**Nickel-Catalyzed Asymmetric Transfer Hydrogenation of Unsaturated
C=C and C=N Bonds Using Formic Acid**

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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Abstract

This thesis describes my work on nickel-catalyzed asymmetric transfer hydrogenation of unsaturated C=C and C=N bonds using formic acid. It contains three main parts.

Chapter one reports a highly enantioselective asymmetric hydrogenation of hydrazones with a chiral ligand, (*S*)-Binapine. Both aryl and aliphatic methyl hydrazones afforded the desired products in good to excellent *ee* values. Furthermore, DFT calculation revealed that the nickel catalyst controls the asymmetric hydride insertion to unsaturated C=N bonds by controlling the binding conformation of the amide directing group, instead of differentiating group on the imine fragment.

Chapter two describes asymmetric reductive amination of simple ketones with sulfonamides in one pot. With a nickel/(*S*)-Binapine catalytic system, a series of chiral tosylamines were obtained in high enantioselectivities. This one-pot reductive amination of simple ketones is operationally simple and avoids the isolation and purification of the intermediate tosylimines.

Chapter three reports the asymmetric hydrogenation of olefins for the synthesis of unnatural amino acid derivatives, using a nickel catalyst ligated by a chiral bisphosphine (*S*)-Binapine. In some cases of cyclic *tetra*-substituted dehydroamino acid derivatives, good yields and excellent *ee* values were achieved.

PUBLICATIONS

1. Nickel-Catalyzed Asymmetric Transfer Hydrogenation of Hydrazones and Other Ketimines

Haiyan Xu, Peng Yang, Pratanphorn Chuanprasit, Hajime Hirao* and Jianrong (Steve) Zhou, *Angew. Chem., Int. Ed.* **2015**, *54*, 5112-5116.

2. Nickel-Catalyzed Asymmetric Transfer Hydrogenation of Olefins for the Synthesis of α - and β - Amino Acids

Peng Yang, **Haiyan Xu** (equal contribution), and Jianrong (Steve) Zhou, *Angew. Chem., Int. Ed.* **2014**, *53*, 12210-12213.

LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
Ad	adamantly
Ar	aryl
BINAP	(1,1'-Binaphthalene-2,2'-diyl)bis(diphenylphosphine)
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bu	butyl
calcd	calculated
CDCl ₃	deuterated chloroform
CH ₂ Cl ₂	dichloromethane
conv.	conversion
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
DME	1,2-dimethoxyethane
DMF	dimethylformamide
dt	doublet of triplets
ee	enantiomeric excess
EI	electronic ionization
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
Et ₂ O	diethyl ether
EtOAc	ethyl acetate
g	gram
GC	gas chromatography
h	hour(s)
Hz	hertz
IMes	1,3-bis(mesityl)imidazole-2-ylidene
<i>i</i> -Pr	<i>iso</i> -propyl

m	multiplet
M ⁺	parent ion peak (mass spectrum)
Me	methyl
min	minute(s)
mL	milliliter(s)
mmol	millimole
mol%	mole percent
MS	mass spectrometry
Nap	Na phthyl
<i>n</i> -Bu	<i>n</i> -butyl
<i>n</i> -hex	<i>n</i> -hexyl
NMR	nuclear magnetic resonance
°C	degree centigrade
OTf	trifluoromethanesulfonate
PCy ₃	tricyclopentylphosphine
Ph	phenyl
PhCF ₃	α, α, α -trifluorotoluene
PhMe	toluene
ppm	perts per million
q	quartet
rt	room temperature
TBME	methyl <i>tert</i> -butyl ether
<i>t</i> -Bu	<i>tert</i> -butyl
THF	tetrahydrofuran
TMEDA	<i>N,N,N',N'</i> -Tetramethylethylenediamine
TMS	trimethylsilyl
Tol	toluene
δ	chemical shift

Chapter 1 Nickel-Catalyzed Asymmetric Transfer Hydrogenation of Hydrazones

1.1 Introduction

Chiral amines are crucial structural units in bioactive molecules. Many brand-name drugs contain at least one chiral amine fragment, such as Cinacalcet, Flomax, Rivastidine and Zoloft. Flomax is used to improve urination in men with enlarged prostate (Figure 1.1).¹ Among well-developed synthetic methods of chiral amines, metal-catalyzed asymmetric hydrogenation of C=N bond has proved to be one of the most useful and practical techniques. Nowadays, impressive breakthrough has been achieved in the field of asymmetric (transfer) hydrogenation of imines in the presence of heavy metal catalysts, such as Rh², Ru³, Ir⁴, and Pd⁵. It is noteworthy that millions of turnover numbers was reported in asymmetric hydrogenation using an Ir-Xyliphos catalyst for the synthesis of Metolachlor, an herbicide.⁶ Despite high selectivity and reactivity, the use of these metals has several intrinsic problems, such as high price, depleting reserve in Earth's crust, additional cost in waste disposal and in removal of residual metals from products after hydrogenation. Replacing these expensive and toxic metals with abundant first-row transition metals as metal catalysts in the field of asymmetric hydrogenation, such as copper⁷, iron⁸, cobalt⁹ and nickel¹⁰, is a promising research area and has gained much attention in recent years.

In terms of substrate scope, the methods of the asymmetric hydrogenation of imines are less successful than hydrogenation of ketones or alkenes.^{5f, 11} Some ketimines are

more challenging to obtain high *ee* values in hydrogenation. Firstly, isomers of acyclic imines would provide different enantiomeric excess under the same reaction conditions. Secondly, some final amine products may act as nitrogen ligands and compete to coordinate with the metal catalyst center.¹²

Figure 1.1. Examples of chiral amines in drugs

1.1.1 Asymmetric Hydrogenation of Hydrazones

In 1992, Burk et al. reported the first example of asymmetric hydrogenation of *N*-benzoylhydrazone with high *ee* values (Scheme 1.1).¹³ The carbonyl group of phenylhydrazide can act as a directing group to increase the reactivity and stereoselectivity. *N*-Benzoylhydrazones are quite stable and only *E*-isomers are isolated from aromatic methyl ketones. In addition, the hydrogenation product of *N*-benzoylhydrazone can be easily transformed into a free amine by treatment of SmI_2 ¹³⁻¹⁴ or Raney nickel¹⁵.

Scheme 1.1. The first example of asymmetric hydrogenation of hydrazones

Since then, a number of new catalytic systems have been developed for asymmetric hydrogenation of *N*-benzoylhydrazone. In 1994, Burk's group developed a new type of chiral 1,1'-bis(phospholano)ferrocene ligand, which provided good yields in rhodium-catalyzed asymmetric hydrogenation of C=N bonds, but with a lower *ee* values (31% *ee*) (Scheme 1.2).¹⁶

Scheme 1.2. New chiral ligand for asymmetric hydrogenation of hydrazones

In 1997, Achiwa's group reported a new chiral bisphosphine ligand, NorPhos, and applied it in rhodium-catalyzed asymmetric hydrogenation of *N*-benzoylhydrazones (Scheme 1.3).¹⁷ However, lower enantiomeric excess (57% *ee*) was obtained.

Scheme 1.3. Rh/NorPhos catalyzed asymmetric hydrogenation of
N-benzoylhydrazones

In 2002, Knochel's group synthesized a novel type of chiral 1,5-diphosphanylferrocene ligands and examined them in the asymmetric hydrogenation of C=N bonds (Scheme 1.4).¹⁸ A series of hydrazones were tested in the presence of 1 mol% rhodium catalyst, while the enantioselectivities of those products were moderate. Only 8% *ee* was obtained in the asymmetric hydrogenation of (*E*)-*N'*-(3,4-dihydronaphthalen-1(2*H*)-ylidene)benzohydrazide under the optimized reaction conditions.

Scheme 1.4. Rh/chiral 1,5-diphosphanylferrocene ligands catalyzed asymmetric
hydrogenation of *N*-benzoylhydrazones

In 2007, Zhou's group reported palladium-catalyzed asymmetric hydrogenations of activated imines (Scheme 1.5).^{5f} Up to 95% and 97% enantiomeric excesses were obtained for *N*-tosylimines and *N*-diphenylphosphinyl ketimines respectively in the presence of Pd/SynPhos complex. However, only 58% *ee* was achieved employing

N-benzoylhydrazone as substrate with this catalytic system.

Scheme 1.5. Pd/Synphos-catalyzed asymmetric hydrogenation of *N*-benzoylhydrazone

In 2010, Sheppard's group developed a practical method for the synthesis of chiral hydrazides via Rh-complex catalyzed asymmetric hydrogenation of *N*-alkoxycarbonyl hydrazones (Scheme 1.16).¹⁹ In the presence of this efficient protocol, good results could be achieved by the substrates with three different protective groups (Boc, Methoxycarbonyl and Cbz).

Scheme 1.6. Rh-Catalyzed asymmetric hydrogenation of hydrazones with different protective groups

In 2011, Haddad's group reported Rh-catalyzed asymmetric hydrogenation of

heterocyclic ketone-derived hydrazones (Scheme 1.7).²⁰ In the presence of chiral ligand (*R,S*)-MandyPhos, up to 85% *ee* was obtained using (*E*)-*tert*-butyl 2-(2*H*-pyran-3(4*H*,5*H*,6*H*)-ylidene)hydrazinecarboxylate as substrate. In addition, the enantiometric purity of the corresponding product could be enriched from 85% *ee* to 99% *ee* after recrystallization.

Scheme 1.7. Rh-Catalyzed asymmetric hydrogenation of heterocyclic ketone-derived hydrazones

In 2013, Zhang's group developed the first direct reductive amination of ketones and phenylhydrazide using an Ir/*f*-Binaphane catalyst (Scheme 1.8).¹² Excellent yields and *ee* values of the products were obtained. Previously, the nitrogen sources of asymmetric reductive amination were based on ammonium salts²¹ and anilines²².

Scheme 1.8. Ir/*f*-binaphane catalyzed reductive amination of acetophenone with phenylhydrazide

Recently, Beller^{8a, 8d, 23} and Morris^{8b, 24} employed iron catalysts in asymmetric transfer hydrogenation of imines and achieved high enantioselectivities by using *i*-PrOH as hydrogen source (Scheme 1.9). However, the imines were only limited to *N*-diphenylphosphinyl ones.

Scheme 1.9. Iron-catalyzed asymmetric transfer hydrogenation of imines

1.1.2 Asymmetric Addition of Aldimines

Direct enantioselective addition of organometallic reagent to C=N of aldimines represent a powerful strategy for the synthesis of chiral amines. A series of catalytic systems have been devised for this chemistry of asymmetric addition of dialkylzinc to activate acyl-,²⁵ aryl-,²⁶ sulfonyl-²⁷ and *N*-(diphenylphosphinoyl)imines²⁸. Among them, impressive breakthrough have been made in the enantioselective addition of dialkylzinc to *N*-(diphenylphosphinoyl)imines. However, there were almost no reports related to asymmetric nucleophilic organometallic addition of hydrazones.

Catalytic asymmetric Mannich-type reactions proved to be one of the most efficient methods for the synthesis of chiral hydrazone derivatives.²⁹ For example, Kobayashi's

group developed an efficient catalytic system for Mannich reactions of *N*-acylhydrazones (Scheme 1.10).^{29b} In the presence of a chiral zirconium complex, derived from zirconium(IV) *t*-butoxide and (*R*)-3,3'-dibromo-1,1'-bi-2-naphthol, 4-trifluoromethylbenzoyl hydrazones reacted with silicon enolates to provide the corresponding products in good yields and with high *ee* values. Furthermore, the chiral products could be transformed into β -lactam, β -aminoester and pyrazolidinone derivatives without loss of enantiomeric purity.

Scheme 1.10. Asymmetric catalytic Mannich reactions of 4-trifluoromethylbenzoyl hydrazones

In 2012, Li's group reported asymmetric catalytic Mannich-type reaction of hydrazones with difluoroenoxy silanes with chiral Zinc(II)-imidazoline-phosphine complexes (Scheme 1.11).^{29a} The reactions proceeded smoothly under mild conditions, providing the desired products in good yields with excellent *ee* values.

Scheme 1.11. Asymmetric catalytic Mannich reaction of hydrazones with Zinc(II)

complex

Asymmetric allylation of hydrazones present a powerful technology for the synthesis of chiral hydrazide derivatives.³⁰ Typical examples are indium-mediated asymmetric allylation of acylhydrazones.^{30e, 30f} For example, Jacobsen's group discovered a novel chiral urea catalyst for indium-mediated allylation of hydrazones (Scheme 1.12).^{30e} In the presence of this thiourea catalyst, the corresponding adducts were obtained in good yields and high enantioselectivities. Good results (94% yield, 89% *ee*) were also achieved on a 10-mmol scale with this catalytic system.

Scheme 1.12. Asymmetric allylation of hydrazones with a chiral urea catalyst

In 2010, Kobayashi's group reported a novel indium(I) catalysis for catalytic asymmetric allylation of hydrazones (Scheme 1.13).^{30f} The further mechanistic study of this catalytic asymmetric C-C bond formation showed that the high enantioselectivities of corresponding products were induced by an in situ generated chiral indium(I)-semicorrin

catalyst.

Scheme 1.13. Indium(I)-catalyzed asymmetric allylation of hydrazones

1.2 Nickel-Catalyzed Asymmetric Transfer Hydrogenation of Hydrazones

In asymmetric hydrogenation of hydrazones, some products are essential skeletons existing in many chiral drugs, such as (*S*)-Cinacalcet³¹ and (*S*)-Rivastigmine³² (Figure 1.2). Both drugs are currently made via separation of a mixture of enantiomers via selective crystallization. As the test case, we would like to develop asymmetric hydrogenation reactions to synthesize them by nickel catalysts.

Figure 1.2. The synthesis of two blockbuster drugs by asymmetric hydrogenation of hydrazones

1.3 Results and Discussion

1.3.1 Reaction Optimization

Building on the literature study, (*E*)-*N'*-(1-phenylethylidene)benzohydrazide was employed as the model substrate for asymmetric hydrogenation of *N*-acylhydrazones to optimize the reaction conditions. Firstly, we studied different types of chiral ligands and the results are listed in Table 1.1. We used NiCl₂(DME) as the metal source, HCO₂H/Et₃N as hydrogen source and EtOH as solvent.

Table 1.1. Effect of chiral ligands

Entry	Ligand	Conv. (%)	Yield (%)	Ee (%)
1	(<i>S</i>)-Binapine	96	95	97
2	(<i>R,R</i>)-BenzP*	52	50	91

3		94	92	84
<i>(R,R)</i> -QuinoxP*				
4		91	90	62
<i>(S,S)</i> -Ph-BPE				
5		92	90	51
<i>(R,R)</i> -Me-DuPhos				
6		89	87	80
<i>(R,R)</i> - <i>i</i> -Pr-DuPhos				
7		0	0	
8		92	91	74
<i>(S,S',R,R')</i> -TangPhos				
9		90	89	-56
DuanPhos				

10		0	0	-
(1 <i>S</i> ,1' <i>S</i> ,2 <i>S</i> ,2' <i>S</i>)-WingPhos				
11		0	0	-
(1 <i>S</i> ,1' <i>S</i> ,2 <i>S</i> ,2' <i>S</i>)-BIBOP				
12		82	82	85
(R,Sp)-CyPF-Cy				
13		90	90	99
14		0	0	-
15		5	5	-
(R,Sp)-PPF-Cy				
16		0	0	-
17		0	0	-
(R)-BINAP				

18		0	0	-
<i>(R)</i> -i-Pr-MeO-Biphep				
19		0	0	-
20		0	0	-
21		0	0	-

From Table 1.1, we found that nickel catalysts showed significant catalytic activities only when ligated by highly electron-rich and sterically demanding bisphosphines in this model reaction. In particular, (*S*)-Binapine, which was developed by Xumu Zhang's group, provided the desired product with excellent conversion and 97% *ee*.³³ Another chiral bisphosphine of (*R,R*)-BenzP* afforded up to 91% *ee*, but the conversion was lower.^{2e} (*R,R*)-QuinoxP*, one of Imamoto's *P*-chiral ligands, provided 84% *ee*.³⁴ Two related bisphosphines TangPhos and DuanPhos were less selective (74% *ee* and 56% *ee*). Ph-BPE and Me-DuPhos, which were synthesized by Mark Burk's group, also showed catalytic activity, but the *ee* values were not high.³⁵ Catalytic activities of JosiPhos ligands were dependent on their substituent groups. For example, (*R,S**p*)-PPF-Cy did not show catalytic activity while (*R,S**p*)-CyPF-Cy afforded good conversion and 85% *ee*. To our delight, (*R,S**p*)-CyPF-*t*-Bu was also found to be another outstanding chiral ligand in this model

reaction, which provided the desired product with 90% yield and 99% *ee* values. Other less electron-rich phosphine chiral ligands, such as BINAP, SegPhos, SiPhos and PHOX, were not efficient in this model reaction.

With the optimized chiral ligand (*S*)-Binapine in hand, we screened the effect of the nickel(II) salts in the model reaction (Table 1.2). Most of them provided the same enantioselectivity and similar yields of the product, except that Ni(acac)₂ and Ni(PPh₃)₄ did not form the active catalyst.

Table 1.2. Effect of nickel salts

Entry	Nickel salt	Conv. (%) 12 h	Conv. (%) 48 h	Yield (%)	Ee (%)
1	Ni(OAc) ₂	37	93	92	97
2	Ni(OTf) ₂	30	94	93	97
3	NiBr ₂ (DME)	36	93	91	97
4	NiCl ₂ (DME)	37	95	95	97
5	Ni(ClO ₄) ₂ · 6H ₂ O	26	75	73	97
6	Ni(acac) ₂	0	0	0	-
7	Ni(PPh ₃) ₄	0	0	0	-

Next we examined the effect of solvents (Table 1.3) and the ratio of HCO₂H and Et₃N (Table 1.4) by varying the established reaction conditions. From Table 1.3, the

model reaction proceeded smoothly and afforded good conversion and high enantioselectivity in alcoholic solvents (Table 1.3, entries 1-5). However, other common solvents, such as THF, dioxane, toluene, and PhCF₃ provided much lower conversion (Table 1.3, entries 8-11).

Table 1.3. Effect of solvents

Entry	Solvent	Conv. (%) 12 h	Conv. (%) 48 h	Yield (%)	Ee (%)
1	MeOH	38	94	92	96
2	EtOH	37	96	95	97
3	<i>n</i> -PrOH	38	95	93	97
4	<i>i</i> -PrOH	31	94	93	97
5	<i>n</i> -BuOH	37	94	92	97
6	DMSO	26	82	82	96
7	DMF	35	92	92	89
8	Dioxane	5	15	14	94
9	THF	13	17	17	96
10	PhCH ₃	23	25	23	95
11	PhCF ₃	13	35	34	97

In the model reaction, a 2:2 molar ratio mixture of HCO₂H and Et₃N was optimal in terms of both catalytic activity and enantioselectivity (Table 1.4). Molecular sieves were employed to remove water, so that partial hydrolysis of the starting material was minimized.

Table 1.4. Effect of the ratio of HCO₂H and Et₃N

Entry	Hydrogen source	Conv. (%)	Yield (%)	Ee (%)
1	HCO ₂ H:Et ₃ N 2:2	96	95	97
2	3:2	91	90	96
3	4:2	94	94	96
4	5:2	93	91	97

1.3.2 Scope of Hydrazones in Ni-Catalyzed Asymmetric Transfer Hydrogenation

With the optimal conditions in hand, we explored the scope of *N*-acylhydrazones using Ni/Binapine catalyst (Scheme 1.14 a). Hydrazones with both electron-withdrawing and electron-donating aryl groups afforded the corresponding products in high yields and excellent *ee* values. A slight drop of *ee* was found when *ortho*-substituted *N*-acylhydrazone was tested. It is remarkable that some heteroaryl rings were also efficiently hydrogenated with excellent enantioselectivity. For example, 96% *ee* of the

desired product was obtained in the asymmetric hydrogenation reaction of (*E*)-*N'*-(1-(pyridin-3-yl)ethylidene)benzohydrazide. The absolute configuration of *N*-(1-(thiophen-2-yl)ethyl)benzohydrazide was determined to be *R* by X-ray diffraction analysis. A hydrazone, derived from α -tetralone, was reduced in good yield and high enantioselectivity. It is noteworthy that *N*-acetyl hydrazone also provided the corresponding product in 93% yield and 97% *ee*. When (*E*)-1-phenyl-2-(1-phenylethylidene)hydrazine was tested, 87% *ee* was obtained. However, this product, when purified, slowly oxidized in air, owing to the rich electron nature of its nitrogen atom. To our delight, one of the reactions was scaled up to a gram scale when the nickel catalyst loading was reduced to 1 mol% (Scheme 1.14 b).

Further extension of this protocol to aliphatic hydrazones was also explored. The substrate (*E*)-*N'*-(3,3-dimethylbutan-2-ylidene)benzohydrazide proceeded very efficiently in 95% *ee* values under the optimized reaction conditions (Scheme 1.14c). Other hydrazones with *sec*-alkyl and methyl groups failed to give high *ee* values when (*S*)-Binapine was used. However, when (*R,S**p*)-CyPF-Cy, a Josiphos ligand, was employed, better results were obtained (Scheme 1.14 d).

a)

b)

c)

d)

Scheme 1.14. Nickel-catalyzed asymmetric hydrogenation of aryl and alkyl hydrazones

In addition, we found that more than 90% *ee* was achieved in nickel-catalyzed asymmetric transfer hydrogenation of some benzosultams when Ph-BPE was used as a ligand (Scheme 1.15).^{5g} However, only 17% conversion has been observed when (*S*)-Binapine was used. Other activated ketimines, such as *N*-tosylketimine and *N*-tosylhydrazone, provided the corresponding products in 30% and 40% *ee*, respectively.

Scheme 1.15. Asymmetric transfer hydrogenation of benzosultams

1.3.3 Mechanistic Study

We used [D₁] and [D₂] formic acid as hydrogen source to further study the mechanism of this reaction (Scheme 1.16). Obviously, one of the hydrides was donated by formic acid to form Ni-H/D catalytic species after decarboxylation of the cationic Ni(II) complex. From the results of these deuterium experiments, we could see that some of the hydrogen atoms in the methyl group of the product were replaced with deuterium ones, when [D₁] formic acid was employed (Scheme 1.16 a). The number of hydrogen atoms in the methyl group was increased when the concentration of [D₂] formic acid was increased (Scheme 1.16 b, c). Both α and α' positions of the dialkyl hydrazine were deuterated (Scheme 1.16 f). These results can be explained via the equilibration between the imine

and enamine tautomers of the starting hydrazones (Scheme 1.16 d). What's more, the deuterium incorporation into the benzylic position revealed that this process involved two steps: a nickel hydride, produced by a decarboxylation of the formate, incorporated to the benzylic position to form a nickel complex firstly; then subsequently via the procedure of protonation to the desired product (Scheme 1.16 e).

Scheme 1.16. Deuterium-labeling experiments

With Morokuma's ONIOM-DFT method, the hydride-insertion process between $\{[(S)\text{-Binapine}]\text{Ni-H}\}$ and hydrazone was investigated by Prof. Hajime Hirao and his student Pratanphorn Chuanprasit (Figure 1.3). According to the computational results, several points are worth of note: 1) The chelation between the hydrazone amide group and nickel center is readily available. 2) The energy gap between the two diastereomeric pathways is $2.9 \text{ kcal mol}^{-1}$ apart and this result is in a good agreement with the experimental data (97% *ee*, *R*). The insertion barrier to form the *R* isomer was about 10 kcal mol^{-1} . 3) Pathways via relatively unstable *s-cisoid* conformer had a $2\text{-}3 \text{ kcal mol}^{-1}$ higher transition-state energy than those via *s-transoid* one, so it was less favorable. 4)

The possibility of insertion of a neutral nickel(I) hydride species was small, because the energy gap between the two transition states was too small to account for the experimental observation of high enantioselectivity. 5) The pathways of direct formate addition are impossible, because the cationic (formyl)nickel(II) complex is likely to carry out a facile decarboxylation and produce CO_2 and a cationic (hydrido)Ni(II) complex. 6) The phenyl substituent in the benzamide moiety did not provide any benefits to stereinduction, owing to the high energy gap of the step of hydride-insertion.

(a) Nickel(II) hydride insertion: chelation pathways

(b) Nickel(I) hydride insertion: chelation pathways

(c) Asymmetric induction: the nickel catalyst controls the asymmetric hydride insertion to unsaturated $\text{C}=\text{N}$ bonds by controlling the binding conformation of the amide directing group, instead of differentiating group on the imine fragment.

