Asymmetric Hydrogenations (Nobel Lecture 2001)

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Abstract: The start of the development of catalysts for asymmetric hydrogenation was the concept of replacing the triphenylphosphane ligand of the Wilkinson catalyst with a chiral ligand. With the new catalysts, it should be possible to hydrogenate prochiral olefins. Knowles and his co-workers were convinced that the phosphorus atom played a central role in this selectivity, as only chiral phosphorus ligands such as (*R*,*R*)-DIPAMP, whose stereogenic center lies directly on the phosphorus atom, lead to high enantiomeric excesses when used as catalysts in asymmetric hydrogenation reactions. This hypothesis was disproven by the development of ligands with chiral carbon backbones. Although the exact mechanism of action of the phosphane ligands is not incontrovertibly determined to this day, they provide a simple entry to a large number of chiral compounds.

Keywords: asymmetric catalysis; asymmetric hydrogenation; DIPAMP; Monsanto L-DOPA process; Nobel lecture; P ligands; rhodium

1 My Biography

I was born in Taunton, Massachusetts on June 1, 1917, but I actually grew up in nearby New Bedford. My family background was heavily slanted toward business and seafaring matters. I can't think of any relatives that ever went into science. My family gave me the best in education. To my father, business was the highest calling, but to my mother, medicine was the top profession. She would probably have gone to medical school if she had been born in a more enlightened era.

I went to boarding school at Berkshire in western Massachusetts, definitely the most beautiful part of the state. I'll never forget the fall colors on the Berkshires. In those days I was terrible at athletics and never made a team, but quite easily led my class in academics. I was particularly good at math and science. I also got a good lesson in New England thrift. To get free ice for our physics experiments, we had to wait until it snowed.

On graduating, I was easily admitted to Harvard. In that era, all one had to do was pass the College Board exams. If anyone in my family went to college, that was where he went. My father spent a year there and quit to go into the textile business. At this point I was strongly advised that I was too young socially to go to college, so I took a second senior year at Andover, another boarding school. At that time many students did this. At Andover, I took my first chemistry course from a teacher named Bushy Graham and was fascinated by the subject. I remember him trying to explain Avogadro's number, and his discussion of the dangers of hydrogen and oxygen. At the end of the year, I took a competitive exam and won my first prize, the $50 Boylston Prize in Chemistry.

That summer I took a cruise on a 75-foot schooner with no engine, and sailed from Gloucester, Massachusetts to Norway. We sailed around the Baltic and ended up at Stockholm. I didn't think of it at the time, but we spent most of three weeks on the north Atlantic with no contact at all with the outside world. Today, one is always in touch with home base, even if one goes to the South Pole or the Moon. Memories of this sailing trip have always been vivid. On one instance I was mistakenly arrested in Tallinn, Estonia and got a ride in the paddy-wagon. Later we were released without comment. Little did I think that one day, years later, I would be returning to Stockholm to share the Nobel Prize in Chemistry.

At Harvard I majored in chemistry with a strong inclination for math. I took the minimum of humanities. I was told I'd be a natural for physical chemistry but taking organic with Louis Fieser changed my mind. It was there I got my introduction to optical isomerism and the tetrahedral carbon atom. At Harvard, competition was fierce and I always got a solid B, but not the straight As of many of my class mates. These were the days when most got a gentleman's C.

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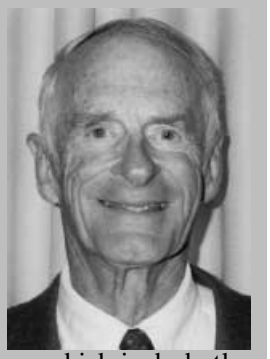


Dr. William S. Knowles received an AB from Harvard in 1939 and a Ph.D. from Columbia in 1942, under Professor Robert C. Elderfield, in synthetic organic chemistry. He went to Monsanto in 1942 and did a company-sponsored post-doc with Professor Robert B. Woodward at Harvard in 1951. He has been involved in a variety of synthetic problems, which include the total synthesis of steroids and Chloramphenicol. Later in his career, he became interested in selective hydrogenation reactions. He retired from Monsanto in 1986, after many years as a Distinguished Science Fellow. He now lives in St. Louis, Missouri, in the winter and Jackson Hole, Wyoming, in the summer. Amongst the many awards and prizes that Knowles has received are the IR 100 Awards for Asymmetric Hydrogenation (1974), the St. Louis ACS Section Award (1978), the Monsanto Thomas and Hochwalt Award (1981), the ACS Award for Creative Invention (1982), and The Organic Reactions Catalysis Society - Paul N. Rylander Award (1996). In 2001 he shared the Nobel prize for chemistry with R. Noyori and K. B. Sharpless.

On graduating in 1939, I was strongly advised to go elsewhere to graduate school. I went to Columbia with Professor Elderfield and worked on making simple analogues of the cardiac aglucones. These were tested at Eli Lilly for cardiac activity. Bob Elderfield was at his best when he talked steroids at Rockefeller Institute. In parallel with Nobel's experience, I too had an explosion. Mine came when distilling diazomethane. No one was hurt, but a bottle of intermediate that I had labored on for months was destroyed.

In those days, Professor Elderfield spent a lot of time away on the antimalarial project in the military, and we were on our own a lot. Professor Nelson Leonard, long at the University of Illinois in Champagne, was in our research group. Later he consulted at Monsanto.

New York was an exciting place to be in those war years, and my draft board forced Columbia to push me out sooner than would ordinarily happen. In those days, industry would hire any chemist that could breathe. In 1942, I started in Dayton, Ohio, at the Thomas and Hock Walt laboratories, which had recently joined Monsanto. Most of my assignments were pretty mundane, such as making super-pure hexamethylenetetramine, to be used for making the explosive cyclonite.

