ChemPubSoc Europe

DOI: 10.1002/chem.201600732

CHEMISTRY A European Journal Full Paper

Synthetic Methods |*Hot Paper*|

Asymmetric Hydrogenation of Isoxazolium Triflates with a Chiral Iridium Catalyst

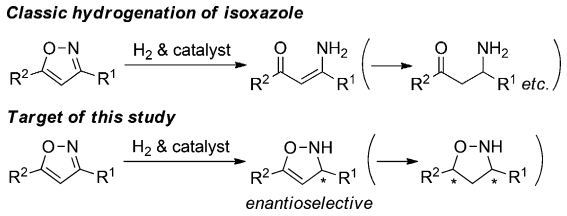
Ryuhei Ikeda and Ryoichi Kuwano*[a]

Abstract: The iridium catalyst $[IrCl(cod)]_2$–phosphine–I_2 (cod = 1,5-cyclooctadiene) selectively reduced isoxazolium triflates to isoxazolines or isoxazolidines in the presence of H_2. The iridium-catalyzed hydrogenation proceeded in high-to-good enantioselectivity when an optically active phosphine–oxazoline ligand was used. The 3-substituted 5-aryl-isoxazolium salts were transformed into 4-isoxazolines with up to 95:5 enantiomeric ratio (e.r.). Chiral *cis*-isoxazolidines were obtained in up to 89:11 e.r., with no formation of their *trans* isomers, when the substrates had a primary alkyl substituent at the 5-position. The mechanistic studies indicate that the hydridoiridium(III) species prefers to deliver its hydride to the C5 atom of the isoxazole ring. The hydride attack leads to the formation of the chiral isoxazolidine via a 3-isoxazoline intermediate. Meanwhile, in the selective formation of 4-isoxazolines, hydride attack at the C5 atom may be obstructed by steric hindrance from the 5-aryl substituent.

Introduction

Catalytic asymmetric hydrogenation of heteroarenes offers a versatile method to synthesize optically active five- or six-membered heterocycles.[1] During the past decade, many chemists, including us,[2] have devoted great effort to develop chiral catalysts for the reduction of prochiral heteroarenes. Nowadays, various heteroarenes, for example, pyrroles,[2d,3] pyridines,[4] indoles,[2a–c,5,6] and quinolines,[7] are reduced with H_2 to yield the corresponding chiral heterocycles with high enantioselectivities.[8–10] However, many heteroarene substrates still remain unexplored or strenuous targets for asymmetric hydrogenation.

To our knowledge, the asymmetric hydrogenation of isoxazoles remains unexplored, although we previously reported a ruthenium-catalyzed asymmetric hydrogenation of benzisoxazoles to give chiral α-substituted *o*-hydroxybenzylamines.[11] Based on the resonance energy of the aromatic π system,[12] the dearomatization of isoxazoles is considered to be comparable in difficulty to the dearomatization of pyrroles and more difficult than the dearomatization of furans or oxazoles. Moreover, isoxazole reduction is commonly accompanied by a ring-opening reaction[13] because the N–O bond is amenable to cleavage with a low-valence transition metal (Scheme 1).[14,15] Therefore, the selective transformation of isoxazoles to isoxazolines or isoxazolidines is a formidable task in organic chemistry.[16]



Scheme 1. Possible reactions of isoxazoles with H_2.

The asymmetric hydrogenation of isoxazoles is a useful method to prepare optically active isoxazolines or isoxazolidines. These compounds are often used as intermediates in the syntheses of useful compounds.[17,18] The isoxazoline or isoxazolidine framework is found in some biologically active molecules.[19,20] Furthermore, the isoxazolidine structural motif is useful for designing DNA intercalators.[21]

In this study, we found a useful chiral catalyst for the hydrogenation of isoxazolium salts. The asymmetric reaction provides isoxazolines or isoxazolidines with high stereoselectivity in the presence of an iridium complex that bears a chiral phosphine–oxazoline ligand.[5] Use of the iridium complex allows the hydrogenation to proceed without formation of the ring-opening side product.

Results and Discussion

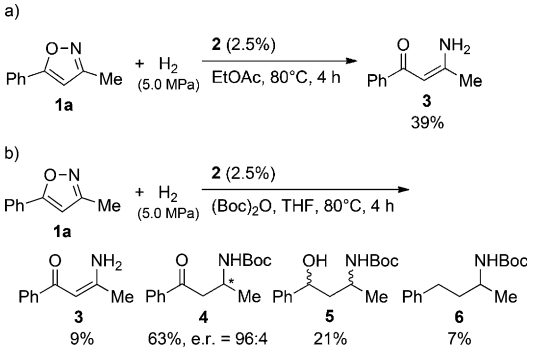
Optimization of the reaction conditions

First, the hydrogenation of 3-methyl-5-phenylisoxazole (**1a**) was attempted with [RuCl(*p*-cymene){(*R*,*R*)-(*S*,*S*)-PhTRAP}]Cl (**2**, PhTRAP = (*R*,*R*)-bis[(*S*)-(diphenylphosphino)ethyl]-1,1′′-biferro-

[a] *R. Ikeda, Prof. R. Kuwano*
Department of Chemistry, Faculty of Science and
International Research Center for Molecular Systems (IRCMS)
Kyushu University, 744 Motooka, Nishi-ku, Fukuoka 819-0395 (Japan)
E-mail: rkuwano@chem.kyushu-univ.jp

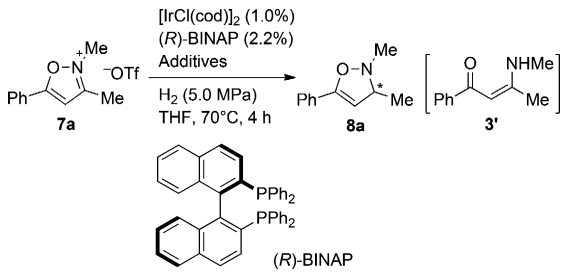
*Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/chem.201600732. It contains details of the preparation of compounds **7**, assignment of the stereochemistry of compound **9q**, and details of the mechanistic studies.*

cene),[2c] which catalyzed the transformation of benzisoxazoles to *o*-hydroxybenzylamines with moderate enantiomeric ratio (e.r.) values in our previous study.[11] As with the benzisoxazoles, the isoxazole ring of **1a** opened to yield achiral enaminone **3** in 39% yield (Scheme 2a). Enaminone **3** was further reduced with H_2 to give a mixture of products **3**–**6** when the reaction was carried out in the presence of stoichiometric $(Boc)_2O$ (Scheme 2b; Boc = *tert*-butoxycarbonyl). The formation of further saturated products **4**–**6** may be enabled by in situ *N*-Boc protection of the β-amino ketone intermediate. It is noteworthy that **4** was obtained in moderate yield with 96:4 e.r., and that the e.r. might be enhanced by kinetic resolution in the further reduction of **4** to **5**.



