DEVELOPMENT IN PHOSPHORUS LIGANDS AND THEIR APPLICATIONS

IN RHODIUM-CATALYZED REACTIONS

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ABSTRACT OF THE DISSERTATION

DEVELOPMENT IN PHOSPHORUS LIGAND AND ITS APPLICATION IN

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Transition-metal-catalyzed reactions have become powerful tools in the production of pharmaceuticals and fine chemicals. In the past decades, asymmetric catalysis, especially chiral rhodium catalysts, hold an increasing role of efficiently building up chirality. In this dissertation, we will focus on the development of several rhodium phosphorus catalysts and their applications in hydroformylation and asymmetric hydrogenation reactions.

Chapter I outlined the development of a new family of sterrically rigid hybrid phosphine-phosphoramidite ligands. The new catalyst system shows excellent compatibility versus styrene, vinyl acetate, allyl cyanide and their derivatives. The relationship between the enantioselectivity and the substituent on ligands is investigated by systematic variation on the ligand structures.

In chapter II, further application of phosphine-phosphoramidite ligands in asymmetric hydroformylation of *N*-allylamides and *N*-allylsulfonamides provides a new approach to chiral β_2-amino aldehydes, acids, and alcohols for pharmaceutical and synthetic chemistry. Up to 99% ee and 9700 turnovers stands as the best result achieved in this type of hydroformylation reaction.

Chapter III focuses on the synthesis of a series of aryl substituted dihydropyrroles via this hydroformylation. The significant improvement in reactivity and chemoselectivity suggests a potential application in building large heterocycles in an atom efficient fashion.

In chapter IV, I report a successful monodentate phosphoramidite ligand for the catalytic asymmetric hydrogenation of dehydroamino esters. The easy modulared structure allowed us to further expand the scope of the ligand.

ACKNOWLEDGEMENTS

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Chapter 1

Introduction

1.1 Introduction to Rhodium-Catalyzed Hydroformylation

1.1.1 Background

Hydroformylation is the reaction with the addition of carbon monoxide and hydrogen atom to carbon-carbon double bond (Scheme 1-1).[1] It was first discovered by Otto Roelen in 1938 using cobalt catalyst.[2] Although this cobalt based reaction usually accompanied with harsh conditions and low reactivity, cobalt catalysts dominated industrial processes at its early ages. In 1960's, the first rhodium-catalyzed hydroformylation was reported by Wilkinson and co-workers.[3] Because Rh catalysts could control hydroformylation reaction at mild conditions with much higher activity and selectivity compared to cobalt catalysts, it later replaced cobalt catalysts since 1970's.[4] Nowadays, hydroformylation has become one of the most important homogenous catalysis processes in industry. Over 9 million tons of oxo products are produced based on rhodium-catalyzed hydroformylation each year.

R= → (Catalyst, CO/H$_2$) → branched *–CHO + Linear R–CHO
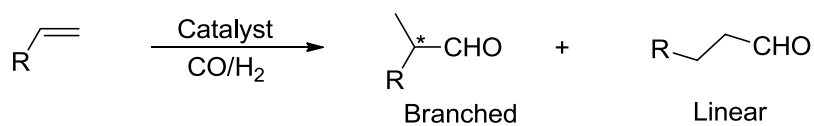
Scheme 1-1 Hydroformylation Reaction.

1.1.2 Mechanism for Rhodium-Catalyzed Hydroformylation

The widely accepted mechanism of hydroformylation reaction was proposed by Breslow and Heck in the early 1960s.[1f, 5] The so-called dissociative mechanism was first proposed based on cobalt-catalyzed hydroformylation which could also be applied to rhodium complex catalyzed hydroformylation (Scheme 1-2).
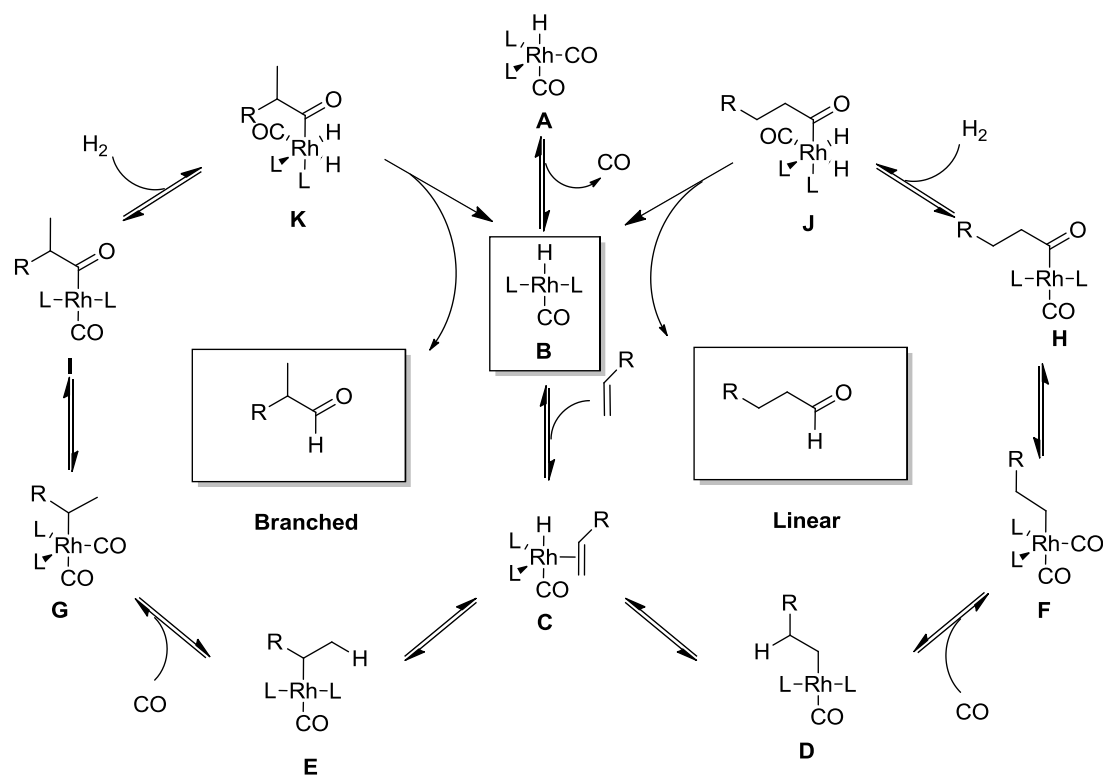
***Scheme 1-2* Mechanism for Rhodium-catalyzed Hydroformylation.**

In this mechanism, the rhodium precursor first combines with the phosphine ligands in the presence of CO and H_2 to form a trigonal bipyramidal intermediate **A**. The dissociation of one carbon monoxide leads to a coordinatively unsaturated 16e unsaturated compound **B** and the main catalytic cycle will start from this active species **B**. Coordination of the olefin to the rhodium center will generates olefin complex **C**, which can undergoes subsequent olefin insertion at either end of the olefin to provide intermediate **D** (leading to linear product) and **E** (leading to linear products). Next, trigonal bipyramidal complexes **F** and **G** are formed

respectively via coordination of another carbon monoxide, which are followed by migratory insertion of the alkyl group to one of the coordinated carbon monoxides that yields tetragonal acyl complexes **H** and **I**. Finally, oxidative addition of hydrogen followed by reductive elimination from **J** and **K** affords the linear aldehyde **L** and the branched aldehyde **M** and regenerates the catalytically active species **B**.

1.1.3 Chiral Phosphorus Ligands for Rhodium-Catalyzed Asymmetric Hydroformylation

Asymmetric hydroformylation is a carbon-carbon bond formation of great importance. Enantiomerically pure aldehydes prepared by asymmetric hydroformylation are versatile building blocks leading to various useful chiral amines, alcohols, acids, olefins, etc.[1, 6] For example, enantiomerically pure 2-arylpropanoic acids such as Ibuprofen, Naproxen and Ketoprofen, which are important nonsteroidal anti-inflammatory drugs, can be directly synthesized by oxidation of corresponding aldehydes derived from the asymmetric hydroformylation of vinylarenes.[6]

Despite the importance of hydroformylation in industry, in contrast to the well developed linear selective hydroformylation reaction, the asymmetric hydroformylation has not been studied extensively until the early 1990's. Major efforts in asymmetric hydroformylation were focused on the design and synthesis

of new chiral ligands, however, no ligands could afford enantioselectivities exceeding 60 % ee until 1992, when Babin and Whiteker at Union Carbide reported an important breakthrough.[7] The so called Chiraphite **1** (Figure 1-1) ligand was prepared from a chiral (2R,4R)-pentane-2, 4-diol backbone. It was the first successful diphosphite ligand that achieved over 90 % ee in the asymmetric hydroformylation of styrene under mild reaction conditions. It is believed that the bulky *t*-butyl groups at ortho-postions help to transfer chirality of the backbone to the non-chiral biphenyl moieties which dictate the outcome of high enantioselectivities.

This pioneering work encouraged a number of research groups investigating on Chiraphite **1** (Figure 1-1) related structures by introducing chiral backbone to diphosphite ligands. Chan and co-workers developed a series of spiro backboned chiral diphosphite ligands **2** and **3** from [4.4] nonane-1,6-diol for the asymmetric hydroformylation of styrene, however, only moderate results (up to 65% ee) have been obtained.[8]
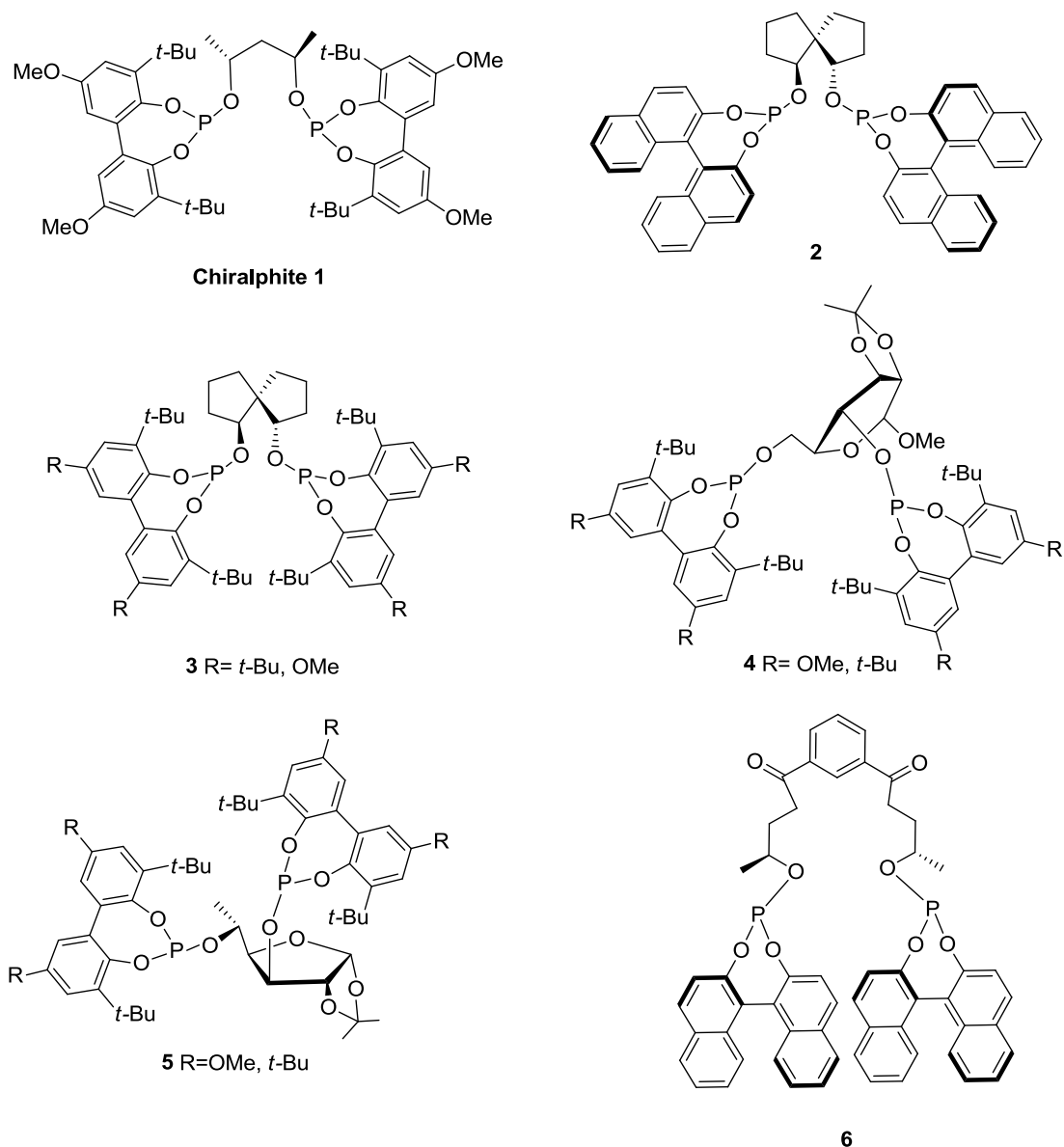
Figure 1-1 **Chiral Diphosphite Ligands for Asymmetric Hydroformylation.**

Chiral structures such as sugar scaffold have also drawn people's attention due to their high enantioselectivity and more importantly, their readily availability. Van Leeuwen and co-workers reported the first successful example of sugar-based

diphosphite ligand **4** (Figure 1-1) for asymmetric hydroformylation. Up to 65 % ee were reported for styrene derivatives.[9] Diéguez designed a new diphosphite ligand **5** bearing a furanoside backbone which achieved excellent enantioselectivities (up to 91% ee) towards styrene derivatives.[10]

Another interesting diphosphite ligand **6** (Figure 1-1) bearing a chiral macrocyclic backbone was developed by Freixa with a reported moderate enantioselectivity (up to 76 % ee) for the asymmetric hydroformylation of styrene.[11]

Kelliphite 7

Binophos 8

Biphemphos 9
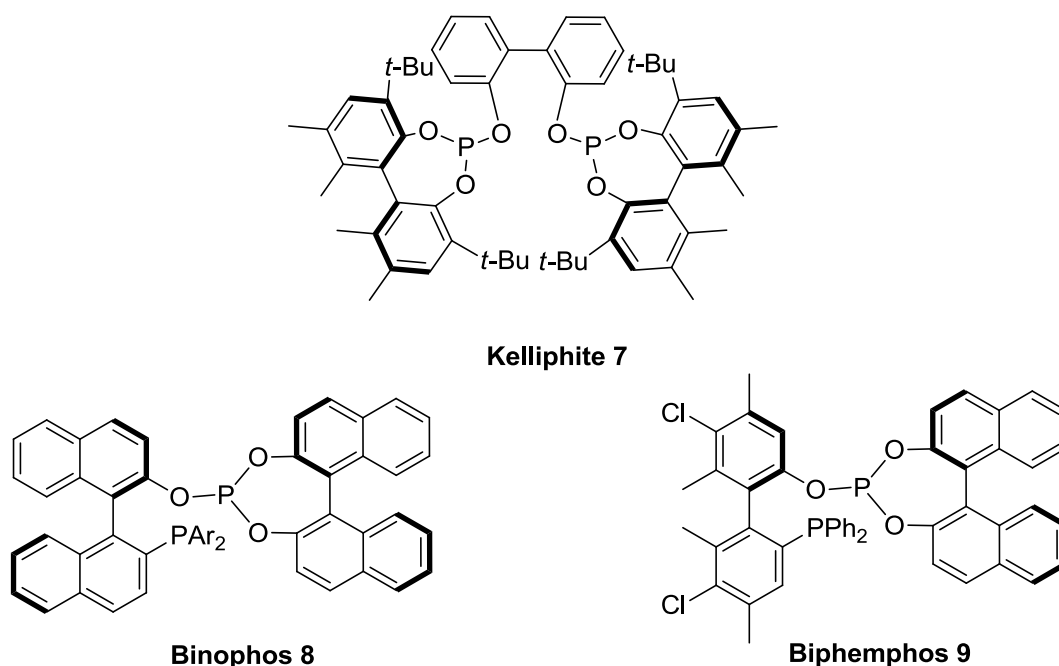
Figure 1-2 **Phosphite Ligands for Asymmetric Hydroformylation.**

Diphosphite ligands without chiral linker also showed success in asymmetric hydroformylation reactions. In 1992, Klosin and co-workers at Dow

Chemical reported a diphosphite ligand, known as Kelliphite **7** (Figure 1-2), with a non-chiral 2,2-biphenol backbone and chiral phosphite moieties.[11] The ligand was used in converting allyl cyanide to corresponding chiral aldehyde which can be further transformed into (*R*)-2-methyl-4-aminobutanol, a useful chiral building block for the drug synthesis. High enantioselectivity (80 % ee) and activity were obtained in this transformation by using Kelliphite **7**.

The major breakthrough of asymmetric hydroformylation was the development of Binophos **8**. In 1993, Takaya and Nozaki reported a hybrid phosphine-phosphite ligand based on the binaphthyl backbone.[12] The so called Binophos ligand (Figure 1-2) not only showed good compatibility towards a broad scope of substrates, but also bearing two different phosphorus atoms on the ligand moiety which is different from tranditional *C2* symmetric ligands. After investigating the ligand in the asymmetric hydroformylation of a variety of prochiral olefins, the ligand has been proven to be efficient for styrene derivatives and vinyl carboxylates (up to 94 % ee and 92 % ee has been achieved respectively). In the presence of CO and H_2, the ligand complexed with rhodium center to form a trigonal bipyramidal structure. In this trigonal bipyramidal rhodium complex, the phosphite is selectively located in the equatorial-axial coordination fashion. This important structural feature allowed researchers to further modify the structure of Binaphos **8** to improve the catalyst performance. Nozaki and co-workers later reported Biphemphos **9**,[13] a structurally closely related ligand bearing a chiral biphenyl backbone, which afforded very high

enantioselectivity comparable to Binaphos **8**. Also, by introducing substituent groups onto the 3,3'-position of Binaphos **8** or changing the phenyl groups on phosphorus into substituted aryl groups resulted in a slightly improved enantioselectivity.

10   **11**

12   **13**
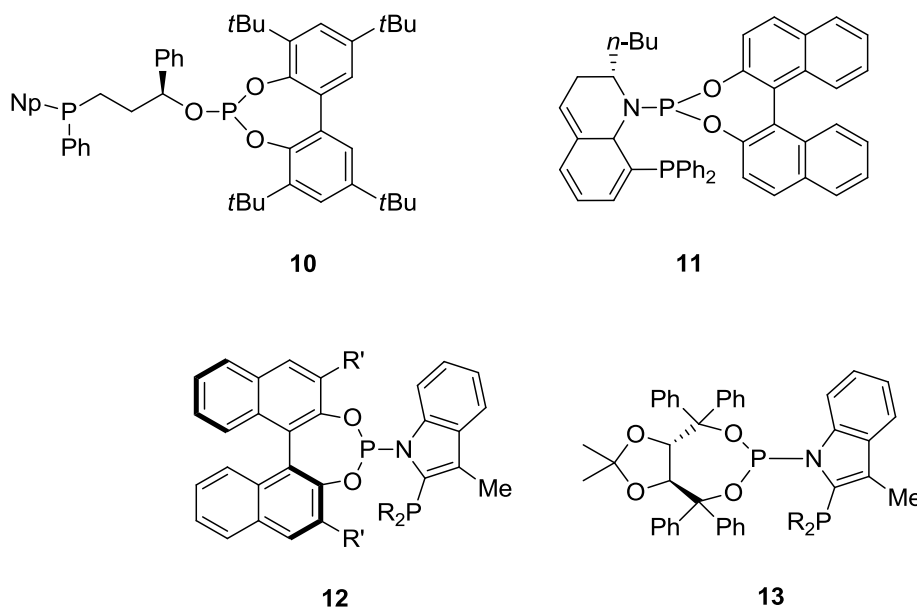
Figure 1-3 **Phosphite and Phosphine-phosphoramidite Ligands for Asymmetric Hydroformylation.**

Inspired by the excellent results achieved by Takaya and Nozaki, more hybrid ligands bearing different phosphorus environment have been developed. Van Leeuwen reported phosphine-phosphite **10** (Figure 1-3), a P-chiral/phosphite hybrid ligand, which achieved 63 % ee enantioselectivity in the asymmetric hydroformylation of styrene substrates.[14]

With the breakthrough success of phosphite ligands, a new class of phosphinephosphoramidite ligands was also well studied. The

1,2-dihydroquinoline based QUINAPhos **11** (Figure 1-3) which developed in Leitner's lab,[15] showed good enantioselectivity (up to 74 % ee) in the asymmetric hydroformylation of styrene. Lately, Reek group reported a new family of phosphine-phosphoramidite ligands, IndolPhos ligands **12** and **13** (Figure 1-3) started from Binol and Taddol, respectively.[16] IndolPhos ligands afforded good enantioselectivities (up to 74 % ee) in the asymmetric hydroformylation of styrene, vinyl acetate, and allyl cyanide.

Another class of successful phosphorus ligands for rhodium-catalyzed hydroformylation is based on bisphosphacyclic ligands, as shown in Figure 1-4. C_2-Symmetric bisphospholane-type ligands, (S,S)-Esphos **14** developed by Wills et al.,[17] provide high enantioselectivity (up to 90 % ee) for asymmetric hydroformylation of vinyl acetate but are unselective for styrene. Landis and co-workers developed a new family of bis-3,4-diazaphospholane ligands **16** and achieved good to excellent enantioselectivities in the rhodium-catalyzed asymmetric hydroformylation of three standard substrates (up to 82 % ee, 96 % ee and 87 % ee for styrene, vinyl acetate and allyl cynide, respectively).[18]
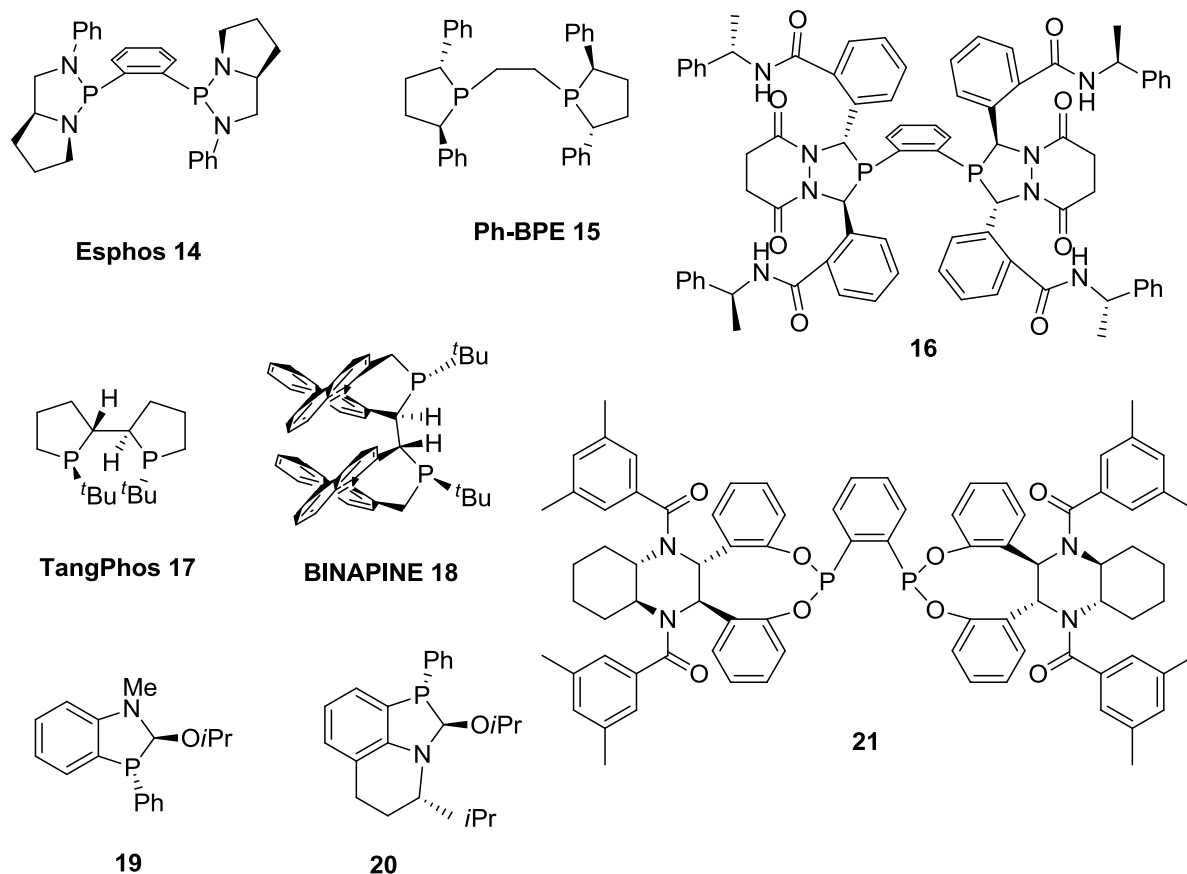
Figure 1-4 Recent Ligands for Asymmetric Hydroformylation.

Inspired by the excellent enantiosectivities of bis-3,4-diazaphospholanes **16**, Klosin and co-workers investigated a variety of bisphosphacyclic ligands in asymmetric hydroformylation. (R,R)-Ph-BPE **15** was found to be an excellent ligand for asymmetric hydroformylation and up to 94 %, 82 % and 90 % ee were obtained in the hydroformylation of styrene, vinyl acetate and allyl cyanide, respectively.[19] They also found that several P-chiral bisphospholane ligands, originally developed for asymmetric hydrogenation by the Zhang group, provided

very high enantioselectivities in asymmetric hydroformylation. For the three standard substrate, (S,S,R,R)-TangPhos **17** achieved up to 90 % ee, 93 % ee and 83 % ee, respectively, while (S,R)-BINAPINE **18** obtained up to 94 % ee, 94 % ee and 87 % ee, respectively.[20] Tan and co-workers introduced the direct substrate binding groups to a new class of chiral mono-dentate phosphorus ligands **19** and **20**.[21] The concept helped transforming several challenging olefins into corresponding chiral aldehydes. Recently, a class of C_2-symmetric bidentate phosphonite ligands **21**, reported by Ding's group, also displayed high selectivity (up to 79 % ee, 91 % ee and 79 % ee for standard substrates, respectively) in rhodium-catalyzed asymmetric hydroformylation.[22]

1.2 Introduction of Mono-dentate Phosphorus Ligands in Asymmetric Hydrogenation

1.2.1 Backgroud

Asymmetric hydrogenation is a highly efficient, environmental friendly and cost effective method for the catalytic reduction of prochiral alkenes, ketones, and imines into the corresponding chiral products.[23] It remains one of the most investigated areas in homogeneous catalysis.[24] Hundreds of catalytic systems have been developed after its first breakthrough with the work of Knowles,[25] Horner, [26] and Kagan.[27] The most successful development in asymmetric hydrogenation history came from Noyori and Takaya in the use of the ligand BINAP.[28] In 1991, Burk reported a steric rigid electrondonating bis(phospholane),[29] named DuPhos which allowed versatile functional olefins hydrogenated under this transformation. Nowadays, asymmetric hydrogenation still remains one of the most active research areas, especially in the development of catalysts with increased substrate scope.

