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SYNTHESIS OF NEW PHOSPHORUS LIGANDS FOR ASYMMETRIC CATALYSIS

A Thesis in

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by

Yaping Zou

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The thesis of Yaping Zou was reviewed and approved* by the following:

Xumu Zhang
Professor of Chemisry
Thesis Advisor

Ken S. Feldman
Professor of Chemistry

Harry R. Allcock
Professor of Chemistry

Gong Chen
Assistant Professor of Chemistry

Ayusman Sen
Professor of Chemistry
Head of the Department of Chemistry

*Signatures are on file in the Graduate School

ABSTRACT

Asymmetric hydroformylation is one of the most challenging transformations because it requires both high enantioselectivities and regioselectivies with high activity. Also, there are few effective ways to prepare chiral ligands. To address these challenges, a series of new diphosphite ligands have been developed in our lab. These new ligands have been investigated in rhodium-catalyzed asymmetric hydroformylation of vinyl acetate and its derivatives. They provide moderate enantioselectivities (up to 80 % ee) and excellent regioselectivies (b/l up to 98/2) in rhodium-catalyzed asymmetric hydroformylations of vinyl acetate and its derivatives.

Although numerous efficient chiral ligands have been developed for asymmetric hydrogenation, there is no universal ligand which can be applied in all prochiral substrates with high enantioselectivity. To expand the substrate scope, the development of new chiral ligands is highly desirable. A chiral diphosphine ligand has been designed and synthesized. This new ligand bearing chiral C_3-biphenyl backbone provides excellent enantioselectivies in rhodium-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters and itaconate.

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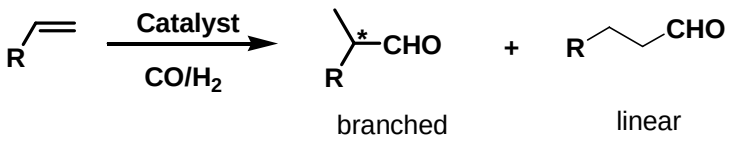
Chapter 1

Introduction

1.1 Rhodium-Catalyzed Asymmetric Hydroformylation

1.1.1 Background

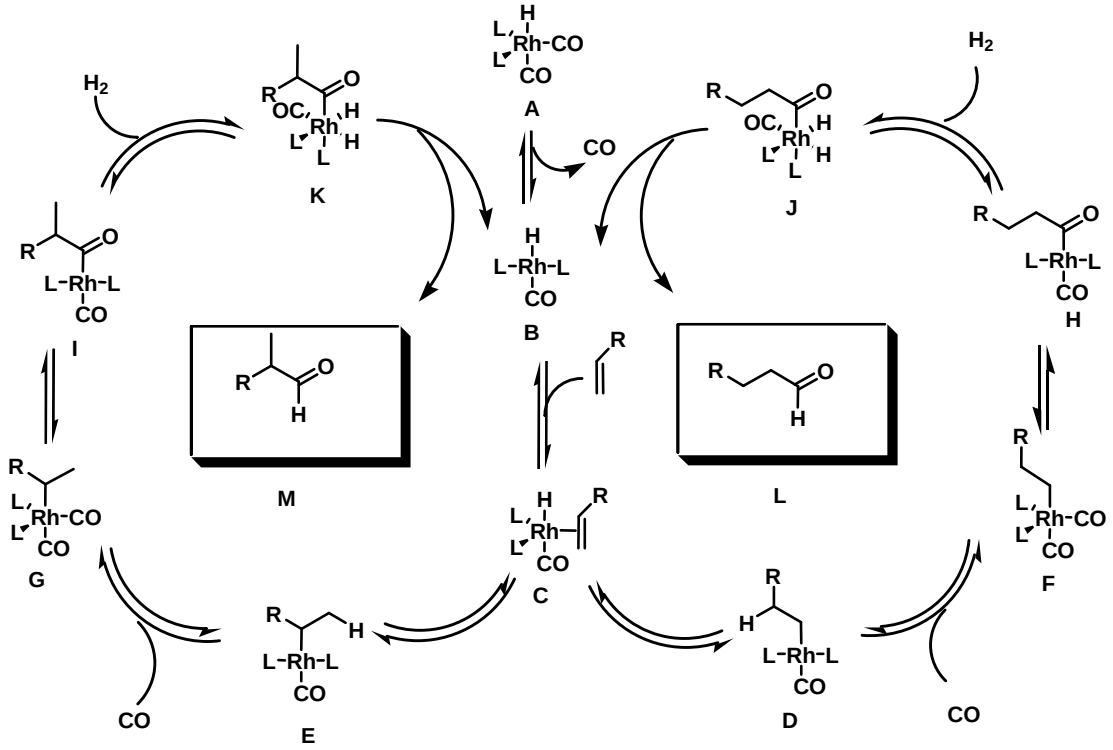
Hydroformylation is the reaction of olefins with carbon monoxide and hydrogen to form aldehydes (eq. 1).[1] It was discovered by Otto Roelen in 1938, using cobalt catalysts.[2] In 1966, Wilkinson and coworkers found rhodium catalysts were much more reactive and selective than cobalt catalysts.[3] Rhodium complexes modified by phosphine ligands were commercialized by Union Carbide in 1970's.[4] Now it is one of the most important homogeneous catalysis in industry. For asymmetric hydroformylation[5], the chiral branched aldehyde is the desired product. It is essential to control both enantioselectivity and regioselectivity. Asymmetric hydroformylation has been applied in the synthesis of drugs and pharmaceutical intermediates.[6]



(1)

1.1.2 Mechanism for Rhodium-Catalyzed Hydroformylation

The mechanism of hydroformylation was first proposed by Breslow and Heck in the early 1960s.[1b,7] The so-called dissociative mechanism is widely accepted (Scheme **1-1**). First, the rhodium precursor reacts with the ligand in the presence of CO and H_2 and forms a trigonal bipyramidal intermediate **A**. Then, dissociation of one carbon monoxide yields a 16e unsaturated compound **B**, which is an active species to begin the catalytic cycle. Coordination of the olefin to the rhodium center generates olefin complex **C**, which can go to either **D** (leading to linear product) or **E** (leading to branched product) depending on the direction of olefin insertion. Trigonal bipyramidal complexes **F** and **G** are formed via coordination of carbon monoxide to the rhodium center. Migratory insertion of the alkyl group to one of the coordinated carbon monoxides gives complexes **H** and **I**. 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**.



Scheme **1-1**. Mechanism for rhodium-catalyzed hydroformylation

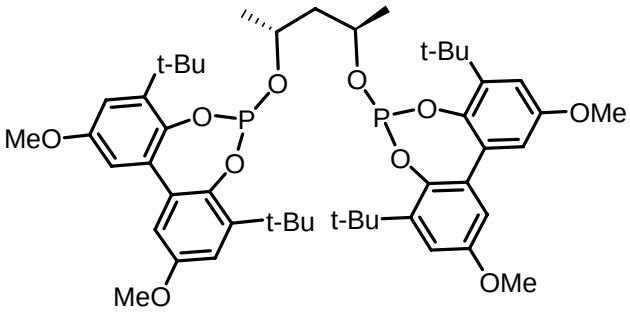
1.1.3 Some Chiral Phosphorus Ligands for Rhodium-Catalyzed Asymmetric Hydroformylation

The development of highly selective phosphorus ligands is the most attractive but also challenging research area in hydroformylation. It is hard to control both enantioselectivities and activities. High enantioselectivies could be obtained at low temperature, but the activities of the catalysts are very low. High activities of the catalysts could be achieved at high temperature, but the enantioselectivies are diminished. Also, it is not easy to obtain both high enantioselectivity (high ee value) and high regioselectivity (high b/l ratio).

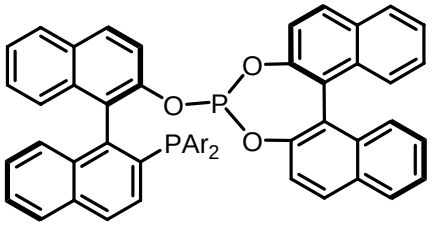
Some representative ligands are shown in Figure **1-1**. Chiraphite **1** was the first successful diphosphite ligand for highly enantioselective hydroformylation developed by Babin and Whiteker at Union Carbide in 1992.[8] Excellent enantioselectivity (up to 90% ee) has been achieved by using this ligand in the hydroformylation of styrene. Kelliphite **3**, which was developed by Klosin and coworkers at Dow, shows high enantioselectivity (80% ee) as well as high activity in the hydroformylation of allyl cyanide.[9]

Binaphos **2**, reported by Takaya, was a hybrid phosphine-phosphite ligand based on the binaphthyl backbone.[10] It was demonstrated to be an efficient ligand for styrene derivatives and vinyl carboxylates. Up to 94% ee for styrene and 92% ee for vinyl acetate was achieved in asymmetric hydroformylation. YanPhos **4**, which was reported by our group in 2006, was designed based on a Binaphos template. By changing the oxygen to nitrogen, the highest ee's (up to 99% ee) for styrene and vinyl acetate derivatives have been obtained.[11] So far, diphosphite ligands constitute a major family of ligands in asymmetric hydroformylation because catalysts with diphosphite ligands exhibit higher activities in hydroformylation than those with diphosphine ligands.

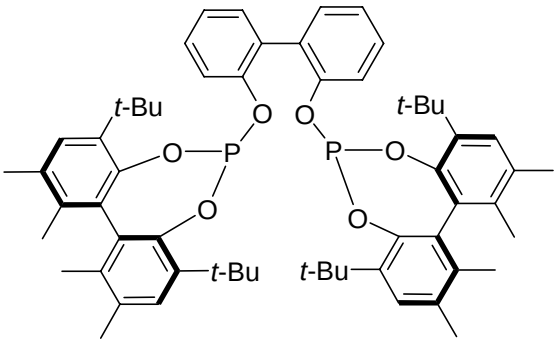
In 2005, Landis and coworkers developed a new family of bis-3,4-diazaphospholane ligands **5** and applied them to rhodium-catalyzed asymmetric hydroformylation.[12] Excellent enantioselectivities have been achieved in asymmetric hydroformylation of vinyl acetate and good enantioselectivities for styrene and allyl cynide were observed as well. Another bisphospholane ligand, Ph-BPE **6**, which was reported by Klosin and coworkers, resulted in similar enantioselectivities as the bis-3,4-diazaphospholane ligands.[13]



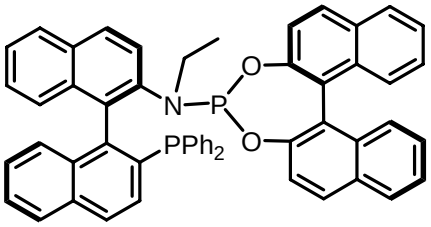
(2*R*, 4*R*) chiraphite 1



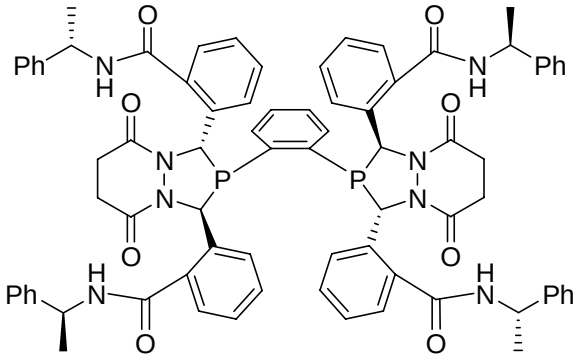
(*R*, *S*) Binaphos 2



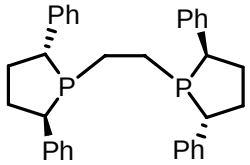
(*S*, *S*) Kelliphite 3



(*R*, *S*) YanPhos 4



diazaphospholane 5



(*R*, *R*)-Ph-BPE 6

Figure **1-1**. Representative Ligands for Asymmetric Hydroformylation

1.2 Rhodium-Catalyzed Asymmetric Hydrogenation

1.2.1 Background

The history of asymmetric hydrogenation goes back to the late 1960's (Figure **1-2**). The first example of asymmetric hydrogenation was reported by Knowles and coworkers in 1968.[14] They obtained a 15 % ee in the hydrogenation of phenylacrylic acid with a chiral monophosphine **7**. Later, Kagan found that chelating bisphosphorus ligands **8** with chiral backbones were effective for asymmetric hydrogenation.[15] In 1977, Knowles developed P-chiral bisphosphine ligands **9** and **10**.[16] Numerous chiral phosphorus ligands have been developed since then and today asymmetric hydrogenation has become one of the most efficient methods for the preparation of chiral compounds.[17] A lot of metals have been utilized in asymmetric hydrogenation. In this thesis, we will discuss rhodium catalyzed asymmetric hydrogenation.

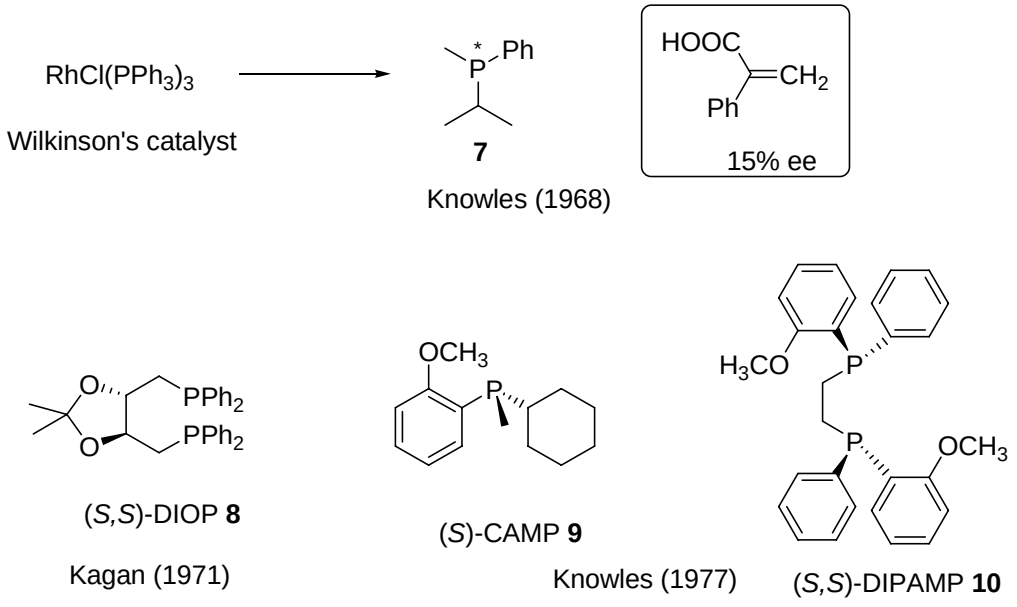
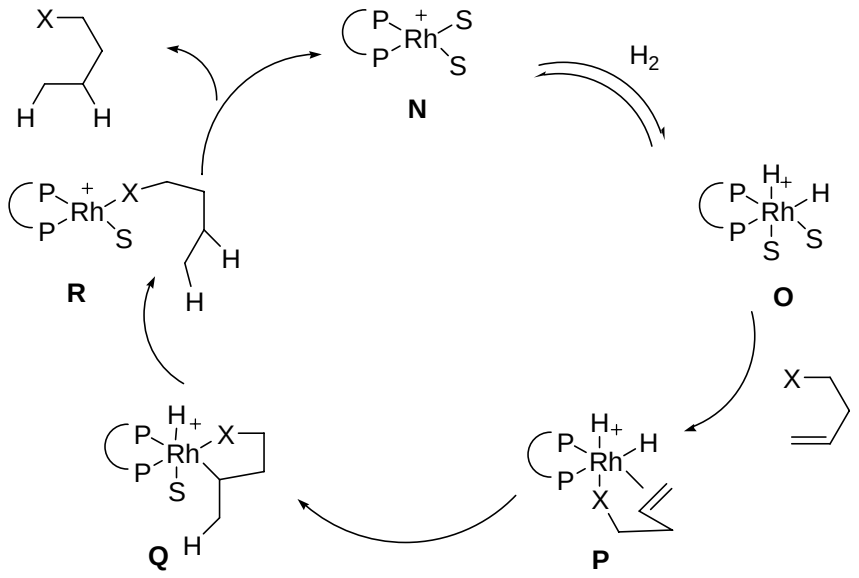


Figure **1-2**. Early Ligands for Asymmetric Hydrogenation.

