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Implementation of Asymmetric Hydroformylation with Rhodium Bisdiazaphos Catalysts: AHF in Flow and Rh-Catalyzed Hydroacylation

By

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Chapter 1

Introduction for the non-chemist

1.1 Introduction

Catalysis is all around us; from the ammonia used in fertilizer to the plastics we encounter every day, catalysis has tremendously shaped our world. Catalysis is the acceleration of the rate of a chemical reaction by use of a catalyst, a material that is present in a chemical reaction, but is not consumed during the reaction. One commonly encountered example of a catalyst is the catalytic converter on cars. This device contains rare metals (including platinum, palladium, and rhodium, among others) which act as catalysts to convert harmful materials in exhaust to less harmful ones. Catalysts act by lowering the energy barrier (called the activation energy). Catalysts provide a lower-energy alternative route for reaction. The reaction can proceed more quickly when the activation energy is lower. A reaction may change from not occurring at all to happening very quickly.

Figure 1.1 below shows how chemists typically describe the effect of catalysts. On the x-axis, we plot 'reaction coordinate', or reaction progress and energy is on the y-axis. By reducing the activation energy (Figure 1.1b), the energy barrier for the reaction is lower, and the reaction proceeds more quickly. Even if we add additional steps, the rate will be dependent on the highest overall activation energy. Consider that you live on the line labeled 'starting material' and you work at the line labeled product. While your walk to work is overall downhill, the large mountain in the middle (activation energy) means walking over it to get to work is quite tiring. However, if there were a different path, perhaps a route around the side of the mountain, your walk would be much easier, because you don't have to walk uphill as much. A catalyst acts to provide the alternate path, to avoid the large mountain that is the activation energy.

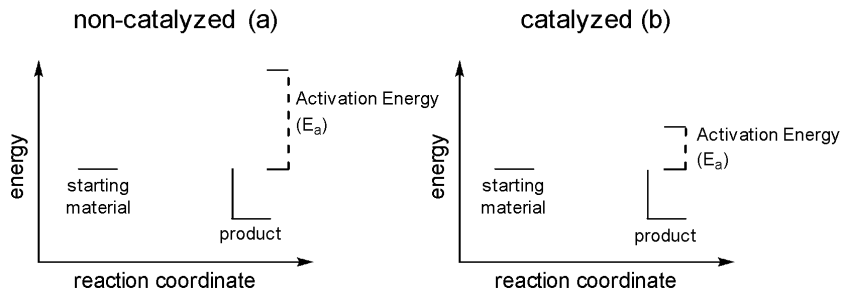
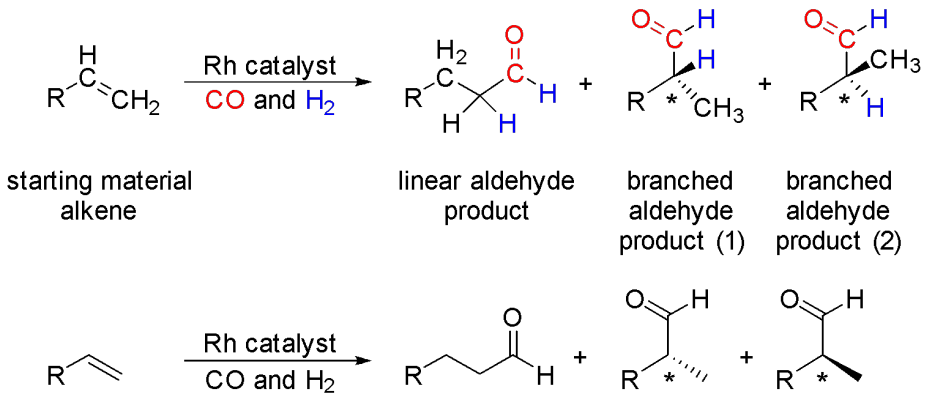


Figure 1.1 Diagram showing an energy landscape for a non-catalyzed reaction (a) and a catalyzed reaction (b)

