ASYMMETRIC HYDROGENATIONS

by

WILLIAM S. KNOWLES

Monsanto Co., St. Louis, MO 63167, USA.

Actually this account is the story of the genesis of an invention[1]. The inventative 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, that 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 like 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 1960's 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, when an asymmetric center was formed, would direct the reaction to give a predominance of the desired isomer. 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, starting in the mid fifties, modifying heterogeneous catalysts like Raney Ni and palladium with a chiral agent. Always the asymmetric bias was 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. 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 thru several new employees on a number of projects when I became aware of Professor Wilkinson's discovery of chlorotris(triphenyl-phosphine) 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-sixties was the development of methods for making chiral phosphines 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 phosphines the lone pair of electrons counts as a substituent. Earlier it was thought that phosphines might pyramidally invert like their nitrogen analogs but Mislow and also Horner showed they were stable at room temperature. They turned out to have a half-life of a couple of hours at 115°. For our contemplated hydrogenations this stability would be quite adequate. Then the basic strategy was to replace the triphenylphosphine 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 methylpropylphenylphosphine, giving an enantomeric excess (ee) of 15% (Figure 1).

ee (enantiomeric excess) = 15%

Figure 1
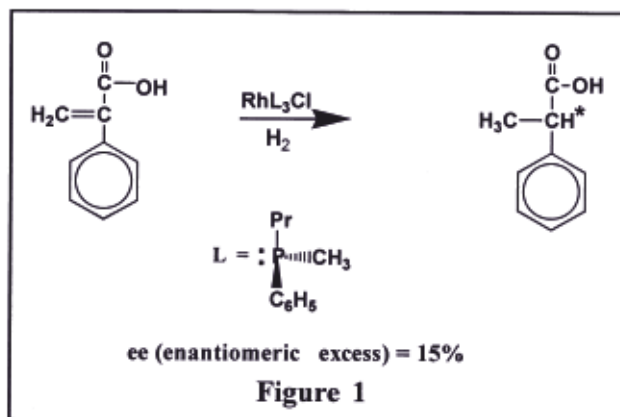
This modest result of course was of no preparative value, but it did establish that the hydrogenation technique gave a definite asymmetric bias. In order to achieve this bias the hydrogen, the ligand, and the substrate all had to be on the metal at the same time. Furthermore we established that the hydrogenation 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 methylpropylphenylphosphine on a substituted styrene. There were others using other phosphines with uninteresting results. Seemingly we may have been the only ones naïve 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 sizeable 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 was resolving and deblocking to L-DOPA. The synthesis, which followed closely the Erlenmeyer azlactone procedure described in Organic Syntheses, went by way of a prochiral enamide, which was hydrogenated to blocked DL-DOPA (Figure 2).

Hoffman - LaRoche L-Dopa Process

Figure 2
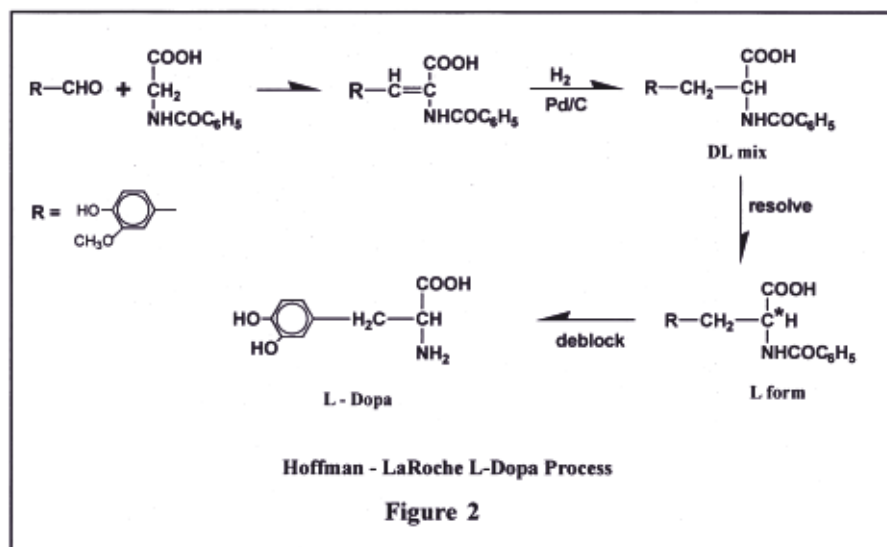
This enamide offered a golden opportunity for commercializing this burgeoning technology. We soon found out that these prochiral enamide precursors of α-amino acids hydrogenated much faster than one would expect for such a highly substituted olefin. Even so the chiral results were only 28%, but the stage was nicely set to make a structure vs. activity study. We had a good test reaction in Figure 3 where 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 phosphine
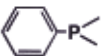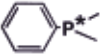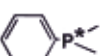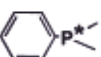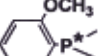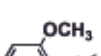

