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# Ruthenium-Catalyzed Chemo- and Enantioselective Hydrogenation of Isoquinoline Carbocycles

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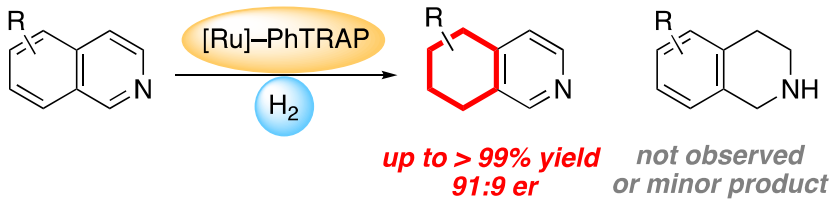
## TOC GRAPHIC




## ABSTRACT

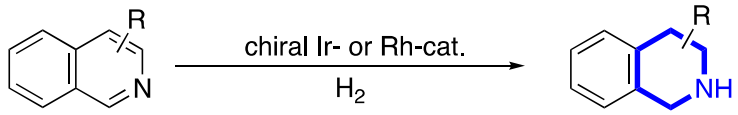
A chemoselective hydrogenation of isoquinoline carbocycles was achieved by using the catalyst prepared from Ru(methallyl)$_2$(cod) and *trans*-chelate chiral ligand PhTRAP. The unique chemoselectivity achieved in this hydrogenation could be ascribed to the *trans*-chelation of the chiral ligand. The procedure for preparing the catalyst strongly affects the reproducibility of the carbocycle hydrogenation. Various 5-, 6-, 7-, and 8-substituted isoquinolines were selectively hydrogenated at their carbocycles to afford 5,6,7,8-tetrahydroisoquinolines as major products in high yields with moderate or good enantioselectivities. Some mechanistic studies suggested that

the stereogenic center was created during the initial addition of $H_2$ to the aromatic ring in the hydrogenation of 5-substituted isoquinolines. In other words, the stereochemical control accompanied with the dearomatization.

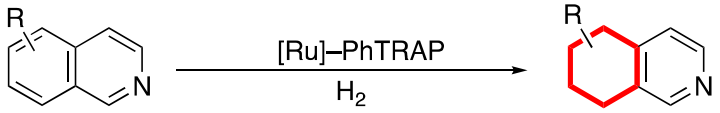
## INTRODUCTION

Hydrogenation of isoquinolines offers a straightforward and powerful approach for constructing hydroisoquinoline structures. The heterocyclic structural motif is often seen in biologically active compounds, such as isoquinoline alkaloids[1] and drug candidates.[2] The reaction has been classically carried out with heterogeneous metal particle catalysts under harsh reaction conditions,[3,4] because the isoquinoline rings are unreactive to the hydrogenation due to their own aromatic stabilization. Commonly, the dearomative reduction selectively takes place on the pyridine ring to give 1,2,3,4-tetrahydroisoquinolines as the major product. Some transition-metal complexes are also known to work as catalysts for the hydrogenation of isoquinolines under mild conditions (Scheme 1a).[5] With the homogeneous iridium catalyst, Zhou[5a,b,d,e,h] and Mashima[5c,f] independently developed the hydrogenation of isoquinolines to exclusively produce the 1,2,3,4-tetrahydroiqoquinolines with high enantioselectivities. Zhang recently reported that a chiral rhodium catalyst is also useful for the transformation.[5g]

***(a) Previous Works: Hydrogenation of the Heterocycle***




***(b) This Work: Hydrogenation of the Carbocycle***



**Scheme 1. Chemo- and Enantioselective Hydrogenation of Isoquinolines**

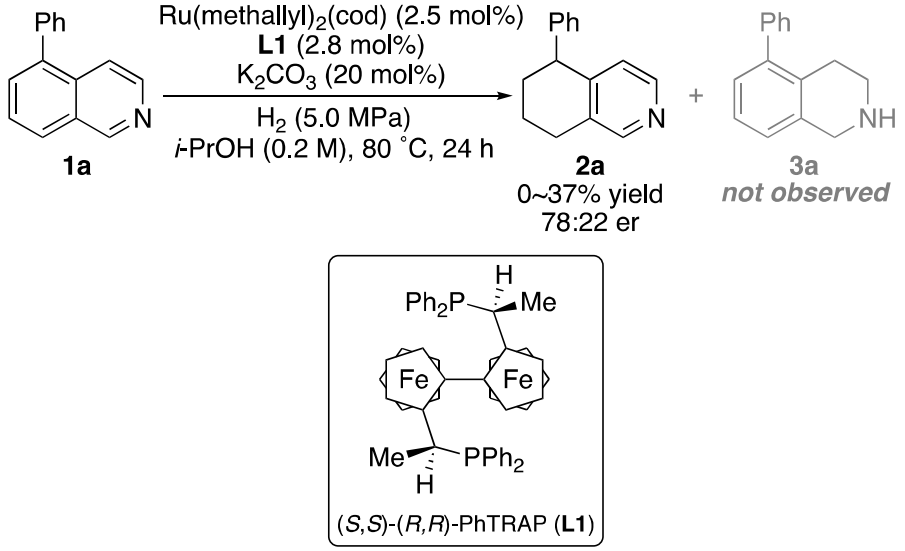
Selective hydrogenation of the benzene ring in the isoquinoline may be unforeseen for many chemists, because the carbocycle is much more stabilized with the aromaticity than the heteroarene. Nevertheless, some catalysts are known to preferentially reduce the isoquinoline carbocycles.[3a,b,4,6] The chemoselective reduction of isoquinoline carbocycles is enabled by $RuH_2(\eta^2\text{-}H_2)_2(PCy_3)_2$[6a] as well as heterogeneous metal-supported catalysts, such as $PtO_2$[3a,4a-e] and Raney Nickel.[3b] There has been no report on the enantioselective hydrogenation of isoquinoline carbocycles, although the chiral 5,6,7,8-tetrahydroisoquinoline motifs are often used as an important pharmacophore in drug development.[7]

A variety of substituted heteroarenes can be converted to the corresponding chiral heterocycles with high enantioselectivities through the hydrogenation with asymmetric catalysis.[8] Meanwhile, enantioselective hydrogenation of carbocyclic arenes still remains one of the formidable issues in asymmetric catalysis. In 2011, Glorius had reported the enantioselective hydrogenation of quinoxaline carbocycles with a chiral NHC–ruthenium catalyst.[9] This report is the first success in the enantioselective hydrogenation of carbocyclic arenes with asymmetric catalysis. Our group has also developed the asymmetric hydrogenations of naphthalenes[10,11] and quinoline carbocycles[12] by using the ruthenium complex bearing chiral *trans*-chelate bisphosphine ligand, (*R,R*)-2,2”-bis[(*S*)-(diphenylphosphino)ethyl-1,1”-biberrocene [(*S*,*S*)-(*R*,*R*)-PhTRAP] (**L1**).[13] It is noteworthy that the pyridine ring remained intact during the reduction process in the asymmetric hydrogenation of quinolines. In this context, we applied the **L1**–ruthenium catalyst to the chemo- and enantioselective hydrogenation of isoquinoline carbocycles (Scheme 1b). The catalyst allowed the hydrogenation to proceed with no formation of 1,2,3,4-

tetrahydroisoquinolines when 5- or 8-substituted isoquinolines were used as the substrate. Furthermore, the ruthenium-catalyzed hydrogenation could provide the chiral 5,6,7,8-tetrahydroisoquinolines with up to 91:9 enantiomer ratio (er).

## RESULTS AND DISCUSSION

**Optimization of Procedure and Reaction Conditions.** First, the hydrogenation of 5-phenylisoquinoline (**1a**) was attempted in *i*-PrOH at 80 °C under 5.0 MPa of $H_2$ for 24 h in the presence of *in situ* generated Ru(methallyl)$_2$(cod)–**L1** catalyst as shown in Scheme 2. The reaction condition is optimal for the selective hydrogenation of quinoline carbocycles.[12] As with the reaction of quinolines, the hydrogenation could take place on the carbocycle of **1a** to give 5,6,7,8-tetrahydroisoquinoline **2a** as the sole product in up to 37% NMR yield with 78:22 er, but the hydrogenation lacked reproducibility. From the reaction mixture, the substrate–ruthenium complex, $RuCl_2$(**1a**)$_4$, was isolated after a chromatographic purification. The formation of $RuCl_2$(**1a**)$_4$ suggested that the chelation of **L1** to the ruthenium might be obstructed by the strong interaction between the isoquinoline and metal atom. Furthermore, the poor solubility of **L1** in the alcoholic solvent at ambient temperature might be disadvantageous for the complexation of the ligand and the catalyst precursor.

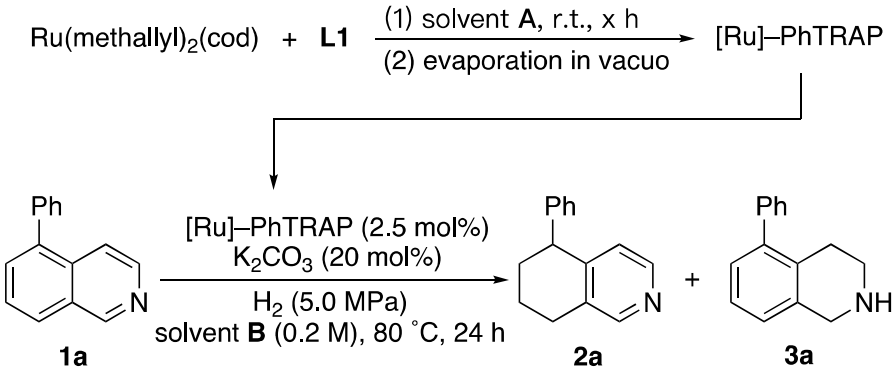



**Scheme 2. Initial Attempts at the Hydrogenation of Isoquinoline Carbocycles**

To overcome this difficulty, the preparation method of the **L1**–ruthenium catalyst was investigated. The hydrogenation of **1a** was attempted with [RuCl(*p*-cymene)(**L1**)]Cl catalyst, which was employed for the enantioselective hydrogenation of naphthalenes (Table 1, entry 1).[10] However, no hydrogenation was observed in the reaction mixture. Next, the catalyst was prepared by mixing Ru(methallyl)$_2$(cod) and **L1** in *i*-PrOH in the absence of **1a** for certain hours (entries 2–6). When the solution of the catalyst precursor and **L1** was stirred for 18 h, the desired hydrogenation product **2a** was obtained quantitatively with 79:21 er (entry 5). Various solvents were next evaluated for the catalyst preparation (entries 7–9). Using $CH_2Cl_2$ or toluene caused significant decrease in the yield of **2a**, while the desired product was quantitatively obtained with the **L1**–ruthenium catalyst prepared in THF. The catalyst efficiency was affected by the premixing time in the case of preparing the catalyst in THF (entries 10 and 11). Even with the catalyst prepared in THF, *i*-PrOH is the solvent of choice for the hydrogenation. The hydrogenation in aprotic solvents including THF resulted in no or a little production of **2a**

(entries 12–14). Use of primary alcohols led to slight increase in the enantioselecitivity of the hydrogenation, but it caused a deterioration of the catalytic activity (entries 15 and 16). The hydrogenation scarcely proceeded in *tert*-amyl alcohol probably due to the poor solubility of substrate and catalyst in this solvent (entry 17). Lowering the reaction temperature slightly improved the enantioselectivity without loss of the chemoselectivity as well as the yield of **2a** (entry 18). It is noteworthy that no formation of 1,2,3,4-tetrahydroisoquinoline **3a** was detected in the $^1$H NMR analyses of the crude mixtures in these experiments except for entry 13. Moreover, the stereoselectivity was hardly affected by the reaction parameters.