Figure 1.3. Nickel(II) hydride insertion: different transition states TS-R and TS-S via metal chelation. The chiral ligand (*S*)-Binapine was showed in space-filling mode while other TS atoms were presented in ball-and-stick model. The hydride atom was black, nickel atom was the dark red, the nitrogen atom of the hydrazone was blue, carbon and oxygen atoms were green and red respectively.

Some interesting conclusions were revealed by the two transition-state structures: a) The bulky (*S*)-Binapine had no deep crevice or pocket. b) Simple steric repulsion model was impossible, because the catalyst and hydrazone have no close contact. c) Owing to a close contact with one of aryl rings in Binapine, the Ni $\cdots$ O bond is 2.7 Å in TS-S, while the Ni $\cdots$ O bond is 2.4 Å in TS-R. d) The configuration of chiral ligand (*S*)-Binapine was more beneficial to coordinate with *s-transoid* hydrazone in TS-R than in TS-S. Therefore, the CH $\cdots$ O hydrogen bond interplayed in TS-S was very weak.³⁶ The high chirality of the final product was induced via the nickel catalyst controls the asymmetric hydride insertion to unsaturated C=N bonds by controlling the binding conformation of the amide directing group, instead of differentiating groups on the imine fragment.

According to the results of Deuterium-labeling experiments and DFT calculation, we proposed a catalytic cycle for this transformation (Scheme 1.17). Firstly, a nickel hydride,

produced by a decarboxylation of the cationic (formyl)nickel(II) complex, coordinated with hydrazone to form the intermediate **A**. Then, the nickel hydride inserted to the C=N bond of hydrazone to form the intermediate **B**, which provided the final product via the procedure of the protonation.

Scheme 1.17. A catalytic cycle for Nickel-catalyzed asymmetric hydrogenation of hydrazones

Following this work, Dr Yang Peng in our group reported enantioselective reductive amination between ketones and benzohydrazide.³⁷ Under optimized reaction conditions,

good results were achieved on a 5 mmol scale by reducing the catalyst loading to 1 mol% (Scheme 1.18).

Scheme 1.18. Direct asymmetric reductive amination of acetophenone with phenylhydrazide

1.3.4 Conclusions

We have developed a novel method for asymmetric transfer hydrogenation of a series of hydrazones using a nickel catalyst. Both aromatic and aliphatic methyl hydrazones afforded the desired products in good to excellent *ee* values when ligated by electron-donating bisphosphine (*S*)-Binapine. Furthermore, 200 turnovers were achieved in one test case. DFT calculation revealed that the nickel catalyst controls the asymmetric hydride insertion to unsaturated C=N bonds by controlling the binding conformation of the amide directing group, instead of differentiating groups on the imine fragment.

1.4 Experimental Section

1.4.1 General

^1H NMR spectra were acquired on Bruker AV 300 MHz or 500 MHz NMR spectrometers. ^1H NMR (300 MHz) chemical shifts were recorded relative to SiMe_4 (δ 0.00) or residual protiated solvents (CDCl_3 : δ 7.26). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by nH. Coupling constants were reported as a J value in Hz. ^{13}C NMR (75 MHz) chemical shifts were recorded relative to solvent resonance (CDCl_3 : δ 77.16). Proof of purity products were demonstrated by ^1H and ^{13}C NMR.

Glassware was dried at 120 °C for at least 3 h before use. Dry toluene, hexane, diethyl ether and dichloromethane were collected from a solvent purification system containing a column of activated alumina (1 m x 2) under argon. Dry THF was freshly distilled from sodium/benzophenone under argon. The MeOH, EtOH, and isopropanol were distilled from CaH_2 under argon and stored over activated 4Å molecular sieve beads in an argon-filled glove box. Unless noted otherwise, readily available chemicals were used directly with no further purification. The GC internal standard, $n\text{-C}_{14}\text{H}_{30}$ was degassed with argon and dried over activated 3Å molecular sieve beads before use.

Flash chromatography was performed using Merck 40-63D 60Å silica gel. Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument with Agilent J & W GC column DB-5MS-UI. GC/MS analysis was conducted on a Thermo Scientific DSQ II single quadrupole GC/MS instrument with Agilent J & W GC column DB-5MS-UI. Chiral HPLC analysis was performed on a Shimadzu LC-20AD instrument using Daicel Chiracel columns at 25 °C and a mixture of HPLC-grade hexanes and isopropanol as eluent. Optical rotation was measured using a JASCO P-1030 Polarimeter

equipped with a sodium vapor lamp at 589 nm and the concentration of samples was denoted as *c*.

1.4.2 Condition Optimization for Transfer Hydrogenation of *N*-Acylhydrazones

A typical procedure for condition optimization: In an argon-filled glove box, NiCl₂(DME) (1.1 mg, 0.005 mmol), (*S*)-Binapine (4.4 mg, 0.006 mmol), 3 Å molecular sieve (0.05 g) and dry EtOH (0.3 mL) were charged into a 10-mL reaction tube. After stirring for 10 min, (*E*)-*N'*-(1-phenylethylidene)benzohydrazide (23.8 mg, 0.1 mmol), formic acid (7.6 µL, 0.2 mmol), Et₃N (28 µL, 0.2 mmol) and GC standard *n*-C₁₄H₃₀ (10 µL) were added. The reaction mixture was stirred in an oil bath maintained at 70 °C. In the course of the reaction, aliquots were taken from the reaction mixture in the glove box, and passed through a short plug of silica gel with EtOAc washing (about 3 mL). The filtrate was subjected to GC analysis to determine the conversion of hydrazone and the yield of product. In order to determine the enantioselectivity of the product, the filtrate was dissolved in 1:10 *i*-PrOH/hexane and subjected to chiral HPLC analysis (Daicel CHIRCEL OJ-H; 10% *i*-PrOH in hexane; flow rate 0.5 mL/min). The racemic sample was prepared by hydrogenation using 5% Pd/C under 8 bar of hydrogen gas in ethyl acetate at room temperature.

1.4.3 Isolation of Asymmetric Hydrogenation Products

General procedure for asymmetric hydrogenation reaction: In an argon-filled glove box, NiCl₂(DME) (5.5 mg, 0.025 mmol), (*S*)-Binapine (22 mg, 0.03 mmol), dry 3 Å molecular sieve (0.1 g) and dry EtOH (1.5 mL) were charged into a 10-mL reaction tube. After stirring for 30 min, (*E*)-*N'*-(1-phenylethylidene)benzohydrazide (119 mg, 0.5 mmol),

formic acid (38 μL , 1.0 mmol, 2 equiv) and Et_3N (140 μL , 1.0 mmol, 2 equiv) were added. The reaction mixture was heated with stirring in an oil bath maintained at 70 $^{\circ}\text{C}$, until the hydrazone was fully consumed (monitored by GC). Until the reaction mixture was cooled down to room temperature, then evaporation of the solvent on a rotary evaporator, the residue was purified by flash chromatography using EA/hexane as eluent. The enantioselectivity (*ee*) of the purified product was determined by chiral HPLC analysis using Daicel Chiralcel columns.

(*R*)-*N'*-(1-Phenylethyl)benzohydrazide [142068-35-7]

The reaction completed after 48 h at 70 $^{\circ}\text{C}$. The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. Yield: 109 mg, 92%.

$[\alpha]_{\text{D}}^{23} = +169.2^{\circ}$ ($c = 1.0$, CHCl_3).

Ee: 97%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

^1H NMR (300 MHz, CDCl_3): δ 7.66-7.57 (m, 2H), 7.52-7.28 (m, 8H), 4.26 (q, $J = 6.6$ Hz, 1H), 1.44 (d, $J = 6.6$ Hz, 3H).

LC-MS (ESI): Calcd for C₁₅H₁₆N₂O [M+H]⁺: 241.1. Found: 240.9.

(R)-N'-(1-*p*-Tolyylethyl)benzohydrazide [1449674-20-7]

The reaction completed after 24 h at 70 °C. The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. Yield: 119 mg, 94%.

$[\alpha]_D^{23} = +162.2^\circ$ ($c = 1.0$, CHCl₃).

Ee: 97%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	16.077	28257800	50.614
2	24.990	27572177	49.386
Total		55829977	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	16.582	11774582	98.219
2	25.587	213471	1.781
Total		11988052	100.000

¹H NMR (300 MHz, CDCl₃): δ 7.66-7.61 (m, 2H), 7.48-7.45 (m, 2H), 7.38 (dd, $J = 10.2$, 4.6 Hz, 2H), 7.28 (t, $J = 6.9$ Hz, 2H), 7.16 (d, $J = 8.0$ Hz, 2H), 4.91 (br s, 1H), 4.21 (q, $J = 6.6$ Hz, 1H), 2.35 (s, 3H), 1.41 (d, $J = 6.6$ Hz, 3H).

LC-MS (ESI): Calcd for C₁₆H₁₈N₂O [M+H]⁺: 255.1. Found: 254.8.

(R)-N'-(1-*p*-Anisylethyl)benzohydrazide [159041-70-0]

The reaction completed after 24 h at 70 °C. The product was isolated by flash

chromatography (EA/hexanes 1:2) as white solid. Yield: 129 mg, 96%.

$[\alpha]_D^{23} = +155.7^\circ$ ($c = 1.0$, CHCl_3).

Ee: 97%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

^1H NMR (300 MHz, CDCl_3): δ 7.68-7.56 (m, 2H), 7.53-7.44 (m, 1H), 7.38 (t, $J = 7.4$ Hz, 2H), 7.36-7.28 (m, 2H), 6.87 (t, $J = 5.7$ Hz, 2H), 4.88 (br s, 1H), 4.21 (q, $J = 6.6$ Hz, 1H), 3.80 (s, 3H), 1.40 (d, $J = 6.6$ Hz, 3H).

LC-MS (ESI): Calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_2\text{M}^+$: 270.1. Found: 270.3.

(R)-N'-[1-(*p*-Fluorophenyl)ethyl]benzohydrazide [1449674-21-8]

The reaction completed after 24 h at 70 °C. The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. Yield: 123 mg, 96%.

$[\alpha]_D^{23} = +149.6^\circ$ ($c = 1.0$, CHCl_3).

Ee: 97%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 95/5, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	35.109	2974572	50.290
2	41.550	2940260	49.710
Total		5914831	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	36.263	6882973	98.683
2	43.465	91855	1.317
Total		6974828	100.000

^1H NMR (300 MHz, CDCl_3): δ 7.67-7.58 (m, 2H), 7.57-7.44 (m, 2H), 7.44-7.29 (m, 4H), 7.11-6.93 (m, 2H), 4.68 (br s, 1H), 4.25 (q, J = 6.6 Hz, 1H), 1.40 (d, J = 6.6 Hz, 3H).

LC-MS (ESI): Calcd for $\text{C}_{15}\text{H}_{15}\text{FN}_2\text{O}$ $[\text{M}+\text{H}]^+$: 259.1. Found: 258.8.

(*R*)-*N'*-[1-(*p*-Trifluoromethylphenyl)ethyl]benzohydrazide

The reaction completed after 24 h at 70 °C. The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. Yield: 142 mg, 93%.

$[\alpha]_{\text{D}}^{23} = +146.8^\circ$ (c = 1.0, CHCl_3).

Ee: 96%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	38.838	5878612	49.780
2	42.302	5930553	50.220
Total		11809165	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	39.246	220610	2.059
2	42.194	10493986	97.941
Total		10714596	100.000

^1H NMR (300 MHz, CDCl_3): δ 7.67-7.57 (m, 4H), 7.49-7.49 (m, 4H), 7.44-7.34 (m, 2H),

4.99 (br s, 1H), 4.33 (q, $J = 6.6$ Hz, 1H), 1.42 (d, $J = 6.6$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ 167.6, 147.6, 132.6, 131.9, 129.9, 129.6, 128.7, 127.5, 125.8, 125.5, 125.5, 123.0, 59.7, 21.3;

LC-MS (ESI): Calcd for $\text{C}_{16}\text{H}_{15}\text{F}_3\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 309.1. Found: 308.9.

A procedure on 4 mmol scale: Under argon, $\text{NiCl}_2(\text{DME})$ (4.0 mg, 0.02 mmol), (*S*)-Binapine (22 mg, 0.03 mmol), dry $3\text{\AA}$ molecular sieve (0.10 g) and dry EtOH (12 mL) were charged into a 50-mL Schlenck tube. After stirring for 30 min, a hydrazone (1.224 g, 4.0 mmol), formic acid (304 μL , 8.0 mmol, 2 equiv) and Et_3N (1.12 mL, 8.0 mmol, 2 equiv) were added. The reaction mixture was heated for 24 hours with stirring in an oil bath maintained at $80\text{ }^\circ\text{C}$, until the hydrazone was fully consumed (monitored by GC). Until the reaction mixture was cooled down to room temperature, then evaporation of the solvent on a rotary evaporator, the residue was purified by flash chromatography using EA/hexane (1:2) as eluent. White solid: 1.19 g, 97% yield after purification. The enantioselectivity of the purified product was determined to be 96% *ee* by chiral HPLC analysis using Daicel Chiralcel columns.

(*R*)-*N'*-[1-(2-Naphthyl)ethyl]benzohydrazide [159042-07-6]

The reaction completed after 24 h at 70 °C. The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. Yield: 137 mg, 95%.

$[\alpha]_D^{23} = +183.4^\circ$ ($c = 1.0$, CHCl_3).

Ee: 98%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 85/15, flow rate = 1.0 mL/min.

^1H NMR (300 MHz, CDCl_3): δ 7.89-7.76 (m, 4H), 7.67-7.51 (m, 4H), 7.52-7.38 (m, 3H), 7.32 (t, $J = 7.5$ Hz, 2H), 5.19 (br s, 1H), 4.41 (q, $J = 6.6$ Hz, 1H), 1.49 (d, $J = 6.6$ Hz, 3H).

LC-MS (ESI): Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 291.1. Found: 290.8.

(R)-N'-[1-(1-Naphthyl)ethyl]benzohydrazide [(S)-isomer: 431052-25-4]

The reaction completed after 24 h at 70 °C. The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. Yield: 136 mg, 93%.

$[\alpha]_D^{23} = +91.5^\circ$ ($c = 1.0$, CHCl_3).

Ee: 97%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 95/5, flow rate = 1.0 mL/min.

^1H NMR (300 MHz, CDCl_3): δ 8.30 (d, $J = 7.5$ Hz, 1H), 7.91-7.84 (m, 1H), 7.79 (dd, $J = 7.7, 3.7$ Hz, 2H), 7.58 (dd, $J = 5.2, 3.3$ Hz, 2H), 7.54-7.39 (m, 4H), 7.40-7.29 (m, 2H), 5.27 (s, 1H), 5.13 (q, $J = 6.6$ Hz, 1H), 1.59 (d, $J = 6.6$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ 167.5, 138.8, 134.0, 132.8, 131.7, 131.5, 128.8, 128.5, 127.9, 126.8, 126.1, 125.5, 123.5, 123.3, 55.8, 20.7.

LC-MS (ESI): Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 291.1. Found: 290.8.

(R)-N'-[1-(2-Thienyl)ethyl]benzohydrazide

(*E*)-Hydrazone (122 mg, 0.5 mmol), HCO_2H (5 equiv, 19 μL) and Et_3N (2 equiv, 28 μL) were used. The reaction completed after 24 h at 70 $^\circ\text{C}$. The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. Yield: 116 mg, 94%.

$[\alpha]_{\text{D}}^{23} = +116.6^\circ$ ($c = 1.0$, CHCl_3).

Ee: 94%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

^1H NMR (300 MHz, CDCl_3): δ 7.73-7.58 (m, 3H), 7.54-7.46 (m, 1H), 7.45-7.36 (m, 2H), 7.25 (dd, J = 4.8, 1.5 Hz, 1H), 7.02-6.92 (m, 2H), 5.29 (s, 1H), 4.97 (br s, 1 H), 4.57 (q, J = 6.5 Hz, 1H), 1.52 (d, J = 6.5 Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ 167.4, 147.0, 132.7, 131.9, 128.6, 126.8, 126.6, 124.8, 124.5, 55.7, 21.8.

LC-MS (ESI): Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{OS}$ $[\text{M}+\text{H}]^+$: 247.1. Found: 246.9.

(R)-N'-[1-(2-Furyl)ethyl]benzohydrazide [1449674-27-4]

The reaction completed after 24 h at 70 °C. The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. Yield: 106 mg, 93%.

$[\alpha]_{\text{D}}^{23} = +100.1^\circ$ (c = 1.0, CHCl_3).

Ee: 82%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 85/15, flow rate = 0.5 mL/min.

^1H NMR (300 MHz, CDCl_3): δ 7.70 (dd, $J = 5.3, 3.2$ Hz, 3H), 7.51 (ddd, $J = 6.4, 3.7, 1.3$ Hz, 1H), 7.47-7.33 (m, 3H), 6.32 (dd, $J = 3.2, 1.9$ Hz, 1H), 6.23 (d, $J = 3.2$ Hz, 1H), 5.12 (br s, 1H), 4.31 (q, $J = 6.5$ Hz, 1H), 1.47 (d, $J = 6.7$ Hz, 3H).

LC-MS (ESI): Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 231.1. Found: 230.9.

(*R*)-*N'*-[1-(3-Pyridyl)ethyl]benzohydrazide.

The reaction completed after 24 h at 70 °C. The product was isolated by flash chromatography (EA) as white solid. Yield: 109 mg, 92%.

$[\alpha]_{\text{D}}^{23} = +80.1^\circ$ ($c = 0.6$, CHCl_3).

Ee: 96%. Daicel Chiralcel IC-H, *n*-hexane/isopropanol 70/30, flow rate = 0.5 mL/min.

^1H NMR (300 MHz, CDCl_3): δ 8.64 (d, $J = 1.8$ Hz, 1H), 8.42 (dd, $J = 4.8, 1.6$ Hz, 1H), 8.30 (s, 1H), 7.85-7.58 (m, 3H), 7.58-7.45 (m, 1H), 7.45-7.31 (m, 2H), 7.31-7.16 (m, 1H), 4.31 (q, $J = 6.6$ Hz, 1H), 1.46 (d, $J = 6.7$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ 167.8, 149.2, 148.7, 138.7, 135.1, 132.7, 131.8, 128.6, 126.9, 123.4, 57.9, 21.1.

LC-MS (ESI): Calcd for $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 242.1. Found: 242.1.

(*R*)-*N'*-[1-(*o*-Tolyl)ethyl]benzohydrazide

The reaction completed after 24 h at 70 °C. The product was isolated by flash chromatography (EA/hexanes 1:2) as colorless oil. Yield: 109 mg, 92%.

$[\alpha]_{\text{D}}^{23} = +143.1^\circ$ ($c = 0.8$, CHCl_3).

Ee: 89%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	15.918	29316443	50.293
2	21.931	28974397	49.707
Total		58290840	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	16.637	20279214	94.617
2	22.594	1153747	5.383
Total		21432961	100.000

^1H NMR (300 MHz, CDCl_3): δ 7.66-7.55 (m, 3H), 7.53-7.45 (m, 1H), 7.45-7.32 (m, 3H), 7.30-7.22 (m, 2H), 7.17-7.13 (m, 2H), 5.08 (d, $J = 5.0$ Hz, 1H), 4.73-4.40 (m, 1H), 2.34 (s, 3H), 1.39 (d, $J = 6.6$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ 167.4, 141.1, 136.1, 132.9, 131.7, 130.5, 128.6, 127.0, 126.8, 126.3, 125.8, 55.4, 20.4, 19.2.

LC-MS (ESI): Calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 255.1. Found: 254.9.

(R)-N'-(1-Phenylpropyl)benzohydrazide [159042-05-4]

The reaction completed after 48 h at 70 °C. The product was isolated by flash chromatography (EA/hexanes 1:2) as colorless oil. Yield: 118 mg, 94%.

$[\alpha]_{\text{D}}^{23} = +160.6^\circ$ ($c = 1.0$, CHCl_3).

Ee: 91%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

1 PDA Multi 1 / 200nm 4nm

PeakTable			
Peak#	Ret. Time	Area	Area %
1	15.142	44584554	50.847
2	16.768	43099978	49.153
Total		87684532	100.000

1 PDA Multi 1 / 200nm 4nm

PeakTable			
Peak#	Ret. Time	Area	Area %
1	15.678	10334848	95.493
2	17.209	487784	4.507
Total		10822632	100.000

^1H NMR (300 MHz, CDCl_3): δ 7.63-7.54 (m, 2H), 7.49-7.44 (m, 1H), 7.42-7.27 (m, 7H), 5.18 (d, $J = 5.3$ Hz, 1H), 4.00 (dd, $J = 10.0, 3.9$ Hz, 1H), 1.97-1.80 (m, 1H), 1.80-1.64 (m, 1H), 0.87 (t, $J = 7.4$ Hz, 3H).

LC-MS (ESI): Calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 255.1. Found: 254.9.

(R)-N'-(1,2,3,4-Tetrahydro-1-naphthyl)benzohydrazide [276855-24-4]

The reaction completed after 48 h at 70 °C. The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. Yield: 121 mg, 92%.

$[\alpha]_D^{23} = +48.9^\circ$ ($c = 1.0$, CHCl_3).

Ee: 84%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	29.152	39301804	49.973
2	39.214	39344921	50.027
Total		78646725	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	29.521	20705777	92.039
2	40.074	2655911	7.961
Total		33361688	100.000

^1H NMR (300 MHz, CDCl_3): δ 7.88 (s, 1H), 7.81-7.72 (m, 2H), 7.64-7.53 (m, 1H), 7.51 (dd, $J = 10.6, 4.3$ Hz, 1H), 7.42 (dd, $J = 9.6, 5.6$ Hz, 2H), 7.23-7.17 (m, 2H), 7.16-7.07 (m, 1H), 4.95 (br s, 1H), 4.18 (s, 1H), 2.83 (dd, $J = 12.5, 4.8$ Hz, 1H), 2.79-2.65 (m, 1H), 2.17-1.99 (m, 2H), 1.84-1.68 (m, 2H)

LC-MS (ESI): Calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 267.1. Found: 266.9.

(R)-N'-(1-Phenylethyl)acetohydrazide [152922-45-7]

The reaction completed after 48 h at 70 °C. The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. Yield: 82 mg, 93%.

$[\alpha]_{\text{D}}^{23} = +294.4^{\circ}$ ($c = 0.5$, CHCl_3).

Ee: 97%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

Major ^1H NMR (300 MHz, CDCl_3): δ 7.42-7.24 (m, 5H), 7.17 (s, 1H), 4.81 (s, 1H), 4.11 (q, $J = 6.6$ Hz, 1H), 1.85 (s, 3H), 1.34 (d, $J = 6.6$ Hz, 3H).

LC-MS (ESI): Calcd for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 179.1. Found: 178.9.

(R)-N'-[1-(3,4-Difluorophenyl)ethyl]benzohydrazide

The reaction completed after 24 h at 70 °C. The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. Yield: 129 mg, 95%.

$[\alpha]_{\text{D}}^{23} = +114.6^{\circ}$ ($c = 1.0$, CHCl_3).

Ee: 95%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

1 PDA Multi 1 / 200nm 4nm

PeakTable			
Peak#	Ret. Time	Area	Area %
1	18.592	18027467	49.360
2	19.817	18494801	50.640
Total		36522268	100.000

1 PDA Multi 1 / 200nm 4nm

PeakTable			
Peak#	Ret. Time	Area	Area %
1	18.821	221887	2.351
2	20.029	9217196	97.649
Total		9439084	100.000

^1H NMR (500 MHz, CDCl_3): δ 7.64 (d, J = 7.7 Hz, 2H), 7.56 (s, 1H), 7.50 (t, J = 7.3 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.26 (dd, J = 11.3, 6.9 Hz, 1H), 7.11 (dd, J = 17.6, 7.2 Hz, 2H), 5.03 (s, 1H), 4.23 (q, J = 6.4 Hz, 1H), 1.39 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3): δ 167.6, 140.4, 132.6, 132.0, 128.7, 126.8, 123.2, 117.3, 117.1, 115.9, 115.8, 59.1, 21.4.

^{19}F NMR (282 MHz, CDCl_3): δ -137.32, -137.35, -137.36, -137.39, -137.41, -137.42, -137.44, -137.46, -137.49, -139.53, -139.55, -139.58, -139.60, -139.62, -139.63, -139.65, -139.65, -139.66, -139.68.

