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Mechanism of catalytic asymmetric hydrogenation of 2-formyl-1-methylene-1,2,3,4-tetrahydroisoquinoline using $Ru(CH_3COO)_2$[(*S*)-binap]

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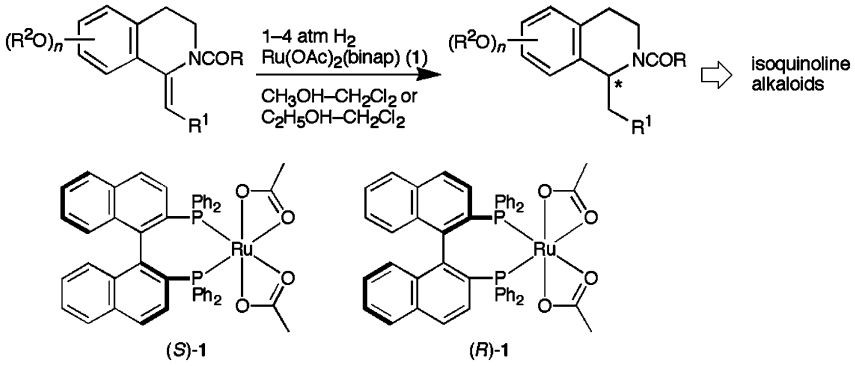
Abstract—The mechanism of the asymmetric hydrogenation of 2-acyl-1-alkylidene-1,2,3,4-tetrahydroisoquinolines, the first reported reaction with the Noyori–Takaya $Ru(CH_3COO)_2$(binap) complex, has been investigated by means of deuterium labeling, kinetics, and NMR analysis. A series of experiments has revealed that (1) a monohydride-unsaturated mechanism operates involving the initial formation of RuH followed by reaction with the enamide substrate, (2) the hydride transfer from RuH to the olefinic double bond is endothermic and reversible, and (3) the rate is determined in the hydrogenolysis step. This view is consistent with that of proposed for the BINAP–Ru catalyzed Kagan reaction.

1. Introduction

The Ru(II) dicarboxylate complex **1** with 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) is a milestone catalyst in asymmetric hydrogenation chemistry. The complex was reported in 1986 in the hydrogenation of 2-acyl-1-alkylidene-1,2,3,4-tetrahydroisoquinolines, opening a new route to the general asymmetric synthesis of biologically active isoquinoline alkaloid derivatives such as morphine, morphinane, benzomorphane, and salsolidine (Scheme 1).[1] This initial reaction has prompted the asymmetric hydrogenation of a variety of functionalized olefins including unsaturated alcohols, carboxylic acids, and phosphonic acid derivatives, making a great impact in both industry and academia.[2] However, in deference to Kagan's 1971 report,[3] in which α-(acylamino)acrylic acids or esters were first used successfully in combination with a DIOP–Rh(I) complex, we have studied the mechanisms of the BINAP–Ru analogues of his system.[4] In response to many inquiries,[1] we now describe in full the details of the mechanism of our original reaction system using **1**.

Based on the results obtained in the mechanistic study of BINAP–Ru catalyzed hydrogenation in the Kagan system,[4] the reaction in Scheme 1 is thought to proceed via a monohydride-unsaturated route as shown in Scheme 2. First, (*S*)-**1**



Scheme 1. BINAP–Ru catalyzed hydrogenation toward the general asymmetric synthesis of isoquinoline alkaloids.

