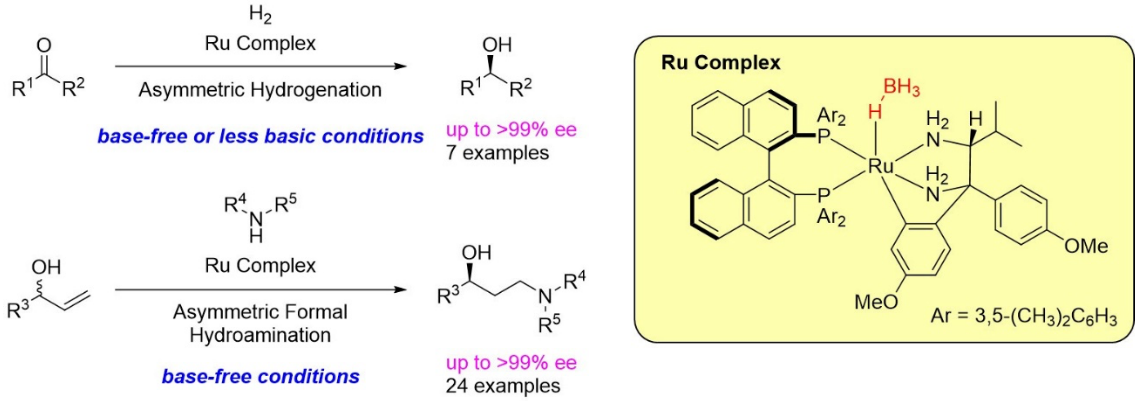
Title	Ru(η1-BH4)(daipena)(diphosphine): Ruthenabicyclic borohydride complexes for asymmetric hydrogenation of ketones and asymmetric formal hydroamination of allylic alcohols under base-free conditions
Author(s)	Ishizaka, Tomohiro; Nakayama, Yuji; Touge, Taichiro et al.
Citation	Tetrahedron, 149, 133705 https://doi.org/10.1016/j.tet.2023.133705
Issue Date	2023-12-04
Doc URL	https://hdl.handle.net/2115/96113
Rights	© <2023>. This manuscript version is made available under the CC-BY-NC-ND 4.0 license http://creativecommons.org/licenses/by-nc-nd/4.0/
Rights(URL)	https://creativecommons.org/licenses/by-nc-nd/4.0/
Type	journal article
File Information	Tetrahedron 149 133705.pdf

Graphical Abstract



Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Ru(η^1-BH$_4$)(daipena)(diphosphine): Ruthenabicyclic Borohydride Complexes for Asymmetric Hydrogenation of Ketones and Asymmetric Formal Hydroamination of Allylic Alcohols under Base-Free Conditions

Tomohiro Ishizaka [a], Yuji Nakayama [a], Taichiro Touge [a], Yamato Yuki [a], Kazuhiko Matsumura [a], Taiga Yurino [b], Takeshi Ohkuma [b,*]

[a] *Takasago International Corporation, Corporate Research & Development Division, 1-4-11 Nishi-yawata, Hiratsuka City, Kanagawa 254-0073, Japan*
[b] *Division of Applied Chemistry and Frontier Chemistry Center, Faculty of Engineering, Hokkaido University, Sapporo, Hokkaido 060-8628, Japan*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Ruthenium
Borohydride
Base free
Hydrogenation
Hydroamination
Asymmetric catalysis

ABSTRACT

Ruthenabicyclic complexes bearing a η^1-BH$_4$ ligand and exhibiting notable stability under air were developed. These novel Ru complexes were efficient catalyst precursors for asymmetric hydrogenation of simple ketones under base-free conditions or with a small amount of DABCO to afford the corresponding alcohols with high enantioselectivity (>99% ee in the best cases). Asymmetric formal hydroamination of allylic alcohols without an addition of base, via a borrowing hydrogenation strategy, was also achieved. A variety of allylic alcohols and amines were applicable to the reaction (>99% ee in the best cases).

1. Introduction

Ru-hydride (RuH) complexes are known as active species in chemical transformations, such as hydrogenation and transfer hydrogenation.[1] These complexes are generally unstable and unsuitable for preservation under air, and therefore Ru-hydride complexes are usually generated *in situ* from more stable Ru-halide complexes. Among the Ru-halide complexes, RuCl$_2$(diphosphine)(diamine) are particularly useful precatalysts for hydrogenation of ketones, producing active RuH$_2$(diphosphine)(diamine) through elimination of HCl by an alkaline base in the presence of H$_2$ gas.[2] Consequently, the RuCl$_2$(diphosphine)(diamine)/base catalyst systems are unsuitable for hydrogenation of base-labile substrates. In contrast, RuH(η^1-BH$_4$)(diphosphine)(diamine) synthesized from RuCl$_2$(diphosphine)(diamine) and NaBH$_4$ are sufficiently stable for isolation and preservation, and generate the RuH$_2$ active species without the addition of a base to the reaction system.[3]

We have previously reported that Ru complexes with a ruthenabicyclic skeleton, RuCl(daipena)(diphosphine) (daipena = anion of DAIPEN at the 2-position of an anisyl group, diphosphine = XylBINAP (**1a**), DM-SEGPHOS (**1b**)), exhibit excellent catalytic properties for asymmetric hydrogenation of ketones, quinoxalines, and α-amino esters under basic conditions.[4] We expected that Ru(η^1-BH$_4$) complexes with the ruthenabicyclic structure could act as efficient precursors for the corresponding RuH active species under base-free or less basic conditions.

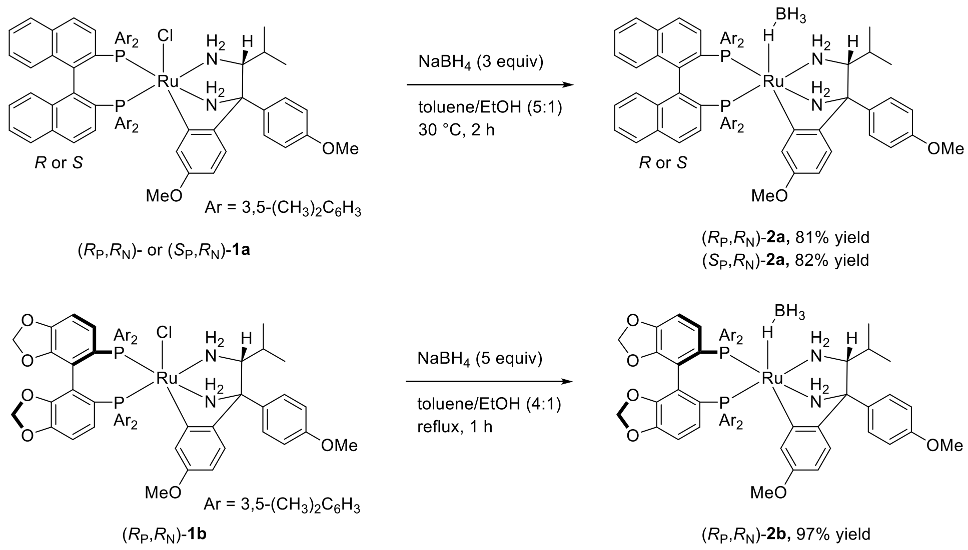
Herein, we report the synthesis and structure determination of Ru(η^1-BH$_4$)(daipena)(diphosphine). The catalyst performance of the Ru(η^1-BH$_4$) complexes in asymmetric hydrogenation of ketones and asymmetric formal hydroamination of allylic alcohols is also described. Both reactions afforded the desired chiral alcohols in reasonably high yields with >99% ee in the best cases.