In 1944, I was transferred to St. Louis to work on plasticizers and intermediates. We did make a lot of benzyl benzoate as a mite repellent for soldiers clothing. We later had a DDT project which never got into production until the war was over. More interestingly, we had a synthetic process for vanillin but lost out to lignin as a way to get that desirable molecule. In those days we did get involved with the custom manufacture of the antibiotic Chloramphenicol and made 10 – 15 000 lb before it was taken off the market because a very small percentage of patients developed aplastic anemia. At the time my dog had a fungus on her chest that wouldn't heal and resisted treatment. I made an ointment with our product and it cleared up in two days. She lived to 17 years.

Shortly after the war, the discovery that cortisone might become a large-volume pharmaceutical caused Monsanto to engage Professor Woodward, with the hope of commercializing his synthetic approach. I was selected to join this effort since I had a steroid background. Actually, I got to spend nine months in his lab at Cambridge on this total synthesis. The experience working with the "great man" is one I'll never forget. For the first three months in his lab, he would come in at noon and say, "Let's go to Schraft's". We would spend an hour or more scribbling chemical structures on the menu or place mats. His phenomenal memory was beyond anything I'd ever seen. In those days he never kept a file or wrote a reference. He'd just say "Look on page so-and-so in Beilstein and you'll find something on that". He lost some of this ability as he grew older and it bothered him. He really hoped Monsanto would commercialize his steroid synthesis, but the Mexican yam, with its high content of diosgenin, eventually killed our effort. Our program for cortisone got fairly well along. We made a few milligrams of racemic cortisone and we had resolved an early intermediate, which we intended to carry through to the real thing. It was made too complex to compete with the lowly yam.

Later in the fifties I got involved in kinetic studies, and used my long-forgotten math background. These studies led to improvements in several of our processes by doubling production with little or no additional capital. In those days, industry was hungry for chemicals and much effort was spent to get more out in the same equipment.

Monsanto had developed a separate line of advancement for those who wished to stay in technology, and I rose to the top of that ladder before I even thought of asymmetric hydrogenations. I was one who liked to work with my hands as well as my brain. Chemical research in the lab was ideal for filling this need. The work on the asymmetric project, which started in the mid-1960s, is the subject of my lecture. Obviously, I kept active in this area[1] until I retired in 1986, and continued in a consulting capacity for several years after.

On the home front, we had purchased a cabin in Jackson Hole, Wyoming, 25 years ago, and have spent summers and some winter skiing time there ever since. It is there that our four children and four grand children

often meet. On several occasions, Professor Kagan has visited us there and we've been able to talk asymmetric hydrogenations. I have always loved doing things outdoors, such as fly-fishing, hiking, and biking. When things are going wrong, I find splitting wood quite therapeutic.

2 The Development of Chiral Phosphane Ligands

Actually, this account is the story of the genesis of an invention. The inventive process is not clearly understood, but one factor that seems to be important is to have a heavy infusion of naivety. That is why, so frequently, it is not the experts that do the inventing, but they are the ones who, once the lead is established, come in and exploit the area. Our work is an excellent illustration of this phenomenon.

In the study of any of the life sciences, chiral compounds are important. In the past when chiral compounds were needed, chemists have had to use biochemical processes or make racemic mixtures followed by laborious resolutions. In industry the problem is particularly severe, since resolution, with its numerous recycle loops and fractional crystallizations, is an inherently expensive process. Thus, large-volume products such as monosodium L-glutamate, L-lysine, and L-menthol have been made traditionally by biochemical routes, even though efficient procedures are available to make their racemic forms.

In the early 1960s we became aware of this problem when we made a paper evaluation of a monosodium glutamate process. The racemic mixture was easy to obtain, but by the time we had resolved, the projected costs doubled, even though we racemized and recycled back the unwanted D isomer. It looked as though, if one wanted to beat "the bug", it would be necessary to have a catalyst which would direct the reaction to give a predominance of the desired isomer, when an asymmetric center was formed. For this purpose, the 100% efficiency of enzymes would not be needed to have something of real value.

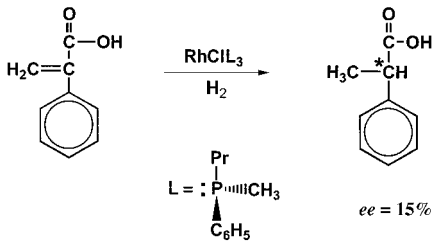
At this point in time I was aware of the extensive studies by Akabori, which started in the mid-1950s, in which heterogeneous catalysts such as Raney nickel and palladium were modified with a chiral agent. The asymmetric bias was always too small to be of preparative interest. All these thoughts remained fallow for several years.

In the interim, I became part of a program for doing exploratory research. I was given a new Ph.D. student to train for a year before going into more pressing things. Industrial labs are always wrestling with the problem of how much undirected research they should do and this was just one of many ways to achieve this goal. I had been through several new employees on a number of projects, when I became aware of Professor Wilkinson's discovery of chlorotris(triphenylphosphane)rhodium, $[RhCl(PPh_3)_3]$, and its amazing properties as a soluble hydrogenation catalyst for unhindered olefins. Homogeneous catalysts had been reported before, but this was the first one that compared in rates with the well-known heterogeneous counterparts.