1.2.2 Mechanism for Rhodium-Catalyzed Hydrogenation

For rhodium-catalyzed asymmetric hydrogenation with electron-rich phosphine ligands, the "dihydride" mechanism is the most accepted mechanism.[18] This mechanism was proposed by Imamoto and coworkers and it involves several steps (Scheme **1-2**): first, the oxidative addition of hydrogen to the solvate complex **N** to form the solvate dihydride complex **O**. Then, coordination of the substrate to the rhodium center generates the dihydride intermediate **P**. Migratory insertion of the substrate provides the rhodium-hydridoalkyl species **Q**. Finally, catalyst-product complex **R** is formed by reductive elimination and it is solvated to liberate the hydrogenation product and regenerate the catalyst **N**.



Scheme **1-2**: "Dihydride" Mechanism for Rhodium-Catalyzed Asymmetric Hydrogenation

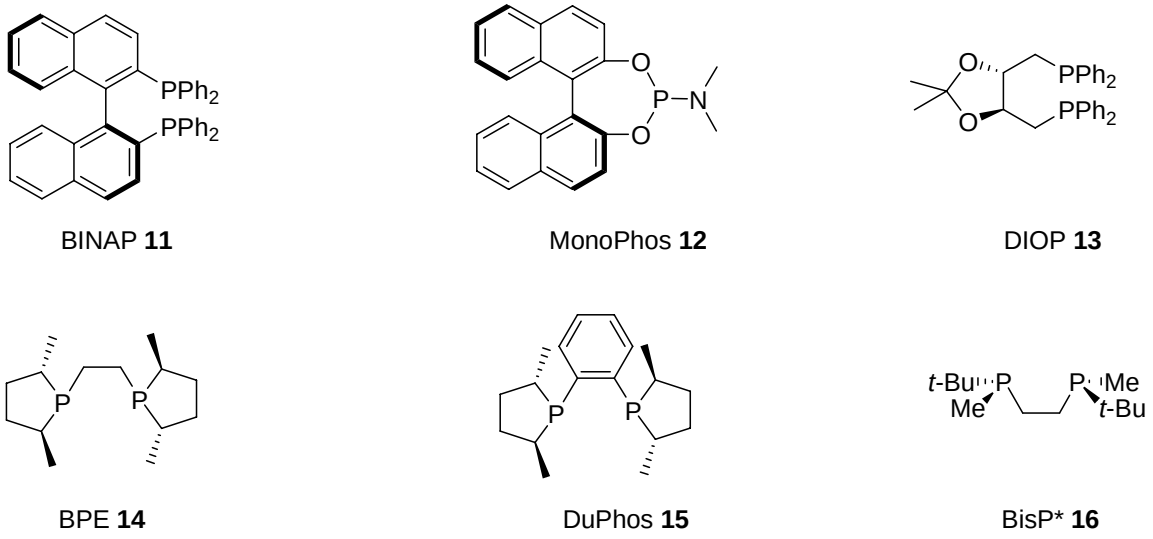
1.2.3 Some Chiral Phosphorus Ligands for Rhodium-Catalyzed Asymmetric Hydrogenation

There are numerous ligands developed for asymmetric hydrogenation. In this section, we will only discuss some representative ligands for rhodium-catalyzed asymmetric hydrogenation (Figure **1-3**).

One of the most successful chiral phosphorus ligands for asymmetric hydrogenation is BINAP **11**, an atropisomeric biaryl bisphosphine ligand developed by Noyori and coworkers.[19] It was first used in rhodium-catalyzed asymmetric hydrogenation, but the substrate scope was very limited. Later the substrate scope was expanded by applying BINAP in ruthenium-catalyzed asymmetric hydrogenation. Even today, BINAP and its derivatives are the most versatile ligands in asymmetric hydrogenation and catalysis.

MonoPhos **12** was found to be a very good mondentate phosphine in asymmetric hydrogenation of dehydroamino acid derivatives, itaconates and aryl enamides.[20] DIOP **13** was developed by Kagan and coworkers in 1971 as the first successful bidentate phosphorus ligand for rhodium-catalyzed asymmetric hydrogenation.[15] The chiral centers in the backbone can effectively transfer stereochemical information to the phosphite moieties and this concept has been applied to the design of new ligands.

A new series of efficient chiral bisphospholane, ligands BPE **14** and DuPhos **15**, were developed by Burk and coworkers in the early 1990s.[21] They greatly broadened the substrate scope of rhodium-catalyzed asymmetric hydrogenation and a variety of prochiral unsaturated substrates could be hydrogenated with excellent enantioselectivities. Later, Imamoto and coworkers discovered several efficient trialkyl P-chiral ligands such as BisP* **16** for asymmetric hydrogenation with high activities and enantioselectivities.[22]



BINAP **11** MonoPhos **12** DIOP **13**

BPE **14** DuPhos **15** BisP* **16**

Figure **1-3**. Representative Ligands for Rhodium-Catalyzed Asymmetric Hydrogenation.

1.3 Objectives

Asymmetric hydroformylation is one of the most challenging transformations because it requires both high enantioselectivities and regioselectivies with high activity. Also, there are few effective ways to prepare chiral ligands. To address these challenges, a series of new diphosphite ligands have been developed in our lab. In chapter 2, the design, synthesis and application of these new ligands in asymmetric hydroformylation will be discussed in detail. They provide moderate enantioselectivities (up to 80 % ee) and excellent regioselectivies (b/l up to 49/1) in the rhodium-catalyzed asymmetric hydroformylation of vinyl acetate.

Although numerous efficient chiral ligands have been developed for asymmetric hydrogenation, there is no universal ligand which can be applied to all prochiral

substrates with high enantioselectivity. To expand the substrate scope, the development of new chiral ligands is highly desirable. In chapter 3, the development of an efficient chiral diphosphine ligand will be discussed. This new ligand bearing a chiral C_3-biphenyl backbone provides excellent enantioselectivies in the rhodium-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters and itaconate.

Reference

1. For recent reviews, see: (a) Claver, C.; van Leeuwen, P. W. N. M. In *Rhodium Catalyzed Hydroformylation*; Eds: Claver, C.; van Leeuwen, P. W. N. M. Kluwer Academic Publishers, Dordrecht, The Netherlands, **2000**; (b) Breit, B.; Seiche, W. *Synthesis* **2001**, 1.

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

3. (a) Evans, D. A.; Osborn, J. A.; Wilkinson, G. *J. Chem. Soc. A,* **1968**, 3133; (b) Brown, C. K.; Wilkinson, G. *J. Chem. Soc. A* **1970**, *17*, 2753; (c) Wilkinson, G. *Bull. Soc. Chim. Fr.* **1968**, 5055; (d) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J .Chem. Soc. A.* **1966**, 1711.

4. Pruett, R. L.;Smith, J. A. *J. Org. Chem*. **1969**, *34*, 327.

5. For recent reviews, see: (a) Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113; (b) Agbossou, F.; Carpentier, J.; Mortreux. A. *Chem. Rev*. **1995**, *95*, 2485; (c) Gladiali, S.; Bayön, J. C.; Claver. C. *Tetrahedron: Asymmetry*, **1995**, *6*, 1453;

6. (a) Agbossou, F.; Carpentier, J.; Mortreux. A. *Chem. Rev*. **1995**, *95*, 2485; (b) Gladiali, S.; Bayön, J. C.; Claver. C. *Tetrahedron: Asymmetry*, **1995**, *6*, 1453; (c) Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113; (d) Botteghi,C.; Paganelli, S.; Schionato, A.; Marchetti, M. *Chirality*, **1991**, *3*, 355.

7. Heck, R. F.; Breslow, D. S. *J. Am. Chem. Soc.* **1961**, *83*, 4023.

8. Babin, J. E.;Whiteker, G. T. (Union Carbide Chem. Plastics Technol. Co.) *WO 93/03839*, **1992**.

9. Cobley, C. J. ; Gardner, K. ; Klosin, J.; Praquin, C.; Hill, C.; Whiteker, G. T.; Zanotti-Gerosa, A.; Petersen, J. L.; Abboud, K. A. *J. Org. Chem.* **2004**, *69*, 4031.

10. (a) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc*, **1993**, *115*, 7033; (b) Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. *J. Am. Chem. Soc.* **1997**, *119*, 4413; (c) Solinas, M.; Gladiali, S.; Marchetti, M. *J. Mol. Cat. A: Chem.* **2005**, *226*, 141; (d) Nozaki, K.; Matsuo, T.; Shibahara, F.; Hiyama, T., *Adv. Synth. Catal*. **2001**, *343*, 61; (e) Horiuchi, T.; Ohta, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1997**, *62*, 4285; (f) Nozaki, K.; Hidemasa, T.; Tamejiro, H. *Top. Catal.* **1998**, *4*, 175; (g) Horiuchi, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *Organometallics* **1997**, *16*, 2981; (h) Nozaki, K.; Nanno, T.; Takaya, H. *J. Organomet. Chem*. **1997**, *527*, 103; (i) Nozaki, K.; Li, W.-G. Horiuchi, T. Takaya, H. *Tetrahedron Lett.* **1997**, *38*, 4611; (j) Horiuchi, T.; Ohta, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *Tetrahedron*, **1997**, *53*, 7795; (k) Nozaki, K.; Li, W.-G. Horiuchi, T. Takaya, H.; Saito, T.; Yoshida, A.; Matsumura, K.; Kato, Y.; Imai, T.; Miura, T.; Kumobayashi, H. *J. Org. Chem*. **1996**, *61*, 7658; (l) Horiuchi, T.; Ohta, T.; Nozaki, K.; Takaya, H. *Chem. Commun*. **1996**, 155; (m) Nanno, T.; Sakai, N.; Nozaki, K.; Takaya, H. *Tetrahedron: Asymmetry* **1995**, *6*, 2583; (n) Sakai, N.; Nozaki, K.; Takaya, H. *J. Chem. Soc., Chem. Commun*. **1994**, 395.

11. Yan, Y.; Zhang, X. *J. Am. Chem. Soc*. **200**6, *128*, 7198.

12. Clark,; T. P. Landis, C. R. ; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc*. **2005**, *127*, 5040.

13. Axtell, A. T.; Cobley, C. J.; Klosin, J.; Whiteker, G. T.; Zanotti-Gerosa, A.; Abboud, K. A. *Angew. Chem. Int. Ed*. **2005**, *44*, 2.

14. Knowles, W. S.; Sabacky, M. J. *Chem. Commun*. **1968**, 1445.

15. (a) Kagan, H. B.; Dang, T. P. *J. Chem. Soc., Chem. Commun.* **1971**, 481; (b) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429; (c) Kagan, H. B.; Langlois, N.; Dang, T. P. *J. Organomet. Chem.* **1975**, *90*, 353.

16. (a) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, O. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946. (b) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106.

17. (a) Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hormann, E.; McIntyre, S.; Menges, F.; Schonleber, M.; Smidt, S. P.; Wustenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2003**, *345*, 33; (b) Crepy, K. V. L.; Imamoto, T. *Adv. Synth. Catal.* **2003**, *345*, 79; (c) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103; (d) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029; (e) Chelucci, G.; Orru, G.; Pinna, G. A. *Tetrahedron* **2003**, *59*, 9471; (f) Clark, T. P.; Landis, C. R. *Tetrahedron: Asymmetry* **2004**, *15*, 2123; (g) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497.

18. (a) Gridnev, I. D.; Higashi, N.; Asakura, K.; Imamoto, T. *J. Am. Chem. Soc.* **2000**, *122*, 7183; (b) Gridnev, I. D.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2000**, *122*, 10486; (c) Gridnev, I. D.; Imamoto, T. *Organometallics* **2001**, *20*, 545; (d) *Acc. Chem. Res.* **2004**, *37*, 633.

19. (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito. T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932; (b) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245; (c) R. Noyori, Nobel Lecture, *Angew. Chem. Int. Ed*. **2002**, *41*, 2008.

20. Van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc*. **2000**, *122*, 11539.

21. (a) Nugent, W. A.; RajanBabu, T. V.; Burk, M. J. *Science* **1993**, *259*, 479; (b) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363.

22. (a) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635; (b) Crepy, K. V. L.; Imamoto, T. *Adv. Synth. Catal.* **2004**, *345*,79.

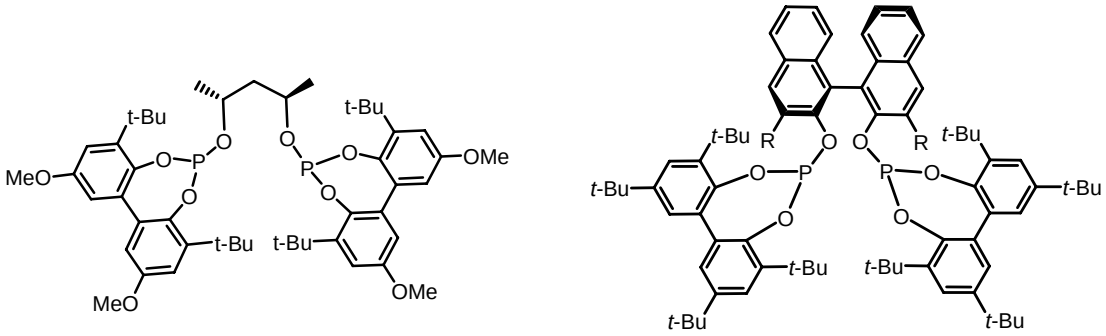
Chapter 2

Development of New Diphosphite Ligands for Enantioselective Asymmetric Hydroformylation

2.1 Introduction

Homogeneous catalytic hydroformylation has been extensively applied in the fine chemical and pharmaceutical industry. Asymmetric hydroformylation[1] provides a highly efficient method for the preparation of various chiral aldehydes species, which can be utilized in the synthesis of important drug intermediates and pharmaceuticals. This great demand has prompted tremendous effort towards the development of effective phosphorus ligands that achieve both high enantioselectivities and regioselectivities in hydroformylation reactions. However, so far only a few successful ligand systems have been reported.[2] One such example is Chiraphite, a bisphosphite ligand developed by Babin and Whiteker at Union Carbide in 1992 (Figure **2-1**).[2a,3] Excellent enantioselectivities (up to 90% ee) have been achieved in the hydroformylation of styrene, albeit with only moderate enantioselectivities (up to 50% ee) reported for vinyl acetate. The chiral centers in the (2*R*,4*R*)-pentane-2,4-diol backbone can effectively transfer stereochemical chiral information to the phosphite moieties. The presence of a bulky substituent (*t*-butyl) at the *ortho*-position of the biphenyl moieties is necessary for good regio- and enantioselectivities.

In this chapter, the design and synthesis of a series of new diphosphite ligands as well as their application in asymmetric hydroformylation will be discussed. With the new ligands, moderate enantioselectivities (up to 80% ee) and excellent regioselectivities (b/l up to 49/1) have been achieved in the Rh-catalyzed asymmetric hydroformylation of vinyl acetate.



