Asymmetric Hydrogenation of Ketones with Polymer-Bound BINAP/Diamine Ruthenium Catalysts

Takeshi Ohkuma, Hiroshi Takeno, Yuji Honda, Ryoji Noyori*

Department of Chemistry and Research Center for Materials Science, Nagoya University, Chikusa, Nagoya 464–8602, Japan
Fax: (+81)-52-783-4177, e-mail: noyori@chem3.chem.nagoya-u.ac.jp

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Abstract: The BINAP/1,2-diphenylethylenediamine $RuCl_2$ complexes bound to a polystyrene resin act as precatalysts for asymmetric hydrogenation of various simple ketones. The enantioselectivity, turnover number, and turnover frequency are comparable to those attained under homogeneous conditions.

Keywords: asymmetric hydrogenation; BINAP; ketone hydrogenation; polymer-bound catalyst.

Introduction

Homogeneous asymmetric catalysis provides a fundamental tool for the preparation of chiral building blocks for biologically important substances and advanced materials.[1] Polymer-bound catalysts have inherent operational and economical advantages: immobilization on solid matrices facilitates the separation from reaction mixtures, recovery, and reuse of the expensive chiral compounds.[2] Further, the solid-phase reaction offers a technical basis for diversity-oriented combinatorial synthesis.[3] Numerous resin-supported (pre)catalysts have been developed along this line, though their practical application application is limited to only a few cases.[2] Many of these are much less reactive than the homogeneous catalyst systems, and their stereoselectivity is often reduced, impeding practical use. We previously found that $RuCl_2$(phosphine)$_2$(1,2-diamine) complexes, coupled with an alkaline base in 2-propanol, hydrogenate a C=O function preferentially over coexisting conjugated or non-conjugated C=C linkages, halogen atoms, various hetrocycles, and many other functional groups.[4] The use of appropriate chiral diphosphines and diamines results in rapid and productive asymmetric hydrogenation of a range of achiral and chiral ketones. Their high efficiency prompted us and other groups[5] to immobilize the BINAP/diamine $RuCl_2$ complexes. This report describes our study on asymmetric hydrogenation of simple ketones using polystyrene-anchored chiral Ru catalysts.[5] This reaction exhibits a turnover number (TON) as high as 12,300/batch or a total of 33,000 by repeated use. The enantioselectivity, productivity, and rate of hydrogenation using the polymer-bound catalysts are comparable to those attained under homogeneous conditions.

Results and Discussion

Synthesis of Precatalysts

The resin-supported Ru precatalysts **3** were prepared by using (*R*)-BINAP ligands bound to polystyrene via an amide-based spacer.[6] [$RuCl_2(\eta^6$-benzene)]$_2$ was reacted first with (*R*)-**1a** in *N*,*N*-dimethylacetamide (DMA) (Ru:diphosphine = 3 : 1) at 80 °C for 24 h and then with (*R*,*R*)-1,2-diphenylethylenediamine [(*R*,*R*)-DPEN] [(*R*,*R*)-**2**] (Ru : diamine = 1 : 5) in the same medium at 80 °C for 24 h *without stirring*.[7] At each step, the unreacted materials were removed by washing with DMA. The ^{31}P NMR analysis[8] of the solid suggested that the resulting diphosphine/diamine mixed-ligand Ru complex (*R*,*RR*)-**3a** was a 7 : 1 mixture of the *trans*-dichloro complex (singlet at 47.5 ppm) and its *cis* isomer (broad singlets at 50.0 and 57.5 ppm) contaminated with unreacted (*R*)-**1a** (–15.8 ppm) and some unknown compounds. The purity of the diphosphine/diamine Ru complex was ca. 81%. Both *trans*- and *cis*-$RuCl_2$[(*R*)-binap][(*R*,*R*)-dpen] are known to be reactive for homogeneous hydrogenation of ketones.[8] As shown in Figure 1, the polymer beads are better swelled in DMF than in 2-propanol, which serves as a standard solvent of hydrogenation.[4] DMA can also be used in place of DMF. In a similar manner, the diastereomer (*R*,*SS*)-**3a** [^{31}P NMR, δ = 46.9 ppm (*trans*) and 50.7 and 57.1 ppm (*cis*)] was prepared from (*R*)-**1a** and (*S*,*S*)-**2**. Reaction of **1a** and racemic **2** proceeds without discrimination of the diamine chirality to result in a 1 : 1 mixture of the *R*,*RR* and *R*,*SS* isomers [(*R*,*RR*/*SS*)-**3a**] (Scheme 1). The analogue (*R*,*RR*)-**3b** was also obtained by use of the *N*-propyl compound (*R*)-**1b**, (*R*,*R*)-**2**, and [$RuCl(\eta^6$-benzene)]$_2$ in a similar procedure.

