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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 various hydride sources. It contains three main parts.

Chapter one reported a highly enantioselective asymmetric transfer hydrogenation of α,β -unsaturated esters with a chiral phosphine ligand, (*R*)-Me-DuPhos. With formic acid and triethyl amine worked as hydride source, excellent conversion and enantioselectivity were obtained. Furthermore, deuterium labeling experiments revealed a possible mechanism. I also reported asymmetric transfer hydrogenation of α,β -unsaturated esters with DMF and water as hydride source.

Chapter two described asymmetric transfer hydrogenation of cinnamates, beta-dehydroacetamidoesters and hydrazones with acetic acid and indium powder. With nickel/(*S*)-Binapine or (*R*)-Me-DuPhos catalytic system, a series of C=C and C=N gave high enantioselectivities.

Chapter three reported asymmetric deuteration of α,β -unsaturated esters with deuterium water and indium powder as hydride source. For all the substrates tested, excellent conversion, enantioselectivity and deuterium ratio were obtained. This work provided a novel methodology for the synthesis of chiral deuterated products without expensive and explosive deuterium gas.

PUBLICATIONS

1. Nickel-catalyzed asymmetric transfer hydrogenation of conjugated olefins

Siyu Guo, Peng Yang, and Jianrong (Steve) Zhou, *Chem. Commun.* **2015**, 51, 12115-12117.

2. *N,N*-Dimethylformamide as Hydride Source in Nickel-Catalyzed Asymmetric Hydrogenation of α,β -Unsaturated Esters

Siyu Guo, and Jianrong (Steve) Zhou, *Org. Lett.* **2016**, 18, 5344–5347.

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	Naphthyl
<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 Using Formic Acid

1.1 Introduction

1.1.1 Background of asymmetric hydrogenation and industry applications

Asymmetric hydrogenation is a reaction that adds two atoms of hydrogen to prochiral molecules forming chiral fine chemicals.¹⁻³ It is frequently used in industry to prepare enantiopure or enriched drugs, agrochemicals and fragrance.⁴ Attractive features include, high enantioselectivity, very high catalytic turnovers (often in the range of 10,000 and up to millions for simple substrates), atom economy and production of water as the only by-product. Common substrates for hydrogenation include enoates, enamines, and dehydroamino acid derivatives, using chiral phosphine complexes of rhodium, ruthenium and iridium.⁵⁻⁷

In 2001, Knowles and Noyori were awarded Nobel Prize in Chemistry for their seminal work in asymmetric hydrogenation.⁸⁻¹⁰ In the classic example, Knowles invented and applied C_2 -symmetric DIPAMP ligand in rhodium catalysis to prepare *L*-DOPA (Scheme 1.1.1).¹¹ *L*-DOPA is used to increase dopamine concentration in the management of Parkinson's symptom and dopamine-responsive memory loss. In this process, *N*-acyl group serves as a directing group and is essential for the high level of enantioselectivity.

Scheme 1.1.1 Synthesis of L-DOPA

In another selected industrial application of hydrogenation, Moexipril was prepared by Chowhan *et al.* at UCB pharma in 1990 (Scheme 1.1.2).¹² Moexipril is a marketed angiotensin converting enzyme inhibitor, which is used for the treatment of hypertension and congestive heart failure. Moexipril was synthesized by asymmetric hydrogenation of α -dehydroamino ester with a combination of $\text{Rh}(\text{NBE})_2\text{BF}_4$ and (*R*)-ProPhos under ambient temperature and 1 bar of hydrogen gas. After further recrystallization, the α -amidoester can be obtained in 95-97% *ee*.

Scheme 1.1.2 Synthesis of Moexipril

Recently, Rossen *et al.* reported the preparation of a chiral piperazine moiety via asymmetric hydrogenation, which is used to make an *anti*-HIV drug (Scheme 1.1.3).¹³

This first-generation HIV-protease inhibitor indinavir was produced by Merck every year. The best ligand was (*R*)-BINAP, which afforded excellent enantioselectivity.

Scheme 1.1.3 Synthesis of Indinavir

1.1.2 First row metal-catalyzed asymmetric hydrogenation

Although Rh, Ru and Ir catalysts have outstanding performance in asymmetric hydrogenation after optimization and many of them are applied on large scales to prepare chiral drugs or agrochemicals, several inherent problems still exist. Noble metals are produced in small amount per year. For example, only 30 tons of rhodium is produced annually and most of it is used in converters in auto industry. Therefore, those metals are very expensive and their reserve in the earth's crust is limited. Rh, Ru and Ir are also toxic heavy metals and they are damaging to environment. For example, rhodium(III) salts are genotoxic and mutagenic in bacteria. Therefore, it takes extra costs in removal from industrial products, especially orally available medicines, and waste treatment. Especially, heavy metal residues must be reduced to ppm levels in orally taken pharmaceutical active ingredients.

As alternative catalysts for asymmetric hydrogenation, first-row metals such as Fe, Co, Cu and Ni are produced in millions of tons a year and they are thousands fold cheaper than noble metals.¹⁴ Nickel, as a bulk base metal, is produced in 2.5 million tons annually, while iron is produced 3.3 trillion tons annually. Compared to genotoxic ruthenium salts, the first-row metals, especially iron, are less toxic. Nickel compounds enter human body via drinking water and food, but their absorption through digestive system is poor. Pulmonary absorption of nickel oxides, however, is a dangerous way that will result in retention in lungs. Iron is an important microelement in human. However, continuous excess of excessive iron may lead to overload of chronic iron, which will cause damage to liver, heart and other organs.

1.1.2.1 Co-catalyzed asymmetric hydrogenation

In 2013, Chirik *et al.* disclosed seminal work on asymmetric hydrogenation of acetamidoacrylates with cobalt and (*R,R*)-*i*Pr-DuPhos (Scheme 1.1.4).¹⁵ The combination of a cobalt trimethylsilylmethyl complex and (*R,R*)-*i*Pr-DuPhos was active for enantioselective hydrogenation of amino acid and enamine derivatives.

Scheme 1.1.4 Cobalt-catalyzed asymmetric hydrogenation of acetamidoacrylates

and enamides

In 2016, Chirik and co-workers reported cobalt-catalyzed asymmetric hydrogenation of styrene derivatives using a chiral diiminopyridine ligand (Scheme 1.1.5).¹⁶ In this system, excellent results were obtained without adding $\text{LiCH}_2\text{SiMe}_3$.

Scheme 1.1.5 Cobalt-catalyzed asymmetric hydrogenation of acetamidoacrylates

and enamides

1.1.2.2 Iron-catalyzed asymmetric hydrogenation

In 2014, Morris *et al.* made a discovery of asymmetric hydrogenation of ketones with iron catalysts (Scheme 1.1.6).¹⁷⁻¹⁸ Since then, his group has improved the iron catalysts by modifying the multidentate ligands of phosphorus and nitrogen for asymmetric hydrogenation using H₂ or alcohols.¹⁹

Scheme 1.1.6 Iron-catalyzed asymmetric hydrogenation of ketones

In the same year, Beller *et al.* also disclosed iron-catalyzed asymmetric hydrogenation of unsaturated nitrogen heterocycles such as quinoxalines and 2*H*-1,4-benzoxazines in the presence of chiral Brønsted acids (Scheme 1.1.7).

Scheme 1.1.7 Iron-catalyzed asymmetric hydrogenation of ketones

1.1.2.3 Titanium-catalyzed asymmetric hydrogenation

In 1994, Buchwald *et al.* reported asymmetric hydrogenation of ketimines with a chiral titanocene catalyst (Scheme 1.1.8).²⁰ After treatment of an air-stable titanocene precursor with *n*-butyllithium and phenylsilane, the active hydrogenation catalyst, titanacenium(III) hydride was made. However, the active titanocene catalyst was very sensitive to moisture and high pressure of hydrogen gas was necessary. Later, they disclosed asymmetric transfer hydrogenation of cyclic imines with silanes as hydride source.²¹

Scheme 1.1.8 Titanium-catalyzed asymmetric hydrogenation of ketones

1.1.2.4 Nickel-catalyzed asymmetric hydrogenation and transfer hydrogenation

Raney nickel has been used for hydrogenation of a range of unsaturated compounds for more than a decade. In 1978, Izumi *et al.* reported modified Raney nickel catalyzed heterogeneous asymmetric hydrogenation of C=O bonds.²² In 2009,

Hamada *et al.* reported homogeneous asymmetric hydrogenation of aromatic α -aminoketones through concomitant dynamic kinetic resolution of the α center.²³ In 2016, Chirik *et al.* reported asymmetric hydrogenation of simple α,β -unsaturated esters with β,β -disubstituents using a combination of nickel acetate and (*R*)-Me-DuPhos under 34 bar of hydrogen gas (Scheme 1.1.9).²⁴ The additive of tetrabutylammonium iodide was used to accelerate the reaction dramatically. Various electron-rich and -poor aryl groups were tolerated at the β carbon of the substrates. They found that the acetate anion was critical in facilitating heterolytic cleavage of dihydrogen on the nickel center to generate the key nickel monohydride species. Unfortunately, the turnover number and frequency are still low, high pressure of hydrogen gas is needed and the substrate scope is quite limited.

Scheme 1.1.9 Nickel-catalyzed asymmetric hydrogenation of α,β -unsaturated esters

In 2017, Xumu Zhang *et al.* extended the nickel-catalyzed asymmetric hydrogenation to β -acylamino nitroolefins using 51 bar of hydrogen gas (Scheme 1.1.10).²⁵ The catalyst provided high yields and *ee* values. Using deuterium labelling experiments, they demonstrated the hydrogen atom at β position came from hydrogen gas and the hydrogen atom at α position originated from the alcohol solvent.

Scheme 1.1.10 Nickel-catalyzed asymmetric hydrogenation of β -acylamino nitroolefins

In 2013, our group explored nickel catalysts for hydrogenation of unsaturated compounds using hydrogen gas, but no catalytic reactivity was found at a pressure of 10 bar. Later, I turned my attention to transfer hydrogenation conditions using a combination of formic acid and triethylamine. Since 2014, our group published several papers on asymmetric transfer hydrogenation of different C=C and C=N bonds. In the first example, Dr Peng Yang and Haiyan Xu in our lab reported asymmetric transfer hydrogenation for the synthesis of both α - and β -amino acids using a ligand invented by Xumu Zhang, (*S*)-binapine (Scheme 1.1.11).²⁶ The cinnamates bearing an extra methyl or ethyl groups at the β -position provided excellent conversions and *ee* values. In a mechanistic study using HCO₂D, deuterium was found to end at both C-H bonds alpha to the ester group. This suggests that the reaction did not proceed via a classical dihydride pathway. Instead, nickel hydride insertion to the polar C=C bond produced a nickel enolate species, which was quenched by the proton source in the reaction medium, in this case, the excess formic acid. I believe that the bulky strongly donating diphosphine was critical in promoting decomposition of the formate to produce the key nickel hydride species (unpublished

result) and it also helped to prevent the formation of catalytic inactive species of $\text{NiX}_2(\text{diphosphine})_2$.

Scheme 1.1.11 Nickel-catalyzed asymmetric transfer hydrogenation of β -amino acids

Later, our group turned attention to asymmetric reduction of polar $\text{C}=\text{N}$ bonds since the Ni-H bond has more hydridic character than a Rh-H bond. In 2015, Haiyan Xu in our lab published examples of asymmetric hydrogenation of hydrazones and other cyclic ketimines (benzosultams) (Scheme 1.1.12).²⁷ By using ONIOM-DFT method of Morokuma's group,²⁸ Prof Hajime Hirao's group in collaboration with us found the amide fragment of hydrazone chelated to the nickel and accelerated asymmetric hydride insertion. The calculated energy gap of two diastereomeric transition states leading to enantiomeric products, $2.9 \text{ kcal mol}^{-1}$, is consistent with the observed 98% ee. The neutral nickel(I) hydride pathways were also computed, but the energy gap for two transition states was too small for the high enantioselectivity observed. Importantly, I found that the nickel/binapine catalyst controls the asymmetric hydride insertion by controlling the binding conformation of the amide directing group, instead of steric differentiation of two groups on the $\text{C}=\text{N}$ bond.

Scheme 1.1.12 Nickel-catalyzed asymmetric transfer hydrogenation of hydrazones

Next, our group embarked onto exploration of one-pot asymmetric reductive amination of ketones, which helps to avoid the synthesis and purification of ketimines. Dr. Peng Yang established suitable one-flask conditions for condensation of ketimines from arylamines and benzhydrazides and the nickel-catalyzed reduction (Scheme 1.1.13).²⁹ In addition, asymmetric double reductive amination of 1,2-diaminobenzene with α -ketoaldehydes was achieved, too.

Scheme 1.1.13 Nickel-catalyzed asymmetric reductive amination of ketones with both arylamines and benzhydrazides

1.2 Asymmetric hydrogenation of α,β -unsaturated esters using HCOOH

During my initial exploration of nickel catalysts in asymmetric transfer hydrogenation using formic acid, I wondered whether the nickel catalysts can be applied to other unsaturated bonds such as polar C=C bonds. Unfortunately, no reactivity was seen with simple aliphatic olefin and aryl olefins. Later, I examined asymmetric hydrogenation of α,β -unsaturated esters using nickel catalysts and found that the bond polarization caused by the electron-withdrawing groups was important for the catalytic activity. In other words, the nickel hydride species is more “hydridic” and prefers to react with polar unsaturated bonds.

1.2.1 Reaction optimization

Ethyl (*E*)-3-phenyl-2-butenate was chosen to be the model substrate for asymmetric hydrogenation. Firstly, I screened various chiral ligands, aiming to find active nickel catalysts (Table 1.1). Using HCOOH/Et₃N as hydrogen source, isopropanol as solvent and NiBr₂ as nickel source, I screened different ligands. I found that (*R,R*)-Me-Duphos afforded good enantioselectivity (91% *ee*, entry 1). (*R,R*)-Ph-BPE, (*R,R*)-*i*Pr-DuPhos, (*S,S'*,*R,R'*)-TangPhos and (*R,R*)-QuinoxP* also formed active catalysts but giving unsatisfactory *ees* (entry 2,4,7 and 9). All of these active diphosphines are strongly donating ligands with *P*-alkyl groups.

Table 1.1 The effect of organic ligands

Entry	Ligand	Conv (%)	Yield (%)	Ee (%)
1		95	92	91
2		18	16	--
3		0	0	--
4		27	22	82
5		0	0	
6		0	0	

7		55	48	49
8		0	0	--
9		12	5	29
10		0	0	
11		0	0	
12		0	0	
13		0	0	
14		0	0	

16		0	0	
17	(R)-BINAP	0	0	
18	(R)-Segphos	0	0	
19	(R)-DTBM-Segphos	0	0	
20		0	0	
21		0	0	
22		0	0	
23		0	0	
24		0	0	
25		0	0	

The transfer hydrogenation proceeded in good to excellent conversion in most common solvents (Table 1.2) and gave almost the same *ee* (around 91-92%). In several alcohols (except MeOH), the reaction rate was the fastest (entry 1-4). In ethereal solvents and amide solvents, the reaction can also proceed efficiently (entry 5-6 and 11).

Table 1.2 The effect of organic solvents

Entry	Solvent	Conversion (%)	Yield (%)	Ee (%)
1	MeOH	45	45	90
2	EtOH	98	95	90
3	<i>n</i> -BuOH	95	92	91
4	<i>i</i>-PrOH	99	92	91
5	DMA	78	64	92
6	DMF	88	87	91
7	DMSO	49	48	90
8	THF	53	39	92
9	1,4-Dioxane	53	47	92
10	DME	55	52	93
11	Diglyme	97	96	93
12	Toluene	72	55	93

13	PhCF ₃	83	81	94
14	EtOAc	73	71	91
15	DCE	45	22	91

All the nickel salts I tried catalyzed this reaction and gave good to excellent conversion with high *ee* values (Table 1.3). Among them, NiBr₂(DME) and Ni(acac)₂ provided the highest catalytic activity. I believe that the precursor to the active catalyst is (diphosphine)NiX₂, which dissociates one of the anionic ligand in the alcohol to create a cationic active species (entry 1 and 5). The reaction cannot be catalyzed by other salts of cobalt, iron and copper in the presence of formic acid (entry 6-9).

Table 1.3 The effect of metal salts

Entry	Nickel and other metal salts	Conversion (%)	Yield(%)	<i>Ee</i> (%)
1	NiBr ₂ (DME)	98	92	91
2	NiCl ₂ (DME)	38	24	88
3	Ni(OAc) ₂	40	32	84
4	Ni(OTf) ₂	37	10	--
5	Ni(acac) ₂	94	92	90
6	Ni(cod) ₂ or Ni(PPh ₃) ₄	0	-	-
7	Ni(PPh ₃) ₄ and 100 °C, 24 h	14	14	-

8	CoBr ₂ , CoI ₂ or Co(acac) ₂	0	-	-
9	FeCl ₂ , FeBr ₂ , FeCl ₃ , Fe(acac) ₂ or Fe(acac) ₃	0	-	-
10	CuBr, CuI, CuCl ₂ , CuBr ₂ or Cu(OAc) ₂	0	-	-

The reaction was sensitive to the amounts and ratio of formic acid and the amine (Table 1.4). I found that 5:2 and 5:5 were the combinations that gave the best activity (entry 2-3). However, when using 5:1 or 1:5 mixture, the conversion decreased significantly (entry 1 and 5).

