10 minutes depending on the glassware.

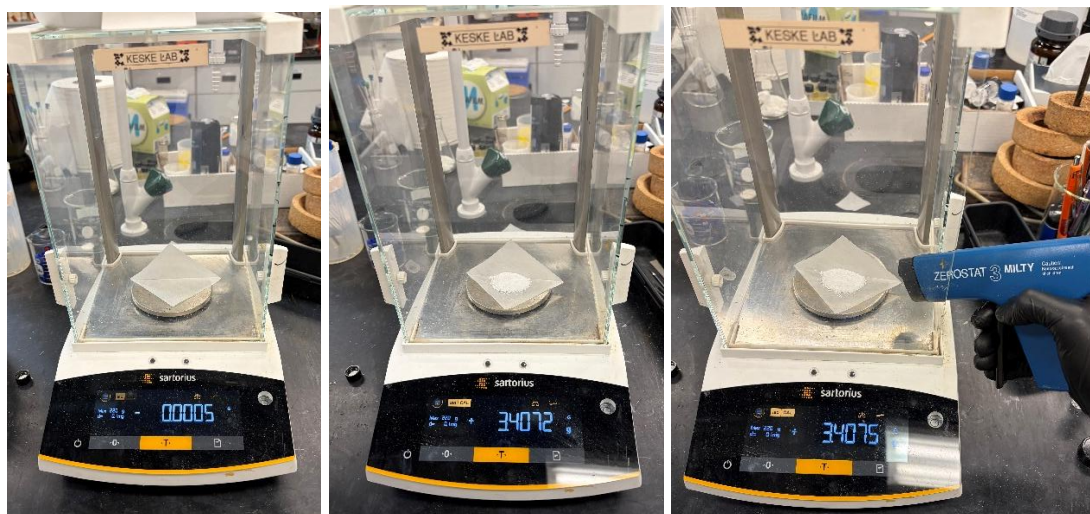


Analytical Balances

Any time a solid is weighed out in our lab, it will likely be done so with one of the two analytical balances. If much larger weighing is needed (>50 g), we also have a top load balance which is rarely used. Both top load balances have four decimal places, and the weight is displayed in grams (by our elective choice). Members of our group regularly weigh out masses between 2 -10 mg as an extreme using these balances. NB. This would appear as 0.0020 (2 mg) and 0.0100 (10 mg).

The most common way to weigh out is by using weighing paper. Boxes of weighing paper are stored on top of the balances, and can be purchased at Science Stores. The best way to use weighing paper is to pre-fold the weighing paper on a diagonal and then tear the balance weight. Carefully weigh the solid in the middle of the paper (to prevent spilling).

If the solid you are weighing is very polar, or even ionic – like a salt – you may have issues associated with static. This can manifest itself into the balance having trouble stabilizing a mass, or the compound even sticking to the reagent bottle, the spatula, your gloves, or seemingly flying in the air. This can commonly be rectified by using an anti-static gun. Point the gun directly at your sample about 2 inches away, and pull the trigger once gently. You may need to also use the static gun to transfer the solid into your flask.



When transferring the solid into a flask, the diagonal crease will help maintain the general shape of the weighing paper. You should always pour the solid in carefully to prevent spilling. Here, the receiving flask is a culture tube which has been clamped and angled at almost 45°. After you have positioned the weighing paper, with light pressure, the paper will self-assemble into a funnel shape which you can see in the picture. If the solid does not transfer easily, you can then use a spatula or an anti-static gun (or both) to help get the remainder. This is a common method to prevent spilling.

NB. If you do not think you transferred all of the compound into your flask, you can reweigh the weighing paper after and take the difference for what was added.



Measuring Liquids – Syringes

When measuring liquids, there are several ways this can be done, and it depends on your application. If you are measuring 5 – 100 mL of a solvent for something that is not air sensitive, a graduated cylinder will suffice. For reagents to be used in a reaction (0.1 – 10 mL), a syringe is preferable as they are far more

accurate. Most commonly, a syringe will be capped with a 20-gauge needle (yellow). A syringe should never be used without a needle to measure something.

Graduated Cylinder	Syringe with needle	Microlitre syringe
		

Syringes with needles can puncture septa which is ideal for adding reagents to flasks while under an inert atmosphere (*vide infra*). Yellow needles can be carefully bent, allowing you to measure out liquids from reagent bottles conveniently. Hold the syringe upright to inject the air bubble back into the bottle. Depending on the bottle and your syringe, you may need to use two hands for this process to hold both the bottle and the syringe. This will likely require some practice.



If small amounts (15 – 500 μL) of a liquid is required, it is recommended to use a glass microlitre syringe. While many people prefer to use an Eppendorf pipette, these are calibrated for H_2O and commonly suffer from reproducibility errors when using organic liquids. A microlitre syringe is the most accurate way to measure small amounts of liquids out. This is particularly important if you are doing screening for catalysis.

When using a syringe, you must measure the amount without the air bubble if possible.

Capping Syringes

Likely, more accidents occur in the lab associated with the use of needles than anything else. Needles are very sharp, and it is remarkably easy to injure yourself with one. This often occurs while trying to re-cap a needle on a syringe.

The safest way to put the cap back onto a syringe is to use the 'one hand method'. Always leave the needle cap on a flat surface which is easily accessible. While holding the syringe with one hand, position the needle directly into the cap. Once enough of the needle is into the cap, rotate the syringe vertically, allowing the cap to cover the needle. Using your thumb and first finger, pull down on the cap to securely cap the needle.