**Table 1. Optimization of Procedure and Reaction Parameters**[a]



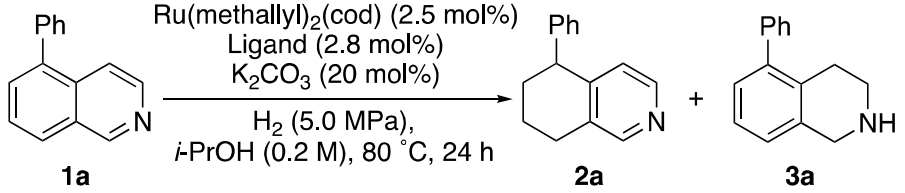

| entry | **A** | x (h) | **B** | yield of **2a** (%)[b] | yield of **3a** (%)[b] | **2a**:**3a**[b] | er of **2a**[c] |
|---|---|---|---|---|---|---|---|
| 1[d] | – | – | *i*-PrOH | 0 | 0 | – | – |
| 2 | *i*-PrOH | 0.5 | *i*-PrOH | 0 | 0 | – | – |
| 3 | *i*-PrOH | 4 | *i*-PrOH | 13 | 0 | 100:0 | – |
| 4 | *i*-PrOH | 12 | *i*-PrOH | 2 | 0 | 100:0 | – |
| 5 | *i*-PrOH | 18 | *i*-PrOH | >99[e] | 0 | 100:0 | 79:21 |
| 6 | *i*-PrOH | 24 | *i*-PrOH | 76 | 0 | 100:0 | 80:20 |
| 7 | $CH_2Cl_2$ | 8 | *i*-PrOH | 8 | 0 | 100:0 | – |
| 8 | toluene | 8 | *i*-PrOH | 11 | 0 | 100:0 | – |
| 9[f] | THF | 8 | *i*-PrOH | >99[e] | 0 | 100:0 | 79:21 |

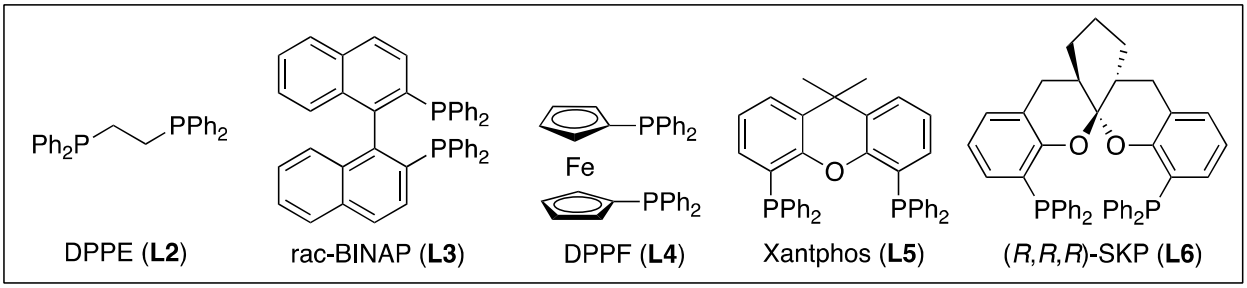
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 10[f] | THF | 4 | *i*-PrOH | 80 | 0 | 100:0 | 79:21 |
| 11[f] | THF | 0.5 | *i*-PrOH | 24 | 0 | 100:0 | – |
| 12 | THF | 8 | THF | 0 | 0 | – | – |
| 13 | THF | 8 | toluene | 15 | 5 | 75:25 | – |
| 14 | THF | 8 | EtOAc | 0 | 0 | – | – |
| 15 | THF | 8 | MeOH | 31 | 0 | 100:0 | 81:19 |
| 16 | THF | 8 | EtOH | 53 | 0 | 100:0 | 82:18 |
| 17 | THF | 8 | *t*-AmylOH | 0 | 0 | – | – |
| 18[f,g] | THF | 8 | *i*-PrOH | >99[e] | 0 | 100:0 | 80:20 |

[a]Reaction were conducted on a 0.1 mmol scale under 5.0 MPa of $H_2$ at 80 ˚C for 24 h unless otherwise noted. The ratio of **1a** (0.2 M)/Ru/**L1**/$K_2CO_3$ was 40/1.0/1.1/8.0. [b]Determined by $^1$H NMR analysis. [c]Determined by chiral HPLC analysis. [d][RuCl(*p*-cymene)(**L1**)]Cl (1.0 mmol%) was used in place of Ru(methallyl)$_2$(cod)/**L1**. [e]**2a** was isolated from the reaction mixture quantitatively. [f]On a 0.2 mmol scale. [g]At 60 ˚C.

**Effect of Ligand on Chemoselectivity.** To shed light on the origin of the unique chemoselectivity, the hydrogenation of **1a** was attempted by using various phosphine ligands in place of **L1** (Table 2). Monophosphine–ruthenium catalysts could reduce the isoquinoline, but the reduction exclusively took place on the pyridine ring to give 1,2,3,4-tetrahydroisoquinoline **3a** in low yield as the sole product (entry 1). The undesired **3a** was also formed as the major product when typical bidentate bisphosphines were employed as the ligand (entries 2–4). As increasing in bite angle of the ligand, the ruthenium catalyst facilitated the hydrogenation of the carbocycle. The use of Xantphos (**L5**), which was designed to chelate a metal atom with large bite angle,[14] resulted in slightly increasing the yield of **2a** (entry 5). The chemoselectivity toward the carbocycle reduction was remarkably enhanced by the catalyst composed of Ru(methallyl)$_2$(cod) and (*R*,*R*,*R*)-SKP (**L6**),[15] which can form *trans*-chelate metal complex as with **L1**. The reaction using **L6** gave an approximately 1:1 mixture of **2a** and **3a**, and the enantiomer ratio of **2a** was moderate (entry 6). These results suggest that the extremely large bite angle of **L1** is crucial for the unusual chemoselectivity in the present reaction.

**Table 2. Effect of Ligand on the Chemoselectivity**




| entry | ligand | yield of **2a** (%)[b] | yield of **3a** (%)[b] | **2a**:**3a**[b] | er of **2a**[c] |
|---|---|---|---|---|---|
| 1 | $PPh_3$[d] | 0 | 21 | 0:100 | – |
| 2 | **L2** | 0 | 21 | 0:100 | – |
| 3 | **L3** | 2 | 92 | 2:98 | – |
| 4 | **L4** | 5 | 77 | 6:94 | – |
| 5 | **L5** | 9 | 49 | 16:84 | – |
| 6 | **L6** | 54 | 44 | 55:45 | 70:30 |
| 7[e] | **L1** | >99[f] | 0 | 100:0 | 79:21 |

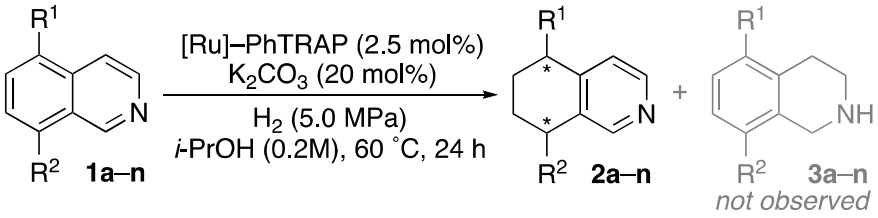
[a]Reactions were conducted on a 0.1 mmol scale under 5.0 MPa of $H_2$ at 80 °C for 24 h unless otherwise noted. The ratio of **1a** (0.2 M)/Ru/**L1**/$K_2CO_3$ was 40/1.0/1.1/8.0. [b]Determined by $^1$H NMR analysis. [c]Determined by chiral HPLC analysis. [d]5.5 mol% of $PPh_3$ was used. [e]On a 0.2 mmol scale. [f]**2a** was isolated from the reaction mixture quantitatively.

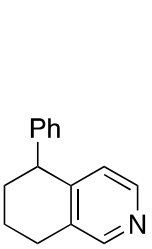
**Scope and Limitation.** A series of 5- or 8-substituted isoquinolines were submitted to the hydrogenation using PhTRAP–ruthenium catalyst (Table 3). In the hydrogenations of 5-substituted isoquinolines **1a**–**1i**, no formation of the undesired 1,2,3,4-tetrahydroisoquinolines was observed in each reaction. The enantioselectivity of the reaction was affected by the electronic property of the aryl group. The substrate **1b** bearing *p*-anisyl group was converted to **2b** in 96% yield with 87:13 er. The absolute configuration of the hydrogenation product was

assigned to be *S* by its X-ray crystallography. Meanwhile, the trifluoromethyl group of **1c** caused the significant decrease in the enantioselectivity. The stereoselectivity was scarcely affected by the methoxy group on the *meta* position in **1d**. The alkyl-substituted carbocycles of **1e** and **1f** were also exclusively saturated in good enantioselectivities. The silyloxy group at the benzylic position of **1g** had little effect on the enantioselectivity. The product **2g** could be performed as a key intermediate for the syntheses of natural product dihydronitraraine.[16] Methoxyisoquinoline **1h** gave the chiral product **2h** with 88:12 er, but the hydrogenation was accompanied by the formation of 5,6,7,8-tetrahydroisoquinoline. The methoxy group in **2h** would readily undergo the hydrogenolysis because it is located on the benzylic position.[12] Secondary amide is compatible with the ruthenium catalysis. The **L1**–ruthenium catalyst converted **1i** to **2i** in 91% yield with moderate er.

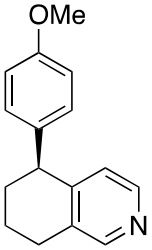
As with the reactions of **1a**–**1i**, the reduction exclusively took places on the carbocycles in the ruthenium-catalyzed hydrogenation of the 8-substituted isoquinolines **1j**–**1n**. The reaction of phenylisoquinoline **1j** proceeded in poorer enantioselectivity than that of **1a**. The stereoselectivity was hardly affected by the electronic property of the aryl substituent. The methoxy- and *N*-acylamidoisoquinolines **1m** and **1n** were transformed into **2m** and **2n** with good enantiomer ratios, but the former product underwent the undesired hydrogenolysis. The latter chiral amide may be a useful chiral building block for developing an aldosterone synthase (CYP11B2) inhibitor, which may be used for the treatment of hypertension and renal disorders.[7e]

**Table 3. Chemo- and Enantioselective Hydrogenation of 5- and 8-Substituted Isoquinolines**[a]

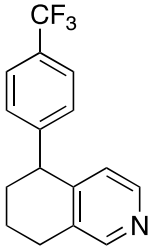


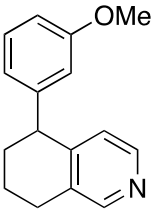

**2a**
>99% yield, 80:20 er



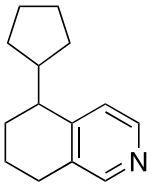

**2b**
96% yield, 87:13 er



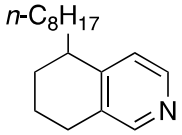

**2c**
92% yield, 70:30 er



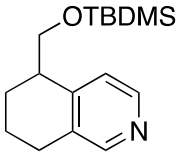

**2d**[b]
94% yield, 80:20 er



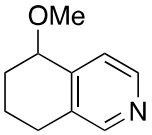

**2e**[b]
99% yield, 88:12 er



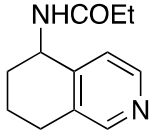

**2f**[b]
96% yield, 86:14 er



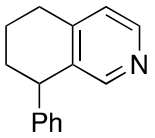

**2g**[b]
99% yield, 87:13 er



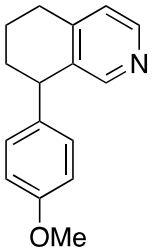

**2h**[bc]
84% yield, 88:12 er



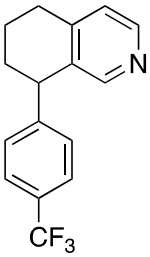

**2i**[d]
91% yield, 79:21 er



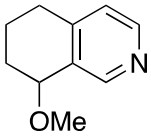

**2j**
97% yield, 76:24 er




**2k**[b]
93% yield, 77:23 er




**2l**[b]
92% yield, 75:25 er



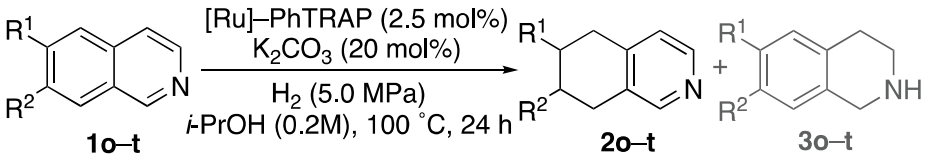

**2m**[bc]
89% yield, 86:14 er


**2n**
97% yield, 86:14 er

[a]Reactions were conducted on a 0.2 mmol scale in 1.0 mL *i*-PrOH at 60 ˚C for 24 h unless otherwise noted. The ratio of **1**/Ru/**L1**/$K_2CO_3$ was 40/1.0/1.1/8.0. Isolated yields of **2** were given in all cases. The enantiomer ratios were determined by chiral HPLC analysis. [b]At 80 ˚C. [c]The hydrogenolysis product was formed in 15% and 11% NMR yield from **2h** and **2m**, respectively. [d]For 48 h.

The **L1**–ruthenium catalyst is also applicable to the hydrogenation of 6- or 7-substituted isoquinolines **1o**–**1t** (Table 4). The reactions were carried out at higher temperature (80–100 °C) to achieve complete conversion of the isoquinoline substrate. The substituent at 6- or 7-position might hinder the catalytic reduction of the isoquinoline carbocycle. Furthermore, the undesired 1,2,3,4-tetrahydroisoquinolines **3** were formed as side products in considerable yields. The reaction of 6-phenylisoquinoline (**1o**) give **2o** in 85% yield with 91:9 er, but **3o** was concurrently formed in 12% NMR yield (entry 1). The methoxy group on the aryl substituent of **1p** caused a significant decrease in the chemoselectivity (entry 2). In contrast, the hydrogenation of trifluoromethylated substrate **1q** occurred on its isoquinoline carbocycle with high chemoselectivity (entry 3). Both the methoxy and trifluoromethyl groups caused decrease in the enantioselectivity. Methoxyisoquinoline **1r** could be converted to **2r** with good chemo- and enantioselectivities, but its reactivity was much lower than other isoquinolines (entry 4). Poor chemoselectivity was observed in the reaction of 7-phenylisoquinoline (**1s**) (entry 5), while 7-methoxyisoquinoline **1t** was converted to **2t** in high yield without formation of **3t** (entry 6). Small amount (<5% yield) of the undesired hydrogenolysis product was detected in the hydrogenation of **1r**, while the side reaction was not observed at all in the reduction of **1t**.