Development of Chiral Ligands
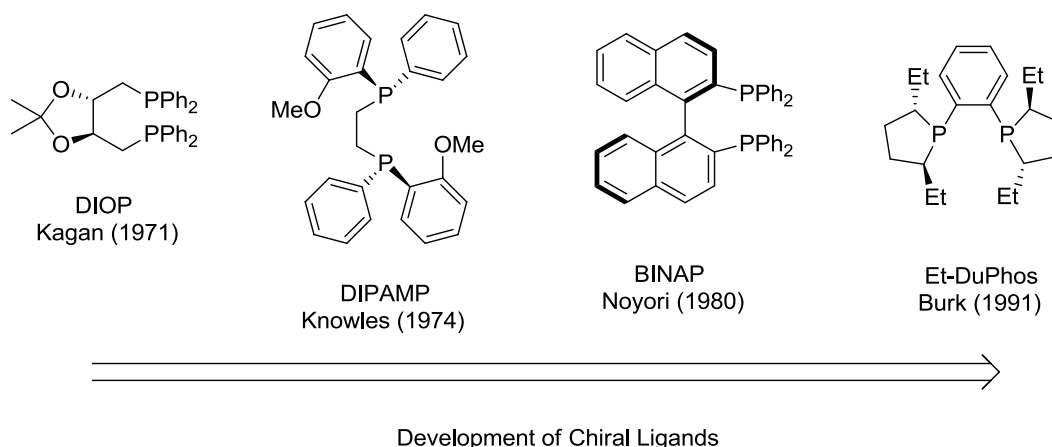
Figure 1-5 **Development of Chiral Ligands for Asymmetric Hydrogenation.**

1.2.2 Mono-dentate Phosporus Ligands for Asymmetric Hydrogenation

Despite the tremendous accomplishments of chelating bidentate ligand, mono-dentate phosphines also appear to attract people's attention by delivering promising results in asymmetric hydrogenation. Feringa and co-workers have successfully developed a new class of monophosphorus ligands based on BINOL and Taddol moieties.[30] These easily synthesized ligands exhibited up to 99% ee in the asymmetric hydrogenation of protected dehydroamino acids and aryl enamides. Inspired by their work, many synthetic groups have developed new classes of ligands (**22-30**),[31] including SIPHOS,[32] which possess a more rigid spiro backbones compared to BINOL.
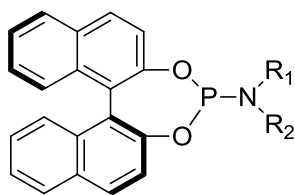
Monophos: $R^1= R^2=$ Me
22: $R^1=$ Bn, $R^2=$ Me
23: $R^1=$ (R)-MeCHPh, $R^2=$ H
24: $R^1= R^2=$ Et
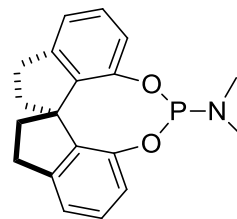
SIPHOS
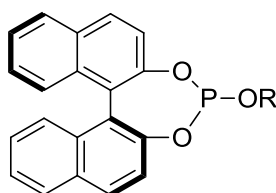
(S)-**25**: R= *i*Pr
(S)-**26**: R= Ph
(S)-(R)-**27**: R= (R)-CH(Me)Ph
(S)-(S)-**28**: R= (S)-CH(CH$_2$OMe)Ph
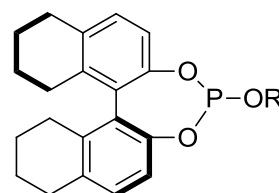
(S)-**29**: R= CH(CH$_3$)Ph
(S)-**30**: R= CH(CH$_3$)$_2$

Figure 1-6 **Monodentate Ligands.**

Monodentate phosphorus ligands have the advantage of easier syntheses and tuning as compared with their bidentate counterparts. Although more and more efficient chiral monodentate phosphorus ligands were developed and some of them have shown high chiral inducements in the rhodium-catalyzed asymmetric hydrogenation of enamides, these monodentate chiral phosphorus ligands were all based on binaphthyl or spirobiindane backbones. Chiral phosphorous bidentate ligands based on biaryl backbone are well known for their high efficiency in transition metal catalyzed asymmetric transformations. However, chiral monodentate phosphorous ligands bearing biaryl backbone are not very well developed. It is high desire to design and synthesize a new class of monodentate

phosphorus ligands using birayl backbone.

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Chapter 2

Synthesis Phosphine-phosphoramidite Ligands and Their Applications in Asymmetric Hydroformylation

2.1 Introduction

Hydroformylation is a transformation that generates aldehydes directly from alkenes in the presence of carbon monoxide and hydrogen gas (Scheme 2-1).[1] It provides an atom economic protocol to convert prochiral olefins into enantiomerically pure aldehydes. The wide application in industry has drawn much of attention for chemist to investigate the nature of the reaction. Million tons of oxo products are produced based on rhodium-catalyzed hydroformylation each year and it is regarded as the world largest industrially homogeneous catalytic process.
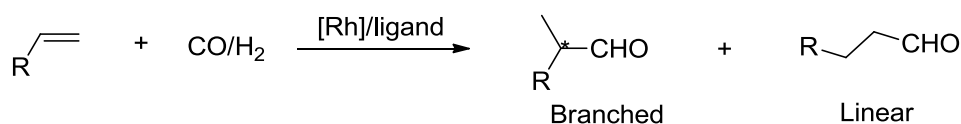
Scheme 2-1 **Hydroformylation Reaction.**

As we know, aldehyde bears a versatile functionality which can be easily converted into derivate products such as alcohol, acid and amine.[2, 3] Therefore, asymmetric hydroformylation (AHF) in particularly, has become an important research area in organometallic chemistry due to its ability to generate chiral aldehydes that could be used as precursors for synthesizing a variety of biologically active products and fine chemicals.
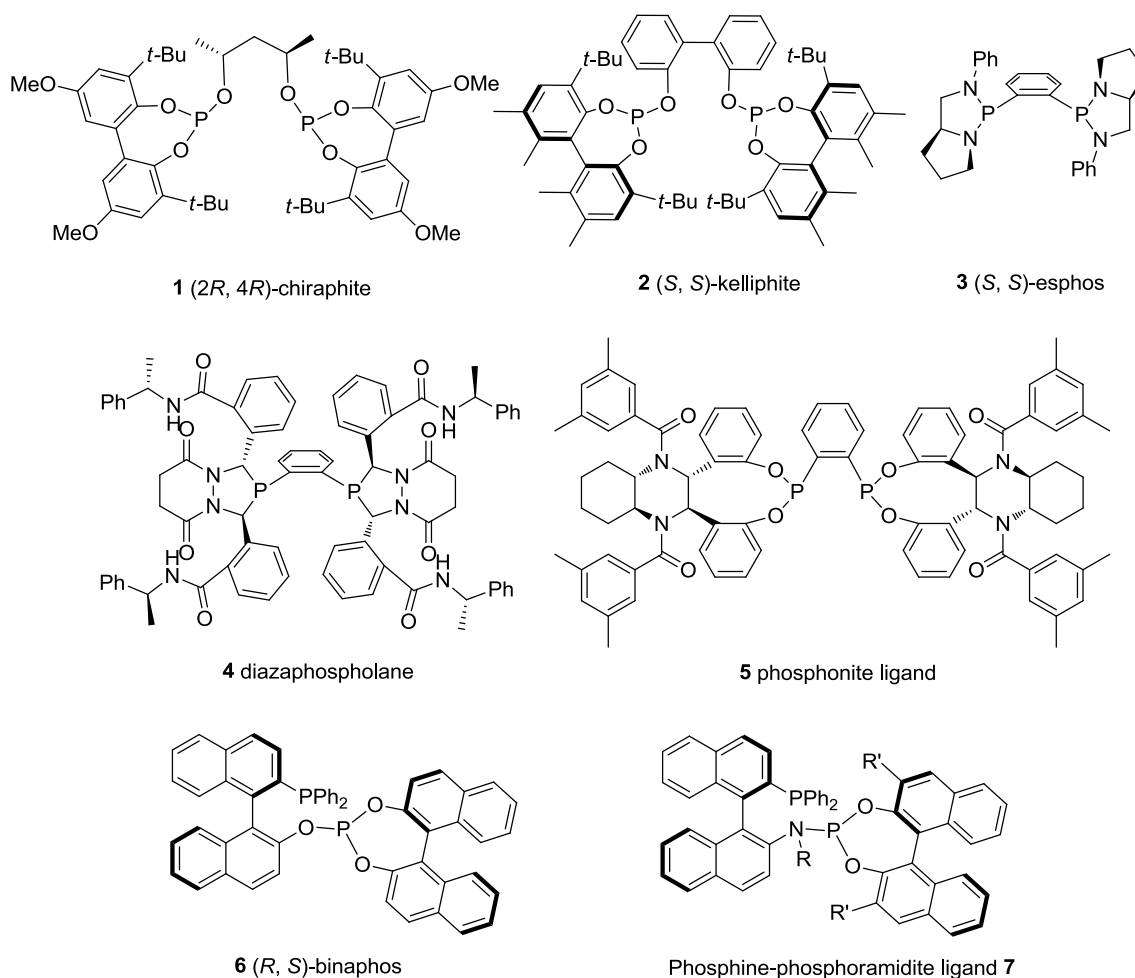
Figure 2-1 **Recent examples of chiral ligands for AHF reactions.**

The asymmetric hydroformylation reaction was carried out at high temperature and pressure to achieve good activity, however, harsh reaction conditions are usually accompanied with low enantioselectivity. Although new ligands have been designed to provide chiral aldehydes at considerable high temperatures without sacrificing their selectivities, only a few successful examples were documented in the past two decades (Figure 2-1).

(2R, 4R)-chiraphite **1** and (S, S)-kelliphite **2** were early examples were proved to be active in AHF reactions.[4,5] These bidentate phosphite ligands show high enantioselectivity (nearly 90 % ee) for the hydroformylation of styrene, allyl cyanide [75 % ee, b/l (branched/linear ratio) = 16] and vinyl acetate (88 % ee, b/l = 56) at low temperature. Another successful ligand is C_2-symmetric bisphospholane, known as (S, S)-Esphos **3**, was reported by Wills.[6] It guaranteed a high selectivity for vinyl acetate (90 % ee, b/l =16), but nearly no selectivity for styrene. Recent breakthrough on AHF came from Landis's research group.[7] A new class of diazaphospholane ligand **4** and its analogues showed excellent compatibility in the AHF of styrene, vinyl acetate and allyl cyanide with high enantioselectivities (82, 96, 87 % ee, respectively) and regioselectivities (b/l = 7, 4, 37, respectively) at higher temperature. Recently, Ding's group reported a new C_2-symmetric phosphonite ligands, which also provides promising results in Rh-catalyzed AHF of the above terminal olefins.[8] Despite the achievement in recent years, the most attractive development in this area was made in 1993, when Takaya and Nozaki reported (R,S)-binaphos (**6**),[9] a hybrid ligands which offered

high enantioselectivities in the AHF of a variety of substrates (up to 94 % ee, b/l = 7.3 for styrene). The unique C_1-symmetric design allowed the ligand bear two different phosphorus in the structure. However, with binaphos as the ligand, chiral aldehyde products prone to undergo racemization as the reaction time elaborates.[9] It still remains high desire to develop new ligands with better tolerance for asymmetric hydroformylation.

In this chapter, the design and synthesis of a new hybrid phosphine-phosphoramidite ligand, YanPhos **7**, as well as its application in Rh catalyzed AHF of styrene, vinyl acetate, allyl cyanide and their derivatives, will be discussed (as shown in Figure 2-1). The relationship between the ligand structure and their control of enantioselectivity will be extensively studied.

2.2 Results and Discussion

2.2.1 Synthesis of Phosphine-phosphoramidite Ligands

Although our design is structurely related to binaphos, there are significant differences between binaphos and our new phosphine-phosphoramidite ligands. It is believed that by introducing a nitrogen group to the structure, a more electron-donating property could be observed in the new phosphine-phosphoramidite ligands due to the difference in the electronegativity of nitrogen (3.04) and oxygen (3.44). Sterically, the N substituent on the

phosphoramidite group can create a more closed chiral pocket in the active catalytic complex than that of binaphos, based on the models from CAChe MM2 calculation.[10]

We synthesized ligands **7a**, **7b** with (S)-BINOL (1, 1'-bi-2-naphthol) **8** as starting material (Scheme 2-2). Ditriflate **9** was obtained in 95 % yield by reacting triflic anhydride under basic conditions, followed by Hayashi' procedure,[11] the phosphorous was introduced to the backbone which gave 95 % yield of (S)-**10** without racemization. The reaction was carried out in the presence of diphenylphosphine oxide, catalytic amount of palladium diacetate and 1,4-bis(diphenylphosphino)butane (dppb) in dimethyl sulfoxide at 120 ℃. (S)-**10** was then reacted with potassium cyanide in the presence of nickel bromide as a catalyst and activated zinc powder afforded (S)-**11**, which was quickly oxidized into amide (S)-**12** with hydrogen peroxide.[12] Hofmann rearrangement was used in the next step to generate carbamate (S)-**13** in 83 % yield, which was directly reduced by borane to afford phosphine-amine (S)-**14a** with N-methyl group. On the other hand, alkaline hydrolysis of (S)-**13**, followed by acylation with acetyl chloride or benzoyl chloride and then borane reduction, afforded phosphine-amine (S)-**14b** and the (S)-**14c** with N-ethyl and N-benzyl substituents, respectively. Lastly, the two fragments, (S)-**14** and corresponding phosphorochloridite was connected by using n-BuLi as deprotonation reagent to get the desired ligand (S, R)-**7a-f** as air-stable solids.

Scheme 2-2 Synthetic route of Phosphine-phosphoramidite Ligands (S,R)-7a-f.

2.2.2 Optimization of Rh-Catalyzed Asymmetric Hydroformylation of Styrene with (R,S)-7b.

Ligand (R,S)-**7b** and styrene were selected as representative ligand and substrate to optimize the Rh-catalyzed asymmetric hydroformylation reaction. The catalyst was prepared in situ by mixing $Rh(acac)(CO)_2$ with YanPhos at certain ratios. The reactions were performed using 0.1 mol % of catalyst loading and 1:1 CO/H_2 gas.

The ligand metal ratio was first examined. As shown in Table 2-1, entries 1-4, we found that increasing the ligand/Rh ratio could significantly improve both regioselectivity (up to 7.3) and enantioselectivity (up to 98 % ee) with a peak at 4:1 ratio, further increasing the ratio did not result in improvement.

Table 2-1 **Optimization of Rh-Catalyzed Asymmetric Hydroformylation of Styrene with (R,S)-7b.**[a]

Entry	**7b**/Rh	T $^{\circ}$C	Solvent	CO/H_2(atm)	Conv.(%)[b]	b/l	ee. (%)[c]
1	1/1	60	Benzene	10/10	99	3.0	21
2	2/1	60	Benzene	10/10	99	5.7	54
3	6/1	60	Benzene	10/10	99	7.3	98
4	4/1	60	Benzene	10/10	99	7.3	98
5	4/1	60	Toluene	10/10	99	7.2	98
6	4/1	60	THF	10/10	95	7.3	78

7	4/1	60	EtOAc	10/10	98	8.1	84
8	4/1	60	CH_2Cl_2	10/10	93	10.1	97
9	4/1	60	Toluene	20/20	91	8	98
10	4/1	60	Toluene	30/30	83	7.3	98
11	4/1	40	Toluene	10/10	25	10.1	99
12	4/1	80	Toluene	10/10	99	5.1	81
13[d]	4/1	60	Toluene	10/10	87	8.1	99
14[e]	4/1	60	Toluene	10/10	99	7.3	97

[a]All reactions were carried out with substrate/Rh =1000. [b] Conversions and branchedlinear ratio (b/l) were determined on the basis of ^{1}H NMR. [c] Determined by converting the aldehyde to the corresponding alcohol with $NaBH_4$ followed by GC analysis (Supelco's Beta Dex 225).[d] The reaction was carried out for 12h. [e] The reaction was carried out for 36h.

Nonpolar solvents, such as toluene and benzene, offered best enantioselectivities (Table 2-1, entries 4-8) among all regular solvent. The best temperature for this reaction is 60 ℃ where full conversion and 98 % ee were achieved. As expected, increasing reaction temperature will led to lower ee values (Table 2-1, entries 1, 11 and 12). Up to 99 % ee was obtained when the reaction was lowered to 40 ℃ with 25 % conversion, while the ee value dropped to 81 % at 80 ℃.

The effect of syngas pressure was not obvious on the enantioselectivity but the reactivity would drop significantly at higher pressure (Table 2-1, entries 3, 9 and 10). It is mainly because the high concentration of CO would push the equilibrium of CO coordination to Rh centre towards unreactive carbonyl bound

Rh species. Elongated reaction time only slightly affected the enantioselectivity (Table 2-1, entries 3, 13 and 14) which suggested less racemization of the Rh/**7b** catalyzed hydroformylation compared to that of binaphos. After screening reaction conditions, Entry 5 in Table 2-1 was selected as the optimized reaction condition with a ligand/Rh ration of 4:1, 60 ℃, CO/H$_2$= 10/10, 24h and toluene as solvent.

With the optimized reaction condition in hand, we used styrene **11**, vinyl acetate **12** and allyl cyanide **13** as standard substrate to further investigate the structure-selectivity relationship of phosphine-phosphoramidite ligands.

2.2.3 Relationship Between Ligand and Hydroformylation Reaction

The effect of the N-substituent to the ligand selectivity was tested by comparing the performance of ligand **7a**, **7b** and **7c** (Table 2-2, entries 1-3). Under the same reaction condition, increasing the steric hinderence of N-substituent from methyl to benzyl group slightly improved the regioselectivity and decreased the enantioselectivity with N-Ethyl substituted ligand, (S,R)-**7b**, provided the best enantioselectivities (98 % ee for styrene and 96 % ee for vinyl acetate (Table 2-2, entries 2). N-Methyl substituted ligand, (S,R)-**7a** gave slightly lower regio- and enantioselectivities to all substrates than ligand (S, R)-**7b** (Table 2-2, entries 1). Similarly, N-benzyl substituted ligand, (S,R)-**7c** didn't show much improvement towards regio- and enantioselectivities, although it give a slightly higher

regioselectivities for allyl cyanide and vinly acetate (Table 2-2, entries 3). It is note that the variation of N-substituent does not have direct influence on the reactivities and selectivities of phosphine-phosphoramidite ligands.

As expected, the ligand (R,S)-**7b** which is the enantiomer of ligand (S,R)-**7b** showed exactly same regio- and enantioselectivities towards all three substrates, except only the contrary absolute configuration of the products (Table 2-2, entries 2 and 4). To our interest, we investigated the steric effect of the phosphite part to the regio- and enantioselectivities of phosphine-phosphoramidite ligands. Although binaphos bearing the two methyl groups on the 3,3'-position of the binaphthyl moitey was reported to have higher reactivity and enantioselectivity compared to the original design, similar influence was not observed on ligand (R,S)-**7d** (Table 2-2, entries 4 and 5). Depite the higher regioselectivities for styrene and vinyl acetate (b/l = 8.0 and 65.2 respectively), a decreased reactivity and ee values suggested the reaction favor a less hindered phosphate stie. As expected, a more steric bulky phosphoramidite fragment (R,S)-**7e** led to a much less effective enantiomeric control with only moderate ee values for all three substrates (66, 65, and 65 %, respectively, Table 2-2, entry 6). However, an improvement in regioselectivity for styrene (b/l = 27.6) revealed that an increased steric demand with phosphate part would led to more branch product. Lastly, (R)-**7f** was prepared to investigate the role of the chirality of phosphoramidite unit. Surprisingly, the loss of one chiral center had no effect on the enantioselectivity (75, 66 and 69 % respectively, Table 2-2, entry 7).[9] It is noteworth that ligand

(R)-**7f** afforded the highest regioselectivity (b/l = 56.6), which to our best knowledge, is the best result in this reaction.

***Table 2-2* Rh-catalyzed AHF of Styrene, Vinyl Acetate and Allyl Cyanide with Phosphine-phosphoramidite Ligands.[a]**

$$R\!\!=\!\!\text{=} + CO/H_2 \xrightarrow[\text{Toluene}]{Rh(acac)(CO)_2/\textbf{L}} R\overset{*}{\underset{}{\diagdown}}\!\!-CHO + R\diagup\!\!\!\diagup CHO$$

11: R = Ph   **14**: R = Ph   **17**: R = Ph
12: R = AcO   **15**: R = AcO   **18**: R = AcO
13: R = CNCH$_2$ **16**: R = CNCH$_2$ **19**: R = CNCH$_2$

Entry	Ligand	**11** Conv.[%][b]	b/l[b]	ee[%][b]	**12** AcO Conv.[%][b]	b/l[b]	ee[%][b]	**13** NC Conv.[%][b]	b/l[b]	ee[%][c]
1	(S,R)-**7a**	99(24)[d]	6.6	97(S)	76	12.1	95(R)	97	3.8	96(S)
2	(S,R)-**7b**	99(22)[d]	**7.2**	**98(S)**	**76**	**14.0**	**96(R)**	**99**	**4.0**	**96(S)**
3	(S,R)-**7c**	99(22)[d]	7.1	95(S)	77	16.5	95(R)	99	4.1	93(S)
4	(R,S)-**7b**	99(22)[d]	**7.2**	**98(R)**	**76**	**13.5**	**96(S)**	**99**	**4.0**	**96(R)**
5	(R,S)-**7d**	96(13)[d]	8.0	91(R)	69	65.2	84(S)	89	3.0	90(R)
6	(R,S)-**7e**	99(27)[d]	27.6	66(R)	88	22.9	65(S)	95	2.5	65(R)
7	(R)-**7f**	99(29)[d]	56.6	75(R)	95	7.5	66(S)	98	2.9	69(R)

[a] All reactions were carried out at 60 °C in toluene with L:Rh = 4:1, substrate/Rh = 1000, 20 bar 1:1 CO/H$_2$, and 24 h reaction time for stryene, vinyl acetate and 18 h reaction time for allyl cyanide. [b] Conversions, branched/linear ratio and ee values

were determined by GC analysis (Supelco's Beta Dex 225). [c] Determined by converting the aldehyde to the corresponding acid and then reacting with aniline to afford corresponding amide followed by HPLC analysis. [d] The number in parentheses represents the conversion of a 3 h reaction.

In order to investigate the effect of ligand structure to their catalytic activities, we applied ligands **7a-f** in the AHF of styrene with 3 h reaction time (as shown in parentheses in Table 2-2). It was found that the N-substituents did not influence the ligand activity very much. The conversions of styrene with ligand **7a-c** were 24, 22 and 22 percent, respectively. The activity of **7d** was much slower than other ligands, which is possibly due to its poor solubility in toluene. Ligand **7e** and **7f** resulted in higher activity with 27 % and 29 % conversion, respectively.

2.2.4 Proposed Mechanism of Ligand 7 in Asymmetric Hydroformylation

Takaya and co-workers revealed a single trigonal bypyramidal complex Rh[(R,S)-binaphos)H(CO)$_2$] exists in the reaction cycle with both phosphines located at equatorial and axial position respectively. Since ligand (R,S)-**7b** is structurally related to (R,S)-binaphos ligand, to better understand our ligand in the catalytic cycle, a model for the transition states in asymmetric hydroformylation with ligand **7b** was proposed based on the mechanistic study conducted by Takaya and co-workers.

In this proposed mechanism, a trigonal bypyramidal complex **20** would be formed in the presence of Rh(CO)$_2$(acac) and ligand **7**. The dissociation of one

carbon monoxide leads to a coordinatively unsaturated 16e unsaturated compound **21**. The main catalytic cycle begin with the coordination of styrene preferably in the equatorial position thus affording hydrido olefin complex **22**. Subsequent olefin insertion into the Rh-H bond gives tetragonal alkyl rhodium complexes **23**. Next, acyl complexe **25** is formed via coordination of another carbon monoxide followed by migratory insertion. Lastly, oxidative addition of hydrogen will lead to tetragonal bipyramidal rhodium(II) complexes **26**, which undergoes reductive elimination to generate the 2-Phenylpropan-1-ol and the catalytically active species **21** (Scheme 2-3).
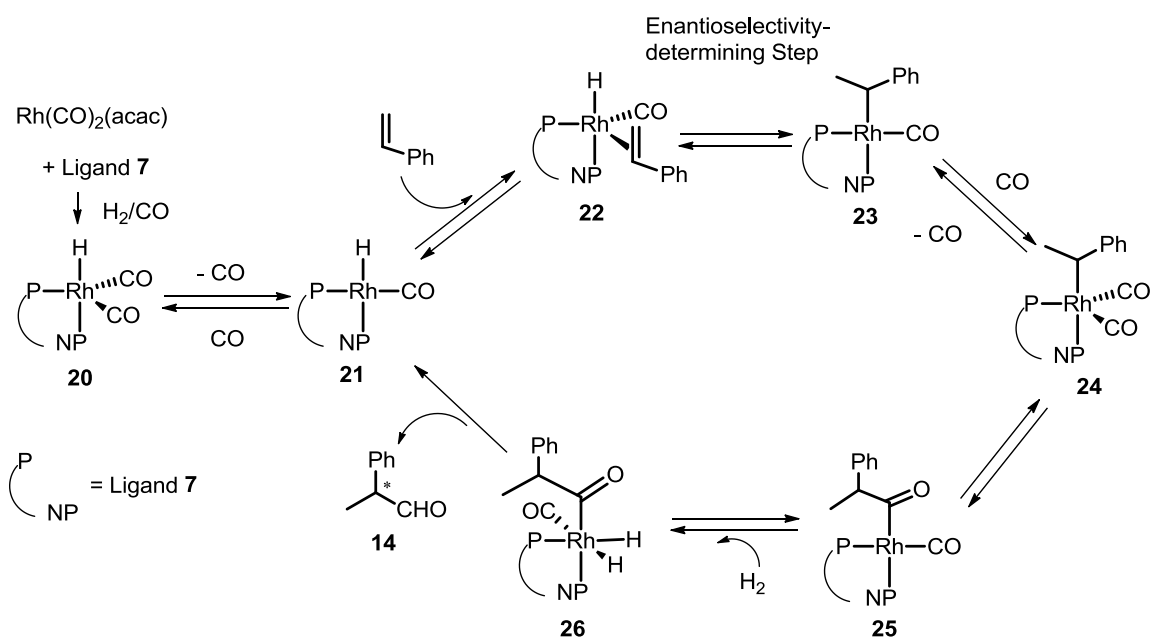
Scheme 2-3 **Proposed Catalytic Cycle for Rh/7 Catalyzed Asymmetric Hydroformylation.**

It is believed that the olefin insertion into the Rh-H bond to form rhodium complexes **23** is the enantioselectivity-determining step of the whole catalytic cycle. A semiquantitative theoretical model was proposed by Herrmann to help explain the stereo outcome of the reaction.[13] According to Herrmann's theory and CAChe MM2 calculation, we postulate the key intermediate of the enantioselectivity-determining step in the hydroformylation with our ligand (as shown in Scheme 2-4). Four possible transition states (TS I, II, III and IV, as shown in upper part of Scheme 2-4) are outlined to represent the olefin insertion step. In TS I and TS IV, a strong interaction between the phenyl ring of substrate and the ligand is easily observed. It enforces both TS I and TS IV to be less favored intermediate in the catalytic cycle when compared to a less hindered TS II and TS III. Both TS II and TS III allowed the olefin to approach from the same prochiral face which dictate the enantioselectivity of the insertion step, although both transition states possess different steric environment. In TS II, it is the naphthyl from the binol backbone to repell the phenyl ring, while it is the one from the phosphoramidite in TS III. Since the N atom stretches far away from both metal center and substrate in the model, the influence of N-substituent will be limited in the reaction, which help explained our experiment results. However, increasing the steric hinderence of naphthyl or phosphoramidite will make TS II and TS III less favorable and close up the gap between all four transition states. Herein, a decrease in enantioselectivity is observed when changing the phosphoramidite fragment of ligands.