Table 1.4 Effect of the ratio of formic acid and Et₃N

Entry	HCO ₂ H (equiv)	Et ₃ N (equiv)	Conversion (%)	Yield (%)	Ee (%)
1	5	1	<5	-	-
2	5	2	99	92	91
3	5	5	94	86	91
4	2	5	46	41	91
5	1	5	23	11	-
6	2	2	72	71	91

1.2.2 Scope of substrate for Ni-catalyzed asymmetric transfer hydrogenation

Next, I screened different α,β -unsaturated esters under optimized condition (Scheme 1.2.1). Substrates with both electron-rich and -poor β -aryl groups gave high enantioselectivity and high conversion. Both methyl and *t*-butyl esters also reacted well under the reaction conditions. A slight drop in the enantioselectivity (88%) was found with bulky *t*-butyl ester. Thiophene and pyridine substituents were also tolerated. At the β -position of cinnamates, an ethyl group could be tolerated, but an isopropyl group slowed down the reaction and reduced the selectivity. Moreover, β -*t*-butyl group completely inhibited the hydride insertion. Two cyclic substrates provided high yield and good enantioselectivity. For the reaction of dimethyl phenylsuccinate, the optimal ligand was TangPhos while Me-DuPhos only afforded 65% *ee*. Other electron-withdrawing groups, for example, amides and nitriles, could also be used to activate the olefin for insertion.

Notably, in the reaction of *p*-chloro- β -methylcinnamate, the C-Cl bond was reduced to a C-H bond completely in the product, which indicated the oxidative addition of C-Cl bond to a nickel(0) species.

Scheme 1.2.1 Scope of Substrates for Ni-Catalyzed Asymmetric Transfer

Hydrogenation

1.2.3 Proposed reaction mechanism

When I used d_1 -formic acid, 30% deuterium rate was found at β -position, surprisingly (Scheme 1.2.2a). When I reduced the amount of the d_1 -formic acid, the deuterium ratio at both α - and β -position were reduced (Scheme 1.2.2b). In order to gain insight into the reaction mechanism, I used d_2 -formic acid in the model reaction, to observe complete deuteration of β -position, on the other hand, α position was partially deuterated. The deuterium content at α position added up to around 100% (Scheme 1.2.2c). The main pathway undergoes formate decarboxylation on nickel, hydride insertion of the olefin and subsequent non-enantioselective protonation of resulting enolates. This pathway is distinct from classical dihydride *syn*-addition pathways using noble metal catalysts and hydrogen gas. In addition, H-D exchange was not observed when I treated the hydrogenation product with d_1 -formic acid (Scheme 1.2.2d). I proposed a minor reaction pathway reversible deprotonation that undergo (DuPhos)Ni(H)⁺ and (DuPhos)Ni(0) via reversible deprotonation, which provided reasonable explanation for exchange (DuPhos)Ni(H)⁺ and (DuPhos)Ni(D)⁺.

Scheme 1.2.2 Deuterium labelling experiment and proposed mechanism

1.2.4 Conclusion

I have developed Ni-catalyzed asymmetric transfer hydrogenation of α,β -unsaturated esters and amides using formic acid, which displays good conversion and good enantioselectivity. Nickel is a cheap and abundant metal for a board range of

substrates. Formic acid is a safe, cheap and easy to handle source of hydrogen, unlike explosive high-pressure hydrogen gas.

1.3 Asymmetric hydrogenation of (*E*)- α,β -unsaturated esters using DMF and water as hydrogen resource

The mixture of formic acid and triethylamine is cheaper and more convenient than hydrogenation gas. However, carbon dioxide will be released after β elimination of formate anion. The pressure should be concerned during the reaction process. As such, alternative hydrogen sources are desirable. Water is apparently one of the cheapest reagents in the world as 70% of the earth is covered with water. However, there have been reported only few cases in asymmetric hydrogenation with water as hydride source. Hence, I attempt to use water as hydride source in my nickel-catalyzed asymmetric hydrogenation reactions.

Inoue discovered rhodium-catalyzed asymmetric transfer hydrogenation of olefins with water and zinc.³ They found rhodium would insert into O-H bond of water to form rhodium(III) hydride (Scheme 1.3.1). After reduction by zinc, rhodium(I) species were regenerated. Learned from our previous research, α,β -unsaturated esters could be reduced by nickel(II) hydride complex. Hence, I designed the use of nickel(II) and metallic reductant to generate nickel(0) in situ. The thus-formed nickel(0) complex would insert into H-O bond and form nickel(II) hydride species to catalyse the reaction.

Proposed Mechanism

Scheme 1.3.1 Rhodium-catalyzed asymmetric transfer hydrogenation of olefins with water and zinc

After a few attempts, I found asymmetric hydrogenation of α,β -unsaturated esters processed smoothly with water, zinc and AlCl_3 in DMF at 120 °C. Further control experiments showed the reaction processed without zinc and that no products were formed using solvents other than DMF. The observation suggested that DMF would decompose into formic acid and dimethylamine under high temperature and acid conditions and then formic acid would transfer hydride to nickel(II) center by β elimination.

1.3.1 Reaction optimization

Based on the initially found reaction conditions, various Lewis acids were screened. When no additive was added, the rate of DMF decomposition was too slow and no product was found (Table 1.5). Aluminium chloride was found to be most

effective with 99% yield and 91% *ee* (entry 5). InCl₃, ZnCl₂ and PTSA also provided excellent conversions, however, the *ee* value dropped to 81%. (entry 4,6 and 8)

Table 1.5 The effect of Lewis acid

Entry	Lewis Acid	Yield	<i>ee</i>
1	No additive	NR	-
2	BF ₃ • OEt	66	27
3	LiCl	30	89
4	InCl ₃	99	81
5	AlCl ₃	99	91
6	ZnCl ₂	90	81
7	Zn(OTf) ₂	39	81
8	PTSA	94	78
9	TfOH	65	81
10	AgSbF ₆	57	73
11	AgBF ₄	62	71
12	FeF ₃	35	77

With the optimized Lewis acid, aluminum chloride, I discovered the effect of organic solvents (Table 1.6). Since solvents other than DMF could not provide formate anion, none of them was found effective (entry 2-7).

Table 1.6 The effect of organic solvents

Entry	Solvent	Yield	<i>ee</i>
1	DMF	99	91
2	<i>i</i> PrOH	NR	-
3	EtOH	NR	-
4	MeOH	NR	-
5	DMA	NR	-
6	DMSO	NR	-
7	Dioxane	NR	-

The best temperature was proved to be 120 °C (Table 1.7, entry 3). When the temperature was too low, the conversion of olefin was reduced (entry 1-2). At 90 °C, the decomposition rate of DMF is too slow to give any product.

Table 1.7 The effect of reaction temperature

Entry	Temperature	Yield	<i>ee</i>
1	90	NR	-
2	100	32	91
3	110	100	91

A variety of nickel salts were found reactive, exhibit the same enantioselectivity (Table 1.8). Among those nickel salts, $\text{NiBr}_2(\text{DME})$ provided the highest conversion (entry 1).

Table 1.8 The effect of nickel salt

Entry	Nickel Salt	Yield	<i>ee</i>
1	$\text{NiBr}_2(\text{DME})$	100	91
2	$\text{NiCl}_2(\text{DME})$	98	90
3	$\text{Ni}(\text{OAc})_2$	97	91
4	$\text{Ni}(\text{OTf})_2$	69	91
5	$\text{NiClO}_4 \cdot 6\text{H}_2\text{O}$	92	91

1.3.2 Scope of substrate in Ni-catalyzed asymmetric transfer hydrogenation using DMF and Water

Scheme 1.3.2 Scope of Substrate in Ni-Catalyzed Asymmetric Transfer

Hydrogenation using DMF and water

With the optimized conditions, I screened various α,β -unsaturated esters (Scheme 1.3.2). The methyl, ethyl and *tert*-butyl group on ester were tolerated in the reaction condition and had slight influence on both enantioselectivity. Both electron-rich and -poor substrates were tolerated on aryl rings. Heterocyclic olefins were also

applicable to the reaction. Two cyclic substrates provided high *ee* values and conversions.

1.3.3 Conclusion

In conclusion, I discovered asymmetric transfer hydrogenation of α,β -unsaturated esters with DMF and water as hydride source. Compared with the former work, DMF could provide formic acid and dimethylamine in situ. It is not necessary to add formic acid and triethylamine separately. A board scope of α,β -unsaturated esters provided excellent conversions and *ee* values.

1.4 Experiment section

1.4.1 Genenral

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 THF was freshly distilled from sodium/benzophenone under argon before use. Anhydrous 1,4-dioxane (Aldrich) was stored over activated 4 Å molecular sieve beads in an argon-filled glove

box. Dry toluene was collected from a solvent purification system containing a column of activated alumina (1 m x 2) under argon. Methanol, ethanol and isopropanol were degassed and stored over dried molecular sieve in an argon-filled glove box before use. All anhydrous solvents were stored in Schlenk tubes in the glove box.

Unless noted otherwise, commercially available chemicals were used as received without purification. The GC internal standard, $n\text{-C}_{12}\text{H}_{26}$ and $n\text{-C}_{14}\text{H}_{30}$ was degassed with argon and dried over activated 4 Å molecular sieve beads before use. Flash chromatography was performed using Merck 40-63D 60 Å silica gel. Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument with Agilent J & W GCcolumn 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. ESI/MS analysis was conducted on a ThermoFinnigan LCQ Fleet MS spectrometer. 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 asymmetric transfer hydrogenation of α,β -unsaturated esters

A typical procedure for condition optimization: In an argon-filled glove box, $\text{NiBr}_2(\text{DME})$ (0.9 mg, 0.003 mmol), (*R*)-Me-DuPhos (0.9 mg, 0.003 mmol), *tetra-n*-butylammonium iodide (7.2 mg, 0.02 mmol), indium powder (12.6 mg, 0.11 mmol, Alfa Aesar, 100 mesh, 99.9%) and dry THF (0.3 mL) were charged into a 10-mL reaction tube. After stirring for 10 min, acetic acid (17 μL , 0.3 mmol), (*E*)-ethyl 3-methylcinnamate (19 mg, 0.1 mmol) and GC standard *n*- $\text{C}_{12}\text{H}_{26}$ (10 μL) were added. The reaction mixture was heated with stirring in an oil bath maintained at 80 $^\circ\text{C}$. Aliquots were taken from the reaction mixture after 12 h in the glove box and passed through a short plug of silica gel with Et_2O washing (about 3 mL). The filtrate was subjected to GC analysis to determine the conversion of the olefin and the yield of the product. To determine the enantioselectivity of product, the filtered sample was subjected to chiral HPLC analysis (Daicel Chiralcel OD-H; 2% *i*-PrOH in hexanes; flow rate 0.5 mL/min). The racemic product was prepared by hydrogenation with hydrogen gas (8 bar) over 10% Pd/C in methanol at room temperature.

1.4.3 Isolated products of asymmetric transfer hydrogenation

(*S*)-Methyl 3-phenylbutanoate [1441-20-9]. Methyl (*E*)-3-phenylcrotonate (88 mg, 0.5 mmol) were used. The reaction was complete after 24 h at 80 $^\circ\text{C}$. The product was

isolated by flash chromatography (Et₂O/hexanes 1:20) as colorless oil. Yield: 82 mg, 92%.

$[\alpha]_D^{23} = 19.7^\circ$ ($c = 0.94$, CHCl₃).

Ee: 94%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 98/2, flow rate = 0.5 mL/min.

1 PDA Multi 1 / 200nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	11.045	10605745	49.098
2	23.166	10995491	50.902
Total		21601236	100.000

1 PDA Multi 1 / 200nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	11.137	807617	3.249
2	22.993	24047816	96.751
Total		24855433	100.000

¹H NMR (300 MHz, CDCl₃): δ 7.36-7.16 (m, 5H), 3.62 (s, 3H), 3.36-3.20 (m, 1H), 2.69-2.49 (m, 2H), 1.30 (d, $J = 7.0$ Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 172.9, 145.7, 128.5, 126.7, 126.4, 51.5, 42.8, 36.5, 21.8.

GC-MS (EI): Calcd for C₁₁H₁₄O₂: 178.1. Found: 179.0.

(S)-Ethyl 3-phenylbutanoate [1134-71-0]. Ethyl (*E*)-3-phenyl-2-butenate (95 mg, 0.5 mmol) were used. The reaction was complete after 24 h at 80 °C. The product was isolated by flash chromatography (Et₂O/hexanes 1:20) as colorless oil. Yield: 88 mg, 92%.

$[\alpha]_D^{23} = 25.1^\circ$ ($c = 0.95$, CHCl₃).

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

¹H NMR (300 MHz, CDCl₃): δ 7.41-7.09 (m, 5H), 4.08 (q, $J = 7.1$ Hz, 2H), 3.47-3.18 (m, 1H), 2.67-2.47 (m, 2H), 1.3 (d, $J = 7.0$ Hz, 3H), 1.18 (t, $J = 7.1$ Hz, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 172.4, 145.8, 128.5, 126.8, 126.4, 60.3, 43.0, 36.5, 21.8, 14.2.

GC-MS (EI): Calcd for C₁₁H₁₆O₂: 192.1. Found: 193.0.

A gram-scale transfer hydrogenation for isolation: Under argon, NiBr₂(DME) (30 mg, 0.1 mmol, 2 mol%), (*R*)-Me-DuPhos (38 mg, 0.12 mmol, 2.4 mol%) and dry diglyme (5 mL) were charged into a dry 50-mL Schlenk tube. After stirring for 15 min at room temperature, dry Et₃N (1.4 mL, 10 mmol, 2 equiv), formic acid (0.95 mL,

25 mmol, 5 equiv), ethyl (*E*)-3-phenylcrotonate (0.95 g, 5 mmol) were added. The reaction mixture was heated with vigorous stirring in an oil bath maintained at 90 °C for 3 days until almost full conversion, as monitored by GC. After the reaction mixture was cooled to room temperature, solid NaHCO₃ was added to basify the mixture. After workup and flash chromatography, the product was isolated as colorless oil. 881 mg, 92% yield. 90% ee. If isopropanol was used as the solvent, lower conversion was seen.

(*S*)-*t*-Butyl 3-phenylbutanoate [67217-41-8]. *t*-Butyl (*E*)-3-phenyl-2-butenate (109 mg, 0.5 mmol) were used. The reaction was complete after 24 h at 80 °C. The product was isolated by flash chromatography (Et₂O/hexanes 1:20) as colorless oil. Yield: 102 mg, 93%.

$[\alpha]_D^{23} = 27.3^\circ$ ($c = 0.80$, CHCl₃).

Ee: 88%. Daicel Chiralcel OD-H, n-hexane/isopropanol 99.5/0.5, flow rate = 0.5 mL/min.

^1H NMR (300 MHz, CDCl_3): δ 7.29-7.14 (m, 5H), 3.31-3.14 (m, 1H), 2.60- 2.36 (m, 2H), 1.35 (s, 9H), 1.29 (d, $J = 7.0$ Hz, 3H).

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2$: 220.15. Found: 220.0.

(S)-Ethyl 3-phenylpentanoate [2845-23-0]. (*E*)-Ethyl 3-phenyl-2-pentenoate (102 mg, 0.5 mmol) were used. The reaction completed after 36 h at 80 °C. The product was isolated by flash chromatography (Et_2O /hexanes 1:20) as colorless oil. Yield: 91 mg, 88%.

$[\alpha]_{\text{D}}^{23} = 14.3^\circ$ ($c = 0.91$, CHCl_3).

Ee: 92%. Daicel Chiralcel OD-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	10.613	4145374	50.691
2	21.656	4032387	49.309
Total		8177762	100.000

1 PDA Multi 1 / 200nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	10.599	259613	4.165
2	21.208	5973670	95.835
Total		6233283	100.000

^1H NMR (300 MHz, CDCl_3): δ 7.39-7.16 (m, 5H), 4.03 (q, $J = 7.1$ Hz, 2H), 3.07-2.93 (m, 1H), 2.69-2.48 (m, 2H), 1.80-1.50 (m, 2H), 1.13 (t, $J = 7.1$ Hz, 3H), 0.79 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 172.53, 143.93, 128.34, 127.56, 126.38, 60.19, 43.97, 41.52, 29.14, 14.12, 11.91.

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_2$: 206.1. Found: 206.0.

(S)-Ethyl 3-(4-tolyl)butanoate [1461-11-6]. (*E*)-Ethyl 3-(4-tolyl)-2-butenate (102 mg, 0.5 mmol) were used. The reaction completed after 24 h at 80 °C. The product was isolated by flash chromatography (Et_2O /hexanes 1:20) as colorless oil. Yield: 96 mg, 93%.

$[\alpha]_D^{23} = 26.4^\circ$ ($c = 0.91$, CHCl_3).

Ee: 92%. Daicel Chiralcel OJ-H, n-hexane/isopropanol 99/1, flow rate = 0.5 mL/min.