**Table 4. Chemo- and Enantioselective Hydrogenation of 6- and 7-Substituted Isoquinolines**[a]




**1o–t** **2o–t** **3o–t**

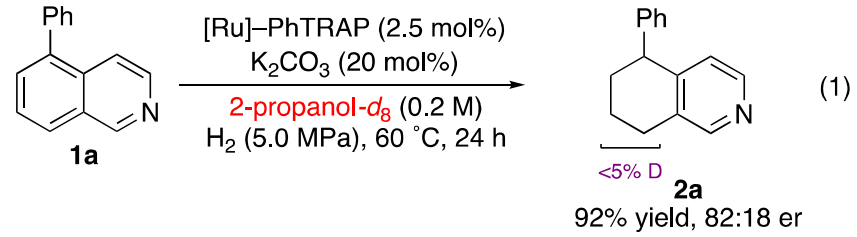
| entry | $R^1$ | $R^2$ | **1** | **2**:**3**[b] | yield of **2** (%)[c] | er of **2**[d] |
|---|---|---|---|---|---|---|
| 1 | Ph | H | **1o** | 88:12 | 85 | 91:9 |
| 2 | 4-$MeOC_6H_4$ | H | **1p** | 63:37 | 61 | 87:13 |
| 3 | 4-$CF_3C_6H_4$ | H | **1q** | 95:5 | 91 | 87:13 |
| 4[e] | MeO | H | **1r** | 87:13 | 41 | 81:19 |
| 5 | H | Ph | **1s** | 69:31 | 67 | 82:18 |
| 6[f] | H | MeO | **1t** | 100:0 | 93 | 71:29 |

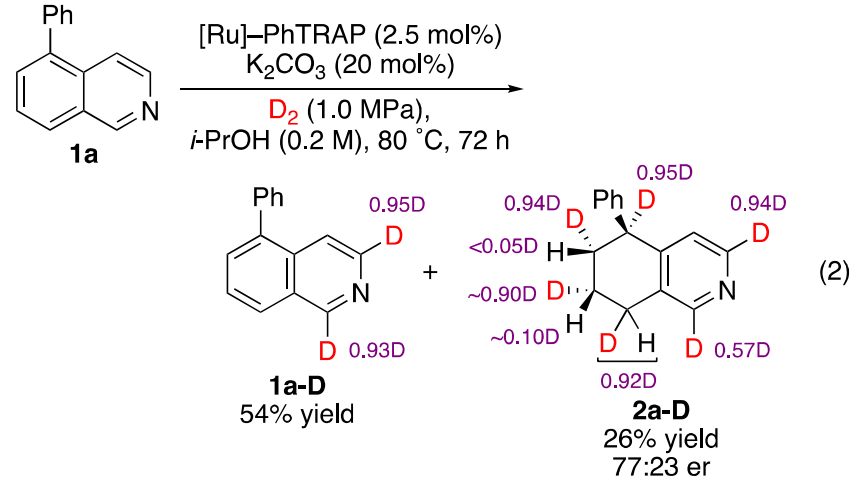
[a]Reactions were conducted on a 0.2 mmol scale in 1.0 mL solvent at 100 ˚C for 24 h unless otherwise noted. The ratio of **1**/Ru/**L1**/$K_2CO_3$ was 40/1.0/1.1/8.0. [b]Determied by $^1$H NMR analysis. [c]Isolated yields. [d]Determined by chiral HPLC analysis. [e]61% conversion. The hydrogenolysis product was formed in 3% NMR yield. [f]At 80 ˚C for 36 h.

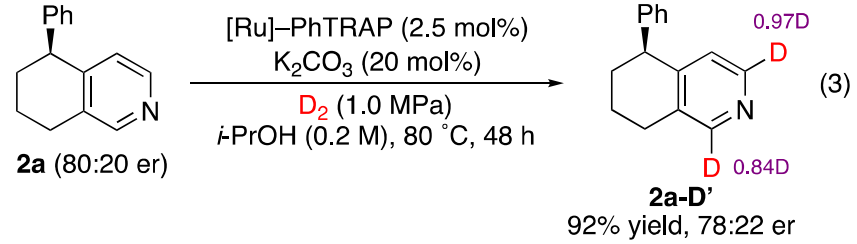
**Mechanistic Study.** To get some mechanic insights of the ruthenium-catalyzed hydrogenation of isoquinoline carbocycles, we conducted some reactions of **1a** by using deuterium-labelled compound. In eq. 1, the hydrogenation of **1a** was carried out in 2-propanol-$d_8$. The reaction provided **2a** in 92% yield with 82:28 er. No deuterium atom was incorporated in the product. This observation suggests that the *i*-PrOH solvent did not participate in the hydrogenation of isoquinoline carbocycles as a reducing agent. Next, the deuteration of **1a** was carried out in *i*-PrOH under 1.0 MPa of $D_2$ at 80 °C for 72 h (eq. 2). The reaction provided a 2:1 mixture of the deuterated starting material **1a-D** and the desired product **2a-D**. In the product, four deuterium atoms were incorporated at each of the 5-, 6-, 7-, and 8-positions on its carbocycle. The former three deuterium atoms were positioned one another in *cis*-configurations. Although the stereochemistry of the 8-position is impossible to be directly assigned with the NMR analyses, it is deduced that the deuterium on C8 locates in the *cis*-position to other deuterium atoms because the addition of $H_2$ ordinarily proceeds through *syn* stereochemistry. The deuterium distribution indicates that the hydrogenation of isoquinolines proceeds through the pathway similar to that of quinolines.[12] Three possible pathways can be proposed for the hydrogenation of **1a** as shown in Scheme 3. Path A starts from the addition of

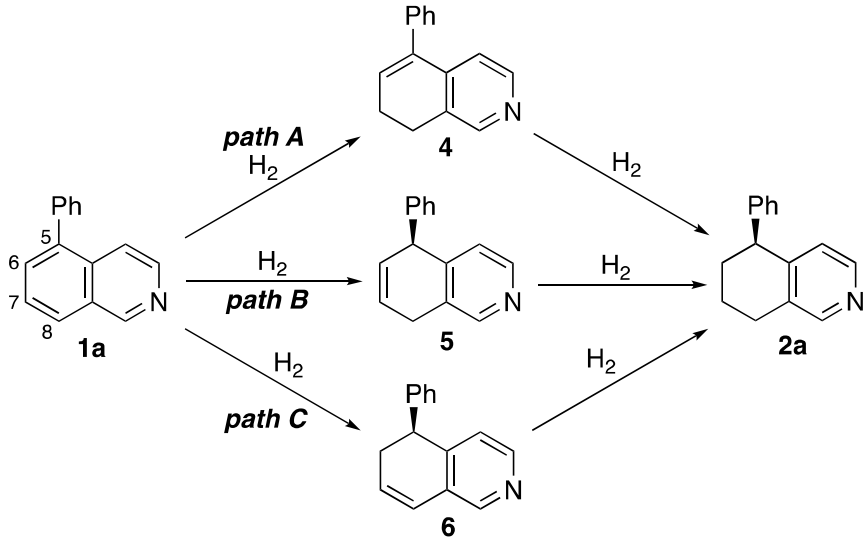
$H_2$ across the less congested C7–C8 double bond to give achiral dihydroisoquinoline **4**. If the hydrogenation proceeded through path A, diastereoisomeric 6,7-*trans*-**2a-D** would also be formed in the above deuteration of **1a** (Chart 1). In the reaction, the intermediate **4-D** resulting from the first addition of $D_2$ has two vicinal stereogenic centers. However, these stereogenic centers are impossible to control the stereochemistry of the second addition of $H_2$ to **4-D**. Therefore, path A is inconsistent with the result of eq. 2. Meanwhile, in path B or C, the isoquinoline **1a** is dearomatized through the hydrogenation of C5–C6 double bond or the 1,4-addition of $H_2$ to give the intermediate **5** or **6**, respectively. In each case, the initial hydrogen addition was accompanied by providing a new stereogenic center at the 5-position. The phenyl substituent on the stereogenic center can sterically hinder the catalyst from accessing one of the enantiofaces of remaining C–C double bond, leading to the selective formation of **2a-D** with all *cis* stereochemistry in the deuteration. Consequently, path B or C is more plausible than path A in the present hydrogenation of isoquinoline carbocycles.

The hydrogen atoms on the 1- and 3-carbons were significantly replaced by deuterium ones in the product **2a-D** in eq. 2.[17] The H/D scrambling between $D_2$ and the pyridine ring would take place independently of the hydrogenation of the carbocycle, because it was observed in the recovered starting material **1a-D**. The deuterium atoms were incorporated into the pyridine ring when the solution of the hydrogenation product **2a** was exposed to pressurized $D_2$ in the presence of **L1**–ruthenium catalyst (eq. 3). Consequently, the deuterium atoms on the pyridine ring in the product **2a-D** were installed before and after the reduction of the quinoline carbocycle. Furthermore, these observations may suggest that the **L1**–ruthenium catalyst is capable of cleaving the pyridine C–H bond through the oxidative addition.[18]


Ph
N
1a
[Ru]–PhTRAP (2.5 mol%)
K2CO3 (20 mol%)
2-propanol-d8 (0.2 M)
H2 (5.0 MPa), 60 °C, 24 h
Ph
N
<5% D
2a
92% yield, 82:18 er
(1)

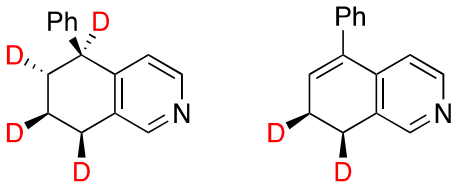

Ph
N
1a
[Ru]–PhTRAP (2.5 mol%)
K2CO3 (20 mol%)
D2 (1.0 MPa),
i-PrOH (0.2 M), 80 °C, 72 h
Ph
0.95D
D
N
D 0.93D
1a-D
54% yield
+
0.95D
0.94D
Ph
D
0.94D
D
<0.05D
H
N
~0.90D
D
H
~0.10D
D H
D 0.57D
0.92D
2a-D
26% yield
77:23 er
(2)


Ph
N
2a (80:20 er)
[Ru]–PhTRAP (2.5 mol%)
K2CO3 (20 mol%)
D2 (1.0 MPa)
i-PrOH (0.2 M), 80 °C, 48 h
Ph
0.97D
D
N
D 0.84D
2a-D'
92% yield, 78:22 er
(3)


Ph
5
6
7
8
N
1a
path A
H2
4
H2
H2
path B
5
H2
H2
path C
6
Ph
N
2a

**Scheme 3. Three Possible Pathways for the Hydrogenation of Isoquinoline Carbocycles**

**Chart 1**




6,7-*trans*-**2a-D** **4-D**

## CONCLUSION

We found that the hydrogenation of isoquinolines selectively took place on their carbocycles with the ruthenium catalyst, which was generated *in situ* from Ru(methallyl)$_2$(cod) and optically active bisphosphine ligand, PhTRAP (**L1**). It is surprising that the heterocyclic moiety of the isoquinoline remained intact in the reduction of the carbocycle, despite the fact that pyridine is generally more reactive for the dearomative reaction than benzene. The bite angle of the chelate bisphosphine ligand is crucial for achieving the unforeseen chemoselectivity. The *trans*-chelation of **L1** may lead to the selective formation of 5,6,7,8-tetrahydroisoquinolines. With the **L1**–ruthenium catalyst, various 5- and 8-substituted isoquinoline carbocycles were exclusively transformed into the corresponding 5,6,7,8-tetrahydroisoquinolines, while the hydrogenations of 6- and 7-substituted isoquinolines proceed with moderate to high chemoselectivities. Furthermore, the hydrogenation products were obtained with moderate to good enantioselectivities (up to 91:9 er).

## EXPERIMENTAL SECTION

**General Information.** All NMR spectra were measured with Bruker AVANCE 400 or AVANCE III HD 400 Nanobay spectrometer. Optical rotations, IR spectra, and melting points were measured with JASCO P-1020, JASCO FT/IR-4100, and Büchi Melting Point B-545, respectively. Elemental analyses were performed by Service Centre of Elementary Analysis of Organic Compounds, Kyushu University. High-resolution mass spectra (FAB) were measured on a JEOL JMS-700 double-focusing mass spectrometer by Network Joint Research Center for Materials and Devices (Institute for Materials Chemistry and Engineering, Kyushu University). Unless otherwise noted, all reactions were carried out under nitrogen atmosphere in dry solvent. Hydrogenations were conducted in stainless autoclaves. Ru(methallyl)$_2$(cod),[19] (*S*,*S*)-(*R*,*R*)-PhTRAP (**L1**),[13b] [RuCl(*p*-cymene)(**L1**)]Cl,[20] 5-phenylisoquinoline (**1a**),[21] 8-methoxyisoquinoline (**1m**),[22] 6-phenylisoquinoline (**1o**),[23] 6-methoxyisoquinoline (**1r**),[24] and 7-methoxyisoquinoline (**1t**)[25] were prepared according to literature procedures. All other reagents were purchased from commercial suppliers and used without further purification.

**Preparation of Isoquinoline Substrates 1.**

**5-(4-Methoxyphenyl)isoquinoline (1b).**[26] A mixture of 5-bromoisoquinoline[27] (416 mg, 2.0 mmol), 4-methoxyphenylboronic acid (456 mg, 3.0 mmol), Pd(PPh$_3$)$_4$ (116 mg, 0.10 mmol), and $Na_2CO_3$ (382 mg, 3.6 mmol) in 1,4-dioxane (8.0 mL) and water (4.0 mL) was stirred at 85 ˚C for 20 h. The resulting mixture was dilueted with water, and then extracted twice with EtOAc. The combined organic layer was dried with $Na_2SO_4$, and then evaporated under reduced pressure. The residue was purified with a flash column chromatography on alumina (EtOAc/Hexane = 1/5 to 1/3) to give **1b** (416 mg, 1.8 mmol, 88%) as an off-white solid: $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 3.91 (s, 3H), 7.06 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.63–7.68 (m, 2H), 7.75

(d, $J$ = 6.1 Hz, 1H), 7.94–7.99 (m, 1H), 8.48 (d, $J$ = 6.1 Hz, 1H), 9.30 (s, 1H); $^{13}$C {$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 55.2, 113.9, 118.5, 126.67, 126.73, 128.9, 130.7, 130.8, 131.2, 134.1, 138.7, 143.1, 152.7, 159.2.

