Communicating Research to the General Public

At the March 5, 2010 UW-Madison Chemistry Department Colloquium, the director of the Wisconsin Initiative for Science Literacy (WISL) encouraged all Ph.D. chemistry 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, state legislators, and members of the U.S. Congress.

Ten Ph.D. degree recipients have successfully completed their theses and included such a chapter, less than a year after the program was first announced; each was awarded $500.

WISL will continue to encourage Ph.D. chemistry students to share the joy of their discoveries with non-specialists and also will assist in the public dissemination of these scholarly contributions. WISL is now seeking funding for additional awards.

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.

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January 2011

Synthetic and Mechanistic Studies of Rhodium-Catalyzed Asymmetric Hydroformylation with Diazaphospholane Ligands

My Research Communicated to a Lay Audience

Avery Watkins

During the course of my graduate career, I have often found myself struggling to explain to a friend, or family member what exactly I have been researching for the past five years. This is a position that perhaps all scientists have found themselves in at some point or another. The difficulty in effectively communicating science to a person lacking a scientific background lies in that the language of science (especially chemistry) is comprised primarily of technical jargon. In this chapter I will attempt to explain my graduate research to a general audience. It is my hope that after reading this chapter, you will have a clear understanding not only what I have been doing for the last five years, but why this research is of a broad societal interest.

1.1 Catalysis and Society

My graduate research has focused on developing chemical reactions that are able to sustain our existence on planet earth. As the world's population continues to grow, our ability to continue to enjoy a high standard of living will depend on the availability of food, clean water, and synthetic materials. The synthetic materials that we rely on for the homes that we live in, cars we drive, and clothes that we wear, are all derived from so called 'raw' materials. Conversion of these raw materials, which are harvested from the earth, into useful synthetic materials requires a series of chemical transformations or reactions. While the demand for synthetic materials is steadily increasing, our supply of the raw materials needed to make them is constantly being depleted. Thus, chemist are faced with the challenge of discovering new chemical reactions that are capable of producing synthetic materials while making more efficient use of our precious supply of raw materials.

To fully understand the challenges associated with increasing the efficiency of a chemical reaction, we must first examine the anatomy of a chemical reaction. A chemical reaction converts reactants **A** and **B** into a desired product **A-B** (equation 1). The reaction shown in equation 1 is an example of an atom economical reaction in which the two reactants combine to produce only the desired product. In many instances, the two reactants combine to produce an unwanted product **C** in addition to the desired product (equation 2). At the completion of the reaction the unconsumed reactants and the unwanted product must disposed of as chemical waste. In the context of large scale chemical reactions, this is a significant problem because it wastes precious raw materials (especially if they are expensive) and the disposal of these undesired materials can have a deleterious environmental effect.

Atom Economical Chemical Reaction

$$\underset{\text{reactants}}{\mathbf{A+B}} \longrightarrow \underset{\text{product}}{\mathbf{A\text{-}B}} \qquad (1)$$

Non-Atom Economical Chemical Reaction

$$\underset{\text{reactants}}{\mathbf{A+B}} \longrightarrow \underset{\text{products}}{\mathbf{A\text{-}B + C}} \qquad (2)$$

So how can we make our desired product **A-B** in a more efficient way? Perhaps the best solution would be to find a process that completely and directly converts the reactants into **A-B** without the formation of **C**. Inherent to chemical reactions is the idea of an activation barrier. The activation barrier is the amount of energy required to make a reaction "go". Imagine a rollercoaster. Before you can enjoy all of its thrilling drops, bends and turns, a mechanical lift is required to get you to the top of the hill. In a chemical reaction, the activation barrier is this hill, and a certain amount of energy is required to get over the hill. Reactions with large activation

barriers proceed slowly if at all. The energy needed to overcome this barrier is most commonly supplied in the form of heat. However, there are certain instances in which heating a reaction results in the unwanted decomposition of the reactants and/or products into chemical waste. Furthermore, the activation barrier for some chemical reactions is so large that no reaction takes place even when heat is applied. One can overcome extremely high activation barriers by using a catalyst. Catalysts are chemical species that make chemical reactions possible or speed them up by lowering their activation barrier. A key characteristic of a catalyst is that it is not consumed in a reaction. Thus, a tiny amount of catalyst facilitates the generation of thousands of pounds of a desired product. Chemical reactions that make use of a catalyst are deemed catalytic reactions, and the field that studies the use of catalysts is known as catalysis.