LC-MS (ESI): Calcd for $\text{C}_{15}\text{H}_{14}\text{F}_2\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 277.1. Found: 276.8.

(*R*)-*N'*-(1-Phenylethyl)-2-hydroxybenzohydrazide

The reaction completed after 48 h at 70 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 71 mg, 56%.

$[\alpha]_{\text{D}}^{23} = +140.0^\circ$ (c = 1.0, CHCl_3).

Ee: 98%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

^1H NMR (300 MHz, CDCl_3): δ 11.78 (s, 1H), 7.70 (s, 1H), 7.47-7.28 (m, 6H), 7.11 (dd, J = 7.9, 1.2 Hz, 1H), 6.97 (dd, J = 8.4, 0.8 Hz, 1H), 6.81-6.68 (m, 1H), 5.06 (s, 1H), 4.20 (q, J = 6.6 Hz, 1H), 1.43 (d, J = 6.6 Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ 169.4, 161.1, 142.6, 134.4, 128.7, 127.7, 127.1, 124.9, 118.8, 118.5, 113.0, 60.2, 21.1.

LC-MS (ESI): Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 257.1. Found: 256.9.

(S)-N'-(1-Phenyl-2,2,2-trifluoroethyl)benzohydrazide

(R, R)-BenP* was used as chiral ligand. The reaction completed after 24 h at 70 °C. The product was isolated by flash chromatography (EA/hexanes1:2) as colorless oil. Yield: 140 mg, 95%. When (S)-Binapine was used as the ligand, 71% *ee* was seen.

$[\alpha]_{\text{D}}^{23}$ = -53.6° (c = 1.0, CHCl_3).

Ee: 91%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

1 PDA Multi 1 / 200nm 4nm

PeakTable			
Peak#	Ret. Time	Area	Area %
1	30.426	34949311	50.025
2	36.211	34914873	49.975
Total		69864184	100.000

1 PDA Multi 1 / 200nm 4nm

PeakTable			
Peak#	Ret. Time	Area	Area %
1	31.051	25078973	95.270
2	37.395	1245102	4.730
Total		26324075	100.000

^1H NMR (500 MHz, CDCl_3): δ 8.00 (s, 1H), 7.76-7.61 (m, 2H), 7.54-7.44 (m, 3H), 7.44-7.32 (m, 5H), 5.17 (s, 1H), 4.62 (q, $J = 7.2$ Hz, 1H)

^{13}C NMR (126 MHz, CDCl_3): δ 167.7, 132.2, 132.1, 132.0, 129.6, 129.0, 128.8, 128.7, 126.9, 126.1, 123.9, 65.9, 65.7

^{19}F NMR (376 MHz, CDCl_3): δ -73.0

LC-MS (ESI): Calcd for $\text{C}_{15}\text{H}_{13}\text{F}_3\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 294.1. Found: 294.8.

(R)-N'-[1-(m-Hydroxyphenyl)ethyl]benzohydrazide

The reaction completed after 24 h at 70 °C. The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. Yield: 127 mg, 99%.

$[\alpha]_D^{23} = 88.6^\circ$ ($c = 1.0$, CHCl_3).

Ee: 94%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate = 1 mL/min.

1 PDA Multi 1 / 200nm 4nm

PeakTable			
PDA Ch1 200nm 4nm			
Peak#	Ret. Time	Area	Area %
1	14.831	19211112	50.203
2	19.568	19055371	49.797
Total		38266484	100.000

1 PDA Multi 1 / 200nm 4nm

PeakTable			
PDA Ch1 200nm 4nm			
Peak#	Ret. Time	Area	Area %
1	14.998	3441483	96.980
2	20.317	107181	3.020
Total		3548663	100.000

^1H NMR (500 MHz, CDCl_3): δ 7.95 (s, 1H), 7.67-7.57 (m, 2H), 7.44 (t, $J = 7.4$ Hz, 1H), 7.33 (t, $J = 7.7$ Hz, 2H), 7.15 (t, $J = 7.8$ Hz, 1H), 6.92 (d, $J = 1.8$ Hz, 1H), 6.87 (d, $J = 7.6$ Hz, 1H), 6.76 (dd, $J = 8.0, 1.9$ Hz, 1H), 5.15 (s, 1H), 4.15 (q, $J = 6.5$ Hz, 1H), 1.34 (d, $J = 6.6$ Hz, 3H)

^{13}C NMR (126 MHz, CDCl_3): δ 167.8, 156.5, 144.4, 132.5, 132.0, 129.8, 128.7, 127.0, 119.2, 115.0, 114.0, 60.0, 20.9

LC-MS (ESI): Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 257.1. Found: 256.8.

(S)-N'-(1-Cyclohexylethyl)benzohydrazide [142068-44-8]

(*R,S*)-CyPF-Cy was used as chiral ligand. The ratio of HCO_2H and Et_3N was 5:2. The reaction completed after 24 h at 50 °C by using *t*-BuOH as solvent. The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. 118 mg, 95% yield. When (*S*)-Binapine was used as the ligand, full conversion and 34% *ee* were observed.

$[\alpha]_{\text{D}}^{23} = -1.4^\circ$ ($c = 0.6$, CHCl_3).

Ee: 91%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 99/1, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	37.001	3242775	50.448
2	40.786	3185135	49.552
Total		6427909	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	37.018	2914543	95.741
2	41.739	129661	4.259
Total		3044204	100.000

^1H NMR (500 MHz, CDCl_3): δ 7.76 (m, 3H), 7.51 (m, 1H), 7.43 (m, 2H), 4.91 (s, 1H),

2.98-2.84 (m, 1H), 1.77 (m, 4H), 1.68 (m, 1H), 1.51-1.36 (m, 1H), 1.30-1.04 (m, 8H)

^{13}C NMR (126 MHz, CDCl_3): δ 167.3, 133.0, 131.8, 128.7, 126.9, 60.5, 41.6, 29.8, 27.9,

26.7, 26.5, 26.4, 15.2

LC-MS (ESI): Calcd for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}$ [M]: 246.1. Found: 246.1.

(S)-N'-(3,3-Dimethylbut-2-yl)benzohydrazide [159042-03-2]

The reaction completed after 24 h at 70 °C. The ratio of HCO_2H and Et_3N was 5:2. The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. Yield: 103 mg, 93%.

$[\alpha]_D^{23} = -53.7^\circ$ ($c = 0.5$, CHCl_3).

Ee: 95%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate = 0.5mL/min.

^1H NMR (500 MHz, CDCl_3): δ 7.74 (m, 2H), 7.68 (s, 1H), 7.55-7.46 (m, 1H), 7.43 (t, J = 7.5 Hz, 2H), 4.96 (s, 1H), 2.78 (d, J = 6.5 Hz, 1H), 1.08 (d, J = 6.5 Hz, 3H), 0.99 (s, 9H)

^{13}C NMR (126 MHz, CDCl_3): δ 167.3, 133.1, 131.7, 128.7, 126.8, 64.6, 33.7, 26.5, 14.0

LC-MS (ESI): Calcd for $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}$ [M]: 220.1. Found: 220.1.

(S)-N'-(3-Methylbut-2-yl)benzohydrazide

(*R,S*)-CyPF-Cy was used as chiral ligand. The ratio of HCO_2H and Et_3N was 5:2. The reaction completed after 24 h at 60 °C by using *t*-BuOH as solvent. The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. Yield: 89.6 mg, 87%.

$[\alpha]_{\text{D}}^{23} = -16.5^\circ$ ($c = 0.6$, CHCl_3).

Ee: 86%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 99/1, flow rate = 0.5 mL/min.

1 PDA Multi 1 / 200nm 4nm

PeakTable			
Peak#	Ret. Time	Area	Area %
1	34.241	3749686	49.963
2	38.310	3755267	50.037
Total		7504952	100.000

1 PDA Multi 1 / 200nm 4nm

PeakTable			
Peak#	Ret. Time	Area	Area %
1	34.907	1698691	93.005
2	39.538	127753	6.995
Total		1826443	100.000

^1H NMR (500 MHz, CDCl_3): δ 7.82-7.71 (m, 2H), 7.66 (s, 1H), 7.57-7.49 (m, 1H), 7.43 (dd, J = 10.5, 4.6 Hz, 2H), 4.88 (s, 1H), 3.01-2.85 (m, 1H), 1.79 (m, 1H), 1.03 (d, J = 6.5 Hz, 3H), 0.96 (dd, J = 14.0, 6.8 Hz, 6H)

^{13}C NMR (126 MHz, CDCl_3): δ 167.3, 133.0, 131.8, 128.7, 126.8, 60.8, 30.9, 19.4, 17.0, 14.2

LC-MS (ESI): Calcd for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}$ [M]: 206.1. Found: 206.1.

(S)-N'-(4-Methylpent-2-yl)benzohydrazide

(*R,Sp*)-CyPF-Cy was used as chiral ligand. The ratio of HCO_2H and Et_3N was 5:2. The reaction completed after 24 h at 60 °C by using *t*-BuOH as solvent. The product was isolated by flash chromatography (EA/pentanes 1:2) as colorless oil. Yield: 106 mg, 96%.

When (*S*)-Binapine was used, full conversion and 67% *ee* were observed.

$[\alpha]_{\text{D}}^{23} = -5.5^\circ$ (c = 0.7, CHCl_3).

Ee: 70%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate = 0.5mL/min.

^1H NMR (500 MHz, CDCl_3): δ 7.84 (s, 1H), 7.76 (m, 2H), 7.61-7.49 (m, 1H), 7.44 (m, 2H), 4.93 (s, 1H), 3.14 (dd, $J = 13.3, 6.4$ Hz, 1H), 1.74 (m, 1H), 1.40 (m, 1H), 1.26-1.14 (m, 1H), 1.09 (d, $J = 6.3$ Hz, 3H), 0.96 (d, $J = 6.6$ Hz, 4H), 0.89 (d, $J = 6.6$ Hz, 3H)

^{13}C NMR (126 MHz, CDCl_3): δ 167.5, 133.0, 131.8, 128.7, 126.9, 53.9, 44.6, 24.9, 23.2, 22.6, 19.0

LC-MS (ESI): Calcd for $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}$ [M]: 220.1. Found: 220.1.

(*R*)-1-Phenyl-2-(1-phenylethyl)hydrazine

The reaction completed after 48 h at 70 °C. The product was isolated by flash chromatography (EA/hexanes 1:15) as yellow oil. Nitrogen gas was used instead of air to pressurize the column chromatography to prevent oxidation of the product. Yield: 99.6 mg, 94%.

$[\alpha]_{\text{D}}^{23} = +120.5^\circ$ ($c = 1.0$, CHCl_3).

Ee: 87%. Daicel Chiralcel OD-H, *n*-hexane, flow rate = 0.5 mL/min.

PeakTable

Peak#	Ret. Time	Area	Area %
1	14.462	1297.094	49.950
2	16.868	12997005	50.050
Total		25968100	100.000

PeakTable

Peak#	Ret. Time	Area	Area %
1	14.622	190574	6.333
2	17.087	2818442	93.667
Total		3009015	100.000

^1H NMR (300 MHz, CDCl_3): δ 7.39-7.32 (m, 5H), 7.24-7.16(m, 2H), 6.87-6.84(m, 2H), 6.79-6.74 (m, 1H), 4.97 (br s, NH), 4.04 (q, J = 6.7 Hz, 1H), 3.67 (br s, 1H), 1.39 (d, J = 6.7 Hz, 3H)

^{13}C NMR (75 MHz, CDCl_3): δ 149.1, 143.2, 129.1, 128.7, 127.6, 126.9, 119.1 113.1, 58.9, 20.9

LC-MS (ESI): Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2$ [M]: 212.1. Found: 212.1.

(*R*)-3-Phenyl-1,2-benzisothiazoline 1,1-dioxide [296776-37-9]

The isolation was conducted with 0.2 mmol of the imine. 3-Phenyl-1,2-benziothiazole 1,1-dioxide (49 mg, 0.2 mmol), $\text{NiCl}_2(\text{DME})$ (2.2 mg, 0.01 mmol), (*R,R*)-Ph-BPE (6.1 mg, 0.012 mmol), formic acid (38 μL , 1.0 mmol, 5 equiv) and Et_3N (56 μL , 0.4 mmol, 2 equiv) and $\text{CF}_3\text{CH}_2\text{OH}$ (0.6 mL) were used. The reaction finished in 48 h at 100 $^\circ\text{C}$. The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. Yield: 49 mg, 98%. When (*S*)-Binapine was used, low conversion was seen.

$[\alpha]_D^{23} = -74.0^\circ$ (c = 1.0, CHCl_3).

Ee: 91%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 80/20, flow rate = 1.0 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	18.994	398868	50.469
2	21.670	391448	49.531
Total		790316	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	19.023	154022	3.622
2	21.617	4098305	96.378
Total		4252327	100.000

^1H NMR (300 MHz, CDCl_3): δ 7.83-7.75 (m, 1H), 7.59-7.47 (m, 2H), 7.36 (m, 5H), 7.11-7.14 (m, 1H), 5.71 (d, $J = 4.1$ Hz, 1H), 5.17 (d, $J = 4.1$ Hz, NH).

LC-MS (ESI): Calcd for $\text{C}_{13}\text{H}_{12}\text{NO}_2\text{S}$ [M]: 245.0. Found: 245.0.

(*R*)-3-Methyl-1,2-benzisothiazoline 1,1-dioxide [130973-53-4]

The reaction was conducted on 0.5 mmol scale of the imine using (*R,R*)-Ph-BPE as ligand and $\text{CF}_3\text{CH}_2\text{OH}$ as solvent (1.5 mL). The reaction finished in 48 h at 100 °C. The product was isolated by flash chromatography (EA/pentanes 1:2) as white solid. Yield: 91 mg, 99%.

$[\alpha]_D^{23} = 27.8^\circ$ ($c = 1.0$, CHCl_3)

Ee: 96%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 80/20, flow rate = 0.8 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	13.075	10579192	49.941
2	16.340	10604033	50.059
Total		21183225	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	13.253	2071	2.066
2	16.465	98180	97.934
Total		100251	100.000

^1H NMR (300 MHz, CDCl_3): δ 7.73 (d, $J = 7.7$ Hz, 1H), 7.61 (t, $J = 7.2$ Hz, 1H), 7.49 (t, $J = 7.5$ Hz, 1H), 7.38 (d, $J = 7.7$ Hz, 1H), 5.34 (br s, NH), 4.88-4.64 (m, 1H), 1.58 (d, $J = 6.7$ Hz, 3H)

LC-MS (ESI): Calcd for $\text{C}_8\text{H}_{10}\text{NO}_2\text{S}$ [M]: 183.0. Found: 183.0.

1.4.4 General Procedure for Deuterium Labeling Experiments

General procedure for asymmetric hydrogenation reaction using $[\text{D}_1]$ or $[\text{D}_2]$ formic acid: In an argon-filled glove box, $\text{NiCl}_2(\text{DME})$ (1.1 mg, 0.005 mmol), (*S*)-Binapine (4.4 mg, 0.006 mmol) and dry CD_3OD (0.3 mL) were charged into a 10-mL reaction tube. After stirring for 10 min, (*E*)-hydrazone (0.1 mmol), deuterated formic acid (7.6 μL , 0.2 mmol, 2 equiv) and Et_3N (28 μL , 0.2 mmol, 2 equiv) were added. The reaction mixture was heated with stirring in an oil bath maintained at 70 $^\circ\text{C}$ for 48 h. The reaction mixture was filtered to remove the catalyst and evaporated to give the crude product residue. The pure product was obtained by preparative TLC (EA/hexane 1:2). The deuterium content of the isolated product was analyzed by quantitative ^1H NMR spectroscopy.

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Chapter 2 Nickel-Catalyzed Asymmetric Reductive Amination: One Pot Synthesis of Chiral *N*-Tosylamines

2.1 Introduction

Direct asymmetric reductive amination (DARA) of simple ketones to synthesize chiral amines has proved to be one of the most convenient and atom economical pathway in organic chemistry. One of the biggest advantages of these reactions is that it is not necessary to isolate the intermediate imines, which are often prone to undergo hydrolysis and sometimes need multiple steps to synthesize. The pioneering work on asymmetric reductive amination was presented by Blaser's group for the synthesis of (*S*)-Metolachlor using an Ir-Xyliphos catalyst (Scheme 2.1).¹ Since then, enormous effort has been devoted to develop novel catalytic systems for DARA and almost all the great advances depended on precious metal catalysts, such as Rh², Ru³, Ir⁴ and Pd⁵. However, successful examples of DARA based on the first row metals are scarce.⁶

The first row metals, such as iron, cobalt, copper and nickel are relatively cheap and abundant. For example, recent price of nickel is around \$16 per kg and every year as much as 2.1 million tons of nickel is produced. Moreover, some of them are less toxic and friendlier to the ecosystem, such as iron, which is an essential element for humans and thus the U.S. Food and Drug Administration (FDA) allows trace amounts of iron residue in pharmaceutical drugs. Therefore, using first-row metals as catalysts for DARA will be a promising project for the development of asymmetric hydrogenation in the future.

Scheme 2.1. The first asymmetric reductive amination for the synthesis of (*S*)-Metolachlor

2.1.1 Noble Metal-Catalyzed Asymmetric Reductive Amination

The first outstanding example of asymmetric reductive amination for the synthesis of Metolachlor, which was reported by Blaser in 1999,¹ had an important effect on the research field of asymmetric reductive amination. Owing to some advantages of direct reductive amination, increasing attention has been paid to the field of asymmetric reductive amination and notable achievements have been made. For example, Zhang's group has developed the reductive amination of simple aromatic ketones and *p*-anisidine using an Ir-*f*-Binaphane catalyst (Scheme 2.2).^{4d} In the presence of efficient additives Ti(O*i*-Pr)₄ and iodine, the yields of these reductive amination products were up to 99%, but the *ee* values varied. Up to 94% *ee* was achieved in asymmetric reductive amination of acetophenone, while only 44% *ee* was obtained in the case of 1-*o*-tolylethanone. According to their proposed mechanism, the Ir^{III}/*f*-Binaphane, formed by the oxidative addition of I₂ to Ir^I catalyst precursor, was the real catalyst to provide highly active [Ir^{III}-H] intermediate in the presence of hydrogen. However, this catalyst failed to work for the asymmetric reductive amination of aliphatic ketones.

Scheme 2.2. Iridium-based reductive amination and its mechanism

In 2009, Xiao's group developed a series of half sandwich Cp*Ir(III) complexes for reductive amination with different chiral monosulfonated DPEN ligands (Scheme 2.3).^{4a} Excellent enantioselectivities and yields were achieved for a wide substrate scope of aromatic ketones. Furthermore, they employed a chiral Brønsted acid as cooperative catalyst for DARA, which might assist both the formation of the ketimine and the subsequent step of hydrogenation.

Scheme 2.3. Metal-Brønsted acid cooperative catalysis for asymmetric reductive amination and its catalytic pathway

Recently, Zhang's group developed a highly efficient direct reductive amination of arylacetones for the synthesis of enantiomerically pure β -arylamines using an iridium catalyst (Scheme 2.4).^{4c} They employed diphenylmethylenamines as the nitrogen source, which likely reduces poisoning of the metal catalyst through covalent binding of the

product. In addition, compared to other amines, such as aniline and benzylamine, the diphenylmethamines might be of benefit for improving the stereoselectivity, owing to the steric effect. In the presence of efficient additives, such as TFA and $\text{Ti}(\text{O}i\text{-Pr})_4$, the iridium catalyst showed excellent reactivity and enantioselectivity for the preparation of chiral β -arylamines, some of which might be used as key intermediates for pharmaceuticals.

Scheme 2.4. Iridium-catalyzed asymmetric reductive amination of arylacetones for the synthesis of (R)-Tamsulosin

Riermeier's group developed an efficient and novel method for the preparation of primary amines from simple ketones via hydrogen-transfer reductive amination (Scheme 2.5).² Up to 95% *ee* was achieved in Leuckart-Wallach-type reductive amination of aromatic ketones by using $\{[(R)\text{-tol-binap}]\text{RuCl}_2\}$ as a catalyst. However, in cases of aliphatic ketones, both yields and conversions were lower. For example, only 44% yield and 24% *ee* were obtained for 2-octanone.

Scheme 2.5. Catalytic asymmetric synthesis of primary amines

In 2011, Wright's group reported the first example of Ru-catalyzed intramolecular asymmetric reductive amination for the preparation of Suvorexant (MK-4305), which is used for the treatment of sleep disorders (Scheme 2.6).^{3a} This novel Ru catalyst offered the desired product in 97% yield and 94% *ee* in an intramolecular asymmetric transfer hydrogenation of a dialkyl ketone and primary amine. Furthermore, the mechanistic studies pointed out that the byproduct CO₂ had an important effect on both catalytic activity and reaction rates. Therefore, an increase in the rate of reaction and quantitative yield of the final product was achieved by purging CO₂ from the reaction system.

Scheme 2.6. Ru-catalyzed intramolecular asymmetric reductive amination

Rubio-Perez's group developed an efficient chiral diphosphine palladium(II) dibromide catalytic system for the asymmetric reductive amination of simple ketones.⁵

The results of those reactions with palladium catalysts were not uncommon. For example, excellent yields and good *ee* values were obtained in asymmetric reductive amination of aliphatic ketones and some of them were displayed in Scheme 2.7. In contrast, in some cases of aromatic methyl ketones, only moderate yields (53-67%) and *ee* values (34-43%) were observed.

Scheme 2.7. Palladium catalyzed reductive amination

2.1.2 First-Row Metal-Catalyzed Asymmetric Reductive Amination

Successful hydrogenation catalytic systems involving iron, cobalt, nickel and copper have been reported in recent years, while with respect to the asymmetric reductive amination of ketones, the first case has been published by Beller's group (Scheme 2.8).⁷ They reported many examples of reductive amination between aromatic amines and simple ketones by employing non-chiral iron complex and chiral Brønsted acid as cooperative catalysts. The corresponding products were obtained in good yields with moderate *ee* values.

Scheme 2.8. The first example of iron-catalyzed asymmetric reductive amination

In 2016, Dr Yang Peng in our group reported an enantioselective reductive amination of simple ketones with both arylamines and benzhydrazide using a nickel catalysts (Scheme 2.9).⁸ A series of aromatic methyl ketones with 3,5-dimethyl-4-anisidine provided the desired products in good yields and *ee* values in the presence of chiral ligand (*R*)-Ph-BPE. Furthermore, the reductive amination of ketones with benzohydrazide also afforded the desired products in good yields and high enantioselectivities with chiral ligand (*S*)-Binapine. To our delight, good results on a 5 mmol scale were obtained at catalyst loading as low as 1 mol%. In addition, double reductive amination of 1,2-diaminobenzene and α -ketoaldehydes successfully proceeded to produce substituted tetrahydroquinoxalines using a nickel/TangPhos catalyst.

Scheme 2.9. Nickel-catalyzed asymmetric reductive amination of acetophenone with both arylamines and benzhydrazides

2.1.3 Enantioselective Organocatalytic Reductive Amination

Except for these metal catalyst cases, List⁹ and MacMillan¹⁰ have made great contribution to the development of DARA with organocatalysts. They employed chiral phosphoric acids to promote the formation of imines, activate the imines by protonation and induce chirality by the effect of ion pairing. MacMillan's group has reported the first example of direct reductive amination with an organocatalyst, which involved Hantzsch's

ester as hydrogen source and chiral phosphoric acids as catalyst (Scheme 2.10). Several chiral phosphoric acids, designed by Terada¹¹ and Akiyama¹², were used to examine their catalytic activities. One of chiral phosphoric acids incorporates fully triphenylsilyl groups, provided the desired product with 87% yield and 94% *ee* in the model reaction. Moreover, this novel method of asymmetric reductive amination provided good yields and excellent enantioselectivity for both aromatic and dialkyl ketones.

Scheme 2.10. Organocatalytic reductive amination

2.2 Asymmetric Hydrogenation of *N*-Tosyl Ketimines

Due to the importance of chiral amines in agrochemical and pharmaceutical industry, immense effort has been devoted to develop new methods for the synthesis of the chiral amines and among them, asymmetric hydrogenation has been proven to be an efficient pathway. However, using asymmetric hydrogenation for the synthesis of chiral amines is

still a challenge. The main problems in this research field include the instability of some imines, different results for the *Z/E* isomers of acyclic imines and product inhibition on the metal catalysts. As Zhang's group discovered,¹³ *N*-tosylimines were optimal candidates for asymmetric hydrogenation, because they were quite stable and only *E* isomer could be isolated from aromatic methyl ketones.¹⁴ Moreover, the electronic properties of the tosyl group likely reduce the inhibitory effect of the amines on the metal catalysts. The tosyl group might also act as a directing group, which leads to higher stereoselectivity and reactivity. In addition, the tosyl group can be easily removed by treatment of SmI_2 to provide free secondary amines.¹⁵ Owing to these good properties, *N*-tosylimines were chosen as substrates to synthesize the chiral amines via asymmetric hydrogenation. Until now, some catalytic systems have proved to be efficient for asymmetric hydrogenation of *N*-tosylimines, while no reports exist that relate to asymmetric reductive amination of corresponding ketones with TsNH_2 in a one pot reaction.