Figure 3

162
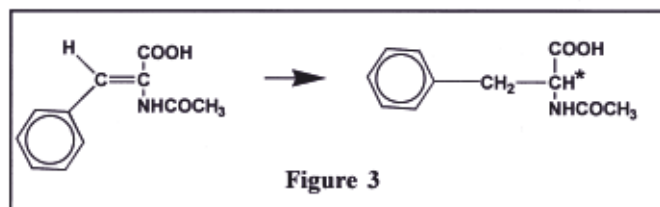
of the proper structure. Early on we tried phosphines with a chiral alkyl side chain, and the asymmetric bias was barely detectible. We felt strongly that if one wanted to get high ee's the asymmetry would have to be directly on the phosphorus. That is where the action is.

Initially we varied the alkyl groups on the phosphorus converting the normal propyl to the more hindered isopropyl or cyclohexyl but ee's 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 phosphine 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.

We made methylphenyl-o-anisylphosphine (PAMP) and got ee's after playing with hydrogenation conditions up to 58%. Further modification of this molecule gave us methylcyclohexyl-o-anisylphosphine (CAMP), this change gave up to 88%. These results are summarized in Figure 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 vs. 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

Figure 4 Ligands for Asymmetric Hydrogenation

	PHOSPHINE		ee
1		$[CH_2CH^*(Me)(Et)]_2$	1%
2		Me, n-Pr	28%
3		Me, i-Pr	28%
4		Me, cyclohexyl	32%
5	OCH₃	Me, phenyl- (PAMP)	58%
6	OCH₃	Me, cyclohexyl - (CAMP)	88%

emotionally equipped to realize what we had done. Here with this simplest of molecules (CAMP), we had solved one of the toughest of 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 phosphines 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 phosphine synthesis, but being a catalyst a small amount of L-menthol could lead to a large amount of chiral product.

CAMP worked equally well in the L-DOPA precursor, Figure 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 phosphines and concentrated on converting this unique hydrogenation to 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 starting with vanillin (Figure 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 product, which could be filtered leaving 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 $[Rh(1,5-COD)L_2]^+BF_4^-$. These catalysts were fast so that mole ratios of substrate to catalyst were about 20,000 to 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 then it is possible to get out easily, only 75 to 80% pure enantiomer. With lower ee's the losses become prohibitive. For such a system a catalyst of very high efficiency must be used. Unfortunately, most com-

Figure 5 Monsanto L-DOPA Process
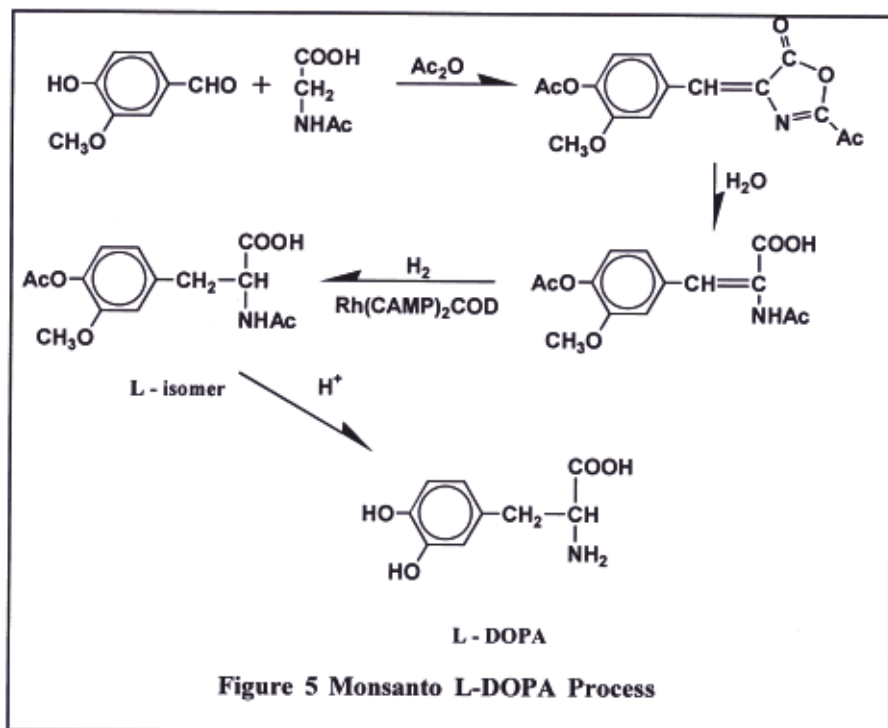
pounds are of this type. If on the other hand the racemic modification is a conglomerate or an equal mix of D and L crystals, then recovery of excess L can be achieved with no losses. Since the L and DL are not independently soluble a 90% ee easily gives a 90% recovery of pure isomer. In our L-DOPA process 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 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 Professor Kagan, which he called DIOP (Figure 6).

