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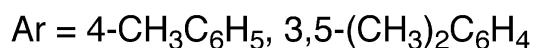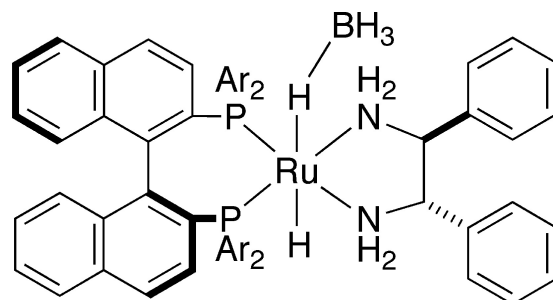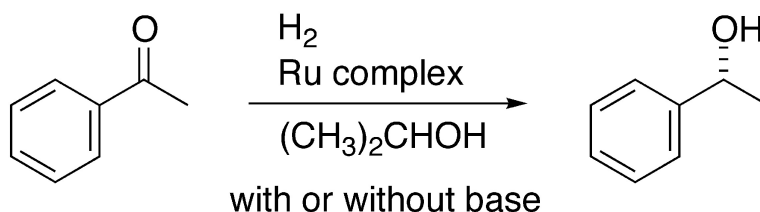
Mechanism of Asymmetric Hydrogenation of Ketones Catalyzed by BINAP/1,2-Diamine–Ruthenium(II) Complexes

Christian A. Sandoval, Takeshi Ohkuma, Kilian Muiz, and Ryoji Noyori

Ar = 4-CH$_3$C$_6$H$_5$, 3,5-(CH$_3$)$_2$C$_6$H$_4$

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Mechanism of Asymmetric Hydrogenation of Ketones Catalyzed by BINAP/1,2-Diamine−Ruthenium(II) Complexes

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Abstract: Asymmetric hydrogenation of acetophenone with *trans*-RuH(η^1-BH$_4$)[(*S*)-tolbinap][(*S*,*S*)-dpen] (TolBINAP = 2,2′-bis(di-4-tolylphosphino)-1,1′-binaphthyl; DPEN = 1,2-diphenylethylenediamine) in 2-propanol gives (*R*)-phenylethanol in 82% ee. The reaction proceeds smoothly even at an atmospheric pressure of H$_2$ at room temperature and is further accelerated by addition of an alkaline base or a strong organic base. Most importantly, the hydrogenation rate is initially increased to a great extent with an increase in base molarity but subsequently decreases. Without a base, the rate is independent of H$_2$ pressure in the range of 1−16 atm, while in the presence of a base, the reaction is accelerated with increasing H$_2$ pressure. The extent of enantioselection is unaffected by hydrogen pressure, the presence or absence of base, the kind of base and coexisting metallic or organic cations, the nature of the solvent, or the substrate concentrations. The reaction with H$_2$/(CH$_3$)$_2$CHOH proceeds 50 times faster than that with D$_2$/(CD$_3$)$_2$CDOD in the absence of base, but the rate differs only by a factor of 2 in the presence of KO-*t*-C$_4$H$_9$. These findings indicate that dual mechanisms are in operation, both of which are dependent on reaction conditions and involve heterolytic cleavage of H$_2$ to form a common reactive intermediate. The key [RuH(diphosphine)(diamine)]$^+$ and its solvate complex have been detected by ESI-TOFMS and NMR spectroscopy. The hydrogenation of ketones is proposed to occur via a nonclassical metal−ligand bifunctional mechanism involving a chiral RuH$_2$(diphosphine)(diamine), where a hydride on Ru and a proton of the NH$_2$ ligand are simultaneously transferred to the C=O function via a six-membered pericyclic transition state. The NH$_2$ unit in the diamine ligand plays a pivotal role in the catalysis. The reaction occurs in the outer coordination sphere of the 18e RuH$_2$ complex without C=O/metal interaction. The enantiofaces of prochiral aromatic ketones are kinetically differentiated on the molecular surface of the coordinatively saturated chiral RuH$_2$ intermediate rather than in a coordinatively unsaturated Ru template.

Introduction

Ideal asymmetric catalysis can be achieved only by suitable architectural and functional molecular engineering of chiral catalysts and selection of suitable reaction parameters.[1−3] Recently, we focused on the development of an efficient method to hydrogenate unfunctionalized simple ketones to optically active secondary alcohols.[4−8] Among the best catalysts for the carbonyl hydrogenation thus discovered is the chiral diphosphine/1,2-diamine−Ru(II) combination in 2-propanol solvent.[5,6] This catalytic hydrogenation proceeds with an exceptionally high turnover number (TON, defined as mol of substrate hydrogenated per mol of catalyst), high turnover frequency (TOF, defined as TON per h), and excellent enantioselectivity for various simple ketones. For example, as illustrated in Figure 1,

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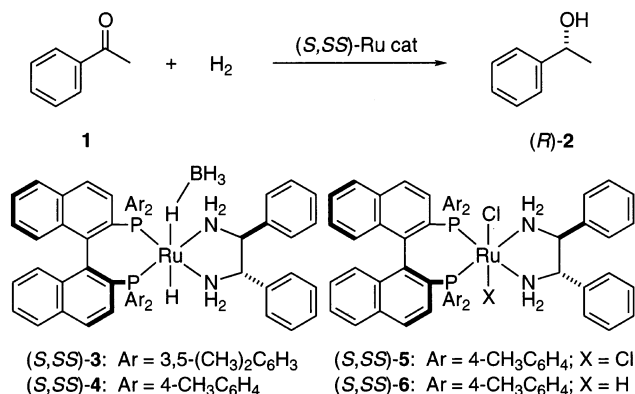
Figure 1. Asymmetric hydrogenation of acetophenone (**1**) to (*R*)-1-phenylethanol [(*R*)-**2**] with (*S*)-BINAP/(*S*,*S*)-DPEN Ru(II) catalysts.

acetophenone (**1**) (102 g) is hydrogenated to (*R*)-1-phenylethanol [(*R*)-**2**] in 99% ee and 100% yield in 2-propanol (106 mL) containing *trans*-RuH(η^1-BH$_4$)[(*S*)-xylbinap][(*S*,*S*)-dpen] [(*S*,*SS*)-**3**] (9.0 mg).[9,10] The reaction with a substrate/catalyst molar ratio (*S*/*C*) of 100 000 takes place smoothly at 8 atm of H$_2$ and 45 °C and is completed within 7 h. Addition of 14 mM KO-*t*-C$_4$H$_9$ further facilitates the hydrogenation, completing the reaction of **1** in 45 min to give (*R*)-**2** with the same 99% ee. Hydrogenation with the simpler TolBINAP/DPEN complex (*S*,*SS*)-**4** is faster but less enantioselective, affording (*R*)-**2** in 82% ee and 100% yield.[9,10]

Earlier, we used the corresponding chiral diphosphine/diamine−RuCl$_2$ complexes, including **5**, with the aid of a strong base such as KOH, KOCH(CH$_3$)$_2$, or KO-*t*-C$_4$H$_9$ to give the same ee in high yield.[6] As seen in the related transfer hydrogenation developed in our laboratories,[11−16] the NH$_2$ or NH moiety in the 1,2-diamine ligand is crucial for high catalytic activity. The N(CH$_3$)$_2$ analogues are totally inactive. This integrated molecular approach allows for practical hydrogenation of a wide range of simple aromatic, heteroaromatic, olefinic, and aliphatic ketones.[5,6] Certain dialkyl ketones are hydrogenated with a high diastereoselectivity.[17] Furthermore, this catalytic system is chemoselective for a C=O linkage and tolerates many substituents including C=C, F, Cl, Br, I, CF$_3$, OCH$_3$, OCH$_2$C$_6$H$_5$, COOR, NO$_2$, NH$_2$, and NHR^{1}COR^2 as well as various heterocycles.[6] The reaction occurs facilely with benzophenone derivatives, confirming that the C=O function is hydrogenated rather than taking the enol form.[18]

Hydrogen is the simplest molecule but its reaction with organic molecules is not straightforward. In fact, regardless of the substrate structures, H$_2$ can be activated by various transition metal complexes by forming a metal hydride or dihydride.[19] However, catalytic hydrogenation of the unsaturated compounds is not always easy. Normally a requisite reaction between a metal hydride (or dihydride) intermediate and the C=O function is thought to occur by a $\sigma2 + \pi2$ reaction.[20] Such a classical mechanism, however, does not account for the characteristics of the hydrogenation reaction of Figure 1. The chemistry displayed by the BINAP/diamine−Ru complexes is entirely different from that of diamine-free BINAP−Ru catalysts, which are widely used for the hydrogenation of functionalized ketones such as β-keto esters.[21] Various mechanisms have been proposed by our[6,7] and other[22,23] group(s) for the unique hydrogenation of simple ketones. Here, we describe our study of the hydrogenation with *trans*-RuH(η^1-BH$_4$)(diphosphine)(1,2-diamine), which proceeds by utilizing a unique NH effect. Most notably, the reduction occurs in the outer sphere of a coordinatively saturated metal hydride species and the carbonyl substrate. This is in contrast to the traditional notion that the substrate/metal complexation is essential for hydrogenation of unsaturated compounds.[20]