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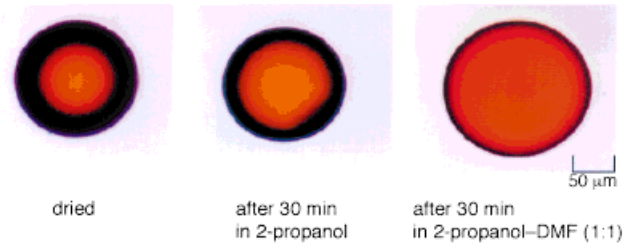
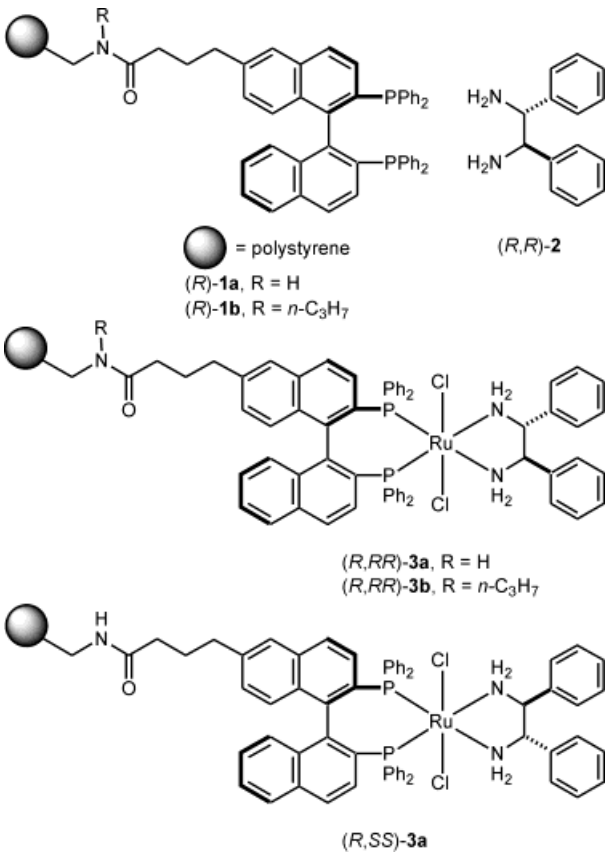


Figure 1. Polystyrene beads possessing (*R*)-BINAP/(*R*,*R*)-DPEN $RuCl_2$ units observed under a microscope (×200).

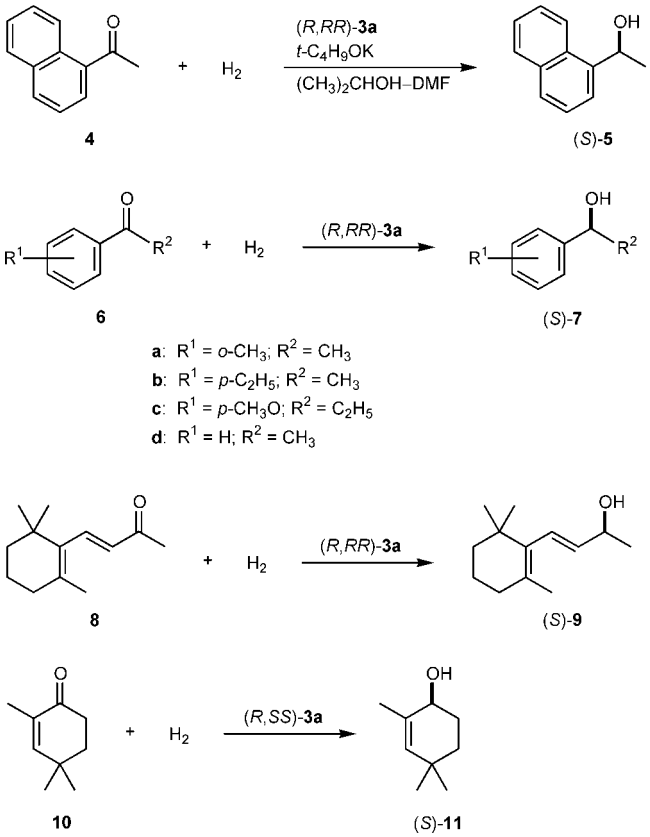


Scheme 1. Structures of compounds **1**, **2**, and **3**.