Keywords: Asymmetric hydrogenation; BINAP–Ru; 2-Acyl-1-alkylidene-1,2,3,4-tetrahydroisoquinoline; Monohydride-unsaturated mechanism.
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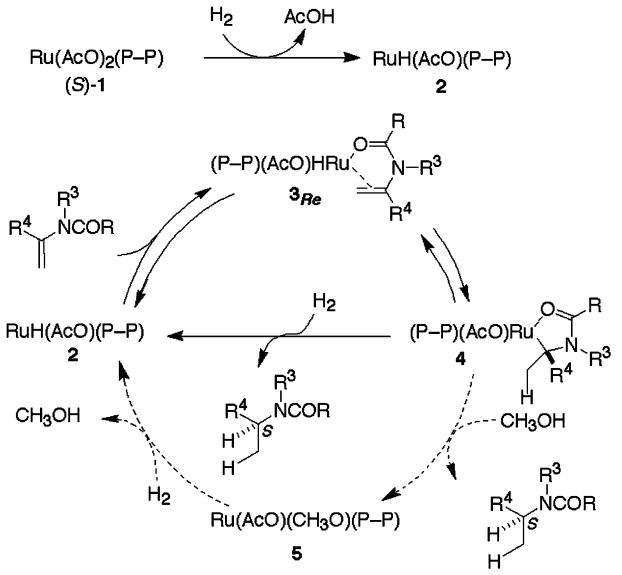
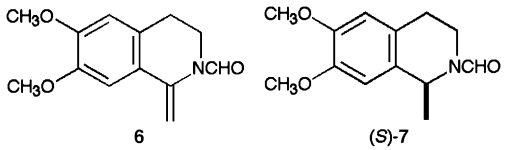
reacts with molecular hydrogen to generate the monohydride complex **2**, which then interacts with an enamide. In a short-lived substrate–catalyst complex **3**, the olefin inserts into the Ru–H bond to generate the five-membered metallacycle **4** in a reversible manner. The Ru–C bond in **4** is preferentially cleaved by H_2 rather than CH_3OH to regenerate **2** together with release of the saturated product, completing the catalytic cycle. Protonolysis of the Ru–C linkage by a coordinated methanol occurs to a lesser extent, giving the product and the Ru(II) species **5**. The Ru–OCH_3 bond in **5** is hydrogenolyzed to regenerate the catalyst **2**.



Scheme 2. Supposed catalytic cycle of (*S*)-BINAP–Ru catalyzed hydrogenation of 1-methylene tetrahydroisoquinoline in methanol. Tetrahydroisoquinoline aromatic rings in the substrates are omitted for clarity. P–P=(*S*)-BINAP.

To confirm the present mechanistic view, the simple 2-formyl-1-methylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**6**), for which there is no problem of *Z*/*E* isomerism, was selected as a standard substrate to do a series of experiments: (1) examination of the isotope incorporation patterns of the product obtained under H_2/CH_3OD, HD/CH_3OD, and D_2/CH_3OD conditions, (2) kinetic study to deduce the order of the reaction, and (3) rate law analysis to determine the energy profile of the catalytic cycle.



2. Results and discussion

The optimized reaction conditions ([(*S*)-**1**]$_0$=0.075 mM, [**6**]$_0$=15 mM (substrate/catalyst ratio (S/C)=200:1), temperature=30 °C, 5:1 CH_3OH/CH_2Cl_2) in the original 1986 report quantitatively gives (*S*)-2-formyl-1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*S*)-**7**] in 97% ee.[1a,1c] As the initial concentration of **6** is too dilute to conduct an effective rate measurement by monitoring the total pressure decrease in the closed reaction vessel (vide infra), the concentration of **6** was set to 100 mM in a 1:1 CH_3OH/CH_2Cl_2 solvent system. The increase in the CH_2Cl_2 ratio solves the low solubility problem at the cost of enantioselectivity. Thus, under the following conditions, [(*S*)-**1**]$_0$= 0.5 mM, [**6**]$_0$=100 mM (S/C=200:1), temperature=30 °C, H_2 pressure=2–16 atm, reaction time=12–24 h, (*S*)-**7** was obtained quantitatively in 89–94% ee. A significant decrease in ee (67%) was observed at 100 atm. The pressure effect is similar to that observed in the reactions of methyl (*Z*)-α-(acetamido)cinnamate[4] and dehydro amino phosphonic acids.[5]

