How to become efficient in the research laboratory?

This is a very important question, both for success and work-life balance. If you are very efficient in the laboratory, you will have automatically more free time! Unfortunately, there is no magic answer to this question. Practical experience is certainly the most important: Each reaction you perform will help you become more efficient. Nevertheless, a few practical hints are given here to help you increase your efficiency in the lab. If some of the hints appear abstract to you, please discuss them with me or another group member.

1) Working Rhythm/Balance

- A PhD is taking several years. Finding the right working rhythm is essential to be both productive and enjoy what you do! Here there is no method which is best, and you can profit from the liberty of academia, working at the time of the day you are more efficient (nevertheless, you should check to have sufficient hourly overlap with me and other group members to profit of the team, and participation to group meetings is mandatory!) and either for shorter time on high intensity, or longer on lower intensity. Personally, I would prefer the high intensity style: it gives you more free time at the end of the day, and it will be the way of working in industry. It makes it also easier to reach a good work/life brain/body/soul balance.

- Take the right start in the day! If you are efficient in the first 2 hours of work, your day will be successful! When you come in the lab, it will help you a lot if you already have in mind what you will do.

- The right working rhythm is the one that allow you to enjoy fully your passion for organic chemistry, without feeling overworked!

2) Planning: From Brain to Hand

2.1 The Literature Search: Which reaction

- Citation: "**One day in the library can win you one month in the lab**" (Jeff Bode)

- The first phase of planning is nearly always a literature search. The original idea (from me or yourself) need to be compared with knowledge in the literature. For the preparation of starting materials, this is relatively easy, as you may find exactly what you are looking for. Nevertheless, always check several procedures to see which one looks more reproducible. Sometimes, there is a bad synthesis for the exact compound you want to make, but a good one for a compound very closely related! It is one of the main reasons why a good chemical knowledge is required, even with the new databases available. At the beginning, ask senior students or me for advice. Looking for conditions for a new reaction is much more difficult, because if it is new it will not be in the literature! In this case, you have to proceed by analogies, to get a start (similar substrate reactivity, or similar reagent, or similar catalytic system,…). Be as broad as possible at the beginning; don't assume you know a lot!

- Technical support: personally I am a big fan of Reaxys, but Scifinder is also very good. Cross-check between databases is often good, as they don't give the same solution. For key words search, I tend to favor Web of Science. Try not to base your search on a single source of information (for example look for structures and key words).

- From the search, you should get a list of reactions you want to do. Especially when starting a screening, it is important to stay open, because you may assume too much about the reaction (examples: you think that an apolar solvent should be better, still try a few polar one to check, the best base should have a pka of 10-14, still test one around 8 and around 20. Pd is your favored catalyst, still try a few other metals (Ni, Au, ….). BOX should be the best ligand, still try phosphine and diols).

- Citation "**Never talk you out of an experiment**" (Erick M. Carreira). Sometimes, based on intuition, you got an idea. If you think carefully on a reaction, you will always find many reasons why it should not work. Nevertheless, we are privileged in chemistry, as we can test ideas very fast and at low cost (with some exception, naturally). Just follow your first idea and do it. Sometimes it is even the way new projects start. You even don't have to ask me before (exception: safety issue, high costs, too much work required).

2.2 When Planning?

- To ensure a smooth start, it will be very helpful to plan your research the day before, not the morning when you arrive. Think about dry glasswares, required consumables, chemicals, plan also reservation on the analytical equipment (NMR, HPLC, GC). Plan especially carefully your first hour of work in the morning, as it could decide your day. It can help you to write down the most important information that you take with you at the hood. Decide in advance on the order of the reactions you want to start. Do not hesitate to come to me if you want to discuss planning.

- Planning becomes more difficult, but also more important during semester, when you have a lot of teaching duties and seminars. In this case, one hour of careful planning can win several days in research.

- Take the habit to think about the new chemicals you need for the next week a few hours before the shop will send the last orders of the week.

2.3 The Chemicals

- Unfortunately, the chemical inventory is nearly never completely up to date. It is consequently important to check for the physical presence of a chemical when planning.

- For catalysts/reagents/substrates you need regularly, it is important to check how much is left. Starting to synthesize a new batch in parallel with performing new reactions is a very good way to become more efficient.

- Think carefully of the required purity of the starting materials: will you need to distill, recrystallize, repurify something?

2.4 The Timing

- Planning the right order of reactions/purifications can decide the efficiency of your day! Typical example; you need to purify three compounds from the day before, make 4 screening reactions which take 8 h and make starting material for 16 h. The right way to do it is start your 4 reactions first, then the preparation of the starting material, then you do the purifications probably just in time to make the work-up of the 4 reactions and let for example the GC-analyze the results of the reaction overnight.

- Make chemistry work when you are not there: plan long reactions during night, weekend, teaching, seminars….

2.5 The Reaction

- Scale: Plan the scale of the reaction according to the information you need. Classically you will have three most frequent modes: screening (about 0.04 mmol, 10 mg, 1-10 reactions in parallel), scope (about 0.4 mmol, 100 mg, 1-4 reactions in parallel) and synthesis (1-10 mmol, 1-10 g, 1-2 reactions in parallel). With experience, you will be able to increase the number of reactions in parallel.

- Catalyst loading and concentration: These are dependent also of the scale, usually a classical case is to work at lower concentration and higher catalyst loading when doing screening (typically 20 mol%), this avoids especially false negative due to catalyst decomposition.

