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The Graduate School

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DESIGN AND SYNTHESIS OF CHIRAL LIGANDS AND THEIR APPLICATIONS IN TRANSITION METAL-CATALYZED ASYMMETRIC REACTIONS

A Dissertation in

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ABSTRACT

Transition metal catalyzed reactions are among the most powerful and direct approaches for the synthesis of organic molecules. During the past several decades, phosphorous-containing ligands have been extensively studied in transition metal - catalyzed transformations particularly asymmetric hydrogenations. Development of new chiral ligands and efficient catalyst systems for various prochiral unsaturated substrates in asymmetric hydrogenations are the focus of this dissertation. An important family of atropisomeric biaryl bisphosphine ligands, C_3*-TunePhos and related bisaminophosphines have been designed and synthesized. The Ru catalysts of the highly modular C_3*-TunePhos have been proved to be highly efficient (up to 99.8% ee, up to 1,000,000 TON) for practical asymmetric hydrogenations of a wide range of unfunctionalized ketones as well as *α*-, *β*- keto esters and *N*-2-substituted allylphthalimides. The synthetic utility of bisaminophosphine ligands was studied for rhodium-catalyzed asymmetric hydrogenations of *α*-dehydroamino acid esters, affording up to 98% ee's. A new chiral tridentate NNN-type indan-Ambox ligand was designed and synthesized targeting the direct hydrogenation of unfunctionalized aryl and alkyl ketones. Successful examples of unfunctionalized ketone reduction in a enantioselective catalytic pathway display the potential of tridentate ligands in asymmetric catalysis. Another rational design and synthesis of PNP-type bulky chiral tridentate ligand was also fulfilled, yet it failed to provide superior enantioselectivity. To solve the problems of asymmetric hydrogenation of imines and heteroaromatics, a series of Ir- or Pd-based catalyst systems have been developed. Highly enantioselective and highly efficient hydrogenation of *N*-

aryl imine, N-H imines, β-enamine esters, quinoline derivatives and unprotected indole derivatives have been successfully achieved respectively, with up to 98% ee and 10,000 TON. Catalyst systems containing strongly electron-donating and sterically hindered bisphosphine ligand have displayed significant advantages and will lead to more updated breakthroughs. Other examples of transition metal-catalyzed reactions such as Cu-catalyzed conjugate reduction of cyclic α,β-unsaturated ketones and Ru-catalyzed dynamic kinetic resolution of α-substituted cyclic ketones have also been investigated. Some preliminary results were discussed accordingly.

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Chapter 1

Introduction and Background

1.1 Introduction

Among all the catalytic asymmetric methodologies to chiral compounds, homogenous transition metal-catalyzed asymmetric hydrogenation plays a particularly important role.[1] Its highly efficient, environmental friendly and cost effective natures have undoubtedly made it one of the most studied methodologies during the past forty years. As a result, the vast number of catalytic systems developed have also had a significant impact on other areas of asymmetric catalysis.[2] More significantly, the achievements from academia research on asymmetric hydrogenation were frequently acknowledged with industrial applications, which in turn, provide an important driving force for its basic research.[3]

Hundreds of catalytic systems have been developed since the seminal discoveries from Knowles,[4] Kagan[5] and Horner.[6] In many cases, series of chiral catalysts were developed based on the similar scaffolds and were prepared for the same reactions. Although these analogous ligands are more likely prepared for the purpose of patent protection other than academic curiosity, they indeed provide us an excellent opportunity to compare, evaluate and study every aspect of the catalysts in asymmetric hydrogenation. In the meantime, a large number of prochiral unsaturated compounds have been

successfully hydrogenated with excellent enantioselectivities. Practical applications with very low catalyst loadings and complex substrate structures have continued to emerge.

This chapter introduces the up-to-date overview of the achievements of chiral ligand development in homogeneous transition metal catalyzed-asymmetric hydrogenation. The development of effective catalytic systems and their applications in the preparation of various chiral compounds are summarized. Chiral ligand development and study of transition metal catalyst systems has always been serving as the most fundamental corner stone in homogeneous asymmetric catalysis including asymmetric hydrogenation.

1.2 Chiral Ligands for Asymmetric Hydrogenation

In addition to a suitable transition metal species, chiral ligands play a crucial role in asymmetric hydrogenation. The good enantioselectivity and high activity of the catalyst are often the results of the structurally well defined and electron-donating chiral ligands. Continuing development of novel ligands and modifications of the current ligands are especially significant for asymmetric hydrogenation.

Similar to other areas of science, the fast development of chiral ligands are often triggered and continuously influenced by a few milestone discoveries. The pioneering

discoveries of CAMP and DIPAMP by Knowles[4] and DIOP by Kagan[5] have prompted the early studies on chiral ligand synthesis A few important concepts were also introduced by these pioneering works, such as mono-dentate phosphine ligands, P-chiral ligands and C_2-symmetric ligands. The early study on phosphorus ligand produced a number of chiral phosphorus ligands such as Bosnich's CHIRAPHOS[7]and PROPHOS[8], Rhone Poulenc's CBD[9], Giongo's bis(aminophosphine) ligand PNNP,[10] Kumada's ferrocene ligand BPPFA,[11] BPPFOH[12] and Achiwa's BPPM[13] (Figure 1-1). The first few attempts on the modifications of Kagan's DIOP were also initiated and resulted in a few related ligands which provided superior performance in many cases (Figure 1-2).[14]

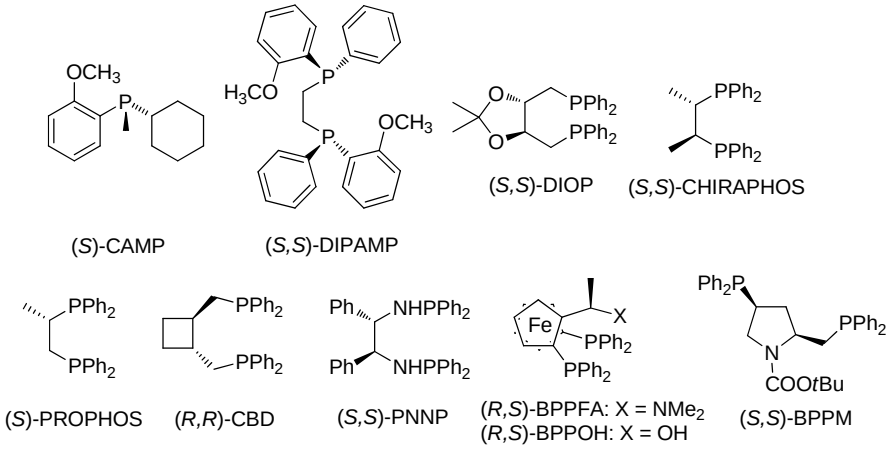

Figure 1-1: Early Development in Chiral Phosphorus Ligands.

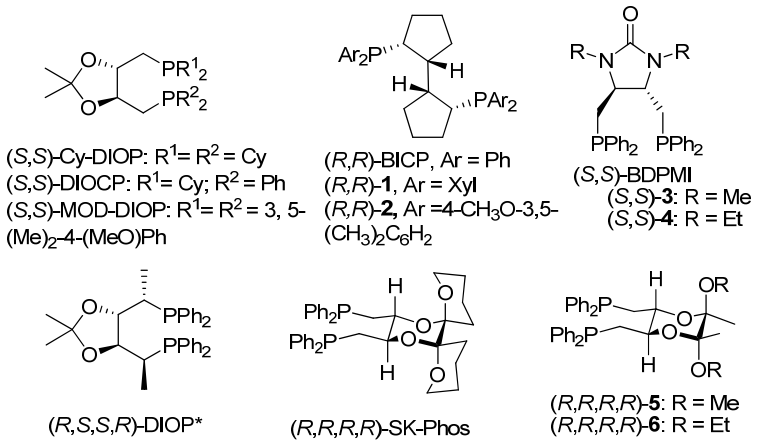

Figure 1-2: Chiral Phosphine Ligands Based on the Modification of DIOP.

A few years later, the discovery of binaphthyl moiety as chiral ligand motifs by Noyori led to the milestone ligand BINAP,[15] which soon delivered extraordinary results in olefin[16,17] and ketone[18,19] hydrogenation (Figure 1-3). The great impact of BINAP on ligand design can be easily recognized from arguably the largest family of analogous ligands (Figure 1-4 and Figure 1-5). Modifications of BINAP on the P-substituents and/or the binaphthyl backbone have been studied in great detail. The well tuning of its electronic and structural properties has expanded the application of these ligands in almost every type of substrates. For example, partially hydrogenation of the binaphthyl rings and/or replace the aromatic rings with fused heterocycles has resulted in a few analogous ligands with different electronic properties.

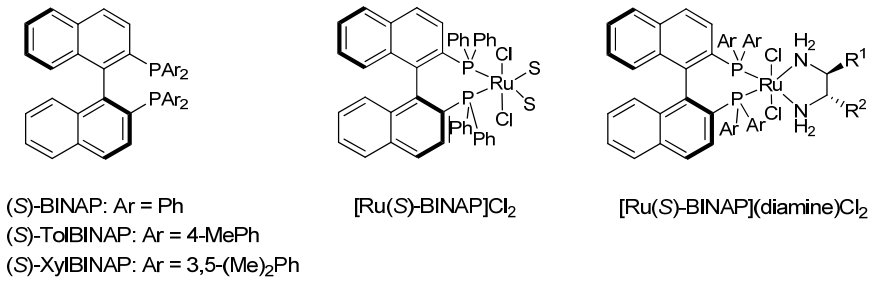

Figure 1-3: BINAP and Its Ru Complexes.

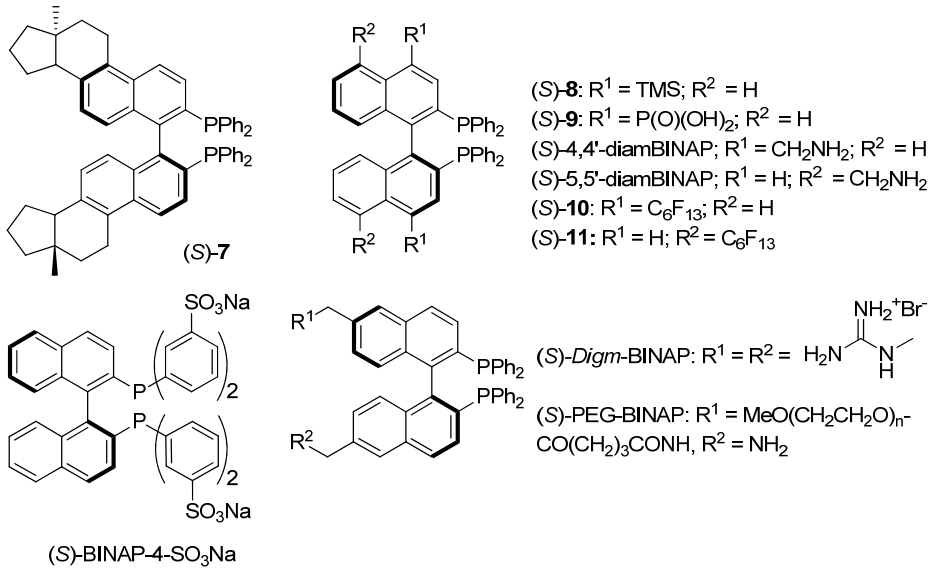

Figure 1-4: Examples of BINAP Analogues with Substituents on the Backbone or the Phosphorus Atom.

The electron rich H_8-BINAP developed by Takaya was found to be more efficient in the hydrogenation of unsaturated carboxylic acids.[20] SEGPHOS, developed by Takasago International Corp., was believed to also have a narrower bite angle compared with BINAP. This ligand was proved to be more selective than BINAP in the Ru-catalyzed asymmetric hydrogenation of a wide variety of carbonyl compounds.[21] A recent report

revealed that it also delivered good results in imine reductions.[22] To systematically study the relationship between bite angles and enantioselectivities, the Zhang group has developed a family of ligands with tunable linkers within biphenyl backbone. It was found that the favorable bite angle was strongly related to the specific type of substrate.[23] For instance, C_2-TunePhos was the most efficient ligand for Ru-catalyzed hydrogenation of enol acetate[23b] while the C_3-TunePhos was more effective for cyclic *β*-dehydroamino acids and α-phthalimide ketones.[23c,d] Recently another variation of this ligand family was prepared by Chan and Zhang possessing a chiral linker. The recently developed analogous C_3*-TunePhos not only improved the enantioselectivity, the synthetic route was also significantly improved.[24]

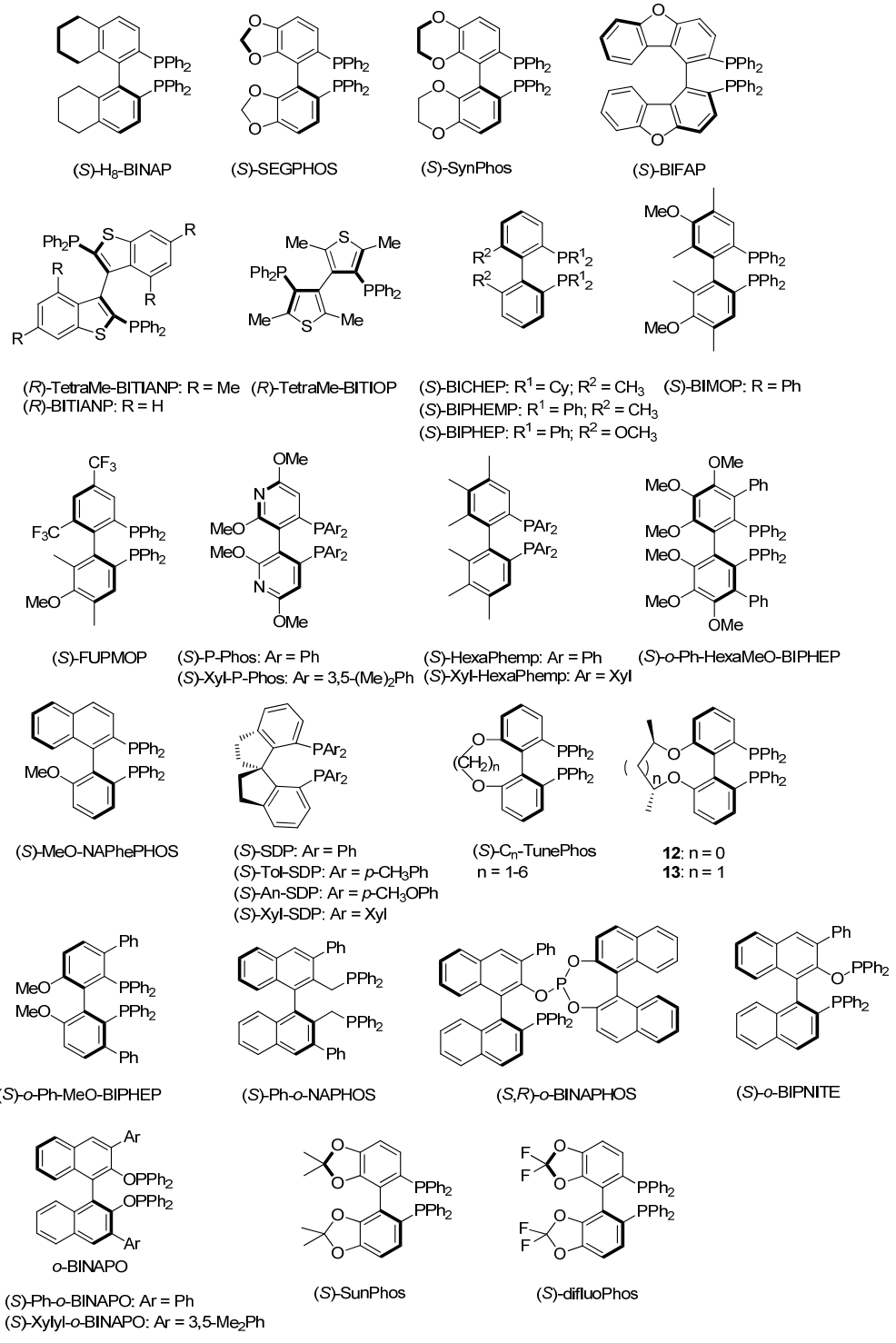

Figure 1-5: Examples of BINAP Analogues with Modifications on the Backbone.

It seems that the great inspiration emerges every ten years. In the early 1990s, Burk and coworkers made another great contribution to asymmetric hydrogenation by introducing their first *trans*-2,5-dialkyl substituted phospholane ligand BPE,[25] followed by the more famous 1,2-phenyl linked DuPhos family (Figure 1-6) .[26,27] These dialkyl or trialkyl substituted phosphines are considered to be more electron rich compared with the triaryl substituted BINAP family. The cyclic structures also provide great rigidity. These advantages have entitled BPE and DuPhos as one of the most efficient ligands for a wide variety of substrates such as α- and β-dehydroamino acid derivatives,[28a,b] enol acetates,[28c] *N*-acylhydrazones,[28d] enamides, enol esters, itaconic acids and β-keto ester derivatives.[26,27,28]

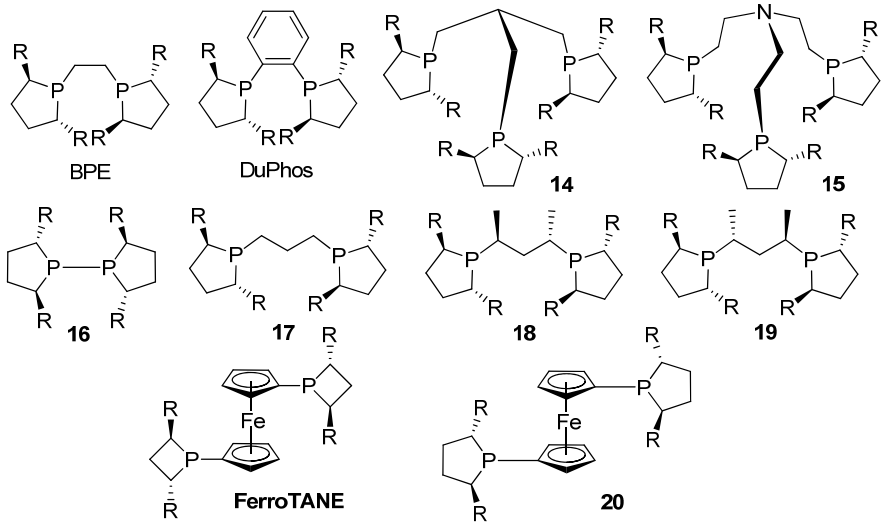

Figure 1-6: BPE, DuPhos and Analogues.

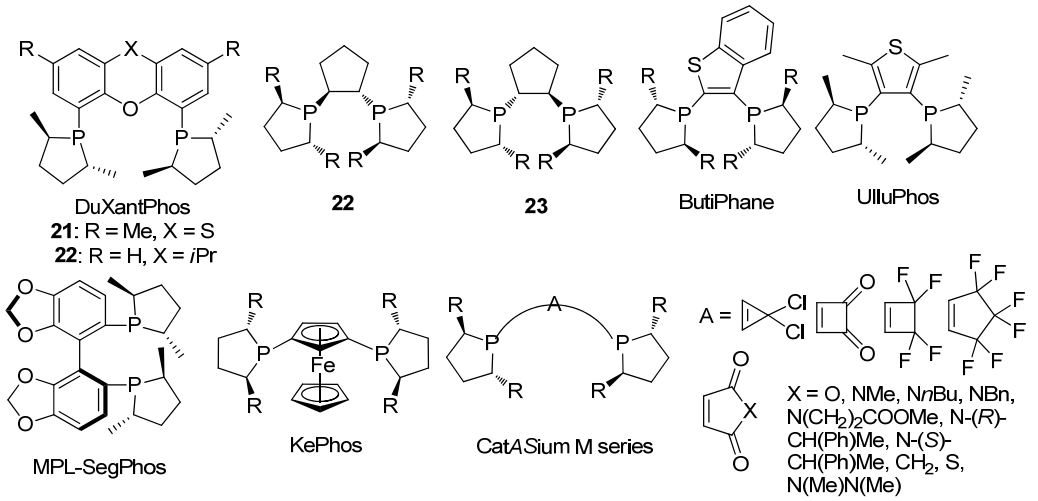

Figure 1-7: BPE and DuPhos Analogues with Modified Linkers.

The successful early application and modification of these two ligands have soon promoted the intensive studies on the phospholane structure motif. A large number of ligands were developed for various purposes. Some of the good examples are Cat*A*Sium M® series,[29] KetalPhos[30,31] and Ph-BPE (Figure 1-7, Figure 1-8).[32,33,34]

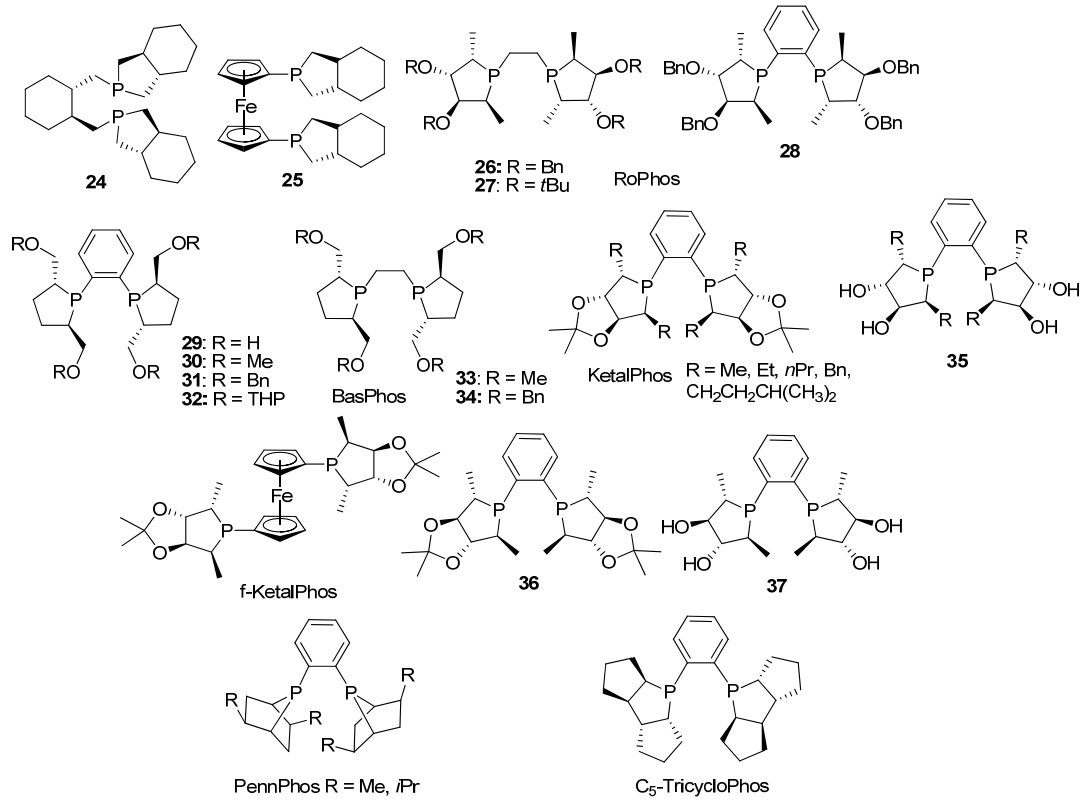

Figure 1-8: Ligands with Modifications on Phospholane Rings of BPE and DuPhos.

In the 21st century, the research on the development of high performance ligands has been accelerating and diverse. Some of the early concepts which had been overlooked for a long time have been investigated again. For instance, the P-chiral ligands can, in theory, produce high enantioselectivities since they can bring the chiral information closely into the catalytic center. However, the first significant contribution after Knowles's first P-chiral CAMP did not come to true until almost 30 years later when Imamoto reported his P-chiral BisP* ligands.[35] Soon after Imamoto's study, our group developed the more rigid cyclic P-chiral TangPhos[36] and DuanPhos[37] (Figure 1-9).

These ligands provided both high enantioselectivities and turnover numbers for a wide range of substrates.

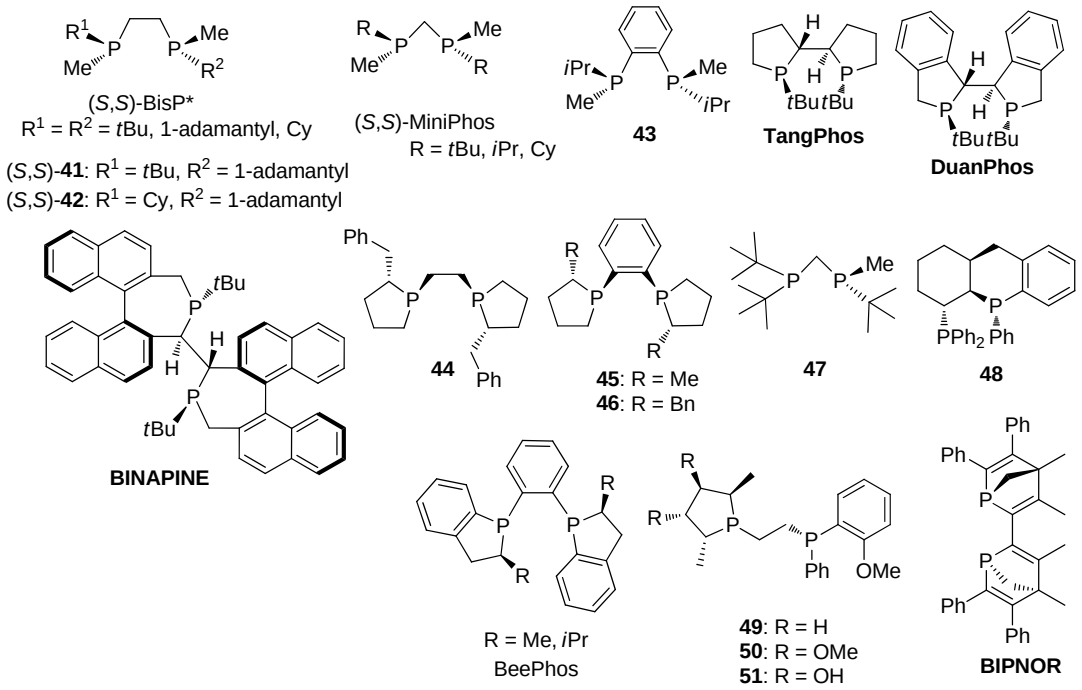

Figure 1-9: P-Chirogenic Ligands.

While great achievement was obtained in developing chelating-bidentate ligands, mono-dentate phosphines had been disappeared from our sight even though the very first chiral phosphorus ligand CAMP was one of this kind. Feringa and de Vries recently demonstrated that monophosphorus ligands can deliver excellent performance in asymmetric hydrogenation. The MonoPhos ligand family, easily synthesized from BINOL in two steps, exhibited up to 99% ee in the Rh-catalyzed hydrogenation of dehydroamino acids and aryl enamides.[38] Two modified monophosphorus ligands

SIPHOS[39] and **27** [40] with more rigid backbones were also developed by Chan and Zhang respectively (Figure 1-10).

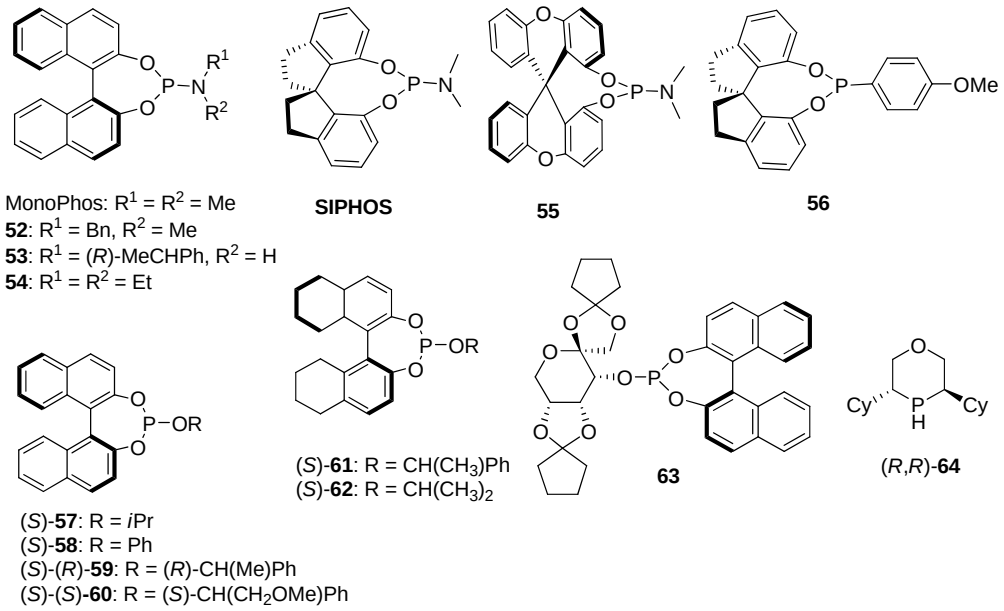

Figure 1-10: Monodentate Ligands.

The discovery of the Crabtree's catalyst opened up a new field for the development of chelating chiral P,N-ligands for asymmetric hydrogenation.[41]A very successful example was demonstrated by Pfaltz and coworkers on their PHOX ligands.[42] These chelating aryl phosphine and oxazoline ligands achieved exceptionally good results in the iridium-catalyzed hydrogenation of unfunctionalized alkenes, which have been challenging substrates for other types of catalysts. Prompted by the good performance of PHOX, a number of P,N-ligands were developed thereafter(Figure 1-11).

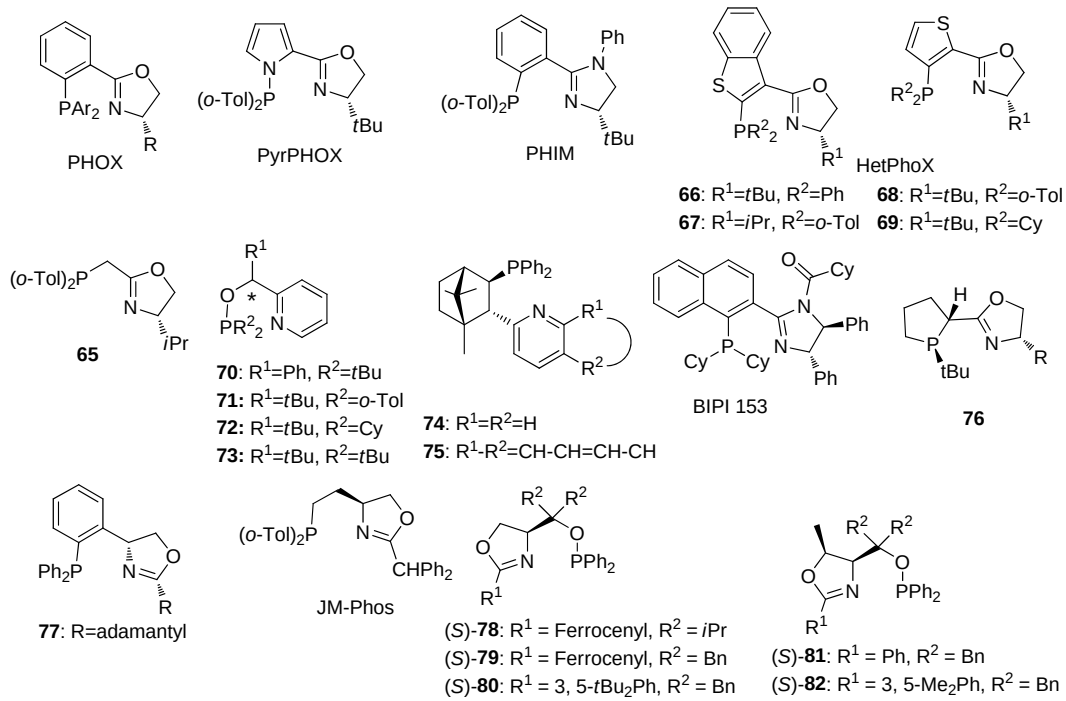

Figure 1-11: P,N-Ligands.

Examples of many other chiral phosphorus ligand structures such as ferrocene backbone-based ligands and more are summarized in Figure 1-12 and Figure 1-13.

1.3 Conclusion

The past two decades has witnessed tremendous progress in asymmetric catalysis particularly asymmetric hydrogenation along with the development of many powerful chiral ligands. As more chiral ligands that are more useful in terms of stability, accessibility, reactivity, selectivity and modularity, and their applications in different

transformations are discovered and studied, our knowledge of ligand design will continue to grow.

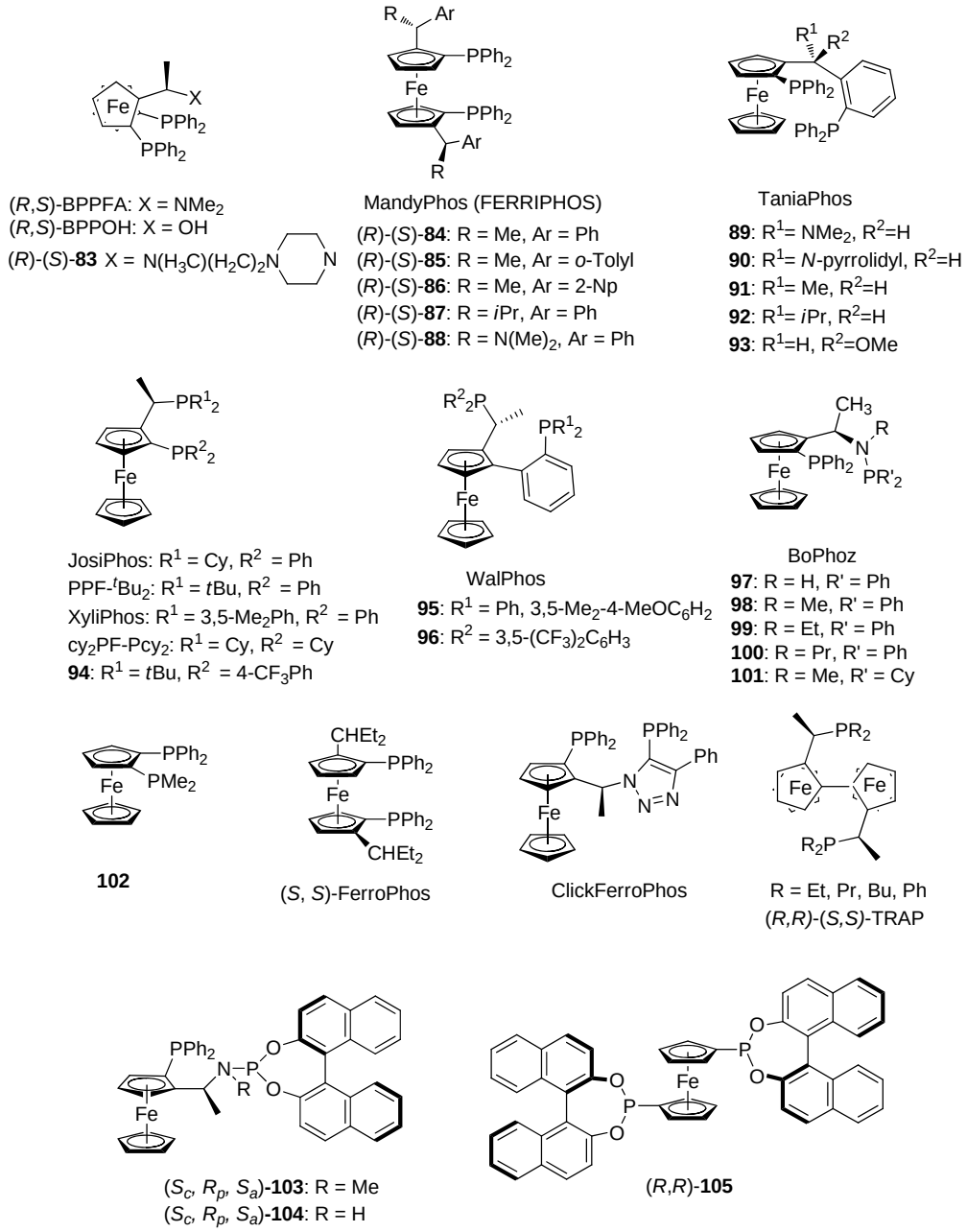

Figure 1-12: Ferrocene Based Ligands.

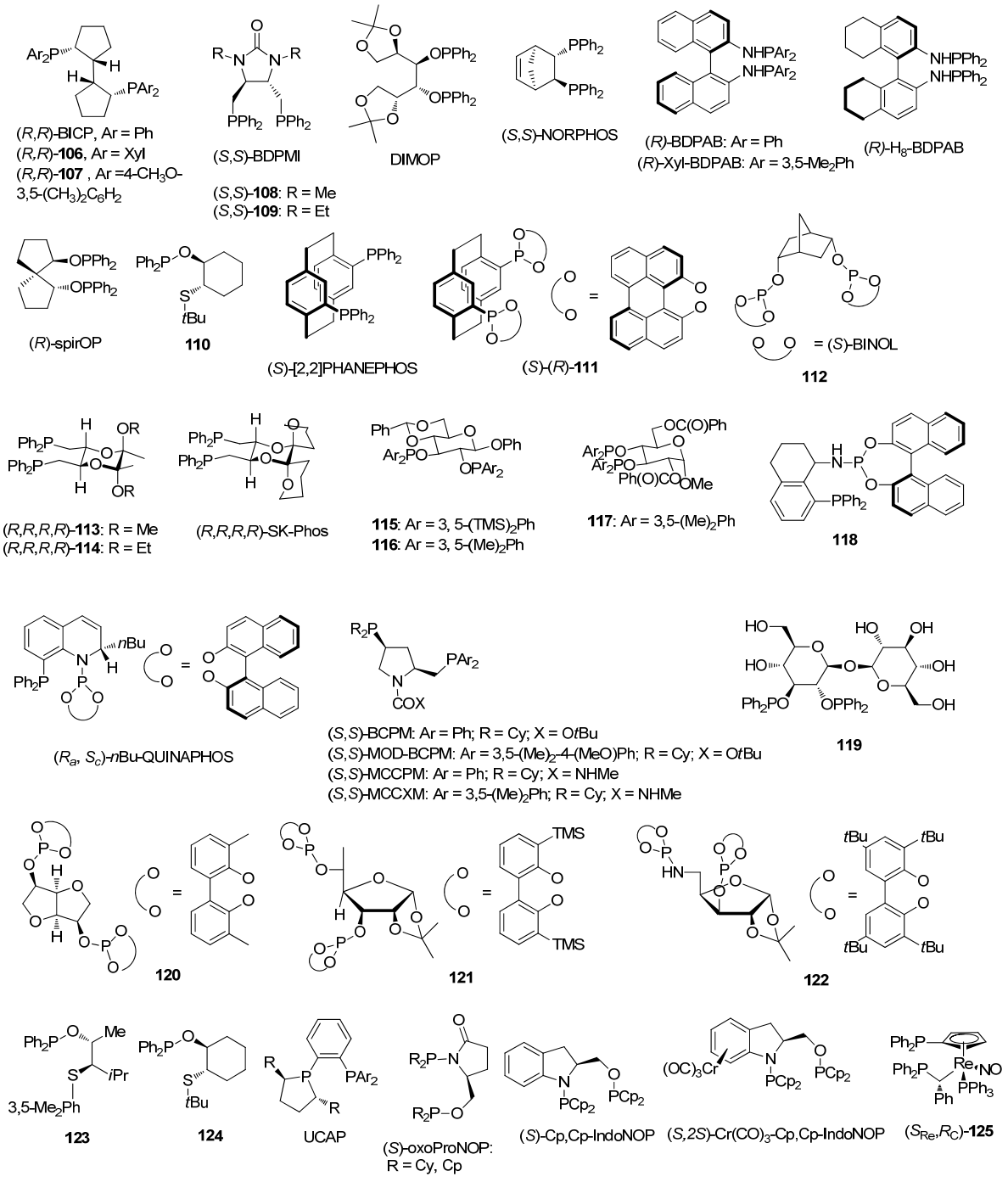

Figure 1-13: Other Chiral Phosphorus Ligands.

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Chapter 2

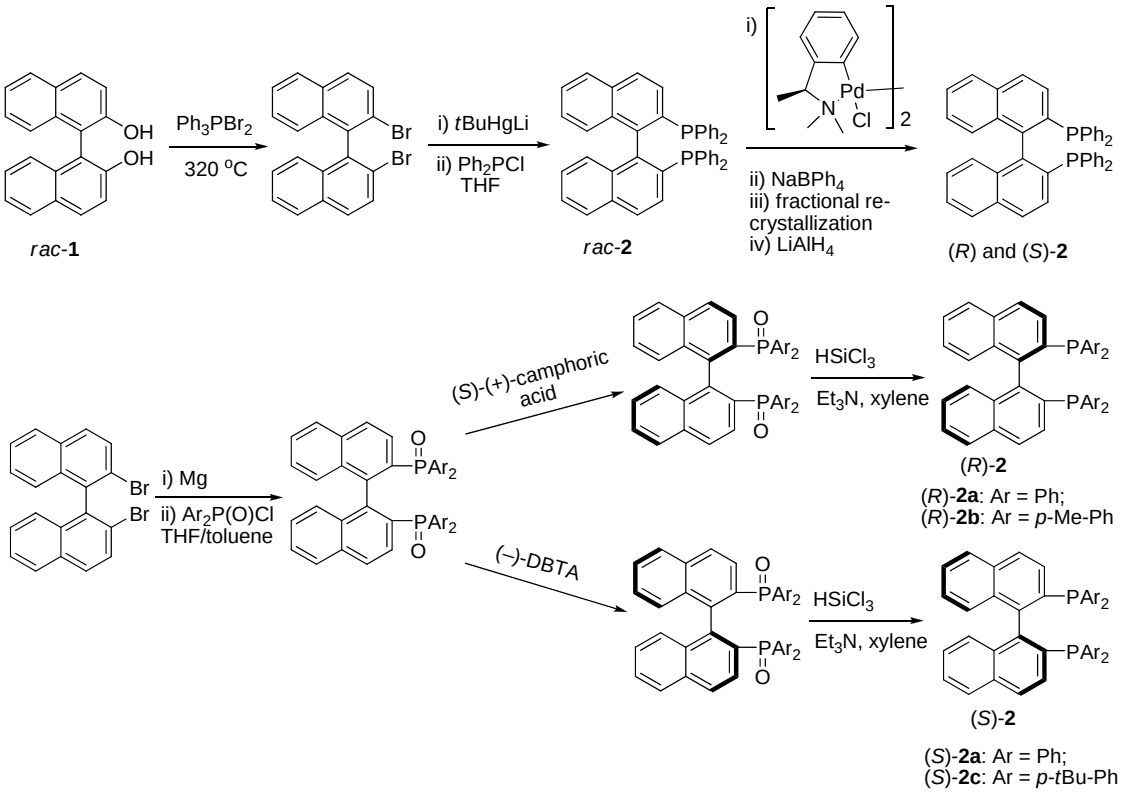
Synthesis of C_3*-TunePhos Chiral Bisphosphine Ligands and Their Applications in Asymmetric Hydrogenation of Unfunctionalized Ketones and Keto Esters

2.1. Introduction and Background

During the fast development of asymmetric catalysis in the past decades, different categories of well-defined chiral ligands have been designed and investigated to pursue high enantioselectivities to meet the increasing demand for optically active compounds. Chelating C_2-symmetric atropisomeric bisphosphine ligands are one important class of ligands that have fundamental significance and influence on the asymmetric catalysis area. The most remarkable milestone of the development history this ligand class was BINAP, which was first reported by Noyori and Takaya in 1980, decades after the discovery of practical asymmetric catalysis.[1] BINAP became one of the most successful chiral bisphosphine ligands, and its great success in a wide range of asymmetric catalysis involving various metal-ligand complex attributed to its unique structural features including the rigid 1,1′-binaphthyl backbone of high stability and steric influence, as well as its conformational flexibility from the (partially) revolving axial single bond.[2] Although BINAP was originally designed for Rh-catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids, more and more breakthroughs have been made in other asymmetric transformations such as Rh-catalyzed asymmetric isomerization and Ru-

catalyzed asymmetric hydrogenation of functionalized ketones and simple ketones since then. Inspired by Noyori's work on the BINAP chemistry, other research groups developed many excellent atropisomeric biaryl bisphosphine ligands, such as BICHEP, BIPHEMP, TunePhos, and MeO-BIPHEP. Moreover, many examples of modifications of BINAP backbone structure have been developed to achieve better performances.

2.1.1. Synthesis of BINAP and Its Derivatives



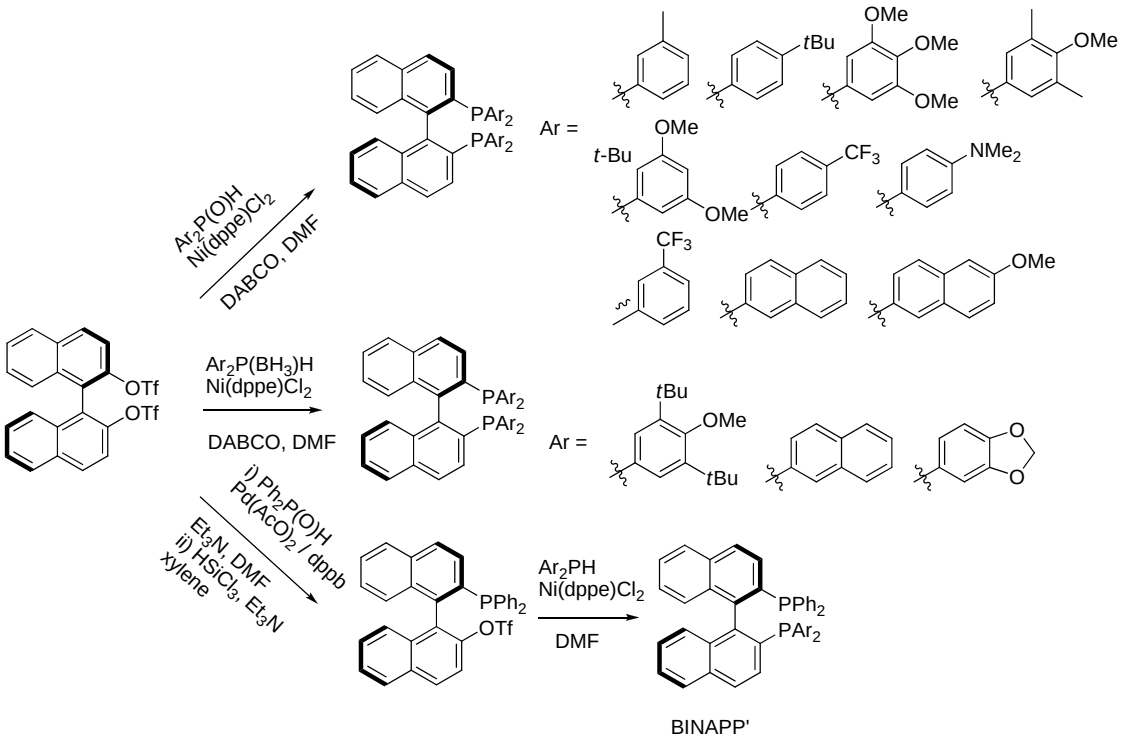
Scheme 2-1: Synthesis of BINAP via Optical Resolution.

