Growing Good Crystals

Garbage in = Garbage out

In other words, merely trying something which 'looks' crystalline may not result in a structure. For X-ray crystallography we require 'good quality' crystals and hence:

Good crystals = good diffraction = good data = good result.

So what is a good crystal? For X-ray diffraction, size really does matter; think somewhere between a grain of salt and a grain of sugar. The bigger the crystals are, the better the diffraction. Usually during a synthesis "recrystallisation" means a method of obtaining your product in a pure form and crystal size is unimportant. It may take just a few seconds on the rotavap, or perhaps overnight in the fridge, to obtain your pure product.

However for crystallography, "recrystallisation" has a different meaning. We wish to grow large crystals, large enough that your sample looks like a collection of crystals, and not like a powder. Growing crystals for a crystal structure usually takes time (occasionally several months!) and requires a bit of patience. You may spend many weeks developing a synthesis towards your target molecule, so why would you want to rush the preparation of your crystals for analysis?

The best way to grow large crystals is usually to leave your sample somewhere cool and out of the way (and then go to Mexico for a fortnight). At the back of the fridge in an nmr tube is ideal; here the crystals are unlikely to be disturbed and the smooth surface of the inside of the tube contains few nucleation sites so it is more likely that two or three large crystals will grow as opposed to tens or hundreds of tiny ones. Deuterated solvents also tend to be conducive to the growth of good crystals. The little coloured cap used to seal the nmr tube actually allows a very slow evaporation of solvent, encouraging crystal growth.

If you're not up to foreign holidays, or you only have one nmr tube in your whole group, then there are some other methods of crystal growth:

Other Methods of crystal growth

In all cases, the location of your flasks for crystal growth should be vibration free if possible. Storing them right next to a vacuum pump may not be such a good idea!

1. Solvent evaporation
Sloven evaporating of the solvent is probably the most common way of crystal growth. Rather than simply taking the lid off the vial, it should be carried out in a controlled manner so as to encourage the growth of few large, rather than many small, crystals. Prepare an almost saturated solution of your product and transfer a few cm$^3$ to a clean vial (make sure there is no dust; rinse out with the mother liquor solvent first). Cover either with Parafilm, aluminium foil or some other covering and pierce a very small hole in the covering. Allow to stand undisturbed.

**Pros**: easy to do.

**Cons**: you need quite a bit of sample; not good for air-sensitives; can take a long time.

2. Solvent cooling.
This takes advantage of the fact that things tend to be more highly soluble in hot solutions than in cold ones. It also works better when the cooling is as slow as possible. Prepare an almost saturated solution in hot solvent and cover the vial. Stand the vial either in a Dewar of boiling water (for high-boiling solvents) or a thermostatted bath. The surrounding heat will slow down the rate of solvent cooling and, hopefully, encourage nucleation.

An alternative is to prepare a room-temperature solution in a low-freezing solvent and store in a freezer.

**Pros**: easy to do

**Cons**: requires more equipment and space; needs a lot of sample; may lead to powders.
For this method you need two miscible solvents in which your product is very soluble in one, and insoluble in the other (combining polar and non-polar solvents is often best; ether and hexane is often a good choice). Prepare a saturated solution and place in a small sample vial. Place this vial inside a larger vial and surround with the second, non-dissolving solvent. Seal the larger vial and wait. Hopefully the non-dissolving solvent will condense inside the smaller tube, and begin to mix slowly with the solution. As the sample is insoluble in one of the solvents, crystals should begin to form at the interface.

Pros: only requires a small amount of sample, controllable
Cons: requires careful solvent choice to find appropriate combination of solubility, miscibility and volatility.

4. Anti-solvent diffusion
This is similar to vapour diffusion, requiring two contrasting solvents, except that you use just one vial. Transfer a small amount of saturated solution into a vial and onto this carefully layer the non-dissolving solvent. As the solvents mix, crystals form at the interface.

Pros: only requires a small amount of sample, controllable
Cons: requires careful solvent choice to find appropriate combination of solubility and miscibility; doesn't always work!

5. Other tips
The above techniques may not work first time. Don't be disheartened! Often changing the solvent can significantly affect crystal growth, even though there may be no solvent incorporated into the structure. So try combinations of every solvent in your lab. All you need is one crystal to grow!

You should also use perfectly clean and smooth glassware; old, scratched vessels provide a greater number of nucleation sites for the crystals and tend to lead to the formation of microcrystalline compounds.

Alternatively you could try changing the day of the week on which you grow the crystals, the colour of your shirt, not doing it when there is an 'r' in the month etc etc etc...