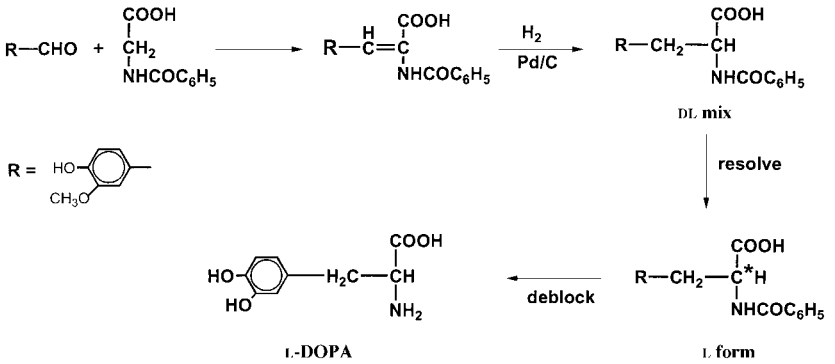
A second development in the mid-1960s was the development of methods for making chiral phosphanes by Mislow and also by Horner. Phosphorus, like carbon, is tetrahedral and, when four different substituents are attached, can exist in D and L forms. In the case of phosphanes, the lone pair of electrons counts as a substituent. Earlier, it was thought that phosphanes might pyramidally invert like their nitrogen analogues, but Mislow and also Horner showed that they were stable at room temperature. They turned out to have a half-life of a couple of hours at 115 °C. For our contemplated hydrogenations, this stability would be quite adequate. Then the basic strategy was to replace the triphenylphosphane of Wilkinson's catalyst with a chiral counterpart and hydrogenate a prochiral olefin. This experiment was performed on α-phenylacrylic acid using the known chiral methylpropylphenylphosphane, and gave an enantiomeric excess (ee) value of 15% (Scheme 1).

This modest result, of course, was of no preparative value, but it did establish that the hydrogenation technique gave a definite asymmetric bias. In order to achieve this bias, the hydrogen atom, the ligand, and the substrate all had to be on the metal at the same time. Furthermore, we established that the hydrogenation was accomplished in solution and not from some extraneous rhodium plating out in our reactor. The inherent generality of the method offered almost unlimited opportunities for matching substrate and catalyst for moving toward the goal of achieving efficient results.

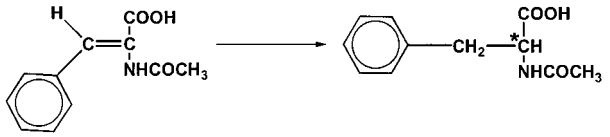
We were not alone in having this idea, but were the first to report on it. I think it was discussed in the question session after Wilkinson's lecture on his soluble hydrogenation catalyst at a Welch Foundation conference. Horner, shortly after our paper, reported even more modest results with the same methylpropylphenylphosphane on a substituted styrene. There were



Scheme 1. First use of a chiral ligand in the hydrogenation of an olefin.



Scheme 2. The Hoffman–LaRoche L-Dopa process.



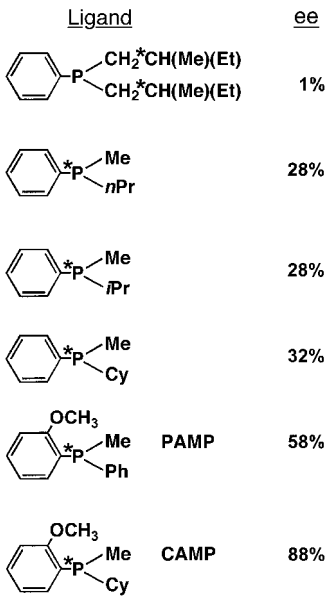
Scheme 3. Test reaction for the structure – activity-relationship study.

others using other phosphanes with uninteresting results. Seemingly, we may have been the only ones naive enough to pursue this lead in depth. Actually there was definitely nothing in the literature to encourage us to proceed further. A mechanistic study showed that just two ligands were all that were needed and not the three, as in Wilkinson's structure. α-Phenylacrylic acid worked better as a triethylamine salt, but even so we never got good results with this system.

While groping in this area, another seemingly unrelated development appeared, which played an important role in our project. This was the discovery that a fairly massive dose of L-DOPA was useful in treating Parkinson's disease. It created a sizable demand for this rare amino acid. Because of Monsanto's position in vanillin, which provided the 3,4-dihydroxyphenyl moiety, we found that they were custom-manufacturing a racemic intermediate, which Hoffman–LaRoche resolved and deblocked to give L-DOPA. The synthesis, which closely followed the Erlenmeyer azlactone procedure described in *Organic Syntheses*, went by way of a prochiral enamide, which was hydrogenated to give blocked DL-DOPA (Scheme 2). This enamide offered a golden opportunity for commercializing this burgeoning technology. We soon found out that these prochiral enamide precursors of α-amino acids hydrogenated much faster than one would expect for such a highly substituted olefin. Even so, the chiral results were only 28%, but the stage was nicely set to make a structure versus activity study. We had a good test reaction in Scheme 3, in which we used the simple phenylalanine intermediate.

We also had a good test for efficiency, since all we had to do was run rotations on a properly diluted reaction mixture. Our job was to find a phosphane of the proper structure. Early on we tried phosphanes with a chiral alkyl side-chain, and the asymmetric bias was barely detectable. We felt strongly that, if one wanted to get high ee values, the asymmetry would have to be directly on the phosphorus. That is where the action is.

Initially, we varied the alkyl groups on the phosphorus, by converting the normal propyl to the more hindered isopropyl or cyclohexyl, but ee values still remained in the range of 28 – 32%. Our first real variation was to introduce the *o*-anisyl group. This should provide some steric hindrance as well as a possible hydrogen-bonding site. Furthermore, the ether linkage would be stable enough to survive the rigors of a phosphane synthesis. In those days, our small group was in continuous contact and what we decided to do was arrived at by informal consensus. I hate to admit it, but it's much easier to invent in a small, under-funded group. Being lean and hungry is conducive to invention.



