DEVELOPMENT OF EFFICIENT PHOSPHORUS LIGANDS FOR TRANSITION METAL CATALYZED REACTIONS

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by
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ABSTRACT

Asymmetric hydroformylation is one of the most challenging transformations because it requires simultaneous control of both regio- and enantioselectivities. Though numerous chiral ligands have been developed for asymmetric hydroformylation, few of them can afford enantioselectivities of over 90% ee. To address these challenges, a new hybrid phosphine-phosphoramidite ligand, namely YanPhos, has been developed. The ligand has been investigated in the rhodium-catalyzed asymmetric hydroformylation of styrene derivatives, vinyl carboxylates and cyclic internal olefins. To the best of our knowledge, YanPhos provides the highest enantioselectivities ever reported in the asymmetric hydroformylations of styrene derivatives (up to 99 % ee) and vinyl carboxylates (up to 98 % ee).

Since linear aldehydes are very important raw materials for the polymer and detergent industries, highly regioselective hydroformylation catalysts are highly desirable. From the economic point of view, regioselective catalysts for the hydroformylation of internal olefins are very important. However, the regioselectivities achieved with current ligands are far from satisfactory. We have developed a new concept in designing ligands for regioselective hydroformylation: tetraphosphorous ligands with enhanced chelating ability through multiple chelating modes and increased local phosphorus concentration can provide higher regioselectivity than their corresponding bisphosphorus ligands. Based on this concept, two tetraphosphorus ligands have been designed, synthesized and successfully applied in highly regioselective hydroformylations. To the best of our knowledge, tetraphosphoramidite ligand provides the highest regioselectivity ever
reported in the homogenous isomerization-hydroformylation of internal olefins. Tetraphosphine ligand exhibits remarkable improved high temperature performance in the hydroformylation of terminal olefins.

Though many efficient chiral ligands have been developed for asymmetric hydrogenation, there is no universal ligand which can hydrogenate all prochiral substrates with high enantioselectivity. To expand the substrate scope, the development of new chiral ligands with novel structural motifs is highly desirable. Furthermore, efficient chiral ligands made from inexpensive readily available starting material are of significant importance for large scale industrial applications. Thus, an efficient chiral bis(azaphosphorinane) ligand has been developed. This ligand can be synthesized from inexpensive chiral epoxide and provides comparable or even better enantioselectivities than DuPhos in the rhodium-catalyzed asymmetric hydrogenations of β-dehydroamino acid derivatives and aryl enamides (up to > 99 % ee for both types of substrates). Two hybrid phosphorus ligands have also been developed. These hybrid ligands bearing binaphthyl backbone with ortho phenyl substituents provide excellent enantioselectivities in the rhodium-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives (up to >99 % ee).
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Chapter 1

Introduction

1.1 Rhodium-Catalyzed Hydroformylation

1.1.1 Background

Hydroformylation is the reaction of olefins with carbon monoxide and hydrogen to form aldehydes (Eq. 1.1).\(^1\) It was discovered by Otto Roelen in 1938.\(^2\) Roelen’s original research in hydroformylation involved the use of cobalt catalysts. Not surprisingly, cobalt catalysts dominated industrial hydroformylation processes during the early stages. In the 1960’s, Wilkinson and coworkers found that rhodium complexes modified by phosphine ligands can also catalyze hydroformylation with high activity and selectivity.\(^3\) Because rhodium catalysts are much more reactive and selective than cobalt catalysts,\(^4\) they have replaced the latter since the early 1970’s. Today, rhodium-catalyzed hydroformylation is one of the most important applications of homogeneous catalysis in industry. Over 6 million tons of hydroformylation products have been produced by this way every year. The most active research area in hydroformylation is the development of highly selective phosphorus ligands. The selectivities in hydroformylation include enantioselectivity (high enantiomeric excess if the branched product is desired) and regioselectivity (high linear/branched ratio if the linear product is desired).
1.1.2 Mechanism for Rhodium-Catalyzed Hydroformylation

The currently widely accepted mechanism for the rhodium-catalyzed hydroformylation reaction is similar to the one originally proposed by Breslow and Heck for cobalt-catalyzed hydroformylation (Scheme 1-1).\(^{1b,5}\) Thus, an 18e trigonal bipyramidal intermediate \(A\) is formed after the reaction of rhodium precursor with ligand in the presence of CO and H\(_2\). The dissociation of one carbon monoxide from this intermediate generates a 16e coordinatively unsaturated species \(B\). Then the coordination of olefin to the rhodium center in the equatorial position takes place, forming a trigonal bipyramidal hydrido olefin complex \(C\). The regio- and enantioselectivities of the hydroformylation reaction are determined in the subsequent olefin insertion step which generates tetragonal alkyl rhodium complexes \(D\) (leading to branched product) and \(E\) (leading to linear product). Trigonal bipyramidal complexes \(F\) and \(G\) are then formed via the coordination of carbon monoxide to the rhodium center. The migratory insertion of the alkyl group to one of the coordinated carbon monoxide yields tetragonal acyl complexes \(H\) and \(I\). The subsequent oxidative addition of hydrogen generates tetragonal bipyramidal rhodium complexes \(J\) and \(K\). Finally, Reductive elimination affords the branched aldehydes \(L\) and the linear aldehyde \(M\) and regenerates the catalytically active species \(B\).
Scheme 1-1: Mechanism for Rhodium-Catalyzed Hydroformylation
1.1.3 Chiral Phosphorus Ligands for Rhodium-Catalyzed Asymmetric Hydroformylation

Asymmetric hydroformylation is of great importance for the pharmaceutical and agrochemical industries.\textsuperscript{1, 6} Optically active aldehydes which can be prepared by asymmetric hydroformylation are valuable intermediates for the preparation of a variety of biologically active compounds. For example, enantiomerically pure 2-arylpropanoic acids such as Ibuprofen, Ketoprofen and Naproxen, which are important nonsteroidal anti-inflammatory agents, can be synthesized by the asymmetric hydroformylation of vinylarenes followed by oxidation; optically active $\alpha$-amino acids such as L-isoleucine, D-threonine and D-alanine can also be conveniently prepared from chiral aldehydes obtained by the asymmetric hydroformylation of simple olefins.\textsuperscript{6} The major efforts in asymmetric hydroformylation are focused on the design and synthesis of new chiral ligands. Though rhodium-catalyzed asymmetric hydroformylation has been studied extensively, before the end of 1992 no phosphorus ligand capable of affording over 60 % ee was reported. Since then, considerable progress has been achieved in this area. In this section, we will briefly review the progress in asymmetric hydroformylation since the early 1990’s.

Rhodium complexes modified with diphosphite ligands exhibit higher activity in hydroformylation than those modified with diphosphine ligands because diphosphite ligands are less electron-donating. The high activity of rhodium-diphosphite catalysts enable hydroformylation reactions to be conducted at relatively low temperature which is preferable in order to obtain high enantioselectivity. Chiral diphosphite ligands now
constitute a major family of ligands in asymmetric hydroformylation. Several representative diphosphite ligands are shown in Figure 1-1.

The first successful diphosphite ligand for highly enantioselective hydroformylation was developed by Babin and Whiteker at Union Carbide in 1992. The ligand, named Chiraphite 1, was prepared from chiral (2R, 4R)-pentane-2, 4-diol. Excellent enantioselectivities (up to 90 % ee) have been achieved using this ligand in the asymmetric hydroformylation of styrene under mild reaction conditions. The key to the high enantioselectivity of this ligand is the introduction of bulky substituents at the ortho-positions of the biphenyl moieties. It is believed that steric hindered substituents such as t-Butyl groups help to effectively transfer the chiral information of the backbone to the non-chiral biphenyl moieties.

Encouraged by the excellent results obtained with Chiraphite 1, van Leeuwen and coworkers prepared and evaluated a number of chiral diphosphite ligands structurally related to Chiraphite 1 in asymmetric hydroformylation. Systematic studies on the influence of the bridge length, phosphite moieties, ortho-substituents and backbone substituents have been conducted. However, none of these ligands could afford higher enantioselectivity than the original Chiraphite 1.

Inspired by the success of BINOL-derived ligands in asymmetric catalysis, several research groups studied diphosphite ligands bearing a chiral binaphthyl backbone in asymmetric hydroformylation. However, the enantioselectivities obtained were disappointingly low (ee’s up to 37%).
Figure 1-1: Diphosphite Ligands for Asymmetric Hydroformylation
Another type of diphosphite ligand was based on a spiro backbone.\textsuperscript{10} Chan and coworkers developed a series of chiral diphosphite ligands 2 and 3 from spiro [4.4]nonane-1,6-diol for the asymmetric hydroformylation of styrene. Moderate enantioselectivities (up to 65% ee) have been obtained using this type of ligand.

Chiral diphosphite ligands bearing sugar backbones have gained much attention recently due to their readily availability and high enantioselectivity. Van Leeuwen reported the first example of diphosphite ligand 4 prepared from a sugar for asymmetric hydroformylation. Moderate enantioselectivities (65 % ee) have been achieved for styrene derivatives.\textsuperscript{11} Diéguez studied diphosphite ligand 5 bearing a furanoside backbone.\textsuperscript{12} Excellent enantioselectivities (up to 91%) have been achieved in the hydroformylation of styrene derivatives with ligand 5a. For the more difficult 2, 5- and 2, 3-dihydrofuran substrates, ligand 5b afforded better enantioselectivities (up to 74% ee) compared with 5a.

An interesting diphosphite ligand 6 with a chiral macrocyclic backbone was reported by Freixa and coworkers for the asymmetric hydroformylation of styrene.\textsuperscript{13} The enantioselectivity was moderate (up to 76 % ee).

Most of diphosphone ligands have a chiral backbone. Recently, a chiral diphosphite ligand, known as Kelliphite 7, with a non-chiral 2, 2-biphenol backbone and chiral phosphite moieties, was developed by Klosin and coworkers at Dow.\textsuperscript{14} Good enantioselectivity (80 % ee) as well as high activity have been obtained using this ligand in the asymmetric hydroformylation of allyl cyanide. The chiral aldehyde product can be subsequently transformed into (R)-2-methyl-4-aminobutanol, a useful chiral building block for the pharmaceutical industry.
Though C2 symmetric ligands dominate in asymmetric catalysis, hybrid ligands bearing different phosphorus ligands have proved especially successful in asymmetric hydroformylation (Figure 1-2). The major breakthrough in rhodium-catalyzed asymmetric hydroformylation was made in 1993, when Takaya and Nozaki reported a hybrid phosphine-phosphite ligand based on the binaphthyl backbone. The ligand, known as Binaphos 8, has been investigated in the asymmetric hydroformylation of a variety of prochiral olefins and proved to be efficient for styrene derivatives and vinyl carboxylates. For example, up to 94 % ee and 92 % ee has been achieved for styrene and vinyl acetate, respectively. In order to obtain high enantioselectivity, the configurations of the two binaphthyl moieties in Binaphos 8 need to be opposite (a matched case). One important structural feature of Binaphos 8 is that only equatorial-axial coordination is possible when the ligand complexed with rhodium center in the presence of CO and H₂. In the trigonal bipyramidal rhodium complex, the phosphite selectively takes up the axial position while the phosphine occupies the equatorial position. The formation of the single isomer is believed to originate from the different electronic properties of the two phosphorus groups.

Since then, modifications of Binaphos 8 have been made in order to improve the catalyst performance. Nozaki reported a structurally closely related Binaphos derivative bearing a chiral biphenyl backbone, Biphemphos 9, which exhibited similar enantioselectivities as the parent Binaphos 8 ligand. Changing the phenyl groups of Binaphos 8 with substituted aryl groups led to slightly improved enantioselectivity. Perfluoroalkyl-substitution of the aryl groups in Binaphos 8 provided high affinity of the ligand for super critical CO₂ and allowed for the use of compressed CO₂ as an
environmentally and toxicologically benign solvent without any decrease of enantioselectivity. Ojima and coworkers developed another type of fluorinated Binaphos derivative by introducing perfluoroalkyl substituents onto the binaphthyl moiety of Binaphos ligand. With these ligands, asymmetric hydroformylation can also be conducted in supercritical CO$_2$ with high enantioselectivity.

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**Figure 1-2: Hybrid Ligands for Asymmetric Hydroformylation**

Inspired by the excellent results achieved with the hybrid Binaphos 8 ligand, more hybrid bidentate ligands bearing different phosphorus groups have been developed. Van Leeuwen investigated phosphine-phosphite 10, bearing a P-chiral phosphine and chiral backbone, in the rhodium-catalyzed asymmetric hydroformylation of styrene. Enantioselectivity of 63% ee and regioselectivities of up to 92% were obtained.

Starting from ephedrine, van Leeuwen and coworkers developed a new aminophosphine-phosphinite ligand 11 bearing a stereogenic center at the
aminophosphine phosphorus atom. The ligand was tested in the asymmetric hydroformylations of styrene and other vinylic substrates. Good enantioselectivity (up to 77%) has been obtained under mild reaction conditions.

Leitner used a phosphine-phosphoramidite ligand with a 1, 2 dihydroquinoline backbone, QUINAPHOS, for the asymmetric hydroformylation of styrene. The best enantioselectivity was 74 % ee.

Phosphorus ligands other than diphosphites and hybrid ligands with high enantioselectivities are listed in Figure 1-3.

Ligand 13, which was developed by Wills and coworkers, has been successfully applied to the asymmetric hydroformylation of vinyl acetate with up to 90% ee. Interestingly, the hydroformylation of styrene with this ligand only gave racemic products.

Lu and coworkers reported a bidentate bisphosphine ligand prepared from d-glucose, 1, 6-anhydro-2, 4-bis(diphenylphosphino)pyranose, for asymmetric hydroformylation. Like ligand 13, ligand 14 only provided high enantioselectivity (92 % ee) for vinyl acetate. For styrene and other substrates, the results were not so good.

Though bidentate bisphosphorus ligands dominate in asymmetric hydroformylation, a recent study has shown that monodentate phosphoramidite ligands were also effective in asymmetric hydroformylation. Ojima and coworkers developed a series of phosphoramidite ligands based on enantiopure 6, 6-dimethylbiphenols. Good enantioselectivity were obtained in the asymmetric hydroformylation of allyl cyanide (80 % ee) when the ligand 15 bare t-Butyl groups in the 3, 3’ position of the biphenol backbone.
Very recently, Landis and coworkers developed a new family of bis-3, 4-diazaphospholane ligands and studied their performance in rhodium-catalyzed asymmetric hydroformylation. With ligand 16, good to excellent enantioselectivities have been achieved in the rhodium-catalyzed asymmetric hydroformylation of three different classes of substrates (vinyl acetate: 96 % ee, allyl cyanide: 87 % ee, styrene 82 %). However, the ligand synthesis involved the use of preparative chiral HPLC which limits the ligand to small-scale applications.

Inspired by the excellent enantioselectivities achieved with bis-3, 4-diazaphospholanes 16, Klosin and coworkers investigated several structural related bisphospholanes in asymmetric hydroformylation. \((R, R)\)-Ph-BPE 17 was found to be an excellent ligand for asymmetric hydroformylation. For example, up to 94 % ee and 90
% ee have been achieved in the hydroformylation of styrene and allyl cyanide, respectively. This ligand gave good enantioselectivity for vinyl acetate substrate (82 % ee).

1.1.4 Phosphorus Ligands for Rhodium-Catalyzed Regioselective Hydroformylation

Linear aldehydes are important raw materials for the preparation of polymer plasticizers and detergents. Most of the 6 million tons of aldehydes produced annually by hydroformylation process are used in these applications. Since the linear products generally afford better properties than branched ones, highly regioselective hydroformylation is an important issue in industrial applications.¹

Hydroformylation of internal olefins to linear aldehydes became a highly active research area recently because of this enormous industrial interest (Eq. 1.2).²⁸ For example, regioselective hydroformylation of “Raffinate-2” followed by aldol condensation and hydrogenation leads to a linear C10 alcohol which is an important raw material for the preparation of plasticizers. “Raffinate-2” is a C4 feedstock mainly composing of internal butenes derived from mixed C4 streams of steam crackers. Thus, the development of highly selective and active hydroformylation catalysts for internal olefins is of great importance from economic and energy points of view.

$$\text{RCHO} + [\text{Rh/ligand}] \xrightarrow{\text{CO/H}_2} \text{CHO} \quad \text{1.2}$$

Commercial hydroformylation processes use monophosphines as ligands. Recently, bidentate ligands have attracted much more attention because they generally
afford higher regioselectivity than monophosphines. In this section, we will briefly review phosphorus ligands used in regioselective hydroformylation, with the focus on bidentate ligands.

Highly regioselective rhodium-catalyzed hydroformylation using a bidentate phosphorus ligand was first reported in 1987. The chelating bisphosphine known as Bisbi 18 (Figure 1-4) developed by Devon and coworkers at Eastman Kodak provided exceptionally high regioselectivity for the hydroformylation of propene. Casey and coworkers systematically investigated the correlation between ligand bite angles and the regioselectivity in hydroformylation. They found that ligands with a natural bite angle of about 120° such as Bisbi 18 are capable of forming equatorial-equatorial coordination at the rhodium center, thus leads to high regioselectivity in hydroformylation. Beller and coworkers later found that NaPhos ligands 19 with strong electron-withdrawing substituents are excellent ligands for regioselective hydroformylation of internal olefins to linear aldehydes (linear/branched ratio n:i of up to 9.5:1) 31

![Figure 1-4: Ligands Derived from Bisbi for Regioselective Hydroformylation](image)

A number of highly regioselective ligands have been developed based on this ‘natural bite angle’ concept. Among them, XantPhos 20 (Figure 1-5) developed by van Leeuwen and coworkers has proved to be one of the best ligands for regioselective
hydroformylation. For example, linear/branched ratios of up to 53:1 has been achieved with Xantphos 20 in the hydroformylation of 1-octene.\textsuperscript{32} However, a detailed structural study showed that although regioselectivity for linear aldehyde correlates well to the natural bite angle, the coordination modes in the rhodium complexes do not determine the regiochemistry in the hydroformylation reaction. For example, van Leeuwen found that several Xanphos family ligands that prefer equatorial-axial coordination can also produce product with high regioselectivity, which is in contrast to Casey’s proposal that bisequatorial coordination is a prerequisite for highly regioselective hydroformylation. The bite angle effect on regioselectivity is now believed to influence steric interactions between ligand and substrates in the steps of olefin coordination and hydride migration. Widening the bite angle leads to an increase in steric congestion around the rhodium center which results in the formation of the sterically less demanding linear alkyl rhodium species.\textsuperscript{33} Dibenzophospholy1 and phenoxaphosphanyl-substituted XantPhos type ligands 21 and 22 were later developed by van Leeuwen and coworkers.\textsuperscript{34} These ligands showed high activity and regioselectivity in the rhodium-catalyzed hydroformylation of both terminal and internal octenes. Van Leeuwen also synthesized bulky diphosphite ligands 23\textsuperscript{35} and phosphorus diamide ligands 24\textsuperscript{36} based on the xanthene backbone. However, the regioselectivity with ligands 23 and 24 was not good.
Another important family of ligands for highly regioselective hydroformylation is the bulky diphosphites (Figure 1-6). With Biphephos 25, originally developed by Billig and coworkers at Union Carbide, Buchwald studied hydroformylation of a variety of functionalized olefins under mild reaction conditions, and observed high linear selectivity. Typically, linear/branched ratios of over 40:1 were achieved, and the catalyst can tolerate ketones, carboxylic acids, helides, acetals and thioacetals. Unsymmetrical Biphephos derivative 26 developed by van Leeuwen and coworkers also showed high regioselectivity in the hydroformylation of terminal olefins. For example, linear/branched ratios of up to 48 have been reported in the hydroformylation of 1-octene.
Using molecular modeling calculations, Paciello and coworkers designed and synthesized a chelating diphosphite ligand 27 based on the \( p \)-tert-butyl calix[4]arene backbone.\textsuperscript{40} With this ligand, very high regioselectivity has been observed in the rhodium-catalyzed hydroformylation of 1-octene.

Börner used unsymmetrical phosphite-acylphosphite ligands 28 for the hydroformylation of \( n \)-octene mixtures with very high activity, leading to mainly linear aldehyde products.\textsuperscript{41}

\textbf{Figure 1-6: Bulky Diphosphites for Regioselective Hydroformylation}
Bisbi derivatives, Xantphos derivatives and bulky diphosphites are the three most successful types of ligands in regioselective hydroformylation. Figure 1-7 lists some other types of phosphorus ligands used in regioselective hydroformylation.

Electron-withdrawing N-sulfonylphosphoramidate ligand 29 was developed by Hersh and coworkers. Moderate regioselectivity with a linear/branched ratio of up to 15.8 was obtained with this ligand in the hydroformylation of 1-hexene. Ziółkowski and coworkers first reported pyrrole-based ligands in regioselective hydroformylation. Later, van Leeuwen used bidentate pyrrole-based phosphorus amidite ligand 30 for the hydroformylation of 1-octene. Very high regioselectivity for the linear aldehyde (linear/branched ratio ≈ 100) has been achieved together with moderate isomerization to form 2-octenes. Breit and coworkers used phosphabenzenzene ligand 31 in rhodium-
catalyzed hydroformylation reactions. The catalyst exhibits very high reactivity, as even tetrasubstituted olefins were hydroformylated with noticeable rates.\textsuperscript{45} Phosphabarrelene has been synthesized and tested in the hydroformylation of internal olefins by Breit and coworkers. Interestingly, unlike other known catalysts designed for the hydroformylation of internal alkenes, which usually undergo isomerization before hydroformylation, the rhodium-phosphabarrelene catalysts hydroformylate an internal double bond without olefin isomerization.\textsuperscript{46} Recently, Breit developed a new type of ligand \textsuperscript{33}.\textsuperscript{47} This ligand was formed by self-assembly through the hydrogen bonding of 6-(diphenylphosphino) pyridin-2(1H)-one with its hydroxypyridine tautomer. High regioselectivity has been achieved in the hydroformylation of simple terminal olefins as well as with a wide range of functionalized terminal olefins.

1.2 Rhodium-Catalyzed Asymmetric Hydrogenation

1.2.1 Background

In late 1960’s, the first example of asymmetric hydrogenation was reported by Knowles and coworkers.\textsuperscript{48} By replacing the triphenylphosphine of Wilkinson’s catalyst [RhCl(PPh$_3$)$_3$] with a chiral monophosphine, Knowles obtained enantiomeric excess of 15 % in the hydrogenation of phenylacrylic acid. Kagan and coworkers later found that chelating bisphosphorus ligands with chiral backbones were also effective for asymmetric hydrogenation.\textsuperscript{49} The famous P-chiral bisphosphine ligand DIPAMP was developed by Knowles and later successfully applied in the industrial production of l-DOPA.\textsuperscript{50}
Following the pioneering work of Knowles and Kagan, people have developed numerous chiral ligands for asymmetric hydrogenation. Today, asymmetric hydrogenation has become one of the most efficient methods for the preparation of chiral compounds.\textsuperscript{51} In the following sections, we will restrict the discussion to rhodium-catalyzed asymmetric hydrogenation, although other transition metals such as ruthenium, iridium and palladium have also been used in asymmetric hydrogenation with high efficiency.

1.2.2 Mechanisms for Rhodium-Catalyzed Hydrogenation

There are two generally accepted mechanisms for rhodium-catalyzed asymmetric hydrogenation: the “unsaturated” mechanism and the “dihydride” mechanism. The so-called “unsaturated” mechanism proposed by Halpern\textsuperscript{52} consists of the following steps (Scheme 1-2): (1) the coordination of the substrate to the solvate complex $N$ to form the catalyst-substrate complex $O$; (2) the oxidative addition of $H_2$ to the rhodium center to furnish the dihydride intermediate $P$; (3) the migratory insertion (rate determining step) of the substrate to provide the rhodium-hydridoalkyl species $Q$; (4) the reductive elimination to afford the catalyst-product complex $R$ and (5) the solvation of the catalyst-product complex $R$ to liberate the hydrogenation product and regenerate the catalyst $N$. In this mechanism, when a $C_2$ symmetric chiral ligand is used, the asymmetric induction is controlled by the relative activity of two possible diastereoisomers of catalyst-substrate complex $O$ rather than their relative abundance. Halpern’s mechanism can explain the experimental results in some catalytic systems such as the rhodium-DIPAMP catalyst and was commonly accepted in the 1980s. However, this theory can
not explain the experimental results of other rhodium catalysts, especially those prepared from newly developed electron-rich phosphine ligands.

Scheme 1-2: “Unsaturated” Mechanism for Rhodium-Catalyzed Asymmetric Hydrogenation

Imamoto and coworkers studied the asymmetric rhodium-catalyzed hydrogenation with electron-rich ligands in detail and proposed the so-called “dihydride” mechanism. The “dihydride” mechanism involves the following steps (Scheme 1-3): (1) the oxidative addition of hydrogen to the solvate complex N to form the solvate dihydride complex T; (2) the coordination of the substrate to the rhodium center to generate the dihydride intermediate U; (3) the migratory insertion of the substrate to provide the rhodium-hydridoalkyl species Q; (4) the reductive elimination to afford the catalyst-product complex R, and (5) the solvation of the catalyst-product complex R to liberate the hydrogenation product and regenerate the catalyst N. This mechanism is in contrast
to the classic “unsaturated” mechanism of Halpern, where the coordination of the substrate takes place before the oxidative addition of hydrogen. For rhodium-catalyzed asymmetric hydrogenation with electron-rich phosphine ligands, the reaction is more likely to proceed via the “dihydride” mechanism.

Scheme 1-3: “Dihydride” Mechanism for Rhodium-Catalyzed Asymmetric Hydrogenation

1.2.3 Chiral Phosphorus Ligands for Rhodium-Catalyzed Hydrogenation

The development of chiral ligands plays an important role in asymmetric hydrogenation. Though numerous ligands have been developed for asymmetric hydrogenation, they can be fit into only a few categories: 1) chiral monodentate phosphorus ligands; 2) atropisomeric biaryl bisphosphine ligands 3) cyclic bisphospholanes 4) P-chiral phosphines; 5) ferrocenyl based ligands and 6) bidentate
ligands with P-O or P-N bonds. In this section, we will discuss only those representative ligands (Figure 1-8) since most of the efficient ligands are derived from them.

Figure 1-8: Representative Chiral Ligands for Rhodium-Catalyzed Asymmetric Hydrogenation
Monodentate phosphines were the first chiral ligands used in asymmetric hydrogenation. For several decades, they were thought to be less effective than bidentate phosphorus ligands. Recently, a number of efficient monodentate phosphorus ligands have been developed for rhodium-catalyzed asymmetric hydrogenation with excellent enantioselectivity. The most successful monodentate ligands are monophosphite (developed by Reetz), monophosphoramidite ligand based on Binol (developed by Feringa) and SiPhos (developed by Zhou) based on spiro 1, 1’-spirobiindane-7.7-diol. The substrate scope of monophosphorus ligands includes dehydroamino acid derivatives, itaconates and aryl enamides.

The first successful bidentate phosphorus ligand for rhodium-catalyzed asymmetric hydrogenation was DIOP developed by Kagan and coworkers. The ligand, which bears a chiral backbone, affords enantioselectivity comparable to those with chirality directly on the phosphorus atom. The invention of DIOP had a significant impact on the design of new ligands with chiral backbone for highly enantioselective asymmetric hydrogenation. Though DIOP itself only provided moderate enantioselectivity, a number of DIOP derivatives have been developed for asymmetric hydrogenation that proceed with excellent enantioselectivities.

One of the most successful chiral phosphorus ligands for asymmetric hydrogenation is Binap, an atropisomeric biaryl bisphosphine ligand developed by Noyori and coworkers. It was first used in rhodium-catalyzed asymmetric hydrogenation but displayed only limited substrate scope. Later Binap was applied to ruthenium-catalyzed asymmetric hydrogenation with broadened substrate scope. Today, Binap and its derivatives are without any doubt the most versatile ligands in asymmetric...
hydrogenation and other important enantioselective transformations.

A significant advance in rhodium-catalyzed asymmetric hydrogenation was achieved in the early 1990s, when Burk and coworkers developed a new series of efficient chiral bisphospholane ligands BPE 39 and DuPhos 40. The invention of BPE and DuPhos greatly broadened the substrate scope of rhodium-catalyzed asymmetric hydrogenation. With these electron-rich phospholane ligands, a variety of prochiral unsaturated substrates could be hydrogenated with excellent enantioselectivity.

The first P-chiral bisphosphine ligand DIPAMP 41 was developed by Knowles and coworkers. Rhodium-DIPAMP complex catalyzed asymmetric hydrogenation has been successfully applied to the preparation of l-DOPA with enantioselectivities of up to 96 % ee. Recently, Imamoto and coworkers discovered a series of efficient trialkyl P-chiral ligands such as Bisp* 42 for asymmetric hydrogenation. A variety of prochiral substrates have been hydrogenated with this ligand with high activity and enantioselectivity.

JosiPhos 43 developed by Togni and coworkers represents the most versatile and successful ferrocenyl based ligand. A variety of Josiphos derivative are available by tuning the steric and electronic properties of the two phosphine groups. The ligand has been successfully applied in industrial scale for the preparation of pharmaceutical products.
1.3 Objectives

Asymmetric hydroformylation is one of the most challenging transformations because it requires simultaneous control of both regio- and enantioselectivities. Furthermore, chiral aldehyde products may undergo racemization under hydroformylation conditions. The extent of racemization can be severe for certain substrates. Although numerous chiral ligands have been developed for asymmetric hydroformylation, few of them can afford enantioselectivities of over 90% ee. To address these challenges, a new hybrid phosphine-phosphoramidite ligand, namely YanPhos, has been developed in our lab. In chapter 2, the design, synthesis and application of YanPhos in asymmetric hydroformylation will be discussed in detail. To the best of our knowledge, this new ligand provides the highest enantioselectivities in the asymmetric hydroformylations of styrene derivatives (up to 99 % ee) and vinyl carboxylates (up to 98 % ee).

Since linear aldehydes are very important raw materials for polymer and detergent industries, highly regioselective hydroformylation catalysts are highly desirable. From the economic point of view, regioselective catalysts for hydroformylation of internal olefins are very important. However, the regioselectivity achieved with current ligands is far from satisfactory. In chapter 3, the development of two conceptually new tetraphosphorus ligands will be discussed. These ligands have showed very high regioselectivity in rhodium-catalyzed hydroformylation of both internal olefins and terminal olefins. The regioselectivity achieved with the tetraphosphoramidite ligand in the homogenous hydroformylation of internal olefins, to the best of our knowledge, is the best ever reported.
Although many efficient chiral ligands have been developed for asymmetric hydrogenation, there is no universal ligand which can hydrogenate all prochiral substrates with high enantioselectivity. To expand the substrate scope, the development of new chiral ligands with novel structural motifs is highly desirable. Furthermore, from the economic point of view, efficient chiral ligands made from inexpensive readily available starting materials are of significant importance for large scale industrial applications. In chapter 4, the development of an efficient chiral bis(azaphosphorinane) ligand will be discussed. This ligand can be synthesized from inexpensive chiral epoxide and provides comparable or even better enantioselectivity than DuPhos in the asymmetric hydrogenation of β-dehydroamino acid derivatives and aryl enamides. In chapter 5, the development of two hybrid phosphorus ligands will be discussed. These hybrid ligands bearing the binaphthyl backbone with ortho phenyl substituents provide excellent enantioselectivity in the rhodium-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives.
References


2. (a) Roelen, O. (Chemische Verwertungsgesellschaft, mbH Oberhausen) German Patent DE 849548, **1938/1952**; (b) Roelen, O. (Chemische Verwertungsgesellschaft, mbH Oberhausen) U.S. Patent 2327066, **1943**.


Chapter 2

Development of Hybrid Phosphorus Ligand for Highly Enantioselective Asymmetric Hydroformylation

2.1 Introduction

Hydroformylation is the reaction of olefins with carbon monoxide and hydrogen to form aldehydes, which provides a versatile method for the functionalization of C-C double bonds [Eq. 2.1]. Styrene derivatives and olefins with adjacent functional groups such as vinyl carboxylates allow $\alpha$-regioselective hydroformylation, leading to the selective formation of branched aldehydes with new stereogenic centers generated. Because chiral aldehydes can be easily converted into a variety of enantiomerically pure compounds, asymmetric hydroformylation\(^1\) is potentially useful for the preparation of pharmaceutical products.

\[ \frac{[\text{Rh}]/\text{ligand}}{\text{CO}/\text{H}_2} \rightarrow \begin{cases} \text{R} & \text{Branched} \\ \text{R} & \text{Linear} \end{cases} \]

Despite its importance, asymmetric hydroformylation is underdeveloped. Achieving high ee’s (≥ 98% ee) remains a challenging goal due to the following reasons: First, hydroformylation reactions are often carried out at elevated temperature in order to achieve acceptable reaction rate. However, high enantioselectivities are generally observed at low temperature with relatively low reaction rates and at low conversion. This situation limits the utility of this important transformation. Second, the aldehyde products, especially for those hydroformylated from styrene derivatives, can undergo
This racemization results in lower ee’s at high conversion in some catalytic systems. To the best of our knowledge, only a few ligands\textsuperscript{2} are capable of affording over 90\% ee’s in asymmetric hydroformylation. Recent reports have shown that mixed phosphorus ligands bearing two different phosphorus groups are effective in asymmetric hydroformylation.\textsuperscript{2a-2b, 3} Binaphos\textsuperscript{2a-2b, 4} (Figure 2-1) a hybrid phosphine-phosphite ligand developed by Takaya and coworkers, has proved to be one of the benchmark ligands for the asymmetric hydroformylation of vinylarenes. For example, up to 94\% ee has been achieved for the hydroformylation of styrene with rhodium-Binaphos catalyst. However, racemization remains a major problem for Binaphos\textsuperscript{2b,4a} and the enantioselectivity can be further improved. The development of chiral phosphorus ligands for highly enantioselective hydroformylation without the racemization of chiral products is highly desirable.

In this chapter, the design and synthesis of a new hybrid phosphine-phosphoramidite ligand, YanPhos \textbf{1}, as well as its application in asymmetric hydroformylation, will be discussed. With \((R, S)\)-YanPhos \textbf{1} as the ligand, unprecedented
high enantioselectivities (up to 99% ee) have been achieved for asymmetric hydroformylation and significant performance enhancement has been obtained compared with the benchmark ligand, Binaphos.