(2*R*, 4*R*)-chiraphite

New ligands

Figure **2-1**. Chiraphite and New Ligands

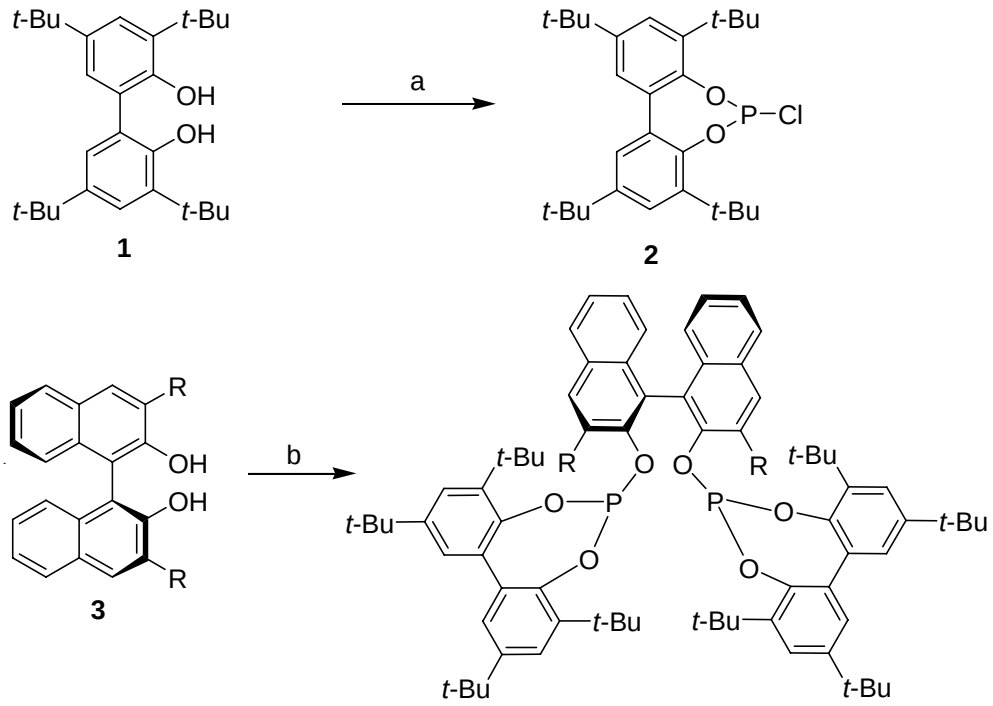
2.2 Results and Discussion

2.2.1 Design and Synthesis of New Diphosphite Ligands

Prompted by the excellent results obtained with Chiraphite, we have designed a series of new diphosphite ligands using chiral binaphthyl as the backbone. The ligand design was based on the following considerations: (i) ligands bearing binaphthyl backbones such as BINAP can provide excellent chiral induction in asymmetric reactions;[4] (ii) introduction of substitutes at the 3,3′-positions of the binaphthyl backbone can lock the orientation of biphenyl groups of the phosphite moieties, which, in turn, can facilitate

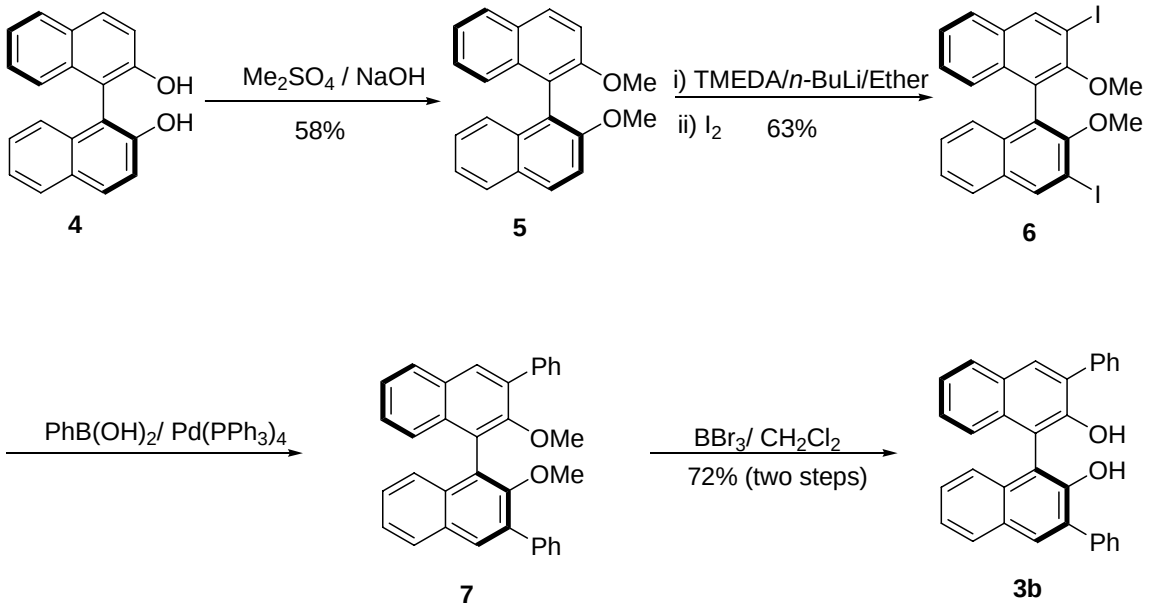
highly enantioselective hydroformylation ; (iii) subtle tuning of steric and electronic properties of the ligand can be achieved by varying the substituents on the 3,3′-positions.

The synthetic route to ligands **L1**-**L4** is depicted in Scheme **2-1**.[5] In the presence of a catalytic amount of 1-methylpyrrolidin-2-one, reaction of PCl_3 with 3,3′-bis-*t*-butyl biphenol **1** at 95 °C for 18 h afforded phosphorochloridite **2**, which was used in the next step without further purification.[6] Deprotonation of BINOL derivative **3** with *n*-butyl lithium followed by quenching of the resulting dialkoxide with phosphorochloridite **2** afforded ligands **L1**-**L4** in moderate yields.



Scheme **2-1.** Synthesis of Diphosphite Ligands **L1**-**L4**. Reagents and conditions: (a) PCl_3, 1-methylpyrrolidin-2-one, 95 °C, toluene; (b) (i) *n*-BuLi (3 equiv), THF; (ii) **2** (3 equiv), 20-60% (two steps).

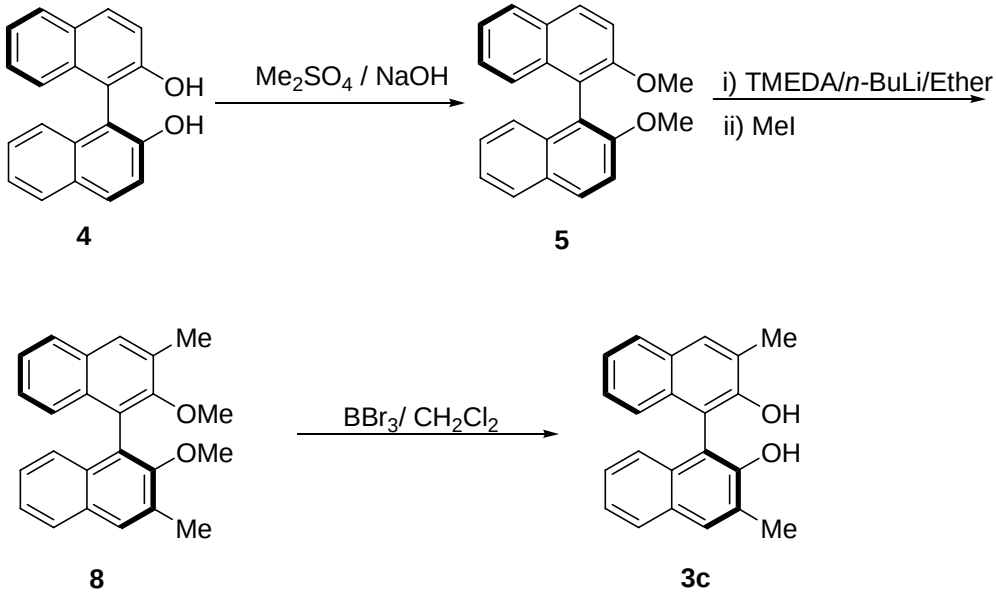
The 3,3'-disubstituted BINOL derivatives could be synthesized from commercially available BINOL **4** according to known literature methods.[7] The synthetic route for 3,3'-diphenyl substituted BINOL **3b** is outlined in Scheme **2-2**. First, the two hydroxyl groups of BINOL **4** are protected by using Me_2SO_4. Then, iodines are introduced to the *ortho*-positions of **5** in 63% yield. By Suzuki coupling, phenyl groups can replace the iodines in the 3,3'-positions of **6** to produce **7**. Finally, deprotection of the methoxy groups gives the 3,3'-biphenyl substituted BINOL **3b**. The yield for the last two steps is 72%.



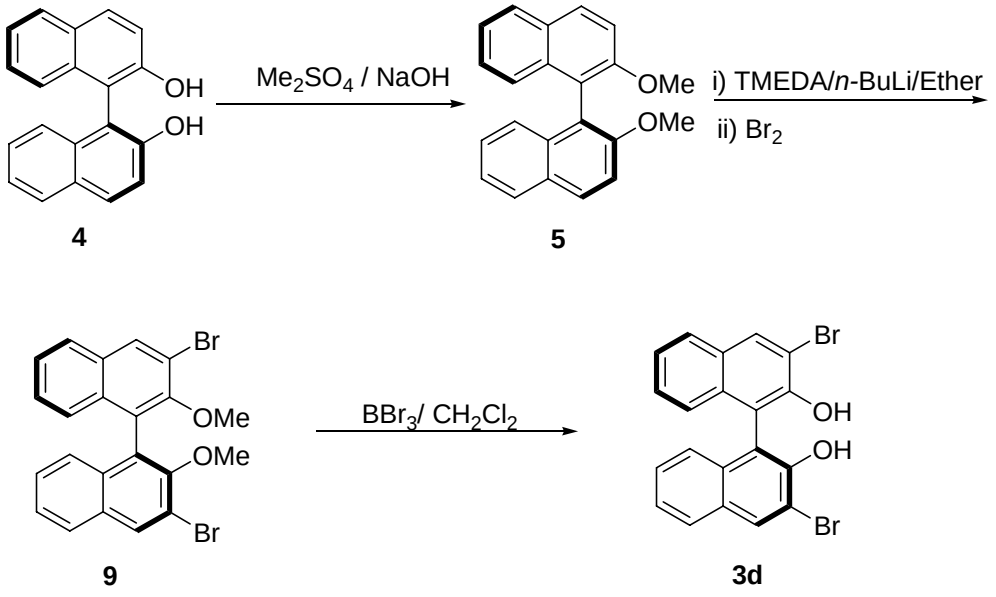
Scheme **2-2**. Synthesis of BINOL Derivative **3b**.

Other BINOL derivatives could be synthesized in a similar way. The synthetic of 3,3'-dimethyl substituted BINOL **3c** is depicted in Scheme **2-3**. After the hydroxyl groups were protected, iodomethane was used as the electrophile instead of iodine. 3,3'-dibromo

substituted BINOL **3d** was synthesized in a similar way by changing the electrophile to bromine (Scheme **2-4**).



Scheme **2-3**. Synthesis of BINOL Derivative **3c**.



Scheme **2-4**. Synthesis of BINOL Derivative **3d**.

2.2.2 Asymmetric Hydroformylation of Vinyl Acetate with New Ligands

Using ligands **L1**-**L4**, rhodium-catalyzed asymmetric hydroformylation of vinyl acetate was chosen as a preliminary screen of the four ligands. The catalyst was prepared *in situ* by mixing $Rh(acac)(CO)_2$ with **L1**-**L4**. Hydroformylation reactions were performed using 1:1 CO/H_2 gas with 0.1 mol % catalyst loading at 40 °C for 24 h. Screening of ligands **L1**-**L4** showed a strong dependence of ee's on the substituentes on the 3,3′-positions of the ligands. The best results were obtained with **L2** and **L3** (Table **2-1**, entries 2 and 3), whereas the enantioselectivities were significantly lower using **L1** and **L4** (Table **2-1**, entries 1 and 4). These results imply that the steric properties of the 3,3′-substituents may play an important role in the observed chiral induction. Good to excellent regioselectivities were achieved using these ligands (Table **2-1**, entries 1-4).

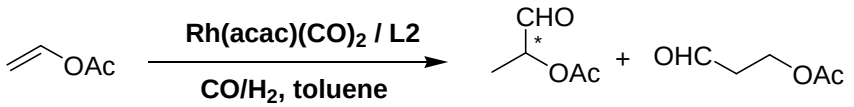
Table **2-1**. Screening of Ligands for Asymmetric Hydroformylation[a]

Ligand	conv (%)[b]	b/l[c]	ee(%)[d]
L1	29	96/4	13(*S*)
L2	23	97/3	71(*S*)
L3	45	98/2	75(*S*)
L4	23	98/2	16(*S*)

[a] Reactions were carried out under 10 atom of H_2 and CO at 40 °C for 24 h. Substrate/Rh =1000. L/Rh = 4:1. [b] Conversion was based on ^{1}H NMR. [c] Branched/linear ratio. Determined based on ^{1}H NMR. [d] Determined by GC analysis (Supelco's Beta Dex 225). The absolute configuration (*S*) was assigned by comparing the optical rotation of the product with (*S*)-1-formylethyl acetate.

The effect of the ligand/metal ratio on the hydroformylation reaction was investigated first. The reactions were performed at ligand/metal ratios ranging from 1:1 to 6:1. As shown in Table **2-2**, the enantioselectivity increased from 35% to 77% when ligand/metal ratios increased from 1:1 to 4:1. Further increasing the ligand/metal ratio to 6:1 did not improve the enantioselectivity.

Table **2-2**. Asymmetric Hydroformylation of Vinyl Acetate at Different Ligand/Metal Ratios[a]

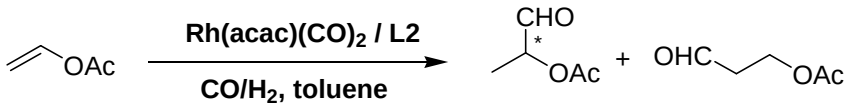


entry	L/Rh	conv (%)[b]	b/l[c]	ee (%)[d]
1	1:1	6	98/2	35(*S*)
2	2:1	16	98/2	69(*S*)
3	4:1	23	98/2	77(*S*)
4	6:1	3	98/2	77(*S*)

[a] The reactions were conducted in toluene at 40 °C for 12 h, substrate: Rh = 1000, CO/H_2 = 10/10 atm. [b] Conversion was based on ^1H NMR. [c] Branched/linear ratio. Determined based on ^1H NMR. [d] Determined by GC analysis (Supelco's Beta Dex 225). The absolute configuration (*S*) was assigned by comparing the optical rotation of the product with (*S*)-1-formylethyl acetate.

The effect of the reaction temperature was investigated next. As shown in Table **2-3**, increasing the reaction temperature increased the reaction rate but decreased the enantioselectivities. An enantiomeric excess of 77% was achieved when the reaction was run at 40 °C with 23% conversion. Close to complete conversion was achieved at 80 °C though with diminished enantioselectivity (56% ee). The regioselectivity didn't change significantly when increasing reaction temperature.

Table **2-3**. Asymmetric Hydroformylation of Vinyl Acetate at Different Reaction Temperatures[a]

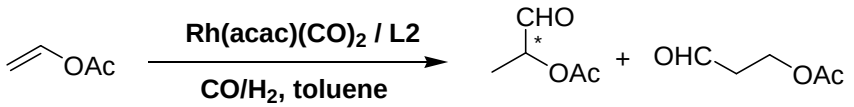


entry	T (°C)	conv (%)[b]	b/l[c]	ee (%)[d]
1	40	23	98/2	77(*S*)
2	60	43	97/3	72(*S*)
3	80	>99	98/2	56(*S*)

[a] The reactions were conducted with L:Rh = 4:1 in toluene for 12 h, substrate: Rh = 1000, CO/H_2 = 10/10 atm. [b] Conversion was based on ^1H NMR. [c] Branched/linear ratio. Determined based on ^1H NMR. [d] Determined by GC analysis (Supelco's Beta Dex 225). The absolute configuration (*S*) was assigned by comparing the optical rotation of the product with (*S*)-1-formylethyl acetate.