Hydroformylation

This work focuses primarily on a reaction called hydroformylation. In the hydroformylation reaction shown below (Scheme 1.1), the starting material on the left is converted to the products on the right, using a rhodium catalyst and a mixture of hydrogen (H_2) and carbon monoxide (CO) gasses (this mixture is called synthesis gas, or syn gas). The CO and H_2 mixture is added across a molecule containing a carbon-carbon double bond (called an alkene) to produce an aldehyde, where a carbon atom has two bonds to oxygen and one to hydrogen. In the top of Scheme 1.1, the aldehyde consists of the C=O (colored red) and the H attached to it (colored blue). The red and blue colors show where the CO and H_2 end up in the products. Chemists usually don't draw out the full molecule and instead let lines represent carbon atoms. Whenever a line intersects or is bent, a carbon atom is implied. The line structures are shown below the drawn out structures in Scheme 1.1. A total of three products can be formed, two (very similar) branched products (where the CO is added to the carbon closest to the R group) and a linear product (where the CO is added to the second carbon to give a straight chain.) The hydroformylation reaction is one of the largest reactions performed industrially, where billions of pounds of aldehydes are produced and used in plasticizers, detergents, and

other industrial chemicals. The aldehydes produced industrially are almost entirely linear aldehydes, as in the first product below, where CO has been added on the end, to extend the chain.



Scheme 1.1 The hydroformylation reaction, showing all carbons explicitly (above) and commonly drawn structures (below)

Enantiomers and chirality

The two branched products shown above in Scheme 1.1 are very similar, but not identical. These molecules each have a carbon atom with four different groups. However, depending on the position of these four groups, the two molecules are different. This carbon atom is called a chiral center and is labeled with an asterisk in Scheme 1.1. Because the molecules each have one chiral center, and these chiral centers are opposite each other, these molecules are called enantiomers. Enantiomers are non-superimposable mirror images. Our hands are enantiomers; our left and right hand are mirror images, but we can't superimpose them. Molecules can have this 'handed-ness' as well as seen in Figure 1.2.

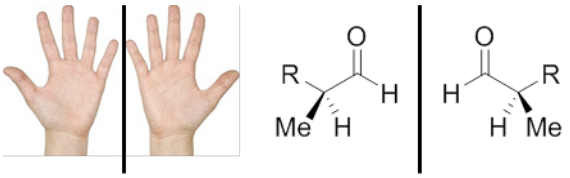


Figure 1.2 Demonstration of enantiomers

Ligands and Selectivity

Controlling what products are formed in a reaction, called the selectivity of the reaction, is a major focus of catalysis. Chemistry and cooking have a lot in common as cooking also has selectivity concerns. Cookies, brownies, and cake are all different, yet all three contain similar ingredients: butter, sugar, eggs, and flour. By combining these in slightly different ratios, with help from some other minor ingredients, we can choose to make brownies, instead of cake or cookies. Cookies are more different than the other two, cookies start as thicker cookie dough and are baked individually on sheets. Brownies and cake however are similar, both start as a runnier batter and both are baked in pans. In hydroformylation, we generally only want to form one of the three products (one linear aldehyde, similar to cookies, and two branched aldehydes, similar to brownies and cake). But how can we control which one we form? In hydroformylation and other catalyzed reactions, the selectivity is dependent on the catalyst. We can control what products we get by choosing a specific catalyst. While we use rhodium, we can modify the molecules that are bonded to it, forming different metal complexes. These molecules attached to the metal are called ligands. Ligands can have different shapes, which will help promote formation of one product over another. The shape of the ligand can have a huge impact on the selectivity. In hydroformylation, one ligand can give an almost entirely linear product, while another can give almost entirely branched products. Hydroformylation to give branched

products, called asymmetric hydroformylation (AHF) is underdeveloped compared to hydroformylation to give linear ones. Part of this is because there are, again, two branched products that can be formed. We not only want to form the branched product – described as regioselectivity, selecting for a specific region of the molecule, but we also only want a specific enantiomer as well, called enantioselectivity. This is similar to the baking description above. The linear aldehyde (the cookie) is relatively easy to avoid if we are looking to make branched products (cake or brownies), but controlling between these two branched products is more difficult, because they're very similar. If we want to produce one chiral product, we will need a chiral ligand to transfer that chiral information, giving us the enantioselectivity. The Landis group has developed a class of ligands named bisdiazaphospholane ligands which show high regio- and enantioselectivity in hydroformylation, similar to making the brownies, instead of cake or cookies. An example of these ligands is shown in Figure 1.3.