PeakTable

Peak#	Ret. Time	Area	Area %
1	18.907	392641	49.951
2	19.933	393417	50.049
Total		786058	100.000

PeakTable

Peak#	Ret. Time	Area	Area %
1	18.930	2699524	96.384
2	19.991	101286	3.616
Total		2800810	100.000

^1H NMR (300 MHz, CDCl_3): δ 7.13-7.10 (m, 4H), 4.08 (q, $J = 7.1$ Hz, 2H), 3.38-3.12 (m, 1H), 2.67-2.48 (m, 2H), 2.31 (s, 3H), 1.28 (d, $J = 7.0$ Hz, 3H), 1.19 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 172.5, 142.8, 135.8, 129.2, 126.6, 60.2, 43.1, 36.1, 21.9, 21.0, 14.2.

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_2$: 206.1. Found: 205.9.

(S)-Ethyl 3-(4-anisyl)butanoate [1242409-36-4]. (*E*)-Ethyl 3-(4-anisyl)-2-butenate

(110 mg, 0.5 mmol) were used. The reaction completed after 24 h at 80 °C. The product was isolated by flash chromatography (Et_2O /hexanes 1:20) as colorless oil.

Yield: 104 mg, 94%.

$[\alpha]_D^{23} = 26.2^\circ$ ($c = 0.94$, CHCl_3).

Ee: 92%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 99.5/0.5, flow rate = 0.5 mL/min.

1 PDA Multi 1 / 200nm 4nm

PeakTable

PDA Ch1 200nm 4nm			
Peak#	Ret. Time	Area	Area %
1	16.744	10073862	50.134
2	21.521	10019859	49.866
Total		20093721	100.000

1 PDA Multi 1 / 254nm 4nm

PeakTable

PDA Ch1 254nm 4nm			
Peak#	Ret. Time	Area	Area %
1	17.023	89354	4.093
2	21.784	2093892	95.907
Total		2183246	100.000

^1H NMR (300 MHz, CDCl_3): δ 7.16-7.12 (m, 2H), 6.86-6.81 (m, 2H), 4.07 (q, $J = 7.1$ Hz, 2H), 3.78 (s, 3H), 3.37- 3.14 (m, 1H), 2.71- 2.38 (m, 2H), 1.27 (d, $J = 7.0$ Hz, 3H), 1.18 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 172.4, 158.1, 137.9, 127.7, 113.9, 60.2, 55.3, 43.3, 35.8, 22.0, 14.2.

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_3$: 222.1. Found: 222.0.

(S)-Ethyl 3-(*o*-anisyl)butanoate[128950-12-9]. (*E*)-Ethyl 3-(*o*-anisyl)but-2-enoate

(110 mg, 0.5 mmol), formic acid (10 equiv) and Et_3N (4 equiv) were used. The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (Et_2O /hexanes 1:30) as colorless oil. 82% yield, 89 mg. If a 5:2 mixture of formic acid and Et_3N was used, 71% conversion at 24 hours at 80 °C.

Ee: 80%. Daicel Chiralcel IC-H, *n*-hexane/isopropanol 98/2, flow rate = 0.5 mL/min.

Peak#	Ret. Time	Area	Area %
1	13.950	9822157	50.313
2	15.276	9699917	49.687
Total		19522074	100.000

Peak#	Ret. Time	Area	Area %
1	14.086	70530	9.899
2	14.814	641947	90.101
Total		712477	100.000

^1H NMR (500 MHz, CDCl_3): δ 7.21-7.16 (m, 2H), 6.91 (*ψ*td, $J = 7.5, 1.0$ Hz, 1H), 6.85 (d, $J = 8.1$ Hz, 1H), 4.09 (q, $J = 7.1$ Hz, 2H), 3.83 (s, 3H), 3.72-3.58 (m, 1H), 2.68 (dd, $J = 15.0, 6.0$ Hz 1H), 2.50 (dd, $J = 15.0, 8.9$ Hz 1H), 1.28 (d, $J = 7.0$ Hz, 3H), 1.20 (d, $J = 7.1$ Hz, 3H).

MS (ESI): Calcd for $\text{C}_{13}\text{H}_{19}\text{O}_3$ $[\text{M}+1]$: 223.1. Found: 222.9.

(S)-Ethyl 3-(*m*-tolyl)butanoate[130378-45-9]. (*E*)-Ethyl 3-(*m*-tolyl)but-2-enoate (102 mg, 0.5 mmol) were used. The reaction completed after 24 h at 80 °C. The product was isolated by flash chromatography (Et_2O /hexanes 1:30) as colorless oil. Yield: 91 mg, 88%.

$[\alpha]_{\text{D}}^{23} = 22.0^\circ$ ($c = 0.91$, CHCl_3).

Ee: 94%. Daicel Chiralcel OD-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	7.717	14152343	51.589
2	8.756	13280292	48.411
Total		27432635	100.000

1 PDA Multi 1 / 200nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	7.762	342828	3.159
2	8.827	10510786	96.841
Total		10853614	100.000

^1H NMR (300 MHz, CDCl_3): δ 7.21-7.16 (m, 1H), 7.03-7.01 (m, 3H), 4.09 (q, $J = 7.1$ Hz, 2H), 3.37-3.12 (m, 1H), 2.63-2.33 (m, 2H), 2.33 (s, 3H), 1.29 (d, $J = 6.9$ Hz, 3H), 1.19 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 172.5, 145.8, 138.0, 128.4, 127.6, 127.1, 123.7, 60.2, 43.0, 36.5, 21.8, 21.5, 14.2.

MS (ESI): Calcd for $\text{C}_{13}\text{H}_{19}\text{O}_2$ $[\text{M}+1]$: 207.1. Found: 206.8.

(S)-Ethyl 3-(2-naphthyl)butanoate [52086-00-7]. (*E*)-Ethyl 3-(2-naphthyl)-2-

butenoate (120 mg, 0.5 mmol) were used. The reaction completed after 24 h at 80 °C.

The product was isolated by flash chromatography (Et_2O /hexanes 1:20) as colorless oil. Yield: 111 mg, 92%.

$[\alpha]_{\text{D}}^{23} = 25.1^\circ$ ($c = 0.91$, CHCl_3).

Ee: 91%. Daicel Chiralcel OJ-H, n-hexane/isopropanol 95/5, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	18.245	35527713	49.929
2	19.867	35628083	50.071
Total		71155796	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	18.668	449656	4.639
2	20.290	9242925	95.361
Total		9692581	100.000

^1H NMR (300 MHz, CDCl_3): δ 7.81-7.78 (m, 3H), δ 7.66 (s, 1H), δ 7.48-7.26 (m, 3H), 4.07 (q, $J = 7.0$ Hz, 2H), 3.54-3.34 (m, 1H), 2.78-2.56 (m, 2H), 1.39 (d, $J = 7.0$ Hz, 3H), 1.17 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 172.4, 143.2, 133.6, 132.4, 128.2, 127.7, 127.6, 126.0, 125.6, 125.4, 125.0, 60.3, 43.0, 36.7, 21.9, 14.2.

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{18}\text{O}_2$: 242.1. Found: 242.0.

(*S*)-Ethyl 3-(2-thienyl)butanoate [27050-13-1]. (*E*)-Ethyl 3-(2-thienyl)-2-butenate (120 mg, 0.5 mmol) were used. The reaction completed after 24 h at 80 °C. The product was isolated by flash chromatography (Et_2O /hexanes 1:20) as colorless oil. Yield: 90 mg, 91%.

$[\alpha]_{\text{D}}^{23} = 17.6^\circ$ ($c = 0.80$, CHCl_3).

Ee: 89% ee. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 99.5/0.5, flow rate = 0.5 mL/min.

1 PDA Multi 1 / 223nm 4nm

PeakTable			
PDA Ch1 223nm 4nm			
Peak#	Ret. Time	Area	Area %
1	13.380	896008	50.060
2	23.021	893859	49.940
Total		1789867	100.000

1 PDA Multi 1 / 225nm 4nm

PeakTable			
PDA Ch1 225nm 4nm			
Peak#	Ret. Time	Area	Area %
1	13.321	890248	5.462
2	22.546	15409287	94.538
Total		16299535	100.000

^1H NMR (300 MHz, CDCl_3): δ 7.13 (dd, $J = 5.1, 1.2$ Hz, 1H), 6.91 (dd, $J = 5.1, 3.5$ Hz, 1H), 6.84-6.83 (m, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 3.59 (ddq, $J = 8.0, 6.9, 6.8$ Hz, 1H), 2.69 (dd, $J = 15.2, 6.8$ Hz, 1H), 2.55 (dd, $J = 15.2, 8.0$ Hz, 1H), 1.39 (d, $J = 6.9$ Hz, 3H), 1.22 (t, $J = 7.1$ Hz, 3H).

GC-MS (EI): Calcd for $\text{C}_{10}\text{H}_{14}\text{O}_2\text{S}$: 198.0. Found: 198.0.

(*S*)-Ethyl 3-(3-pyridyl)butanoate [71351-56-9]. (*E*)-Ethyl 3-(3-pyridyl)-2-butenolate (96 mg, 0.5 mmol) were used. The reaction completed after 36 h at 80 °C. The product was isolated by flash chromatography (Et_2O /hexanes 1:20) as colorless oil. Yield: 90 mg, 92%.

$[\alpha]_{\text{D}}^{23} = 21.9^\circ$ ($c = 0.99$, CHCl_3).

Ee: 82%. Daicel Chiralcel AS-H, *n*-hexane/isopropanol 98/2, flow rate = 0.5 mL/min.

^1H NMR (300 MHz, CDCl_3): δ 8.50 (d, $J = 2.1$ Hz, 1H), 8.45 (dd, $J = 4.8, 1.6$ Hz, 1H), 7.55-7.52 (m, 1H), 7.24-7.20 (m, 1H), 4.07 (q, $J = 7.1$ Hz, 2H), 3.37-3.23 (m, 1H), 2.64-2.54 (m, 2H), 1.32 (d, $J = 7.0$ Hz, 3H), 1.17 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 171.8, 148.8, 147.9, 140.8, 134.2, 123.4, 60.5, 42.5, 34.1, 21.6, 14.1.

GC-MS (EI): Calcd for $\text{C}_{11}\text{H}_{15}\text{NO}_2$: 193.1. Found: 194.0.

(S)-Ethyl 3-(4-(trifluoromethyl)phenyl)butanoate. (*E*)-Ethyl 3-(4-(trifluoromethyl)phenyl)-2-butenate (129 mg, 0.5 mmol) were used. The reaction completed after 36 h at 80 °C. The product was isolated by flash chromatography (Et_2O /hexanes 1:20) as colorless oil. Yield: 120 mg, 92%.

$[\alpha]_D^{23} = 17.1^\circ$ ($c = 1.09$, CHCl_3).

Ee: 90%. Daicel Chiralcel IC-H, n-hexane/isopropanol 99.9/0.1, flow rate = 0.5 mL/min.

^1H NMR (300 MHz, CDCl_3): δ 7.56 (d, $J = 8.2$ Hz, 2H), 7.34 (d, $J = 8.2$, 2H), 4.07 (q, $J = 7.1$ Hz, 2H), 3.44-3.27 (m, 1H), 2.71-2.45 (m, 2H), 1.32 (d, $J = 7.0$ Hz, 3H), 1.17 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 171.9, 149.76, 128.75 (q, $J = 32.4$ Hz), 127.2, 125.5 (q, $J = 3.7$ Hz), 124.2 (q, $J = 271.8$ Hz), 60.42, 42.55, 36.38, 21.71, 14.11

^{19}F NMR (376 MHz, CDCl_3): δ -62.4.

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{15}\text{F}_3\text{O}_2$: 260.1. Found: 260.0.

(S)-Ethyl 2-(1-tetralinyl)acetate. The (*E*)-isomer of starting material was used. The reaction completed after 24 h at 80 °C. The product was isolated by flash chromatography (Et_2O /hexanes 1:15) as colorless oil. Yield: 107 mg, 98%.

$[\alpha]_{\text{D}}^{23} = 1.2$ ($c = 1$, CHCl_3)

Ee: 94%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 98/2, flow rate = 1.0 mL/min.

^1H NMR (500 MHz, CDCl_3): δ 7.25-6.78 (m, 4H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.35 (m, 1H), 2.79-2.73 (m, 2H), 2.70 (dd, $J = 15.2, 4.8$ Hz, 1H), 2.52 (dd, $J = 15.2, 9.9$ Hz, 1H), 1.95-1.67 (m, 4H), 1.27 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 172.9, 139.4, 137.2, 129.3, 128.3, 126.1, 125.9, 60.4, 42.1, 34.7, 29.6, 28.3, 19.7, 14.4.

MS (ESI): Calcd for $\text{C}_{14}\text{H}_{19}\text{O}_2$ $[\text{M}+\text{H}]$: 219.1. Found: 219.0

(S)-Ethyl 2-(4-chromanyl)acetate. The (*E*)-isomer of starting material was used.

The reaction completed after 24 h at 80 °C. The product was isolated by flash chromatography (EtOAc/hexanes 1:4) as colorless oil. Yield: 108 mg, 98%.

$[\alpha]_D^{23} = 6.8$ ($c = 1$, CHCl_3)

Ee: 93%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 1.0 mL/min.

^1H NMR (500 MHz, CDCl_3): δ 7.12-7.07 (m, 2H), 6.88-6.82 (m, 1H), 6.79 (d, J = 8.1 Hz, 1H), 4.20-4.13 (m, 4H), 3.35 (m, 1H), 2.78 (dd, J = 15.6, 4.7 Hz, 1H), 2.51 (dd, J = 15.6, 10.0 Hz, 1H), 2.16-2.12 (m, 1H), 1.83 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 172.1, 154.6, 128.7, 127.8, 124.6, 120.4, 117.1, 63.2, 60.6, 41.4, 30.5, 27.4, 14.3.

MS (ESI): Calcd for $\text{C}_{13}\text{H}_{17}\text{O}_3$ $[\text{M}+\text{H}]$: 221.1 Found: 221.0

(S)-3-Phenylbutyronitrile [211203-12-5]. (*E*)-3-Phenylbut-2-enenitrile (71 mg, 0.5 mmol) were used. The reaction completed after 24 h at 80 °C. The product was isolated by flash chromatography (Et_2O /hexanes 1:15) as colorless oil. Yield: 62 mg, 85%.

$[\alpha]_{\text{D}}^{23} = -2.81^\circ$ (c = 0.80, CHCl_3).

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

^1H NMR (300 MHz, CDCl_3): δ 7.42-7.20 (m, 5H), 3.28-3.02 (m, 1H), 2.74-2.44 (m, 2H), 1.46 (d, $J = 7.0$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 143.2, 128.9, 127.4, 126.6, 118.6, 36.6, 26.4, 20.7.

MS (ESI): Calcd for $\text{C}_{10}\text{H}_{12}\text{N}$ $[\text{M}+\text{H}]$: 146.2. Found: 146.0.

(S)-N,N-Diethyl 3-phenylbutyramide [857779-92-0]. *N,N*-diethyl (*E*)-3-

methylcinnamide (110 mg, 0.5 mmol) were used. The reaction completed after 48 h at 80 °C. The product was isolated by flash chromatography (Ethyl acetate/hexanes 1:30) as colorless oil. Yield: 96 mg, 87%.

82% ee. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 98/2, flow rate = 0.5 mL/min.

^1H NMR (500 MHz, CDCl_3): δ 7.30-7.17 (m, 5H), 3.45-3.34 (m, 2H), 3.32-3.25 (m, 1H), 3.23-3.12 (m, 1H), 2.59-2.46 (m, 2H), 1.33 (d, $J = 7.0$ Hz, 3H), 1.12-1.02 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ 170.8, 146.6, 128.4, 126.9, 126.2, 41.9, 41.7, 40.2, 36.7, 21.4, 14.4, 13.0.

GC-MS (EI): Calcd for $\text{C}_{11}\text{H}_{15}\text{NO}_2$ M: 219.3. Found: 219.1.

(S)-Dimethyl 2-phenylsuccinate (*E*)-Dimethyl 2-phenylfumarate (110 mg, 0.5 mmol) was used. NiBr_2 (DME) (6.0 mg, 0.02 mmol), (*S,S',R,R'*)-TangPhos (6.9 mg, 0.024 mmol) and dry toluene (1.5 mL) were used. After stirring for 10 min at room temperature, Et_3N (140 μL , 1.0 mmol, 2 equiv), formic acid (95 μL , 2.5 mmol, 5 equiv) and (*Z*)-olefin (0.5 mmol) were added. The reaction completed after 24 h at 60 $^\circ\text{C}$. The product was isolated by flash chromatography (Et_2O /hexanes 1:20) as colorless oil. Yield: 108 mg, 97%. When Me-DuPhos ligand was used in *i*-PrOH at 80 $^\circ\text{C}$, 65% ee was obtained.

$[\alpha]_D^{23} = 114.9^\circ$ ($c = 0.82$, CHCl_3).

Ee: 94%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 80/20, flow rate = 1.0 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.35-7.27 (m, 5H), 4.09 (dd, J = 10.1, 5.2 Hz, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 3.28 (dd, J = 17.0, 10.1 Hz, 1H), 2.67 (dd, J = 17.0, 5.2 Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ 173.4, 172.0, 137.7, 128.9, 127.7, 127.7, 52.3, 51.8, 47.1, 37.6.