TS I **TS II** **TS III** **TS IV**

VS *VS*

minor **major** **major** minor
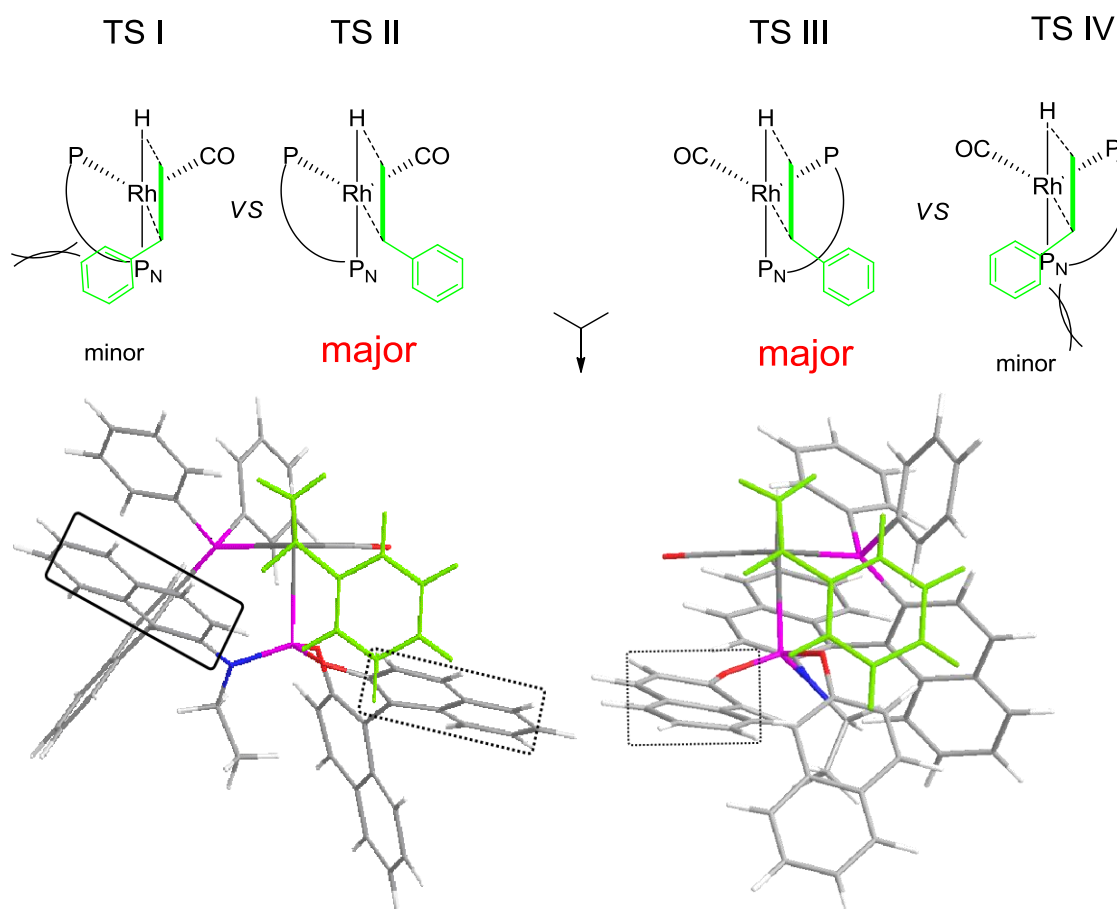
Scheme 2-4 **Proposed Catalytic Cycle for Rh/7 Catalyzed Asymmetric Hydroformylation.**

2.3 Conclusion

In summary, a series of hybrid phosphine-phosphoramidite ligands has been developed and systematically applied in Rh-catalyzed asymmetric hydroformylation of styrene, vinyl acetate, allyl cyanide and their derivatives with highly regio- and enantioselectivities under mild conditions. With ligand **7b**, 99 %

ee for styrene derivatives, 98 % ee for vinyl acetate derivatives and 96 % ee allyl cyanide were achieved, which represents the best result up to date. The relationship between the substituent and the enantioselectivity of the ligands was concluded, which was successfully rationalized by Herrmann's theoretical model with CAChe MM2 calculation. Further understanding of the origination of the selectivity of phosphine-phospharamidite ligands and their application in other metal-catalyzed transformations are in progress in our lab.

Experimental Section

General Methods: All reactions and manipulations that were sensitive to moisture or air were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise noted. Solvents were dried with standard procedures and degassed with N_2. Column chromatography was performed using 200-400 mesh silica gel supplied by Natland International Corp. Molecular mechanics calculations were carried out with CAChe[®] program (Fujitsu Ltd.). Thinlayer chromatography (TLC) was performed on EM reagents 0.25 mm silica 60-F plates. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ or CD_2Cl_2 on Bruker Avance 400 MHz spectrometers or Varian Mercury 500 MHz FT-NMR spectrometer. Optical rotation was obtained on a Perkin-Elmer 341 MC polarimeter. HRMS were recorded on a Thermo LTQ Orbitrap hybrid mass spectrometer. GC analysis was carried out on Hewlett-Packard 7890 gas chromatography using chiral capillary columns.

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Synthesis of (*S*)-2,2'-bistriflate-1,1'-binaphthyl (9)[14]
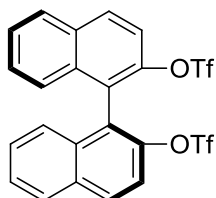
To a solution of (*S*)-BINOL **8** (4.03 g, 14.1 mmol) in 100 mL of CH_2Cl_2 was added pyridine (40 mL) and followed by dropwise addition of triflic anhydride

(5.05 mL, 30 mmol) at 0 ˚C. The mixture was stirred at r.t. for 6 h. After removal

of the solvent, the residue was diluted with EtOAc (50 mL) and then washed with

5% aqueous HCl (50 mL), saturated NaHCO$_3$ (50 mL) and brine (50 mL). The

organic layer was dried over anhydrous sodium sulfate, concentrated and passed

through a silica gel plug (eluted with CH$_2$Cl$_2$) to give the (*S*)-**9** (7.4 g, 95%). [1]H

NMR (400 MHz, CDCl$_3$) δ: 7.27 (d, *J* = 8.5, 2H), 7.42 (ddd, *J* = 1.1, 6.8, 8.2, 2H),

7.59 (ddd, *J* = 1.0, 7.0, 8.1, 2H), 7.63 (d, *J* = 9.1, 2H), 8.02 (d, *J* = 8.2, 2 H), 8.15

(d, *J* = 9.1, 2 H) ; ^{13}C NMR (100 MHz, CDCl$_3$) δ: 118.3, 119.4, 123.6, 126.8,

127.4, 128.1, 128.5, 132.1, 132.5, 133.2, 145.5.

Synthesis of (*S*)-2-(Diphenylphosphinyl)-2'-[(trifluoromethanesulfonyl) oxy]-1,1'-binaphthyl (10)
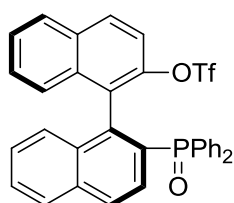
To a mixture of (*S*)-**9** (6.25 g, 11.74 mmol), diphenylphosphine oxide (4.59 g,

22.7 mmol), palladium diacetate (127 mg, 0.57 mmol), and

1,4-bis(dipheny1phosphino)butane (dppb, 242 mg, 0.57 mmol) were added 50 mL

of DMSO and diisopropylethylamine (5.85 g, 45.4 mmol), and the mixture was

stirred and heated at 120 ˚C for 12 h. After cooling to room temperature, the

solvent was removed under reduce pressure. The residue was diluted with 100 mL

EtOAc, washed with water (60 mL X 2), dried over MgSO$_4$, and concentrated

under reduced pressure. The residue was subjected column chromatography on

silica gel (elution with hexane/EtOAc 1:1) to give (*S*)-**10** as a white solid (7.5 g, 95%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 6.98-8.01 (m, 22H, Ar); ^{31}P NMR (202 MHz, CDCl$_3$) δ: 29.2.

Synthesis of (*S*)-2-Cyano-2'-diphenylphosphinyl-1,1'-binaphthyl (11)
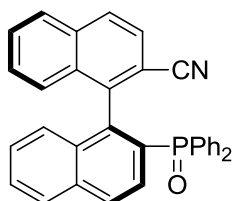
To a mixture of (*S*)-**10** (7.05 g, 11.7 mmol), potassium cyanide (7.55 g, 116 mmol), nickel dibromide (1.13 g, 5.2 mmol), triphenylphosphine (6.04 g, 23.0 mmol) and activated zinc powder (1.05 g, 16.1 mmol) was added 70 mL of acetonitrile. The mixture was stirred and refluxed under N$_2$ for 3 h. After cooling to r. t., the mixture was diluted with EtOAc and washed with water and brine. The organic phase was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified with column chromatography on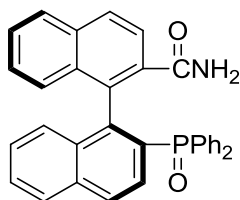 silica gel (elution with hexane/EtOAc, 1:3) to give (*S*)-**11** as a white solid (5.56 g, 99%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.02 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.84 (dd, *J* = 8.2, 5.3 Hz, 1H), 7.7–7.1 (m, 16H), 7.02 (t, *J* = 9.6 Hz, 2H); ^{31}P NMR (202 MHz, CDCl$_3$) δ: 28.2.

Synthesis of (*S*)-2-Carbamoyl-2'-diphenylphosphinyl-1,1'-binaphthyl (12)

To a stirred cooled solution of (*S*)-**11** (5.00 g, 10.4 mmol) in DMSO (50 mL) were added 30% H_2O_2 (25 mL) dropwisely and then anhydrous K_2CO_3 (28.8 g) in an ice bath. The mixture was allowed to warm up to r.t. (warning: exothermic process). After 30 min, the mixture was added distilled water (20 mL) and DMSO (20 mL) in an ice bath, and then stirred at r.t. overnight. The reaction mixture was diluted with EtOAc and quenched with saturated NH_4Cl (50 mL). The organic phase was washed twice with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with EtOAc) to afford (*S*)-**12** as a white solid (5.11 g, 95%). ^1H NMR (400 MHz, CDCl$_3$) δ: 9.45 (bs, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.8–7.7 (m, 3H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.6–7.4 (m, 5H), 7.3–7.2 (m, 1H), 7.2–7.0 (m, 5H), 7.0–6.9 (m, 2H), 6.64 (t, *J* = 7.0 Hz, 1H), 6.33 (d, *J* = 8.4 Hz, 1H), 5.52 (bs, 1H); ^{31}P NMR (202 MHz, CDCl$_3$) δ: 30.8.

Synthesis of

**(*S*)-2-Methoxycarbonylamino-2'-diphenylphosphinyl-1,1'-binaphthyl (13)**
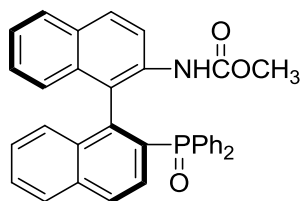
To a solution of 25 wt% sodium methoxide in methanol (11.1 mL, 48.7 mmol) was added methanol (80 mL). The solution was cooled to −78 ℃ and bromine (0.92 mL, 17.9 mmol) was added dropwise with vigorous stirring. After stirring at −78 ℃ for 15 min, a solution of (*S*)-**12** (4.03 g, 8.1 mmol) in methanol (72 mL)

and dioxane (72 mL) was added dropwise for 30 min. The reaction mixture was stirred at r.t. for 1 h and then stirred at 55 °C for 1 h. After being cooled to r.t., the mixture was diluted with EtOAc and quenched with saturated NH$_4$Cl. The organic layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (elution with hexane/EtOAc, 1:2) to give (S)-**13** as white solid (3.60 g, 83%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.74 (bs, 1H), 7.9–7.6 (m, 5H), 7.67 (d, J = 8.8 Hz, 1H), 7.6–7.4 (m, 6H), 7.3–7.1 (m, 4H), 7.09 (d, J = 8.8 Hz, 1H), 6.95 (t, J = 7.2 Hz, 1H), 6.82 (t, J = 7.0 Hz, 1H), 6.7–6.6 (m, 2H), 6.51 (d, J = 6.8 Hz, 1H), 3.05 (bs, 3H); ^{31}P NMR (202 MHz, CDCl$_3$) δ: 28.2.

Synthesis of (S)-2-Methylamino-2'-diphenylphosphino-1,1'-binaphthyl (14a)
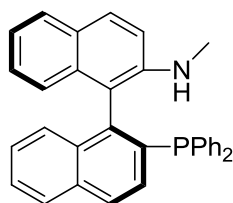
To a solution of (S)-**13** (1.80 g, 3.40 mmol) in THF (90 mL) was added 2 M borane-dimethyl sulfide complex in THF (13.6 mL, 27.2 mmol) at 0 °C, the mixture was refluxed under N$_2$ for 16 h. After cooling to r.t., the mixture was diluted with EtOAc and quenched with saturated aqueous NH$_4$Cl. The organic phase was washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. To the residue was added 120 mL of diethylamine and the reaction mixture was stirred at r.t. for 30 min. After removal of diethylamine, the residue was chromatographed on silica gel (elution with hexane/EtOAc, 20:1 to 10:1) to

give (*S*)-**14a** as a yellow solid (1.10 g, 69%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.9–7.8 (m, 3H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.5–7.4 (m, 2H), 7.3–6.9 (m, 15H), 6.70 (d, *J* = 8.3 Hz, 1H), 3.04 (bs, 1H), 2,37 (s, 3H). ^{31}P NMR (202 MHz, CDCl$_3$) δ: −13.8.
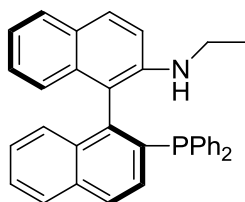
Synthesis of (*S*)-2-Ethylamino-2'-diphenylphosphino-1,1'-binaphthyl (14b)

To a solution of (*S*)-**13** (2.00 g, 3.80 mmol) in methanol (75 mL) was added a 40% KOH solution (40 mL) and the mixture was refluxed for 2 h. After being cooling to r.t., the mixture was diluted with EtOAc. The organic phase was washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude (*S*)-2-Amino-2'-diphenylphosphinyl-1,1'-binaphthyl (1.79 g, quantitative) was used for next step without further purification. ^{31}P NMR (202 MHz, CDCl$_3$) δ: −13.8.

To a solution of above amine (1.79 mg, 3.80 mmol) in 75 mL of CH2Cl2 were added pyridine (0.37 mL, 4.57 mmol) and acetyl chloride (0.31 mL, 4.19 mmol) at 0 ℃ and the mixture was stirred at rt for 1 h. The mixture was diluted with CH$_2$Cl$_2$. The organic phase was washed with saturated NH$_4$Cl and brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was passed through a silica gel plug (elution with hexane/EtOAc, 3:1) to afford (*S*)-2-Acetylamino-2'-diphenylphosphinyl-1,1'-binaphthyl (1.96 g, 99%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.73 (s, 1H), 8.0–7.9 (m, 4H), 7.8–7.6 (m, 2H), 7.6–7.4 (m,

6H), 7.3–7.1 (m, 5H), 7.0–6.9 (m, 1H), 6.8–6.7 (m, 1H), 6.7–6.6 (m, 1H), 6.53 (d, $J = 8.3$ Hz, 1H), 1.93 (s, 3H). ^{31}P NMR (202 MHz, CDCl$_3$) δ: 29.6.

To a solution of above acetylamino (1.27 g, 2.50 mmol) in THF (60 mL) was added 2M borane-dimethyl sulfide complex in THF (6.20 mL, 12.4 mmol) at 0 ℃, the mixture was refluxed for 16 h. After cooling to r.t., the mixture was diluted with EtOAc and quenched with saturated NH$_4$Cl. The organic layer was washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. To the residue was added 82.0 mL of diethylamine and the reaction mixture was stirred at r.t. for 3 h. After removal of diethylamine, the residue was chromatographed on silica gel (elution with hexane/EtOAc, 20:1) to give (*S*)-**14b** as a yellow solid (0.83 g, 69%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.0–7.8 (m, 3H), 7.74 (d, $J = 8.5$ Hz, 1H), 7.5–7.4 (m, 2H), 7.3–6.9 (m, 16H), 6.59 (d, $J = 8.5$ Hz, 1H), 3.07 (m, 2H), 2.9–2.7 (m, 1H), 0.78 (t, $J = 7.0$ Hz, 3H). ^{31}P NMR (202 MHz, CDCl$_3$) δ: −13.8.

Synthesis of (*S*)-2-Benzylamino-2'-diphenylphosphino-1,1'-binaphthyl (14c)
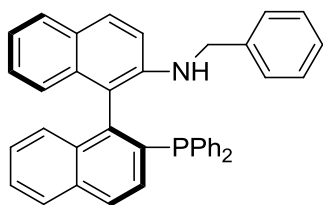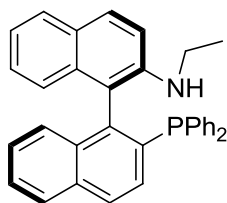

The synthesis of (*S*)-**14c** is following the same procedure as (*S*)-**14b** except using benzoyl chloride instead of acetyl chloride.

(*S*)-2-Benzoylamino-2'-diphenylphosphinyl-1,1'-binaphthyl (99%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 10.60 (s, 1H), 8.0–7.8 (m, 7H), 7.71 (d, $J = 8.0$ Hz, 1H), 7.8–7.1

(m, 15H), 7.0–6.9 (m, 1H), 6.9–6.7 (m, 1H), 6.7–6.6 (m, 1H), 6.51 (d, J = 8.0 Hz, 1H). ^{31}P NMR (202 MHz, CDCl$_3$) δ: 30.2.

(*S*)-**14c** as a yellow solid (82%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.9–7.8 (m, 2H), 7.82 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.6–7.4 (m, 2H), 7.4–7.0 (m, 19H), 7.0–6.9 (m, 1H), 6.62 (d, J = 8.4 Hz, 1H), 4.16 (d, J = 15.2 Hz, 1H), 3.98 (d, J = 15.2 Hz, 1H), 3,68 (bs, 1H). ^{31}P NMR (202 MHz, CDCl$_3$) δ: −13.4.

Synthesis of (*R*)-2-Ethylamino-2'-diphenylphosphino-1,1'-binaphthyl (14b)

The synthesis of (*R*)-**14b** is following the same procedure as (*S*)-**14b**. ^{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) , 7.54-7.7.44 (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.

A Typical Procedure for The Preparation of Phosphorochloridite 15.
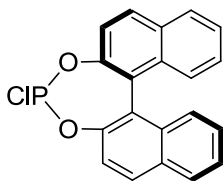
To a mixture of (*R*)-BINOL (1.75 g, 6.0 mmol) and Phosphorus trichloride (12.5 g, 90.0 mmol) was added a drop of *N*-methylpyrrolidone (NMP) (catalytic amount) at room temperature under nitrogen. The resulting solution was heated at reflux for 6 h. After cooling to room temperature, the excess phosphorus trichloride was removed under reduced pressure. Azeotropic evaporation of the trace amount of phosphorus trichloride in the rsidue with degassed toluene twice (2 X 10 mL) under reduced pressure afforded the (*R*)-**15a** as white foam in quantitative yield (2.2 g). The crude product was pure enough and was used in the next step without further purification: ^{1}H NMR (360 MHz, CD_2Cl_2) δ: 8.07-7.98 (m, 4H), 7.57-7.46 (m, 4H), 7.39-7.29 (m, 4H); ^{13}C NMR (90 MHz, CD_2Cl_2) δ: 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_2Cl_2) δ: 178.8.

(*S*)-3,3'-Dimethyl-1,1'-binaphthalene-2,2'-dioxychlorophosphine (15d): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.4-7.8 (m, 6H), 7.2-7.4 (m, 2H), 6.9-7.1 (m, 2H), 2.27 (s, 3H), 2.04 (s, 3H); ^{31}P NMR (202 MHz, $CDCl_3$) δ: 175.5.

3,3',5,5'-Tetra(*tert*butyl)-2,2'-bisphenol Phosphorochloridite (15f): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (d, *J* = 2.4Hz, 2H), 7.22 (d, *J* = 2.4 Hz, 2H), 1.51 (s, 18H), 1.39 (s, 18H); ^{31}P NMR (202 MHz, $CDCl_3$) δ: 175.5.

Synthesis of (*S*) 3,3'-Di-*tert*butyl-5,5',6,6'-tetramethyl-2,2'-bisphenol Phosphorobromidite (15e)[15]
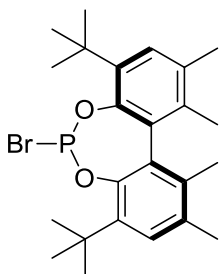
To a solution of (*S*)-3,3'-di-*tert*-butyl-5,5',6,6'-tetramethyl-biphenyl-2,2'-diol [(*S*)-BIPHEN-H2] (1.01 g, 2.86 mmol) in 25 mL of toluene were added NEt$_3$ (0.81 mL, 5.83 mmol) and PBr$_3$ (0.28 mL, 2.9 mmol) at room temperature. The reaction mixture was then stirred for 12 h. The suspension was filtered, and the filtrate was evaporated to give (*S*)-**15e** as a white solid (0.85 g, 68 % yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.18 (s, 1H), 7.08 (s, 1H), 1.93 (s, 3H), 1.92 (s, 3H), 1.57 (s, 3H), 1.56 (s, 3H), 1.48 (s, 9H), 1.39 (s, 9H); ^{31}P NMR (202 MHz, CDCl$_3$) δ: 183.2.

A Typical Procedure for The Preparation of Phosphine-phosphoramidite Ligand 7:

Synthesis of Ligand (*S,R*)-7a
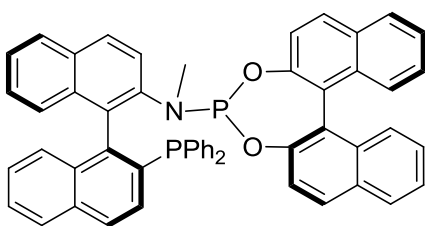
To a solution of (*S*)-**14a** (480 mg, 1.0 mmol) in anhydrous THF (10 mL) at -78 ˚C

under N_2 atmosphere was added dropwise nBuLi (1.2 mmol, 0.48 mL of 2.5 M hexane solution). The reaction mixture was turned out to a deep red solution and stirred for 4 h at that temperature. Then (*R*)-**15a** (454 mg, 1.3 mmol) in THF (6 mL) was added dropwise. After addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent were removed under vacuum. To the residue was added CH_2Cl_2 (5 mL) and the mixture was filtered to remove the inorganic salt. The filtration was concentrated and subjected to flash chromatography on silica gel (eluted with hexane/EtOAc/NEt$_3$ 100:10:1) to afford pure ligand (*S,R*)-**7a** as white solid (257 mg, 33 %). $[\alpha]_D^{20} = -32.6$ (*c* = 0.3, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ: 8.04-8.01 (m, 3H), 7.85 (t, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.61-7.57 (m, 2H), 7.38-6.93 (m, 21H), 6.59 (dd, *J* = 8.5, 7.0 Hz, 1H), 6.49 (d, *J* = 8.5 Hz, 1H), 6.31 (d, *J* = 8.5 Hz, 1H), 2.45 ppm (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 150.45, 150.41, 149.61, 142.76, 142.49, 138.60, 138.49, 137.88, 137.79, 136.63, 135.25, 135.07, 134.08, 133.16, 133.03, 132.65, 131.61, 131.50, 130.73, 130.28, 129.94, 129.87, 128.84, 128.48, 128.31, 128.28, 128.20, 128.02, 127.75, 127.56, 127.42, 127.24, 127.16, 126.99, 126.53, 126.09, 125.69, 125.35, 124.86, 124.64, 124.12, 124.08, 122.28, 122.20, 35.67, 35.64 ppm; ^{31}P NMR (202 MHz, CDCl$_3$) δ: 141.09 (d, *J* = 45.2 Hz), -12.67 ppm (d, *J* = 45.2 Hz); HRMS (ESI): *m/z*: calcd for $C_{53}H_{38}NO_2P_2$ ([*M*+H$^+$]): 782.2578; found: 782.2374.