To determine the optimal reaction time, hydroformylation reactions were carried out at different durations ranging from 12 h to 36 h (Table **2-4**). Increasing of the reaction time lowered the enantioselectivity due to product isomerization but the conversion was increased. This factor was examined in detail with different reaction times. For example the enantioselectivity dropped from 72% at 12 h to only 41% at 36 h, while the conversion increased from 43% to 98%.

Table **2-4**. Asymmetric Hydroformylation of Vinyl Acetate at Different Reaction Times[a]

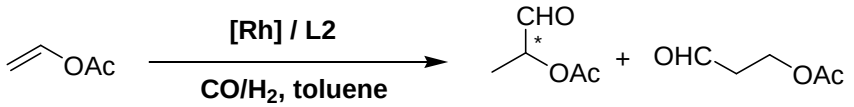


entry	time (h)	conv (%)[b]	b/l[c]	ee (%)[d]
1	12	43	97/3	72(*S*)
2	24	80	98/2	66(*S*)
3	36	98	98/2	41(*S*)

[a] The reactions were conducted with L:Rh = 4:1 in toluene at 60 °C , substrate: Rh = 1000, CO/H_2 = 10/10 atm. [b] Conversion was based on ^1H NMR. [c] Branched/linear ratio. Determined based on ^1H NMR. [d] Determined by GC analysis (Supelco's Beta Dex 225). The absolute configuration (*S*) was assigned by comparing the optical rotation of the product with (*S*)-1-formylethyl acetate.

We then studied the role of the Rh catalyst precursor. Two precursors were used in the reactions (Table **2-5**). At 40 °C, the enantioselectivity increased from 77% to 82% when changing the precursor $Rh(acac)(CO)_2$ to Rh(acac)(COD). When the temperature increased to 60 °C, the enantioselectivity changed a little when using different precursors. It seems that Rh(acac)(COD) produced branched aldehyde with better enantioselectivities than $Rh(acac)(CO)_2$ in most cases, but with lower conversions. The regioselectivities remained the same for the two precursors.

Table **2-5**. Asymmetric Hydroformylation of Vinyl Acetate using Different Precursors[a]

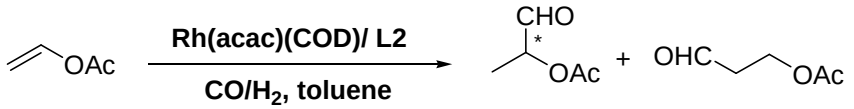


entry	precursor	T (°C)	conv (%)[b]	b/l[c]	ee (%)[d]
1	$Rh(acac)(CO)_2$	40	23	98/2	77(*S*)
2	Rh(acac)(COD)	40	3	98/2	82(*S*)
3	$Rh(acac)(CO)_2$	60	43	97/3	72(*S*)
4	Rh(acac)(COD)	60	31	97/3	73(*S*)

[a] The reactions were conducted with L:Rh = 4:1 in toluene for 12 h, substrate: Rh = 1000, CO/H_2 = 10/10 atm. [b] Conversion was based on ^1H NMR. [c] Branched/linear ratio. Determined based on ^1H NMR. [d] Determined by GC analysis (Supelco's Beta Dex 225). The absolute configuration (*S*) was assigned by comparing the optical rotation of the product with (*S*)-1-formylethyl acetate.

The effect of CO/H_2 pressure on these hydroformylation reactions was then investigated. As shown in Table **2-6**, the conversion decreased when the pressure increased from 5 atm to 10 atm, but increased when the pressure CO/H_2 again increased from 10 atm to 20 atm. There seemed to be no linear relationship between the conversion and the pressure. The same observations pertain to the enantioselectivities observed. The enantioselectivity was the highest at 10 atm.

Table **2-6**. Asymmetric Hydroformylation of Vinyl Acetate under Different Pressures[a]

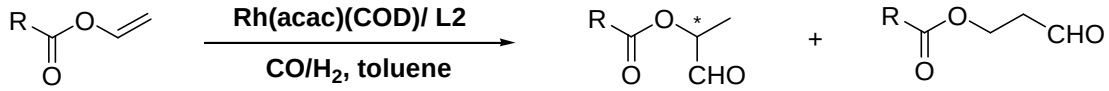


entry	CO/H_2 (atm)	conv (%)[b]	b/l[c]	ee (%)[d]
1	5	70	98/2	66(*S*)
2	10	31	97/3	73(*S*)
3	20	43	97/3	54(*S*)

[a] The reactions were conducted with L:Rh = 4:1 in toluene at 60 °C for 12 h, substrate: Rh = 1000. [b] Conversion was based on ^{1}H NMR. [c] Branched/linear ratio. Determined based on ^{1}H NMR. [d] Determined by GC analysis (Supelco's Beta Dex 225). The absolute configuration (*S*) was assigned by comparing the optical rotation of the product with (*S*)-1-formylethyl acetate.

After screening reaction conditions, hydroformylation of vinyl acetate with Rh-**L2** catalyst was performed under 20 atm of 1:1 CO/H_2 at 60 °C in toluene using Rh(acac)(COD) as the precusor. Optimized conversion, regioselectivity and enantioselectivity were achieved under these conditions. A series of vinyl acetate derivatives then were tested in these hydroformylation reactions using Rh-**L2** under the optimized reaction conditions (Table **2-7**). The highest enantioselectivity was obtained with vinyl propionate, 57% (Table **2-7**, entry 2). Generally, hydroformylation of vinyl carboxylates resulted in moderate enantioselectivities. The branched/linear ratios were above 90/10 for all substrates tested.

Table **2-7**. Asymmetric Hydroformylation of Vinyl Carboxylates[a]

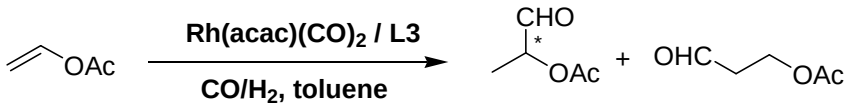


entry	R	conv (%)[b]	b/l[c]	ee (%)[d]
1	CH_3	80	98/2	55(*S*)
2	CH_3CH_2	85	98/2	57(*S*)
3	$CH_3(CH_2)_2$	82	98/2	40(*S*)
4	$CH_3(CH_2)_8$	80	97/3	46(*S*)
5	*t*-Bu	30	94/6	18(*S*)
6	Ph	64	98/2	28(*S*)

[a] The reactions were conducted with L:Rh = 4:1 in toluene at 60 °C for 24 h, substrate: Rh = 1000, CO/H_2 = 10/10 atm. [b] Conversion was based on ^1H NMR. [c] Branched/linear ratio. Determined based on ^1H NMR. [d] Determined by GC analysis (Supelco's Beta Dex 225). The absolute configuration (*S*) was assigned by comparing the optical rotation of the product with (*S*)-1-formylethyl acetate.

Based on the optimized reaction conditions for ligand **L2**, hydroformylation with ligand **L3** also was examined (Table **2-8**). The reaction performed at 40 °C for 12 h gave the best enantioselectivity (80%) (Table **2-8**, entry 1), but the conversion was only 9%. Increasing the temperature to 60 °C and increasing the reaction time to 24 h resulted in 98% conversion, while the enantioselectivity was a little bit lower (69%, Table **2-8**, entry 4).

Table **2-8**. Optimization of Ligand **L3**[a]



entry	time (h)	T (°C)	conv (%)[b]	b/l[c]	ee (%)[d]
1	12	40	9	98/2	80(*S*)
2	12	60	69	98/2	73(*S*)
3	24	40	45	98/2	75(*S*)
4	24	60	98	98/2	69(*S*)

[a] The reactions were conducted with L:Rh = 4:1 in toluene, substrate: Rh = 1000, CO/H_2 = 10/10 atm. [b] Conversion was based on ^1H NMR. [c] Branched/linear ratio. Determined based on ^1H NMR. [d] Determined by GC analysis (Supelco's Beta Dex 225). The absolute configuration (*S*) was assigned by comparing the optical rotation of the product with (*S*)-1-formylethyl acetate.

2.2.3 Proposed Models for the Transition States

The structure of the rhodium-diphosphite complexes formed under hydroformylation conditions has been studied by Casey[8] and van Leeuwen[9]. It is well known that the complex has a trigonal bipyramidal geometry and numerious studies has shown that diphosphite generally coordinates to the metal in an equatorial-equatorial mode. The proposed models for the coordination of the olefin to the rhodium complex are shown in Figure **2-2**. Diphosphite ligands occupy two equatorial sites. The steric repulsion between

the substituent on the olefin and the ligand determines the absolute configuration of the aldehyde product. There are two possible transition states with diphosphite as ligand, models (a) and (b). The transition state in model (a) is consistent with the experimental results with vinyl acetate and its derivatives. The other transition state, model (b), would give the opposite configuration to that observed experimentally.

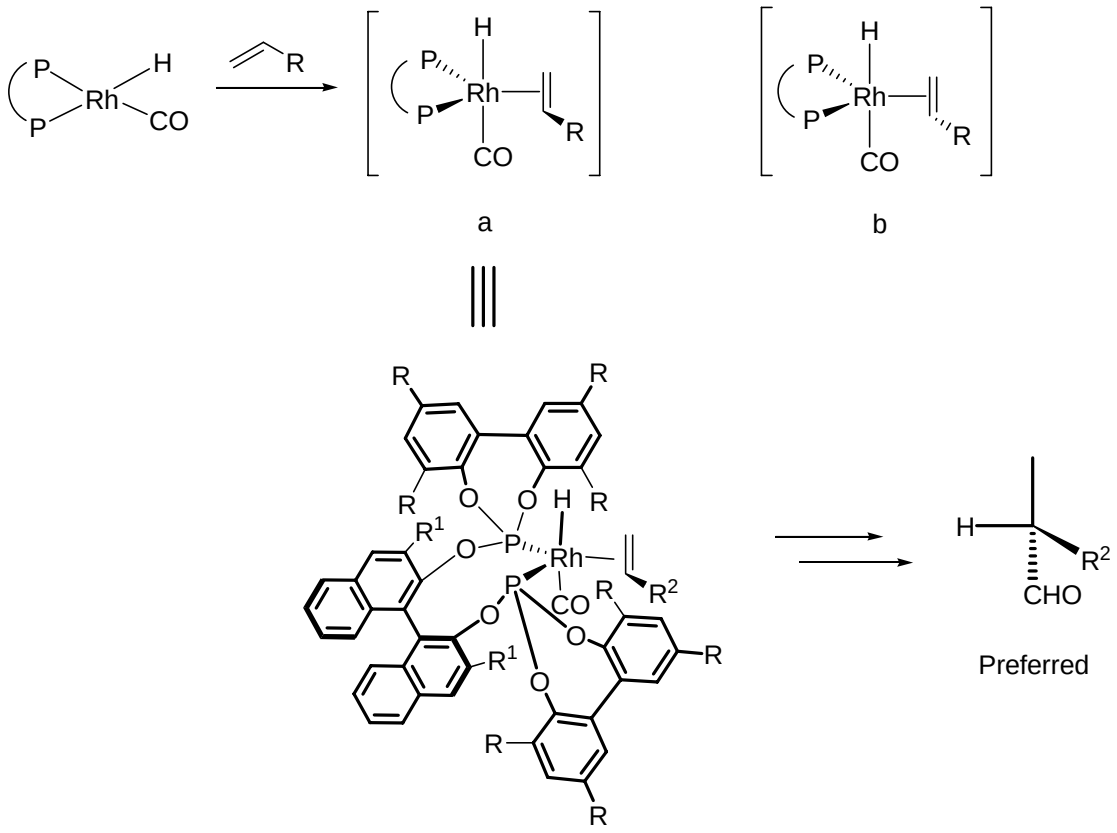


Figure **2-2**. Proposed Models for the Transition States in Asymmetric Hydroformylation

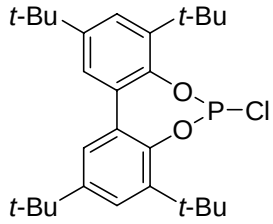
2.3 Conclusion

In conclusion, four structural related diphosphite ligands **L1**-**L4** have been synthesized from readily available starting materials. Their application in asymmetric hydroformylation reactions of vinyl acetate has been investigated. Moderate enantioselectivities (up to 80% ee) and excellent regioselectivities (b/l up to 49/1) have been achieved. Further ligand structural modifications are currently under exploration in order to increase the enantioselectivity and the reactivity of the derived catalyst.

Experimental Section

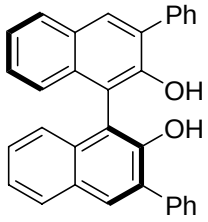
General Methods. All reactions and manipulations were performed using standard Schlenk techniques. Solvents were dried with standard procedures and degassed with N_2. Thin layer chromatography (TLC) was performed on EM reagents 0.25 mm silica 60-F plates. Column chromatography was performed using 200-400 mesh silica gel supplied by Natland International Corp. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker AM-300 and AMX-360 spectrometers. MS spectra were recorded on a KRATOS mass spectrometer MS 9/50. Optical rotation was carried out on a Perkin-Elmer 241 polarimeter. GC analysis was obtained on Hewlett-Packard 6890 gas chromatography using chiral capillary columns.

Synthesis of 3,3',5,5'-Tetra-tert-butylbiphenyl-2,2'-dioxychlorophosphine (2)



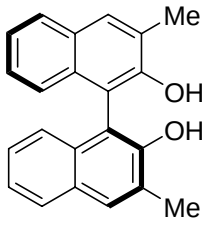
To a solution of 2,2'-Dihydroxy-3,3',5,5'-tetra-tert-butylbiphenyl (2.0 g, 4.9 mmol) and catalytic amount of 1-methyl 2-pyrrolidinone (NMP) in 20 ml toluene was added dropwise PCl_3 (1.0 g, 7.3 mmol) at r.t. The reaction mixture was heated to 95 °C for 17 h. Solvent was removed to afford **2**, which was used for next step without purification. ^{31}P NMR (360 MHz, $CDCl_3$): δ 173.3 (s).

Synthesis of (*S*)-3,3'-Diphenyl-1,1'-binaphthyl-2,2'-diol (3b)



Compound **7** (1.51 g, 3 mmol) was dissolved in dry CH_2Cl_2 (80 mL) and the reaction solution was cooled to -78 °C. BBr_3 (1.5 mL) was added in 10 min. The reaction solution was warmed to r.t. slowly after stirring at -78 °C for 2 h. Stirred at r.t. for overnight. The brown solution was cooled to 0 °C and added water (200 mL) carefully. Extracted with EtOAc and washed with brine. After dried over Na_2SO_4, the crude product was purified by column chromatography (eluent: hexane/EtOAc = 3:1) to give **3b** (0.95 g) in 72% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.36 (s, 2H), 7.15-7.42 (m, 12H), 7.45 (m, 4H), 7.93 (d, J = 7.7 Hz, 2H), 8.03 (s, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 150.10, 137.44, 132.93, 131.36, 130.65, 129.58, 129.42, 128.45, 128.42, 127.74, 127.32, 124.30, 124.25, 112.37.