Transferring Solids

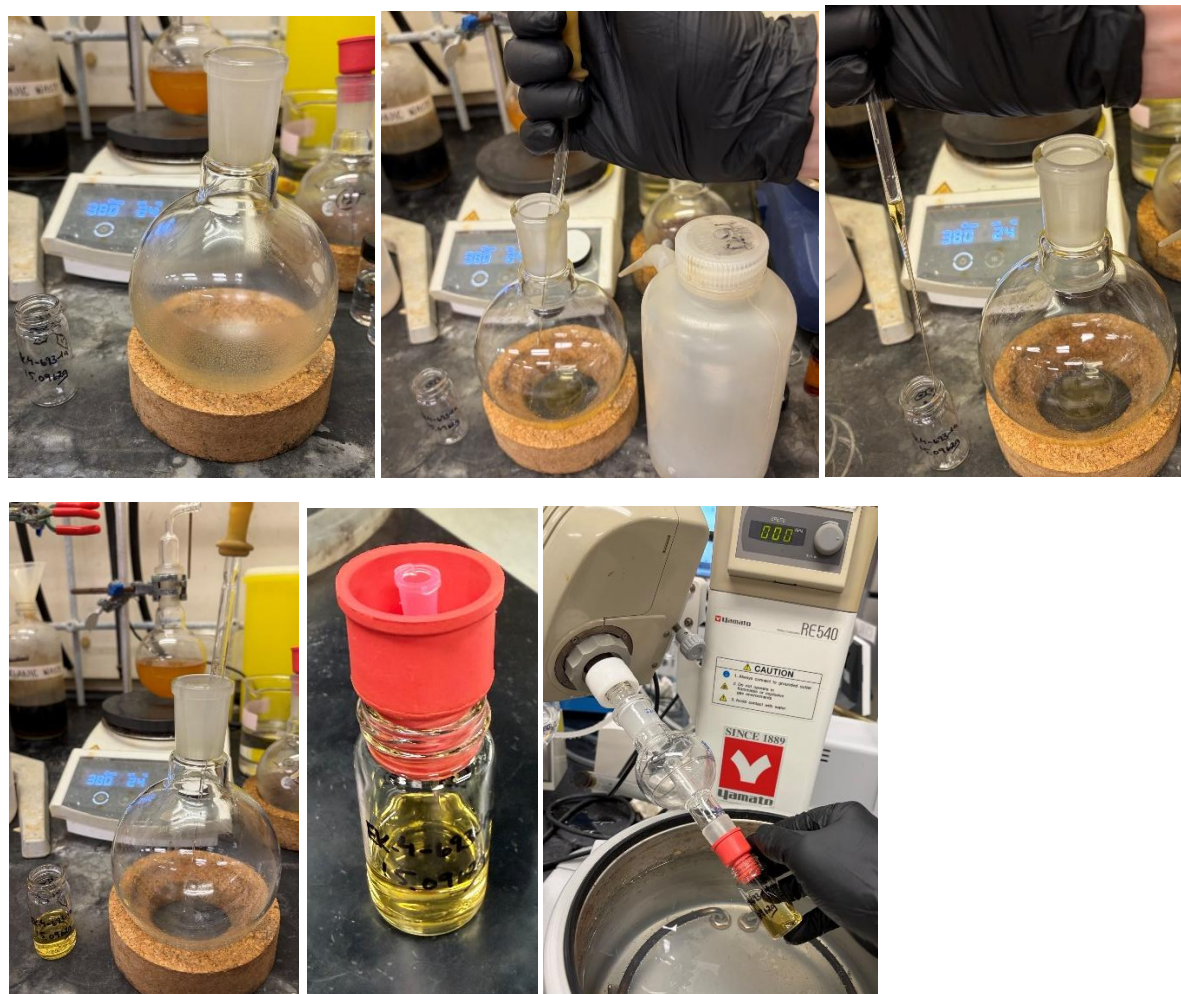
When you isolate a solid product in a round bottom flask, and need to transfer it to something else, like a storage vial, there are a few ways you can do this.

A common method is to pour the solid out of the flask onto weighing paper and then pour the solid into a pre-tarred vial. Depending on what the solid is, significant amounts of static might make this process tricky. Use the static gun to help you here.

This method is particularly effective for transferring large amounts of a solid that are not soluble in a volatile solvent. The solid in the photo is a sulfinate salt, which is only soluble in water and alcohols. The downside to this method is that it is essentially impossible to ensure that you transfer all of the solid.



Another very common method is to dissolve the solid (or residue) in a minimal amount of a volatile solvent such as dichloromethane and transfer the solution to a new flask or vial with a Pasteur pipette. The solution can then be evaporated *in vacuo* using a rotovap (*vide infra*). This method is particularly effective at transferring small amounts of compounds. This is also ideal whenever you will be reporting an isolated yield, for example after column chromatography, as you typically do not throw any remaining product away.



Rotary Evaporators (Rotovaps)

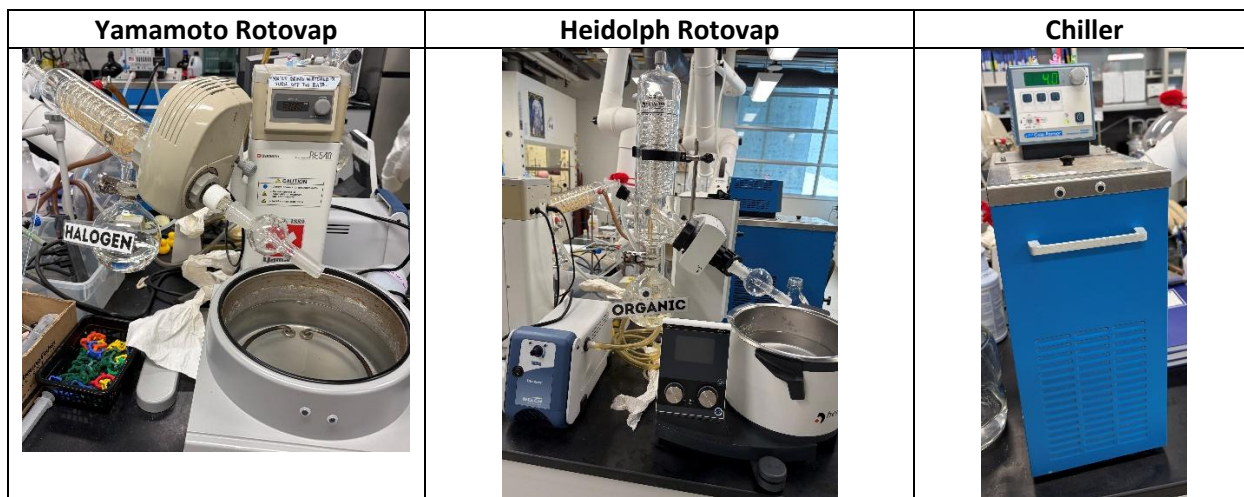
A very common requirement is to remove solvent from a solution. The most common way to do this is by using the rotovaps. Rotovaps are simple distillation apparatuses, which have condensers to collect evaporated solvent. They operate by attaching a sample at one end, and applying vacuum. They have motors which rotate your sample to prevent bumping during this process. Additionally, they have heated water baths to help the process.

