Working with air and moisture sensitive compounds

Marco W. Bouwkamp

(4/12/2008)

Stratingh Institute for Chemistry, University of Groningen

Introduction

Compounds are unstable towards hydrolysis and oxidation. Our existence therefore relies on the kinetic barrier that prohibits hydrolysis and oxidation processes. Biomolecules and many common organic molecules are good examples of compounds that do not suffer from oxidation and hydrolysis reactions under ambient conditions; they are air stable. In the case of transition metal complexes, this is often not the case. In particular electronically and coordinatively unsaturated compounds of early transition metals and lanthanides, organometallic complexes, and main group metal complexes can be highly reactive toward oxygen and water; they are air sensitive.

Nevertheless, these types of complexes are very important, for example for their use in catalysis. Therefore, many techniques have been developed for the manipulation of air and moisture sensitive compounds, the most important of which are described in this document. Among these are Schlenk line, vacuum line and glovebox techniques. These make use of vacuum and/or inert gasses, such as dinitrogen or argon. Nevertheless, it is without doubt that a certain degree of decomposition will occur, as residual oxygen and water will be present in reagents, solvents and in the protective atmosphere (at best at ppm level). Furthermore, water can be absorbed to, for example, glass walls of reaction flasks, glass frits and stoppers.

Depending on the scale of the reaction, residual amounts of water and oxygen can result in a significant decrease of the isolated yield of a reaction, or the ability to store an air sensitive compound for longer periods of time. In the case of small scale reactions (<1 mmol), even the smallest amount of impurities can have a significant impact on the outcome of a reaction, whereas less precaution is needed in case a reaction is performed on a larger scale (>0.1 mol). For example, in the case of large scale reactions, predrying of glassware in an oven at 150° C is sufficient, whereas it might be necessary to flame-dry a flask while applying vacuum in case of small scale reactions.

Schlenk line, vacuum line and glovebox techniques

Schlenk line techniques. Schlenk line techniques are specially developed to work with air sensitive compounds using glassware that is not too different from more traditional glassware. In principle no special glassware is required when using Schlenk line techniques, although Schlenk glassware in different shapes and sizes has been developed for experimental convenience. The most noticeable feature of Schlenk line techniques is the Schlenk line itself. Many different designs are known, but in all cases the general idea behind its design is that a flask, which is attached to the Schlenk line, can easily be connected to both vacuum and to an inert gas. The most common design for a Schlenk line consists of two manifolds, one that is attached to a vacuum pump (via a cold trap to protect the pump from solvents and reagents), and one that is attached to an inert gas source, and several ports with two-way valves that allows the port to be connected to either manifold. The pressure inside the gas manifold of a Schlenk line is regulated by the reducing valve in combination with an overpressure valve.

Typically, reactions and manipulations of air and moisture sensitive compounds are performed while the flask is connected to the inert gas manifold, whereas the vacuum manifold is used to remove air and moisture before an experiment and for the removal of solvents or volatiles during workup procedures. By cycling vacuum and inert gas before the start of an experiment, an inert atmosphere can be created in the flask that prevents hydrolysis and oxidation of the reagents and products. Typically three of these cycles of vacuum and the inert gas are more than enough to provide an inert atmosphere suitable for the manipulation of air and moisture sensitive compounds.

Each connection in a reaction setup is a potential leak. Therefore, it is best to minimize the number of joints in your setup. For this reason Schlenk flasks have been developed. Schlenk flasks are usually comprised of a flask with a built in hose adapter with valve and a male and female glass ground joint. Typically Schlenk flasks are attached to a Schlenk line via flexible rubber or plastic hoses, hence the hose adapter that is attached to the flask. The combination of a male and female glass ground joint provides a straightforward method to connect different Schlenk flasks in order to transfer reagents and products