In Noyori and Takaya's original work, they presented the successful synthesis of BINAP starting from the racemic atropisomers of 1,1′-binaphthyl-2,2′-diol (BINOL)

(*rac*-**1**).[1] The racemic BINAP (*rac*-**2**) was subsequently obtained by treatment of *t*BuHgLi and Ph_2PCl. It was noteworthy that one step of optical resolution was performed by using the chiral palladium(II) complex through fractional recrystallization to obtained the final optically pure **2** (Scheme 2-1). Noyori and coworkers then improved the resolution process to find a more practical access to BINAP, using camphorsulfonic acid or DBTA as the resolving reagent (Scheme 2-1).

Shortly after the BINAP's initial synthesis report and excellent performances in the asymmetric hydrogenation, other improved synthetic routes were developed to prepare enantiopure BINAP on large scale, even on an industrial scale.[3] Merck Inc. developed a short synthetic route involving a Ni(II)-facilitated coupling with diphenylphosphine.[4]

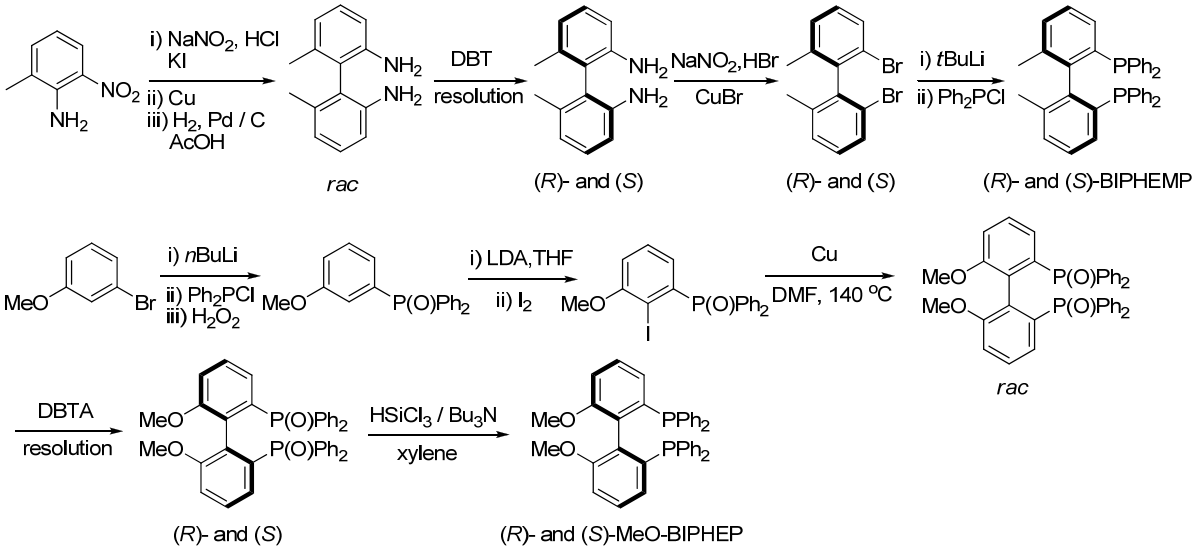
Modifications of the BINAP ligand have been extensively studied, including: 1) replacement of the phenyl group on the phosphorus atoms to various substituted phenyl groups or aliphatic or heteroaromatic groups; 2) introduction of substituents on the binaphthyl backbone; 3) partially reduction of the binaphthyl backbone to H_8-BINAP family ligands (Scheme 2-2).[3] All these modifications systematically investigated the BINAP family ligands by manipulating the electronic and steric properties of both the backbone and phosphine groups. Moreover, some modifications also altered the bite angles of the binaphthyl scaffold.



Scheme 2-2: Syntheses of Modified BINAP with Aryl Substituents on the Phosphorus Atoms.

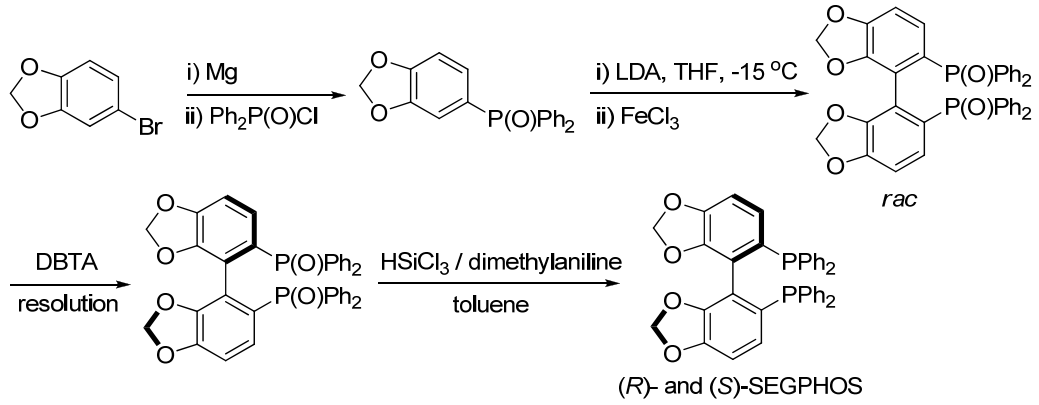
2.1.2. Synthesis of Atropisomeric Biaryl Ligands

Inspired by the tremendous success achieved in the use of Rh− and Ru−BINAP-catalyzed asymmetric, many atropisomeric C_2-symmetric biaryl bisphosphine ligands were synthesized and extensively studied. Roche chemists reported the earliest examples of preparation of axial chiral biaryl bisphosphine BIPHEMP and MeO-BIPHEP. The common steps in the two independent synthetic routes are Ullmann coupling reaction step to form the biaryl scaffold from two monomers and optical resolution to obtain both enantiomers of the key intermediates (Scheme 2-3).[5]



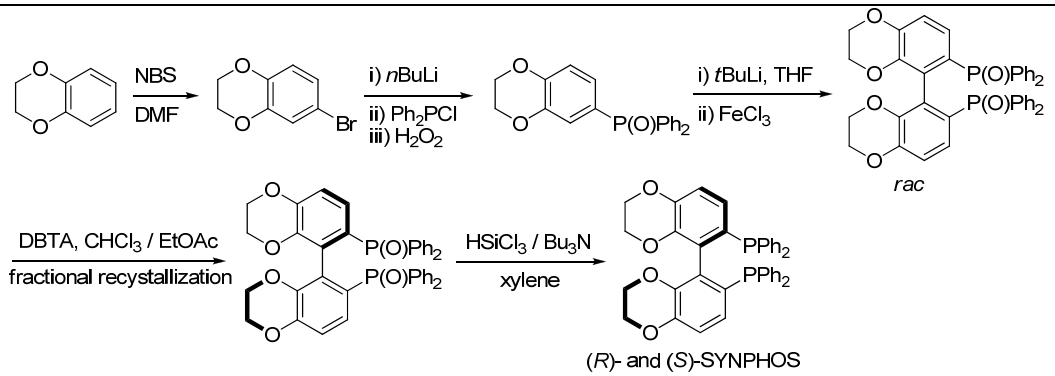
Scheme 2-3: Synthetic Routes of BIPHEMP and MeO-BIPHEP.

An alternative oxidative coupling method for aryl-aryl coupling between two lithiated phosphine oxides was developed for the synthesis of SEGPHOS.[6] Use of $FeCl_3$ instead of Cu could lead to the desired bisphosphine oxide in a racemic mixture. Further optical resolution with DBTA and reduction with $HSiCl_3$/dimethylaniline afforded the final product (*R*)- and (*S*)-SEGPHOS (Scheme 2-4).



Scheme 2-4: Synthesis of SEGPHOS via Oxidative Coupling Method.

Other modifications led to the preparations of atropisomeric variants of MeO-BIPHEP. Chan and Genêt independently reported the closely related bisbenzodioxanPhos, SYNPHOS (Scheme 2-5). The synthesis route was very similar to that of SEGPHOS, which relied on Cu-catalyzed Ullmann coupling and the resolution with DBTA.[7]



Scheme 2-5: Synthesis of SYNPHOS.

2.1.3. General Strategies of Synthesizing of Atropisomeric Biaryl Ligands

Although the synthetic route of different atropisomeric biaryl ligands vary from case to case, they all are generally based upon the same elementary steps for constructing chiral bisphosphine, yet applied in different sequences of the combination. Introduction of the phosphine moiety (**a**), introduction of axial chirality (**b**), coupling of two aryl fragments (**c**) and reduction of phosphine oxide (**d**) are the basic elements. The general synthesis strategies could be summarized:

(I) Starting with a racemic biaryl backbone, followed by introduction of directly bisphosphine moieties or bisphosphine oxides (reduction required in the final step),

enantiomeric ligands (or oxide derivatives) are obtained from optical resolution (**b** or **c** → **b** → **d**);

(II) Starting with an enantiomeric biaryl backbone, bisphosphine moieties or bisphosphine oxides (reduction required in the final step) are incorporated (**b** → **a** or **b** → **a** → **d**);

(III) Starting with a monomeric disubstituted aryl phosphine oxide, racemic bisphosphine oxide is formed from non-chiral coupling (Cu(0)-, Cu(II)- or Fe(III)-catalyzed), and then resolved and reduced to afford enantiomeric ligands (**a** → **c** → **b** →**d**);

(IV) Starting with a monomeric disubstituted aryl phosphine oxide, diastereoselective coupling (Cu(0)-, Cu(II)- or Fe(III)-catalyzed) with tethered chiral linker affords chiral biaryl phosphine oxide that is further reduced (**a** → **bc** → **d**).

In this chapter, the development of synthetic routes for a series of C_3*-TunePhos bisphosphine ligands and related bisaminophosphine ligands will be discussed. Their applications in Ru-catalyzed asymmetric hydrogenation of unfunctionalized ketones and keto ester, as well as in Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives will be studied.

2.2. Results and Discussion

2.2.1. TunePhos and C_3*-TunePhos Ligand Synthesis

According to the research work in the past decades, the fact that enantioselectivities are mostly substrate-dependent determines the necessity of

developing a chiral ligand library for different substrate types. Within the library, finely tuning of the steric and/or electronic properties of the chiral ligand may result in significant variations of its performance in asymmetric catalysis, in terms of reactivity and/or enantioselectivity. The tunable feature of chiral ligands provides latitudes to minimize the transition state energy when the substrate approaches. From the mechanistic perspective, the dihedral angle of the biaryl backbone is expected to have a strong influence on enantioselectivity.[8] Extensive studies by several research groups have demonstrated that changing bite angles of chelating bisphosphines have dramatic effects on the reactivity and stereoselectivity of reactions.[9] Thus, a family of modular C_n-TunePhos were designed and synthesized in our research group to connect the two phenyl rings in the biaryl scaffold with a linking bridge of tunable length (Figure 2-1).[10,11]

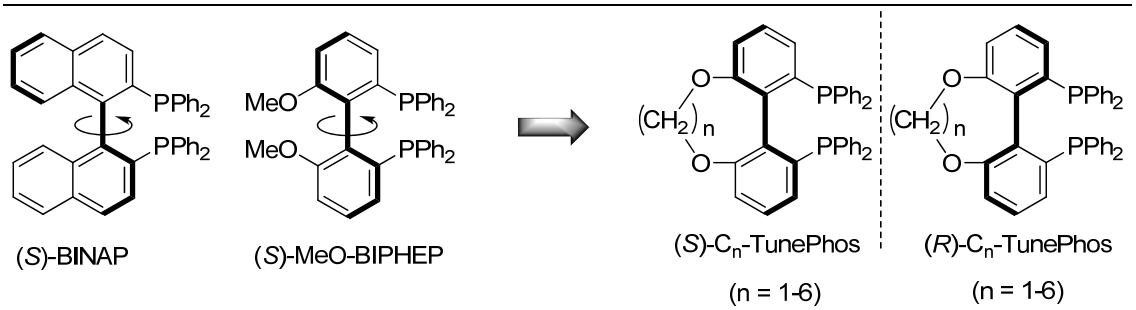
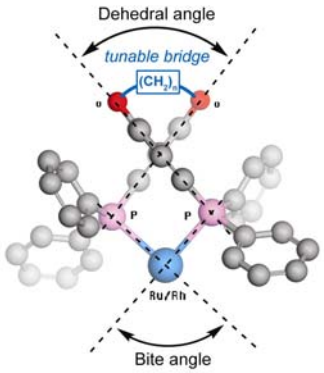


Figure 2-1: Design of C_n-TunePhos.

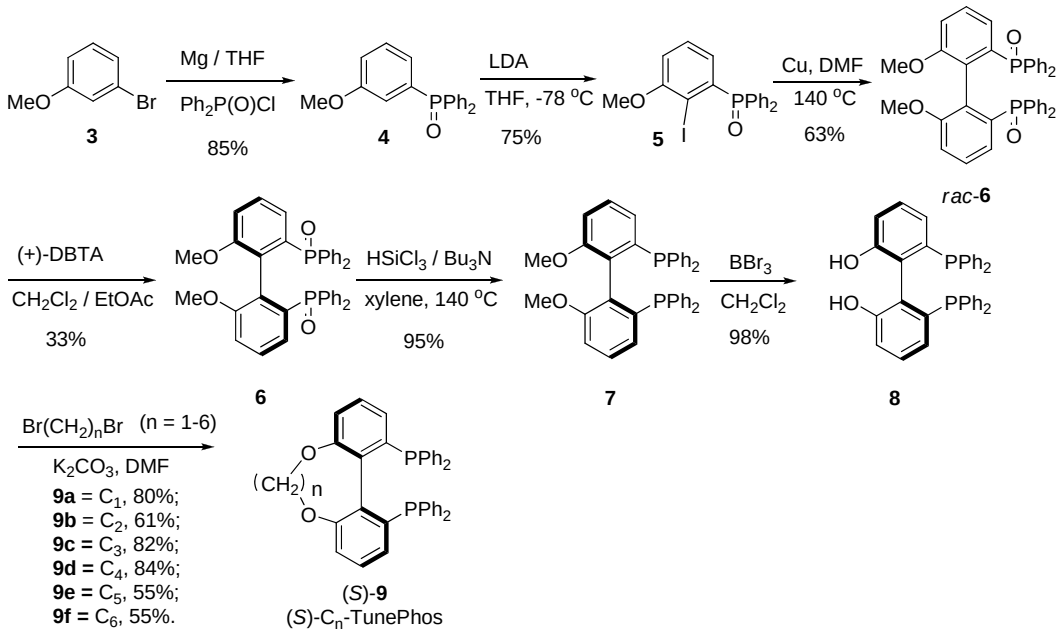
The added linkage not only minimizes the conformational rotation but also defines the dihedral angle and hence further the bite angle with enhanced precision. MM2 calculation indicated that the bite angle of the C_n-TunePhos family in the form of free ligand range from 60^o to 106^o; for each ligand, a discrete value is settled by the tethering linkage (Figure 2-2).



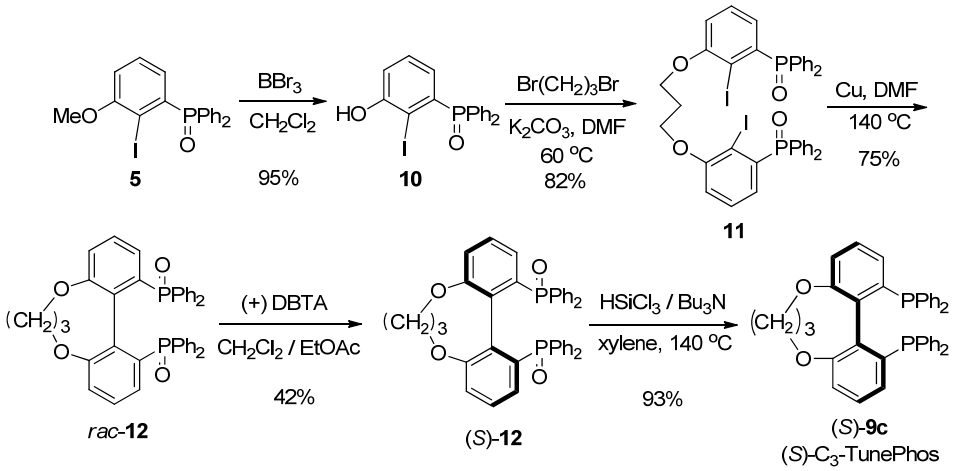
C_n-TunePhos						BINAP
C_1	C_2	C_3	C_4	C_5	C_6	
60°	74°	77°	88°	94°	106°	87°

Figure 2-2: MM2 Calculation of Bite Angles of C_n-TunePhos and BINAP (free ligand).

The initially developed synthetic route started from optically pure MeO-BIPHEP, which could be prepared according to the reported procedure. Reaction of HO-BIPHEP with different length of dibromo alkanes in the presence of excess anhydrous K_2CO_3 in DMF formed C_1- to C_6-TunePhos ligand in moderate yields (55−84%) (Scheme 2-6). To prepare the TunePhos ligands more efficiently in large scales, an improved route was explored to avoid column chromatography for the purification of intermediates as well as the final products. It is noteworthy that the copper-catalyzed intramolecular Ullmann coupling of the racemic diphenylphosphine oxide **11** gave 82% yield and the resolution of racemic **12** was achieved by either (+)- or (−)-2,3-dibenzoyl tartaric acid (DBTA) (Scheme 2-7). Development of this improved and scalable route provided practical accessibility of TunePhos, especially C_3-TunePhos, even on kilogram scale.



Scheme 2-6: Initial Synthetic Route of C_n-TunePhos Ligands.



Scheme 2-7: Improved Synthetic Route of C_3-TunePhos

The linker effect study provided significant advantages of optimizing bite angles towards enantioselectivities for different substrates, such as enol acetates,[12 a] α-phthalimide ketones,[12b] and cyclic β-dehydroamino esters.[12c] Beside optimization of the alkyl linker length, we envision that other strategies, such as P-substituent effect and

ortho-substituent effect, could also help to vary the properties of TunePhos ligands within the family library (Figure 2-3). Based upon the reports from Takasago group and other research groups, BINAP and SEGPHOS derivatives with various installed aryl and alkyl P-substituents displayed unique steric and electronic properties.[13] We expect that introduction of more steric hindered P-substituents other than phenyl group (e.g. 3,5-xylyl) in TunePhos ligands will be an important structural modification, which may lead to significant enhancement of ligand performance towards many substrates such as unfunctionalized ketones.

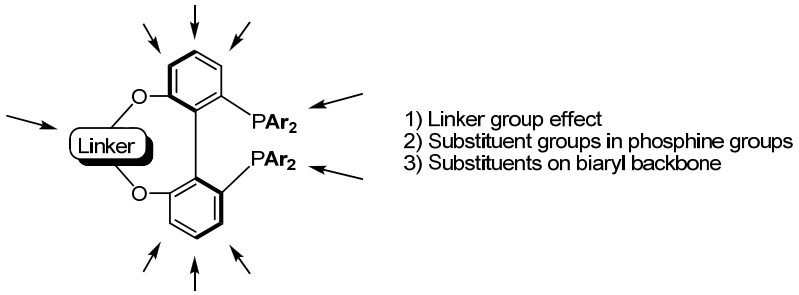


Figure 2-3: Strategies of Developing TunePhos Ligand Derivatives.

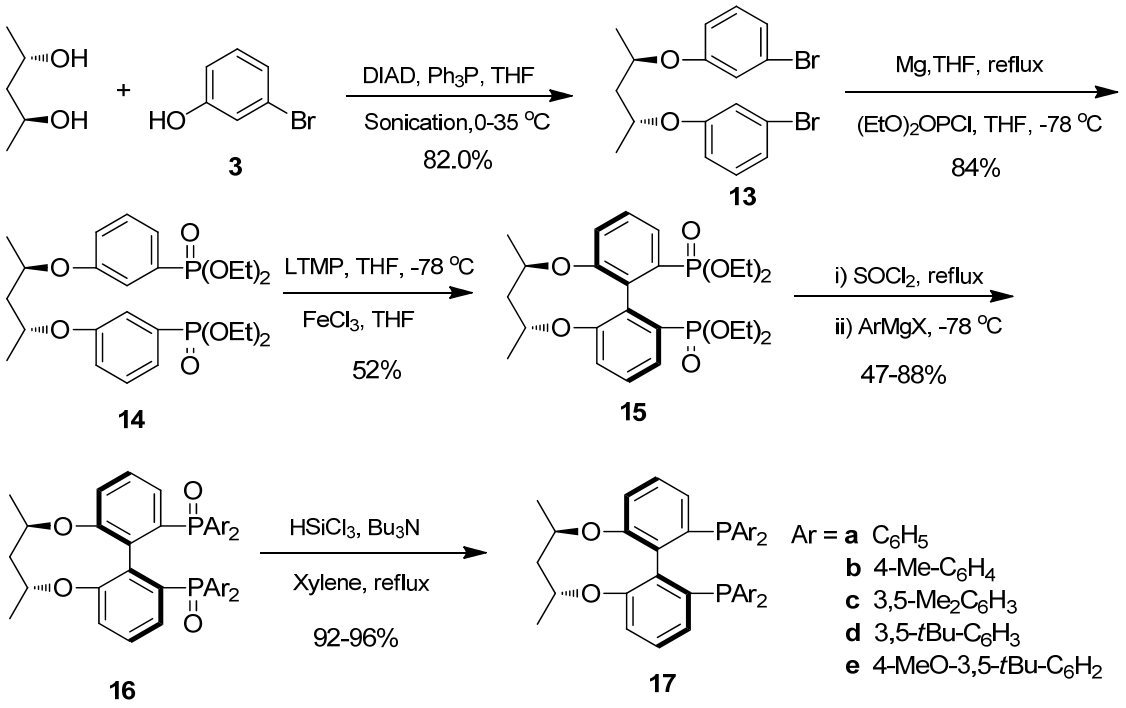
Owing to the success of the previously mentioned improved synthetic path of C_3-TunePhos, we attempted to synthesize 3,5-xylyl-C_3-TunePhos via similar convenient procedure, however the key step of which involved the resolution of the corresponding racemic diphosphine oxides with (+)- or (−)-2,3-dibenzoyl tartaric acid (DBTA). The unsuccessful attempts after extensive efforts urged us to reevaluate this synthetic strategy. The intrinsic drawbacks of this strategy encouraged us to search for other solutions: i) to obtain enantiopure diphosphine oxides, the resolution step is essential yet highly tedious, in terms of the many parameters involved, such as resolution reagents, solvents (single or mixture), temperature, etc.; ii) the optimal yield is limited to only 50%, let along the loss

after several fractional recrystallizations that are often necessary for ee improvement; iii) the high cost of the resolution reagent and waste of the undesired enantiomer made this strategy an expensive and noneconomic procedure, especially for further practical applications.

A subsequent careful screening of different strategies of chirality introduction such as desymmetrization of prochiral biaryls and kinetic resolution of racemic substrates, resulted in our particular attention to the methodology of central-to-axial chiral induction. This strategy could be described as chemoselective and highly diastereoselective coupling of two aryl fragments linked to a chiral tether auxiliary, e.g. enantiopure 1,2-diphenyl-1,2-ethane diol or 2,3-butanediol.[14] The Sugimura group successful application of enantiopure 2,4-pentanediol in the chirality transfer to synthesize BINOL analogues demonstrated the strict stereo-control during the process that two moieties connected to the chiral diol tether are coupled on *ortho* positions.[15] Subsequent report by the Chan group further applied similar strategy to the synthesis biaryl bisphosphines, in which an intramolecular Ullmann coupling or Fe(III)-catalyzed oxidative coupling fulfilled the chirality transfer.[16]

Therefore, enlightened by all these previous related work, we successfully developed a highly efficient and divergent synthetic route for the synthesis of a series of C_3*-TunePhos with different aryl groups on the phosphorus atoms (Scheme 2-8).[17] This straightforward route started Mitsunobu reaction of 3-bromophenol and chiral 2,4-pentanediol under sonication conditions (88% yield). Then, the dibromide **13** was converted to corresponding bisphosphate **14** before the one-pot reaction consisting of *ortho*-lithiation by lithium 2,2,5,5-tetramethylpiperidide (LTMP) and Fe(III)-catalyzed

oxidative coupling. The product of the diastereoselective coupling, **15**(>99% de confirmed by ^{1}H NMR and HPLC analyses), then serve as the late-stage common intermediate, which lead to a modular series of C_3*-TunePhos after undergoing substitution with various Grignard reagents and reduction with $HSiCl_3$ and Bu_4N. Different steric hindered aryl groups such as 4-Tol, 3,5-Xyl, 3,5-*t*Bu-Ph, 4-MeO-3,5-*t*Bu -Ph groups were introduced with decent overall yields.

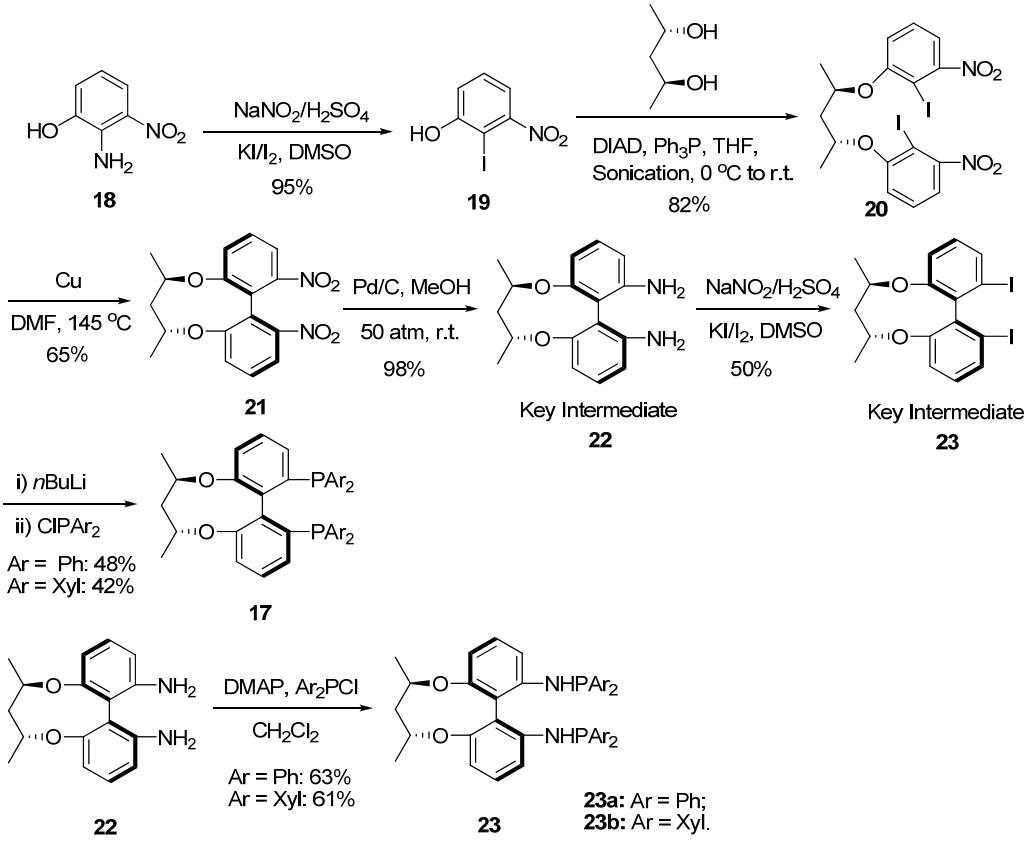


Scheme 2-8: Divergent Synthesis of C_3*-TunePhos Ligands.

The introduction of the additional chiral centers on the linker group provides restriction of the conformational flexibility and possibly influence the ligand performance in asymmetric hydrogenations. Intramolecular coupling of the less steric hindered bisphosphate **14** improves the usually limiting yield of the coupling step and facilitates the convenience of introducing bulky aryl substituents. All these advantages made this

route a strategically well-defined and practical process for the preparation of the new C_3*-TunePhos.

2.2.2. Alternative Efficient Synthesis of C_3*-TunePhos and Related Bisaminophosphine Ligands



Scheme 2-9: Alternative Divergent Synthesis of C_3*-TunePhos and Preparation of Chiral Bisaminophoshpine Ligands **23**.

As a parallel attempt to achieve the same goal, C_3*-TunePhos ligands, an alternative synthetic route was also successfully developed based upon the same central-to-axial chirality transfer strategy yet from different starting materials (Scheme 2-9). [18]

2-Iodo-3-nitrophenol **19** underwent Mitsunobu reaction with chiral 2,4-pentanediol to afford bisnitro species with 87% yield. In this path, Ullmann coupling proceeded in an intramolecular fashion to accomplish the induction of the axial chirality from the stereogenic center on the linker group. Followed by the smooth hydrogenation by Pd/C (98% yield) and a one-pot iodination step (50% yield), a key enantiomerically pure 2,2′-diiodo intermediate **20** was afforded. Subsequently, the 2,2′-diiodo intermediate **20** was readily transformed to corresponding bisphosphine ligand product in moderate yields by consecutive treatment of **23** with *n*BuLi and corresponding diarylphosphine chloride at low temperature (−78 ^{o}C).

The X-ray structure analysis confirmed the *S* configuration of the axial chirality in the well-defined single crystal structure. Furthermore, the accessibility of this bisamino intermediate **22** could make the preparation of related C_2-symmetric bidentate ligand such as bisaminophosphines. Recently, the Chan group reported the synthesis of H8-BDPAB and BDPAB, and their application in asymmetric hydrogenation of arylenamides and α-dehydroamino acid derivatives.[19]

Therefore, based upon the bisamino intermediate **22** that we prepared, we developed novel bisaminophosphine ligands with phenyl and xylyl P-substituent in one-step synthesis. In the presence of 4-dimethylaminopyridine (DMAP), bisaminophosphine ligand were obtained in moderate yields after reaction with the corresponding diarylphosphine chlorides (63% and 61% yield respectively for **23a** and **23b**) (Scheme 2-9).[20]

2.2.3. Ru−C_3*-TunePhos Catalyzed Asymmetric Hydrogenations

Catalytic enantioselective hydrogenation of prochiral ketones has been a powerful method to prepare enantiomerically pure secondary alcohols, which are key structural elements in a large number of pharmaceutical products.[21] For example, (*R*)-1-(3,5-bis(trifluoromethyl)phenyl)ethanol is a key intermediate in the synthesis of the neurokinin 1 (NK_1) receptor antagonist Emend®(Aprepitant; Figure 2-4).[22] This FDA approved drug is for prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV).

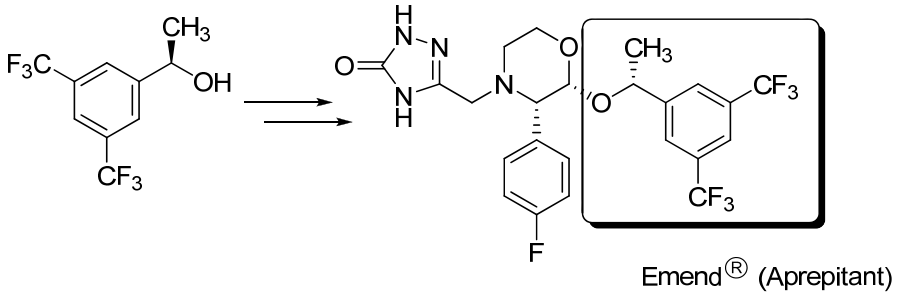
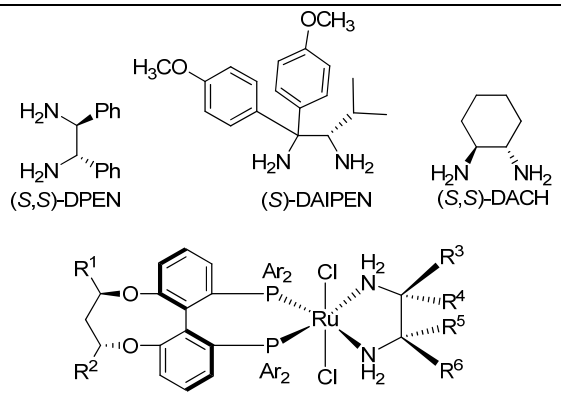


Figure 2-4: Structure of Emend® (Aprepitant).

The milestone discoveries have been done by Noyori and coworkers who developed the BINAP–ruthenium–diamine complexes as a highly effective catalyst system for asymmetric hydrogenation of ketones.[23] Prompted by this fundamental study, a few analogue ligands, such as PhanePhos,[24] P-Phos,[25] and SDP ligand,[26] were developed and proved to be effective for the ruthenium-catalyzed asymmetric hydrogenation. However, development of more efficient catalyst systems comprising of more readily accessible ligands of high enantioselectivity for practical applications[27] is still of significant importance for chemists.[28]

Despite of great success that has been achieved, asymmetric hydrogenation of ketones has not gained as same amount of attentions in the practical applications as in academia. The main obstacles include the use of high level of metal catalysts which not only dramatically increases the cost but also raise serious issues of heavy metal contamination. Thus it is necessary to develop and demonstrate such catalytic systems, which remain effective even at an extremely low level without compromising the selectivity.



(*S*),(*S*,*S*)-**24a**: Ar = C_6H_5; $R^1 = R^2$ = H; diamine = (*S*,*S*)-DPEN;
(*S*),(*S*,*S*)-**24b**: Ar = C_6H_5; $R^1 = R^2 = CH_3$; diamine = (*S*,*S*)-DPEN;
(*S*),(*S*,*S*)-**24c**: Ar =4-MeC_6H_4; $R^1 = R^2 = CH_3$; diamine = (*S*,*S*)-DPEN;
(*S*),(*S*,*S*)-**24d**: Ar =3,5-$Me_2C_6H_3$; $R^1 = R^2 = CH_3$; diamine = (*S*,*S*)-DPEN;
(*S*),(*S*,*S*)-**24e**: Ar = 3,5-$Me_2C_6H_3$; $R^1 = R^2 = CH_3$; diamine = (*S*,*S*)-DACH;
(*S*),(*S*)-**24f**: Ar = 3,5-$Me_2C_6H_3$; $R^1 = R^2 = CH_3$; diamine = (*S*,*S*)-DAIPEN;

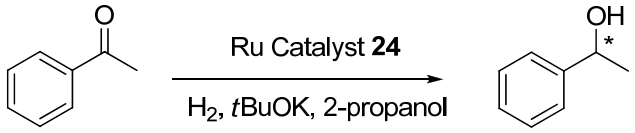
Figure 2-5: Structures of Various Chiral 1,2-Diamines Studied and TunePhos–Ru(II)–1,2-diamine Precatalysts.

To illustrate potential utilities of the synthesized C_3*-TunePhos ligands that were designed to achieve superior enantioselectivities by their highly modular nature, envisioned that application of these ligands in diphosphine–ruthenium–diamine system for reduction of simple ketones is a natural choice.

By employing Noyori's protocol,[23a] the bisphosphine ligands C_3-TunePhos and C_3*-TunePhos were reacted with $[Ru(benzene)Cl_2]_2$ in DMF and this was followed by addition of different chiral diamines (Figure 2-5). The resulting diphosphine–ruthenium–diamine complexes were used as the precatalyst directly in the hydrogenation reactions without any further purification. We initiated our studies by screening catalysts **24a**–**f** in the hydrogenation of acetophenone. Under the conditions of room temperature (20–22 ˚C), 50 atm H_2, 2-propanol as solvent, and *t*BuOK as the base (substrate/base = 220), (*S*)-C_3-TunePhos and DPEN (DPEN = 1,2-diphenyl ethylenediamine) were utilized to distinguish the matching/mismatching stereochemical elements between the two chiral components in this catalyst system. From the results in entries 1 and 2 in Table 2-1, it can be derived that the (*S*,*S)*- isomer of DPEN should be the matching partner with (*S*)-C_3-TunePhos.

Thereafter when switching to the modular (*S*)-C_3*-TunePhos, the highest enantioselectivity 98.0% ee was achieved by applying precatalyst (*S*),(*S*,*S*)-**24d** (Table 2-1, entry 6) when assessing the effect from aryl substituents in the phosphine moiety. On the other hand, when the chiral diamine was further replaced by DACH (*trans*-1,2-diaminocyclohexane), the ee value decreased to 91.2% (Table 2-1, entry 7).

Table 2-1: Screening of Ru(II)−TunePhos−Diamine Precatalyst **24** for the Hydrogenation of Acetophenone.[a]



Entry	Catalyst	S/C[b]	t (h)	Conv. (%)[c]	Ee % (Config.)[d]
1	(*S*),(*S*,*S*)-**24a**	10,000	2	>99.9	83.3 (*R*)
2	(*S*),(*R*,*R*)-**24a**	10,000	2	>99.9	24.3 (*S*)
3	(*S*),(*S*,*S*)-**24b**	10,000	2	>99.9	83.0 (*R*)
4	(*S*),(*S*,*S*)-**24c**	10,000	2	>99.9	79.5 (*R*)
5	(*S*),(*R*,*R*)-**24d**	10,000	2	>99.9	72.1 (*R*)
6	(*S*),(*S*,*S*)-**24d**	10,000	2	>99.9	98.0 (*R*)
7	(*S*),(*S*,*S*)-**24e**	10,000	2	>99.9	91.2 (*R*)
8	(*S*),(*S*)-**24f**	10,000	2	>99.9	99.8 (*R*)

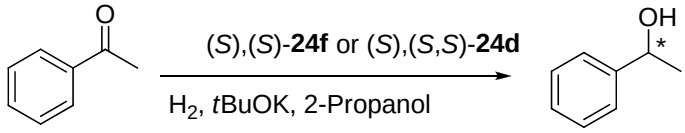
[a] Reactions were performed with 2-2.5 M solutions of acetophenone in 2-propanol with added *t*BuOK (base/Ru = 220/1) at 20-22 °C and 50 atm initial hydrogen pressure. [b] Substrate-to-catalyst molar ratio. [c] Determined by GC analysis. [d] The ee was determined by chiral GC analysis. The absolute configuration was determined by comparison of the retention times with literature data.

The best combination was then discovered until (*S*)-DAIPEN (1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine) was introduced to serve as the diamine partner. 99.8% ee was achieved (Table 2-1, entry 9) with turnover number (TON) of 10,000. It is noteworthy that this best combination is consistent with Noyori's finding with Xyl-BINAP–Ru(II)–DAIPEN system.[23b]

High catalytic capability of the catalyst (*S*),(*S*)-**24f** was further explored at even lower catalyst loading (0.001%) and milder conditions (10 atm H_2). The acetophenone substrate was smoothly hydrogenated within 12 hours, without any ee value erosion (99.8% ee) (Table 2-2, entry 2). Furthermore, when TON was increased to 500,000, this

highly active catalyst can still retain over 99% ee enantioselectivity within 24 hours under 50 atm H_2 pressure (Table 2-2, entry 3). To test the maximum catalytic reactivity, in an illustrative extreme example of high TON (TON=1,000,000), the catalyst reached 94.5% conversion with 98.0% ee (Table 2-2, entry 4). These results indicate that this ruthenium catalyst is practically useful to prepare a variety of chiral alcohols under mild operational pressure. [29,23a]

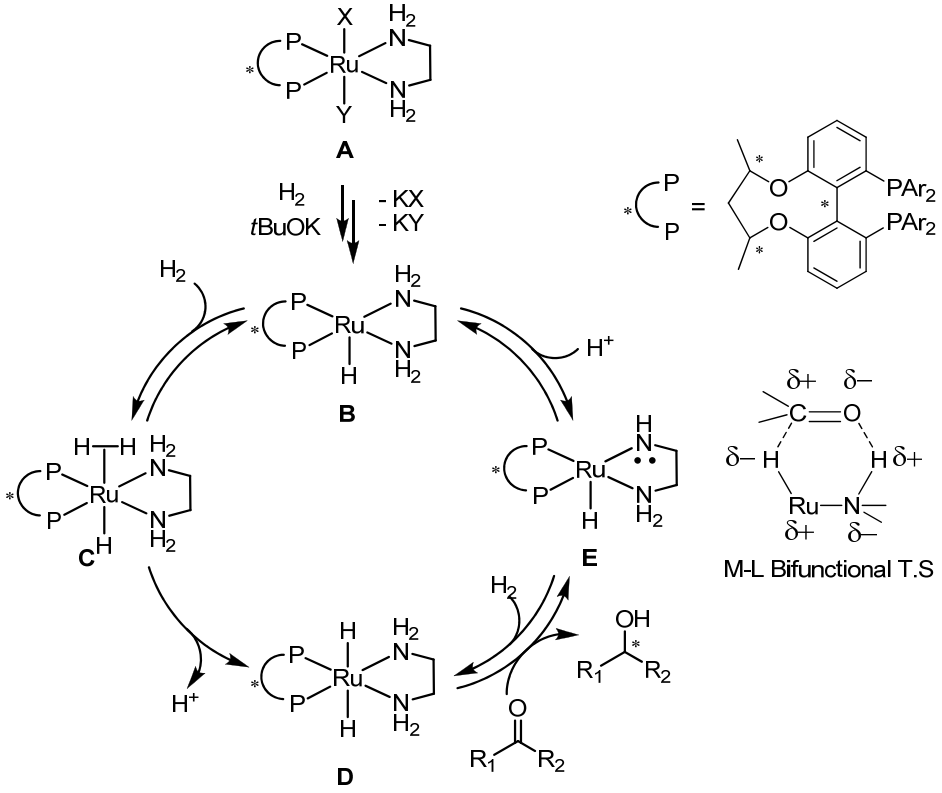
Table 2-2: High Turnover Number (TON) Studies.[a]



25a **26a**

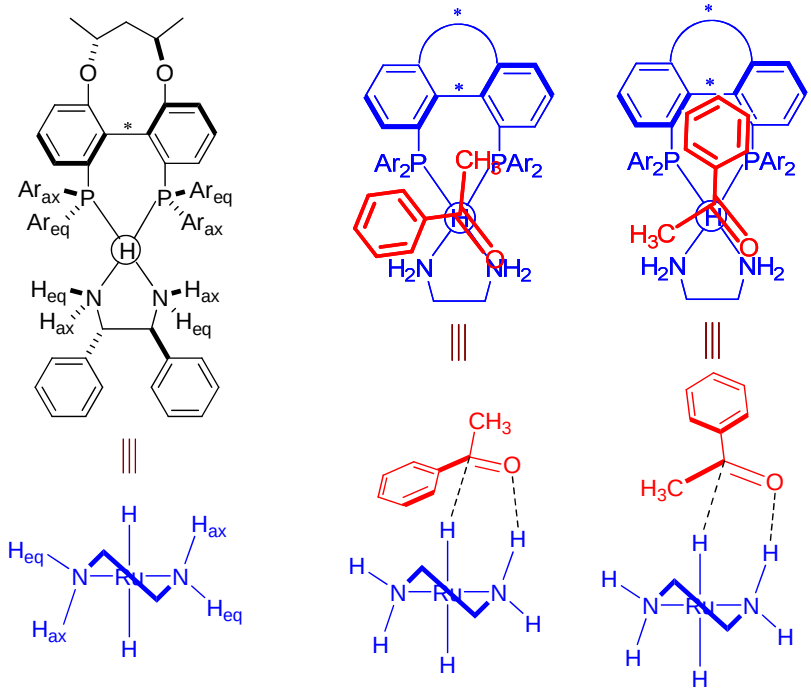
Entry	Catalyst	S/C[b]	t (h)	H_2 Pressure (atm)	Conv. (%)[c]	ee %(config.)[d]
1	(*S*),(*S*)-**24f**	10,000	4	10	>99.9	99.8 (*R*)
2	(*S*),(*S*)-**24f**	100,000	12	10	>99.9	99.8 (*R*)
3	(*S*),(*S*)-**24f**	500,000	24	50	97.0	99.2 (*R*)
4	(*S*),(*S*,*S*)-**24d**	1,000,000	48	50	94.5	98.0 (*R*)

[a] Reactions were performed with 2-2.5 M solutions of acetophenone in 2-propanol with added *t*BuOK (base/Ru = 220/1) at 20-22 ^{o}C . [b] Substrate-to-catalyst molar ratio.[c] Determined by GC analysis. [d] The ee was determined by chiralGC analysis. The absolute configuration was determined by comparison of the retention times with literature data.



Scheme 2-10: Proposed Mechanism for Ru-Catalyzed Hydrogenation of Simple Ketones.

The mechanism of such ketone hydrogenation reaction by Ru–C_3*-TunePhos of extremely high reactivity and outstanding enantioselectivity could be postulated analogous to that of Ru–BINAP catalyst (Scheme 2-10).[30] The base additive (typically *t*BuOK) played a crucial role in the initiation step (**A** to **B**) and also importantly a kinetic role. As suggested by Noyori *et al*.,[30,31] the cationic 16e complex **B** reacts with H_2 reversibly to form the 18e complex **C**, which undergoes deprotonation from the η^2-H_2 ligand to generate the reducing Ru dihydride species **D**. The ketone comes into the cycle to react with the catalytically reactive species **D** through a key six-membered ring transition state. When the ketone substrate reacts with the coordinatively saturated metal complex **D**, a metal-ligand bifunctional mechanism proceeded by delivering a hydride from the Ru center and a proton from the NH_2 moiety simultaneously (Scheme 2-10).



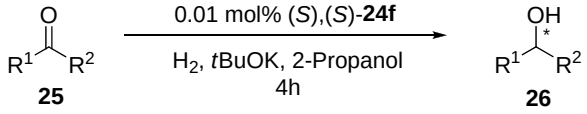
Scheme 2-11: Mechanistic Scenario of the Origin of Enantioselectivity.

The C=O group in the substrate does not actually interact with the Ru metal center, and the alcohol product is formed without forming a metal alkoxide intermediate. This irreversible step determines the enantioselection via the steric interaction of the aryl group and the bulk in the catalyst that provides a well-defined chiral environment (Scheme 2-11). After the protonation of **E** by the alcoholic solvent, the regeneration of **B** completed the cycle.

To explore the synthetic utility of this catalyst, we have surveyed the substrate scope. A systematic study of the general efficiency included different acetophenone analogues bearing different substituent groups on the phenyl ring, heteroaromatic ketones, and some aliphatic ketones (**25a-r**)(Table 2-3). Good conversions (>99.9%) were observed for all substrates, with ee values ranging from 93.2% to 99.8%. The catalyst showed high tolerance of the various substituent groups on the *meta*- and *para*- positions

bearing different electronic properties (entries 3 to 9). Substrates containing electron-donating groups such as methyl group or methoxy group, and substrates containing electron-withdrawing groups such as Cl group (**25e** and **25h**) or F (**25i**) group were hydrogenated successfully at 0.01% catalyst loading within 4 hours under 10 atm H_2 pressure, all giving >99% ee.