Our lab has two rotovaps – the older Yamamoto rotovap uses house vacuum (from the yellow taps on the bench) and the newer Heidolph uses the Welch pump next to it for vacuum. Both rotovaps have cold

water pumped through their condensers by the nearby chiller, which we set at 4.0 °C. ***The chiller is switched on at the start of everyday and off at the end of the day.***

The older Yamamoto rotovap no longer moves up and down. Instead, you can place the flask in the water bath by swiveling the flask in and out of the water. The Heidolph rotovap is left at the same angle, and is moved up and down to place the flask in the water bath.

Water will evaporate from the baths overtime. They are refilled with DI water, not tap water. In general, water baths are used in the range of 30 – 50 °C, depending what solvent you are removing. They can be heated here to remove solvents like H₂O or toluene, but this will cause fast evaporation of water in the bath. Ensure you turn the water baths off when not using them.



Bump traps are located in the box nearby the rotovaps and should always be used to prevent damage to the instruments. Keck Clips can be utilized, but they should never be relied on. A good rule is to always hold onto your flask until you are sure it is under vacuum (as in picture). Ensure that the stop cock on the condenser is open, and turn on the vacuum (either house vacuum or the vacuum pump), leaving your hand in place holding the flask. Turn on the spinning, still leaving your hand in place holding the flask. Finally, close the stopcock on the condenser which will put your system under vacuum. Now that vacuum has been applied, you can remove your hand and lower the round bottom flask into the heated water bath.

The solvent that is evaporated will then be collected in the solvent trap. Please ensure that you dump the collected solvent into the solvent waste when you are done.



Vials: For drying samples in vials, we attach 19/22 (medium size) septa into the top of vials which are then punctured with 18G (pink) needles. This specific size of septum conveniently fits on the outside of 24/40 ground glass joint. **The vial is held in place by the vacuum.** You should not remove your hand from supporting the vial until you are sure that the vacuum has been applied.

A pink needle is preferred here as it will help the evaporation process. A yellow needle will also work, but it will go slower.



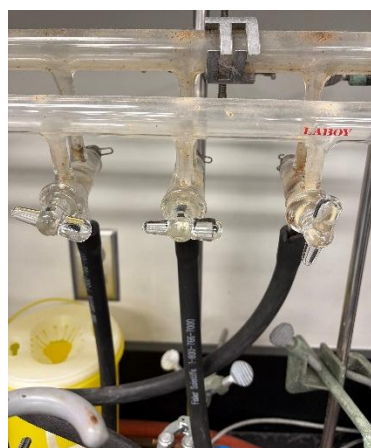
Sonicator

The small sonicator is very useful to help dissolve solids into solvents. It operates by sending sonic pulses through a water bath which effectively acts as aggressive stirring. *This instrument can be very annoying to have on in the lab as it is a bit loud.* This instrument is not used heavily, but is very useful when fighting with a compound that is resistant to dissolving in a solvent. Simply make sure the water bath is full with deionized before use, and turn the dial. If using for a long time, clamp your flask on a near by retort stand – don't leave the flask sitting on the bottom of the bath.



Schlenk Line (Double Manifold)

Each fumehood is equipped with a double manifold Schlenk line. The Schlenk line allows users to put flasks under inert atmosphere. One of the horizontal glass tubes is connected to vacuum, and one is connected to nitrogen gas. Each Schlenk line is connected to five glass taps which can be rotated 360 degrees. The taps have rubber tubing which extends below the Schlenk line which can be attached directly to reaction flasks. Depending which way the tap is rotated, the flask connected through the rubber tubing will be exposed to different atmosphere (nitrogen or vacuum).



To use the Schlenk line, ensure you properly attach your flask with the rubber tubing ensuring no leaks. If you wish to put your flask under N_2 gas, you should typically (where possible) first apply vacuum to your flask to remove any air, before you then fill the flask with N_2 .

Drying Line

The drying line is a series of three Schlenk lines attached to each other. The line is attached to a high vacuum pump, and house vacuum. The house vacuum is weaker than the high vacuum, but is very convenient to dry samples for extended times, for example after solvent removal using the rotovap.

Samples in vials are commonly dried by attaching 19/22 (medium size) septa into the vials equipped with a needle (typically a 18G pink needle), which is then put under a glass adapter. The adapter is clamped to a retort stand. *The sample vial is held in place by the vacuum.*



Strauss Flasks

Anhydrous solvents are stored under an inert atmosphere in flasks known as Strauss flasks, typically with molecular sieves. These flasks are stored in the flammables cabinet, and a wide range of common solvents are kept at all times such as THF, toluene, Et₂O, dioxane, tAmOH, CH₂Cl₂, etc.

