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Chapter 8

An Affordable Catalyst for the Production of Amino Acids

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Asymmetric hydrogenation has been demonstrated to be a useful synthetic approach to amino acids and derivatives. The asymmetric reduction step itself is usually straightforward, but the synthesis of the ligand that invokes the asymmetric induction can be difficult. Use of MonoPhos^{TM}, a phosphoramidite, allows for a low cost solution as it is derived in a single step from BINOL, an item of commerce available as either antipode. Rhodium catalyzed asymmetric hydrogenations proceed with high enantioselectivities, especially to substituted phenylalanine derivatives. A large solvent effect is observed.

Introduction

Many ligands have been developed and advocated for the asymmetric reduction of enamides by a transition metal catalyst to α -amino acid derivatives (Scheme 1) (1,2). Most known ligands are bidentate. The ligand's chirality can be derived from stereogenic phosphorus atoms, as in the DIPAMP (**1**) system of Knowles, or from carbon stereocenters. Examples are given in Figure 1. There has also been a number of systems developed, of which BINAP (**2**) is the best known, where the asymmetry is derived from hindered rotation.

Scheme 1.

1
DIPAMP

DIOP

Chiraphos

BPPM

Josiphos

Duphos

2
BINAP

3
BICP

Figure 1: Some examples of ligands used to effect asymmetric reductions.

Whatever the source of chirality, all these systems have a major drawback in that their synthesis is expensive, can involve a long sequence, be low yielding, or tedious. Often a resolution has to be performed. In a few cases, as in BICP (3), the chirality originates from the chiral pool and access to the antipode can be problematic (3). In most papers on asymmetric hydrogenations, these problems are treated in a cursory manner or completely ignored. To perform an asymmetric hydrogenation reaction at scale, the ligand synthesis can be the greatest problem that has to be overcome. In addition, the emphasis on enantioselectivity is usually to the detriment of low catalyst usage, which can have a large impact on the economics of the process. The kinetics of the reaction are often ignored in publications, and these can also have a large effect on the economics of the process.

Although Knowles' catalyst has been known for almost thirty years, and has been used at industrial scale (2), there are still relatively few asymmetric hydrogenations performed at scale. If we consider Knowles' catalyst, which has been used for the production of L-Dopa (Scheme 1; R = 3-AcO, 4-MeOC₆H₃; cat = [Rh(DIPAMP)(COD)]BF₄), the synthesis of the ligand is long, low yielding (4) and tedious (5). However, a wide range of enamides can be reduced and the method is useful for the production of unnatural amino acids as long as there is no substituent at the β -position (4). The development of the DuPhos and related systems overcame the β -substituent problem, but again the synthesis of the ligand is not a trivial undertaking (6). There is also a dogma that bidentate ligands are required to obtain high asymmetric induction.

A recent survey by Blaser *et al.* shows that at best a dozen processes based on asymmetric hydrogenation have been implemented for the production of enantiopure intermediates on ton-scale (7). We believe that this scant use of such a well-studied technology is caused by the following main reasons: Time-to-market constraints often do not allow sufficient time to develop a catalytic process for new products. The costs of metal or ligand may be too high. The third reason can be poor availability of ligands (both lab and production scale) on short notice. The result of these problems in the fine chemical industry, especially for pharmaceutically related products, is that methodology that is easier to screen and implement is used in preference to asymmetric hydrogenations.

MonoPhos^{TM} reductions

With the knowledge that there is still a need for better asymmetric hydrogenation catalysts, it was fascinating that phosphoramidite

derivatives of binaphthol (**4**) (BINOL) have been used to effect asymmetric conjugate additions to enones (**8**). The ligand system, was therefore, tried in the context of an asymmetric hydrogenation as libraries of ligands could be prepared by a simple procedure (*vide infra*). The common perception that a bidentate ligand is required for good asymmetric induction was found not to be the case. In addition to the synthesis of α -amino acids, application of monodentate phosphoramidites in the rhodium catalysed hydrogenations of aromatic enamides (**9**) and dehydro-beta-amino acids (**10**) have recently been reported.

The initial experiments to prepare α -amino acids were performed with the dimethylamino phosphoramidite, that has become known as MonoPhos^{TM} (**5**). The model enamide is methyl α -*N*-acetylamidocinnamate (**6**) (Scheme 2).

Scheme 2.