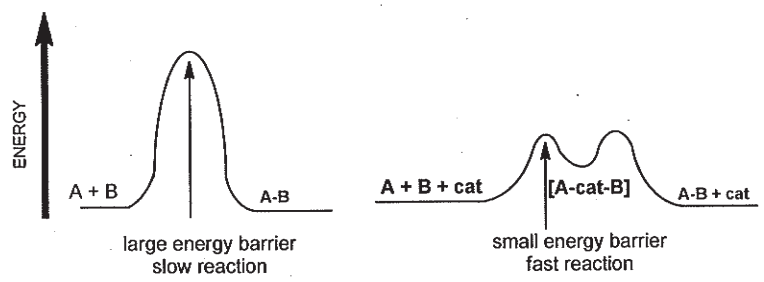


Figure 1.1. Examples of catalyzed and non catalyzed chemical reactions

The beneficial effect of a catalyst is depicted in Figure 1. On the left hand side is an example of a non catalytic reaction with a large activation barrier. In the catalytic reaction on the right, the reactants **A** and **B** interact with the catalyst (cat) to form a so-called intermediate, [**A-cat-B**] which is further transformed into to the desired product **A-B** and the catalyst regenerated in its unaltered form. Even though the two reactions give the same net outcome (product **A-B**), the activation barrier required to form this intermediate is lower and therefore the catalytic

reaction requires less energy input and proceeds at a faster rate. The discovery of new catalysts has led to the widespread availability of many of the materials that greatly impact our standard of living.

1.2 Asymmetric Transition-Metal Catalysts

My research has been focused on the application of '**transition metals**' as **catalysts** in reactions which produce **chiral** molecules, a field of study referred to as 'asymmetric catalysis'. Although the previous sentence is a bit hard to digest, it can be better understood by explaining what each of the complicated scientific terms mean.