- Screening of conditions: it is important to use the right technical support (flasks, tubes or parallel synthesizer), to plan carefully the reactions (scale, inert gas or not) and the analytics (TLC only, or NMR, or GC or HPLC or MS). It is often good to test the robustness of the reaction (Is it really sensitive or not?) before starting.

2.6 Purification and Analysis

- Think carefully of the best way to purify your compound: extraction, precipitation, crystallization, column chromatography of flash column chromatography… Do you really need a purification? Especially for screening, you should always find a way to get the information you need without purification! (GC or LC-MS, NMR of crude, TLC,…)

- Think carefully of the best way to analyze your result: TLC? Isolated yield? Crude NMR? Crude NMR with calibration? GC-MS? GC-MS with calibration? HPLC? HPLC with calibration. You goal is to get all the information you need, but only the information you need, in the shorter time possible. A typical example: screening of 10 reactions: 1. TLC for yes and now, if product observed, than calibrated GC-MS for quantification, without purification

- Timing the analysis: do you need to reserve a machine in advance? Do you need to wait for the result from a service (for example X-rays, MS). Can you run the analysis automatically over night?

- **It is important not to postpone the characterization of compounds**! Many organic molecules are not very stable and may decompose over time. Check especially carefully that your NMR's are pure enough, that you did not forget analytical data like a melting point or a IR. It is important to compare with the literature data for known compounds! If you have enough compounds, the easiest is to make a relatively concentrated NMR sample, take then all the NMR data a once and use the solution for IR:

3) Implementation

- Increasing efficiency via routine and innovation: There are two main ways to become more efficient in the lab: **Routine**: if you make a procedure very often (typically packing a column), you can constantly accelerate your action to make it faster and faster (for example you know exactly how much silica gel, how much solvent in which flask to pack as specific size of column). **Innovation**: there may well be techniques you don't know yet, which could make you much more

efficient! Here the team becomes important: profit from more experienced scientists and also from inputs from outside the group. **It is important to stay open to more efficient and clean way of working**, either developed in the group for newcomers, or outside the group when newcomers arrive.

- **Do reactions in parallel!** With experience, you will be able to make more and more reactions in parallel. You will also learn when it is possible without doing mistakes (sometimes you can do 20 reactions in parallel, sometimes you have to concentrate on a single reaction, else it will fail). Try to push your limits.

- Micro-Optimization: **No gain in efficiency is too small!** In fact, efficient work is the combination of many small details. A few examples: Know by heart at which pressure and temperature each solvent is more efficiently removed at the rotavap, but still condenses correctly. Optimize the flow of your columns, for example: the flow is fast enough just to let you change the fractions. Or a little slower, which allow you to spot on TLC during each fraction. Ideally, the column and the TLC should be run in parallel. TLC size should correspond to the time needed to finish the solvent in the reservoir on top of the column, so that you can let the TLC go up during the time you add new solvent. For complicated column, you will be able to adapt your solvent gradient faster this way.

- **Rule of three**: For many actions in the organic laboratory, it is always a good start to do it three times. For example: evacuate/flush with inert gas three times, degassed solvents three times, extract the water layer with organic solvent three times, wash your filtration flask three times, and so on.

- **Take precautions, but only when required!** Not needed precautions only mean a loss of time. The best way when you start a new optimization is to do it first with extreme care (distill all the solvents and liquid starting materials and reagents, recrystallize all the solids), then do the same without any precaution, and see if the result is different. If you obtain the same result with technical solvents under air, you will be faster for your optimization! You need to check again sensitivity to water and air when you expand your reaction to a new system.

- Find the **right ratio between care and speed**: It is impossible to generate the same quality of data when doing screening and when doing a reaction on a preparative scale. The goal of screening is not the get the best data immediately, but to generate a trend. The most interesting results of the screen need later to be checked on preparative scale to see if they are reproducible.

4) Analysis

- Carefully analyze your data, it allows you to go back to planning the next reaction.

- Did I get the information I was looking for? If no, is it a result of technique (I did not choose the right scale, the right analysis method, the right purification method) or chemistry (the reaction conditions, the catalysts, the substrate, the reagent were not right).

- Is the result I got significant, or do I need to repeat it first before I can be sure?

- Analysis of the results is often very difficult; do not hesitate to discuss it with me and/or senior students.

5) The Team

- Mentoring: educate as soon as possible new students in correct planning. It is important to help them, but also that they learn to organize their job.

- **Please take great care of your group jobs**, the other group members will appreciate! When you are using a common equipment, please do it with as much care you can and clean it well after you are done.

- **Think, then ask, but do not be afraid to ask!** The goal of a PhD is to become independent, so you should always think about your problem before asking somebody. But if you are not sure you have the best solution/plan for the future, do not hesitate to ask me or other group members, else you will not profit from the team!

- **Team spirit is very important at LCSO**. Profiting from the specific strengths of each group member and contributing to the common good will at the end make each individual more successful. Ideas or suggestions of other group members have always to be met with great respect. Of course it will come that you think that an idea/suggestion of somebody is not good, but then discuss it with him to explain your standpoint. In particular, Junior members should implement the suggestions of seniors or myself if we still think they are important after discussion. Even if they are not convinced, this is a demonstration of respect for people with a longer experience in the field.

- I will participate actively to your education and help you to make you more efficient. Nevertheless, as I am not working in the laboratory anymore, it will be older group members and especially Stefano who will introduce you in the techniques of research.

6) Safety

Each group member will follow a safety introduction when joining the group. I am **always open for discussion on many topics, but not on safety**: **Safety rules have to be followed without concessions**.

There is no magic way to become more efficient in the Laboratory, but if you want to do it every day, you will improve!

Never Forget: Safety goes first!