This was a chelating bisphosphine made from tartaric acid with chirality on

Figure 6 R,R-DIOP, Kagan
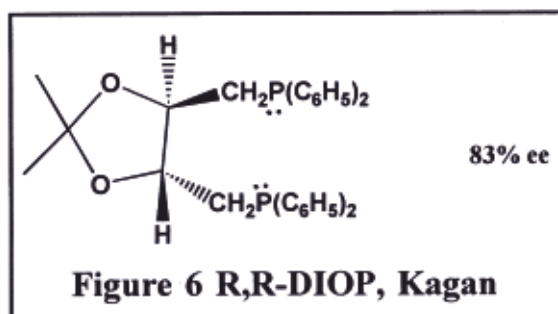
the carbon backbone and it gave results comparable to CAMP. We had hypothesized that to get good results one needed chirality directly on the phosphorous atom. It made sense, but Professor Kagan showed us to be totally wrong. It is most appropriate that this invention using tartaric acid should have 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 bisphosphine ligands with asymmetry on the chiral backbone.

Shortly after we came up with our own chelating bisphosphine by dimerizing PAMP with another Mislow procedure. We called it DiPAMP, where chirality resided on the phosphorus (Figure 7).

Figure 7 R,R-DiPAMP
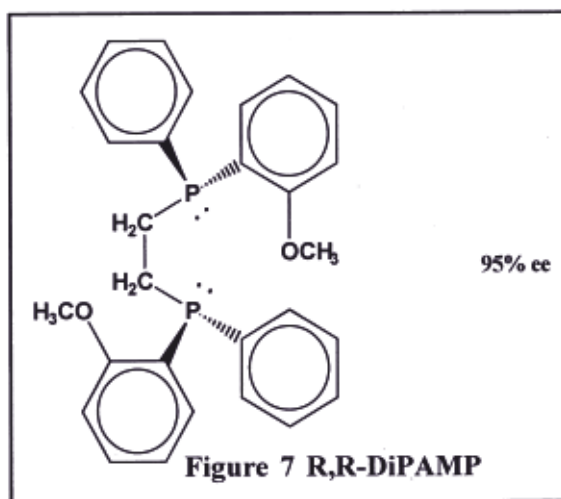
It worked at about 95% ee in our L-DOPA system and we quickly converted our commercial process to use it. Part of our motivation to make a quick change was that DiPAMP was easier to make than CAMP, and in addition was a nice crystalline air-stable solid.

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 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 hydrogenates efficiently whereas the E is less so. Both give the same product. Fortunately for us the base condensation used in their preparation gives us only the desirable Z form.[3c]

In Figure 8, R can be just about anything except – COOH. It's easy to see how our rhodium catalyst could become confused with two carboxyls so close together. Thus aspartic acid is best made by an enzyme process.

Figure 8 Generality for Z-Enamides
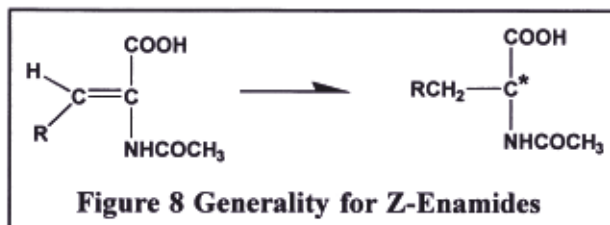
However, almost all the known familiar α-amino acids can be prepared this way since at least in principle an enamide precursor is possible. Evidently the polar carboxyl and amide overwhelm any variation in the R-group. Also the carboxyl and the nitrogen blocking group can be varied extensively. Once 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 Figure 9. Our colleagues at Hoffman LaRoche have added about a dozen more non-aromatic members to this list using DiPAMP.