Chiral *N*-tosylamine products were firstly prepared with acceptable enantioselectivities by the Charette's group using Ru-Binap catalyst in 1996 (Scheme 2.11).¹⁴ However, the *ee* values were not high and the reaction conditions were quite harsh. For example, high pressure of H_2 (75 bar) gas was required for the reaction.

Scheme 2.11. Ru/BINAP-catalyzed asymmetric hydrogenation of aromatic *N*-tosylimines

In 2006, Zhang's group reported a highly efficient Pd/TangPhos catalytic system for asymmetric hydrogenation of *N*-tosylimines and up to 99% *ee* and 99% yield were achieved (Scheme 2.12). Moreover, the substrate scope was wide. *N*-tosylimines, prepared from aromatic, aliphatic as well as cyclic ketones, provided good to excellent results under optimal reaction conditions, although high pressure of hydrogen gas was necessary.

Scheme 2.12. Pd-catalyzed asymmetric hydrogenation of *N*-tosylimines

One year later, up to 97% *ee* was achieved in asymmetric hydrogenation of 4-methyl-*N*-(1-phenylethylidene)benzenesulfonamide by Zhou's group employing a $\text{Pd}(\text{CF}_3\text{CO}_2)_2/(S)\text{-SynPhos}$ catalyst (Scheme 2.13).¹⁶ Good to excellent yields and enantioselectivities have been obtained with various *N*-tosylimine derivatives using 2,2,2-trifluoroethanol (TFE) as solvent. Moreover, this palladium catalytic system has also provided good results for other substituted imines.

Scheme 2.13. Highly enantioselective Pd-catalyzed asymmetric hydrogenation of activated imines

Two efficient Rh-catalyzed asymmetric transfer hydrogenation of *N*-sulfonyl ketimines with TsDPEN chiral ligand were reported by Lee¹⁷ and Deng¹⁸ (Scheme 2.14). Lee's group employed $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$ as hydrogen source. Various substituted aromatic *N*-tosylimines were reduced in good to excellent yields and enantioselectivities, except for aliphatic ones. Deng's group used HCO_2Na as hydrogen source and water as solvent, which was found to be a green route for the synthesis of bioactive drug with the amine functionality in them.

Scheme 2.14. Rh-TsDPEN catalyzed asymmetric hydrogenation of *N*-tosylimines

Well-defined iron(II)-PNNP catalytic system, designed by Morris's group, has also

been widely employed for asymmetric hydrogenation of ketones with excellent results, and its mechanism has been further studied. However, this efficient catalytic system only provided 26% conversion of 4-methyl-*N*-(1-phenylethylidene)benzenesulfonamide, but with 94% *ee* (Scheme 2.15).¹⁹

Scheme 2.15. Fe(II)-PNNP catalyzed asymmetric hydrogenation of activated imines

To the best of our knowledge, almost all the procedures for preparing *N*-tosylimines were very complicated (Scheme 2.16).¹⁶ The general method involved the condensation of corresponding ketones with sulfinamides, and then followed by *m*-CPBA oxidation of the relative *N*-sulfinylimines. Herein, our group reports a highly efficient direct asymmetric reductive amination of simple ketones and sulfonamides using a nickel catalyst. One-pot multi-step transformations, which reduce several synthetic procedures and help to cut down waste generation, are considered to be among the most economic and green method in organic synthesis. Due to the strong electron-withdrawing property of the tosyl group, the condensation of corresponding ketones with sulfonamides is not as easy as the condensation using primary amines and only two reports focused on the synthesis of *N*-tosylimines by direct condensation of simple ketone and sulfonamides with harsh reaction conditions.²⁰

(1) Multi-step synthesis

(2) one pot synthesis under Microwave irradiation

(3) our one pot synthesis under heating

Scheme 2.16. Procedures for the synthesis of chiral *N*-sulfonyl imines

2.3 Results and Discussion

2.3.1 Reaction Optimization

Direct asymmetric reductive amination has proved to be an efficient and convenient approach to produce chiral amines. Several problems in this research field stand as obstacles in the way of progress, especially for simple ketones with strong electron-withdrawing TsNH_2 : (1) Aromatic ketones are by themselves reactive substrates for hydrogenation, and hence their reduction could occur faster than the desired reductive amination. (2) Aldol condensation of excess ketones in the presence of titanium alkoxides can take place prior to the reductive amination of corresponding ketones with sulfonamides. In order to solve these problems, 1.5 equivalents of simple ketone were added and higher reaction temperature (120 °C) has been used for promoting prior

formation of the *N*-tosylimines (Table 2.1). All conversions of sulfonamide and yields of the product were determined by GC analysis with *n*-C₁₄H₃₀ as internal standard. As shown in table 2.1, 1.2 equivalents Ti(OEt)₄ and high reaction temperature (120 °C) were optimal for the formation of *N*-tosylimines (Table 2.1, entry 3). Low equivalents of Ti(OEt)₄ and moderate reaction temperature were proven to be more benefit for the aldol condensation of acetophenone (Table 2.1, entries 1 and 4).

Table 2.1. Optimization for the formation of tosyl imine

Entry	Ti(OEt) ₄ (x equiv)	Temp. (°C)	Time (h)	Conv. (%)	GC yield (%)
1	1.2	80	24	73	69
2	1.2	100	24	85	82
3	1.2	120	24	96	95
4	0.2	120	24	57	54
5	0.5	120	24	77	73
6	1.0	120	24	91	88
7	1.5	120	24	96	95
8	1.2	120	2.0	91	89
9	1.2	120	3.5	92	89
10	1.2	120	6.0	95	94
11	1.2	120	20	95	95

Based on the literature study, we initially attempted a model reaction between 4-methylbenzenesulfonamide and acetophenone. The one-pot experimental procedures were set up as following: the Ti-mediated condensation was directly followed by the

addition of the nickel precatalyst, ligand, formic acid, triethylamine, molecular sieves, and trifluoroethanol to the toluene solution. Firstly, we screened different types of chiral ligands as shown in Table 2.2.

Table 2.2. Effect of chiral ligand

Entry	Ligand	Conv. (%)	Yield (%)	Ee (%)
1	<i>(S,S)</i> -Binapine	93	87	93
2	<i>(R,R)</i> -BenzP*	82	81	89
3	<i>(R,R)</i> -QuinoxP*	90	73	91
4	<i>(S,S)</i> -Ph-BPE	85	62	91
5	<i>(S,S)</i> -Ph-BPE	91	80	82

<i>(S,S)</i> - <i>i</i> -Pr-BPE				
6		65	46	66
<i>(R,R)</i> -Me-DuPhos				
7		47	30	67
<i>(R,R)</i> -Et-DuPhos				
8		80	79	89
<i>(R,R)</i> - <i>i</i> -Pr-DuPhos				
9		97	73	59
<i>(S,S',R,R')</i> -TangPhos				
10		83	76	75
<i>(1S,1'S,2R,2'R)</i> -DuanPhos				
11		93	78	73
<i>(R,Sp)</i> -CyPF-Cy				
12		80	79	80
13		0	0	
<i>(R)</i> -BINAP				

14		0	0
	(<i>R</i>)- <i>i</i> -Pr-MeO-Biphep		
16		0	0
	(<i>R,R</i>)-Dipamp		

From Table 2.2, we found that the nickel catalyst showed high reactivity in this model reaction only in the presence of highly electron-donating and sterically hindered bisphosphine ligands. A series of chiral diphosphine ligands, such as Binapine²¹, TangPhos²² and DuanPhos²³, which were synthesized by Xumu Zhang's group, provided good results (Table 2.2, entries 1, 9 and 10). Among them, (*S*)-Binapine was particularly good in terms of both yields and *ee* values in the model reaction. 81% yield and 89% *ee* was achieved by the chiral bisphosphine ligand (*R,R*)-BenzP*²⁴ (Table 2.2, entry 2). (*R,R*)-QuinoxP*, one of Imamoto's *P*-chiral ligands²⁵, provided the desired product in 73% yield and 91% *ee* (Table 2.2, entry 3). 2,5-Disubstituted bisphospholane ligands Ph-BPE and *i*-Pr-BPE afforded good results (Table 1, entries 4 and 5). DuPhos family ligands, which were synthesized by Mark Burk's group²⁶, such as Me-Duphos, Et-Duphos and *i*-Pr-Duphos, showed low reactivity (Table 2.2, entries 6-8). Other two chiral ferrocene-based bisphosphane ligands, such as (*R,Sp*)-CyPF-Cy and (*R,Sp*)-CyPF-*t*-Bu, showed high reactivity but with moderate *ee* values²⁷ (Table 2.2, entries 11 and 12). Others less electron-rich phosphine chiral ligands, such as BINAP²⁸, DIPAMP²⁹ and

i-Pr-MeO-Biphep³⁰ were inactive at all in this model reaction.

With the optimal chiral ligand (*S*)-Binapine in hand, we examined the effect of nickel(II) salts (Table 2.3). Most of them provided similar enantioselectivities and yields of the product, except that Ni(acac)₂ did not form an active catalyst.

Table 2.3. Effect of nickel salts

Entry	Nickel salt	Conv. (%)	Yield (%)	Ee (%)
1	Ni(OAc) ₂	87	86	90
2	Ni(OTf) ₂	86	85	85
3	NiBr ₂ (DME)	91	87	90
4	NiCl ₂ (DME)	92	87	93
5	Ni(acac) ₂	0	0	--

As shown in Table 2.4, both reactivities and enantioselectivities were dramatically improved by employing CF₃CH₂OH (TFE) as solvent (Table 2.4, entry 3). The main role of TFE was suggested to activate the *N*-tosyl imine by protonation or hydrogen bonding of imino group.³¹ Other common solvents provided quite low yield of the desired product, while self-condensation of acetophenone and asymmetric hydrogenation of excess acetophenone were observed.

Table 2.4. Effect of solvents

Entry	Solvent	Conv. (%)	Yield (%)	Ee (%)
1	MeOH	< 5	-	-
2	EtOH	< 5	-	-
3	CF ₃ CH ₂ OH	93	87	93
4	<i>i</i> -PrOH	< 10	< 5	-
5	<i>n</i> -BuOH	< 5	0	-
6	Dioxane	0	0	-
7	THF	0	0	-
8	PhCH ₃	0	0	-
9	PhCF ₃	0	0	-
10	DMF	0	0	-

The results in the Table 2.5 showed that an increase in the yield of the desired product was observed with an increase in the amount of Ti(OEt)₄ and 1.2 Equiv Ti(OEt)₄ proved to be optimal for this model reaction.

Table 2.5. Effect of equivalent Ti(OEt)₄

Entry	Ti(OEt) ₄ (x equiv)	Conv. (%)	Yield (%)	Ee (%)
1	0.2	45	43	95
2	0.5	73	69	94
3	1.0	77	75	94

4	1.2	93	87	93
5	1.5	94	87	93

As the results shown in Table 2.1 and Table 2.6, the reaction temperature had an important effect on the yield of desired product, mainly owing to the effect of the formation of imine. High reaction temperature (120 °C) facilitated the formation of imine, and then subsequently promoted an increase in the yield of the final product.

Table 2.6. Effect of reaction temperature for the formation of tosyl imine

Entry	Temperature (°C)	Conv. (%)	Yield (%)	Ee (%)
1	80	64	61	95
2	100	73	71	94
3	120	93	87	94

We next moved to examine the effect of nickel catalyst loading as shown in Table 2.7. A catalyst loading of 5 mol% was found optimal for this model reaction (Table 2.7, entry 3). Only 50% conversion was observed when the catalyst loading was reduced to 1 mol% under the established reaction conditions (Table 2.7, entry 1).

Table 2.7. Effect of nickel loading

Entry	Nickel loading (mol%)	Conv. (%)	Yield (%)	Ee (%)
1	1.0	57	55	93
2	2.5	79	73	93
3	5.0	92	87	93

A 2:2 molar ratio mixture of HCO_2H and Et_3N was optimal in terms of both catalytic activity and enantioselectivity. Molecular sieves were employed to remove trace amount of water, so that the progress of the reaction could be facilitated.

3.3.2 Substrate Scope of *N*-Tosylamines

With the optimal reaction conditions in hand, we explored the scope of simple ketones, which could react with 4-methylbenzenesulfonamide (0.2 mmol scale) in the presence of Ni/Binapine catalyst via direct asymmetric reductive amination (Scheme 2.17). The ketones with electron-donating group provided good to excellent yields and *ee* values. However, a low yield (< 10%) was observed employing 1-(4-(trifluoromethyl)phenyl)ethanone as a substrate. Only 60% yield was obtained in direct asymmetric hydrogenation of 4-methyl-*N*-(1-(4-(trifluoromethyl)phenyl)ethylidene)benzenesulfonamide. A slight drop in *ee* values was observed when the acetophenone (94% *ee*) was replaced by propiophenone (82% *ee*). *Ortho*-substituted ketones, such as 1-*o*-tolylethanone and 1-(2-fluorophenyl)ethanone, were successfully reduced without steric effects. The cyclic ketones provided 99% *ee*, while a low yield was observed in the case of 2,3-dihydro-1*H*-inden-1-one. To our delight, some heteroaryl imines were also hydrogenated with excellent enantioselectivity. The absolute configuration of the amine

derived from benzothiophenyl methyl ketone was unambiguously determined by X-ray diffraction analysis.

Scheme 2.17. Asymmetric reductive amination of aromatic ketones with TsNH_2

Further expansion of this protocol to aliphatic ketones was also explored. The direct asymmetric reductive amination of aliphatic ketones with TsNH_2 proceeded smoothly under the optimized reaction conditions (Scheme 2.18). The aliphatic ketones with bulky substituents, such as *t*-Bu, *i*-Pr and cyclohexyl, provided the desired products with excellent enantioselectivity, while others offered moderate ee values. In addition, (*R,S*)-CyPF-Cy, a Josiphos ligand and (*R,R*)-QuinoxP* were found to be more active than (*S*)-Binapine in some special cases.

Scheme 2.18. Asymmetric reductive amination of aliphatic ketones with TsNH_2

Several sulfonamides with other substituents were also examined under the optimized reaction conditions as shown in Scheme 2.19. The *ee* values for electron-rich sulfonyl amides were up to 90%. However, only 15% yield was achieved in the direct asymmetric reductive amination of acetophenone with 2-methylpropane-2-sulfonamide. A slightly higher yield of the desired product (*R*)-*N*-(2,3-dihydro-1*H*-inden-1-yl)-4-methylbenzenesulfonamide was obtained by direct asymmetric hydrogenation of the related *N*-tosylimine. No desired amine product was obtained using strongly electron-withdrawing $\text{CF}_3\text{SO}_2\text{NH}_2$. To our delight, the nickel/(1*S*)-TangPhos catalytic system provided the final product (*S*)-*P,P*-diphenyl-*N*-(1-phenylethyl)phosphinic amide with 82% yield and 75% *ee* (Scheme 2.20).

Scheme 2.19. Asymmetric reductive amination of acetophenone with several sulfonamides

Scheme 2.20. Asymmetric reductive amination of acetophenone with diphenylphosphinic amide (0.2 mmol scale)

2.3.3 Conclusions

We have developed a highly enantioselective nickel-catalyzed asymmetric reductive of imines generated in situ from ketones and electron-withdrawing sulfonamides. Various chiral N -tosylamines were obtained in high enantioselectivity employing (*S*)-Binapine as the supporting ligand. Further studies will be focused on the application of chiral tosylamines in synthesis and on improving the novel nickel catalysts' turnover numbers.

2.4 Experimental Section

2.4.1 General

^1H NMR spectra were acquired on Bruker AV 300 MHz or 400 MHz NMR spectrometers. ^1H NMR (300 MHz) chemical shifts were recorded relative to SiMe_4 (δ 0.00) or residual protiated solvents (CDCl_3 : δ 7.26). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by $n\text{H}$. Coupling constants were reported as a J value in Hz. ^{13}C NMR (75 MHz) chemical shifts were recorded relative to solvent resonance (CDCl_3 : δ 77.16). Proof of purity products were demonstrated by ^1H and ^{13}C NMR.

Glassware was dried at 120 $^\circ\text{C}$ for at least 3 h before use. Dry toluene, hexane, diethyl ether and dichloromethane were collected from a solvent purification system containing a column of activated alumina (1 m x 2) under argon. Dry THF was freshly distilled from sodium/benzophenone under argon. The MeOH, EtOH, and isopropanol were distilled from CaH_2 under argon and stored over activated 4Å molecular sieve beads in an argon-filled glove box. Unless noted otherwise, readily available chemicals were used directly with no further purification. The GC internal standard, $n\text{-C}_{14}\text{H}_{30}$ was degassed with argon and dried over activated 3Å molecular sieve beads before use.

Flash chromatography was performed using Merck 40-63D 60Å silica gel. Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument with Agilent J & W GC column DB-5MS-UI. GC/MS analysis was conducted on a Thermo Scientific DSQ II single quadrupole GC/MS instrument with Agilent J & W GC column DB-5MS-UI. Chiral HPLC analysis was performed on a Shimadzu LC-20AD instrument using Daicel Chiracel columns at 25 $^\circ\text{C}$ and a mixture of HPLC-grade hexanes and isopropanol as eluent. Optical rotation was measured using a JASCO P-1030 Polarimeter

equipped with a sodium vapor lamp at 589 nm and the concentration of samples was denoted as *c*.

2.4.2 Condition Optimization for Direct Asymmetric Reductive Amination of

Acetophenone with TsNH₂

A general procedure for condition optimization: In an argon-filled glove box, acetophenone (0.3 mmol, 1.5 equiv), sulfonamide (0.2 mmol, 1.0 equiv), Ti(OEt)₄ (1.2 equiv) and dry toluene (0.2 mL) was added to a 10-mL Schlenk tube, and then the mixture was heated with stirring at 120 °C for 24 h. After the reaction mixture was cooled down to room temperature, NiCl₂(DME) (2.1 mg, 0.010 mmol), (*S*)-Binapine (8.8 mg, 0.012 mmol), 3Å molecular sieve (0.05 g) and dry CF₃CH₂OH (0.4 mL) were added in the glove box. Then after stirring for 10 min, formic acid (15.2 µL, 0.4 mmol), Et₃N (56 µL, 0.4 mmol), dry CF₃CH₂OH (0.2 mL) and GC standard *n*-C₁₄H₃₀ (10 µL) were added. The reaction mixture was stirred for 48 h in an oil bath at 80 °C. In the course of the reaction, aliquots were taken out from the reaction mixture in the glove box, and passed through a short plug of silica gel with EtOAc washing (about 3 mL). The filtrate was subjected to GC analysis to determine the conversion of sulfonamide and the yield of product. In order to determine the enantioselectivity of the product, the filtrate was dissolved in 1:10 *i*-PrOH/hexane and analyzed by chiral HPLC chromatography (Daicel CHIRCEL OD-H; 10% *i*-PrOH in hexane; flow rate 0.5 mL/min).

2.4.3 Isolated Products of Direct Asymmetric Reductive Amination

General procedure for direct asymmetric reductive amination: In an argon-filled glove box, ketone (0.3 mmol, 1.5 equiv), substituted amide (0.2 mmol, 1.0 equiv),

Ti(OEt)₄ (1.2 equiv) and dry toluene (0.2 mL) was added to a 10-mL reaction tube, then the mixture was heated with stirring at 120 °C. After 24 h, the reaction was cooled down to room temperature, NiCl₂(DME) (2.1 mg, 0.010 mmol), (*S*)-Binapine (8.8 mg, 0.012 mmol), 3Å molecular sieve (0.05 g) and dry CF₃CH₂OH (0.4 mL) were added in an argon-filled glove box. After stirring for 10 min, formic acid (15.2 µL, 0.4 mmol), Et₃N (56 µL, 0.4 mmol), and dry CF₃CH₂OH (0.2 mL) were added. The reaction mixture was stirred in an oil bath maintained at 80 °C for 48 h. The solvent was removed under reduced pressure to produce crude product, then the product was purified by a flash chromatograph to obtain pure product.

(*R*)-4-Methyl-*N*-(1-phenylethyl)benzenesulfonamide [72984-27-1]

The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 48 mg, 86%.

$[\alpha]_D^{23} = +50.5^\circ$ ($c = 1.0$, CHCl₃).

Ee: 94%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

Peak Table			
Peak#	Ret. Time	Area	Area %
1	20.258	13248232	49.946
2	24.170	13276837	50.054
Total		26525069	100.000

Peak Table			
Peak#	Ret. Time	Area	Area %
1	20.085	27064669	97.330
2	24.154	742357	2.670
Total		27807026	100.000

¹H NMR (400 MHz, CDCl₃): δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.19-7.16 (m, 5H), 7.10-7.08 (m, 2H), 4.94 (d, *J* = 6.9 Hz, 1H), 4.45 (p, *J* = 6.9 Hz, 1H), 2.37 (s, 3H), 1.41 (d, *J* = 6.9 Hz,

3H).

^{13}C NMR (101 MHz, CDCl_3): δ 143.1, 142.1, 137.7, 129.4, 128.5, 127.4, 127.1, 126.1, 53.6, 23.5, 21.5.

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 276.1. Found: 275.9.

(R)-4-Methyl-N-(1-p-tolyethyl)benzenesulfonamide [905273-00-9]

The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 48 mg, 84%.

$[\alpha]_D^{23} = +76.8^\circ$ ($c = 0.7$, CHCl_3).

Ee: 96%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	18.699	5197110	49.888
2	21.089	5220430	50.112
Total		10417540	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	18.665	22095852	98.004
2	21.213	449925	1.996
Total		22545777	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.65 (d, $J = 8.2$ Hz, 2H), 7.21 (d, $J = 8.0$ Hz, 2H), 7.04-6.99 (m, 4H), 4.80 (d, $J = 6.7$ Hz, 1H), 4.44 (p, $J = 6.8$ Hz, 1H), 2.42 (s, 3H), 2.30 (s, 3H), 1.43 (d, $J = 6.8$ Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 143.0, 139.1, 137.7, 137.2, 129.4, 129.2, 127.1, 126.1, 53.4, 23.5, 21.5, 21.0

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 290.1. Found: 289.9.

(*R*)-*N*-(1-(4-Methoxyphenyl)ethyl)-4-methylbenzenesulfonamide [1125576-35-3]

The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 54 mg, 89%.

$[\alpha]_D^{23} = +54.2^\circ$ ($c = 1.0$, CHCl_3).

Ee: 93%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 98/2, flow rate = 0.5 mL/min.

PeakTable

Peak#	Ret. Time	Area	Area %
1	129.144	4974410	49.415
2	138.759	5092132	50.585
Total		10066542	100.000

PeakTable

Peak#	Ret. Time	Area	Area %
1	129.104	4784374	96.714
2	140.783	162536	3.286
Total		4946910	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.61 (d, $J = 8.3$ Hz, 2H), 7.19 (d, $J = 8.1$ Hz, 2H), 7.02-6.99 (m, 2H), 6.73-6.70 (m, 2H), 4.77 (d, $J = 6.6$ Hz, 1H), 4.40 (t, $J = 6.8$ Hz, 1H), 3.75 (s, 3H), 2.39 (s, 3H), 1.40 (d, $J = 6.8$ Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 158.9, 158.9, 143.0, 134.3, 129.4, 127.4, 127.1, 113.8, 55.3, 53.1, 23.4, 21.5

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$: 306.1. Found: 305.9.

(*R*)-*N*-(1-(4-Fluorophenyl)ethyl)-4-methylbenzenesulfonamide [905273-02-1]

The reaction completed after 48 h at 80 °C. The product was isolated by flash

chromatography (EA/hexanes 1:4) as white solid. Yield: 50 mg, 86%.

$[\alpha]_D^{23} = +51.6^\circ$ ($c = 0.5$, CHCl_3).

