TRANSITION METAL-CATALYZED ASYMMETRIC HYDROGENATION FOR

SYNTHESIS OF CHIRAL AMINES

By

MINGXIN CHANG

A dissertation submitted to the

Graduated School-New Brunswick

Rutgers, The State University of New Jersey

In Partial Fulfillment of the Requirements

For the degree of

Doctor of Philosophy

Graduate Program in Chemistry and Chemical Biology

Written under the direction of

Professor Xumu Zhang

And approved by

New Brunswick, New Jersey

October, 2013

ABSTRACT OF THE DISSERTATION

TRANSITION METAL-CATALYZED ASYMMETRIC HYDROGENATION FOR SYNTHESIS OF CHIRAL AMINES

by MINGXIN CHANG

Dissertation Director:

Professor Xumu Zhang

Synthesis of chiral amine is one of the major tasks in organic chemistry since chiral amines play important roles in pharmaceutical and agrochemical industry. Among those various methods for chiral amine synthesis, transition metal-catalyzed asymmetric hydrogenation is one of the most efficient asymmetric catalytic technology both on the laboratory and the production scale in synthetic organic chemistry due to its high efficiency and atom economy. In this dissertation, the asymmetric hydrogenation of two types of cyclic imines, direct asymmetric reductive amination and the asymmetric hydrogenation of pyridines were explored for makingof chiral amines.

The asymmetric reduction of cyclic imines and *N*-hereromatic compounds remains a challenge in modern synthesis due to the inhibitory effect from the amine product and the coordination difficulty of the imine substrates to the transition metal center. Our

Ir–f-Binaphane catalytic system was proved to be efficient for two types of cyclic imine substrates, 2-arylpyrrolines and dihydroisoquinoline.

A 'green' method, the direct reductive amination of simple ketones was explored using phenylhydrazide as the nitrogen source. With help of several additives, excellent reactivity (up to 1000 TONs) and enantioselectivities (up to 99% *ee*) were achieved in iridium–f-Binaphane catalyzed reaction.

The direct hydrogenation of pyridines is hard to achieve. The strategy we used is to dearomatize the pyridine ring by addition of an easy-removal protecting group, benzyl, on the nitrogen of pyridines. Collaborating with Merck Catalysis group, and using the neutral iridium–MP2-SegPhos catalytic system, various *N*-benzyl-2-arylpyridines were hydrogenated under mild condition and high enantioselectivities were achieved.

ACKNOLEDGEMENTS

I am heartily thankful to my supervisor, Professor Xumu Zhang, whose encouragement, guidance and support enabled me to accomplish this dissertation. Xumu was a fabulous advisor: sharp, cheery, perceptive, and enthusiasm.

I would like to thank my committee members, Professor Leslie Jimenez, Professor Ralf Warmuth and Professor Longqin Hu for their time and valuable discussions.

I would like to thank Dr. Wei Li and Dr. Guohua Hou for their generous help, and my collaborators Ms. Yuhua Huang and Mr. Shaodong Liu. I would like to thank all other former and current group members in Zhang group including Dr. Weicheng Zhang, Dr. Shichao Yu, Dr. Xiaowei Zhang, Mr. Kexuang Huang, Dr. Bonan Cao, Dr. Tian Sun, Dr. Huiling Geng, Dr. Miaofeng Ma, Dr. Farong Gou, Mr. Qingyang Zhao, and Ms. Xin Zheng. I would also like to thank Merck collaborator Dr. Yonggang Chen.

I would like to express special thanks to my parents. Their love and support has always been a great encouragement for me. I deeply thank my wife, Juxiang Zhou, whose love and encouragement allowed me to finish this journey. This dissertation is dedicated to my wife Juxiang, my son Matthew and my daughter Claire.

Lastly, I offer my regards and blessings to all of those who supported me in any respect during my doctoral study.

TABLE OF CONTENTS

ABSTR	ACT	ii
ACKN	DWLEGEMENT	iv
LIST O	F TABLES	vii
LIST O	F FIGURES	ix
LIST O	F SCHEMES	X
Chapter	1 Introduction	1
1.1	Overview	1
1.2	Asymmetric hydrogenation of enamines leading to chiral amines	4
1.3	Other methods for chiral amine synthesis	14
	1.3.1 Nucleophilic addition of organometallic compounds to imines	14
	1.3.2 Enantioselective vinylogous Mannich reactions	17
	1.3.3 Asymmetric hydroamination	19
	1.3.4 Asymmetric aza-Morita–Baylis–Hillman reaction	22
	1.3.5 Enantioselective C-H amination	25
1.4	Conclusion	28
Refe	erences	29
Chapter	2 Iridium-Catalyzed Enantioselective Hydrogenation of Cyclic Imines	32
2.1	Introduction and background	32
2.2	Iridium-catalyzed asymmetric hydrogenation mechanism	37
2.3	Asymmetric hydrogenation of 2-aryl(alkyl)pyrrolines	42
	2.3.1 Background	42
	2.3.2 Results and discussion	42
	2.3.3 Conclusion	51
2.4	Asymmetric hydrogenation of 1-alkyl/aryl-3,4-dihydroisoquinolines	51
	2.4.1 Bachground	51
	2.4.2 Results and discussion	53
	2.4.2 Conclusion	58
2.5	Experimental section	59

2.5.1 General Remarks
2.5.2 General procedure for synthesis of cyclic imines 1
2.5.3 General procedure for asymmetric hydrogenation of cyclic imines 162
2.5.4 General procedure for synthesis of cyclic imines 3
2.5.5 General Procedure for Asymmetric Hydrogenation of 3,4-dihydro-
isoquinoline 370
References76
Chapter 3 Direct Catalytic Asymmetric Reductive Amination of Simple Aromatic
Ketones
3.1 Introduction and background80
3.2 Reductive amination using benzylamine as nitrogen source
3.3 Reductive amination of simple ketones using phenylhydrazide88
3.4 Experimental section94
3.4.1 General Remarks94
3.4.2 General Procedure for reductive amination of acetophenone with
benzylamine95
3.4.3 General Procedure for reductive amination of ketone with
phenylhydrazide96
References102
Chapter 4 Iridium-catalyzed Asymmetric Hydrogenation of Pyridinium Salts104
4.1 Introduction and background104
4.2 Results and discussion
4.2.1 Direct asymmetric hydrogenation of methyl nicotinate
4.2.2 Asymmetric hydrogenation of <i>N</i> -benzylpyridinium salts113
4.3 Experimental section
References
Publications

LIST OF TABLES

Table 1-1. Hydrogenation of enamines using TangPhos
Table 1-2. Hydrogenation of enamines using ZhangPhos
Table 1-3. Hydrogenation of N-H enamines using f-Binaphane
<i>Table 1-4</i> . Diastereoselective addition to N-tert-butanesulfinyl imines16
Table 2-1. Asymmetric hydrogenation of N-aryl imine using iridium-TangPhos36
Table 2-2. Asymmetric hydrogenation of N-H imines using iridium-f-Binaphane
catalyst
<i>Table 2-3.</i> Asymmetric hydrogenation of 2-phenyl-1-pyrroline by Ir–f-Binaphane45
<i>Table 2-4.</i> Solvent effects on asymmetric hydrogenation of 2-phenyl-1-pyrroline46
<i>Table 2-5.</i> Additive effects on asymmetric hydrogenation of 2-phenyl-1-pyrroline47
Table 2-6. Screening of chiral phosphine ligands
<i>Table 2-7.</i> Asymmetric hydrogenation of cyclic imines by Ir–f-Binaphan50
Table 2-8. Asymmetric hydrogenation of 1-phenyl-3,4-dihydroisoquinoline by
Ir–f-Binaphane55
<i>Table 2-9.</i> Asymmetric hydrogenation of 3,4-dihydroisoquinolines by
Ir–f-Binaphane
Table 3-1. Reductive amination of acetophenone using benzylamine
<i>Table 3-2.</i> Anion effect on reductive amination of acetophenone using benzylamine.88
Table 3-3. Direct asymmetric reductive amination of acetophenone with

phenylhydrazide using iridium–f-Binaphane91
Table 3-4. Asymmetric hydrogenation of N-benzoylhydrazone 6a92
Table 3-5. Direct asymmetric reductive amination of simple aromatic ketones using
iridium–f-Binaphane94
Table 4-1. Asymmetric hydrogenation of methyl nicotinate• TFA111
Table 4-2. Asymmetric hydrogenation of methyl nicotinate•HA112
Table 4-4. Solvent screening for asymmetric hydrogenation of N-Benzylpyridinium
salt115
Table 4-5. Solvents and catalyst loading screening for asymmetric hydrogenation of
<i>N</i> -Benzylpyridinium salt116
Table 4-6. Substrate scope for asymmetric hydrogenation of N-Benzylpyridinium
salts118

LIST OF FIGURES

<i>Figure 1-1</i> . Examples of industrial produced chiral compounds2
<i>Figure 1-2</i> . Milestones in chiral ligands design
<i>Figure 1-3</i> . Chiral compounds yielded from asymmetric hydrogenation4
<i>Figure 1-4</i> . Chiral ligands developed by our group for hydrogenation of enamines9
<i>Figure 1-5. ab initio</i> calculations of LUMO energy in eV15
<i>Figure 1-6.</i> Chiral catalysts used in aza-Morita-Baylis-Hillman reactions25
<i>Figure 2-1.</i> Structures of some chiral cyclic amines
<i>Figure 2-2.</i> Imine substrates for asymmetric hydrogenation32
<i>Figure 2-3.</i> Ferrocene-based chiral ligands35
<i>Figure 2-4.</i> Structures of chiral ligands for initial screening
<i>Figure 2-5.</i> Structures of chiral ligands46
<i>Figure 3-1.</i> Structures of arydrazide and pyrazolidine
<i>Figure 3-2.</i> Structures of chiral phosphine ligands90
Figure 4-1. Structures of ropivacaine, dexmethylphenidate, paroxtine, and
alogliptin105

LIST OF SCHEMES

Scheme 1-1. The first example of enantioselective hydrogenation of <i>N</i> -acyl
Scheme 1-2. Ruthenium-BINAP system for enamine hydrogenation
Scheme 1-3. Rh-Me-DuPhos/Me-BPE system for enamine hydrogenation
<i>Scheme 1-4.</i> Rh-Spiro-ligand system for enamine hydrogenation7
Scheme 1-5. Asymmetric hydrogenation of enamine esters and enamine amides8
Scheme 1-6. Hydrogenation of enamine amides for production of sitagliptin
Scheme 1-7. Hydrogenation of enamines using BICP and BICPO10
Scheme 1-8. Hydrogenation of enamines using Me-PennPhos
Scheme 1-9. Hydrogenation of enamines using Binaphane11
Scheme 1-10. Hydrogenation of enamines using DIOP*11
<i>Scheme 1-11</i> . Necleophilic addition to imines15
<i>Scheme 1-12</i> . Nucleophilic addition to imines derived from chiral aldehydes16
<i>Scheme 1-13</i> . Electrophilic attack on dienolate17
<i>Scheme 1-14</i> . The first catalytic enantioselective vinylogous Mannich reaction18
<i>Scheme 1-15</i> . Vinylogous Mannich reaction catalyzed by phosphoric acid18
Scheme 1-16. Direct Vinylogous Mannich reaction catalyzed by phosphoric acid19
Scheme 1-17. Gold-catalyzed intermolecular hydroamination of inactivated
alkenes
<i>Scheme 1-18.</i> Palladium-catalyzed intermolecular hydroamination of aniline with styrene
<i>Scheme 1-19</i> . Proposed mechanism for hydroamination of aniline with styrene21

<i>Scheme 1-20</i> . Iridium-catalyzed intermolecular hydroamination of aniline with norbornadiene
<i>Scheme 1-21</i> . Proposed mechanism for intramolecular hydroamination23
<i>Scheme 1-22</i> . Aza-Morita–Baylis–Hillman reaction
<i>Scheme 1-23</i> . Thiourea-catalyzed aza-Morita–Baylis–Hillman reaction
<i>Scheme 1-24</i> . Generally accepted mechanism of the aza-Baylis-Hillman reaction25
<i>Scheme 1-25</i> . Sulfoxamines as amine source for C-H amination27
<i>Scheme 1-26</i> . RuBr ₂ -pybox catalyzed C-H amination27
<i>Scheme 2-1</i> . Industrial production of herbicide (<i>S</i>)-Metolachlor35
<i>Scheme 2-2</i> . Iridium-catalyzed imine reduction mechanism
Scheme 2-3. Iridium-catalyzed imine reduction mechanism proposed by Hopmann et
<i>al</i> 40
Scheme 2-4. Generally accepted mechanism for Ir-catalyzed hydrogenation of
imine40
Scheme 2-5. Mechanism for Ir-diphosphine-catalyzed hydrogenation of imine41
Scheme 2-6. Mechanism for Ir-catalyzed hydrogenation of imine based on Ir(III)42
Scheme 2-7. Formation of the dimeric and trimeric Ir-H clusters
<i>Scheme 2-8.</i> Industrial production of solifenacin
<i>Scheme 3-1.</i> First reductive amination reported by Blaser <i>et al</i> 82
<i>Scheme 3-2.</i> HCOONH ₄ as nitrogen source
<i>Scheme 3-3.</i> Reductivee amination for synthesis of β-amino ester82
Scheme 3-4. Intramolecular reductive amination

<i>Scheme 3-6.</i> Ir-chiral diamine/phosphorus acid-catalyzed reductive amination84
<i>Scheme 3-7.</i> The Cleavage of N–N and N–(C=O) bond85
Scheme 3-8. Proposed mechanism
Scheme 4-1. First highly enantioselective asymmetric hydrogenation of quinolines. 105
Scheme 4-2. Proposed mechanism for asymmetric hydrogenation of quinolines106
<i>Scheme 4-3.</i> The first example for asymmetric hydrogenation of pyridines108
<i>Scheme 4-4.</i> Direct asymmetric hydrogenation of pyridines108
Scheme 4-5. Utility of chiral auxiliary on the 2 position of pyridine to induce chirality
<i>Scheme 4-6.</i> Step-wise hydrogenation of pyridine109
<i>Scheme 4-7.</i> Asymmetric hydrogenation of <i>N</i> -iminopyridinium ylides109
Scheme 4-8. Asymmetric hydrogenation of pyridinium salts110
<i>Scheme 4-8.</i> Chiral ligands structures114
Scheme 4-9. Asymmetric hydrogenation of pyridinium salts with different benzyl substitutes

Chapter 1

Introduction

1.1 Overview

The synthesis of chiral amine is one of the major tasks in organic chemistry.¹ Chiral amines play important roles in pharmaceutical and agrochemical industry. For instance, 45 out of 200 top brand name drugs by US retail sales in 2010 contain one or more chiral amine centers.² A number of methods are available for chiral amine synthesis, including stereoselective nucleophilic organometalic compounds addition to imino compounds, catalytic enantioselective vinylogous Mannich reactions, transition metal and organo molecules catalyzed hydrogenation and transfer hydrogenation of imines / enamides / enamines / N-hetereoaromatic compounds, asymmetric reductive amination, asymmetric hydroamination, enantioselective C-H amination, asymmetric Aza-Morita-Baylis- Hillman reaction, enzyme catalysis, and so on.¹ Among those various methods for chiral amine synthesis, asymmetric hydrogenation is the most mature one on both the laboratory and the production scale in synthetic organic chemistry due to its high efficiency and atom economy.³ Some well-known large-scale processes include the production of L-DOPA by Monsanto,⁴ a key intermediate for carbapenems by Takasago,⁵ Metolachlor by Syngenta,⁶ Sitagliptin by Merck,⁷ and Aliskiren⁸ by Novartis (Figure 1-1).



Figure 1-1. Examples of industrial produced chiral compounds.

In the late 1960s Knowles⁹ and Horner¹⁰ initiated the development of homogeneous asymmetric hydrogenation. Ever since, thousands of chiral ligands were developed for asymmetric hydrogenation. Early milestone in chiral ligands design was DIOP, the first C_2 symmetric bisphosphine ligand, which was used in Rh-catalyzed asymmetric hydrogenation (Figure 1-2).¹¹ Another early successful example was DIPAMP developed by Knowles (Figure 1-2).¹² In 1980 Noyori and co-workers made a major breakthrough for their pioneering studies on axially chiral BINAP (Figure 1-2).¹³ Noyori's BINAP-Ru system was not only useful for hydrogenation of olefins, but also worked excellently for ketone reduction, which was a big substrates scope expansion compared with other systems. For their outstanding work, Knowles and Noyori were awarded the Nobel Prize in 2001. DuPhos,¹⁴

JosiPhos,¹⁵ PHOX¹⁶ and MonoPhos¹⁷ were also among those successful ligands and added new motifs for chiral ligands design (Figure 1-2).



Figure 1-2. Milestones in chiral ligands design.

Until now, with the help of efficient transition metal complexes, quite broad scope of various unsaturated substrates, such as cyclic and acyclic imines, iminium salts, functionalized and unfunctionalized olefins (including dehydro amino acids and esters, dehydro amino alcohols, enamines and enamides), simple and functionalized ketones, and heteroaromatic compounds, have been hydrogenated to yield corresponding chiral compounds with excellent enantioselectivity and reactivity (Figure 1-3).^{3,18} The transition metals also were expanded from precious rhodium, ruthenium and iridium

to cobalt, nickel and even iron.



Figure 1-3. Chiral compounds yielded from asymmetric hydrogenation.

1.2 Asymmetric hydrogenation of enamines leading to chiral amines

Transition metal-catalyzed asymmetric hydrogenation is one of the most efficient and convenient methods for the preparation of chiral amines and their derivatives. Enamines are one class of earliest hydrogenation substrates. And the research on *N*-acyl enamines dominates in enamines hydrogenation since the *N*-acyl group acting as a second chelation site. The most frequently used metal is rodium. In 1972 Kagan and coworker reported the first example of enantioselective hydrogenation of *N*-acyl enamines using Rh-DIOP catalyst (Scheme 1-1).¹⁹ Although the enantioselectivity for



Scheme 1-1. The first example of enantioselective hydrogenation of N-acyl enamines.



Scheme 1-2. Ruthenium-BINAP system for enamine hydrogenation.



Scheme 1-3. Rh-Me-DuPhos/Me-BPE system for enamine hydrogenation.

this reaction was not even high gauged by today's standard, this study opened up a new door for chiral amine synthesis. The ruthenium-BINAP system was also successfully applied in the asymmetric hydrogenation of *N*-acyl-1-alkylidenetetrahydroisoquinolines, and the *ee*'s for products was up to 99.5%. But this system only worked for (*Z*)-isomer of the substrates and (*E*)-isomer was recovered intact (Scheme 1-2). ²⁰ Rodium-Me-DuPhos/Me-BPE solved this problem. The *Z/E*-mixtures of β -substituted *N*-acyl arylenamines were hydrogenated with high enantioselectivities (Scheme 1-3). ²¹

The catalytic enantioselective hydrogenation of *N*-alkyl enamines also progressed in recent years. Zhou and co-workers reported highly enantioselective rhodium-catalyzed hydrogenation of 1-(1,2-diarylvinyl)pyrrolidines and iridiumcatalyzed hydrogenation of cyclic *N*,*N*-dialkyl enamines (Scheme 1-4).²²



Scheme 1-4. Rh-Spiro-ligand system for enamine hydrogenation.

There were some examples for *N*-H enamine reduction. The ferrocene-based chiral ligands were proved to be very efficient for this type of substrates. Using the rhodium-JosiPhos complexes, enamine esters and enamine amides were hydrogenated in high enantioselectivities (Scheme 1-5).²³ And this exact catalyst was successfully used in the production of sitagliptin by Merck & Co., which is a type of enzyme-inhibiting drug for treatment of diabetes mellitus type 2 (Scheme 1-6).²⁴



Scheme 1-5. Asymmetric hydrogenation of enamine esters and enamine amides.



Scheme 1-6. Hydrogenation of enamine amides for production of sitagliptin.

Our group contributed in this research area. Chiral ligands BICP and BICPO, PennPhos, Binaphane, DIOP*, TangPhos, DuanPhos, ZhangPhos and f-Binaphane all shown excellent performance towards the enamines hydrogenation (Figure 1-4).



Figure 1-4. Chiral ligands developed by our group for hydrogenation of enamines.

BICP²⁵ and BICPO²⁶ were early chiral ligands in our group used for dehydroamino acids hydrogenation (Scheme 1-7). PennPhos²⁷ was very efficient for cyclic enamide reduction (Scheme 1-8). The rhodium-Binaphane²⁸ catalyst worked excellently for both (*E*) and (*Z*)-isomers of enamines (Scheme 1-9). The DIOP analog, DIOP* along with rhodium catalyzed the hydrogenation of enamide with high enantioselectivities (Scheme 1-10).²⁹ The *p*-chiral ligands family, TangPhos³⁰ (Table 1-1), DuanPhos³¹ and ZhangPhos³² (Table 1-2), were outstanding ligands in the hydrogenation of enamines. The f-Binaphane ligand is quite unique in structure: a flexible ferrocene-based backbone allowing to accommodate a wide range of substrates to the transition metal center. Its electron-donating feature can minimize the inhibition effect from the amine product. So it performed outstandingly for *N*-H enamine hydrogenation³³ (Table 1-2).



Scheme 1-7. Hydrogenation of enamines using BICP and BICPO.



Scheme 1-8. Hydrogenation of enamines using Me-PennPhos.



Scheme 1-9. Hydrogenation of enamines using Binaphane.



Scheme 1-10. Hydrogenation of enamines using DIOP*.







Table 1-2. Hydrogenation of enamines using ZhangPhos.

Table 1-3. Hydrogenation of *N*-H enamines using f-Binaphane.



