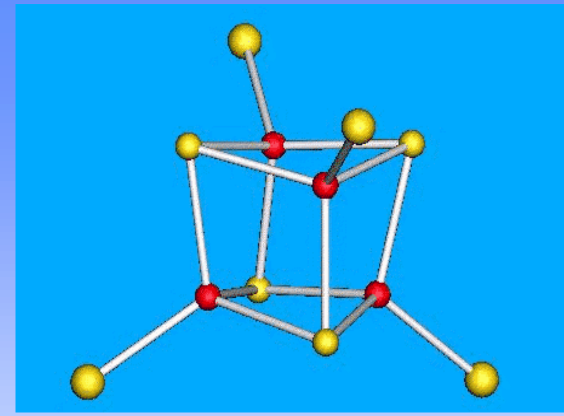


Getting Crystals Your Crystallographer Will Treasure

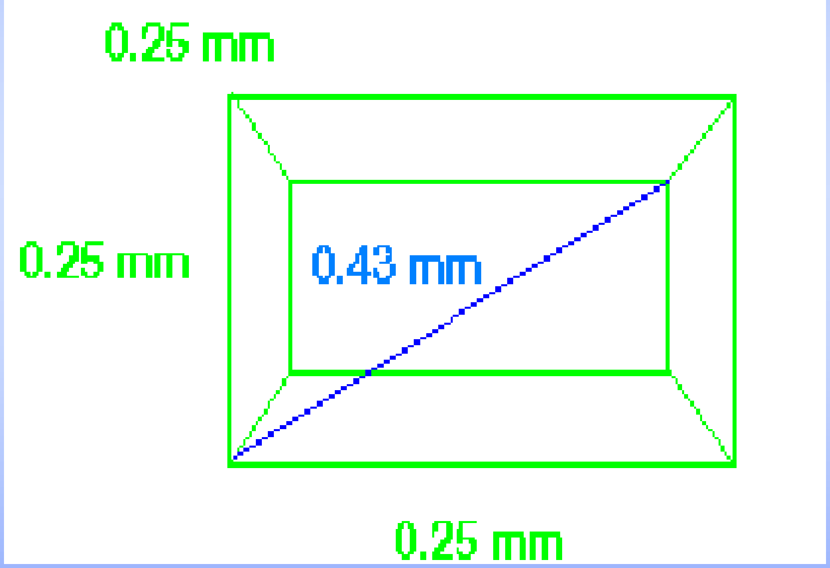
Richard J. Staples
Crystallographer
Harvard University

What do I need to bring to the Laboratory?

- Single Crystals
- Bring what you can grow
- Chemical Formula
- Compound Name
- If not single: Discuss recrystallization

Crystal Size

- Size should be 0.25 x 0.25 x 0.25 mm — perfect.
- Gives 0.43 mm diagonal.
- Smaller crystals are very possible!
- Larger crystals can be cut!

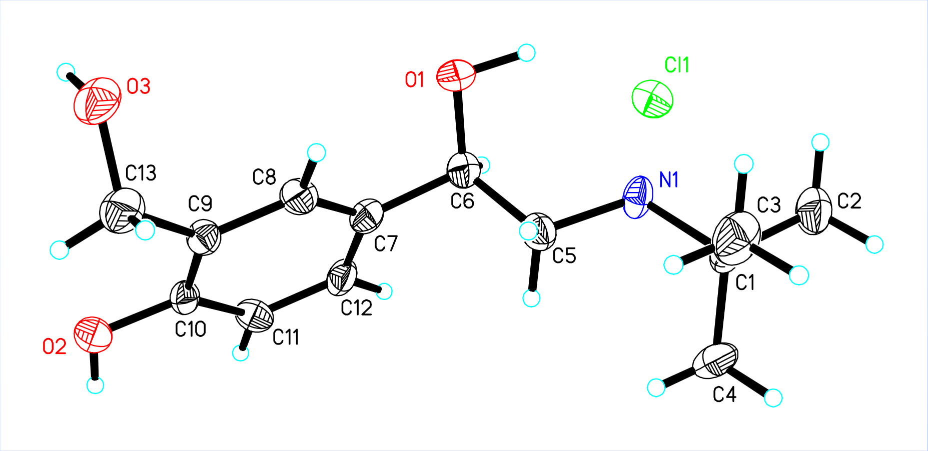


Techniques for Growing Crystals

- Key factors in obtaining good crystals.
- Read: "Crystal Growing", Peter G. Jones,
  Chemistry in Britain, 17(**1981**) 222-225.
- See www site by Paul D. Boyle (http://www.xray.ncsu.edu/GrowXtal.html)
- Various techniques.

Where Do I Start?

- Simple recrystallization.
- During purification did you create crystalline material?



- Are these crystals big enough?

These crystals were 0.05 x 0.025 x0.002 mm

How much Material Do You Need?

- Depends on the vessel you are going to use to grow the crystals.
- Depend on solubility of sample in the solvent.
- NMR sample generally a good concentration level.

How much Material is in a Single Crystal?