To use these flasks, you must attach them to a Schlenk line in the fumehood. Complete three vacuum/N₂ cycles to place the flask under an inert atmosphere before opening the tap. Ensure that the N₂ is bubbling at a sufficient rate, and then remove the tap altogether and replace it with a rubber septum. In general, the 14/20 rubber septa fit perfectly over these joints when placed upside down. Now a long solvent needle can be used to access the solvent. **NB.** Ensure you purge the syringe three times with inert gas before taking solvent.



Working Under Inert Atmosphere

The vast majority of the reactions we run in our group are sensitive to either air, moisture or both. Reagents such as strong bases (anything stronger than NaOH), Grignard reagents, or alkyl lithiums (nBuLi, etc.) have the risk of reacting with H₂O, O₂ or even CO₂, impacting their reactivity dramatically. It is imperative that whenever in doubt, you operate under “inert atmosphere”.

Most commonly, this means using an atmosphere of either N₂ gas or Ar gas. N₂ has the advantage of being much cheaper, but it is lighter than O₂, and as a result can be displaced by atmospheric O₂, leaving the reaction flask if it's not sealed properly. Argon, while much more expensive, is heavier than air and offers more flexibility. Each fumehood is equipped with a N₂ cylinder attached to the Schlenk line, and a single Argon cylinder is present in the lab. There is also a house N₂ hookup on the west wall.

There are three common ways to work under inert atmosphere:

- 1) Inert Atmosphere Balloons
- 2) Schlenk technique using the Schlenk line (double manifold)
- 3) Glovebox

Inert Atmosphere balloons

This is the most common way utilized in our group. While balloons are simple and may look silly, they are incredibly convenient, inexpensive, and they work very well. Simple party balloons can be purchased from the dollar store, filled with N₂ or Ar. They are also very flexible and your reactions are not tethered to a fumehood (as you would be with the Schlenk line). You can easily set a reaction up and move it elsewhere very easily. The other benefit of a balloon is that the pressure in a balloon is higher than the atmosphere and you don't have to worry about setting the pressure correctly on a regulator. The pressure is set by the outlet needle, which are interchangeable based on need.

A balloon is incredible versatile. They can also be fun if you get ones with pictures on them.

A word of caution, balloons pop easily. As a result, we always double line our balloons to prevent problems if a balloon pops while in use. When a balloon pops, continue use with it, but replace it afterwards. The second skin of a balloon is cautionary, you shouldn't rely on it.

Making a double-skin balloon

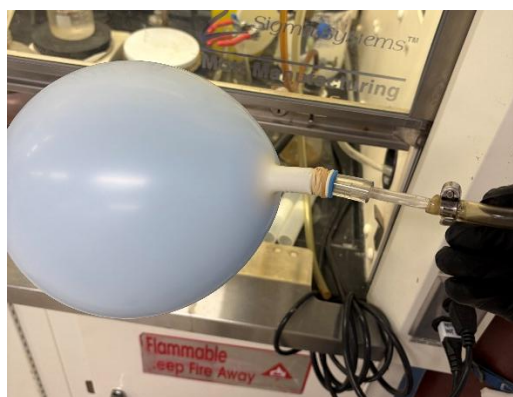


- 1) Obtain two balloons from the drawer, a small piece of tubing, an elastic, and something long and not sharp (like a pencil).
- 2) Use the pencil to stretch out one of the balloons
- 3) Insert the pencil and first balloon into the second balloon
- 4) Remove the pencil, and roll both balloons over the piece of tubing
- 5) Wrap around the balloon with an elastic to help keep it tightly sealed around the tubing
- 6) Place a cut off 1 mL syringe barrel into the tubing
- 7) Good to go

Using a Balloon

Before you equip your reaction flask with a balloon, it is best to first put it under vacuum to remove any air present. Placing a balloon on a flask filled with air will do little to provide an air-free environment. Typically, the drying line (the connected three Schlenk lines) are used to put reaction flasks under vacuum.

The regulator on the Argon cylinder is attached to tygon tubing which conveniently fits a 1 mL syringe. You can simply insert the balloon into this tubing and you will be able to fill it with Argon gas.



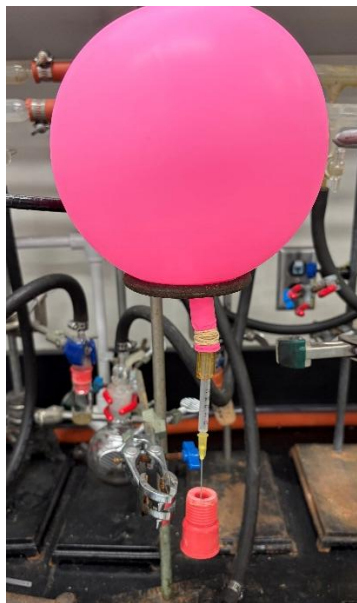
In general, you should assume that balloons are filled with air before use. As a result, you should always purge them with inert gas before use. To do this, simply fill the balloon with a **small** amount of gas and deflate the balloon three times before filling.

Depending on your usage, the size you fill the balloon will vary. You likely don't need a beachball. A balloon the size somewhere between a grapefruit and a cantaloupe is likely good. Twist the balloon when you take it off of the cylinder so you don't let all of the gas out.

Balloons are then attached to your reaction flask by using a needle at its end and puncturing a septum on a reaction flask. Often, needles used for this application are heavily reused unless they get dirty. As a result, the needles may get plugged or blocked with various debris. It is always good form to first ensure that gas is flowing out of the balloon through the needle by squirting a very small amount of something like acetone on the bottom of your fumehood, and holding the balloon overtop of the puddle. If you do not see ripples in the liquid, gas is likely not flowing and you should get a new needle.



