General Thoughts

- Growing crystals is a skill, which can only be mastered well after attempting numerous crystallizations.
- Be persistent - do not give up if the first, or second crystallization attempt fails. There is a lot of conditions at your disposal that you can change such as solvent ratio, solvent volume, temperature, add second or even third solvent to your crystallization mixture. The bottom line is experimentation - the more you play with crystallizations the more successful you get.
- Be observant! Pay close attention to the compound's behavior during its preparation and work-up - how soluble it is in a given solvent, what happens when a drop of solution is left to evaporate? This might give you important clues regarding what solvents to use in your crystallization.
- The purer compound you start with the better your chance of growing good crystals. I usually do not start growing crystals until the compound is at least 90% pure.
- Crystallization solution must be homogenous! When a compound is dissolved in any solvent the resulted solution should be filtered (syringe filter works well for this purpose) to remove any floater before it is put aside - in my opinion this is probably the most important step in setting-up crystallization!

Practical Aspects

- All of my crystallizations were performed using five different solvents or their mixtures: toluene, hexane, THF, diethyl ether and methylene chloride. So far I did not have to resort to other solvents in my work but this does not mean that these five solvents will always work very well for your crystallization. All of the crystals I have obtained were either grown by cooling (drybox freezer set at \(-25^\circ C\)) or evaporating solution containing dissolved compound. Most of the compounds I crystallized were organometallic complexes (MW = 300 - 1000) although I also obtained crystals of several organic molecules.
- In my experience, salts are somewhat more difficult to crystallize than neutral compounds - some of them tend to oil out. Solvent mixtures for salt crystallization that I successfully used were methylene chloride/hexane and THF/hexane.
- Choice of crystallization solvent or solvent mixture depends, of course, on the compound's solubility. In any crystallization technique the idea is to exceed saturation level of the solution and force the solute to come out hopefully in the form of beautiful crystals. If the compound is very soluble even in hydrocarbons then solvent evaporation is a technique of choice. Slow evaporation (1-7 days) is usually recommended but at times good crystals can be obtained within 1 hr. by simply leaving the solution vessel wide open.

A Few Example Crystallizations from My Work

1. Organic compound (~ 30 mg) was dissolved in a mixture of 0.5 mL of methylene chloride and 2 mL of hexane (compound was very soluble in methylene chloride but much less soluble in hexane). Solution was filtered and put aside at room temp. Since methylene chloride evaporates faster then hexane after a few days solution reached saturation level and crystals formed.

2. Two reactants (~ 35 mg each) were dissolved in 0.6 mL of C6D6 in the NMR tube. The product of this reaction was a salt, which had much lower solubility in benzene that the starting materials. Good quality crystals were obtained within an hour in the NMR tube.
3. Organic salt (~150 mg) was dissolved in 1 mL of ether followed by 2 mL of hexane (hexane was added until solution became slightly cloudy). Solution was filtered and put aside on the shelf in the dry box (room temp.). After 14 hr. colorless crystals formed.

4. Organometallic complex (50 mg) (highly soluble even in hydrocarbons) was dissolved in 1 mL of hexane and the vial was left opened in the drybox. After 8 hr. hexane evaporated leaving nice crystals. One way to slow down evaporation is to leave a closed NMR tube for a couple of weeks. Although this is a very slow process it quite often gives very nice crystals.

5. Organometallic complex (~ 300 mg) was dissolved in 1 mL of toluene followed by 4 mL of hexane. Solution was mixed, filtered and put into freezer (-25 °C). Next day crystals were formed.

6. Organometallic complex (~ 300 mg) was dissolved in 3 mL hexane. Solution was filtered and put into freezer (-25 °C). Next day crystals were formed.

7. Introduction of some solvents might change the interaction between cation and anion and help with crystallization. In one case, small amount of THF was added to crystallization mixture (ether/hexane). Obtained crystals contained THF molecule that formed hydrogen bond with ammonium cation of my compound. THF helped in crystallization by changing the composition of the compound.

8. Many solvents get incorporated into crystal lattice. This is an extremely common phenomenon. Aromatic solvents (toluene, benzene), for example, are among the most common solvents found in crystal lattices. If you have difficulty growing crystals from one set of solvents (even though you did everything right) you might want to introduce small amount of second or third solvent with the hope it will be used by Nature as a building block of the crystal lattice thus allowing good crystal formation.

Happy crystal growing!