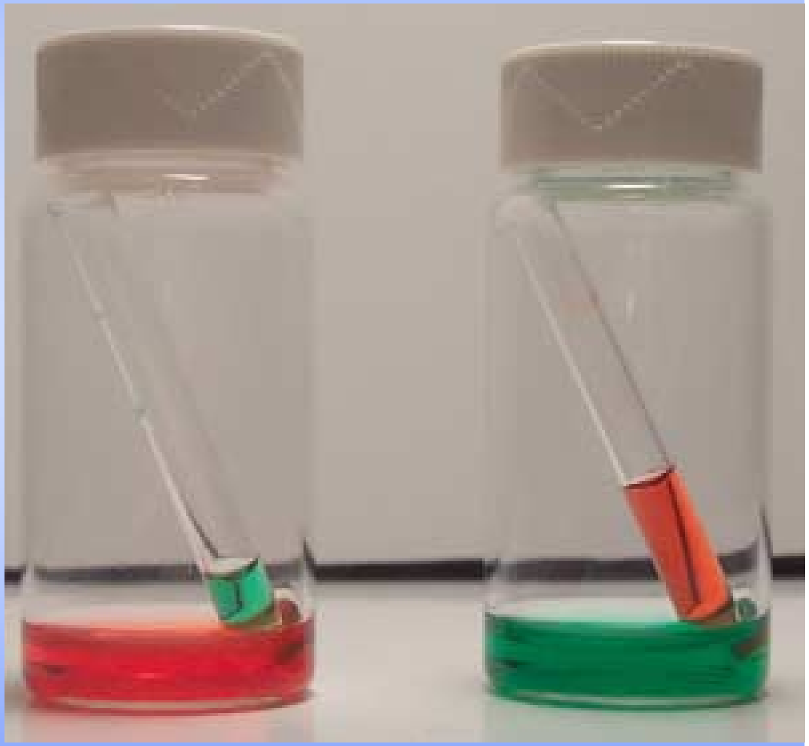
- If the crystal for x-ray diffraction is to be 0.3 x 0.3 x 0.3 mm, volume = 0.027 mm^3
- Typical unit cell is 12 x 12 x12 Å; volume = 1728 $Å^3$
- Å = 10^{-10} meters = 10^{-8} cm = 100 pm (picometers)
- Therefore in a typical crystal: 1.6 x 10^{16} unit cells
- 1.3 x 10^{17} molecules for 8 molecules per cell.
- MW= 206.2 then only 2.49 x 10^{-7} moles in the cell. 5.1 x 10^{-5} g, 0.051 mg
- Unfortunately more than one crystal grows in the vessel so more material is needed.

What is the Goal

- *To create a single crystal which diffracts such that an analysis can be accomplished.*
  - Generally this means to get the material to go from solution to a solid very slowly.
  - Create an environment that slowly changes over time to cause crystallization.

What do I grow the Crystals In?

- Clean glassware, most of the time.
- Consider location
- Consider volume needed to grow the crystal.
- Usually clean new vials that fit inside one another work well.



Solvent Choice

- Polar – polar solvent layered with a non-polar solvent

- Non-polar – Non-polar solvent, evaporation or layer with polar solvent (more difficult).

Hydrogen Bonding

- Hydrogen bonding is very important in the crystallization process.
- Consider whether a hydrogen-bonding solvent might help or hinder crystallization.
- Amides generally do better with hydrogen bonding solvents.

Solvents to Use and NOT to Use

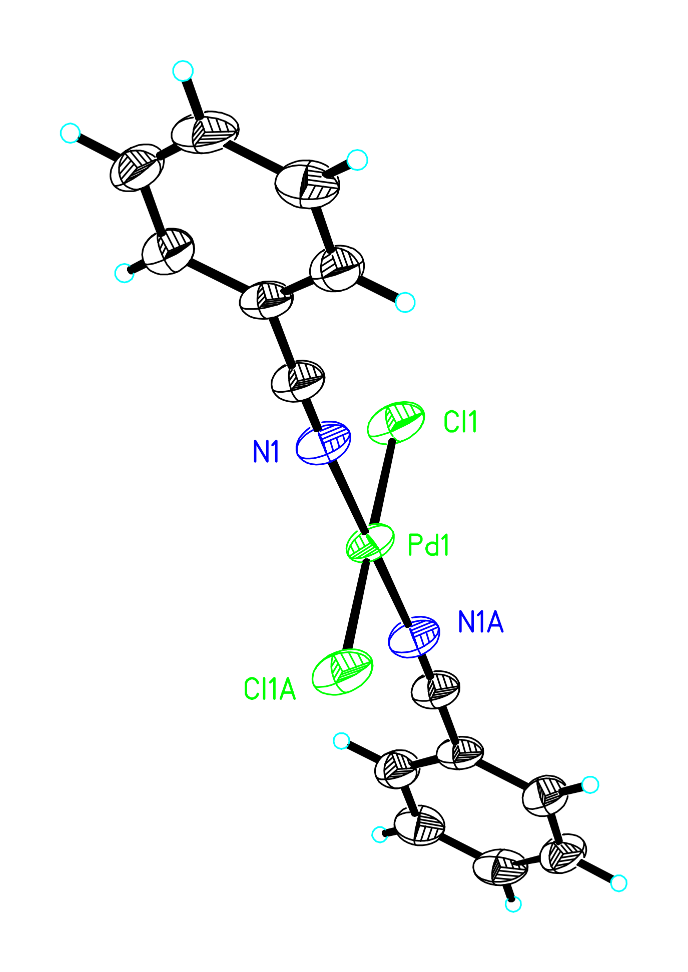
- Use benzene! Seems to be a magic solvent. It has been seen that toluene can do the same sort of thing.
- Aromatic rings seems to help fill holes in lattice as well.
- Ethyl Acetate works for a lot of compounds.
- Avoid volatile solvents, CH_2Cl_2, Diethyl Ether.
- Avoid long alkyl chains, cause disorder.

Solvent Layering

- Layering must be very careful.
- Place a solvent between the two layers.
- Do not disturb the vessel.
- Set it so you can view it without moving it.

Example of Layering

- Grown by layering a solution of methylene chloride with pentane.