2.2 Results and Discussions

2.2.1 Design and Synthesis of Phosphine-Phosphoramidite YanPhos

Takaya and coworkers have demonstrated that configuration matched \((R, S\) and \(S, R)\) Binaphos lead to better enantioselectivity than mis-matched \((R, R\) and \(S, S)\) Binaphos.\(^{2b}\) As the phosphine-phosphoramidite analogue of Binaphos, we anticipated that \((R, S)\)-YanPhos and its enantiomer are the configuration matched isomers. We thus synthesized \((R, S)\)-YanPhos for the current study. Despite the similarity, there are significant differences between Binaphos and the YanPhos ligand, both electronically (phosphoramidites are more electron-donating than phosphites since the electronegativity of nitrogen (3.04) is less than that of oxygen (3.44)) and sterically. Hence, replacing the phosphite group in Binaphos with the \(N\)-substituted phosphoramidite group in ligand YanPhos represents substantial change. Figure 2-2 shows the space-filling and stick models (based on CAChe MM2 calculation) for \(\text{Rh}[(R, S)\text{-YanPhos}]\text{H(CO)}_2\) and \(\text{Rh}[(R, S)\text{-Binaphos}]\text{H(CO)}_2\) complexes, which are presumed to be the active intermediates in hydroformylation reactions.\(^{2a-2b}\) As shown in Figure 2-2, in the presence of the crowded \(N\)-substituent, the \(\text{Rh}[(R, S)\text{-YanPhos}]\text{H(CO)}_2\) complex can provide a deeper and more closed chiral pocket than the corresponding \(\text{Rh}[(R, S)\text{-Binaphos}]\text{H(CO)}_2\) complex.
Molecular dynamics simulations based on the CAChe program also indicate that the rhodium complex of ligand YanPhos is more conformationally rigid than the analogous Binaphos complex due to the presence of the \(N\)-substituent of the phosphoramidite part in YanPhos. We envision that a more closed rigid chiral pocket provided by \(\text{Rh}[(R, S) - \text{YanPhos}]\text{H(CO)}_2\) complex could lead to high asymmetric induction.

**Figure 2-2:** Space-Filling and Stick Models for \(\text{Rh}[(R, S) - \text{YanPhos}]\text{H(CO)}_2\) and \(\text{Rh}[(R, S) - \text{Binaphos}]\text{H(CO)}_2\) Based on CAChe MM2 Calculation
The synthetic route for (R, S)-YanPhos is outlined in Scheme 2-1, starting from 2-naphthol 2. 2-Naphthalenamine 3 was obtained in 80 % yield by reacting 2 with concentrated aqueous NH₃ solution and (NH₄)₂SO₃ in a sealed autoclave at high temperature. 2-Naphthol 2 and 2-naphthalenamine 3 formed molecular crystal 4 which was used for subsequent cross coupling reaction with FeCl₃ as oxidant to produce racemic 2-amino-2'-hydroxy-1, 1'-binaphthyl (NOBIN) 5 in moderate yield (49 %). The major byproducts in this step were [1, 1']binaphthalenyl-2, 2'-diol and [1, 1']Binaphthalenyl-2, 2'-diamine resulted from homocoupling. Optical resolution of NOBIN was carried out with both (1S)-10-camphorsulfonic acid and N-benzylcinchonidium chloride according to the literature reported procedures. The latter procedure turned out to be more reliable. Following the literature procedure, acetylation of chiral (R)-NOBIN 6 provided the hydroxyl amide 7, which reacted with triflic anhydride under basic conditions to form the N-protected triflate 8 in high yield. Palladium catalyzed phosphinooylation of the triflate 8 with diphenylphosphine oxide afforded the phosphine oxide amide 9 in 84 % yield. Reduction of both phosphine oxide and amide groups with excess BH₃, followed by treatment with diethylamine, gave 10 in 49% yield. After deprotonation with n-BuLi and quenching the derived anion with phosphorochloridite, the desired ligand (R, S)-YanPhos 1 was obtained in 37% yield as an air-stable solid.
Scheme 2-1: Synthesis of YanPhos
2.2.2 Asymmetric Hydroformylation with YanPhos

2.2.2.1 Asymmetric Hydroformylation of Styrene Derivatives

Using the chiral hybrid ligand (R, S)-YanPhos, rhodium-catalyzed asymmetric hydroformylation has been explored. Styrene was selected as the standard substrate for the optimization of reaction conditions. The catalyst was prepared in situ by mixing Rh(acac)(CO)₂ with YanPhos at certain ratios. Hydroformylation reactions were performed using 1:1 CO/H₂ gas with 0.1 mol% of the catalyst. The chemoselectivities of the hydroformylation reactions were excellent and no hydrogenation product was detected by ¹H NMR. The regioselectivities were moderate with branched/linear ratios generally over 85:15, which were comparable to the results with Binaphos.²a-²b The enantioselectivities strongly depended on reaction conditions.

The effect of ligand/metal ratio on the hydroformylation reaction was first investigated. The reactions were performed at ligand/metal ratios ranging from 1:1 to 6:1. As shown in Table 2-1, the ligand/metal ratio significantly influenced the hydroformylation reaction. Increasing the ligand/metal ratio from 1:1 to 4:1 improved both regioselectivity and enantioselectivity. In particular, the enantioselectivity can be improved from 21 % ee at ligand/metal ratio of 1:1 to 98 % ee at ligand/metal ratio of 4:1. Further increasing the ligand/metal ratio to 6:1 did not result in higher regioselectivity and enantioselectivity.
Table 2-1: Asymmetric Hydroformylation of Styrene at Different Ligand/Metal Ratios$^a$

![Chemical structure](image)

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<td>6:1</td>
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$^a$The reactions were carried out in benzene at 60 °C for 24 h, substrate:Rh = 1000, CO/H$_2$ = 10/10 atm. $^b$Conversions were determined based on $^1$H NMR. $^c$Branched/linear ratio. $^d$ Determined based on $^1$H NMR. $^b$ Determined by converting the aldehyde to the corresponding alcohol with NaBH$_4$ followed by GC analysis (Supelco’s Beta Dex 225). The absolute configuration (R) was assigned by comparing the optical rotation of the resulting alcohol with (R)-2-Phenylpropan-1-ol.

We then studied the solvent effect. Several common solvents were screened. A significant solvent effect was observed (Table 2-2). High enantioselectivities were obtained when the reactions were run in nonpolar solvents such as methylene chloride and benzene whereas low ee values were observed in THF and EtOAc. The competition for coordination sites between polar solvents and substrates may account for this solvent effect.$^{1b}$
Table 2-2: Asymmetric Hydroformylation of Styrene in Different Solvents

\[
\text{Ph} \stackrel{\text{Rh(acac)(CO)}_2/(R, S)-\text{YanPhos}}{\text{H}_2/\text{CO}} \rightarrow \text{Ph}^\downarrow \text{CHO} + \text{Ph}^\downarrow \text{CHO}
\]

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\textsuperscript{a}The reactions were carried out with L:Rh = 4:1 at 60 °C for 24 h, substrate:Rh = 1000, CO/H\textsubscript{2} = 10/10 atm. \textsuperscript{b}Conversions were determined based on \textsuperscript{1}H NMR. \textsuperscript{c}Branched/linear ratio. Determined based on \textsuperscript{1}H NMR. \textsuperscript{d}Determined by converting the aldehyde to the corresponding alcohol with NaBH\textsubscript{4} followed by GC analysis (Supelco’s Beta Dex 225). The absolute configuration (R) was assigned by comparing the optical rotation of the resulting alcohol with (R)-2-Phenylpropan-1-ol.

To determine the right reaction temperature, hydroformylation reactions were carried out at different temperatures ranging from 40 °C to 80 °C. As shown in Table 2-3, increasing reaction temperature led to faster reaction rate and lower ee. Enantiomeric excess of 99% was achieved when the reaction was run at 40 °C with 25% conversion. Up to 98% ee was achieved in asymmetric hydroformylation with 100% conversion at 60 °C, whereas the enantioselectivity dropped to 81% ee at 80 °C. The regioselectivity also decreased with increased reaction temperature.
Table 2-3: Asymmetric Hydroformylation of Styrene at Different Temperatures

\[ \text{Ph} \xrightarrow{\text{Rh(acac)(CO)}_2/(R, S)-YanPhos \text{H}_2/\text{CO}} \text{Ph}^\Delta \text{CHO} + \text{Ph}^\Delta \text{CHO} \]

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<sup>a</sup>The reactions were carried out with L:Rh = 4:1 in benzene for 24 h, substrate:Rh = 1000, CO/H₂ = 10/10 atm. <sup>b</sup>Conversions were determined based on ¹H NMR. <sup>c</sup>Branched/linear ratio. Determined based on ¹H NMR. <sup>d</sup>Determined by converting the aldehyde to the corresponding alcohol with NaBH₄ followed by GC analysis (Supelco's Beta Dex 225). The absolute configuration (R) was assigned by comparing the optical rotation of the resulting alcohol with (R)-2-Phenylpropan-1-ol.

The effect of CO/H₂ pressure on the hydroformylation reaction was then investigated. No significant influence of the CO/H₂ pressure on regio- and enantioselectivity was observed (Table 2-4). However, the total pressure dramatically affected the reaction rate. Under low CO/H₂ pressure, the reaction was fast and complete conversion was achieved in 24 h under 20 atm of CO/H₂. The pressure effect on the reaction rate can be explained by the lower dissociation rate of CO from the rhodium center at higher pressure.
Table 2-4: Asymmetric Hydroformylation of Styrene under Different Pressures

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{Rh(acac)(CO)\textsubscript{2}/(R, S)-YanPhos}} \text{H\textsubscript{2}/CO} \quad \text{Ph} \backslash \text{CHO} & + & \text{Ph} \backslash \text{CHO} \\
\end{align*}
\]

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</table>

\textsuperscript{a}The reactions were carried out with L:Rh = 4:1 in benzene at 60 °C for 24 h, substrate:Rh = 1000. \textsuperscript{b}Conversions were determined based on \textsuperscript{1}H NMR. \textsuperscript{c}Branched/linear ratio. Determined based on \textsuperscript{1}H NMR. \textsuperscript{d}Determined by converting the aldehyde to the corresponding alcohol with NaBH\textsubscript{4} followed by GC analysis (Supelco's Beta Dex 225). The absolute configuration (R) was assigned by comparing the optical rotation of the resulting alcohol with (R)-2-Phenylpropan-1-ol.

It is worth noting that racemization of the hydroformylation product was significantly lower with YanPhos than with Binaphos.\textsuperscript{2b} Elongation of the reaction time after the reaction was complete only slightly lowered the enantiomeric excess of the chiral product with YanPhos as ligand (Table 2-5). With Binaphos as the ligand, dramatic decrease of enantiomeric excess after full conversion has been observed.\textsuperscript{2b} For example, the enantioselectivity dropped from 94 % ee to only 45 % ee when the reaction continued for another 16 h after full conversion. It has also been reported that significant
racemization may occur even before full conversion was reached in the hydroformylation of styrene with Binaphos.$^{4a}$

Table 2-5: Asymmetric Hydroformylation of Styrene at Different Reaction Time$^a$

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{entry} & \text{t (h)} & \text{conv (\%)}^b & \text{b/l}^c & \text{ee (\%)}^d \\
\hline
1 & 12 & 87 & 89/11 & 99 \\
2 & 24 & >99 & 88/12 & 98 \\
3 & 36 & >99 & 88/12 & 97 \\
\hline
\end{array}
\]

$^a$The reactions were carried out with L:Rh = 4:1 in benzene at 60 °C, substrate:Rh = 1000, CO/H$_2$ = 10/10 atm. $^b$Conversions were determined based on $^1$H NMR. $^c$Branched/linear ratio. Determined based on $^1$H NMR. $^d$Determined by converting the aldehyde to the corresponding alcohol with NaBH$_4$ followed by GC analysis (Supelco's Beta Dex 225). The absolute configuration (R) was assigned by comparing the optical rotation of the resulting alcohol with (R)-2-Phenylpropan-1-ol.

After screening reaction conditions, hydroformylation of styrene with the Rh-(R, S)-YanPhos catalyst was performed under 20 atm of 1:1 CO/H$_2$ at 60 °C in benzene. Optimized conversion, regioselectivity and enantioselectivity were achieved under these conditions.
A series of styrene derivatives were then hydroformylated using the rhodium-\((R, S)\)-YanPhos catalyst under the optimized reaction conditions (Table 2-6). Under the same reaction condition, 98% ee (entry 1) in the hydroformylation of styrene was achieved with YanPhos, while only 84% ee (entry 2) was obtained with Binaphos. The result with Binaphos under current reaction conditions is much lower than the literature reported result (entry 3, 94% ee).\(^{2a-2b}\) Since optimized reaction conditions for Binaphos and YanPhos are very different due to the different steric and electronic properties of two ligands, direct comparison of YanPhos with Binaphos under the same reaction condition is not appropriate. To demonstrate the utility of this new ligand, we have selected the best reported results with Binaphos for a side-by-side comparison. With YanPhos, up to 99% ee was obtained for the hydroformylation of \textit{para}-methyl styrene (entry 4). Halogen substituted styrene derivatives were also hydroformylated with excellent enantioselectivities with YanPhos (entries 6, 8 and 10). It is worth noting that high enantioselectivities at high conversions were achieved for fluorinated styrene derivatives (entries 6 and 8). For comparison, the reactions with Binaphos needed to be terminated at moderate conversions to obtain high enantioselectivities due to racemization of the chiral products (entries 7 and 9).\(^{2b}\) With YanPhos, \textit{para}-methoxy styrene was hydroformylated with high enantioselectivity (98% ee) (entry 12), which is significantly higher than the result (88% ee) reported with Binaphos.\(^{2a-2b}\) Up to 98% ee for the hydroformylation of \textit{para}-isobutyl styrene was achieved with YanPhos (entry 14). Oxidation of the aldehyde product affords the corresponding acid ibuprofen, one of the most widely used nonsteroidal anti-inflammatory agents. \((S)\)-ibuprofen is the biological active form of two enantiomers. Asymmetric hydroformylation of \textit{para}-isobutyl styrene with rhodium-
YanPhos catalyst thus provides an attract way for the preparation of this important drug (Eq. 2.2). With Binaphos, only 92% ee was obtained in the hydroformylation of para-isobutyl styrene (entry 15) and the turnover frequency was very low (300 turnover after 66 h).\textsuperscript{2a-2b} To demonstrate the catalytic efficiency of the rhodium-\((R, S)\)-YanPhos catalyst, hydroformylation of styrene was carried out with a substrate to catalyst molar ratio of 10000:1 (entry 16). With this low catalyst loading, the rhodium-\((R, S)\)-YanPhos catalyst still showed high reactivity (89% conversion after 24h) and maintained high enantioselectivity (98% ee) for the hydroformylation reaction.
Table 2-6: Asymmetric Hydroformylations of Styrene Derivatives

\[
\begin{align*}
\text{R} & \quad \overset{\text{Rh(acac)(CO)_{2}/(R, S)-YanPhos}}{\text{H}_2/\text{CO}} \quad \text{CHO} \quad \text{CHO} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>L</th>
<th>S/C (^{b})</th>
<th>T (°C)</th>
<th>CO/H(_2) (atm)</th>
<th>t (h)</th>
<th>conv (%) (^{c})</th>
<th>b/l (^{d})</th>
<th>ee (%) (^{c})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>(R,S)-YanPhos</td>
<td>1000</td>
<td>60</td>
<td>10/10</td>
<td>24</td>
<td>&gt;99</td>
<td>88/12</td>
<td>98(R)</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>(S,R)-Binaphos</td>
<td>1000</td>
<td>60</td>
<td>10/10</td>
<td>24</td>
<td>&gt;99</td>
<td>83/17</td>
<td>84(S)</td>
</tr>
<tr>
<td>3(^{f})</td>
<td>Ph</td>
<td>(S,R)-Binaphos</td>
<td>2000</td>
<td>60</td>
<td>50/50</td>
<td>43</td>
<td>&gt;99</td>
<td>88/12</td>
<td>94(S)</td>
</tr>
<tr>
<td>4</td>
<td>p-Me-Ph</td>
<td>(R,S)-YanPhos</td>
<td>1000</td>
<td>60</td>
<td>10/10</td>
<td>24</td>
<td>98</td>
<td>87/13</td>
<td>99(R)</td>
</tr>
<tr>
<td>5(^{f})</td>
<td>p-Me-Ph</td>
<td>(S,R)-Binaphos</td>
<td>1000</td>
<td>60</td>
<td>50/50</td>
<td>20</td>
<td>97</td>
<td>86/14</td>
<td>95(S)</td>
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<tr>
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<td>1000</td>
<td>60</td>
<td>10/10</td>
<td>24</td>
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<td>88/12</td>
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<tr>
<td>7(^{f})</td>
<td>p-F-Ph</td>
<td>(R,S)-Binaphos</td>
<td>2000</td>
<td>40</td>
<td>50/50</td>
<td>39</td>
<td>43</td>
<td>89/11</td>
<td>92(R)</td>
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<td>8</td>
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<td>1000</td>
<td>60</td>
<td>10/10</td>
<td>24</td>
<td>99</td>
<td>91/9</td>
<td>98(R)</td>
</tr>
<tr>
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<td>(R,S)-Binaphos</td>
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<tr>
<td>10</td>
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<td>1000</td>
<td>60</td>
<td>10/10</td>
<td>24</td>
<td>&gt;99</td>
<td>87/13</td>
<td>98(R)</td>
</tr>
<tr>
<td>11(^{f})</td>
<td>p-Cl-Ph</td>
<td>(S,R)-Binaphos</td>
<td>1000</td>
<td>60</td>
<td>50/50</td>
<td>34</td>
<td>&gt;99</td>
<td>87/13</td>
<td>93(S)</td>
</tr>
<tr>
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<td>(R,S)-YanPhos</td>
<td>1000</td>
<td>60</td>
<td>10/10</td>
<td>24</td>
<td>97</td>
<td>86/14</td>
<td>98(R)</td>
</tr>
<tr>
<td>13(^{f})</td>
<td>p-MeO-Ph</td>
<td>(S,R)-Binaphos</td>
<td>2000</td>
<td>60</td>
<td>50/50</td>
<td>34</td>
<td>&gt;99</td>
<td>87/13</td>
<td>88(S)</td>
</tr>
<tr>
<td>14</td>
<td>p-iBu-Ph</td>
<td>(R,S)-YanPhos</td>
<td>1000</td>
<td>60</td>
<td>10/10</td>
<td>24</td>
<td>98</td>
<td>89/11</td>
<td>98(R)</td>
</tr>
<tr>
<td>15(^{f})</td>
<td>p-iBu-Ph</td>
<td>(S,R)-Binaphos</td>
<td>400</td>
<td>60</td>
<td>50/50</td>
<td>66</td>
<td>&gt;99</td>
<td>88/12</td>
<td>92(S)</td>
</tr>
<tr>
<td>16</td>
<td>Ph</td>
<td>(R,S)-YanPhos</td>
<td>1000</td>
<td>60</td>
<td>10/10</td>
<td>24</td>
<td>89</td>
<td>88/12</td>
<td>98(R)</td>
</tr>
</tbody>
</table>

\(^{a}\)The reactions were carried out with L:Rh = 4:1 in benzene. \(^{b}\)Substrate/catalyst ratio. \(^{c}\)Conversions were determined based on \(^{1}\)H NMR. \(^{d}\)Branched/linear ratio. Determined based on \(^{1}\)H NMR. \(^{e}\)See experimental section for detail. \(^{f}\)Data taken from ref. 2a for comparison.
2.2.2.2 Asymmetric Hydroformylation of Vinyl Carboxylates

Vinyl carboxylates represent another type of common substrate extensively studied in asymmetric hydroformylation. After successfully applied the rhodium-YanPhos catalyst in the asymmetric hydroformylation of styrene derivatives, we further tested the asymmetric hydroformylation of vinyl carboxylates with this catalyst system (Table 2-7). The hydroformylation was performed under the identical reaction condition for styrene. For the hydroformylation of vinyl acetate, the most studied vinyl carboxylate substrate, 75% of the starting material was converted to aldehyde after 24 h with 96% ee and 13:1 branch/linear ratio (entry 1). The enantioselectivity with YanPhos was higher compared with Binaphos ligand (92% ee) \(^{2a-2b}\) and matched with the previous best result using chiral diazaphospholane ligand (96% ee).\(^{2c}\) The hydroformylation product 2-acetoxypropanal is a precursor for the Strecker synthesis of the amino acid threonine.\(^8\)

The hydroformylations of other vinyl carboxylates with YanPhos also proceeded in high regio- and enantioselectivities. In particular, asymmetric hydroformylation of 2, 2-dimethyl-propionic acid vinyl ester (entry 7), bearing a bulky alkyl residue on the carboxyl group, gave the highest enantioselectivity (98 % ee). Generally, the regioselectivity of vinyl carboxylates in asymmetric hydroformylation was higher than that of styrene derivatives. The branched/linear ratios were above 90/10 for all substrates tested. The activity of vinyl carboxylates, however, was lower than styrene derivatives.
Table 2-7: Asymmetric Hydroformylation of Vinyl Carboxylates\textsuperscript{a}

\[
\begin{array}{cccc}
\text{entry} & R & \text{conv (%)}\textsuperscript{b} & \text{b/l}\textsuperscript{c} & \text{ee (%)}\textsuperscript{d} \\
1 & \text{CH}_3 & 75 & 93/7 & 96 \\
2 & \text{CH}_3\text{CH}_2 & 67 & 96/4 & 93 \\
3 & \text{CH}_3(\text{CH}_2)_2 & 53 & 94/6 & 94 \\
4 & \text{CH}_3(\text{CH}_2)_6 & 56 & 94/6 & 94 \\
5 & \text{CH}_3(\text{CH}_2)_8 & 69 & 94/6 & 96 \\
6 & \text{t-Bu} & 40 & 94/6 & 98 \\
7 & \text{Ph} & 69 & 96/4 & 93 \\
\end{array}
\]

\textsuperscript{a}The reactions were carried out with L:Rh = 4:1 in benzene at 60 °C for 24 h, substrate:Rh = 1000, CO/H\textsubscript{2} = 10/10 atm. \textsuperscript{b}Conversions were determined based on \textsuperscript{1}H NMR. \textsuperscript{c}Branched/linear ratio. Determined based on \textsuperscript{1}H NMR. \textsuperscript{d}Determined by GC analysis (Supelco's Beta Dex 225). The absolute configuration (S) was assigned by comparing the optical rotation of the resulting alcohol with (S)-2-acetoxypropanal.
2.2.2.3 Asymmetric Hydroformylation of Cyclic Internal Olefins

Cyclic internal olefins such as indene and 1, 2-dihydronaphthalene are important substrates in asymmetric hydroformylation. Hydroformylation reactions generally introduce formyl groups at the \( \alpha \)-position of the phenyl rings. The hydroformylation product of indene, 1-formylindane, is an important intermediate for the preparation of amines with hypotensive activity. Likewise, the hydroformylation product of 1,2-dihydronaphthalene, 1-formyl-1,2,3,4-tetrahydronaphthalene, can be used for the preparation of the vasoconstrictor tetrahydrozoline.\(^1d\) Our preliminary results showed that the rhodium-YanPhos catalyst also catalyzed the hydroformylation reaction of indene and 1,2-dihydronaphthalene, affording the corresponding aldehydes, with high enantioselectivities (Table 2-8). However, since the activities of these trisubstituted cyclic internal olefins are low, a high reaction temperature (80 °C) was used in order to ensure high conversion. The enantioselectivities are slightly lower at this temperature than those obtained at 60 °C.
2.2.3 Proposed Models for the Transition States

Mechanistic studies by Takaya and coworkers have revealed that the Rh [(R, S)-Binaphos) H(CO)₂] complex exists as a single species with the phosphine occupied an equatorial position and the phosphite located at an apical position\(^b\). Models for the transition states in asymmetric hydroformylation with Binaphos were also proposed. We

---

Table 2-8: Asymmetric Hydroformylation of Cyclic Internal Olefins\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>n</th>
<th>T (°C)</th>
<th>conv (%)(^b)</th>
<th>b/l(^c)</th>
<th>ee (%)(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>60</td>
<td>13</td>
<td>85/15</td>
<td>92(-)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>80</td>
<td>71</td>
<td>87/13</td>
<td>90(-)</td>
</tr>
<tr>
<td>3(^e)</td>
<td>1</td>
<td>60</td>
<td>13</td>
<td>88/12</td>
<td>94(-)</td>
</tr>
<tr>
<td>4(^e)</td>
<td>1</td>
<td>80</td>
<td>93</td>
<td>87/13</td>
<td>84(-)</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>80</td>
<td>72</td>
<td>71/29</td>
<td>90(-)</td>
</tr>
</tbody>
</table>

\(^a\)The reactions were carried out with L:Rh = 4:1 in benzene for 24 h, substrate:Rh = 1000, CO/H\(_2\) = 10/10 atm unless otherwise noted. \(^b\)Conversions were determined based on \(^1\)H NMR. \(^c\)Determined based on \(^1\)H NMR. \(^d\)Determined by converting the aldehyde to the corresponding alcohol with NaBH\(_4\) followed by GC analysis (Supelco's Beta Dex 225). \(^e\)CO/H\(_2\) = 5/5 atm.
assume that the transition states in hydroformylation with YanPhos as ligand would be similar to that with Binaphos. The proposed models for the coordination of the olefin to the rhodium complex are shown in Figure 2-3. Model (a) is the general transition state proposed by Consiglio and Pino for rhodium-catalyzed asymmetric hydroformylation. The space for accommodating the substituent(s) of the olefin is divided into four quadrants. L, S, and Z represent a large, a small, and an apical ligand, respectively. Branched aldehydes are formed via transition states where either R₁ or R₂ is occupied by the substituent. The steric repulsion between the substituent of the olefin and the ligand determines the absolute configuration of the aldehyde product. There are two possible transition states with YanPhos as ligand, models (b) and (c), where the “large group L” is the phosphine of (R, S)-YanPhos and the “small group S” is the carbonyl. The apical position Z is occupied by the phosphoramidite group of the ligand. The transition state in model (b) is consistent with the experimental results of both styrene derivatives and vinyl carboxylates. In this model, to minimize the steric repulsion between the substituent on the olefin and the ligand, the olefin is expected to approach and coordinate to the rhodium center with the substituent occupies R₁ position to give the branched aldehyde. The other transition state in model (c), however, would give the opposite configurations which were not observed in hydroformylation experiments.
2.3 Conclusion

In conclusion, a new hybrid phosphine-phosphoramidite ligand, YanPhos, has been rationally designed and synthesized. It has been applied in rhodium-catalyzed asymmetric hydroformylation reactions. To the best of our knowledge, the enantioselectivities achieved with YanPhos for the hydroformylation of styrene derivatives and vinyl carboxylates are the best in the literature. The high reactivity and excellent enantioselectivity of this new ligand make the catalyst system potentially useful for industrial applications. It is anticipated that further structural variations of the $N$-
substituted phosphoramidite ligand will be developed in the future for asymmetric hydroformylation and other metal-catalyzed transformations
Experimental Section

General Methods: All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise noted. Solvents were dried with standard procedures and degassed with N₂. Column chromatography was performed using 200–400 mesh silica gel supplied by Natland International Corporation. Thin layer chromatography (TLC) was performed on EM reagents 0.25 mm silica 60-F plates. ¹H, ¹³C, ³¹P NMR spectrum were recorded on Bruker AM-300 and AMX-360 spectrometers. Optical rotation was obtained on a Perkin-Elmer 241 polarimeter. MS spectra were recorded on a KRATOS mass spectrometer MS 9/50. GC analysis was carried on Helwett-Packard 6890 gas chromatography using chiral capillary columns.

Synthesis of Naphthalen-2-ylamine (3)

To a 300 ml autoclave was added naphthalen-2-ol 2 (36.5 g, 0.253 mol), NH₄SO₃ (34.0 g, 0.254 mol), and concentrated aqueous ammonia (85 ml). The autoclave was sealed and the reaction mixture was heated to 150 °C. After stirring for 10 h at 150 °C, the reaction mixture was cooled to room temperature while keeping stirring. The mixture was filtered. The residue was washed with water (100 mL). To the residue was added concentrated HCl (70 mL), ethanol (300 mL) and water (200 mL). The mixture was heated to 70 °C, and activated carbon (5 g) was added and stirred for 30 min at this temperature to remove the color. After filtration, the organic impurity was removed by extraction with toluene (200 mL). The aqueous phase was cooled to room temperature and neutralized with ammonia (90 mL). The precipitation was extracted with toluene (2 x
400 mL). The organic phase was separated and washed with water (2 x 100 mL). After degassing with nitrogen for 15 min, water was removed by dean-stark separation, and concentrated. The crude product was purified by recrystallization from degassed toluene (200 mL) to afford the desired title compound (29.3 g, 84 % yield). $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ: 7.97-7.85 (m, 3H), 7.66-7.61 (m, 1H), 7.52-7.47 (m, 1H), 7.24-7.19 (m, 2H), 4.07 (s, 2H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ: 144.0, 134.9, 129.2, 127.9, 127.7, 126.3, 125.8, 122.4, 118.2, 108.5.

### Preparation of Molecular Crystal (4)

![Molecular Crystal Diagram](image)

To a 50 mL Schlenk flask was added naphthalen-2-ol 2 (1.44 g, 10 mmol) and naphthalen-2-ylamine 3 (1.43g, 10 mmol). The flask was degassed and charged with nitrogen. To the mixture was added toluene (10 mL). The suspension was heated until a clear solution was formed. The solution was then slowly cooled to room temperature to obtain the title molecular crystal. Concentration of the mother liquid afforded the second crop of molecular crystal. The combined molecular crystal was 2.80 g (98% yield).

### Synthesis of Racemic (R)-2'-Amino-[1,1']binaphthalenyl-2-ol (NOBIN) (5)

![Racemic NOBIN Diagram](image)

To a solution of FeCl$_3$.6H$_2$O (81 g, 0.3 mol) in water (400 mL) was added molecular crystal 4 (23 g, 0.08 mol). The reaction mixture was heated to 55 °C and stirred for 6 h. The reaction mixture was cooled to room temperature and filtered. The residue
was washed with water until no colorful filtrate was obtained. The residue was dissolved in 1000 ml acetone and dried over Na$_2$SO$_4$. The dried solution was passed through a short column of silica gel and a short column of activated carbon flushed with 1000 ml of acetone. The solvent was then removed under reduced pressure. The residue was dissolved in a mixture of concentrated HCL (40 mL) and ethanol (300 mL). The resulting solution was diluted with water (100 mL). The byproduct was removed by extraction with toluene (3 x 200 mL). The aqueous phase was cooled to 0 °C by adding ice (100 g). To the cooled solution was added concentrated ammonia (60 mL) to neutralize the solution. Precipitation was formed immediately upon addition. After filtration, the residue was dissolved in 1000 ml of acetone. The resulting solution was dried over Na$_2$SO$_4$ and concentrated. The crude product was purified by recrystallization from toluene (500 mL) to obtained the title racemic NOBIN (11.2 g, 49 %). $^1$H NMR (300 MHz, CD$_3$COCD$_3$) δ: 7.96-7.89 (m, 2H), 7.80-7.73 (m, 2H), 7.65 (s, 1H), 7.38 (d, $J$ = 8.8 Hz, 1H), 7.32-7.19 (m, 3H), 7.16-7.10 (m, 3H), 6.95-6.88 (m, 1H), 4.43 (s, 2H). $^{13}$C NMR (75 MHz, CD$_3$COCD$_3$) δ: 154.15, 145.66, 135.65, 134.89, 130.58, 130.28, 130.19, 129.20, 129.09, 128.93, 128.89, 127.26, 127.06, 125.45, 124.54, 123.91, 122.33, 119.58, 119.45, 115.96, 110.78.

**Optical Resolution of 2'-Amino-[1,1']binaphthalenyl-2-ol (6)**

\[
\begin{align*}
&\text{NH}_2 \\
&\text{OH}
\end{align*}
\]

To a solution of racemic NOBIN 5 (5.70 g, 20 mmol) in acetone (100 mL) was added N-benzylcinchonidium chloride (4.20 g, 10 mmol). The resulting suspension was
heated to reflux and stirred for 4 h. The reaction mixture was then cooled to room
temperature. After filtration, the white residue was washed with acetone (3 x 10 mL). To
the residue was added aqueous 1N HCl (50 mL) and ethyl acetate (100 mL). The
resulting suspension was stirred for 10 min until all white solids disappeared. The organic
layer was then separated, washed with brine (20 mL) and dried over Na₂SO₄. The solvent
was removed under reduced pressure. The residue was recrystallized from benzene to
afford (R) - 2'-Amino-[1, 1']binaphthalenyl-2-ol (1.97 g, 69 %) with >99% ee
determined by HPLC on a CHIRALCEL OD-H column (eluting with 90:10
hexane/isopropanol). The mother liquid was concentrated under reduced pressure to
dryness. The residue was dissolved in ethyl acetate (50 mL). The resulting solution was
washed with aqueous 1N HCl solution (10 mL), brine (20 mL) and dried over Na₂SO₄.
The solvent was removed under reduced pressure. The residue was recrystallized from
benzene to afford (S) - 2'-Amino-[1, 1']binaphthalenyl-2-ol (1.7 g, 60 %) with >99% ee.