2. Results and discussion

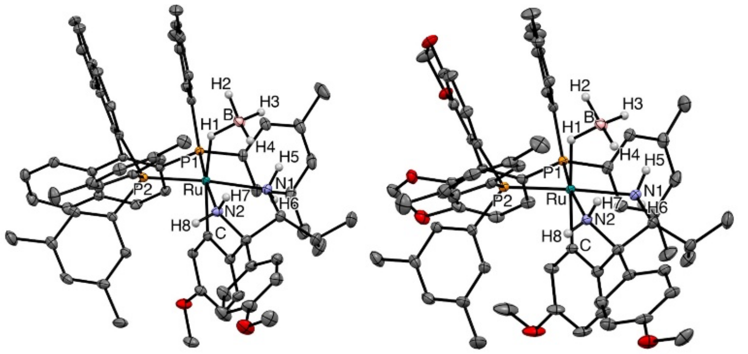
The Ru(η^1-BH$_4$) complexes, Ru(η^1-BH$_4$)(daipena)(diphosphine) (diphosphine = XylBINAP (**2a**), DM-SEGPHOS (**2b**)), were readily synthesized from the corresponding RuCl complexes, RuCl(daipena)(diphosphine) **1**, and an excess amount of NaBH$_4$ in a mixture of toluene and ethanol (Scheme 1). These complexes **2** were isolated in high yields by simple procedures, such as salt filtration followed by crystallization or concentration, based on their properties (see the Supplementary Information for details). The structures of (R_P,R_N)-**2a** and (R_P,R_N)-**2b** were determined by single crystal X-ray diffraction analysis to bear a η^1-BH$_4$ ligand at the *trans* position to the anisyl ligand (Fig 1). Mass spectrometry detected molecular ions corresponding to the target Ru(η^1-BH$_4$) complexes. Characteristic IR peaks derived from the B–H stretching band and BH$_3$ deformation frequencies were observed at 2312 cm^{-1} and 1074 cm^{-1} for (R_P,R_N)-**2a**, at 2311 cm^{-1} and 1068

---

* Corresponding author.
E-mail address: ohkuma@eng.hokudai.ac.jp (T. Ohkuma)



Scheme 1. Synthesis of chiral ruthenabicyclic borohydride complexes.



(R_P,R_N)-**2a** (R_P,R_N)-**2b**

Fig 1. ORTEP diagrams of the structures of (R_P,R_N)-**2a** and (R_P,R_N)-**2b**. All hydrogen atoms, except for the amino protons and borohydride hydrogens, are omitted for clarity.

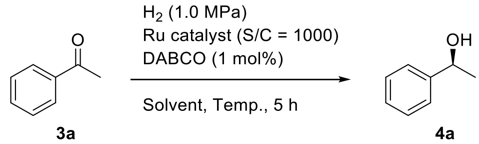
cm^{-1} for (S_P,R_N)-**2a**, and at 2312 cm^{-1} and 1076 cm^{-1} for (R_P,R_N)-**2b**, respectively. The bond length of H1–BH$_3$ was 1.26(3) Å for (R_P,R_N)-**2a**, and 1.27(4) Å for (R_P,R_N)-**2b** (Fig 1). These were shorter than the previously reported H1–BH$_3$ bond length of 1.32(7) Å for RuH(η^1-BH$_4$)[(*R*)-tolbinap][(*R*,*R*)-dpen], suggesting that the dissociation of the BH$_3$ group in (R_P,R_N)-**2a** and (R_P,R_N)-**2b** is more difficult than that of RuH(η^1-BH$_4$)[(*R*)-tolbinap][(*R*,*R*)-dpen].[3a] The H1–Ru–C bond angle was 170° for (R_P,R_N)-**2a** and 172° for (R_P,R_N)-**2b**. In contrast, the Cl–Ru–C bond angle of the RuCl complex, (R_P,R_N)-**1b**, was reported to be 153°, indicating that the ruthenabicyclic octahedral structures of (R_P,R_N)-**2a** and (R_P,R_N)-**2b** are less distorted than that of (R_P,R_N)-**1b**.[4a] Therefore, (R_P,R_N)-**2a** and (R_P,R_N)-**2b** were expected to be stable complexes and suitable for long-term preservation. In fact, even when (R_P,R_N)-**2a** and (R_P,R_N)-**2b** were exposed to air for a month, their appearance, and ^{1}H and ^{31}P NMR signals, remained unchanged.

2.1. Asymmetric hydrogenation of ketones

The catalytic efficiency of Ru(η^1-BH$_4$) complexes **2** was investigated in the asymmetric hydrogenation of acetophenone (**3a**) as a model substrate (Table 1). When the reaction was conducted in ethanol under 1.0 MPa of H$_2$ at 40 °C for 5 h in the presence of (R_P,R_N)-**2a** with a substrate-to-catalyst molar ratio (S/C) of 1000, (*S*)-1-phenylethan-1-ol (**4a**) was obtained in 55% yield with 99.4% ee (entry 1). Complete conversion was achieved under higher pressure (5.0 M Pa) of H$_2$ without any loss of enantioselectivity (entry 2). Importantly, when the catalyst loading was reduced to an S/C of 10000 under 5.0 MPa of H$_2$, **3a** was completely converted into **4a** (97% isolated yield) in 99.2% ee for 9 h (entry 3). The complex (R_P,R_N)-**2b** was also found to exhibit similar catalytic performance (entry 4). The reaction rate in methanol or 2-propanol was slower than in ethanol (entries 5 and 6). The enantioselectivity was also decreased. While the reaction in acetonitrile afforded **4a** in 26% yield with 99.0% ee, other aprotic solvents were found to be unsuitable for this reaction (entries 7–11). Under milder conditions, i.e., 1.0 MPa of H$_2$ at 25 °C, the hydrogenation hardly proceeded in ethanol, THF, and toluene (entries 12–14). Notably, the addition of a catalytic amount of DABCO (1 mol%) improved the reactivity under otherwise identical conditions, suggesting that DABCO promotes the generation of the active RuH species from (R_P,R_N)-**2a** (entries 15–17). Complete conversion was achieved in toluene to afford **4a** in 99.7% ee. The corresponding RuCl complex (R_P,R_N)-**1a** combined with DABCO showed marginal catalytic activity for this reaction (entry 18). DABCO is insufficiently basic to activate (R_P,R_N)-**1a** as a catalyst. When the Ru complex with DM-SEGPHOS (R_P,R_N)-**2b** was used under the same conditions, a slight decrease in the yield was observed (entry 19). The catalyst loading could be reduced to an S/C of 3000 under 1.0 MPa of H$_2$ at 40 °C to give **4a** in 93% isolated yield with 99.3% ee quantitatively (entries 20 and 21). The catalytic efficiency of (R_P,R_N)-**2a** was lower than that of the corresponding **1a** in the presence of an alkaline base (hydrogenation of **3a**: S/C = 100000, 5.0 MPa of H$_2$, 6 min, **4a**: >99% yield, >99% ee),[4a] but the high catalytic activity of **2a** under base-free or weakly basic conditions is noteworthy.