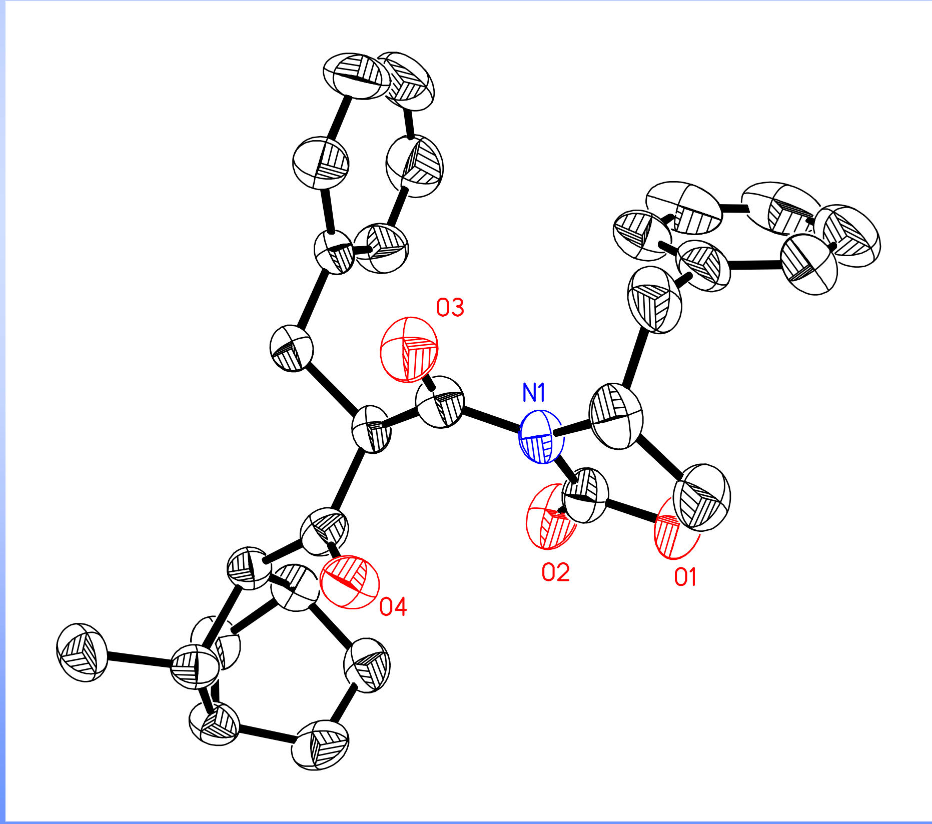
Staples, Swiatek *Z. Krist*.

Vapor Diffusion

- Good for milligram amounts.
- Volatile solvents.
- Slowly create a less desirable solvent.
- Need to be aware of vapor pressures of solvents.

Example of a Crystallized Compound from Vapor Diffusion

- Used a diffusion chamber with compound in the dichloromethane and then hexane in the outside chamber.



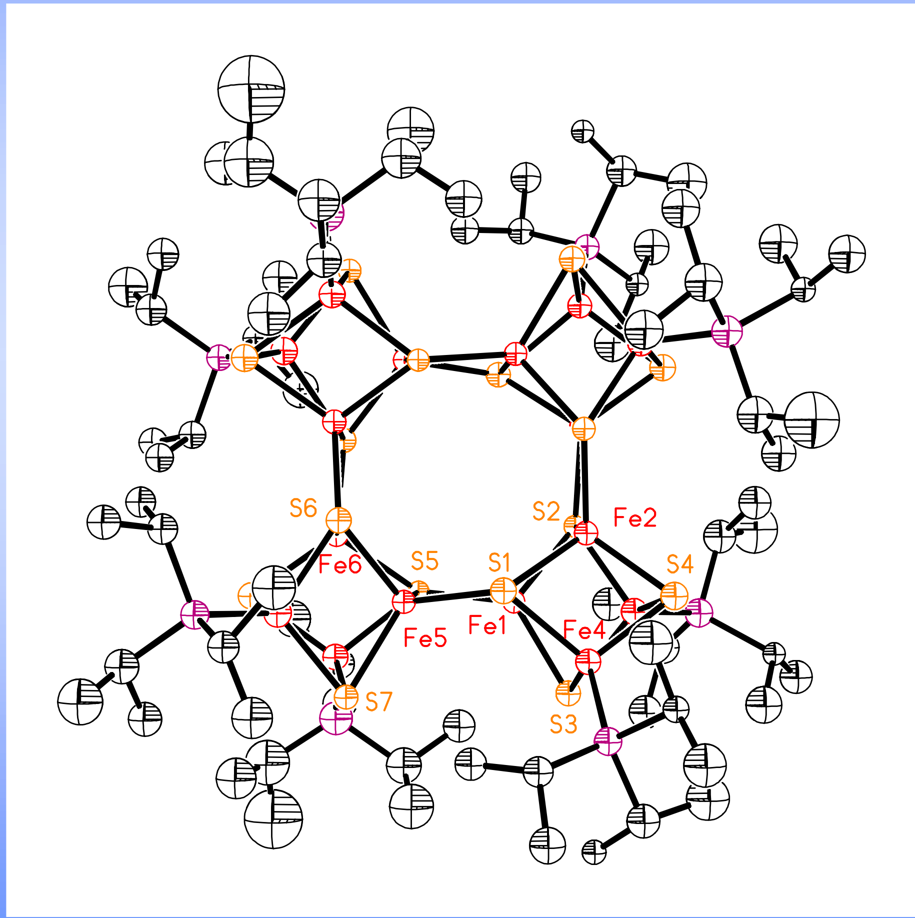
Evans's group, CH_2Cl_2/hexane

Reactant Diffusion

- Perform the reaction on a small scale compared to surface area.
- Layer one reactant on top of the other reactant and allow diffusion to control reaction rate and crystal formation.
- Good when product formed is highly insoluble.

Slow Evaporation

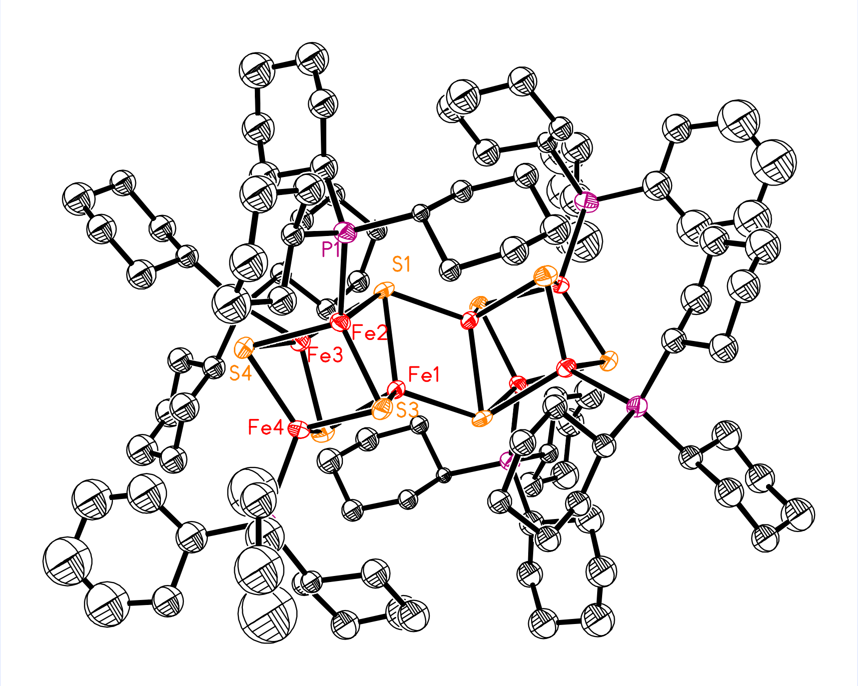
- Allow the material to crystallize out as the solvent evaporates.
- Keep the solution clean and covered to avoid dust particles.



