**Advanced Synthesis Course**

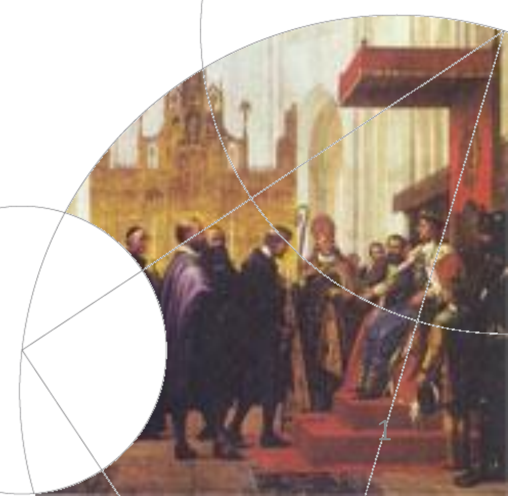
4.08.2017

# Metal-Organic Chemistry

**Christian R. Parker**

SYNTESE

THE UNIVERSITY of ADELAIDE



SYNTESE

FERRING PHARMACEUTICALS

# Ferring Pharmaceuticals

Head office: Saint-Prex Switzerland
Office in DK: Copenhagen S

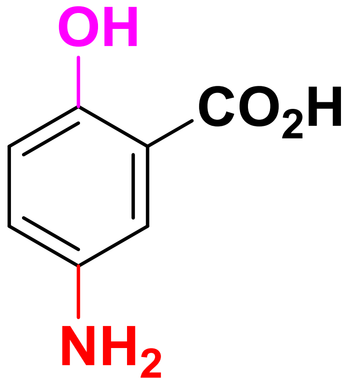
http://www.ferring.com/en/about-ferring/

Syntese is owed
by Ferring and is at Hvidovre

http://www.syntese.dk/

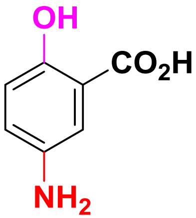
We are the worlds largest producer of 5-Amino salicylic acid (5-ASA) – which is the API Mesalazine.

Used for treating Inflammatory Bowel Diseases




600-650 tons per year (ca 2 tons a day)

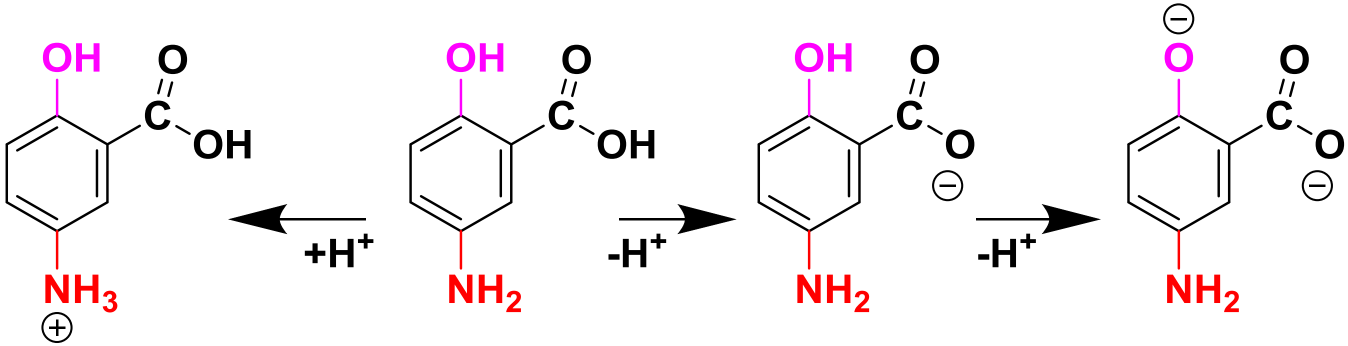
# Pilot plan




Manufacturing Scale
10 000 L reaction vessel

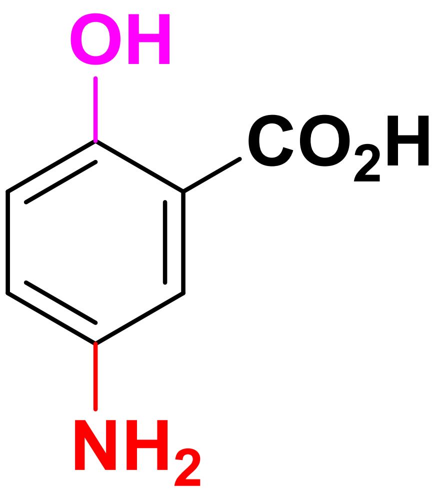
SYNTESE

FERRING PHARMACEUTICALS




| Charge: | | | |
|---|---|---|---|
| Cation | neutral | anion | dianion |
| **water solubility:** | | | |
| ok | poor | good | good |
| **air stability** | | | |
| good | ok | poor | bad |

# How do you synthesise 5-ASA?



# Organometallic Chemistry

## Carbon – Metal bond

**Causing bond formation either C-C, C-R or C-M**

**Changing functional groups**

**To add a metal-centre to an organic molecule**
**(or co-ordinating an organic ligand to the metal-centre)**

# Organometallic Chemistry

**Catalysis**

e.g. Pd

Sonogashira, Suzuki, Negishi, Heck and Stille reactions for C-C bond formation and Buchwald amination for C-N bond formation.

**Strong Bases and Nucleophiles**

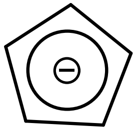
eg Li-R (alkyl lithium reagents), X-Mg-R (Grignard)

**Reducing agents**

eg Cobaltocene - $CoCp_2$

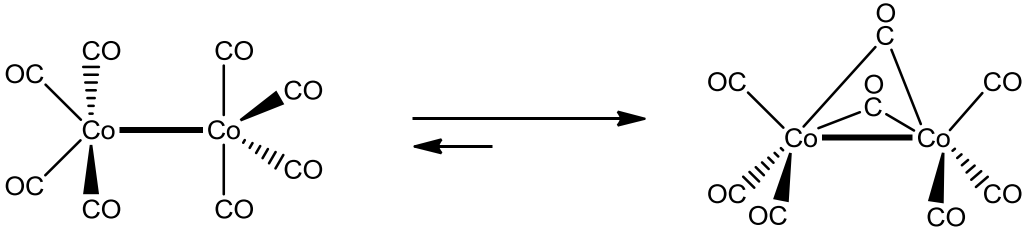
**Oxidising agents**

eg Ferrocenium - $[FeCp_2]PF_6$

$Cp = C_5H_5 =$ 

# Organometallic Chemistry

## Cobalt Carbonyl - $Co_2(CO)_8$




Brown crystalline solid (purple when decomposed)

