Studies on Catalytic Asymmetric Hydrogenation of Heteroarenes and Arenes: Isoxazoles and Salicylic Acid Derivatives

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https://doi.org/10.15017/1654656

出版情報：九州大学, 2015, 博士（理学）, 課程博士
バージョン：

Studies on Catalytic Asymmetric Hydrogenation of Heteroarenes and Arenes: Isoxazoles and Salicylic Acid Derivatives

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2016

Contents

Abbreviations

Me	methyl	DMF	*N*,*N*-dimethylformamide
Et	ethyl	BINAP	2,2'-bis(diphenylphos-
Pr	propyl		-phanyl)-1,1-dinaphthyl
Bu	butyl	cod	cyclooctadiene
Cy	cyclohexyl	°C	degrees Celsius
Bn	benzyl	ee	enantiomeric excess
Ph	phenyl	XRF	energy dispelse X-ray
Ar	aryl		spectrometry
Ts	tosyl	NMR	nuclear magnetic
Ac	acetyl		resonance
Bz	benzoyl	GC	gas chromatography
Boc	*tert*-butoxycarbonyl	*cat*.	catalyst
Cbz	benzyloxycabonyl	*aq*.	aqueous
Fmoc	9-fluorenylmethyloxy-	*sat*.	saturated
	-carbonyl	calcd.	calcurated
Tf	trifluoromethanesurfonyl	*lit.*	literature
TMS	trimethylsilyl	δ	chemicall shift (ppm, NMR)
TBS	*tert*-butyldimethylsiliyl	*J*	coupling constant
MOM	methoxymethyl	ESI	electrospray ionization
PG	protecting group	CSI	cold spray ionization
TFAA	trifleoroacetic anhydride	FAB	fast atom bombardent
Boc-ON	2-(*tert*-butoxycarbonyloxy-	HPLC	high performance liquid
	-imino)-2-phenylacetonitrile		chromatography
Cbz-OSu	*N*-(benzyloxycarbonyloxy)-	MPLC	medium-pressure liquid
	-succinimide		chromatography
Fmoc-OSu	*N*-(9-fluorenylmethyloxy-	HRMS	high resolution mass
	-carbonyloxy)succinimide		spectrometry
THF	tetrahydrofuran	MS	mass spectrometry
CPME	cyclopentyl methyl ether	M	molarity
t-AmylOH	2-methyl-2-butanol	mp.	melting point
DMSO	dimethylsulfoxide	n.d.	not determined
DCE	1,2-dichloroethane	*o*	*oltho*

p	*para*
s	singlet (NMR)
d	doublet (NMR)
t	triplet (NMR)
q	quintet (NMR)

Chapter 1

General Introduction

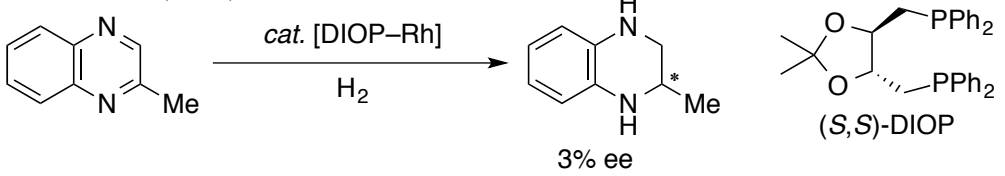
Asymmetric synthesis of chiral compounds is an important issue in modern organic synthesis, because each enantiomer exhibits different biological activity from the other. For developing the asymmetric synthesis, various approaches have been proposed. Among these approaches, the catalytic reaction using transition-metal complexes has intensively been studied because the structure of the metal complex is easily modified through designing its ligand. The first study of transition-metal-catalyzed asymmetric reactions had been reported on copper-catalyzed cyclopropanation by Noyori in 1966.[1] In 1968, Knowles and Horner independently reported the first attempt of the catalytic asymmetric hydrogenation of alkenes with homogeneous chiral phosphine–rhodium catalysts.[2,3] Since then, many researchers have developed various chiral catalysts for the catalytic asymmetric hydrogenation. Nowadays, various prochiral unsaturated groups, such as alkenes, ketones, and imines, can be hydrogenated to the corresponding enantiopure products through the asymmetric catalysis. Catalytic asymmetric hydrogenation is regarded as a powerful method for organic synthesis and often used for the industrial production of optically active compounds.

On the other hand, (hetero)aromatic rings, which are also unsaturated functionalities, were believed difficult to reduce with high enantioselectivity because the reduction of (hetero)arenes would require a harsh reaction condition to break their resonance stabilization. Furthermore, the Lewis basic heteroatom in the substrates as well as the products may strongly interact to the metal atom in the chiral catalyst. However, the hydrogenation of (hetero)arenes will efficiently provide chiral 5- or 6-membered rings, which are seen in many natural products and useful biologically active molecules. The reaction creates multiple chiral centers in a single process if the aromatic ring of the substrate has multitude substituents. Therefore, the catalytic asymmetric hydrogenation of (hetero)arenes will be a useful tool for organic synthesis, if it will routinely proceed with high enantioselectivity.

The first report of catalytic asymmetric hydrogenation of heteroarenes had been made by Murata and coworkers in 1987 (eq. 1).[4] They had attempted the hydrogenation of 2-methylquinoxaline by using a DIOP–rhodium catalyst. The chiral rhodium catalyst allowed the substrate to be converted into 1,2,3,4-tetrahydro-2-methylquinoxaline in moderate yield, but the chiral product was obtained with only 3% ee. In 1995, Takaya and coworkers reported the hydrogenation

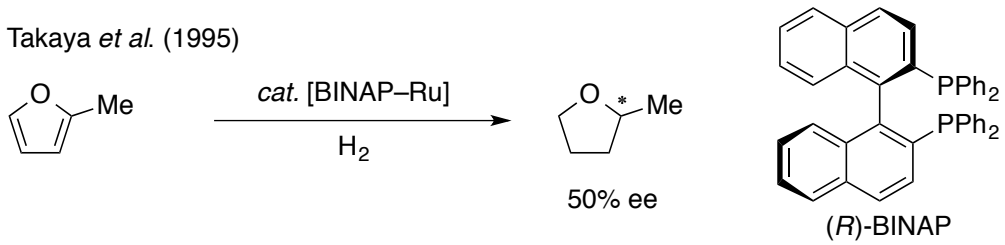
of 2-methylfuran with an optically active BINAP–ruthenium catalyst (eq. 2).[5] The chiral catalyst produced 2-methyltetrahydrofurane with moderate enantiomeric excess. In 1996, Lonza AG disclosed a method for the catalytic asymmetric hydrogenation of pyrazine-2-carboxylic acid derivatives in patent (eq. 3).[6] The asymmetric hydrogenation proceeded with 78% ee in the presence of a Josiphos–rhodium catalyst. In these pioneering works, however, the enantioselectivities and catalytic efficacies were insufficient for the preparation of optically active compounds, and the substrate scopes were limited to several substrates. The first successful report achieving high stereoselectivity had been made by Bianchini and coworkers (eq. 4).[7] They successfully obtained the hydrogenation product with 90% ee. However, the yield of the tetrahydroquinoxaline was insufficient (54% conversion). The iridium-catalyzed asymmetric hydrogenation was applied to only one substrate.

Murata *et al.* (1987)



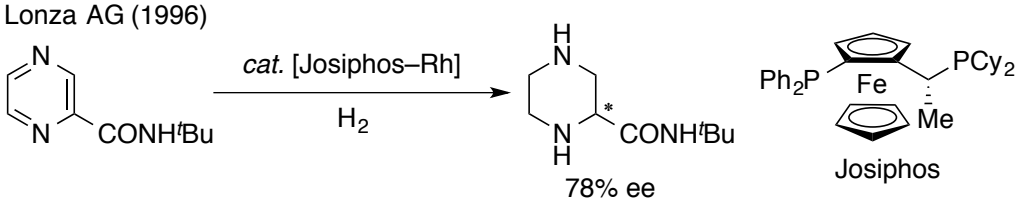
(1)

Takaya *et al.* (1995)



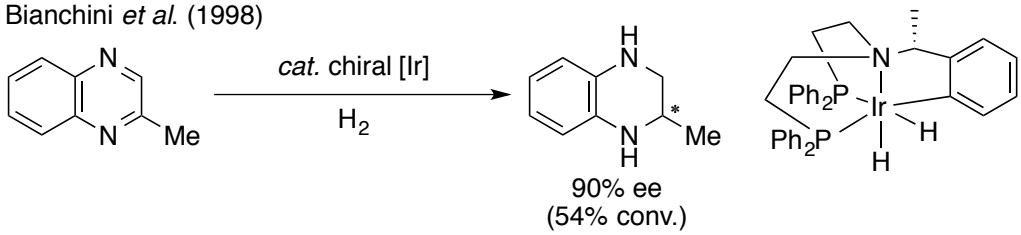
(2)

Lonza AG (1996)



(3)

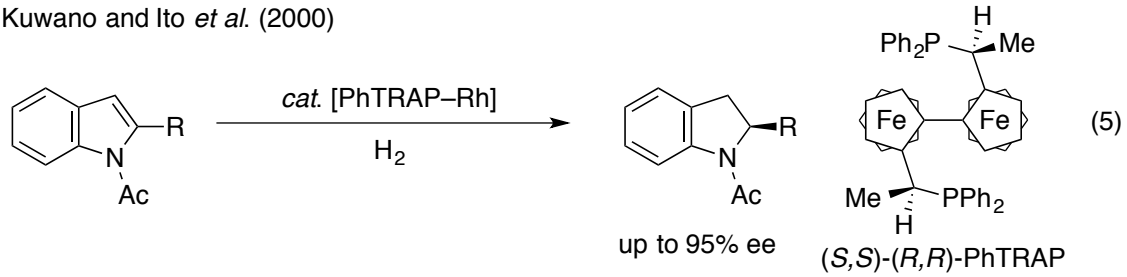
Bianchini *et al.* (1998)



(4)

In 2000, Kuwano and Ito successfully developed the rhodium-catalyzed enantioselective hydrogenation of *N*-acetylindoles, which were converted into *N*-acetylindolines with up to 95% ees (eq. 5).[8a] The chiral rhodium catalyst developed in this report was applicable to the synthesis of various chiral 2-substituted indolines. In this study, a *trans*-chelating chiral diphosphine, PhTRAP,[9] was used as the chiral ligand on the rhodium. The use of the *trans*-chelating ligand is crucial for achieving the high stereoselectivity. The PhTRAP–rhodium catalyst allowed the hydrogenation of 3-substituted *N*-tosylindoles to proceed with high enantioselectivity.[8b,8c]

Kuwano and Ito *et al.* (2000)



(5)

Since the successful report on the asymmetric hydrogenation of indoles, catalytic asymmetric hydrogenations of (hetero)arenes have been studied intensively by many researchers. Nowadays, various heteroarenes can be reduced with hydrogen gas through asymmetric catalysis, giving the corresponding chiral heterocycles with high enantiomeric excess as shown in Figure 1.[10] Despite these efforts, however, asymmetric catalysis is not applicable to the asymmetric reduction of many heteroarenes.

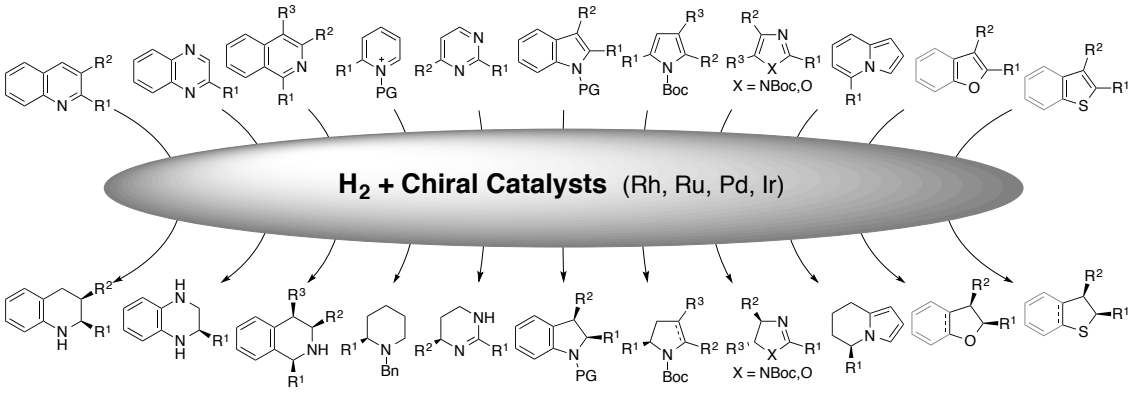
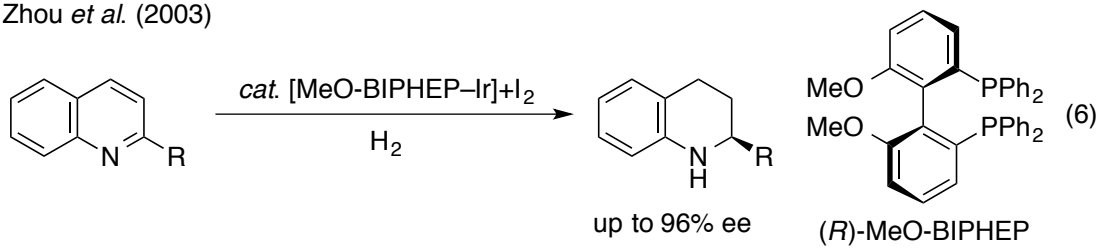


Figure 1. Catalytic Asymmetric Hydrogenations of Heteroarenes

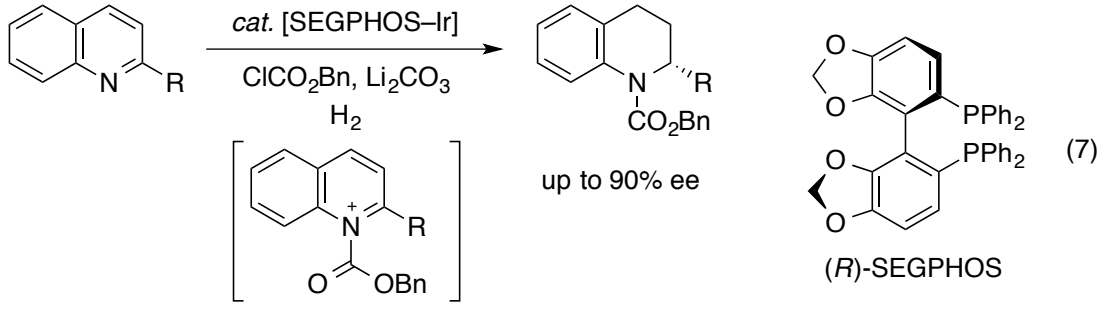
For the asymmetric hydrogenation of azines, which are 6-membered nitrogen-containing heteroarenes, chiral bisphosphine–iridium complexes are commonly used as the catalysts. In 2003, Zhou and his coworkers reported the first success in the asymmetric hydrogenation of azines, 2-alkylquinolines (eq. 6).[11] The authors proved that the iridium complexes generated by mixing $[IrCl(cod)]_2$, a chiral bisphosphine, and iodine efficiently catalyzes the hydrogenation of azines. In the reports, MeO-BIPHEP was the chiral ligand of choice for the iridium-catalyzed hydrogenation of 2-methylquinoline. The MeO-BIPHEP–iridium catalyst produced 2-methyl-1,2,3,4-tetrahydroquinoline with 94% ee.

Zhou *et al.* (2003)



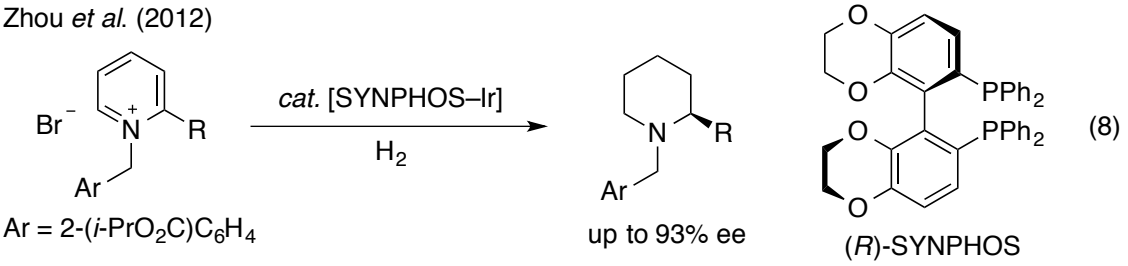
Electrophilicity of azines is known to be enhanced by quaternizing their nitrogen atom with an alkyl or acyl halide. The quaternization of azines is often utilized for improving the iridium-catalyzed hydrogenation of azines. Zhou demonstrated that the activation method was applicable to the iridium-catalyzed asymmetric hydrogenation of quinolines (eq. 7).[12] By activating the substrate with benzyl chlorocarbonate, the bisphosphine–iridium complex can catalyze the hydrogenation without use of the iodine additive. The hydrogenation of isoquinolines was allowed by the quaternization approach, but the enantioselectivity was moderate.

Zhou *et al.* (2006)



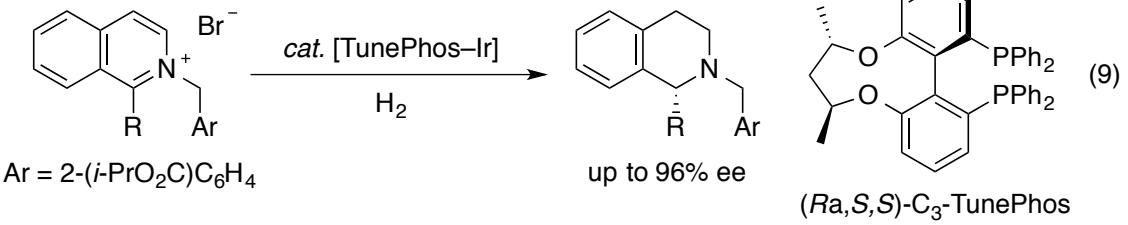
Zhou has applied the activation of azine substrates with benzylic halides to the asymmetric hydrogenations of pyridines, isoquinolines, and pyrro[1,2-*a*]pyrazines (eqs. 8–10).[13a-c] These heteroaromatic substrates were reduced to the corresponding chiral heterocycles with over 90% ee. Chen and Zhang also used this methodology for developing the asymmetric hydrogenation of pyridines with a chiral phosphole–iridium catalyst (eq. 11).[13d]

Zhou *et al.* (2012)



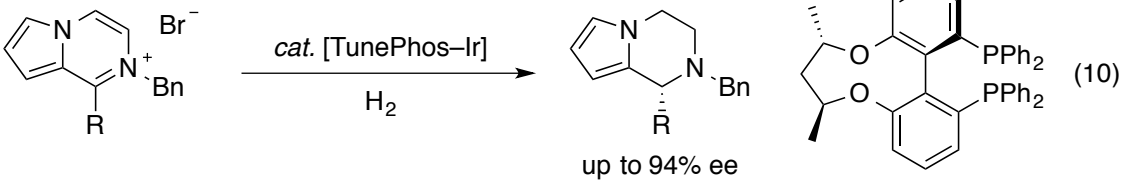
Ar = 2-(*i*-PrO_2C)C_6H_4 up to 93% ee (*R*)-SYNPHOS (8)

Zhou *et al.* (2013)



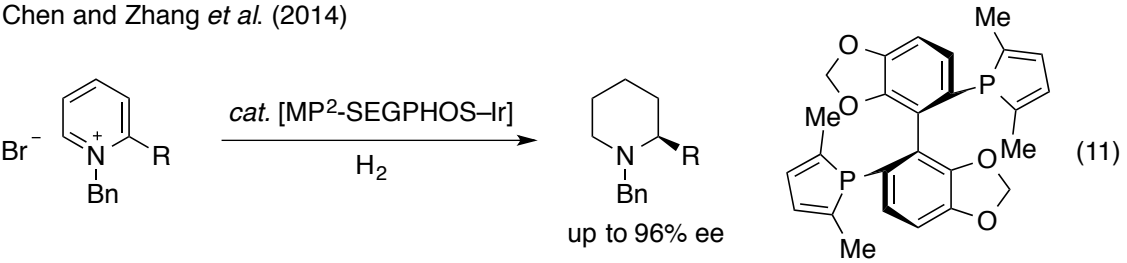
Ar = 2-(*i*-PrO_2C)C_6H_4 up to 96% ee (*R*a,*S*,*S*)-C_3-TunePhos (9)

Zhou *et al.* (2014)



up to 94% ee (*R*a,*S*,*S*)-C_3-TunePhos (10)

Chen and Zhang *et al.* (2014)

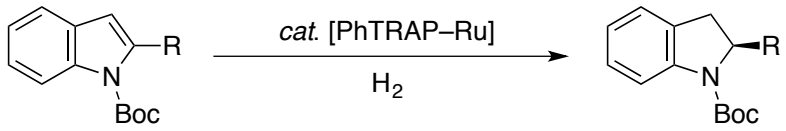


up to 96% ee (*R*)-MP^2-SEGPHOS (11)

In parallel with the above studies by other researchers, Kuwano's group, including me, has continued to develop the asymmetric hydrogenation of

heteroaromatics with PhTRAP ligand. In 2006, Kuwano's group reported that the ruthenium complex modified with PhTRAP also worked as a chiral catalyst for the asymmetric hydrogenation of *N*-Boc-indoles.[14] The PhTRAP–ruthenium catalyst allows a series of Boc-protected indoles to be hydrogenated with high enantioselectivity, producing *N*-Boc-indolines with up to 96% ee (eq. 12). The Boc-protection is favorable for obtaining unprotected indolines, because the protective group is readily eliminated under a mild acidic condition.

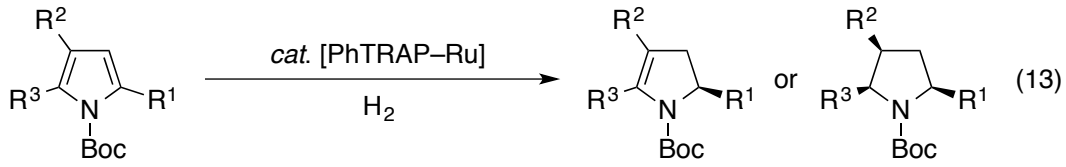
Kuwano *et al.* (2006)



up to 96% ee (12)

The PhTRAP–ruthenium catalyst is effective for the asymmetric hydrogenation of pyrroles. The chiral catalyst transformed various *N*-Boc-2,3,5-trisubstituted pyrroles into the chiral pyrrolidines or 2,3-dihydropyrroles with high enantiomeric excesses (eq. 13).[15] In particular, the reaction of 2,3,5-triarylpyrroles produced the 2,3,5-triaryl-4,5-dihydropyrroles with up to 99.7% ee.

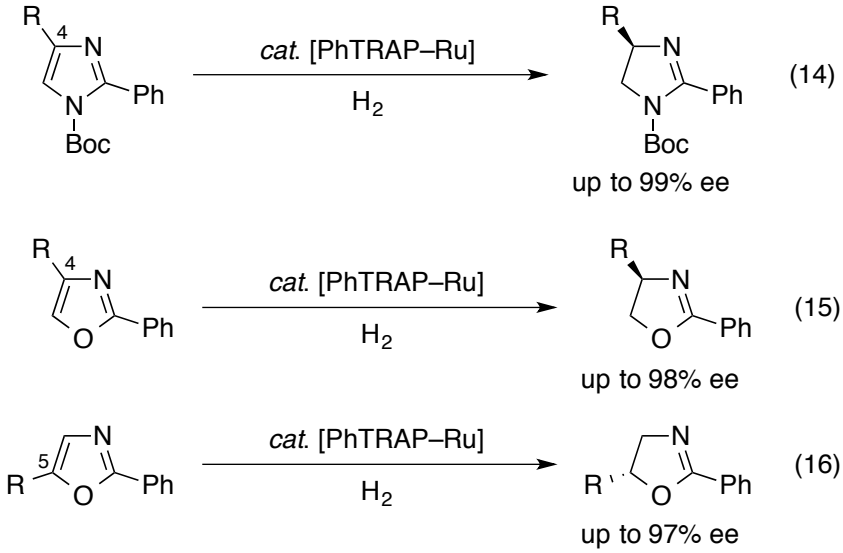
Kuwano *et al.* (2008)



up to 99.7% ee up to 96% ee (13)

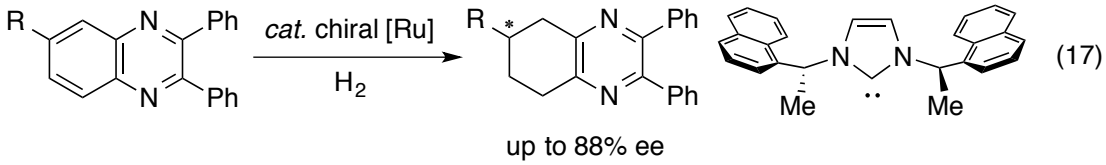
2,4-Disubstituted *N*-Boc-imidazoles are also hydrogenated in high enantioselectivity with the PhTRAP–ruthenium catalyst. The ruthenium-catalyzed hydrogenation selectively produced chiral imidazolines with up to 99% ees (eq. 14).[16] No formation of fully-saturated imidazolidines was observed in the asymmetric reaction. Furthermore, the chiral ruthenium catalyst allows the hydrogenation of 4- or 5-substituted oxazoles to produce the corresponding chiral oxazolines with high enantioselectivity (eqs. 15 and 16).

Kuwano *et al.* (2011)



In contrast to heteroarenes, the asymmetric hydrogenation of carbocyclic arenes remains a formidable issue in organic chemistry. To date, catalytic asymmetric hydrogenations of aromatic carbocycles are known only three reports. In 2011, Glorious and coworkers were demonstrated the carbocycle-selective hydrogenation of quinoxalines bearing phenyl groups on 1,2-position giving 5,6,7,8-tetrahydroqunoxalines with up to 88% ee using the chiral carben–ruthenium catalyst (eq. 17).[17] Also, Kuwano's group had been reported the enantioselective hydrogenations of arenes using PhTRAP–ruthenium catalyst. In 2012, they reported the enantioselective hydrogenations of arenes containing no heteroatoms, naphthalenes (eq. 18).[18] The PhTRAP–ruthenium catalyst allowed a series of 2,6- or 2,7-disubstituted naphthelenes to be hydrogenated with high enantioselectivity, and gave 1,2,3,4-hetrahydronaphthalene with up to 96% ee. The PhTRAP–ruthenium catalyst also reduces quinoline carbocycles selectively (eq. 19).[19] 8-substituted quinolines substrates were reduced to the corresponding chiral 5,6,7,8-tetrahydroquinolines were obtained with up to 83% ees.

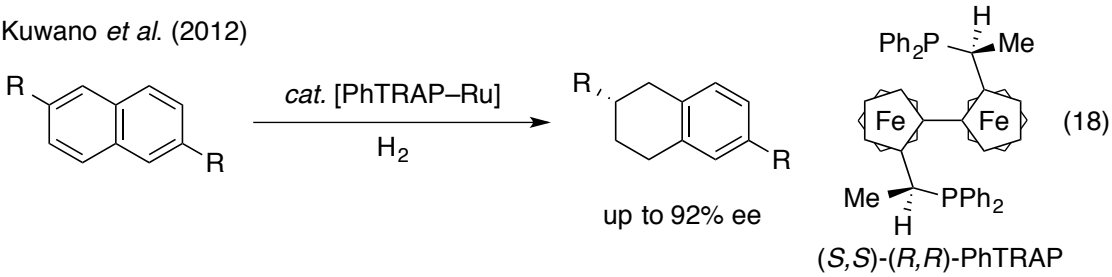
Glorious *et al.* (2011)



(17)

up to 88% ee

Kuwano *et al.* (2012)

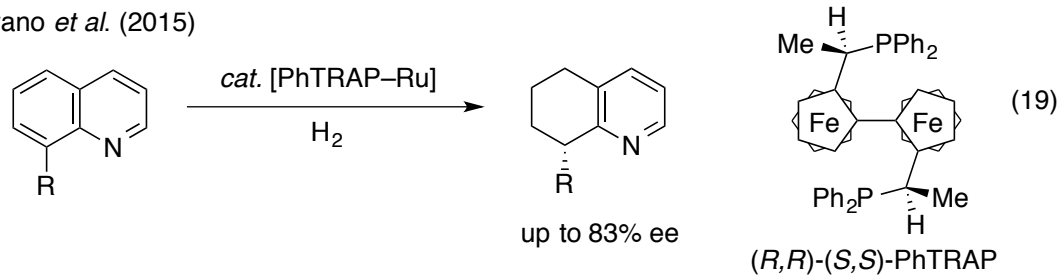


(18)

up to 92% ee

(*S,S*)-(*R,R*)-PhTRAP

Kuwano *et al.* (2015)



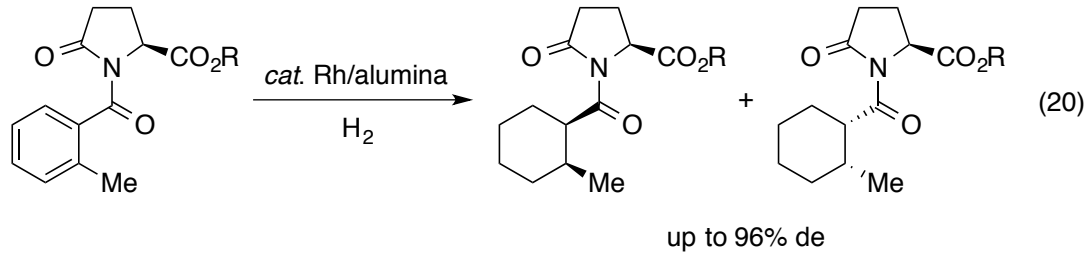
(19)

up to 83% ee

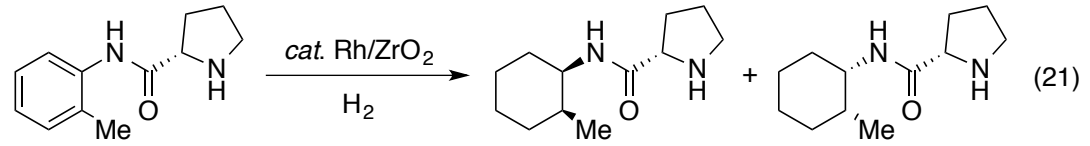
(*R,R*)-(*S,S*)-PhTRAP

However, these substrates are polycyclic aromatics. The reaction of monocyclic arenes, which are more stabilized with the aromaticity, has been hardly studied. A few challenging reports are known. For example, Besson and his coworkers were successful in highly stereoselective hydrogenation of 2-methylbenzoic acid with chiral auxiliary catalyzed by the supported metal catalysts (eq. 20).[20] In addition, 2-methylaniline was also hydrogenated with moderate stereoselectivity using the similar method by Prins (eq. 21).[21] However, these methods required a stoichiometric amount of chiral sauce and some steps to induce and remove the chiral auxiliary groups. In addition, the substrate scope was limited only one substrate in these reactions.

Besson *et al.* (1997–2000)

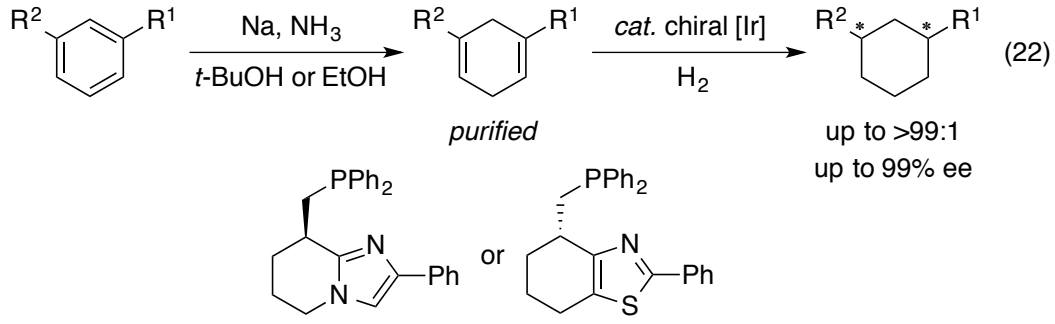


Prins *et al.* (1999)



Philippot, RouCous, and Claver attempted the hydrogenation of aromatics in the presence of the supported metal catalyst coordinated on chiral organic compounds, but all products were observed as racemic form.[22] Furthermore, Andersson reported the enantioselective reduction of disubstituted benzenes through Birch reduction and hydrogenation using a chiral iridium catalyst (eq. 22).[23] However, it should be called the hydrogenation of 1,4-cyclohexadienes, not the direct hydrogenation of benzene rings because the aromaticity-breaking step is not a hydrogenation and 1,4-cyclohexadienes were purified.

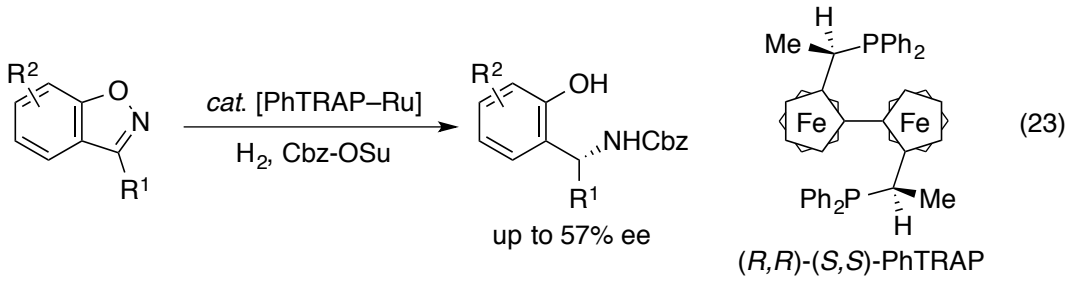
Andersson *et al.* (2011)



Consequently, the catalytic asymmetric hydrogenation of benzene rings is one of the most difficult issues in the organic synthesis.

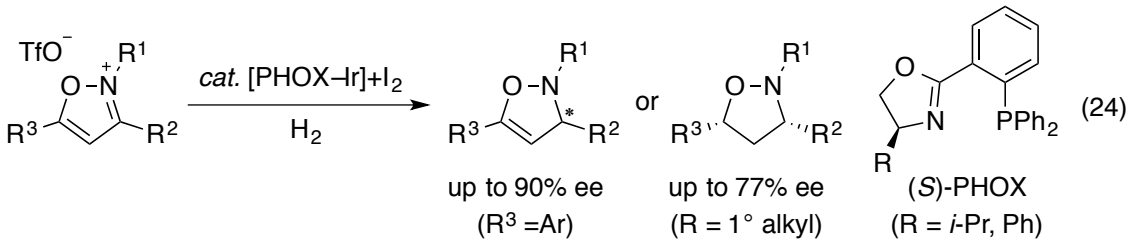
In my Ph. D. course study, I envisioned that PhTRAP–ruthenium complex

also might exhibit high enantioselectivity for the hydrogenation of isoxazoles. The asymmetric hydrogenation would provide optically active isoxazolines or isoxazolidines, which are often seen in biologically active compounds. In Chapter 2 of this thesis, I have investigated the catalytic asymmetric hydrogenation of 3-substituted benzisoxazoles with the PhTRAP–ruthenium catalyst.[24] The hydrogenation is unanticipatedly accompanied by the N–O bond cleavage to yield chiral α-substituted *o*-hydroxybenzylamines (eq. 23).



(23)

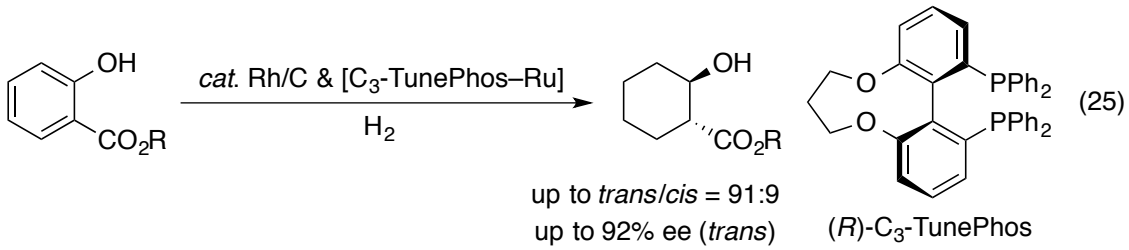
In contrast, I have also developed a method for the asymmetric hydrogenation of isoxazoles without the cleavage of N–O bonds. In Capter 3, I will show the hydrogenation of isoxazolium salts by using a chiral iridium catalyst. The asymmetric reaction gave 4-isoxazolines with up to 90% ees or *cis*-isoxazolidines with up to 77% ees (eq. 24).[25]



(24)

Furthermore, I envisioned that combinational use of metal supported catalysts and chiral transition-metal catalysts might be effective for the hydrogenation of benzene rings. In Capter 4, I have also investigated the first catalytic asymmetric hydrogenation of benzene rings with high stereoselectivity. Salicylic acid derivatives were quantitatively converted to 2-hydroxycyclohecanecarboxylic acid derivateves with high stereoselectivity in the presence of rhodium on activated carbon and C_3-Tunehos–

ruthenium complex as catalysts (eq. 25).[26]



(25)

up to *trans*/*cis* = 91:9
up to 92% ee (*trans*)

(*R*)-C_3-TunePhos

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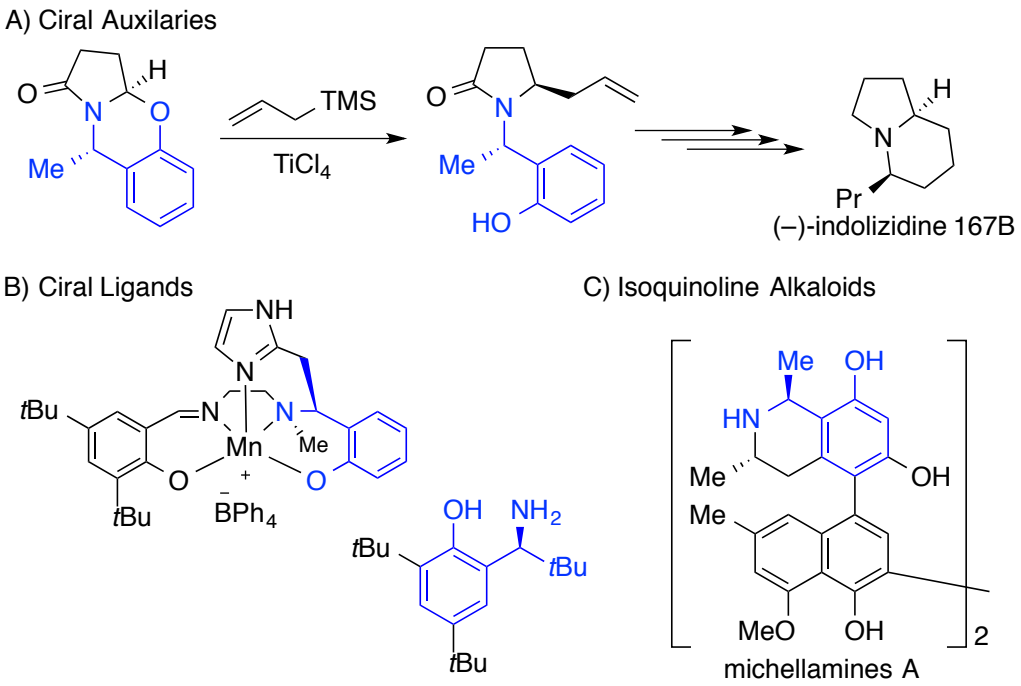
Chapter 2

Catalytic Asymmetric Hydrogenation of Benzisoxazoles

2.1. Introduction

Kuwano's group has developed the catalytic asymmetric hydrogenation of nitrogen-containing 5-membered heteroarenes using PhTRAP–ruthenium catalyst. I conceived that PhTRAP–ruthenium complex might also catalyze the hydrogenation of 5-membered heteroarenes containing an N–O bond, such as benzisoxazoles. If the hydrogenation of 3-substituted benzisoxazoles were to proceed with high enantioselectivity, it would provide optically active benzisoxazolines bearing a stereogenic center at the 3-position. The benzisoxazoline products can be transformed into optically active α-substituted *o*-hydroxybenzylamines, because N–O bonds are known to break through heterogeneous catalysis under hydrogenation conditions.[1] Enantiomeric benzylamines are often used as chiral auxiliaries[2] and constituents of catalysts for asymmetric synthesis (Scheme 1A and 1B).[3] Furthermore, the structural motives are seen in many isoquinoline alkaloids (Scheme 1C).[4]



Scheme 1. Optically Active α-Substituted *o*-Hydroxybenzylamines Moieties

Chiral amines are typically prepared through enzymatic[5] or chemical resolution of their racemates.[6] The diastereoselective nucleophilic additions to imines have been applied to the asymmetric synthesis of the chiral amines.[7] However, to my knowledge, there have been only a few reports on the enantioselective synthesis of α-substituted

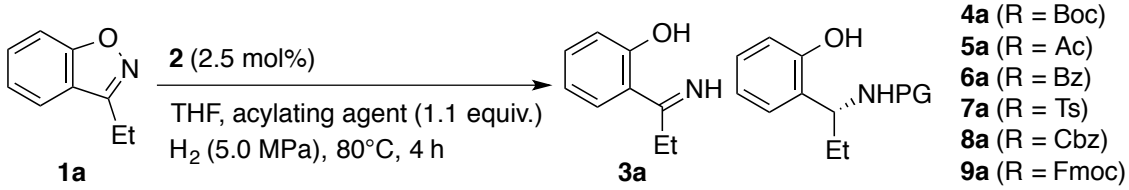
o-hydroxybenzylamines.[8] In this chapter, I report a catalytic asymmetric hydrogenation of benzisoxazoles to yield chiral α-substituted *o*-hydroxybenzylamines. The asymmetric reaction proceeded through the PhTRAP–ruthenium catalysis, which transformed the benzo-fused heteroaromatics into α-substituted *o*-hydroxybenzylamines in high yields and up to 57% *ee*.

2.2. Results and Discussions

In my initial attempts, 3-ethylbenzisoxazole (**1a**) was treated with 5.0 MPa of hydrogen in toluene or isobutyl alcohol at 80 °C for 4 h in the presence of {RuCl(*p*-cymene)[(*R*,*R*)-(*S*,*S*)-PhTRAP]}Cl (**2**) (Table 1, entries 1 and 2).[9] A small amount of **1a** reacted with hydrogen, but no saturation of the C–N double bond was observed in either reaction, which afforded only the achiral imine **3a**, formed through the hydrogenolytic cleavage of the N–O bond of **1a**.[10] The ruthenium catalyst failed to reduce the C–N double bond even in the presence of *N*,*N*,*N*',*N*'-tetramethylguanidine (TMG) (entries 3 and 4), even though in our previous reports the base additive brought about a remarkable acceleration of hydrogenations of heteroaromatics.[11] I was pleased that the hydrogenation of the benzisoxazole was accompanied by the reduction of the C–N double bond in the presence of stoichiometric Boc_2O, which afforded *N*-Boc-protected (*R*)-1-(2-hydroxyphenyl)-1-propylamine **4a** with 25% ee (entry 5). Surprisingly, no formation of **4a** was observed in the reaction using both Boc_2O and TMG (entry 6). The base additive might inhibit the hydrogenation of imine **3a**. Various aprotic solvents were evaluated for the asymmetric hydrogenation (entries 7–10). As a result, **4a** was obtained with the highest ee value when the hydrogenation was conducted in an ethereal solvent, such as THF or CPME. The benzisoxazole was fully converted to the *N*-protected amine **4a** with 44% ee after 24 h (entry 11). The hydrogenation of **1a** was conducted by using other amino group protecting agents in place of Boc_2O. Carboxylic anhydrides, Ac_2O and Bz_2O, also worked as the acylating agent in the asymmetric reduction of the benzisoxazole to give the corresponding chiral amine with 43% and 47% ee, respectively (entries 12 and 13). Use of sulfonic anhydride resulted in a complex mixture, which contained a small amount of **3a** (entry 14). Various *N*-acylating agents other than acid anhydrides were applied to the asymmetric reactions. No conversion of **1a** took place when the reaction was

conducted with Boc-ON (entry 15). Use of *O*-alkoxycarbonyl-*N*-hydroxysuccinimide led to a remarkable increase in the reaction rate and some improvement of the stereoselectivity (entries 16–18). The reactions with Cbz-OSu and Fmoc-OSu in THF gave the desired products **8a** and **9a** with 52% and 56% ee, respectively. The hydrogenation product **4a** was formed under 1.0 MPa of hydrogen, but the lower hydrogen pressure caused a significant decrease in the reaction rate (entry 19). Substrate **1a** and imine **3a** completely disappeared from the reaction mixture at 24 h.

