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Phosphoramidite-Controlled Asymmetric Hydrogenation with Rhodium Catalysts

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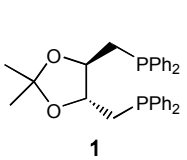
Phosphoramidites, and in particular those derived from BINOL, the MonoPhos family of ligands, have proven extremely useful for the asymmetric hydrogenation of carbon–carbon unsaturation using a rhodium catalyst. Many classes of alkenes can be reduced by these catalyst systems. The use of high-throughput experimentation can be applied to the synthesis of MonoPhos ligands and their subsequent screening, in order to find an appropriate candidate for a specific transformation. Suitable mixtures of ligands can also be found by these high-throughput methods.

The finding by Knowles, building on the observation of Kagan (1, 2) with diop, **1**, that a bisphosphine ligand led to high asymmetric induction when compared with a monophosphine, gave rise to the development of the dipamp, **2**, ligand for the asymmetric hydrogenation of enamides (3, 4). Since that time, an abundance of bisphosphines have been developed to perform asymmetric reductions of a wide variety of substrates (5, 6). The reason behind this move to bidentate ligands is the argument that there is increased rigidity in the metal–ligand complex (6). However, until relatively recently, little attention had been paid to monodentate ligands, such as phosphoramidites, as agents to perform asymmetric hydrogenations.



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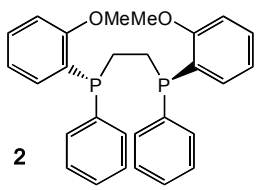

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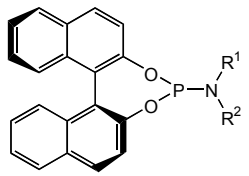
It had already been established that phosphoramidite ligands could effect high enantioselectivities for conjugate additions of alkylzinc agents to enones (7). The precedent for asymmetric reactions with this class of ligand had thus been established. In addition, since phosphoramidites can be considered modular, as the diol and amine moieties can be varied a large library of these ligands is readily available. Some of this work on phosphoramidites in asymmetric hydrogenations has already been reviewed (8–14).

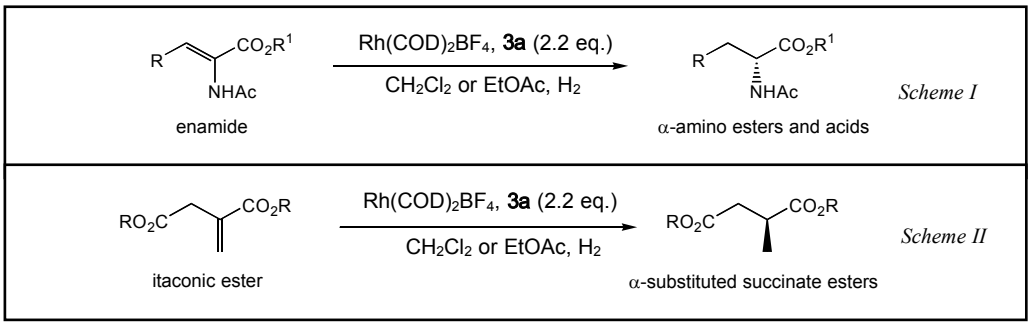
1. Reductions to α-Amino Acid and α-Alkyl Succinic Acid Derivatives

The first phosphoramidite to be investigated for asymmetric hydrogenations was MonoPhos™, **3a**. It was satisfying to find that the asymmetric hydrogenation of an enamide resulted in significant enantioselectivity. The degree of asymmetric