Ee: 94%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

^1H NMR (500 MHz, CDCl_3): δ 7.60 (d, $J = 8.3$ Hz, 2H), 7.19 (d, $J = 8.0$ Hz, 2H), 7.08-7.05 (m, 2H), 6.89-6.85 (m, 2H), 4.82 (d, $J = 6.6$ Hz, 1H), 4.46 (dd, $J = 13.7, 6.8$ Hz, 1H), 2.39 (s, 3H), 1.39 (d, $J = 6.8$ Hz, 3H)

^{13}C NMR (126 MHz, CDCl_3): δ 162.9, 161.0, 143.2, 138.0, 138.1, 137.6, 129.4, 127.9, 127.8, 127.1, 115.3, 115.1, 53.0, 23.6, 21.4

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{16}\text{FNO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 294.1. Found: 293.9.

(*R*)-4-Methyl-*N*-(1-(4-(trifluoromethyl)phenyl)ethyl)benzenesulfonamide [(*S*)-isomer 881770-16-7]

The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield below 10%.

$[\alpha]_D^{23} = +8.5^\circ$ ($c = 1.0$, CHCl_3).

Ee: 92%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate = 0.5 mL/min.

1 PDA Multi 1 / 200nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	35.987	2342729	50.592
2	40.783	2297651	49.408
Total		4640379	100.000

1 PDA Multi 1 / 200nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	36.102	996851	96.108
2	41.220	40371	3.892
Total		1037222	100.000

^1H NMR (300 MHz, CDCl_3): δ 7.55 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 5.12 (d, J = 6.9 Hz, 1H), 4.55 (p, J = 6.9 Hz, 1H), 2.37 (s, 3H), 1.43 (d, J = 6.9 Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 145.9, 143.4, 137.3, 129.4, 127.1, 126.6, 125.4, 125.4, 125.3, 53.3, 23.5, 21.3.

^{19}F NMR (376 MHz, CDCl_3): δ -62.59, -62.65

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{16}\text{F}_3\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 344.1. Found: 344.0.

(R)-4-Methyl-N-(1-phenylpropyl)benzenesulfonamide [93241-22-6]

The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 53 mg, 91%.

$[\alpha]_{\text{D}}^{23} = +30.9^\circ$ (c = 0.5, CHCl_3).

Ee: 82%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	27.145	2774602	49.884
2	36.410	2787520	50.116
Total		5562123	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	28.109	5042298	91.628
2	36.636	460691	8.372
Total		5502989	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.56 (d, J = 8.3 Hz, 2H), 7.18-7.12 (m, 5H), 7.05-7.02 (m, 2H), 4.96 (d, J = 7.2 Hz, 1H), 4.21 (q, J = 7.2 Hz, 1H), 2.38 (s, 3H), 1.87-1.70 (m, 2H), 0.81 (t, J = 7.4 Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 142.9, 140.8, 137.7, 129.3, 128.4, 127.3, 127.0, 126.6, 59.8, 30.6, 21.4, 10.4

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 290.1. Found: 289.9.

(R)-4-Methyl-N-(1-*o*-tolylethyl)benzenesulfonamide [(S)-isomer 881770-46-3]

The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 53 mg, 91%.

$[\alpha]_{\text{D}}^{23} = +24.2^\circ$ (c = 1.0, CHCl_3).

Ee: 95%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	17.801	2333416	49.260
2	22.475	2403480	50.740
Total		4736896	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	17.803	20560071	97.889
2	22.918	486462	2.311
Total		21046533	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.61 (d, J = 8.3 Hz, 2H), 7.18-7.12 (m, 3H), 7.11-7.03 (m, 3H), 4.93 (s, 1H), 4.75 (p, J = 6.8 Hz, 1H), 2.39 (s, 3H), 2.22 (s, 3H), 1.41 (d, J = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 143.0, 140.3, 137.7, 134.4, 130.4, 129.3, 127.2, 127.0, 126.4, 125.3, 49.7, 23.1, 21.4, 19.0

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 290.1. Found: 289.9.

**(*R*)-*N*-(1-(2-Fluorophenyl)ethyl)-4-methylbenzenesulfonamide [(*S*)-isomer
1481656-67-0]**

The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 48 mg, 81%.

$[\alpha]_{\text{D}}^{23} = +53.2^\circ$ (c = 0.6, CHCl_3).

Ee: 93%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.61-7.59 (m, 2H), 7.17-7.10 (m, 4H), 6.99-6.95 (m, 1H), 6.87-6.82 (m, 1H), 5.13 (d, J = 7.4 Hz, 1H), 4.69 (dq, J = 14.2, 7.0 Hz, 1H), 2.36 (s, 3H), 1.47 (d, J = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 161.2, 158.8, 143.0, 137.4, 129.3, 129.2, 129.0, 128.9, 128.8, 128.1, 128.0, 127.0, 124.2, 124.2, 115.7, 115.5, 49.7, 22.9, 21.4

^{19}F NMR (376 MHz, CDCl_3): δ -118.96

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{16}\text{FNO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 294.1. Found: 294.0.

(R)-N-(1-(Benzo[d][1,3]dioxol-5-yl)ethyl)-4-methylbenzenesulfonamide

The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 57 mg, 89%.

$[\alpha]_D^{23} = +40.2^\circ$ ($c = 0.5$, CHCl_3).

Ee: 96%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.63-7.61 (m, 2H), 7.19 (d, $J = 8.0$ Hz, 2H), 6.63-6.54 (m, 3H), 5.88 (dd, $J = 7.0, 1.4$ Hz, 2H), 4.97 (s, 1H), 4.39 (p, $J = 6.8$ Hz, 1H), 2.39 (s, 3H), 1.38 (d, $J = 6.8$ Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 147.7, 146.8, 143.1, 137.7, 136.1, 129.4, 127.1, 119.6, 108.0, 106.7, 101.0, 53.5, 23.5, 21.4

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 320.1. Found: 320.0.

(R)-4-Methyl-N-(1-(naphthalen-2-yl)ethyl)benzenesulfonamide [182949-59-3]

The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 55 mg, 84%.

$[\alpha]_D^{23} = +60.4^\circ$ ($c = 0.7$, CHCl_3).

Ee: 96%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

^1H NMR (500 MHz, CDCl_3): δ 7.74-7.73 (m, 1H), 7.64 (d, $J = 7.8$ Hz, 2H), 7.57 (d, $J = 8.2$ Hz, 2H), 7.46-7.41 (m, 3H), 7.21-7.19 (m, 1H), 7.01 (d, $J = 8.0$ Hz, 2H), 5.16 (d, $J = 7.1$ Hz, 1H), 4.63 (p, $J = 6.9$ Hz, 1H), 2.23 (s, 3H), 1.50 (d, $J = 6.9$ Hz, 3H)

^{13}C NMR (126 MHz, CDCl_3): δ 143.1, 139.1, 137.6, 133.1, 132.7, 129.3, 128.4, 127.8, 127.5, 127.1, 126.2, 125.9, 125.1, 124.1, 53.8, 23.4, 21.3

GC-MS (EI): Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 326.1. Found: 326.9.

(R)-N-(1-(Furan-2-yl)ethyl)-4-methylbenzenesulfonamide [158568-75-3]

The reaction completed after 48 h at 80 °C. The product was isolated by flash

chromatography (EA/hexanes 1:4) as white solid. Yield: 41 mg, 78%.

$[\alpha]_{\text{D}}^{23} = +87.3^{\circ}$ ($c = 0.5$, CHCl_3).

Ee: 97%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate = 0.5 mL/min.

^1H NMR (300 MHz, CDCl_3): δ 7.72-7.68 (m, 2H), 7.26-7.23 (m, 2H), 7.19-7.18 (m, 1H), 6.18-6.16 (m, 1H), 6.01-5.99 (m, 1H), 4.98 (d, $J = 8.0$ Hz, 1H), 4.56 (p, $J = 7.1$ Hz, 1H), 2.41 (s, 3H), 1.47 (d, $J = 6.9$ Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 154.1, 143.1, 141.9, 137.7, 129.5, 127.1, 110.1, 106.1, 47.4, 21.5, 20.9

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$: 266.1. Found: 265.9.

(R)-4-Methyl-N-(1-(thiophen-2-yl)ethyl)benzenesulfonamide [1446468-54-7]

The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 39 mg, 68%.

$[\alpha]_{\text{D}}^{23} = +21^{\circ}$ ($c = 1.0$, CHCl_3).

Ee: 97%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.70-7.67 (m, 2H), 7.23 (d, $J = 8.0$ Hz, 2H), 7.10 (dd, $J = 5.1, 1.2$ Hz, 1H), 6.80 (dd, $J = 5.1, 3.5$ Hz, 1H), 6.75-6.74 (m, 1H), 4.95 (d, $J = 7.7$ Hz, 1H), 4.73 (dd, $J = 13.7, 6.9$ Hz, 1H), 2.39 (s, 3H), 1.51 (d, $J = 6.8$ Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 146.1, 143.3, 137.7, 129.8, 127.1, 126.7, 124.7, 124.4, 49.3, 23.9, 21.5

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_2\text{S}_2$ [M]: 281.1. Found: 281.0.

(R)-N-(1-(Benzo[*b*]thiophen-2-yl)ethyl)-4-methylbenzenesulfonamide

The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 54 mg, 81%.

$[\alpha]_{\text{D}}^{23} = +107.3^\circ$ ($c = 0.5$, CHCl_3).

Ee: 97%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.70-7.68 (m, 3H), 7.61-6.59 (m, 1H), 7.32-7.24 (m, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.95 (s, 1H), 4.84-4.80 (m, 2H), 2.32 (s, 3H), 1.60-1.55 (m, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 146.5, 143.4, 139.3, 139.2, 137.5, 129.4, 127.1, 124.3, 123.5, 122.3, 121.2, 49.9, 23.6, 21.4

GC-MS (EI): Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_2\text{S}_2$ [M]: 332.1. Found: 332.0.

(R)-4-Methyl-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzenesulfonamide

The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 50 mg, 89%.

$[\alpha]_{\text{D}}^{23} = +25.4^\circ$ (c = 1.0, CHCl_3).

Ee: 98%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	17.910	9606235	49.865
2	23.529	9658382	50.135
Total		19264617	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	17.565	17347578	99.295
2	22.874	123094	0.705
Total		17470673	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.83 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.15-7.11 (m, 1H), 7.07-7.02 (m, 2H), 6.95-6.93 (m, 1H), 4.61 (d, J = 7.7 Hz, 1H), 4.47-4.43 (m, 1H), 2.78-2.64 (m, 2H), 2.46 (s, 3H), 1.83-1.80 (m, 3H), 1.75-1.70 (m, 1H)

^{13}C NMR (101 MHz, CDCl_3): δ 143.4, 138.2, 137.6, 135.6, 129.8, 129.2, 128.8, 127.7, 127.2, 126.3, 51.9, 30.8, 28.9, 21.6, 19.1

GC-MS (EI): Calcd for $\text{C}_{17}\text{H}_{19}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 302.4. Found: 302.0.

(R)-N-(2,3-Dihydro-1H-inden-1-yl)-4-methylbenzenesulfonamide

The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 23 mg, 40%.

$[\alpha]_D^{23} = +17.6^\circ$ ($c = 0.5$, CHCl_3).

Ee: 99%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.83-7.81 (m, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.21-7.08 (m, 4H), 4.87-4.77 (m, 2H), 2.92-2.84 (m, 1H), 2.76-2.68 (m, 1H), 2.44 (s, 3H), 2.32-2.28 (m, 1H), 1.76-1.66 (m, 1H)

^{13}C NMR (101 MHz, CDCl_3): δ 143.5, 142.8, 142.0, 138.2, 129.8, 128.3, 127.2, 126.8, 124.80, 124.1, 58.7, 34.7, 30.0, 21.6

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 288.1. Found: 288.1.

(R)-N-(1-Phenylethyl)benzenesulfonamide [204907-36-8]

The reaction completed after 48 h at 80 °C. The product was isolated by flash

chromatography (EA/hexanes 1:4) as white solid. Yield: 42 mg, 81%.

$[\alpha]_D^{23} = +40.5^\circ$ ($c = 1.0$, CHCl_3).

Ee: 91%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 98/2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.73-7.71 (m, 2H), 7.51-7.46 (m, 1H), 7.40-7.36 (m, 2H), 7.21-7.16 (m, 2H), 7.11-7.07 (m, 2H), 4.88 (s, 1H), 4.53-4.46 (m, 1H), 1.44 (d, $J = 6.9$ Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 141.8, 140.6, 132.4, 128.8, 128.6, 127.6, 127.0, 126.1, 53.7, 23.6

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 262.1. Found: 261.9.

(R)-N-(1-Phenylethyl)methanesulfonamide [316363-65-2]

The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as colorless oil. Yield: 24 mg, 61%.

$[\alpha]_D^{23} = +34.7^\circ$ ($c = 1.0$, CHCl_3).

Ee: 96%. Daicel Chiralcel ID-H, *n*-hexane/isopropanol 96/4, flow rate = 0.5 mL/min.

^1H NMR (300 MHz, CDCl_3): δ 7.40-7.25 (m, 5H), 5.13 (d, $J = 6.8$ Hz, 1H), 4.66-4.62 (m, 1H), 2.61 (s, 3H), 1.54 (d, $J = 6.9$ Hz, 3H)

^{13}C NMR (75 MHz, CDCl_3): δ 142.5, 128.9, 127.9, 126.3, 53.8, 41.7, 24.0

GC-MS (EI): Calcd for $\text{C}_9\text{H}_{13}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 200.1. Found: 200.0.

(R)-2-Methyl-N-(1-phenylethyl)propane-2-sulfonamide [450368-93-1]

The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 6.5 mg, 15%.

$[\alpha]_D^{23} = +14.5^\circ$ ($c = 1.0$, CHCl_3).

Ee: 91%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.37-7.25 (m, 5H), 4.69-4.66 (m, 1H), 4.38 (s, 1H), 1.57 (d, $J = 6.9$ Hz, 3H), 1.32 (s, 9H)

^{13}C NMR (101 MHz, CDCl_3): δ 143.5, 128.8, 127.5, 125.9, 59.8, 54.5, 25.6, 24.2

GC-MS (EI): Calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 242.1. Found: 242.1.

(*R*)-*N*-(1-Cyclohexylethyl)-4-methylbenzenesulfonamide [180720-33-6]

6 mol% (*R,S*)-CyPF-Cy was used. The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 47 mg, 79%.

$[\alpha]_{\text{D}}^{23} = +11.3^\circ$ ($c = 1.0$, CHCl_3).

Ee: 95%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 98/2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.76-7.74 (m, 2H), 7.30-7.26 (m, 2H), 4.31 (d, $J = 8.4$ Hz, 1H), 3.18-3.13 (m, 1H), 2.42 (s, 3H), 1.71-1.52 (m, 5H), 1.25-1.24 (m, 1H), 1.16-1.08 (m, 4H), 0.98 (d, $J = 6.8$ Hz, 3H), 0.97-0.82 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3): δ 143.2, 138.4, 129.6, 127.0, 54.4, 43.5, 28.7, 28.5, 26.3, 26.1, 26.1, 21.5, 18.4

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{23}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 282.1. Found: 282.1.

(*R*)-*N*-(3,3-Dimethylbutan-2-yl)-4-methylbenzenesulfonamide [254745-75-0]

The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 45 mg, 88%.

$[\alpha]_D^{23} = +5.6^\circ$ ($c = 0.6$, CHCl_3).

Ee: 97%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.76 (d, $J = 8.3$ Hz, 2H), 7.30-7.26 (m, 2H), 4.33 (d, $J = 9.5$ Hz, 1H), 3.05 (dd, $J = 9.6, 6.7$ Hz, 1H), 2.42 (s, 3H), 0.89 (d, $J = 6.7$ Hz, 3H), 0.83 (s, 9H)

^{13}C NMR (101 MHz, CDCl_3): δ 143.1, 138.3, 129.6, 127.1, 58.4, 34.5, 26.1, 21.5, 16.6

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{21}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 256.1. Found: 256.0.

(*R*)-4-Methyl-*N*-(3-methylbutan-2-yl)benzenesulfonamide [51859-00-8]

6 mol% (*R,R*)-QuinoxP* were used. The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 48 mg, 83%.

$[\alpha]_{\text{D}}^{23} = +1.8^{\circ}$ ($c = 0.6$, CHCl_3).

Ee: 90%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.78 (d, $J = 8.2$ Hz, 2H), 7.29 (d, $J = 8.2$ Hz, 2H), 4.79 (d, $J = 8.4$ Hz, 1H), 3.18-3.13 (m, 1H), 2.42 (s, 3H), 1.66-1.61 (m, 1H), 0.93 (d, $J = 6.7$ Hz, 3H), 0.81 (d, $J = 6.8$ Hz, 6H)

^{13}C NMR (101 MHz, CDCl_3): δ 143.0, 138.4, 129.5, 127.0, 54.9, 33.4, 21.5, 18.1, 17.9, 17.9

GC-MS (EI): Calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 242.1. Found: 242.0.

(*R*)-4-Methyl-N-(4-methylpentan-2-yl)benzenesulfonamide [24118-70-5]

6 mol% (*R,Sp*)-CyPF-Cy was used. The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 43 mg, 84%.

$[\alpha]_{\text{D}}^{23} = -1.2^{\circ}$ ($c = 1.0$, CHCl_3).

Ee: 93%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 98/2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.77 (d, J = 8.3 Hz, 2H), 7.30-7.27 (m, 2H), 4.40 (d, J = 8.1 Hz, 1H), 3.38-3.31 (m, 1H), 2.42 (s, 3H), 1.62-1.53 (m, 1H), 1.27-1.25 (m, 1H), 1.17-1.14 (m, 1H), 1.01 (d, J = 6.5 Hz, 3H), 0.80 (d, J = 6.6 Hz, 3H), 0.73 (d, J = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 143.1, 138.4, 129.6, 127.1, 48.2, 47.10, 24.6, 22.5, 22.2, 22.1, 21.5

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{21}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 256.1. Found: 256.1.

(S)-N-sec-Butyl-4-methylbenzenesulfonamide

6 mol% (*R,R*)-QuinoxP* was used. The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as white solid. Yield: 38 mg, 84%.

$[\alpha]_{\text{D}}^{23} = -4.2^\circ$ (c = 1.0, CHCl_3).

Ee: 73%. Daicel Chiralcel ID-H, *n*-hexane/isopropanol 96/4, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	51.481	19891144	50.075
2	56.493	19831624	49.925
Total		39722768	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	52.239	10298092	86.786
2	57.338	1568043	13.214
Total		11866135	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.79 (d, J = 8.3 Hz, 2H), 7.31-7.28 (m, 2H), 4.82 (d, J = 7.7 Hz, 1H), 3.27-3.20 (m, 1H), 2.43 (s, 3H), 1.44-1.37 (m, 2H), 1.02 (d, J = 6.6 Hz, 3H), 0.80 (t, J = 7.4 Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 143.1, 138.3, 129.6, 127.0, 51.4, 30.2, 21.5, 21.1, 9.9

GC-MS (EI): Calcd for $\text{C}_{11}\text{H}_{17}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 228.1. Found: 228.1.

(S)-N-(Hexan-2-yl)-4-methylbenzenesulfonamide [racemic 81329-98-8]

6 mol% (*R,S*)-CyPF-Cy was used. The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as colorless oil. Yield: 39 mg, 75%.

$[\alpha]_{\text{D}}^{23} = +3.15^\circ$ (c = 1, CHCl_3).

Ee: 77%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 99/1, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	66.437	2475061	51.086
2	71.781	2369848	48.914
Total		4844909	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	66.106	1142034	11.436
2	70.737	8844218	88.564
Total		9986252	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.79 (d, J = 8.1 Hz, 2H), 7.32-7.28 (m, 2H), 4.61 (d, J = 7.5 Hz, 1H), 3.33-3.26 (m, 1H), 2.44 (s, 3H), 1.39-1.33 (m, 2H), 1.25-1.12 (m, 4H), 1.03 (d, J = 6.5 Hz, 3H), 0.81 (t, J = 6.9 Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 143.1, 138.3, 129.6, 127.0, 50.0, 37.2, 27.6, 22.3, 21.7, 21.5, 13.9

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{21}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$: 256.1. Found: 256.1.

(R)-4-Methyl-N-(1-phenylpropan-2-yl)benzenesulfonamide [72938-94-4]

The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:4) as yellow oil. Yield: 47 mg, 81%.

$[\alpha]_D^{23} = +3.18^\circ$ (c = 0.5, CHCl_3).

Ee: 68%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	31.768	1207256	50.638
2	35.858	1176845	49.362
Total		2384101	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	31.316	22031954	84.198
2	35.525	4134777	15.802
Total		26166731	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.63 (d, J = 8.2 Hz, 2H), 7.25-7.18 (m, 5H), 7.02-7.00 (m, 2H), 4.52 (s, 1H), 3.55-3.48 (m, 1H), 2.73-2.62 (m, 2H), 2.41 (s, 3H), 1.09 (d, J = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 143.1, 137.7, 137.2, 129.6, 129.4, 128.5, 127.0, 126.6, 50.9, 43.5, 21.5, 21.3

GC-MS (EI): Calcd for C₁₆H₁₉NO₂S [M+H]⁺: 290.1. Found: 290.0.

(S)-P,P-Diphenyl-N-(1-phenylethyl)phosphinic amide [82637-15-8]

6 mol% (*S,S',R,R'*)-TangPhos was used. The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:1) as white solid. Yield: 52 mg, 82%.

[α]_D²³ = +21.5° (*c* = 1.0, CHCl₃).

Ee: 75%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	23.265	29000978	49.893
2	33.377	29125550	50.107
Total		58126527	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	23.344	26169389	87.297
2	33.887	3808189	12.703
Total		29977578	100.000

¹H NMR (400 MHz, CDCl₃): δ 7.94-7.89 (m, 2H), 7.85-7.80 (m, 2H), 7.52-7.42 (m, 4H), 7.39-7.22 (m, 7H), 4.43-4.37 (m, 1H), 3.19-3.16 (m, 1H), 1.58 (d, *J* = 6.8 Hz, 3H)

¹³C NMR (101 MHz, CDCl₃): δ 145.1, 145.0, 133.9, 132.8, 132.6, 132.5, 132.4, 131.9, 131.9, 131.8, 131.8, 131.7, 131.7, 131.3, 128.6, 128.5, 128.4, 128.4, 128.3, 127.1, 126.0, 51.0, 26.0, 26.0

³¹P NMR (162 MHz, CDCl₃): δ 22.48

GC-MS (EI): Calcd for C₂₀H₂₀NOP [M+H]⁺: 322.1. Found: 322.1

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Chapter 3 Nickel-Catalyzed Asymmetric Transfer Hydrogenation of Olefins for the Synthesis of Unnatural Amino Acids

3.1 Introduction

Numerous optically active α -amino acid derivatives have proved to be useful synthetic intermediates for preparation of biologically active peptides and peptidomimetic drugs.¹ Various approaches have been developed for the synthesis of chiral α -amino acids, among which catalytic asymmetric hydrogenation of dehydroamino acid derivatives has been demonstrated as one of the most valuable and convenient methods. With the development of asymmetric hydrogenation reactions, α -dehydroamino acid derivatives have been considered as one of the most common substrates, employed for hydrogenation reaction, to test the activity of various chiral phosphorus ligands. Until now, many achievements have been obtained in the heavy transition metal-catalyzed asymmetric hydrogenation of α -dehydroamino acid derivatives with a diversity structurally distinct chiral phosphorus ligands.² However, these heavy metal catalysts based on rhodium, ruthenium and iridium have some disadvantages, such as costs, toxicity, pollution and process sustainability. Therefore, the catalysts of asymmetric hydrogenation based on the first row metals, such as iron, cobalt and nickel, have proven to be highly promising and have been gaining more and more attention.

