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.

Wisconsin Initiative for Science Literacy

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.

UW-Madison Department of Chemistry
1101 University Avenue
Madison, WI 53706-1396
Contact: Prof. Bassam Z. Shakhashiri
bassam@chem.wisc.edu
www.scifun.org

May 2014

Controlling the Chemistry of Photogenerated Radicals with Lewis and Brønsted Acid Co-Catalysts

By

Laura Ruiz Espelt

A dissertation submitted in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

(Chemistry)

at the

UNIVERSITY OF WISCONSIN−MADISON

2014

Date of final oral examination: 08/06/2014

The dissertation is approved by the following members of the Final Oral Committee:

Tehshik Yoon, Professor, Chemistry

Clark Landis, Professor, Chemistry

Shannon Stahl, Professor, Chemistry

Jennifer Schomaker. Assistant Professor, Chemistry

Weiping Tang, Associate Professor, Pharmaceutical Sciences

Chapter 6. Wisconsin Initiative for Science Literacy: My PhD Work Beyond the Technical Jargon

My Ph.D. work has focused on the synthesis of enantiopure amines via the generation of alpha amino radicals. Making use of Ruthenium bipyridine complexes, I was able to employ visible light in this process, offering a greener alternative to the generation of these radicals. I know that sounds pretty complicated, so let's break this down and see if we can make any sense out of all that technical jargon.

What Do Organic Chemists Do?

Fundamentally, organic chemistry is the science of taking molecules apart and putting them back together in new and interesting ways. One of the most fascinating things about molecules is that any molecule can theoretically be combined with any other molecule, as long as the conditions are right. You can think of molecules like Legos, since Legos are designed so that any Lego piece can be connected to any other Lego piece.

However, just because all the pieces can fit together doesn't mean that you'll end up with anything useful. Imagine you had 1,000 Lego pieces scattered on the floor in front of you. If you put them together in one way, you might end up with a castle; arrange them another way, and you might get a spaceship. But there are plenty of ways to put 1,000 Legos together that wouldn't look like anything. You'd just end up with a giant blob. Molecules work the same way – some molecular arrangements are useful (like the combination of molecules that you and I are made of) and some don't do anything at all. What chemists try to do is connect molecules in such a way that we create something we can use, like a new drug or material. The building blocks are right

there in front of us, waiting to be used just like Legos scattered on the floor. We just have to find the right way to put them all together.

A great example of the power of chemistry is the science behind making new drugs. You may have heard that many of the drugs we use are based on compounds found in the natural world; aspirin, for example, is derived from a molecular compound that is naturally found in the bark of a willow tree. Did you know you can chew the bark of a willow tree and it will help cure a headache? Well you can. But chemists have figured out a way to recombine those molecules in a way that works better than what nature developed on its own. That's really what organic chemists do; we try to improve upon what nature has done by itself, or we try to find new combinations of molecules that nature never got around to making. That's how we've made everything that isn't natural – plastics, drugs, sugar substitutes, and the stretchy Spandex in your clothes that make you look sexier than medieval people did. All of those products are the result of chemists putting molecules together in new and interesting ways.

So How Do You Make New Combinations of Molecules?

Really the only way to make new molecular combinations is to break the bonds between existing molecular chains so that they can recombine with new partners. In order to do so, chemists have to apply energy to a group of molecules in order to force them apart, in exactly the same way you have to apply energy to a hammer in order to separate a nail from the board it's been driven into. Not only that, but we have to apply the *right amount* of energy. If we don't use enough energy, then nothing will happen, just like the nail won't come out of the board if you don't try hard enough. But if we use

too much energy, then sometimes we end up breaking more things than we wanted to, just like you might end up destroying the board if you tried to pull the nail out with a bulldozer.