Reacts with Oxygen

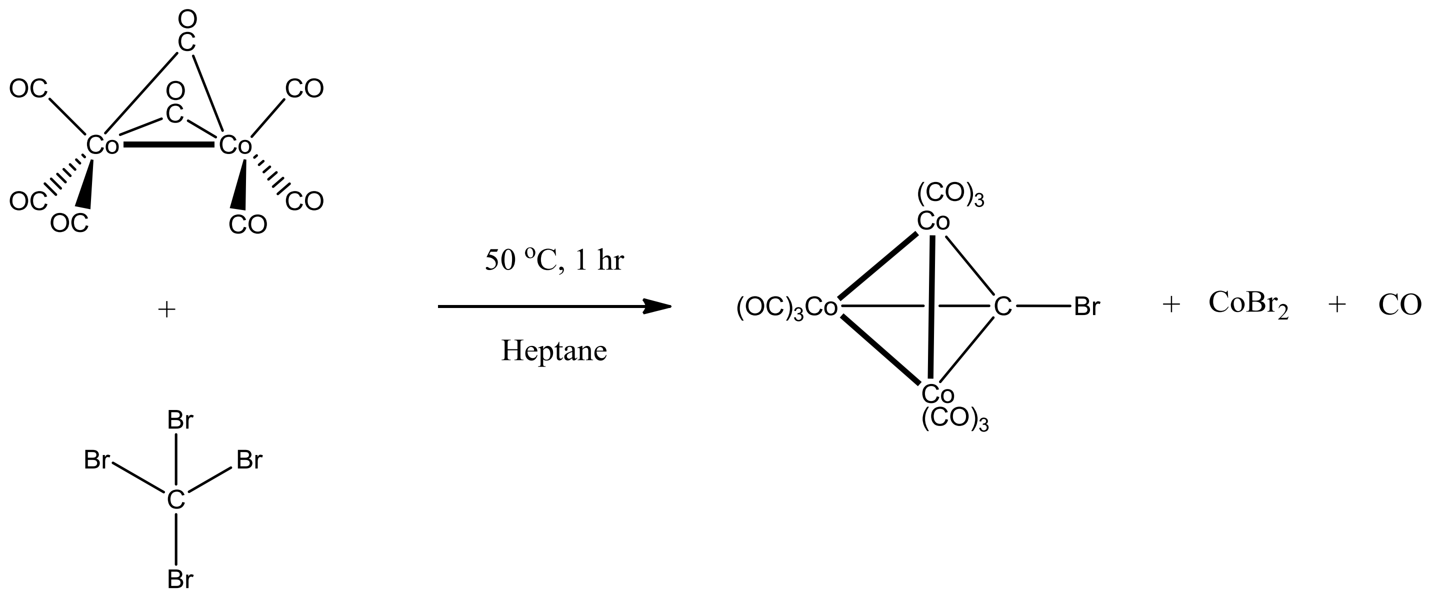
Thermally unstable

Releases carbon monoxide - CO

Pyrophoric

# Cobalt Carbonyl - $Co_2(CO)_8$

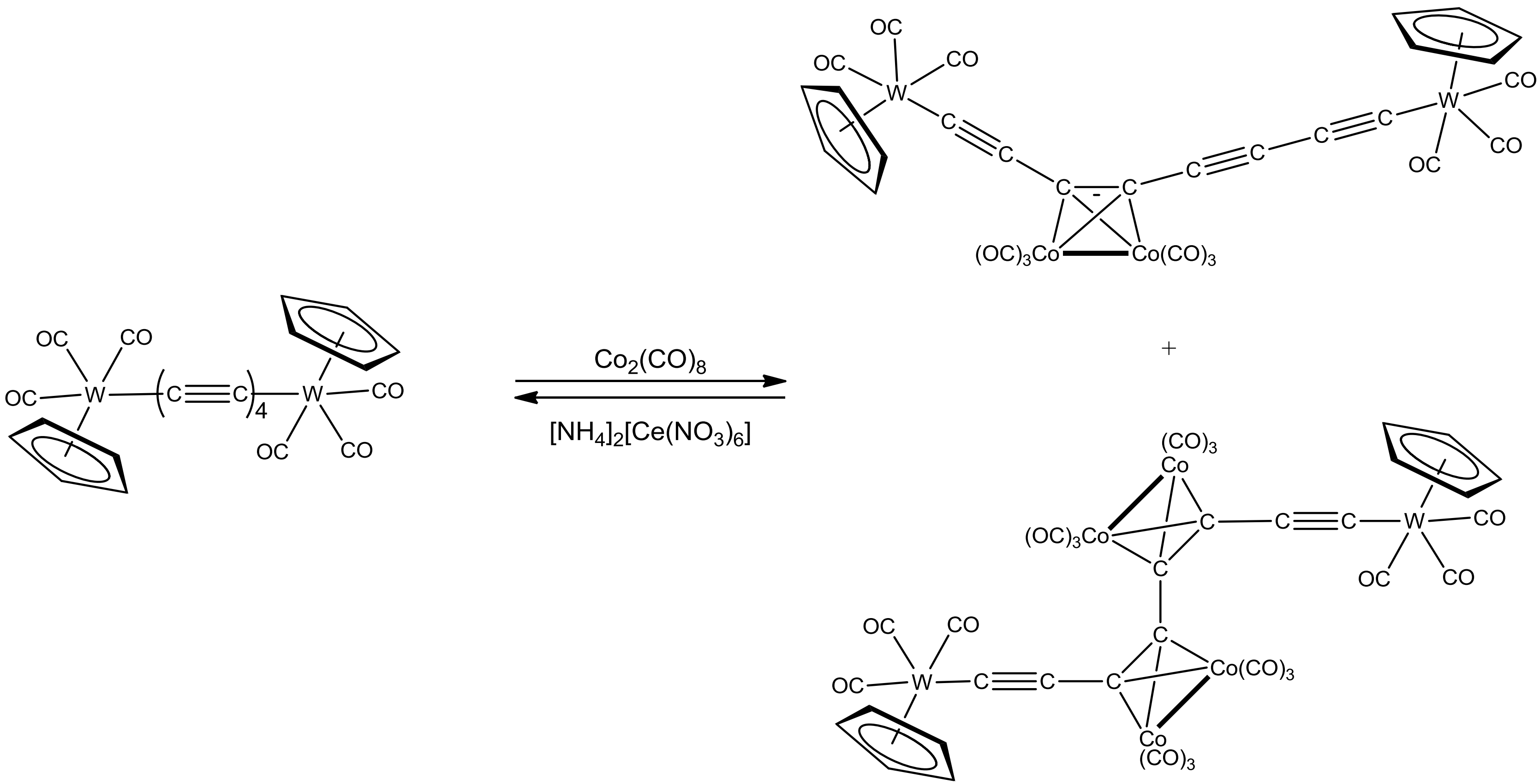
# Cluster formation




R.B.King, Organomet. Synth., vol.1, p.133

# Cobalt Carbonyl - $Co_2(CO)_8$

# Reaction and Protection of alkynes - RC≡CR

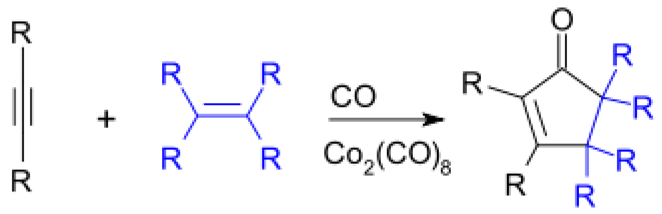



Bruce, M. I.; Kelly, B. D.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1999**, 847.
Seyferth, D.; Nestle, M. O.; Wehman, A. T. *J. Am. Chem. Soc.* **1975**, *97*, 7417.