**5-[4-(Trifluoromethyl)phenyl]isoquinoline (1c).** The procedure for preparing **1b** was followed with use of 5-bromoisoquinoline[27] (208 mg, 1.0 mmol) and 4-(trifluoromethyl)phenylbronic acid (285 mg, 1.5 mmol). The crude product was purified with a flash column chromatography on alumina (EtOAc/hexane = 1/5 to 1/3) to give **1c** (272 mg, 1.0 mmol, >99%) as an off-white solid: mp. 53.5–53.6 ˚C; $^{1}$H NMR (400 MHz, $CDCl_3$, TMS) δ 7.59–7.72 (m, 5H), 7.79 (d, $J$ = 8.0 Hz, 2H), 8.05 (ddd, $J$ = 0.9, 1.6, 7.7 Hz, 1H), 8.52 (d, $J$ = 6.0 Hz, 1H), 9.34 (s, 1H); $^{13}$C {$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 117.9, 124.1 (q, $J$ = 272 Hz), 125.5 (q, $J$ = 4 Hz), 126.7, 127.9, 128.8, 129.9 (q, $J$ = 33 Hz), 130.2, 130.9, 133.7, 137.6, 142.6, 143.7, 153.0; IR (thin film) 3046, 1617, 1325, 1166, 1123, 1067, 837, 762 cm$^{-1}$; Anal. Calcd for $C_{16}H_{10}F_3N$: C, 70.33; H, 3.69; N, 5.13. Found: C, 70.29; H, 3.70; N, 5.17.

**5-(3-Methoxyphenyl)isoquinoline (1d).** The procedure for preparing **1b** was followed with use of 5-bromoisoquinoline[27] (208 mg, 1.0 mmol) and 3-methoxyphenylbronic acid (228 mg, 1.5 mmol). The crude product was purified with a flash column chromatography on alumina (EtOAc/hexane = 1/10 to 1/7) to give **1d** (416 mg, 1.8 mmol, 88%) as an off-white solid: mp. 70.5–70.6 ˚C; $^{1}$H NMR (400 MHz, $CDCl_3$, TMS) δ 3.87 (s, 3H), 6.69–7.03 (m, 2H), 7.07 (dt, $J$ = 7.5, 1.2 Hz, 1H), 7.40–7.46 (m, 1H), 7.63–7.69 (m, 2H), 7.75 (dt, $J$ = 6.0, 0.9 Hz, 1H), 7.97–8.02 (m, 1H), 8.49 (d, $J$ = 6.0 Hz, 1H), 9.31 (d, $J$ = 0.9 Hz, 1H); $^{13}$C {$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 55.3, 113.2, 115.5, 118.5, 122.3, 126.7, 127.2, 128.9, 129.5, 130.7, 134.1, 139.0, 140.4, 143.4, 152.8, 159.6; IR (thin film) 3055, 2947, 2836, 1583, 1475, 1291, 1169, 1043, 790 cm$^{-1}$; Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.46; H, 5.57; N, 5.87.

**5-Cyclopentylisoquinoline (1e).** The procedure for preparing **1b** was followed with use of 5-bromoisoquinoline[27] (312 mg, 1.5 mmol) and 1-cyclopentenylbronic acid (252 mg, 2.3 mmol). The crude product was purified with a flash column chromatography on silica gel (EtOAc/hexane = 1/5 to 1/3) to give 5-(1-cyclopentenyl)isoquinoline (273 mg, 1.4 mmol, 93%) as yellow oil.

A suspension of 5-(1-cyclopentenyl)isoquinoline (195 mg, 1.0 mmol) and 5% palladium on carbon (42.0 mg, 20 μmol) in MeOH (3.0 mL) was vigorously stirred under 1.0 MPa of $H_2$ at room temperature for 12 h. After the resulting mixture was filtered through a Celite pad, the resulting filtrate was evaporated under reduced pressure. The residue was purified with column chromatography on silica gel (EtOAc/Hexane = 1/3) to give 5-cyclopentylisoquinoline **1e** (168 mg, 0.85 mmol, 85%) as colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 1.70–1.94 (m, 6H), 2.15–2.25 (m, 2H), 3.71 (quintet, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 7.1 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 6.1 Hz, 1H), 8.54 (d, *J* = 6.1 Hz, 1H), 9.24 (s, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 25.3, 33.5, 40.7, 116.9, 125.7, 126.1, 126.9, 129.0, 134.8, 141.6, 142.8, 153.2; IR (neat): 2952, 2869, 1588, 1380, 1261, 1038, 907, 757 cm$^{-1}$; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{14}H_{16}N$ 198.1283; Found 198.1287.

**5-Octylisoquinoline (1f).** To a solution of 5-bromoisoquinoline[27] (624 mg, 3.0 mmol), $PdCl_2(PPh_3)_2$ (105 mg, 0.15 mmol), and CuI (68.6 mg, 0.36 mmol) in MeCN (10 mL) were added 1-octyne (0.88 mL, *d* 0.75 g/mL, 6.0 mmol) and $Et_3N$ (1.2 mL, *d* 0.73 g/mL, 9.0 mmol). The reaction mixture was stirred at 90 ˚C for 12 h. The resulting mixture was diluted with EtOAc and then filtered through a Celite pad. After diluted with water, the filtrate was extracted twice with EtOAc. The combined organic layer was dried with $Na_2SO_4$, and then evaporated under reduced pressure. The residue was purified with column chromatography on silica gel

(EtOAc/Hexane = 1/7) to give 5-(1-octynyl)isoquinoline (719 mg) as brown oil. The product was immediately used for the following step, because it is thermally unstable.

A mixture of the brown oil (719 mg) and 5% palladium on carbon (120 mg, 60 μmol) in MeOH (3.0 mL) was vigorously stirred under 2.0 MPa of $H_2$ at 40 ˚C for 24 h. After the resulting mixture was filtered through a Celite pad, the filtrate was evaporated under reduced pressure. The residue was purified with column chromatography on silica gel (EtOAc/Hexane = 1/5) to give an *E*/*Z* isomeric mixture of 5-(1-octenyl)isoquinoline (568 mg, 2.4 mmol, 79% for two steps, *Z*/*E* > 10/1) as yellow oil.

A suspension of 5-(1-octenyl)isoquinoline (192 mg, 0.8 mmol) and 5% palladium on carbon (Degussa type E, 105NN/W) (37.6 mg, 8.0 μmol) in MeOH (2.0 mL) was vigorously stirred under 1.0 MPa of $H_2$ at room temperature for 3 h. After the mixture was filtered through a Celite pad, the filtrate was evaporated under reduced pressure. The residue was purified with a flash column chromatography on silica gel (EtOAc/hexane = 1/3) to give **1f** (185 mg, 0.77 mmol, 96%) as colorless oil: $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.20–1.47 (m, 10H), 1.73 (quintet, *J* = 7.6 Hz, 2H), 3.03 (t, *J* = 7.8 Hz, 2H), 7.50–7.55 (m, 2H), 7.79–7.85 (m, 2H), 8.54 (d, *J* = 6.0 Hz, 1H), 9.24 (d, *J* = 0.8 Hz 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 14.1, 22.6, 29.2, 29.4, 29.7, 30.7, 31.8, 32.3, 116.8, 125.8, 126.9, 129.0, 129.8, 134.6, 138.3, 142.9, 153.2; IR (neat) 2926, 2857, 1621, 1584, 1460, 1378, 821, 756 cm$^{-1}$; Anal. Calcd for $C_{17}H_{23}N$: C, 84.59; H, 9.60; N, 5.80. Found: C, 84.46; H, 9.60; N, 5.83.

**5-(*tert*-Butyldimethylsilyloxymethyl)isoquinoline (1g).** Methyl isoquinoline-5-carboxylate was prepared with a modified procedure for the palladium-catalyzed alkoxycarbonylation of bromoarenes.[28] To a mixture of 5-bromoisoquinoline[27] (624 mg, 3.0 mmol), $Pd(OAc)_2$ (13.5 mg, 60 μmol), and Xantphos (69.4 mg, 0.12 mmol) were added MeOH (1.2 mL, 30 mmol) and $Et_3N$

(6.0 mL) under CO atmosphere. The reaction mixture was stirred vigorously at 70 ˚C for 24 h. After the mixture was filtered through a Celite pad, the filtrate was evaporated under reduced pressure. The residue was purified with a flash column chromatography on silica gel (EtOAc/hexane = 1/2) to give methyl isoquinoline-5-carboxylate (554 mg, 3.0 mmol, 99%) as a pale yellow solid.

A solution of methyl isoquinoline-5-carboxylate (187 mg, 1.0 mmol) in THF (4.0 mL) was added dropwise to a suspension of $LiAlH_4$ (75.9 mg, 2.0 mmol) in THF (4.0 mL) at ambient temperature. The reaction mixture was stirred for 2 h. 1 *N* KOH *aq.* was carefully added to the resulting mixture with vigorously stirring until the hydrogen gas evolution ceased. After stirred for 10 min, the mixture was diluted with THF, and then filtered through a Celite pad. The filtrate was dried with $Na_2SO_4$, and then evaporated under reduced pressure. The residue was used in the next step without further purification.

To a solution of the residue in THF (5.0 mL) were added imidazole (81.7 mg, 1.2 mmol) and TBDMSCl (181 mg, 1.2 mmol). The reaction mixture was stirred at ambient temperature for 24 h. After diluted with water, the resulting mixture was extracted twice with EtOAc. The combined organic layer was dried with $Na_2SO_4$, and then evaporated under reduced pressure. The residue was purified with a flash column chromatography on silica gel (EtOAc/hexane = 1/5) to give **1g** (234 mg, 0.86 mmol, 86% for two steps) as pale yellow oil: $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 0.13 (s, 6H), 0.95 (s, 9H), 5.16 (s, 2H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.76–7.80 (m, 2H), 7.89 (d, *J* = 8.2 Hz, 1H), 8.55 (d, *J* = 6.1 Hz, 1H), 9.26 (s, 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ –5.3, 18.4, 25.9, 62.7, 116.4, 126.8, 126.9, 127.8, 128.6, 133.5, 136.1, 143.0, 153.0; IR (neat) 2947, 2859, 1464, 1255, 1115, 1070, 838, 773 cm$^{-1}$; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{24}NOSi$ 274.1627; Found 274.1625.

***N*-(5-Isoquinolinyl)propionamide (1i).**[29] To a solution of 5-aminoisoquinoline (216 mg, 1.5 mmol) in pyridine (1.5 mL) was added propionic anhydride (0.29 mL, *d* 1.01 g/mL, 2.3 mmol). The reaction mixture was stirred at ambient temperature for 24 h. After diluted with water, the resulting mixture was extracted twice with $CH_2Cl_2$. The combined organic layer was washed twice with saturated $Na_2CO_3$ aq., dried with $Na_2SO_4$, and then filtered. The filtrate was evaporated under reduced pressure to give **1i** (246 mg, 1.2 mmol, 82%) as an off-white solid: mp. 164.2–164.3 ˚C; $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 1.36 (br t, *J* = 6.9 Hz, 3H), 2.58 (br q, *J* = 7.2 Hz, 2H), 7.54 (br, 1H), 7.62 (t, *J* = 7.9 Hz, 2H), 7.83 (d, *J* = 7.8 Hz, 1H), 8.20 (d, *J* = 7.4 Hz, 1H), 8.57 (d, *J* = 5.9 Hz, 1H), 9.27 (s, 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 9.8, 30.5, 113.9, 124.7, 125.0, 127.2, 129.0, 129.7, 131.7, 143.1, 153.0, 172.7; IR (thin film) 3265, 2979, 1657, 1529, 1379, 1216, 813 cm$^{-1}$; Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.79; H, 6.05; N, 13.95.

**8-Phenylisoquinoline (1j).**[23] The procedure for preparing **1b** was followed with use of 8-bromoisoquinoline (208 mg, 1.0 mmol) and phenylboronic acid (183 mg, 1.5 mmol). The crude product was purified with a flash column chromatography on silica gel (EtOAc/hexane = 1/5 to 1/3) to give **1j** (203 mg, 0.99 mmol, 99%) as a pale yellow oil: $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 7.45–7.55 (m, 6H), 7.69–7.76 (m, 2H), 7.83 (d, *J* = 8.2 Hz, 1H), 8.55 (d, *J* = 5.5 Hz, 1H), 9.31 (s, 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 120.5, 126.0, 126.7, 127.9, 128.2, 128.5, 129.9, 130.1, 136.2, 138.7, 141.1, 142.8, 151.2.

**8-(4-Methoxyphenyl)isoquinoline (1k).**[30] The procedure for preparing **1b** was followed with use of 8-bromoisoquinoline (208 mg, 1.0 mmol) and 4-methoxyphenylboronic acid (228 mg, 1.5 mmol). The crude product was purified with a flash column chromatography on silica gel (EtOAc/hexane = 1/5 to 1/3) to give **1k** (221mg, 0.94 mmol, 94%) as a pale yellow solid: mp.

85.4–85.5 °C; $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 3.91 (s, 3H), 7.06 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.51 (dd, *J* = 7.0, 1.1 Hz, 1H), 7.68–7.74 (m, 2H), 7.80 (d, *J* = 8.2 Hz, 1H), 8.54 (d, *J* = 5.7 Hz, 1H), 9.34 (s, 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 55.4, 114.0, 120.5, 125.6, 126.8, 128.1, 129.9, 131.0, 131.2, 136.2, 140.7, 142.8, 151.3, 159.4; IR (thin film) 3050, 1612, 1387, 838, 758, 699 cm$^{-1}$; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{15}H_{12}N$ 206.0970; Found 206.0996.