Table 2-3: Asymmetric Hydrogenation of Ketones **25**.[a]



Entry	Substrate	R^1	R^2	Product	Conv.(%)[b]	Ee % (Config.)[c]
1	**25a**	C_6H_5	CH_3	**26a**	>99.9	99.8 (*R*)
2[d]	**25b**	C_6H_5	C_2H_5	**26b**	>99.9	99.8(*R*)
3	**25c**	*m*-$CH_3C_6H_4$	CH_3	**26c**	>99.9	99.7(*R*)
4	**25d**	*m*-$CH_3OC_6H_4$	CH_3	**26d**	>99.9	99.6(*R*)
5	**25e**	*m*-ClC_6H_4	CH_3	**26e**	>99.9	99.5(*R*)
6	**25f**	*p*-$CH_3C_6H_4$	CH_3	**26f**	>99.9	99.6(*R*)
7	**25g**	*p*-$CH_3OC_6H_4$	CH_3	**26g**	>99.9	99.6(*R*)
8	**25h**	*p*-ClC_6H_4	CH_3	**26h**	>99.9	99.6(*R*)
9	**25i**	*p*-FC_6H_4	CH_3	**26i**	>99.9	99.3(*R*)
10	**25j**	3,5-$(CF_3)_2C_6H_3$	CH_3	**26j**	>99.9	99.6(*R*)
11	**25k**	2-furyl	CH_3	**26k**	>99.9	99.6(*R*)
12	**25l**	2-thienyl	CH_3	**26l**	>99.9	99.7(*R*)
13	**25m**	2-naphthyl	CH_3	**26m**	>99.9	99.7(*R*)
14	**25n**	1-naphthyl	CH_3	**26n**	>99.9	97.0(*R*)
15	**25o**	*o*-$CH_3C_6H_4$	CH_3	**26o**	>99.9	97.5(*R*)
16	**25p**	cyclopropyl	CH_3	**26p**	>99.9	97.9(*R*)
17	**25q**	*trans*-PhCH=CH	CH_3	**26q**	>99.9	97.4(*R*)
18[d]	**25r**	C_6H_5	cyclopropyl	**26r**	>99.9	93.2(*R*)

[a] Unless otherwise noted, reactions were performed with 2-2.5 M solutions of acetophenone in 2-propanol with added *t*BuOK (base/Ru = 220/1) at 20-22 ^oC for 4h and 10 atm initial hydrogen pressure. Catalyst loading was 10,000. [b] Determined by GC. [c] The *ee* were determined by chiral GC analysis. The absolute configuration was determined by comparison of the retention times withliterature data. [d] Reaction time was 8 h.

Meanwhile, heteroaromatic ketones, 2-acetofuran (**25k**) and 2-acetothiophene (**25l**), were also equally converted to corresponding alcohol products with >99% ee. The

hydrogenation of some alkyl ketones, for example cyclopropyl methyl ketone (**25p**), also proceeded efficiently (97.9% ee, entry 16).

In another example, under the mild conditions, hydrogenation of *trans*-4-phenyl-3-butenone (**25q**) afforded the product quantitatively in 97.4% ee, highly selectively reducing the ketone without reduction of the C=C bond (entry 17). It noteworthy that the result (99.6% ee) in Table 2-3, entry 10 justified the potential utility of this Ru–C_3*-TunePhos complex in the practical synthesis of Emend® (Aprepitant).

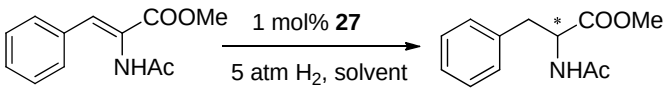
2.2.4. Rh−Bisaminophosphine Catalyzed Asymmetric Hydrogenations

The great importance of chiral α-amino acids and their derivatives in pharmaceutical, agricultural and biological chemistry has made their synthesis a central theme in organic chemistry. Asymmetric hydrogenation of *α*- and *β*-dehydroamino acids has been demonstrated as one of the most successful synthetic approaches. Since the very first achievements by Knowles [32] and Kagan [33], asymmetric hydrogenation of dehydroamino acids has now become a typical reaction to evaluate the efficiency of new chiral phosphine ligands. A large number of catalysts have been examined and considerable success has been made.[34]

To study the application of the synthesized bisaminophosphine ligands, we have explored the Rh-catalyzed hydrogenations of α-dehydroamino acid esters. The catalysts [Rh (cod)**23a**]BF_4 (**27a**) and [Rh (cod)**23b**] BF_4 (**27b**)were prepared as a reddish brown solids from [Rh $(cod)_2$]BF_4 and the corresponding ligand in dichloromethane at room temperature for 20 minutes. The complexes obtained were used directly in the catalytic reactions without further purifications.

We initiated our studies by screening catalysts **27a,b** and solvents in the asymmetric hydrogenation of methyl 2-acetamido-3-phenylpropanoate (**28a**) as the model. Under optimized conditions, the reaction was performed at room temperature under 5 atm hydrogen pressure. Both catalysts were found to be effective for this hydrogenation reaction, giving complete conversion within 12 h with 1 mol% catalyst loading.

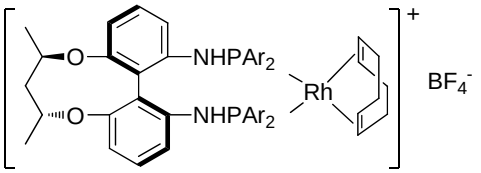
Table 2-4: Ligand and Solvent Screening for the Asymmetric Hydrogenation of Methyl 2-Acetamido-3-phenylpropanoate **28a**.[a]



28a **29a**

Entry	Catalyst	Solvent	Conv. (%)[b]	Ee % (Config.)[c]
1	(*S*)-**27a**	THF	>99	93 (*S*)
2	(*S*)-**27a**	CH_2Cl_2	>99	97 (*S*)
3	(*S*)-**27a**	CH_3OH	>99	95 (*S*)
4	(*S*)-**27b**	Acetone	>99	95 (*S*)
5	(*S*)-**27b**	EtOAc	>99	91 (*S*)
6	(*S*)-**27b**	Toluene	>99	97 (*S*)
7	(*S*)-**27b**	CH_2Cl_2	>99	97 (*S*)
8	(*S*)-**27b**	CH_3OH	>99	98 (*S*)

[a] All reactions were performed under 5 atm initial hydrogen pressure for 12h at room temperature. [b] Conversions and enantiomeri excesses were determined by chiral GC using a Chiralsil-Val column. [c] Absolute configurations of the product were determined by comparison of the GC retention times with the reported data in the literature.



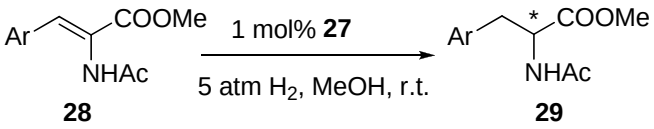
27

27a: Ar = Ph;
27b: Ar = Xyl.

The enantioselectivities achieved in these reactions are shown in Table 2-4. In the presence of complex **27a**, up to 97% ee and >99% conversion were observed (entry 2). The initial screen indicated that the introduction of more sterically bulky 3,5-dimethyl groups gave the best enantioselectivity, up to 98% ee in methanol (Table 2-4, entry 8).

Under the optimized reaction conditions, a variety of α-dehydroamino acid esters **28a–l** was examined (Table 2-5). For all substrates tested, the catalyst **27b** displayed the same or superior performance than **27a** under the same conditions. All the substrates were reduced to form chiral aminocarboxylic acids with excellent enantioselectivities (93–98% ee). The electronic and steric nature of a substituent on the phenyl ring of the substrate had minimal influence on the enantioselectivity and reactivity of the reaction. These enantiomeric excesses were comparable or better in some cases than those obtained when the similar ligand system Xyl-BDPAB or DMBDPPABD was employed.[35] In addition, hydrogenation of the substrate **28c** with a reduced catalyst loading (ligand **27b**, 0.1 mol %) still afforded the corresponding product in full conversion with 96% ee. (Table 2-5, entry 4).

Table 2-5: Rh-catalyzed Asymmetric Hydrogenation of α-Dehydroamino Acid Esters **28**.[a]



28 **29**

Entry	Ar	Product	Ee (%)[b] (Config.)[c]	
			27a	**27b**
1	Ph	**29a**	95 (*S*)	98 (*S*)
2	3,5-F-C_6H_3	**29b**	94 (*S*)	96 (*S*)
3	*o*-FC_6H_4	**29c**	96 (*S*)	98 (*S*)
4[d]	*o*-FC_6H_4	**29c**	-	96 (*S*)
5	*o*-ClC_6H_4	**29d**	96 (*S*)	96 (*S*)
6	*o*-BrC_6H_4	**29e**	97 (*S*)	97 (*S*)
7	*m*-BrC_6H_4	**29f**	93 (*S*)	94 (*S*)
8	*p*-FC_6H_4	**29g**	96 (*S*)	98 (*S*)
9	*p*-ClC_6H_4	**29h**	95 (*S*)	98 (*S*)
10	*p*-BrC_6H_4	**29i**	96 (*S*)	96 (*S*)
11	*p*-$CF_3C_6H_4$	**29j**	93 (*S*)	95 (*S*)
12	*p*-$MeOC_6H_4$	**29k**	93 (*S*)	96 (*S*)
13	*p*-$NO_2C_6H_4$	**29l**	95 (*S*)	95 (*S*)

[a] Unless otherwise noted, all reactions were performed with 1mol% catalyst loading under 5 atm initial hydrogen pressure for 12h at room temperature. All conversions were >99%. [b] Enantiomeric excesses were determined by chiral GC using a Chirasil-Val column or chiral HPLC using Chiral cel OD-H column. [c] Absolute configurations of the products were determined by comparison of the retention times with the reported data in the literature.[d] Catalyst loading was 0.1 mol%.

2.3. Conclusion

In conclusion, we have designed and synthesized an important family of atropisomeric biaryl bisphosphine ligands, C_3*-TunePhos and related bisaminophosphines. These new ligands with highly modular P-substituents have been

explored to be highly efficient for the asymmetric hydrogenation of *α*-, *β*- keto esters and *N*-2-substituted allylphthalimides. We have developed a highly efficient Ru catalyst system for practical asymmetric hydrogenations of a wide range of unfunctionalized ketones. Its nature of extremely high reactivity and enantioselectivity, broad substrate scope and mild reaction conditions enables practical application for production of enantiomerically enriched alcohols. The synthetic utility of bisaminophosphine ligands was studied for rhodium-catalyzed asymmetric hydrogenations of *α*-dehydroamino acid esters. Up to 98% ee values were achieved for the enantioselective syntheses of aminocarboxylic acid derivatives.

Experimental Section

General Remarks. All reactions and manipulations were performed in a nitrogen-filled glovebox or under nitrogen using standard 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, and DRX-400 MHz spectrometers. J values are in Hz. Chemical shifts were reported in ppm upfield to tetramethylsilane with the solvent resonance as the internal standard. MS spectra were recorded on a KRATOS mass spectrometer MS 9/50 for electrospray (-). Enantiomeric ratios were determined by chiral GC or HPLC analysis.

Synthesis of (2*R*,4*R*)-2,4-Bis(3-bromophenoxyl)pentane 3:[17] A solution of (2*S*,4*S*)-pentanediol (8.0 g, 76.9 mmol), 3-Bromophenol (28.2g, 160 mmol), PPh_3 (42.0g, 160 mmol) in anhydrous THF (38 mL) in a 500 mL conical flask was stirred at 0 °C for 30 min. To the above highly concentrated solution was added dropwise diisopropylazadicarboxylate (DIAD, 31.4 mL, 160 mmol). The reaction flask was then placed in an ice-water bath and was sonicated for at 0 ^{o}C for several hours until large amount of white participates formed during the reaction. After triturated with 100 mL cold hexane-THF (2:1, v/v) solvent, the solids were filtered off and washed 3 times with 100 mL of hexane/THF mixture solvent. The solvents were evaporated to give a vicious yellow liquid crude product. Further purification was carried out with recrystallization in ethyl alcohol to afford pure compound **13** as a white crystal (27.9g, 82.0% yield). ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.31 (d, J = 6.1 Hz, 6H), 1.94-1.98 (m, 2H), 4.56-4.64 (m, 2H), 6.72-6.76 (m, 2H), 6.97-7.08 (m, 6H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 20.03, 44.70, 70.97, 114.68, 119.35, 122.79, 123.86, 130.51, 158.77.

Synthesis of Bisphosphate 14:[17] A suspension of dry magnesium tunings (0.129 g, 5.31 mmol) in 2.5 ml of anhydrous THF was placed under N_2 in a 50 mL three-necked flask and 0.01g I_2 were added. The suspension was heated to reflux and a solution of compound **13** (1.0 g, 5.07 mmol) in 5 mL of anhydrous THF was added dropwise via syringe. The majority of the compound **13** solution was added after the reaction was initiated. The reaction completion was indicated by the amount of Mg tunings. The resulting Grignard reagent was stirred at reflux for further 1 h. To diethyl chlorophosphate (0.93 g, 5.41 mmol) solution in THF (10 mL) was added dropwise the

above Grignard solution at –78 ^{o}C. The reaction mixture was stirred overnight. When working up, clear gray reaction mixture was quenched with saturated NH_4Cl (aq.) The aqueous layer was separated and further extracted with CH_2Cl_2 (50 mL×3) before, the combined organic layers were dried and concentrated *in vacuo*. The oily residue was purified by silica gel chromatography (EtOAc/MeOH = 20:1) to give a colorless to light yellowish oil (22.3g, 84.3% yield). ^{1}H NMR (CD_2Cl_2, TMS, 300 MHz) δ 1.23-1.33 (m, 18H), 1.98-2.03 (m, 2H), 3.97-4.06 (m, 8H), 6.67-6.69 (m, 2H), 6.98-7.00 (m, 2H) 7.20-7.29 (m, 6H); ^{13}C NMR (CD_2Cl_2, TMS, 75 MHz) δ 16.43, 16.52, 20.08, 44.83, 62.29, 62.36, 71.21, 119.13, 119.26, 120.18, 120.22, 123.99, 124.11, 129.15, 129.96, 130.19, 131.62, 158.15, 158.40; ^{31}P NMR (CD_2Cl_2, TMS, 145 MHz) δ 17.93; ESCI-HRMS Calcd. for $C_{25}H_{38}O_8P_2$ [M+H$^+$]: 529.2120. Found 529.2118; $[\alpha]^{25}_{D}$ = - 62.48 (c 1.0, MeOH).

Synthesis of Bisphosphonates 15:[17] *n*BuLi (15.4 mmol, 6.57 mL, 2.5 M solution in hexane) was added dropwise to a solution of 2, 2, 6, 6-tetramethylpiperidine (TMP, 3.08 mL, 18.3 mmol) in anhydrous THF (30 mL) at −78 ^{o}C. The cooling bath was changed to an ice/ethanol bath and the reaction mixture was stirred at about −15 ^{o}C for extra 0.5 h, then again cooled to –78 ^{o}C. A solution of compound **14** (2.412 g , 4.56 mmol) in anhydrous THF (15 mL) was added dropwise into the above reaction mixture. After stirred at −78 °C for 5 h, a suspension of anhydrous $FeCl_3$ (2.22 g, 13.7 mmol) in 30 ml THF was added in one portion to the reaction mixture. After completion of the reaction overnight (monitored with TLC), the solvent was removed under vacuum and the dark oily mixture was dissolved in CH_2Cl_2 and 2N HCl (aq.). The organic layer was separated, washed with 2N HCl (aq.), brine, dried over anhydrous Na_2SO_4 and concentrated. The

solid residue was purified by silica gel chorography (EtOAc/MeOH = 100:5). A white solid compound **15** was obtained (1.245 g, 51.8% yield). ^{1}H NMR (CD_2Cl_2, TMS, 300 MHz) δ 1.04 (t, *J* = 7.1, 6H), 1.14 (t, *J* = 7.1, 6H), 1.23 (d, *J* = 6.5, 6H), 1.65 (t, *J* = 4.0, 2H), 3.75-3.89 (m, 8H) 4.43-4.45 (m, 2H) 7.22-7.26 (m, 2H), 7.39-7.43 (m, 2H), 7.53-7.60 (m, 2H); ^{13}C NMR (CD_2Cl_2, TMS, 75 MHz) δ 16.18, 16.27, 21.99, 40.81, 61.72, 61.80, 61.84, 61.91, 76.66, 122.07, 122.12, 127.20, 127.31, 128.62, 128.85, 129.80, 132.28, 134.37, 134.43, 134.50, 134.55, 157.42, 157.68; ^{31}P NMR (CD_2Cl_2, TMS, 145 MHz) δ 16.45; ESCI-HRMS Calcd. for $C_{25}H_{36}O_8P_2$ [M+H$^+$]: 527.1964. Found 527.1970; $[\alpha]^{25}_D$ = +51.5 (c 0.86, CH_2Cl_2).

Synthesis of Bis(diphenyl phosphonates) (*S*)-16c:[17] To a solution of 4.2 g (8 mmol) of compound **15** in 20 mL of $SOCl_2$ under nitrogen was added 0.8 mL of DMF. The mixture was stirred under reflux for 36 h. After the solvent was evaporated, the residue was dissolve in THF (80 mL) and concentrated *in vacuo*. To a 3,5-Me-phenyl magnesium bromide solution prepared from a suspension of magnesium turning (1.944 g, 80 mmol) and 5-bromo-*m*-xylene (14.8 g, 80 mmol) in 80 mL THF, was added dropwise the solution of the above prepared bisphosphonate chloride solution in 80 mL THF at −78 ^{o}C. After stirring for another 1.5 h at −78 ^{o}C, the mixture was quenched with saturated NH_4Cl (aq.) at 0 ^{o}C and extracted CH_2Cl_2 (3×200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with EtOAc/MeOH = 100:4, to give compound **16a** as a white solid (5.3 g, 86.6%). ^{1}H NMR (CD_2Cl_2, TMS, 300 MHz) δ 1.20 (d, *J* = 6.4 Hz, 6H), 1.66 (t, *J* = 4.1, 2H), 4.36-4.41 (m, 2H), 6.77-6.82 (dd, *J* = 7.6 Hz, 13.5 Hz, 2H),

6.93 (d, *J* = 8.1 Hz, 2H), 7.10-7.23 (m, 6H), 7.29-7.48 (m, 12 H), 7.70-7.76 (dd, *J* = 6.8 Hz, 11.6 Hz, 4H) ; ^{13}C NMR (CD_2Cl_2, TMS, 100 MHz) δ 21.92, 40.74, 76.08, 120.88, 120.92, 126.75, 126.91, 127.69, 127.85, 128.17, 128.33, 128.38, 128.58, 130.89, 130.93, 131.33, 131.37, 132.61, 132.74, 132.67, 132.99, 133.42, 133.89, 133.98, 134.33, 134.50, 134.80, 135.71, 135.88, 157.53, 157.72; ^{31}P NMR (CD_2Cl_2, TMS, 145 MHz) δ 27.46.

Synthesis of Bisphosphonate (*S*)-16a−e:[17] Compounds **16a−e** were prepared from compound **15** by following the similar procedure described above for compound **16c**. (*S*)-**16a**: white solid (88.1% yield); (*S*)-**16b**: white solid (66.5% yield); (*S*)-**16d**: white solid (59.1% yield); (*S*)-**16e**: white solid (46.7% yield).

Synthesis of Ligand (*S*)-17a:[17] HCl_3SiH (16.8 mL, 160 mmol) was added to a solution of **16a** (5.22 g, 8 mmol) and Bu_3N (37.6 mL, 160 mmol) in anhydrous and degassed xylene (100 mL) under nitrogen atmosphere, and the mixture was heated under reflux overnight. After cooling to 0 ^{o}C, 240 mL 30% NaOH (aq.) was added, and the mixture was stirred at 60 ºC until the organic and aqueous layers well separated. The organic product was extracted with degassed toluene (3×120 mL), and the combined organic layer was washed with water (2×80 mL), saturated NaCl (aq.) and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under vacuum. The residue was washed with cold hexane (3×20 mL) to give the product **17a** as a white powder (4.98 g, 95.8%). **17a** could also be purified by flash chromatography on silica gel, eluting with EtOAc /Hexanes = 20:1. ^{1}H NMR (CD_2Cl_2, TMS, 300 MHz) δ 1.25 (d, *J* = 6.4 Hz, 6H), 1.74 (t, *J* = 3.9, 2H), 4.22-4.66 (m, 2H), 6.67 (d, J = 7.4, 2H), 6.92 (d, J =

8.0, 6H), 7.05-7.21 (m, 12H), 7.26-7.27 (m, 6H), 7.44-7.46 (m, 4H); ^{13}C NMR (CD_2Cl_2, TMS, 75 MHz) δ 22.12, 40.91, 75.69, 118.63, 127.91, 128.12, 128.15, 128.20, 128.61, 128.65, 128.68, 129.11, 133.54, 133.67, 133.81, 133.97, 134.11, 134.25, 135.84, 136.06, 136.28, 137.71, 137.77, 137.84, 138.62, 138.66, 138.70, 138.83, 138.94, 139.05, 158.14, 158.21, 158.28; ^{31}P NMR (CD_2Cl_2, TMS, 145 MHz) δ –11.89.

Synthesis of Ligand (*S*)-17b−e: Compound (*S*)-**17b−e** were prepared from corresponding bisphosphate (*S*)-**16b−e** by following the same procedure for compound (*S*)-**17a**. (*S*)-**16b**: white solid (92.7% yield); (*S*)-**16c**: white solid (93.2% yield); (*S*)-**16d**: white solid (92.2% yield); (*S*)-**16e**: white solid (91.6% yield).

Synthesis of (2*R*,4*R*)-2,4-Bis(2-iodide-3-nitrophenoxyl)pentane 20: A solution of (2*S*,4*S*)-pentanediol (4.2 g, 40.0 mmol), 2-iodo-3-nitrophenol **19** (21.8 g, 82.4 mmol), PPh3 (21.6 g, 82.4 mmol) in anhydrous THF (28.0 mL) in a 500 mL conical flask was stirred at 0 °C for 30 min. To this highly concentrated solution was added dropwise diisopropylazadicarboxylate (DIAD, 16.3 mL, 82.4 mmol) slowly. The reaction flask was then placed in an ice-water bath and was sonicated for at 0 ^{o}C for 3 hours and white participates formed during the reaction. After triturated with 500 mL cold hexane/EtOAc (4:1, v/v) solvent, the solids were filtered off and washed with hexane/EtOAc mixture solvent (3×50 mL) to give a yellow solid crude product. Further purification was carried out with recrystallization in ethanol to afford pure light yellow needle diiodide compound **20** (18.7 g, 78.2%). ^{1}H NMR (CD_2Cl_2, TMS, 300 MHz) δ 1.43 (d, *J* = 6.1, 6H), 2.14-2.19 (m, 2H), 4.83-4.92 (m, 2H), 6.87 (d, *J* = 8.4, 2H), 7.09 (d, *J* = 9.2, 2H), 7.23 (t, *J* =

8.2, 2H); ^{13}C NMR (CD_2Cl_2, TMS, 75 MHz) δ 20.19, 44.78, 74.19, 81.20, 116.18, 118.85, 130.48, 155.87, 158.40; ESCI-HRMS Calcd. for $C_{17}H_{20}N_3O_6I_2$ [M+NH^{4+}]: 615.9442. Found 615.9440; $[\alpha]^{25}_D$ = −216.5 (c = 1.24, CH_2Cl_2).

Synthesis of (*S*)-[6,6′-(2*R*,4*R*-Pentadioxy)]-(2,2′)-Bis(nitro)-(1,1′)-Biphenyl (*S*)-21: Freshly activated fine copper powder (8.00 g) and DMF (125mL) were added to a three-neck 1L round-bottom flask, a magnetic stirrer, and water condenser. The flask was vacuumed, refilled with N_2 and put in the oil bath preheated to reflux at about 140°C. The solution of diiodide **20** (17.3 g, 29.0 mmol) in DMF (20 mL) was added to the copper suspension by syringe pump with rate 5 mL/h during intensive stirring. The solution gradually changed color from yellow to dark brown. After completion of the addition, the reaction mixture was kept under the reflux for two more hours. Another batch of copper powder (4.00 g) was added in one pot to the reaction mixture which was stirred overnight. To work up, the solution was cooled and concentrated on a rotary evaporator. The residue was redissolved in CH_2Cl_2 (250 mL) followed by removal of the copper salt and excess copper powder by filtration. After washed with water and brine, the organic solvent was removed under vacuum to afford a crude yellowish brown solid. The residue was further purified via flash column chromatography on silica gel (hexane/EtOAc =6:1) to afford a brown yellow solid product (9.78 g, 97.9%). ^{1}H NMR (CD_2Cl_2, TMS, 300 MHz) δ 1.32 (d, *J* = 6.6, 6H), 1.79-1.82 (m, 2H), 4.61-4.66 (m, 2H), 7.45 (d, *J* = 8.2, 2H), 7.54 (t, *J* = 8.2, 2H), 7.85 (d, *J* = 8.2, 2H); ^{13}C NMR (CD_2Cl_2, TMS, 75 MHz) δ 21.71, 40.04, 77.32, 118.98, 123.15, 123.71, 129.83, 148.96, 158.08; ESCI-HRMS Calcd. for $C_{17}H_{20}N_3O_6$ [M+NH^{4+}]: 362.1352. Found 362.1337; $[\alpha]^{25}_D$ = +520.87 (c = 0.42, CH_2Cl_2).

Synthesis of (*S*)-[6,6′-(2*R*,4*R*-Pentadioxy)]-(2,2′)-Bis(amino)-(1,1′)-Biphenyl (*S*)-22. A catalytic amount of Pd/C (5%) in a solution of compound **21** (9.48 g, 27.5 mmol) in toluene (150 mL) was stirred at room temp under 50 atm hydrogen atmosphere for 5 hours until there was no more uptake of hydrogen. Filtration of the mixture over the Celite®, followed by evaporation of the solvent, afforded diamine product **22** as a brown solid (7.75 g, 99.2%). The product was used for the next step without further purification. ESCI-HRMS Calcd. for $C_{17}H_{21}N_2O_2$ [M+H$^+$]: 285.1603. Found 285.1599; $[\alpha]^{25}_D$ = +299.5 (c = 0.54,CH_2Cl_2).

Synthesis of (*S*)-[6,6′-(2*R*,4*R*-Pentadioxy)]-(2,2′)-Bis(aminodiphenylphosphino)-(1,1′)-Biphenyl (*S*)-23a: To a 100 ml round bottom Schlenk flask charged with diamine **22** (199mg, 0.700 mmol) and DMAP (10 mg) were added 10 mL anhydrous CH_2Cl_2 and 0.7 mL dried Et_3N. The solution was cooled with an ice-bath to 0°C. Chlorodiphenylphosphine (353 mg, 1.6 mmol) was added dropwise to the reaction mixture. After the reaction mixture was stirred at room temperature overnight, the solvent was evaporated *in vacuo*. The solid residue was purified by column chorography on silica gel (hexane/EtOAc = 6:1) under N_2. Concentration of the filtrate and removal of solvent under vacuum gave bisaminophosphine ligand **1a** (289 mg, 63.2%) as a white solid. ^{1}H NMR (CD_2Cl_2, TMS, 300 MHz) δ 1.34 (d, J = 6.5, 6H), 1.14 (t, J = 4.1, 2H), 4.54-4.56 (m, 2H), 4.62 (d, J = 7.7, 2H), 6.69 (d, J = 6.0, 2H), 7.04-7.05 (m, 2H), 7.15-7.27 (m, 22H); ^{13}C NMR (CD_2Cl_2, TMS, 75 MHz) δ 22.39, 41.25, 75.85, 110.13, 110.18, 110.42, 115.91, 115.95, 128.72, 128.79, 128.81, 129.08, 129.29, 129.92,

130.58, 130.85, 131.31, 131.60, 139.90, 140.02, 141.11, 141.35, 145.62, 145.83, 159.36; ^{31}P NMR (CD_2Cl_2, TMS, 145 MHz) δ 30.89 (s); ESCI-HRMS Calcd. For $C_{41}H_{39}N_2O_2P_2$ [M+H$^+$]: 653.2487. Found 653.2465; $[\alpha]^{25}_D$ = +72.1 (c = 0.57, CH_2Cl_2).

Synthesis of (*S*)-[6,6'-(2R,4*R*-Pentadioxy)]-(2,2′)-Bis(amino-3,5-dimethylphenylphosphino)-(1,1′)-Biphenyl (*S*)-23b: (*S*)-**23b** was prepared from corresponding bis-(3,5-dimethylphenyl)chlorophosphine by following the same procedure for compound (*S*)-**23a**. (*S*)-**23b** was obtained as white solid (61.0% yield). ^{1}H NMR (CD_2Cl_2, TMS, 300 MHz) δ 1.40 (d, *J* = 6.5, 6H), 1.87 (t, *J* = 3.9, 2H), 2.12 (s, 12H), 2.24 (s, 12H), 4.57-4.66 (m, 2H), 4.78 (d, *J* = 8.6, 2H), 6.75 (dd, *J* = 7.9, 0.8, 2H), 6.85-6.95 (m, 12H), 7.18-7.21 (m, 2H), 7.29 (t, *J* = 8.0, 2H); ^{13}C NMR (CD_2Cl_2, TMS, 75 MHz) δ 21.22, 21.31, 22.53, 41.54, 75.96, 110.09, 110.36, 115.94, 115.99, 128.15, 128.42, 128.55, 128.83, 130.03, 130.76, 130.90, 138.12, 138.21, 138.34, 138.43, 139.60, 139.68, 141.90, 142.16, 145.92, 146.15, 159.43, 159.44; ^{31}P NMR (CD_2Cl_2, TMS, 145 MHz) δ 29.04 (s); ESCI-HRMS Calcd. for $C_{49}H_{55}N_2O_2P_2$ [M+H$^+$]: 765.3739. Found 765.3724; $[\alpha]^{25}_D$ = +38.97 (c = 0.5, CH_2Cl_2).

General Procedure for Preparation of C_3-TunesPhos-Ru(II)-Diamine Precatalysts:[23a] TunePhos (0.105 mmol) and $[Ru(benzene)Cl_2]_2$ (0.05 mmol) were dissolved in anhydrous degassed DMF (6 mL) under nitrogen protection. The reaction was heated to 100˚C for 0.5-1 hours, followed by addition of diamine (0.105 mmol) at room temperature (20─22 ˚C) and stirring for 0.5−1 hours. The solvent was removed

under high vacuum and the residue was used for hydrogenations without further purification.

^{31}P NMR (162 MHz, CD_3Cl) of precatalysts:

Ru[(*S*)-Ph-C_3-TunePhos][(*S*,*S*)-DPEN] ((*S*),(*S*,*S*)-**24a**): δ = 48.49(s)

Ru[(*S*)-Ph-C_3-TunePhos][(*R*,*R*)-DPEN] ((*S*),(*R*,*R*)-**24a**): δ = 48.65(s)

Ru[(*S*)-Ph-C_3*-TunePhos][(*S*,*S*)-DPEN] ((S),(*S*,*S*)-**24b**): δ = 47.90(s)

Ru[(*S*)-*p*-Tol-C_3*-TunePhos][(*S*,*S*)-DPEN] ((*S*),(*S*,*S*)-**24c**): δ = 46.83(s)

Ru[(*S*)-Xyl-C_3*-TunePhos][(*S*,*S*)-DPEN] ((*S*),(*S*,*S*)-**24d**): δ = 48.98(s)

Ru[(*S*)-Xyl-C_3*-TunePhos][(*R*,*R*)-DPEN] ((*S*),(*R*,*R*)-**24d**): δ = 48.85(s)

Ru[(*S*)-Xyl-C_3*-TunePhos][(*S*,*S*)-DACH] ((*S*),(*S*,*S*)-**24e**): δ = 47.50(s)

Ru[(*S*)-Xyl-C_3*-TunePhos][(*S*)-DAIPEN] ((*S*),(*S*)-**24f**): δ = 50.22(s), 50.32(s)

General Hydrogenation Procedure for Asymmetric Hydrogenation of Unfunctionalized Ketones at S/C = 10,000:[26] The precatalyst **24** (0.0025 mmol) was dissolved in degassed 2-propanol (8 mL) in a 20 mL vial. A solution of *t*BuOK (1 mol/L, 0.114 mL, 0.114 mmol) and acetophenone (3.0 g, 25 mmol) were added via syringe. The resulting mixture was transferred into an autoclave, and the autoclave was purged with H_2 (50 atm, for three times) and charged with H_2 (50 atm). After stirring at room temperature (20–22 ˚C) for 2 hours, the H_2 was carefully released. The reaction solution was purified by a silica gel column to give the corresponding hydrogenation product, which was then directly analyzed by chiral GC to determine the enantiomeric excess. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.49 (d, *J* = 6.4 Hz, 3H), 2.02 (br, 1H), 4.88 (q, *J* = 6.4 Hz, 1H), 7.25-7.29 (m, 1H), 7.29-7.39 (m, 4H). Column, Supelco BETA DEX 120, 30 m × 0.25 mm × 0.25

μm; carrier gas, He (flow rate 1 mL/min); column temperature, 120 ˚C; t_R of (*R*)-1-phenylethanol, 11.46 min; t_R of (*S*)-1-phenylethanol, 12.17 min.

Procedure of High TON Tests: Reaction with Ru[(*S*)-Xyl-C_3*-TunePhos][(*S*)-DAIPEN] ((*S*),(*S*)-**1f**) at S/C = 100,000: (*S*),(*S*)-**24f** (3.1 mg, 0.0025 mmol) was dissolved in degassed 2-propanol (10 mL). 1 mL of this catalyst solution was placed in a 20 mL vial. Acetophenone (3.0 g, 25 mmol), 2-propanol (8.0 mL), and *t*BuOK in 2-propanol (1 mol/L, 0.114 mL, 0.114 mmol) were added thereafter. The resulting mixture was transferred into an autoclave, and the autoclave was purged with H_2 (10 atm, for three times) and charged with H_2 (10 atm). After stirring at room temperature (20─22 ˚C) for 12 hours, the H_2 was carefully released. The reaction solution was purified by a silica gel column to give the corresponding hydrogenation product, which was then directly analyzed by chiral GC to determine the enantiomeric excess. (*R*)-1-phenylethanol, >99.9% conversion, 99.8% ee.

Reaction with Ru[(*S*)-Xyl-C_3*-TunePhos][(*S*)-DAIPEN] ((*S*),(*S*)-**1f**) at S/C = 500,000: (*S*),(*S*)-**1f** (3.1 mg, 0.0025 mmol) was dissolved in degassed 2-propanol (10 mL). 0.2 ML of this catalyst solution was placed in a 20 mL vial. Acetophenone (3.0 g, 25 mmol), 2-propanol (8.0 mL), and *t*BuOK in 2-propanol (1 mol/L, 0.114 mL, 0.114 mmol) were added thereafter. The resulting mixture was transferred into an autoclave, and the autoclave was purged with H_2 (50 atm, for three times) and charged with H_2 (50 atm). After stirring at room temperature (20─22 ˚C) for 24 hours, the H_2 was carefully released. The reaction solution was purified by a silica gel column to give the corresponding

hydrogenation product, which was then directly analyzed by chiral GC to determine the enantiomeric excess. (*R*)-1-phenylethanol, 97.0% conversion, 99.2% ee.

Reaction with Ru[(*S*)-Xyl-C_3*-TunePhos][(*S*,*S*)-DPEN] ((*S*),(*S*,*S*)-**24d**) at S/C = 1,000,000: (*S*),(*S*,*S*)-**24d** (2.8 mg, 0.0025 mmol) was dissolved in degassed 2-propanol (10 mL). 1 mL of this catalyst solution was placed in a 20 mL vial. Acetophenone (3.0 g, 25 mmol), 2-propanol (8.0 mL), and *t*BuOK in 2-propanol (1 mol/L, 0.114 mL, 0.114 mmol) were added thereafter. The resulting mixture was transferred into an autoclave, and the autoclave was purged with H_2 (50 atm, for three times) and charged with H_2 (50 atm). After stirring at room temperature (20─22 ˚C) for 48 hours, the H_2 was carefully released. The reaction solution was purified by a silica gel column to give the corresponding hydrogenation product, which was then directly analyzed by chiral GC to determine the enantiomeric excess. (*R*)-1-phenylethanol, 94.5% conversion, 98% ee.

(*R*)-Phenylpropanol (**26b**, Table 2-3, entry 2):[36] Chiral GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 100 ˚C; t_R of (*R*)-isomer, 47.95 min; t_R of (*S*)-isomer, 52.62 min. >99.9% conversion, 99.8% ee.

(*R*)-1-(3′-Methylphenyl)ethanol (**26c**, Table 2-3, entry 3):[37] Chiral GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 120 ˚C; t_R of (*R*)-isomer, 17.45 min; t_R of (*S*)-isomer, 18.66 min. >99.9% conversion, 99.7% ee.

(*R*)-1-(3′-Methoxyphenyl)ethanol (**26d**, Table 2-3, entry 4):[36] Chiral GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 130 ˚C; t_R of (*R*)-isomer, 28.40 min; t_R of (*S*)-isomer, 30.06 min. >99.9% conversion, 99.6% ee.

(*R*)-1-(3′-Chlorophenyl)ethanol (**26e**, Table 2, entry 5):[36] Chiral GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 140 ˚C; t_R of (*R*)-isomer, 15,24 min; t_R of (*S*)-isomer, 15.97 min. >99.9% conversion, 99.5% ee.

(*R*)-1-(4′-Methylphenyl)ethanol (**26f**, Table 2-3, entry 6):[26] Chiral GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 120 ˚C; t_R of (*R*)-isomer, 16.85 min; t_R of (*S*)-isomer, 18.20 min. >99.9% conversion, 99.6% ee.

(*R*)-1-(4′-Methoxyphenyl)ethanol (**26g**, Table 2-3, entry 7):[37] Chiral GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 130 ˚C; t_R of (*R*)-isomer, 28.89 min; t_R of (*S*)-isomer, 30.21 min. >99.9% conversion, 99.6% ee.

(*R*)-1-(4′-Chlorophenyl)ethanol (**26h**, Table 2-3, entry 8):[37] Chiral GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min);

column temperature, 140 ˚C; t_R of (*R*)-isomer, 15.52 min; t_R of (*S*)-isomer, 16.59 min. >99.9% conversion, 99.6% ee.

(*R*)-1-(4′-Fluorophenyl)ethanol (**26i**, Table 2-3, entry 9):[38] Chiral GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 120 ˚C; t_R of (*R*)-isomer, 12.52 min; t_R of (*S*)-isomer, 13.67 min. >99.9% conversion, 99.6% ee.

(*R*)-1-(3,5-Bis(trifluoromethyl)phenyl)ethanol (**26j**, Table 2-3, entry 10): [39] Chiral GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 100 ˚C; t_R of (*S*)-isomer, 16.77 min; t_R of (*R*)-isomer, 18.38 min. >99.9% conversion, 99.3% ee.

(*R*)-1-(2′-Furyl)ethanol (**26k**, Table 2-3, entry 11):[26] Chiral GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 70 ˚C; t_R of (*R*)-isomer, 36.21 min; t_R of (*S*)-isomer, 39.79 min. >99.9% conversion, 99.6% ee.

(*R*)-1-(2′-Thienyl)ethanol (**26l**, Table 2-3, entry 12):[26] Chiral GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 100 ˚C; t_R of (*R*)-isomer, 30.63 min; t_R of (*S*)-isomer, 33.81 min. >99.9% conversion, 99.7% ee.

(*R*)-1-(2′-Naphthyl)ethanol (**26m**, Table 2-3, entry 13):[26] Chiral GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 145 ˚C; t_R of (*R*)-isomer, 68.84 min; t_R of (*S*)-isomer, 71.72 min. >99.9% conversion, 99.7% ee.

(*R*)-1-(1′-Naphthyl)ethanol (**26n**, Table 2-3, entry 14):[40] Chiral GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 145 ˚C; t_R of (*S*)-isomer, 73.59 min; t_R of (*R*)-isomer, 75.94 min. >99.9% conversion, 97.0% ee.

(*R*)-1-(2′-Methylphenyl)ethanol (**26o**, Table 2-3, entry 15):[40] Chiral GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 140 ˚C; t_R of (*R*)-isomer, 9.35 min; t_R of (*S*)-isomer, 10.15 min. >99.9% conversion, 97.5% ee.

(*R*)-1-Cyclopropylethanol (**26p**, Table 2-3, entry 16):[37] Chiral GC (Supelco ALPHA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 30 ˚C; t_R of (*R*)-isomer, 23.83 min; t_R of (*S*)-isomer, 26.48 min. >99.9% conversion, 97.9% ee.

(*R*)-(*E*)-4-Phenyl-3-buten-2-ol (**26q**, Table 2-3, entry 17):[26] (*S*),(*S*)-**24f** (0.00025 mmol), *trans*-4-phenyl-3-butenone (0.37 g, 2.5 mmol, S/C = 10,000), 2-propanol (2.1 mL), *t*BuOK in 2-propanol (11.4 μmol), 10 atm H_2, room temperature (20─22 ˚C), 4 h.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.37 (d, *J* = 6.4 Hz, 3H), 1.68 (br, 1H), 4.47-4.50 (m, 1H), 6.26(dd, *J* = 6.4 Hz, 16Hz, 1H), 6.56 (d, *J* = 16 Hz, 1H), 7.21-7.25 (m, 1H), 7.29-7.33 (m, 2H), 7.38-7.39 (m, 2H). HPLC (column, Chiralcel OD; eluent, hexane/2-propanol = 96/4; r.t.; flow rate, 1 mL/min; detector, 254nm), t_R of (*R*)-isomer, 16.77 min; t_R of (*S*)-isomer, 25.08 min. >99.9% conversion, 97.4% ee.

(*R*)-Cyclopropyl(phenyl)methanol (**26r**, Table 2-3, entry 18):37 Chiral GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 90 ˚C; t_R of (*R*)-isomer, 76.33 min; t_R of (*S*)-isomer, 79.46 min. >99.9% conversion, 93.2% ee.

General Procedure for Rh-Catalyzed Asymmetric Hydrogenation of α-Dehydroamino Acid Derivative by Bisaminophosphines (*S*)-27a and (*S*)-27b:[35] To a solution of $[Rh(COD)_2]BF_4$ (4.1 mg, 0.01 mmol) in 4 mL of degassed anhydrous CH_2Cl_2, was added a solution of bisaminophoshine ligand **23** (8.4 mg, 0.011 mmol) in CH_2Cl_2 (4 mL) at room temperature. The reaction mixture was stirred at room temperature for 20 min before the solvent was removed under vacuum. The resulting complex **27** was used for hydrogenation without further purification. The resulting complex **27** was dissolved in degassed MeOH (5 mL) and 0.5 mL catalyst solution was added to the vial charged with substrate **28** (1 mmol). After 3.5 mL MeOH was added, the mixture was stirred at room temperature for 10 min. The vial was then transferred into an autoclave, and the autoclave was purged with H_2 (5 atm, for three times) and charged with H_2 (5 atm). After stirring at room temperature for 12 hours, the H_2 was carefully released. The ^{1}H NMR of the crude

product and GC were used to determine the conversion. The reaction solution was purified by a silica gel column to give the corresponding hydrogenation product, which was then directly analyzed by chiral GC to determine the enantiomeric excess.

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Chapter 3

Synthesis of Chiral Tridentate Ligands and Their Application in Enantioselective Hydrogenation of Unfunctionalized Ketones

3.1. Introduction and Background

The well developed and widely applied chiral phosphine and bisphosphine ligands have often exhibited satisfactory performance in asymmetric direct hydrogenations as well as other asymmetric catalytic reaction. However, in transfer hydrogenation they have not been as successful as many other systems developed in the past decades. Particularly, among these systems, the incorporation of one or more primary or

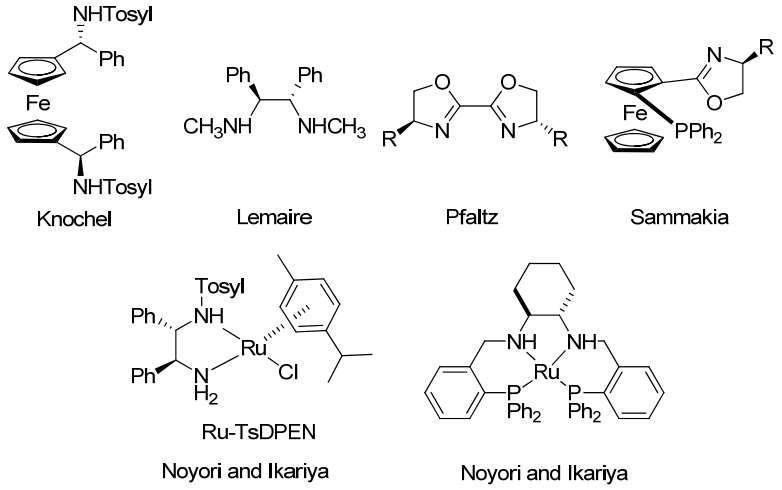


Figure 3-1: Examples of Related Chiral Ligand for Asymmetric Transfer Hydrogenation and Direct Hydrogenation.

substituted primary amine groups or oxazoline groups as the ligand binding sites has exemplified (Figure 3-1).[1]

Historically, majority of the chiral ligands invented for asymmetric catalysis are bidentate type ligands.[2] Limited efforts have been put of the development of tridentate ligand even after the great success of Pybox (Figure 3-2) in many reactions.[3] Mechanistically, chiral tridentate ligands should, in general, be able to provide a deeper and more well-defined chiral pocket around the reactive site (transition metal center) than the bidentate counterpart (Figure 3-2). With enhanced conformational rigidity and strong electron donating capability, such formed chiral environment could serve as the key to high enantioselectivity if there is no secondary interaction group in the substrate, e.g. simple ketone substrate.

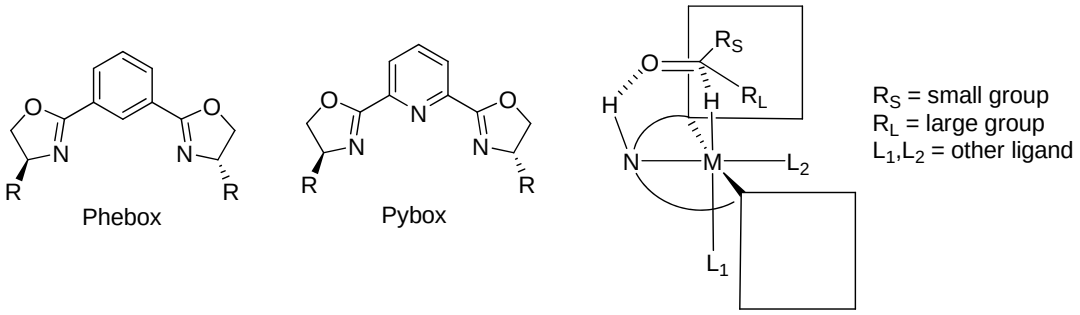


Figure 3-2: Structures of Tridentate Ligands Phebox and Pybox, and Rational Design of Tridentate Ligand for Asymmetric Ketone Hydrogenation.

In the past two decades, asymmetric transfer hydrogenation and asymmetric hydrogenation both using transition metal complexes have been demonstrated to be the most effective strategies to achieve the ketone reduction catalytically.[4] The milestone

discoveries have been done by Noyori and Ikariya who developed the Ru-TsDPEN complexes (Figure 3-1) as a highly effective catalyst system for asymmetric transfer hydrogenation of ketones and demonstrated the mechanistic insight of the metal-ligand bifunctional catalysis.[5] More extensive studies have been carried out based on the Ru-TsDPEN complex.[6]

The essential role of the NH moiety from the diamine ligand TsDPEN was explained to form the key six-membered pericyclic transition state in the key step of the catalytic cycle. Recently, Grützmacher *et al*. synthesized rhodium(I) amide olefin complexes as active hydrogenation and transfer hydrogenation catalysts from tridentate ligands containing the "NH" moiety, and studied the heterolytic splitting of hydrogen by the rhodium(I) amide species.[7] This "NH effect" was also utilized in the design of Ru–diphosphine–diamine complexes by Noyori and coworkers for direct hydrogenation of simple ketones and other ketonic substrates.[8] Prompted by this fundamental study, a few analogue ligands, such as PhanePhos,[9] P-Phos,[10] SDP ligand,[11] C_3*-TunePhos[12] were developed and proved to be effective for the ruthenium-catalyzed asymmetric hydrogenation of simple ketones. However, due to lack of CH/π interaction which acts as the direct origin of the enantiocontrol in Noyori and Ikariya's Ru(II)–η^6-arene–TsDPEN system, the enantioselective hydrogenation of aliphatic ketone has been a more challenging task than that of the aromatic counterpart.[13] The above mentioned Ru–diphosphine–diamine systems developed by different groups were also mostly

limited to aromatic ketones. Only Rh(I)–PennPhos[14] and Ru(II)–BINAP[8b, 15] have achieved over 90% ee for the asymmetric hydrogenation of alkyl alkyl ketones. In pursuit of solutions of this challenging problem, we rationally designed the NNN- and PNP-types tridentate ligands and attempted to apply them in asymmetric hydrogenations.

