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Over 40 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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Kinetic and Mechanistic Studies of Rh(Bis(diazaphospholane))-Catalyzed

Asymmetric Hydroformylation

By

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Chapter 1

Introduction for a Lay Audience

1.1 Introduction

The overall goal of my Ph.D. was to *understand the selectivity in asymmetric rhodium-catalyzed hydroformylation*. Likely, very few of the words of this one sentence description made much sense—chemistry is absolutely like a foreign language. There are terminologies and phrases that become second nature to chemists, but we need to explain them in order to discuss our research with a lay audience. Therefore, the goal of this chapter is to break down the explanation of my Ph.D. goals so that the reader can walk away from this having a better idea of what I spent the last 4.5 years working on, obsessing over, and talking about non-stop.

1.2 What is "asymmetric?"

The first word that I want to expand is "asymmetric." Before explaining that, we need to discuss some physical characteristics of molecules—specifically that they can be left- or right-handed. Your hands are non-superimposable mirror images of one another. There is no way to orient your hands such that they both have the knuckles up and thumb pointing to the left. In the same manner, molecules can be right- or left-handed. An example of this (with balls instead of atoms) is shown in **Figure 1-1**, in the bottom is the way a chemist would depict this. We use a wedge to indicate that an atom is coming out of the plane of the page, and a dash means it is going backwards behind the page. As you can see, there is no way to rotate the molecule on the right to overlay with the molecule on the left.
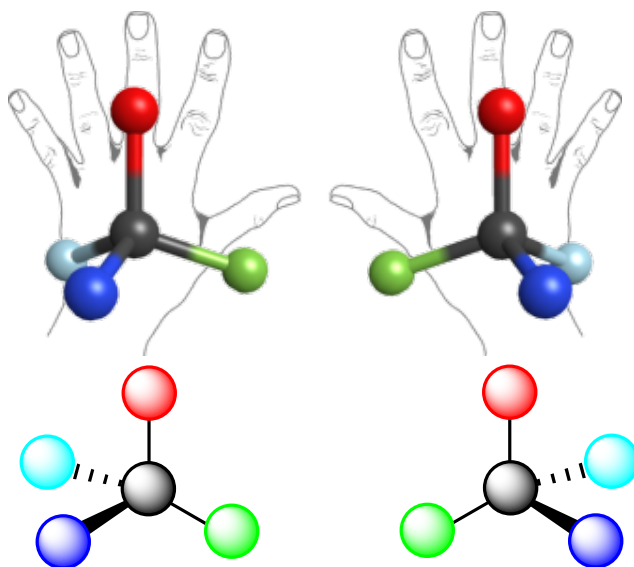
Figure 1-1. Example of left- and right-handed molecules (top) with a 2-dimensional depiction of the same molecules (bottom).

At this point, you might be asking yourself, "Why do I care if molecules are right- or left-handed?" The simplest answer is because our bodies react differently with the two hands. The amino acids in our bodies that make up proteins are handed.[1] This means that they will interact differently with molecules of opposite handedness. A classic example of this is the molecule carvone: the left-handed molecule smells like caraway; the right-handed molecule smells like spearmint (**Figure 1-2**).
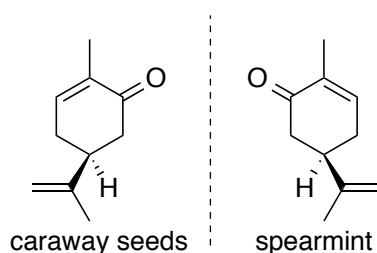

caraway seeds   spearmint

Figure 1-2. Left- and right-handed carvone smell different to humans.

Although different smells are interesting, a more important, and potentially dangerous, way handedness affects our bodies is when it comes to medicine. In many cases, the wrong hand

of a drug is ineffective, but harmless. For example, only the left-handed version of ibuprofen (Advil) treats pain, but the drug is sold as a 50:50 ratio of both hands. The way ibuprofen is made, it is obtained as a equal mixture of the two hands. Because separating them is not trivial, the companies keep each tablet as a mixture: if you are taking a 200 mg tablet, only 100 mg is actually helping your headache.

