



On the trail of nature's solutions

From a group interview by Patrick S. Regan (PSR) with Hans Fischer Senior Fellow Polly L. Arnold, University of Edinburgh (PLA); Prof. Fritz E. Kühn, TUM (FEK); and doctoral candidates Max McMullon, University of Edinburgh (MM); and Julia Rieb, TUM (JR).

PSR: Your group is focusing wide-ranging expertise in chemical synthesis and catalysts on new approaches to activating carbon-hydrogen bonds. What's the aim?

PLA: We want to show how, working together, we can more easily make compounds that break some of the hardest bonds to break, in molecules that we currently burn when we should be using them to do useful things.

PSR: Molecules such as oil and natural gas?

MM: We want to use the resources that we have in the correct way, with maximum efficiency. At the moment we burn a lot of methane as a by-product, but if we could transform the molecules – for example, activating the bonds of the molecules to make them easier to transport – then that's a higher-value product. That's the aim of the project.

FEK: The final goal is to activate C-H bonds, particularly in methane. Methane is a very abundant molecule on the earth, as methane hydrate or as natural gas. If you transform methane gas into methanol, alcohol, it becomes a liquid and can be much more easily transported. The art is to stop the oxidation of methane after the oxidation to methanol and not go all the way through to carbon dioxide. If you have methanol, you can use it as a liquid fuel, on the one hand, or as a starting material for a variety of value-added chemicals.

PLA: Fossil fuels and biorenewables all contain a large number of very similar carbon-hydrogen bonds. The molecules have carbon skeletons with carbon-hydrogen bonds all over them. The bonds aren't the strongest bonds known, but the compounds are very symmetrical, and selectively choosing just one carbon-hydrogen bond and then converting that – either in the absence or presence of other potentially useful functional groups of other atoms – that's the hard thing to do. So if you have methane, you just have a perfect tetrahedron with very inaccessible, identical carbon-hydrogen bonds. To get just one, that's the real trick.

48 If you have a very good catalyst that functions at low temperature – so if we really do make a good asymmetric molecule, as we are trying to do with cerium – that can pick up selectively just one carbon-hydrogen bond, there might be interesting fine chemicals or more complex molecules where, instead of ignoring every other carbon-hydrogen bond, we can treat those as the functional group. So we could selectively pick out a carbon-hydrogen bond in a very complex structure and then would not have to go through all the atom-inefficient processes of putting in other groups earlier on in the synthesis. So we can do a late-stage transformation and make exactly the drug molecule that we want, with perfect atom economy. All the basic molecules start with carbon-hydrogen bonds everywhere, so to control the carbon-hydrogen bond in the presence of all sorts of atoms is extremely useful in a variety of ways.

FEK: Nature can do this. Nature can transform methane into methanol. But mimicking the natural compounds, the enzymes, is difficult, because usually they have an organometallic element but then a lot of biochemistry around it. These bio-ligands we cannot yet synthesize easily. So what we need are molecules that are easier to make than those natural compounds but achieve similar purposes. There are several metals at hand that are common enough, and promising enough, to be used. Our groups utilize different approaches with different metals, but we can compare how close they come to the solutions of nature.

PSR: And you are working with solutions, aren't you?

PLA: There are some really high-energy solid-state processes where instead of just burning a hydrocarbon you can partially transform it – which is pretty much what we're trying to do – but it's a lot more aggressive. For us, taking a solution approach, where everything is all dissolved up together, gives us perfect control – not only allowing us to trap every intermediate product as we go along so we understand what we're doing and then can design a better one, but also enabling us to do this at low energy, so we can behave more like nature does.



Polly L. Arnold

PSR: How do you gain that kind of insight into a reaction?

PLA: Say you're looking at the transient intermediate that forms when you bring one of these traditionally inert small molecules, one of these hydrocarbons, right up to the metal center – and it just starts to form that interaction. Sometimes you can trap these in a crystalline form. You can look at the structure and see how you might want to design or redesign your molecule to get that perfect approach and then get enough electron density from your metal into that small molecule to break up that carbon-hydrogen bond – just that one and not the others. Crystallizing these is hugely important for us, and that's one of the things that our sorts of chemistry allow us to do.