# Cobalt Carbonyl - $Co_2(CO)_8$

## Pauson–Khand reaction

The **Pauson–Khand reaction** (or **PKR** or **PK-type reaction**) is a chemical reaction described as a [2+2+1] cycloaddition between an alkyne, an alkene and carbon monoxide to form a α,β-cyclopentenone.[1][2] This reaction was originally mediated by stoichiometric amounts of dicobalt octacarbonyl, but this has since been replaced by newer and more efficient catalyst systems.[3][4]




Source of information http://www.wikipedia.org/

1) P. L. Pauson and I. U. Khand. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 2.
2) Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32.
3) Schore, N. E. *Org. React.*, **1991**, *40*, 1.
4) S. E. Gibson and A. Stevenazzi, *Angew. Chem. Int. Ed.*, **2003**, 42, 1800-1810.

# Organometallic Chemistry

**Catalysis**

e.g. Pd (**sensitive to $O_2$**)

Sonogashira, Suzuki, Negishi, Heck and Stille reactions for C-C bond formation and Buchwald amination for C-N bond formation.

**Strong Bases and Nucleophiles**

eg Li-R (alkyl lithium reagents), X-Mg-R (Grignard) (**sensitive to $H_2O$**)

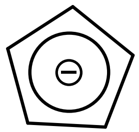
**Reducing agents**

eg Cobaltocene - $CoCp_2$ (**sensitive to $O_2$**)

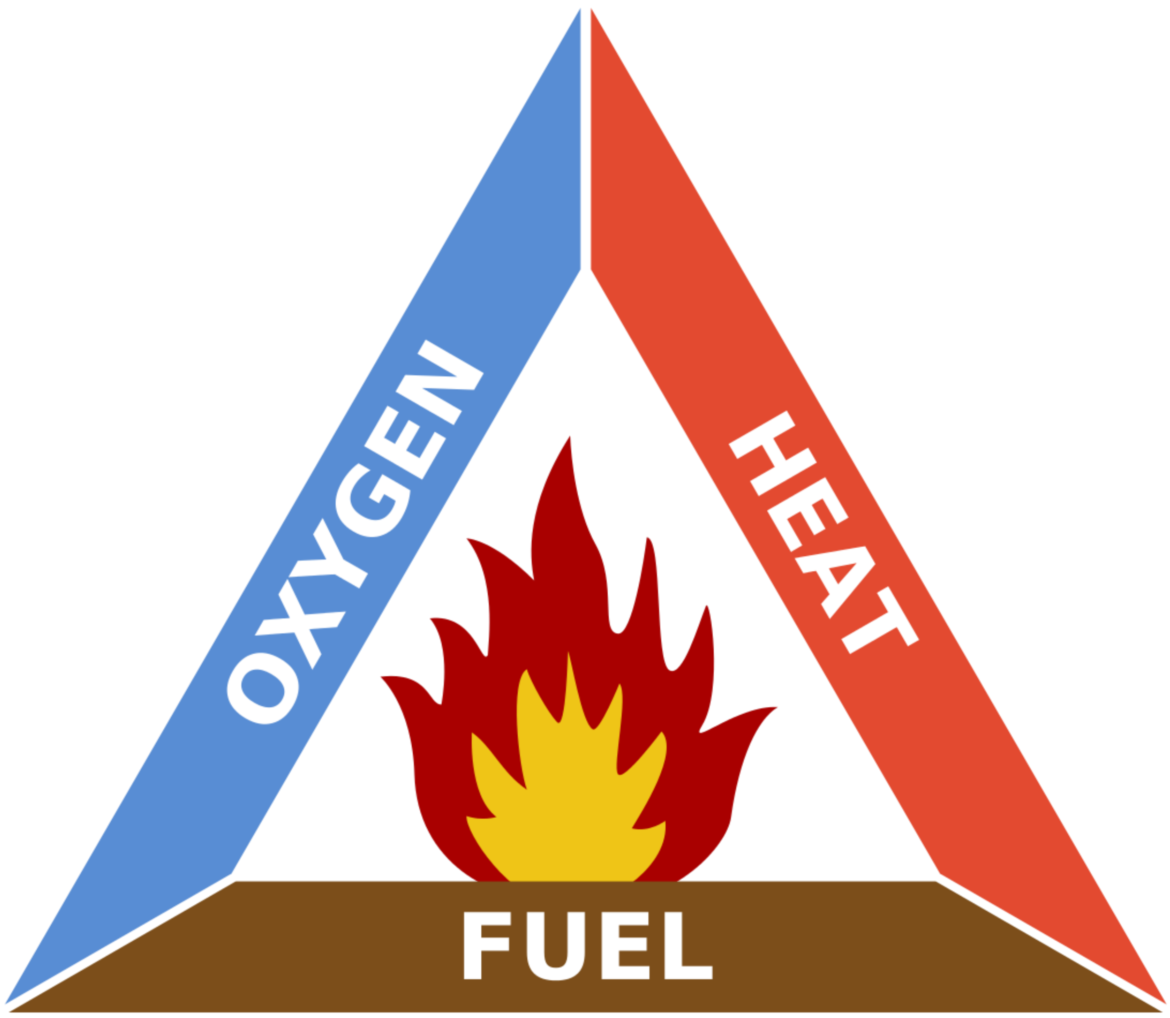
**Oxidising agents**

eg Ferrocenium - $[FeCp_2]PF_6$

Cp = $C_5H_5$ =



# Keeping out water and oxygen from reactions



# Safety with strong bases eg BuLi

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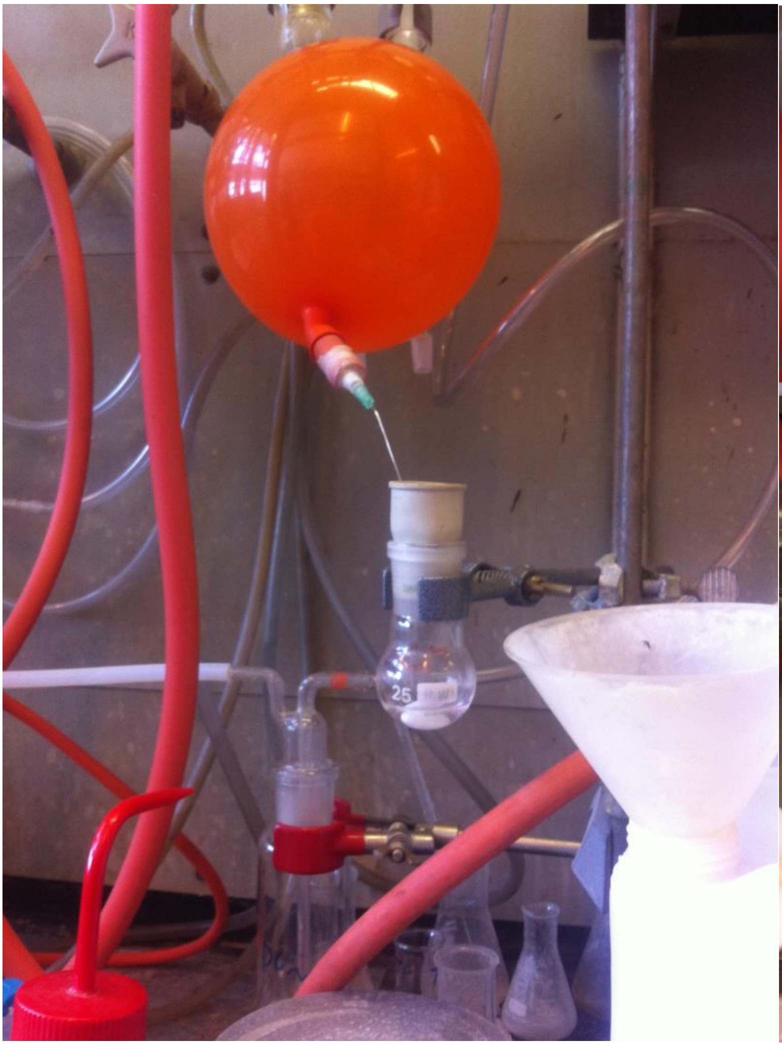

