Communicating Research to the General Public

At the March 5, 2010 UW-Madison Chemistry Department Colloquium, Prof. Bassam Z. Shakhashiri, the director of the Wisconsin Initiative for Science Literacy (WISL), encouraged all UW-Madison chemistry Ph.D. candidates to include a chapter in their Ph.D. thesis communicating their research to non-specialists. The goal is to explain the candidate's scholarly research and its significance to a wider audience that includes family members, friends, civic groups, newspaper reporters, program officers at appropriate funding agencies, state legislators, and members of the U.S. Congress.

Over 20 Ph.D. degree recipients have successfully completed their theses and included such a chapter.

WISL encourages the inclusion of such chapters in all Ph.D. theses everywhere through the cooperation of Ph.D. candidates and their mentors. WISL is now offering additional awards of $250 for UW-Madison chemistry Ph.D. candidates.

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The dual mission of the Wisconsin Initiative for Science Literacy is to promote literacy in science, mathematics and technology among the general public and to attract future generations to careers in research, teaching and public service.

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New Strategies for Catalytic Stereocontrol in Photochemical Synthesis

By

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Chapter 1. Wisconsin Initiative for Science Literacy:

How to Control the 3D Structure of Molecules

1.1 Introduction

My Ph.D. thesis is entitled: "New Strategies for Catalytic Stereocontrol in Photochemical Synthesis." Most of the time when I tell this to friends or family members, I get the following response:

New Strategies — "Okay, got it! So good so far."

for Catalytic Stereocontrol — "Uhhhh. I don't really understand what those words mean."

in Photochemical Synthesis — "I'm not sure…doesn't that have something to do with how plants grow?"

The purpose of this chapter is to break down that title into something more digestible, something more comprehensible, and something that ultimately explains what I've done in grad school, and why. In this section, I hope to answer the following three questions:

1. What do all of those words mean in your thesis title?
2. Putting that all together, what do you do? What is your Ph.D. work?
3. Okay, but what do you actually *do*? What does a typical day look like for a graduate researcher in organic chemistry?

I'll do my best to focus on only the key ideas you'll need to understand my work, and not to introduce unnecessary technical jargon. Endnotes direct the reader to further elaboration on some of these concepts. However, I can't avoid every bit of terminology, so we're going to start by unpacking some of the words from my thesis title, and getting a little context for what organic chemists do.

1.2 What is an Organic Molecule?

The words "organic chemistry" have a lot of baggage. For some, the phrase conjures up nightmares from college, and of a relentlessly difficult course that stood between them and medical school. For others, it has more to do with nature, and making sure their vegetables were grown without pesticides. But we're

going to approach the phrase from a chemistry perspective. What is "organic?" And what is an organic molecule?

Let's start with the periodic table: That chart hanging in chemistry classrooms across the country, and, if you're like me, adorning mugs, shower curtains, bookmarks, and anything else that well-intentioned family members could get their hands on. The periodic table lists all the known kinds of atoms in the universe, and these are the fundamental building blocks of nature. When atoms are combined with other atoms, **we call that a molecule**. Now there's no limit on what "counts" as a molecule. They can be as small as two or three atoms, such as the oxygen we breathe (O_2) or the water we drink (H_2O). They can also go all the way up to millions or billions of atoms in size, such as the DNA that makes you, *you*.

Despite having that entire periodic table to play around with, nature only uses a fraction of these elements in most important molecules like proteins or DNA. Carbon in particular, along with hydrogen, nitrogen, and oxygen make up an overwhelming percentage of these structures, with some other atoms sprinkled in occasionally. This domain is called **organic chemistry: the study of carbon-containing molecules**. Notice that this doesn't specify anything about how the molecule was made, or where it came from. Nor does it tell you if it's healthy, or toxic, or purple, or foul-smelling, or flammable, or expensive. In chemistry, "organic" just means that the molecule contains carbon; it doesn't say anything else about its structure or properties. So, your 100% cotton T-shirt is just as "organic" as something made from nylon, polyester, and spandex. The plastic bag you get at the grocery store is just as "organic" as a reusable canvas one. The protein in your ethically-sourced, farm-raised, pesticide-free food is just as "organic" as the pesticide itself. That's not to say that these distinctions aren't important — clearly they are — but rather to clarify that "organic" means something different in chemistry than it does in everyday life.

Organic chemists are interested in what these various molecules look like, what they do, and how they behave. The physicist Richard Feynman famously wrote:[1] "What I cannot create, I do not understand," and this mentality holds true for organic chemistry as well. We can speculate endlessly about how a particular drug might work in the body, or how a new plastic could be super strong yet biodegradable, but at the end of the day, we can't answer those questions until we have actually *made* the molecules in question.

