THE DESIGN OF NEW SUBSTRATES AND LIGANDS FOR RHODIUM CATALYZED ASYMMETRIC HYDROGENATION

by

TIAN SUN

A dissertation submitted to the

Graduated School-New Brunswick

Rutgers, The State University of New Jersey

In Partial Fulfillment of the Requirements

For the degree of

Doctor of Philosophy

Graduate Program in Chemistry and Chemical Biology

Written under the direction of

Xumu Zhang

And approved by

_____

_____

_____

_____

New Brunswick, New Jersey

MAY, 2013

ABSTRACT OF THE DISSERTATION

The Design of New Substrates and Ligands for Rhodium Catalyzed Asymmetric Hydrogenation

by

TIAN SUN

Dissertation Director:

Xumu Zhang

Asymmetric hydrogenation is a significant research field in modern catalytic organic synthesis. In the past 50 years, the design of catalysts and substrates has been widely studied. A great number of phosphorus ligands for asymmetric hydrogenation have been developed. Three generations of catalysts have been reported by a number of scientists. The asymmetric hydrogenation becomes more and more efficient and applicable. High enantioselectivities and activities have been achieved. The design of substrates also makes significant progresses. Many successful examples have been reported in asymmetric hydrogenation of olefins, ketones, and imines.

In chapter one, the development of phosphorus ligands is reported. The characters of phosphorus ligands are discussed and compared. Examples of representative catalysts are listed. The asymmetric hydrogenation of different substrates is also summarized and discussed.

In chapter two, asymmetric hydrogenation of α-dehydroamino ketones catalyzed by a rhodium-chiral phosphorus ligand complex (up to 99% ee, 1000 TON) is reported. This reaction represents an efficient approach to chiral α-amino ketones. The reduction of α-amino ketones catalyzed by Palladium on carbon (Pd/C) leads to amphetamine precursors with quantitative yield and no significant enantioselectivity loss.

In chapter three, high enantioselectivities (up to 99% ee) have been observed for the catalytic asymmetric hydrogenation of the α-ketone enol acetates. DuanPhos has been proved to be the most effective ligand for this reaction. High yield and enantioselectivity of the asymmetric hydrogenation of the α-ketone enol acetates demonstrates a feasible synthetic route to important pharmaceutical building blocks: α-hydroxy ketones.

In chapter four, a series of new chiral secondary phosphine oxide (SPO) ligands are reported. Compared with traditional bisphosphine ligands, the SPO ligands are air stable, and have shorter synthetic routes. However, poor to moderate results are obtained using the new chiral SPO ligands. The study of SPO ligands still has many unsolved problems. The potential applications and challenges of SPO ligands are also discussed in chapter four.

ACKNOLEDGEMENTS

I would like to sincerely thank Professor Xumu Zhang for his support during the last six years. I could never accomplish this dissertation without the encouragement and guidance by Professor Zhang. It is my great honor to be part of Professor Zhang's research group. I would also like to thank my former and current committee members: Professor Alan Goldman, Professor Longqin Hu, Professor Kai Hultzsch, Professor Leslie Jimenez, Professor Daniel Seidel, and Professor Ralf Warmuth for their time and supports during my graduate study. I would also like to thank all the former and current group members: Dr. Gao Shang, Dr. Guohua Hou, Dr. Wei Li, Dr. Xiaowei Zhang, Dr. Weicheng Zhang, Dr. Xianfeng Sun, Dr. Qian Dai, Dr. Bonan Cao, Dr. Kexuan Huang, Mr. Yuming Xie, Mr. Stephen Spenalla, Mr. Mingxing Chang, Mr. Bin Qian, Mr. Shaodong Liu, Mr. Shengkun Li, Dr. Huiling Geng, Dr. Miaofeng Ma, and Dr. Jian Chen for their collaborations and helps. I am very grateful to Dr. Gao Shang and Dr. Guohua Hou for their valuable guidance in my research and experiments. I would like to give the special thanks to my parents. Their love and support has always been a great encouragement for me. I would also like to deliver my deepest thanks to my husband, Zhe Liang. He is the one who encourages me when I doubt myself, who worries about me when I am overconfident, who sits up all night to help me with the research projects, who takes care of me during my sickness. I could never go this far without Zhe’s love. Finally, I would like to thank Rutgers University for the excellent education, research environments, financial support, health insurance, and on-campus housing. I met my husband on the third day at Rutgers, and then got married at our second year of Ph.D. study. My son Daniel came at the third year. As a researcher, teaching assistant, wife, and mother, I

have encountered several difficulties. Rutgers, my dear alma mater, made everything much easier for me. Because of the above mentioned professors, colleagues, and my family, my experience at Rutgers becomes a wonderful adventure and a pleasant journey.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Chapter 1

Introduction

1.1 Ligand design for Rhodium-catalyzed asymmetric hydrogenation.

Hydrogenation uses hydrogen to reduce unsaturated chemical bonds. This simple and elegant methodology is critical for the development of green chemistry, because the ideal hydrogenation reaction is atom economical. For decades, the applications and modifications of hydrogenation have drawn great attention. Among several research topics related to hydrogenation, asymmetric hydrogenation has been developed into an important research direction because of its high efficiency and enantioselectivity.

The success of asymmetric hydrogenation relies heavily on the choice of catalysts, more specifically, on the combination of transition metals and phosphorus ligands. The development of phosphorus ligands realizes numerous difficult reactions, achieves high enantioselectivities, and shortens tedious synthetic routes. In less than 50 years, three generations of phosphorus ligands targeting at asymmetric hydrogenation have been invented.

1.1.1 First generation of phosphorus-containing ligands.

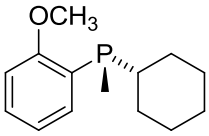
The first generation of phosphorus ligands was developed in the early 1970's. Knowles and his coworkers designed and synthesized a chiral monophosphine ligand CAMP

(Figure 1-1). CAMP is the first chiral phosphorus ligand with synthetically practical results (up to 88% ee). Development of the first generation ligands is also driven by the pharmaceutical application of amino acids. Amino acids are one of the most important natural compounds and pharmaceutical building blocks. Many efforts have been devoted into finding an industrial applicable synthetic route to chiral amino acids. The asymmetric hydrogenation of dehydroamino acids is straightforward, efficient, and atom economical, given the correct catalysts and reaction conditions. In order to achieve high yield and excellent enantioselectivity, the design and synthesis of new types of catalysts for asymmetric hydrogenation are of key importance. One of the asymmetric hydrogenation catalysts milestones is the synthesis of DIPAMP[2], a bidentate diphosphine ligand. DIPAMP is found to be very selective to the synthesis of L-DOPA. L-DOPA is a chiral amino acid which is used in the clinical treatment of Parkinson's disease and dopamine-responsive dystonia. The discovery of DIPAMP realizes the industrial production of L-DOPA. Knowles is awarded the 2001 Nobel Prize in Chemistry because of his work on the synthesis of L-DOPA using asymmetric hydrogenation. The success of the bidentate diphosphine ligands inspires many scientists in the field of asymmetric hydrogenation, and stimulates the blossom of a large family of bidentate phosphorus ligands. Even to this day, the majority of asymmetric hydrogenation ligands belong to the bidentate category.

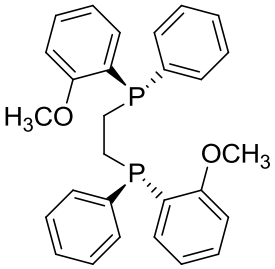
Followed by the success of CAMP and DIPAMP ligands, several bidentate ligands were subsequently discovered during 1970 to 1980, such as Kagan's DIOP[10], Bosnich's

CHIRAPHOS[3] and PROPHOS[4], Kumada's BPPFA[5] and BPPFOH[6], Achiwa's BPPM[7], Phone Poulenc's CBD[8], and Giongo's PNNP[9] ligands (Figure 1-1).

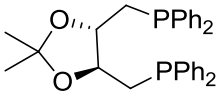
Figure 1-1 Chiral phosphorus ligands from 1970 to 1980.



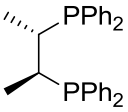
(*S*)-CAMP



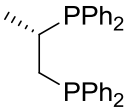
(S,S)-DIPAMP



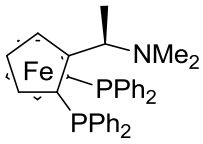
(*S,S*)-DIOP



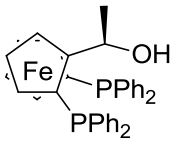
(*S,S*)-CHIRAPHOS



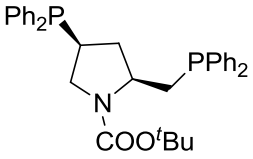
(*S*)-PROPHOS



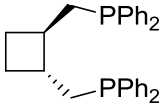
(*R,S*)-BPPFA



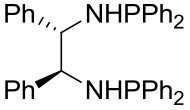
(*R,S*)-BPPOH



(*S,S*)-BPPM



(*R,R*)-CBD

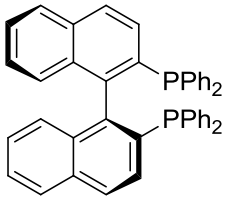


(*S,S*)-PNNP

Bidentate phosphorus ligands also inspired scientists in the ligand structure design. The reason why bidentate ligands have better performance than monodentate ligands is possibly due to the structure rigidity of the bidentate ligands. However, not all bidentate ligands have well-defined and rigid structures. The early development of bidentate phosphorus ligands often suffers problems from lack of rigidity. That's why ligands such as CAMP, DIPAMP, DIOP, and etc. only show poor to moderate results in asymmetric hydrogenation of alkenes. Compared with the above mentioned ligands, a new class of ligands, BINAP[11] and its analogues achieve excellent results, because of the ligands' rigid backbone structures. The discovery of BINAP (Figure 1-2) was reported by Noyori and coworkers in 1980. BINAP's backbone structure is composed by two linked binaphthyl rings. This special type of rigid backbone provides good enantioselectivities in the Rh-catalyzed hydrogenation of olefins. However, people hadn't discovered the power of BINAP until the Ru-BINAP dicarboxylate complex was discovered[12]. The asymmetric hydrogenation of ketones is considered to be more challenging than the asymmetric hydrogenation of alkenes. Noyori and coworkers are pioneers in the research of asymmetric hydrogenation of ketones. The Ru-BINAP complexes are proven to be very efficient for a range of functionalized ketones[13]. And the Ru-BINAP/diamine complexes made significant progresses in conquering the asymmetric hydrogenation of some unfunctionalized ketones[14]. The efficiency of Ru-BINAP catalytic systems in hydrogenation of ketones is excellent. As a matter of fact, Ru-BINAP catalytic system is able to target specifically on the ketone group instead of carbon-carbon double bonds[15]. This special chemoselectivity made the application of asymmetric hydrogenation more broad and flexible. BINAP could be viewed as the first generation of ligands designed

specifically for the Ru catalytic system. With the development of BIPAMP, DIOP, and BINAP, both Rh- and Ru- phosphorus ligand catalytic systems made significant progresses. The second generation of ligands was developed soon after.

Figure 1-2 Structure of BINAP.

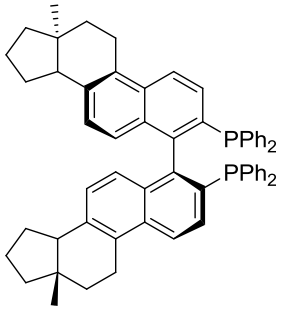


1.1.2 Second generation of phosphorus-containing ligands.

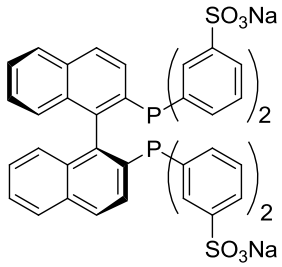
Inspired by Noyori's work on the discovery of BINAP, many scientists have attempted to develop new ligands with better activities and selectivities using BINAP as the base structure. Some of the BINAP derivatives achieve significantly improved results (Figure 1-3). Scientists found out that ligands' structure and electronic properties could have great impact on the catalytic process. Modifications at different positions on the naphthyl group of BINAP have been reported by several research groups. Ligand **1** was reported by Mohr in 1997[16]. However, although an additional chiral cyclic structure was added on the 4,4' and 5,5' positions of the binaphthyl backbone, no significant improvement was observed comparing with BINAP. Ligand **2**[17] and **3**[18] were reported by Lin in 2004 and 2005. Up to 99.6% ee was achieved in the hydrogenation of β-keto esters. A series of recyclable substituted BINAP ligands, such as (*S*)-4,4'diamBINAP, (*S*)-5,5'-diamBINAP, (*S*)-**4**, (*S*)-**5** were developed by Lemaire[19] in 2004. The water soluble Digm-BINAP and

PEG-BINAP were reported by Davis[20] in 1993. Another research direction related with BINAP is to study the polymer-supported BINAP ligands, because the asymmetric hydrogenation's catalysts are expensive, and the Rh or Ru could be harmful if the catalyst is not removed from the product, especially for the pharmaceutical applications. A highly effective polyester-supported BINAP ligand was developed by Chan[21]. The ligand achieves high enantioselectivity in the Ru-catalyzed asymmetric hydrogenation of 2-(6'-methoxy-2-naphthyl) acrylic acid. Another polymer-based chiral ligand BINOL-BINAP was developed by Pu[22], with high efficiency in the Ru-catalyzed hydrogenation of simple ketones.

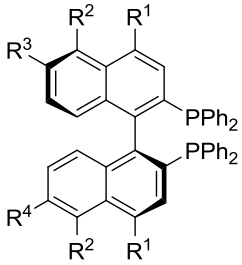
Figure 1-3 BINAP analogues.



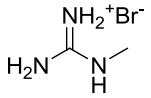
(*S*)-**1**



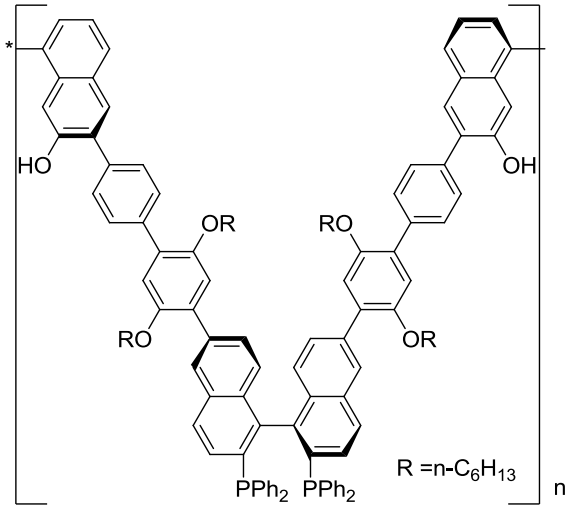
(*S*)-BINAP-4-SO_3Na



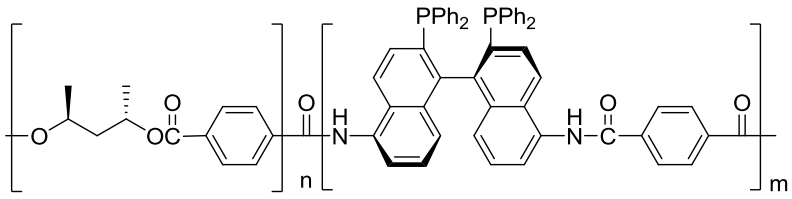
(*S*)-**2**: R^1 = TMS; R^2 = H; R^3=R^4=H
(*S*)-**3**: R^1 = P(O)(OH)2; R^2 = H;R^3=R^4=H
(*S*)-**4**,4'-diamBINAP: R^1= CH2NH2; R^2 = H; R^3=R^4=H
(*S*)-5,5'-diamBINAP: R^1 = H; R^2 = CH_2NH_2; R^3=R^4=H
(*S*)-**4**: R^1 = C_6F_{13}; R^2= H; R^3=R^4=H
(*S*)-**5**: R^1 = H; R^2= C_6F_{13}; R^3=R^4=H

Digm-BINAP: R^1=R^2=H; R^3=R^4= 

PEG-BINAP: R^3=MeO(CH_2CH_2O)N-CO(CH_2)$_3$CONH;
R^4=NH_2; R^1=R^2=H



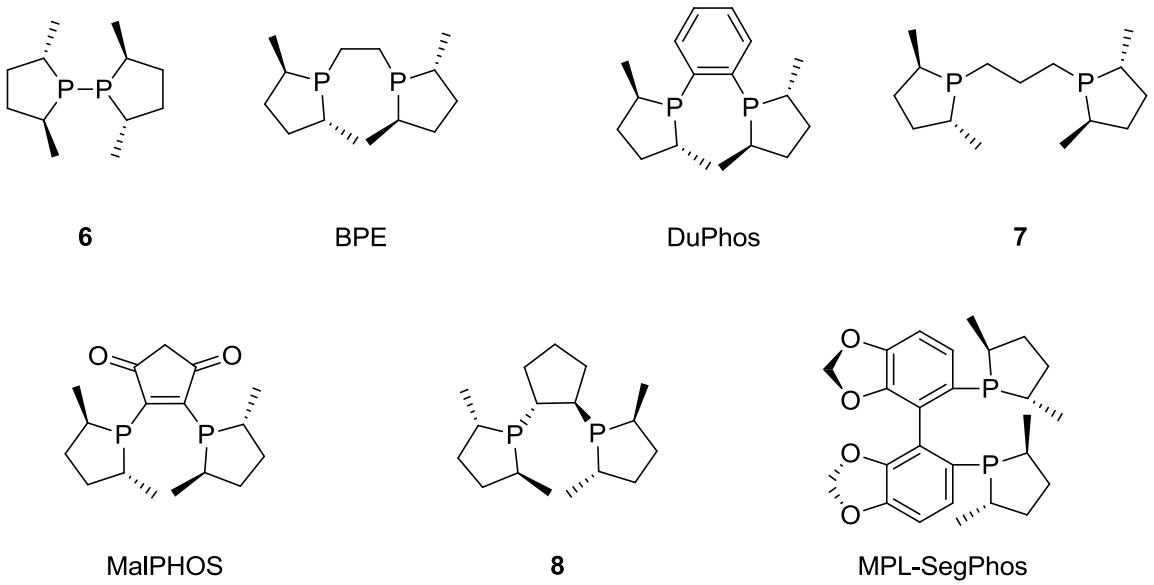
BINOL-BINAP



polyester-supported BINAP

While the Ru-BINAP catalytic systems were flourishing, the Rh-ligand catalytic systems also made significant progress. The development of second generation ligands for Rh catalytic systems started with the discovery of BPE[23] and DuPhos[24] (Figure 1-4) by Burk in the early 1990's. BPE is a 2, 5-dialkyl substituted phospholane ligand reported by Burk and coworkers. DuPhos applied the 1, 2-phenyl linker to the BPE backbone.

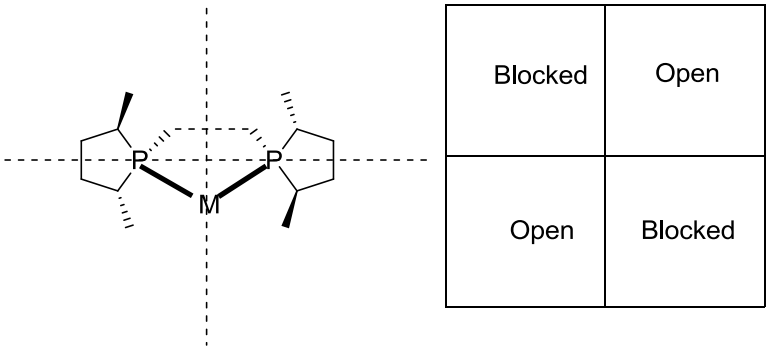
Figure 1-4 BPE, DuPhos, and their analogues.



Compared with BINAP, the BPE and DuPhos ligands are more electron rich. The electronic properties are critical for the high catalytic activities of transition metal catalytic systems. In particular, the Rh catalytic systems need electron rich ligands to achieve high activities. BPE and DuPhos show strong evidence to support the study on the catalytic mechanism. The alkyl substituted BPE and DuPhos achieve very high turnover numbers (high turnover means that the catalyst to substrate ratio is low) in

several asymmetric hydrogenation reactions. The BPE and DuPhos ligands also achieve high enantioselectivities. This can be explained by a quadrant diagram (Figure 1-5). The quadrant diagram divides the substrate binding space into four quadrants, and the center of the diagram is the transition metal. A favorable ligand structure should block the diagonal two quadrants, while leaving the rest two quadrants open. By blocking the particular quadrants, the metal-ligand complex creates a chiral site to bind with substrates, so high enantioselectivities could be achieved. As shown in Figure 1-5, the substitutes on the 2, 5 positions of the ring containing phospholane successfully block two of the four quadrants in the Rh-Ligand complex. Because of their excellent electronic and structural properties, BPE and DuPhos have been applied to catalyze a wide range of substrates, such as dehydroamino acid derivatives[24a, 25], enol acetates[26], enamides[28], β-keto ester derivates[31], itaconic acids[30], N-acylhydrazones[27], etc. For most of the above substrates, both high enantioselectivities and turnover numbers have been achieved. As a matter of fact, BPE and DuPhos are still widely used in both academic and industrial fields nowadays.

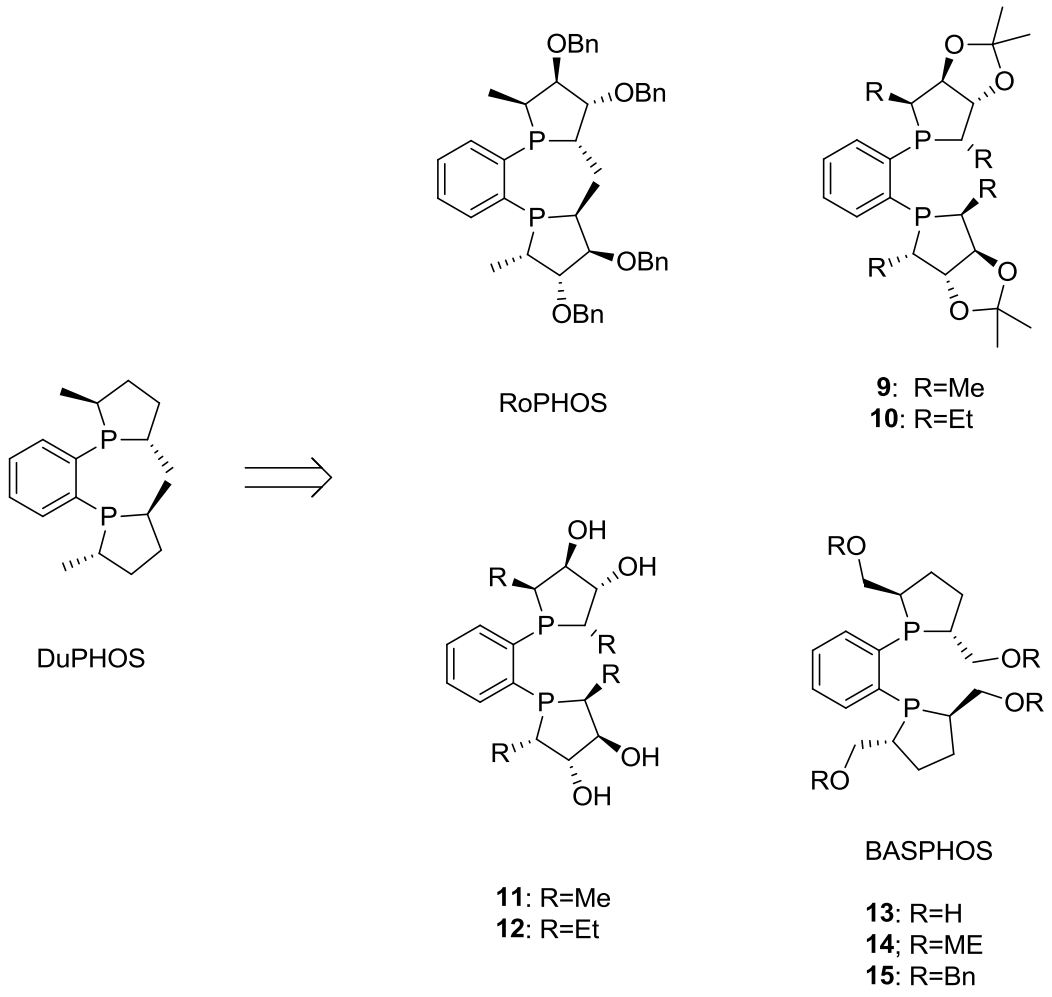
Figure 1-5 Configuration of BPE and the quadrant diagram.



As shown in Figure 1-4, the two 2, 5-substituted phospholane rings are the most critical components of BPE and DuPhos. By changing the linkers between the two phospholane rings, Buck and other scientists designed several new ligands (Figure 1-4). MalPHOS[32] is reported by Holz and Börner, using a maleic anhydride linker. The MalPHOS ligand achieves high enantioselectivities in hydrogenation of (β-acylamino) acrylates. Ligand **8** is reported by Pringle to study the matching/mismatching effect of the chiral linkers[33]. As the BINAP backbone provided excellent resulting in Ru catalytic systems, the combination of BINAP analogue as a linker and phospholane ring components produces a new ligand, SegPhos.

Another direction to modify the BPE and DuPhos structures is to directly change the substitutes on the two 2, 5-substituted phospholane rings. Following this direction, several new ligands were developed (Figure 1-6, Figure 1-7). Starting from the easily available D-mannitol, several DuPhos analogues such as RoPHOS, **9**, **10**, **11**, and **12** were synthesized by Börner[35], Zhang[36], and RajanBadu[37]. The above mentioned ligands use ether, ketal, and hydroxyl groups to modify the 3, 4 positions on the phospholane rings. Compared with DuPhos, the above mentioned ligands are easier to prepare, and show comparable asymmetric hydrogenation results. Holz and Börner also developed water soluble ligands BASPHOS **13**, **14** based on the BPE and DuPhos structures. Using water as solvent for organic reactions is an important research topic, because water is the most environment safe, cheap, and abundant solvent. BASPHOS achieved high efficiency in asymmetric hydrogenation using water as solvent.

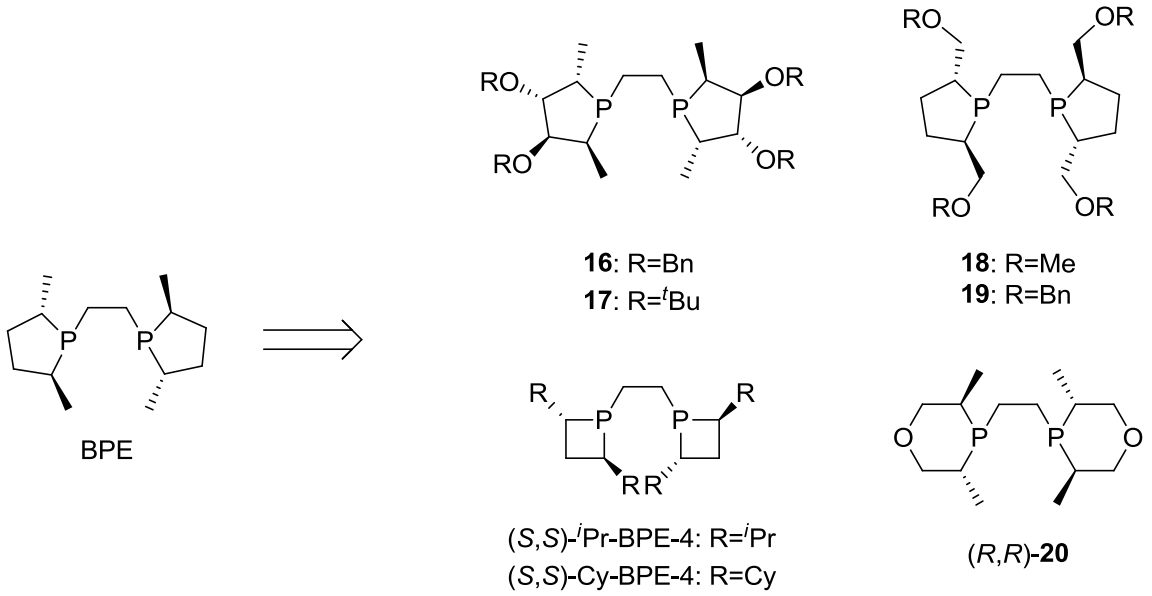
Figure 1-6 Ligand modification based on DuPhos structure.



Modifications on the BPE structure also achieved good results. Ligands **16**, **17** were prepared from easily available D-mannitol[35, 36]; and Ligand **18** is a water soluble ligand developed by Holz and Börner[37]. Marinetti[38] and coworkers changed the five-member ring of the BPE into a four-membered ring, and develop the BPE-**4** ligand. Interestingly, BPE-**4** showed similar properties comparing with BINAP: BPE-**4** achieved high enantioselectivities in Ru-catalyzed asymmetric hydrogenation, while having moderate results in Rh-catalyzed asymmetric hydrogenation. The bisoxaphosphinane ligand (*R*, *R*)-

20 was developed by Helmchen[39], and showed high efficiency in the asymmetric hydrogenation of dehydroamino acids derivatives and itaconic acid derivatives.