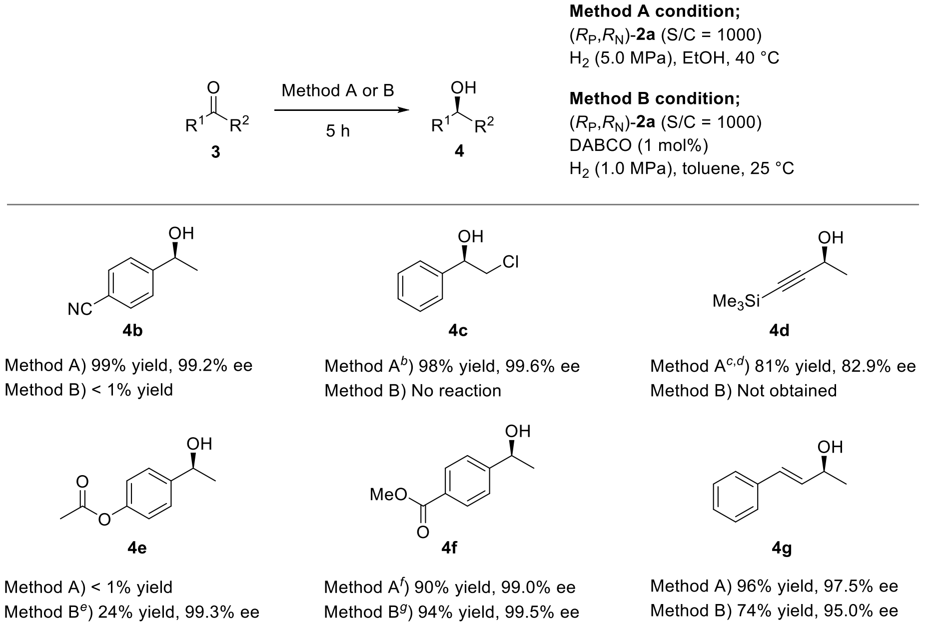
We next examined asymmetric hydrogenation of various base-labile ketones by using the Ru(η^1-BH$_4$) complex (R_P,R_N)-**2a** (S/C = 1000) under two typical conditions: Method A: 5.0 MPa of H$_2$, ethanol solution, 40 °C; Method B: 1

Table 1.
Asymmetric hydrogenation of acetophenone (**3a**)[a].



Entry	Ru catalyst[b]	DABCO[c]	Solvent	Temp (°C)	Yield[d] (%)	ee[d] (%)
1	**2a**	-	EtOH	40	55	99.4
2[e]	**2a**	-	EtOH	40	99.6	99.4
3[e,f]	**2a**	-	EtOH	40	99.6 (97)	99.2
4[e]	**2b**	-	EtOH	40	99.7	99.4
5	**2a**	-	MeOH	40	36	98.4
6	**2a**	-	*i*PrOH	40	9	96.2
7	**2a**	-	CH_3CN	40	26	99.0
8	**2a**	-	THF	40	3	97.3
9	**2a**	-	1,4-dioxane	40	3	97.2
10	**2a**	-	toluene	40	N.R.	-
11	**2a**	-	EtOAc	40	N.R.	-
12	**2a**	-	EtOH	25	3	97.3
13	**2a**	-	THF	25	N.R.	-
14	**2a**	-	toluene	25	N.R.	-
15	**2a**	Add	EtOH	25	46	99.7
16	**2a**	Add	THF	25	73	99.2
17	**2a**	Add	toluene	25	99.5	99.7
18	**1a**	Add	toluene	25	N.R.	-
19	**2b**	Add	toluene	25	71	99.6
20[g,h]	**2a**	Add	toluene	25	74	99.4
21[g,i]	**2a**	Add	toluene	40	99.9 (93)	99.3

[a] Unless otherwise stated, reactions were conducted in 1.0 M solution. [b] (R_P,R_N)-Ru catalysts were used. [c] DABCO/Ru = 10, Add = added. [d] Determined by chiral GC analysis. The isolated yield is shown in parenthesis. [e] The hydrogen pressure was 5.0 MPa. [f] The reaction was conducted with an S/C of 10000 for 9 h. [g] S/C = 3000, DABCO/Ru = 30. [h] The reaction was conducted in 4.0 M solution for 14 h. [i] The reaction was conducted in 4.0 M solution.



Scheme 2. Asymmetric hydrogenation of base-labile ketones[a].

[a] Unless otherwise stated, reactions were conducted in 1.0 M solution. Isolated yields are shown. The ee values were determined by chiral GC or HPLC analysis. [b] Reaction at 30 °C for 18 h. [c] Reaction for 7 h. [d] The ee was determined by HPLC after converting into the 3,5-dinitrobenzoate. [e] Reaction at 40 °C. [f] The reaction was conducted in MeOH. [g] Reaction for 15 h.

mol% of DABCO, 1.0 MPa of H_2, toluene solution, 25 °C (Scheme 2). An aromatic ketone 4'-cyanoacetophenone (**3b**) readily takes the less-reactive enolate form with a base. As anticipated, **3b** was quantitatively transformed to **4b** in 99.2% ee in Method A; however, the reaction of **3b** hardly proceeded in Method B. Generally, the hydrogenation of 2-chloroacetophenone (**3c**) is difficult when the reaction is conducted with a catalytic system which requires the assistance of a base. In fact, when we carried out the hydrogenation of **3c** with the RuCl complex (R_P,R_N)-**1a**/base system, the chlorohydrin **4c** was not obtained at all (see the Supplementary Information). In contrast, **3c** was successfully hydrogenated in Method A at 30 °C to afford **4c** in 98% yield with 99.6% ee after 18 h.[5] No reaction, however, was observed in Method B. Alkynyl ketones are also typical substrates that are challenging to hydrogenate in the presence of a base due to substrate degradation.[6] The hydrogenation of 4-(trimethylsilyl)-3-butyn-2-one (**3d**) in Method A gave the desired propargylic alcohol **4d** in 81% yield with 82.9% ee. In Method B, the trimethylsilyl group was removed by the action of DABCO, and degradation products were observed. These results clearly demonstrated the usefulness of the Ru(η^1-BH$_4$) complex for asymmetric hydrogenation under the base-free condition (Method A). The hydrogenation of 4'-acetoxyacetophenone (**3e**) marginally afforded **4e** in Method A. The desired **4e** was obtained in a high ee of 99.3% with a medium yield of 24% in Method B at 40 °C. In both cases, generation of a small amount of 4'-hydroxyacetophenone was observed, and the phenolic byproduct probably acted as a catalytic poison. In addition, the hydrogenation of methyl 4-acetylbenzoate (**3f**) in Method A gave **4f** in 89% yield with 97.1% ee, along with a small amount (3% yield) of the ethyl ester via transesterification. When the hydrogenation of **3f** was conducted in methanol instead of ethanol, **4f** was obtained in 90% yield with 99.0% ee. The reaction time was prolonged to 15 h in Method B, affording **4f** in 94% yield with 99.5% ee. Benzalacetone (**3g**), an α,β-unsaturated ketone, was hydrogenated to give the allylic alcohol **4g** in 96% yield with 97.5% ee in Method A. Furthermore, no saturated alcohol or polymeric byproducts were detected. The reaction in Method B was slightly slower.