A far less innocuous example is the pharmaceutical thalidomide; it was prescribed from 1957–1961 for insomnia, tension, and morning sickness. The commercial drug was sold as a 50:50 mixture of the two hands. Scientists were unaware of the side effects until women started giving birth to babies with severe birth defects (usually deformed limbs). Since then, we have learned that it was the left-handed thalidomide molecule that caused these devastating effects (**Figure 1-3**), but the right-handed version was relatively benign.
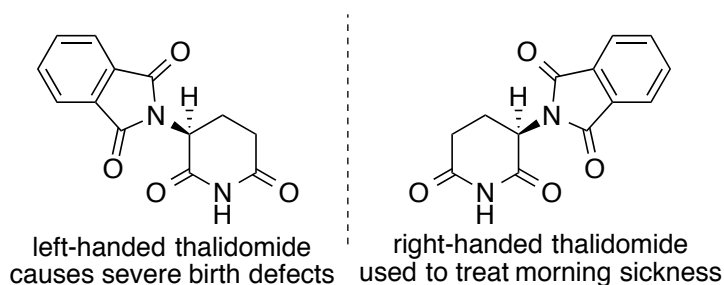

left-handed thalidomide
causes severe birth defects

right-handed thalidomide
used to treat morning sickness

Figure 1-3. Left- and right-handed thalidomide molecules have extremely different effects on the body.

In part due to examples such as thalidomide, there has been a push from pharmaceutical companies to sell drugs that are only one hand (instead of a 50:50 mixture of both). This brings us back to the original point of this chapter: asymmetry. If a reaction is asymmetric, it simply means that it forms one hand of the product preferentially over the other.

Asymmetric synthesis is challenging because under normal reaction conditions, we will always form a 50:50 mixture of the two hands. In order to make one hand in excess over the

other, we need something else in the reaction that *also* is handed. The easiest way to think about this is literally with hands. If you had a hook for hand, it wouldn't matter to you if you shook someone's left or right hand. If you are only going to use your right hand, you know that it will be much easier to only shake someone else's right hand. That's the same for synthesis. If you perform a non-asymmetric reaction, meaning you don't add anything handed to the reaction flask (a hook), you will obtain equal amounts of both left and right molecules. If instead, you add something right-handed, the reaction will preferentially make right-handed molecules.

In theory, if you did a non-asymmetric reaction (using a hook) to form equal amounts of both the left- and right-handed molecules, they could be separated and you could obtain just the one you want. If you think about this from the viewpoint of a pharmaceutical company, that means they are throwing away half of their reaction product every time. Because this is extremely wasteful, they would rather just make one of the hands in the first place. Therefore, they want to utilize asymmetric reactions as much as possible.

Bringing this back to my Ph.D. research, I was studying *asymmetric* rhodium-catalyzed hydroformylation. At this point, you should understand that I was making handed molecules, and more specifically, making one in excess over the other. But the next issue we need to tackle is what does it mean to be catalyzed.

1.3 What is "rhodium-catalyzed?"

If you imagine a reaction as going over a mountain, you will understand that it takes energy to do such a process. As we know, in a reaction, we break some bonds and form new ones. The act of breaking bonds requires a lot of energy—just like climbing up the mountain. When we form the new bonds, it is like going down the other side. In some cases, the mountain might be so tall that it would be impossible for you to climb over the top on your own. This is