There are several different ways to provide the perfect amount of energy necessary to break bonds in molecules. Sometimes we heat molecules to extremely high temperatures. Sometimes we put them under an enormous amount of pressure. Sometimes we introduce other chemicals that cause them to split apart. All of these approaches work, and there is a lot of chemistry devoted to using these methods. However, each of these approaches has its own problems. It takes a lot of energy to heat molecules to high temperatures or create high-pressure environments; and many of the chemicals that are currently used for breaking bonds are toxic or poisonous. In a perfect world, we'd be able to do chemistry without using huge amounts of energy or dangerous compounds.

That's why I've spent my Ph.D. career focusing on visible light photochemistry, which uses natural light as the energy source. Light is both abundant and free, making it the ideal energy source for chemistry. Plants use light as the energy source for photosynthesis, which is a natural form of organic chemistry – the sunlight allows molecules inside plants to recombine in new ways that provide energy and allow them to grow and reproduce. If we could use natural light as the energy source for all chemical reactions, we'd be able to do chemistry at almost no cost. Imagine a world where every drug, every plastic, and every gallon of gasoline could be made without having to spend a dime on the energy necessary to make those reactions happen.

The Problem With Visible Light As an Energy Source

Unfortunately, using natural light as an energy source isn't quite as easy as that. For one thing, light doesn't provide enough energy to break most chemical bonds. This is mostly a good thing, since otherwise you'd disintegrate every time you went to the beach. But if we want to use natural light as our energy source for chemical reactions, how are we supposed to do that if it doesn't provide enough energy to break molecules apart?

That's a good question. And the answer is that we use things called *catalysts* in order to make our reactions work.

What Is a Catalyst?

A catalyst is a something that reduces the amount of energy necessary to perform a transformation (that's the word chemists often use instead of 'chemical reaction'). They're basically chemical machines that allow us to do more work with less effort. Chemists are always looking for ways to do reactions with as little energy as possible, so catalysts are a fundamental part of how chemistry happens.

Picture the shuttle at an airport. Every day that shuttle carries thousands of people from one end of the airport to the other. Without the shuttle, you might still be able to walk from your car to the plane, but with the shuttle you can accomplish the same job with a lot less energy. That's how catalysts work. Without a catalyst, we might be able to do the same reactions, but we wouldn't be able to do them with visible light because light just doesn't provide enough energy.

There are some other nice things about catalysts as well. Catalysts can be re-used over and over again without interfering with the chemical reactions we're trying to study; in other words, a catalyst can perform the same task hundreds of times, just like an airport shuttle can make hundreds of trips every day without needing to be repaired or replaced. Also, catalysts can be used to provide energy to a lot of different kinds of reactions, just like airport shuttles can be used to transport all different kinds of people. So you can use catalysts to do a lot of work with a small amount of energy, you don't need very much material because you can re-use the catalyst over and over, and you can perform reactions that you might not be able to do otherwise. This is why catalysts are ideal helpers for chemical reactions.

There are hundreds of different catalysts that chemists use, but my research has focused on using ruthenium bipyridine as a catalyst because it happens to respond to natural light. Ruthenium bipyridine is a complex molecule that contains the metal ruthenium surrounded by a combination of carbon, hydrogen, nitrogen and oxygen atoms. Since ruthenium bipyridine is a bit of a mouthful to say, we usually shorten it to Ru(bpy), which is pronounced *ruby pea*.

But now you might be asking this: if Ru(bpy) responds to natural light, why doesn't it break apart like the molecules you're trying to study? Well, what I said earlier about chemistry being the science of breaking things apart and putting them back together in new ways is still true. But remember, molecules need the *right amount* of energy in order to break apart. Natural light doesn't provide Ru(bpy) with enough energy to break it apart. It does, however, provide just the right amount of energy to put

Ru(bpy) in an excited state, which in turn provides the energy necessary to break apart the molecules I'm trying to manipulate.

What Is an Excited State?

All molecules are made of atoms, and all atoms are made of a nucleus surrounded by electrons, which orbit the nucleus exactly like the planets in our solar system orbit the sun. Also like planets, electrons usually orbit in well-defined paths around the nucleus. These orbital paths are called *orbitals* (chemists are so inventive with their names, aren't they?), and most of the time electrons stay in the same orbital all the time.