This generality can be extended to a variety of enol-esters and itaconic derivatives. Evidently what is required is the ability to chelate with the metal. Thus the nitrogen can be replaced with oxygen or methylene (Figure 10).[3c]

One system which did not work well in our system was our original model, α-phenylacrylic acid. A number of these aryl propionic acids have value as non-steroidal anti-arthritics. 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. I'm afraid this is just another example in the history of inven-

enamides   enol-esters

carboxylic acids

Figure 10

Figure 9 Amino Acids	
PRODUCT	%ee
L - DOPA	94
L - Phenylalanine	96
L - Tryptophane	93
L - Alanine	90
L - Lysine	85
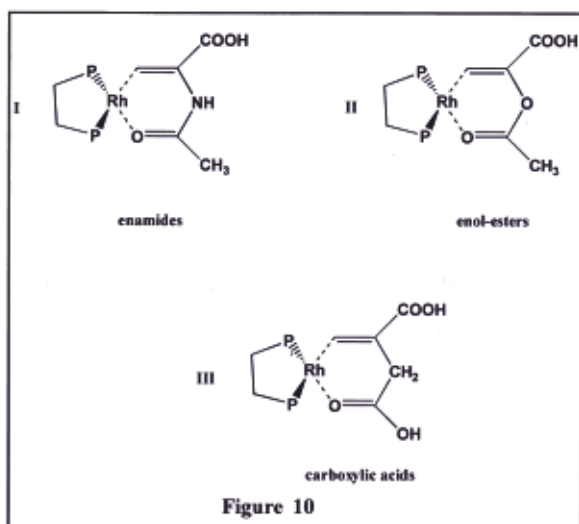
tion. The one who makes the first discovery seldom makes the second. On a grander stage this may explain why there are so few Nobel Laureate repeats.

Soon after the appearance of DiOP and DiPAMP a considerable number of bisphosphines with chiral carbon backbones were found. All of these worked well with the same enamides and on related oxygen analogs. A few of these are shown in Figure 11.[3a]

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

In our hands DiPAMP was by far the most versatile and remained supreme for enamides for many years. Later in the nineties an improved bisphosphine was reported by Burk, then working at DuPont, which he gave the name DuPHOS (Figure 12).[2]

This bisphosphine 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's can be important where the racemate is not a conglomerate.

PHOSPHINES

The key to asymmetric hydrogenation is the structure of the chiral ligand. The phosphines are prepared by a multi-step route and are quite expensive, but fortunately one mole will make many thousands of moles of product.

Figure 11 2-α-Acetamidocinnamic Acid

DuPHOS, Burk
Figure 12
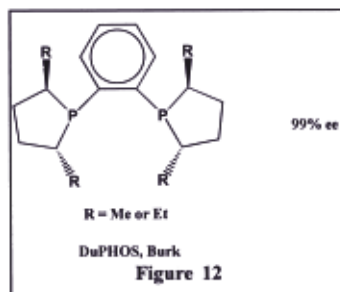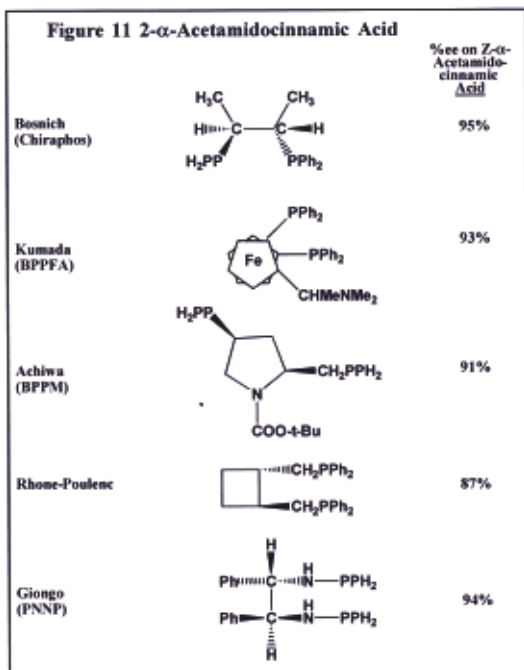
Even so, the ligand must be made from cheap starting materials. Some economy of scale is achieved by making a 10 year supply in a few plant-size batches. At first CAMP was prepared from phenyldichlorophosphine via Mislow's menthyl ester, introducing the *o*-anisyl group last. Unfortunately, the desired isomer was produced in minor amount and, to correct this situation, it was necessary to reverse the order of addition of aryl groups. The sequence starting with trimethylphosphite is outlined in Figures 13 and 14.