Scheme 2.

Table 1. Effect of additives on the hydrogenation of **7a**.[a]



Entry	Additive/s (mol%)	Yield [%][b]	e.r.[c]
1[d]	–	0	–
2	–	0	–
3	I_2 (8.0)	0	–
4	$KHCO_3$ (110)	61[e]	56:43
5	$KHCO_3$ (110), I_2 (8.0)	96	41:59

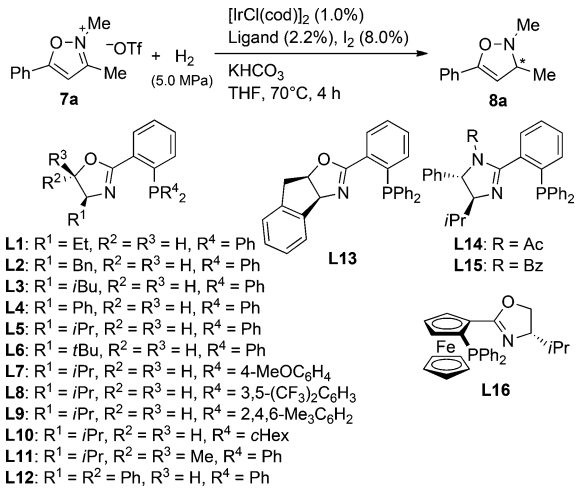
[a] Reactions were conducted on 0.20 mmol scale in THF (1.0 mL) under H_2 (5.0 MPa) at 70 °C for 4 h. The ratio of **7a**/$[IrCl(cod)]_2$/(*R*)-BINAP was 100:1.0:2.2. [b] Determined by ^1H NMR spectroscopic analysis. [c] Determined by chiral HPLC analysis. [d] Isoxazole **1** was used in place of **7a**. [e] Enaminone **3'** was also formed in 18% yield.

Iridium-catalyzed isoxazole ring reduction proceeds without N–O bond cleavage. Although isoxazole **1a** remained intact when a solution of **1a** in THF was heated at 70 °C under H_2 (5.0 MPa) for 4 h in the presence of an $[IrCl(cod)]_2$–(*R*)-BINAP complex[22] (cod = 1,5-cyclooctadiene, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) the iridium catalyst could convert isoxazolium triflate **7a** into 4-isoxazoline **8a** in good yield (Table 1, entry 1 versus 4).[23,24] The reduction of the isoxazolium salt required a stoichiometric amount of $KHCO_3$ to neutralize the triflic acid byproduct. The absence of the base resulted in no formation of **8a** (Table 1, entries 2 and 3). The ring-opening reaction of **7a** was observed as a side reaction (Table 1, entry 4). This undesired N–O bond cleavage was suppressed by the addition of I_2 (Table 1, entry 5). The I_2 additive allowed the BINAP–iridium catalyst to produce **8a** quantitatively, but the enantioselectivity was low.

The enantioselectivity remained low when chiral biaryl bisphosphine ligands were used. To improve the low stereoselectivity, a variety of chiral phosphine ligands were evaluated for the iridium-catalyzed hydrogenation of **7a**. A series of phosphine–oxazoline ligands[5,25] exhibited higher enantioselectivity than other types of chiral ligand (Table 2). The R^1 substituent at the C4 carbon atom of the oxazoline ring affects the catalytic activity and stereoselectivity. The iridium complex prepared from $[IrCl(cod)]_2$, I_2, and ethyl-substituted ligand **L1** yielded **8a** with a 73:27 e.r. (Table 2, entry 1). Increasing the size of substituent R^1 improved the yield as well as the e.r. of the hydrogenation product (Table 2, entries 2–6). Isopropyl is the optimal R^1 substituent for the asymmetric hydrogenation (**L5**). Bulkier ligand **L6** was comparable in enantioselectivity to **L5**, but its *tert*-butyl group caused a decreased yield of **8a**. Both the yield and enantioselectivity decreased when either electron-donating or electron-withdrawing substituents were present on the diarylphosphino group (Table 2, entries 7 and 8). Sterically congested aryl or secondary alkyl substituents on the phosphorus atom disturbed the stereochemical control (Table 2, entries 9 and 10). Substituents R^2 and R^3 scarcely impacted the stereoselectivity (Table 2, entries 11–13). The e.r. of **8a** was only marginally affected by replacing the oxazoline ring with an imidazoline ring (Table 2, entries 14 and 15). Use of ferrocene-tethered ligand **L16** gave almost racemic **8a** (Table 2, entry 16).

The reaction conditions were further optimized with the **L5**–iridium catalyst (Table 3). No change of the enantioselectivity was observed when K_2CO_3 was used as the base in place of $KHCO_3$ (Table 3, entry 2 versus 1), but the base did affect the efficiency of the iridium catalyst (Table 3, entries 1–6). No significant decrease in the stereoselectivity was observed even in the reaction using KOAc (Table 3, entry 6). Use of the strong base KO*t*Bu induced the undesired ring-opening reaction (Table 3, entry 7). Meanwhile, the solvent remarkably affected the e.r. as well as the yield of the hydrogenation product (Table 3, entries 8–13). The solvent of choice for the hydrogenation of **7a** was 2-methyl-2-butanol (*tert*-amyl alcohol; *t*-AmOH); the reaction in *t*-AmOH gave the isoxazoline product **8a** with 92:8 e.r. (Table 3, entry 13). Notably, racemic **8a** was obtained from the reaction in acetonitrile (Table 3, entry 12). The enantioselectivity was slightly improved by conducting the hydrogenation reaction at a lower temperature (Table 3, entry 14). Under the optimized condition, the catalyst loading can be reduced to 1.0 mol% without loss of the enantioselectivity (Table 4, entry 1). Although we tried to evaluate the counteranion of the substrate, we failed to prepare the isoxa-