However, when you irradiate a molecule with light you end up causing some of the electrons to jump into a higher orbital than where they started. (Imagine the Earth suddenly changing its orbit around the Sun to be in the same path that Mars is in, or Jupiter or Saturn.) Electrons always try to return to the same orbital they started in, and the only way they can do that is to release the extra energy they absorbed.

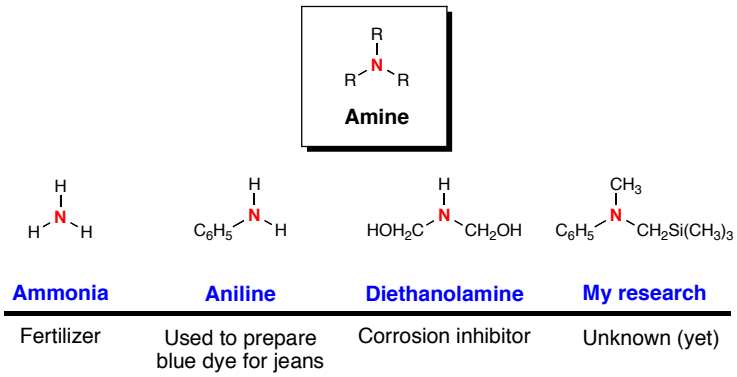
So here's how visible light photochemistry works. Because natural light doesn't provide enough energy to break apart molecules all by itself, we use Ru(bpy) as a catalyst. Natural light excites some of the electrons in Ru(bpy), and those excited electrons then release energy as they return to their normal orbital; and *that* energy is what I've been using to perform my chemical reactions. If it all sounds a little complicated, that's because it is. One of the most challenging (and fascinating)

elements of chemistry is figuring out how to get just the right amount of energy to go exactly where it needs to be, when it needs to be there.

My Research

My graduate research has focused on using photochemical processes to manipulate *amines*. Amines are a class of molecule that contains a nitrogen atom attached to three different R-groups. An R-group can be any kind of molecule you can imagine, although most R-groups usually contain carbon, hydrogen and oxygen. By using different R-groups, we can create completely different amines with completely different properties. For example, ammonia is a simple amine with three hydrogen atoms attached to a single nitrogen atom, and it is used as a fertilizer. If you change one or more of those hydrogens and replace it with something a bit more complicated, however, you can generate molecules that have all sorts of properties, from dyes to corrosion inhibitors. (See Figure 6-1.) You may also have heard of amino acids, which are the building blocks for every protein in our bodies – amino acids are another example of an amine. As you can see, amines pop up in a lot of places and can do a lot of different things, which is why studying them is so important.

Figure 6-1. Different types of amines

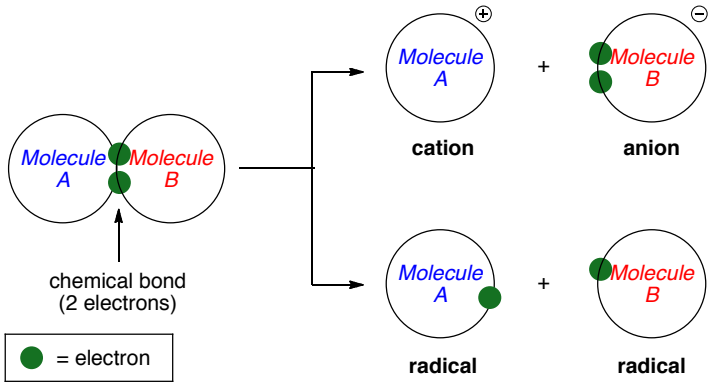


What I have found in my research is that we can use the Ru(bpy) catalyst in combination with visible light to modify the R-groups on the amines I've been studying. Since modification results in different properties, I have been able to create compounds that might turn into new drugs, fertilizers, plastics, and so on. Specifically, this R-group modification is happening because the Ru(bpy) catalyst is breaking bonds to generate radicals. These radicals can then react with other molecules to create new and interesting bonds.