A large excess of trimethylphosphite was needed to get good yields of monosubstitution product I. In the sequence I–III only the nicely crystalline phosphinic acid III was isolated. The fact that the acid chloride IV can be converted to an 80/20 mix of (*S*)*p* and (*R*)*p* 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 *l*-menthol.

Figure 13 Resolved Menthyl Ester

Figure 14 CAMP and DiPAMP

169
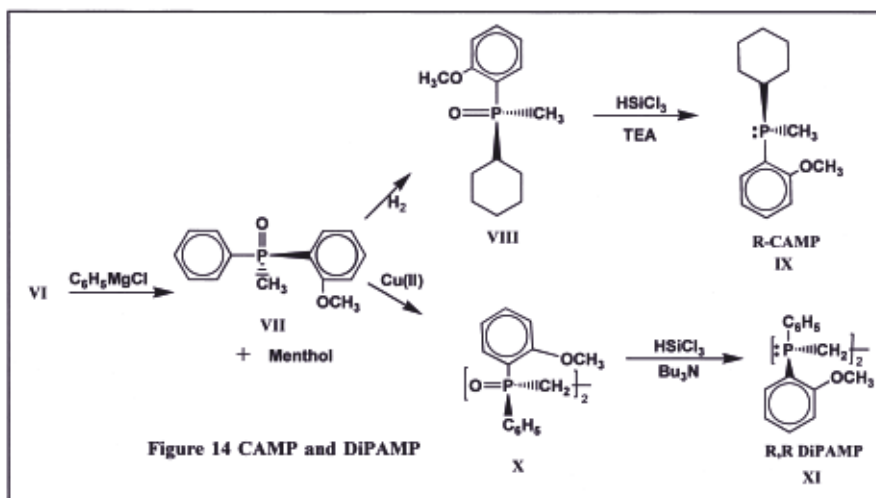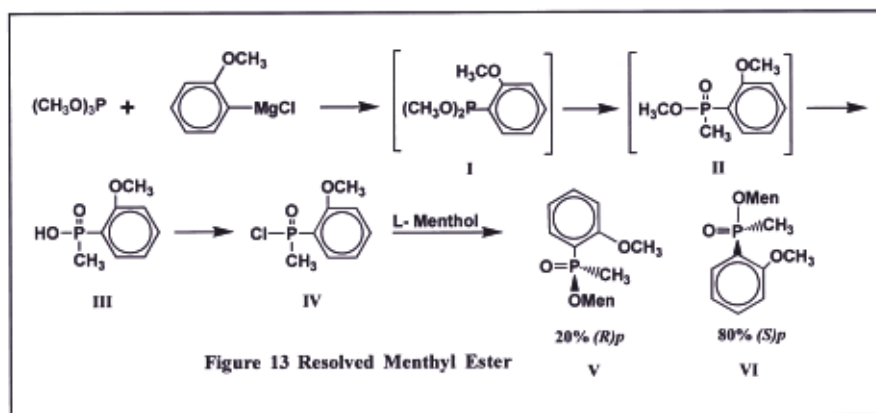
Another advantage of the sequence in Figures 13 and 14 was that CAMP and DiPAMP were prepared from a common intermediate VII and no new resolution procedure needed to be worked out. Thus, the change to an improved ligand could be done with minimum dislocation both at the synthesis and the utilization end. It is a clear advantage of catalytic processes that it is often easy to shift from the old to the new.

CAMP was prepared by a selective hydrogenation of VII, Figure 14, 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 TEA gave R-CAMP, IX, with inversion. The (R)p menthyl ester V could also have been used in this sequence if the last step was run with pure $HSiCl_3$ which goes with retention.