2.2. Asymmetric formal hydroamination of racemic allylic alcohols

Wang and co-workers reported that RuCl complex (R_P,R_N)-**1a** catalyzes the synthesis of optically active γ-amino alcohols by anti-Markovnikov hydroamination of racemic allylic alcohols in the presence of excess amounts of K$_3$PO$_4$ (Fig 2).[7] Their mechanistic studies revealed that the transformation proceeded via a borrowing hydrogenation mechanism consisting of three steps: (1) dehydrogenative oxidation of allylic alcohol (formation of Ru-H$_2$ species); (2) aza-Michael addition; and (3) asymmetric reduction of the β-amino ketone intermediate by the resultant Ru-H$_2$ species. Indeed, this sequential process has attracted significant attention, and some examples with Ru[8] and Mn[9] complexes other than (R_P,R_N)-**1a** have been reported. In all examples, addition of an inorganic base, such as K$_3$PO$_4$ or *t*BuOK, was required for the activation of catalysts. We speculated that the addition of the base also promotes undesired dehydrogenative oxidation of the γ-amino alcohol (the reverse process of Step 3), thereby lowering the enantioselectivity. As a consequence, we examined the asymmetric formal hydroamination with the Ru(η^1-BH$_4$) complex **2** under base-free conditions.

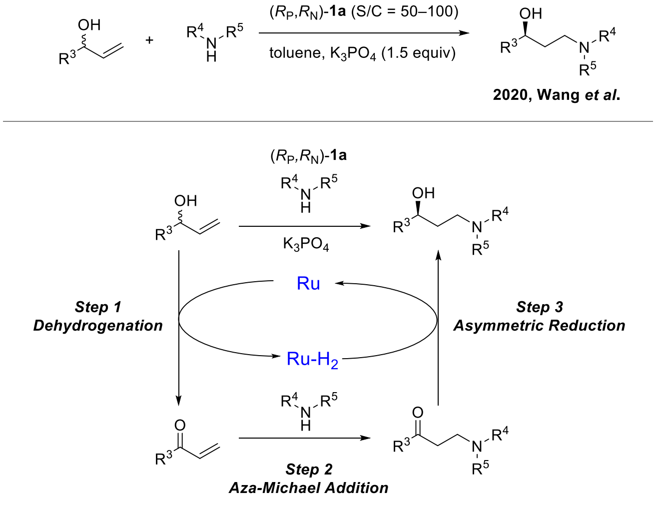
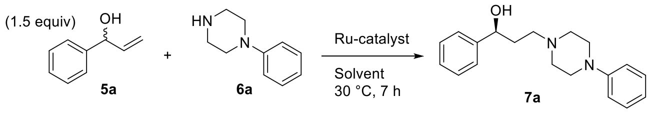


Fig 2. Ru-catalyzed formal hydroamination of allylic alcohols using the (R_P,R_N)-**1a** and K$_3$PO$_4$ system.

As shown in Table 2, the reaction of racemic allylic alcohol **5a** and 1-phenylpiperazine (**6a**) in the presence of (R_P,R_N)-**2a** with an S/C of 100 in cyclohexane at 30 °C for 7 h gave the desired optically active γ-amino alcohol **7a** in 97% NMR yield with 99.6% ee (entry 1). Interestingly, when (R_P,R_N)-**2b** was used as a catalyst, the yield of **7a** decreased significantly to 9% (entry 2). (R_P,R_N)-**2a** showed lower catalytic activity and the yield of **7a** was 64% in toluene, which was employed for the reaction using the (R_P,R_N)-**1a**/K$_3$PO$_4$ system (entry 3). Because the addition of DABCO in toluene was effective in Method B for the asymmetric hydrogenation of ketones (cf. Table 1, entry 17), we attempted to add DABCO in this reaction system, as well. The yield was improved to 87%, but the enantiomeric purity was somewhat lowered, to 98.3% (entry 4). The reaction proceeded with high enantioselectivity in ether solvents, such as THF and 1,4-dioxane, as well as polar solvents, such as butyl acetate and DMF, although the yield remained moderate (entries 5–8). Acetonitrile and alcohol solvents, such as methanol and 2-propanol, were unsuitable for this reaction, yielding only trace amounts of **7a** (entries 9–11). The catalyst loading could be reduced to an S/C of 200 when the reaction was conducted at 40 °C (entries 12 and 13). The yield of **7a** was significantly decreased in the reaction with an S/C of 500 (entry 14).

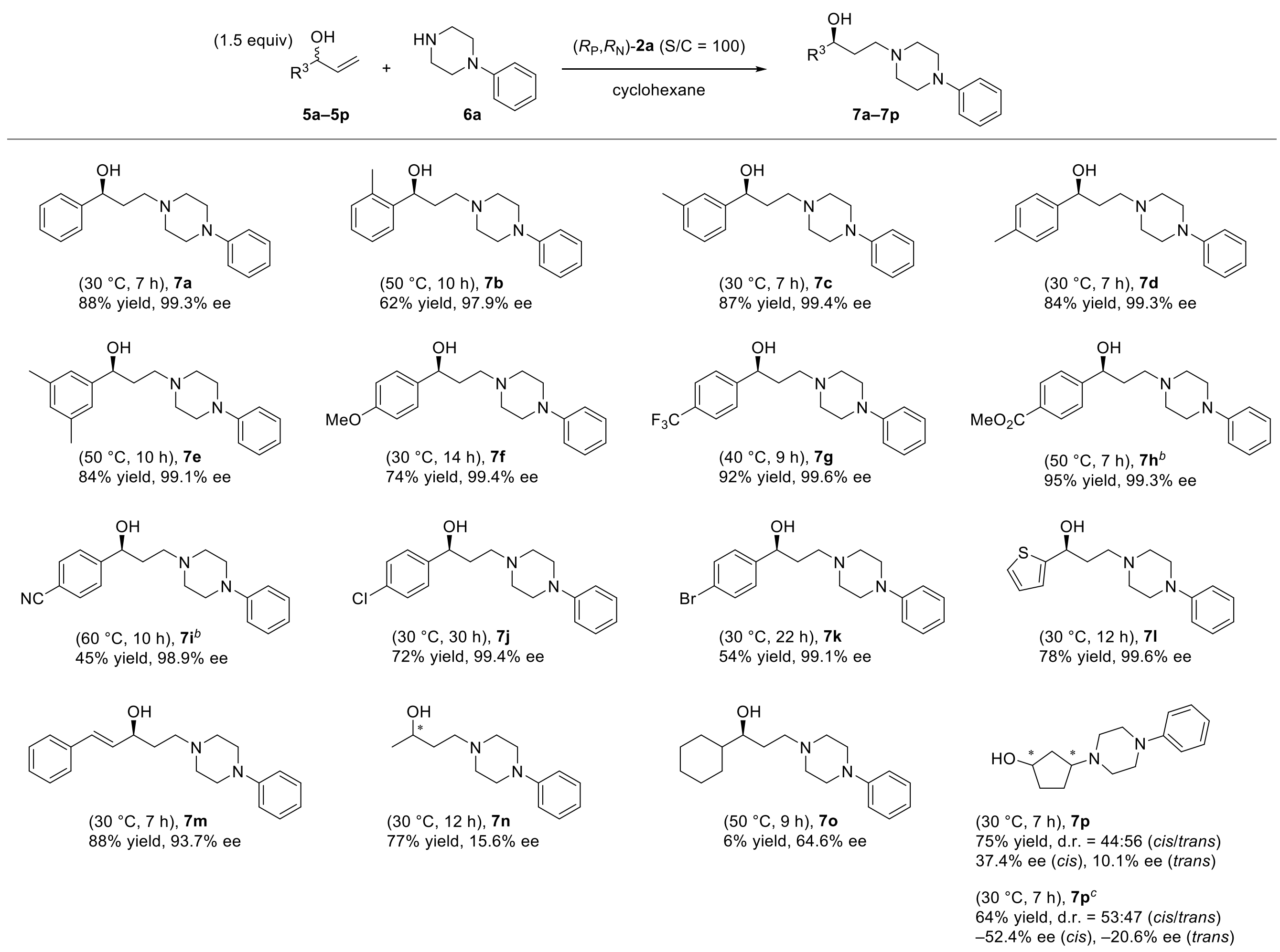
Table 2.
Optimization of reaction conditions.