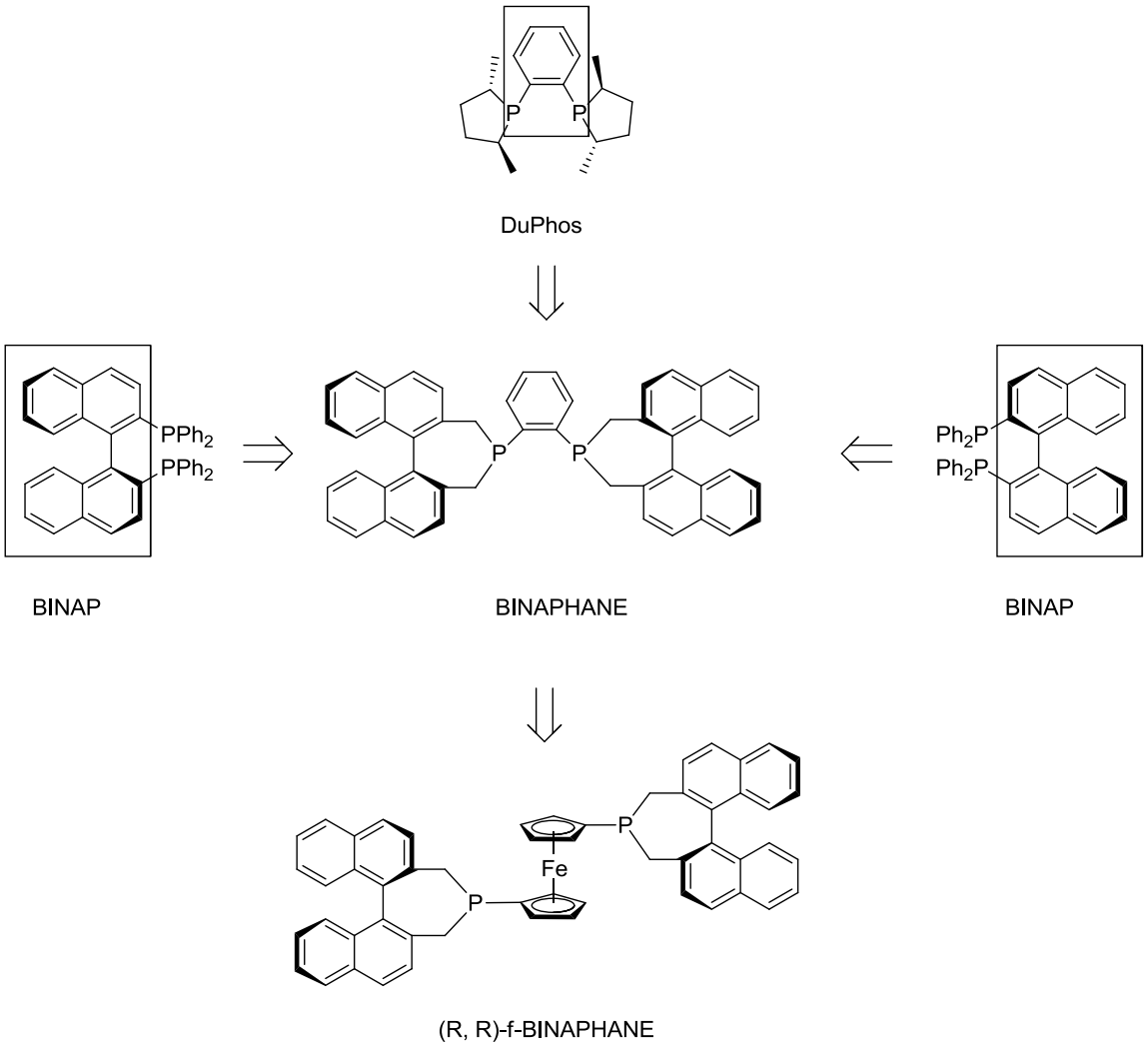
Figure 1-7 Ligand modification based on BPE structure.



Inspired by DuPhos and BINAP, Zhang developed the BINAPHANE ligand[41]. BINAPHANE changes the 5-membered phospholane ring of DuPhos with a BINAP backbone structure (Figure 1-8). BINAPHANE has been proven to be very effective in hydrogenation of E/Z isomers of β-substituted arylenamides. Zhang also developed f-BINAPHANE[41], a C_2-symmetric bisphosphane ligand, with high enantioselectivity in the Ir-catalyzed asymmetric hydrogenation of acyclic arylimines. Compared with the first generation of ligands, the second generation is more versatile, effective, and practical. Asymmetric hydrogenation has drawn increasing attention because of its wide choices of ligands, broad substrate scopes, high yields, and excellent enantioselectivities. However,

there are many problems waiting to be solved, and researchers continue to search for new concepts to design superior phosphorus ligands.

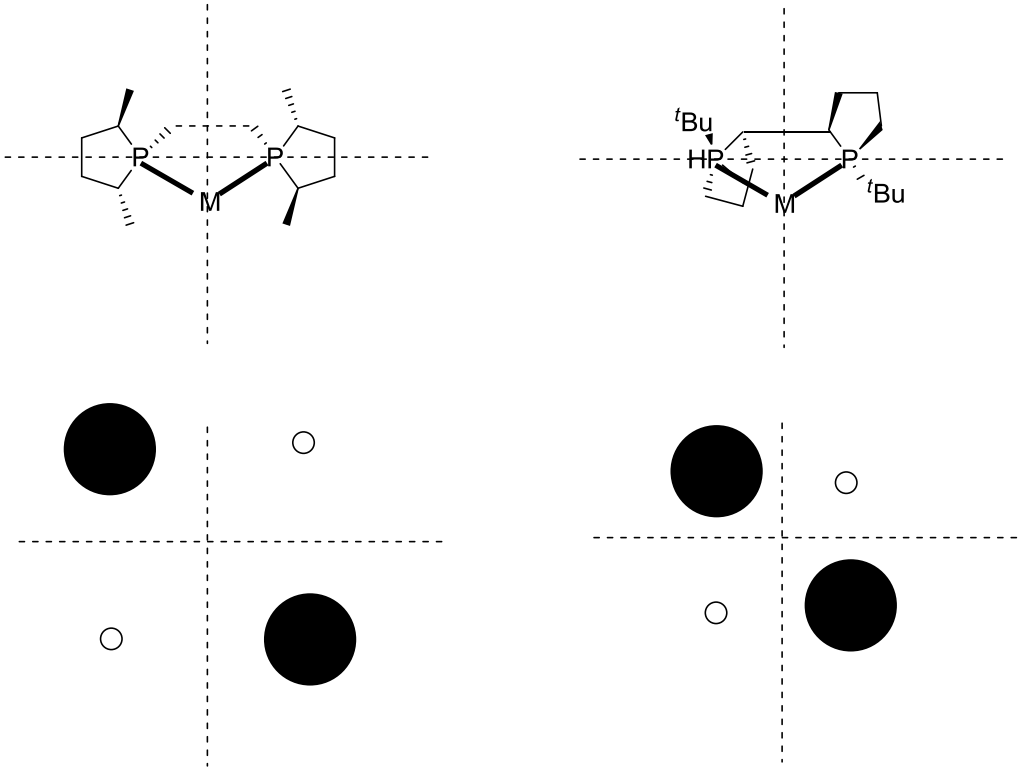
Figure 1-8 The design of BINAPHANE and f-BINAPHANE.



1.1.3 Third generation of phosphorus ligands: the new development of P-chiral bisphosphane ligands.

Successes of the first generation of ligands provide scientists with some hints about ligand design. The bidentate DIPAMP ligand's superior performance indicates that the bidentate ligands could have better chelating effect than monodentate ligands. Following this hint, the majority of second generation ligands are bidentate. In order to improve the ligand design, many scientists have focused on the development of more defined and rigid backbone structures, such as BINAP and DuPhos. However, another character of the DIPAMP structure is not fully appreciated. That is, DIPAMP is a “P-chiral” ligand. The chiral center of P-chiral ligands is located on the phosphorus atom, while the chiral center of the C_2-symmetric ligands is located on the backbone. Theoretically, when the phosphorus atom chelates to the transition metal, the closer the chiral components are to the metal center, the better the enantioselectivity (Figure 1-9). This explains why DIPAMP exhibits excellent enantioselectivities even with a flexible and undefined backbone structure.

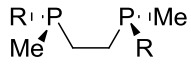
Figure 1-9 The quadrant diagram of P-chiral ligands and C_2-symmetric ligands.



The further exploration of P-chiral bisphosphane ligands has been overlooked until Imamoto discovered the BisP*[42] and MiniPhos[43] ligands (Figure 1-10). Zhang and coworkers report a series of P-chiral phospholane ligands, such as TangPhos[44], DuanPhos[45], and BINAPINE[46]. TangPhos has been found to be very effective in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acids, β-(acylamino) acrylates, itaconic acids, enol acetates, enamides, and imine derivatives[47]. DuanPhos has shown comparable results for the above mentioned substrates. DuanPhos is also proven to be more synthetic straightforward and effective for the asymmetric hydrogenation of α- and β-amino ketones[48]. Following the successes of TangPhos and DuanPhos, a more rigid and

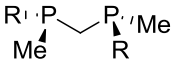
electro donating ligand, ZhangPhos, is developed by Zhang. ZhangPhos exhibits better or comparable efficiency than TangPhos and DuanPhos[49]. ^{i}Pr-BeePhos[50] is reported by Saito, and has been proven to be effective in the asymmetric hydrogenation of enamides. BIPNOR[51] was discovered by Mathey, and showed excellent results in the asymmetric hydrogenation of α-(acetomido)-cinnamic acids and itaconic acids.

Figure 1-10 P-chiral phosphorus ligands.



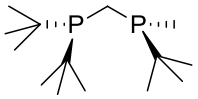
(*S*,*S*)-BisP*

(*S*,*S*)-^{t}Bu-BisP*: R=^{t}Bu
(*S*,*S*)-Ad-BisP*: R=1-adamantyl
(*S*,*S*)-Cy-BisP*: R=Cy

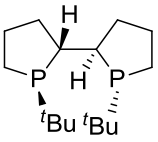


(*S*,*S*)-MiniPhos

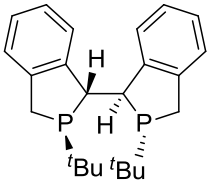
(*S*,*S*)-^{t}Bu-MiniPhos: R=^{t}Bu
(*S*,*S*)-Cy-MiniPhos: R=Cy
(*S*,*S*)-^{i}Pr-MiniPhos: R=^{i}Pr



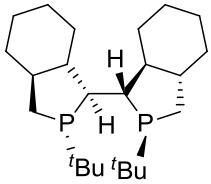
Trichikenfootphos



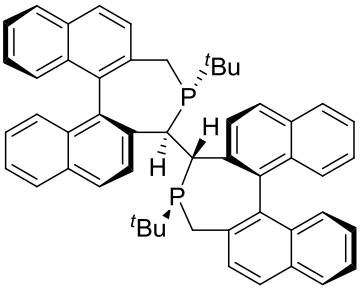
(S,S,R,R)-TangPhos



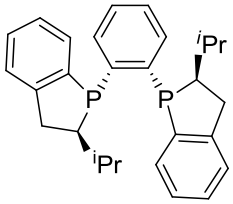
(S,S,R,R)-DuanPhos



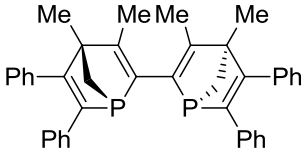
ZhangPhos



BINAPINE



^{i}Pr-BeePhos



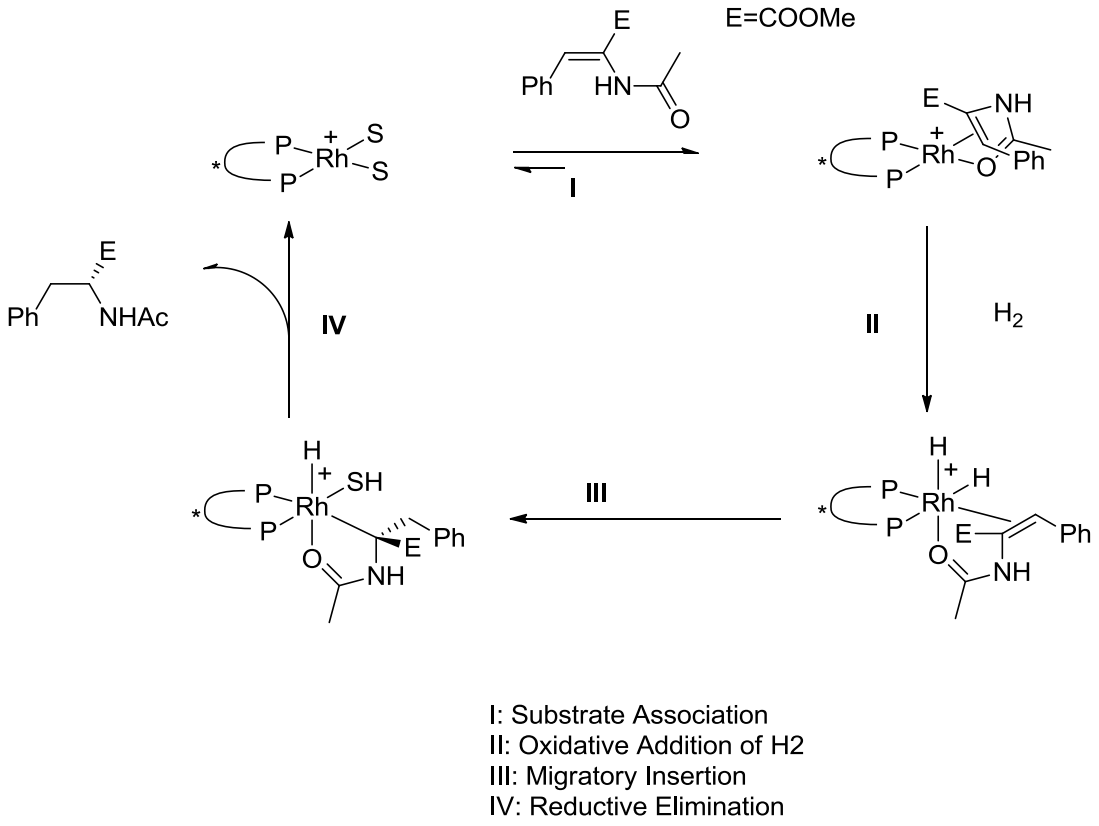
(S,S)-BIPNOR

1.2 Mechanisms for Rhodium-catalyzed asymmetric hydrogenation

Two mechanisms have been reported for the Rhodium-catalyzed asymmetric hydrogenation. In early 1970's, Halpern[52] developed the so-called "unsaturated" mechanism. The "unsaturated" mechanism includes four steps: substrate association,

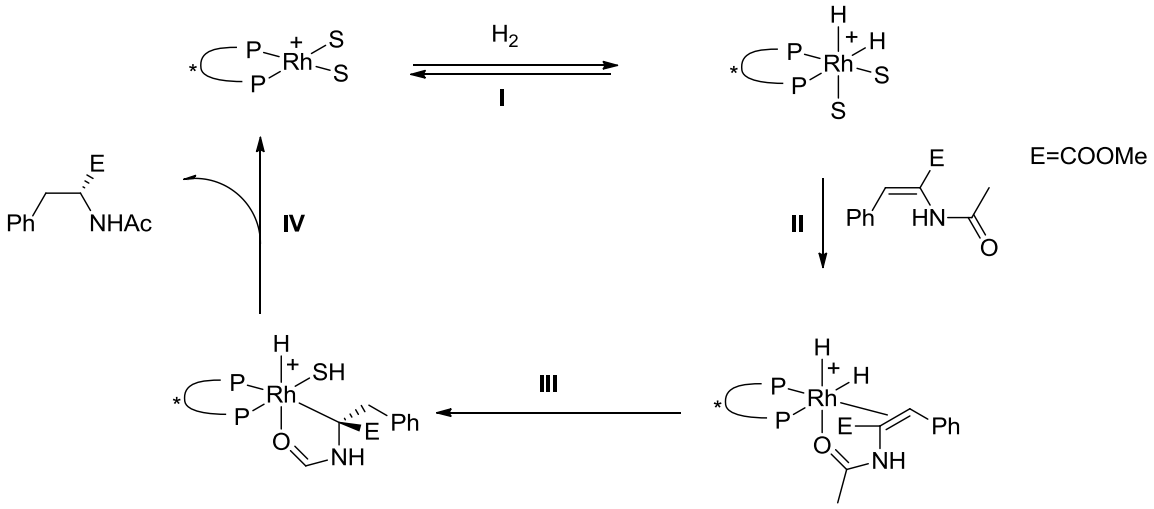
oxidative addition of H_2， migratory insertion, and reductive elimination. In the substrate association step, the substrate coordinates with the square planar Rh (I, d^8)-ligand catalyst. The two solvent molecules on the Rh metal complex are replaced by the substrate's double bond and secondary coordinating group. In the oxidative addition step, hydrogen is split into two hydrides and added to the square planar metal-ligand-substrate complex, resulting in a new octahedral Rh (III, d^6) complex. In the migratory insertion step, the hydride migrates to the double bond. This is the rate determining step in the catalytic circle. In the reductive elimination step, the hydrogenation product disassociates from the Rh metal center. The octahedral Rh (III, d^6)-ligand complex changes back to the square planar Rh(I, d^8)-ligand complex.

Figure 1-11 "Unsaturated" mechanism for asymmetric hydrogenation.



However, the "unsaturated" mechanism could not explain why the electron-rich phosphine ligands, like DuPhos, TangPhos, and DuanPhos are effective in the Rh-catalyzed asymmetric hydrogenation. Imamoto[53] investigated the mechanism for the electron-rich phosphine ligands, and proposed the so-called "dihydride" mechanism. The "dihydride" mechanism includes oxidative addition, substrate association, migratory insertion, and reductive elimination. Unlike the "saturated" mechanism, the oxidative addition happens before the substrate association. For electron-rich ligands, the dihydride complex Rh (III, d^6) is more stable, so the Rhodium-catalyzed asymmetric hydrogenation is more likely to undergo the "dihydride" mechanism.

Figure 1-12 "Dihydride" mechanism for Rhodium-catalyzed asymmetric hydrogenation.



I: Oxidative Addition of H_2
II:Substrate Association
III: Migratory Insertion
IV: Reductive Elimination

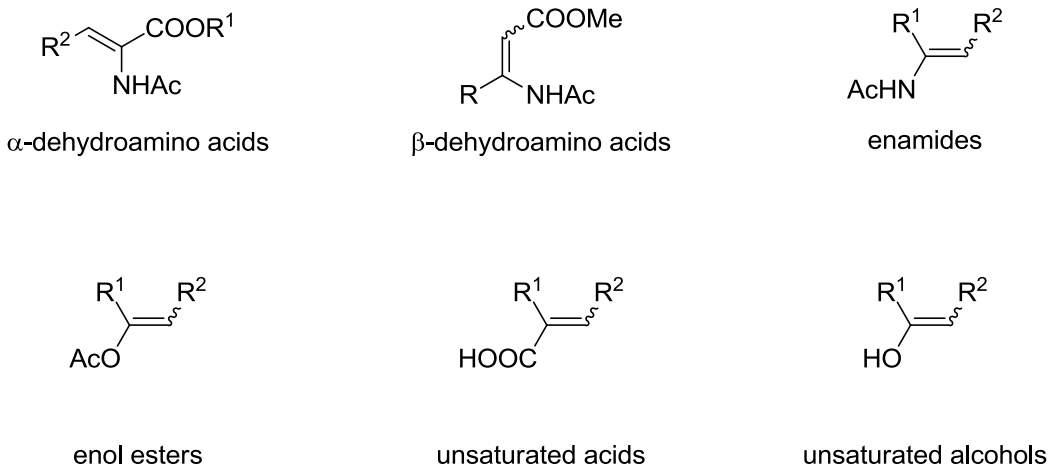
1.3 Substrate design for Rhodium-catalyzed asymmetric hydrogenation.

As mentioned before, hydrogenation uses hydrogen to reduce unsaturated chemical bonds. In most of the cases, the unsaturated chemical bonds are double bonds, such as C=C, C=O, and C=N double bonds. Therefore, there are three categories of substrates for asymmetric hydrogenation: olefins, ketones, and imines. The development of substrate design and synthesis in asymmetric hydrogenation has direct impact on industrial and pharmaceutical applications. Many scientists have developed new concepts and routes for new substrates design, so that the asymmetric hydrogenation methodology could be developed into a useful tool for total synthesis and complicated organic synthesis.

1.3.1 Asymmetric hydrogenation of olefins

Olefins are the most widely studied substrates in asymmetric hydrogenation for decades. Excellent enantioselectivities and reactivities have been achieved using a number of chiral ligands. In the following sections, asymmetric hydrogenation of dehydroamino acids, enamides, enol esters, and other types of substrates will be discussed (Figure 1-13).

Figure 1-13 Olefins substrates for asymmetric hydrogenation.



1.3.1.1 Asymmetric hydrogenation of α-dehydroamino acid derivatives.

The successful application of asymmetric hydrogenation to the synthesis of L-DOPA by Knowles[1] triggers the studies of asymmetric hydrogenation of α-dehydroamino acids. These types of compounds have been the standard substrates to test the performance of new chiral phosphorus ligands. From the first generation ligands to the third generation ligands, such as DIPAMP[2], PYRPHOS[54], Et-DuPhos[24b], TangPhos[44], DuanPhos[45], ZhangPhos[49] etc., high enantioselectivities and high turnover numbers have been achieved.

1.3.1.2 Asymmetric hydrogenation of β-dehydroamino acid derivatives.

Similar to the α-amino acid derivatives, the β-amino acid derivatives are also important pharmaceutical building blocks. Several ligands have been reported to be effective for the asymmetric hydrogenation of β-dehydroamino acid derivatives[55]. The β-dehydroamino acid derivatives often have E/Z isomers, and different enantioselectivities could be achieved by using different E and Z isomeric substrates. TangPhos has been reported to obtain up to 99.5% ee in the hydrogenation of a mixture of E/Z isomers of methyl 3-acetamido-2-butenoate[44].

1.3.1.3 Asymmetric hydrogenation of enamides.

The α-aryl enamide is also a standard substrate to test the performance of new chiral phosphorus ligands. Several ligands, such as Me-BPE[28], BINAPINE[40], UCAP[56], BisP*[42], BDPAB[57], TangPhos[44], SIPHOS[58], etc. have achieved very high enantioselectivities and turnover numbers. The alkyl enamides can also be used as asymmetric hydrogenation substrates. The ^{t}Bu-BisP[42] and Me-DuPhos[28] ligands are reported to achieve up to 99% ee in the asymmetric hydrogenation of tert-butylenamide and 1-admantylenamide.

1.3.1.4 Asymmetric hydrogenation of enol esters.

Enol esters are considered as challenging substrates, and only a few ligands have been reported to be successful in the asymmetric hydrogenation of these substrates. For the asymmetric hydrogenation of α-(acyloxy) acrylates, several ligands such as DIPAMP,

DuPhos, FERRIPHOS[59], and TaniaPhos[60] are effective in terms of high enantioselectivities. The β-substituted enol esters have E/Z isomers, and Et-DuPhos ligands can achieve high enantioselectivity using the E/Z isomer mixtures.

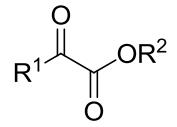
1.3.1.5 Asymmetric hydrogenation of unsaturated acids, alcohols, esters, and unfunctionalized olefins.

The Ru-BINAP catalyst and its analogues achieve high enantioselectivities in asymmetric hydrogenation of α, β-unsaturated acids and unsaturated alcohols[12,61]. However, Rh-catalyzed hydrogenation has fewer successful examples in these fields. Ito[62] reported an (aminoalkyl) ferrocenylphosphine ligand with high enantioselectivities in the asymmetric hydrogenation of tri-substituted acrylic acids. Among all the olefin substrates, the unfunctionalized olefins are the most challenging substrates in asymmetric hydrogenation. The complex Me-DuPhos-Ru with *t*BuOK achieves up to 89% ee for asymmetric hydrogenation of 3-phenylbutenes[63].

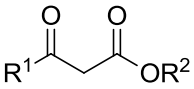
1.3.2 Asymmetric hydrogenation of ketones.

Chiral alcohols are important pharmaceutical compounds, and the asymmetric hydrogenation of ketones is a straightforward route to obtain chiral alcohols[61]. Many studies have been done in the hydrogenation of functionalized and unfunctionalized ketones. Different ketone substrates have been developed and tested (Figure 1-14).

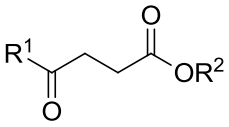
Figure 1-14 Ketone substrates for asymmetric hydrogenation.



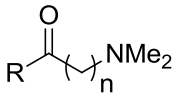
α-keto esters



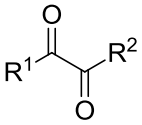
β-keto esters



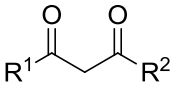
γ-keto esters



amino ketones



α-diketones



β-diketones

1.3.2.1 Asymmetric Hydrogenation of Keto Esters

Asymmetric hydrogenation of α-, β-, γ- keto Esters has been studied by several research groups. Both Rh- and Ru- catalytic systems show excellent results in asymmetric hydrogenation of α-keto esters[61b,64]. A cyclic α-keto ester, dihydro-4,4-dimethyl-2,3-furandion has also been studied and high enantioselectivities and high turnover numbers have been achieved[64]. The β-keto esters have been well studied, and many successes have been achieved by BINAP and other C_2 symmetric ligands[65]. A few γ-keto esters have been investigated as well using Ru catalytic systems such as BINAP and SEGPHOS[66].

1.3.2.2 Asymmetric hydrogenation of amino ketones and diketones

The chiral synthesis of amino alcohols has drawn much attention recently, because of its important application in pharmaceutics. For example, a chiral β-adrenergic blocking

agent, 1-amino-3-aryloxy-2-propanol, can be prepared directly from asymmetric hydrogenation of 3-aryloxy-2-oxo-1-propylamine using the MCCPM-Rh complex[67]. The amino ketone hydrochloride salts were well studied too, using both of the Rh-ligand and Ru-ligand complexes[6b, 64f, g, 68].

Asymmetric hydrogenation of diketones is an interesting topic, because two chiral centers are generated simultaneously after the reaction. Although high enantioselectivities have been achieved in both α- and β- diketones, the selectivity between meso and anti diols is moderate[13b, 69].

1.3.2.3 Asymmetric hydrogenation of simple ketones.

Simple ketones are challenging substrates for asymmetric hydrogenation. Two catalytic systems, the Ru-diphosphane-diamine catalyst and the Rh-PennPhos catalyst, achieve excellent results. Combined with additives 2, 6-lutidine and KBr, the asymmetric hydrogenation of both aromatic and aliphatic ketones using the Rh-PennPhos catalyst is very efficient. Inspired by the success of PennPhos, research on additives for asymmetric hydrogenation starts to draw more and more attentions.

1.3.3 Asymmetric hydrogenation of imines.

In contrast to many successful examples in asymmetric hydrogenation of olefins and ketones, the development of asymmetric hydrogenation of imines is still limited[70]. As pharmaceutical applications of chiral amines draw more and more attention recently, the reduction of imines or enamides has been studied by several scientists. Although both imines and enamides can be reduced to chiral amines, asymmetric hydrogenation of imines is more challenging for several reasons. First, some aliphatic imines are not air stable. Second, acyclic imines have inseparable E/Z isomers[71], and they sometimes have impact on the enantioselectivities. Third, the products are unprotected chiral amines. The unprotected amines tend to deactivate the catalyst by tightly coordinating to the metal center.

References

1. (a) Knowles, W. S.; Sabacky, M. J. *Chem. Commun*. **1968**, 1445. (b) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *Chem. Commun.***1972**, 10.
2. (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.
3. (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.
4. Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491.
5. Hayashi, T.; Mise, T.; Mitachi, S.; Yamamoto, K.; Kumada, M. *Tetrahedron Lett.* **1976**, 1133. (b) Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138. (c) Hayashi, T.; Kumada, M. *Acc. Chem. Res.* **1982**, *15*, 395.
6. Hayashi, T.; Mise, T.; Kumada, M. *Teterahedron Lett.* **1976**, 4351. (b) Hayashi, T.; Katsumura, A.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1979**, 425.
7. Achima, K. *J. Am. Chem. Soc.* **1976**, *98*, 8265.
8. Rhone Poulenc, S. A. Fr. Patent 2,230,654, 1974. (b) Glaser, R.; Geresh, S.; Twaik, M. *Isr. J. Chem*. **1980**, *20*, 102.
9. Fiorini, M.; Giongo, G. M. *J. Mol. Catal.* **1979**, *5*, 303.
10. (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.
11. Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K. Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.
12. (a) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am.Chem. Soc.* **1986**, *108*, 7117. (b) Hitamura, M.; Hsiao, Y.; Noyori, R.; Takaya, H. *Tetrahedron Lett.* **1987**, *28*, 4829. (c) Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.-I.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596. (d) Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3174.
13. (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856. (b) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629. (c) Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.* **1988**, *53*, 708. (d) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134.
14. Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.***1995**, *117*, 2675.
15. Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc*. **1995**, *117*, 10417.
16. Enev, V.; Ewers, Ch. L. J.; Harre, M.; Nickisch, K.; Mohr, J. T. *J. Org. Chem.* **1997**, *62*, 7092.
17. Hu, A.; Ngo, H. L.; Lin, W. *Angew Chem. Int. Ed.* **2004**, *43*, 2501.
18. Hu, A. Lin, W. *Org. Lett*. **2005**, *7*, 455.

