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# Improving Accessibility of Asymmetric Hydroformylation through Ligand Libraries and Immobilization

By

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## 1.1 Introduction

Catalysis is a necessary tool to provide the chemicals needed for a modern society. It is estimated that 80% of all commodity chemicals involve a catalytic reaction at some point in their production.[1] Catalysis as a field is simply any chemical reaction that involves a catalyst, which is a compound that is not consumed in the reaction and changes the mechanism of the reaction, to one with a lower activation energy. In more practical terms a catalyst changes how chemicals react with each other. The figure below provides a graphical depiction of what a catalyst does. The height of the hill in the top plot is equivalent to the amount of energy required to take starting materials and turn them into product, which is reduced when using a catalyst. The bottom plots show the same thing but describe a reaction where two products are possible. If similar amounts of energy are required to make A and B, then similar amounts of A and B will be produced. If the catalyst was added that decreased the energy required to make product B, more product B gets produced over product A. Specific examples illustrate how this one principle effects many different reactions.

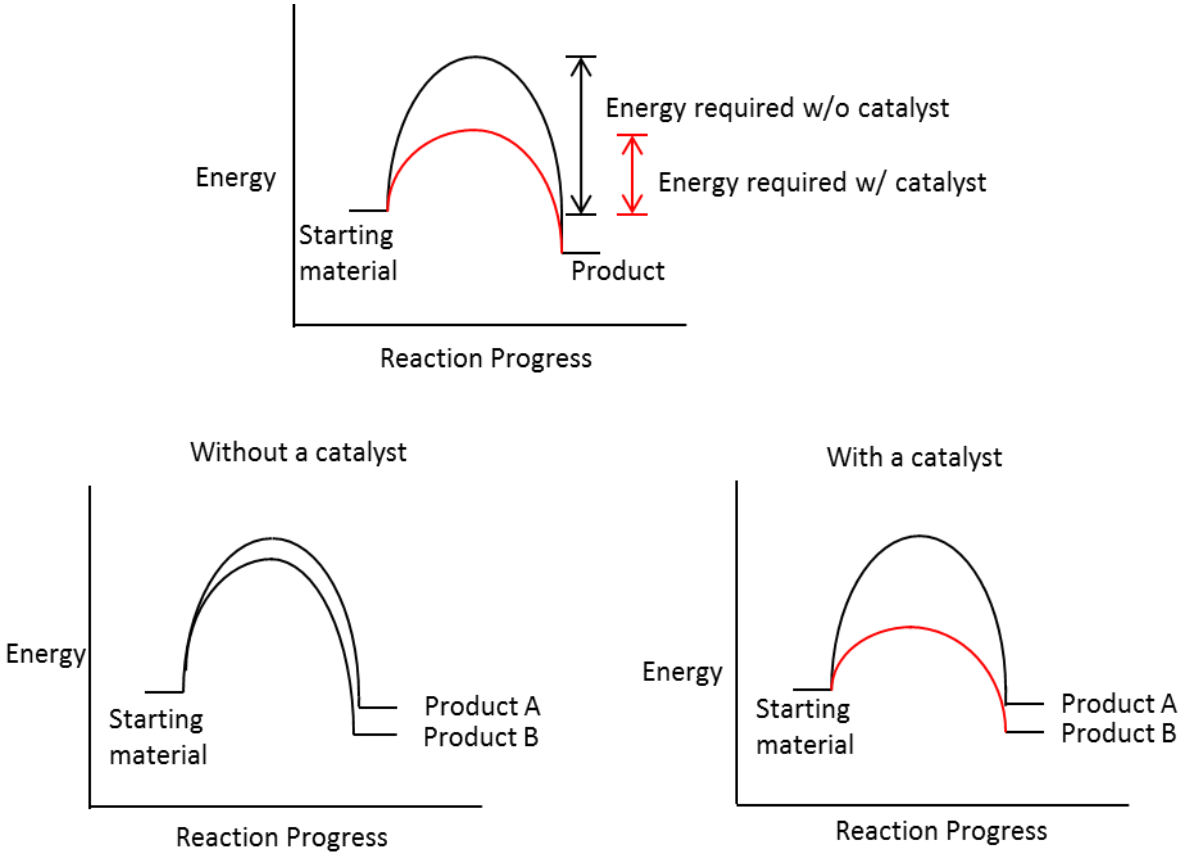



**Figure 1.1** Reaction diagram emphasizing how a catalyst reduces the amount of energy used in a reaction (top) and how a catalyst affects the selectivity between products A and B (bottom).