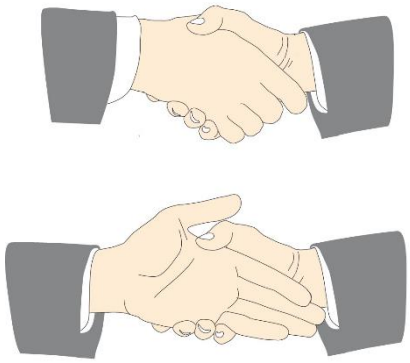
Sometimes we can get the molecules we're interested in from nature, but this is not always practical or sustainable. As an example, take the anti-cancer drug Taxol (paclitaxel), which can be isolated from the bark of the Pacific yew tree. However, almost an entire tree's worth of bark is necessary to obtain enough Taxol to dose a single patient.[2] Clearly, isolation from the natural source is not a realistic solution; we need a way to make Taxol ourselves. In other situations, we may want to deliberately make an *unnatural* molecule, perhaps with new or unexplored properties. In both cases, we want the ability to make our own molecules in a controlled laboratory setting. This brings us to **organic synthesis**, which as it sounds, means the formation of organic molecules.

Since the mid-19th century, organic chemists have worked on how to make new molecules, make old molecules but more efficiently, or just generally improve our control over chemical processes. For example, in a reaction where some molecule **A** is converted to some other molecule **B**, we would prefer to make *only* **B**, and not also **C**, **D**, **E**, etc. A great deal of progress over the last 150 years has been focused on these problems, and we now have many methods and procedures for highly controllable organic synthesis. However, one area that is still relatively underdeveloped is our ability to dictate the 3D structure of molecules, and that's where we'll head next.

1.3 Stereochemistry: Molecules in 3D

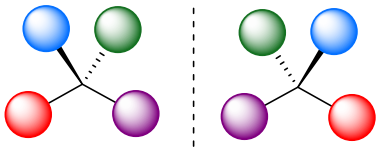
"Hi there, nice to meet you, I'm Kaz." Imagine that I'm reaching out, and you shake my hand. That's great, everything worked perfectly, and we can go about our business. Now imagine it again: "Hi there, nice to meet you, I'm Kaz" but this time I'm holding out my left hand instead of my right. That wouldn't work very well. We'd awkwardly bump into each other, trying in vain to grasp each other (Figure 1-1). Why is this? Well obviously it has something to do with our left and right hands not being the same. More specifically, this occurs because our hands are mirror images that cannot be superimposed on top of each other.

Figure 1-1. A matched and mismatched handshake (adapted from ref. 3)



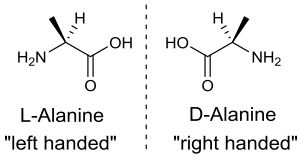
It turns out that many organic molecules have the same property. The technical term for this so-called "handedness" is **chirality** (pronounced "kai-**ral**-ity"), which actually originates from the Greek word for hand, *chiros*. Just like your hands, chiral molecules have mirror images that are non-superimposable.[4] Figure 1-2 shows a schematic example with four colored balls attached to a central point.[5] The red and purple spheres are sitting on the page, while the solid wedge indicates the group is coming out of the page at us, and the dashed wedge signifies that the group is going behind the page away from us. Although these two molecules are mirror images, there is no way to move them around in space that will allow you to stack them on top of one another. No matter which two colors you try to line up, the other two will not match.

Figure 1-2. Mirror image molecules that cannot be superimposed



Now, let's move to an actual molecule: the amino acid **alanine** (Figure 1-3). Once again, you can see that L-alanine and D-alanine are mirror images, but if you imagine picking one up and trying to place it on top of the other, they would not match up.[5]

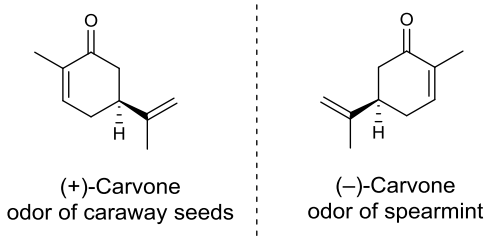
Figure 1-3. Left and right hands of the amino acid alanine



In a more general sense, **stereochemistry** is the subfield of organic chemistry that focuses on the **spatial arrangement of atoms in molecules**. This is perhaps a misleading name, as it has nothing to do with sound. Instead, **stereochemistry is really the study of molecules in 3D**. Chirality and chiral molecules are just one of the many subfields that fall into the broad area of organic stereochemistry.[6]