If you are done with the balloon and you have extra inert gas, a common thing to do is to wedge the needle of the balloon into the thick part of a rubber septum. This will largely maintain the argon in the balloon for later use.



Sure-seal Reagents

Several commercially available reagents come with Sure-seal[®] caps. In general, these reagents are air and moisture sensitive and should be treated carefully. These are effectively septa which can be punctured with needles to access the contents. As you remove the solution from these bottles, you will create a vacuum in the flask, and thus an inert atmosphere must be provided during this process to maintain working pressure in the bottle.

It is recommended to use an argon filled balloon for this process (rather than a Schlenk line), as you will have flexibility and mobility. You should always use a yellow needle (20G) to prevent puncture holes that are too large.



Reaction Baths

Commonly, reactions are run at elevated temperatures. Depending on the nature of your reaction, and the desired temperature, there are different ways of heating your reaction. Likely the most common method is using an oil bath on a heated stir plate.

Each hot plate is different, but they should all have a thermocouple probe to measure the temperature of the bath. ***Always make sure that this is placed directly in the oil bath.*** Additionally, all oil baths need to have a metallic object in it to help stir the oil and ensure homogeneity. This commonly something like a paper clip.

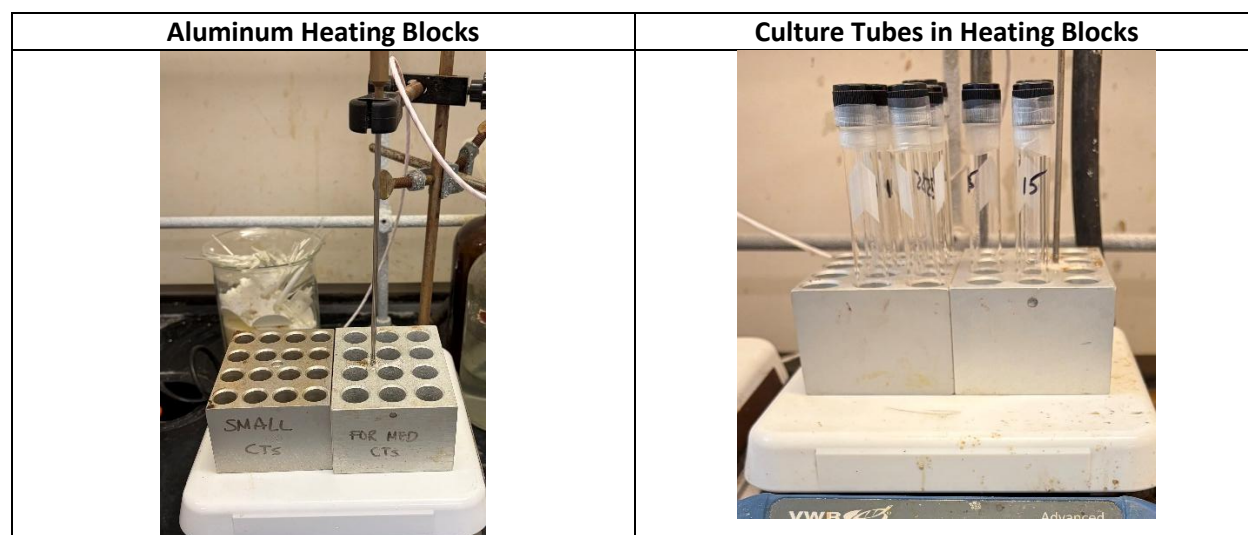
When using an oil bath, ensure that a round bottom flask is submerged in oil to roughly the fill point of the flask (see picture). Do not completely submerge the entire flask in oil. Similarly, a flask barely in the oil bath will not be heated thoroughly. As you place objects in the oil bath, you will displace some oil. If it does not look possible to place your flask in the oil bath without spilling oil, use a different bath.

There are different kinds of oil used in a laboratory, each has different thermal capacities. Mineral oil or paraffin oil is acceptable for use with temperatures below 100 °C. Even extended heating at 80-90 °C can lead to discoloration of the oil, and subsequently a fire may start.

The most ideal heating bath is either silicone oil which can safely be heated to ~180 °C, or a solid material like aluminum or sand. Sand often suffers from poor heat homogeneity. Aluminum heating blocks are often ideal for culture tubes, but they do not make extensive contact with your glass reaction flasks and can lead to problems with consistent heating. ***Ensure that the thermocouple probe is covered in sand in a heating block.***

Reaction being heating in a silicone oil bath	Culture tube reactions in an oil bath
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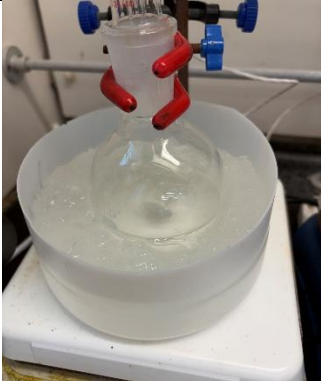


Ice baths are also commonly required. When some reagents are mixed, it can be very exothermic. This is common when reactions are quenched or initially set up. As a result, a bath of ice and water is very common for helping to stabilize the temperature. ***Do not just use ice, use an ice/water mixture.*** This will ensure contact with the glass and will more efficiently cool your reaction flask.

Most commonly, we use recycled solvent bottles that have been cut up into water/ice baths. They provide temperatures of approximately 5 °C.

On occasion, you may need to cool your reaction to much lower temperatures. For example, lithium-halogen exchanges, as well as many other lithiation reactions are commonly conducted at -78 °C. This is most easily achieved by using dry ice in a bath of isopropanol or acetone. *However, as Trent University does not have access to dry ice on demand we have to get creative.*

Our lab has often utilized liquid nitrogen baths along with acetone or iPrOH as a substitute. Depending on the reaction, this can be a suitable solution however it is harder to assemble and maintain temperature. Additionally, the resulting temperature will actually be colder than -78 °C. We have utilized this method successfully for deprotonation and metallation of NHC-HX salts, however we have had issues with lithium halogen exchange reactions.