true of a reaction as well—sometimes the energy required is so great that the bonds will not break under any normal conditions. This is the case in which a catalyst is crucial. A catalyst is something that lowers the energy barrier to a reaction, but is not consumed in it. In our analogy of a mountain, it would be a trolley that utilizes a tunnel that cuts through the center of the mountain, drops you off at the end (the products), and then picks up new people (starting material) to bring across (**Figure 1-4**).
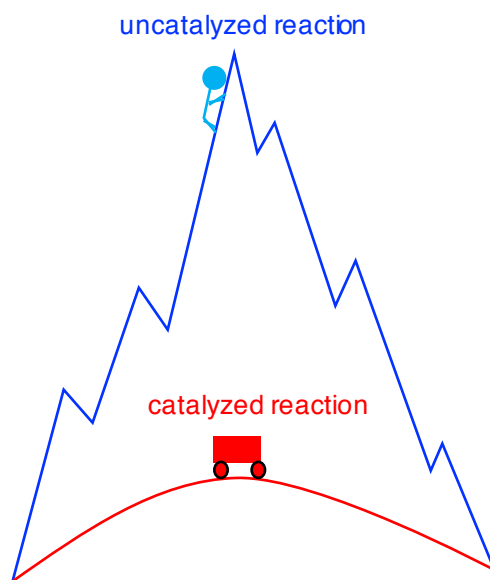

Figure 1-4. Climbing a mountain as an analogy for an uncatalyzed reaction versus a trolley as a catalyst.

Of course in reality, the catalyst is another molecule that is present during the reaction. In my case, we use rhodium metal, hence the term "rhodium-catalyzed." There are other atoms in the catalyst (hydrogen, carbon, phosphorus, nitrogen, and oxygen) that are attached to the rhodium, but chemists typically refer to the metal as the catalyst in these types of species.

Up until now, I have not discussed the actual reaction that I am studying. You know that it is asymmetric and catalyzed by rhodium, but not the specifics—which leads us to the next section.

1.4 What is hydroformylation?

Hydroformylation is the reaction of a molecule with a carbon–carbon (C–C) double bond, carbon monoxide, and hydrogen gas. A generic reaction is shown in **Scheme 1-1**; instead of showing the rest of the molecule, I am simplifying it as a green circle. This reaction would normally take far too much energy to accomplish, so we need to add a catalyst to the reaction to speed it up. Without a catalyst, you could mix these three starting materials together and let them stir in a flask forever, but nothing would happen. With our rhodium catalyst, the reaction is complete in an hour.

Scheme 1-1. Generic Hydroformylation Reaction
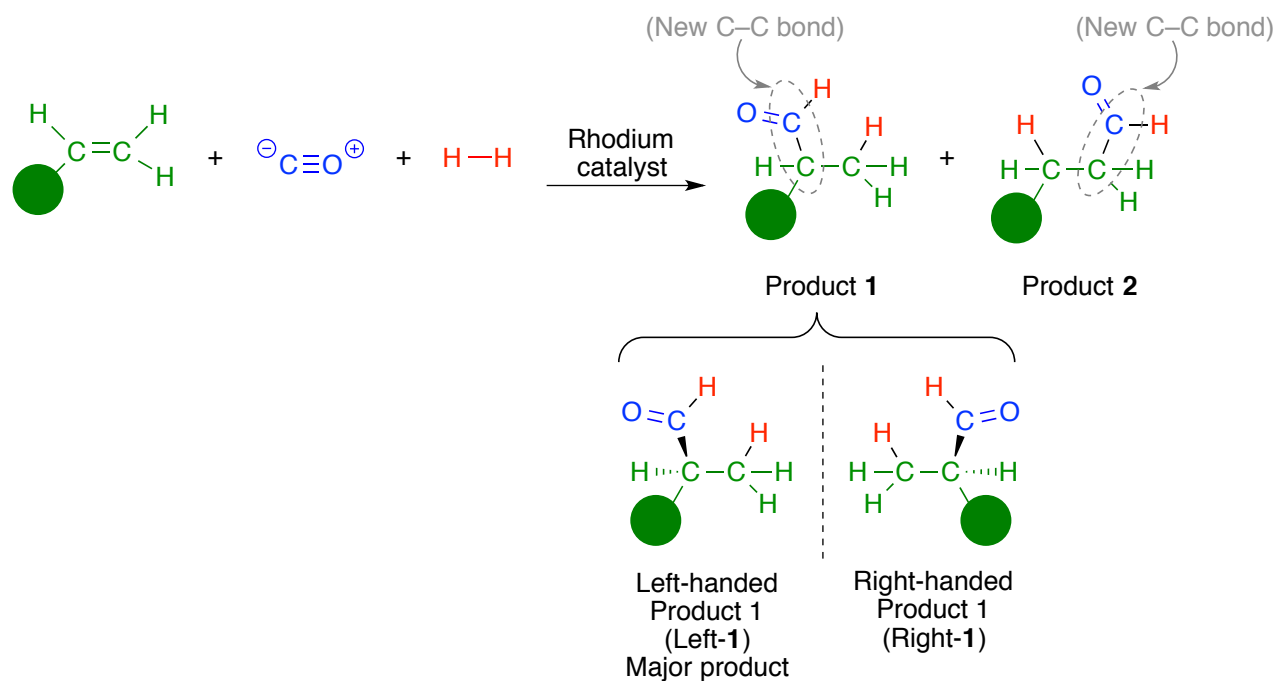
Product **1** is formed when the new C–C bond is formed closest to the rest of the molecule. Product **2** is generated when it is formed on the carbon atom farther away from the rest of the molecule. There are not really only two products, though; **1** is actually a handed molecule. Therefore, there are 3 products from hydroformylation of this starting material: Left-**1**, Right-**1**,