Table 2. Evaluation of phosphine–oxazoline ligands **L** for the hydrogenation of **7a**.[a]



L1: R^1 = Et, R^2 = R^3 = H, R^4 = Ph
L2: R^1 = Bn, R^2 = R^3 = H, R^4 = Ph
L3: R^1 = *i*Bu, R^2 = R^3 = H, R^4 = Ph
L4: R^1 = Ph, R^2 = R^3 = H, R^4 = Ph
L5: R^1 = *i*Pr, R^2 = R^3 = H, R^4 = Ph
L6: R^1 = *t*Bu, R^2 = R^3 = H, R^4 = Ph
L7: R^1 = *i*Pr, R^2 = R^3 = H, R^4 = 4-$MeOC_6H_4$
L8: R^1 = *i*Pr, R^2 = R^3 = H, R^4 = 3,5-$(CF_3)_2C_6H_3$
L9: R^1 = *i*Pr, R^2 = R^3 = H, R^4 = 2,4,6-$Me_3C_6H_2$
L10: R^1 = *i*Pr, R^2 = R^3 = H, R^4 = *c*Hex
L11: R^1 = *i*Pr, R^2 = R^3 = Me, R^4 = Ph
L12: R^1 = R^2 = Ph, R^3 = H, R^4 = Ph

Entry	Ligand	Yield [%][b]	e.r.[c]
1	**L1**	33	73:27
2	**L2**	34	76:24
3	**L3**	51	84:16
4	**L4**	91	83:17
5	**L5**	83	85:15
6	**L6**	68	86:14
7	**L7**	52	83:17
8	**L8**	45	69:31
9	**L9**	43	43:57
10	**L10**	63	52:48
11	**L11**	53	81:19
12	**L12**	69	79:21
13	**L13**	87	83:17
14	**L14**	55	80:20
15	**L15**	79	73:27
16	**L16**	64	48:52

[a] Reactions were conducted on 0.20 mmol scale in THF (1.0 mL) under H_2 (5.0 MPa) at 70 °C for 4 h. The ratio of **7a**/[IrCl(cod)]$_2$/ligand/I_2/$KHCO_3$ was 100:1.0:2.2:8.0:110. [b] Determined by ^{1}H NMR spectroscopic analysis. [c] Determined by chiral HPLC analysis.

zolium iodide from **1a** because the isoxazole did not react with iodomethane.

Substrate scope of the asymmetric hydrogenation of 5-arylisoxazolium triflates

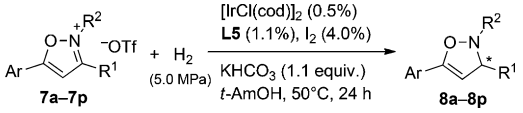
A variety of 5-arylisoxazolium triflates **7** were converted into chiral isoxazolines **8** in high yields. Under the conditions optimized above, 3-alkylisoxazolium triflates **7b**–**7f** were reduced with H_2 to yield **8b**–**8f** with 93:7–95:5 e.r. (Table 4, entries 2–6). Branching at the β-position of the alkyl substituent scarcely affected the enantioselectivity (Table 4, entries 4–6). The hydrogenation of **7g** gave the product **8g** in high yield, but the secondary alkyl substituent caused a significant decrease in the stereoselectivity (Table 4, entry 7). 3,5-Diphenylisoxazolium salt **7h** was converted into **8h** with a high e.r., but the reaction was slow because of the low solubility of **7h** in *t*-AmOH (Table 4, entry 8). However, the chiral product was successfully obtained in high yield by conducting the reaction at 70 °C in THF (Table 4, entry 9). The enantioselectivity was slightly enhanced by installing an electron-donating group on the 3-aryl group (Table 4, entry 10). The trifluoromethyl group of **7j** caused elimination of methyl group from the substrate and de-

Table 3. Effect of the base and solvent on the hydrogenation reaction of **7a**.[a]

Entry	Base	Solvent	Temp [°C]	Yield [%][b]	e.r.[c]
1	$KHCO_3$	THF	70	91	83:17
2	K_2CO_3[d]	THF	70	63	83:17
3	Li_2CO_3[d]	THF	70	13	–
4	Na_2CO_3[d]	THF	70	40	77:23
5	Cs_2CO_3[d]	THF	70	23	–
6	KOAc	THF	70	37	81:19
7	KO*t*Bu	THF	70	13[e]	–
8	$KHCO_3$	toluene	70	30	84:16
9	$KHCO_3$	$ClCH_2CH_2Cl$	70	17	71:29
10	$KHCO_3$	CPME[f]	70	8	–
11	$KHCO_3$	EtOAc	70	71	85:15
12	$KHCO_3$	MeCN	70	33[e]	50:50
13	$KHCO_3$	*t*-AmOH	70	86[g]	92:8
14	$KHCO_3$	*t*-AmOH	50	94[g]	93:7

[a] Unless otherwise noted, reactions were conducted on 0.20 mmol scale in the specified solvent (1.0 mL) under H_2 (5.0 MPa) at 70 °C for 4 h. The ratio of **7a**/[IrCl(cod)]$_2$/**L5**/I_2/base was 100:1.0:2.2:8.0:110. [b] Determined by ^{1}H NMR spectroscopic analysis. [c] Determined by chiral HPLC analysis. [d] The ratio of **7a**/base was 100:55. [e] A small amount of **3′** was detected. [f] CPME = cyclopentyl methyl ether. [g] Isolated yield.

Table 4. Asymmetric hydrogenation of 5-arylisoxazolium salts **7a**–**7p**.[a]



Entry	Substrate	R^1	Ar	R^2	Product	Yield [%][b]	e.r.[c]
1	**7a**	Me	Ph	Me	**8a**	84	93:7
2	**7b**	Pr	Ph	Me	**8b**	97	93:7
3	**7c**	nC_7H_{15}	Ph	Me	**8c**	98	93:7
4	**7d**	*i*Bu	Ph	Me	**8d**	97	93:7
5	**7e**	CH_2tBu	Ph	Me	**8e**	99	95:5
6	**7f**	CH_2Ph	Ph	Me	**8f**	94	93:7
7	**7g**	*c*Hex	Ph	Me	**8g**	85	62:38
8	**7h**	Ph	Ph	Me	**8h**	34	94:6
9[d]	**7h**	Ph	Ph	Me	**8h**	81	93:7
10[d]	**7i**	4-$MeOC_6H_4$	Ph	Me	**8i**	84	94:6
11[d]	**7j**	4-$CF_3C_6H_4$	Ph	Me	**8j**	(50)[e]	88:12
12	**7k**	Me	4-$MeOC_6H_4$	Me	**8k**	67	81:19
13	**7l**	Me	4-MeC_6H_4	Me	**8l**	81	91:9
14	**7m**	Me	4-$CF_3C_6H_4$	Me	**8m**	93	86:14
15	**7n**	Me	4-$MeO_2CC_6H_4$	Me	**8n**	77	83:17
16	**7o**	Me	2-MeC_6H_4	Me	**8o**	56	51:49
17	**7p**	Me	Ph	Et	**8p**	96	95:5