Asymmetric Hydrogenation

Aromatic Ketones

The polymer-bound Ru complexes **3** are excellent precatalysts for asymmetric hydrogenation of aromatic ketones giving the chiral secondary alcohols (Scheme 2). When 1′-acetonaphthone (**4**) (2.46 mmol, 1.0 M), (*R*,*RR*)-**3a** (0.40 mM), and *t*-C_4H_9OK (20 mM) (S/C = 2470), in a 1:1 2-propanol–DMF mixture placed in a glass autoclave, was stirred with a magnetic stirrer gently at ca. 500 rpm[7] under 8 atm of H_2 and 26 °C for 26 h, the chiral alcohol, (*S*)-**5**, was obtained in 98% ee with 99% conversion. The ee value was identical to that obtained in the homogeneous system using $RuCl_2$[(*R*)-binap][(*R*,*R*)-dpen] in 2-propanol.[8,9] The catalyst was recovered by removing the solution phase by cannula, and reused for hydrogenation.



Scheme 2. Asymmetric hydrogenation of ketones.

The durability of the catalyst was tested by hydrogenation of **4** with S/C = 2470/batch by repeating the above procedure. The results are summarized in Table 1. The product ee remained consistently high, 97–98%, even after the 14th experiment. The catalytic activity was gradually decreased after the tenth experiment, then required a longer reaction period. The total TON achieved in 14 experiments was 33,000. Notably, use of a 0.02 M *t*-C_4H_9OK solution is necessary in the reuse of the recovered catalyst; reaction was very slow without the strong base. Thus, the catalytic efficiency of the polymer-supported Ru complex **3a** was evaluated as acceptable for some laboratory syntheses. During the repeated runs, a new polymer-bound Ru complex(es) is formed at the expense of the starting $RuCl_2$ complex (*R*,*RR*)-**3a**. This complex, showing a broad ^{31}P NMR signal centered at 69 ppm,[10] acted as a hydrogenation catalyst with the aid of *t*-C_4H_9OK.

Hydrogenation of **4** on a 20-g scale with a catalyst molar ratio (S/C) of 12,300 gave (*S*)-**5** in 97% ee with 96% conversion. The second run with such a high S/C

Table 1. Asymmetric hydrogenation of 1′-acetonaphthone (**4**) with (*R*,*RR*)-**3a**.[a]

Reusing run[b]	Time [h]	Conversion [%][c]	ee of (*S*)-**5** [%][c]
1	26	99	98
2	20	100	97
3	27	100	97
4	24	100	97
5	24	100	97
6	25	100	98
7	36	100	98
8	28	99	98
9	30	99	98
10	84	100	98
11	50	99	97
12	52	97	98
13	48	96	97
14	86	93	97

[a] Reactions were conducted at 8 atm of H_2 and at 25 °C using a 1.0 M solution of the ketone (2.4–2.5 mmol) in a 1 : 1 2-propanol–DMF mixture containing *t*-C_4H_9OK and the polymer-bound complex (*R*,*RR*)-**3a**. Substrate:catalyst:*t*-C_4H_9OK = 2470 : 1 : 50.
[b] Number of times the catalyst was used. See experimental section for details.
[c] Conversion and ee were determined by chiral GC analysis. Absolute configuration was determined by the sign of rotation.

significantly lowered the conversion, probably due to deterioration of the Ru catalyst.

Matching the chirality of the diphosphine and the diamine is important to achieve a high level of enantioselectivity. The diastereomeric catalyst (*R*,*SS*)-**3a** was less reactive and stereoselective than (*R*,*RR*)-**3a** in hydrogenation of **4**, leading to (*S*)-**5** in only 8% ee. The complex (*R*,*RR*)-**3b** possessing a modified linker, coupled with *t*-C_4H_9OK as a cocatalyst, hydrogenated **4** in a 1 : 1 2-propanol–DMF mixture (S/C = 2000, 8 atm, 25 °C, 42 h) to afford **5** in the same 96% ee. This catalyst was somewhat less reactive than **3a**.

In addition, different kinds of ketonic substrates, **4** and **6a–c**, can be hydrogenated sequentially in the same flask without changing the polymer-supported catalyst. The result obtained by using (*R*,*RR*)-**3a** with S/C = 2470/batch at 8 atm and 25 °C is illustrated in Table 2. The extent of enantioselectivity was very similar to that obtained by the individual reaction using $RuCl_2$[(*R*)-binap][(*R*,*R*)-dpen] in a homogeneous phase.