The Periodic Table of the Elements

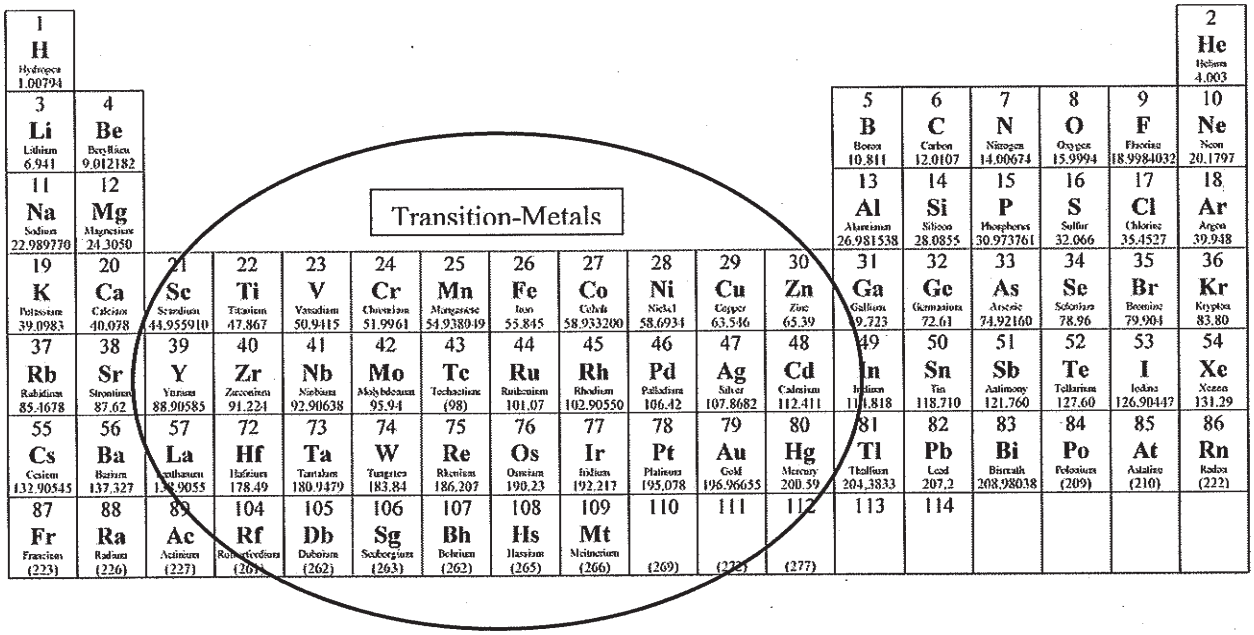


Figure 1.2. Periodic table of the elements

Transition metals occupy the middle of the periodic table of elements (Figure 2.), and are termed 'transition' because they posses properties of both the metals on the left hand side, and metalloids on the right hand side. These elements are well known for their uses in jewelry

(platinum or Pt, silver of Ag, and gold or Au) and construction (iron or Fe, and copper or Cu). However, many of these elements possess atomic properties that make the uniquely suited to serve as catalysts. However, throwing your gold watch into a chemical reaction will not generate a catalyst. In most instances, transition metals serve as catalysts only in the presence of the appropriate number and type of ligands. The term "ligand" is derived from the Latin word *ligare*, which means to bind. Thus, ligands attach themselves (bind) to a transition-metal atom (or several atoms). When bound to the transition-metal, ligands greatly alter the transition-metals' ability to undergo a chemical reaction (its reactivity). Chemist have examined the beneficial effect of ligands for many years, and at present much is known about how and why transition-metals behave in a particular manner when bound to the appropriate ligands.

Chiral molecules are perhaps one of nature's most puzzling creations. Chiral molecules are molecules, which although they are comprised of the same type, number and arrangement of atoms, display different chemical properties. That is to say that they are the same yet different. Chemists define chiral molecules as molecules that exist as non superimposable mirror images. Take for example your hands. If you hold them palm-to-palm you will see that they are mirror images of each other. Now try to lay your hands back-to-palm such that one thumb overlaps the other. You should have found that they do not overlap or cannot be superimposed. Your hands are non-superimposable mirror images and are therefore chiral, or asymmetric (meaning without symmetry). Now see if you can identify the chiral molecule in Figure 3.