and **2**.[2] Product **2** is only formed in small amounts in our reaction. As I have already told you, this reaction is asymmetric: when using the Landis catalyst, the reaction yields much more of Left-**1** than Right-**1**. Bringing it all together, it should now make sense when I say that I studied rhodium-catalyzed asymmetric hydroformylation!

Why would I want to study this reaction? As we've already discussed, asymmetric reactions are extremely useful for pharmaceutical synthesis because we make one hand of the molecule in preference over the other. The reason hydroformylation is so useful is because the products we form are extremely versatile. A group that contains carbon, oxygen, and hydrogen bonded together in this way is called an aldehyde; these can be easily transformed it into a wide variety of other type of molecules (**Figure 1-5**).
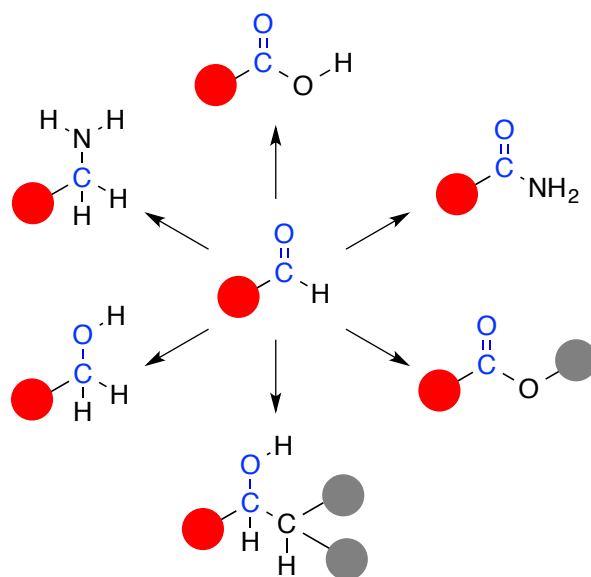

Figure 1-5. Aldehydes (center) can be easily transformed into other molecules.

At this point, you might be asking yourself what exactly I study about this reaction. As I mentioned previously, our catalyst is quite good at making only the Left-**1** product. The major question I asked in my research is: why? If we can understand why this catalyst is effective, we can learn how to make even better ones.