3.1.1 Noble Metal-Catalyzed Asymmetric Hydrogenation of α -Dehydroamino Acid Derivatives

In the initial stage of the development in asymmetric hydrogenation, several chiral

phosphorus ligands were discovered for Rh-catalyzed asymmetric hydrogenation of dehydroamino acid derivatives. For example, Knowles's *P*-chiral phosphines DIPAMP³ and Noyori's *C*₂-symmetric bisphosphine ligand BINAP⁴ showed high efficiency and enantioselectivity in asymmetric hydrogenation of dehydroamino acid derivatives. The enantioselectivity of the Rh-BINAP catalytic system depends on the reactivity and equilibrium ratio of diastereomeric intermediates, formed by the substrate with precatalyst Rh (Scheme 3.1). Furthermore, owing to the high activity and enantioselectivity of chiral phosphine ligand DIPAMP in Rh-catalyzed asymmetric hydrogenation of dehydroamino acids, this catalytic system has been successfully employed for the industrial production of L-DOPA, which was found to be an effective ingredient for the management of the symptom of Parkinson's patients (Scheme 3.2).⁵ For this milestone work, Knowles shared the 2001 Noble Prize in chemistry with Noyori and Sharpless.⁶

(P-P) = (R)-BINAP

S = alcohol

Scheme 3.1. Rh(I)-BINAP-catalyzed asymmetric hydrogenation of α -(acylamino)acrylic acids

Scheme 3.2. Asymmetric hydrogenation for the synthesis of L-DOPA

Since then, tremendous work has been devoted to develop novel chiral phosphorus

ligands with Rh catalyst for asymmetric hydrogenation of dehydroamino acid derivatives. For example, a series of *P*-chirogenic phosphines, such as BisP*⁷ and MiniPhos⁸ developed by Imamoto's group, exhibited high catalytic activities in Rh-catalyzed asymmetric hydrogenation of dehydroamino acid derivatives (Scheme 3.3).⁹ Furthermore, extensive experiments have been done to reveal the mechanism of this reaction. According to the mechanistic study, the oxidative addition of dihydrogen onto the solvated precursor Rh catalyst led to dihydride Rh complexes in 10:1 ratio. Then subsequently, the sterically more favored dihydride Rh complex coordinated with the substrate and the NMR data characteristics of the catalyst-substrate complex at low temperature showed that the catalytic Rh complex was chelated by (*Z*)- α -acetamidocinnamic acid through the amide group and the alkene. Finally, migratory insertion took place on the α -carbon atom of this intermediate, which would lead to the *R*-configuration of desired product.¹⁰

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derivatives failed by using this catalyst, presumably because the nitrogen atom of pyridine binds to the Rh center and makes it inactive.

Scheme 3.4. Preparation of L-azatyrosine via asymmetric hydrogenation

Furthermore, the efficient Rh-Et-DuPhos catalyst was successfully employed for the preparation of benzoxalone derivative, which is the key intermediate for the CGRP-receptor antagonist (Scheme 3.5).¹² The asymmetric hydrogenation of (*Z*)-methyl-2-(benzyloxycarbonylamino)-3-(3-hydroxy-4-nitrophenyl)acrylate proceeded smoothly with high yield and excellent enantioselectivity in the presence of 1 mol% Rh catalyst.

Scheme 3.5. Process to a CGRP-receptor antagonist

Owing to many advantages of the ferrocene-derived ligands, numerous chiral ferrocene-based bisphosphine ligands have been developed for asymmetric hydrogenation.¹³ The Josiphos ligand, developed by Togni and Spindler, has high catalytic activity in the Rh-catalyzed asymmetric hydrogenation of α -dehydroamino acids (Scheme 3.6).^{13a}

Scheme 3.6. Rh-catalyzed asymmetric hydrogenation of α -dehydroamino acids

Many chiral α -amino acid-based key intermediates for pharmaceutical drugs have been synthesized by asymmetric hydrogenation with Rh catalysts and chiral ferrocenyl diphosphine ligands. For example, the chiral unnatural amino acid,

(*S*)-2-acetamido-3-(3-bromo-4-fluorophenyl)propanoic acid, an important intermediate for the preparation of pharmaceutical molecular CCK1/CCK2 receptor antagonist, was obtained in 85% yield and 94% *ee* via the asymmetric hydrogenation of (*Z*)-2-acetamido-3-(3-bromo-4-fluorophenyl)acrylic acid in the presence of 0.15% Rh catalyst (Scheme 3.7).¹⁴ Moreover, this highly efficient Rh catalyst was also employed for asymmetric hydrogenation of (*Z*)-methyl 2-acetamido-3-(naphthalen-2-yl)acrylate, which was the first step for the preparation of analgesic agent SDZ NKT 343.¹⁵ The desired product was obtained in 96% yield and 98% *ee* on the kilogram scale at Rh catalyst loading as low as 0.05 mol% (Scheme 3.8).

Scheme 3.7. Preparation for a dual CCK1/CCK2 receptor antagonist

Scheme 3.8. The synthesis of analgesic agent SDZ NKT 343

Chiral precursor piperazine-2-carboxamide is a valuable intermediate for the preparation of the HIV protease inhibitor indinavir (Crixivan). A highly enantioselective pathway was developed to prepare chiral piperazine-2-carboxamide by Ito's group via the asymmetric hydrogenation of 4-*tert*-butyl-1-phenyl-5-(*tert*-butylcarbamoyl)-2,3-dihydropyrazine-1,4-dicarboxylate (Scheme 3.9).¹⁶ Compared to other methods¹⁷ for preparation of related intermediates, this pathway was found more practical and efficient. The desired product was obtained quantitatively with 97% *ee* under mild reaction conditions.

Scheme 3.9. Synthetic route to the HIV protease inhibitor indinavir

Another rare uncommon type of bisphosphine ligands, derived from monophosphorus ligands, has been developed for Rh-catalyzed asymmetric hydrogenation of α -dehydroamino acid derivatives. They have the binol skeleton, which plays an important role in the process of achieving high *ee* values. For example, chiral P-OP ligands, developed by Vidal-Ferran's group, showed high catalytic activity in Rh-catalyzed asymmetric hydrogenation for the synthesis of chiral pharmaceutical drugs.¹⁸ A typical example is that Lacosamide, which was used for management of epilepsy, has been synthesized by Rh-catalyzed asymmetric hydrogenation of (Z)-2-acetamido-*N*-benzyl-3-methoxyacrylamide in the presence of chiral Cy-P-OP ligand (Scheme 3.10). The desired product was obtained in 99% yield and 99% *ee* values. Furthermore, the chiral Ph-P-OP ligand, showed high catalytic activity in the synthesis of the (*R*)-methyl 2-acetamido-3-(2,5-difluorophenyl)propanoate, which was an important intermediate to synthesize LY2497282 and prepared by Rh-catalyzed asymmetric hydrogenation of (Z)-methyl 2-acetamido-3-(2,5-difluorophenyl)acrylate (Scheme 3.11).

Scheme 3.10. Preparation of the Lacosamide

Scheme 3.11. Preparation of the DPP IV inhibitor LY2497282

3.1.2 Noble Metal-Catalyzed Asymmetric Hydrogenation of β -Dehydroamino Acid

Derivatives

Optically active β -amino acids and their derivatives have proved to be useful synthetic intermediates for preparation of biologically β -peptides and β -lactam antibiotics.¹⁹ Owing to the importance of chiral β -amino acids in medicinal chemistry, several synthetic approaches have been developed for preparing them and their

derivatives.²⁰ Among these methods, direct asymmetric hydrogenation of β -dehydroamino acid derivatives proved to be one of the most efficient and atom economic routes. Although this simple and efficient approach has been successfully used for the synthesis of enantiomerically pure α -amino acids, it turns out to be more problematic for the asymmetric hydrogenation of β -dehydroamino acid derivatives, mainly because the configurational isomers of the substrates (*Z* or *E* isomers).²¹ Good to excellent enantioselectivity were obtained in the asymmetric hydrogenation of (*E*)- β -(acylamino)acrylates with a series of known catalytic systems,^{21a, 21c, 22} while the results of (*Z*)- β -(acylamino)acrylates were less than satisfying.²³ For example, an Ru-BINAP catalytic system gave 96% *ee* in asymmetric hydrogenation of (*E*)-methyl 3-acetamido-2-butenate, while only 5% *ee* was obtained using (*Z*)-isomer.^{21a}

In 1999, Zhang's group reported an important breakthrough on the asymmetric hydrogenation of alkyl 3-acetamido-2-butenates with Rh(I)-BICP complex (Scheme 3.12).^{22a} 96% *ee* and 88% *ee* were obtained respectively for asymmetric hydrogenation of (*E*)-ethyl 3-acetamidobut-2-enoate and (*Z*)-ethyl 3-acetamidobut-2-enoate in the presence of this novel Rh(I)-BICP catalytic system. A limitation of this reaction is that only moderate *ee* values were obtained in the asymmetric hydrogenation of aryl β -(acylamino)acrylates.

Scheme 3.12. Rhodium-catalyzed asymmetric hydrogenation of β -(acylamino)acrylates

Since then, several new catalytic systems have been developed to work well for both isomeric substrates.²³⁻²⁴ In 2002, Zhang's group developed a highly efficient Rh-TangPhos catalytic system for making enantiomerically pure β -amino acids (Scheme 3.13).^{24b} High enantioselectivities (up to 99.6%) were obtained in the hydrogenation of *Z/E* isomeric mixtures of both β -alkyl and β -aryl β -(acylamino)acrylates.

Scheme 3.13. Highly efficient synthesis of chiral β -amino acids with Rh-TangPhos complex

In 2002, Feringa's group reported rhodium catalyzed asymmetric hydrogenation of β -dehydroamino acid derivatives with monodentate phosphoramidites (Scheme 3.14).^{24a} Excellent *ee* values and full conversion have been obtained in the asymmetric hydrogenation of (*E*)- and (*Z*)- β -dehydroamino acid derivatives with both aliphatic and aromatic substituent. These readily accessible monodentate phosphoramidite ligands were firstly reported in asymmetric hydrogenation of β -dehydroamino acid derivatives and offered better results than those reported with bidentate ligands.

Scheme 3.14. Highly enantioselective Rh-catalyzed hydrogenation of β -dehydroamino acid derivatives using monodentate phosphoramidites

In 2004, Malan's group developed an efficient method for the synthesis of chiral β -amino acids via asymmetric hydrogenation of unprotected enamines (Scheme 3.15).²⁵ High enantioselectivity and yield were obtained in the hydrogenation of enamine ester with Josiphos-type ligand.

Scheme 3.15. Asymmetric hydrogenation of unprotect enamines for the synthesis of chiral β -amino acids

In addition, many chiral β -amino acid-based key intermediates for pharmaceutical drugs have been synthesized via asymmetric hydrogenation with Rh catalysts.²⁶ For example, Gridnev's group discovered that Rh-complex derived from P-stereogenic

ligands (R,R) -QuinoxP* and (R,R) -DioxyBenzP* showed high catalytic reactivity and enantioselectivity for asymmetric hydrogenation of (Z) -ethyl 3-acetamido-3-(3,4-dimethoxyphenyl)acrylate (Scheme 3.16).^{26a} Full conversion and high *ee* values were obtained with 0.1 mol% catalyst loading. The hydrogenated product chiral (S) -ethyl 3-acetamido-3-(3,4-dimethoxyphenyl)propanoate is an important build block for preparing the VLA-4 antagonist S9059, which has worked potential as an anti-inflammatory agent.²⁷

Scheme 3.16. Preparation for the VLA-4 antagonist S9059

One of the most notable industrial applications of this chemistry is rhodium-catalyzed asymmetric hydrogenation of unprotected β -(amino)acylamide for the preparation of sitagliptin (Scheme 3.17).²⁸ Sitagliptin, an active pharmaceutical ingredient of chiral drugs Januvia[®] and Janumet[®], can be used for the treatment of type 2 diabetes mellitus.²⁹ Merck research laboratory discovered an efficient Ru complex derived from the chiral ligand (S,R) -*t*Bu-JOSIPHOS, which has showed high catalytic activity and

enantioselectivity in asymmetric hydrogenation of unprotected β -(amino)acylamide with as low as 0.15 mol% catalyst loading.²⁸ The addition of NH_4Cl is necessary, because it not only promoted the reproducibility of the process but also maintained the pH values required for tautomerisation. This optimized reaction provided the sitagliptin in 98% yield and with 95% *ee*. The enantiomeric purity of its final pharmaceutical form was up to 99.9% *ee* after crystallization.

Scheme 3.17. Route to the DPP IV inhibitor sitagliptin

3.1.3 The First-row Metal-Catalyzed Asymmetric Hydrogenation of α -Dehydroamino Acid Derivatives

The literature study has revealed that numerous applications of catalytic asymmetric hydrogenation to synthesize unnatural chiral amino acid derivatives have relied on Rh catalysts. Only one case of asymmetric hydrogenation of dehydroamino acid derivatives has been reported with a cobalt catalyst until now (Scheme 3.18).³⁰ In the presence of chiral ligand $(R,R)\text{-}i\text{-Pr-DuPhos}$, excellent results were achieved. Therefore, it is desirable to develop asymmetric hydrogenation reactions for the synthesis of unnatural chiral amino acid derivatives by using cheap and abundant first-row metal catalysts.

Scheme 3.18. Asymmetric hydrogenation of dehydroamino acid derivatives with Co(II) complex

In 2016, Chirik's group developed nickel-catalyzed asymmetric hydrogenation of α,β -unsaturated esters with chiral ligand (*S,S*)-Me-DuPhos (Scheme 3.19).³¹ This is the first example of using H₂ gas as hydrogen source in nickel-catalyzed asymmetric hydrogenation of olefins. Significant effort was devoted to study the mechanism. From the mechanistic study, the formation of a Ni-H intermediate was found to be the rate determining step. The results of deuterium labeling experiments have indicated that it was unlikely to form a nickel hydride via oxidative addition of dihydrogen to nickel catalyst. However, the scope of the substrates was limited and high pressure of hydrogen gas was required.

Scheme 3.19. A proposed mechanism of nickel-catalyzed asymmetric hydrogenation of α,β -unsaturated esters using hydrogen gas

3.2 Results and Discussion

Encouraged by the good results achieved in asymmetric hydrogenation with the first-row metals, such as Fe^{32} and Co^{30} , our group has focused on this research area with the first row metal nickel. Nickel, as one of the elements in the periodic table, was isolated in 1751. Due to the properties of easy accessibility with various oxidation states and facile oxidative addition, nickel, as one of the abundant and cheap first-row metals,

has gained more attention as metal catalyst for a wide range of reactions.³³ The first example of nickel-catalyzed ethylene hydrogenation was found by Sabatier, for which he shared the 1912 Nobel Prize in chemistry with Victor and Grignard.³³ Although nickel has a long history as a metal catalyst for hydrogenation, the successful cases of nickel-catalyzed asymmetric hydrogenation for the synthesis of chiral amines are limited.³⁴

3.2.1 Reaction Optimization for Preparing β -Amino Acid Derivatives

Firstly, we employed $\text{Ni}(\text{OAc})_2$ as a catalyst and (Z)-ethyl 3-acetamidobut-2-enoate as a model substrate to screen the reaction conditions. To our delight, we found high catalytic activities when the nickel catalyst is ligated by electron-rich chiral bisphosphine ligands, especially with (S)-Binapine.³⁵ Up to 99% yield and 96% *ee* values were obtained with Ni/(S)-Binapine catalyst (Table 3.1, entry 1). The results with other chiral ligands are listed in Table 3.1. *P*-Chiral bisphosphines ligands, such as (R,R)-BenzP* and (R,R)-QuinoxP*, which were synthesized by Imamoto's group, provided full conversion, albeit with lower *ee* values (63% and 72% *ee*) (Table 3.1, entries 2 and 3). For 2,5-Disubstituted bisphospholane ligands Ph-BPE and *i*-Pr-BPE, only Ph-BPE showed catalytic activity (Table 3.1, entries 4 and 5). For DuPhos family ligands, only 53% yield and 28% *ee* values were provided by Me-Duphos (Table 3.1, entry 6). Et-Duphos and *i*-Pr-DuPhos did not show catalytic activity with the nickel catalyst (Table 3.1, entries 7 and 8). (S,S',R,R')-TangPhos and (1S,1'S,2R,2'R)-DuanPhos, which were also synthesized by Xumu Zhang's group, showed much less selectivity (Table 3.1, entries 9 and 10).

(*R,S*)-CyPF-Cy, a Josiphos ligand provided 95% yield and 53% *ee* values (Table 3.1, entry 11). Other less electric-rich ligands (Table 3.1, entries 13-16) did not form active catalysts.

Table 3.1. Effect of chiral ligands

$ \begin{array}{c} \text{NHAc} \\ \\ \text{Me}-\text{CH}=\text{CH}-\text{CO}_2\text{Et} \xrightarrow[\text{1,4-dioxane, 60 }^\circ\text{C, 36 h}]{\text{Ni(OAc)}_2 \text{ (5 mol\%)} \\ \text{chiral ligand (6 mol\%)} \\ \text{HCO}_2\text{H/Et}_3\text{N (5:2)}} \text{NHAc} \\ \\ \text{Me}-\text{CH}-\text{CH}_2-\text{CO}_2\text{Et} \end{array} $				
Entry	Ligands	Conv. (%)	Yield (%)	Ee (%)
1	(<i>S</i>)-Binapine	100	99	96
2	(<i>R,R</i>)-BenzP*	99	99	63
3	(<i>R,R</i>)-QuinoxP*	100	100	72
4	(<i>S,S</i>)-Ph-BPE	100	100	67
5	(<i>S,S</i>)-Ph-BPE	0	0	-

6		55	53	-28
	(<i>R,R</i>)-Me-DuPhos			
7		0	0	-
	(<i>R,R</i>)-Et-DuPhos			
8		0	0	-
	(<i>R,R</i>)- <i>i</i> -Pr-DuPhos			
9		71	71	35
	(<i>S,S'</i> , <i>R,R'</i>)-TangPhos			
10		27	19	36
	(1 <i>S</i> ,1' <i>S</i> ,2 <i>R</i> ,2' <i>R</i>)-DuanPhos			
11		95	95	53
	(<i>R,Sp</i>)-CyPF-Cy			
12		0	0	0
	(<i>R,Sp</i>)-CyPF- <i>t</i> -Bu			
13		0	0	-
	(1 <i>S</i> ,1' <i>S</i> ,2 <i>S</i> ,2' <i>S</i>)-BIBOP			

14		0	0	-
15		0	0	-
16		0	0	-

With the optimized chiral ligands (*S*)-Binapine in hand, we examined various available nickel and cobalt salts. The results are listed in Table 3.2. Different nickel sources provided similar *ee* values, but with varying conversions and yields. In comparison, Ni(OAc)₂ showed higher catalytic activity than other nickel precatalysts (Table 3.2, entry 2). The cobalt catalysts were completely inactive (Table 3.2, entry 8).

Table 3.2. Effect of the first row metal catalysts

Entry	Nickle(II) salts	Conv. (%)	Yield (%)	Ee (%)
1	Ni(OTf) ₂	82	81	91
2	Ni(OAc) ₂	99	99	96
3	NiBr ₂ (DME)	59	59	90
4	NiCl ₂ (DME)	90	90	92
5	Ni(PPh ₃) ₂ Cl ₂	81	81	93

6	Ni(ClO ₄) ₂ · 6H ₂ O	81	81	83
7	Ni(acac) ₂	44	39	94
8	CoCl ₂ , CoBr ₂ or CoI ₂	0	0	-

As shown in Table 3.3, the model reaction worked out efficiently in many solvents with good conversions and excellent *ee* values. However, the reactivity was quenched when CH₃CN was employed as a solvent, presumably owing to solvent-coordination that made the nickel catalyst inactive.

Table 3.3. Effect of solvents

$ \begin{array}{c} \text{NHAc} \\ \\ \text{Me} - \text{C} = \text{CH} - \text{CO}_2\text{Et} \end{array} \xrightarrow[\text{solvent, 60 } ^\circ\text{C, 36 h}]{\begin{array}{c} \text{Ni(OAc)}_2 \text{ (5 mol\%)} \\ \text{(S)-Binapine (6 mol\%)} \\ \text{HCO}_2\text{H/Et}_3\text{N (5:2)} \end{array}} \begin{array}{c} \text{NHAc} \\ \\ \text{Me} - \text{CH} - \text{CH}_2 - \text{CO}_2\text{Et} \end{array} $				
Entry	Solvent	Conv. (%)	Yield (%)	Ee (%)
1	Dioxane	99	99	96
2	THF	96	95	96
3	MeOH	97	97	92
4	EtOH	100	99	93
5	<i>i</i> -PrOH	100	99	93
6	Ethyl Acetate	97	96	95
7	Toluene	99	99	95
8	DMF	92	92	96
9	DME	92	92	95
10	CH ₃ CN	0	0	-

Both catalytic reactivity and *ee* values were increased by the addition of formic acid (Table 3.4, entries 2-4). More than 99% conversion and 96% *ee* values was obtained with a 5:2 molar ratio mixture of formic acid and triethylamine. Other formate salts, such as NaCO₂H and NH₄CO₂H, were not effective in this reaction (Table 3.4, entry 5).

Table 3.4. Effect of the ratio of formic acid and triethylamine

$ \begin{array}{ccc} \text{NHAc} & & \text{NHAc} \\ & & \\ \text{Me}-\text{C}=\text{CH}-\text{CO}_2\text{Et} & \xrightarrow[\text{1,4-dioxane, 60 }^\circ\text{C, 36 h}]{\text{Ni(OAc)}_2 \text{ (5 mol\%)} \\ \text{(S)-Binapine (6 mol\%)} \\ \text{HCO}_2\text{H/Et}_3\text{N}} & \text{Me}-\text{CH}-\text{CH}_2-\text{CO}_2\text{Et} \\ & & \\ & & \text{NHAc} \end{array} $				
Entry	HCO ₂ H/Et ₃ N	Conv. (%)	Yield (%)	Ee (%)
1	2:2	57	57	83
2	2:5	55	55	79
3	3:5	78	78	90
4	5:2	99	99	96
5	NaCO ₂ H or NH ₄ CO ₂ H	0	0	0

With the optimized reaction conditions in hand, the scope of α and β -amino acid derivatives was examined. The excellent results of β -amino acid derivatives using nickel/Binapine catalytic system are displayed in Scheme 3.20. Both electron-donating and electron-withdrawing substituted olefins provided the desired products with high yields and excellent enantioselectivity. Only 30% *ee* was obtained for the substrate bearing beta-anilino group as a directing group. Dr Peng Yang conducted most of the experiments of the synthesis chiral β -amino acids after I optimized the reaction conditions,

thus the related experimental procedure and compound characterization data are not presented in this thesis. Then, more attention was paid to optimize the reaction conditions for α -amino acids.

Scheme 3.20. The scope of β -amino acid derivatives

Compared to beta-dehydroamino acids, alpha-dehydroamino acids proved to be more challenging substrates for asymmetric hydrogenation, owing to the difficulty in stereoselective protonation step. Several results of asymmetric transfer hydrogenation of α -dehydroamino acid derivatives under optimized reaction conditions are shown in Scheme 3.21.

Scheme 3.21. Asymmetric transfer hydrogenation of unsaturated α -amino acids

In order to further investigate the reaction mechanism, Dr Peng Yang employed [D₁]- and [D₂]- formic acid to conduct deuterium-labeling experiments (Scheme 3.22). Almost no deuterium was incorporated at the β -position, while a 3:1 anti/syn deuterium ratio have been found both at α -positions, when [D₁] formic acid was employed (Scheme 3.22 a). Both α -position and β -position were deuterated when [D₂] formic acid was employed (Scheme 3.22 b). These results revealed that this process involved two steps: a nickel hydride, produced by a decarboxylation of the formate, incorporated to the β -position to form a nickel enolate intermediate firstly; then subsequently via the procedure of protonation to the desired product.

Scheme 3.22. Deuterium-labeling experiments with $[\text{D}_1]$ and $[\text{D}_2]$ formic acid

The reaction conditions for nickel-catalyzed asymmetric transfer hydrogenation of α -dehydroamino acid derivatives were modified afterwards. In the step of protonation, there are also some other factors, such as ammonium cation, the polarity of solvent and pH values of reaction system, have an important effect on the enantioselectivity of final α -amino acid derivatives, except for the nickel complex.

3.2.2 Reaction Optimization for Preparing α -Amino Acid Derivatives

Building on the results obtained in asymmetric hydrogenation of β -amino acid derivatives, we chose (Z)-methyl 2-acetamido-3-phenylacrylate as the model substrate for asymmetric transfer hydrogenation to optimize the reaction conditions. Firstly, we studied different types of chiral ligands, which have proved to be very efficient in Rh-catalyzed asymmetric hydrogenation of α -dehydroamino acid derivatives. The results are listed in Table 3.5. We used $\text{Ni}(\text{OTf})_2$ as the precursor salt, $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$ as the hydrogen source and PhCF_3 as the solvent.