Reaction cooled in Ice Bath	Liquid Nitrogen Acetone/iPrOH
	

Reaction Progress by Thin Layer Chromatography (TLC)

The most common analytical tool used in most synthetic chemistry labs is actually a simple TLC setup. This is incredibly useful to help determine if a reaction is successful, or complete.

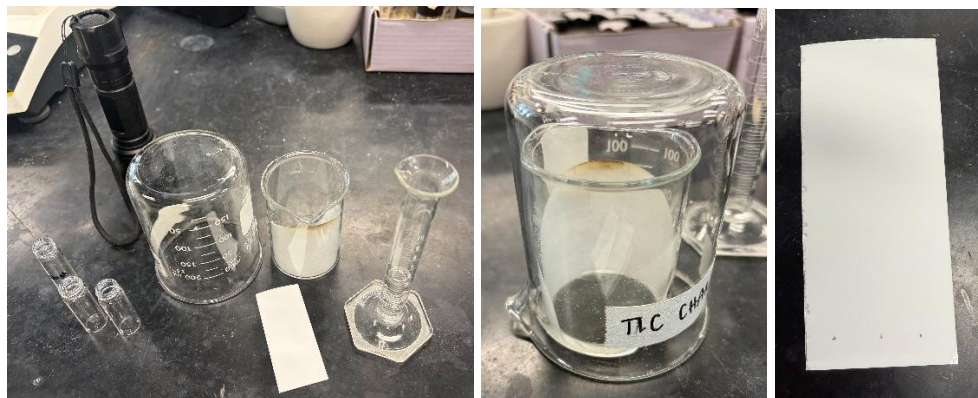
A quick TLC is taken of almost all preparative organic reactions to ensure completeness. It should also always be completed before attempting purification (*vide infra*). Part of the power of TLC analysis is its simplicity. Very little is required for a TLC setup. Commonly two beakers (one smaller than the other) are utilized to make a TLC developing jar. A small piece of filter paper is cut and placed inside the inner beaker to help create a saturated atmosphere in the chamber. This paper is heavily reused and *very rarely* changed.

This setup is perfect for analysis of TLC plates done in many synthetic labs. If you add 5 mL of eluent (measured with a graduated cylinder) it is the perfect volume for a standard TLC plate. The most common starting eluent in our group is 4:1 hexanes:EtOAc. This is often sufficiently polar to allow for separation between compounds that is visible by your eye. You may need to adjust this for your mixture, but this is commonly the starting point. Using squirt bottles, add 1 mL of EtOAc and 4 mL of hexanes to a graduated cylinder and pour it into the chamber. You will also require three clean small vials and a capillary spotter. One will be for a rinse to wash the capillary, the other two will be used for solutions to be spotted on the TLC plate. We will use UV irradiation at 254 nm to observe compounds on the TLC plate. Our lab uses a UV flashlight for this as it is very convenient.

Eluents: As mentioned, the “go-to” eluent mixture for TLCs is 4:1 hexane:EtOAc. Depending on the reaction, this may be inappropriate. If you require a faster eluent, you can increase the amount of EtOAc, slower, you can decrease it. If the spots do not move off the baseline at all, it might be advisable to use a CH_2Cl_2 :MeOH mixture instead. A maximum of 10% MeOH should be used. This is essentially as polar as you can get.

TLC plates: Our lab buys large sheets of TLC plates which need to be cut by the paper cutter in the undergrad labs. Before running a TLC, ensure your TLC plate has a straight edge, otherwise trim it with a pair of scissors. A standard TLC plate for reaction progress should always be marked with 3 lanes – starting material, co-spot, and a reaction lane. Mark the plate with a pencil (not a pen) with three small dots or

lines for where your mixtures will be spotted (as in picture). This should be approximately 0.5 – 1.0 cm from the bottom of the plate.



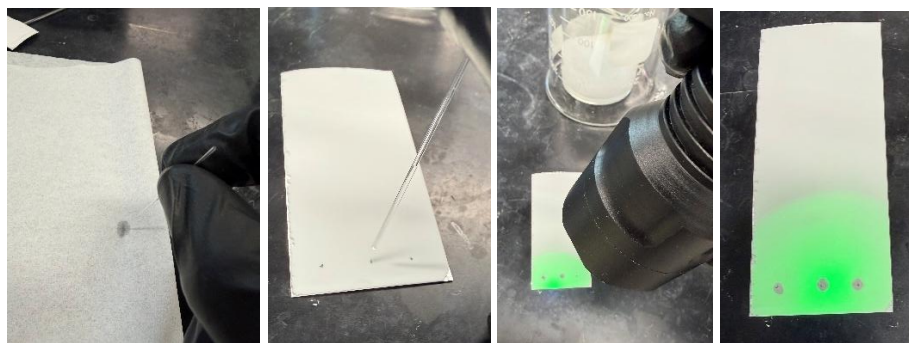
Fill the rinse vial with a small amount (~1-2 mL of acetone). And place the capillary spotter in this vial. Next, make your solutions in the other vials. If your starting material is a commercial reagent, it is recommended to take a small amount from the bottle using a Pasteur pipette. If the reagent is a liquid, a single drop is likely needed. If your reagent is a solid, dip a pipette into the bottle and try to fill the pipette tip with compound (as in picture) and shake it into the vial. This is far cleaner and you're less likely to spill compound than using a spatula.

For your reaction mixture, complete a similar process. Take an aliquot from your reaction – often this is done with a Pasteur pipette and then dilute it with a solvent such as acetone. The reaction mixture is likely far too concentrated to run directly, but it of course depends. Make sure the vials you are using are well labelled. Often a sharpie marking such as “SM” and “Rxn” will suffice.