**Synthesis of (R)-N-(2'-Hydroxy-[1, 1']binaphthalenyl-2-yl)-acetamide (7)**

![Chemical structure of (R)-N-(2'-Hydroxy-[1, 1']binaphthalenyl-2-yl)-acetamide (7)]

To a solution of (R) - 2'-amino-[1, 1']binaphthalenyl-2-ol 6 (5.7 g, 20 mmol) in
dry pyridine (80 mL) was slowly added acetyl chloride (3.2 mL, 22 mmol) at 0 °C. The
reaction mixture was allowed to warm to room temperature and stirred for 8 h. The
reaction mixture was then poured into icy water (80 mL) and extracted with
dichloromethane (3 x 100 mL). The extract was successively washed with 5% aqueous
HCl solution (100 mL), saturated aqueous NaHCO₃ solution (100 mL) and water (100
mL). The solution was dried over Na₂SO₄. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (eluting with toluene/ethyl acetate 2:1) to give N,O-diacetate intermediate. The diacetate was dissolved in dry methanol (600 mL). To the resulting solution was added catalytic amount of NaOMe (40 mg). The reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (eluting with hexane/ethyl acetate 1:1) to give the title compound (6.21 g, 95 %): 

\[ ^1H \text{NMR (300 MHz, CD}_2\text{Cl}_2) \delta: 8.44 \text{ (d, } J = 8.86 \text{ Hz, 1H),} \]
\[ 8.04-7.90 \text{ (m, 4H),} \]
\[ 7.47-7.23 \text{ (m, 5H),} \]
\[ 7.11 \text{ (d, } J = 8.42 \text{ Hz, 1H),} \]
\[ 6.99 \text{ (m, 2H),} \]
\[ 5.79 \text{ (bs, 1H),} \]
\[ 1.77 \text{ (s, 3H);} \]
\[ ^{13}C \text{NMR (75 MHz, CD}_2\text{Cl}_2) \delta: 169.4, 152.6, 136.0, 133.6, 133.2, 131.8, 131.3, 130.0, 129.7, 128.7, 128.6, 127.6, 127.4, 125.8, 125.6, 124.4, 124.2, 121.9, 119.87, 118.5, 113.6, 24.5.} \]

**Synthesis of (R)-Trifluoro-methanesulfonic Acid 2'-Acetylamino-[1,1']binaphthalenyl-2-yl Ester (8)**

To a solution of (R)-N-(2'-hydroxy-[1, 1']binaphthalenyl-2-yl)-acetamide 7 (5.1 g, 15.6 mmol) in dichloromethane (100 mL) and pyridine (1.4 mL, 17.2 mmol) was slowly added trifluoromethanesulfonic anhydride (2.9 mL, 17.2 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was then diluted with dichloromethane (200 mL). The diluted solution was washed with aqueous 5% HCl (2 x 60 mL), saturated NaHCO₃ (50 mL), and water (50
(6.52 g, 91%): \(^1\)H NMR (300 MHz, CD\(_2\)Cl\(_2\)) \(\delta\): 8.46 (d, \(J = 8.8\) Hz, 1H), 8.23 (d, \(J = 9.1\) Hz, 1H), 8.10 (t, \(J = 8.8\) Hz, 2H), 7.99 (d, \(J = 8.1\) Hz, 1H), 7.67-7.62 (m, 2H), 7.50-7.43 (m, 2H), 7.38-7.29 (m, 2H), 7.08 (d, \(J = 8.43\) Hz, 1H), 6.97 (bs, 1H); \(^{13}\)C NMR (75 MHz, CD\(_2\)Cl\(_2\)) \(\delta\): 168.7, 146.0, 135.8, 133.4, 133.2, 132.7, 132.3, 131.4, 130.3, 128.9, 128.8, 128.6, 128.1, 127.3, 126.7, 126.4, 125.7, 125.2, 125.0, 122.5, 120.7, 119.9, 119.1, 116.5, 112.2, 24.3.

**Synthesis of (R)-N-[2'-((Diphenyl-phosphinoyl)-[1,1']binaphthalenyl-2-yl]-acetamide (9)**

![Chemical structure](image)

To a 250 mL Schlenk flask was added (R)-trifluoro-methanesulfonic acid 2'-acetylamino-[1,1']binaphthalenyl-2-yl ester (6.3 g, 13.7 mmol), diphenylphosphine oxide 8 (6.0 g, 30 mmol), palladium(II) acetate (690 mg, 6.85 mmol), and 1,4-bis(diphenylphosphino) butane (dppb, 1.29 g, 6.85 mmol). The flask was degassed and charged with nitrogen. To the flask were then added dimethyl sulfoxide (300 mL) and diisopropylethylamine (9.0 mL, 118 mmol). The reaction mixture was stirred at 120 °C for 4 h. After cooling to 80 °C, the solvent was removed under reduced pressure. To the residue was added 5% aqueous HCl solution (300 mL). The product was extracted with dichloromethane (3 x 300 mL). The combined extracts were washed with 1% aqueous HCl (300 mL) and water (300 mL) and dried over Na\(_2\)SO\(_4\). The solvent was removed
under reduced pressure. The residue was purified by flash chromatography on silica gel (eluting with toluene/dichloromethane/methanol 15:4:1) to afford the title compound as a colorless solid (5.88 g, 84%): $^1$H NMR (360 MHz, CD$_2$Cl$_2$) δ: 9.86 (s, 1H), 8.05-7.96 (m, 4H), 7.75 (q, $J$ = 7.3 Hz, 2H), 7.63-7.52 (m, 6H), 7.28-7.23 (m, 4H), 7.13 (d, $J$ = 8.6 Hz, 1H), 7.01 (t, $J$ = 7.9 Hz, 1H), 6.84 (t, $J$ = 7.3Hz, 1H), 6.73-6.70 (m, 2H), 6.56 (d, $J$ = 8.4 Hz, 1H), 1.91 (s, 3H). $^{13}$C NMR (91MHz, CD$_2$Cl$_2$) δ: 169.29, 141.49, 141.40, 136.43, 135.37, 135.35, 133.68, 133.36, 132.74, 132.37, 132.31, 132.27, 131.30, 130.51, 130.48, 130.03, 129.92, 129.59, 129.31, 129.07, 128.94, 128.74, 128.70, 128.61, 128.24, 128.18, 128.04, 127.94, 127.61, 127.58, 127.52, 127.47, 126.84, 126.01, 125.28, 23.78. $^{31}$P NMR (146 MHz, CH$_2$Cl$_2$) δ: 28.5.

**Synthesis of (R)-(2'-Diphenylphosphanyl-[1,1']binaphthalenyl-2-yl)-ethyl-amine (10)**

![Chemical structure](image)

To a 500 mL Schlenk flask was added (R)-N-[2'-((diphenyl-phosphinoyl)-[1,1']binaphthalenyl-2-yl]-acetamide 9 (3.70 g, 7.24 mmol). The flask was degassed and charged with nitrogen. To the flask was added THF (200 mL). The resulting solution was cooled to 0 °C in an ice/water bath. To the cooled solution was added dropwise 10 M borane – dimethyl sulfide complex in THF (7.24 mL, 72.4 mmol). The mixture was refluxed for 18 h. After being cooled to room temperature, the mixture was diluted with EtOAc (200 mL) and poured into icy water (200 mL). The mixture was stirred for 30 min. the organic layer was separated and washed with brine (200 mL). The organic phase was
dried over Na$_2$SO$_4$ and concentrated under reduced pressure. To the residue was added 270 mL of diethyl amine and the reaction mixture was stirred at room temperature for 30 min. Diethyl amine was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 16:1) to give the title compound (1.71 g) in 49% yield. $^1$H NMR (360 MHz, CD$_2$Cl$_2$) δ: 7.91 (t, $J$ = 8.92 Hz, 3H), 7.77 (d, $J$ = 8.01 Hz, 1H), 7.54-7.14 (m, 2H), 7.33-7.16 (m, 11H), 7.12 (t, $J$ = 7.40 Hz, 1H), 7.07-7.01 (m, 3H), 6.65 (d, $J$ = 8.47 Hz, 1H), 3.21, (m, 1H), 3.07-3.00 (m, 1H), 2.81-2.72 (m, 1H), 0.76 (t, $J$ = 7.11 Hz, 3H); $^{13}$C NMR (91MHz, CD$_2$Cl$_2$) δ: 144.81, 144.78, 142.62, 142.24, 138.65, 138.50, 138.12, 137.65, 134.79, 134.18, 133.96, 133.63, 133.42, 133.35, 131.34, 129.91, 128.97, 128.91, 128.90, 128.81, 128.66, 128.59, 128.56, 128.47, 128.31, 127.60, 127.34, 127.19, 126.77, 126.74, 126.57, 124.31, 121.79, 116.24, 116.14, 113.92, 38.68, 15.17; $^{31}$P NMR (146 MHz, CH$_2$Cl$_2$) δ: –14.2 (s). ES+ HRMS calcd for C$_{34}$H$_{29}$NP: 482.2038; found: 482.2029.

**Preparation of (S)-1,1'-Binaphthyl-2,2'-dioxychlorophosphine.**

![Diagram](image)

To a 50 mL Schlenk flask was added (S)-2, 2'-dihydroxy-1,1'-binaphthyl (3.5 g, 12 mmol). The flask was degassed and charged with nitrogen. Phosphorus trichloride (25 g, 0.18 mol) was added. The resulting solution was heated at reflux for 18 h. After cooling to room temperature, the excess phosphorus trichloride was removed under reduced pressure. To the residue was added degassed toluene (20 mL). Azeotropic evaporation of the trace amount of phosphorus trichloride with toluene under reduced
pressure afforded the title compound in almost quantitative yield (4.4 g). The crude product was essentially pure and was used in the next step without further purification:

$^1$H NMR (360 MHz, CD$_2$Cl$_2$) $\delta$: 8.07-7.98 (m, 4H), 7.57-7.46 (m, 4H), 7.39-7.29 (m, 4H);

$^{13}$C NMR (90 MHz, CD$_2$Cl$_2$) $\delta$: 148.2 (d, $J = 3.1$ Hz), 147.6 (d, $J = 4.5$ Hz), 133.0 (d, $J = 1.7$ Hz), 132.7 (d, $J = 1.6$ Hz), 132.4, 131.9, 131.4, 130.5, 128.9 (d, $J = 0.9$ Hz), 127.2, 127.1, 126.9, 126.1, 125.9, 124.7 (d, $J = 5.7$ Hz), 123.4 (d, $J = 2.3$ Hz), 121.9 (d, $J = 1.2$ Hz), 121.4 (d, $J = 1.6$ Hz).

$^{31}$P NMR (146 MHz, CD$_2$Cl$_2$) $\delta$: 178.8.

**Synthesis of YanPhos (1)**

![Synthesis of YanPhos (1)](image)

To a 25 ml Schlenk flask was added $(R$)-(2'-diphenylphosphanyl-[1,1']binaphthalenyl-2-yl)-ethyl-amine 10 (0.24 g, 0.5mmol). The flask was degassed and charged with nitrogen. THF (5 mL) was added. The resulting solution was cooled to 0 °C in an ice/water bath. To the cooled solution was added $n$-BuLi (0.65 mmol, 0.26 mL of 2.5 M hexane solution) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 30 min to give a deep red solution. The reaction mixture was then re-cooled to 0°C in an ice/water bath and $(S$)-1',1'-Binaphthyl-2, 2'-dioxochlorophosphine (262 mg, 0.75 mmol) in THF (5 mL) was added dropwise. After addition, the cooling bath was removed and the mixture was stirred at room temperature overnight. The volatiles were evaporated under reduced pressure. To the residue was added CH$_2$Cl$_2$ (10 mL), and the mixture was filtered to remove the salt. The filtration was concentrated and subject to chromatography on silica gel (eluting with hexane/EtOAc 9:1)
to afford pure YanPhos (145 mg) in 37% yield. \(^1\)H NMR (300 MHz, CD\(_2\)Cl\(_2\)) \(\delta\): 8.10-8.01 (m, 3H), 7.96-7.91 (t, \(J = 7.28\) Hz, 2H), 7.81(d, \(J = 8.2\) Hz, 2H), 7.67-7.55 (m, 4H), 7.41-6.87 (m, 20H), 6.57 (t, \(J = 7.68\) Hz, 1H), 6.41-6.32 (m, 2H), 2.79-2.72 (m, 1H), 2.38-2.31 (m, 1H), 0.66 (t, \(J = 7.01\) Hz, 1H). \(^{13}\)C NMR (75 MHz, CD\(_2\)Cl\(_2\)) \(\delta\):150.30, 150.21, 149.92, 142.36, 141.94, 138.59, 138.39, 138.27, 138.20, 135.44, 135.14, 134.10, 133.57, 133.36, 131.68, 130.51, 129.88, 129.11, 128.66, 128.58, 128.55, 128.49, 128.46, 128.42, 128.30, 128.12, 127.56, 127.19, 127.12, 127.03, 126.66, 126.29, 126.18, 125.71, 125.54, 125.06, 124.75, 122.49, 122.23, 122.19, 41.03, 14.98; \(^{31}\)P NMR (146 MHz, CDCl\(_2\)) \(\delta\): 141.63 (d, \(J = 53.3\)), -13.57 (d, \(J = 53.3\) Hz). ES+ HRMS calcd for C\(_{54}\)H\(_{40}\)NO\(_2\)P\(_2\): 796.2534; found: 796.2552.

**Synthesis of (S)-Trifluoro-methanesulfonic Acid 2'-**

**Trifluoromethanesulfonyloxy - [1,1']binaphthalenyl-2-yl Ester**

![Chemical structure](attachment:image.png)

To a solution of (S)-binaphthol (14.3 g, 50 mmol) and pyridine (12 mL) in CH\(_2\)Cl\(_2\) (250 mL) was added dropwise trifluoromethanesulfonic anhydride (20.0 mL, 119 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 6 h. The solvent was removed under reduced pressure. The residue was diluted with EtOAc (200 mL). The diluted solution was washed with aqueous 5% HCl solution (100 mL), aqueous saturated NaHCO\(_3\) solution (100 mL), and brine (100 mL) and dried over Na\(_2\)SO\(_4\). The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (eluting with CH\(_2\)Cl\(_2\)) to give the title compound as a
white powder (26.1 g, 95 %).\(^1\)H NMR (300 MHz, CD\(_2\)Cl\(_2\)) \(\delta\): 8.21 (d, \(J = 9.12\) Hz, 1H), 8.07 (d, \(J = 8.23\) Hz, 1H), 7.67-7.60 (m, 2H), 7.43 (t, \(J = 8.22\) Hz, 1H), 7.26 (d, \(J = 8.54\) Hz); \(^{13}\)C NMR (75 MHz, CD\(_2\)Cl\(_2\)) \(\delta\): 145.9, 133.5, 132.9, 132.5, 128.8, 128.4, 127.8, 127.0, 123.8, 120.7, 119.6, 116.4.

**Synthesis of (S)-Trifluoro-methanesulfonic Acid 2'-{(Diphenyl-phosphinoyl)-[1,1']binaphthalenyl-2-yl Ester**

\[
\begin{align*}
\text{OTf} \\
\text{P(O)Ph}_2
\end{align*}
\]

To a 250 mL Schlenk flask was added (S)-trifluoro-methanesulfonic acid 2'-trifluoromethanesulfonyloxy - [1,1']binaphthalenyl-2-yl ester (6.3 g, 11.4 mmol), diphenylphosphine oxide (4.6 g, 22.7 mol), palladium diacetate (128 mg, 0.57 mmol), and 1, 1-bis(diphenylphosphino)butane (dppb, 242 mg, 0.57 mmol). The flask was degassed and charged with nitrogen. To the flask were added dimethylsulfoxide (50 ml) and diisopropylethylamine (5.9 g, 45.4 mmol). The reaction mixture was heated to 100°C and stirred for 12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to give a dark brown residue. The residue was diluted with EtOAc (120 mL), washed with water (50 mL) and dried over Na\(_2\)SO\(_4\). The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (eluting with hexane/EtOAc 5:1) to give the title compound as a white solid (6.53 g, 95 %).\(^1\)H NMR (300 MHz, CD\(_2\)Cl\(_2\)) \(\delta\): 8.04-7.89 (m, 3H), 7.74-7.21 (m, 16H), 7.18-6.91 (m, 3H); \(^{13}\)C NMR (75 MHz, CD\(_2\)Cl\(_2\)) \(\delta\): 145.95, 134.94, 134.22, 133.92, 132.23, 132.10, 131.97, 131.54, 131.40, 131.26, 128.98, 128.88,
128.81, 128.65, 128.59, 128.48, 128.43, 128.32, 128.23, 127.55, 127.47, 127.31, 127.15, 126.90; $^{31}$P NMR (146 Hz, CD$_2$Cl$_2$) $\delta$: 28.3.

**Synthesis of (S)- 2'-((Diphenyl-phosphinoyl)-[1,1']binaphthalenyl-2-ol**

![Chemical Structure](image)

To a solution of (S)-trifluoro-methanesulfonic acid 2'-((diphenyl-phosphinoyl)-[1,1']binaphthalenyl-2-yl ester (6.02 g, 10.0 mmol) in a mixture of 1,4-dioxane (40 mL) and MeOH (20 mL) was added aqueous 3 N NaOH solution (60 mL). The reaction mixture was stirred for 12 h at room temperature. To the reaction mixture was added dropwise aqueous concentrated HCl solution to adjust the pH = 1. The resulting mixture was extracted with EtOAc (2 x 50 mL). The combined extracts was dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (eluting with hexane/EtOAc 1:1) to give the title compound as a white solid (4.32 g, 92%). $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 9.20 (s, 1H), 8.01-7.91 (m, 4H), 7.70-7.53 (m, 6H), 7.48-7.41 (m, 1H), 7.35 (d, $J$ = 8.82 Hz), 7.29-7.22 (m, 3H), 7.15-7.07 (m, 2H), 6.96 (m, 1H), 6.87-6.84 (m, 1H), 6.79-6.76 (m, 2H), 6.45 (d, $J$ = 8.42Hz, 1H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$: 154.06, 141.87, 135.58, 133.91, 133.79, 132.57, 132.53, 132.49, 132.44, 130.72, 130.55, 130.51, 130.11, 129.98, 129.41, 129.17, 129.01, 128.61, 128.47, 128.42, 128.31, 128.07, 127.80, 127.77, 127.60, 127.43, 126.13, 125.82, 123.55, 123.37; $^{31}$P NMR (146 Hz, CD$_2$Cl$_2$) $\delta$: 30.6.
Synthesis of (S)-2'-Diphenylphosphanyl-[1,1']binaphthalenyl-2-ol

To a 250 mL Schlenk flask was added (S)-2'-(diphenyl-phosphinoyl)-[1,1']binaphthalenyl-2-ol (940 mg, 1.0 mmol). The flask was degassed and charged with nitrogen. To the flask was added toluene (40 mL) and triethyl amine (2.0 mL, 14.4 mmol). The resulting solution was cooled to 0 °C in an ice/water bath. To the cooled solution was added dropwise pre-cooled Cl\textsubscript{3}SiH (1.0 mL, 10.0 mmol). The reaction mixture was heated to 100 °C and stirred for 16 h. After being cooled to room temperature, the mixture was diluted with Et\textsubscript{2}O (60 mL) and quenched with a small amount of saturated aqueous NaHCO\textsubscript{3} solution. The resulting suspension was filtered through a short pad of Celite. The residue was washed with Et\textsubscript{2}O (400 mL). The combined organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 3:1) to give the title compound as a white solid (672 mg, 74 %). \textsuperscript{1}H NMR (300 MHz, CD\textsubscript{2}Cl\textsubscript{2}) δ: 7.98-7.94 (m, 3H), 7.87 (d, J = 8.13 Hz, 1H), 7.57-7.48 (m, 2H), 7.36-7.21 (m, 12H), 7.12-7.10 (m, 3H), 6.85 (d, J = 8.45 Hz, 1H); \textsuperscript{13}C NMR (75 MHz, CD\textsubscript{2}Cl\textsubscript{2}) δ: 151.72, 151.69, 139.25, 138.68, 138.51, 137.79, 137.62, 137.47, 137.30, 134.46, 134.28, 134.25, 134.11, 133.85, 133.84, 133.59, 133.51, 130.71, 130.56, 129.45, 129.21, 129.00, 128.96, 128.87, 128.7, 128.66, 128.57, 128.28, 127.66, 127.44, 127.77, 126.36, 126.32, 125.17, 123.62, 118.83, 118.71, 117.77, 31.0. \textsuperscript{31}P NMR (146 Hz, CD\textsubscript{2}Cl\textsubscript{2}) δ: -14.1.
Synthesis of \((R,S)\)-Binaphos

To a 25 mL Schlenk flask was added \((S)\)-2'-diphenylphosphanylidene-\([1,1']\)binaphthyl-2-ol (454 mg, 1.0 mmol) and \((R)\)-1,1'-binaphthyl-2,2'-dioxochlorophosphine (550 mg, 1.5 mmol). The flask was degassed and charged with nitrogen. Ether (10 mL) was added. The resulting solution was cooled to 0 °C in an ice/water bath. To the cooled solution was added triethylamine (0.28 mL, 2.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 10 h. To the reaction mixture was added small amount of methanol to quench the reaction. The volatiles were evaporated under reduced pressure. To the residue was added \(\text{CH}_2\text{Cl}_2\) (10 mL), and the mixture was filtered to remove the salt. The filtration was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc 9:1) to afford the title compound \((S, R)\)-Binaphos as a white solid (622 mg, 81%). \(^1\)H NMR (300 MHz, CD\(_2\)Cl\(_2\)) \(\delta\): 8.07 (t, \(J = 8.3\) Hz, 3H), 7.95-7.87 (m, 3H), 7.79 (d, \(J = 8.24\) Hz, 1H), 7.60-7.56 (m, 2H), 7.49-7.36 (m, 3H), 7.34-6.88 (m, 20H), 6.17 (d, \(J = 5.80\) Hz, 1H); \(^{13}\)C NMR (75 MHz, CD\(_2\)Cl\(_2\)) \(\delta\): 147.79, 147.73, 147.52, 147.48, 141.40, 140.95, 137.93, 137.76, 137.03, 136.86, 136.73, 136.59, 134.50, 134.22, 134.16, 133.48, 133.23, 131.00, 130.60, 130.32, 129.56, 128.84, 128.80, 128.72, 128.67, 128.54, 128.51, 128.44, 128.34, 128.18, 128.16, 127.38, 127.08, 126.96, 126.91, 126.68, 126.60,
126.42, 126.39, 125.20, 125.14, 122.86, 121.89, 120.77, 120.66; $^{31}$P NMR (146 Hz, CD$_2$Cl$_2$) δ: 145.9 (d, $J$ = 23.3 Hz), -14.3 (d, $J$ = 24.8 Hz).

**Synthesis of $p$-Isobutylstryrene**

To a 500 mL Schlenk flask was added bis(diphenylphosphino)propane) nickel(II) chloride (0.15 g, 0.29 mmol). The flask was degassed and charged with nitrogen. Ether (150 mL) and $p$-bromostyrene (9.15 g, 50 mmol) were then added. To the resulting solution was added dropwise isobutylmagnesium chloride (25 mL 2.38 M solution in ether, 60 mmol). The reaction mixture was heated at refluxed for 18 h. After cooling to 0 °C, saturated aqueous NH$_4$Cl solution (50 mL) was added dropwise to quench the reaction. The organic phase was separated and the aqueous phase was extracted with ether (3 x 50 mL). The combined organic phase was dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure. Purification of the crude product by flash chromatography on SiO$_2$ (eluted with hexane) afforded $p$-isobutylstyrene as a colorless liquid (6.0 g, 75% yield). $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ: 7.36-7.33 (m, 2H), 7.14-7.07 (m, 2H), 6.72 (dd, $J$ =17.62, 10.9 Hz, 1H), 5.73 (dd, $J$ = 17.63, 1.03 Hz, 1H), 5.20 (dd, $J$ = 10.89, 1.01 Hz, 1H), 2.48 (d, $J$ = 12.63 Hz, 2H), 1.87 (m, 1H), 0.92 (d, $J$ = 6.62 Hz, 6H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ: 142.0, 137.1, 135.4, 129.6, 129.4, 127.8, 126.2, 112.9, 45.4, 30.6, 22.4.
General Procedure for the Asymmetric Hydroformylation of Styrene Derivatives

In a glovebox filled with nitrogen, to a 2 mL vial equipped with a magnetic bar was added YanPhos (0.004 mmol), Rh(acac)(CO)$_2$ (0.001 mmol in 0.10 mL benzene) and styrene derivative (1.0 mmol), additional benzene was charged to bring the total volume of the reaction mixture to 1.0 mL. After stirring for 10 min, the vial was transferred into an autoclave and taken out of the glovebox. Carbon monoxide (10 atm) and dihydrogen (10 atm) were charged in sequence. The reaction mixture was stirred (60 rpm) at 60 °C (oil bath) for 24 h. The reaction was cooled and the pressure was carefully released in a well ventilated hood. The conversion and regioselectivity were determined by $^1$H NMR spectroscopy of the crude reaction mixture without evaporation of the solvent. The enantiomeric excess of the product was determined by reduction with NaBH$_4$ or oxidation with Jones reagent to the corresponding alcohol or carboxylic acid, and then analyzed by GC. The absolute configuration was assigned by comparing the sign of the optical rotation of the resulting alcohol or acid with (R)-2-phenylpropan-1-ol or (R)-ibuprofen.

General Procedure for the Asymmetric Hydroformylation of Vinyl Carboxylates

In a glovebox filled with nitrogen, to a 2 mL vial equipped with a magnetic bar was added YanPhos (0.004 mmol), Rh(acac)(CO)$_2$ (0.001 mmol in 0.10 mL benzene) and vinyl carboxylate (1.0 mmol), additional benzene was charged to bring the total volume of the reaction mixture to 1.0 mL. After stirring for 10 min, the vial was transferred into an autoclave and taken out of the glovebox. Carbon monoxide (10 atm) and dihydrogen
(10 atm) were charged in sequence. The reaction mixture was stirred (60 rpm) at 60 °C (oil bath) for 24 h. The reaction was cooled and the pressure was carefully released in a well ventilated hood. The conversion and regioselectivity were determined by $^1$H NMR spectroscopy of the crude reaction mixture without evaporation of the solvent. The enantiomeric excess was determined directly by GC analysis of the crude reaction mixture and the absolute configuration was determined by comparing the sign of the optical rotation with literature data (N. Sakai, S. Mano, K. Nozaki, H. Takaya, J. Am. Chem. Soc, 1993, 115, 7033-7034).

**General Procedure for the Asymmetric Hydroformylation of Cyclic Internal Olefins**

In a glovebox filled with nitrogen, to a 2 mL vial equipped with a magnetic bar was added YanPhos (0.004 mmol), Rh(acac)(CO)$_2$ (0.001 mmol in 0.10 mL benzene) and internal olefin (1.0 mmol), additional benzene was charged to bring the total volume of the reaction mixture to 1.0 mL. After stirring for 10 min, the vial was transferred into an autoclave and taken out of the glovebox. Carbon monoxide (10 atm) and dihydrogen (10 atm) were charged in sequence. The reaction mixture was stirred (60 rpm) at 80 °C (oil bath) for 24 h. The reaction was cooled and the pressure was carefully released in a well ventilated hood. The conversion and regioselectivity were determined by $^1$H NMR spectroscopy of the crude reaction mixture without evaporation of the solvent. The enantiomeric excess of the product was determined by reduction with NaBH$_4$ to the corresponding alcohol, and then analyzed by GC.
Hydroformylation of Styrene at High S/C Ratio

In a glovebox filled with nitrogen, to a 2 mL vial equipped with a magnetic bar was added YanPhos (0.004 mmol), Rh(acac)(CO)$_2$ (0.001 mmol in 0.10 mL benzene) and styrene (10.0 mmol), additional benzene was charged to bring the total volume of the reaction mixture to 1.5 mL. After stirring for 10 min, the vial was transferred into an autoclave and taken out of the glovebox. Carbon monoxide (10 atm) and dihydrogen (10 atm) were charged in sequence. The reaction mixture was stirred (60 rpm) at 60 °C (oil bath) for 24 h. The reaction was cooled and the pressure was carefully released in a well ventilated hood. The conversion and regioselectivity were determined by $^1$H NMR spectroscopy of the crude reaction mixture without evaporation of the solvent. The enantiomeric excess of the product was determined by reduction with NaBH$_4$ to the corresponding alcohol and then analyzed by GC (Supelco β-dex 225). The absolute configuration was assigned by comparing the sign of the optical rotation of the resulting alcohol with (R)-2-phenylpropan-1-ol.

Determine the Enantiomeric Excess by Oxidation:

A portion of the reaction mixture was diluted with acetone (10 mL) and 1ml of Jones reagent was added. The solution was allowed to stir at room temperature for 1 h. To the resulting green mixture was added water (10 mL). The resulting mixture was stirred for 5 min and extracted with CH$_2$Cl$_2$ (10 mL). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated. The residue was subjected to column chromatography on silica gel to get the acid product which was analyzed by Chiral GC (Supelco β-120) to determine the enantiomeric excess.
**Determine the Enantiomeric Excess by Reduction:**

A portion of the reaction mixture was diluted with MeOH (2 mL) and cooled to 0 °C. NaBH$_4$ (40 mg) was added in portion. The reaction mixture was allowed to stir at 0 °C for 2 h. Then water (5 mL) was added to quench the excess NaBH$_4$. To the resulting mixture was then added hexane (2 mL) and EtOAc (2 mL). The mixture was vigorously stirred for 5 min. The organic phase was separated, dried over Na$_2$SO$_4$ and concentrated. The residue was subjected to column chromatography on silica gel to get the reduced alcohol product, which was analyzed by chiral GC (Supelco β-dex 225) to determine the enantiomeric excess.

**Characterization Data (NMR and GC condition) of Hydroformylation Products and Their Derivatives**

![CHO](image)

2-Phenyl-propionaldehyde. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ: 9.69 (d, $J$ = 1.3 Hz, 1H), 7.43-7.38 (m, 2H), 7.35-7.29 (m, 1H), 7.26-7.16 (m, 2H), 3.65 (q, $J$ = 7.1 Hz, 1H), 1.45 (d, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ: 201.4, 138.4, 129.3, 128.7, 127.8, 53.3, 14.8.

![F](image)

2-(4-Fluoro-phenyl)-propionaldehyde. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ: 9.66 (d, $J$ = 1.3 Hz, 1H), 7.23-7.18 (m, 2H), 7.11-7.06 (m, 2H), 3.64 (q, $J$ = 7.1 Hz, 1H), 1.42 (d, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ: 201.1, 162.5 (d, $J$ = 245 Hz), 134.2 (d, $J$ = 3.1 Hz), 130.4 (d, $J$ = 8.1 Hz), 116.1 (d, $J$ = 21.5 Hz), 52.5, 14.9.
2-(2-Fluoro-phenyl)-propionaldehyde. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 9.71 (d, $J$ = 1.65 Hz, 1H), 7.35-7.28 (m, 1H), 7.22-7.09 (m, 3H), 3.89 (q, $J$ = 7.23 Hz, 1H), 1.44 (d, $J$ = 7.20 Hz, 3H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$: 200.4, 161.3 (d, $J$ = 245 Hz), 130.0 (d, $J$ = 4.52 Hz), 129.6 (d, $J$ = 8.37 Hz), 125.9 (d, $J$ = 15.2 Hz), 125.0 (d, $J$ = 3.47 Hz), 116.0 (d, $J$ = 22.17 Hz), 46.9, 13.8.

2-(4-Chloro-phenyl)-propionaldehyde. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 9.65 (d, $J$ = 1.25 Hz, 1H), 7.38-7.34 (m, 2H), 7.19-7.15 (m, 2H), 3.65 (q, $J$ = 7.12 Hz, 1H), 1.42 (d, $J$ = 7.13 Hz, 3H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$: 200.8, 136.9, 133.5, 130.1, 129.4, 52.5, 14.7.

2-$p$-Tolyl-propionaldehyde. $^1$H NMR (360 MHz, CD$_2$Cl$_2$) $\delta$: 9.65 (d, $J$ = 1.36 Hz, 1H), 7.22-7.19 (m, 2H), 7.12-7.10 (m, 2H), 3.60 (q, $J$ = 6.05 Hz, 1H), 2.35 (s, 3H), 1.41 (d, $J$ = 7.08 Hz, 3H). $^{13}$C NMR (90 MHz, CD$_2$Cl$_2$) $\delta$: 201.5, 137.6, 135.3, 130.0, 128.5, 52.9, 21.1, 14.8.

2-(4-Methoxy-phenyl)-propionaldehyde. $^1$H NMR (360 MHz, CD$_2$Cl$_2$) $\delta$: 9.63 (d, $J$ = 1.41 Hz, 1H), 7.15-7.11 (m, 2H), 6.93-6.89 (m, 2H), 3.79 (s, 3H), 3.58 (q, $J$ = 5.94
Hz, 1H), 1.39 (d, \( J = 7.09 \) Hz, 3H); \(^{13}\)C NMR (90 MHz, CD\(_2\)Cl\(_2\)) \( \delta \): 201.4, 159.4, 130.2, 129.7, 114.7, 55.6, 52.4, 14.8.

![2-(4-Isobutyl-phenyl)-propionaldehyde](image)

2-(4-Isobutyl-phenyl)-propionaldehyde. \(^1\)H NMR (300 MHz, CD\(_2\)Cl\(_2\)) \( \delta \): 9.66 (d, \( J = 1.41 \) Hz, 1H), 7.19-7.11 (m, 4H), 3.61 (dq, \( J = 7.1, 1.2 \) Hz, 1H), 2.48 (d, \( J = 7.2 \) Hz, 2H), 1.86 (M, 1H), 1.42 (d, \( J = 7.1 \) Hz, 3H), 0.91 (d, \( J = 6.6 \) Hz, 6H); \(^{13}\)C NMR (75 MHz, CD\(_2\)Cl\(_2\)) \( \delta \): 201.5, 141.4, 135.5, 130.1, 128.4, 126.3, 52.9, 45.2, 30.6, 22.4, 14.8.

![2-Phenyl-propan-1-ol](image)

2-Phenyl-propan-1-ol. \(^1\)H NMR (300 MHz, CD\(_2\)Cl\(_2\)) \( \delta \): 7.37-7.30 (m, 2H), 7.26-7.20 (m, 3H), 3.67 (d, \( J = 7.1 \) Hz, 2H), 2.89 (m, 1H), 1.49 (bs, 1H), 1.26 (d, \( J = 6.0 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, CD\(_2\)Cl\(_2\)) \( \delta \): 144.5, 128.8, 127.8, 126.8, 68.8, 42.8, 17.8.

Supelco’s Beta Dex 225, 105\(^\circ\)C, 1mL/min, \( t_{(major)} = 35.7 \) min, \( t_{(minor)} = 37.2 \) min

![2-(4-Fluoro-phenyl)-propan-1-ol](image)

2-(4-Fluoro-phenyl)-propan-1-ol. \(^1\)H NMR (300 MHz, CD\(_2\)Cl\(_2\)) \( \delta \): 7.24-7.20 (m, 2H), 7.05-7.00 (m, 2H), 3.65 (d, \( J = 6.78 \) Hz, 2H), 2.92 (m, 1H), 1.38 (bs, 1H), 1.24 (d, \( J = 7.03 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, CD\(_2\)Cl\(_2\)) \( \delta \): 161.9 (d, \( J = 243.2 \) Hz), 140.2 (d, \( J = 3.5 \) Hz), 129.3 (d, \( J = 7.9 \) Hz), 115.4 (d, \( J = 21.1 \) Hz), 68.8, 42.1, 17.9.