Table 3.5. Effect of chiral ligands

Entry	Ligands	Conv. (%)	Yield (%)	Ee (%)
1	(S)-Binapine	100	92	81
2	(S,S)-Ph-BPE	45	44	0
3	(S,S)-Ph-BPE	34	33	45

4		100	96	0
<i>(R,R)</i> -Me-DuPhos				
5		100	97	0
<i>(R,R)</i> -Et-DuPhos				
6		100	100	25
<i>(R,R)</i> -QuinoxP*				
7		100	96	19
<i>(S,S',R,R')</i> -TangPhos				
8		99	98	9
<i>(1S,1'S,2R,2'R)</i> -DuanPhos				
9		0	0	-
<i>(1S,1'S,2S,2'S)</i> -BIBOP				
10		0	0	-
<i>(R)</i> -BINAP				
11		0	0	-
12		0	0	-

13

0

0

-

From results gathered in Table 3.5, we found that nickel catalyst showed catalytic activity in asymmetric transfer hydrogenation of α -dehydroamino acid derivatives in the presence of (*S*)-Binapine, which is a highly electron-donating and sterically demanding chiral ligand.² No *ee* values was detected using 2,5-disubstituted bisphospholane ligand Ph-BPE as chiral ligand (Table 3.5, entry 2). DuPhos family ligands, such as Et-DuPhos and Me-DuPhos, showed high activity in Rh-catalyzed asymmetric hydrogenation of α -dehydroamino acid derivatives, while they did not have activities in nickel catalysis (Table 3.5, entries 4 and 5). Only 25% *ee* was provided by Imamoto's *P*-chiral ligand (*R,R*)-QuinoxP* (Table 3.5, entry 6). Other related *P*-stereogenic ligand, such as TangPhos and DuanPhos, provided good yields, but with lower *ee* values (19% *ee* and 9% *ee*) (Table 3.5, entries 7 and 8). Others ligands, such as (1*S*,1'*S*,2*S*,2'*S*)-BIBOP, BINAP and so on, did not show catalytic activities in Ni-catalyzed asymmetric hydrogenation of α -dehydroamino acid derivatives (Table 3.5, entries 9-13).

PhCF₃ was found optimal in terms of the yield and enantioselectivity of the product in the model reaction (Table 3.6, entry 5). The reaction proceeded smoothly in alcohol solvents and provided similar results (Table 3.6, entries 1-3). Low conversion was observed when DCE was used as a solvent, probably due to activation of the C(*sp*³)-Cl bond by the nickel metal³⁶ (Table 3.6, entry 11).

Table 3.6. Effect of solvents

Entry	Solvent	Conv. (%)	Yield (%)	Ee (%)
1	EtOH	78	78	71
2	<i>i</i> -PrOH	79	79	72
3	<i>t</i> -AmOH	81	81	78
4	Toluene	99	99	77
5	PhCF ₃	100	100	77
6	<i>o</i> -Xylene	100	100	75
7	Dioxane	58	58	80
8	THF	98	96	79
9	DME	90	90	78
10	Ethyl Acetate	99	99	78
11	DCE	35	35	48

As shown in Table 3.7, the *ee* values dropped slightly with the increasing amount of formic acid. In the model reaction, a 2:5 molar ratio of HCO₂H and Et₃N was optimal in terms of both catalytic activity and enantioselectivity.

Table 3.7. Effect of ratio between HCO₂H and Et₃N

Entry	HCO ₂ H/Et ₃ N	Conv. (%)	Yield (%)	Ee (%)
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1	2:5	100	99	77
2	4:5	100	100	66
3	5:5	100	100	65
4	5:2	100	100	43
5	5:4	100	100	62

We next moved to survey different amines and their effect on the reaction outcome as shown in Table 3.8. The enantioselectivity increased slightly when the alkyl substituent of amines became more sterically hindered (Table 3.8, entries 1-3). Low yield and *ee* values were observed with secondary amines (Table 3.8, entries 7 and 8), which may compete to coordinate with the active nickel catalyst and make it inactive. The *ee* values dropped dramatically when one of the alkyl groups was replaced by aryl group (Table 3.8, entries 9-11). Proton sponge provided good yields, albeit with low enantioselectivities (Table 3.8, entry 12).

Table 3.8. Effect of amines

Entry	Amine	Conv. (%)	Yield (%)	Ee (%)
1	Et ₃ N	100	98	74
2	<i>i</i> -Pr ₂ NEt	100	99	82
3	Cy ₂ NMe	100	94	82

4	<chem>BnNMe2</chem>	100	98	51
5	<chem>HOCH2CH2NMe2</chem>	86	85	67
6		100	97	51
7		63	57	15
8		10%	-	-
9		100	94	9
10		100	94	9
11		100	97	14
12		100	94	57

With the optimal conditions in hand, we explored the scope of α -dehydroamino acid derivatives (Scheme 3.23). A series of substituted (*Z*)-methyl 2-acetamidocinnamate derivatives were hydrogenated successfully in the presence of nickel/Binapine catalyst. Methyl 2-acetamido-3-(naphthalen-1-yl)acrylate provided the desired product with 78% *ee* values. To our delight, up to 93% *ee* values were observed using an isopropyl ester derivative. However, only 43% *ee* was achieved using benzoyl group as a directing group. Therefore, several (*Z*)-isopropyl 2-acetamido-3-phenylacrylate derivatives were tested by

using this nickel catalyst. As we speculated, substrates with both electron-rich and electron-withdrawing aryl groups afforded excellent enantioselectivity, except for (*Z*)-isopropyl 2-acetamido-3-*o*-tolylacrylate, which provided lower *ee* values, presumably owing to the steric effect.

Scheme 3.23. Asymmetric hydrogenation for the synthesis of unnatural chiral α -acylamidoesters

We have also employed $[\text{D}_1]$ -formic acid to do deuterium-labeling experiments for the asymmetric transfer hydrogenation of (*Z*)-isopropyl 2-acetamido-3-*o*-tolylacrylate (Scheme 3.24). The result, obtained after the reaction was suspended at 90 °C for 24 h, showed that deuterium incorporation was observed only for the α -position to a moderate extent. In this case, a sterically hindered triethylammonium cation, formed in situ from a mixture of HCO_2H and Et_3N , was very important for the stereoselective protonation of the nickel enolate, which was significant for determining the *ee* values in this catalytic hydrogenation.

Scheme 3.24. Deuterium-labeling experiment of α -acetamidoacrylate

3.2.3 Reaction Optimization for Preparing β -Tetrasubstituted Dehydroamino Acid Derivatives

Further expansion of this protocol to *tetra*-substituted olefins was also explored. It would be one of the best methods for the synthesis of cyclic β -amino acid derivatives. Zhang's group have firstly reported the synthesis of chiral cyclic β -amino acids via asymmetric hydrogenation with a Ru-(S)-C₃-Tunaphos catalyst and great success has been achieved.³⁷ However, it is not clear whether this novel catalyst system is suitable for the synthesis of chiral 1-acetamido-1,2,3,4-tetrahydronaphthalene-2-carboxylate derivatives, which are important building block for pharmaceutical drugs.³⁸ We employed methyl 1-acetamido-3,4-dihydronaphthalene-2-carboxylate as substrate to screen the reaction conditions. We firstly screened a series of electron-rich diphosphine ligands (Table 3.9). Except for (R)-BINAP, other bisphospholane ligands provided the corresponding product with good conversion and excellent enantioselectivity, but with varying *dr* values. Among them, (R,R)-QuinoxP* was optimal in terms of *dr* values for this model reaction (Table

3.9, entry 6). The *cis* configuration was determined by comparing with NMR data characteristics in the literature [(*cis*) CAS: 126662-38-4].³⁹

Table 3.9. Effect of chiral ligands

Entry	Ligands	Conv. (%)	Yield (%)	d.r.	Ee (%) cis/trans
1	(<i>S</i>)-Binapine	82	81	90/10	99/99
2	(<i>S,S</i>)-Ph-BPE	100	96	77/22	99/99
3	(<i>S,S</i>)-Ph-BPE	100	98	67/33	99/99
4	(<i>R,R</i>)-Me-DuPhos	77	74	87/13	99/97
5	(<i>R,R</i>)-Et-DuPhos	100	96	80/20	99/99

6		100	97	87/13	99/99
	(<i>R,R</i>)-QuinoxP*				
7		96	96	84/16	97/99
	(<i>S,S',R,R'</i>)-TangPhos				
8		62	59	64/36	99/93
	DuanPhos				
9		76	74	80/20	91/34
10		0	0	0	
	(<i>R</i>)-BINAP				

In addition, we also screened other conditions, such as solvents and amines for this model reaction. All the results are listed in the Table 3.10 and 3.11.

Table 3.10. Effect of solvents

Entry	Solvent	Conv. (%)	Yield (%)	d.r.	Ee (%) cis/trans
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1	MeOH	100	98	87/13	99/99
2	<i>i</i> -PrOH	100	97	85/15	92/80
3	<i>t</i> -BuOH	88	87	80/20	87/80
4	CF ₃ CH ₂ OH	98	96	82/18	85/73
5	Toluene	72	69	67/33	53/13
6	PhCF ₃	69	67	66/34	82/75
7	Dioxane	68	65	67/33	61/39

The model reaction proceeded well and offered good conversion and excellent *ee* in alcohol solvents (Table 3.10, entries 1-4). For example, 99% *ee* and 87/13 *dr* values were obtained in MeOH, at full conversion. However, the results were not good in aprotic solvents, such as toluene, PhCF₃ and dioxane (Table 3.10, entries 5-7).

Table 3.11. Effect of amines

Entry	Amine	Conv. (%)	Yield (%)	d.r.	Ee (%) cis/trans
1	Et ₃ N	100	98	81/19	99/99
2	<i>i</i> -Pr ₂ NEt	100	97	82/18	99/99
3		100	98	87/13	99/99

4		100	98	86/14	99/99
5		94	91	81/19	99/99
6		100	96	68/32	99/99
7		100	97	80/20	99/99

Under the established optimal reaction conditions, *N,N*-dimethylaniline proved to be optimal in terms of diastereoselectivity in the model reaction (Table 3.11, entry 3). For other amines, good conversion and excellent *ee* values were obtained, albeit with a little drop of *dr* values (Table 3.11).

With this modified protocol, we examined a series of methyl 1-acetamido-3,4-dihydronaphthalene-2-carboxylate derivatives. Up to 99% enantioselectivities were achieved, albeit with a moderate diastereoselectivity. All the results are summarized in Scheme 3.25. The substrates with different position substituted aryl groups provided full conversion, excellent enantioselectivity and good diastereoselectivity. Due to the steric effect, poor catalytic activity was observed using *t*-Bu as substituent group. Methyl 3-acetamido-1*H*-indene-2-carboxylate could also be hydrogenated with excellent enantioselectivity.

Scheme 3.25. Scope of cyclic β -amino acid derivatives

In addition, we also examined the effect of amines for the synthesis of acyclic β -amino acid derivatives as shown in Table 3.12. The use of Et_3N as the base led to better *ee* and *dr* values than that obtained in N,N -dimethylaniline in the synthesis of acyclic β -amino acid derivatives (Table 3.12, entries 1 and 7).

Table 3.12. Effect of amines

Entry	Amine	Conv. (%)	Yield (%)	d.r.	Ee (%) cis/trans

1	Et ₃ N	100	97	72/28	90/94
2	<i>i</i> -Pr ₂ NEt	100	98	67/33	90/93
3	Cy ₂ NMe	100	97	76/24	73/82
4	BnNMe ₂	100	96	58/42	85/82
5		100	96	63/37	87/87
6		100	97	48/52	79/75
7		100	99	45/55	85/94
8		100	99	40/60	93/91
9		100	99	44/56	85/94
10		100	97	60/40	93/91
11		100	96	75/25	85/87
12		100	96	49/51	89/91

Under the optimized reaction conditions, chiral acyclic *tetra*-substituted β -amino acid derivatives, such as 3-acetamido-2-methyl-3-phenylpropanoate and ethyl 3-acetamido-2-methyl-3-phenylpropanoate were obtained in good yields with high enantioselectivity. Owing to the steric effect, the yield of *t*-Bu substituted acyclic

tetra-substituted β -dehydroaminoesters was quite low (< 5%). Moreover, when (*Z*)-ethyl 3-acetamido-2,3-diphenylacrylate was employed, no product was detected (Scheme 3.26).

Scheme 3.26. Scope of acyclic *tetra*-substituted β -amino acid derivatives

3.2.4 Conclusions

We have developed a novel nickel-catalyzed asymmetric transfer hydrogenation of olefins for the synthesis of unnatural amino acid derivatives. Good to excellent enantioselectivity has been achieved in asymmetric transfer hydrogenation of dehydroamino acid derivatives in the presence of chiral bisphosphine (*S*)-Binapine. The nickel catalysis also allowed efficient and highly enantioselective hydrogenation of cyclic *tetra*-substituted β -amino acid derivatives, while there remains room for further improvement in *dr* values.

3.3 Experimental Section

3.3.1 General

All NMR spectra were acquired on Bruker AV 500 MHz or 300 MHz NMR

spectrometers. ^1H NMR (500 MHz) chemical shifts were recorded relative to SiMe_4 (δ 0.00) or residual protiated solvents (CDCl_3 : δ 7.26). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by nH. Coupling constants were reported as a J value in Hz. ^{13}C NMR (125 MHz) chemical shifts were recorded relative to solvent resonance (CDCl_3 : δ 77.16).

Glassware was dried at 120 °C for at least 3 h before use. Dry toluene, hexane, diethyl ether and dichloromethane were collected from a solvent purification system containing a column of activated alumina (1 m x 2) under argon. Dry THF was freshly distilled from sodium/benzophenone under argon. The MeOH, EtOH, and isopropanol were distilled from CaH_2 under argon and stored over activated 4Å molecular sieve beads in an argon-filled glove box. Unless noted otherwise, readily available chemicals were used directly with no further purification. The GC internal standard, $n\text{-C}_{14}\text{H}_{30}$ was degassed with argon and dried over activated 3Å molecular sieve beads before use.

Flash chromatography was performed using Merck 40-63D 60Å silica gel. Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument with Agilent J & W GC column DB-5MS-UI. GC/MS analysis was conducted on a Thermo Scientific DSQ II single quadrupole GC/MS instrument with Agilent J & W GC column DB-5MS-UI. Chiral HPLC analysis was performed on a Shimadzu LC-20AD instrument using Daicel Chiracel columns at 25 °C and a mixture of HPLC-grade hexanes and isopropanol as eluent. Optical rotation was measured using a JASCO P-1030 Polarimeter equipped with a sodium vapor lamp at 589 nm and the concentration of samples was

denoted as *c*.

3.3.2 Condition Optimization for Asymmetric Transfer Hydrogenation of α -(Acylamido)acrylates

A general procedure for condition optimization: In an argon-filled glove box, Ni(OTf)₂ (1.8 mg, 0.005 mmol), (*S*)-Binapine (4.4 mg, 0.006 mmol) and dry PhCF₃ (0.3 mL) were charged into a 10-mL reaction tube. After stirring for 10 min, (*Z*)-methyl 2-acetamido-3-phenylacrylate (0.1 mmol, 0.0219 g), formic acid (7.6 μ L, 0.2 mmol), Et₃N (70 μ L, 0.5 mmol) and GC standard *n*-C₁₄H₃₀ (10 μ L) were added. The reaction mixture was stirred in an oil bath maintained at 90 °C. In the course of the reaction, aliquots were taken from the reaction mixture in the glove box and passed through a short plug of silica gel with EtOAc washing (about 3 mL). The filtrate was subjected to GC analysis to determine the conversion of the olefin and yield of the product. To determine the enantioselectivity of the product, the filtrate was dissolved in 1:10 *i*-PrOH/hexanes and subjected to chiral HPLC analysis (Daicel CHIRCEL OJ-H; 5% *i*-PrOH in hexanes; flow rate 0.5 mL/min).

3.3.3 Isolated Products of Asymmetric Hydrogenation of α -Dehydroamino Acids

General procedure for asymmetric transfer hydrogenation: In an argon-filled glove box, Ni(OTf)₂ (9.0 mg, 0.025 mmol), (*S*)-Binapine (22 mg, 0.03 mmol) and dry PhCF₃ (1.5 mL) were charged into a 10-mL Schlenk tube. After stirring for 30 min, (*Z*)- α -(acylamido)acrylate (0.5 mmol), formic acid (38 μ L, 1.0 mmol, 2 equiv) and *i*-Pr₂NEt (430 μ L, 2.5 mmol, 5 equiv) were added. The reaction mixture was heated with stirring in an oil bath maintained at 90 °C, until the olefin was fully consumed (monitored

by GC). After the reaction mixture was cooled down to room temperature, the solvent was removed under reduced pressure to produce crude product, then the residue was purified by flash chromatography using EA/hexanes as eluent. The enantioselectivity (*ee*) of the purified product was determined by chiral HPLC analysis using Daicel Chiralcel columns. Similar results were obtained by using a vacuum manifold and Schlenk tubes.

(R)-Methyl 2-acetamido-3-phenylpropanoate [21156-62-7]

(Z)-Methyl 2-acetamido-3-phenylacrylate (0.5 mmol, 110 mg) was used. The reaction was stopped in 48 h at 90 °C with 100% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as white solid. Yield: 97 mg, 92%.

$[\alpha]_D^{23} = -91.6^\circ$ ($c = 0.5$, CHCl_3).

Ee: 82%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 1.0 mL/min

^1H NMR (400 MHz, CDCl_3): δ 7.39-7.19 (m, 3H), 7.11 (dd, $J = 5.1, 3.0$ Hz, 2H), 6.01 (d, $J = 6.9$ Hz, 1H), 4.90 (dt, $J = 7.8, 5.8$ Hz, 1H), 3.74 (s, 3H), 3.13 (qd, $J = 13.9, 5.8$ Hz, 2H), 1.99 (s, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 172.1, 169.6, 135.9, 129.2, 128.6, 127.1, 53.1, 52.3, 37.8, 23.1

GC-MS (EI): Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 222.1. Found: 222.0.

(R)-Ethyl 2-acetamido-3-phenylpropanoate [20918-84-7]

(Z)-Ethyl 2-acetamido-3-phenylacrylate (0.5 mmol, 106 mg) was used. The reaction was stopped in 48 h at 90 °C with 100% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as white solid. Yield: 106 mg, 91%.

$[\alpha]_D^{23} = -75.4^\circ$ ($c = 0.5$, CHCl_3).

Ee: 86%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 95/5, flow rate = 1.0 mL/min

^1H NMR (400 MHz, CDCl_3): δ 7.35-7.21 (m, 3H), 7.13 (dd, $J = 5.1, 3.0$ Hz, 2H), 5.98 (d, $J = 6.9$ Hz, 1H), 4.88 (dt, $J = 7.8, 5.8$ Hz, 1H), 4.19 (qd, $J = 7.1, 1.1$ Hz, 2H), 3.14 (dd, $J = 5.6, 4.5$ Hz, 2H), 2.00 (s, 3H), 1.26 (t, $J = 7.2$ Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 171.7, 169.5, 135.9, 129.3, 128.5, 127.1, 61.5, 53.1, 37.9, 23.2, 14.1

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 236.1. Found: 236.0.

(R)-Methyl 2-acetamido-3-(4-methoxyphenyl)propanoate [93634-66-3]

(Z)-Methyl 2-acetamido-3-(4-methoxyphenyl)acrylate (0.5 mmol, 126 mg) was used. The reaction was stopped in 48 h at 90 °C with 100% conversion. The product was isolated by

flash chromatography (EA/hexanes 1:2 to 1:1) as white solid. Yield: 112 mg, 89%.

$[\alpha]_D^{23} = -126.3^\circ$ ($c = 0.6$, CHCl_3).

Ee: 82%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate = 1.0 mL/min

^1H NMR (400 MHz, CDCl_3): δ 7.11-6.89 (m, 2H), 6.91-6.59 (m, 2H), 5.96 (d, $J = 7.3$ Hz, 1H), 4.86 (dt, $J = 7.8, 5.7$ Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.07 (dt, $J = 14.0, 7.1$ Hz, 2H), 2.00 (s, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 172.2, 169.6, 158.7, 130.2, 127.7, 114.0, 55.2, 53.2, 52.3, 37.0, 23.1

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 252.1. Found: 251.9.

(R)-Methyl 2-acetamido-3-(*p*-tolyl)propanoate [93634-64-1]

(*Z*)-Methyl 2-acetamido-3-*p*-tolylacrylate (0.5 mmol, 116 mg) was used. The reaction was stopped in 48 h at 90 °C with 100% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as white solid. Yield: 110 mg, 94%.

$[\alpha]_D^{23} = -86.0^\circ$ ($c = 0.7$, CHCl_3).

Ee: 82%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 1.0 mL/min

^1H NMR (400 MHz, CDCl_3): δ 7.11 (d, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 8.0$ Hz, 2H), 5.96 (d, $J = 7.1$ Hz, 1H), 4.88 (dt, $J = 7.8, 5.7$ Hz, 1H), 3.75 (s, 3H), 3.10 (qd, $J = 13.9, 5.7$ Hz, 2H), 2.33 (s, 3H), 2.00 (s, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 172.2, 169.6, 136.7, 132.7, 129.3, 129.1, 53.1, 52.3, 37.4, 23.1, 21.0

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 236.1. Found: 236.0.

(R)-Ethyl 2-benzamido-3-phenylpropanoate [racemic 19817-70-0]

(Z)-Ethyl 2-benzamido-3-phenylacrylate (0.5 mmol, 148 mg) was used. The reaction was stopped in 48 h at 90 °C with 100% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as white solid. Yield: 135 mg, 91%.

$[\alpha]_D^{23} = -34.2^\circ$ ($c = 0.6$, CHCl_3).

Ee: 43%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 1.0 mL/min

^1H NMR (400 MHz, CDCl_3): δ 7.75 (d, $J = 7.6$ Hz, 2H), 7.53 (t, $J = 7.3$ Hz, 1H), 7.44 (t, $J = 7.4$ Hz, 2H), 7.29 (dq, $J = 13.2, 6.5$ Hz, 3H), 7.18 (d, $J = 7.3$ Hz, 2H), 6.64 (d, $J = 6.8$ Hz, 1H), 5.09 (dd, $J = 12.4, 6.2$ Hz, 1H), 4.24 (q, $J = 7.1$ Hz, 2H), 3.40-3.12 (m, 2H), 1.30 (t, $J = 7.1$ Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 171.6, 166.8, 135.9, 134.0, 131.7, 129.4, 128.6, 128.6, 127.1, 127.0, 61.6, 53.5, 38.0, 14.1

GC-MS (EI): Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 298.1. Found: 298.0.

(R)-Methyl 2-acetamido-2-(naphthalen-1-yl)acetate [36060-97-6]

(Z)-Methyl 2-acetamido-3-(naphthalen-1-yl)acrylate (0.5 mmol, 135 mg) was used. The reaction was stopped in 48 h at 90 °C with 100% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as white solid. Yield: 126 mg, 93%.

$[\alpha]_{\text{D}}^{23} = -36.2^\circ$ ($c = 0.7$, CHCl_3).

Ee: 78%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 1.0 mL/min

PeakTable			
Peak#	Ret. Time	Area	Area %
1	30.686	31145203	49.778
2	34.925	31423360	50.222
Total		62568563	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	30.663	8063731	10.972
2	34.421	65431737	89.028
Total		73495468	100.000

^1H NMR (400 MHz, CDCl_3): δ 8.11 (d, $J = 8.5$ Hz, 1H), 7.91-7.84 (m, 1H), 7.79 (d, $J = 8.2$ Hz, 1H), 7.58-7.49 (m, 2H), 7.41 (dd, $J = 8.1, 7.1$ Hz, 1H), 7.27 (dd, $J = 7.3, 6.7$ Hz, 1H), 6.05 (s, 1H), 5.04 (dd, $J = 14.1, 6.5$ Hz, 1H), 3.79-3.37 (m, 5H), 1.95 (s, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 172.4, 169.7, 133.9, 132.4, 132.3, 128.8, 128.0, 127.4, 126.3, 125.8, 125.2, 123.5, 53.3, 52.2, 35.1, 23.1

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 272.1. Found: 272.0.

(R)-Isopropyl 2-acetamido-3-phenylpropanoate [66789-46-6]

(Z)-Isopropyl 2-acetamido-3-phenylacrylate (0.5 mmol, 124 mg) was used. The reaction was stopped in 48 h at 90 °C with 98% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as colorless oil. Yield: 109 mg, 88%.

$[\alpha]_{\text{D}}^{23} = -60.4^\circ$ ($c = 0.5$, CHCl_3).