MS (ESI): Calcd for $\text{C}_{12}\text{H}_{15}\text{O}_4$ [$\text{M}+1$]: 223.1. Found: 222.8.

(S)-Ethyl 3-benzylbutanoate [72277-22-6]. Ethyl (*E*)-3-benzyl-2-butenate (102 mg, 0.5 mmol) was used. The reaction was complete after 48 h at 80 °C. The product was isolated by flash chromatography (Et_2O /hexanes 1:50) as colorless oil. Yield: 90 mg, 87%.

54% ee. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 99.5/0.5, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.33-7.24 (m, 2H), 7.22-7.13 (m, 3H), 4.11 (q, $J = 7.1$ Hz, 2H), 4.13-4.08 (m, 2H), 2.37-2.21 (m, 2H), 2.20-2.08 (m, 1H), 1.24 (t, $J = 7.1$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3): δ 173.1, 140.3, 129.2, 128.3, 126.0, 60.2, 43.0, 41.2, 32.3, 19.6, 14.3.

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_2$: 206.3. Found: 206.0.

The reaction was conducted using 0.1 mmol of the olefin. The hydrogenation product was not detected. Instead a byproduct was formed, probably via oxidative addition of nickel(0) to an allylic C-F bond to form a nickel-allyl species, which then formed a new C-H bond via C-H reductive elimination with a hydride.

^1H NMR (500 MHz, CDCl_3): δ 7.38-7.31 (m, 4H), 7.31-7.26 (m, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 3.39 (s, 2H), 1.20 (t, $J = 7.1$ Hz, 3H).

^{19}F NMR (282 MHz, CDCl_3): δ -87.9 (dt, $J = 35.1, 2.2$ Hz), -89.2 (d, $J = 35.2$ Hz).

GC-MS (EI): Calcd for $\text{C}_{12}\text{H}_{12}\text{F}_2\text{O}_2$: 226.2. Found: 226.0.

Deuterium labelling experiments

A general procedure using deuterated formic acid: In an argon-filled glove box, $\text{NiBr}_2(\text{DME})$ (2.4 mg, 0.008 mmol), (*R*)-Me-DuPhos (3.2 mg, 0.0096 mmol) and dry PhCF_3 (0.6 mL) were charged into a 10-mL reaction tube. Isopropanol was not used to avoid complication of H/D exchange with the solvent. After stirring for 10 min, Et_3N (56 μL , 0.4 mmol, 2 equiv), *deuterio*-formic acid (38 μL , 1.0 mmol, 5 equiv) and (*E*)-ethyl 3-phenylbut-2-enoate (0.2 mmol) were added. The reaction mixture was heated with stirring in an oil bath maintained at 80 $^\circ\text{C}$ for 24 h. After cooling down, the reaction mixture was diluted with 3 mL of EA/hexanes (1:4) and passed through a short plug of silica gel washing with another 5 mL of EA/hexanes (1:4). The solvent was evaporated to give the product. The deuterium content of the product was analyzed by quantitative ^1H NMR spectroscopy. The enantioselectivity (ee) of the product was determined by chiral HPLC analysis using Daicel Chiralcel OD-H, *n*-hexane/isopropanol 98/2, flow rate = 0.5 mL/min.

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Chapter 2 Nickel-Catalyzed Asymmetric Hydrogenation Using Acetic Acid and Indium

2.1 Introduction

Asymmetric hydrogenation is one of the most powerful methods to prepare chiral fine chemicals in pharmaceutical and agrochemical industries.¹⁻³ However, most hydrogenation processes rely on the use of noble metal catalysts, such as ruthenium, rhodium and iridium, which are rare and expensive. At the same time, operators must take special trainings to handle with high pressure and explosive hydrogen gas. Hence, many studies have been disclosed in asymmetric transfer hydrogenation.⁴ However, only limited cases of asymmetric hydrogenation using acid or water as hydride donor have been reported. Since hydride would react with proton source rapidly, the key step, umpolung of proton cation into hydride, is difficult.

2.1.1 Hydrogenation with water and weak acids

In the past decade, several processes of transfer hydrogenation of simple unsaturated compounds were published that used water or acids as hydrogen source in the presence of main group metals as reductants.⁵⁻⁹ To the best of my knowledge, no example has been published in asymmetric version of such hydrogenation.

In 2006 Inoue and coworkers discovered rhodium-catalyzed transfer hydrogenation of olefins with water and zinc powder (Scheme 2.1.1).¹⁰ Unfunctionalized simple olefins and α,β -unsaturated ketones were reduced smoothly.

However, more hindered 3,5,5-trimethyl-2-cyclohexenone only gave 15% yield. Hydrogen gas was not involved in the reaction. In a proposed catalytic cycle, a rhodium(I) complex undergoes oxidative addition of the H-O bond of water to generate a rhodium(III) hydride complex. Then rhodium(III) hydride undergoes olefin insertion and then gets reduced by zinc to regenerate the rhodium(I) complex. No hydrogen gas evolution was found with gas burette during the reaction.

Proposed Mechanism

Scheme 2.1.1 Rh-catalyzed hydrogenation reaction of simple olefins

Oltra's group reported palladium-catalyzed transfer hydrogenation of both alkynes and alkenes with titanocene(III) chloride and water (Scheme 2.1.2).¹¹ Using the above combination, they found that Lindlar catalyst promoted hydrogenation of alkynes to

give only (*Z*)-alkenes. This phenomenon indicated monohydride transfer was forbidden in the process, because otherwise (*E*)-configuration of alkenes would be obtained. Finally, they proved two equivalents of titanocene(III) helped transfer of two hydrides from water into palladium center followed by dihydride transfer process to provide the products.

Scheme 2.1.2 Palladium-catalyzed transfer hydrogenation of alkenes and alkynes

Stokes *et al.* discovered palladium-catalyzed transfer hydrogenation of simple unfunctionalized alkenes with water as hydrogen donor and $B_2(OH)_4$ as a reductant (Scheme 2.1.3).¹² Deuteration can also be conducted with D_2O . After palladium(0) insertion into B-B bond of tetrahydroxydiboron, water would coordinate to the Pd-bound boryl group and undergo β hydride elimination to produce a Pd hydride species.

Scheme 2.1.3 Palladium-catalyzed transfer hydrogenation of alkenes with water and tetrahydroxydiboron

Plietker *et al.* discovered Ru complexes can be used for selective reduction of alkynes, ketones and nitro compounds using water as a hydrogen donor in the presence of zinc (Scheme 2.1.4).¹³ Interestingly, the chemoselectivity can be controlled by using different additives. In the presence of CuI, alkynes were reduced into alkenes selectively while ketones and nitro compounds were reduced in the presence of KOH. The reason for the difference was unknown.

Scheme 2.1.4 Ru-catalyzed transfer hydrogenation of alkynes, ketones and with water

The combination of lithium and nickel salts provided alternative reagents for transfer hydrogenation. In 2006, Yus *et al.* reported conjugate reduction of ketones promoted by nickel(0) nanoparticles generated in situ (Scheme 2.1.5).¹⁴ A polymer-supported biphenyl can be used as the electron carrier catalyst in the reaction.

Scheme 2.1.5 Nickel-catalyzed reduction of ketones

Cohen *et al.* later reexamined Yus' procedure and found that a combination of lithium and hydrated salts $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ or $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ allowed stereoselective hydrogenation of ketones (Scheme 2.1.6).¹⁵ Monocyclic and bicyclic six-membered ring ketones were reduced with high diastereoselectivity and the result was different from Yus method which includes a biaryl electron transfer catalyst. The hydrogen source was the hydrated transition metal salts.

Scheme 2.1.6 Stereoselective hydrogenation of ketones with lithium and hydrated

salts

In 2015, Moran et al. published a nickel-catalyzed hydrogenation of alkynes to alkenes with zinc and formic acid (Scheme 2.1.7).¹⁶ This method was applicable to wide range of substrates providing terminal, (*E*)- and (*Z*)-alkenes selectively. In the presence of triphos ligand, only (*E*)-olefins were obtained. However, deuterium labeling experiments are still required to determine whether the real hydride comes from the formyl group of formic acid.

Scheme 2.1.7 Nickel-catalyzed hydrogenation of alkynes to alkenes with zinc and formic acid

2.2 Nickel-catalyzed asymmetric hydrogenation reactions of C=C and C=N bonds using acetic acid and indium

Previously, our group disclosed enantioselective nickel-catalyzed asymmetric transfer hydrogenation using formic acid to produce a variety of chiral compounds. However, in the reaction process, carbon dioxide accumulates and can inhibit further decarboxylation of formate in closed vessels. Furthermore, at high turnovers, increased pressure of carbon dioxide is a concern. To solve the pressure problem, alternative hydride sources are demanded.

The key step in nickel-catalyzed asymmetric transfer hydrogenation is the formation of nickel hydride intermediate. As an alternative hydride donor, acetic acid is attractive as it can be collected from fermented food easily. Transferring proton from acetic acid or other industrially available weak organic acid to form nickel hydride will broaden the horizon in asymmetric transfer hydrogenation. However, only a few cases have been reported using weak acids or water as hydride source. The key step, umpolung of proton cation in protic conditions, is difficult since the resulting hydride would react with proton rapidly.

In the last chapter, I found that the reaction of *p*-chloro- β -methyl cinnamate was accompanied by reduction of the C-Cl bond to a C-H bond, which indicated the oxidative addition of C-Cl bond into the a nickel(0) species. In addition, during deuterium labeling experiments using HCOOD, I observed the deuteration of the β position of α,β -unsaturated esters. I proposed a minor reaction pathway involving reversible deprotonation/protonation between (DuPhos)Ni(H)⁺ and (DuPhos)Ni(0), which provided reasonable explanation for the exchange between (DuPhos)Ni(H)⁺ and (DuPhos)Ni(D)⁺. This pathway reveals that nickel(0) species could possibly transfer proton cation into hydride species, which is applicable in nickel-catalyzed asymmetric hydrogenation reactions. The nickel(0) species could be generated in situ by the reduction of nickel(II) with reductive metals. Hence, I try to carry out nickel-catalyzed asymmetric hydrogenation of α,β -unsaturated esters with acetic acid as hydride source.

2.2.1 Reaction optimization

I chose (*E*)-ethyl 3-methylcinnamate as a model compound to search for suitable reaction conditions and nickel catalysts. After a few attempts, I found that a combination of weak organic acids and indium powder enabled asymmetric hydrogenation to proceed. After screening of diphosphine ligands, electron-rich diphosphine ligands were found to be active (Table 2.1). In particular, commercially available (*R*)-Me-DuPhos provide the desired product in 84% yield and 94% *ee* (entry 1). However, (*R*)-Et-DuPhos and (*R*)-*i*Pr-DuPhos did not catalyze the reaction because of steric effect of the bulkier groups (entry 2 and 3). (*R*)-Me-BPE and (*R*)-Et-BPE also provided relatively high enantioselectivity, but the yield dropped to 72% and 43% (entry 4 and 5), respectively. Other commercially available diphosphines such as (*S*)-binaphine, (*S,S*)-Chiraphos and (*R*)-BINAP did not afford the desired products (entry 6-11).

Table 2.1 The effect of chiral ligands

Entry	Ligand	Conv (%)	Yield (%)	Ee (%)
1	 (<i>R,R</i>)-Me-DuPhos	84	84	94

2	<p><i>(R,R)</i>-Et-DuPhos</p>	0	0	-
3	<p><i>(R,R)</i>-iPr-DuPhos</p>	0	0	-
4	<p><i>(R,R)</i>-Me-BPE</p>	72	72	86
5	<p><i>(R,R)</i>-Et-BPE</p>	43	42	86
6	<p><i>(S,S)</i>-Ph-BPE</p>	<5	<5	-
7	<p><i>(R)</i>-QuinoxP*</p>	<5	<5	-

8	(1 <i>S</i>)-TangPhos	0	0	-
9	(1 <i>S</i>)-DuanPhos	0	0	-
9	(<i>R,S</i>)-CyPF-Cy	0	0	-
10	(<i>S,S</i>)-Chiraphos	0	0	-
11	(<i>R</i>)-BINAP	0	0	-

With the optimized ligand, I next explored different nickel salts (Table 2.2). The enantioselectivity was virtually unaffected by the precatalyst. The highest yield was obtained using NiBr₂(DME) (entry 1).

Table 2.2 The effect of nickel salts

Enty	Nickel Salt	Conv (%)	Yield (%)	Ee (%)

1	NiBr ₂ (DME)	82	81	94
2	NiCl ₂ (DME)	78	77	94
3	NiBr ₂	63	62	94
4	NiCl ₂	57	57	92
5	NiI ₂	56	54	94
6	Ni(OTf) ₂	70	70	92

Then, I explored metal powders as the terminal reductants in the model reaction (Table 2.3). When I used magnesium powder, only 39% yield and 60% *ee* were obtained (entry 2). Manganese and zinc powder provided 80% *ee*, or higher enantioselectivity. The best result was gained using indium, which provided satisfactory 94% *ee* (entry 3-6). Note that at least 1 equivalent of Indium was necessary for high conversion, as the use of 0.5 equivalent of In afforded only 52% yield (entry 6).

Table 2.3 The effect of metal reductants

$ \begin{array}{c} \text{Me} \\ \\ \text{Ph}-\text{C}=\text{CH}-\text{CO}_2\text{Et} \end{array} \xrightarrow[\text{80 } ^\circ\text{C, 12 h}]{\begin{array}{l} \text{NiBr}_2(\text{DME}) \text{ 3 mol\%} \\ (R)\text{-MeDuPhos 3 mol\%} \\ \text{Metals + AcOH (3.0 equiv)} \\ (n\text{-Bu})_4\text{NI (0.2 equiv), THF} \end{array}} \begin{array}{c} \text{Me} \\ \\ \text{Ph}-\text{CH}-\text{CH}_2-\text{CO}_2\text{Et} \end{array} $					
Entry	Metal	Equivalent	Conv (%)	Yield (%)	Ee (%)
1	Mg	0.5	13	12	47
2	Mg	1.1	40	39	60
3	Mn	0.5	27	26	80
4	Mn	1.1	40	39	89

5	Zn	0.5	13	13	87
6	Zn	1.1	11	10	88
7	In	0.5	52	52	94
8	In	1.1	84	84	94
9	In	3.0	86	86	94

I have screened different weak organic acids (Table 2.4). I obtained the desired product from the model reaction in 81% yield and 94% *ee* with acetic acid after 12 hours (entry 1). In pure water, low yield resulted (entry 6). Other weak organic acids, pivalic acid and benzoic acid, could provide moderate yields and excellent enantioselectivity (entry 2 and 3). On the other hand, stronger acids such as *p*-PTSA and oxalic acid led to hydrogen gas evolution with indium powder and no desired product was produced (entry 4 and 5). Previously, Chirik et al reported that hydrogenation of the same α,β -unsaturated ester required hydrogen gas of 100 psi at 50 °C.¹⁷ Therefore, conditions with acetic acid did not involve hydrogenation using in situ generated hydrogen gas.

Table 2.4 The effect of acids

Enty	Acid	Conv (%)	Yield (%)	Ee (%)
1	AcOH	82	81	94

2	PivOH	78	77	92
3	PhCO ₂ H	65	65	93
4	<i>p</i> -Tosylic acid	<5%	<5%	-
5	(COOH) ₂	<5%	<5%	-
6	Water	<5%	<5%	-

During condition optimization, I found a surprising additive effect of *n*-Bu₄NI, which improved the the reaction rate significantly (Table 2.5). In the absence of *n*-Bu₄NI, only 29% yield was obtained (entryl 1). In comparison, the use of *n*-Bu₄NBr and *n*-Bu₄NCl only led to 10% and 44% yield after 12 h (entry 4 and 5).

Table 2.5 The effect of *n*-Bu₄NI equivalent

Enty	Equiv (x)	Conv (%)	Yield (%)	Ee (%)
1	0	29	29	93
2	0.2	83	83	94
3	0.5	84	84	92
4	<i>n</i> -Bu ₄ NBr 0.2	10	10	94
5	<i>n</i> -Bu ₄ NCl 0.2	47	44	93

The reaction proceed smoothly in all the solvents I tested (Table 2.6). Tetrahydrofuran proved to be the most efficient solvent, which gave 84% yield and

94% *ee* (entry 1).

Table 2.6 The effect of solvents

Entry	Solvent	Conv (%)	Yield (%)	Ee (%)
1	THF	84	83	94
2	DME	60	60	93
3	diglyme	78	77	93
4	MeOH	70	70	94
5	EtOH	73	71	94
6	<i>i</i> -PrOH	39	39	94
7	DMF	68	67	94

2.2.2 Scope of substrates for Ni-catalyzed asymmetric transfer hydrogenation using acetic acid and indium

I found that cinnamate derivatives bearing β electron-rich and -poor aryl rings furnished high enantioselectivity and high conversion (Scheme 2.2.1). Heterocycles such as thiophene and pyridine were also tolerated. Additionally, two cyclic substrates reacted smoothly. The β -position did not tolerate isopropyl and *t*-butyl groups due to slow reaction rates. An acrylonitrile derivative also reacted to give the product in high yield and good *ee* values.