Holm's Group, Evaporation of acetonitrile over several days.

Use The NMR Tube

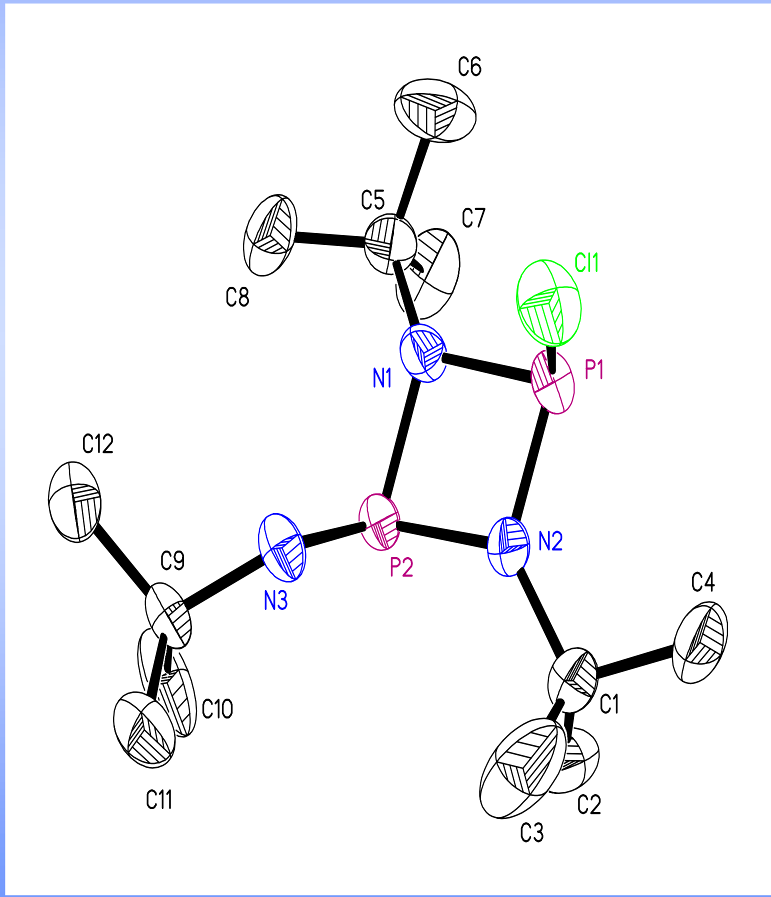
- Often crystals have been obtained by allowing the solvent to evaporate slowly from the NMR tube.
- Remember to keep the tube covered to avoid dust and dirt.



Holm’s Group, Left in NMR tube overnight, Benzene-d6

Slow Cooling

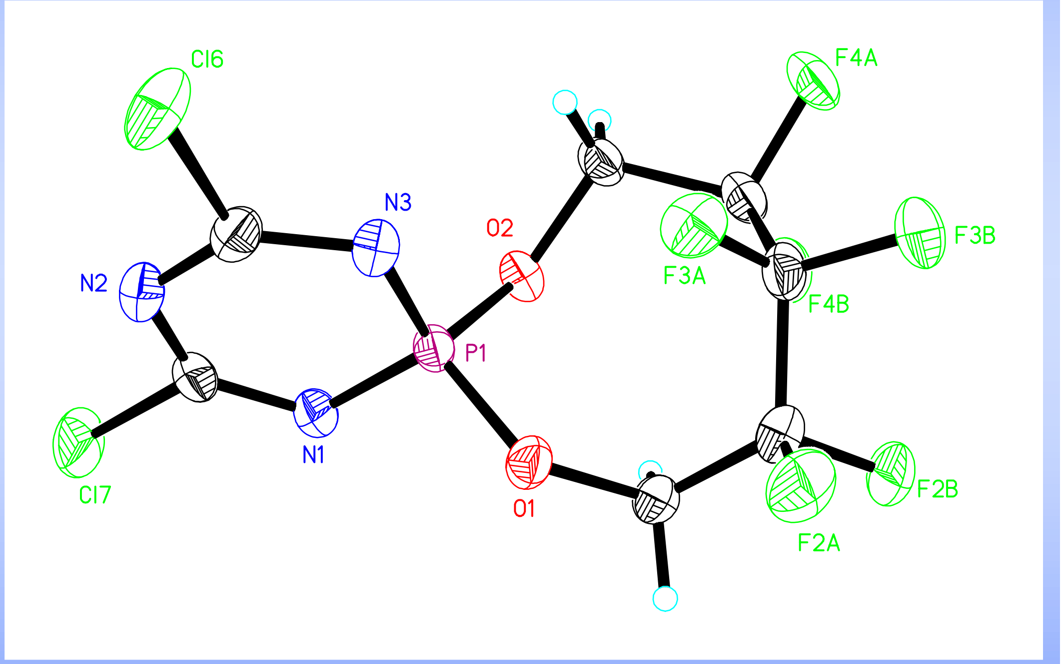
- Standard recrystallization technique.
- Must perform this slowly to work well.
- Slow reduction of the temperature is best.



Grocholl, Huch, Stahl, Staples, Steinhart, Johnson *Inorg. Chem*. **1997**, *36*, 4451.