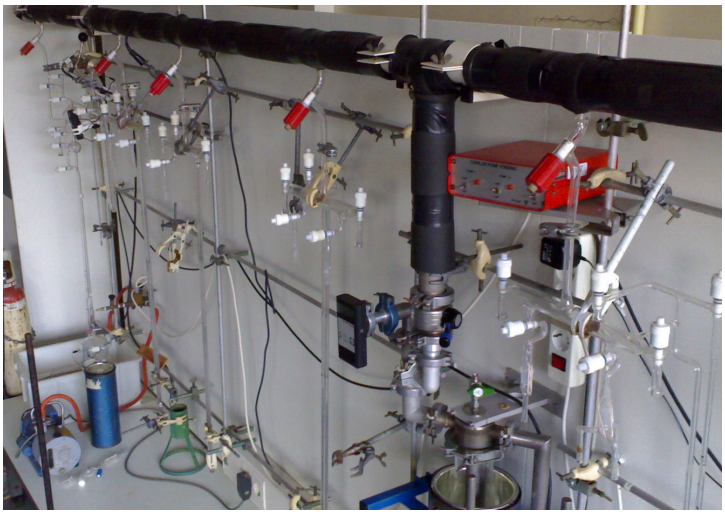
Schlenk line

Schlenk flasks

under an inert atmosphere. As Schlenk flasks are typically attached to the Schlenk line by flexible hoses, a reaction setup has a large degree of freedom. This allows for easy filtration, decanting or transfer of reaction mixtures, reagents and products.

When working with Schlenk line techniques it is important to use the correct amount of the correct type of grease. Too much grease will end up in your product, too little can cause leakage. Also the type of grease is important. Silicon grease for example is very versatile, but soluble in some of the commonly used solvents, such as toluene and THF. The more inert PTFE cream, on the other hand, is not applicable at lower temperatures and is more expensive.

Sometimes, Schlenk flasks are equipped with Young valves, instead of glass ground stopcocks. It is good to note that these too are not to be used at lower temperatures. Shrinkage of the Teflon at lower temperatures may cause leakage of the flask. Another point of notice with Young valves is that they should not be tightened too much. Once closed, a white line will appear where the valve touches the glass, and in this case closed=closed.



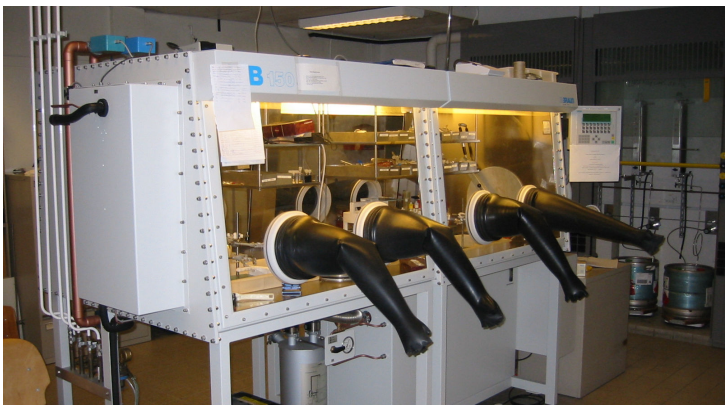
Vacuum line

Vacuum line techniques. A vacuum line operates under (relatively) high vacuum, thus protecting air sensitive materials. Vacuum lines are particularly useful for reactions involving small or stoichiometric amounts of gas. Whereas this technique is more rigorous compared to Schlenk line techniques, the disadvantage is the lack of flexibility: flasks are directly connected to the vacuum line via joints. Therefore, transferring reagents or solvents from one flask to another relies on vacuum transfer or the use of highly specialized glassware. In case a vacuum line is equipped with a Toepler pump (there are only few labs that have one; Groningen has two), it is possible to determine the amount of a gas that evolves during a reaction.

Glovebox. Gloveboxes, sealed containers filled with an inert gas and equipped with gloves allowing the manipulation of items inside, are very convenient when handling air and moisture sensitive compounds. The inert gas is continuously cycled over a catalyst that scrubs the atmosphere inside the box (to a <1 ppm water and oxygen level).