Reaction Rate

Hydrogenation of **4** using the polymer-bound catalyst (*R*,*RR*)-**3a** with S/C of 2470 at 8 atm and 25 °C (the first run of Table 1) gave an initial turnover frequency (TOF defined as moles of product/mole of catalyst · h) of 390. The TOF was increased to 1520 when the reaction was conducted at 50 °C, whereas the ee of **5** was decreased from 98 to 93%. The catalytic activity of

Table 2. Sequential asymmetric hydrogenation of different aromatic ketones.[a]

Reusing run[b]	Ketone	Time [h]	Conversion [%][c]	ee of *S* alcohol [%][c]
1	**4**	7	100	97
2	**6a**	13	100	95
3	**6b**	22	100	84
4	**6c**	24	99	84

[a] See footnote [a] of Table 1.
[b] See footnote [b] of Table 1.
[c] See footnote [c] of Table 1.

(*R*,*RR*)-**3a** was also examined by using acetophenone (**6d**), which gave **7d** in 77–79% ee.[11] Hydrogenation of **6d** with (*R*,*RR*)-**3a** in a 1 : 1 2-propanol–DMF mixture at 8 atm of H_2 and 25 °C ([**6d**] = 1.0 M, ketone : Ru:*t*-C_4H_9OK = 2000 : 1 : 40) showed a TOF of 510 at 40–90% conversion, which was only slightly lower than the value of 604 (1 : 1 2-propanol–DMF) or 572 (pure 2-propanol), observed with the homogeneous (*R*)-BINAP/(*R*,*R*)-DPEN catalyst under otherwise identical conditions.[12] Although the polymer-bound catalyst showed a somewhat longer induction period than that of the homogenous system, the high TOF was sustained over at least eight repeated runs. DMF did not retard the hydrogenation.

α,β-Unsaturated Ketones

Hydrogenation of β-ionone (**8**), a dienone, using (*R*,*RR*)-**3a** with S/C = 2470 at 8 atm and 25 °C occurred selectively at the carbonyl function to give

Table 3. Asymmetric hydrogenation of β-ionone (**8**) with (*R*,*RR*)-**3a**.[a]

Reusing run[b]	Time [h]	Conversion [%][c]	ee of (*S*)-**9** [%][d]
1	15	100	84
2	20	100	84
3	24	100	85
4	23	100	85
5	26	100	85
6	30	100	85
7	45	99	84
8	47	100	85
9	25	100	86
10	78	99	86
11	72	100	87
12	75	87	–[e]

[a] See footnote [a] of Table 1.
[b] See footnote [b] of Table 1.
[c] Conversion was determined by ^1H NMR analysis. No conjugate reduction products were observed.
[d] The ee was determined by chiral HPLC analysis. Absolute configuration was determined by the sign of rotation.
[e] Not determined.

Table 4. Asymmetric hydrogenation of 2,4,4-trimethyl-2-cyclohexenone (**10**) with (*R*,*SS*)-**3a**.[a]

Reusing run[b]	Time [h]	Conversion [%][c]	ee of (*S*)-**11** [%][c]
1	22	99	93
2	24	99	94
3	24	99	93
4	26	99	93
5	27	99	94
6	25	98	94
7	71	100	94
8	48	94	94
9	49	85	95

[a] Reactions were conducted at 8 atm of H_2 and at 25 °C using a 1.0 M solution of the ketone (2.5 mmol) in a 1 : 1 2-propanol–DMF mixture containing *t*-C_4H_9OK and the polymer-bound complex (*R*,*SS*)-**3a**. Substrate:catalyst:*t*-C_4H_9OK = 3125 : 1 : 65.
[b] See footnote [b] of Table 1.
[c] Conversion and ee were determined by chiral GC analysis. No conjugate reduction products were observed. Absolute configuration was determined by the sign of rotation.

(*S*)-β-ionol [(*S*)-**9**] in 84% ee.[13] The high chemo- and enantioselectivity were sustained over ten repeated runs, affording a total TON of 29,260 (Table 3). The product solution was separated from the catalyst by transfer with a cannula, concentrated under reduced pressure, and distilled to give the chiral alcohol. This procedure is operationally beneficial in the preparation of certain allylic alcohols including **9**. In homogeneous hydrogenation, because of the general instability of allylic alcohols,[13a] removal of the Ru residue by filtration through a short silica-gel column, prior to distillation, is recommended.