In this chapter, we designed and synthesized both NNN-type tridentate ligand indan-Ambox and PNP- type tridentate ligand, and investigated their applications in asymmetric hydrogenations, particularly of unfunctionalized ketones.

3.2. Results and Discussions

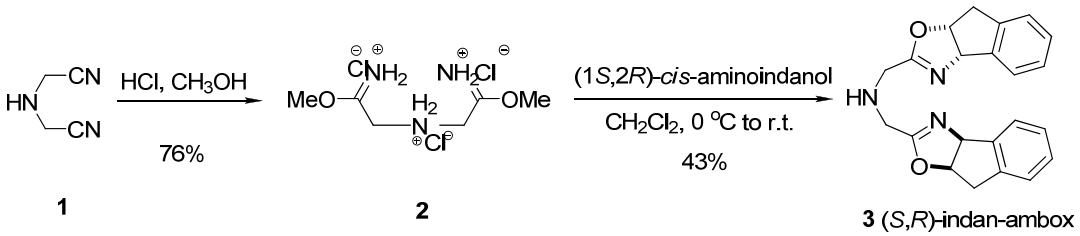
3.2.1. Development of Indan-Ambox Ligand and Its Application in the Hydrogenation of Unfunctionalized Ketone

Enantioselective reduction of prochiral ketones via asymmetric catalysis is a powerful tool for stereo-controlled organic synthesis. It can provide a useful and convenient method to prepare chiral alcohols in the pharmaceutical, agricultural and synthetic chemistry.[2]

In 1998, our group designed and synthesized bis(oxazolinylmethyl)amine (Ambox) ligand, and successfully applied the *in situ* generated Ru(II)–ph-Ambox complex in the asymmetric transfer hydrogenation (ATH) of simple ketones achieving high enantioselectivities.[16] We also proved the "NH effect" in the chiral tridentate

Ambox ligand by control experiments. Thus, we attempt to apply the Ru complex of the synthesized similar but sterically more hindered indan-Ambox ligand in direct asymmetric hydrogenation of simple ketones, especially aliphatic ketones. Here we report our achievements in highly enantioselective asymmetric hydrogenation of a variety of aromatic and aliphatic ketones by using Ru(II)–indan-Ambox catalyst.

The synthesis of the air-stable (*S*,*R*)-indan-Ambox (bis[8,8a-dihydro-3aH-1-oxa-3aza-cyclopenta<α>inden-2-yl]methyl]amine) was straightforward and efficient by following the similar synthetic route of Ph-Ambox. First, the iminodiacetonitrile **1** was converted to the imidate salt **2** and then reacted with chiral *cis* amino-indanol[17] **3** in a condensation step (Scheme 3-1).



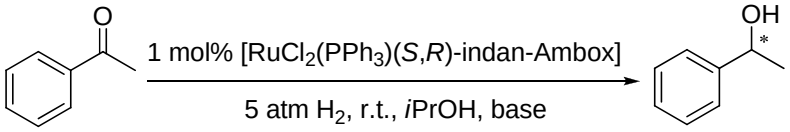
Scheme 3-1: Synthesis of (*S*,*R*)-indan-Ambox **3**.

With the newly synthesized indan-Ambox ligand in hand, we tried to exam its catalytic capability in Ru catalyst systems. However, various of Ru precursors have been screened until we found that only $RuCl_2(PPh_3)_3$ appeared to be the best choice for catalyst preparation. The catalyst [$RuCl_2$(indan-Ambox)PPh_3] was prepared by refluxing the

indan-Ambox ligand with $RuCl_2(PPh_3)_3$ in 2-propanol and subsequently removing the free PPh_3 generated from the coordination of the ligand to the metal precursor by dissolving free PPh3 in cold anhydrous ether. This step of PPh_3 removal is critical for achieving high ee's. Otherwise, only sluggish enantioselectivity was obtained.

Our initial study began with acetophenone (**3a**) as the model substrate and a brief screening of the ruthenium complex's performance in different solvents. Under 30 atm of H_2, dichloromethane could give high enantioselectivity but only moderate conversion (Table 3-1, entry 3). Whereas, switching to polar protic solvent such as methanol, ethanol and 2-propanol, good ee values (>99% ee) were observed in (Table 3-1, entries 4–6). However, only in 2-propanol the ketone substrate was fully converted to the desired product (Table 3-1, entry 6). Subsequently, the pressure effect on the enantioselectivity as well as the reaction rate was tested when the hydrogen pressure was reduce to 5 atm, and the results showed that the milder reaction condition gave slightly higher ee value (95% ee; Table 3-1, entry 9). Furthermore, the control experiment without presence of base revealed the key role of base as the co-catalyst, as the hydrogenation reaction did not even slightly proceed when the base was absent (Table 3-1, entry 7). Also in comparison, much lower conversion was obtained when the amount of base was insufficient (only 1 equiv.; Table 3-1, entry 8). Moreover, further changing the inorganic base from *i*PrONa to *t*BuOK or KOH (all 2.5 equiv.; Table 3-1, entries 9–12), did not significantly affect the hydrogenation results.

Table 3-1: Condition Screening for Ru-Catalyzed Asymmetric Hydrogenation of Acetophenone **4a**.[a]



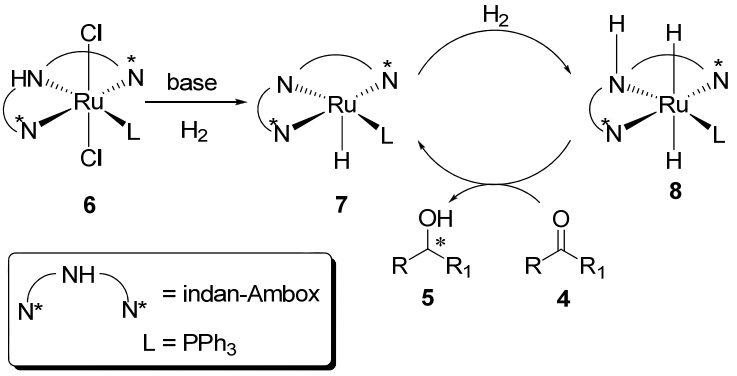
4a **5a**

Entry	Solvent	Base	H_2 (atm)	Conv.[b] (%)	Ee[c] (%) (config.)
1	toluene	*t*BuOK (2.5 eq.)	30	71	59 (*R*)
2	THF	*t*BuOK (2.5 eq.)	30	78	67 (*R*)
3	CH_2Cl_2	*t*BuOK (2.5 eq.)	30	42	95 (*R*)
4	MeOH	*t*BuOK (2.5 eq.)	30	62	92 (*R*)
5	EtOH	*t*BuOK (2.5 eq.)	30	56	95 (*R*)
6	*i*PrOH	*t*BuOK (2.5 eq.)	30	>99	94 (*R*)
7	*i*PrOH	none	5	n.r.[d]	n.a.[e]
8	*i*PrOH	*t*BuOK (1 eq.)	5	53	82 (*R*)
9	*i*PrOH	*t*BuOK (2.5 eq.)	5	>99	95 (*R*)
10	*i*PrOH	*t*BuOK (10 eq.)	5	>99	94 (*R*)
11	*i*PrOH	*i*PrONa (2.5 eq.)	5	>99	94 (*R*)
12	*i*PrOH	KOH (2.5 eq.)	5	>99	93 (*R*)

[a] The reactions were carried out with 0.4 mmol of substrate in 2 mL of solvent in the presence of 1 mol% of Ru catalyst for 12 h. [b] The conversions were determined by GC. [c] The enantiomeric excesses were determined by chiral GC. The absolute configuration was determined by comparison of the retention times and sign of the optical rotation with the reported data (see Supporting Information). [d] n.r. = no reaction. [e] n.a. = not analyzed.

Although the same Ru(II)–Ambox system could also catalyze the transfer hydrogenation of most of the simple ketone substrates with comparable enantioselectivity results,[14] it was proven that the reduction in this study was a direct asymmetric

hydrogenation (AH) with H_2 and the asymmetric transfer hydrogenation (ATH) pathway was completely suppressed in the H_2 atmosphere. The key evidences are: (a) the same ketone substrates were quantitatively hydrogenated at a much higher reaction rate (r.t., completed within 12 h) than by asymmetric transfer hydrogenation. The ATH catalyzed by Ru(II)−Ph-Ambox usually needed at least 24 h to reach the same level of conversion at room temperature. (b) In this study, when applying up to 10 equiv. of base in the hydrogenation using the same catalyst, no significant ee erosion was observed (Table 3-1, entry 10). In sharp contrast, it was proven that using 1 equiv. base was critical in ATH for achieving high ee values. Even a slight increase of base from 1 to 2 equiv. caused the ee of the phenylethanol product to drop from 98% ee to 68% ee. (c) Under 30 atm of H_2 in THF, hydrogenation of acetophenone proceeded with 78% conversion although with much lower ee (67% ee in THF vs. 94% ee in 2-propanol; Table 3-1, entry 2). These observations of the asymmetric hydrogenation pathway of this reaction were in accordance with the studies of the bifunctional catalysis performance of the Cp*Ru(II)−P,N-ligand system in ATH and AH by Ikariya et al.,[18] and also with the mechanistic scenario investigated by *et al*..[19]



Scheme 3-2: Proposed Mechanism of Metal–Ligand Bifunctional Catalysis.

Both the key role of the base as the co-catalyst and the "NH effect" studied by Noyori *et al*. based upon experimental data and detailed theoretical calculations could help us to understand the mechanism of this catalysis.[13] In a similar way that Noyori's Ru(II)–η^6-arene–TsDPEN active species is formed, the catalytically active Ru dihydride complex **8** is generated with the facilitation of two equivalent base and H_2. Hence the hydridic Ru–H and the protic N–H moiety from the Ambox ligand can work in a synergetic fashion to catalyze as a bifunctional catalyst by forming a six-membered pericyclic ring transition state. After reducing the ketone substrate, the catalytic species can be regenerated dominantly by the hetero-cleavage of hydrogen molecule under the hydrogenation atmosphere (Scheme 3-2). The crucial role of the N–H moiety could also be demonstrated by substituting the NH with NCH_2Ph. Under the same optimized conditions for the acetophenone hydrogenation, the Ru complex prepared from the similar but *N*-substituted ligand **9** only gave 66% conversion and 25% ee (Figure 3-3).[20]

Our mechanism hypothesis is in agreement with the mechanistic studies on Ru–η^6-arene–TsDPEN catalyst systems for the hydrogenation of simple ketones.[19] However, the major difference is that the origin of enantioselectivity in this study mainly comes from the steric interaction of the substrate and the rigid C_2-symmetric scaffold of the Ambox ligand other than the CH/π interaction (Figure 3-4).

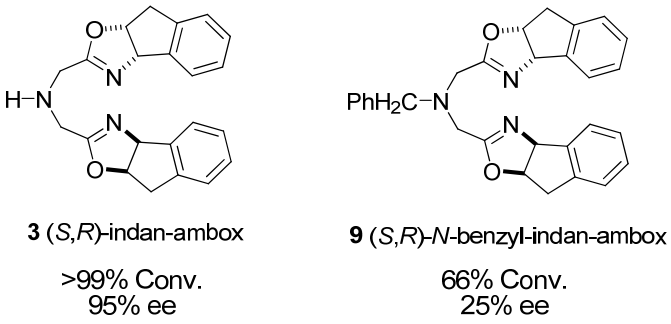


Figure 3-3: Control Experiment Study of N-H Effect.

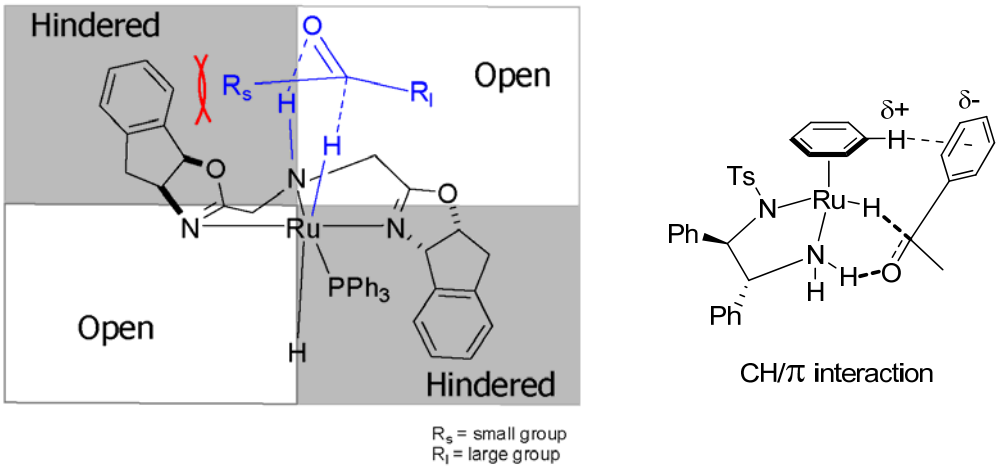
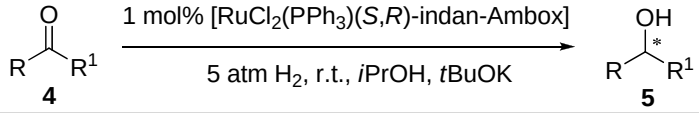


Figure 3-4: Proposed Transition State of Formation of the Six-Membered Pericyclic Ring, and Comparison of Origin of Enantioselectivity to Ru-TsDPEN System.

We also investigate the scope of ketone substrates including a series of substituted acetophenone derivatives and aliphatic ketones. With 1 mol% of Ru–indan-Ambox catalyst, the ketone substrates could be reduced smoothly with good to excellent enantioselectivities under the optimized conditions (Table 3-2).

Table 3-2: Asymmetric Hydrogenation of Ketones **4** by Ru−indan-Ambox.[a]



Entry	Subtrate	R	R^1	Prodcut	Conv.[b] (%)	Ee[c] (%) (config.)
1	**4a**	C_6H_5	CH_3	**5a**	>99	95 (*R*)
2[d]	**4a**	C_6H_5	CH_3	**5a**	97	95 (*R*)
3	**4b**	*o*-MeC_6H_4	CH_3	**5b**	>99	97 (*R*)
4	**4c**	*o*-ClC_6H_4	CH_3	**5c**	>99	92 (*R*)
5	**4d**	*o*-$MeOC_6H_4$	CH_3	**5d**	82	93 (*R*)
6	**4e**	*m*-MeC_6H_4	CH_3	**5e**	>99	95 (*R*)
7	**4f**	*m*-ClC_6H_4	CH_3	**5f**	>99	81 (*R*)
8	**4g**	*m*-$MeOC_6H_4$	CH_3	**5g**	>99	90 (*R*)
9	**4h**	*p*-MeC_6H_4	CH_3	**5h**	>99	93 (*R*)
10	**4i**	*p*-ClC_6H_4	CH_3	**5i**	>99	80 (*R*)
11	**4j**	*p*-FC_6H_4	CH_3	**5j**	>99	83 (*R*)
12	**4k**	*p*-$MeOC_6H_4$	CH_3	**5k**	>99	92 (*R*)
13	**4l**	1-naphthyl	CH_3	**5l**	>99	94 (*R*)
14	**4m**	2-naphthyl	CH_3	**5m**	>99	87 (*R*)
15	**4n**	C_6H_5	C_2H_5	**5n**	>99	93 (*R*)
16	**4o**	C_6H_5	$CH(CH_3)_2$	**5o**	95	91 (*R*)
17	**4p**	C_6H_5	cyclopropyl	**5p**	80	92 (*R*)
18	**4q**	cyclohexyl	CH_3	**5q**	>99	95 (*R*)

[a] The reactions were carried out with 0.4 mmol of substrate in 2 mL of solvent in the presence of 1 mol% of Ru catalyst at r.t. for 15 h unless otherwise specified . [b] The conversions were determined by GC. [c] The enantiomeric excesses were determined by chiral GC. [d] 0.1 % Catalyst loading.

Higher catalytic capability of the catalyst was also explored when 0.1 mol% catalyst converted the acetophenone to (*R*)-phenylethanol under the same mild conditions without any ee erosion (95% ee, entry 2).

As shown in Table 3-2, substrates containing an *ortho* substituent on the phenyl ring in R group gave the highest enantioselectivities (up to 97% ee; Table 3-2, entries 3–5, 13), since the *ortho*-substituted R group has larger steric bulk thus a better steric differentiation from R^1 (methyl group). However, substituents capable of chelating to the metal could decrease the reactivity of the catalyst (82% conversion; entry 5). Substrates containing electron-withdrawing groups such as Cl or F group were hydrogenated successfully but with lower ee values (Table 3-2, entries 7,10,11). When R^1 group is changed to larger alkyl groups such ethyl, isopropyl, cyclopropyl groups, the enantioselectivities slightly decrease and the conversions also decrease to 80%. We also tried to extend the substrate scope to more challenging substrates such as alkyl alkyl ketones (Table 3-2, entries 18–20). Notably, the hydrogenation of cyclohexyl methyl ketone gave 95% ee, which to our best knowledge is the best ee result for this alkyl alkyl substrate (Table 3-2, entry 18)

There were still limitations of this catalyst system in terms of reactivity and substrate scope. Only up to 1000 turnover (TON) has been achieved, and further decrease of catalyst loading would lead to both significant conversion and enantioselectivity drop. Furthermore, when screening other ketone substrates such as tetralone and other alkyl

alkyl ketones using Ru–Ambox catalyst, poor to moderate results were given (Figure 3-5).

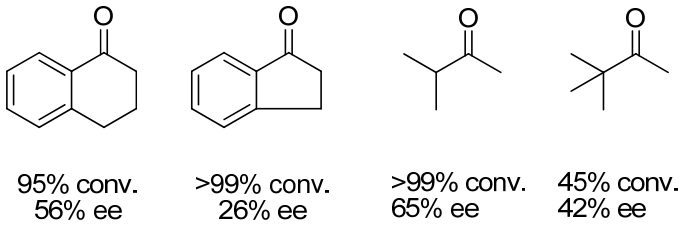


Figure 3-5: Preliminary Results of Further Extended Substrate Screening.

3.2.2 Synthesis of PNP-Type Ligand and Its Application in the Hydrogenation of Unfunctionalized Ketone

Based on the successful design of Ambox ligands in the asymmetric ketone hydrogenation, we attempted to combine the NH moiety with more electron-donating and steric hindered phospholane moiety in our new design of PNP- type ligand. Because the generations of rigid P-chiral bisphospholane ligand such as TangPhos,[21] DuanPhos,[22] Binapine[23] and ZhangPhos[24] (Figure 3-6) have approved to be carrying extraordinary electronic and stereo properties which lead to high enantioselectivities and reactivities towards a wide range of functionalized olefin substrates like dehydroamino acid derivatives and enamides.

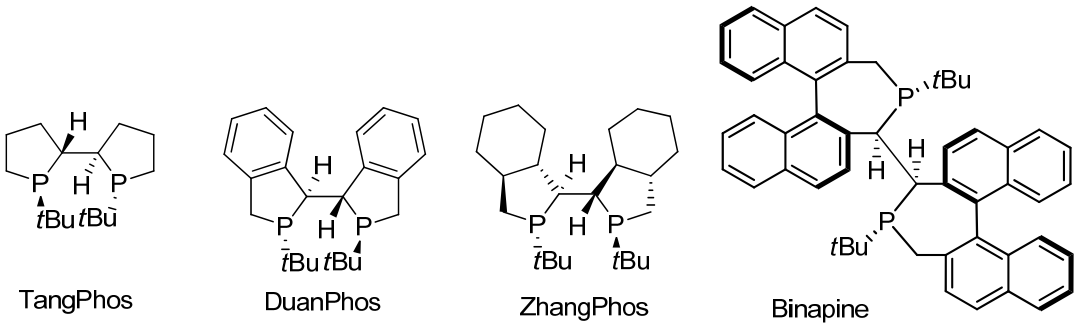
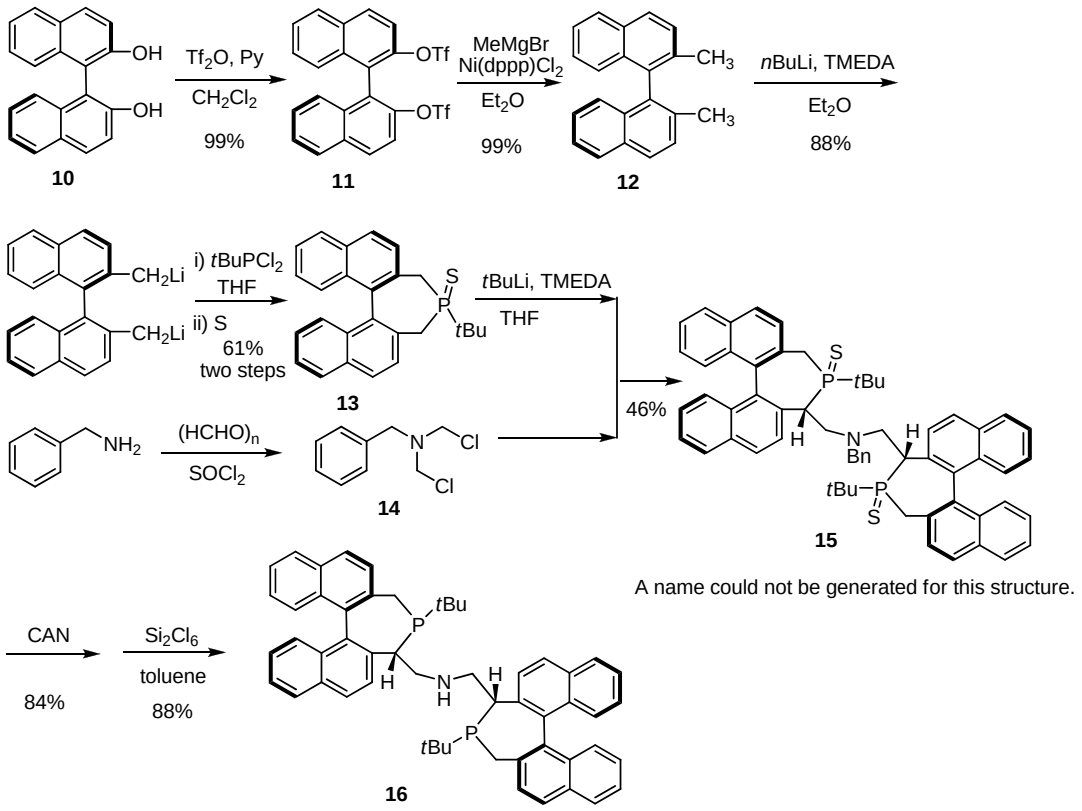


Figure 3-6: Structures of P-Chiral Ligands.

The structural features of these bisphospholane scaffolds play an important role in generating high enantioselectivity and reactivity. For instance in Binapine, it possesses an endocyclic P-donor inserted in a seven-membered ring embedded in the C_2-symmetrical environment created by the binaphthalene template; it also has the P-atom connected to the diaryl scaffold through two heteroatoms of higher electronegativity; it features a stereogenic axis as the unique chiral element. The outstanding performance of Rh−Binapine catalyst in asymmetric reduction of β-dehydroamino acid derivatives proved the advantages of these features. [23]



Scheme 3-3: Synthesis of PNP-Type Ligand **16**.

To take these advantageous structural features into our new PNP-type ligand design, we envisioned that the hindered *tert*-butyl phosphine in the phosphepine rings will be more electron-donating and stereo-restrictive than the previous discussed oxazoline moiety in Ambox ligands. Thus, we successfully developed the PNP- type ligand (*R*,*R*)-**16**. Bases on the synthetic route of Binapine, we first synthesized S-protected monomeric fragment of Binapine **13** starting from chiral BINOL **10**.[23] After stereoselective deprotonation of the benzylic 3- position, two monomers can be tethered

by a protected amine linker. After two consecutive deprotection steps, the final PNP-ligand was obtained with decent yields (Scheme 3-3).

With the newly synthesized PNP- ligand **16** in hand, we prepared its Ru(II) complex in a similar way to that of Ambox in our initial trial. Interestingly, Ru/**16** showed doublet-doublet peaks on ^{31}P NMR spectrum. Moreover, when we applied such Ru(II) complex in the hydrogenation of acetophenone in 2-propanol, only 69% ee was found. Further efforts of switching Ru precursor from $RuCl_2(PPh_3)_3$ to $RuH_2(PP_3)_4$, $RuHCl(PP_3)_4$ and other ruthenium metal complexes did not give satisfactory results in ketone hydrogenation. Our rationale for such poor performance was that the PNP- ligand **16** may be too bulky to work in our proposed working mechanism of bifunctional catalysis. Literature reports of esters or lactones using PNP-type ligand or PNNP-type ligand[25] showed other potential application such as ester reduction by using our synthesized steric hindered and highly electron-donation PNP-ligand. Furthermore, the modular structural feature of this PNP- ligand design will allow the access of a series of PNP- chiral ligands by switching the phosphepine fragments to other scaffold such as phospholane moieties in TangPhos and DuanPhos.

3.3. Conclusion

In conclusion, a new chiral tridentate NNN-type indan-Ambox ligand was synthesized and has formed a highly enantioselective ruthenium catalyst for direct hydrogenation of unfunctionalized aryl and more importantly for some examples of aliphatic ketones. The tunable nature of this ligand leaves a great potential for broadening the ketone substrate scope especially the pure aliphatic ketones. Another rational design and synthesis of PNP-type bulky chiral tridentate ligand was also fulfilled, yet it failed to provide superior enantioselectivity. Further investigation of Ambox ligand system and the application of PNP-type ligand in asymmetric hydrogenation will be further investigated.

Experimental Section

General Remarks. All reactions and manipulations were performed in a nitrogen-filled glovebox or under nitrogen using standard Schlenk techniques unless otherwise noted. Column chromatography was performed using Sorbent silica gel 60 Å (230×450 mesh). ^{1}H ^{13}C NMR spectral data were recorded on Bruker 360 MHz, Bruker 400 MHz spectrometers. Chemical shifts were reported in ppm. Enantiomeric excess values were determined by chiral GC on Agilent 7890 GC equipment and chiral HPLC on Agilent 1200 Series equipment.

Preparation of Bis(Acetimido Methyl Ether Hydrochloride) Amino hydrochloride 2:[14] To a 125 mL filter flash was added iminodiacetonitrile **1** (9.5 g, 0.1 mol, the Aldrich chemical was recrystallized from EtOAc before use), anhydrous methanol (6.4 g, 0.2 mol) and diethyl ether (60 mL). The suspension was cooled to 0˚C. Anhydrous HCl gas was bubbled into the above suspension while stirring. After about 2h, the bubbling was stopped and the reaction mixture was kept under HCl atmosphere at 0˚C overnight. The resulting white solid was filtered under nitrogen, washed with ether (3 × 20 mL), and dried under vacuum. The final product was a white hydroscopic power (20.4 g, 76%) and used for following step without further purification.

Preparation of Indan-Ambox 3 (Bis[8,8a-dihydro-3aH-1-oxa-3aza-cyclopenta<α>inden-2-yl]methyl]amine):[14] To a 50 mL Schlenk flask was added **2** (7.7 g, 28.7 mmol) and CH_2Cl_2 (100 mL). The white suspension was first cooled to 0˚C, then (*S*,*R*)-*cis*-1-amino-indan-2-ol (12.9 g, 86.6 mmol). The white suspension turned yellowish shortly after addition of aminoindanol. The reaction was slowly warmed up to r.t. and stirred overnight. The yellowish color gradually turned to white. After stirring at r.t. for 40h, the reaction was poured onto ice, and the aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were first greenish but then slowly changed to brownish. It was dried over Na_2SO_4

and concentrated under reduced pressure until solid was about to precipitate out. It was cooled on ice bath for 1h, and the subsequent filtration gave an off-white solid (2.6 g), which was the unreacted aminoindanol. The rest of the crude product was then recrystallized from CH_2Cl_2/hexanes, washed with H_2O and drying over P_2O_5 under high vacuum to give the pure product **2** as an off-white powder: 4.39 g, 43% yield. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 1.95 (br s, 1H), 3.19–3.24 (m, 2H), 3.37–3.42 (m, 6H), 5.28–5.32 (m, 2H), 5.51 (d, *J* = 8.0 Hz, 2H), 7.24–7.26 (m, 6H), 7.44–7.46 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.7, 45.8, 76.4, 83.3, 125.3, 125.5, 127.5, 128.5, 139.6, 141.8, 165.8. HRMS $[MH]^+$ Calcd: 360.1712, Found: 360.1697.

Preparation of 9 (*N*-Benzyl-1-((3a*S*,8a*R*)-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-yl)-*N*-(((3a*S*,8a*R*)-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-2-yl)methyl)methanamine):[14] To a 50 mL Schlenk flask was added **3** (144 mg, 0.4 mmol), Cs_2CO_3 (261 mg, 0.8 mmol) and DMF (15 mL). $PhCH_2Br$ (69 mg, 0.4 mmol) was added slowly to the suspension. The suspension was stirred overnight at r.t.. After the reaction is finished, the solvent was removed and dissolved in CH_2Cl_2 (20 mL). The solution was washed with H_2O, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography on silica gel gave the product **9** as light yellow oil: 110 mg, 61% yield.

^{1}H NMR (400 MHz, acetone-d_6): δ 3.00 (d, J = 20.0 Hz, 2H), 3.16–3.29 (m, 6H), 3.51 (s, 1H), 3.87–4.07 (m, 1H), 5.10–5.18 (m, 2H), 5.28–5.33 (m, 2H), 6.99–7.13 (m, 6H), 7.23–7.25 (m, 2H). MS $[MH]^+$ Calcd: 450.5, Found: 450.3.

Procedure for Preparation of [$RuCl_2$(indan-Ambox)(PPh_3)] complex: To a flame-dried 50 mL Schlenk flask was charged $Ru(PPh_3)_3Cl_2$ (38.4 mg, 0.04 mmol) and (*S*,*R*)-indan-Ambox **3** (15.0 mg, 0.044 mmol). Under nitrogen protection anhydrous 2-propanol (15 mL) was added and the reaction mixture was heated to reflux for 3–4 h. The reaction mixture turned to dark greenish color. The solvent was removed under vacuum and the greenish solid complex was washed with cold anhydrous Et_2O (5mL × 3) to remove free PPh_3. ^{31}P NMR (162 MHz, acetone-d_6) of the Ru(II)–indan-Ambox complex after wash: δ = 32.40 (s).

General Procedure for Asymmetric Hydrogenation: The above precatalyst was dissolved in degassed 2-propanol (10 mL). The solution was equally divided into 10 vials. A solution of *t*BuOK (1 mol/L, 0.020 mL, 0.02 mmol), ketone substrate (0.4 mmol, S/C = 100) and 1 mL of 2-propanol were added via syringe. The resulting mixture was transferred into an autoclave, and the autoclave was purged with H_2 (5 atm, for three times) and charged with H_2 (5 atm). After stirring at room temperature for 15 hours, the H_2 was carefully released. The reaction solution was purified by a silica gel column to

give the corresponding hydrogenation product, which was then directly analyzed by chiral GC to determine the enantiomeric excess.

(*R*)-1-Phenylethanol (5a):[12] $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), acetophenone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (20 μmol), 5 atm, r.t., 15 h. GC (BETA DEX 120, 30 m × 0.25 mm × 0.25 μm; carrier gas, He (flow rate 1 mL/min); column temperature, 120 ˚C). t_R of (*R*)-1-phenylethanol, 11.46 min; t_R of (*S*)-1-phenylethanol, 12.17 min. >99% conversion, 95% ee.

(*R*)-1-(2′-Methylphenyl)ethanol (5b):[12] $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), 2′-methylacetophenone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (20 μmol), 5 atm, r.t., 12 h. GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 140 ˚C; t_R of (*R*)-isomer, 9.35 min; t_R of (*S*)-isomer, 10.15 min. >99% conversion, 97% ee.

(*R*)-1-(2′-chlorophenyl)ethanol (5c):[9] $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), 2′-methylacetophenone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (20 μmol), 5 atm, r.t., 12 h. GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 140 ˚C; t_R of (*R*)-isomer, 9.35 min; t_R of (*S*)-isomer, 10.15 min. >99% conversion, 92% ee.

(*R*)-1-(2′-Methoxyphenyl)ethanol (5d):[9] $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), 2′-methylacetophenone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (20 μmol), 5 atm, r.t., 12 h. GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 140 ˚C; t_R of (*R*)-isomer, 9.35 min; t_R of (*S*)-isomer, 10.15 min. 82% conversion, 93% ee.

(*R*)-1-(3′-Methylphenyl)ethanol (5e):[12] $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), 3′-methylacetophenone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (20 μmol), 5 atm, r.t., 15 h. GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 120 ˚C; t_R of (*R*)-isomer, 17.45 min; t_R of (*S*)-isomer, 18.66 min. >99% conversion, 95% ee.

(*R*)-1-(3′-Chlorophenyl)ethanol (5f):[12] $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), 3′-chlorolacetophenone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (20 μmol), 5 atm, r.t., 15 h. GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 140 ˚C; t_R of (*R*)-isomer, 15,24 min; t_R of (*S*)-isomer, 15.97 min. >99% conversion, 81% ee.

(*R*)-1-(3′-Methoxyphenyl)ethanol (5g):[12] $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), 3′-methoxyacetophenone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (20 μmol), 10 atm, r.t., 4 h. GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 130 ˚C; t_R of (*R*)-isomer, 28.40 min; t_R of (*S*)-isomer, 30.06 min. >99% conversion, 90% ee.

(*R*)-1-(4′-Methylphenyl)ethanol (5h):[12] $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), 4′-methylacetophenone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (2.0 μmol), 5 atm, r.t., 15 h. GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 120 ˚C; t_R of (*R*)-isomer, 16.85 min; t_R of (*S*)-isomer, 18.20 min. >99.9% conversion, 93% ee.

(*R*)-1-(4′-Chlorophenyl)ethanol (5i):[12] $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), 4′-chloroacetophenone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (20 μmol), 5 atm, r.t., 15 h. GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 140 ˚C; t_R of (*R*)-isomer, 15.52 min; t_R of (*S*)-isomer, 16.59 min. >99% conversion, 80% ee.

(*R*)-1-(4′-Fluorophenyl)ethanol (5j):[12] $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), 4′-fluoroacetophenone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in

2-propanol (20 μmol), 5 atm, r.t., 15 h. GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 120 ˚C; t_R of (*R*)-isomer, 12.52 min; t_R of (*S*)-isomer, 13.67 min. >99% conversion, 83% ee.

(*R*)-1-(4′-Methoxyphenyl)ethanol (5k):[12] $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), 4′-methoxyacetophenone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (20 μmol), 5 atm, r.t., 15 h. GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 130 ˚C; t_R of (*R*)-isomer, 28.89 min; t_R of (*S*)-isomer, 30.21 min. >99% conversion, 92% ee.

(*R*)-1-(1′-Naphthyl)ethanol (5l):[12] $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), 1′-acetonaphthone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (20 μmol), 5 atm, r.t., 15 h. GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 145 ˚C; t_R of (*S*)-isomer, 73.59 min; t_R of (*R*)-isomer, 75.94 min. >99% conversion, 94% ee.

(*R*)-1-(2′-Naphthyl)ethanol (5m):[12] $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), 2′-acetonaphthone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (20 μmol), 5 atm, r.t., 15 h. GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm);

carrier gas, He (flow rate 1 mL/min); column temperature, 145 ˚C; t_R of (*R*)-isomer, 68.84 min; t_R of (*S*)-isomer, 71.72 min. >99% conversion, 87% ee.

(*R*)-Phenylpropanol (5n):[12] $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), phenylpropanone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (20 μmol), 5 atm, r.t., 15 h. GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 100 ˚C; t_R of (*R*)-isomer, 47.95 min; t_R of (*S*)-isomer, 52.62 min. >99% conversion, 93% ee.

(*R*)-2-Methyl-1-phenylpropanol (5o):[9, 26] $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), isobutyrophenone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (20 μmol), 5 atm, r.t., 15 h. GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 100 ˚C; t_R of (*R*)-isomer, 47.95 min; t_R of (*S*)-isomer, 52.62 min. 95% conversion, 91% ee.

(*R*)-Cyclopropyl(phenyl)methanol (5p):[12] $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), cyclopropyl phenyl ketone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (20 μmol), 5 atm, r.t., 15 h. GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 90 ˚C; t_R of (*R*)-isomer, 76.33 min; t_R of (*S*)-isomer, 79.46 min. 80% conversion, 92% ee.

(*R*)-1-Cyclohexylethanol (5q): [27] $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), cyclohexyl methyl ketone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (20 μmol), 5 atm, r.t., 15 h. GC (Supelco ALPHA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 2 mL/min); column temperature, 60 ˚C; t_R of (*R*)-isomer, 47.39 min; t_R of (*S*)-isomer, 7.62 min. >99% conversion, 95% ee.

(*R*)-3,3-Dimethylbutan-2-ol: $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), pinacolone (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (20 μmol), 5 atm, r.t., 15 h. GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 2 mL/min); column temperature, 65 ˚C; t_R of (*R*)-isomer, 15.28 min; t_R of (*S*)-isomer, 15.48 min. 45% conversion, 42% ee.

(*R*)-3-methylbutan-2-ol: $RuCl_2$(indan-Ambox)(PPh_3) (0.004 mmol), 3-methylbutan-2-one (0.4 mmol, S/C = 100), 2-propanol (2.0 mL), *t*BuOK in 2-propanol (20 μmol), 5 atm, r.t., 15 h. GC (Supelco BETA DEX 120 , 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 2 mL/min); column temperature, 50 ˚C; t_R of (*R*)-isomer, 18.47 min; t_R of (*S*)-isomer, 19.14 min. >99% conversion, 65% ee.

Synthesis of 12 ((*R*)-2,2′-Dimethyl-1,1′-Binaphthyl: Compound **12** was synthesized by following the reported literature,[28] with 86% yield for three steps from (*R*)-BINOL.

Synthesis of 13 (4-*tert*-Butyl-4,5-dihydro-3*H*-dinaphtho[2,1-c;1′,2′-e]phosphepine Sulfide): Compound **13** was synthesized from **12** by following the reported literature,[23] however, without separation of the dilithium salt intermediate. The product was obtained as light yellow solid (61% yield).

Synthesis of 14 (*N*-Benzyl-1-Chloro-*N*-(Chloromethyl)Methanamine):[29] A mixture of benzylamine (1.364 mL, 12.5 mmol), paraformaldehyde (0.93 g, 3.25 mmol), and 15 mL CH_2Cl_2 was stirred for about 3h. The resulting suspension was treated dropwise with $SOCl_2$ (5.95 g, 50 mmol). After gas evolution had ceased, solvent and unreacted $SOCl_2$ were removed under vacuum and the product were purified by extraction into Et_2O. The combined extracts were concentrated under vacuum to give the product as colorless oil, which was confirmed to be pure by ^{1}H NMR and used for the next step without further purification due to the high polarity and low b.p. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.37 (m, 5H, Ar-H), 5.21 (s, 4H, Cl-CH_2), 4.16 (s, 2H, Ar-CH_2).

Synthesis of 15:[23] At −78 ^{o}C, to a solution of **13** (0.80 g, 2.0 mmol), TMEDA (0.36 mL, 2.4 mmol) in 25 mL THF was added dropwise *t*BuLi (1.8 mL, 1.6 M in pentane, 0.75 mmol). The resulting mixture was kept stirring at −78 ^{o}C for 4 h. To the reaction mixture was added the newly prepared **14** (0.204 g, 1.0 mmol) in ether (8 mL). The resulting mixture was kept at −78 ^{o}C for 1 h. And then it was allowed to warm to room temperature and stirred overnight. The reaction was quenched with NH_4Cl (aq.), extracted with ether. The combined organic phase was dried over Na_2SO_4, concentrated and the crude product mixture was purified by column chromatography on silica gel to give the product was light yellow solid (0.429 g, 46% yield). ^{1}H NMR($CDCl_3$, 500 MHz): δ 7.91 (d, 2H, *J* = 4.0 Hz), 7.83 (d, 2H, *J* = 4.0 Hz), 7.77-7.74 (m, 4H), 7.57 (d, 2H, *J* = 5.3 Hz), 7.47 (d, 2H, *J* = 4.5 Hz), 7.36 (t, 2H, *J* = 4.5 Hz), 7.15 (t, 2H, *J* = 4.5 Hz), 7.06 (t, 2H, *J* = 4.5 Hz), 6.92 (d, 2H, *J* = 4.5 Hz), 6.52 (t, 2H, *J* = 4.5 Hz), 6.45 (t, 2H, *J* = 4.5 Hz), 6.15 (d, 2H, *J* = 4.25 Hz), 5.85 (d, 2H, *J* = 3.75 Hz), 3.70 (t, 2H, *J* = 3.75 Hz), 3.49-3.45 (m, 4H), 3.33 (d, 2H, *J* = 4.0 Hz), 2.81 (t, 2H, *J* = 4.5 Hz), 2.08-2.03 (m, 1H), 1.88-1.80 (m, 2H), 1.27 (d, 18H, *J* = 8.0 Hz). ^{31}P NMR ($CDCl_3$, 202 MHz) δ 95.08.

Synthesis of 16:[30] To a solution of **15** (50 mg, 0.054 mmol) in CH_3CN/H_2O (5:1), was added cesium ammonium nitrate (CAN, 61.8 mg, 0.112 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture

was neutralized with $NaHCO_3$ (aq., sat.). Then the mixture was extracted with ether and the combined organic phase was combined, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel to give the product as light yellow solid (37 mg, 81.9% yield). ^{1}H NMR($CDCl_3$, 500 MHz): δ 7.91 (d, 2H, *J* = 4.0 Hz), 7.85 (d, 4H, *J* = 4.25 Hz), 7.72 (d, 2H, *J* = 4.25 Hz), 7.54 (d, 2H, *J* = 4.25 Hz), 7.40 (t, 2H, *J* = 4.5 Hz), 7.37 (t, 2H, *J* = 4.5 Hz), 7.15 (t, 2H, *J* = 4.5 Hz), 7.06-7.02 (m, 6H), 6.81 (d, 2H, *J* = 4.25 Hz), 3.45 (dd, 2H, J_1 = 4.5 Hz, J_2 = 6.5 Hz), 3.38-3.33 (m, 2H), 2.77 (t, 2H, *J* = 11.0 Hz), 2.54-2.49 (m, 2H), 2.32 (s, 1H), 2.27 (s, 1H), 1.15 (d, 18H, *J* = 8.0 Hz). ^{31}P NMR ($CDCl_3$, 202 MHz) δ 89.48. [M+H$^+$]: 842.32. Found 842.2.

Synthesis of 17:[23] To a solution of **16** (100 mg, 0.12 mmol) in anhydrous toluene (5 mL) was added dropwise hexachlorodisilane (0.41 mL, 2.4 mmol) under N_2. The mixture was heated and stirred at reflux overnight and monitored by TLC and ^{31}P NMR. To quench the reaction mixture, 5 mL of degassed NaOH (aq. 4N) was added at 0 ^{o}C. After the gas production is complete, the mixture suspension was heated to 60−70 oC and stirred until the aqueous phase and the organic phase were well separated. The organic phase was transferred via canula and the aqueous phase was extracted with anhydrous ether (4 x 5 mL). The organic extracts were combined and concentrated under vacuum to give the product as off white solid (82 mg, 88% yield). ^{1}H NMR($CDCl_3$, 500 MHz): δ

7.89-7.84 (m, 6H), 7.77 (d, 2H, J = 4.25 Hz), 7.78-7.71 (m, 2H), 7.58-7.56 (m, 2H), 7.51 (d, 2H, J = 4.25 Hz), 7.41-7.36 (m, 4H), 7.17-7.07 (m, 4H), 6.89 (d, 2H, J = 4.5 Hz), 4.16 (dd, 4H, J_1 = 3.0 Hz, J_2 = 4.0 Hz), 2.72 (t, 2H, J = 8.0 Hz), 2.72-2.64 (m, 4H), 0.93 (d, 18H, J = 8.0 Hz). ^{31}P NMR (CD_2Cl_2, 202 MHz) δ 35.71. [M+H^+]: 778.37. Found 778.3.

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Chapter 4

Ir-Catalyzed Asymmetric Hydrogenation of Imines, Enamine Esters and Heteroaromatics

4.1. Introduction and Background

Chiral amines are powerful pharmacophores and structural moieties for pharmaceutical drugs and many natural products. However, the problem of synthesizing amines in an state of art manner, in other words preferable with complete control of chemo- regio- and stereoselectivities have risen as the challenge for all synthetic chemists ever since.[1] Unsurprisingly, such great significance has intrigued a large field of developing diverse methodologies to tackle the standing problem to meet the great demands of both academic research as well as industrial production of commodity and pharmaceutical intermediates. Among all these different strategies from various perspectives such as enantioselective Mannich reaction, asymmetric reductive amination, C-H amination and many, asymmetric direct hydrogenation of prochiral imines and *N*-based heteroaromatic compounds has been the most efficient and widely investigated approach, particularly towards practical applications in industry.

Compared with the success achieved in olefin and ketone hydrogenation, the

method developed for asymmetric imine reduction was much less abundant.[2] Relatively low catalytic activities were usually observed probably due to the strong coordination of the amine product to the transition metal catalyst. The amine adduct of the catalyst loses activity toward hydrogenation and thus results in low turnover numbers and yields. The inseparable *E/Z* isomers of imines can also results in poor enantioselectivity.[3,4] Nevertheless, a few catalytic systems provided good to excellent enantioselectivities in imine hydrogenation, especially the iridium-catalyzed asymmetric hydrogenation of imines (*N*-benzyl and *N*-aryl imines). The asymmetric hydrogenation of imines has also been discussed in reviews covering asymmetric imine reduction,[5a] chiral amine synthesis,[5b-d] additives and co-catalysts in asymmetric catalysis,[5e,f] asymmetric hydrogenation in the production of commercial and fine chemicals[5g,h] and of pharmaceutical ingredients[5i,j].

Asymmetric hydrogenation of substituted *N*-based aromatic heterocycles represents one of the most concise and direct approaches to chiral amines which are important building blocks for many biologically active compounds. However, these aromatic molecules are generally stable and resistant to hydrogenation under mild or even harsh conditions. Asymmetric hydrogenation of these compounds using currently available catalysts usually requires high temperature and hydrogen pressure. Additives and/or activators which destabilize the aromatic system are usually used to improve the conversion of the hydrogenation.[6]

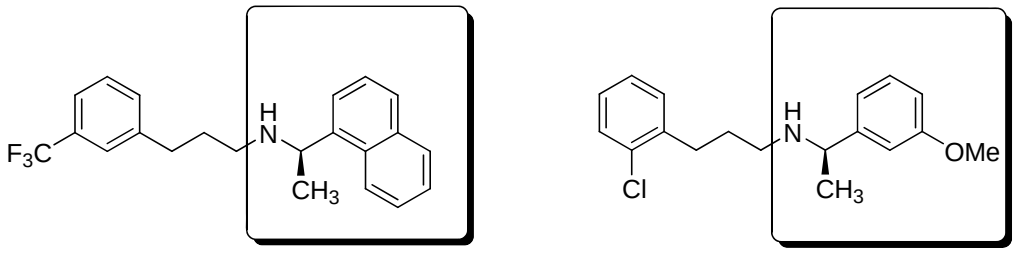
In this chapter, we investigated several cases of direct hydrogenation of imines

and *N*-based heteroaromatics based on the chiral phosphine ligand library we have developed and also the applicability to each specific substrate type that we designed or sought to solve.