19. (a) Berthod, M.; Saluzzo, C.; Mignani, G.; Lemaire, M. *Tetrahedron: Asymmetry* **2004**, *15*, 639. (b) Berthod, M.; Mignani, G.; Lemaire, M. *Tetrahedron: Asymmetry* **2004**, *15*, 1121.
20. (a) Wan, K. T.; Davis, M. E. *J. Chem. Soc., Chem. Commun.* **1993**, 1262; (b) Wan.K. T.; Davis, M. E. *Tetrahedron: Asymmetry* **1993**, *4*, 2461. (c) Wan. K. T.; Davis, M. E. *J. Catal*. **1994**, *148*, 1.
21. (a) Fan, Q.-H.; Deng, G.-J.; Lin, C.-C.; Chan, A. S. C. *J. Am. Chem. Soc.* **1999**, *121*, 7407. (b) Fan, Q.-H.; Ren, C.-Y.; Yeung, C.-H.; Hu, W.-H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1241.
22. (a) Yu, H.-B.; Hu, Q.-S.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 1681. (b) Yu, H.-B.; Hu, Q.-S.; Pu, L. *J. Am. Chem. Soc.* **2000**, *122*, 6500.
23. (a) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics*, **1990**, *9*, 2653. (b) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Tetrahedron: Asymmetry* **1991**, *2*, 569.
24. (a) Burk, M. J. *J. Am. Chem. Soc*, **1991**, *113*, 8518. (b) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc*., **1993**, *115*, 10125.
25. (a) Burk, M. J. (E. I. du Pont de Nemours and Company), US 5008457, 1991. (b)Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc*., **1995**, *117*, 9375.
26. Burk, M. J.; Allen, J. G.; Kiesman, W. F. *J. Am. Chem. Soc*., **1998**, *120*, 657.
27. Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc*., **1992**, *114*, 6266.
28. Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc*., **1996**, *118*, 5142.
29. Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc*., **1998**, *120*, 4345.
30. Burk, M. J.; Bienewald, F.; Harris, M.; Zanotti-Gerosa, A. *Angew. Chem. Int. Ed*. **1998**, *37*, 1931.
31. Burk, M. J.; Harper, T. G. P.; Kalberg, C. S. *J. Am. Chem. Soc*., **1995**, *117*, 4423.
32. Holz, J.; Monsees, A.; Jiao, H.; You, J.; Komarov, I. V.; Fischer, C.; Drauz, K.; Bo¨rner, A. *J. Org. Chem.* **2003**, *68*, 1701.
33. Fernandez, E.; Gillon, A.; Heslop, K.; Horwood, E.; Hyett, D. J.; Orpen, A. G.; Pringle, P. G.; *Chem. Commun*. **2000**, 1663.
34. Shimizu, H.; Ishizaki, T.; Fujiwara, T.; Saito, T. *Tetrahedron: Asymmetry*, **2004**, *15*, 2169.
35. (a) Holz, J.; Quirmbach, M.; Schmidt, U.; Heller, D.; Stürmer, R.; Börner, A. *J. Org. Chem.* **1998**, *63*, 8031. (b) Holz, J.; Stürmer, R.; Schmidt, U.; Drexler, H.-J.; Heller, D.; Krimmer, H.-P.; Börner, A. *Eur. J. Org. Chem.* **2000**, 4615.
36. (a) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *Tetrahedron Lett.* **1999**, *40*, 6701. (b) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 3489.
37. (a) Yan, Y.-Y.; RajanBabu, T. V. *J. Org. Chem.* **2000**, *65*, 900. (b) Yan, Y.-Y.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 199. (c) RajanBabu, T. V.; Yan, Y.-Y.; Shin, S. *J. Am. Chem. Soc*. **2001**, *123*, 10207.
38. (a) Marinetti, A.; Kruger, V.; Buzin, F.-X. *Tetrahedron Lett.* **1997**,*38*, 2947. (b) Marinetti, A.; Labrue, F.; Genêt, J.-P. *Synlett* **1999**, 1975. (c) Marinetti, A.; Jus, S.; Genêt, J.-P. *Tetrahedron Lett.* **1999**, *40*, 8365. (d) Marinetti, A.; Genêt, J.-P.; Jus, S.; Blanc, D.; Ratovelomanana Vidal, V. *Chem. Euro. J.* **1999**, *5*, 1160. (e) Marinetti, A.; Jus, S.; Genêt, J.-P.; Ricard, L. *Tetrahedron* **2000**, *56*, 95. (f) Marinnetti, A.; Jus, S.; Genêt, J.-P.; Ricard, L. *J. Organomet. Chem.* **2001**, *624*, 162.

39. Ostermeier, M.; Priess, J.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 612.
40. (a) Xiao, D.; Zhang, Z.; Zhang, X. *Org. Lett.* **1999**, *1*, 1679. (b) Chi, Y.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 4849.
41. Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 3425.
42. (a) Gridnev, I. D.; Yasutake, M.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2001**, *123*, 5268. (b) Yasutake, M.; Gridnev, I. D.; Higashi, N.; Imamoto, T. *Org. Lett.* **2001**, *3*, 1701. (c) Gridnev, I. D.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2001**, *123*, 4631. (d) Gridnev, I. D.; Higashi, N.; Asakura, K.; Imamoto, T. *J. Am. Chem. Soc.* **2000**, *122*, 7183. (e) Gridnev, I. D.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2000**, *122*, 10486. (f) Gridnev, I. D.; Imamoto, T. *Organometallics* **2001**, *20*, 545.
43. Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988.
44. Tang, W.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1612.
45. (a) Liu, D.; Zhang, X. *Eur. J. Org. Chem*. **2005**, 646; (b) Zhang, X.; Tang, W. (The Penn State Research Foundation) US 2004/0229846 A1, 2004.
46. Tang, W.; Wang, W.; Chi, Y.; Zhang, X. *Angew. Chem. Int. Ed*. **2003**, *42*, 3509.
47. (a) Tang, W. and Zhang, X. *Angew. Chem. Int. Ed.* **2002**, *41*, 1612; (b) Tang, W. and Zhang, X. *Org. Lett.* **2002**, *4*, 4159; (c) Tang, W., Liu, D. and Zhang, X. *Org. Lett.* **2003**, *5*, 205; (d) Yang, Q.; Shang, G.; Gao, W.; Deng, J.; Zhang, X. *Angew. Chem. Int. Ed.* **2006**, *45*, 3832; (e) Shang, G.; Yang, Q.; Zhang, X. *Angew. Chem. Int. Ed.* **2006**, *45*, 6360.
48. (a) Liu, D.; Gao, W.; Wang, C.; Zhang, X. *Angew. Chem. Int. Ed*. **2005**, *44*, 1687. (b) Shang, G.; Liu, D.; Allen, S. E.; Yang, Q.; Zhang, X. *Chem. Eur. J.* **2007**, *13*, 7780.
49. (a) Zhang, X.; Huang, K.; Hou, G.; Cao, B.; Zhang, X. *Angew. Chem. Int. Ed*. **2010**, *49*, 6421. (b) Huang, K.; Zhang, X.; Geng, H.; Li, S.; Zhang, X. *ACS Catalysis*, **2012**, *2*, 1343.
50. Shimizu, H.; Saito, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2003**, *345*, 185.
51. (a) Robin, F.; Mercier, F.; Ricard, L.; Mathey, F.; Spagnol, M.*Chem. Eur. J.* **1997**, *3*, 1365. (b) Mathey, F.; Mercier, F.; Robin, F.; Ricard, L. *J. Organometallic Chem.* **1998**, *577*, 117
52. (a) Halpern, J.; Riley, D. P.; Chan, A. S. C.; Pluth, J. J. *J. Am. Chem. Soc*. **1977**, *99*, 8055. (b) Chan, A. S. C.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 838. (c) Chan, A. S. C.; Pluth, J. J.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 5952. (d) Halpern, J. *Science* **1982**, *217*, 401. (e) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746. (f) Landis, C. R.; Hilfenhaus, P.; Feldgus, S.; *J. Am. Chem. Soc.* **1999**, *121*, 8741. (g) Feldgus, S.; Landis, C. R. *J. Am. Chem. Soc.* **2000**, *122*, 12714.
53. (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.
54. Nagel, U.; Kinzel, E.; Andrade, J.; Prescher, G. *Chem. Ber.* **1986**, *119*, 3326.
55. (a) Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543. (b) Heller, D.; Holz, J.; Drexler, H.-J.; Lang, J.; Drauz, K.; Krimmer, H.-P.; Bo ̈rner, A. *J. Org. Chem.* **2001**, *66*, 6816. (c) Zhu, G.; Chen, Z.; Zhang, X. *J.*

Org. Chem. **1999**, *64*, 6907. (d) Lee, S.-g.; Zhang, Y. J. *Org. Lett.* **2002**, *4*, 2429. (e) Yasutake, M.; Gridnev, I. D.; Higashi, N.; Imamoto, T. *Org. Lett.* **2001**, *3*, 1701. (f) Pen˜a, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552. (g) You, J.; Drexler, H.-J.; Zhang, S.; Fischer, C.; Heller, D. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 913. (h) Zhou, Y.-G.; Tang, W.; Wang, W.-B.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952.

56. Matsumura, K.; Shimizu, H.; Saito, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2003**, *345*, 180.
57. (a) Zhang, F.-Y.; Pai, C.-C.; Chan, A. S. C. *J. Am. Chem. Soc.* **1998**, *120*, 5808. (b) Zhang, F.-Y.; Kwok, W. H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2337.
58. (a) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2348. (b) Fu, Y.; Xie, J.-H.; Hu, A.-G.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Chem. Commun.* **2002**, 480.
59. (a) Almena Perea, J. J.; Bo ̈rner, A.; Knochel, P. *Tetrahedron Lett.* **1998**, *39*, 8073. (b) Almena Perea, J. J.; Lotz, M.; Knochel, P. *Tetrahedron: Asymmetry* **1999**, *10*, 375. (c) Lotz, M.; Ireland, T.; Almena Perea J. J.; Knochel, P. *Tetrahedron: Asymmetry* **1999**, *10*, 1839.
60. Sturm, T.; Weissensteiner, W.; Spindler, F. *Adv. Synth. Catal.* **2003**, *345*, 160.
61. (a) Benincori, T.; Brenna, E.; Sannicolo`, F.; Trimarco, L.; Antognazza, P.; Cesarotti, E. *J. Chem. Soc., Chem. Commun.* **1995**, 685. (b) Benincori, T.; Brenna, E.; Sannicolo`, F.; Trimarco, L.; Antognazza, P.; Cesarotti, E. Demartin, F.; Pilati, T. *J. Org. Chem.* **1996**, *61*, 6244. (c) Benincori, T.; Cesarotti, E.; Piccolo, O.; Sannicolo`, F. *J. Org. Chem.* **2000**, *65*, 2043. (d) Pai C.-C.; Lin, C.-W.; Lin, C.-C.; Chen, C.-C.; Chan, A. S. C. *J. Am. Chem. Soc.* **2000**, *122*, 11513. (e) Wu, J.; Chen, H.; Kwok, W. H.; Lam, K. H.; Zhou, Z. Y.; Yeung, C. H.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 1539. (f) Wu, J.; Chen, X.; Guo, R.; Yeung, C.-h.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 2490. (g) Zhang, X.; Uemura, T.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Takaya, H. *Synlett* **1994**, 501. (h) Uemura, T.; Zhang, X.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Ohta, T.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1996**, *61*, 5510. (i) Geneˆt, J. P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Bischoff, L.; Cano De Andrade, M. C.; Darses, S.; Galopin, C.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 675. (j) Manimaran, T.; Wu, T.-C.; Klobucar, W. D.; Kolich, C. H.; Stahly, G. P. *Organometallics* **1993**, *12*, 1467.
62. Hayashi, T.; Kawamura, N.; Ito, Y. *J. Am. Chem. Soc.* **1987**, *109*, 7876.
63. Forman, G. S.; Ohkuma, T.; Hems, W. P.; Noyori, R. *Tetrahedron Lett.* **2000**, *41*, 9471.
64. (a) Takahashi, H.; Morimoto, T.; Achiwa, K. *Chem. Lett.* **1987**, 855. (b) Inoguchi, K.; Sakuraba, S.; Achiwa, K. *Synlett* **1992**, 169. (c) Roucoux, A.; Agbossou, F.; Mortreux, A.; Petit, F. *Tetrahedron: Asymmetry* **1993**, *4*, 2279. (b) Agbossou, F.; Carpentier, J.-F.; Hatat, C.; Kokel, N.; Mortreux, A. *Organometallics* **1995**, *14*, 2480. (d) Roucoux, A.; Devocelle, M.; Carpentier, J.-F.; Agbossou, F.; Mortreux, A. *Synlett.* **1995**, 358. (e) Roucoux, A.; Thieffry, L.; Carpentier, J.-F.; Devocelle, M.; Me ̈liet, C.; Agbossou, F.; Mortreux, A. *Organometallics* **1996**, *15*, 2440. (f) Devocelle, M.; Agbossou, F.; Mortreux, A. *Synlett* **1997**, 1306. (g) Carpentier, J.-

F.; Mortreux, A. *Tetrahedron Asymmetry* **1997**, *8*, 1083.(h) Pasquier, C.; Naili, S.; Pelinski, L.; Brocard, J.; Mortreux, A.; Agbossou, F. *Tetrahedron: Asymmetry* **1998**, *9*, 193. (i) Agbossou, F.; Carpentier, J.-F.; Hapiot, F.; Suisse, I.; Mortreux, A. *Coord. Chem. Rev.* **1998**, *178–180*, 1615. (j) Miyashita, A.; Karino, H.; Shimamura, J.; Chiba, T.; Nagano, K.; Nohira, H.; Takaya, H. *Chem. Lett.* **1989**, 1007. (k) Miyashita, A.; Karino, H.; Shimamura, J.; Chiba, T.; Nagano, K.; Nohira, H.; Takaya, H. *Chem. Lett.* **1989**, 1849. (l) Chiba, T.; Miyashita, A.; Nohira, H. *Tetrahedron Lett.* **1991**, *32*, 4745. (m) Chiba, T.; Miyashita, A.; Nohira, H.; Takaya H. *Tetrahedron Lett.* **1993**, *34*, 2351.

65. (a) Ager, D. J.; Laneman, S. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3327. (b) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, *Tetrahedron Lett.* **1991**, *32*, 4163. (c) Geneˆt, J. P.; Pinel, C.; Ratovelomanana- Vidal, V.; Mallart, S.; Pfister, X.; Bischoff, L.; Cano De Andrade, M. C.; Darses, S.; Galopin, C.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 675. (d) Geneˆt, J. P.; Ratovelomanana- Vidal, V.; Cano De Andrade, M. C.; Pfister, X.; Guerreiro, P.; Lenoir, J. Y. *Tetrahedron Lett.* **1995**, *36*, 4801. (e) Heiser, B.; Broger, E. A.; Crameri, Y. *Tetrahedron: Asymmetry* **1991**, *1*, 51. (f) Kawano, H.; Ikariya, T.; Ishii, Y.; Saburi, M.; Yoshikawa, S.; Uchida, Y.; Kumobayashi, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1571. (g) Ohta, T.; Tonomura, Y.; Nozaki, K.; Takaya, H.; Mashima, K. *Organometallics* **1996**, *15*, 1521. (h) Hoke, J. B.; Hollis, S.; Stern, E. W. *J. Organomet. Chem.* **1993**, *455*, 193. (i) Shao, L.; Takeuchi, K.; Ikemoto, M.; Kawai, T.; Ogasawara, M.; Takeuchi, H.; Kawano, H.; Saburi, M. *J. Organomet. Chem.* **1992**, *435*, 133. (j) Yamano, T.; Taya, N.; Kawada, M. Huang, T.; Imamoto. T. *Tetrahedron Lett.* **1999**, *40*, 2577.
66. Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.
67. Takeda, H.; Tachinami, T.; Aburatani, M.; Takahashi, H.; Morimoto, T.; Achiwa, K. *Tetrahedron Lett.* **1989**, *30*, 363.
68. (a) Mashima, K.; Kusano, K.; Sato, H.; Matsumura, Y.; Nazaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064. (b) Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 6510.
69. (a) Brunner, H.; Terfort, A. *Tetrahedron: Asymmetry* **1995**, *6*, 919. (b) Mezzetti, A.; Tschumper, A.; Consiglio, G. *J. Chem. Soc., Dalton Trans*. **1995**, 49. (c) Blandin, V.; Carpentier, J.-F.; Mortreux, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2765. (d) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3212. (e) Lotz, M.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4708. (f) Sturm, T.; Weissensteiner, W.; Spindler, F. *Adv. Synth. Catal.* **2003**, *345*, 160.
70. (a) Zhu, Q. C.; Hutchins, R. O. *Org. Prep. Proced. Int.* **1994**, *26*, 193; (b) Kobayashi, S.; Ishitani, H.; *Chem. Rev*. **1999**, *99*, 1069; (c) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045; (d) Blaser, H.-U.; Spindler, F. in *Comprehensive Asymmetric Catalysis,* Vol. 1 (Eds.: Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.), Springer, Berlin, 1999, pp. 247-265; (e) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal*. **2003**, *345*, 103;

(f) Spindler, F.; Blaser, H.-U. in *Transition Metals for Organic Synthesis, 2nd ed*., Vol. 2: Beller, M.; Bolm, C. Eds., Wiley-VCH, Weinheim, 2004, pp. 113-123.

71. (a) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562; (b) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1994**, *116*, 8952; (c) Verdaguer, X.; Lange, U. E. W.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **1998**, *37*, 1103; (d) Ringwald, M.; Stűrmer, R.; Brintzinger, H. H. *J. Am. Chem. Soc*. **1999**, *121*, 1524; (e) Hansen, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 713. 7 (f) Sablong, R.; Osborn, J. A. *Tetrahedron Lett*. **1996**, *37*, 4937 (g) Kainz, S.; Brinkmann, A.; Leitner, W.; Pfaltz, A. *J. Am. Chem. Soc*. **1999**, *121*, 6421 (c) Xiao, D.; Zhang, X. *Angew. Chem. Int. Ed*. **2001**, *40*, 3425 (h) Menges, F.; Pfaltz, A. *Adv. Synth. Catal*. **2002**, *344*, 40 (i) Jiang, X.-B.; Minnaard, A. J.; Hessen, B.; Feringa, B. L.; Duchateau, A. L. L.; Andrien, J. G. O.; Boogers, J. A. F.; de Vries, J. G. *Org. Lett*. **2003**, *5*, 1503 (f) Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett*. **2004**, *6*, 3825 (g) Moessner, C.; Bolm, C. *Angew. Chem. Int. Ed*. **2005**, *44*, 7564.

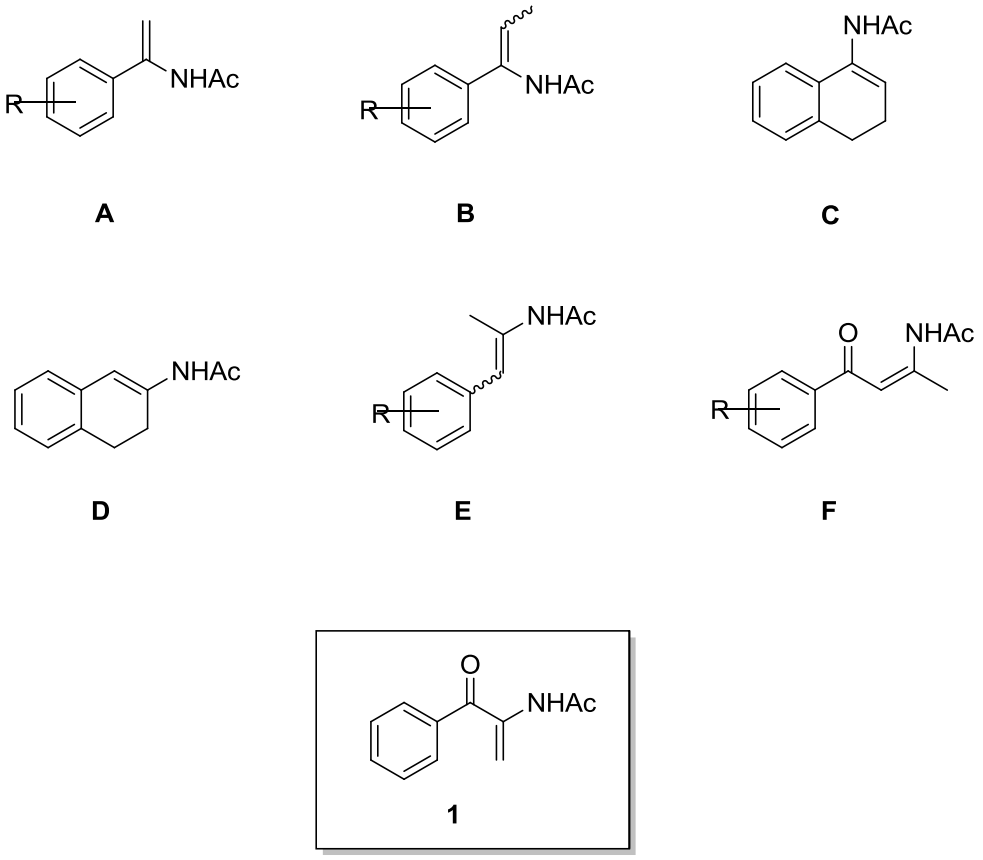
Chapter 2

Highly efficient synthesis of β-ketoamphetamines and amphetamines by chemoselective asymmetric hydrogenation

2.1 Introduction

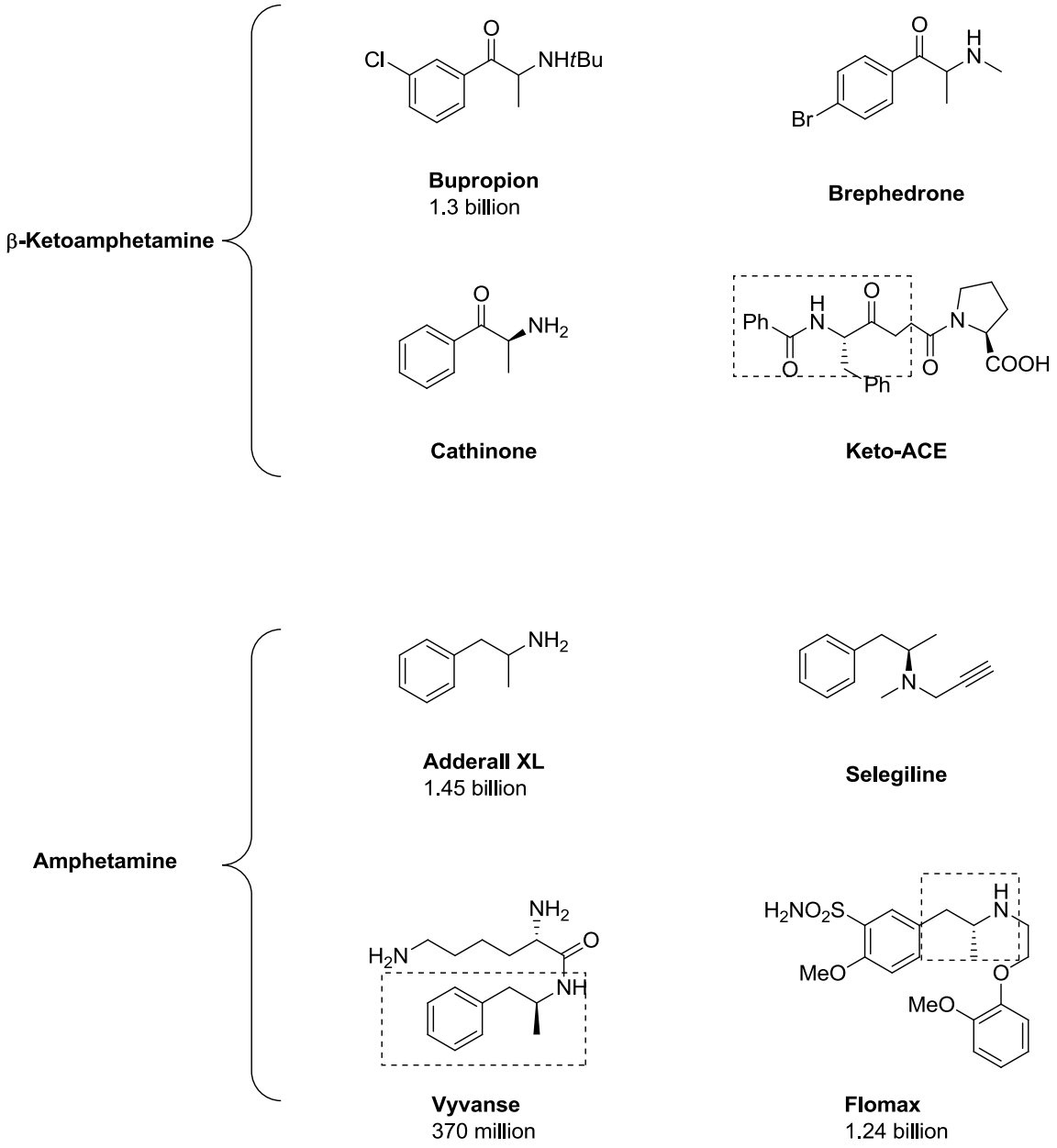
As mentioned before, asymmetric hydrogenation of enamides has more successful examples than asymmetric hydrogenation of imines. The synthetic methods for the preparation of enamides include rearrangement reactions[20], the reduction of nitro alkenes[21] or ketoximines[22], the acylation of imines[23], direct condensation of ketone by amide[24] and palladium-catalyzed amidation[25]. Several types of enamides have been studied for asymmetric hydrogenation, such as **A**[26], **B**[26a-c, e, g], **C**[27], **D**[28], **E**[19], and **F**[29]. Substrates **A** to **D** have been reported with high enantioselectivities and turnover numbers. The Z-configured enamides of substrate **E** has also achieved up to 99% ee in Rh-catalyzed asymmetric hydrogenation. The β-keto enamides **F** have been proven to be efficient substrates for the synthesis of 1, 3-amino alcohols with high enantioselectivities and high diastereoselectivities in Rh-catalyzed asymmetric hydrogenation. In this chapter, a new enamide substrate, α-keto enamide **1** is reported and shows high enantioselectivities in asymmetric hydrogenation with Rh-DuanPhos as catalyst.

Figure 2-1 Enamide substrates for asymmetric hydrogenation.



Asymmetric hydrogenation of substrate **1** provides feasible solutions for the development of β-ketoamphetamine derivatives, which are the important pharmaceutical compounds to treat psychological diseases. Psychological diseases have drawn widespread attention in modern society, affecting both adults and children. For example, depression affects approximately 14.8 million American adults in 2002.[1] ADHD (attention deficit hyperactivity disorder) affects 3-5% of children globally.[2] Two related chemical catalogs, β-ketoamphetamines and amphetamines are very effective in treating depression and ADHD respectively (Table 1). Bupropion, marketed as antidepressant,[3] is a racemic β-ketoamphetamine derivative. Adderall,[4] most commonly used to treat ADHD, is the racemic amphetamine. The medical usage of β-ketoamphetamine and amphetamine is not only limited to the psychological treatments. There are several more medicines belonging to these two catalogs with various applications. Keto-ACE,[5] Flomax,[6] and Selegiline[7] have been proven effective to treat hypertension, enlarged prostates, and Parkinson's disease respectively. In Figure 2-2, I show a set of important medicines belonging to β-keto amphetamine and amphetamine catalogs. To the best of my knowledge, there are more than 4 billion dollars of retail sale of above medicines in 2008.[8]

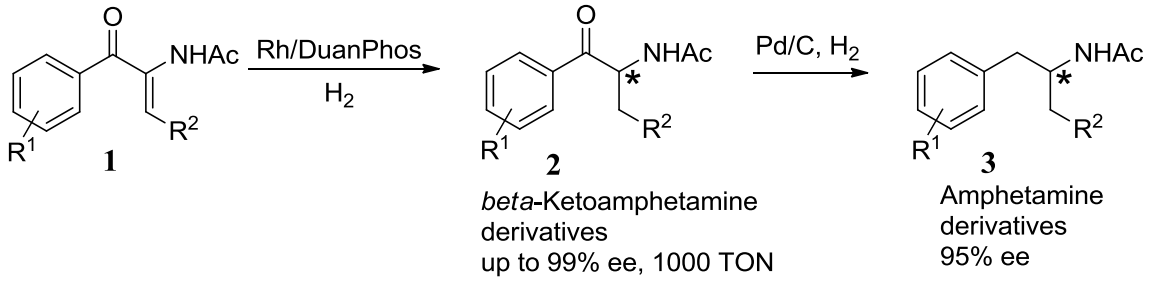
Figure 2-2 Important medicines bearing β-ketoamphetamine and amphetamine units.



2.2 Results and discussion

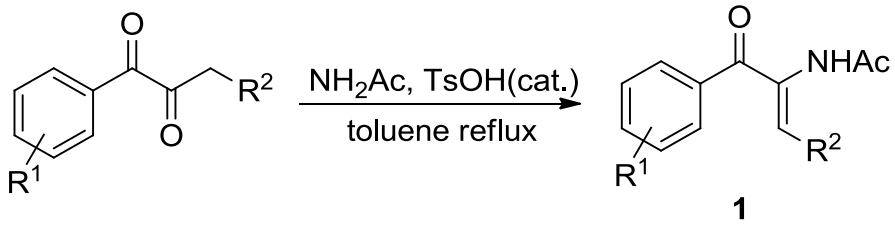
Despite the important pharmaceutical applications of chiral compounds, the asymmetric synthesis of β-ketoamphetamines and amphetamines is limited. Structurally, β ketoamphetamines are protected α-amino ketones. Extensive efforts have been made on the construction of enantiopure α-amino ketones starting from chiral amino acids derivatives.[9-11] These metal-catalyzed coupling reactions now have achieved a sophisticated level in terms of mild reaction conditions, high enantioselectivity and broad substrate scope.[10,11] Yet, one of the most significant challenges remains: stoichiometric or excess chiral reagents are required and consumed. Herein, we address a new strategy to solve this issue: asymmetric hydrogenation of readily accessible and highly modular a dehydroamino ketones as a direct entry to chiral α-amino ketones and their derivatives.

Figure 2-3 Asymmetric hydrogenation of substrate **1** as entry to β-ketoamphetamine and amphetamine.



As the above synthetic route is proposed, it is critical to design a synthetic route to substrates **1**. Substrates **1** could be viewed as α-ketone enamides, so the synthesis of simple enamides is utilized (Figure 2-4). Starting from 1, 2-diketones, the substrates **1** are synthesized in one step with up to 90% yield. 1, 2-diketones are readily available substrates; some of 1, 2-diketones are already commercially available.

Figure 2-4 Synthesis of substrate **1**.

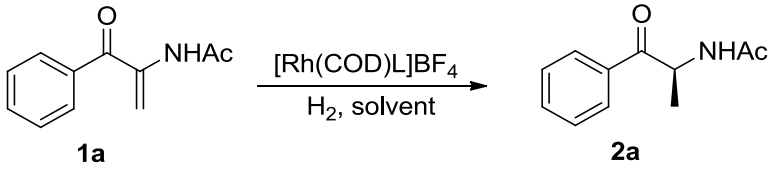


As a consequence of their high efficiency, atom economy, and operational simplicity, asymmetric hydrogenations have provided powerful routes to enantiomerically enriched compounds.[12] Actually, the asymmetric hydrogenation of dehydroamino acids for the synthesis of l-DOPA accomplished by Knowles (Nobel Prize, 2001) is the first industrial catalytic asymmetric synthesis.[13] Despite the remarkable success achieved in the hydrogenation of various dehydroamino acids,[14] the hydrogenation of α-dehydro-amino ketones remains unexplored. In this research, we report the synthesis of a series of new substrates, α-dehydroamino ketones **1**. Then we successfully obtained the chiral α-amino ketones **2** by hydrogenation with absolute chemoselectivity (enamide over ketone), excellent enantioselectivity (up to 99% ee) and high reactivity (1000 TON). We also

report the reduction of α-amino ketones catalyzed by Pd/C producing amphetamine precursors **3** with quantitative yield and no significant enantioselectivity loss (Figure 2-3).