The fixation of nitrogen and hydrogen to form ammonia is critical to human life and an example of a reaction that is entirely dependent on catalysis. Biologically, bacteria are capable of performing this reaction using a metal containing enzyme, typically a complex containing iron(Fe) and molybdenum(Mo). Industrially, we are capable of doing the same reaction using an Fe based catalyst, though it requires extreme temperatures and pressures of these gases, upwards of 400°C and 200 atmospheres of pressure. While very energy intensive, this process has been in use for over a hundred years and is responsible for the increased supply of fertilizer for food production.

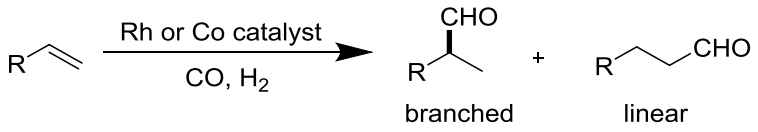
The production of plastics is heavily reliant on catalysts, not only to make certain reactions occur more readily, but also to control what types of materials are made. Low density polyethylene (LDPE) and high density polyethylene (HDPE) are two of the most ubiquitous polymers used to form many of the plastics we consume every day. LDPE is used to make goods such as plastic bags that are flexible, while HDPE is used to make milk jugs and other more rigid materials. More importantly, both are produced from the same chemical, ethylene, and the major difference in their production is that HDPE uses a catalyst (while LDPE is made using free-radical polymerization). The use of an appropriate catalyst (commonly referred to as Zeigler-Natta catalysts) allows for high selectivity as polymerization occurs, resulting in polymers with different mechanical properties.

These examples highlight how catalysts can provide selectivity for a reaction or activate molecules. Activation using a catalyst is particularly attractive when we consider the other methods used to produce chemicals. This includes harsh reaction conditions such as high temperatures and pressures, which increase the amount of energy and cost of the reaction or the use of specialized/activated starting materials. While these are often more straightforward alternatives to catalysis, these activated starting materials typically produce large amounts of waste. Non-catalytic methods are more commonly practiced in fine chemical synthesis such as pharmaceuticals, where they can still be profitable while using costly and waste-generating reactions.

Regarding waste in chemistry there is one clear trend, the larger the industry, the more efficient it has to be in terms of product produced versus waste produced. The two extremes of this are the oil industry and pharmaceuticals. Oil refineries have optimized how to use every segment of crude oil for some product or function while generating only a small fraction of wasted material, an economic necessity considering the scale involved. A small pharmaceutical company on the other hand will produce many times over more waste than actual product and continues to do so due to the larger margins on their products.

Transitioning to an increased number of catalytic reactions, reducing waste and cost of fine chemical synthesis, requires new catalysts to be developed. The pharmaceutical industry relies on reliable and well understood reactions to meet their goals, which often requires the rapid synthesis of large libraries of molecules in order to find one that meets the growing number of requirements for success. Thus for a catalytic route to be considered it has to be equally reliable and predictable.

*Asymmetric hydroformylation* (AHF) is one such reaction that could have a significant impact on the synthesis of fine chemicals and pharmaceuticals. This reaction takes a carbon-carbon double bond (olefin) and adds one equivalent of carbon monoxide and hydrogen gas to produce a new functional group, an aldehyde (CHO). This process is easily scaled up as huge quantities of linear aldehydes are produced annually for use in commodity chemicals such as plasticizers and detergents.