A glovebox allows the use of standard glassware. In order to insert glassware or reagents into the box, it is equipped with at least one antechamber. By evacuating the antechamber, filled with the items that need to be inserted and refilling with an inert gas, they can be inserted without introducing air into the box. Usually two or three of these cycles of vacuum and an inert gas are used to make sure the antechamber is under an inert atmosphere.

Especially for the manipulation of small quantities of air and moisture sensitive compounds (i.e. situations where even the smallest amount of air can ruin an experiment) a glovebox can be an ideal solution. Also when it is very cumbersome to attach glassware to a Schlenk or vacuum line (such as NMR tubes) a glovebox can be a good solution. Nowadays, an increasing amount of research groups are starting to abandon typical Schlenk and vacuum line techniques to perform entire syntheses inside the glovebox. It is important to realize, though, that certain solvents and reagents (THF, CH_2Cl_2, phosphines, sulfides) can bind irreversibly to the catalyst that is used to clean the box atmosphere. In that case, regeneration of the catalyst columns is no longer effective. Another disadvantage of a glovebox is that,



Glovebox

after using a low boiling solvent or reagent, the atmosphere inside the box will be saturated with this reagent or solvent. This can have a significant impact on other compounds or reaction mixtures present in the glovebox.

Inert atmosphere. As a protective gas usually dinitrogen or argon are being used, both of which have their own advantages and disadvantages. Whereas dinitrogen is less expensive, it is not always inert. There are many examples where dinitrogen can act as a ligand for transition metal complexes. On the other hand, these interactions are usually weak and reversible. Argon is truly inert. Also, the density of argon gas is higher compared to dinitrogen or air, which makes it easier to generate a protective blanket of the inert gas. It should be noted though that argon is much more expensive than dinitrogen.

Solvent purification and drying. Solvents are often a main source of moisture (and other impurities), thus its purification and drying is very important when working with moisture sensitive compounds. Whereas many drying agents are available, not all of these are suitable. Many drying agents that are commonly used in organic chemistry bind water reversibly. This is not desirable, especially when the solvent is distilled from the drying agent. Chemical drying agents, drying agents that react irreversibly with water, are better suited for this purpose.

A technique that is often used and very effective, is the distillation of solvents from a drying agent, such as sodium or sodium potassium alloy (alkanes, toluene, benzene, THF, ether) or calcium hydride (chlorinated solvents, esters). Whereas so-called solvent stills are very effective, many labs are no longer using these types of distillations, as they are a major safety hazard.

An alternative method to dry solvents is percolation of the solvent over a column of molecular sieves or alumina to remove water in combination with a supported copper based oxygen scavenger. This way, the solvent can be dried to ppm level.

The result of a solvent still gone wrong

Solvent purification by percolation

In the case of both techniques the solvent can be collected under a positive flow of nitrogen or argon. Nevertheless, it is advisory to degas the solvent before usage. There are two general methods. The first is straightforward, but not suitable for volatile solvents or reagents. It involves brief opening of the solvent flask to the vacuum manifold of a Schlenk line while stirring. A more elegant manner is to perform freeze-pump-thaw cycles. The solvent is frozen, vacuum is applied to remove gasses present in the flask, and the solvent is thawed. By repeating the cycle two or three times, all gasses that were present, either in the headspace of the flask or dissolved in the solvent will be removed.

Storage of air sensitive compounds. The most straightforward method to store air and moisture sensitive compounds is to keep them inside a glovebox. However, one has to take into account that the compounds inside a glovebox are protected from air and moisture, but not from other compounds that are being used inside. A fail-safe storage method is to isolate a compound in an ampoule and to seal this ampoule under a protective atmosphere or under vacuum using a blowtorch.