3

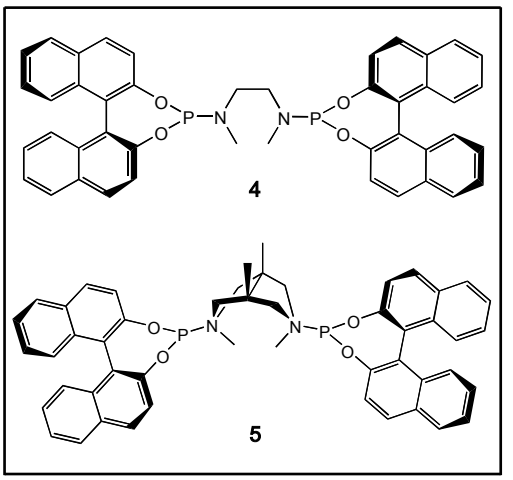
a $R^1 = R^2 = Me$ (MonoPhos)
b $R^1 = R^2 = Et$
c $R^1, R^2 = -(CH_2)_5-$ (PipPhos)
d $R^1, R^2 = -[(CH_2)_2]_2O$ (MorfPhos)
e $R^1 = H$, $R^2 = (R)$-CHMePh
f $R^1 = H$, $R^2 = i$-Pr

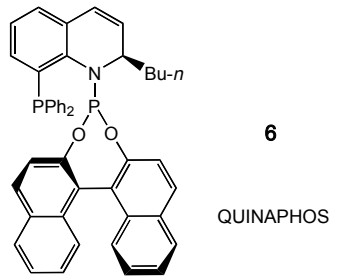


induction was found to be solvent dependent, with dichloromethane and ethyl acetate, in general, providing the highest selectivities. α-Amino esters ($R^1 \neq H$) and acids ($R^1 = H$) as well as α-substituted succinate esters were produced in high enantiomeric excesses (ees) (Schemes I and II) (15, 16).

A simple variation in the substituent on the nitrogen to the diethyl analogue, **3b**, of MonoPhos led to higher ees for the reductions of α-(acylamino)acrylates to α-amino ester derivatives (17). This enhancement was improved by the use of PipPhos, **3c**, and MorfPhos, **3d**, for the preparation of α-amino acids and succinates (18).

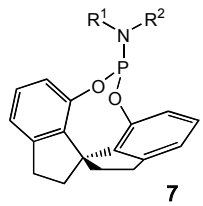
It was found that bidentate ligand **4** gave lower ees in the reduction of enamide esters (*cf.* Scheme I) than the monodentate ligand **3a** (15). However, others found that the use of a different diamine bridge, as in **5**, could provide an ee up to 90% for an itaconic ester reduction (*cf.* Scheme II) (19).

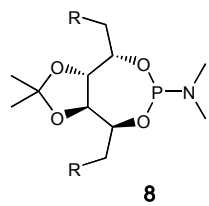




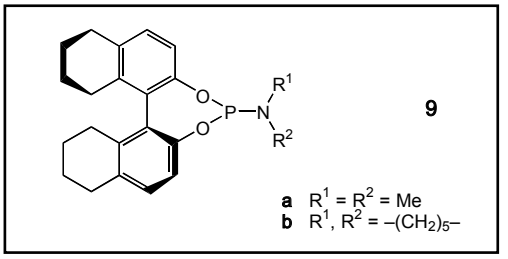
Just prior to the first publication describing hydrogenation by MonoPhos, it had been noted that the bidentate ligand QUINAPHOS, **6**, which possesses a phosphine group as well as a phosphoramidite, could provide high ees for the hydrogenations shown in Schemes I and II (20).

The diol backbone does not have to be derived from BINOL (bis-β-naphthol) to achieve high asymmetric induction for the hydrogenations of enamides to α-amino acid derivatives, and of itaconic acid and esters to succinates. The spirocyclopentane derivatives, SIPHOS, **7**, provide one family of successful ligands (21), although the phosphoramidites, **8**, derived from D-mannitol did not give high ees for these reductions (22).





The H_8-BINOL derivative, **9a**, also showed increased enantioselectivities compared with

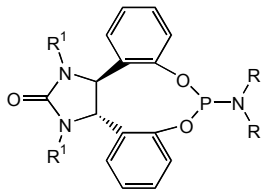


9

a $R^1 = R^2 = Me$
b $R^1, R^2 = -(CH_2)_5-$

MonoPhos, **3a**, for the reductions of α-dehydroamino acids (23).