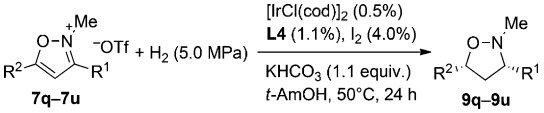
[a] Unless otherwise noted, reactions were conducted on 0.40 mmol scale in *t*-AmOH (1.0 mL) under H_2 (5.0 MPa) at 50 °C for 24 h. The ratio of **7**/[IrCl(cod)]$_2$/**L5**/I_2/base was 100:0.5:1.1:4.0:110. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The reactions were conducted on 0.20 mmol scale with a 2% catalyst loading in THF at 70 °C for 4 h. [e] Compound **8j** was obtained as a mixture with 5-phenyl-3-[4-(trifluoromethyl)phenyl]isoxazole (**1j**); the yield in the parentheses was estimated by ^{1}H NMR spectroscopic analysis.

creased the e.r. of the hydrogenation product (Table 4, entry 11). The *para* substituent on the 5-aryl group in **7k**–**7n** affected the enantioselectivity, but there was no clear pattern (Table 4, entries 12–15). The *o*-tolyl group of **7o** disturbs the enantiodiscrimination by the chiral **L5**–iridium catalyst (Table 4, entry 16). Replacing the *N*-methyl group by an *N*-ethyl group increased the enantioselectivity of the reaction (Table 4, entry 17 versus 1).

Asymmetric hydrogenation of 5-alkylisoxazolium triflates

The **L5**–iridium catalyst was applied to the asymmetric hydrogenation of 5-methyl-3-phenylisoxazolium triflate (**7q**), but the reaction did not yield isoxazoline **8q** (Table 5, entry 1). To our surprise, the isoxazole ring in **7q** was fully saturated to give *cis*-isoxazolidine **9q** without any formation of the *trans* isomer.

Table 5. Asymmetric hydrogenation of 5-alkylisoxazolinium salts **7q**–**7u**.[a]

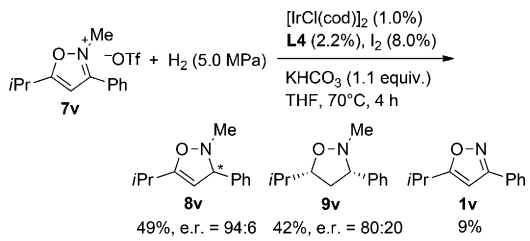


Entry	Substrate	R^1	R^2	Product	Yield [%][c]	e.r.[d]
1[d]	**7q**	Ph	Me	**9q**	98	82:18[e]
2	**7q**	Ph	Me	**9q**	96	87:13[e]
3[d]	**7r**	Ph	*n*Bu	**9r**	94	89:11
4[f]	**7s**	Ph	CH_2CH_2Ph	**9s**	96	88:12
5[f]	**7t**	Me	CH_2CH_2Ph	**9t**	86	84:16
6	**7u**	Ph	H	**9u**	98	70:30

[a] Unless otherwise noted, reactions were conducted on 0.40 mmol scale in *t*-AmOH (1.0 mL) under H_2 (5.0 MPa) at 50 °C for 24 h. The ratio of **7**/$[IrCl(cod)]_2$/**L4**/I_2/base was 100:0.5:1.1:4.0:110. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] **L5** was used in place of **L4**. [e] The absolute configuration of the major enantiomer of **9q** is (3*S*,5*S*). [f] The reaction was conducted on 0.20 mmol scale with a 2% catalyst loading.

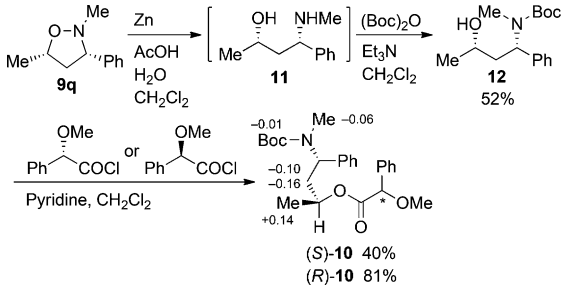
The e.r. of the product was improved to 87:13 by using **L4** as the chiral ligand (Table 5, entry 2). The 5-alkylisoxazolium triflates **7r** and **7s** were also exclusively converted into isoxazolidines **9r** and **9s** with good enantioselectivity (Table 5, entries 3 and 4). The hydrogenation of 5-isopropyl substrate **7v** was sluggish: isoxazoline **8v** was obtained in less than 10% yield and isoxazolidine **9v** was not formed. Reduction of the heteroarene would be hampered by the low solubility of **7v** as well as the steric hindrance from the secondary alkyl group. In THF, the **L4**–iridium catalyst promoted hydrogenation of **7v**, and a mixture of **8v** and **9v** was obtained in high combined yield (Scheme 3). The phenyl group at the 3-position is not crucial for selective formation of the isoxazolidine product. The 3,5-dialkylisoxazolium triflate **7t** also selectively gave **9t** with good enantioselectivity (Table 5, entry 5). The **L4**–iridium catalyst is capable of reducing mono-substituted isoxazolinium **7u** to isoxazolidine **9u**, but with a moderate e.r. (Table 5, entry 6).

The absolute configuration of the hydrogenation product **9q** was assigned by comparison to the ^1H NMR spectra of the



Scheme 3. Yields were determined by ^1H NMR analysis.