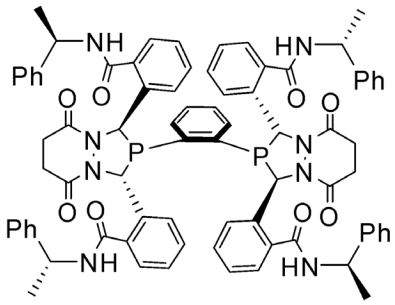


Figure 1.3 An example of a bisdiazaphospholane ligand, (*R*,*R*,*R*)-Bisdiazaphos-SPE

This thesis describes efforts to make hydroformylation easier for other chemists to use. This has been done by making the ligands more available, demonstrating hydroformylation in a different style reactor, and developing new ways to use the aldehydes produced in hydroformylation.

1.2 Improved ligand synthesis

The bisdiazaphospholane (BDP) ligand shown above in Figure 1.3 is a rather complicated molecule. It is inconvenient to make and not available from any chemical supplier, making it harder for other chemists use the ligand in hydroformylation. Efforts have been made, in collaboration with scientists from the pharmaceutical company Eli Lilly to improve the synthesis of this ligand.

One of the major developments in this work is what we call a resolution of enantiomers to obtain one chiral product from a mixture of two. If we want chiral products, we need to use chiral material to transfer that chirality. In hydroformylation, we seek to transfer the chirality from the ligand on the catalyst to the product. In order to do this most effectively, the ligand itself must be obtained as only one enantiomer. Eli Lilly, in collaboration with another company, FreeSlate, discovered a molecule which can help separate our ligands of different handedness. I used their result to develop a procedure to carry this out easily. With this new method, we no longer need expensive instruments to do this separation.

We also noticed that our ligands were not as pure as we had thought; the ligands were contaminated with other molecules. During this study we discovered that the previous way we used to make our ligands was giving material that was not very clean. We call the purity of the ligand the ‘potency’, the amount of desired compound in a given sample, expressed as a percentage, so it is ideally 100%, or close to it. However, our ligands were around 50% potent. Additionally, some of the materials we used in the synthesis are unfriendly and undesirable substances because they are expensive and very reactive. These materials are difficult to handle and thus, harder to use on a large scale. Because we would like these ligands to be easy to make,

the material we use to make them must be safe and scalable – easy to use in large amounts in case someone wants to make a lot of ligand.

To meet our goals of higher purity and safer reagents, the substance which causes a reaction, I developed a new process for forming our ligand from the starting material. The reagents we employ can easily be used in a chemical manufacturing plant. Previously, we could access our ligands in about 50% potency and yield. To a chemist, yield is what we expect to get of a reaction. Continuing the dessert analogy, if you bake cookies, you may expect to get three dozen, if we run a reaction, we expect a certain amount of product. The new process enables these ligands to be synthesized in 70% yield and 90% potency, a large boost. This translates to getting more cookies from the same amount of dough, and these cookies are better quality. This new process uses only common equipment and avoids using expensive and time-consuming techniques for isolating molecules. We hope that other chemists looking to use our ligands will be more inclined to do so, since the synthesis is now easier.