Table 1. Optimization of Reaction Conditions[a]

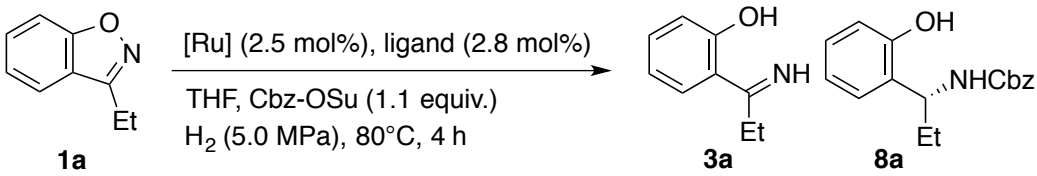


entry	solvent	acylating agent	yield (**3a**)[b]	yield[b]	ee[c]
1	toluene	-	23%	0% (**4a**)	-
2	*i*-BuOH	-	12%	0% (**4a**)	-
3[d]	toluene	-	9%	0% (**4a**)	-
4[d]	*i*-BuOH	-	13%	0% (**4a**)	-
5	toluene	Boc_2O	39%	22% (**4a**)	25% (*R*)
6[d]	toluene	Boc_2O	22%	0% (**4a**)	-
7	DCE	Boc_2O	63%	19% (**4a**)	30% (*R*)
8	CPME	Boc_2O	32%	18% (**4a**)	40% (*R*)
9	THF	Boc_2O	18%	31% (**4a**)	39% (*R*)
10	EtOAc	Boc_2O	22%	14% (**4a**)	21% (*R*)
11[e]	THF	Boc_2O	0%	>99% (93%) (**4a**)	44% (*R*)
12	THF	Ac_2O	0%	87% (**5a**)	43%
13	THF	Bz_2O	0%	85% (**6a**)	47%
14	THF	Ts_2O	17%	0% (**7a**)	-
15	THF	Boc-ON	0%	0% (**4a**)	-
16	CPME	Cbz-OSu	15%	58% (**8a**)	43%
17	THF	Cbz-OSu	0%	>99% (89%) (**8a**)	52%
18	THF	Fmoc-OSu	0%	>99% (93%) (**9a**)	56%
19[e,f]	THF	Cbz-OSu	0%	82% (**8a**)	52%

[a] Reactions were conducted on a 0.20 mmol scale in 1.0 mL of solvent under 5.0 MPa of H_2 at 80°C for 4 h. The ratio of **1a**/**2**/acylating agent was 100:2.5:110. [b] Determined by ^1H NMR analysis of the crude products. Isolated yields were indicated in parentheses. [c] Determined by HPLC analysis. [d] The reaction were conducted in the presence of TMG (25 mol%). [e] 24 h. [f] 1.0 MPa of H_2.

Various chiral ligands other than PhTRAP were evaluated for the hydrogenation of **1a** (Table 2). Before the evaluation of ligands, I attempted the catalytic asymmetric reactions by means of a few *in-situ*-generated PhTRAP–ruthenium catalysts. In my previous study on the asymmetric hydrogenation of oxazoles, the chiral catalyst was generated *in situ* from Ru(η^3-methallyl)$_2$(cod) and the chiral bisphosphine.[11f] However, the chiral ruthenium complex failed to catalyze the conversion of **1a** to imine **3a** (entry 1). No reduction of the C–N double bond was observed in the reaction mixture. The hydrogenation of **1a** was conducted in the presence of the crude ruthenium complex, which was prepared by mixing [RuCl$_2$(*p*-cymene)]$_2$ and (*R*,*R*)-(*S*,*S*)-PhTRAP in CH_2Cl_2–EtOH (1:2) at 50 °C for 1 h and then removing the solvent in vacuo. The resulting residue worked as the chiral catalyst as with the isolated complex **2**, although its catalyst efficiency was lower than that of **2** (entry 2).

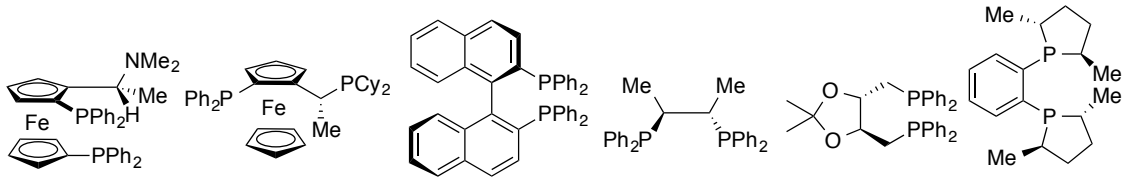
Table 2. Effect of Chiral Ligand[a]



1a **3a** **8a**

entry	ligand	[Ru]	yield (**3a**)[b]	yield (**8a**)[b]	ee[c]
1	(*R*,*R*)-(*S*,*S*)-PhTRAP	Ru(η^3-methalyl)$_2$(cod)	0%	0%	–
2	(*R*,*R*)-(*S*,*S*)-PhTRAP	[RuCl$_2$(*p*-cymene)]$_2$	25%	47%	53%
3	(*R*)-(*S*)-BPPFA	[RuCl$_2$(*p*-cymene)]$_2$	28%	6%	–
4	Josiphos (SL-J001-1)	[RuCl$_2$(*p*-cymene)]$_2$	67%	15%	3%
5	(*R*)-BINAP	[RuCl$_2$(*p*-cymene)]$_2$	0%	8%	17%
6	(*S*,*S*)-Chiraphos	[RuCl$_2$(*p*-cymene)]$_2$	49%	10%	16%
7	(*S*,*S*)-DIOP	[RuCl$_2$(*p*-cymene)]$_2$	0%	0%	–
8	(*R*,*R*)-MeDuPhod	[RuCl$_2$(*p*-cymene)]$_2$	0%	0%	–

[a] Reactions were conducted on a 0.20 mmol scale in 1.0 mL of THF under 5.0 MPa of H_2 at 80°C for 4 h. The ratio of **1a**/[Ru]/ligand/acylating agent was 100:2.5:2.8:110. [b] Determined by ^{1}H NMR analysis of the crude products. [c] Determined by HPLC analysis.



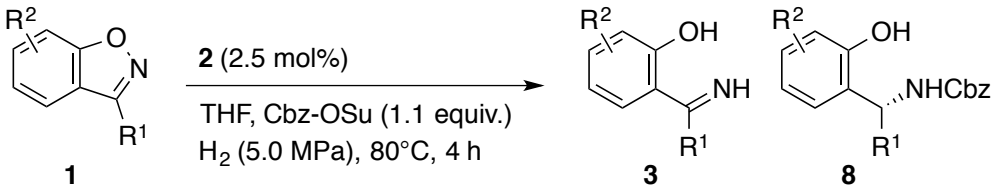
(*R*)-(*S*)-BPPFA (*R*)-(*S*)-Josiphos (*R*)-BINAP (*S*,*S*)-Chiraphos (*S*,*S*)-DIOP (*R*,*R*)-MeDuPhod

By using the procedure for preparing the chiral catalyst from $[RuCl_2(p\text{-cymene})]_2$, the hydrogenation of **1a** was conducted with a series of chiral bisphosphines (entries 3–8). As a result of the ligand evaluation, PhTRAP was found to be the most effective ligand for the asymmetric hydrogenation of benzisoxazoles. The ruthenium catalysts prepared from BPPFA, Josiphos, and Chiraphos could cleave the N–O bond in **1a** to give imine **3a** under the hydrogenation conditions, while they are ineffective for the conversion of **3a** into **8a**. Furthermore, the enantiomeric excesses of the chiral products were lower than 20% ee. In contrast, BINAP–$[RuCl_2(p\text{-cymene})]_2$ might be competent to reduce the C–N double bond of **3a**, but the catalyst failed to cleave the N–O bond of **1a** with sufficient reaction rate. Furthermore, no conversion of **1a** was observed in the reactions using DIOP, MeDuPhos.

As shown in Table 3, the PhTRAP–ruthenium catalyst **2** converted various 3-substituted benzisoxazoles **1** to the corresponding *N*-Cbz-protected *o*-hydroxybenzylamines **8** under the optimized conditions. Reaction rates of the catalytic transformations were affected by the bulkiness of the substituent at the 3-position in **1**. As with **1a**, 3-methylbenzisoxazole **1b** was converted to **8b** with moderate enantiomeric excess (entry 1). Chiral benzylamines **8c** and **8d** were obtained in high yields from the benzisoxazoles bearing 2-phenethyl and isopropyl groups at their 3-position, but complete conversions of **1c** and **1d** needed long reaction times as compared to **1a** or **1b** (entries 2 and 3). Furthermore, the reactions of **1c** and **1d** were less enantioselective. The asymmetric hydrogenation of aryl-substituted substrate **1e** produced the desired chiral diarylamine **8e** with 55% ee, but a small amount of achiral diarylmethane was formed through the undesired hydrogenolysis of the benzylic C–N bond (entry 4). The stereoselectivity of the asymmetric reaction may correlate with the electronic property of the substituent at the 5-position of benzisoxazole. Electron-donating groups in **1f** or **1g** slightly improved the enantioselectivity (entries 5 and 6). In contrast, the fluorine atom in **1h** caused a decrease in the ee value of the

hydrogenation product (entry 7). The substituent at the 6-position unsystematically affects the stereoselectivity. The reaction of 3,6-dimethylbenzisoxazole (**1j**) proceeded with a comparable stereoselectivity to **1b** (entry 9). However, the selectivity deteriorated in the reaction of the substrate bearing either electron-donating or electron-withdrawing groups at the 6-position (entries 8 and 10). Steric hindrance of the methoxy group in **1l** scarcely affected the yield of the hydrogenation product, but it did cause significant decrease in enantioselectivity (entry 11).

Table 3. Catalytic Asymmetric Hydrogenation of 3-Substituted Benzisoxazoles **1**[a].



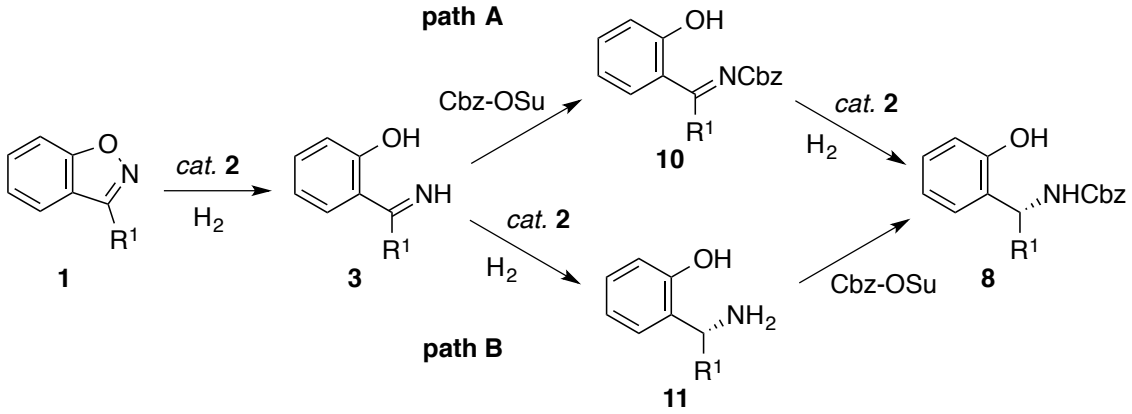
1 **3** **8**

entry	R^1	R^2	**1**	**8**	yield[b]	ee[c]
1	Me	H	**1b**	**8b**	78%	48%
2[d]	CH_2CH_2Ph	H	**1c**	**8c**	87%	35%
3[d]	*i*-Pr	H	**1d**	**8d**	99%	40%
4[d]	Ph	6-MeO	**1e**	**8e**	74%	55%
5	Me	5-MeO	**1f**	**8f**	82%	54%
6	Me	5-Me	**1g**	**8g**	87%	57%
7[d]	Me	5-F	**1h**	**8h**	76%	38%
8	Me	6-MeO	**1i**	**8i**	69%	40%
9	Me	6-Me	**1i**	**8j**	87%	51%
10[d]	Me	6-F	**1k**	**8k**	82%	23%
11[d]	Me	4-MeO	**1l**	**8l**	76%	25%

[a] Reactions were conducted on a 0.20 mmol scale in 1.0 mL of THF under 5.0 MPa of H_2 at 80°C for 4 h. The ratio of **1**/**2**/Cbz-OSu was 100:2.5:110. [b] Isolated yield. [c] Determined by HPLC analysis. [d] 24 h.

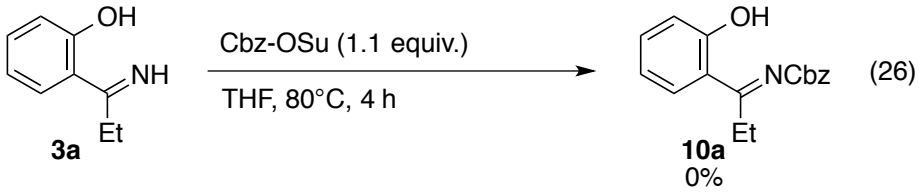
As described above, the hydrogenation of benzisoxazoles **1** proceeds through the reductive N–O bond cleavage to form *o*-hydroxyphenyl imine **3**, yielding α-substituted *N*-Cbz-benzylamine **8** in the presence of Cbz-OSu. The acylating agent is indispensable for the reduction of the imine to amine. Furthermore, the absence of the ruthenium complex prevents the conversion of **1** to **3** as well as the formation of **8**.

In light of these observations, two reaction pathways are conceivable for the catalytic asymmetric hydrogenation of benzisoxazoles, as shown in Scheme 2. In both pathways, the ruthenium catalyst **2** initially cleaves the N–O bond in **1**, giving imine **3**.[10] One involves the acylation of the imine NH with Cbz-OSu to form intermediate **10**,[12] which is reduced to **8** by hydrogen through the ruthenium catalysis (path A). In the other possible pathway, the hydrogenation of C–N double bond in **3** occurs prior to the Cbz-protection of the nitrogen atom (path B).[13]

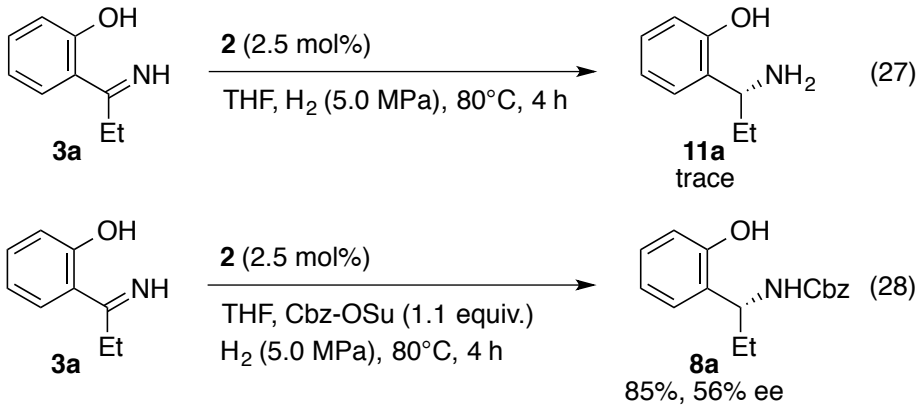


Scheme 2. Possible Pathways for the Asymmetric Hydrogenation of Benzisoxazoles

To ascertain these two possibilities, the following reactions were conducted by using the imine **3a** as the substrate. First, the imine **3a** was treated with Cbz-OSu at 80 °C for 4 h in the absence of catalyst **2** (eq. 26).



No formation of *N*-Cbz-imine **10a** was observed in the resulting mixture, and the substrate **3a** remained intact, hence path A can be ruled out. Next, the hydrogenation of **3a** was conducted with the ruthenium catalyst in the absence of Cbz-OSu, but the reaction produced only a small amount of the expected primary amine **11** (eq. 27). The reduction of the imine **3a**, however, proceeded in the presence of Cbz-OSu, affording **8a** in high yield (eq. 28).



Consequently, the present hydrogenation of the benzisoxazoles should occur through path B. Although the resulting primary amine **11** may strongly inhibit the catalysis of the PhTRAP–ruthenium complex, the generated amino group is rapidly protected by the coexistent Cbz-OSu under the hydrogenation conditions.[14] Thus, the rapid acylation effectively avoids the inhibition of the ruthenium catalyst by the free amino group of **11**.[14]

2.3. Conclusion

In this study, I proved that 3-substituted benzisoxazoles **1** react with hydrogen in the presence of the chiral ruthenium catalyst **2**. The ruthenium-catalyzed hydrogenation proceeds in the presence of an acylating agent (Cbz-OSu), to afford α-substituted *N*-Cbz-*o*-hydroxybenzylamines **8** in high yields with moderate enantioselectivities. The conversion of **1** to the chiral amines proceeds through the imine intermediate **3**, which is generated from the reductive cleavage of the N–O bond in the benzisoxazole ring. The C–N double bond of **3** is hydrogenated with moderate enantioselectivity by the PhTRAP–ruthenium catalyst, however, the resulting primary amine **11** causes deactivation of the catalyst **2**. The deterioration of **2** can be avoided by the coexistent acylating agent, which rapidly reacts with the amino group.

2.4. Experimental Section

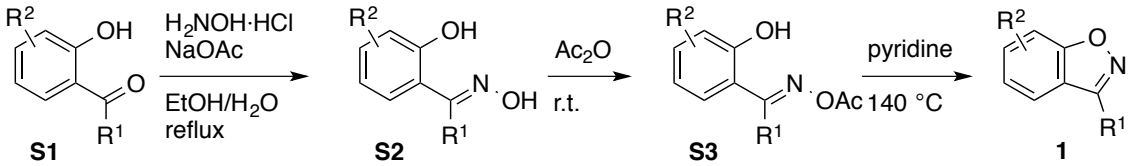
2.4.1 General and Materials

All NMR spectra were measured with Bruker AVANCE 400 or AVANCE III HD 400 Nanobay (9.4 T magnet) spectrometer at ambient temperature. In ^{1}H NMR spectra, chemical shifts (ppm) referenced to internal tetramethylsilane (0.00 ppm in $CDCl_3$), or CD_3COCD_2H (2.05 ppm in acetone-d_6). In ^{13}C NMR spectra, chemical shifts (ppm) referenced to the carbon signal of the deuterated solvents (77.0 ppm in $CDCl_3$, 30.0 ppm in acetone-d_6). IR spectra and melting points were measured with JASCO FT/IR-4100 and Büchi Melting Point B-545, respectively. Elemental analyses and high-resolution mass spectra (FAB) were performed by Service Center of Elementary Analysis of Organic Compounds and Network Joint Research Center for Materials and Devices (Institute for Materials Chemistry and Engineering, Kyushu University), respectively. Flash column chromatographies and medium-pressure liquid chromatographies (MPLC) were performed with silica gel 60 (230–400 mesh, Merck) and C.I.G. pre-packed column CPS-223L-1 (Kusano, Tokyo, Japan), respectively.

1,2-dichloroethane (DCE) was dried with calcium hydride. Ethyl acetate (EtOAc) was dried with P_2O_5. These solvents were distilled under nitrogen atmosphere. Tetrahydrofuran (THF) (HPLC grade, without inhibitor) was deoxidized by purging with nitrogen for 30 min and was dried with an alumina and copper column system (GlassContour). Dry diethyl ether (Et_2O, Kanto), dichloromethane (CH_2Cl_2, Kanto), distilled water (Wako) were purchased.

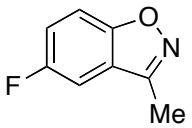
3-ethylbenzisoxazole (**1a**),[15] 3-methylbenzisoxazole (**1b**),[15] 3-phenethylbenzisoxazole (**1c**),[15] 3-isopropylbenzisoxazole (**1d**),[16] 6-methoxy-3-phenylbenzisoxazole (**1e**),[15] 5-methoxy-3-methylbenzisoxazole (**1f**),[17] 3,5-dimethylbenzisoxazole (**1g**),[15] 6-methoxy-3-methylbenzisoxazole (**1i**),[15] 3,6-dimethylbenzisoxazole (**1j**),[18] 6-fluoro-3-methylbenzisoxazole (**1k**),[15] 2-(1-iminopropyl)phenol (**3a**),[19a] and {RuCl(*p*-cymene)[(*R*,*R*)-(*S*,*S*)-PhTRAP]} (**2**)[9] were prepared according to literature procedures. 2'-hydroxy-5'-fluoroacetophenone, 2'-hydroxy-6'-methoxyacetophenone, hydroxylamine hydrochloride, sodium acetate (NaOAc), ethanol (EtOH), *N*-(Benzyloxycarbonyloxy)succinimide (Cbz-OSu), *N*-(9-Fluorenylmethoxycarbonyloxy)succinimide (Fmoc-OSu), di-*tert*-butyl dicarbonate (Boc_2O), 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (Boc-ON) acetic anhydride (Ac_2O), benzoic anhydride (Bz_2O), *p*-toluenesulfonic anhydride (Ts_2O), pyridine, cyclopenthyl methyl ether (CPME), and 1,1,3,3-tetramethylguanidine were purchased and used without further purification.

2.4.2 Preparation of Benzisoxazoles



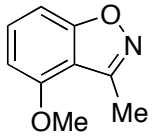
Sodium acetate (1.2 equiv) and hydroxylamine hydrochloride (1.2 equiv) were separately dissolved in minimum amount of water, mixed and added to *o*-hydroxyaryl alkyl ketone **S1** (1.0 equiv). Ethanol was then added until a clear solution was obtained (approximately 4 mL/mol), the reaction mixture refluxed for 1 h. The reaction mixture was cooled to room temperature, concentrated by evaporation under vacuum. The mixture was extracted with EtOAc. The organic layers were pooled, washed with brine, dried over anhydrous sodium sulfate, and evaporated under vacuum to give sufficiently pure **S2**. Next, oxime **S2** was dissolved in acetic anhydride (0.40 mL/mol) in a schlenk flask at room temperature with gentle swirling. The flask became warm to the touch. Swirling was continued for overnight, following which white precipitates separated out. The reaction mixture was concentrated by evaporation under vacuum to give sufficiently pure product **S3**. Finally, **S3** was heated under reflux with anhydrous pyridine (0.50 mL/mol) for 24 h at 140 °C. Following reflux, the dark red reaction mixture was allowed to cool to room temperature and acidified with 1*N* HCl (approximately 50 mL). The mixture was extracted with EtOAc. The organic layers were pooled, washed with 1*N* HCl and brine, dried over anhydrous sodium sulfate, and evaporated under vacuum to give brown-colored oily residue as crude product. The crude product was purified using column chromatography with hexane/EtOAc as the eluting solvent. Fractions containing the desired compound were combined and dried under vacuum to give benzisoxazole **1.**

5-fluoro-3-methylbenzoisoxazole (**1h**)



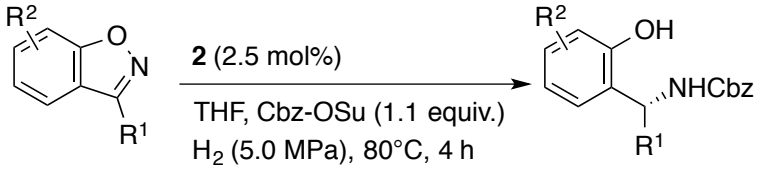
The procedure for preparing 2'-hydroxy-5'-fluoroacetophenone was followed with use of **S1** (1.52 g, 9.9 mmol). The crude product was purified with a flash column chromatography (EtOAc/hexane = 1/10) to give **1h** (950 mg, 64%) as a colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.56 (s, 3H), 7.23-7.35 (m, 2H), 7.50 (dd, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 10.1, 106.0 (d, J = 24.8 Hz), 110.8 (d, J = 9.3 Hz), 118.4 (d, J = 26.9 Hz), 122.8 (d, J = 10.3 Hz), 155.1 (d, J = 4.4 Hz), 159.0 (d, J = 241 Hz), 159.4; IR (neat) 1479, 1452, 908, 734 cm^{-1}; Anal. Calcd for C_8H_6FNO: C, 63.57; H, 4.00; N, 9.27. Found: C, 63.47; H, 3.95; N, 9.26.

4-methoxy-3-methylbenzoisoxazole (**1l**)



The procedure for preparing 2'-hydroxy-6'-methoxyacetophenone was followed with use of **S1** (836 mg, 5.0 mmol). The crude product was purified with a flash column chromatography (EtOAc/hexane = 1/10) to give **1l** (168 mg, 21%) as a colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.64 (s, 3H), 3.94 (s, 3H), 6.59 (d, 1H), 7.09 (d, 1H), 7.41 (t, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.9, 55.6, 102.5, 102.7, 112.4, 131.3, 154.7, 155.4, 164.9; IR (neat) 1614, 1266, 1103, 738 cm^{-1}; Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.05; H, 5.54; N, 8.32.

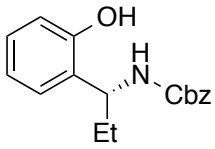
2.4.3. General Procedure for the Catalytic Asymmetric Hydrogenation of Benzisoxazoles **1**.



[RuCl(*p*-cymene)((*R*,*R*)-(*S*,*S*)-PhTRAP)]Cl (**2**) (5.5 mg, 5.0 μmol), Cbz-OSu (54.8 mg, 0.22 mmol) and a stirring bar were placed in a 50 mL test tube, which was sealed with a rubber septum, and then the tube was evacuated and charged with nitrogen gas three times. THF (1.0 mL) was added into the test tube, then benzisoxazole **1** (0.20 mmol) was added. After the rubber septum was removed, the test tube was quickly inserted into a nitrogen-purged stainless autoclave, and then the autoclave was

sealed immediately. Hydrogen gas was introduced into the autoclave until the pressure gauge indicated over 5.0 MPa, and then the pressure was carefully released to 0.1 MPa. This procedure was repeated twice, and finally the inside of the autoclave was pressurized with hydrogen to 5.0 MPa. After the mixture was stirred at 80 °C for 4 h, the autoclave was allowed to cool to room temperature. Excess hydrogen was released carefully, and then the resulting reaction mixture was evaporated under reduced pressure. The residue was analyzed with ^{1}H NMR spectrum in order to determine its composition, and then purified with a flash column chromatography (EtOAc/hexane) to give **8**.

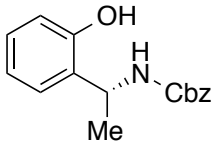
(+)-Benzyl (*R*)-1-(2-hydroxyphenyl)-1-propylcarbamate (**8a**)



The general procedure was followed with use of **1a** (29.4 mg, 0.20 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/4) to give **8a** (50.5 mg, 89%) as a colorless oil: $[\alpha]_D^{26}$ = +14.1 (c 0.51, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.93 (quintet, *J* = 7.4 Hz, 2H), 4.77 (q, *J* = 7.8 Hz, 1H), 5.04 (d, *J* = 12.1 Hz, 1H), 5.14 (d, *J* = 12.1 Hz, 1H), 5.14–6.24 (br, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.29–7.38 (m, 5H), 7.68–7.88 (br, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, at 50 °C) δ 11.1, 27.5, 52.9 (br), 67.3, 117.3, 120.4, 127.2 (br), 128.1, 128.2, 128.5, 128.6, 136.2, 154.6, 157.5; Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.43; H, 6.64; N, 4.87.

The enantiomeric excess of (+)-**8a** was determined to be 52% ee by HPLC analysis with Chiralpak OZH (4.6 mm ϕ Å~ 250 mm): 4% 2-propanol in hexane, 0.5 mL/min flow, at room temperature, UV 222 nm detection, (-) t_1 = 40.0 min, (+) t_2 = 46.4 min.

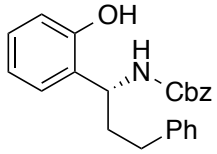
(+)-Benzyl 1-(2-hydroxyphenyl)-1-ethylcarbamate (**8b**)



The general procedure was followed with use of **1b** (26.6 mg, 0.20 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/4) to give **8b** (41.8 mg, 78%) as a colorless oil; $[\alpha]_D^{26}$ = +16.9 (c 0.72, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.57 (d, *J* = 6.9 Hz, 3H), 5.04 (d, *J* = 12.1 Hz, 1H), 5.09 (quintet, *J* = 7.5 Hz, 1H), 5.15 (d, *J* = 12.1 Hz, 1H), 5.14–5.24 (br, 1H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.28–7.38 (m, 5H), 7.90–8.10 (br, 1H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 20.3, 45.9 (br), 67.4, 117.7, 120.6, 126.3, 128.16, 128.25, 128.5, 128.9, 129.2, 136.1, 154.5, 157.3; Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.46; H, 6.36; N, 5.18.

The enantiomeric excess of (+)-**8b** was determined to be 48% ee by HPLC analysis with Chiralpak ADH (4.6 mm ϕ Å~ 250 mm): 10% 2-propanol in hexane, 0.5 mL/min flow, at room temperature, UV 275 nm detection, (-) t_1 = 28.1 min, (+) t_2 = 31.8 min.

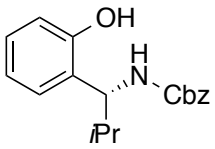
(+)-Benzyl 1-(2-hydroxyphenyl)-3-phenyl-1-propylcarbamate (**8c**)



The general procedure was followed with use of **1c** (41.9 mg, 0.20 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/4) to give **8c** (63.0 mg, 87%) as a colorless solid; $[\alpha]_D^{27}$ = +8.5 (c 1.31, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 2.22 (q, *J* = 7.7 Hz, 2H), 2.59–2.74 (m, 2H), 4.88 (q, *J* = 7.6 Hz, 1H), 5.05 (d, *J* = 12.1 Hz, 1H), 5.15 (d, *J* = 12.1 Hz, 1H), 5.20–5.36 (br, 1H), 6.87–6.94 (m, 2H), 7.11–7.22 (m, 5H), 7.24–7.38 (m, 7H), 7.61–7.78 (br, 1H); ^{13}C {^1H} NMR (100 MHz, CDCl3, at 50 °C) δ 32.9, 36.1, 50.9 (br), 67.4, 117.5, 120.6, 126.0, 127.2 (br), 128.0, 128.1, 128.2, 128.36, 128.44, 128.5, 128.9, 136.2, 141.2, 154.6, 157.4; Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.27; H, 6.45; N, 3.90.

The enantiomeric excess of (+)-**8c** was determined to be 35% ee by HPLC analysis with Chiralpak OZH (4.6 mm ϕ Å~ 250 mm): 10% 2-propanol in hexane, 0.5 mL/min flow, at room temperature, UV 225 nm detection, (-) t_1 = 16.1 min, (+) t_2 = 21.8 min.

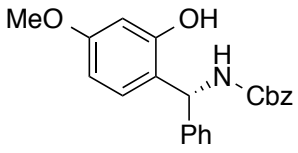
(+)-Benzyl 1-(2-hydroxyphenyl)-2-methyl-1-ethylcarbamate (**8d**)



The general procedure was followed with use of **1d** (32.2 mg, 0.20 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/4) to give **8d** (59.9 mg, 99%) as a colorless solid; $[\alpha]_D^{27}$ = +12.9 (c 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.80 (d, J = 6.6 Hz, 3H), 1.10 (d, J = 6.5 Hz, 3H), 2.21 (double septet, J = 9.8, 6.6 Hz, 1H), 4.48 (t, J = 9.7 Hz, 1H), 5.04 (d, J = 12.2 Hz, 1H), 5.13 (d, J = 12.2 Hz, 1H), 5.32–5.48 (br, 1H), 6.84–6.91 (m, 2H), 7.02–7.17 (m, 3H), 7.27–7.38 (m, 5H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, at 50 °C) δ 19.6, 20.2, 31.9, 58.6 (br), 67.2, 116.9, 120.3, 127.8, 128.0, 128.1, 128.4, 128.5, 136.4, 154.3, 157.4; Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.03; N, 4.68. Found: C, 71.95; H, 7.06; N, 4.71.

The enantiomeric excess of (+)-**8d** was determined to be 40% ee by HPLC analysis with Chiralpak ODH (4.6 mm ϕ Å~ 250 mm): 10% 2-propanol in hexane, 0.5 mL/min flow, at room temperature, UV 222 nm detection, (-) t_1 = 13.6 min, (+) t_2 = 21.1 min.

(+)-Benzyl (2-hydroxy-4-methoxyphenyl)phenylmethylcarbamate (**8e**)

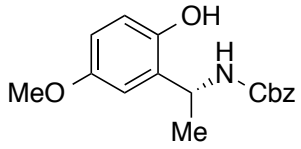


The general procedure was followed with use of **1e** (45.1mg, 0.20 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/3) to give **8e** (54.0 mg, 74%) as a colorless solid; $[\alpha]_D^{26}$ = +30.5 (c 0.53, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.76 (s, 3H), 5.11 (d, J = 12.1 Hz, 1H), 5.18 (d, J =

12.1 Hz, 1H), 5.75 (brd, J = 7.6 Hz, 1H), 6.16 (d, J = 8.7 Hz, 1H), 6.40 (dd, J = 2.4, 8.5 Hz, 1H), 6.46 (s, 1H), 6.85 (d, J = 8.5 Hz, 1H), 6.75–7.15 (br, 1H), 7.25–7.37 (m, 10H); ^{13}C {^{1}H} NMR (100 MHz, acetone-d_6, at 50 °C) δ 55.3, 55.8, 67.1, 103.2, 106.2, 122.5, 127.6, 128.0, 128.78, 128.81, 129.1, 129.4, 130.5, 138.7, 144.3, 156.6, 157.0, 161.4; Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.63; H, 5.83; N, 3.79.

The enantiomeric excess of (+)-**8e** was determined to be 55% ee by HPLC analysis with Chiralpak OZH (4.6 mm ϕ Å~ 250 mm): 10% 2-propanol in hexane, 0.5 mL/min flow, at room temperature, UV 230 nm detection, (-) t_1 = 28.0 min, (+) t_2 = 38.5 min.

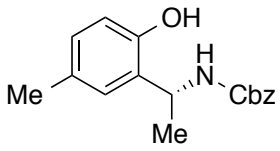
(+)-Benzyl 1-(2-hydroxy-5-methoxyphenyl)-1-ethylcarbamate (**8f**)



The general procedure was followed with use of **1f** (32.6 mg, 0.20 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/3) to give **8f** (49.5 mg, 82%) as a colorless oil; $[\alpha]_D^{26}$ = +28.2 (c 0.99, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.54 (d, J = 6.9 Hz, 3H), 3.75 (s, 3H), 5.02 (d, J = 12.1 Hz, 1H), 5.05 (quintet, J = 7.5 Hz, 1H), 5.14 (d, J = 12.1 Hz, 1H), 5.18 (br d, J = 7.8 Hz, 1H), 6.72–6.76 (m, 2H), 6.87 (d, J = 8.2 Hz, 1H), 7.29–7.38 (m, 5H), 7.52–7.70 (br, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, at 50 °C) δ 20.2, 45.9, 55.8, 67.4, 112.4, 113.8, 118.4, 128.16, 128.24, 128.5, 130.3, 136.1, 148.3, 153.8, 157.2; Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.58; H, 6.21; N, 4.64.

The enantiomeric excess of (+)-**8f** was determined to be 54% ee by HPLC analysis with Chiralpak ADH (4.6 mm ϕ Å~ 250 mm): 10% 2-propanol in hexane, 0.5 mL/min flow, at room temperature, UV 225 nm detection, (-) t_1 = 42.0 min, (+) t_2 = 48.4 min.

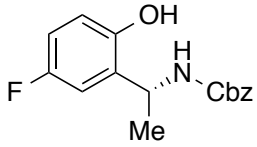
(+)-Benzyl 1-(2-hydroxy-5-methylphenyl)-1-ethylcarbamate (**8g**)



The general procedure was followed with use of **1g** (29.4 mg, 0.20 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/4) to give **8g** (50.4 mg, 87%) as a colorless oil; $[\alpha]_D^{26}$ = +27.4 (c 0.93, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.55 (d, *J* = 7.0 Hz, 3H), 2.26 (s, 3H), 5.03 (d, *J* = 12.1 Hz, 1H), 5.04 (quintet, *J* = 7.4 Hz, 1H), 5.14 (d, *J* = 12.1 Hz, 1H), 5.17–5.27 (br, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.95–7.00 (m, 2H), 7.25–7.38 (m, 5H), 7.48–7.80 (br, 1H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$, at 50 °C) δ 20.3, 20.6, 45.9 (br), 67.4, 117.5, 126.8, 128.17, 128.23, 128.5, 129.0, 129.3, 129.8, 136.2, 152.1, 157.2; Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.72; N, 4.91. Found: C, 71.23; H, 6.74; N, 4.86.

The enantiomeric excess of (+)-**8g** was determined to be 57% ee by HPLC analysis with Chiralpak ADH (4.6 mm ϕ Å~ 250 mm): 10% 2-propanol in hexane, 0.5 mL/min flow, at room temperature, UV 281 nm detection, (-) t_1 = 24.8 min, (+) t_2 = 28.9 min.

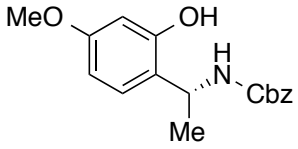
(+)-Benzyl 1-(5-fluoro-2-hydroxyphenyl)-1-ethylcarbamate (**8h**)



The general procedure was followed with use of **1h** (30.2 mg, 0.20 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/4) to give **8h** (44.8 mg, 76%) as a colorless oil; $[\alpha]_D^{26}$ = +6.2 (c 1.12, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.55 (d, *J* = 6.9 Hz, 3H), 5.04 (d, *J* = 12.1 Hz, 1H), 5.05 (quintet, *J* = 7.4 Hz, 1H), 5.09–5.17 (br 1H), 5.16 (d, *J* = 12.1 Hz, 1H), 6.86–6.91 (m, 3H), 7.28–7.29 (m, 5H), 7.95–8.20 (m, 1H); ^{13}C {^1H} NMR (100 MHz, CDCl3, at 50 °C) δ 20.1, 45.3 (br), 67.6, 112.4 (d, *J* = 24 Hz), 115.2 (d, *J* = 23 Hz), 118.8 (d, *J* = 7 Hz), 128.2, 128.4, 128.6, 130.6 (d, *J* = 6 Hz), 135.9, 150.5 (d, *J* = 2 Hz), 157.1 (d, *J* = 238 Hz), 157.4; Anal. Calcd for $C_{16}H_{16}FNO_3$: C, 66.43; H, 5.57; N, 4.84. Found: C, 66.20; H, 5.56; N, 4.86.

The enantiomeric excess of (+)-**8h** was determined to be 38% ee by HPLC analysis with Chiralpak ADH (4.6 mm ϕ Å~ 250 mm): 10% 2-propanol in hexane, 0.5 mL/min flow, at room temperature, UV 283 nm detection, (-) t_1 = 23.8 min, (+) t_2 = 29.4 min.

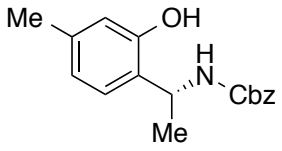
(+)-Benzyl 1-(2-hydroxy-4-methoxyphenyl)-1-ethylcarbamate (**8i**)



The general procedure was followed with use of **1i** (32.6 mg, 0.20 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/4) to give **8i** (40.9 mg, 69%) as a colorless solid; $[\alpha]_D^{27}$ = +14.9 (c 0.53, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.55 (d, *J* = 6.9 Hz, 3H), 3.76 (s, 3H), 5.02 (quintet, *J* = 7.4 Hz, 1H), 5.03 (d, *J* = 12.1 Hz, 1H), 5.10–5.19 (br, 1H), 5.15 (d, *J* = 12.1 Hz, 1H), 6.46 (dd, *J* = 2.4, 8.5 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 7.29–7.38 (m, 5H), 8.30–8.50 (br, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, at 50 °C) d 20.3, 45.3 (br), 55.2, 67.4, 103.2, 106.5, 121.7, 126.8, 128.1, 128.2, 128.5, 136.1, 155.8, 157.4, 160.4; Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.56; H, 6.21; N, 4.56.

The enantiomeric excess of (+)-**8i** was determined to be 40% ee by HPLC analysis with Chiralpak ODH (4.6 mm ϕ Å~ 250 mm): 10% 2-propanol in hexane, 0.5 mL/min flow, at room temperature, UV 278 nm detection, (+) t_1 = 22.6 min, (-) t_2 = 25.8 min.

(+)-Benzyl 1-(2-hydroxy-4-methylphenyl)-1-ethylcarbamate (**8j**)

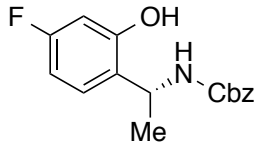


The general procedure was followed with use of **1j** (29.4 mg, 0.20 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/4) to give **8j** (50.9 mg, 87%) as a colorless oil; $[\alpha]_D^{26}$ = +16.4 (c 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.55 (d, *J* = 7.0 Hz, 3H), 2.28 (s, 3H), 4.99–5.08 (m,

2H), 5.14 (d, J = 12.1 Hz, 1H), 5.13–5.25 (br 1H), 6.71 (d, J = 7.8 Hz, 1H), 6.74 (s, 1H), 7.08 (d, J = 7.8 Hz, 1H), 7.28–7.38 (m, 5H), 7.80–8.10 (br, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, at 50 °C) δ 20.3, 20.9, 45.6 (br), 67.4, 118.3, 121.3, 126.1, 126.3, 128.16, 128.23, 128.5, 136.2, 139.0, 154.6, 157.3; Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.72; N, 4.91. Found: C, 71.28; H, 6.75; N, 4.87.

The enantiomeric excess of (+)-**8j** was determined to be 51% ee by HPLC analysis with Chiralpak ODH (4.6 mm ϕ Å~ 250 mm): 10% 2-propanol in hexane, 0.5 mL/min flow, at room temperature, UV 225 nm detection, (+) t_1 = 15.5 min, (-) t_2 = 19.0 min.

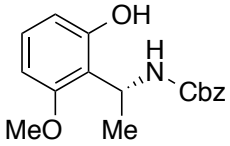
(–)-Benzyl 1-(4-fluoro-2-hydroxyphenyl)-1-ethylcarbamate (**8k**)



The general procedure was followed with use of **1k** (30.2 mg, 0.20 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/4) to give **8k** (48.1 mg, 82%) as a colorless oil; $[\alpha]_D^{26}$ = –9.6 (c 0.69, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.54 (d, J = 6.8 Hz, 3H), 5.02 (quintet, J = 7.3 Hz, 1H), 5.06 (d, J = 12.2 Hz, 1H), 5.16 (d, J = 12.2 Hz, 1H), 5.10–5.26 (br, 1H), 6.54–6.64 (m, 2H), 7.12 (t, J = 7.4 Hz, 1H), 7.28–7.39 (m, 5H), 8.62–8.74 (br, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, at 50 °C) δ 20.3, 45.4 (br), 67.6, 104.9 (d, J = 24 Hz), 107.1 (d, J = 22 Hz), 125.2 (d, J = 3 Hz), 127.0 (d, J = 10 Hz), 128.2, 128.4, 128.6, 135.9, 156.1 (d, J = 12 Hz), 157.5, 163.0 (d, J = 246 Hz); Anal. Calcd for $C_{16}H_{16}FNO_3$: C, 66.43; H, 5.57; N, 4.84. Found: C, 66.23; H, 5.39; N, 4.84.

The enantiomeric excess of (–)-**8k** was determined to be 23% ee by HPLC analysis with Chiralpak ADH (4.6 mm ϕ Å~ 250 mm): 10% 2-propanol in hexane, 0.5 mL/min flow, at room temperature, UV 225 nm detection, (+) t_1 = 23.1 min, (-) t_2 = 26.9 min.

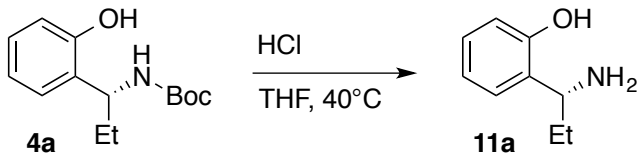
(–)-Benzyl 1-(2-hydroxy-6-methoxyphenyl)-1-ethylcarbamate (**8l**)



The general procedure was followed with use of **1l** (32.6 mg, 0.20 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/3) to give **8k** (45.6 mg, 76%) as a colorless solid; $[\alpha]_D^{27}$ = –0.68 (c 0.59, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.52 (d, *J* = 7.0 Hz, 3H), 3.81 (s, 3H), 5.04 (d, *J* = 12.3 Hz, 1H), 5.14 (d, *J* = 12.3 Hz, 1H), 5.39 (dq, *J* = 9.2, 7.0 Hz, 1H), 5.86–5.98 (br, 1H), 6.47 (d, *J* = 8.2 Hz, 1H), 6.49 (d, *J* = 8.1 Hz, 1H), 7.07 (t, *J* = 8.3 Hz, 1H), 7.24–7.38 (m, 5H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$, at 50 °C) δ 20.6, 43.2, 55.7, 66.9, 103.5, 109.8, 117.8, 128.0, 128.2, 128.5, 136.7, 154.9, 156.9, 158.1; Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.65; H, 6.29; N, 4.68.

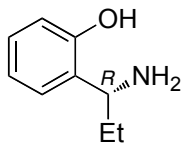
The enantiomeric excess of (–)-**5l** was determined to be 25% ee by HPLC analysis with Chiralpak ADH (4.6 mm ϕ Å~ 250 mm): 10% 2-propanol in hexane, 0.5 mL/min flow, at room temperature, UV 225 nm detection, (-) t_1 = 21.1 min, (+) t_2 = 25.8 min.

2.4.4. Deprotection and Assignment of Absolute Configuration.



4a (47.2 mg, 0.19 mmol, 42% ee) was added to HCl/THF solution (1.0 ml, *conc*. HCl *aq*./THF = 1:4) in a schlenk flask. The reaction mixture stirred at 40°C for 30 min. The reaction mixture was cooled to room temperature, neutralized by 1.0 ml of 7 *N* NH_3 methanol solution, concentrated by evaporation under vacuum. The crude product was directly purified by silica gel column chromatography (hexane/EtOAc = 3/1, then a mixture of 7 *N* NH_3 methanol solution/MeCN (1/10)). Fractions containing the desired compound were combined and dried under vacuum to give aminophenol **11a**.

(*R*)-(–)-2-(1-aminopropyl)phenol (**11a**)



Colorless oil: $[\alpha]_D^{26}$ = –10.7 (*c* 2.02, $CHCl_3$) [*lit.*[19] $[\alpha]_D^{26}$ = +21.2 (*c* 1.34, $CHCl_3$) and +17.21 (c 1.32, $CHCl_3$)for the *S* enantiomer]; ^{1}H NMR (400 MHz, $CDCl_3$, TMS)) δ 0.89 (d, 3H), 1.88–1.65 (m, 2H), 3.98 (t, 1H), 4.63 (brs, 3H), 6.74 (dt, 1H), 6.81 (dd, 1H), 6.90 (dd, 1H), 7.12 (dt, 1H).