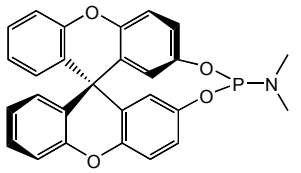
Another class of phosphoramidites that has proved successful for the synthesis of α-amino esters is DpenPhos, **10**, (24). The highest ees were seen for bulky substituents on the imide nitrogens (R^1 = 3,5-(*t*-Bu)$_2$C$_6$H$_3$CH$_2$), although the simple benzyl (R^1 = PhCH$_2$) does give acceptable values. The change from a methyl group in **10** (R = Me) in the phosphoramidite itself to the bulkier ethyl (R = Et) was detrimental to asymmetric induction. These ligands, **10**, also provided good enantioselectivity for the hydrogenation of dimethyl itaconate (24).



DpenPhos

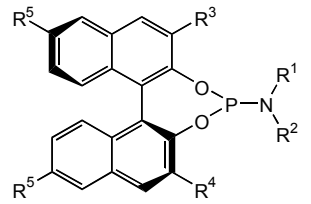
10

Another variation on the atropisomeric theme which provides high asymmetric induction for the preparation of α-amino acid and succinic acid derivatives is the spirocyclic system, **11** (25).



11

With BINOL as the backbone of the phosphoramidite, variations are available for its modification. The simplest substitutions to perform are the symmetrical ones at the 3,3′- and 6,6′-positions, **12a** and **12b**, respectively (16). As will be seen, these substitutions can be important to achieve high degrees of asymmetric induction. The substituted BINOLs are simply used in place of BINOL in the phosphoramidite syntheses (see Section 6).

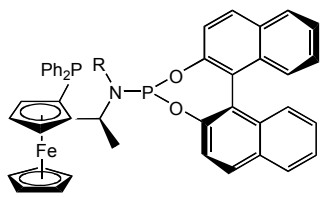


12

a $R^3 = R^4 \neq H$, $R^5 = H$
b $R^3 = R^4 = H$, $R^5 \neq H$
c $R^3 \neq H$, $R^4 = R^5 = H$
d $R^1, R^2 = -(CH_2)_5-$, $R^3 = R^4 = Me$, $R^5 = H$

A system with only a 3-substituent on the BINOL moiety has been prepared, **12c**. The asymmetry in the system also makes the phosphorus a stereogenic centre. Reductions of dehydroamino acids and itaconates proceed with high selectivities in most cases. The chirality of the BINOL moiety controls the stereochemical outcome of the reaction (26).

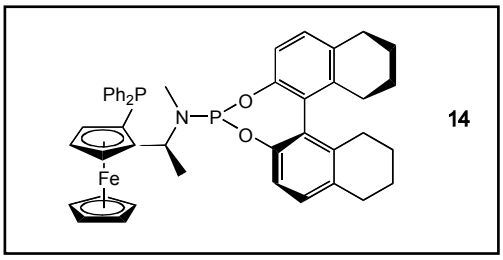
The coupling of a BINOL with a ferrocene-based system, as in **13a**, leads to high turnover numbers while still retaining high enantioselectivities for the reductions of an α-amidoacrylate ester and itaconate (27, 28). Although two stereogenic moieties are present in the ligand, the stereochemistry of the BINOL controls the stereochemical outcome of the reaction even though there is a phosphine group on the ferrocene unit. However, in the case of mismatched chirality in the subunits, the enantioselectivity can suffer (29).



13

a R = Me **b** R = H

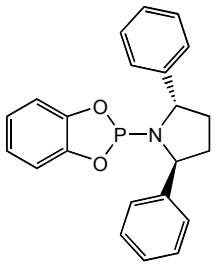
The use of an octahydrobinaphthyl system has some advantages for reducing enamides (see



14

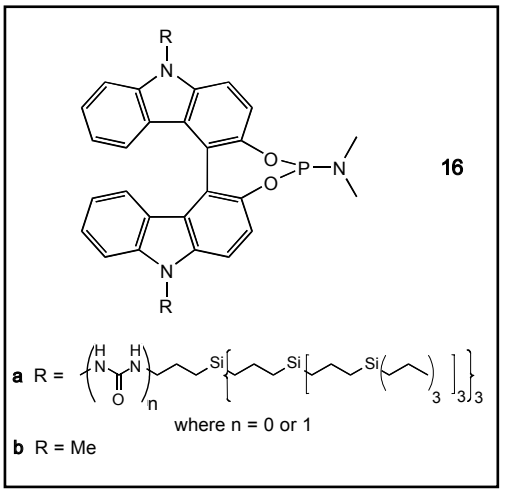
Section 2). This reduced system has also been used to modify the hybrid system, **14**, to enhance the enantioselectivities for the preparation of α-amino esters and dimethyl succinates (30).