Supelco’s Beta Dex 225, 105\(^\circ\)C, 1mL/min, \( t_{(major)} = 38.1 \) min, \( t_{(minor)} = 46.8 \) min.
2-(2-Fluoro-phenyl)-propan-1-ol. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 7.30-7.18 (m, 2H), 7.15-7.12 (m, 1H), 7.10-7.00 (m, 1H), 3.72 (m, 2H), 3.28 (m, 1H), 1.45 (bs, 1H), 1.27 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$: 161.5 (d, $J$ = 244.3 Hz), 131.2 (d, $J$ = 8.3 Hz), 128.8 (d, $J$ = 7.85 Hz), 128.2 (d, $J$ = 8.3 Hz), 124.6 (d, $J$ = 3.5 Hz), 115.7 (d, $J$ = 22.9 Hz), 67.5, 35.9, 16.8.

Supelco’s Beta Dex 225, 95°C, 1mL/min, $t_{(major)}$ = 37.6 min, $t_{(minor)}$ = 39.2 min

2-(4-Chloro-phenyl)-propan-1-ol. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 7.32-7.28 (m, 2H), 7.21-7.18 (m, 2H), 3.65 (d, $J$ = 6.8 Hz, 2H), 2.90 (m, 1H), 1.48 (bs, 1H), 1.24 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$: 143.1, 132.3, 129.3, 128.8, 68.6, 42.2, 17.7.

Supelco’s Beta Dex 225, 120°C, 1mL/min, $t_{(major)}$ = 58.1 min, $t_{(minor)}$ = 69.4 min

2-$p$-Tolyl-propan-1-ol. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 7.13 (s, 1H), 3.64 (d, $J$ = 6.8 Hz, 2H), 2.87 (m, 1H), 2.32 (s, 3H), 1.35 (bs, 1H), 1.23 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$: 141.3, 136.4, 129.5, 127.6, 68.9, 42.4, 21.0, 17.9.

Supelco’s Beta Dex 225, 105°C, 1mL/min, $t_{(major)}$ = 41.8 min, $t_{(minor)}$ = 46.5 min.
2-(4-Methoxy-phenyl)-propan-1-ol. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ: 7.18-7.13 (m, 2H), 6.88-6.83 (m, 2H), 3.77 (s, 3H), 3.62 (d, $J = 6.9$ Hz), 2.86 (m, 1H), 1.36 (bs, 1H), 1.22 (d, $J = 7.0$ Hz); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ: 158.7, 136.3, 128.7, 114.2, 69.0, 55.5, 42.0, 17.9.

Supelco’s Beta Dex 225, 130°C, 1mL/min, $t_{(major)} = 34.6$ min, $t_{(minor)} = 36.2$ min.

2-(4-Isobutyl-phenyl)-propionic acid. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ: 11.8 (bs, 1H), 7.24-7.21 (m, 2H), 7.14-7.11 (m, 2H), 3.72 (q, $J = 7.1$ Hz, 1H), 2.46 (d, $J = 7.1$ Hz, 2H), 1.85 (m, 1H), 1.50 (d, $J = 7.2$ Hz, 3H), 0.91 (d, $J = 6.6$ Hz, 6H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ: 181.5, 141.3, 137.6, 129.7, 127.6, 45.3, 30.6, 22.5, 18.3.

Supelco’s Beta Dex 120, 180°C, 1mL/min, $t_{(minor)} = 30.1$ min, $t_{(major)} = 31.2$ min

Acetic acid 1-methyl-2-oxo-ethyl ester.$^1$H NMR (400 MHz, CDCl$_3$) δ: 9.52 (s, 1H), 5.05 (q, $J = 7.20$ Hz, 1H), 2.15 (s, 3H), 1.38 (d, $J = 7.22$ Hz, 3H).

Supelco’s Beta Dex 225, 100°C, 1mL/min, $t_{(minor)} = 7.0$ min, $t_{(major)} = 8.3$ min

Propionic acid 1-methyl-2-oxo-ethyl ester. $^1$H NMR (300 MHz, CDCl$_3$) δ: 9.54 (s, 1H), 5.08 (q, $J = 7.19$ Hz, 1H), 2.45 (dq, $J = 5.96$, 1.70 Hz, 2H), 1.40 (d, $J = 7.20$ Hz, 3H),
1.19 (t, J = 7.57 Hz, 3H);¹³C NMR (75 MHz, CDCl₃) δ: 198.6, 173.9, 74.4, 27.3, 14.1, 9.0.

Supelco’s Beta Dex 225, 100°C, 1mL/min, tₘₙₐᵢₙ = 8.3 min, tₘₐᵢₐᵢ = 9.0 min

Butyric acid 1-methyl-2-oxo-ethyl ester. ¹H NMR (300 MHz, CDCl₃) δ: 9.54, 5.08 (q, J = 7.16 Hz, 1H), 2.40 (t, J = 7.48 Hz, 2H), 1.70 (m, 2H), 1.39 (d, J = 7.18 Hz, 3H), 0.98 (t, J = 7.41 Hz, 3H);¹³C NMR (75 MHz, CDCl₃) δ: 198.6, 173.1, 74.4, 35.8, 18.4, 14.1, 13.6.

Supelco’s Beta Dex 225, 105°C, 1mL/min, tₘₙₐᵢₙ = 9.4 min, tₘₐᵢₐᵢ = 9.7 min

Octanoic acid 1-methyl-2-oxo-ethyl ester. ¹H NMR (300 MHz, CDCl₃) δ: 9.54 (s, 1H), 5.08 (q, J = 7.19 Hz, 1H), 2.42 (dt, J = 7.49, 1.22 Hz, 2H), 1.67 (m, 2H), 1.40 (d, J = 7.19 Hz, 3H), 1.32-1.24 (m, 8H), 0.89 (t, J = 7.01 Hz, 3H);¹³C NMR (75 MHz, CDCl₃) δ: 198.6, 173.3, 74.4, 33.9, 31.6, 29.0, 28.9, 24.8, 22.6, 14.1, 14.0.

Supelco’s Beta Dex 225, 130°C, 1mL/min, tₘₙₐᵢₙ = 20.1 min, tₘₐᵢₐᵢ = 20.6 min

Decanoic acid 1-methyl-2-oxo-ethyl ester. ¹H NMR (300 MHz, CDCl₃) δ: 9.51 (d, J = 0.50 Hz, 1H), 5.04 (q, J = 7.21 Hz, 1H), 2.39 (dq, J = 7.49, 1.25 Hz, 2H), 1.64 (m, 2H), 1.37 (d, J = 7.19 Hz, 3H), 1.31-1.24 (m, 12H), 0.85 (t, J = 6.94 Hz, 3H);¹³C NMR (75 MHz, CDCl₃) δ: 198.61, 173.26, 74.35, 33.93, 31.81, 29.36, 29.21, 29.04, 24.83, 22.63, 14.13, 14.07.
Supelco’s Beta Dex 225, 130°C, 1mL/min, t_{(minor)} = 54.7 min, t_{(major)} = 58.4 min

\[ \text{2, 2-Dimethyl-propionic acid 1-methyl-2-oxo-ethyl ester.} \]
\[ ^1H \text{ NMR (300 MHz, CDCl}_3\text{) } \delta: 9.52 \text{ (d, } J = 0.59 \text{ Hz, 1H), 5.03} \text{ (dq, } J = 7.17, 0.62 \text{ Hz, 1H), 1.40} \text{ (d, } J = 7.17 \text{ Hz, 3H), 1.27} \text{ (s, 3H); } ^{13}C \text{ NMR (75 MHz, CDCl}_3\text{) } \delta: 198.7, 178.0, 74.3, 38.7, 27.1, 14.0. \]

Supelco’s Beta Dex 225, 100°C, 1mL/min, t_{(minor)} = 41.6 min, t_{(major)} = 45.0 min

\[ \text{Benzoic acid 1-methyl-2-oxo-ethyl ester.} \]
\[ ^1H \text{ NMR (300 MHz, CDCl}_3\text{) } \delta: 9.66 \text{ (d, } J = 0.63 \text{ Hz, 1H), 8.11-8.08} \text{ (m, 2H), 7.63-7.57} \text{ (m, 1H), 7.49-7.44} \text{ (m, 2H), 5.30} \text{ (dq, } J = 7.16, 0.60 \text{ Hz, 1H), 1.53} \text{ (d, } J = 7.17 \text{ Hz, 3H); } ^{13}C \text{ NMR (75 MHz, CDCl}_3\text{) } \delta: 198.6, 165.9, 133.5, 129.8, 129.1, 128.5, 75.1, 14.3. \]

Supelco’s Beta Dex 225, 135°C, 1mL/min, t_{(minor)} = 21.9 min, t_{(major)} = 24.3 min

\[ \text{Indan-1-carbaldehyde.} \]
\[ ^1H \text{ NMR (300 MHz, CD}_2\text{Cl}_2\text{) } \delta: 9.67 \text{ (d, } J = 2.6 \text{ Hz, 1H), 7.31-7.27} \text{ (m, 2H), 7.26-7.20} \text{ (m, 2H), 3.98-3.92} \text{ (m, 1H), 3.07-2.95(m, 2H), 2.49-2.26} \text{ (m, 2H); } ^{13}C \text{ NMR (75 MHz, CD}_2\text{Cl}_2\text{) } \delta: 200.9, 145.3, 139.1, 128.2, 126.9, 125.4, 125.3, 58.3, 32.0, 25.8. \]
1,2,3,4-Tetrahydro-naphthalene-1-carbaldehyde. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ: 9.68 (d, $J = 1.76$ Hz, 1H), 7.23-7.16 (m, 4H), 3.61 (t, $J = 4.9$ Hz, 1H), 2.79 (t, $J = 6.3$ Hz, 2H), 2.26-2.21 (m, 1H), 1.97-1.92 (m, 1H), 1.85-1.76 (m, 2H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ: 202.3, 138.5, 131.5, 130.0, 127.3, 126.3, 52.0, 29.5, 23.3, 20.9.

Indan-1-yl-methanol. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ: 7.37-7.23 (m, 2H), 7.20-7.15 (m, 2H), 3.77 (m, 2H), 3.33 (m, 1H), 2.91 (m, 2H), 2.25 (m, 1H), 1.93 (m, 1H), 1.71 (bs, 1H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ: 145.2, 144.5, 127.1, 126.4, 124.9, 124.4, 66.1, 48.0, 31.6, 28.8.

Supelco’s Beta Dex 225, 130°C, 1mL/min, $t_{(minor)} = 20.7$ min, $t_{(major)} = 21.5$ min

(1,2,3,4-Tetrahydro-naphthalen-1-yl)-methanol. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ: 7.24-7.21 (m, 1H), 7.15-7.08 (m, 3H), 3.75 (d, $J = 6.75$ Hz, 2H), 2.95 (m, 1H), 2.76 (t, $J = 5.81$ Hz, 2H), 1.95-1.82 (m, 3H), 1.77-1.71 (m, 1H), 1.61 (bs, 1H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ: 138.0, 136.7, 129.2, 128.7, 126.0, 125.6, 66.9, 40.2, 29.6, 25.0, 19.6.

Supelco’s Beta Dex 225, 130°C, 1mL/min, $t_{(minor)} = 40.0$ min, $t_{(major)} = 40.3$ min.
References


Chapter 3

Development of Conceptual New Tetraphosphorus Ligands for Highly Regioselective Hydroformylation

3.1 Introduction

Hydroformylation is the largest scale homogeneous catalytic process used industrially. Most of 6 million tons of oxo products produced annually are used for the preparation of polymer plasticizers and detergents. Because plasticizers and detergents prepared from linear aldehydes generally exhibit better properties than those made from branched aldehydes, the linear aldehydes are the desired intermediates for polymer and detergent industries. One of the key issues in the hydroformylation process is the control of regiochemistry. Most commercial hydroformylation processes use rhodium catalysts modified with monophosphorus ligands with moderate regioselectivity. A number of catalysts based on bisphosphorus ligands have been developed to address the issue of regioselectivity. When coordinated with metal, bisphosphorus ligands can form chelating structures and afford better regioselectivities than monophosphorus ligands. To date, high regioselectivity in the hydroformylation of terminal olefins has been achieved by employing some bidentate bisphosphorus ligands.\(^1\)

Since internal olefins are cheaper and more readily available feedstock than terminal olefins, the development of highly selective and active isomerization-hydroformylation catalysts for internal olefins is of great importance from the economic and energy points of view (Eq. 3.1). Recently, some progresses have been made in this
area using van Leeuwen’s Xantphos derivatives (linear/branched ratio $n:i = 9.5$ for 2-octene), Beller’s electron-withdrawing Naphos type ligands ($n:i = 10.1$ for 2-octene), Börner’s acylphosphite ligands ($n:i = 2.2$ for mixtures of octene isomers) and bulky phosphite ligands of UCC ($n:i = 19$ and $17$ for 2-hexene and 2-octene, respectively) and DuPont/DSM ($n:i = 36$ for 2-hexene). Highly regioselective isomerization-hydroformylation of internal olefins also has been reported in a biphasic system using a sulfonated Naphos derivative through careful controlling pH and CO partial pressure ($n:i = 99:1$ for 2-octene).

![Diagram](3.1)

In this chapter, we would like to report the design and synthesis of two conceptually new tetraphosphorus ligands 1 and 2 (Figure 3-1) as well as their applications in highly regioselective hydroformylation. Both ligands showed better regioselectivities compared to their corresponding bisphosphorus ligands. In particular, tetraphosphoramidite ligand 1 provided the highest regioselectivity ever reported in the homogenous isomerization-hydroformylation of internal olefins ($n:i$ up to 80.6 for 2-hexene and up to 51.7 for 2-octene have been achieved with ligand 1). Ligand 2 exhibited high regioselectivity for the hydroformylation of terminal olefins at temperature as high as 140 °C ($n:i$ up to 43.8 and 45.2 for 1-hexene and 1-octene, respectively).
3.2 Results and Discussions

3.2.1 Design and Synthesis of Tetraphosphoramidite Ligand

A goal of this new ligand design is aimed at the issue of ligand dissociation, a major problem encountered in achieving high regioselectivity in hydroformylation (Scheme 3-1). In commercial hydroformylation processes that are based on monophosphorus ligands, the catalytic species with two phosphines coordinated to the metal center is the desired regioselective catalytic species. The dissociation of phosphorus ligands from the metal center followed by replacement with CO leads to the formation of highly reactive yet unselective catalytic species. In order to prevent the formation of unselective catalytic species and achieve high regioselectivities, a large excess of ligands are employed. For known bidentate bisphosphorus ligands capable of affording high regioselectivities in hydroformylation, typically eight or nine-membered ring chelates are formed. The chelating effects of eight or nine-membered ring chelations
are weaker compared with five and six-membered chelations. We reasoned that the
dissociation of bisphosphorus ligands from the metal in eight or nine-membered ring
chelates also can happen under some hydroformylation conditions. In the isomerization-
hydroformylation of internal olefins, to facilitate the isomerization of internal olefins, the
reactions are generally conducted at higher temperature than hydroformylation of
terminal olefins, which may make the ligand dissociation problem even worse.

**Scheme 3-1: Ligand Dissociation in Rhodium-Catalyzed Hydroformylation**

In order to achieve high regioselectivity in the isomerization-hydroformylation of
internal olefins, a new strategy to enhance the chelating ability of ligands is needed. We
envision that chelating ability could be enhanced by using ligands capable of forming
multiple chelating modes. As illustrated in Scheme 3-1, there are four identical chelating
modes when a tetraphosphorus ligand is complexed with rhodium. On the other hand,
when the tetraphosphorus ligand coordinates with the metal, the existing free phosphorus
atoms can effectively increase the local phosphorus concentration around the metal center and enhance the coordination ability of the tetraphosphorus ligand compared with the corresponding bisphosphorus ligand.

\[
\begin{align*}
P_3P_1P_2P_4 \quad & \quad P_3P_1P_2P_4 \\
& \quad P_3P_1P_2P_4
\end{align*}
\]

Scheme 3-1: Enhanced Chelating Ability of Tetraphosphorus Ligand through Multiple Chelating Modes and Increased Local Phosphorus Concentration

To achieve high regioselectivity in the isomerization-hydroformylation of internal olefins, a high isomerization rate of internal olefin to terminal olefin, as well as high regioselectivity for the hydroformylation of the terminal olefin, is required. Recently, \( \text{N-pyrrolylphosphorus} \) ligands such as bisphosphorus ligand 3\(^7\) have been used for rhodium-catalyzed hydroformylation reactions. Fast isomerization rates and high regioselectivities for terminal olefins have been reported with ligand 3. Based on the enhanced chelating ability of tetraphosphoramidite ligand 1 and the unique properties of the \( \text{N-pyrrolylphosphorus} \) ligand, we envision tetraphosphoramidite ligand 1 could serve as an effective ligand for isomerization-hydroformylation of internal olefins (Figure 3-2).
One of the key requirements of a ligand for practical applications is that the ligand synthesis has to be simple. The symmetric nature of tetraphosphoramidite ligand 1 makes its synthesis straightforward (Scheme 3-3). Tetraol 4 can be synthesized in two steps starting from inexpensive 1, 3-dimethoxy benzene. Thus, deprotonation of 1, 3-dimethoxy benzene followed by an oxidative coupling reaction using FeCl₃ as catalyst afforded tetramethoxy biphenyl in 70 % yield. Tetraol 4 was obtained in 81 % yield by deprotecting the aromatic methoxy moieties with boron tribromide. Reaction of chlorodipyrrolyphosphine with tetraol 4 in the presence of NEt₃ afforded the desired tetraphosphoramidite ligand 1 in 36% unoptimized yield. Chlorodipyrrolyphosphine itself was made by reaction of pyrrole with 0.5 equiv of phosphorus trichloride in the presence of NEt₃. Distillation of crude chlorodipyrrolyphosphine under reduced pressure afforded the pure product as a colorless liquid. It should be noted that chlorodipyrrolyphosphine is unstable. Even if it was stored in refrigerator under inert atmosphere, precipitate may form after 24 h. To ensure high purity, chlorodipyrrolyphosphine has to be freshly made...
before use. The resulting tetraphosphoramidite ligand 1 is an air stable crystalline solid that can be handled easily in the hydroformylation reaction set-up.

Scheme 3-2: Synthesis of Tetraphosphoramidite Ligand

3.2.2 Isomerization-Hydroformylation of Internal Olefins with Tetraphosphoramidite Ligand

With tetraphosphoramidite ligand 1 in hand, the isomerization-hydroformylation of internal olefins was then tested. Since the hydroformylation reaction is highly dependent on the reaction conditions, the effects of ligand/metal ratio, temperature and pressure on regioselectivity were first evaluated. The catalyst were prepared in situ by mixing ligand 1 with Rh(acac)(CO)$_2$ at certain ratios. The reactions were carried out in toluene with decane as the internal standard. The rhodium concentration was 0.57 mM.
for 2-octene and 0.69 mM for 2-hexene, respectively. Typically a substrate catalyst ratio of 10000 was used.

Table 3-1: Isomerization-Hydroformylation of Internal Olefins at Different Ligand/Metal Ratios

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>L/Rh</th>
<th>n:i$^b$</th>
<th>linear (%)$^c$</th>
<th>TON$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-octene</td>
<td>1:2</td>
<td>2.92</td>
<td>74.5</td>
<td>2.1x10³</td>
</tr>
<tr>
<td>2</td>
<td>2-octene</td>
<td>1:1</td>
<td>17.7</td>
<td>94.7</td>
<td>1.8 x10³</td>
</tr>
<tr>
<td>3</td>
<td>2-octene</td>
<td>2:1</td>
<td>43.4</td>
<td>97.7</td>
<td>1.5 x10³</td>
</tr>
<tr>
<td>4</td>
<td>2-octene</td>
<td>4:1</td>
<td>46</td>
<td>97.9</td>
<td>1.5x10³</td>
</tr>
<tr>
<td>5</td>
<td>2-hexene</td>
<td>1:2</td>
<td>12.7</td>
<td>92.7</td>
<td>2.2x10³</td>
</tr>
<tr>
<td>6</td>
<td>2-hexene</td>
<td>1:1</td>
<td>42</td>
<td>97.7</td>
<td>1.9 x10³</td>
</tr>
<tr>
<td>7</td>
<td>2-hexene</td>
<td>2:1</td>
<td>68.5</td>
<td>98.6</td>
<td>1.9 x10³</td>
</tr>
<tr>
<td>8</td>
<td>2-hexene</td>
<td>4:1</td>
<td>70.3</td>
<td>98.6</td>
<td>1.8x10³</td>
</tr>
</tbody>
</table>

$^a$S/C = 10000, [Rh] = 0.57 mM (for 2-octene) or 0.69 mM (for 2-hexene), temperature = 100 °C, CO/H$_2$ = 10/10 atm, reaction time = 1 h, toluene as solvent, decane as internal standard. $^b$Linear/branched ratio, determined based on GC. $^c$Percentage of linear aldehyde in all aldehydes. $^d$Turn over number, determined based on GC.

The ligand/metal molar ratio is one of the most important reaction parameters influencing the hydroformylation activity and regioselectivity. Numerous reports have shown that below certain ligand-to-metal ratios, a selective catalyst can not be formed $in situ$ by reaction of the rhodium precursor and phosphorus ligand.$^1$ The presence of other
catalytic species may lead to low regioselectivity. Different ligands have their own minimum ligand/metal ratio to ensure high regioselectivity. To investigate the influence of ligand/metal ratio on the regioselectivity and activity of the isomerization-hydroformylation of internal olefins, the isomerization-hydroformylation reactions of 2-octene and 2-hexene were conducted at various ligand/metal ratios ranging from 1:2 to 4:1. As shown in Table 3-1, increasing the ligand/metal ratio slightly decreased the reaction rate. On the other hand, the ligand/metal ratio significantly affected the regioselectivity. At ligand/metal ratio = 0.5, the highest isomerization-hydroformylation activity was observed, however, the regioselectivity was very low. A minimum ligand/metal ratio of 1 is required to achieve high regioselectivity. At ligand/metal ratio = 2, very high regioselectivity was observed. Further increasing the ligand/metal ratio did not significantly improve the regioselectivity.

The effects of reaction temperature on isomerization-hydroformylation were also investigated. The isomerization-hydroformylation reactions of 2-octene and 2-hexene were carried out at various temperatures ranging from 60 °C to 140 °C under otherwise identical conditions. The results were summarized in Table 3-2. As indicated in the table, the reaction temperature plays a key role in isomerization-hydroformylation. At low temperature (below 100 °C), although high regioselectivity was observed, the reaction rate was low. This low activity at low temperature can be explained by a slow isomerization rate of internal olefins at low temperature. To facilitate the olefin isomerization and hydroformylation, high temperature is desired. The preferred temperature is 100 °C. At this temperature, both high regioselectivity and acceptable reaction rate were achieved.
Table 3-2: Isomerization-Hydroformylation of Internal Olefins at Different Temperatures

![Chemical Reaction Formula]

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>T°C</th>
<th>n:i$^b$</th>
<th>linear (%)$^c$</th>
<th>TON$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-octene</td>
<td>140</td>
<td>29.5</td>
<td>96.7</td>
<td>3.7x10^3</td>
</tr>
<tr>
<td>2</td>
<td>2-octene</td>
<td>120</td>
<td>30.4</td>
<td>96.8</td>
<td>3.4 x10^3</td>
</tr>
<tr>
<td>3</td>
<td>2-octene</td>
<td>100</td>
<td>46</td>
<td>97.9</td>
<td>1.6 x10^4</td>
</tr>
<tr>
<td>4</td>
<td>2-octene</td>
<td>80</td>
<td>47.7</td>
<td>97.9</td>
<td>0.77x10^3</td>
</tr>
<tr>
<td>5</td>
<td>2-octene</td>
<td>60</td>
<td>53.6</td>
<td>98.2</td>
<td>0.14x10^3</td>
</tr>
<tr>
<td>6</td>
<td>2-hexene</td>
<td>140</td>
<td>24.3</td>
<td>96</td>
<td>4.4x10^3</td>
</tr>
<tr>
<td>7</td>
<td>2-hexene</td>
<td>120</td>
<td>49.5</td>
<td>98</td>
<td>2.8 x10^3</td>
</tr>
<tr>
<td>8</td>
<td>2-hexene</td>
<td>100</td>
<td>68.1</td>
<td>98.6</td>
<td>1.7 x10^4</td>
</tr>
<tr>
<td>9</td>
<td>2-hexene</td>
<td>80</td>
<td>114</td>
<td>99.1</td>
<td>0.99x10^3</td>
</tr>
<tr>
<td>10</td>
<td>2-hexene</td>
<td>60</td>
<td>179</td>
<td>99.4</td>
<td>0.67x10^3</td>
</tr>
</tbody>
</table>

$^a$S/C = 10000, [Rh] = 0.57 mM (for 2-octene) or 0.69 mM (for 2-hexene), ligand/Rh ratio = 3:1, CO/H$_2$ = 10/10 atm, reaction time = 1 h, toluene as solvent, decane as internal standard. $^b$Linear/branched ratio, determined based on GC. $^c$Percentage of linear aldehyde in all aldehydes. $^d$Turn over number, determined based on GC.

The effects of total pressure of CO/H$_2$ were then evaluated. The isomerization-hydroformylation reactions were conducted under CO/H$_2$ total pressure ranging from 5/5...
to 30/30 atm. As shown in Table 3-3, the CO/H\textsubscript{2} total pressure significantly influences the isomerization-hydroformylation reaction. At high pressure, both reaction rate and regioselectivity were low. Lowering the pressure generally resulted in higher reaction rate and regioselectivity. However, decreasing the CO/H\textsubscript{2} pressure from 10/10 atm to 5/5 atm did not change the reaction rate very much, while the regioselectivity could be improved to some extent.

Table 3-3: Isomerization-Hydroformylation of Internal Olefins under Different Pressures\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>CO/H\textsubscript{2} (atm)</th>
<th>n:i\textsuperscript{b}</th>
<th>linear (%)\textsuperscript{c}</th>
<th>TON\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-octene</td>
<td>30/30</td>
<td>24.3</td>
<td>96</td>
<td>0.31x10\textsuperscript{3}</td>
</tr>
<tr>
<td>2</td>
<td>2-octene</td>
<td>20/20</td>
<td>30</td>
<td>96.8</td>
<td>0.51x10\textsuperscript{3}</td>
</tr>
<tr>
<td>3</td>
<td>2-octene</td>
<td>10/10</td>
<td>46</td>
<td>98</td>
<td>1.6x10\textsuperscript{3}</td>
</tr>
<tr>
<td>4</td>
<td>2-octene</td>
<td>5/5</td>
<td>51.7</td>
<td>98.1</td>
<td>1.5x10\textsuperscript{3}</td>
</tr>
<tr>
<td>5</td>
<td>2-hexene</td>
<td>30/30</td>
<td>54.8</td>
<td>98.2</td>
<td>0.96x10\textsuperscript{3}</td>
</tr>
<tr>
<td>6</td>
<td>2-hexene</td>
<td>20/20</td>
<td>58.8</td>
<td>98.3</td>
<td>1.3x10\textsuperscript{3}</td>
</tr>
<tr>
<td>7</td>
<td>2-hexene</td>
<td>10/10</td>
<td>68.1</td>
<td>98.6</td>
<td>1.7x10\textsuperscript{3}</td>
</tr>
<tr>
<td>8</td>
<td>2-hexene</td>
<td>5/5</td>
<td>80.6</td>
<td>98.8</td>
<td>1.7x10\textsuperscript{3}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}S/C = 10000, [Rh] = 0.57 mM (for 2-octene) or 0.69 mM (for 2-hexene), ligand/Rh ratio = 3:1, temperature = 100\degree C, reaction time = 1 h, toluene as solvent, decane as internal standard. \textsuperscript{b}Linear/branched ratio, determined based on GC. \textsuperscript{c}Percentage of linear aldehyde in all aldehydes. \textsuperscript{d}Turn over number, determined based on GC.
Table 3-4: Isomerization-Hydroformylation of Internal Olefins at Different Reaction Times$^a$

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{entry} & \text{substrate} & t (h) & n:i^b & \text{linear} (%)^c & \text{TON}^d \\
\hline
1 & 2-octene & 1 & 51.7 & 98.1 & 1.5x10^3 \\
2 & 2-octene & 2 & 51.3 & 98.1 & 2.8x10^3 \\
3 & 2-octene & 6 & 41.3 & 97.6 & 5.7x10^3 \\
4 & 2-octene & 12 & 38 & 97.4 & 7.7x10^3 \\
5 & 2-octene & 18 & 27.7 & 96.5 & 8.1x10^3 \\
6 & 2-hexene & 1 & 80.6 & 98.8 & 1.7x10^3 \\
7 & 2-hexene & 2 & 71.9 & 98.6 & 2.4x10^3 \\
8 & 2-hexene & 6 & 63 & 97.4 & 5.5x10^3 \\
9 & 2-hexene & 12 & 56 & 98.2 & 6.0x10^3 \\
10 & 2-hexene & 18 & 51.9 & 98.1 & 6.7x10^3 \\
\hline
\end{array}
\]

$^a$S/C = 10000, [Rh] = 0.57 mM (for 2-octene) or 0.69 mM (for 2-hexene), ligand/Rh ratio = 3:1, temperature = 100°C, CO/H$_2$ = 5/5 atm, toluene as solvent, decane as internal standard. $^b$Linear/branched ratio, determined based on GC. $^c$Percentage of linear aldehyde in all aldehydes. $^d$Turn over number, determined based on GC.

The effects of reaction time (ranging from 1h to 18h) have been studied. The results are illustrated in Table 3-4. As can be seen in the table, the reaction time also
affects the regioselectivity of isomerization-hydroformylation. Lengthening the reaction time gradually diminished the regioselectivity. Further increasing the reaction time from 12 h to 18 h only slightly improved the TON, however, at the expense of decreased regioselectivity. The decreased reactivity can be explained by lower isomerization rate resulted from decreased concentration of internal olefins at high conversion.

Table 3-5: Comparison of Tetraphosphoramidite and Bisphosphoramidite Ligands

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>ligand</th>
<th>t(h)</th>
<th>n:i&lt;sup&gt;b&lt;/sup&gt;</th>
<th>linear(&lt;sup&gt;c&lt;/sup&gt;) (%)&lt;sup&gt;o&lt;/sup&gt;</th>
<th>TON&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-octene</td>
<td>1</td>
<td>1</td>
<td>51.7</td>
<td>98.1</td>
<td>1.5 x10&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>2-octene</td>
<td>1</td>
<td>12</td>
<td>38</td>
<td>97.4</td>
<td>7.7 x10&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>2-octene</td>
<td>3</td>
<td>1</td>
<td>10.1</td>
<td>91</td>
<td>2.3 x10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>2-octene</td>
<td>3</td>
<td>12</td>
<td>5.49</td>
<td>84.6</td>
<td>8.4 x10&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>2-hexene</td>
<td>1</td>
<td>1</td>
<td>80.6</td>
<td>98.8</td>
<td>1.7 x10&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>2-hexene</td>
<td>1</td>
<td>12</td>
<td>56</td>
<td>98.2</td>
<td>6.0 x10&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>2-hexene</td>
<td>3</td>
<td>1</td>
<td>15</td>
<td>93.8</td>
<td>2.1 x10&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>2-hexene</td>
<td>3</td>
<td>12</td>
<td>13.5</td>
<td>93.1</td>
<td>6.8 x10&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>S/C = 10000, [Rh] = 0.57 mM (for 2-octene) or 0.69 mM (for 2-hexene), ligand/Rh ratio = 3:1, temperature = 100 °C, CO/H<sub>2</sub> = 5/5 atm, toluene as solvent, decane as internal standard. <sup>b</sup>Linear/branched ratio, determined based on GC. <sup>c</sup>Percentage of linear aldehyde in all aldehydes. <sup>d</sup>Turn over number, determined based on GC.
For comparison, bisphosphoramidite ligand 3 was also prepared and tested in the rhodium-catalyzed isomerization-hydroformylation of internal olefins. The results are summarized in Table 3-5. Clearly, tetraphosphoramidite ligand 1 always gave higher regioselectivity than the corresponding bisphosphoramidite ligand 3. For example, the highest $n:i$ for the isomerization-hydroformylation of 2-octene with bisphosphoramidite ligand 3 was only 10.1

3.2.3 Hydroformylation of Terminal Olefins with Tetraphosphoramidite Ligand

The tetraphosphoramidite ligand 1 was also tested in the hydroformylation reaction of terminal olefins. As the case of isomerization-hydroformylation of internal olefins, the optimization of reaction condition was first conducted.

The hydroformylation reactions of 1-octene and 1-hexene were carried out at various temperatures ranging from 40 °C to 100 °C under otherwise identical conditions. The results are summarized in Table 3-6. High temperature generally led to high reaction rates and high isomerization. Even though the results indicate that hydroformylation at higher temperature resulted in lower regioselectivity, the regioselectivity remained very high. For example, in the hydroformylation of 1-octene, the linear/branched ratio ($n:i$) at 40 °C was 461, while this number decreased to 236 at 100 °C. It should be noted that the linear/branched ratio of 236 corresponds to as high as 99.6 % linear aldehyde. Since hydroformylation of terminal olefins at high temperature resulted in the formation of a high percentage of isomerization products, low temperature (80 °C) was preferred in the hydroformylation of terminal olefins.
Table 3-6: Hydroformylation of Terminal Olefins with Tetraphosphoramidite at Different Temperatures

\[ \text{R} \rightleftharpoons \frac{[\text{Rh}]/\text{ligand 1}}{\text{CO}/\text{H}_2} \text{R} \rightleftharpoons \text{CHO} + \text{R} \rightleftharpoons \text{CHO} \]

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>T (°C)</th>
<th>n:i(^b)</th>
<th>linear(%)(^c)</th>
<th>isomerization (%)(^d)</th>
<th>TON(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-octene</td>
<td>100</td>
<td>236</td>
<td>99.6</td>
<td>21.6</td>
<td>7.6 x10(^3)</td>
</tr>
<tr>
<td>2</td>
<td>1-octene</td>
<td>80</td>
<td>372</td>
<td>99.7</td>
<td>15.3</td>
<td>6.9 x10(^3)</td>
</tr>
<tr>
<td>3</td>
<td>1-octene</td>
<td>60</td>
<td>442</td>
<td>99.8</td>
<td>5.4</td>
<td>3.5 x10(^3)</td>
</tr>
<tr>
<td>4</td>
<td>1-octene</td>
<td>40</td>
<td>461</td>
<td>99.8</td>
<td>3.9</td>
<td>0.64 x10(^3)</td>
</tr>
<tr>
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<td>1-hexene</td>
<td>100</td>
<td>288</td>
<td>99.7</td>
<td>26.6</td>
<td>7.2 x10(^3)</td>
</tr>
<tr>
<td>6</td>
<td>1-hexene</td>
<td>80</td>
<td>382</td>
<td>99.7</td>
<td>18.7</td>
<td>6.7 x10(^3)</td>
</tr>
<tr>
<td>7</td>
<td>1-hexene</td>
<td>60</td>
<td>452</td>
<td>99.8</td>
<td>11.4</td>
<td>3.1 x10(^3)</td>
</tr>
<tr>
<td>8</td>
<td>1-hexene</td>
<td>40</td>
<td>f</td>
<td>&gt;99.9</td>
<td>6.9</td>
<td>0.69 x10(^3)</td>
</tr>
</tbody>
</table>

\(^a\)S/C = 10000, [Rh] = 0.2 mM, ligand/Rh ratio = 3:1, CO/H\(_2\) = 10/10 atm, reaction time = 1 h, toluene as solvent, decane as internal standard. \(^b\)Linear/branched ratio, determined based on GC. \(^c\)Percentage of linear aldehyde in all aldehydes. \(^d\)Isomerization to internal olefins. \(^e\)Turn over number, determined based on GC. \(^f\)No branched product detected.