2.1. Isotopomer ratios

By detailed analysis of the isotopomeric products, **7**-*h*,*h*, **7**-*d*,*h*, **7**-*h*,*d*, and **7**-*d*,*d*, which are obtained by the reactions in a 1:1 mixture of CH_3OD and CH_2Cl_2 using HD, H_2, or D_2 it is possible to discriminate between monohydride/dihydride mechanisms as well as hydrogenolysis/protonolysis routes. The ratio of these four isotopomers can be determined by spectral analysis of phase-sensitive $^{13}C\{^1H,^2H\}$–^1H correlation NMR and $^{13}C\{^1H\}$ NMR. Figure 1 shows the β-carbon region of the correlation spectrum of a mixture of **7**-*h*,*h*, **7**-*d*,*h*, **7**-*h*,*d*, and **7**-*d*,*d* in a 19:30:17:33 ratio. The ^{13}C signals of these four isotopomers appear at δ 20.86 (s), 20.75 (s), 20.58 (s), and 20.47 (s), respectively, which are correlated with β-proton signals at δ 1.448 (d, *J*=6.3 Hz), 1.440 (s), 1.432 (d, *J*=6.3 Hz), and 1.424 (s), respectively. Considering the coupling patterns of ^1H-decoupled ^{13}C and ^1H signals, the four carbon signals are unequivocally assigned to **7**-*h*,*h*, **7**-*d*,*h*, **7**-*h*,*d*, and **7**-*d*,*d* from low to high field. This is consistent with the empirical rule that carbon

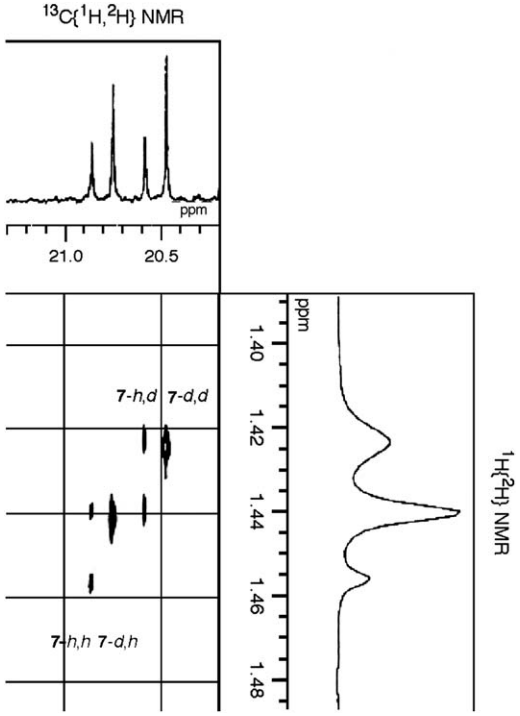
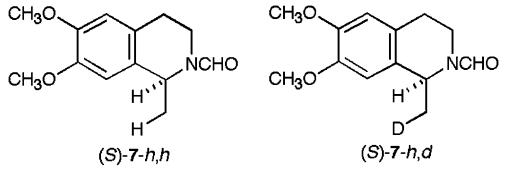


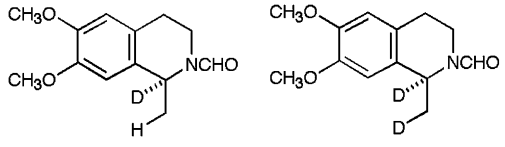
Figure 1. Phase-sensitive $^{13}C\{^1H,^2H\}$–^1H correlation spectrum (β position) of a 19:30:17:33 mixture of **7**-*h*,*h*, **7**-*d*,*h*, **7**-*h*,*d* and **7**-*d*,*d* in $CDCl_3$ at 23 °C.

atoms bearing deuterium resonate at a higher field in proportion to the number of deuterium.[6] Another set of four ^{13}C signals around δ 23.5 with similar correlation patterns to above is assignable to the amide conformers.[7]