A phosphoramidite derived from the achiral catechol, **15**, provides high ee for the synthesis of methyl α-amino esters. In this series the substitution pattern on nitrogen is extremely important, as *N*-alkyl-*N*-phenylethyl analogues give low ees (31).



15

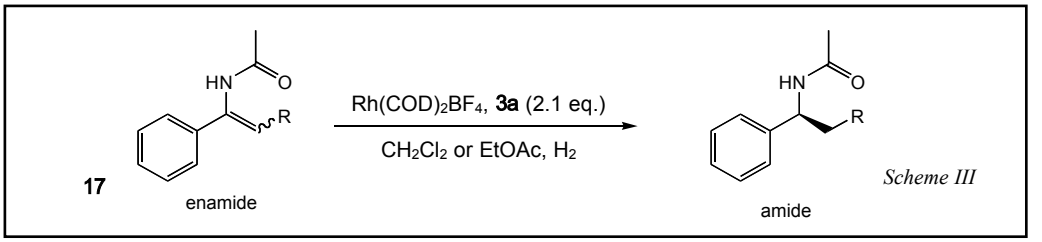
An atropisomeric phosphoramidite can be incorporated into a polymer, but the ees for the α-amino acids and succinate produced are usually lower (32). A similar effect was seen when the catalyst was immobilised on an aluminosilicate (33). The use of the dendritic phosphoramidite ligands, **16a**, showed that the dendrimer inhibited the formation of inactive rhodium–ligand species, as the ligand:metal ratio could be increased over the monomeric series. Reductions of methyl 2-acetamidocinnamate with the parent ligand, **16b**, as well as with the dendrimers, **16a**, gave enantioselectivities comparable to those obtained with MonoPhos, **3a**, itself (34).



16

2. Reduction of Enamides

In addition to being used for the preparation of α-amino acid derivatives, enamides can be reduced to form amides using MonoPhos, **3a**, as the chiral ligand (Scheme III). When the potential for *E*- and *Z*-isomers occurs in the substrate, **17**, then the *Z*-isomer is reduced with high ee with MonoPhos, **3a**, while the *E*-isomer gives substantially lower selectivity. Again, for this reaction, the ee has some solvent dependence (16, 35). It was found that in dichloromethane the *E*-isomer of the enamide (**17**, R = Et) underwent isomerisation to the *Z*-isomer; this isomerisation did not occur in ethyl acetate (16, 36). Higher ees were obtained for these reductions when the diethyl derivative of MonoPhos, **3b**, was employed (17). Again, as in the reductions of dehydroamino acid derivatives,



17

enamide

amide

Scheme III

the use of PipPhos, **3c**, and MorfPhos, **3d**, gave exceptional enantioselectivities for enamide reductions (18).

A solvent effect on enantioselectivity was also seen when the phosphoramidite (SIPHOS), **7**, was used as the ligand, although very high ees could still be achieved for the transformation summarised in Scheme III. It was found that small groups on nitrogen gave the highest selectivity (21). The introduction of substituents at the 4- and 4′-positions of SIPHOS did not increase enantioselectivity compared to the parent system (37). The ees for enamide reductions can be improved by use of the H_8-BINOL analogue of MonoPhos, **9a** (38). Even better improvements were observed with the catechol-derived phosphoramidite, **15** (31).

The use of the DpenPhos ligands, **10**, also provides high enantioselectivities for the reduction of aryl enamides (24), while the hybrid ligand, **13a**, also gives high turnovers (27, 28). In contrast, the reduced naphthyl analogue, **14**, gives reduced enantioselectivities (30).