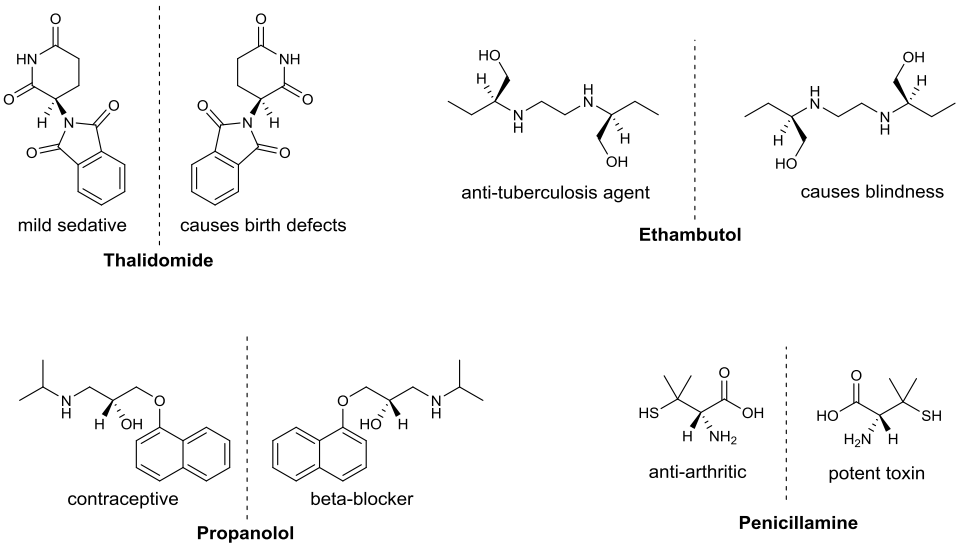
Okay, so chirality is certainly an interesting phenomenon, but why is it important? Well, just like trying to shake someone's right hand with your left, or trying to put your right hand into a left-handed glove, when chiral molecules encounter *other* chiral molecules, there can be profound effects. For example, consider the molecule carvone, shown in Figure 1-4. The left-handed version of this smells like caraway seeds or rye bread, but the right-handed version gives the smell of spearmint. How is this possible? The scent receptors in your nose are also chiral, but exist exclusively in the left-handed form. As a result, their interaction with left-handed molecules is fundamentally different than with right-handed molecules (just like Figure 1-1).

Figure 1-4. The left- and right-handed forms of carvone



This can have dire consequences, especially in the context of pharmaceuticals, where one hand may have the desired effect, but the other may be inactive or even toxic. Figure 1-5 shows a series of drugs whose left and right hands have dramatically different properties. Hopefully this illustrates the importance of being able to obtain chiral organic molecules as a single hand only!

Figure 1-5. Examples of pharmaceuticals with drastically different left- and right-handed effects



Unfortunately, most chemical processes that produce chiral molecules do so with no selectivity, giving a perfectly 50/50 mixture of left- and right-handed products. To make matters worse, because they are mirror images, these two molecules cannot be separated using typical purification techniques. And even if they could, that means that 50% of your material is going to waste, since it's not the version that you want.

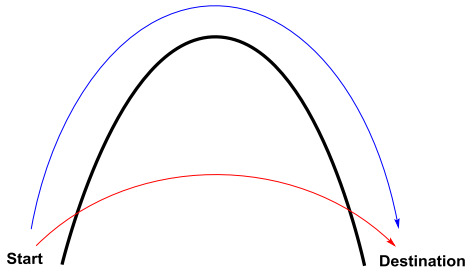
This brings us back to the concept of **organic synthesis**. What we really want is a way to synthesize a chiral molecule where we are able to *control* which hand we make, and select for only left, or only right. Putting these two ideas together, if we want to control the 3D structure of molecules, we call that **stereocontrol**, which is one of the key words in my thesis title. So good so far! Well, only sort of good, actually. Because I've only told you *what* we want to do, but not at all *how* we're going to do it. So keep that objective in the back of your mind as we move into the next section.

1.4 Catalysis

I mentioned earlier that organic chemists have spent the last 150 years coming up with new and improved ways to carry out reactions. One of the most important developments in this area is the concept of **catalysis**. Broadly speaking, a catalyst is something that **increases the rate of a reaction, but is not**