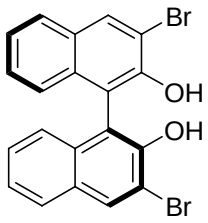
Synthesis of (*S*)-3,3'-Dimethyl-1,1'-binaphthyl-2,2'-diol (3c)



Compound **3c** was synthesized by a similar procedure as for compound **6**. Iodomethane was used as the electrophile instead of iodine. The next deprotection step followed the same procedure for compound **3b**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20-7.26

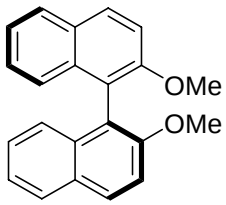
(2H, d, *J* = 4.4 Hz), 7.07 (2H, d, *J* = 8.3 Hz), 5.11 (2H, s), 2.51 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 132.5, 131.9, 130.5, 129.2, 127.3, 126.8, 126.2, 123.7, 110.2, 16.8.

Synthesis of (*S*)-3,3'-Dibromo-1,1'-binaphthyl-2,2'-diol (3d)



Compound **3d** was synthesized by a similar procedure as for compound **6**. Bromine was used as the electrophile instead of iodine. The next deprotection step followed the same procedure for compound **3b**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (2H, s), 7.80-7.82 (2H, d, *J* = 7.5 Hz), 7.28-7.41 (4H, m), 7.08-7.11 (2H, d, *J* = 8.5 Hz), 5.35 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.4, 137.7, 133.2, 130.2, 128.0, 127.8, 125.3, 125.1, 115.0, 112.7.

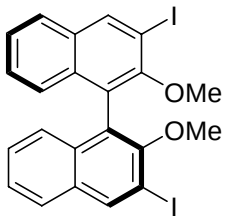
Synthesis of (*S*)-2,2'-Dimethoxy-1,1'-binaphthyl (5)



(S)-BINOL **4** (14.3 g, 50 mmol) was dissolved in 95% EtOH (200 mL). Drop wise added dimethyl sulfate and NaOH to the reaction solution. The reaction solution refluxed for 4 h and cooled to r.t. The solid was filtered and washed with water and recrystallized in toluene (80 mL) to give **5** (8.29 g) in 58% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 6H), 7.06–7.34 (m, 6H), 7.45 (d, *J* =9.2 Hz, 2 H), 7.86 (d, *J* = 7.2 Hz, 2 H), 7.98 (d, *J* =

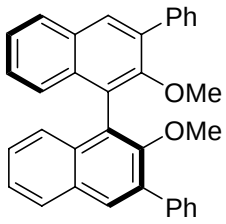
8.5 Hz, 2H); ^{13}C NMR(75 MHz, $CDCl_3$): δ 56.8, 114.2, 119.5, 123.5, 125.2, 126.3, 127.9, 129.2, 129.4, 134.0, 154.9.

Synthesis of (*S*)- 3,3'-Diiodo-2,2'-dimethoxy-1,1'-binaphthyl (6)



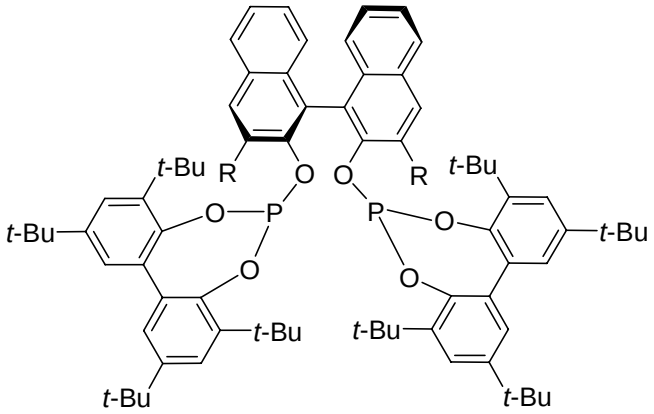
n-BuLi (7.4 mL of a 2.5M sol. in hexane, 18 mmol) was added to a solution of TMEDA (2.72 mL, 18 mmol) in Et_2O (80 mL) at r.t.. After 30 min., compound **5** (1.88g, 6 mmol) was added. The resulting solution was stirred for 3 h at r.t. and then, cooled to – 78 ºC. Iodine (4.72 g, 18 mmol) was added. After 30 min at low temperature the reaction mixture was allowed to warm to room temperature and stirred overnight. Saturated aqueous solution of $Na_2S_2O_3$ was added and the solvent was removed. It was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried (Na_2SO4), and evaporated under reduced pressure. The crude was purified by column chromatography (eluent: hexane/CH_2Cl_2 = 4:1) on silica gel to afford **6** (1.19 g, 63% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.73 (s, 6H), 7.00 (d, *J* = 8 Hz, 2H), 7.18 (m, 2H), 7.32 (m, 2H), 7.70 (d, *J* = 8 Hz, 2H), 8.44 (s, 2H); ^{13}C NMR(75 MHz, $CDCl_3$): δ 154.28, 139.67, 133.96, 132.01, 126.98, 126.93, 125.88, 125.55, 125.48, 93.07, 69.74.

Synthesis of (*S*)-2,2'-Dimethoxy-3,3'-diphenyl-1,1'-binaphthyl (7)



In a 100 mL schlenk flask was placed compound **6** (1.17g, 2 mmol), $PhB(OH)_2$ (732 mg, 6 mmol), K_2CO_3 (20 mL, 1M). Added THF (20 mL), water (20 mL) and heated the reaction solution to reflux for 24 h. The reaction solution was cooled to r.t. and extracted with EtOAc The combined organic layers were dried (Na_2SO4), and evaporated under reduced pressure. The crude product was used in the next step without further purification. ^1H NMR (300 MHz, $CDCl_3$): δ 7.00-8.00 (m, 20H), 3.74 (s, 6H).

General Procedure for Synthesis of Ligands L1-L4.



To a solution of **3** (1 mmol) in THF (15 mL) at 0 °C was added dropwise *n*-BuLi (3 mmol, 1.2 mL of 2.5 M hexane solution). The reaction mixture was allowed to warm to room temperature and stirred for 30 min to give a deep red solution. The reaction mixture was then recooled to 0 °C, and then was added dropwise to **2** (1.43g, 3 mmol) in THF (10

mL). After addition, the cooling bath was removed and the mixture was stirred at room temperature overnight. The volatiles were evaporated under reduced pressure. To the residue was added CH_2Cl_2 (10 mL), and the mixture was filtered to remove the salt. The filtration was concentrated and subjected to chromatography on silica gel (eluted with hexane/EtOAc 25:1) to afford pure ligands **L1**-**L4** in 20-60 % yields.

Spectra Data for Ligand L1: ^{1}H NMR (360 MHz, $CDCl_3$): δ 7.76 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 7.29-7.25 (m, 6H), 7.13-7.09 (m, 6H), 7.02 (d, J = 8.5 Hz, 2H), 1.28 (s, 18H), 1.26 (s, 18H), 1.04 (s, 18H), 1.00 (s, 18H). ^{13}C NMR(500 MHz, $CDCl_3$): δ 147.99, 146.82, 146.44, 145.93, 140.92, 140.46, 134.32, 133.26, 132.72, 130.98, 129.04, 127.98, 126.84, 126.80, 126.72, 126.63, 126.61, 124.93, 124.55, 124.46, 123.39, 122.81, 122.76, 35.42, 35.41, 34.94, 34.88, 31.82, 31.71, 31.18, 31.14, 31.04, 29.98. ^{31}P NMR (146 MHz, $CDCl_3$): δ 130.88 (s). ES+HRMS calcd for $C_{76}H_{92}O_6P_2$ +Na (M+Na): 1185.6267; found: 1185.6255.

Spectra Data for Ligand L2: ^{1}H NMR (360 MHz, CD_2Cl_2): δ 8.04 (s, 2H), 7.85 (d, J = 8.1 Hz, 2H), 7.51 (d, J = 7.9 Hz, 4H), 7.40-7.31 (m, 6H), 7.19-7.12 (m, 4H), 6.93 (t, J = 7.2 Hz, 2H), 6.84-6.77 (m, 8H), 1.31 (s, 18H), 1.16 (s, 18H), 1.14 (s, 18H), 1.00 (s, 18H). ^{13}C NMR(126 MHz, $CDCl_3$): δ 146.34, 146.10, 145.80, 145.46, 140.10, 139.92, 137.94, 135.57, 134.39, 133.04, 132.26, 130.96, 130.26, 128.12, 127.82, 127.03, 126.98, 126.53, 126.38, 126.30, 126.24, 125.22, 123.94, 35.27, 35.09, 34.59, 34.46, 31.63, 31.50, 31.28, 31.23, 31.20. ^{31}P NMR (146 MHz, CD_2Cl_2): δ 140.18 (s). ES+HRMS calcd for $C_{88}H_{101}O_6P_2$ [MH^+] 1315.7073, found 1315.6960.

Spectra Data for Ligand L3: ^{1}H NMR (360 MHz, CD_2Cl_2): δ 7.72-7.67 (m, 4H), 7.31-7.22 (m, 6H), 7.17-7.06 (m, 6H), 6.99 (d, J = 2.2 Hz, 2H), 2.09 (s, 6H), 1.28 (s, 18H), 1.21 (s, 18H), 1.10 (s, 18H), 1.05 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 147.26, 146.60, 146.55, 146.29, 146.25, 145.80, 145.74, 140.43, 140.21, 133.95, 132.97, 132.68, 132.41, 130.95, 130.35, 127.57, 127.34, 126.85, 126.52, 126.47, 125.49, 124.84, 123.93, 123.69, 35.34, 35.28, 34.85, 34.80, 31.80, 31.70, 31.29, 31.10, 31.08, 18.36. ^{31}P NMR (146 MHz, CD_2Cl_2): δ 143.69 (s). ES+HRMS calcd for $C_{78}H_{97}O_6P_2$ [MH^+] 1191.6760, found 1191.6681.

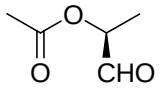
Spectra Data for Ligand L4: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 2H), 7.74 (d, J = 7.6 Hz, 2H), 7.37-7.34 (m, 4H), 7.27-7.21 (m, 6H), 7.10-7.05 (m, 4H), 1.35 (s, 18H), 1.28 (s, 18H), 1.21 (s, 18H), 1.14 (s, 18H). ^{13}C NMR(126 MHz, $CDCl_3$): δ 147.99, 146.82, 146.44, 145.93, 140.92, 140.46, 134.32, 133.26, 132.72, 130.98, 129.04, 127.98, 126.84, 126.80, 126.72, 126.63, 126.61, 124.93, 124.55, 124.46, 123.39, 122.81, 122.76, 35.42, 35.41, 34.94, 34.88, 31.82, 31.71, 31.18, 31.14, 31.04, 29.98. ^{31}P NMR (162 MHz, $CDCl_3$): δ 146.05 (s).

General Procedure for Asymmetric Hydroformylation of Vinyl Acetate and Its Derivatives

To a 2 mL vial equipped with a magnetic bar were added ligand (0.004 mmol), $Rh(acac)(CO)_2$ (0.001 mmol in 0.10 mL of toluene), and vinyl acetate (1.0 mmol), and additional benzene was charged to bring the total volume of the reaction mixture to 1.0 mL. Carbon monoxide (10 atm) and dihydrogen (10 atm) were charged in sequence. The reaction mixture was stirred (120 rpm) at 40 °C (oil bath) for 24 h. The conversion and

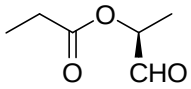
regioselectivity were determined by ^{1}H NMR spectroscopy from the crude reaction mixture. The enantiomeric excess was determined directly by GC analysis of the crude reaction mixture.

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



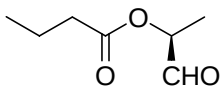
Acetic acid 1-methyl-2-oxo-ethyl ester.^{1}H NMR (400 MHz, CDCl3) δ: 9.52 (s, 1H), 5.05 (q, J = 7.20 Hz, 1H), 2.15 (s, 3H), 1.38 (d, J = 7.22 Hz, 3H).

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



Propionic acid 1-methyl-2-oxo-ethyl ester. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.48 (s, 1H), 5.08 (q, J = 7.19 Hz, 1H), 2.45 (dq, J = 5.96, 1.70 Hz, 2H), 1.40 (d, J = 7.20 Hz, 3H), 1.19 (t, J = 7.57 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 198.6, 173.9, 74.4, 27.3, 14.1, 9.0.

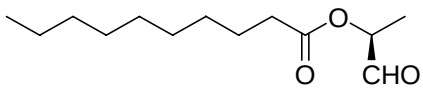
Supelco's Beta Dex 225, 100°C, 1mL/min, $t_{(minor)}$ = 8.3 min, $t_{(major)}$ = 9.0 min



Butyric acid 1-methyl-2-oxo-ethyl ester. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.54, 5.08 (q, J = 7.16 Hz, 1H), 2.40 (t, J = 7.48 Hz, 2H), 1.70 (m, 2H), 1.39 (d, J = 7.18 Hz, 3H),

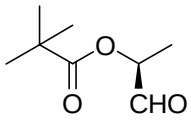
0.98 (t, J = 7.41 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 198.6, 173.1, 74.4, 35.8, 18.4, 14.1, 13.6.

Supelco's Beta Dex 225, 100°C, 1mL/min, $t_{(minor)}$ = 9.4 min, $t_{(major)}$ = 9.7 min



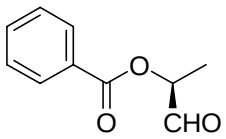
Octanoic acid 1-methyl-2-oxo-ethyl ester. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.54 (s, 1H), 5.08 (q, J = 7.19 Hz, 1H), 2.42 (dt, J = 7.49, 1.22 Hz, 2H), 1.67 (m, 2H), 1.40 (d, J = 7.19 Hz, 3H), 1.32-1.24 (m, 8H), 0.89 (t, J = 7.01 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 198.6, 173.3, 74.4, 33.9, 31.6, 29.0, 28.9, 24.8, 22.6, 14.1, 14.0.

Supelco's Beta Dex 225, 100°C, 1mL/min, $t_{(minor)}$ = 20.1 min, $t_{(major)}$ = 20.6 min



2, 2-Dimethyl-propionic acid 1-methyl-2-oxo-ethyl ester. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.52 (d, J = 0.59 Hz, 1H), 5.03 (dq, J = 7.17, 0.62 Hz, 1H), 1.40 (d, J = 7.17 Hz, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 198.7, 178.0, 74.3, 38.7, 27.1, 14.0.

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



Benzoic acid 1-methyl-2-oxo-ethyl ester. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.66 (d, J = 0.63 Hz, 1H), 8.11-8.08 (m, 2H), 7.63-7.57 (m, 1H), 7.49-7.44 (m, 2H), 5.30 (dd, J = 7.16,

0.60 Hz, 1H), 1.53 (d, J = 7.17 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 198.6, 165.9, 133.5, 129.8, 129.1, 128.5, 75.1, 14.3.