Results and Discussion

Hydrogenation Profiles. Hydrogenation of the aromatic ketone **1** to the secondary alcohol **2** (Figure 1) was selected as a standard reaction. The simple, well-characterized TolBINAP/DPEN complex (*S*,*SS*)-**4** was used as precatalyst,[24] although more elaborate complexes, including (*S*,*SS*)-**3**, give better ee values.[9] Hydrogenation was conducted in a glass autoclave equipped with a sampling needle connected to a stop valve. Aliquots were taken from an active hydrogenation mixture and analyzed by chiral GC. For example, hydrogenation of a 0.60 M solution of **1** in 2-propanol containing (*S*,*SS*)-**4** (0.33 mM, *S*/*C* = 1800) at 4 atm and 30 °C for 12 h gave (*R*)-**2** in 82% ee with near quantitative yield. The color of the solution remained yellow throughout the hydrogenation under these conditions. Figure 2 shows a typical reaction profile. The substrate consumption as a function of time is sigmoidal in nature (Figure 2a), with a direct relationship between substrate expenditure and product formation and without any side products. The hydrogenation was significantly accelerated upon base addition, as shown in Figure 2b, where an 18 mM KO-*t*-C$_4$H$_9$ solution

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(24) Unless otherwise stated, the *S*,*SS*-configured complex is used throughout this paper for the sake of formal consistency and simplicity. In the actual experiment, the *R*,*RR* enantiomer may have been utilized.
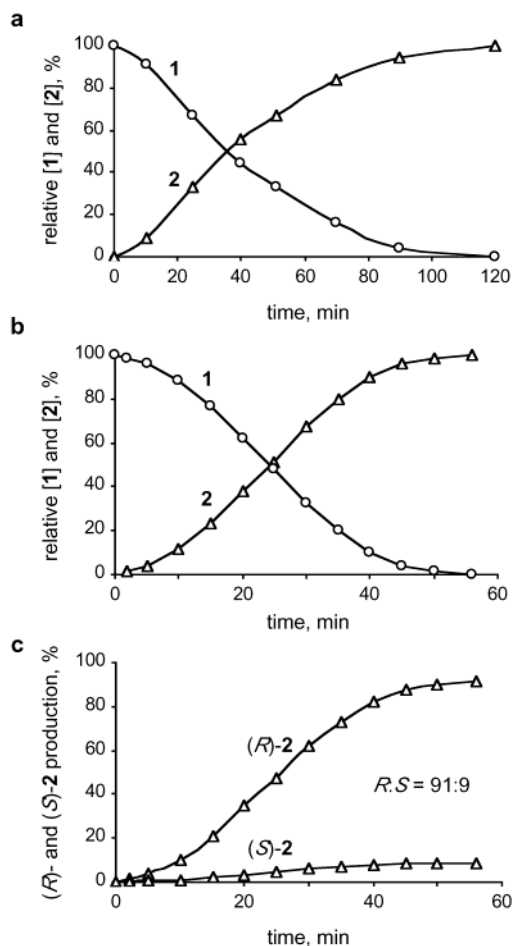
Figure 2. Typical profile of asymmetric hydrogenation of acetophenone (**1**) in 2-propanol catalyzed by *trans*-RuH(η^1-BH$_4$)[(*S*)-tolbinap][(*S*,*S*)-dpen] [(*S*,*SS*)-**4**]. Conditions: [**1**] = 0.60 M, [**4**] = 0.33 mM (*S*/*C* = 1800), [KO-*t*-C$_4$H$_9$] = 18 mM, P_{H_2} = 4 atm, *T* = 30 °C. (a) Relative [**1**] and [**2**] vs reaction time without base. (b) Relative [**1**] and [**2**] vs reaction time in the presence of KO-*t*-C$_4$H$_9$. (c) Production of (*R*)- and (*S*)-**2** during hydrogenation of **1** in the presence of KO-*t*-C$_4$H$_9$.

was used. The product ee was independent of substrate concentration and/or TOF (Figure 2c). The absence or presence of KO-*t*-C$_4$H$_9$ or other bases did not change the ee value of (*R*)-**2**. Furthermore, the enantioselectivity was insensitive to hydrogen pressure or reaction temperature in a 20−50 °C range, giving (*R*)-**2** consistently with 82% ee. Below 10 °C, the reaction was very slow.

Catalytic Cycle. Any proposed mechanisms must reasonably explain the characteristic base and H$_2$-pressure dependency of the reaction rate. Based on the series of experimental findings detailed below, we postulate the mechanism shown in Figure 3 for the hydrogenation of simple ketones catalyzed by diphosphine/diamine−Ru complexes. The mechanism consists of the generation of real catalysts from precatalyst **4** and the steady-state catalytic cycles I and II.

First, the 18e precatalyst **4** dissociates a BH$_4$ anion to generate the cationic complex **7**, which upon deprotonation forms the 16e Ru amide complex **8**. Alternatively, with the aid of an ambient base, **4** is converted to **8** via **9** through a D$_{cb}$ mechanism.[25] All these steps are reversible, in principle. Thus, destruction of BH$_4^-$ in alcoholic solvent (ROH) leads to

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formation of H$_2$, RO$^-$, and B(OR)$_3$ and thereby shifts the equilibrium toward the formation of the pentacoordinate complexes **7** and **8**, both of which act as true hydrogenation catalysts. The **7**/**8** ratio is determined by the basicity of the reaction media.

Dependent on the reaction conditions, two catalytic cycles operate, as we suggested earlier.[11−15] The cationic 16e complex **7** reacts with H$_2$ reversibly to form the 18e complex **10**, which undergoes deprotonation from the η^2-H$_2$ ligand to generate the reducing Ru dihydride **11**. Reaction of **11** and ketone **1** gives the 16e amido Ru species **8** and the alcoholic product **2**. This irreversible step determines the absolute stereochemistry of **2**. Protonation of the nitrogen atom of **8** by alcoholic solvent regenerates **7**, completing *catalytic cycle I*. This is the major pathway under standard conditons. Alternatively, the reducing species **11** can also be regenerated from **8** by way of the complex **12**, making *catalytic cycle II*. This pathway is normally not significant but becomes important under certain conditions.

The coordinatively saturated metal complex **11** reacts with the organic substrate directly by a metal−ligand bifunctional mechanism.[11] Thus reduction of ketones with **11** proceeds via the six-membered pericyclic transition state **13**, in which the C=O function does not interact with the Ru center. Delivery of a hydride from the Ru center and a proton from the NH$_2$ ligand takes place simultaneously, giving alcohols without forming metal alkoxide intermediates. The formal 16e complex **8** is stabilized by electron release from the amido ligand to Ru, forming a partial Ru−N double bond.[26] The Ru center in **8** accommodates an H$_2$ molecule and cleaves it to regenerate **11** directly. The heterolytic cleavage of H$_2$ in **12** occurs via the four-membered TS **14**[27] or the six-membered structure **15** mediated by a hydrogen-bonded alcohol molecule. Alternatively, the 2 + 2 reaction via **14** may occur by a bimolecular reaction between **8** and H$_2$. In any case, cationic **7** has a higher electron-deficiency at Ru and accepts H$_2$ more readily than does **8**.[26] This, combined with the easy protonation of **8** to give **7** under standard conditions, prevents dehydrogenation of alcohols[11−16] to ketones and **11**.

Figure 3 does not define the geometry of the Ru complexes. Stereoisomers are possible for the hexacoordinate complexes, while the formal pentacoordinate species may have a trigonal bipyramidal structure[28] or actually exist as solvated hexacoordinate complexes. Cationic **7** originally produced from **4** is paired with a [BH$_n$(OR)$_{4-n}$]$^-$ or RO$^-$ anion. In any event, the possible cationic **7**(ROH), neutral **8**(ROH), or alkoxide complexes would be in equilibrium with the pentacoordinate

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(27) Ru[(*S*,*S*)-NTsCH(C$_6$H$_5$)CH(C$_6$H$_5$)NH](η^6-cymene), a 16e Ru amide complex, reacts with H$_2$ at 80 °C to give RuH[(*S*,*S*)-NTsCH(C$_6$H$_5$)CH(C$_6$H$_5$)-NH$_2$](η^6-cymene).[12]
(28) An ab initio MO calculation suggests that RuCl(H$_2$NCH$_2$CH$_2$NH)(PH$_3$)$_2$ has a trigonal bipyramidal geometry (private communication from Professor Masashi Yamakawa, Kinjo Gakuin University).
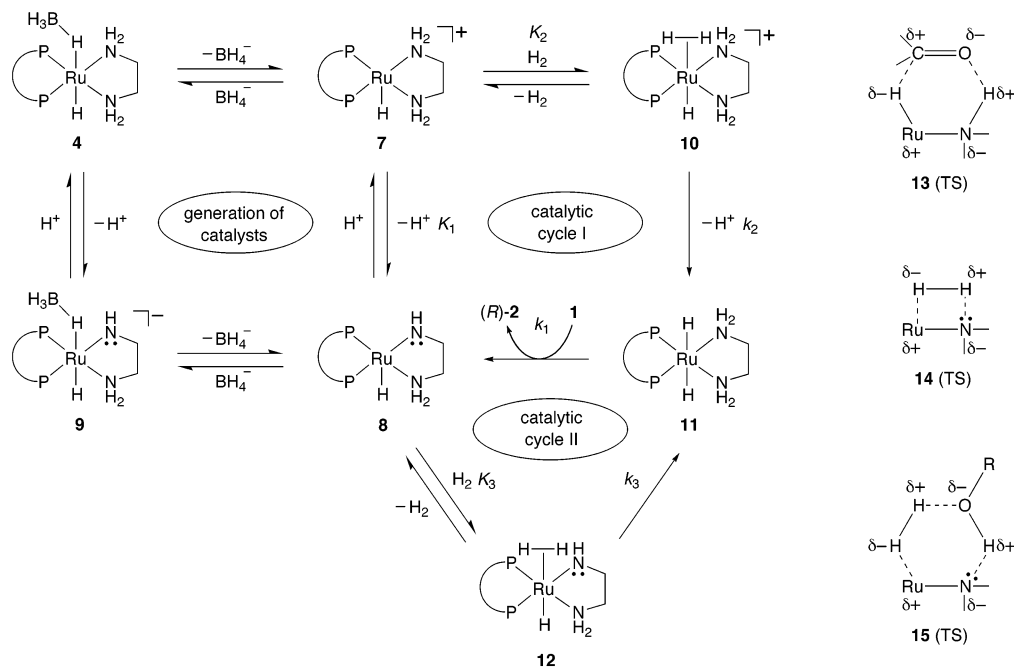
Figure 3. Mechanism of hydrogenation of **1** catalyzed by (*S,SS*)-**4** in 2-propanol. ROH = 2-propanol; P−P = (*S*)-TolBINAP; two phenyl substituents in (*S,S*)-DPEN are omitted for clarity. Under the "base-free" conditions, ROH acts as a base.