1.5 How do we understand this reaction?

All of my projects in graduate school have centered on trying to understand what makes the Landis catalyst selective for the Left-**1** product. The reason this is a complicated topic is that the mechanism for transforming the starting materials to these products is complex. **Scheme 1-1** shows the overall transformation for hydroformylation, but not the individual steps; not all of the atoms move at once, there are intermediate molecules formed along the way. An analogy that I will use throughout the section is simply doing the dishes. You cannot immediately go from dirty dishes in the sink to clean, dry dishes in the cabinet (you just wish you could!). There are several steps along the way: wash, dry, and then finally put the dishes away. In this case, our 'starting material' is dirty dishes. The first intermediate is clean, wet dishes. The second is dry dishes on the counter. The final products are dishes in the cabinet (**Scheme 1-2**).

Scheme 1-2. Analogy for Forming Intermediates in a Chemical Reaction.

dirty dishes   washer   →   clean, wet dishes
(starting material)   (intermediate A)

clean, wet dishes   dryer   →   clean, dry dishes on the counter
(intermediate A)   (intermediate B)

clean, dry dishes on the counter   storer   →   clean dishes in the cabinet
(intermediate B)   (final product)
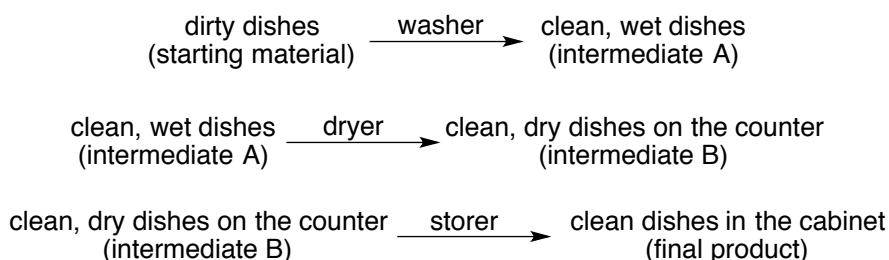
In this example, if mostly bowls are getting put away into the cabinet, this is analogous to the Left-**1** product being mostly formed in hydroformylation. The question I wanted to study is: what step (or steps) is controlling this selectivity? In our analogy, this is essentially asking: is it the washer, the dryer, or the person putting dishes away (the storer) that keeps choosing to handle bowls and not plates or cups?

The first way I studied this reaction was by characterizing the intermediates along the pathway. In order to understand how they are formed, it was imperative to know what they were.

This is kind of silly when it comes to the dishes, but makes more sense when we are talking about chemicals that you cannot actually see.

How do you visualize these compounds? We used a technique called 'nuclear magnetic resonance spectroscopy' or NMR. You don't need to know how the instrument works to understand how I used it. NMR spectrometers are the forefather of the MRI machine; instead of visualizing your body, it is used to visualize molecules. It is complicated because the output for an NMR spectrometer doesn't look like a picture of a molecule. It is a series of lines that need to be interpreted to determine the structure (**Figure 1-6**).[3]
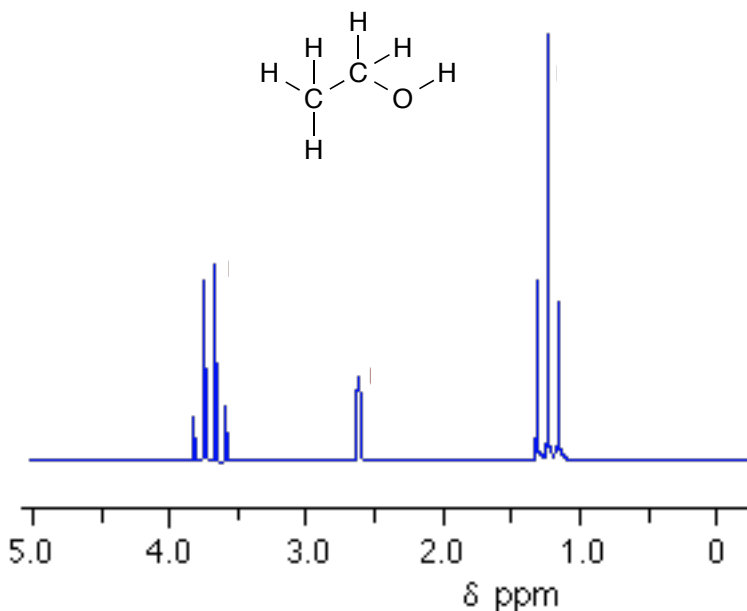

Figure 1-6. Example NMR spectrum of ethanol.