When transferring a solid into an ampoule, it often happens, that part of the material will end up stuck to the glass wall. This will frustrate sealing of the ampoule, as the hot flame of the blowtorch will burn the compound and thus prevent proper sealing. Therefore, it is recommended to clean the glass wall. When sealing compounds in an ampoule under inert atmosphere, it is necessary to do so using an outflow of the protective gas (i.e. take the stopper off). In the case that an ampoule will be sealed while the ampoule is closed off, expansion of the protective gas as a result of heating the gas will cause the ampoule to burst open.

Transferring air sensitive compounds

Solids. Solid materials that are stored in ampoules can be easily inserted into a flask by inserting the opening of the ampoule into the flask while applying a positive gas flow. When scratching the neck of an ampoule with a glass knife, it can be broken in a controlled manner in a steam of the protective gas before insertion. The ampoule can be closed using a rubber stopper. Whereas rubber stoppers are reasonably efficient in closing an ampoule it is better, in the long run, to reseal an ampoule instead. In order to weigh out an air sensitive compound, one can simply weigh the ampoule before and after the addition of the material. In case a solid is stored in a Schlenk flask, the Schlenk flask and the reaction flask can be connected while applying a positive gas flow.

Liquids or solutions. Air sensitive liquids or solutions are typically transferred using syringes. To determine the amount that is transferred, the syringe can be weighed before and after addition. Alternatively, the volume in combination with a compound's density or the concentration of a solution can be used.

In the case that the exact amount of a liquid is not important, it is possible to transfer the liquid using a cannula. A slight pressure difference to help transferring the liquid from one flask to another can be accomplished by opening one flask to the gas manifold of a Schlenk line, while closing the other. Furthermore, the septum that is being used to attach the cannula to Schlenk flask can be punctured with a needle to promote the flow of the liquid. Cannula are often made from stainless steel or Teflon.

A third method to transfer a liquid from one flask to another which is often applied when working at a vacuum line is to transfer the liquid *in vacuo*, by cooling the receiving flask and, if necessary, warming the other.

Gasses. Gasses can be added to a reaction mixture after the latter has been degassed (see above). A vacuum line is typically equipped with a mercury manometer, allowing the addition of certain pressures of a gas. In case a gas is condensable it is possible, by using a calibrated gas bulb and the ideal gas law, to add stoichiometric amounts of the gas to a reaction mixture (see below).

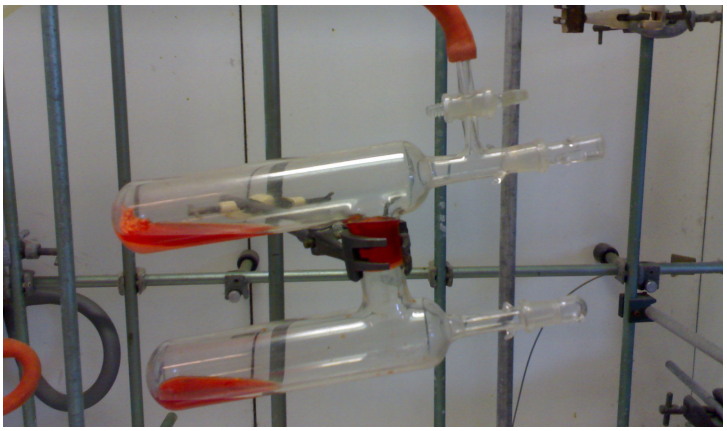
Specialized manipulations

NMR tubes

Sample preparation. Whereas most types of sample preparations (IR, NMR, X-ray) can be performed using Schlenk line techniques, it is often more convenient to perform these in a glovebox. Specialized NMR tubes have been designed for air and moisture sensitive compounds. These tubes are equipped with Young valves allowing sealing of the tubes. At the same time it is possible, when using these tubes, to open the tube to a Schlenk or vacuum line. This way, volatiles can be removed, or gasses can be added. In case a compound is less sensitive, it is possible to use regular NMR tubes closed with a small septum, or NMR tubes with a screw-cap that have been constructed from NMR tubes and GC-vials. In case a compound has to be stored in an NMR tube for very long periods of time, it may be advisable to flame-seal an NMR tube.