(*S*)- and (*R*)-*O*-methylmandelate derivatives (*S*)- and (*R*)-**10**.[26] Compound **9q** was transformed into γ-amino alcohol **11** by reductive N–O bond cleavage with zinc powder (Scheme 4). Crude **11** was treated with $(Boc)_2O$ to give the *N*-Boc-protected amino alcohol **12** in 52% yield. Furthermore, the hydroxyl



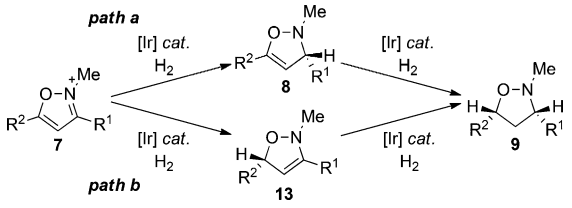
Scheme 4. Assignment of the absolute configuration of **9q**: The preparation of *O*-methylmandelates **10** and the difference in chemical shifts between (*S*)- and (*R*)-**10** ($\Delta\delta = \delta_S - \delta_R$).

group of **12** was esterified with (*S*)- or (*R*)-*O*-methylmandelyl chloride to form **10**. The differences in chemical shifts between (*S*)- and (*R*)-**10** are summarized in Scheme 4 and indicate that the absolute configuration at the 5-position of **9q** is *S*. The relative configuration of **9q** was assigned as *cis* by ^1H NOE analysis and NOESY spectroscopy. Consequently, (3*S*,5*S*)-**9q** was preferentially obtained from the hydrogenation reaction of **7q** with the **L5**–iridium catalyst.

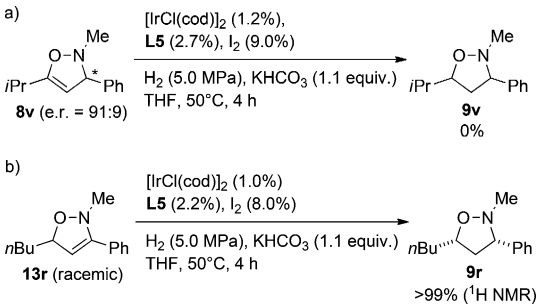
Mechanistic study

Initially, we supposed that the hydrogenation of 5-alkylisoxazolium triflates **7q**–**7u** (Table 3) proceed via 4-isoxazoline **8** to give isoxazolidine **9** (Scheme 5a). To confirm the reaction pathway, the hydrogenation of **8v** was attempted with the **L5**–iridium catalyst (Scheme 6a). However, **8v** remained almost intact after the reaction mixture was heated at 70 °C under H_2 (5.0 MPa) for 6 h. This result suggested that **8v** is not involved in the production of **9v**. Meanwhile, the **L5**–$[IrCl(cod)]_2$–I_2 catalyst fully converted racemic 3-isoxazoline **13r** into *cis*-isoxazoline **9r** within 4 h in high yield (Scheme 6b). These observations indicate that the isoxazolidine products are formed via the 3-isoxazoline intermediate **13** (Scheme 5b).

Some reactions were carried out with D_2 to investigate the pathway from the cyclic enamine **13** to **9**. Prior to the labeling

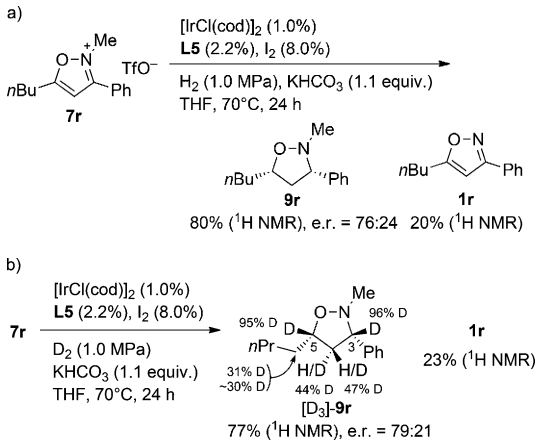


Scheme 5. Possible pathways of the iridium-catalyzed hydrogenation of isoxazoles **7** to give isoxazolidine **9**.



Scheme 6.

experiments, the hydrogenation of **7r** was attempted in THF under H_2 (1.0 MPa). From the reaction, the desired product **9r** was obtained with 76:24 e.r. in good yield. A small amount of isoxazole **1r** was detected from the crude reaction mixture (Scheme 7a). In the deuteration of **7r** under identical conditions, the substrate was fully transformed into a mixture of [D_3]-**9r** and **1r** (Scheme 7b). The use of D_2 instead of H_2 scarcely affected the enantioselectivity and the yield of the isoxazolidine product. In [D_3]-**9r** almost complete deuterium incorporation was observed at the 3- and 5-positions. About 50% of the deuterium atoms were incorporated at each face of the C4 atom. The resonances of the protons on the C4 carbon atom in the ^{1}H NMR spectrum of [D_3]-**9r** are shown in Figure 1. The splitting patterns of these peaks indicate that the isoxazolidine



Scheme 7.

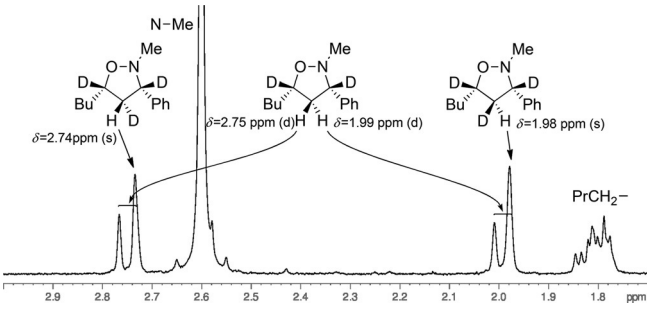
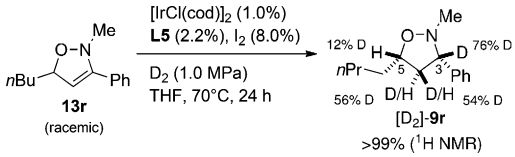


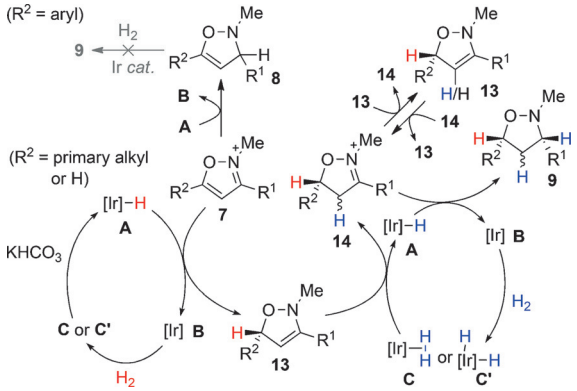
Figure 1. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of [D_3]-**9r**.

product shown in Scheme 7b contains four deuterated products: 3,5-di, 3,4,5-tri- (two isomers), and 3,4,4,5-tetradeuterated **9r**. Furthermore, 30% of the deuterium atoms were incorporated at the α-position of the butyl group. The H/D scrambling might occur independently of the hydrogenation and proceed through iridium-catalyzed C–H bond activation. As with isoxazole **7r**, 3-isoxazoline **13r** was saturated with D_2 to give [D_2]-**9r**, in which H/D scrambling took place on the C4 atom (Scheme 8).