1.3 Development of Asymmetric Hydroformylation in Flow

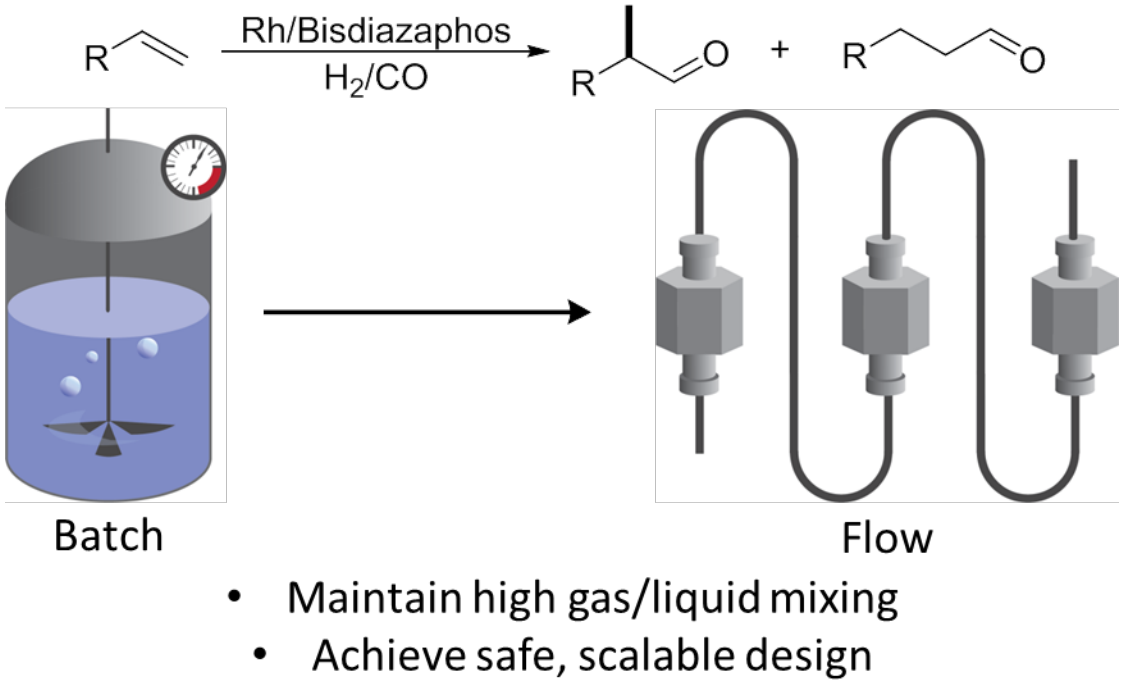


Figure 1.4 Representation of a batch reactor and the flow reactor developed in this project

In chemistry, we generally run reactions in what are called 'batch' reactors. In a batch reaction, all the materials are added to a reaction vessel, stirred for a period of time, and then all the material taken out when the reaction is finished. Alternatively, we could run a reaction in 'flow'. In a flow reaction, materials are continuously pumped through a tube, and they exit the reactor some time later, after the reaction is complete. In these flow reactions, material is produced continuously, instead of all at once as in batches. These flow reactors are similar to an assembly line. Molecules move through the reactor, a reaction occurs, and the molecules ultimately come out as something different than what went in. In the chemical industry, there is a large drive to move reactions from being performed in batch to flow. Flow reactors can be more

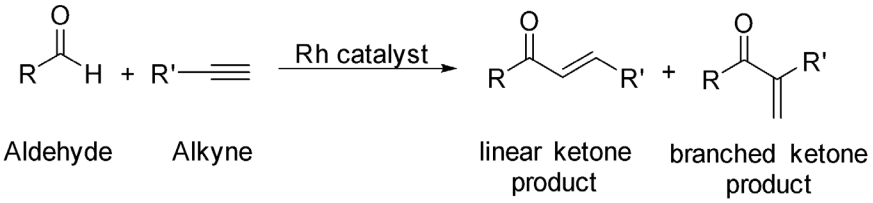
flexible and less expensive than batch reactors, are often safer, and they can also give more consistent results, since we can monitor the material as it comes out of the reactor.

In collaboration with Eli Lilly, we designed and built a flow reactor for asymmetric hydroformylation (AHF). As gaseous CO and H_2 are used in hydroformylation, one major challenge in this project was to achieve high gas-liquid mixing. Gasses and liquids are generally pretty hard to mix, and it is hard to tell if they were mixing fully in the reactor. However, the regioselectivity (controlling branched vs. linear products) and the enantioselectivity (controlling branched product handedness) in AHF is dependent on the amount of CO in solution, and the amount of CO in solution is dependent on gas-liquid mixing. So we are able to look at the results from the reaction to identify whether our reactor is mixing gas and liquid well. Since we can easily control gas-liquid mixing in batch reactions by stirring rapidly, if our flow results matched our batch results for the amount of branched product formed, we considered the reactor to have good gas-liquid mixing.