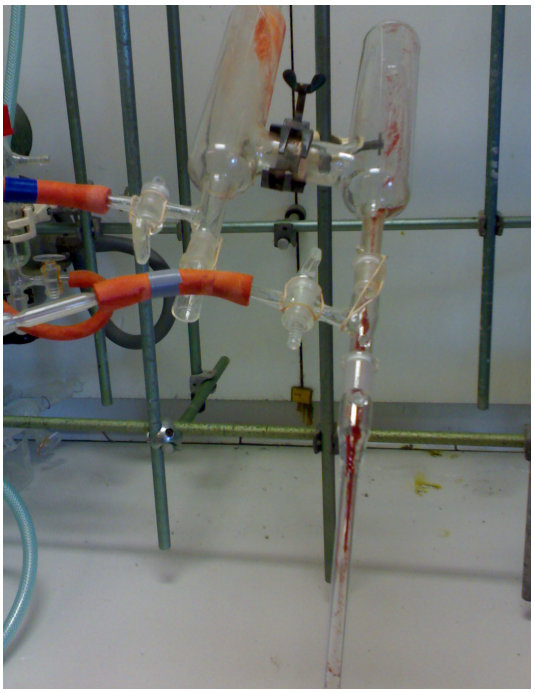
Filtration. In order to filter a reaction mixture during workup, a tubular coupling piece with frit can be used to connect two Schlenk flasks. At first, the connection will be attached to the receiving flask, after which it will be evacuated and, if necessary, flame dried. While applying a positive gas flow in both the receiving flask and the flask with the reaction mixture, the two flaks can be connected and the solution can be passed through the frit. To help gravity, vacuum can be applied in the receiving flask, or the flask can be cooled using an in liquid nitrogen soaked piece of cotton.

As stated earlier, every connection is a potential leak in a setup. Therefore, a special type of Schlenk flask has been designed: the so-called two-bulb Schlenk flask (or double Schlenk flask). In that case, the receiving flask and the reaction flask are incorporated in one piece of glassware with two joints to enter reagents and isolate products, and one valve only.



Filtration using a two-bulb Schlenk flask

Isolation. As mentioned earlier, the best way to store air and moisture sensitive compounds is isolation in an ampoule. Ampoules are available in different sizes and shapes, but in each case a glass ground joint is attached that allows connection to a Schlenk flask. In order to connect an ampoule to the Schlenk flask without introducing air into the system, a coupling piece has been developed, that can be attached to the ampoule and closed off with a stopper. This way, the ampoule can be evacuated before it is connected, while applying a positive gas flow, to the Schlenk flask with the product. After transferring the solid into the ampoule the ampoule can be disconnected, again while applying a positive gas flow.