Initially, we chose [Rh(COD)(S_c,R_p)-DuanPhos]BF_4 as the catalyst, which has been proven to be efficient for asymmetric hydrogenation of enamides, and N-(1-benzoylethenyl)-acetamide **1a** as the standard substrate. When the hydrogenation was performed in EtOAc (**1a**=0.3 mmol, S/C=100, EtOAc=3 mL) under 5 bar of H_2 at room temperature, the substrate **1a** was fully converted to the hydrogenation product **2a** with 92% ee (Table 2-1, entry 1). Solvent screening revealed that THF led to the best selectivity (Table 2-1, 95% ee, entry 6). We also tested other commercially available ligands: TangPhos (**L2**), BINAP (**L3**), and BINAPINE (**L4**) in THF. Either low enantioselectivity or low activity was observed with these ligands (Table 2-1, entries 7–9). An increase in the hydrogen pressure to 20 bar (Table 2-1, entry 10) led to low enantioselectivity (85%) and no side product (amino alcohol) was detected (Table 2-1, entry 10). We also tested the hydrogenation of **1a** under atmospheric pressure monitored by TLC. The reaction was complete within 1 hour with 95% ee to our great delight. The high efficiency of the catalyst Rh/DuanPhos was further demonstrated in an experiment with a lower catalyst loading (S/C=1000, 10 bar of H_2), giving identical ee, albeit the reaction required a longer time of 24 h (Table 2-1, entry 11).

Table 2-1 Rhodium-catalyzed asymmetric hydrogenation of **1a** under various conditions.[a]



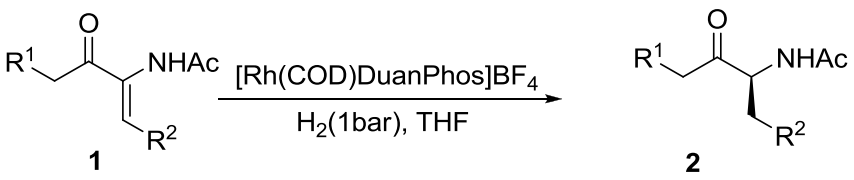
1a **2a**

Entry	Ligand[b]	Solvent	H_2 Pressure (bar)	Yield (%)	ee (%)[c,d]
1	**L1**	EtOAc	5	100	92
2	**L1**	MeOH	5	100	87
3	**L1**	Toluene	5	100	90
4	**L1**	CH_2Cl_2	5	100	85
5	**L1**	Acetone	5	100	92
6	**L1**	THF	5	100	95
7	**L2**	THF	5	100	65
8	**L3**	THF	5	100	5
9	**L4**	THF	5	N.R.	-
10	**L1**	THF	20	100	85
11[e]	**L1**	THF	1	100	95

a. Reaction conditions: [substrate]=0.1M, S/C=100, room temperature.
b. **L1**=(SC,RP)-DuanPhos, **L2**=(1S,1S', 2R,2R')-TangPhos, **L3**=(S)-BINAP, **L4**=(S)-Binapine.
c. Determined by chiral HPLC.
d. The absolute configuration was determined by reducing **2a** to **3a**, then comparison with reported data.
e. S/C=1000, room temperature, 10 bar of H_2, 24 h.

Using the optimized reaction conditions, we conducted the hydrogenation of a set of substrates **1b–1j** under atmospheric pressure (Table 2-2). All the substrates were completely converted to the corresponding N-protected α-amino ketones **2** with high enantioselectivity. The presence of a substituent on the phenyl moiety in **2** resulted in a slight decrease in the ee of the products (Table 2-2, entries 2, 5 and 6), except for a higher 97% ee provided by the *p*-MeO-substituted substrate **1c** (Table 2-2, entry 7). Interestingly, we found that trisubstituted enamide moieties **1g–1i** showed higher ee (95%–98%). We further expanded the substrate scope to the aliphatic substrate **1j**, 99% ee was observed, showing that the catalyst Rh/DuanPhos is effective with a wide scope of substrates.

Table 2-2 Rhodium-catalyzed asymmetric hydrogenation of **1a–1m**.[a]

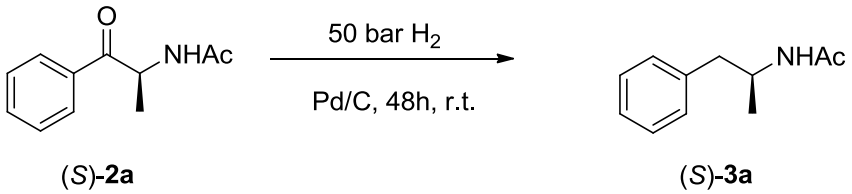


Entry	Substrates	R^1	R^2	Time (Hour)	Product	ee (%)[b]
1	**1a**	Ph	H	1	**2a**	95
2	**1b**	p-Me-Ph	H	1	**2b**	90
3	**1c**	p-MeO-Ph	H	1	**2c**	97
4	**1d**	p-F-Ph	H	1	**2d**	95
5	**1e**	p-Cl-Ph	H	1	**2e**	92
6	**1f**	m-Cl-Ph	H	0.5	**2f**	94
7	**1g**	Ph	Me	2	**2g**	95
8	**1h**	p-MeO-Ph	Me	2	**2h**	98
9	**1i**	p-Cl-Ph	Me	2	**2i**	97
10	**1j**	Et	Me	2	2j	99
11[c]	**2a**	Ph	H	48	2k	95

a. Reaction conditions: substrate/catalyst=100.
b. Determined by GC or HPLC.
c. [1a]=0.1M, Pd/C:1a=100, MeOH, 50 bar of H2, room temperature, 48 h.

We have demonstrated that hydrogenation of both aryl- and alkyl-substituted α-dehydroamino ketones leads to good enantioselectivity. As a result, this methodology has great potential for important pharmaceutical molecules (Figure 2-2). Aryl α-amino ketones like bupropion,[3] cathionone,[15] and brephedrone[16] are effective in treating psychological diseases. Keto-ACE,[17] the alkyl-substituted a-amino ketone derivative, is a key medicine to treat hypertension that affects an estimated 26% of the world's adult population. Another important family of α-amino ketones are peptidyl ketones, which have been intensively studied because of their biological activities.[18] Furthermore, it is of key importance to explore the combination of asymmetric hydrogenation with other methodologies to develop efficient protocols for pharmaceutical and industrial applications. Herein, we propose a new protocol integrating Rh-catalyzed hydrogenation and Pd/C-catalyzed reduction to maximize the efficiency of chiral amphetamine synthesis. Previously, Zhang's group reported the synthesis of enantiopure amphetamines by asymmetric hydrogenation of β-arylenamides.[19] However, Z/E isomers of arylenamides were generated simultaneously, resulting in an extra separation step. In this research, we developed a simple route to obtain enantiopure α-amino ketones, and amphetamine building blocks subsequently (Figure 2-3). For example, the hydrogenation product **2a** was directly reduced to generate protected amphetamine **3a** catalyzed by Pd/C with no significant loss of ee % (Figure 2-5). The new protocol may further contribute to the synthesis of diverse amphetamine medicines like adderall,[4] selegilline,[7] and flomax[6] that have been proven effective to treat ADHD, Parkinson's disease and enlarged prostate, respectively.

Figure 2-5 Pd/C-catalyzed reduction of α-amino ketone as entry to amphetamines.



(*S*)-**2a** (*S*)-**3a**

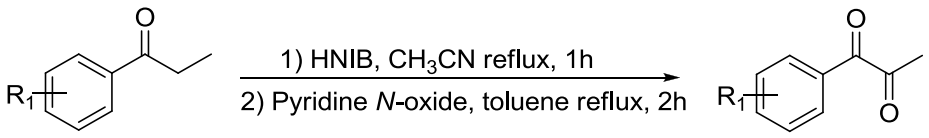
2.3 Conclusion

In summary, we have demonstrated that chemoselective asymmetric hydrogenation of substrates **1** is a powerful entry to β-ketoamphetamines in terms of activity (1000 TON), chemoselectivity (100%), and enantioselectivity (up to 99% ee). We have also demonstrated that the combination of Rh/DuanPhos and Pd/C is an elegant approach to amphetamines. Further exploration on substrate scope and catalyst combination is currently under progress.

Experimental Section

General: Unless otherwise noted, all reagents and solvents were purchased from commercial suppliers and used without further purification. NMR spectra were recorded on 400 MHz for ^{1}H NMR and ^{13}C NMR. $CDCl_3$ was the solvent used for the NMR analysis. Chemical shifts were reported in ppm downfield from internal Me_4Si. Optical rotations were determined using a Perkin Elmer 341 MC polarimeter. HRMS were recorded on a Thermo LTQ Orbitrap hybrid mass spectrometer. GC analyses were performed using Hewlett Packard Model HP 7890 Series. HPLC analysis was conducted on an Agilent 1200 Series instrument.

(A) General procedure for the synthesis of 1, 2-diketones 4b-4g.[30]

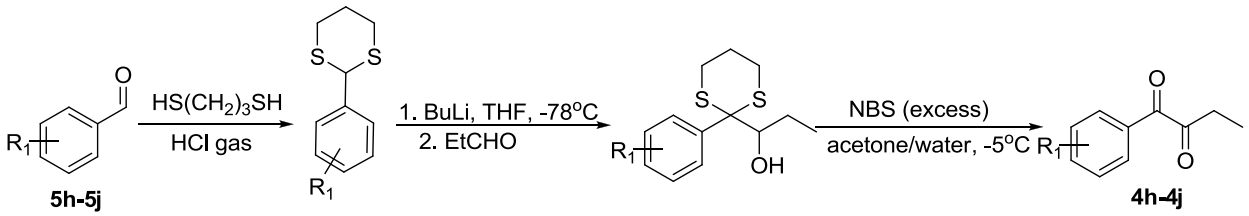


5b-5g **4b-4g**

A suspension of ketone (3.0 mmol) and [hydroxy(*p*-nitrobenzenesulfonyloxy) iodo]benzene (HNIB[2])(1.521 g, 3.6 mmol) in CH_3CN was refluxed for 1 h monitored by TLC. After reaction was complete, evaporate the solvent. To the resulting crude residue,

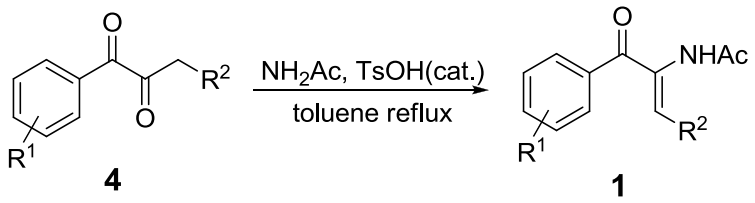
add pyridine N-oxide (0.342g, 3.6 mmol) and toluene, reflux for 2 h and monitor the reaction by TLC. The reaction mixture was extracted with dichloromethane (2×25 mL) and washed with water (2×30 mL). The dichloromethane layer was separated and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (SiO_2, ethyl acetate:hexane=1:3) to give the desired 1,2-diketone as yellow oil.

(B) General procedure for the synthesis of 1,2-diketones 5h-5j.

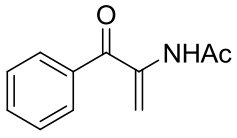


HCl gas was bubbled through a solution of benzaldehyde (5 mmol) and 1,3-propanedithiol (6 mmol) in dichloromethane (100ml) at 4 ^{0}C for 1 h, work up and recrystallization from methanol gave white crystal. To the above product in THF, a solution of *n*-BuLi in hexane (1.1 equiv.) was added at -78 ^{0}C for 2 h. To the resulting anion was added propionaldehyde (1.2 equiv.) at -78 ^{0}C and the reation allowed to reach room temperature overnight. Work up by brine and pure water and purified by flash column chromatography using 10% ethyl acetate/petroleum ether to give the product as a white solid. Dissolve the solid in acetone and add dropwise to the a solution of N-bromosuccinimide (15eq) in 3% water/acetone at 5 ^{0}C. Work up and purified by flash column chromatography using 5% ethyl acetate/hexane to give the product as yellow oil.

(C) Preparation and physical data for substrate 1

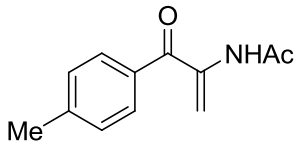


A catalytic amount of an acid (*p*-toluenesulfonic acid, TsOH) and acetamide (5 equiv) were added to a stirred solution of **4** (1.0 equiv) in toluene. The mixture was heated under refflux using a Dean-Stark apparatus. Use TLC to monitor the reaction process, and stop the reaction when the side product with distinctive fluorescent blue color is detected under UV lamp. The precipitate of acetamide was separated by filtration and the filter residue was washed with EtOAc thoroughly. The combined filtrate was washed with saturated $NaHCO_3$ solution and water, dried over Na_2SO_4. Removing the solvent by rotary evaporation, the product mixture was purified by flash column chromatography using 25% ethyl acetate/hexane.

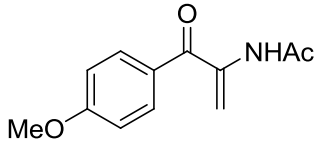


N-(3-oxo-3-phenylprop-1-en-2-yl)acetamide (1a): Yield: 65%. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.07 (bs, 1H, N-H). 7.70-7.68 (m, 2H, Ar-H). 7.58-7.56 (m, 1H, Ar-H).7.48-7.44

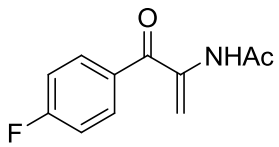
(m, 2H, Ar-H). 7.07 (s, 1H, Csp^2-H). 5.59 (s, 1H, Csp^2-H). 2.19 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.07, 169.23, 137.79, 135.98, 132.41, 129.39, 128.32, 114.80, 24.78; HRMS (EI) Calcd for $C_{11}H_{12}NO_2$:190.0868. Found: 190.0873.



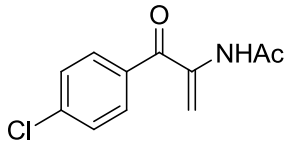
N-(3-oxo-3-p-tolylprop-1-en-2-yl)acetamide (1b): Yield: 50%. ^1H NMR: ($CDCl_3$, 400 MHz) δ 8.00 (bs, 1H, N-H). 7.56-7.54 (d, 2H, *J* = 8.0 Hz, Ar-H). 7.20-7.18 (d, 2H, *J* = 8.0 Hz, Ar-H). 7.07 (s, 1H, Csp^2-H). 5.52 (s, 1H, Csp^2-H). 2.35 (s, 3H, CH_3). 2.12 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.73, 169.32, 143.35, 137.76, 133.26, 129.65, 129.00, 114.32, 24.30, 21.61; HRMS (EI) Calcd for $C_{12}H_{14}NO_2$: 204.1025. Found: 204.1022.



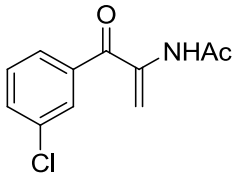
N-(3-(4-methoxyphenyl)-3-oxoprop-1-en-2-yl)acetamide (1c): Yield: 60%. ^1H NMR: ($CDCl_3$, 400 MHz) δ 8.00 (bs, 1H, N-H). 7.76-7.74 (d, 2H, *J* = 8.0 Hz, Ar-H). 6.97-6.94 (d, 2H, *J* = 12.0 Hz, Ar-H). 7.00 (s, 1H, Csp^2-H). 5.57 (s, 1H, Csp^2-H). 3.88 (s, 3H, CH_3). 2.18 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.84, 169.37, 163.35, 137.75, 131.96, 113.67, 113.47, 55.51, 24.81.



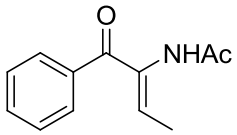
N-(3-(4-fluorophenyl)-3-oxoprop-1-en-2-yl)acetamide (1d): Yield: 75%. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.00 (bs, 1H, N-H). 7.77-7.73 (m, 2H, Ar-H). 7.16 (m, 2H, Ar-H). 7.06 (s, 1H, Csp^2-H). 5.55 (s, 1H, Csp^2-H). 2.19 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.61, 169.21, 166.65, 164.12, 137.68, 132.06, 115.60, 24.78; HRMS (EI) Calcd for $C_{11}H_{11}NO_2F$: 208.0774. Found: 208.0775.



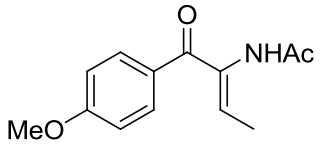
N-(3-(4-chlorophenyl)-3-oxoprop-1-en-2-yl)acetamide (1e): Yield: 60%. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.02 (bs, 1H, N-H). 7.69-7.67 (d, 2H, *J* = 8.0 Hz, Ar-H). 7.43-7.41 (d, 2H, *J* = 8.0 Hz, Ar-H). 7.09 (s, 1H, Csp^2-H). 5.57 (s, 1H, Csp^2-H). 2.12 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 192.17, 168.02, 136.61, 135.25, 130.76, 128.59, 115.19, 23.59; HRMS (EI) Calcd for $C_{11}H_{11}NO_2Cl$: 224.0478. Found: 224.0473.



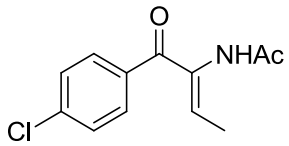
N-(3-(3-chlorophenyl)-3-oxoprop-1-en-2-yl)acetamide (1f): Yield 50%. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.02 (bs, 1H, N-H). 7.69-7.67 (d, 2H, *J* = 8.0 Hz, Ar-H). 7.43-7.41 (d, 2H, *J* = 8.0 Hz, Ar-H). 7.09 (s, 1H, Csp^2-H). 5.57 (s, 1H, Csp^2-H). 2.12 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.17, 168.02, 136.61, 135.25, 130.76, 128.59, 115.19, 23.59; HRMS (EI) Calcd for $C_{11}H_{11}NO_2Cl$: 224.0478. Found: 224.0473.



(Z)-N-(1-oxo-1-phenylbut-2-en-2-yl)acetamide (1g): Yield 50%. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.65-7.35 (m, 5H, Ar-H). 7.50 (s, 1H, N-H). 6.25-6.23 (m, 1H, Csp^2-H). 2.07 (s, 3H, CH_3). 1.79-1.77 (d, 3H, *J* = 8.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.54, 168.22, 137.00, 135.94, 132.12, 130.13, 129.34, 128.21, 20.47, 15.12; HRMS (EI) Calcd for $C_{12}H_{14}NO_2$: 204.1025. Found: 204.1023.

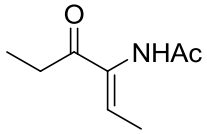


(Z)-N-(1-(4-methoxyphenyl)-1-oxobut-2-en-2-yl)acetamide (1h): Yield 40%. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.41 (bs, 1H, N-H). 7.71-7.69 (d, 2H, *J* = 8.0 Hz, Ar-H). 6.87-6.84 (d, 2H, *J* = 12.0 Hz, Ar-H). 6.21-6.19 (m, 1H, Csp^2-H). 3.78 (s, 3H, CH_3). 2.08 (s, 3H, CH_3). 1.79-1.77 (d, 3H, *J* = 8.0Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.05, 163.11, 134.26, 131.89, 131.71, 129.21, 113.55, 55.47, 23.57, 15.04; HRMS (EI) Calcd for C13H16NO3: 234.1130. Found: 234.1140.



(Z)-N-(1-(4-chlorophenyl)-1-oxobut-2-en-2-yl)acetamide (1i): Yield 50%.^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.02 (bs, 1H, N-H). 7.69-7.67 (d, 2H, *J* = 8.0 Hz, Ar-H). 7.43-7.41 (d, 2H, *J* = 8.0 Hz, Ar-H). 7.09 (s, 1H, Csp^2-H). 5.57 (s, 1H, Csp^2-H). 2.12 (s, 3H, CH_3);

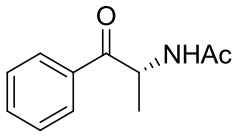
^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.17, 166.02, 126.61, 125.05, 120.76, 128.59, 23.50, 15.11; HRMS (EI) Calcd for $C_{12}H_{13}NO_2Cl$: 238.0635. Found: 238.0634.



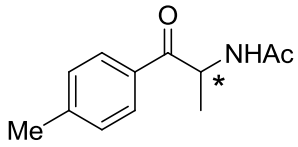
(Z)-N-(4-oxohex-2-en-3-yl)acetamide (1j):[4] Yield 65%. ^1H NMR: ($CDCl_3$, 400 MHz) δ 7.39 (bs, 1H, N-H). 6.61-6.59 (m, 1H, Csp^2-H). 2.66-2.64 (m, 2H, CH_2). 2.06 (s, 3H, CH_3). 1.77-1.75 (d, 3H, J = 8.0 Hz, CH_3). 1.05-1.02 (m,3H CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.20, 168.22, 134.34, 132.60, 29.62, 23.51, 15.40, 3.39.

(D) General procedure for asymmetric hydrogenation of enamide 1.

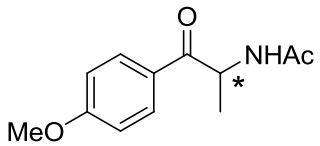
A 10.0 ml Schlenk tube was loaded with substrate **1** (0.3mmol) and [Rh(cod)(S_c, R_p)-duanphos]BF_4 (3×10^{-4}mmol, 2.04mg). The mixture was dissolve in 3ml THF at rt in the glovebox. Then the schlenk tube was brought to hood and connected to a hydrogen balloon. The inert atmosphere was replaced by H2 and the reaction mixture was stirred under rt by TLC monitor. After reaction was complete(20mins to 2 h). Hydrogen was released and the catalyst was removed through a silicon gel loaded plug. The enantiomeric excess was directly determined by chiral GC or HPLC under the following conditions.



(R)-N-(1-oxo-1-phenylpropan-2-yl)acetamide (2a): [4]95% ee. HPLC condition: Chiralpak OD-H column, Hex/IPA=95:5, 1.0 mL/min, t_{major}=16.1min, t_{minor}=20.3 min. $[\alpha]^{20}_{D}$=10.7 ° (c =1.0, $CHCl_3$). ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.93-7.91(m, 2H, Ar-H). 7.54 (m, 1H, Ar-H). 7.45-7.43 (m, 2H, Ar-H). 6.57 (bs, 1H, N-H). 5.52-5.48 (m, 1H). 2.00 (s, 3H, CH_3). 1.36-1.35 (d, 3H, *J* = 4.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.5, 133.95, 128.90, 107.92, 67.65, 50.09, 29.15, 23.91, 23.30, 19.84; HRMS (EI) Calcd for $C_{11}H_{14}NO_2$: 192.1025. Found: 192.1034.

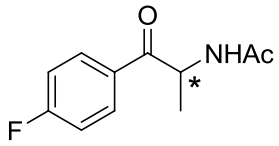


N-(1-oxo-1-p-tolylpropan-2-yl)acetamide (2b): 90% ee. HPLC condition: Chiralpak OD-H column, Hex/IPA=95:5, 1.0 mL/min, t_{major} = 21.1 min, t_{minor} = 14.2 min. $[\alpha]^{20}_{D}$=-2.0 (c =1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83-7.81(d, 2H, *J* = 8.0 Hz, Ar-H). 7.24-7.22 (d, 2H, *J* = 8.0 Hz, Ar-H). 6.56 (bs, 1H, N-H). 5.48-5.45 (m, 1H). 2.36(s, 3H, CH_3). 1.99 (s, 3H, CH_3). 1.36-1.34 (d, 3H, *J* = 8.0 Hz CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.73, 168.51, 144.05, 130.32, 128.10, 49.02, 22.33, 20.70, 19.03; HRMS (EI) Calcd for $C_{12}H_{16}NO_2$: 206.1181. Found: 206.1173.

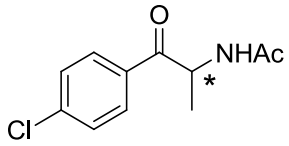


N-(1-(4-methoxyphenyl)-1-oxopropan-2-yl)acetamide (2c): 97% ee. HPLC condition: Chiralpak OD-H column, Hex/IPA=90:10, 1.0 mL/min, t_{major} = 19.6 min, t_{minor} = 18.2 min. $[\alpha]^{20}_{D}$=5.0(c =1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92-7.90(d, 2H, *J* = 8.0 Hz,

Ar-H). 6.91-6.89 (d, 2H, *J* = 8.0 Hz, Ar-H). 6.56 (bs, 1H, N-H). 5.46-5.42 (m, 1H). 3.82(s, 3H, CH_3). 1.98 (s, 3H, CH_3). 1.36-1.34 (d, 3H, *J* = 8.0 Hz CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.5, 168.33, 163.22, 130.12, 125.65, 113.11, 54.55, 48.71, 22.39, 19.22; HRMS (EI) Calcd for $C_{12}H_{16}NO_3$: 222.1130. Found: 222.1124.

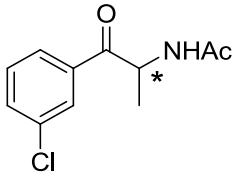


N-(1-(4-fluorophenyl)-1-oxopropan-2-yl)acetamide (2d): 95% ee. HPLC condition: Chiralpak OJ-H column, Hex/IPA=90:10, 1.0 mL/min, t_{major} = 9.0 min, t_{minor} = 6.7 min. $[\alpha]^{20}_D$= -6.8(c =1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.98-7.95(m, 2H, Ar-H). 7.13-7.09 (m, 2H, Ar-H). 6.48 (bs, 1H, N-H). 5.48-5.44 (m, 1H). 1.99 (s, 3H, CH_3). 1.36-1.34 (d, 3H, *J* = 8.0 Hz CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.62, 169.42, 131.53, 116.27, 49.91, 23.33, 19.82; HRMS (EI) Calcd for $C_{11}H_{13}NO_2F$: 210.0930. Found: 210.0929.

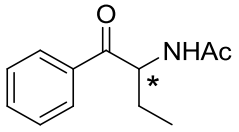


N-(1-(4-chlorophenyl)-1-oxopropan-2-yl)acetamide (2e): 92% ee. HPLC condition: Chiralpak OD-H column, Hex/IPA=95:5, 1.0 mL/min, t_{major} = 17.5 min, t_{minor} = 16.2 min. $[\alpha]^{20}_D$= -9.5(c =1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.88-7.86(d, 2H, *J* = 8.0 Hz, Ar-H). 7.42-7.40 (d, 2H, *J* = 8.0 Hz, Ar-H). 6.48 (bs, 1H, N-H). 5.47-5.43 (m, 1H). 1.96 (s, 3H, CH_3). 1.35-1.33 (d, 3H, *J* = 8.0 Hz CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.03,

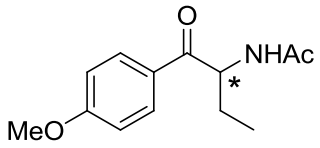
168.41, 139.54, 131.22, 129.11, 128.28, 48.96, 28.68, 22.30, 18.70; HRMS (EI) Calcd for $C_{11}H_{13}NO_2Cl$: 226.0635. Found: 226.0634.



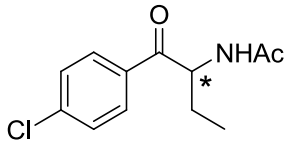
N-(1-(3-chlorophenyl)-1-oxopropan-2-yl)acetamide (2f) : 94% ee. HPLC condition: Chiralpak OD-H column, Hex/IPA=95:5, 1.0 mL/min, t_{major} = 14.0 min, t_{minor} = 16.0 min. $[\alpha]^{20}_D$= -8.3(c =1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98-7.45(m, 4H, Ar-H). 6.54 (bs, 1H, N-H). 5.54-5.50 (m, 1H). 2.06 (s, 3H, CH_3). 1.43-1.41 (d, 3H, *J* = 8.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.10, 169.49, 135.53, 135.38, 133.89, 130.23, 128.79, 126.76, 50.19, 23.30, 19.65 HRMS (EI) Calcd for $C_{11}H_{13}NO_2Cl$: 226.0635. Found: 226.0634.



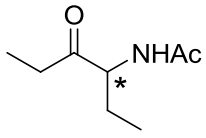
N-(1-oxo-1-phenylbutan-2-yl)acetamide (2g): 95% ee. HPLC condition: Chiralpak OD-H column, Hex/IPA=95:5, 1.0 mL/min, t_{major} = 14.0 min, t_{minor} = 16.0 min. $[\alpha]^{20}_D$= -9.2(c =1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93-7.91(m, 2H, Ar-H). 7.55(m, 1H, Ar-H). 7.45-7.41(m, 2H, Ar-H).6.45 (bs, 1H, N-H). 5.55-5.52 (m, 1H).2.01 (s, 3H, CH_3). 1.61-1.60 (m, 1H). 0.79-0.75 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.02, 169.75, 133.91, 128.90, 54.76, 26.37, 23.38, 8.92; HRMS (EI) Calcd for $C_{12}H_{16}NO_2$: 206.1181. Found: 206.1176.



N-(1-(4-methoxyphenyl)-1-oxobutan-2-yl)acetamide (2h): 98% ee. HPLC condition: Chiralpak OD-H column, Hex/IPA=90:10, 1.0 mL/min, t_{major} = 19.2 min, t_{minor} = 10.0 min. $[\alpha]^{20}_{D}$= 4.1(c =0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92-7.90(d, 2H, *J* = 8.0 Hz, Ar-H). 6.90-6.88 (d, 2H, *J* = 8.0 Hz, Ar-H).6.50 (bs, 1H, N-H). 5.50-5.46 (m, 1H). 3.81(s, 3H, CH_3). 1.98 (s, 3H, CH_3). 1.61-1.58 (m, 1H). 0.77 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.31, 168.77, 163.19, 130.03, 126.33, 113.09, 106.90, 54,53, 53.32, 25.67, 22.34, 7.95; HRMS (EI) Calcd for $C_{13}H_{18}NO_3$: 236.1287. Found: 236.1292.



N-(1-(4-chlorophenyl)-1-oxobutan-2-yl)acetamide (2i): 97% ee. HPLC condition: Chiralpak OD-H column, Hex/IPA=95:5, 1.0 mL/min, t_{major} = 15.6 min, t_{minor} = 12.9 min. $[\alpha]^{20}_{D}$= 32.94(c =1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88-7.86(d, 2H, *J* = 8.0 Hz, Ar-H). 7.42-7.39 (d, 2H, *J* = 12.0 Hz, Ar-H).6.40 (bs, 1H, N-H). 5.49-5.45 (m, 1H). 1.96 (s, 3H, CH_3). 1.59-1.54 (m, 1H). 0.79-0.75 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.93, 169.76, 140.47 132.88, 130.03, 129.27, 54.57, 26.27, 23.31, 9.00; HRMS (EI) Calcd for $C_{12}H_{15}NO_2Cl$: 240.0791. Found: 240.0794.