Ee: 93%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 98/2, flow rate = 1.0 mL/min

^1H NMR (400 MHz, CDCl_3): δ 7.39-7.18 (m, 3H), 7.19-6.94 (m, 2H), 5.99 (d, $J = 7.1$ Hz, 1H), 5.03 (dt, $J = 12.5$, 6.3 Hz, 1H), 4.85 (dt, $J = 7.8$, 5.9 Hz, 1H), 3.13 (dd, $J = 5.8$, 3.1 Hz, 2H), 2.01 (s, 3H), 1.24 (dd, $J = 10.0$, 6.3 Hz, 6H)

^{13}C NMR (101 MHz, CDCl_3): δ 171.2, 169.5, 136.0, 129.4, 128.5, 127.0, 69.4, 53.2, 37.9, 23.2, 21.8, 21.7

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 250.1. Found: 250.0.

(R)-Isopropyl 2-acetamido-3-(*o*-tolyl)propanoate [1642855-17-1]

(Z)-Isopropyl 2-acetamido-3-*o*-tolylacrylate (0.5 mmol, 131 mg) was used. The reaction was stopped in 48 h at 90 °C with 100% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as colorless oil. Yield: 122 mg, 93%.

$[\alpha]_D^{23} = -40.3^\circ$ ($c = 0.6$, CHCl_3).

Ee: 79%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 95/5, flow rate = 1.0 mL/min

^1H NMR (400 MHz, CDCl_3): δ 7.23-7.02 (m, 4H), 5.97 (d, $J = 7.6$ Hz, 1H), 4.98 (dt, $J = 12.5, 6.3$ Hz, 1H), 4.84 (dd, $J = 15.1, 7.0$ Hz, 1H), 3.21-2.95 (m, 2H), 2.37 (s, 3H), 1.99 (s, 3H), 1.23 (d, $J = 6.2$ Hz, 3H), 1.11 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 171.9, 169.7, 136.8, 134.4, 130.5, 129.9, 127.1, 125.9, 69.2, 52.6, 36.0, 23.1, 21.7, 21.4, 19.4

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 264.1. Found: 264.1.

(R)-Isopropyl 2-acetamido-3-(*p*-tolyl)propanoate

(Z)-Isopropyl 2-acetamido-3-*p*-tolylacrylate (0.5 mmol, 131 mg) was used. The reaction was stopped in 48 h at 90 °C with 100% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as white solid. Yield: 119 mg, 88%.

$[\alpha]_D^{23} = -57.2^\circ$ ($c = 0.5$, CHCl_3).

Ee: 87%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 95/5, flow rate = 1.0 mL/min

^1H NMR (400 MHz, CDCl_3): δ 7.10 (d, J = 7.8 Hz, 2H), 7.02 (d, J = 8.0 Hz, 2H), 6.02 (d, J = 7.6 Hz, 1H), 5.02 (dt, J = 12.6, 6.3 Hz, 1H), 4.82 (dt, J = 7.8, 5.8 Hz, 1H), 3.22-2.87 (m, 2H), 2.32 (s, 3H), 1.99 (s, 3H), 1.25 (t, J = 6.1 Hz, 6H)

^{13}C NMR (101 MHz, CDCl_3): δ 171.3, 169.5, 136.6, 132.8, 129.2, 129.1, 69.3, 53.2, 37.4, 23.2, 21.8, 21.7, 21.0

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 264.1. Found: 264.0.

(R)-Isopropyl 2-acetamido-3-(4-fluorophenyl)propanoate [1026133-85-6]

(Z)-Isopropyl 2-acetamido-3-(4-fluorophenyl)acrylate (0.5 mmol, 133 mg) was used. The reaction was stopped in 48 h at 90 °C with 100% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as white solid. Yield: 123 mg, 92%.

$[\alpha]_D^{23}$ = -72.8° (c = 0.6, CHCl_3).

Ee: 91%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate = 1.0 mL/min

^1H NMR (400 MHz, CDCl_3): δ 7.20-7.03 (m, 2H), 7.03-6.83 (m, 2H), 6.04 (d, $J = 7.2$ Hz, 1H), 5.02 (dt, $J = 12.6, 6.3$ Hz, 1H), 4.81 (dt, $J = 7.7, 5.9$ Hz, 1H), 3.29-2.93 (m, 2H), 2.01 (s, 3H), 1.23 (dd, $J = 10.2, 6.3$ Hz, 6H)

^{13}C NMR (101 MHz, CDCl_3): δ 171.1, 169.5, 163.2, 160.8, 131.7, 131.7, 130.9, 130.8, 115.4, 115.2, 69.5, 53.2, 37.2, 23.1, 21.7, 21.7

^{19}F NMR (377 MHz, CDCl_3): δ -115.81

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{18}\text{NFO}_3$ $[\text{M}+\text{H}]^+$: 268.1. Found: 268.0.

(R)-Isopropyl 2-acetamido-3-(4-methoxyphenyl)propanoate [1642855-16-0]

(Z)-Isopropyl 2-acetamido-3-(4-methoxyphenyl)acrylate (0.5 mmol, 139 mg) was used.

The reaction was stopped in 48 h at 90 °C with 100% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as colorless oil. Yield: 121 mg, 87%.

$[\alpha]_{\text{D}}^{23} = -66.3^\circ$ ($c = 0.6$, CHCl_3).

Ee: 91%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate = 1.0 mL/min

PeakTable			
Peak#	Ret. Time	Area	Area %
1	23.480	24988765	50.158
2	35.292	24831671	49.842
Total		49820436	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	23.574	15565591	95.314
2	36.039	765259	4.686
Total		16330851	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.05 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 5.96 (d, $J = 7.4$ Hz, 1H), 5.03 (dt, $J = 12.5, 6.3$ Hz, 1H), 4.81 (dt, $J = 7.7, 5.8$ Hz, 1H), 3.80 (s, 3H), 3.06 (dd, $J = 12.3, 7.1$ Hz, 2H), 2.01 (s, 3H), 1.25 (dd, $J = 6.0, 5.1$ Hz, 6H)

^{13}C NMR (101 MHz, CDCl_3): δ 171.3, 169.5, 158.7, 130.4, 127.9, 113.9, 69.3, 55.2, 53.3, 37.0, 23.2, 21.8, 21.7

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_4$ $[\text{M}+\text{H}]^+$:280.1. Found: 280.0.

(R)-Isopropyl 2-acetamido-3-(4-(trifluoromethyl)phenyl)propanoate

(Z)-Isopropyl 2-acetamido-3-(4-(trifluoromethyl)phenyl)acrylate (0.5 mmol, 158 mg) was used. The reaction was stopped in 48 h at 90 °C with 50% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as white solid. Yield: 65 mg, 41%.

$[\alpha]_{\text{D}}^{23} = -49.0^\circ$ ($c = 0.6$, CHCl_3).

Ee: 84%. Daicel Chiralcel IC-H, *n*-hexane/isopropanol 90/10, flow rate = 1.0 mL/min

^1H NMR (400 MHz, CDCl_3): δ 7.56 (d, J = 8.0 Hz, 2H), 7.27 (t, J = 5.9 Hz, 2H), 6.06 (d, J = 7.3 Hz, 1H), 5.02 (dt, J = 12.6, 6.3 Hz, 1H), 4.86 (dt, J = 7.5, 6.0 Hz, 1H), 3.19 (dd, J = 7.6, 6.2 Hz, 2H), 2.01 (s, 3H), 1.23 (dd, J = 13.0, 6.3 Hz, 6H).

^{13}C NMR (101 MHz, CDCl_3): δ 170.8, 169.6, 140.3, 129.7, 129.5, 129.2, 125.3, 125.3, 125.3, 69.7, 53.0, 37.8, 23.1, 21.7, 21.6

^{19}F NMR (376 MHz, CDCl_3): δ -62.5

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{18}\text{F}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$: 280.1. Found: 280.0.

3.3.4 Deuterium labeling experiment of α -acetamidoacrylate

General procedure for asymmetric transfer hydrogenation of (*Z*)-methyl 2-acetamido-3-*o*-tolylacrylate with $[\text{D}_1]$ formic acid: $\text{Ni}(\text{OAc})_2$ (0.9 mg, 0.005 mmol), (*S*)-Binapine (4.4 mg, 0.006 mmol), and dry PhCF_3 (0.3 mL) were charged into a 10 mL-reaction tube. After stirring for 10 min, (*Z*)-methyl 2-acetamido-3-*o*-tolylacrylate (0.1 mmol), HCO_2D (23 μL , 0.3 mmol, 3 equiv), Et_3N (42 μL , 0.3 mmol, 3 equiv) were added. The reaction mixture was stirred in an oil bath maintained at 90 $^\circ\text{C}$ for 24 h. The reaction mixture was filtered to remove the catalyst and evaporated to give the crude product residue. The pure product was obtained by preparative TLC (1:2 EA/hexanes). The deuterium content of the isolated product was analyzed by quantitative ^1H NMR

spectroscopy.

3.3.5 Typical Procedure for Synthesis of Tetrasubstituted β -(acylamino)acrylates

The procedure was reported in the literature: W. J. Tang, S. L. Wu, X. M. Zhang, *J. Am. Chem. Soc.*, **2003**, 125, 9570.

Modified procedure: A mixture β -keto ester A (10 mmol) and ammonium acetate (3.85 g, 50 mmol) in MeOH (30 mL) was reflux at 80 °C for 12 h. After the reaction cooled down to the room temperature, the whole reaction mixture was then concentrated. The residue was diluted with water (30 mL) and EtOAc (30 mL). The aqueous layer was extracted with EtOAc and the combined organic layers were dried by Na_2SO_4 . The solution was concentrated under vacuum to give enamine B, which was used in next step without purification.

Enamine B was dissolved in toluene (50 mL), pyridine (1.8 mL, 2.25 equiv) and acetyl chloride (0.79 mL, 1.25 equiv) was added. The mixture was stirred at room temperature for overnight and then quenched by addition of 1N HCl (30 mL), the aqueous layer was extracted by EtOAc. The organic phase was washed with HCl (1N, 50 mL) and water, dried by Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatograph.

3.3.6 Condition Optimization for Asymmetric Transfer Hydrogenation of Tetrasubstituted Olefins of Cyclic β -(Acylamido)acrylates

A typical procedure for condition optimization: In an argon-filled glove box,

Ni(OAc)₂ (0.9 mg, 0.005 mmol), (*R,R*)-QuinoxP* (2.0 mg, 0.006 mmol) and dry MeOH (0.3 mL) were charged into a 10-mL reaction tube. After stirring for 10 min, methyl 1-acetamido-3,4-dihydronaphthalene-2-carboxylate (0.1 mmol, 0.0245 g), formic acid (19 μ L, 0.5 mmol), Et₃N (28 μ L, 0.2 mmol) and GC standard *n*-C₁₄H₃₀ (10 μ L) were added. The reaction mixture was stirred in an oil bath maintained at 80 °C. After 48 h, aliquots were taken from the reaction mixture in the glove box and passed through a short plug of silica gel with EtOAc washing (about 3 mL). The filtrate was subjected to GC analysis to determine the conversion of the olefin and yield of the product. To determine the enantioselectivity of the product, the filtrate was dissolved in 1:10 *i*-PrOH/hexanes and subjected to chiral HPLC analysis (Daicel CHIRCEL OJ-H; 5% *i*-PrOH in hexanes; flow rate 0.5 mL/min).

3.3.7 Asymmetric Transfer Hydrogenation of Tetrasubstituted Olefins of Cyclic β -(Acylamido)acrylates

General procedure for asymmetric transfer hydrogenation: In an argon-filled glove box, Ni(OAc)₂ (4.5 mg, 0.025 mmol), (*R,R*)-QuinoxP* (11 mg, 0.03 mmol) and dry MeOH (1.5 mL) were charged into a 10-mL Schlenk tube. After stirring for 30 min, methyl 1-acetamido-3,4-dihydronaphthalene-2-carboxylate (0.5 mmol), formic acid (95 μ L, 2.5 mmol, 5 equiv) and *N,N*-dimethylaniline (0.121 g, 1.0 mmol, 2 equiv) were added. The reaction mixture was heated with stirring in an oil bath maintained at 80 °C, until the olefin was fully consumed (monitored by GC). After the reaction mixture was cooled down to room temperature, the solvent was removed under reduced pressure to produce crude product, then the residue was purified by flash chromatography using EA/hexanes

as eluent. The enantioselectivity (*ee*) of the purified product was determined by chiral HPLC analysis using Daicel Chiralcel columns. The racemic product was obtained by the optimized conditions using racemic ligands.

(1*S*,2*S*)-Methyl 1-acetamido-1,2,3,4-tetrahydronaphthalene-2-carboxylate

Methyl 1-acetamido-3,4-dihydronaphthalene-2-carboxylate (0.5 mmol, 123 mg) was used.

The reaction was stopped in 48 h at 80 °C with 100% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as colorless oil in a diastereomeric ratio of 87/13 (*syn*/*anti*). Yield: 106 mg, 86%.

$[\alpha]_D^{23} = +50.5^\circ$ ($c = 1.0$, CHCl_3).

Ee: 99/97%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min

Major product NMR: ^1H NMR (400 MHz, CDCl_3): δ 7.32-7.25 (m, 1H), 7.22-7.13 (m,

2H), 7.10-7.01 (m, 1H), 6.29 (d, $J = 9.3$ Hz, 1H), 5.56-5.53 (m, 1H), 3.69 (s, 3H), 3.11-2.99 (m, 1H), 2.91-2.69 (m, 2H), 2.20-2.06 (m, 2H), 2.02 (d, $J = 9.6$ Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 173.8, 169.5, 135.8, 135.6, 128.9, 128.1, 127.4, 126.5, 51.9, 47.9, 43.9, 27.0, 23.4, 22.6

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 248.1. Found: 248.0.

(1S,2S)-Ethyl 1-acetamido-1,2,3,4-tetrahydronaphthalene-2-carboxylate

Ethyl 1-acetamido-3,4-dihydronaphthalene-2-carboxylate (0.5 mmol, 130 mg) was used.

The reaction was stopped in 48 h at 80 °C with 100% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as white solid in a diastereomeric ratio of 88/12 (syn/anti). Yield: 114 mg, 87%.

$[\alpha]_{\text{D}}^{23} = +55.4^\circ$ ($c = 0.8$, CHCl_3).

Ee: 99/81%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 95/5, flow rate = 0.5 mL/min

Major product NMR: ^1H NMR (400 MHz, CDCl_3): δ 7.31-7.29 (m, 1H), 7.22-7.12 (m, 2H), 7.12-7.01 (m, 1H), 6.31 (d, $J = 9.3$ Hz, 1H), 5.58-5.55 (m, 1H), 4.14 (q, $J = 7.0$ Hz, 2H), 3.04 (dd, $J = 11.8, 4.9$ Hz, 1H), 2.97-2.70 (m, 2H), 2.24-2.04 (m, 2H), 2.01 (s, 3H), 1.26 (t, $J = 7.1$ Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 173.4, 169.5, 136.0, 135.6, 128.8, 128.0, 127.3, 126.5, 60.8, 47.8, 43.9, 26.9, 23.5, 22.7, 14.1

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 262.1. Found: 262.0.

(1S,2S)-Methyl

1-acetamido-7-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate

Methyl 1-acetamido-7-methoxy-3,4-dihydronaphthalene-2-carboxylate (0.5 mmol, 138 mg) was used. The reaction was stopped in 48 h at 80 °C with 100% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as white solid in a diastereomeric ratio of 87/13 (syn/anti). Yield: 120 mg, 87%.

$[\alpha]_{\text{D}}^{23} = +41.3^\circ$ ($c = 0.7$, CHCl_3).

Ee: 99/99%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min

Major product NMR: ^1H NMR (400 MHz, CDCl_3): δ 6.99 (d, $J = 8.4$ Hz, 1H), 6.81 (s, 1H), 6.77-6.74 (m, 1H), 6.25 (d, $J = 9.6$ Hz, 1H), 5.53-5.49 (m, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.16-2.92 (m, 1H), 2.76-2.71 (m, 2H), 2.23-2.07 (m, 2H), 2.03 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 173.9, 169.5, 158.2, 136.9, 129.9, 127.7, 113.9, 112.4, 55.3, 51.9, 48.1, 43.9, 26.1, 23.5, 22.9

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 278.1. Found: 278.0.

(1S,2S)-Methyl

1-acetamido-6-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate

Methyl 1-acetamido-6-methoxy-3,4-dihydronaphthalene-2-carboxylate (0.5 mmol, 138 mg) was used. The reaction was stopped in 48 h at 80 °C with 100% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as white solid in a

diasereomeric ratio of 87/13 (syn/anti). Yield: 115 mg, 88%.

$[\alpha]_D^{23} = +68.3^\circ$ ($c = 1.0$, CHCl_3).

Ee: 97/97%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min

PeakTable			
Peak#	Ret. Time	Area	Area %
1	29.787	27689696	55.694
2	33.841	22027584	44.306
Total		49717280	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	43.868	3859831	55.735
2	47.824	3065548	44.265
Total		6925378	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	30.820	567389	1.352
2	33.850	41413571	98.648
Total		41980960	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	44.621	93331	1.266
2	47.921	7276125	98.734
Total		7369456	100.000

Major product NMR: ^1H NMR (400 MHz, CDCl_3): δ 7.20 (d, $J = 8.6$ Hz, 1H), 6.75-6.73 (m, 1H), 6.60 (s, 1H), 6.16 (d, $J = 9.5$ Hz, 1H), 5.52-5.49 (m, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 3.03-2.99 (m, 1H), 2.87-2.64 (m, 2H), 2.09 (q, $J = 6.7$ Hz, 2H), 2.00 (s, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 173.9, 169.4, 158.7, 136.9, 129.5, 128.1, 113.2, 112.9, 55.2, 51.9, 47.4, 44.0, 27.4, 23.5, 22.3

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 278.1. Found: 278.0.

(1S,2S)-Methyl

1-acetamido-5-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate

Methyl 1-acetamido-5-methoxy-3,4-dihydronaphthalene-2-carboxylate (0.5 mmol, 138 mg) was used. The reaction was stopped in 48 h at 80 °C with 100% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as colorless oil in a diasereomeric ratio of 93/7 (syn/anti). Yield: 123 mg, 89%.

$[\alpha]_D^{23} = +86.9^\circ$ ($c = 0.4$, CHCl_3).

Ee: 99/99%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 95/5, flow rate = 0.5 mL/min

PeakTable			
Peak#	Ret. Time	Area	Area %
1	30.622	48324726	59.098
2	37.635	33446214	40.902
Total		81770941	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	41.081	3307195	45.819
2	46.312	3910734	54.181
Total		7217929	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	30.029	268115	0.514
2	36.637	51936450	99.486
Total		52204565	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	40.623	42343	0.838
2	45.177	5010972	99.162
Total		5053315	100.000

Major product NMR: ^1H NMR (400 MHz, CDCl_3): δ 7.16 (t, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 7.8$ Hz, 1H), 6.73 (d, $J = 8.1$ Hz, 1H), 6.26 (d, $J = 9.5$ Hz, 1H), 5.55-5.51 (m 1H), 3.81 (s, 3H), 3.68 (s, 3H), 3.03-2.99 (m, 1H), 2.73-2.62 (m, 2H), 2.14-2.08 (m, 2H), 2.01 (s, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 173.9, 169.5, 156.8, 137.0, 126.9, 124.7, 119.9, 108.4, 55.3, 51.8, 47.9, 43.5, 23.5, 22.1, 21.1

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 278.1. Found: 278.0.

(1*S*,2*S*)-Methyl 1-acetamido-2,3-dihydro-1*H*-indene-2-carboxylate

Methyl 3-acetamido-1*H*-indene-2-carboxylate (0.5 mmol, 112 mg), 5 mol% (*S*)-PhBPE was used. The reaction was stopped in 48 h at 80 °C with 100% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as white solid in a diastereomeric ratio of 87/13 (syn/anti). Yield: 71 mg, 61%.

$[\alpha]_D^{23} = +73.7^\circ$ ($c = 1.0$, CHCl_3).

Ee: 95/95%. Daicel Chiralcel AD-H, *n*-hexane/isopropanol 95/5, flow rate = 0.5 mL/min

PeakTable

Peak#	Ret. Time	Area	Area %
1	23.695	1140771	50.301
2	28.919	1127104	49.699
Total		2267876	100.000

PeakTable

Peak#	Ret. Time	Area	Area %
1	39.686	3397674	52.848
2	50.309	4815973	47.152
Total		10213647	100.000

PeakTable

Peak#	Ret. Time	Area	Area %
1	23.661	47958	2.345
2	28.863	1996903	97.655
Total		2044861	100.000

PeakTable

Peak#	Ret. Time	Area	Area %
1	39.579	11178389	97.883
2	50.364	241780	2.117
Total		11420168	100.000

Major product NMR: ^1H NMR (400 MHz, CDCl_3): δ 7.26-7.21 (m, 4H), 5.83 (d, $J = 7.5$ Hz, 1H), 5.74 (t, $J = 8.1$ Hz, 1H), 3.75 (s, 3H), 3.23 (d, $J = 8.8$ Hz, 2H), 3.09-3.03 (m, 1H), 2.05 (s, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 174.0, 169.9, 141.3, 140.6, 128.5, 127.3, 124.7, 123.7, 58.3, 52.6, 52.2, 34.2, 23.3

GC-MS (EI): Calcd for C₁₃H₁₅NO₃ [M+H]⁺: 234.1. Found: 234.0.

(2S,3S)-Ethyl 3-acetamido-2-methyl-3-phenylpropanoate

(Z)-Ethyl 3-acetamido-2-methyl-3-phenylacrylate (0.5 mmol, 124 mg) was used. The reaction was stopped in 48 h at 80 °C with 100% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as colorless oil in a diastereomeric ratio of 70/30 (syn/anti). Yield: 113 mg, 91%.

$[\alpha]_D^{23} = +51.3^\circ$ ($c = 0.7$, CHCl₃).

Ee: 93/92%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min

PeakTable			
Peak#	Ret. Time	Area	Area %
1	17.832	7419469	46.426
2	25.005	8561978	53.574
Total		15981447	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	18.930	2616267	49.642
2	22.228	2654010	50.358
Total		5270277	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	17.821	301999	3.913
2	24.798	7416169	96.087
Total		7718169	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	18.673	22005791	96.798
2	22.167	727989	3.202
Total		22733780	100.000

Major product NMR: ¹H NMR (400 MHz, CDCl₃): δ 7.32-7.28 (m, 2H), 7.25-7.21 (m, 3H), 7.00 (d, *J* = 8.6 Hz, 1H), 5.21-5.17 (m, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 2.99-2.92 (m, 1H), 2.05 (s, 3H), 1.25 (d, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 175.4, 169.7, 140.5, 128.5, 127.4, 126.3, 60.7, 55.0, 44.6, 23.4, 15.7, 14.0

Mino product NMR: ^1H NMR (400 MHz, CDCl_3): δ 7.33-7.24 (m, 5H), 6.45 (d, $J = 8.2$ Hz, 1H), 5.28-5.25 (m, 1H), 4.05 (q, $J = 7.1$ Hz, 2H), 2.97-2.90 (m, 1H), 2.01 (s, 3H), 1.18-1.12(m, 6H)

^{13}C NMR (101 MHz, CDCl_3): δ 173.9, 169.1, 139.4, 128.5, 127.7, 127.1, 60.7, 55.1, 44.7, 23.5, 14.0, 13.5

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 249.1. Found: 249.0.

(2S,3S)-Methyl 3-acetamido-2-methyl-3-phenylpropanoate

(Z)-Methyl 3-acetamido-2-methyl-3-phenylacrylate (0.5 mmol, 117 mg) was used. The reaction was stopped in 48 h at 80 °C with 100% conversion. The product was isolated by flash chromatography (EA/hexanes 1:2 to 1:1) as colorless oil in a diastereomeric ratio of 75/25 (syn/anti). Yield: 104 mg, 89%.

$[\alpha]_{\text{D}}^{23} = -44.7^\circ$ ($c = 0.7$, CHCl_3).

Ee: 87/84%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 96/4, flow rate = 0.5 mL/min

Major product NMR: ^1H NMR (400 MHz, CDCl_3): δ 7.33-7.23 (m, 5H), 7.02 (d, $J = 8.7$ Hz, 1H), 5.21-5.18 (m, 1H), 3.58 (s, 3H), 3.00-2.94 (m, 1H), 2.05 (s, 3H), 1.26 (d, $J = 7.1$ Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 175.8, 169.7, 140.5, 128.6, 127.6, 126.3, 55.0, 51.8, 44.6, 23.4, 15.7

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 236.1. Found: 236.0.

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