1.3 Other methods for chiral amine synthesis

1.3.1 Nucleophilic addition of organometallic compounds to imines

One efficient method to synthesize amine is nucleophilic addition to imines (Scheme 1-11).³⁴ For some less electrophilic *N*-alkyl-substituted imines, very reactive nucleophiles, such as organolithium, Grignard, organocuprate/BF₃, and organocerium



Scheme 1-11. Necleophilic addition to imines.

reagents, are required. To accommodate larger nucleophile scope, an important strategy is to increase the electrophilicity of these imines can be increased via the selection of an appropriate electron-withdrawing *N*-substituent. Some common activating *N*-substituents include phosphinoyl, sulfonyl, sulfinyl, benzoyl, acyl and carbamoyl groups. And the electrophilicity and electron-withdrawing ability relationship was confirmed by *ab initio* calculations (Figure 1-5).³⁵



Figure 1-5. ab initio calculations of LUMO energy in eV.

Chiral auxiliaries were used in the early study of the nucleophilic addition to imines.³⁶ The imines substrates could be either derived from chiral aldehydes, or from



Scheme 1-12. Nucleophilic addition to imines derived from chiral aldehydes.

N ^S 'tBu R ¹ H	+ R ² MgBr	Et ₂ O/CH	$ \begin{array}{c} & O \\ & 2^{Cl_2} \\ & HN \\ & R^{1 + R^2} \end{array} $	′ [′] Bu 2
Entry	R ¹	R ²	Yield (%)	Dr
1	Et	Ме	96	93:7
2	Et	Ph	98	96:4
3	iPr	Ме	97	98:2
4	iPr	Ph	98	89:11
5	Bn	Ме	89	95:5
6	Bn	Ph	81	95:5
7	Ph	Ме	96	97:3
8	Ph	Et	98	92:8
9	Ph	Vinyl	79	94:6

Table 1-4. Diastereoselective addition to N-tert-butanesulfinyl imines.

achiral aldehydes with chiral amines. One example for the former is shown in scheme 1-12.³⁷ The chiral amine product was achieved in 86% yield as a single diastereomer.

And *N-tert*-butanesulfinamide is a popular *N*-protecting/activating group (Table 1-4).³⁸

1.3.2 Enantioselective vinylogous Mannich reactions

Dienolates are ambident nucleophiles. Thus imines as electrophiles could attack both the α - and γ -positions (Scheme 1-13). This reaction is very useful in β -amino acids synthesis.³⁹ The regioselectivity highly depends on the metal species on the dienolate.⁴⁰ For lithium dienolates, α -attack most like takes place since it has the larger HOMO coefficient. As for silicon dienolates, more HOMO coefficient is on γ -position and thus the γ -addition products will be the major products. At the same time, the steric factor also will affect the regioselectivity. For example, a bulky α -substituent will enforce the γ -addition.



Scheme 1-13. Electrophilic attack on dienolate.

Ojima group systematically investigated the Lewis acid-catalyzed vinylogous Mukaiyama–Mannich reaction.⁴¹ The first catalytic enantioselective vinylogous Mannich reaction was reported by Martin and Lopez, and only moderate enantioselectivity was achieved (Scheme 1-14).⁴² Besides lewis acid, chiral phosphoric acids also catalyze this reaction quite efficiently. Schneider and coworkers excellent vinylogous Mannich reactions with just 1 mol% of phosphoric acid (Scheme 1-15).⁴³



Scheme 1-14. The first catalytic enantioselective vinylogous Mannich reaction.



Scheme 1-15. Vinylogous Mannich reaction catalyzed by phosphoric acid.

But silyl enolates require extra step to prepare and the silicon fragment is chopped off during the reaction, which makes this reaction not atom economy. So the direct vinylogous Mannich reactions are highly desired. In 2004 Terada group discovered 2-methoxyfuran was a good nucleophile for *Boc*-imines. The corresponding γ -aminoalkyl-substituted furans were obtained in excellent yields and *ee*'s (Scheme 1-16).⁴⁴ Since then, progress has been made in this research area, and the nucleophile scope was expanded from silyl enolates to other olefins, such as α, α -dicyanoalkenes ⁴⁵ and γ -butenolides ⁴⁶.



Scheme 1-16. Direct Vinylogous Mannich reaction catalyzed by phosphoric acid.

1.3.3 Asymmetric hydroamination

Hydroamination, the addition of an amine *N*-H bond to an unsaturated carbon–carbon bond, is an efficient method for amine synthesis.⁴⁷ Significant progresses have been made for catalytic inter- and intramolecular asymmetric hydroamination reactions. However, for most of these catalyst systems substrate

scope is very limited. For example, in many cases activated C=C bonds are required. There are no reports on intermolecular hydroamination of nonactivated alkenes with unprotected amines, and until very recently the first asymmetric intermolecular hydroamination of terminal,nonactivated alkenes with cyclic ureas was disclosed (Scheme 1-17), but tremendous amount of alkene was necessary.⁴⁸ Hartwig reported the hydroamination of anilines with vinyl arenes (Scheme 1-18) ⁴⁹ and reaction mechanism⁵⁰ was proposed (Scheme 1-19). Besides vinyl arenes, strained polycyclic olefins are another class of popular substrates for hydroamination. The iridium-SegPhos complex worked excellently for the asymmetric hydroamination of norbornadiene with anilines (Scheme 1-20).⁵¹



Scheme 1-17. Gold-catalyzed intermolecular hydroamination of inactivated alkenes.



Scheme 1-18. Palladium-catalyzed intermolecular hydroamination of aniline with styrene.



Scheme 1-19. Proposed mechanism for hydroamination of aniline with styrene.



Scheme 1-20. Iridium-catalyzed intermolecular hydroamination of aniline with

norbornadiene.

For the intramolecular asymmetric hydroamination reactions, rare earth metals were proved to be very reactive even for the nonactivated alkenes.⁵² The mechanism was proposed (Scheme 1-21).⁵³ Alkali metal lithium⁵⁴ and group 4 Metal zirconium⁵⁵ were also successfully applied in the intramolecular hydroamination.



Scheme 1-21. Proposed mechanism for intramolecular hydroamination.

1.3.4 Asymmetric aza-Morita–Baylis–Hillman reaction

The aza-Morita–Baylis–Hillman reaction, electron-deficient alkene reacting with acylimine in the presence of nucleophilic catalysts commonly tertiary amines and phosphines, is an atom economic reaction to afford α -methylene- β -aminocarbonyl products in good yields under mild conditions (Scheme 1-22).⁵⁶ Jacobsen reported highly enantioselective aza-Baylis--Hillman reactions (Scheme 1-23) catalyzed by chiral thiourea derivatives and presented a generally accepted mechanism (Scheme 1-24).⁵⁷ The products are densely functionalized and could undergo a variety of transformations.⁵⁷ Many chiral catalysts were used in aza-Morita– Baylis-Hillman reactions, such as cinchona-⁵⁸ and BINOL-derived⁵⁹ tertiary amines, and chiral phosphines⁶⁰ (Figure 1-6).



EWG=electron-withdrawing group

Scheme 1-22. Aza-Morita-Baylis-Hillman reaction.



Scheme 1-23. Thiourea-catalyzed aza-Morita-Baylis-Hillman reaction.



Scheme 1-24. Generally accepted mechanism of the aza-Baylis-Hillman reaction.


Figure 1-6. Chiral catalysts used in aza-Morita-Baylis-Hillman reactions.

1.3.5 Enantioselective C-H amination

Enantioselective C-H amination is an attractive methodology for chiral amine synthesis due to the availability of various C-H bonds. But progress in this research area is not much and most are intramolecular C-H aminations.⁶¹ The challenge in this research area is that the chiral catalysts should be able to support a reactive oxidant, and meanwhile distinguish two hydrogen atoms on a prochiral carbon center.

The first asymmetric intermolecular C-H amination was reported by Muller and coworkers using dirhodium(II) tetrakis [(*R*)-binaphthylphosphate], with moderate ee^{3} s.⁶² About 10 years later Muller group made a breakthrough in this field by introducing enantioenriched sulfoxamines as amine sources (Scheme 1-25).⁶³ High enantioselectivities were achieved from this approach. Blakey *et al.* utilized a new RuBr₂-pybox (pybox=pyridine bisoxazoline) catalyst and excellent

enantioselectivities were ontained under mild conditions for the C-H amination of sulfamate esters (Scheme 1-26).⁶⁴



Scheme 1-25. Sulfoxamines as amine source for C-H amination.



Scheme 1-26. RuBr₂-pybox catalyzed C-H amination.

1.4 Conclusion

To satisfy the increasing demanding of enantiopure chiral amines, more and more methods have been developed. Compared with others, catalytic asymmetric hydrogenation offers several advantages. The first is its atom efficiency and environmental benignity. It minimizes the generation of by-products and waste. Secondly its high reactivity and enantioselectivity meets the prerequisite of practical large scale production. The readily availability of substrates also makes asymmetric hydrogenation the desired method for chiral amine synthesis. But compared with the extremely high turn over numbers (>1,000,000) on asymmetric hydrogenation of olefins and ketones, very few imine reduction examples achieved comparable results. So the challenge is how to improve the reactivity of the catalyst to make the asymmetric hydrogenation more practical towards chiral amine synthesis.

References:

- 1. T. C. Nugent (Ed.), Chiral Amine Synthesis, Wiley-VCH, Weinheim, 2010.
- Compiled and Produced by the Njardarson Group (The University of Arizona): D. J. Mack, M. L. Weinrich, E. Vitaku, J. T. Njarðarson.
- (a) W. Tang, X. Zhang, *Chem. Rev.* 2003, 103, 3029. (b) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Soc. Rev.* 2012, 41, 4126.
- 4. W. S. Knowles, Angew. Chem. Int. Ed. 2002, 41, 1998.
- 5. (a) R. Noyori, T. Ohkuma, Angew. Chem. Int. Ed. 2001, 40, 40. (b) R. Noyori, Angew. Chem.Int. Ed. 2002, 41, 2008.
- 6. H.-U. Blaser, Adv. Synth. Catal. 2002, 344, 17.
- K. B. Hansen, Y. Hsiao, F. Xu, N. Rivera, A. Clausen, M. Kubryk, S. Krska, T. Rosner, B. Simmons, J. Balsells, N. Ikemoto, Y. Sun, F. Spindler, C. Malan, E. J. J. Grabowski, J. D. Armstrong, *J. Am. Chem. Soc.* 2009, 131, 8798.
- 8. T. Sturm, W. Weissensteiner, F. Spindler, Adv. Synth. Catal. 2003, 345, 160.
- 9. W. S. Knowles, M. J. Sabacky, Chem. Commun. 1968, 1445.
- 10. L. Hörner, H. Siegel, H. Büthe, Angew. Chem. Int. Ed. Engl. 1968, 7, 941.
- (a) H. B. Kagan, T. P. Dang, *Chem. Commun.* **1971**, 481. (b) H. B. Kagan, T. P. Dang, *J. Am. Chem. Soc.* **1972**, 94, 6429. (c) H. B. Kagan, N. Langlois, T. P. Dang, *J. Organomet. Chem.* **1975**, 90, 353.
- (a) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, O. J. Weinkauff, J. Am. Chem. Soc. 1977, 99, 5946. (b) W. S. Knowles, Acc. Chem. Res. 1983, 16, 106.
- A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, J. *Am. Chem. Soc.* **1980**, *102*, 7932.
- 14. (a) M. J. Burk, J. Am. Chem. Soc. 1991, 113, 8518. (b) M. J. Burk, J. E. Feaster, W. A. Nugent, R. L. Harlow, J. Am. Chem. Soc. 1993, 115, 10125. (c) M. J. Burk, Acc. Chem. Res. 2000, 33, 363.
- (a) A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, J. Am. Chem. Soc. 1994, 116, 4062. (b) H.-U. Blaser, W. Brieden, B. Pugin, F. Spindler, M. Studer, A. Togni, Top. Catal. 2002, 19, 3.
- 16. (a) G. Helmchen, A. Pfaltz, Acc. Chem. Res. 2000, 33, 336. (b) A. Pfaltz, W. J. Drury III, Proc. Natl. Acad. Sci. 2004, 101, 5723. (c) S. Bell, B. Wustenberg, S. Kaiser, F. Menges, T. Netscher, A. Pfaltz, Science 2006, 311, 642.
- (a) C. Claver, E. Fernandez, A. Gillon, K. Heslop, D. J. Hyett, A. Martorell, A. G. Orpen, P. G. Pringle, *Chem. Commun.* 2000, 961. (b) M. T. Reetz, G. Mehler, *Angew. Chem. Int. Ed.* 2000, *39*, 3889. (c) M. Van den Berg, A. J. Minnaard, E. P.Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* 2000, *122*, 11539.
- I. Ojima (Ed.), Handbook of Homogeneous Hydrogenation, Wiley-VCH, Hoboken, 2010.
- 19. H. B. Kagan, T.-P. Dang, J. Am. Chem. Soc. 1972, 94, 6429.
- 20. R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, T. Ohta, H. Takaya, *J. Am. Chem. Soc.* **1986**, *108*, 7117.

- 21. M. J. Burk, Y. M. Wang, J. R. Lee, J. Am. Chem. Soc. 1996, 118, 5142.
- 22. (a) G.-H. Hou, J.-H. Xie, L.-X. Wang, Q.-L. Zhou, J. Am. Chem. Soc. 2006, 128, 11774. (b) G.-H. Hou, J.-H. Xie, P.-C. Yan, Q.-L. Zhou, J. Am. Chem. Soc. 2009, 131, 1366.
- 23. Y. Hsiao, N. R. Rivera, T. Rosner, S. W. Krska, E. Njolito, F. Wang, Y. Sun, J. D. Armstrong III, E. J. J. Grabowski, R. D.Tillyer, F. Spindler, C. Malan, J. Am. Chem. Soc. 2004, 126, 9918.
- (a) A. M. Clausen, B. Dziadul, K. L. Cappuccio, M. Kaba, C. Starbuck, Y. Hsiao, T. M. Dowling, Org. Process Res. Dev. 2006, 10, 723. (b) K. B. Hansen, Y. Hsiao, F. Xu, N. Rivera, A. Clausen, M. Kubryk, S. Krska, T. Rosner, B. Simmons, J. Balsells, N. Ikemoto, Y. Sun, F. Spindler, C. Malan, E. J. J. Grabowski, J. D. III Armstrong, J. Am. Chem. Soc. 2009, 131, 8798.
- 25. G. Zhu, P. Cao, Q. Jiang, X. Zhang, J. Am. Chem. Soc. 1997, 119, 1799.
- 26. G. Zhu, X. Zhang, J. Org. Chem. 1998, 63, 3133.
- 27. Z. Zhang, G. Zhu, Q. Jiang, D. Xiao, X. Zhang, J. Org. Chem. 1999, 64, 1774.
- 28. D. Xiao, Z. Zhang, X. Zhang, Org. Lett. 1999, 1, 1679.
- 29. W. Li, Z. Zhang, D. Xiao, X. Zhang, J. Org. Chem. 2000, 65, 3489.
- 30. (a) W. Tang, X. Zhang, Angew. Chem. Int. Ed. 2002, 41, 1612. (b) W. Tang, X. Zhang, Org. Lett. 2002, 4, 4159. (c) W. Tang, S. Wu, X. Zhang, J. Am. Chem. Soc. 2003, 125, 9570. (d) Q. Dai, W. Yang, X. Zhang, Org. Lett. 2005, 7, 5343. (e) Q. Yang, W. Gao, J. Deng, X. Zhang, Tetrahedron Letters, 2006, 47, 821. (f) J. Chen, Q. Liu, W. Zhang, S. Spinella, A. Lei, X. Zhang, Org. Lett. 2008, 10, 3033. (g) J. Chen, W. Zhang, H. Geng, W. Li, G. Hou, A. Lei, X. Zhang, Angew. Chem. Int. Ed. 2009, 48, 800.
- 31. D. Liu, X. Zhang, Eur. J. Org. Chem. 2005, 646.
- (a) X. Zhang, K. Huang, G. Hou, B. Cao, X. Zhang, *Angew. Chem., Int. Ed.* 2010, 49, 6421. (b) K. Huang, X. Zhang, H. Geng, S. Li, X. Zhang, *ACS Catalysis* 2012, 2, 1343.
- 33. G. Hou, W. Li, M. Ma, X. Zhang, X. Zhang, J. Am. Chem. Soc. 2010, 132, 12844.
- 34. (a) A. B. Charette, in: Stereoselective Synthesis of a-Branched Amines by Nucleophilic Addition of Unstabilized Carbanions to Imines, (Ed.: T. C. Nugent), Wiley-VCH, Weinheim, 2010. (b) K. Yamada, K. Tomioka, Chem. Rev. 2008, 108, 2874. (c) T. Vilaivan, W. Bhanthumnavin, Y. Sritana-Anant, Curr.Org. Chem. 2005, 9, 1315.
- A. B. Charette, A. A. Boezio, A. Côte, E. Moreau, J. Pytkowicz, J.-N. Desrosiers, C. Legault, *Pure Appl. Chem.* 2005, 77, 1259.
- 36. (a) F. A. Davis, P. Zhou, B. C. Chen, *Chem. Soc. Rev.* **1998**, 27, 13. (b) J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984.
- 37. A. Alexakis, J. P. Tranchier, N. Lensen, P. Mangeney, J. Am. Chem. Soc. 1995, 117, 10767.
- 38. (a) G. C. Liu, D. A. Cogan, J. A. Ellman, J. Am. Chem. Soc. 1997, 119, 9913. (b)
 D. A. Cogan, G. C. Liu, J. Ellman, Tetrahedron, 1999, 55, 8883. (c) T. Mukade, D.
 R. Dragoli, J. A. Ellman, J. Comb. Chem. 2003, 5, 590. (d) T. E. Reynolds, M. S.
 Binkley, K. A. Scheidt, Org. Lett. 2008, 10, 5227.

- (a) S. E. Denmark, O. J.-C. Nicaise, *Comprehensive Asymmetric Catalysis* (Eds: E.N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer-Verlag, **1999**, p. 923. (b) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102.
- 40. (a) K. Fukui, T. Yonezawa, C. Nagata, H. Shingu, J. Chem. Phys. 1954, 22, 1433.
 (b) S. E. Denmark, J. R. Heemstra, G. L. Beutner, Angew. Chem. Int. Ed. 2005, 44, 4682.
- 41. S. H. Brandstadter, I. Ojima, Tetrahedron Lett. 1987, 28, 613.
- 42. S. F. Martin, O. D. Lopez, Tetrahedron Lett. 1999, 40, 8949.
- 43. D. S. Giera, M. Sickert, C. Schneider, Org. Lett. 2008, 10, 4259.
- 44. D. Uraguchi, K. Sorimachi, M. Terada, J. Am. Chem. Soc. 2004, 126, 11804.
- 45. (a) T.-Y. Liu, H.-L. Cui, J. Long, B.-J. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, J. Am. Chem. Soc. 2007, 129, 1878. (b) B. Niess, K. A. Jørgensen, Chem. Commun. 2007, 1620.
- 46. A. Yamaguchi, S. Matsunaga, M. Shibasaki, Org. Lett. 2008, 10, 2319.
- 47. (a) T. E. Muller, M. Beller, *Chem. Rev.* 1998, 98, 675. (b) T. E. Muller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* 2008, 108, 3795.
- 48. Z. Zhang, S. D. Lee, R. A. Widenhoefer, J. Am. Chem. Soc. 2009, 131, 5372.
- 49. M. Kawatsura, J. F. Hartwig, J. Am. Chem. Soc. 2000, 122, 9546.
- 50. U. Nettekoven, J. F. Hartwig, J. Am. Chem. Soc. 2002, 124, 1166.
- 51. J. Zhou, J. F. Hartwig, J. Am. Chem. Soc. 2008, 130, 12220.
- 52. S. Hong, T. J. Marks, Acc. Chem. Res. 2004, 37, 673.
- 53. A. Motta, G. Lanza, I. L. Fragala, T. J. Marks, Organometallics, 2004, 23, 4097.
- 54. (a) J. Seayad, A. Tillack, C. G. Hartung, M. Beller, *Adv. Synth. Catal.* 2002, 344, 795. (b) P. Horrillo Martinez, K. C. Hultzsch, F. Hampel, *Chem. Commun.* 2006, 2221.
- 55. (a) F. Pohlki, S. Doye, *Chem. Soc. Rev.* **2003**, *32*, 104. (b) R. Severin, S. Doye, *Chem. Soc. Rev.* **2007**, *36*, 1407.
- 56. (a) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* 2003, 103, 811. (b) D. Basavaiah, K. V. Rao, R. J. Reddy, *Chem. Soc. Rev.* 2007, 36, 1581.
- 57. I. T. Raheem, E. N. Jacobsen, Adv. Synth. Catal. 2005, 347, 1701.
- 58. (a) M. Shi, Y.-M. Xu, Angew. Chem. Int. Ed. 2002, 41, 4507. (b) M. Shi, Y.-M. Xu, Y.-L. Shi, Chem. Eur. J. 2005, 11, 1794. (b) M. Shi, M.-J. Qi, X.-G. Liu, Chem. Commun. 2008, 6025.
- 59. K. Matsui, S. Takizawa, H. Sasai, J. Am. Chem. Soc. 2005, 127, 3680.
- 60. (a) M. Shi, L.-H. Chen, *Chem. Commun.* 2003, 1310. (b) M. Shi, L.-H. Chen, C.-Q. Li, *J. Am.Chem. Soc.* 2005, *127*, 3790. (c) M. Shi, G.-N. Ma, J. Gao, *J. Org. Chem.* 2007, 72, 9779. (d) Y.-L. Shi, M. Shi, *Adv. Synth. Catal.* 2007, *349*, 2129.
- 61. A. R. Dick, M. S. Sanford, Tetrahedron, 2006, 62, 2439.
- 62. I. Nageli, C. Baud, G. Bernardinelli, Y. Jacquier, M. Moran, P. Muller, *Helv. Chim. Acta*, **1997**, *80*, 1087.
- 63. (a) C. Liang, F. Robert-Peillard, C. Fruit, P. Muller, R. H. Dodd, P. Dauban, *Angew. Chem., Int. Ed.* 2006, 45, 4641. (b) C. Liang, F. Collet, F. Robert-Peillard, P. Muller, R. H. Dodd, P. Dauban, *J. Am. Chem. Soc.* 2008, 130, 343.
- 64. E. Milczek, N. Boudet, S. Blakey, Angew. Chem., Int. Ed. 2008, 47, 6825.