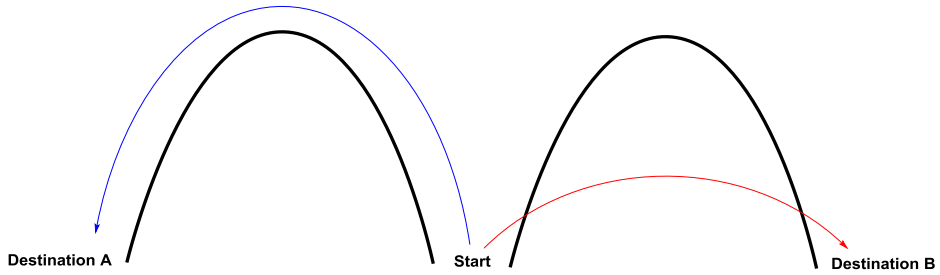
consumed in the process. Catalysts are able to do this by changing the mechanism of the reaction in order to make certain steps easier, and thus proceed faster. As an analogy, imagine that we want to travel to a neighboring town, but there is a mountain in the way (Figure 1-6). A catalyst is like a drill that bores right through the side of the mountain, allowing us to go straight to our destination (red path) instead of all the way up and over the top of the mountain (blue path). Another important feature is that a catalyst is not destroyed in the process, meaning it can be reused. In this analogy, that means that the drill actually is more like a shuttle, returning to the starting point to pick up more passengers for another trip.[7]

Figure 1-6. Normal and catalyzed pathways from a starting point to a destination



Not only can catalysts speed up the *overall* rate of a reaction, but they can also be designed to selectively accelerate one specific process. So let's say we're just trying to leave town in *any* direction, but we have mountains of equal height on all sides. Without a catalyst, we're just going to randomly choose a mountain, and eventually we'll climb over it. But if we design a catalyst that only cuts through one of the mountains, that's the pathway we're going to take (Figure 1-7).

Figure 1-7. Selective route to Destination B using a catalyst

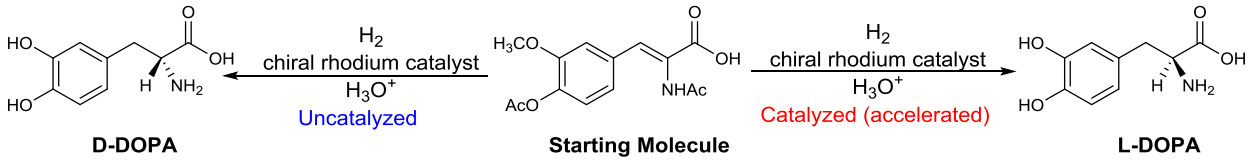


Putting this back in terms of chemistry, remember that hypothetical reaction where molecule **A** goes to an unselective mixture of **B**, **C**, **D**, **E**, etc.? A catalyst could speed up the formation of **B**, while at

the same time not affecting (or even slowing down) all those other side products we don't want. The result would be a highly selective reaction that forms only **B**. Now if the catalyst itself is chiral, it can selectively accelerate the pathway leading to *one hand* of a given product, without affecting the route that forms the other hand. In other words, instead of Destination A and B above, Figure 1-7 could just as easily be showing the preferential formation of a right-handed molecule over a left-handed one (or vice versa).

Okay, so how does this all connect? Instead of mountains or vague molecules, let's consider the reaction shown below in Scheme 1-1, which converts a **Starting Molecule** into either **D-DOPA** or **L-DOPA**. They're drawn a little differently from the structures we've seen before in Figure 1-2 through 1-5, but these two products are non-superimposable mirror images of each other — in other words, left and right hands.[4] In terms of biological activity, L-DOPA is an important drug for the treatment of Parkinson's disease. If you've read the book or seen the movie *Awakenings*, this is the molecule that inspired that story. D-DOPA, on the other hand, is biologically inactive, and has no effect on Parkinson's patients.

Scheme 1-1. Selective formation of L-DOPA using a chiral rhodium catalyst[8]



Using a chiral catalyst that incorporates the transition metal rhodium, we can selectively accelerate the process leading to L-DOPA, which will result in only that hand being generated during the reaction.[8] Thus, we can achieve **catalytic stereocontrol** and form a single hand exclusively. This avoids a difficult-to-separate (and wasteful) 50/50 mixture of desired and undesired product. Even better, because it's not destroyed during the process, a single molecule of catalyst can be reused to form many molecules of the product. The importance of this strategy cannot be overstated, and in fact William Knowles won the 2001 Nobel prize in part for his work on this reaction.[3]