Me

70

Scheme 2.2.2 Nickel-catalyzed reductive amination of ketones and benzhydrazide using acetic acid and indium powder

Chiral β -amino acids are important building blocks in the synthesis of chiral pharmaceuticals, for example, Ampicillin (antibiotic drug) and Taxol (anti-cancer drug) (Scheme 2.2.3).¹⁸⁻¹⁹

Scheme 2.2.3 Chiral β -amino acids in bioactive molecules

Under the optimized conditions, various (*Z*)- β -(acylamido)acrylates were hydrogenated to form chiral β -amino acid precursor (Scheme 2.1.4). Electronic perturbations on the β -aryl rings were well tolerated. When 1-naphthyl ring was present

on the β -carbon, the ee dropped to 84%. I also found that a phthalimide group can serve as a directing group in place of the β -acetamide in the model substrate. To my disappointment, α -(acylamido)acrylate derivatives gave only moderate ee.

Scheme 2.2.4 Nickel-catalyzed asymmetric transfer hydrogen of (*Z*)- β -(acylamido)acrylates using acetic acid and indium powder

2.2.3 Proposed reaction mechanism

Scheme 2.2.5 Deuterium labelling experiment and proposed mechanism

First, the nickel(II) species was reduced to nickel(0) species in the presence of indium powder. Then I proposed a reaction pathway involving reversible deprotonation that undergoes $(DuPhos)Ni(H)^+$ and $(DuPhos)Ni(0)$ via reversible deprotonation. Then the olefin insertion to the formed nickel(II) hydride species and subsequent non-enantioselective protonation of resulting enolates (Scheme 2.2.5).

2.2.4 Conclusion

I have discovered that indium metal and weak acids such as acetic acid and benzoic acid can be used in nickel-catalyzed hydrogenation of unsaturated bonds under mild conditions, in place of hydrogen gas. Cinnamates, β -dehydroacetamidoesters and hydrazones reacted smoothly to give the chiral products in good ee values. The process avoids the use of explosive hydrogen gas. In addition, indium is a metal of low toxicity with a human tolerance (LD_{50} 7.5 mg/kg for rats)²⁰.

2.3 Experiment section

2.3.1 General

All NMR spectra were acquired on Bruker AV 500 MHz, BBFO 400 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 THF was freshly distilled from sodium/benzophenone under argon before use and stored in an argon filled glove box. Anhydrous 1,4-dioxane (Aldrich) was stored over activated 4 Å molecular sieve beads in an argon-filled glove box. Dry toluene was collected from a solvent purification system containing a column of activated alumina (1 m x 2) under

argon. Methanol, ethanol and isopropanol were degassed and stored over dried molecular sieve in an argon-filled glove box before use. All anhydrous solvents were stored in Schlenk tubes in the glove box.

Unless noted otherwise, commercially available chemicals were used as received without purification. The GC internal standard, *n*-C₁₂H₂₆ and *n*-C₁₄H₃₀ was degassed with argon and dried over activated 4 Å 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. ESI/MS analysis was conducted on a Thermo Finnigan LCQ Fleet MS spectrometer. 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*.

2.3.2 Condition optimization for asymmetric transfer hydrogenation of α,β -unsaturated esters

A typical procedure for condition optimization: In an argon-filled glove box, NiBr₂(DME) (0.9 mg, 0.003 mmol), (*R*)-Me-DuPhos (0.9 mg, 0.003 mmol), *tetra-n*-butylammonium iodide (7.4 mg, 0.02 mmol), indium powder (12.6 mg, 0.11 mmol,

Alfa Aesar, 100 mesh, 99.9%) and dry THF (0.3 mL) were charged into a 10-mL Schlenk tube. After stirring for 10 min at rt, acetic acid (17 μ L, 0.3 mmol), (*E*)-ethyl 3-methylcinnamate (19 mg, 0.1 mmol) and GC standard *n*-C₁₂H₂₆ (10 μ L) were added. The reaction mixture was heated with stirring in an oil bath maintained at 80 °C. Aliquots were taken from the reaction mixture after 12 h in the glove box and passed through a short plug of silica gel with Et₂O washing (about 3 mL). The filtrate was subjected to GC analysis to determine the conversion of the olefin and the yield of the product. To determine the enantioselectivity of product, the filtered sample was subjected to chiral HPLC analysis (Daicel Chiralcel OD-H; 2% *i*-PrOH in hexanes; flow rate 0.5 mL/min). The racemic product was prepared by hydrogenation with hydrogen gas (8 bar) over 10% Pd/C in methanol at room temperature.

2.3.3 Procedure of asymmetric transfer hydrogenation

A general procedure for asymmetric hydrogenation of α,β -unsaturated esters: In an argon-filled glove box, NiBr₂(DME) (2.8 mg, 0.009 mmol), (*R*)-Me-DuPhos (2.8 mg, 0.009 mmol), *tetra-n*-butylammonium iodide (22 mg, 0.06 mmol), indium powder (37.9 mg, 0.33 mmol) and dry THF (0.6 mL) were charged into a dry 10-mL Schlenk tube. After stirring for 15 min at room temperature, acetic acid (51 μ L, 0.9 mmol, 3 equiv), an olefin (0.3 mmol) and GC standard *n*-C₁₂H₂₆ (10 μ L) were added. The reaction mixture was heated with vigorous stirring in an oil bath maintained at 80 °C, until the olefin was fully or almost fully consumed as monitored by GC. After the reaction mixture was cooled to room temperature, solid NaHCO₃ was added to basify

the mixture. The residue was dry loaded on a silica gel column and purified by flash chromatography using ethyl acetate and hexanes as eluent. The enantioselectivity (ee) of the purified product was determined by chiral HPLC analysis with Daicel Chiralcel columns. The use of Schlenk tubes and a vacuum manifold instead of a glove box gave similar results.

(S)-Ethyl 3-phenylbutanoate [1134-71-0]. The product was isolated by flash chromatography (Et₂O/hexanes 1:20) as colorless oil. Yield: 53 mg, 92%. 94% ee. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 98/2, flow rate = 0.5 mL/min.

1 PDA Multi 1 / 200nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	10.024	14659864	49.045
2	15.586	15230861	50.955
Total		29890724	100.000

1 PDA Multi 1 / 200nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	9.934	100777	3.140
2	15.128	3108225	96.860
Total		3209003	100.000

¹H NMR (400 MHz, CDCl₃): δ 7.33-7.15 (m, 5H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.34-3.21 (m, 1H), 2.66-2.46 (m, 2H), 1.30 (d, *J* = 7.0 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

GC-MS (EI): Calcd for C₁₂H₁₆O₂ [M]⁺: 192.1 Found: 192.1.

(S)-Methyl 3-phenylbutanoate [1441-20-9]. The product was isolated by flash

chromatography (Et₂O/hexanes 1:20) as colorless oil. Yield: 49 mg, 92%.

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

¹H NMR (400 MHz, CDCl₃): δ 7.36-7.27 (m, 2H), 7.24-7.16 (m, 3H), 3.62 (s, 3H),

3.40-3.21 (m, 1H), 2.68-2.50 (m, 2H), 1.30 (d, *J* = 6.9 Hz, 3H).

GC-MS (EI): Calcd for C₁₁H₁₄O₂ [M]⁺: 178.1 Found: 178.1.

(S)-Ethyl 3-phenylpentanoate [2845-23-0]. The product was isolated by flash

chromatography (Et₂O/hexanes 1:20) as colorless oil. Yield: 54 mg, 87%.

Ee: 93%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 99/1, flow rate = 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.33-7.26 (m, 2H), 7.23-7.10 (m, 3H), 4.03 (q, *J* = 7.1

Hz, 2H), 3.13-2.92 (m, 1H), 2.65-2.48 (m, 2H), 1.79-1.59 (m, 2H), 1.13 (t, $J = 7.1$ Hz, 3H), 0.79 (t, $J = 7.3$ Hz, 3H).

GC-MS (EI): Calcd for $C_{13}H_{18}O_2$ $[M]^+$: 206.1 Found: 206.2.

(S)-Ethyl 3-(2-naphthyl)butanoate [52086-00-7]. The product was isolated by flash chromatography (Et_2O /hexanes 1:20) as colorless oil. Yield: 65 mg, 90%.

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

1 PDA Multi 1 / 260nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	25.574	6974002	49.896
2	28.000	7003086	50.104
Total		13977088	100.000

1 PDA Multi 1 / 217nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	25.014	243557	4.133
2	27.550	5649263	95.867
Total		5892819	100.000

1H NMR (400 MHz, $CDCl_3$): δ 7.91-7.72 (M, 3H), 7.65 (s, 1H), 7.54-7.29 (m, 3H), 4.07 (q, $J = 7.1$ Hz, 2H), 3.56-3.32 (m, 1H), 3.62-3.30 (m, 2H), 1.39 (d, $J = 6.9$ Hz, 3H), 1.17 (t, $J = 7.1$ Hz, 3H).

GC-MS (EI): Calcd for $C_{16}H_{18}O_2$ $[M]^+$: 242.1 Found: 242.1.

(S)-Ethyl 3-(4-tolyl)butanoate [1461-11-6]. The product was isolated by flash

chromatography (Et₂O/hexanes 1:20) as colorless oil. Yield: 56 mg, 91%.

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

1 PDA Multi 1 / 250nm 4nm

PeakTable			
Peak#	Ret. Time	Area	Area %
1	22.332	395857	50.030
2	23.294	395386	49.970
Total		791243	100.000

1 PDA Multi 1 / 200nm 4nm

PeakTable			
Peak#	Ret. Time	Area	Area %
1	21.694	5679954	95.373
2	22.855	275583	4.627
Total		5955538	100.000

¹H NMR (400 MHz, CDCl₃): δ 7.11 (s, 4H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.33-3.11 (m, 1H), 2.71-2.44 (m, 2H), 2.31 (s, 3H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.18 (d, *J* = 7.1 Hz, 3H).

GC-MS (EI): Calcd for C₁₃H₁₈O₂ [M]⁺: 206.1 Found: 206.1.

(S)-Ethyl 3-(4-anisyl)butanoate 2f [1242409-36-4]. The product was isolated by

flash chromatography (Et₂O/hexanes 1:20) as colorless oil. Yield: 59 mg, 88%.

Ee: 92%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 99.5/0.5, flow rate = 0.5 mL/min.

1 PDA Multi 1 / 216nm 4nm

PeakTable

PDA Ch1 216nm 4nm			
Peak#	Ret. Time	Area	Area %
1	15.848	1016063	49.936
2	16.721	1018674	50.064
Total		2034736	100.000

1 PDA Multi 1 / 218nm 4nm

PeakTable

PDA Ch1 218nm 4nm			
Peak#	Ret. Time	Area	Area %
1	16.257	21757	3.941
2	17.167	530350	96.059
Total		552107	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.18-7.09 (m, 2H), 6.91-6.79 (m, 2H), 4.12-4.01 (m, 2H), 3.78 (s, 3H), 3.31-3.16 (m, 1H), 2.62-2.45 (m, 2H), 1.27 (d, $J = 7.0$ Hz, 3H), 1.18 (t, $J = 7.1$ Hz, 3H).

(S)-Ethyl 3-(3,4-methylenedioxyphenyl)butanoate [1225537-44-9]. The product was isolated by flash chromatography (Et_2O /hexanes 1:30) as colorless oil. Yield: 62 mg, 87%. Ee: 92%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 1.0 mL/min.

1 PDA Multi 1 / 254nm 4nm

PeakTable

PDA Ch1 254nm 4nm			
Peak#	Ret. Time	Area	Area %
1	5.823	152183	49.944
2	6.181	152525	50.056
Total		304708	100.000

1 PDA Multi 1 / 200nm 4nm

PeakTable

PDA Ch1 200nm 4nm			
Peak#	Ret. Time	Area	Area %
1	6.032	30381	4.276
2	6.448	680122	95.724
Total		710503	100.000

^1H NMR (400 MHz, CDCl_3): δ 6.79-6.69 (m, 2H), 6.69-6.64 (m, 1H), 5.92 (s, 2H),

4.08 (q, $J = 7.1$ Hz, 2H), 3.28-3.13 (m, 1H), 2.60-2.43 (m, 2H), 1.26 (d, $J = 7.0$ Hz, 3H), 1.19 (t, $J = 7.1$ Hz, 3H).

GC-MS (EI): Calcd for $C_{13}H_{16}O_4$ $[M]^+$: 236.1 Found: 236.0.

(S)-Ethyl 3-(4-(trifluoromethyl)phenyl)butanoate [1883373-69-0]. The product was isolated by flash chromatography (Et_2O /hexanes 1:20) as colorless oil. Yield: 68 mg, 87%. Ee: 93%. Daicel Chiralcel IC-H, n-hexane/isopropanol 99.9/0.1, flow rate = 0.5 mL/min.

1 PDA Multi 1 / 200nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	14.448	5098263	50.061
2	14.871	5085882	49.939
Total		10184145	100.000

1 PDA Multi 1 / 210nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	13.514	72370	3.755
2	13.985	1854878	96.245
Total		1927248	100.000

1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, $J = 7.9$ Hz, 2H), 7.33 (d, $J = 7.9$ Hz, 2H), 4.07 (q, $J = 7.1$ Hz, 2H), 3.42-3.27 (m, 1H), 2.66-2.50 (m, 2H), 1.31 (d, $J = 7.0$ Hz, 3H), 1.17 (t, $J = 7.1$ Hz, 3H).

GC-MS (EI): Calcd for $C_{13}H_{15}F_3O_2$ $[M]^+$: 260.1 Found: 260.1.

(S)-Ethyl 3-(3-tolyl)butanoate [130378-45-9]. The product was isolated by flash chromatography (Et₂O/hexanes 1:30) as colorless oil. Yield: 58 mg, 93%.

Ee: 91%. Daicel Chiralcel OD-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	7.717	14152343	51.589
2	8.756	13280292	48.411
Total		27432635	100.000

1 PDA Multi 1 / 210nm 4nm

PeakTable			
Peak#	Ret. Time	Area	Area %
1	7.767	38976	4.370
2	8.765	852899	95.630
Total		891875	100.000

¹H NMR (400 MHz, CDCl₃): δ 7.23-7.13 (m, 1H), 7.05-6.90 (m, 3H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.33-3.13 (m, 1H), 2.70-2.45 (m, 2H), 2.33 (s, 3H), 1.29 (d, *J* = 6.9 Hz, 3H), 1.18 (d, *J* = 7.1 Hz, 3H).

GC-MS (EI): Calcd for C₁₃H₁₈O₂ [M]⁺: 206.1 Found: 206.1.

(S)-Ethyl 3-(3-pyridyl)butanoate [71351-56-9]. The product was isolated by flash chromatography (Et₂O/hexanes 1:5) as colorless oil. Yield: 52 mg, 90%.

Ee: 92%. Daicel Chiralcel AS-H, *n*-hexane/isopropanol 95/2, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3) δ 8.52 (s, 2H), 7.15 (s, 2H), 4.07 (q, $J = 7.1$ Hz, 2H), 3.35-3.16 (m, 1H), 2.69-2.48 (m, 2H), 1.30 (d, $J = 7.0$ Hz, 3H), 1.18 (t, $J = 7.1$ Hz, 3H).

GC-MS (EI): Calcd for $\text{C}_{11}\text{H}_{15}\text{NO}_2$ $[\text{M}]^+$: 193.1 Found: 193.1.

(S)-Ethyl 3-(2-thienyl)butanoate [27050-13-1]. The product was isolated by flash chromatography (Et_2O /hexanes 1:20) as colorless oil. Yield: 52 mg, 88%.

Ee: 90% ee. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 99.5/0.5, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.16-7.10 (m, 1H), 5.95-6.87 (m, 1H), 6.87-6.78 (m,

1H), 4.12 (q, $J = 7.1$ Hz, 2H), 3.72-3.45 (m, 1H), 2.75-2.44 (m, 2H), 1.38 (d, $J = 6.9$ Hz, 3H), 1.22 (t, $J = 7.1$ Hz, 3H).

GC-MS (EI): Calcd for $C_{10}H_{14}O_2S$ $[M]^+$: 198.1 Found: 198.0.

(S)-Ethyl 2-(1-tetralinyl)acetate [1800587-4504]. The (*E*)-isomer of starting material was used. The product was isolated by flash chromatography (Et_2O /hexanes 1:15) as colorless oil. Yield: 58 mg, 89%.

Ee: 85%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 98/2, flow rate = 1.0 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	5.901	6843130	50.062
2	6.346	6826070	49.938
Total		13669200	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	6.110	181877	7.362
2	6.749	2288505	92.638
Total		2470382	100.000

1H NMR (400 MHz, $CDCl_3$): δ 7.21-7.00 (m, 4H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.42-3.24 (m, 1H), 2.87-2.43 (m, 4H), 2.04-1.63 (m, 4H), 1.27 (t, $J = 7.1$ Hz, 3H).

GC-MS (EI): Calcd for $C_{14}H_{18}O_2$ $[M]^+$: 218.1 Found: 218.0.

(S)-Ethyl 2-(4-chromanyl)acetate [1800576-12-8]. The (*E*)-isomer of starting material was used. The product was isolated by flash chromatography

(EtOAc/hexanes 1:4) as colorless oil. Yield: 63 mg, 95%.