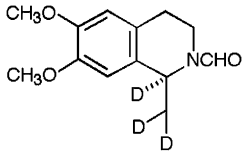
(*S*)-**7**-*h*,*h*

(*S*)-**7**-*h*,*d*



(*S*)-**7**-*d*,*h*

(*S*)-**7**-*d*,*d*



(*S*)-**7**-*d*,d_2

The deuterium labeling experiments at 4 atm under the above standard conditions gave the *S*-enriched isotopomers in 93% ee. The results of the product analysis are summarized in Table 1. The reactions using HD and H_2 were stopped at an early stage of conversion (7–16%) to avoid the complication caused by gas/solvent and gas/gas isotope exchange.[8] The initial proportion of the isotopes in gas and solvent was confirmed to be virtually unchanged by careful GC analysis of the unreacted hydrogen[9] and GC–MS analysis of the recovered solvent.[4a] The use of HD/CH_3OD (H_2/HD/D_2=1:98:1) afforded, after 7% conversion, **7**-*h*,*h*, **7**-*d*,*h*, **7**-*h*,*d*, and **7**-*d*,*d* in a 25:30:14:30 ratio with an average ee of 93%. The approximately even distribution amongst the four isotopomers indicates that RuH but not RuH_2 is operating as the catalytic species. If the dihydride mechanism were predominant,[10,11] **7**-*d*,*h* and **7**-*h*,*d* would be the major isotopomers. Replacement of HD with H_2 gave, after 16% conversion, a mixture of **7**-*h*,*h*, **7**-*d*,*h*, **7**-*h*,*d*, and **7**-*d*,*d* in an 82:13:5:0 ratio. This distribution indicates that the RuH species generated from (*S*)-**1** and H_2 delivers its H to the β carbon of enamide **6**, giving a five-membered metallacycle intermediate **4**. The Ru–C bond is then cleaved by H_2 and CH_3OD in an 82:13 ratio. Preference for the hydrogenolysis route is also supported by the 5:0 ratio of **7**-*h*,*d* and **7**-*d*,*d*. The enamide bond C_α=C_β is inserted into the RuD species, which is probably formed by H/D exchange between the RuH chain carrier and CH_3OD,[8] to form Ru–C_α–C_β–D. Cleavage of the Ru–C_α bond with H_2 produces **7**-*h*,*d*. Use of D_2 and CH_3OD under the standard conditions requires 49 h to complete the reaction. As would be expected, the isotopomeric product is **7**-*d*,*d*. However, a significant amount of **7**-*d*,d_2 (6%) was obtained, and the amount of **7**-*d*,d_2 was increased to 16% at 1 atm. The incorporation of multiple deuterium atoms at the β carbon suggests that the migratory insertion of RuH in C_α=C_β is reversible.[4a,b]

Table 1. Analysis of *S*-enriched product **7** obtained by isotope labeling experiments using **6** and (*S*)-**1**[a] in a 1:1 mixture of CH_3OD and CH_2Cl_2

	Gas		
	HD	H_2	D_2
Time	15 min	16 min	49 h
Conversion, %	7	16	>99
% ee[b]	93	93	93
Product distribution, %			
7-*h*,*h*	25	82	<1
7-*d*,*h*	30	13	<1
7-*h*,*d*	14	5	<1
7-*d*,*d*	30	0	94
7-*d*,d_2	1	0	6

[a] Reactions were carried out at 4 atm under the standard conditions. The detailed procedures for the reaction and analysis are described in Section 4. Solvent CH_3OD contains 0.5% of CH_3OH. HD gas contains 1% each of H_2 and D_2. D_2 gas contains 0.4% of HD.

[b] The ee was determined by HPLC analysis.

2.2. Rate measurements

The rate of hydrogenation of **6** with (*S*)-**1** in a 1:1 mixture of methanol and CH_2Cl_2 under 4 atm of H_2 at 30 °C was determined by monitoring the decrease in hydrogen pressure in a closed Teflon-coated hydrogenation vessel. The relationship between ln[**6**]$_t$ and time was reasonably linear for the initial concentrations, [**6**]$_0$=100 mM and [(*S*)-**1**]$_0$=0.50 mM, indicating a pseudo first-order dependence on the enamide concentration in the reaction system. Therefore, the rate is described simply by the rate law $-d[\mathbf{6}]/dt=k_{obs}[\mathbf{6}]$, where k_{obs} is 6.0×10^{-3} min^{-1}. In order to deduce the rate law and to gain insight into the catalytic cycle, the reaction rates were measured at varying concentrations of (*S*)-**1** and hydrogen pressures. As shown in Figure 2a and b, the reaction follows first-order kinetics both in [(*S*)-**1**] and in H_2 in a boundary region of the standard conditions ([(*S*)-**1**]$_0$=0.25–1.0 mM; 2–16 atm H_2). On the basis of this kinetic study, the present catalysis can be simply viewed as a bis-substrate/uni-product system. The catalyst **2** reversibly binds **6** to form a catalyst–substrate complex, which then transfers a hydride to **6**. The resulting intermediary Ru–alkyl complex **4** reacts with H_2, releasing the product by regenerating the catalyst **2**. As the monohydride formation step from (*S*)-**1** to **2** is independent of hydrogen pressure and controlled only by acid/base thermodynamics under the standard conditions,[4a] the total concentration of the Ru hydride species, either active or inactive, is constant ([**2**]=a[(*S*)-**1**]$_0$).[12] Thus, the turnover rate is limited by the hydrogenolysis step but not by the hydride-transfer step or by the hydride formation step.