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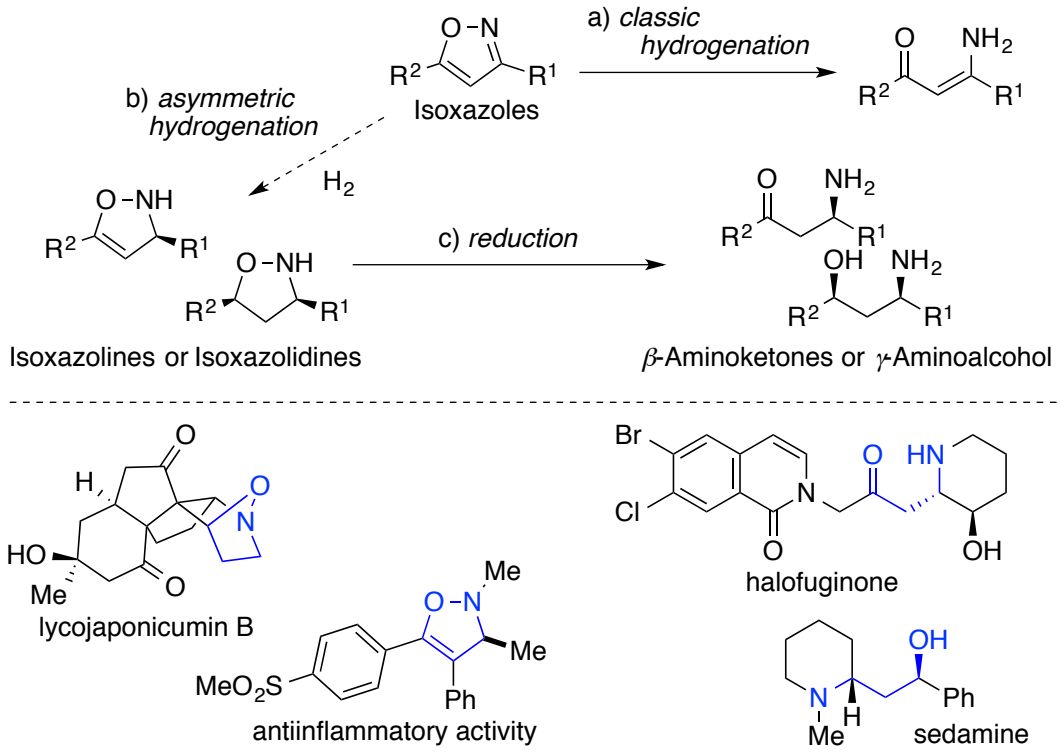
Chapter 3

Catalytic Asymmetric Hydrogenation of Isoxazolium Salts

3.1. Introduction

Optically active isoxazolines and isoxazolidines, which are the products of asymmetric hydrogenation of isoxazoles, are important compounds because these are often used as intermediates in the synthesis of useful compounds[1,2] and are found in some biological active molecules (Scheme 3c).[3,4] Isoxazolidine structural motif is useful for designing DNA intercalator.[5] Because of easiness to cleave these N–O bonds, these products are also the precursors of the optically active *β*-aminoketones or *γ*-aminoalcohols, which are precursors of natural product or chiral ligands (Scheme 3c).[6] However, to my knowledge, the asymmetric hydrogenation of isoxazoles have not be known yet.[7,8] Because N–O bond of isoxazole is easy to cleave under the hydrogenation condition,[9] it would be difficult to obtain the heterocyclic products through the hydrogenation of isoxazoles (Scheme 3a). In addition, isoxazoles are capable in resonance energy to pyrrole, and more stabilized with the resonance than furan or oxazole.[10] The dearomatization of isoxazoles would be as hard as those of other heteroarenes. From the above reasons, the asymmetric hydrogenation of isoxazoles is a formidable target in organic chemistry.

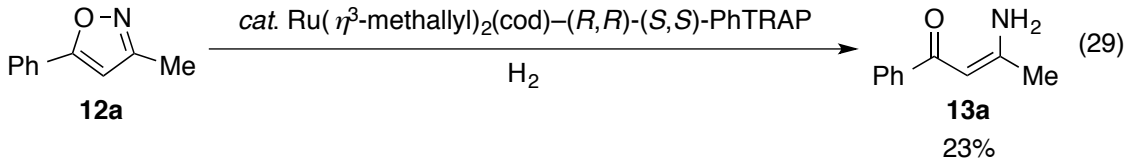


Scheme 3. Chiral Products structures of the Asymmetric Hydrogenation of Isoxazoles

In this chapter, I demonstrate the catalytic asymmetric hydrogenation of isoxazolium salts. Use of a chiral iridium catalyst led to the restriction of the ring opening reaction as well as the enantioselective formation of chiral 4-isoxazolines or isoxazolidines.

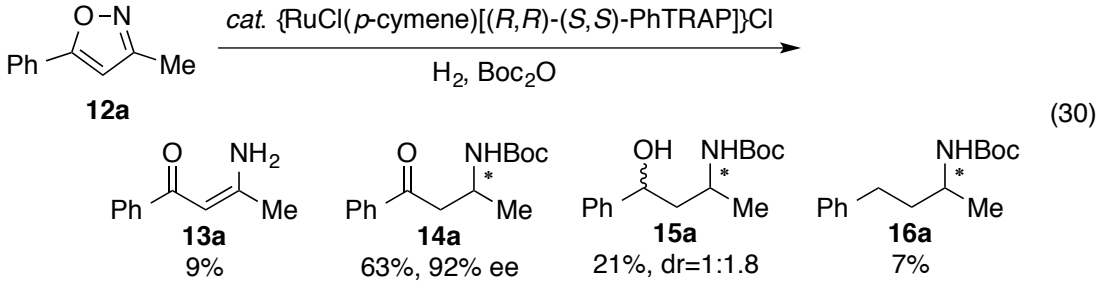
3.2. Results and Discussions

The Kuwano's group has achieved the high enantioselective catalytic hydrogenations of 5-membered heteroarenes using PhTRAP–ruthenium catalyst. In 2011, the research group, including me, reported high enantioselective hydrogenation of oxazoles using PhTRAP–ruthenium catalyst.[11] I thought that isoxazoles might be reduced by the ruthenium catalyst with high enantioselectivity because of the structural similarity of the target compounds and oxazoles. First, the hydrogenation of isoxazole **12a** was conducted with PhTRAP–ruthenium catalyst using for the hydrogenation of isoxazoles, but only achiral enaminone **13a**, which was generated through the htdrogenolysis of N–O bond of **12a**, was observed in the reaction mixture (eq. 29). In this reaction, no other product (cyclic products, β-aminoketones or γ-aminoalcohols reduced from **13a**) was detected in the reaction mixture.



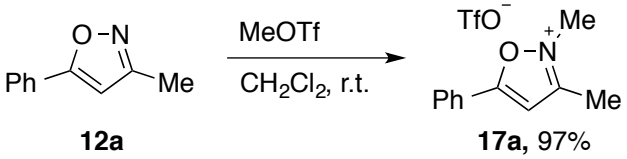
(29)

Next, the hydrogenation of **12a** attempted with PhTRAP–ruthenium catalyst in the presence of acylating agent (Boc_2O), which was the hydrogenation condition of benzisoxazoles.[9] From the reaction, *N*-Boc-β-aminoketone **14a** was obtained as a major product with high enantiomeric excess (eq. 30). However, the suppression of some side reactions (*e.g.* reduction carbonyl moiety of **14a** and hydrogenolysis at benzyl position of **15a**) was impossible unfortunately.



(30)

Iridium complexes are known as the most common catalysts for asymmetric hydrogenation of heteroarenes.[12] The hydrogenation of **12a** conducted with the iridium catalyst, but **12a** was hardly consumed. From this result, I speculated that iridium catalysts might reduce isoxazole rings without the reductive cleavage of N–O bond. In the hydrogenation with iridium catalyst, several novel and efficient strategies were developed.[12] Quaternization of nitrogen atom is one of the substrate activation strategies of the hydrogenation of heteroarenes.[13,14] Inspired from these reports, the hydrogenation of isoxazolium salts was attempted by using an iridium catalyst. Isoxazolium triflate **17a** was easily synthesized by the methylation of **12a** using methyl trifluoromethanesulfonate (eq. 31).

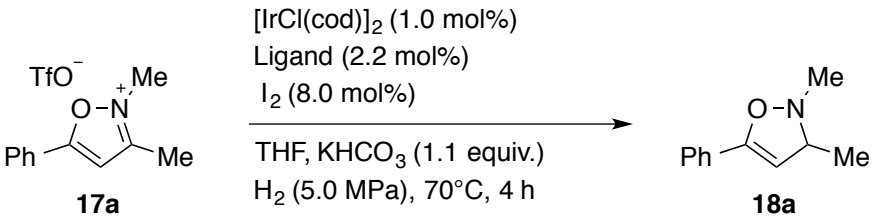


(31)

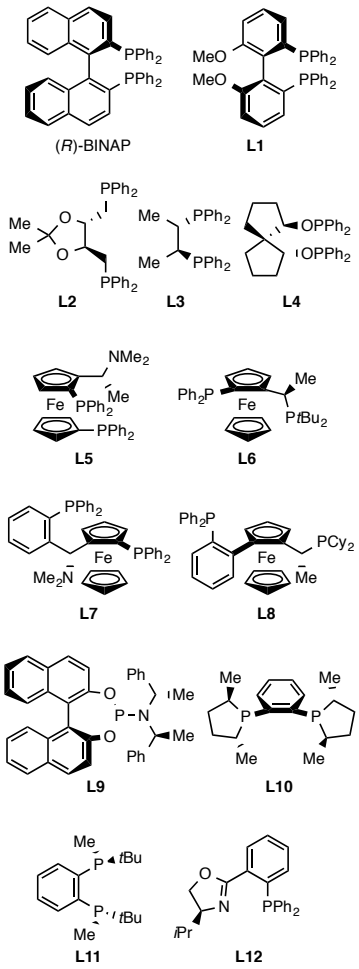
At first, I conducted the hydrogenation of **17a** with BINAP–$[IrCl(cod)]_2$ catalyst, but no reaction occurred (Table. 4, entries 1 and 2). Because trifluoromethanesurfonic acid generated as a byproduct from the hydrogenation might stultify the iridium catalyst, I decided to add a base to the reaction. $KHCO_3$ was effective, and 4-isoxazoline **18a** was observed as a major product (entry 3). I_2, the common activator of iridium catalysts,[14] suppressed generation of the side-product generated through the hydrogenolysis of N–O bond in the substrate (entry 4). Next, the hydrogenation was conducted with various chiral ligands to improve the enantioselectivity. Fortunately, I found the phosphonooxazoline type ligand (PHOX) led to good enantioselective reaction while other common chiral bisphosphine ligands

were not suitable for the hydrogenation. (entries 4–16).

Table 4. Screening of Ligand[a]



entry	Ligand	yield[b]	ee[c]
1[d,e]	(*R*)-BINAP	0%	-
2[d]	(*R*)-BINAP	0%	-
3[e]	(*R*)-BINAP	61%	13%
4	(*R*)-BINAP	96%	-18%
5	**L1**	90%	-27%
6	**L2**	61%	-4%
7	**L3**	63%	-18%
8	**L4**	27%	n.d.
9	**L5**	71%	-3%
10	**L6**	80%	8%
11	**L7**	54%	-18%
12	**L8**	48%	-2%
13	**L9**	27%	n.d.
14	**L10**	43%	-9%
15	**L11**	70%	13%
16	**L12**	83%	71%

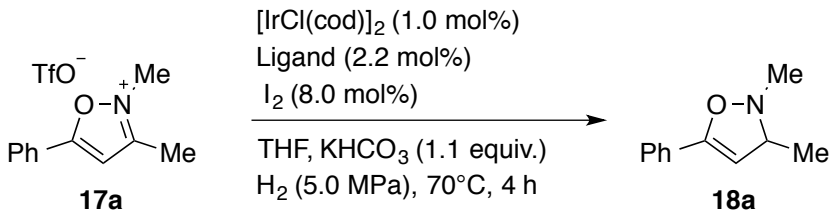


[a] Reactions were conducted on a 0.20 mmol scale in 1.0 mL of THF under 5.0 MPa of H_2 at 70°C for 4 h. The ratio of **17a**/[Ir]/ligand/I_2/$KHCO_3$ was 100:1:2.2:8:110. [b] Determined by ^{1}H NMR in comparison to a 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by HPLC analysis. [d] Without $KHCO_3$, [e] Without I_2

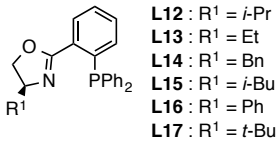
The size of R^1 group of PHOX ligand affects yield and enantioselectivity. The smaller R^1 group, such as ethyl or benzyl group, caused significant decrease in the stereoselectivity (Table 5, entries 2 and 3). On the other hand, the reaction proceeded with good yield and enantioselectivity used with the ligand containing large R^1 (entries 1 and 5). However, **L17**, which has larger R^1 group than **L12** and **L16**, exhibited a

comparable stereoselectivity to **L12** (entry 6). The substituents on phosphorus atom are also correlated with the yield as well as the stereoselectivity. **L18** and **L19**, which ware containing the electron-rich or electron-poor aryl groups on phosphorus atom declined the enantioselectivity (entries 7 and 8). In addition, the ligand substituted bulky group such as mesityl group produced the opposite enantiomer with the low optical purity (entry 9).

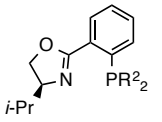
Table 5. Screening of Phosphinooxazoline Ligand[a]



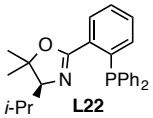
entry	Ligand	yield[b]	ee[c]
1	**L12**	83%	71%
2	**L13**	33%	45%
3	**L14**	34%	52%
4	**L15**	51%	67%
5	**L16**	91%	66%
6	**L17**	68%	71%
7	**L18**	52%	65%
8	**L19**	45%	38%
9	**L20**	43%	-13%
10	**L21**	63%	3%
11	**L22**	53%	62%
12	**L23**	69%	57%
13	**L24**	55%	60%
14	**L25**	79%	46%
15	**L26**	87%	66%
16	**L27**	63%	4%



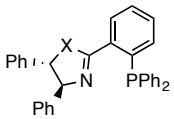
L12 : R^1 = *i*-Pr
L13 : R^1 = Et
L14 : R^1 = Bn
L15 : R^1 = *i*-Bu
L16 : R^1 = Ph
L17 : R^1 = *t*-Bu



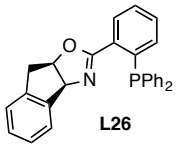
L18 : R^2 = 4-$MeOC_6H_4$
L19 : R^2 = 3,5-$(CF_3)C_6H_3$
L20 : R^2 = 2,4,6-$Me_3C_6H_2$
L21 : R^2 = Cy



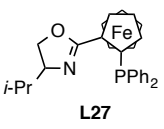
L22



L23 : X = O
L24 : X = NAc
L25 : X = NBz



L26



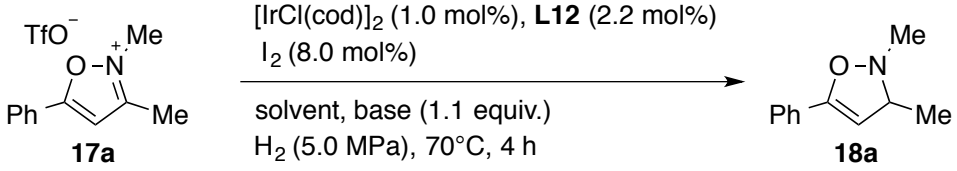
L27

[a] Reactions were conducted on a 0.20 mmol scale in 1.0 mL of THF under 5.0 MPa of H_2 at 70°C for 4 h. The ratio of **17a**/[Ir]/ligand/I_2/$KHCO_3$ was 100:1:2.2:8:110. [b] Determined by ^{1}H NMR in comparison to a 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by HPLC analysis.

Furthermore, almost racemic **18a** was generated when dialkylphosphine-type PHOX **L21** was used (entry 10). From these results, the simple phenyl group was the best substituent on the phosphorus atom for this reaction. **L22**, **L23**, and **L26**, which had substituents on the 5-position of the oxazoline rings, exhibited comparable ees to non-substituted PHOX **L12** or **L16** (entries 5 vs 11, 4 vs 12 and 15). These observations mean that the substituent on the 5-position little affected the enantioselectivity in the reaction. Phosphinoimidazoline type ligands **L24**, **L25**[16] allowed the hydrogenation to proceed with comparable enantioselectivity to **L16**. On the other hand, the ferrocene-based ligand **L27** diminished the enantioselectivity dramatically (entry 16).

When K_2CO_3 was used as a base, **18a** was obtained in moderate yield and comparable enantioselectivity to the reaction with $KHCO_3$ (Table 6, entry 1). The reaction with 0.55 equivalent of K_2CO_3, **17a** was completely consumed and 1**8a** was observed with comparable yield and optical purity to the reaction with an equivalent of the base (entry 2). The other metal carbonates decreased the yield (entries 3–6). A strong base such as KO*t*-Bu reduced the yield because of the decomposition of the substrate (entry 7). When KOAc was used as a base, **18a** was obtained with comparable enantioselectivity to the reaction with $KHCO_3$, but low yield (entry 8). No comparable result to the case using $KHCO_3$ was obtained in the presence of KF (entry 9). The solvent also affected the yield and enantioselectivity. Unreacted **17a** remained after the hydrogenation in toluene, DCE, and cyclopentylmethy ether (CPME) certainly because of the insolubility of **17a** (entries 10–12). The racemic product was generated in acetonitrile (entry 14). PHOX–iridium complex might not be generated in acetonitrile because of the coordination of the solvent. *t*-Amyl alcohol was the best solvent for the hydrogenation of **17a** (entry 15). Furthermore, the enantioselectivity was enhanced at low temperature (entry 16).

Table 6. Effects of base and solvent[a]



entry	base	solvent	yield[b]	ee[c]
1	K_2CO_3	THF	55%	70%
2[d]	K_2CO_3	THF	63%	67%
3[d]	Li_2CO_3	THF	13%	–
4[d]	Na_2CO_3	THF	40%	54%
5[d]	Cs_2CO_3	THF	23%	–
6[d]	$CaCO_3$	THF	0%	–
7	KO*t*-Bu	THF	13%[e]	–
8	KOAc	THF	37%	62%
9	KF	THF	11%[f]	–
10	$KHCO_3$	toluene	30%[g]	69%
11	$KHCO_3$	DCE	17%[h]	42%
12	$KHCO_3$	CPME	8%[i]	–
13	$KHCO_3$	EtOAc	71%	69%
14	$KHCO_3$	MeCN	33%[e]	0%
15	$KHCO_3$	*t*-AmylOH	86%[j]	84%
16	$KHCO_3$	*t*-AmylOH	94%[j]	86%

[a] Reactions were conducted on a 0.20 mmol scale in 1.0 mL of THF under 5.0 MPa of H_2 at 70°C for 4 h. The ratio of **17a**/[Ir]/ligand/I_2/$KHCO_3$ was 100:1:2.2:8:110. [b] Determined by ^{1}H NMR in comparison to a 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by HPLC analysis. [d] The ratio of **17a**:base was 100:55. [e] A small amount (<10% yield) of 3-(*N*-Methylamino)-1-phenyl-2-buten-1-one was detected. [f] 51% conv. [g] 58% conv. [h] 62% conv. [i] 42% conv. [j]Isolated yield.

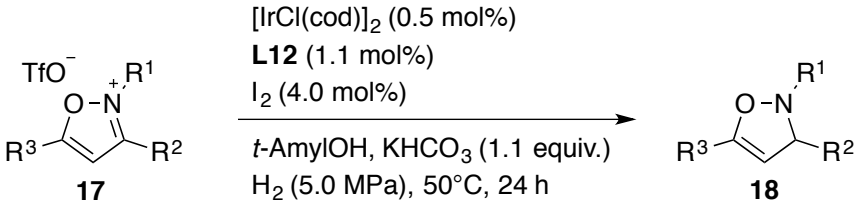
With the optimized condition, various 3-substituted 5-arylisoxazolium **17** were reduced to 4-isoxazolines **18** as shown in Table 7. Primary alkyl substituted substrates converted to **18** in high yield and enantioselectivity (enties 1–6). Especially, 3-neopentylated isoxazolium **17e** converted to **18e** with 89% ee (entry 5). On the other hand, a secondary alkyl substituent such as cyclohexyl group decreased the enantioselectivity of the hydrogenation (entry 7). The reaction of 3,5-diphenylisoxazolium **17h** proceeded slowly under the optimized condition because

of the insolubility of the substrate. The substrate **17h** was reduced to 4-isoxazoline **18h** in good yield and high enantioselectivity by conducting the reaction by using **L16**–iridium catalyst in THF at 70°C (entry 8). With this condition, **17j** bearing the electron-rich aryl group was converted with good yield and high enantioselectivity, although the hydrogenation of **17i** bearing the electron-poor aryl group on 3-position proceeded with low yield and ee (entries 9 and 10). It is noted that demethylation occurred in the reaction of **17h** and **17i**. The substituent on the aryl group of 5-position affected the yield and ee. Unfortunately, the electronic effect of the substituent on *para*-position was uncertainly, the enantioselectivity was decreased as methoxy, trifluoromethyl, and methoxycarbonyl groups on para-position (entries 11–14). On the other hand, the bulky aryl group on the 5-position brought about significant decrease in stereoselectivity (entry 15). *N*-Ethylisoxazolium **17p** was quantitatively reduced to **18p** with 90% ee (entry 16).

Next, the hydrogenation of **17q** was attempted, which had the opposite substituent on 3- and 5-position to **17a**. Surprisingly, isoxazolidine **19q** was quantitatively obtained with moderate enantiomeric excess as the sole product, and 4-isoxazoline **18q** was not detected in the crude product (Table 8, entry 1). **L16** was the best ligand, and **19q** was obtained with 75% ee (entry 2). The hydrogenation of isoxazoliums bearing primary alkyl group **17r**–**17t** also produced isoxazolines **19** with good yield and ee (entries 3–5). In addition, **17u** also converted to the isoxazolidine **19u**, but the enantiomeric excess of **19u** was 40% ee (entry 6).

The N–O bond of isoxazolidine **19q** easily cleaved under acidic condition in the presence of zinc powder.[17] *N*-Boc-1,3-aminoalcohol **20a** was obtained after the protection of the resulting amino group by Boc_2O (eq. 32). I attempted to determine the absolute configuration at α-position of hydroxyl group by using Trost method.[18] The differences chemical shifts of ^{1}H NMR between (*S*)- and (*R*)-*O*-methylmandelates **21q** are summarized in Figure 2. With the results, the absolute configuration at 5-position of **19q** was assigned to be *S*. Because **19q** was *cis*-isomer determined by nOe and NOESY, the absolute configuration of **19q** is assigned to be (3*S*,5*S*).

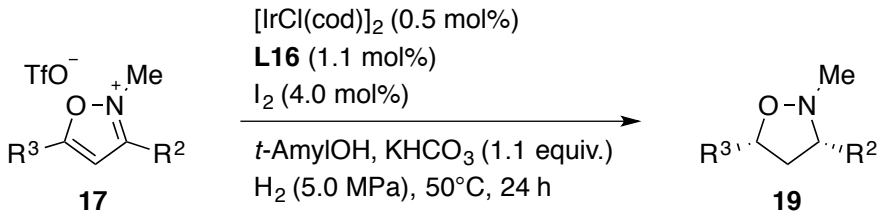
Table 7. Catalytic Asymmetric Hydrogenation of 5-Arylated Isoxazolium Salts[a]



entry	R^1	R^2	R^3	**18**	yield[b]	ee[c]
1	Me	Me	Ph	**18a**	84%	85%
2	Me	*n*-Pr	Ph	**18b**	97%	85%
3	Me	*n*-C_7H_{15}	Ph	**18c**	98%	86%
4	Me	*i*-Bu	Ph	**18d**	97%	87%
5	Me	CH_2(*t*-Bu)	Ph	**18e**	99%	89%
6	Me	Bn	Ph	**18f**	94%	86%
7	Me	Cy	Ph	**18g**	86%	24%
8[d,e]	Me	Ph	Ph	**18h**	81%	86%
9[d]	Me	*p*-$MeOC_6H_4$	Ph	**18i**	84%	88%
10[d,f]	Me	*p*-$CF_3C_6H_4$	Ph	**18j**	(50%)	75%
11	Me	Me	*p*-$MeOC_6H_4$	**18k**	67%	63%
12	Me	Me	*p*-MeC_6H_4	**18l**	81%	84%
13	Me	Me	*p*-$CF_3C_6H_4$	**18m**	93%	73%
14	Me	Me	*p*-$MeOCOC_6H_4$	**18n**	77%	65%
15	Me	Me	*o*-MeC_6H_4	**18o**	56%	2%
16	Et	Me	Ph	**18p**	96%	90%

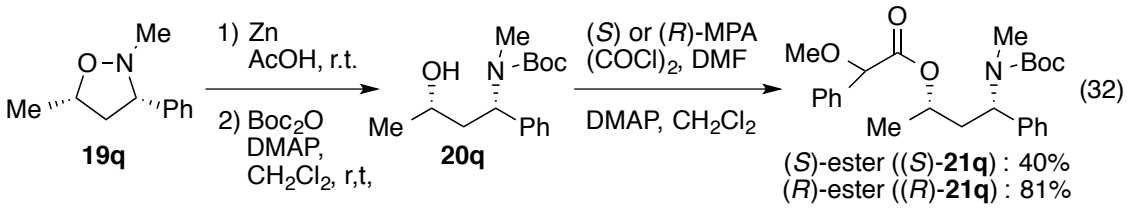
[a] Reactions were conducted on a 0.40 mmol scale in 1.0 mL of *t*-AmylOH under 5.0 MPa of H_2 at 50°C for 24 h. The ratio of **17**/[Ir]/**L12**/I_2/$KHCO_3$ was 100:0.5:1.1:4:110. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Reactions were conducted on a 0.20 mmol scale in 1.0 mL of THF under 5.0 MPa of H_2 at 70°C for 4 h. The ratio of **17**/[Ir]/**L16**/I_2/$KHCO_3$ was 100:1:2.2:8:110. [e] Small amount of **12h** was obserbed (<10%). [f] **18j** was obtained as a mixture of **18j** and **12j**. The yield in the parentheses was estimated with ^1H NMR analysis.

Table 8. Catalytic Asymmetric Hydrogenation of 5-Alkylated Isoxazolium Salts[a]



entry	R^2	R^3	**19**	yield[b]	ee[c]
1[d]	Ph	Me	**19q**	97%	65%
2	Ph	Me	**19q**	96%	75%
3[d]	Ph	Bu	**19r**	97%	77%
4[e]	Ph	CH_2CH_2Ph	**19s**	96%	77%
5[e]	Me	CH_2CH_2Ph	**19t**	81%	66%
6	Ph	H	**19u**	98%	40%

[a] Reactions were conducted on a 0.40 mmol scale in 1.0 mL of *t*-AmylOH under 5.0 MPa of H_2 at 50°C for 24 h. The ratio of **17**/[Ir]/**L16**/I_2/$KHCO_3$ was 100:0.5:1.1:4:110. [b] Isolated yield. [c] Determined by HPLC analysis. [d] **L12** instead of **L16**. [e] Reactions were conducted on a 0.20 mmol scale. The ratio of **6**/[Ir]/**L16**/I_2/$KHCO_3$ was 100:1:2.2:8:110.



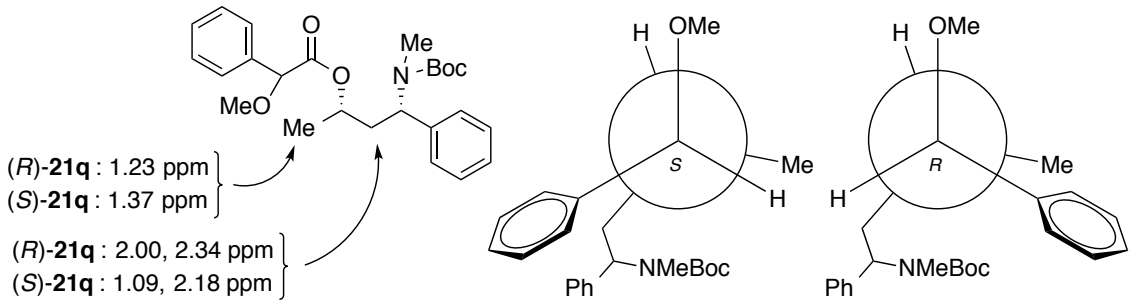
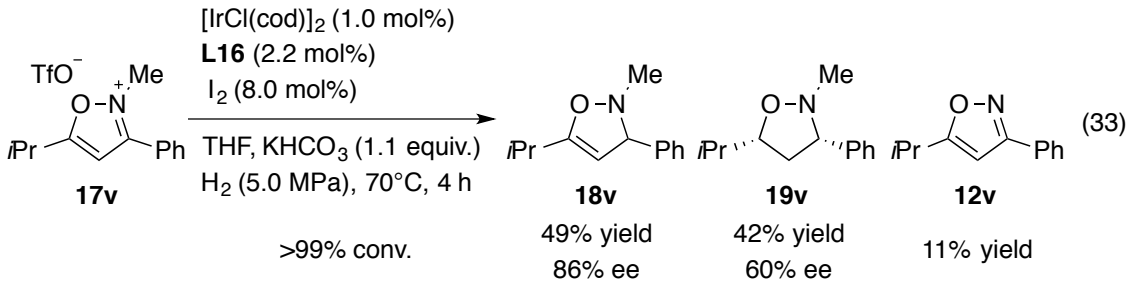
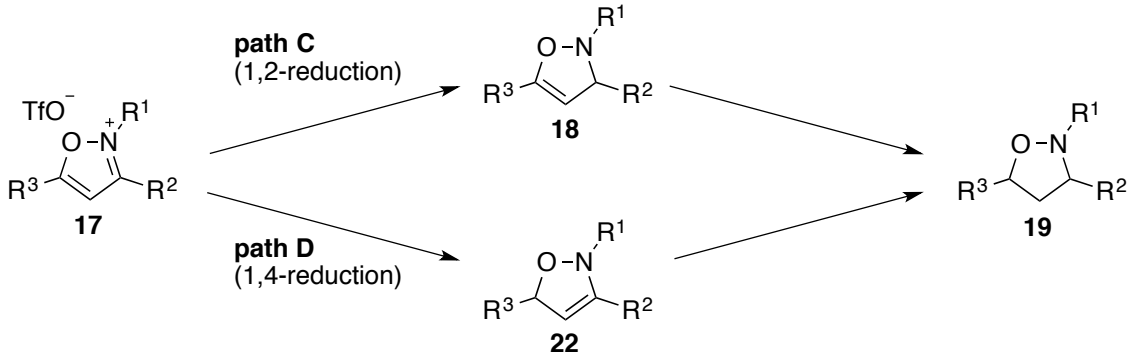


Figure 2. Determination of Absolute Configuration by Trost Method

While the substrates bearing primary alkyl group on the 5-position were converted to isoxazolidines **19** quantitatively, the hydrogenation of 5-isopropylated substrate **17v** gave the mixture of 4-isoxazoline **18v** and isoxazolidine **19v** (eq. 33).

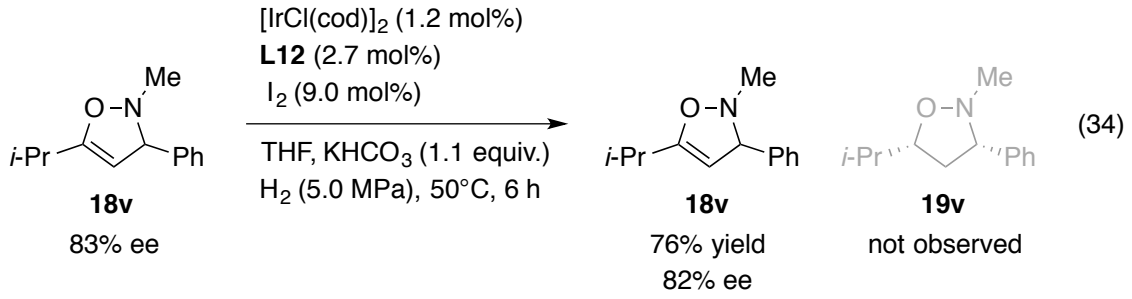


Two pathways are supposed for the hydrogenation giving **19** (Scheme 4). First pathway is through the reduction of C–N double bond of **17** (path C). On the other hand, it is possible that **17** was reduced to 3-isoxazoline **22** by hydridoiridium species through 1,4-addition-like pathway (path D).

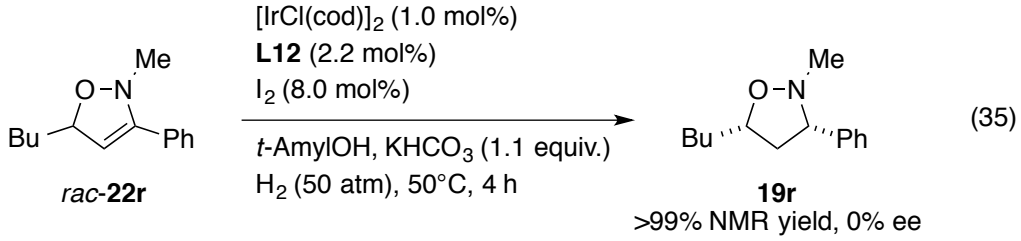


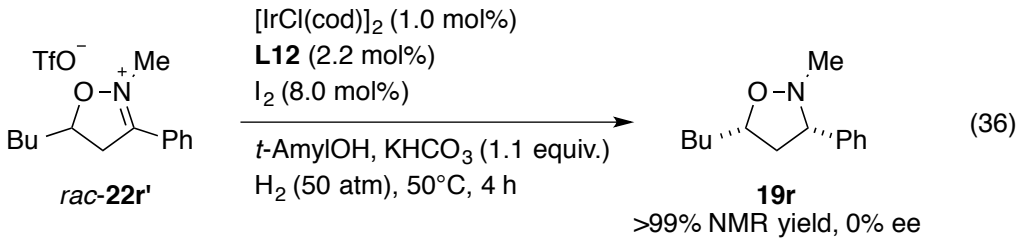
Scheme 4. Possible Reaction Pathways

In order to verify to proceed through ether route, some experiments were conducted as follows. First, the **L12**–iridium-catalyzed hydrogenation of 4-isoxazoline **18v** obtained from the hydrogenation of **17v** was conducted, but no **19v** formed in the reaction (eq. 34).

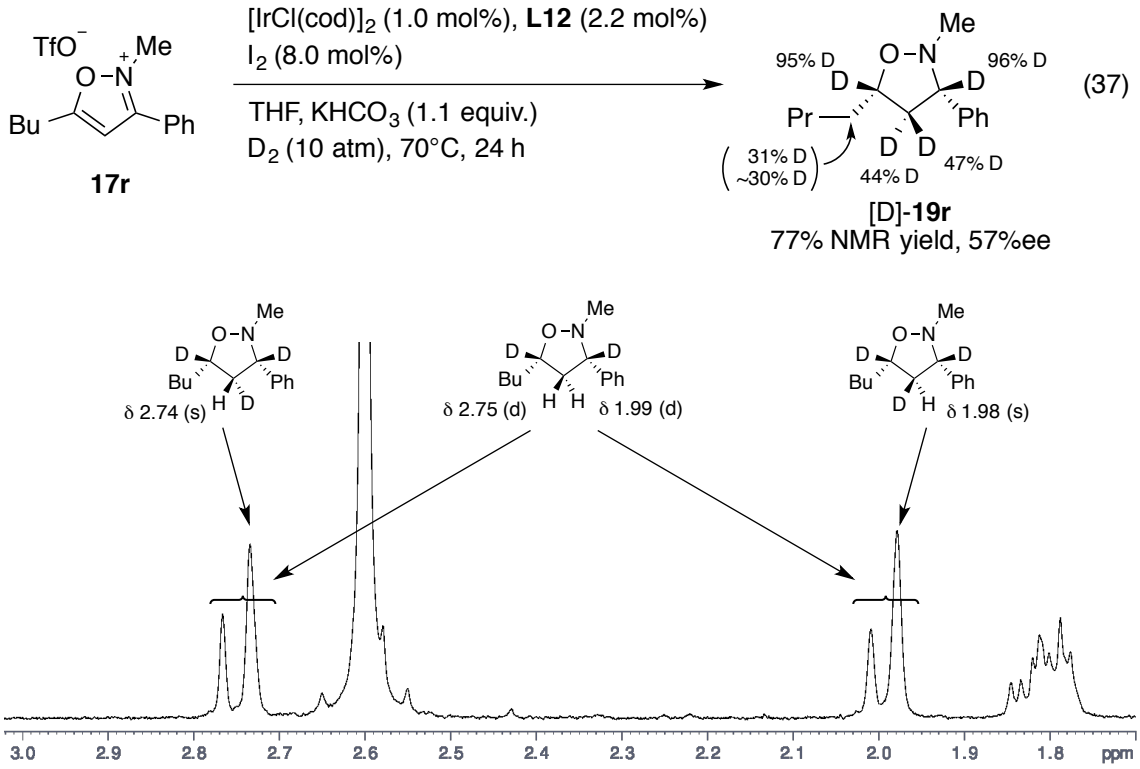


On the other hand, the hydrogenation racemic 3-isoxazoline **22r** under the optimized condition yielded to *cis*-**19r** in high yield (eq. 35). Similarly, 2-isoxazolinium salt **22r'** was also quantitatively converted into *cis*-**19r** (eq. 36). Both of the hydrogenations were not accompanied with the kinetic resolution of the chiral isoxazolium salts.





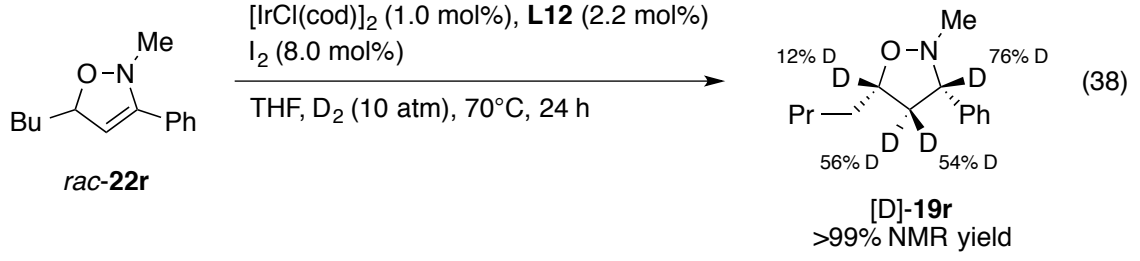
From the above results, this reaction is supposed to proceed through path D. Next, the deuteration of **17r** conducted in THF (eq. 37). Deuterium was incorporated into 3- and 5-position completely. In addition, interestingly, the each positions on C4 atom were deuterated *ca.* 50%. The resonances of the protons on C4 appeared in the ^{1}H NMR spectrum of [D]-**19r** as shown in Figure 3. The split patterns of these peaks indicate that [D]-**19r** obtained from eq. 37 contains four deuterium-incorporated products, 3,5-di, 3,4,5-tri- (two isomers), and 3,4,4,5-tetradeuterated **19r**.



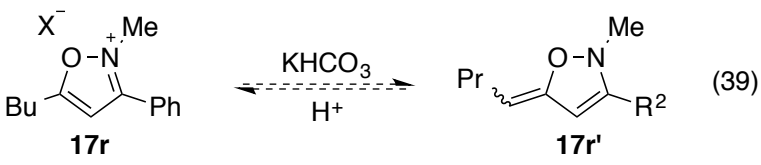
(37)

Figure 3. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of [D]-**19r**

Similar H/D scramble was observed in the deuteration of **22r** (eq. 38). It means that the equilibrium between **22** and **22'** takes place under this reaction condition. It is noted that the deuteration at 1-position of butyl group of **19r** was observed. **17r** might be in equilibrium with **17r'** under the condition (eq. 39).

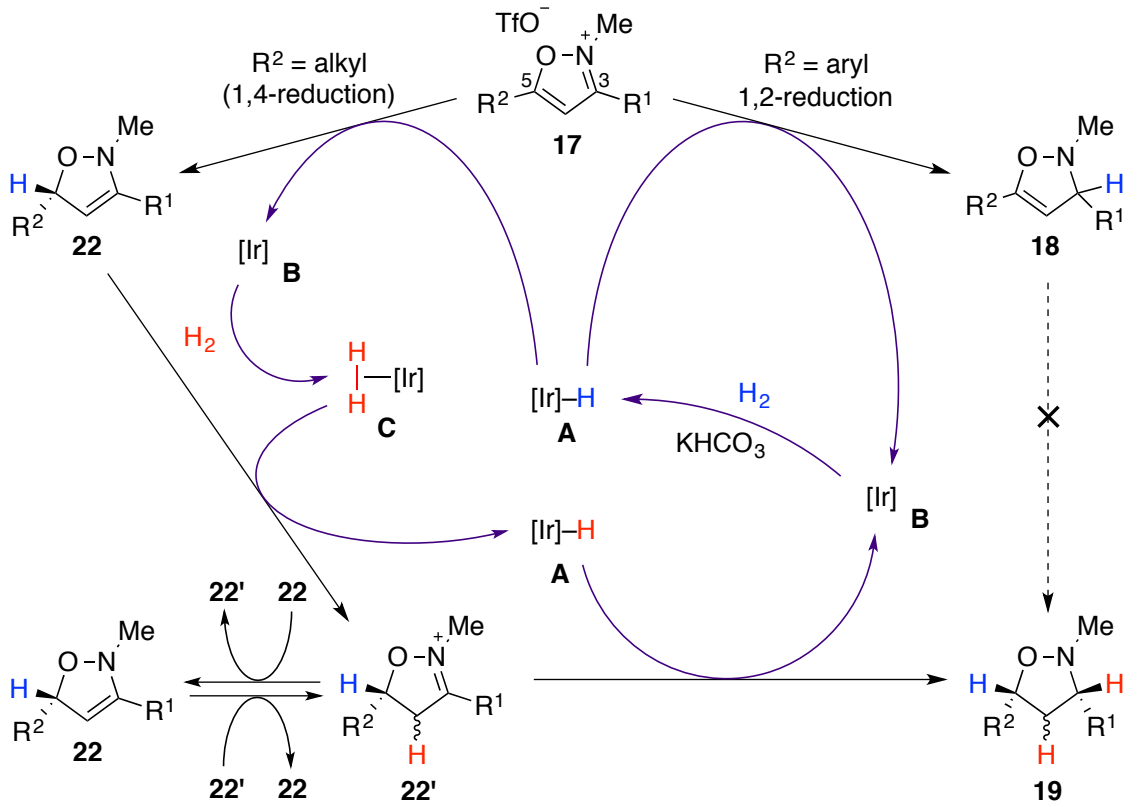


(38)



(39)

The iridium-catalyzed hydrogenation of **17** may proceed through the pathway as shown in Scheme 5. It has been reported that a hydridoiridium(III) species is involved with the catalytic cycle of the hydrogenation using $[IrCl(cod)]_2$–bisphosphine–I_2 catalyst.[14] In the reaction of the 5-alkylisoxazoliums, the hydridoiridium(III) **A** derivers its hydride to the C5 atom through 1,4-addition-like pathway. The resulting 3-isoxazoline **22** is protonated at its 4-position by the molecular hydrogen complex **C** to form 2-isoxazolinium **22'** and **A**. The hydride in **A** reduces the C–N double bond of **22** to isoxazolidine **19**. The cationic iridium species **B** would be converted into **A** through the formation of molecular hydrogen complex and the deprotonation with $KHCO_3$. The H/D scramble at the 4-position may indicate that the intermolecular proton transfer occurs between **22** and **22**' in equilibrium.[19] When a 5-arylisoxazolium is used as the substrate, the aryl substituent may sterically obstruct the access of **A** to the C5 atom in **17**. Therefore, the addition of **A** to the isoxazolium ring proceeds through 1,2-addition-like pathway to give 4-isoxazoline **18** with high enantiomeric excess. The **L12**–iridium catalyst is impossible to further reduce **18**.



Scheme 5. Plausible Reaction Pathway

3.3. Conclusion

In conclusion, I developed the enantioselective hydrogenation of isoxazolium triflates **17**. In contrast to the hydrogenation of benzisoxazoles, the hydrogenation proceeded without the cleavage of N–O bond in the substrates by using phosphinooxazoline type ligand **L12**(**L16**), $[IrCl(cod)]_2$, and I_2 catalyst system. The chiral catalyst exclusively converted 5-arylisoxazolines **18** in high yields and high enantioselectivities. On the other hand, when **17** has a primary alkyl group at its 5-position, its heteroarene ring was fully saturated to exclusively give *cis*-isoxazolidine **19** with good enantioselectivity. From some mechanistic experiments, it is disclosed that **19** are gave from 3-isoxazolines **22** produced through 1,4-reduction of the substrates while 4-isoxazoline **18** was produced through the hydrogenation of C–N double bond of **17**.