4.2. Results and Discussions

4.2.1. Ir-Catalyzed Asymmetric Hydrogenation of *N*-Aryl Imines

Enantiomerically pure amines and their derivatives are of great significance in pharmaceutical, biological and synthetic chemistry.[7] The importance of chiral amines such as serving as key moieties in drugs or drug candidates drives chemists to develop efficient synthetic methodologies of approaching them. The importance of chiral amines such as those serving as key moieties in drugs or drug candidates, for example, Cinacalcet,[8] and NPS *R*-568 (Figure 1),[9] drives chemists to develop efficient synthetic methodologies for approaching them.



Cinacalcet NPS *R*-568

Figure 4-1: Structures of Cinacalcet and NPS *R*-568.

The groups of List,[10] MacMillan,[11] and Xiao[12] have recently made a major progress in direct asymmetric reductive amination by employing chiral organocatalyst or combination of transition metal catalyst and Brønsted acid to access chiral amines. Kadyrov and Börner also reported on transition metal-catalyzed asymmetric reductive amination providing chiral amines.[13] However, catalytic asymmetric hydrogenation of imines is still a powerful method to afford amine product enantiomerically due to its high efficiency, low catalyst loading and atom economy.[14a]

The asymmetric reduction of imines remains a challenge in modern synthesis, in contrast to the significant progress made in the catalytic asymmetric hydrogenation of ketones and olefins over the last few decades.[7b,14] A number of chiral transition metal complexes, such as Ti, Rh, Ru, and Ir complexes have been investigated and exhibited promising results in the asymmetric hydrogenation of imines.[15] Buchwald and co-workers developed highly effective chiral Titanocene catalyst for the hydrogenation of cyclic imines.[15a] On the other hand, chiral Ir complexes have shown more potentials recently for the reduction of acyclic imines. Imamoto reported asymmetric hydrogenation of acyclic imines using Ir–bisP* complexes with high enantioselectivities.[15h] Ir–P,N ligand complexes that catalyzed asymmetric hydrogenation of acyclic *N*-aryl ketimine have been reported by Zhou *et al*.[15i] and Knochel *et al*..[15j] Xiao and coworkers demonstrated the catalytic capability of Cp*Ir(III)–diamine for the reduction of a wide variety of imines.[15k] More recently, Feringa and de Vries reported the use of Ir–monodentate phosphoramidite in imine hydrogenations.[16] However, the high catalyst

loading (0.5–1 mol%) remains an obstacle to the practical application of these methodologies. The only successful example of asymmetric hydrogenation of imine in industrial synthesis is the application of neutral iridium complex $[Ir(cod)Cl]_2$ and XyliPhos in the production of herbicide (*S*)-metolachlor, achieving turnover number (TON) up to 106 and 80% ee.[17] The low TON problem in most systems may possibly attribute to the inhibitory effect of the amine product on the catalysts,[18] and to the possible formation of undesired polymeric Ir clusters.[15i, 19] We envisioned that introducing a highly electron- donating and highly steric-hindered bisphospholane ligand exerting strong *trans* effect could minimize binding of the amine product to the catalyst and inhibiting the formation of Ir clusters. Thus we envisioned that the series of electron-donating, rigid and steric-hindered ligands developed in our research group, such as TangPhos, [20] DuanPhos, [21] Binapine, [22] could be excellent candidates for Ir–bisphosphine complex catalyzed imines hydrogenation (Figure 4-2).

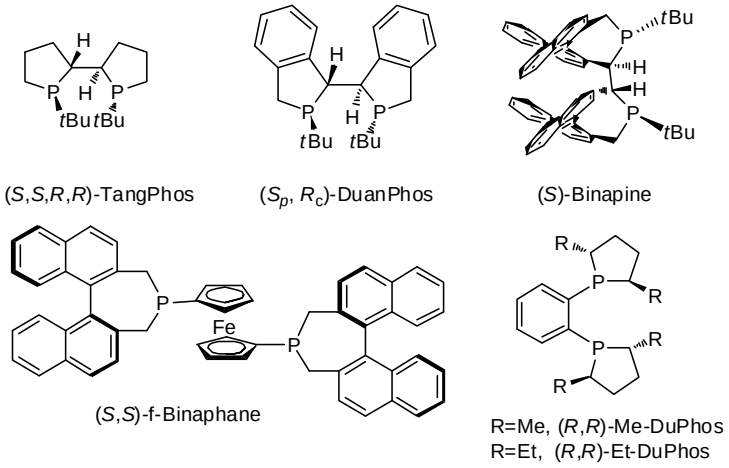
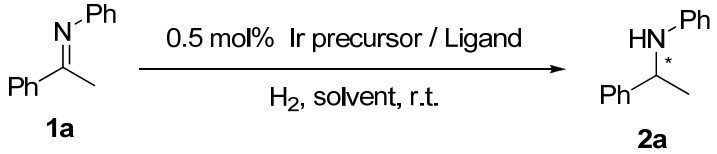


Figure 4-2: Structures of Electron-Donating Ligands for Asymmetric Hydrogenation.

Our initial study began with *N*-(1-phenylethylidene)aniline (**1a**) as the model substrate and a brief screening of Ir precursors and different chiral phosphorus ligand (Table 4-1 and Table 4-2). First, we investigated the performance of TangPhos in combination with different Ir salt. Under 50 atm H_2, neutral iridium chloride complex and the cationic complex with BF_4^- counterion gave incomplete conversion and only moderate ee (Table 4-1, entries 1 and 2). Whereas, the imine substrate was fully converted to the amine product with 73% ee in the presence of BARF (tetrakis(3,5-trifluoromethylphenyl)borate) counterion (entry 3). These results are consistent with the reported acceleration effect of BARF in Ir-catalyzed hydrogenation reactions.[23]

Table 4-1: Ir-Catalyzed Asymmetric Hydrogenation of *N*-aryl Imine **1a**: Ir Precursor Effect Study.[a]



1a **2a**

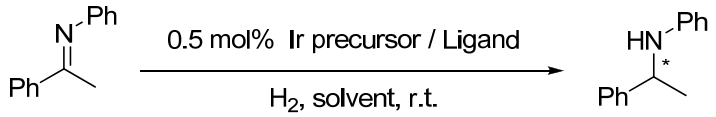
Entry	Ir precursor	Ligand	Solvent	Conv.(%)[b]	Ee (%)(Config.)[c]
1	$[Ir(cod)Cl]_2$	(*S*,*S*,*R*,*R*)-TangPhos	CH_2Cl_2	89	62 (*R*)
2	$Ir(cod)_2BF_4$	(*S*,*S*,*R*,*R*)-TangPhos	CH_2Cl_2	93	63 (*R*)
3	$Ir(cod)_2BARF$	(*S*,*S*,*R*,*R*)-TangPhos	CH_2Cl_2	> 99	73 (*R*)

[a] The reactions were carried out with 0.1 mmol of substrate in 2 mL of solvent in the presence of 0.5 mol% of Ir catalyst for 20 h under an initial hydrogen pressure of 50 atm. [b] The conversions were determined by GC. [c] The enantiomeric excesses were determined by chiral HPLC or GC.The absolute configuration was determined by comparison of the retention times and sign of the optical rotation with the reported data

Subsequently, the effect of solvents was investigated in an effort to attain higher enantioselectivities (Table 4-2). Dichloromethane was the only solvent that gave both good ee values and complete conversions during the screening.

Furthermore, Ir complexes of different chiral phosphorus ligands were prepared and tested (Table 4-3). The hydrogenation with other Ir catalysts containing electron-donating phosphines such as Ir–(*R*,*R*)-DuPhos or Ir–(*S*,*S*)-f-Binaphane proceeded smoothly with high conversions; however, the enantioselectivities are only comparable or lower to that of Ir–TangPhos (entries 3–6). To our delight, the best result was obtained with the Ir–(S_p,R_c)-DuanPhos with 93% ee and >99% conversions (entry 8).

Table 4-2: Ir-Catalyzed Asymmetric Hydrogenation of *N*-aryl Imine **1a**: Solvent Effect Study.[a]



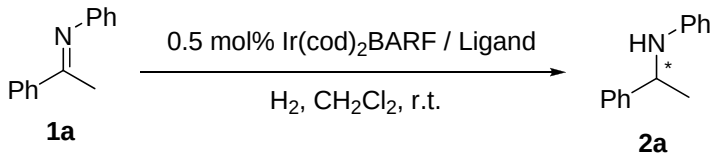
1a **2a**

Entry	Ir precursor	Ligand	Solvent	Conv.(%)[b]	Ee (%)(Config.)[c]
1	Ir(cod)$_2$BARF	(*S*,*S*,*R*,*R*)-TangPhos	CH_2Cl_2	> 99	73 (*R*)
2	Ir(cod)$_2$BARF	(*S*,*S*,*R*,*R*)-TangPhos	THF	> 99	4 (*R*)
3	Ir(cod)$_2$BARF	(*S*,*S*,*R*,*R*)-TangPhos	Ethyl acetate	> 99	7 (*R*)
4	Ir(cod)$_2$BARF	(*S*,*S*,*R*,*R*)-TangPhos	IPA	67	16 (*S*)
5	Ir(cod)$_2$BARF	(*S*,*S*,*R*,*R*)-TangPhos	Methanol	92	15 (*S*)
6	Ir(cod)$_2$BARF	(*S*,*S*,*R*,*R*)-TangPhos	Ethyl ether	90	23 (*R*)

[a] The reactions were carried out with 0.1 mmol of substrate in 2 mL of solvent in the presence of 0.5 mol% of Ir catalyst for 20 h under an initial hydrogen pressure of 50 atm. [b] The conversions were determined by GC. [c] The enantiomeric excesses were determined by chiral HPLC or GC.The absolute configuration was determined by comparison of the retention times and sign of the optical rotation with the reported data.

The hydrogen pressure showed no obvious effect on the activity or enantioselectivity. Even under 5 atm H_2, the reaction reached completion within 3 hours, and the ee remained the same under the milder conditions (entry 9). In comparison, Ir complex of less electron-donating and less steric-hindered BINAP ligand gave lower enantioselectivities (entry 7).

Table 4-3: Ir-Catalyzed Asymmetric Hydrogenation of *N*-aryl Imine **1a**: Ligand Screening.[a]



1a **2a**

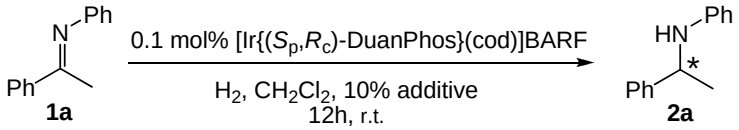
Entry	Ligand	Solvent	Conv.(%)[b]	Ee (%)(Config.)[c]
1	Ir(cod)$_2$BARF (*S*,*S*,*R*,*R*)-TangPhos	CH_2Cl_2	> 99	73 (*R*)
2	Ir(cod)$_2$BARF (*S*)-Binapine	CH_2Cl_2	5	37 (*S*)
3	Ir(cod)$_2$BARF (*S*,*S*)-f-Binaphane	CH_2Cl_2	>99	74 (*R*)
4	Ir(cod)$_2$BARF (*R*,*R*)-Me-DuPhos	CH_2Cl_2	>99	49 (*S*)
5	Ir(cod)$_2$BARF (*R*,*R*)-Et-DuPhos	CH_2Cl_2	>99	67 (*S*)
6	Ir(cod)$_2$BARF (*R*,*S*)-CyPF-*t*Bu-Josiphos	CH_2Cl_2	>99	48 (*S*)
7	Ir(cod)$_2$BARF (*R*)-BINAP	CH_2Cl_2	>99	14 (*S*)
8	Ir(cod)$_2$BARF (S_p,R_c)-DuanPhos	CH_2Cl_2	>99	93 (*R*)
9[d]	Ir(cod)$_2$BARF (S_p,R_c)-DuanPhos	CH_2Cl_2	>99	93 (*R*)

[a] The reactions were carried out with 0.1 mmol of substrate in 2 mL of solvent in the presence of 0.5 mol% of Ir catalyst for 20 h under an initial hydrogen pressure of 50 atm. [b] The conversions were determined by GC. [c] The enantiomeric excesses were determined by chiral HPLC or GC.The absolute configuration was determined by comparison of the retention times and sign of the optical rotation with the reported data . [d] Initial hydrogenation pressure was 5 atm.

Considering the crucial influence of additives in some reported examples of olefins, ketones, and imines hydrogenations,[24] we investigated the additive effect on this

asymmetric hydrogenation of *N*-aryl imines (Table 4-4).

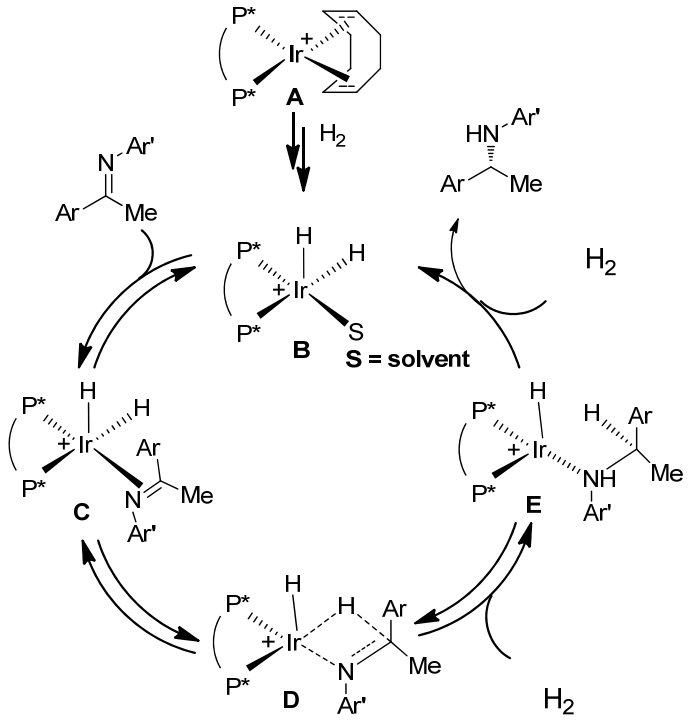
Table 4-4: Study of Additive Effect.[a]



Entry	Additive	Conv. (%)[b]	ee (%)(conifg.)[c]
1	CH_3COOH	98	92 (*R*)
2	Et_3N	<5	n.a.
3	I_2	<5	n.a.
4	K_2CO_3	50	92 (*R*)
5	phthalimide	99	93 (*R*)
6	Bu_4NI	<5	n.a.

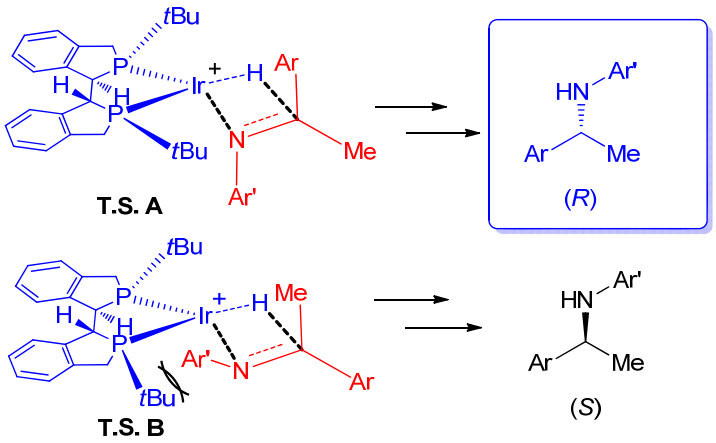
[a]The reactions were carried out with 0.1 mmol of substrate in 2 mL of solvent in the presence of 0.1 %mol of Ir catalyst for 12 h under an initial hydrogen pressure of 50 atm, n.a.= not analyzed. [b] The conversions were determined by chiral HPLC or GC. [c] The enantiomeric excesses were determined by chiral HPLC or GC, the absolute configuration was determined by comparison of the retention times and sign of the optical rotation with the reported data.

It is interesting to consider the mechanistic view of the enantioselection of this asymmetric hydrogenation of imines. Although the stereochemical outcome of the examined reactions is not clear in most cases, the configuration of the product (*R* enantiomer obtained) provided some sense of enantioselection. Thus, based upon the extensively investigated mechanism underlying the Ir-catalyzed asymmetric hydrogenation of alkenes and imines as well as experimental findings and theoretical calculations, we proposed the mechanism of this hydrogenation catalysis.



Scheme 4-1: Proposed Mechanism.

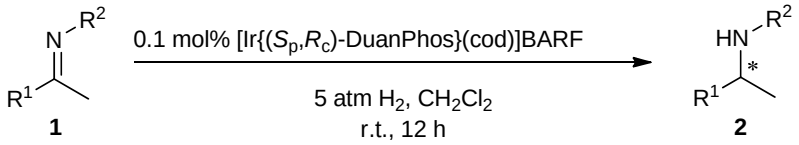
The proposed catalytic cycle (Scheme 4-1) described the addition of H_2 to the C=N double bonds from the *Si* face, and it suggests that the enantioselection is determined at the migratory insertion step (**D** to **E**). The stereochemical outcome can be explained in terms of both steric and electronic factors, when the transition state is hypothesized to be a four-membered ring transition state. The steric hindrance from the tert-Bu group mainly determines the enantioselection which serves as the outcome of a lower/favorable energy transition state (Scheme 4-2).



Scheme 4-2: Proposed Origin of Enantioselectivity.

To explore the efficiency and the applicability of this Ir–DuanPhos catalyst, the hydrogenation of a series of substituted *N*-aryl imines was studied under the optimized conditions. Asymmetric hydrogenation was performed using 0.1 mol% catalyst loading (Table 4-5). Full conversions (>99 %) were observed for all substrates, with excellent ee values ranging from 89% to 98%. The electronic properties of the substituents on the R and R′ group of the imine have limited effect on the yields or the enantioselectivities. As shown in Table 4-5, the introduction of an electron-donating group on the R phenyl ring slightly decreased the enantioselectivity (entries 2 and 3); an electron-withdrawing substituent on the R′ phenyl also affords slightly lower ee values (entries 11 and 12). Notably, 98% ee was achieved with the presence of more sterically hindered 2-naphthyl group in the imine substrate (entry 8).

Table 4-5: Substrate Scope Study of Ir−DuanPhos-Catalyzed Asymmetric Hydrogenation of *N*-aryl Imine **1**.[a]

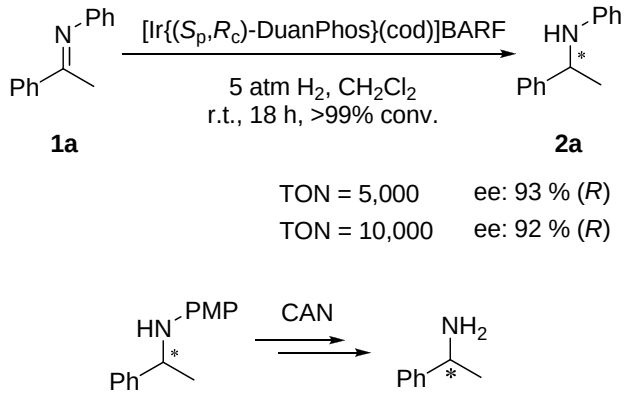


Entry	Substrate	R^1	R^2	Product	Conv.(%)[b]	ee (%)[b]	Config.
1	**2a**	C_6H_5	C_6H_5	**2a**	>99%	93	(*R*)
2	**2b**	*m*-MeC_6H_4	C_6H_5	**2b**	>99%	90	(+)
3	**2c**	*p*-$MeOC_6H_4$	C_6H_5	**2c**	>99%	90	(+)
4	**2d**	*p*-FC_6H_4	C_6H_5	**2d**	>99%	93	(-)
5	**2e**	*p*-ClC_6H_4	C_6H_5	**2e**	>99%	92	(+)
6	**2f**	*p*-BrC_6H_4	C_6H_5	**2f**	>99%	92	(+)
7	**2g**	*m*-ClC_6H_4	C_6H_5	**2g**	>99%	93	(-)
8	**2h**	2-naphthyl	C_6H_5	**2h**	>99%	98	(+)
9	**2i**	C_6H_5	*p*-MeC_6H_4	**2i**	>99%	92	(+)
10	**2j**	C_6H_5	*p*-$MeOC_6H_4$	**2j**	>99%	93	(-)
11	**2k**	C_6H_5	*p*-FC_6H_4	**2k**	>99%	89	(-)
12	**2l**	C_6H_5	*p*-ClC_6H_4	**2l**	>99%	90	(+)

[a] The reactions were carried out with 0.1 mmol of substrate in 2 mL of solvent in the presence of 0.1 mol% of Ir catalyst for 12 h under an initial hydrogen pressure of 5 atm. [b] The conversions and enantiomeric excesses were determined by chiral HPLC or GC. The absolute configuration was determined by comparison of the retention times and sign of the optical rotation with the reported data.

To explore the potential of Ir-catalyzed asymmetric hydrogenation of imines as a practical means to synthesize chiral amines, the catalyst loading was further decreased to 0.02 mol% and 0.01 mol% (TON = 5,000 and 10,000). The model imine substrate **1a** was smoothly hydrogenated with full conversion, and over 92 % ee can still be retained under the mild reaction conditions (5 atm H_2, r.t.; Scheme 4-1). To our best knowledge, this

result represents the highest reactivity (TONs) in the asymmetric hydrogenation of imines using chiral cationic iridium catalysts. Also, this hydrogenation proceeded under ambient hydrogen pressure (1 atm) within 3 h (0.05 mol% catalyst loading, >99 % conversion). No obvious ee value erosion of the hydrogenation was observed. Some methoxy-substituted *N*-aryl groups such as the 4-methoxyphenyl in **2j** could be easily removed by CAN (cerium ammonium nitrate) to obtain corresponding primary amines without affecting the ee values (Scheme 4-3).[25]

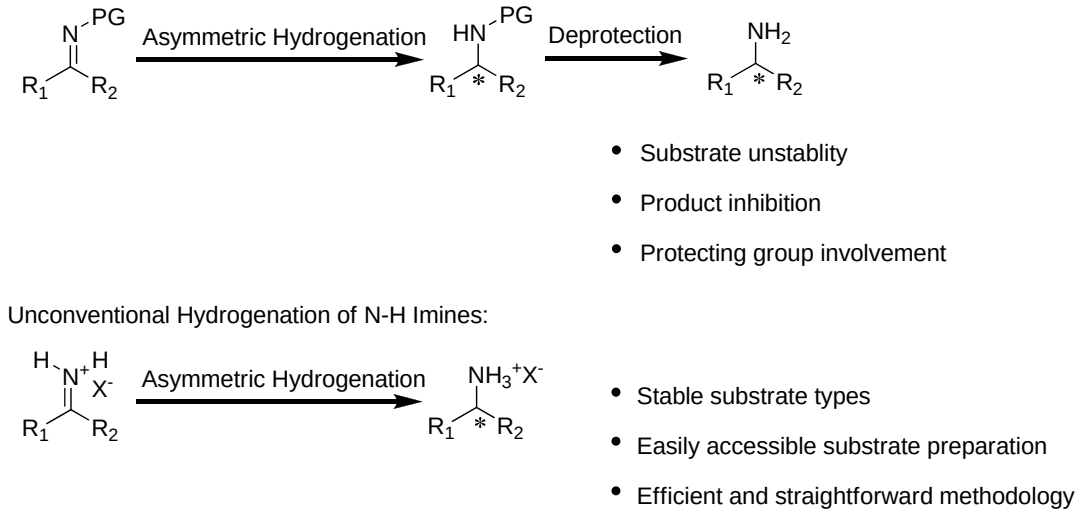


Scheme 4-3: A Potential Methodology for Practical Chiral Primary Amine Synthesis: High TON Test Results and Simple Deprotection Step.

4.2.2. Ir-Catalyzed Asymmetric Hydrogenation of N-H Imines

Chiral amines are ubiquitous structural elements of small molecule pharmaceuticals and agrochemicals that improve human life. While several approaches have been developed to prepare chiral amines, decades of research have evolved catalytic

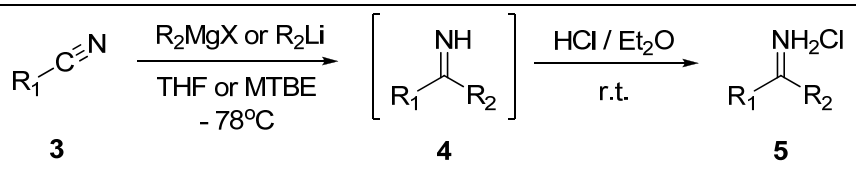
hydrogenation into a technology ideally suited for their stereoselective synthesis.[26] Although success has been achieved with enantioselective hydrogenation of protected enamides, enamines, and imines, many catalysts fail to deliver the same levels of control and efficiency demonstrated with ketones and olefins.[15, 27] Diminished enantioselectivities may be observed because of ambiguous catalyst-substrate interactions complicated by imine-enamine tautomerization and interconversion of imine *E*/*Z* stereoisomers.[26] Furthermore, available methods often require cumbersome protecting group manipulations to provide a substrate suited for hydrogenation and subsequent release of the desired amine products (Scheme 4-4).



Scheme 4-4: Comparison of Traditional Imine Hydrogenation and N-H Imines Hydrogenation.

Therefore, we proposed and studied enantioselective hydrogenations of *unprotected* N-H imines,[28] a fundamental step in the development of an ideal direct

asymmetric reductive amination of ketones. To the best of our knowledge, N-H ketoimines have been completely overlooked as substrates for enantioselective hydrogenation. This is possibly because they have been considered difficult to synthesize and isolate and often exist as complex mixtures of *E*/*Z* isomers and imine-enamine tautomers. Multigram amounts of N-H ketoimines **5a**-**5v** were readily prepared via organometallic addition to nitriles **3** followed by quenching with anhydrous MeOH and isolation of the corresponding hydrochloride salts as single isomers, free-flowing, bench-stable solids (Scheme 4-5).

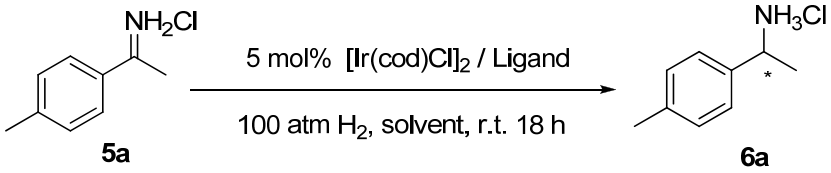


3 **4** **5**

Scheme 4-5: Synthesis of N-H Imine Substrates **5 (5a-v)**.

Inspired by a number of imine hydrogenation studies,[29,30] we anticipated that rigid electron-rich ligands could lead to high enantioselectivities with N-H ketoimines. Our initial evaluation began with hydrogenation of N-H imine **5a** as the model substrate with a series of catalysts. Few promising results were obtained using Rh-phosphine catalysts. A number of electron-rich chiral Ir-phosphine complexes were also evaluated (Table 4-6). While poor results were obtained using TangPhos,[20] DuanPhos,[21] BINAP, and Me-DuPhos, we were gratified to find that axially chiral Ir-(*S*,*S*)-f-Binaphane (Figure 4-3) was a promising candidate for further optimization.

Table 4-6: Ir-Catalyzed Asymmetric Hydrogenation of N-H Imine **5a**: Ligand Screening.[a]



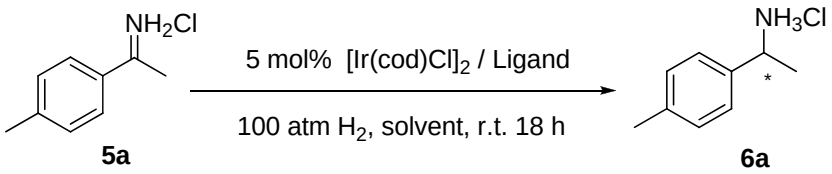
5a **6a**

Entry	Ligand	Solvent	Conv.(%)[b]	Ee (%)[c]
1	(*S*,*S*,*R*,*R*)-TangPhos	TFE	99	0
2	(S_c,R_p)-DuanPhos	TFE	41	8
3	(*R*)-BINAP	TFE	40	14
4	(*R*,*R*)-Me-DuPhos	TFE	20	20
5	(*S*,*S*)-f-Binaphane	TFE	31	52

[a] Reactions conditions: [Ir(COD)Cl$_2$ / phosphine ligand / substrate = 2.5 : 5: 100, 1:1 ligand /metal, r.t. 100 atm H_2. [b] The conversions were determined by GC. [c] The enantiomeric excesses were determined by chiral GC analysis of the corresponding acetamides.

In the solvent screening experiments, only moderate or poor conversion was observed in most solvents (Table 4-7, entries 1-5). Use of MeOH as solvent gave complete conversion albeit with poor enantioselectivity (Table 4-7, entry 6). We found that the best enantioselectivity was obtained using CH_2Cl_2 as solvent (80% ee, Table 4-7, entry 2). We optimized the solvent combination and ratio with MeOH to achieve complete conversion and high enantioselectivity (Table 4-7, entries 8-14). Interestingly, under these optimized conditions we observed a negative impact on enantioselectivities when the chloride counterion in **5a** was replaced with noncoordinating counterions: methanesulfonate (75% conversion, 51% ee), $PF6^-$ (90% conversion, 91% ee), $BF4^-$ (99% conversion, 88% ee).

Table 4-7: Ir-Catalyzed Asymmetric Hydrogenation of N-H Imine **5a**: Solvent Effect Study and Optimization.[a]

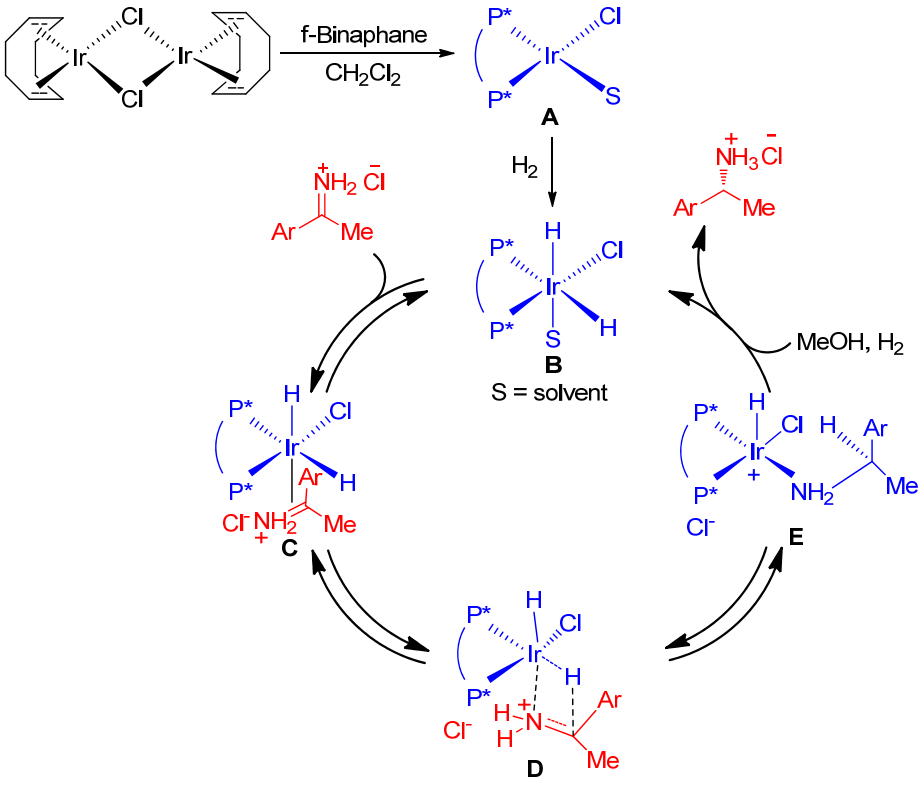


5a **6a**

Entry	Ligand	Solvent	Conv.(%)[b]	Ee (%) (Config.)[c]
1	(*S*,*S*)-f-Binaphane	TFE	31	52 (*R*)
2	(*S*,*S*)-f-Binaphane	CH_2Cl_2	60	80 (*R*)
3	(*S*,*S*)-f-Binaphane	Toluene	15	70 (*R*)
4	(*S*,*S*)-f-Binaphane	DCE	60	32 (*R*)
5	(*S*,*S*)-f-Binaphane	EtOAc	37	38 (*R*)
6	(*S*,*S*)-f-Binaphane	THF	30	20 (*R*)
7	(*S*,*S*)-f-Binaphane	MeOH	99	9 (*R*)
8	(*S*,*S*)-f-Binaphane	MeOH/TFE (2:1)	99	10 (*R*)
9	(*S*,*S*)-f-Binaphane	MeOH/DCE (2:1)	99	20 (*R*)
10	(*S*,*S*)-f-Binaphane	MeOH/CH_2Cl_2 (1:2)	99	89 (*R*)
11[d]	(*S*,*S*)-f-Binaphane	MeOH/CH_2Cl_2 (2:1)	99	95 (*R*)
12[e]	(*S*,*S*)-f-Binaphane	MeOH/CH_2Cl_2 (2:1)	99	95 (*R*)
13[f]	(*S*,*S*)-f-Binaphane	MeOH/CH_2Cl_2 (2:1)	98	95 (*R*)
14[g]	(*S*,*S*)-f-Binaphane	MeOH/CH_2Cl_2 (2:1)	99	73 (*R*)

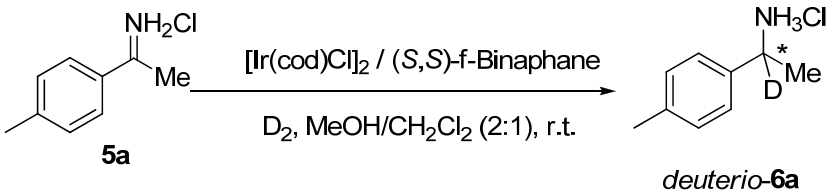
[a] Reactions conditions: [Ir(COD)Cl_2 / phosphine ligand / substrate = 2.5 : 5: 100, 1:1 ligand /metal, r.t. 100 atm H_2. [b] The conversions were determined by GC. [c] The enantiomeric excesses were determined by chiral GC analysis of the corresponding acetamides. [d] Initial pressure of H_2 was 30 atm. [e] Initial pressure of H_2 was 10 atm. [f] Initial pressure of H_2 was 5 atm. [g] Initial pressure of H_2 was 10 atm, catalyst loading = 1 mol%

To investigate this reaction from the mechanistic perspective, we believe that the acidic condition of this asymmetric hydrogenation remarkably promotes the reduction process because the protonation of the primary product could reduce or prevent the inhibitory effect and release the active iridium catalyst species for the next catalytic cycle (Scheme 4-6).



Scheme 4-6: Proposed Mechanism of Asymmetric Hydrogenation of N-H Imines.

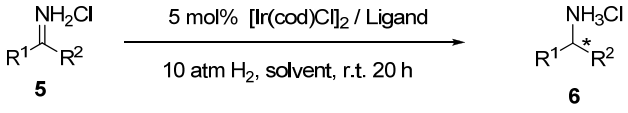
Experimental evidence was gathered through isotopic labeling of imine **5a** with D_2 in $MeOH/CH_2Cl_2$ (Scheme 4-7). ^1H NMR analysis of the crude product showed exclusive formation of α-*deuterio*-amine hydrochloride **6a**, suggesting a pathway consistent with reduction of the imine tautomer.[40] This result is also consistent with our proposed mechanism. In addition, enantioface selection of imine **5a** by the Ir−f-Binaphane catalyst was found to be identical to that of 4′-methylacetophenone (*R* enantiomer).



Scheme 4-7: Isotopic Study of Asymmetric Hydrogenation of N-H Imine **5a**.

A variety of N-H imine substrates **5a**-**5v** were then examined using the Ir−f-Binaphane catalyst system (Table 4-8). The bulkiness of the R^2 group in substrates had an influence on the enantioselectivities. As the R^2 group changed from Me to *t*Bu, the enantioselectivity of the product gradually decreased from 93% to 80% ee (entries 2-5). Substrates bearing both electron-donating and -withdrawing substituents on the aromatic ring in R^1 were hydrogenated with uniformly high enantioselectivities (entries 6-14). Both the 1- and 2-naphthyl N-H imines afforded product amines in 92 and 93% ee, respectively (entries 18 and 19). We found that the presence of either a methyl- or chloro-substituent at the *ortho*-position resulted in a slightly reduced ee (entry 15 and 17). The reduction of enantioselectivity may be attributed to the steric hindrance of the *ortho*-substituents in the substrates. However, an *ortho*-methoxy group did not exhibit a similar effect (entry 16).

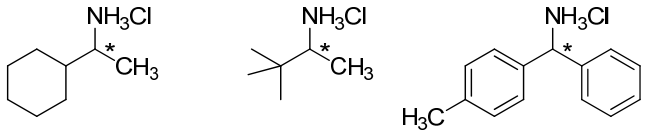
Table 4-8: Enantioselective Hydrogenation of N-H Imines **5**.[a]



Entry	Substrate	R^1	R^2	Substrate	Yield (%)[b]	Ee (%) (Config.)[c]
1	**5a**	*p*-MeC_6H_4	CH_3	**6a**	95	95 (*R*)
2	**5b**	C_6H_5	CH_3	**6b**	93	93 (*R*)
3	**5c**	C_6H_5	C_2H_5	**6c**	92	86 (*R*)
4	**5d**	C_6H_5	*n*Bu	**6d**	92	88 (*R*)
5	**5e**	C_6H_5	*t*Bu	**6e**	90	80 (*R*)
6	**5f**	*p*-$MeOC_6H_4$	CH_3	**6f**	95	93 (*R*)
7	**5g**	*p*-FC_6H_4	CH_3	**6g**	95	92 (*R*)
8	**5h**	*p*-ClC_6H_4	CH_3	**6h**	95	94
9	**5i**	*p*-BrC_6H_4	CH_3	**6i**	94	93 (*R*)
10	**5j**	*p*-$CF_3C_6H_4$	CH_3	**6j**	93	93 (*R*)
11	**5k**	*m*-MeC_6H_4	CH_3	**6k**	95	92
12	**5l**	*m*-$MeOC_6H_4$	CH_3	**6l**	94	94
13	**5m**	*m*-ClC_6H_4	CH_3	**6m**	92	92
14	**5n**	*m*-BrC_6H_4	CH_3	**6n**	93	91
15	**5o**	*o*-MeC_6H_4	CH_3	**6o**	92	81
16	**5p**	*o*-$MeOC_6H_4$	CH_3	**6p**	93	92 (*R*)
17	**5q**	*o*-ClC_6H_4	CH_3	**6q**	92	81
18	**5r**	1-naphthyl	CH_3	**6r**	95	93
19	**5s**	2-naphthyl	CH_3	**6s**	94	92 (*R*)

[a] Reactions conditions: [Ir(COD)Cl_2 / phosphine ligand / substrate = 2.5 : 5: 100, 1:1 ligand /metal, 10 atm H_2, r.t., 20h, >99% conversion. [b] The conversions were determined by GC. [c] The enantiomeric excesses were determined by chiral GC analysis of the corresponding acetamides.

Significant erosion in enantioselectivity was observed when the aryl substituent was replaced with a sterically hindered *t*Bu group (Figure 4-3). Finally, in our further substrate scope extension studies, the Ir catalyst showed promising enantioselectivities on dialkyl imine **5u** and diaryl imine **5v**, substrates with a more limited steric and electronic bias (Figure 4-3).



6t 98 % yield
73 % ee

6u 90 % yield
17 % ee

6v 95 % yield
23 % ee

Figure 4-3: Extended Substrate Scope Study.

4.2.3. Ir-Catalyzed Asymmetric Hydrogenation of Unprotected *β*-Enamine Esters

Enantiopure *β*-amino acids and their derivatives are ubiquitous important structural motifs in important natural products and pharmaceuticals.[31] In life sciences, extensive existence and applications of chiral *β*-amino acids have been found in biologically active peptides. Chiral *β*-amino acids are also widely used as key intermediates or chiral building blocks in the synthesis of small molecule pharmaceuticals,[32] such as (*S*)-dapoxetine,[33] which is used for the treatment of a variety of disorders as depression, bulimia or anxiety, and some antiretroviral agents, (*S*)-maraviroc,[34] compound **7** and **8** (Figure 4-4).[35,36]

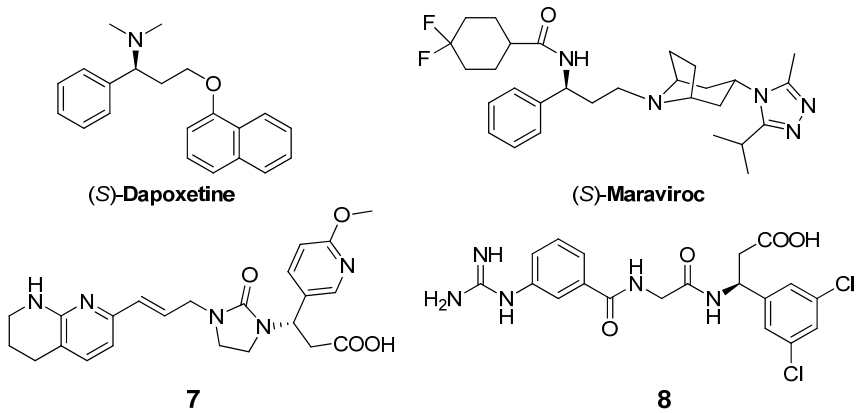
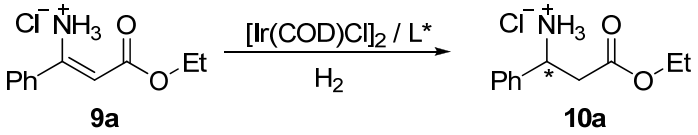


Figure 4-4: Structures of (*S*)-Dapoxetine, (*S*)-Maraviroc, and Compound **7** and **8**.

Due to its significance in chemical synthesis, many approaches have been developed for the enantioselective synthesis of chiral *β*-amino acids.[37] Although catalytic asymmetric hydrogenation could be a successful methodology for the preparation chiral α-amino acids in industry,[38] its application for large-scale synthesis of enantiopure *β*-amino acids has been largely limited by the indispensable involvement of *N*-acyl in current/most hydrogenation approaches. The chelating assistance of the *N*-protecting group plays a crucial role in achieving high reactivity and enantioselectivity.[39] To avoid the redundancy of introduction and removal of the acyl group, developing a generally applicable and highly efficient catalyst system for direct hydrogenation of unprotected enamine esters would be an ideal solution to access free enantiopure *β*-amino acids. However, only few related works were reported. In 2004, Merck and Solvias groups reported the first example of catalytic asymmetric hydrogenation of unprotected *β*-enamine esters and amides by using Rh−Josiphos complexes with excellent enantioselectivity.[40] One drawback of this method is really low turnovers (<1000) due to product inhibition. Later, Ru catalysts were also reported to catalyze asymmetric hydrogenation of unprotected *β*-enamine esters with high ee's by the Takasago group.[41] More recently, both of these methodologies have been successfully applied to the synthesis of Sitagliptin, achieving excellent enantioselectivities.[37d,42] Inspired by these encouraging results and our recent work on the asymmetric hydrogenation of unprotected N-H imines,[43] we decided to tackle the asymmetric hydrogenation of this class of challenging substrates.[44]

Table 4-9: Ir-Catalyzed Asymmetric Hydrogenation of *β*-Enamine Hydrochloride Ester **9a**: Ligand Screening.[a]



9a **10a**

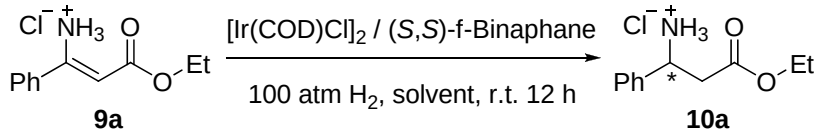
Entry	Ligand	Solvent	Conv.(%)[b]	Ee (%)[c]
1	(*S*,*S*,*R*,*R*)-TangPhos	MeOH/CH_2Cl_2 (2:1)	>99	46
2	(S_c,R_p)-DuanPhos	MeOH/CH_2Cl_2 (2:1)	>99	37
3	(*S*,*S*)-f-Binaphane	MeOH/CH_2Cl_2 (2:1)	>99	97
4	(*R*,*R*)-Me-DuPhos	MeOH/CH_2Cl_2 (2:1)	60	6
5	(*R*)-BINAP	MeOH/CH_2Cl_2 (2:1)	>99	14
6	(*R*)-SEGPHOS	MeOH/CH_2Cl_2 (2:1)	>99	29
7	(*S*)-PhanePhos	MeOH/CH_2Cl_2 (2:1)	23	35
8	(*R*,*S*)-*t*Bu-JosiPhos	MeOH/CH_2Cl_2 (2:1)	78	19
9	(*S*)-NMe-NBn -MonosPhos	MeOH/CH_2Cl_2 (2:1)	98	20
10	(*R*)-MonoPhos	MeOH/CH_2Cl_2 (2:1)	74	3
11	(*S*,*RR*)-MonoPhos-PE	MeOH/CH_2Cl_2 (2:1)	96	12

[a] Reactions conditions: [Ir(COD)Cl_2 / phosphine ligand / substrate = 0.5 : 5: 100, 1:1 ligand /metal, 100 atm H_2, r.t., 12 h. [b] The conversions were determined by GC. [c] The enantiomeric excesses were determined by chiral GC analysis of the corresponding acetamides.

Considering the fact that the primary beta amine ester products in this transformation could have a strong inhibitory effect on the catalyst,[45] and also the fact that the products are unstable with ester substrates in some solvent,[37a] we chose *β*-enamine hydrochloride esters as the substrates for our study. Our initial evaluation began with hydrogenation of *β*-enamine hydrochloride ester **9a** as the model substrate with a series of catalysts. Few promising results were obtained using Rh-phosphine catalysts. A number of Ir-phosphine complexes were also screened (Table 4-9). We were

gratified to find that (*S*,*S*)-f-Binaphane ligand was able to achieve excellent enantioselectivity as well as full conversion (entry 3). Other types of bidentate diphosphine ligands, such as TangPhos, Me-DuPhos, BINAP, *t*Bu-Josiphos, and monodentate phosphorus ligands, such as MonoPhos, NMe-NBn-MonoPhos, showed either significantly lower enantioselectivities or reactivities (entries 1-2 and 4-11). Interestingly, the solvent played a key role in this Ir-f-Binaphane catalyst system (Table 4-10).