3. Reductions to β-Amino Acid Derivatives

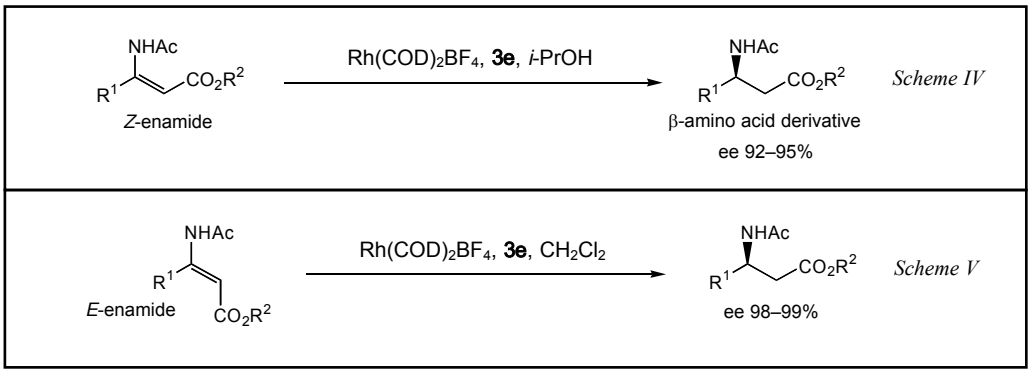
By comparison with α-amino acid derivatives, β-amino acid derivatives have not been so easy to access by asymmetric hydrogenation. One of the problems is that the substrate (enamide) is usually formed as a mixture of the *E*- and *Z*-isomers. To some extent this has now been solved, and the *E*-isomer (the one easier to reduce as there is no internal hydrogen bond in the substrate) can now be prepared in good yield (without resorting to chromatography) (39). The reduction of the *Z*-isomer of the enamide with bisphosphines has not been easy to achieve. However, the MonoPhos derivative, **3e**, was found to give good ees for the reduction of both the *E*- and *Z*-substrates (Schemes IV and V, respectively) (40). Although ligand **3e** has a stereogenic centre in the amine moiety, the asymmetric sense of the reduction is controlled by the atropisomerism of the ligand.

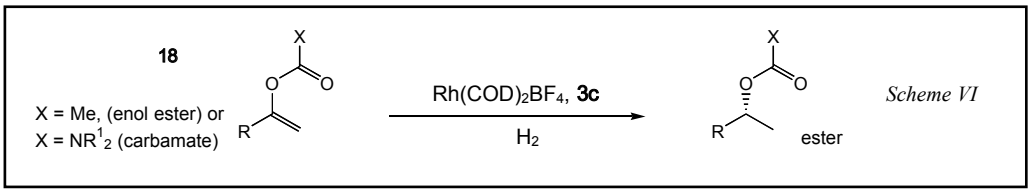
Once a screening tool for ligand libraries had been developed (see Section 8 on screening) it became clear from the validation studies that the phosphoramidite ligand, **3f**, derived from BINOL and isopropylamine gave the same enantioselectivities as **3e**, but the reduction was about five times faster (41).

Unlike other reductions with phosphoramidites, the best ligands to produce a β-amino acid derivative contain a proton on the nitrogen atom. This has been shown to be crucial to high selectivity with other systems, for instance, using hybrid ligand, **13b** (42).

4. Reduction of Enol Acetates and Carbamates

Enol acetates and carbamates can be reduced in the presence of phosphoramidite ligands (Scheme VI). The ligand PipPhos, **3c**, and its octahydro analogue, **9b**, have proved to be the most effective for this reduction (43). In addition, the highest asymmetric induction was observed with the *N*, *N*-diethyl carbamates (**18**, R^1 = Et). The overall transformation can be considered as the reduction of a ketone to a chiral secondary alcohol.

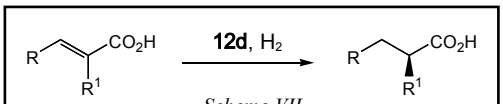




Scheme VI

5. Reduction of α,β-Unsaturated Acids

Reductions of α,β-unsaturated acids (Scheme VII) can be accomplished by MonoPhos ligands. However, it seems that the substitution in the BINOL system helps with enantioselectivity, as illustrated by the 3,3′-dimethyl derivative, **12d** (44). Also, the presence of an additional phosphine ligand, as discussed in Section 8, can enhance the enantioselectivity significantly, even when the phosphine is achiral.