Entry	Ru catalyst[a]	S/C	Solvent	Yield[b] (%)	ee[c] (%)
1	**2a**	100	cyclohexane	97	99.6
2	**2b**	100	cyclohexane	9	99.5
3	**2a**	100	toluene	64	99.6
4[d]	**2a**	100	toluene	87	98.3
5	**2a**	100	THF	65	99.4
6	**2a**	100	1,4-dioxane	53	99.0
7	**2a**	100	BuOAc	40	99.6
8	**2a**	100	DMF	63	99.2
9	**2a**	100	CH$_3$CN	< 1	-
10	**2a**	100	MeOH	< 1	-
11	**2a**	100	*i*PrOH	< 1	-
12[e]	**2a**	200	cyclohexane	75	99.6
13[f]	**2a**	200	cyclohexane	97	99.5
14[g]	**2a**	500	cyclohexane	24	99.5

[a] (R_P,R_N)-Ru catalysts were used. [b] Determined by ^{1}H NMR analysis with pyrazine as an internal standard. [c] Determined by chiral HPLC analysis of the reaction mixture. [d] 10 mol% of DABCO was added. [e] Reaction for 14 h. [f] Reaction at 40 °C. [g] Reaction at 40 °C for 14 h.

Under the optimized reaction conditions, the scope of allylic alcohols with **6a** was demonstrated, and various aromatic and aliphatic allylic alcohols were well tolerated (Scheme 3). Because differences in reactivity were observed depending on the properties of substituent R^3 of allylic alcohols **5**, the reaction temperature and time were changed individually. The reactions of **5** with a 2-, 3-, or 4-methylphenyl group afforded the corresponding γ-amino alcohols **7b**, **7c**, and **7d** in 97.9% ee, 99.4% ee, and 99.3% ee, respectively. The relatively low yield of **7b** was possibly due to the slow reduction rate of the β-amino ketone intermediate, which is ascribed to steric hindrance of the 2-methylphenyl ring. The alcoholic product 7**e**, with a 3,5-dimethylphenyl group, was also obtained in high ee. We next evaluated the influence of electronic properties of the aryl ring. The allylic alcohol bearing an electron-rich 4-methoxyphenyl group was transformed to the γ-amino alcohol **7f** in 99.4% ee. In addition, the same level of enantioselectivity was obtained in the reactions forming the products with electron-withdrawing 4-trifluoromethyl, 4-methoxycarbonyl, and 4-cyano groups, **7g**–**7i**. These results indicate that the hydroamination proceeded with high enantioselectivity, irrespective of the electronic environment on the aromatic ring of the allylic alcohol **5**. The yield



(30 °C, 7 h), **7a**
88% yield, 99.3% ee

(50 °C, 10 h), **7b**
62% yield, 97.9% ee

(30 °C, 7 h), **7c**
87% yield, 99.4% ee

(30 °C, 7 h), **7d**
84% yield, 99.3% ee

(50 °C, 10 h), **7e**
84% yield, 99.1% ee

(30 °C, 14 h), **7f**
74% yield, 99.4% ee

(40 °C, 9 h), **7g**
92% yield, 99.6% ee

(50 °C, 7 h), **7h**[b]
95% yield, 99.3% ee

(60 °C, 10 h), **7i**[b]
45% yield, 98.9% ee

(30 °C, 30 h), **7j**
72% yield, 99.4% ee

(30 °C, 22 h), **7k**
54% yield, 99.1% ee

(30 °C, 12 h), **7l**
78% yield, 99.6% ee

(30 °C, 7 h), **7m**
88% yield, 93.7% ee

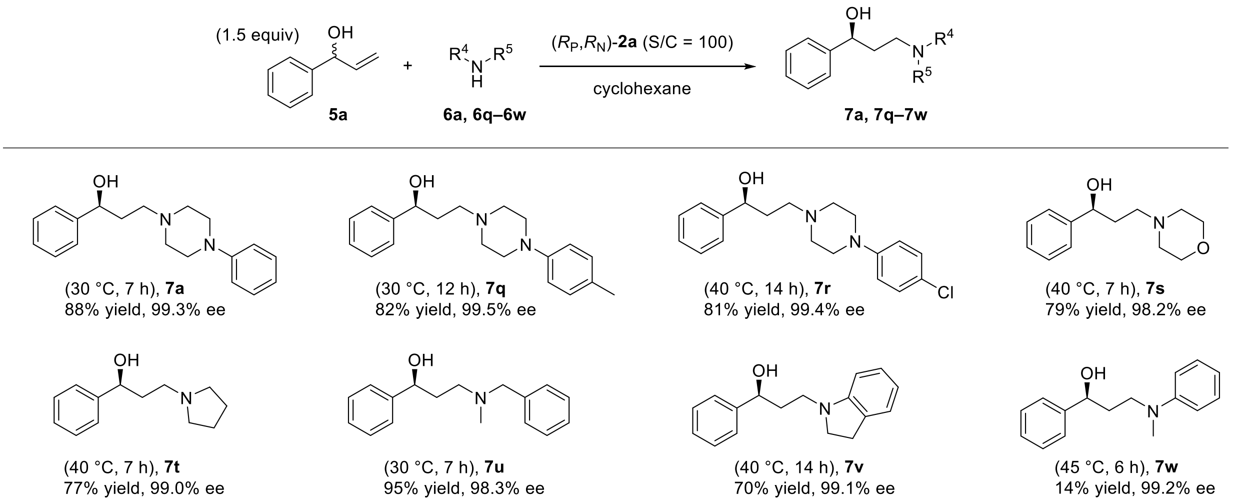
(30 °C, 12 h), **7n**
77% yield, 15.6% ee

(50 °C, 9 h), **7o**
6% yield, 64.6% ee

(30 °C, 7 h), **7p**
75% yield, d.r. = 44:56 (*cis*/*trans*)
37.4% ee (*cis*), 10.1% ee (*trans*)

(30 °C, 7 h), **7p**[c]
64% yield, d.r. = 53:47 (*cis*/*trans*)
–52.4% ee (*cis*), –20.6% ee (*trans*)

Scheme 3. Substrate scope of allylic alcohols[a].
[a] Isolated yields are given. [b] The reaction was conducted in toluene due to the low solubility of **5** in cyclohexane. [c] (S_P,R_N)-**2a** was used instead of (R_P,R_N)-**2a**.