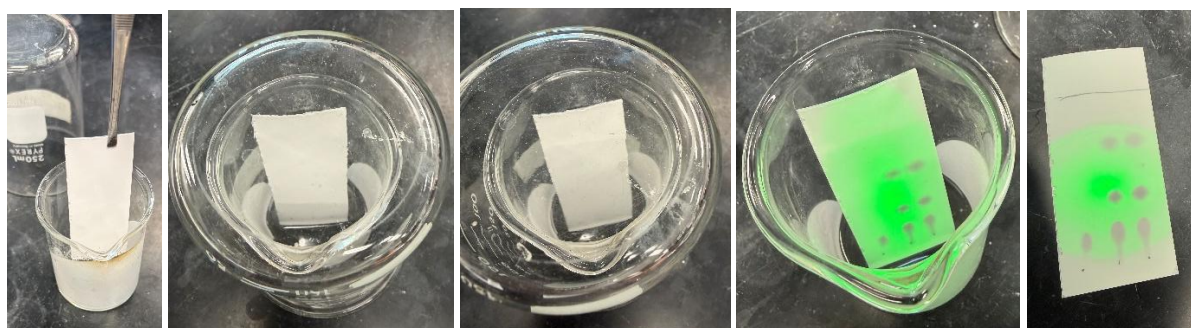


Obtain a small piece of paper towel and place it near by. Before spotting your TLC plate, run the rinse solvent out of the capillary onto paper towel (as in picture). The solvent should flow easily and quickly. If it does not, it might mean your capillary is blocked and broken. Dip the capillary into your SM vial and put a single small drop of the solution on the left and middle lanes of the TLC plate. Be very quick and precise with this ensuring a small spot. Practice is required to keep this spot small and tight in size. Failure to do this will result in a big blob, which will be hard to interpret.

After you spot these lanes, use the flashlight to detect the spots (as shown). If you cannot see the spot you just put on, your solution is likely not concentrated enough. You can either apply additional spots or make a more concentrated solution. After you have completed this process, rinse your capillary by dipping it in the rinse vial, and running out the solvent onto paper towel *three times*. Repeat this whole process with the RXN solution, with the middle and right lanes.



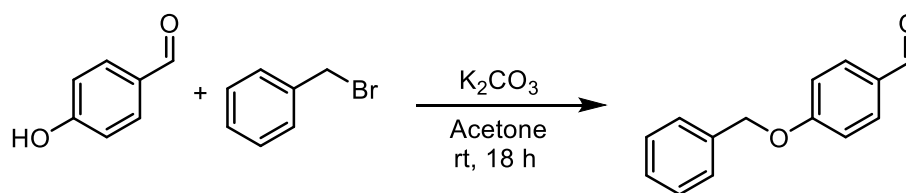
If you are able to see all three lanes clearly as tight spots (as in picture), carefully place the TLC plate into the TLC developing jar with the spots at the bottom using a pair of tweezers. Place the big beaker on top and wait. You should see the solvent front moving up the plate.



When the solvent front is about 1-2 cm from the top of the plate, which should take about 4-5 minutes, the TLC experiment is complete. Remove the big beaker, and shine the flash light on the plate. You should see the spots have moved up the plate.

Remove the TLC plate from the chamber with a pair of tweezers. Mark the solvent front with a pencil in case you need to calculate R_f values and allow the plate to dry. You may want to carefully circle any spots you see with a pencil. Many compounds are slightly volatile, and overtime will disappear from the TLC plate.

The reaction being monitored in the above TLC experiment is the alkylation of 4-hydroxybenzaldehyde with benzyl bromide. This reaction came from the literature and was conducted on the same scale as the literature report.



The TLC plate example above shows incomplete conversion to product. The bottom spot is clearly starting material, which is confirmed with the co-spot. The top spot is benzyl bromide, and the product is the middle spot. From this, we can clearly see that the reaction is working but is not complete. As such, it will be left to react for longer time before progress is checked again.

If a reaction progress TLC experiment was not conducted, it may have been incorrectly assumed to have gone to full conversion. Where possible, a TLC (or potentially GCMS/NMR where applicable) should always be tested, *even when following literature procedures*.

Aqueous Workup

One of the most common things done in a synthetic chemistry lab is an aqueous workup. The purpose of an aqueous workup is a preliminary purification to remove any water-soluble species such as salts. It is also common to remove water soluble solvents such as alcohols or MeCN/DMF/DMSO.

The terminology in written procedures can be confusing. Commonly we would say something to the effect of “you are extracting your product into an organic solvent and washing it with an aqueous solution” or something similar. The two most common organic solvents used for this process in our lab are likely ethyl acetate and dichloromethane. However other solvents can be used here. Importantly, *all organic solvents commonly used in our lab EXCEPT for halogenated ones (dichloromethane and chloroform) have a lower density than water and will therefore be the top layer*.

Most commonly you will preform an aqueous workup like in the example below where your crude product is extracted into an organic solvent from its reaction mixture. In this example, it will remove water soluble metal ions as well as silicon related byproducts. The isolated organic layers are then dried to remove any residual water leaving a much purer reaction mixture.

To preform an aqueous workup, you will need a separatory funnel with a cap, two clean Erlenmeyer flasks. Pressure will be developed in the separatory funnel, so often extra large separatory funnels are utilized.

In the example below, a crude reaction mixture is transferred directly to a separatory funnel. To this solution, water (approx. 100 mL) and ethyl acetate (approx. 40 mL) are added. Amounts needed will depend case by case. A lid is placed tightly on the separatory funnel, and the flask is shaken. It is best to hold the separatory funnel by firmly placing your hand on the lid to keep it secured during this process (as in picture). The separatory funnel should be inverted while shaken – **do not just swirl it**. Vent the separatory funnel through the stop cock. Re-seal the stop cock and allow the solution to settle in its ring clamp with the lid off.