Table 4-10: Ir-Catalyzed Asymmetric Hydrogenation of *β*-Enamine Hydrochloride Ester **9a**: Solvent Screening.[a]



9a **10a**

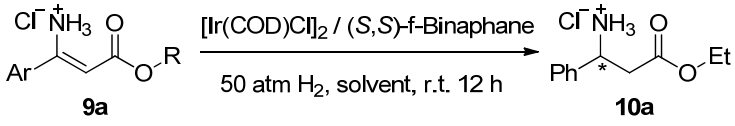
Entry	Ligand	Solvent	Conv.(%)[b]	Ee (%) [c]
1	(*S*,*S*)-f-Binaphane	MeOH	>99	75
2	(*S*,*S*)-f-Binaphane	EtOH	>99	4
3	(*S*,*S*)-f-Binaphane	CH_2Cl_2	10	41
4	(*S*,*S*)-f-Binaphane	Toluene	5	33
5	(*S*,*S*)-f-Binaphane	THF	14	89
6	(*S*,*S*)-f-Binaphane	MeOH/CH_2Cl_2 (1:1)	>99	87
7	(*S*,*S*)-f-Binaphane	MeOH/CH_2Cl_2 (3:1)	>99	94
8	(*S*,*S*)-f-Binaphane	MeOH/THF (2:1)	>99	94
9[d]	(*S*,*S*)-f-Binaphane	MeOH/CH_2Cl_2 (2:1)	>99	97
10[e]	(*S*,*S*)-f-Binaphane	MeOH/CH_2Cl_2 (2:1)	69	97

[a] Reactions conditions: [Ir(COD)Cl_2 / (*S*,*S*)-f-Binaphane / substrate = 0.5 : 1: 100, 1:1 ligand /metal, 100 atm H_2, r.t., 12 h. [b] The conversions were determined by GC. [c] The enantiomeric excesses were determined by chiral GC analysis of the corresponding acetamides. [d] Initial pressure of H_2 was 50 atm. [e] Initial pressure of H_2 was 20 atm.

Low conversions were observed in CH_2Cl_2, THF, or toluene (entries 3-5). Only moderate

enantioselectivities were obtained in MeOH and EtOH, although full conversions were achieved (entries 1-2).However, consistent with the asymmetric hydrogenation of N-H imines,[43] we discovered that a mixture solvent of MeOH/CH_2Cl_2 could provide the best ee's and high reactivities. By adjusting the solvent ratio of MeOH/CH_2Cl_2 to 2:1, 97% ee was obtained under the optimized conditions (entry 9). Examination of the hydrogen pressure effect revealed that insufficient H_2 pressure could result in incomplete conversion albeit without any enantioselectivity loss (entry 10).

Table 4-11: Asymmetric Hydrogenation of Enamine Esters **9**.[a]



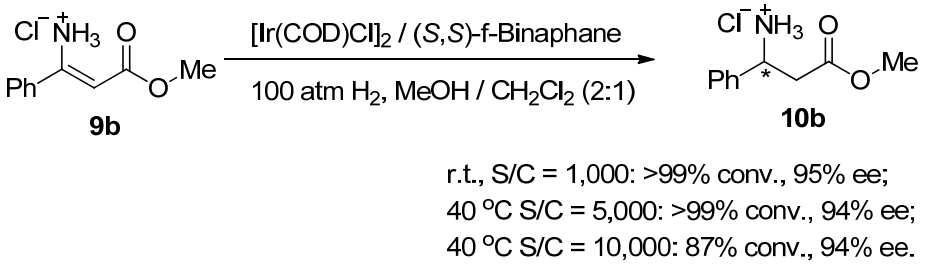
9a **10a**

Entry	Substrate	Ar	R	Substrate	Ee (%) (Config.)[b,c]
1	**9a**	C_6H_5	C_2H_5	**10a**	97 (*R*)
2	**9b**	C_6H_5	CH_3	**10b**	96 (*R*)
3	**9c**	*p*-$MeOC_6H_4$	CH_3	**10c**	95 (*R*)
4	**9d**	*p*-MeC_6H_4	CH_3	**10d**	94 (*R*)
5	**9e**	*p*-FC_6H_4	CH_3	**10e**	95 (*R*)
6	**9f**	*p*-ClC_6H_4	CH_3	**10f**	96 (*R*)
7	**9g**	*p*-BrC_6H_4	CH_3	**10g**	97 (*R*)
8	**9h**	*m*-MeC_6H_4	CH_3	**10h**	92 (–)
9	**9i**	*m*-ClC_6H_4	CH_3	**10i**	94 (–)
10	**9j**	*o*-MeC_6H_4	CH_3	**10j**	84 (*R*)
11	**9k**	1-naphthyl	CH_3	**10k**	90 (*R*)
12	**9l**	2-naphthyl	CH_3	**10l**	92 (*R*)
13	**9m**	2-thienyl	CH_3	**10m**	95 (*R*)

[a] Reactions conditions: [Ir(COD)Cl_2 / (*S*,*S*)-f-Binaphane / substrate = 0.5 : 1.0: 100, 1:1 ligand /metal, 50 atm H_2, r.t., 12h, >99% conversion, isolated yields >90%. [b] The conversions were determined by GC. [c] The enantiomeric excesses were determined by chiral GC analysis of the corresponding acetamides.

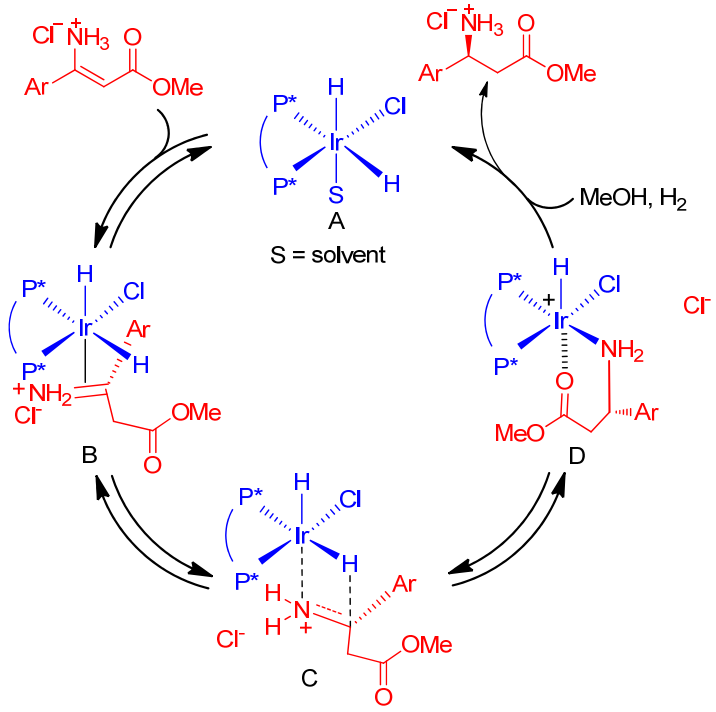
Encouraged by the promising result in the hydrogenation of substrate **9a**, a variety of *β*-enamine hydrochloride esters were examined using the Ir−f-Binaphane catalyst system (Table 4-11). The R group in the ester moiety had no obvious influence on the reactivity and enantioselectivity of this reaction (entries 1-2). The electronic property of substituents on the aryl ring of the substrate had very little effect on the enantiomeric excess of the product. Substrates bearing electron-donating or electron-withdrawing substituents on the aromatic ring were all smoothly hydrogenated to the corresponding products with high enatioselectivities, 92-97% ee (entries 3-9). The substrate with a substituent at the *ortho* position (**9j**) and with a 1-naphthyl group (**9k**) resulted in diminished ee values possibly due to the steric hindrance (entries 10-11). Both the 2-naphthyl substrate **9l** and 2-thienyl **9m** afforded products in 94 and 95% ee, respectively (entries 12-13).

To explore the potential application of the Ir-(*S*,*S*)-f-Binaphane catalyst system in the practical synthesis of chiral *β*-amino acids, we further studied the reactivity and the turnover number (TON) limit of the hydrogenation of **9b** (Scheme 4-8). The transformation was completed with 0.1 mol % catalyst (TON = 1000) at r.t. and even with as low as 0.02 mol % catalyst (TON = 5000) at 40 °C. Only very slight erosions of ee were observed. Furthermore, when the substrate to catalyst ratio (S/C) was furthered increased to 10 000 (0.01 mol % catalyst), the excellent enantioselectivity still remained unchanged. To our best knowledge, this is the highest turnover for asymmetric hydrogenation of unprotected *β*-enamine esters to date.



Scheme 4-8: High TON Experiments of Asymmetric Hydrogenation of Enamine Ester **9b**.

The high reactivity suggested that the hydrogenation possibly proceeded via a "nonchelate" mechanism as proposed in Scheme 4-9.



Scheme 4-9: Proposed Mechanism for Asymmetric Hydrogenation of *β*-Enamine Ester Hydrochlorides.

Very similarly, we rationalized that the formation of ammonium salt could largely reduce the coordination ability of the amine moiety in the product. However, the major

difference in this case is the dramatic enhance of the catalyst reactivity, due the introduced ester group in the substrate. We envision that the ester group could stabilize the active iridium catalyst intermediate by a labile coordination to the open site. Such stabilization effect could prevent the formation of undesired (also inactive in many cases) polymeric iridium clusters.[15i,46]

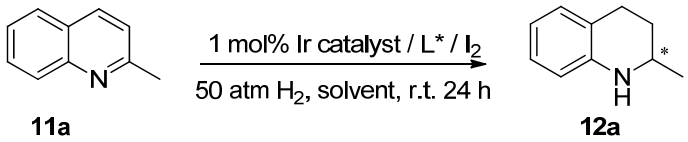
4.2.4. Ir-Catalyzed Asymmetric Hydrogenation of Quinoline Derivatives

The direct catalytic asymmetric hydrogenation of quinolines constitutes the most convenient route to enantiomerically pure tetrahydroquinolines,[6,47] which are not only useful synthetic intermediates[48] but also structural moieties in alkaloids which are natural products and biologically active compounds.[49] The first example of asymmetric hydrogenation of quinolines was reported by Zhou[50a] and co-workers, and some progresses have been achieved thereafter.[50,51] However, the challenges of developing easily accessible air-stable chiral ligands and their application in the direct asymmetric hydrogenation of highly substituted quinolines still remain.

Our initial study began with hydrogenation of 2-methylquinoline **11a** as the model substrate and a brief screening of the performance of different catalysts. Key results are shown in Table 4-12. First, different iridium precursors were screened using C_3-TunePhos as the ligand. It was shown that the neutral precursor $[Ir(COD)Cl]_2$ was superior to the cationic iridium species with BF_4^- and $BARF^-$

{tetrakis[3,5-bis(trifluoromethyl)phenyl]borate} counterion, and afforded 96% conversion and 84% ee (Table 4-12, entries 1–3). Further studies showed that the reactions proceeded smoothly with high conversions and ee values when switching to C_3^*-TunePhos ligand family with various aryl substituents on the phosphine moiety (entries 4–8).

Table 4-12: Catalytic Asymmetric Hydrogenation of **11a**: Catalyst Screening and Reaction Condition Optimization.[a]



11a **12a**

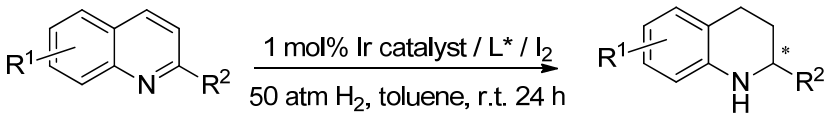
Entry	Metal Precursor	Ligand	Solvent	Conv.(%)[b]	Ee (%)[c]
1	$[Ir(cod)Cl]_2$	(*S*)-Ph-C_3-TunePhos	toluene	96	84
2	$Ir(cod)_2BARF$	(*S*)-Ph-C_3-TunePhos	toluene	99	70
3	$Ir(cod)_2BF_4$	(*S*)-Ph-C_3-TunePhos	toluene	99	62
4	$[Ir(cod)Cl]_2$	(*S*)-Ph-C_3^*-TunePhos	toluene	99	90
5	$[Ir(cod)Cl]_2$	(*S*)-Tol-C_3^*-TunePhos	toluene	98	91
6	$[Ir(cod)Cl]_2$	(*S*)-Xyl-C_3^*-TunePhos	toluene	98	88
7	$[Ir(cod)Cl]_2$	(*S*)-3,5-*t*Bu-C_3^*-TunePhos	toluene	97	93
8	$[Ir(cod)Cl]_2$	(*S*)-3,5-*t*Bu-4-MeO-C_3^*-TunePhos	toluene	98	91
9	$[Ir(cod)Cl]_2$	(*S*)-3,5-*t*Bu-C_3^*-TunePhos	THF	92	64
10	$[Ir(cod)Cl]_2$	(*S*)-3,5-*t*Bu-C_3^*-TunePhos	CH_2Cl_2	96	82
11	$[Ir(cod)Cl]_2$	(*S*)-3,5-*t*Bu-C_3^*-TunePhos	EtOAc	95	86
12	$[Ir(cod)Cl]_2$	(*S*)-3,5-*t*Bu-C_3^*-TunePhos	IPA	95	84
13[d]	$[Ir(cod)Cl]_2$	(*S*)-3,5-*t*Bu-C_3^*-TunePhos	toluene	98	93
14[e]	$[Ir(cod)Cl]_2$	(*S*)-3,5-*t*Bu-C_3^*-TunePhos	toluene	99	91

[a] All reactions were performed on a 0.5 mmol scale: metal / ligand / I_2= 0.5 / 1.05 / 5, 1 mol% Ir catalyst loading, 2.5 mL solvent, 50 atm initial H_2 pressure, r.t., 24 h.. [b] The conversions were determined by GC. [c] The enantiomeric excesses were determined by chiral GC or HPLC. [d] Initial H_2 pressure was 20 atm. [e] Initial H_2 pressure was 10 atm.

To our delight, the highest enantioselectivity of 93% ee was achieved by applying the 3,5-*t*Bu-phenyl-substituted ligand (*S*)-C_3*-TunePhos (entry 7). Greater than 90% conversions were achieved in all solvents examined, either protic or aprotic solvents (entries 9–12). But the use of THF as solvent resulted in low enantioselectivity and somewhat a little lower conversion (entry 9). Compared with other solvents, toluene was more effective. The best result was obtained under 20 atm H_2 and the ee value remained the same under the milder conditions (entries 13, 14). Considering the crucial influence of additives on reactivity,[24,52] we further evaluated a number of additives including KI, NaI, LiI, tetrabutylammonium iodide and some organic and inorganic acids, such as CF_3SO_3H, CF_3COOH, CH_3COOH, HCl and H_2SO_4, etc., I_2 was found to be essential and the most effective additive.

Despite the recent progresses in the asymmetric hydrogenation of quinolines, highly enantioselective hydrogenation of various functionalized quinolines still remains as a challenging. However, reactivity and enantioselectivity are often substrate dependent. Because subtle variations of steric and electronic properties of the substituents could lead to significant changes in both reactivity and enantioselectivity. Nevertheless, previous reports of hydrogenation of quinolines have mainly focused on 2- or 6-substituted analogues, yet the systematic examination of substrate scope of substituted quinolines is rare. Thus, under the optimized conditions, a general application of the iridium–C_3^*-TunePhos catalyst was further investigated, and the results are summarized in Table 4-13.

Table 4-13: Catalytic Asymmetric Hydrogenation of Quinoline Derivatives **11**.[a]



11 **12**

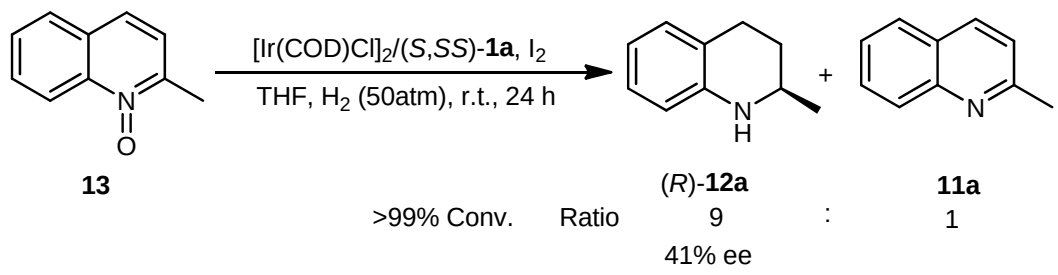
Entry	Substrate	R^1	R^2	Product	Conv.(%)[b]	Ee (%)(Config.)[c]
1	**11a**	H	CH_3	**12a**	98	93 (*S*)
2	**11b**	H	C_2H_5	**12b**	94	88 (*S*)
3	**11c**	H	C_6H_5	**12c**	98	73 (*S*)
4	**11d**	6-F	CH_3	**12d**	97	91 (*S*)
5	**11e**	6-Cl	CH_3	**12e**	99	90 (–)
6	**11f**	6-Br	CH_3	**12f**	99	90 (–)
7	**11g**	6-Me	CH_3	**12g**	95	92 (*S*)
8	**11h**	6-MeO	CH_3	**12h**	84	89 (*S*)
9	**11i**	6-NO_2	CH_3	**12i**	98	75 (–)
10	**11j**	7-F	CH_3	**12j**	99	92 (–)
11	**11k**	7-Cl	CH_3	**12k**	99	90 (–)
12	**11l**	8-Cl	CH_3	**12l**	99	56 (–)

[a] All reactions were performed on a 0.5 mmol scale: metal / ligand / I_2= 0.5 / 1.05 / 5, 1 mol% Ir catalyst loading, 2.5 mL solvent, 20 atm initial H_2 pressure, r.t., 24 h.. [b] The conversions were determined by GC. [c] The enantiomeric excesses were determined by chiral GC or HPLC. The absolute configuration of product was assigned by comparison of rotation sign with literature data.

Slightly decreased conversion and ee values were observed in the hydrogenation of substrate **11b** which bears a more bulky alkyl group (Table 4-13, entry 2). However, changing the alkyl group at the 2-position to phenyl group resulted in significant erosion of the enantioselectivity (entry 3). On the other hand, this hydrogenation could tolerate various substituents at 6- or 7- position, including fluoro-, chloro-, bromo-, methyl and methoxy groups (entries 4–11). However, nitro- substituted substrate afforded lower

enantioselectivity (75% ee; entry 9), possibly due to the strong electronic property of nitro group. When switching to 8-substituted substrate **1l**, a dramatic drop of ee was observed (entry 12), In this case, the lower enantioselectivity may be attributed to the steric hindrance of the substituent. Additional attempts to examine 3- or 4-substituted quinolines exhibited no effect, and the result is consistent with Zhou's finding with the iridium−MeO-BIPHEP catalyst system.[47a]

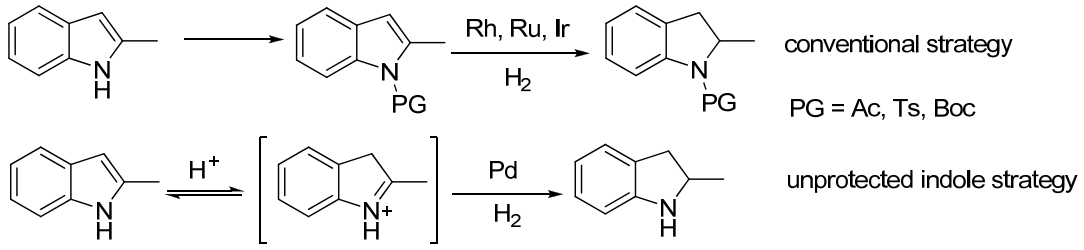
The above results encouraged us to extend our investigation of asymmetric hydrogenation to other related substrates by applying the Ir–C_3^*-TunePhos catalyst. We envisioned that our approach could be applied to enantioselectively reduce quinoline *N*-oxide derivatives (Scheme 4-10). Utilizing substrate **13** as a model substrate, the reaction conditions were optimized to achieve this goal. The best result was achieved in THF under 50 atm H_2. The reaction produced a 9:1 ratio of (*R*)-2-methyl-1,2,3,4-tetrahydroquinoline (*R*)-**12a** with 41% ee and 2-methylquinoline (**11a**) (>99% conversion). We envisioned one pathway of this transformation might have proceeded in two sequential steps, involving an iridium-catalyzed reduction of quinoline *N*-oxide step which afforded the key intermediate **11a**，followed by an asymmetric hydrogenation step to form the final product **12a** with the opposite configuration. We also believe that there exist other hydrogenation pathways because of the only moderate enantioselectivity and more importantly the fact that the opposite configuration was obtained in product **12a**. To our best knowledge, this preliminary study is the first report of homogeneous catalytic asymmetric hydrogenation of quinoline *N*-oxides.



Scheme 4-10: Preliminary Result of Asymmetric Hydrogenation of Quinoline *N*-Oxide **13**.

4.2.5. Pd-Catalyzed Asymmetric Hydrogenation of 2-Indole Derivatives

Chiral indolines are ubiquitous structural motifs in naturally occurring alkaloids and many biological active molecules.[53] Despite the progress achieved in asymmetric hydrogenation of indoles and other heteroaromatic compounds in the past decade,[54] efficient hydrogenation of simple unprotected indoles remains a great challenge in organic synthesis. Kuwano and Ito developed the first highly effective hydrogenation of a series of *N*-protected indoles by application of Rh or Ru complex.[55a-d] Feringa and coworkers reported Rh-catalyzed asymmetric hydrogenation of 2-substituted *N*-protected indoles with moderate enantioselectivity.[55e] Very recently, Pfaltz group revealed Ir/N,P catalyzed hydrogenation *N*-protected indoles with high enantioselectivity but low reactivity. [55f] To the best of our knowledge, no report on asymmetric hydrogenation of unprotected indoles has appeared despite the operational simplicity (Scheme 4-11).



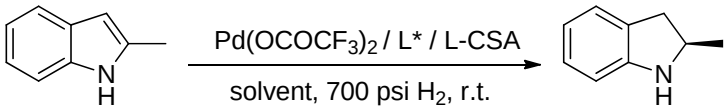
Scheme 4-11: Comparison of Conventional Strategy and New Strategy of Enantioselective Indole Hydrogenation.

We envision that in searching hydrogenation of five-membered heteroaromatic unprotected indoles, the development of a new activation strategy is highly desirable. Considering that the simple unprotected indoles can react with a strong Brønsted acid to form the iminium salt by protonation of carbon-carbon double bond, [56] and the aromaticity of indole is destroyed, the *in situ* formed iminium salts would be prone to be hydrogenated.

In this study, 2-methylindole was selected as a model substrate for the condition optimization. $Pd(OCOCF_3)_2$/(*S*)-TunePhos was used as catalyst. In a control experiment, without the addition of a Brønsted acid, the reaction did not occur. When the stoichiometric amount of trifluoroacetic acid was added, the reaction proceeded smoothly to give the expected 2-methylindoline **15** with full conversion and 8% ee. Screening of different acids found that L-CSA gave the best result. Solvent experiments showed that mixture solvent DCM/TFE was the best choice.[57] Under the optimized conditions, we examined the performance of C_3-TunePhos and various C_3*-TunePhos ligands (Table 4-14). *p*-Tol-C_3*-TunePhos appeared to give the highest enantiomeric excess among

TunePhos ligand family, although in the subsequent broad screening of biaryl phosphine ligands, H_8-BINAP was found to be the optimal choice among all tested.

Table 4-14: Ligand Screening of Pd-Catalyzed Asymmetric Hydrogenation of Simple Indole **14**.[a]



14 **15**

Entry	Ligand	Solvent	Conv.(%)[b]	Ee (%)[c]
1	C_3-TunePhos	CH_2Cl_2	>95	83
2	Ph-C_3*-TunePhos	CH_2Cl_2	>95	67
3	Ph-C_3*-TunePhos	CH_2Cl_2/TFE(10:1)	30	56
4	*p*-Tol-C_3*-TunePhos	CH_2Cl_2	>95	85
5	*p*-Tol-C_3*-TunePhos	CH_2Cl_2/TFE(10:1)	>95	81
6	Xyl-C_3*-TunePhos	CH_2Cl_2	>95	77
7	Xyl-C_3*-TunePhos	CH_2Cl_2/TFE(10:1)	>95	80
8	3,5-*t*Bu-C_3*-TunePhos	CH_2Cl_2	>95	75
9	4-MeO-3,5-*t*Bu-C_3*-TunePhos	CH_2Cl_2	79	81

[a] Reactions conditions: 0.25 mmol substrate **14**, 2 mol % $Pd(OCOCF_3)_2$, 2.4 mol % ligand, 1 equiv. L-CSA, 3 mL solvent, 700 psi H_2, r.t., 24h. [b] The conversions were determined by ^1H NMR. [c] The enantiomeric excesses were determined by chiral HPLC analysis on Chiralcel OD-H column.

In this collaborative work with Dr. Yongui Zhou's research group, we found that (*R*)-H_8-BINAP gave the highest 91% ee after various commercially available chiral bisphosphine ligands were tested. Moreover, under the optimal conditions, a variety of 2-alkylsubstituted indoles and 2,3-disubstited indoles were hydrogenated smoothly with excellent yields and 84-96% ee regardless of length and steric hindrance of side chain.[57]

4.3. Conclusion

In conclusion, in the area of asymmetric hydrogenation of imines and *N*-based heteroaromatics we have achieved some encouraging discoveries, some of which are unprecedented innovations of great significance. In our efforts, we have achieved highly efficient and enantioselective (up to 98% ee and TONs up to 10000) hydrogenation of acyclic *N*-aryl imines by cationic Ir catalyst; developed unprecedented, operationally simple, and mild asymmetric hydrogenation of N-H imines without use of protecting groups; unprecedented Ir-catalyzed asymmetric hydrogenation of unprotected *β*-enamine esters with excellent enantioselectivities and reactivities (up to 97% ee, TONs over 5000); developed an efficient enantioselective hydrogenation of a wide range of functionalized quinoline derivatives using Ir–(*S*)-C_3^*-TunePhos catalyst; investigated the performance of C_3^*-TunePhos in the hydrogenation of simple indoles.

Based on these successful examples covered in this chapter, we have found some fundamental understandings of imine/heteroaromatics hydrogenations: 1) Ir complexes, in both neutral and cationic form, have displayed significant advantages in this area and will lead to more updated breakthroughs; 2) highly rigid and strongly electron-donating phosphine or bisphospholane ligands will generally favor both high reactivities and enantioselectivities, by reducing the product inhibitory effect of the amine (both primary and secondary); 3) our research results strongly suggest that imine/heteroaromatics hydrogenation would be a remarkably more efficient process under *acidic* conditions (in

presence of stoichiometric or sub-stoichiometric quantity of *weakly* (or non-) coordinating acid; 4) the redundancy of introducing protecting groups can be avoided to improve the practical utility and synthetic simplicity of new methodologies.

Experimental Section

General Remarks. All reactions and manipulations were performed in a nitrogen-filled glovebox or under nitrogen using standard Schlenk techniques unless otherwise noted. Column chromatography was performed using Sorbent silica gel 60 Å (230×450 mesh). ^{1}H ^{13}C NMR spectral data were recorded on Bruker 360 MHz, Bruker 400 MHz spectrometers. Chemical shifts were reported in ppm. Enantiomeric excess values were determined by chiral GC on Agilent 7890 GC equipment and chiral HPLC on Agilent 1200 Series equipment.

General Procedure for Preparation of Ir(L*)BARF Complexes. Method A:[15h] To an oven-dried Schlenk bottle charged with NaBARF (sodium tetrakis[3,5(trifluoromethyl)phenyl]borate, 89 mg, 0.103 mmol), $[Ir(cod)Cl]_2$(28.9 mg, 0.043 mmol) and dry CH_2Cl_2(3 mL), was added excess cod (1,5-cyclooctadiene, 0.73 mL, 0.65 g, 6.0 mmol) under N_2 atmosphere. After stirring for 20 min, a solution of chiral phosphorus ligand (0.103 mmol) in CH_2Cl_2 (3 mL) was added to the mixture. After the reaction was further stirred for 30 min, degassed H_2O (3 x 5 mL) was added to wash the

organic layer. The organic layer was dried over $NaSO_4$ before the solvent and excessive COD were removed *in vacuo*. The residual greenish solid was purified by column chromatography on alumina gel with CH_2Cl_2 under N_2 atmosphere to afford the desired complex (41% to 73% yield).

Method B: To an oven-dried Schlenk bottle charged with a solution of $Ir(cod)_2BARF$ (63.6 mg, 0.05 mmol) in dry CH_2Cl_2(5 mL), was added a solution of chiral phosphorus ligand (0.103 mmol) under N_2 atmosphere. After stirring for 30 min, the solvent and excessive COD were removed *in vacuo*. The solid complex was used for hydrogenation without further purification.

^{31}P NMR (162 MHz, CD_3Cl) of precatalysts:

[Ir{(*S*,*S*,*R*,*R*)-TangPhos}(cod)]BARF: δ = 89.6 (s)

[Ir{(*S*)-Binapine}(cod)]BARF: δ = 85.6 (s)

[Ir{(*S*)-C_3-TunePhos}(cod)]BARF: δ = 14.6 (s)

[Ir{(*S*,*S*)-f-Binaphane}(cod)]BARF: δ = 33.0 (s)

[Ir{(S_p,R_c)-DuanPhos}(cod)]BARF: δ = 92.0 (s)

General Procedure for *N*-Aryl Imine Preparation: All of the imines were prepared from corresponding aniline and acetophenone according to literature methods with modificaiton.[15,58] This procedure was carried out in air atmosphere. The mixture of

aniline (30 mmol), acetophenone (25 mmol), *p*-toluenesulfonic acid monohydrate (0.1 g) and toluene (30 mL) in a round bottom bottle was heated at reflux temperature using a Dean-Stark apparatus. The reaction was monitored by TLC. After being heated overnight, the reaction was filtered through Celite. Evaporation of the solvent *in vacuo* and distillation of the residue or recrystallization with ethanol afford the imine substrates (33–75 % yield).

***N*-(1-phenylethylidene)aniline (1a)**: Yellow solid, 61% Yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 4.0, 8.0 Hz, 2H), 7.49–7.46 (m, 2H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.81(d, *J* = 8.0 Hz, 2H), 2.25 (s, 3H).

***N*-(1-(4-methylphenyl)ethylidene)aniline (1b)**: Light yellow solid, 42 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.26 (t, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 2H), 2.33 (s, 3H), 2.13 (s, 3H).

***N*-(1-(4-methoxyphenyl)ethylidene)aniline (1c)**: Pale yellow crystal, 44 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.08 (t, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 8.0 Hz, 2H), 3.88 (s, 3H), 2.21 (s, 3H).

***N*-(1-(4-fluorophenyl)ethylidene)aniline (1d)**: Pale yellow solid, 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 4.0, 4.0 Hz, 2H), 7.26 (t, *J* = 8.0 Hz, 2H), 7.05–6.99 (m, 3H), 6.70 (d, *J* = 8.0 Hz, 2H), 2.13 (s, 3H).

***N*-(1-(4-chlorophenyl)ethylidene)aniline (1e)**: Pale yellow solid, 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.11 (t, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 2H), 2.23 (s, 3H).

***N*-(1-(4-bromophenyl)ethylidene)aniline (1f)**: Pale yellow cystal, yield 46%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.11 (t, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 2H), 2.22 (s, 3H).

***N*-(1-(3-chlorophenyl)ethylidene)aniline (1g)**: Yellow solid, yield 43%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.38 (dd, *J* = 4.0, 4.0 Hz, 3H), 7.12 (t, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 2H), 2.23 (s, 3H).

***N*-(1-(2-naphthyl)-ethylidene)aniline (1h)**: white solid, yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.92 (dd, *J* = 4.0, 4.0 Hz, 2H), 7.55 (t, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H).

***N*-(1-Phenylethylidene)-4-methylaniline (1i)**: Yellow solid, 33 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.99 (m, 2H), 7.49–7.46 (m, 3H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.74 (d, *J* = 8.0 Hz, 2H), 2.38 (s, 3H), 2.27 (s, 3H).

***N*-(1-Phenylethylidene)-4-methoxyaniline (1j)**: Yellow solid, 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99–7.95 (m, 2H), 7.47–7.44 (m, 3H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 8.0 Hz, 2H), 3.83 (s, 3H), 2.27 (s, 3H).

***N*-(1-Phenylethylidene)-4-fluoroaniline (1k)**: Yellow solid, 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.97 (m, 2H), 7.48–7.43 (m, 3H), 7.08–7.03 (m, 2H), 6.76–6.74 (m, 2H), 2.24 (s, 3H).

***N*-(1-Phenylethylidene)-4-chloroaniline (1l)**: Yellow solid, 47% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.50–7.45 (m, 3H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 8.0 Hz, 2H), 2.25 (s, 3H).

General Procedure for Asymmetric Hydrogenation of *N*-Aryl Imines: In the nitrogen filled glovebox, the solid complex [Ir{(S_p,R_c)-DuanPhos}(cod)]BARF (3.1 mg, 0.002 mmol) was dissolved in degassed CH_2Cl_2 (10 mL) and divided equally between 20 vials. To each vial, imine substrate (0.1 mmol, S/C = 1000) was then added to the catalyst

solution and 1.5 mL degassed CH_2Cl_2 was added to each vials. The resulting solution was transferred to an autoclave, which was charged with 5 atm of H_2. The hydrogenation was performed at room temperature for 12 h and the hydrogen was released carefully. The solvent was then evaporated and the residue was purified by column chromatography to give the corresponding hydrogenation product, which was then analyzed directly by chiral GC (Gamma Dex 225 or Beta Dex 390) or HPLC (Chiralcel OD-H) to determine the enantiomeric excess.

(*R*)-*N*-Phenyl-1-phenylethylamine (2a): Colorless oil. $[\alpha]^{20}_D$ –4.9 (c = 1.00 in $CHCl_3$); ^{1}H NMR (MHz, $CDCl_3$) δ 7.40–7.30 (m, 4H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.13–7.07 (m, 2H), 6.69–6.63 (m, 1H), 6.53 (d, *J* = 8.8 Hz, 2H), 4.50 (q, *J* = 6.8 Hz, 1H), 4.11 (br, 1H), 1.53 (d, *J* = 6.4 Hz, 3H). Enantiomer ratio was determine by GC using a Beta Dex 390 column (30 m × 0.25 mm × 0.25 μm; carrier gas, He (flow rate 1 mL/min); column temperature, 130 ˚C, hold for 90 min, programmed from 90 ˚C to 160 ˚C at 1 ˚C/min, hold for 20 min) t_R = 114.4 min (*S*); t_R = 115.0 min (*R*), >99% conversion; 93% ee.

(+)-*N*-Phenyl-1-(4-methylphenyl)ethylamine (2b): Colorless oil. $[\alpha]^{20}_D$ +12.3 (c = 1.00 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 9.0 Hz, 2H), 7.16–7.10 (m, 4H), 6.67 (t, *J* = 9.0 Hz, 1H), 6.55 (d, *J* = 9.0 Hz, 2H), 4.49 (q, *J* = 6.5 Hz, 1H), 4.17 (br, 1H), 2.35 (s, 3H), 1.53 (d, *J* = 6.5 Hz, 3H). Enantiomer ratio was determine by HPLC using a Chiralcel OD-H column (flow rate 1 mL/min, Hexanes:*i*PrOH = 98:2, λ = 254 nm,

room temperature), t_R = 8.0 min (minor); t_R = 9.1 min (major), >99% conversion; 90% ee.

(+)-*N*-Phenyl-1-(4-methoxyphenyl)ethylamine (2c): White solid. $[\alpha]^{20}_D$ +8.7 (c = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 8.0 Hz, 2H), 7.01 (t, *J* = 8.0 Hz, 2H), 6.78 (d, *J* = 8.0 Hz, 2H), 6.56 (t, *J* = 8.0 Hz, 1H), 6.44 (d, *J* = 8.0 Hz, 2H), 4.37 (q, *J* = 8.0 Hz, 1H), 3.58 (br, 1H), 3.70 (s, 3H), 1.41 (d, *J* = 4.0 Hz, 3H). Enantiomer ratio was determine by HPLC using a Chiralcel OD-H column (flow rate 1 mL/min, Hexanes:*i*PrOH = 98:2, λ = 254 nm, room temperature), t_R = 10.0 min (minor); t_R = 10.5 min (major), >99% conversion; 90% ee.

(–)-*N*-Phenyl-1-(4-fluorophenyl)ethylamine (2d): Light yellow oil. $[\alpha]^{20}_D$ –24.8 (c = 1.00 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 5.5, 8.5 Hz, 2H), 7.11 (t, *J* = 8.0 Hz, 2H), 7.01 (t, *J* = 8.5 Hz, 2H), 6.68 (t, *J* = 7.5 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 2H), 4.48 (q, *J* = 6.5 Hz, 1H), 4.17 (br, 1H), 1.52 (d, *J* = 6.5 Hz, 3H). Enantiomer ratio was determine by GC using a Gamma Dex 225 column (30 m × 0.25 mm × 0.25 μm; carrier gas, He (flow rate 1 mL/min); column temperature, 160 ˚C) t_R = 30.1 min (minor); t_R = 30.7 min (major), >99% conversion; 93% ee.

(+)-*N*-Phenyl-1-(4-chlorophenyl)ethylamine (2e): Colorless oil. $[\alpha]^{20}_D$ +1.5 (c = 1.00 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ7.32–7.26 (m, 4H), 7.11 (t, *J* = 7.5 Hz, 2H),

6.69 (t, *J* = 7.5 Hz, 1H), 6.50 (d, *J* = 8.5 Hz, 2H), 4.46 (q, *J* = 7.0 Hz, 1H), 4.18 (br, 1H), 1.51 (d, *J* = 6.5 Hz, 3H). Enantiomer ratio was determine by GC using a Gamma Dex 225 column (30 m × 0.25 mm × 0.25 μm; carrier gas, He (flow rate 1 mL/min); column temperature, 160 ˚C) t_R = 74.8 min (minor); t_R = 76.8 min (major), >99% conversion; 92% ee.

(+)-*N*-Phenyl-1-(4-bromophenyl)ethylamine (2f): White solid. $[\alpha]^{20}_D$ +9.0 (c = 1.00 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 6.5 Hz, 2H), 7.28 (d, *J* = 6.5 Hz, 2H), 7.13 (t, *J* = 8.0 Hz, 2H), 6.70 (t, *J* = 7.5 Hz, 1H), 6.51 (d, *J* = 7.5 Hz, 2H), 4.47 (q, *J* = 7.0 Hz, 1H), 4.17 (br, 1H), 1.52 (d, *J* = 6.5 Hz, 3H). Enantiomer ratio was determine by HPLC using a Chiralcel OD-H column (flow rate 1 mL/min, Hexanes:*i*PrOH = 98:2, λ = 254 nm, room temperature), t_R = 12.2 min (minor); t_R = 14.5 min (major), >99% conversion; 92 % ee.

(–)-*N*-Phenyl-1-(3-chlorophenyl)ethylamine (2g): Light yellow oil. $[\alpha]^{20}_D$ –9.1 (c = 1.00 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.22–7.30 (m, 3H), 7.15 (t, *J* = 8.0 Hz, 2H), 6.71 (t, *J* = 8.0 Hz, 1H), 6.54 (d, *J* = 8.0 Hz, 2H), 4.49 (q, *J* = 6.5 Hz, 1H), 4.13 (br, 1H), 1.55 (d, *J* = 7.0 Hz, 3H). Enantiomer ratio was determine by GC using a Gamma Dex 225 column (30 m × 0.25 mm × 0.25 μm; carrier gas, He (flow rate 1 mL/min); column temperature, 150 ˚C) t_R = 110.5 min (minor); t_R = 113.2 min (major), >99% conversion; 93% ee.

(+)-*N*-Phenyl-1-(2-naphthyl)ethylamine (2h): White solid. $[\alpha]^{20}_{D}$ +13.0 (c = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 4H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.37–7.34 (m, 2H), 6.99 (t, *J* = 8.0 Hz, 2H), 6.55 (t, *J* = 8.0 Hz, 1H), 6.47 (d, *J* = 8.0 Hz, 2H), 4.56 (q, *J* = 8.0 Hz, 1H), 4.02 (br, 1H), 1.50 (d, *J* = 8.0 Hz, 3H). Enantiomer ratio was determine by HPLC using a Chiralcel OD-H column (flow rate 1 mL/min, Hexanes:*i*PrOH = 98:2, λ = 254 nm, room temperature), t_R = 11.9 min (minor); t_R = 12.6 min (major), >99% conversion; 98 % ee.

(+)-*N*-(4-Methylphenyl)-1-phenylethylamine (2i): colorless oil. $[\alpha]^{20}_{D}$ +4.4 (c = 1.00 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.0 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.54 (d, *J* = 8.0 Hz, 2H), 4.47 (q, *J* = 6.5 Hz, 1H), 3.93 (br, 1H), 2.20 (s, 3H), 1.52 (d, *J* =6.5 Hz, 3H). Enantiomer ratio was determine by GC using a Gamma Dex 225 column (30 m × 0.25 mm × 0.25 μm; carrier gas, He (flow rate 1 mL/min); column temperature, 150 ˚C) t_R = 62.9 min (minor); t_R = 65.0 min (major), >99% conversion, 93% ee.

(–)-*N*-(4-Methoxyphenyl)-1-phenylethylamine (2j): colorless oil. $[\alpha]^{20}_{D}$ –1.3 (c = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 2H), 6.47 (d, *J* = 8.0 Hz, 2H), 4.41 (q, *J* = 6.8 Hz, 1H), 3.90 (br, 1H), 3.68 (s, 3H), 1.49 (d, *J* =6.8 Hz, 3H). Enantiomer ratio

was determine by GC using a Gamma Dex 225 column (30 m × 0.25 mm × 0.25 μm; carrier gas, He (flow rate 1 mL/min); column temperature, 150 ˚C) t_R = 137.2 min (minor); t_R = 140.7 min (major), >99% conversion, 93% ee.

(–)-*N*-(4-Fluorophenyl)-1-phenylethylamine (2k): colorless oil. $[\alpha]^{20}_D$ –7.5 (c = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.39–7.27 (m, 5H), 6.88–6.84 (m, 2H), 6.49–6.46 (m, 2H), 4.46 (q, *J* = 6.5 Hz, 1H), 4.14 (br, 1H), 1.55 (d, *J* =6.5 Hz, 3H). Enantiomer ratio was determine by GC using a Gamma Dex 225 column (30 m × 0.25 mm × 0.25 μm; carrier gas, He (flow rate 1 mL/min); column temperature, 150 ˚C) t_R = 46.0 min (minor); t_R = 47.3 min (major), >99% conversion, 90% ee.

(+)-*N*-(4-Chlorophenyl)-1-phenylethylamine (2l): colorless oil. $[\alpha]^{20}_D$ +13.2 (c = 1.00 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20–7.54 (m, 5H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.45–6.42 (m, 2H), 4.45 (q, *J* = 6.5 Hz, 1H), 4.12 (br, 1H), 1.54 (d, *J* =6.5 Hz, 3H). Enantiomer ratio was determine by GC using a Gamma Dex 225 column (30 m × 0.25 mm × 0.25 μm; carrier gas, He (flow rate 1 mL/min); column temperature, 160 ˚C) t_R = 84.0 min (minor); t_R = 88.3 min (major), >99% conversion, 90% ee.

Typical Procedure for Asymmetric Hydrogenation of *N*-(1-phenylethylidene)aniline (1a) with Low Catalyst Loading (S/C = 5000 or S/C = 10000): The solid complex [Ir{(S_p,R_c)-DuanPhos}(cod)]BARF (3.1 mg, 0.002 mmol)

was dissolved in degassed CH_2Cl_2 (10 mL). To a solution of imine substrate **1a** (39.9 mg, 0.2 mmol) in degassed CH_2Cl_2 (1.8 mL) was then added 0.2 mL(S/C = 5000) or 0.1 mL(S/C = 10000) of the catalyst solution. The resulting solution was transferred to an autoclave, which was charged with 5 atm of H_2. The hydrogenation was performed at room temperature for 18 h and the hydrogen was released carefully. The solvent was then evaporated and the residue was purified by column chromatography to give the corresponding hydrogenation product, which was then analyzed directly by chiral GC (Beta Dex 390) or HPLC (Chiralcel OD-H) to determine the conversion and the enantiomeric excess.

Typical Procedure of Preparing N-H Imine Substrate 5: A round-bottom flask was charged with nitrile (50.0 mmol) and THF (50 mL). The mixture was cooled to −78 ºC and MeLi (50.0 mL, 1.6 M in diethyl ether) was added dropwise over 1h. After addition, the resulting mixture was stirred for 2 h and quenched with anhydrous MeOH (12 mL). The mixture was then stirred at rt for 2 h. The suspension was filtered on Solka-Floc or Celite and the filtrate was concentrated under vacuum. The residue was dissolved in MTBE (50 mL) and treated with HCl/Et_2O (50.0 mL, 1 M). The slurry was stirred for 30 min and filtered to obtain the product as free-flowing off-white to yellow solids.

1-*p*-Tolylethaniminium chloride (5a): Yield: 98%. ^1H NMR (CD_3OD, 500 MHz)

δ 8.00 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.51 (d, 2H, *J* = 8.0 Hz, Ar-H), 2.90 (s, 3H, CH_3), 2.49 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 186.7, 148.7, 130.3, 129.5, 127.5, 20.9, 20.7; HRMS (EI) Calcd for $C_9H_{12}N$: 134.0970. Found: 134.0964.

1-Phenylethaniminium chloride (5b):[59a] Yield: 96%. ^1H NMR (CD_3OD, 400 MHz) δ 8.07–8.04 (m, 2H, Ar-H), 7.86–7.82 (m, 2H, Ar-H), 7.70–7.65 (m, 2H, Ar-H), 2.91 (s, 3H, CH_3).

1-Phenylpropan-1-iminium chloride (5c):[59b] Yield: 94%. ^1H NMR (DMSO-d_6, 400 MHz) δ 12.44 (bs, 2H, NH_2), 8.04 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.79 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.64 (t, 2H, *J* = 7.2 Hz, Ar-H), 3.20 (dd, 2H, *J* = 7.2 and 14.8 Hz, CH_2), 1.19 (t, 3H, *J* = 7.2 Hz, CH_3).

1-Phenylpentan-1-iminium chloride (5d): Yield: 95%. ^1H NMR (DMSO-d_6, 400 MHz) δ 12.77 (bs, 2H, NH_2), 8.12–8.10 (m, 2H, Ar-H), 7.85–7.81 (m, 1H, Ar-H), 7.70–7.66 (m, 2H, Ar-H), 3.24 (t, 2H, *J* = 7.6 Hz, CH_2), 1.61-1.53 (m, 2H, CH_2), 1.40-1.31 (m, 2H, CH_2), 0.89 (t, 3H, *J* = 7.6 Hz , CH_3).

2,2-Dimethyl-1-phenylpropan-1-iminium chloride (5e): Yield: 90%. ^1H NMR (DMSO-d_6, 400 MHz) δ 12.74 (bs, 2H, NH_2), 7.66–7.61 (m, 1H, Ar-H), 7.56–7.55 (m,

4H, Ar-H), 1.33 (s, 9H, CH_3).

1-(4-Methoxyphenyl)ethaniminium chloride (5f): Yield: 98%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.23 (bs, 2H, NH_2), 8.17 (d, 2H, J = 9.2 Hz, Ar-H), 7.18 (d, 2H, J = 8.8 Hz, Ar-H), 3.89 (s, 3H, OCH_3), 2.79 (s, 3H, CH_3); ^{13}C NMR (CD_3OD, 125 MHz): δ 184.3, 166.9, 132.5, 121.9, 115.2, 55.7, 20.7; HRMS (EI) Calcd for $C_9H_{12}NO$: 150.0919. Found: 150.0913.

1-(4-Fluorophenyl)ethaniminium chloride (5g): Yield: 99%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.63 (bs, 2H, NH_2), 8.25–8.21 (m, 2H, Ar-H), 7.55–7.50 (m, 2H, Ar-H), 2.83 (s, 3H, CH_3); ^{13}C NMR (CD_3OD, 125 MHz): δ 186.1, 168.7, 166.7, 133.0, 132.9, 126.9, 126.8, 117.0, 116.8, 21.4; HRMS (EI) Calcd for C_8H_9NF: 138.0719. Found: 138.0714.