N-(4-oxohexan-3-yl)acetamide (2j): 99% ee. GC condition: Beta dex 225 column, 150^0C, 1.0 mL/min, t_{major} = 7.7 min, t_{minor} = 7.6 min. $[\alpha]^{20}_D$= -21.4(c =1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.74 (bs, 1H, N-H). 3.86 (m, 1H). 3.56 (m, 1H). 2.02(s, 3H). 1.58-1.43 (m, 4H). 0.99-0.95 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.84, 74.23, 55.30, 54.10, 27.50, 26.12, 25.50, 23.32, 21.31, 10.84, 10.42, 10.61, 10.02; HRMS (EI) Calcd for $C_8H_{18}NO_2$: 160.1338. Found: 160.1337.

Reference

1. Kessler, R. C.; Chiu, W. T.; Demler, O.; Walters, E. E. *Archives of General Psychiatry* **2005**,*62*,617.
2. Nair, J.; Ehimare, U.; Beitman, B. D.; Nair, S. S.; Lavin, A. *Mo. Med.* **2006,** *103,* 617.
3. (a). Fava, M.; Rush, A. J.; Thase, M. E.; Clayton, A.; Stahl, S. M.; Pradko, J. F.; Johnston, J. A. *Prim. Care. Companion. J. Clin. Psychiatry.* **2005,** *7*, 106. (b)Tonnesen, P.; Tonstad, S.; Hjalmarson, A.; Lebargy, F.; Van Spiegel, P. I.; Hider, A., Sweet, R., Townsend, J. *J. Intern. Med.* **2003,** *254*, 184.
4. Biederman, J.; Lopez, F. A.; Boellner, S. W., Chandler, M. C. *Pediatrics* **2002,** *110*, 258.
5. Redelinghuys, P.; Nchinda, A. T.; Sturrock, E. D. *New York Academy of Science* **2005,** *1056,* 160.
6. Roehrborn, C. G.; Siami, P.; Barkin, J.; Dami ão, R.; Major, W. K.; Morrill, B.; Montorsi, F. *J. Urol.* **2008**, *179*, 616.
7. Birkmayer, W.; Riederer, P.; Youdim, M. B.; Linauer, W. J. *Neural. Transm.* **1975,** *36* ,303.
8. The bupropion prescriptions were calculated as a total of prescriptions for Wellbutrin XL, Budeprion XL, Budeprion SR using data from the charts for top 200 brand-name drugs by retail dollars in 2008, see: http://www.chem.cornell.edu/jn96/docs/Top%20200%20Generic%20Drugs%20by%20Retail%20Dollars%20in%202008(1).pdf (accessed March 08, 2010)
9. For the synthesis of a-amino ketones from amino acids, see: a) Fisher, L. E.; Muchowshi, J. M. *Org. Prep. Proced. Int.* **1990**, *22*, 399; b) Paleo, M. R.; Calaza, M. I.; Sardina, F. J. *J. Org. Chem.* **1997**, *62*, 6862; c) Sengupta, S.; Mondal, S.; Das, A. *Tetrahedron Lett.* **1999**,*40*, 4107; d) Di Gioia, M. L.; Legio, A.; Liguori, A.; Napoli, A.; Siciliano, C.; Sindona, G. *J. Org. Chem.* **2001**, *66*, 7002; e) Sharma, A. K.; Hergenrother, P. J. *Org. Lett.* **2003**, *5*, 2107; f) Reetz, M. T.; *Angew. Chem.* **1991**, *103*, 1559; *Angew. Chem. Int. Ed. Engl*. **1991**, *30*, 1531.
10. For synthesis of a-amino ketones by amino acid amides, see: Ooi, T.; Takeuchi, M.; Kato, D.; Uematsu, Y.; Tayama, E.; Sakai, D.; Maruoka, K.; *J. Am. Chem. Soc.* **2005**, *127*, 5073.

11. For synthesis of a-amino ketones by thioesters, see: a) Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1132; b) Yang, H.; Liebeskind, L. S. *Org. Lett.* **2007**, *9*, 2993; c) Li, H.; Yang, H.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 4375; d) Liebeskind, L. S.; Yang, H.; Li, H. *Angew. Chem.* **2009**, *121*, 1445; *Angew. Chem. Int. Ed.* **2009**, *48*,1417.
12. a) Noyori, R.; Ohkuma, T. *Angew. Chem.* **2001**, *113*, 40; *Angew. Chem. Int. Ed.* **2001**, *40*, 40; b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029; c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069; d) Shultz, C. S.; Krska, S. W. *Acc. Chem. Res.* **2007**, *40*, 1320; e) de Vries, J. G.; Elsevier, C. J. (Eds.), *Handbook of Homogeneous Hydrogenation*, Wiley-VCH, Weinheim, **2007**.
13. http://nobelprize.org/nobel_prizes/chemistry/laureates/2001/public.html (accessed May 17, **2010**).
14. Drexler, H.-J.; You, J.; Zhang, S.; Fischer, C.; Baumann, W.; Spannenberg, A.; Heller, D. *Org. Process Res. Dev.* **2003**, *7*, 355.
15. Kalix, P. *Psychopharmacology* **1981**, *74*, 269.
16. Foley, K. F.; Cozzi, N. V. *Novel Drug Devel. Res.* **2003**, *60*, 252.
17. Redelinghuys, P.; Nchinda, A. T.; Sturrock, E. D. *New York Academy of Science* **2005**, *1056*, 160.
18. a) DeGraw, J. I.; Almquist, R. G.; Hiebert, C. K.; Colwell, W. T.; Crase, J.; Hayano, T.; Judd, A. K.; Dousman, L.; Smith, R. L.; Waud, W. R.; Uchida, I. *J. Med. Chem.* **1997**, *40*, 2386; b) Eda, M.; Ashimori, A.; Akahoshi, F.; Yoshimura, T.; Inoue, Y.; Fukaya, C.; Nakajima, M.; Fukuyama, H.; Imada, T.; Nakamura, N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 913; c) Dragovich, P. S.; Zhou, R.; S. Webber, E.; Prins, T. J.; Kwok, A. K.; Okano, K.; Fuhrman, S. A.; Zalman, L. S.; Maldonado, F. C.; Brown, E. L.; Meador III, J. W.; Patick, A. K.; Ford, C. E.; Brothers, M. A.; Binford, S. L.; Matthews, D. A.; Ferre, R. A.; Worland, S. T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 45.
19. Chen, J.; Zhang, W.; Geng, H.; Li, W.; Hou, G.; Lei, A.; Zhang, X. *Angew. Chem.* **2009**, *121*, 814; *Angew. Chem. Int. Ed.* **2009**, *48*, 800.
20. (a) Bachman, G. L.; Vineyard, B. D. *Ger. Offen.,* **1977**, DE 2638072. (b) Smith, P. A. S.; Horwitz, J. P. *J. Am. Chem. Soc.* **1950**, *72* , 3718.
21. Laso, N. M.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 1605.
22. a) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084; b) Zhang, Z.; Zhu, G.; Jiang, Q.; Xiao, D.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 1774; c) Zhao, H.; Vandenbossche, C. P.; Koenig, S. G.; Singh, S. P.; Bakale, R. P. *Org. Lett.* **2008**, *10*, 505.
23. Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907.
24. a) Elaridi, J.; Thaqi, A.; Prosser, A.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry.* **2005**, *16*, 1309; b) Guin, J.; Muck- Lichtenfeld, C.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2007**, *129*, 4498.
25. a) Wallace, D. J.; Klauber, D. J.; Chen, C.-Y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749; b) Klapars, A.; Campos, K. R.; Chen, C.-Y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185.
26. a) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142; b) Gridnev, I. D.; Yasutake, M.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2001**, *123*, 5268; c) Tang, W.; Zhang, X. *Angew. Chem.* **2002**, *114*, 1682; *Angew. Chem.*

Int. Ed. **2002**, *41*, 1612; d) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem.* **2002**, *114*, 2454; *Angew. Chem. Int. Ed.* **2002**, *41*, 2348; e) Bernsmann, H.; van den Berg, M.; Hoen, R.; Minnaard, A. J.; Mehler, G.; Reetz, M. T.; De Vries, J. G.; Feringa, B. L. *J. Org. Chem.* **2005**, *70*, 943; f) Liu, Y.; Ding, K. *J. Am. Chem. Soc.* **2005**, *127*, 10488; g) Zhang, W.; Zhang, X. *Angew. Chem.* **2006**, *118*, 5641; *Angew. Chem. Int. Ed.* **2006**, *45*, 5515; h) Huang, J.-D.; Hu, X.-P.; Duan, Z.-C.; Zeng, Q.- H.; Yu, S.-B.; Deng, J.; Wang, D.-Y.; Zheng, Z. *Org. Lett.* **2006**, *8*, 4367; i) Gridnev, I. D.; Imamoto, T.; Hoge, G.; Kouchi, M.; Takahashi, H. *J. Am. Chem. Soc.* **2008**, *130*, 2560.

27. a) Zhang, Z.; Zhu, G.; Jiang, Q.; Xiao, D.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 1774; b) Tang, W.; Chi, Y.; Zhang, X. *Org. Lett*. **2002**, *4*, 1695.
28. a) Tschaen, D. M.; Abramson, L.; Cai, D.; Desmond, R.; Dolling, U.-H.; Frey, L.; Karady, S.; Shi, Y.-J.; Verhoeven, T. R. *J. Org. Chem.* **1995**, *60*, 4324; b) Dupau, P.; Le Gendre, P.; Bruneau, C.; Dixneuf, P. H. *Synlett* **1999**, 1832; c) Jiang, X.-B.; Lefort, L.; de Vries, A. H. H.; van Leeuwen, P. W. N. M.; de Vries, J. G.; Reek, J. N. H. *Angew. Chem*. **2006**, *118*, 1245; *Angew. Chem. Int. Ed.* **2006**, *45*, 1223.
29. Geng, H.; Zhang, W.; Chen, J.; Hou, G.; Zhou, L.; Zou, Y.; Wu, W.; Zhang, X. *Angew. Chem*. **2009**, *48*, 6052
30. Lee, J. C.; Park, H. J.; Park, J. Y. *Tetrahedron Lett*. **2002**, *43*, 5661.
31. The HNIB was easily prepared in 93% yield by the reaction of iodobenzene diacetate and *p*-nitrobenzenesulfonic acid: Lee, J. C.; Oh, Y. S.; Cho, S. H. *Bull. Korean. Chem. Soc*. **1996**, *17*, 989.
32. Page, P. C. B.; Graham, A. E.; Park, B. K. *Tetrahedron*.**1992**, *48*, 7265.
33. Shemyakin, M. M.; Maimind, V. I.; Ermolaev, K. M.; Bamdas, E. M. *Tetrahedron*.**1965**, *21*, 2771.

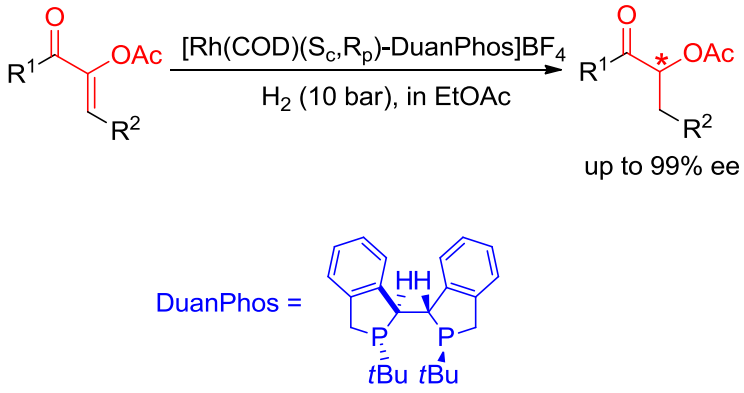
Chapter 3

A simple synthetic route to enantiopure α-hydroxy ketone derivatives by asymmetric hydrogenation

3.1 Introduction

α-Hydroxy ketones and their derivatives are important structural moieties of pharmacologically useful substances and biologically active natural compounds.[1] In particular, enantiomerically pure α-hydroxy ketones often serve as the chiral building blocks for the asymmetric synthesis of natural products.[2] Several methods have been developed in the field of chiral α-hydroxy ketone synthesis, including oxidation of enolates[3a-e] and enol ethers,[3e-g] and kinetic resolution of racemic α-hydroxy ketones.[4] In addition, several research groups report that both enzyme and transition metal can catalyse the reduction of α-diketones.[4] The last approach in principle should be the most straightforward and atom economical route to α-hydroxy ketones. Unfortunately, it is often difficult to control the chemoselectivity between the two ketone groups, and mixtures of α-hydroxy ketones and 1, 2-diols are generated.[4] Alternatively, the asymmetric hydrogenation of enol acetates has been reported by several groups to avoid the problems raised by direct hydrogenation of ketones.[5] However, the asymmetric hydrogenation of α-ketone enol acetates remains unexplored. Herein, we would like to propose a simple synthetic route to the substituted enantiomerically pure α-hydroxyl ketones.

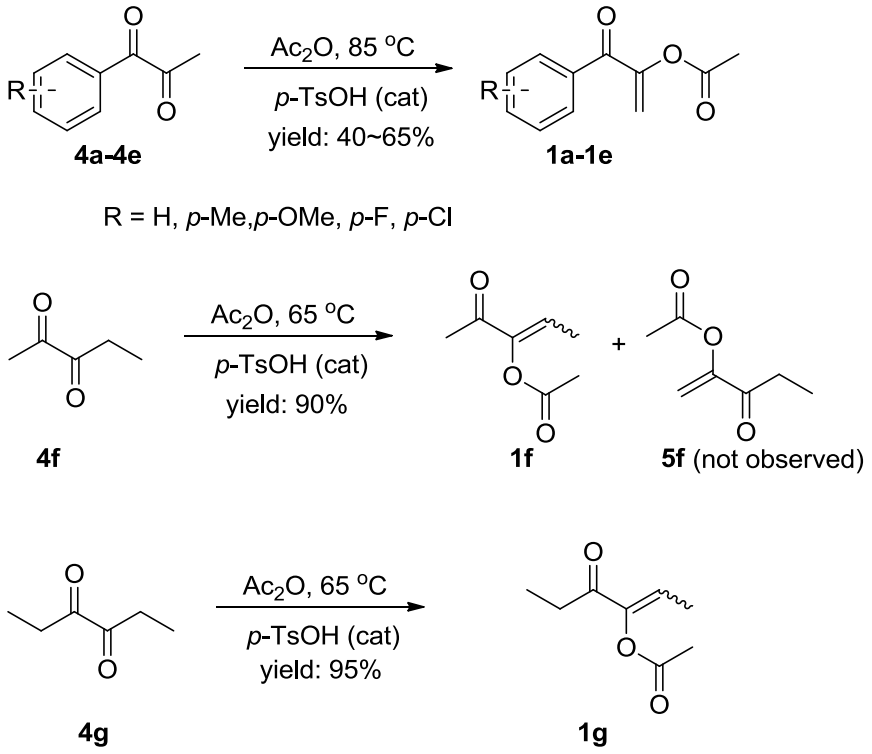
Figure 3-1 Asymmetric hydrogenation of α-keto esters.



3.2 Results and discussion

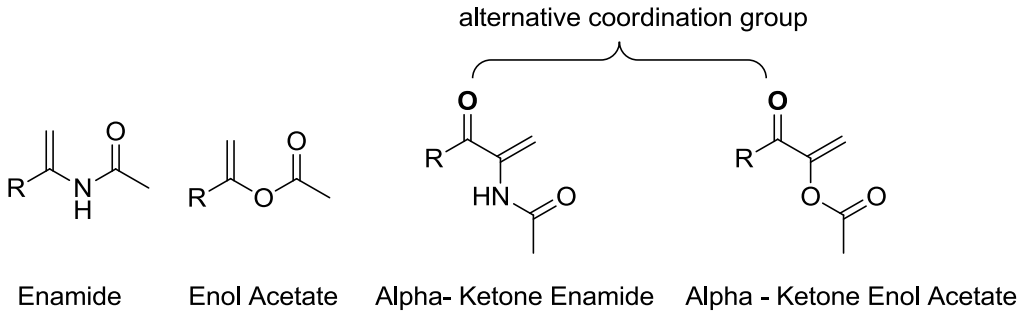
Recently, we have reported the asymmetric hydrogenation of α-ketone enamides.[6] Inspired by these results, we realized that the asymmetric hydrogenation of α-ketone enol acetates might be a direct and efficient approach to the α-hydroxyl ketones (Figure 3-1). In addition, the synthesis of α-ketone enol acetates is proved to be very straightforward (Figure 3-2).[7] Starting from the readily available diketones **4a-4g,** the α-ketone enol acetates **1a-1g** can be obtained through a one-step reaction. Herein, we report the asymmetric hydrogenation of α-ketone enol acetates catalyzed by Rh-DuanPhos (up to 99% ee), revealing an efficient approach to synthesize the enantiomerically pure α-hydroxy ketone derivatives (**2a-2g**).

Figure 3-2 The Synthesis of α-Ketone Enol Acetates.



Although the enol acetate has a similar structure to the enamide (Figure 3-3), the asymmetric hydrogenation of enol acetates is more challenging than that of enamides.[8] One possible reason is that the acyl group of the enol acetate has a weaker coordinating ability to the transition metal than the amide group of the enamide. It has been reported that both Rh-phosphine and Ru-phosphine catalytic systems have successfully catalyzed the hydrogenation of simple enol acetates. [5,9,11] Rh-DuPhos is the first effective catalyst for the asymmetric hydrogenation of enol acetates.[5a,5b] Rh-TangPhos was reported with up to 99% ee for the hydrogenation of enol acetates.[5f] Ru-TunePhos and Rh-PennPhos were found to be efficient for the hydrogenation of cyclic enol acetates (up to 99% ee).[5i,9] Rh-MonoPhos was also reported with up to 94% ee for the more difficult substrates: alkenyl carboxylates.[11] From the above examples, we envision that the alternative coordination group (Figure 3-3) would improve the binding capability of the substrates to the transition metal, resulting in a good enantioselectivity of the substrate **1a**. In order to find the most efficient catalyst, several ligands were screened for the proposed reaction: the asymmetric hydrogenation of α-ketone enol acetates **1**.

Figure 3-3 Substrates of enamides and enol acetates and their derivatives.



As shown in Table 3-1, the chiral phosphine ligands: TangPhos, DuanPhos, Et-DuPhos, MonoPhos, and C_2-TunePhos were tested using the standard substrate **1a**. Rh-DuanPhos was found to be the most efficient with 92% ee. Rh-TangPhos also gave good enantioselectivity of 89% ee, but the side product **3a** was generated. Ru-TunePhos gave poor conversion and chemoselectivity (Table 3-1, Entry 5). In case of the C_2-TunePhos, a Ruthenium precursor instead of a Rhodium precursor is tested. The reason is that the ligand with two phenyl groups on the chiral phosphine (like BINAP[13] and TunePhos) is less electron-rich than the alkyl substituted phosphine ligands (like DuPhos, TangPhos, and DuanPhos). Therefore, TunePhos generally has better activity with a Ruthenium precursor. This also explains why Ru-TunePhos was applied in the hydrogenation of cyclic enol acetates[5i].

Figure 3-4 Structures of TangPhos[5f,8a], DuanPhos[12a], DuPhos[5a], MonoPhos[11], and C_2-TunePhos[12b].

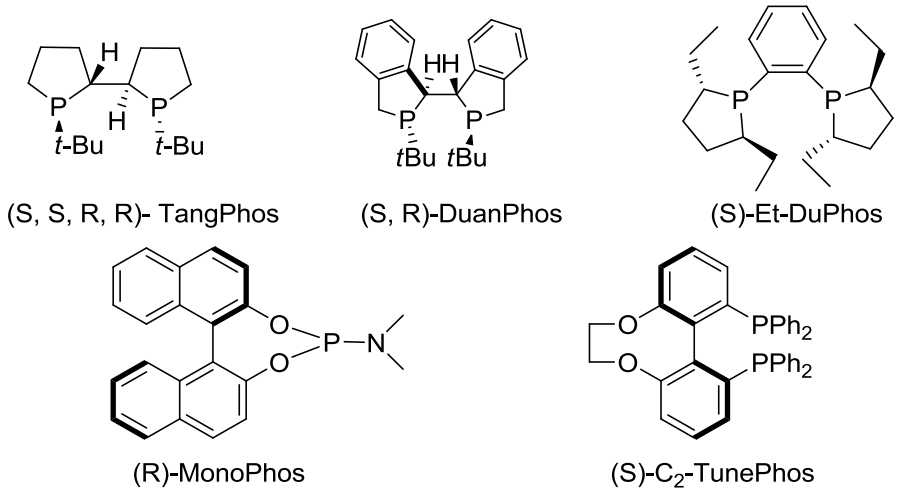
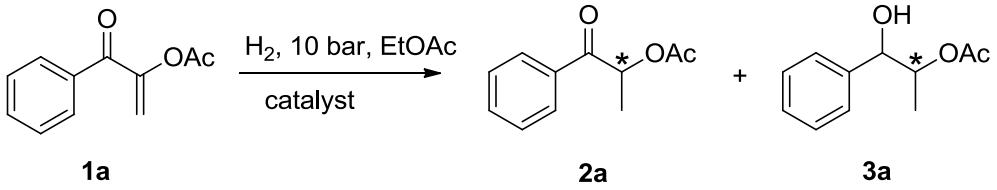


Table 3-1 Ligand Screening for Asymmetric Hydrogenation of α-Ketone Enol Acetate **1a**.



1a **2a** **3a**

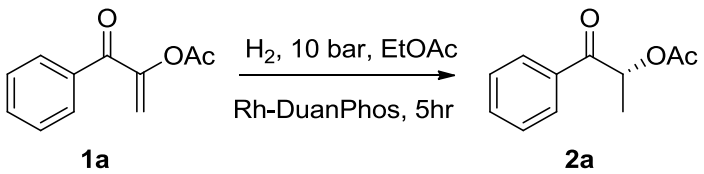
Entry	*Precursor*[a]	*Ligand*	P_{H2}[b] *(Bar)*	*con*[c] *(%)*	***2a:3a***	*ee*[d] *(%)*
1[e]	$Rh(COD)_2BF_4$	(S,S,R,R)-TangPhos	10	100	80:20	89
2[e]	$Rh(COD)_2BF_4$	(S,R)-DuanPhos	10	100	95:5	91
3[e]	$Rh(COD)_2BF_4$	(S)-Et-DuPhos	10	100	90:10	89
4[f]	$Rh(COD)_2BF_4$	(R)-MonoPhos	10	0	n.a.	n.a.
5[g]	$[RuCl_2(\eta^6\text{-}C_6H_6)]_2$	(S)-C_2-TunePhos	10	20	50:50	0
6[e]	$Rh(COD)_2BF_4$	(S,S,R,R)-TangPhos	5	90	85:15	89
7[e]	$Rh(COD)_2BF_4$	(S,S,R,R)-TangPhos	1	0	n.a.	n.a.
8[h]	$Rh(COD)_2BF_4$	(S,S,R,R)-TangPhos	20	100	80:20	88
9[h]	$Rh(COD)_2BF_4$	(S,R)-DuanPhos	10	100	100:0	92
10[h]	$Rh(COD)_2BF_4$	(S,R)-DuanPhos	20	100	100:0	92

[a]Complexes: [Rh(COD)(S_c,R_p)-DuanPhos]BF_4, [Rh(COD)(S,S,R,R)-TangPhos]BF_4, [Rh(COD)(*S*)-Et-DuPhos]BF_4, and [RuCl(benzene)(S)-C_2-TunePhos]Cl are used in the reaction. The Rh-MonoPhos catalyst is generated in situ.
[b]P_{H2} measures pressure of the hydrogen gas, using 'Bar' as the unit.
[c]con(%) measures the conversion of starting material **1a** and is determined by ^{1}H NMR spectroscopy of the crude products.

[d]ee (%) measures the enantiomeric excess of 2a.
[e]Reaction condition: Metal-Ligand Complex : **1a** =1:100, room temperature,12 hours, in EtOAc.
[f]Reaction condition: $[Rh(COD)_2]BF_4$:MonoPhos: **1a** = 1:2:100, room temperature, 12 hours, in EtOAc.
[g]Reaction condition: [RuCl(benzene)(S)-C_2-TunePhos]Cl : **1a** =1:100, room temperature, 12 hours, in MeOH. We have also tested the ligand C_3-TunePhos, resulting in no reaction.
[h]Reation condition: Metal-Ligand Complex: **1a** = 1:100, room temperature, 5 hours, in EtOAc.

Further experiments with Rh-DuanPhos and Rh-TangPhos revealed strong pressure effects. We have tried to reduce the hydrogen gas pressure to avoid generating side product **3a**. However, when the hydrogen gas pressure was 5 bar (Table 3-1, Entry 6), **3a** was still generated using Rh-TangPhos. When the hydrogen gas pressure was reduced to 1 bar, no reaction was observed (Table 3-1, Entry 7). We also found out that if the reaction time was kept within 5 hours, we could guarantee the 100% chemoselectivity of **2a** over **3a** even under a higher hydrogen gas pressure (20 bar) using Rh-DuanPhos (Table 3-1, Entry 10). Therefore, we selected Rh-DuanPhos for further experiments, and ran the experiments under 10 bar for 5 hours. As shown in Table 3-2, dramatic solvent effects were observed in this hydrogenation reaction. The highest enantioselectivity was obtained when ethyl acetate was used as the solvent.

Table 3-2 Optimization of Reaction Conditions for Rh- DuanPhos Catalyzed Hydrogenation of α-Ketone Enol Acetate **1a**.



1a **2a**

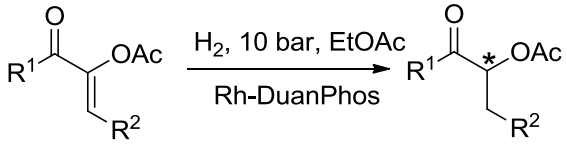
Entry[a]	*Ligand*	*Solvent*	*con(%)*[b]	*ee (%)*[c]
1	DuanPhos	EtOAc	>99	92
2	DuanPhos	Methnol	>99	80
3	DuanPhos	THF	>99	85
4	DuanPhos	CH_2Cl_2	0	n.a.
5	DuanPhos	Toluene	0	n.a.

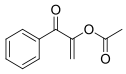
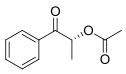
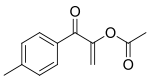
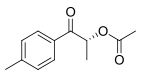
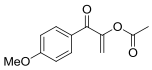
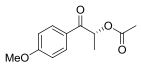
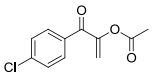
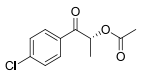
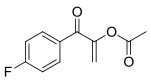
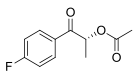
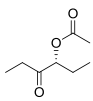
[a]Reation condition: [Rh(COD)(S_c,R_p)-DuanPhos]BF_4 : **1** = 1:100, room temperature,10 bar, 5 hours.
[b]Conversion is determined by ^{1}H NMR spectroscopy of the crude products.[c]ee is determined by chiral HPLC.

With optimized reaction conditions, several other α-ketone enol acetates were examined. As shown in Table 3-3, the substrates can be classified into two groups: aromatic α-ketone enol acetates (**1a**-**1e**) and aliphatic α-ketone enol acetates (**1f** and **1g**). To our delight, the synthesis of aliphatic substrates **1f** and **1g** were highly efficient with over 90% yield. As shown in Figure 3-2, **4g** was readily converted into **1g** without generating the side product **5g**. The asymmetric hydrogenations of **1f** and **1g** achieved up to 99% enantioselectivities. However, the asymmetric hydrogenations of substituted aromatic α-ketone enol acetates (**1b**-**1e**) had lower enantioselectivities. For the electron withdrawing group substituted substrates **1d** and **1e**, the enantioselectivities dropped to 85% and 88%. The conversion of **1e** to **2e** was only 60%. Comparing aliphatic substrates (**1f**-**1g**) with aromatic substrates (**1a**-**1e**), we discovered that the aliphatic substrates significantly outperformed the aromatic substrates. The reason might be that the phenyl

substitute group served as an unnecessary coordinating group, and disrupted the coordination of the acetyl group to the transition metal. To the best of our knowledge, none of the substrates have been tested by asymmetric hydrogenations before.

Table 3-3 Asymmetric Hydrogenation of α-Ketone Enol Acetates Catalyzed by Rh-DuanPhos.



Substrate[a]		*Product*		*con(%)*[b]	*ee (%)*[c]
	**1a**		**(*R*)-2a**	>99	92
	**1b**		**(*R*)-2b**	>99	90
	**1c**[b]		**(*R*)-2c**	>99	90
	**1d**[b]		**(*R*)-2d**	>99	85
	**1e**[b]		**(*R*)-2e**	60	88
	**1f**		**(*S*)-2f**	>99	**99**
	**1g**		**(*S*)-2g**	>99	**98**

[a]Reation condition: [Rh(COD)(S_c,R_p)-DuanPhos]BF_4: **1** = 1:100, room temperature,10 bar, 5 hours, in EtOAc.

[b]Conversion is determined by ^{1}H NMR spectroscopy of the crude products.[c]ee is determined by chiral HPLC and GC.

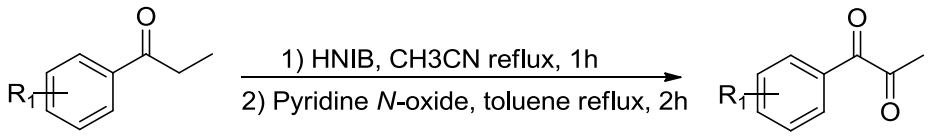
3.3 Conclusion

In conclusion, we have applied DuanPhos for the asymmetric hydrogenation of various substituted α-ketone enol acetates. High enantioselectivities have been observed for most of the tested substrates. The presented results demonstrate that DuanPhos is a very efficient hydrogenation ligand for the synthesis of chiral α-hydroxyl ketones.

Experimental Section

General: Unless otherwise noted, all reagents and solvents were purchased from commercial suppliers and used without further purification. NMR spectra were recorded on 400 MHz for ^{1}H NMR and ^{13}C NMR. $CDCl_3$ was the solvent used for the NMR analysis. Chemical shifts were reported in ppm downfield from internal Me_4Si. Optical rotations were determined using a Perkin Elmer 341 MC polarimeter. HRMS were recorded on a Thermo LTQ Orbitrap hybrid mass spectrometer. GC analyses were performed using Hewlett Packard Model HP 7890 Series. HPLC analysis was conducted on an Agilent 1200 Series instrument.