Ligands **7b-f** were synthesized in moderate yields following the above procedure. Their characterization data are summarized as following.
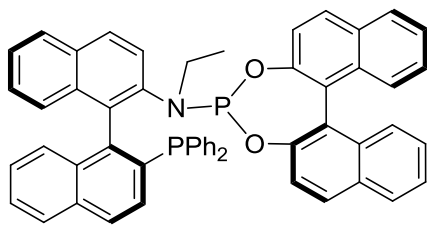
(*S*,*R*)-**7b**: Yield = 38 %; white solid; [α] $_D^{20}$ = −18.3 (*c* = 0.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ: 8.07-7.98 (m, 3H), 7.90 (t, *J* = 7.3 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.64-7.57 (m, 4H), 7.38-6.99 (m, 16H), 6.96 (t, *J* = 6.8 Hz, 2H), 6.85 (t, *J* = 7.1 Hz, 2H), 6.55 (t, *J* = 7.7 Hz, 1H), 6.38-6.29 (m, 2H), 2.75-2.67 (m, 1H), 2.37-2.29 (m, 1H), 0.65 ppm (t, *J* = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 150.29, 150.22, 149.94, 142.34, 141.95, 138.57, 138.36, 138.27, 138.20, 135.44, 135.14, 134.10, 133.57, 133.36, 131.68, 130.50, 129.88, 129.11, 128.66, 128.59, 128.55, 128.49, 128.46, 128.42, 128.30, 128.12, 127.56, 127.19, 127.12, 127.03, 126.66, 126.29, 126.17, 125.71, 125.53, 125.06, 124.76, 122.49, 122.24, 122.21, 41.05, 14.99 ppm; ³¹P NMR (162 MHz, CDCl₃) δ: 141.00 (d, *J* = 59.1 Hz), -13.48 ppm (d, *J* = 59.1 Hz); HRMS (ESI): *m/z*: calcd for $C_{54}H_{40}NO_2P_2$ ([*M*+H⁺]): 796.2534; found: 796.2536.
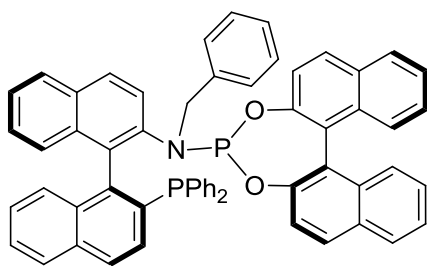
(*S*,*R*)-**7c**: Yield = 42 %; white solid; [α] $_D^{20}$ = +32.5 (*c* = 0.3, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ: 8.17 (d, *J* = 8.5 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.74-7.60 (m, 5H), 7.43-7.01 (m, 23H), 6.87-6.83 (m, 2H), 6.79-6.75 (m, 2H), 6.45-6.42 (m, 1H), 6.24 (d, *J* = 8.5 Hz, 1H), 5.93 (d, *J* = 8.5 Hz, 1H), 3.82 (d, *J* = 14.5 Hz, 1H), 3.21 (d, *J* = 14.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ: 150.09,

150.05, 149.84, 142.04, 141.91, 138.75, 128.24, 127.92, 137.81, 135.61, 135.42,

133.97, 133.56, 133.43, 132.01, 131.81, 131.75, 131.61, 130.72, 130.50, 130.35,

129.87, 129.81, 128.83, 128.74, 128.56, 128.48, 128.40, 128.37, 128.33, 128.21,

128.11, 128.04, 127.89, 127.84, 127.79, 127.40, 127.23, 127.20, 127.04, 126.88,

126.71, 126.08, 126.03, 125.32, 124.88, 124.63, 122.78, 122.55, 122.10, 51.32

ppm; ^{31}P NMR (202 MHz, CDCl$_3$) δ: 138.41 (d, J = 78.6 Hz), -11.86 ppm (d, J =

78.6 Hz); HRMS (ESI): m/z: calcd for C$_{59}$H$_{42}$NO$_2$P$_2$ ([M+H$^+$]): 858.2691; found:

858.2692.
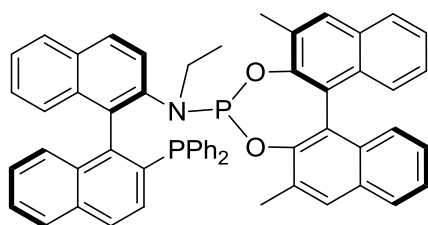
(*R*,*S*)-**7d**: Yield = 41 %; white solid; [α]$_D^{20}$ =

−15.9 (*c* = 0.1, CHCl$_3$); ^{1}H NMR (400 MHz, CD$_2$Cl$_2$) δ: 8.04-7.96 (m, 3H),

7.86-7.79 (m, 3H), 7.72 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.53-7.45 (m,

2H), 7.39-7.28 (m, 5H), 7.26-7.05 (m, 11H), 6.96-6.93 (m, 2H), 6.86-6.81 (m, 2H),

6.61-6.57 (m, 1H), 6.33 (d, J = 8.4 Hz, 1H), 2.94-2.83 (m, 1H), 2.58 (s, 3H),

2.50-2.45 (m, 1H), 1.66 (s, 3H), 0.70 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100

MHz, CD$_2$Cl$_2$) δ: 150.19, 150.12, 149.84, 142.23, 141.90, 138.93, 138.61, 138.57,

138.34,   137.72, 135.86, 135.34, 135.12, 134.41, 134.11, 133.94, 133.75, 133.74,

132.18, 132.01, 131.75, 131.68, 131.23, 131.07, 130.80, 130.06, 129.49, 129.09,

128.91, 128.58, 128.48, 128.29, 128.21, 127.93, 127.64, 127.29, 127.11, 127.02,

126.66, 125.80, 125.56, 125.32, 125.23, 125.07, 124.73, 121.81, 41.54, 17.66,

14.76 ppm; ^{31}P NMR (162 MHz, CD$_2$Cl$_2$) δ: 139.00 (d, J = 61.6 Hz), -14.60 ppm

(d, J = 61.6 Hz); HRMS (ESI): *m/z*: calcd for $C_{56}H_{44}NO_2P_2$ ($[M+H^+]$): 824.2847; found: 824.2843.
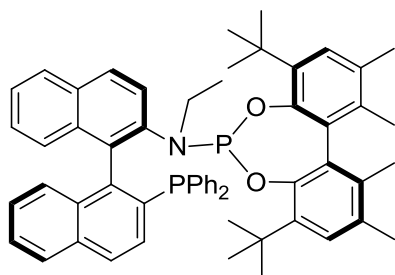
(*R,S*)-**7e**: Yield = 38 %; white solid; $[\alpha]_D^{20}$ = +91.7 (*c* = 0.5, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.98 (d, J = 8.8 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.63 (dd, J = 8.4, 2.4 Hz, 1H), 7.50-7.46 (m, 1H), 7.24-7.12 (m, 6H), 7.06-6.87 (m, 9H), 6.65 (t, J = 8.0 Hz, 1H), 3.58-3.50 (m, 1H), 2.80-2.73 (m, 1H), 2.23 (s, 3H), 2.20 (s, 3H), 1.78 (s, 3H), 1.76 (s, 3H), 1.34 (s, 9H), 0.81 (t, J = 7.2 Hz, 3H), 0.74 ppm (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 148.95, 148.84, 147.74, 147.69, 142.72, 142.39, 138.85, 138.69, 138.46, 137.80, 137.77, 136.43, 135.12, 134.89, 134.57, 134.31, 134.05, 133.68, 133.29, 133.23, 133.13, 133.07, 131.80, 131.73, 131.25, 131.05, 130.76, 129.55, 129.38, 128.13, 128.06, 128.03, 127.72, 127.64, 127.46, 127.25, 127.20, 126.64, 126.55, 125.75, 125.15, 124.70, 40.05, 34.63, 34.07, 31.29, 31.26, 30.05, 20.19, 16.80, 16.31, 13.06 ppm; ^{31}P NMR (162 MHz, CDCl$_3$) δ: 130.50 (d, J = 97.2 Hz), -14.89 ppm (d, J = 97.2 Hz); HRMS (ESI): *m/z*: calcd for $C_{58}H_{60}NO_2P_2$ ($[M+H^+]$): 864.4099; found: 864.4105.
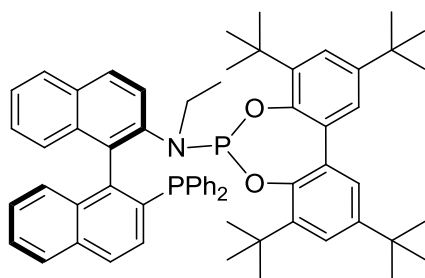
(*R*)-**7f**: Yield = 52 %; white solid; $[\alpha]_D^{20}$ =

+40.7 (c = 0.5, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.91 (d, J = 7.2 Hz, 1H),

7.83 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.50 (dd, J = 7.2, 2.8 Hz, 1H),

7.39 (t, J = 7.2 Hz, 1H) 7.24-7.00 (m, 11H), 6.97-6.93 (m, 4H), 6.85 (t, J = 7.6 Hz,

2H), 6.51-6.47 (m, 1H), 6.27 (d, J = 8.4 Hz, 1H), 3.39-3.32 (m, 1H), 3.06-2.97 (m,

1H), 1.24 (s, 9H), 1.23 (s, 9H), 1.04-0.98 (m, 18H), 0.82 ppm (t, J = 6.4 Hz, 3H);

^{13}C NMR (100 MHz, CDCl$_3$) δ: 147.50, 147.40, 146.82, 146.77, 144.32, 144.26,

143.68, 143.63, 138.82, 138.49, 137.93, 137.77, 136.99, 136.85, 133.97, 133.74,

133.48, 133.42, 133.12, 132.29, 132.22, 132.02, 131.97, 131.85, 131.80, 131.48,

130.24, 129.84, 129.73, 128.01, 127.79, 127.24, 127.05, 126.96, 126.87, 126.79,

126.68, 126.63, 126.39, 126.19, 126.14, 125.95, 125.77, 125.40, 125.04, 124.28,

124.14, 123.98, 122.77, 122.74, 37.77, 34.09, 33.67, 33.53, 33.45, 30.53, 30.49,

29.73, 29.34, 20.43 ppm; ^{31}P NMR (162 MHz, CDCl$_3$) δ: 136.29 (br), -14.93 ppm

(d, J = 62.4 Hz); HRMS (ESI): m/z: calcd for C$_{62}$H$_{68}$NO$_2$P$_2$ ([M+H$^+$]): 920.4725;

found: 920.4749.

General Procedure for Asymmetric Hydroformylation:

In a glovebox filled with nitrogen, to a 2 mL vial equipped with a magnetic bar

was added ligand **7** (0.004 mmol), Rh(acac)(CO)$_2$ (0.001 mmol in 0.10 mL

solvent), dodecane (50 μL, as a GC internal standard, if applicable) and substrate

(1.0 mmol), additional solvent 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 at 60 ℃ (oil bath) for 24 h. The reaction was cooled and the pressure was carefully released in a well ventilated hood. For analysis of the products of styrene and vinyl acetate, the conversion and regioselectivity were determined by ^{1}H NMR spectroscopy of the crude reaction mixture without evaporation of the solvent. The enantiomeric excesses were determined following the reported method with a Supelco's Beta Dex 225 column.[5b] The absolute configuration of styrene and vinyl acetate product were assigned by comparing the sign of the optical rotation with that of (*R*)-2-phenylpropan-1-ol or literature data.[9a] For analysis of the products of allyl cyanide, the conversion and regioselectivity were determined by GC with a Supelco's Beta Dex 120 column.[8] The enantiomeric excesses of product **16** was determined by oxidation with Jones reagent to afford the corresponding carboxylic acid, followed by reacting with aniline to give the corresponding amide which was analyzed by HPLC (Column: Chiralcel AS; solvent: hexane/*i*PrOH = 80:20; flow: 1.0 mL/min; 254 nm; (*S*) enantiomer: t_R = 7.75 min, (*R*) enantiomer: t_R = 9.74 min). For styrene and vinyl acetate derivatives, the conversion and regioselectivity were determined by ^{1}H NMR spectroscopy from the crude reaction mixture. The enantiomeric excesses of the hydroformylation products of styrene derivatives were reduced into alcohols and then determined by GC with Supelco's Beta Dex 225 column, while the ee values of the products of vinyl acetate derivatives were determined directly by GC with Supelco's Beta Dex 225 column.

Determination of The Enantiomeric Excess of Hydroformylation Products of

Allyl Cyanide:

The ee of product 3-methyl-4-oxobutanenitrile (**16**) was determined by oxidation

with Jones reagent as follows. The hydroformylation reaction mixture was diluted

in acetone (5 mL) and cooled to 0 ˚C. Jone's reagent (1 mL) was added dropwise.

The mixture was stirred at room temperature for 1 h, then H_2O (8 mL) was added.

The solution was extracted with CH_2Cl_2 (10 mL) and the organic layer was dried

over Na_2SO_4 and concentrated to afford the corresponding carboxylic acid. The

acid was dissolved in THF (2 mL). To this solution was added aniline (0.1 mL),

DMAP (8 mg) and DCC (220 mg). The reaction mixture was stirred for 30 min,

and then filter through celite. The filtrate was pass a fast chromatography on silica

gel to yield the branched amide (**27**) and linear amide (**28**). **27** was analyzed by

HPLC (Column: Chiralcel AS; solvent: hexane/*i*PrOH = 80:20; flow: 1.0 mL/min;

254 nm; (*S*) enantiomer: t_R=7.75 min, (*R*) enantiomer: t_R=9.74 min).
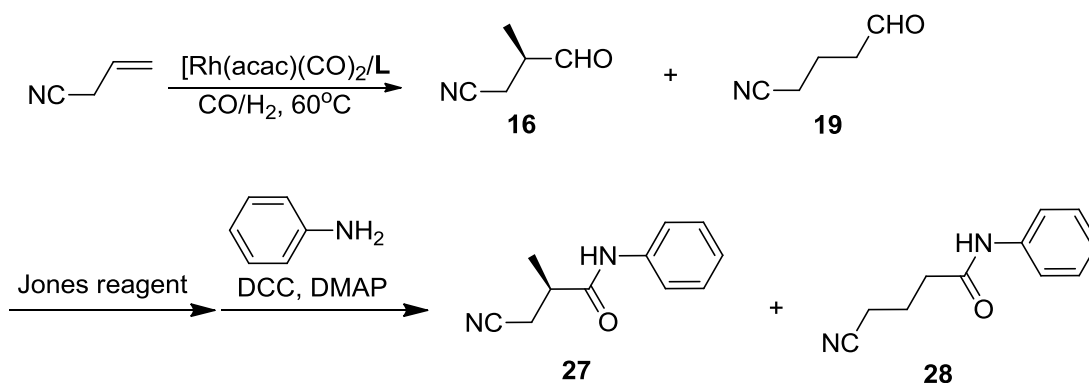
Scheme **2-5**: The Derivation of Hydroformylation Products of Allyl Cyanide.

3-cyano-2-methyl-N-phenylpropanamide (**27**): $[\alpha]_D^{20} = +7.5$ ($c = 0.5$, CHCl$_3$) at 96 % ee; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.06 (s, 1H), 7.44 (d, $J = 7.72$ Hz, 2H), 7.23 (t, $J = 7.56$ Hz, 2H), 7.04 (t, $J = 7.40$ Hz, 1H), 2.73 (q, $J = 6.96$ Hz, 1H), 2.63 (dd, $J = 16.72, 6.6$ Hz, 1H), 2.47 (dd, $J = 16.72, 6.64$ Hz, 1H), 1.31 ppm (d, $J = 6.88$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 171.3, 137.5, 129.0, 124.8, 120.3, 118.4, 38.5, 21.3, 17.8 ppm.

4-cyano-N-phenylbutanamide (**28**): ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.77 (s, 1H), 7.44 (d, $J = 7.60$ Hz, 2H), 7.24 (t, $J = 7.64$ Hz, 2H), 7.03 (t, $J = 7.40$ Hz, 1H), 2.46 (t, $J = 7.00$ Hz, 2H), 2.43 (t, $J = 6.96$ Hz, 2H),1.99 ppm (tt, $J = 7.00, 6.92$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 168.3, 136.7, 128.0, 123.5, 119.0, 118.3, 33.9, 19.9, 15.6 ppm.

Determination of The Enantiomeric Excess of Hydroformylation Products of Styrene Derivatives :

A portion of the reaction mixture was diluted with MeOH (2 mL) and cooled to 0 ^{o}C. To the mixture was added NaBH$_4$ (40 mg) in portion. The reaction mixture was allowed to stir at 0 ^{o}C for 2 h. Then water (5 mL) was added dropwise 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 5min. The organic

phase was separated, dried over Na_2SO_4 and concentrated under reduced pressure. 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.

For 2-(4-Isobutyl-phenyl)-propionaldehyde, 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 5min and extracted with CH_2Cl_2 (10 mL). The combined organic layer was dried over Na_2SO_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.

NMR and Chiral GC Analysis of Hydroformylation Products of Styrene Derivatives and Their Reduction Products:
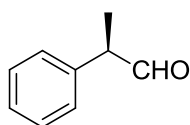
2-Phenyl-propionaldehyde. ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 9.69 (d, *J* = 1.3 Hz, 1H), 7.43-7.38 (m, 2H), 7.35-7.29 (m, 1H), 7.26-7.16 (m, 2H), 3.65 (q, *J* = 7.1 Hz, 1H), 1.45 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 201.4, 138.4, 129.3, 128.7, 127.8, 53.3, 14.8.

Supelco's Beta Dex 225 column, Temperature program: 100 ˚C for 5 min, then 4

˚C/min to160 ˚C; Flow rate: 1.0 mL/min, $t_{(major)}$ = 12.4 min, $t_{(minor)}$ = 12.5 min

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Chapter 3

Rh-Catalysed Asymmetric Hydroformylation of *N*-allylamides: A Highly Enantioselective Approach to β^2-Amino Aldehydes

3.1 Introduction

Asymmetric hydroformylation provides an atom-economically protocol to synthesize enantiomerically pure aldehydes, which are important intermediates in the synthesis of a variety of pharmaceuticals and fine chemicals.[1] The aldehydes could be easily converted to various useful chiral amines, alcohols, acids, olefins, etc. However, the substrate scope of olefin that have been hydroformylated is usually limited to terminal olefins without α hydrogens, such as vinyl acetate and styrene derivatives, etc.. It still remains great demand to further expand the substrate scope and their potential applications.
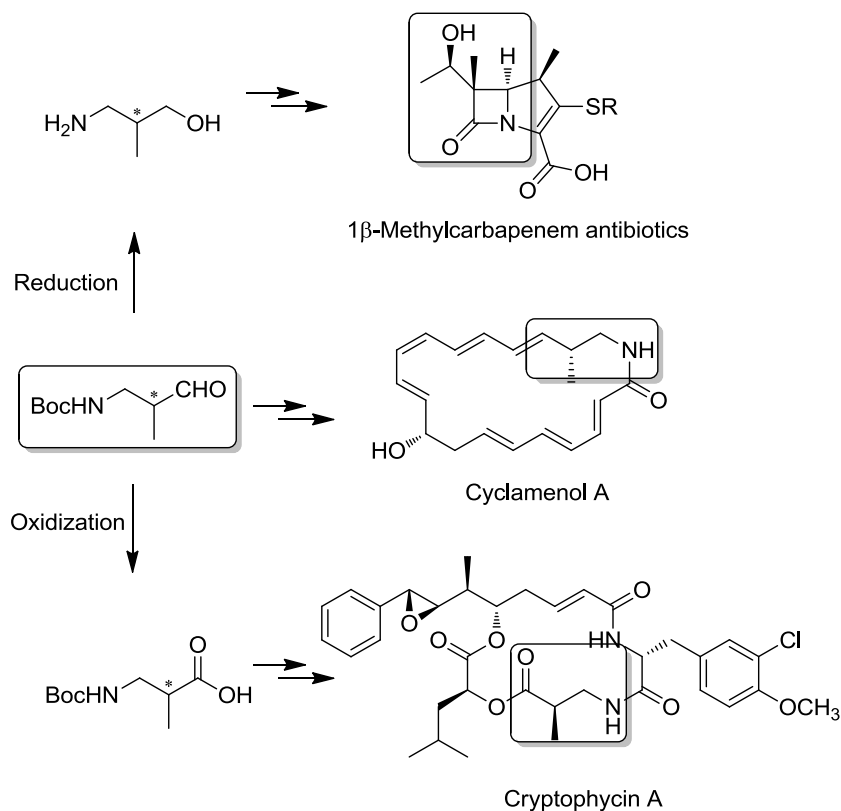
Scheme 3-1 Application of 3-(*N*-Boc-amino)-2-methylpropanol in Pharmaceutical and Synthetic Chemistry.

Enantiomerically pure β^2-amino aldehydes are important building block in natural products and have potential applications in pharmaceuticals and fine chemical industry due to the high reactivity of aldehydes.[3] As shown in Scheme 3-1, all three nature products, Cyclamenol A, Cryptophycins and β-methylcarbapenem antibiotics possess a chiral β^2-amino aldehydes building block or its derivatives (Scheme 3-1). Those key intermediates could be easily obtained from chiral β^2-amino aldehydes by either oxidation or reduction reactions. Howerver, the synthesis of enantiomerically pure

3-(*N*-Boc-amino)-2-methylpropanol requires multi step synthesis, starting from very expensive chiral source, hydroxyisobutyric acid with moderate yields (Scheme 3-2).[4,6] Herein, asymmetric hydroformylation provides an alternative approach to this chiral building block simply by hydroformylating *N*-allylamides olefins.
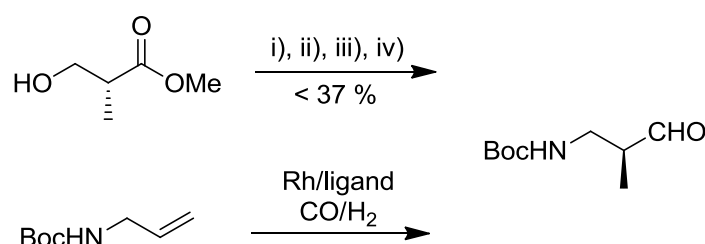
Scheme 3-2 **New Approach to Chiral β^2-Amino Aldehydes. i) NH$_3$, MeOH, NaCN, 50˚C; ii) BH$_3$·Me$_2$S, THF, reflux; iii) (Boc)$_2$O, Et$_3$N, MeOH; iv) (COCl)$_2$, DMSO, Et$_3$N.**

As we mentioned before, allylic olefins have not been very well studied for rhodium-catalyzed asymmetric hydroformylation reactions. It is known that the substrate could undergo isomerization at high reaction temperature due to the presense of α hydrogens. The resulting internal olefin tends to be less reactive and eventually kills the reaction. Other than reactivity, the regioselectivity brings even bigger challenge to the reaction. In most cases, the linear aldehyde is the major product observed in this type of reaction. For example, hydroformylation of allylbenzene[7] derivatives and allylamines[8] affords predominately linear isomers.

Breit and co-workers have reported that phosphine protected allylic alcohol could orientate the regioselectivity of hydroformylation and gives branch aldehyde as major produc, based on the concept of substrate bound catalyst-directing phosphine groups. However, this stoichiometric procedure requires protecting/deprotecting steps and the phosphine byproduct generated in situ is difficult to purify. Early in 1980s, Ojima and co-workers found that *N*-allylamides could be successfully hydroformylated with good regioselectivity. The chelating ability of amides to the metal center is believed to play an important role in the catalytic cycle.

Inspired by their work, we decide to use an amide as directing group in the synthesis of chiral β^2-amino aldehydes. Herein, we report a rhodium-catalyzed asymmetric hydroformylation reaction of *N*-allylamides and *N*-allylsulfonamides substrates with excellent enantioselectivity (92 – 99% ee) and high reactivity (up to 9700 TON); this transformation provides an alternative synthetic approach to chiral β^2-amino aldehydes and its derivatives.

3.2 Results and Discussion

3.2.1 Optimization of Asymmetric Hydroformylation of N-allylamide

Commercially available Boc-protected allyl amine was used as standard substrate to investigate the asymmetric hydroformylation reaction. In the previous chapter, we reported a class of hybrid phosphine-phosphoramidite ligands (YanPhos A-C; Figure **3-1**), that showed good compatibility and excellent enantioselectivity in the asymmetric hydroformylation of simple olefins.[13] The success of Yanphos prompted us to chose them as primary target catalyst in the hydroformylation of **1a**. For comparison, several commercially available chiral ligands (Figure **3-1**), which have a history of success in the asymmetric hydroformylation of a variety of functionalized olefins, were also screened. The asymmetric hydroformylation reactions were carried out with 0.1 mol% catalyst and 20 bar CO/H_2 (1:1) gas at 60 ˚C. The catalyst was prepared in situ by mixing [Rh(acac)(CO)$_2$] with the ligand in toluene.
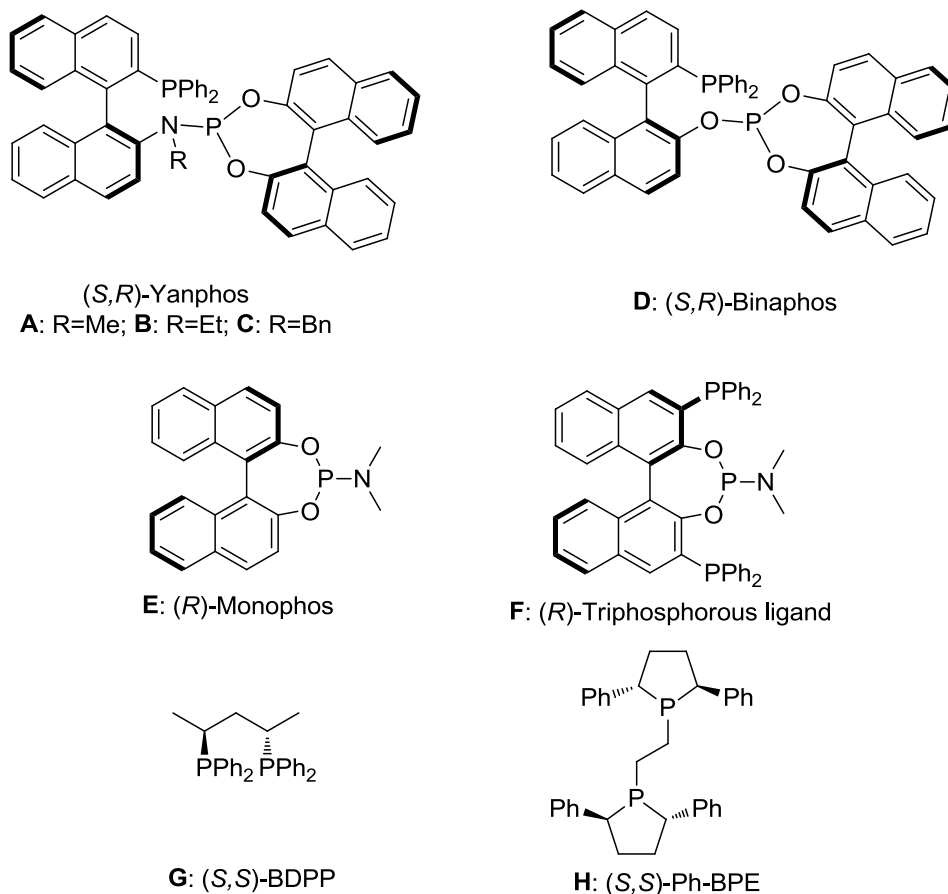
Figure 3-1 Chiral Ligands for Asymmetric Hydroformylation.