1-(4-Chlorophenyl)ethaniminium chloride (5h): Yield: 98%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.66 (bs, 2H, NH_2), 8.11 (d, 2H, J = 8.8 Hz, Ar-H), 7.75 (d, 2H, J = 8.8 Hz, Ar-H), 2.83 (s, 3H, CH_3); ^{13}C NMR (CD_3OD, 125 MHz): δ 186.7, 142.7, 131.1, 129.9, 129.1, 21.4; HRMS (EI) Calcd for C_8H_9NCl: 154.0424. Found: 154.0418.

1-(4-Bromophenyl)ethaniminium chloride (5i): Yield: 80%. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.98 (d, 2H, J = 9.2 Hz, Ar-H), 7.88–7.84 (m, 2H, Ar-H), 2.90 (s, 3H, CH_3);

^{13}C NMR (CD_3OD, 100 MHz): δ 187.0, 148.7, 132.9, 132.0, 130.9, 129.9, 21.4; HRMS (EI) Calcd for C_8H_9NBr: 197.9918. Found: 197.9913.

1-(4-(Trifluoromethyl)phenyl)ethaniminium chloride (5j): Yield: 81%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.11 (d, 2H, J = 8.0 Hz, Ar-H), 7.86 (d, 2H, J = 8.0 Hz, Ar-H), 2.83 (s, 3H, CH_3);

1-*m*-Tolylethaniminium chloride (5k): Yield: 95%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.60 (bs, 2H, NH_2), 7.95 (s, 1H, Ar-H), 7.91 (d, 1H, J = 8.0 Hz, Ar-H), 7.62 (d, 1H, J = 8.0 Hz, Ar-H), 7.53 (t, 1H, J = 8.0 Hz, Ar-H), 2.83 (s, 3H, CH_3), 2.39 (s, 3H, CH_3); ^{13}C NMR (CD_3OD, 100 MHz): δ 187.7, 140.1, 137.1, 130.4, 129.6, 126.6, 21.3, 20.1; HRMS (EI) Calcd for $C_9H_{12}N$: 134.0970. Found: 134.0964.

1-(3-Methoxyphenyl)ethaniminium chloride (5l): Yield: 96%. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.64–7.56 (m, 3H, Ar-H), 7.41–7.38 (m, 1H, Ar-H), 3.90 (s, 3H, OCH_3), 2.90 (s, 3H, CH_3); ^{13}C NMR (CD_3OD, 100 MHz): δ 187.5, 160.6, 131.6, 130.8, 122.5, 121.9, 113.5, 55.4, 21.4; HRMS (EI) Calcd for $C_9H_{12}NO$: 150.0919. Found: 150.0913.

1-(3-Chlorophenyl)ethaniminium chloride (5m): Yield: 80%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.63 (bs, 2H, NH_2), 8.20–8.18 (m, 1H, Ar-H), 8.05–8.02 (m,

1H, Ar-H), 7.88–7.85 (m, 2H, Ar-H), 2.85 (s, 3H, CH_3).

1-(3-Bromophenyl)ethaniminium chloride (5n): Yield: 72%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.65 (bs, 2H, NH_2), 8.12–8.07 (m, 1H, Ar-H), 7.76–7.74 (m, 1H, Ar-H), 7.54–7.47 (m, 2H, Ar-H), 2.88 (s, 3H, CH_3).

1-*o*-Tolylethaniminium chloride (5o): Yield: 82%. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.85 (bs, 2H, NH_2), 7.59 (d, 1H, J = 8.0 Hz, Ar-H), 7.56–7.52 (m, 1H, Ar-H), 7.42–7.38 (m, 2H, Ar-H), 2.81 (s, 3H, CH_3), 2.41 (s, 3H, CH_3); ^{13}C NMR (CD_3OD, 100 MHz): δ 193.3, 135.7, 135.6, 133.1, 131.9, 127.8, 126.6, 24.7, 18.7; HRMS (EI) Calcd for $C_9H_{12}N$: 134.0970. Found: 134.0964.

1-(2-Methoxyphenyl)ethaniminium chloride (5p): Yield: 84%. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.54 (bs, 2H, NH_2), 7.93–7.91 (m, 1H, Ar-H), 7.81–7.78 (m, 1H, Ar-H), 7.34 (d, 1H, J = 8.5 Hz, Ar-H), 7.21–7.18 (m, 1H, Ar-H), 3.99 (s, 3H, OCH_3), 2.82 (s, 3H, CH_3); ^{13}C NMR (CD_3OD, 100 MHz): δ 183.1, 161.1, 138.9, 133.5, 121.6, 117.2, 112.9, 56.2, 22.0; HRMS (EI) Calcd for $C_9H_{12}NO$: 150.0919. Found: 150.0913.

1-(2-Chlorophenyl)ethaniminium chloride (5q): Yield: 65%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.94 (bs, 2H, NH_2), 7.72–7.63 (m, 3H, Ar-H), 7.59–7.55 (m, 1H, Ar-H), 2.80 (s, 3H, CH_3).

1-(Naphthalen-1-yl)ethaniminium chloride (5r): Yield: 98%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.98 (bs, 2H, NH_2), 8.24 (d, 1H, J = 8.4 Hz, Ar-H), 8.11–8.09 (m, 1H, Ar-H), 8.03–8.01 (m, 1H, Ar-H), 7.90–7.88 (m, 1H, Ar-H), 7.73–7.65 (m, 3H, Ar-H), 2.97 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 190.3, 133.7, 131.6, 129.5, 128.9, 128.7, 128.6, 128.0, 127.8, 125.7, 124.9, 26.2; HRMS (EI) Calcd for $C_{12}H_{12}N$: 170.0970. Found: 170.0964.

1-(Naphthalen-2-yl)ethaniminium chloride (5s): Yield: 99%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.58 (bs, 2H, NH_2), 8.85 (s, 1H, Ar-H), 8.17–8.13 (m, 3H, Ar-H), 8.06 (d, 1H, J = 8.0 Hz, Ar-H), 7.79–7.75 (m, 1H, Ar-H), 7.72–7.68 (m, 1H, Ar-H), 2.92 (s, 3H, CH_3); ^{13}C NMR (CD_3OD, 100 MHz): δ 186.6, 136.8, 133.5, 132.5, 130.6, 130.2, 129.5, 127.9, 127.2, 122.6, 21.2; HRMS (EI) Calcd for $C_{12}H_{12}N$: 170.0970. Found: 170.0964.

3,3-Dimethylbutan-2-iminium chloride (5t): Yield: 52%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.14 (bs, 2H, NH_2), 2.44 (s, 3H, CH_3), 1.22 (s, 9H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 203.1, 43.6, 26.6, 26.0, 24.7, 20.4; HRMS (EI) Calcd for $C_6H_{14}N$: 100.1126. Found: 100.1120.

1-Cyclohexylethaniminium chloride (5u): Yield: 71%. ^{1}H NMR (DMSO-d_6,

400 MHz) δ 12.95 (bs, 1H, NH_2), 12.36 (bs, 1H, NH_2), 2.72–2.67 (m, 1H, CH), 2.43 (s, 3H, CH_3), 1.80–1.74 (m, 4H, CH_2), 1.65–1.63 (m, 1H, CH_2), 1.43–1.34 (m, 2H, CH_2), 1.27–1.14 (m, 3H, CH_3); ^{13}C NMR (CD_3OD, 100 MHz): δ 199.9, 45.3, 28.5, 24.8, 24.7, 20.9; HRMS (EI) Calcd for $C_8H_{16}N$: 126.1277. Found: 126.1271.

Phenyl(*p*-tolyl)methaniminium chloride (5v): Yield: 95%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.58 (bs, 2H, NH_2), 7.87–7.83 (m, 1H, Ar-H), 7.76–7.74 (m, 2H, Ar-H), 7.70–7.63 (m, 4H, Ar-H), 7.50 (d, 1H, J = 8.0 Hz, Ar-H), 2.46 (s, 3H, CH_3).

Typical Procedure for Asymmetric Hydrogenation of N–H imines Hydrochloride salts: A 5.0 mL vial was loaded with $[Ir(COD)Cl]_2$ (2.1 mg, 0.003 mmol) and (*S*, *S*)-f-Binaphane (5.1 mg, 0.006 mmol). The mixture was dissolved in CH_2Cl_2 (1 mL) and stirred for 20 min at r.t. in the glovebox. To this solution was added the NH imine HCl salt in MeOH (2 mL). The vial was then placed into a steel autoclave. The inert atmosphere was replaced by H_2 and the reaction mixture was stirred under 10 atm H_2 (150 psi) at r.t. for 12h. The resulting mixture was concentrated under vacuum and dissolved in saturated aqueous $NaHCO_3$ (5 mL). After stirring for 10 min, the mixture was extracted with CH_2Cl_2 (3×2 mL) and dried over Na_2SO_4. To the resulting solution was added Ac_2O (300 μL) and stirred for 30 min. The resulting solution was then analyzed for conversion and enantiomeric excess directly by GC. The product was purified by chromatography on silica gel column with dichloromethane/methanol

(85:15).

(*R*)-1-*p*-Tolylethanaminium chloride (6a):[59c] $[\alpha]_D^{20}$ +6.2 (*c* 0.5, CH_2Cl_2), 95% *ee*,; GC condition for corresponding acetamide: Supelco Beta Dex 390 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 140 °C; t_R = 57.5 min (*R*), t_R = 59.7 min (*S*). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.66 (bs, 3H, NH_3), 7.34 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.14 (d, 2H, *J* = 8.0 Hz, Ar-H), 4.32 (dd, 1H, *J* = 6.4 and 13.2 Hz, CH), 2.32 (s, 3H, CH_3), 1.63 (d, 3H, *J* = 6.8 Hz, CH_3).

(+)-1-Phenylethanaminium chloride (6b):[59d] $[\alpha]_D^{20}$ +13.4 (*c* 0.5, CH_2Cl_2), 93% *ee*,; GC condition for corresponding acetamide: Supelco Beta Dex 390 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 140 °C; t_R = 35.2 min (*R*), t_R = 36.9 min (*S*). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (bs, 3H, NH_3), 7.48–7.45 (m, 2H, Ar-H), 7.37–7.30 (m, 3H, Ar-H), 4.42 (dd, 1H, *J* = 6.0 and 13.5 Hz, CH), 1.64 (d, 3H, *J* =7.0 Hz, CH_3).

(+)-1-Phenylpropan-1-aminium chloride (6c): $[\alpha]_D^{20}$ +7.6 (*c* 0.5, CH_2Cl_2), 86% *ee*,; GC condition for corresponding acetamide: Supelco Beta Dex 390 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 140 °C; t_R = 43.8 min (minor), t_R = 45.7 min (major). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.73 (bs, 3H, NH_3), 7.44–7.41 (m, 2H, Ar-H), 7.35–7.33 (m, 3H, Ar-H), 4.06 (dd, 1H, *J* = 5.5 and 9.0 Hz, CH), 2.14–2.08

(m, 1H, CH_2), 2.01–1.93 (m, 1H, CH_2), 0.83 (t, 3H, J =7.0 Hz, CH_3).

(+)-1-Phenylpentan-1-aminium chloride (6d): $[\alpha]_D^{20}$ +7.2 (*c* 0.5, CH_2Cl_2), 88% *ee*,; GC condition for corresponding acetamide: Supelco Gamma Dex 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, programmed from 100 ^oC to 150 ^oC at 1.0 ^oC/min, hold 60 minutes; t_R = 87.8 min (major), t_R = 89.1 min (minor). ^1H NMR ($CDCl_3$, 500 MHz) δ 8.70 (bs, 3H, NH_3), 7.43–7.41 (m, 2H, Ar-H), 7.35–7.33 (m, 3H, Ar-H), 4.11 (dd, 1H, J = 5.5 and 9.5 Hz, CH), 2.10–2.03 (m, 1H, CH_2), 1.97–1.89 (m, 1H, CH_2), 1.33–1.18 (m, 3H, CH_2), 1.13–1.05 (m, 1H, CH_2), 0.82 (t, 3H, J =7.0 Hz, CH_3).

(+)-2,2-Dimethyl-1-phenylpropan-1-aminium chloride (6e): $[\alpha]_D^{20}$ +7.0 (*c* 0.5, CH_2Cl_2), 80% *ee*,; GC condition for corresponding acetamide: Supelco Gamma Dex 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 160 ^oC; t_R = 20.8 min (minor), t_R = 21.3 min (major). ^1H NMR ($CDCl_3$, 500 MHz) δ 8.80 (bs, 3H, NH_3), 7.70–7.67 (m, 2H, Ar-H), 7.42–7.38 (m, 3H, Ar-H), 4.02 (dd, 1H, J = 5.5 and 9.0 Hz, CH), 1.02 (s, 9H, CH_3).

(+)-1-(4-methoxyphenyl)ethanaminium chloride (6f): $[\alpha]_D^{20}$ −14.4 (*c* 0.5, CH_2Cl_2), 93% *ee*,; GC condition for corresponding acetamide: Supelco Gamma Dex 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 160 ^oC; t_R = 55.5 min (minor), t_R = 58.1 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.11 (bs, 3H,

NH_3), 7.38 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.14 (d, 2H, *J* = 8.8 Hz, Ar-H), 4.29 (dd, 1H, *J* = 6.4 and 13.2 Hz, CH), 3.77 (s, 3H, OCH_3), 1.61 (d, 3H, *J* = 6.8 Hz, CH_3).

(+)-1-(4-Fluorophenyl)ethanaminium chloride (6g): $[\alpha]_D^{20}$ +13.4 (*c* 0.5, CH_2Cl_2), 92% *ee*,; GC condition for corresponding acetamide: Supelco Beta Dex 390 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, programmed from 100 ^oC to 180 ^oC at 1.0 ^oC/min; t_R = 56.8 min (minor), t_R = 57.7 min (major). ^1H NMR ($CDCl_3$, 500 MHz) δ 8.12 (bs, 3H, NH_3), 7.47–7.43 (m, 2H, Ar-H), 7.06–7.02 (m, 2H, Ar-H), 4.34 (dd, 1H, *J* = 8.5 and 13.0 Hz, CH), 1.62 (d, 3H, *J* = 6.8 Hz, CH_3).

(+)-1-(4-chlorophenyl)ethanaminium chloride (6h): $[\alpha]_D^{20}$ +12.8 (*c* 0.5, CH_2Cl_2), 94% *ee*,; GC condition for corresponding acetamide: Supelco Gamma Dex 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 160 ^oC; t_R = 59.3 min (minor), t_R = 61.9 min (major). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.39 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.33 (d, 2H, *J* = 8.5 Hz, Ar-H), 4.29 (dd, 1H, *J* = 8.5 and 13.0 Hz, CH), 1.59 (d, 3H, *J* = 6.5 Hz, CH_3).

(+)-1-(4-Bromophenyl)ethanaminium chloride (6i): $[\alpha]_D^{20}$ +15.2 (*c* 0.5, CH_2Cl_2), 93% *ee*,; GC condition for corresponding acetamide: Supelco Beta Dex 390 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 150 ^oC; t_R = 130.8 min (minor), t_R = 136.0 min (major). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.46 (d, 2H, *J*

= 8.5 Hz, Ar-H), 7.26 (d, 2H, *J* = 8.5 Hz, Ar-H), 4.17 (dd, 1H, *J* = 8.5 and 13.0 Hz, CH), 1.44 (d, 3H, *J* = 6.5 Hz, CH_3).

(+)-1-(4-(Trifluoromethyl)phenyl)ethanaminium chloride (6j): $[\alpha]_D^{20}$ +5.4 (*c* 0.5, CH_2Cl_2), 93% *ee*,; GC condition for corresponding acetamide: Supelco Gamma Dex 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 150 °C; t_R = 43.0 min (minor), t_R = 46.1 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (bs, 3H, NH_3), 7.52–7.50 (m, 2H, Ar-H), 7.49–7.48 (m, 2H, Ar-H), 4.40 (dd, 1H, *J* = 8.5 and 13.0 Hz, CH), 1.63 (d, 3H, *J* = 6.8 Hz, CH_3).

(+)-1-*m*-Tolylethanaminium chloride (6k): $[\alpha]_D^{20}$ +12.4 (*c* 0.5, CH_2Cl_2), 92% *ee*,; GC condition for corresponding acetamide: Supelco Beta Dex 390 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, programmed from 100 °C to 180 °C at 1.0 °C/min; t_R = 60.2 min (minor), t_R = 61.2 min (major). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.56 (bs, 3H, NH_3), 7.29–7.22 (m, 3H, Ar-H), 7.13 (d, 1H, *J* = 7.0 Hz, Ar-H), 4.32 (dd, 1H, *J* = 6.5 and 13.5 Hz, CH), 2.32 (s, 3H, CH_3), 1.65 (d, 3H, *J* = 7.0 Hz, CH_3).

(+)-1-(3-Methoxyphenyl)ethanaminium chloride (6l): $[\alpha]_D^{20}$ +13.6 (*c* 0.5, CH_2Cl_2), 94% *ee*,; GC condition for corresponding acetamide: Supelco Gamma Dex 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 160 °C; t_R = 45.9 min (minor), t_R = 49.1 min (major). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.68 (bs, 3H,

NH_3), 7.24 (t, 1H, J = 8.0 Hz, Ar-H), 7.09 (s, 1H, Ar-H), 7.01 (d, 1H, J = 7.5 Hz, Ar-H), 6.85 (dd, 1H, J = 2.0 and 7.0 Hz), 4.34 (dd, 1H, J = 6.5 and 13.5 Hz, CH), 3.73 (s, 3H, OCH_3), 1.66 (d, 3H, J = 7.0 Hz, CH_3).

(+)-1-(3-Chlorophenyl)ethanaminium chloride (6m): $[\alpha]_D^{20}$ +2.1 (*c* 0.5, CH_2Cl_2), 92% *ee*,; GC condition for corresponding acetamide: Supelco Gamma Dex 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 150 ^oC; t_R = 83.6 min (minor), t_R = 98.7 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.65 (bs, 3H, NH_3), 7.48–7.47 (m, 1H, Ar-H), 7.40–7.37 (m, 1H, Ar-H), 7.31–7.29 (m, 2H, Ar-H), 4.32 (dd, 1H, J = 6.4 and 13.2 Hz, CH), 1.63 (d, 3H, J = 6.4 Hz, CH_3).

(+)-1-(3-Bromophenyl)ethanaminium chloride (6n): $[\alpha]_D^{20}$ +8.4 (*c* 0.5, CH_2Cl_2), 91% *ee*,; GC condition for corresponding acetamide: Supelco Beta Dex 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 160 ^oC; t_R = 71.2 min (minor), t_R = 78.5 min (major). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.62 (bs, 3H, NH_3), 7.60 (s, 1H, Ar-H), 7.45–7.40 (m, 2H, Ar-H), 7.24–7.20 (m, 1H, Ar-H), 4.29 (dd, 1H, J = 6.4 and 13.2 Hz, CH), 1.61 (d, 3H, J = 6.8 Hz, CH_3).

(+)-1-*o*-Tolylethanaminium chloride (6o): $[\alpha]_D^{20}$ +14.6 (*c* 0.5, CH_2Cl_2), 81% *ee*,; GC condition for corresponding acetamide: Supelco Gamma Dex 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 160 ^oC; t_R = 20.8 min

(minor), t_R = 21.4 min (major). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.20 (bs, 3H, NH_3), 7.62–7.60 (m, 1H, Ar-H), 7.24–7.19 (m, 2H, Ar-H), 7.17–7.15 (m, 1H, Ar-H), 4.64 (dd, 1H, J = 6.4 and 13.2 Hz, CH), 2.37 (s, 3H, CH_3), 1.62 (d, 3H, J = 6.5 Hz, CH_3).

(−)-1-(2-Methoxyphenyl)ethanaminium chloride (6p): $[\alpha]_D^{20}$ −12.2 (*c* 0.5, CH_2Cl_2), 92% *ee*,; GC condition for corresponding acetamide: Supelco Beta Dex 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 150 ^oC; t_R = 44.5 min (minor), t_R = 46.7 min (major). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.47 (bs, 3H, NH_3), 7.41–7.39 (m, 1H, Ar-H), 7.32–7.28 (m, 1H, Ar-H), 6.96–6.94 (m, 1H, Ar-H), 6.87–6.85 (m, 1H, Ar-H), 4.69 (dd, 1H, J = 6.5 and 13.5 Hz, CH), 3.83 (s, 3H, OCH_3), 1.69 (d, 3H, J = 7.0 Hz, CH_3).

(+)-1-(2-Chlorophenyl)ethanaminium chloride (6q): $[\alpha]_D^{20}$ +15.9 (*c* 0.5, CH_2Cl_2), 81% *ee*,; GC condition for corresponding acetamide: Supelco Gamma Dex 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 150 ^oC; t_R = 55.4 min (minor), t_R = 64.4 min (major). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65–7.62 (m, 1H, Ar-H), 7.38–7.36 (m, 1H, Ar-H), 7.31–7.27 (m, 1H, Ar-H), 7.24–7.20 (m, 1H, Ar-H), 4.74 (dd, 1H, J = 6.5 and 13.0 Hz, CH), 2.37 (s, 3H, CH_3), 1.55 (d, 3H, J = 6.5 Hz, CH_3).

(−)-1-(Naphthalen-1-yl)ethanaminium chloride (6r):[59e] $[\alpha]_D^{20}$ −14.2 (*c* 0.5, CH_2Cl_2), 93% *ee*,; GC condition for corresponding acetamide: Supelco Gamma Dex 225

column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 175 °C; t_R = 70.1 min (minor), t_R = 78.6 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02–7.99 (m, 1H, Ar-H), 7.89–7.86 (m, 1H, Ar-H), 7.80–7.77 (m, 2H, Ar-H), 7.56–7.44 (m, 3H, Ar-H), 6.06 (bs, 3H, NH_3), 5.18 (dd, 1H, *J* = 6.4 and 13.2 Hz, CH), 1.72 (d, 3H, *J* = 6.4 Hz, CH_3).

(+)-1-(Naphthalen-2-yl)ethanaminium chloride (6s): $[\alpha]_D^{20}$ +9.2 (*c* 1.0, CH_2Cl_2), 92% *ee*,; GC condition for corresponding acetamide: Supelco Beta Dex 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, programmed from 165 °C to 185 °C at 1.0 °C/min, hold 100 minutes at 185 °C; t_R = 62.1 min (minor), t_R = 65.5 min (major). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (s, 1H, Ar-H), 7.78–7.72 (m, 3H, Ar-H), 7.55–7.53 (m, 1H, Ar-H), 7.50–7.44 (m, 2H, Ar-H), 4.42 (dd, 1H, *J* = 6.5 and 13.5 Hz, CH), 1.64 (d, 3H, *J* = 7.0 Hz, CH_3).

(−)-3,3-Dimethylbutan-2-aminium chloride (6t): $[\alpha]_D^{20}$ −2.8 (*c* 0.5, CH_2Cl_2), 17% *ee*,; GC condition for corresponding acetamide: Supelco Gamma Dex 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 120 °C; t_R = 18.5 min (major), t_R = 20.5 min (minor). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.33 (bs, 3H, NH_3), 3.10 (dd, 1H, *J* = 7.0 and 13.5 Hz, CH), 1.37 (d, 3H, *J* = 7.0 Hz, CH_3), 1.07 (s, 9H, CH_3).

(+)-1-Cyclohexylethanaminium chloride (6u):[59f] $[\alpha]_D^{20}$ +5.1 (*c* 1.0, CH_2Cl_2),

73% *ee*,; GC condition for corresponding acetamide: Supelco Beta Dex 390 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 140 ^{o}C; t_R = 27.8 min (major), t_R = 29.2 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (bs, 3H, NH_3), 3.16–3.10 (m, 1H, CH), 1.90–1.66 (m, 5H, CH, CH_2), 1.37 (d, 3H, J = 6.8 Hz, CH_3), 1.29–1.04 (m, 6H, CH_2).

(−)-Phenyl(*p*-tolyl)methanaminium chloride (6v): $[\alpha]_D^{20}$ −6.2 (*c* 1.0, CH_2Cl_2), 17% *ee*,; HPLC condition for corresponding acetamide: Chiralcel OD-H column, hexanes/2-propanol = 90:10, 1.0 mL/min, 222 nm UV detector, t_R = 7.7 min (minor), t_R = 9.4 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.10 (bs, 3H, NH_2), 7.36 (d, 2H, J = 6.4 Hz, Ar-H), 7.27–7.24 (m, 5H, Ar-H), 7.07 (d, 2H, J = 7.6 Hz, Ar-H), 5.38 (s, 1H, CH), 2.33 (s, 3H, CH_3).

Isotopic Experiment of N-H Imine Hydrogenation: Imine hydrochloride **5a** (22 mg, 0.129 mmol) was dissolved in anhydrous MeOH (2 mL). In a separate vessel were dissolved $[Ir(COD)Cl]_2$ (2.1 mg, 0.003 mmol) and (*S*,*S*)-f-Binaphane (5.1 mg, 0.006 mmol) in anhydrous CH_2Cl_2 (1 mL). The resulting solution was stirred for 20 min at rt. The catalyst solution was added to the imine solution. The resulting solution was degassed and then pressurized with D_2 (150 psi) with shaking for 20 h at 25 ºC on a Symyx® HPR/HOSS system. After venting, the solution was concentrated under vacuum and dissolved in $CDCl_3$ for 500 MHz ^{1}H NMR spectroscopic analysis which showed

exclusive formation of ***deuterio*-6a** (~60% D-incorporation).

Typical Procedure for the Preparation of *β*-Enamine Ester Salts 9: A round-bottom flask was charged with β-keto ester (50.0 mmol), NH_4OAc (250 mmol) and MeOH (100 mL). The mixture was refluxed for 12h. After removal of the solvent, the residue was dissolved into 150 ml water, extracted with ethyl acetate, dried with anhydrous Na_2SO_4 and concentrated under vacuum. The residue was dissolved in methyl *tert*-Butyl ether (50 mL) and treated with HCl/Et_2O (50.0 mL, 1 M). The slurry was stirred for 30 min and filtered to obtain the product as free-flowing off-white to yellow solids.

General Procedure for Asymmetric Hydrogenation of *β*-Enamine Ester Salts 9: A 20.0 mL vial was loaded with $[Ir(COD)Cl]_2$ (2.1 mg, 0.003 mmol) and (*S*,*S*)-f-Binaphane (5.1 mg, 0.006 mmol). The mixture was dissolved in CH_2Cl_2 (5.0 mL) and stirred for 20 min at r.t. in the glove box, and divided equally among 10 vials. To each of the vials was added the solution of substrate **9** in MeOH (2 mL). The vial was then placed into a steel autoclave. The inert atmosphere was replaced by H_2 and the reaction mixture was stirred under 50 atm H_2 (750 psi) at r.t. for 12h. The resulting mixture was concentrated under vacuum and dissolved in saturated aqueous $NaHCO_3$ (5mL). After stirring for 10 min, the mixture was extracted with CH_2Cl_2 (2 mL, 3×) and dried over Na_2SO_4. To the resulting solution was added Ac_2O (300 μL) and stirred for 30

min. The resulting solution was then analyzed for conversion and enantiomeric excess directly by GC or by HPLC after the product was purified by silica gel chromatography using ethyl acetate / hexane (1:2) as the eluent.

(*S*)-3-ethoxy-3-oxo-1-phenylpropan-1-aminium chloride (10a):[60a] $[\alpha]_D^{20}$ +5.4 (*c* 1.0, MeOH), 97% *ee*; GC condition for corresponding acetamide: Beta Dex 390 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 160 °C; t_R = 75.0 min (*R*), t_R = 78.5 min (*S*). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.77 (bs, 3H, NH_3), 7.61–7.52 (m, 2H, Ar-H), 7.42–7.34 (m, 3H, Ar-H), 4.72–4.70 (m, 1H, CH), 4.04 (m, 2H, OCH_2), 3.29–3.25 (m, 1H, CH_2), 3.08–3.02 (m, 1H, CH_2), 1.15 (t, 3H, *J* = 6.4 Hz, CH_3).

(*S*)-3-methoxy-3-oxo-1-phenylpropan-1-aminium chloride (10b):[60b] $[\alpha]_D^{20}$ –26.4 (*c* 1.0, MeOH), 96% *ee*; GC condition for corresponding acetamide: Beta Dex 390 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 160 °C; t_R = 59.0 min (*R*), t_R = 62.4 min (*S*). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54–7.52 (m, 2H, Ar-H), 7.37–7.28 (m, 3H, Ar-H), 4.78–4.66 (m, 1H, CH), 3.60 (s, 3H, OCH_3), 3.32–3.26 (m, 1H, CH_2), 3.06–3.00 (m, 1H, CH_2).

(*S*)-3-methoxy-3-oxo-1-p-tolylpropan-1-aminium chloride (10c):[60c] $[\alpha]_D^{20}$ –18.9 (*c* 1.0, MeOH), 95% *ee*; GC condition for corresponding acetamide: Beta Dex 390 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 160 °C; t_R =

90.6 min (*R*), t_R = 92.3 min (*S*). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.69 (bs, 3H, NH_3), 7.43 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.21 (d, 2H, *J* = 8.0 Hz, Ar-H), 4.52 (dd, 1H, *J* = 5.6 and 8.8 Hz, CH), 3.54 (s, 3H, OCH_3), 3.26–3.20 (m, 1H, CH_2), 3.03–2.96 (m, 1H, CH_2), 2.30 (s, 3H, CH_3).

(*S*)-3-methoxy-1-(4-methoxyphenyl)-3-oxopropan-1-aminium chloride (10d):[60d] $[\alpha]_D^{20}$ −19.4 (*c* 1.0, MeOH), 94% *ee*; HPLC condition for corresponding acetamide: Chiralcel OD-H column, hexanes/2-propanol = 90:10, 1.0 mL/min, 222 nm UV detector, t_R = 17.4 min (*S*), t_R = 21.5 min (*R*). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.62 (bs, 3H, NH_3), 7.48 (d, 2H, *J* = 8.8 Hz, Ar-H), 6.95 (d, 2H, *J* = 8.8 Hz, Ar-H), 4.52 (dd, 1H, *J* = 5.6 and 8.8 Hz, CH), 3.76 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.25–3.20 (m, 1H, CH_2), 3.02–2.96 (m, 1H, CH_2).

(*S*)-1-(4-fluorophenyl)-3-methoxy-3-oxopropan-1-aminium chloride (10e):[60e] $[\alpha]_D^{20}$ −22.1 (*c* 1.0, MeOH), 95% *ee*; GC condition for corresponding acetamide: Beta Dex 390 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 160 ^oC; t_R = 65.7 min (*R*), t_R = 69.4 min (*S*). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.19 (bs, 3H, NH_3), 7.65–7.61 (m, 2H, Ar-H), 7.27–7.23 (m, 2H, Ar-H), 7.43 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.21 (d, 2H, *J* = 8.0 Hz, Ar-H), 4.60 (dd, 1H, *J* = 6.0 and 8.8 Hz, CH), 3.54 (s, 3H, OCH_3), 3.27–3.22 (m, 1H, CH_2), 3.06–2.97 (m, 1H, CH_2).

(*S*)-1-(4-chlorophenyl)-3-methoxy-3-oxopropan-1-aminium chloride (10f):[60f] $[\alpha]_D^{20}$ –20.4 (*c* 1.0, MeOH), 96% *ee*; GC condition for corresponding acetamide: Beta Dex 390 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 160 ^oC; t_R = 120.0 min (*R*), t_R = 123.5 min (*S*). ^1H NMR (DMSO-d_6, 400 MHz): δ 8.74 (bs, 3H, NH_3), 7.61 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.48 (d, 2H, *J* = 8.4 Hz, Ar-H), 4.60 (dd, 1H, *J* = 6.0 and 8.8 Hz, CH), 3.54 (s, 3H, OCH_3), 3.27–3.21 (m, 1H, CH_2), 3.06–3.00 (m, 1H, CH_2).

(*S*)-1-(4-bromophenyl)-3-methoxy-3-oxopropan-1-aminium chloride (10g):[60g] $[\alpha]_D^{20}$ –20.4 (*c* 1.0, MeOH), 97% *ee*; HPLC condition for corresponding acetamide: Chiralcel OD-H column, hexanes/2-propanol = 90:10, 1.0 mL/min, 222 nm UV detector, t_R = 13.0 min (*S*), t_R = 16.6 min (*R*). ^1H NMR (DMSO-d_6, 400 MHz): δ 8.74 (bs, 3H, NH_3), 7.62 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.53 (d, 2H, *J* = 8.4 Hz, Ar-H), 4.58 (dd, 1H, *J* = 6.0 and 8.8 Hz, CH), 3.55 (s, 3H, OCH_3), 3.26–3.20 (m, 1H, CH_2), 3.05–2.99 (m, 1H, CH_2).

(*S*)-3-methoxy-3-oxo-1-m-tolylpropan-1-aminium chloride (10h): $[\alpha]_D^{20}$ –20.6 (*c* 1.0, MeOH), 92% *ee*; GC condition for corresponding acetamide: Supelco Beta Dex 390 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 160 ^oC; t_R = 79.0 min (*R*), t_R = 83.1 min (*S*). ^1H NMR (DMSO-d_6, 400 MHz): δ 8.50 (bs, 3H, NH_3), 7.38–7.18 (m, 4H, Ar-H), 4.52 (dd, 1H, *J* = 6.4 and 8.4 Hz, CH), 3.55 (s, 3H,

OCH_3), 3.27–3.21 (m, 1H, CH_2), 3.04–2.94 (m, 1H, CH_2), 2.32 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 169.5, 137.8, 136.9, 129.3, 128.5, 128.2, 124.6, 51.7, 51.0, 38.5, 21.0; HRMS (EI) Calcd for $C_{11}H_{16}NO_2$: 194.1181. Found: 194.1184.

(*S*)-1-(3-chlorophenyl)-3-methoxy-3-oxopropan-1-aminium chloride (10i): $[\alpha]_D^{20}$ –30.7 (*c* 1.0, MeOH), 94% *ee*; GC condition for corresponding acetamide: Beta Dex 390 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 160 ^oC; t_R = 106.7 min (*R*), t_R = 109.7 min (*S*). ^1H NMR (DMSO-d_6, 400 MHz): δ 8.65 (bs, 3H, NH_3), 7.72 (s, 1H, Ar-H), 7.54–7.45 (m, 3H, Ar-H), 4.61 (s, 1H, CH), 3.56 (s, 3H, OCH_3), 3.08–3.06 (m, 1H, CH_2), 3.05–3.02 (m, 1H, CH_2); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 169.5, 139.4, 133.1, 130.5, 128.7, 127.8, 126.5, 51.8, 50.4, 38.3; HRMS (EI) Calcd for $C_{10}H_{13}NO_2Cl$: 214.0635. Found: 214.0626.

(*S*)-3-methoxy-3-oxo-1-o-tolylpropan-1-aminium chloride (10j): $[\alpha]_D^{20}$ –30.7 (*c* 1.0, MeOH), 94% *ee*; GC condition for corresponding acetamide: Supelco Beta Dex 390 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 160 ^oC; t_R = 106.7 min (*R*), t_R = 109.7 min (*S*). ^1H NMR (DMSO-d_6, 400 MHz): δ 8.66 (bs, 3H, NH_3), 7.67–7.65 (m, 1H, Ar-H), 7.30–7.21 (m, 3H, Ar-H), 4.76–4.71 (m, 1H, CH), 3.53 (s, 3H, OCH_3), 3.19–3.13 (m, 1H, CH_2), 3.00–2.94 (m, 1H, CH_2), 2.41 (s, 3H, CH_3).

(*S*)-3-methoxy-1-(naphthalen-1-yl)-3-oxopropan-1-aminium chloride

(10k):[60h] $[\alpha]_D^{20}$ −18.2 (*c* 1.0, MeOH), 92% *ee*; HPLC condition for corresponding acetamide: Chiralcel OD-H column, hexanes/2-propanol = 90:10, 1.0 mL/min, 222 nm UV detector, t_R = 7.1 min (*S*), t_R = 12.3 min (*R*). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.23–8.19 (m, 1H, Ar-H), 8.01–7.97 (m, 2H, Ar-H), 7.65–7.57 (m, 4H, Ar-H), 5.52–5.49 (m, 1H, CH), 3.50 (s, 3H, OCH_3), 3.40–3.36 (m, 1H, CH_2), 3.25–3.19 (m, 1H, CH_2).

(*S*)-3-methoxy-1-(naphthalen-2-yl)-3-oxopropan-1-aminium chloride (10l): $[\alpha]_D^{20}$ −20.4 (*c* 1.0, MeOH), 90% *ee*; HPLC condition for corresponding acetamide: Chiralcel OD-H column, hexanes/2-propanol = 90:10, 1.0 mL/min, 222 nm UV detector, t_R = 9.4 min (*S*), t_R = 13.5 min (*R*). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.83 (bs, 3H, NH_3), 8.10 (s, 1H, Ar-H), 7.99–7.91 (m, 3H, Ar-H), 7.76 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.57–7.55 (m, 2H, Ar-H), 4.76 (dd, 1H, *J* = 6.0 and 8.0 Hz, CH), 3.53 (s, 3H, OCH_3), 3.39–3.34 (m, 1H, CH_2), 3.21–3.14 (m, 1H, CH_2).

(*S*)-3-methoxy-3-oxo-1-(thiophen-2-yl)propan-1-aminium chloride (10m):[60i] $[\alpha]_D^{20}$ −7.6 (*c* 1.0, MeOH), 95% *ee*; GC condition for corresponding acetamide: Beta Dex 390 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 160 ^oC; t_R = 56.0 min (*R*), t_R = 58.6 min (*S*). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.86 (bs, 3H, NH_3), 7.57 (d, 1H, *J* = 4.8 Hz, Ar-H), 7.36 (d, 1H, *J* = 3.2 Hz, Ar-H), 7.08–7.05 (m, 3H, Ar-H), 4.87 (dd, 1H, *J* = 5.6 and 8.8 Hz, CH), 3.58 (s, 3H, OCH_3), 3.32–3.27 (m, 1H, CH_2), 3.11–3.04 (m, 1H, CH_2).

General Procedure for Asymmetric Hydrogenation of Quinoline Derivative: A mixture of $[Ir(COD)Cl]_2$ (1.7 mg, 0.0025 mmol) and (*S*)-3,5-*t*Bu-C_3*-TunePhos (5.6 mg, 0.00525 mmol) in toluene (1 mL) was stirred at room temperature for 10 min in a glovebox, then I_2 (6.4 mg, 0.025 mmol) and substrate (0.5 mmol) together with 1.5 mL of toluene were added and the solution was stirred for another 10 min. The hydrogenation was performed under 20 atm H_2 at room temperature for 24 h. After the hydrogen was carefully released, the reaction solution was purified by a silica gel column to give the product, which was then analyzed by chiral GC to determine conversions and the enantiomeric excesses.

(*S*)-2-Methyl-1,2,3,4-tetrahydroquinoline (12a):[50] 98% conversion, 93% ee; Chiral GC: Gamma Dex 225, 30 m x 0.25 mm, column temperature: 120 ^oC, carrier gas: He, 1.0 mL/min, t_1 = 30.60 min, t_2 = 31.64 min. $[\alpha]^{20}_D$ = -66.8 (c 0.5, $CHCl_3$).

(*S*)-2-Ethyl-1,2,3,4-tetrahydroquinoline (12b):[50] 94% conversion, 88% ee; Chiral GC: Gamma Dex 225, 30 m x 0.25 mm, column temperature: 120 ^oC, carrier gas: He, 1.0 mL/min, t_1 = 51.01 min, t_2 = 53.71 min. $[\alpha]^{20}_D$ = -58.4 (c 0.5, $CHCl_3$).

(*S*)-2-Phenyl-1,2,3,4-tetrahydroquinoline (12c):[50] 98% conversion, 73% ee; the conversion was determined by GC analysis (HP-5, 30 m x 0.32 mm, column temperature:

180 ^{o}C, carrier gas: He, 1.5 mL/min): t_1 = 11.93 min, t_2 = 13.66 min; the enantiomeric ratios were determined by chiral HPLC analysis (Chiralcel OD-H, elute: Hexanes / *i*PrOH = 95/5, detector: 254 nm, flow rate: 0.6 ml/min): t_1 = 16.94 min, t_2 = 22.41 min. $[\alpha]^{20}_{D}$ = 33.7 (c 0.5, $CHCl_3$).

(*S*)-6-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (12d):[50] 97% conversion, 91% ee; Chiral GC: Gamma Dex 225, 30 m x 0.25 mm, column temperature: 120 ^{o}C, carrier gas: He, 1.0 mL/min, t_1 = 38.95 min, t_2 = 40.44 min. $[\alpha]^{20}_{D}$ = -59.6 (c 0.5, $CHCl_3$).

(−)-6-Chloro-2-methyl-1,2,3,4-tetrahydroquinoline (12e):[50] 99% conversion, 90% ee; Chiral GC: Gamma Dex 225, 30 m x 0.25 mm, column temperature: 160 ^{o}C, carrier gas: He, 1.0 mL/min, t_1 = 22.82 min, t_2 = 23.48 min. $[\alpha]^{20}_{D}$ = −81.8 (c 0.5, $CHCl_3$).

(−)-6-Bromo-2-methyl-1,2,3,4-tetrahydroquinoline (12f):[50] 99% conversion, 90% ee; Chiral GC: Gamma Dex 225, 30 m x 0.25 mm, column temperature: 160 ^{o}C, carrier gas: He, 1.0 mL/min, t_1 = 36.41 min, t_2 = 37.65 min. $[\alpha]^{20}_{D}$ = −69.6 (c 0.5, $CHCl_3$).

(*S*)-2,6-Dimethyl-1,2,3,4-tetrahydroquinoline (12g):[50] 95% conversion, 92% ee; Chiral GC: Gamma Dex 225, 30 m x 0.25 mm, column temperature: 120 ^{o}C, carrier gas:

He, 1.0 mL/min, t_1 = 47.09 min, t_2 = 48.35 min. $[\alpha]^{20}_D$ = -69.6 (c 0.5, $CHCl_3$).

(*S*)-6-Methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (12h):[50] 84% conversion, 89% ee; Chiral GC: Gamma Dex 225, 30 m x 0.25 mm, column temperature: 130 ^oC, carrier gas: He, 1.0 mL/min, t_1 = 72.78 min, t_2 = 74.20 min. $[\alpha]^{20}_D$ = -51.6 (c 0.5, $CHCl_3$).

(−)-6-Nitro-2-methyl-1,2,3,4-tetrahydroquinoline (12i): [61] 98% conversion, 75% ee; the conversion was determined by GC analysis (HP-5, 30 m x 0.32 mm, column temperature: 180 ^oC, carrier gas: He, 1.5 mL/min): t_1 = 6.16 min, t_2 = 15.22 min; the enantiomeric ratios were determined by chiral HPLC analysis (Chiralcel OD-H, Hexanes / *i*PrOH = 95/5, detector: 254 nm, flow rate: 1.0 ml/min): t_1 = 19.57 min, t_2 = 21.34 min. $[\alpha]^{20}_D$ = −14.7 (c 0.5, $CHCl_3$).

(−)-7-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (12j):[50] 99% conversion, 92% ee; Chiral GC: Gamma Dex 225, 30 m x 0.25 mm, column temperature: 120 ^oC, carrier gas: He, 1.0 mL/min, t_1 = 47.67 min, t_2 = 51.49 min. $[\alpha]^{20}_D$ = −70.9 (c 0.5, $CHCl_3$).

(−)-7-Chloro-2-methyl-1,2,3,4-tetrahydroquinoline (12k): 99% conversion, 90% ee; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.76 (d, *J* = 4.0 Hz, 1H), 6.47-6.44 (m, 1H), 6.34 (s, 1H), 3.62 (s, 1H), 3.32-3.27 (m, 1H), 2.67-2.60 (m, 2H), 1.85-1.80 (m, 1H),

1.49-1.43 (m, 1H), 1.11 (d, J = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 145.7, 131.9, 130.2, 119.4, 116.6, 113.3, 47.0, 29.8, 26.1, 22.5; IR (neat, cm^{-1}) 1602, 1494, 1330, 1296, 1139, 1081, 933, 820, 756; Chiral GC: Gamma Dex 225, 30 m x 0.25 mm, column temperature: 130 ^{o}C, carrier gas: He, 1.0 mL/min, t_1 = 81.12 min, t_2 = 83.83 min. HRMS for $C_{10}H_{13}ClN$ $[M+H]^+$: m/z calcd 182.0737, found 182.0741; $[\alpha]^{20}_D$ = −68.5 (c 0.5, $CHCl_3$).

(−)-8-Chloro-2-methyl-1,2,3,4-tetrahydroquinoline (12l): 99% conversion, 56% ee; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.98 (d, J = 8.0 Hz, 1H), 6.79-6.77 (m, 1H), 6.44-6.41 (m, 1H), 4.17 (s, 1H), 3.40-3.36 (m, 1H), 2.75-2.67 (m, 2H), 1.88-1.83 (m, 1H), 1.55-1.48 (m, 1H), 1.19 (d, J = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 140.7, 127.5, 126.7, 122.4, 117.9, 116.4, 47.2, 29.6, 26.8, 22.5; IR (neat, cm^{-1}) 1599, 1492, 1327, 1244, 1087, 973, 848, 790; Chiral GC: Gamma Dex 225, 30 m x 0.25 mm, column temperature: 120 ^{o}C, carrier gas: He, 1.0 mL/min, t_1 = 52.46 min, t_2 = 53.62 min. HRMS for $C_{10}H_{13}ClN$ $[M+H]^+$: m/z calcd 182.0737, found 182.0741; $[\alpha]^{20}_D$ = −45.9 (c 0.5, $CHCl_3$).

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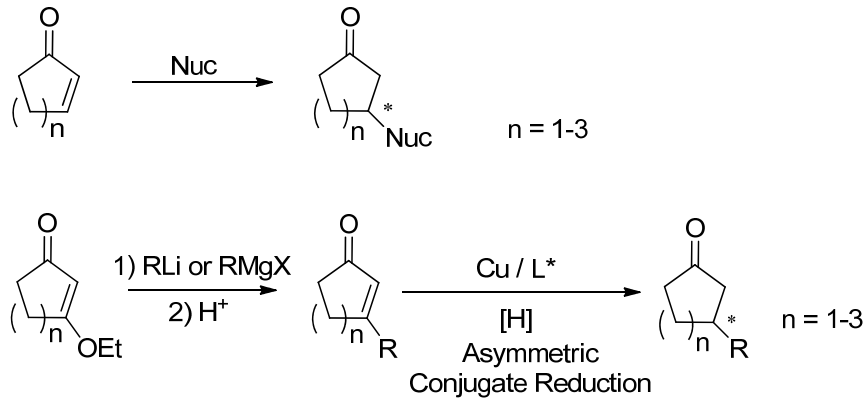
Chapter 5

Metal-Catalyzed Asymmetric Conjugate Reduction and Dynamic Kinetic Resolution

5.1. Introduction and Background

5.1.1. Cu-Catalyzed Asymmetric Conjugate Reduction

Most synthetic routes to chiral *β*-substituted cyclic ketones are based on the conjugate addition of nucleophiles to cyclic *α*,*β*-unsaturated ketones (Scheme 5-1).[1] Excellent catalysts for the asymmetric conjugate addition of nucleophiles to cyclic enones that contain a 6- or 7-membered ring have been discovered.[2] However, another strategy based on asymmetric reduction of *β*-substituted enones could also provide a useful but more efficient synthetic route to access enantiomerically enriched *β*-substituted cyclic ketones (Scheme 5-1). The substrate, *β*-substituted enones can be readily synthesized via the Stork-Danheiser procedure.[3]

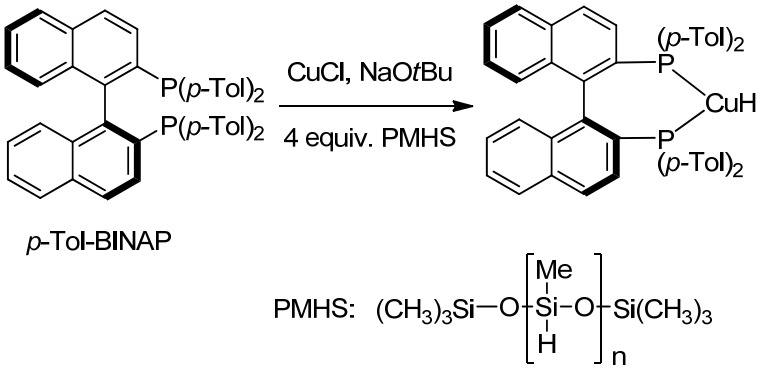


Scheme 5-1: Synthetic Strategies for *β*-Substituted Cyclic Ketones.