What Is a Radical, and How Do You Generate Them?

We'll explain that by taking a quick step backward. The way molecules bond themselves to each other is by sharing electrons, and electrons like to be joined in pairs. When we break them apart, one of two things can happen. One of the molecules can take both electrons, leaving the other with none; or each molecule can take one electron. When this second scenario happens, we call each of the molecules *radicals* – or in other words, a molecule with one unpaired electron.

Figure 6-2. Breaking chemical bonds

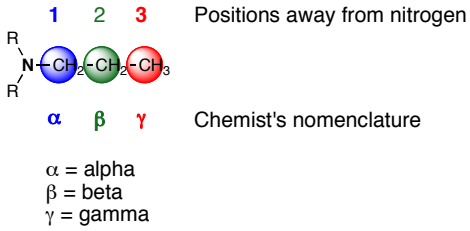


The reason they're called *radicals* is because these types of molecules like to do crazy and unpredictable things. Like I said, electrons like to be joined in pairs, which means radicals are constantly looking for another molecule to connect with, and they're happy to connect to whatever they can find. Luckily, chemists have managed to find ways to control these crazy creatures and come up with some very interesting types of reactions. For example, most of the plastics we use are made through a *radical polymerization* reaction in which one radical reacts with another (and then another and another and another) to create very long chains of molecules.

Since there are many different types of bonds that can be broken, and the radical can be located in many different types of molecules, chemists have to be able to distinguish one kind of radical from another. As you'll remember from the very beginning of this chapter, I've been working on the generation of *alpha amino radicals*. Let's take a moment to explain what that means.

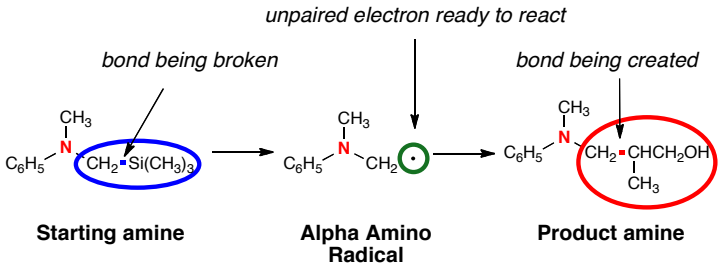
There are two things that matter when naming a radical. The first is to define what type of molecule we're working with. The word *amino* simply refers to the fact that the radical is located in an amine molecule. So far so good. The second question is, where exactly in that amine is this radical? Since all amines contain a nitrogen atom, we determine a radical's position by using nitrogen as our starting point and then counting outward, which you can see in Figure 6-3. Unfortunately for everyone who's not a chemist, we like to make things a bit more complicated than necessary, so we count with Greek letters. Thus the first position away from the nitrogen is the *alpha* position, the next one is the *beta* position, and so forth.

Figure 6-3. Amine nomenclature



So when I'm generating alpha amino radicals, I'm creating radicals in a very specific spot of the molecule I'm manipulating, and I'm doing so because this particular type of radical can react with new molecules and essentially change the entire R-group that is attached to the nitrogen. (You'll see an example of this in Figure 6-4.) Imagine the endless possibilities we have now to create new amines! And all of this just with the use of visible light and a little help from our Ru(bpy) catalyst.

Figure 6-4. Alpha amino radicals



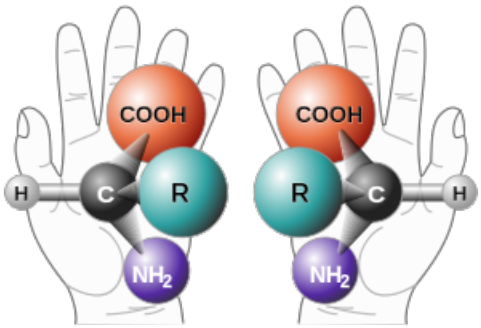
So, you now know how I've been using natural light to break bonds in order to generate alpha amino radicals and change the R-groups of my amines in new and interesting ways. But there's one other thing I've needed to pay careful attention to, and that is making sure the molecules I'm creating are enantiopure. As you'll see in just a

moment, when it comes to chemistry, enantiopurity can literally be a matter of life and death.