Some representative results are summarized in Table **3-1**. Phosphoramidite ligands, (*R*)-monophos (**E**) and (*R*)-triphosphorus ligand **F**,[14] only afforded less than 50% ee (Table **3-1**, entries 5 and 6). Although (*S, R*)-Binaphos[2a] provided a promising 78% ee, but the less desired branched product force us to skip it (Table **3-1**, entry 4). Hydroformylation with (*S,S*)-BDPP [(2*S*,4*S*)-2,4-Bis(diphenylphosphino)pentane] and (*S,S*)-Ph-BPE [(+)-1,2-Bis((2*S*,5*S*)-2,5-diphenylphospholano)ethane][2e] offered good regioselectivity (83:17 and 86:14, respectively), but the enantioselectivities were

less satisfying (Table **3-1**, entries 7 and 8). Finally, by using (S, R)-yanphos

derivatives as ligands, up to 93% ee, full conversion, and good regioselectivity

was achieved (Table **3-1**, entries 1-3). It is noteworthy that, under current reaction

conditions, all linear aldehyde **3a** was transformed into 2-hydroxy pyrrolidine **4a**

in quantitative yield by intramolecular cyclization (as shown in Table **3-1**).[15]

Table 3-1 **Ligand Screening for Asymmetric Hydroformylation of**
N-allylamide 1a.[a]
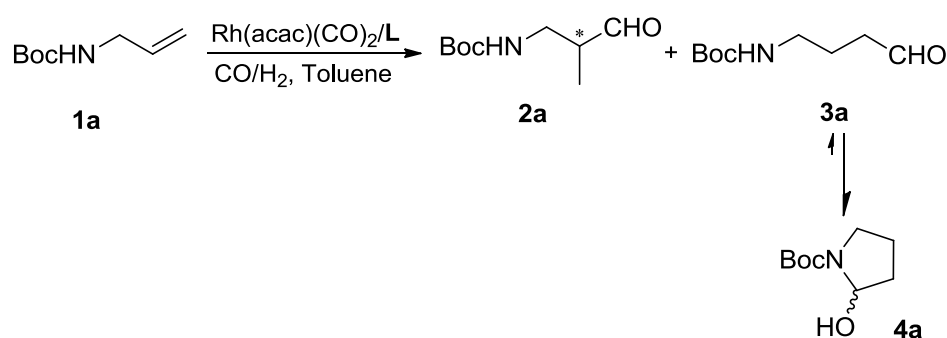
Entry	Ligand	Conversion [%][b]	b/l[b]	ee [%][c]
1	**A**	98	64/36	92(S)
2	**B**	>99	65/35	93(S)
3	**C**	98	64/36	92(S)
4	**D**	99	47/53	78(S)
5	**E**	84	46/54	4 (R)
6	**F**	97	62/38	50(S)
7	**G**	43	83/17	56(R)

| 8 | **H** | 93 | 86/14 | 87(*R*) |

a Reactions were performed on a 1.0 mmol scale at 60 ˚C in toluene with substrate/Rh=1000, L:Rh=4:1, 20 bar 1:1 CO/H$_2$, and a reaction time of 20 h. *b* Determined by ^{1}H NMR, b/l (branched/linear ratio) = **2a/4a**. *c* Determined by chiral GC analysis. The absolute configuration was assigned by comparing the sign of the optical rotation of the reduced product, *tert*-butyl (3-hydroxy-2-methylpropyl)carbamate, with literature[4].

With current results in hand, we decided to further optimize reaction conditions by varying solvent, syngas pressure, and reaction temperature to obtain optimal conditions. First, ligand B was used to generate rhodium-**B** complexes in situ to test solvent effect. Obvious solvent dependency was observed in the asymmetric hydroformylation reactions (Table **3-2**, entries 1-5). Nonpolar solvent such as toluene provided better activity and selectivity than polar solvent. Of the solvents tested, toluene gave the best conversion, regio- and enantioselectivity. By decreasing the pressure from 20 to 10 bar, it resulted in a slight increase of the regio- and enantioselectivity, and the inverse was also observed (Table **3-2**, entries 6 and 7). Lowering the temperature from 60 ˚C to 40 ˚C led to a slight increase in ee value, but a dramatic decrease in conversion. Likewise, a higher temperature lowered the enantioselectivity (Table **3-2**, entries 8 and 9).

Table 3-2 **Asymmetric Hydroformylation of N-allylamide 1a under Different Reaction Conditions.**^{a}
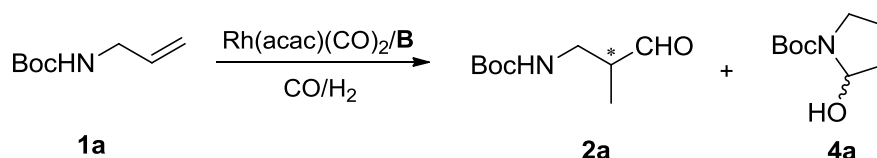
Entry	Solvent	CO/H$_2$ [bar]	T [˚C]	Conv. [%][b]	b/l[b]	ee [%][c]
1	PhH	10/10	60	97	62/38	93
2	PhMe	10/10	60	>99	65/35	93
3	Acetone	10/10	60	88	65/35	83
4	tBuOMe	10/10	60	96	60/40	81
5	EtOAc	10/10	60	92	63/37	80
6	PhMe	5/5	60	>99	66/34	94
7	PhMe	15/15	60	77	65/35	91
8	PhMe	5/5	40	61	66/34	94
9	PhMe	5/5	80	>99	66/34	91

[a] Reactions were performed on a 1.0 mmol scale with substrate/Rh=1000, **B**:Rh=4:1, and a reaction time of 20 h. [b] Determined by ^{1}H NMR, b/l (branched/linear ratio) = **2a**/**4a.** [c] See footnote of Table **3-1**.

3.2.2 Asymmetric Hydroformylation of *N*-Allylamide with Ligand B

With the optimized reaction conditions in hand (Table **3**-**3**, entry 6), we examined the scope of the methodology with regards to functional group tolerance. Using a rhodium-**B** catalyst, a variety of *N*-allylamides, *N*-allylsulfonamides, and *N*-allylphthalimide were hydroformylated with complete conversion, good regioselectivity, and excellent enantioselectivity (> 92 % ee). The functionality on the amide had no significant effect on the enantioselectivity, but slightly influenced the regioselectivity (Table **3**-**3**, entries 1-3). For the sulfonamide substrates, the electronic properties of the substituents at the *para* position of the

phenyl group had a marked effect on the branched/linear selectivity. Electron-rich groups increased the enantioselectivity (Table **3-3**, entries 3-5), whilst introducing a methyl group onto the nitrogen atom of **1c** did not affect the hydroformylation reaction (Table **3-3**, entries 6). However, substrates that contained *N,N*-bis(carbonyl) groups showed much better regio- and enantioselectvities. *N*-allylphthalimide afforded 96 % ee and a branched/linear ratio of 84:16 (Table **3-3**, entry 7). Notably, 99 % ee was achieved in the hydroformylation of *N,N*-bis(Boc)-*N*-allylamine (Table **3-3**, entry 8). To further investigate the reactivity of rhodium-**B** system in the hydroformylation of *N*-allylamides, a reaction was carried out on a 10.0 mmol scale with substrate/Rh=10000:1 for 24 hours; 97 % conversion (TON = 9700) was achieved without sacrificing the regio- and enantioselectivity (Table **3-3**, entry 9). *N*-Boc-protected β^2-amino aldehyde **2a** was obtained by flash chromatography in 62 % yield.
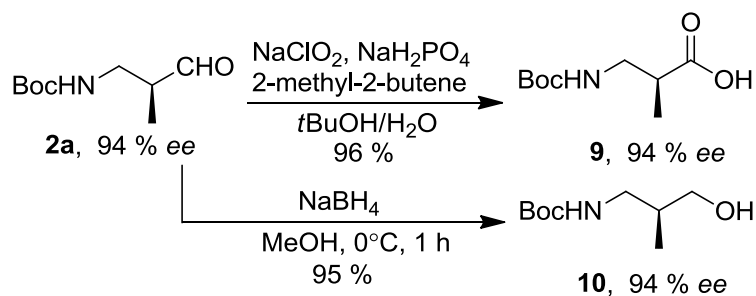
Table 3-3 **Asymmetric Hydroformylation of N-Allylamides 1.**[a]

Entry	R^1	R^2	Conv. [%][b]	b/l[b]	ee [%][c]
1	Boc (**1a**)	H	>99	66/34	94
2	Bz (**1b**)	H	>99	78/22	95
3	Ts (**1c**)	H	>99	67/33	94
4	p-NO$_2$PhSO$_2$ (**1d**)	H	>99	72/28	92

5	p-MeOPhSO$_2$ (**1e**)	H	>99	71/29	96
6	Ts (**1f**)	Me	>99	67/33	94
7	Phthaloyl (**1g**)		>99	84/16	96
8	Boc (**1h**)	Boc	>99	72/28	99
9[d]	Boc (**1a**)	H	97	66/34	94

[a] Reactions were performed on a 1.0 mmol scale at 60 ˚C in toluene with substrate/Rh=1000, **B**:Rh=4:1, 10 bar 1:1 CO/H$_2$ and a reaction time of 20 h. When R^2 = H, the linear product **3a-e** transformed to 2-hydroxy pyrrolidines in quantitative yield. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral GC or chiral HPLC analysis [d] Reaction were performed on a 10.0 mmol scale with substrate/Rh=10000 for 24h.
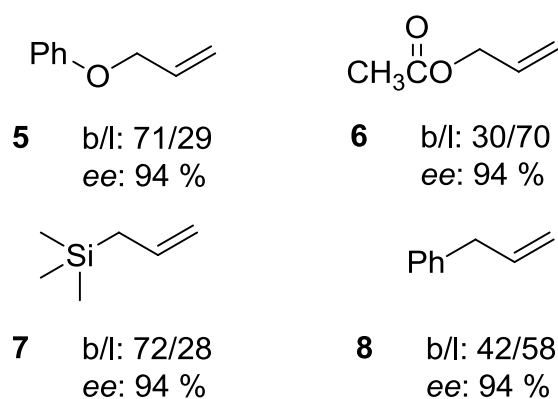
The further transformation of β^2-amino aldehyde **2a** into the corresponding acid and alcohol was proven to be straightforward and practical. **2a** was treated with NaClO$_2$, 2-methyl-2-butene in sodium dihydrogen phosphate to afford β^2-amino acid **9** in high yield and without sacrificing the ee values (96 % yield, 94 % ee). β^2-Amino acid **9** is an important building block for a number of natural products, such as cryptophycins 1-4.[6] Reduction of aldehyde **2a** with sodium borohydride gave β^2-amino alcohol **10** (95 % yield, 94 % ee), a starting material for 1β-methylcarbapenem antibiotics (Scheme **3-3**).[5]

Scheme 3-3 **Synthesis of β^2-Amino Acid and Alcohol.**

3.2.3 Asymmetric Hydroformylation of Other Allylic Compounds with Ligand B

To further explore the application of this methodology, several other functionalized allylic substrates were employed in the rhodium-**B**-catalyzed asymmetric hydroformylation reaction (Scheme **3-4**). The results showed that the functional group on the substrate has no obvious effect on the enantioselectivity, but influenced the branch/linear product ratio very much. Allyl phenyl ether **5** and allyltrimethylsilane **7** gave comparable results to *N*-allylamide substrates. Allyl acetate **6** and allylbenzene **8** both afforded high enantioselectivity (94%), but linear aldehydes predominated in the product.

Ph∖O⟋⟍⟋

O
‖
CH₃CO⟋⟍⟋

5   b/l: 71/29
     ee: 94 %

6   b/l: 30/70
     ee: 94 %

∖Si⟋⟍⟋
|

Ph⟋⟍⟋

7   b/l: 72/28
     ee: 94 %

8   b/l: 42/58
     ee: 94 %

Scheme 3-4 **Asymmetric Hydroformylation of Functional Allyl Substrates.**

3.3 Conclusion

In conclusion, a variety of allylic substrates have been successfully employed in a rhodium-yanphos-catalyzed hydroformylation reaction under mild conditions, with up to 99 % ee and 9700 TON. To the best of our knowledge, this is the first example of applying *N*-allylamides and *N*-allylsulfonamides in asymmetric hydroformylation. This reaction provides an alternative catalytic route to β^2-amino aldehydes, acids, and alcohols, which have promising application in pharmaceutical and synthetic chemistry. Further studies to improve the regio- and enantioselectivity and to explore more applications of this catalyst are underway.

Experimental Section

General Methods: All reactions and manipulations that were sensitive to moisture or air were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise noted. Solvents were dried with standard procedures and degassed with N_2. Column chromatography was performed using 200-400 mesh silica gel supplied by Natland International Corp. Thin-layer chromatography (TLC) was performed on EM reagents 0.25 mm silica 60-F plates. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ or CD_2Cl_2 on Bruker Avance 400 MHz spectrometers or Varian Mercury 500 MHz FT-NMR spectrometer. Optical rotation was obtained on a Perkin-Elmer 341 MC polarimeter. HRMS were recorded on a Thermo LTQ Orbitrap hybrid mass spectrometer. GC analysis was carried out on Hewlett-Packard 7890 gas chromatography using chiral capillary columns. HPLC analysis was carried out on Agilent 1200 series. Compound **1a** is commercially available from Sigma-Aldrich company.

General Procedure for The Preparation of *N*-Allylamides:

To a solution of benzoyl chloride (2.40 mL, 20.7 mmol) in CH_2Cl_2 (80 mL) was added dropwise a solotion of allylamine (1.52 mL, 20.0 mmol) and Et_3N (2.90 mL, 20.7 mmol) in CH_2Cl_2 (20 mL)   at 0 ℃. After the addition, the reaction was allowed to warm to room temperature and stirred overnight. The reaction was

quenched with water (50 mL) and the aqueous layer was washed with CH_2Cl_2 (50 mL). The organic layers were combined and evaporated under vacuum. The residue was subjected to column chromatography on silica-gel to afford **1b**.
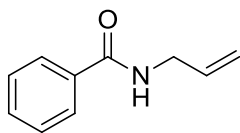
N-allylbenzamide (1b): yield = 95 %; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, J = 8.0 Hz, 2H), 7.41-7.37 (m, 1H), 7.32-7.29 (m, 2H), 6.67 (br, 1H), 5.82 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H), 5.14 (dq, J = 17.2, 1.6 Hz, 1H), 5.06 (dq, J = 10.4, 1.6 Hz, 1H), 3.98-3.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.5, 134.5, 134.2, 131.4, 128.5, 127.0, 116.5, 42.4 ppm.
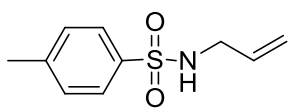
N-allyl-4-methylbenzenesulfonamide (1c): yield = 92 %; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 5.60 (ddt, J = 17.2, 10.4, 7.0 Hz, 1H), 5.27 (t, J = 7.0 Hz, 1H), 5.05 (dq, J = 17.2, 1.6 Hz, 1H), 4.94 (dq, J = 10.4, 1.2 Hz, 1H), 3.45 (tt, J = 7.0, 1.6 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.4, 137.0, 133.1, 129.7, 127.2, 117.4, 45.7, 21.5 ppm.
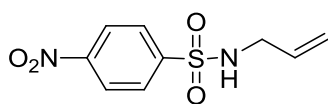

N-allyl-4-nitrobenzenesulfonamide (1d): yield = 99 %; pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.37 (dt, J = 8.8, 2.0 Hz, 2H), 8.06 (dt, J = 9.2, 2.0 Hz, 2H), 5.72 (ddt, J = 17.2, 10.4, 7.0 Hz, 1H), 5.18 (dq, J =

17.2, 1.2 Hz, 1H), 5.14 (dq, *J* = 10.4, 0.9 Hz, 1H), 4.72 (t, *J* = 4.8 Hz, 1H), 3.70 (tt,

J = 7.0, 1.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 150.2, 146.2, 132.4, 128.4,

124.4, 118.4 45.9 ppm.
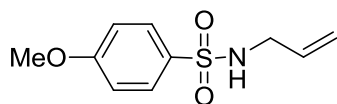
_N_-allyl-4-methoxybenzenesulfonamide (1e): yield =

96 %; pale yellow solid; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.71 (d, *J* = 9.2 Hz, 2H),

6.88 (d, *J* = 8.8 Hz, 2H), 5.60 (ddt, *J* = 17.2, 10.0, 7.0 Hz, 1H), 5.30 (t, *J* = 7.0 Hz,

2H), 5.24 (dd, *J* = 17.2, 1.2 Hz, 1H), 4.94 (dq, *J* = 10.0, 1.2 Hz, 1H), 3.74 (s, 3H),

3.44 (t, *J* = 7.0, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 162.9, 133.2, 131.5, 129.2,

117.4, 114.3, 55.7, 45.7 ppm.
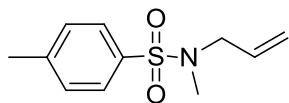
_N_-allyl-_N_-methyl-4-methylbenzenesulfonamide (1f):[16]

N-allyl-4-methylbenzenesulfonamide **1c** (2.11 g, 10.0 mmol) was added   in

portions to a suspension of sodium hydride (0.53 g, 22.0 mmol) in anhydrous THF

at 0 ℃ and stirred for 1 h at room temperature. Then methyl iodide (12.45 mL,

200.0 mmol) was added to this solution at 0 ℃. The mixture was refluxed

overnight. Water was added and THF was removed under vacuum. The product

was extracted with ethyl acetate. The extracts were dried over sodium sulfate, the

solvents were removed, and the residue was subjected to column chromatography

on silica-gel with ethylacetate-hexane mixture (5:1) to afford **1f** (yield = 99 %) as

pale yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.68 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J*

= 8.0 Hz, 2H), 5.60 (ddt, *J* = 17.2, 10.0, 9.6 Hz, 1H), 5.20 (dt, *J* = 3.2, 1.6 Hz, 1H),

5.17 (dd, *J* = 2.8, 1.6 Hz, 1H), 3.62 (d, *J* = 6.4 Hz, 2H), 2.66 (s, 3H), 2.44 (s, 3H),

3.44 (t, *J* = 7.0, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 143.4, 134.6, 132.7, 129.7,

127.5, 119.1, 53.1, 34.2, 21.5 ppm.
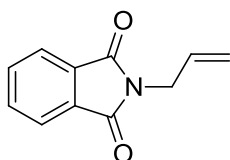
N-allylphthalimide (1g):[17] To a suspension of 10.2 g (54

mmol) potassium phthalimide (9.46 g, 50.0 mmol) and

tetrabutylammoniumbromide (0.32 g, 1.0 mmol) in 50ml anhydrous DMF was

added allylbromide (4.37 mL, 50.0 mmol) dropwise. The mixture is stirred at

room temperature over night and then poured into 50ml water. The solid is

filtrated and washed with water. The crude product is purified by recrystallization

from hexane to yield **1g** (yield = 80 %) as white crystal; ^{1}H NMR (400 MHz,

CDCl$_3$) δ: 7.86 (ddd, *J* = 6.4, 4.4, 1.2 Hz, 2H), 7.72 (ddd, *J* = 6.4, 4.4, 1.2 Hz, 2H),

5.89 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.25 (dt, *J* = 17.2, 1.2 Hz, 1H), 5.20 (dt, *J* =

10.4, 1.2 Hz, 1H), 4.30 (dq, *J* = 5.6, 1.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ:

167.9, 134.0, 132.2, 131.6, 123.3, 117.8, 40.1 ppm.
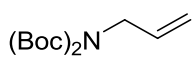
 N,N-Bis(*tert*-butoxycarbonyl)allylamine (1h):[18] To a 100 mL

flask were charged di-*tert*-butyliminodicarboxylate (2.0 g, 9.2 mmol), allyl

bromide (0.97 mL, 11.0 mmol), terabutylammonium bromide (0.44 g, 0.14 mmol),

NaOH (50% w/w, 4 mL, 46 mmol), water (10 mL), and 2-Methyl-THF (10 mL),

and the mixture was heated to 42 ˚C for 2 h with stirring. The product was

extracted with ethyl acetate. The extracts were dried over sodium sulfate, the

solvents were removed, and the residue was subjected to column chromatography on silica-gel with ethylacetate-hexane mixture (5:1) to afford **1h** (yield = 95 %) as colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 5.89 (ddt, J = 17.2, 10.0, 6.4 Hz, 1H), 5.16 (dd, J = 17.2, 1.6 Hz, 1H), 5.20 (dt, J =10.0, 1.6 Hz, 1H), 4.17 (dq, J = 6.4, 1.2 Hz, 2H), 1.50 (s, 18H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 152.3, 133.8, 116.2, 82.3, 48.5, 28.0 ppm.

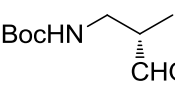**General Procedure for Asymmetric Hydroformylation:**

In a glovebox filled with nitrogen, to a 2 mL vial equipped with a magnetic bar was added ligand **B** (0.004 mmol) and Rh(acac)(CO)$_2$ (0.001 mmol in 0.20 mL solvent). After stirring for 10 min, substrate (1.0 mmol) and additional solvent was charged to bring the total volume of the reaction mixture to 1.0 mL. The vial was transferred into an autoclave and taken out of the glovebox. Carbon monoxide (5 atm) and hydrogen (5 atm) were charged in sequence. The reaction mixture was stirred at 60 ℃ (oil bath) for 20 h. The reaction was cooled and the pressure was carefully released in a well ventilated hood. The conversion and branch/linear ratio were determined by ^{1}H NMR spectroscopy from the crude reaction mixture. The enantiomeric excesses of **2a** and products of **5-8** were determined by chiral GC analysis with a Supelco's Beta Dex 225 column from the crude reaction mixture. The ee of **2b-2f** and **2h** were determined by reducing them to alcohol with NaBH$_4$ and analyzing with HPLC under condition in the following. The ee of **2g** by oxidizing it into acid with Jone's reagent and then reacting with TMSCH$_2$N$_2$

to afford the corresponding ester which was analyzed with HPLC.

Hydroformylation of Styrene at High Substrate/Catalyst Ratio:

In a glovebox filled with nitrogen, to a 20 mL vial equipped with a magnetic bar was added ligand **B** (0.004 mmol) and Rh(acac)(CO)$_2$ (0.001 mmol in 0.10 mL solvent). After stirring for 10 min, substrate (10.0 mmol) and additional solvent was charged to bring the total volume of the reaction mixture to 10.0 mL. The vial was transferred into an autoclave and taken out of the glovebox. Carbon monoxide (5 atm) and hydrogen (5 atm) were charged in sequence. The reaction mixture was stirred at 60 ℃ (oil bath) for 20 h. The reaction was cooled and the pressure was carefully released in a well ventilated hood. The conversion, branch/linear ratio and enantiomeric excesses of **2a** were determined in the same method as above.
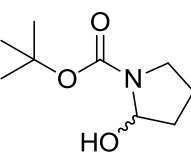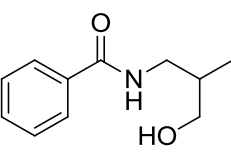
Determine the Enantiomeric Excess of Product 2g:

A portion of the reaction mixture (about 1/10) was diluted with acetone (10 mL) and 1ml of Jones reagent was added dropwise in a ice bath. 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 dissolved in a mixture of THF/Methanol (2 mL, v/v 2:1). To this solution, (trimethylsilyl)diazomethane solution (0.2 mL, 2.0 M in diethyl ether) was added in a ice bath under nitrogen atmosphere. The mixture was

allowed to stir at room temperature for 30 min, then was concentrated under reduced pressure. The residue was subjected a flash chromatography on silica gel (elution with Hexane/EtOAc 3:1). The obtained ester was analyzed by Chiral GC (Supelco β-120) to determine the enantiomeric excess.

Characterization Data (Optical Rotation, NMR and GC/HPLC condition) of

Hydroformylation Products and Their Derivatives

BocHN— CHO **(S)-*tert*-butyl (2-methyl-3-oxopropyl)carbamate (2a):** $[\alpha]^{24}_D =$ -26.5 (c = 1.5, CHCl$_3$) at 94% *ee*; Enantiomeric excess was determined by GC with a Supelco's Beta Dex 225 column, Temperature program: 120 ˚C, 1 ˚C/min to 150 ˚C, stay 10 mins, Flow rate = 1.0 mL/min, t$_{minor}$ = 20.9 min, t$_{major}$ = 21.1 min; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.64 (s, 1H), 4.99 (m, 1H), 3.28 (d, *J* = 6.4 Hz, 2H), 2.56-2.61 (m, 1H), 1.31 (s, 9H), 1.11 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 203.9, 155.9, 79.4, 47.2, 40.6, 28.3, 11.2 ppm; HRMS (ESI): *m/z*: calcd for C$_9$H$_{18}$NO$_3$ ([*M*+H]$^+$): 188.1287; found: 188.1281.

***tert*-butyl 2-hydroxypyrrolidine-1-carboxylate (4a):** ^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.64 (s, 1H), 4.99 (m, 1H), 3.28 (d, *J* = 6.4 Hz, 2H), 2.56-2.61 (m, 1H), 1.31 (s, 9H), 1.11 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 203.9, 155.9, 79.4, 47.2, 40.6, 28.3, 11.2 ppm.

***N*-(3-hydroxy-2-methylpropyl)benzamide (Table 3, entry 2):** $[\alpha]^{24}_D = 15.1$ ° (c = 1.0, CHCl$_3$) at 95% *ee*; Enantiomeric excess was determined by HPLC analysis: Daicel Chiralcel OD-H, hexane/*i*PrOH = 95:5, flow rate = 1.0 mL/min, λ = 254 nm, t$_{minor}$ = 27.2 min, t$_{major}$ = 30.2 min; ^{1}H NMR (400 MHz,

CDCl$_3$) δ: 7.77 (d, J = 7.2 Hz, 2H), 7.49 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.13 (br, 1H), 3.86 (br, 1H), 3.65-3.59 (m, 2H), 3.40-3.29 m, 2H), 1.95-1.86 (m, 1H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 168.8, 134.2, 131.6, 128.6, 127.0, 65.2, 43.1, 35,9, 14.7 ppm; HRMS (ESI): m/z: calcd for C$_{11}$H$_{16}$NO$_2$ ([M+H]$^+$): 194.1181; found: 194.1174.
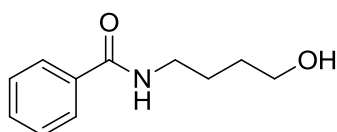
N-(4-hydroxybutyl)benzamide (Table 3, entry 2):
^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.75 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 7.0 Hz, 1H), 7.37 (t, J = 7.5 Hz, 2H), 6.93 (br, 1H), 3.66 (t, J = 6.0 Hz, 2H), 3.44 (m, 1H), 2.87 (br, 1H), 1.65 (tt, J = 6.0, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 167.9, 134.6, 131.4, 128.5, 126.9, 62.2, 39.9, 29.8, 26.2 ppm.
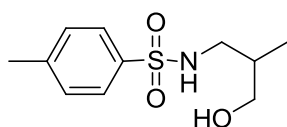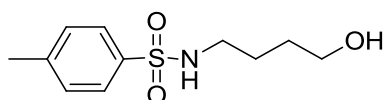

N-(3-hydroxy-2-methylpropyl)-4-methylbenzenesulfonamide (Table 3, entry 3): [α]^{24}$_D$ = 5.3 (c = 2.0, CHCl$_3$) at 94% ee; Enantiomeric excess was determined by HPLC analysis: Daicel Chiralcel AD, hexane/iPrOH = 85:15, flow rate = 1.0 mL/min, λ = 205 nm, t$_{major}$ = 14.0 min, t$_{minor}$ = 19.4 min; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.75 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 5.50 (t, J = 6.4 Hz, 1H), 3.67-3.63 (m, 1H), 3.49-3.44 (m, 1H), 3.01-2.94 (m, 1H), 2.91-2.84 (m, 1H), 2.50 (br, 1H), 2.43 (s, 3H), 1.90-1.80 (m, 1H), 0.85 (d, J = 6.8 Hz, 3H); ^{13}C NMR

(100 MHz, CDCl$_3$) δ: 143.2, 136.9, 129.6, 126.9, 65.4, 46.5, 35.3, 21.4, 14.3 ppm;
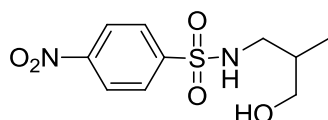
HRMS (ESI): *m/z*: calcd for C$_{11}$H$_{18}$NO$_3$S ([*M*+H]$^+$): 244.1007; found: 244.1007.