**8-[4-(Trifluoromethyl)phenyl]isoquinoline (1l).** The procedure for preparing **1b** was followed with use of 8-bromoisoquinoline (208 mg, 1.0 mmol) and 4-(trifluoromethyl)phenylboronic acid (285 mg, 1.5 mmol). The crude product was purified with a flash column chromatography on silica gel (EtOAc/hexane = 1/5 to 1/3) to give **1l** (234.7 mg, 0.86 mmol, 86%) as a colorless solid: mp. 72.9–73.0 °C; $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 7.53 (dd, *J* = 1.1, 7.1 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.72–7.82 (m, 4H), 7.89 (d, *J* = 8.4 Hz, 1H), 8.59 (d, *J* = 5.6 Hz, 1H), 9.24 (s, 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 120.6, 124.1 (q, *J* = 272 Hz), 125.5 (q, *J* = 4 Hz), 126.4, 126.8, 128.3, 129.8, 130.2 (q, *J* = 33 Hz), 130.4, 136.2, 139.4, 142.4, 143.2, 150.6; IR (KBr pellet) 3049, 1613, 1401, 1326, 1165, 1114, 1064, 838 cm$^{-1}$; Anal. Calcd for $C_{16}H_{10}F_3N$: C, 70.33; H, 3.69; N, 5.13. Found: C, 70.27; H, 3.65; N, 5.15.

***N*-(8-Isoquinolinyl)propionamide (1n).** The procedure for preparing **1i** was followed with use of 8-aminoisoquinoline (216 mg, 1.5 mmol). The crude product was purified with a flash column chromatography on silica gel (EtOAc/hexane = 1/1 to 2/1 to EtOAc) to give **1n** (276 mg, 1.4 mmol, 92%) as an off-white solid: mp. 138.7–138.8 °C; $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 1.32 (br t, *J* = 6.8 Hz, 3H), 2.57 (br q, *J* = 6.8 Hz, 2H), 7.58–7.68 (br m, 3H), 7.98 (br d, *J* = 5.1 Hz, 1H), 8.18 (br s, 1H), 8.52 (br d, *J* = 5.6 Hz, 1H), 9.37 (s, 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 9.7, 30.1, 120.6, 122.5 (2C), 123.7, 130.4, 133.7, 136.3, 142.5, 146.8, 173.6; IR (thin

film) 3276, 3060, 2984, 1663, 1540, 1403, 1213, 835 $cm^{-1}$; Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.05; H, 6.01; N, 13.98.

**6-(4-Methoxyphenyl)isoquinoline (1p).**[31] The procedure for preparing **1b** was followed with use of 6-bromoisoquinoline (416 mg, 2.0 mmol) and 4-methoxyphenylboronic acid (456 mg, 3.0 mmol). The crude product was purified with a flash column chromatography on alumina (EtOAc/hexane = 1/7 to 1/5) to give **1p** (428 mg, 1.8 mmol, 91%) as an off-white solid: $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 3.89 (s, 3H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.65–7.70 (m, 3H), 7.85 (dd, *J* = 1.8, 8.5 Hz, 1H), 7.95 (br s, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 8.53 (d, *J* = 5.9 Hz, 1H), 9.25 (s, 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 55.4, 114.5, 120.5, 123.3, 126.9, 127.5, 128.1, 128.7, 132.6, 136.2, 142.6, 143.4, 152.2, 159.9.

**6-[4-(Trifluoromethyl)phenyl]isoquinoline (1q).** The procedure for preparing **1b** was followed with use of 6-bromoisoquinoline (312 mg, 1.5 mmol), and 4-(trifluoromenthyl)phenylboronic acid (427 mg, 2.3 mmol). The crude product was purified with a flash column chromatography on silica gel (EtOAc/hexane = 1/3 to 1/2) to give **1q** (373 mg, 1.4 mmol, 91%) as an off-white solid: mp. 70.3–70.4 ˚C; $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 7.71–7.87 (m, 6H), 8.03 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 8.59 (d, *J* = 5.8 Hz, 1H), 9.31 (s, 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 120.6, 124.1 (q, *J* = 272 Hz), 124.8, 125.9 (q, *J* = 4 Hz), 126.7, 127.88, 127.94, 128.5, 130.2 (q, *J* = 32 Hz), 135.9, 141.5, 143.68, 143.73, 152.3; IR (KBr pellet) 3057, 1619, 1411, 1331, 1161, 1109, 1067, 836 $cm^{-1}$; Anal. Calcd for $C_{16}H_{10}F_3N$: C, 70.33; H, 3.69; N, 5.13. Found: C, 70.19; H, 3.70; N, 5.13.

**7-Phenylisoquinoline (1s).**[30] The procedure for preparing **1b** was followed with use of 7-bromoisoquinoline (208 mg, 1.0 mmol) and phenylboronic acid (183 mg, 1.5 mmol). The crude product was purified with a flash column chromatography on silica gel (EtOAc/hexane = 1/5 to

1/3) to give **1s** (161 mg, 0.79 mmol, 79%) as an off-white solid: mp. 91.5–91.6 ˚C; $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 7.42 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.68 (d, *J* = 5.8 Hz, 1H), 7.71–7.75 (m, 2H), 7.91 (d, *J* = 8.6 Hz, 1H), 7.98 (dd, *J* = 1.8, 8.6 Hz, 1H), 8.17 (br m, 1H), 8.54 (d, *J* = 5.7 Hz, 1H), 9.33 (s, 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 120.2, 125.3, 127.0, 127.4, 127.9, 129.0, 130.1, 134.9, 140.13, 140.19, 143.1, 152.8; IR (KBr pellet) 3006, 1581, 1481, 1348, 1222, 1025, 938, 799, 755 cm$^{-1}$; Anal. Calcd for $C_{15}H_{11}N$: C, 87.77; H, 5.40; N, 6.82. Found: C, 87.51; H, 5.40; N, 6.84.

**General Procedure for the Chemo- and Enantioselective Hydrogenation of Isoquinolines 1.** In a nitrogen-filled drybox, a mixture of Ru(methallyl)$_2$(cod) (1.6 mg, 5.0 μmol) and (*S*,*S*)-(*R*,*R*)-PhTRAP (**L1**) (4.4 mg, 5.5 μmol) in THF (1.0 mL) was stirred at ambient temperature for 8 h. The solvent was then removed in vacuo. To the residue were added $K_2CO_3$ (5.6 mg, 40 μmol), isoquinoline **1** (0.2 mmol), and *i*-PrOH (1.0 mL). After removed from the drybox, the mixture was transferred into a nitrogen-purged stainless autoclave. After the autoclave was charged with 5.0 MPa of $H_2$, the reaction mixture was vigorously stirred at 60–100 ˚C for 24–48 h. The resulting mixture was evaporated under reduced pressure. The residue was purified with a column chromatography on silica gel (EtOAc/hexane or $CH_2Cl_2$/MeOH) to give the desired 5,6,7,8-tetrahydroisoquinoline **2**.

**(+)-5-Phenyl-5,6,7,8-tetrahydroisoquinoline (2a).** The general procedure was followed with use of 5-phenylisoquinoline (**1a**) (41.0 mg, 0.20 mmol). The reaction was carried out at 60 ˚C for 24 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/3 to 1/2) to give **2a** (41.8 mg, 0.20 mmol, >99%) as an off-white solid: $[\alpha]_D^{28}$ +16.2 (*c* 1.03, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 1.74–1.92 (m, 2H), 1.92–2.02 (m, 1H), 2.15–2.23 (m, 1H), 2.80–2.95 (m, 2H), 4.04 (t, *J* = 6.9 Hz, 1H), 6.73 (d, *J* = 5.2 Hz,

1H), 7.06–7.10 (m, 1H), 7.21–7.26 (m, 1H), 7.28–7.33 (m, 2H), 8.22 (d, $J$ = 5.2 Hz, 1H), 8.39 (d, $J$ = 0.6 Hz, 1H); $^{13}$C {$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 20.8, 26.5, 32.6, 45.1, 124.4, 126.4, 128.5, 128.7, 133.1, 145.5, 146.7, 148.2, 150.5; IR (thin film) 2934, 2863, 1593, 1488, 1444, 1411, 831, 753, 700 cm$^{-1}$; HRMS (FAB) $m/z$: [M+H]$^+$ Calcd for $C_{15}H_{16}N$ 210.1283; Found 210.1315. The enantiomer ratio of **2a** was determined to be (+):(–) = 80:20 (60% ee) by the HPLC analysis with Chiralcel OD-H.

**(*S*)-5-(4-Methoxyphenyl)-5,6,7,8-tetrahydroisoquinoline (2b).** The general procedure was followed with use of 5-(4-methoxyphenyl)isoquinoline (**1b**) (47.1 mg, 0.20 mmol). The reaction was carried out at 60 ˚C for 24 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/5 to 1/3) to give **2b** (45.9 mg, 0.19 mmol, 96%) as an off-white solid: $[\alpha]_D^{27}$ +35.2 (*c* 1.01, $CHCl_3$); $^{1}$H NMR (400 MHz, $CDCl_3$, TMS) δ 1.72–1.89 (m, 2H), 1.91–2.01 (m, 1H), 2.11–2.20 (m, 1H), 2.78–2.93 (m, 2H), 3.80 (s, 3H), 3.99 (t, $J$ = 6.7 Hz, 1H), 6.74 (d, $J$ = 5.1 Hz, 1H), 6.84 (d, $J$ = 8.7 Hz, 2H), 6.99 (d, $J$ = 8.7 Hz, 2H), 8.22 (d, $J$ = 5.1 Hz, 1H), 8.37 (s, 1H); $^{13}$C {$^{1}$H} NMR (101 MHz, $CDCl_3$) δ 20.9, 26.5, 32.7, 44.3, 55.2, 113.8, 124.4, 129.6, 133.1, 137.6, 146.7, 148.6, 150.4, 158.2; IR (thin film) 2936, 2861, 1604, 1509, 1247, 1177, 1034, 829 cm$^{-1}$; Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.13; H, 7.15; N, 5.90. The enantiomer ratio of **2b** was determined to be (*S*):(*R*) = 87:13 (74% ee) by the HPLC analysis with Chiralcel OD-H. The absolute configuration of **2b** was determined to be *S* by its X-ray crystallography. Suitable crystals of **2b** for the diffraction study were obtained from its solution in MeOH by slow evaporation. All measurements as well as refinement details are given in Supporting Information and its CIF file, which have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1586482).

**(+)-5-[4-(Trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinoline (2c).** The general

procedure was followed with use of 5-[4-(trifluoromethyl)phenyl]isoquinoline (**1c**) (54.7 mg, 0.20 mmol). The reaction was carried out at 60 ˚C for 24 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/5 to 1/3) to give **2c** (51.0 mg, 0.18 mmol, 92%) as pale yellow oil: $[\alpha]_D^{27}$ +5.0 (*c* 1.03, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 1.75–1.90 (m, 2H), 1.92–2.01 (m, 1H), 2.15–2.25 (m, 1H), 2.82–2.96 (m, 2H), 4.12 (t, *J* = 6.8 Hz, 1H), 6.69 (d, *J* = 5.1 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 8.24 (d, *J* = 5.1 Hz, 1H), 8.42 (s, 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 20.7, 26.4, 32.5, 45.0, 124.1 (q, *J* = 272 Hz), 124.2, 125.5 (q, *J* = 4 Hz), 128.8 (q, *J* = 32 Hz), 129.0, 133.2, 146.9, 147.1, 149.6, 150.7; IR (neat) 2939, 2866, 1693, 1593, 1414, 1325, 1120, 836 $cm^{-1}$; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{16}H_{15}F_3N$ 278.1157; Found 278.1165. The enantiomer ratio of **2c** was determined to (+):(–) = 70:30 (40% ee) by the HPLC analysis with Chiralcel OD-H.

**(+)-5-(3-Methoxyphenyl)-5,6,7,8-tetrahydroisoquinoline (2d).** The general procedure was followed with use of 5-(3-methoxyphenyl)isoquinoline (**1d**) (47.1 mg, 0.20 mmol). The reaction was carried out at 80 ˚C for 24 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/2) to give **2d** (45.0 mg, 0.19 mmol, 94%) as pale brown oil: $[\alpha]_D^{28}$ +14.1 (*c* 1.02, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 1.73–1.92 (m, 2H), 1.93–2.02 (m, 1H), 2.14–2.23 (m, 1H), 2.79–2.94 (m, 2H), 3.77 (s, 3H), 4.01 (t, *J* = 7.0 Hz, 1H), 6.62 (t, *J* = 2.1 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 5.2 Hz, 1H), 6.78 (ddd, *J* = 0.8, 2.6, 8.2 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 8.22 (d, *J* = 5.2 Hz, 1H), 8.38 (s, 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 20.9, 26.5, 32.4, 45.2, 55.1, 111.4, 114.8, 121.1, 124.4, 129.4, 133.1, 146.7, 147.1, 148.1, 150.4, 159.7; IR (neat) 2936, 2863, 1592, 1485, 1442, 1257, 1159, 1046, 837, 781, 705 $cm^{-1}$; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{16}H_{18}NO$ 240.1388; Found 240.1394. The enantiomer ratio of **2d** was determined to be (+):(–) = 80:20 (59% ee) by the HPLC analysis

with Chiralcel OD-H.