2.3. Rate law analysis

Since the rate of conversion of enamide is estimated by that of the turnover-limiting step **4**→**2**, by assuming a steady-state for [**4**] together with the relation [**2**]=a[(*S*)-**1**]$_0$, the rate law can be expressed as Eq. 1.

$$-d[\mathbf{6}]/dt = ak_1[(S)\text{-}\mathbf{1}]_0[\mathbf{6}](k_2[H_2]+k_3[CH_3OH]) \times (k_{-1}+k_2[H_2]+k_3[CH_3OH])^{-1} \quad (1)$$

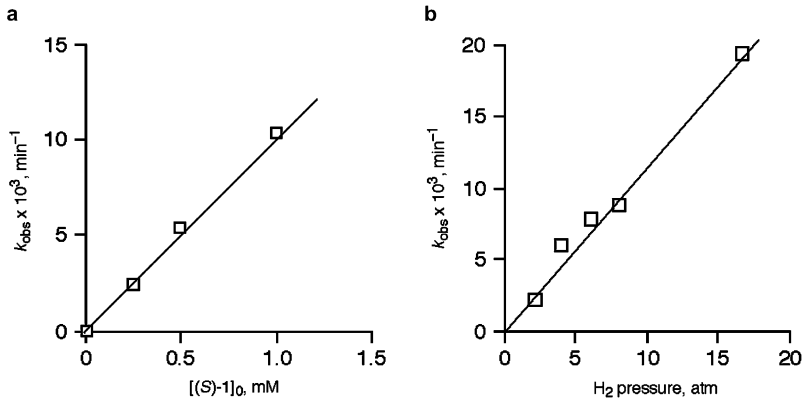


Figure 2. Dependence of $[(S)\text{-}\mathbf{1}]_0$, and H_2 pressure on the rate constant k_{obs} in hydrogenation of **6** ($[\mathbf{6}]_0$=100 mM) in a 1:1 mixture of CH_3OH and dichloromethane at 30 °C. a: Plots of k_{obs} as a function of $[(S)\text{-}\mathbf{1}]_0$ (4 atm H_2). b: Plots of k_{obs} as a function of H_2 pressure ($[(S)\text{-}\mathbf{1}]_0$=0.50 mM).

Here, k_1 is for the intramolecular hydride transfer, **2**→**4**, k_{-1} for the β-elimination, **4**→**2**, k_2 for the hydrogenolysis, **4**→**2**, and k_3 for the methanolysis, **4**→**5**. In order to satisfy the experimental results (the first-order kinetics in $[(S)\text{-}\mathbf{1}]_0$ and $[H_2]$), the $k_2[H_2]+k_3[CH_3OH]$ term in the denominator of the rate law should be negligible in comparison to k_{-1}. The inequality $k_{-1} \gg k_2[H_2]+k_3[CH_3OH]$ indicates that the rate of β-elimination is significant in comparison to the overall rate of reaction expressed as Eq. 2, and that the hydride-transfer step is endothermic. The energy profile obtained by the rate law analysis is consistent with formation of **7**-d,d_2 under D_2/CH_3OD conditions.

$$-\mathrm{d}[\mathbf{6}]/\mathrm{d}t = ak_1k_{-1}^{-1}[(S)\text{-}\mathbf{1}]_0[\mathbf{6}](k_2[H_2] + k_3[CH_3OH]) \qquad (2)$$