PSR: What are you after besides lowering the energy threshold for a reaction?



Fritz E. Kühn

FEK: Allowing pathways that otherwise would not be available, or that would be available only with more difficulty. So if we examine different molecules, we can also open up new ways in which we can do a reaction that, before, was energetically not favored and just didn't happen. This can also lead to somewhat different pathways, and we have to see if we get side products, do we get what we want, in which direction does the whole thing go. Of course we need to know more about the reaction pathways, we need to know intermediates. If we have just the starting and product molecules, there would be a lot of possible ways, and when we modify the process, it would just be trial and error. The more we know of the steps in between, the more tailor-made our catalysts can be.

PSR: What kinds of alternatives are available?

PLA: To convert single carbon-hydrogen bonds you can take a big bed of solid-state material and heat it up to 800 degrees, so fast that only some of the bonds transform – and that's not going to work for a fine chemical. Or you can work with very expensive, very rare metals on the right-hand side of the periodic table – such as palladium and platinum, metals that don't exist very much in the earth's crust. Cerium and iron, the metals that our labs focus on, are ubiquitous, very cheap, and practically non-toxic. The drug companies will take many extra steps to avoid using palladium; if it gets left in a drug, it's very toxic. But cerium and other lanthanides are ten times less toxic than iron, which already is regarded as being non-toxic or nearly so.

FEK: Iron is one of the most common elements. It's not, in most of its compounds, toxic, because nature has had time to cope with it and use it safely for various purposes. Some of the less common elements either are toxic to living beings or have little influence on biological processes.

PSR: And now your Focus Group has brought together the Edinburgh lab's experience working with lanthanides and the TUM lab's experience with iron. How does this work in practice?

JR: In my master's thesis at TUM, I worked with metalorganic complexes of iron. When I switched to this project, we decided to keep my ligands, the organic framework around a metal center, and try them with these unusual metals. We don't know so much about them, but they seem to do very interesting chemistry. We kept my ligands, and took these metals, and we tried to combine the expertise. My focus is just to explore if there is any possibility to activate these inert molecules with cerium organometallic complexes, so-called NHC-complexes. Using my ligands I already worked with makes it a little bit easier.

PLA: We have been developing a large variety of the sorts of frameworks that you would think could bind, particularly working in my group, the lanthanide ions. We've also both been interested in opportunities perhaps to put two metals together. If we could

combine the cerium and iron that we have so much expertise in, using the same large organic ligand structures that we've been working with, we might see cooperativity from compounds that people haven't been able to isolate before. This is something that's really quite different to what other people are doing. One of the simplest ways to build up from this is to take both types using ligands and see just how we combine first iron and then cerium in there. We're finding that you need to have a much bigger ligand framework for that – which we could predict – but it's also thrown up other interesting routes. Julia was able to come to our lab, where we have a smorgasbord of reagents that can insert just that metal ion in a whole different range of starting materials.

PSR: Is this like a chemical library, or a toolbox?

PLA: Yes. She was able to take some ligand into the glovebox and go along the shelves and just pick one reagent after another and have a look. In almost all cases the solutions went purple, and then in almost all cases they decomposed. However, we identified a couple that didn't, and things began to look good, so Julia was able to come back here into the iron expertise area, with the different ligand set, knowing which cerium compounds she wanted to focus on while she was here. And then she could draw on Max's expertise by keeping contact, to help characterize what was going on.

PSR: And is this the kind of thing that you really can't do yet, or that you can't accelerate, through computational chemistry?