complexes and also undergo ready alcohol or alkoxide exchange in alcoholic media.[29]

The dual mechanisms operating in this catalytic hydrogenation are constructed assuming the effective relative basicity of :NH in **12** > :NH in **8** > (RO⁻)(2-propanol)$_n$ and the relative acidity of η^2-H$_2$ in **10** > NH$_2$ in **7** ≥ 2-propanol > NH$_2$ in **4** > NH$_2$ in **11**. The major pathway and the turnover-limiting step are determined by the equilibrium constants, K_1, K_2, and K_3, and the rate constants, k_1, k_2, and k_3, as well as the reaction conditions. The relative significance of the two cycles is determined by various parameters. Reactions in alcoholic media proceed via catalytic cycle I involving **7/10** as the resting state. Here, a high concentration of the η^2-H$_2$ complex **10** and its easy deprotonation are required to achieve high catalytic efficiency. On the other hand, for reaction in aprotic solvents or with a high concentration of base, catalytic cycle II becomes meaningful, where **8** is the resting species. The latter cycle has been proposed by investigating the behavior of a model RuH$_2$ species largely in toluene,[23] but this behavior is only a small part of the whole catalytic system in protic solvents.

Kinetics. The proposed mechanism agrees well with a kinetic investigation of the present system. Data were collected from the reaction using conditions of [**1**] (initial **1** concentration) = 0.44−1.65 M in 2-propanol, [(*S,SS*)-**4**] = 0.22−0.47 mM, [KO-*t*-C$_4$H$_9$] = 0−130 mM, P_{H_2} = 1−16 atm, and T = 30 °C. To obtain direct measurement of the experimentally observed reaction rate (k_{obs}), it was necessary to overcome the initial incubation step that converts the precatalyst **4** to a real catalyst. Addition of an aliquot of substrate ([**1**]$_{aliquot}$, typically 0.85 M)

under a hydrogen atmosphere at the point of reaction such that >90% conversion had been achieved resulted in the disappearance of the sigmodial behavior (seen in Figure 2a), as shown in Figure 4a. Under such conditions, consumption of acetophenone in the system followed *pseudo*-first order kinetics, with the initial (typically 2−20 min) linearity for the expression ln-[**1**]$_t$ = $k_{obs}(t)$ + ln[**1**]$_0$ ([**1**]$_0$ = [**1**] at aliquot addition, t = 0) allowing for k_{obs} determination (Figure 4b). The concentration of active catalytic species is considered to remain constant throughout aliquot addition and hydrogenation mixture sampling.

First, as seen in Figure 4c, regardless of the absence or presence of base, the rate was independent of the initial substrate concentration ([**1**]$_0$) above an *S/C* ratio of 500 where saturation kinetics were in effect.[30] The reaction using [**1**] = 0.15−4.25 M and [**4**] = 0.41−0.43 mM in 2-propanol (*S/C* range of 344 to 10 110), P_{H_2} = 4 atm, and T = 30 °C afforded the near constant k_{obs}/[**4**] values of ca. 0.17, 1.7, and 0.54 M^{-1} s^{-1} for [KO-*t*-C$_4$H$_9$] = 0, 8, and 69 mM, respectively. The base-concentration effect on rate will be discussed below. Under various base concentrations, the same ee for (*R*)-**2** of 82% was obtained. Thus, under the standard catalytic conditions, **11** reduces **1** readily to give **2** and **8**. This step, common to both catalytic cycles I and II, was shown not to limit the turnover rate during acetophenone reduction.

The hydrogenation rate reflects the concentration of **11** undergoing rapid bimolecular reaction with a ketonic substrate. The rate law of hydrogenation caused by catalytic cycles I and II is given by $-\mathrm{d}[\mathbf{1}]/\mathrm{d}t = k_2K_2[\mathbf{7}][\mathrm{H}_2] + k_3K_3[\mathbf{8}][\mathrm{H}_2]$. Under base-free conditions where catalytic cycle I is dominant, the rate is independent of H$_2$ pressure in the range of 1−16 atm (Figure 5). Here, because H$_2$ concentration in solution is sufficient, even under an atmospheric pressure, to fully saturate

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(30) The lower values obtained at ca. *S/C* > 10 000 are considered to be the result of substrate/product solvent inhibition under the required experimental conditions (discussed below; see Supporting Information) as the 2-propanol: acetophenone/phenylethanol ratio nears 1:1 (v/v).
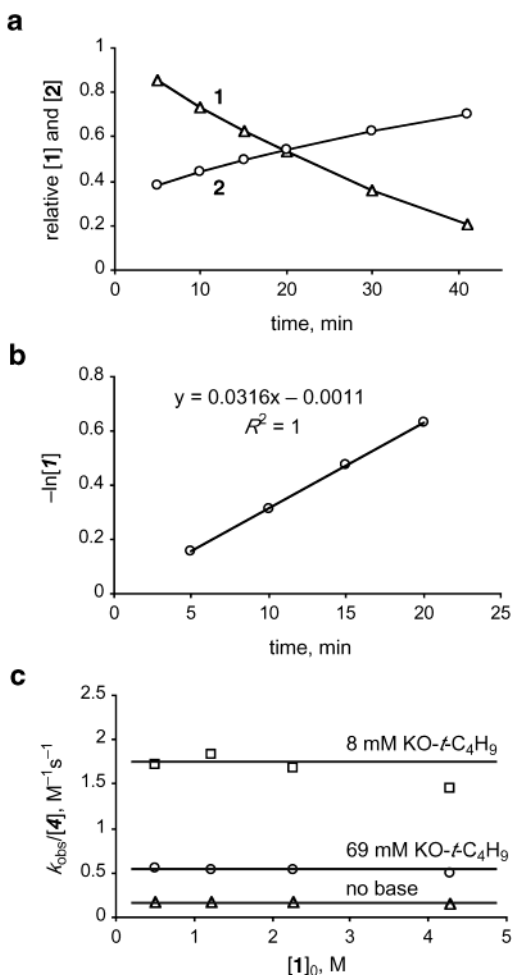
Figure 4. (a) Relative [**1**] and [**2**] vs reaction time following aliquot addition of **1** at >90% conversion for standard hydrogenation conditions. Conditions: [**1**]$_{aliquot}$ = 0.85 M [**4**] = 0.46 mM (S/C = 1800), [KO-t-C$_4$H$_9$] = 16 mM, P_{H_2} = 4 atm, T = 30 °C. (b) Determination of observed rate constant (k_{obs}, gradient of $-\ln[\mathbf{1}]$ vs reaction time) for data in part a. (c) Dependence of hydrogenation rate on initial concentration of acetophenone ([**1**]$_0$) under steady-state conditions.
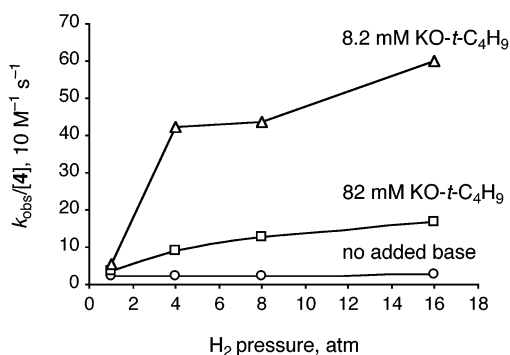
Figure 5. Dependence of hydrogenation rate on hydrogen pressure. Conditions: solvent = 2-propanol, [**1**] = 0.89−0.98 M, [**4**] = 0.41−0.46 mM (S/C = 2000), T = 30 °C.

7 forming **10**, deprotonation of the latter[31] limits the turnover of the hydrogenation cycle. The observed temperature effect indicates that the activation energy (E_a) of the reaction rate, given by $-d[\mathbf{1}]/dt = k_2[\mathbf{10}]$, is 23 kcal mol^{-1}. Addition of a strong base facilitates this process (Figure 6), with the TOF initially increasing with increasing molarity. In the presence of a base, catalytic cycle II starts to make a contribution. At very
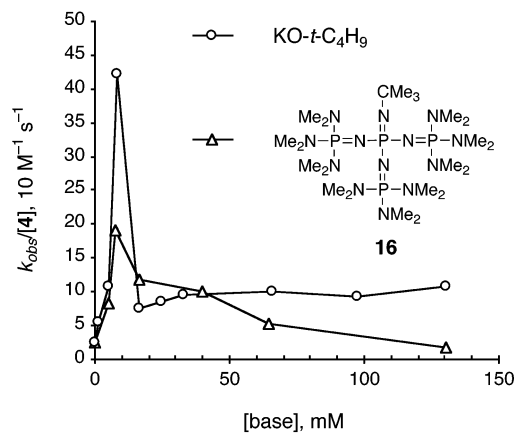
Figure 6. Dependence of hydrogenation rate on base molarity. Conditions: solvent = 2-propanol, [**1**] = 0.89−0.99 M, [**4**] = 0.42−0.47 mM (S/C = 1800), P_{H_2} = 4 atm, T = 30 °C.

high-base conditions under which [**8**] ≫ [**7**] is assumed, the TOF becomes near independent of the base concentration and, in turn, shows a *pseudo*-first-order dependence on H$_2$ pressure (Figures 5 and 6). The η^2-H$_2$ complex **12** in catalytic cycle II is a short-lived species; the rate constant k_3 is large, while the equilibrium constant K_3 is rather small in comparison to $1/K_1$ and K_2 of catalytic cycle I. Thus, at low H$_2$ pressures, the TOF is relatively insensitive to a base concentration, and the rate is limited by deprotonation of **10**. The characteristic effects of base and hydrogen pressure are detailed below.