3. Conclusion

Deuterium labeling experiments, kinetic studies as well as rate law analysis have suggested that the (*S*)-BINAP–Ru catalyzed hydrogenation of 2-formyl-1-methylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline proceeds via a monohydride-unsaturated mechanism in a similar way as α-(acylamino)acrylic esters. An RuH species, which is first generated from the diacetate and H_2 with the liberation of acetic acid, forms a short-lived catalyst–substrate complex. A reversible and endothermic intramolecular hydride transfer from RuH to the β carbon of the coordinating enamide substrate occurs to generate the five-membered metallacycle, the Ru–C bond of which is then cleaved largely by H_2 and partly by protic CH_3OH. Consequently, the two protiums at the α and β positions of the enamide substrate are derived from two different hydrogen molecules. The overall rate is limited by the hydrogenolysis step. Although the present results can be used only for the mechanism in the formation of the major enantiomeric product, the minor product may also be expected to be generated via the same monohydride-unsaturated pathway but diastereomorphic to the major cycle.[13] Higher enantioselectivity with **6** than with α-(acylamino)acrylic esters can be ascribed to a bulkier substituent at the α-position and to a restricted ring system. The structural features would enhance the stereo-complementarity in the major RuH/enamide complexes, resulting in the higher $\Delta\Delta G^{\ddagger}$. Consistent with the model, dehydro amino phosphonic acids[5] and *N*-acyl-4-methylene-1,3-oxazolidin-2-ones[14] show high enantioselectivities in our catalyst system.

4. Experimental

4.1. General

Nuclear magnetic resonance (NMR) spectra were measured on a JEOL JNM-A400 equipped with a pulsed field gradient unit and a triple-resonance probe or a JEOL JNM-ECP500 instrument. The chemical shifts are expressed in parts per million (ppm) downfield from $Si(CH_3)_4$ or in ppm relative to $CHCl_3$ (δ 7.26 in ^{1}H NMR and δ 77.0 in ^{13}C NMR). Signal patterns of ^{1}H NMR as well as ^{13}C NMR are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. GC–MS analyses were conducted using a Shimadzu QP-5000. All melting points were determined on a Yanaco melting point apparatus and were uncorrected. Analytical thin-layer chromatography (TLC) was performed using Merck 5715 indicating plates precoated with silica-gel 60 F254 (layer thickness 0.25 mm). Liquid chromatographic purifications were performed by flash column chromatography, using glass columns packed with Merck 9385 (230–400 mesh). All manipulations in the BINAP–Ru catalyzed hydrogenation were carried out by using standard Schlenk techniques on a dual manifold vacuum/Ar system. The conversions of **6** to **7** were determined by comparing ratios of the formyl ^{1}H NMR signals at δ 8.64 (sickle isomer of **6**), δ 8.38 (U isomer of **6**), δ 8.28 (**7**), and δ 8.12 (**7**).[7] The % ee of **7**, after deprotection of the formyl group, was determined by the GITC (2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl isothiocyanate) method employing a reversed-phase C_{18} silica-gel column (column, Nomura Chemical Co. Develosil ODS-5; eluent, 1:2 CH_3CN/H_2O containing ammonium phosphate (1.4 g/L); flow rate, 1.0 mL/min; detection, 254-nm light, retention times (t_R) of the thiourea of (*R*)-**7** and (*S*)-**7**, 71.6 min and 74.9 min).[1c] $H_2/HD/D_2$ and CH_3OH/CH_3OD analyses were conducted by the reported methods.[4a,13a]

4.2. Materials

CH_3OH and CH_3OD for hydrogenation were degassed at refluxing temperature in the presence of Mg (250 mg/

100 mL) under an argon stream for 6 h and distilled into Schlenk flasks. CH_3OD contained 0.5% of OH species. CH_2Cl_2 was distilled from CaH_2. The solvent was degassed by three freeze–thaw cycles before hydrogenation. $CDCl_3$ was purchased from Aldrich and used without further purification. Argon gas was purified by passing through a column of the BASF catalyst R3-11 at 80 °C and then a column of $CaSO_4$ at room temperature. H_2 gas of 99.99999% grade and D_2 gas containing 0.4% HD were purchased from Nippon Sanso, and HD gas containing 1% H_2 and 1% D_2 was obtained from Isotec. These gases were used for hydrogenation without purification. $Ru(CH_3COO)_2$[(*S*)-binap] [(*S*)-**1**][15] and 2-formyl-6,7-dimethoxy-l-methylene-1,2,3,4-tetrahydroisoquinoline (**6**)[1c] were prepared by the reported methods.