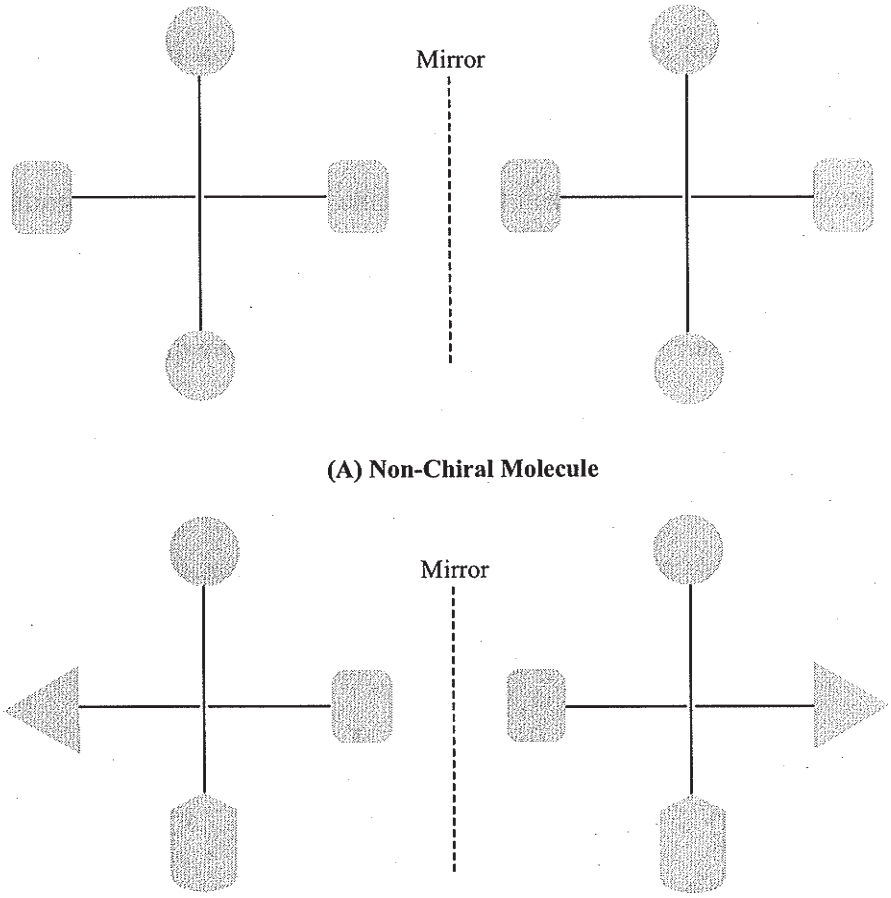
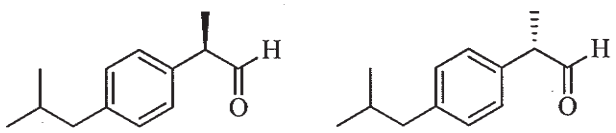


Figure 1.3. Example of a non-chiral molecule (A) and a chiral molecule (B)

Chiral molecules differ only in their 3-dimensional orientation and each orientation ('hand') is referred to as an enantiomer. When referring to a specific orientation, scientists often refer to its 'handedness'. The handedness of a chiral molecule will determine how it interacts with another chiral molecule. Take for example the interaction between a pair of gloves (which are chiral, try to superimpose them) and your hands which are also chiral. You will immediately recognize that one glove fits better on a particular hand than the other. While having two right-handed gloves is really annoying during a winter storm, the stakes can be much higher when it comes to the reactivity of molecules within the human body.

Amino acids, which serve as the primary building blocks for the human body, are chiral molecules. Therefore, the human body is an intrinsically chiral environment. This means that the different enantiomers of man-made chiral molecules, such as pharmaceuticals, may have different interactions inside the body. In some cases, only one enantiomer of a drug molecule produces the desired therapeutic effects, while the other is either harmful or therapeutic. Such is the case the drug molecule ibuprofen, ((*R,S*)-2-(4-(2-methylpropyl)phenyl)propanoic acid (Figure 4), which is widely used in the treatment of pain. Even though only one enantiomer possesses the desired medicinal effect, the product that we purchase from our local pharmacy comes as a 50:50 mixture of the two ibuprofen enantiomers.



(R)-Ibuprofen **(S)-Ibuprofen**

Figure 1.4. Two enantiomers of Ibuprofen

You might be wondering at this point, why pharmaceutical companies do not sell you a package containing only the useful form of the drug? It all has to do with the economics of producing Ibuprofen and how it is metabolized. We must remember that drug companies are in the business of making profit. It is much cheaper to synthesize Ibuprofen as a mixture of the two enantiomers, and since the drug can be administered as such with no significant side effects, companies simply forgo the expensive task of separating the two enantiomers. Although cost effective, the current commercial synthetic route to ibufroven produces roughly 64 tons of waste per 32 tons of ibuprofen. Separation of the two enantiomers increases the amount of waste to 160

