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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Part I. Synthesis of Garner's Aldehyde and Efforts Toward the Synthesis of Tapentadol via an Asymmetric Hydroformylation/Reductive Amination Sequence

Part II. Development of a Rhodium-Mediated Domino Annulation and Efforts Toward the Total Synthesis of Linderagalactone C

By

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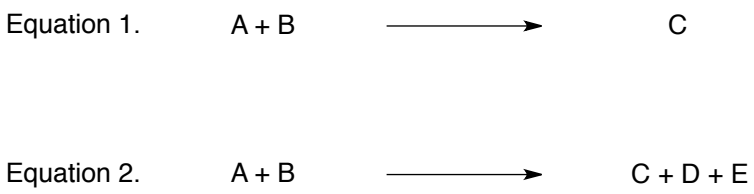
Appendix C. Increasing Efficiency in Organic Synthesis through the Development of New Reaction Technology

Prepared for the WISL Graduate Student Award to Promote Graduate Chemistry to the Public, announced by Prof. Bassam Shakhashiri.

Organic synthesis, the combination of available carbon-containing molecules to make larger, more complex molecules, is a mature field. Given time, an organic chemist can synthesize virtually any molecule desired, regardless of size and complexity. But chemical reactions are not perfect; they create byproducts and generate waste as well as the desired product. Because of this, modern organic chemistry has focused on developing new reactions that have greater efficiency. My research has focused on two specific areas: broadening the application of an established efficient reaction and the development of a completely new efficient reaction.

One common measurement of efficiency in chemical reactions is "atom economy." As illustrated in Figure 5A, if all or most of the starting reagents' (A and B) atoms end up in the product molecule (C) then a reaction is atom economical (Equation 1). However, if there are many atoms that are waste or byproducts (D and E), then the reaction is not atom economical (Equation 2). Improving atom economy is an excellent method of increasing efficiency.

Figure 5A. Atom Economy in Chemical Reactions

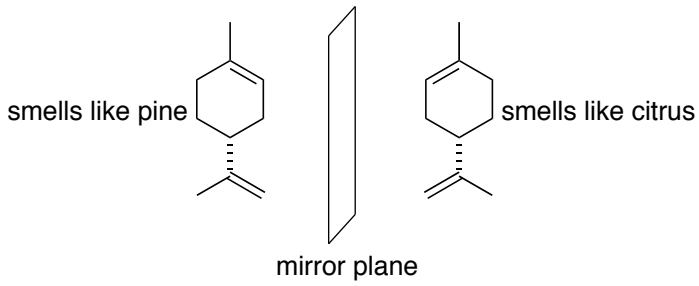


My first area of research involves new applications of a reaction that is actually fairly old. It was discovered in 1938 and is still used by the chemical industry to turn petroleum products into useful chemicals that are part of many plastics and other consumer products. This reaction, called hydroformylation, is popular in industry because it is atom economical, but its use in the synthesis of more complex molecules has been limited. My research is applying this reaction to produce chiral molecules.

Chirality is a fundamental concept of organic chemistry. It is the sense of "handedness" in nature. The best example of chirality is your hands themselves. Your left and right hands are mirror images of one another, but they are not identical. If you line up your fingers, your palms are facing one another. If your palms both face up, your thumbs are on the outside of both hands. This mirror-image-but-not-identical relationship is the essence of chirality, and molecules with this relationship are called "enantiomers." A chiral molecule always has exactly two enantiomers.

Chirality is extremely important in interactions of molecules. Let's return to the hand analogy. Because of the chiral nature of your hands, shaking hands with your right hand and someone else's left hand is a much different "fit" than if you both used your right or left hands. This is the same with molecules as well. Different enantiomers (hands) of the same molecule interact differently in chiral environments (your friend's hand in the above example), such as our bodies. Take the molecule limonene, for example. As shown in Figure 5B, limonene's two enantiomers (related by a mirror plane) each have an entirely different smell because they interact differently with the chiral receptors in your nose.

Figure 5B. Enantiomers of Limonene Have Different Odors



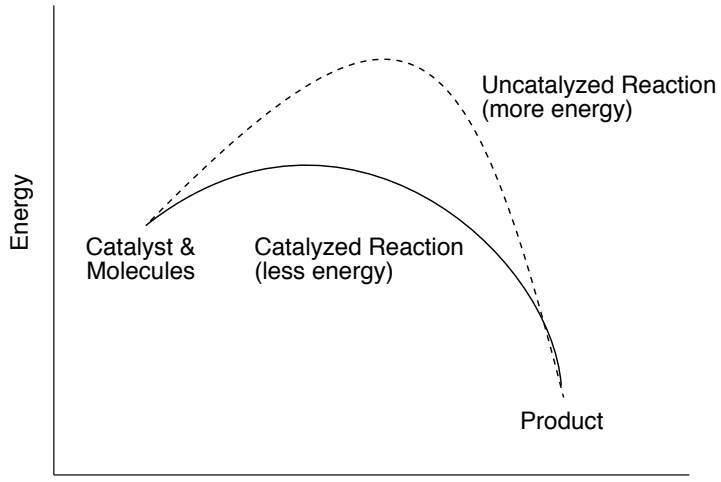
Many of the molecules that make up organic life are chiral, including sugars, amino acids and the proteins they comprise, and many of the architecturally complex molecules found in

plants, animals, and bacteria. Many molecules synthesized by chemists, whether based on molecules found in nature or not, are chiral as well.