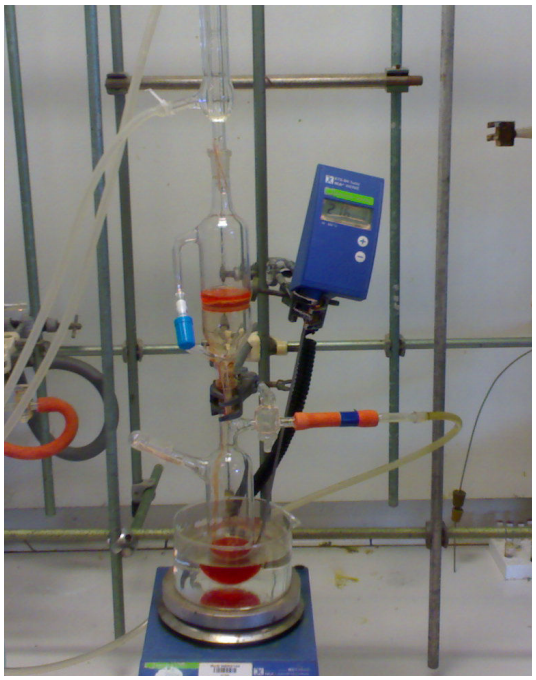


Isolation into an ampoule

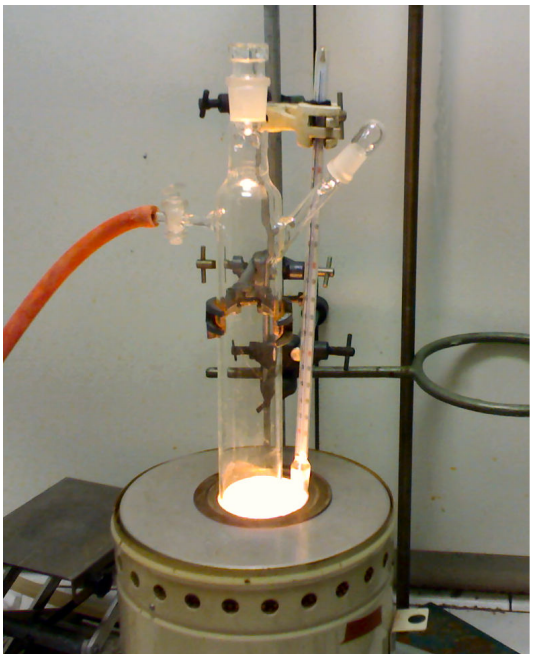
Extraction. Extraction of air sensitive compounds can be done using the filtration technique described above. In the case that multiple extractions are needed, it is best to reuse the solvent that was used for the first extraction. This can be done by transferring the solvent under a reduced atmosphere from one flask to another, by cooling the receiving end and, if necessary, warming the extract. Also in this case, the use of a two-bulb Schlenk flask is very convenient.

Extraction of poorly soluble compounds can be performed using a specialized piece of glassware, designed solely for this purpose, and which is closely related to a soxhlet extraction. The setup consists of a receiving flask, filled with the eluent that is connected to the extraction frit, with the compound, and a reflux condenser. By refluxing the eluent, the compound can be extracted.

In the case of a continuous extraction, a number of problems may arise: clogging of the filter, formation of channels in the raw material, and boiling dry of the extract. The first can be avoided by adding coarse material, such as glass beads or sea sand, to the raw material, preventing the formation of an impenetrable layer. In case it does happen, the only solution is to agitate the material. Formation of channels in the raw material can be solved in the same way. The last problem can be easily avoided by starting with sufficient eluent in the first place.



Continuous extraction



Sublimation

Sublimation. The most common way to sublime compounds it to use a cold-finger. However, in the case of air sensitive compounds, it is not trivial to isolate the compound from the cold finger. Alternatively, it is possible to perform sublimations in a long and narrow Schlenk flask. In that case, the raw material will be in the bottom of the Schlenk, which will be warmed to the temperature where sublimation starts (at a particular pressure). The material will condense on the wall of the Schlenk flask and can be isolated after attaching an ampoule. In the case that cooling is required to help condensation of the material, Schlenk flasks have been designed with cooling mantels. Whereas sublimations are typically performed by using an oil bath, alternatively a lamp can be used. Its main advantage is a uniform heating of the material.

Calibrated gas bulb addition. A stoichiometric amount of a gas or a volatile reagent can be added to a reaction mixture by using a calibrated gas bulb addition. The reaction mixture is equipped with a calibrated gas bulb and attached to a vacuum line. After evacuating the gas bulb and degassing the reaction mixture, the gas bulb is closed off from the reaction mixture and filled with the desired pressure of the volatile reagent. When the bulb is closed off from the vacuum line, the gas bulb can be opened to the reaction mixture, allowing slow diffusion or condensation of the calibrated amount of the reagent into the reaction mixture. By applying the ideal gas law, it is easy to determine which pressure is needed in conjunction with a certain volume to add the correct amount of gas. The gas law in the following form is most convenient to use in a calibrated gas bulb addition experiment, as the pressure is listed in mmHg, the volume in mL, the amount of material in μmol, and the temperature in K:

$$P\,V = n\,0.06326\,T$$

Calibrated gas bulb addition