We developed a pipes-in-series reactor which is drawn in Figure 1.4 which consists of small tubes called jumpers connected to the larger pipes. Our reactor consists of 20 of these pipes. In order to use less of our expensive catalysts, we wanted the material to spend a long time in the reactor. Our reactor has a residence time, which is how long material stays in the reactor, of about 8 hours, which is a long time for flow reactors, and is consistent with our batch reactions taking about 8 hours as well. Ultimately, we demonstrated that the flow reactor gave selectivity that is consistent with batch, successfully demonstrating AHF in flow. We hope that this demonstration will show how robust the AHF reaction is.

1.4 Development of Hydroacylation methodology

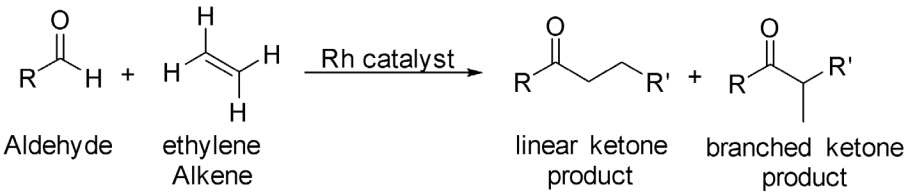
The final two chapters in this dissertation describe efforts to develop new methodology using products from AHF. New methodology adds new tools to the toolbox of reactions available to chemists. This work focuses on expanding a reaction named hydroacylation. Hydroacylation is a powerful reaction because it forms a carbon-carbon bond by adding an aldehyde across an alkene or alkyne, a molecule with a carbon-carbon double or triple bond respectively. Alkyne hydroacylation, as shown in Scheme 1.2, breaks the carbon-hydrogen bond of the aldehyde and forms a new carbon-carbon bond. Forming new carbon-carbon bonds is central to organic chemistry and chemists' ability to make more complicated molecules. Just like a woodworker has different options available to attach pieces of wood together (screws, glue, nails, etc.) and can choose based on the situation; chemists also need different ways to make carbon-carbon bonds. Hydroacylation is one of these methods, but the reaction does not yet work on all aldehydes and alkenes or alkynes. The scope of what does works in hydroacylation is relatively narrow, as many starting materials can react through a side pathway which results in the reaction stopping before it has finished. We aimed to use specific aldehydes made from our hydroformylation chemistry which would hopefully prevent this undesired reaction.



Scheme 1.2 Alkyne hydroacylation, the addition of an aldehyde across the carbon-carbon triple bond of an alkyne.

I began by looking at alkyne hydroacylation, as alkynes are generally more reactive in hydroacylation. However, alkyne hydroacylation was found to be largely unsuccessful. I discovered a different side reaction was occurring, preventing the desired hydroacylation. Between this side reaction and the difficulty in making the starting materials, I suspended efforts on this project.

Recently, I have been working on developing hydroacylation using ethylene, a gaseous alkene, instead of the alkynes. Molecules which were previously unreactive now show reactivity in this new system. It is currently unclear to us why we see this boost in reactivity, but we are currently investigating it. This reaction is a useful tool for making other molecules and we are collaborating with another research group to use this chemistry in a complicated synthesis.



Scheme 1.3 Alkene hydroacylation, the addition of an aldehyde across a carbon-carbon double bond of an alkene

1.5 Conclusion

In summary, my work has focused on expanding the asymmetric hydroformylation reaction in three main ways. First, improved ways to make our ligands allow the highly selective ligands to be accessed more readily, so more chemists can use asymmetric hydroformylation. Second, by demonstrating hydroformylation in flow, we hope that hydroformylation will be used in the pharmaceutical and other industries where flow chemistry is becoming increasing popular.

Finally, we are adding new tools to the organic chemist's toolbox with the hydroacylation reaction; we demonstrate further uses of the aldehyde product from hydroformylation.