# Keeping out water and oxygen from reactions

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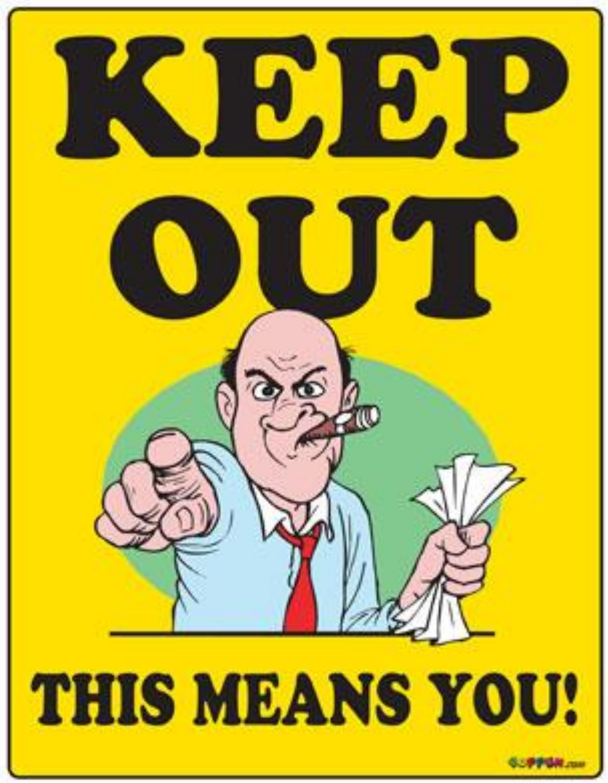
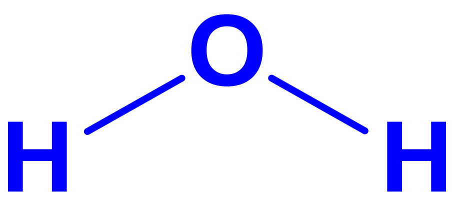



# Keeping out water and oxygen from reactions

## Best is a glove box


# Glove box

**Good things**

- Can have very dry and oxygen free conditions
- Can be set up as dry or wet
- Storage of compounds
- Can do reactions inside it

**Bad things**

- Expensive and expensive to maintain (time, gas, space)
- Take time to set up
- Not easy to manipulate the compounds (So things take longer)
- Some training needed
- Risk of contamination

# Keeping out water and oxygen from reagents

## Desiccators or Schlenk tubes under inert atmosphere

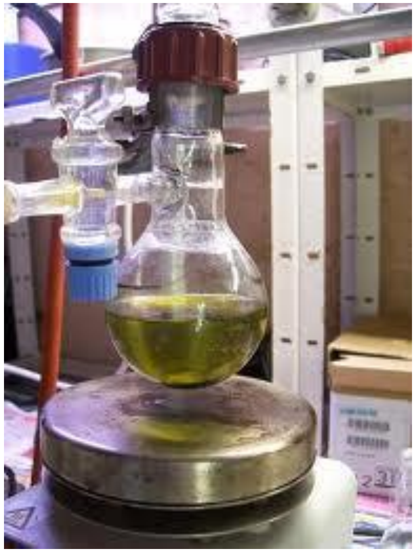
Add drying agent eg Drierite
And doped silica gel to show if it is dry (blue) or wet (pink)

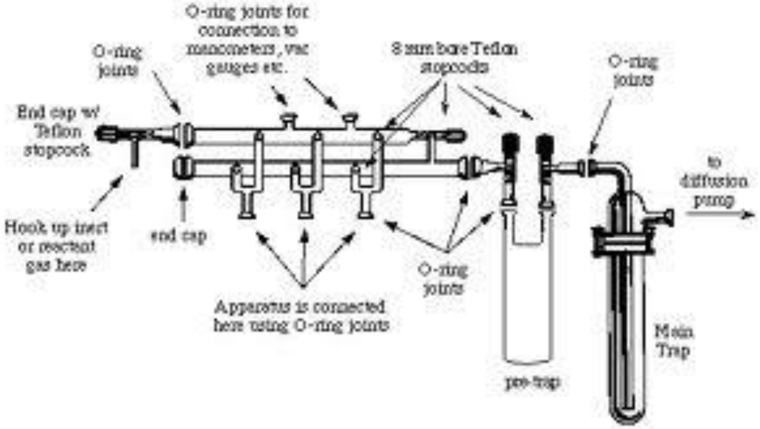
# Keeping out water and oxygen from reagents