Scheme 4. Phosphane ligands for asymmetric hydrogenation.

We made methylphenyl-*o*-anisylphosphane (PAMP) and got ee values, after playing with hydrogenation conditions, up to 58%. Further modification of this molecule gave us methylcyclohexyl-*o*-anisylphosphane (CAMP); this change gave up to 88%. These results are summarized in Scheme 4.

It all seems too easy and simple, but this was the first time ever that anyone had obtained enzyme-like selectivity with a man-made catalyst! Never in our wildest imagination did we think a structure versus activity study would converge so quickly to a product with commercial potential. CAMP was our sixth candidate. As I look back from this perspective, I don't think that even we were emotionally equipped to realize what we had done. Here, with this simplest of molecules (CAMP), we had solved one of the toughest synthetic problems. For the past hundred years, it had been almost axiomatic among chemists that only nature's enzymes could ever do this job.

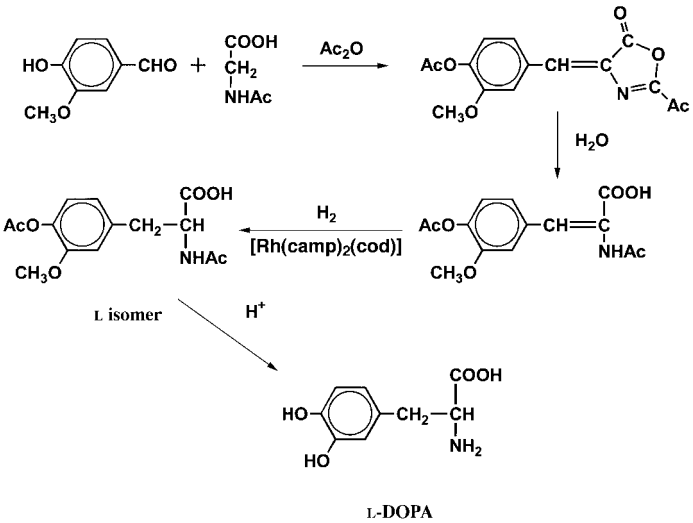
Our patent department always considered our invention was the use of chiral phosphanes with rhodium but, of course, without finding PAMP and CAMP, we would have had only a new way of doing what had been done before. The lawyers felt that this first result wasn't much, but that we could very rapidly come up with an improved embodiment, and in this they were unusually prescient.

We have called these catalysts man-made but this is not strictly true. We have not violated the general principal that, if you want chiral molecules, you will have to get them with the assistance of previously formed natural products. Our asymmetry was obtained from the (–)-menthol used in the chiral phosphane synthesis, but being a catalyst, a small amount of (–)-menthol could lead to a large amount of chiral product. CAMP worked equally well for the L-DOPA precursor (Scheme 2), and it made no difference whether the amine-blocking group was benzoyl or acetyl.

At this point, we were strongly motivated to develop a commercial L-DOPA process. It is a rare thing that the emergence of a substantial demand for a chemical is so closely timed with an invention for a new way of making it. Our management reluctantly increased our manpower but didn't really believe we could do it until the hydrogenation was done on a 50-gallon scale without incident.

Since CAMP was already good enough, we stopped exploring phosphanes and concentrated on converting this unique hydrogenation into large-scale production. This process was helped when another fortuitous event occurred. Monsanto decided to get out of its first product, saccharin, and an idle plant was now available for this kind of fine-chemical manufacture. These things were then put together to give our simplified L-DOPA process, which started with vanillin (Scheme 5).

The chiral hydrogenation was the simplest step in the sequence. We started with a slurry of prochiral olefin in an alcohol-water mix and ended with a slurry of chiral

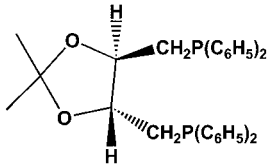


L-DOPA

Scheme 5. Monsanto L-DOPA process.

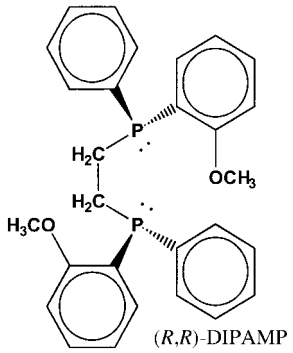
product which could be filtered, to leave the catalyst and residual racemate in the mother liquor. We could use an in situ prepared catalyst, but it was more convenient to use a solid air-stable complex of the type $[Rh(1,5\text{-cod})L_2]^+BF_4^-$ (cod = cyclooctadiene). These catalysts were fast, so that mole ratios of substrate:catalyst were about 20000:1. Thus, even this super-expensive complex was used at close to throwaway levels.

Even in the best case, some racemic product is made and must be separated. This separation is easy or hard, depending on the nature of the racemate. If the racemic modification has a different crystalline form than pure D or L, then separation of the pure excess enantiomer will be inefficient. If one achieves a 90% ee value, then it is possible to get out easily only 75 – 80% pure enantiomer. With lower ee values, the losses become prohibitive. For such a system, a catalyst of very high efficiency must be used. Unfortunately, most compounds are of this type; their racemic modifications do not crystallize as pure D or L forms. If, on the other hand, the racemic modification is a conglomerate or an equal mix of D and L crystals, then recovery of the excess L form can be achieved with no losses. Since the L and DL forms are not independently soluble, a 90% ee value easily gives a 90% recovery of pure isomer. In our L-DOPA process, the intermediate is such a conglomerate and separations are efficient. This lucky break was most welcome. If one thinks back, ours was the same luck that Pasteur



83% ee

(*R*,*R*)-DIOP, Kagan



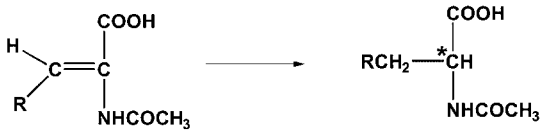
95% ee

encountered in his classical tartaric acid separations, 150 years ago.