You should see the solution slowly settling. Once the solution has settled forming a bilayer, place one of the Erlenmeyer flasks underneath the separatory funnel and open the stop cock. Drain the lower layer (in this case aqueous) into the flask. Close the stopcock just at the organic solvent front. Switch the Erlenmeyer flasks and drain the organic layer into the flask.



The organic layer is set aside, and the aqueous layer is then poured back into the separatory funnel, more ethyl acetate (~30-40 mL) is added, and the process is repeated (total of 3 times). Each organic layer is combined together into the same Erlenmeyer flask. The organic layer is then poured back into the separatory funnel, and brine is added. Brine (saturated aqueous NaCl) is used to “pre-dry” the organic layer. Again, separate the two layers into their respective flasks. That is, add the brine wash to the aqueous flask, and isolate the organic layers together.

The organic layer is then dried with MgSO_4 by adding small amounts of the powder to the flask. Swirl the flask until you see the ‘snow globe effect’, which implies as you swirl it you should see powdered MgSO_4 floating in the flask. If all of the MgSO_4 has clumped to the bottom, you need more.



The solid MgSO_4 is then filtered off. This can be done by a gravity filtration or preferentially by a vacuum filtration (as shown). Vacuum filtrations are much faster, and typically easier than gravity filtrations. You should not use a fritted funnel for this however, instead using a Buchner funnel with filter paper. Ensure to wet the filter paper with solvent before pouring the solution on the filter and pour the solution slowly. If you see solid moving through the filter, your paper was likely not fitted properly. You will need to repeat this process with a new flask.





Once the solution has been filtered, you can transfer it to a round bottom flask and remove the solvent on the rotovap. The resulting crude product can then be further purified. **NB.** Notice how in the example above, the final solution is clear and colourless, despite starting from a murky brown/grey solution.

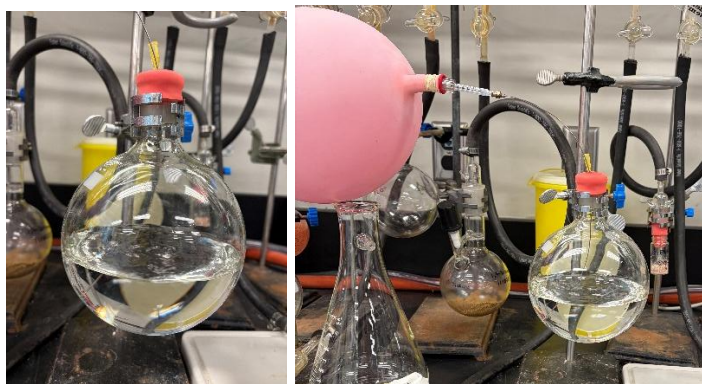
Degassing and Drying Solvents

In most syntheses, anhydrous and degassed solvents are utilized. Depending on what solvent you are using, sometimes commercial anhydrous solvents are used directly from commercial bottles sealed with Sureseals®. In most cases however, solvents will be taken from Strauss flasks which are stored (sealed) under inert atmosphere containing 3Å molecular sieves. Common solvents are taken from the solvent purification system (SPS), and are additionally degassed and dried as below.

Degas Solvents by Sparging: First get a flask such as a round bottom flask that is sufficiently large for the amount of solvent needed (typically 500 mL – 1L). Flame dry the flask, and place it under Argon. Add the solvent to be degassed/dried, and seal the flask again with a septum. Only fill the flask approximately half full ideally.

Using a large solvent needle from the oven, secure a balloon of inert gas (ideally argon) to the flask and also equip an outlet needle. A simple yellow needle is usually sufficient here. Lower the long solvent needle into the flask so that it is submerged into the solvent. You should see noticeable bubbling occurring. Leave the balloon to bubble through the solution for 30-40 minutes minimum (depending on the amount you have). If no bubbling is observed, you either have a leak or the needle is blocked.

Once complete, remove the outlet needle, and pull the argon balloon needle out of solution. Leave the flask under the balloon. You can now access the sparged solvent with a syringe or cannula. Typically, we then transfer this degassed solution into a Strauss flask containing 3Å molecular sieves via a cannula (as below).



Dry Solvents: Add 3Å molecular sieves to a Strauss Flask and leave the flask in the oven. The sieves are always stored in the lab oven and should be read to use. If you ever see the sieves are getting low, feel free to top up the beaker. Once you have poured the sieves into a flask carefully, the flask should then be placed in the oven until you are ready to use it.

Place the hot Strauss flask containing the molecular sieves on the drying line (with its Teflon tap attached), and leave under vacuum until room temperature. It is best to attach it with a septum (not a ground glass joint) so you can backfill it with inert atmosphere afterwards. Once cool, equip the flask with a balloon through the septum. Remove the Teflon cap completely, and place a clean inverted 14/20 septum over the threading (see below pictures).

Cannulas are stored at the bottom of the oven. They are effectively long double-sided needles and are convenient to transfer large volumes of liquids. Place one end in the solvent flask and allow gas to flow for a few seconds to purge the cannula which will help cool it. Then put the other end into the Strauss flask through the inverted septum.

Submerge the one end of the cannula into the solvent. The other end of the cannula should be at the top of the Strauss flask (through the white septum as below). Commonly a vacuum line is attached through the ground glass joint septum (through the red septum as below). As vacuum is applied, this will create a pressure differential and should effectively move the solvent from one flask to the other.

Do not fill the Strauss flask too much. Once you are done, turn the vacuum off, and back fill the flask with Argon gas with a balloon. Then remove the cannula and seal the flask with the Teflon tap under argon. Label the flask with the solvent and the date. Do not use the solvent right away. It's best to wait 2-3 days for the Sieves to work their magic.