Solution Behavior of Precatalyst (*S*,*SS*)-4. (a) Structures. The X-ray crystallographic analysis of the precatalyst (*S*,*SS*)-**4** shows that the BH$_4$ anion is bound to the Ru center in an η^1 manner and is located trans to the hydride ligand.[9] The BH$_4$ moiety is further supported in the complex through BH···HN hydrogen bonds, while toluene-d_8 solutions at room temperature exhibited a broad NMR signal at δ −0.79 ppm, suggesting a fluxional structure. The NH$_2$ ligand in **4** readily undergoes proton exchange in alcoholic solvents. Thus, as shown in Figure 7, addition of (CD$_3$)$_2$CDOD resulted in a gradual decrease in the NH$_2$ resonances with time due to H/D exchange.[32] In the presence of 10 mM KO-t-C$_4$H$_9$, this exchange was completed within 4 min. Importantly, RuH in **4** was not affected to any significant extent.[33]

Figure 8 shows the ESI-TOFMS spectra obtained for the precatalyst (*S*,*SS*)-**4** in a 1:1 mixture of 2-propanol and toluene. Before the hydrogenation, the spectrum exhibited eminent peaks centered at m/z = 1007 due to [(*S*,*SS*)-**4**]$^+$ (Figure 8a). Figure 8 parts b and c show the behavior of **4** under standard conditions of acetophenone hydrogenation (S/C = 2000, [KO-t-C$_4$H$_9$] = 8.3 mM, P_{H_2} = 4 atm, T = 30 °C). The spectra showed the appearance and continual increase of cationic fragments with m/z ratios consistent with the cationic complex **7** ([**7**]$^+$ = 993
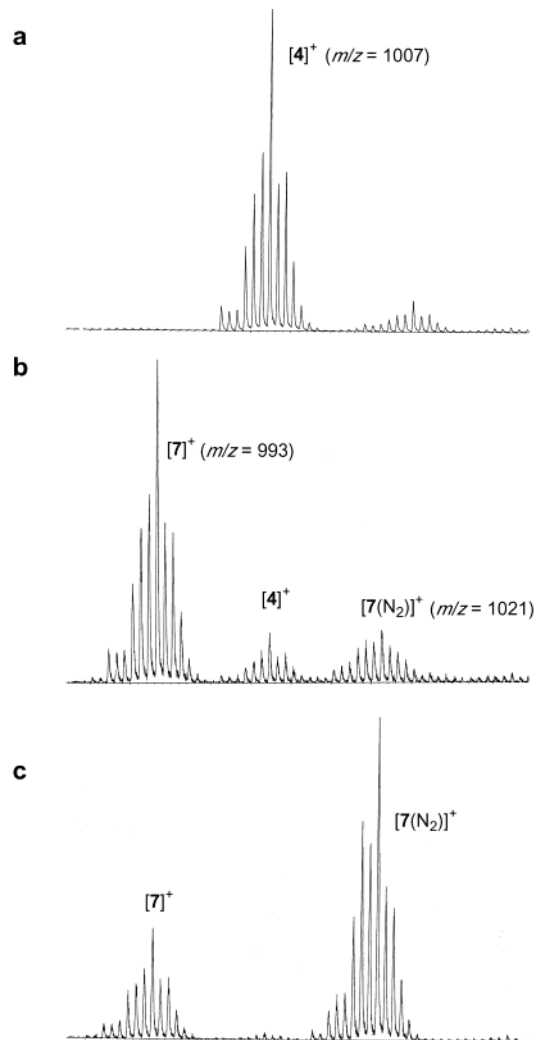
(31) (a) Darensbourg, M. Y.; Ludvig, M. M. *Inorg. Chem.* **1986**, *25*, 2894−2898. (b) Cappellani, E. P.; Maltby, P. A.; Morris, R. H.; Schweitzer, C. T.; Steele, M. R. *Inorg. Chem.* **1989**, *28*, 4437−4438. (c) Hembre, R. T.; McQueen, S. *J. Am. Chem. Soc.* **1994**, *116*, 2141−2142. (d) Schlaf, M.; Lough, A. J.; Maltby, P. A.; Morris, R. H. *Organometallics* **1996**, *15*, 2270−2278. (e) Smith, K.-T.; Norton, J. R.; Tilset, M. *Organometallics* **1996**, *15*, 4515−4520. (f) Scott, A. P.; Golding, B. T.; Radom, L. *New J. Chem.* **1998**, 1171−1173. (g) Nishibayashi, Y.; Takei, I.; Hidai, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3047−3050.

(32) No H/D exchange took place with **5** and **6** in (CD$_3$)$_2$CDOD containing no base.

(33) In CH$_3$OD with or without KO-t-C$_4$H$_9$, both NH$_2$ and the RuH hydride itself in **4** undergo rapid H/D exchange.
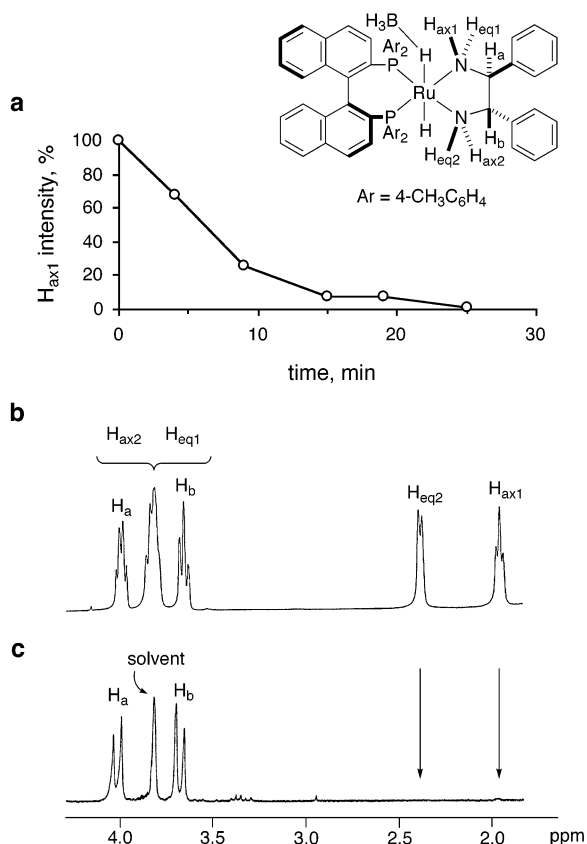
Figure 7. H/D exchange of precatalyst (S,SS)-**4** in $(CD_3)_2CDOD$. (a) Rate of exchange without base. ^1H NMR spectrum of the amine region (b) in toluene-d_8 and (c) after addition of $(CD_3)_2CDOD$.

and $[7(N_2)]^+ = 1021$,[34,35] coupled with a declining precatalyst concentration. After 50% conversion, the cationic Ru complexes became the sole (detectable) dominant species in solution. Thus, considering the high affinity of **7** for H_2, complex **10** is the possible resting state for the steady-state catalytic system in 2-propanol in a close equilibrium with the detectable complex **7**. The same spectra were obtained in the absence of KO-t-C_4H_9. The possible RuH(OR)(tolbinap)(dpen), Ru(OR)$_2$(tolbinap)-(dpen), or [RuOR(tolbinap)(dpen)]$^+$ complexes were not detected by this ESI-TOFMS technique.

The long-life catalyst more likely exists as a solvent-separated ion pair, $[7(ROH)]^+ [(RO)(ROH)_n]^-$. In fact, the cation was observed together with precatalyst **4** in NMR spectra of similar hydrogenating mixtures taken under $D_2/(CD_3)_2CDOD$ conditions.[36] A hydride signal appeared at δ −17.8 ppm, while, in complicated ^{31}P spectra, the characteristic doublets were seen at δ 62.2 and 70.8 ppm with $J = 41.5$ Hz. No interaction was observed between the two ionic species on the NMR time scale (NOESY).[29,37] A 40 mM solution of **4** in benzene-d_6 (50 μL of

(34) (a) Yamaguchi, K.; Sakamoto, S.; Tsuruta, H.; Imamoto, T. *Chem. Commun.* **1998**, 2123−2124. (b) Kenny, J. A.; Versluis, K.; Heck, A. J. R.; Walsgrove, T.; Wills, M. *Chem. Commun.* **2000**, 99−100.

(35) The [**7**]$^+$ peak may partly result from protonation of **8** under the ESI-TOFMS experimental conditions.

(36) The required high concentration (16 mM) for NMR measurement is unrealistic. Consequently, noninvolved species, shown not to participate in ketone reduction, were observed (Supporting Information).

(37) (a) Shvo, Y.; Czarkie, D.; Rahamim, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7400−7402. (b) Bryndza, H. E.; Fong, L. K.; Paciello, R. A.; Tam, W.; Bercaw, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 1444−1456. (c) Durfee, L. D.; Rothwell, I. P. *Chem. Rev.* **1988**, *88*, 1059−1079. (d) Bücken, K.; Koelle, U.; Pasch, R.; Ganter, B. *Organometallics* **1996**, *15*, 3095−3098. (e) Zuccaccia, C.; Bellachioma, G.; Cardaci, G.; Macchioni, A. *J. Am. Chem. Soc.* **2002**, *123*, 11020−11028.