At the time of our initial commercialization, we learned of a new, efficient ligand invented by Kagan et al., which he called DIOP. This was a chelating bisphosphane ligand made from tartaric acid with chirality on the carbon backbone and it gave results comparable to CAMP. We had hypothesized that, to get good results, one needed chirality directly on the phosphorus atom. It made sense, but Kagan showed us to be totally wrong. It is most appropriate that this invention using tartaric acid should have come from a Frenchman in the land of Louis Pasteur, who, of course, was the one who got it all started. Kagan's discovery was the wave of the future for a whole series of bisphosphane ligands with asymmetry on the chiral backbone.[2]

Shortly afterwards, we came up with our own chelating bisphosphane ligand, by dimerizing PAMP by another Mislow procedure. We called it DIPAMP, and chirality resided on the phosphorus atom. DIPAMP worked at about 95% ee in our L-DOPA system and we quickly converted our commercial process to use it. Part of our motivation to make a quick change was that DIPAMP was easier to make than CAMP, and, in addition, it was a nice, crystalline air-stable solid.

When we started this work we expected these man-made systems to have a highly specific match between substrate and ligand, just like enzymes. Generally, in our hands and in the hands of those that followed us, a good candidate has been useful for quite a range of applications. This feature has substantially enhanced their value in synthesis. It turned out that these chiral hydrogenations, as applied to enamides, were entirely general, especially with DIPAMP. Here it should be pointed out that these prochiral enamides can exist in both *E* and *Z* forms. The *Z* form hydrogenates efficiently whereas the *E* form hydrogenates less efficiently. Both give the same product. Fortunately for us, the base condensation used in their preparation gives us only the desirable *Z* form (Scheme 6).[3] The R group can be just about anything except -COOH. It's easy to see how our rhodium catalyst could become confused with two carboxy groups so close together. Thus, aspartic acid is best made by an enzymatic process.



Scheme 6. Generality for *Z* enamides.

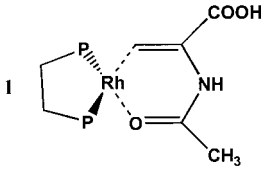
Table 1. Important amino acids produced by asymmetric catalysis.

Product	ee[a] value [%]
L-DOPA	94
L-phenylalanine	96
L-tryptophan	93
L-alanine	90
L-lysine	85

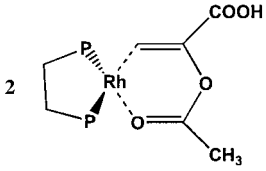
[a] ee = enantiomeric excess.

However, almost all the known familiar α-amino acids can be prepared this way since, at least in principle, an enamide precursor is possible. Evidently the polar carboxy and amide groups overwhelm any variation in the R group. Also, the carboxy- and the nitrogen-blocking group can be varied extensively. Once again lady luck was with us, since if we had a choice where the catalyst would be useful, we couldn't have selected a more important area than the α-amino acids, the building blocks of the proteins.

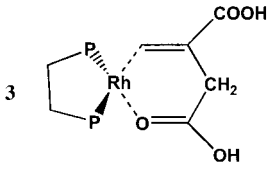
A few of the more important ones are listed in Table 1. Our colleagues at Hoffman LaRoche have added about a dozen more nonaromatic members to this list using DIPAMP. This generality can be extended to a variety of enol esters and itaconic acid derivatives. Evidently what is required is the ability to chelate with the metal. Thus, the nitrogen atom can be replaced with an oxygen atom or a methylene group (**1**–**3**).[3]



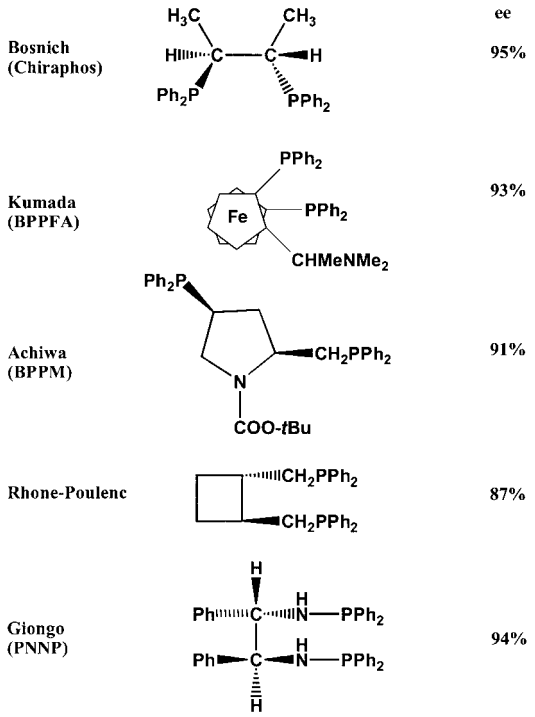
enamides



enol esters



carboxylic acids



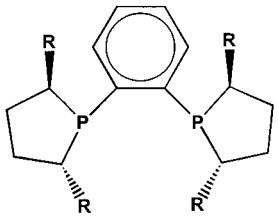
Scheme 7. Phosphane catalysts used in the catalytic hydrogenation of 2-α-acetamidocinnamic acid.