Chapter 2

Iridium-Catalyzed Enantioselective Hydrogenation of Cyclic Imines

2.1 Introduction and background

Chiral cyclic amines are ubiquitous moieties in many natural products,¹ and in pharmaceutical drugs and drug candidates,² for example, nicotine,³ BMS-394136,⁴ LY-394681,⁵ (+)-cryptostyline II,⁶ (+)-cryptostyline III,⁶ and solifenacin⁷ (Figure 2-1). The catalytic asymmetric hydrogenation of imines is a powerful method to afford the amine products enantiomerically due to its high efficiency, low catalyst loading and atom economy.

In contrast to the significant progress made in the catalytic asymmetric hydrogenation of ketones and olefins over the last few decades, the highly enantioselective and efficient reduction of imines remains a challenge in modern synthesis. Some reasons are as follows: (1) Electron-rich imines are poor hydrogenation substrates; (2) Certain imines are not stable as they are sensitive to moisture and hydrolyze; (3) The E/Z isomers often lead to opposite enantiomers and thus reduce the enantioselectivity; (4) Unfunctionalized imines coordinate to the transition metal center in η^1 or η^2 fashion, which is configurationally unstable, thus

makes the enantiocontrol difficult; (5) The amine products inhibit the reactivity of metal center and thus lowers the turn over numbers.⁸



Figure 2-1. Structures of some chiral cyclic amines.



Figure 2-2. Imine substrates for asymmetric hydrogenation.

The common imine substrates for asymmetric hydrogenation are shown as follows (Figure 2-2). In 1975, Scorrano and co-workers reported the first example of catalytic enantioselective hydrogenation of *N*-(α -methylbenzylidene)benzylamine using a rhodium-DIOP complex, although only 22% *ee* was obtained.⁹ One of the early successful examples was the industrial production of herbicide (*S*)-Metolachlor using iridium-Xyliphos catalyst with turn over number of 1,000,000 (Scheme 2-1). During the past decades, Ti, Rh, Ru, and Ir complexes, have been investigated in the asymmetric hydrogenation of imines.⁸ Among those systems, chiral Ir complexes have shown more potential in the imine reduction.



Scheme 2-1. Industrial production of herbicide (S)-Metolachlor.

The iridium-TangPhos system was quite efficient for the N-aryl imine reduction and achieved highest turn over number at that time.¹⁰ The ferrocene-based diphosphines (Figure 2-3) are the most promising ligands in the enantioselective

N ⁻ R² ∥	0.1 mol % {lr[(F HN ^{-R²}					
R ¹	H ₂ (5 atm),	H ₂ (5 atm), CH ₂ Cl ₂ , r. t., 12h, > 99% conv.					
entry	R ₁	R ₂	product	ee %(Conf.)			
1	C_6H_5	C_6H_5	2a	93 (<i>R</i>)			
2	4-Me-C ₆ H ₄	C_6H_5	2b	90 (+)			
3	4-MeO-C ₆ H ₄	C_6H_5	2c	90 (+)			
4	4-F-C ₆ H ₄	C_6H_5	2d	93 (-)			
5	4-CI-C ₆ H ₄	C_6H_5	2e	92 (+)			
6	4-Br-C ₆ H ₄	C_6H_5	2f	92 (-)			
7	3-CI-C ₆ H ₄	C_6H_5	2g	93 (-)			
8	2-naphthyl	C_6H_5	2h	98 (+)			
9	C_6H_5	4-Me-C ₆ H ₄	2i	92 (+)			
10	C_6H_5	4-MeO-C ₆ H ₄	2j	93 (-)			
11	C_6H_5	$4-F-C_6H_4$	2k	89 (-)			
12	C_6H_5	4-CI-C ₆ H ₄	21	90 (+)			

Table 2-1. Asymmetric hydrogenation of N-aryl imine using iridium-TangPhos.

 R^2

hydrogenation of imines. Blaser et al. developed a series of JosiPhos-type ligands.¹¹ From this systematic study of the electronic and steric effects of the ligands on imine hydrogenations they found substitutes on the ferrocene backbone of the ligands affected the reaction greatly. Different ligands could accommodate different imine substrates. In recent years a breakthrough has been made by Zhang's group for the asymmetric hydrogenation of N-H imine to directly provide the chiral amines (Table 2-2).12



Figure 2-3. Ferrocene-based chiral ligands.

Table 2-2. Asymmetric hydrogenation of N-H imines using iridium-f-Binaphane catalyst.



At the same time, there have been few reports on enantioselective hydrogenation of cyclic imines than those on acyclic imines. The chiral titanocene developed by Buchwald *et al.* showed good reactivity and high enantioselectivity¹³ for both cyclic imines and acyclic imines. Highly enantioselective cationic Rh(I) catalysts were applied by Xiao *et al.* in asymmetric hydrogenation of imines to afford tetrahydroisoquinolines and tetrahydro- β -carbolines.¹⁴ Catalyzed by [RuCl₂((*S*)-MeO-BIPHEP)((*S,S*)-ANDEN)] system, the hydrogenation of 2,3,3-trimethylindolenine was achieved up to 88% *ee.*¹⁵

2.2 Iridium-catalyzed asymmetric hydrogenation mechanism

There are some mechanism for iridium-catalyzed imine reduction were proposed (Scheme 2-2).¹⁶ Most of them are based on the Ir(I)/Ir(III) cycle. From the computation study of Hopmann and Bayer, they proposed a mechanism for Ir-PHOX-mediated asymmetric hydrogenation of imine in which the imine substrate is not binding to the metal cental when the H₂ is added (Scheme 2-3).^{16a} But generally accepted mechanism involves the Ir-N(of imine) coordination for the hydride addition step (Scheme 2-4).^{16d} As for chiral diphosphine ligands, the mechanism is shown in Scheme 2-5. If oxidant additive like I₂ was added, then the mechanistic cycle will solely be based Ir(III) transformation (Scheme 2-6).¹⁷ The formation of dimeric and trimeric Ir-H clusters results in the deactivation of the catalyst (Scheme 2-7).¹⁸



Scheme 2-2. Iridium-catalyzed imine reduction mechanism.



Scheme 2-3. Iridium-catalyzed imine reduction mechanism proposed by Hopmann *et al*.



Scheme 2-4. Generally accepted mechanism for Ir-catalyzed hydrogenation of imine.



Scheme 2-5. Mechanism for Ir-diphosphine-catalyzed hydrogenation of imine.



Scheme 2-6. Mechanism for Ir-catalyzed hydrogenation of imine based on Ir(III).



Scheme 2-7. Formation of the dimeric and trimeric Ir-H clusters.

2.3 Asymmetric hydrogenation of 2-aryl(alkyl)pyrrolines

2.3.1 Background

Chiral 2-aryl(alkyl)-*N*-cyclic amines are one class of important compound for pharmaceutical drugs and drug candidates exhibiting bioactivity.⁸ Some examples are showing in Figure 2-1. There were some reports on the asymmetric hydrogenation of the corresponding imines.^{13,19} But more efficient and better enantioselective catalytic catalysts are required for this transformation. We decided to focus on Ir catalyst systems based on our studies of asymmetric hydrogenation of N–H imine using Ir–f-Binaphane catalyst¹² and other reports on Ir(I)²⁰ and Ir(III)²¹ complexes with chiral phosphines in the asymmetric hydrogenation of cyclic imines. We envisioned that the ferrocene-based electron-donating bisphosphine f-Binaphane could possibly minimize the inhibitory effect from the amine product²¹ and the embedded axial chirality in the ligand could facilitate the enantiocontrol.

2.3.2 Results and discussion

With 2-phenyl-1-pyrroline **1a** as the standard substrate, initially several transition metal precursors with chiral ligands (Figure 2-4) were explored as hydrogenation catalysts. Results are summarized in Table 2-3 (entries 1–3). Ir catalyst prepared *in situ* from [Ir(COD)Cl]₂ precursor and f-Binaphane ligand developed by our group,²²

gave 85% *ee* with good conversion (Table 2-3, entry 1). The reaction was complete with the addition of 10 mol% of I_2 , but *ee* dropes significantly. f-Binaphane is featured with high electron donation and a flexible backbone allowing to accommodate sterically demanding cyclic imines to the Ir center. Subsequently the



Figure 2-4. Structures of chiral ligands for initial screening.

1 mol % catalyst							
	Ph	H ₂ , Solvent, I.	" Ph´ N H 2a				
Entry	Catalyst	Solvent	Additive	Conv. [%] ^[b,c]	<i>ee</i> [%] (Config.) ^[b,c]		
1	[Ir(COD)Cl] ₂ +f-Bianaphane	THF	-	65	85(+)		
2	[Ir(COD) ₂]BARF+f-Binaphane	THF	10 mol % I ₂	>99	61(+)		
3	[Ir(COD) ₂]BARF+f-Binaphane	THF	-	5	30(+)		
4	[RuCl ₂ -(<i>S</i>)-C3*](<i>S</i> , <i>S</i>)-DPEN	Toluene	^t BuOK 10%	n.r.	n.d.		
5	[RuCl ₂ -(<i>S</i>)-C3*](<i>S</i> , <i>S</i>)-DACH	Toluene	^t BuOK 10%	2	n.d.		
6	[Ir(COD)Cl] ₂ +TangPhos	THF	-	1	n.d.		
7	[Ir(COD)Cl] ₂ +DuanPhos	THF	-	12	5		
8	[Ir(COD)Cl] ₂ +Binapine	THF		5	44		
9	[Ir(COD)Tang]BArF	THF	10 mol % I ₂	83	56		
10	[Ir(COD)Duan]BArF	THF	10 mol % I ₂	78	51		
11	[Ir(COD)Cl] ₂ +f-Bianaphane	THF	10 mol % I ₂	>99	57(+)		

Table 2-3. Asymmetric hydrogenation of 2-phenyl-1-pyrroline by Ir–f-Binaphane.^[a]

^[a] The reactions were carried out with 0.2 mmol of substrate in 2.4 mL of solvent in the presence of 1 mol% of *in situ* prepared Ir catalyst under an initial hydrogen pressure of 50 atm for 25 h.

^[b] Conversions and enantiomeric excesses were determined by chiral GC after the amine products were converted to the corresponding trifluoroacetamides.

^[c] n.r.= no reaction. n.d.= not determined.

	1 mol % [li	\square	
	Ph N 50 atr	n H ₂ , solvent, r. t.	Ph [*] N H
	1a		2a
Entry	Solvent	Conv. [%] ^[b,c]	<i>ee</i> [%] (Config.) ^[b,c]
1	THF	65	85(+)
2	Toluene	53	85(+)
3	EtOAc	61	85(+)
4	МеОН	33	31(+)
5	CH ₂ Cl ₂	n.r.	n.d.
6	THF / MeOH 1:1	1	n.d.
7	THF / EtOAc 1:1	12	5(+)
8	CH ₂ Cl ₂ / MeOH 1:3	5	44(+)
9	$EtOAc / CH_2Cl_2 2:1$	89	88(+)
10	EtOAc / CH ₂ Cl ₂ 1:2	62	87(+)
11	EtOAc / CH_2Cl_2 4:1	69	87(+)
12 ^[d]	EtOAc / CH ₂ Cl ₂ 2:1	>99	84(+)

Table 2-4. Solvent effects on asymmetric hydrogenation of 2-phenyl-1-pyrroline.^[a]

^[a] The reactions were carried out with 0.2 mmol of substrate in 2.4 mL of solvent in the presence of 1 mol% of *in situ* prepared Ir catalyst under an initial hydrogen pressure of 50 atm for 25 h.

^[b] Conversions and enantiomeric excesses were determined by chiral GC after the amine products were converted to the corresponding trifluoroacetamides.

^[b] Reaction temperature was 50 °C.

effect of solvents was investigated (Table 2-4). The highest enantioselectivity was achieved from the combination of ethyl acetate / dichloromethane with a ratio of 2:1

(Table 2-4, entry 9). Interestingly no reaction occurred when dichloromethane itself was used as a solvent. When reaction temperature was increased to 50 °C, complete conversion was achieved with slightly lower ee (Table 2-4, entry 12). The additive effect was also studied (Table 2-5).

	1 mol % [I	r(COD)Cl] ₂ /f-Binaphane	\square
	Ph N 50 atm H ₂	, EtOAc/CH ₂ Cl ₂ 2:1, r. t.	Ph N H
	1a		2a
Entry	Additive	Conv. [%] ^[b]	<i>ee</i> [%] (Config.) ^[b]
1	-	65	85(+)
2	2 mol % I ₂	>99	68(+)
3	20 mol % AcOH	84	88(+)
4 ^[c]	HI	>99	83(+)
5 ^[d]	HI	>99	73(+)
6 ^[e]	HI	75	72(+)

Table 2-5. Additive effects on asymmetric hydrogenation of 2-phenyl-1-pyrroline.^[a]

[a] The reactions were carried out with 0.2 mmol of substrate in 2.4 mL of solvent in the presence of 1 mol% of in situ prepared Ir catalyst under an initial hydrogen pressure of 50 atm for 25 h.

^[b] Conversions and enantiomeric excesses were determined by chiral GC after the amine products were converted to the corresponding trifluoroacetamides.

[C] HI was used for preparation of the iodine-bridged dimeric iridium complex $[Ir(H)[(S,S)-f-Binaphane]_2(\mu-I)_3]^+I^-$ to enhance the catalytic reactivity according to reference. $[Ir(H)[(S,S)-f-Binaphane]_2(\mu-I)_3]^+I^-$ loading is 1 mol%. S / C = 100.

[e] $[Ir(H)[(S,S)-f-Binaphane]_2(\mu-I)_3]^{\dagger}I^{-}$ loading is 0.1 mol%. S / C = 1000. Reaction temperature was 50 °C.

[f] $[Ir(H)[(S,S)-f-Binaphane]_2(\mu-I)_3]^{\dagger}I^{-}$ loading is 0.01 mol%. S / C = 10000. Reaction temperature was 50 °C.

 \frown

The reaction completed with a full conversion in the presence of 2 mol% of I₂, but the enantiomeric excess dropped dramatically (Table 2-5, entry 2). Inspired by Genet and coworkers' work,^{16c} we prepared the iodine-bridged dimeric iridium complex $[Ir(H)[(S,S)-(f)-Binaphane]_2(\mu-I)_3]^+\Gamma$. As expected, this complex was more reactive and yielded 83% *ee* (Table 2-5, entry 4); using 0.1 mol% of Ir catalyst, the reaction still proceeded smoothly but offered lower *ee* (Table 2-5, entry 5); when the catalyst loading was further decreased to 0.01 mol%, 75% conversion and 72% *ee* were obtained (Table 2-5, entry 6). The enhanced catalytic reactivity of this iodine-bridged dimeric iridium complex was assumed to be due to the cleavage of Ir–N bond of the hydrogenation intermediate by HI.^{19c}



Figure 2-5. Structures of chiral ligands.

In a control study, $[Ir(COD)Cl]_2$ with other chiral phosphines (Figure 2-5) were investigated (Table 2-6). None of the ligands offered higher enantioselectivity or conversion compared with f-Binaphane. Two monodentate ligands (*R*)-MOP and (*R*)-MonoPhos were tested and yielded poor conversions and enantioselectivities

Table 2-6. Screening of chiral phosphine ligands.^[a]

$$\frac{1 \mod \% [Ir(COD)CI]_2 / Iigand}{50 \operatorname{atm} H_2, \operatorname{EtOAc} / \operatorname{CH}_2\operatorname{CI}_2, r.t.} \xrightarrow{Ph} \overset{*}{\underset{H}{\overset{N}{\overset{N}{\overset{}}}}$$

Entry	Ligand	Conv. [%] ^[b]	ee [%](Config.) ^[b]
1	<i>(R)</i> -MOP	10	4 (+)
2	(R)-MonoPhos	13	9 (-)
3	(R,S)-JosiPhos	20	13 (+)
4	(R,R)-Me-DuPhos	46	2 (+)
5	(S)-C ₃ -TunePhos	58	69 (+)
6	(R)-BINAP	64	74 (+)
7	(R)-SegPhos	63	78 (+)
8	(S,S)-f-Binaphane	89	88 (+)

^[a] The reactions were carried out with 0.2 mmol of substrate in 2.4 mL of solvent in the presence of 1 mol% of *in situ* prepared Ir catalyst under an initial hydrogen pressure of 50 atm for 25 h.

^[b] Conversions and enantiomeric excesses were determined by chiral GC after the amine products were converted to the corresponding trifluoroacetamides.



Table 2-7. Asymmetric hydrogenation of cyclic imines by Ir-f-Binaphane.^[a]

-	Substrate	-			ee [%](Config.)
Entry		R	n	Conv. [%] ^[0]	[b]
1	1a	C ₆ H ₅	1	>99	85 (+)
2	1b	$4-Me-C_6H_4$	1	>99	84 (+)
3	1c	4-MeO-C ₆ H ₄	1	>99	84 (+)
4	1d	4-F-C ₆ H ₄	1	>99	85 (+)
5	1e	4 - Cl - C_6H_4	1	>99	86 (+)
6	1f	4-Br-C ₆ H ₄	1	>99	84 (+)
7	1g	3-Cl-C ₆ H ₄	1	99	80 (+)
8	1h	3-Me-C ₆ H ₄	1	98	66 (+)
9	1i	3-MeO-C ₆ H ₄	1	96	74 (+)
10	1j	2-MeO-C ₆ H ₄	1	98	50 (+)
11	1k	<i>n</i> -Bu	1	>99	58 (+)
12	11	C_6H_5	2	99	89 (+)
13	1m	C_6H_5	3	99	75 (+)

^[a] The reactions were carried out with 0.2 mmol of substrate in 2.4 mL of solvent in the presence of 1 mol% of *in situ* prepared Ir catalyst under an initial hydrogen pressure of 50 atm for 25 h at 50 °C.

^[b] Conversions and enantiomeric excesses were determined by chiral GC after the products were converted to the corresponding trifluoroacetamides.

(Table 2-6, entries 1 and 2). Interestingly BINAP (Table 2-6, entry 6) and its analogues such as SegPhos (Table 2-6, entry 7) and C₃-TunePhos (Table 2-6, entry 8) showed good *ee*'s.

To explore the applicability of this Ir–f-Binaphane catalytic system, a range of substituted aryl pyrrolines, an alkyl pyrroline, 2,3,4,5-tetrahydro-6-phenylpyridine and 2-Phenyl-4,5,6,7-tetrahydro-3H-azepine were prepared and hydrogenated under the optimal conditions. The results are summarized in Table 2-7. It is evident that the electronicproperties of the substituents at para position of phenyl ring have no obvious effects on conversion and enantioselectivity (Table 2-7, entries 1–6). But when the substituents go to meta and ortho position, the enantioselectivity varies dramatically with different substituted groups (Table 2-7, entries 7–10). Increasing the ring size of the cyclic imine from 5-membered to 6-membered, the enantiomeric excess was slightly improved (Table 2-7, entries 1 and 12); when it was 7-membered, the enantioselectivity dropped to 75% (Table 2-7, entry 13). This catalytic system does not work well for alkyl substituted pyrroline and only 58% *ee* was achieved with one substrate (Table 2-7, entry 10).

2.3.3 Conclusion

In conclusion, an Ir–(*S*,*S*)-f-Binaphane catalyst has been applied in asymmetric hydrogenation of a series of cyclic imines. With this system, readily prepared from $[Ir(COD)Cl]_2$ and air-stable (*S*,*S*)-f-Binaphane ligand, high reactivity and good enantioselectivity were achieved. Using HI as additive, high turnover number (> 5000) was achieved. This highly reactive catalytic system provides us an efficient approach for the synthesis of chiral cyclic amines.

2.4 Asymmetric hydrogenation of 1-alkyl/aryl-3,4-dihydroisoquinolines

2.4.1 Background

Tetrahydroisoquinolines are an important class of alkaloids dis-playing high bioactivities.²³ They are present in numerous natural products, and in pharmaceutical drugs and drug candidates, for example, (+)-cryptostyline II, (+)-cryptostyline III, and solifenacin (Figure 2-1). Among those various synthetic methods developed in recent decades to afford enantiomerically pure tetrahydroisoquinolines,^{23,24} catalytic asymmetric hydrogenation of corresponding imines shows most promising as a highly efficient and straightforward approach.²⁵

During the past two decades, a number of catalytic systems for asymmetric hydrogenation²⁶ and asymmetric transfer hydrogenation²⁷ of this class of imines have been invented. With the chiral titanocene developed by Buchwald et al., 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline was hydrogenated at 98% ee.^{26a} Initiated by Noyori and co-workers, the Ru(II)-TsDPEN complex showed high enantioselectivity on transfer hydrogenation of 3,4-dihydroisoqui-nolines.^{27a} Since then, intense research has been focused on this system and modifications have taken place on all components of this catalytic complex, the diamine ligand, the transition metal center, the coordinating-arene, and the counterion.^{26h,27b-27i} Although these titanocene Ru/Rh-DPEN and systems addressed the reduction of 1-alkyl-3,4-dihydroisoquinolines effectively, the asymmetric hydro-genation leading to enantiomerically pure 1-aryl-tetrahydro-isoquinolines remains a challenge, probably due to the relatively rigid and space demanding spatial features of these imines. For example, there is no report on asymmetric hydrogenation of 1-phenyl-3,4-dihydroisoquinoline, which leads to a pharmaceutical drug, solifenacin (Figure 2-1), and the industrial production of this particular tetrahydroisoquinoline depends on optical resolution of the racemic mixture using tartaric acid (Scheme 2-8).²⁸



Scheme 2-8. Industrial production of solifenacin.