Scheme VII

6. Phosphoramidite Variations and Synthesis

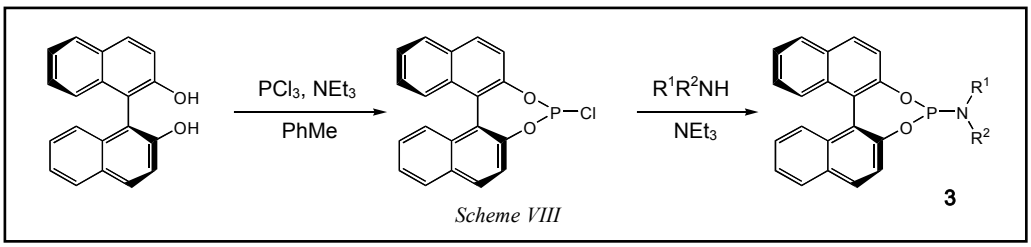
Although phosphoramidites can provide useful monodentate ligands to effect asymmetric hydrogenations over a wide range of carbon–carbon unsaturation, some variation in structure is required to obtain high enantioselectivity and reactivity. This is also an issue with other classes of ligands, when even a minor variation in a bisphosphine structure can result in a lengthy synthesis having to be undertaken to achieve the desired end product. By contrast, the MonoPhos family is simple to modify, and the reaction parameters can be modified by the use of other ligands (Section 8).

As with bisphosphines, empirical means have to be used to find the optimal balance between reaction rates, catalysis usage and stereoselectivity. (This article focuses on rhodium, but other metals may be used.) Some general rules can be drawn:

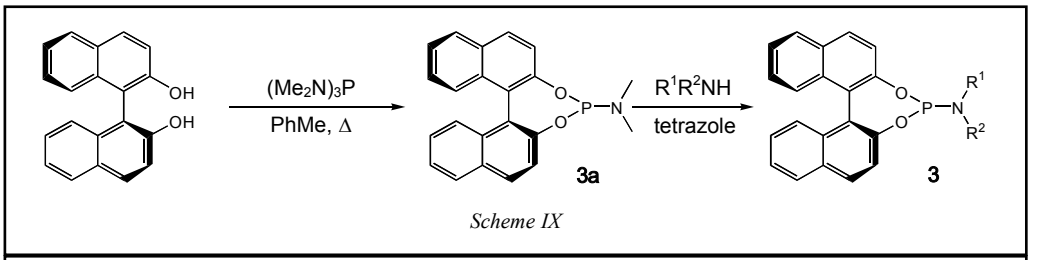
- using a 3,3′-disubstituted BINOL as the backbone results in slower reactions (16);
- protic solvents (with the exception of isopropanol) are less suitable (15, 16);
- lower temperatures increase enantioselectivity (15, 16); and
- an increase in hydrogen pressure increases the reaction rate without affecting enantioselectivity (13, 15, 16).

However, the subtle differences in reactivities between different groups on the nitrogen are not simple to predict (13), and screening studies are the best way to establish the best ligand for a reaction. Indeed, the ease of synthesis of the MonoPhos family of ligands lends itself to application in rapid screening methodology.

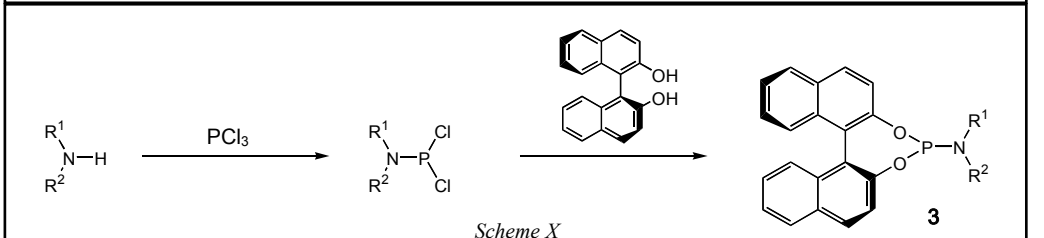
MonoPhos, **3a**, is simple to prepare in high yield from BINOL (bis-β-naphthol) and hexamethylphosphorus triamide (HMPT) (45). In addition to the parent, **3a**, the structure of the BINOL-derived phosphoramidites is simple to vary, merely by the use of a different amine in a modified synthetic sequence (Scheme VIII) (17, 46–48). A lithium amide can also be used in place of the reactive amine and base (16, 46). The amine group can also be modified by an amine exchange