Scheme 8.

Based on the above experimental results, the iridium-catalyzed hydrogenation of isoxazolium salts could proceed through the pathway shown in Scheme 9. It has been proposed that a hydridoiridium(III) species is involved in the catalytic cycle of the hydrogenation with the [IrCl(cod)]$_2$–bisphosphine–I_2 catalyst.[27] The hydridoiridium(III) species **A** is generated by deprotonation of an iridium(III) dihydrogen[28] or dihydridoiridium(V) complex.[29] When the isoxazolium substrate has



Scheme 9. A possible pathway for the iridium-catalyzed hydrogenation of **7**. [Ir] = (**L4** or **L5**)Ir$^+$X$_2$ (X = I or Cl).

a proton or primary alkyl group at its 5-position, **A** delivers its hydride to the C5 atom through a 1,4-addition-like pathway. The resulting cyclic enamine **13** is protonated at its 4-position by cationic iridium(III) dihydrogen species **C** or dihydridoiridium(V) species **C'** to form 2-isoxazolinium **14** and **A**. The hydride in **A** reduces the C=N double bond of **14** to give isoxazolidine **9**. The cationic iridium(III) species **B** is converted into **A** through formation of **C** or **C'**, followed by deprotonation with $KHCO_3$. The H/D scrambling shown in Schemes 7b and 8 would be caused by rapid intermolecular proton transfer between intermediates **13** and **14**. In the case of 5-arylisoxazolium salts **7a**–**7p**, the aryl substituent may sterically hinder the access of iridium hydride **A** to the C5 atom in **7**. Therefore, the hydride on iridium selectively attacks the C3 atom to give 4-isoxazoline **8** and create the new stereogenic center.

In summary, the chiral iridium catalyst prefers to deliver the hydride to the C5 carbon atom of the isoxazole ring rather than the C3 carbon atom. However, hydride attack on the C5 atom may be obstructed by steric hindrance of the 5-substituent when a 5-arylisoxazolium salt is used as the substrate. The iridium hydride selectively reduces the N2=C3 double bond to give 4-isoxazoline **8**. In the case of 5-alkylisoxazolium salts, the C5 carbon atom is attacked by hydridoiridium(III) species **A** without steric hindrance from the alkyl group. The formation of the 3-isoxazoline intermediate **13** leads to selective formation of the chiral isoxazolidine product **9**.

Conclusion

We have developed a method for the enantioselective hydrogenation of isoxazolium triflates **7** to give chiral 4-isoxazolines **8** or isoxazolidines **9**. Although the reaction of an isoxazole ring with H_2 is commonly accompanied by N–O bond cleavage, the undesired bond cleavage was suppressed by the use of an iridium catalyst. With the chiral catalyst prepared from $[IrCl(cod)]_2$, chiral phosphine–oxazoline ligand **L5**, and I_2 the hydrogenation of 5-arylisoxazolium triflates exclusively provided the corresponding 4-isoxazolines **8** with good or high e.r. values (up to 95:5 e.r.). Meanwhile, 5-alkylated substrates were selectively converted into *cis*-3,5-disubstituted isoxazolidines **9** by using the **L4**–iridium or **L5**–iridium catalysts. Furthermore, mechanistic studies indicated that the selectivity between **8** and **9** is strongly affected by steric hindrance from the 5-substituent on the isoxazole ring.

Experimental Section

NMR spectra were recorded with a Bruker AVANCE 400 or AVANCE III HD 400 Nanobay (9.4 T magnet) spectrometer at ambient temperature. In the ^1H and ^{13}C NMR spectra the chemical shift (δ) values [ppm] are referenced to internal tetramethylsilane ($\delta = 0.00$ ppm) in $CDCl_3$ or the residual proton ($\delta = 2.05$ ppm) in [D6]acetone and the carbon atom resonance of the deuterated solvent ($\delta = 77.0$ ppm ($CDCl_3$), 30.0 ppm ([D_6]acetone), respectively. IR spectra, optical rotations, and melting points were measured with a JASCO FT/IR-4100 spectrometer, JASCO P-1020 polarimeter, and Büchi Melting Point B-545 apparatus, respectively. *t*-AmOH was dried with calcium hydride and distilled under a nitrogen atmosphere. THF was purged with nitrogen for 30 min, and then dried with an alumina and copper column system (GlassContour). $[IrCl(cod)]_2$ was prepared according to a literature procedure.[30] Chiral ligands **L4** and **L5**, I_2, and $KHCO_3$ were purchased and used without further purification.

Typical procedure for the asymmetric hydrogenation of 7

Under a nitrogen atmosphere, a solution of $[IrCl(cod)]_2$ (1.3 mg, 2.0 μmol) and **L5** (1.6 mg, 4.3 μmol) in dry *t*-AmOH or THF (1.0 mL) was stirred at ambient temperature for 10 min. The solution of the iridium–ligand complex was transferred via cannula to a mixture of **7** (0.40 mmol), $KHCO_3$ (44.0 mg, 0.44 mmol), and I_2 (4.0 mg, 16 μmol). The reaction mixture was stirred under H_2 (5.0 MPa) at 50 °C or 70 °C. The resulting mixture was evaporated under reduced pressure, and then the residue was passed through a short column of silica gel (EtOAc/hexane) to give the desired chiral 4-isoxazoline **8** or isoxazolidine **9**.

Compound 8a:[31] Compound **8a** (84%, 93:7 e.r.) was obtained as a colorless oil. $[\alpha]_D^{25} = +145.4$ ($c = 1.14$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.28$ (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 ppm (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 21.7$, 46.4, 68.8, 97.0, 125.6, 128.3, 128.7, 129.3, 152.0 ppm.