## Cone of Nitrogen
## on hydroscopic or air sensitive compounds

# Keeping out water and oxygen from reactions

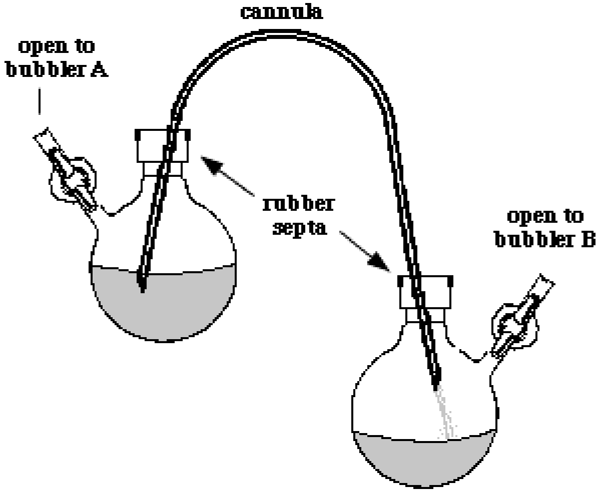
## Schlenk techniques

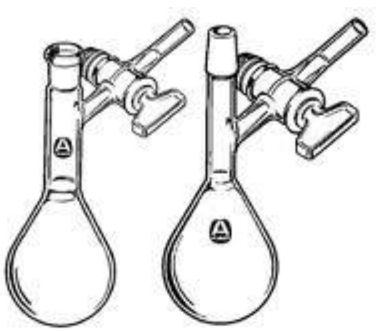


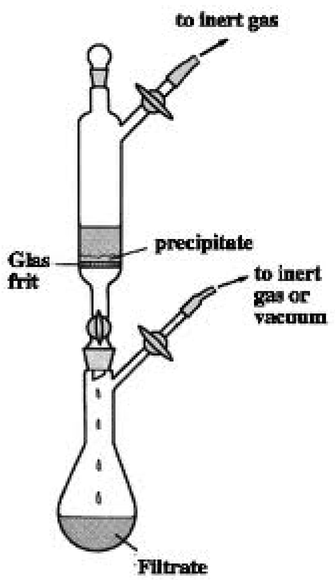


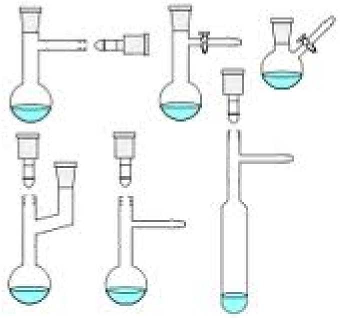

# Keeping out water and oxygen from reactions

## Schlenk techniques





# Schlenk technique

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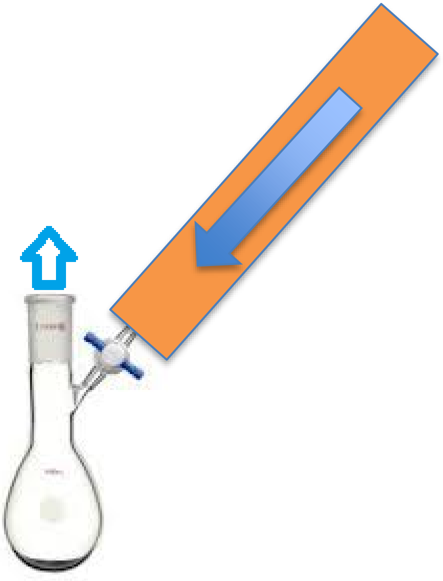

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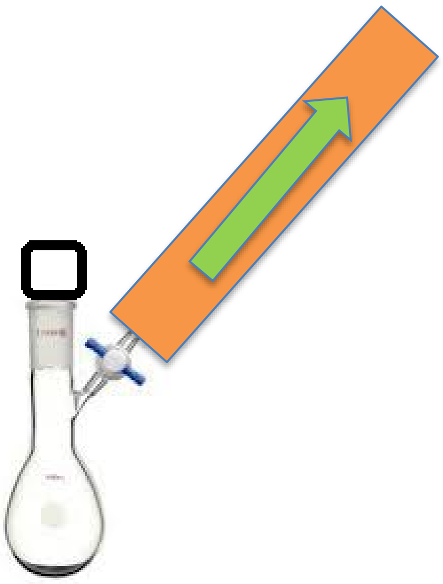

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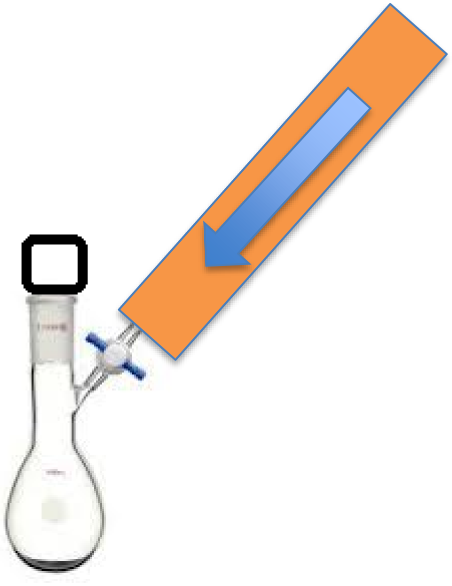

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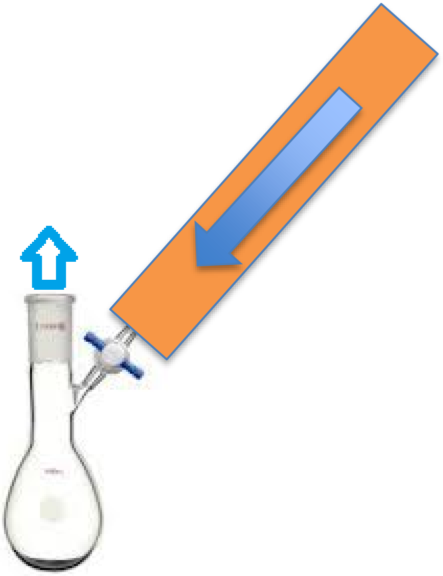

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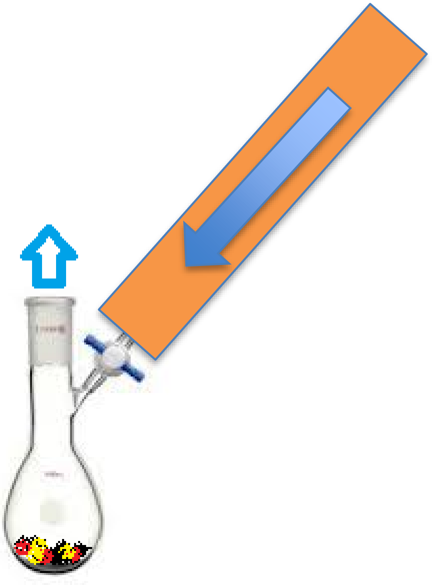
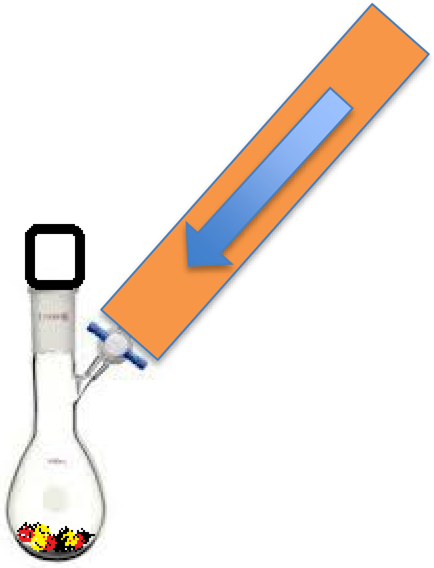


Add solid to flask

# Schlenk technique



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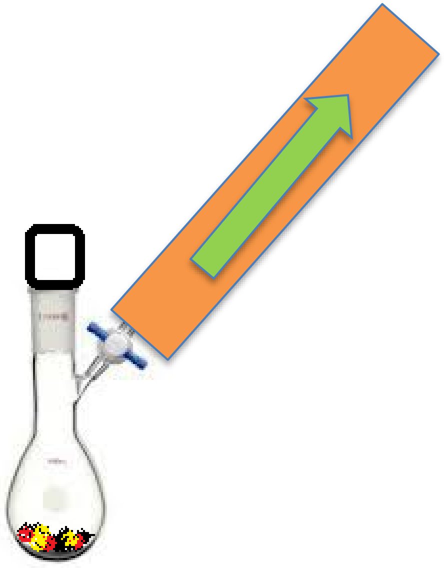
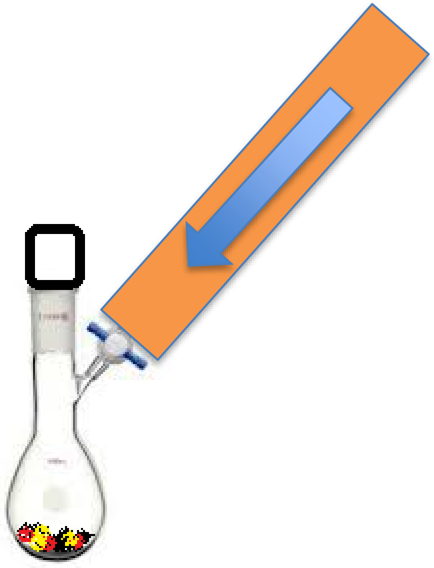