In many chemical reactions, we cannot normally observe the intermediates along the way because they are very short-lived (i.e. as soon as they are formed, they react away). This would be like being only able to see the pile of dirty dishes in the sink and clean ones in the cabinet. The rest of the process would be invisible to you—it is unknown who keeps choosing bowls. Thus, the only way to observe the intermediates is to leave out one or more of the starting

materials. In my case, hydroformylation cannot go to completion in the absence of hydrogen, just as clean, dry dishes cannot appear in the cabinet without the storer. Therefore, in the absence of hydrogen, the reaction *had* to stop part way through, because not all of the reactants were there to form the product—allowing me to observe the intermediates using NMR spectroscopy (**Scheme 1-3**). Without the storer, you could actually see the pile of clean dishes on the counter. As I noted previously, an NMR spectrum is a series of peaks that need to be interpreted. Thus, an important part of this project was deciphering exactly what I had made.

**Scheme 1-3. Formation of Intermediates in the Absence of Hydrogen Gas.**
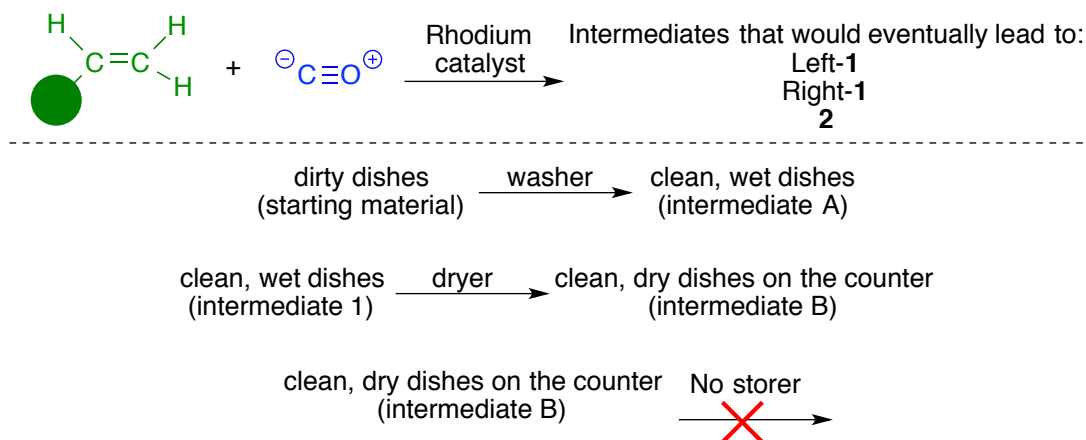
The next step was to assess the selectivity for the intermediates being formed. Was there an excess of clean, dry bowls on the counter at this stage? If so, it means that either the washer or the dryer is choosing to only handle bowls—and it is probably not the storer being selective. Was there a random assortment of all types of dishes on the counter? This would imply that the storer was the one choosing (setting selectivity) for bowls, and the washer and dryer handled anything without being particular. What I actually observed in the absence of hydrogen was a lot of the intermediate being formed that eventually gives the Left-**1** product. This implies that the earlier steps are selective toward forming Left-**1**.

As you might have noticed, I am not differentiating the washer and dryer. The way these experiments are set up, I cannot tell the difference between the washer and dryer's selectivity. I can tell from my experiments that one (or both) of them is choosing mostly bowls, but not which one. This is a limitation of my experiments. And in fact, this remained a problem throughout my Ph.D.; there was no direct way for me to separate these two steps.