2.4.2 Results and discussion

Herein, we chose 1-phenyl-3,4-dihydroisoquinoline **3a** as the standard substrate for asymmetric hydrogenation with the iridium-f-Binaphane system used in the hydrogenation of 2-phenyl-1-pyrroline (Table 2-8). Initially we tried two iridium precursor along with f-Binaphane. The neutral [Ir(cod)Cl]₂ (cod=1,5-cycloocta-diene) yielded better conversion yet with a limited *ee* (Table 2-8, entries 1 and 2). From the solvents screening (Table 2-8, entries 3–7), CH₂Cl₂ afforded the best enantioselectivity and a good conversion. With the addition of 10 mol% of I₂,^{29a} enantiomeric excess was enhanced to 88% and a full conversion was achieved (Table 2-8, entry 8). When the amount of I₂ was reduced to 1 mol%, the *ee* value dropped to 81% (Table 2-8, entry 9). Other common additives,²⁹ such as potassium carbonate, triethyl amine, phthylamide and trifluoroacetic acid were also investigated and proved

Table 2-8. Asymmetric hydrogenation of 1-phenyl-3,4-dihydroisoquinoline by Ir–f-Binaphane.^[a]



Entry	Ir precursor	Ligand	Solvent	Additive	Conv. [%] ^[b]	<i>ee</i> [%] ^[b]
1	Ir(COD) ₂ BF ₄	f-Binaphane	EtOAc/CH ₂ Cl ₂ 1:1	-	30	22
2	[Ir(COD)Cl] ₂	f-Binaphane	EtOAc/CH ₂ Cl ₂ 1:1	-	52	23
3	[Ir(COD)Cl] ₂	f-Binaphane	EtOAc	-	98	32
4	[Ir(COD)Cl] ₂	f-Binaphane	CH_2Cl_2	-	86	46
5	[Ir(COD)Cl] ₂	f-Binaphane	THF	-	99	22
6	[Ir(COD)Cl] ₂	f-Binaphane	toluene	-	84	20
7	[Ir(COD)Cl] ₂	f-Binaphane	MeOH/CH ₂ Cl ₂ 6:1	-	11	35
8	[Ir(COD)Cl] ₂	f-Binaphane	CH_2Cl_2	10 mol % I ₂	>99	88
9	[Ir(COD)Cl] ₂	f-Binaphane	CH_2Cl_2	1 mol % I ₂	>99	81
10	[Ir(COD)Cl] ₂	TangPhos	CH_2Cl_2	10 mol % I ₂	70	34
11	[Ir(COD)Cl] ₂	DuanPhos	CH_2Cl_2	10 mol % I ₂	<5	-
12	[Ir(COD)Cl] ₂	C ₃ *-TunePhos	CH_2Cl_2	10 mol % I ₂	<5	-
13 ^[c,d]	[Ir(COD)Cl] ₂	f-Binaphane	CH_2Cl_2	I_2/HI	>99	95
14 ^[c,e]	[Ir(COD)Cl] ₂	f-Binaphane	CH ₂ Cl ₂	I_2/HI	>99	95
15 ^[c,f]	[Ir(COD)Cl] ₂	f-Binaphane	CH_2Cl_2	I_2/HI	93	93

[a] Reaction conditions: [Ir] / ligand / substrate=1:1:100, ligand / metal 1:1, 50 atm of

H₂, rt, 24 h.

[b] Conversions and enantiomeric excesses were determined by chiral HPLC after the amine products were converted to the corresponding acetamides.

[c] HI was used for preparation of the iodine-bridged dimeric iridium complex $[{Ir(H)[(S,S)-(f)-Binaphane]}_2(\mu-I)_3]^+I^- A$ according to references.

[d] Complex **A** loading is 0.5 mol%. [e] Complex **A** loading is 0.05 mol%. [f] Complex **A** loading is 0.005 mol%.

to have no positive effect on this hydrogenation. In a control study, a brief screening of other diphosphines was carried out. As expected, none of these ligands yielded comparable results as f-Binaphane (Table 2-8, entries 10–12). The iodine-bridged dimeric iridium complexes, initially reported by Genet and coworkers,^{19b} have shown excellent reactivity in our previous research on asymmetric hydrogenation of cyclic imines. So complex [{Ir(H)[(*S*,*S*)-(f)-Binaphane]} $_2(\mu$ -I)₃]⁺T **A** was also applied in our study. To our delight, the enantiomeric excess was further improved to 95% with a complete conversion (Table 2-8, entry 13). Using 0.05 mol% of this Ir catalyst, the reaction still preceded smoothly without compromising the enantioselectivity; when the catalyst loading was further decreased to 0.005 mol%, a slightly lower conversion and *ee* were obtained (Table 2-8, entries 14 and 15).



Table2-9.Asymmetrichydrogenationof3,4-dihydroisoquinolinesIr-f-Binaphane.[a]

R ²	N CH ₂ C R ³ r.t. 10	$\begin{array}{c} x \ A \ 0.05 \ \text{mol}\% \\ \hline I_2, 50 \ \text{atm} \ H_2, \\ 0 \ \text{mol}\% \ I_2 \\ \end{array} \\ R^2 \\ 4 \end{array}$	NH Y* R ³	Completion of the second secon	
Entry	$R^1 \& R^2$	R ³	Product	Conv. [%] ^[b]	<i>ee</i> [%] (Config.) ^[b]
1	Н (За)	C_6H_5	4 a	>99	95 (<i>S</i>)
2	Н (3b)	ⁱ Pr	4 b	>99	96 (-)
3	H (3c)	Су	4c	>99	95 (-)
4	H (3d)	4-Me-C ₆ H ₄	4d	>99	94 (+)
5	Н (3e)	4 - Cl - C_6H_4	4 e	>99	96 (<i>S</i>)

		<u> </u>			
6	H (3f)	4-MeO-C ₆ H ₄	4 f	>99	95 (<i>S</i>)
7	Н (3g)	$4-CF_3-C_6H_4$	4g	>99	97 (+)
8	H (3h)	3-Me-C ₆ H ₄	4h	>99	95 (+)
9	H (3i)	3-Cl-C ₆ H ₄	4 i	>99	98 (+)
10 ^[c]	H (3j)	2-Me-C ₆ H ₄	4j	98	79 (+)
11 ^[c]	H (3k)	2-MeO-C ₆ H ₄	4k	>99	98 (-)
12	H (3l)	2-Furoyl	41	>99	96 (+)
13	OMe (3m)	C ₆ H ₅	4m	>99	97 (<i>S</i>)
14	OMe (3n)	ⁱ Pr	4n	>99	95 (<i>S</i>)
15	OMe (30)	3,4-(MeO) ₂ -C ₆ H ₃	40	99	>99 (<i>S</i>)
16	OMe (3p)	3,4,5-(MeO) ₃ -C ₆ H ₂	4 p	99	>99 (<i>S</i>)

[a] Reaction conditions: complex **A** / I_2 / substrate=0.05:10:100, 50 atm of H_2 , rt, 24 h.

by

[b] Conversions and enantiomeric excesses were determined by chiral HPLC and GC after the products were converted to the corresponding acetamides. The absolute configuration of product is assigned by comparison of rotation sign with literature data.
[c] Complex A / substrate=0.25:100.

To explore the scope and limitations of this Ir-f-Binaphane catalytic system, a range of 1-substituted 3,4-dihydroisoquinoline imines (3a-3p) were synthesized and hydrogenated under the optimized conditions. The results are summarized in Table 2. This iridium complex reduced both 1-alkyl- (entries 2, 3 and 14) and 1-aryl-3,4-dihydroisoquinolines effectively with excellent enantioselectivities. As for 1-aryl-3,4-dihydroisoquinoline imines, whether the substituents are at para (3d–3g) or meta (3h-3i) position of the phenyl ring, all substrates afforded corresponding tetrahydroisoquinoline alkaloids with high enantioselectivities (ee values range from 94% to 99%), regardless of the electronic properties of the substituents; interestingly, when the imines bear a 1-ortho substituted phenyl ring (**3j** and **3k**), the hydrogenation results vary dramatically, and a higher catalyst loading was required (Table 2-9, entries 10 and 11). The high ee value for 1-(2'-OMe-C₆H₄) imine is probably attributed to the coordination effect of the oxygen to the transition metal center, while the poor result for 1-(2'-Me-C₆H₄) imine stems from its steric hindrance. This catalytic system also worked quite well for 1-heteroaromatic imine 31, yielding 96% ee with a full conversion (Table 2-9, entry 12). It is worth to mention that both enantiomerically pure (S)-(-)-norcryptostyline II 40 and (S)-(-)-norcryptostyline III 4p were obtained with more than 99% of ee (Table 2-9, entries 15 and 16).

2.4.3 Conclusion

In summary, the highly effective iodine-bridged dimeric $[{Ir(H)[(S,S)-(f)-Binaphane]}_2(\mu-I)_3]^+\Gamma$ complex has been applied in asymmetric hydrogenation of a wide range of 3,4-dihydro-isoquinolines with excellent enantioselectivities and high turnover numbers (up to 10,000). The using of I₂ as additive enhanced the performance of this catalyst. This catalytic system offers an efficient access to various enantiomerically pure tetrahydroisoquinoline alkaloids, including the substructure of the pharmaceutical drug of solifenacin. Further applications of this complex on asymmetric hydrogenation of 3,4-dihydroquinolines and other cyclic imines are in progress.

2.5 Experimental Section

2.5.1 General Remarks.

All reactions were performed in the nitrogen-filled glovebox or under nitrogen using standard Schlenk techniques unless otherwise noted. Column chromatography was performed using Sorbent silica gel 60 (230 – 450 mesh). ¹H NMR, and ¹³C NMR spectral data were obtaineded from Bruker 400 MHz spectrometers. Chemical shifts are reported in ppm. Enantiomeric excess values were determined by chiral HPLC on an Agilent 1200 Series instrument or chiral GC on Agilent 7890 GC equipment. All new products were further characterized by HRMS. A positive ion mass spectrum of sample was acquired on a Micromass 70-VSE mass spectrometer with an electron ionization source.

2.5.2 General procedure for synthesis of cyclic imines 1.

Cyclic imines were synthesized according to modified literature method.³⁰ To a solution of 2.80 g of 1-(trimethylsilyl)-2-pyrrolidinone or 1-(trimethylsilyl)-2-piperidinone (0.018 mol) in anhydrous THF (15 mL) was added arylmagnesium bromide or alkyl lithium reagents (0.022 mol in THF). Then the reaction was heated to reflux for 3 h, quenched with aq. NH₄Cl solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, and

concentrated under vacuum. The crude product was purified with column chromatography (EtOAc / Hex) or distillation to yield desired product (yield: 25 – 92%).

2-phenyl-1-pyrroline (1a):³² light yellow solid, 48% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.77 (m, 2H), 7.34 (m, 2H), 7.19 (s, 1H), 4.00(m, 2H), 2.88 (m, 2H), 1.97 (m, 2H).

2-(4'-Me-phenyl)-1-pyrroline (**1b**):³² light yellow solid, 55% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.72 (m, 2H), 7.18 (m, 2H), 4.04 (m, 2H), 2.90 (m, 2H), 2.36(s, 3H), 2.00 (m, 2H).

2-(4'-OMe-phenyl)-1-pyrroline (**1c**):³² light yellow solid, 60% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, *J*=8 Hz, 2H), 6.92 (m, *J*=8 Hz, 2H), 4.05 (m, 2H), 3.82 (s, 3H), 2.90 (m, 2H), 2.00 (m, 2H).

2-(4'-F-phenyl)-1-pyrroline (**1d**):³⁴ white solid, 25% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.84 (m, 2H), 7.10 (m, 2H), 4.06 (m, 2H), 2.94 (m, 2H), 2.05 (m, 2H).

2-(4'-Cl-phenyl)-1-pyrroline (**1e**):³² light yellow solid, 30% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.65 (t, *J*=4 Hz, 2H), 7.25 (t, *J*=4 Hz, 2H), 3.94 (m, 2H), 2.80 (m, 2H), 1.93 (m, 2H).

2-(4'-Brphenyl)-1-pyrroline (**1f**):³³ light yellow solid, 38% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.84 (m, 1H), 7.71 (m, 1H), 7.55 (m, 1H), 7.41 (m, 1H), 4.05 (m, 2H), 2.91 (m, 2H), 2.04 (m, 2H).

2-(3'-Cl-phenyl)-1-pyrroline (1g):³³ yellow oil, 26% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.89 (s, 1H), 7.57 (m, 1H), 7.32 (m, 2H), 3.92 (m, 2H), 2.76 (m, 2H), 1.90 (m, 2H).

2-(3'-Me-phenyl)-1-pyrroline (**1h**):³⁵ yellow oil, 45% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.50 (s, 1H), 7.46 (m,1H), 7.11 (m, 2H), 3.91 (m, 2H), 2.78 (m, 2H), 2.20 (s, 3H), 1.89 (m, 2H).

2-(3'-OMe-phenyl)-1-pyrroline (**1i**):³⁶ yellow oil, 53% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.17 (m, 1H), 7.14 (m, 2H), 6.83 (m, 1H), 3.94 (m, 2H), 3.60 (s, 3H), 2.78 (m, 2H), 1.88 (m, 2H).

2-butyl-1-pyrroline (**1j**):³¹ light yellow oil, 92% Yield. ¹H NMR (400 MHz, CDCl₃) δ 3.73 (m, 2H), 2.39 (m, 2H), 2.27 (m, 2H), 1.80 (m, 2H), 1.51 (m, 2H), 1.29 (m, 2H), 0.86 (t, *J*=7.2 Hz, 3H).

2,3,4,5-tetrahydro-6-phenylpyridine (1k):³⁷ yellow solid, 42% Yield. ¹H NMR (400
MHz, CDCl₃) δ 7.68 (m, 2H), 7.30 (m, 3H), 3.77 (m, 2H), 2.56 (m, 2H), 1.76 (m, 2H), 1.61 (m, 2H).

2-(2'-OMe-phenyl)-1-pyrroline (**11**):³⁸ yellow oil, 58% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.74 (m, 1H), 7.36 (m, 1H), 6.96 (m, 2H), 3.98 (m, 2H), 3.85 (s, 3H), 3.00 (m, 2H), 1.97 (m, 2H).

2-Phenyl-4,5,6,7- tetrahydro-3H-azepine (**1m**):³⁷ yellow oil, 32% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.69 (m, 2H), 7.36 (m, 3H), 3.84 (m, 2H), 2.86 (m, 2H), 1.88 (m, 2H), 1.61 (m, 4H).

2.5.3 General procedure for asymmetric hydrogenation of cyclic imines 1.

In the nitrogen-filled glovebox, $[Ir(COD)Cl]_2$ (5.4 mg, 0.008 mmol) and (*S*,*S*)-f-Binaphane (12.8 mg, 0.016 mmol) was dissolved in anhydrous CH₂Cl₂ (6.4 mL) and equally divided into 8 vials charged with imine substrates (0.2 mmol) in anhydrous ethyl acetate solution (1.6 mL). The resulting solution was transferred to an autoclave, which was charged with 50 atm of H₂. The hydrogenation was performed at 50 °C for 25 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 reacted with trifluoroacetic anhydride to

yield the corresponding trifluoroacetamides, and then analyzed by chiral GC (Gamma Dex 225 or Beta Dex 390) to determine the enantiomeric excesses.

[Ir(H)[(*S*,*S*)-(f)-Binaphane] $_2(\mu$ -I)₃]⁺Γ was prepared according to literature report.^{19b} To a mixture of [Ir (cod)₂Cl]₂ (20.2 mg, 30 mol) and (*S*,*S*)-f-Binaphane (53.3 mg, 66.0 mol) in toluene (5 mL) was added aqueous HI (45%, 33 µL) via a syringe at room temperature. Then the reaction mixture was stirred overnight. Solvent was removed under reduced pressure. The residue was dissolved in dichloromethane Upon addition of hexane, product precipitated as an airstable pale yellow powder (53.6 mg, 75% yield), ³¹P NMR (162 MHz, CDCl₃) δ -0.42 (d, *J*=8.1 Hz), -2.88 (d, *J*=8.1 Hz). HRMALDI: Calculated for C₁₀₈H₈₂Fe₂I₄Ir₂P₄ (M⁺): 2507.9509, found 2507.9484.

2-phenylpyrrolidine (**2a**):³⁹ colorless oil, [α]²⁰_D +29.6(c = 0.25 in CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 6.99-7.38 (m, 5H), 4.05-4.09 (t, *J*=8 Hz, 1H), 3.10-3.28 (m, 1H), 2.88-3.00 (m, 1H), 2.08-2.18 (m, 1H), 1.68-1.90 (m, 2H), 1.54-1.68 (m, 1H).

2-(4'-Me-Phenyl)-1-pyrrolidine (**2b**):³⁹ colorless oil, [α]²⁰_D +59.5(c = 0.25 in CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.26-7.28 (d, *J*=8 Hz, 2H), 7.11-7.13 (d, *J*=8 Hz, 2H), 4.02-4.18 (m, 2H), 3.16-3.24 (m, 1H), 2.96-3.06 (m, 1H), 2.34 (s, 3H), 2.14-2.22 (m, 1H), 1.68-2.00 (m, 3H). **2-(4'-OMe-Phenyl)-1- pyrrolidine (2c):** ³⁹ colorless oil, $[\alpha]^{20}{}_{D}$ +45.4 (c = 0.25 in CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.38 (m, 2H), 6.80-6.88 (m, 2H), 4.12-4.20 (m, 1H), 3.78 (s, 3H), 3.18-3.24 (m, 1H), 2.98-3.08 (m, 1H), 2.14-2.22 (m, 1H), 1.68-2.08 (m, 3H).

2-(4'-F-Phenyl)-1-pyrrolidine (2d): ³⁹ colorless oil, [α]²⁰_D +46.5 (c = 0.25 in CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃)δ 7.30-7.44 (m, 2H), 6.97-7.01 (m, 2H), 4.09-4.13 (t, *J*=8 Hz,1H), 3.18-3.26 (m, 1H), 2.98-3.10 (m, 2H), 2.14-2.26 (m, 1H), 1.80-2.00 (m, 2H), 1.66-1.72 (m, 1H).

2-(4'-Cl-Phenyl)-1-pyrrolidine (2e): ⁴⁰ colorless oil, $[\alpha]_{D}^{20}$ +49.8 (c = 0.25 in CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.20-7.38 (m, 4H), 4.08-4.11 (t, *J*=8 Hz,1H), 3.00-3.32 (m, 3H), 2.14-2.26 (m, 1H), 1.80-2.00 (m, 2H), 1.60-1.70 (m, 1H).

2-(4'-Br-Phenyl)-1-pyrrolidine (**2f**): ³⁹ colorless oil, $[\alpha]^{20}{}_{D}$ +56.4 (c = 0.25 in CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.43 (m, 2H), 7.23-7.25 (m, 2H), 4.06-4.09 (m, 1H), 3.14-3.22 (m, 1H), 2.14-2.22 (m, 1H), 1.82-2.01 (m, 2H), 1.52-1.68 (m, 1H).

2-(3'-Cl-Phenyl)-1-pyrrolidine (2g): ³⁹ colorless oil, [α]²⁰_D +45.6 (c = 0.25 in CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃)δ 7.37 (s, 1H), 7.19-7.23 (m, 3H), 4.08-4.18 (m, 1H), 3.16-3.28 (m, 1H), 3.00-3.12 (m, 1H), 2.78 (s, 1H), 2.16-2.24 (m, 1H), 1.78-2.00

2-(3'-Me-Phenyl)-1-pyrrolidine (**2h**): ³⁹ colorless oil, $[\alpha]^{20}_{D}$ +26.8 (c = 0.25 in CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.19-7.23 (m, 3H), 7.06-7.12 (m, 1H), 4.84 (s, 1H), 4.14-4.18 (m, 1H), 3.22-3.32 (m, 1H), 3.00-3.12 (m, 1H), 3.34 (s, 3H), 2.18-2.26 (m, 1H), 1.76-2.04 (m, 3H)

2-(3'-OMe-Phenyl)-1- pyrrolidine (2i): ⁴¹ colorless oil, $[\alpha]^{20}_{D}$ +36.5 (c = 0.25 in CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.18-7.30 (m, 1H), 6.74-7.00 (m, 3H), 4.08-4.18 (m, 1H), 3.62-3.82 (m, 4H), 3.18-3.26 (m, 1H), 2.98-3.06 (m, 1H), 2.16-2.26 (m, 1H), 1.68-2.00 (m, 3H).

2-butyl-1-pyrrolidine (**2j**): ³² colorless oil, $[\alpha]^{20}{}_{D}$ +0.7 (c = 0.25 in CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 2.48-3.56 (m, 3H), 1.52-2.16 (m, 14H).

2-phenyl-1-piperidine(**2k**): ³⁷ colorless oil, $[\alpha]^{20}{}_{D}$ +31.2 (c = 0.25 in CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.14-7.40 (m, 5H), 3.50-3.64 (m, 1H), 3.08-3.20 (m, 1H), 2.60-2.82 (m, 2H), 1.72-1.90 (m, 2H), 1.40-1.70 (m, 4H).

2-(2'-OMe-Phenyl)-1- pyrrolidine (**2l**): ³⁸ colorless oil, $[\alpha]^{20}{}_{D}$ +29.5 (c = 0.25 in CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.39 (m, 1H), 7.20 (m, 1H), 6.93 (m, 1H), 6.86 (m, 1H), 4.36 (m, 1H), 3.82 (s, 3H), 3.18 (m, 1H), 2.97 (m, 1H), 2.38 (b, 1H),

2.18 (m, 1H), 1.84 (m, 2H), 1.68 (m, 1H).