The effects of total pressure of CO/H\(_2\) were also evaluated in the hydroformylation of terminal olefins (Table 3-7). The hydroformylation reactions were
conducted under CO/H$_2$ total pressure ranging from 5/5 to 30/30 atm. Low pressure generally resulted in slightly decreased reactivity. An opposite trend between regioselectivity and isomerization was observed: whereas decreasing the pressure leads to high regioselectivity, the isomerization increased dramatically. For example, as high as 28.3 % isomerization was observed in the hydroformylation of 1-octene at CO/H$_2$ total pressure of 5/5 atm.

Table 3-7: Hydroformylation of Terminal Olefins under Different Pressures$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>CO/H$_2$ (atm)</th>
<th>n:i$^b$</th>
<th>linear$^c$(%)</th>
<th>isomerization (%)$^d$</th>
<th>TON$^e$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-octene</td>
<td>30/30</td>
<td>242</td>
<td>99.6</td>
<td>8</td>
<td>7.7 x10$^3$</td>
</tr>
<tr>
<td>2</td>
<td>1-octene</td>
<td>10/10</td>
<td>372</td>
<td>99.7</td>
<td>15.3</td>
<td>6.9 x10$^3$</td>
</tr>
<tr>
<td>3</td>
<td>1-octene</td>
<td>5/5</td>
<td>405</td>
<td>99.8</td>
<td>28.3</td>
<td>6.2 x10$^3$</td>
</tr>
<tr>
<td>4</td>
<td>1-hexene</td>
<td>30/30</td>
<td>258</td>
<td>99.6</td>
<td>11.3</td>
<td>6.7 x10$^3$</td>
</tr>
<tr>
<td>5</td>
<td>1-hexene</td>
<td>10/10</td>
<td>382</td>
<td>99.7</td>
<td>18.7</td>
<td>6.7 x10$^3$</td>
</tr>
<tr>
<td>6</td>
<td>1-hexene</td>
<td>5/5</td>
<td>394</td>
<td>99.7</td>
<td>34.4</td>
<td>6.1 x10$^3$</td>
</tr>
</tbody>
</table>

$^a$S/C = 10000, [Rh] = 0.2 mM, ligand/Rh ratio = 3:1, temperature = 100 °C, reaction time = 1 h, toluene as solvent, decane as internal standard. $^b$Linear/branched ratio, determined based on GC. $^c$Percentage of linear aldehyde in all aldehydes. $^d$Isomerization to internal olefins. $^e$Turn over number, determined based on GC.
For comparison, hydroformylation of terminal olefins with bisphosphoramidite ligand 3 were also conducted (Table 3-8). As in the case of hydroformylation of internal olefins, tetraphosphoramidite ligand 1 also afforded higher regioselectivity than bisphosphoramidite ligand 3. The isomerization of terminal olefins with bisphosphoramidite ligand 3, however, was lower than tetraphosphoramidite ligand 1.

Table 3-8: Comparison of Tetraphosphoramidite and Bisphosphoramidite Ligands

\[
\text{R-C=C-R} \xrightarrow{[\text{Rh}] / \text{ligand}} \text{R-CHO} + \text{R'-CHO}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>ligand</th>
<th>t (h)</th>
<th>(n:i^b)</th>
<th>linear (%^c)</th>
<th>isomerization (%^d)</th>
<th>TON(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-octene</td>
<td>1</td>
<td>1</td>
<td>372</td>
<td>99.7</td>
<td>15.3</td>
<td>6.9 \times 10^3</td>
</tr>
<tr>
<td>2</td>
<td>1-octene</td>
<td>1</td>
<td>2</td>
<td>369</td>
<td>99.7</td>
<td>15.1</td>
<td>8.4 \times 10^3</td>
</tr>
<tr>
<td>3</td>
<td>1-octene</td>
<td>3</td>
<td>1</td>
<td>74.1</td>
<td>98.7</td>
<td>10</td>
<td>8.4 \times 10^3</td>
</tr>
<tr>
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<td>1-octene</td>
<td>3</td>
<td>2</td>
<td>69.4</td>
<td>98.6</td>
<td>10.7</td>
<td>8.9 \times 10^3</td>
</tr>
<tr>
<td>5</td>
<td>1-hexene</td>
<td>1</td>
<td>1</td>
<td>382</td>
<td>99.7</td>
<td>18.7</td>
<td>6.7 \times 10^3</td>
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<tr>
<td>6</td>
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<td>380</td>
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<td>18.4</td>
<td>8.0 \times 10^3</td>
</tr>
<tr>
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<td>7.9 \times 10^4</td>
</tr>
<tr>
<td>8</td>
<td>1-hexene</td>
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<td>78.1</td>
<td>98.7</td>
<td>12.4</td>
<td>8.7 \times 10^3</td>
</tr>
</tbody>
</table>

\(^a\)S/C = 10000, [Rh] = 0.2 mM, ligand/Rh ratio = 3:1, temperature = 80 °C, CO/H\(_2\) = 10/10 atm, toluene as solvent, decane as internal standard. \(^b\)Linear/branched ratio, determined based on GC. \(^c\)Percentage of linear aldehyde in all aldehydes. \(^d\)Isomerization to internal olefins. \(^e\)Turn over number, determined based on GC.
3.2.4 Design and Synthesis of Tetraphosphine Ligand

Tetraphosphoramidite ligand 1 exhibited high reactivity and regioselectivity in the hydroformylation of both terminal and internal olefins. However, in the hydroformylation of terminal olefins, a high level of isomerization was observed at high temperature. Thus, tetraphosphoramidite ligand 1 is more suitable for the hydroformylation of internal olefins. The development of a tetraphosphorus ligand with less isomerization rate for the hydroformylation of terminal olefins is also desirable. Since hydroformylation with more electron-donating bisphosphines such as Bisbi$^8$ is less likely to undergo isomerization, we then designed tetraphosphine ligand 2 based on a biphenyl backbone (Figure 3-3) for the hydroformylation of terminal olefins.

![Bisphosphine Bisbi and tetraphosphine Ligand 2](image)

Figure 3-3: Design of Tetraphosphine Ligand

We first tried to synthesize tetraphosphine ligand 2 by employing a similar strategy as used for the synthesis of Bisbi.$^8$ In the literature, Bisbi was synthesized by the reaction of lithium diphenylphosphine with 2, 2’-bisbromomethyl-1, 1’biphenyl; the latter was obtained by reduction of diphenic acid with LiAlH$_4$ followed by bromination. Despite the structural similarity of tetraphosphine ligand 2 and bisphosphine Bisbi, the
results turned out that the synthetic rout for Bisbi is not applicable for the preparation of tetraphosphine ligand 2. Following the literature procedure,\(^9\) we prepared tetraacid 5 by the oxidation of pyrene with \(\text{RuCl}_3/\text{NaIO}_4\) catalytic system. The yield was 71%. However, an attempt to reduce tetraacid 5 with \(\text{LiAlH}_4\) in THF under refluxing condition was not successful as no desired tetraol was obtained. Since the solubility of tetraacid 5 in THF was poor, we then transformed the tetraacid 5 into its methyl ester 6 and subjected it to reduction with \(\text{LiAlH}_4\). To our surprise, still no desired tetraol was obtained. The reactivity of tetraacid 5 was very different from its corresponding diacid, diphenic acid, which can be easily reduced with \(\text{LiAlH}_4\).\(^8\)

We then tried another rout to prepare the tetrol 7 by reducing tetraaldehyde 8 with \(\text{NaBH}_4\).\(^{10}\) The tetraaldehyde was obtained in moderate yield by ozonolysis of pyrene in THF at \(-78^\circ\text{C}\) following the literature procedure.\(^{10}\) Reduction of tetraaldehyde 8 with 4 equiv \(\text{NaBH}_4\), under mild reaction conditions (room temperature, 4 h) afforded tetraol 7 in high yield (93%). Following the similar procedure for the preparation of Bisbi ligand,\(^8\) tetrabromide 9 was obtained in 72% yield by reaction of tetraol with 4 equiv of
phosphorus tribromide under anhydrous conditions. Whereas the literature reported the synthesis of Bisbi by reaction of lithium diphenylphosphine with 2, 2’-bisbromomethyl-1, 1’biphenyl in high yield, the reaction of tetrabromide 9 with lithium diphenyl phosphine gave very complex products under the same reaction conditions. The reaction was monitored by in situ $^{31}$P NMR and a messy spectra was obtained indicating over 10 phosphorus species presented in the reaction mixture. The reactivity of tetrabromide 9 was very different from its corresponding dibromide, 2, 2’-bisbromomethyl-1,1’biphenyl.

To overcome this problem, we transferred tetrabromide 9 to less reactive tetrachloride 10 by the reaction of tetrabromide with LiCl in DMF at room temperature. The tetrachloride 10 was obtained in high yield (93%). We were then pleased to find that the reaction of tetrachloride 10 with lithium diphenylphosphine afforded the desired tetraphosphine cleanly as indicated by $^{31}$P NMR.
Since tetraphosphine 2 is an air-sensitive compound, for convenience in the following work-up procedure, the tetraphosphine 2 was protected in situ with borane. The borane protected tetraphosphine 11 is an air-stable compound. A simple deprotection with DABCO afforded the desired tetraphosphine ligand 2 in 79% yield. The overall synthetic route is outlined in Scheme 3-3. The key issue for the successful synthesis is the use of less reactive tetrachloride 10 instead of highly reactive tetrabromide 9 in the last phosphinylation step.

Scheme 3-3: Synthesis of Tetraphosphine Ligand
3.2.5 Hydroformylation of Terminal Olefins with Tetraphosphine Ligand

Hydroformylation of terminal olefins with the new tetraphosphine ligand 2 was investigated. The reactions were carried out in toluene with decane as internal standard. The rhodium catalyst was prepared in situ by mixing the tetraphosphine ligand with Rh(acac)(CO)₂. The substrate catalyst ratio was 2000 and the catalyst concentration was 1.0 mM. The reaction was terminated after 1 h. As in the case of isomerization-hydroformylation of internal olefins, optimizations of ligand/metal ratio, temperature and pressure was conducted.

The effects of ligand/metal ratio on hydroformylation of terminal olefins with the tetraphosphine ligand 2 were first evaluated. The hydroformylation reactions were conducted with ligand/metal ratios ranging from 1:2 to 6:1 while keeping the reaction temperature (100 °C) and total CO/H₂ (1:1) pressure (10/10 atm) constant. The results are summarized in Table 3-9. When the ligand/metal ratio was below 1:1, both reactivity and regioselectivity were low. However, the isomerization of terminal olefins to internal olefins was high at this low ligand metal ratio. When the ligand/metal ratio reached 1:1, dramatic improvements in linear selectivity were observed. For example, in the hydroformylation of 1-octene, the n:i ratio increased from 1.75 (ligand/metal ratio of 1:2) to 53.7 (ligand/metal ratio of 1:1). At the same time, aldehyde yields also improved and isomerization of olefins decreased. Further increasing the ligand/metal ratio slightly decreased the n:i ratio and isomerization.
Table 3-9: Hydroformylation of Terminal Olefins at Different Ligand/Metal Ratios\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>L/Rh</th>
<th>(n:i^b)</th>
<th>linear (%)(^c)</th>
<th>isomerization (%)(^d)</th>
<th>TON(^e)</th>
</tr>
</thead>
<tbody>
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<td>1-octene</td>
<td>1:2</td>
<td>1.75</td>
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<td>1:1</td>
<td>53.7</td>
<td>98.2</td>
<td>7.9</td>
<td>1.8 x10(^3)</td>
</tr>
<tr>
<td>3</td>
<td>1-octene</td>
<td>2:1</td>
<td>53.4</td>
<td>98.2</td>
<td>7.3</td>
<td>1.8 x10(^3)</td>
</tr>
<tr>
<td>4</td>
<td>1-octene</td>
<td>4:1</td>
<td>50.5</td>
<td>98.1</td>
<td>5.6</td>
<td>1.8 x10(^3)</td>
</tr>
<tr>
<td>5</td>
<td>1-octene</td>
<td>6:1</td>
<td>48.9</td>
<td>98.0</td>
<td>5.6</td>
<td>1.8 x10(^3)</td>
</tr>
<tr>
<td>6</td>
<td>1-hexene</td>
<td>1:2</td>
<td>1.5</td>
<td>60.0</td>
<td>21</td>
<td>1.6 x10(^3)</td>
</tr>
<tr>
<td>7</td>
<td>1-hexene</td>
<td>1:1</td>
<td>51.9</td>
<td>98.1</td>
<td>10</td>
<td>1.8 x10(^3)</td>
</tr>
<tr>
<td>8</td>
<td>1-hexene</td>
<td>2:1</td>
<td>52.3</td>
<td>98.1</td>
<td>7.9</td>
<td>1.8 x10(^3)</td>
</tr>
<tr>
<td>9</td>
<td>1-hexene</td>
<td>4:1</td>
<td>48.6</td>
<td>98.0</td>
<td>6.6</td>
<td>1.8 x10(^3)</td>
</tr>
<tr>
<td>10</td>
<td>1-hexene</td>
<td>6:1</td>
<td>46.6</td>
<td>97.9</td>
<td>4.7</td>
<td>1.9 x10(^3)</td>
</tr>
</tbody>
</table>

\(^a\)S/C = 2000, [Rh] = 1.0 mM, temperature = 100 °C, CO/H\(_2\) = 10/10 atm, reaction time = 1 h, toluene as solvent, decane as internal standard. \(^b\)Linear/branched ratio, determined based on GC. \(^c\)Percentage of linear aldehyde in all aldehydes. \(^d\)Isomerization to internal olefins. \(^e\)Turn over number, determined based on GC.
The effects of reaction temperature on the hydroformylation of terminal olefins then were evaluated. The hydroformylation reactions were conducted at temperatures ranging from 60 °C to 140 °C while keeping the ligand/metal ratio (4:1) and total CO/H₂ (1:1) pressure (10/10 atm) constant. The results are summarized in Table 3-10. Generally, hydroformylation at lower temperatures lead to less olefin isomerization. Only a slight decrease in \( n/i \) ratio was observed when the reaction increased from 100 °C to 140 °C. Interestingly, when the hydroformylation was carried out below 100 °C, the regioselectivity dropped. For example, the \( n/i \) ratio dropped from 50.5 (100 °C) to 22.8 (60 °C) for the hydroformylation of 1-octene. This observation is very different from the tetraphosphoramidite ligand 1 which shows an increase of regioselectivity at low temperature. Such differences may be explained by different activities of tetraphosphine 2 and tetraphosphoramidite 1 to form rhodium complexes. Due to the different electronic properties, tetraphosphoramidite ligand 1 is more reactive to form the rhodium complex than electron-donating tetraphosphine ligand 2. Since the catalyst was prepared \textit{in situ}, at low temperature, the reaction of Rh(acac)(CO)₂ with tetraphosphine 2, CO and H₂ to form the real catalyst RhH(CO)₂(L) may be slow. Participation of other rhodium species in the hydroformylation reaction may result in low regioselectivity.
Table 3-10: Hydroformylation of Terminal Olefins at Different Temperatures

![Chemical Structure]

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>T (°C)</th>
<th>$n:i^{b}$</th>
<th>linear (%)$^{c}$</th>
<th>isomerization (%)$^{d}$</th>
<th>TON$^{e}$</th>
</tr>
</thead>
<tbody>
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<td>97.8</td>
<td>6.5</td>
<td>1.8 x10^4</td>
</tr>
<tr>
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<td>1-octene</td>
<td>120</td>
<td>49.8</td>
<td>98.0</td>
<td>5.8</td>
<td>1.8 x10^4</td>
</tr>
<tr>
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<td>1-octene</td>
<td>100</td>
<td>50.5</td>
<td>98.1</td>
<td>5.6</td>
<td>1.8 x10^4</td>
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<td>97.2</td>
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<td>1.4 x10^4</td>
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<td>95.8</td>
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<td>0.44 x10^3</td>
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<td>1.8 x10^4</td>
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<tr>
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<td>1-hexene</td>
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<td>48.5</td>
<td>98.0</td>
<td>7.1</td>
<td>1.8 x10^4</td>
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<tr>
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<td>98.0</td>
<td>6.6</td>
<td>1.8 x10^4</td>
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<td>32.6</td>
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<td>4.8</td>
<td>1.8 x10^4</td>
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<td>1-hexene</td>
<td>60</td>
<td>21.4</td>
<td>95.5</td>
<td>2.7</td>
<td>1.8 x10^4</td>
</tr>
</tbody>
</table>

$^{a}$S/C = 2000, [Rh] = 1.0 mM, ligand/Rh ratio = 4:1, CO/H$_2$ = 10/10 atm, reaction time = 1 h, toluene as solvent, decane as internal standard. $^{b}$Linear/branched ratio, determined based on GC. $^{c}$Percentage of linear aldehyde in all aldehydes. $^{d}$Isomerization to internal olefins. $^{e}$Turn over number, determined based on GC.
Table 3-11: Hydroformylation of Terminal Olefins under Different Pressures<sup>a</sup>

\[
R = \frac{[\text{Rh}] + \text{ligand} + \text{CO/H}_2}{2} \to R \text{CHO} + R \text{CHO}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>CO/H&lt;sub&gt;2&lt;/sub&gt; (atm)</th>
<th>n:i&lt;sup&gt;b&lt;/sup&gt;</th>
<th>linear (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>isomerization (%)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>TON&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-octene</td>
<td>30/30</td>
<td>16.5</td>
<td>94.3</td>
<td>2.9</td>
<td>1.2 x10&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
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<td>1-octene</td>
<td>20/20</td>
<td>22.3</td>
<td>95.7</td>
<td>3.0</td>
<td>1.2 x10&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
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<td>10/10</td>
<td>50.5</td>
<td>98.1</td>
<td>5.6</td>
<td>1.8 x10&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
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<td>66.7</td>
<td>98.5</td>
<td>17.3</td>
<td>1.6 x10&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
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<td>41.8</td>
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<td>26.1</td>
<td>1.4 x10&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>30/30</td>
<td>15.4</td>
<td>93.9</td>
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<td>20/20</td>
<td>20.2</td>
<td>95.3</td>
<td>3.2</td>
<td>1.1 x10&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>1-hexene</td>
<td>10/10</td>
<td>48.6</td>
<td>98.0</td>
<td>6.6</td>
<td>1.8 x10&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
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<td>1-hexene</td>
<td>5/5</td>
<td>65.5</td>
<td>98.5</td>
<td>12.7</td>
<td>1.7 x10&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td>10</td>
<td>1-hexene</td>
<td>2.5/2.5</td>
<td>47.6</td>
<td>97.9</td>
<td>22.9</td>
<td>1.5 x10&lt;sup&gt;3&lt;/sup&gt;</td>
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</table>

<sup>a</sup>S/C = 2000, [Rh] = 1.0 mM, ligand/Rh ratio = 4:1, temperature = 100 °C, reaction time = 1 h, toluene as solvent, decane as internal standard. <sup>b</sup>Linear/branched ratio, determined based on GC. <sup>c</sup>Percentage of linear aldehyde in all aldehydes. <sup>d</sup>Isomerization to internal olefins. <sup>e</sup>Turn over number, determined based on GC.
The effects of CO/H₂ pressure were also tested. The hydroformylation reactions were conducted at CO/H₂ pressures ranging from 2.5/2.5 to 30/30 atm while keeping the ligand/metal ratio (4:1) and reaction temperature (100 °C) constant. The results are summarized in Table 3-11. A general trend of olefin isomerization has been observed. Low CO/H₂ pressures generally facilitate the olefin isomerization. For example, the isomerization increased from 2.9 % to 26.1% in the hydroformylation of 1-octene with CO/H₂ pressure decreased from 30/30 atm to 2.5/2.5 atm. At high CO/H₂ pressure, the regioselectivities were also low. The regioselectivities could be increased by lowering the CO/H₂ pressure. The highest regioselectivity was obtained under a CO/H₂ pressure of 5/5 atm. However, further decreasing the pressure to 2.5/2.5 atm resulted in a lower n:i ratio. The turnover numbers (TON) were also affected by CO/H₂ pressure. The highest TONs were obtained under CO/H₂ pressure of 10/10 atm.

For comparison, bisphosphine ligand Bisbi was prepared and employed in the hydroformylation of terminal olefins. The reaction conditions with Bisbi were identical to those with the tetraphosphine ligand 2. The results are summarized in Table 3-12. As can be seen clearly, tetraphosphine ligand 2 always afforded higher regioselectivity than bisphosphine ligand Bisbi. Most importantly, dramatic improvements in regioselectivity have been achieved with tetraphosphine 2 when the hydroformylation reaction was conducted at high temperature. For example, in the hydroformylation of 1-octene, whereas the regioselectivity remained high (n:i ratio = 45.2) using tetraphosphine ligand 2 at the temperature of as high as 140 °C, the regioselectivity with Bisbi was significant lower (n:i = 2.4). This result is important from the practical point of view because high
reaction rates which usually require the reaction to be carried out at high temperature are highly desirable for industrially applications. It also confirmed our prediction that ligand dissociation at high temperature, a major problem for bisphosphorus ligands to achieve high linear selectivity, can be minimized by using a tetraphosphorus ligand.

### 3.3 Conclusion

In conclusion, we have developed a new concept in designing ligands for regioselective hydroformylation: tetraphosphorus ligands with enhanced chelating ability through multiple chelating modes and increased local phosphorus concentration can provide higher regioselectivity than their corresponding bisphosphorus ligands. Based on this concept, two tetraphosphorus ligands, tetraphosphoramidite ligand 1 and tetraphosphine ligand 2, were designed, synthesized and successfully applied in highly regioselective hydroformylations. To the best of our knowledge, tetraphosphoramidite ligand 1 provides the highest regioselectivity ever reported in the homogenous isomerization-hydroformylation of internal olefins. Tetraphosphine ligand 2 exhibited remarkably improved high temperature performance in the hydroformylation of terminal olefins.
Table 3-12: Comparison of Tetraphosphine and Bisphosphine Ligands

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<th>entry</th>
<th>substrate</th>
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<th>ligand</th>
<th>n:i (^b)</th>
<th>linear (^c) (%)</th>
<th>isomerization (^d) (%)</th>
<th>TON (^e)</th>
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</thead>
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<td>1</td>
<td>1-octene</td>
<td>140</td>
<td>2</td>
<td>45.2</td>
<td>97.8</td>
<td>6.5</td>
<td>1.8x10^3</td>
</tr>
<tr>
<td>2</td>
<td>1-octene</td>
<td>140</td>
<td>Bisbi</td>
<td>2.4</td>
<td>70.6</td>
<td>24</td>
<td>1.5 x10^4</td>
</tr>
<tr>
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<td>120</td>
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<td>49.8</td>
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<td>1.8 x10^3</td>
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<td>Bisbi</td>
<td>29.5</td>
<td>96.7</td>
<td>8.7</td>
<td>1.8 x10^3</td>
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<td>1.8 x10^4</td>
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<td>Bisbi</td>
<td>45.2</td>
<td>97.8</td>
<td>6.7</td>
<td>1.6 x10^4</td>
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<td>97.3</td>
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<tr>
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<tr>
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<td>43.2</td>
<td>97.7</td>
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<td>1.7 x10^4</td>
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</tbody>
</table>

\(^a\)S/C = 2000, [Rh] = 1.0 mM, ligand/Rh ratio = 4:1, CO/H₂ = 10/10 atm, reaction time = 1 h, toluene as solvent, decane as internal standard. \(^b\)Linear/branched ratio, determined based on GC. \(^c\)Percentage of linear aldehyde in all aldehydes. \(^d\)Isomerization to internal olefins. \(^e\)Turn over number, determined based on GC.
Experimental Section

**General Methods:** All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise noted. Solvents were dried with standard procedures and degassed with N₂. Column chromatography was performed using 200–400 mesh silica gel supplied by Natland International Corporation. Thin layer chromatography (TLC) was performed on EM reagents 0.25 mm silica 60-F plates. \(^1\)H, \(^{13}\)C, \(^{31}\)P NMR spectrum were recorded on Bruker AM-300 and AMX-360 spectrometers. GC analysis was carried on Helwett–Packard 6890 gas chromatography using capillary columns.

**Synthesis of Chlorodipyrrolylphosphine**

\[
\begin{array}{c}
\text{N} \\
\text{P} \quad \text{Cl} \\
\text{N}
\end{array}
\]

To a 100 mL flask was charged THF (60 mL) followed by PCl₅ (2.71 mL, 0.03 mol). The resulting solution was then cooled to 0 °C in an ice bath. To the cooled solution was added dropwise a solution of pyrrole (4.20 mL, 0.06 mol) and NEt₃ (3 mL) in THF (15 mL) while maintaining the temperature at 0 °C. The precipitation of triethylamine.HCl salt was formed immediately upon addition. After addition, the cold bath was removed and the reaction mixture was allowed to warm to room temperature and stirred for 6 h. The reaction mixture was diluted with THF (30 ml) and filtered to remove the salts. The salts were washed with THF (3 x 10 mL). The combined THF solution was concentrated under reduced pressure. The residue was vacuum distilled to
afford chlorodipyrrolylphosphine (2.35 g, 39 % yield) as a colorless liquid. $^1$H NMR (300 MHz, CDCl$_2$) $\delta$: 6.51-6.50 (m, 4H), 7.24-7.21 (m, 4H); $^{31}$P NMR (146 Hz, CD$_2$Cl$_2$) $\delta$: 102.9.

**Synthesis of 2, 6, 2', 6'-Tetramethoxy-biphenyl**

![Structural formula of 2, 6, 2', 6'-Tetramethoxy-biphenyl]

To a 250 mL Schlenk flask was added 1, 3-dimethoxybenzene (8.26 g, 60 mmol). The flask was degassed and charged with nitrogen. To the flask was added THF (40 mL). The resulting solution was cooled to -78 °C in a dry ice/acetone bath. To the cooled solution was added n-BuLi (26.4 mL, 2.5 M solution in hexane, 66 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. the mixture was cooled again to -78 °C and added through cannula to a cold (- 78 °C) solution of FeCl$_3$ (13.5 g, 83 mmol) in THF (40 mL). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was concentrated under reduced pressure. To the residue was added aqueous 2N HCl solution (100 mL), CH$_2$Cl$_2$ (60 mL). After stirring for 5 min, the organic phase was separated. The organic phase was washed with aqueous 2N HCl solution (2 x 20 mL), dried over Na$_2$SO$_4$ and passed through a short silica gel plug. The pure title product was obtained by recrystallization from EtOH. (5.7 g, 70 %). $^1$H NMR (300 Hz, CDCl$_3$) $\delta$: 7.31 (t, $J = 8.30$ Hz, 2H), 6.68 (d, $J = 8.33$ Hz, 4H), 3.73 (s, 12H); $^{13}$C NMR (75 Hz, CDCl$_3$) $\delta$: 158.3, 128.7, 112.4, 104.4, 56.1.
Synthesis of Biphenyl-2,6,2’,6’-tetraol (4)

To a 250 mL Schlenk flask was added 2, 2’, 6, 6’-tetramethoxybiphenyl (5.48 g, 20 mmol). The flask was degassed and charged with nitrogen. To the flask was added CH$_2$Cl$_2$ (100 mL). The resulting solution was cooled to -78 °C in a dry ice/acetone bath. To the cooled solution was added boron tribromide (7.7 mL) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 5 h. After cooled to 0 °C, water (50 mL) was added dropwise to quench the reaction. The organic phase was separated and the aqueous phase was extracted with ether (3 x 25 mL). The combined organic layers was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by recrystallization from ethanol to give the title compound (3.57 g, 81%). $^1$H NMR (300 Hz, CD$_2$Cl$_2$) δ: 7.59 (s, 4H), 7.02 (t, $J = 8.13$ Hz, 2H), 6.48 (d, $J = 8.10$ Hz, 4H); $^{13}$C NMR (75 Hz, CD$_2$Cl$_2$) δ: 207.0, 157.2, 129.8, 108.1.

Synthesis of 1, 1’-Biphenyl-2, 2’, 6, 6’-tetrakis-(dipyrrolylphosphoramidite) (1)

To a solution of chlorodipyrrolyphosphine (4.4 mmol, 0.87g) in THF (10 mL) was added dropwise triethylamine (1mL) and a solution of biphenyl-2,6,2’,6’-tetraol 4 (1 mmol, 0.218g) in THF (5 mL) at room temperature. The triethylamine.HCl salts were
formed immediately after the addition. The reaction mixture was stirred for 6 h at room
temperature. The triethylamine.HCl salts were then filtered off and the solvent was
removed under vacuum. The crude product was purified by flash chromatography on
basic aluminum oxide (eluting with hexane/EtOAc/NEt\textsubscript{3} 6:1:0.1) to afford the pure ligand
(0.31 g, 36 %) as an air-stable colorless solid. \textsuperscript{1}H NMR (300 Hz, CD\textsubscript{2}Cl\textsubscript{2}) δ: 7.23 (t, J =
8.3 Hz, 2H), 6.68 (m, 20H), 6.21 (m, 16H); \textsuperscript{13}C NMR (75 Hz, CD\textsubscript{2}Cl\textsubscript{2}) δ 152.86 (d, J =
12.2Hz) 131.0, 121.5 (d, J = 16.8Hz), 118.1, 115.3(d, J = 13.7 Hz), 112.7; \textsuperscript{31}P NMR
(146Hz, CDCl\textsubscript{2}) δ 107.3. HRMS (ES\textsuperscript{+}) calcd. for C\textsubscript{44}H\textsubscript{39}N\textsubscript{8}O\textsubscript{4}P [MH\textsuperscript{+}]
867.2045, found 867.2021.

**Synthesis of Biphenyl-2,\textsuperscript{′} 2,\textsuperscript{′},6, 6\textsuperscript{′}-tetracarboxaldehyde (8)**

To a 1-L three-neck flask equipped with a magnetic stirrer, a gas inlet tube, and a
drying tube was charged pyrene (10 g, 50 mmol) and dry CH\textsubscript{2}Cl\textsubscript{2} (350 mL). The
resulting solution was cooled to -78 °C in a dry ice/acetone bath. Ozone was introduced
to the stirred solution at -78 °C for 2.5 h, and the temperature of the reaction mixture was
maintained at -78 °C. The excess ozone was removed by bubbling oxygen through the
solution for 5 min at -78 °C and stirred for another 1 h. A solution of sodium iodide (68 g)
in glacial acetic acid (500 mL) was added dropwise during 1 h to the reaction mixture at
-78 °C. After stirring for 30 min at -78 °C, the reaction mixture was allowed to warm
gradually to 0 °C. The mixture was stored in a refrigerator (4 °C) for 24 h. The reaction
mixture was successively washed with aqueous NaS\textsubscript{2}O\textsubscript{3} (10 %, 800 mL), aqueous
NaHCO₃ (5%, 1.5 L), and water (500 mL) until the pH of aqueous layer = 7. The organic layer was then dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was dissolved in a minimum of CH₂Cl₂ and chromatographed on a silica gel column using n-hexane and CH₂Cl₂ as eluents. Pyrene was first eluted with n-hexane. It was followed by the tetraaldehyde which was eluted with CH₂Cl₂. The solvent was removed under reduced pressure. The crude product was recrystallized from toluene to give the title tetraaldehyde as a bright yellow solid (6.4 g, 50%). §H NMR (300 MHz, CDCl₃) δ: 9.69 (s, 4H), 8.25 (d, J = 7.72 Hz, 4H), 7.84 (t, J = 7.66 Hz, 2H); §C NMR (75 MHz, CDCl₃) δ: 189.72, 139.23, 135.83, 135.76, 129.94.

Synthesis of 2,2',6,6'-Tetrakis (hydroxymethyl) Biphenyl (7)

To a mixture of biphenyl-2, 2', 6, 6'-tetracarboxaldehyde 8 (6.3 g, 23.7 mmol) in absolute methanol (150 mL) was added portionwise sodium borohydride (2.7 g, 75 mmol) under anhydrous conditions. The addition was completed in 1 h. The reaction mixture was heated to 40 °C and stirred for 4 h. The mixture became clear during the reaction. To the reaction mixture was added dropwise aqueous 9 % HCl solution until pH = 7. The neutralized solution was concentrated under reduced pressure. The residue was extracted with boiling isopropanol (3 x 150 mL). The combined extractions were concentrated under reduced pressure. The crude product was recrystallized from hot water to give the title tetraol (6.0 g, 93 %) as a colorless plates. §H NMR (300 MHz, CDCl₃) δ: 7.45-7.42
(m, 4H), 7.36-7.31 (m, 2H), 4.72 (bs, 4H), 3.97 (s, 8H); $^{13}$C NMR (75MHz, CDCl$_3$) δ: 137.8, 132.7, 126.0, 125.2, 59.8.