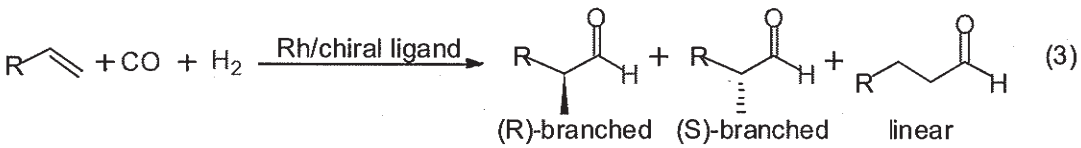
tons of waste per 32 tons of Ibuprofen sold. Such egregious waste production, which is quite common within the chemical industry, leads not only to the depletion of natural resources, but it creates many environmental hazards associated with safely disposing of waste materials.

The field of asymmetric catalysis aims to address these challenges by proving direct access to a single enantiomer of a chiral molecule. Asymmetric catalysis has the potential to increase the efficiency of chemical synthesis by eliminating the occurrence of unwanted enantiomers. It is also possible that the new chemical reactions made possible through the use of catalysts alone will result in significant decreases in waste production. In fact, the 2001 Nobel Prize in Chemistry was awarded to a group of chemistry in honor of their pioneering work in the area of asymmetric catalysis. One class of asymmetric catalysts comprise transition-metals bound by ligands which are themselves chiral molecules. These 'chiral catalysts' function by reducing the activation barrier for the formation of one product enantiomer more than that of the other enantiomer. This results in the more rapid formation of one enantiomer, and the production of mainly one product enantiomer. Reactions that produce and excess of one enantiomer of a chiral molecule are deemed 'enantioselective'.

1.3 Enantioselective Hydroformylation

Now that you have a good introduction to many of the key concepts that you will encounter in the following chapters, I will now give a more detailed description of my own research. My research has focused on the development of asymmetric catalyst for the hydroformylation reaction. This reaction (Equation 3) successfully combines an alkene with a molecule of hydrogen (H_2) and carbon monoxide (CO) to produce an aldehyde as the product. The hydroformylation reaction is possible only in the presence of a transition-metal catalyst, and

produces aldehydes as mixtures of two branched aldehyde enantiomers and a linear aldehyde isomer. The production of a single branched aldehyde enantiomer is the primary goal of this reaction. This requires a catalyst capable of controlling both the selectivity between branched and linear isomers (regioselectivity) and the selectivity between the two enantiomers of the branched aldehyde (enantioselectivity). Only a few catalysts capable of achieving this type of dual selectivity have been discovered to date.



(3)

1.4 Overview of this work

In 2005, researchers in the Landis group at UW-Madison and Dow Chemical discovered a very effective catalyst for asymmetric hydroformylation. The catalyst was comprised of the transition metal rhodium (Rh) bound by bis-3,4-diazaphospholanes as ligands (Figure 5). Initial results suggested that these new catalysts were far superior to most catalysts that been previously reported for the asymmetric hydroformylation reaction. My first project (Chapter 2) examined the use of three diazaphospholane-based catalysts in the asymmetric hydroformylation aromatic alkenes. Successful asymmetric hydroformylation of these compounds is of enormous potential societal impact because the branched chiral aldehyde product gives straightforward access to 2-arylpropionic acids such as ibuprofen.

The asymmetric hydroformylation of aromatic alkenes with diazaphospholane catalyst was very successful. For most of the 12 aromatic alkene derivatives that I examined, the (R)-branched aldehyde constituted greater than 95% of the products. In many cases, the selectivity

for the (R)-branched aldehydes depended on the quantity (partial pressure) of carbon monoxide (CO) that was used in the reaction. High pressures of CO resulted in the greatest hydroformylation regioselectivity and enantioselectivity. The results obtained in this study represent the greatest degree of selectivity observed in the asymmetric hydroformylation of aromatic alkenes to date, and was published in 2008 in the chemistry journal Organic Letters.