**Scheme 1.1** General hydroformylation reaction of a olefin to give a branched and linear aldehyde

To understand why improvement of this process is a problem for chemists and not engineers an understanding of how catalysts are modified or improved needs to presented. The addition of organic molecules with a strong affinity for a metal catalyst, or ligand, is the most common method used to control a reaction when selectivity is desired. For this reaction, the addition of a ligand has many effects: the selectivity between the

branched and linear aldehyde products (regioselectivity), preventing an undesirable reaction between the olefin and only hydrogen gas (chemoselectivity), as well as the *chirality* in the branched aldehyde (enantioselectivity).

Chirality or handedness of a molecule has to do with the three dimensional structure of that molecule. For example in Figure 1.2 below, using a branched aldehyde as an example, these two molecules are of opposite chirality, but identical in every other way. If you were to imagine you were the R group of that molecule, looking at the other atoms you were attached to, they would be in a different order. The importance of chirality however can be simplified to a few simple concepts. Molecules of a different chirality (typically designated as *R* or *S* in the example below) only behave differently when interacting with other chiral molecules. The relevance of this is two-fold; many biologically relevant molecules are chiral and this is a key feature of how proteins and enzymes interact, and therefore drugs; on top of that there are only a limited number of ways to control or set the chirality of a molecule, and this greatly adds to the cost. The purity of a chiral material is often reported as *enantiomeric excess* or % *ee*, and is the amount of one product in excess of the other. While it depends what step of a process it's involved in, 90% *ee* is often regarded as the breakpoint for being useful in chiral synthesis and >99% *ee* can often be used without further purification.

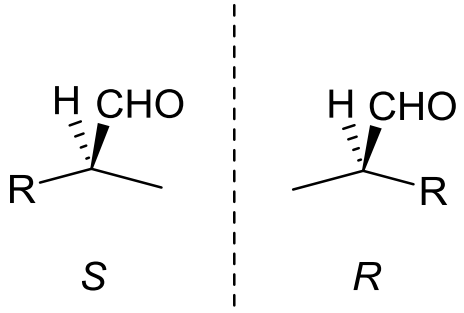
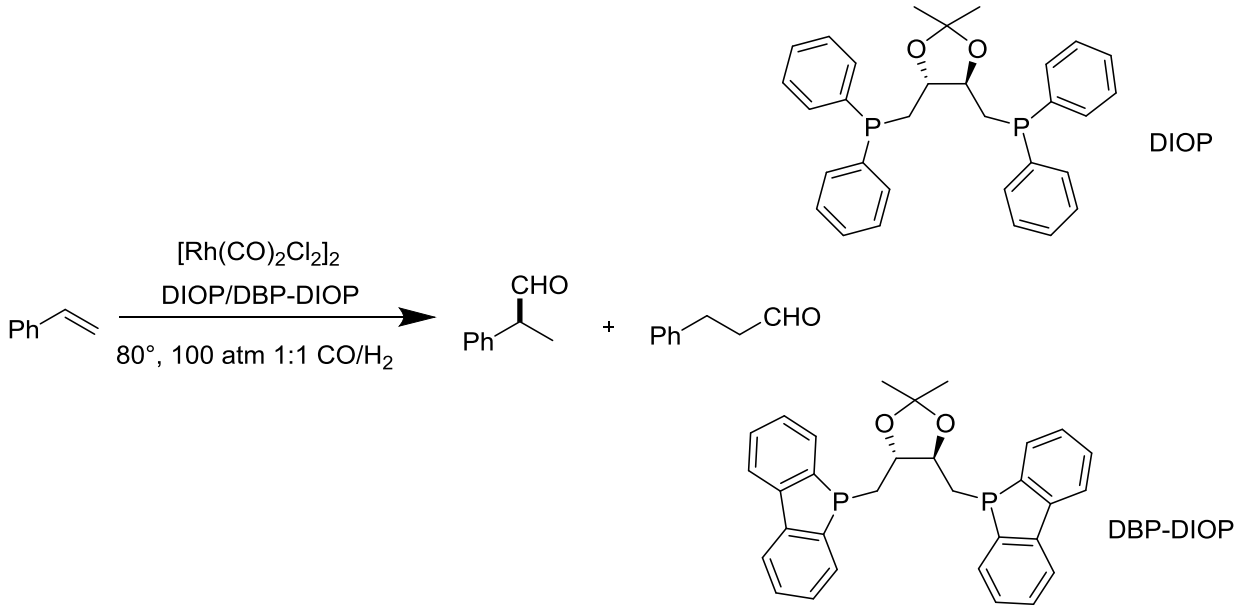