Sublimation

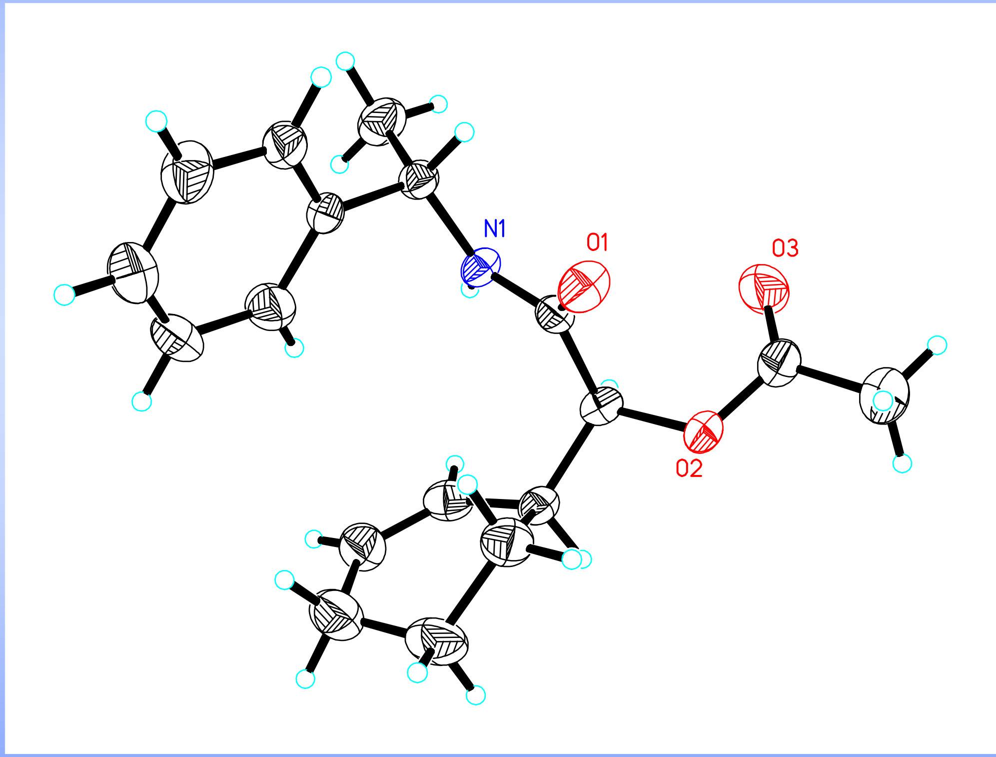
- Works extremely well when can be done.
- Must be performed slowly to achieve good size crystals.



Vij, Elias, Kirchmeier, Shreeve, *Inorg. Chem.* **1997**, *36*, 2730-2745.

Chiral Compounds

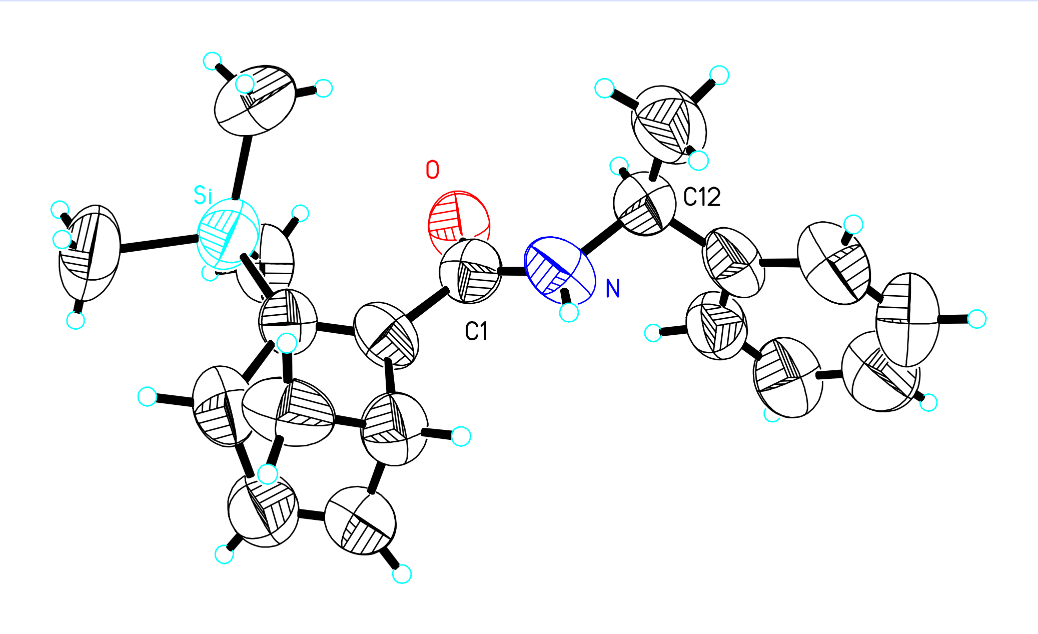
- These tend to be more difficult.
- Try to make derivatives which will improve packing. i.e. phenyl rings.
- Have atoms heavier than carbon.