Figure 8. ESI-TOFMS spectra of active acetophenone hydrogenation mixtures in a 2-propanol/toluene solvent mixture (1:1, v/v) after (a) $t = 0$ min, (b) $t = 60$ min (30% conversion), and (c) $t = 145$ min reaction time (78% conversion). Conditions: [**1**] = 0.68 M, [(S,SS)-**4**] = 0.48 mM (S/C = 1400), [KO-t-C_4H_9] = 8.2 mM, P_{H_2} = 4 atm, T = 22 °C.

2-propanol-d_8) containing 5.3 equiv of KO-t-C_4H_9 (1.60 M; for NMR study) was wine-red in color due to the 16e amido Ru complex **8** but, upon dilution to 20 mM (a solution with the same equiv but now 8.7 mM base in 50% $(CD_3)_2CDOD$), turned to orange-yellow owing to the formation of the amine complex **7**. Thus the acidity difference between 2-propanol (pK_a 16.5)[38] and NH_2 in **7** must be rather small, resulting in the coexistence of **7** and **8** under the catalytic conditions.

(b) Reaction. Without hydrogen, (S,SS)-**4** does not reduce **1** stoichiometrically in 2-propanol. However, it serves as an excellent precatalyst effecting hydrogenation at a limiting low base concentration, viz., under near neutral conditions without any added base.[9] Significantly, samples containing **7** (NMR and MS) were found to be the most reactive, effecting hydrogenation with no incubation period and the apparent highest TOF of up to 7150 h^{-1} ([**4**] = 0.57 mM, S/C = 1800, P_{H_2} = 4 atm, T = 30 °C, no added base). 2-Propanol was inert in the presence of (S,SS)-**4** at room temperature but, upon heating at 80 °C for 16 h, was converted to acetone (12% yield), probably by releasing H_2 gas. In a similar manner, (S,SS)-**4** did not affect the structure

(38) Wade, L. G. *Organic Chemistry*; Prentice Hall: New Jersey, 1999.

of (*R*)-**2** at room temperature. When a neat mixture was heated at 150 °C, however, acetophenone (20%) and racemic **2** (80%) were obtained. Significantly, such reaction mixtures were red in color due to the existence of **8**, in equilibrium with its protonated form **7**.

Hydrogen Source. 2-Propanol is known to be a hydrogen donor in the Ru-catalyzed transfer hydrogenation of ketones.[11−16] However, hydrogenation of **1** by (*S,SS*)-**4** in (CH$_3$)$_2$CDOH without a base or with KO-*t*-C$_4$H$_9$ (98 mM) (*S/C* = 1800, [**4**] = 0.45−0.48 mM, P_{H_2} = 4 atm, *T* = 30 °C) resulted in no detectable deuterated (*R*)-**2** in the ^{2}H NMR spectra of the product mixture.[39] Thus this reaction is a net hydrogenation using H$_2$, though largely mediated by alcoholic media. The 16e Ru amide complex **8**, although potentially active toward 2-propanol and product alcohol, must preferentially abstract a proton from the alcoholic solvent to give cationic **7** under *standard* catalytic conditions. The latter then overwhelmingly reacts with hydrogen gas, rendering the otherwise probable transfer hydrogenation process unable to compete.

Solvent Effects. The nature of the solvent used significantly influences the reaction rate, with alcoholic solvents being necessary for optimum reactivity. Consistent with catalytic cycle I in Figure 3, a rapid proton transfer is required to achieve the maximum reaction rate. In fact, under base-free conditions, 2-propanol is the solvent of choice. The reaction occurred slowly in ethanol, while almost no reaction took place in *tert*-butyl alcohol or methanol.

In the presence of KO-*t*-C$_4$H$_9$, secondary alcohols such as 2-propanol or 2-butanol again gave a high TOF number. Under basic conditions, hydrogenation occurred in various solvents including DMF, toluene, methanol, and *tert*-butyl alcohol, although the latter somewhat retarded hydrogenation in 2-propanol.[40] Thus the structure/reactivity relationship of alcoholic solvents is not straightforward; the observed TOFs (h^{-1}) are 2650 in (CH$_3$)$_2$CHOH, 1770 in CH$_3$CH$_2$CH(OH)CH$_3$, 920 in C$_6$H$_5$CH(OH)CH$_3$, 41 in C$_2$H$_5$OH, and 8 in CH$_3$OH ([**1**] = 0.61 M, [**4**] = 0.33 mM (*S/C* = 1800), [KO-*t*-C$_4$H$_9$] = 18 mM, P_{H_2} = 4 atm, *T* = 30 °C). Interestingly, even the chirality of the solvent affects the rate. For example, hydrogenation of 4′-methoxyacetophenone ([ketone] = 1.70 M, [(*R,RR*)-**4**] = 0.7 mM (*S/C* = 2560), [KO-*t*-C$_4$H$_9$] = 92 mM, P_{H_2} = 4 atm, *T* = 30 °C) proceeded 6 times faster in (*S*)-1-phenylethanol than in the *R* enantiomer, the TOF values at 20 min being 97 and 16 h^{-1}, respectively.[41] A similar chirality effect was observed in hydrogenation of 4-methoxybenzophenone (*S/C* = 2830), giving initial TOFs of 53 and 8 h^{-1} in (*S*)- and (*R*)-1-phenylethanol, respectively.

We consider that the marked alcohol dependency is associated with the formation of TolBINAP/DPEN−RuH(OR) or −Ru-(OR)$_2$ complex(es) which serve as a reservoir to the reactive catalyst. In alcoholic solvents, these 18e Ru alkoxides equilibrate with the corresponding cationic 16e Ru species and alkoxide

anion. The stability of the alkoxy compounds as well as the ease and frequency with which regeneration of real catalysts takes place would be dependent on the properties of RO groups. Moreover, hydrogen-donative secondary alcohols, particularly 2-propanol containing a base, could assist in the recovery of the catalytically active species **7** from the inactive Ru(OR)$^+$ or Ru(OR)$_2$ sink that is formed, if any.[11]

Catalytic cycle I (Figure 3) is the major pathway in alcohols. Regardless of the solvent used, or the absence or presence of KO-*t*-C$_4$H$_9$, hydrogenation of **1** (*S/C* = 1800−2000, P_{H_2} = 4 or 8 atm, *T* = 28−30 °C) gave (*R*)-**2** with a constant ee of 82−83%. The chirality of solvents did not affect the ee value. Thus hydrogenation of 4′-bromoacetophenone in (*R*)- or (*S*)-1-phenylethanol with (*S,SS*)-**4** (*S/C* = 2000, [KO-*t*-C$_4$H$_9$] = 18 mM, P_{H_2} = 4 atm, *T* = 30 °C) gave (*R*)-1-(4-bromophenyl)-ethanol in 83% ee. However, a relatively high reactivity was observed with a strong base in aprotic DMF ([KO-*t*-C$_4$H$_9$] = 18 mM, TOF 148 h^{-1}) or toluene (wine-red color with solid KO-*t*-C$_4$H$_9$, TOF 56 h^{-1}). Although an alcoholic product is produced through hydrogenation under such conditions (<0.80 M), no significant autoacceleration was detected. This was further confirmed by control experiments in toluene by adding small amounts of 2-propanol. These results indicate that, at least in the absence or with a low concentration of alcohols, under basic conditions, hydrogenation occurs largely via catalytic cycle II. When this cycle becomes the dominant pathway, the enantioselectivity is expected to decrease as a function of conversion due to the concomitant dehydrogenation of (*R*)-**2**.[13] In fact, reaction of **1** with (*S,S*)-**4** and KO-*t*-C$_4$H$_9$ in toluene (*S/C* = 1800, P_{H_2} = 4 atm, [KO-*t*-C$_4$H$_9$] = 21 mM, *T* = 30 °C) gave (*R*)-**2** in 78% ee, less than the normal 82% ee.

Inhibitors. Hydrogenation of **1** with **4** under the standard conditions (with base) was inhibited completely by addition of a small amount of phenol, acetic acid, or acetylacetone. Interestingly, certain *β*-amino alcohols such as ethanolamine, *N,N*-dimethylethanolamine, or 2-picolyl alcohol also inhibited the hydrogenation. This could be explained by the formation of a stable chelate Ru aminoalkoxide complex.

Effects of Base. (a) Rate. As expected from the mechanistic model of Figure 3, a basic additive plays important kinetic roles. The reaction is greatly facilitated upon base addition by a combined reduction in the incubation period and acceleration of the catalytic cycle. Both alkaline bases, typically KO-*t*-C$_4$H$_9$, and strong organic bases such as phosphazenes (sterically hindered, neutral nitrogen bases) exhibited the rate enhancement. Hydrogenation in a 10:1 mixture of *tert*-butyl alcohol and triethylamine (*S/C* = 1800, P_{H_2} = 4 atm) was somewhat slower than the reaction in *tert*-butyl alcohol containing 18 mM KO-*t*-C$_4$H$_9$.