**Figure 1.2** Two enantiomers of a generalized branched aldehyde (where R is larger than methyl)

The connection between the importance of chirality and asymmetric hydroformylation is that the chiral branched aldehydes created from this process could impact the way drugs are made, by providing access to new chiral building blocks that go into drug design. Recently, when a round-table discussion of the prominent pharmaceutical companies was held, asymmetric hydroformylation was one of ten reactions identified as needing further exploration and incorporation into their standard procedures.[2] Obviously there are currently limitations to why this reaction is not already being used by these companies and these problems are the type that chemists are able to address. These problems include: controlling the selectivity for the desired product, demonstrating the range of products that can be accessed, and accomplishing all of this with as mild of conditions as possible while keeping the reaction fast. While high pressures are routinely handled at the commodity scale, the safety concerns of high pressures of synthesis gas are problematic in small, multi-purpose laboratories such as those used in the pharmaceutical industry. Now that we have identified the reasons why asymmetric hydroformylation can be useful, we can look at what has been done previously and what can still be explored.

### 1.2 Asymmetric Hydroformylation

Hydroformylation was first discovered in 1938 by Otto Roelen, and the first asymmetric hydroformylation reaction was carried out in 1974 by Tanaka using a rhodium catalyst. Phosphorous containing ligands were well known to bind to metal catalysts, modulating their selectivity, activity, and in this case, the chirality of the products. The two ligands examined, DIOP and BDP-DIOP, only imparted minor enantioselectivity on the desired aldehyde (1.2% and 44% *ee*, respectively), but demonstrated the utility of this reaction.[3]



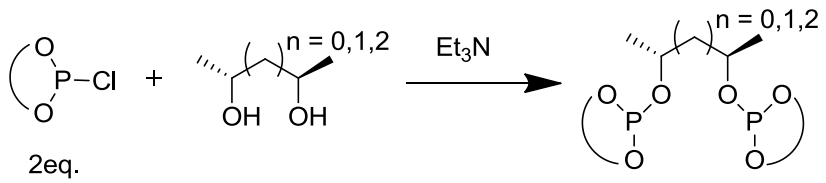

**Scheme 1.2** Asymmetric hydroformylation of styrene using DIOP/DBP-DIOP ligands

These two ligands and the resulting enantioselectivities underscore the difficulty in this reaction. These two ligands appear very similar, with the BDP-DIOP ligand being more rigid due to the added bond between the aromatic rings. There are a number of intermediate steps involved in this reaction, all of which cannot be directly observed or can be assigned as the step responsible for controlling the enantioselectivity of the product. Furthermore, trends or knowledge learned about one olefin may not necessarily apply to another.

Because of this intrinsic difficulty in improving enantioselectivity of asymmetric hydroformylation, many researchers have focused on ligands that are easily made and easily modifiable. This allows for the synthesis of libraries of chiral ligands that can be screened for intriguing results, a method quite common across asymmetric reactions in general. However, the added difficulty of trying to control regioselectivity for the branched or linear aldehyde makes this process difficult to optimize.

**1.3 Chiral Ligand Libraries**

The synthesis of libraries of chiral ligands is limited for many of the same reasons asymmetric synthesis is limited. There are only a limited number of ways of obtaining pure chiral materials. These materials must then be incorporated into the chiral ligand, within a reasonable number of steps so that these ligands can then be screened for reactivity. One type of easily modifiable ligands are *bisphosphites,* that are typically made from coupling chlorophosphites and alcohols, both of which have a readily available pool of chiral starting materials (Scheme 1.3).