2-phenylazepane(2m): ³⁷ colorless oil, $[\alpha]^{20}{}_{D}$ +24.8 (c = 0.25 in CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.18-7.36 (m, 5H), 3.75 (m, 1H), 3.14 (m, 1H), 2.86 (m, 1H), 1.98 (m, 1H), 1.46-1.88 (m, 8H).

2.5.4 General procedure for synthesis of cyclic imines 3.

1-substituted 3,4-dihydroisoquinoline imines (**3a–3p**) were synthesized from corresponding 2-arylethyl amine and alkyl- or arylcarbonyl chloride in two steps according to modified literature methods.^{42,43} This procedure was carried out in air atmosphere. Carbonyl chloride (10.0 mmol) was slowly added to a solution of 2-arylethylamine 7 (10.0 mmol) and triethylamine (15 mmol) in CH₂Cl₂ (60 mL) at 0 °C. After stirring at room temperature for 12 h, the mixture was concentrated by rotary evaporation. The residue was dissolved in EtOAc (40 mL) and washed with 1 N HCl solution (40 mL). The aqueous layer was further extracted with EtOAc (2×40 mL). The combined organic extracts were washed with brine (80 mL) and dried over Na₂SO₄. Solvent was evaporated to give the corresponding amide, which was used in the next step without further purification.

To a solution of the resulting amide (10.0 mmol) and 2-chloropyridine (12.0 mmol)

in CH₂Cl₂ (60 mL) was added trifluoromethanesulfonic anhydride (11.0 mmol, 1.1 equiv) via syringe dropwise at -78 °C. Then the reaction was stirred at this temperature for 15 min and slowly warm to room temperature overnight. The reaction was quenched with aq. NaHCO₃ solution and extracted with CH₂Cl₂ (3×50 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated under vacuum. The crude product was purified with column chromatography (EtOAc / Hex) to yield desired product (yield: 75 – 96%).

1-phenyl-3,4-dihydroisoquinoline (3a): ⁴² light yellow liqhid, 93% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.60 (m, 2H), 7.30-7.50 (m, 4H), 7.18-7.32 (m, 3H), 3.84 (m, 2H), 2.78 (m, 2H).

1-isopropyl-3,4-dihydroisoquinoline (**3b**): ⁴⁴ light yellow liquid, 95% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (m, 1H), 7.28-7.40 (m, 2H), 7.18 (m,1H), 4.68 (m, 2H), 3.26 (m, 1H), 2.66(m, 2H), 1.20 (d, 6H).

1-cyclohexyl-3,4-dihydroisoquinoline (**3c**): ⁴⁴ clear liquid, 85% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.50 (m, 1H), 7.22-7.34 (m, 2H), 7.18 (m, 1H), 3.66 (m, 2H), 2.90 (m, 1H), 2.64 (m, 2H), 1.70-1.96 (m, 5H), 1.20-1.50 (m, 5H).

1-(4'-Methylphenyl)-3,4-dihydroisoquinoline (**3d**): ⁴⁵ white solid, 96% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.50 (m, 2H), 7.38 (m, 1H), 7.24 (m, 5H), 4.84 (m, 2H), 2.80 (m, 2H), 2.41 (s, 3H).

1-(4'-Chlorophenyl)-3,4-dihydroisoquinoline (**3e**): ⁴⁵ white solid, 95% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.56 (m, 2H), 7.38 (m, 3H), 7.26 (m, 3H), 3.86 (m, 2H), 2.80 (m, 2H).

1-(4'-methoxylphenyl)-3,4-dihydroisoquinoline (**3f**): ⁴⁵ light yellow solid, 90% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (m, 2H), 7.40 (m, 1H), 7.38 (m, 3H), 6.96 (m, 2H), 3.98 (s, 3H), 3.82 (m, 2H), 2.80 (m, 2H).

1-(4'-trifluoromethylphenyl)-3,4-dihydroisoquinoline (**3g**): ⁴⁶ white solid, 94% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.70(m, 4H), 7.40 (m, 1H), 7.26 (m, 2H), 7.20 (m, 1H), 3.88 (m, 2H), 2.82 (m, 2H).

1-(3'-Methylphenyl)-3,4-dihydroisoquinoline (**3h**): light yellow oil, 92% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.44 (s, 1H), 7.36 (m,2H), 7.26 (m, 5H), 3.84 (m, 2H), 2.80 (m, 2H), 2.40 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 167.4, 139.0, 138.8, 137.9, 130.6, 130.1, 129.3, 128.9, 128.0, 127.3, 126.5, 125.9, 47.6, 26.4, 21.4. ESI-HRMS: Calculated for C₁₆H₁₆N⁺([M+H]⁺): 222.1283, found 222.1280.

1-(3'-Chlorophenyl)-3,4-dihydroisoquinoline (**3i**): ⁴⁷ light yellow oil, 90% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.60 (s, 1H), 7.48 (m, 2H), 7.46 (m, 2H), 7.22 (m, 3H), 3.84 (m, 2H), 2.80 (m, 2H).

1-(2'-Methylphenyl)-3,4-dihydroisoquinoline (**3j**): ⁴⁸ white solid, 75% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.06-7.32 (m, 7H), 6.84 (m,1H), 3.84 (m, 2H), 2.80 (m, 2H), 2.06 (s, 3H).

1-(2'-methoxylphenyl)-3,4-dihydroisoquinoline (**3k**): ⁴⁹ yellow solid, 80% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.28-7.42 (m, 3H), 7.10-7.24 (m, 2H), 7.02 (m, 1H), 6.94 (m, 2H), 3.90 (b, 2H), 3.68 (s, 3H), 2.86 (m, 2H).

1-(2-furoyl)-3,4-dihydroisoquinoline (3l): ⁵⁰ yellow oil, 82% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.72 (m, 1H), 7.58 (s, 1H), 7.26-7.44 (m, 3H), 6.88 (d, *J*=4Hz, 1H), 6.52 (d, *J*=4Hz, 1H), 3.84 (m, 2H), 2.76 (m, 2H).

1-phenyl-3,4-dihydro-6,7-dimethoxyisoquinoline (**3m**): ⁵¹ white solid, 94% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.60 (m, 2H), 7.44 (m, 3H), 6.80 (m, 2H), 3.96 (s, 3H), 3.82 (m, 2H), 3.74 (s, 3H), 2.74 (m, 2H).

1-phenyl-3,4-dihydro-6,7-dimethoxyisoquinoline (**3n**): ⁴⁴ light yellow oil, 94% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.05 (s, 1H), 6.70 (s, 1H), 3.92 (m, 6H), 3.64 (m, 2H), 3.20 (m, 1H), 2.60 (m, 2H), 1.22 (m, 6H).

1-(3,4-dimethoxylphenyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (**3o**): ⁵¹ white solid, 94% Yield. ¹H NMR (400 MHz, CDCl₃) δ 7.24 (s, 1H), 7.16 (d, *J*=4Hz, 1H), 6.88 (m, 2H), 6.78 (s, 1H), 3.94 (m, 9H), 3.74-3.84 (m, 5H), 2.72 (m, 2H).

1-(3,4,5-trimethoxylphenyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (3p): ⁵² white solid, 92% Yield. ¹H NMR (400 MHz, CDCl₃) δ 6.88 (s, 1H), 6.85 (s, 2H), 6.79 (s, 1H), 3.96 (s, 3H), 3.92 (s, 3H), 3.90 (s, 6H), 3.80 (m, 2H), 3.76 (s, 3H), 2.74 (m, 2H).

2.5.5 General Procedure for Asymmetric Hydrogenation of 3,4-dihydroisoquinoline 3.

In a nitrogen-filled glovebox, complex **A** (2.5 mg, 0.001 mmol) was dissolved in anhydrous CH_2Cl_2 (1.0 mL) and equally divided into 10 vials charged with imine substrates **3** (0.2 mmol) in anhydrous CH_2Cl_2 solution (1.0 mL). Then I_2 (5.1 mg, 0.02 mmol) was added and the total solution was made to 2.0 mL for each vial. The resulting vials were transferred to an autoclave, which was charged with 50 atm of H_2 , and stirred at room temperature for 24 h. The hydrogen gas was released slowly and the solution was concentrated and passed through a short column of silica gel to remove the metal complex. The chiral amine products reacted with acetic anhydride to yield the corresponding acetamides, which were then analyzed by chiral HPLC & GC to determine the enantiomeric excesses.

(*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (4a): ⁴² white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.14-7.40 (m, 7H), 7.08 (m, 1H), 6.76 (d, *J*=8 Hz, 1H), 5.30 (s, 1H), 3.30 (m, 1H), 3.02-3.20 (m, 2H), 2.92 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 142.2, 136.0, 134.4, 129.3, 129.0, 128.6, 128.2, 128.1, 128.0, 126.9, 126.1, 60.7, 40.7, 28.3. Enantiomeric excess was determined by HPLC for the the corresponding acetamide, Chiralpak OD-H column, Hex/IPA=99:1, 1 mL/min.

(-)-**1-isopropyl-1,2,3,4-tetrahydroisoquinoline** (**4b**): ⁴⁴ yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.08-7.24 (m, 4H), 4.16 (d, *J*=4 Hz, 1H), 3.46 (m, 1H), 2.90-3.08 (m,

2H), 2.78 (m, 1H), 2.40 (m, 1H), 1.18 (d, J=8 Hz, 3H), 0.80 (d, J=8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 136.3, 135.1, 129.1, 126.3, 126.2, 126.1, 60.5, 41.5, 32.4, 28.9, 19.8, 15.9. Enantiomer ratio was determine by GC for the the corresponding acetamide using a Beta Dex 390 column (30 m×0.25 mm×0.25 µm; carrier gas, He (flow rate 1 mL/min); column temperature, 150 °C.

(-)-**1-cyclohexyl-1,2,3,4-tetrahydroisoquinoline** (**4c**): ⁴⁴ light yellow oil. ¹H NMR (400 MHz, CDCl₃)δ 7.04-7.20 (m, 4H), 4.00 (d, *J*=4 Hz, 1H), 3.28-3.40 (m, 1H), 2.82-3.04 (m, 2H), 2.68-2.76 (m, 1H), 1.90 (m, 2H), 1.82 (m, 1H), 1.60-1.78 (m, 3H), 1.26-1.48 (m, 3H), 1.04-1.26 (m, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 137.2, 135.6, 129.1, 126.3, 125.9, 125.8, 60.4, 43.0, 41.7, 30.7, 29.5, 27.0, 26.6, 26.6, 26.5. Enantiomeric excess was determined by HPLC for the the corresponding acetamide, Chiralpak AD-H column, Hex/IPA=96:4, 1 mL/min.

(+)-**1-(4'-Methylphenyl)-1,2,3,4-tetrahydroisoquinoline** (**4d**): ⁵⁴ white solid. ¹H NMR (400 MHz, CDCl₃) δ 6.88-7.06 (m, 7H), 6.68 (d, *J*=8 Hz,1H), 5.00 (s, 1H), 3.12-3.24 (m, 1H), 2.88-3.06 (m, 2H), 2.68-2.80 (m, 1H), 2.26 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 140.3, 136.9, 136.1, 134.2, 128.1, 128.0, 127.9, 127.1, 125.3, 124.7, 60.4, 40.8, 28.4, 20.1. Enantiomeric excess was determined by HPLC for the the corresponding acetamide, Chiralpak OD-H column, Hex/IPA=99:1, 1 mL/min.

(S)-1-(4'-chlorophenyl)-1,2,3,4-dihydroisoquinoline (4e): ⁵⁴ white solid. ¹H NMR (400 MHz, CDCl₃)δ 7.28 (d, *J*=8 Hz, 2H), 7.20 (d, *J*=8 Hz, 2H), 7.14 (d, *J*=4 Hz, 2H),

7.04 (m, 1H), 6.70 (d, *J*=8 Hz, 1H), 5.08 (s,1H), 3.20-3.30 (m, 1H), 2.96-3.16 (m, 2H), 2.78-2.88 (m, 1H), 2.56 (b, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 143.2, 137.6, 135.4, 133.2, 130.9, 128.8, 128. 2, 127.8, 126.4, 125.7, 61.3, 42.1, 29.6. Enantiomeric excess was determined by HPLC for the the corresponding acetamide, Chiralpak OD-H column, Hex/IPA=99:1, 1 mL/min.

(*S*)-1-(4'-methoxylphenyl)-1,2,3,4-dihydroisoquinoline (4f): ⁵⁴ yellow oil. ¹H NMR (400 MHz, CDCl₃)δ 7.06-7.20 (m, 4H), 7.00 (m, 1H), 6.76 (d, *J*=8 Hz, 2H), 6.70 (d, *J*=8 Hz, 1H), 5.21 (s, 1H), 3.70 (s, 3H), 3.16-3.26 (m, 1H), 2.94-3.12 (m, 2H), 2.78-2.90 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 159.6, 135.4, 133.9, 133.1, 130.7, 128.9, 128.2, 127.1, 126.2, 114.0, 59.6, 55.3, 40.1, 27.6. Enantiomeric excess was determined by HPLC for the the corresponding acetamide, Chiralpak OD-H column, Hex/IPA=98:2, 1 mL/min.

(+)-1-(4'-trifluoromethylphenyl)-1,2,3,4-dihydroisoquinoline (4g): ⁵⁴ white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, *J*=8 Hz, 2H), 7.39 (d, *J*=8 Hz, 2H), 7.16 ((d, *J*=8 Hz, 2H), 7.04 (m, 1H), 6.70 (d, *J*=8 Hz, 1H), 5.15 (s, 1H), 3.20-3.30 (m, 1H), 2.96-3.14 (m, 2H), 2.76-2.90 (m, 1H), 1.96 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 148.9, 137.3, 135.5, 129.4, 129.3, 127.9, 126.6, 125.8, 125.4, 125.3, 61.6, 42.1, 29.7. Enantiomeric excess was determined by HPLC for the the corresponding acetamide, Chiralpak OD-H column, Hex/IPA=100:0 \rightarrow 99:1, 1 mL/min.

(+)-1-(3'-methylphenyl)-1,2,3,4-dihydroisoquinoline (4h): ⁵⁵ white solid. ¹H NMR

(400 MHz, CDCl₃)δ 7.16-7.26 (m, 1H), 7.14 (d, *J*=4 Hz, 2H), 7.09 (s, 2H), 7.04 (d, *J*=4 Hz, 2H), 6.76 (d, *J*=8 Hz, 1H), 5.08 (s, 1H), 3.37 (s, 1H), 3.20-3.34 (m, 1H), 2.98-3.16 (m, 2H), 2.31 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 144.3, 138.1, 135.2, 129.7, 129.4, 129.0, 128.3, 128.2, 126.3, 126.2, 126.0, 125.7, 61.9, 42.0, 29.7, 21.4. Enantiomeric excess was determined by HPLC for the the corresponding acetamide, Chiralpak AS column, Hex/IPA=95:5, 1 mL/min.

(+)-**1**-(**3'-chlorophenyl)-1,2,3,4-dihydroisoquinoline** (**4i**):⁵⁴ white solid. ¹H NMR (400 MHz, CDCl₃)δ 7.22-7.30 (m, 3H), 7.16 (m, 3H), 7.04 (m, 1H), 6.73 (d, *J*=8 Hz, 1H), 5.07 (s, 1H), 3.20-3.30 (m, 1H), 2.96-3.14 (m, 2H), 2.76-2.88 (m, 1H), 2.00 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 147.0, 137.5, 135.4, 134.3, 129.6, 129.2, 129.1, 128.0, 127.6, 127.2, 126.5, 125.8, 61.6, 42.1, 29.7. Enantiomeric excess was determined by HPLC for the the corresponding acetamide, Chiralpak AS column, Hex/IPA=94:6, 1 mL/min.

(-)-**1**-(**2'-methylphenyl**)-**1**,**2**,**3**,**4**-**dihydroisoquinoline** (**4j**): ⁵⁵ colorless oil. ¹H NMR (400 MHz, CDCl₃)δ 6.96-7.20 (m, 7H), 6.68 (d, *J*=8 Hz, 1H), 5.46 (s, 1H), 3.28-3.38 (m, 1H), 3.04-3.20 (m, 2H), 2.82-2.92 (m, 1H), 2.42 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 142.3, 138.4, 136.7, 135.4, 130.8, 129.6, 129.0, 127.6, 127.3, 126.2, 125.9, 125.8, 58.9, 42.4, 29.7, 19.5. Enantiomeric excess was determined by HPLC for the the corresponding acetamide, Chiralpak OD-H column, Hex/IPA=99:1, 1 mL/min.

(-)-1-(2'-methoxylphenyl)-1,2,3,4-dihydroisoquinoline (4k): ⁴⁹ light yellow oil. ¹H

NMR (400 MHz, CDCl₃)δ 7.12-7.18 (m, 1H), 7.07 (m, 2H), 6.92-7.00 (m, 1H), 6.86 (d, *J*=8 Hz, 1H), 6.70-6.78 (m, 3H), 5.48 (s, 1H), 3.78 (s, 3H), 3.06-3.24 (m, 2H), 2.78-2.86 (m, 2H), 1.87 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 157.3, 136.1, 135.0, 130.7, 130.6, 129.0, 128.9, 128.0, 126.5, 125.9, 120.4, 110.8, 55.5, 54.9, 40.2, 28.6. Enantiomeric excess was determined by HPLC for the the corresponding acetamide, Chiralpak OD-H column, Hex/IPA=99:1, 1 mL/min.

(+)-**1**-(**2**-furoyl)-**1**,**2**,**3**,**4**-tetrahydroisoquinoline (**4**l): ⁵⁰ yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.39 (s, 1H), 7.08-7.30 (m, 3H), 7.02 (d, *J*=8 Hz, 1H), 6.28 (d, *J*=4 Hz, 1H), 5.98 (d, *J*=4 Hz, 1H), 5.21 (s, 1H), 3.01-3.28 (m, 2H), 2.80-2.98 (m, 2H), 2.12 (b, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 156.6, 142.1, 135.3, 134.9, 129.3, 127.8, 126.8, 125.6, 109.9, 108.4, 54.3, 40.3, 29.2. Enantiomeric excess was determined by HPLC for the the corresponding acetamide, Chiralpak AD-H column, Hex/IPA=97:3, 1 mL/min.

(*S*)-**1**-**phenyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline** (**4m**): ⁵⁶ white solid. ¹H NMR (400 MHz, CDCl₃)δ 7.22-7.36 (m, 5H), 6.63 (s, 1H), 6.26 (s, 1H), 5.25 (s, 1H), 3.88 (s, 3H), 3.64 (s, 3H), 3.18-3.26 (m, 1H), 3.00-3.10 (m, 1H), 2.86-2.98 (m, 1H), 2.70-2.80 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 148.0, 147.4, 143.1, 129.1, 128.5, 128.3, 127.8, 127.0, 111.4, 111.0, 60.5, 55.9, 55.8, 40.7, 28.3. Enantiomeric excess was determined by HPLC for the the corresponding acetamide, Chiralpak AD-H column, Hex/IPA=93:7, 1 mL/min.

(*S*)-**1**-isopropyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**4**n): ⁴⁴ white solid. ¹H NMR (400 MHz, CDCl₃)δ 6.63 (s, 1H), 6.58 (s, 1H), 4.04 (d, *J*=4 Hz, 1H), 3.85 (d, *J*=4 Hz, 6H), 3.36-3.44 (m, 1H), 2.80-3.00 (m, 2H), 2.60-2.70 (m, 1H), 2.28-2.40 (m, 1H),1.25 (d, *J*=8 Hz, 3H), 0.80 (d, *J*=8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 147.5, 147.5, 128.7, 127.6, 111.7, 109.3, 60.2, 56.1, 55.8, 41.8, 32.5, 28.7, 19.9, 15.9. Enantiomeric excess was determined by HPLC for the the corresponding acetamide, Chiralpak AD-H column, Hex/IPA=90:10, 1 mL/min.

(S)-1-1-(3',4'-bimethoxylphenyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline

(4o): ⁵⁶ white solid. ¹H NMR (400 MHz, CDCl₃)δ 6.90 (s, 1H), 6.80 (m, 2H), 6.63 (s, 1H), 6.28 (s, 1H), 5.20 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.66 (s, 3H), 3.20-3.30 (m, 1H), 2.96-3.18 (m, 2H), 2.80-2.92 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 149.1, 149.0, 148.4, 147.6, 133.2, 126.7, 126.1, 122.1, 112.5, 111.3, 110.9, 110.8, 59.6, 55.9, 55.8, 40.1, 27.0. Enantiomeric excess was determined by HPLC for the the corresponding acetamide, Chiralpak AS column, Hex/IPA=92:8, 1 mL/min.

(*S*)-1-(3',4',5'-trimethoxylphenyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**4p**): ⁵² white solid. ¹H NMR (400 MHz, CDCl₃)δ 6.56 (s, 1H), 6.45 (s, 2H), 6.23 (s, 1H), 5.06 (s, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.77 (s, 6H), 3.61 (s, 3H), 3.14-3.22 (m, 1H), 2.86-3.08 (m, 2H), 2.68-2.80 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 153.3, 148.3, 147.5, 137.9, 137.4, 127.3, 126.6, 122.1, 111.4, 111.0, 106.6, 60.8, 60.6, 56.2, 56.0, 55.8, 40.8, 27.7. Enantiomeric excess was determined by HPLC for the the corresponding acetamide, Chiralpak AD-H column, Hex/IPA=80:20, 1 mL/min.