**(–)-5-Cyclopentyl-5,6,7,8-tetrahydroisoquinoline (2e).** The general procedure was followed with use of 5-cyclopentylisoquinoline (**1e**) (39.5 mg, 0.20 mmol). The reaction was carried out at 80 ˚C for 24 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/3) to give **2e** (39.8 mg, 0.20 mmol, 99%) as a pale yellow oil: $[\alpha]_D^{27}$ –12.5 (*c* 1.02, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 1.11–1.22 (m, 1H), 1.31–1.42 (m, 1H), 1.43–1.59 (m, 2H), 1.59–1.83 (m, 7H), 1.88–1.99 (m, 1H), 2.04–2.16 (m, 1H), 2.64 (dt, *J* = 8.1, 5.2 Hz, 1H), 2.72 (dt, *J* = 16.5, 6.8, Hz, 1H), 2.77 (dt, *J* = 16.5, 6.1, Hz, 1H), 7.07 (d, *J* = 5.2 Hz, 1H), 8.26 (d, *J* = 5.2 Hz, 1H), 8.29 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 19.1, 24.7, 25.29, 25.33, 26.1, 29.5, 31.5, 41.8, 44.3, 123.6, 132.8, 146.0, 149.9, 150.4; IR (neat) 2946, 2867, 1684, 1593, 1442, 1412, 1284, 827 $cm^{-1}$; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{14}H_{20}N$ 202.1596; Found 202.1608. The enantiomer ratio of **2e** was determined to be (–):(+) = 88:12 (75% ee) by the HPLC analysis with Chiralpak AD-H.

**(–)-5-Octyl-5,6,7,8-tetrahydroisoquinoline (2f).** The general procedure was followed with use of 5-octylisoquinoline (**1f**) (48.3 mg, 0.20 mmol). The reaction was carried out at 80 ˚C for 24 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/3) to give **2f** (47.1 mg, 0.19 mmol, 96%) as colorless oil: $[\alpha]_D^{27}$ –7.8 (*c* 1.02, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.20–1.47 (m, 12H), 1.48–1.59 (m, 1H), 1.60–1.77 (m, 3H), 1.81–1.93 (m, 2H), 2.65–2.79 (m, 3H), 7.06 (d, *J* = 5.1 Hz, 1H), 8.26–8.33 (m, 2H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 14.1, 19.7, 22.6, 26.6, 26.9, 27.1, 29.3, 29.5, 29.8, 31.9, 36.0, 37.0, 123.0, 132.8, 146.6, 150.3, 150.4; IR (neat) 2926, 2857. 1639, 1598, 1458, 826 $cm^{-1}$; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{17}H_{28}N$ 246.2222; Found 246.2223. The enantiomer ratio of **2f** was determined to be (–):(+) = 86:14 (71% ee) by the HPLC analysis with

Chiralcel OD-H.

**(+)-5-(tert-Butyldimethylsilyloxymethyl)-5,6,7,8-tetrahydroisoquinoline (2g).** The general procedure was followed with use of 5-(*tert*-butyldimethylsilyloxymethyl)isoquinoline (**1g**) (54.7 mg, 0.20 mmol). The reaction was carried out at 80 ˚C for 24 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/5) to give **2g** (54.9 mg, 0.20 mmol, 99%) as colorless oil: $[\alpha]_D^{27}$ +3.3 (*c* 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 0.02 (s, 3H), 0.04 (s, 3H), 0.89 (s, 9H), 1.69–1.93 (m, 4H), 2.65–2.79 (m, 2H), 2.87–2.95 (m, 1H), 3.67 (dd, *J* = 7.9, 10.0 Hz, 1H), 3.76 (dd, *J* = 5.5, 10.0 Hz, 1H), 7.14 (d, *J* = 5.1 Hz, 1H), 8.29 (d, *J* = 5.1 Hz, 1H), 8.31 (s, 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ –5.5, –5.4, 18.3, 19.3, 24.6, 25.9, 26.6, 39.8, 66.7, 123.7, 133.5, 146.45, 146.47, 150.4; IR (neat) 2936, 2861, 1598, 1465, 1409, 1254, 1099, 837, 776 $cm^{-1}$; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{16}H_{28}NOSi$ 278.1940; Found 278.1942. The enantiomer ratio of **2g** was determined to be (+):(–) = 87:13 (73% ee) by the HPLC analysis with Chiralpak AD-H.

**(–)-5-Methoxy-5,6,7,8-tetrahydroisoquinoline (2h).** The general procedure was followed with use of 5-methoxyisoquinoline (**1h**) (31.8 mg, 0.20 mmol). The reaction was carried out at 80 ˚C for 24 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/3 to 1/1) to give **2h** (27.4 mg, 0.17 mmol, 84%) as colorless oil: $[\alpha]_D^{28}$ –20.8 (*c* 0.98, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 1.71–1.83 (m, 1H), 1.85–1.95 (m, 1H), 1.96–2.08 (m, 2H), 2.71 (dt, *J* = 16.9, 6.1 Hz, 1H), 2.81 (dt, *J* = 16.9, 6.2 Hz, 1H), 3.48 (s, 3H), 4.29 (dd, *J* = 4.0, 6.8 Hz, 1H), 7.29 (d, *J* = 5.1 Hz, 1H), 8.37 (s, 1H), 8.40 (d, *J* = 5.1 Hz, 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 18.8, 25.9, 26.9, 56.5, 75.8, 122.8, 132.6, 145.2, 147.0, 150.5; IR (neat) 2941, 1640, 1417, 1350, 1280, 1193, 1094 $cm^{-1}$; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{10}H_{14}NO$ 164.1075; Found 164.1076. The enantiomer ratio of **2h** was determined to

be (–):(+) = 88:12 (77% ee) by the HPLC analysis with Chiralpak AD-H.

**(+)-*N*-(5,6,7,8-Tetrahydroisoquinolin-5-yl)propionamide (2i).** The general procedure was followed with use of *N*-(5-isoquinolinyl)propionamide (**1i**) (40.0 mg, 0.20 mmol). The reaction was carried out at 60 ˚C for 48 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/1 to EtOAc to $CH_2Cl_2$/MeOH = 20/1) to give **2i** (37.3 mg, 0.18 mmol, 91%) as a pale brown solid: $[\alpha]_D^{27}$ +59.4 (*c* 1.04, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 1.21 (t, *J* = 7.6 Hz, 3H), 1.65–1.75 (m, 1H), 1.81–1.97 (m, 2H), 2.08–2.17 (m, 1H), 2.28 (q, *J* = 7.6 Hz, 2H), 2.78 (t, *J* = 6.3 Hz, 2H), 5.20 (dt, *J* = 5.6, 8.3 Hz, 1H), 5.64 (br d, *J* = 8.6 Hz, 1H), 7.16 (d, *J* = 5.1 Hz, 1H), 8.33–8.38 (m, 2H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 9.9, 20.1, 25.9, 29.64, 29.70, 46.4, 122.3, 132.8, 146.0, 147.0, 150.2, 173.5; IR (thin film) 3281, 3061, 2940, 1648, 1546, 1455, 1235, 1111, 1063, 831 cm$^{-1}$; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{17}N_2O$ 205.1341; Found 205.1340. The enantiomer ratio of **2i** was determined to be (+):(–) = 79:21 (59% ee) by the HPLC analysis with Chiralpak ID.

**(–)-8-Phenyl-5,6,7,8-Tetrahydroisoquinoline (2j).** The general procedure was followed with use of 8-phenylisoquinoline (**1j**) (41.0 mg, 0.20 mmol). The reaction was carried out at 60 ˚C for 24 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/3 to 1/2) to give **2j** (40.6 mg, 0.19 mmol, 97%) as an off-white solid: $[\alpha]_D^{26}$ –3.5 (*c* 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 1.71–1.82 (m, 1H), 1.84–1.95 (m, 2H), 2.13–2.22 (m, 1H), 2.80 (dt, *J* = 17.7, 5.9 Hz, 1H), 2.89 (dt, *J* = 17.7, 6.8 Hz, 1H), 4.14 (t, *J* = 6.6 Hz, 1H), 7.04 (d, *J* = 5.0 Hz, 1H), 7.07 (d, *J* = 7.0 Hz, , 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.29 (t, *J* = 7.3 Hz, 2H), 8.08 (s, 1H), 8.30 (d, *J* = 5.0 Hz, 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 20.0, 28.9, 32.7, 42.8, 123.6, 126.3, 128.4, 128.6, 135.2, 146.0, 146.4, 146.6, 151.7; IR (thin film) 2934, 1635, 1488, 1414, 751, 697 cm$^{-1}$; Anal. Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N,

6.69. Found: C, 85.91; H, 7.20; N, 6.80. The enantiomer ratio of **2j** was determined to be (–):(+) = 76:24 (51% ee) by the HPLC analysis with Chiralcel OD-H.

**(+)-8-(4-Methoxyphenyl)-5,6,7,8-tetrahydroisoquinoline (2k).** The reaction general procedure was followed with use of 8-(4-methoxyphenyl)isoquinoline (**1k**) (47.1 mg, 0.20 mmol). The reaction was carried out at 80 ˚C for 24 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/3) to give **2k** (45.0 mg, 0.19 mmol, 94%) as colorless oil: $[\alpha]_D^{28}$ +2.59 (*c* 1.01, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 1.69–1.80 (m, 1H), 1.81–1.93 (m, 2H), 2.09–2.19 (m, 1H), 2.80 (dt, *J* = 17.4, 6.0 Hz, 1H), 2.87 (ddd, *J* = 17.4, 6.9 Hz, 1H), 3.79 (s, 3H), 4.09 (t, *J* = 6.5 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 1H), 7.03 (d, *J* = 5.0 Hz, 1H), 8.08 (s, 1H), 8.29 (d, *J* = 5.0 Hz, 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 20.0, 28.9, 32.7, 42.0, 55.2, 113.8, 123.6, 129.5, 135.6, 138.1, 146.3, 146.5, 151.7, 158.0; IR (neat) 2934, 1603, 1507, 1452, 1415, 1246, 1178, 1033, 824 $cm^{-1}$; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{16}H_{18}NO$ 240.1388; Found 240.1386. The enantiomer ratio of **2k** was determined to be (+):(–) = 77:23 (53% ee) by the HPLC analysis with Chiralcel OD-H.

**(–)-8-[4-(Trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinoline (2l).** The general procedure was followed with use of 8-[4-(trifluoromethyl)phenyl]isoquinoline (**1l**) (54.7 mg, 0.20 mmol). The reaction was carried out at 80 ˚C for 24 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/3) to afford **3c** (50.8 mg, 0.18 mmol, 92%) as colorless oil: $[\alpha]_D^{28}$ –2.4 (*c* 1.03, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 1.72–1.93 (m, 3H), 2.15–2.25 (m, 1H), 2.83 (dt, *J* = 17.7, 6.0 Hz, 1H), 2.90 (dt, *J* = 17.7, 6.8 Hz, 1H), 4.21 (t, *J* = 6.4 Hz, 1H), 7.07 (d, *J* = 5.4 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 8.04 (s, 1H), 8.32 (d, *J* = 5.4 Hz, 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 19.8, 28.8, 32.5, 42.7, 123.8, 124.1 (q, *J* = 272 Hz), 125.4 (q, *J* = 4 Hz), 128.7 (q, *J* = 32 Hz), 128.9, 134.3, 146.5,

146.9, 150.0, 151.4; IR (neat) 2938, 1596, 1415, 1325, 1163, 1119, 1068, 833 $cm^{-1}$; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{16}H_{15}F_3N$ 278.1157; Found 278.1156. The enantiomer ratio of **2l** was determined to be (–):(+) = 75:25 (50% ee) by the HPLC analysis with Chiralcel OD-H.

**(+)-8-Methoxy-5,6,7,8-tetrahydroisoquinoline (2m).** The general procedure was followed with use of 8-methoxyisoquinoline (**1m**) (31.8 mg, 0.20 mmol). The reaction was carried out at 80 ˚C for 24 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/1) to give **2m** (29.0 mg, 0.18 mmol, 89%) as pale yellow oil: $[\alpha]_D^{29}$ +3.0 (*c* 1.01, $CHCl_3$) (for 86:14 er of **2m**); $^1H$ NMR (400 MHz, $CDCl_3$, TMS) δ 1.71–1.81 (m, 1H), 1.81–1.90 (m, 1H), 1.95–2.05 (m, 1H), 2.05–2.14 (m, 1H), 2.69 (ddd, *J* = 6.2, 8.9, 17.7 Hz, 1H), 2.82 (dt, *J* = 17.7, 5.4 Hz, 1H), 3.45 (s, 3H), 4.34 (t, *J* = 4.4 Hz, 1H), 7.02 (d, *J* = 5.0 Hz, 1H), 8.37 (d, *J* = 5.0 Hz, 1H), 8.55 (s, 1H); $^{13}C$ {$^1H$} NMR (150 MHz, $CDCl_3$) δ 17.5, 27.0, 28.2, 56.2, 74.2, 123.7, 132.3, 146.5, 148.2, 150.9; IR (neat) 2939, 1601, 1421, 1353, 1186, 1089, 835 $cm^{-1}$; HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{10}H_{14}NO$ 164.1075; Found 164.1072. The enantiomer ratio of **2m** was determined to be (+):(–) = 86:14 (71% ee) by the HPLC analysis with Chiralpak AD-H.