N-(4-hydroxybutyl)-4-methylbenzenesulfonamide (Table 3, entry 3): ^{1}H NMR

(500 MHz, CDCl$_3$) δ: 7.74 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 3.60 (t, *J*

= 6.0 Hz, 2H), 2.95 (t, *J* = 6.5 Hz, 2H), 2.42 (s, 3H), 1.56 (tt, *J* = 6.5, 6.0 Hz, 4H);

^{13}C NMR (100 MHz, CDCl$_3$) δ: 143.3, 136.9, 129.7, 127.1, 62.2, 43.0, 29.5, 26.3,

21.5 ppm.

N-(3-hydroxy-2-methylpropyl)-4-nitrobenzenesulfonamide (Table 3, entry 4):

[α]^{24}$_D$ = 5.6 (c = 1.0, CHCl$_3$) at 92% *ee*; Enantiomeric excess was determined by

HPLC analysis: Daicel Chiralcel AD, hexane/*i*PrOH = 85:15, flow rate = 1.0

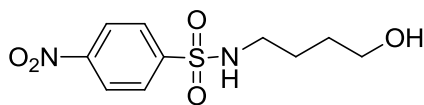mL/min, λ = 254 nm, t$_{major}$ = 32.4 min, t$_{minor}$ = 40.1 min; ^{1}H NMR (400 MHz,

CDCl$_3$) δ: 8.37 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 8.0 Hz, 1H), 5.65 (br, 1H),

3.74-3.70 (m, 1H), 3.50-3.45 (m, 1H), 3.14-3.08 (m, 1H), 2.99-2.93 (m, 1H), 2.01

(br, 1H), 1.96-1.85 (m, 1H), 0.88 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$)

δ: 150.1, 146.1, 128.3, 124.4, 66.7, 47.6, 35.0, 14.3 ppm; HRMS (ESI): *m/z*: calcd

for C$_{10}$H$_{15}$N$_2$O$_5$S ([*M*+H]$^+$): 275.0702; found: 275.0697.

N-(4-hydroxybutyl)-4-nitrobenzenesulfonamide (Table 3, entry 4): ^{1}H NMR (500 MHz, CDCl$_3$) δ: 8.36 (d, J = 7.5 Hz, 2H), 8.05 (d, J = 7.5 Hz, 2H), 5.47 (br, 1H), 3.66 (t, J = 6.0 Hz, 2H), 3.05 (t, J = 6.5 Hz, 2H), 1.73 (br, 1H), 1.61 (tt, J = 6.5, 6.0 Hz, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 150.0, 146.2, 128.3, 124.4, 62.3, 43.3, 29.4, 26.7 ppm.
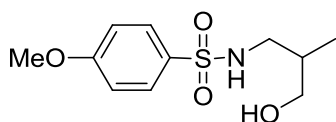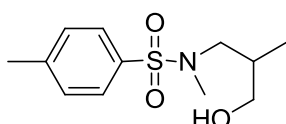

N-(3-hydroxy-2-methylpropyl)-4-methoxybenzenesulfonamide (Table 3, entry 5): [α]$^{24}_D$ = 3.6 (c = 2.0, CHCl$_3$) at 96% *ee*; Enantiomeric excess was determined by HPLC analysis: Daicel Chiralcel AD, hexane/*i*PrOH = 85:15, flow rate = 1.0 mL/min, λ = 254 nm, t$_{major}$ = 20.7 min, t$_{minor}$ = 28.6 min; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.78 (dd, J = 9.0, 1.5 Hz, 2H), 6.96 (dd, J = 9.0, 1.5 Hz, 2H), 3.85 (s, 3H), 3.64-3.61 (m, 1H), 3.47-3.43 (m, 1H), 2.96-2.92 (m, 1H), 2.87-2.83 (m, 1H), 1.86-1.79 (m, 1H), 0.83 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 162.9, 131.5, 129.1, 114.3, 65.9, 55.6, 46.7, 35.3, 14.4 ppm; HRMS (ESI): *m/z*: calcd for C$_{11}$H$_{18}$NO$_4$S ([*M*+H]$^+$): 260.0957; found: 260.0954.
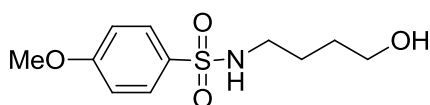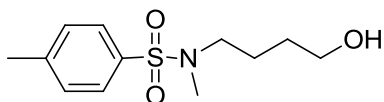

N-(4-hydroxybutyl)-4-methoxybenzenesulfonamide (Table 3, entry 5): [1]H

NMR (500 MHz, CDCl$_3$) δ: 7.79 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H),

3.87 (s, 3H), 3.62 (t, J = 6.0 Hz, 2H), 2.96 (t, J = 6.5 Hz, 2H), 1.57 (tt, J = 6.5, 6.0

Hz, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 162.9, 131.6, 129.2, 114.3, 62.2, 55.6,

43.0, 29.6, 26.3 ppm.

**N-(3-hydroxy-2-methylpropyl)-N-Methyl-4-methylbenzenesulfonamide**

(Table 3, entry 6): $[\alpha]^{24}_D$ = -13.6 (c = 2.0, CHCl$_3$) at 94% ee; Enantiomeric

excess was determined by HPLC analysis: Daicel Chiralcel AS, hexane/iPrOH =

94:6, flow rate = 1.0 mL/min, λ = 205 nm, t$_{minor}$ = 32.6 min, t$_{major}$ = 36.5 min; ^{1}H

NMR (500 MHz, CDCl$_3$) δ: 7.57 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H),

3.61 (dd, J = 11.0, 4.5 Hz, 1H), 3.43 (dd, J = 11.0, 5.0 Hz, 1H), 3.00 (dd, J = 13.5,

8.0 Hz, 1H), 2.65 (s, 3H), 2.91-2.84 (dd, J = 14.5, 8.0 Hz, 1H), 2.34 (s, 3H),

1.85-1.79 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 143.5,

134.0, 129.7, 127.3, 64.3, 53.0, 35.7, 34.0, 21.4, 14.5 ppm; HRMS (ESI): m/z:

calcd for C$_{12}$H$_{20}$NO$_3$S ([M+H]$^+$): 258.1164; found: 258.1161.

N-(4-hydroxybutyl)-N-Methyl-4-methylbenzenesulfonamide (Table 3, entry

6): ^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.64 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 7.5 Hz,

2H), 3.66 (t, J = 5.5 Hz, 2H), 3.01 (t, J = 6.5 Hz, 2H), 2.69 (s, 3H), 2.41 (s, 3H),

1.88 (br, 1H), 1.61 (tt, J = 6.5, 5.5 Hz, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 143.3,

134.5, 129.7, 127.4, 62.3, 49.9, 34.6, 29.4, 24.0, 21.5 ppm.
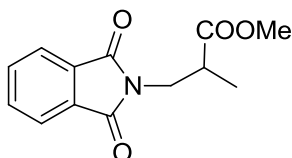
**Methyl 2-(phthalimidomethyl)-propanoate (Table 3,**

entry 7): $[\alpha]^{24}_D$ = 18.7 (c = 1.0, CHCl$_3$) at 96% *ee*; (*R*): lit.[19] $[\alpha]^{25}_D$ = -17.2 (c =

0.95, CHCl3) for 84% *ee*; Enantiomeric excess was determined by HPLC analysis:

Daicel Chiralcel OD-H, hexane/*i*PrOH = 90:10, flow rate = 0.5 mL/min, λ = 254

nm, t$_{minor}$ = 19.6 min, t$_{major}$ = 21.9 min; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.79 (dd, J

= 5.5, 3.0 Hz, 2H), 7.68 (dd, J = 5.5, 3.0 Hz, 2H), 3.92 (dd, J = 14.0, 7.5 Hz, 1H),

3.73 (dd, J = 14.0, 7.0 Hz, 1H), 3.62 (s, 3H), 2.97-2.90 (m, 1H), 1.16 (d, J = 7.0

Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 174.3, 168.1, 134.0, 131.9, 123.3, 52.0,

40.5, 38.5, 14.6 ppm.
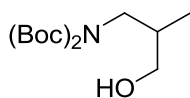
N,*N*-**Bis(*tert*-butoxycarbonyl)-3-hydroxy-2-methylpropylamine (Table 3,**

entry 8): $[\alpha]^{24}_D$ = -9.5 (c = 1.0, CHCl$_3$) at 99% *ee*; Enantiomeric excess was

determined by HPLC analysis: Daicel Chiralcel AD, hexane/*i*PrOH = 95:5, flow

rate = 0.5 mL/min, λ = 205 nm, t$_{minor}$ = 9.9 min, t$_{major}$ = 12.5 min; ^{1}H NMR (400

MHz, CDCl$_3$) δ: 3.63-3.29 (m, 4H), 1.86-1.78 (m, 1H), 1.44 (s, 18H), 0.88 (d, J =

7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 152.8, 82.2, 62.5, 46.0, 29.7, 28.1,

25.4 ppm; HRMS (ESI): *m/z*: calcd for $C_{14}H_{28}NO_5$ ([*M*+H]$^+$): 290.1967; found: 290.1968.
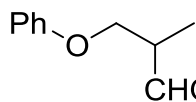
2-methyl-3-phenoxypropanal (product of 5): Enantiomeric excess was determined by GC with a Supelco's Beta Dex 225 column, Temperature program: 90 °C, 1 °C/min to 160 °C, Flow rate = 1.0 mL/min, t_{minor} = 44.3 min, t_{major} = 44.5 min; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.80 (s, 1H), 7.31-7.25 (m, 2H), 6.98-6.94 (m, 1H), 6.94-6.87 (m, 2H), 4.22-4.18 (m, 1H), 4.15-4.12 (m, 1H), 2.89-2.81 (m, 1H), 1.26 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 202.9, 158.6, 129.5, 121.2, 114.6, 67.7, 46.3, 10.8 ppm.
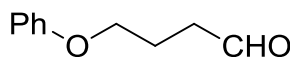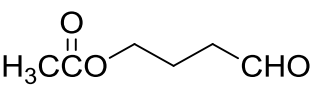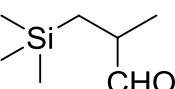
4-phenoxybutanal (product of 5): ^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.87 (s, 1H), 7.31-7.25 (m, 2H), 6.98-6.94 (m, 1H), 6.94-6.87 (m, 2H), 4.00 (t, *J* = 6.0 Hz, 2H), 2.66 (t, *J* = 7.2 Hz, 2H), 2.12 (tt, *J* = 7.2, 6.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 158.7, 129.5, 120.9, 114.5, 66.6, 40.7, 22.1 ppm.
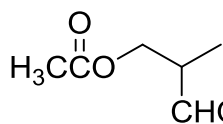
2-methyl-3-oxopropyl acetate (product of 6): Enantiomeric excess was determined by GC with a Supelco's Beta Dex 225 column, Temperature program: 90 °C, 1 °C/min to 108 °C, 4 °C/min to 132 °C, Flow rate = 1.0 mL/min, t_{minor} = 16.7 min, t_{major} = 17.0 min; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.70 (s, 1H), 4.33-4.25 (m, 2H), 2.76-2.66 (m, 1H), 1.17 (d, *J* = 7.2 Hz, 2H); ^{13}C

NMR (100 MHz, CDCl$_3$) δ: 202.0, 170.8, 63.7, 45.7, 20.7, 10.6 ppm.

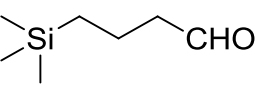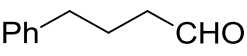**4-oxobutyl acetate (product of 6):** ^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.80 (s, 1H), 4.10 (t, J = 6.0 Hz, 2H), 2.55 (t, J = 7.2 Hz, 2H), 2.05 (s, 3H), 1.98 (tt, J = 7.2, 6.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 201.1, 170.9, 63.4, 40.5, 21.3, 20.9 ppm.

2-methyl-3-(trimethylsilyl)propanal (product of 7): Enantiomeric excess was determined by GC with a Supelco's Beta Dex 225 column, Temperature program: 100 ˚C, 1 ˚C/min to 120 ˚C, Flow rate = 1.0 mL/min, t$_{major}$ = 6.9 min, t$_{minor}$ = 7.1 min; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.56 (s, 1H), 2.38-2.31 (m, 1H), 1.13 (d, J =8 6. Hz, 3H), 1.01-0.95 (m, 2H), 0.06 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 206.7, 44.4, 19.5, 18.0, 1.0 ppm.

4-(trimethylsilyl)butanal (product of 7): ^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.77 (s, 1H), 2.46 (t, J = 7.2 Hz, 2H), 1.65 (tt, J = 8.4, 7.2 Hz, 2H), 0.53 (t, J = 8.4 Hz, 2H), 0.01 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 204.8, 49.3, 18.7, 18.4, 0.02 ppm.

**2-methyl-3-phenylpropanal (product of 8):** Enantiomeric excess

was determined by GC with a Supelco's Beta Dex 225 column, Temperature program: 95 ˚C, 60 mins, 5 ˚C/min to 140 ˚C, 10 mins, Flow rate = 1.0 mL/min, t_{minor} = 53.2 min, t_{major} = 54.0 min; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.70 (s, 1H), 7.31-7.27 (m, 2H), 7.23-7.16 (m, 3H), 3.08 (dd, J = 13.2, 5.6 Hz, 1H), 2.71-2.64 (m, 1H), 2.59 (dd, J = 13.2, 5.6 Hz, 1H), 1.09 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 204.3, 138.9, 129.0, 128.5, 126.4, 48.1, 36.7, 13.2 ppm.

Ph⌒⌒CHO **4-phenylbutanal (product of 8)**: ^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.80 (s, 1H), 7.31-7.27 (m, 2H), 7.23-7.16 (m, 3H), 2.67 (t, J = 7.6 Hz, 2H), 2.45 (t, J = 7.2 Hz, 2H), 1.96 (tt, J = 7.6, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 202.2, 141.2, 129.0, 128.5, 126.1, 43.2, 35.0, 23.7 ppm.

BocHN⌒COOH **(S)-3-(tert-butoxycarbonylamino)-2-methylpropanoic acid (9):**[20] To a stirred solution of (S)-tert-butyl (2-methyl-3-oxopropyl)carbamate **(2a)** (374 mg, 2.0 mmol) in tert-butyl alcohol/water (5:1, 20 mL) were added successively NaH$_2$PO$_4$ 2H$_2$O (528 mg, 3.4 mmol), 2-methyl-2-butene (1.49 mL, 14.0 mmol), and NaClO$_2$ (634 mg, 7.0 mmol). The resulting mixture was stirred for 5 h. The solvent was removed under reduced pressure. The residue was extracted with ethyl acetate, washed with water and brine, and dried over MgSO$_4$. The combined organic layers were concentrated under reduced pressure to give **9** (389 mg, 96% yield) as a viscous oil (>95% purity by ^{1}H NMR analysis). The crystals were obtained by dissolving the oil in minimum CH$_2$Cl$_2$, adding hexanes

(20 mL) and then standing in the freezer. $[\alpha]^{24}_D = 26.1$ (c = 1.5, CHCl$_3$) at 94% *ee*;

(*R*): lit.[21] $[\alpha]^{23}_D = -25.5$ (c= 1.41, CHCl$_3$); Enantiomeric excess was determined

according to literature;[22] ^{1}H NMR (400 MHz, CDCl$_3$) δ: 5.09 (br, 1H), 3.39 (m,

1H), 3.28 (m, 1H), 2.71 (m, 1H), 1.44 (s, 9H), 1.21 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR

(100 MHz, CDCl$_3$) δ: 181.9, 156.9, 81.4, 43.2, 40.6, 28.7, 15.2 ppm.
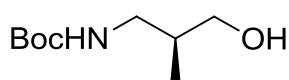
BocHN⌇⌇OH **(*S*)-*tert*-butyl (3-hydroxy-2-methylpropyl)carbamate**

(10):

To a cooled solution of (*S*)-*tert*-butyl (2-methyl-3-oxopropyl)carbamate **(2a)** (187

mg, 1.0 mmol) in 20 mL of MeOH was added NaBH$_4$ (40 mg, 1.1 mmol) in

portions at 0 ℃. After stirring at room temperature for 1h, the reaction mixture

was quenched with saturated aqueous NH$_4$Cl (10 mL) and extracted 3 times with

ethyl acetate (30 mL). The combined organic layers were washed with brine and

dried over Na$_2$SO$_4$, the solvents were removed under reduced pressure. The crude

product was purified by silica-gel column chromatography (Hexanes/EtOAc = 2:1)

to yield **10** (180 mg, 95% yield) as a colorless oil. $[\alpha]^{24}_D = 12.1$ (c = 1.0, CHCl$_3$)

at 94% *ee*; (*R*): lit.[21] $[\alpha]^{23}_D = -25.5$ (c = 1.41, CHCl3); Enantiomeric excess was

determined according to literature;[22] ^{1}H NMR (400 MHz, CDCl$_3$) δ: 5.09 (br, 1H),

3.57 (m, 1H), 3.28 (m, 1H), 3.15 (m, 1H), 2.99 (m, 1H), 1.74(m, 1H), 1.41 (s, 9H),

0.82 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 157.6, 79.6, 64.5, 43.0,

36.4, 28.5, 14.6 ppm.[23]

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Chapter 4

Synthesis of Aryl Substituted Dihydropyrroles via Rh-Catalyzed Hydroformylation Reaction

4.1 Backgroud

The increasing number of heterocyclic natural products and the well known applications of heterocyclic chemistry to pharmaceutical research dictate the development of new synthetic methods for aquiring heterocycles.[1] Aryl substituted dihydropyrroles have been utilized as both annelation[2] and Diels-Alder[3] substrates in the synthesis of various natural products, such as Mesembrine[4] and Epimeloscine (Scheme 4-1).[5] The traditional method to this heterocycle intermediate involves multi steps, low yield synthesis including the cyclopropyliminium ion rearrangement.[3, 4] It is believed that hydroformylation could offer an atom efficient approach to this molecular frameworks by simply using an allylic olefin and its derivatives as substrates.
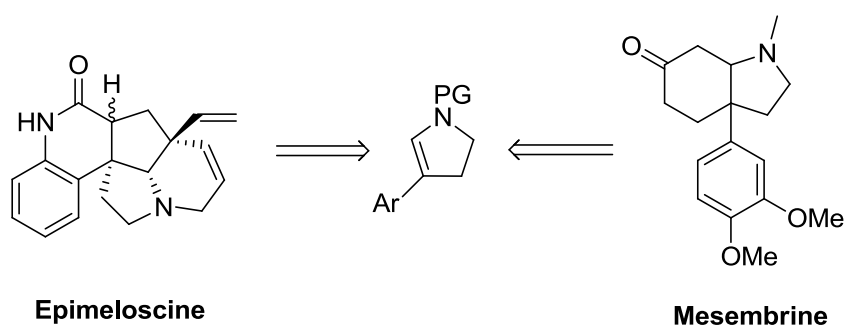
Scheme 4-1 Application of 4-Aryl-2,3-Dihydropyrroles.

Busacca and co-workers have reported a facile synthesis of 4-Aryl-2,3-Dihydropyrroles via hydroformylation of N-allylsulfonamides.[6] Despite their success, the reactivity of their approach turns out to be extremely slow and more importantly, the hydroformylation reaction only gives hydroxypyrrolidines as final product. The more desired dihydropyrrole products requires further transformation. As we know, the highly reactive dihydropyrrole exhibit excellent convertible ability in many synthetic applications, such as oxidation, reduction,[7] annelation[2] and Diels-Alder,[3] etc. These interesting features attract our attention to develop a more useful procotol to reach our target products.
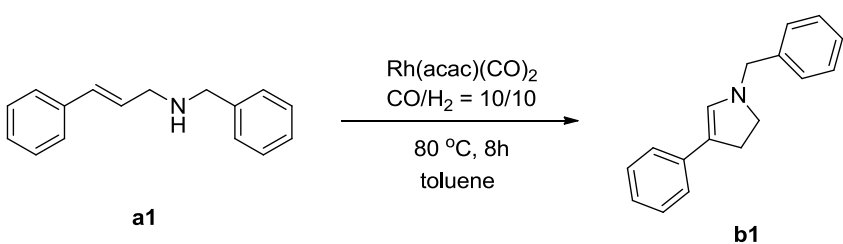
4.2 Results and Discussion

4.2.1 Optimizing Reaction Conditions

In this chapter, we report an efficient synthetic route for the construction of 4-aryl-2,3-dihydropyrroles. Recently, Nozaki and several other groups have employed allylic alcohols and homoallylic alcohols as substrates for AHF to prepare substituted tetrahydrofurans and γ-butyrolactones.[8] We envision that allylamines which have similar property as allylic alcohols, are very good substrate candidates in synthesizing dihydropyrroles and its derivatives.

The initial test was carried out in toluene with (E)-N-Benzylcinnamylamine as standard substrate. The effect of ligand on hydroformylation of these internal olefins was first evaluated and the results are summarized in Table 4-1. The rhodium catalyst was prepared in situ by mixing the ligand with $Rh(acac)(CO)_2$. When using bidentate ligands as catalyst, such as, Xantphos,[9] dppb[10] (Table **4-1**, entry 1, 3), the reaction barely happened, expecpt Bisbi[11] which gave moderate conversion (Table **4-1**, entry 2). The reaction was also sensitive to size of the catalyst, when introducing the sterically more hindered $P(o\text{-toyl})_3$ as ligand, the reaction conversion was limited to 11% (Table **4-1**, entry 4). Triphenyl phosphite ligand which was usually efficient towards a variety of substrates, was not able to generate any product (Table **4-1**, entry 4), on the contrary, triphenyl phosphine

provided the best results comparing to all ligands we had tested (Table **4-1**, entry

6-8). Internal olefins were usually known as low reactive substrates towards

hydroformylation, however, in this catalytic system, only 0.5 mol% loading was

needed. More importantly, the cheap triphenyl phosphine made this reaction more

economically favored.

Table 4-1 **Screening Different Ligands.**[a]

Entry	Ligand	Ligand/Metal	Conv.(%)[b]
1	Xantphos	10/1	1
2	Bisbi	10/1	57
3	dppb	10/1	3
4	P(OPh)$_3$	10/1	N.R.
5	P(*o*-tolyl)$_3$	10/1	11
6	PPh$_3$	5/1	78
7	PPh$_3$	10/1	83
8	PPh$_3$	15/1	67

[a] The reactions were carried out with 0.5 mol % of Rh(acac)(CO)$_2$ as the catalyst precursor. [b] The conversion were determined by ^{1}H NMR.

After the best ligand was chosen, we started to test the effect of solvent on the reaction. Not surprisingly, nonpolar solvent such as toluene gave the best conversion of the reaction compared to results led by polar solvents (Table **4-2**, entry 1-4). CH_2Cl_2 only provides 5 % conversion possibly due to the contradictory between the high reaction temperature and its low boiling point (Table **4-2**, entry 5). The best combination of H_2/CO pressure was found to be 10/10 atm though hardly much difference was observed after varying the pressure of the reaction (Table **4-2**, entry 6-9). Finally, by lowering the concentration of the reaction to 0.001 mol%, we could reach full conversion without changing other critierias (Table **4-2**, entry 12-15).

Table 4-2 **Optimizing Reaction Conditions.**[a]
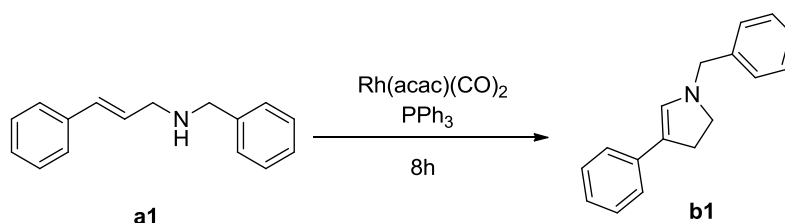
Entry	Solvent	H_2/CO(atm)	Temp.(^{o}C)	[Rh]	Conv.(%)[b]
1	Toluene	10/10	80	0.002	83
2	EtOAc	10/10	80	0.002	71
3	Aceton	10/10	80	0.002	60
4	THF	10/10	80	0.002	60
5	CH_2Cl_2	10/10	80	0.002	5
6	Toluene	5/5	80	0.002	76

7	Toluene	15/15	80	0.002	81
8	Toluene	10/20	80	0.002	82
9	Toluene	20/10	80	0.002	68
10	Toluene	10/10	60	0.002	40
11	Toluene	10/10	80	0.002	83
12	Toluene	10/10	80	0.002	83
13	Toluene	10/10	80	0.001	90
14	Toluene	10/10	80	0.004	68
15[c]	Toluene	10/10	80	0.001	99

[a] The reactions were carried out with 0.5 mol % of Rh(acac)(CO)$_2$ as the catalyst precursor. [b] The conversion were determined by ^{1}H NMR. [c] Reaction time of 16 h

4.2.2 Expanding Substrate Scope

With the optimized reaction condition in hands, we then expanded the scope of the substrates (Table **4-3**). By simply combining corresponding cinnamaldehydes with different amins, all substrates could be easily synthesized with good yields. Our initial research focused on benzyl protected cinnamamines (Results shown in Table **4-3**). All (*E*)-N-Benzylcinnamylamine derivatives could be successfully converted to corresponding 4-aryl-2, 3-dihydropyrroles with excellent conversion and good yield. The readily formed hydroxypyrrolidines spontaneously underwent dehydroxylation and gave out our desired product without losing conversion in this step. The electronic donating group would result

in a lower conversion, mainly because the electron rich olefin unwilling underwent olefin insertion compared to electron deficient carbon-carbon double bond in the catalytic cycle. To our surprise, alkyl group protected amine substrates showed better reactivity under the same reaction conditions (Table **4-3**, entry 10-13). It suggested that the following Schiff base reaction requires more electron rich amine to attack the aldehyde that generated from the hydroformylation step. By using this method, 6 membered 1,2,3,4-tetrahydropyridine could also be synthesized at excellent yield (Table **4-3**, entry 14). It indicated by adopting this method, it might open a potential chemo controlled atom efficient way to build large heterocyclic rings.