**Synthesis of 2, 6, 2’, 6’-Tetrakis-bromomethyl-biphenyl (9)**

![Structure of 2, 6, 2’, 6’-Tetrakis-bromomethyl-biphenyl](image)

To a solution of 2, 2’, 6, 6’-tetrakis( hydroxymethyl) biphenyl 7 (5 g, 18.2 mmol) in CH$_2$Cl$_2$ (80 mL) was added dropwise, under anhydrous conditions at room temperature, a solution of phosphorus tribromide (30 mL, excess) in CH$_2$Cl$_2$ (30 mL). After the addition was completed, the reaction mixture was heated to reflux (bath temperature 50 °C) and stirred for 4 h. The reaction mixture was cooled to room temperature, and treated dropwise with water (80 mL). Caution: Hydrogen bromide was vigorously evolved during addition. After stirring for 5 min, the organic phase was separated, washed with water (3 x 30 mL) and dried over Na$_2$SO$_4$. The solvent was evaporated under reduced pressure. The residue was purified by recrystallization from hexane to afford the title tetrabromide as a white solid (6.9 g, 72 %). $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ: 7.64-7.61 (m, 4H), 7.56-7.51 (m, 2H), 4.25 (s, 8H); $^{13}$C NMR (75MHz, CD$_2$Cl$_2$) δ: 137.1, 135.6, 131.9, 130.4, 32.6.

**Synthesis of 2, 6, 2’, 6’-Tetrakis-chloromethyl-biphenyl (10)**

![Structure of 2, 6, 2’, 6’-Tetrakis-chloromethyl-biphenyl](image)
To a solution of 2, 6, 2', 6'-tetrakis-bromomethyl-biphenyl 9 (2.2 g, 4.2 mmol) in DMF (80 mL) was added LiCl (2.82 g, 67.2 mmol). The reaction mixture was stirred at room temperature for 6 h. After the reaction was complete, the reaction mixture was cooled to 0 °C. To the cooled mixture was then added carefully 5% aqueous HCl solution (30 mL) (exothermic reaction). After stirring for 5 min, the mixture was extracted with ether (4 x 40mL) and washed with saturated aqueous NaCl solution (80 mL). The organic layer was separated, dried over Na₂SO₄ and concentrated to dryness. Pure product was obtained by recrystallization from CH₂Cl₂/hexanes as a white solid (1.35 g, 93% yield).

¹H NMR (300 MHz, CD₂Cl₂) δ: 7.64-7.62 (m, 4H), 7.59-7.56 (m, 2H), 4.28 (s, 8H); ¹³C NMR (75MHz, CD₂Cl₂) δ: 137.0, 135.8, 131.2, 130.2, 45.0; HRMS (EI⁺) calcd. for C₁₈H₁₄Cl₂ [M⁺] 345.9853, found 345.9850.

**Synthesis of 2, 6, 2’, 6’-Tetrakis-borane[(diphenylphosphanyl)-methyl]-biphenyl (11)**

![Chemical structure of 11](image)

To a 50 mL Schlenk flask was added fresh distilled THF (10 mL), followed by diphenylphosphine (2.32 mL, 13.2 mmol). The mixture was cooled to -78 °C and n-BuLi (5.28 mL, 2.5 M solution in hexane, 13.2 mmol) was added dropwise. The resulting yellow mixture was stirred at -78°C for 10 min. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and stirred for 30 min. The reaction mixture was again cooled to -78 °C. To the cooled reaction mixture was added dropwise 2, 6, 2’, 6’-tetrakis-chloromethyl-biphenyl 10 (1.05g, 3 mmol) in THF (10 mL).
The yellow color faded upon addition. After addition, the reaction mixture was allowed to warm to room temperature slowly and stirred overnight. A small volume of the reaction mixture was taken out and subjected to $^{31}$P NMR to monitor the reaction progress. After the reaction was complete, the reaction mixture was cooled to 0 °C and a cold 1.0M THF solution of BH$_3$ (132 mL, 132 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 4h. After the reaction was complete (monitored by $^{31}$P NMR), the reaction mixture was cooled to 0 °C and water was added carefully to quench the excess BH$_3$. (Caution: gas generated vigorously upon the addition of water). The volatile was removed under vacuum. To the residue was added CH$_2$Cl$_2$ (50 mL) and water (50 mL). The mixture was stirred for 10 min until all residues dissolved. The organic phase was separated. The aqueous phase was extracted twice with CH$_2$Cl$_2$ (25 mL). The combined organic phase was washed with saturated aqueous NaCl solution (50 mL) and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure to obtain an off white crude solid. To the crude solid was added EtOAc (10 mL). The resulting suspension was stirred for 30 min and filtered. The residue was washed twice with cold EtOAC (5 mL) to give the pure borane protected title compound (2.5 g, 73.8 %) as a colorless solid. $^1$H NMR (300 MHz, CDCl$_2$) $\delta$: 7.58-7.52 (m, 16 H), 7.45-.39 (m, 8 H), 7.36-7.31 (m, 16H), 7.03-6.97 (m, 2H), 6.87-6.84 (m, 4H), 3.16 (d, $J = 13.4$ Hz, 8H), 1.53-0.75 (bs, 12H); $^{13}$C NMR (75MHz, CD$_2$Cl$_2$) $\delta$: 133.1, 132.5 (d, $J = 9.1$ Hz), 131.5, 131.3, 130.6, 130.4, 129.2 (d, $J = 9.9$ Hz), 127.5, 30.2 (d, $J = 30$ Hz); $^{31}$P NMR (146 Hz, CD$_2$Cl$_2$) $\delta$:15.2. HRMS (ES$^+$) calcd. For C$_{64}$H$_{66}$NaP$_4$B$_4$ [M+Na$^+$] 1025.4385, found 1025.4431.
Synthesis of 2, 6, 2',6'-Tetrakis-[(diphenylphosphanyl)-methyl]-biphenyl (2)

\[\text{Ph}_2P\text{PPh}_2\]

\[\text{Ph}_2P\text{PPh}_2\]

To a 50 mL Schlenk flask was added DABCO (448 mg, 4 mmol). The flask was degassed and charged with nitrogen. To the flask was added fresh distilled toluene (10 mL). To the resulting solution was added 2, 6, 2', 6'-tetrakis-borane[(diphenylphosphanyl)-methyl]-biphenyl 11 (501 mg, 0.5 mmol) in portions. The resulting suspension was stirred for 30 min at room temperature and slowly heated to 60 °C. A clear solution was formed upon heating. The stirring was continued for 6 h at 60 °C. A small volume of reaction mixture was taken out and subjected to $^{31}$P NMR to monitor the reaction progress. After the reaction was complete, the heating bath was removed and the reaction mixture was cooled to room temperature. To the resulting mixture was added degassed toluene (10 mL). The diluted solution was charged on a short silica gel column through cannula and eluted with toluene (40 mL). The solvent was removed under vacuum to give the desired ligand (376 mg, 79.4%) as a white solid. The ligand was stored under nitrogen due to its air sensitivity. $^1$H NMR (300 MHz, CDCl$_2$) $\delta$: 7.32-7.22 (m, 40H), 6.91-6.86 (m, 2H), 6.76-6.74 (m, 4H), 3.24 (s, 8H); $^{13}$C NMR (75MHz, CD$_2$Cl$_2$) $\delta$: 139.6, 139.3, 137.1, 137.0, 133.5, 133.3, 128.9, 128.7, 127.4, 35.0 (d, $J = 25.8$ Hz); $^{31}$P NMR (146 Hz, CD$_2$Cl$_2$) $\delta$: -15.3. HRMS (ES$^+$) calcd. for C$_{64}$H$_{55}$P$_4$ [MH$^+$] 947.3254, found 947.3237.
Synthesis of 2,2'-DiyI-bis(dipyrrrolylphosphoramidite)- 1,1'-Biphenyl (3)

To a solution of chlorodi pyrrolyphosphine (4.4 mmol, 0.69 mL) in THF (10 mL) was added dropwise triethylamine (1 mL) and a solution of biphenyl-2,2'-diol (2 mmol, 0.37 g ) in THF (5 mL) at room temperature. The triethylamine.HCl salts were formed immediately after the addition. The reaction mixture was stirred for 6 h at room temperature. The triethylamine.HCl salts were then filtered off and the solvent was removed under vacuum. The crude product was purified by flash chromatography on basic aluminum oxide eluted with hexane/EtOAc/NEt$_3$ (6:1:0.01) to afford the title ligand (0.46 g, 45 %) as an air-stable colorless solid. $^1$H NMR (300 Hz, CD$_2$Cl$_2$) $\delta$: 7.33-7.27 (m, 4H), 7.19 (t, $J$=7.3 Hz, 2H), 6.90 (d, $J$ = 8.03 Hz, 2H), 6.74 (m, 8 H), 6.23 (m, 8 H); $^{13}$C NMR (90 Hz, CD$_2$Cl$_2$) $\delta$: 151.3 (d, $J$ = 10.9 Hz), 132.2, 130.3 (d, $J$ = 3.6 Hz), 129.9, 124.9, 121.7 (d, $J$ = 16.3 Hz), 119.5 (d, $J$ = 12.7 Hz), 112.6 (d, $J$ = 4.5 Hz); $^{31}$P NMR (146Hz, CDCl$_2$) $\delta$ 107.5.

Synthesis of 2,2'-Bis-borane[(diphenylphosphanyl)-methyl]-biphenyl

To a 50 mL Schlenk flask was added fresh distilled THF (10 mL), followed by diphenylphosphine (0.19 mL, 1.1 mmol). The mixture was cooled to -78 °C and $n$-BuLi
(0.44 mL, 2.5 M solution in hexane, 1.1 mmol) was added dropwise. The resulting yellow mixture was stirred at \(-78^\circ C\) for 10 min. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and stirred for 30 min. The reaction mixture was again cooled to \(-78^\circ C\). To the cooled reaction mixture was added dropwise 2,2'-bis-bromomethyl-biphenyl (0.17 g, 0.5 mmol) in THF (5 mL). The yellow color faded upon addition. After addition, the reaction mixture was allowed to warm to room temperature slowly and stirred overnight. A small volume of the reaction mixture was taken out and subjected to \(^{31}\text{P}\) NMR to monitor the reaction progress. After the reaction was complete, the reaction mixture was cooled to 0 °C and a cold 1.0M THF solution of BH\(_3\) (10 mL, 10 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 4 h. After the reaction was complete (monitored by \(^{31}\text{P}\) NMR), the reaction mixture was cooled to 0 °C and water was added carefully to quench the excess BH\(_3\). (Caution: gas generated vigorously upon the addition of water). The volatile was removed under vacuum. To the residue was added CH\(_2\)Cl\(_2\) (10 mL) and water (10 mL). The mixture was stirred for 10 min until all residues dissolved. The organic phase was separated. The aqueous phase was extracted twice with CH\(_2\)Cl\(_2\) (10 mL). The combined organic phase was washed with saturated aqueous NaCl solution (10 mL) and dried over Na\(_2\)SO\(_4\). The solvent was removed under vacuum to obtain an off white crude solid. The crude product was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc/NEt\(_3\) 7:1:0.1) to afford the title compound as a colorless solid (0.24 g, 74 %). \(^1\text{H}\) NMR (300 MHz, CD\(_2\)Cl\(_2\)) \(\delta\): 7.53-7.38 (m, 12H), 7.33-7.18 (m, 12H), 7.09-7.03 (m, 2H), 6.34 (m, 2H), 3.41 (m, 4H), 1.65-0.30 (bs, 6H); \(^{13}\text{C}\) NMR (75 MHz, CD\(_2\)Cl\(_2\)) \(\delta\): 140.90, 133.17, 133.06, 132.78, 132.66, 131.76, 131.73, 131.36, 131.33,
Synthesis of 2,2'-Bis-[(diphenylphosphanyl)-methyl]-biphenyl (Bisbi)

To a 25 mL Schlenk flask was added DABCO (170 mg, 1.5 mmol). The flask was degassed and charged with nitrogen. To the flask was added fresh distilled toluene (5 mL). To the resulting solution was added 2, 2'-bis-borane[(diphenylphosphanyl)-methyl]-biphenyl (0.24 g, 0.38 mmol). The reaction mixture was stirred for 30 min at room temperature and slowly heated to 60 °C. The stirring was continued for 6 h at 60 °C. A small volume of reaction mixture was taken out and subjected to $^{31}$P NMR to monitor the reaction progress. After the reaction was complete, the reaction mixture was cooled to room temperature. To the resulting mixture was added degassed toluene (5 mL). The diluted solution was charged on a short silica gel column through cannula and eluted with toluene (20 mL). The solvent was removed under vacuum to give the desired ligand (0.14 g, 74 % yield) as a white solid. The ligand was stored under nitrogen due to its air sensitivity. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ: 7.31-7.21 (m, 16H), 7.15-7.09 (m, 8H), 7.06-7.05 (m, 2H), 6.96-6.93 (m, 2H), 3.21(dd, $J$ =41.63 Hz, $J$ = 13.55 Hz, 4H); $^{13}$C NMR (75MHz, CD$_2$Cl$_2$) δ: 141.2, 139.1, 138.8, 136.2, 136.1, 133.6, 133.4, 133.2, 132.9, 130.9, 130.1, 130.0, 129.1, 128.8, 128.7, 128.6, 127.5, 126.1, 33.7 (d, $J$ = 15.3 Hz); $^{31}$P NMR (146 Hz, CD$_2$Cl$_2$) δ:-10.3.
General Procedure for the Regioselective Isomerization-hydroformylation of Internal Olefins with Tetraphosphoramidite Ligand 1

To a 2 mL vial with a magnetic stirring bar was charged tetraphosphoramidite ligand 1 (3 μmol) and Rh(acac)(CO)$_2$ (1 μmol in 0.1 mL of toluene). The mixture was stirred for 5 min. Then 2-octene (10 mmol) was added followed by decane (0.1 mL) as internal standard. The reaction mixture was transferred to an autoclave. The autoclave was purged with nitrogen for three times and subsequently charged with CO (5 bar) and H$_2$ (5 bar). The autoclave was then heated to 100°C (oil bath). After 12 h, the autoclave was cooled in icy water and the pressure was carefully released in a well ventilated hood. The reaction mixture was immediately analyzed by GC.

General Procedure for the Regioselective Hydroformylation of Terminal Olefins with Tetraphosphoramidite Ligand 1

To a 2 mL vial with a magnetic stirring bar was charged tetraphosphoramidite ligand 1 (0.6 μmol in 0.2 mL toluene) and Rh(acac)(CO)$_2$ (0.2 μmol in 0.2 mL toluene). The mixture was stirred for 5 min. Then 1-octene (2 mmol) was added followed by decane (0.1 mL) as internal standard. Additional toluene was added to bring the total reaction volume to 1 mL. The reaction mixture was transferred to an autoclave. The autoclave was purged with nitrogen for three times and subsequently charged with CO (10 bar) and H$_2$ (10 bar). The autoclave was then heated to 80°C (oil bath). After 1 h, the autoclave was cooled in icy water and the pressure was carefully released in a well ventilated hood. The reaction mixture was immediately analyzed by GC.
General Procedure for the Regioselective Hydroformylation of Terminal Olefins with Tetrrophosphine Ligand 2

To a 2 mL vial with a magnetic stirring bar was charged tetrrophosphine ligand 2 (4 μmol) and Rh(acac)(CO)$_2$ (1 μmol in 0.1 mL toluene). The mixture was stirred for 5 min. Then 1-octene (2 mmol) was added followed by decane (0.1 mL) as internal standard. Additional toluene was added to bring the total reaction volume to 1 mL. The reaction mixture was transferred to an autoclave. The autoclave was sealed and purged with nitrogen for three times and subsequently charged with CO (10 bar) and H$_2$ (10 bar). The autoclave was then heated to 100°C (oil bath). After 1 h, the autoclave was taken out of the oil bath and cooled in icy water. The pressure was carefully released in a well ventilated hood. The reaction mixture was immediately analyzed by GC.
References


Chapter 4

Development of Readily Available Bis(azaphosphorinane) Ligand for Highly Enantioselective Hydrogenation

4.1 Introduction

Transition-metal catalyzed asymmetric hydrogenation is one of the most efficient methods for preparing chiral compounds. Most of the efforts in this area have been focused on the search for new highly enantioselective chiral ligands because enantioselectivities are often substrate dependent. To obtain maximum enantioselectivity for a particular substrate, an individual catalyst has to be identified.

Among numerous ligands reported, DuPhos 1 and BPE 2 developed by Burk et al. in the early 1990s are highly efficient for asymmetric hydrogenations of functionalized prochiral olefins and ketones. One important structural feature of the DuPhos and BPE ligands is the pseudochirality placed on phosphorus. This feature makes the enantioselection independent of the conformational properties of the chelate cycle and results in high enantioselectivities. During the past decade, many bis(phospholane) ligands derived from DuPhos and BPE have been reported. Figure 4-1 shows some representative examples. Starting from readily available D-mannitol, Börner, Zhang, and RajanBabu have, independently, developed a series of DuPhos and BPE derivatives 3-7. These ligands exhibited similar high enantioselectivity as DuPhos and BPE in rhodium-catalyzed asymmetric hydrogenation. Unlike DuPhos and BPE-complex catalyzed hydrogenation that can only be conducted in organic solutions, highly
enantioselective hydrogenation can be performed in aqueous solution with ligands bearing four hydroxyl groups such as Hydrophos 7 and BasPhos 8. The aqueous solution of the catalyst could be reused without the erosion of enantioselectivity. Changing the backbone of DuPhos and BPE led to several new ligands 9-11. Holz and Börner reported a bisphospholane ligand bearing a maleic anhydride backbone, MalPHOS 9. With this ligand, excellent enantioselectivities were obtained in the hydrogenation of (β-acylamino)acrylates. In particular, it afforded better enantioselectivity for (Z)-configured β-dehydroamino acid derivatives compared to DuPhos. Ligand 10, with a 1, 2-cyclopentane backbone, was also synthesized and investigated in rhodium-catalyzed hydrogenation. Since there are two additional chiral carbon centers on the backbone, only matched (R, R, R)-1,2-bis(phospholano)cyclopentane provides good enantioselectivity. A remarkable influence of the P-hetero ring size has been found. Marinetti prepared a series of four-membered bisphosphetane ligands such as CnrPHOS 12 and BPE-4 13. With these ligands, although only moderate enantioselectivity was obtained in rhodium-catalyzed hydrogenation of dehydroamino acid derivatives, good enantioselectivity was achieved in ruthenium-catalyzed asymmetric hydrogenation of β-diketones. The bisphosphetane ligand bearing a ferrocene backbone such as Ferrotane 14 has shown excellent enantioselectivity in the rhodium-catalyzed asymmetric hydrogenation of β-aryl dehydroamino acid derivatives. Helmchen has developed a six-membered bisoxaphosphorinane ligand 15 for the rhodium-catalyzed hydrogenation of α-dehydroamino acid derivatives and itaconic acid with up to 97% ee.
Figure 4-1: Ligands Derived from Duphos and BPE
Our goal in asymmetric hydrogenation is to develop new chiral ligands which are highly efficient, yet easily obtainable from inexpensive and readily available starting materials. In this chapter, the development of a novel six-membered bis(azaphosphorinane) ligand, 4,4’-(1,2-ethanediyl)bis[(3R,5R)-1,3,5-trimethyl-1,4-azaphosphorinane] 16 (Figure 4-2), will be discussed. This new ligand has been applied to rhodium-catalyzed asymmetric hydrogenations. Excellent enantioselectivities (up to over 99 % ee) have been achieved in the hydrogenations of β-dehydroamino acid derivatives and α-arylenamides.

![Figure 4-2: New Six-Membered Bis(azaphosphorinane) Ligand](image)

### 4.2 Results and Discussions

#### 4.2.1 Design and Synthesis of Bis(azaphosphorinane) Ligand

Typically, the synthesis of a phospholane ligand involves the use of a chiral 1, 4-diol. The expensive chiral 1, 4-diols used for the preparation of DuPhos and BPE were originally synthesized through electrochemical Kolbe coupling. Biocatalysis route was introduced later. Other chiral 1, 4-diols prepared from inexpensive chiral pool species such as D-mannitol were prepared by multi step synthesis.
Although many five-membered bis(phospholane) ligands have been developed, there is only one known six-membered bis(oxaphosphorinane) ligand 15 reported for asymmetric hydrogenations.\(^ {11}\) Up to 97.5 % ee and 94.2 % ee have been achieved with this ligand in the rhodium-catalyzed asymmetric hydrogenation of \(\alpha\)-dehydroamino acid derivatives and itaconic acid, respectively. However, the ligand is made through a seven-step synthetic sequence.

For practical considerations, a ligand has to be easily made from inexpensive, readily available starting materials. We envision that a chiral 1, 5-diol 17, the precursor to the six-membered phosphorinane ring, can be readily prepared by reacting a primary amine with an inexpensive chiral epoxide such as \((S)\)-propylene oxide 18 in a single step. Following the standard procedure for the preparation of DuPhos and BPE ligands, the new bis(azaphosphorinane) can be synthesized very efficiently from the 1, 5-diol (Scheme 4-1).

![Scheme 4-1: Retrosynthesis of Bis(azaphosphorinane) Ligand](image_url)

A molecular model of rhodium-16 complex (MM2 calculation based on CAChe program) is shown in Figure 4-3. The corresponding simplified quadrant diagrams are shown in Figure 4-4. As can be seen from Figure 4-3 and Figure 4-4, two methyl groups
of the ligand protrude and block the upper-left and bottom-right quadrants while the other methyl groups stay back and leaves the upper-right and bottom-left quadrants open. Thus, bis(azaphosphorinane) ligand 16 can provide a similar chiral environment as DuPhos or BPE. Furthermore, the structure of bis(azaphosphorinane) could be easily tuned by using different chiral epoxides or different backbones.

Figure 4-3: CAChe Model of Rhodium-Bis(azaphosphorinane)Complex

Figure 4-4: Quadrant Diagram of Rhodium-Bis(azaphosphorinane)Complex
Next, the synthesis of the new bis(azaphosphorinane) ligand 16 was investigated. Thus, aqueous methyl amine reacted with 2.2 equiv. of (S)-propylene oxide 18 in methanol at 60 °C to afford the chiral 1, 5-diol 17 in 95% yield. After removing the solvent, the ring-opening product was pure enough and was used directly for the next step without further purification.

Following the standard procedure for the preparation of cyclic sulfites used for the synthesis of five-membered phospholanes,\(^3\) we tried the cyclization reaction of 17 with thionyl chloride in dry dichloromethane in the presence of triethylamine at 0°C. The reaction proceeded smoothly, affording cyclic sulfite in high yield as indicated by TLC. However, the attempt to oxidize the cyclic sulfite intermediate to cyclic sulfate 19 using the RuCl\(_3/\)NaIO\(_4\) catalytic system developed by Sharpless and coworkers\(^{12}\) under the standard reaction condition was unsuccessful. No desired oxidized product was observed. The oxidation reaction did not occur because the cyclic sulfite intermediate contains a tertiary amine moiety, which poisoned the ruthenium catalyst in the oxidation process.

Since the cyclic sulfite intermediate itself is a poison to the ruthenium catalyst, we then attempted to make dimesylate 20 which may also capable of forming the six-membered phosphorinane ring upon reaction with a primary phosphine. Unfortunately, reaction of diol 17 with mesyl chloride in the presence of NEt\(_3\) at 0 °C afforded 2, 4, 6-
trimethyl-morpholine 21 instead of dimesylate 20. Obviously, the intramolecular ring closing product was formed under basic condition by SN2 reaction of the deprotonated hydroxyl group with the mesylate group of the monomesylated intermediate.

\[
\begin{align*}
\text{MsCl, NEt}_3 & \quad \rightarrow \\
\text{17} & \quad \rightarrow \\
\text{20} & \quad \rightarrow \\
\text{21} & \quad \rightarrow \\
\end{align*}
\]

We then returned to the preparation of the cyclic sulfate, and hoped to find a way to overcome the self-poisoning problem. Since the free tertiary amine is a poison, we envision that protecting the free tertiary amine with Boc may help to prevent the self-poisoning. The bis(azaphosphorinane) ligand 16 was eventually synthesized by the route shown in Scheme 4-2. Reaction of benzyl amine with chiral epoxide 18 in methanol afforded 1, 5-diol 22 in excellent yield (95%) as a viscous liquid. Removing the benzyl group by hydrogenation with Pd/C produced amino diol 23 in 95% yield. The free secondary amine was further protected by reacting with (Boc)_2O in the presence of NEt_3 in 94% yield. Cyclization of 24 with thionyl chloride and oxidation under standard Sharpless oxidation condition using RuCl_3/NaIO_4 system were performed without any difficulty, affording the Boc protected cyclic sulfate 25 in 84% overall yield. Removing the Boc protecting group was then carried out by stirring the cyclic sulfate 25 in a 1:1
mixture of TFA/CH₂Cl₂. The amino cyclic sulfate 26 was obtained in 90% yield. The methylation of cyclic sulfate 26 with HCHO/HCOOH afforded cyclic sulfate 19 in 40% unoptimized yield. Metallation of 1, 2-bis(phosphino)ethane with 2 equiv. of n-BuLi at room temperature followed by addition of 2 equiv. of cyclic sulfate 19 and another 2.2 equiv of n-BuLi finally provided the desired bis(azaphosphorinane) ligand 16 in 36% yield as an air-sensitive viscous oil.

Scheme 4-2: Synthesis of Bis(azaphosphorinane) Ligand

Although the bis(azaphosphorinane) ligand 16 has been prepared, the current route is relatively long (7 steps) and not efficient. If the ligand has to be prepared by this way,
our goal to prepare a readily accessible ligand will be missed. Thus, a new strategy has to be found to make the synthesis of this new ligand attractive for practical applications. During the synthesis of the bis(azaphosphorinane) ligand 16, we knew that if the free amine were protected, then the ruthenium-catalyzed oxidation step could proceed without any difficulty. If we want to synthesis cyclic sulfate 19 directly from amino diol 17, we have to find a simply and efficient way to protect the free amine moiety in the ruthenium-catalyzed oxidation step. Although the standard oxidation condition requires the removing of acidic species, we envision that adding acid to the reaction mixture to form the quarterly ammonium salt of amino diol 17 may mask the nitrogen atom and protect the ruthenium catalyst from poisoning. We tried acetic acid and concentrated HCl as the additive and were pleased to find that adjusting the pH to <1 by simply adding concentrated HCl to the reaction mixture could efficiently mask the amine moiety and promote the oxidation reaction. Less acidic acetic acid was not as good as HCl for this purpose. Since the acidified cyclic sulfite is a salt and soluble in water, a 1:1 CH$_3$CN/H$_2$O mixture was used as solvent instead of CCl$_4$/CH$_3$CN/H$_2$O. A basic work up procedure provided the free amino cyclic sulfate. The overall yield of cyclic sulfate 19 from the chiral 1, 5-diol 17 was 61%.

Thus, a concise method for the synthesis of bis(azaphosphoranine) ligand 16 has been developed. The new synthetic route for ligand 16 is depicted in Scheme 4-1. Amino diol 17 was obtained by reaction of methyl amine with chiral epoxide 18. Cyclic sulfate 19 was prepared by cyclization with thionyl chloride followed by oxidation with RuCl$_3$/NaIO$_4$ at pH <1. Deprotonation of 1, 2-bis(phosphino)ethane followed by
cyclization with cyclic sulfate 19 through an SN2 mechanism afforded the desired bis(azaphosphorinane) ligand 16. The key point to the facile synthesis of ligand 16 is to mask the free tertiary amine to facilitate the ruthenium-catalyzed oxidation reaction.

Scheme 4-1: Facile Synthesis of Bis(azaphosphorinane) Ligand

4.2.2 Asymmetric Hydrogenation with Bis(azaphosphorinane) Ligand

4.2.2.1 Asymmetric Hydrogenation of Aryl Enamides

Chiral amines have been extensively utilized as resolving agents and chiral auxiliaries. They are also precursors to various biologically active compounds and constitute an important class of building blocks in synthetic chemistry. Thus, the development of efficient methods for the preparation of enantiomerically pure amines is of great importance. Traditional methods for the preparation of chiral amines include
optical resolution, enzymatic transaminase technology and stoichiometric usage of chiral auxiliaries. During the last decade, considerable progress has been achieved in the asymmetric hydrogenation of prochiral enamides. A number of efficient chiral ligands have been developed for this transformation and enantioselectivities up to over 99% ee have been achieved in the asymmetric hydrogenation of α-aryl enamides. Today, the asymmetric hydrogenation of enamides has become one of the most efficient methods for the preparation of chiral amines. However, only few chiral ligands can tolerate E/Z-isomeric mixtures of β-substituted enamides. The development of efficient chiral ligands for the asymmetric hydrogenation of E/Z-isomeric mixtures of β-substituted enamides still remains a major challenge.

Bis(azaphosphorinane) ligand 16 has been employed in the asymmetric hydrogenations of aryl enamides. The hydrogenation reactions were carried out at room temperature under 15 psi of H\textsubscript{2} in the presence of 1 mol % [Rh(16)(NBD)]SbF\textsubscript{6} prepared by mixing bis(azaphosphorinane) ligand 16 with 1.0 equiv of [Rh(NBD)\textsubscript{2}]SbF\textsubscript{6}. Trisubstituted N-(1-Phenyl-propyl)-acetamide 27a was selected as the standard substrate. We first screened several common solvents used in asymmetric hydrogenation. The results are summarized in Table 4-1. No significant solvent effect was observed. Full conversions were obtained in all screened solvents. Hydrogenations in THF, CH\textsubscript{2}Cl\textsubscript{2} and EtOAc afforded the highest enantioselectivity (99 % ee in all three solvents), while reaction in toluene gave 97 % ee.
Table 4-1: Asymmetric Hydrogenation of \(N\)-(1-Phenyl-propyl)-acetamide\(^a\)

\[
\begin{array}{c|c|c|c}
entry & solvent & conv (%) & ee (%) \\
\hline
1 & CH\(_3\)OH & 100 & 98 \\
2 & THF & 100 & 99 \\
3 & toluene & 100 & 97 \\
4 & CH\(_2\)Cl\(_2\) & 100 & 99 \\
5 & EtOAc & 100 & 99 \\
\end{array}
\]

\(^a\) The reactions were carried out at rt under 15 psi of H\(_2\) in solvent for 24 h. Substrate/[Rh(16)(NBD)]SbF\(_6\) = 100:1. The ee’s were determined by chiral GC using a Chiralselect 1000 column. The absolute configurations were determined as \(R\) by comparing the optical rotations with reported values.

With the rhodium-bis(azaphosphorinane) 16 complex, a variety of \(\alpha\)-aryl enamides 27 were hydrogenated to afford chiral amides with excellent enantioselectivities (Table 4-2). For terminal \(\alpha\)-aryl enamides 27b-g (entries 1-6), \(para\)-substituted phenyl enamides 27d-f (entries 3-5) generally led to better enantioselectivities than non-substituted \(\alpha\)-phenyl enamide 27b (entry 1), whereas enantioselectivity decreased for a \(meta\)-substituted phenyl enamide 27c (entry 2). It should be noted that for the hydrogenations of \(\beta\)-substituted aryl enamides 27a, 27h-l (entries 7-12), \(E/Z\) isomeric mixtures were employed and the hydrogenation reactions can tolerate the mixed
geometry of the substrates. A series of β-substituted phenyl enamides 27a, 27k-1 (entries 7, 11 and 12), as E/Z isomeric mixtures, were hydrogenated with excellent enantioselectivities regardless of different β-substituents. No significant electronic effect of the substitution at the aryl group of the enamides was observed on the enantioselectivities (entries 8 and 9). Enantiomeric excesses of over 99% were obtained in the hydrogenations of more bulky 2-naphthyl enamides 27g and 27j (entries 6 and 10). The enantioselectivities achieved with bis(azaphosphorinane) ligand 16 for the hydrogenation of E/Z isomeric mixtures of β-substituted α-aryl enamides are comparable to or better than those reported with Me-DuPhos and BPE ligands.15

Since bis(azaphosphorinane) ligand 16 is a trialkyl phosphine with very strong electron-donating character, the mechanism (Scheme 4-2) of the hydrogenation reactions is believed to involve a “dihydride” pathway as proposed by Imamoto and coworkers.16 Thus, the oxidative addition of hydrogen to the rhodium-bis(azaphosphorinane) complex A will produce a mixture of rhodium-dihydride complexes B and C. Substrate coordination to the rhodium center then leads to the intermediates D and E whose relative stability controls the enantioselectivity. Because the dihydride complex E experiences severe steric interactions between the methyl group of the ligand and the substrate chelate ring, the dihydride complex D is more stable than E. The mono-hydride rhodium species F will be formed after migratory insertion of hydrogen, a step which is believed to be a turn-over limiting and irreversible in the catalytic cycle. Reductive elimination finally affords the hydrogenation product with R configuration and regenerates the rhodium-bis(azaphosphorinane) catalyst A.
Table 4-2: Asymmetric Hydrogenation of α-Aryl Enamides

\[
\begin{align*}
\text{Ar} & \quad \text{NHAc} & \quad \text{R} & \quad [\text{Rh(16)(NBD)}]_{\text{SbF}_6} & \quad \text{CH}_2\text{Cl}_2, \text{H}_2 (15\ psi), rt & \quad \text{Ar} & \quad \text{NHAc}
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>Ar</th>
<th>R</th>
<th>ee (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>27b</td>
<td>Ph</td>
<td>H</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>27c</td>
<td>m-MePh</td>
<td>H</td>
<td>95</td>
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<td>3</td>
<td>27d</td>
<td>p-CF\textsubscript{3}Ph</td>
<td>H</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>27e</td>
<td>p-CyPh</td>
<td>H</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>27f</td>
<td>p-PhPh</td>
<td>H</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>27g</td>
<td>2-Np</td>
<td>H</td>
<td>&gt;99</td>
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<td>27a</td>
<td>Ph</td>
<td>Me</td>
<td>99</td>
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<td>98</td>
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<td>10</td>
<td>27j</td>
<td>2-Np</td>
<td>Me</td>
<td>&gt;99</td>
</tr>
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<td>27k</td>
<td>Ph</td>
<td>i-Pr</td>
<td>98</td>
</tr>
<tr>
<td>12</td>
<td>27l</td>
<td>Ph</td>
<td>Bn</td>
<td>97</td>
</tr>
</tbody>
</table>

\(^a\)The reactions were carried out under 15 psi of H\textsubscript{2} in CH\textsubscript{2}Cl\textsubscript{2} at rt for 24 h with full conversion. Substrate/[Rh(16)(NBD)]\textsubscript{SbF}_6 = 100:1. For the E/Z ratio of 27a-l, absolute configuration and ee (%) value determinations, see reference 14 for detail.
Scheme 4-2: Mechanism for the Rhodium-Catalyzed Hydrogenation of α-Aryl Enamides

4.2.2.2 Asymmetric Hydrogenation of α-Dehydroamino Acid Derivatives

Enantiomerically pure α-amino acids are important biological molecules, being widely used for biological, biochemical, and pharmaceutical studies. In organic synthesis, they are useful building blocks for the synthesis of complex natural products. They also serve as useful starting materials for the preparation of pharmaceutical target molecules,
chiral auxiliaries and catalysts.\textsuperscript{17} Optically pure $\alpha$-amino acids can be obtained by biotechnological methods, resolution, chemical synthesis using chiral pool species and asymmetric synthesis. Recently, catalytic asymmetric hydrogenation of $\alpha$-dehydroamino acid derivatives has attracted much attention due to its high efficiency. Many chiral ligands have been successfully developed for rhodium-catalyzed asymmetric hydrogenation with excellent enantioselectivity and reactivity.\textsuperscript{1}

The bis(azaphosphorinane) ligand 16 was employed in the asymmetric hydrogenations of $\alpha$–dehydroamino acid derivatives. Again, solvent effects were first evaluated. The hydrogenation reactions were carried out at room temperature under 15 psi of H$_2$ in the presence of 1 mol % [Rh(16)(NBD)]SbF$_6$, prepared by mixing ligand 16 with 1.0 equiv of [Rh(NBD)$_2$]SbF$_6$. 2-Acetylamino-3-phenyl-acrylic acid methyl ester 28a was selected as the standard substrate. The results are summarized in Table 4-3. Significant solvent effects on enantioselectivity were observed. The highest enantioselectivity was obtained when the hydrogenation reaction was performed in methanol (92 % ee) while only 77 % ee was observed in toluene. The activities were good and full conversion was observed in all screened solvents.