Evans's group, CH_2Cl_2/hexane

S-alpha-methylbenzylamine

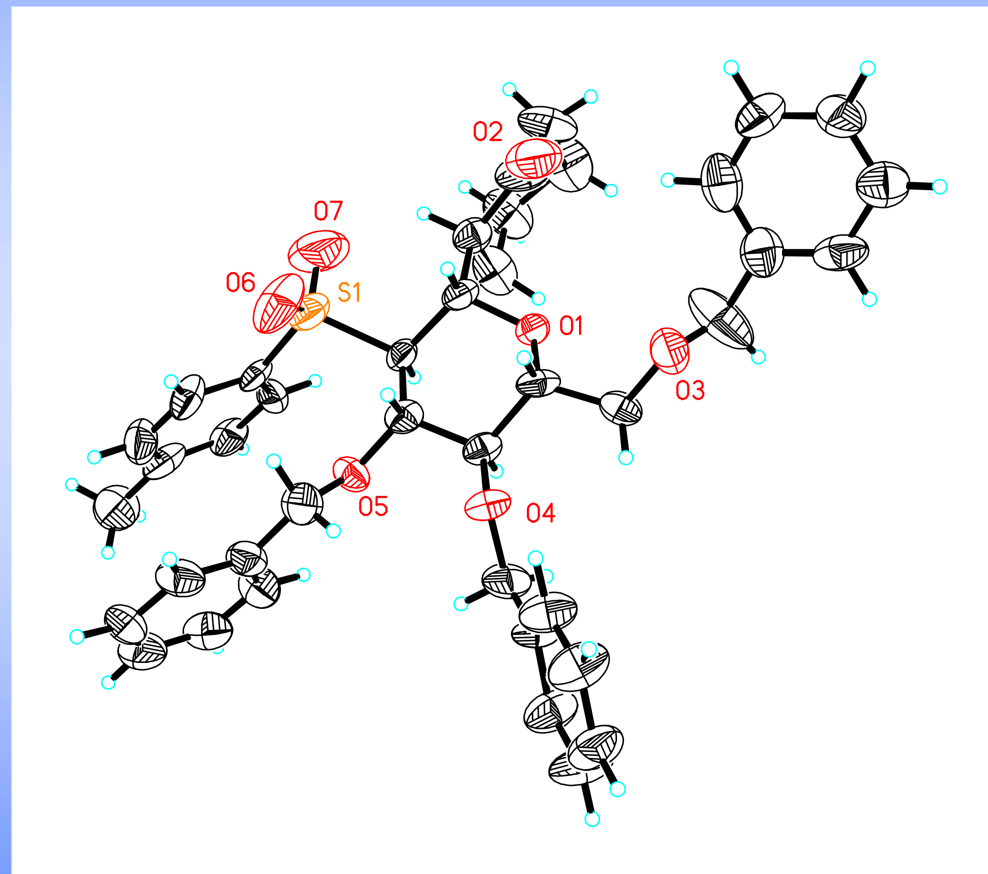
- Use with carboxylic acids, could be generated from alcohol or aldehydes.
- Cheap and usually easily crystallized.



Aldehyde converted to acid then to the amide.
Corey, Lee, *Tetrahedron Lett*. **1997**, *38*, 5755.

Improve heavy atom and crystallization

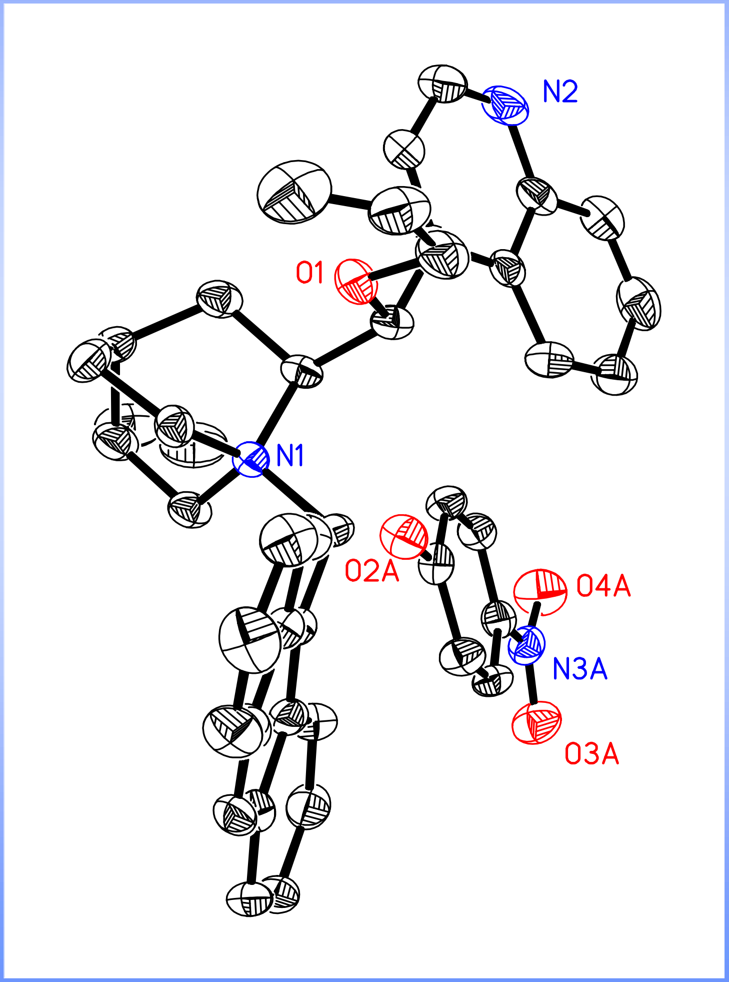
- Have heavy atom present.
- Alcohols and Amines make derivative with *p*-Bromobenzoate
- Include aromatic components in derivative.



Crystal was 0.1 x 0.05 x 0.05 mm, grown benzene layered with hexane.

Counterions or Ionization

- Change a counterion in the complex.
- Ions of the same size tend to pack well.
- If neutral compound does not crystallize or is liquid, create an ion. Deprotonation or protonation. Good to confirm the identity of the material.



Corey, Xu, Feng, Noe, *JACS* **1997**, *119*, 1214

Odd Methods

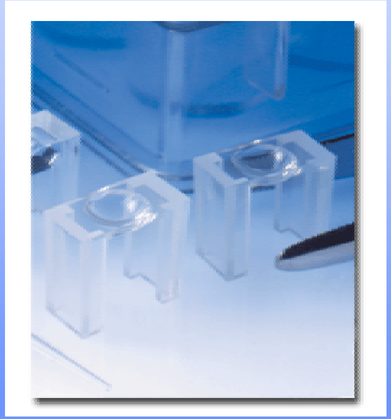
- Melting the compound and letting it recrystallize!
- Seeding a solution with similar crystallized material.