1,4-addition reactions to *α,β*-unsaturated carbonyl derivatives, in particular with nonstabilized nucleophiles, remains primarily associated with organocopper chemistry.[4] In recognition of this important fact, several procedures have been developed over the past two decades, although Stryker's reagent $[(Ph_3P)CuH]_6$ is perhaps the most widely used.[5] In early reports, Stryker's reagent, the source of hydride, was only used as a stoichiometric reducing agent or used catalytically in a hydrogen atmosphere at pressures around 1000 psi. Later, Lipshutz and his co-workers reported treatment of an enone or enal with catalytic amount of $[(Ph_3P)CuH]_6$ in the presence of stoichiometric other hydride sources, such as $PhSiH_3$ or Bu_3SnH.[6]

Asymmetric 1,4-hydrosilylations of conjugated carbonyl systems has played a significant role in the asymmetric catalyzed reactions. When asymmetric conjugate reduction is investigated, achiral phosphine-copper hydride complexes, such as $[(Ph_3P)CuH]_6$, should be changed to chiral phosphine-containing catalyst.[7] Buchwald and co-workers reported that a catalyst formed from *p*-Tol-BINAP, CuCl, and NaO*t*Bu affects

the asymmetric conjugate reduction of α,β-unsaturated esters in the presence of 4 equiv. of polymethylhydrosiloxane (PMHS) (Scheme 5-2).[7] PMHS is a safe and inexpensive polymer that has been previously employed as a stoichiometric reducing agent in metal-catalyzed reductions of ketones and imines.[8]



Scheme 5-2: Preparation of Chiral "CuH" Catalyst from *p*-Tol-BINAP.

In the further screening work, Lipshutz and co-workers described the remarkable accelerating effect imparted by nonracemic biaryl ligands such DTBM-SEGPHOS or Xyl-MeO-BIPHEP and CuH, resulting in a highly effective Cu(I)-catalyzed method for asymmetric hydrosilylation (Figure 5-1).[9]

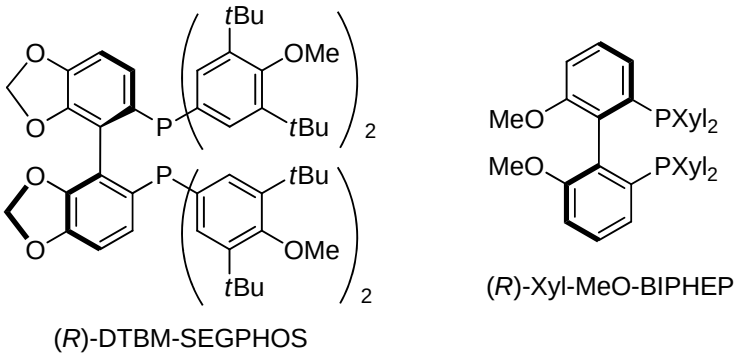


Figure 5-1: Structures of DTBM-SEGPHOS and Xyl-MeO-BIPHEP.

5.1.2. Ru-Catalyzed Dynamic Kinetic Resolution

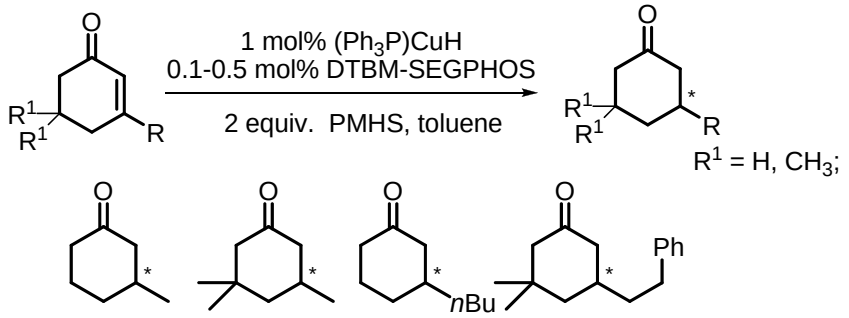
Asymmetric hydrogenation of functionalized ketones is a key methodology providing synthetically useful chiral functionalized alcohols as chiral building blocks.[10] Among the variety of Ru and Rh catalysts synthesized for this important transformation, Ru−diphosphine−diamine catalyst system has been the most successful and has been well recognized in not only research purpose but also in industrial applications, as discussed in Chapter 2. However, to further investigate the utility of such catalytic system and to solve the more challenging problem of related functionalized substrates one or two adjacent stereogenic centers, such as α-hydroxy carbonyl compounds, 1,2-diols, α-branched alcohols, Ru−diphosphine−diamine catalyst system has been tested to be effective in Dynamic Kinetic Resolution (DKR). Highly efficient and stereoselective DKR could be of crucial importance that the racemic α-substituted ketone starting material could be readily reduced and two chiral centers could be well-established diastereoselectively.

In this chapter, in the first section of this chapter we systematically investigated the Cu-catalyzed conjugate hydrosilylation of cyclic enones, by studying our developed "toolbox" of chiral ligands as well as other reaction conditions. A modification synthesis of the bisphosphine ligand f-Binaphane was carried out in order to improve the ligand's performance although unsuccessful. Moreover, attempts of applying Ru−C_3*-TunePhos in dynamic hydrogenation of racemic α-substituted ketones were discussed.

5.2. Results and Discussions

5.2.1. Cu-Catalyzed Asymmetric Conjugate Reduction

Aromatic ketones, hindered cyclic enones, aryl imines, and selected α,β-unsaturated esters and lactones all reacted with [(DTBM-SEGPHOS)CuH] in the presence of stoichiometric PMHS to afford the corresponding products.[11] Particularly, asymmetric hydrosilylation of cyclic enones take place using SEGPHOS-ligated CuH with high enantioselectivities even in very sterically demanding cases (Scheme 5-3).[11d]



Scheme 5-3: Best Representative Results by Cu–DTBM-SEGPHOS Catalyst.

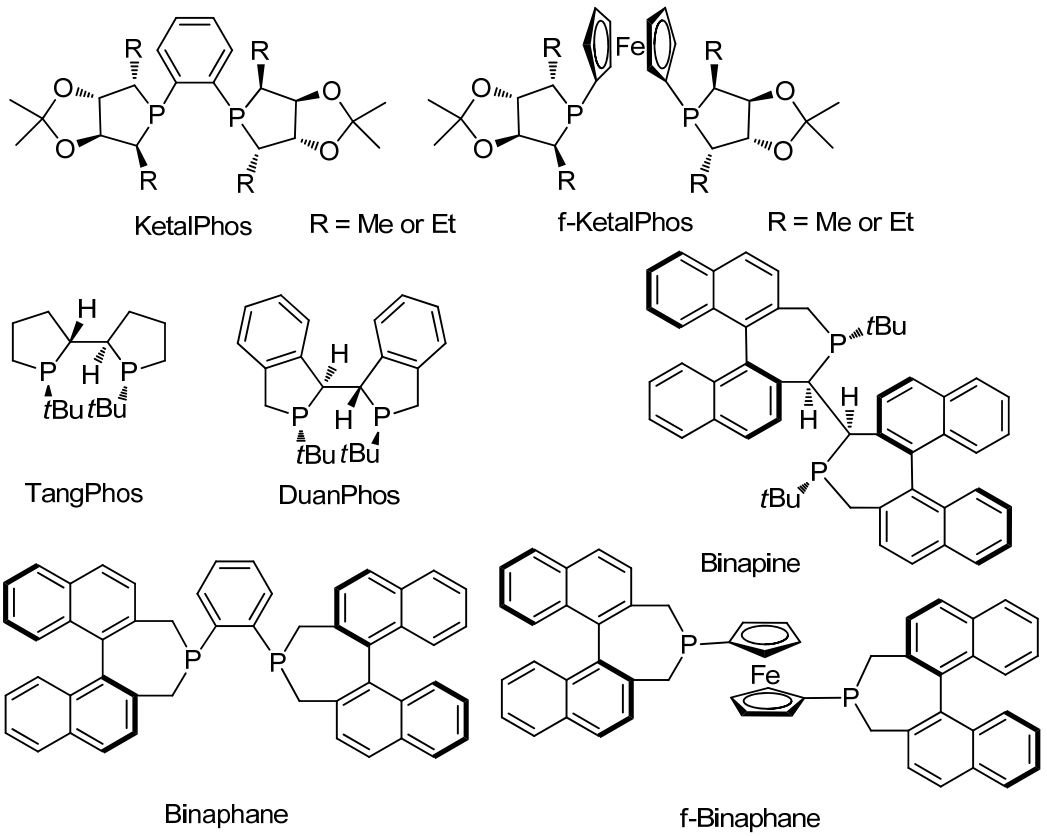


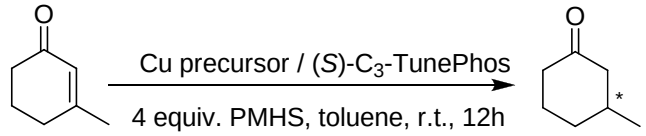
Figure 5-2: Structures of Representative Bisphosphine Ligands in Zhang Group's Chiral Toolbox.

Thus, for the reduction of cyclic enones, we envisioned to achieve better results by applying our developed bisphosphine ligands, particularly our similarly structured C_3*-TunePhos ligands with bulky P-substituents, after careful optimization of different condition parameters, such as chiral ligands, copper source, etc..

First of all, we screened various Cu(I) and Cu(II) salts as the metal precursor in our assay when using the readily available (*S*)-C_3-TunePhos as the ligand and 3-methylhexen-1-one as the substrate (Table 5-1). In this assay, although moderate ee's were observed for $Cu(MeCN)_4PF_6$ and CuCl (entries 3 and 4), in terms of both reactivity

and enantioselectivity, only $Cu(OAc)_2 \cdot H_2O$ and CuOAc displayed promising results toward this chosen substrate (entries 6 and 7). Moreover, when adjusting the ratio of the copper salt to the ligand ((*S*)-C_3-TunePhos) would not remarkably affect either the reactivity or the enantioselectivity (entries 7−11).

Table 5-1: Screening of Cu Salts and Metal-to-Ligand Ratio for Catalytic Conjugate Reduction of 3-Methylhexen-1-one.[a]



1 **2**

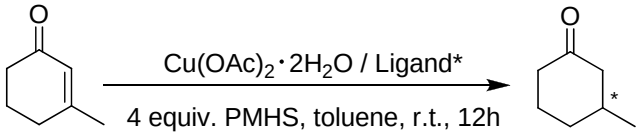
Entry	Cu Precursor	M/L ratio	Conv. (%)	Ee (%)[b]
1	CuCN	1:1	<20	n.d.[c]
2	$Cu(MeCN)_4ClO_4$	1:1	<20	n.d.
3	$Cu(MeCN)_4PF_6$	1:1	<20	74.3
4	CuCl	1:1	<20	76.2
5	CuBr	1:1	<20	n.d.
6	$Cu(OAc)_2 \cdot H_2O$	1:1	>99	67.6
7	CuOAc	1:1	>99	71.7
8	CuOAc	5:1	>99	66.7
9	CuOAc	3:1	>99	69.8
10	CuOAc	1:3	>99	70.6
11	CuOAc	1:5	>99	70.4

[a] Reactions were carried out in toluene at r.t. for 12 h, using (*S*)-C_3-TunePhos as the ligand and 4 equiv. of polymethylhydrosiloxane (PMHS). [b] Conversions and enantiomeric excesses were determined by chiral capillary GC. [c] Not determined.

Based upon the condition optimizations, we performed further screening of the bisphosphine ligand library available in our laboratory (Table 5-2), including TunePhos ligands, DIOP-related ligands, KetalPhos series ligands, and electron-donating

bisphospholanes and bisphosphepines, such as TangPhos, DuanPhos, Binapine, Binaphane and f-Binaphane (Figure 5-2). To out delight, the combination of f-Binaphane and $Cu(OAc)_2 \cdot 2H_2O$ afforded >99% conversion and 87.4% ee, the best result among all ligands tested. This result is comparable to that Lipshutz group reported (90% ee, at 0 ^oC).

Table 5-2: Cu-Catalyzed Conjugate Hydrosilylation of Cyclic Enone **1**: Ligand Screening.[a]



1 **2**

Entry	Ligand	Conv.[b] (%)	Ee[b] (%)	Entry	Ligand	Conv.[b](%)	Ee[b](%)
1	Binapine	>99	58	11	HO-DIOP*	>99	7
2	Binaphane	>99	39	12	BnO-DIOP*	>99	50
3	TangPhos	>99	46	13	DIOP*	>99	30
4	DuanPhos	>99	44	14	FAP	>99	57
5	T-Phos	>99	3	15	Xyl-FAP	>99	63
6	Me-Ketaphos	>99	43	16	C_1-TunePhos	>99	58
7	Et-Ketaphos	>99	52	17	C_2-TunePhos	>99	63
8	Me-f-Ketaphos	>99	26	18	C_3-TunePhos	>99	66
9	Et-f-Ketaphos	>99	26	19	C_4-TunePhos	>99	67
10	f-Binaphane	>99	87	20	C_5-TunePhos	>99	67
				21	C_6-TunePhos	>99	43

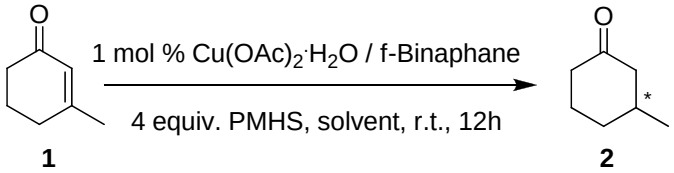
[a] Reactions were carried out in toluene at r.t. for 12 h, using 5 mol% of ligand and 5 mol% of $Cu(OAc)_2 \cdot 2H_2O$, 4 equiv. of polymethylhydrosiloxane (PMHS). [b] Conversions and enantiomeric excesses were determined by chiral capillary GC.

A brief screening of solvents was also performed (Table 5-3). Interestingly, when I_2 was introduced as additive, the reaction is remarkably suppressed while ee remained

similar (<10 conversion, 92.9% ee).

Due to the great success of convenient preparation method of C_3*-TunePhos ligands with different aryl substituents, as described in Chapter 2, and also due to the structural similarity of the C_3*-TunePhos ligands to the well-studied substituted SEGPHOS and MeO-BIPHEP, we further systematically investigated the performance of all the C_3*-TunePhos family members in the conjugate reduction of 3-methyl-hexen-1-one (**1**), expecting that the 4-MeO-3,5-*t*Bu-C_3*-TunePhos could provide superior enantioselectivity over the others (Table 5-4).

Table 5-3: Cu-Catalyzed Conjugate Hydrosilylation of Cyclic Enone **1**: Solvent Screening.[a]

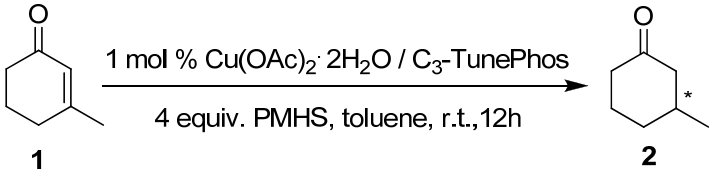


1 **2**

Entry	Solvent	Conv. (%)	Ee (%)[b]
1	Et_2O	>99	80.3
2	THF	<20	n.d.
3	dioxane	80	53.9
4	benzene	>99	81.0
5	DMF	<20	n.d.
6	DMSO	35	30.5
7	toluene	>99	87.4

[a] Reactions were carried out in toluene at r.t. for 12 h, using 1 mol % $Cu(OAc)_2 \cdot H_2O$ and 1 mol % of (*S*,*S*)-f-Binaphane as the ligand, and 4 equiv. of polymethylhydrosiloxane (PMHS). [b] Conversions and enantiomeric excesses were determined by chiral capillary GC. [c] Not determined.

Table 5-4: Screening of C_3-TunePhos Ligands in Cu-Catalyzed Conjugate Hydrosilylation of Cyclic Enone **1**.[a]



1 **2**

Entry	Ligand	Conv. (%)[b]	Ee (%)[b]
1	C_3-TunePhos	>99	80.3
2	Ph-C_3*-TunePhos	>99	59.5
3	*p*-Tol-C_3*-TunePhos	>99	62.3
4	Xyl-C_3*-TunePhos	>99	46.0
5	3,5-*t*Bu-C_3*-TunePhos	>99	85.7
6	4-MeO-3,5-*t*Bu-C_3*-TunePhos	>99	88.8

[a] Reactions were carried out in toluene at r.t. for 12 h, 1 mol % ligand and 1 mol % Cu salt, and 4 equiv. of polymethylhydrosiloxane (PMHS). [b] Conversions and enantiomeric excesses were determined by chiral capillary GC.

Under the optimized conditions, in the presence of $Cu(OAc)_2 \cdot 2H_2O$, in toluene the bulky 3,5-*t*Bu- and 4-MeO-3,5-*t*Bu-C_3*-TunePhos displayed satisfactory results (85.7% and 88.8% ee, entry 5-6). To further extend the scope of this conjugate reduction, a broader scoped of cyclic *α,β*-unsaturated ketones, lactones or lactams could be studied (Figure 5-3).

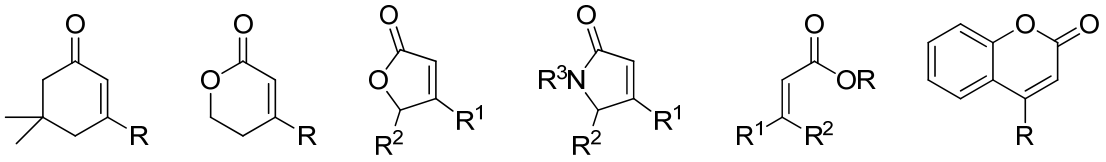
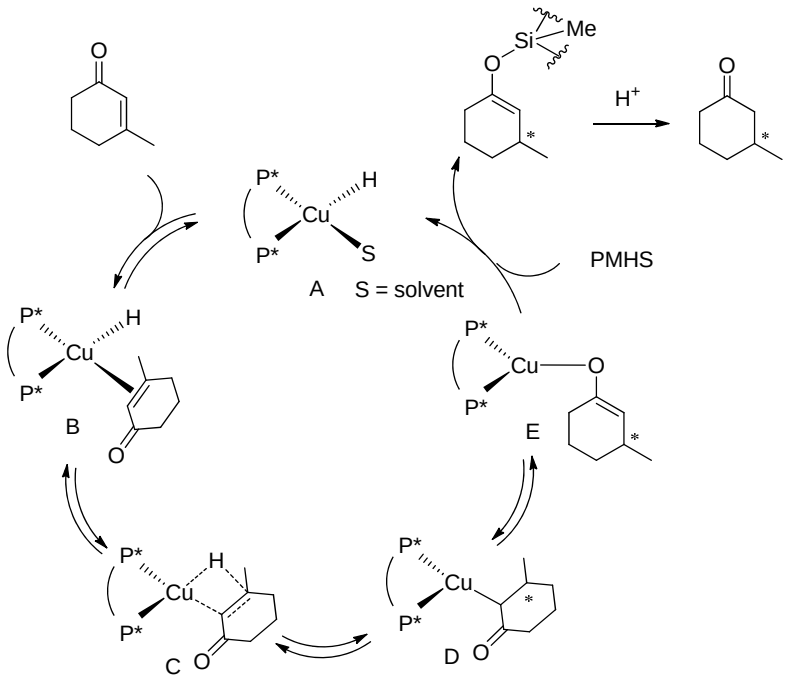


Figure 5-3: Substrate Scope Extension of Conjugate Reduction.

In the current proposed mechanism, the bisphosphine-CuH complex is the key intermediate in the catalytic cycle of the reduction. Conjugate reduction of

cyclohexenones by such a complex should result in formation of a copper enolate that subsequently undergoes metathesis with a silane to form a silyl enol ether (Scheme 5-4).[12]



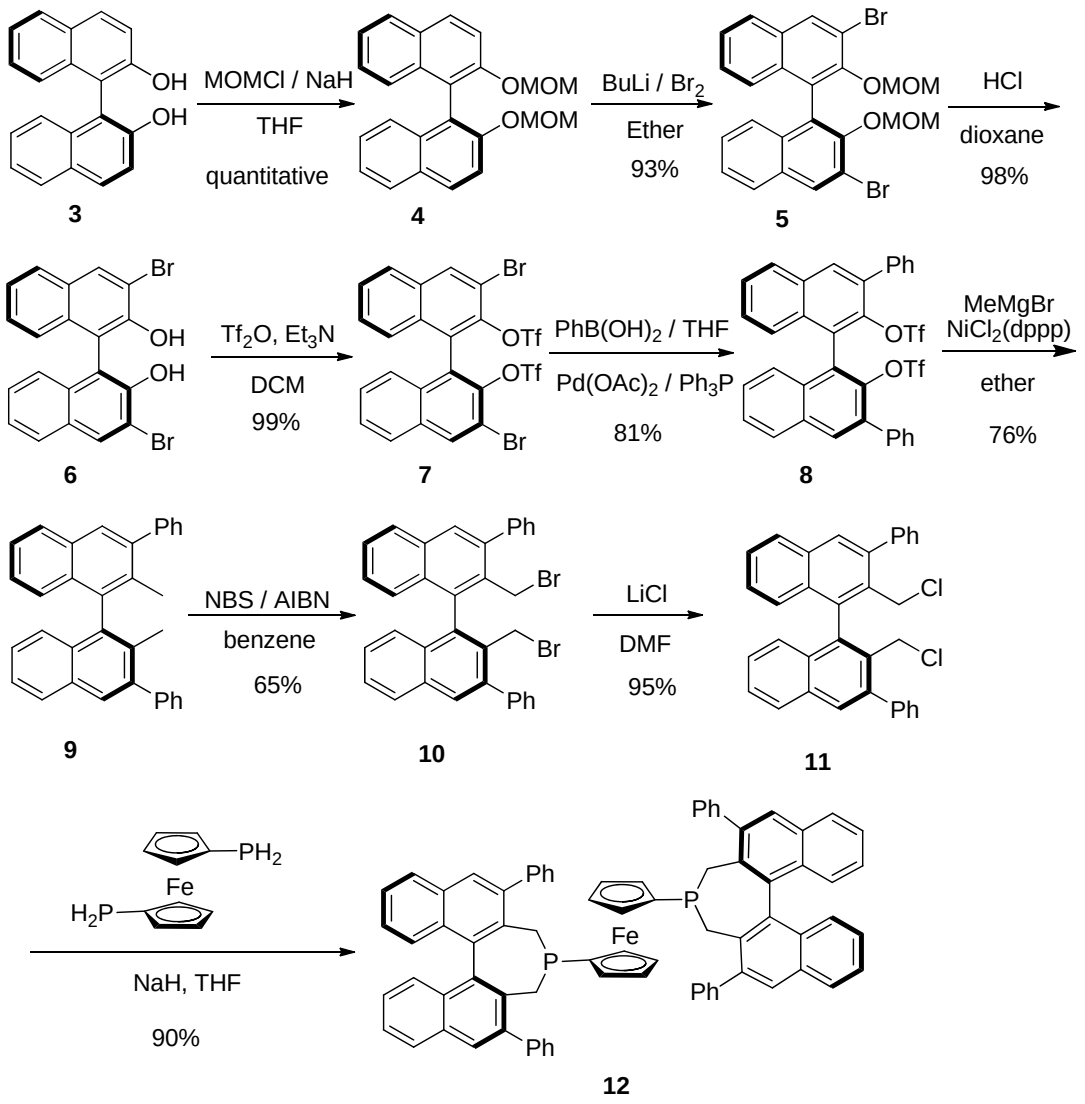
Scheme 5-4: Proposed Mechanism for Cu-Catalyzed Conjugate Reduction of Cyclic *α,β*-Unsaturated Ketone **1**.

5.2.2. Structural Modification and Modified Ligand Synthesis

To achieve a better result for this asymmetric 1,4-hydrosilylation of the enones, further modification of the screened out ligand f-Binaphane was proposed. When comparing the structural features of DTBM-SEGPHOS to other biaryl bisphosphine and other phosphine categories, its uniquely bulky aryl substituent group DTBM

(4-MeO-3,5-*t*Bu-Phenyl) may contribute to the high enantioselectivity in this reaction. Enlightened by such structural features, we envisioned that structural extensions on the 3,3′ positions on the binaphthyl moieties in f-Binaphane could be the target of modifications. Because 3 and 3′ are the positions for which modifications could most influence both the electron density on the phosphorus atoms and the steric hindrance around the catalytic site. It was proposed that the introduction of sterically bulky 3,3′-substituted groups can restrict the rotation of groups adjacent to phosphorus atoms. Therefore, a well-defined chiral pocket around the metal center is formed.[13]

In this work, phenyl groups were induced to extend the axial chirality of the binaphthyl. Three synthetic routes were attempted before the target ligand was successfully synthesized (Scheme 5-5).[14] The key step of introducing substituents on 3- and 3′- positions were approached by Suzuki-Miyaura coupling reaction without affecting the triflate moiety after protecting with bis(methoxymethyl) ether and crimination on 3 and 3′ positions. This step was followed by another cross-coupling reaction with $NiCl_2$(dppp). Importantly, an anion exchange step to change the dibromo- species to less reactive dichloro- species successfully suppressed the intermolecular reaction in the subsequent ring-closing step to give the final product.



Scheme 5-5: Synthetic Route of the Modified 3,3′-Ph-f-Binaphane **12**.

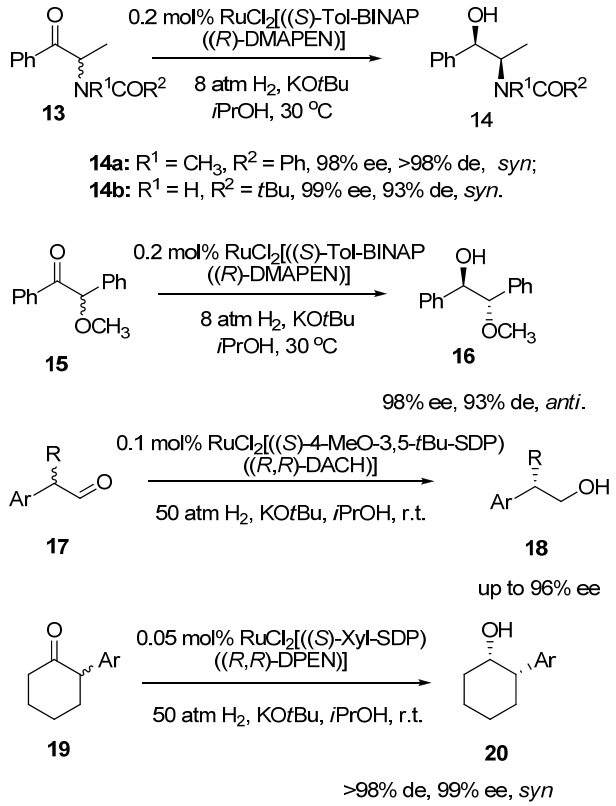
However, to our surprise, the subsequent experimental results showed that with this modified ligand **12**, very low reactivity and enantioselectivity were obtained under the same optimized conditions, even comparing to f-Binaphane. The time for reaction completion was extended to 48−72 h and ee dropped to 45%, comparing to 87% ee of f-Binaphane. The unexpected failure of modification may attribute to the oversize of the

introduced steric bulk on 3- and 3′- positions, possibly weakening the metal-ligand coordination. Thus, we turned to other solutions of further improvement of the enantioselectivities, such as application of the newly synthesized C_3*-TunePhos series ligands, particularly of DTBM-C_3*-TunePhos.

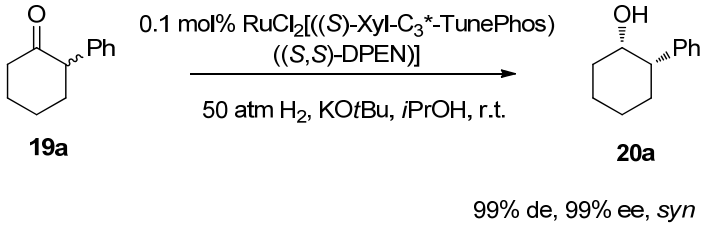
5.2.3. Ru-Catalyzed Dynamic Kinetic Resolution

Based upon the reported examples of successful asymmetric hydrogenation of α-branched aromatic ketones by Ru−Tol-BINAP−DMAPEN, [15] dynamic kinetic resolution of α-branched aldehyde [16] and dynamic kinetic resolution of racemic 2-arylcyclohexanones[17], we decide to examine our C_3*-TunePhos in our preliminary experiments (Scheme 5-6).

In our initial test, we synthesized racemic 2-phenylcyclohexanone **19a** and applied it as the standard substrate. Under optimized condition as reported by Zhou *et al.*[17], in the presence of base KO*t*Bu in *i*PrOH, 1 mol% Ru(II) catalyst of (*S*)-Xylyl-C_3*-TunePhos and (*S*,*S*)-DPEN afforded almost pure enantiomer of the product **20a** with both high enantioselectivity and diastereoselectivity (Scheme 5-7). Further optimization of the hydrogenation pressure and the equivalence of base could be worth testing for improving the ee and more importantly the reactivity (high TONs).



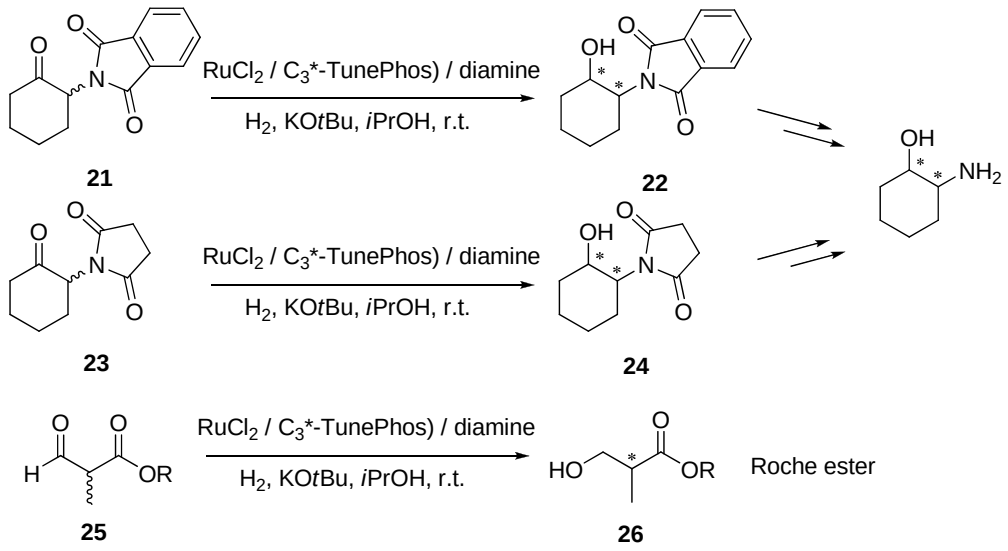
Scheme 5-6: Examples of Dynamic Kinetic Resolution of α-Substituted Ketones and Aldehydes.



Scheme 5-7: Preliminary Results of Ru-Catalyzed DKR of Racemic Cyclohexanone **19a** Using Xyl-C_3*-TunePhos.

In our further plan of taking advantage of DKR, we designed several protected α-amido ketone substrates as well as an α-branched aldehyde substrate, which will lead to

fundamental and highly valuable chiral intermediates such as chiral *cis*-2-aminocyclohexanol and 3-hydroxy-2-methylpropionic acid methyl ester (Roche ester) (Scheme 5-8). However, the initial experiment with substrate **21** was not satisfactory due to its poor solubility in *i*PrOH, which is the most prevalently used for ketone hydrogenation and also DKR. Furthermore, the substrate 23 appeared sensitive to the excessive amount of base present in the catalytic system. Thus, further fine-tuning of the base equivalence and possibly modification of the current Ru−diphosphine−diamine catalyst to the corresponding base-free counterpart with BH_4 moiety[18] may resolve this issue.



Scheme 5-8: Designed Substrates for Ru-Catalyzed DKR Providing Important Intermediates.

5.3. Conclusion

After our successful achievement of the newly designed and synthesized biaryl ligand family C_3*-TunePhos as a supplementary fulfillment of the chiral ligand toolbox, we attempted to search for wide range of transition metal-catalyzed asymmetric catalysis. To our delight, the C_3*-TunePhos with highly steric hindered aryl substituents provided excellent ee in Cu-catalyzed conjugate reduction of cyclic *α*,*β*-unsaturated ketones and potentially for other related *α*,*β*-unsaturated substrates. Moreover, in a reaction closely related to unfunctionalized ketone hydrogenation, we discovered that our C_3*-TunePhos is also highly effective in Ru-catalyzed dynamic kinetic resolution of *α*-aryl cyclic ketones.

These examples of applications provided solid evidence of the synthetic significance of development of chiral ligand toolbox. In our continuing investigation, more asymmetric catalytic methodologies will be extensively studied to unveiled the powerful capability of chiral technology in practical organic synthesis in the fields of agriculture and pharmaceutical industry. *These innovations will set a major paradigm shift of organic synthesis into the real world.*

Experimental Section

General Remarks. All reactions and manipulations were performed in a nitrogen-filled glovebox or under nitrogen using standard Schlenk techniques unless otherwise noted. Column chromatography was performed using Sorbent silica gel 60 Å (230×450 mesh). ^{1}H ^{13}C NMR spectral data were recorded on Bruker 360 MHz, Bruker 400 MHz spectrometers. Chemical shifts were reported in ppm. Enantiomeric excess values were determined by chiral GC on Agilent 6890 and 7890 GC equipment and chiral HPLC on Agilent 1200 Series equipment.

General Procedure for Asymmetric Conjugate Reduction: To a Schlenk tube containing CuOAc (1.22 mg, 0.01 mmol, S/C = 100) and (*S*)-C_3-TunePhos (6.0 mg, 0.01 mmol) under N_2 atmosphere was added 0.88 mL anhydrous toluene. To the stirring mixture was added degassed polymethylhydrosiloxane (PMHS, 0.12 mL, 2 mmol) and the substrate 3-methylhexen-1-one **1** (110 μL, 1mmol). After stirring at room temperature for 12 hours, the reaction was carefully quenched with 10 mL of NaOH aq.(4N), and further stirred until the two layers well separated. The aqueous layer was then extracted with Et_2O (3 x 10 mL). The organic layers were combined, washed with brine, and dried over Na_2SO_4. The reaction mixture was concentrated in vacuo and then purified through a short silica gel column before it was analyzed by GC to determine the conversion and enantiomeric excess.

3-Methylcyclohexanone 2:[11] ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.40-2.16 (m, 3H), 2.08-1.82 (m, 4H), 1.70 (m, 1H), 1.34 (m, 1H), 1.01 (d, *J* = 6.0 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H). GC (Gamma DEX 225, 30 m × 0.25 mm × 0.25 μm; carrier gas, He (flow rate 1 mL/min); column temperature, 100 ˚C). t_{R1} = 19.39 min; t_{R2} = 20.35 min.

Synthesis of (*S*)-2,2′-Bis(methoxymethoxy)-1,1′-Binaphthyl 4: To a three necked flask charged with NaH (5.75g, 0.24 mol) was added 40 ml anhydrous THF. The reaction suspension was stirred and cooled to 0 ^{o}C in an ice-bath and (*S*)-1,1′-binaphthol (BINOL, 28.6 g, 0.1 mol) was slowly added in one batch. After stirred at 0 ^{o}C for 10 min, MOMCl (18.25 mL, 0.24 mol) was added dropwise into the reaction mixture which was afterwards stirred overnight at room temperature. The reaction was quenched with NaOH (aq. 10%) until pH >7, and extracted with Et_2O. After dried over Na_2SO4 and concentrated under vacuum, it provided the crude product as white solid: 35.9 g, 96% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (d, *J* = 4.4 Hz, 2H), 7.88 (d, *J* = 4.4 Hz, 2H), 7.58 (d, *J* = 4.4 Hz, 2H), 7.47-7.33 (m, 2H), 7.26-7.20 (m, 2H), 7.17-7.15 (m, 2H), 5.09 (d, *J* = 3.4 Hz, 2H), 4.98 (d, *J* = 3.4 Hz, 2H), 3.15 (s, 6H).

Synthesis of (*S*)-3,3′-Dibromo-2,2′-Bis(methoxymethoxy)-1,1′-Binaphthyl 5: To a solution of **4** (7.49 g, 20 mmol) in THF (60 mL) was added *n*BuLi (1.6M solution in Hexanes, 30 mL, 48 mmol) at −78 ^{o}C. After the reaction was kept stirring at −78 ^{o}C for 1

h, a solution of Br_2 in pentane (3.07 mL Br_2, 60 mmol, 15 mL pentane) was added dropwise. The acetone/dry ice bath was removed after 1 h and the reaction mixture was slowly warmed up to room temperature and stirred overnight. Upon completion, the reaction mixture was poured into saturated Na_2SO_3 (aq.), and the aqueous layer was extracted with ethyl acetate. The combined organic phase was washed with brine and dried over Na_2SO_4. The crude product was confirmed by ^{1}H NMR but not further purified by chromatography, as off white solid: 9.9 g, 93% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27 (s, 2H), 7.81 (d, *J* = 5.6 Hz, 2H), 7.45-7.42 (m, 2H), 7.31-7.26 (m, 2H), 7.20-7.17 (m, 2H), 4.83 (s, 4H), 2.57 (s, 6H).

Synthesis of (*S*)-3,3′-Dibromo-1,1′-Binaphthyl-2,2′-diol 6: In a 100 mL round bottom flask, **5** (9.9 g, 18.6 mmol) was dissolved in 40 mL 1,4-dioxane and 1 mL of concentrated HCl (aq.) was added. The reaction mixture was then heated to 50 ^{o}C and stirred overnight. Upon completion, the reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated to give the crude product. The purity of the crude product was confirmed by ^{1}H NMR, as white solid: 8.1 g, 98% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (s, 2H), 7.73 (d, *J* = 5.6 Hz, 2H), 7.32-7.18 (m, 4H), 7.01 (d, *J* = 5.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.11, 132.77, 129.71, 127.54, 127.36, 124.82, 124.61, 114.61, 112.28.

Synthesis of (*S*)-3,3′-Dibromo-1,1′-Binaphthyl-2,2′-Diyl Dis(trifluoromethanesulfonate) 7:[14d,e] To a 100 mL flask containing solution of **6** (8.1 g, 18.2 mmol) and Et_3N (8.36 mL, 60 mmol) in 50 mL CH_2Cl_2 was added triflate anhydride (7.4 mL, 44 mmol) at −78 ^oC. The acetone/dry ice bath was removed and let the reaction slowly warm up to room temperature. After stirred for 2 h, the reaction mixture was poured into 300 mL ice-cooled HCl (aq.,1N). After extraction with CH_2Cl_2, the organic phase was washed with saturated $NaHCO_3$ and brine, and then dried over Na_2SO_4. The crude product was obtained after vacuum evaporation as white solid: 12.78 g, 99% yield. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.44 (s, 2H), 7.91 (d, J = 4.0 Hz, 2H), 7.63-7.59 (m, 2H), 7.43-7.39 (m, 2H), 7.26-7.20 (m, 2H).

Synthesis of (*S*)-3,3'-Diphenyl-1,1'-Binaphthyl-2,2'-Diyl Bis(trifluoromethanesulfonate) 8:[14a] A mixture of **7** (12.78 g, 18.0 mmol), phenylboronic acid (5.84 g, 40 mmol), $Pd(OAc)_2$ (232 mg, 5 mol%), PPh_3 (1.12 g, 4.4 mmol), $K_3PO_4{\cdot}nH_2O$ (20 g, 60 mmol) in 200 mL THF was heated to 65 ^oC and stirred for 12 h under N_2 atmosphere. The resulting mixture was poured into saturated NH_4Cl (aq.), and the whole mixture was filtered to remove the catalyst. The filtrate was extracted with ethyl acetate. The organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (CH_2Cl_2/hexane as eluent) to afford the product as off white solid: 9.64 g, 76 % yield. ^1H NMR (CD_3Cl, 300 MHz): δ 8.02 (s, 2H, Ar-H), 7.88 (d, 2H, J = 4.1 Hz Ar-H), 7.58−7.14 (m, 16H, Ar-H).

Synthesis of (*S*)-2,2'-Dimethyl-3,3'-Diphenyl-1,1'-Binaphthyl 9:[14d,e] To a solution of bistriflate **8** (10.3 g, 14.66 mmol) and $NiCl_2$•dppp (0.396 g, 5 mol %) in ether (110 mL) was added dropwise the methyl magnesium bromide (3.0 M, 24.43 mL) at 0°C. The reaction mixture was heated to refluxing for 24h. The reaction was quenched by addition of water (250 mL) slowly at 0°C and then diluted with 30 mL HCl (aq.,5%). The aqueous layer was extracted with ether (3 × 30 mL). The combined organic layer was washed with $NaHCO_3$, dried over Na_2SO_4 and concentrated to afford **9** as light yellow color solid (5.48 g, 86% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80-7.75 (m, 4H), 7.40-7.26 (m, 12H), 7.16-7.12 (m, 2H), 7.03 (d, J = 4.0 Hz, 2H).

Synthesis of 10 ((*S*)-2,2′-Dibromomethyl-1,1′-Binaphthyl):[14a] A mixture of **9** (5.48 g, 12.6 mmol), *N*-bromosuccinimide (NBS, 4.7 g, 26.4 mmol) and 2,2′-azobis(isobutyronitrile) (AIBN, 0.21 g, 10 mol) in benzene (60 mL) was heated to reflux for 3 h. After being cooled to room temperature, this mixture was poured into water and extracted with ethyl acetate. The organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by recrystallization from CH_2Cl_2/hexane to give **10** (4.85g, 65% yield).

Synthesis of 11 ((*S*)-2,2′-Dichloromethyl-1,1′-Binaphthyl):[14d] **10** (4.85 g, 8.19 mmol) and LiCl (2.78 g, 707 mmol) in DMF (100 mL) was mixed together and stirred at

room temperature for 6 h. To this mixture was added carefully 5% aqueous HCl (50 mL), and the mixture was then extracted with ether (4 x 100 mL). The organic layer was dried over Na_2SO_4, concentrated and recrystallized from CH2Cl2/hexane to gave **11** as white solid (3.92 g, 95%).

Synthesis of 12 (3,3′-Ph-f-Binaphane):[14d,e] To a mixture of **11** (2.012 g, 4.0 mmol) and NaH (0.384 g, 16.0 mmol) in a 250 mL round bottom flask was added 80 mL THF at 0 ^oC. Then the reaction was cooled to −78 ^oC and solution of 1,1'-bis(phosphano)ferrocene (0.500 g, 2.0 mmol) was added dropwise at −78 ^oC. The reaction was warmed to room temperature and kept stirring at the same temperature for 24 h, reflux for 34 h. The solvent was removed under low pressure. Then 100 mL CH_2Cl_2 was added and 20 mL H_2O was added dropwise at 0 ^oC. The aqueous phase was extracted by CH_2Cl_2 and the organic phase was combined, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on Al_2O_3 to give the product as light yellow solid (2.0g, 90% yield). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.84 (s, 2H), 7.75-7.66 (m, 10H), 7.50-7.41 (m, 6H), 7.22-7.01 (m, 18H), 6.74 (s, 4H), 3.67 (s, 2H), 3.62 (s, 2H), 3.50 (s, 2H), 2.98 (s, 2H), 2.91-2.96 (m, 4H), 2.65-2.56 (m, 4H). ^{31}P NMR (C_6D_6, 146 MHz) δ 9.59.

Synthesis of 2-chlorocyclohexanone: The reaction was carried out in a three-liter three necked flask fit with a gas inlet tube, a gas outlet tube connected to a silicon oil

valve connected with an equipment absorbing the gas excess. The flask was charged with cyclohexanone (228 g, 2.0 mol) and water (600 mL), and it was cooled with ice-bath. Chlorine gas with bubbled into the reaction mixture while stirred. After the reaction completion, the organic layer was separated and the aqueous phase was extracted with ether. After removal of the ether, the residue was distilled under vacuum. Fraction of 90−95 ^{o}C b.p./ 15 mmHg was collected as colorless liquid (158 g, 60%).

Synthesis of 2-phenylcyclohexanone (19a):[17] To a newly prepared phenylmagnesium bromide solution in ether (0.3 mol) was added 2-chlorocyclohexanone (26 g, 0.2 mol) in 80 mL of anhydrous ether dropwise via drop funnel. The addition rate kept the reaction gently refluxing. After the addition is complete, the solvent was completely distilled out, 70 mL of anhydrous benzene was added, and the mixture was heated at 85 ^{o}C for 8 hours. The reaction mixture was cooled to room temperature, quenched with water and extracted with EtOAc. The extract was concentrated and distilled (106−108 ^{o}C / 1mmHg) to give 25g crude product. Further purification by recrystallization in ethyl acetate gave the pure α-phenylcyclohexanone as colorless solid (22 g, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71-1.93 (m, 2H), 1.98-2.05 (m, 2H), 2.13-2.22 (m, 1H), 2.24-2.31 (m, 1H), 2.41-2.57 (m, 2H), 3.67 (dd, J = 12.0, 5.4 Hz, 1H), 7.13 (d, J = 6.6 Hz, 2H), 7.30-7.36 (m, 3H).

General Procedure for Asymmetric Hydrogenation of

2-Phenyl-cyclohexanone: [17]To a vial containing 2-phenyl-cyclohexanones **19a** (0.436 g, 2.5mmol, S/C = 1000) in 2 mL of *i*PrOH was added precatalyst complex $RuCl_2$[((*S*)-Xyl-C_3*-TunePhos)(*S*,*S*)-DPEN] catalyst (2.8 mg, 0.0025 mmol 2.2 mg, 0.002 mmol) and a solution of *t*BuOK in *i*PrOH (1.0 M, 0.04 mL, 0.04 mmol). The resulting mixture was transferred into an autoclave, and the autoclave was purged with H_2 (50 atm, for three times) and charged with H_2 (50 atm). After stirring at room temperature for 24 hours, the H_2 was carefully released. The reaction mixture was filtered through a short silica gel column, and the filtrate was diluted with acetone and analyzed by GC to determine the conversion, *cis*/*trans* selectivity, and enantioselectivity. Chiral GC (Supelco BETA DEX 225, 30 m × 0.25 mm × 0.25 μm); carrier gas, He (flow rate 1 mL/min); column temperature, 100 ˚C then 0.5 ^{o}C/min to 180 ^{o}C; t_R of (*R*,*R*)-isomer, 51.83 min; t_R of (*S*,*S*)-isomer, 52.52 min.

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