One compound which did not work well in our system was our original model, α-phenylacrylic acid. A number of these arylpropionic acids have value as nonsteroidal antiarthritics. Here, as is the usual case, only one enantiomer is active and thus a process to make one isomer directly was needed. We tried hard to solve this problem, even using ruthenium-ligand systems, but without success. It took Professor Noyori with his BINAP-ruthenium complex to solve this problem.[4] I'm afraid this is just another example in the history of invention. The one who makes the first discovery seldom makes the second. On a grander stage, this may explain why there are so few Nobel Laureate repeats.

Soon after the appearance of DIOP and DIPAMP, a considerable number of bisphosphane ligands with chiral carbon backbones were found. All of these worked well with the same enamides and on related oxygen analogues. A few of these are shown in Scheme 7.[5]

It is interesting, that over the years, we made a lot of chiral phosphanes but never got a good one without our beloved *o*-anisyl group. Others have used it in connection with their bisphosphanes but it gives them no particular advantage. Thus, the choice of suitable structures is still pretty much guesswork.

In our hands, DIPAMP was by far the most versatile ligand, and remained supreme for enamides for many years. Later, in the 1990s, an improved bisphosphane ligand was reported by Burk, then at DuPont, to which he gave the name DuPHOS.[6]



99% ee

R = Me or Et

DuPHOS, Burk

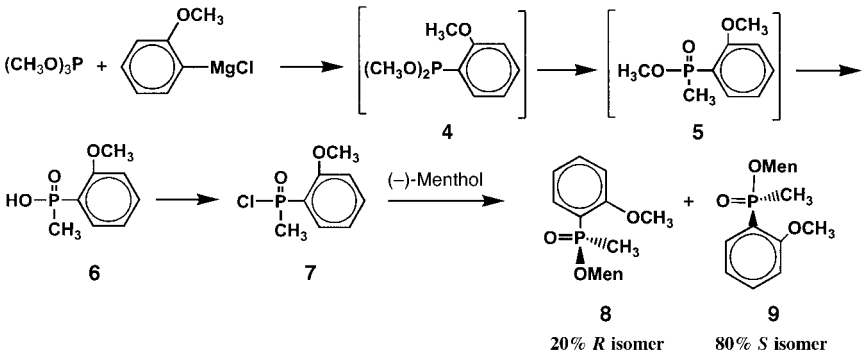
This bisphosphane ligand, complexed with rhodium, gave fast hydrogenations of enamides with efficiencies of 99%. Once again, the next invention was made by someone else. These high ee values can be important where the racemate is not a conglomerate.

3 Synthesis and Properties of the Phosphanes

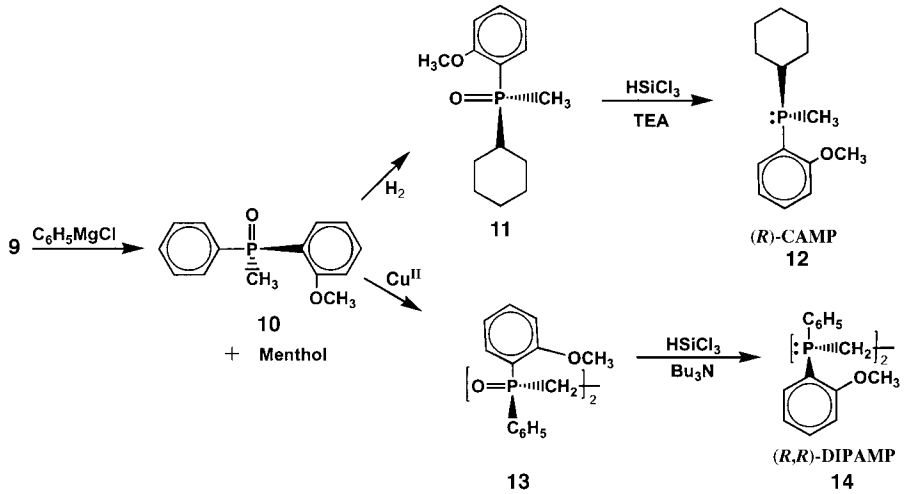
The key to asymmetric hydrogenation is the structure of the chiral ligand. The phosphanes are prepared by a multistep route and are quite expensive, but fortunately one mole of catalyst will make many thousands of moles of product. Even so, the ligand must be made from cheap starting materials. Some economy of scale is achieved by making a ten year supply in a few plant-size batches. At first, CAMP was prepared from phenyldichlorophosphane via Mislow's menthyl ester, by introducing the *o*-anisyl group last. Unfortunately, the desired isomer was produced in minor amounts and, to correct this situation, it was necessary to reverse the order of addition of the aryl groups. The sequence starting with trimethyl phosphite is outlined in Scheme 8 and Scheme 9.

A large excess of trimethyl phosphite was needed to get good yields of monosubstituted product **4**. In the sequence **4**→**6**, only the nicely crystalline phosphinic acid **6** was isolated. The fact that the acid chloride **7** can be converted to an 80:20 mix of (*S*) and (*R*) isomers means that the menthol preferentially reacts with one form while the other isomer rapidly racemizes. Thus, the catalyst preparation was greatly facilitated by an asymmetric synthesis of its own directed by (−)-menthol.

Another advantage of the sequence in Schemes 8 and 9 was that CAMP and DIPAMP were prepared from a common intermediate (**10**) and no new resolution procedure needed to be worked out. Thus, the change to an improved ligand could be done with minimum dislocation, both at the synthesis and the utilization end. It is a clear advantage of catalytic processes that it is often easy to shift from the old to the new.



Scheme 8. Synthesis and resolution of the menthyl ester. men = menthyl.



Scheme 9. Improved synthetic procedure for CAMP and DIPAMP.