3.4. Experimental Section

3.4.1 General and Materials

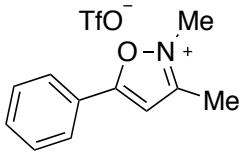
All NMR spectra were measured with Bruker AVANCE 400 or AVANCE III HD 400 Nanobay (9.4 T magnet) spectrometer at ambient temperature. In ^{1}H NMR spectra, chemical shifts (ppm) referenced to internal tetramethylsilane (0.00 ppm in $CDCl_3$), CD_3SOCD_2H (2.50 ppm in DMSO-d_6), or CD_3COCD_2H (2.05 ppm in acetone-d_6). In ^{13}C NMR spectra, chemical shifts (ppm) referenced to the carbon signal of the deuterated solvents (77.0 ppm in $CDCl_3$, 40.0 ppm in DMSO-d_6, 30.0 ppm in acetone-d_6). In ^{2}H NMR spectra, chemical shifts (ppm) referenced to internal $CDHCl_2$ (5.30 ppm in CH_2Cl_2). IR spectra and melting points were measured with JASCO FT/IR-4100 and Büchi Melting Point B-545, respectively. Elemental analyses and high-resolution mass spectra (FAB) were performed by Service Centre of Elementary Analysis of Organic Compounds and Network Joint Research Center for Materials and Devices (Institute for Materials Chemistry and Engineering, Kyushu University), respectively. Flash column chromatographies and medium-pressure liquid chromatographies (MPLC) were performed with silica gel 60 (230–400 mesh, Merck) and C.I.G. pre-packed column CPS-223L-1 (Kusano, Tokyo, Japan), respectively.

2-Methyl-2-butanol (*tert*-AmylOH), *N*,*N*-dimethylfromamide (DMF), and triethylamine (Et_3N) were dried with calcium hydride. EtOAc was dried with P_2O_5. These solvents and reagents were distilled under nitrogen atmosphere. Tetrahydrofuran (THF) (HPLC grade, without inhibitor) was deoxidized by purging with nitrogen for 30 min and was dried with an alumina and copper column system (GlassContour). Dry diethyl ether (Et_2O, Kanto), dichloromethane (CH_2Cl_2, Kanto), distilled water (Wako) were purchased. Di-μ-chlorobis[(1,2,5,6-η)-1,5-cyclooctadiene]diiridium(I) {$[IrCl(cod)]_2$},[20] 3-methyl-5-phenylisoxazole,[21] 5-phenyl-3-propylisoxazole,[22] 3-benzyl-5-phenylisoxazole,[23] 3-cyclohexyl-5-phenylisoxazole,[24] 3,5-diphenylisoxazole,[25] 3-(4-methoxyphenyl)-5-phenylisoxazole,[26] 5-methyl-3-phenylisoxazole,[27] 5-butyl-3-phenylisoxazole,[28] 3-phenyl-5-(2-phenylethyl)isoxazole,[29] (3-phenylisoxazol-5-yl)methanol,[30] 3-methyl-5-(2-phenylethyl)isoxazole,[31] 3-phenylisoxazole,[32] diethyl 1-(1-methylethyl)ethenylphosphonate[33] were prepared according to literature procedures. (*S*)-2-[2-(Diphenylphosphino)phenyl]-4-(1-methylethyl)-2-oxazoline (**L12**), (*S*)-2-[2-(diphenylphosphino)phenyl]-4-phenyl-2-oxazoline (**L16**) were purchased from Aldrich. Iodine (I_2), potassium bicarbonate ($KHCO_3$), methyl

trifluoromethanesulfonate (MeOTf), hydroxylamine hydrochloride, sodium acetate (NaOAc), ethanol (EtOH), octanal, *N*-chlorosuccinimide, 3-methylbutanal, phenylacetylene, 3,3-dimethylbutanal, 4-(trifluoromethyl)benzaldehyde, acetaldehyde oxime, 4-methoxyphenylacetylene, 4-methylphenylacetylene, 4-(trifluoromethyl)phenylacetylene, methyl 4-ethynylbenzoate, 2-methylphenylacetylene, ethyl trifluoromethanesulfonate, 4-(dimethylamino)pyridine (DMAP), benzaldehyde oxime, zinc powder (Nacalai Tesque), acetic acid, di-*tert*-butyl dicarbonate (Boc_2O), (*S*)- and (*R*)-*O*-methylmandelic acids, and 1-hexene were purchased and used without further purification.

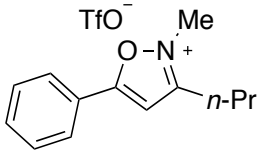
3.4.2 Preparation of Isoxazolium Triflates

2,3-Dimethyl-5-phenylisoxazolium trifluoromethanesulfonate (**17a**)



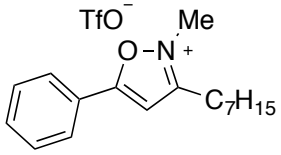
3-Methyl-5-phenylisoxazole (**12a**) (2.05 g, 13 mmol) was placed in a 200 mL two-neck flask, which was equipped with a stirring bar, rubber septum, and three-way stopcock. After the reaction vessel was evacuated and charged with nitrogen gas three times, dry CH_2Cl_2 (25 mL) was added into the flask. MeOTf (1.5 mL, *d* 1.45 g/mL, 13 mmol) was carefully added to the mixture. After stirred at ambient temperature for 14 h, the mixture was diluted with Et_2O (100 mL) and then stirred for 10 min. The resulting precipitation was collected with filtration, washed with Et_2O, and then dried in vacuo to give **17a** (4.03 g, 97%) as colorless powder: mp. 123.5–124.9°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.68 (s, 3H), 4.32 (s, 3H), 7.68 (t, J = 7.3 Hz, 2H), 7.74 (t, J = 7.5 Hz, 1H), 7.77 (s, 1H), 8.00 (d, J = 7.4 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 12.4, 38.8, 105.9, 121.2 (q, J = 322 Hz), 123.5, 127.4, 130.3, 134.2, 161.2, 169.3; IR (KBr) 3125, 1620, 1551, 1486, 1257, 1161, 1029, 779, 694, 638 cm^{-1}; Anal. Calcd for $C_{12}H_{12}F_3NO_4S$: C, 44.58; H, 3.74; N, 4.33. Found: C, 44.46; H, 3.71; N, 4.32.

2-Methyl-5-phenyl-3-propylisoxazolium trifluoromethanesulfonate (**17b**)



The procedure for preparing **17a** was followed with use of 5-phenyl-3-propylisoxazole[22] (748 mg, 4.0 mmol). The reaction was conducted for 13 h to give **17b** (881 mg, 63%) as colorless powder: mp. 108.9–109.3°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.04 (t, J = 7.4 Hz, 3H), 1.81 (sextet, J = 7.5 Hz, 2H), 2.98 (t, J = 7.6 Hz, 2H), 4.34 (s, 3H), 7.68 (t, J = 7.3 Hz, 2H), 7.74 (t, J = 7.3 Hz, 1H), 7.89 (s, 1H), 8.02 (d, J = 7.6 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 13.8, 20.1, 27.4, 38.9, 104.8, 121.2 (q, J = 322 Hz), 123.6, 127.5, 130.3, 134.2, 164.1, 169.7; IR (KBr) 3118, 2969, 1613, 1541, 1469, 1268, 1162, 1030, 767, 687, 634 cm^{-1}; Anal. Calcd for $C_{14}H_{16}F_3NO_4S$: C, 47.86; H, 4.59; N, 3.99. Found: C, 47.97; H, 4.54; N, 4.05.

3-Heptyl-2-methyl-5-phenylisoxazolium trifluoromethanesulfonate (**17c**)



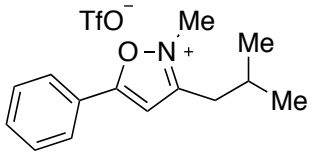
Hydroxylamine hydrochloride (776 mg, 11 mmol) and NaOAc (919 mg, 11 mmol) were placed in a 100 mL two-neck flask, which was equipped with a stirring bar, rubber septum, and Dimroth condenser. EtOH (10 mL), distilled water (10 mL), octanal (1.30 g, 10 mmol) were added into the flask, and then the solution was stirred under reflux for 2 h. After cooled to room temperature, the resulting mixture was extracted three times with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and then evaporated under reduced pressure. The residue containing octanal oxime was used for the following reaction without further purification

The residue was placed in a 100 mL two-neck flask, which was equipped with a stirring bar, three-way stopcock, and plug. After the reaction vessel was evacuated and charged with nitrogen gas three times, dry DMF (20 mL) was added into the flask. The plug was removed from the vessel under nitrogen flow, and then *N*-chlorosuccinimide (1.47 g, 11 mmol) was fractionally added to the solution. When an exothermic reaction started in the mixture, the flask was cooled with a water bath at 10°C. After stirred at ambient temperature for 2 h, the resulting mixture was diluted with water and then extracted three times with 1:1 mixture of EtOAc and hexane. The combined organic layer was washed with brine, dried over Na_2SO_4, and then evaporated under reduced pressure. The residue containing *N*-hydroxyoctanimidoyl chloride was used for the following reaction without further purification.

The residue was placed in a 100 mL three-neck flask, which was equipped with a stirring bar, rubber septum, three-way stopcock, and dropping funnel with a rubber septum. After the reaction vessel was evacuated and charged with nitrogen gas three times, dry Et_2O (40 mL) and phenylacetylene (1.12 g, 11 mmol) were added into the flask. A solution of dry Et_3N (1.65 mL, *d* 0.73 g/mL, 12 mmol) in Et_2O (10 mL), which was prepared in the dropping funnel, was added dropwise to the mixture at 0 °C for 1 h. After stirred at ambient temperature for 12 h, the resulting mixture was diluted with water and then extracted three times with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and then evaporated under reduced pressure. The residue was purified with a flash column chromatography (EtOAc/hexane = 1/20) to give 3-heptyl-5-phenylisoxazole containing 3,5-diheptyl-1,2,4-oxadiazole 4-oxide.

The procedure for preparing **17a** was followed with use of the above mixture containing 3-heptyl-5-phenylisoxazole. The reaction was conducted for 19 h to give **17c** (987 mg, 24%) as colorless powder: mp. 117.8–117.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.88 (t, *J* = 6.4 Hz, 3H), 1.23–1.47 (m, 8H), 1.77 (quintet, *J* = 7.5 Hz, 2H), 2.99 (t, *J* = 7.7 Hz, 2H), 4.34 (s, 3H), 7.68 (t, *J* = 7.1 Hz, 2H), 7.74 (t, *J* = 7.0 Hz, 1H), 7.91 (s, 1H), 8.02 (d, *J* = 7.2 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 14.4, 22.5, 25.7, 26.5, 28.73, 28.77, 31.5, 38.9, 104.8, 121.2 (q, *J* = 322 Hz), 123.6, 127.5, 130.3, 134.1, 164.3, 169.6; IR (KBr) 3115, 2934, 2858, 1610, 1540, 1470, 1264, 1155, 1034, 773, 689, 639 cm^{-1}; Anal. Calcd for $C_{18}H_{24}F_3NO_4S$: C, 53.06; H, 5.94; N, 3.44. Found: C, 53.11; H, 5.81; N, 3.46.

2-Methyl-3-(2-methylpropyl)-5-phenylisoxazolium trifluoromethanesulfonate (**17d**)

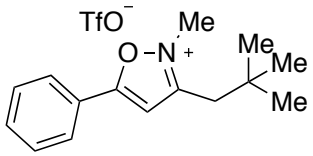


The procedure for preparing 3-heptyl-5-phenylisoxazole was followed with use of 3-methylbutanal (1.76 g, 20 mmol) and phenylacetylene (973 mg, 9.5 mmol). The crude product was purified with a flash column chromatography (EtOAc/hexane = 1/20) to give a mixture of 3-(2-methylpropyl)-5-phenylisoxazole and 3,5-bis(2-methylpropyl)-1,2,4-oxadiazole 4-oxide (1.39 g).

The procedure for preparing **17a** was followed with use of the above mixture (603 mg). The reaction was conducted for 18 h to give **17d** (561 mg, 1.5 mmol) as colorless powder: mp. 75.3–75.4°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.03 (d, *J* = 6.6

Hz, 6H), 2.14 (nonet, J = 6.8 Hz, 1H), 2.93 (d, J = 7.0 Hz, 2H), 4.37 (s, 3H), 7.59 (s, 1H), 7.73 (t, J = 7.3 Hz, 2H), 7.80 (t, J = 7.5 Hz, 1H), 7.90 (d, J = 7.7 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 22.3, 27.6, 34.9, 40.7, 108.0, 121.2 (q, J = 322 Hz), 123.0, 130.11, 130.13, 133.9, 159.4, 175.8; IR (KBr) 3144, 2970, 2877, 1605, 1543, 1467, 1271, 1151, 1032, 774, 698, 635 cm^{-1}; Anal. Calcd for $C_{15}H_{18}F_3NO_4S$: C, 49.31; H, 4.97; N, 3.83. Found: C, 49.35; H, 4.84; N, 3.86.

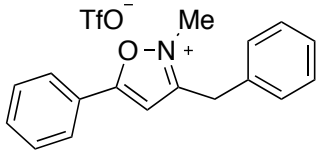
3-(2,2-Dimethylpropyl)-2-methyl-5-phenylisoxazolium trifluoromethanesulfonate (**17e**)



The procedure for preparing 3-heptyl-5-phenylisoxazole was followed with use of 3,3-dimethylbutanal (2.5 mL, d 0.80 g/mL, 20 mmol) and phenylacetylene (1.00 g, 9.79 mmol). The crude product was purified with a flash column chromatography (EtOAc/hexane = 1/20) to give a mixture of 3-(2,2-dimethylpropyl)-5-phenylisoxazole and 3,5-bis(2,2-dimethylpropyl)-1,2,4-oxadiazole 4-oxide (1.45 g).

The procedure for preparing **17a** was followed with use of the above mixture (647 mg). The reaction was conducted for 18 h to give **17e** (877 mg, 2.3 mmol) as colorless powder: mp. 115.5–115.6°C; ^{1}H NMR (400 MHz, DMSO-d_6) 1.07 (s, 9H), 2.99 (s, 2H), 4.39 (s, 3H), 7.68 (t, J = 7.3 Hz, 2H), 7.74 (t, J = 7.3 Hz, 1H), 7.82 (s, 1H), 8.06 (d, J = 7.7 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 29.4, 33.7, 38.7, 39.3, 106.3, 121.2 (q, J = 322 Hz), 123.6, 127.6, 130.3, 134.2, 162.0, 169.5; IR (KBr) 3116, 2969, 1607, 1536, 1476, 1265, 1153, 1029, 780, 694, 634 cm^{-1}; Anal. Calcd for $C_{16}H_{20}F_3NO_4S$: C, 50.65; H, 5.31; N, 3.69. Found: C, 50.67; H, 5.28; N, 3.79.

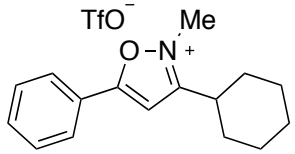
3-Benzyl-2-methyl-5-phenylisoxazolium trifluoromethanesulfonate (**17f**)



The procedure for preparing **17a** was followed with use of 3-benzyl-5-phenylisoxazole[23] (653 mg, 2.8 mmol). The reaction was conducted for 16 h to give **17f** (518 mg, 47%) as colorless powder: mp. 85.5–85.6°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.44 (s, 3H), 4.47 (s, 2H), 7.35–7.46 (m, 5H), 7.65 (t, J = 7.4 Hz, 2H),

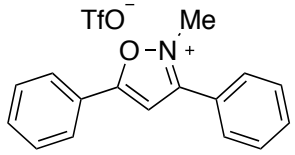
7.68 (s, 1H), 7.72 (t, J = 7.4 Hz, 1H), 8.03 (d, J = 7.8 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 31.6, 39.3, 105.3, 121.2 (q, J = 322 Hz), 123.5, 127.6, 128.4, 129.6, 129.9, 130.2, 133.6, 134.2, 162.9, 167.0; IR (KBr) 3161, 3033, 2954, 1608, 1538, 1466, 1266, 1152, 1032, 775, 742, 699, 689, 637 cm^{-1}; HRMS (FAB) Calcd for $C_{17}H_{16}NO$: 250.1232. Found: m/z = 250.1230 (M^+).

3-Cyclohexyl-2-methyl-5-phenylisoxazolium trifluoromethanesulfonate (**17g**)



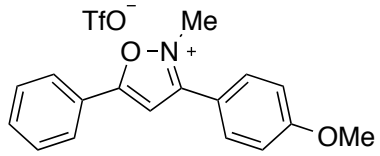
The procedure for preparing **17a** was followed with use of 3-cyclohexyl-5-phenylisoxazole[24] (683 mg, 3.0 mmol). The reaction was conducted for 16 h to give **17g** (538 mg, 46%) as colorless powder: mp. 123.7–124.2°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.22–1.59 (m, 5H), 1.72–2.02 (m, 5H), 3.09–3.20 (m, 1H), 4.38 (s, 3H), 7.69 (t, J = 7.3 Hz, 2H), 7.74 (t, J = 7.3 Hz, 1H), 7.98 (s, 1H), 8.01 (d, J = 7.6 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 25.1, 25.3, 30.4, 35.0, 38.9, 103.5, 121.2 (q, J = 322 Hz), 123.6, 127.4, 130.3, 134.2, 167.0, 169.9; IR (KBr) 3112, 2949, 2934, 2863, 1609, 1537, 1467, 1264, 1166, 1034, 784, 692, 640 cm^{-1}; Anal. Calcd for $C_{17}H_{20}F_3NO_4S$: C, 52.17; H, 5.15; N, 3.58. Found: C, 52.10; H, 5.05; N, 3.57.

2-Methyl-3,5-diphenylisoxazolium trifluoromethanesulfonate (**17h**)



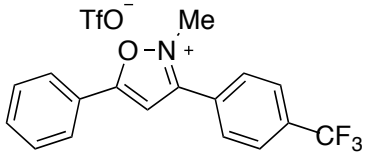
The procedure for preparing **17a** was followed with use of 3,5-diphenylisoxazole[25] (1.11 g, 5.0 mmol). The reaction was conducted for 16 h to give **17h** (1.57 g, 82%) as colorless powder: mp. 163.0–163.3°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.47 (s, 3H), 7.71–7.87 (m, 6H), 7.96 (d, J = 7.4 Hz, 2H), 8.10 (d, J = 7.4 Hz, 2H), 8.32 (s, 1H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 40.9, 105.4, 121.2 (q, J = 322 Hz), 123.1, 123.6, 127.6, 130.1, 130.2, 130.4, 134.1, 134.4, 160.0, 169.9; IR (KBr) 3118, 1613, 1488, 1468, 1266, 1146, 1035, 776, 764, 700, 639 cm^{-1}; Anal. Calcd for $C_{17}H_{14}F_3NO_4S$: C, 52.99; H, 3.66; N, 3.63. Found: C, 52.84; H, 3.64; N, 3.63.

3-(4-Methoxyphenyl)-2-methyl-5-phenylisoxazolium trifluoromethanesulfonate (**17i**)



The procedure for preparing **17a** was followed with use of 3-(4-methoxyphenyl)-5-phenylisoxazole[26] (503 mg, 2.0 mmol). The reaction was conducted for 22 h to give **17i** (784 mg, 94%) as colorless powder: mp. 193.7–193.8°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.93 (s, 3H), 4.47 (s, 3H), 7.32 (d, J = 9.0 Hz, 2H), 7.69–7.80 (m, 3H), 7.95 (d, J = 9.0 Hz, 2H), 8.05–8.09 (m, 2H), 8.26 (s, 1H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 41.0, 56.3, 104.8, 114.8, 115.8, 121.2 (q, J = 322 Hz), 123.6, 127.5, 130.3, 132.3, 134.2, 159.5, 163.9, 169.3; IR (KBr) 3116, 1604, 1463, 1267, 1157, 1031, 835, 768, 686, 634 cm^{-1}; Anal. Calcd for $C_{18}H_{16}F_3NO_5S$: C, 52.05; H, 3.88; N, 3.37. Found: C, 52.03; H, 3.83; N, 3.38.

2-Methyl-5-phenyl-3-[4-(trifluoromethyl)phenyl]isoxazolium trifluoromethanesulfonate (**17j**)

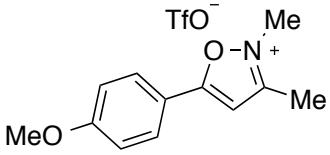


The procedure for preparing 3-heptyl-5-phenylisoxazole was followed with use of 4-(trifluoromethyl)benzaldehyde (1.74 g, 10 mmol) and phenylacetylene (1.18 g, 12 mmol). The crude product was recrystallized from EtOAc/hexane to give 5-phenyl-3-[4-(trifluoromethyl)phenyl]isoxazole (1.45 g, 50%) as colorless crystals: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 6.87 (s, 1H), 7.45–7.54 (m, 3H), 7.75 (d, J = 8.1 Hz, 2H), 7.86 (d, J = 7.8 Hz, 2H), 8.00 (d, J = 8.1 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 97.4, 123.9 (q, J = 272 Hz), 125.89, 125.93 (q, J = 4 Hz), 127.14, 127.16, 129.1, 130.5, 131.9 (q, J = 33Hz), 132.6, 161.8, 171.1.

The procedure for preparing **17a** was followed with use of 5-phenyl-3-propylisoxazole (579 mg, 2.0 mmol). The reaction was conducted for 22 h to give **17j** (605 mg, 67%) as colorless powder: mp. 210.7–212.2°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.47 (s, 3H), 7.75 (d, J = 7.2 Hz, 2H), 7.80 (d, J = 7.3 Hz, 1H), 8.11 (d, J = 7.7 Hz, 2H), 8.15 (d, J = 9.2 Hz, 2H), 8.18 (d, J = 9.2 Hz, 2H), 8.36 (s, 1H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 40.9, 105.9, 121.2 (q, J = 322 Hz), 123.4, 124.0 (q,

J = 273 Hz), 127.06 (q, *J* = 4 Hz), 127.12, 127.7, 130.5, 131.2, 133.4 (q, *J* = 32 Hz), 134.6, 159.0, 170.3; IR (KBr) 3114, 1614, 1465, 1325, 1271, 1158, 1028, 848, 766, 691, 634 cm^{-1}; Anal. Calcd for $C_{18}H_{13}F_6NO_4S$: C, 47.69; H, 2.89; N, 3.09. Found: C, 47.59; H, 2.88; N, 3.16.

5-(4-Methoxyphenyl)-2,3-dimethylisoxazolium trifluoromethanesulfonate (**17k**)



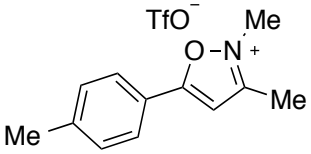
Under nitrogen atmosphere, dry DMF (40 mL) and acetaldehyde oxime (1.21 g, 20 mmol) were charged into a 100 mL two-neck flask, which was equipped with a stirring bar, three-way stopcock, and plug. The plug was removed from the vessel under a nitrogen purge, and then *N*-chlorosuccinimide (2.66 g, 20 mmol) was fractionally added to the solution. When an exothermic reaction started in the mixture, the flask was cooled with a water bath at 10°C. The mixture was stirred at ambient temperature for 2 h to give a solution of *N*-hydroxymethanimidoyl chloride.

Under nitrogen atmosphere, dry Et_2O (100 mL) and 4-methoxyphenylacetylene (1.00 g, 7.6 mmol) was charged into a 500 mL three-neck flask, which was equipped with a stirring bar, rubber septum, three-way stopcock, and dropping funnel with a rubber septum. The solution of *N*-hydroxymethanimidoyl chloride prepared above was transferred through a cannula into the flask. A solution of Et_3N (3.2 mL, *d* 0.73 g/mL, 23 mmol)) in dry Et_2O (50 mL) was added dropwise to the reaction mixture at 0°C for 1 h. After stirred at ambient temperature for 12 h, the resulting mixture was diluted with distilled water, and then extracted three times with 1:1 mixture of EtOAc and hexane. The combined organic layer was washed with brine, dried over Na_2SO_4, and then evaporated under reduced pressure. The residue was purified with a flash column chromatography (EtOAc/hexane = 1/10) to give 5-(4-methoxyphenyl)-3-methylisoxazole[S15] (390 mg, 27%) as a colorless solid: ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 2.34 (s, 3H), 3.86 (s, 3H), 6.24 (s, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 8.7 Hz, 2H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 11.5, 55.3, 98.8, 114.3, 120.4, 127.3, 160.3, 160.9, 169.6.

The procedure for preparing **17a** was followed with use of 5-(4-methoxyphenyl)-3-methylisoxazole (366 mg, 1.9 mmol). The reaction was conducted for 14 h to give **17k** (666 mg, 97%) as colorless powder: mp. 144.4–144.5°C;

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.65 (s, 3H), 3.88 (s, 3H), 4.27 (s, 3H), 7.21 (d, J = 9.0 Hz, 2H), 7.60 (s, 1H), 7.95 (d, J = 9.0 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 12.3, 38.6, 56.3, 104.1, 115.8, 115.9, 121.2 (q, J = 322 Hz), 129.6, 160.9, 163.9, 169.5; IR (KBr) 3159, 3018, 2959, 1608, 1500, 1259, 1188, 1163, 1027, 849, 810, 634 cm^{-1}; Anal. Calcd for $C_{13}H_{14}F_3NO_5S$: C, 44.19; H, 3.99; N, 3.96. Found: C, 44.23; H, 3.86; N, 3.95.

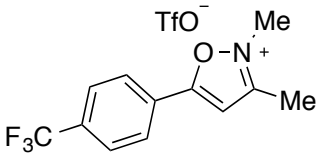
2,3-Dimethyl-5-(4-methylphenyl)isoxazolium trifluoromethanesulfonate (**17l**)



The procedure for preparing 5-(4-methoxyphenyl)-3-methylisoxazole was followed with use of acetaldehyde oxime (600 mg, 10 mmol) and 4-methylphenylacetylene (1.74 g, 15 mmol). The crude product was purified with a flash column chromatography (EtOAc/hexane = 1/10) to give 3-methyl-5-(4-methylphenyl)isoxazole[24] (345 mg, 20%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.34 (s, 3H), 2.39 (s, 3H), 6.30 (s, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H).; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.5, 21.4, 99.5, 124.9, 125.7, 129.6, 140.2, 160.3, 169.8.

The procedure for preparing **17a** was followed with use of 3-methyl-5-(4-methylphenyl)isoxazole (330 mg, 1.9 mmol). The reaction was conducted for 18 h to give **17l** (624 mg, 97%) as colorless powder: mp. 143.3–143.4°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.43 (s, 3H), 2.66 (s, 3H), 4.29 (s, 3H), 7.49 (d, J = 8.1 Hz, 2H), 7.69 (s, 1H), 7.90 (d, J = 8.1 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 12.4, 21.8, 38.8, 105.2, 120.8, 121.2 (q, J = 322 Hz), 127.4, 130.9, 145.0, 161.1, 169.5; IR (KBr) 3164, 3028, 1619, 1554, 1500, 1475, 1265, 1161, 1030, 803, 635 cm^{-1}; Anal. Calcd for $C_{13}H_{14}F_3NO_4S$: C, 46.29; H, 4.18; N, 4.15. Found: C, 46.26; H, 4.09; N, 4.18.

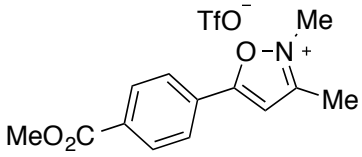
2,3-Dimethyl-5-[4-(trifluoromethyl)phenyl]isoxazolium trifluoromethanesulfonate (**17m**)



The procedure for preparing 5-(4-methoxyphenyl)-3-methylisoxazole was followed with use of acetaldehyde oxime (1.21 g, 20 mmol) and 4-(trifluoromethyl)phenylacetylene (1.70 g, 10 mmol). The crude product was purified with a flash column chromatography (EtOAc/hexane = 1/10) to give 3-methyl-5-[4-(trifluoromethyl)phenyl]isoxazole (1.77 g, 78%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.37 (s, 3H), 6.46 (s, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.86 (d, J = 8.2 Hz, 2H).; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.4, 101.6, 123.7 (q, J = 272 Hz), 125.94 (q, J = 4 Hz), 125.95, 130.6, 131.6 (q, J = 33 Hz), 160.5, 168.0.

The procedure for preparing **17a** was followed with use of 3-methyl-5-[4-(trifluoromethyl)phenyl]isoxazole (456 mg, 2.0 mmol). The reaction was conducted for 19 h to give **17m** (749 mg, 95%) as colorless powder: mp. 131.1–131.2°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.73 (s, 3H), 4.37 (s, 3H), 7.94 (s, 1H), 8.04 (d, J = 8.2 Hz, 2H), 8.22 (d, J = 8.2 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 12.5, 39.1, 107.6, 121.2 (q, J = 322 Hz), 124.0 (q, J = 273 Hz), 127.2 (q, J = 3 Hz), 128.4, 133.3 (q, J = 32 Hz), 161.6, 167.6; IR (KBr) 3161, 3073, 3033, 1609, 1556, 1506, 1478, 1419, 1322, 1263, 1181, 1031, 855, 816, 681, 638 cm^{-1}; Anal. Calcd for $C_{13}H_{11}F_6NO_4S$: C, 39.90; H, 2.83; N, 3.58. Found: C, 39.90; H, 2.71; N, 3.59.

2,3-Dimethyl-5-[4-(methoxycarbonyl)phenyl]isoxazolium trifluoromethanesulfonate (**17n**)

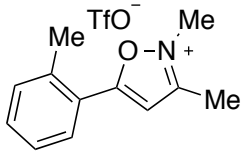


The procedure for preparing 5-(4-methoxyphenyl)-3-methylisoxazole was followed with use of acetaldehyde oxime (1.21 g, 20 mmol) and methyl 4-ethynylbenzoate (1.10 g, 6.9 mmol). The crude product was purified with a flash column chromatography (EtOAc/hexane = 1/5) to give methyl 3-methyl-5-[4-(methoxycarbonyl)phenyl]isoxazole[25] (969 mg, 65%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.37 (s, 3H), 3.95 (s, 3H), 6.47 (s, 1H), 7.82

(d, J = 8.5 Hz, 2H), 8.12 (d, J = 8.5 Hz, 2H).; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.5, 52.3, 101.6, 125.6, 130.2, 131.2, 131.3, 160.5, 166.3, 168.4.

The procedure for preparing **17a** was followed with use of 3-methyl-5-[4-(methoxycarbonyl)phenyl]isoxazole (435 mg, 2.0 mmol). The reaction was conducted for 15 h to give **17n** (649 mg, 85%) as colorless powder: mp. 147.0–147.1°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.70 (s, 3H), 3.91 (s, 3H), 4.34 (s, 3H), 7.91 (s, 1H), 8.14 (d, J = 8.7 Hz, 2H), 8.22 (d, J = 8.7 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 12.5, 39.1, 53.2, 107.4, 121.2 (q, J = 322 Hz), 127.3, 127.8, 130.8, 134.0, 161.5, 165.7, 167.9; IR (KBr) 3129, 1724, 1607, 1554, 1498, 1442, 1413, 1277, 1256, 1159, 1033, 771, 698, 643 cm^{-1}; Anal. Calcd for $C_{14}H_{14}F_3NO_6S$: C, 44.10; H, 3.70; N, 3.67. Found: C, 44.04; H, 3.60; N, 3.61.

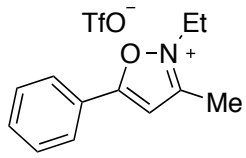
2,3-Dimethyl-5-(2-methylphenyl)isoxazolium trifluoromethanesulfonate (**17o**)



The procedure for preparing 5-(4-methoxyphenyl)-3-methylisoxazole was followed with use of acetaldehyde oxime (1.21 mg, 20 mmol) and 2-methylphenylacetylene (1.00 g, 8.6 mmol). The crude product was purified with a flash column chromatography (EtOAc/hexane = 1/10) to give 3-methyl-5-(2-methylphenyl)isoxazole[25] (432 mg, 29%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.38 (s, 3H), 2.50 (s, 3H), 6.26 (s, 1H), 7.24–7.37 (m, 3H), 7.69 (d, J = 8.3 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.5, 21.4, 103.3, 126.1, 127.2, 128.4, 129.8, 131.2, 136.1, 159.9, 169.7.

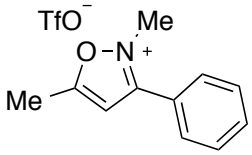
The procedure for preparing **17a** was followed with use of 3-methyl-5-(2-methylphenyl)isoxazole (417 mg, 2.4 mmol). The reaction was conducted for 14 h to give **17o** (773 mg, 95%) as colorless powder: mp. 114.3–114.5°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.55 (s, 3H), 2.70 (s, 3H), 4.33 (s, 3H), 7.45–7.52 (m, 2H), 7.58–7.63 (m, 2H), 7.82 (dd, J = 1.4, 7.9 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 12.3, 21.2, 38.8, 108.6, 121.2 (q, J = 322 Hz), 123.0, 127.4, 129.7, 132.6, 133.5, 138.3, 160.7, 169.5; IR (KBr) 3156, 2992, 1611, 1538, 1469, 1265, 1147, 1032, 780, 726, 637 cm^{-1}; Anal. Calcd for $C_{13}H_{14}F_3NO_4S$: C, 46.29; H, 4.18; N, 4.15. Found: C, 46.32; H, 3.96; N, 4.18.

2-Ethyl-3-methyl-5-phenylisoxazolium trifluoromethanesulfonate (**17p**)



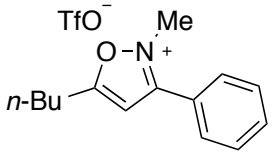
The procedure for preparing **17a** was followed with use of 3-methyl-5-phenylisoxazole[21] (479 mg, 3.0 mmol) and ethyl trifluoromethanesulfonate (560 mg, 3.14 mmol). The reaction was conducted for 15 h to give **17p** (957 mg, 94%) as colorless powder: mp. 104.5–105.1°C; ^{1}H NMR (400 MHz, DMSO, TMS) δ 1.58 (t, *J* = 7.2 Hz, 3H), 2.72 (s, 3H), 4.71 (q, *J* = 7.2 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 2H), 7.73 (t, *J* = 7.3 Hz, 1H), 7.77 (s, 1H), 8.02 (d, *J* = 7.4 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 12.3, 13.0, 47.8, 105.9, 121.2 (q, *J* = 322 Hz), 123.6, 126.0, 127.5, 130.2, 134.1, 160.8, 169.6; IR (KBr) 3129, 2995, 1611, 1536, 1485, 1264, 1153, 1032, 779, 689, 639 cm^{-1}; Anal. Calcd for $C_{13}H_{14}F_3NO_4S$: C, 46.29; H, 4.18; N, 4.15. Found: C, 46.22; H, 4.17; N, 4.13.

2,3-Dimethyl-5-phenylisoxazolium trifluoromethanesulfonate (**17q**)



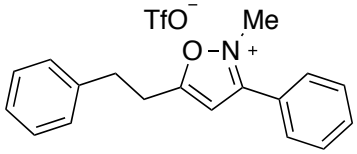
The procedure for preparing **17a** was followed with use of 5-methyl-3-phenylisoxazole[27] (805 mg, 5.0 mmol). The reaction was conducted for 15 h to give **17q** (1.20 g, 74%) as colorless powder: mp. 105.6–106.8°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.72 (s, 3H), 4.36 (s, 3H), 7.52 (s, 1H), 7.73 (t, *J* = 7.4 Hz, 2H), 7.80 (t, *J* = 7.3 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 12.7, 40.6, 108.0, 121.2 (q, *J* = 322 Hz), 123.0, 130.0, 130.1, 133.9, 159.5, 173.6; IR (KBr) 3127, 1619, 1556, 1501, 1469, 1270, 1145, 1038, 776, 699, 642 cm^{-1}; Anal. Calcd for $C_{12}H_{12}F_3NO_4S$: C, 44.58; H, 3.74; N, 4.33. Found: C, 44.48; H, 3.69; N, 4.33.

5-Butyl-2-methyl-3-phenylisoxazolium trifluoromethanesulfonate (**17r**)



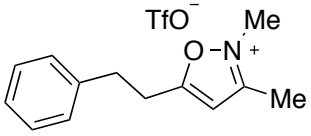
The procedure for preparing **17a** was followed with use of 5-butyl-3-phenylisoxazole[22] (1.02 g, 5.1 mmol). The reaction was conducted for 19 h to give **17r** (1.43 g, 77%) as colorless powder: mp. 60.8–60.9°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.94 (t, J = 7.4 Hz, 3H), 1.44 (sextet, J = 7.4 Hz, 2H), 1.76 (quintet, J = 7.5 Hz, 2H), 3.03 (t, J = 7.5 Hz, 2H), 4.37 (s, 3H), 7.61 (s, 1H), 7.73 (t, J = 7.4 Hz, 2H), 7.80 (t, J = 7.3 Hz, 1H), 7.90 (d, J = 7.4 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 13.9, 21.8, 26.1, 28.6, 40.6, 107.3, 121.2 (q, J = 322 Hz), 123.0, 130.09, 130.11, 133.9, 159.4, 176.7; IR (KBr) 3131, 2964, 2879, 1612, 1549, 1503, 1468, 1266, 1154, 1036, 770, 699, 641 cm^{-1}; Anal. Calcd for $C_{15}H_{18}F_3NO_4S$: C, 49.31; H, 4.97; N, 3.83. Found: C, 49.36; H, 4.88; N, 3.88.

2-Methyl-5-(2-phenylethyl)-3-phenylisoxazolium trifluoromethanesulfonate (**17s**)



The procedure for preparing **17a** was followed with use of 3-phenyl-5-(2-phenylethyl)isoxazole[29] (536 mg, 2.2 mmol). The reaction was conducted for 17 h to give **17s** (713 mg, 80%) as colorless powder: mp. 69.6–69.8°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.11 (t, J = 7.8 Hz, 2H), 3.37 (t, J = 7.8 Hz, 2H), 4.37 (s, 3H), 7.22–7.31 (m, 1H), 7.31–7.38 (m, 4H), 7.61 (s, 1H), 7.74 (t, J = 7.4 Hz, 2H), 7.80 (t, J = 7.4 Hz, 1H), 7.88 (d, J = 7.8 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 28.1, 32.0, 40.8, 107.6, 121.2 (q, J = 322 Hz), 122.9, 127.1, 128.9, 129.0, 130.1, 130.2, 134.0, 139.6, 159.3, 175.9; IR (KBr) 3133, 3035, 2933, 1607, 1547, 1463, 1270, 1151, 1032, 772, 700, 636 cm^{-1}; Anal. Calcd for $C_{19}H_{18}F_3NO_4S$: C, 55.20; H, 4.39; N, 3.39. Found: C, 55.00; H, 4.34; N, 3.40.

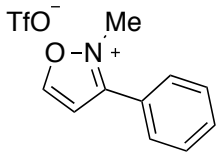
2.3-Dimethyl-5-(2-phenylethyl)isoxazolium trifluoromethanesulfonate (**17t**)



The procedure for preparing **17a** was followed with use of 3-methyl-5-(2-phenylethyl)isoxazole[31] (937 mg, 5.0 mmol). The reaction was conducted for 14 h to give **17t** (1.53 g, 87%) as colorless powder: mp. 66.5–67.4°C; ^{1}H

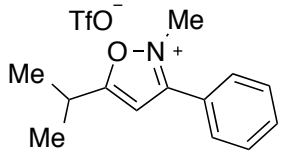
NMR (400 MHz, DMSO-d_6) δ 2.59 (s, 3H), 3.02 (t, J = 7.7 Hz, 2H), 3.28 (t, J = 7.7 Hz, 2H), 4.20 (s, 3H), 7.06 (s, 1H), 7.18–7.35 (m, 5H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 12.2, 27.8, 32.1, 38.6, 108.3, 121.2 (q, J = 322 Hz), 127.1, 128.9, 129.0, 139.6, 160.7, 175.2; IR (KBr) 3127, 3034, 1610, 1547, 1465, 1269, 1155, 1032, 758, 704, 638 cm^{-1}; Anal. Calcd for $C_{14}H_{16}F_3NO_4S$: C, 47.86; H, 4.59; N, 3.99. Found: C, 47.84; H, 4.61; N, 3.87.

2-Methyl-3-phenylisoxazolium trifluoromethanesulfonate (**17u**)



The procedure for preparing **17a** was followed with use of 3-phenylisoxazole (73.0 mg, 0.50 mmol). The reaction was conducted for 16 h to give **17u** (124 mg, 80%) as colorless powder: mp. 89.6–90.3°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.44 (s, 3H), 7.74 (t, J = 7.5 Hz, 2H), 7.81 (t, J = 7.3 Hz, 1H), 7.84 (d, J = 1.5 Hz, 1H), 7.93 (d, J = 7.6 Hz, 2H), 9.67 (d, J = 1.5 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 41.0, 110.7, 121.2 (q, J = 322 Hz), 122.7, 130.1, 130.3, 134.0, 158.6, 162.6; IR (KBr) 3142, 3129, 1604, 1587, 1575, 1462, 1264, 1154, 1032, 772, 702, 639 cm^{-1}; Anal. Calcd for $C_{11}H_{10}F_3NO_4S$: C, 42.72; H, 3.26; N, 4.53. Found: C, 42.49; H, 3.26; N, 4.54.

2-Methyl-5-(1-methylethyl)-3-phenylisoxazolium trifluoromethanesulfonate (**17v**)



Benzaldehyde oxime (1.25 g, 10 mmol) was placed in a 200 mL three-neck flask, which was equipped with a stirring bar, three-way stopcock, rubber septum, and dropping funnel with a rubber septum. After the reaction vessel was evacuated and charged with nitrogen gas three times, dry DMF (20 mL) was added into the flask. The rubber septum was removed from the vessel under a nitrogen flow, and then *N*-chlorosuccinimide (1.40 g, 10 mmol) was fractionally added to the solution. When an exothermic reaction started in the mixture, the flask was cooled with a water bath at 10°C. After stirred at ambient temperature for 1 h, the resulting mixture was diluted with Et_2O (20 mL). After diethyl 1-(1-methylethyl)ethenylphosphonate (2.23 g, 10

mmol) was added, a solution of Et_3N (5.5 mL, *d* 0.73 g/mL, 40 mmol) in Et_2O (30 mL) was added dropwise to the mixture at 0°C for 1.5 h. After stirred at ambient temperature for 12 h, the resulting mixture was diluted with water and then extracted three times with 1:1 mixture of EtOAc and hexane. The combined organic layer was washed with brine, dried over Na_2SO_4, and then evaporated under reduced pressure. The residue was purified with a flash column chromatography (EtOAc/hexane = 1/20) to give 5-(1-methylethyl)-3-phenylisoxazole (999 mg, 53%) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.37 (d, *J* = 7.0 Hz, 6H), 3.36 (double septet, *J* = 0.8, 7.0 Hz, 1H), 6.26 (d, *J* = 0.8 Hz, 1H), 7.41–7.47 (m, 3H), 7.77–7.82 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 20.9, 27.3, 97.0, 126.7, 128.8, 129.7, 162.2, 179.3.

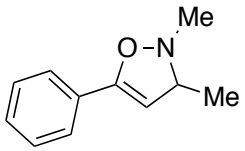
The procedure for preparing **17a** was followed with use of 5-(1-methylethyl)-3-phenylisoxazole (751 mg, 4.0 mmol). The reaction was conducted for 18 h to give **17v** (1.11 g, 79%) as colorless powder: mp. 101.2–101.7°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.39 (d, *J* = 6.9 Hz, 6H), 3.36 (septet, *J* = 6.9 Hz, 1H), 4.38 (s, 3H), 7.63 (s, 1H), 7.73 (t, *J* = 7.4 Hz, 2H), 7.80 (t, *J* = 7.1 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 20.1, 27.5, 40.6, 106.1, 121.2 (q, *J* = 322 Hz), 123.1, 130.10, 130.12, 133.9, 159.4, 180.9; IR (KBr) 3125, 2982, 1604, 1468, 1271, 1149, 1031, 774, 703, 634 cm^{-1}; Anal. Calcd for $C_{14}H_{16}F_3NO_4S$: C, 47.86; H, 4.59; N, 3.99. Found: C, 47,94; H, 4.51; N, 3.97.

3.4.3. General Procedure for the Catalytic Asymmetric Hydrogenation of Isoxazoliums **17**.

$[IrCl(cod)]_2$ (1.3 mg, 2.0 μmol) and (*S*)-2-[2-(diphenylphosphino)phenyl]-4-(1-methylethyl)-2-oxazoline (**L12**) (1.6 mg, 4.3 μmol) were placed in a 2 mL Schlenk tube, which was equipped with a stirring bar and two-way stopcock. After the tube was evacuated and charged with nitrogen gas three times, dry *tert*-amyl alcohol (1.0 mL) was added into the tube through the septum with a syringe. The solution was stirred at ambient temperature for 10 min. Concurrently, **17** (0.40 mmol), $KHCO_3$ (44.0 mg, 0.44 mmol), and a stirring bar were placed in a 50 mL test tube, which was sealed with a rubber septum. After the tube was evacuated and charged with nitrogen gas three times, I_2 (4.0 mg, 16 μmol) was quickly added to the solution under a nitrogen flow. The above solution containing the chiral iridium catalyst was transferred through a cannula into the test tube. After the septum was removed, the test tube was quickly inserted into the nitrogen-purged stainless autoclave and then the autoclave was sealed immediately. Hydrogen gas was introduced into the autoclave until the pressure gauge indicated over 5.0 MPa, and then the pressure was

carefully released to 0.1 MPa. This procedure was repeated twice, and finally the inside of the autoclave was pressurized with hydrogen to 5.0 MPa. The mixture was stirred at 50°C for 24 h. After the autoclave was allowed to cool to room temperature, excess hydrogen was released carefully. The resulting mixture was evaporated under reduced pressure. The residue was passed through a short column of silica gel (EtOAc/hexane) to give the desired chiral 4-isoxazoline **18** or isoxazolidine **19**.