Scheme VIII



Scheme IX



Scheme X

reaction with MonoPhos, **3a**, in the presence of tetrazole (Scheme IX) (16, 40, 48). For bulky amines, the reverse sequence to Scheme VIII has proven advantageous (Scheme X) (16, 23, 49).

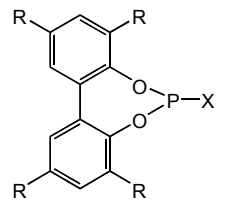
7. Mechanistic Considerations

Although just over two equivalents of the MonoPhos ligand, compared to the rhodium metal precursor, were used in the initial studies, a systematic series of experiments showed that reducing the amount of the phosphoramidite ligand to 1.5 equivalents, and even less, led to slightly faster reaction rates without any deleterious effect on the asymmetric selectivity (16, 48). Enantioselectivity does not alter during the course of a hydrogenation. When a number of reactions are compared a slight positive asymmetric amplification is seen (16). The mechanism of the reaction is far from being understood. However, it does seem that two phosphoramidite ligands are needed on the rhodium to explain the asymmetric amplification. Presumably, the two ligands generate the chiral environment, although it is not known how many phosphoramidites are on the metal in the key reduction step, as one phosphoramidite could have been displaced.

The use of slightly under two equivalents of the ligand can be explained by the many equilibria that are taking place in the reaction media and the formation of rhodium species (with three or four phosphoramidite ligands). These seem to be thermodynamically favoured structures which do not take part in the asymmetric hydrogenation (16).

Studies with the SIPHOS system, **7**, showed that reductions of dehydroamino esters were of zero order in the concentration of the substrate, and first order in hydrogen pressure. The reaction was also first order with respect to the rhodium catalyst, but the rate of hydrogenation decreased as the metal:ligand ratio was increased (50). These findings parallel the results obtained with the MonoPhos system (51).

In addition to variations in the ligand structure itself, increased asymmetric induction and reaction rates can also be seen when a second ligand, either chiral or achiral, is added. As an example, for the



19

a X = NR^1R^* **b** X = NR^*R^*
c X = OR^* **d** X = O-(1*S*,2*R*)-2-Ph-*c*-C_6H_{10}
e X = N(*S*-2-PhCHMe)$_2$

* denotes a group containing a stereogenic centre
c denotes cyclo-

formation of β-amino esters (*cf.* Scheme IV), the use of one equivalent of ligand **3e** with one equivalent of the octahydroBINOL-derived ligand, **9a**, resulted in higher ees and reaction rates than for either ligand by itself (52). A similar result had been observed by Reetz with phosphites and phosphonites in other reductions (53).

This use of mixtures greatly increases the number of possible permutations with chiral ligands: just ten examples give rise to fifty-five different combinations. Obviously, this mixing is not available with bisphosphine ligands.

Phosphoramidite monodentate ligands can also be used in combination with phosphite ligands, which may also be chiral. When a tropos backbone based on the biphenyl system, **19**, was used with two different chiral amine moieties for the formation of *N*-acetyl alanine, only moderate enantioselectivities were observed; these were generally lower than when a single phosphoramidite was used. However, reaction rate and asymmetric induction could be increased by a mixture of a phosphite, **19c**, and the phosphoramidite, **19a** or **19b**. The initial screening gave a combination of ligands that achieved an 87% ee for the reduction. Optimisation of the reaction parameters increased the selectivity to 94% ee (54).