When 2,4,4-trimethyl-2-cyclohexenone (**10**), a cyclic enone, was hydrogenated with (*R*,*SS*)-**3a** in a 1 : 1 2-propanol–DMA mixture with S/C = 3125 at 8 atm and 25 °C for 21 h, the cyclic allylic alcohol (*S*)-**11** was produced in 93% ee and in 99% yield. The *S* and *R* alcohols are very important as synthetic intermediates of bioactive terpenes and odorants.[14] The degree and sense of the enantioselection were comparable with those obtained with $RuCl_2$[(*R*)-binap][(*S*,*S*)-dpen].[8,15] The catalyst was reused seven times without problems, after which the rate was to some extent lowered. The reaction gave a total TON of 27,250, while the product ee was consistently in the range of 93–95% (Table 4). The diastereomeric catalyst (*R*,*RR*)-**3a** hydrogenated the enone **10**, giving (*S*)-**11** in 81% ee.[16]

Reaction with Catalysts Formed from the Racemic DPEN Ligand

Hydrogenation of the aromatic ketone **4** is known to proceed with a higher rate and better enantioselectivity with $RuCl_2$[(*R*)-binap][(*R*,*R*)-dpen] than with the *R*/*S*,*S* combined system.[9] In contrast, reaction of the cyclohexenone **10** is better effected by an (*R*)-BINAP/(*S*,*S*)-**2** combination.[15,17] These phenomena have been utilized in the asymmetric activation of a racemic BINAP Ru complex with an enantiomerically pure diamine ligand.[17,18] As expected from the homogeneous chemistry, when **4** was hydrogenated with a polymer catalyst, (*R*,*RR*/*SS*)-**3a**, that had been formed from (*R*)-**1a** and racemic **2** (S/C = 2940, 8 atm, 25 °C, 9 h), (*S*)-**5** was obtained in 87% ee in 100% yield. On the other hand, reaction of the enone **10** with the same Ru catalyst with S/C = 2960 afforded (*S*)-**11** in 91% ee with 99% conversion. The observed ee's were much higher than the simple averages of ee's obtained with the *R*/*R*,*R* and *R*/*S*,*S* diastereomeric catalysts: 53% ee for (*S*)-**5**, and 87% ee for (*S*)-**11**.[17,18]

Conclusion

This polymer-anchored catalyst system demonstrates excellent performance. The asymmetric hydrogenation is usable for certain practical synthesis of chiral alcohols, because: (1) the extent of enantioselection is very similar to that of homogeneous hydrogenation; (2) the repeated use of the recovered catalyst leads to a relatively high total TON, up to 33,000; (3) the hydrogenation rate is comparable to that of the corresponding homogeneous reaction under similar conditions. This method will be useful for combinatorial synthesis of chiral alcohols.

Experimental Section

General Remarks

Gas chromatographic (GC) analysis was conducted on a Shimazu GC-17A instrument with a Chirasildex CB column (β-cyclodextrin, df = 0.25 mm, 0.32 mm i. d. × 25 m, CHROMPAC) using helium carrier gas (40–50 kPa) with a split ratio of 20 : 1. High-performance liquid chromatographic (HPLC) analysis was conducted on a Shimazu SCL10A instrument with a CHIRALPAK AS column (4.6 mm i. d. × 250 mm, Daicel Chemical Ind.) eluted with a 1 : 200 2-propanol–hexane mixture (0.5 mL/min). ^1H and ^{31}P NMR spectra (400 and 162 MHz, respectively) were recorded on a JEOL α 400 FT-NMR. The chemical shifts of ^1H NMR resonances are reported in parts-per-million (δ) relative to tetramethylsilane. The chemical shifts of ^{31}P NMR resonances are reported in parts-per-million (δ) relative to external phosphoric acid. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Optical rotation measurements of chiral products were performed on a JASCO P-1010-GT polarimater using a sodium lamp in the indicated solvent in a 5 mm i. d. × 5 cm cell.

Materials

Polymer-bound BINAPs, (*R*)-**1a** and (*R*)-**1b**, were furnished by Oxford Asymmetry International. The loading amounts of the BINAPs on the polymer were 0.40 mmol/g and 0.59 mmol/g, respectively. $[RuCl_2(\eta^6\text{-benzene})]_2$ was purchased from Aldrich Chemical Co. and used without further purification. (*R*,*R*)-DPEN [(*R*,*R*)-**2**] was purchased from Kankyo Kagaku Co. and used without further purification. The cyclic enone **10** was purchased from Aldrich, and the other ketone substrates for hydrogenation were purchased from Tokyo Chemical Industry Co. All substrates were washed with a 0.1 M KOH solution and purified by distillation or recrystallization. Guaranteed-reagent grade 2-propanol was freshly distilled over CaH_2 before use. Guaranteed-reagent grade DMA and DMF were distilled over CaH_2 and stored in Schlenk tubes. Hydrogen of 99.99999% purity (Nippon Sanaso) was used. Argon gas (99.998%) was further purified by passage through a BASF catalyst R3–11 column at 80 °C.