The initial findings were that there is a strong solvent effect. Use of methanol provides moderate asymmetric induction but when methylene chloride is the solvent, excellent asymmetric induction is observed (Scheme 2 and Table I) (*11,12*). The reaction also works well for a variety of substituted phenylalanine derivatives (Table II and Scheme 3) (*13*).

The initial hydrogenation experiments were performed in Schlenk tubes at 1 bar using a small magnetic stirring bar. Rates of these reactions were not very high. However, upon transferring the hydrogenation into well-stirred autoclaves, and raising the pressure to 5 bar we could raise the turnover frequency (TOF) to 300 h⁻¹ (Table II, Entry 3). At high pressure (60 bar) an unoptimized TOF of 1667 h⁻¹ has been achieved. Obviously, the reaction has a positive order in hydrogen pressure. Most gratifyingly we found that, unlike with many bisphosphine ligands, the enantioselectivity does not decrease with increasing pressure.

A variety of substituents on the phenyl group in the substrate have little or no effect on the enantioselectivity of the hydrogenation, although the rate was affected significantly (Table II).

Table I. Summary of enantioselectivity for the preparation of phenylalanine from 6 as described in Scheme 2 with 1 bar of hydrogen.

<i>Solvent</i>	<i>Temp</i>	<i>ee (%)</i>
CH ₃ OH	rt ^a	70
CH ₂ Cl ₂	rt	95
CH ₂ Cl ₂	5°C	97
THF	rt	93
Me ₂ CO	rt	92
EtOAc	rt	95
PrOCH ₂ CH ₂ OH	rt	77

^a Denotes room temperature.

Scheme 3.

Table II. Reductions of substituted phenylalanine derivatives as shown in Scheme 3.¹³

<i>Entry</i>	<i>R</i>	<i>R</i> ^I	<i>Solvent</i>	<i>pH₂ (bar)</i>	<i>Time</i>	<i>ee (%)</i>
1	H	H	CH ₂ Cl ₂	5	3 h	97
2	H	Me	CH ₂ Cl ₂	1	3 h	95
3	H	Me	CH ₂ Cl ₂	5	40 min	95
4	H	Me	EtOAc	1	2 h	96
5	3-MeO	Me	CH ₂ Cl ₂	5	2 h	97
6	4-MeO	Me	CH ₂ Cl ₂	5	2 h	94
7	4-AcO, 3-MeO	Me	EtOAc	5	nd ^a	96
8	4-F	H	CH ₂ Cl ₂	27	10 min	93
9	4-F	Me	CH ₂ Cl ₂	5	25 min	96
10	3-F	H	CH ₂ Cl ₂	10	2 h	96
11	3-F	Me	CH ₂ Cl ₂	5	30 min	95
12	2-F	Me	CH ₂ Cl ₂	5	15 min	95
13	4-Cl	Me	CH ₂ Cl ₂	5	20 min	94
14	3,4-Cl ₂	H	CH ₂ Cl ₂	5	2 h	97
15	3,4-Cl ₂	Me	CH ₂ Cl ₂	5	30 min	99
16	3-NO ₂	Me	CH ₂ Cl ₂	5	2 h	95
17	4-NO ₂	Me	CH ₂ Cl ₂	5	nd	95
18	4-F, 3-NO ₂	Me	CH ₂ Cl ₂	5	2 h	95
19	4-Ph	Me	CH ₂ Cl ₂	5	25 min	95
20	3-F, 4-Ph	Me	CH ₂ Cl ₂	5	25 min	93
21	4-Ac	Me	CH ₂ Cl ₂	5	15 min	99
22	4-PhCO	Me	CH ₂ Cl ₂	5	30 min	94
23	4-CN	Me	CH ₂ Cl ₂	5	18 h	92
24	1-naphthyl ^b	Me	CH ₂ Cl ₂	5	10 min	93

^a Denotes not determined. ^b This is the aryl substituent.

Ligand synthesis

Although MonoPhos^{TM} is a monodentate ligand, good asymmetric induction is observed. The power of this approach is that the ligand is readily available from BINOL (**4**) (Scheme 4) (*14*). Other analogues **7** of MonoPhos^{TM} are available by substitution of the amine moiety or by a short synthesis (Scheme 4) (*15-17*).

Scheme 4.

Scheme 5.

The complex formation between the ligand and the metal can be performed prior to the reduction either as a separate step, or *in situ*. The procedure alleviates some of the problems associated with oxygen sensitivity seen with other systems.