Reference:

- (a) A. R. Pinder, *Nat. Rod. Rep.* 1992, 9, 17. (b) J. P. Michael, *Nat. Rod. Rep.* 1991, 8, 563.
- (a) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069. (b) H.-U. Blaser, C. Malan, B. Pugin, F. Spinder, H. Steiner, M. Studer, *Adv. Synth. Catal.* **2003**, *345*, 103.
- 3. T. Spangenberg, B. Breit, A. Mann, Org. Lett. 2009, 11, 261.
- J. Lloyd, H. J. Finlay, W. Vacarro, T. Hyunh, A. Kover, R. Bhandaru, L. Yan, K. Atwal, M. L. Conder, T. Jenkins-West, H. Shi, C. Huang, D. Li, H. Sun, P. Levesque, *Bioorg. Med. Chem.* 2010, 20, 1436.
- A. K. Amegadzie, K. M. Gardinier, E. J. Hembre, P. A. Hipskind, L. N. Jungheim, B. S. Muehl, K. A. Savin, K. J. Thrasher, S. A. Boyd, WO 2005000821 A1(Lilly), 2005.
- 6. A. Brossi, S. Teitel, Helv. Chim. Acta 1971, 54, 1564.
- 7. H. M. Kothari, M. G. Dave, B. Pandey, Patent WO 2011048607, 2011.
- (a) W. Tang, X. Zhang, *Chem. Rev.* 2003, 103, 3029. (b) T. C. Nugent (Ed.), *Chiral Amine Synthesis*, Wiley-VCH, Weinheim, 2010. (c) I. Ojima (Ed.), *Handbook of Homogeneous Hydrogenation*, Wiley-VCH, Hoboken, 2010. (d) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Soc. Rev.* 2012, 41, 4126.
- 9. A. Levi, G. Modena, G. Scorrano, J. Chem. Soc., Chem. Commun. 1975, 6.
- 10. W. Li, G. Hou, M. Chang, X. Zhang, Adv. Synth. Catal. 2009, 351, 3123.
- 11. H.-U. Blaser, H.-P. Buser, R. Hausel, H.-P. Jalett, F. Spindler, *J. Organomet. Chem.* **2001**, *621*, 34.
- G. Hou, F. Gosselin, W. Li, J. C. McWilliams, Y. Sun, M. Wiesel, P. D. O'Shea, C.-Y. Chen, I. W. Davies, X. Zhang, J. Am. Chem. Soc. 2009, 131, 9882.
- 13. C. A. Willoughby, S. L. Buchwald, J. Am. Chem. Soc. 1994, 116, 8952.
- 14. C. Li, J. Xiao, J. Am. Chem. Soc. 2008, 130, 13208.
- 15. C. J. Cobley, J. P. Henschke, Adv. Synth. Catal. 2003, 345, 195.
- 16. (a) K. H. Hopmann, A. Bayer, *Organometallics* 2011, *30*, 2483. (b) V. Herrera, B. Munoz, V. Landaeta, N. Canduas, *J. Mol. Catal. A: Chem.* 2001, *174*, 141. (c) D. Balcells, A. Noca, E. Clot, D. Gnanamgari, R. H. Crabtree, O. Eisenstein, *Organometallics* 2008, *27*, 2529. (d) A. Fabrello, A. Bacheliera, M. Urrutigoïtya, P. Kalcka, *Coord. Chem. Rev.* 2010, *254*, 273. (e) M. Martín, E. Sola, S. Tejero, J.-L. Andres, L. A. Oro, *Chem.—Eur. J.* 2006, *12*, 4043. (f) M. Martín, E. Sola, S. Tejero, J. A. Lopez, L. A. Oro, *Chem.—Eur. J.* 2006, *12*, 4057.
- 17. D. Xiao, X. Zhang, Angew. Chem. Int. Ed. 2001, 40, 3425.
- 18. A. Dervisi, C. Carcedo, L.-l. Ooi, Adv. Synth. Catal. 2006, 348, 175.
- (a) K. Tani, J.-I. Onouchi, T. Yamagata, Y. Kataoka, *Chem. Lett.* 1995, 955. (b) T. Yamagata, H. Tadaoka, M. Nagata, T. Hirao, Y. Kataoka, V. Ratovelomanana-Vidal, J. P. Genet, K. Mashima, *Organometallics* 2006, 25, 2505. (c) M. Ringwald, Sturmer, H. H. Brintzinger, J. Am. Chem. Soc.1999, 121, 1524.
- 20. (a) G.-J. Kang, W. R. Cullen, M. D. Fryzuk, B. R. James, J. P. Kutney, J. Chem.

Soc. Chem. Commun. 1988, 1466. (b) T. Morimoto, N. Nakajima, K. Achiwa, Chem. Pharm. Bull. 1994, 42, 1951. (c) T. Morimoto, K. Achiwa, Tetrahedron: Asymmetry 1995, 6, 2661. (d) T. Morimoto, N. Suzuki, K. Achiwa, Heterocycles 1996, 43, 1557. (e) T. Morimoto, N. Suzuki, K. Achiwa, Tetrahedron: Asymmetry 1998, 9, 183. (f) K. Tani, J.-I. Onouchi, T. Yamagata, Y. Kataoka, Chem. Lett. 1995, 955. (g) G. Zhu, X. Zhang, Tetrahedron: Asymmetry 1998, 9. 2415.

- (a) Y. N. C. Chan, J. A. Osborn, J. Am. Chem. Soc. 1990, 112, 9400; (b) R. Sablong, J. A. Osborn, *Tetrahedron: Asymmetry* 1996, 7, 3059.
- 22. Q. Yang, G. Shang, W. Gao, J. Deng, X. Zhang, Angew. Chem. Int. Ed. 2006, 45, 3832.
- 23. (a) R. Paul, J. A. Coppola, E. Cohen, J. Med. Chem. 1972, 15, 720. (b) J. D. Phillipson, M. F. Roberts, M. H. Zenk (Eds.), The Chemistry and Biology of Isoquinoline Alkaloids, Springer, Berlin, 1985. (c) D. Jack, R. Williams, Chem. Rev. 2002, 102, 1669. (d) P. M. Dewick, Medicinal Natural Products: A Biosynthetic Approach, Wiley, Chichester, 2002, pp. 315. (e) K. W. Bentley, Nat. Prod. Rep. 2006, 23, 444. (f) M. Chrzanowska, M. D. Rozwadowska, Chem. Rev. 2004, 104, 3341.
- 24. (a) D. Taniyama, M. Hasegawa, K. Tomioka, *Tetrahedron: Asymmetry* 1999, 10, 221. (b) K. T. Wanner, H. Beerb, G. Hofnera, M. Ludwig, *Eur. J. Org. Chem.* 1998, 2019. (c) K. Kurihara, Y. Yamamoto, N. Miyauraa, *Adv. Synth. Catal.* 2009, 351, 260. (d) K. Umetsu, N. Asao, *Tetrahedron Lett.* 2008, 49, 2722. (e) S. Wang, M. B. Onaran, C. T. Seto, *Org. Lett.* 2010, 12, 2690. (f) F. Louafi, J.-P. Hurvois, A. Chibani, T. Roisnel, *J. Org. Chem.* 2010, 75, 5721. (g) M. Amat, V. Elias, N. Llor, F. Subrizi, E. Molins, J. Bosch, *Eur. J. Org. Chem.* 2010, 4017.
- T. Ohkuma, M. Kitamura, R. Noyori, in *Catalytic Asymmetric Synthesis*, 2nd edn., (Ed.: I. Ojima), Wiley, New York, 2000, pp. 1.
- 26. (a) C. A. Willoughby, S. L. Buchwald, J. Am. Chem. Soc. 1994, 116, 8952. (b) T. Morimoto, K. Achiwa, Tetrahedron: Asymmetry 1995, 6, 2661. (c) T. Morimoto, N. Suzuki, K. Achiwa, Heterocycles 1996, 43, 2557. (d) G. Zhu, X. Zhang, Tetrahedron: Asymmetry 1998, 9, 2415. (e) C. J. Cobley, J. P. Henschke, Adv. Synth. Catal. 2003, 345, 195. (f) E. Guiu, C. Claver, J. Benet-Buchholz, S. Castillon, Tetrahedron: Asymmetry 2004, 15, 3365. (g) M. Jackson, I. C. Lennon, Tetrahedron Lett. 2007, 48, 1831. (h) C. Li, J. Xiao, J. Am. Chem. Soc. 2008, 130, 13208.
- (a) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, J. Am. Chem. Soc. **1996**, 118, 4916. (b) J. Mao, D. C. Baker, Org. Lett. **1999**, 1, 841. (c) P. Roszkowski, K. Wojtasiewicz, A. Leniewski, J. K. Maurin, T. Lis, Z. Czarnocki, J. Mol. Catal. A: Chem. **2005**, 232, 143. (d) J. Wu, F. Wang, Y. Ma, X. Cui, L. Cun, J. Zhu, J. Deng, B. Yu, Chem. Commun. **2006**, 1766. (e) J. Canivet, G. Suss-Fink, Green Chem. **2007**, 9, 391. (f) D. S. Matharu, J. E. D. Martins, M. Wills, Chem. Asian J. **2008**, 3, 1374. (g) J. E. D. Martins, G. J. Clarkson, M. Wills, Org. Lett. **2009**, 11, 847. (h) L. Evanno, J. Ormala, P. M. Pihko, Chem. Eur. J. **2009**, 15, 12963. (i) J. E. D. Martins, M. A. C. Redondo, M. Wills, Tetrahedron: Asymmetry **2010**, 21, 2258.

- Y. Ishii, K. Takaoka, M. Inakoshi, S. Nakagawa, K. Nagata, N. Yorimoto, M. Takeuchi, Y. Yonetoku, Patent WO 2005075474 A1, 2005.
- 29. For reviews, see: (a) K. Fagnou, M. Lautens, *Angew. Chem. Int. Ed.* 2002, *41*, 26.
 (b) E. M. Vogl, H. Groeger, M. Shibasaki, *Angew. Chem. Int. Ed.* 1999, *38*, 1570;
 (c) D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem. Int. Ed.* 1995, *34*, 1059.
- (a) C. A. Zezza, M. B. Smith, B. A. Ross, A. Arhin, P. L. E. Cronin, *J. org. Chem.* 1984, 49, 4397. (b) D. H. Hua, S. W. Miao, S. N. Bharathi, T. Katsuhira, A. A. Bravo, *J. Org. Chem.* 1990, 55, 3682.
- N. D. Kimpe, K. A. Tehrani, C. Stevens, P. D. Cooman, *Tetrahedron*, **1997**, 53, 3693.
- 32. C. Coindet, A. Comel, G. Kirsch Tetra.Lett. 2001, 42, 6101.
- N. E. Shevchenko, C.-V. Roschenthaler, A. S. Mitiaev, E. Lork, V. G. Nenajdenko, J. Fluor. Chem. 2008, 129, 637.
- 34. J. B. Cloke, L. H. Baer, J. M. Robbins, G. E. Smith, J. Am. Chem. Soc. 1945, 67, 2155.
- 35. J. H. Burckhalter, J. H. Short, J. Org. Chem. 1958, 23, 1278.
- 36. C. A. Willoughby, S. L. Buchwald, J. Am. Chem. Soc. 1994, 116, 8952.
- B. E. Maryanoff, D. F. McComsey, J. F. Gardocki, R. P. Shank, M. J. Costanzo, S. O. Nortey, C. R. Schneider, P. E. Setler, *J. Med. Chem.* **1987**, *30*, 1433.
- T. Yamagata, H. Tadaoka, M. Nagata, T Hirao, Y. Kataoka, V. R.-Vidal, J. P. Genet, K. Mashima. *Organometallics* 2006, 25, 2505.
- 39. V. Mutel, E. Vieira, J. Wichmann, WO 2000058285 A1, 2005.
- 40. D. M. Bradley, W. N. Chan, K. M. Thewlis, S. E. Ward, WO 2008053031 A1, 2008.
- 41. A. I. Meyers, P. D. Edwards, W. F. Rieker, T. R. Bailey, J. Am. Chem. Soc. 1945, 67, 2155.
- 42. M. Movassaghi, M. D. Hill, Org. Lett. 2008, 10, 3485.
- 43. J. M. Joo, R. A. David, Y. Yuan, C. Lee, Org. Lett. 2010, 12, 5704.
- 44. C. Li, J. Xiao, J. Am. Chem. Soc. 2008, 130, 13208.
- 45. S. A.-M. Ahmed, Mol. Cryst. Liq. Cryst. 2005, 430, 295.
- M. H. Norman, Y. Y. Bo, V. K. Gore, D. Horne, M. Kaller, V. V. Ma, H. Monenschein, T. Nguyen, N. Nishimura, N. Tamayo, Patent WO 2009073203 A1, 2009.
- 47. J. A. Christopher, F. L. Atkinson, B. D. Bax, M. J. B. Brown, A. C. Champigny, T. T. Chuang, E.J. Jones, J.E. Mosley, J.R. Musgrave, *Bioorg. Med. Chem. Lett.* 2009, 19, 2230.
- 48. S. Mitchell, R.Ohliger, L. Zhang, H. Zhao, K. Currie, K. Lee, Patent WO 2003082828 A1, 2003.
- J.-I. Shishikura, M. Inoue, T. Ogiyama, K. Yonezawa, S. Yamaki, K. Yokoyama, S. Kakimoto, H. Okada, Patent WO 2008143263 A1, 2008.
- F. I. Zubkov, J. D. Ershova, A. A. Orlova, V. P. Zaytsev, E. V. Nikitina, A. S. Peregudov, A. V. Gurbanov, R. S Borisov, V. N. Khrustalev, A. M. Maharramov, A. V. Varlamov, *Tetrahedron* 2009, 65, 3789.

- 51. J. Mao, D. C. Baker, Org. Lett. 1999, 1, 841.
- 52. V. Samano, J. A. Ray, J. B. Thompson, R A. Mook, D. K. Jung, C. S. Koble, M. T. Martin, E. C. Bigham, C. S. Regitz, P. L. Feldman, E. E. Boros, *Org. Lett.* **1999**, *1*, 1993.
- 53. T. Yamagata, H. Tadaoka, M. Nagata, T. Hirao, Y. Kataoka, V. Ratovelomanana-Vidal, J. P. Genet, K. Mashima, *Organometallics* **2006**, *25*, 2505.
- 54. R. Paul, J. A. Coppola, E. Cohen, J. Med. Chem. 1972, 15, 720.
- 55. M. Ludwig, C. E. Hoesl, G. Hoefner, K. T. Wanner, *Eur. J. Med. Chem.* 2006, *41*, 1003.
- 56. E. Awuah, A. Capretta, J. Org. Chem. 2010, 75, 5627.

Chapter 3

Direct Catalytic Asymmetric Reductive Amination of Simple Aromatic

Ketones

3.1 Introduction and background

The direct catalytic asymmetric reductive amination is a more efficient and operational simpler method compared with asymmetric hydrogenation of imines. However, it was rarely studied.¹ Successful asymmetric reductive amination systems are sparse, and the substrate scope is very limited.² Several major problems stands as obstacle to the advance in this research area: 1) The starting ketones can be reduced before the reductive amination takes place; 2) The *E*/*Z* isomers resulting from the acyclic imine intermediate make stereoselective reduction difficult; 3) The amine used as nitrogen source inhibits the reactivity of the transition metal.^{3,2b}

In 1999, Blaser *et al.* explored the first asymmetric reductive amination in the synthesis of (*S*)-metolachlor with a turn over number of 10,000 (Scheme 3-1).^{2c} Then Kadyrov reported highly enantioselective hydrogen-transfer reductive amination using ammonium formate, and this system created a large amount of side products (Scheme 3-2).^{2d} Ammonium salts were proved to be a good nitrogen source for the



Scheme 3-1. First reductive amination reported by Blaser et al.



Scheme 3-2. HCOONH₄ as nitrogen source.



Scheme 3-3. Reductive amination for synthesis of β -amino ester.

synthesis of β -amino ester or β -amino amide (Scheme 3-3).^{2e-2g} Chiral amine 1-methyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline was synthesized by Wills and coworker via intramolecular reductive amination (Scheme 3-4).^{2h} Our group



Scheme 3-4. Intramolecular reductive amination.



Scheme 3-5. Reductive amination using aniline as nitrogen source.

contributed efficient reductive amination of simple aryl ketones using aniline in the presence of titanium(IV) isopropoxide and iodine with excellent enantioselectivity in high yields (Scheme 3-5).²ⁱ Since then, several papers published using anilines as

nitrogen source.^{2j-2l} Although in some systems^{2j,2l} the anilines offer excellent enantioselectivity (Scheme 3-6), the removal of anilines as protecting group is not easy.⁴ So it is still a challenge to find out suitable nitrogen sources that can be used and removed for asymmetric reductive amination of simple ketones.



Scheme 3-6. Ir-chiral diamine/phosphorus acid-catalyzed reductive amination.

The chiral hydrazide productc **3** (Scheme 3-7) were made in high enantioselectivity by Burk and Feaster in 1992 from the asymmetric hydrogenation of *N*-benzoylhydrazone of aromatic and aliphatic ketones.^{5a} However, the direct reductive amination was not realized in this system.^{5b} Phenylhydrazide is a desired nitrogen source due to its carbonyl group acting as a chelation group and formation of *E*-imine structure in Burk's system to ensure high enantioselectivity, and the easiness to cleave the N–N or N–C(O) bond to form chiral hydrazine **4** and chiral amine **5** (Scheme 3-7).^{5b} Chiral hydrazines are substructures of many clinically relevant pharmaceutical compounds.⁶ Arylhydrazide itself is common moiety in nature products and drug candidates displaying high bioactivities (Figure 3-1).⁷ Its derivatives, pyrazolidines are of great importance in biological and medicinal chemistry (Figure 3-1).⁸ At the same time, pyrazolidines are also important synthetic intermediates for making useful 1,3-diamines.⁹



Scheme 3-7. The Cleavage of N–N and N–(C=O) bond.



Figure 3-1. Structures of arydrazide and pyrazolidine.

3.2 Reductive amination using benzylamine as nitrogen source

In early study, benzylamine was used for the reductive amination of acetophenone. The reaction conditions were adopted from previous reductive amination reported by our group. From the initial experiment, the $[Ir(COD)Cl]_2$ and f-Binaphane system yielded 73% *ee* using I₂ as additive and 1.5 eq of Ti(OiPr)₄ (Table 3-1, entry 1). Among the various precious metal precursors, Rh(COD)₂BF₄ gave the best *ee* value (Table 3-1, entry 1). From the solvents screening, weakly coordinated solvents such as THF, toluene and dichloromethane shown good enantioselectivity with the *ee* range between 70% and 80%. The highest *ee* was obtained from ethyl acetate (Table 3-1, entry 1).

Table 3-1. Reductive amination of acetophenone using benzylamine.^[a]



Entry	Metal	Solvent	Conversion(%) ^[b]	Ee(%) ^[b]
1	[Ir(COD)Cl] ₂	CH_2Cl_2	98	73
2	Pd(OAc) ₂	CH ₂ Cl ₂	<5	-
3	[RuCl(benzene)] ₂	CH_2Cl_2	<1	-
4	Ir(COD) ₂ BF ₄	CH_2Cl_2	97	68
5	Ir(COD) ₂ Barf	CH_2Cl_2	97	69
6	Rh(COD) ₂ BF ₄	CH ₂ Cl ₂	94	74
7	[Rh(COD)Cl] ₂	CH_2Cl_2	99	66
8	Rh(COD) ₂ BF ₄	CH ₂ Cl ₂	97	71
9	Rh(COD) ₂ BF ₄	CH ₂ ClCH ₂ Cl	37	60
10	Rh(COD) ₂ BF ₄	МеОН	58	41
11	Rh(COD) ₂ BF ₄	EtOAc	94	81
12	Rh(COD) ₂ BF ₄	THF	98	78
13	Rh(COD) ₂ BF ₄	Toluene	87	79
14	Rh(COD) ₂ BF ₄	DMF	98	-71

[a] Reaction conditions: [M] / ligand / ketone / benzylamine / I_2 / Ti(OiPr)₄ =1:1:100:120:10:150, 50 atm of H₂, 55°C, 24 h.

[b] Conversions of acetophenone and enantiomeric excesses were were determined by chiral GC on Agilent 7890 GC equipment after converted the amine products into the corresponding trifluoroacetamides.

Table 3-2. Anion effect on reductive amination of acetophenone using benzylamine.^[a]



Entry	Metal precursor	Conversion(%) ^[b]	Ee(%) ^[b]
1	Rh(COD) ₂ BF ₄	94	81
2	[Rh(COD)Cl] ₂	99	75
3	Rh(COD) ₂ PF ₆	93	78
4	Rh(COD) ₂ SbF ₆	93	80
5	Rh(COD) ₂ OTf	96	78
6	Rh(COD) ₂ OTs	92	84
7	[Ir(COD)Cl] ₂	99	74
8	Ir(COD) ₂ BF ₄	99	82
9	Ir(COD) ₂ Barf	98	70
10	Ir(COD) ₂ PF ₆	95	57
11	Ir(COD) ₂ OTf	94	72

[a] Reaction conditions: [M] / ligand / ketone / benzylamine / I_2 / Ti(OiPr)₄ =1:1:100:120:10:150, 50 atm of H₂, 55°C, 24 h.

[b] Conversions of acetophenone and enantiomeric excesses were determined by chiral GC on Agilent 7890 GC equipment after converted the amine products into the corresponding trifluoroacetamides.

From further study, we found the anion of metal precursors also have effects on the enantioselectivity (Table 3-2). The highest ee was achieved when Rh(COD)₂OTs was used as metal precursor.

3.3 Reductive amination of simple ketones using phenylhydrazide

In our experiment, we explored phenylhydrazide as nitrogen source for reductive amination using acetophenone as a standard ketone, and results are summarized in table 1. We selected a iridium–f-Binaphane complex as the catalyst because it does not reduce a ketone under a neutral condition, and it has an excellent performance on asymmetric hydrogenation imines and reductive amination.¹⁰

Additives are the key for the success of this reaction. Without any additive, there was no reaction at all (Table 3-3, entry 1). With the addition of 10 mol% p-toluenesulfonic acid, the major product was *N*-benzoylhydrazone intermediate **6a** and some alcohol product **7**; with the addition of iodine along with *p*-toluenesulfonic acid, some product **3a** started to appear; and when molecular sieves (4\AA) , *p*-toluenesulfonic acid and iodine were added at the same time, the desired product **3a**

was obtained as the major product with 88% *ee*, and the alcohol side product **7** disappeared (Table 3-3, entries 2-5). From the data in table 1 addition of molecular sieves and p-toluenesulfonic acid facilitated the formation of intermediate imine **6a**, and addition of I_2 benefited the yield of the desired product **3a**. After screening solvents, the highest enantioselectivity and reactivity were achieved from the combination of methanol and dichloromethane (Table 3-3, entry 8). When the catalyst loading was 0.1 mol%, full conversion was still achieved (Table 3-3, entry 10). Under the same reaction condition, other chiral diphosphine ligands were tested (Figure 3-2). DuanPhos, JosiPhos, Et-DuPhos and BINAP all yielded predominately the hydrozone intermediate **6a**.