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

^1H NMR (400 MHz, CDCl_3) δ 7.16-7.04 (m, 2H), 6.92-6.75 (m, 2H), 4.25-4.11 (m, 4H), 3.43-3.29 (m, 1H), 2.84-2.72 (m, 1H), 2.58-2.46 (m, 1H), 2.15 (d, J = 11.1 Hz, 6H), 1.93-1.76 (m, 1H), 1.27 (dd, J = 11.5, 4.2 Hz, 3H).

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3$ $[\text{M}]^+$: 220.1 Found: 220.0.

(S)-3-phenylbutanenitrile The product was isolated by flash chromatography

(Et₂O/hexanes 1:15) as colorless oil. Yield: 40 mg, 93%.

Ee: 93%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3) δ 7.38-7.32 (m, 2H), 7.30-7.26 (m, 1H), 7.26-7.21 (m, 2H), 3.27-3.08 (m, 1H), 2.70-2.43 (m, 2H), 1.46 (d, $J = 7.0$ Hz, 3H).

GC-MS (EI): Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_2$ $[\text{M}]^+$: 145.1 Found: 145.1.

A general procedure for reductive amination of ketones and benzhydrazide. In an argon-filled glove box, benzhydrazide (32.6 mg, 0.24 mmol), a ketone (0.2 mmol), acetic acid (35 μL , 0.6 mmol), dried 3Å molecular sieve (40 mg) and dry isopropanol (0.6 mL) were charged into a 10-mL Schlenk tube. After stirring for 6 hours at 80 $^\circ\text{C}$, $\text{Ni}(\text{OTf})_2$ (2.2 mg, 0.006 mmol), (*S*)-binapine (4.4 mg, 0.006 mmol), tetra-*n*-butylammonium iodide (14.4 mg, 0.02 mmol), indium powder (25.2 mg, 0.22 mmol, Alfa Aesar, 100 mesh, 99.9% purity) and GC standard *n*- $\text{C}_{12}\text{H}_{26}$ (10 μL) were added to the tube. The reaction mixture was then capped and vigorously stirred in an oil bath maintained at 80 $^\circ\text{C}$ for 48 hours. After the mixture was cooled down to rt, the residue was dry loaded on a silica gel column and purified by flash chromatography using ethyl acetate and hexanes as eluent.

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

The reaction was complete after 48 h at 80 °C. The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. Yield: 66 mg, 92%. Ee: 98%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

1 PDA Multi 1 / 200nm 4nm

PeakTable			
PDA Ch1 200nm 4nm			
Peak#	Ret. Time	Area	Area %
1	17.657	38127834	50.565
2	23.653	37275501	49.435
Total		75403335	100.000

1 PDA Multi 1 / 200nm 4nm

PeakTable			
PDA Ch1 200nm 4nm			
Peak#	Ret. Time	Area	Area %
1	18.363	6558903	98.740
2	25.070	83699	1.260
Total		6642602	100.000

¹H NMR (400 MHz, CDCl₃): δ 7.69-7.53 (m, 2H), 7.56-7.45 (m, 1H), 7.44-7.27 (m, 7H), 5.10 (s, 1H), 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*-Anisylethyl)benzohydrazide [159041-70-0].

The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid. Yield: 52 mg, 96%. Ee: 96%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min.

PeakTable

Peak#	Ret. Time	Area	Area %
1	30.878	21666202	50.192
2	45.366	21500480	49.808
Total		43166682	100.000

PeakTable

Peak#	Ret. Time	Area	Area %
1	30.836	3690700	98.182
2	46.897	68328	1.818
Total		3759028	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.69-7.59 (m, 2H), 7.54-7.45 (m, 1H), 7.45-7.36 (m, 2H), 7.36-7.29 (m, 2H), 6.98-6.83 (m, 2H), 4.21 (q, J = 6.6 Hz, 1H), 3.81 (s, 3H), 1.41 (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-Trifluoromethylphenyl)ethyl]benzohydrazide[1807988-68-6].

The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid.

Yield: 86 mg, 93%.

Ee: 98%. 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	37.222	10314	0.718
2	38.942	1426115	99.282
Total		1436429	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.67-7.58 (m, 4H), 7.55-7.46 (m, 3H), 7.42-7.35 (m,

1H), 5.08 (s, 1H), 4.34 (q, $J = 6.6$ Hz, 1H), 1.43 (d, $J = 6.6$ Hz, 3H).

LC-MS (ESI): Calcd for $C_{16}H_{15}F_3N_2O$ $[M+H]^+$: 309.1. Found: 308.9.

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

The product was isolated by flash chromatography (EA/hexanes 1:2) as white solid.

Yield: 50 mg, 86%.

Ee: 97%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 85/15, flow rate = 1.0 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	15.658	54695508	51.425
2	18.894	51664902	48.575
Total		106360411	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	15.686	6706834	98.694
2	18.707	88750	1.306
Total		6795584	100.000

1H NMR (400 MHz,) δ 7.94-7.78 (m, 4H), 7.64-7.55 (m, 3H), 7.52-7.44 (m, 3H), 7.39-7.31 (m, 2H), 5.18 (s, 1H), 4.44 (q, $J = 6.6$ Hz, 1H), 1.52 (d, $J = 6.6$ Hz, 3H).

LC-MS (ESI): Calcd for $C_{19}H_{18}N_2O$ $[M+H]^+$: 291.1. Found: 290.8.

(R)-N'-[1-(3-Pyridyl)ethyl]benzohydrazide[1807988-73-3].

The reaction was complete after 24 h at 70 °C. The product was isolated by flash chromatography (EA) as white solid. Yield: 43 mg, 88%.

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

1 PDA Multi 1 / 200nm 4nm

PeakTable			
Peak#	Ret. Time	Area	Area %
1	21.972	15974010	49.416
2	31.638	16351598	50.584
Total		32325608	100.000

1 PDA Multi 1 / 200nm 4nm

PeakTable			
Peak#	Ret. Time	Area	Area %
1	21.653	110418309	97.819
2	32.815	2461622	2.181
Total		112879931	100.000

^1H NMR (300 MHz, CDCl_3): δ 8.63 (d, J = 1.8 Hz, 1H), 8.42 (dd, J = 4.8, 1.7 Hz, 1H), 8.30 (s, 1H), 7.83-7.60 (m, 3H), 7.57-7.45 (m, 1H), 7.43-7.32 (m, 2H), 7.33-7.16 (m, 1H), 4.31 (q, J = 6.56 Hz, 1H), 1.47 (d, J = 6.7 Hz, 3H).

(*R*)-*N'*-[1-(*o*-Tolyl)ethyl]benzohydrazide[1807988-71-1].

The product was isolated by flash chromatography (EA/hexanes 1:2) as colorless oil.

Yield: 47 mg, 93%.

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

^1H NMR (400 MHz, CDCl_3) δ 7.66-7.55 (m, 3H), 7.52-7.46 (m, 1H), 7.42-7.36 (m, 2H), 7.30-7.22 (m, 1H), 7.20-7.12 (m, 2H), 5.09 (s, 1H), 4.58 (q, J = 6.5 Hz, 1H), 2.34 (s, 3H), 1.40 (d, J = 6.6 Hz, 3H).

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

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

The product was isolated by flash chromatography (EA/hexanes 1:2) as colorless oil.

Yield: 69 mg, 91%.

Ee: 92 %. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 0.5 mL/min

^1H NMR (400 MHz, CDCl_3) δ 7.62-7.54 (m, 2H), 7.50-7.43 (m, 1H), 7.42-7.27 (m, 7H),

5.19 (s, 1H), 4.06-3.88 (m, 1H), 1.96-1.64 (m, 2H), 0.88 (t, $J = 7.4$ Hz, 3H).

LC-MS (ESI): Calcd for $C_{16}H_{18}N_2O$ $[M+H]^+$: 255.1. Found: 254.9.

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

(*R,S*)-CyPF-Cy was used as chiral ligand. The product was isolated by flash chromatography (EA/PE = 1/2) as white solid. 42 mg, 86% yield. When ligand (*S*)-binapine was used instead, full conversion and 40% *ee* were observed.

Ee: 90%. 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	37.051	376399	94.384
2	40.899	22397	5.616
Total		398796	100.000

1H NMR (400 MHz, $CDCl_3$): δ 7.78-7.71 (m, 2H), 7.56-7.50 (m, 1H), 7.48-7.41 (m, 2H), 4.89 (s, 1H), 2.94-2.87 (m, 1H), 1.84-1.71 (m, 4H), 1.71-1.62 (m, 1H), 1.49-1.37 (m, 1H), 1.36-1.08 (m, 5H), 1.06 (d, $J=6.4$, 3H).

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

A Josiphos (*R,S*)-CyPF-Cy was used as chiral ligand. The product was isolated by flash chromatography (EA/pentane 1/2) as white solid. Yield: 36.2 mg, 88%.

Ee: 83%. 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 / 270nm 4nm

PeakTable			
Peak#	Ret. Time	Area	Area %
1	34.128	658112	91.436
2	38.532	61637	8.564
Total		719750	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)

LC-MS (ESI): Calcd for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 206.9. Found: 206.1.

A general procedure of asymmetric hydrogenation for (Z)- β -(acylamido)acrylates.

In an argon-filled glove box, $\text{Ni}(\text{OAc})_2$ (1.1 mg, 0.006 mmol), (*S*)-binapine (4.4 mg, 0.006 mmol) and dry methanol (0.6 mL) were charged into a 10-mL Schlenk tube. After stirring for 15 min, acetic acid (35 μL , 0.6 mmol, 3 equiv) and (*Z*)- β -(acylamido)acrylate (0.2 mmol) were added. The reaction mixture was heated with stirring in an oil bath maintained at 60 $^\circ\text{C}$, until the olefin was fully consumed (monitored by GC). After the reaction mixture was cooled to room temperature and evaporation of the solvent on a rotary evaporator, 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 3-acetamido-3-phenyl-propanoate [67654-57-3]. The reaction was complete in 36 h at 60 °C. The product was isolated by flash chromatography (EA/hexanes 1:1 to 2:1) as white solid. Yield: 44 mg, 96%,

Ee: 91%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 1.0 mL/min.

1 PDA Multi 1 / 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	18.628	3543176	49.868
2	21.649	3561978	50.132
Total		7105154	100.000

1 PDA Multi 1 / 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	18.082	957107	95.484
2	20.162	45272	4.516
Total		1002379	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.45-7.13 (m, 5H), 6.68 (d, $J = 7.5$ Hz, 1H), 5.50-5.39 (m, 1H), 3.63 (s, 3H), 2.95 (dd, $J = 15.7, 6.0$ Hz, 1H), 2.85 (dd, $J = 15.7, 6.0$ Hz, 1H), 2.03 (s, 3H).

GC-MS (EI): Calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_3$ ($\text{M}+\text{H}$) $^+$: 222.1. Found: 222.0.

(R)-Ethyl 3-acetamido-3-phenyl-propanoate [609849-87-8]. The reaction was

complete in 36 h at 60 °C. The product was isolated by flash chromatography (EA/hexanes 1:1 to 2:1) as white solid. Yield: 46 mg, 97%, Ee: 96%. Daicel Chiralcel OD-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	10.704	1316006	50.415
2	12.515	1294335	49.585
Total		2610341	100.000

1 PDA Multi 1 / 200nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	9.879	1238150	98.041
2	11.551	24738	1.959
Total		1262888	100.000

^1H NMR (400 MHz, CDCl_3) δ 7.43-7.18 (m, 5H), 6.66 (d, $J = 7.6$ Hz, 1H), 5.57-5.36 (m, 1H), 4.06 (q, $J = 7.1$ Hz, 2H), 2.91 (dd, $J = 15.6, 6.0$ Hz, 1H), 2.81 (dd, $J = 15.6, 6.0$ Hz, 1H), 2.01 (s, 3H), 1.16 (t, $J = 7.1$ Hz, 3H).

GC-MS (EI): Calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_3$ ($\text{M}+\text{H}$) $^+$: 222.1. Found: 222.0.

(R)-Methyl 3-acetamido-3-(4-methoxyphenyl)propanoate [810670-02-1]. The reaction completed in 24 h at 60 °C. The product was isolated by flash chromatography (EA/hexanes 1:1 to 2:1) as white solid. Yield: 48 mg, 96%.

Ee: 92%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 1.0 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.19 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.60 (br s, 1H), 5.47-5.23 (m, 1H), 3.76 (s, 3H), 3.60 (s, 3H), 2.90 (dd, J = 15.6, 6.0 Hz, 1H), 2.78 (dd, J = 15.7, 6.3 Hz, 1H), 1.97 (d, J = 0.8 Hz, 3H).

GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_4$ ($\text{M}+\text{H}$) $^+$: 252.1. Found: 252.0.

(*R*)-Methyl 3-acetamido-3-(4-fluorophenyl)propanoate [844439-54-9].

The reaction completed in 36 h at 60 °C. The product was isolated by flash chromatography (EA/hexanes 1:1 to 2:1) as white solid. Yield: 45 mg, 96%.

Ee: 94%. Daicel Chiralcel OJ-H, n-hexane/isopropanol 90/10, flow rate = 1.0 mL/min.

^1H NMR (400 MHz, CDCl_3) δ 7.37-7.18 (m, 2H), 7.06-6.94 (m, 2H), 6.66 (d, J = 7.7

Hz, 1H), 5.51-5.29 (m, 1H), 3.61 (s, 3H), 2.90 (dd, $J = 15.8, 5.8$ Hz, 1H), 2.81 (dd, $J = 15.8, 5.9$ Hz, 1H), 2.01 (s, 3H).

GC-MS (EI): Calcd for $C_{12}H_{14}FNO_3$ ($M+H$)⁺: 240.1. Found: 240.0.

(*R*)-Methyl 3-acetamido-3-[4-(trifluoromethyl)phenyl]propanoate[1642855-02-4].

The reaction was complete in 36 h at 60 °C. The product was isolated by flash chromatography (EA/hexane 1:1 to 2:1) as white solid. Yield: 55 mg, 95%.

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

1 PDA Multi 1 / 254nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	19.090	425046	50.073
2	20.209	423800	49.927
Total		848846	100.000

1 PDA Multi 1 / 254nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	18.031	181668	94.020
2	20.357	11555	5.980
Total		193223	100.000

1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, $J = 8.2$ Hz, 1H), 7.40 (d, $J = 8.1$ Hz, 1H), 6.93 (d, $J = 8.0$ Hz, 1H), 2.00 (s, 2H).

1H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, $J = 8.2$ Hz, 2H), 7.40 (d, $J = 8.1$ Hz, 2H), 6.93 (d, $J = 8.0$ Hz, 1H), 5.44 (dd, $J = 14.0, 6.0$ Hz, 1H), 3.61 (s, 3H), 2.98-2.72 (m, 2H), 2.00 (s, 3H).

GC-MS (EI): Calcd for $C_{13}H_{14}F_3NO_3$ M^+ : 289.1. Found: 289.0.

(R)-Methyl 3-acetamido-3-(2-naphthyl)propanoate[1642872-44-3]. The reaction completed in 36 h at 60 °C. The product was isolated by flash chromatography (EA/hexanes 1:1 to 2:1) as white solid. Yield: 52 mg, 96%. Ee: 92%. Daicel Chiralcel OJ-H, n-hexane/isopropanol 90/10, flow rate = 1.0 mL/min.

1H NMR (400 MHz, $CDCl_3$) δ 7.86-7.76 (m, 3H), 7.73 (s, 1H), 7.53-7.44 (m, 2H), 7.43-7.36 (m, 1H), 6.69 (d, J = 8.0 Hz, 1H), 5.60 (dd, J = 14.2, 5.9 Hz, 1H), 3.60 (s, 3H), 3.03 (dd, J = 15.8, 5.8 Hz, 1H), 2.93 (dd, J = 15.8, 6.0 Hz, 1H), 2.05 (s, 3H).

GC-MS (EI): Calcd for $C_{16}H_{17}NO_3$ M^+ : 271.1. Found: 271.0.

(R)-Methyl 3-acetamido-3-(1-naphthyl)propanoate[1642855-01-3]. The reaction was finished in 24 h at 60 °C. The product was isolated by flash chromatography

(EA/hexanes 1:1 to 2:1) as white solid. Yield: 49 mg, 92%.

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

PeakTable			
Peak#	Ret. Time	Area	Area %
1	16.661	4004906	49.593
2	18.843	4070568	50.407
Total		8075474	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	15.368	2773474	91.232
2	17.927	266545	8.768
Total		3040020	100.000

^1H NMR (400 MHz, CDCl_3): δ 8.10 (d, $J = 8.4$ Hz, 1H), 7.90-7.83 (m, 1H), 7.83-7.76 (m, 1H), 7.63-7.37 (m, 4H), 6.50 (d, $J = 8.0$ Hz, 1H), 6.31-6.15 (m, 1H), 3.59 (s, 3H), 3.10-2.96 (m, 2H), 1.98 (s, 3H).

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_3$ M^+ : 271.1. Found: 271.0.

(R)-Methyl 3-acetamido-3-(3-pyridyl)propanoate[1642855-03-5]. The reaction was complete in 36 h at 60 °C. The product was isolated by flash chromatography (MeOH/DCM 1:10) as yellow solid. Yield: 41 mg, 92%.