The time-conversion curve shows a sigmoidal feature (Figure 2a) due to the presence of the initial incubation step, **4** → **7** → **8**. This period is largely diminished by base addition. Consequently, the initial reaction velocity (TOF after 20 min) increased by a factor of 2.5 (TOF 1260 to 3000 h^{-1}) when 36 mM KO-*t*-C$_4$H$_9$ was added. This phenomenon was in accord with the above NMR study of **4** in (CD$_3$)$_2$CDOD. The reduction of the incubation period is due to the enhanced D$_{cb}$ elimination of an HBH$_4$ element from **4** by an alkoxide base. Resulting **8** equilibrates with **7** in 2-propanol. Moreover, the added base significantly facilitates the catalytic cycle itself. Acceleration

(39) The same result was obtained by reaction with (*S,SS*)-**5** and 18 mM KO-*t*-C$_4$H$_9$ under otherwise identical conditions. When (CD$_3$)$_2$CDOD was used, 4% deuterated (*R*)-**2** was obtained due to H/D exchange between solvent and H$_2$.

(40) The initial velocity for acetophenone hydrogenation by (*R,RR*)-**4** steadily decreases with increasing *tert*-butyl alcohol content for 2-propanol/*tert*-butyl alcohol solvent mixtures (Supporting Information).

(41) Different relative rates for the formation of a proposed cationic fragment [(*R,RR*)-**7**]$^+$ from (*R,RR*)-**4** were also observed. The formation is faster with (*S*)-1-phenylethanol (>95% after 18 h) than with the enantiomer (>95% after 36 h) (see Supporting Information).

observed after a 30−40 min or even 2 h reaction time (>90% conversion) during the k_{obs} measurement is due to the base dependence of the catalytic turnover and is independent of the incubation process. *Most importantly, there exists an optimum base concentration to achieve the highest turnover rate.* As shown in Figure 6, the rate of hydrogenation at 4 atm and 30 °C in 2-propanol (S/C = 2000) was steadily enhanced with increasing base concentration and reached a maximum with [KO-t-C$_4$H$_9$] = 10−15 mM, resulting in a 25-fold TOF enhancement relative to the reaction without base. Beyond this value, however, the TOF dropped sharply and then remained relatively constant, with only a 4−5-fold enhancement in the range of [KO-t-C$_4$H$_9$] = 20 to 130 mM.[42] Notably, the extent of the acceleration depends on the base concentration, viz., the molarity in 2-propanol and not the base/catalyst molar ratio. Similarly, in the presence of 7.4 mM phosphazene base **16** under otherwise identical conditions, the catalytic cycle turned over more rapidly by a factor of 8 in comparison to the no-base conditions.[43] Being culminated with [**16**] = 9−12 mM, the TOF gradually decreased with increasing base molarity, as illustrated in Figure 6.

H$_2$ is known to undergo heterolytic cleavage by various Ru-(II) complexes, depending on their electronic properties, giving RuH species. The reaction with BINAP−RuCl$_2$ complexes occurs in alcohols even under acidic conditions.[44] The present hydrogenation proceeds under nearly neutral to basic conditions, while only a modest base molarity is optimum for rate enhancement. This marked but delicate base dependency is explained by the catalytic scheme of Figure 3 that involves two kinetically important acidic entities, **7** and **10**. In the absence of base, **7** establishes an equilibrium with **10** under an H$_2$ atmosphere. Here, deprotonation of the η^2-H$_2$ ligand, **10** → **11**, limits the turnover rate, since the reduction of **1** to **2** is a low-barrier process. An added base facilitates this process, enhancing the TOF of catalytic cycle I. Under a high base concentration, however, concomitant deprotonation of **7** to **8** (confirmed by a color change; vide supra) decreases the effective concentration of **10**,[45] mitigating the above acceleration effect. This effect in turn increases the relative contribution of the process, **8** → **12** → **11** (catalytic cycle II). However, this process is slower due to the reduced electrophilicity of the amido group of complex **8**, showing a partial N=Ru bond. The observed TOF change with increasing base molarity is thus a result of the coexistence of catalytic cycles I and II. Since the former is at least 5 times faster than the latter under optimum conditions, the "dip" in k_{obs} values in the KO-t-C$_4$H$_9$-aided reaction reflects the rapid decrease in **7** (and **10**) beyond an ambient *effective pH* of 13.4−13.6 ([KO-t-C$_4$H$_9$] = 10−15 mM).[46]

We earlier discovered a mechanistically related enantio-selective transfer hydrogenation of ketones in 2-propanol aided by chiral RuCl[YCH(C$_6$H$_5$)CH(C$_6$H$_5$)NH$_2$](η^6-arene) (Y = NTs or O).[12,13] This system is effective for transfer hydrogenation but not for hydrogenation using H$_2$. Here, a strong base is required only for generating true catalytic intermediates, Ru-[YCH(C$_6$H$_5$)CH(C$_6$H$_5$)NH](η^6-arene) (16e complex) and RuH-[YCH(C$_6$H$_5$)CH(C$_6$H$_5$)NH$_2$](η^6-arene) (18e complex), from the precatalyst but is unnecessary for the catalytic cycle in which 2-propanol acts as a hydrogen donor. This effect has been fully substantiated both experimentally[12,16b−d] and in theoretical investigations.[11,14,16a] The complex Ru[YCH(C$_6$H$_5$)CH(C$_6$H$_5$)-NH](η^6-arene) is not sufficiently basic to abstract a proton from 2-propanol solvent. Therefore, the asymmetric hydrogen transfer is reversible and the chiral alcohol product, together with 2-propanol, is dehydrogenated by this 16e complex. As a result, the enantioselectivity tends to decrease as a function of conversion. Such an equilibrium is insignificant in the present hydrogenation even in toluene media (vide supra). Thus the amide moieties in the respective 16e complexes show different behavior toward H$_2$ and 2-propanol in the Ru-catalyzed reactions.

(b) Enantioselectivity. Addition of KO-t-C$_4$H$_9$, triethylamine, or the phosphazene **16** did not affect the ee of (*R*)-**2**, 82%.

Pressure Effects. The efficiency of both catalyst generation and the catalytic cycle is affected by hydrogen pressure. The extent of this effect is highly dependent on the solution basicity. Since the dissociation of BH$_4$$^-$ from **4** is reversible, a high H$_2$ concentration facilitates the process **7** → **10**, thereby shortening the incubation period. Thus, with the pressure increasing from 1 to 16 atm, reaction profile data (Figure 2) show the initial velocity of reaction for **1** in 2-propanol with S/C = 1800 at 30 °C increases by a factor of 16 (TOF 120 to 1920 h^{-1}) without base or 9 (TOF 600 to 5160 h^{-1}) at [KO-t-C$_4$H$_9$] = 69 mM.

Hydrogen pressure notably influences the rate of hydrogenation, as illustrated in Figure 5. Without base, beyond the incubation period (Figure 4), the rate remained constant in a range of 1 to 16 atm, suggesting that **10** deprotonates much slower than it forms. When a base promoter is present, however, the rate of the deprotonation is strongly linked with the equilibration between **7** and **10**. At a low molarity of KO-t-C$_4$H$_9$ (8.2 mM), the rate rapidly increased to a factor of 11 with the pressure increasing from 1 to 16 atm. When the base concentration was increased by a factor of 10, up to 82 mM, hydrogenation became slower as described above and the rate enhancement was only 4.5 times over the same pressure range. These findings imply the coexistence of the process **8** → **12** → **11** (catalytic cycle II), which is also sensitive to H$_2$ pressure but to a lesser extent, and the progression **7** → **10** → **11** (catalytic cycle I). Cationic **7** displays an enhanced interaction and consequent activation of H$_2$ relative to neutral **8**.[26] Thus the turnover-limiting step is different under nonbasic and highly basic conditions. As the mechanistic model predicts, hydrogen pressure did not affect the enantioselectivity.

Cation Effects. The nature of coexisting cations affects the rate of hydrogenation to some extent. The highest TOF was attained by combination of a suitable base and cationic species. Upon addition of M$^+$[B(C$_6$H$_5$)$_4$]$^-$ (M$^+$= K$^+$, Na$^+$ or (n-C$_4$H$_9$)$_4$N$^+$, Ru:base:M = 1:20:20), the TOF of hydrogenation for **1** (0.81 M) aided by (*S*,*SS*)-**4** (0.42−0.43 mM) and

(42) Reaction of KO-t-C$_4$H$_9$ and 2-propanol produces *tert*-butyl alcohol and KO-i-C$_3$H$_7$. However, the rate reduction is not due to the inhibitory effect of *tert*-butyl alcohol. No measurable difference was observed in k_{obs} values at 100 mM base concentration for KO-t-C$_4$H$_9$ and KO-i-C$_3$H$_7$.

(43) Under such conditions, hydrogenation proceeds easily even when (*S*,*SS*)-**5** is used as a precatalyst coupled with [**16**] = 8.2 or 18.0 mM.

(44) Hydrogenation of functionalized ketones with [RuCl$_2$(binap)]$_n$ is best carried out in methanol or ethanol containing a small amount of a mineral acid, where an η^2-H$_2$ ligand on Ru is deprotonated by the alcoholic media.[21]

(45) (a) Chang, R. *Physical Chemistry with Applications to Biological Systems*; Macmillan: New York, 1977; Chapter 16. (b) Fleck, G. M. *Equilibria in Solution*; Holt, Reinhart and Winston: New York, 1966.

(46) *Effective pH*, ignoring the [H$^+$] contribution from HOR and **7**, and assuming constant [HOR] is given by pH = pK_a + log([OR$^-$]/[HOR]). Assuming this to be [H$^+$] and **8**/**7** to be in a 0.01−0.001 range (from NMR), the pK_a of **7** is calculated to be in the range of 15.3−16.3. 2-Propanol has a pK_a value of 16.5.