Figure 3-2. Structures of chiral phosphine ligands.



Entry	Solvent	Additives ^[b]	Conversio n ^[c]	Ratio (3a:6a:7) ^[c]	Ee(%) of 3 ^[c]
1	CH ₂ Cl ₂	none	N. R.	-	-
2	CH ₂ Cl ₂	TsOH	>95	0:75:25	-
3	CH ₂ Cl ₂	TsOH, I ₂	>95	14:81:5	-
4	CH ₂ Cl ₂	MS, I ₂	65	9:48:43	-
5	CH ₂ Cl ₂	TsOH, MS, I ₂	>99	85:15:0	88
6	EtOAc	TsOH, MS, I ₂	<5	-	-
7	МеОН	TsOH, MS, I ₂	>99	3:97:0	-
8	MeOH / CH ₂ Cl ₂ 1:1	TsOH, MS, I ₂	>99	100:0:0	92
9 ^[d]	MeOH / CH ₂ Cl ₂ 1:1	TsOH, MS, I ₂	>99	100:0:0	94
$10^{[d,e]}$	MeOH / CH ₂ Cl ₂ 1:1	TsOH, MS, I ₂	>99	100:0:0	94

[a] Reaction conditions: [Ir] / ligand / ketone / phenylhydrazide =1:1:110:100, ligand / metal 1:1, 50 atm of H_2 , 60°C, 24 h.

[b] TsOH = p-toluenesulfonic acid, 10 mol%; MS = 4Å molecular sieves, 0.2 gram; I₂ = iodine, 10 mol%.

[c] Conversions, product ratios and enantiomeric excesses were determined by chiral HPLC.

[d] Reaction temperature was room temperature.[e] Catalyst loading was 0.1 mol%.

To gain better understanding of the functions of additives, asymmetric hydrogenation of corresponding imine **6a** was carried out (Table 3-4). Surprisingly, 4Å molecular sieves facilitated this reaction. This result is interesting since molecular sieves were commonly believed to only promote imine formation in reductive amination.^[15] Based on the experiment results, a reaction pathway was proposed (Scheme 3-8).

Table 3-4. Asymmetric hydrogenation of N-benzoylhydrazone 6a.^[a]

H N N K K	$(Ir(COD)CI]_2-f-BinalMeOH/CH_2CI_2,additiv$	uphane 1 mol% 50 atm, r.t. es 3a	
Entry	Additives ^[b]	Yield ^[c]	Ee(%) of 3 ^[c]
1	I ₂	18	92
2	I ₂ , TsOH	16	92
3	I ₂ , MS	>99	94
4	I ₂ , MS, TsOH	>99	94

[a] Reaction conditions: [Ir] / ligand / **6a**=1:1:110:100, ligand / metal 1:1, 50 atm of H₂, room temperature, 24 h.

[b] TsOH = p-toluenesulfonic acid 10 mol%, MS = 4Å molecular sieves 0.2 gram, I_2 =

iodine 10 mol%.

[c] yields and enantiomeric excesses were determined by chiral HPLC.



Scheme 3-8. Proposed mechanism.

After established the optimized reaction conditions, a range of commercial available aromatic ketones were reductive animated using this Ir–f-Binaphane catalyst. Results are summarized in Table 3-5. As we can see, for all chosen *para-* (**1a-1f**) and *meta-*substituted (**1g-1i**) aromatic ketones, the chiral hydrazide products**3** were all obtained in excellent yields and *ee*'s (*ee* ranged from 94% to 99%), regardless their electronic properties. For *ortho-*substituted aromatic ketone (**1j**), the reactivity and enantio-selectivity decreased slightly, maybe due to its sterical hindrance. This

catalytic system also worked quite well for heteroaromatic ketone (11) and 2-naphthalene ketone (1k).

Table 3-5. Direct asymmetric reductive amination of simple aromatic ketones using iridium–f-Binaphane.^[a]



[a] Reaction conditions: [Ir] / ligand / TsOH / I₂ / ketone / phenylhydrazide =1:1:10:10:110:100, ligand / metal 1:1, 50 atm of H₂, rt, 24 h. TsOH = *p*-toluenesulfonic acid, MS = 4 Å molecular sieves 0.2 gram, I₂ = iodine. Yields are isolated yields. Enantiomeric excesses were determined by chiral HPLC. The absolute configuration of product is assigned by comparison of rotation sign with literature data.^[9b]

[b] Reaction temperature was 60 °C.

In summary, we have demonstrated highly enantioseletive direct reductive amination of aromatic ketones. With phenyl-hydrazide as the nitrogen source, various chiral hydrazides were synthesized in excellent enationseletivities and yields. The success of this reaction results from several factors: a) H^+ facilitated the formation of imine intermediates; b) 4Å molecular sieves not only helped to remove H₂O to form imines, but also promoted reduction of imines; c) With the addition of I₂, Ir(III)I₂Cl(f-Binaphane) was formed,^[14a] which is an effective catalytic precursor for hydrogenation of imines; d) Phenyl-hydrazide and the amine products have weak coordination ability to Ir, so catalytic reaction can proceed smoothly; e) f-Binaphane is a unique electron-donating ligand with a big bite angle (P*-Ir-P*).^[16] It minimizes the inhibition effect from amines and can coordinate with sterically demanding imines, thus leads to smooth reaction. The superb performance of the methodology offers an attractive route for chiral amine and chiral hydrazine derived heterocyclic compounds synthesis. We are currently examining the extension of this methodology to other substrates.

3.4 Experimental section

3.4.1 General remarks

All reactions were performed in the nitrogen-filled glovebox or under nitrogen

using standard Schlenk techniques unless otherwise noted. Column chromatography was performed using Sorbent silica gel 60 (230 – 450 mesh). ¹H NMR, and ¹³C NMR spectral data were obtaineded from Bruker 400 MHz spectrometers. Chemical shifts are reported in ppm. Enantiomeric excess values were determined by chiral GC on an Agilent 6890 Series instrument or chiral HPLC on an Agilent 1200 Series instrument. All new products were further characterized by HRMS. A positive ion mass spectrum of sample was acquired on a Micromass 70-VSE mass spectrometer with an electron ionization source..

3.4.2 General Procedure for reductive amination of acetophenone with benzylamine.

Typical reductive amination procedure: In a nitrogen-filled glovebox, acetophenone (0.2 mmol) and benzylamine (0.24 mmol) were stired in anhydrous solvent (0.5 mL) 10 min in a vial. Then $Ti(O^{i}Pr)_{4}$ (0.3 mmol) was added and the resulting solution was stirred for 10 more min. [Ir(COD)f-Binaphane]Cl (0.002 mmol) in situ generated from [Ir(COD)Cl]₂ and f-Binaphane in solvent was added to this vial, followed by I₂ (5.1 mg, 0.02 mmol). The total solution was made to 2.0 mL. The resulting vial was transferred to an autoclave, which was charged with 50 atm of H₂, and stirred at 55 °C for 24 h. The hydrogen gas was released slowly and the solution was concentrated and passed through a short column of silica gel to remove the metal

complex and Ti(O^{*i*}Pr)₄. The product was converted into the corresponding trifluoroacetamides and then analyzed by chiral GC to determine the enantiomeric excesses.

N-benzyl-1-phenylethanamine:¹³ ¹H NMR (CDCl3) δ 7.37-7.20 (m, 10H), 3.80 (q, 1H, J = 6.6 Hz), 3.64 (1H, J = 13.3 Hz), 3.59 (1H, J = 13.3 Hz), 1.63 (broad s, 1H), 1.36 (d, 3H, J = 6.6 Hz). ¹³C NMR (CDCl3) δ 145.3, 140.4, 128.3, 128.2, 127.9 126.7, 126.6, 126.5, 57.3, 51.4 (t), 24.3.

3.4.3 General Procedure for reductive amination of ketone with phenylhydrazide.

In a nitrogen-filled glovebox, ketone (0.22 mmol), 4Å molecular sieves (0.2 g), p-toluenesulfonic acid (0.02 mmol) and phenylhydrazide (0.20 mmol) were stired in anhydrous CH₂Cl₂ (0.5 mL) and MeOH (0.5 mL) for 10 min in a vial. Then [Ir(COD)f-Binaphane]Cl (0.002 mmol) *in situ* generated from [Ir(COD)Cl]₂ and f-Binaphane in CH₂Cl₂ was added to this vial, followed by I₂ (5.1 mg, 0.02 mmol). The total solution was made to 2.0 mL at a MeOH / CH₂Cl₂ ratio of 1:1. The resulting vial was transferred to an autoclave, which was charged with 50 atm of H₂, and stirred at room temperature for 24 h. The hydrogen gas was released slowly and the solution was concentrated and passed through a short column of silica gel to remove the metal

complex and molecular sieves. The product was then analyzed by chiral HPLC to determine the enantiomeric excesses.

(*R*)- *N*'-(1-phenylethyl)benzohydrazide (3a): ⁵ white solid. $[\alpha]^{20}_{D}$ +167.2 (c = 1 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.22-7.76 (m, 11H), 4.22 (q, *J*=6.6 Hz, 1H), 1.41 (d, *J*=6.6 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 167.3, 143.1, 133.0, 131.8, 128.6, 127.6, 127.3, 126.8, 60.1, 22.7. Enantiomeric excess was determined by HPLCusing Chiralcel OJ-H column, Hex/IPA=90:10, 1 mL/min.

(+)- *N*'-(1-(p-tolyl)ethyl)benzohydrazide (3b): white solid. $[\alpha]^{20}_{D}$ +164.6 (c = 0.25 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, *J*=7.2 Hz, 2H), 7.38-7.53 (m, 4H), 7.28 (d, *J*=8 Hz, 2H), 7.10 (d, *J*=7.2 Hz, 2H), 4.18 (q, *J*=6.6 Hz, 1H), 2.33 (s, 3H), 1.41 (d, *J*=6.6 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 167.2, 140.1, 137.2, 133.0, 131.7, 129.3,128.6, 127.1, 126.8, 59.8, 21.2, 21.1. EI-HRMS: 255.1499 (Calculated for C₁₆H₁₉N₂O⁺([M+H]⁺): 255.1497). Enantiomer ratio was determine by HPLC using a Chiralcel OJ-H column, Hex/IPA=90:10, 1 mL/min.

(*R*)- *N*'-(1-(4-methoxyphenyl)ethyl)benzohydrazide (3c): ⁵ light yellow oil. $[\alpha]^{20}_{D}$ +148.3 (c = 1 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, *J*=7.2 Hz, 2H), 7.40 (m, 1H), 7.32 (m, 2H), 7.28 (d, *J*=7.2 Hz, 2H), 6.82 (d, *J*=7.2 Hz, 2H), 4.18 (q, *J*=6.6
Hz, 1H), 3.79 (s, 3H), 1.40 (d, *J*=6.6 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 166.2, 158.1, 134.0, 132.0, 130.7, 128.0, 127.8, 125.8, 113.0, 58.4, 54.3, 20.2. Enantiomer ratio was determine by HPLC using a Chiralcel OJ-H column, Hex/IPA=90:10, 1 mL/min.

(+)-*N*'-(1-(4-fluorophenyl)ethyl)benzohydrazide (3d): white solid. $[\alpha]^{20}_{D}$ +177.6 (c = 0.5 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.72 (m, 2H), 7.54 (m, 2H), 7.32 (m, 4H), 6.98 (m, 2H), 5.02 (s, br,1H), 4.24 (q, *J*=6.6 Hz,1H), 1.30 (d, *J*=6.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 167.4, 163.5, 161.0, 138.9, 132.8, 131.9, 128.8, 128.7, 126.8, 115.5, 115.3, 59.3, 29.7, 21.3. EI-HRMS: 259.1253 (Calculated for C₁₅H₁₆N₂OF⁺([M+H]⁺): 259.1247). Enantiomer ratio was determine by HPLC using a Chiralcel OJ-H column, Hex/IPA=94:6, 1 mL/min.

(+)-*N*'-(1-(4-chlorophenyl)ethyl)benzohydrazide (3e): white solid. $[\alpha]^{20}_{D}$ +159.3 (c = 0.5 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, *J*=7.2 Hz, 2H), 7.48 (m, 1H), 7.28-7.44 (m, 7H), 4.24 (q, *J*=6.6 Hz, 1H), 1.42 (d, *J*=6.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 167.4, 141.8, 133.3, 132.7, 131.9, 128.8, 128.7, 128.6, 126.8, 59.4, 21.3. EI-HRMS: 275.0946 (Calculated for C₁₅H₁₆N₂OCl⁺([M+H]⁺): 275.0951). Enantiomer ratio was determine by HPLC using a Chiralcel OJ-H column, Hex/IPA=94:6, 1 mL/min. (*R*)-*N*'-(1-(4-bromophenyl)ethyl)benzohydrazide (3f):⁵ white solid. $[\alpha]^{20}_{D}$ +144.3 (c = 1 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, *J*=7.2 Hz, 2H), 7.20-7.50 (m, 8H), 4.24 (q, *J*=6.6 Hz, 1H), 1.42 (d, *J*=6.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 167.4, 142.3, 132.7, 131.9, 131.7, 129.0, 128.7, 126.8, 121.4, 59.5, 21.3. Enantiomer ratio was determine by HPLC using a Chiralcel OJ-H column, Hex/IPA=94:6, 1 mL/min.

(+)-*N*'-(1-(3,4-dimethoxyphenyl)ethyl)benzohydrazide (3g): white solid. $[\alpha]^{20}_{D}$ +143.9 (c = 1 in CHCl₃); ¹H NMR (400 MHz, CDCl₃)δ 7.64 (d, *J*=7.2 Hz, 2H), 7.50 (m, 1H), 7.40 (m, 2H), 7.04 (m, 1H), 6.88-7.00 (m, 2H), 6.84 (d, *J*=7.2 Hz,1H), 4.26 (q, *J*=6.6 Hz, 1H), 3.90 (m, 2H), 1.46 (d, *J*=6.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ167.2, 149.2, 148.6, 135.0, 132.7, 131.9, 128.7, 126.9, 119.6, 111.2, 110.2, 60.0, 55.9, 20.9. EI-HRMS: 301.1560 (Calculated for C₁₇H₂₁N₂O₃⁺([M+H]⁺): 301.1552). Enantiomer ratio was determine by HPLC using a Chiralcel OJ-H column, Hex/IPA=90:10, 1 mL/min.

(+)-*N*'-(1-(3-methoxyphenyl)ethyl)benzohydrazide (3h): white solid. $[\alpha]^{20}_{D}$ +176.5 (c = 0.25 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, *J*=7.2 Hz, 2H), 7.24-7.52 (m, 5H), 7.00 (m, 2H), 6.82 (m, 1H), 6.76 (d, *J*=6.6 Hz, 1H), 4.24 (q, *J*=6.6 Hz, 1H), 3.80 (s, 3H), 1.42 (d, *J*=6.6 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 167.3, 159.9, 144.9, 132.9, 131.8, 129.6, 128.7, 126.8, 119.6, 113.0, 112.6, 60.1, 55.2, 21.4. EI-HRMS: 271.1457 (Calculated for $C_{16}H_{19}N_2O_2^+([M+H]^+)$: 271.1447). Enantiomeric excess was determined by HPLC using Chiralcel OJ-H column, Hex/IPA=90:10, 1 mL/min.

(+)-*N*'-(1-(m-tolyl)ethyl)benzohydrazide (3i): colorless liquid. $[\alpha]^{20}_{D}$ +156.6 (c = 1 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.60 (m, 3H), 7.40 (m, 1H), 7.30 (m, 2H), 7.16 (m, 3H), 7.00 (d, *J*=7.2 Hz,1H), 4.12 (q, *J*=6.6 Hz, 1H), 1.32 (q, *J*=6.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 167.3, 143.0, 138.2, 133.0, 131.7, 131.5, 128.6, 128.5, 128.4, 128.0, 126.9, 124.3. EI-HRMS: 255.1503 (Calculated for C₁₆H₁₉N₂O⁺([M+H]⁺): 255.1497). Enantiomeric excess was determined by HPLC using Chiralpak AD-H column, Hex/IPA=96:4, 1 mL/min.

(+)- *N*'-(1-(2-methoxyphenyl)ethyl)benzohydrazide (3j): white solid. $[\alpha]^{20}_{D}$ +87.2 (c = 1 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.62 (m, 2H), 7.32-7.48 (m, 5H), 7.22 (m, 1H), 6.94 (m, 1H), 6.82 (d, *J*=7.2 Hz,1H), 4.58 (q, *J*=6.6 Hz, 1H), 3.73 (s, 3H),1.36 (q, *J*=6.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 166.9, 157.4, 133.2, 131.6, 131.1, 128.6, 128.3, 126.9, 126.8, 120.7, 110.7, 55.4, 53.9, 19.6. EI-HRMS: 269.1292 (Calculated for C₁₆H₁₇N₂O₂⁺([M+H]⁺): 269.1290). Enantiomeric excess was determined by HPLC using Chiralpak AS-H column, Hex/IPA=75:25, 1 mL/min. (*R*)- *N*'-(1-(naphthalen-2-yl)ethyl)benzohydrazide (3k):⁵ white solid. $[\alpha]^{20}_{D}$ +195.9 (c = 1 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.76 (m, 4H), 7.54 (m, 4H), 7.40 (m, 3H), 7.30 (m, 2H), 6.70-6.78 (m, 3H), 4.40 (q, *J*=6.6 Hz, 1H), 1.42 (q, *J*=6.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 167.4,140.6, 133.5, 133.1, 132.9, 131.8, 128.6, 128.4, 127.9, 127.7, 127.2, 126.9, 126.1, 126.1, 125.8, 125.2, 60.2, 21.3. Enantiomeric excess was determined by HPLC using Chiralcel OJ-H column, Hex/IPA=85:15, 1 mL/min.

(+)-*N*'-(1-(furan-2-yl)ethyl)benzohydrazide (3l): yellow oil. $[\alpha]^{20}_{D}$ +105.1 (c = 0.25 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.70 (m, 2H), 7.62 (s, 1H), 7.50 (m, 1H), 7.42 (m, 3H), 6.32 (m, 1H), 6.20 (m, 1H), 4.32 (q, *J*=6.6 Hz, 1H), 1.48 (q, *J*=6.6 Hz, 3H).. ¹³C NMR (100 MHz, CDCl₃) δ 167.3, 155.5, 142.1, 132.9, 131.9, 128.7, 126.9, 110.1, 106.7, 53.6, 17.6. EI-HRMS: 231.1138 (Calculated for C₁₃H₁₅N₂O₂⁺([M+H]⁺): 231.1134). Enantiomeric excess was determined by HPLC using Chiralcel OJ-H column, Hex/IPA=85:15, 1 mL/min.

Reference:

- D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* 2007, 9, 411.
- (a) V. I. Tararov, A. Börner, Synlett. 2005, 203. (b) T. C. Nugent, M. El-Shazly, Adv. Synth. Catal. 2010, 352, 753. (c) H.-U. Blaser, H.-P. Buser, H.-P. Jalett, B. Pugin, F. Spindler, Synlett. 1999, 867. (d) R. Kadyrov, T. H. Riermeier, Angew. Chem. Int. Ed. 2003, 42, 5472. (e) V. I. Tararov, A. Börner, Synlett. 2005, 203. (f) D. Steinhuebel, Y. Sun, K. Matsumura, N. Sayo, T. Saito, J. Am. Chem. Soc. 2009, 131, 11316. (g) P. Mattei, G. Moine, K. Püntener, R. Schmid, Org. Process Res. Dev. 2011, 15, 353. (h) G. D. Williams, R. A. Pike, C. E. Wade, M. Wills, Org. Lett. 2003, 5, 4227. (i) Y. Chi, Y. Zhou, X. Zhang, J. Org. Chem. 2003, 68, 4120. (j) L. Rubio-Pe'rez, F. J. Pe'rez-Flores, P. Sharma, L. Velasco, A. Cabrera, Org. Lett. 2009, 11, 265. (k) C. Li, B. Villa-Marcos, J. Xiao, J. Am. Chem. Soc. 2009, 131, 6967. (l) B. Villa-Marcos, C. Li , K. R. Mulholland, P. J. Hogan, J. Xiao, Molecules 2010, 15, 2453. (m) G. F. Busscher, L. Lefort, J. G. O. Cremers, M. Mottinelli, R. W. Wiertz, B. d. Lange, Y. Okamura, Y. Yusa, K. Matsumura, H. Shimizu, J. G. de Vries, A. H. M. de Vries, Tetrahedron: Asymmetry 2010, 21,1709.
- 3. T. C. Nugent (Ed.), Chiral Amine Synthesis, Wiley-VCH, Weinheim, 2010.
- 4. (a) F. Palacios, D. Aparicio, J. Garca, E. Rodrguez, *Eur. J. Org. Chem.* 1998, 1413.
 (b) D. Taniyama, M. Hasegawa, K. Tomioka, *Tetrahedron Lett.* 2000, *41*, 5533.
- (a) M. J. Burk, J. E. Feaster, J. Am. Chem. Soc. 1992, 114, 6267. (b) M. J. Burk, J. P. Martinez, J. E. Feaster, N. Cosforda, *Tetrahedron* 1994, 50, 4399.
- (a) J. M. Coteron, D. Catterick, J. Castro, M. J. Chaparro, B. Diaz, E. Fernandez, S. Ferrer, F. J. Gamo, M. Gordo, J. Gut, H. L. de las, J. Legac, M. Marco, J. Miguel, V. Munoz, E. Porras, J. C. de la Rosa, J. R. Ruiz, E. Sandoval, P. Ventosa, P. Rosenthal, J. M. Fiandor, *J. Med. Chem.* 2010, *53*, 6129. (b) R. E. Parmee, Y. Xiong, J. Guo, L. Brockunler, U.S. Patent 20070088070 A1, 2007. (c) R. E. Hormann, C. M. Tice, O. Chortyk, H. Smith, T. Meteyer, U.S. Patent WO. 2004/072254 A2, 2004. (d) N. C. Giampietro, J. P. Wolfe, *J. Am. Chem. Soc.* 2008, *130*, 12907.
- 7. R. E. Hormann, B. Li, PCT Int. Appl. WO 2008153801 A1, 2008.
- Z.-C. Geng, J. Chen, N. Li, X.-F. Huang, Y. Zhang, Y.-W. Zhang, X.-W. Wang, Beilstein J. Org. Chem. 2012, 8, 1710.
- (a) K. Tran, P. J. Lombardi, J. L. Leighton, Org. Lett. 2008, 10, 3165. (b) Y. Yamashita, S. Kobayashi, J. Am. Chem. Soc. 2004, 126, 11279. (c) S. Shirakawa, P. J. Lombardi, J. L. Leighton, J. Am. Chem. Soc. 2005, 127, 9974.
- (a) D. Xiao, X. Zhang, Angew. Chem. Int. Ed. 2001, 40, 3425. (b) G. Hou, F. Gosselin, W. Li, J. C. McWilliams, Y. Sun, M. Weisel, P. D. O'Shea, C.-Y. Chen, I. W. Davies, X. Zhang, J. Am. Chem. Soc. 2009, 131, 9882. (c) G. Hou, W. Li, M. Ma, X. Zhang, X. Zhang, J. Am. Chem. Soc. 2010, 132, 12844. (d) M. Chang, W. Li, G. Hou, X. Zhang, Adv. Synth. Catal. 2010, 352, 3121. (e) M. Chang, W. Li, X.