I could tell from my data that it was not only the first two steps that were setting the selectivity. In our example, the percentage of bowls after the dryer (let's say 70% bowls) was lower than what was in the cabinet (90%). This implied that the storer was *also* choosing primarily bowls in this step of the process.

I studied this by taking those same intermediates formed in the absence of H_2 then adding hydrogen to see how they react (**Scheme 1-4**). By following this reaction in the NMR spectrometer, I was able to tell that, yes, in fact the last part of the reaction was also being selective for forming the Left-**1** product. In the analogy, this would be like giving the storer a huge stack of clean, dry dishes of all types and watching him to see which ones he chooses to put away.

Scheme 1-4. Reaction of Intermediates with Hydrogen Gas.
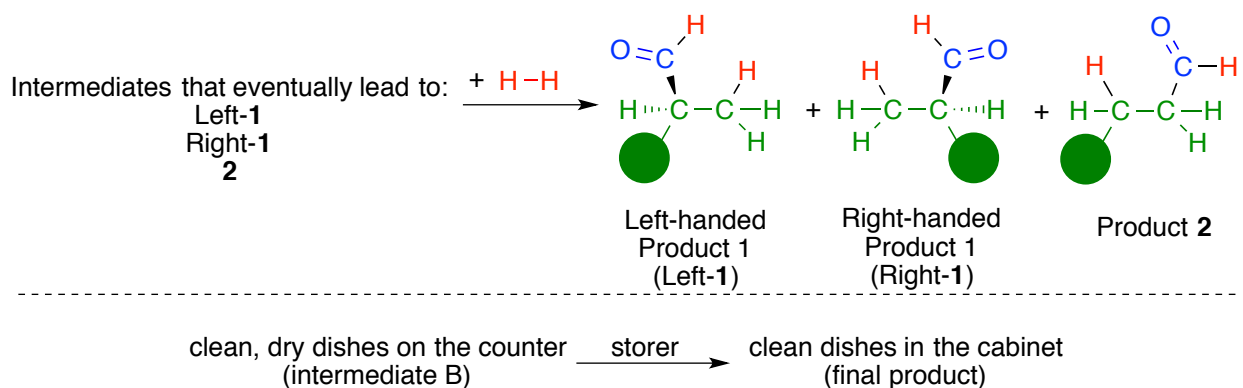
Consistent with my hypothesis, I observed that the last step of the reaction was also selective for the Left-**1** product. What this meant is that both forming the intermediates was selective, as well as the reaction taking them away. Both the washer/dryer combination was selecting mostly bowls, and the storer was also choosing mostly bowls to put in the cabinet!

This was really interesting (in my opinion) because chemists usually like to choose one step of the reaction and say, "That one step is determining selectivity!" For example, saying it was only the washer choosing bowls, and everyone else was indiscriminate. But my Ph.D. research showed us that, in fact, it was a combination of all of the steps that were involved in setting the selectivity for the Left-**1** product. We think this conclusion can be relevant to other reactions, as well. Maybe it is more common than we think to have all the steps cooperate to yield a highly selective reaction.

I hope this Chapter has made my last 4.5 years slightly more digestible. I want you to take away knowing what I mean when I tell you that I studied the selectivity of rhodium-catalyzed asymmetric hydroformylation. This reaction is a powerful method for making useful products for pharmaceuticals, and I wanted to understand how the Landis catalyst was so selective for forming only one product. In the end, we learned that it wasn't only one step that was good, but a combination of all of them that together make it work so well.

Notes:

(1)   Interestingly, almost all living things on Earth produce molecules of the same hand. There are theories about the origins of handedness (homochirality), but there is no consensus, yet.

(2)   Product 2 is not a handed molecule. The mirror image of it can be superimposed.

(3)   Groups of atoms connected in certain ways essentially leave a fingerprint that you can assign. How far something is to the left or right of the spectrum tells us something about the nearby atoms in the molecule. The shape of the signal tells me different information about the nearby atoms. Solving a spectrum like this is basically a complicated, but really fun, puzzle.