In the case of DiPAMP the copper coupling step run with lithium diisopropyl amide and CuCl did not affect the stereochemistry. However, only the base promoted trichlorosilane to give a double inversion was applicable. In this case an empirical study showed that use of tributylamine minimized meso formation.

In principle, the menthol recovered in Figure 4 could be recycled, making 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)p menthyl ester (Figure 13).

In contrast to CAMP, DiPAMP is a stable solid melting at 102°. Heated at 100° it has a half-life of 3–5 hrs. This racemization was somewhat faster than Mislow's phosphines, which did not invert appreciably until 10–15° higher. The rate was reasonable if one considers that inversion at either end destroys chirality. Use of DiPAMP complexed with rhodium must invert much more slowly because efficient asymmetric hydrogenations have been obtained at 95–100°.

For the sake of convenience, particularly on a large scale, a solid complex was made by reacting two equivalents of phosphine 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 VII to make a variety of phosphines. The first and most obvious is to convert DiPAMP to DiCAMP. You will recall that in the monophosphine series converting a phenyl to a cyclohexyl gave an enormous increase in selectivity. Not so with DiCAMP which gave only 60–65% ee on our enamide systems. It was, however, our best candidate for preparing the more hindered amino acid valine, where the other systems were very poor (Figure 15).

In the monophosphine series we only found one that was marginally better than CAMP. This rarity of good monophosphines shows how lucky we were to find an efficient one on almost the first try (Figure 16).

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
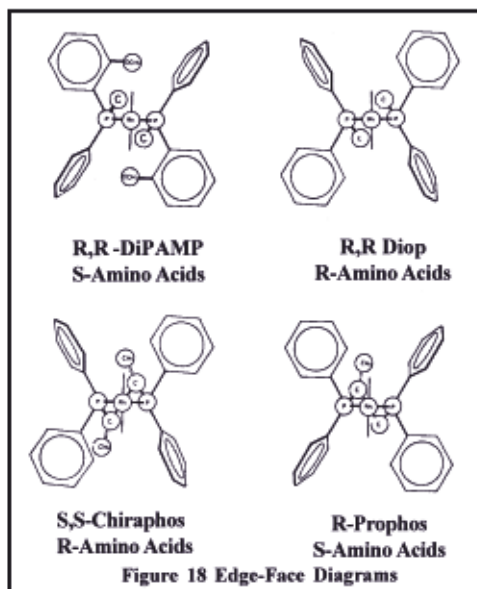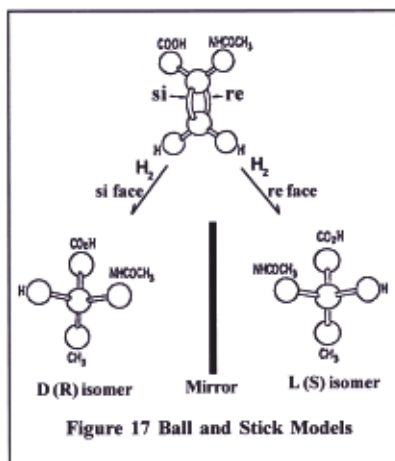
Figure 15 Valine

Figure 16
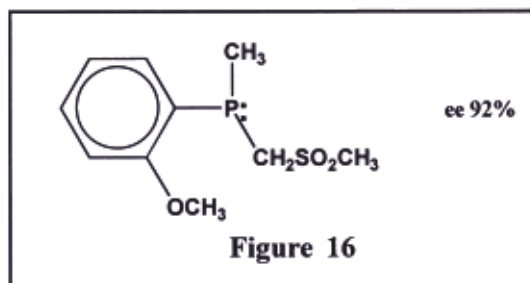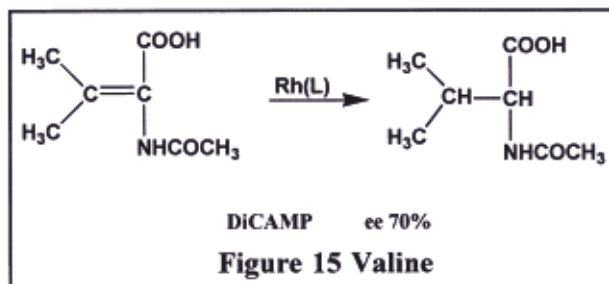
gave only 85% ee which by current standards is too low. I winced when I came in one morning and saw our valuable DiPAMPO being treated with concentrated sulfuric acid, but it worked. This exploratory effort suffices to show that as one might expect the catalysis continues to be a very sensitive function of ligand structure and that our ability to predict or proceed in a rational manner is severely limited.