**Scheme 1.3** Synthesis of a generalized bisphosphite ligand

One of the most well studied ligands for AHF is BINAPHOS, a mixed phosphine-phosphite.[4] An advantage of this ligand is the different structural components (phosphine, phosphite, and linker) can be easily substituted during

its synthesis, allowing for optimization. Multiple studies have examined changes to the substitution of the phosphine, the phosphite, and the linker between the two.

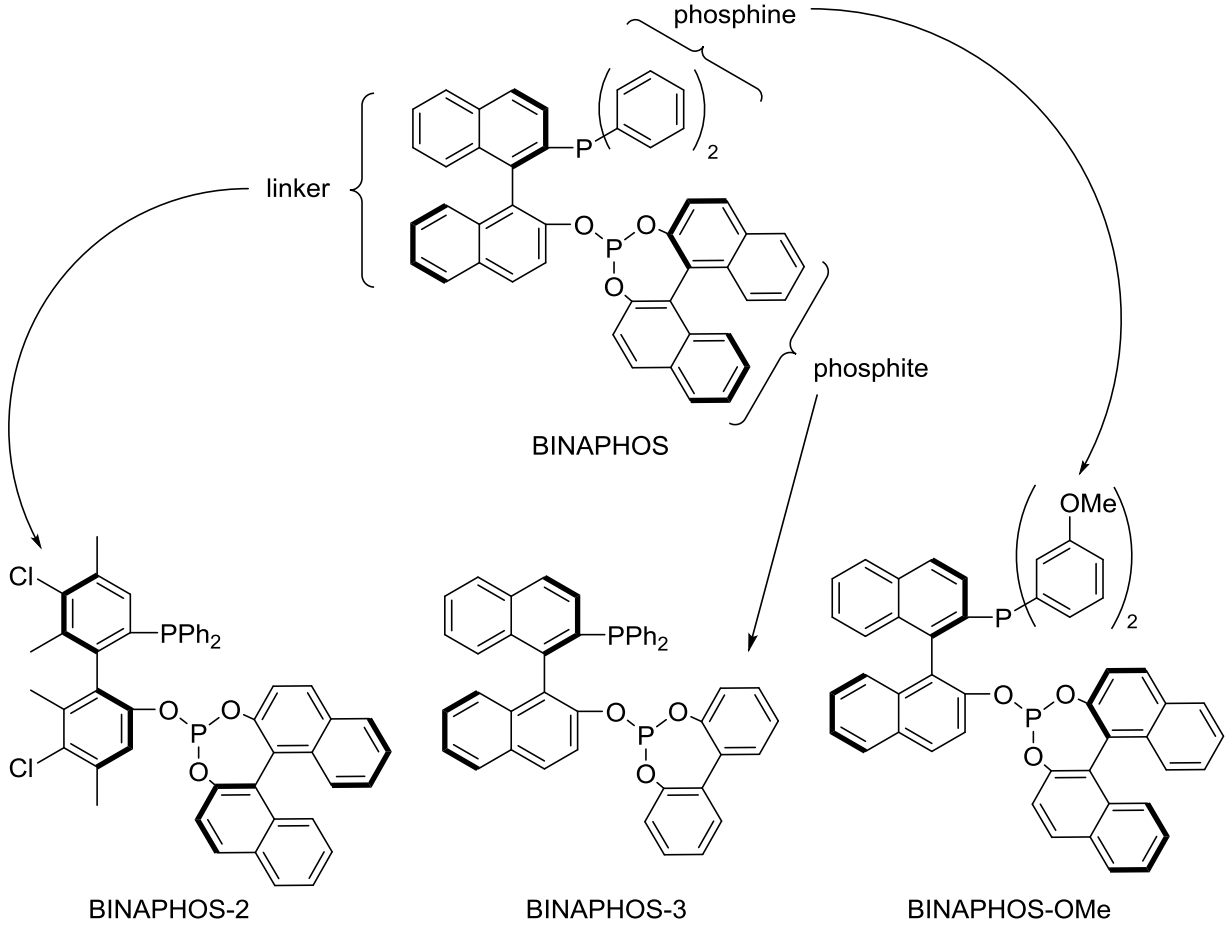
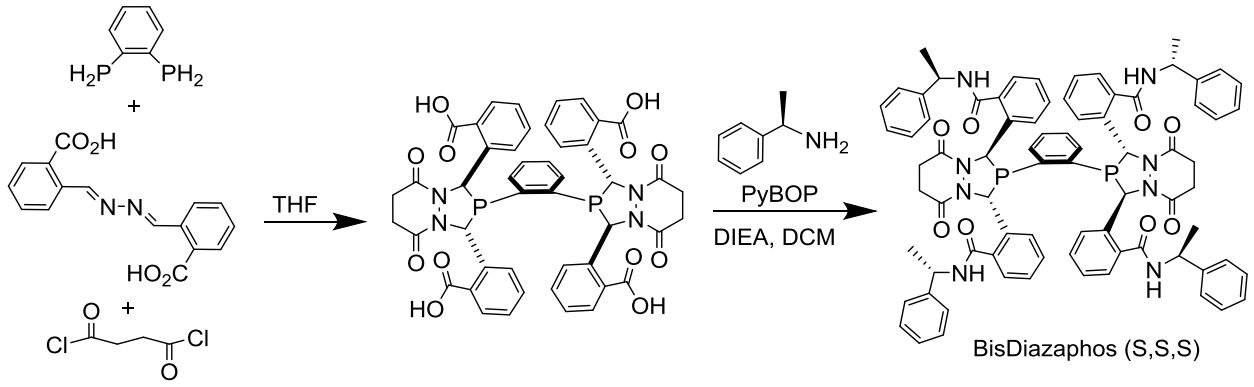