Macro Type Methods

- Hampton Research one of the first company to address small molecules using macro techniques
  - Problem, organic solvents, not water
- Solution to use alcohols and small quantities of organics
- Success at Harvard has been limited

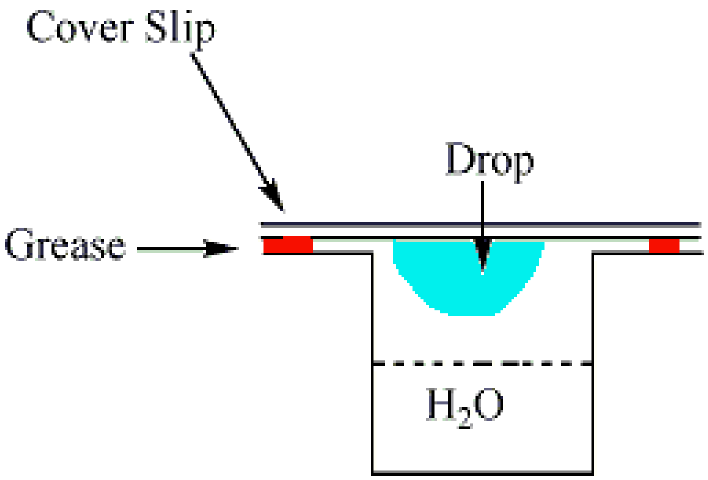
New plates and bridges

- Formulation of new plates and bridges
- Polypropylene
- They have developed some great initial starting solutions. Download small molecule catalog.



http://www.hamptonresearch.com

Plate Crystallizations, Hanging Drop



Drop Contains

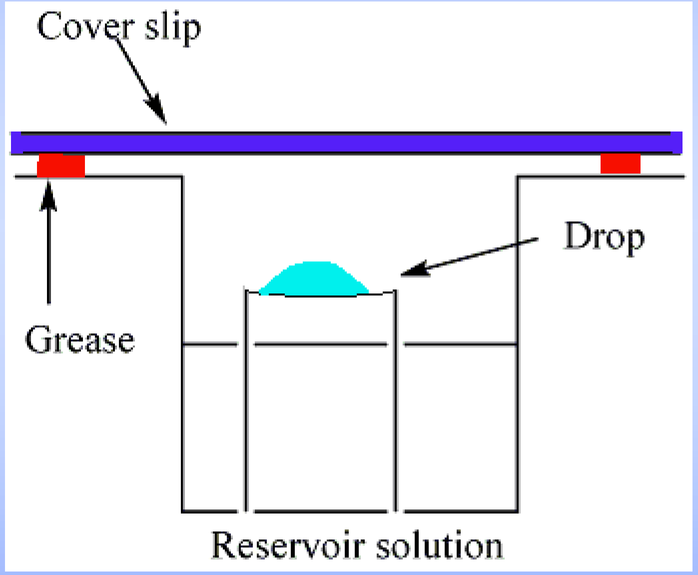
Compound
H_2O
Solvent A

Over time the drop loses Solvent A to the lower reservoir and compound crystallizes

Solvent A = Organic, water soluble solvent, Alcohols, CH_2Cl_2

See Hampton Research catalog or web sit for a very good tutorial on crystal growing by these methods. http://www.hamptonresearch.com

Plate Crystallizations, Sitting Drop



See Hampton Research catalog or web sit for a very good tutorial on crystal growing by these methods. http://www.hamptonresearch.com

Example Organic Plate

Some possible solvent combinations that may work

- 1 10% v/v ethyl acetate
- 2 15% v/v ethyl acetate
- 3 30% v/v ethanol
- 4 40% v/v 1,6 hexanediol
- 5 40% v/v ethylene glycol
- 6 40% v/v 2,5 hexanediol
- 7 40% v/v Glycerol
- 8 40% v/v 1,3 butanediol
- 9 20% v/v methanol
- 10 40% v/v Polypropylene glycol 400
- 11 40% v/v 1, 4 butanediol
- 12 40% v/v 1,3 propanediol
- 13 40% v/v acetonitrile
- 14 30% v/v acetonitrile
- 15 40% v/v n propanol
- 16 5% v/v ethyl acetate
- 17 40% v/v acetone
- 18 2.5% v/v dichloromethane
- 19 5% v/v dichloromethane
- 20 40% v/v ethanol
- 21 40% v/v methanol
- 22 40% v/v 2,2,2 trifluoroethanol
- 23 30% DMSO
- 24 40% Isopropanol

Thanks to Bob Cudney (*Hampton Research*) for the initial list and thanks to CHEM 154 courses to help improve the list of solvents.

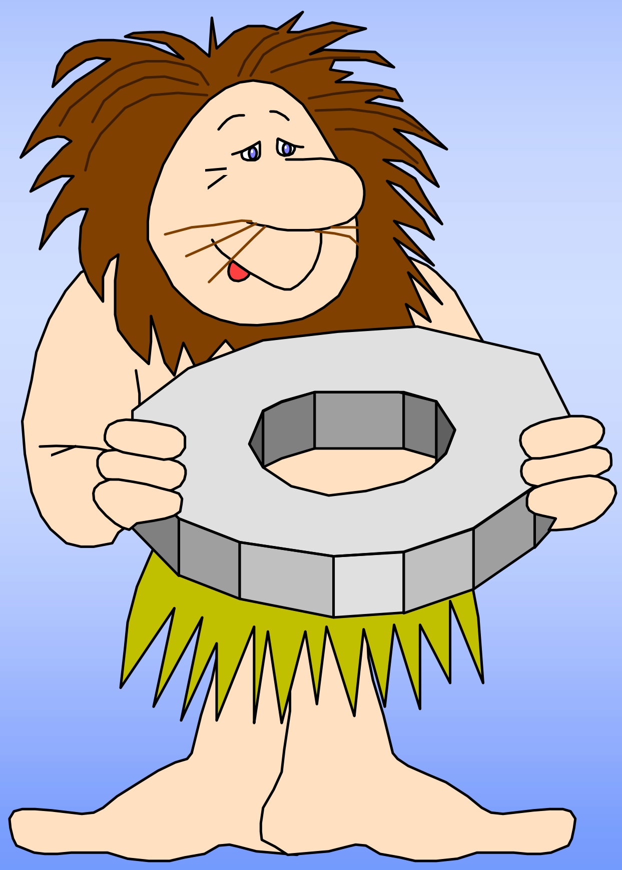
Nextal Biotechnologies

- Their screw cap version is preferred by some chemists, but the seal is not always organic safe and costs are higher.

http://www.nextalbiotech.com/

Key Factors to Good Crystals.