(A) General procedure for the synthesis of 1, 2-diketones 4b-4e.[22]

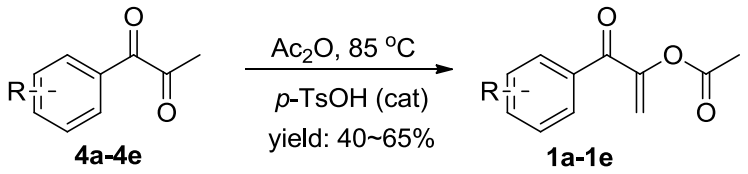


5b-5e **4b-4e**

A suspension of ketone (3.0 mmol) and [hydroxy(*p*-nitrobenzenesulfonyloxy) iodo]benzene (HNIB[2])(1.521 g, 3.6 mmol) in CH_3CN was refluxed for 1 h monitored by TLC. After reaction was complete, evaporate the solvent. To the resulting crude residue, add pyridine N-oxide (0.342g, 3.6 mmol) and toluene, reflux for 2 h and monitor the reaction by TLC. The reaction mixture was extracted with dichloromethane (2×25 mL) and washed with water (2×30 mL). The dichloromethane layer was separated and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column

chromatography (SiO_2, ethyl acetate:hexane=1:3) to give the desired 1,2-diketone as yellow oil.

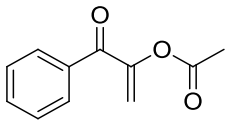
(B) Preparation and physical data for substrate 1a-1e.



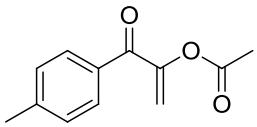
4a-4e **1a-1e**

R = H, *p*-Me,*p*-OMe, *p*-F, *p*-Cl

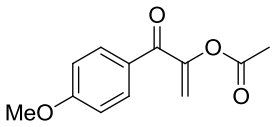
A catalytic amount of an acid (*p*-toluenesulfonic acid, TsOH) and Ac_2O (5 ml) was added to a stirred solution of **4** (20mmol) in toluene. The mixture was heated in a closed vial at 85 ^{0}C for 48hr. The reaction mixture was then washed with EtOAc and water thoroughly. The EtOAc layer was washed with saturated $NaHCO_3$ solution and water, dried over Na_2SO_4. Removing the solvent by rotary evaporation, the product mixture was purified by flash column chromatography using 25% ethyl acetate/hexane. Immediately refrigerate at -20^{0}C after pure product was obtained.



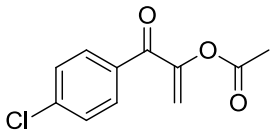
3-oxo-3-phenylprop-1-en-2-yl acetate (1a): Yield: 50%. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.76-7.68 (m, 2H, Ar-H). 7.47-7.49 (m, 1H, Ar-H).7.35-7.39 (m, 2H, Ar-H). 5.63 (s, 1H, Csp^2-H). 5.50 (s, 1H, Csp^2-H). 2.15 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.63, 167.66, 150.17, 135.21, 131.89, 128.48, 127.34, 113.45, 76.05, 19.35. Novel Compound: HRMS (EI) Calcd for $C_{11}H_{10}O_3$:190.06300. Found: 190.06313.



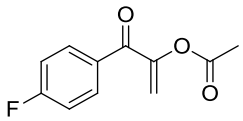
3-oxo-3-(p-tolyl)prop-1-en-2-yl acetate (1b): Yield: 50%. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.76-7.78 (d, 2H, Ar-H). 7.24-7.26 (d, 2H, Ar-H). 5.56 (s, 1H, Csp^2-H). 5.57 (s, 1H, Csp^2-H). 2.42 (s, 3H, CH_3). 2.22 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.28, 168.83, 151.31, 143.77, 129.69, 129.04, 113.76, 77.32, 77.06, 76.69, 21.62, 20.36. Novel Compound: HRMS (EI) Calcd for $C_{12}H_{12}O_3$:204.07865. Found: 204.07911.



3-(4-methoxyphenyl)-3-oxoprop-1-en-2-yl acetate (1c): Yield: 60%. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.88-7.90 (d, 2H, Ar-H). 6.93-6.96 (d, 2H, Ar-H). 5.65 (s, 1H, Csp^2-H). 5.53 (s, 1H, Csp^2-H). 3.88 (s, 3H, CH_3). 2.23 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.93, 163.63, 151.22, 132.00, 128.79, 113.68, 113.01, 55.50, 20.42. Novel Compound: HRMS (EI) Calcd for $C_{12}H_{12}O_4$:220.07356. Found: 220.07438.

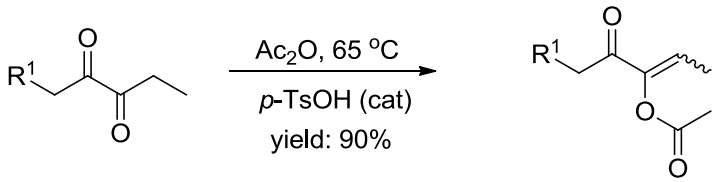


3-(4-chlorophenyl)-3-oxoprop-1-en-2-yl acetate (1d): Yield: 40%. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.02 (d, 2H, Ar-H). 7.80 (d, 2H, Ar-H). 5.70 (s, 1H, Csp^2-H). 5.54 (s, 1H, Csp^2-H). 2.22 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.53, 168.92, 150.97, 139.49, 134.52, 130.93, 128.78, 114.21, 20.37. Novel Compound: HRMS (EI) Calcd for $C_{11}H_9O_3Cl$: 222.00838. Found: 222.00776.



3-(4-fluorophenyl)-3-oxoprop-1-en-2-yl acetate (1e): Yield: 40%. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.89-7.92 (m, 2H, Ar-H). 7.12-7.16 (m, 2H, Ar-H). 5.69 (s, 1H, Csp^2-H). 5.53 (s, 1H, Csp^2-H). 2.22 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.18, 168.84, 151.07, 132.16, 132.09, 115.69, 115.47, 113.77, 77.30, 76.67, 20.29. Novel Compound: HRMS (EI) Calcd for $C_{11}H_9O_3F$: 208.05358. Found: 208.05317.

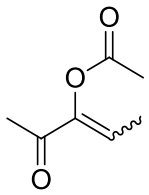
(C) Preparation and physical data for substrate 1f and 1g.



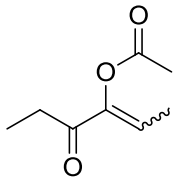
1f: R^1 = H
1g: R^1 = CH_3

4f: R^1 = H
4g: R^1 = CH_3

A catalytic amount of an acid (*p*-toluenesulfonic acid, TsOH) and Ac_2O (5 ml) was added to a stirred solution of **4** (20mmol) in toluene. The mixture was heated in a closed vial at 65 ^{0}C for 48hr. The reaction mixture was then washed with EtOAc and water thoroughly. The EtOAc layer was washed with saturated $NaHCO_3$ solution and water, dried over Na_2SO_4. Removing the solvent by rotary evaporation, the product mixture was purified by flash column chromatography using 25% ethyl acetate/hexane. Immediately refrigerate at -20^{0}C after pure product was obtained.



4-oxopent-2-en-3-yl acetate (1f): Yield: 90%. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.02 (d, 2H, Ar-H). 6.55-6.57 (m, 1H, Csp^2-H). 2.30 (s, 3H, CH_3). 2.27 (s, 3H, CH_3). 1.79-1.81 (d, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.17, 168.37, 147.31, 128.09, 25.09, 20.26, 11.82. Known Compound.[14]

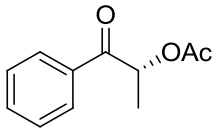


4-oxohex-2-en-3-yl acetate (1g): Yield: 90%. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 6.51-6.57 (m, 1H, Csp^2-H). 2.63-2.64 (m, 2H, CH_2). 2.26 (s, 3H, CH_3). 1.77-1.79 (d, 3H, CH_3). 1.13-1.09 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.14, 168.56, 146.95, 126.59, 112.15, 30.33, 20.33, 14.28, 11.64, 7.95. Known Compound.[15]

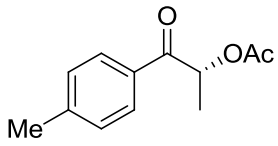
(D) General procedure for asymmetric hydrogenation of 1a-1g

The complex [Rh(COD)(S_c,R_p)-DuanPhos]BF_4 (3×10^{-4} mmol, 2.04 mg) was loaded with substrate **1a** (0.3 mmol) into a 10.0 ml vial. Ethyl acetate (3ml) was added into the vial at

room temperature in the glove-box. The vial was added with a magnetic stirring bar, and was placed into the Parr bomb (autoclave). The bomb was purged three times with H_2, and the pressure of H_2 was set to 10 bar (measured by the Parr bomb's pressure gauge). The hydrogenation reaction was performed at room temperature for 5 hours. After carefully releasing the hydrogen gas, the solvent was removed under reduced pressure. The crude product was purified through a silica gel plug, eluting with ethyl acetate, to afford product **2a**. The enantiomeric excess (ee) value was determined by chiral HPLC.

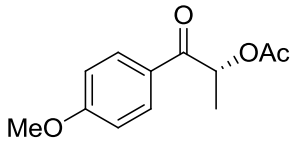


(R)-1-oxo-1-phenylpropan-2-yl acetate (2a): 92% ee. >99% yield. HPLC condition: Chiralpak OD-H column, Hex/IPA=96:4, 0.8 mL/min, t_{major}=11.3min, t_{minor}=7.5 min. $[\alpha]^{20}_D$=10.7 ° (c =1.0, $CHCl_3$). ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.93-7.96(m, 2H, Ar-H). 7.58-7.60 (m, 1H, Ar-H). 7.41-7.50 (m, 2H, Ar-H). 5.96-5.98 (m, 1H). 2.12 (s, 3H, CH_3). 1.52-1.54 (d, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.37, 170.36, 144.46, 131.91, 129.44, 128.58, 71.33, 21.66, 20.72, 17.22. Known Compound.[16]

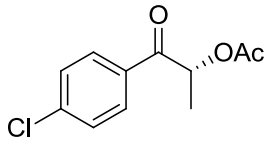


(R)-1-oxo-1-(p-tolyl)propan-2-yl acetate (2b): 90% ee. >99% yield. HPLC condition: Chiralpak OD-H column, Hex/IPA=95:5, 1.0 mL/min, t_{major} = 21.1 min, t_{minor} = 14.2 min. $[\alpha]^{20}_D$=-2.0 (c =1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83-7.85(d, 2H, Ar-H). 7.26-7.28 (d, 2H, *J* = 8.0 Hz, Ar-H). 5.94 - 5.96 (m, 1H). 2.32(s, 3H, CH_3). 2.14 (s, 3H,

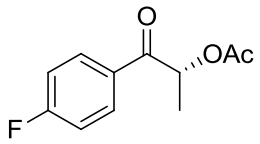
CH_3). 1.51-1.53 (d, 3H, *J* = 8.0 Hz CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.37, 170.36, 144.46, 131.91, 129.64, 128.58, 71.33, 21.66, 20.72, 17.22. Known Compound.[17]



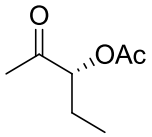
(R)-1-(4-methoxyphenyl)-1-oxopropan-2-yl acetate (2c): 90% ee. >99% yield. HPLC condition: Chiralpak OD-H column, Hex/IPA=97:3, 1.0 mL/min, t_{major} = 37.1 min, t_{minor} = 19.1 min. $[\alpha]^{20}_D$=5.0(c =1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.92-7.95(d, 2H, *J* = 8.0 Hz, Ar-H). 6.94-6.06 (d, 2H, *J* = 8.0 Hz, Ar-H). 5.92-5.97 (m, 1H). 3.88(s, 3H, CH_3). 2.15 (s, 3H, CH_3). 1.51-1.53 (d, 3H CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.23, 170.42, 163.89, 130.81, 127.25, 114.00, 71.14, 55.50, 20.77, 17.35. Known Compound.[18]



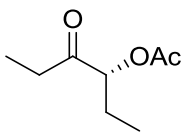
(R)-1-(4-chlorophenyl)-1-oxopropan-2-yl acetate (2d): 85% ee. >99% yield. HPLC condition: Chiralpak OD-H column, Hex/IPA=99:1, 0.6 mL/min, t_{major} = 21.3 min, t_{minor} = 19.2 min. $[\alpha]^{20}_D$= -9.5(c =1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.02-8.04(d, 2H, Ar-H). 7.87-7.89 (d, 2H, Ar-H). 5.88-5.90 (m, 1H). 2.13 (s, 3H, CH_3). 1.51-1.52 (d, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.79, 170.36, 132.83, 131.55, 129.84, 129.13, 71.31, 20.83, 16.98 . Known Compound.[19]



(R)-1-(4-fluorophenyl)-1-oxopropan-2-yl acetate (2e): 88% ee. 60% Yield. HPLC condition: Chiralpak OD-H column, Hex/IPA=97:3, 0.8 mL/min, t_{major} = 11.7 min, t_{minor} = 10.4 min. $[\alpha]^{20}_D$= -6.8(c =1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96-7.99(m, 2H, Ar-H). 7.13-7.16 (m, 2H, Ar-H). 5.92-5.90 (m, 1H). 2.14 (s, 3H, CH_3). 1.53-1.51 (d, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.36, 170.41, 167.25, 131.20, 131.10, 116.10, 115.88, 71.25, 20.69, 17.08. Novel Compound. HRMS (EI) Calcd for $C_{11}H_{11}O_3F$:210.06923. Found: 210.06868.



(R)-2-oxopentan-3-yl acetate (2f): 99% ee. >99% yield. GC condition: Beta dex 120 column, 85^{0}C,keep 10min to 120 ^{0}C. 1^{0}C /min. 1.0 mL/min, t_{major} = 18.9 min, t_{minor} = 19.2 min. $[\alpha]^{20}_D$= -21.4(c =1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.86 (m, 1H). 3.56 (m, 1H). 2.02(s, 3H). 1.58-1.43 (m, 4H). 0.99-0.95 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.84, 74.23, 55.30, 54.10, 27.50, 26.12, 25.50, 23.32, 21.31, 10.84, 10.42, 10.61, 10.02; Known Compound.[20]



(R)-4-oxohexan-3-yl acetate (2g): 99% ee. >99% yield. GC condition: Beta dex 120 column, 85^0C,keep 10min to 120 ^{0}C. 1^0C /min. 1.0 mL/min, t_{major} = 13.1 min, t_{minor} = 21.1 min. $[\alpha]^{20}_D$= -21.4(c =1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.96-4.99 (m, 1H). 2.44-2.52 (m, 2H). 2.15(s, 3H). 1.79-1.84 (m, 2H). 1.07-1.09 (m, 3H). 0.99-0.95 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.99, 170.67, 32.02, 23.99, 20.66, 9.62, 7.20. Known Compound.[21]

References

1. a) B. E. Rossiter, *Asymmtric Synthesis*, Morrison, J.D., Ed.; Academic Press: Orlando, Orlando, 1985 Vol. 5; b) R. Noyori, M. Kitamura, *Modern Synthetic Methods*, R. Scheffold, Ed., Springer: Heidelbery: 1989, Vol. 5; c) A. G. Chandhary, D. G. I. Kingston, *Tetrahedron Lett.* **1993**, *34*, 4921; d) J. Du Bois, C. S. Tomooka, J. Hong, E. M. Carreira, *Acc. Chem. Res.* **1997**, *30*, 364; e) J. K. Whitesell, C. M. Buchanan, *J. Org. Chem.* **1986**, *51*, 5443.
2. a) S. Hanessian, *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon Press: New York, New York, 1983, Chapter 2; b) W. Oppolzer, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 876; c) M. T. Reetz, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556; d) S. Masamune, W. Choy, J. S. Petersen, L.R. Sita, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1.
3. a) M. P. Gore, J. C. Vederas, *J. Org. Chem.* **1986**, *51*, 3700; b) D. Enders, V. Bushan, *Tetrahedron Lett.* **1988**, *29*, 2437; c) F. A. Davis, M. S. Hakue, *J. Org. Chem.* **1986**, *51*, 4083; d) F. A. Davis, C. Clark, A. Kumar, B. C. Chen, M.S. Hakue, *J. Am. Chem. Soc.* **1990**, *112*, 6679; e) F. A. Davis, C. Clark, A. Kumar, B. Chen, *J. Org.Chem.* **1994**, *59*, 1184; f) W. Adam, F. Prechtl, *Chem. Ber.* **1994**, *127*, 667; g) W. Adam, R. Fell, V. R. Stegman, C. R. Saha-Moller, *J. Am. Chem. Soc.* **1998**, *120*, 708.
4. a) R. Csuk, B. I. Glanzer, *Chem. Rev.* **1991**, *91*, 49; b) K. Nakamura, S. I. Kondo, Y. Kawai, K. Hida, K. Kitano, A. Ohno, *Tetrahedron: Asymmetry* **1996**, *7*, 409; c) Y. Kawai, K. Hida, M. Tsujimoto, S. Kondo, K. Kitano, K. Nakamura, A. Ohno, *Bull. Chem. Soc. Jpn.* **1999**, *72*; d) T. Koike, K. Muruta, T. Ikariya, *Org. Lett.* **2000**, *2*, 3833; e) P. Muthupandi, G. Sekar, *Tetrahedron: Asymmetry*, **2011**, *22*, 512; f) J. F. Briere, S. Oudeyer, V. Dalla, V. Levacher, *Chem. Soc. Rev.*, **2012**, *41*, 1696.
5. a) M. J. Burk, *J. Am. Chem. Soc.* **1991**, *113*, 8518; b) M. J. Burk, C. S. Kalberg, A. J. Pizzano, *J. Am. Chem. Soc.* **1998**, *120*, 4345; c) M. Lotz, T. Ireland, J. J. Almena Perea, P. Knochel, *Tetrahedron: Asymmetr*, **1999**, *10*, 1839; d) N. W. Boaz, *Tetrahedron Letters* **1998**, *39*, 5505; e) Y. Kuroki, D. Asada, Y. Sakamaki, K. Iseki, *Tetrahedron Letters* **2000**, *41*, 4603**;** f) W. Tang, D. Liu, X. Zhang, *Org. Lett.* **2003**, *5*, 205; g) L. Qiu, J. Wu, S. Chan, T. T.-L. Au-Yeung, J. X. Ji, R. Guo, C. C. Pai, Z. Zhou, X. Li, Q. H. Fan, A. S. C. Chan, *PNAS* **2004**, *101*, 5815; h) T. Ohta, T. Miyake, N. Seido, H. Kumobayashi, H. Takaya, *J. Org. Chem.* **1995**, *60*, 357; i) S. Wu, W. Wang, W. Tang, M. Lin, X. Zhang, *Org. Lett.* **2002**, *4*, 4495; g) H. M. Jung, J. H. Koh, M. J. Kim, *Org. Lett.* **2000**, *2*, 2487; h) N. S. Shaikh, S. Enthaler, K. Junge, M. Beller, *Angew. Chem.* **2008**, *120*, 2531; *Angew. Chem. Int. Ed*. **2008**, *47*, 2497; i) B. K. Langlotz, H. Wadepohl, L. H. Gade, *Angew. Chem.* **2008**, *120*, 4748; *Angew. Chem. Int. Ed.* **2008**, *47*, 4670; g) A. Mikhailine, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2009**, *131*, 1394.
6. T. Sun, G. Hou, M. Ma, X. Zhang, *Adv. Synth. Catal.* **2011**, *353*, 253.
7. The α-ketone acetates was synthesized by the one-step reaction of commercially available α-diketones in dehydrated Acetic anhydride. From more details, please refer to the supporting information.

8. a) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029; b) B. T. Cho, *Chem. Soc. Rev.* **2009**, *38*, 443; c) J. H. Xie, S. F. Zhu, Q. L. Zhou, *Chem. Rev*. **2011**, *111*, 1713; d) R. H. Morris, *Chem. Soc. Rev*. **2009**, *38*, 2288; e) J. Chen, W. Zhang, H. Geng, W. Li, G. Hou, A. Lei, X. Zhang, *Angew. Chem.* **2009**, *121*, 814; *Angew. Chem. Int. Ed.* **2009**, *48*, 800; f)F. W. Partureau, S. de Boer, M. Kuil, J. Meeuwissen, P. A. R. Breuil, M. A. Siegler, A. L. Spek, A. J. Sandee, B. de Bruin, J. N. H. Reek, *J. Am. Chem. Soc.* **2009**, *131*, 6683; g) C. Li, J. Xiao, *J. Am. Chem. Soc*. **2008**, *130*, 13208.
9. Q. Jiang, D. Xiao, Z. Zhang, P. Cao, X. Zhang, *Angew. Chem.* **1999**, *4*, 578; *Angew*. *Chem.*, *Int. Ed.* **1999**, *38*, 516.
10. a) M. T. Reetz, L. J. Goossen, A. Meiswinkel, J. Paetzold, J. F. Jensen, *Org. Lett.* **2003**, *5*, 3099; b) L. Panella, B. L. Feringa, J. G. de Vries, A. J. Minnaard, *Org. Lett.* **2005**, *7*, 4177.
11. a) M. Van den Berg, A. J. Minnaard, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* **2000**, *122*, 11539; b) M. van den Berg, A. J. Minnaard, R. M. Haak, M. Leeman, E. P. Schudde, A. Meetsma, B. L. Feringa, A. H. M. de Vries, C. E. P. Maljaars, C. E. Willans, D. Hyett, J. A. F. Boogers, H. J. W. Henderickx, J. G. de Vries, *Adv. Synth. Catal.* **2003**, *345*, 308.
12. a) D. Liu, X. Zhang, *Eur. J. Org. Chem.* ***2005***, *4*,646; b) C.-J. Wang, X. Sun, X. Zhang, *Synlett*, **2006**, *38*, 1169-1172
13. R. Noyori, M. Kitamura, T. Ohkuma, *PNAS*, **2004**, *15*, 5356.
14. J.T. Kung, Epstein, Martin Franklin ,From U.S. **1977**, US 4051164 A 19770927.
15. a) Grab, Willi, PCT Int. Appl. (**2008**), WO 2008011742 A1 20080131. b) Light, Kenneth K. U.S. (**1975**), US 3928419 A 19751223.
16. a) H. Ohta, *Chemistry Letters* **1986**, *7*, 1169. b) M. Fujita, *Journal of Organic Chemistry* **1988**, *23*, 5405 c) M. P. DeNinno, *Tetrahedron Letters* **1990**, 51, 7415. d) K. Bogar, *Organic Letters* **2007**, 17, 3401.
17. J. C. Lee, Y. S. Jin, J. H. Choi, *Chemical Communications (Cambridge, United Kingdom)* **2001**, *11*, 956.
18. G. Cahiez, E. Metais, *Tetrahedron Lett*. **1995**, *36*, 6449.
19. T. H. Duh, Y. F. Wang, M. J. Wu, *Tetrahedron: Asymmetry* **1993**, *8*, 1793.
20. N. Matsuo, T. Yano, H. Yoshioka, S. Kuwahara, K. Mori, *Agricultural and Biological Chemistry* **1981**, *45*, 1915.
21. J. R. Zoeller, C. J. Ackerman, *Journal of Organic Chemistry* **1990**, 55, 1354.
22. For detailed experimental data of diketones (**4b**-**4f**), please refer to the supporting information of the publication: T. Sun, G. Hou, M. Ma, X. Zhang, *Adv. Synth. Catal*. **2011**, *353*, 253.

Chapter 4

Air-stable chiral secondary phosphine oxides in catalysis

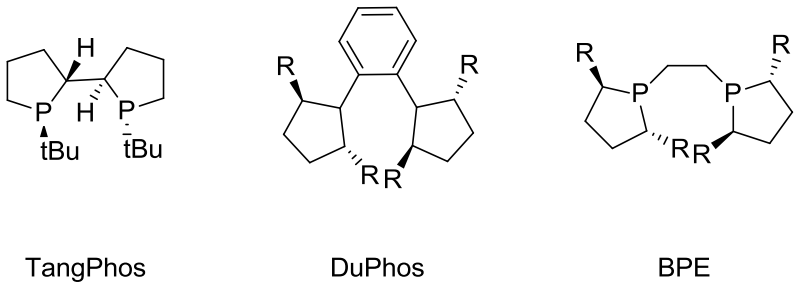
4.1 Introduction

Enantioselective transformations have attracted broad interests because of their importance in the preparation of numerous chiral building blocks. In principle, the asymmetric catalytic technology is the most desirable method for producing enantiopure chemicals. Compared to the method based on the resolution of racemic mixtures, the asymmetric catalytic methods provide much higher atom economy. Transition metal complexes play an important role in such transformations, and several phosphorous ligands associated with transition metals have been developed[1].

4.1.1 Advantages and limitations of bisphosphine ligands

Since the first bisphosphine ligand, DIOP [2], was developed by Knowles, many bisphosphine ligands have been reported with high enantioselectivities. Following the pioneering ligands like DuPhos, TangPhos, and Duanphos[3], more and more efficient chelating bisphosphine ligands have been discovered with high enantioselectivities and activities (Figure 4-1). The rigid structure and well defined geometry of phosphorus ligands provide high enantioselectivity. Also, the high activity (high turnover number) is achieved because of the desirable electronic properties of these ligands. For example, electron donating ligands are very efficient for the activation of aryl chloride in cross coupling.

Figure 4-1 Representative bisphosphine ligands.



TangPhos DuPhos BPE

Despite the abundance of bisphosphine ligands, the applications in large scale industrial processes are still rare because of several limitations. First of all, many ligands require complicated synthetic steps including the resolution of racemates. Second, many ligands are air sensitive, which brings many difficulties in manufacturing, storage and application. For instance, many synthetic steps of ligands require nitrogen protection. Last but not least, the activity of current catalytic system still needs to be further enhanced for the industrial production. Demand for more active ligands continues to grow, which encourages us to further modify the electron properties of phosphorus ligands. As a result, air-stable, easy accessible ligands with high selectivity and activity need to be developed to further expand the applications of phosphorus ligands.

4.1.2 Two approaches to conquer the limitations of bisphosphine ligands

Several approaches can be used to further develop the current ligand system. Here, two significant approaches are explored. First, Self-assembly chiral phosphorus ligands can be easily obtained by using natural chiral compounds[4]. Although the performance of these ligands needs to be improved, it gives the possibility to simplify the synthetic route and to maintain the well-defined geometry by self-assembly interactions (Figure 4-2). Second, some air-stable monophosphorus[5] ligands show comparable enantioselectivity as bisphosphorus ligands (Figure 4-3). These monophosphorus ligands can serve as candidates for easy accessible and air-stable ligands.

Figure 4-2 Self-assembly phosphorus ligands[4].

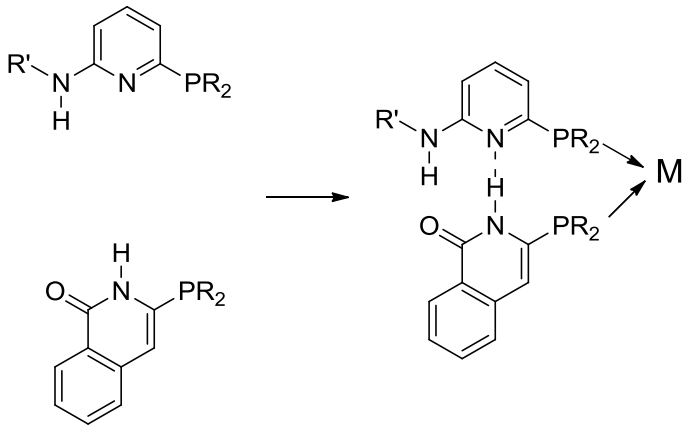
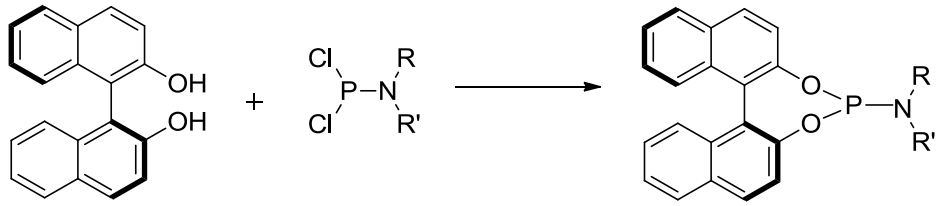


Figure 4-3 MonoPhos and its preparation[5]



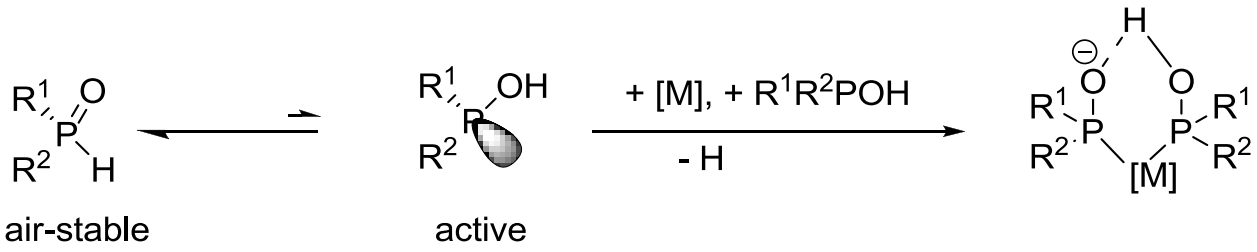
4.1.3 Chiral secondary phosphine oxides as ligands

Encouraged by the above two approaches, we design a new generation of secondary phosphorus ligands, which are monodentate but also can have a well-defined structure by self-assembly. In this section, we will explain the chiral secondary phosphine oxides in details.

Chiral secondary phosphine oxides were used as air- and moister-stable ligand precursors recently. Secondary phosphine oxides exist as equilibrium between pentavalent and trivalent tautomeric structures [6] (Figure 4-4). At room temperature, the air-stable pentavalent tautomer predominates. However, only trivalent phosphorus showed reactivity as ligand. In the presence of late-transition metals, the equilibrium is shifted to generate the trivalent phosphorus tautomer coordinating to the metal. As a result, the two tautomers contribute differently: the pentavalent tautomer helps resist to oxidation, while the trivalent tautomer coordinates to metal as catalyst. This means SPO ligands are air-stable and can be used as ligands. More importantly, secondary phosphine oxides can be easily synthesized from the corresponding phosphine chlorides and phosphoramides.