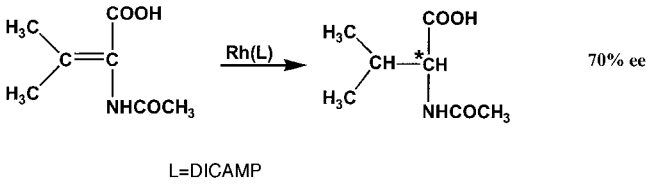
CAMP was prepared by a selective hydrogenation reaction of **10** (Scheme 9) using a rhodium-on-carbon heterogeneous catalyst. It was important to monitor the reaction closely and stop before the anisyl ring started to hydrogenate. Reduction with trichlorosilane and triethylamine (TEA) gave (*R*)-CAMP **12**, with inversion. The (*R*)-menthyl ester **8** could also have been used in this sequence if the last step was run with pure $HSiCl_3$; this modification results in retention of configuration.

In the case of DIPAMP the copper-coupling step, run with lithium diisopropylamide and $CuCl_2$, did not affect the stereochemistry. However, only the base-promoted reaction with trichlorosilane to give a double inversion was applicable. In this case, an empirical study showed that use of tributylamine minimized formation of the *meso* product.

In principle, the menthol recovered in Scheme 9 could be recycled, which makes the usage of chiral agent derived from nature truly minimal, but in practice it has not been worth the effort. More useful is the recovery by hydrolysis of the phosphinic acid from the (*R*)-menthyl ester (Scheme 8).

In contrast to CAMP, DIPAMP is a stable solid that melts at 102 °C. Heated at 100 °C, it has a half-life of 3–5 h. This racemization was somewhat faster than Mislow's phosphanes, which did not invert appreciably until 10–15 °C higher. The rate was reasonable, if one considers that inversion at either end destroys chirality. DIPAMP complexed to rhodium must invert much more slowly because efficient, asymmetric hydrogenations have been obtained at 95–100 °C. For the sake of convenience, particularly on a large scale, a solid complex was made by reacting two equivalents of phosphane with one equivalent of $[Rh(cod)Cl]_2$ in alcohol. This air-stable orange solid $[Rh(bisligand)(cod)]^+BF_4^-$ made a most suitable catalyst precursor.

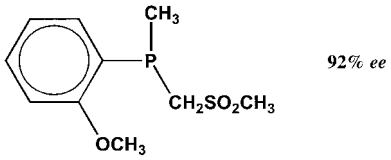
We have used the resolved menthyl ester **9** to make a variety of phosphane ligands. The first and most obvious use is to convert DIPAMP into DICAMP. You will recall that, in the monophosphane series, the exchange of a phenyl group for a cyclohexyl group gave an enormous increase in selectivity. Not so with DICAMP, which gave only 60–65% ee in our enamide systems. It was, however, our best candidate for preparing the more



Scheme 10. Synthesis of valine by use of the DICAMP ligand.

hindered amino acid, valine, for which the other systems were very poor (Scheme 10).

In the monophosphane series, we only found one ligand that was marginally better than CAMP. This rarity of good monophosphanes shows how lucky we were to find an efficient one on almost the first try. We never found a good candidate without the *o*-anisyl group. This is contrasted with all our colleagues in other labs who never found much benefit from it.



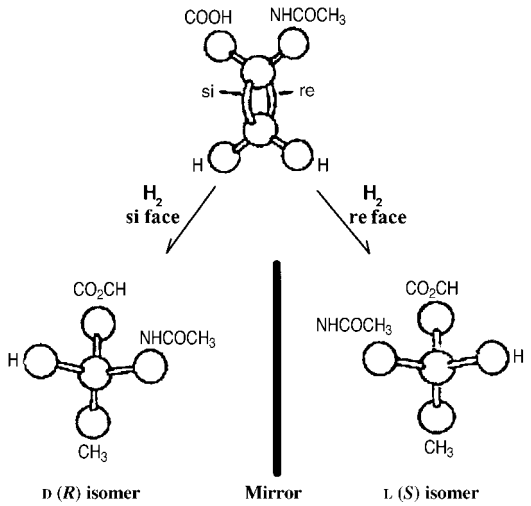
We could sulfonate DIPAMP and make it water soluble. It worked fine but gave only 85% ee which, by current standards, is too low. I winced when I came in one morning and saw our valuable DIPAMPO being treated with concentrated sulfuric acid, but it worked. This exploratory effort suffices to show that, as one might expect, the catalysis continues to be a very sensitive function of ligand structure and that our ability to predict or proceed in a rational manner is severely limited.

4 Mechanism of the Asymmetric Catalysis

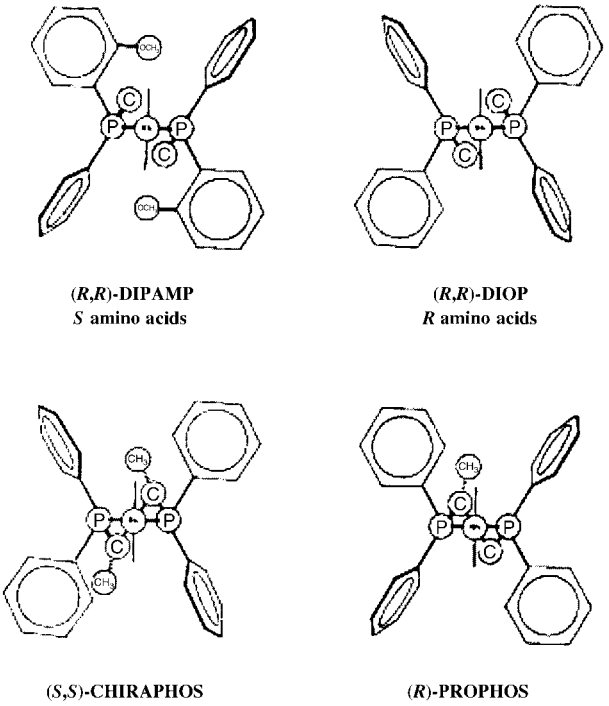
Now that we have these catalysts and have the ability to use them commercially, we would like to know how they work. When we look at energy calculations and realize that, to get 90% ee, we are talking about only a 2 kcal difference, and this is just about the same as the rotation barrier in ethane. Thus, the asymmetric bias may be caused by very subtle effects.