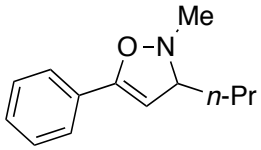
(+)-2,3-Dimethyl-5-phenyl-4-isoxazoline [52266-11-2] (**18a**)[36]



The general procedure was followed with use of **17a** (129 mg, 0.40 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/5) to give **18a** (59.0 mg, 84%) as colorless oil: $[\alpha]_D^{25}$ = +145.4 (*c* 1.14, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.28 (d, *J* = 6.2 Hz, 3H), 2.83 (s, 3H), 3.86 (br, 1H), 5.24 (d, *J* = 2.4 Hz, 1H), 7.28–7.38 (m, 3H), 7.54 (d, *J* = 7.4 Hz, 2H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$, 50°C) δ 21.7, 46.4, 68.8, 97.0, 125.6, 128.3, 128.7, 129.3, 152.0.

The enantiomeric excess of (+)-**18a** was determined to be 85% ee by HPLC analysis with Chiralcel OD-H (4.6 mm ϕ × 250 mm): 4% 2-propanol in hexane, 0.5 mL/min flow, 35°C, UV 280 nm detection, (+) t_1 = 11.2 min, (–) t_2 = 13.4 min.

(+)-2-Methyl-5-phenyl-3-propyl-4-isoxazoline (**18b**)

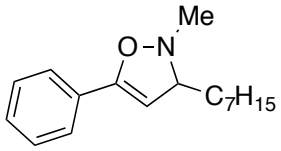


The general procedure was followed with use of **17b** (140 mg, 0.40 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/5) to give **18b** (78.6 mg, 97%) as colorless oil: $[\alpha]_D^{27}$ = +145.5 (*c* 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 0.94 (t, *J* = 7.2 Hz, 3H), 1.32–1.64 (m, 4H), 2.82 (s, 3H), 3.73 (br, 1H), 5.23 (d, *J* = 2.7 Hz, 1H), 7.27–7.37 (m, 3H), 7.54 (dd, *J* = 1.6, 8.1 Hz, 2H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$, 50°C) δ 14.0, 19.0, 38.6, 47.2, 73.5, 95.3, 125.6, 128.3, 128.7, 129.4, 152.1; IR (neat) 2956, 2930, 2872, 1651, 1494, 1448, 1270,

765, 724, 690 cm^{-1}; Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.82; H, 8.44; N, 6.84.

The enantiomeric excess of (+)-**18b** was determined to be 85% ee by HPLC analysis with Chiralcel OJ-H (4.6 mm ϕ × 250 mm): 1% 2-propanol in hexane, 0.5 mL/min flow, 35°C, UV 280 nm detection, (+) t_1 = 19.1 min, (–) t_2 = 21.6 min.

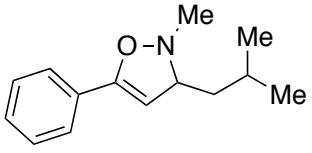
(+)-3-Heptyl-2-methyl-5-phenyl-4-isoxazoline (**18c**)



The general procedure was followed with use of **17c** (163 mg, 0.40 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/5) to give **18c** (101 mg, 98%) as colorless oil: $[\alpha]_D^{25}$ = +120.2 (*c* 1.30, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.20–1.64 (m, 12H), 2.81 (s, 3H), 3.71 (br, 1H), 5.23 (d, *J* = 2.4 Hz, 1H), 7.27–7.37 (m, 3H), 7.54 (d, *J* = 7.5 Hz, 2H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$, 50°C) δ 14.0, 22.6, 25.8, 29.3, 29.6, 31.8, 36.4, 47.2, 73.8, 95.3, 125.6, 128.3, 128.7, 129.4, 152.1; IR (neat) 2954, 2926, 2854, 1652, 1494, 1449, 1266, 1022, 768, 721, 690 cm^{-1}; Anal. Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.25; H, 9.57; N, 5.43.

The enantiomeric excess of (+)-**18c** was determined to be 86% ee by HPLC analysis with Chiralpak AD-H (4.6 mm ϕ × 250 mm): 1% 2-propanol in hexane, 0.5 mL/min flow, 35°C, UV 228 nm detection, (+) t_1 = 12.1 min, (–) t_2 = 14.3 min.

(+)-2-Methyl-3-(2-methylpropyl)-5-phenyl-4-isoxazoline (**18d**)

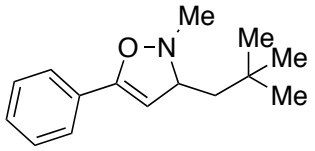


The general procedure was followed with use of **17d** (146 mg, 0.40 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/10) to give **18d** (84.0 mg, 97%) as colorless oil: $[\alpha]_D^{27}$ = +136.9 (*c* 1.14, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 0.94 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H) 1.31–1.40 (m, 1H), 1.49–1.59 (m, 1H), 1.81 (nonet, *J* = 6.7 Hz, 1H), 2.81 (s, 3H), 3.79 (br, 1H), 5.24 (d, *J* = 2.4 Hz, 1H), 7.28–7.37 (m, 3H), 7.53 (d, *J* = 7.7 Hz, 2H); ^{13}C {^1H}

NMR (100 MHz, $CDCl_3$, 50°C) δ 22.6, 22.9, 25.0, 45.5, 46.9, 71.8, 95.7, 125.6, 128.3, 128.7, 129.4, 152.1; IR (neat) 2955, 2925, 2870, 1651, 1494, 1448, 1271, 1014, 770, 720, 690 cm^{-1}; Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.47; H, 8.80; N, 6.34.

The enantiomeric excess of (+)-**18d** was determined to be 87% ee by HPLC analysis with Chiralcel OJ-H (4.6 mm ϕ × 250 mm): 1% 2-propanol in hexane, 0.5 mL/min flow, 35°C, UV 280 nm detection, (+) t_1 = 15.5 min, (–) t_2 = 18.8 min.

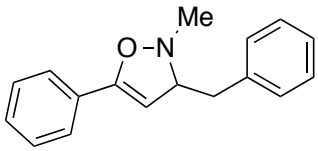
(+)-3-(2,2-Dimethylpropyl)-2-methyl-5-phenyl-4-isoxazoline (**18e**)



The general procedure was followed with use of **17e** (152 mg, 0.40 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/10) to give **18e** (91.7 mg, 99%) as colorless oil: $[\alpha]_D^{25}$ = +119.3 (*c* 1.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 0.98 (s, 9H), 1.41 (dd, *J* = 14.2, 5.2 Hz, 1H), 1.66 (dd, *J* = 14.2, 6.7 Hz, 1H), 2.81 (s, 3H), 3.80 (br, 1H), 5.22 (d, *J* = 2.2 Hz, 1H), 7.27–7.38 (m, 3H), 7.53 (d, *J* = 7.8 Hz, 2H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$, 50°C) δ 30.1, 30.3, 46.2, 50.0, 70.7, 96.9, 125.6, 128.3, 128.7, 129.4, 151.8; IR (neat) 2954, 2871, 1651, 1494, 1448, 1364, 1274, 1250, 1009, 718, 689 cm^{-1}; Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.89; H, 9.11; N, 5.94.

The enantiomeric excess of (+)-**18e** was determined to be 89% ee by HPLC analysis with Chiralpak AD-H (4.6 mm ϕ × 250 mm): 1% 2-propanol in hexane, 0.5 mL/min flow, 25°C, UV 280 nm detection, (–) t_1 = 12.8 min, (+) t_2 = 15.8 min.

(+)-3-Benzyl-2-methyl-5-phenyl-4-isoxazoline (**18f**)

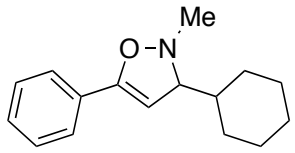


The general procedure was followed with use of **17f** (161 mg, 0.40 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/10) to give **18f** (95.3 mg, 94%) as colorless oil: $[\alpha]_D^{26}$ = +125.0 (*c* 1.06, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 2.76 (s, 3H), 2.82 (dd, *J* = 13.3, 7.1 Hz, 1H), 2.97 (dd,

J = 13.3, 6.9 Hz, 1H), 3.98 (br, 1H), 5.19 (d, J = 2.1 Hz, 1H), 7.19–7.37 (m, 8H), 7.53 (d, J = 7.5 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 50°C) δ 43.0, 46.9, 75.3, 94.9, 125.7, 126.3, 128.33, 128.36, 128.9, 129.2, 129.4, 138.6, 152.7; IR (neat) 3060, 3027, 2955, 2913, 1651, 1601, 1580, 1494, 1450, 1323, 1277, 1062, 1024, 721, 700 cm^{-1}; Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.48; H,6.66; N, 4.78.

The enantiomeric excess of (+)-**18f** was determined to be 86% ee by HPLC analysis with Chiralpak AD-H (4.6 mm ϕ × 250 mm): 1% 2-propanol in hexane, 0.5 mL/min flow, 25°C, UV 228 nm detection, (+) t_1 = 18.5 min, (–) t_2 = 21.5 min.

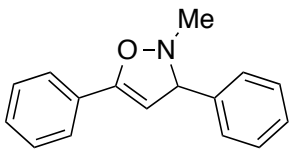
(+)-3-Cyclohexyl-2-methyl-5-phenyl-4-isoxazoline (**18g**)



The general procedure was followed with use of **17g** (156 mg, 0.40 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/10) to give **18g** (82.2 mg, 85%) as a colorless solid: $[\alpha]_D^{26}$ = +32.9 (c 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.92–1.31 (m, 5H), 1.38–1.50 (m, 1H), 1.62–1.80 (m, 4H), 1.84–1.93 (m, 1H), 2.80 (s, 3H), 3.49 (dd, J = 2.0, 6.2 Hz, 1H), 5.22 (d, J = 2.0 Hz, 1H), 7.27–7.37 (m, 3H), 7.54 (d, J = 6.9 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 50 °C) δ 26.1, 26.2, 26.6, 29.0, 29.2, 43.8, 48.0, 79.0, 93.1, 125.6, 128.3, 128.7, 129.4, 152.1; IR (KBr) 2921, 2849, 1652, 1494, 1446, 1261, 1039, 1020, 754, 691, 634 cm^{-1}; HRMS (FAB) Calcd for $C_{16}H_{22}NO$: 244.1701. Found: m/z = 244.1715 ($[M+H]^+$).

The enantiomeric excess of (+)-**18g** was determined to be 24% ee by HPLC analysis with Chiralpak AD-H (4.6 mm ϕ × 250 mm): 1% 2-propanol in hexane, 0.5 mL/min flow, 25°C, UV 280 nm detection, (+) t_1 = 10.2 min, (–) t_2 = 12.4 min.

(–)-2-Methyl-2,3-diphenyl-4-isoxazoline [52266-12-3] (**18h**)[37]

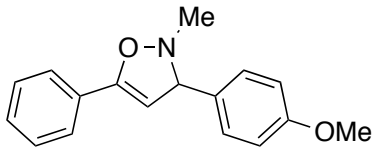


The general procedure was followed with use of **17h** (77.4 mg, 0.20 mmol) and (*S*)-2-[2-(diphenylphosphino)phenyl]-4-phenyl-2-oxazoline (**L16**) (1.8 mg, 4.4

μmol). The hydrogenation was conducted in THF at 70°C for 4 h with 2% catalyst loading. The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/10) to give **18h** (38.6 mg, 81%) as a colorless solid: $[\alpha]_D^{25} = -162.1$ (*c* 1.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.98 (s, 3H), 4.85 (s, 1H), 5.37 (d, *J* = 2.4 Hz, 1H), 7.24–7.43 (m, 8H), 7.59 (d, *J* = 7.8 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 50 °C) δ 47.1, 77.2, 95.8, 125.8, 127.1, 127.7, 128.4, 128.6, 129.00, 129.02, 142.1, 152.7.

The enantiomeric excess of (–)-**18h** was determined to be 86% ee by HPLC analysis with Chiralpak AD-H (4.6 mm ϕ × 250 mm): 4% 2-propanol in hexane, 0.5 mL/min flow, 35°C, UV 280 nm detection, (+) t_1 = 14.2 min, (–) t_2 = 18.3 min.

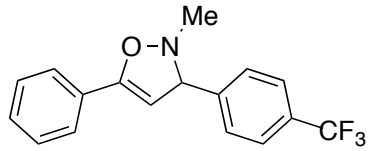
(–)-3-(4-methoxyphenyl)-2-methyl-5-phenyl-4-isoxazoline (**18i**)



The general procedure was followed with use of **17i** (83.6 mg, 0.20 mmol) and **L16** (1.8 mg, 4.4 μmol). The hydrogenation was conducted in THF at 70°C for 4 h with 2% catalyst loading. The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/5) to give **18i** (45.1 mg, 84%) as a colorless solid: $[\alpha]_D^{28} = -126.3$ (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 2.90 (s, 3H), 3.77 (s, 3H), 4.82 (br d, *J* = 2.6 Hz, 1H), 5.55 (d, *J* = 2.6 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.36–7.43 (m, 3H), 7.60–7.64 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, acetone-d_6) δ 47.3, 55.7, 77.0, 97.5, 114.7, 126.5, 129.3, 129.5, 129.9, 130.3, 135.8 (br), 152.9, 160.3; IR (neat) 2956, 1654, 1604, 1506, 1453, 1250, 1174, 1031, 831, 768, 719 cm^{-1}; HRMS (FAB) Calcd for $C_{17}H_{18}NO_2$: 268.1338. Found: *m*/*z* = 268.1339 ($[M+H]^+$).

The enantiomeric excess of (–)-**18i** was determined to be 88% ee by HPLC analysis with Chiralpak AS-H (4.6 mm ϕ × 250 mm): 10% 2-propanol in hexane, 0.5 mL/min flow, ambient temperature, UV 280 nm detection, (+) t_1 = 10.0 min, (–) t_2 = 15.2 min.

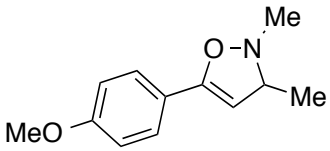
2-Methyl-5-phenyl-3-[4-(trifluoromethyl)phenyl]-4-isoxazoline (**18j**)



The general procedure was followed with use of **17j** (90.6 mg, 0.20 mmol) and **L16** (1.8 mg, 4.4 μmol). The hydrogenation was conducted in THF at 70°C for 4 h with 2% catalyst loading. The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/10) to give a mixture of **18j** and 5-phenyl-3-[4-(trifluoromethyl)phenyl]isoxazole (46.5 mg) with 64:36 molar ratio. The yield of **18j** was estimated to be 50%: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 3.00 (s, 1.9H), 4.89 (d, J = 2.6 Hz, 0.7H), 5.36 (d, J = 2.7 Hz, 0.6H), 6.87 (s, 0.4H), 7.34–8.02 (m, 9H).

The enantiomeric excess of **18j** was determined to be 75% ee by HPLC analysis with Chiralcel OJ-H (4.6 mm ϕ × 250 mm): 10% 2-propanol in hexane, 0.5 mL/min flow, 35 °C, UV 280 nm detection, (+) t_1 = 11.6 min, (–) t_2 = 16.3 min.

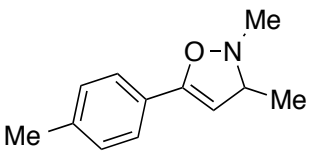
(+)-5-(4-Methoxyphenyl)-2,3-dimethyl-4-isoxazoline (**18k**)



The general procedure was followed with use of **17k** (141.6 mg, 0.40 mmol). The crude product was purified with a flash column chromatography (EtOAc/hexane = 1/5) to give **18k** (55.1 mg, 67%) as colorless oil: $[\alpha]_D^{27}$ = +111.1 (c 0.61, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.26 (d, J = 6.4 Hz, 3H), 2.81 (s, 3H), 3.81 (s, 3H), 3.84 (br, 1H), 5.09 (d, J = 2.6 Hz, 1H), 6.87 (d, J = 9.0 Hz, 2H), 7.47 (d, J = 9.0 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$ 50 °C) δ 21.8, 46.4, 55.3, 68.8, 95.2, 113.8, 122.1, 127.1, 151.8, 160.2; IR (neat) 2964, 2925, 1651, 1603, 1506, 1448, 1254, 1175, 1030, 833, 745, 706 cm^{-1}; HRMS (FAB) Calcd for $C_{12}H_{16}NO_2$: 206.1181. Found: m/z = 268.1180 ([M+H]$^+$).

The enantiomeric excess of (+)-**18k** was determined to be 62% ee by HPLC analysis with Chiralpak AD-H (4.6 mm ϕ × 250 mm): 4% 2-propanol in hexane, 0.5 mL/min flow, 35 °C, UV 300 nm detection, (–) t_1 = 14.2 min, (+) t_2 = 16.3 min.

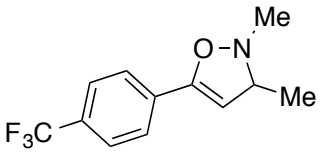
(+)-2,3-Dimethyl-5-(4-methylphenyl)-4-isoxazoline (**18l**)



The general procedure was followed with use of **17l** (134.5 mg, 0.40 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/5) to give **18l** (60.8 mg, 81%) as colorless oil: $[\alpha]_D^{26}$ = +125.5 (*c* 0.83, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.27 (d, *J* = 6.4 Hz, 3H), 2.35 (s, 3H), 2.81 (s, 3H), 3.85 (br, 1H), 5.17 (d, *J* = 2.6 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$, 50 °C) δ 21.3, 21.7, 46.4, 68.8, 96.1, 125.6, 126.5, 129.0, 138.7, 152.1; IR (neat) 2967, 2920, 1658, 1610, 1510, 1445, 1308, 1178, 1060, 822, 748 cm^{-1}; Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.94; H, 8.00; N, 7.42.

The enantiomeric excess of (+)-**18l** was determined to be 82% ee by HPLC analysis with Chiralpak AD-H (4.6 mm ϕ × 250 mm): 4% 2-propanol in hexane, 0.5 mL/min flow, 35 °C, UV 280 nm detection, (–) t_1 = 10.5 min, (+) t_2 = 11.6 min.

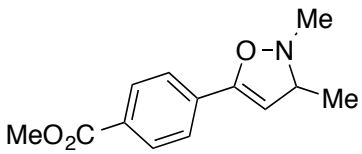
(+)-2,3-Dimethyl-5-[4-(trifluoromethyl)phenyl]-4-isoxazoline (**18m**)



The general procedure was followed with use of **17m** (157 mg, 0.40 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/10) to give **18m** (90.2 mg, 93%) as colorless oil: $[\alpha]_D^{27}$ = +88.8 (*c* 1.09, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.29 (d, *J* = 6.4 Hz, 3H), 2.83 (s, 3H), 3.90 (br, 1H), 5.37 (d, *J* = 2.5 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$, 50 °C) δ 21.5, 46.4, 68.9, 99.4, 124.1 (q, *J* = 272 Hz), 125.3 (q, *J* = 4 Hz), 125.8, 130.7 (q, *J* = 33 Hz), 132.7, 150.9; IR (neat) 2972, 2925, 2875, 1615, 1412, 1326, 1168, 1126, 1069, 846, 765, 722 cm^{-1}; Anal. Calcd for $C_{12}H_{12}F_3NO$: C, 59.26; H, 4.97; N, 5.76. Found: C, 59.21; H, 4.97; N, 5.64.

The enantiomeric excess of (+)-**18m** was determined to be 73% ee by HPLC analysis with Chiralcel OJ-H (4.6 mm ϕ × 250 mm): 4% 2-propanol in hexane, 0.5 mL/min flow, 35 °C, UV 294 nm detection, (+) t_1 = 10.7 min, (–) t_2 = 13.7 min.

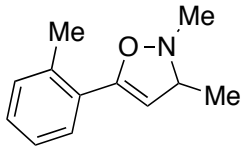
(+)-5-[4-(Methoxycarbonyl)phenyl-2,3-dimethyl-4-isoxazoline (**18n**)



The general procedure was followed with use of **17n** (152 mg, 0.40 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/1) to give **18n** (71.9 mg, 77%) as colorless oil: $[\alpha]_D^{26}$ = +56.7 (*c* 0.60, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.29 (d, *J* = 6.4 Hz, 3H), 2.84 (s, 3H), 3.84−3.98 (br, 1H), 3.92 (s, 3H), 5.38 (d, *J* = 2.5 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 8.01 (d, *J* = 8.3 Hz, 2H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$, 50 °C) δ 21.5, 46.4, 52.0, 68.9, 99.5, 125.5, 129.7, 130.3, 133.4, 151.3, 166.6; IR (neat) 2955, 1721, 1609, 1436, 1279, 1108, 741 cm^{-1}; Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.89; H, 6.37; N, 5.99.

The enantiomeric excess of (+)-**18n** was determined to be 65% ee by HPLC analysis with Chiralcel OJ-H (4.6 mm ϕ × 250 mm): 10% 2-propanol in hexane, 0.5 mL/min flow, 35 °C, UV 310 nm detection, (+) t_1 = 16.9 min, (–) t_2 = 29.2 min.

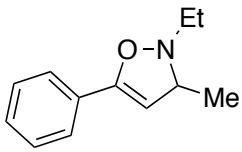
2,3-Dimethyl-5-(2-methylphenyl)-4-isoxazoline (**18o**)



The general procedure was followed with use of **17o** (135 mg, 0.40 mmol). The crude product was purified with a flash column chromatography (EtOAc/hexane = 1/5) to give **18o** (42.6 mg, 56%) as colorless oil: ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.29 (d, *J* = 6.4 Hz, 3H), 2.44 (s, 3H), 2.83 (s, 3H), 3.88 (br, 1H), 5.01 (d, *J* = 2.4 Hz, 1H), 7.15–7.26 (m, 3H), 7.48 (d, *J* = 7.4 Hz, 1H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$, 50 °C) δ 21.1, 21.9, 46.4, 68.9, 100.5, 125.7, 128.6, 128.7, 128.8, 130.7, 136.6, 151.9; IR (neat) 2967, 2923, 1639, 1455, 1304, 741 cm^{-1}; Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.97; H, 8.04; N, 7.37.

The enantiomeric excess of **18o** was determined to be 1% ee by HPLC analysis with Chiralcel OD-H (4.6 mm ϕ × 250 mm): 4% 2-propanol in hexane, 0.5 mL/min flow, 35 °C, UV 280 nm detection, t_1 = 10.3 min, t_2 = 12.0 min.

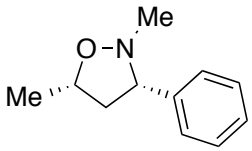
(+)-2-Ethyl-3-methyl-5-phenyl-4-isoxazoline (**18p**)



The general procedure was followed with use of **17p** (135 mg, 0.40 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/10) to give **18p** (72.1 mg, 96%) as colorless oil: $[\alpha]_D^{27}$ = +194.8 (*c* 1.38, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.27 (t, *J* = 7.1 Hz, 3H), 1.29 (d, *J* =6.4 Hz, 3H), 2.80 (dq, *J* = 12.4, 7.1 Hz, 1H), 3.12 (dt, *J* = 12.4, 7.0 Hz, 1H), 3.97 (br, 1H), 5.24 (d, *J* = 2.6 Hz, 1H), 7.27–7.37 (m, 3H), 7.54 (d, *J* = 7.8 Hz, 2H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$ 50 °C) δ 12.4, 22.3, 53.6, 66.8, 97.4, 125.6, 128.3, 128.7, 129.4, 152.1; IR (neat) 2973, 2925, 1653, 1494, 1447, 1333, 1055, 1004, 752, 731, 690 cm^{-1}; Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.05; H, 7.93; N, 7.43.

The enantiomeric excess of (+)-**18p** was determined to be 90% ee by HPLC analysis with Chiralcel OD-H (4.6 mm ϕ × 250 mm): 1% 2-propanol in hexane, 0.5 mL/min flow, 25 °C, UV 280 nm detection, (+) t_1 = 11.2 min, (–) t_2 = 14.6 min.

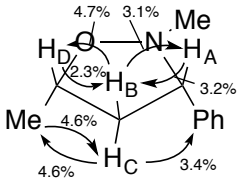
(–)-(3*S*,5*S*)-2,5-Dimethyl-3-phenylisoxazolidine (**19q**)



The general procedure was followed with use of **17q** (129 mg, 0.40 mmol) and **L16** (1.8 mg, 4.4 μmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/10) to give **19q** (72.1 mg, 96%) as colorless oil: $[\alpha]_D^{26}$ = –137.7 (*c* 1.23, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.38 (d, *J* = 6.1 Hz, 3H), 1.99 (ddd, *J* = 7.5, 9.1, 12.2 Hz, 1H), 2.62 (s, 3H), 2.80 (dt, *J* = 12.2, 7.1 Hz, 1H), 3.66 (br, 1H), 4.42 (sextet, *J* = 6.5 Hz, 1H), 7.24–7.40 (m, 5H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$, 50°C) δ 21.3, 43.8, 47.5, 72.8, 73.6, 127.4, 127.5, 128.5, 140.2.; IR (neat) 2975, 2872, 1454, 1370, 1216, 754, 700 cm^{-1}; Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.51; H, 8.49; N, 7.97.

The enantiomeric excess of (–)-**19q** was determined to be 75% ee by HPLC analysis with Chiralcel OD-H (4.6 mm ϕ × 250 mm): 1% 2-propanol in hexane, 0.5 mL/min flow, 35 °C, UV 220 nm detection, (+) t_1 = 12.5 min, (–) t_2 = 15.0 min.

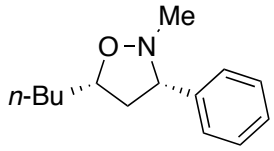
The results of the $^1H\{^1H\}$ nOe experiments of **19q** were summarized in Figure S-1. The experiments and NOESY spectrum indicates that the relative configuration of **19q** is *cis*.



H_A: δ 3.66
H_B: δ 2.80
H_C: δ 1.99
H_D: δ 4.42

Figure S-1. Selected nOe enhancements in **19q**.

(+)-5-Butyl-2-methyl-3-phenylisoxazolidine (**19r**)



The general procedure was followed with use of **17r** (147 mg, 0.40 mmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/10) to give **19r** (82.3 mg, 94%) as colorless oil: $[\alpha]_D^{26}$ = –122.8 (*c* 1.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.91 (t, *J* = 7.0 Hz, 3H), 1.26–1.64 (m, 5H), 1.76–1.87 (m, 1H), 2.01 (ddd, *J* = 7.4, 9.5, 12.2 Hz, 1H) 2.60 (s, 3H), 2.76 (dt, *J* = 12.2, 7.2 Hz, 1H), 3.61 (br, 1H), 4.22 (quintet, *J* = 6.9 Hz, 1H), 7.26 (t, *J* = 6.9 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H); ^{1}H NMR (400 MHz, acetone-d_6) δ 0.90 (t, *J* = 7.1 Hz, 3H), 1.26–1.56 (m, 5H), 1.69–1.79 (m, 1H), 1.90 (ddd, *J* = 6.7, 9.0, 12.1 Hz, 1H) 2.49 (s, 3H), 2.82 (dt, *J* = 12.1, 7.4 Hz, 1H), 3.62 (br t, *J* = 8.1 Hz, 1H), 4.22 (dq, *J* = 5.4, 7.2 Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.39 (d, *J* = 7.2 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, acetone-d_6) δ 14.5, 23.5, 29.5, 36.7, 44.0, 47.0, 74.0, 77.4, 128.3, 128.4, 129.4, 142.0; IR (neat) 2956, 2871, 1455, 755, 699 cm^{-1}; Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.64; H, 9.77; N, 6.48.

The enantiomeric excess of (–)-**19r** was determined to be 77% ee by HPLC analysis with Chiralpak AD-H (4.6 mm ϕ × 250 mm): 1% 2-propanol in hexane, 0.5 mL/min flow, 35 °C, UV 220 nm detection, (+) t_1 = 10.2 min, (–) t_2 = 15.9 min.

The results of the ^{1}H{^{1}H} nOe experiments of **19r** were summarized in Figure S-2. The experiments and NOESY spectrum indicates that the relative configuration of **19r** is *cis*.

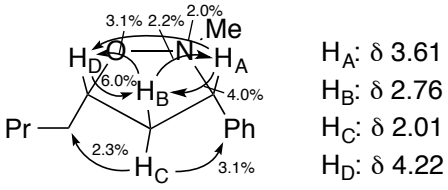
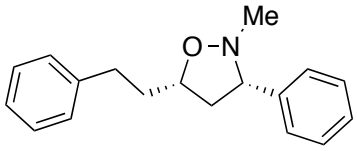


Figure S-2. Selected nOe enhancements in **19r**.

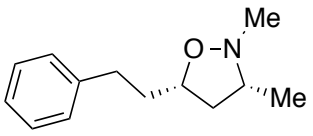
(–)-2-Methyl-3-phenyl-5-(2-phenylethyl)isoxazolidine (**19s**)



The general procedure was followed with use of **17s** (82.7 mg, 0.20 mmol) and **L16** (1.8 mg, 4.4 μmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/5) to give **19s** (52.2 mg, 96%) as colorless oil: $[\alpha]_D^{26}$ = –93.0 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.84 (dddd, *J* = 5.1, 6.6, 9.8, 13.6 Hz, 1H), 2.03 (ddd, *J* = 7.0, 9.4, 12.3 Hz, 1H), 2.17 (dddd, *J* = 5.7, 8.1, 9.5, 13.6 Hz, 1H), 2.62 (s, 3H), 2.65–2.86 (m, 3H), 3.61 (br, 1H), 4.23 (dq, *J* = 5.1, 7.4 Hz, 1H), 7.15–7.39 (m, 10H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 50°C) δ 32.6, 37.6, 43.7, 46.0, 73.5, 76.1, 125.8, 127.5, 127.6, 128.4, 128.5, 128.6, 140.0, 142.0; IR (neat) 3026, 2915, 2856, 1494, 1449, 1023, 726, 698 cm^{-1}; Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.80; H, 7.81; N, 5.18.

The enantiomeric excess of (–)-**19s** was determined to be 77% ee by HPLC analysis with Chiralcel OJ-H (4.6 mm ϕ × 250 mm): 4% 2-propanol in hexane, 0.5 mL/min flow, 35 °C, UV 220 nm detection, (–) t_1 = 16.6 min, (+) t_2 = 20.0 min.

(–)-2,3-Dimethyl-5-(2-phenylethyl)isoxazolidine (**19t**)

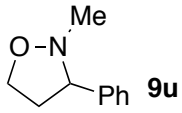


The general procedure was followed with use of **17t** (70.3 mg, 0.20 mmol) and **L16** (1.8 mg, 4.4 μmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/3) to give **19t** (35.3 mg, 86%) as colorless oil: $[\alpha]_D^{25}$ = –47.5 (*c* 0.97, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.16 (d, *J* = 6.2 Hz, 3H),

1.60 (ddd, J = 7.2, 8.3, 12.0 Hz, 1H), 1.73–1.83 (m, 1H), 2.01 (dddd, J = 5.7, 7.8, 9.6, 13.5 Hz, 1H) 2.51 (dt, J = 12.0, 7.1 Hz, 1H), 2.59–2.82 (m, 3H), 2.65 (s, 3H), 4.05–4.15 (m, 1H), 7.14–7.21 (m, 3H), 7.24–7.30 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 18.1 (br), 32.6, 37.6, 43.6 (br, 2C), 63.9 (br), 75.3 (br), 125.7, 128.3, 128.5, 142.0; IR (neat) 2962, 2862, 1493, 1452, 1022, 745, 698 cm^{-1}; Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.71; H, 9.37; N, 6.76.

The enantiomeric excess of (–)-**19t** was determined to be 67% ee by HPLC analysis with Chiralcel OD-H (4.6 mm ϕ × 250 mm): 1% 2-propanol in hexane, 0.5 mL/min flow, 35 °C, UV 220 nm detection, (–) t_1 = 13.3 min, (+) t_2 = 17.9 min.

(–)-2-Methyl-3-phenylisoxazolidine (**19u**)

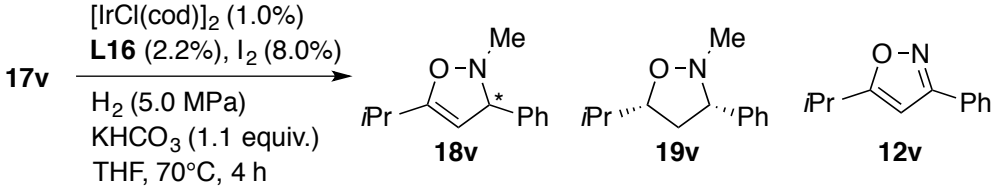


9u

The general procedure was followed with use of **17u** (124 mg, 0.40 mmol) and **L16** (1.8 mg, 4.4 μmol). The crude product was passed through a short column of silica gel (EtOAc/hexane = 1/10) to give **19u** (64.0 mg, 98%) as colorless oil: $[\alpha]_D^{26}$ = –59.4 (*c* 1.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.31 (dq, J = 7.3, 12.1 Hz, 1H), 2.61 (s, 3H), 2.70 (dq, J = 7.7, 12.1, 1H), 3.53 (br, 1H), 4.07 (t, J = 7.4 Hz,, 2H), 7.28 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.4 Hz, 2H), 7.38 (d, J = 7.3 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$ 50 °C) δ 39.3, 43.3, 65.7, 72.4, 127.57, 127.61, 128.6, 140.2; IR (neat) 2957, 2872, 1492, 1453, 1033, 1012, 753, 700 cm^{-1}; HRMS (FAB) Calcd for $C_{10}H_{13}NO$: 163.0997. Found: m/z = 163.0989 (M^+).

The enantiomeric excess of (–)-**19u** was determined to be 40% ee by HPLC analysis with Chiralcel OJ-H (4.6 mm ϕ × 250 mm): 1% 2-propanol in hexane, 0.5 mL/min flow, 35 °C, UV 220 nm detection, (+) t_1 = 18.4 min, (–) t_2 = 20.7 min.

3.4.4. Hydrogenation of **17v** (eq. 33)



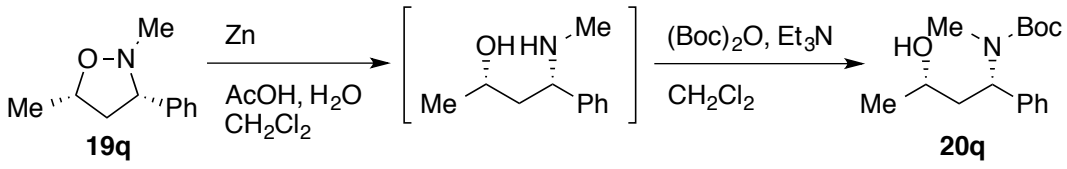
The general procedure was followed with use of **7v** (70.2 mg, 0.20 mmol) and **L16** (1.8 mg, 4.4 μmol). The reaction was conducted at 70°C for 4 h. The ^{1}H NMR analysis of the resulting mixture indicated that the reaction produced a mixture of 2-methyl-5-(1-methylethyl)-3-phenyl-4-isoxazoline (**18v**) (49%), 2-methyl-5-(1-methylethyl)-3-phenylisoxazolidine (**19v**) (42%), and 5-(1-methylethyl)-3-phenylisoxazole (**12v**) (9%). The crude product was purified with MPLC (EtOAc/hexane = 1/10) after passing through a short silica gel column (EtOAc) to give 2-methyl-5-(1-methylethyl)-3-phenyl-4-isoxazoline (**18v**) (10.5 mg, 26%) and 2-methyl-5-(1-methylethyl)-3-phenylisoxazolidine (**19v**) (8.6 mg, 21%). **18v**: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.16 (d, J = 6.9 Hz, 3H), 1.17 (d, J = 6.9 Hz, 3H), 2.49 (septet, J = 6.9 Hz, 1H), 2.86 (s, 3H), 4.58–4.63 (m, 2H), 7.23–7.36 (m, 5H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 20.4, 26.1, 47.0, 76.5, 93.0, 126.9, 127.5, 128.5, 142.9, 160.7. **19v**: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.88 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H), 1.87 (octet, J = 6.9 Hz, 1H), 2.09 (dt, J = 12.1, 9.0 Hz, 1H), 2.60 (s, 3H), 2.68 (dt, J = 12.1, 6.9 Hz, 1H), 3.63 (br, 1H), 3.86 (q, J = 7.7 Hz, 1H), 7.24–7.39 (m 5H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 18.4, 19.5, 33.4, 43.8, 44.2, 73.4, 82.5, 127.4, 127.6, 128.6, 140.1.

The enantiomeric excess of **18v** was determined to be 88% ee by HPLC analysis with Chiralpak AD-H (4.6 mm ϕ × 250 mm): 1% 2-propanol in hexane, 0.5 mL/min flow, 35 °C, UV 220 nm detection, t_1 = 9.4 min, t_2 = 11.5 min. The enantiomeric excess of **19v** was determined to be 61% ee by HPLC analysis with Chiralpak AD-H (4.6 mm ϕ × 250 mm): 1% 2-propanol in hexane, 0.5 mL/min flow, 35 °C, UV 220 nm detection, t_1 = 8.8 min, t_2 = 10.6 min.

3.4.5. Assignment of the Stereochemistry of Isoxazolidine **19q** (eq. 32, Figure 2)

The stereochemistry of the hydrogenation product **19q** (Table 8, entry 2) was determined by the ^{1}H NMR spectra of (*R*)- and (*S*)-*O*-methylmandelic acid esters of the γ-amino alcohol, which was derived from the isoxazolidine.

3.4.5.1. Synthesis of *tert*-Butyl *N*-(3-hydroxy-1-phenylbutyl)-*N*-methylcarbamate (**20q**)



Isoxazolidine **19q** (33.6 mg, 0.19 mmol) was placed in a 2 mL Schlenk tube, which was equipped with a three-way stopcock, rubber septum, and stirring bar. After the reaction vessel was evacuated and charged with nitrogen gas three times, zinc powder (128 mg, 2.0 mmol), acetic acid (0.24 mL), distilled water (0.10 mL), and CH_2Cl_2 (0.30 mL) was added into the tube. The reaction mixture was stirred at ambient temperature for 5 h. After sat. Na_2CO_3 *aq.* was added, the mixture was extracted five times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and then evaporated in a 10 mL Schlenk tube under reduced pressure.

After the tube containing 4-(methylamino)-4-phenyl-2-butanol was equipped with a three-way stopcock, rubber septum, and stirring bar, dry CH_2Cl_2 (1.0 mL), Boc_2O (44.0 mg, 0.20 mmol), and dry Et_3N (28 μl, *d* 0.73 g/mL, 0.20 mmol) were added into the tube. After stirred at ambient temperature for 24 h, the resulting solution was evaporated under reduced pressure. The residue was purified with a flash column chromatography (EtOAc/hexane = 1/2) to give the titled compound (27.5 mg, 52%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.31 (d. *J* = 6.1 Hz, 3H), 1.50 (s, 9H), 1.98–2.23 (br m, 3H), 2.57 (br s, 3H), 3.80–3.98 (br, 1H), 5.25–5.63 (br, 1H), 7.24–7.37 (m, 5H).

3.4.5.2. Esterification of *tert*-Butyl *N*-(3-hydroxy-1-phenylbutyl)-*N*--methylcarbamate with *O*-Methylmandelic Acid

(*S*)- Or (*R*)-*O*-methylmandelic acid (17.7 mg, 0.11 mmol) was placed in a 10 mL Schlenk tube, which was equipped with a three-way stopcock, rubber septum, and stirring bar. The reaction vessel was evacuated and charged with nitrogen gas three times. Dry CH_2Cl_2 (0.4 mL) was added into the tube. After the tube was immersed in an ice-water bath, oxalyl chloride (13 μl, *d* 1.48 g/mL,) and dry DMF (two drops with a micro syringe) were added to the solution. The mixture was stirred at ambient temperature for 30 min. The resulting solution in the tube was concentrated under reduced pressure. The tube was charged with nitrogen gas.

Tert-butyl *N*-(3-hydroxy-1-phenylbutyl)-*N*-methylcarbamate (27.5 mg, 98 μmol) was placed in a 2 mL Schlenk tube, which was equipped with a three-way stopcock and rubber septum. The reaction vessel was evacuated and charged with nitrogen gas three times. Dry CH_2Cl_2 (0.4 mL) and pyridine (40 μL, *d* 0.98 g/mL, 0.50 mmol) were added into the tube. After the *N*-protected β-amino alcohol was dissolved in the solvent, the solution was transfer through a cannula into the 10 mL Schlenk tube containing *O*-methylmandelic chloride. After stirred at ambient temperature for 24 h, the mixture was evaporated under reduced pressure. The residue was purified with a

flash column chromatography (EtOAc/hexane = 1/5) followed by MPLC (EtOAc/hexane = 1/3) to give the desired ester. (*S*)-*O*-Methylmandelate **21q**: 40% yield; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.37 (d, *J* = 6.2 Hz, 3H), 1.47 (s, 9H), 1.90 (ddd, *J* = 5.3, 8.4, 13.7 Hz, 1H), 2.18 (m, 1H), 2.54 (s, 3H), 3.42 (s, 3H), 4.75 (s, 1H), 4.83–4.93 (m, 1H), 5.05–5.55 (br, 1H), 7.09 (d, *J* = 6.6 Hz, 2H), 7.20–7.49 (m, 10H). (*R*)-*O*-Methylmandelate **21q**: 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.23 (d, *J* = 6.0 Hz, 3H), 1.48 (s, 9H), 2.00 (ddd, *J* = 5.3, 8.2, 13.6 Hz, 1H), 2.34 (ddd, *J* = 5.4, 11.1, 13.6 Hz, 1H), 2.60 (s, 3H), 3.41 (s, 3H), 4.74 (s, 1H), 4.83–5.00 (br m, 1H), 5.20–5.65 (br, 1H), 7.18–7.50 (m, 10H).

The differences of chemical shifts between (*S*)- and (*R*)-*O*-methylmandelates are summarized in Figure S-3. With the results, the absolute configuration at 5-position of **19q** is assigned to be *S*.

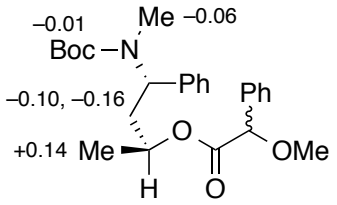
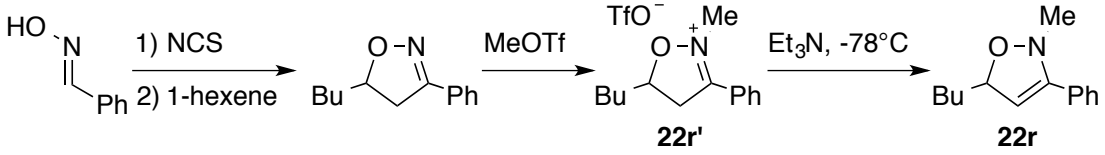


Figure S-3. The differences of chemical shifts between (*S*)- and (*R*)-*O*-methylmandelates **21q** ($\Delta\delta = \delta_S - \delta_R$).

3.4.6. Mechanistic Studies on the Iridium-catalyzed Hydrogenation of Isoxazoliums

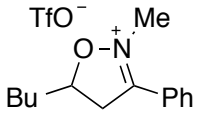
3.4.6.1. Preparation of 5-Butyl-3-methyl-3-isoxazoline (**22r**)



A 200 mL three-neck flask, which was equipped with a stirring bar, rubber septum, three-way stopcock, and a 50 mL dropping funnel having a rubber septum was evacuated and charged with nitrogen gas three times. Benzaldehyde oxime (1.22 g, 10 mmol) and dry DMF (20 mL) were added through the septum into the flask. After the flask was immersed in a water bath, *N*-chlorosuccinimide (1.40 g, 11 mmol) was intermittently added to the solution for 20 min under nitrogen flow. After stirred at

ambient temperature for 2 h, the solution was diluted with dry Et_2O (20 mL). To the resulting solution was added 1-hexene (6.4 mL, *d* 0.673 g/mL, 51 mmol). A solution of Et_3N (1.5 mL, *d* 0.73 g/mL, 11 mmol) in dry Et_2O (40 mL) was added dropwise for 40 min to the solution. After stirred at ambient temperature for 12 h, the resulting mixture was diluted with water and then extracted three times with EtOAc. The combined organic layer was dried over Na_2SO_4, and then evaporated under reduced pressure. The residue was purified with a flash column chromatography (EtOAc/hexane = 1/20) to give 5-butyl-3-phenyl-2-isoxazoline[18] [1017-09-0] (1.81 g, 88%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.93 (t, *J* = 7.1 Hz, 3H), 1.33–1.52 (m, 4H), 1.58–1.68 (m, 1H), 1.75–1.85 (m, 1H), 2.97 (dd, *J* = 8.2, 16.4 Hz, 1H), 3.39 (dd, *J* = 10.3, 16.4 Hz, 1H), 4.74 (dddd, *J* = 6.1, 6.8, 8.2, 10.3 Hz, 1H), 7.37–7.42 (m, 3H), 7.64–7.70 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.0, 22.5, 27.6, 35.0, 39.9, 81.5, 126.6, 128.6, 129.86, 129.94, 156.4.

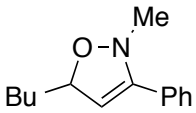
5-Butyl-3-phenyl-2-isoxazoline (611 mg, 3.0 mmol) was placed in a 50 mL two-neck flask, which was equipped with a stirring bar, rubber septum, and three-way stopcock. After the reaction vessel was evacuated and charged with nitrogen gas three times, dry CH_2Cl_2 (6.0 mL) and MeOTf (501 mg, 3.1 mmol) were added into the flask. After stirred at ambient temperature for 24 h, the mixture was diluted with Et_2O (24 mL) and then stirred for 10 min. The resulting precipitation was collected with filtration, washed with Et_2O, and then dried in vacuo to give 5-butyl-2-methyl-3-phenyl-2-isoxazolinium trifluoromethanesulfonate (**22r'**) (967 mg, 88%) as colorless powder.



mp. 97.0–97.1°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91 (t, *J* = 7.0 Hz, 3H), 1.30–1.46 (m, 4H), 1.75–1.86 (m, 1H), 1.88–1.99 (m, 1H), 3.88–4.00 (m, 4H), 4.20–4.30 (m, 1H), 5.14–5.24 (m, 1H), 7.70 (t, *J* = 7.6 Hz, 2H), 7.80 (t, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 14.3, 22.3, 26.9, 33.1, 40.9, 43.7, 83.4, 121.2 (q, *J* = 323 Hz), 123.9, 129.9, 130.4, 134.8, 163.5.