Table 1. Rates of Hydrogenation of Acetophenone (**1**) Catalyzed by *trans*-RuH(η^1-BH$_4$)[(S)-tolbinap][(S,S)-dpen] [(S,SS)-**4**][a]

conditions						
[**1**] M	[**4**] mM	[KO-t-C$_4$H$_9$] mM	gas	solvent	k_{obs} 10^{-3} s^{-1}	k_{obs}/[**4**] 10 M^{-1} s^{-1}
0.85	0.45	0	D$_2$	(CD$_3$)$_2$CDOD	0.2(0)	0.04(5)
0.85	0.41	0	H$_2$	(CH$_3$)$_2$CHOH	10.3	2.5
0.83	0.42	81.6	D$_2$	(CD$_3$)$_2$CDOD	22.3	5.3
0.83	0.42	83.1	H$_2$	(CH$_3$)$_2$CHOH	43.8	10.4

[a] $S/C = 1800$, $P_{H_2} = 4$ atm, $T = 30°$. Product was (R)-**2** in 82% ee.

phosphazene base **16** (9 mM) ($S/C = 1800$, $P_{H_2} = 4$ atm, $T = 30$ °C) was increased by a factor of 2. The k_{obs} values of 40.6, 38.8, and 38.6 M^{-1} s^{-1} for K$^+$, Na$^+$, and (n-C$_4$H$_9$)$_4$N$^+$, respectively, are in the range obtained with KO-t-C$_4$H$_9$ under otherwise identical conditions.[47] Such rate enhancement was seen only under basic conditions. In contrast, hydrogenation was retarded by addition of M$^+$ [B(C$_6$H$_5$)$_4$]$^-$ in the absence of base, TOF being reduced from 900 h^{-1} (no base and no additive) to 140 ((n-C$_4$H$_9$)$_4$N$^+$), 80 (Na$^+$), and 20 h^{-1} (K$^+$). The properties and reactivities of ion pair intermediates present in the reaction system are subtly influenced by the nature of cations, although the exact origin of the effects remains unclear.

All hydrogenations produced (R)-**2** in 82% ee regardless of the cation present, that is, K$^+$, Na$^+$, (n-C$_4$H$_9$)$_4$N$^+$, or protonated phosphazene **16**.

Isotope Effects. The rates of the reaction using an H$_2$/(CH$_3$)$_2$-CHOH or a D$_2$/(CD$_3$)$_2$CDOD combination were compared under the standard conditions ($S/C = 1800$, [**1**] = 0.85 M, [(S,SS)-**4**] = 0.41−0.45 mM, P_{H_2} = 4 atm, T = 30 °C). Table 1 summarizes the results. In the absence of base, a large deuterium isotope effect, $k_H/k_D = 55$, was observed. This value is much larger than the value, $k_H/k_D = 2$, obtained at an 82 mM KO-t-C$_4$H$_9$ concentration.[48] This marked condition dependence of the isotope effect agrees with the proposed mechanism (Figure 3). Under base-free conditions, 2-propanol acts as the ambient base that deprotonates the η^2-H$_2$ Ru complex **10**, giving **11**, by a bimolecular process. The extremely low TOF observed for the D$_2$/(CD$_3$)$_2$CDOD conditions reflects the increase in the relative pK_a value for the η^2-D$_2$ analogue of **10** and the weaker basic strength of the system as a whole.[49] This normally difficult step is accelerated by base addition. Thus both cases involve the deprotonation of **10** as the turnover-limiting step (catalytic cycle I), although they exhibit a marked difference in isotope effect. The small isotope effect observed with *high* [KO-t-C$_4$H$_9$] reflects the dominance of catalytic cycle II, where H$_2$ (D$_2$) heterolysis is induced by the amido nitrogen in **8**. This view is further supported by the appearance of the above-mentioned pressure effects.

Reducing Species. The Ru hydride species generated in this asymmetric hydrogenation saturates a C=O linkage selectively, leaving C=C bonds intact,[4,6] because of the operation of a metal−ligand bifunctional mechanism.[6] Although the reaction
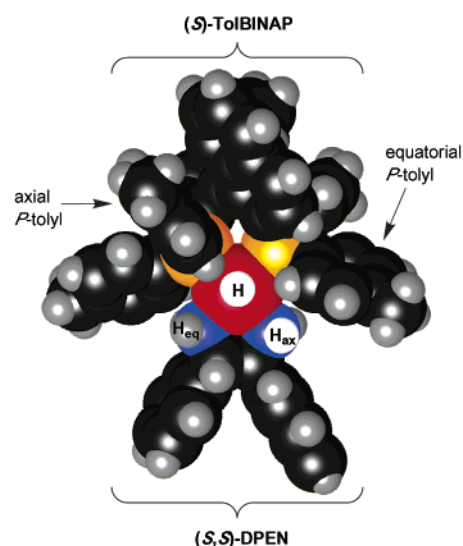
Figure 9. Molecular model of active *trans*-RuH$_2$ species (S,SS)-**11** showing the hydride and amine proton (H−Ru−N−H$_{ax}$) involved in transition state **13** (see Figures 3 and 10).

rate is influenced by various experimental parameters, importantly, the sense and extent of enantioselectivity are unaffected by hydrogen pressure, the nature of the solvent (protic or aprotic, bulkiness and chirality of alcohols), substrate concentration, the extent of conversion, the presence or absence of base, base concentration, or the nature of the base or coexisting metallic and organic cations. This feature indicates that the stereodetermining step involves a common Ru hydride, although the manner of the formation or the concentration of this hydride may vary. We propose the chiral Ru dihydride (S,SS)-**11** having a trans configuration as the species that reduces the ketonic substrates (Figure 9). A structurally similar, well-defined *trans*-RuH$_2$ complex has been shown to act as a precatalyst or catalyst of the hydrogenation of **1**.[23] The ESI-TOFMS experiments and the lack of influence of alcohol structures on enantioselectivity, together with the mechanism of enantioselection shown below, exclude the possibility that RuH(OR) complexes are major reducing species. The RuHCl complex **6** is unreactive under base-free conditions.[50] The stability of *trans*-RuHX decreases in the order of X = Cl, OR, H, while the order of relative reactivity toward the C=O function would be reversed. Although the possibility of *cis*-RuH$_2$ cannot be eliminated, *trans*-RuH$_2$ (S,SS)-**11** is expected to be highly reactive due to the trans influence of the σ-donating hydride.[26g,h,51]

Mechanism of Enantioselection. The combination of the S diphosphine and the S,S diamine (or R/R,R combination) is important for high enantioselectivity in the hydrogenation of simple aromatic ketones.[4,6,52] The *trans*-RuH$_2$ intermediate (S,SS)-**11** explains the stereochemical outcome in the simplest manner.[22,23] The absolute configuration of the alcoholic products is determined kinetically in the reaction of the chiral diphosphine/diamine complex and prochial ketones occurring via the six-membered pericyclic TS **13**. Both the (S)-TolBINAP and (S,S)-DPEN ligands would be accommodated in the same Ru

(47) Similar acceleration effects have been observed for analogous RuCl$_2$ systems.[22]

(48) A large isotope effect was seen in the KO-t-C$_4$H$_9$ catalyzed hydrogenation of benzophenone. See: Berkessel, A.; Schubert, T. J. S.; Muller, T. N. *J. Am. Chem. Soc.* **2002**, *124*, 8693−8698.

(49) (a) Mosberg, H. I.; Beard, C. B.; Schmidt, P. G. *Biophys. Chem.* **1976**, 6, 1−8. (b) Washabaugh, M. W.; Jencks, W. P. *Biochemistry*, **1988**, 27, 5054−53. (c) Mamaev, V. M.; Gloriozov, I. P.; Prisyajnyuk, A. V.; Babin, Y. V. *Mendeleev. Commun.* **1999**, *4*, 136−139. (d) Hsu, M.-C.; Jwo, J.-J. *Int. J. Chem. Kinet.* **1999**, *31*, 455−461. (e) Zhang, B.-L.; Pionnier, S. *J. Phys. Org. Chem.* **2001**, *14*, 239−246.

(50) Abdur-Rashid, K.; Lough, A. J.; Morris, R. H. *Organometallics* **2001**, *20*, 1047−1049.

(51) Repulsion of the filled p and d orbitals has also been postulated: Caulton, K. G. *New J. Chem.* **1994**, *18*, 25−41.
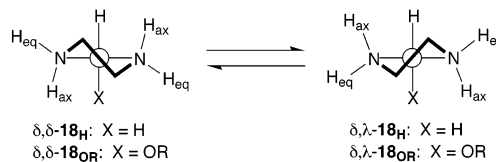
(52) Asymmetric hydrogenation of certain ketones such as 2,4,4-trimethyl-2-cyclohexenone requires the S/R,R or R/S,S combination.[4,6]
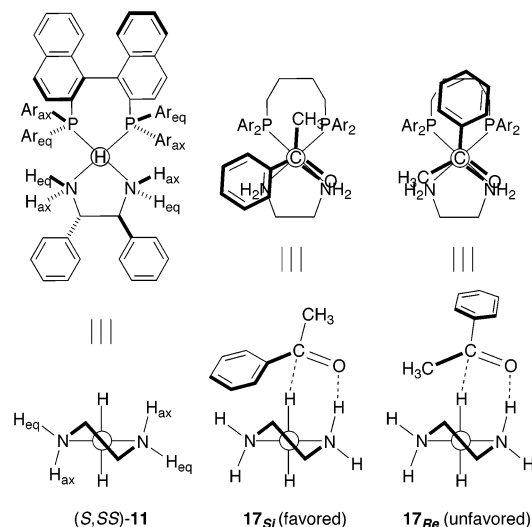
Figure 10. Reducing RuH$_2$ species (*S*,*SS*)-**11** and diastereomeric transition states in the metal−ligand bifunctional catalysis (see Figure 9). In the TSs **17**$_{Si}$ and **17**$_{Re}$, the equatorially oriented phenyl substituents in the DPEN ligand are omitted. Ar = 4-CH$_3$C$_6$H$_4$.