MECHANISM[3b]

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 only a 2 kg cal 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 Figure 17 to illustrate a typical pro-chiral olefin we can see that attack at the si face gives the D isomer and at the re face the L, corresponding to R and S in more modern nomenclature. These of course are mirror images and our catalyst must discriminate between them.

We did an x-ray crystal structure of the catalyst precursor Rh(DiPAMP) (COD)$^+$BF$_4^-$ and we noticed that this system presented an array of four aryl groups arranged in an edge-face manner. The phenyl groups present an edge and the *o*-anisyl group a face. This is depicted in Figure 18 where for clarity's sake we have omitted the cyclooctadiene and the counter ion as well as over simplifying the x-ray chart.

Figure 17 Ball and Stick Models

R,R -DiPAMP
S-Amino Acids

R,R Diop
R-Amino Acids

S,S-Chiraphos
R-Amino Acids

R-Prophos
S-Amino Acids

Figure 18 Edge-Face Diagrams

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 19, where the shaded quadrants represent the edge or hindered side. We speculated that a prochiral olefin might prefer to lie in the unhindered quadrant.

You will note that all the other bisphosphines in Figure 11 also present in their x-ray structures a similar array of four phenyl groups, though not quite as convincingly, but always there was a face-exposed ring next to the skewed methylene.

It makes no difference whether one attributes the bias to the edge-face configuration, as I prefer, or the skewed methylene. Using this quadrant interpretation we could predict from the chirality of the phosphine what the chirality of the product would be. Since 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 structures were available one gains credibility. We felt pretty good with how things were fitting into place.

Then along came Halpern's studies.[3b] He had been able to isolate a more advanced intermediate where 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 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 where 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 these steric factors may not be important. However, to get asymmetric bias we know

re Face   **si Face**

Figure 19
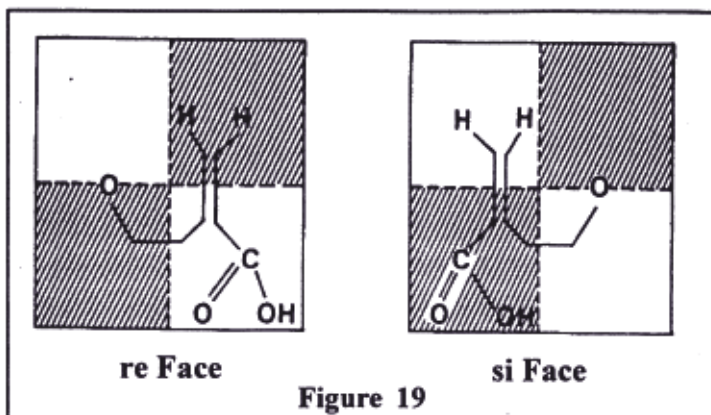
that the hydrogen, the ligand, and the substrate must all be on the metal at the same time. Such a configuration requires an octahedral structure. Perhaps then these quadrant constraints are important. So far as I know there is no evidence either to support or reject this contention. Our theory, though 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 sights on the metal and acts like a bi-dentate species. [3b]

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

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. They can be a nice alternative but by no means will replace biochemical processes. Here the problems with dilute solutions and difficult isolations are often less then the problems of a multi-step 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, has 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.

REFERENCES

1) Accounts of Chemical Research, **1983**, 16, 106. William S. Knowles and references cited therein.
2) M. J. Burk, J. E. Feaster, W. A. Nugent, and R. L. Harlow, *J. Am. Chem. Soc.* 115, 10125 (1993).
   M. J. Burk, M. F. Gross, and J. P. Martinez, *J. Am. Chem. Soc.* 117, 9375 (**1995**).
3) *Asymmetric Synthesis*, Vol. 5, Chiral Catalysis, James D. Morrison, Editor, Academic Press, **1985**.
   a) Chapter 1. *Chiral Ligands for Asymmetric Catalysis* – Henri B. Kagan.
   b) Chapter 2. *Asymmetric Catalytic Hydrogenation: Mechanism and Origin of Enantioselection* – Jack Halpern.
   c) Chapter 3. *The Applicability of Asymmetric Homogeneous Catalytic Hydrogenation* – Karl E. Koenig.