With methanol as solvent, a series of $\alpha$-dehydroamino acid esters were then hydrogenated with rhodium-bis(azaphosphorinane) 16 complex. The results are summarized in Table 4-4. Full conversions were obtained in all cases. However, the enantioselectivities were relatively disappointing because the highest enantioselectivities were only 92 % ee, a value which was achieved in the hydrogenation of 2-acetylamino-3-phenyl-acrylic acid methyl ester 28a and 2-acetylamino-acrylic acid methyl ester 28b.
(entries 1-2). It is not surprising because there is no universal ligand and we have to identify a unique ligand in order to obtain the maximum enantioselectivity for a particular substrate.

Table 4-3: Asymmetric Hydrogenation of 2-Acetylamino-3-phenyl-acrylic Acid Methyl Ester$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>conv (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_3$OH</td>
<td>100</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>100</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>toluene</td>
<td>100</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>CH$_2$Cl$_2$</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>EtOAc</td>
<td>100</td>
<td>85</td>
</tr>
</tbody>
</table>

$^a$ The reactions were carried out at rt under 15 psi of H$_2$ in solvent for 24 h. Substrate/[Rh(16)(NBD)]SbF$_6$ = 100:1. The ee’s were determined by chiral GC using a Chrialsil- VAL III FSOT column. The absolute configurations were determined as R by comparing the optical rotations with reported values.
Similar to the case of the hydrogenation of α-aryl enamides, the mechanism (Scheme 4-3) of the hydrogenation of α-dehydroamino acid derivatives is also believed to involve a “dihydride” pathway. The only difference is that after the formation of intermediate I, coordination rearrangement will occur, providing the rhodium monohydride species J; species J affords the hydrogenation product and regenerates the

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>Ar</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28b</td>
<td>H</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>28a</td>
<td>Ph</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>28c</td>
<td>p-FPh</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>28d</td>
<td>m-BrPh</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>28e</td>
<td>o-ClPh</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>28f</td>
<td>2-naphthyl</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>28h</td>
<td>2-thienyl</td>
<td>86</td>
</tr>
</tbody>
</table>

The reactions were carried out under 15 psi of H\textsubscript{2} in MeOH at rt for 24 h with full conversion. Substrate/[Rh(16)(NBD)]SbF\textsubscript{6} = 100:1. The ee’s were determined by chiral GC using a Chrialsil- VAL III FSOT column. The absolute configurations were determined as R by comparing the optical rotations with reported values.
rhodium-bis(azaphosphorinane) catalyst A after reductive elimination. Since the enantioselectivity is controlled by the relative stability of G and H, the more stable G, which is subjected to less steric interaction, will eventually lead to the hydrogenation product with R configuration.

\[ \text{Scheme 4-3}: \text{Mechanism for the Rhodium-Catalyzed Hydrogenation of } \alpha\text{-Dehydroamino Acid Derivatives} \]
4.2.2.3 Asymmetric Hydrogenation of β–Dehydroamino Acid Derivatives

Enantiomerically pure β–amino acids and their derivatives now play a significant role in the pharmaceutical industry.\textsuperscript{18} Not only do they exhibit broad biological activity but also they are important intermediates for the preparation of β–peptides and β–lactams. Due to their importance in the pharmaceutical industry, the development of efficient synthesis of chiral β–amino acids and their derivatives has attracted a great deal of attention. Among numerous methods reported for the syntheses of β–amino acid derivatives, the direct asymmetric hydrogenation of β–dehydroamino acid derivatives represents one of the most efficient and practical methods. Both rhodium and ruthenium-catalyzed asymmetric hydrogenation of β–dehydroamino acid derivatives have been studied extensively with chiral phosphorus ligands. Successful ligands include BINAP, BICP, DuPhos, Bisp*, TangPhos and DuanPhos.\textsuperscript{1} While excellent enantioselectivities have been achieved in the asymmetric hydrogenation of (E)-isomers of β–dehydroamino acid derivatives, the asymmetric hydrogenation of (Z)-isomers is less successful. There are only a few ligands capable of providing over 95% ee for the asymmetric hydrogenation of (Z)-isomers. Since the prochiral β–dehydroamino acid derivatives are generally obtained as $E/Z$ mixtures that not easy to separate, from the practical point of view, catalytic systems which can provide excellent enantioselectivities for both (E) and (Z)-isomers are highly desirable.
The bis(azaphosphorinane) ligand 16 was employed in the asymmetric hydrogenations of β–dehydroamino acid derivatives. We first investigated solvent effects by performing asymmetric hydrogenations in several common solvents. The hydrogenation reactions were carried out at room temperature under 15 psi of H₂ in the presence of 1 mol % [Rh(16)(NBD)]SbF₆. The catalyst was prepared by mixing ligand 16 with 1.0 equiv. of [Rh(NBD)₂]SbF₆. (E)-methyl 3-acetamido-2-butenoate was used as the

---

Table 4-5: Asymmetric Hydrogenation of Methyl 3-Acetamido-2-butenoate

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>conv (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃OH</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>100</td>
<td>99</td>
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<tr>
<td>3</td>
<td>toluene</td>
<td>82</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>100</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>EtOAc</td>
<td>100</td>
<td>99</td>
</tr>
</tbody>
</table>

*The reactions were carried out at rt under 15 psi of H₂ in solvent for 24 h. Substrate/[Rh(16)(NBD)]SbF₆ = 100:1. The ee’s were determined by chiral GC using a Chiralselect 1000 column. The absolute configurations were determined as R by comparing the optical rotations with reported values.*
standard substrate. The hydrogenation results are shown in Table 4-5. As can be seen from the table, solvent affects both the reactivity of the substrate and the enantioselectivity of the reaction. In toluene, the reaction did not go to completion after 24 h. In other solvents, full conversions were observed. The highest enantioselectivity was observed when the hydrogenation reaction was performed in CH₂Cl₂ (>99 % ee), while in MeOH the reaction gave the lowest enantioselectivity (95 % ee).

After determining a suitable solvent for hydrogenation, a series of β-dehydroamino acid derivatives then were tested using the bis(azaphosphorine) ligand 16. As shown in Table 4-6, a variety of β-alkyl β-(acylamino) acrylates 29 have been hydrogenated with excellent enantioselectivities. Both (E)- and (Z)-isomeric substrates gave the hydrogenation products with the same configuration using rhodium-16 catalyst. For hydrogenations of the (E)-isomers 29a-g, high enantioselectivities (99 to >99% ee) were obtained (entries 1-7). Changing the ester groups and alkyl substituents caused no significant variation in the enantioselectivities. Ligand 16 also gave excellent enantioselectivities for the hydrogenations of (Z)-isomers 29h-i (entries 8 and 9) although the ee values were slightly less than those of the corresponding (E)-isomers 29a and 29e (entries 1 and 5). Compared with the rhodium-Me-DuPhos catalyst (which gave 98.2% ee and 87.8% ee for the asymmetric hydrogenations of (E)-6a and (Z)-6h, respectively),¹⁹ rhodium-bis(azaphosphorinane) 16 catalyst provided much higher ee value for the (Z) isomer (entries 1 and 8). There are only a few catalytic systems which can achieve over 95 % ee for the asymmetric hydrogenations of (Z)-isomers of β-alkyl β-(acylamino)
acrylates. These results are among the highest enantioselectivities achieved to date for the hydrogenations of \(\beta\)-alkyl \(\beta\)-(acylamino) acrylates.

Table 4-6: Asymmetric Hydrogenation of \(\beta\)-Dehydroamino Acid Esters

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>Me</td>
<td>Me</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>((E))-29b</td>
<td>Et</td>
<td>Me</td>
<td>&gt;99</td>
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<tr>
<td>3</td>
<td>((E))-29c</td>
<td>i-Pr</td>
<td>Me</td>
<td>&gt;99</td>
</tr>
<tr>
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<td>((E))-29d</td>
<td>i-Bu</td>
<td>Me</td>
<td>99</td>
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<td>5</td>
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<td>Me</td>
<td>Et</td>
<td>96</td>
</tr>
</tbody>
</table>

\(a\) The reactions were carried out under 15 psi of \(H_2\) in \(CH_2Cl_2\) at rt for 24 h with full conversion. Substrate/ [Rh\((16)\)(NBD)]SbF\(_6\) = 100:1. The ee’s were determined by chiral GC using a Chiralsel ect 1000 column. The absolute configurations were determined as \(R\) by comparing the optical rotations with reported values.
The mechanism of the asymmetric hydrogenation of β-dehydroamino acid derivatives with the rhodium-bis(azaphosphorinane) 16 is believed to be “dihydride” mechanism as in the case of α-dehydroamino acid derivatives (Scheme 4-4). However, the migrations undergo different reaction pathways. In the case of α-dehydroamino acid derivatives, the monohydride complex I where the α-carbon atom is bound to rhodium is formed by transferring a hydrogen atom to the β-carbon. In the case of the β-dehydroamino acid derivatives, the first hydrogen is transferred to the α-carbon, yielding the monohydride complex M with the β-carbon bounded to rhodium. After coordination rearrangement and reductive elimination, the hydrogenation product with R configuration is obtained along with the regeneration of the rhodium-bis(azaphosphorinane) complex A.

4.3 Conclusion

In conclusion, the new bis(azaphosphorinane) ligand 16 was easily prepared from inexpensive, readily available starting materials. To the best of our knowledge, this ligand provides the first example of six-membered bis(phosphorinane) ligands for the highly enantioselective asymmetric hydrogenations of β-dehydroamino acid derivatives and α-aryl enamides. The easy access to the ligand as well as the high enantioselectivity it provides makes the ligand potentially useful for large-scale industrial applications.
Scheme 4-4: Mechanism for the Rhodium-Catalyzed Hydrogenation of β-Dehydroamino Acid Derivatives
Experimental Section

General Methods: All reactions and manipulations were performed under nitrogen using standard Schlenk techniques unless otherwise stated. THF and toluene were dried and distilled from sodium-benzophenone ketyl under nitrogen. Methylene chloride was dried over CaH$_2$ and flushed with nitrogen. Methanol and isopropanol were distilled from Mg under nitrogen. Column chromatography was performed using EM silica gel 60 (230–400 mesh). $^1$H, $^{13}$C, and $^{31}$P NMR spectrum were recorded on Bruker AM-300, AMX-360, and APX-400 spectrometers. Chemical shifts were reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard. Mass spectra were recorded on a KRATOS mass spectrometer MS 9/50 for LR-ESI and HR-ESI. GC analysis was carried out on a Helwett-Packard 6890 gas chromatograph using chiral capillary columns.

Synthesis of 1-[(2S-Hydroxy-propyl)-methyl-amino]-propan-2S-ol (17)

![Chemical Structure]

To a solution of (S)-propylene oxide 18 (10.2 g, 176 mmol) in 150 mL of methanol was added 6.20 g of 40% aqueous methyl amine (80.0 mmol). After stirring for 2 h at room temperature, the reaction mixture was slowly heated to 60 °C and stirred for another 12 h. The solvent was then removed under reduced pressure to afford 11.2 g of the title compound (95%) as a viscous liquid. The crude product was essentially pure and was used directly for the next step. If further purification is desired, the product may be purified by flash chromatography on silica gel (eluting with dichloromethane/methanol...
Synthesis of (4S,8S)-4,6,8-Trimethyl-[1,3,2,6]dioxathiazocane 2,2-dioxide (19)

To a solution of 1-[(2S-hydroxy-propyl)-methyl-amino]-propan-2S-ol 17 (10 g, 68 mmol) in 200 mL of dichloromethane at 0 °C was slowly added, in succession, thionyl chloride (5.4 mL 75 mmol) and triethylamine (19 mL, 136 mmol). The reaction mixture was then slowly warmed to room temperature. After stirring for 2 h, 10% aqueous NaOH solution was slowly added to adjust the pH to > 12, the organic phase was then separated and volatile materials were removed under reduced pressure. The residue was dissolved in a mixture of CH$_3$CN (100 mL) and H$_2$O (100 mL). To this solution was added slowly concentrated HCl to adjust the pH to < 1, the mixture was then cooled down to 0 °C, and 100 mg of RuCl$_3$·3H$_2$O was added. Sodium periodate (16 g, 75 mmol) was added in small portions, the mixture was stirred at 0 °C for another 30 min. At this point, aqueous 10% NaOH was added to adjust the pH to > 12, the aqueous solution was extracted with ethyl acetate (3 x 100 mL). The combined extracts was dried over Na$_2$SO$_4$ and concentrated. The crude product was purified by recrystallization from ether/hexane to afford 8.7 g (61%) of title cyclic sulfate as a white solid. $^1$H NMR (300 MHz, CDCl$_3$) δ: 4.78-4.73 (m, 2H), 3.03 (d, $J = 2.75$ Hz, 1H), 2.98 (d, $J = 2.73$ Hz, 1H), 2.56 (d, $J = 5.81$ Hz, 1H), 2.51 (d, $J = 6.00$ Hz, 1H), 2.50 (s, 3H), 1.36 (d, $J = 6.5$ Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ:
Synthesis of 4,4’-(1,2-Ethanediyl)bis[(3R,5R)-1,3,5-trimethyl-1,4-azaphosphorinane] (16)

To a 50 mL Schlenk flask was added THF (10 mL) and 1,2-bis(phosphino)ethane (0.14 g, 1.5 mmol) under inert atmosphere. To the resulting solution was slowly added n-BuLi (1.2 mL of 2.5 M solution in hexane, 3 mmol) at room temperature. The color of reaction mixture turned yellow upon addition. The reaction mixture was stirred at room temperature for 1.5 h. To the resulting yellow solution was added dropwise (4S, 8S)-4,6,8-trimethyl-[1,3,2,6]dioxathiazocane 2,2-dioxide 19 (0.63 g, 3.0 mmol) in 10 mL of THF, and the reaction mixture was stirred for an additional 2 h at rt, n-BuLi (1.3 mL of 2.5 M solution in hexane, 3.3 mmol) was slowly added again, and the reaction mixture was allowed to stir overnight at room temperature. A small amount of methanol (0.3 mL) was added to quench any excess n-BuLi. The solvent was removed under reduced pressure. To the residue were added 30 mL of degassed ether and 30 mL of degassed water. After stirring for 5 minutes, the organic phase was separated, dried over Na₂SO₄ and concentrated. The crude product was purified by flash chromatography on basic aluminum oxide (eluting with ether/hexane 7:1) in a glove box filled with nitrogen) to give 0.17 g of bis(azaphosphorinane) ligand (36%) as a viscous oil. ¹H NMR (360 MHz, CD₂Cl₂) δ: 2.53-2.46 (m, 4H), 2.30-2.17 (m, 10H), 2.01-1.93 (m, 2H), 1.80-1.75 (m, 2H), 1.56-1.51(m, 2H), 1.45-1.37 (m, 2H), 1.26-1.11 (m, 6H), 1.09-0.98 (m, 6H); ¹³C NMR
(90 MHz, CD$_2$Cl$_2$) δ: 60.55, 59.60, 47.58, 25.85 (m), 24.39 (m), 18.02 (m), 16.60, 15.20; 
$^{31}$P NMR (146 MHz, CD$_2$Cl$_2$) δ: -23.17. HRMS (APCI) calcd for C$_{16}$H$_{35}$N$_2$P$_2$ [MH$^+$] 317.2264, found 317.2282.

**Synthesis of 1-[Benzyl-(2S-hydroxy-propyl)-amino]-propan-2S-ol (22)**

$$\begin{align*}
\text{Ph} & \quad \text{N} \\
\text{OH} & \quad \text{OH}
\end{align*}$$

To a solution of (S)-propylene oxide 18 (1.16 g, 20 mmol) in 50 mL of methanol was added benzyl amine (1.09 mL, 10 mmol). After stirring for 2 h at room temperature, the reaction mixture was slowly heated to 75°C and stirred for 24 h. The solvent was then removed under reduced pressure to afford the title amino diol (2.82 g, 95%) as a viscous liquid. The crude product was essentially pure and was used directly for the next step. If further purification is desired, the product may be purified by flash chromatography on silica gel (eluting with dichloromethane/methanol 15:1). $^1$H NMR (360 MHz, CDCl$_3$) δ: 7.28-7.19 (m, 5H), 3.80 (m, 3H), 3.44 (d, $J$ = 13.6 Hz, 1H), 2.55 (bs, 2H), 2.41 (d, $J$ = 5.76 Hz, 4H), 1.03 (d, 4H, $J$ = 6.19 Hz, 6H); $^{13}$C NMR (75MHz, CDCl$_3$) δ: 138.4, 129.0, 128.5, 127.4, 64.0, 62.1, 59.8, 20.3.

**Synthesis of 1-(2S-Hydroxy-propylamino)-propan-2S-ol (23)**

$$\begin{align*}
\text{HN} & \quad \text{OH} \\
\text{OH} &
\end{align*}$$

To a 300 mL autoclave was charged 200 mg of 10% palladium on activated carbon,1-[benzyl-(2S-hydroxy-propyl)-amino]-propan-2S-ol 22 (2.23 g, 10 mmol) and
methanol (50 mL). The autoclave was sealed. After purging with nitrogen for three times, the autoclave was charged with hydrogen (20 atm). The reaction was stirred for 4 h at room temperature. The hydrogen pressure was then carefully released in a well ventilated fume hood. The mixture was filtered on a pad of Celite to remove the catalyst. The solution was removed under reduced pressure. Distillation of the residue in vacuum afforded the pure product (1.26 g, 95 %). $^1$H NMR (400 MHz, CDCl$_3$) δ: 4.29 (bs, 3H), 3.92 (m, 2H), 2.73-2.59 (m, 4H), 1.15 (d, $J$ = 6.27 Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 65.0, 56.1, 20.8.

**Synthesis of Bis-(2S-hydroxy-propyl)-carbamic Acid tert-Butyl Ester (24)**

To a solution of 1-(2S-hydroxy-propylamino)-propan-2S-ol 23 (1.20 g, 9 mmol) in CH$_2$Cl$_2$ (100 mL), was added (Boc)$_2$O (2.18 g, 10 mmol) and NEt$_3$ (1.5 mL, 10 mmol) under inert atmosphere at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. Precipitation formed during reaction. The reaction mixture was diluted with CH$_2$Cl$_2$ (100 mL). To the diluted solution was added H$_2$O (100 mL). The resulting mixture was stirred for 5 min. The organic phase was separated and dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with CH$_2$Cl$_2$/MeOH 200:15) to afforded the title pure product (1.97 g, 94%) as a viscous oil. $^1$H NMR (400 MHz, CDCl$_3$) δ: 4.13-4.12 (m, 4H), 3.22-3.08 (m, 4H), 1.38 (s, 9H), 1.08 (d, $J$ = 6.29 Hz, 6H); $^{13}$C NMR (75MHz, CDCl$_3$) δ: 156.9, 80.1, 66.7, 56.6, 28.3, 20.6.
Synthesis of 4S, 8S-Dimethyl-2,2-dioxo-[1,3,2,6]dioxathiazocane-6-carboxylic Acid tert-Butyl Ester (25)

To a solution of bis-(2S-hydroxy-propyl)-carbamic acid tert-butyl ester 24 (0.233 g, 1 mmol) in CH$_2$Cl$_2$ (5 mL) was added NEt$_3$ (0.58 mL, 4 mmol). The resulting solution was cooled to 0 °C in an ice water bath. To the cooled solution, thinly chloride (0.109 mL, 1.5 mmol) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C. Then a small amount of water (0.2 mL) was added to quench the reaction. The resulting mixture was diluted with CH$_2$Cl$_2$ (10 mL), and washed with saturate aqueous NaCl solution (10 mL). The solvent was removed under reduced pressure to obtain a red residue. The residue was dissolved in minimum amount of CH$_2$Cl$_2$ and passed through a short silica gel pad (eluting with Hexane/EtOAc). The crude cyclic sulfite was obtained as a colorless solid after removing the solvents under reduced pressure. To the cyclic sulfite was added CH$_3$CN (30 mL), CH$_2$Cl$_2$ (30 mL) and H$_2$O (45 mL). The resulting suspension was then cooled to 0 °C. To the cooled suspension was added catalytic amount of RuCl$_3$ (10 mg) and NaIO$_4$ (0.32 g, 1.5 mmol) in portions. The reaction mixture was stirred for 1 h at 0 °C. Then aqueous saturated NaCl solution (30 mL) was added. The resulting mixture was extracted with CH$_2$Cl$_2$ (2 x 30 mL). The combined extracts was dried over NaSO$_4$ and concentrated. Further purification by flash chromatography on silica gel (eluting with hexane/EtoAc) provided the title pure cyclic sulfate (0.248 g, 84 %) as a colorless solid.

$^1$H NMR (360 MHz, CDCl$_3$) δ: 4.91-4.83 (m, 2H), 3.72-3.41 (m, 4H), 1.49 (s, 9H), 1.44
163

(d, J = 6.52 Hz, 6H); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$: 155.7, 81.6, 80.7, 80.1, 52.3, 28.5, 19.5, 19.2.

**Synthesis of 4S, 8S-Dimethyl-[1,3,2,6]dioxathiazocane 2,2-dioxide (26)**

\[
\begin{array}{c}
\text{HN} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\]

4S, 8S-Dimethyl-2,2-dioxo-[1,3,2,6]dioxathiazocane-6-carboxylic acid tert-butyl ester 25 (4.4 g, 15 mmol) was dissolved in a mixture of CF$_3$COOH (50 mL) and CH$_2$Cl$_2$ (50 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Solvents were removed under reduced pressure. To the residue was added CH$_2$Cl$_2$ (100 mL) and 10 % aqueous NaOH solution (100 mL). After stirring for 10 min, the organic phase was separated, washed with brine (50 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with Hexane/ EtOAc 2:1) to afford the title pure product (2.62 g, 90% yield) as a white solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 4.71 (m, 2H), 3.16 (d, $J = 3.05$ Hz, 1H), 3.11 (d, $J = 3.04$ Hz, 1H), 2.87 (d, $J = 6.27$ Hz, 1H), 2.82 (d, $J = 6.26$ Hz, 1H), 1.67 (bs, 1H), 1.33 (d, $J = 5.8$ Hz, 6H); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$: 82.9, 52.8, 18.7.

**Synthesis of (4S, 8S)-4,6,8-Trimethyl-[1,3,2,6]dioxathiazocane 2,2-dioxide (19)**

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\]

To a 10 mL Schlenk tube was added 4S, 8S-dimethyl-[1,3,2,6]dioxathiazocane 2,2-dioxide 26 (0.195 g, 1 mmol). The tube was degassed and charged with nitrogen.
HCOOH (1.6 mL) was added. To the resulting solution was added aqueous 37% HCHO solution (1.4 mL). The reaction mixture was heated to 80 °C and stirred overnight. The reaction mixture was cooled to room temperature and 25% aqueous NaOH solution was added dropwise to adjust pH = 12. The aqueous phase was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with CH₂Cl₂/ether 10:1) to afford the title pure product (84 mg, 40 %).

**General Procedure for the Asymmetric Hydrogenation of Aryl Enamides**

To a solution of an aryl enamide (0.2 mmol) in dichloromethane (2.0 mL) was added a solution of [Rh(16)(NBD)]SbF₆ (0.002 mmol, preformed by mixing ligand 16 with 1.0 equiv. of Rh(NBD)₂SbF₆) in dichloromethane (2.0 mL)) in a glove box filled with nitrogen. The whole solution was transferred into an autoclave and charged with hydrogen (15 psi). The hydrogenation was performed at room temperature for 24 h. After the reaction, the hydrogen was released carefully and the reaction mixture was passed through a silica gel plug and flushed with ether. A small amount of sample was subjected to chiral GC (Chiral select 1000) or HPLC analysis. For the E/Z ratio of α-aryl enamides, the absolute configuration and ee (%) value determinations, see Zhu, G.; Zhang, X. *J. Org. Chem.* 1998, 63, 9590.

**General Procedure for Asymmetric Hydrogenation of α-Amino Acid Esters**

To a solution of an α-amino acid ester (0.2 mmol) in methanol (2.0 mL) was added a solution of [Rh(16)(NBD)]SbF₆ (0.002 mmol, preformed by mixing ligand 16 with 1.0 equiv. of Rh(NBD)₂SbF₆) in methanol (2.0 mL)) in a glove box filled with nitrogen. The whole solution was transferred into an autoclave and charged with
hydrogen (15 psi). The hydrogenation was performed at room temperature for 24 h. After the reaction, the hydrogen was released carefully and the reaction mixture was passed through a silica gel plug and flushed with ether. The ee’s were determined by chiral GC (Chrialsil- VAL III FSOT). The $R$ absolute configuration was assigned by comparing the optical rotations with reported values.

**General Procedure for Asymmetric Hydrogenation of $\beta$-amino acid esters**

To a solution of a $\beta$-amino acid ester (0.2 mmol) in dichloromethane (2.0 mL) was added a solution of $[\text{Rh}(16)(\text{NBD})]\text{SbF}_6$ (0.002 mmol, preformed by mixing ligand 16 with 1.0 equiv. of $\text{Rh(\text{NBD})}_2\text{SbF}_6$) in dichloromethane (2.0 mL)) in a glove box filled with nitrogen. The whole solution was transferred into an autoclave and charged with hydrogen (15 psi). The hydrogenation was performed at room temperature for 24 h. After the reaction, the hydrogen was released carefully and the reaction mixture was passed through a silica gel plug and flushed with ether. The ee’s were determined by chiral GC using a Chiralselect 1000 column. The absolute configurations were determined as $R$ by comparing the optical rotations with reported values.
References


Chapter 5

Development of Hybrid Phosphorus Ligands for Highly Enantioselective Asymmetric Hydrogenation

5.1 Introduction

Transition metal complex catalyzed asymmetric hydrogenation has attracted a great deal of interest because of its high efficiency for the preparation of enantiomerically pure compounds.\textsuperscript{1} Since the enantioselectivity is dependent on the chiral environment provided by the ligands when coordinated to the metal center and subtle changes of electronic and/or steric properties of the chiral ligands often have dramatic influence on the enantioselectivity, the search for new well-designed chiral ligands plays an important role in the field of catalytic asymmetric hydrogenation.\textsuperscript{1a}

Chiral bidentate electron-donating bisphosphines and bisphospholanes are the most widely used classes of ligands for catalytic asymmetric hydrogenation.\textsuperscript{1a} Recently, hybrid ligands which combine phosphorus groups with different electronic properties have also demonstrated their potential utility in asymmetric hydrogenation.\textsuperscript{2} Because the two different phosphorus groups can affect the reactivity and selectivity of the metal catalyst in different ways, hybrid ligands may be advantageous in catalyst design for achieving chiral environments inaccessible with symmetrical ligands. Figure 5-1 shows some representative hybrid ligands employed in asymmetric hydrogenation.
Figure 5-1: Hybrid Phosphorus Ligands for Asymmetric Hydrogenation
Agbossou and coworkers used aminophosphate-carboxyphosphinites ligands **1-3** prepared from chiral amino acids in the rhodium-catalyzed asymmetric hydrogenation of dihydro-2,4-dimethyl-2,3-furandione. Moderate enantioselectivities (up to 42% ee) were obtained with these ligands.\(^2\text{a}\) Reetz reported phosphine-phosphonite ligands **4-6** in the rhodium-catalyzed asymmetric hydrogenation of dimethyl itaconate with up to 88% ee.\(^2\text{b}\) Pizzano prepared a family of phosphine-phosphite ligands **7** and examined their performance in the rhodium-catalyzed asymmetric hydrogenation of dimethyl itaconate.\(^2\text{c}\) Excellent enantioselectivity (>99% ee) was achieved with low catalysts loading (S/C = 3000–10000). Phosphine-phosphite ligand **8** with a flexible backbone also was prepared and employed in the iridium-catalyzed asymmetric hydrogenation of N-aryl imines.\(^2\text{d}\) Good enantioselectivity (up to 84% ee) was obtained. Interestingly, ligands with flexible backbones have better enantioselectivities than ligands with rigid backbones. Phosphine-phosphite ligand **9** developed by Claver and coworkers was prepared from D-(+)-xylose. Excellent enantioselectivities (>99%) were achieved with this ligand in the rhodium-catalyzed asymmetric hydrogenation of dehydroaminoacid derivatives under mild reaction conditions.\(^2\text{c}\) A novel water-soluble phosphine–phosphinite ligand **10** was prepared from α, α-trehalose in Ohe’s lab.\(^2\text{f}\) Rhodium-catalyzed asymmetric hydrogenation of dehydroamino acid derivatives was investigated in aqueous media using this ligand. A simple phase separation could recover the catalyst. The catalyst recovered was reused in asymmetric hydrogenation without significant loss of enantioselectivity. Phosphinoferrocenylaminophosphine ligand **11**, known as BoPhoz, has been used in rhodium-catalyzed asymmetric hydrogenation.\(^2\text{g, h}\) Good-to-excellent enantioselectivities
were achieved in the asymmetric hydrogenation of dehydroamino acids, itaconates and β-
ketoesters. Ferrocene-based phosphine-phosphoramidites 12-13 was reported by Zheng and coworkers.\textsuperscript{2}\textsuperscript{i-k} These ligands showed excellent enantioselectivities (over 99% ee) in the rhodium-catalyzed asymmetric hydrogenation of a variety of substrates including enamides, dimethyl itaconate, methyl (Z)-acetamidocinnamate and β-dehydroamino acid derivatives. Recently, a perfluoroalkyl-substituted Binaphos derivative was utilized in the asymmetric hydrogenation of 2-acetamido methyl acrylate and dimethyl itaconate in supercritical carbon dioxide with 97 % ee,\textsuperscript{2l} indicating the potential of Binaphos type ligands in asymmetric hydrogenation.