FEK: To a certain degree, yes. The problem is, we have a toolbox with a lot of tools, and we do not know what all of them can do. And by putting them together, we try to find how much we can predict and see what we might be able to use for something we are not aware of yet. It's like building something with very versatile building blocks, which can do more than we already know. Of course we can make predictions based on what we know. But we always have, so to say, an exchange between what we already know and what we think we could achieve. If we don't know what kind of intermediates we have, it's like having two valleys, and you just know

that there are mountains in between, but you don't know the mountain passes, and you might not exactly know the height of the mountains. If you just try to get to the other side of the mountain ridge without additional information, the theoretician may find one way, but there could be other pathways that lead over lower passes and would be easier to walk.

PLA: Max and I wouldn't dream of trusting our own calculations on the metals we use, because we're working right at the bottom of the periodic table, where the nuclei are so densely packed that relativistic effects apply. It's very difficult to know how to even start the calculations. It's really not our area of expertise. Calculations on iron for example are much more straightforward, because all the atoms in those calculations are so much lighter. So we actually collaborate a lot with computational chemists.

PSR: And physicists?

PLA: Yes. To try and understand where the electrons are, and to help them better explain the bonding in these materials, which are also nuclear waste-relevant. But for us, computation has never been a predictive option. So it's nice to make weird molecules that help the computational chemists improve their models.

FEK: Maybe I can tell you another anecdote to explain how problematic this is. In the 1960s, after Ernst Otto Fischer and Geoffrey Wilkinson had determined the structure of ferrocene, for which they got the Nobel Prize, they wanted to make other compounds of that type. Fischer's method was to draw a molecule on a sheet of paper, show it to a co-worker, and say: "Make it. I don't know how." And then the coworker started trying. Wilkinson thought this would be a waste of time and already had a theoretician calculating whether a molecule would be possible. In one particular case his theoretician told him the molecule he wanted could not exist, for it would not be stable. So his coworkers didn't even try to make it, while Fischer's group was able to make it, and published it. When Wilkinson came into the library of the university where he regularly checked the periodicals, he came upon this publication. And Wilkinson had a temper.

He got mad about this, he threw the journal on the floor and jumped on it, and you can still see Wilkinson's footstep on this article. This story shows that theory is not always the best approach – even today, and particularly with the heavier elements, for example the actinides and the lanthanides. With the lighter ones it's easier now, for several reasons.

PLA: There are monsters out there.

JR: Yes.

PLA: We actually had an argument last week.

JR: Exactly. We are trying right now to do a calculation on the molecules I'm trying to synthesize, and because of these relativistic effects we had to simplify the ligand framework. But that small change could be very important, just possibly exactly this part of the ligand and this metal could be very important. But we had to simplify it because it would consume so much time to do this calculation, so it's a problem. It's probably the best way to have the compounds, know it's working, and *then* try to do computational chemistry on it.

PLA: It's actually quite funny to have Julia sitting in Fritz's office going: "No. No. I don't want to do that calculation." That was very good. That means she's coming into her own as a scientist.

PSR: Julia, you and Max are facing a classic challenge for doctoral research. It should be bold and original – yet at the same time you should be able to get results within a few short years. How do you find the right balance when doing something that's daring, interesting, and potentially high-impact but also has a high risk?

JR: From the start I knew that it would be a very challenging project, because these organometallic compounds with cerium are very air-sensitive, they are moisture-sensitive, and they require extremely careful handling. I love the challenge, even though at times it's really frustrating. Most of the time, unfortunately, it doesn't work, just because it's still so much trial and error. You have an idea and you try something out, and many times what comes out is some-



Julia Rieb

thing different you were not thinking about. But even that is a very interesting aspect of the research.

PSR: Finding out why something you tried has failed?

JR: Exactly. What's different there? I wanted this compound, and I got another one. Why? Or maybe, how do I get it there? Right now I am working on synthesis of the cerium NHC-compounds. And so my problem is sometimes, because such a compound is not very stable, how will I stabilize it and crystallize it.

MM: That's the nature of our work. Our focus is on making the reactive molecules themselves and, using the ligand framework and quite unusual metals, to effectively reduce the energy barrier for reactions. When those things succeed and you get chemistry that is really interesting or molecules with a really interesting activity, part of the challenge is to find out why.