Supelco's Beta Dex 225, 100°C, 1mL/min, $t_{(minor)}$ = 21.9 min, $t_{(major)}$ = 24.3 min

References

1. For recent reviews, see: (a) Claver, C.; Diéguez, M.; Pàmies, O.; Castillón, S. *Topics in Organometallic Chemistry* **2006**, *18*, 35; (b) Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113; (c) Agbossou, F.; Carpentier, J.; Mortreux, A. *Chem. Rev.* **1995**, *95*, 2485; (d) Gladiali, S.; Bayön, J. C.; Claver, C. *Tetrahedron Asymmetry*, **1995**, *6*, 1453; (e) Breit, B.; Seiche, W. *Synthesis*, **2001**, 1; (f) Claver, C.; van Leeuwen, P. W. N. M. In *Rhodium Catalyzed Hydroformylation*; Claven, C., van Leeuwen, P. W. N. M., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, **2000**.
2. (a) Babin, J. E.; Whiteker, G. T. Patent WO 9303839, 1992; (b) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc*. **1993**, *115*, 7033; (c) Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. *J. Am. Chem. Soc.* **1997**, *119*, 4413; (d) Breeden, S.; Cole-Hamilton, D. J.; Foster, D. F.; Schwarz, G. J.; Wills, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4106; (e) Dieguez, M.; Pamies, O.; Ruiz, A.; Castillon, S.; Claver, C. *Chem.-Eur. J.* **2001**, *7*, 3086; (f) Cobley, C. J. ; Gardner, K. ; Klosin, J.; Praquin, C.; Hill, C.; Whiteker, G. T.; Zanotti-Gerosa, A.; Petersen, J. L.; Abboud, K. A. *J. Org. Chem.* **2004**, *69*, 4031; (g) Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5040; (h) Axtell, A. T.; Cobley, C. J.; Klosin, J.; Whiteker, G. T.; Zanotti-Gerosa, A.; Abboud, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5834; (i) Huang, J.; Bunel, E.; Allgeier, A.; Tedrow, J.; Storz, T.; Preston, J.; Correll, T.; Manley, D.; Soukup, T.; Jensen, R.; Syed, R.; Moniz, G.;

Larsen, R.; Martinelli, M.; Reider, P. *Tetrahedron Lett.* **2005**, *46*, 7831; (j) Yan, Y.; Zhang, X. *J. Am. Chem. Soc.* **2006**, *128*, 7198.

3. Whiteker, G. T.; Briggs, J. R.; Babin, J. E.; Barner, B. A. In *Catalysis of Organic Reactions*; Morrell, D. G., Ed.; Marcel Dekker: New York, 2003; p 359.
4. For recent reviews, see: (a) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857; (b) Kocovsky, P.; Vyskocyl, S.; Smrcina, M. *Chem. Rev.* **2003**, *103*, 3213; (c) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155.
5. Zhou, Y.G.; Zhang, X. *Chem. Commun.* **2002**, 1124.
6. Pastor, S. D. *et al*. *Helv. Chim. Acta*. **1993**, 76900.
7. (a) Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett*. **1992**, *33*, 2253; (b) Simonsen, K. B.; Gothelf, K. V.; Jorgenson, K. A. *J. Org. Chem.* **1998**, *63*, 7536.
8. Casey, C. P.; Whiteker, G. T.; Melville, M. G.; Petrovich, L. M.; Gavney, J. A.; Powell, D. R. *J. Am. Chem. Soc.* **1992**, *114*, 5535.
9. Kranenbury, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081.

Chapter 3

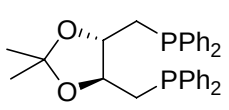
Development of a New Diphosphine Ligand for Enantioselective Asymmetric Hydrogenation

3.1 Introduction

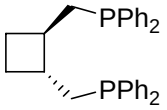
Homogeneous catalytic asymmetric hydrogenation is one of the most efficient methods for preparing chiral compounds.[1] It has been widely applied in pharmaceuticals and total synthesis. So far, numerous diphosphine ligands with chiral backbones have been developed. Some representative diphosphine ligands with chiral backbones are shown in Figure **3-1**.

In the early stages of 1970-1980, several successful chiral phosphorus ligands were discovered such as DIOP **1**[2], CBD **2**[3], and CHIRAPHOS **3**[4]. Applications were mostly limited in Rh-catalyzed asymmetric hydrogenation of dehydroamino acids.

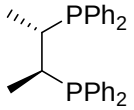
Schmid et al. reported the MeO-BIPHEP **4** ligand in 1991, which was successfully applied in many Ru-catalyzed hydrogenations.[5] Achiwa also developed several atropisomeric ligands such as BIMOP **5** in the same year.[6] The Cn-TunePhos **6** family of ligands was developed by our group in 2000; these species consist of a series of chiral bisphosphines with tunable dihedral angles. They were utilized in the Ru-catalyzed asymmetric hydrogenation of α-keto esters, and the obtained ee's varied according to the different dihedral angles of the TunePhos unit.[7]



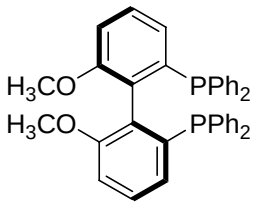
(*S*, *S*)-DIOP **1**



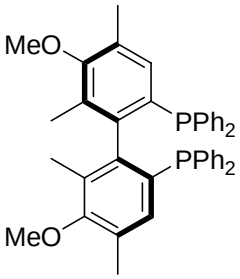
(*R*,*R*)-CBD **2**



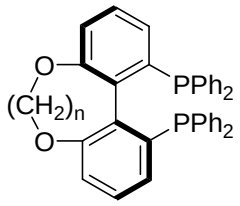
(*S*, *S*)-CHIRAPHOS **3**



(*S*)-MeO-BIPHEP **4**



(*S*)-BIMOP **5**



(*S*)-C_n-TunePhos **6**

Figure **3-1**. Some of the Representative Diphosphine ligands with Chiral Backbones

In this chapter, the design and synthesis of a new diphosphine ligand as well as its applications in asymmetric hydrogenation will be discussed. With the new ligand, excellent enantioselectivities (up to 99% ee) have been achieved in the Rh-catalyzed asymmetric hydrogenation of α-dehydro-amino acid esters and dimethyl itaconate.

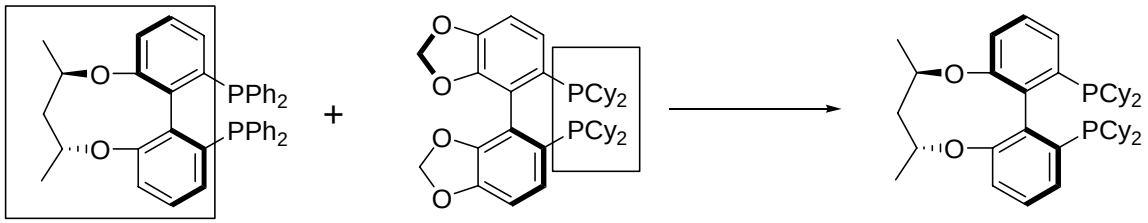
3.2 Results and Discussion

3.2.1 Design and Synthesis of a New Diphosphine Ligand

C_3-TunePhos has been used in the enantioselective asymmetric hydrogenation of α–phthalimide ketones and excellent enantioselectivities were obtained.[8] Cy-SegPhos,

which was reported by Saito's group, also generated high enantioselectivities (98% ee) in the asymmetric hydrogenation of α-dehydro-amino acid ester.[9]

Inspired by the excellent results obtained with C_3-TunePhos and Cy-SegPhos, we have designed a new diphosphine ligand **7** by combining the backbone of C_3-TunePhos and the phosphine part of Cy-SegPhos (Scheme **3-1**). The ligand design was based on the following considerations: (i) The chiral C_3-biphenyl backbone is more rigid than the chiral binaphthyl backbone, as the reaction with C_3-TunePhos showed better enantioselectivity than that with BINAP in the asymmetric hydrogenation of α–phthalimide ketone.[8] (ii) The cyclohexyl group is more electron donating than a phenyl group, a property that may facilitate highly active hydrogenation.



Scheme **3-1**. Design of a New Phosphine Ligand.

The quadrant diagram model is the most effective and simplest guide for the design of diphosphines for the asymmetric hydrogenation.[10] Gridnev and Imamoto have elegantly shown how quadrant diagrams can be used to predict accurately the sense of enantioselectivity.[11] The simplified quadrant diagrams are shown in Figure **3-2**. The dicyclohexyl groups of the ligand protrude and block the upper-left and bottom-right

quadrants while leaving the upper-right and bottom-left quadrants open. Thus, the new ligand can provide a similar chiral environment as does C_3-TunePhos.

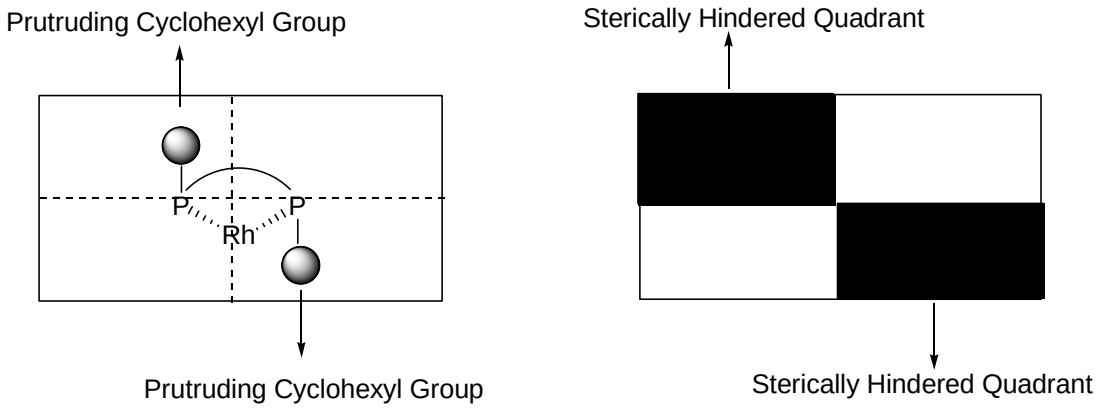
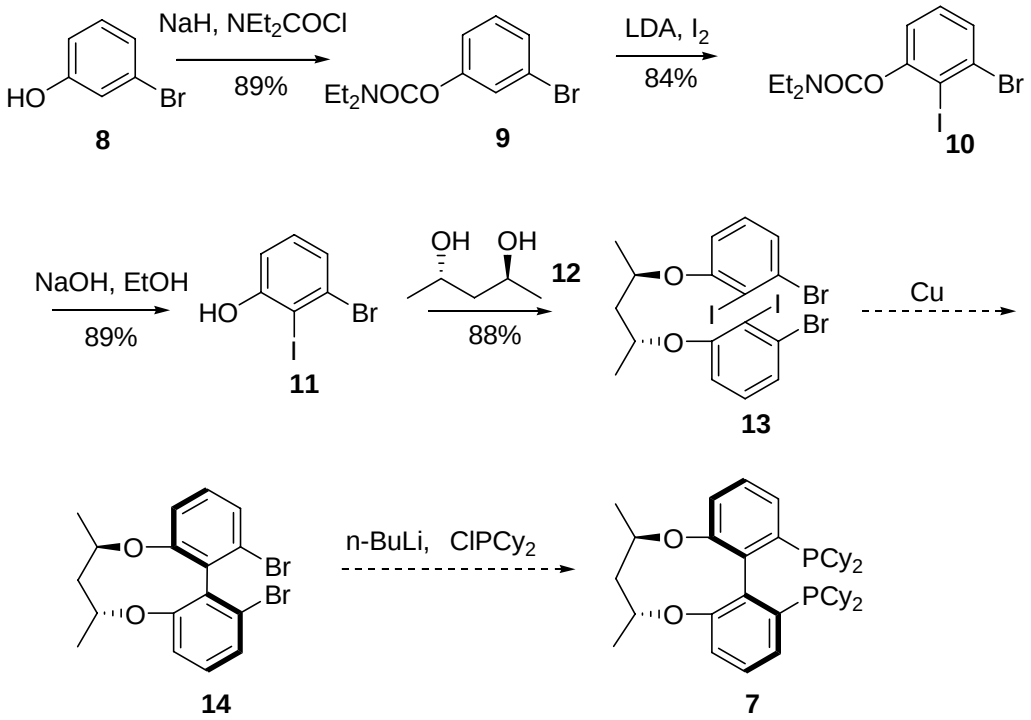


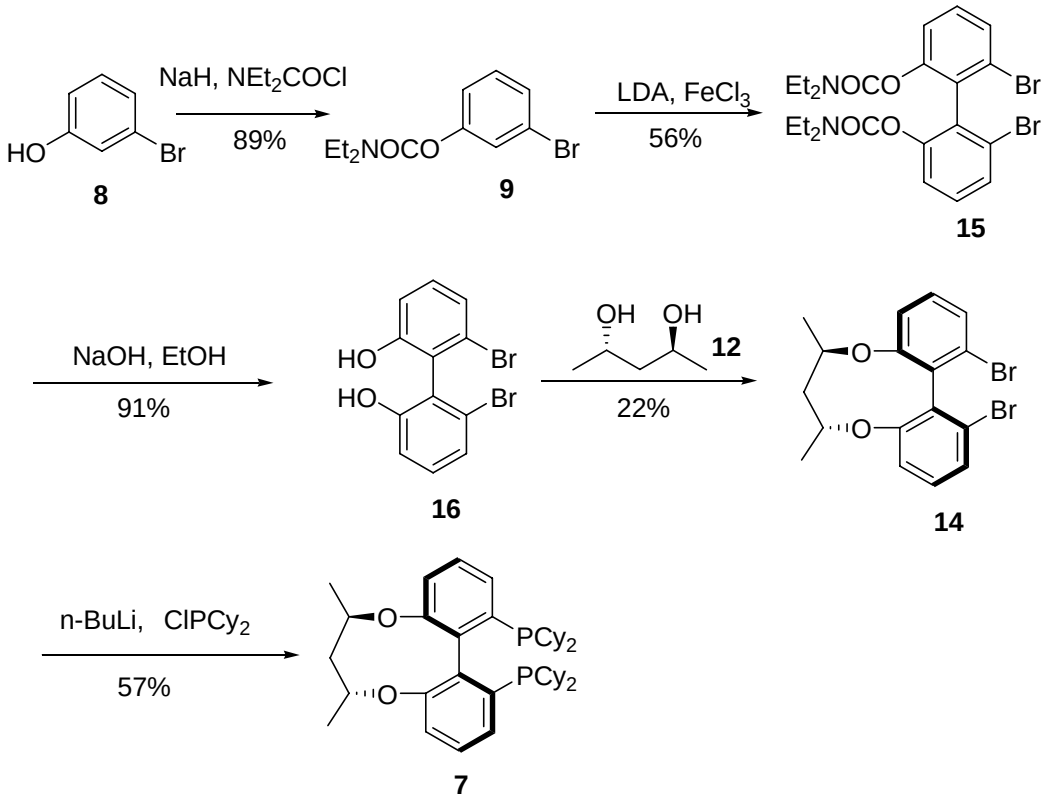
Figure **3-2**. Quadrant Diagram of Rhodium-diphosphine Complex

To synthesize the new ligand, we first designed route A (Scheme **3-2**). Starting from the 3-bromophenol **8**, the hydroxyl group was protected as its carbamate.[12] Then iodination at the ortho position of **9** followed by deprotection of **10** gave the di-halogen substituted phenol **11** in good yield.[12] Mitsunobu reaction of the phenol **11** with chiral C_3-diol **12** followed by Ullmann coupling of **13** should give the dibromide structure **14**. Lithiation of the dibromide **14** and quenching with dicyclohexylphine chloride should produce the new ligand **7**.[9] The first four steps went well and the yield for each step was satisfactory. However, the Ullmann coupling reaction didn't go well, probably because of the similar properties of bromine and iodine. The yield for this step was too low to proceed with this synthesis plan. We could not get a large amount of dibromide **14** and route A failed.



Scheme **3-2**. Synthetic Route A for the New Diphosphine Ligand.

We designed route B as an improvement over route A. Since the coupling step didn't go well, we now plan to execute the coupling step first. So, after we secured the protected carbamate **9**, we used ion trichloride to run the coupling reaction and got the compound **15** in 56% yield. Mitsunobu reaction of the deprotected diphenol structure **16** with chiral C_3-diol **12** gave the dibromide structure **14**. From this step, we got two diastereomers with different biphenyl configurations. Product **14** was obtained after column chromatography in 22% yield. The new ligand **7** was obtained in 57% yield from dibromide structure **14** following the procedure described in route A.



Scheme **3-3**. Synthetic Route B for the New Phosphine Ligand.