**(+)-*N*-(5,6,7,8-Tetrahydroisoquinolin-8-yl)propionamide (2n).** The general procedure was followed with use of *N*-(8-isoquinolinyl)propionamide (**1n**) (40.0 mg, 0.20 mmol). The reaction was carried out at 60 ˚C for 48 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/1 to EtOAc to $CH_2Cl_2$/MeOH = 20/1) to give **2n** (39.6 mg, 0.19 mmol, 97%) as an off-white solid: $[\alpha]_D^{27}$ +40.7 (*c* 1.02, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, TMS) δ 1.20 (t, *J* = 7.6 Hz, 3H), 1.76–1.92 (m, 3H), 2.00–2.11 (m, 1H), 2.26 (q, *J* = 7.6 Hz, 2H), 2.67–2.84 (m, 2H), 5.20–5.28 (m, 1H), 5.82 (br d, *J* = 6.3 Hz, 1H), 6.99 (d, *J* = 4.8 Hz, 1H), 8.32 (d, *J* = 4.8 Hz, 1H), 8.45 (s, 1H); $^{13}C$ {$^1H$} NMR (101 MHz, $CDCl_3$) δ 9.9,

19.3, 28.4, 29.7 (2C), 44.9, 123.6, 133.1, 146.5, 147.5, 150.1, 173.2; IR (thin film) 3266, 3053, 2939, 1647, 1544, 1420, 1235, 823 $cm^{-1}$; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{17}N_2O$ 205.1341; Found 205.1338. The enantiomer ratio of **2n** was determined to be (+):(–) = 86:14 (72% ee) by the HPLC analysis with Chiralpak ID.

**(–)-6-Phenyl-5,6,7,8-tetrahydroisoquinoline (2o).** The general procedure was followed with use of 6-phenylisoquinoline (**1o**) (41.0 mg, 0.20 mmol). The reaction was carried out at 100 ˚C for 24 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/3) to give **2o** (35.6 mg, 0.17 mmol, 85%) as an off-white solid: $[\alpha]_D^{27}$ –35.6 (*c* 0.99, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, TMS) δ 1.80–2.00 (m, 1H), 2.16–2.23 (m, 1H), 2.83–3.07 (m, 5H), 7.00 (d, *J* = 5.0 Hz, 1H), 7.22–7.28 (m, 3H), 7.35 (t, *J* = 7.4 Hz, 2H), 8.30 (d, *J* = 5.0 Hz, 1H), 8.37 (s, 1H); $^{13}C$ {$^1H$} NMR (101 MHz, $CDCl_3$) δ 26.5, 29.7, 36.7, 39.8, 123.7, 126.5, 126.7, 128.6, 132.1, 145.53, 145.60, 146.6, 150.3; IR (thin film) 2925, 1637, 1600, 1492, 1422, 1259, 813, 754, 697 $cm^{-1}$; Anal. Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 85.81; H, 7.24; N, 6.64. The enantiomer ratio of **2o** was determined to be (–):(+) = 91:9 (81% ee) by the HPLC analysis with Chiralcel OJ-H.

**(–)-6-(4-Methoxyphenyl)-5,6,7,8-tetrahydroisoquinoline (2p).** The general procedure was followed with use of 6-(4-methoxyphenyl)isoquinoline (**1p**) (47.1 mg, 0.20 mmol). The reaction was carried out at 100 ˚C for 24 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/3 to 1/1) to give **2p** (29.2 mg, 0.12 mmol, 61%) as an off-white solid: $[\alpha]_D^{27}$ –28.9 (*c* 1.01, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, TMS) δ 1.84–1.96 (m, 1H), 2.12–2.20 (m, 1H), 2.79–3.04 (m, 5H), 3.81 (s, 3H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 4.9 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 8.30 (d, *J* = 4.9 Hz, 1H), 8.37 (s, 1H); $^{13}C$ {$^1H$} NMR (101 MHz, $CDCl_3$) δ 26.5, 29.9, 36.8, 38.9, 55.2, 113.9, 123.6, 127.6, 132.1, 137.7,

145.6, 146.5, 150.2, 158.1; IR (thin film) 2929, 1618, 1510, 1442, 1247, 1181, 1033, 820 $cm^{-1}$; Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.23; H, 7.16; N, 5.81. The enantiomer ratio of **2p** was determined to be (–):(+) = 87:13 (74% ee) by the HPLC analysis with Chiralcel OJ-H.

**(–)-6-[4-(Trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinoline (2q).** The general procedure was followed with use of 6-[4-(trifluoromethyl)phenyl]isoquinoline (**1q**) (54.7 mg, 0.20 mmol). The reaction was carried out at 100 ˚C for 24 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/3) to give **2q** (50.5 mg, 0.18 mmol, 91%) as a pale yellow solid: $[\alpha]_D^{27}$ –24.9 (*c* 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 1.90–2.02 (m, 1H), 2.17–2.25 (m, 1H), 2.85–3.13 (m, 5H), 7.01 (d, *J* = 4.9 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.60 (d, *J* = 8.1 Hz, 2H), 8.32 (d, *J* = 4.9 Hz, 1H), 8.39 (s, 1H); $^{13}$C {$^1$H} NMR (101 MHz, $CDCl_3$) δ 26.3, 29.5, 36.3, 39.8, 123.6, 124.2 (q, *J* = 272 Hz), 125.5 (q, *J* = 4 Hz), 127.1, 128.8 (q, *J* = 32 Hz), 131.9, 144.9, 146.7, 149.6, 150.3; IR (thin film) 2930, 1596, 1421, 1326, 1163, 1119, 1065, 839 $cm^{-1}$; Anal. Calcd for $C_{16}H_{14}F_3N$: C, 69.31; H, 5.09; N, 5.05. Found: C, 69.15; H, 5.12; N, 5.07. The enantiomer ratio of **2q** was determined to be (–):(+) = 87:13 (74% ee) by the HPLC analysis with Chiralcel OJ-H.

**(+)-6-Methoxy-5,6,7,8-tetrahydroisoquinoline (2r).** The general procedure was followed with use of 6-methoxyisoquinoline (**1r**) (31.8 mg, 0.20 mmol). The reaction was carried out at 100 ˚C for 24 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/1) to give **2r** (13.4 mg, 0.08 mmol, 41%) as colorless oil: $[\alpha]_D^{27}$ +7.0 (*c* 1.02, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 1.87–1.97 (m, 1H), 2.00–2.08 (m, 1H), 2.69–2.83 (m, 2H), 2.93 (dt, *J* = 16.9, 6.5 Hz, 1H), 3.02 (dd, *J* = 17.3, 4.8 Hz, 1H), 3.42 (s, 3H), 3.67–3.73 (m, 1H), 6.99 (d, *J* = 5.1 Hz, 1H), 8.28 (d, *J* = 5.1 Hz, 1H), 8.32 (s, 1H); $^{13}$C {$^1$H} NMR (101

MHz, $CDCl_3$) δ 23.2, 26.8, 34.4, 55.9, 74.5, 124.1, 132.0, 143.6, 146.7, 149.9; IR (neat) 2932, 1599, 1423, 1379, 1199, 1095, 825 $cm^{-1}$; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{10}H_{14}NO$ 164.1075; Found 164.1095. The enantiomer ratio of **2r** was determined to be (+):(–) = 81:19 (63% ee) by the HPLC analysis with Chiralpak AD-H.

**(–)-7-Phenyl-5,6,7,8-tetrahydroisoquinoline (2s).** The general procedure was followed with use of 6-phenylisoquinoline (**1s**) (41.1 mg, 0.20 mmol). The reaction was carried out at 100 ˚C for 24 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/5 to 1/3) to give **2s** (28.0 mg, 0.13 mmol, 67%) as colorless oil: $[\alpha]_D^{27}$ –25.9 (*c* 1.05, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, TMS) δ 1.95 (ddt, *J* = 11.3, 13.1, 8.5 Hz, 1H), 2.13–2.20 (m, 1H), 2.83–3.10 (m, 5H), 7.03 (d, *J* = 5.0 Hz, 1H), 7.22–7.29 (m, 3H), 7.35 (t, *J* = 7.3 Hz, 2H), 8.28–8.38 (m, 2H); $^{13}C$ {$^1H$} NMR (101 MHz, $CDCl_3$) δ 29.0, 29.5, 34.3, 40.0, 123.6, 126.4, 126.8, 128.6, 132.6, 145.3, 145.7, 146.7, 150.3; IR (neat) 2925, 1599, 1492, 1422, 1254, 829, 754, 697 $cm^{-1}$; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{16}N$ 210.1283; Found 210.1296. The enantiomer ratio of **2s** was determined to be (–):(+) = 82:18 (64% ee) by the HPLC analysis with Chiralcel OJ-H.

**(–)-7-Methoxy-5,6,7,8-tetrahydroisoquinoline (2t).** The general procedure was followed with use of 7-methoxyisoquinoline (**1t**) (31.8 mg, 0.20 mmol). The reaction was carried out at 80 ˚C for 36 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/1) to give **2t** (30.3 mg, 0.19 mmol, 93%) as reddish yellow oil: $[\alpha]_D^{28}$ –13.3 (*c* 0.99, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, TMS) δ 1.86–1.96 (m, 1H), 1.98–2.07 (m, 1H), 2.69–2.84 (m, 2H), 2.92 (dt, *J* = 17.7, 6.6 Hz, 1H), 3.03 (dd, *J* = 16.5, 4.5 Hz, 1H), 3.42 (d, *J* = 1.4 Hz, 3H), 3.68–3.75 (m, 1H), 6.98 (d, *J* = 5.0 Hz, 1H), 8.28 (d, *J* = 5.0 Hz, 1H), 8.32 (s, 1H); $^{13}C$ {$^1H$} NMR (150 MHz, $CDCl_3$) δ 25.7, 26.6, 31.7, 55.9, 74.5, 123.2, 130.0, 145.0, 146.7,

150.7; IR (neat) 2933, 1599, 1422, 1355, 1188, 1094, 834 $cm^{-1}$; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{10}H_{14}NO$ 164.1075; Found 164.1080. The enantiomer ratio of **2t** was determined to be (–):(+) = 71:29 (41% ee) by the HPLC analysis with Chiralpak AD-H.

**Isolation of Dichlorotetrakis(5-phenylisoquinoline)ruthenium(II) [$RuCl_2$(1a)$_4$].** Ten reactions of **1a** (0.1 mmol scale each) for optimizing reaction conditions were conducted with the optimal or slightly modified procedures and conditions for the asymmetric hydrogenation of quinoline carbocycles.[12] The resulting mixtures were diluted with $CH_2Cl_2$, and then combined in a round-bottomed flask. After about 0.5 h, the solution was evaporated under reduced pressure. The flash column chromatography (EtOAc/hexane = 1/5) on silica gel of the residue gave Ru(**1a**)$_4Cl_2$ (22.0 mg, 0.02 mmol) as a dark-red solid: $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ 7.38–7.41 (m, 4H), 7.43–7.51 (m, 20H), 7.54 (d, *J* = 7.4 Hz, 4H), 7.60 (dd, *J* = 7.1, 1.2 Hz, 4H), 7.71 (d, *J* = 8.1 Hz, 4H), 8.51 (d, *J* = 6.8 Hz, 4H), 9.41 (s, 4H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 118.1, 126.7, 126.9, 127.8, 128.5, 129.2, 129.8, 130.9, 132.7, 138.7, 139.1, 150.2, 161.1; HRMS (FAB) *m/z*: $[M]^+$ Calcd for $C_{60}H_{44}Cl_2N_4Ru$ 992.1987; Found 992.1983. The FAB-MS spectra of [$RuCl_2$(**1a**)$_4$] with the observed and calculated mass distribution are given in Supporting Information.

**Hydrogenation of 1a in 2-propanol-$d_8$ (eq. 1).** The general procedure for the chemo- and enantioselective hydrogenation of **1** was followed with use of **1a** (41.1 mg, 0.20 mmol) and 2-propanol-$d_8$ (1.0 mL). The reaction was conducted at 60 ˚C for 24 h. The crude product was purified with a flash column chromatography on silica gel (EtOAc/hexane = 1/5) to give **2a** (38.5 mg, 0.18 mmol, 92%, 82:18 er) as an off-white solid. The $^1$H NMR spectrum of the product is given in Supporting Information.

**Deuteration of 1a (eq. 2).** The general procedure for the chemo- and enantioselective

hydrogenation of **1** was followed with use of $D_2$ (1.0 MPa) and **1a** (41.1 mg, 0.20 mmol). The reaction was carried out at 80 ˚C for 72 h. The crude product was purified with a flash column chromatography on silica gel (EtOAc/hexane = 1/5) to give **2a-D** (11.3 mg, 0.05 mmol, 26%, 77:23 er) as an off-white solid and the remaining starting material **1a-D** (22.4 mg, 0.11 mmol, 54%) as an off-white solid. The deuterium distributions in **1a-D** and **2a-D** were determined by their $^1H$ and $^2H$ NMR spectra (see Supporting Information). **2a-D**: HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{15}H_{10}D_6N$ 216.1659; Found 216.1655.

**Treatment of 2a with Deuterium in the presence of ruthenium catalyst (eq. 3).** The general procedure was followed with use of $D_2$ (1.0 MPa) and **2a** (41.9 mg, 0.20 mmol, 80:20 er). The treatment of **2a** with $D_2$ was carried out at 80 ˚C for 48 h. The crude product was purified with a column chromatography on silica gel (EtOAc/hexane = 1/5) to give **2a-D'** (38.5 mg, 0.18 mmol, 92%, 78:22 er) as an off-white solid. The deuterium distribution in **2a-D'** was determined by $^1H$ and $^2H$ NMR spectra (see Supporting Information).