Preparation of Polymer-Bound BINAP/Diamine Ru complex (*R*,*RR*)-3a

$[RuCl_2(\eta^6\text{-benzene})]_2$ (102.9 mg, 0.206 mmol) and (*R*)-**1a** (333.0 mg, BINAP content 0.133 mmol) were placed in a 20-mL Schlenk flask. After the air in the flask had been replaced with argon, degassed DMA (7.5 mL) was added. The mixture was degassed and heated at 80 °C without stirring[7] for 24 h. After the mixture had cooled to 25 °C, the solution phase was removed with a cannula fitted with filter paper, and the beads were rinsed five times with DMA (5.0 mL). Then (*R*,*R*)-**2** (141.6 mg, 0.667 mmol) and DMA (7.5 mL) were added, and the mixture was degassed and heated at 80 °C without stirring[7] for 24 h. After the mixture had cooled to 25 °C, the separated beads were rinsed seven times with DMA (5.0 mL), seven times with ether (5.0 mL), and dried under reduced pressure (1 torr) at 40 °C for 24 h to give (*R*,*RR*)-**3a** (yield: 341 mg). The purity of (*R*,*RR*)-**3a** estimated by gel-phase ^{31}P NMR analysis was 81%. ^{31}P NMR (DMA with a portion of DMSO-d_6): δ = 47.5 (s, *trans* isomer), 50.0 (br s, *cis* isomer), 57.5 (br s, *cis* isomer). The *trans : cis* ratio was 7 : 1.

(*R*,*SS*)-3a: The complex was prepared by the same procedure as described above: $[RuCl_2(\eta^6\text{-benzene})]_2$ (49.8 mg, 0.0996 mmol), (*R*)-**1a** (154.4 mg, 0.0618 mmol), (*S*,*S*)-**2** (62.2 mg, 0.293 mmol). (*R*,*SS*)-**3a** (yield: 155.8 mg). The purity was 80%. ^{31}P NMR (DMA with a portion of DMSO-d_6): δ = 46.9 (s, *trans* isomer), 50.7 (br s, *cis* isomer), 57.1 (br s, *cis* isomer). The *trans:cis* ratio was 21 : 1.

(*R*,*RR*/*SS*)-3a: The complex was prepared by the same procedure as described above: $[RuCl_2(\eta^6\text{-benzene})]_2$ (11.0 mg, 0.022 mmol), (*R*)-**1a** (72.6 mg, 0.029 mmol), (±)-**2** (29.1 mg, 0.137 mmol). (*R*,*SS*)-**3a** (yield: 72.6 mg). The purity was 68%. The (*R*,*RR*)-**3a** and (*R*,*SS*)-**3a** were mixed at a ratio of 1 : 1.

(*R*,*RR*)-3b: This complex was prepared by the same procedure as that used for **3a**: $[RuCl_2(\eta^6\text{-benzene})]_2$ (67.7 mg, 0.135 mmol), (*R*)-**1b** (153.5 mg, 0.0910 mmol), (*S*,*S*)-**2** (95.9 mg, 0.452 mmol). (*R*,*RR*)-**3b** (yield: 160.2 mg). The purity was 84%. ^{31}P NMR (DMA with a portion of DMSO-d_6): δ = 47.6 (s, *trans* isomer), 49.9 (br s, *cis* isomer), 57.5 (br s, *cis* isomer). The *trans:cis* ratio could not be determined because the peaks were not completely separated.

Asymmetric Hydrogenation of 1′-Acetonaphthone (4)

The Ru complex (*R*,*RR*)-**3a** (29.3 mg, catalyst content 9.48 μmol) was placed in a 500-mL glass autoclave equipped with a Teflon-coated magnetic stirring bar, and the air in the autoclave was replaced with argon. A solution of ketone **4** (20.1 g, 118 mmol, S/C = 12,300) in a 1 : 1 mixture of 2-propanol and DMF (120 mL), and a 1.0 M *t*-C_4H_9OK solution in *t*-C_4H_9OH (2.3 mL, 2.3 mmol), which had been degassed by bubbling argon, were added to the autoclave. The mixture was degassed by five vacuum–filling with argon cycles. Hydrogen was initially introduced into the autoclave at a pressure of 5 atm, then reduced to 2 atm by careful release of the stop valve. After this procedure had been repeated seven times, the vessel was pressurized to 8 atm. The mixture was stirred by a magnetic stirrer at ca. 500 rpm[7] at 25 °C for 97 h. The yield was determined by GC to be 96%. GC: column temp, 150 °C; injection temp, 200 °C; He, 50 kPa; retention time (t_R) of (*R*)-**5**, 41.5 min (1.5%); t_R of (*S*)-**5**, 35.3 min (94.5%); t_R of **4**, 16.7 min (4.0%). The solution phase was moved into a separation funnel, diluted with ether (100 mL), washed three times with brine (30 mL), and dried with anhydrous Na_2SO_4. After removal of Na_2SO_4, the residue was purified by bulb-to-bulb distillation to give (*S*)-**5** (18.7 g, 92% yield, 96% purity, 97% ee). $[\alpha]_D^{24}$: –81.9 (*c* = 1.01, ether).[8,19] ^{1}H NMR ($CDCl_3$): δ = 1.68 (d, 3H, *J* = 6.8 Hz, CH_3), 5.69 (q, 1H, *J* = 6.8 Hz, C*H*OH), 7.47–7.55 (m, 3H, aromatics), 7.68 (d, 1H, *J* = 7.2 Hz, aromatic), 7.78 (d, 1H, *J* = 8.4 Hz, aromatic), 7.89 (d, 1H, *J* = 7.2 Hz, aromatic), 8.13 (d, 1H, *J* = 8.4 Hz, aromatic).