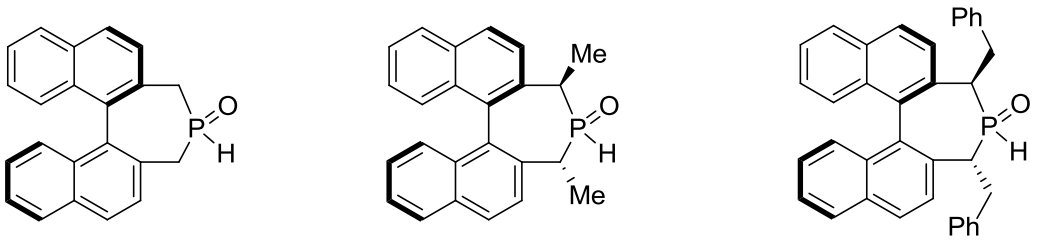
Therefore, the secondary phosphine oxides may fulfill the two requirements for industrial process: stability and readily availability.

Figure 4-4 Equilibrium of the SPO tautomers



Recently, several research groups have discovered that secondary phosphine oxides showed special catalytic reactivity in cross coupling reactions[7]. Asymmetric secondary phosphine oxides were also reported as preligand in asymmetric hydrogenation[8]. However, the enantiopure ligands were generated by expensive preparative chiral HPLC. In this research, we anticipate that the new class of chiral phosphorus ligands will maintain the high activity with simpler synthetic route (Figure 4-5).

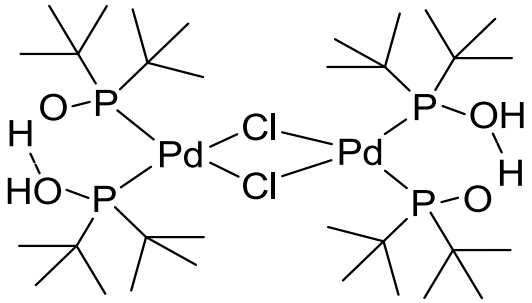
Figure 4-5 New generation of SPO ligand **1**



1a **1b** **1c**

As mentioned before, self-assembly interactions may provide well defined geometry. In 2001, Li's group reported a new Palladium-SPO complex (Figure 4-6). The hydrogen bond of this complex indicates an interesting self-assembly interaction. This phenomenon reveals that under certain conditions, the two mono-dentate SPO ligands associated with metal could form a linked bi-dentate species. With the hydrogen bond bridge, we can mimic the well-defined bisphosphines (Figure 4-7).

Figure 4-6 Structure of POPd1



4.1.4 BPE and BINAP structures

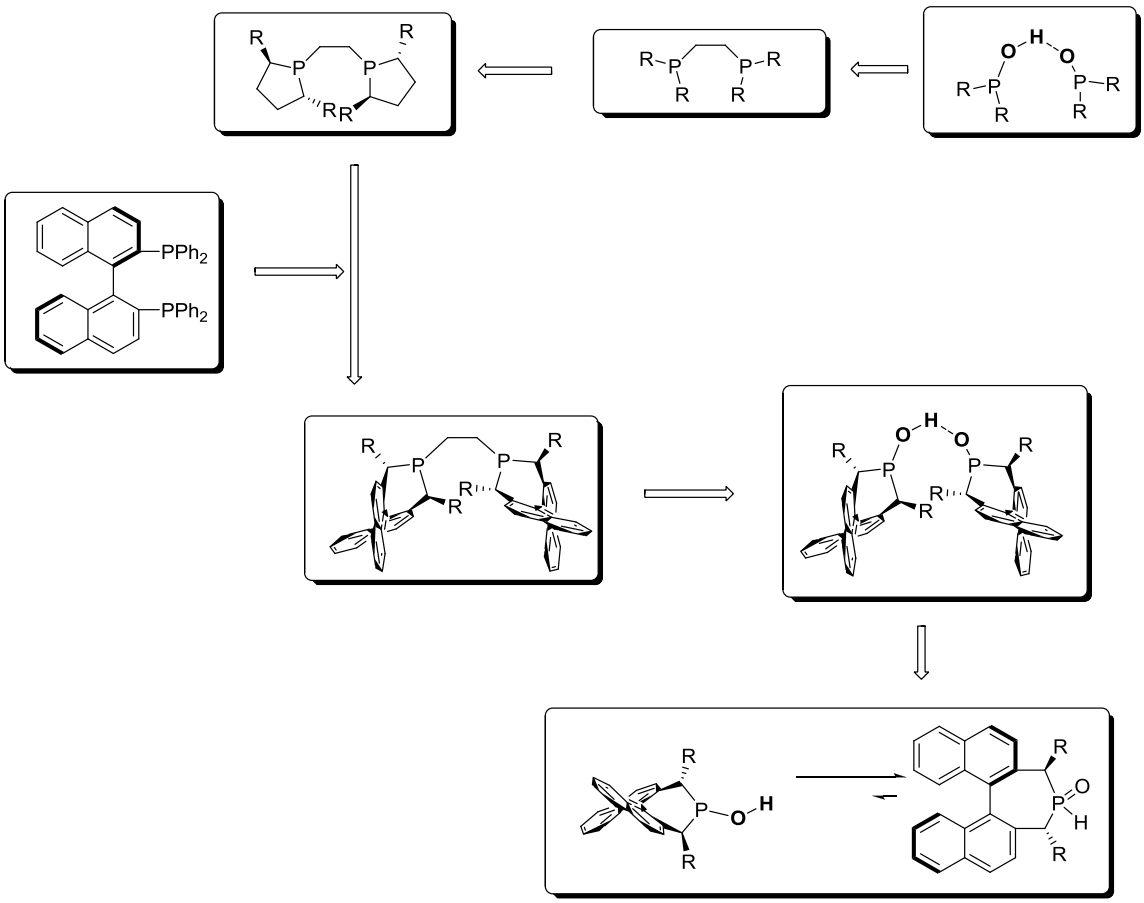
BPE[2] and BINAP[9] are two representative bisphosphines. The alkyl substituted BPE shows high catalytic activities in asymmetric hydrogenation because of the high electron donating property. The 2, 5-substituted structure provides high enantioselectivity. However, such alkyl substituted phosphines are extremely air sensitive and requires tedious synthetic steps.

Unlike BPE, the aryl substituted BINAP is relatively air-stable. BINAP can also get high enantioselectivity with the rigid structure of binaphthyl. However, the aryl substituted BINAP is less reactive than BPE.

4.1.5 Structure of New SPO Ligands

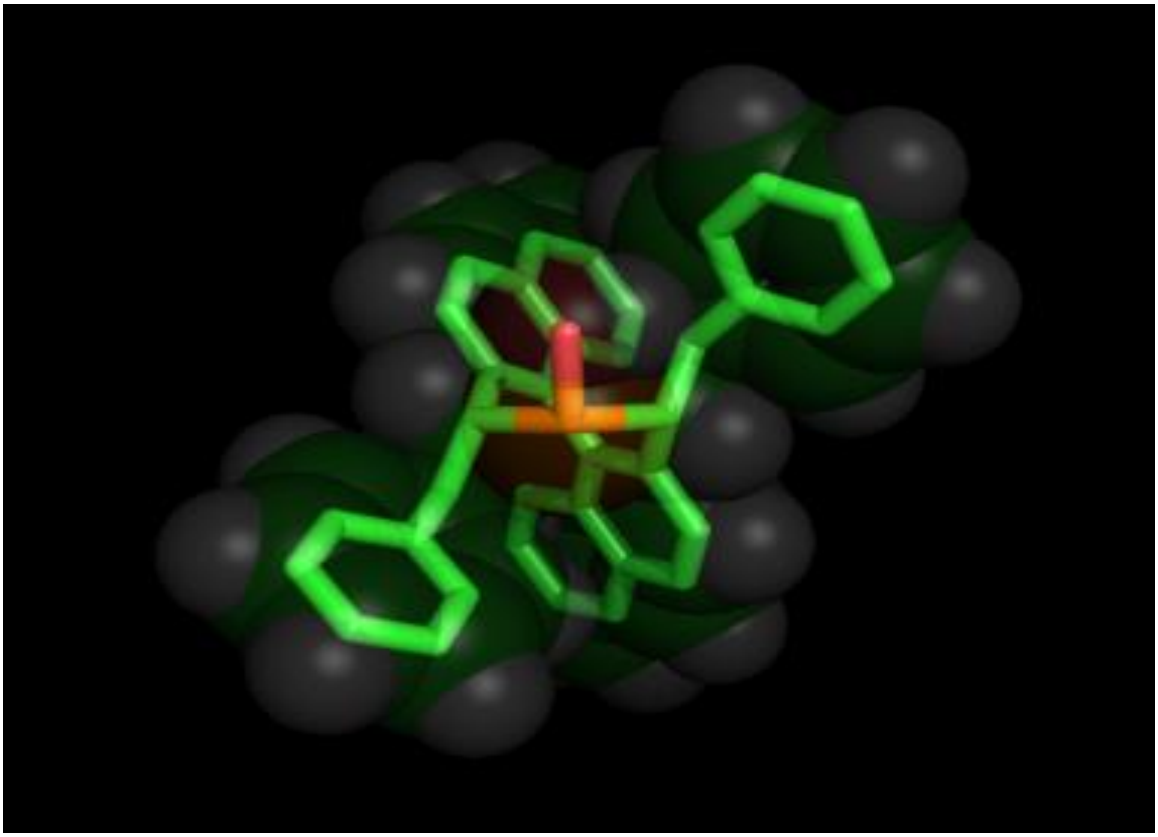
In our research, we found a way to combine the advantages of BINAP and BPE together. As showed in Figure 4-7, we designed a new alkyl substituted structure by using the BINAP chiral backbone. We anticipate that the new structure is more rigid than BPE and retains the electron donating property.

Figure 4-7 Design of ligand **1.**



The computational modeling of the ligand **1c** (Figure 4-8) with benzyl substitutes is generated by Maestro®. It notes that the ligand has a rigid and well-defined geometry. Two of the quadrants are blocked with benzyl groups whereas the other two quadrants are widely open. This modeling structure indicates the possibility of good enantioselectivity by its rigid geometry.

Figure 4-8 Computational model of ligand **1c.**



4.2 Results and Discussion

4.2.1 Synthesis of new SPO ligands (Figure 4-9)

Starting from commercially available optically pure (R)-BINOL, 2,2'-dimethyl-1,1'-binaphthyl was prepared in two steps with 88% overall yield. Using this compound, ligand **1a**, **1b**, and **1c** can be synthesized by different procedures. The synthesis of **1a** started from the deprotonation of both methyl groups by butyl lithium followed by the cyclization with Cl_2PNEt_2 to get compound **3**. Diethyl amine protecting group was removed by dry HCl in ether followed by hydrolysis resulted in 1a in 85% yield. The synthesis of α-substituted ligand **1b** and **1c** start from different protecting reagent-Cl_2PONEt_2 instead of Cl_2PNEt_2 to get compound **4**. Stepwise deprotonation on the α-position of the phosphorus and the S_{N2} reaction with alkyl halides gave **6a-d**. The similar ^1H NMR shifts of the two α-hydrogens clearly indicate that exo-configuration was exclusively formed. Reduction with trichlorosilane gave the final product **1b** and **1c**. The structure of ligand **1a**, **1b** and **1c** was confirmed by the signature large splitting of the hydrogen atom on the phosphorus from ^1H NMR. A single crystal X-ray analysis also provides a solid proof for the structure of **1b** (Figure 4-11). As we can see from the X-ray structure, the exo-configuration of the two substituents did not change during the reduction step.

Figure 4-9 Synthetic route of ligand **1a**, **1b** and **1c.**

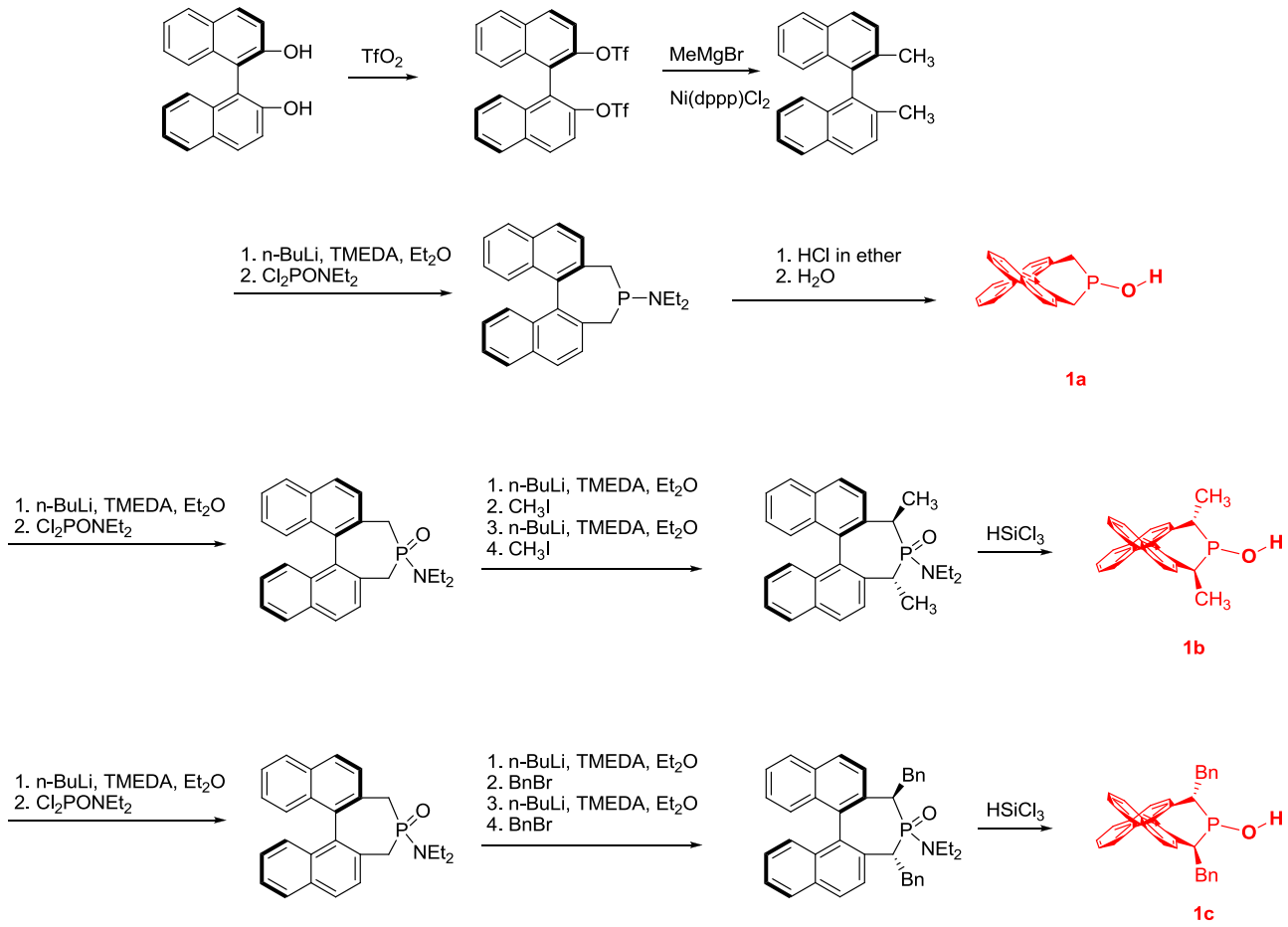
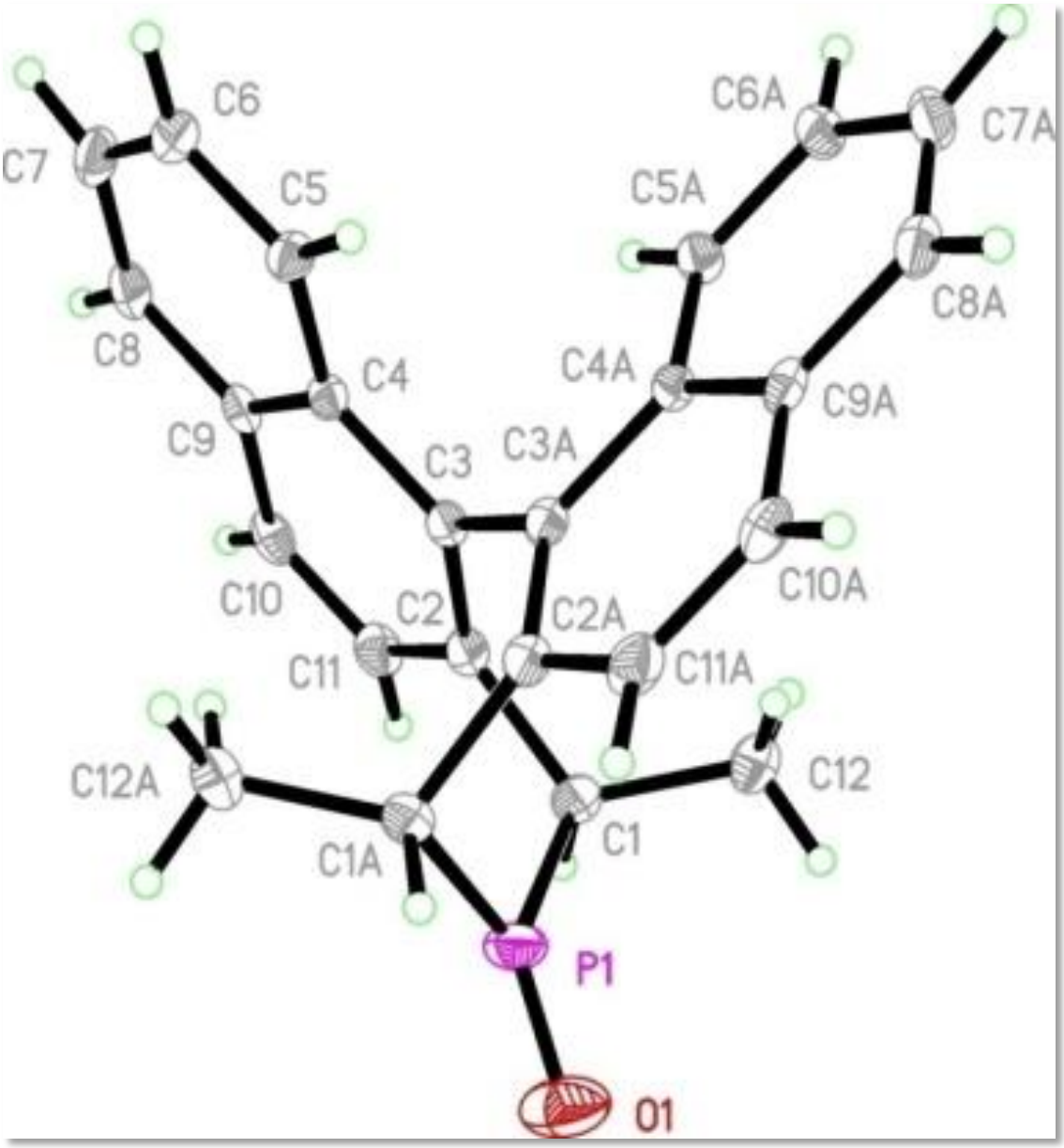


Figure 4-10 X-ray structure of ligand **1b.**



4.2.2 Preliminary results of asymmetric hydrogenation

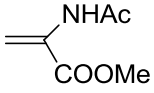
4.2.2.1 Preliminary results of asymmetric hydrogenation

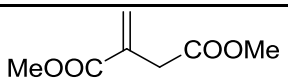
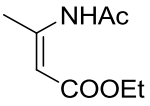
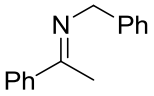
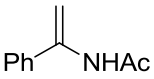
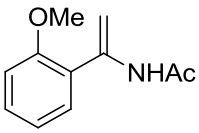
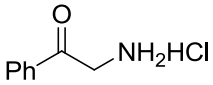
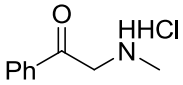
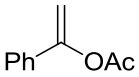
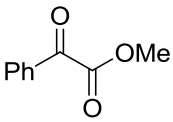
Asymmetric hydrogenation is a technique that enantioselectively reduces prochiral olefins, ketones, and imines by molecular hydrogen. This method is one of the efficient techniques to produce chiral compounds. Asymmetric secondary phosphine oxides were reported as preligand in asymmetric hydrogenation.

a). Asymmetric hydrogenation with ligand **1a**

We tested ligand **1a** as ligand for asymmetric hydrogenation for β-dehydroamino acids, itaconic acids, unfunctionalized imines, unsaturated esters and enamides (Table 4-1). The Rh complex has moderate to good activity with 18-100% conversion. Unfortunately, the enantioselectivity was poor. Only the α-primary amino ketone (entry 8) was enantioselectively reduced with acceptable 83% ee. Although ligand **1a** did not perform well, we anticipate that the more rigid structure of **1b** and **1c** will be better than **1a**.

Table 4-1 Asymmetric hydrogenation with Ligand **1a**[10]

entry[a]	**substrate**	**Solvent**	**conversion(%)**[b]	**ee(%)**[c]
1		CH_2Cl_2	73	14

2		CH_2Cl_2	100	1
3		CH_2Cl_2	70	22
4		CH_2Cl_2	<50	N.A.
5		CH_2Cl_2	100	17
6		MeOH		17
7		CF_3CH_2OH	>95	83
8		MeOH	>95	42
9		CH_2Cl_2	69	10
10		MeOH	18	0

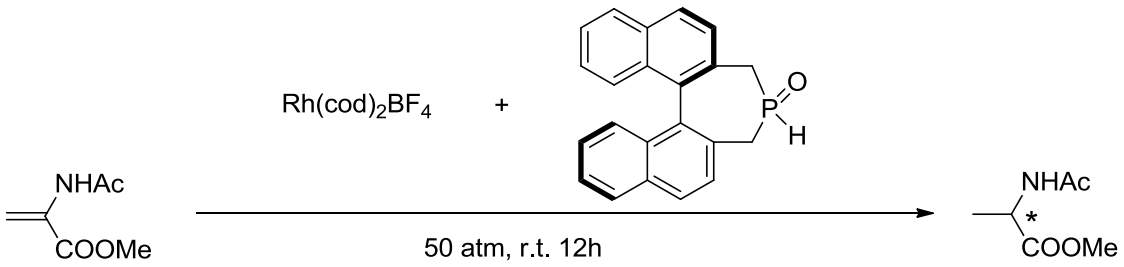
a. The hydrogenation was carried out with in situ made catalyst (Rh:**1a**:substrate= 0.01:0.005:1) at rt and 50 atm of H_2 pressure for 12 h.
b. conversions were based on ^{1}H NMR of crude product or GC analysis.
c. The enantiomeric excess was determined by chiral HPLC or chiral GC.

b) Solvent effect

We conducted an examination of solvent effect, because the solvent may have strong effects on the self-assembly interaction. Among the ten solvents that have been tested, the asymmetric hydrogenation of dehydroamino acid showed strong solvent dependence and

varied from 4%ee to 34%ee (Table 4-2). THF showed highest enantioselectivity with 34%ee, which implies the hydrogen bond formation between two mono-dentate SPO ligands. If we further adjust the reaction conditions, better selectivity can be expected.

Table 4-2 Solvent effect of the asymmetric hydrogenation of dehydroamino acid



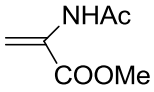
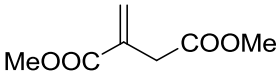
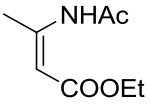
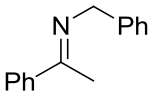
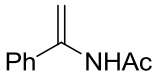
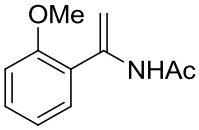
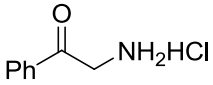
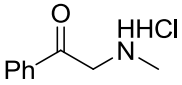
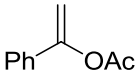
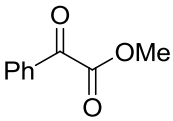
entry[a]	solvent	conversion(%)[b]	ee(%)[c]
1	MeOH	100	17
2	EtOH	100	19
3	*i*-PrOH	100	24
4	CF_3CH_2OH	100	12
5	EtOAc	100	11
6	Acetone	100	20
7	THF	100	34
8	Toluene	100	11
9	Heptanes	90	4
10	CH_2Cl_2	78	4

a. The hydrogenation was carried out with in situ made catalyst (Rh:1a:substrate= 0.01:0.005:1) at rt and 50 atm of H2 presure for 12 h.
b. conversions were based on 1H NMR of crude product or GC analysis.
c. The enantiomeric excess wasdetermined by chiral HPLC or chiral GC.

c) Asymmetric hydrogenation with ligand **1b** and **1c**

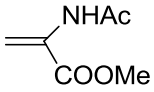
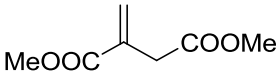
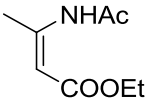
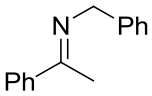
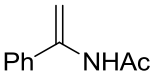
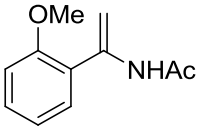
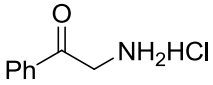
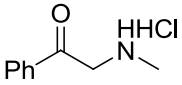
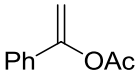
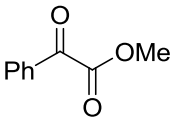
Ligand **1b** and **1c** should show better enantioselectivity, because they have more bulky structures with α-substitutes. However, no significant improvement was observed in the experiment (Table 4-3), the ee values even dropped for certain substrates. The unexpected poor results drove us to re-examine the X-ray structure. Although the structure is highly consistent with the calculated structure, the α-methyl group stretches away from phosphorus and fails to provide good shielding. Additionally, with α-substitutes, the hydrogen bond interaction might be broken due to stereo repulsion of more bulky SPO ligands comparing to **1a**.

Table 4-3 Asymmetric hydrogenation with ligand **1b**.

entry[a]	Substrate	solvent	conversion(%)[b]	ee(%)[c]
1		THF	100	9
2		THF	100	11
3		THF	100	18
4		THF	<5	N.A.
5		THF	100	20
6		THF	100	3
7		CF_3CH_2OH	>95	25
8		THF	>95	20
9		THF	>95	20
10		THF	100	20

a. The hydrogenation was carried out with in situ made catalyst (Rh:1a:substrate= 0.01:0.005:1) at rt and 50 atm of H_2 pressure for 12 h.
b. Conversions were based on ^{1}H NMR of crude product or GC analysis.
c. The enantiomeric excess was determined by chiral HPLC or chiral GC.

Table 4-4 Asymmetric hydrogenation with ligand **1c**.

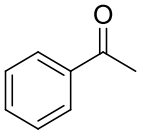
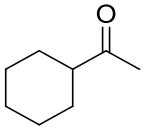
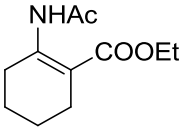
entry[a]	Substrate	solvent	conversion(%)[b]	ee(%)[c]
1		THF	100	20
2		THF	100	0
3		THF	100	0
4		THF	<5	N.A.
5		THF	100	18
6		THF	100	36
7		CF_3CH_2OH	<5	N.A.
8		THF	>95	20
9		THF	100	22
10		THF	100	1

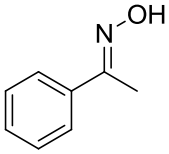
a. The hydrogenation was carried out with in situ made catalyst (Rh:**1a**:substrate= 0.01:0.005:1) at rt and 50 atm of H_2 presure for 12 h.
b. conversions were based on ^{1}H NMR of crude product or GC analysis.
c. The enantiomeric excess wasdetermined by chiral HPLC or chiral GC.

d) Asymmetric hydrogenation of challenging substrates

Several studies[7] of SPO ligands revealed that addition of base might increase the reactivity and promote a well-defined structure as mentioned before. Therefore, we tried the asymmetric hydrogenation of some challenging substrates such as simple ketones with addition of base. We found that the addition of a weak base 2, 6-lutidine increased the selectivity, however, decreased the reactivity (Table 4-5). Additionally, our ligands showed high activity even without base for the hydrogenation of ketones, which is rare comparing with current catalytic systems [11] . If we can further control the enantioselectivity by screening different conditions, our ligands may show special application in certain challenging topics.

Table 4-5 Asymmetric hydrogenation of challenging substrates.

entry[a]	substrate	additive[b]	ligand	conversion(%)[c]	ee(%)[d]
1		None	**1a**	100	0
2		2, 6-lutidine	**1a**	60	36
3		2, 6-lutidine	**1b**	100	0
4		2, 6-lutidine	**1c**	40	2
5		None	**1a**	100	0
6		2, 6-lutidine, KBr	**1a**	73	44
7		2, 6-lutidine, KBr	**1a**	10	26
8		2, 6-lutidine, KBr	**1b**	7	30
9		2, 6-lutidine, KBr	**1c**	40	26
10		None	**1a**	0	n.a.

11		None	**1a**	0	n.a.

a. The hydrogenation was carried out with in situ made catalyst (Rh:1a:substrate= 0.01:0.005:1) at rt and 50 atm of H_2 pressure for 12 h.
b. 0.8 equiv. 2, 6-lutidine to Rh. 1.0 equiv. of KBr to Rh.
c. Conversions were based on ^{1}H NMR of crude product or GC analysis.
d. The enantiomeric excess was determined by chiral HPLC or chiral GC.

Although the new chiral SPO ligands show poor to moderate results in asymmetric hydrogenation, we can explore their applications in broad fields. As mentioned in section 1.3, air-stable, easily accessible chiral SPO ligands systems start to gain lots of interests recently. The ligand **1**, as one of the few successfully synthesized chiral SPO ligands, requires further exploration and modification. Recent studies of SPO ligands in asymmetric hydrogenation and cross coupling in several research groups inspire the possible applications of our ligand **1**.

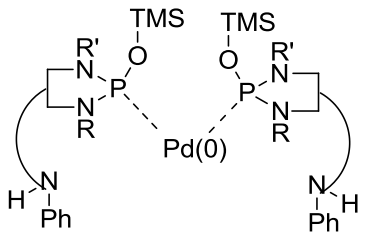
The mechanism study of SPO ligands in asymmetric hydrogenation is still rare. We are not clear about how ligand **1** coordinates to transition metal. Further examinations require isolated ligand-metal complex. In fact, we did try to isolate the Rh-ligand **1** complex several times. However, we failed to get clean crystals because the Rh complex was not very stable. In the future, we can first try to get palladium (II)-ligand **1** complexes, which supposed to be more stable. With the palladium complex, we may interpret the orientation of our ligands better, which will facilitate further modification.

If we look back at other asymmetric hydrogenation systems, we can see that many reactions require specific reaction conditions, and numerous studies of solvent effect, additive effects and temperature have been reported[12]. For our SPO ligand system, the study of solvent effects reveal the possibility of self-assembly; however, the screen of additives and other conditions are not developed. As a prototype, we only tried one additive (2, 6-lutidine) and KBr; while there are lots of additives like inorganic or organic bases, and weak or strong bases used in other ligand systems. We expect that screening of additives can further increase the enantioselectivity.