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Optimization and spectral data (PDF)

X-ray data for compound **2b** (CIF)

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### Notes

The authors declare no competing financial interest.

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## REFERENCES

(1) (a) Ibragimov, A. A.; Yunusov, S. Y. *Chem. Nat. Compd.* **1985**, *21*, 502–509. (b) Bentley, K. W. *Nat. Prod. Rep.* **2006**, *23*, 444–463. (c) Diamond, A.; Desgagne-Penix, I. *Plant Biotechnol. J.* **2016**, *14*, 1319–1328. (d) Chrzanowska, M.; Grajewska, A.; Rozwadowska, M. D. *Chem. Rev.* **2016**, *116*, 12369–12465.

(2) (a) Madsen, U.; Stensbøl, T.; Krogsgaard-Larsen, P. *Curr. Med. Chem.* **2001**, *8*, 1291–1301. (b) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730. (c) Nagase, H.; Imaide, S.; Yamada, T.; Hirayama, S.; Nemoto, T.; Yamaotsu, N.; Hirono, S.; Fujii, H. *Chem. Pharm. Bull.* **2012**, *60*, 945–948.

(3) (a) Ginos, J. Z. *J. Org. Chem.* **1975**, *40*, 1191–1195. (b) Okazaki, H.; Soeda, M.; Onishi, K.; Tamura, R. *Appl. Catal.* **1988**, *41*, 99–108. (c) Fang, M.; Machalaba, N.; Sanchez-Delgado, R. A. *Dalton Trans.* **2011**, *40*, 10621–10632. (d) Ren, D.; He, L.; Yu, L.; Ding, R.-S.; Liu, Y.-M.; Cao, Y.; He, H.-Y.; Fan, K.-N. *J. Am. Chem. Soc.* **2012**, *134*, 17592–17598. (e) Sánchez, A.; Fang, M.; Ahmed, A.; Sánchez-Delgado, R. A. *Appl. Catal., A* **2014**, *477*, 117–124. (f) Zhang, L.; Wang, X.; Xue, Y.; Zeng, X.; Chen, H.; Li, R.; Wang, S. *Catal. Sci. Technol.* **2014**, *4*, 1939–1948. (g) Wei, Z.; Chen, Y.; Wang, J.; Su, D.; Tang, M.; Mao, S.; Wang, Y. *ACS Catal.* **2016**, *6*, 5816–5822. (h) He, Z.; Liu, H.; Liu, H.; Qian, Q.; Meng, Q.; Mei, Q.; Han, B. *ChemCatChem* **2017**, *9*, 1947–1952.

(4) (a) Vierhapper, F. W.; Eliel, E. L. *J. Org. Chem.* **1975**, *40*, 2729–2734. (b) Reimann, E.; Höglmüller, A. *Arch. Pharm. (Weinheim, Ger.)* **1982**, *315*, 813–815. (c) Reimann, E.; Höglmüller, A. *Arch. Pharm. (Weinheim, Ger.)* **1985**, *318*, 559–566. (d) Skupinska, K. A.; McEachern, E. J.; Skerlj, R. T.; Bridger, G. J. *J. Org. Chem.* **2002**, *67*, 7890–7893. (e) Skupinska, K. A.; McEachern, E. J.; Baird, I. R.; Skerlj, R. T.; Bridger, G. J. *J. Org. Chem.* **2003**, *68*, 3546–3551. (f) Reimann, E.; Renz, M.; Polborn, K. *Monatsh. Chem.* **2006**, *137*, 1411–1419. (g) Konnerth, H.; Prechtl, M. H. G. *Green Chem.* **2017**, *19*, 2762–2767.

(5) (a) Lu, S.-M.; Wang, Y.-Q.; Han, X.-W.; Zhou, Y.-G. *Angew. Chem. Int. Ed.* **2006**, *45*, 2260–2263. (b) Shi, L.; Ye, Z.-S.; Cao, L.-L.; Guo, R.-N.; Hu, Y.; Zhou, Y.-G. *Angew. Chem. Int. Ed.* **2012**, *51*, 8286–8289. (c) Iimuro, A.; Yamaji, K.; Kandula, S.; Nagano, T.; Kita, Y.; Mashima, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 2046–2050. (d) Ye, Z.-S.; Guo, R.-N.; Cai, X.-F.; Chen, M.-W.; Shi, L.; Zhou, Y.-G. *Angew. Chem. Int. Ed.* **2013**, *52*, 3685–3689. (e) Guo, R.-N.; Cai, X.-F.; Shi, L.; Ye, Z.-S.; Chen, M.-W.; Zhou, Y.-G. *Chem. Commun.* **2013**, *49*, 8537–8539. (f) Kita, Y.; Yamaji, K.; Higashida, K.; Sathaiah, K.; Iimuro, A.; Mashima, K. *Chem. Eur. J.* **2015**, *21*, 1915–1927. (g) Wen, J.; Tan, R.; Liu, S.; Zhao, Q.; Zhang, X. *Chem. Sci.* **2016**, *7*, 3047–3051. (h) Chen, M.-W.; Ji, Y.; Wang, J.; Chen, Q.-A.; Shi, L.; Zhou, Y.-G. *Org. Lett.* **2017**, *19*, 4988–4991. (i) Zhao, D.; Glorius, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 9616–9618.

(6) (a) Borowski, A. F.; Sabo-Etienne, S.; Donnadieu, B.; Chaudret, B. *Organometallics* **2003**, *22*, 1630–1637. (b) Frediani, P.; Pistolesi, V.; Frediani, M.; Rosi, L. *Inorg. Chim. Acta* **2006**, *359*, 917–925. (c) Borowski, A. F.; Vendier, L.; Sabo-Etienne, S.; Rozycka-Sokolowska, E.; Gaudyn, A. V. *Dalton Trans.* **2012**, *41*, 14117–14125.

(7) (a) Rana, S.; Hong, H.-S.; Barrigan, L.; Jin, L.-W.; Hua, D. H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 670–674. (b) Zheng, F.; McConnell, M. J.; Zhan, C.-G.; Dwoskin, L. P.; Crooks, P. A. *Bioorg. Med. Chem.* **2009**, *17*, 4477–4485. (c) Rowan, A. S.; Moody, T. S.; Howard, R. M.; Underwood, T. J.; Miskelly, I. R.; He, Y.; Wang, B. *Tetrahedron: Asymmetry* **2013**, *24*, 1369–1381. (d) Pinto, D. J.; Smallheer, J. M.; Corte, J. R.; Austin, E. J.; Wang, C.; Fang, T.; Smith, L. M., II; Rossi, K. A.; Rendina, A. R.; Bozarth, J. M.; Zhang, G.; Wei, A.; Ramamurthy, V.; Sheriff,

S.; Myers, J. E., Jr.; Morin, P. E.; Luettgen, J. M.; Seiffert, D. A.; Quan, M. L.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 1635–1642. (e) Martin, R. E.; Aebi, J. D.; Hornsperger, B.; Krebs, H.-J.; Kuhn, B.; Kuglstatter, A.; Alker, A. M.; Marki, H. P.; Muller, S.; Burger, D.; Ottaviani, G.; Riboulet, W.; Verry, P.; Tan, X.; Amrein, K.; Mayweg, A. V. *J. Med. Chem.* **2015**, *58*, 8054–8065. (f) Martin, R. E.; Lehmann, J.; Alzieu, T.; Lenz, M.; Carnero Corrales, M. A.; Aebi, J. D.; Marki, H. P.; Kuhn, B.; Amrein, K.; Mayweg, A. V.; Britton, R. *Org. Biomol. Chem.* **2016**, *14*, 5922–5927, and references cited therein.

(8) (a) Glorius, F. *Org. Biomol. Chem.* **2005**, *3*, 4171–4175. (b) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357–1366. (c) Kuwano, R. *Heterocycles* **2008**, *76*, 909–922. (d) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2012**, *112*, 2557–2590. (e) Chen, Q.-A.; Ye, Z.-S.; Duan, Y.; Zhou, Y.-G. *Chem. Soc. Rev.* **2013**, *42*, 497–511. (f) Kuwano, R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2014**, *190*, 715–719. (g) Giustra, Z. X.; Ishibashi, J. S. A.; Liu, S.-Y. *Coord. Chem. Rev.* **2016**, *314*, 134–181. (h) Luo, Y.-E.; He, Y.-M.; Fan, Q.-H. *Chem. Rec.* **2016**, *16*, 2693–2707.

(9) Urban, S.; Ortega, N.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 3803–3806.

(10) Kuwano, R.; Morioka, R.; Kashiwabara, M.; Kameyama, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 4136–4139.

(11) During the revision of this manuscript, ruthenium-catalyzed asymmetric hydrogenation of aromatic amines with extended π-systems (phenanthrenes and chrysenes) was reported: Yan, Z.; Xie, H.-P.; Shen, H-Q.; Zhou, Y.-G. *Org. Lett.* **2018**, *50*, 1094–1097.

(12) Kuwano, R.; Ikeda, R.; Hirasada, K. *Chem. Commun.* **2015**, *51*, 7558–7561.

(13) (a) Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 593–596. (b) Sawamura, M.; Hamashima, H.; Sugawara, M.; Kuwano, R.; Ito, Y. *Organometallics* **1995**, *14*, 4549–4558. (c) Kuwano, R.; Sawamura, M. Regio- and Stereo-Controlled Oxidations and Reductions. in *Catalysts for Fine Chemical Synthesis, Volume 5;* S. M. Roberts, J. Whittall, Eds.; John Wiley & Sons, West Sussex, 2007; pp 73–86.

(14) Saikia, K.; Deb, B.; Borah, B. J.; Sarmah, P. P.; Dutta, D. K. *J. Organomet. Chem.* **2012**, *696*, 4293–4297.

(15) (a) Wang, X.; Han, Z.; Wang, Z.; Ding, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 936–940. (b) Wang, X.; Meng, F.; Wang, Y.; Han, Z.; Chen, Y. J.; Liu, L.; Wang, Z.; Ding, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 9276–9282. (c) Wang, X.; Guo, P.; Wang, X.; Wang, Z.; Ding, K. *Adv. Synth. Catal.* **2013**, *355*, 2900–2907. (d) Wang, X.; Guo, P.; Han, Z.; Wang, X.; Wang, Z.; Ding, K. *J. Am. Chem. Soc.* **2014**, *136*, 405–411.

(16) (a) Ibragimov, A. A.; Yunusov, S. Y. *Chem. Nat. Compd.* **1985**, *21*, 510–512. (b) Takano, S.; Samizu, K.; Sugihara, T.; Satoh, S.; Ogasawara, K. *Chem. Lett.* **1989**, *18*, 1777–1780. (c) Jokela, R.; Päiviö, E.; Berner, M.; Tolvanen, A. *Heterocycles* **2000**, *53*, 2241–2246. (d) Gravel, E.; Poupon, E. *Nat. Prod. Rep.* **2010**, *27*, 32–56.

(17) (a) Rubottom, G. M.; Evain, E. J. *Tetrahedron* **1990**, *46*, 5055–5064. (b) Alexakis, E.; Jones, J. R.; Lockley, W. J. S. *Tetrahedron Lett.* **2006**, *47*, 5025–5028. (c) Pieters, G.; Taglang, C.; Bonnefille, E.; Gutmann, T.; Puente, C.; Berthet, J.-C.; Dugave, C.; Chaudret, B.; Rousseau, B. *Angew. Chem. Int. Ed.* **2014**, *53*, 230–234. (d) Atzrodt, J.; Derdau, V.; Fey, T.; Zimmermann, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 7744–7765. (e) Lockley, W. J. S.; Hesk, D. *J. Labelled Compd. Radiopharm.* **2010**, *53*, 704–715.

(18) Nakao, Y. *Synthesis* **2011**, 3209–3219.

(19) Schrock, R. R.; Johnson, B. F. G.; Lewis, J. *J. Chem. Soc., Dalton Trans.* **1974**, 951–959.

(20) Kuwano, R.; Kashiwabara, M. *Org. Lett.* **2006**, *8*, 2653–2655.

(21) Wieting, J. M.; Fisher, T. J.; Schafer, A. G.; Visco, M. D.; Gallucci, J. C.; Mattson, A. E. *Eur. J. Org. Chem.* **2015**, 525–533.
(22) Graulich, A.; Scuvée-Moreau, J.; Seutin, V.; Liegeois, J.-F. *J. Med. Chem.* **2005**, *48*, 4972–4982.
(23) Chen, D.; Xu, G.; Zhou, Q.; Chung, L. W.; Tang, W. *J. Am. Chem. Soc.* **2017**, *139*, 9767–9770.
(24) Choudhury, A. R.; Mukherjee, S. *Chem. Sci.* **2016**, *7*, 6940–6945.
(25) Choi, H. Y.; Srisook, E.; Jang, K. S.; Chi, D. Y. *J. Org. Chem.* **2005**, *70*, 1222–1226.
(26) Bhayana, B.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 3954–3957.
(27) Brown, W. D.; Gouliaev, A. H. *Synthesis* **2002**, 83–86.
(28) Martinelli, J. R.; Watson, D. A.; Freckmann, D. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102–7107.
(29) Chakrabarty, M.; Mukherji, A.; Karmakar, S.; Mukherjee, R.; Nagai, K.; Geronikaki, A.; Eleni, P. *ARKIVOC* **2010**, 265–290.
(30) Pridgen, L. N. *J. Heterocycl. Chem.* **1980**, *17*, 1289–1291.
(31) Bratt, E.; Verho, O.; Johansson, M. J.; Bäckvall, J.-E. *J. Org. Chem.* **2014**, *79*, 3946–3954.