**Figure 1.3** Structure of BINAPHOS and several derivatives

Styrene hydroformylation was used to compare these different BINAPHOS ligands and how what effect each component has on the reaction. Using BINAPHOS-OMe compared to the original BINAPHOS ligand results in rates that are roughly twice as fast, demonstrating how phosphines with different electronic properties can affect the rate of hydroformylation. Selectivity on the other hand was determined to arise from a combination of the two chiral groups, the phosphite and the linker, as evidenced by BINAPHOS-3 which is less enantioselective than BINAPHOS and has only a chiral linker. BINAPHOS-2 gives the same high enantioselectivity (94% *ee*) as BINAPHOS with slightly higher regioselectivity (9.0:1 vs. 7.3:1).[5,6]

**1.4 Bisdiazaphospholanes**

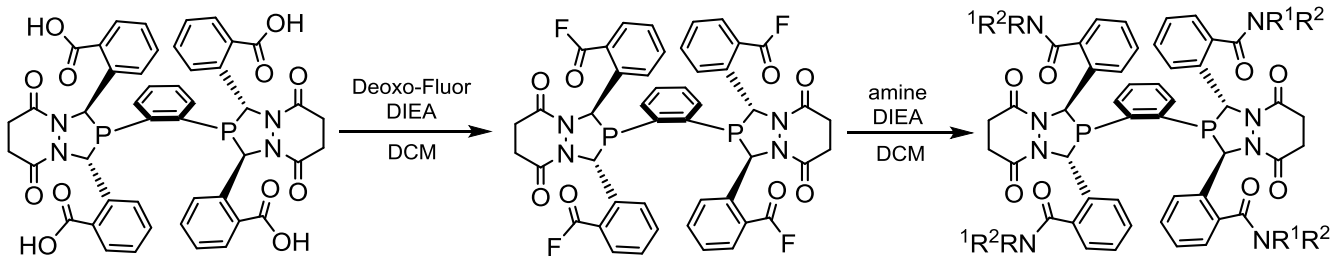
Bisdiazaphospholanes are another group of ligands used for asymmetric hydroformylation that have been developed with modularity in mind similar to the BINAPHOS type catalysts. Landis et al developed a small library of tetracarboxamide bisdiazaphospholanes using amide coupling to a tetraacid precursor. Several of these ligands were found to give rates competitive and faster than BINAPHOS.[7] BisDiazaphos(*S*,*S*,*S*) shown below resulted in the highest enantioselectivity for a series of commonly used olefins and has since been the focus of continued hydroformylation research.