Can repeat 3 or more times

Careful not to suck your compound up the line

# Schlenk technique



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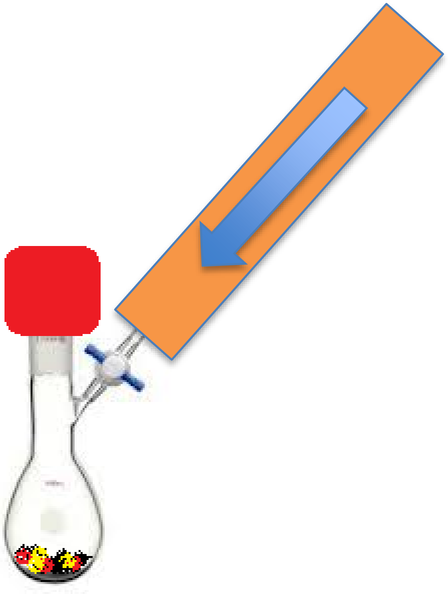

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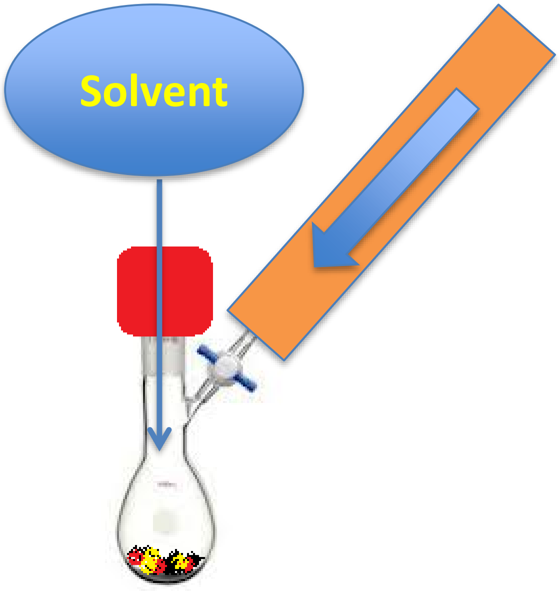

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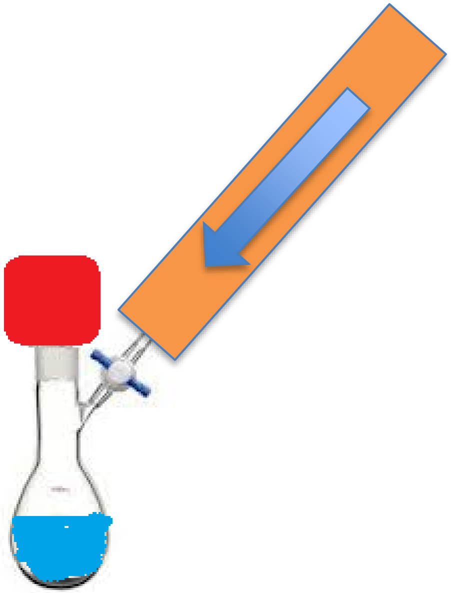