Mechanistic considerations

This aspect of the work is still ongoing. Many studies have appeared investigating the mechanism of rhodium-bisphosphine catalyzed asymmetric hydrogenation of dehydroamino acids (18). In the Halpern mechanism oxidative addition of hydrogen to the Rh-bisphosphine olefin complex is the rate-determining step (19,20). Recently, Imamoto has published evidence for the formation of a Rh-bisphosphine dihydride complex at low temperature, which has reopened the debate on the mechanism (21).

One of the more surprising characteristics of the use of monodentate phosphoramidites in rhodium-catalyzed hydrogenations is the effect of the ligand/rhodium ratio. Phosphoramidites bind very strongly to rhodium, in spite of their reduced sigma donating properties due to their greatly enhanced π acceptor properties as compared to phosphines. It thus did not come as a surprise that catalytic activity ceased when the L/Rh ratio was increased to 3 (Figure 2) in the hydrogenation of **6**.

Figure 2: Rate dependence on the MonoPhos:Rh ratio for the reduction of **6**

However, when the ratio of **5**:Rh was lowered to 1.5 or 1 we found an unexpected increase of the rate. Even more interesting was the finding that the ee remained the same over the whole L/Rh range from 1-2 equivalents of MonoPhos:Rh and remained the same throughout the hydrogenation reaction. This suggests that a single rhodium species is the active catalyst in all these hydrogenations independent of the **5**:Rh ratio. We have performed these experiments both at 1 bar with 5 mol% of catalyst and at 15 bar with 0.015 mol% of catalyst and found essentially the same results. Thus far we had assumed that in the entire catalytic cycle two ligands would be bound to rhodium. However, these results suggest that this may not be the case.

To shed more light on this dilemma, we decided to perform a test for non-linear effects after the work of Kagan *et al* (22). We performed this test using MonoPhos^{TM} (**5**) of varying degrees of enantiomeric purity in the rhodium-catalyzed hydrogenation of **6**. As can be seen from Figure 3, we obtained a weak, but reproducible, positive non-linear effect. Although this definitely establishes the presence of complexes with two

or more ligands it still does not rule out the possibility that these complexes dissociate into a mono-ligated complex, which could be the actual catalytic species. It is clear that more information is necessary.

Figure 3: Asymmetric amplification with MonoPhos.

As a comparison a number of different ligands were prepared. One variation was changing of the nitrogen substituents (**8,9**). Hydrogenation of BINOL over PtO_2 (**23**), followed by reaction with HMPT gave **10**. The effect of substituents on the BINOL skeleton in the 6- (**11**) and 3-positions (**12**) was probed. In addition, bridged systems with two phosphoramidite moieties were prepared (**13-15**).

13; $n = 1$, $R = \text{Me}$

14; $n = 2$, $R = i\text{-Pr}$

15; $n = 2$, $R = (S)\text{-PhMeCH}$

The ligands were tested in the Rh-catalysed hydrogenation of a limited number of dehydrophenylalanine derivatives; most experiments were performed on **6**. In the dehydroamino acid hydrogenations the two methyl substituents on nitrogen as in **5** are unsurpassed up to now. The 6,6'-dibromo-MonoPhos **11** behaved very similar to MonoPhos in the hydrogenation of **6**, although the rate is somewhat lower (Figure 4). Enantioselectivity did suffer when this ligand was applied for the hydrogenation of the 4-fluoro-derivative. The effect of the 3,3'-dimethyl substituents of **12** was more marked and led to a strongly reduced rate as well as a somewhat lower enantioselectivity in the hydrogenation of **6**. Surprisingly, the configuration of the product is the same as that of the BINOL, in contrast to results with the other BINOL ligands. Hydrogenations with octahydro-MonoPhos **11** gave results that were comparable to those obtained with MonoPhos itself. This was recently confirmed by the work of Chan *et al.* (24). Use of bidentate ligands such as **13-15** was not so successful. In methanol hardly any reaction took place, although in CH_2Cl_2 a reasonable rate could be attained, depending on bridge length. Nevertheless, enantioselectivity was much lower than with the monodentate ligands.