1.5 Photochemistry

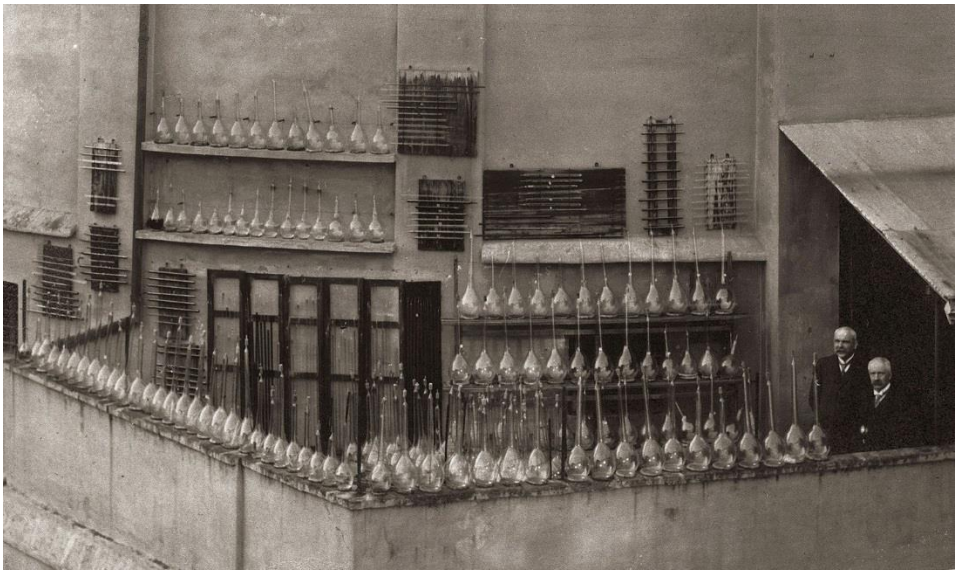
Over the last several decades, there has been a tremendous amount of research aimed at harnessing solar power, and this technology is actually starting to become economically viable. The sun emits so much energy that the amount absorbed by the earth in one hour is enough to supply the worldwide electricity demand for more than a year.[9] You're probably already familiar with the idea of converting solar energy into electricity that can be used to power homes, offices, and factories. My research focuses on a related goal: instead of having light power our appliances, have it power our chemical reactions.

In a broad sense, **photochemistry is the study of how molecules interact with light.** It's not a coincidence that the word sounds similar to "photography" as both originate from the Greek word for light: *photos*. One of the main reasons that photochemistry is so interesting is that it can form new and unusual molecules, many of which are difficult or even impossible to access using other methods. A classic example is a cyclobutane, a type of organic molecule that contains four carbon atoms linked together in ring to make a square. Cyclobutanes are found in many natural products with interesting and useful biological properties, so it would be valuable for us to be able to make them ourselves. Although we can synthesize these compounds using non-photochemical reactions, these approaches tend to be very inefficient and require numerous steps to reach the desired product. In contrast, photochemical reactions allow chemists to form cyclobutanes easily and efficiently in a single step from inexpensive starting materials. So, if the interaction between molecules and light is called **photochemistry**, and we're using it to perform **organic synthesis**, then it should be clear that this topic is called **photochemical synthesis**,[10] which is the last part of my thesis title!

Even though it might seem like harnessing solar energy is a recent development, photochemical synthesis has been studied for more than 100 years. Pioneering work by Dr. Giacomo Ciamician around the turn of the 20th century established the fundamentals of what we understand today about how light can drive chemical reactions.[11] Figure 1-8 shows a picture of Ciamician on the rooftop of his laboratory, and all

around him you can see flasks filled with different chemicals. He was exploring the effects of shining light on various molecules, and actually discovered several new reactions in the process.

Figure 1-8. Giacomo Ciamician and assistant Paolo Silber on the rooftop of his laboratory[12]



At this point, you might be wondering what any of this has to do with stereochemistry, and with chiral molecules. After all, I made such a big point of it in the earlier sections of this chapter. Well it turns out that photochemical reactions are notoriously difficult to control, especially in terms of the 3D arrangement of their products. There has been considerable progress over the last 50 years in the areas of stereochemistry (Ch. 1.3) and catalysis (Ch. 1.4), but applying these concepts to photochemical synthesis has proven extremely challenging.

1.6 What do I do?

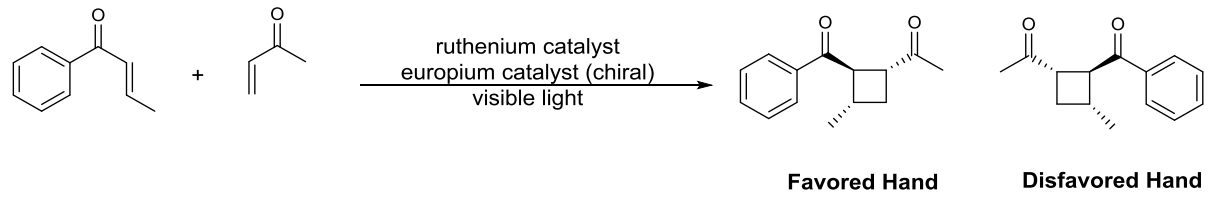
Now armed with some background information and a few new vocabulary words, we should be better equipped to tackle that thesis title: **New Strategies for Catalytic Stereocontrol in Photochemical Synthesis.** Okay, so I'm performing photochemical synthesis, meaning that I'm carrying out chemical reactions and making new molecules, and light is powering that process. I'm also controlling the stereochemistry — the 3D structure — of the molecules I make. When there's a chance to make either a

left- or right-handed product, I want the ability to dictate which one is formed. And the way that I'm doing that by using a catalyst. This is some additional molecule that goes into the reaction and selectively cuts through the mountain leading to the hand I want. So, the one sentence version is: **I use light to power chemical reactions while also trying to control the 3D structure of the products with a reusable molecule.**