FEK: Of course, our job is also to carefully observe each doctoral candidate to make sure he or she does not come out with nothing. In some cases we



Patrick S. Regan

have to shift the main topic a bit or add something else for the PhD thesis. Another point is, sometimes something totally unexpected comes out. This has happened a lot through the history of chemistry. For example, the carbenes and the carbynes were found by accident by Ernst Otto Fischer's co-workers. He wanted something else, and he got these compounds, but these were interesting findings, so he asked his co-workers to continue in this direction and did not switch back to the original goal. This is also part of the art, to give a certain freedom and to judge which of the unexpected things might be interesting.

PSR: This brings us to another topic, connecting basic research with industry. You've mentioned both energy and pharmaceuticals. Do you always have in the back of your mind the question of how your research will influence or enable industrial processes?

FEK: These of course are very different aims. Energy has to be cheap, pharmaceuticals not necessarily. It depends on what you gain with them, and they can be comparatively expensive. So you can use rather exotic techniques and chemicals for pharmaceuticals as long as they do a very specific job.

But for energy, you need cheap methods, you have to utilize broadly available things, otherwise it will be unaffordable for most of the human beings on earth. So you have to go a bit in different directions. But if a discovery turns out to be useless for one purpose, it may be useful for the other. And in research, when we know almost nothing, we have to learn on a very basic level to see in which direction it might develop and for what it might be useful.

MM: You want to have that link with potential applications, but also, understanding the reactions that we do is really helpful for everybody in the field. If you can understand what we do, if we can explain something, then it may help someone else in a different area or further down the line understand what's going on in similar processes. It's important that we collaborate with people, and actually understanding the reaction is just as important as making the molecules themselves. That really helps other people as well as us.

JR: Basically it is the same for me. I see my research as fundamental research, and I know that in the three years I have, it's almost impossible for me to go from zero to some useful applications in the pharmaceutical industry. I see my research as a small step toward this big goal.

PSR: One last question for all of you: Are there advantages to doing this collaboration within framework of the TUM-IAS that might not have been available to you otherwise?

FEK: It's not bureaucratic.

PLA: It's given us space to explore, and to think deeply, then talk to someone who's thinking deeply about exactly the same thing – which is rare.

JR: I'm very grateful that I was able to go to Edinburgh. I learned so much there and brought a couple of techniques back to TUM. Also, I think it's really great that we can work on the fundamental chemistry without much pressure put on us to get such high output, because fundamental research is high-risk. You need a little bit more space to do things creatively. It needs time.



Max McMullon

MM: I'd say the same thing. Being able to do fundamental research is kind of refreshing. You don't get that so often these days. Also, as chemists we're quite separated into our areas, and chemists in different fields don't necessarily get to work together a lot. But in this kind of relationship you can. You can collaborate much more easily and talk about things in a way you don't get to very often.

FEK: The TUM-IAS Focus Group is a starting point. I learned a lot about rare earth chemistry during this time and there is still a lot for me to learn, because I'm usually dealing with "ordinary" transition metals and not so much with the lanthanides and the actinides. After a while we can better see what we can do with these metals, what we can do with the ligands, in which direction we want to go, and we will publish some papers. And based on this we can apply for further funding and increase the size of the group.

PSR: So would you describe it as a chance to make a constructive disruption in the normal course of your work?

PLA: Yes.

FEK: You also have these meetings here with people from other fields, which I think otherwise is much more difficult to achieve. And then maybe through the exchange of ideas you can see, for example in medicine, materials science, or whatever, possible applications you have not been aware of before.

PLA: One of the things that's come out is lots of extra little collaborations around us. Friends and colleagues of both of our groups have begun to work together, and are submitting papers. I've been talking a lot about my TUM interactions back home, and since Edinburgh and Munich are twin cities, I've actually generated a lot of interest locally. Not just Edinburgh, but also Heriot-Watt and LMU are beginning to talk as a set of universities about doing something collaboratively. With the prospect of Horizon 2020 funding, I think this might actually be a very interesting springboard, to put us in a position to lead the way, because we have such connections.