Thus, mixtures of ligands can potentially improve performance in reductions of α- and β-amino esters, enamides, and itaconates, as compared with the use of a single chiral ligand. For instance, a mixture of **19d** and **19e** performed the best in preparing α-amino acids, as outlined in Scheme I (55).

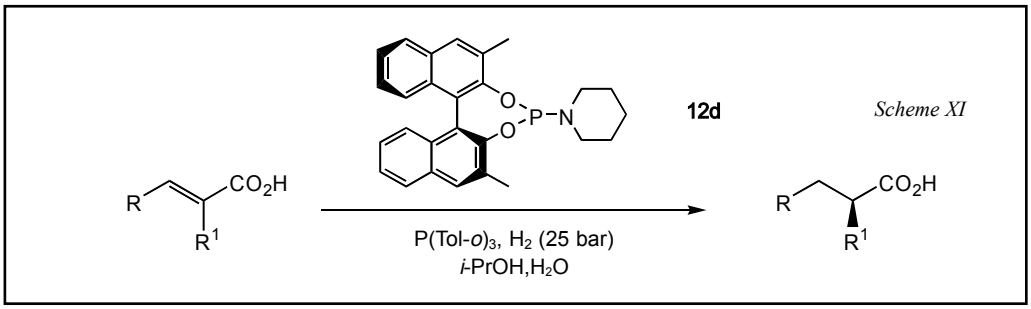
In general, asymmetric hydrogenations with monodentate phosphoramidite are slower than comparable ones with a phosphite ligand (55). A comparative rate study showed that monodentate ligands can perform at comparable rates on a specific substrate when the monodentate ligand is a phosphite or a phosphoramidite with one of groups on the nitrogen being a proton, as in **3e** (56). MonoPhos, **3a**, is significantly slower in asymmetric reductions than phosphite or bisphosphine ligands.

When a mixture of ligands is employed, the stoichiometry of the mixture may affect reaction rate. The use of a phosphite with a phosphoramidite results in a faster reduction than when just a phosphoramidite is employed. For optimal enantioselectivities, non-stoichiometric mixtures often give the best results (55).

8. Screening

The ease of synthesis of these ligands, and the need to investigate the reaction parameters to ensure high reaction rates and selectivities, are highly suited for high-throughput screening reactions (48).

A protocol has been designed for the parallel synthesis of ligand libraries in 96 well plates. A discrete ligand is prepared in each individual well. Key to the process is the removal of the chloride ions, as these can be detrimental to the subsequent asymmetric hydrogenation (21, 57). Filtration was found to be the easiest and best procedure for the removal. The resultant solution can then be evaporated in order to change the solvent from toluene (used in the ligand preparation step) to the reaction solvent. Substrate and metal precursor are then added, using a robot, and parallel hydrogenation reactions can then be performed. This method was



Scheme XI

validated for the reductions of methyl *N*-acetylamidocinnamate and methyl 3-(*N*-acetoamido)-but-2-enoate. The trends were the same as those seen with purified ligands, although the ees were slightly lower (41).

The high-throughput method can also be used to screen mixtures of ligands, and this includes examples with the addition of achiral phosphines. For the reductions of α,β-unsaturated acids (*cf.* Scheme VII), the addition of an achiral phosphone was found to enhance the reaction rate and enantioselectivity (Scheme XI) (44).

The rate of a reaction can be monitored *via* hydrogen uptake. An Endeavor® catalyst screening system is used in our laboratories, and this can monitor eight independent reactions at the same time (16). The ligand library approach can also be used for reactions other than asymmetric hydrogenations, as has been illustrated with conjugate additions to cyclic enones (58, 59).

Conclusions

Phosphoramidites, and in particular those derived from BINOL, the MonoPhos family of ligands, have proven extremely useful for the asymmetric hydrogenation of carbon–carbon unsaturation using a rhodium catalyst. The simple sequence to prepare these MonoPhos ligands, combined with the cheap starting material, makes them very competitive at an industrial scale when compared with bisphosphine ligands. Another advantage of the simple synthetic sequence is that it has been adapted for high-throughput experimentation, which allows for rapid screening for an appropriate ligand. The high-throughput experimentation can also be used to define reaction parameters.

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