Sequential Asymmetric Hydrogenation of Aromatic Ketones, 4 and 6a–c

(*R*,*RR*)-**3a** (3.1 mg, catalyst content 1.00 μmol) was placed in a 100-mL glass autoclave. A solution of **4** (419.4 mg, 2.46 mmol, S/C = 2470/batch) in a 1 : 1 2-propanol–DMF mixture (2.5 mL) and a 1.0 M *t*-C_4H_9OK solution in *t*-C_4H_9OH (50 μL, 50 μmol) were added to the autoclave, and hydrogen was introduced to a pressure of 8 atm. The mixture was stirred at ca. 500 rpm[7] at 25 °C. The solution phase was removed by cannula and the remaining catalyst beads were washed five times with a 1 : 1 2-propanol–DMF mixture (2.5 mL). (*S*)-**5** was purified using the same procedure as that described in the former section. To this glass autoclave, **6a** (334.4 mg, 2.49 mmol) dissolved in a 1 : 1 2-propanol–DMF mixture (2.5 mL) and a 1.0 M *t*-C_4H_9OK solution in *t*-C_4H_9OH (50 μL, 50 μmol) were added, and hydrogenation was conducted using the same procedure as that outlined above. The four different chiral alcohols, (*S*)-**5a** and (*S*)-**7a–c**, were obtained by repeating the hydrogenation procedure with use of the same catalyst. The data of each product is described below.

(*S*)-**5**: 84% yield (358.2 mg), 97% ee. $[\alpha]_D^{24}$: –82.4 (*c* = 1.00, ether).[8,19] GC and ^{1}H NMR data are described in the former section.

(*S*)-**7a**: 77% yield (261.5 mg), 95% ee. $[\alpha]_D^{31}$: –70.3 (*c* = 1.01, $CHCl_3$).[8,20] GC: column temp, 125 °C; t_R of (*R*)-**7a**, 14.3 min (2.3%); t_R of (*S*)-**7a**, 16.3 min (97.5%); t_R of **6a**, 5.5 min (0.2%).

(*S*)-**7b**: 83% yield (312.6 mg), 84% ee. $[\alpha]_D^{32}$: –42.3 (*c* = 1.05, $CHCl_3$).[8,21] GC: column temp, 110 °C; t_R of (*R*)-

7b, 35.4 min (7.8%); t_R of (*S*)-**7b**, 38.6 min (91.9%); t_R of **6b**, 21.3 min (0.3%).

(*S*)-**7c**: 85% yield (353.2 mg), 84% ee. $[\alpha]_D^{32}$: –29.3 (*c* = 1.14, benzene).[8,22] GC: column temp, 140 °C; t_R of (*R*)-**7c**, 18.7 min (7.7%); t_R of (*S*)-**7c**, 19.1 min (91.5%); t_R of **6c**, 13.9 min (0.8%).

Asymmetric Hydrogenation of β-Ionone (8)

Conditions [(*R*,*RR*)-**3a** (3.1 mg, catalyst content 1.00 μmol), **8** (477.0 mg, 2.48 mmol, S/C = 2470), 1.0 M *t*-C_4H_9OK in *t*-C_4H_9OH (50 μL, 50 μmol), 2-propanol (1.25 mL), DMF (1.25 mL), 8 atm H_2, 25 °C, 15 h]. (*S*)-**9** (400.0 mg, 83% yield). No conjugate reduction products were observed by ^{1}H NMR analysis. HPLC [t_R of (*R*)-**9**, 24.8 min (8.1%); t_R of (*S*)-**9**, 19.8 min (91.9%)]. $[\alpha]_D^{25}$: –5.1 (*c* = 2.77, $CHCl_3$),[25] 84% ee.