A comparison of the kinetics of the hydrogenation of **6** using ligands **5**, **10-12** is given in Figure 4. These traces represent hydrogen uptake during hydrogenation at 5 bar pressure that were performed simultaneously in the Endeavor^{TM}, a semi-automated device which allows 8 parallel gas-liquid reactions with continuous monitoring of hydrogen uptake. The first 30 minutes are used for repeated purging with N_2 . After the solution has been pressurised with H_2 the reaction starts almost immediately and seemingly follows zero order kinetics with **5** and **10**. Although hydrogenation using **11** is clearly slower the kinetic profile is very similar to that of **5** and **10**. Quite different kinetics are observed with the 3,3'-dimethyl derivative **12**; an induction period is apparent and after a much slower reaction the rate gradually decreases which might point to some catalyst deactivation. The induction period usually is related to the catalyst activation step by hydrogenation of the remaining bound COD, which can be very slow with some ligands (25-27). However, a similar profile would be obtained if the reaction was first order in substrate. At present, we have no kinetic data to support this theory.

Figure 4: Hydrogen uptake in the rhodium catalysed hydrogenation of **6** at 5 bar with different ligands.

So far we have not been able to glean much information from NMR experiments as broad absorptions were observed. We thus decided to use electrospray mass spectrometry to further investigate the rhodium species that are present during hydrogenation. Samples of a hydrogenation of **6** in CH_2Cl_2 using 5 mol% of $[\text{Rh}(\text{nbd})_2]\text{BF}_4/\text{MonoPhos}$ (**5**) (1:2) as catalyst at 1 bar H_2 pressure were taken at regular intervals and examined by ES-MS (Table III).

Table III. Rhodium species observed with ES-MS in the hydrogenation of **6 with $[\text{Rh}(\text{nbd})_2]\text{BF}_4/5$.**

<i>Time (min)</i>	<i>Species^a</i>
30	RhLS^* , $\text{RhL}_2(\text{nbd})$, RhL_2S^* , RhL_3 , RhL_3S
60	RhLS^* , $\text{RhL}_2(\text{nbd})$, RhL_2S^* , RhL_3 , RhL_4
120	RhLS^* , RhL_2S^* , RhL_3 , RhL_4

* Small peaks. ^a Where L= ligand, S=substrate.

As can be seen from Table III the catalyst containing two ligands and 1 norbornadiene (nbd) remains present in solution for at least 60 min; after 120 min it has disappeared completely. Its persistent presence might well be due to the poor mass-transfer in these magnetically stirred solutions. We have never experienced a lag-time in the hydrogenations that were performed at higher pressures in the autoclave. We also observe complexes containing 1, 2 or 3 ligands and 1 substrate molecule, however

these peaks are very small. The dependence of the rate on the hydrogen pressure confirms the fact that oxidative addition of hydrogen on the $\text{RhL}_n(\text{Substrate})$ complex is the rate-determining step as in Halpern's original proposal (19). The most important conclusion of this experiment is that part of the rhodium is locked up in complexes such as RhL_3 or RhL_4 that would not seem to be part of the catalytic cycle. The higher rate of hydrogenation when the L/Rh ratio is less than 2 might well be explained by a shift in this unfavorable equilibrium towards the lower ligated species. That these higher ligated rhodium species are present in substantial amounts was proven by the isolation of $[\text{Rh}(\mathbf{5})_4]\text{BF}_4$ as pentane/ CH_2Cl_2 solvate crystals from one of the 1 bar hydrogenation experiments with L/Rh 2.2. The crystal structure is shown in Figure 5. The highly symmetrical structure of the square planar complex is remarkable. Surprisingly, the dimethylamino groups of all 4 ligands are located in the same hemisphere. The helical structure of one of the ligands is shown in Figure 6. We are currently performing kinetic experiments, which should allow us to determine the composition of the catalytic species.

Figure 5: ORTEP representation of $[\text{Rh}(\mathbf{5})_4]\text{BF}_4$; hydrogen atoms are omitted for clarity.

Figure 6: Detail of ORTEP representation of complex $[Rh(5)_4]BF_4$ showing one of the ligands with its helical shaped diol moiety.

Summary

Phosphoramidites are excellent ligands for rhodium-catalyzed asymmetric hydrogenations. MonoPhos™ (**5**) provides the highest enantioselectivity in most cases for the synthesis of α -amino acid derivatives. Although the exact nature of the catalytic species is not known, likely candidates are complexes with one or two phosphoramidite ligands attached to rhodium. Work continues to understand the interactions between the ligands and metal. The reactions have been scaled up.

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