We illustrated the self-assembly interactions in section 4.1. However, given the current experiment results, two possibilities are still maintained. First, the formation of hydrogen bond might be uncontrollable. Second, the enantioselectivity could not be enhanced by self-assembly interactions. In either case, we need to explore alternative approaches to control the geometry of metal-ligand complex.

In fact, many monophosphorus ligands do not need the self-assembly interactions. For example, in the MonoPhos family, the amino group on the phosphorus provides a main shielding to block the quadrants. In ligand **1**, the OH group might not be bulky enough comparing with amino groups. If we can readily introduce a way to change the OH group into a more bulky one, we might get similar or even better enantioselectivity compared to the MonoPhos. Hamada's research inspired us[13]. With addition of BSA, OH group can be transferred into a more bulky OTMS group (Figure 4-11). If we follow a similar procedure, we may get the modified ligands isolated or generated in situ. These new generation of ligands may provide better enantioselectivities.

Figure 4-11 Hamada's Ligand

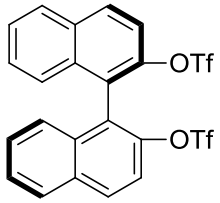


4.3 Conclusion

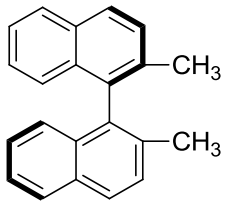
In conclusion, we have design and synthesized a new generation of air-stable, active and rigid secondary phosphine oxide (SPO) ligands. The examination for transition-metal-catalyzed asymmetric hydrogenation showed poor to moderate results. The ultimate goal of this research is to develop highly practical and efficient chiral SPO ligands.

Experimental Section[10]

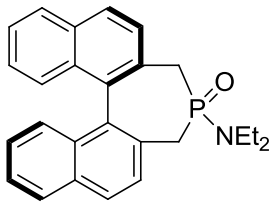
General Methods: All reactions and manipulations were performed in a nitrogen-filled glove box or under nitrogen using Schlenk techniques unless otherwise noted. Column chromatography was performed using Sorbent silica gel 60 Å (230×450 mesh). ^{1}H NMR and ^{13}C NMR spectral data were recorded on Bruker DPX-300, CDPX-300, AMX-360, DRX-400 MHz, Varian VNMRS 500 MHz and VNMRS 400 MHz spectrometers. Chemical shifts were reported in ppm with solvent resonance as the internal standard. MSspectra were recorded on a KRATOS mass spectrometer MS 9/50 for LR-APCI and HRAPCI.



(*R*)-1,1'-Binaphthyl-2,2'-diyl bis(trifluoromethanesulfonate): Pyridine (288 mL, 3.6 mol) was added to a solution of (R)-BINOL (344g, 1.2 mol) in 800 mL of CH_2Cl_2 (288 mL, 3.6 mol) and followed by dropwise addition of triflic anhydride (444 mL, 2.64 mol) in 600 mL of CH_2Cl_2 at 0 ^{o}C. The mixture was stirred at rt for 6 h. After removal of the solvent, the residue was diluted with ethyl acetate (2000 mL) and washed with 2N HCl (3 x 600 mL), saturated sodium bicarbonate (600 mL) and brine (600 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated and filtered through a silica gel plug (eluent: CH_2Cl_2 : EtOAc = 10:1) to give product as a white powder (615 g, 92%). ^{1}H NMR (CDCl3) 360 MHz : δ 7.27 (m, 2H), 7.42 (m, 2H), 7.59 (m, 2H), 7.63 (m, 2H), 8.02 (m, 2H), 8.15 (m, 2H).



(*R*)-2,2'-Dimethyl-1,1'-binaphthyl (2): To a solution of (*R*)-triflate (409 g, 0.74 mol) and Ni(dppp)Cl_2 (8.04 g, 0.0148 mol) in ethyl ether (2000 mL) was added dropwise methylmagnesium bromide (3.0 M in Et_2O, 800 mL, 2.4 mol) at 0 ^oC. The reaction mixture was heated at reflux for 3 h before being cooled to rt and quenched carefully with H_2O (400 mL) and 4 N HCl (400 mL). The aqueous phase was extracted with ethyl ether (3 x 500 mL). The combined organic phases was washed with $NaHCO_3$ (2 x 400 mL), brine (500 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude product was filtered through a silica gel plug (eluent: hexanes : EtOAc = 10:1) to produce the product as a yellow solid (201 g, 96%). ^1H NMR ($CDCl_3$) 360 MHz: δ 2.00 (s, 6H), 6.80-8.21 (m, 12H).



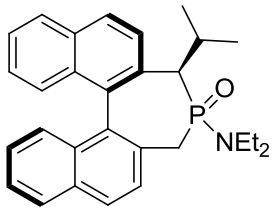
(*R*)-*N,N*-diethyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1',2'-*e*]phosphepine amide (3) A solution of *n*-BuLi in hexane (2.5 M, 213 mL, 0.532 mol) was concentrated under vacuum to half of its volume and 100 mL of dry ethyl ether and TMEDA (80 mL, 0.532 mol) were added at 0 ^oC. The resulting mixture was stirred for an additional 30 min before an ethyl ether solution of **2** (50 g in 500 mL) was added dropwise. The reaction

solution was allowed to warm to rt and stirred for 24 h. After recooling to 0 ^{o}C and stirring for 4 h, the resulting suspension was filtered under N_2 and rinsed with dry hexanes (2 x 50 mL). The dilithium TMEDA complex of **2** was obtained as a dark red powder (56.7 g, 61%).

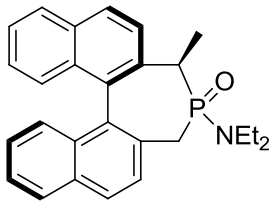
To an ether solution (80 mL) of diethylphosphoramidic dichloride (21.5 g, 0.108 mol), an ether suspension of the dilithium TMEDA complex of **2** was added in portions at -78 ^{o}C. The resulting mixture was stirred for 12 h before being quenched with H_2O (300 mL). The aqueous phase was separated and washed with CH_2Cl_2. The combined organic phase was concentrated and filtered through a silica gel plug (eluent: EtOAc) to give the product as a light yellow powder (15.5 g, 36%). ^{1}H NMR ($CDCl_3$) 400 MHz: δ 8.05-7.90 (m, 4H), 7.69-7.60 (m, 1H), 7.58-7.39 (3H), 7.30-7.18 (m, 3H), 7.13-7.08 (m, 1H), 3.22-3.03 (m, 3H), 3.03-2.90 (m, 5H), 1.06 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.5 (d, *J* = 3.7 Hz), 133.2 (d, *J* = 4.5 Hz), 132.7 (d, *J* = 3.0 Hz), 132.4 (d, *J* = 2.2 Hz), 132.3 (d, *J* = 2.2 Hz), 132.0 (d, *J* = 2.2 Hz), 131.86 (d, *J* = 8.2 Hz), 130.1 (d, *J* = 9.0 Hz), 129.1 (d, *J* = 2.2 Hz), 128.6 (d, *J* = 2.2 Hz), 128.5 (d, *J* = 4.4 Hz), 128.2, 128.1, 127.7 (d, *J* = 5.2 Hz), 127.0, 126.6 (d, *J* = 1.4 Hz), 126.3, 126.0, 125.5, 125.3, 38.9 (d, *J* = 2.3 Hz), 36.8 (d, *J* = 81.0 Hz), 34.4 (d, *J* = 78.1 Hz), 14.7 (d, *J* = 1.5Hz); ^{31}P NMR (161 MHz, $CDCl_3$): δ 59.6.

General procedures for the preparation of 4a-4c from 3 and for the preparation of 5a-c from 4 To a THF solution of **3** (1.0 g in 20 mL, 2.5 mmol) was added TMEDA (0.412 mL, 2.75 mmol) and *tert*-BuLi (1.7 M in pentane, 1.62 mL, 2.75 mmol) at -40 ^{o}C,

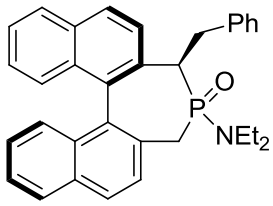
and the resulting dark red solution was stirred for 5 min before 5.0 equivalent of *i*PrI (1.25 mL, 12.5 mmol) was added. The reaction was stirred for another 30 min at -40 ^{o}C before it was warmed to rt and stirred overnight. After quenching the mixture with H_2O (10 mL), the aqueous phase was separated and extracted with CH_2Cl_2. The combined organic phases were concentrated and purified by silica gel chromatography (eluent: EtOAc).



(*R*, *Ra*, *SP*)-3-*iso*-propyl-*N*,*N*-diethyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1',2'-*e*]phosphepine amide (4a): White powder, 84% yield. ^{1}H NMR (CDCl3) 500 MHz: δ 7.90-7.78 (m, 4H), 7.60-7.56 (m, 1H), 7.40-7.28 (m, 3H), 7.19-7.08 (m, 4H), 3.20-3.12 (m, 1H), 2.93-2.80 (m, 5H), 2.80-2.70 (m, 2H), 1.02-0.94 (m, 9H), 0.24-0.20 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9 (d, *J* = 5.2 Hz), 133.8, 133.6 (d, *J* = 4.5 Hz), 132.65 (d, *J* = 1.5 Hz), 132.6 (d, *J* = 5.9 Hz), 131.9 (d, *J* = 2.2 Hz), 131.3 (d, *J* = 6.7 Hz), 129.3 (d, *J* = 2.2 Hz), 128.7, 128.66 (d, *J* = 4.4 Hz), 128.62. 128.5 (d, *J* = 1.5 Hz), 128.3, 127.9 (d, *J* = 1.4 Hz), 127.0, 126.9, 126.2, 125.9, 125.7, 125.2 (d, *J* = 1.4 Hz), 59.4 (d, *J* = 77.3 Hz), 38.9 (d, *J* = 3.0 Hz), 35.3 (d, *J* = 75.9 Hz), 29.6 (d, *J* = 2.3 Hz), 25.4, 23.5 (d, *J* = 11.2 Hz), 14.9 (d, *J* = 2.3 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 58.3.

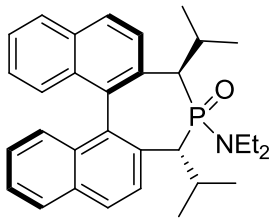


(*R*, *Ra*, *SP*)-3-Methyl-*N*,*N*-diethyl-4,5-dihydro-3*H*dinaphtho[2,1-*c*;1',2'-*e*]phosphepine amide (4b): White powder, 96% yield. ^{1}H NMR (CDCl3) 500 MHz: δ 7.98-7.95 (m, 1H), 7.93-7.87 (m, 3H), 7.68-7.66 (m, 1H), 7.48-7.45 (m, 1H), 7.45-7.36 (m, 2H), 7.29-7.26 (m, 1H), 7.24-7.16 (m, 2H), 7.13-7.10 (m, 1H), 3.35-3.45 (m, 2H), 3.03-2.80 (m, 5H), 1.05 (t, 3H, *J* = 7.5 Hz), 0.62 (dd, 3H, *J*1 = 15.5 Hz, *J*2 = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.6 (d, *J* = 5.1 Hz), 133.7 (d, *J* = 4.6 Hz), 133.1 (d, *J* = 2.8 Hz), 132.7 (d, J = 1.9 Hz), 132.48 (d, *J* = 2.2 Hz), 132.45 (d, *J* = 1.9 Hz), 132.5 (d, *J* = 2.3 Hz), 129.1 (d, *J* = 6.5 Hz), 128.9 (d, *J* = 1.4 Hz), 128.5, 128.46, 128.3 (d, *J* = 8.4 Hz), 128.0, 127.8, 126.7, 126.4, 126.1, 126.0, 125.5, 125.1, 44.6 (d, *J* = 79.1 Hz), 38.5 (d, *J* = 2.3 Hz), 34.5 (d, *J* = 74.5 Hz), 15.8 (d, *J* = 4.3 Hz), 14.5 (d, *J* = 1.8Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 57.9.

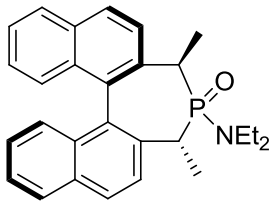


(*R*, *Ra*, S_P)-3-benzyl-*N*,*N*-diethyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1',2'-*e*]phosphepine amide (4c): White powder, 88% yield. ^{1}H NMR ($CDCl_3$) 400 MHz: δ 8.02-7.98 (m, 1H), 7.96-7.92 (m, 1H), 7.88-7.84 (m, 1H), 7.75-7.68 (m, 2H), 7.46-7.40 (m, 2H), 7.31-7.20 (m, 3H), 7.18-7.14 (m, 1H), 7.08-7.04 (m, 1H), 7.02-6.96 (m, 3H),

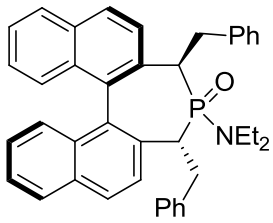
6.67-6.03 (m, 2H), 3.42-3.30 (m, 2H), 3.12-2.90 (m, 6H), 1.78-1.69 (m, 1H), 1.04 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.0 (d, J = 13.1 Hz), 136.5 (d, J = 6.2 Hz), 134.0 (d, J = 5.8 Hz), 133.8 (d, J = 2.8 Hz), 133.2 (d, J = 2.2 Hz), 133.0 (d, J = 3.0 Hz), 132.9 (d, J = 2.0 Hz), 132.5 (d, J = 2.9 Hz), 131.0 (d, J = 6.7 Hz), 129.6 (d, J = 2.2 Hz), 129.1, 128.9, 128.8, 128.7, 128.6, 128.2, 128.1, 127.3, 127.25, 126.5, 126.4, 126.1, 125.9, 125.85; ^{31}P NMR (202 MHz, $CDCl_3$): δ 57.7.



(*R*, *R*, *R*)-3,5-Di-*iso*-propyl-*N*,*N*-diethyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1',2'-*e*]phosphepine amide (5b): White powder, 65% yield. ^{1}H NMR ($CDCl_3$) 500 MHz: δ 7.84-7.78 (m, 4 H), 7.45-7.42 (m,1H), 7.35-7.25 (m, 3H), 7.20-7.17 (m, 1H), 7.14-7.06 (m, 3H), 3.15-3.00 (m, 4H), 2.95-2.86 (m, 1H), 2.84-2.75 (m, 1H), 1.25-1.15 (m, 12H), 1.10-1.00 (m, 1H), 0.85-0.75 (m, 1H), 0.30-0.18 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.2 (d, J = 4.3 Hz), 134.9 (d, J = 6.5 Hz), 134.7 (d, J = 2.4 Hz), 133.2 (d, J = 4.3 Hz), 132.8 (d, J = 1.9 Hz), 132.7 (d, J = 1.9 Hz), 132.68 (d, J = 1.4 Hz), 132.64 (d, J = 5.6 Hz), 132.4 (d, J = 2.4 Hz), 130.4 (d, J = 7.9 Hz), 128.93, 128.92, 128.5 (d, J = 1.0 Hz), 128.2, 127.9, 127.1, 126.2, 125.9 (d, J = 7.9 Hz), 125.5, 62.6 (d, J = 56.5 Hz), 57.6 (d, J = 72.6 Hz), 41.4 (d, J = 3.1 Hz), 30.5, 27.3 (d, J = 2.8 Hz), 25.5, 24.1, 16.8; ^{31}P NMR (202 MHz, $CDCl_3$): δ 53.7.

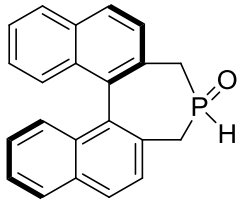


(*R*, *R*, *R*)-3,5-Dimethyl-*N*,*N*-diethyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1',2'-*e*]phosphepine amide (5b): White powder, 93% yield. ^{1}H NMR ($CDCl_3$) 500 MHz: δ 7.84-7.80 (m, 2H), 7.79-7.74 (m, 2H), 7.49-7.45 (m, 1H), 7.38-7.35 (m, 1H), 7.33-7.28 (m, 1H), 7.28-7.24 (m, 1H), 7.10-7.07 (m, 2H), 7.05-7.00 (m, 1H), 6.94-6.91 (m, 1H), 3.38-3.12 (m, 4H), 2.94-2.85 (m, 2H), 1.06 (t, 3H, J = 7.0 Hz), 0.81 (dd, 3H, *J*1 = 14.3 Hz, *J*2 = 7.5 Hz), 0.64 (dd, 3H, *J*1 = 7.5 Hz, *J*2 = 15.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.2 (d, *J* = 4.6 Hz), 134.9 (d, *J* = 5.5 Hz), 134.5 (d, *J* =2.8 Hz), 133.5 (d, *J* = 1.3 Hz), 133.2, 133.1, 132.4 (d, *J* = 1.9 Hz), 132.3 (d, *J* = 1.4 Hz), 129.9 (d, *J* = 5.6 Hz), 129.0, 128.8, 128.4 (d, *J* = 7.4 Hz), 128.0, 127.8, 127.0, 126.4, 126.3, 126.0, 125.7, 125.3 (d, *J* = 1.0 Hz) 47.5 (d, *J* = 72.6 Hz), 42.4 (d, *J* = 75.0 Hz), 38.6 (d, *J* = 2.4 Hz), 16.3 (d, *J* = 3.8 Hz), 14.9 (d, *J* = 2.3 Hz), 14.5 (d, *J* = 1.4 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 56.5.



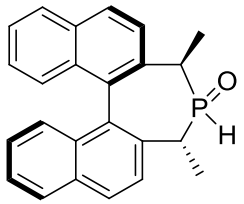
(*R*, *Ra*, *SP*)-3,5-Dibenzyl-*N*,*N*-diethyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1',2'-*e*]phosphepine oxide (5c): White powder, 68% yield. ^{1}H NMR ($CDCl_3$). 7.90-7.86 (m, 2H), 7.85-7.82 (m, 1H), 7.80-7.76 (m, 1H), 7.49-7.40 (m, 2H), 7.34- 7.31 (m, 1H), 7.27-7.19 (m, 4H), 7.18-7.14 (m, 1H), 7.08-7.00 (m, 6H), 6.76-6.72 (m, 2H), 6.63-6.59 (m, 2H), 3.82-3.72 (m, 1H), 3.78-3.70 (m, 1H), 3.42-3.32 (m, 2H), 3.28- 3.22 (m, 1H), 3.14-3.04 (m, 2H), 2.74-2.68 (m, 1H), 2.00-1.86 (m, 2H), 1.26 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR

(125 MHz, $CDCl_3$): δ 140.2 (d, *J* = 12.9 Hz), 139.5 (d, *J* = 13.9 Hz), 134.5 (d, *J* = 2.8 Hz), 133.9 (m, 4.1 Hz), 133.1, 133.0 (d, *J* = 3.8 Hz), 132.8 (d, *J* = 1.8 Hz), 132.7 (d, *J* = 2.4 Hz), 132.6 (d, *J* = 1.4 Hz), 132.5 (d, *J* = 5.6 Hz), 131.6 (d, *J* = 5.5 Hz), 130.1 (d, *J* = 7.4 Hz), 129.1, 128.3, 128.7, 128.3, 128.29, 128.0, 127.9, 127.8, 127.1, 126.2, 126.1, 126.0, 125.98, 125.8, 125.7, one phenyl peak is obscured; ^{31}P NMR (202 MHz, $CDCl_3$): δ 56.9.



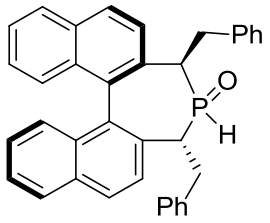
(*R*)-4,5-Dihydro-3*H*-dinaphtho[2,1-*c*;1',2'-*e*]phosphepine oxide (1a): The dilithium TMEDA complex of **2** was prepared following the same procedure used in the synthesis of **3**. To a hexanes suspension of the complex (5 g, 9.5 mmol, 50 mL) was added 1,1-dichloro-*N*,*N*-diethylphosphinamine (1.38 mL, 9.5 mmol) dropwise at -78 ^oC. The mixture was allowed to warm to rt and stir overnight. Dry HCl in ether (2.0 M, 14 mL, 28.5 mmol) was added to the reaction at 0 ^oC and the mixture was vigorously stirred for another 2 h. H_2O (30 mL) was added slowly and the solution was stirred for 30 min at rt. The aqueous phase was washed with CH_2Cl_2 (3 x 20 mL) and brine (20 mL). The combined organic phases were concentrated and purified by silica gel chromatography. The product was obtained as a white powder in 86% yield. ^1H NMR ($CDCl_3$) 500 MHz: δ 8.10-7.90 (m, 4H), 7.75-7.64 (m, 1.5H), 7.58-7.50 (m, 3H), 7.34-7.20 (m, 4H), 6.82-6.78 (m, 0.5H), 3.44-3.30 (m, 2H), 3.18-2.96 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.4 (d, *J* = 5.6 Hz), 133.8 (d, *J* = 3.7 Hz), 133.22, 133.21, 132.6, 132.2, 129.7, 129.3 (d, *J* = 3.0 Hz), 128.9 (d, *J* = 11.1 Hz), 128.7, 128.6, 128.5 (d, *J* = 5.0 Hz), 128.2 (d, *J* = 8.2 Hz),

127.7 (d, *J* = 5.0 Hz), 127.2, 126.9 (two carbons), 126.8, 126.3, 126.1, 35.0, 34.6, 34.4, 33.9; ^{31}P NMR (202 MHz, $CDCl_3$): δ 43.1.



(*R*, *R*, *R*)-3,5-Dimethyl-*N*,*N*-diethyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1',2'-*e*]phosphepine oxide (1b): To a xylene solution of **5b** (0.5g, 1.2 mmol, 4 mL) in a 50 mL Schlenck tube equipped with a high vacuum valve, trichlorosilane (3.5 mL, 35 mmol) was added in one portion at rt. This reaction tube was sealed and heated to 120 ^{o}C. The reaction was monitored by TLC or in situ by ^{31}P NMR. Upon completion of the reaction, the solution was cooled to 0 ^{o}C and the pressure was carefully released. Excess trichlorosilane was blown out by N_2 before the reaction solution was quenched with cold 1 N NaOH (100 mL). The mixture was then stirred at 0 ^{o}C for another 2 h. The aqueous phase was separated and washed with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under vacuum, the crude product was purified by silica gel chromatography. The product was obtained as a white powder in 65% yield. ^{1}H NMR ($CDCl_3$) 500 MHz: δ 7.85-7.80 (m, 4H), 7.51-7.46 (m, 1H), 7.40-7.32 (m, 3H), 7.18-7.08 (m, 3H), 7.06-7.02 (m, 1H), 6.78 (dd, 1H, *J*1 = 450 Hz, *J*2 = 1.5 Hz), 3.51-3.50 (m, 1H), 3.50-3.38 (m, 1H), 0.72-0.65 (m, 6H); 13C NMR (125 MHz, CDCl3): δ 135.3 (d, *J* = 4.6 Hz), 134.5 (d, *J* = 7.0 Hz), 133.9 (d, *J* = 2.8 Hz), 133.6 (d, *J* = 2.4 Hz), 133.3 (d, *J* = 0.9 Hz), 132.8 (d, *J* = 1.4 Hz), 132.79 (d, *J* = 2.8 Hz), 131.6 (d, *J* = 4.6 Hz), 129.4 (d, *J* = 5.0 Hz), 129.2 (two carbons),

129.21, 129.1 (d, *J* = 1.9 Hz), 128.2, 128.1 (d, *J* = 0.9 Hz), 126.7, 126.65, 126.5 (d, *J* = 2.8 Hz), 126.1, 125.9, 43.3 (d, *J* = 57.3 Hz), 40.8 (d, *J* = 59.3), 16.8, 10.0 (d, *J* = 5.5 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 57.1.



(*R*, *R*, *R*)-3,5-Dimethyl-*N*,*N*-diethyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1',2'-*e*]phosphepine oxide (1c): White powder, 65% yield. ^{1}H NMR ($CDCl_3$) 500 MHz: δ 7.98-7.84 (m, 4H), 7.52-7.44 (m, 2.5H), 7.38-7.34 (m, 1H), 7.32-7.22 (m, 6H), 7.18-7.15 (m, 1H), 7.10-6.98 (m, 4H), 6.74-6.62 (m, 4H), 6.60-6.58 (m, 0.5H), 3.85-3.70 (m, 2H), 2.95-2.80 (m, 1H), 2.53-2.45 (m, 1H), 1.98-1.88 (m, 1H), 1.80-1.70 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.5 (d, *J* = 12.7 Hz), 138.1 (d, 14.6 Hz), 137.5 (d, *J* = 6.4 Hz), 134.2 (d, *J* = 6.2 Hz), 133.9 (d, *J* = 4.0 Hz), 133.2 (d, *J* = 2.8 Hz), 133.1, 133.0 (d, *J* = 2.7 Hz), 132.9, 132.8, 132.7, 130.7 (d, *J* = 7.4 Hz), 130.5 (d, *J* = 7.5 Hz), 129.4, 129.3, 128.6, 128.56, 128.5, 128.3, 128.0, 127.9, 127.1, 127.0, 126.7, 126.5, 126.4, 126.2, 126.0; ^{31}P NMR (202 MHz, $CDCl_3$): δ 54.4.

General Procedures for Asymmetric Hydrogenation: $Rh(cod)_2BF_4$ (20.3 mg, 0.05mmol) and **1a** (32.8 mg, 0.1 mmol) were dissolved in 2 mL degassed dichloromethane in a Schlenk tube under N_2. After stirring at room temperature for 1 h, 10 mL degassed hexanes was added and the resulting precipitate was filtered off under

nitrogen to give the complex as an orange solid (36 mg, 77% yield). This orange complex was stored in a nitrogen filled glovebox for further usage.

The complex (4.8 mg, 0.005 mmol) was dissolved in degassed anhydrous CH_2Cl_2 (0.5 mL) in a glovebox. A 4 mL vial was charged with a half-inch stirring bar, substrate (0.2 mmol), a stoichiometric amount of base (for amino ketones), the preformed complex solution (0.2 mL for S/C = 100) and a suitable solvent to reach 2 mL. The vial was transferred to an autoclave which was charged with H_2 (50 atm). The hydrogenation was performed at rt for 12 h. After carefully releasing the H_2, the solvent was removed under reduced pressure. Yield of the hydrogenation was determined by ^{1}H NMR of the crude products. In other cases, the reaction mixture was filtered through a short silica gel plug and directly analyzed by GC for conversion and ee value.

References

1. Tang, W.; Zhang, X. *Chem. Rev*. **2003**, 103, 3029.
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
3. (a) Burk, M. J. *Acc. Chem. Res*., **2000**, *33*,363; (b) Zhang, W.; Chi, Y.; Zhang, X. *Acc. Chem. Res.* **2007,** 40, 1278.
4. (a) Jiang, X.; Lefort, L.; Goudriaan, P. E.; de Vries, A.H. M.; van Leeuwen, P. W. N. M. de Vries, J. G.; Reek, J. N. H; *Angew. Chem. Intl.Ed.* **2006**, *45*, 1223. (b) Chevallier, F.; Breit, B. *Angew. Chem. Intl. Ed.* **2006**, *45*, 1599.(c) Weis, M.; Waloch, C.; Seiche, W. Breit, B. *J. Am. Chem. Soc.*, **2006**, *128*, 4188. (d)Breit, B.; Seiche, W. *Angew. Chem. Int. Ed.* **2005**, *44*, 1640.

5 (a) 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; (b) Peňa,D.;Minnaard, A. J.; de Vries,J. G.; Feringa, B. L. *J. Am. Chem. Soc.,* **2002**, *124*, 14552. (c) van den Berg, M.; Haak, R. M.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Adv. Synth. Catal*., **2002**, 344.

6. (a)Roundhill, D. M.; Sperline, R. P.; Beaulieu, W. B. *Coord. Chem. Rev*. 1**978**, 26,263. (b)Walther, B. *Coord. Chem. Rev.* **1984**, 60, 67. (c) Appleby, T.; Woollins, J. D. *Coord. Chem. Rev.* **2002**, 235, 121
7. (a) Li, G. Y. *Angew. Chem. Intl. Ed*., **2001**, *40*, 1513; (b) Li, G. Y.; Zheng, G.; Noonan, A. F.; *J. Org. Chem*., **2001**, *66*, 8677; (c) Li, G. Y. *J. Org. Chem.*, **2002**, *67*, 3643. (d) Ackermann, L.; Born, R.; Spatz, J. H.; Meyer, D. *Angew. Chem. Intl. Ed*., **2005**, *44*, 7216. (e) Nemoto, T.; Masuda, T.; Akimoto, Y.; Fukuyama, T.; Hamada, Y. *Org. lett.*, **2005**, *7*, 4447. (f) Dai, W.-M.; Yeung, K. Y.; Haynes, R. K. *Tetrahedron: Asymmety*, **2003**, *14*, 2821
8. (a) Jiang, X.-B.; Minnaard, A. J.; Hessen, B.; Feringa, B. L.; Duchateau, A. L. L.; Anddrien, J. G. O.; Boogers, J. A. F.; de Vries, J. G. *Org. Lett.*, **2003**, *5*, 1503. (b) Galland, A.; Dobrota, C.; Toffano, M.; Fiaud, J.-C. *Tetrahedron: Asymmetry*, **2006**, *17*, 2354; (c) Jiang, X.-B.; van den Berg, M.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Tetrahedron: Asymmetry*, **2004**, *15*, 2223.
9. Miyashita, A.; Yasuda, A.; Takaya, H; Toriumi, K.; Ito. T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980,** *102*, 7932
10. All experimental data were reported by coworker Gao Shang in his dissertation.
11. (a) Jiang, Q., Jiang, Y., Xiao, D., Cao, P. and Zhang, X. *Angew. Chem. Int. Ed.* **1998**, *37*, 1100. (b)
12. (a)Chaloner, P. A.; Esteruelas, M. A.; Joó, F.; Oro, L. A. *Homogeneous Hydrogenation*; Kluwer: Dordrecht, **1994**. (b) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, **1999**; Vol. 1, Chapter 5.1. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley & Sons: New York, **1994**; Chapter 2.
13. Nemoto, T.; Masuda, T.; Matsumoto, T.; Hamada, Y. *J. Org. Chem*. **2005**, *70*,7172