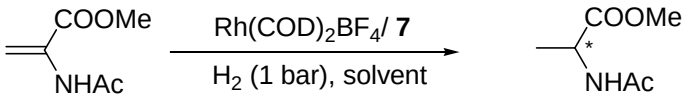
3.2.2 Asymmetric Hydrogenation with the New Diphosphine Ligand 7

Chiral α–amino acids are important biological molecules, being widely used for biological, biochemical, and pharmaceutical studies. They serve as useful starting materials for the preparation of pharmaceutical intermediates and other target molecules.[13] In organic synthesis, they have been applied as useful building blocks for the synthesis of complex natural products. Recently, catalytic asymmetric hydrogenation of α-dehydroamino acid derivatives has gained much attention due to its high efficiency.

Many chiral ligands have been successfully applied to rhodium-catalyzed asymmetric hydrogenation with excellent enantioselectivity and reactivity.[1d]

With the new ligand, Rh-catalyzed asymmetric hydrogenation of α-dehydro-amino acid esters was explored. First, asymmetric hydrogenation of methyl-2-acetamido acrylate was conducted in different solvents to determine if there was any exploitable solvent effect (Table **3-1**). The reactions were performed with a substrate-to-catalyst ratio of 100 at room temperature for 18 h to achieve full conversion. Up to 99% ee was obtained using more polar solvents and up to 95% ee was obtained using a nonpolar solvent such as toluene (Table **3-1**, entry 2). It seems that the solvent didn't have a big influence on the enantioselectivities of the hydrogenation of methyl-2-acetamido acrylate. The activities were good and full conversion was observed for all screened solvents.

Table **3-1**. Asymmetric Hydrogenation of Methyl-2-acetamido Acrylate[a]



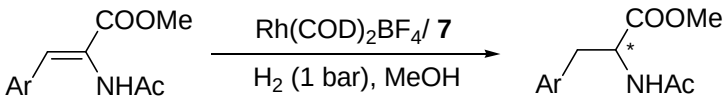
entry	solvent	ee (%)
1	CH_2Cl_2	98(*R*)
2	toluene	95(*R*)
3	THF	99(*R*)
4	EtOAc	99(*R*)
5	acetone	99(*R*)
6	MeOH	99(*R*)
7	TFE	93(*R*)

[a] The reactions were carried out at r.t. under 1 atm H_2 for 18 h. Full conversion. Substrate/Catalyst = 100. The ee's were determined by chiral GC using a Chirasil-Val column. The absolute configurations were determined by comparing the optical rotations with reported values.

With methanol as solvent, a series of α-dehydroamino acid esters were then hydrogenated with rhodium-diphosphine complex. The results are summarized in Table **3-2**. Full conversion to product was obtained in all cases. When the substituent group on the phenyl ring was changed from fluoro to methoxyl, the enantioselectivities remained the same (99% ee). The position of the substituent group varied, and excellent enantioselectivities were obtained for all the substrates tested. In general, asymmetric hydrogenation of α-dehydroamino acid esters with ligand **7** resulted in excellent

enantioselectivities irrespective of the differing steric and electronic properties of the substrates.

Table **3-2**. Asymmetric Hydrogenation of α-Dehydro-amino Acid Esters[a]

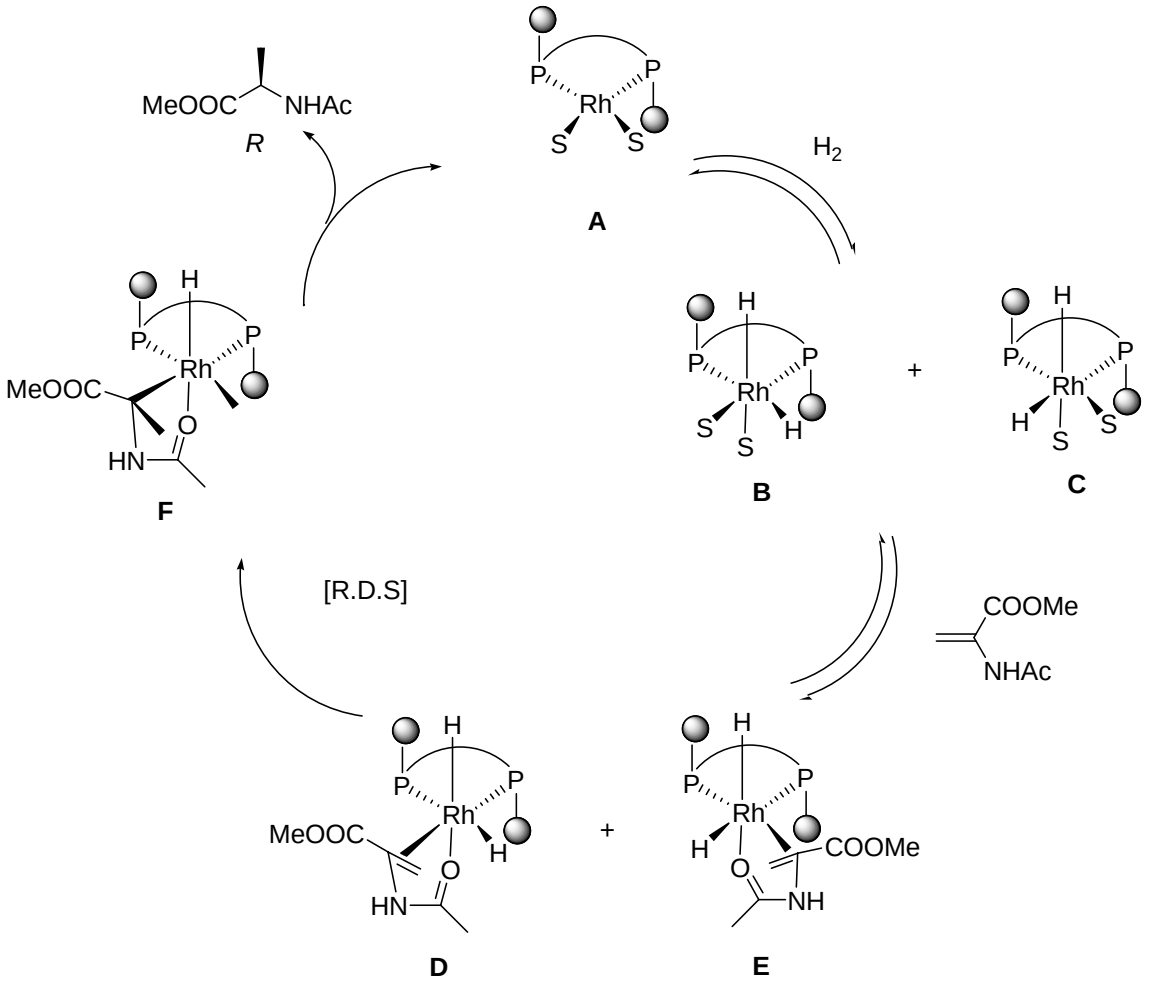


entry	Ar	ee (%)
1	2-F-Ph	99(*R*)
2	4-F-Ph	99(*R*)
3	3,5-difluoro-Ph	99(*R*)
4	2-Br-Ph	99(*R*)
5	4-Br-Ph	99(*R*)
6	4-MeO-Ph	99(*R*)

[a] The reactions were carried out at r.t. under 1 atm H_2 for 18 h. Full conversion. Substrate/Catalyst = 100. The ee's were determined by chiral GC using a Chirasil-Val column. The absolute configurations were determined by comparing the optical rotations with reported values.

Since dicyclohexyl phosphine is a highly electron-donating group, the mechanism of the hydrogenation reaction with the new ligand **7** is believed to proceed in a "dihydride" pathway which was proposed by Imamoto and coworkers (Scheme **3-4**).[14] First, the oxidative addition of hydrogen to the rhodium-diphosphine complex **A** produces a mixture of rhodium-dihydride complexes **B** and **C**. The substrate then coordinates to the rhodium center to form the intermediates **D** and **E** whose relative

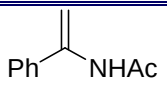
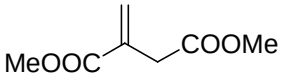
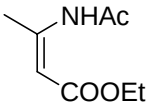
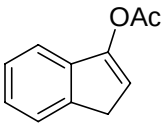
stability controls the enantioselectivity. The dihydride complex **D** is more stable than **E** because the dihydride complex **E** experiences severe steric interaction between the cyclohexyl groups of the ligand and the substrates chelating ring. Migratory insertion of hydrogen leads to the mono-hydride rhodium species **F**. This step is believed to be the rate-determine step in the catalytic cycle. Reductive elimination finally affords the hydrogenation product with *R* configuration and regenerates the rhodium-diphosphine catalyst **A**.



Scheme **3-4**. Mechanism for Rhodium-Catalyzed Hydrogenation of α-Dehydroamino Acid Esters

To investigate the substrate scope, other common prochiral substrates were hydrogenated using new ligand **7**. The reaction conditions were the same as in the hydrogenation of the α-dehydro-amino acid esters. Some representative results are listed in Table **3-3**. Good enantioselectivity (88% ee) was achieved in the hydrogenation of dimentyl itaconate (Table **3-3**, entry 2). Moderate enantioselectivity was obtained for the enamide in entry 3 with full conversion to product (Table **3-3**, entry 1). Both the conversion and enantioselectivity were not high for the β–dehydroamino acid ester and the cyclic vinyl acetate examined (Table **3-3**, entries 3 and 4).

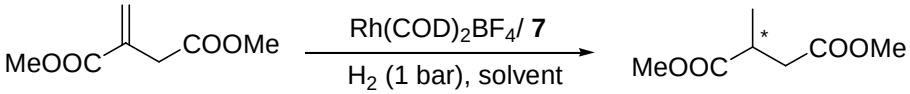
Table **3-3**. Asymmetric Hydrogenation of Some Prochiral Substrates[a]

entry	Substrate	conv (%)	ee (%)
1		100	45(*S*)
2		100	88(*S*)
3		63	56(*S*)
4		25	45(*S*)

[a] The reactions were carried out in CH_2Cl_2 at r.t. under 1 atm H_2 for 18 h. Substrate/Catalyst = 100. The ee's were deterined by chiral GC. The absolute configurations were determined by comparing the optical rotations with reported values.

Asymmetric hydrogenation of dimethyl itaconate was conducted with different solvents to probe for a solvent effect (Table **3-4**). Up to 90% ee was obtained using polar solvents and up to 78% ee was obtained using a nonpolar solvent such as toluene (Table **3-4**, entry 2). The best enantioselectivity was obtained using THF as the solvent, while other polar solvent such as ethyl acetate, acetone and methanol gave similar enantioselectivities.

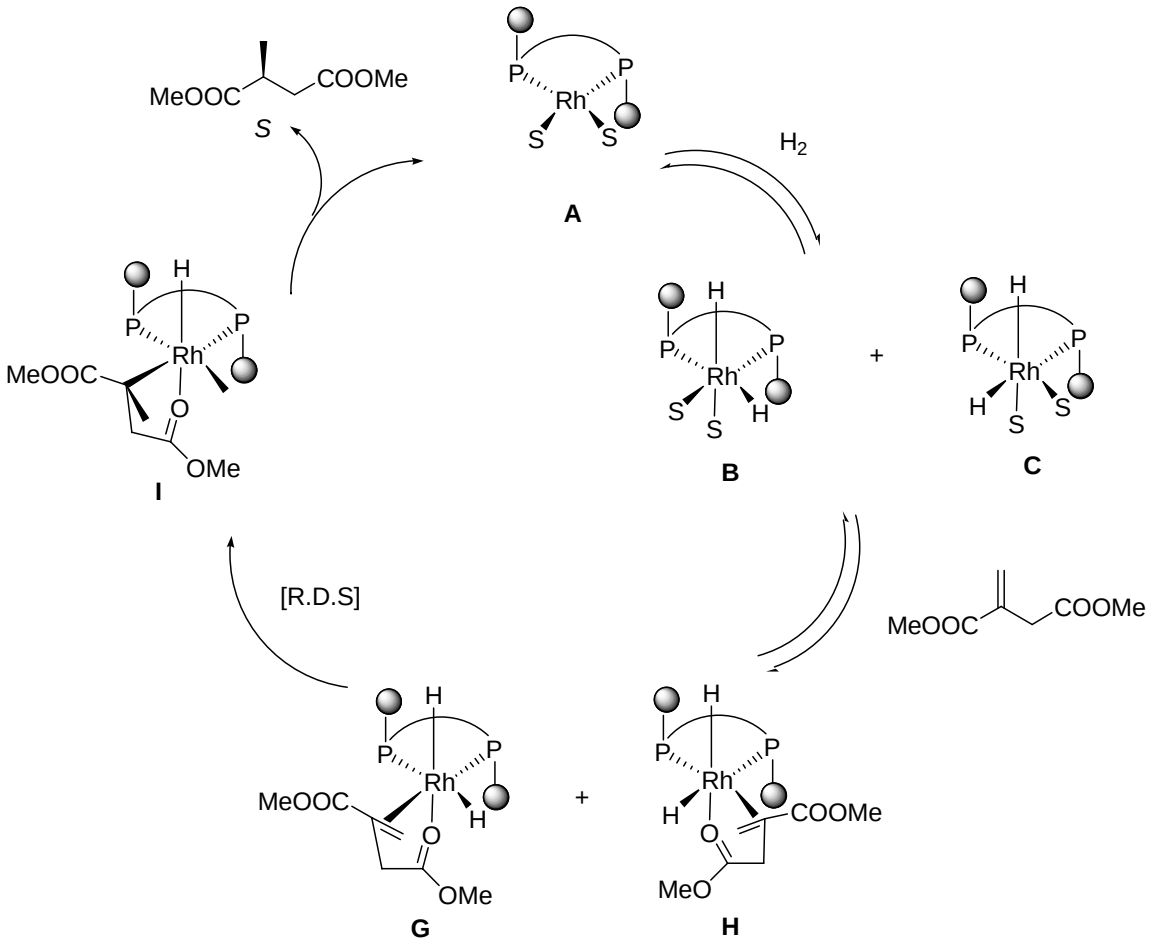
Table **3-4** . Asymmetric Hydrogenation of Dimethyl Itaconate[a]



entry	solvent	ee (%)
1	CH_2Cl_2	88(*S*)
2	toluene	78(*S*)
3	THF	90(*S*)
4	EtOAc	89(*S*)
5	acetone	89(*S*)
6	MeOH	87(*S*)
7	TFE	89(*S*)

[a] The reactions were carried out at r.t. under 1 atm H_2 for 18 h. Full conversion. Substrate/Catalyst = 100. The ee's were deterined by chiral GC using a γ-225 column. The absolute configurations were determined by comparing the optical rotations with reported values.

The mechanism of the hydrogenation of dimethyl itaconate is similar to the case of the hydrogenation of α-dehydro-amino acid esters. It likely also proceeds through a "dihydride" pathway. The more stable **G** with less steric interaction will finally lead to the hydrogenation product with *S* configuration.



Scheme **3-5**. Mechanism for Rhodium-Catalyzed Hydrogenation of Dimethyl Itaconate

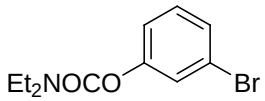
3.3 Conclusion

In conclusion, new diphosphine ligand **7** has been designed and synthesized. Its application in asymmetric hydrogenation of α-dehydro-amino acid esters and dimethyl itaconate has been investigated. Excellent enantioselectivities (up to 99% ee) for α-dehydro-amino acid esters and good enantioselectivities (up to 90% ee) for dimethyl itaconate have been achieved.

Experimental Section

General Methods. All reactions and manipulations were performed using standard Schlenk techniques. Solvents were dried with standard procedures and degassed with N_2. Thin layer chromatography (TLC) was performed on EM reagents 0.25 mm silica 60-F plates. Column chromatography was performed using 200-400 mesh silica gel supplied by Natland International Corp. ^1H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker AM-300 and AMX-360 spectrometers. MS spectra were recorded on a KRATOS mass spectrometer MS 9/50. Optical rotation was carried out on a Perkin-Elmer 241 polarimeter. GC analysis was obtained on Hewlett-Packard 6890 gas chromatography using chiral capillary columns.