Since the two enantiomers (hands) of molecules, including drugs, interact differently with our bodies, it is important that medications contain *only* the enantiomer of the drug that is responsible for the desired effect instead of a mix of both enantiomers. Because of this, reactions that make chiral molecules must be designed to selectively make one enantiomer instead of the other. This is called "enantioselectivity." Many times a catalyst is used to control the reaction and produce one enantiomer enantioselectively.

Catalysts are chemicals added to a reaction that make the reaction go faster, but are not consumed by the reaction. Catalysts are not part of the product, and often the catalyst can be recovered and reused in another reaction. These catalysts make reactions go faster by allowing for a new reaction pathway that requires less energy, and thus is easier and faster than the uncatalyzed pathway. This is illustrated in Figure 5C.

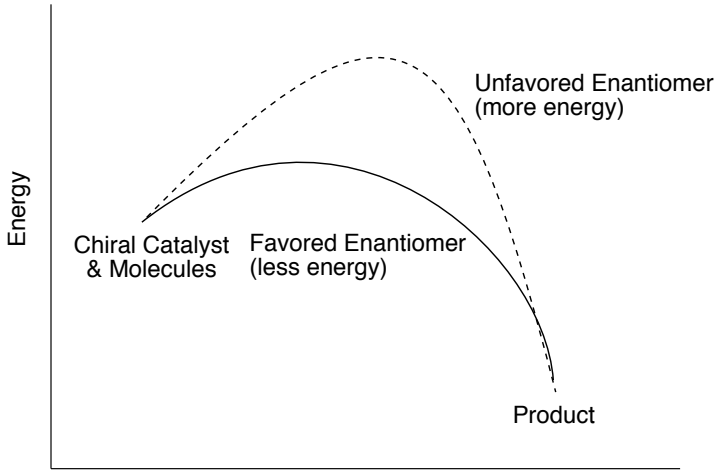
Figure 5C. Energy Diagram of a Catalyzed Reaction



The diagram shows the difference between the energy required for a catalyzed (solid line) and an uncatalyzed reaction (dashed line). As you can see, the catalyzed reaction requires less energy because the peak of its curve is lower than that of the uncatalyzed reaction.

Figure 5D shows a similar diagram, but for a chiral catalyst making two different enantiomers. Recall that enantiomers interact differently with chiral entities, like your nose or a chiral catalyst, so there will be one enantiomer that is produced by the catalyst using less energy. Since it takes less energy to make, and is thus faster and easier, the catalyst will make that enantiomer selectively.

Figure 5D. Energy Diagram for Enantioselective Catalysis



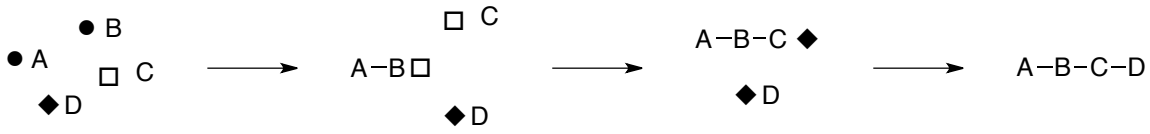
The catalysts in your body and in plants, animals, and bacteria are proteins called enzymes. Enzymes are excellent catalysts, combining near perfect enantioselectivity and great speed. Organic chemists typically use metals such as palladium, rhodium, and copper as catalysts; some of these synthetic catalysts rival enzymes in enantioselectivity and speed.

Recently developed chiral catalysts for hydroformylation select for one enantiomer of the product over the other, enabling organic chemists to use hydroformylation to make complex chiral molecules much more efficiently than they have been prepared previously. Other catalysts for hydroformylation do not produce chiral products or are not very enantioselective. My work

seeks to demonstrate the versatility of hydroformylation by using these catalysts to synthesize chiral molecules very efficiently.

The other focus of my research is the development and study of a reaction that I discovered. Chemical reactions change of the bonds of the atoms of molecules. Bonding is the tight association of two atoms, though atoms of different elements form a varied number of bonds according to their nature. Hydrogen forms one bond and carbon forms four bonds, but oxygen almost always forms two. Most reactions form or change just one bond in a molecule, but some reactions can form several bonds during a single reaction. One type of these reactions is called a "domino reaction." Just as when a row of dominos standing on end falls, with each domino knocking its neighbor down, in a chemical domino reaction the formation of a new bond leads directly to the formation of another bond. The bonds have to be made in a specific order, however, just as a domino has to be knocked over by its neighbor. Figure 5E shows an example of a domino reaction that makes three bonds. The atoms that are able form bonds are indicated by the same shape. First, A and B react to form a bond, which causes a change in B that allows B to form a bond with C, but not D. After B and C bond, C is altered and reacts with D to form the product (A-B-C-D).

Figure 5E. A Domino Reaction



Commonly, about three bonds are formed in a domino reaction, meaning one domino reaction can take the place of three non-domino reactions. In my research, I have discovered one such domino reaction that makes three new bonds, including two new carbon-carbon bonds, which can be difficult to make. This new domino reaction allows for the more effective synthesis

of certain types of molecules, and by making several bonds in the same reaction there is no need to make them individually in single reactions. This increases efficiency by cutting down the number of reactions required to reach a desired molecule. The reaction has no enantioselectivity yet, so it makes equal amounts of both enantiomers, but I hope to discover a chiral catalyst that will make the reaction enantioselective.

My research focuses on two ways to increase efficiency in organic synthesis: adaptation of an existing efficient reaction to new applications and the development of a new domino reaction that forms multiple bonds during a single reaction. This expands both basic knowledge of organic chemistry and the available reactions useful for synthesizing organic molecules. Even so, there remains much room for improvement in the efficiency of organic synthesis.