(30 °C, 7 h), **7a**
88% yield, 99.3% ee

(30 °C, 12 h), **7q**
82% yield, 99.5% ee

(40 °C, 14 h), **7r**
81% yield, 99.4% ee

(40 °C, 7 h), **7s**
79% yield, 98.2% ee

(40 °C, 7 h), **7t**
77% yield, 99.0% ee

(30 °C, 7 h), **7u**
95% yield, 98.3% ee

(40 °C, 14 h), **7v**
70% yield, 99.1% ee

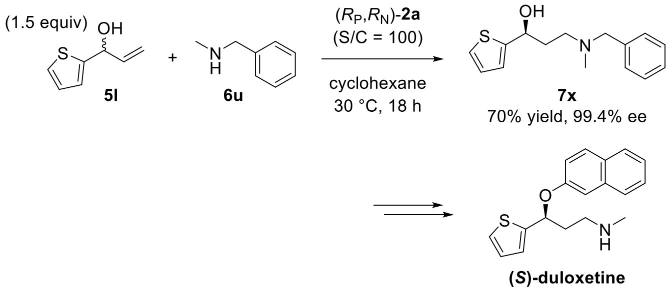
(45 °C, 6 h), **7w**
14% yield, 99.2% ee

Scheme 4. Substrate scope of amines[a].
[a] Isolated yields are given.

of **7i** was slightly lower. The products with 4-chlorophenyl and 4-bromophenyl groups, **7j** and **7k**, were obtained in high ee without dehalogenated compounds. Formation of the 4-bromo substituted product **7k** was somewhat slower, and some of the β-amino ketone intermediate remained. Introduction of a heteroaromatic group was allowed. The 2-thienyl-substituted γ-amino alcohol **7l** was obtained in 99.6% ee. The reaction of the unsymmetrical bis-allylic alcohol selectively afforded the γ-amino allylic alcohol **7m** in 93.7% ee without formation of the regioisomer. The reaction of aliphatic allylic alcohols gave the alcoholic products, **7n** and **7o**, with low to medium enantiomeric purity. Furthermore, the reactivity of **5o** was very low, and the formation of cyclohexyl ethyl ketone and 1-cyclohexylpropanol derived from **5o** was also observed. The reaction of 2-cyclopentenol (**5p**) afforded the cyclic amino alcohol **7p** as a mixture of diastereomers (*cis*/*trans* = 44/56). The ee values of *cis*-**7p** and the *trans* isomer were 37.4% and 10.1%, respectively. When the reaction was conducted with (S_P,R_N)-**2a**, instead of the R_P,R_N diastereomer, the enantiomeric purity of the products was improved: 52.4% ee for *cis*-**7p** and 20.6% ee for the *trans*-**7p**, although the diastereoselectivity remained low. The sense of enantioselection in the reaction of **5p** was found to depend on the XylBINAP ligand. An achiral hydroamination of 2-cyclohexenol using a Fe-PNP complex was previously reported,[10] but our trial is the first example of the catalytic asymmetric version for a cyclic allylic alcohol. In the previous study shown in Fig 2, the hydroamination using RuCl complex (R_P,R_N)-**1a** in the presence of K_3PO_4 was reported to give **7b**, **7d**, **7e**, and **7f** in 92% ee, 96% ee, 82% ee, and 97% ee, respectively. (R_P,R_N)-**2a** in the absence of an inorganic base was found to afford these products in even higher enantiomeric purity, as we expected, because the racemization process via dehydrogenation of the target γ-amino alcohol products **7** promoted by an inorganic base could be inhibited with our catalytic system.

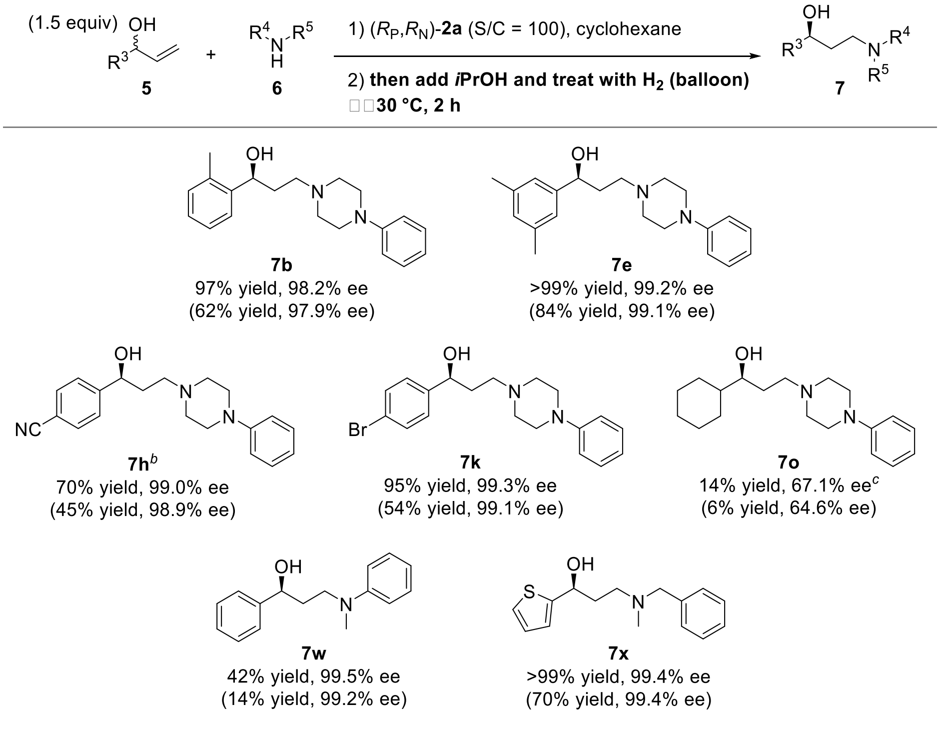
The scope of amines in the reaction with **5a** was then examined, and a variety of secondary amines **6** were found to be applicable to the transformation, affording the γ-amino alcohols **7** with excellent enantioselectivity (Scheme 4). The reactions of phenyl piperazines with a methyl or chloro substituent at the para position afforded the corresponding γ-amino alcohols **7q** and **7r** in 99.5% ee and 99.4% ee, respectively. Morpholine (**6s**) and pyrrolidine (**6t**) were also suitable for this reaction, and gave **7s** and **7t** in high ee. The reaction of linear-shaped *N*-methylbenzylamine (**6u**) resulted in the desired **7u** in a high ee value of 98.3%. Indoline (**6v**), an aryl amine with a fused ring structure, was successfully applied as an amine nucleophile. *N*-methylaniline (**6w**) was converted to **7w** in 14% yield with 99.2% ee. The unsatisfactory yield of **7w** was presumably attributable to the inferior nucleophilicity compared with other amines. In this case, propiophenone and 1-phenylpropanol derived from **5a** were observed as byproducts, and some β-amino ketone intermediate also remained.

To verify the usefulness of this reaction, we attempted to synthesize the intermediate **7x** of the antidepressant (*S*)-duloxetine. The reaction of **5l** and **6u** gave the target product **7x** in 70% yield with 99.4% ee (Scheme 5).[11]



Scheme 5. Synthetic application to a pharmaceutical ingredient.