Ee: 98%. Daicel Chiralcel OJ-H, n-hexane/isopropanol 90/10, flow rate = 1.0 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	15.455	1338310	49.785
2	17.921	1349848	50.215
Total		2688158	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	13.862	8922	0.942
2	15.920	938391	99.058
Total		947312	100.000

^1H NMR (400 MHz, CDCl_3): δ 8.56 (s, 1H), 8.49 (d, $J = 4.0$ Hz, 1H), 7.67-7.58 (m, 1H), 7.26-7.20 (m, 1H), 6.95 (d, $J = 8.1$ Hz, 1H), 5.62-5.23 (m, 1H), 3.62 (s, 3H), 3.01-3.64 (m, 2H), 2.02 (s, 3H).

GC-MS (EI): Calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_3$ M^+ : 222.1. Found: 222.0.

(R)-Ethyl 3-phthalimido-3-phenylpropanoate [1204518-31-9]. The product was isolated by flash chromatography (EA/hexane 1:3) as white solid. Yield: 59 mg, 96%. Ee: 88%. Daicel Chiralcel OJ-H, n-hexane/isopropanol 90/10, flow rate = 1.0 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	21.021	13661903	50.053
2	27.023	13632928	49.947
Total		27294831	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	19.106	647414	6.755
2	24.876	8936670	93.245
Total		9584083	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.86-7.76 (m, 2H), 7.72-7.64 (m, 2H), 7.56-7.44 (m, 2H), 7.38-7.24 (m, 2H), 5.91-5.73 (m, 1H), 4.22-4.39 (m, 2H), 3.79 (dd, $J = 16.4, 10.2$ Hz, 1H), 3.24 (dd, $J = 16.4, 5.7$ Hz, 1H), 1.14 (t, $J = 7.1$ Hz, 3H).

GC-MS (EI): Calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_4$ M^+ : 323.1. Found: 323.0.

2.4 Reference

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Chapter 3 Nickel-Catalyzed Asymmetric Transfer Hydrogenation of Electron-Poor Alkenes Using H₂O and Related Deuteration Using D₂O

3.1 Introduction

Isotopically labelled compounds are important in mechanistic studies of reactions. Deuteration at strategic positions of drugs can also alter rates of metabolism, for example, P450 oxidation in live, and half-lives of drugs in body. In addition, deuterium labelled pharmaceuticals are important for ADME (absorption, distribution, metabolism and excretion) studies and tracking of drug metabolism.¹ In recent years, deuterium drugs have been also extensively tested to achieve optimal pharmacokinetic and pharmacodynamic properties of drugs without introducing or changing substituents on the drugs.²⁻³

There are two types of common reactions to introduce deuterium atoms into organic compounds. Firstly, transition metal-catalyzed H/D exchange of C-H bonds is conveniently practiced in aromatic compounds with D₂O. In the presence of directing groups on arenes, ortho C-H bonds can be selectively exchanged with D₂O. The other reaction is asymmetric addition of D₂ to unsaturated bonds such as C=C and C=N bonds using established noble metal catalysts (Rh, Ir and Ru), which also allow introduction of C-D bonds to new stereocenters. However, D₂ is expensive and explosive. Other deuterium sources such as deuterated silanes and deuterated alcohols are also expensive.

3.1.1 Deuterated drugs

The first attempt of introducing deuterium atom into drugs was reported 50 years ago.⁴ In the past decade, there is renewed interest in developing deuterium drugs. By replacing a hydrogen atom with deuterium in drug candidates, the half-lives and toxicity of drugs can be fine-tuned to achieve optimal pharmacokinetics. The C-D bonds are more difficult to be oxidized than C-H bonds during metabolic oxidation in body. Therefore, strategical placement of deuterium in drugs can elongate the lifetime of drugs.

Pharmaceutical industry has started pile up deuterated drug patents since 2005. Deutetrabenazine developed by Teva was the first approved deuterium drug on market. Tetrabenazine is a vesicular amine transporter 2 inhibitor and is used for the treatment of chorea (abnormal involuntary movement disorder) associated with Huntington's disease. The deuterium version slowed down the rate of drug metabolism and allowed reduction of drug dosage.⁵⁻⁶

Deutetrabenazine

A deuterated version of a cough suppressant dextromethorphan, AVP-786, was developed by Avanir Pharmaceuticals in 2015.⁷ AVP-786 is intended for the treatment of pseudobulbar affect, an emotional problem due to brain damage. It is at a preclinical stage currently.

AVP-786 active ingredient

Concert developed a deuterated version of cystic fibrosis drug Kalydeco, which was processed into Phase II clinical trials in 2017.⁸ The half-life of CTP-656 is much longer than Kalydeco (27 versus 12 hours). In addition, CTP-656 does not require to be taken with a fatty meal.

CTP-656

Vertex developed VX-984, a drug to enhance the efficacy of cancer treatment. Without deuteration, other structural analogs failed to reduce the rate of metabolism. Finally, the deuterated VX-984 was found to slow down the metabolic oxidation by aldehyde oxidase and achieved an optimal pharmacokinetic profile.

VX-984

3.1.2 Deuteration via H/D exchange

Deuterium oxide, also known as heavy water, is obtained by vacuum distillation

from water. It is the ultimate source of all deuterated compounds. In comparison, deuterium gas is more expensive. It is obtained from separation from liquid H₂ or electrolysis of deuterium water.

Today, H/D exchange of C-H bonds using D₂O or D₂ and addition of D₂ or other deuterated reagents to unsaturated compounds are two types of most common methods to prepared deuterated compounds.

In 2002, Bergman *et al.* disclosed iridium-catalyzed H/D exchange into organic compounds in water (Scheme 3.1.1).⁹ They found an air stable Ir(III) catalyst, Cp*(PMe₃)IrCl₂, could be applied in H/D exchange with D₂O as the deuterium source. However, electron deficient substituents, such as amylbenzene and naphthalene, underwent low levels of deuterium incorporation.

Scheme 3.1.1 Iridium-catalyzed deuteration of organic compounds with H/D exchange

Later, Bergman *et al.* developed methods for efficient stoichiometric D incorporation in pharmaceutical compounds (Scheme 3.1.2). They also reported catalytic H/D exchange into aromatic compounds in acetone-d₆ at moderate temperature.¹⁰

Scheme 3.1.2 Iridium-catalyzed deuteration with directing groups

In 2016, Chirik's group developed an efficient iron-catalyzed deuteration of pharmaceuticals with H/D exchange (Scheme 3.1.3).¹ Introduction of deuterium atoms into pharmaceuticals provide a novel method for ADME studies. Various functional groups in pharmaceuticals were tolerated in polar solvents at low pressure of deuterium gas.

Scheme 3.1.3 Iron-catalyzed deuteration of pharmaceuticals with H/D exchange

3.1.3 Metal-catalyzed deuteration of unsaturated bonds with deuterium water

In 2005, Hayashi disclosed palladium-catalyzed transfer hydrogenation of alkynes

with deuterium oxide and hexamethyldisilane (Scheme 3.1.4).¹¹ The reaction afforded (*E*)-1,2-dideuterioalkenes with good selectivity. Hexamethyldisilane reacts with deuterium oxide to provide deuterium trimethylsilane which in turn transfers deuterium to palladium complex.

Scheme 3.1.4 Palladium-catalyzed transfer hydrogenation of alkynes with palladium catalyst with deuterium oxide and hexamethyldisilane

The same palladium catalysis was applied to hydrogenation of α,β -unsaturated ketones with deuterium oxide that resulted in selective conjugate reduction (Scheme 3.1.5).¹² They observed greater than 100% deuterium incorporation at both the α - and β - positions, which is caused by β -hydrogen elimination and reinsertion of deuterium.

Scheme 3.1.5 Palladium catalyzed transfer hydrogenation of α,β -unsaturated ketones with deuterium oxide and hexamethyldisilane

Lledós *et al.* reported ruthenium-catalyzed enantioselective transfer hydrogenation of ketones with formic acid in D_2O (Scheme 3.1.6).¹³ As a key component of the reaction pathway, ruthenium hydride was formed from β hydrogen elimination of

ruthenium formate generate ruthenium hydride, which then undergoes H/D exchange with D_2O to produce a Ru-D species. A small fraction of deuterium was also introduced into the α -position of the ketone/alcohol due to ketone-enol tautomerization.

Scheme 3.1.6 Ruthenium-catalyzed enantioselective transfer hydrogenation of ketones with D_2O

3.1.3 Deuteration of unsaturated bonds with D_2 and deuterated formic acid

Asymmetric hydrogenation with deuterium gas is an important methodology for building chiral deuterium labeled products. Aldini *et al.* reported production of deuterium labelled histidine by rhodium-catalyzed asymmetric hydrogenation with deuterium gas (Scheme 3.1.7).¹⁴ Good yields and *ee* values were obtained with (-)-Me-DuPhos.

Scheme 3.1.7 Rhodium-catalyzed asymmetric hydrogenation with deuterium gas

Instead of using deuterium gas, our group reported asymmetric transfer hydrogenation of various C=C and C=N bonds using d_2 -formic acid (Scheme 3.1.8).¹⁵⁻¹⁷ Excellent *ees* and yields were observed for α,β -conjugated amidoesters and ketimines in the presence of nickel catalysts of (*S*)-Binapine and (*R*)-Me-DuPhos. Interestingly, in the reaction of a hydrozone, the methyl group of the hydrazine product was extensively deuterated (>80% D).

In the last chapter, I describe an asymmetric transfer hydrogenation of α,β -unsaturated esters involving umpolung of H^+ to hydride in protic conditions with acetic acid as a hydride donor. If I added acetic acid and heavy water together, deuterium cation should be formed rapidly through H-D exchange. Then umpolung of D^+ would take place, which would offer the possibility for asymmetric deuteration. Hence, I developed asymmetric transfer hydrogenation of α,β -unsaturated esters with water and deuterium oxide as hydride donor.

I chose (*E*)-ethyl 3-methylcinnamate for model reaction searching for optimal conditions. As learnt from the last chapter, I found pH value influenced reaction conversion significantly. 0.1 M acetic acid in water provided the highest conversion. Then I screened various nickel salts and found nickel salts have little influence on enantioselectivity (Table 3.1). With respect to the conversion, NiBr₂(DME) was found

to provide an excellent yield (entry 1).

Table 3.1 The effect of nickel salts

$ \begin{array}{c} \text{Me} \\ \\ \text{Ph}-\text{C}=\text{CH}-\text{CO}_2\text{Et} \end{array} + \text{indium} + \text{AcOH} + \text{H}_2\text{O} \xrightarrow[\text{PhCF}_3, 80^\circ\text{C}, 12\text{ h}]{\text{Nickel salt } 3\text{ mol\%} \quad (R)\text{-Me-DuPhos } 3\text{ mol\%}} \begin{array}{c} \text{Me} \\ \\ \text{Ph}-\text{CH}-\text{CH}_2-\text{CO}_2\text{Et} \end{array} $				
		1.1 equiv	0.2 equiv	50 equiv
				$n\text{-Bu}_4\text{NI}$ (0.2 equiv)
Entry	Nickel salt	Conv (%)	Yield (%)	ee (%)
1	$\text{NiBr}_2(\text{DME})$	99	99	91
2	$\text{NiCl}_2(\text{DME})$	72	69	92
3	$\text{Ni}(\text{acac})_2$	85	82	92
4	$\text{Ni}(\text{OAc})_2$	88	86	91
5	$\text{Ni}(\text{OTf})_2$	90	90	91

I explored different metals in the model reaction. The use of indium afforded excellent enantioselectivity and full conversion when over 1 equiv of indium was used (Table 3.2). Full conversion and quantitatively yield were achieved with 1 equivalent indium (entry 4). I found that the correlation between the conversion of the ester and stoichiometry of indium(0) was consistent with the conversion of indium(0) to indium(III). In comparison, aluminum, zinc and manganese powder provided low conversions because they reacted with acetic acid to generate hydrogen gas (entry 5-8). In Chirik's report, 33 bar of hydrogen gas was needed for asymmetric hydrogenation of α,β -unsaturated esters.

Table 3.2 The effect of reductive metals

Entry	Metal	Equiv	Conv (%)	Yield (%)	ee (%)
1	In	0.2	30	27	93
2	In	0.5	80	74	92
3	In	0.8	94	91	92
4	In	1.1	99	99	93
5	Mg	1.1	<3	<3	-
6	Mn	1.1	0	0	-
7	Al	1.1	15	12	47
8	Zn	1.1	26	24	84

I found that some additives dramatically improved the conversion of the model asymmetric hydrogenation (Table 3.3). Tetrabutylammonium iodide was found the highest conversion after 12 h (entry 2-4), while the bromide and chloride salts only provided 15% and 50% yields, respectively (entry 5 and 6).

Table 3.3 The effect of additives

Entry	Additive	Equiv	Conv (%)	Yield (%)	ee (%)
1	TBAI	0.1	45	42	91

2	TBAI	0.2	99	99	92
3	TBAI	0.3	99	99	91
4	TBAI	0.5	96	94	92
5	TBAB	0.5	15	10	93
6	TBAC	0.5	50	44	95

With the optimized condition, (*E*)-Cinnamates scope was explored (Scheme 3.2.1). (*E*)-Cinnamates with small β groups *cis* to the ester groups gave good *ee*. Both electron-donating and withdrawing groups on aryl groups were well tolerated. Thiophene and pyridine rings were also compatible in the substrates. Additionally, cyclic olefins were hydrogenated to give tetraline derivatives.

Scheme 3.2.1 Asymmetric transfer hydrogenation with water and indium powder

Next, replacement of water with D₂O in the hydrogenation protocol enabled deuteration of the model olefin in high percentage of deuterium incorporation at the β position (98%). The D₂O procedure can be applied to the same substrates (Scheme 3.2.2) with very similar ee values and yields. High deuterium percentage was incorporated in both the β - and α -positions. In addition, the ratio of deuteration at two α -positions is only moderate (around 2:1) during protonation of the key nickel enolates.

Scheme 3.2.2 Scopes of asymmetric deuteration with water and indium powder

3.2.2 Conclusion

I have developed asymmetric transfer hydrogenation of α,β -unsaturated esters with water and deuterium oxide as hydrogen and deuterium source respectively. Deuterated chiral center at β position was obtained with excellent deuterium ratio and enantioselectivity. The present method would be useful for the preparation of deuterated chiral building blocks without explosive and expensive deuterium gas or other expensive deuterated reagents.

3.3 Experiment section

3.3.1 General

All NMR spectra were acquired on Bruker AV 500 MHz, BBFO 400 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 THF was freshly distilled from sodium/benzophenone under argon before use and stored in an argon filled glove box. Anhydrous 1,4-dioxane (Aldrich) was stored over activated 4 Å molecular sieve beads in an argon-filled glove box. Dry toluene was collected from a solvent purification system containing a column of activated alumina (1 m x 2) under argon. Methanol, ethanol and isopropanol were degassed and stored over dried molecular sieve in an argon-filled glove box before use. All anhydrous solvents were stored in Schlenk tubes in the glove box.

Unless noted otherwise, commercially available chemicals were used as received without purification. The GC internal standard, $n\text{-C}_{12}\text{H}_{26}$ and $n\text{-C}_{14}\text{H}_{30}$ was degassed with argon and dried over activated 4 Å 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. ESI/MS analysis was conducted on a Thermo Finnigan LCQ Fleet MS spectrometer. 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*. The q-NMR spectroscopy was performed using a 90° pulse sequence with 100 s acquisition.

3.3.2 Isolated products of asymmetric transfer hydrogenation with deuterium oxide

A general procedure: In an argon-filled glove box, NiBr₂(DME) (1.8 mg, 0.006 mmol), (*R*)-Me-DuPhos (1.8 mg, 0.006 mmol), tetra-*n*-butylammonium iodide (15 mg, 0.04 mmol), indium (25.2 mg, 0.22 mmol) and dry PhCF₃ (0.6 mL) were charged into a dry 10-mL Schlenk tube. After stirring for 15 min at room temperature, acetic acid in D₂O (0.4 mL, 0.1 M) and olefin (0.2 mmol) were added. The reaction mixture was heated with vigorous stirring in an oil bath maintained at 80 °C, until the olefin was fully or almost fully consumed as monitored by GC. After the reaction mixture was cooled to room temperature, solid NaHCO₃ was added to basify the mixture. After addition of silica gel and evaporation of the solvent on a rotary evaporator, the residue

was dry loaded on a silica gel column and purified by flash chromatography using ethyl acetate and hexanes as eluent. The enantioselectivity (ee) of the purified product was determined by chiral HPLC analysis with Daicel Chiralcel columns. The use of Schlenk tubes and a vacuum manifold instead of a glove box gave similar results.

(S)-2,3-Dideutero-ethyl 3-phenylbutanoate [1800576-15-1]. The product was isolated by flash chromatography (Et₂O/hexanes 1:20) as colorless oil. Yield: 37 mg, 95%.