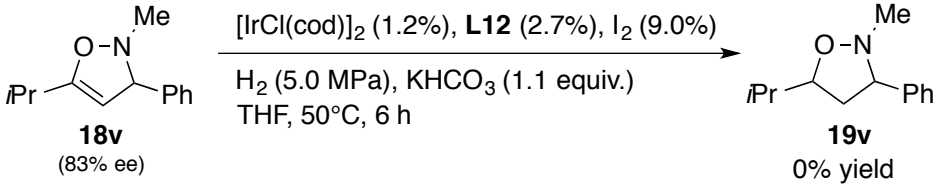
5-Butyl-2-methyl-3-phenyl-2-isoxazolinium trifluoromethanesulfonate (735 mg, 2.0 mmol) was placed in a two-neck flask, which was equipped with a stirring bar, rubber septum, and three-way stopcock. The reaction vessel was evacuated and

charged with nitrogen gas three times. After dry CH_2Cl_2 (30 mL) was added into the flask, the solution was cooled to –50°C. Dry Et_3N (0.32 mL, *d* 0.73 g/mL, 2.3 mmol) was added dropwise to the solution for 10 min by using a gastight microsyringe. After stirred at –50°C for 1 h, the solution was concentrated under reduced pressure. The residue was purified with bulb-to-bulb distillation (110°C, 0.5 mmHg) to give **22r** (268 mg, 62%) as pale yellow oil.



^{1}H NMR (400 MHz, acetone-d_6, TMS) δ 0.91 (t, *J* = 7.1 Hz, 3H), 1.30–1.48 (m, 4H), 1.60–1.67 (m, 2H), 2.80 (s, 3H), 2.82 (s, 3H), 5.13 (dt, *J* = 1.9, 5.9 Hz, 1H), 5.46 (d, *J* = 1.9 Hz, 1H), 7.30–7.42 (m, 3H), 7.44–7.49 (m, 2H); ^{13}C {^{1}H} NMR (100 MHz, acetone-d_6) δ 14.5, 23.6, 28.5, 38.4, 46.0, 85.4, 107.3, 127.9, 129.7, 132.1, 152.2.

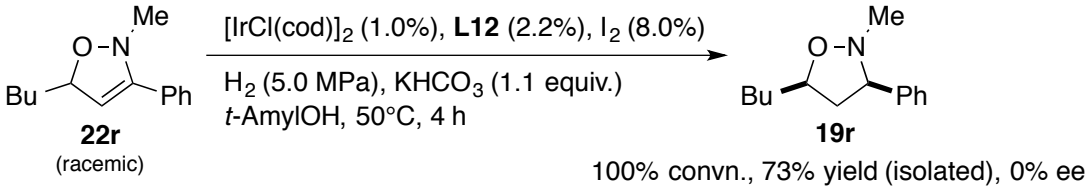
3.4.6.2 Reaction of **18v** with Hydrogen with **L12**–iridium Catalyst (eq. 34)



The general procedure of the catalytic asymmetric hydrogenation was followed with use of **7v** (83% ee, 17.0 mg, 84 μmol), which was obtained from the hydrogenation of **19v** with **L12**–iridium catalyst. The reaction was conducted in THF (1.0 mL) at 50°C for 6 h. The resulting mixture was analyzed with ^{1}H NMR spectrum, which indicates that no isoxazolidine **19v** was formed in the reaction of **7v** and hydrogen. Unreacted **7v** (12.9 mg, 76%) was recovered by passing the mixture through a short silica gel column (CH_2Cl_2). The enantiomeric excess of the recovered material was determined to be 82% ee by HPLC analysis with Chiralpak AD-H (4.6 mm $\phi \times$ 250 mm).

We attempted the hydrogenation of **7v** by using the enantiomer of **L12**. The starting material remained intact and no formation of **7v** was observed after heated at 50°C for 4 h.

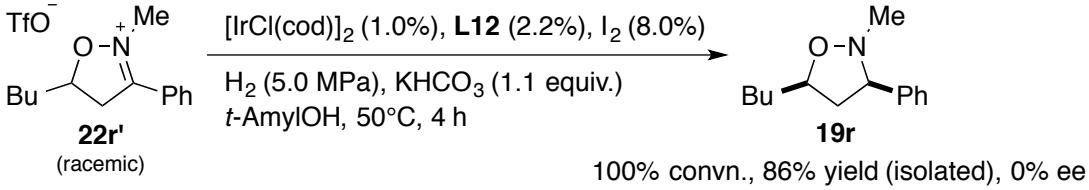
3.4.6.3. Reaction of **22r** with Hydrogen with **L12**–iridium catalyst (eq. 35)



100% convn., 73% yield (isolated), 0% ee

The general procedure of the catalytic asymmetric hydrogenation was followed with use of **22r** (22.0 mg, 0.10 mmol). The reaction was conducted in *t*-AmylOH (0.5 mL) at 50°C for 4 h. The resulting mixture was analyzed with ^{1}H NMR spectrum, which indicated that **22r** was fully converted into **19r**. The product **19r** (16.2 mg, 73%) was obtained from purification of the mixture with a short silica gel column (EtOAc/hexane = 1/20). The enantiomeric excess of the recovered material was determined to be 0% ee by HPLC analysis with Chiralpak AD-H (4.6 mm ϕ × 250 mm).

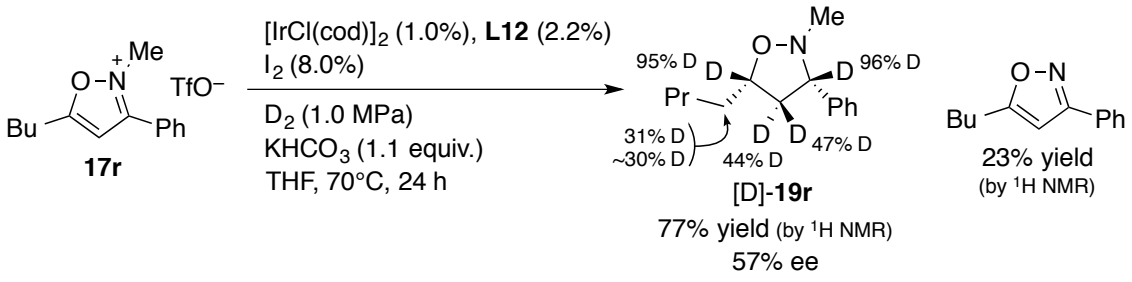
3.4.6.4. Reaction of **22r'** with Hydrogen with **L12**–iridium Catalyst (eq. 36)



100% convn., 86% yield (isolated), 0% ee

The general procedure of the catalytic asymmetric hydrogenation was followed with use of **22r'** (73.4 mg, 0.20 mmol). The reaction was conducted in *t*-AmylOH (1.0 mL) at 50°C for 4 h. The resulting mixture was analyzed with ^{1}H NMR spectrum, which indicated that **22r'** was fully converted into **22r**. The product **22r** (37.8 mg, 86%) was obtained from purification of the mixture with a short silica gel column (EtOAc/hexane = 1/20). The enantiomeric excess of the recovered material was determined to be 0% ee by HPLC analysis with Chiralpak AD-H (4.6 mm ϕ × 250 mm).

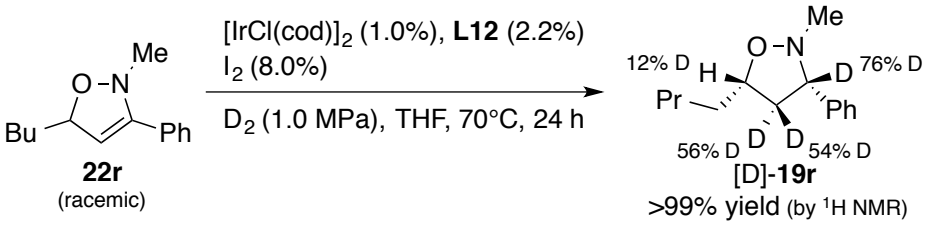
3.4.6.5. Deuteration of **17r** with **L12**–iridium Catalyst (eq. 37).



The general procedure of the catalytic asymmetric hydrogenation was followed with use of **17r** (73.2 mg, 0.20 mmol). The reaction was conducted in THF at 70°C under 1.0 MPa of deuterium with 2% catalyst loading. The resulting mixture contained deuterated [D]-**19r** (77%) and demethylated isoxazole (23%) (by ^{1}H NMR). The crude product was purified with a flash column chromatography (EtOAc/hexane = 1/20) to give [D]-**19r** (23.6 mg, 53%). The enantiomeric excess of [D]-**19r** was determined to be 57% ee by the HPLC analysis with Chiralpak AD-H (4.6 mm ϕ × 250 mm).

The ^{1}H and ^{2}H $\{^{1}$H$\}$ NMR spectra of the deuteration product are given in Figure S-98 and 99. The terminal methyl in butyl group was used as the internal standard for calibrating the integration of each peak. The deuterium distribution in [D]-**19r** is shown in the above equation. The split patterns at 2.01 and 2.82 ppm indicates that the deuteration product contains 3,5-di-, 3,4,5-tri-, and 3,4,4,5-tetradeuterated isoxazolidines.

3.4.6.6. Deuteration of **22r** with **L12**–iridium Catalyst (eq. 38).



The general procedure of the catalytic asymmetric hydrogenation was followed with use of racemic **22r** (43.5 mg, 0.20 mmol) without $KHCO_3$. The reaction was conducted in THF at 70°C under 1.0 MPa of deuterium with 2% catalyst loading. The starting material **22r** was fully converted into [D]-**19r** (by ^{1}H NMR). The crude

product was purified with a flash column chromatography (EtOAc/hexane = 1/20) to give [D]-**19r** (28.5 mg, 64%).

The ^{1}H and ^{2}H $\{^{1}H\}$ NMR spectra of the deuteration product are given in Figure S-100 and 101. The terminal methyl in butyl group was used as the internal standard for calibrating the integration of each peak. The deuterium distribution in [D]-**19r** is shown in the above equation.

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19. The ^{1}H NMR spectrum of the product in eq. 35 indicates that the product was a mixture of 3,5-di-, 3,4,5-tri-, and 3,4,4,5-tetradeuterated **19r**.
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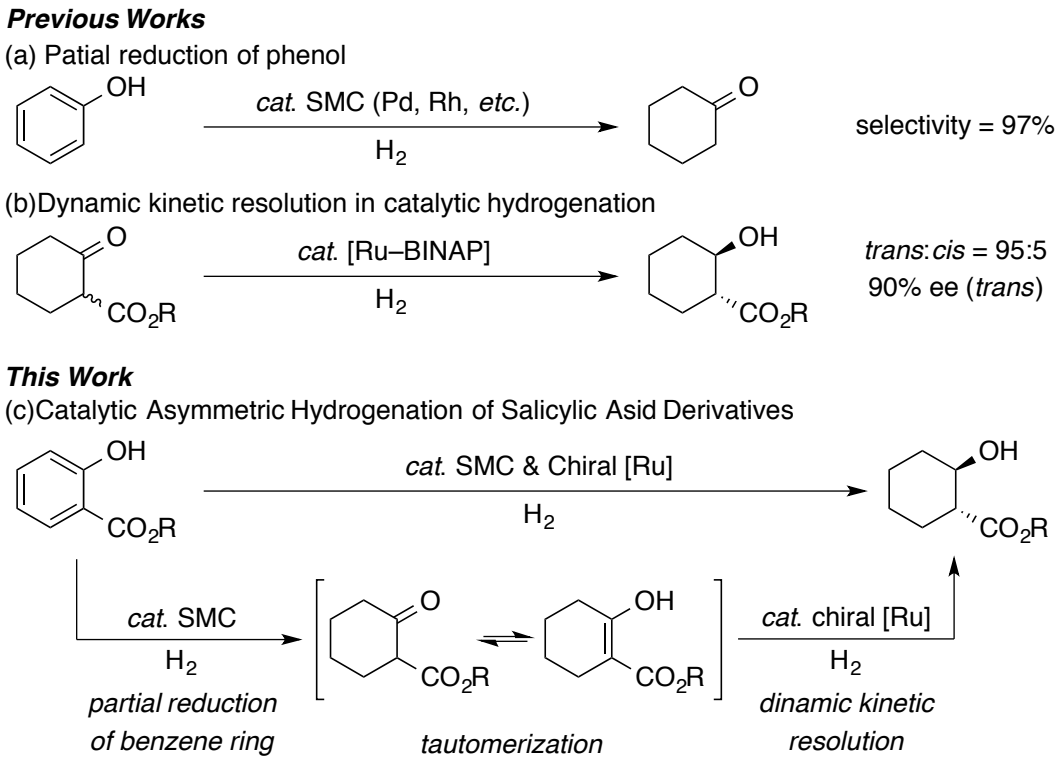
Chapter 4

Catalytic Asymmetric Hydrogenation of Salicylic Acid Derivatives

4.1. Introduction

Nowadays, the catalytic asymmetric hydrogenation of heteroarenes has progressed.[1] Various heteroarenes are reduced with high enantioselectivity by using chiral transition-metal catalysts. On the other hand, the catalytic asymmetric hydrogenation of aromatic carbocycles has been known only three reports, quinoxalines,[2] naphthalenes,[3] and quinolines.[4] Furthermore, these substrates are polycyclic aromatic carbon rings. The reaction of monocyclic arenes, which are more stabilized with the aromaticity, has been hardly studied. Consequently, the catalytic asymmetric hydrogenation of benzene rings is one of the most difficult issues in the organic synthesis. It is a major reason that no high reactive transition-metal catalyst to reduce the benzene rings has been known yet.

Hydrogenation of benzene rings usually conducts with supported metal catalysts (SMCs). Also, SMCs can partially reduce benzenes depending on the condition. For example, phenols are partially reduced to cyclohexanones in the presence of SMCs. In 1995, González-Velasco reported the first partially reduction of phenol using palladium on activated carbon under the batch condition (Scheme 6a).[5] From the reaction, cyclohexanone was obtained with high selectivity. I supposed that the catalytic asymmetric hydrogenation of benzenes would be possible if the asymmetric hydrogenation of the partial reduction products, *e.g.* cyclohexanones, proceeded by using the chiral catalyst in the presence of SMCs. For example of the catalytic asymmetric hydrogenation of cyclohexanones, Noyori's group had reported the catalytic asymmetric hydrogenations of 2-oxocyclohexanecarboxylates.[6] This hydrogenation catalyzed by BINAP–ruthenium complex proceeded through the dynamic kinetic resolution, and selectively generated *trans*-isomer with high enantiomeric excess in CH_2Cl_2 (Scheme 6b). From these reactions, I expected that salicylates were hydrogenated with high stereoselectivity combinational by using a SMC and a chiral ruthenium catalyst (Scheme 6c). In this chapter, I demonstrate the first high stereoselective catalytic asymmetric hydrogenation of benzene rings. Salicylic acid derivatives were hydrogenated with high enantioselectivity by using rhodium on carbon and C_3-TunePhos–ruthenium complex.

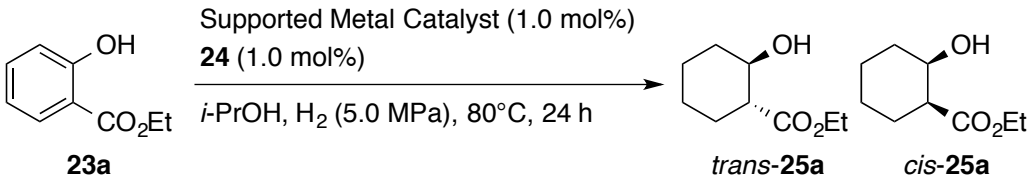


Scheme 6. My Strategy of Catalytic Asymmetric Hydrogenation of Salicylates

4.2. Results and Discussions

Based on the hypothesis, I attempted the hydrogenation of ethyl salicylate (**23a**) catalyzed by {RuCl(*p*-cymene)[(*R*)-BINAP]}Cl (**24**)[6b] in the presence of various SMCs. At first, palladium-supported catalysts, which were common catalysts of the partial reduction of phenol,[5] were tested. However, **23a** was hardly consumed regardless of the catalyst supports (Table 9, entries 1–3). Similarly, other palladium catalysts, which were purchased from other companies or supported on other carriers, were not suitable for this hydrogenation. Next, I conducted the hydrogenation using other metal-supported catalysts. As a result, ruthenium and rhodium catalysts gave better yields than the palladium catalysts (entries 4–7). In particular, **23a** was completely consumed, and converted to **25a** in good yield with moderate stereoselectivities when rhodium on activated carbon was used (entry 6). It is noted that SMCs were not related to diastereo- and enantioselectivity of the reaction in *i*-PrOH because *trans*/*cis* ratios and enantiomeric excesses of the products were nearly the same using any of catalysts.

Table 9. Screening of Supported Metal Catalyst[a]

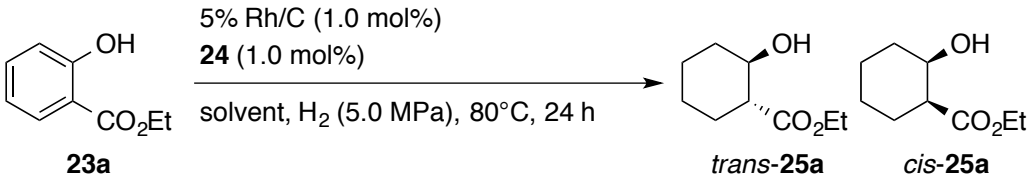


entry	SMC	yield[b]	*trans*:*cis*[b]	ee (*trans* / *cis*)[c]
1	5% Pd/C	7%	67 : 33	n.d.
2	5% Pd/alumina	4%	68 : 32	n.d.
3	5% Pd/silica	0%	-	-
4	5% Pt/C	1%	n.d.	n.d.
5	5% Ru/C	20%	56 : 44	64% / 70%
6	5% Rh/C	88%	55 : 45	65% / 70%
7	5% Rh/alumina	35%	51 : 49	68% / 60%

[a] Reactions were conducted on a 0.20 mmol scale in 1.0 mL of *i*-PrOH under 5.0 MPa of H_2 at 80°C for 24 h. The ratio of **23a**/SMC/**24** was 100:1.0:1.0. [b] Determined by GC in comparison to a 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by chiral GC analysis.

Table 10 shows the result of solvent screening. It is known that solvents affect *trans*/*cis* selectivity of the catalytic asymmetric hydrogenation of *β*-ketoesters.[6b] The hydrogenation of **23a** showed the similar *trans*/*cis* selectivity to the reaction of *β*-ketoesters. The hydrogenation proceeded with low diastereoselectivity in the protic solvents (entries 1 and 2). On the other hand, the high *trans*-selective reactions proceeded in low-polar solvents (entries 3, 4, and 6). Especially, ethyl acetate (EtOAc) solvent showed higher selectivity than halogenated solvent using in the hydrogenation of *β*-ketoesters (entry 3 vs 4).[6b] It is noted that *cis*-**25a** was obtained with low optical purity from the hydrogenation in EtOAc. *Cis*-**25a** might be generated through the hydrogenation catalyzed by only rhodium on carbon in EtOAc. It is surprising that rhodium on carbon purchased from TCI showed higher catalytic activity than purchased from other companies in EtOAc (entries 4 vs 7 and 8). Although this reason is not clear, I suspect that the surface structure of rhodium catalyst is related to the catalytic activity because the material compositions of rhodium on carbons analyzed by XRF are nearly same.

Table 10. Effect of Solvent[a]

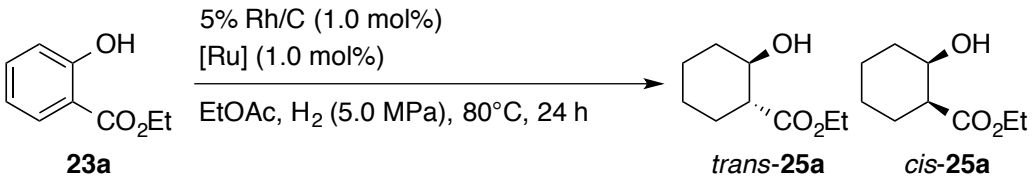


23a *trans*-**25a** *cis*-**25a**

entry	solvent	yield[b]	*trans*:*cis*[b]	ee (*trans* / *cis*)[c]
1	EtOH	89%	48 : 52	87% / 83%
2	*i*-PrOH	88%	55 : 45	65% / 70%
3	DCE	54%	85 : 15	65% / 50%
4	EtOAc	71%	91 : 9	69% / 14%
5	CPME	5%	46 : 54	26% / 8%
6	CyMe	75%	77 : 23	57% / 17%
7[d]	EtOAc	28%	90 : 10	59% / 12%
8[e]	EtOAc	34%	88 : 12	59% / 12%

[a] Reactions were conducted on a 0.20 mmol scale in 1.0 mL of solvent under 5.0 MPa of H_2 at 80°C for 24 h. The ratio of **23a**/SMC/**24** was 100:1.0:1.0. [b] Determined by GC in comparison to a 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by chiral GC analysis. [d]Rh/C was bought from Wako. [e] Rh/C was bought from N.E.CHEMCAT.

Table 11. Effect of Ruthenium Catalyst[a]



23a *trans*-**25a** *cis*-**25a**

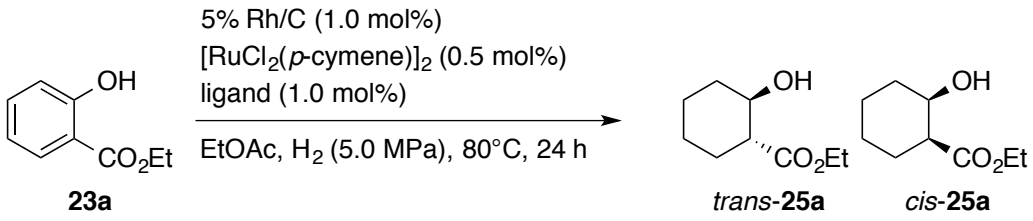
entry	[Ru]	yield[b]	*trans*:*cis*[b]	ee (*trans* / *cis*)[c]
1	**24**	71%	91 : 9	69% / 14%
2	{$RuCl_2$[(*R*)-BINAP]}	99%	91 : 9	69% / 10%
3	({RuCl[(*R*)-BINAP]}$_2$(μ-Cl)$_3$)[NH_2Me_2]	51%	86 : 14	73% / 29%
4	{Ru[(*R*)-BINAP](OAc)$_2$}	76%	33 : 67	22% / 14%
5[d]	Ru(η^3-methallyl)$_2$(cod) + (*R*)-BINAP	94%	35 : 65	26% / 1%

[a] Reactions were conducted on a 0.20 mmol scale in 1.0 mL of EtOAc under 5.0 MPa of H_2 at 80°C for 24 h. The ratio of **23a**/[Rh]/[Ru]* was 100:1.0:1.0. [b] Determined by GC in comparison to a 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by chiral GC analysis. [d] [Ru] and BINAP was heated for 1 h in EtOAc before the reaction.

Next, the ruthenium catalyst was optimized (Table 11). The reactions conducted with chloride-ion-containing BINAP–ruthenium catalysts proceeded with similar stereoselectivities (entries 1–3). On the other hand, the products were very low enantio purity when the reaction was conducted by using acetate complex or methallyl complex for *in situ* (entries 4 and 5). It means that chloride in the ruthenium catalyst is important to achieve high enantioselectivity.

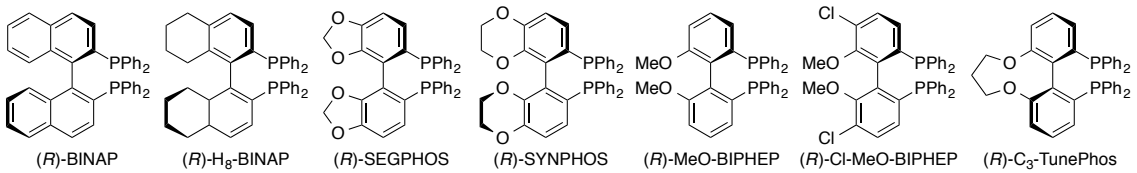
To improve the stereoselectivity, optimization of the ligand was conducted (Table 12). Axialy chiral bisphosphine ligands were suitable for the hydrogenation while other ligands used in the hydrogenation of β-ketoesters gave the cruel results.[7]

Table 12. Optimization of ligand[a]



entry	ligand	yield[b]	*trans*:*cis*[b]	ee (*trans* / *cis*)[c]
1	(*R*)-BINAP	46%	93 : 7	71% / 17%
2	(*R*)-H_8-BINAP	81%	92 : 8	85% / 9%
3	(*R*)-SEGPHOS	97%	92 : 8	87% / 15%
4	(*R*)-SYNPHOS	>99%	91 : 9	90% / 22%
5	(*R*)-MeO-BIPHEP	94%	92 : 8	90% / 11%
6	(*R*)-Cl-MeO-BIPHEP	80%	92 : 8	90% / 10%
7	(*R*)-C_3-TunePhos	>99%	92 : 8	92% / 21%

[a] Reactions were conducted on a 0.20 mmol scale in 1.0 mL of EtOAc under 5.0 MPa of H_2 at 80°C for 24 h. The ratio of **23a**/Rh/[Ru]/ligand was 100:1.0:0.5:1.0. [Ru] were reacted with a ligand in EtOH/CH_2Cl_2 at 50°C for 1 h, then the mixuture was dried under vacuo before the hydrogenation. [b] Determined by GC in comparison to a 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by chiral GC analysis.

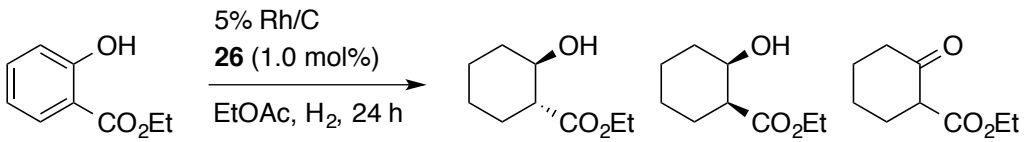


(*R*)-BINAP (*R*)-H_8-BINAP (*R*)-SEGPHOS (*R*)-SYNPHOS (*R*)-MeO-BIPHEP (*R*)-Cl-MeO-BIPHEP (*R*)-C_3-TunePhos

Especially, the ligands substituted the oxygen functional groups on 6,6'-position of biaryl backbones, which had narrower dihedral angles than BINAP, [8] allowed to give high optically active *trans*-product without the decreasing diastereoselectivity (entries 3–7). C_3-TunePhos[8a] was the best ligand in this reaction, and selectively gave *trans*-**25a** as a major product with 92% ee (entry 7).

Finally, the other reaction conditions were examined using {RuCl(*p*-cymene)[(*R*)-C_3-TunePhos]}Cl (**26**) (Table 13). Excellent result was obtained under 3.0 MPa of H_2, but the reaction rate was decrease under 1.0 MPa (entries 1–3). An excess of rhodium catalyst over the ruthenium catalyst was occurred the increasing *cis*-product ratio and the slight decreasing enantiomeric excess of *trans*-isomer (entry 1 vs 4). It means because that the hydrogenation not related with **26** might increase.

Table 13. Effect of Conditions[a]



23a *trans*-**25a** *cis*-**25a** **27a**

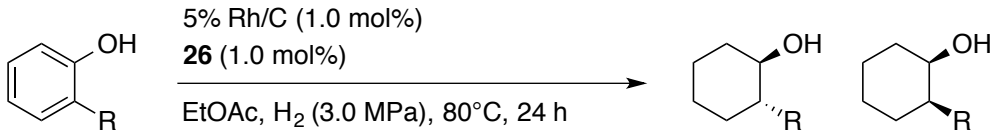
entry	Rh/C	H_2	Temp.	**25a**[b]	**27a**[b]	*trans*:*cis*[b]	ee (*trans* / *cis*)[c]
1	1.0 mol%	5.0 MPa	80°C	>99%	0%	89 : 11	90% / 22%
2	1.0 mol%	3.0 MPa	80°C	98%	0%	91 : 9	91% / 17%
3[d]	1.0 mol%	1.0 MPa	80°C	84%	<1%	87 : 13	86% / 18%
4	2.0 mol%	3.0 MPa	80°C	>99%	0%	84 : 16	87% / 36%
5[e]	0.5 mol%	3.0 MPa	80°C	6%	56%	86 : 14	86% / 19%
6[f]	1.0 mol%	3.0 MPa	80°C	27%	45%	78 : 22	89% / 14%
7[f]	1.0 mol%	3.0 MPa	60°C	10%	43%	57 : 43	81% / 6%
8[f]	1.0 mol%	3.0 MPa	40°C	4%	23%	57 : 43	n.d.

[a] Reactions were conducted on a 0.20 mmol scale in 1.0 mL of EtOAc for 24 h. The ratio of **23a**/SMC/**26** was 100:1.0:1.0. [b] Determined by GC in comparison to a 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by chiral GC analysis. [d] 48 h, 85% conv. [e] 62% conv. [f] 4 h.

On the other hand, the yield of **25a** diminished and *β*-ketoester **27a** was observed as a major product when rhodium catalyst was less then **15** (entry 5). **27a** was also observed when the reaction was stopped in the middle (entry 6). Interestingly, the *trans*/*cis* ratio was slightly low. It means that the disastereoselectivity might change with time. The reaction temperature affected the reaction rate (entries 6–8).

Table 14 showed the substrate scope of this hydrogenation. The reaction of salicylates **23a**–**23d** gave *trans*-isomer as major products with high enantiomeric excesses, although the large ester groups slightly declined the *trans*/*cis* ratio of the products (entries 1, 2, 4, and 5). Amount of the catalysts could be decreased to 0.10 mol% without the dramatically decreasing stereoselectivity in hydrogenation of methyl salicylate (**23b**) (entry 3). Unfortunately, the reaction of benzyl salicylate gave complex mixtures because of the reduction of both phenyl ring and the hydrogenolysis at benzyl position. Unstable substrates under reduction condition might be unsuitable for this hydrogenation. Phenyl salicylate quantitatively converted to cyclohexyl ester product, but *trans*/*cis* ratio and enantio excesses couldn't analyze in my laboratory. This catalyst system also reduced the other salicylic acid derivatives with moderate to high enantioselectivity, although the disasterselectivities dramatically decreased. Salicylic acid (**23e**) was easily hydrogenated in 1,2-dichloroethane (DCE), and both stereoisomers showed good ees (entry 6). The hydrogenation of secondary amide **23f** proceeded with the high enantioselectivity under 5.0 MPa of hydrogen (entry 7), but tertiary amide **23g** was difficult to reduce due to a steric hindrance, and converted to the products with low ees (entry 8). A primary amide was not tried because enantiomeric excess couldn't analyze in my laboratory. Unfortunately, the imide and Weinreb amide synthesized from salicylic acid (**23e**) were hardly reduced in the optimized reaction condition. The catalysts also reduced phosphonate **23h** in EtOH under 5.0 MPa of hydrogen (entry 9). The products **25h** were obtained with good ees. It is noted that *cis*-**25h** was major isomer in this hydrogenation.

Table 14. The Hydrogenation of Salicylic Acid Derivatives[a]



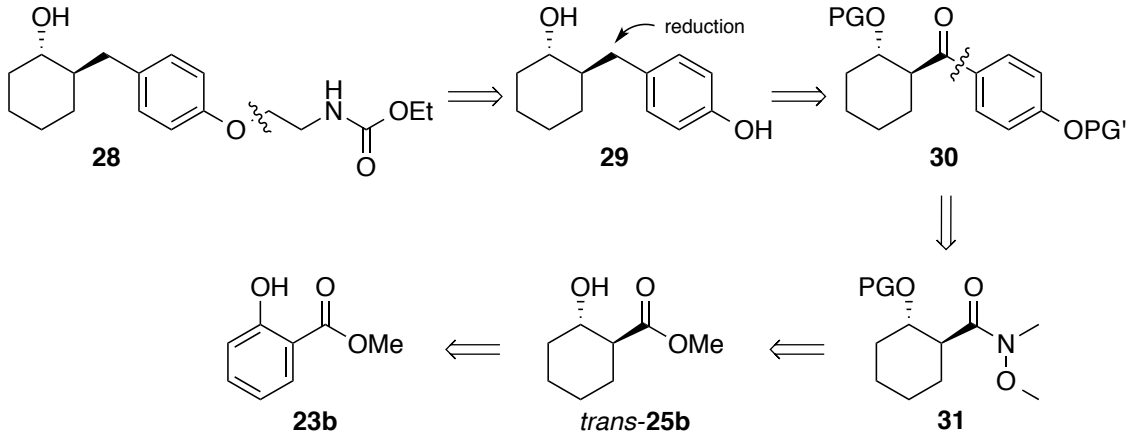
23 *trans*-**25** *cis*-**25**

entry	R	yield[b]	*trans*:*cis*[c]	ee (*trans* / *cis*)[d]
1	CO_2Et (**23a**)	98%	91 : 9[d]	91% / 17%
2	CO_2Me (**23b**)	99%	88 : 12	92% / 20%
3[e]	CO_2Me (**23b**)	>99%[f] (87%)[g]	89 : 11	93% / 21%
4[h]	CO_2(*i*-Pr) (**23c**)	91%	85 : 15	82% / 28%
5[i]	CO_2(*t*-Bu) (**23d**)	90%	82 : 18	89% / n.d.
6[j]	CO_2H (**23e**)	>99%[f]	39 : 61	88% / 75%[k]
7[l]	CONHEt (**23f**)	97%	56 : 44	96% / 77%[m]
8[l]	$CONEt_2$ (**23g**)	>99%	68 : 32	42% / 31%[m]
9[i,l,n]	$P(O)(OEt)_2$ (**23h**)	75%[o]	27 : 73[o]	88% / 77%[p]

[a] Reactions were conducted on a 0.20 mmol scale in 1.0 mL of EtOAc under 3.0 MPa of H_2 at 80°C for 24 h. The ratio of **23**/[Rh]/**26** was 100:1.0:1.0. [b] Isolated yield. Isolated yield of *trans*-**25a** was indicated in parentheses. [c] Determined by ^1H NMR. [d] Determined by GC analysis. [e] Reactions were conducted on a 10 mmol scale in 5.0 mL of EtOAc under 5.0 MPa of H_2 at 80°C for 120 h. The ratio of **23a**/[Rh]/**26** was 1000:1.0:1.0. [f] NMR yields. [g] Isolated yield of *trans*-**25b**. [h] 36 h. [i] 48 h. [j] The solvent was DCE. [k] Determined by GC analysis after *O*-methylation by $TMSCHN_2$. [l] Reactions were conducted under 5.0 MPa of H_2. [m] Determined by GC analysis after *O*-acylation by TFAA. [n] The solvent was EtOH. [o] Determined by ^{31}P NMR analysis. An unknown side-product generate in 25% [p] Determined by HPLC analysis after *O*-acylation by Bz_2O.

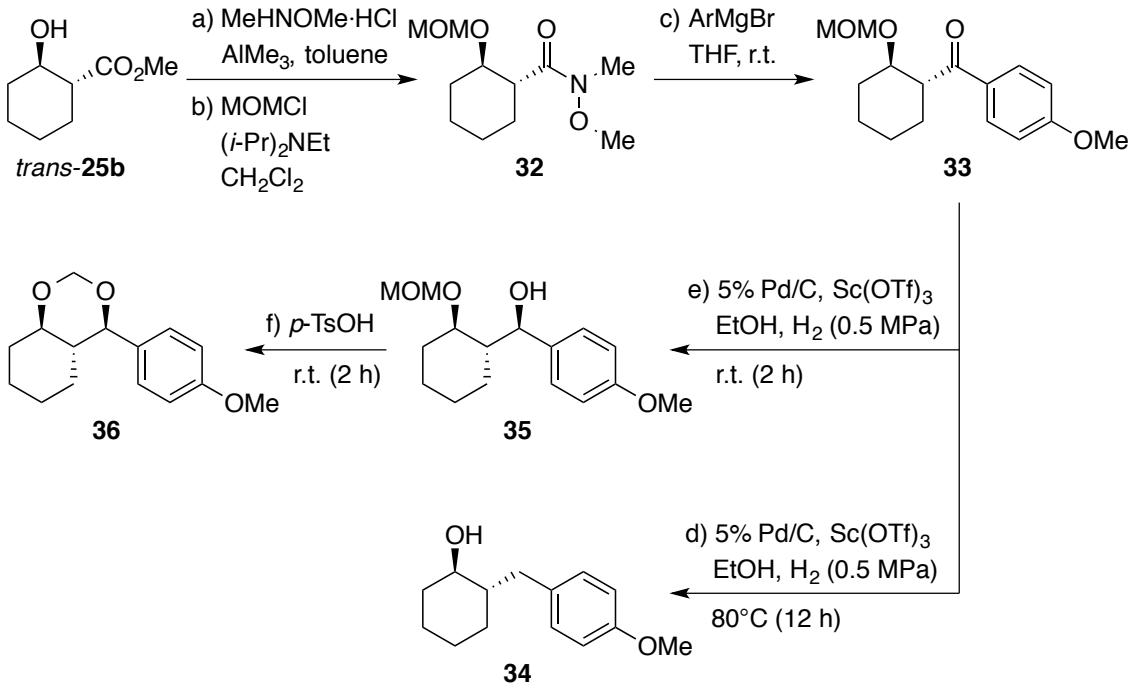
The reaction products contain the optically active 2-substituted *trans*-cyclohexanol structure, which was found in the bioactive compounds and chiral ligands. So, I challenged to synthesize the bioactive compound using my reaction products. Carbamate **28** has the comparable juvenile hormone activity to methoprene utilizing as an insecticide (Scheme 7).[9] This juvenile hormone analogue **28** is mainly used as juvenogens, however, the racemic compounds have been utilized generally in the study in spite of the different activities between the enantiomers.[10] Because the substrates are cheep and gram-scale reaction proceeds without the decreasing the stereoselectivity, it is supposed that my reaction of salicylates is effective to synthesize the enantio pure juvenogens. The retrosynthesis of **28** is showed at Scheme 7. The

aminoalcohol-side-chain can be introduces through the chemoselective noculeophilic substitution finally.[11] Methylene moiety at benzyl position of **29** would be formed by the reduction of ketone **30**. **30** was converted from Weinreb amide **31** synthesized from my reaction product *trans*-**25b**.



Scheme 7. Retrosynthesis of Juvenile Hormone Analogue **16**

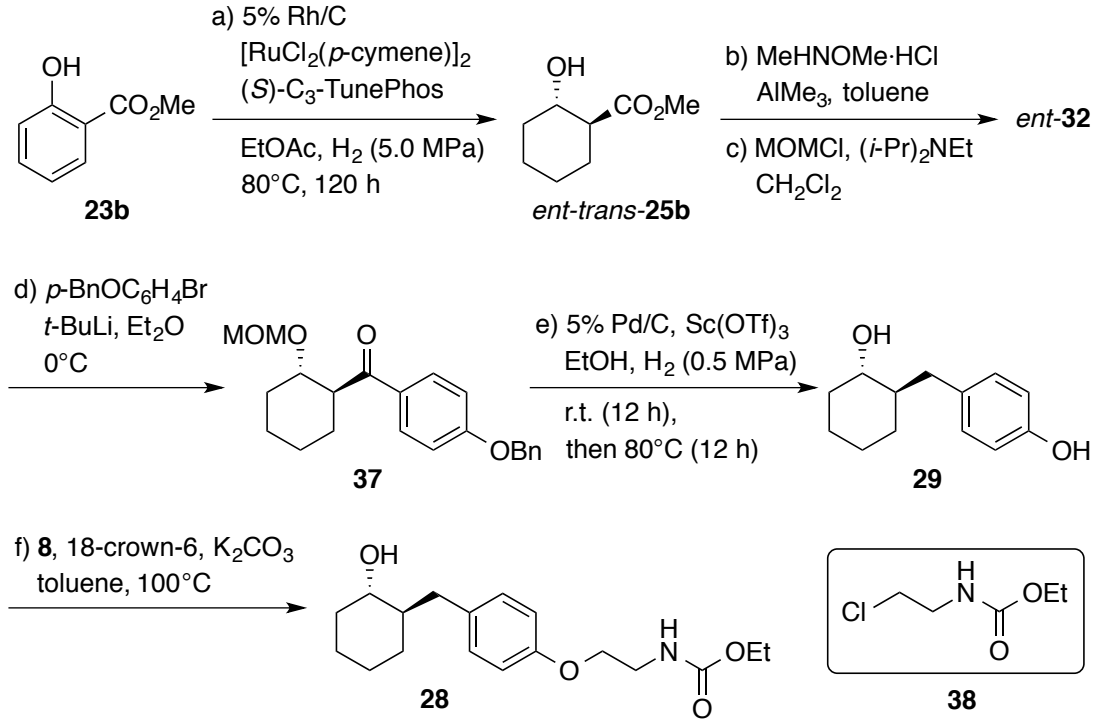
At first, the synthesis of **34**, simplified compound of **28**, was tried as a model reaction (Scheme 8). *Trans*-**25b** synthesized from **23b** was leaded to Weinreb amide using trimethylaluminium,[12] then hydroxyl group was protected with MOM. This protecting group is important because a large protecting group (*e.g.* TBS) disturbed the next nucleophilic addition to carbonyl group. MOM group allowed Grignard reagent to add **32**. The reduction of carbonyl group of **33** was very difficult. No reactions occurred in hydrogenation using various SMCs. Although Brønsted acids promoted the consumption of **33** in the hydrogenation using SMCs, complex mixtures were generated and no **34** was observed. Furthermore, Wolff-Kishner reduction also did not proceeded. After various trials, I found that **34** was obtained with good yield through the hydrogenation of **33** catalyzed palladium on carbon in the presence of scandium triflate at 80ºC. Furthermore, to my surprising, the carbonyl group of **33** was stereoselectively converted to hydroxyl group at room temperature, and sole stereoisomer **35** was generated quantitatively without MOM deprotection. **35** was easily transformed to cyclic acetal **36** under acidic condition, and the new chiral center was assigned *R* analyzed by coupling constants of ^{1}H NMR.



[a] MeHNOMeHCl (2.0 equiv.), 2M $AlMe_3$ heptane solution (2.0 equiv.), toluene, reflux. [b] MOMCl (2.0 equiv.), *i*-Pr_2NEt (2.0 equiv.), CH_2Cl_2, r.t. 85% yield for 2 steps. [c] *p*-$MeOC_6H_4MgBr$ (ArMgBr, 3.3 equiv.), THF, 0°C. 73% yield. [d] 5% Pd/C (10 mol%), $Sc(OTf)_3$ (10 mol%), EtOH, H_2 (0.50 MPa),80°C (12 h). 49% yield. [e] 5% Pd/C (10 mol%), $Sc(OTf)_3$ (10 mol%), EtOH, H_2 (0.50 MPa), r.t. (2 h). >99% yield. [f] *p*-TsOH·H_2O (10 mol%), acetone, r.t., 12 h. 42% yield.

Scheme 8. Synthesis of **34**

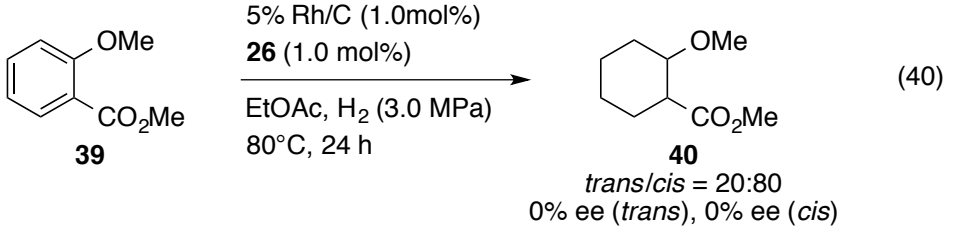
Next, the synthesis of juvenile hormone analogue **28** was attempted with the optimized conditions. **29** was expected to be obtained from the ketone **37** through the reduction of carbonyl group to methylene with deprotection of MOM and benzyl groups under the above condition. The results were illustrated in Scheme 9. *Ent-trans*-**25b** was obtained through the hydrogenation of **23b** by rhodium on carbon–*ent*-**26** catalyst system. In the same way as above, *ent*-**25b** was leaded to Weinreb amide *ent*-**32**. Next, **37** was obtained trough the addition of *p*-benzyloxyphenyl lithium to *ent*-**32**. It is noted that *n*-butyl lithium decrease the yield of **37** because the aryl lithium was consumed by the reaction with butyl bromide generated from the reaction of *p*-arylbromide and butyl lithium. Furthermore, because deprotonation at MOM methylene moiety gave side-products, it was important that *tert*-buthyl lithium were under an equimolecular amount of the aryl bromide. Fortunately, the reduction and the deprotections of **37** successfully proceeded by using palladium on carbon–scandium triflate catalyst system, and produced **29** with good yield. Finally, K_2CO_3 with 18-crown-6 allowed **29** to attack to **38** chemoselectively, and yield **28**.[11]



[a] Reactions were conducted on a 10 mmol scale in 5.0 mL of EtOAc under 50 atm of H_2 at 80°C for 120 h. The ratio of **23b**/[Rh]/[$RuCl_2$(*p*-cymene)]$_2$/(*S*)-C_3-TunePhos was 1000:1.0:0.50:1.0. 87% yield, 93% ee (*trans*). [b] MeHNOMeHCl (2.0 equiv.), 2 M $AlMe_3$ heptane solution (2.0 equiv.), toluene, reflux. [c] MOMCl (2.0 equiv.), *i*-Pr_2NEt (2.0 equiv.), CH_2Cl_2, r.t. 95% yield for 2 steps. [d] *p*-$BnOC_6H_4Br$ (3.3 equiv.), 1.6M *t*-BuLi pentane solution (3.0 equiv.), Et_2O, 0°C. 87% yield. [e] 5% Pd/C (10 mol%), $Sc(OTf)_3$ (10 mol%), EtOH, H_2 (0.50 MPa), r.t. (12 h) to 80°C (12 h). 84% yield. [f] **38** (4.0 equiv.), 18-crown-6 (1.0 equiv.), K_2CO_3 (10 equiv.), toluene, 100°C. 83% yield.