As shown in the reaction mechanism described in Fig 2, the final step (Step 3) of the sequential reaction is the asymmetric reduction of the β-amino ketone intermediate. A small amount of β-amino ketone remains even when 1.5 equivalents of allylic alcohol, which is also a hydride source (Step 1), are used. When the final step proceeds slowly, the amount of β-amino ketone is increased, and the yield of the γ-amino alcohol is decreased. This situation makes this procedure less efficient, and the remaining β-amino ketone interrupts the isolation of the product. In fact, γ-amino alcohols **7** bearing a sterically hindered 2-methylphenyl (**7b**) or 3,5-dimethylphenyl group (**7e**), a 4-cyanophenyl group (**7h**), a 4-bromophenyl ring (**7k**), a cyclohexyl group (**7o**) as a bulky alkyl substituent, or a less nucleophilic *N*-methylaniline moiety (**7w**) were obtained with low to moderate yields (Schemes 3 and 4). Therefore, we aimed to identify a strategy for hydrogenating the remaining β-amino ketone to the γ-amino alcohol after the hydroamination to increase the yield of **7**. It was found that treatment with *i*PrOH (4 mL under the typical condition) under atmospheric pressure of H_2 using a balloon was effective to achieve this purpose. Asymmetric reduction of the remaining β-amino ketones was promoted by this *i*PrOH/H_2 (balloon) system to afford the desired product **7** in higher yield for all of the experiments shown in Scheme 6. In addition, no decrease in enantioselectivity was observed. No significant yield improvement was observed for **7o** and **7w**, probably because the side reaction converting allylic alcohols **5** into the saturated ketones and alcohols was the major reason for the decrease in the yield of **7**. The *i*PrOH/H_2 (balloon) treatment was also effective to synthesize the intermediate **7x** of (*S*)-duloxetine. The yield was significantly increased from 70% to >99%.



Scheme 6. Hydroamination followed by treatment with an *i*PrOH/H_2 (balloon) system[a].

[a] *i*PrOH/H_2 treatment was performed after the hydroamination under the same conditions as shown in Schemes 3–5. Isolated yields are given. Results without *i*PrOH/H_2 treatment are shown in parentheses. [b] The reaction was conducted in toluene due to the low solubility of **5h** in cyclohexane. [c] *i*PrOH/H_2 treatment was conducted at 30 °C for 6 h.

3. Conclusion

Three novel ruthenabicyclic complexes bearing a η^1-BH_4 ligand were developed: (R_P,R_N)-**2a**; (S_P,R_N)-**2a**; and (R_P,R_N)-**2b**. These Ru(η^1-BH_4) complexes **2** were readily prepared from the corresponding RuCl complexes **1** and $NaBH_4$. The structure of Ru(η^1-BH_4) complexes **2** could be determined by X-ray crystallography together with mass spectrometry and IR spectra. Complexes **2** possess excellent stability and are suitable for preservation under air for a long period of time. The complex (R_P,R_N)-**2a** exhibited high catalytic activity and enantioselectivity in the asymmetric hydrogenation of ketones under base-free conditions or with a small amount of DABCO. Some base-labile ketones, such as α-chloroketone and alkynyl ketone containing a trimethylsilyl group, were efficiently converted into the corresponding alcohols with >99% ee in the best cases. The Ru(η^1-BH_4) complex (R_P,R_N)-**2a** was also revealed to be effective for asymmetric formal hydroamination of racemic allylic alcohols without the addition of an inorganic base. The corresponding optically active γ-amino alcohols (24 examples) were obtained in excellent enantiomeric purity of >99% in most cases. The *i*PrOH/H_2 (balloon) treatment facilitated the reduction of the β-amino ketone intermediate and resulted in enhancing the yield of the desired γ-amino alcohol. With these attractive and powerful protocols, our group is currently exploring further applications for the synthesis of useful organic molecules.

4. Experimental

4.1. General experimental

^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and ^{31}P NMR were recorded on an Agilent 400-MR DD2 system and a Bruker BioSpin Avance III 500 system. Chemical shifts of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and ^{31}P NMR are reported in ppm using TMS (0.00 ppm for ^{1}H), $CHCl_3$ (7.26 ppm for ^{1}H, 77.0 ppm for ^{13}C), C_6H_6 (7.15 ppm for ^{1}H, 128.06 ppm for ^{13}C), $C_6H_5CF_3$ (–63.7 ppm for ^{19}F), and H_3PO_4 (0.00 ppm for ^{31}P). NMR data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (*J*), and integration. Optical rotations were obtained on a JASCO P-2200 Polarimeter. Mass spectra were recorded on a Bruker Impact II and a JEOL JMS-T100GCV spectrometer. Chiral GC analysis was performed using a SHIMADZU Nexis GC-2030 system with a CP-Chirasil-Dex CB column. Chiral HPLC analysis was conducted using a HITACHI Chromaster system equipped with a diode array detector with the appropriate Daicel chiral column. IR spectra were measured on a Thermo Scientific Nicolet iS20 spectrophotometer. Flash column chromatography was performed by using silica gel 60N or activated aluminum oxide. Dehydrated solvents were used for the synthesis of Ru(η^1-BH_4) complexes and reactions. Ketones **3** for the asymmetric hydrogenation were purchased from commercial sources and used after purification. Allylic alcohols **5** were prepared according to reported procedures.[12] **5n** was purchased from a commercial source and used without further purification. Amines **6** were purchased from commercial sources and used without further purification.

*4.2. General procedure for the synthesis of a Ru(η^1-BH_4) complex: (R_P,R_N)-**2a***

$NaBH_4$ (96 mg, 2.53 mmol) was added to a solution of RuCl complex (R_P,R_N)-**1a** (1.00 g, 0.844 mmol) in a toluene (10 mL) and EtOH (2 mL) mixture at room temperature. The whole was warmed to 30 °C and stirred for 2 h. The solution was concentrated to ca. 7 mL. Heptane (20 mL) was added to the solution and stirred for 15 min. Then, precipitated salts were removed by Celite filtration and washed using a heptane (8 mL) and toluene (2 mL) mixture. The filtrate was concentrated, and the resulting solid was dissolved in toluene (2 mL). Heptane (10 mL) was added, and the solution was slowly cooled to 5 °C. The resulting solid was collected by filtration and washed with heptane (10 mL). Finally, the yellow solid was dried under reduced pressure to give (R_P,R_N)-**2a**, yield 0.80 g (81%).

4.3. General procedure for the asymmetric hydrogenation of ketones (Method A)

(R_P,R_N)-**2a** (2.32 mg, 0.002 mmol) was charged in a 50 mL stainless steel autoclave. The autoclave was sealed and replaced with nitrogen gas, followed by the addition of EtOH (2 mL, 1.0 M) and ketone **3** (2.00 mmol) (when ketone **3** was solid, ketone **3** was charged with **2a**). The autoclave was purged three times with hydrogen gas (0.8 MPa) and then pressurized with hydrogen gas (5.0 MPa). The reaction mixture was stirred at 40 °C for 5 h. After the hydrogen gas was carefully released, the solution was concentrated in vacuo. The residue was purified by silica gel column chromatography to afford the corresponding chiral alcohol **4**.

4.4. General procedure for the asymmetric hydrogenation of ketones (Method B)

(R_P,R_N)-**2a** (2.32 mg, 0.002 mmol) and DABCO (2.24 mg, 0.020 mmol) were charged in a 50 mL stainless steel autoclave. The autoclave was sealed and replaced with nitrogen gas, followed by the addition of toluene (2 mL, 1.0 M) and ketone **3** (2.00 mmol) (when ketone **3** was solid, ketone **3** was charged with **2a**). The autoclave was purged three times with hydrogen gas (0.8 MPa) and pressurized with hydrogen gas (1.0 MPa). The reaction mixture was stirred at 25 °C for 5 h. The hydrogen gas was carefully released, and then the solution was concentrated in vacuo. The residue was purified by silica gel column chromatography to afford the corresponding chiral alcohol **4**.