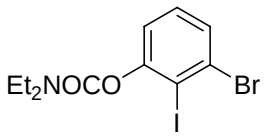
Synthesis of 3-bromophenyl diethylcarbamate (9)



To a well stirred suspension of NaH (1.92 g, 80 mmol) in THF (100 mL), a solution of 3-bromophenol **8** (6.92 g, 40 mmol) in THF (10 mL) was dropwise added at room temperature. After stirring the reaction mixture for 3 h, N,N-diethylcarbamoyl choride (10.84 g, 80 mmol) in THF (14 mL) was added. Stirring was continued for overnight. Usual aqueous work up afforded the crude carbamate which was purified by column chromatography (eluent: hexane/EtOAc = 12:1) on silica gel to afford compounds **9** (9.68 g) in 89% yield. ^1H NMR (500 MHz, $CDCl_3$): δ 7.30 (s, 1H), 7.26 (d, J = 8.5 Hz, 1H), 7.15 (t, J = 8.5 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 3.36-3.33 (m, 4H), 1.18-1.14 (m, 6H).

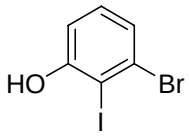
^{13}C NMR (126 MHz, $CDCl_3$): δ 153.71, 152.37, 130.44, 128.32, 125.43, 122.24, 120.87, 42.58, 42.19, 14.47, 13.56.

Synthesis of 3-bromo-2-iodophenyl diethylcarbamate (10)



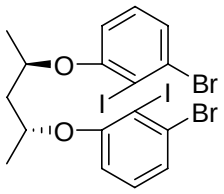
n-BuLi (4.4 mL of a 2.5M sol. in hexane, 11 mmol) was added to a solution of *i*-Pr_2NH (1.54 mL, 11 mmol) in THF (30 mL) at 0 ºC. After 30 min at 0 ºC the LDA solution was cooled at –78 ºC and carbamate **9** (2.72 g, 10 mmol) was added. The resulting solution was stirred for 30 min at –78 ºC and then, iodine (3.05 g, 12 mmol) was added. After 30 min at low temperature the reaction mixture was allowed to warm to room temperature and stirred overnight. Saturated aqueous solution of $Na_2S_2O_3$ was added and the solvent was removed. It was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried (Na_2SO4), and evaporated under reduced pressure. The crude was purified by column chromatography (eluent: hexane/EtOAc = 10:1) on silica gel to afford **10** (3.34 g, 84%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.22 (t, *J* = 8.1 Hz, 1H), 7.08 (dd, *J* = 8.1, 1.5 Hz, 1H), 3.52 (q, *J* = 7.1 Hz, 2H), 3.38 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.4, 152.8, 130.6, 130.0, 129.7, 121.8, 99.9, 42.5, 42.2, 14.5, 13.4.

Synthesis of 3-bromo-2-iodophenol (11)



To a solution of **10** (10 mmol) in EtOH (100 mL) a large excess of NaOH (4 g, 100 mmol) was added. The mixture was refluxed for 8 h. After cooling to room temperature, most of the EtOH was evaporated under reduced pressure, the residue was diluted with Et_2O and the excess of NaOH was neutralized at 0 ºC using a 1 M solution of HCl. The aqueous solution was extracted with Et_2O (3 x 20 mL) and the combined organic phase was washed with brine, dried (anhydrous Na_2SO_4), and evaporated under reduced pressure. The crude was purified by column chromatography (eluent: hexane/EtOAc = 5:1) on silica gel to afford compounds **11** (2.66 g, 89%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.12 (t, *J* = 8.1 Hz, 1H), 6.92 (dd, *J* = 8.1, 1.5 Hz, 1H), 5.54 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.6, 130.8, 129.6, 125.0, 113.3, 94.4.

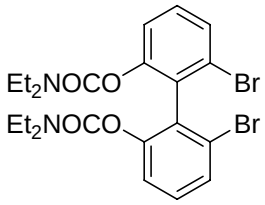
Synthesis of 3,3'-(2*R*,4*R*)-pentane-2,4-diylbis(oxy)bis(1-bromo-2-iodobenzene) (13)



A solution of **11** (2.48 g, 8.3 mmol), (2*S*,4*S*)-pentane-2,4-diol **12** (417 mg, 4 mmol), and PPh_3 (2.19 g, 8.3 mmol) in anhydrous THF (3 mL) in a 25 mL round bottom flask was stirred at 0 ºC for 30 min. DIAD (1.63 mL, 8.3 mmol) was added drop wise to the reaction solution. The reaction system was lowered into a sonication bath with ice-water

and sonicated for 3 h. A large amount of precipitate was formed during reaction. Filtered the precipitate and removed the solvent. The crude was purified by column chromatography (eluent: hexane/EtOAc = 6:1) on silica gel to afford compounds **13** (2.34 g, 88%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.11 (dd, *J* = 8.0, 1.4 Hz, 2H), 6.98 (t, *J* = 7.6Hz, 2H), 6.56 (dd, *J* = 8.2, 1.2 Hz, 2H), 4.77 (m, 2H), 2.09 (m, 2H), 1.39 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 157.61, 129.85, 129.13, 124.13, 110.71, 95.14, 72.52, 44.05, 19.41.

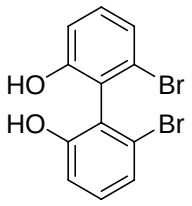
Synthesis of 6,6'-dibromobiphenyl-2,2'-diyl bis(diethylcarbamate) (15)



n-BuLi (4.4 mL of a 2.5M sol. in hexane, 11 mmol) was added to a solution of *i*-Pr_2NH (1.54 mL, 11 mmol) in THF (30 mL) at 0 ºC. After 30 min at 0 ºC the LDA solution was cooled at –78 ºC and carbamate **9** (2.5 g, 9.2 mmol) was added. The resulting solution was stirred for 30 min at –78 ºC and then, $FeCl_3$ (1.95 g, 12 mmol) was added. After 30 min at low temperature the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction solution was added 1 M HCl aqueous solution and the solvent was removed. It was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried (Na_2SO4), and evaporated under reduced pressure. The crude was purified by column chromatography (eluent: hexane/EtOAc = 6:1) on silica gel to afford **15** (1.4 g, 56%) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.65 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.48 (t, *J* = 8.1 Hz, 2H),

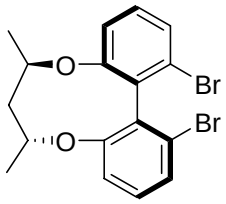
3.40 (m, 4H), 3.18 (m, 4H), 1.26 (t, J = 7.1 Hz, 6H), 0.95 (t, J = 7.1 Hz, 6H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 151.74, 149.21, 130.28, 128.80, 127.65, 123.38, 121.06, 42.5, 42.2, 14.5, 13.4.

Synthesis of 6,6'-dibromobiphenyl-2,2'-diol (16)



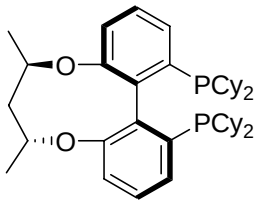
To a solution of **15** (8.69 g, 16 mmol) in EtOH (100 mL) a large excess of NaOH (6.4 g, 160 mmol) was added. The mixture was refluxed for 8 h. After cooling to room temperature, most of the EtOH was evaporated under reduced pressure, the residue was diluted with Et_2O and the excess of NaOH was neutralized at 0 ºC using a 1 M solution of HCl. The aqueous solution was extracted with Et_2O (3 x 20 mL) and the combined organic phase was washed with brine, dried (anhydrous Na_2SO_4), and evaporated under reduced pressure. The crude was purified by column chromatography (eluent: hexane/EtOAc = 3:1) on silica gel to afford compounds **16** (5.025 g, 91%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, J = 8.0 Hz, 2H), 7.25 (t, J = 8.0 Hz, 2H), 7.02 (d, J = 8.0 Hz, 2H), 5.13 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.09, 131.97, 125.48, 125.43, 122.92, 115.50.

Synthesis of the dibromide compound (14)



A solution of **16** (2.04 g, 6 mmol), (2*S*,4*S*)-pentane-2,4-diol **12** (624 mg, 6 mmol), and PPh_3 (3.14 g, 12 mmol) in anhydrous THF (3 mL) in a 25 mL round bottom flask was stirred at 0 ºC for 30 min. DIAD (2.4 mL, 12 mmol) was added drop wise to the reaction solution. The reaction system was lowered into a sonication bath with ice-water and sonicated for 3 h. A large amount of precipitate was formed during reaction. Filtered the precipitate and removed the solvent. The crude was purified by column chromatography (eluent: hexane/EtOAc = 30:1) on silica gel to afford compounds **14** (544 mg, 22%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.0 Hz, 2H), 7.25 (t, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 4.53 (m, 2H), 1.79 (m, 2H), 1.34 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.56, 132.20, 130.16, 127.18, 125.03, 117.50, 76.68, 40.92, 22.44.

Synthesis of new ligand (7)



n-BuLi (0.48 mL of a 2.5 M sol. in hexane, 1.2 mmol) was added to a solution of TMEDA (0.18 mL, 1.2 mmol) and **14** (206 mg, 0.5 mmol) in THF (30 mL) at –78 ºC. After 30 min at –78 ºC, Cy_2PCl (0.26 mL, 1.2 mmol) was added. After 30 min at low

temperature, the reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed. The crude was purified by column chromatography (eluent: hexane/EtOAc = 30:1) on silica gel to afford **7** (184 mg, 57%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.1 Hz, 2H), 7.05 (t, *J* = 8.1 Hz, 2H), 6.91 (d, *J* = 8.1 Hz, 2H), 4.40 (m, 2H), 2.00 (m, 2H), 1.73-0.82 (m, 50H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.93, 137.99, 137.41, 126.90, 126.13, 117.13, 74.75, 40.87, 35.83, 32.51, 30.97, 30.51, 29.81, 28.91, 28.16, 28.04, 27.58, 27.52, 27.27, 26.83. ^{31}P NMR(162 MHz, $CDCl_3$): δ -10.58 (s).

General Procedure for Asymmetric Hydrogenation

To a solution of an α-dehydro-amino acid ester (0.1 mmol) in methanol (1.0 mL) was added a solution of the Rh/**7** complex (1 mmol), preformed by mixing ligand **7** with 1.0 equiv. of $Rh(COD)_2BF_4$ in methanol (1.0 mL)) in a glove box filled with nitrogen. The whole solution was transferred into an autoclave and charged with hydrogen (1 atm). The hydrogenation was performed at room temperature for 18 h. After the reaction, the hydrogen was released carefully and the reaction mixture was passed through a silica gel plug and flushed with ether. The ee's were determined by chiral GC (Chrialsil-L-VAL). The absolute configuration was assigned by comparing the optical rotations with reported values.

References

1. Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hormann, E.; McIntyre, S.; Menges, F.; Schonleber, M.; Smidt, S. P.; Wustenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2003**, *345*, 33; (b) Crepy, K. V. L.; Imamoto, T. *Adv. Synth. Catal.* **2003**, *345*, 79; (c) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103; (d) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029; (e) Chelucci, G.; Orru, G.; Pinna, G. A. *Tetrahedron* **2003**, *59*, 9471; (f) Clark, T. P.; Landis, C. R. *Tetrahedron: Asymmetry* **2004**, *15*, 2123; (g) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497.
2. (a) Kagan, H. B.; Dang, T. P. *Chem. Commun.* **1971**, 481; (b) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429; (c) Kagan, H. B.; Langlois, N.; Dang, T. P. *J. Organomet. Chem.* **1975**, *90*, 353.
3. (a) Rhone Poulenc, S. A. Fr. Patent 2,230,654, 1974. (b) Glaser, R.; Geresh, S.; Twaik, M. *Isr. J. Chem*. **1980**, *20*, 102.
4. (a) Fryzuk, M. B.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262. (b) Fryzuk, M. B.; Bosnich, B. *J. Am. Chem. Soc.* **1979**, *101*, 3043.
5. Schmid, R.; Foricher, J.; Cereghetti, M.; Scho¨nholzer, P. *Helv.Chim. Acta* **1991**, *74*, 870.
6. Yamamoto, N.; Murata, M.; Morimoto, T.; Achiwa, K. *Chem.Pharm. Bull.* **1991**, *39*, 1085.
7. Zhang, Z; Qian, H; Longmire, J; Zhang, X. *J. Org. Chem*. **2000**, *65*, 6224.
8. Lei, A; Wu, S; He, M; Zhang, X. *J. Am. Chem. Soc*. **2004**, *126*, 1626.

9. Shimizu, H.; Ishizaki, T; Fujiwara, T; Saito, T. *Tetrahedron: Asymmetry* **2004**, *15*, 2169.

10. (a) Halpern, J.; Riley, D. P.; Chan, A. S. C.; Pluth, J. J. *J. Am. Chem. Soc.*, 1977, **99**, 8055; (b) Knowles, W. S. *Acc. Chem. Res.*, 1983, **16**, 106; (c) Armstrong, S. K.; Brown, J. M.; Burk, M. J. *Tetrahedron Lett.*, 1993, **34**, 879; (d) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.*, 1998, **120**, 1635.

11. (a) Gridnev, I. D.; Imamoto, T. *Acc. Chem. Res.*, 2004, **37**, 633; (b) Gridnev, I. D.; Higashi, N.; Asakura, K.; Imamoto, T. *J. Am. Chem. Soc.*, 2000, **122**, 7183.

12. Sanz, R; Castroviejo, M. P; Fernandez, Y; Fananas, F. J. *J. Org. Chem*. **2005**, *70*, 6548.

13. (a) Williams, R. M. *Synthesis of Optically Active Amino Acids*; Pergamon Press: Oxford, **1989**; (b) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*; John Wiley and Sons: New York, **1987**; (c) Hanessian, S. *Total Synthesis of Natural Products*: The Chiron Approach; Pergamon Press: Oxford, **1983**; (d) Ma, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 4290.

14. (a) Gridnev, Il. D.; Higashi, N.; Asakura, K.; Imamoto. T. *J. Am. Chem. Soc*. **2000**, 122, 7183.; (b) Gridnev, Il. D.; Imamoto. T. *Acc. Chem. Res.* **2004**, *37*, 663.

VITA

Yaping Zou

EDUCATION

2009 (Expected) M.S., Organic Chemistry, the Pennsylvania State University
Thesis Title: "Synthesis of New Phosphorus Ligands for Asymmetric Catalysis"
Advisor: Professor Xumu Zhang

2003 B.S., Organic Chemistry, Peking University

PUBLICATIONS

1. New diphosphite ligands for enantioselective asymmetric hydroformylation. Zou, Y; Yan, Y; Zhang, X. *Tetrahedron Lett.* **2007**, *48*, 4781.

2. Highly regioselective hydroformylation of styrene and its derivatives catalyzed by Rh complexes with tetraphosphorus ligands. Yu, S; Chie, Y; Guan, Z; Zou, Y; Li, W; Zhang, X. *Org. Lett.* **2009**, *11*, 241.

3. Concise and diastereoselective approach to *syn*- and *anti*-*N*-tosyl-α-hydroxy β-amino acid derivatives. Zhao, Y; Jiang, N; Chen, S; Peng, C; Zhang, X; Zou, Y; Zhang, S; Wang, J. *Tetrahedron* **2005**, *61*, 6546.

4. A highly stereoselective addition of the anion derived from α-diazoacetamide to aromatic *N*-tosylimines. Zhao, Y; Ma, Z; Zhang, X; Zou, Y; Jin, X; Wang, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5977.