I've mentioned before that controlling the **stereochemistry** of organic molecules is an important goal, especially in the context of making pharmaceutical drugs in only left- or only right-handed forms. This is a pretty challenging task to do in the first place (hence the 2001 Nobel prize), but it's *especially* difficult for photochemical reactions. Even though chemists have been tackling this problem for more than 100 years, there are relatively few solutions. As my thesis title suggests, I've worked on a couple different approaches, which I'll briefly outline below:

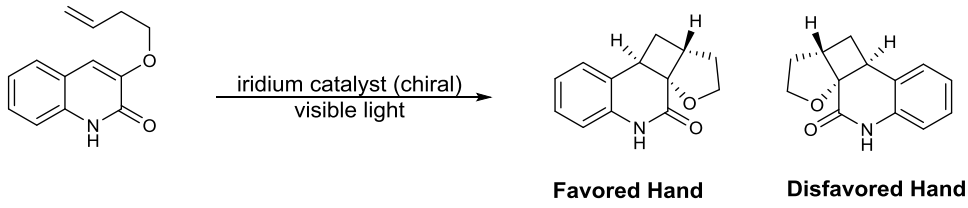
- **Chapter 2** is a review of what other scientists have accomplished, focusing in particular on photochemistry using chiral catalysts built from transition metals.
- **Chapter 3** describes my work on a particular type of photochemical reaction, called a cycloaddition (Scheme 1-2). In particular, this reaction forms a cyclobutane (a ring of four carbon atoms in a square) which I mentioned earlier is very challenging to make by non-photochemical methods. To accomplish this transformation, I actually used two catalysts. The first of these is a bright orange molecule incorporating ruthenium. When you shine light on this molecule, it becomes able to donate an electron. The second catalyst is chiral, and uses the metal europium. It interacts with the organic molecule we want to perform the reaction on, and makes it more willing to accept that electron that the ruthenium catalyst wants to donate. This second catalyst also controls the stereochemistry of the products, much like Knowles' rhodium catalyst did in the synthesis of L-DOPA.

Scheme 1-2. Cycloaddition reaction studied in Chapters 3 and 4



- **Chapter 4** focuses on many of the catalyst variants that I made and tested, as well as my attempts to understand *why* and *how* the catalyst favors one hand over the other.
- **Chapter 5** discusses another cycloaddition reaction, but this one involves a different type of organic molecule, and the reaction doesn't work quite the same way (Scheme 1-3). For this project, I used a chiral iridium catalyst that absorbs visible light, and then transfers that energy to the organic starting material to transform it into the product. Again, the fact that this catalyst is chiral means that it's able to control the stereochemistry of the product.

Scheme 1-3. A different cycloaddition, discussed in Chapters 5 and 6



- **Chapter 6** covers some of the experiments aimed at understanding the mechanism of this reaction, and testing a really crazy idea where the light itself is left- or right-handed.

1.7 No, but really, what do I *do*?

This is all fine from a 20,000 foot view, but I still haven't really explained what I do on a day to day basis. What does life look like for a graduate student in an organic chemistry research group? Well, most of my work involves either setting up reactions, purifying reactions, or analyzing reactions. So I do a lot of reactions!

The setup part is probably pretty close to how you imagine it. I weigh out different amounts of chemicals and mix them together in a flask. Sometimes they need to be heated to a boil; other times I have to cool them down to liquid nitrogen temperatures (–196 °C/–320 °F, very cold!). As noted earlier, many of these reactions are photochemical, meaning that I need to shine light on them. Although it would be ideal to simply run these outside in the sunlight,[13] it's a lot more practical, consistent, and reproducible for us to use household lightbulbs. The reactions I do take anywhere from seconds to hours to complete, and often require that I leave them to stir overnight. We often joke that in chemistry research papers, "overnight" is a common measurement of time, meaning that the grad student went home for the day.

On paper, reactions are clean and beautiful, turning **A** into **B** with perfect efficiency and no mess. But in reality, all sorts of things can go wrong. Undesired side products can form. Strong acids and bases can be generated. Products can keep reacting until they decompose. Thus, an important step at the end of a reaction is **purification**, during which I separate the desired compound from everything else that may be in the flask. There are many different purification techniques, and which one I use depends on the specific situation and the molecules I'm trying to separate. But for the most part, I turn to one of four main strategies.