**Scheme 1.4** Synthesis of tetraacid bisdiazaphospholane and tetracarboxamide BisDiazaphos (*S*,*S*,*S*)

**1.5 This work**

While BisDiazaphos (*S*,*S*,*S*) was previously identified as being highly selective, it was so successful that previous work was heavily focused on finding new reactivity instead of identifying what made it so selective. Using a modified procedure for the conversion of the carboxamide groups (Scheme 1.5), a small library of ligands similar to BisDiazaphos could be easily synthesized and compared. This procedure uses a new intermediate tetraacyl fluoride bisdiazaphospholane.



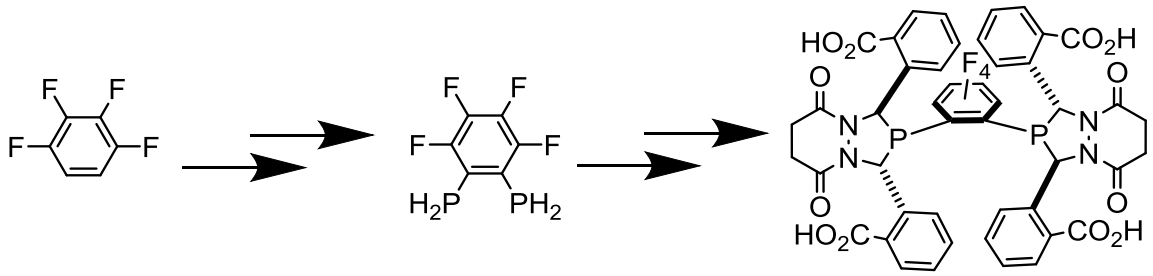

**Scheme 1.5** Synthesis of tetraacyl fluoride bisdiazaphospholane and generalized tetraamide bisdiazaphospholane

A library of thirteen bisdiazaphospholanes was developed along with Gene Wong and used to examine common olefins for AHF, along with BisDiazaphos (Chapter 3), to determine the effect of bulkier bisdiazaphospholanes. BisDiazaphos was found to be the most generally selective. For the AHF of dihydrofurans, BisDiazaphos gives moderate selectivities, which could be improved using bulkier bisdiazaphospholanes identified using this chiral library.

An unexpected consequence of the ligand screen was that it identified that moderate to high selectivity could still be achieved regardless of the carboxamide formed. Using one of these carboxamide groups to immobilize these catalysts on a solid support (Chapter 4) provides a method for separation and recycling of these catalysts. The ligands and catalyst used for these reactions is a significant portion of their overall cost; facile recovery of the catalyst by filtering away a solid is much easier and cheaper than other available methods. The impact of this is not only an economic one, in order to make this reaction more readily used over an alternative method it's not enough to demonstrate the catalyst works well, but also that it is easy to use. By attaching these catalysts to a solid it opens up possibilities in how it is used in a process.

Finally, even though bisdiazaphospholanes are highly modifiable, there are limits to what has been examined due to readily available starting materials. In order to try and develop bisdiazaphospholanes that were faster

than the current state of the art, a new primary phosphine, tetrafluorobisphosphinobenzene, was synthesized with the help of Ian Tonks.



**Scheme 1.6** Synthesis of fluorinated primary phosphine and bisdiazaphospholane

There are limited methods reported for the synthesis of similar primary phosphines, often involving hazardous metal hydride reagents. A synthetic route was established that used milder silane reagents though isolation of the desired compound remains problematic (Chapter 5). While preliminary experiments indicated that synthesis of fluorinated bisdiazaphospholanes was successful, the ultimate goal of using them for hydroformylation has not yet been carried out.

**1.6 References**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