- Solvent
- Nucleation
- Mechanics
- Time
- Patience, Patience
- Art Form

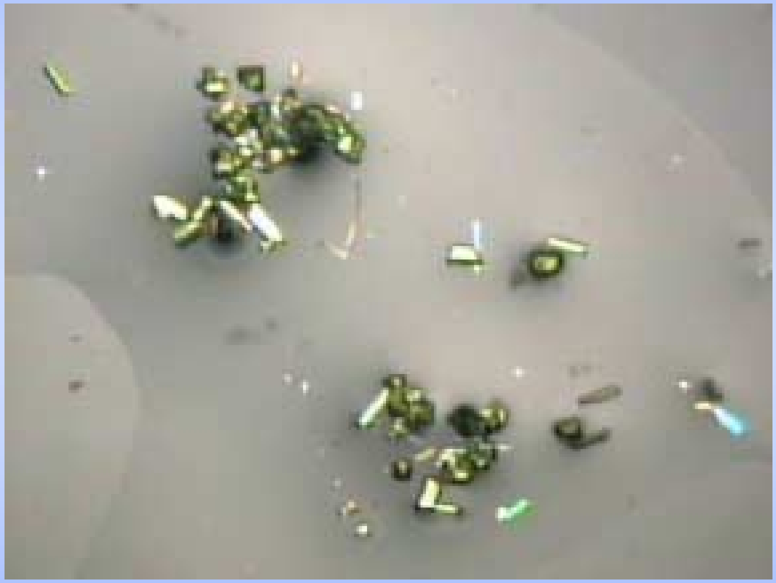


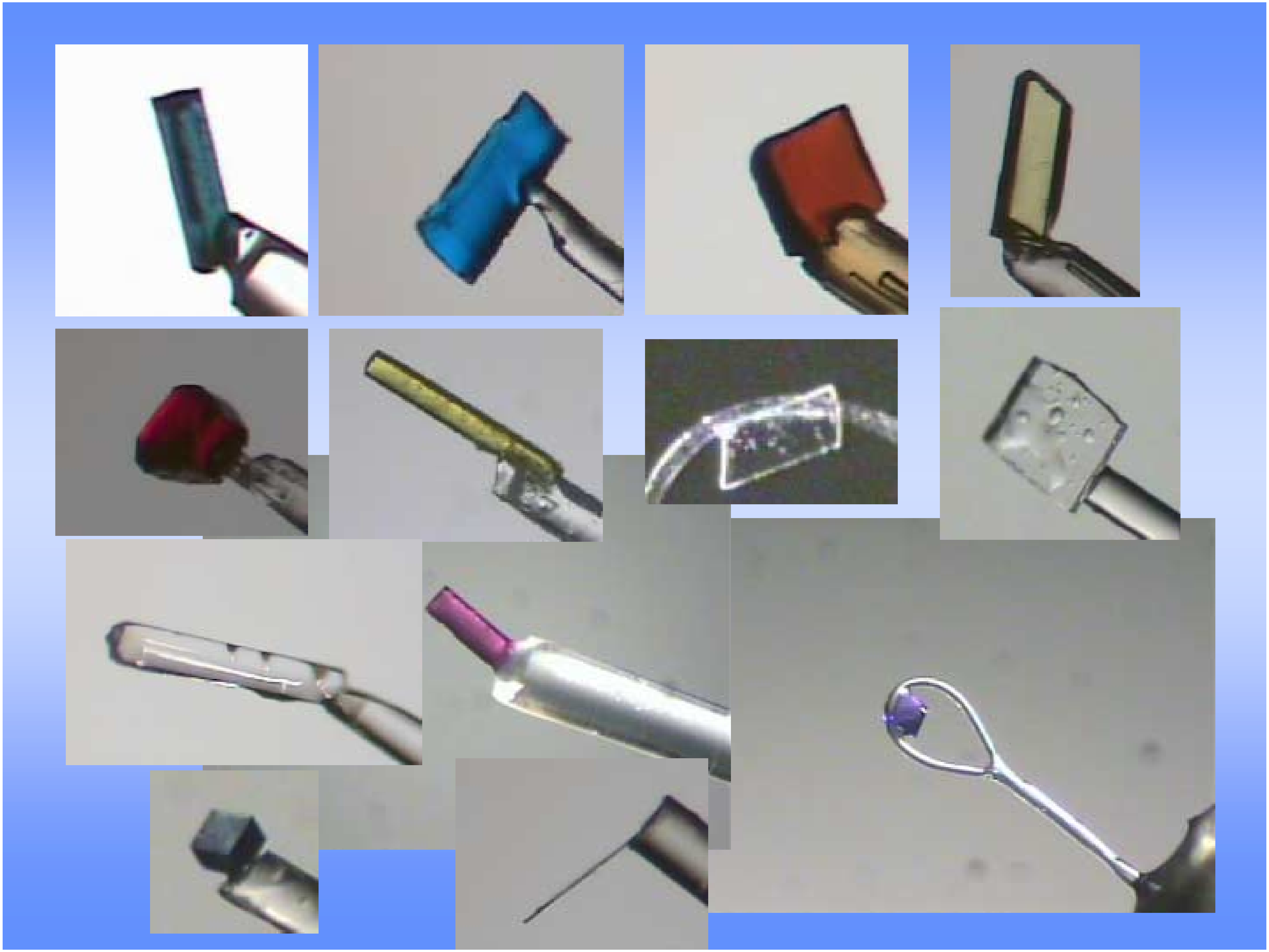
Crystal Evaluation

- Evaluation starts at the microscope. Do they look crystalline and single under cross polarized light?
- Are all the crystals uniform in shape?
- Mount and evaluate the crystal on the diffractometer. Requires about 20 - 30 minutes. Less if it does not diffract at all.

What is a Good Crystal?

- Well defined crystalline shape often results in good crystals.
- Sparkle
- One that works!!
- Gives good spots and spot shapes.





What happens to larger crystals?

- Cut the crystals to size.
- When cutting do they crumble? — these are not likely single.
- Do they become less defined over time? — loss of solvent.

Dr. Richard J. Staples

- Ph.D., Chemistry; December 1989.
  The University of Toledo
- Post-doc Texas A&M University, John P. Fackler,
  Head of Research Group
  Inorganic chemistry, transition metals
- University Crystallographer, University of Idaho.
  Operated one of the first SMART CCD Diffractometers
- Joined Harvard University, Aug. 1997