Table 4-3 **Expanding the Scope of Substrates.**[a]

Entry	R_1	R_2	n	Conv.(%)[b]	Yield.(%)[c]
1	H	Bn	1	99	93
2	*p*-Cl	Bn	1	99	84
3	*o*-Cl	Bn	1	99	95
4	*m*-Cl	Bn	1	90	65
5	*p*-Me	Bn	1	86	64
6	*p*-OMe	Bn	1	80	62
7	*p*-F	Bn	1	73	55
8	3,4-OMe	Bn	1	75	52
9	*p*-NO$_2$	Bn	1	99	85
10	H	*t*Bu	1	99	83
11	H	Bu	1	99	92
12	H	Me	1	99	88
13	H	Ph	1	83	68

14	H	Ph	2	99	90

^a The reactions were carried out with 0.5 mol % of Rh(acac)(CO)$_2$ as the catalyst precursor. ^b The conversion were determined by ¹H NMR. ^c Isolated yield.

5.3 Conclusion

In summary, we have achieved an efficient methodlogy in the synthesis of a series of 4-Aryl-2,3-dihydropyrroles with excellent yields. The core part of the synthesis involves hydroformylation of protected cinnamamines followed by rapid ring closure reaction. The significant improvement in reactivity and chemoselectivity suggest a potential application in building large heterocycles in an atom efficient fashion.

Experimental Section

General Methods: All reactions and manipulations that were sensitive to moisture or air were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise noted. Solvents were dried with standard procedures and degassed with N_2. Column chromatography was performed using 200-400 mesh silica gel supplied by Natland International Corp. Thin-layer chromatography (TLC) was performed on EM reagents 0.25 mm silica 60-F plates. ^1H and ^{13}C spectra were recorded in $CDCl_3$ on Bruker Avance 300 MHz spectrometers or Varian Mercury 500 MHz FT-NMR spectrometer. HRMS were recorded on a Thermo LTQ Orbitrap hybrid mass spectrometer.

**General Procedure for Synthesizing Cinnamamines**

A 100ml round flask was charged with 1.32g cinnamaldehyde (10 mmol, 1 eq) in 20ml methanol. Benzylamine (10 mrmol, 1 eq) was added in one portion. The resulting solution was refluxed for 4 hours, and then the reaction was allowed to cool to r.t. followed by addition of 120mg $NaBH_4$(30 mmol, 3 eq). Upon stirring at r.t. for another 4 hours, the reactionwas quenched by H_2O, and extracted with EtOAc (3X50 mL). The combined EtOAc layers were dried (MgSO4), and the solvents removed in vacuo to give a brown residue. This material was purified on silica gel chromatography eluting with Hexane/EtOAc(3:1) to give 1.51g of **a1** as pale yellow oil.
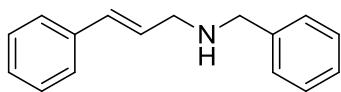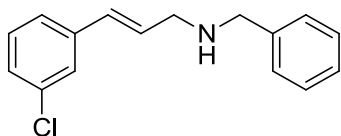
N-[(2E)-3-phenyl-2-propen-1-yl]-Benzenemethanamine (a1): ^{1}H NMR (400 MHz, CDCl$_3$):δ 7.42-7.25 (m, 10H), 7.60-7.55 (d, 1H, *J*=15 Hz), 6.40-6.30 (m, 1H), 3.88 (s, 2H), 3.48-3.46 (d, 2H, *J*=6 Hz).
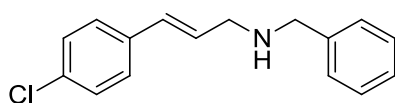
N-[(2E)-3-(4-chlorophenyl)-2-propen-1-yl]-Benzenemethanamine (a2): ^{1}H NMR (400 MHz, CDCl$_3$):δ 7.11-7.20 (m, 9H), 6.31-6.34 (d, 1H, *J*=12 Hz), 6.11-6.14 (d, 1H, *J*=12 Hz), 3.68 (s, 2H), 3.26-3.27 (d, 2H, *J*=4 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 139.17, 134.64, 131.81, 128.91, 128.23, 127.60, 127.37, 127.09, 126.40, 125.93, 52.33, 50.00
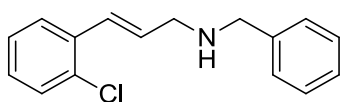
N-[(2E)-3-(2-chlorophenyl)-2-propen-1-yl]-Benzenemethanamine (a3): ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.03-7.45 (m, 9H), 6.19-6.24 (m, 2H), 3.76 (s, 2H), 3.37-3.38 (d, 2H, *J*=4 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 140.39, 135.42, 132.97, 131.69, 129.76, 128.55, 128.47, 128.35, 127.56, 127.11, 126.98, 126.96, 53.42, 51.31
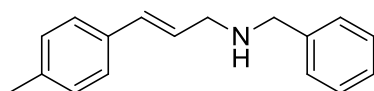
N-[(2E)-3-(3-chlorophenyl)-2-propen-1-yl]-Benzenemethanamine (a4): ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.07-7.23 (m, 9H), 6.34-6.38 (d, 1H, J=16 Hz), 6.18-6.22 (d, 1H, J=16 Hz), 3.71 (s, 2H), 3.30-3.32 (d, 2H, J=8 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ139.11, 138.03, 133.43, 129.10, 129.03, 128.87, 128.69, 127.41, 127.13, 126.21, 125.99, 125.19, 123.39, 52.30, 49.92
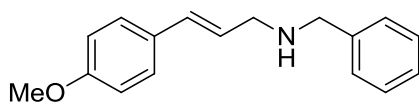

N-[(2E)-3-(4-methylphenyl)-2-propen-1-yl]-Benzenemethanamine (a5): ^{1}H NMR (400 MHz, CDCl$_3$):δ 7.04-7.28 (m, 9H), 6.43-6.47 (d, 1H, J=12 Hz), 6.20-6.24 (d, 1H, J=16 Hz), 3.75 (s, 2H), 3.34-3.35 (d, 2H, J=4 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 139.29, 135.94, 133.37, 130.20, 128.24, 128.16, 127.32, 127.10, 126.35, 125.85, 125.18, 125.14, 52.24, 50.18, 20.07
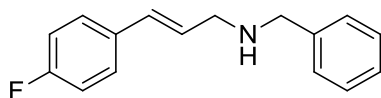

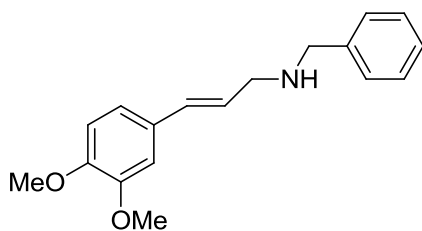**N-[(2E)-3-(4- methoxylphenyl)-2-propen-1-yl]-Benzenemethanamine (a6):** ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.16-7.27 (m, 7H), 6.76-6.78 (m, 2H), 6.38-6.42 (d, 1H, J=16 Hz), 6.08-6.13 (m, 1H), 3.72 (s, 2H), 3.63 (s, 2H), 3.30-3.31 (d, 2H, J=4 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.23, 140.54, 130.97, 130.13, 128.50, 128.30, 127.65, 127.56, 127.03, 126.37, 114.24, 114.14, 55.22, 53.40, 51.41
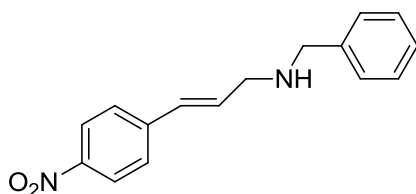
N-[(2E)-3-(4-florolphenyl)-2-propen-1-yl]-Benzenemethanamine (a7): ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.11-7.20 (m, 9H), 6.31-6.34 (d, 1H, J=12 Hz), 6.11-6.14 (d, 1H, J=12 Hz), 3.68 (s, 2H), 3.26-3.27 (d, 2H, J=4 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 139.17, 134.64, 131.81, 128.91, 128.23, 127.60, 127.37, 127.09, 126.40, 125.93, 52.33, 50.73


N-[(2E)-3-(3,4- methoxylphenyl)-2-propen-1-yl]-Benzenemethanamine (a8): ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.18-7.29 (m, 5H), 6.72-6.90 (m, 3H), 6.41-6.45 (d, 1H, J=16 Hz), 6.16-6.19 (d, 1H, J=12 Hz), 3.81 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.36-3.37 (d, 2H, J=4 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 149.06, 148.67, 140.32, 131.01, 130.29, 128.32, 128.09, 126.86, 126.53, 119.26, 111.26, 108.85, 55.80, 55.70, 53.29, 51.21


N-[(2E)-3-(4-nitrophenyl)-2-propen-1-yl]-Benzenemethanamine (a9): [1]H

NMR (400 MHz, CDCl$_3$):δ 7.11-7.20 (m, 9H), 6.31-6.34 (d, 1H, J=12 Hz), 6.11-6.14 (d, 1H, J=12 Hz), 3.68 (s, 2H), 3.26-3.27 (d, 2H, J=4 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 139.17, 134.64, 131.81, 128.91, 128.23, 127.60, 127.37, 127.09, 126.40, 125.93, 52.33, 49.93
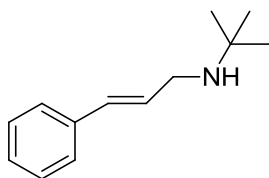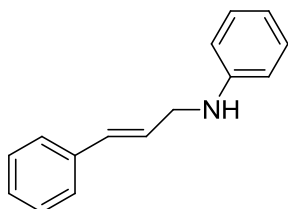

(E)-N-*t*Butylcinnamylamine (a10): ^{1}H NMR (400 MHz, CDCl$_3$):δ 7.17-7.35 (m, 9H), 6.48-6.52 (d, 1H, J=16 Hz), 6.29-6.34 (m, 1H), 3.33-3.35 (d, 2H, J=8 Hz),1.14 (m, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.31, 130.79, 129.41, 128.48, 127.21, 126.24, 50.46, 45.16, 29.10
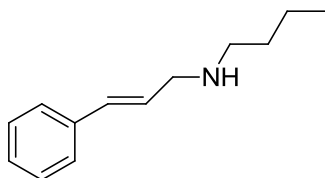

(E)-N-Butylcinnamylamine (a11): ^{1}H NMR (400 MHz, CDCl$_3$):δ 7.21-7.35 (m, 9H), 6.50-6.54 (d, 1H, J=16 Hz), 6.28-6.33 (d, 1H, J=20 Hz), 3.40-3.42 (d, 2H, J=8 Hz), 2.64-2.67 (d, 2H, J=12 Hz), 1.46-1.52 (m, 2H), 1.33-1.39 (m, 2H), 0.90-0.94 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.27, 131.13, 128.78, 128.54, 127.31, 126.28, 52.02, 49.27, 32.36, 20.53, 14.02
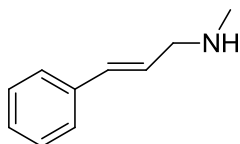
(E)-N-methylcinnamylamine (a12): ^{1}H NMR (400 MHz, CDCl$_3$):δ 7.22-7.39 (m, 9H), 6.51-6.55 (d, 1H, *J*=16 Hz), 6.30-6.33 (d, 1H, *J*=12 Hz), 3.20-3.22 (d, 2H, *J*=8 Hz), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.05, 132.83, 128.51, 127.44, 127.22, 126.32, 59.80, 42.14

(E)-N-phenylcinnamylamine (a13): ^{1}H NMR (400 MHz, CDCl$_3$):δ 7.15-7.30 (m, 7H), 6.69-6.73 (d, 1H, *J*=16 Hz), 6.58-6.66 (m, 3H), 6.28-6.32 (d, 1H, *J*=16 Hz), 3.90-3.92 (d, 2H, *J*=8 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.08, 136.91, 131.55, 129.27, 128.57, 127.52, 127.10, 126.34, 117.65, 113.08
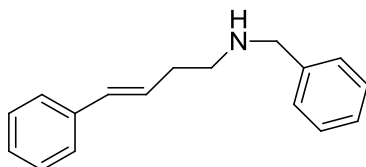

N-[(3E)-4-phenyl-3-buten-1-yl]-Benzenemethanamine (a14):[12] To a suspension of LiAlH$_4$ (900mg, 23.6 mmol) in Et$_2$O (25ml) was added a solution of styrylacetic acid (4g, 23.6 mmol) in Et$_2$O (25ml) at 0 ^{o}C. The resulting mixture was warmed up to r.t. and stirred for 3h. Then, the reaction was carefully

quenched with 2ml of 6N NaOH, extracted with CH_2Cl_2 (2X30ml). The combined CH_2Cl_2 layers were dried over $MgSO_4$, and the solvents removed in vacuo to give the product as colorless oil (98%). The freshly made alcohol (3.7g, 23.6mmol) in CH_2Cl_2 was added to a solution of TsCl (4.57g, 23.6mmol) and Et_3N (4.1ml, 23.6mmol). The reaction was stirred overnight. After purifying the product with the same procedure shown before, the resulting product (4.2g, 13.6mmol) was then subjected to a solution of benzylamine (7.3g, 68mmol) in EtOH (20ml). After the reaction was done, it was extracted with EtOAc (3X50 mL). The combined EtOAc layers were dried ($MgSO_4$), and the solvents removed in vacuo to give a brown residue. This material was purified on silica gel chromatography eluting with Hexane/EtOAc(3:1) to give 3g of **a11** (93% yield) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.07-7.26 (m, 10H), 6.33-6.37 (d, 1H, J=16 Hz), 6.06-6.11 (d, 1H, J=20 Hz), 3.65(s, 2H), 2.62-2.65 (m, 2H), 2.29-2.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.40, 140.38, 137.43, 131.36, 128.37, 128.30, 128.22, 128.14, 127.98, 127.82, 127.80, 126.91, 126.85, 126.78, 126.74, 126.54, 125.94, 53.70, 48.55, 33.52

General Procedure for Hydroformylation

A 300 mL stainless steel autoclave was charged with 2mg PPh_3 (0.008 mmol, 0.2 eq), 0.1mg $Rh(H)(CO)(PPh_3)_2$ (0.002 mmol, 0.05 eq), 88mg cinnamamine **a1** (0.4mmol, 1 eq), and 0.5 mL PhMe. The autoclave was sealed and pressurized to 20 atm with 1:1 H_2: CO, stirred for 20 hours. After the reaction was done, the

resulting solution was subjected to silica gel chromatographed eluting with Hexane/EtOAc(10/1) to give product **1b** as a pale yellow oil. The resulting products **b1-14** directly hydrogenated with Pd/C to form the more stable corresponding pyrolidines **c1-14** and characterized with HRMS.
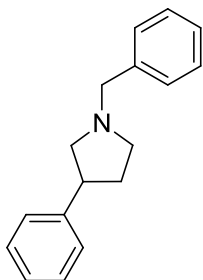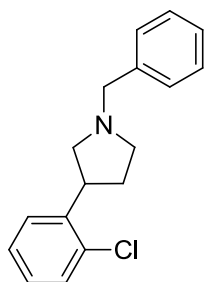

3-phenyl-1-(phenylmethyl)-Pyrrolidine ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.09-7.24 (m, 10H), 3.58 (s, 2H), 3.24-3.31 (m, 1H), 2.93-2.97 (m, 1H), 2.73-2.78 (m, 1H), 2.58-2.64 (m, 1H), 2.40-2.44 (m, 1H), 2.23-2.28 (m, 1H), 1.82-1.84 (m, 1H), 1.77-1.81 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 145.73, 139.37, 128.80, 128.37, 128.25, 127.34, 126.90, 126.03, 62.32, 60.66, 54.65, 43.43, 33.32; HRMS (ESI): m/z: calcd for C$_{17}$H$_{20}$N ([M+H+]): 238.1596; found: 238.1591.
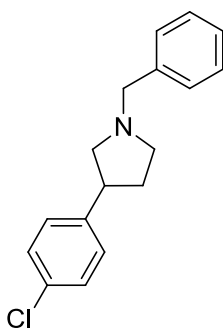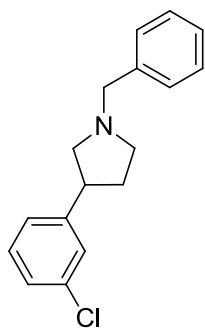

3-(4-chlorophenyl)-1-(phenylmethyl)-Pyrrolidine ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.10-7.42(m, 9H), 3.70 (s, 2H), 3.32-3.38 (dd, J_1 = 11.1, J_2 = 5.4 Hz, 1H), 2.99-3.06 (dddd, $J_1 = J_2$ = 9.2 J_3 = 5.6 J_4 = 5.4 Hz, 1H), 2.92-2.98 (ddd, J_1 = 9.2 J_2 = 6.9 J_3 = 5.8 Hz, 1H), 2.64-2.70 (ddd, J_1 = 9.5 J_2 = 7.4 J_3 = 7.1 Hz, 1H), 2.48-2.52

(m, 1H), 2.24-2.32 (m, 1H), 1.82-1.94 (dddd, $J_1 = 13$ $J_2 = 7.4$ $J_3 = 5.6$ $J_4 = 1.8$ Hz, 1H), 1.74-1.77 (dddd, $J_1 = 13$ $J_2 = 9.4$ $J_3 = 7.4$ $J_4 = 6.9$ Hz, 1H); HRMS (ESI): m/z: calcd for $C_{17}H_{19}ClN$ ([M+H+]): 272.1206; found: 272.1211.

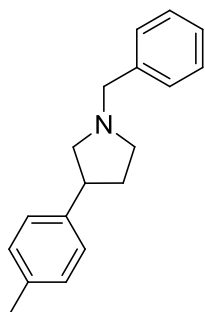**3-(2-chlorophenyl)-1-(phenylmethyl)-Pyrrolidine** ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.10-7.42 (m, 7H), 6.76-6.88 (m, 2H), 3.69 (s, 2H), 3.28-3.34 (dd, $J_1 = 11.1$, $J_2 = 5.4$ Hz, 1H), 2.99-3.05 (dddd, $J_1 = J_2 = 9.2$ $J_3 = 5.6$ $J_4 = 5.4$ Hz, 1H), 2.78-2.84 (ddd, $J_1 = 9.2$ $J_2 = 6.9$ $J_3 = 5.8$ Hz, 1H), 2.60-2.66 (ddd, $J_1 = 9.5$ $J_2 = 7.4$ $J_3 = 7.1$ Hz, 1H), 2.42-2.48 (m, 1H), 2.28-2.38 (m, 1H), 1.82-1.90 (dddd, $J_1 = 13$ $J_2 = 7.4$ $J_3 = 5.6$ $J_4 = 1.8$ Hz, 1H), 1.66-1.75 (dddd, $J_1 = 13$ $J_2 = 9.4$ $J_3 = 7.4$ $J_4 = 6.9$ Hz, 1H); HRMS (ESI): m/z: calcd for $C_{17}H_{19}ClN$ ([M+H+]): 272.1206; found: 272.1211.

3-(3-chlorophenyl)-1-(phenylmethyl)-Pyrrolidine ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.07-7.22 (m, 8H), 6.94-6.97 (m, 1H), 3.65 (s, 2H), 3.14-3.23 (dd, $J_1 = 11.1$, J_2

= 5.4 Hz, 1H), 2.95-2.98 (dddd, $J_1 = J_2 = 9.2$ $J_3 = 5.6$ $J_4 = 5.4$ Hz, 1H), 2.71-2.75 (ddd, $J_1 = 9.2$ $J_2 = 6.9$ $J_3 = 5.8$ Hz, 1H), 2.42-2.48 (ddd, $J_1 = 9.5$ $J_2 = 7.4$ $J_3 = 7.1$ Hz, 1H), 2.32-2.36 (m, 1H), 2.20-2.23 (m, 1H), 1.78-1.84 (dddd, $J_1 = 13$ $J_2 = 7.4$ $J_3 = 5.6$ $J_4 = 1.8$ Hz, 1H), 1.72-1.76 (dddd, $J_1 = 13$ $J_2 = 9.4$ $J_3 = 7.4$ $J_4 = 6.9$ Hz, 1H); HRMS (ESI): m/z: calcd for $C_{17}H_{19}ClN$ ([M+H+]): 272.1206; found: 272.1211.
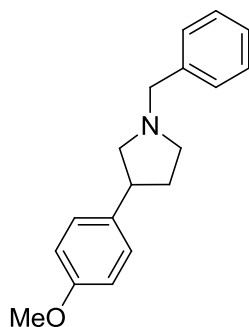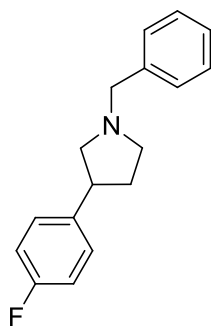

3-(4-methylphenyl)-1-(phenylmethyl)-Pyrrolidine ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.15-7.36 (m, 5H), 7.08-7.10 (m, 4H), 3.67 (s, 2H), 3.31-3.36 (dd, $J_1 = 11.1$, $J_2 = 5.4$ Hz, 1H), 3.01-3.06 (dddd, $J_1 = J_2 = 9.2$ $J_3 = 5.6$ $J_4 = 5.4$ Hz, 1H), 2.81-2.85 (ddd, $J_1 = 9.2$ $J_2 = 6.9$ $J_3 = 5.8$ Hz, 1H), 2.66-2.71 (ddd, $J_1 = 9.5$ $J_2 = 7.4$ $J_3 = 7.1$ Hz, 1H), 2.46-2.50 (m, 1H), 2.33-2.36 (m, 1H), 2.17 (s, 3H), 1.81-1.85 (dddd, $J_1 = 13$ $J_2 = 7.4$ $J_3 = 5.6$ $J_4 = 1.8$ Hz, 1H), 1.70-1.74 (dddd, $J_1 = 13$ $J_2 = 9.4$ $J_3 = 7.4$ $J_4 = 6.9$ Hz, 1H); HRMS (ESI): m/z: calcd for $C_{18}H_{22}N$ ([M+H+]): 252.1752; found: 252.1752.
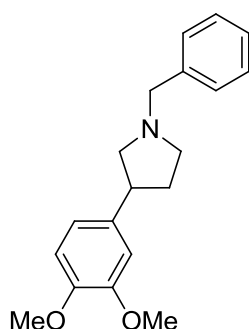
3-(4-methoxyphenyl)-1-(phenylmethyl)-Pyrrolidine ^{1}H NMR (400 MHz, CDCl$_3$):δ 7.24-7.32 (m, 3H) 7.06-7.18 (m, 4H), 6.85-6.89 (m, 3H), 3.74 (s, 3H), 3.66 (s, 2H), 3.14-3.20 (dd, $J_1 = 11.1$, $J_2 = 5.4$ Hz, 1H), 2.84-2.87 (dddd, $J_1 = J_2 = 9.2$ $J_3 = 5.6$ $J_4 = 5.4$ Hz, 1H), 2.71-2.75 (ddd, $J_1 = 9.2$ $J_2 = 6.9$ $J_3 = 5.8$ Hz, 1H), 2.56-2.62 (ddd, $J_1 = 9.5$ $J_2 = 7.4$ $J_3 = 7.1$ Hz, 1H), 2.41-2.44 (m, 1H), 2.20-2.24 (m, 1H), 1.84-1.86 (dddd, $J_1 = 13$ $J_2 = 7.4$ $J_3 = 5.6$ $J_4 = 1.8$ Hz, 1H), 1.67-1.72 (dddd, $J_1 = 13$ $J_2 = 9.4$ $J_3 = 7.4$ $J_4 = 6.9$ Hz, 1H); HRMS (ESI): m/z: calcd for C$_{18}$H$_{21}$NO ([M+H+]): 268.1701; found: 268.1708.

3-(4-florophenyl)-1-(phenylmethyl)-Pyrrolidine ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.26-7.34 (m, 3H) 7.05-7.17 (m, 4H), 6.86-6.89 (m, 3H), 3.69 (s, 2H), 3.16-3.22 (dd, $J_1 = 11.1$, $J_2 = 5.4$ Hz, 1H), 2.85-2.88 (dddd, $J_1 = J_2 = 9.2$ $J_3 = 5.6$ $J_4 = 5.4$ Hz, 1H), 2.74-2.79 (ddd, $J_1 = 9.2$ $J_2 = 6.9$ $J_3 = 5.8$ Hz, 1H), 2.54-2.60 (ddd, $J_1 = 9.5$ $J_2 = 7.4$ $J_3 = 7.1$ Hz, 1H), 2.40-2.44 (m, 1H), 2.21-2.25 (m, 1H), 1.86-1.88 (dddd, J_1

$= 13$ $J_2 = 7.4$ $J_3 = 5.6$ $J_4 = 1.8$ Hz, 1H), 1.66-1.71 (dddd, $J_1 = 13$ $J_2 = 9.4$ $J_3 = 7.4$ J_4

$= 6.9$ Hz, 1H); HRMS (ESI): m/z: calcd for $C_{17}H_{19}FN$ ([M+H+]): 256.1502; found:

256.1500.

3-(3,4-methoxyphenyl)-1-(phenylmethyl)-Pyrrolidine ^{1}H NMR (400 MHz,

CDCl$_3$):δ 7.10-7.22 (m, 5H), 6.67-6.71 (m, 2H), 6.56-6.60 (dd, $J_1 = 8.4$, $J_2 = 2.1$

Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.65 (s, 2H), 3.12-3.18 (dd, $J_1 = 11.1$, $J_2 = 5.4$

Hz, 1H), 2.80-2.84 (dddd, $J_1 = J_2 = 9.2$ $J_3 = 5.6$ $J_4 = 5.4$ Hz, 1H), 2.68-2.71 (ddd, J_1

$= 9.2$ $J_2 = 6.9$ $J_3 = 5.8$ Hz, 1H), 2.51-2.55 (ddd, $J_1 = 9.5$ $J_2 = 7.4$ $J_3 = 7.1$ Hz, 1H),

2.37-2.41 (m, 1H), 2.22-2.26 (m, 1H), 1.80-1.82 (dddd, $J_1 = 13$ $J_2 = 7.4$ $J_3 = 5.6$ J_4

$= 1.8$ Hz, 1H), 1.63-1.67 (dddd, $J_1 = 13$ $J_2 = 9.4$ $J_3 = 7.4$ $J_4 = 6.9$ Hz, 1H); HRMS

(ESI): m/z: calcd for $C_{19}H_{24}NO_2$ ([M+H+]): 298.1807; found: 298.1811.
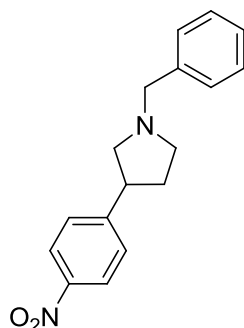
3-(4-nitrophenyl)-1-(phenylmethyl)-Pyrrolidine ^{1}H NMR (400 MHz, CDCl$_3$):

δ 8.01-8.05 (m, 2H), 7.07-7.26 (m, 7H), 3.66 (s, 2H), 3.14-3.20 (dd, $J_1 = 11.1$, J_2

= 5.4 Hz, 1H), 2.82-2.86 (dddd, $J_1 = J_2 = 9.2$ $J_3 = 5.6$ $J_4 = 5.4$ Hz, 1H), 2.70-2.73

(ddd, $J_1 = 9.2$ $J_2 = 6.9$ $J_3 = 5.8$ Hz, 1H), 2.53-2.58 (ddd, $J_1 = 9.5$ $J_2 = 7.4$ $J_3 = 7.1$

Hz, 1H), 2.36-2.40 (m, 1H), 2.24-2.28 (m, 1H), 1.82-1.84 (dddd, $J_1 = 13$ $J_2 = 7.4$

$J_3 = 5.6$ $J_4 = 1.8$ Hz, 1H), 1.59-1.63 (dddd, $J_1 = 13$ $J_2 = 9.4$ $J_3 = 7.4$ $J_4 = 6.9$ Hz,

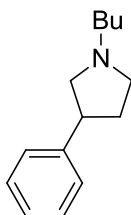1H); HRMS (ESI): m/z: calcd for $C_{17}H_{19}N_2O_2$ ([M+H+]): 283.1447; found:

283.1446.
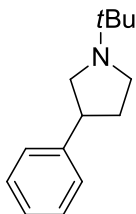
1-*tert*-Butyl-3-phenyl-pyrrolidine ^{1}H NMR (400 MHz, CDCl$_3$):δ 7.19-7.29 (m,

5H), 3.26-3.32 (m, 1H), 3.16-3.20 (ddd, $J_1 = J_2 = 8$, 1H), 2.83-2.94 (m, 2H),

2.59-2.63 (ddd, $J_1 = J_2 = 8$, 1H), 2.21-2.30 (m, 1H), 1.83-1.92 (m, 1H), 1.11 (s,

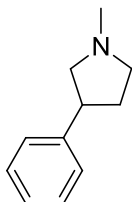9H); HRMS (ESI): m/z: calcd for $C_{14}H_{22}N$ ([M+H+]): 204.1752; found: 204.1752.