In chapter 5, the development of two new (S)-BINOL based phosphine-phosphite (S,R)-o-Binaphos 15 and phosphine-phosphinite (S)-o-Bipnite 16 ligands (Figure 5-2), as well as their applications in asymmetric hydrogenation, will be discussed. These ligands showed excellent enantioselectivities (up to over 99 % ee) in the rhodium-catalyzed asymmetric hydrogenations of α-dehydroaminoacid derivatives and dimethyl itaconate.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5-2.png}
\caption{New Phosphine-phosphite and Phosphine-phosphinite ligands}
\end{figure}
5.2 Results and Discussions

5.2.1 Ligand Design and Synthesis

Ligands bearing chiral binaphthyl backbones have been widely utilized in a variety of asymmetric reactions. Among them, Binaphos 17 and Bipnite 18 (Figure 5-3) have been applied successfully to asymmetric hydroformylation. To the best of our knowledge, asymmetric hydrogenation using these two ligands has not been reported yet. Structural analysis of Binaphos and Bipnite revealed that further modifications are required to achieve higher enantioselectivity. Compared with the chelating phosphorus atoms of the phosphine moieties in Binaphos 17 and Bipnite 18, which are directly attached to the chiral binaphthyl backbone, the phosphorus atoms of the phosphite and phosphinite moieties are one atom far away from the chiral backbone, thus making the asymmetric induction less effective. Moreover, the presence of the flexible C-O-P bonds in the phosphinite and phosphite moieties decreases the conformational rigidity of these ligands. We envision that these disadvantages related to C-O-P bonds might be overcome by the introduction of a phenyl substituent into the ortho position of the binaphthyl backbone. Recently we have successfully applied this strategy in the development of several ortho substituted biphenyl and binaphthyl ligands for highly enantioselective hydrogenations. Based on this rationale, o-Binaphos 15 and o-Bipnite 16 were designed.
The syntheses of ligands \(15\) and \(16\) are outlined in Scheme 5-1, starting from commercially available (S)-BINOL \(19\). Treatment of \(19\) with dimethyl sulphate under basic conditions afforded dimethoxy protected (S)-BINOL \(20\) in 78% yield. Attempts to prepare the mono iodide \(22\) using the Snieckus lithiation-iodination\(^5\) procedure by the reaction of \(20\) with 1 equiv of \(n\)-BuLi followed by quench with iodine were unsuccessful. Under different reaction conditions, the bisiodide \(21\) was always obtained as the major product which was difficult to separate from monoiodide \(22\) using chromatographic technique due to the small difference of \(R_f\) between mono- and bisiodides. To solve this problem, we then tried a two-step synthetic strategy: the first step is to make bisiodide \(21\)
using 2 equiv of \( n\)-BuLi and iodine; the second step is mono-deiodination by treatment of bisiodide 21 with 1 equiv \( n\)-BuLi followed by quenching with \( \text{NH}_4\text{Cl} \). Following this sequence, the mono-iodide 22 was prepared in 63 % isolated yield. Compound 25 was prepared by the Suzuki coupling of monoiodide 22 with phenyl boronic acid in the presence of catalytic amount of \( \text{Pd(PPh}_3\text{)}_4 \). Deprotection of the dimethoxy moieties of compound 23 with \( \text{BBr}_3 \) at -78 °C in \( \text{CH}_2\text{Cl}_2 \) afforded diol 24 in excellent yield. Ditriflation of 24 with trifluoromethanesulfonic anhydride (\( \text{Tf}_2\text{O} \)) in the presence of pyridine in \( \text{CH}_2\text{Cl}_2 \) provided bistriflate 25 in 94 % yield. Subsequent Pd-catalyzed monophosphinylation gave the corresponding phosphine oxide 26 which underwent hydrolysis in aqueous \( \text{NaOH} \) to give the hydroxy phosphine oxide 27 in 72 % overall yield. No phosphinylation products were observed when using Ni as catalyst under a variety of reaction conditions. The steric hindrance of the phosphine oxide and phenyl group at the 3’-position of the binaphthyl skeleton was most likely responsible for the Pd-catalyzed monophosphinylation. The reduction of the hydroxy phosphine oxide 27 with trichlorosilane \( \text{HSiCl}_3 \) in toluene at 100 °C afforded the hydroxy phosphine 28 in 69 % yield. Deprotonation of hydroxy phosphine 28 with \( n\)-BuLi followed by treatment with \((R)-(1, 1’\text{-binaphthalene-2, 2’-dioxy})\text{chlorophosphine} \) and diphenylchlorophosphine provided the desired phosphine-phosphite ligand 15 and phosphine-phosphinite ligand 16 in 75% and 70% yields, respectively.
Scheme 5-1: Synthesis of o-Binaphos and o-Bipnite
5.2.2 Asymmetric Hydrogenation with New Phosphine-Phosphite and Phosphine-Phosphinite Ligands

With phosphine-phosphite 15 and phosphine-phosphinite 16 in hand, we investigated their applications in rhodium-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives. The commercially available α-(N-acetamido)acrylate was used as a standard substrate to screen the reaction conditions. The cationic Rh(I) complexes were prepared in situ by mixing a Rh(COD)PF₆ precursor with 1.1 molar equivalent of ligands in a suitable solvent. Hydrogenation was performed at room temperature and under 15 psi of hydrogen in the presence of the catalyst. Table 5-1 summarizes the results of the hydrogenation of α-(N-acetamido)acrylate in several common solvents. As shown in the table, no significant solvent effect was observed. Hydrogenation reactions performed in various solvents always gave excellent enantioselectivities (>99 % ee). For comparison, phosphine-phosphite 17 and phosphine-phosphinite 18 lacking ortho substituents were also tested in the hydrogenation of α-(N-acetamido)acrylate in THF under identical reaction condition. As can been seen from the table (entries 2, 7, 11-12), ortho phenyl substituted ligands are more enantioselective than their corresponding nonsubstituted ligands. For example, dramatic increases of enantioselectivity were observed when using ortho phenyl substituted phosphine-phosphinite o-Bipnite 16 (over 99% ee) instead of Bipnite 18 (77% ee) (entry 7 vs. 12). The ortho phenyl substituted phosphine-phosphite o-Binaphos 15 also is more effective than the corresponding Binaphos, as the enantioselectivity increased from 96% ee to over 99% ee (entry 2 vs. 11). These results clearly demonstrate that the introduction of an ortho phenyl substituent helps to improve the enantioselectivity.
**Table 5-1: Asymmetric Hydrogenation of α-(N-Acetamido)acrylate**

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>L</th>
<th>conv (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃OH</td>
<td>15</td>
<td>100</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>15</td>
<td>100</td>
<td>&gt;99</td>
</tr>
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<td>3</td>
<td>toluene</td>
<td>15</td>
<td>100</td>
<td>&gt;99</td>
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<td>CH₂Cl₂</td>
<td>15</td>
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<tr>
<td>5</td>
<td>EtOAc</td>
<td>15</td>
<td>100</td>
<td>&gt;99</td>
</tr>
<tr>
<td>6</td>
<td>CH₃OH</td>
<td>16</td>
<td>100</td>
<td>&gt;99</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>16</td>
<td>100</td>
<td>&gt;99</td>
</tr>
<tr>
<td>8</td>
<td>toluene</td>
<td>16</td>
<td>100</td>
<td>&gt;99</td>
</tr>
<tr>
<td>9</td>
<td>CH₂Cl₂</td>
<td>16</td>
<td>100</td>
<td>&gt;99</td>
</tr>
<tr>
<td>10</td>
<td>EtOAc</td>
<td>16</td>
<td>100</td>
<td>&gt;99</td>
</tr>
<tr>
<td>11</td>
<td>THF</td>
<td>17</td>
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<td>96</td>
</tr>
<tr>
<td>12</td>
<td>THF</td>
<td>18</td>
<td>100</td>
<td>77</td>
</tr>
</tbody>
</table>

*a The reactions were carried out at rt under 15 psi of H₂ for 12 h. Substrate/Rh/L = 1:0.01:0.011. The ee’s were determined by chiral GC using a Chiralsil-VAL III FSOT column. The absolute configuration was assigned as S by comparing the optical rotations with reported values.*
Table 5-2 summarizes the results of rhodium-catalyzed asymmetric hydrogenation of a variety of trisubstituted α-dehydroamino acid esters 29b-m. In most cases, extremely high enantioselectivities (≥99% ee) were obtained with full conversion using both ligands 15 and 16. Halogen substituted substrates 29c-e (entries 3-8) were hydrogenated with ≥ 99% ee regardless of the substituent or substitution position. The 2-naphthyl derivative 29f (entries 9-10) was also hydrogenated with high enantioselectivities (>99% ee). The enantioselectivities for 2-thienyl substrate 29g were slightly lower (95% ee for both ligand 15 and 16, entries 11-12).

Rhodium-catalyzed asymmetric hydrogenations of trisubstituted α-dehydroamino acids 29h-l were also carried out. The results are summarized in Table 5-3. Again, excellent enantioselectivities were achieved. It is noteworthy that in non-protic THF, both ligands can tolerate acidic substrates. The enantioselectivities obtained in the rhodium-catalyzed hydrogenation of α-dehydroamino acid derivatives with α-Binaphos 15 and α-Bipinite 16 are the best among phosphine-phosphite and phosphine-phosphinite ligands and comparable to the best enantioselectivities attained previously with other bisphosphine or bisphospholane ligands.
Table 5-2: Asymmetric Hydrogenation of α-Dehydroamino Acid Esters$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>L</th>
<th>Ar</th>
<th>R</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29b</td>
<td>15</td>
<td>Ph</td>
<td>CH₃</td>
<td>&gt;99</td>
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<tr>
<td>2</td>
<td>29b</td>
<td>16</td>
<td>Ph</td>
<td>CH₃</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>29c</td>
<td>15</td>
<td>p-FPh</td>
<td>CH₃</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>29c</td>
<td>16</td>
<td>p-FPh</td>
<td>CH₃</td>
<td>&gt;99</td>
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<tr>
<td>5</td>
<td>29d</td>
<td>15</td>
<td>m-BrPh</td>
<td>CH₃</td>
<td>&gt;99</td>
</tr>
<tr>
<td>6</td>
<td>29d</td>
<td>16</td>
<td>m-BrPh</td>
<td>CH₃</td>
<td>&gt;99</td>
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<tr>
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<td>29e</td>
<td>16</td>
<td>o-ClPh</td>
<td>CH₃</td>
<td>&gt;99</td>
</tr>
<tr>
<td>9</td>
<td>29f</td>
<td>15</td>
<td>2-naphthyl</td>
<td>CH₃</td>
<td>&gt;99</td>
</tr>
<tr>
<td>10</td>
<td>29f</td>
<td>16</td>
<td>2-naphthyl</td>
<td>CH₃</td>
<td>&gt;99</td>
</tr>
<tr>
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<td>CH₃</td>
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<td>12</td>
<td>29g</td>
<td>16</td>
<td>2-thienyl</td>
<td>CH₃</td>
<td>95</td>
</tr>
</tbody>
</table>

$^a$ The reactions were carried out at rt under 15 psi of H₂ for 12 h with 100 % conversion. Substrate/Rh/L = 1:0.01:0.011. The ee’s were determined by chiral GC using a Chiralsil-VAL III FSOT column. The absolute configuration was assigned as S by comparing the optical rotation with reported values.
To investigate the substrate scope, other common prochiral substrates were hydrogenated using ligands 15 and 16. The reaction conditions were the same as in the hydrogenation of the α-dehydroaminoacid derivatives. Some representative results are

Table 5-3: Asymmetric Hydrogenation of α-Dehydroamino Acids$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>L</th>
<th>Ar</th>
<th>R</th>
<th>ee (%)</th>
</tr>
</thead>
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<tr>
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<td>p-FPh</td>
<td>H</td>
<td>99</td>
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<tr>
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<td>29l</td>
<td>16</td>
<td>2-naphthyl</td>
<td>H</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

$^a$The reactions were carried out at rt under 15 psi of H$_2$ for 12 h with 100 % conversion. Substrate/Rh/L = 1:0.01: 0.011. The ee’s were determined by chiral GC using a Chiralsil-VAL III FSOT column after converting to the corresponding methyl esters. The absolute configuration was assigned as S by comparing the optical rotation with reported values.
listed in Table 5-4. Excellent enantioselectivities (> 99% ee for both ligands) were achieved in the hydrogenation of dimethyl itaconic acid ester (entries 1-2). With ligand 16, high enantioselectivity also was obtained in the hydrogenation of non-β-substituted phenyl enamides (entry 3, 91 % ee). However, for trisubstituted N-(1-Phenyl-propenyl)-acetamide, low enantioselectivity was observed, indicating the limitation of ligand 16 in the asymmetric hydrogenation of trisubstituted enamides (entry 4, 76 % ee). Ligand 15 did not show activity in the hydrogenation of aryl enamides under current reaction condition.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>L</th>
<th>conv (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![MeOOC-]**[C=O]**Me</td>
<td>15</td>
<td>100</td>
<td>&gt;99(R)</td>
</tr>
<tr>
<td>2</td>
<td>![MeOOC-]**[C=O]**Me</td>
<td>16</td>
<td>100</td>
<td>&gt;99(R)</td>
</tr>
<tr>
<td>3</td>
<td>![NHAc]<strong>[C]</strong>(NH)</td>
<td>16</td>
<td>100</td>
<td>91(S)</td>
</tr>
<tr>
<td>4</td>
<td>![NHAc]<strong>[C]</strong>(NH)</td>
<td>16</td>
<td>100</td>
<td>76(S)</td>
</tr>
</tbody>
</table>

The reactions were carried out at rt under 15 psi of H₂ for 12 h. Substrate/Rh(COD)₂PF₆/L = 1:0.01: 0.011. The ee’s were determined by chiral GC using a Chiral select 1000 column. The absolute configurations were assigned by comparing the optical rotation with reported values.
5.3 Conclusion

In conclusion, we have developed two new phosphine-phosphite and phosphine-phosphinite ligands derived from ortho phenyl substituted BINOL. These ligands show excellent enantioselectivities in the asymmetric hydrogenation of α-dehydroamino acid derivatives and dimethyl itaconate. The enantioselectivities obtained in the rhodium-catalyzed hydrogenations of α-dehydroamino acid derivatives with these ligands are the best among hybrid phosphine-phosphite and phosphine-phosphinite ligands and comparable to the best enantioselectivity attained previously with other bisphosphine or bisphosphalane ligands. We also demonstrated that an ortho phenyl substituent at the binaphthyl backbone can have dramatic effects on asymmetric induction.
Experimental Section

**General Methods:** All reactions and manipulations were performed under nitrogen using standard Schlenk techniques unless otherwise stated. THF and toluene were dried and distilled from sodium-benzophenone ketyl under nitrogen. Methylene chloride was dried over CaH₂ and flushed with nitrogen. Methanol and isopropanol were distilled from Mg under nitrogen. Column chromatography was performed using EM silica gel 60 (230~400 mesh). ¹H, ¹³C, and ³¹P NMR spectrum were recorded on Bruker AM-300, AMX-360, and APX-400 spectrometers. Chemical shifts were reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard. Mass spectra were recorded on a KRATOS mass spectrometer MS 9/50 for LR-ESI and HR-ESI. GC analysis was carried out on a Helwett-Packard 6890 gas chromatograph using chiral capillary columns.

**Synthesis of (S)-2,2'-Dimethoxy-[1,1']binaphthalenyl (20)**

To a 500 ml flask was added (S)- [1,1']binaphthalenyl-2,2'-diol 19 (14.3 g, 50 mmol). The flask was degassed and charged with nitrogen. Degassed 95% Ethanol (200 mL) was then added. The resulting solution was cooled to 0 °C in an ice-water bath and dimethyl sulfate (13.3 mL, 140 mmol) was added dropwise followed by aqueous sodium hydroxide (25 g in 40 mL of water) The reaction mixture was allowed to warmed to room
temperature and heated at reflux for 3 h. The resulting suspension was filtered. The solid residue was washed with aqueous 1 N sodium hydroxide solution (20 mL), water (20 mL) and dried under vacuum. Pure product was obtained after recrystallization from toluene (12.2 g, 78%). $^1$H NMR (300 MHz, TDF) δ: 7.95 (d, $J = 9.02$ Hz, 2H), 7.83 (d, $J = 8.12$ Hz, 2H), 7.5 (d, $J = 9.02$ Hz, 2H), 7.24 (t, $J = 6.99$ Hz, 2H), 7.12 (t, $J = 8.16$Hz), 7.03 (d, $J = 10.82$ Hz, 2H), 3.70 (s, 6H); $^{13}$C NMR (75 MHz, TDF) δ: 155.8, 134.9, 130.0, 129.6, 128.3, 126.4, 125.7, 123.6, 120.2, 114.4, 56.3.

**Synthesis of (S)-3,3'-Diiodo-2,2'-dimethoxy-[1,1']binaphthalenyl (21)**

To a solution of $N,N,N',N'$-tetramethylethylenediamine (TMEDA) (0.68 mL, 4.5 mmol) in ether (30 mL) was added $n$-BuLi (1.8 mL of 2.5 M solution in hexane, 4.5 mmol) dropwise at room temperature under an inert atmosphere. After stirring for 30 min at room temperature, (S)-2, 2'-dimethoxy-[1,1']binaphthalenyl 20 (0.94g, 3 mmol) was added in portions. After stirring for 4 h at room temperature, the mixture was cooled to $-78^\circ$C with a dry ice/acetone bath and quenched by adding slowly a solution of iodine (1.1 g, 4.5 mmol) in ether (10 ml). The resulting mixture was allowed to warm slowly to room temperature and stirred overnight. To the brown solution was added saturated aqueous Na$_2$S$_2$O$_3$ solution (20 ml). After stirring for 30 min, the brown color faded completely. The organic phase was then separated, and the aqueous phase was extracted with methylene chloride (3 x 20 ml). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash
chromatography on silica gel (eluting with hexane/CH₂Cl₂, 4:1) to give the title product as a white solid (1.39 g, 82 %). ¹H NMR (300 MHz, CD₂Cl₂) δ: 8.57 (s, 2H), 7.83 (d, J = 8.21 Hz, 2H), 7.46-7.40 (m, 2H), 7.31-7.25 (m, 2H), 7.07 (d, J = 7.83 Hz, 2H), 3.40 (s, 6H); ¹³C NMR (75 MHz, CD₂Cl₂) δ: 154.77, 140.27, 134.18, 132.55, 127.39, 127.34, 126.04, 126.01, 125.74, 92.59, 61.33.

**Synthesis of (S)-3-Iodo-2,2'-dimethoxy-[1,1']binaphthalenyl (22)**

![Chemical structure of (S)-3-Iodo-2,2'-dimethoxy-[1,1']binaphthalenyl](image)

To a 50 ml Schlenk flask was charged (S)-3, 3'-diiodo-2,2'-dimethoxy-[1,1']binaphthalenyl 21 (1.16 g, 2.05 mmol). The flask was degassed and charged with nitrogen. THF (50 mL) was added. The resulting solution was cooled to -78 °C in a dry ice/acetone bath and n-BuLi (0.141 mL of 1.6 M solution in hexane, 2.05 mmol) was added dropwise. After stirring for 1 h at -78 °C, the reaction mixture was warmed to room temperature and saturated aqueous NH₄Cl solution (20 mL) was added. After stirring for 5 min, the organic phase was separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layer was washed with water, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluting with hexane/CH₂Cl₂ 4:1) to give the title compound (0.7 g, 77 %). ¹H NMR (300 MHz, CD₂Cl₂) δ: 8.55 (s, 1H), 8.08 (d, J = 9.07 Hz, 1H), 7.93 (d, J = 8.10 Hz, 1H), 7.83 (d, J = 8.13 Hz, 1H), 7.52 (d, J = 9.08 Hz, 1H), 7.45-7.34 (m, 2H), 7.29-7.24 (m, 2H), 7.14-7.07 (m, 2H), 3.82 (s, 3H), 3.44 (s, 3H); ¹³C NMR (75 MHz, CD₂Cl₂)
δ: 155.1, 154.7, 139.4, 134.4, 134.0, 132.7, 130.5, 129.3, 128.4, 127.2, 127.1, 126.3, 125.9, 125.1, 124.0, 118.6, 113.5, 92.9, 61.0, 56.5.

**Synthesis of (S)-2,2'-Dimethoxy-3-phenyl-[1,1']binaphthalenyl (23)**

![Chemical Structure](image)

To a 100 mL Schelenk flask was added (S)-3-iodo-2, 2'-dimethoxy-[1,1']binaphthalenyl 22 (0.7 g, 1.47 mmol), phenylboronic acid (0.27 g, 2.2 mmol) and Pd(PPh₃)₄ (86 mg, 0.07 mmol). The flask was degassed and charged with nitrogen. Degassed THF (20 mL) was added, followed by degassed aqueous 1M K₂CO₃ solution (20 mL). The reaction mixture was heated to 80 °C and stirred for 12 h. The reaction mixture changed color from yellow to brown during the reaction. The resulting mixture was cooled to room temperature and filtered through a Celite pad. The solvent was removed under reduced pressure. To the residue was added EtOAC (30 mL) and saturated aqueous NH₄Cl solution (30 mL). After stirring for 10 min, the organic phase was separated and dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluting with hexanes/EtOAc 10:1) to give the title compound (0.37 g, 65 %) as a colorless solid. ¹H NMR (300 MHz, CD₂Cl₂) δ: 8.06 (d, J = 9.1 Hz, 1H), 7.98 (s, 1H), 7.93 (t, J = 7.7 Hz, 2H), 7.78-7.75 (m, 2H), 7.54-7.16 (m, 9H), 7.12 (d, J = 8.0 Hz, 1H), 3.84, 3.11; ¹³C NMR (75 MHz, CD₂Cl₂) δ: 155.20, 154.45, 139.24, 134.40, 133.78, 131.23, 130.56,
Synthesis of (S)-3-Phenyl-[1,1']binaphthalenyl-2,2'-diol (24)

To a 50 ml Schlenk flask, was charged (S)-2, 2'-dimethoxy-3-phenyl-[1,1']binaphthalenyl 23 (0.37 g, 0.95 mmol). The flask was degassed and charged with nitrogen. CH$_2$Cl$_2$ (10 mL) was added and the resulting solution was cooled to -78 °C in a dry ice/acetone bath. To the cooled solution was added dropwise boron tribromide (0.38 mL, 3.79 mmol). After stirring for 2 h at -78 °C, the reaction mixture was allowed to warm to room temperature slowly and stirred overnight. The reaction mixture was diluted with CH$_2$Cl$_2$ (20 mL) and cooled to 0 °C. Water (10 mL) was added dropwise. After stirring for 10 min, the organic phase was separated and washed with brine (10 mL). The product was purified by flash chromatography on silica gel (eluting with hexane/EtOAc 6:1) to give the title product as a white solid (0.33 g, 95%). $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ: 8.04-7.91 (m, 4H), 7.76-7.72 (m, 2H), 7.53-7.49 (m, 2H), 7.45-7.28 (m, 6H), 7.23 (d, $J$ = 8.3 Hz, 1H), 7.13 (d, $J$ = 8.4 Hz, 1H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ: 153.08, 150.65, 137.91, 133.89, 133.39, 131.76, 131.60, 131.08, 129.93, 129.86, 128.81, 128.73, 128.08, 127.63, 127.60, 124.64, 124.51, 124.35, 124.26, 118.08, 112.32, 112.00.
Synthesis of \((S)\)-Trifluoro-methanesulfonic Acid 3'-Phenyl-2'-(trifluoromethanesulfonyloxy)-[1,1']binaphthalenyl-2-yl Ester (25)

\[
\begin{align*}
\text{Ph} & \quad \text{OTf} \\
\text{OTf} & \quad \text{Ph}
\end{align*}
\]

To a 50 ml Schlenk flask was added \((S)\)-3-phenyl-[1,1']binaphthalenyl-2,2'-diol 24 (1.09 g, 3 mmol). The flask was degassed and charged with nitrogen. Pyridine (0.73 mL, 9 mmol) and CH\(_2\)Cl\(_2\) (5 mL) were added. The resulting solution was cooled to 0 °C in an ice/water bath. To the cooled solution was added trifluoromethanesulfonic anhydride (1.5 mL, 9 mmol) dropwise at 0 °C. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure. The residue was dissolved in 20 mL of CH\(_2\)Cl\(_2\) and washed with 5% HCl (10 mL), saturated NaHCO\(_3\) (10 mL) and brine (10 mL). The organic phase was separated, dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 5:1) to give the title pure product as a white powder (1.76 g, 94%). \(^1\)H NMR (360 MHz, THF) \(\delta\): 8.06-8.01 (m, 2H), 7.90-7.88 (m, 2H), 7.55-7.26 (m, 10H), 7.15-7.13 (m, 2H).

Synthesis of \((S)\)-Trifluoro-methanesulfonic Acid 2'-(Diphenyl-phosphinoyl)-3-phenyl-[1,1']binaphthalenyl-2-yl Ester (26)

\[
\begin{align*}
\text{Ph} & \quad \text{OTf} \\
\text{P(O)Ph}_2 & \quad \text{Ph}
\end{align*}
\]
To a 50 mL Schlenk flask was added (S)-trifluoro-methanesulfonic acid 3'-phenyl-2'-trifluoromethanesulfonyloxy-[1,1']binaphthalenyl-2-yl ester 25 (0.312 g, 0.5 mmol), diphenylphosphine oxide (0.202 g, 1.0 mmol), palladium diacetate (5.6 mg, 0.025 mmol) and 1,1-bis(diphenylphosphino)butane (dppb, 10.7 mg, 0.025 mmol). The flask was degassed and charged with nitrogen. To the mixture was added dimethylsulfoxide (5 mL) and diisopropylethyl amine (0.35 mL, 2 mmol). The reaction mixture was heated at 100 °C and stirred for 12 h. The reaction mixture changed color from green to brown during the reaction. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure to give a dark brown residue. The residue was dissolved in EtOAc (50 mL), washed with water (20 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluting with hexane/EtOAc 2:1) to give the title compound as a white solid (0.29 g, 86 %). $^1$H NMR (300 MHz, CH$_2$Cl$_2$) $\delta$: 8.06-7.95 (m, 3H), 7.88-7.76 (m, 3H), 7.63-7.43 (m, 11H), 7.34-7.22 (m, 5H), 7.17-7.08 (m, 3H), 6.92 (d, $J$ = 8.4 Hz, 1H); $^{13}$C NMR (75 MHz, CH$_2$Cl$_2$) $\delta$: 144.33, 138.00, 137.02, 135.01, 134.40, 133.92, 133.77, 133.22, 132.53, 132.44, 132.32, 132.14, 132.07, 132.04, 131.72, 131.63, 131.50, 130.40, 130.23, 129.38, 129.22, 129.11, 128.94, 128.86, 128.70, 128.55, 128.40, 128.33, 128.27, 127.32, 127.24, 127.13; $^{31}$P NMR (CD$_2$Cl$_2$, 146 MHz) $\delta$: 27.9.

**Synthesis of (S)-2'-(Diphenyl-phosphinoxy)-3-phenyl-[1,1']binaphthalenyl-2-ol (27)**
(S)-Trifluoro-methanesulfonic acid 2’-(diphenyl-phosphinoyl)-3-phenyl-[1,1’]binaphthalenyl-2-yl ester 26 (0.29 g, 4.3 mmol) was dissolved in 2/1 mixture of 1,4-dioxane and MeOH (3 mL) under air. To the resulting solution was added 3 N aqueous NaOH solution (3 mL) at room temperature. The reaction mixture was stirred for 12 h at room temperature. Concentrated HCl was added to adjust the pH = 1. The resulting mixture was then extracted with EtOAc (2 x 10 mL). The combined organic phase was dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give a pale yellow residue. The residue was purified by flash chromatography on silica gel (eluting with hexane/EtOAc 2:1) to give (S)-2’-(diphenyl-phosphinoyl)-3-phenyl-[1,1’]binaphthalenyl-2-ol as a white solid (0.197 g, 84 %). $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 9.42 (bs, 1H), 8.18-8.06 (m, 6H), 7.93 (s, 1H), 7.73-7.63 (m, 8H), 7.59-7.49 (m, 4H), 7.38-7.32 (m, 2H), 7.12 (t, $J = 7.3$ Hz, 1H), 6.99 (t, $J = 7.02$ Hz, 1H), 6.90 (t, $J = 4.9$ Hz, 2H), 6.70 (d, $J = 8.4$ Hz, 1H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) $\delta$: 152.07, 142.42, 142.33, 139.92, 136.24, 135.84, 134.09, 133.67, 132.74, 132.03, 132.01, 130.89, 130.84, 130.58, 130.24, 130.10, 129.73, 129.40, 129.28, 129.08, 128.91, 128.59, 128.25, 128.02, 127.88, 127.68, 127.61, 126.10, 125.61, 125.55, 124.38; $^{31}$P NMR (146 MHz, CD$_2$Cl$_2$) $\delta$: 31.3. HRMS calculated for C$_{38}$H$_{28}$O$_2$P (MH$^+$): 547.1778, Found 547.1821.

Synthesis of (S)-2’-Diphenylphosphanyl-3-phenyl-[1,1’]binaphthalenyl-2-ol

(28)
To a 50 mL Schlenk flask was charged (S)-2′-(diphenyl-phosphinoyl)-3-phenyl-[1,1′]binaphthalenyl-2-ol 27 (180 mg, 0.33 mmol). The flask was degassed and charged with nitrogen. Toluene (5 mL) was added, followed by triethyl amine (0.60 mL, 2.5 mmol). The resulting solution was cooled to 0 °C in an ice water bath and cold Cl$_3$SiH (0.166 mL, 1.65 mmol) was added dropwise at 0 °C. The reaction mixture was heated to 120 °C and stirred for 16 h. After being cooled to room temperature, the reaction mixture was diluted with Et$_2$O (10 mL). A small amount of aqueous saturated NaHCO$_3$ was added to quench the reaction. The resulting suspension was filtered through a short Celite pad. The solid was washed with CH$_2$Cl$_2$ (4 x 10 mL). The combined filtrate was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (eluting with hexane/EtOAc 3:1) gave the title compound as a white solid (120 mg, 69 %). $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ: 8.18-8.07 (m, 4H), 7.80-7.75 (m, 3H), 7.67-7.48 (m, 12H), 7.42-7.41 (m, 5H), 7.33 (t, $J = 7.0$ Hz, 1H), 7.18 (d, $J = 8.4$ Hz, 1H) 5.13 (bs, 1H); $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ: 149.64, 149.62, 140.12, 139.75, 138.62, 138.39, 138.10, 138.00, 137.95, 137.86, 134.72, 134.59, 134.36, 134.17, 134.15, 133.95, 133.87, 133.79, 131.02, 130.17, 129.56, 129.29, 129.24, 129.16, 129.12, 129.00, 128.93, 128.21, 127.87, 127.10, 125.42, 124.34, 119.95, 119.86; $^{31}$P NMR (146 MHz, CD$_2$Cl$_2$) δ: -12.6. HRMS calculated for C$_{38}$H$_{28}$OP (MH$^+$): 531.1841, Found 531.1872.
Synthesis of 4-[[[(1S)-2'-(Diphenylphosphino)-3-phenyl[1,1'-binaphthalen]-2-yl]oxy]-,(1R)-dinaptho[2,1-d;1',2'-f][1,3,2]dioxaphosphepin (15)

To a 50 mL Schlenk flask was added 2'-diphenylphosphanyl-3-phenyl-[1,1']binaphthalen-2-ol 28 (0.53 g, 1 mmol). The flask was degassed and charged with nitrogen. Degassed THF (5 mL) was added. The resulting solution was cooled to -78 °C in a dry ice/acetone bath. To the cooled solution was added n-BuLi (0.44 mL 2.5 M solution in hexane, 0.52 mmol) dropwise at -78 °C. The resulting yellow solution was allowed to warm to room temperature. After stirring for 30 min at room temperature, the reaction mixture was recooled to -78 °C and (S)-1,1'-binaphthyl-2,2'-dioxochlorophosphine (0.385 g, 1.1 mmol) in THF (5 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc/NEt₃ 20:1:0.5, silica gel was pretreated with 5 % triethyl amine in hexane) to give the title ligand as a white solid (0.52 g, 75 %). [α]²⁰D = -193.6 (c 0.5, CH₂Cl₂); ¹H NMR (CD₂Cl₂, 300 MHz) δ: 8.18-8.02 (m, 3H), 7.90-7.82 (m, 3H), 7.78-7.60 (m, 7H), 7.55-7.02 (m, 18H), 6.99-6.93 (m,1H), 6.90-6.85 (m, 1H), 6.76 (d, J = 8.8Hz, 1H), 6.64-6.58 (m, 2H), 6.24 (d, J = 8.8Hz, 1H), 5.84 (d, J = 8.8Hz, 1H); ¹³C NMR (CD₂Cl₂, 75 MHz) δ: 148.07, 148.01, 147.02, 146.25, 146.17, 141.64, 141.19, 138.92, 137.88, 137.71, 137.06, 136.89, 135.79, 135.75, 134.53, 134.26,
Synthesis of Diphenyl-, (1S)-2′-(Diphenylphosphino)-3-phenyl[1,1′-binaphthalen]-2-yl Phosphinous Acid Ester (16)

To a 50 mL Schlenk flask was added 2′-diphenylphosphanyl-3-phenyl-[1,1′]binaphthalen-2-ol 28 (0.212 g, 0.4 mmol). The flask was degassed and charged with nitrogen. Degassed THF (10 mL) was added. The resulting solution was cooled to -78 °C in a dry ice/acetone bath. To the cooled solution was added n-BuLi (0.32 mL 1.6 M solution in hexane, 0.52 mmol) dropwise at -78 °C. The resulting yellow solution was allowed to warm to room temperature and stirred for 30 min at room temperature. The reaction mixture was cooled to -78 °C and chlorodiphenyl phosphine (0.11 mL, 0.6 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc/NEt₃ 20:1:0.5, silica gel was pretreated with 5 % triethyl amine in hexane) to give the title ligand as a white solid (0.2 g, 70 %). [α]^{20}_D = 73.0 (c 0.5, CH₂Cl₂); $^1$H NMR (CD₂Cl₂, 300 MHz) δ: 7.94 (s, 1H), 7.88 (d, $J = 8.1$ Hz, 1H), 7.69 (d, $J = 8.5$ Hz, 1H), 7.62-7.56 (m, 3H), 133.41, 133.17, 132.75, 131.31, 131.27, 131.07, 130.26, 129.48, 128.93, 128.78, 128.71, 128.61, 128.51, 128.41, 128.21, 128.13, 128.05, 128.92, 127.47, 127.05, 126.99, 126.57, 126.53, 126.41, 126.24, 125.69, 125.31, 125.13, 122.25; $^{31}$P NMR (CD₂Cl₂, 146 MHz) δ:145.2 (d, $J_{pp} = 21.1$ Hz), -12.9 (d, $J_{pp} = 21.1$); HRMS calculated for C₅₈H₃₉O₃P₂ (MH⁺): 845.2369, Found 845.2369.
7.49-7.44 (m, 6H), 7.36-6.85 (m, 17H), 6.79-6.67 (m, 5H), 6.55-6.48 (m, 2H); $^{13}$C NMR (CD$_2$Cl$_2$, 75 MHz) $\delta$: 152.66, 152.55, 142.60, 142.43, 142.39, 142.15, 141.97, 141.89, 138.71, 138.67, 138.54, 138.13, 135.91, 134.80, 134.53, 133.98, 133.71, 133.44, 131.18, 130.65, 129.63, 129.37, 129.30, 129.04, 128.96, 128.86, 128.77, 128.68, 128.45, 128.36, 128.27, 127.95, 127.84, 127.73, 127.60, 127.50, 127.49, 126.77, 126.33, 125.16 ppm; $^{31}$P NMR (CD$_2$Cl$_2$, 146 MHz) $\delta$: 114.2 (d, $J_{pp} = 5.2$Hz), -12.4(d, $J_{pp} = 4.7$Hz) ; HRMS calculated for C$_{50}$H$_{37}$OP$_2$ (MH$^+$): 715.2289, Found 715.2314.

**General Procedure for the Asymmetric Hydrogenation of $\alpha$-Dehydroamino Acid Derivatives with Rhodium-$o$-Binaphos Catalyst**

In a glove box filled with nitrogen, to a 20 mL vial was added $o$-Binaphos (10 mg, 0.012 mmol) and [Rh(COD)]PF$_6$ (5.9 mg, 0.012 mmol ), followed by THF (15 mL). The resulting yellow solution was stirred for 10 min and distributed into 10 reaction vials precharged with solutions of $\alpha$-dehydroamino acid derivatives (1.2 mmol) in THF (1.5 mL). The reaction vials was transferred into an autoclave and taken out of the glove box. The autoclave was charged with hydrogen (15 psi) and the hydrogenation reaction was performed at room temperature for 12 h. Then hydrogen pressure was released carefully in a well ventilated hood. The reaction mixture was passed through a silica gel plug and flushed with ether to remove the catalyst. The enantiomeric excess was determined by chiral GC (Chirasil-VAL III FSOT) analysis.

**Determination of the Enantiomeric Excesses of the Hydrogenation Products**

For an amino acid esters product, a small amount of sample was subjected directly to chiral GC analysis to determine the enantiomeric excess.
For an amino acid product, the product was dissolved in methanol (1 mL) and catalytic amount of aqueous concentrated HCl was added. The resulting mixture was stirred at room temperature for 4 h. After usual work up, the resulting methyl ester was subjected to chiral GC analysis to determine the enantiomeric excesses.

The absolute configurations of products were determined by comparing the sign of optical rotation or the elution order of the major enantiomers with the reported data.
References


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PATENTS