Asymmetric Hydrogenation of 2,4,4-Trimethyl-2-cyclohexenone (10)

Conditions [(*R*,*SS*)-**3a** (3.1 mg, catalyst content 0.79 μmol), **10** (348 mg, 2.52 mmol, S/C = 3125), 1.0 M *t*-C_4H_9OK in *t*-C_4H_9OH (50 μL, 50 μmol), 2-propanol (1.25 mL), DMA (1.25 mL), 8 atm H_2, 25 °C, 22 h]. (*S*)-**11** (256.0 mg, 73% yield). No 1,4-reduction products were observed by ^{1}H NMR and GC analyses. GC [column temp, 90 °C; t_R of (*R*)-**11**, 38.5 min (3.5%); t_R of (*S*)-**11**, 40.2 min (95.4%); t_R of **10**, 23.0 min (1.1%)]. $[\alpha]_D^{30}$: –83.8 (*c* = 1.10, ether),[13,14] 93% ee.

Asymmetric Hydrogenation of Ketones with (*R*,*RR*/*SS*)-3a: Hydrogenation of 4

Conditions [(*R*,*RR*/*SS*)-**3a** (3.1 mg, catalyst content 0.84 μmol), **4** (421.5 mg, 2.48 mmol, S/C = 2940), 1.0 M *t*-C_4H_9OK in *t*-C_4H_9OH (50 μL, 50 μmol), 2-propanol (1.25 mL), DMF (1.25 mL), 8 atm H_2, 25 °C, 9 h]. (*S*)-**5** (361.9 mg, 85% yield, 87% ee). GC and ^{1}H NMR data are described above.

Hydrogenation of 10

Conditions [(*R*,*RR*/*SS*)-**3a** (3.1 mg, catalyst content 0.84 μmol), **10** (345.3 mg, 2.50 mmol, S/C = 2960), 1.0 M *t*-C_4H_9OK in *t*-C_4H_9OH (50 μL, 50 μmol), 2-propanol (1.25 mL), DMA (1.25 mL), 8 atm H_2, 25 °C, 39 h]. (*S*)-**11** (262.6 mg, 75% yield, 91% ee). GC data are described above.

Kinetic Experiments of Hydrogenation of Acetophenone (6d)

The kinetic experiments were conducted in a 100-mL glass autoclave equipped with a sampling needle connected to a stop valve. A small portion of the reaction mixture was collected through this system at regular intervals and analyzed by chiral GC.

Hydrogenation with (*R*,*RR*)-3a: Conditions [(*R*,*RR*)-**3a** (7.9 mg, catalyst content 2.50 μmol), **6d** (597.9 mg, 4.98 mmol), 1.0 M *t*-C_4H_9OK in *t*-C_4H_9OH (0.10 mL, 0.10 mmol), 2-propanol (2.5 mL), DMF (2.5 mL), 8 atm H_2, 25 °C]. Conversions and ee's were determined by GC analysis. GC [column temp, 110 °C; t_R of (*R*)-**7d**, 15.0 min; t_R of (*S*)-**7d** 16.2 min; t_R of **6d**, 6.7 min]. Initial rate (TOF) was calculated from eight experiment sets, and values were first-order-plotted to be 508 (moles/mole of Ru · h). Correlations between period, conversion, and % ee of (*S*)-**7d**, are as follows: (10, 3, –), (20, 3, –), (40, 5, –), (80, 29, –), (120, 46, 79), (160, 63, 79), (250, 96, 79), (300, 99, 79).

Hydrogenation with *trans*-$RuCl_2$[(*R*)-binap][(*R*,*R*)-dpen] (homogeneous system): Conditions [*trans*-$RuCl_2$[(*R*)-binap][(*R*,*R*)-dpen] (2.5 mg, 2.48 μmol), **6d** (599.2 mg, 4.99 mmol), 1.0 M *t*-C_4H_9OK in *t*-C_4H_9OH (0.10 mL, 0.10 mmol), 2-propanol (2.5 mL), DMF (2.5 mL), 8 atm H_2, 25 °C]. Conversions and ee's were determined by GC analysis, the conditions and t_R of compounds of which are described above. TOF was calculated from eight experiment sets, and values were first-order-plotted to be 604. Correlations between period, conversion, and % ee of (*S*)-**7d**, were as follows: (5, 1, –), (10, 2, –), (20, 7, 77), (40, 20, 78), (80, 36, 78), (120, 53, 78), (160, 76, 79), (240, 100, 79).

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