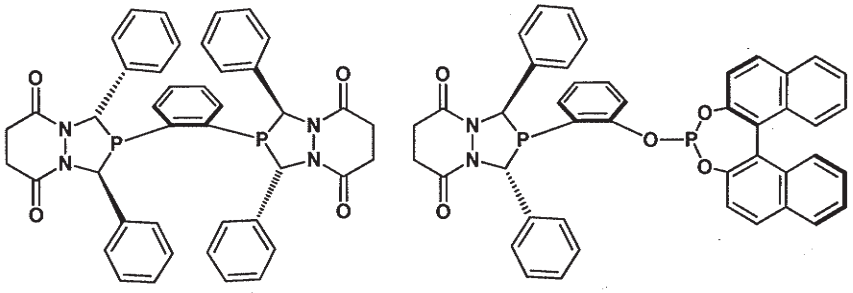


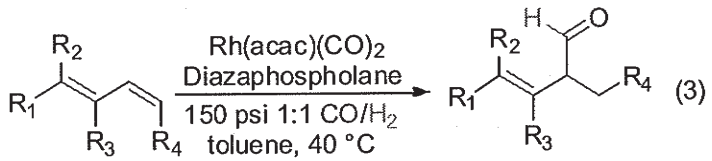
Figure 5. Examples of chiral diszaphospholane ligands

My next project (Chapter 3) aimed to understand origin of the effect of CO pressure on selectivity that was observed in Chapter 1. This project took approximately three years to complete. Central to this project was the examination of the kinetics of the reaction between diazaphospholane catalyst and aromatic alkenes. Because a catalyst speeds up a reaction by lowering its activation barrier, a great amount of detail can be obtained by studying the rate (speed) of the reaction under specific conditions. By measuring how the CO pressure affects the rates for the formation of each of the three possible products (see equation 2), we were able to determine why the selectivity of the reaction increases at higher pressures of CO. The rates at which the (S)-branched aldehyde and the linear aldehyde are produced become slower as the CO pressure is raised . On the other hand, CO pressure has no impact on the rate at which the major reaction product, the (R)-branched aldehyde, is formed. Thus, the reaction yields a greater proportion of the (R)-branched aldehyde as the CO pressure is raised. This results in an overall increase in both the regioselectivity and enantioselectivity of the reaction. The insights gained from these studies could lead to the discovery of new and better asymmetric hydroformylation catalysts. This work was recently published in the Journal of the American Chemical Society.

Whereas my early work focused on the asymmetric hydroformylation in the context of large scale pharmaceutical synthesis, my last project (Chapter 4) dealt with the extension of this reaction to complex molecule synthesis. Complex molecules contain large numbers and types of chemical elements and are difficult to make. Most commonly these molecules are synthesized on a small scale (> 1 gram) so that their biological activity can be assessed. Thus, ease of synthesis becomes more important than the generation of waste. Although asymmetric hydroformylation has been rarely used in this context, it has the potential to streamline the synthesis of complex

molecules through the use of only a small amount of a catalyst, and two gaseous reactants (CO and H_2) which can be vented into the atmosphere at the end of the reaction. This essentially eliminates the need for lengthy, time consuming purification steps.

Toward this goal, I examined the asymmetric hydroformylation of 1,3-dienes (Chapter 4). 1,3-dienes are compounds containing two successive carbon-carbon double bonds separated by one carbon-carbon single bond. These reactions lead to the formation of chiral β,γ-unsaturated aldehydes (eq 3) which are useful intermediates in complex molecule synthesis, but difficult to make via other methods.



(3)

For many of the 1,3-dienes that I examined, nearly exclusive formation of branched aldehydes was observed. The selective formation of a single enantiomer of the branched aldehyde was more difficult to achieve. The enantioselectivity of these reactions depended on the structure of the diazaphospholane ligand, the structure of the 1,3-diene substrate and in some cases the partial pressure of CO employed in the reaction. I was eventually able to find conditions which lead to high levels of enantioselectivity for most of the substrates examined. We recently submitted these results for publication. The application of asymmetric hydroformylation to the synthesis of complex molecules is an exciting new direction for this technology.