4.3. Isotope labeling experiments

4.3.1. Structural determination of isotopomers. A mixture of **7**-*h*,*h*, **7**-*d*,*h*, **7**-*h*,*d*, and **7**-*d*,*d* in a 19:30:17:33 ratio containing 1% of **7**-*d*,d_2 was prepared by the following conditions (for the detailed procedure, see Sections 4.3.2 and 4.3.3): (*S*)-**1** (13.5 mg, 0.016 mmol), **6** (350 mg, 1.50 mmol), CH_3OD (7.5 mL), CH_2Cl_2 (7.5 mL), 4 atm HD, 30 °C, 329 h. The structures of the four isotopomers, **7**-*h*,*h*, **7**-*d*,*h*, **7**-*h*,*d*, and **7**-*d*,*d*, were determined by analysis of the phase-sensitive $^{13}C\{^1H,^2H\}$–^1H correlation spectrum taken in $CDCl_3$ at 24 °C using a JEOL JNM-A400 spectrometer. To minimize the magnetic field instability associated with the lack of a D-spin lock, measuring time was shortened by use of a high concentration of the sample (>100 mg/0.6 mL) under the following conditions: acquisition time=0.70371 s, pulse delay=1.2963 s, scan number=8, and measurement time=90 min.

4.3.2. H_2/CH_3OD conditions. The substrate **6** (1.7229 g, 7.3858 mmol), CH_3OD (36.9 mL), and CH_2Cl_2 (36.9 mL) were placed into a dry, argon-filled Schlenk tube, and the whole mixture was degassed by three freeze–thaw cycles. The solution was transferred via stainless cannula to another Schlenk tube containing a pale brown solid $Ru(CH_3COO)_2$[(*S*)-binap] [(*S*)-**1**] (31.1 mg, 36.9 μmol) under a slightly positive argon pressure. After being further degassed by two freeze–thaw cycles, the mixture was transferred to a 420-mL glass autoclave. Argon gas in the whole system was replaced three times by H_2, and the reaction vessel was pressurized to 4 atm. The yellowish solution was vigorously stirred at 30 °C. After 16 min, a portion of the unreacted gas in the reaction vessel was transferred to an 80-mL evacuated Schlenk tube equipped with a Young's tap, and then ca. 20 mL of the reaction mixture was collected in an argon-filled 80 mL Schlenk tube. The solvent was recovered by distillation. The $H_2/HD/D_2$ and CH_3OH/CH_3OD ratios were analyzed and found to be 99.5:0.5:0 and 1:99, respectively. The residue was subjected to ^1H NMR and HPLC analyses, by which the conversion and ee were determined to be 16% and 93%, respectively, on the basis of the methods described in Section 4.1.

The crude reaction mixture was separated into **6** and **7** by silica-gel chromatography (40 g; eluent; 2:1 hexane/ethyl acetate and then 1:3 hexane/ethyl acetate). The isotopomer ratio was determined by measurements of the $^{13}C_\beta$ signal area in the $^{13}C\{^1H,^2H\}$ NMR spectrum, which was taken using a JEOL JNM-A400 spectrometer under the following conditions: flip angle, 45°; acquisition time (AT), 2.1823 s; pulse delay (PD), 7.8177 s. ^1H and ^2H decoupling was affected only during acquisition time.

4.3.3. HD/CH_3OD conditions. The reaction was conducted similar to that for the H_2/CH_3OD system except for the size of the reactor (130-mL glass autoclave) and the use of HD instead of H_2. The whole reaction mixture was collected for further analysis. Reaction scale: 598 mg of **6**; $[(S)\text{-}\mathbf{1}]_0$= 0.5 mM; $[\mathbf{6}]_0$=100 mM; 4 atm of HD; CH_3OD; 30 °C; 15 min. The conditions converted 7% of **6** to give (*S*)-**7** in 93% ee (HPLC analysis). The $H_2/HD/D_2$ ratio was 3:95:2.