92% ee. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 98/2, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	10.024	14659864	49.045
2	15.586	15230861	50.955
Total		29890724	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	9.735	186786	3.897
2	13.581	4606439	96.103
Total		4793226	100.000

¹H NMR (500 MHz, CDCl₃): δ 7.34-7.26 (m, 2H), 7.26-7.13 (m, 3H), 4.08 (q, *J* = 7.0 Hz, 2H), 3.33-3.14 (m, 1H), 2.59 (s, 1H), 2.52 (s, 1H), 1.30 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

²H NMR (61 MHz, CDCl₃): δ 3.27, 2.61, 2.55.

¹³C NMR (126 MHz, CDCl₃): δ 172.5, 145.7, 128.5, 126.8, 126.5, 60.1, 42.6 (t, *J* = 19.8 Hz), 36.1 (t, *J* = 20.2 Hz), 21.68 (d, *J* = 6.1 Hz), 14.18.

LC-MS (ESI): Calcd for C₁₂H₁₄D₂O₂ [M+H]⁺: 195.1. Found: 195.1.

(S)-2,3-Dideuterio methyl 3-phenylbutanoate. The product was isolated by flash chromatography (Et₂O/hexanes 1:20) as colorless oil. Yield: 34 mg, 95%.

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

PeakTable			
Peak#	Ret. Time	Area	Area %
1	11.045	10605745	49.098
2	23.166	10995491	50.902
Total		21601236	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	10.922	252534	3.701
2	21.546	6570715	96.299
Total		6823249	100.000

¹H NMR (400 MHz, CDCl₃): δ 7.34-7.27 (m, 2H), 7.25-7.17 (m, 3H), 3.62 (s, 3H), 3.31-3.22 (m, 1H), 2.60 (s, 1H), 2.53 (s, 1H), 1.29 (s, 3H).

²H NMR (61 MHz, CDCl₃): δ 3.27, 2.63, 2.55.

¹³C NMR (101 MHz, CDCl₃): δ 172.9, 145.7, 128.5, 126.7, 126.4, 51.5, 42.4 (t, *J* = 19.8 Hz), 36.0 (t, *J* = 20.5 Hz), 21.64 (d, *J* = 4.8 Hz).

LC-MS (ESI): Calcd for C₁₁H₁₂D₂O₂ [M+H]⁺: 181.1. Found: 181.0.

2,3-Dideuterated (S)-ethyl 3-phenylpentanoate. The product was isolated by flash chromatography (Et₂O/hexanes 1:20) as colorless oil. Yield: 38 mg, 93%.

Ee: 96%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 99/1, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.40-7.31 (m, 2H), 7.30-7.21 (m, 3H), 4.33-3.96 (m, 2H), 3.17-2.99 (m, 1H), 2.68 (s, 1H), 2.61 (s, 1H), 1.91-1.57 (m, 2H), 1.20 (td, $J = 7.1$, 1.9 Hz, 3H), 0.87 (t, $J = 7.4$ Hz, 3H).

^2H NMR (61 MHz, CDCl_3): δ 3.00, 2.64, 2.57.

^{13}C NMR (101 MHz, CDCl_3): δ 172.5, 164.5, 143.9, 128.3, 127.5, 126.4, 60.17, 43.5 (t, $J = 19.9$ Hz), 41.1 (t, $J = 19.9$ Hz), 29.02 (d, $J = 3.9$ Hz), 14.12, 11.89.

LC-MS (ESI): Calcd for $\text{C}_{13}\text{H}_{17}\text{D}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 209.2 Found: 209.2.

2,3-Dideuterated (*S*)-ethyl 3-(4-tolyl)butanoate. The product was isolated by flash chromatography (Et_2O /hexanes 1:20) as colorless oil. Yield: 40 mg, 96%.

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

1 PDA Multi 1 / 250nm 4nm

PeakTable

PDA Ch1 250nm 4nm			
Peak#	Ret. Time	Area	Area %
1	22.332	395857	50.030
2	23.294	395386	49.970
Total		791243	100.000

1 PDA Multi 1 / 205nm 4nm

PeakTable

PDA Ch1 205nm 4nm			
Peak#	Ret. Time	Area	Area %
1	21.033	2980830	95.521
2	22.160	139756	4.479
Total		3120585	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.12 (s, 4H), 4.09 (q, $J = 7.1$ Hz, 2H), 3.31-3.17 (m, 1H), 2.57 (s, 1H), 2.51 (s, 1H), 2.33 (s, 3H), 1.28 (d, $J = 2.8$ Hz, 3H), 1.20 (t, $J = 7.1$ Hz, 3H).

^2H NMR (61 MHz, CDCl_3): δ 3.24, 2.60, 2.53.

^{13}C NMR (101 MHz, CDCl_3): δ 172.5, 142.7, 135.8, 129.1, 126.60, 60.22, 42.7 (t, $J = 19.8$ Hz), 35.7 (t, $J = 19.1$ Hz), 21.7 (d, $J = 5.0$ Hz), 21.0, 14.18.

LC-MS (ESI): Calcd for $\text{C}_{14}\text{H}_{19}\text{D}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 223.2 Found: 223.1.

2,3-Dideuterated (*S*)-ethyl 3-(4-anisyl)butanoate. The product was isolated by flash chromatography (Et_2O /hexanes 1:20) as colorless oil. Yield: 42 mg, 95%.

Ee: 90%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 99.5/0.5, flow rate = 0.5 mL/min.

1 PDA Multi 1 / 216nm 4nm

PeakTable

PDA Ch1 216nm 4nm			
Peak#	Ret. Time	Area	Area %
1	15.848	1016063	49.936
2	16.721	1018674	50.064
Total		2034736	100.000

1 PDA Multi 1 / 254nm 4nm

PeakTable

PDA Ch1 254nm 4nm			
Peak#	Ret. Time	Area	Area %
1	16.324	25494	5.228
2	17.238	462134	94.772
Total		487627	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.19-7.08 (m, 2H), 6.94-6.78 (m, 2H), 4.16-4.00 (m, 2H), 3.78 (s, 3H), 3.29-3.17 (m, 1H), 2.54 (s, 1H), 2.49 (s, 1H), 1.27 (s, 3H), 1.18 (td, $J = 7.1, 1.5$ Hz, 3H).

^2H NMR (61 MHz, CDCl_3): δ 3.22, 2.56, 2.53.

^{13}C NMR (101 MHz, CDCl_3): δ 172.5, 158.1, 137.8, 127.7, 113.8, 60.2, 55.2, 42.9 (t, $J = 19.9$ Hz), 35.3 (t, $J = 19.8$ Hz), 21.8 (d, $J = 4.8$ Hz), 14.2.

LC-MS (ESI): Calcd for $\text{C}_{13}\text{H}_{17}\text{D}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 225.2 Found: 225.2.

2,3-Dideuterated (S)-ethyl 3-(3,4-methylenedioxyphenyl)butanoate. The product was isolated by flash chromatography (Et_2O /hexanes 1:30) as colorless oil. Yield: 45 mg, 96%.

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

1 PDA Multi 1 / 254nm 4nm

PeakTable

PDA Ch1 254nm 4nm			
Peak#	Ret. Time	Area	Area %
1	5.823	152183	49.944
2	6.181	152525	50.056
Total		304708	100.000

1 PDA Multi 1 / 200nm 4nm

PeakTable

PDA Ch1 200nm 4nm			
Peak#	Ret. Time	Area	Area %
1	5.787	353558	5.586
2	6.150	5975793	94.414
Total		6329351	100.000

^1H NMR (400 MHz, CDCl_3): δ 6.75-6.61 (m, 3H), 5.90 (s, 2H), 4.07 (q, $J = 7.1$ Hz, 2H), 3.28-3.08 (m, 1D), 2.51 (s, 1H), 2.46 (s, 1H), 1.24 (s, 3H), 1.18 (t, $J = 7.1$ Hz, 3H).

^2H NMR (61 MHz, CDCl_3): δ 3.17, 2.51, 2.47.

^{13}C NMR (101 MHz, CDCl_3): δ 172.3, 147.6, 145.9, 139.7, 119.7, 108.2, 107.2, 100.8, 60.2, 42.8 (t, $J = 19.8$ Hz), 35.9 (t, $J = 19.9$ Hz), 21.89 (d, $J = 4.9$ Hz), 14.19.

LC-MS (ESI): Calcd for $\text{C}_{13}\text{H}_{15}\text{D}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 239.1 Found: 239.1.

2,3-Dideuterated (*S*)-Ethyl 3-(4-trifluoromethylphenyl)butanoate. The product was isolated by flash chromatography (Et_2O /hexanes 1:20) as colorless oil. Yield: 49 mg, 94%.

Ee: 93%. Daicel Chiralcel IC-H, n-hexane/isopropanol 99.9/0.1, flow rate = 0.5 mL/min.

1 PDA Multi 1 / 200nm 4nm

PeakTable

PDA Ch1 200nm 4nm			
Peak#	Ret. Time	Area	Area %
1	14.448	5098263	50.061
2	14.871	5085882	49.939
Total		10184145	100.000

1 PDA Multi 1 / 210nm 4nm

PeakTable

PDA Ch1 210nm 4nm			
Peak#	Ret. Time	Area	Area %
1	14.661	43609	3.518
2	15.054	1195856	96.482
Total		1239465	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.55 (d, $J = 8.1$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 4.12-4.02 (m, 2H), 3.40-3.28 (m, 1H), 2.58 (s, 1H), 2.55 (s, 1H), 1.30 (d, $J = 4.6$ Hz, 3H), 1.17 (td, $J = 7.1, 1.6$ Hz, 3H).

^2H NMR (61 MHz, CDCl_3): δ 3.34, 2.61, 2.51.

^{13}C NMR (101 MHz, CDCl_3): δ 171.9, 149.7, 128.7 (q, $J = 32.4$ Hz), 127.2, 125.4 (q, $J = 3.7$ Hz), 124.2 (q, $J = 271.8$ Hz), 60.4, 42.2 (t, $J = 19.7$ Hz), 35.9 (t, $J = 20.1$ Hz), 21.6 (d, $J = 4.5$ Hz), 14.1.

LC-MS (ESI): Calcd for $\text{C}_{13}\text{H}_{14}\text{D}_2\text{F}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 263.1 Found: 263.0.

2,3-Dideuterated (*S*)-ethyl 3-(3-tolyl)butanoate. The product was isolated by flash chromatography (Et_2O /hexanes 1:30) as colorless oil. Yield: 39 mg, 95%.

Ee: 92%. Daicel Chiralcel OD-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	7.717	14152343	51.589
2	8.756	13280292	48.411
Total		27432635	100.000

1 PDA Multi 1 / 190nm 4nm

PeakTable			
Peak#	Ret. Time	Area	Area %
1	9.753	175709	3.834
2	10.211	4406741	96.166
Total		4582450	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.25-7.13 (m, 1H), 7.08-6.94 (m, 3H), 4.16-4.04 (m, 2H), 3.36-3.13 (m, 1H), 2.59 (s, 1H), 2.52 (s, 1H), 2.35 (s, 3H), 1.30 (s, 3H), 1.20 (td, $J = 7.1, 1.6$ Hz, 3H).

^2H NMR (61 MHz, CDCl_3): δ 3.24, 2.61, 2.54.

^{13}C NMR (101 MHz, CDCl_3): δ 172.5, 145.7, 138.0, 128.4, 127.6, 127.1, 123.7, 60.2, 42.6 (t, $J = 19.7$ Hz), 36.0 (t, $J = 19.9$ Hz), 21.7 (d, $J = 5.1$ Hz), 14.2.

LC-MS (ESI): Calcd for $\text{C}_{13}\text{H}_{17}\text{D}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 209.2 Found: 209.1.

2,3-Dideuterated (*S*)-Ethyl 3-(2-thienyl)butanoate. The product was isolated by flash chromatography (Et_2O /hexanes 1:20) as colorless oil. Yield: 37 mg, 93%.

Ee: 89% ee. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 99.5/0.5, flow rate = 0.5 mL/min.

1 PDA Multi 1 / 223nm 4nm

PeakTable			
PDA Ch1 223nm 4nm			
Peak#	Ret. Time	Area	Area %
1	13.380	896008	50.060
2	23.021	893859	49.940
Total		1789867	100.000

1 PDA Multi 1 / 225nm 4nm

PeakTable			
PDA Ch1 225nm 4nm			
Peak#	Ret. Time	Area	Area %
1	12.915	255263	5.800
2	20.452	4146194	94.200
Total		4401458	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.13 (dd, $J = 5.1, 1.1$ Hz, 1H), 6.91 (dd, $J = 5.1, 3.5$ Hz, 1H), 6.84 (dd, $J = 3.5, 1.1$ Hz, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 3.63-3.55 (m, 1H), 2.66 (s, 1H), 2.54 (s, 1H), 1.38 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 3H).

^2H NMR (61 MHz, CDCl_3): δ 3.59, 2.68, 2.56.

^{13}C NMR (101 MHz, CDCl_3): δ 172.0, 149.6, 126.6, 123.0, 122.9, 60.42, 43.5 (t, $J = 19.8$ Hz), 31.6 (t, $J = 20.1$ Hz), 22.52 (d, $J = 4.7$ Hz), 14.20.

LC-MS (ESI): Calcd for $\text{C}_{10}\text{H}_{13}\text{D}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 201.1 Found: 201.1.

2,3-Dideuterated (*S*)-ethyl 3-(3-pyridyl)butanoate. The product was isolated by flash chromatography (Et_2O /hexanes 1:5) as colorless oil. Yield: 36 mg, 92%.

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

1 PDA Multi 1 / 200nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	18.794	4581211	49.889
2	21.896	4601545	50.111
Total		9182756	100.000

1 PDA Multi 1 / 235nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	24.359	34707	3.042
2	27.012	1106279	96.958
Total		1140986	100.000

^1H NMR (400 MHz, CDCl_3): δ 8.53-8.36 (m, 2H), 7.50 (d, $J = 7.8$ Hz, 1H), 7.23-7.10 (m, 1H), 4.03 (q, $J = 7.1$ Hz, 2H), 3.33-3.15 (m, 1H), 2.53 (s, 1H), 2.43 (s, 1H), 1.28 (s, 3H), 1.13 (t, $J = 7.1$ Hz, 3H).

^2H NMR (61 MHz, CDCl_3): δ 3.25, 2.55.

^{13}C NMR (101 MHz, CDCl_3): δ 171.8, 148.8, 147.9, 140.7, 134.1, 123.4, 60.4, 42.1 (t, $J = 19.8$ Hz), 33.6 (t, $J = 19.9$ Hz), 21.46 (d, $J = 4.0$ Hz), 14.11.

LC-MS (ESI): Calcd for $\text{C}_{11}\text{H}_{14}\text{D}_2\text{NO}_2$ $[\text{M}+\text{H}]^+$: 196.1 Found: 196.1.

2,3-Dideuterated (S)-ethyl 2-(1-tetralinyl)acetate. The (*E*)-isomer of starting material was used. The product was isolated by flash chromatography (Et_2O /hexanes 1:15) as colorless oil. Yield: 40 mg, 93%.

Ee: 84%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 98/2, flow rate = 1.0 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	5.901	6843130	50.062
2	6.546	6826070	49.938
Total		13669200	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	6.110	181877	7.362
2	6.749	2288505	92.638
Total		2470382	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.23-7.04 (m, 4H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.43-3.30 (m, 1H), 2.88-2.71 (m, 2H), 2.69 (s, 1H), 2.52 (s, 1H), 1.98-1.67 (m, 4H), 1.29 (t, $J = 7.1$ Hz, 3H), 0.98-0.71 (m, 1H).

^2H NMR (61 MHz, CDCl_3): δ 3.36, 2.71, 2.54.

^{13}C NMR (101 MHz, CDCl_3): δ 172.9, 139.3, 137.2, 129.3, 128.3, 126.0, 125.8, 60.4, 41.7 (t, $J = 19.8$ Hz), 34.1 (t, $J = 20.0$ Hz), 29.53, 27.98 (d, $J = 4.7$ Hz), 19.52, 14.29.

LC-MS (ESI): Calcd for $\text{C}_{14}\text{H}_{17}\text{D}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 221.2 Found: 221.1.

2,3-Dideuterated (S)-ethyl 2-(4-chromanyl)acetate. The (*E*)-isomer of starting material was used. The product was isolated by flash chromatography (EtOAc/hexanes 1:4) as colorless oil. Yield: 41 mg, 94%.

Ee: 88%. Daicel Chiralcel OJ-H, *n*-hexane/isopropanol 90/10, flow rate = 1.0 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.19-7.03 (m, 2H), 6.91-6.76 (m, 2H), 4.24-4.12 (m, 4H), 3.41-3.31 (m, 1H), 2.77 (s, 1H), 2.50 (s, 1H), 2.23-2.08 (m, 1H), 1.98-1.74 (m, 1H), 1.28 (t, $J = 7.1$ Hz, 3H).

^2H NMR (61 MHz, CDCl_3): δ 3.35, 2.79, 2.53.

^{13}C NMR (101 MHz, CDCl_3): δ 172.2, 154.6, 128.7, 127.9, 124.5, 120.4, 117.1, 63.2, 60.6, 41.0 (t, $J = 19.7$ Hz), 30.0 (t, $J = 18.2$ Hz), 27.2 (d, $J = 3.6$ Hz), 14.3.

LC-MS (ESI): Calcd for $\text{C}_{13}\text{H}_{15}\text{D}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 223.1 Found: 223.1.

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