The first of these is **extraction**, which relies on an everyday piece of information you already know: oil and water don't mix. Just like washing a greasy frying pan or picking up an unshaken bottle of salad dressing, water does not mix with organic solvents (oil and grease are examples of organic solvents). We can use this to our advantage, finding conditions that dissolve the desired molecule in either the organic (oil) layer or the water layer, leaving behind everything else we don't want in the other layer. We then separate the layers to save only the molecule we want.

Figure 1-9. Separation of salad dressing[14] and separation during an extraction[15]

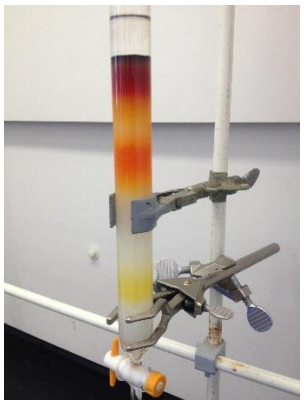
Another common technique is **distillation**, which separates different compounds based on their boiling points. You've probably heard of this technique before as well, whether you realize it or not. On small scales, distillation is common for the purification of liquors (perhaps you've seen something touted as "triple distilled"), and on large scale, distillation is used for the processing of crude oil (that's what those giant stacks are in an oil refinery).

The third technique is called **recrystallization**, and the basic idea should be familiar to anyone who's lived somewhere with unsoftened water. When you have hard water, it just means that there are a bunch of mineral salts (mostly calcium and magnesium) dissolved in the water. If you fill up a glass with hard water, you can't tell that it's anything *except* water. But if you let it evaporate over a couple days, you'll notice that telltale white residue starting to form on the sides, which is the mineral salts beginning to crystallize. For a chemical reaction I want to purify, I try to find conditions where all the molecules in a mixture dissolve, but then as I cool it, or let it start to evaporate, only the desired molecule crystallizes. I can then pour off or wash away all the other undesired compounds.

Another purification strategy I often use is **column chromatography**. In this technique, the mixture of desired and undesired compounds is pushed through a narrow tube filled with a form of sand that has extremely fine grains. As an analogy, imagine a bunch of children all going down a slide at the same time. Based on the clothes they're wearing and how they like to sit, some kids will slowly creep down the slide, while others will come flying off in seconds. The same is true of molecules (well, not the wearing clothes

part). Depending on their properties, some molecules will come out of the tube almost immediately, while others will take minutes or hours to reach the bottom. Figure 1-10 shows an example, where at least three different compounds (one yellow, one orange, and one red) are moving down the column at different rates. This technique is very powerful, and can effectively convert a messy mixture into a series of separate, clean compounds.

Figure 1-10. Example of column chromatography[16]



The last part of my job involves analysis. After running and purifying a reaction, how do I know what happened? How do I know whether it worked or not, or if I did something other than what I was expecting? As with purification, there are many different techniques that I use depending on context, but by far the most common, and most powerful for my type of chemistry is **NMR spectroscopy.** NMR stands for nuclear magnetic resonance, and if that reminds you of magnetic resonance imaging (MRI), that's no coincidence.[17] Both techniques work on the same basic principles. In fact, the easiest way to think about NMR spectroscopy is that I'm essentially giving my molecules an MRI scan to figure out what's going on with them. In particular, this tells me about their structure and how the atoms are connected together. The main thing that NMR spectroscopy *can't* tell me, however, is whether I have a left- or right-handed molecule; they look identical using this technique.

Given how much I've talked in this chapter about the significance of stereochemistry and handedness, it should come as no surprise that figuring this out is an important part of my research. So, how do we actually determine if a reaction was selective or not? Or how selective? It's certainly possible to have

a reaction that *favors* one hand, but maybe it only favors it 70% of the time, not 100% of the time. The most common technique I use is a modified version of **column chromatography**, which was mentioned earlier. I use a chiral form of the sand-like material that the molecules pass through, and as expected, one hand interacts more strongly than the other. If we go back to our "children on a slide" analogy, this is as if the entire slide is lined with outstretched right hands, waiting for a handshake. If a kid has their right hand out, they're going to get slowed down by having to shake all these hands, and it will take them a long time to get to the bottom of the slide. If instead they have their right hand in their pocket and their left hand out, they won't be able to shake hands very effectively, so they'll just pass right on by and reach the bottom of the slide quickly. In reality, these techniques are carried out under extremely high pressures, so a more fitting (if gruesome) analogy is that the kids are being pushed down the slide at 100 miles per hour, and holding onto those handshakes for dear life.