What Is Enantiopurity?

Enantiopurity is an interesting chemical property that is fairly easy to explain. It turns out that most molecules can come in two different shapes, even though their chemical structure is otherwise completely identical. When this happens, we say that a molecule is *chiral* (pronounced KYE-ral), which just means there are two possible versions of the same molecule. The best example of chirality is in your own two hands. Your hands are completely identical to each other in almost every way. However, you can't put one hand on top of the other and make the two match up. Do it and you'll see your thumbs sticking out in different directions. The only way you can make them match perfectly is to face one hand palm up and the other palm down – but even then they're not perfectly matched because they're not oriented in the same direction. So since your hands are identical but can't be superimposed one on top of the other, we call them *enantiomers*. They're built exactly the same, but they're shaped a little different. Chiral molecules also have two enantiomers, a "left hand" version and a "right hand" version. Look at Figure 6-5 below and you'll see two enantiomers of the same molecule.

Figure 6-5. Two enantiomers of a chiral molecule.



Sometimes, the fact that a molecule has two enantiomers isn't a problem; after all, you can do pretty much the same things with your right hand as you can with your left. However, particularly when it comes to drugs, the same molecule can behave in completely different ways depending on which enantiomer you're using. For example, Propranolol A was discovered in the 1960s and is still used in the treatment of heart disease; picture it as the "left hand" enantiomer. However, the "right hand" enantiomer, Propranolol B, is a contraceptive. Propranolol B has the exact same chemical composition as Propranolol A; the only thing that's different is the configuration of its atoms. Imagine the problems doctors would run into if they tried to treat someone for heart disease and accidentally gave them a contraceptive instead. Obviously, chemists need to pay attention not only to the composition of their molecular discoveries, but also the configuration of those discoveries as well.

When I do my reactions, one of the most important things I have to do is create molecular products that are *enantiopure* – in other words, I need to try to make only one

version of a chiral molecule. When my alpha amino radicals are generated, they will have two directions from which they can try to bond with a new molecule. With no external help to dictate what direction to take, these radicals will naturally end up forming a 50:50 mixture of both configurations. This is known as a *racemic* mixture. It's the same as if you wanted to hold hands with a friend. You will either grab their right hand or their left hand, depending on which direction you're coming from, and you have a 50% chance of picking either one. (See Figure 6-6)

Figure 6-6. Two equally probable options (racemic)

So under normal circumstances, radicals have a 50% chance of forming either the "right hand" or "left hand" enantiomer. However, I always want them to form a particular enantiomer, which means I have to introduce something to block one of these two possible pathways. The specifics of how I do that are a little too complicated to explain here, but basically I need to force the radical to approach the molecule from only one direction. It's a little like gluing a coffee cup to your right hand so that everyone you meet will be forced to hold your left hand all the time. By blocking one of the pathways that my alpha amino radicals would normally take, I can ensure that the bonds I'm forming will always have the same configuration, making my molecules *enantiopure.*

Figure 6-7. Only one option (enantiopure)

Conclusion

And that's what I've been doing for my Ph.D. research. Using natural light as our energy source and Ru(bpy) as the catalyst, I've been able to generate alpha amino radicals. These radicals have allowed me to modify the R-groups attached to my amines and generate new molecules in the process. Moreover, by using "blocking" groups, I have been able to make these new molecules enantiopure, which is very important in order to create organic molecules with useful properties. As with all scientific research, more work will need to be done in order to better understand these reactions and also to learn whether or not the compounds I've been able to generate can be of some use as a drug, agrochemical, or something else. But I'm very excited to have been a part of the research that will someday allow us to use natural light as a free and endless energy source to help us create the products of the future.