Compound 8b: Following the typical procedure, compound **8b** (97%, 93:7 e.r.) was obtained as a colorless oil. $[\alpha]_D^{27} = +145.5$ ($c = 1.15$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.94$ (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 ppm (dd, $J = 1.6$, 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 14.0$, 19.0, 38.6, 47.2, 73.5, 95.3, 125.6, 128.3, 128.7, 129.4, 152.1 ppm; IR (neat): $\tilde{\nu} = 2956$, 2930, 2872, 1651, 1494, 1448, 1270, 765, 724, 690 cm^{-1}; elemental analysis 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.

Compound 8c: Following the typical procedure, compound **8c** (98%, 93:7 e.r.) was obtained as a colorless oil. $[\alpha]_D^{25} = +120.2$ ($c = 1.30$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (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 ppm (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 14.0$, 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 ppm; IR (neat): $\tilde{\nu} = 2954$, 2926, 2854, 1652, 1494, 1449, 1266, 1022, 768, 721, 690 cm^{-1}; elemental analysis 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.

Compound 8d: Following the typical procedure, compound **8d** (97%, 93:7 e.r.) was obtained as a colorless oil. $[\alpha]_D^{27} = +136.9$ ($c = 1.14$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.94$ (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 ppm (d, $J = 7.7$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 22.6$, 22.9, 25.0, 45.5, 46.9, 71.8, 95.7, 125.6, 128.3, 128.7, 129.4, 152.1 ppm; IR (neat): $\tilde{\nu} = 2955$, 2925, 2870, 1651, 1494, 1448, 1271, 1014, 770, 720, 690 cm^{-1}; elemental analysis 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.

Compound 8e: Following the typical procedure, compound **8e** (99%, 95:5 e.r.) was obtained as a colorless oil. $[\alpha]_D^{25} = +119.3$ ($c = 1.02$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.98$ (s, 9H), 1.41 (dd, $J = 14.2$, 5.2 Hz, 1H), 1.66 (dd, $J = 6.7$, 14.2 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 ppm (d, $J = 7.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 30.1$, 30.3, 46.2, 50.0, 70.7, 96.9, 125.6, 128.3, 128.7, 129.4, 151.8 ppm; IR (neat): $\tilde{\nu} = 2954$, 2871, 1651, 1494, 1448, 1364, 1274, 1250, 1009, 718,

689 cm^{-1}; elemental analysis 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.

Compound 8f: Following the typical procedure, compound **8f** (94%, 93:7 e.r.) was obtained as a colorless oil. $[\alpha]_D^{26} = +125.0$ ($c = 1.06$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.76$ (s, 3H), 2.82 (dd, $J = 7.1$, 13.3 Hz, 1H), 2.97 (dd, $J = 6.9$, 13.3 Hz, 1H), 3.98 (br, 1H), 5.19 (d, $J = 2.1$ Hz, 1H), 7.19–7.37 (m, 8H), 7.53 ppm (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 43.0$, 46.9, 75.3, 94.9, 125.7, 126.3, 128.3, 128.4, 128.9, 129.2, 129.4, 138.6, 152.7 ppm; IR (neat): $\tilde{\nu} = 3060$, 3027, 2955, 2913, 1651, 1601, 1580, 1494, 1450, 1323, 1277, 1062, 1024, 721, 700 cm^{-1}; elemental analysis 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.

Compound 8g: Following the typical procedure, compound **8g** (85%, 62:38 e.r.) was obtained as a colorless solid. $[\alpha]_D^{26} = +32.9$ ($c = 1.02$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.92$–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 ppm (d, $J = 6.9$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 26.1$, 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 ppm; IR (KBr): $\tilde{\nu} = 2921$, 2849, 1652, 1494, 1446, 1261, 1039, 1020, 754, 691, 634 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{16}H_{22}NO$: 244.1701; found: 244.1715 $[M+H]^+$.

Compound 8h:[31] Following a slightly modified procedure (see Table 4, entry 9), compound **8h** (81%, 93:7 e.r.) was obtained as a colorless solid. $[\alpha]_D^{25} = -162.1$ ($c = 1.17$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.98$ (s, 3H), 4.85 (s, 1H), 5.37 (d, $J = 2.4$ Hz, 1H), 7.24–7.43 (m, 8H), 7.59 ppm (d, $J = 7.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 47.1$, 77.2, 95.8, 125.8, 127.1, 127.7, 128.4, 128.6, 129.00, 129.02, 142.1, 152.7 ppm.

Compound 8i: Following a slightly modified procedure (see Table 4, entry 10), compound **8i** (84%, 88:12 e.r.) was obtained as a colorless solid. $[\alpha]_D^{28} = -126.3$ ($c = 1.04$ in $CHCl_3$); ^1H NMR (400 MHz, [D_6]acetone): $\delta = 2.90$ (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 ppm (m, 2H); ^{13}C NMR (100 MHz, [D_6]acetone): $\delta = 47.3$, 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 ppm; IR (neat): $\tilde{\nu} = 2956$, 1654, 1604, 1506, 1453, 1250, 1174, 1031, 831, 768, 719 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{17}H_{18}NO_2$: 268.1338; found: 268.1339 $[M+H]^+$.

Compound 8j: Following a slightly modified procedure (see Table 4, entry 11), compound **8j** (50% by ^1H NMR spectroscopy, 88:12 e.r.) was obtained as a mixture with 5-phenyl-3-[4-(trifluoromethyl)phenyl]isoxazole. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.00$ (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 ppm (m, 9H).

Compound 8k: Following the typical procedure, compound **8k** (67%, 81:19 e.r.) was obtained as a colorless oil. $[\alpha]_D^{27} = +111.1$ ($c = 0.61$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.26$ (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 ppm (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 21.8$, 46.4, 55.3, 68.8, 95.2, 113.8, 122.1, 127.1, 151.8, 160.2 ppm; IR (neat): $\tilde{\nu} = 2964$, 2925, 1651, 1603, 1506, 1448, 1254, 1175, 1030, 833, 745, 706 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{12}H_{16}NO_2$: 206.1181; found: 206.1180 $[M+H]^+$.