1.8 Conclusion

Hopefully you now have a better sense of what I've been doing during my Ph.D. To reiterate, I work in the broad area of organic synthesis, which means making molecules that contain carbon. In particular, I focus on controlling the 3D shape of these molecules using a variety of catalysts that selectively accelerate one process over another. The specific type of reactions I perform harness the energy from light to power chemical processes.

1.9 References and Notes

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[1] "Richard Feynman's blackboard at the time of his death." ID 1.10-29. CalTech Library Archives. http://archives.caltech.edu/pictures/1.10-29.jpg. Accessed 2017-05-02.

[2] Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis.* Wiley-VCH: Weinheim, 1996.

[3] "The Nobel Prize in Chemistry 2001 — Popular Information." Nobelprize.org. https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2001/popular.html. Accessed 2017-05-27.

[4] Technically, non-superimposable mirror image molecules are called enantiomers. Depending on the molecule, there can also be *other* forms that are chiral, but not mirror images. These are called diastereomers.

[5] Throughout this chapter, I will be using "skeletal" shorthand, in which molecules are depicted as a simple series of lines. You don't need to know exactly how to read these structures in order to understand what I'm saying, though. For example, it should still be straightforward to see that two molecules are mirror images of each other, even if you don't know how to interpret the drawing. If you're curious, any place where two lines meet signifies a carbon atom, and hydrogens are generally implied to make sure that every carbon forms four bonds. All other atoms (e.g., nitrogen, oxygen, sulfur) are shown explicitly.

[6] More rigorously, IUPAC defines stereochemistry as the study of molecules "that possess identical constitution, but which differ in the arrangement of their atoms in space." This does not technically require the molecule to be three dimensional. In fact, there are numerous molecules called alkenes that have two different stereochemical forms despite being flat.

[7] This shuttle analogy comes from a previous graduate student in my research group, and is further explained in her thesis. See: Ruiz Espelt, L. Controlling the Chemistry of Photogenerated Radicals with Lewis and Brønsted Acid Co-Catalysts. Ph.D. Thesis, University of Wisconsin–Madison, Madison, WI, 2014.

[8] As a clarification on Scheme 1-1, the chiral rhodium catalyst is still *present* in both cases, whether the reaction goes to the left to form D-DOPA, or to the right to form L-DOPA. It's just that the catalyst only accelerates the latter pathway.

[9] Based on data from 2014. See: "International Energy Statistics." U.S. Energy Information Administration. https://www.eia.gov/beta/international/data/browser/#/?pa=0000002&tl_id=2-A&vo=0&v=H&start=1980&end=2014. Accessed 2017-06-06.

[10] Not to be confused with *photosynthesis*, which is the process by which plants use light to convert carbon dioxide and water into sugars and oxygen. Technically speaking, photosynthesis is one particular type of photochemical synthesis.

[11] For a great (and non-technical) summary of Prof. Ciamician's work, see: Nebbia, G.; Kauffman, G. B. Prophet of Solar Energy: A Retrospective View of Giacomo Luigi Ciamician (1857–1922), the Founder of Green Chemistry, on the 150th Anniversary of His Birth. *Chem. Educator* **2007**, *12*, 362–369.

[12] Collezione di Chimica "Giacomo Ciamician." Sistema Museale Di Ateno, Universita di Bologna. http://www.sma.unibo.it/il-sistema-museale/collezione-di-chimica-giacomo-ciamician/gallery/giacomo-ciamician-e-paolo-silber-1915-1920/@@images/11a6a52f-631f-4b19-b758-56d3b110816a.jpeg. Accessed 2017-06-06.

[13] Our research group has actually demonstrated that ambient sunlight can be used for some of these reactions. For example, see: Du, J.; Yoon, T. P. Crossed Intermolecular [2+2] Cycloadditions of Acyclic Enones via Visible Light Photocatalysis. *J. Am. Chem. Soc.* **2009**, *131*, 14604–14605.

[14] "Wish-Bone Robusto Italian Dressing." Good Housekeeping. http://ghk.h-cdn.co/assets/cm/15/12/55090e076b952-newmans-own-family-recipe-italian-dressing-xl.jpg. Accessed 2017-06-07.

[15] Hegedüs, K. "Finally back to the lab and starting the work." Labphoto. http://labphoto.tumblr.com/image/128278583672. Accessed 2017-06-07.

[16] "Ferrocene Separation." http://imgur.com/a/CxJDs. Accessed 2017-06-07.

[17] In fact, the proper name for MRI really should be *nuclear* magnetic resonance imaging, but the "nuclear" part was removed because of its negative connotations. To clarify, the technique has to do with the spin of nuclei in atoms, and does not involve radioactivity of any kind.