4.3.4. D_2/CH_3OD conditions. The reaction was conducted similar to that for the HD/CH_3OD system except for the use of D_2 instead of HD. Reaction scale, 202 mg of **6**; $[(S)\text{-}\mathbf{1}]_0$=0.5 mM; $[\mathbf{6}]_0$=100 mM; 4 atm of D_2; 1:1 CH_3OD/CH_2Cl_2; 30 °C; 49 h. The conditions converted >99% of **6** to give (*S*)-**7** in 93% ee (HPLC analysis). The $^{13}C\{^1H,^2H\}$ NMR signal of tri-deuterated isotopomer **7**-*d*,d_2 was assigned at δ 20.36 by the empirical rule.[9] A reaction under 1 atm of D_2 was conducted by use of a 1-L Schlenk tube with a Young's tap: reaction scale, 178 mg of **6**; $[(S)\text{-}\mathbf{1}]_0$=0.5 mM; $[\mathbf{6}]_0$=100 mM; 1 atm of D_2; 1:1 CH_3OD/CH_2Cl_2; 30 °C; 49 h, >99% conversion.

4.4. Kinetics

Kinetics investigations were conducted using a Teflon-coated stainless autoclave fitted with a variable temperature jacket and a magnetically controlled mechanical stirring system. A typical procedure is represented as follows. A yellow solution of a 1:1 mixture of CH_3OH (7.5 mL) and CH_2Cl_2 (7.5 mL) containing **6** (598 mg, 2.56 mmol) and (*S*)-**1** (6.3 mg, 7.5 μmol) in an Ar-filled 80-mL Schlenk tube was introduced into the Ar-filled autoclave by use of Ar pressure. The temperature of the autoclave was set to 30 °C, and the whole system was allowed to equilibrate for 10 min. The inner Ar gas was replaced with H_2 by three pressurization–release cycles, and then the pressure was adjusted to 4 atm. The reaction was started by closing the connection of the autoclave to the H_2 cylinder and then stirring the reaction mixture at 1200 rpm. The total H_2 pressure, which gradually decreased to 3.7 atm over the course of the reaction, was recorded by the pressure sensor for a total of 240 min. The observed rate constant k_{obs} was calculated to be 6.0×10^{-3} min^{-1} on the basis of percentage of conversion and the change in total pressure. The conversion was calculated to be 78% by ^1H NMR analysis. The ee of (*S*)-**7** was determined to be 89% by the GITC method. Likewise, the effects of catalyst concentration and H_2 pressure were examined under the standard conditions ($[\mathbf{6}]_0$=100 mM, solvent=a 1:1 mixture of CH_3OH and CH_2Cl_2, 30 °C). The conditions and the rate constant k_{obs} are as followings. $[(S)\text{-}\mathbf{1}]_0$=*0.25 mM*: (*S*)-**1** (3.2 mg, 3.8 μmol), 4.0 atm H_2, 360 min, 45% convn, 2.4×10^{-3} min^{-1}. After stirring for ca. 2 h, hydrogen pressure started to decrease. $[(S)\text{-}\mathbf{1}]_0$=*1.0 mM*: (*S*)-**1** (12.6 mg, 0.015 mmol), 4.0 atm H_2, 210 min, 90% convn, 1.0×10^{-2} min^{-1}; *2.1 atm* H_2: (*S*)-**1** (6.3 mg, 7.5 μmol), 300 min, 52% convn, 2.2×10^{-3} min^{-1}; *6.1 atm* H_2: (*S*)-**1** (6.3 mg, 7.5 mmol), 240 min, 85% convn, 7.9×10^{-3} min^{-1}; *8.1 atm*

H_2: (*S*)-**1** (6.3 mg, 7.5 μmol), 180 min, 83% convn, 8.8×10^{-3} min^{-1}; *16.6 atm* H_2: (*S*)-**1** (6.3 mg, 7.5 μmol), 120 min, 94% convn, 1.9×10^{-2} min^{-1}.

The reaction at 100 atm in a stainless autoclave[15b] (78 mg of **6**; $[(S)\text{-}\mathbf{1}]_0$=0.7 mM; $[\mathbf{6}]_0$=100 mM) at 30 °C for 48 h in a 1:1 mixture of CH_3OH (1.7 mL) and CH_2Cl_2 (1.7 mL) gave (*S*)-**7** in 67% ee with 91% conversion.

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