Compound 8l: Following the typical procedure, compound **8l** (81%, 91:9 e.r.) was obtained as a colorless oil. $[\alpha]_D^{26} = +125.5$ ($c = 0.83$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.27$ (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 NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 21.3$, 21.7, 46.4, 68.8, 96.1, 125.6, 126.5, 129.0, 138.7, 152.1 ppm; IR (neat): $\tilde{\nu} = 2967$, 2920, 1658, 1610, 1510, 1445, 1308, 1178, 1060, 822, 748 cm^{-1}; elemental analysis 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.

Compound 8m: Following the typical procedure, compound **8m** (93%, 86:14 e.r.) was obtained as a colorless oil; $[\alpha]_D^{27} = +88.8$ ($c = 1.09$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.29$ (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 ppm (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 21.5$, 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 ppm; IR (neat): $\tilde{\nu} = 2972$, 2925, 2875, 1615, 1412, 1326, 1168, 1126, 1069, 846, 765, 722 cm^{-1}; elemental analysis 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.

Compound 8n: Following the typical procedure, compound **8n** (77%, 83:17 e.r.) was obtained as a colorless oil. $[\alpha]_D^{26} = +56.7$ ($c = 0.60$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.29$ (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 ppm (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 21.5$, 46.4, 52.0, 68.9, 99.5, 125.5, 129.7, 130.3, 133.4, 151.3, 166.6 ppm; IR (neat): $\tilde{\nu} = 2955$, 1721, 1609, 1436, 1279, 1108, 741 cm^{-1}; elemental analysis 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.

Compound 8o: Following the typical procedure, compound **8o** (56%, 51:49 e.r.) was obtained as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.29$ (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 ppm (d, $J = 7.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 21.1$, 21.9, 46.4, 68.9, 100.5, 125.7, 128.6, 128.7, 128.8, 130.7, 136.6, 151.9 ppm; IR (neat): $\tilde{\nu} = 2967$, 2923, 1639, 1455, 1304, 741 cm^{-1}; elemental analysis 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.

Compound 8p: Following the typical procedure, compound **8p** (96%, 95:5 e.r.) was obtained as a colorless oil; $[\alpha]_D^{27} = +194.8$ ($c = 1.38$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.27$ (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 ppm (d, $J = 7.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 12.4$, 22.3, 53.6, 66.8, 97.4, 125.6, 128.3, 128.7, 129.4, 152.1 ppm; IR (neat): $\tilde{\nu} = 2973$, 2925, 1653, 1494, 1447, 1333, 1055, 1004, 752, 731, 690 cm^{-1}; elemental analysis 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.

Compound 9q: Following the typical procedure and using ligand **L4**, compound **9q** (96%, 87:13 e.r.) was obtained as a colorless oil. $[\alpha]_D^{26} = -137.7$ ($c = 1.23$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.38$ (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 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 21.3$, 43.8, 47.5, 72.8, 73.6, 127.4, 127.5, 128.5, 140.2 ppm; IR (neat): $\tilde{\nu} = 2975$, 2872, 1454, 1370, 1216, 754, 700 cm^{-1}; elemental analysis 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.

Compound 9r: Following a slightly modified procedure (see Table 5, entry 4), compound **9r** (94%, 89:11 e.r.) was obtained as a colorless oil. $[\alpha]_D^{26} = -122.8$ ($c = 1.23$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (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 ppm (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (100 MHz, [D_6]acetone): $\delta = 14.5$, 23.5, 29.5, 36.7, 44.0, 47.0, 74.0, 77.4, 128.3, 128.4, 129.4, 142.0 ppm; IR (neat): $\tilde{\nu} = 2956$, 2871, 1455, 755, 699 cm^{-1}; elemental analysis 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.

Compound 9s: Following a slightly modified procedure (see Table 5, entry 5), compound **9s** (96%, 88:12 e.r.) was obtained as a colorless oil. $[\alpha]_D^{26} = -93.0$ ($c = 1.02$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.84$ (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 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta =$ 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 ppm; IR (neat): $\tilde{\nu} = 3026, 2915, 2856, 1494, 1449,$ 1023, 726, 698 cm^{-1}; elemental analysis 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.

Compound 9t: Following the typical procedure and using ligand **L4**, compound **9t** (86%; 84:16 e.r.) was obtained as a colorless oil. $[\alpha]_D^{25} = -47.5$ ($c = 0.97$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.16$ (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 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.1$ (br), 32.6, 37.6, 43.6 (br, 2×C), 63.9 (br), 75.3 (br), 125.7, 128.3, 128.5, 142.0 ppm; IR (neat): $\tilde{\nu} = 2962, 2862, 1493,$ 1452, 1022, 745, 698 cm^{-1}; elemental analysis 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.

Compound 9u: Compound **9u** (98%, 70:30 e.r.); was obtained as a colorless oil. $[\alpha]_D^{26} = -59.4$ ($c = 1.33$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.31$ (dq, $J = 7.3, 12.1$ Hz, 1H), 2.61 (s, 3H), 2.70 (dq, $J =$ 7.7, 12.1 Hz, 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 ppm (d, $J = 7.3$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C): $\delta = 39.3, 43.3, 65.7, 72.4, 127.57,$ 127.61, 128.6, 140.2 ppm; IR (neat): $\tilde{\nu} = 2957, 2872, 1492, 1453,$ 1033, 1012, 753, 700 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{10}H_{13}NO$: 163.0997; found: 163.0989 $[M]^+$.

Compounds 8v and 9v: Following the typical procedure and using ligand **L4**, a mixture of compounds **8v** and **9v** were obtained. The yields given here are of the isolated products.

*Compound **8v***: Compound **8v** (26%, 94:6 e.r.) was obtained as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.16$ (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 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.4, 26.1, 47.0, 76.5, 93.0, 126.9, 127.5, 128.5, 142.9,$ 160.7 ppm.

*Compound **9v***: Compound **9v** (21%, 80:20 e.r.) was obtained as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (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 ppm (m 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.4, 19.5, 33.4, 43.8, 44.2, 73.4, 82.5, 127.4,$ 127.6, 128.6, 140.1 ppm.

Acknowledgements

This work was partly supported by the JSPS KAKENHI, grant numbers 15K13698 and 15KT0066. R.I. thanks the JSPS for financial support (JSPS Research Fellow). We thank the Cooperative Research Program of the "Network Joint Research Center for Materials and Devices" for performing the HRMS measurements.

Keywords: asymmetric catalysis · heterocycles · hydrogenation · iridium · isoxazoles

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Received: February 17, 2016
Published online on April 23, 2016