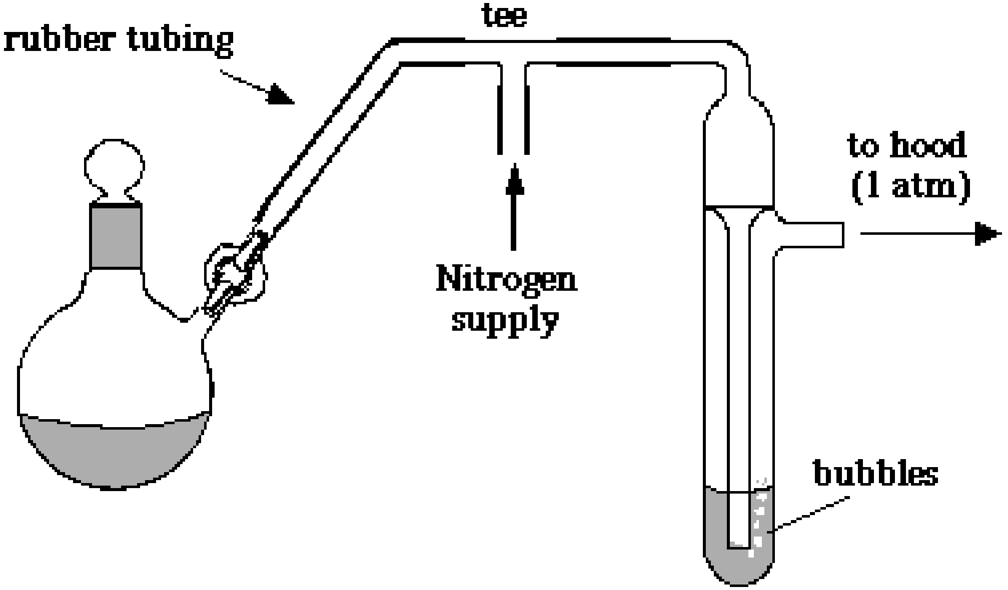

# Schlenk technique

## Bubbler

Silicone

Mercury

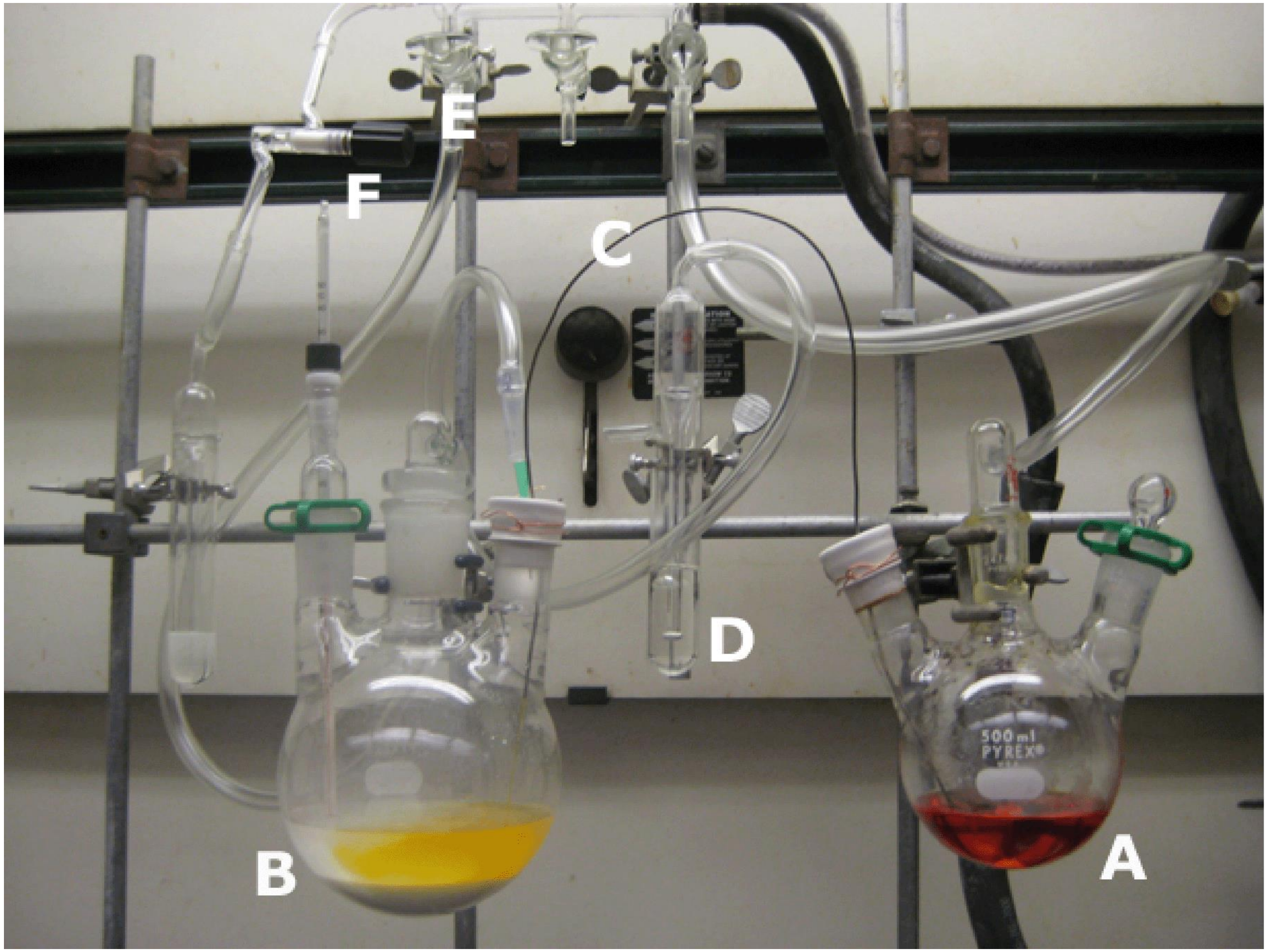
Or a mix of both




http://www.ilpi.com/inorganic/glassware/bubbler.html

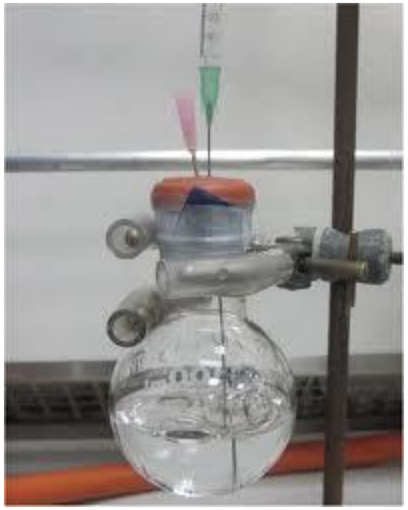
# Keeping out water and oxygen from reactions

## Schlenk reactions



# Keeping out water and oxygen from reactions

## Degassing solvents



Bubble argon or nitrogen through a solution for 5 to 30 min
Sonication helps removes the gas from solution faster

Argon is better because it is more dense it layers on top of the solution
However it is more expensive, you have to get it from a gas cylinder

Nitrogen is cheaper and comes out of the taps in most labs
The in house nitrogen may be slightly wet

# Degassing solvents

## Freeze-Pump-Thaw

1) Place the solvent (or solution) in a Schlenk flask. Make sure the stopcock is closed. Be careful not to use more than 50% of the volume of the flask because overfilled flasks frequently shatter during this process.
2) Hook it up to a Schlenk line (leave the attached hose on vacuum throughout this procedure) and freeze the liquid. Liquid nitrogen is usually best for this. Before freezing make sure that the environment in the flask is free of oxygen to prevent condensing liquid oxygen upon freezing.
3) When the solvent is frozen, open the stopcock to vacuum and pump off the atmosphere for 10-30 minutes
4) Seal the flask.
5) Thaw the solvent until it just melts using a warm water bath. You will see gas bubbles evolve from the solution. Try not to disturb the liquid. Note: Letting the frozen solvent thaw by itself, or using a container of water that melts only the bottom of the frozen solvent may cause the vessel to break.
6) Replace the water bath with the cooling bath and refreeze the solvent.
7) Repeat steps (3) – (7) until you no longer see the evolution of gas as the solution thaws. The solution should be put through a minimum of three cycles.
8) Fill the flask with $N_2$ or Ar gas and seal. The solvent is ready to use.

# Degassing solvents

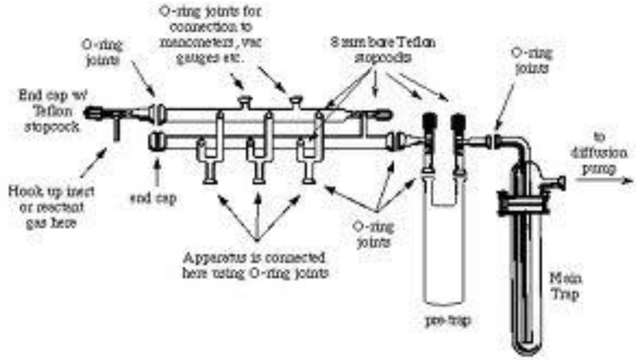
# Cowboy method

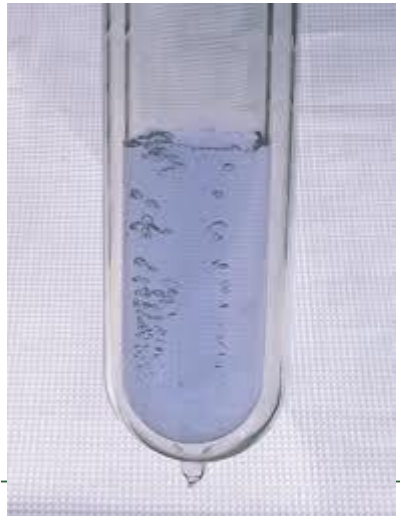
# Keeping out water and oxygen from reactions

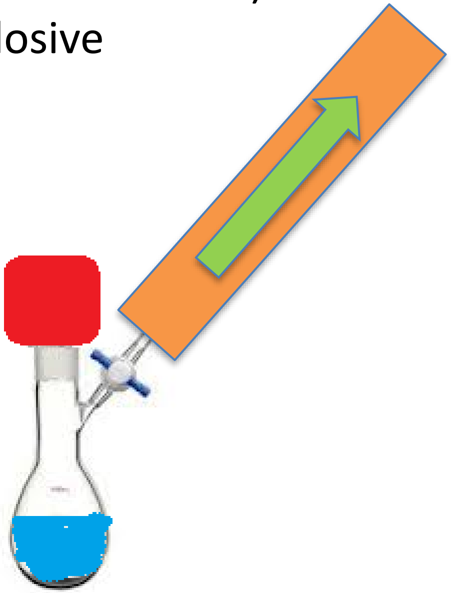
## Removing solvent

Removes solvents from the reaction with out the need of a rotary evaporator (exposing to air)
Dry ice – acetone -78 °C
Liquid nitrogen -196 °C (77 K)
Look after the pump!