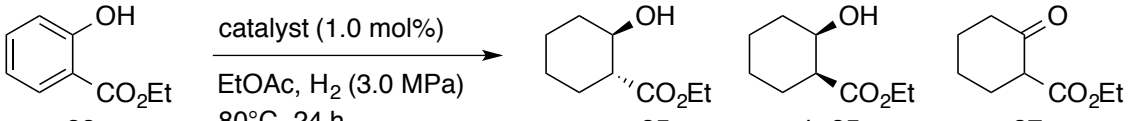
Scheme 9. Synthesis of Juvenile Hormone Analogue **28**

β-Ketoester **27a** was observed when the reaction was stopped in the middle (Table 13, entry 8). In addition, racemic **40** were obtained from hydrogenation of *O*-masked salicylate **39** under the optimized condition (eq. 40). From above these results, it is reasonable to assume that **27** was the intermediate of partial reduction of benzene ring and the hydrogenation of **27** proceeds through the keto-form not the enol-form like as the common catalytic asymmetric hydrogenation of *β*-ketoesters.[6]



(40)

In order to clarify the roles of two catalysts, some control experiments were attempted. First, I attempted the hydrogenation of a salicylate catalyzed by either one catalyst. As expected, no reaction occurred using only **26**. Interestingly, rhodium on carbon quantitatively gave alcohol products **25a**, not **27a** (Scheme 10). This result is contrary to obtain **25** with high ee in the hydrogenation of salicylates **23**.

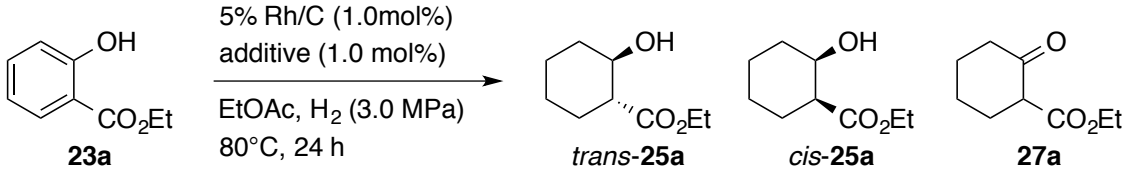


	trans-**25a**	*cis*-**25a**	**27a**
Rh/C + **26**	89% (91%ee)	9% (17% ee)	0%
26	0%	0%	0%
Rh/C	18%	79%	0%

Scheme 10. Control Experiment (Hydrogenation of Salicylate **23a**)

It was suspected that the ruthenium complex occurred the contradiction. So, I conducted the hydrogenation of **23a** with rhodium on carbon in presence of the additives, which were components of **26** (Table 15).

Table 15. Effect of additive in the hydrogenation of salicylate **23a** with Rh/C[a]

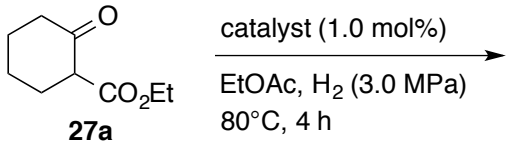


entry	additives	*trans*-**25a**[b]	*cis*-**25a**[b]	**27a**[b]
1	none	18%	79%	0%
2	**26**	89% (91%ee)[c]	9% (17% ee)[c]	0%
3	Bu_4NCl	18%	4%	79%
4	(*R*)-C_3-TunePhos	20% (17% ee)[c]	6% (0% ee)[c]	75%
5	$[RuCl_2(p\text{-cymene})]_2$	51%	6%	40%

[a] Reactions were conducted on a 0.40 mmol scale in 2.0 mL of EtOAc under 3.0 MPa of H_2 at 80°C for 24 h. The ratio of **23a**/[Rh]/additive was 100:1.0:1.0. [b] Determined by GC in comparison to a 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by chiral GC analysis.

As a result, **27a** was observed as a major product in the presence of C_3-TunePhos or chloride ion (entries 3 and 4). Especially, chloride ion in the ruthenium catalyst was involved the stereoselectivity (Table 8). It is anticipated that chloride including in **26** disturbed the reduction of **27** catalyzed by rhodium on carbon. It is noted that **25a** yielded by rhodium catalyst with C_3-TunePhos was low ee (entry 4). It means that C_3-TunePhos–rhodium complexes are not the catalytic active species.

Next, the hydrogenations of *β*-ketoester **27a** were conducted by using rhodium on carbon or/and **26** (Scheme 11). Surprisingly, while rhodium on carbon–**26** system gave the similar result of the hydrogenation of **23a**, no reaction occurred in the hydrogenation catalyzed by only **26**. The no reaction was maybe caused by EtOAc solvent,[13] however, the similar accelerations were observed in 2-propanol and 1,2-dichloroethane under 1.0 MPa of H_2.



Rh/C + **26**	40% (91%ee)	3% (56% ee)
26	0%	0%
Rh/C	10%	48%

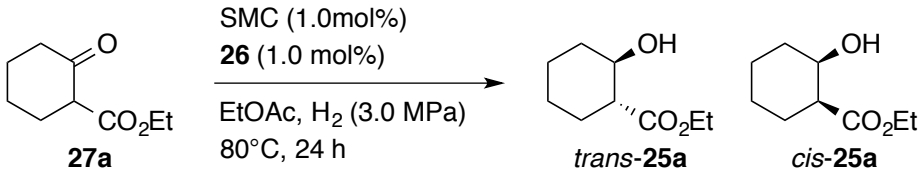
Scheme 11. Control Experiment (Hydrogenation of *β*-ketoester **27a**)

It was estimated that rhodium on carbon activated the ruthenium catalyst. So, I firstly attempted the hydrogenation catalyzed by **26** in the presence of an charcoal or water, which were included in the rhodium on carbon, but no reaction occurred (Table 16, entry 3). After some trials, it was found that not only rhodium on carbon but also ruthenium and platinum on carbon occurred this activation (entries 4 and 5). It means that rhodium–ruthenium multinuclear complexes are not catalytic active species.

Furthermore, 1-isopropyl-4-methylcyclohexane (H_6-**41**) was observed in the reaction of H_2 and **26** with rhodium on carbon (Figure 4a). On the other hand, only *p*-cymene (**41**) was determined in the reaction without the rhodium catalyst (Figure 4b). It is known that the catalytic active species were the arene-ligand-releasing ruthenium complexes in the hydrogenation of *β*-ketoesters.[14] I guessed that SMCs activated the

ruthenium catalyst to reduce the arene ligands.

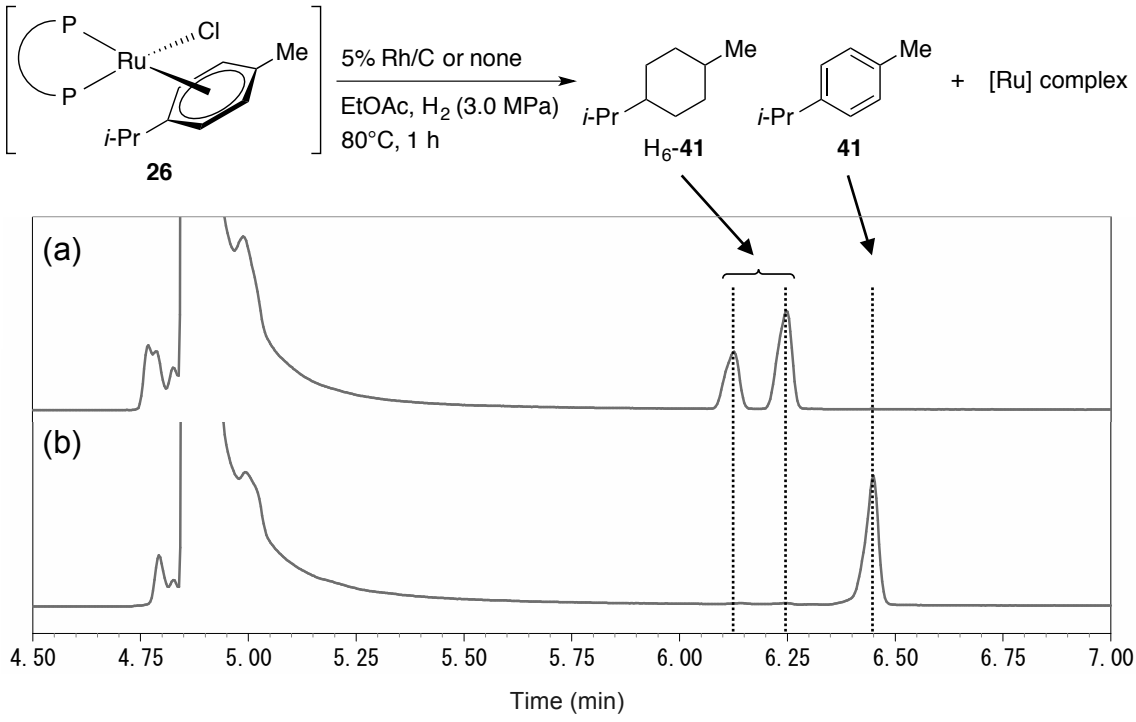
Table 16. Effect of SMC in the hydrogenation of β-ketoester **27a** with **26**[a]



entry	SMC	*trans*-**25a**[b]	*cis*-**25a**[b]	ee (*trans*/*cis*)[c]
1	none	0%	0%	-
2	5% Rh/C	40%	3%	91% / 56%
3	charcoal or H_2O	0%	0%	-
4	5% Ru/C	35%	3%	92% / 30%
5	5% Pt/C	36%	10%	84% / 25%

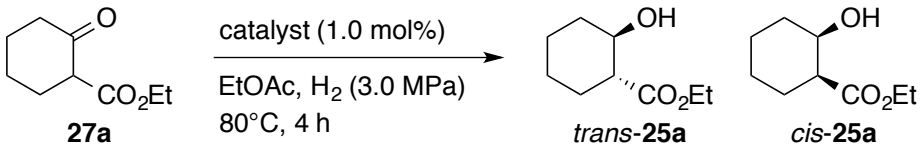
[a] Reactions were conducted on a 0.20 mmol scale in 1.0 mL of EtOAc under 3.0 MPa of H_2 at 80°C for 4 h. The ratio of **23a**/SMC/**26** was 100:1.0:1.0. [b] Determined by GC in comparison to a 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by chiral GC analysis.

Figure 4. GC Analysis and Determination of **41** and H_6-**41**



Determined by GC in comparison to a tetradecane as an internal standard. (a) With 5% Rh/C. H_6-**41**:44% yield, **41**:0% yield. (b) Without 5% Rh/C. H_6-**41**:0% yield, **41**:57% yield.

In order to support my hypothesis, I tried the hydrogenation of **27a** using the non-arene-coordinated ruthenium catalyst, {$RuCl_2$[(*R*)-BINAP]}. However, against our expectation, the activation of ruthenium catalyst by rhodium on carbon was observed (Scheme 12). Although the survey is continuing, the roll of rhodium on carbon might not be only reduction of the arene ligand, but also generation of hydoridoruthenium species.



	trans-**25a**	*cis*-**25a**
Rh/C + {$RuCl_2$[(*R*)-BINAP]}	60% (61%ee)	3% (55% ee)
{$RuCl_2$[(*R*)-BINAP]}	0%	0%

Scheme 12. The Hydrogenation of *β*-Ketoester **17a** Catalyzed by {$RuCl_2$[(*R*)-BINAP]}

To further gain the information of the active ruthenium species, ^{31}P NMR spectroscopy experiment was tried. The trials conducted in 1,2-dichloroethane-d_4 under 1.0 MPa of H_2. No new complex was generated under hydrogen and only decomposition of the **26** was observed when the reaction was conducted without rhodium on carbon (Figure 5). In contrast, rhodium on carbon–**26** system directly produced [RuH(*p*-cymene)(C_3-Tunephos)]$^+$ complex under hydrogen at room temperature,[15] then the new signals was appeared at 48–74 ppm following heating at 80°C for 1 h (Figure 5). I estimate that the new complexes observed by ^{31}P NMR at 48~74 ppm are catalytically active hydridoruthenium species without the arene ligand. In addition, cold spray ionization mass spectrometry (CSI-MS) measurement of the resulting EtOAc solution clearly detected [RuH(*p*-cymene)(C_3-Tunephos)]$^+$ and the anticipated dinuclear C_3-TunePhos–ruthenium complexes (Figure 6). The hydrogenation of **27a** was conducted by using [RuH(*p*-cymene)(C_3-TunePhos)]SbF_6 complex, but no reaction occurred (eq. 41). I estimate that these dinuclear complexes relate to the catalytically active ruthenium species.

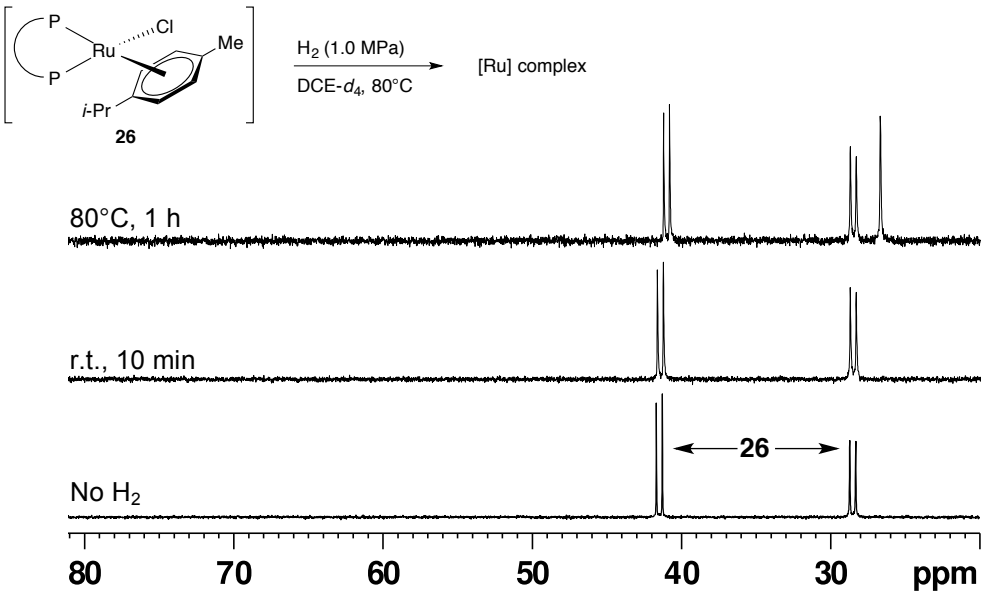


Figure 5. $^{31}P\{^{1}H\}$ NMR (162 MHz, $Cl(CD_2)_2Cl$) Experiment without 5% Rh/C

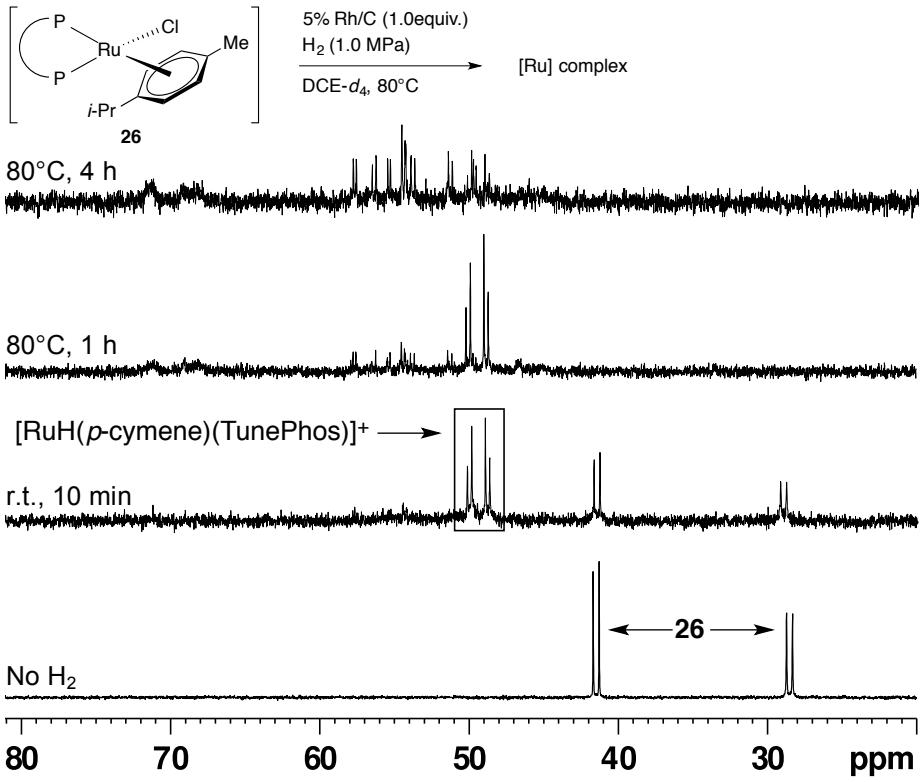


Figure 6. $^{31}P\{^{1}H\}$ NMR (162 MHz, $Cl(CD_2)_2Cl$) Experiment with 5% Rh/C

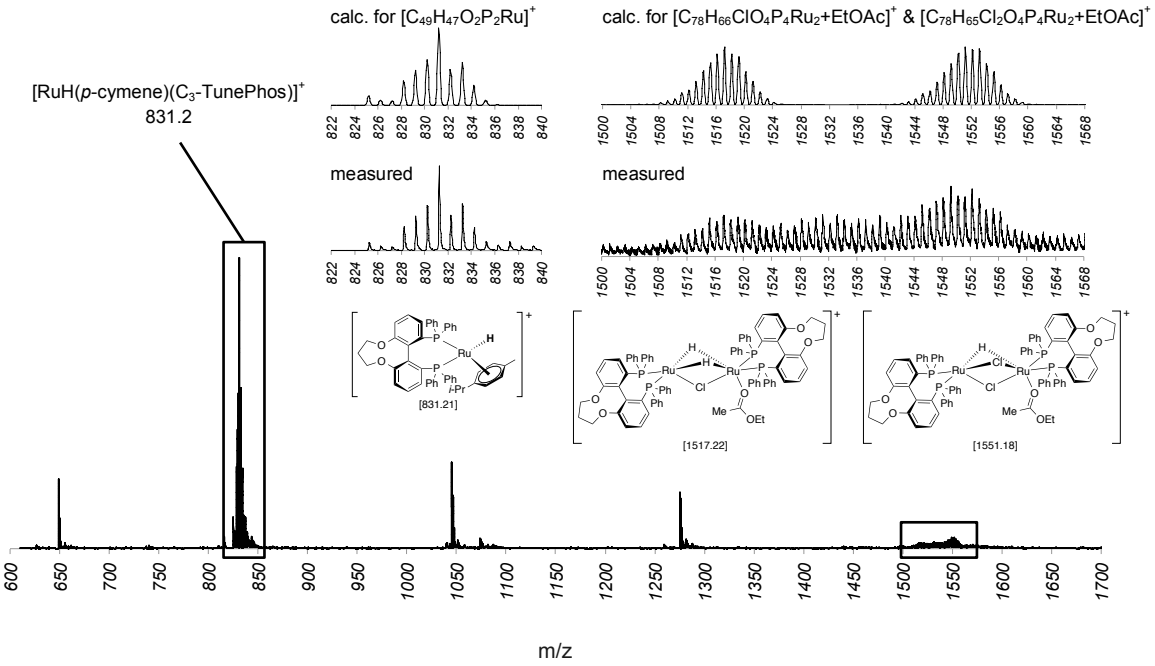
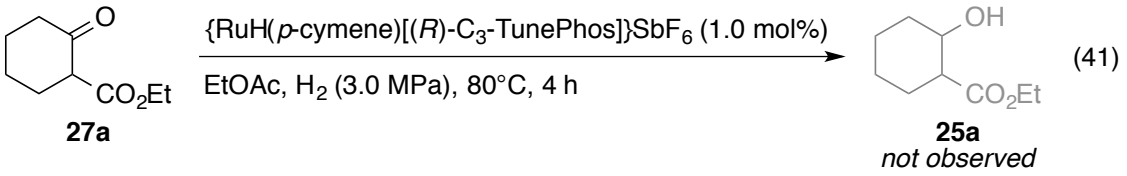
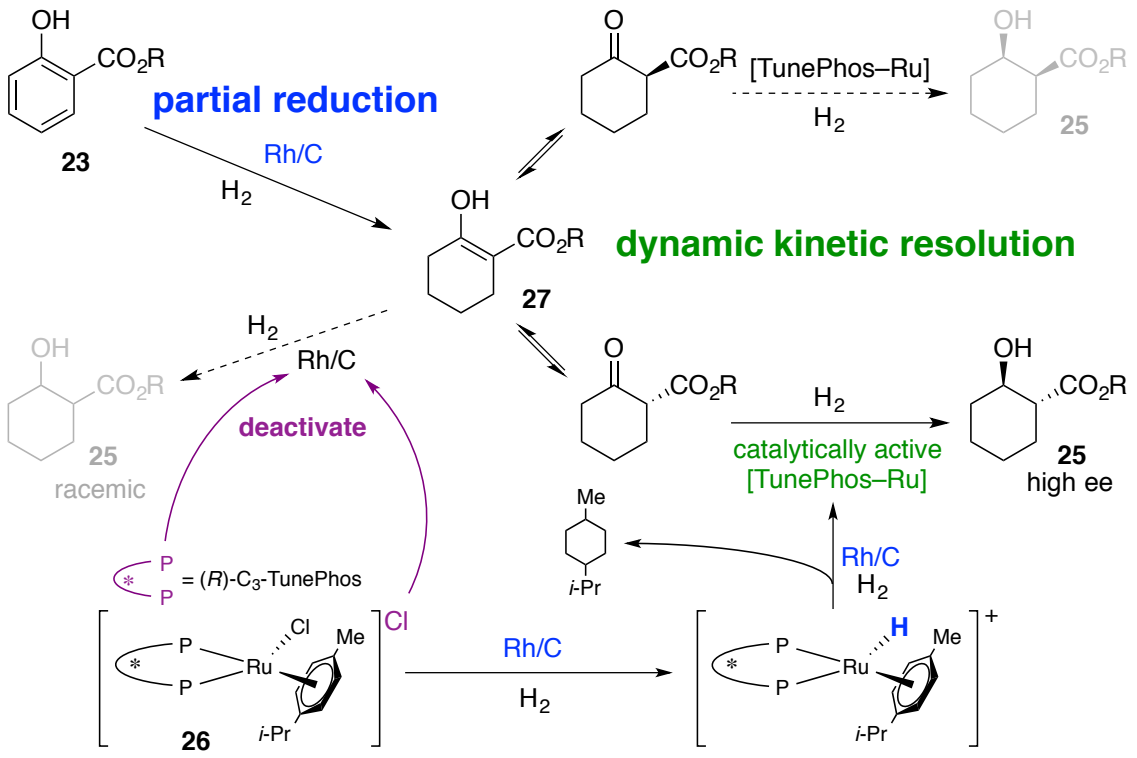


Figure 7. CSI-MS Spectrum of the Reacted Solution



27a **25a** *not observed* (41)

The plausible reaction pathways are shown in Scheme 13. First, rhodium on carbon partially reduces the benzene ring of salicylate to *β*-ketoester **27**. Then, chiral ruthenium catalyst stereoselectively hydrogenates **27** to *trans*-**25** through dynamic kinetic resolution. In addition, **27** was not reduced by rhodium on carbon because chloride or phosphine including in ruthenium catalyst **26** poisons rhodium catalyst. On the other hand, the rhodium on carbon accelerates to generate the catalytic active ruthenium species.



Scheme 13. Plausible Reaction Pathway

4.3. Conclusion

I developed the first high stereoselective catalytic asymmetric hydrogenation of benzene rings. Salicylic acid derivatives were hydrogenated stereoselectively catalyzed by the double catalyst system of rhodium on carbon and **26**, and converted to 2-hydroxycyclohexanecarboxylic acid derivatives with up to *trans*:*cis* = 91:9 and 92% ee (*trans*-isomer). The hydrogenation is very practical because the gram scale reaction proceeds without the decreasing stereoselectivity. Furthermore, optically active juvenile hormone analogue **28** was synthesized by using my reaction. From some experiments, it was disclosed that the two catalysts act cooperatively, not independently. Because rhodium on carbon poisoned by chloride ion including in **26** hardly proceeds the reduction of intermediate **27**, high stereoselectivity is realized in the reaction. In addition, SMC might activate **26** to reduce the arene ligand or/and generate the hydridoruthenium species quickly.

4.4. Experimental Section

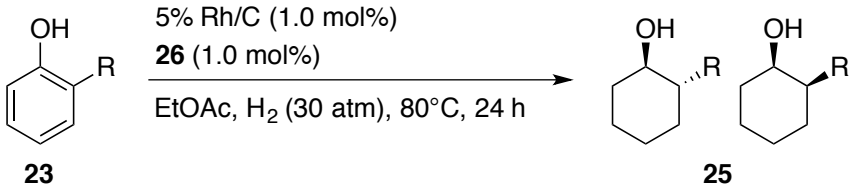
4.4.1 General and Materials

All NMR spectra were measured with Bruker AVANCE 400 or AVANCE III HD 400 Nanobay (9.4 T magnet) spectrometer at ambient temperature. In ^{1}H NMR spectra, chemical shifts (ppm) referenced to internal tetramethylsilane (0.00 ppm in $CDCl_3$). In ^{13}C NMR spectra, chemical shifts (ppm) referenced to the carbon signal of the deuterated solvents (77.0 ppm in $CDCl_3$, 40.0 ppm in DMSO-d_6). In ^{31}P NMR spectra, chemical shifts (ppm) referenced externally to 85% H_3PO_4 at 0 ppm. IR spectra and melting points were measured with JASCO FT/IR-4100 and Büchi Melting Point B-545, respectively. Cold spray ionization mass spectrometry (ESI) was measured with JMS-T100CS. Elemental analyses and high-resolution mass spectra (FAB) were performed by Service Centre of Elementary Analysis of Organic Compounds and Network Joint Research Center for Materials and Devices (Institute for Materials Chemistry and Engineering, Kyushu University), respectively. Flash column chromatographies and medium-pressure liquid chromatographies (MPLC) were performed with silica gel 60 (230–400 mesh, Merck) and C.I.G. pre-packed column CPS-223L-1 (Kusano, Tokyo, Japan), respectively.

2-Propanol (*i*-PrOH) and 1,2-dichloroethane (DCE) were dried with calcium hydride. Ethenol (EtOH) was dried with $Mg(OEt)_2$. Ethyl acetate (EtOAc) was dried with P_2O_5. Methylcyclohexane (CyMe) was dried with sodium and benzophenone ketyl radical. These solvents and reagents were distilled under nitrogen atmosphere. Tetrahydrofuran (THF) (HPLC grade, without inhibitor) was deoxidized by purging with nitrogen for 30 min and was dried with an alumina and copper column system (GlassContour). Dry diethyl ether (Et_2O, Kanto), dichloromethane (CH_2Cl_2, Kanto), distilled water (Wako) were purchased. *tert*-Butyl salicylate (**23d**),[16] *N*-ethyl salicylamide (**23f**),[17] *N*,*N*-diethyl salicylamide (**23g**),[18] diethyl (2-hydroxyphenyl)phosphonate (**23h**),[19] {RuCl(*p*-cymene)[(*R*)-BINAP]}$(DMF)_n$ (**24**),[20] *p*-benzyloxybromobenzene[21] were prepared according to literature procedures. (*R*)- and (*S*)-C_3-TunePhos, {RuCl(*p*-cymene)[(*R*)-C_3-TunePhos]} (**26**) were purchased from Aldrich. 5% Rh/C and $Sc(OTf)_3$ were purchased from TCI. Ethyl salicylate (**23a**), methyl salicylate (**23b**), isopropyl salicylate (**23c**), salicylic acid (**23e**), ethyl 2-oxocyclohexanecarboxylate (**27a**), methyl 2-methoxybenzoate (**39**), *N*,*O*-dimethylhydroxyamine hydrochloride (MeNHOMe·HCl), trimethylalminium (2M heptane solution), chlorodimethylether (MOMCl), diisopropylethyamine (*i*-Pr_2NEt), *p*-bromoanisole, *p*-toluenesulfonic acid monohydroxide (*p*-TsOH·H_2O), 18-crown-6, cyclopentyl methyl ether (CPME), and ethyl (2-chloroethyl)carbamete purchased and

used without further purification.

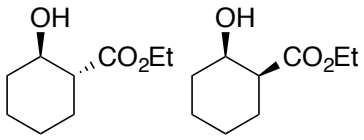
4.4.2. General Procesure for Catalytic Asymmetric Hydrogenation of Salicylic Acid Derivatives



23 **25**

5% Rh/C (9.1 mg, 2.0 μmol), **26** (1.8 mg, 2.0 μmol) and a stirring bar were placed in a 50 mL test tube, which was sealed with a rubber septum, and then the tube was evacuated and charged with nitrogen gas three times. Then EtOAc (1.0 ml) and substrate (0.20 mmol) were added. After the rubber septum was removed, the test tube was quickly inserted into a nitrogen-purged stainless autoclave, and then the autoclave was sealed immediately. Hydrogen gas was introduced into the autoclave until the pressure gauge indicated over 3.0 MPa, and then the pressure was carefully released to 0.1 MPa. This procedure was repeated twice, and finally the inside of the autoclave was pressurized with hydrogen to 3.0 MPa. After the mixture was stirred at 80 °C for 24 h, the autoclave was allowed to cool to room temperature. Excess hydrogen was released carefully, and then the resulting reaction mixture was evaporated under reduced pressure. The residue was analyzed with ^{1}H NMR spectrum in order to determine its composition, and then purified with a flash column chromatography (hexane/EtOAc) to give the desired product.

(–)-ethyl (1*R*,2*R*)-2-hydroxycyclohexane-1-carboxylate (*trans*-**25a**) [119068-36-9]
(–)-ethyl (1*S*,2*R*)-2-hydroxycyclohexane-1-carboxylate (*cis*-**25a**) [119068-37-0]



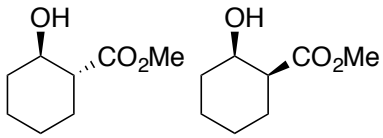
The general procedure was followed with use of ethyl salicylate (**23a**) (33.2 mg, 0.20 mmol). The crude product was purified with flash column chromatography (hexane/EtOAc = 1:1) after passed through a short silica gel column to give mixture of *trans*-**25a** and *cis*-**25a** (32.4 mg, 94%, *trans* : *cis* = 91:9 determined by GC) as colorless oil: $[\alpha]_D^{26}$ = –42.1 (*c* 1.051, $CHCl_3$) [lit.[22] $[\alpha]_D^{20}$ = +40.1 (c 1.0, $CHCl_3$) for the (*S*,*S*)

enantiomer]

trans-**25a**: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.14–1.43 (m, 7H), 1.66–1.84 (m, 1H), 1.96–2.12 (m, 1H), 2.25 (ddd, *J* = 3.8, 9.8, 12.3 Hz, 1H), 2.86 (d, *J* = 3.3 Hz, 1H), 3.70–3.84 (m, 1H), 4.18 (t, *J* = 7.1 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.2, 24.3, 25.1, 28.0, 33.6, 51.3, 60.6, 70.9, 175.3. *cis*-**25a**: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.20–1.38 (m, 4H), 1.38–1.54 (m, 2H), 1.60–1.79 (m, 2H), 1.79–1.98 (m, 2H), 1.66–1.84 (m, 1H), 1.96–2.12 (m, 1H), 2.48 (ddd, *J* = 2.7, 3.7, 11.2 Hz, 1H), 3.20 (dd, *J* = 1.4, 3.7 Hz, 1H), 4.08–3.24 (m, 4H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.2, 20.1, 24.0, 24.8, 31.7, 46.6, 60.6, 66.6, 176.

The enantiomeric excess of (–)-**25a** was determined to be 90% ee (*trans*-**25a**) and 24% ee (*cis*-**25a**) by GC analysis with CP-Chirasil-Dex CB, 110°C, detection, *cis*-**25a**: (+) t_1 = 26.1 min, (–) t_2 = 26.9 min, *trans*-**25a**: (+) t_1 = 31.7 min, (–) t_2 = 32.3 min.

(–)-methyl (1*R*,2*R*)-2-hydroxycyclohexane-1-carboxylate (*trans*-**25b**) [22436-30-2]
(–)-methyl (1*S*,2*R*)-2-hydroxycyclohexane-1-carboxylate (*cis*-**25b**) [13375-11-6]

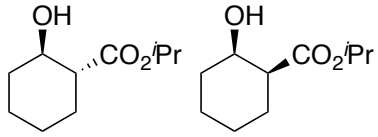


The general procedure was followed with use of methyl salicylate (**23b**) (61 mg, 0.40 mmol). The crude product was purified with flash column chromatography (hexane/EtOAc = 1:2) after passed through a short silica gel column to give mixture of *trans*-**25b** and *cis*-**25b** (62.7 mg, 99%, *trans* : *cis* = 89:11) as colorless oil: $[\alpha]_D^{26}$ = –42.4 (*c* 1.155, $CHCl_3$)

trans-**25b**: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.13–1.45 (m, 4H), 1.65–1.86 (m, 2H), 1.95–2.12 (m, 2H), 2.27 (ddd, *J* = 3.8 Hz, 9.8 Hz, 11.3 Hz, 1H), 5.23 (d, *J* = 2.5 Hz, 1H), 3.65–3.87 (m, 4H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 50 °C) δ 24.3, 25.0, 28.0, 33.6, 51.2, 51.8, 70.9, 175.7. *cis*-**25b**: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.19–1.38 (m, 1H), 1.38–1.58 (m, 2H), 1.58–1.78 (m, 3H), 1.78–1.99 (m, 2H), 2.50 (ddd, *J* = 2.7 Hz, 3.8 Hz, 11.1 Hz, 1H), 5.23 (d, *J* = 2.5 Hz, 1H), 3.71 (s, 1H), 4.06–4.24 (m, 4H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 50 °C) δ 20.0, 23.9, 24.7, 31.7, 46.6, 51.7, 66.7, 176.2.

The enantiomeric excess of (–)-**25b** was determined to be 93% ee (*trans*-**25b**) and 20% ee (*cis*-**25b**) by GC analysis with CP-Chirasil-Dex CB, 120°C, detection, *cis*-**25b**: (+) t_1 = 13.3 min, (–) t_2 = 13.8 min, *trans*-**25b**: (+) t_1 = 15.7 min, (–) t_2 = 15.9 min.

(–)-isopropyl (1*R*,2*R*)-2-hydroxycyclohexane-1-carboxylate (*trans*-**25c**)
(–)-isopropyl (1*S*,2*R*)-2-hydroxycyclohexane-1-carboxylate (*cis*-**25c**)

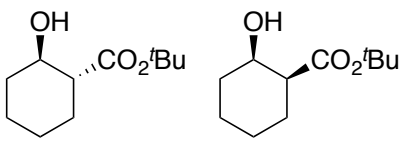


The general procedure was followed with use of isopropyl salicylate (**23c**) (36.0 mg, 0.20 mmol) for 36 h. The crude product was purified with flash column chromatography (hexane/EtOAc = 1:1) after passed through a short silica gel column to give mixture of *trans*-**25c** and *cis*-**25c** (34.0 mg, 91%, *trans* : *cis* = 86:14) as colorless oil: $[\alpha]_D^{26}$ = –39.2 (*c* 0.582, $CHCl_3$)

trans-**25c**: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.14–1.42 (m, 10H), 1.62–1.83 (m, 2H), 1.97–2.10 (m, 2H), 2.21 (ddd, *J* = 3.8, 9.8, 12.2 Hz, 1H), 2.89 (d, *J* = 3.1 Hz, 1H), 3.67–3.85 (m, 1H), 4.18 (qt, *J* = 6.3, 12.5 Hz, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 50 °C) δ 14.2, 24.3, 25.1, 28.0, 33.6, 51.3, 60.6, 70.9, 175.3.; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.76, 21.81, 24.3, 25.1, 28.0, 33.5, 51.4, 67.9, 70.9, 174.8. ; IR (neat) 3451, 2979, 2935, 2863, 1723, 1379, 1260, 1183, 1112 cm^{-1}.; Anal. Calcd for $C_{10}H_{18}O3$: C, 64.49; H, 7.74. Found: C, 64.45; H, 9.84.

The enantiomeric excess of (–)-**25c** was determined to be 83% ee (*trans*-**25c**) and 28% ee (*cis*-**25c**) by GC analysis with CP-Chirasil-Dex CB, 100°C, detection, *cis*-**25c**: (+) t_1 = 46.4 min, (–) t_2 = 47.1 min, *trans*-**25c**: (+) t_1 = 55.8 min, (–) t_2 = 56.6 min.

(–)-*tert*-butyl (1*R*,2*R*)-2-hydroxycyclohexane-1-carboxylate (*trans*-**25d**)
(–)-*tert*-butyl (1*S*,2*R*)-2-hydroxycyclohexane-1-carboxylate (*cis*-**25d**)

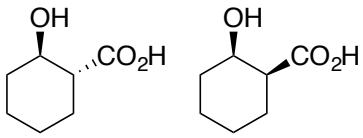


The general procedure was followed with use of *tert*-butyl salicylate (**23d**) (48.8 mg, 0.20 mmol) for 48 h. The crude product was purified with flash column chromatography (hexane/EtOAc = 1:1) after passed through a short silica gel column to give mixture of *trans*-**25d** and *cis*-**25d** (36.0 mg, 90%, *trans* : *cis* = 85:15) as colorless solid: $[\alpha]_D^{25} = -41.7$ (*c* 1.017, $CHCl_3$)

trans-**25d**: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.13–1.38 (m, 4H), 1.46 (s, 9H), 1.65–1.82 (m, 2H), 1.92–2.08 (m, 2H), 2.21 (ddd, *J* = 3.8, 9.8, 12.1 Hz, 1H), 2.96 (d, *J* = 2.1 Hz, 1H), 3.60–3.84 (m, 1H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 50 °C) δ 14.2, 24.3, 25.1, 28.0, 33.6, 51.3, 60.6, 70.9, 175.3.; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 24.4, 25.2, 28.1, 33.5, 52.0, 71.0, 80.9, 174.7. ; IR (neat) 3476, 2979, 2932, 2865, 1711, 1373, 1288, 1158, 1065 cm^{-1}; Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.57; H, 9.95.

The enantiomeric excess of (–)-**25d** was determined to be 89% ee (*trans*-**25d**) by GC analysis with CP-Chirasil-Dex CB, 120°C, detection, *trans*-**25d**: (+) t_1 = 24.1 min, (–) t_2 = 24.7 min.

(1*R*,2*R*)-2-hydroxycyclohexane-1-carboxylic acid (*trans*-**25e**)
(1*S*,2*R*)-2-hydroxycyclohexane-1-carboxylic acid (*trans*-**25e**)

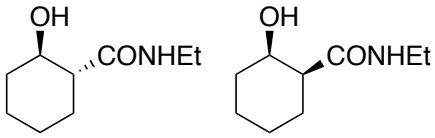


The general procedure was followed with use of salicylic acid (**23e**) (27.6 mg, 0.20 mmol). The residue (including *trans*-**25e** and *cis*-**25e**) was analyzed with ^{1}H NMR spectrum in order to determine its composition (36.0 mg, 90%, *trans* : *cis* = 39:61).: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ, 1.08–2.11 (m), 2.24–2.39 (m, 1H), 2.89 (br d, 1H), 3.56–3.70 (m, 1H), 3.70–3.86 (m, 1H), 4.19 (br 2H).

The enantiomeric excess of (–)-**25e** was determined to be 88% ee (*trans*-**25e**) and 75% ee (*cis*-**25e**) by GC analysis of its methyl ester derivatives (**25b**) (generated from the reaction with $TMSCHN_2$ in MeOH) with CP-Chirasil-Dex CB, 120°C, detection, *cis*-**25b**: (+) t_1 = 13.3 min, (–) t_2 = 13.8 min, *trans*-**25b**: (+) t_1 = 15.7 min, (–) t_2 = 15.9 min.

(–)-(1*R*,2*R*)-*N*-ethyl-2-hydroxycyclohexane-1-carboxamide (*trans*-**25f**)

(–)-(1*S*,2*R*)- *N*-ethyl-2-hydroxycyclohexane-1-carboxamide (*cis*-**25f**)



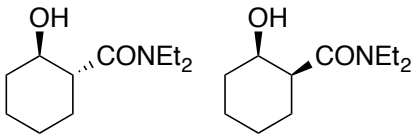
The general procedure (5.0 MPa) was followed with use of *N*-ethyl salicylamide (**23f**) (33.2 mg, 0.20 mmol) under 5.0 MPa of H_2. The crude product was purified with flash column chromatography (EtOAc/MeOH = 10:1) after passed through a short silica gel column to give mixture of *trans*-**25f** and *cis*-**25f** (33.7 mg, 98%, *trans* : *cis* = 56:44) as colorless solid: $[\alpha]_D^{25} = -31.8$ (*c* 1.033, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.15 (t, *J* = 3.8 Hz, 6H), 1.18–2.11 (m, 17H), 2.18 (ddd, *J* = 2.3, 3.7, 12.1 Hz, 1H), 3.35–3.44 (m, 5H), 3.77 (dd, *J* = 4.6, 10.1 Hz, 1H), 4.15 and 4.24 (brs and brs, 2H) 5.83 and 5.92 (brs and brs, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 50 °C) δ 14.7, 14.8, 19.5, 24.3, 24.7, 25.1, 25.7, 28.4, 29.7, 31.9, 34.1, 34.19, 34.25, 47.6, 52.0, 66.7, 71.2, 174.7, 176.2. ; IR (KBr) 3303, 3934, 2862, 1635, 1550, 1446, 1268 cm^{-1}; Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.13. Found: C, 63.32; H, 10.03; N, 7.96.

The enantiomeric excess of (–)-**25f** was determined to be 97% ee (*trans*-**25f**) and 75% ee (*cis*-**25f**) by GC analysis of its *O*-trifluoroacetate derivatives with CP-Chirasil-Dex CB, 120°C, detection, *cis*-**25f**: t_1 = 24.7 min, t_2 = 25.8 min, *transs*-**25f**: t_1 = 27.2 min, t_2 = 28.3 min.

(–)-(1*R*,2*R*)-*N*,*N*-diethyl-2-hydroxycyclohexane-1-carboxamide (*trans*-**25g**)

(–)-(1*R*,2*R*)-*N*,*N*-diethyl-2-hydroxycyclohexane-1-carboxamide (*cis*-**25g**)

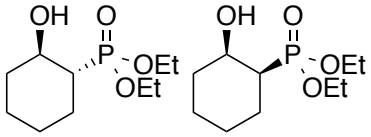


The general procedure was followed with use of *N*,*N*-diethyl salicylamide (**23g**) (38.7 mg, 0.20 mmol) under 5.0 MPa of H_2. The crude product was purified with flash column chromatography (EtOAc/MeOH = 10:1) after passed through a short silica gel column to give mixture of *trans*-**25g** and *cis*-**25g** (39.9 mg, >99%, dr = 68:32) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.15 (t, *J* = 3.8 Hz, 6H), 1.15–2.06 (m), 1.15 (t, *J* = 3.8 Hz, 1H (major)), 1.15 (t, *J* = 3.8 Hz, 1H (minor)), 2.52 (br),

3.16–3.60 (m), 3.89–4.03 (m, 1H (mojor)), 4.08 (brs, 1H (minor)), 5.52 (d, J = 2.5 Hz, 1H (minor)).; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 50 °C), major : δ 13.1, 14.7, 24.6, 25.3, 28.8, 33.3, 39.9, 41.5, 49.6, 71.4, 173.8., minor : δ 12.9, 14.8, 19.2, 23.9, 25.6, 31.9, 40.0, 42.0, 42.7, 66.2, 176.5,

The enantiomeric excess of (–)-**25g** was determined to be 42% ee (major) and 31% ee (minor) by GC analysis of its *O*-trifluoroacetate derivatives with CP-Chirasil-Dex CB, 130°C, detection, minor: t_1 = 36.0 min, t_2 = 36.9 min, major: t_1 = 50.4 min, t_2 = 53.2 min.