Zhang, Angew. Chem. Int. Ed. 2011, 50, 10679. (f) Y. Chi, Y.-G. Zhou, X. Zhang, J. Org. Chem. 2003, 68, 4120.

- 11. (a) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* 2005, 7, 3781. (b) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem. Int. Ed.* 2005, 44, 7424. (c) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* 2006, *128*, 84.
- 12. Q. Yang, G. Shang, W. Gao, J. Deng, X. Zhang. Angew. Chem. Int. Ed. 2006, 45, 3832.
- 13. C. Guérin, V. Bellosta, G. Guillamot, J. Cossy, Org. Lett. 2011, 13, 3534.

Chapter 4

Iridium-catalyzed Asymmetric Hydrogenation of Pyridinium Salts

4.1 Introduction and background

During the last decade progress has been made for the asymmetric hydrogenation of *N*-heteroarenes leading to chiral piperidines. Piperidine derivatives are an important class of amines displaying bioactivity.¹ Examples are ropivacaine,² dexmethylphenidate,³ paroxtine,⁴ and alogliptin⁵ (Figure 4-1). Bicyclic aromatic compounds, such as quinolines and isoquinolines, are relatively easy to hydrogenate due to the relatively low aromaticity, while hydrogenation of single-ring aromatic compounds is much more difficult.⁶

In 2003 Zhou and coworkers reported the first highly enantioselective hydrogenation of quinolines example utilizing iridium catalyst generated in situ from $[Ir(COD)Cl]_2$ and axially chiral bisphosphine ligand MeO-BiPhep (Scheme 4-1) with iodine as additive.⁷ A plausible mechanism was proposed (Scheme 4-2).⁸ Chan *et al.* developed the C_3 -TunePhos in 2006 and applied in the asymmetric hydrogenation of quinoline using the same reaction conditions as Zhou's.⁹ Later on Chan and Xiao respectively developed phosphorus free Ru/Rh-diamine catalytic hydrogenatin and



Ropivacaine



Dexmethylphenidate

H₂N



Paroxtine GSK



NC

Ν

Figure 4-1. Structures of ropivacaine, dexmethylphenidate, paroxtine, and alogliptin.



Scheme 4-1. First highly enantioselective asymmetric hydrogenation of quinolines.



Scheme 4-2. Proposed mechanism for asymmetric hydrogenation of quinolines.

transfer-hydrogeantion of quinolines.¹⁰ As for isoquinolines, these are more difficult substrates compared with quinolines. In 2006, Zhou's group partially hydrogenated the chloroformate derivatives of isoquinolines using [Ir(COD)Cl]₂ / SegPhos to achieve good *ee*'s.¹¹ Last year they reported direct hydrogenation of 3,4-disubstituted isoquinolines.¹² And very recently *N*-benzyl isoquinolines were used as substrates for asymmetric hydrogenation. Mashima and coworkers investigated asymmetric hydrogenation of HCl • isoquinolinium salts and excellent enantioselctivities were achieved.¹³

In contrast, the asymmetric hydrogenation of pyridines remains as a challenge. The examples for direct homogeneous transition-metal-catalyzed asymmetric hydrogenation of pyridines are very limited. Only a few papers conducted direct hydrogenation of pyridines and the substrate scope was confined to only several compounds. The major challenge is to break the aromaticity of the pyridine ring. It is much harder to achieve compared with that of the fused *N*-aromatic rings like quinolines. Another reason is that the pyridines themselves are good ligand for the transition metal center of the catalytic system, thus they will inhibit the activity of the catalyst.

In 2000 Struder and coworkers reported the first example of pyridine reduction.¹⁴ 2- and 3-pyridinecarboxylic acid ethyl esters were hydrogenated using Rh(NBD)₂BF₄ / diphosphine as the catalyst, although only 25% ee was achieved (Scheme 4-3). Zhou's (S)-MeO-Biphep $[Ir(COD)Cl]_2$ / system partially reduced 7,8-dihydro-quinolin-5(6H)-ones with excellent enantioselectivities, but it was not efficient for other types of pyridines (Scheme 4-4).¹⁵ For indirect asymmetric hydrogenation of pyridines, several strategies were applied to address this problem: (1) Chiral auxiliary was introduced to the 2 position of pyridine to induce chirality, and then chopped off after hydrogenation (Scheme 4-5);¹⁶ (2) Step-wise reduction of the pyridine ring (Scheme 4-6);¹⁷ (3) Pyridinium salts derived from pyridines were instead as the hydrogenation substrates (Scheme 4-7). In 2005 Charette et al. examined the asymmetric hydrogenation of N-iminopyridinium ylides and excellent



Scheme 4-3. The first example for asymmetric hydrogenation of pyridines.



ee up to 97%

Scheme 4-4. Direct asymmetric hydrogenation of pyridines.



Scheme 4-5. Utility of chiral auxiliary on the 2 position of pyridine to induce chirality.



Scheme 4-6. Step-wise hydrogenation of pyridine.



Scheme 4-7. Asymmetric hydrogenation of N-iminopyridinium ylides.



Scheme 4-8. Asymmetric hydrogenation of pyridinium salts.

enantioselectivities were achieved (Scheme 4-7).^{18a} Recently Zhou and coworkers made a breakthrough in pyridine reduction (Scheme 4-8).^{18b} They derived the pyridines into pyridinium salts for hydrogenation and superb yields and *ee*'s were obtained. But two steps were required for the products to remove the benzyl protecting group.

4.2 Results and discussion

4.2.1 Direct asymmetric hydrogenation of methyl nicotinate

Initially we tried the direct hydrogenation of pyridines. No surprise it did not work. As we know bronsted acid could dearomatize the pyridines in some degree by protonating the nitrogen and thus reducing the electron density of the aromatic ring. So trifluoroacetic acid salt of methyl nicotinate was tested using 5 mol% of [Ir(COD)Cl]₂-f-Binaphane (Table 4-1). In CH₂Cl₂, the reaction performed the best, with 90% conversion and 23% *ee* (Table 4-1, entry 1). I₂ could increase the catalyst reactivity but reduce the enantioselectivity (Table 4-1, entry 2).

Table 4-1. Asymmetric hydrogenation of methyl nicotinate• TFA.^[a]



Entry	Solvent	Additive	Conversion(%) ^[b]	Ee(%) ^[b]
1	CH_2Cl_2	none	90	23
2	CH_2Cl_2	I ₂ 10 mol%	98	4.5
3	CH_2Cl_2	I ₂ 10 mol% PPh ₃ 5 mol%	81	5.5
4	CH_2Cl_2	morphaline•HCl 20 mol%	>99	7
5	Acetone	none	<10	-6
6	ⁱ PrOH	none	90	-6
7	MeOH/THF	none	37	-6
11	CF ₃ CH ₂ OH	none	78	19

Other Bronsted acids were also screened (Table 4-2). Pyridines combined with HCl or CCl₃COOH did not react at all. MeSO₃H and CF₃SO₃H helped on the conversion of the pyridine substrate to desired product, but led to lower *ee*'s compared with trifluoro acetic acid. With the change of the methyl of the nicotinate to larger groups like ethyl or isopropyl, the *ee*'s indeed increased, but the reactivity of those substrates dropped dramatically.

Table 4-2. Asymmetric hydrogenation of methyl nicotinate•HA.^[a]



Entry	Acid HA	R	Conversion(%) ^[b]	Ee(%) ^[b]
1	CF ₃ COOH	Me	90	23
2	HCl	Me	<5	-
3	CCl ₃ COOH	Me	<10	-
4	MeSO ₃ H	Me	>90	-3
5	CF ₃ SO ₃ H	Me	>90	12
6	HBF_4	Me	23	1
7	CF ₃ COOH	Et	13	33
8	CF ₃ COOH	ⁱ Pr	7	33

4.2.2 Asymmetric hydrogenation of *N*-benzylpyridinium salts

Benzyl group is a one of the mostly used *N*-protecting groups in organic synthesis due to the easiness for removal. In our study, the simple benzyl group was chosen to alleviate the aromaticity of the pyridines thus making them suitable for asymmetric hydrogenation. This pyridium salt was studied but the enantioselectivity for this reaction was not satisfied. In the initial chiral ligands screening (Table 4-3),



Scheme 4-8. Chiral ligands structures.

atropisomeric C_2 -symmetric bisphosphine ligands (Scheme 4-9), such as BINAP, SegaPhos and GarPhos, along with [Ir(COD)Cl]₂ metal precursor showed good enantioselectivity towards the asymmetric hydrogenation of the standard *N*-benzyl-2-phenylpyridium bromide subastrate. From further ligands study, the MP²-SegaPhos yielded excellent *ee*.

The structure for MP²-SegPhos is quite unique. Unlike the original SegPhos, 'two' substituents on phosphorus of MP²-SegPhos are actually one piece. Its structural module is more like that of DuPhos. This diphosphine ligand is quite rigid and thus could define the steric environment around phosphorus very well. At the same time MP²-SegPhos is axial chiral thus gain some flexibility to accommodate various substrates with different size. This ligand was reported by Takasago as early as in 2004 but found no application ever since.¹⁹

From the solvent screening (Table 4-4), polar protic alcohol solvents did not yield good results. Excellent enantioselectivities were obtained from weakly coordinated solvents such as dichloromethane, dioxane, toluene and acetone. Even though many of the solvents yielded similar results, we chose the environmentally benign acetone to do further study. Several of the mixed solvents performed greatly in this reaction (Table 4-5). When the catalyst loading was reduced to 0.1 mol%, the *ee* was slightly lower with 96% conversion.





Entry	Solvent	Conversion(%) ^[b]	Ee(%) ^[b]
1	CH ₂ ClCH ₂ Cl	99	94.1
2	EtOAc	57	93.6
3	CH ₂ Cl ₂	53	93.3
4	Acetone	100	93.1
5	Dioxane	62	92.8
6	Toluene	22	89.1
7	Anisole	81	89.5
8	DMF	100	89.4
9	МеОН	32	63.1
10	MeCN	95	57
11	CF ₃ CH ₂ OH	0	0

[a] Reaction conditions: $[Ir(COD)CI]_2$ / MP2-Segphos 1 mol%, 600 psi of H₂, 30°C, 24 h. [b] Conversions of acetophenone and enantiomeric excesses were determined by chiral SFC on Waters 200 equipment.

Table 4-5. Solvents and catalyst loading screening for asymmetric hydrogenation of *N*-benzyl-2-phenylpyridium bromide.^[a]



Entry	Solvent	Catalyst loading (mol%)	Conversion(%) ^[b]	Ee(%) ^[b]
1	CH ₂ Cl ₂ /Toluene 1:1	0.5	85	96.2
2	EtOAc/CH ₂ Cl ₂ 1:1	0.5	97	96.1
3	CH ₂ Cl ₂ /THF 1:1	0.5	98	96.0
4	CH ₂ Cl ₂ /Acetone 1:1	0.5	98	95.6
5	Acetone	0.5	100	94.6
4	Acetone/tolene 1:1	0.5	99	95.5
5	Acetone/THF 1:1	0.5	100	93.6
6	Acetone	0.25	92	96
7	Acetone	0.1	97	92

[a] Reaction conditions: $[Ir(COD)CI]_2$ / MP2-Segphos 1 mol%, 600 psi of H₂, 30°C, 24 h. [b] Conversions of acetophenone and enantiomeric excesses were determined by chiral SFC on Waters 200 equipment.

In comparison, different benzyl groups were tested (Scheme 4-9). All of them yielded excellent *ee*'s using [Ir(COD)Cl]₂-MP²-SegPhos catalytic system. The advantage for using *para*-methoxylbenzyl group is that the conditions for the removal of this protecting group is very mild and no need of the commonly used Pd/C, which will add versatility and accommodation to different functional group to this method.



Scheme 4-9. Asymmetric hydrogenation of pyridinium salts with different benzyl substitutes.

To evaluate the practical utility of our method, various *N*-benzyl-(2-aryl)pyridinium bromide substrates were prepared and hydrogenated (Table 4-6). For most *para-* and *meta-substituted* substrates, excellent ee's were achieved. For ortho-substituted compounds, the ee's were slightly lower.

Table 4-6. Substrate scope for asymmetric hydrogenation of *N*-Benzylpyridinium salts.



Deprotection of the benzyl group after asymmetric hydrogenation was in very mild conditions. For the removal of the simple benzyl group, one-pot reaction could be utilized (Eq. 1). As for para-methoxylbenzyl protecting group, various methods are available (Eq. 2). Compared with two-steps removal of 2'-COO^{*i*}Pr-benzyl group in Zhou's paper, out method is much simpler and more versatile, if taking the functional group tolerance in to consideration.



4.3 Experimental section

4.3.1 General procedure for synthesis of *N*-benzylpyridinium salts.

Most of the substrates were synthesized iin two steps according to literature.

Step 1:

In glove box in a 40 ml vial was added 2-chloropyridine (or 2-bromopyridine) (5mmol) and dppf (0.5mmol), Pd (II) acetate (0.5 mmol), arylboronic acid (5 mmol) , Cs_2CO_3 (10 mmol) in 5ml H₂O (degassed for 15min) and 20ml 1,4-dioxane. The suspension was stirred and heated to 70 °C for 20 hours. After cooled, removed from the glove box and then diluted with EtOAc, filtered through ceilite. Removed solvent. The resulting residue was purified by chromatography (0-100% Hexane/EtOAc) to obtain colorless oil. NMR confirmed as desired product.

Step 2:



The solution of 2-arylpyridine (4 mmol) and benzyl bromide (4.4 mmol) in acetone was refluxed overnight. In most cases product will precipitate out. Then product was collected from filtration and further purified by recrystallization. In case there was no precipitate, silica column chromatography was required to purify the raw product.

N-benzyl-2-phenylpyridium bromide (**3a**): White solid. ¹H NMR (400 MHz, CDCl₃) δ 9.80 (d, 1H), 8.54 (m, 1H), 8.20 (m, 1H), 7.86 (m, 1H), 7.50-7.78 (m, 5H), 7.30 (m, 4H), 7.10 (m, 2H), 6.20 (s, 2H).

4.3.2 General procedure for asymmetric hydrogenation of *N*-benzylpyridinium salts.

In a nitrogen-filled glovebox, $[Ir(COD)Cl]_2$ (0.5 µmol) and f-Binaphane (1 µmol) was dissolved in acetone and stirred for 0.5 h. Then this solution was added to a vial charged with *N*-benzylpyridiniun salt (0.2 mmol). The resulting vial was transferred to an autoclave, which was charged with 600 psi of H₂, and stirred at30 °C for 24 h. The hydrogen gas was released slowly and the solution was concentrated to yield the raw product, which was then analyzed by chiral SFC to determine the enantiomeric excesses.

Reference:

- (a) S. Källström, R. Leino, *Bioorg. Med. Chem.* 2008, *16*, 601. (b) P. A. Petukhov, J. Zhang, C. Z. Wang, Y. P. Ye, K. M. Johnson and A. P. Kozikowski, *J. Med. Chem.* 2004, *47*, 3009. (c) P. D. Bailey, P. A. Millwood and P. D. Smith, *Chem. Commun.* 1998, 633.
- 2. Hansen TG. Expert Rev Neurother. 2004, 4, 781.
- 3. A. Gutman, I. Zaltsman, A. Shalimov, M. Sotrihin, G. Nisnevich, L. Yudovich, I. Fedotev, U.S. Pat. Appl. Publ. US 20040180928 A1 20040916, 2004.
- 4. J. Buus Lassen, Psychopharmacology 1989, 98, 257.
- 5. J. Feng, Z. Zhang, M. B. Wallace, J. A. Stafford, S. W. Kaldor, D. B. Kassel, M. Navre, L. Shi, R. J. Skene, T. Asakawa, *et al*, *J. Med. Chem.* **2007**, 50, 2297.
- 6. D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, Chem. Rev. 2012, 112, 2557.
- W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han, Y.-G. Zhou, J. Am. Chem. Soc. 2003, 125, 10536.
- D.-W. Wang, X.-B. Wang, D.-S. Wang, S.-M. Lu, Y.-G. Zhou, Y.-X. Li, J. Org. Chem. 2009, 74, 2780.
- L. Q. Qiu, F. Y. Kwong, J. Wu, W. H. Lam, S. Chan, W.-Y. Yu, Y.-M. Li, R. W. Guo, Z. Zhou, A. S. C. Chan, J. Am. Chem. Soc. 2006, 128, 5955.
- (a) H.-F. Zhou, Z.-W. Li, Z.-J. Wang, T.-L. Wang, L.-J. Xu, Y.-M. He, Q.-H. Fan, J. Pan, L.-Q. Gu, A. S. C. Chan, *Angew. Chem., Int. Ed.* 2008, 47, 8464. (b) T.-L. Wang, L. G. Zhuo, Z.-W. Li, F. Chen, Z.-Y. Ding, Y.-M. He, Q.-H. Fan, J.-F. Xiang, Z.-X. Yu, A. S. C. Chan, *J. Am. Chem. Soc.* 2011, 133, 9878. (c) C. Wang, C. Q. Li, X. F. Wu, A. Pettman, J. L. Xiao, *Angew. Chem., Int. Ed.* 2009, 48, 6524.
- 11. S.-M. Lu, Y.-Q. Wang, X.-W. Han, Y.-G. Zhou, Angew. Chem. Int. Ed. 2006, 45, 2260.
- (a) L. Shi, Z.-S. Ye, L.-L. Cao, R.-N. Guo, Y. Hu, Y.-G. Zhou, *Angew. Chem. Int. Ed.* 2012, *51*, 8286. (b) Z.-S. Ye, R.-N. Guo, X.-F. Cai, M.-W. Chen, L. Shi, Y.-G. Zhou, *Angew. Chem. Int. Ed.* 2013, *52*, 3685.
- 13. A. Iimuro, K. Yamaji, S. Kandula, T. Nagano, Y. Kita, K. Mashima, *Angew. Chem. Int. Ed.* **2013**, *52*, 2046.
- 14. M. Studer, C. Wedemeyer-Exl, F. Spindler, H. U. Blaser, *Monatsh. Chem.* 2000, *131*, 1335.
- 15. X.-B. Wang, W. Zeng, Y.-G. Zhou, Tetrahedron Lett. 2008, 49, 4922.
- 16. F. Glorius, N. Spielkamp, S. Holle, R. Goddard, C. W. Lehmann, Angew. Chem. Int. Ed. 2004, 43, 2850.
- 17. A. W. Lei, M. Chen, M. S. He, X. Zhang, Eur. J. Org. Chem. 2006, 4343.
- (a) C. Y. Legault, A. B. Charette, J. Am. Chem. Soc. 2005, 127, 8966. (b) Z.-S. Ye, M.-W. Chen, Q.-A. Chen, L. S., Y. Duan, Y.-G. Zhou, Angew. Chem. Int. Ed. 2012, 51, 10181.
- 19. H. Shimizu, T. Saito, I. Nagasaki, U.S. Pat. Appl. Publ. US 20040092388 A1 20040513, 2004.

Publications

- **1.** Chang, M.; Liu, S.; Huang, K.; Zhang, X. "Direct Asymmetric Reductive Amination of simple ketones with Iridium catalyst", *Org. Lett.* ASAP.
- 2. Chang, M.; Li, W.; Zhang, X. "A Highly Efficient and Enantioselective Access to Tetrahydroisoquinoline Alkaloids via Asymmetric Hydrogenation with Iridium Catalyst", *Angew. Chem. Int. Ed.* 2011, *50*, 10679.
- **3.** Chang, M.; Li, W.; Hou, G.; Zhang, X. "Iridium-Catalyzed Enantioselective Hydrogenation of Cyclic Imines", *Adv. Syn. Cata.* **2010**, *352*, 3121.