Risk of liquid Oxygen (blue colour, forms at 90 K)
– with solvent potentially explosive

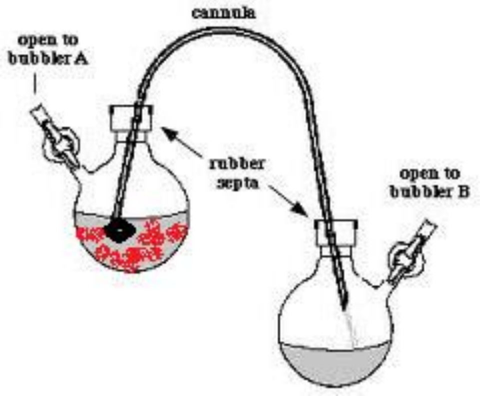




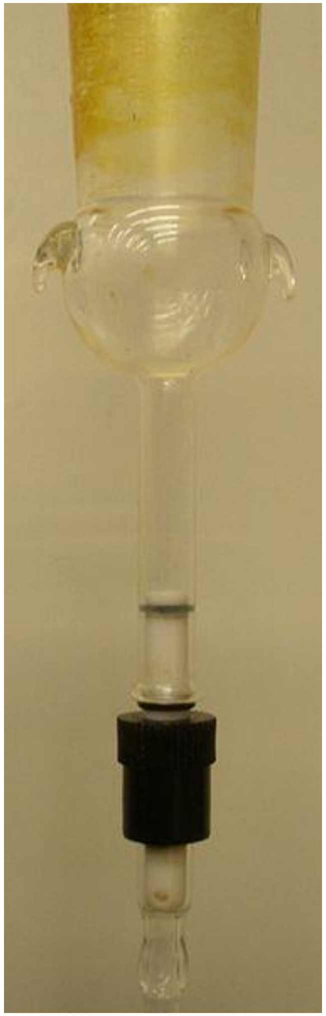
# Keeping out water and oxygen from reactions

## Cannula filter



# Keeping out water and oxygen from reactions

## NMR Tubes



# Removing oxygen from aqueous solutions

Who has made beer or wine here?

Antioxidants like sodium metabisulfite or vitamin C

Can also use membranes to remove oxygen (http://www.liquicel.com/applications/O2.cfm)

# Drying solvents

# Remember

# Glass and the air contain water

Methods to keep glassware dry

- Move to a dry place!
- Work under inert atmosphere
- Pre store glass in a oven
- flame dry glass under vacuum
- Extreme case can wash glass with $Me_3SiCl$ under inert atmosphere (removes Si-OH on glass)

JOC Article
pubs.acs.org/joc

J. Org. Chem. **2010**, *75*, 8351–8354 **8351**

# Drying of Organic Solvents: Quantitative Evaluation of the Efficiency of Several Desiccants

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*Research Centre for Synthesis and Catalysis, Department of Chemistry, University of Johannesburg, P.O. Box 524, Auckland Park 2006, South Africa*

*bwilliams@uj.ac.za*

*Received August 12, 2010*

**TABLE 1. Water Content in THF after Drying[a]**

| desiccant | time (h) | residual water content (ppm) |
|---|---|---|
| none, "wet" solvent | | 107.8 ± 0.7 |
| sodium/benzophenone[b] | 48 | 43.4 ± 0.7 |
| 3 Å molecular sieves (10% m/v) | 24 | 27.7 ± 1.0 |
| 3 Å molecular sieves (20% m/v) | 24 | 14.7 ± 0.3 |
| 3 Å molecular sieves (20% m/v) | 48 | 6.1 ± 0.2 |
| 3 Å molecular sieves (20% m/v) | 72 | 4.1 ± 0.1 |
| silica (28−200 mesh)[c,d] | *c* | 56.2 ± 2.5 |
| silica (35−60 mesh)[c,e] | *c* | 105.7 ± 3.5 |
| silica (60−100 mesh)[c,e] | *c* | 89.4 ± 2.8 |
| silica (70−230 mesh)[c,e] | *c* | 82.5 ± 1.2 |
| silica (100−200 mesh)[c,e] | *c* | 74.6 ± 2.9 |
| silica (200−425 mesh)[c,e] | *c* | 59.5 ± 3.7 |
| silica (100−200 mesh)[c,f] | *c* | 69.0 ± 3.3 |
| silica (200−425 mesh)[c,f] | *c* | 60.8 ± 1.9 |
| neutral alumina[c] | *c* | 5.9 ± 0.4 |

[a] Drying was performed in triplicate; $n = 6$ for each dried solvent analyzed, providing $n = 18$ for each desiccant. [b] THF was distilled from the desiccant once the indicator had turned a persistent blue color. [c] Solvent was passed over a column of the desiccant, 10% m/v, inside the glovebox. The system was not assessed for "breakthrough" of water, i.e., to establish the capacity of the desiccant. [d] Silica (pore size 22 Å). [e] Silica (pore size 60 Å). [f] Silica (pore size 100 Å).

# Keeping out water and oxygen from reactions

## Solvent drying system


# Keeping out water and oxygen from reactions

## Solvent stills

# Solvent drying system Vs solvent stills

Solvent drying system
- expensive
- require maintenance and have to know how to do it, but easy once set up
- may not remove stabiliser or peroxides

Solvent stills
- Works well and removes stabilisers and peroxides
- Cleaning stills after use can be dangerous with sodium metal or NaK!
- Risk of explosion if they run dry due to peroxides (ether solvents)
- Last longer if solvents are pre-dried

| | |
|---|---|
| benzophenone with Na | THF, ether, toluene, Hexane |
| $CaH_2$ | MeCN, $CH_2Cl_2$ |
| Na | Heptane |
| Mg with $I_2$ | MeOH, EtOH |
| NaOH | pyridine, $NEt_3$ |

# Keeping out water and oxygen from reactions

## Molecular sieves

Right poor size for solvent. eg 4 Å pores will also accept MeOH as well as water
Can take time to work but can last a while
Can be used in reactions to remove water an alternative to a Dean-Stark apparatus.
To test if good - put on your hand and spit. If it gets very hot its still good!
Heat to regenerate (hot oven or microwave)
Test water content of solvent with a Karl-Fischer apparatus (**Not ACETONE**)

# Keeping out water and oxygen from reactions

## Basic alumina plug

This is great for drying bulk solvents quickly, easily and cheaply

Excellent for drying $CDCl_3$, it also removes the acid and other junk

Can remove the colour and water from triethylamine

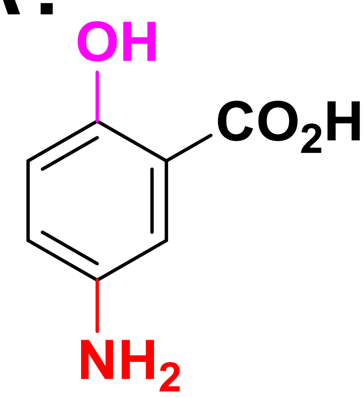
Electrochemistry to get the solvent very dry

Can dry in hot oven to make alumina drier

# Thank you for your attention

# Any questions?

# How can you synthesis 5-ASA?




# then

# To the laboratory for the demonstrations

# Schlenk technique