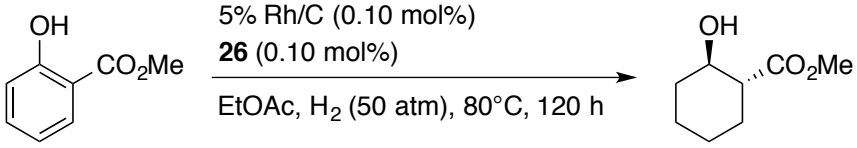
Diethyl-[(1*R*,2*R*)-2-hydroxycyclohexyl]phosphonate (*trans*-**25h**)
Diethyl-[(1*R*,2*R*)-2-hydroxycyclohexyl]phosphonate (*cis*-**25h**)



The general procedure (Method A, 5.0 MPa) was followed with use of diethyl (2-hydroxyphenyl)phosphonate (**23h**) (46 mg, 0.20 mmol) in EtOH under 5.0 MPa of H_2. The crude product was purified with flash column chromatography (EtOAc/MeOH = 10:1) to give a mixture of **25h** and unknown and inseparable side-product (46.4 mg) with 64:36 molar ratio. The yield of **25h** was estimated to be *ca.* 75%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.03–1.57 (m), 1.03–2.02 (m), 2.02–2.17 (m, 1H (major)), 3.44 (brs, 1H (minor)), 3.62–3.80 (m, 1H (major)), 4.01–4.24 (m), 4.24–4.32 (m, 1H (minor)), 4.36 (brs, 1H (minor)).; ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 16.3–16.6(m), 19.3 (d, J = 1.1 Hz (major)), 19.9 (d, J = 2.8 Hz (major)), 24.2 (d, J = 1.3 Hz (minor)), 25.1 (d, J = 5.9 Hz (minor)), 25.2 (d, J = 14.9 Hz (minor)), 25.7 (d, J = 15.8 Hz (major)), 32.4 (d, J = 14.0 Hz (major)), 34.5 (d, J = 15.5 Hz (minor)), 40.1 (d, J = 139.1 Hz (major)), 43.3 (d, J = 137.3 Hz (minor)), 61.8 (d, J = 7.0 Hz (major)), 62.1 (d, J = 6.9 Hz (major)), 64.5 (d, J = 6.0 Hz (major)), 68.8 (d, J = 5.9 Hz (minor)).; ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 31.8, 32.2.

The enantiomeric excess of **25h** was determined to be 77% ee (*trans*-**25h**) and 88% ee (*cis*-**25h**) by HPLC analysis of its *O*-Bz derivatives with Chiralpak AD-H (4.6 mm ϕ × Å~ 250 mm): 4% 2-propanol in hexane, 0.5 mL/min flow, 35 °C, UV 226 nm detection, *trans*-**25h**: t_1 = 46.9 min, t_2 = 53.7 min, *cis*-**25h**: t_1 = 50.8 min, t_2 = 61.4 min.

4.4.4. Gram-Scale Experiment



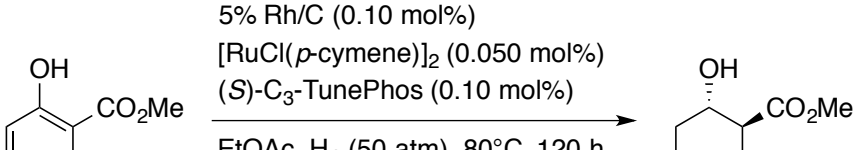
23b *trans*-**23b**

5% Rh/C (45.3 mg, 10.0 μmol), **26** (9.0 mg, 10.0 μmol) and a stirring bar were placed in a 50 mL test tube, which was sealed with a rubber septum, and then the tube was evacuated and charged with nitrogen gas three times. Then EtOAc (5.0 ml) and **23b** (1.52 g, 10 mmol) were added. After the rubber septum was removed, the test tube was quickly inserted into a nitrogen-purged stainless autoclave, and then the autoclave was sealed immediately. Hydrogen gas was introduced into the autoclave until the pressure gauge indicated over 5.0 MPa, and then the pressure was carefully released to 0.1 MPa. This procedure was repeated twice, and finally the inside of the autoclave was pressurized with hydrogen to 5.0 MPa. After the mixture was stirred at 80 °C for 120 h, the autoclave was allowed to cool to room temperature. Excess hydrogen was released carefully, and then the resulting reaction mixture was evaporated under reduced pressure. The residue was analyzed with ^{1}H NMR spectrum in order to determine its composition, and then purified with a flash column chromatography (hexane/EtOAc = 5:1 → 3:1) to give *trans*-**25b** (1.38 g, 87%) as colorless oil.

The enantiomeric excess of (–)-**25b** was determined to be 93% ee (*trans*-**25b**) and 18% ee (*cis*-**25b**) by GC analysis with CP-Chirasil-Dex CB, 120°C.

4.4.5. Synthesis of Juvenile Hormone Analogue **28** (Scheme 8 and 9)

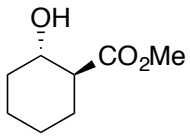
(+)-methyl (1*S*,2*S*)-2-hydroxycyclohexane-1-carboxylate (*ent-trans*-**25b**)



23b *ent-trans*-**23b**

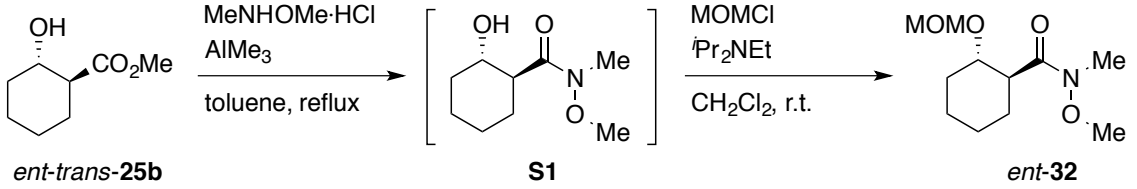
[RuCl(*p*-cymene)]$_2$ (3.2 mg, 5.0 μmol) and (*S*)-C$_3$-TunePhos (6.0 mg, 10 μmol) were placed in a 20 mL Schlenk flask, which was equipped with a stirring bar rubber septum, and two-way stopcock. Dry EtOH (0.80 mL) and dry CH_2Cl_2 (0.20 mL) was successively added into the Schlenk flask through the septum by using a

syringe. The catalyst solution was stirred for 1 h at 50°C, then the solvent was evaporated under reduce pressure. The residue was solved to EtOAc (5.0 mL). 5% Rh/C (45.7 mg, 10 μmol) and a stirring bar were placed in a 50 mL test tube, which was sealed with a rubber septum, and then the tube was evacuated and charged with nitrogen gas three times. The catalyst solution was transferred through a cannula into the test tube, then methyl salicylate (1.52 g, 10 mmol) was added. After the rubber septum was removed, the test tube was quickly inserted into a nitrogen-purged stainless autoclave, and then the autoclave was sealed immediately. Hydrogen gas was introduced into the autoclave until the pressure gauge indicated over 5.0 MPa, and then the pressure was carefully released to 0.1 MPa. This procedure was repeated twice, and finally the inside of the autoclave was pressurized with hydrogen to 5.0 MPa. After the mixture was stirred at 80°C for 120 h, the autoclave was allowed to cool to room temperature. Excess hydrogen was released carefully, and then the resulting reaction mixture was evaporated under reduced pressure. The residue was analyzed with ^{1}H NMR spectrum in order to determine its composition (*trans* : *cis* = 90:10), and then purified with a flash column chromatography (hexane/EtOAc = 5:1 → 3:1) to give *trans*-**25b** (1.38 g, 87%) as colorless oil.



The enantiomeric excess of (+)-**25b** was determined to be 93% ee (*trans*-*ent*-**25b**) and 18% ee (*cis*-*ent*-**25b**) by GC analysis with CP-Chirasil-Dex CB, 120°C, detection, (+) t_1 = 13.0 min, (–) t_2 = 13.5 min.

(*S*,*S*)-*N*,*O*-dimethyl-2-(methoxymethoxy)cyclohexanecarboxylic hydroxymate (*ent*-**32**)

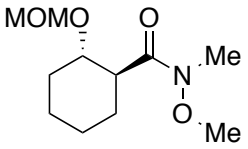


ent-*trans*-**25b** **S1** *ent*-**32**

To a suspension of *N*-methoxymethylamine hydrochloride (1.56 g, 16 mmol) in toluene (16 mL) at 0°C under an N_2 atmosphere, Me_3Al (2 M in heptane, 8.0 mL, 16 mmol) was slowly added via syringe. The ice bath was removed, and the solution was

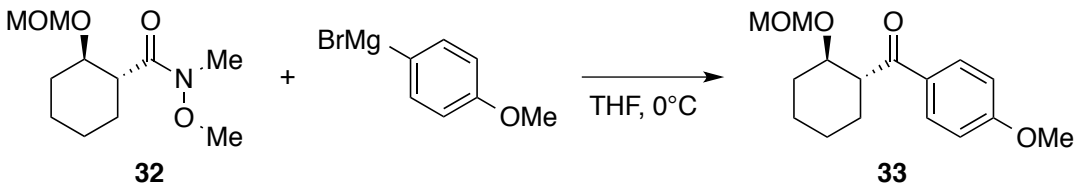
stirred at r.t. for 30 min. The solution was cooled to 0°C, *ent-trans*-**25b** (1.57 g, 8.0 mmol, 8.0 mL toluene solution) was slowly added via syringe and the resulting solution was allowed to reflux for 3 h. This reaction mixture was cooled to 0 °C and carefully quenched by slow addition of H_2O until a clear solution was formed. The layers were separated, the aqueous phase was extracted with Et_2O and three times with CH_2Cl_2. Then, 2 *N* NaOH *aq* was added to the aqueous phase and the solution was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, and then evaporated under reduced pressure. The residue, which contains a corresponding (*S*,*S*)-*N*,*O*-dimethyl-2-hydroxycyclohexanecarboxylic hydroxymate (**S1**) was used for the following reaction without further purification.

The above Weinreb amide **S1** and $^{i}Pr_2NEt$ (2.7 mL, 16 mmol) in CH_2Cl_2 (32 mL) was placed in a 100 mL two-neck flask, which was equipped with a stirring bar. MOMCl (1.2 mL, 16 mmol) was slowly added via syringe. The solution stirred at r.t. for overnight. After the reaction, the resulting mixture was diluted with distilled water, and then extracted three times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, and then evaporated under reduced pressure. The residue was passed through a short silica gel column (EtOAc). The residue, which contains *ent*-**32** (1.41 g, 76%) as colorless oil, was used for he following reaction without further purification.

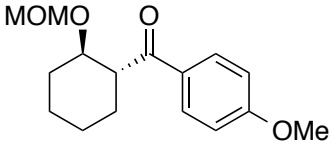


^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.14–1.41 (m, 3H), 1.49 (dq, *J* = 3.5 Hz, 12.6 Hz, 3H), 1.65–1.90 (m, 3H), 2.11–2.22 (m, 1H), 2.88 (br, 1H), 3.20 (s, 3H), 3.22 (s, 3H), 3.73 (s, 3H), 5.23 (d, *J* = 2.5 Hz, 1H), 3.80 (dt, *J* = 4.5 Hz, 10.4 Hz, 3H), 4.64 (s, 2H).

(*R*,*R*)-*N*,*O*-dimethyl-2-(methoxymethoxy)cyclohexanecarboxylic hydroxymate (**33**)

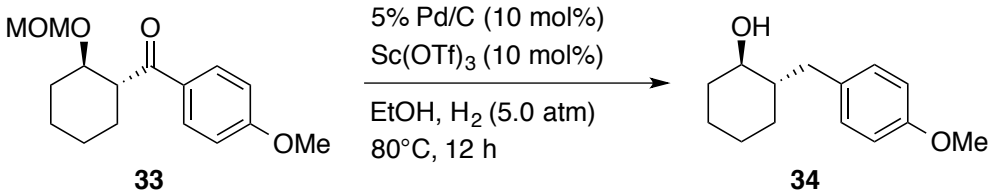


32 (prepared by the above procedure use of *trans*-**25b**, 694 mg, 3.0 mmol) and dry THF (3.0 mL) was placed in a 100 mL three-neck flask, which was equipped with a stirring bar and dropping funnel. The solution was cooled to 0°C, a THF solution of *p*-methoxyphenylmagnesium bromide (0.64 M, 9.5 mL, 6.1 mmol) was slowly added to the solution. The solution stirred at r.t. for 24 h. After the reaction, the resulting mixture was diluted with distilled *sat*. NH_4Cl *aq*, and then extracted three times with EtOAc. The combined organic layer was dried over Na_2SO_4, and then evaporated under reduced pressure. The residue was purified with a flash column chromatography (hexane/EtOAc = 10:1 → 5:1) to give **33** (607 mg, 73%) as colorless oil.



^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.22–1.53 (m, 4H), 1.67–1.93 (m, 3H), 2.15–2.19 (m, 1H), 2.94 (s, 3H), 3.40 (ddd, *J* = 3.7, 9.8, 12.1 Hz, 1H), 3.87 (s, 3H), 3.96 (dt, *J* = 4.5, 10.1 Hz, 1H), 4.57 (s, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 7.98 (d, *J* = 9.0 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 50 °C) δ 24.4, 25.1, 29.7, 32.3, 51.0, 55.3, 55.4, 95.7, 113.7, 130.4, 130.6, 163.4, 201.5. ; IR (neat) 2935, 1671, 1600, 1254, 1172, 1037 cm^{-1}; Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.78; H, 8.03.

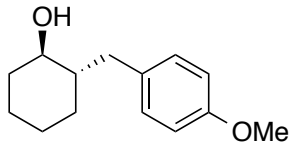
(1*R*,2*S*)-2-(*p*-Methoxybenzyl)cyclohexanol (**34**)



33 **34**

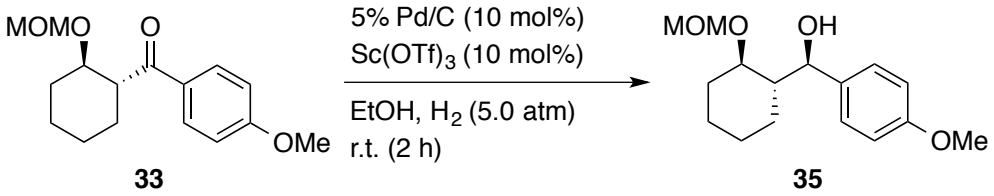
33 (35.8 mg, 0.10 mmol), 5% Pd/C (21.8 mg, 10 μmol), $Sc(OTf)_3$ (5.0 mg, 10 μmol) and a stirring bar were placed in a 50 mL test tube, which was sealed with a rubber septum, and then the tube was evacuated and charged with nitrogen gas three times. Then EtOH (0.50 ml) was added. After the rubber septum was removed, the test tube was quickly inserted into a nitrogen-purged stainless autoclave, and then the autoclave was sealed immediately. Hydrogen gas was introduced into the autoclave until the pressure gauge indicated over 0.5 MPa, and then the pressure was carefully

released to 0.1 MPa. This procedure was repeated ninth, and finally the inside of the autoclave was pressurized with hydrogen to 0.5 MPa. The mixture was stirred at 80°C for 12 h. After the reaction, the autoclave was allowed to cool to room temperature. Excess hydrogen was released carefully, the reaction mixture evaporated under reduced pressure. The crude product was purified with flash column chromatography (hexane/EtOAc = 3:1) to give **34** (30.3mg, 78%) as colorless solid.



^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.79–1.00 (m, 1H), 1.00–1.33 (m, 4H), 1.33–1.52 (m, 2H), 1.52–1.88 (m, 4H), 1.90–2.06 (m, 1H), 2.33 (dd, *J* = 9.0, 13.5 Hz, 1H), 3.07 (dd, *J* = 4.1, 13.5 Hz, 1H), 3.21–3.37 (m, 1H), 3.04 (s, 3H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 50 °C) δ 24.9, 25.4, 30.0, 35.8, 38.1, 47.1, 55.2, 74.5, 113.6, 130.3, 132.7, 157.8. ; IR (KBr) 3348, 3267, 2926, 2857, 1510, 1446, 1245, 1035, 822 cm^{-1}; Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15.

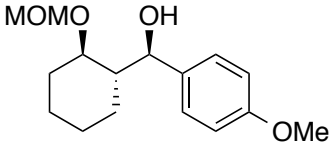
(*R*)-{(1*S*,2*R*)-2-(Methoxymethoxy)cyclohexyl}(4-methoxyphenyl)methanol (**35**)



33 **35**

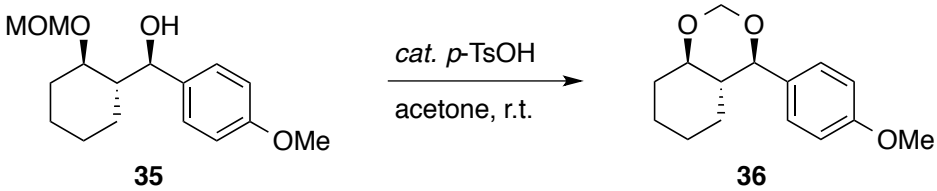
33 (29.6 mg, 0.11 mmol), 5% Pd/C (21.8 mg, 102 μmol), $Sc(OTf)_3$ (4.9 mg, 100 μmol) and a stirring bar were placed in a 50 mL test tube, which was sealed with a rubber septum, and then the tube was evacuated and charged with nitrogen gas three times. Then EtOH (1.0 ml) was added. After the rubber septum was removed, the test tube was quickly inserted into a nitrogen-purged stainless autoclave, and then the autoclave was sealed immediately. Hydrogen gas was introduced into the autoclave until the pressure gauge indicated over 0.5 MPa, and then the pressure was carefully released to 0.1 MPa. This procedure was repeated ninth, and finally the inside of the autoclave was pressurized with hydrogen to 0.5 MPa. The mixture was stirred at r.t. for 2 h. After the reaction, the autoclave was allowed to cool to room temperature. Excess

hydrogen was released carefully, the reaction mixture was diluted with 2 *N* NaOH aq, and then extracted three times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, and then evaporated under reduced pressure to give **35** (30.1 mg, 101%) as colorless solid.



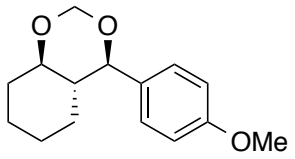
^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.74 (dq, *J* = 3.7, 12.6 Hz, 1H), 0.92–1.35 (m, 5H), 1.44–1.60 (m, 2H), 1.55–1.80 (m, 2H), 2.14–2.25 (m, 2H), 3.48 (s, 3H), 3.65 (dt, *J* = 4.0, 10.1 Hz, 1H), 3.80 (s, 3H), 4.56 (d, *J* = 8.4 Hz, 1H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.80 (s, 1H), 4.92 (d, *J* = 6.9 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 50 °C) δ 24.6, 25.1, 28.2, 31.6, 49.7, 55.2, 56.2, 79.5, 82.594.3, 113.5, 128.3, 135.0, 159.0. ; IR (KBr) 3455, 2933, 2866, 16.8, 1509, 1246, 1036, 904. cm^{-1}; Anal. Calcd for $C_{16}H_{22}O_4$: C, 68.55; H, 8.63. Found: C, 68.63; H, 8.72.

(4*R*,4a*R*,8a*R*)-4-(4-Methoxyphenyl)hexahydrobenzodioxine (**36**)



35 **36**

35 (14.7 mg, 52 μmol), *p*-TsOH·H_2O (1.0 mg, 5.3 μmol) and a stirring bar were placed in a 10 mL Schlenk tube, which was sealed with a rubber septum, and then the tube was evacuated and charged with nitrogen gas three times. Then dry acetone (1.0 ml) was add. The solution stirred at r.t. for 11.5 h. After the reaction, the resulting mixture evaporated under reduced pressure. The residue was purified with a flash column chromatography (hexane/EtOAc = 10:1 → 5:1) to give **36** (5.5 mg, 42%) as colorless solid.



^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.87 (dq, *J* = 3.8, 12.7 Hz, 1H), 1.14 (tq, *J* = 3.7, 12.7 Hz, 1H), 1.20–1.28 (m, 1H), 1.34 (tq, *J* = 3.5, 12.8 Hz, 1H), 1.40–1.51 (m, 1H), 1.55–1.69 (m, 2H), 1.75–1.86 (m, 1H), 1.94–2.04 (m, 1H), 3.37 (ddd, *J* = 4.0, 9.8, 10.7 Hz, 1H), 3.80 (s, 3H), 4.15 (d, *J* = 9.9 Hz, 1H), 4.97 (d, *J* = 6.3 Hz, 1H), 5.21 (d, *J* = 6.3 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H). ; IR (KBr) 3439, 2926, 2846, 1616, 1517, 1453, 1254, 1162, 1086, 1030, 826 cm^{-1}; Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.28; H, 8.23.

The results of the ^{1}H NMR analysis of **36** were summarized in Figure S-4. The coupling constants indicate that the relative configuration of **36** is all *anti*. Because **36** was synthesized from *trans*-**25b**, the absolute configuration at benzylic position of **36** is *R*.

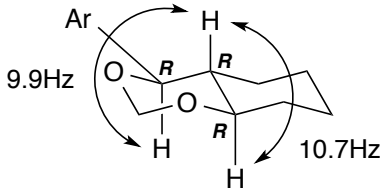
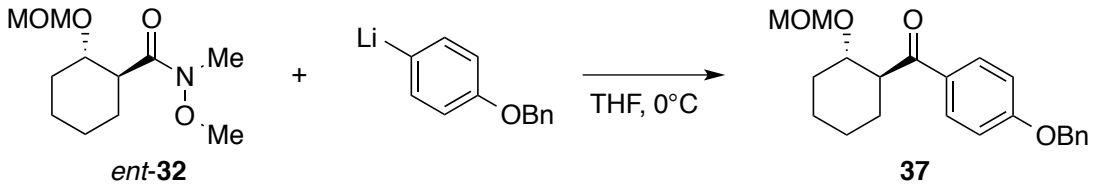


Figure S-4. Coupling conctant of **36**.

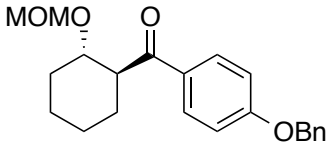
(+)-[4-(Benzyloxy)phenyl][(1*S*,2*S*)-2-(methoxymethoxy)cyclohexyl]methanone (**37**)



ent-**32** **37**

To a suspension of 1-(benzyloxy)-4-bromobenzene (4.34 g, 16.5 mmol) in Et_2O (50 mL) was placed in a 100 mL three-neck flask, which was equipped with a stirring bar and dropping funnel. The solution was cooled to -80°C, *tert*-BuLi (1.6 M, 9.4 mL, 15 mmol) was slowly added to the solution. The solution stirred at -80°C for 1 h, then this solution warm to 0°C. *ent*-**33** (1.16 g, 5.0 mmol) was slowly added to the solution, and then the mixture was stirred at 0 °C for 2.5 h. After the reaction, the resulting mixture was diluted with distilled *sat*. NH_4Cl *aq*, and then extracted three

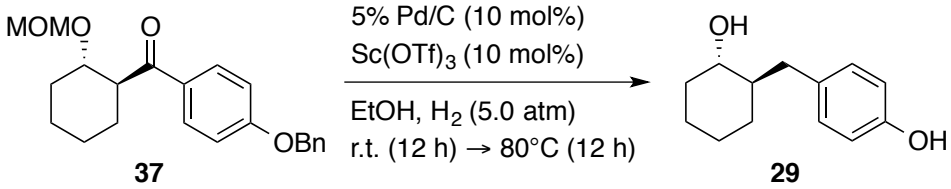
times with EtOAc. The combined organic layer was dried over Na_2SO_4, and then evaporated under reduced pressure. The residue was purified with a flash column chromatography (hexane/EtOAc = 10:1 → 5:1) to give **37** (1.55 g, 87%) as colorless oil: $[\alpha]_D^{28}$ = +13.4 (*c* 1.02, $CHCl_3$).



^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.20–1.41 (m, 3H), 1.46 (dq, *J* = 3.3, 12.9 Hz, 3H), 1.68–1.77 (m, 1H), 1.77–1.93 (m, 2H), 2.17–2.29 (m, 1H), 3.21 (s, 3H), 3.39 (ddd, *J* = 3.7, 9.8, 12.1 Hz, 1H), 2.97 (dt, *J* = 4.5, 15.0 Hz, 1H), 4.56 (s, 2H), 5.13 (s, 3H), 5.19 (d, *J* = 9.0 Hz, 2H), 7.29–7.28 (m, 5H), 5.19 (d, *J* = 9.0 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 50 °C) δ 24.4, 25.1, 29.7, 32.2, 51.0, 55.3, 70.1, 95.7, 114.5, 127.5, 128.2, 128.7, 130.7, 136.2, 162.5, 201.5.; IR (neat) 3510, 2935, 1671, 1578, 1374, 1319, 1249, 1215, 1168, 1035 cm^{-1}; Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.44; H, 7.37.

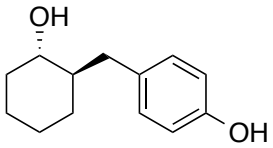
The enantiomeric excess of (+)-**37** was determined to be 92% ee by HPLC analysis with Chiralpak ID (4.6 mm ϕ × Å~ 250 mm): 10% 2-propanol in hexane, 0.5 mL/min flow, r.t., UV 280 nm detection, (+) t_1 = 25.4 min, (–) t_2 = 29.1 min.

(+)-(1*R*,2*S*)-2-(4-Hydroxybenzyl)-1-cyclohexanol (**29**) [150821-13-9]



37 (178 mg, 0.50 mmol), 5% Pd/C (106 mg, 50 μmol), $Sc(OTf)_3$ (25 mg, 50 μmol) and a stirring bar were placed in a 50 mL test tube, which was sealed with a rubber septum, and then the tube was evacuated and charged with nitrogen gas three times. Then EtOH (2.0 ml) was added. After the rubber septum was removed, the test tube was quickly inserted into a nitrogen-purged stainless autoclave, and then the autoclave was sealed immediately. Hydrogen gas was introduced into the autoclave until the pressure gauge indicated over 0.5 MPa, and then the pressure was carefully released to 0.1 MPa. This procedure was repeated ninth, and finally the inside of the

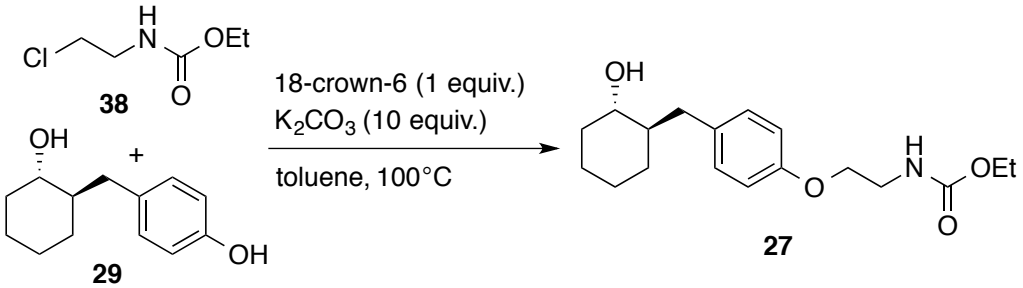
autoclave was pressurized with hydrogen to 0.5 MPa. The mixture was stirred at r.t. for 12 h, then 80°C for 12 h. After the reaction, the autoclave was allowed to cool to room temperature. Excess hydrogen was released carefully, the reaction mixture was diluted with 2 *N* HCl aq, and then extracted three times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, and then evaporated under reduced pressure. The crude product was purified with flash column chromatography (hexane/EtOAc = 5:1 → 3:1) to give **27** (86.5 mg, 84%) as colorless solid: $[\alpha]_D^{28}$ = +45.0 (*c* 1.02, $CHCl_3$) [lit[9] $[\alpha]_D^{24}$ = +55.93].



^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.89 (ddd, *J* = 3.4, 12.7, 24.5 Hz, 5H), 1.09 (tdd, *J* = 3.4, 12.5, 25.3 Hz, 1H), 1.17–1.34 (m, 2H), 1.36–1.79 (m, 4H), 1.90–2.03 (m, 1H), 2.33 (dd, *J* = 8.9, 13.5 Hz, 1H), 3.06 (dd, *J* = 4.1, 13.5 Hz, 1H), 3.26 (dq, *J* = 9.7, 11.2 Hz, 1H), 6.75 (d, *J* = 8.6 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 50 °C) δ 24.9, 25.4, 30.0, 35.8, 38.1, 47.1, 74.6, 115.0, 130.4, 132.7, 153.6.

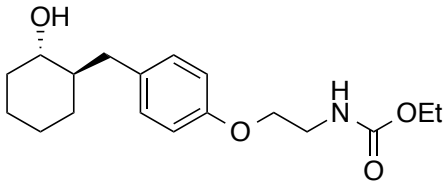
The enantiomeric excess of (+)-**29** was determined to be 94% ee by HPLC analysis with Chiralcel OD-H (4.6 mm ϕ × Å~ 250 mm): 30% 2-propanol in hexane, 0.5 mL/min flow, 35 °C, UV 280 nm detection, (–) t_1 = 12.0 min, (+) t_2 = 14.3 min.

(+)-Ethyl [2-(4-{[(1*R*,2*S*)-2-hydroxycyclohexyl]methyl}phenoxy)ethyl]carbamate (**28**) [158703-38-9]



To a suspension of **29** (62.2 mg, 0.30 mmol), 18-crown-6 (79 mg, 0.30 mmol) and dry K_2CO_3 (415 mg, 3.0 mmol) in toluene (12 mL) was placed in a 100 mL three-neck flask, which was equipped with a stirring bar and Dimroth condenser.

After the suspension was heated to 100°C, **38** (45 mg x 4, 1.2 mmol) was added separately to the solution. The solution stirred at 100°C for overnight, after the reaction, the reaction mixture was diluted with distilled water, and then extracted three times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, and then evaporated under reduced pressure. The crude product was purified with flash column chromatography (CH_2Cl_2/EtOAc = 4:1) to give ethyl **28** (80.4 mg, 83%) as colorless solid: $[\alpha]_D^{28}$ = +24.5 (*c* 0.962, $CHCl_3$) [*lit.*[23] $[\alpha]_D^{24}$ = +16.35 (*c* 0.65, $CHCl_3$)]



^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.82–0.96 (m, 1H), 1.01–1.16 (m, 1H), 1.16–1.35 (m, 5H), 1.35–1.51 (m, 2H), 1.56–1.79 (m, 3H), 1.91–2.03 (m, 1H), 2.33 (dd, *J* = 9.0, 13.5 Hz, 1H), 3.07 (dd, *J* = 4.0, 13.5 Hz, 1H), 3.28 (ddd, *J* = 4.9, 4.9, 9.7 Hz, 1H), 3.57 (q, *J* = 5.3 Hz, 2H), 4.01 (t, *J* = 5.1 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 1H), 5.10 (brs, 1H), 6.80 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$, 50 °C) δ 14.6, 24.9, 25.4, 30.0, 35.8, 38.0, 40.5, 47.1, 60.9, 67.0, 74.5, 114.2, 130.4, 133.2, 156.7.

4.4.5. GC Detection of *p*-Cymene (Figure 4).

26 (7.2 mg, 8.0 μmol) (and 5% Rh/C (36.4 mg, 8.0 μmol)) and a stirring bar were placed in a 50 mL test tube, which was sealed with a rubber septum, and then the tube was evacuated and charged with nitrogen gas three times. Then EtOAc (1.0 ml) and tetradecane (5.0 mg, internal standard) were added. After the rubber septum was removed, the test tube was quickly inserted into a nitrogen-purged stainless autoclave, and then the autoclave was sealed immediately. Hydrogen gas was introduced into the autoclave until the pressure gauge indicated over 3.0 MPa, and then the pressure was carefully released to 0.1 MPa. This procedure was repeated twice, and finally the inside of the autoclave was pressurized with hydrogen to 3.0 MPa. After the mixture was stirred at 80 °C for 1 h, the autoclave was allowed to cool to room temperature. Excess hydrogen was released carefully, and the reacted solution passed through a short Celite® and silica gel column to be analyzed by GC.

The analysis was determined by GC analysis with InertCap 5 (0.25 mm I.D. × 60 m, df = 0.25 μm): N_2 (180 kPa), 150°C for 10 min, then 150°C–250°C at 40°C/min, injector: split (280°C), Detector: FID (280°C)

4.4.6. NMR Experiment (Figure 5 and 6).

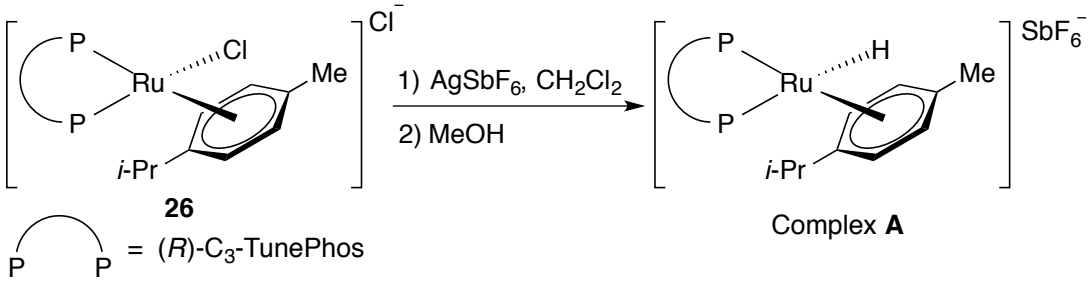
1,2-dichloroethane-d_4 (0.50 ml) was added to the NMR tube with **26** (9.1 mg, 2.0 μmol) (and 5% Rh/C (45.5 mg, μmol)). Then NMR analysis was attempted to the solution under air. Hydrogen gas was introduced into the NMR tube until the pressure gauge indicated over 1.0 MPa, and then the pressure was carefully released to 0.1 MPa. This procedure was repeated four times, and finally the inside of the NMR tube was pressurized with hydrogen to 1.0 MPa. After the NMR analysis under room temperature, the mixture was stirred at 80 °C. NMR analysis was tried after 1 h, 2 h, and 4 h.

4.4.7. CSI-MS Analysis (Figure 7).

5% Rh/C (9.1 mg, 2.0 μmol), **26** (1.8 mg, 2.0 μmol) and a stirring bar were placed in a 50 mL test tube, which was sealed with a rubber septum, and then the tube was evacuated and charged with nitrogen gas three times. Then EtOAc (1.0 ml) was added. After the rubber septum was removed, the test tube was quickly inserted into a nitrogen-purged stainless autoclave, and then the autoclave was sealed immediately. Hydrogen gas was introduced into the autoclave until the pressure gauge indicated over 3.0 MPa, and then the pressure was carefully released to 0.1 atm. This procedure was repeated twice, and finally the inside of the autoclave was pressurized with hydrogen to 3.0 MPa. After the mixture was stirred at 80 °C for 2 h, the autoclave was allowed to cool to room temperature. Excess hydrogen was released carefully, and the reacted solution passed through a membrane filter to be analyzed by CSI-MS.

4.4.8. The Fydrogenation of β-Ketoester Catalyzed by {RuH(*p*-cymene)-[(*R*)-C_3-TunePhos]}SbF_6 (Complex **A**).

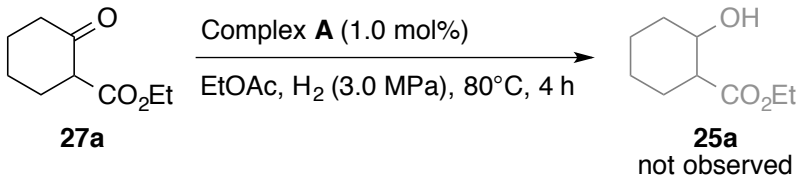
4.4.8.1 Synthesis of Complex **A**



26 (776 mg, 0.025 mmol) and $AgSbF_6$ (17.6 mg, 0.051 mmol) were placed in a 20 mL two-neck flask, which was equipped with a stirring bar, and rubber septum. CH_2Cl_2 (2.0 mL) was added into the flask, and then the solution was stirred under r.t. for 1 h. MeOH (1.0 mL) was added into the orange solution, and then the solution was stirred under r.t. for 1 h. The reaction mixture passed through Celite®, then evaporated under reduced pressure. The residue containing {RuH(*p*-cymene)[(*R*)-C_3-TunePhos]}SbF_6 (27.7 mg) was used for the following reaction without further purification.

^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 0.79 (d, 3H), 1.20 (d, 3H), 1.50–1.60 (m, 2H), 2.02 (s, 3H), 2.36 (quintet, 1H), 3.64 (d, 1H), 3.80–4.03 (m, 4H), 4.16 (d, 1H), 6.03 (d, 1H), 6.41 (d, 1H), 6.50 (d, 1H), 6.93–7.62 (m, 25H).

4.4.8.2 The Hydrogenation of *β*-Ketoester Catalyzed by Complex **A** (eq. 41).



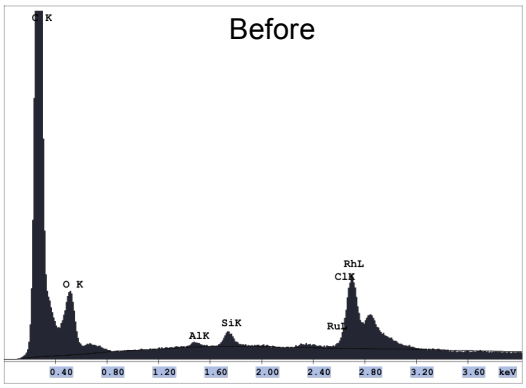
27a → **25a** not observed

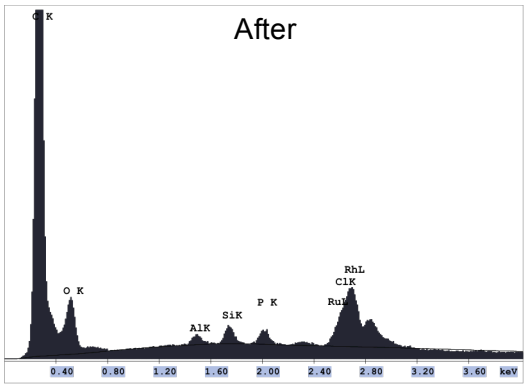
5% Rh/C (9.1 mg, 2.0 μmol), Complex **A** (2.2 mg, 2.0 μmol) and a stirring bar were placed in a 50 mL test tube, which was sealed with a rubber septum, and then the tube was evacuated and charged with nitrogen gas three times. Then EtOAc (1.0 ml) and **27** (34.1 mg, 0.20 mmol) were added. After the rubber septum was removed, the test tube was quickly inserted into a nitrogen-purged stainless autoclave, and then the autoclave was sealed immediately. Hydrogen gas was introduced into the autoclave until the pressure gauge indicated over 3.0 MPa, and then the pressure was carefully released to 0.1 MPa. This procedure was repeated twice, and finally the inside of the

autoclave was pressurized with hydrogen to 3.0 MPa. After the mixture was stirred at 80 °C for 4 h, the autoclave was allowed to cool to room temperature. Excess hydrogen was released carefully, and then the resulting reaction mixture was evaporated under reduced pressure. The residue was analyzed with ^{1}H NMR spectrum in order to determine its composition.

4.4.9. Synthesis of SEM Sample.

5% Rh/C (45.5 mg, μmol), **27** (9.1 mg, 2.0 μmol) and a stirring bar were placed in a 50 mL test tube, which was sealed with a rubber septum, and then the tube was evacuated and charged with nitrogen gas three times. Then $(CH_2Cl)_2$ (5.0 ml) and **12b** (1.52 g, 10 mmol) were added. After the rubber septum was removed, the test tube was quickly inserted into a nitrogen-purged stainless autoclave, and then the autoclave was sealed immediately. Hydrogen gas was introduced into the autoclave until the pressure gauge indicated over 5.0 MPa, and then the pressure was carefully released to 0.1 MPa. This procedure was repeated twice, and finally the inside of the autoclave was pressurized with hydrogen to 5.0 MPa. After the mixture was stirred at 80 °C for 120 h, the autoclave was allowed to cool to room temperature. Excess hydrogen was released carefully, and the test tube was quickly sealed with a rubber septum connected with N_2 line and a bubbler. The resulted solution was diluted with $(CH_2Cl)_2$ (5.0 ml) then stirred for 5 min. After standing, a supernatant was removed through a cannula. This washing procedure was repeated until the color of solution disappeared (~four times), and finally the insoluble residue was filtrated and dried under reduced pressure. This sample was analyzed by SEM-EDX without further purification. SEM-EDX was measured with SU6000.





	C	O	Al	Si	P	Ru	Cl	Rh
before	81.95%	15.87%	0.14%	0.41%	0%	0%	0.08%	1.57%
after	85.58%	11.93%	0.22%	0.36%	0.30%	0.03%	0.65%	0.93%

Figure S-5. Analysis of DEX

The results of the SEM-EDX analysis was summarized in Figure S-5. The sample analysed at 4 spot under × 80. Elemental values are average of 4 spots. Clorine and phosphorus were observed in the reaction residue. However, ruthenium was also detected in same sample. In addition, the peaks of rhodium, ruthenium, and chlorine overlap. So, it would not be a proof that rhodium was poisoned by chloride or phosphine.

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Chapter 5

Conclusion

Catalytic asymmetric hydrogenation of heteroarenes and arenes has been developed in the world. However, many aromatics have been remained as targets of the asymmetric hydrogenation. I researched the catalytic asymmetric hydrogenation of the heteroarenes and arenes, which had not been hydrogenated with high enantioselectivity yet. Consequently, I developed the first catalytic asymmetric hydrogenation of isoxazole rings and benzene rings.

3-Substituted benzisoxazoles were hydrogenated to α-substituted *N*-protected *o*-hydroxybenzylamines catalyzed by PhTRAP–ruthenium catalyst in the presence of an acylating agent with up to 57% ee. The reaction firstly proceed through the hydrogenolysis of N–O bond of benzisoxazole, and gives *o*-hydroxyphenyimine. Then, the C–N double bond of imine is hydrogenated with moderate enantioselectivity by the PhTRAP–ruthenium catalyst. Although the resulting primary amine is poison of the ruthenium catalyst, rapid acylation of amino group avoids the deactivation of the catalyst.

I also achieved the first high enantioselective hydrogenation of isoxazole rings without the hydrogenolysis of N–O bond. Isoxazolium salts, which are generated from the reaction of isoxazoles and alkyl triflates, are hydrogenated by PHOX–iridium–iodine catalyst system. 5-arylated isoxazoliums are converted to optically active 4-isoxazolines with up to 90% ee, and 5-alkylated substrates are selectively converted to *cis*-isoxazolidines with up to 76% ee. Isoxazolidines are gave from 3-isoxazolines produced through 1,4-reduction of the substrates while 4-isoxazoline was produced by hydrogenation of C–N double bond.

In contrast to heteroarenes, the asymmetric hydrogenation of carbocyclic arenes remains a formidable issue in organic chemistry. Only three reports are known. In addition, high stereoselective asymmetric hydrogenation of aromatic mono-carbocycles (benzene rings) has not been reported yet. In Chapter 4, I succeeded in the first high stereoselective catalytic hydrogenation of benzene rings. Salicylic acid derivatives were stereoselectively hydrogenated in combinational using rhodium on carbon and C_3-TunePhos–ruthenium complex as catalysts, and transformed to 2-hydroxycyclohexanecarboxylic acid derivatives with up to *trans*:*cis* = 91:9 and 92% ee of *trans*-isomer. This hydrogenation proceeds with good stereoselectivity even a gram scale. Furthermore, I synthesized juvenile hormone analogue from the product of the hydrogenation. From the mechanistic studies, I disclosed that the two

catalysts act concertedly. Chloride ion including in the ruthenium catalyst impedes the reduction of β-ketoester by rhodium catalyst, and supported metal catalyst activated the ruthenium catalyst.

Acknowledgement

This research was carried out under the supervision of professor Ryoichi Kuwano in Department of Chemistry, Graduate school Science, Kyushu University.

First, I would like to express his utmost gratitude to Prof. Kuwano. It is a wonderful opportunity for me to join the laboratory and study on interesting, exciting and challenging chemistry. During the research, Prof. Kuwano always supported, encouraged and guided the author to be a scientist. His enthusiasm for chemistry always impressed me. Without his countless discussions, instructive suggestions and kind encouragement, the study would never have been accomplished. I do feel fortunate.

I also would like to appreciate to committee members, propessors, Prof. Makoto Tokunaga, and Prof. Tohru Oishi. I am deeply grateful to associate professor Dr. Yoshio Ito and Dr. Tatsuya Uchida for his kind advices.

Gratitude is also due the laboratory staffs. Assistant professor Dr. Satoshi Ueno, he had often helped me for the technical and experimental issues and taught me a lot of scientific topics in the same room for four years since the author became the laboratory member. I also would like to express appreciation to assistant professor Dr. Kentaro Ishizuka. He had always offered constructive suggestion for the experiment. I am deeply grateful to assistant professor Dr. Yusuke Makida. He has always supported my study and discussed lot of scientific topics in the same room for a year.

Without collaborators, the results in the thesis have never been achieved. I would like to express the deepest appreciation to Ms. Nao Kameyama, who researched the catalytic asymmetric hydrogenation of imidazoles and oxazoles in collaboration with me. I researched with her only 2 years in the laboratory, but received considerable and precious advice from her. I also would like to appreciate to Mr. Yuta Hashiguchi, who researched the catalytic asymmetric hydrogenation of pyrimidines with me. His careful, patient experiments and very active discussions with me were definitely essence to achieve the study. I also thankful to Ms. Kayoko Ogi, Mr. Akiharu Abe, Mr. Satoshi Kobayashi, Mr. Takahiro Nakagawa, and Mr. Yuichi Hirano of the Service Center of Elemental Analysis. Kyushu University.

My six years laboratory life was fulfilled thanks to all laboratory members, respectable seniors: Mr. Kazuki Hirasada, who researched the catalytic asymmetric hydrogenation of quinoline carbocycles, Mrs. Kazumi Takai, Mr. Sadakazu Komiya, Mr. Ryosuke Shimizu, Mr. Ryohei Maeda, and Mr. Takeshi Tanaka. The same year

labmates; Ms. Mika Kawabuchi, Mr. Yuji Takagaki, Mr. Wataru Niho, and Mrs. Marie Hamano. Brilliant juniors: Mr. Shohei Yasuoka, Mr. Yushu Jin, and Mr. Masahiro Saita. I would like to express gratitude to all them.

Financial support from the *Research Fellowship of the Japan Society for Promotion of Science for Young Scientists* is gratefully acknowledged.

Finally, I would acknowledge his parents Naoaki and Kazumi, brother Shuhei for their affectionate supports and thoughtful encouragement.

Ryuhei Ikeda

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