4.5. General procedure for the asymmetric hydroamination of racemic allylic alcohols

Amine **5** (1.00 mmol) and allylic alcohol **6** (1.50 mmol) were added to the solution of (R_P,R_N)-**2a** (11.64 mg, 0.010 mmol) in cyclohexane (4 mL). The whole was replaced with nitrogen gas. The reaction mixture was stirred at 30 °C for 7 h. The solution was concentrated in vacuo. The residue was purified by silica gel or activated aluminum oxide column chromatography to afford the corresponding chiral amino alcohol **7**.

4.6. General procedure for the asymmetric hydroamination of racemic allylic alcohols followed by treatment with an iPrOH/H_2 (balloon) system

Allylic alcohol **5** (1.50 mmol) and amine **6** (1.00 mmol) were added to the solution of (R_P,R_N)-**2a** (11.64 mg, 0.010 mmol) in cyclohexane (4 mL). The whole was replaced with nitrogen gas. The reaction mixture was stirred at 30 °C for 7 h. *i*PrOH (4 mL) was added to the reaction mixture, and the whole was replaced with hydrogen gas using the hydrogen balloon. The reaction mixture was stirred at 30 °C for 2 h. Then, the solution was concentrated in vacuo. The residue was purified by silica gel or activated aluminum oxide column chromatography to afford the corresponding chiral amino alcohol **7**.

Detailed experimental procedures, characterization data, and NMR spectra, and a chart for determining enantiomeric purity are provided in the Supplementary Information.

5. Acknowledgments

This work was supported by Grants-in-Aid for the Japan Society for the Promotion of Science (JSPS) (No. 19H02706). The authors are sincerely grateful to Yoshihiro Yaguchi, Satoru Moriya, Akihiro Kawaraya, Kazuhiko Sakaguchi, Nao Tamaki, Ariaki Murata, Jun Kurabe, Tatsuko Izawa, Ryohei Nemoto, and Toshiyuki Ohno at the Takasago International Corporation for the measurement of NMR, mass spectra, IR, optical rotation, and X-ray structural analysis.

6. References

[1]. (a) K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, Angew. Chem. Int. Ed. Engl. 36 (1997) 285–288;
(b) R. Noyori, T. Ohkuma, Angew. Chem. Int. Ed. 40 (2001) 40–73;
(c) K. Abdur-Rashid, M. Faatz, A.J. Lough, R.H. Morris, J. Am. Chem. Soc. 123 (2001) 7473–7474;
(d) T. Ohkuma, N. Arai, Chem. Rec. 16 (2016) 2801–2819.

[2]. (a) T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, J. Am. Chem. Soc. 117 (1995) 2675–2676;
(b) H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya, R. Noyori, Angew. Chem. Int. Ed. 37 (1998) 1703–1707;
(c) T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya, R. Noyori, J. Am. Chem. Soc. 120 (1998) 13529–13530;
(d) T. Ohkuma, M. Koizumi, H. Ikehira, T. Yokozawa, R. Noyori, Org. Lett. 2 (2000) 659–662;
(e) T. Ohkuma, D. Ishii, H. Takeno, R. Noyori, J. Am. Chem. Soc. 122 (2000) 6510–6511;
(f) N. Arai, K. Azuma, N. Nii, T. Ohkuma, Angew. Chem. Int. Ed. 47 (2008) 7457–7460;
(g) H. Ooka, N. Arai, K. Azuma, N. Kurono, T. Ohkuma, J. Org. Chem. 73 (2008) 9084–9093;
(h) N. Arai, H. Satoh, R. Komatsu, T. Ohkuma, Chem. Eur. J. 23 (2017) 8806–8809.

[3]. (a) T. Ohkuma, M. Koizumi, K. Muñiz, G. Hilt, C. Kabuto, R. Noyori, J. Am. Chem. Soc. 124 (2002) 6508–6509;
(b) T. Ohkuma, C. A. Sandoval, R. Srinivasan, Q. Lin, Y. Wei, K. Muñiz, R. Noyori, J. Am. Chem. Soc. 127 (2005), 8288–8289;
(c) W. Kuriyama, Y. Ino, O. Ogata, N. Sayo, T. Saito, Adv. Synth. Catal. 352 (2010) 92–96.

[4]. (a) K. Matsumura, N. Arai, K. Hori, T. Saito, N. Sayo, T. Ohkuma, J. Am. Chem. Soc. 133 (2011) 10696–10699;
(b) N. Arai, Y. Saruwatari, K. Isobe, T. Ohkuma, Adv. Synth. Catal. 355 (2013) 2769–2774;
(c) H. Ishikawa, T. Yurino, R. Komatsu, M.-Y. Gao, N. Arai, T. Touge, K. Matsumura, T. Ohkuma, Org. Lett. 25 (2023) 2355–2360.

[5]. (a) T. Ohkuma, K. Tsutsumi, N. Utsumi, N. Arai, R. Noyori, K. Murata, Org. Lett. 9 (2007) 255–257;
(b) C. Yin, W. Wu, Y. Hu, X. Tan, C. You, Y. Liu, Z. Chen, X.-Q. Dong, X. Zhang, Adv. Synth. Catal. 360 (2018) 2119–2124.

[6]. N. Arai, H. Satoh, N. Utsumi, K. Murata, K. Tsutsumi, T. Ohkuma, Org. Lett. 15 (2013) 3030–3033.

[7]. R. Xu, K. Wang, H. Liu, W. Tang, H. Sun, D. Xue, J. Xiao, C. Wang, Angew. Chem. Int. Ed. 59 (2020) 21959–21964.

[8]. Y. Pan, Y. You, D. He, F. Chen, X. Chang, M. J. Yu, X. Xing, Org. Lett. 22 (2020), 7278–7283.

[9]. F. Li, L. Long, Y.-M. He, Z. Li, H. Chen, Q.-H. Fan, Angew. Chem. Int. Ed. 61 (2022) e202202972

[10]. W. Ma, X. Zhang, J. Fan, Y. Liu, W. Tang, D. Xue, C. Li, J. Xiao, C. Wang, J. Am. Chem. Soc. 141 (2019) 13506–13515.

[11]. J. Bódi, K. Szöke, J. Éles, E. Fogassy, J. Schindler, K. Vukics, J. Faragó, K. Temesvári, T. Gáti, WO 2008078124, March 7, 2008

[12]. (a) Z. Deng, J. Wei, L. Liao, H. Huang, X. Zhao, Org. Lett. 17 (2015) 1834–1837;
(b) H.-K. Lee, T.-L. Choi, ACS Macro Lett. 7 (2018) 531–535;
(c) M. Agirre, S. Henrion, I. Rivilla, J.I. Miranda, F.P. Cossío, B. Carboni, J.M. Villalgordo, F. Carreaux, J. Org. Chem. 83 (2018) 14861–14881;
(d) Y.-B. Wang, B.-Y. Liu, Q. Bu, B. Dai, N. Liu, Adv. Synth. Catal. 362 (2020) 2930–2940;
(e) S. Tang, P. Zhang, C. Wang, Y. Shao, J. Sun, Chem. Commun. 57 (2021) 11080–11083;
(f) Y. Hwang, S.B. Baek, D. Kim, S. Chang, J. Am. Chem. Soc. 144 (2022) 4277–4285.