Using the ball-and-stick models in Scheme 11 to illustrate a typical prochiral olefin, we can see that attack at the si face gives the D isomer and at the re face the L, which correspond to *R* and *S* isomers in more modern nomenclature. These of course are mirror images and our catalyst must discriminate between them.

We examined the X-ray crystal structure of the catalyst precursor $[Rh(cod)(dipamp)]^+BF_4^-$, and we noticed that this system presented an array of four aryl groups arranged in an edge-face manner. The phenyl



Scheme 11. Ball-and-stick models of the prochiral olefin and the resulting isomers.



Scheme 12. Edge-face diagrams.

groups present an edge and the *o*-anisyl group a face. This is depicted in Scheme 12 where, for clarity's sake, we have omitted the cyclooctadiene ligand and the counterion, as well as oversimplifying the structure. In this picture, we are looking along the phosphorus–rhodium–phosphorus plane. One could speculate that an approaching substrate might prefer to lie on the flat face rather than on the hindered edge. We can more easily show this by a quadrant diagram (Figure 1), in which the shaded quadrants represent the edge or hindered side. We speculated that a prochiral olefin

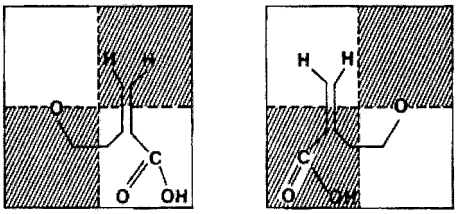


Figure 1. Quadrant diagrams of positioning of the prochiral olefin.

might prefer to lie in the unhindered quadrant. You will note that all the other bisphosphanes in Scheme 7 also present a similar array of four phenyl groups in their X-ray crystal structures, though not quite as convincingly, but there was always a face-exposed ring next to the skewed methylene group.

It makes no difference whether one attributes the bias to the edge-face configuration, as I prefer, or to the skewed methylene group. By using this quadrant interpretation, we could predict what the chirality of the product would be, from the chirality of the phosphane. For any single case where there is a 50% chance of being right, such a prediction has no significance, but having predicted correctly for five cases where X-ray crystal structures were available, one gains credibility. We felt pretty good about how things were fitting into place.

Then along came Halpern's studies.[7] He had been able to isolate a more advanced intermediate, in which the enamide substrate actually formed a complex with the metal-ligand system. He got it crystalline, and it was with considerable eagerness we awaited the X-ray crystallograpic analysis results. It turned out that the enamide was lying nicely in the hindered quadrant.

So much for our theory. As so often happens in science, one comes up with an explanation in which everything seems to be fitting in nicely, and someone else shows your whole interpretation may well be wrong. We were stranded with the argument that, at the square-planar stage, Halpern reported that these steric factors may not be important. However, to get asymmetric bias, we know that the hydrogen atom, the ligand, and the substrate must all be on the metal center at the same time. Such a configuration requires an octahedral structure. Perhaps then these quadrant constraints are important. So far as I know, there is no evidence either to support or reject this contention. Our theory, though possibly wrong, does predict correctly.

All this thinking does not explain CAMP, unless we argue that, during the hydrogenation step, this monodentate ligand prefers to occupy adjacent sites on the metal center and acts as a bidentate species.[3b]

In any case this unique catalysis has enabled chemists to study mechanistic details that it was not previously possible to study. When one thinks of it, it is quite remarkable that we are even in a position to debate such subtle features.

5 Concluding Comments

These soluble hydrogenation catalysts have started a new era in catalytic processes. Since we are now dealing with pure complexes, we can design something to do just the job you want. This catalysis will continue to find many uses in industry, whenever an efficient route to the unsaturated precursor is available. These catalytic processes can be a nice alternative but will by no means replace biochemical processes. Here, the problems with dilute solutions and difficult isolations are often less than the problems of a multistep synthesis. One area where these catalysts will reign supreme is in the preparation of D-amino acids or other unnatural isomers. Here, biochemical alternatives will not be available.

Perhaps the most important use of these catalysts will be to provide an easy way to make a large number of chiral compounds. In the past, research chemists have been reluctant to run laborious resolutions and have done so only when necessary. Now they can get chiral compounds for their life-sciences research with very little effort. We can look on these catalysts as a labor-saving device for the laboratory. For this, they will have an impact for as long as chemists run reactions.

For an invention to succeed, Paul Ehrlich, the father of chemotherapy, stated that four Gs are required; Geist, Geld, Geduld and Gluck. The first of these is axiomatic; you have got to have a good idea. The second is essential; one needs financial support, but I would suggest a proper balance; too much or too little is inhibitory. For the third, you must have patience. Things never move as fast as you would have them. Finally, luck is all-important. I suspect that no invention has ever been made without some fortuitous help.

I have pointed out, and will continue to do so, that ours has been very much a joint effort. It would not have been possible without my associates, Jerry Sabacky and Billy Vineyard. In closing, I would like to add a couple of Gs to Ehrlich's list. We are extremely Grateful to have so Great an honor bestowed on us by your committee.

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