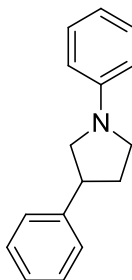**1-Butyl-3-phenyl-pyrrolidine** ^{1}H NMR (400 MHz, CDCl$_3$):δ 7.09-7.46 (m, 5H),

3.32-3.38 (m, 1H), 3.06-3.12 (ddd, $J_1 = J_2 = 12$, 1H), 2.84-2.92 (m, 1H), 2.62-2.68

(m, 1H), 2.54-2.56 (m, 1H), 2.44-2.50 (m, 1H), 2.30-2.38 (m, 1H), 1.84-1.92 (m,

2H), 1.48-1.56 (m, 2H), 1.34-1.40 (m, 2H) 0.90-0.98 (t, 3H); HRMS (ESI): m/z:

calcd for $C_{14}H_{22}N$ ([M+H+]): 204.1752; found: 204.1752.

1-Methyl-3-phenyl-pyrrolidine ^{1}H NMR (400 MHz, CDCl$_3$):δ 7.23-7.34 (m,

5H), 3.61-3.65 (m, 2H), 3.39-3.43 (m, 2H), 3.21-3.25 (m, 1H), 2.85 (s, 3H),

2.35-2.39 (m, 1H), 2.03-2.07 (m, 1H); HRMS (ESI): m/z: calcd for $C_{14}H_{22}N$

([M+H+]): 162.1283; found: 162.1287.

1,3-Diphenyl-pyrrolidine ^{1}H NMR (400 MHz, CDCl$_3$):δ 7.09-7.38 (m, 10H),

3.12-3.18 (dd, J_1 = 11.1, J_2 = 5.4 Hz, 1H), 2.80-2.84 (dddd, $J_1 = J_2$ = 9.2 J_3 = 5.6 J_4

= 5.4 Hz, 1H), 2.68-2.71 (ddd, J_1 = 9.2 J_2 = 6.9 J_3 = 5.8 Hz, 1H), 2.51-2.55 (ddd,

J_1 = 9.5 J_2 = 7.4 J_3 = 7.1 Hz, 1H), 2.37-2.41 (m, 1H), 2.22-2.26 (m, 1H), 1.80-1.82

(dddd, J_1 = 13 J_2 = 7.4 J_3 = 5.6 J_4 = 1.8 Hz, 1H), 1.63-1.67 (dddd, J_1 = 13 J_2 = 9.4

J_3 = 7.4 J_4 = 6.9 Hz, 1H); HRMS (ESI): m/z: calcd for $C_{16}H_{18}N$ ([M+H+]):

224.1439; found: 224.1437.
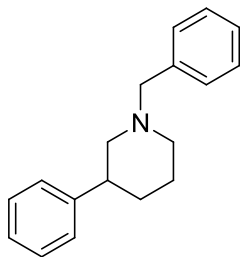
3-Phenyl-1-(phenylmethyl)-piperidine ^{1}H NMR (400 MHz, CDCl$_3$):δ 7.05-7.54 (m, 10H), 3.62 (s, 2H), 3.86-3.02 (m, 2H), 2.78-2.82 (m, 1H), 1.94-2.04 (m, 2H), 1.86-1.92 (m, 1H), 1.62-1.66 (m, 2H), 1.45-1.49 (m, 1H); HRMS (ESI): m/z: calcd for C$_{18}$H$_{22}$N ([M+H+]): 252.1752; found: 252.1754.

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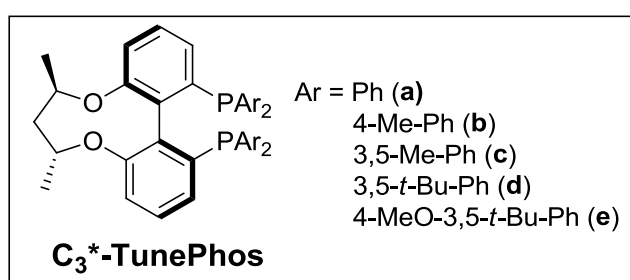
Chapter 5

Synthesis of Chiral Mono-dentate Phosphorus Ligand and its application in Enantioselective Hydrogenation of Dehydroamino Esters

5.1 Backgroud

Asymmetric hydrogenation is one of the most well developed methods to functionalize prochiral olefins.[1] Despite the extreme success of bidentate ligands in the rhodium-catalyzed asymmetric hydrogenation of preparing chiral amines,[2-4] monodentate chiral phosphorus ligands also exhibite promising results for asymmetric hydrogenation. Leading by the pioneering chiral ligand reported by Knowles,[5] a series of new chiral monodentate phosphines, phosphonites and phosporamidites have been proved to be efficient in the rhodium catalyzed asymmetric hydrogenation of dehydroamino acid and itaconic acid derivatives.[6-10,16] It is worth knowing that all reported monodentate ligands that deliver high enantioselectivity are phosphorus derivatives of binaphthol.[11]

Chiral biaryls are valuable auxiliaries in a large number of efficient asymmetric transformations, especially the C_2-symmetric binaphthal/biphenyl diphosphine and their derivatives.[12] Our group have successfully designed and synthesized a series of chiral C_3-type bisphosphines based on chiral

2,4-pentanediol tether with several highlighted features (Scheme **5-1**).[13] The enantiomerically induced coupling reaction between two aryl moieties in the ligand synthesis allows us to avoid the tedious resolution step when we attempt to introduce chirality to the ligand. With the success C_3-type ligands, it is highly desired to design a mono-dentate phosphorus ligand in the use of C_2-symmetric biphenyl moiety and chiral 2,4-pentanediol tether as its backbone.


Scheme 5-1 **Family of C_3*-TunePhos Ligand.**

5.2 Results and Discussion

5.2.1 Design and Synthesis of ligand 8

In this chapter, we report the synthesis of a novel and highly effective chiral monodentate phosphoramidite ligand and its application in the rhodium-catalyzed asymmetric hydrogenation of functionalized olefins. The synthetic route was

condense and straightforward (Scheme **5-2**): starting with commercially available 1,3-benzenediol **1**, methoxymethyl (MOM) group was introduced to phenyl ring in excellent yield. In the meantime, one of the hydroxyl groups was deprotected under base condition to generate compound **3**. In the next step, the coupling precursor **5** was synthesized via Mitsunobu reaction using (2S,4S)-pentanediol as linker,[14] and then Ullmann coupling reaction was conducted to form the biaryl scaffold **6** in good yields.[15] In this particularly step, the chirality of the new forming biaryl backbone was induced at the present of (2S,4S)-pentanediol. After removing the MOM protecting group from the moiety, the phosphorus was introduced to the chiral structure by the treatment with hexamethyl phosphoramide (HMPT) to give the final product ligand **8** as single enantimer.
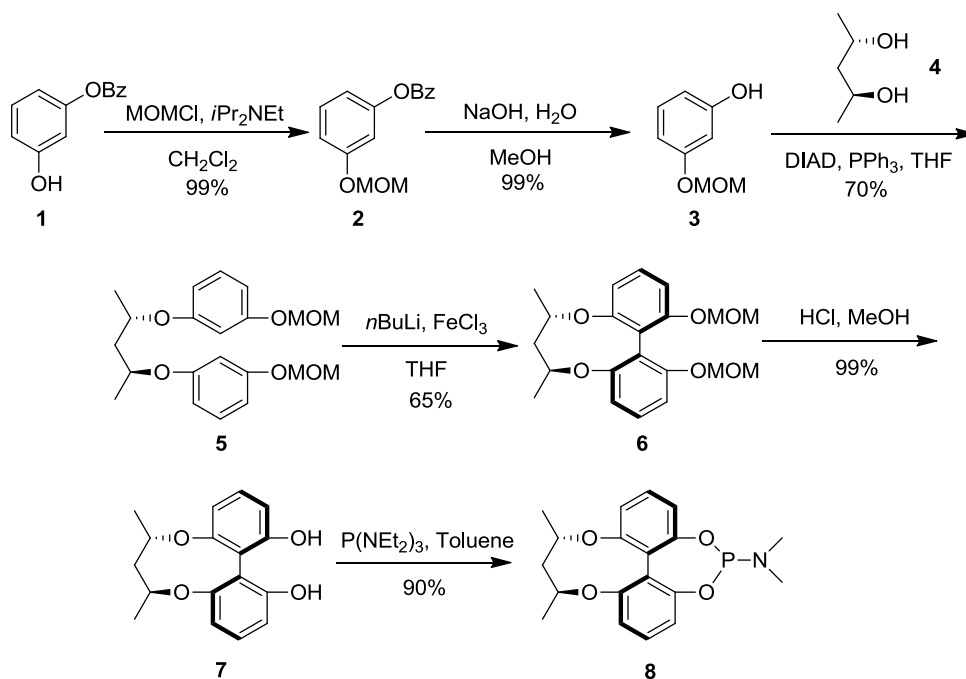
Scheme 5-2 The Synthesis of Mono Phosphoramidite Ligand **8.**

5.2.2 Asymmetric Hydrogenation with Ligand 8

Ligand **8** was found to be highly efficient in the rhodiumcatalyzed hydrogenation of dehydroamino esters. To optimize the reaction condition, (Z)-α -acetamidocinnamate was selected as the substrate. The reaction was performed at 25 ℃ under 10 atm H_2 pressure in the presence of 1 mol% catalyst formed in situ by mixing [Rh(COD)$_2$BF$_4$] with the phosphoramidite ligand **8**. A strong solvent effect was found when good enantioselectivities (80-84% ee) were observed in nonpolar solvents such as CH_2Cl_2 and toluene (Table **5-1**, Entry 1-3), whereas

polar solvent like methanol only gave a 40% ee (Table **5-1**, Entry 4). All solvents showed good reactivity with CH_2Cl_2 giving the best enantioselectivity. When lowering the reaction temperature to 0 ℃, a slightly increase in ee value was observed without sacrificing the reactivity (Table **5-1**, Entry 5).

Table 5-1 **Optimizing Reaction Condition with ligand 8.**[a]
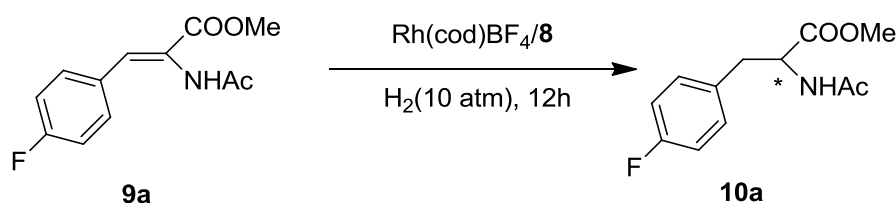
Entry	Solvent	T(℃)	Conv.	ee, %[b]
1	CH_2Cl_2	25	99	84
2	EtOAc	25	99	80
3	Toluene	25	99	80
4	MeOH	25	99	40
5	CH_2Cl_2	0	99	92

[a] The reactions were carried out under 10 atm of H_2 for 12h with **8** (1 mol %) as the catalyst precursor. [b] The ee values were determined by HPLC on a Chiralcel OD-H column.

Table **5-2** summarizes the results of Rh(I)-**8** catalyzed hydrogenation of various α -dehydroamino acid derivatives **9a-m**. All reactions went to completion in 12 h with good ee values observed (from 83-92%). An electron withdrawing substituted group on the aryl ring showed improvement in the ee value compared to other substrates (Table **5-2**, entry 1-6, 12). Entry 7-9, with the size of

substituted group increased at 2-position of the phenyl ring, a slight decrease in enantiometric excess suggested the ortho- substitutes might have interactions with the conformationally rigid ligand. For all the methyl esters, all conversions were quantitative and the enantioselectivities are comparable or higher than those formerly proved monodentate and bidentate phosphorus ligands (e.g. MonoPHOS 93–99%,[9] SIPHOS 95.6–99.3%,[16] BINAP 67–100%,[3] DuPHOS 99–99.4%,[4]).

Table 5-2 **Rhodium-catalyzed Asymmetric Hydrogenation of α-(Acylamino) Acrylic Esters.**[a]

Entry	Sub.	R	Prod.	Conv.	ee, %
1	**9a**	4-F-C_6H_4	**10a**	99	92
2	**9b**	4-Cl-C_6H_4	**10b**	99	91
3	**9c**	4-Br-C_6H_4	**10c**	99	91
4	**9d**	4-MeO-C_6H_4	**10d**	99	92
5	**9e**	4-CF_3-C_6H_4	**10e**	99	91
6	**9f**	4-NO_2-C_6H_4	**10f**	99	92
7	**9g**	2-F-C_6H_4	**10g**	99	90
8	**9h**	2-Cl-C_6H_4	**10h**	99	88
9	**9i**	2-Br-C_6H_4	**10i**	99	87

10	**9j**	3,5-F-C$_6$H$_4$	**10j**	99	90
11	**9k**	3-Br-C$_6$H$_4$	**10k**	99	90
12	**9l**	Ph	**10l**	99	83
13	**9m**	Thiophene	**10m**	99	85

[a] The reactions were carried out under 10 atm of H$_2$ for 12h with **8** (1 mol %) as the catalyst precursor. [b] The ee values were determined by HPLC on a Chiralcel OD-H column.

5.3 Conclusion

In conclusion, a successful monodentate phosphoramidite ligand has been design and synthesized for the catalytic asymmetric hydrogenation of dehydroamino esters. The easy modulared structure allowed us to further expand the scope of the ligand. Its high enantioselectivity and reactivity suggest a potential wide application in asymmetric catalysis.

Experimental Section

General Methods: All reactions and manipulations that were sensitive to air were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise noted. Solvents were dried with standard procedures and degassed with N_2. Column chromatography was performed using 200-400 mesh silica gel supplied by Natland International Corp. Thin-layer chromatography (TLC) was performed on EM reagents 0.25 mm silica 60-F plates. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ or CD_2Cl_2 on Bruker Avance 400 MHz spectrometers or Varian Mercury 500 MHz FT-NMR spectrometer. Optical rotation was obtained on a Perkin- Elmer 341 MC polarimeter. HRMS were recorded on a Thermo LTQ Orbitrap hybrid mass spectrometer. GC analysis was carried out on Hewlett-Packard 7890 gas chromatography using chiral capillary columns. HPLC analysis was carried out on Agilent 1200 series.

3-(Methoxymethoxy)phenyl Benzoate 2:[17]

To a solution of resorcinol monobenzoate (32.0 g, 150 mmol) in CH_2Cl_2 (320 mL) were added i-Pr2NEt (52 mL, 300mmol) and MOMCl (15 mL, 200 mmol) at 0 ^{o}C. The ice bath was immediately removed and the reaction mixture was refluxed for 18h. After the mixture was cooled to room temperature, pH 7 phosphate

buffer was added and the mixturewas extracted with Et$_2$O. The combined organic extracts were washed successively with water and brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 9/1) to afford MOM ether **2** (38.4 g, 99%) as a colorless oil. ^{1}H NMR (400MHz, CDCl$_3$) δ 8.18-8.22 (m, 2H), 7.60-7.66 (m, 1H), 7.48-7.53 (m, 2H), 7.33 (dd, 1H, J_1=J_2=8.1 Hz), 6.96 (ddd, 1H, J_1=8.1, J_2= 2.4, J_3=1.0 Hz), 6.94 (dd, 1H, J_1=2.4, J_2=2.0Hz), 6.88 (ddd, lH, J_1=8.1, J_2=2.0, J_3=1.0Hz), 5.19 (s, 2H), 3.48 (s, 3H).
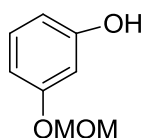
3-(Methoxymethoxy)phenol 3: [17]

To a solution of benzoate **2** (29.4 g, 114 mmol) in MeOH (80 mL) was added 3N aqueous NaOH (77.8 mL, 233 mmol) at 0°C over 15 min. This white suspension was allowed to warm to room temperature and stirred for 2 h. To this solution was added benzene (100 mL) and brine (50 mL). The mixture was cooled to 0°C, and the pH was adjusted to ca. 6 by adding 4 N HCl (ca. 35 mL). After removal of the methanol in vacuo, the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 75/25) to afford phenol 21 (17.6 g, quantitative) as white crystalline solid; ^{1}H NMR (400MHz, CDCl$_3$) δ 7.12 (dd, 1H, J_1 = 8.3, J_2 = 8.1 Hz),

6.61 (ddd, 1H, $J_1 = J_2 = J_3 = 0.7$ Hz), 6.55 (dd, 1H, $J_1 = 2.4$, $J_2 = 2.2$ Hz), 6.49 (ddd, 1H, $J_1 = 8.1$, $J_2 = 2.4$, $J_3 = 0.7$ Hz), 5.60-5.72 (broad, 1H), 5.15 (s, 2H), 3.48 (s, 3H).
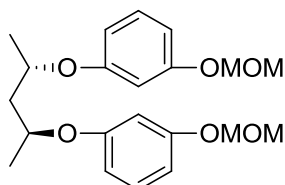
Synthesis of (2S,4S)-2,4-Bis(3-(Methoxymethoxy))pentane 5.[18]

A solution of (2R,4R)-Pentanediol **4** (8.0 g, 76.9 mmol), 3-(Methoxymethoxy)phenol **3** (24.6g, 160 mmol), triphenylphorsphine (42.0g, 160 mmol) in anhydrous THF (54 mL) in a 500 mL conical flask was stirred at 0 °C for 30 min. To the above clear and highly vicious solution was added dropwise Diisopropylzaodicarboxylate (31.4 mL, 160 mmol) within 20 min. The reaction vessel was then lowered into a 40-kHz sonication bath with ice-water and sonicated for 1 h. A large amount of participate was formed during the reaction. After triturated with 100 mL cold hexane-THF (2:1, v/v) solvent, the solids were filtered off and washed 3 times with 50 mL of hexane-THF mixture solvent. The solvents were evaporated to give a vicious yellow liquid crude product. Further purification was carried out with recrystalization in ethyl alcohol to afford pure compound **5** as a white crystal (27.9g, 70% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.05-7.10 (m, 3H) 6.47-6.58 (m, 3H) 5.06 (s, 4H) 4.57-4.62 (m, 2H) 3.43 (s, 6H) 1.93-1.96 (d, $J = 12$ Hz, 2H), 1.29-1.31 (d, $J = 8$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.27, 158.47, 129.84, 109.65, 108.60, 104.86, 94.49, 70.95, 55.97,

44.88, 20.23; HRMS (ESI): m/z: calcd for $C_{21}H_{29}O_6$ ([M+H+]): 377.1964; found: 377.1961.
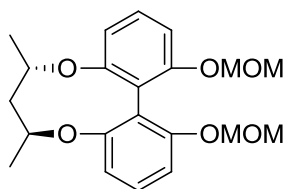
Synthesis of (R)-[6,6-(2S,4S-Pentadioxy)]-(2,2')-bis(3-(Methoxymethoxy))-(1,1')-biphenyl [(RSS)-6]:[18]

*n*BuLi (72 mmol, 29 mL, 2.5 M solution in hexane) was added dropwise to a solution of 2, 2, 6, 6-tetramethylpiperidine (11.3 g, 80 mmol) in dry THF (150 mL) at-78 ^{o}C over a period of 15 min, whereby the temperature rose to about -50 ^{o}C degree and a white precipitate formed (sometimes yellow precipitate was observed). The CO_2/acetone cooling bath was replaced by an ice/ethanol bath and the reaction mixture was stirred at about -15 ^{o}C for a further 30 minutes, then again cooled to −78 ^{o}C. A solution of compound **5** (7.5 g , 20 mmol) in dry tetrahydrofuran (60 mL) was dropwised into the above reaction mixture through a dropping funnel, whereby the temperature rose to about -68 ^{o}C and a translucent caramel-colored solution (sometimes dark green) resulted. After an additional period of 5h at -78 ^{o}C, a suspension consisting of anhydrous $FeCl_3$ (9.7 g, 60mmol) in 150 ml THF was added directly in one portion to the reaction mixture. After completion of the reaction overnight (monitored with TLC), the reaction was quenched with 10 mL saturated ammonium hydroxide at 0 ^{o}C. After filtration, the solvent was removed on rotvapor. The oil residue was dissolved in 200 mL

CH$_2$Cl$_2$, washed with 2N HCl aq., brine, dried over anhydrous Na$_2$SO$_4$ and concentrated. The solid residue was purified by silica gel chorography (EtOAc/MeOH = 100:5). A white solid compound **6** was obtained (4.8g, 65% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.14-7.18 (m, 3H) 6.74-6.89 (m, 3H) 4.96 (s, 4H) 4.48-4.51 (m, 2H) 3.27 (s, 6H) 1.73-1.76 (d, *J* = 12 Hz, 2H), 1.27-1.39 (d, *J* = 8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 158.33, 156.32, 128.55, 117.98, 111.64, 109.80, 95.35, 75.13, 55.64, 41.14, 22.27; HRMS (ESI): m/z: calcd for C$_{21}$H$_{27}$O$_6$ ([M+H+]): 375.1808; found: 375.1805.
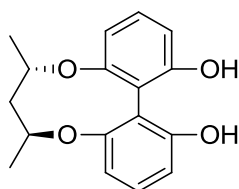
Synthesis of (R)-[6,6-(2S,4S-Pentadioxy)]-(2,2')-bis(hydroxyl)-(1,1')-biphenyl [(RSS)-7]:[19]

To a stirred solution of **6** (1.44 g, 3.6 mmol) in methanol (20 mL) was added 10 drops of concentrated HCl at 60 ℃. Then the mixture was stirred for 0.5 h at the same temperature. After removal of the solvent, the residue was purified by column chromatography on silica gel. Elution with hexene/ethyl acetate (6:1) gave the compound **7** in quantitative yield. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.13-7.18 (m, 3H) 6.62-6.67 (m, 3H) 4.49-4.54 (m, 2H) 1.73-1.76 (d, *J* = 12 Hz, 2H), 1.27-1.28 (d, *J* = 4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.06, 153.74, 129.76, 112.81, 110.76, 100.44, 75.23, 40.98, 22.16; HRMS (ESI): m/z: calcd for C$_{17}$H$_{19}$O$_4$ ([M+H+]): 287.1283; found: 287.1285.
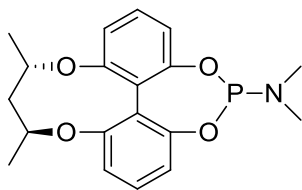
C₃* Mono-dentate phosphinamidate ligand 8:[20]

A mixture of (RSS) diol **7** (200 mg, 0.8 mmol), hexamethylphosphorustriamide (0.2 ml, 1 mmol) and 2 ml dry toluene were heated at reflux under nitrogen for 2 h. After cooling to room temperature, the mixture was concentrated and purified by chromatography on a silica gel column with petroleum ether/EtOAc (16:1) to give (RSS) **8** as white solid (237 mg, 90% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.31-7.37 (m, 2H) 7.08-7.16 (m, 2H) 6.85-6.95 (m, 2H) 4.72-4.75 (m, 2H) 3.39 (s, 6H) 1.89-1.94 (m, 2H), 1.37-1.40 (m, 6H); ^{13}C NMR (100 MHz, DMSO) δ 157.77, 151.82, 129.27, 115.06, 114.78, 112.83, 74.54, 41.12, 35.27, 22.09; ^{31}P NMR (162 MHz, DMSO) δ 145.64; HRMS (ESI): m/z: calcd for $C_{19}H_{22}NO_4P$ ([M+H+]): 360.1365; found: 360.1364.

General Procedure of Hydrogenation with In situ Made Catalyst

A solution of [Rh(COD)₂]BF₄ (2.1 mg, 0.0050 mmol) and ligand **8** (3.6 mg, 0.01 mmol) in CH_2Cl_2 (3 mL) was stirred in a glove-box for 10 min to allow the corresponding catalyst precursor to form. After substrate (0.5 mmol) was added, the mixture was hydrogenated in an autoclave for the time mentioned in the tables. After carefully releasing the hydrogen, the reaction mixture was passed through a short silicagel plug to remove the catalyst. After removing the solvent, the desired product was obtained and chiral HPLC was used to measure the enantiomeric

excess.

Determination of Enantiomeric Excess of Hydrogenation Products:

The ee values of **10a-m** were determined according to reference [21; Zhu. G.;

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Publications

1) "A Facile Synthesis of Aryl Substituted Dihydropyrroles via Rh-Catalyzed Hydroformylation Reaction" **Bonan Cao**, Xiaowei Zhang, Xin Zheng, Xumu Zhang. *Adv. Synth. Catal.* Submitted

2) "Synthesis of New Monodentae Phosphine-phosphoramidite Ligand and Its Applications in Enantioselective Rh-Catalyzed Hydrogenations" **Bonan Cao**, Guohua Hou, Xumu Zhang. *J. Org. Chem.* Submmited

3) "Synthesis and application of modular phosphine-phosphoramidite ligands in asymmetric hydroformylation: Structure-selectivity relationship" Xiaowei Zhang, **Bonan Cao**, Shichao Yu, Xumu Zhang. *Angew. Chem. Int. Ed.* **2010**, *49*, 4047. (Highlighted in Synfact)

4) "Rhodium-Catalyzed Asymmetric Hydroformylation of N-Allylamides: Highly Enantioselective Approach to β^2-Amino Aldehydes" Xiaowei Zhang, Bonan Cao, Yongjun Yan, Shichao Yu, Baoming Ji, Xumu Zhang. *Chem. Eur. J.* **2010**, *16*, 871.