Figure 11. Conformationally flexible diastereomeric reducing species formed from *trans*-RuH(η^1-BH$_4$)[(*S*)-tolbinap](H$_2$NCH$_2$CH$_2$NH$_2$). Ar = 4-CH$_3$C$_6$H$_4$.

plane and have a δ conformation,[53] making the two hydrides spatially equivalent. The five-membered DPEN chelate ring is skewed and possesses two equatorially directed phenyl substituents. The two NH$_2$ ligands and the hydride possess a *fac* relationship. Among the two kinds of diastereotopic hydrogens at the nitrogen atoms, only axially oriented hydrogens, H$_{ax}$, are more reactive for stereoelectronic reasons. The H−Ru−N−H$_{ax}$ moiety having a small dihedral angle forms a 1,4-dipole which fits with the C=O dipole.[54] Then, the Ru center delivers a hydride to the electrophilic C=O carbon, while the nitrogen supplies a proton to the oxygen atom simultaneously. The presence of the NH$_2$ (or NH) end is crucial for the catalytic activity, and this TS model well explains the chemoselectivity for C=O functionality. The electronic effect of the para substituents in **1** on the reaction rate supports this view.[18]

The enantiofaces of the aromatic ketone **1** are then differentiated on the molecular surface of the chiral 18e RuH$_2$ species (*S*,*SS*)-**11**. The prochiral ketone approaches (*S*,*SS*)-**11** (Figure 9) so as to minimize nonbonded repulsion and to maximize electronic attraction. Thus, as illustrated in Figure 10, the TS **17**$_{Si}$ leading to (*R*)-**2** is more favored over the diastereomeric TS **17**$_{Re}$, which suffers significant nonbonded repulsion between the *P*-tolyl ring and the phenyl substituent of **1**.[55] The TS **17**$_{Si}$ would be further stabilized by secondary NH$_{eq}$/phenyl electrostatic attraction.[15,56] This reaction involves hydride attack to the carbonyl carbon. Therefore, electron-withdrawing substituents

at the para position enhance the reactivity[18] but tend to decrease the enantioselectivity; 4′-trifluoromethylacetophenone gave the (*R*)-1-(4-trifluoromethyl)ethanol in 65% ee (82−83% ee for the −H and −CH$_3$ derivatives) due to the decreased NH$_{eq}$/phenyl attraction.[57] Although the more stable but less reactive cis geometry for RuH$_2$[58] cannot be definitively eliminated, the *C$_2$*-symmetric (*S*,*SS*)-**11** rationalizes the *R* absolute stereochemistry of **2** as well as the efficiency of the *S*,*SS* (not *S*,*RR*) catalyst in the most straightforward fashion. Thus, an increase in the bulkiness of the *P*-aryl ring results in an increase of the ee value, as observed with the XylBINAP/DPEN catalyst (*S*,*SS*)-**3** leading to 99% ee for (*R*)-**2**.[9] This TS model also explains the very low reactivity of *tert*-alkyl aryl ketones.[3,4,6] The NH$_{eq}$ group in (*S*,*SS*)-**11** could also donate a proton to C=O, though less effectively than NH$_{ax}$. Such TSs, however, suffer from non-bonded repulsion between the sterically demanding axial *P*-tolyl group and acetophenone methyl or phenyl, though we also note that the increased NH$_{ax}$/phenyl attraction in turn would assist TS stabilization. This possibility is relatively unimportant but may become non-negligible in certain cases.[59]

We tested RuH(η^1-BH$_4$)[(*S*)-tolbinap](H$_2$NCH$_2$CH$_2$NH$_2$) as a precatalyst for asymmetric hydrogenation of 4′-bromo-acetophenone. The reaction in 2-propanol under the standard conditions (S/C = 2000, [ketone] = 0.83 M, [catalyst] = 0.41 mM, [KO-*t*-C$_4$H$_9$] = 18 mM, P_{H_2} = 4 atm, T = 30 °C) gave (*R*)-1-(4-bromophenyl)ethanol in 53% ee (cf. *R* enantiomer in 83% ee with (*S*,*SS*)-**4**). The observed moderate enantioselection is largely due to the conformational flexibility of the simple, unsubstituted ethylenediamine ligand. Thus two diastereomeric species δ,δ-**18**$_H$ and δ,λ-**18**$_H$ are possible for the RuH$_2$ complex (Figure 11). Both of these possess the same δ-shaped TolBINAP ligand but have a different conformation, δ or λ, with respect to the diamine chelate ring. These diastereomers that possess a comparable stability and, in fact, equilibrate in 2-propanol reduce prochiral ketones competitively.[60] Here, the use of the two diastereomeric axial hydrogens of the NH groups leads to an opposite sense of asymmetric induction resulting in a low ee, although the BINAP chirality remains the dominant stereocontrolling factor. When the hydrogenation of 4′-bromoacetophenone was performed in (*R*)- and (*S*)-1-phenylethanol, (*R*)-1-(4-bromophenyl)ethanol was produced in the same 53% ee, which is also identical with the value obtained in 2-propanol. This observation is best interpreted by **18**$_H$ serving as the reducing species. We consider it highly unlikely that possible alkoxy hydrido complexes **18**$_{OR}$ serve as the reducing species. Even if the H and OR have a trans relationship, the properties of OR

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(55) For the structural feature of the BINAP ligands, see: Noyori, R. *Science* **1990**, *248*, 1194−1199.

(56) The Ru center binding increases the amine proton acidity. Ammonium−π(aryl) interactions are well established: (a) Meot-Ner, M.; Deakyne, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 468−474. (b) Singh, J.; Thornton, J. M. *J. Mol. Biol.* **1990**, *211*, 595−615. (c) Dougherty, D. A.; Stauffer, D. A. *Science* **1990**, *250*, 1558−1560. (d) Garel, L.; Lozach, B.; Dutasta, J. P.; Collet, A. *J. Am. Chem. Soc.* **1993**, *115*, 11652−11653. (e) Koh, K. N.; Araki, K.; Ikeda, A.; Otsuka, H.; Shinkai, S. *J. Am. Chem. Soc.* **1996**, *118*, 755−758. (f) Roelens, S.; Torriti, R. *J. Am. Chem. Soc.* **1998**, *120*, 12443−12452. (g) Gallivan, J. P.; Dougherty, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 9459−9464.

(57) Detailed analysis is required to define the exact nature of the NH/aryl attractive force as well as the interacting sites.

(58) The cis geometry is also possible for RuCl$_2$(diphosphine)(diamine) complexes.[53a]

(59) Enantioselective hydrogenation of benzaldehyde-1-*d* remains difficult.

(60) RuCl$_2$[(*S*)-binap][(*S*,*S*)-dpen] and its *S*,*RR* diastereomer have a comparable stability.[61]

are expected to affect the ee value. The enantiomeric OR groups must provide a thermodynamic and/or kinetic bias to the equilibrating diastereomers, δ,δ-**18$_{OR}$** and δ,λ-**18$_{OR}$**. This was not the case when enantiomeric 1-phenylethanols were used as solvents. Furthermore, hydrogenation of **1** with RuH(η^1-BH$_4$)-[(*S*)-tolbinap](H$_2$NCH$_2$CH$_2$NH$_2$) in 2-butanol and *tert*-butyl alcohol (*S/C* = 2000, [**1**] = 0.82 M, [catalyst] = 0.41 mM, [KO-*t*-C$_4$H$_9$] = 18 mM, P_{H_2} = 4 atm, *T* = 30 °C) gave (*R*)-**2** in the same 52% ee.

Reactions with Other Catalyst Precursors. Other chiral diphosphine/diamine complexes such as **5** and **6** also act as excellent precatalysts but only with at least 2 or 1 equiv of strong bases.[5] Both alkaline bases and phosphazene bases can be used as cocatalysts. The reaction of **5** appears to proceed via **6**, and thus the chlorine atoms must be fully removed from these complexes to achieve catalytic hydrogenation.[50] The activation of these halide-containing complexes is considerably more complicated than that of **3** or **4**. The primary role of the strong base is to neutralize HCl formed during the generation of active Ru hydride species, while the catalytic turnover is enhanced with base as well. With the RuH(η^1-BH$_4$) complexes as precatalysts, the BH$_4^-$ moiety is removed by the action of alcoholic solvent to generate a catalytically active species. The alkoxide ion thus produced in a very small amount is paired with or bound to the Ru cation to attain a near neutral condition. As a consequence, these precatalysts have provided a range of synthetic benefits.[9] Since the overall catalytic activity is profoundly affected by various experimental parameters, the reaction conditions must be fine-tuned to meet particular demands.[3,4,6] Hydrogenation with the RuH(η^1-BH$_4$) complexes displayed various characteristics similar to those of the reaction with the halogen-containing complexes.[6,61] Most notably, the extent of enantioselectivity is independent of the precatalyst structures or the way of activation, with complexes **4**–**6** giving the same enantioselectivity for various ketonic substrates. This implies that all the Ru(II) precatalysts possessing the same chiral diphosphine and diamines generate the same stereodetermining reactive species as described above.[62]

Conclusion

A series of experimental findings suggests that the rapid, productive hydrogenation of simple ketones catalyzed by diphosphine/1,2-diamine–Ru(II) complexes proceeds via a nonclassical metal–ligand bifunctional mechanism. The high reactivity of the catalyst originates from the NH$_2$ unit in the diamine ligand. The reduction of the C=O function occurs in an outer coordination sphere of an 18e RuH$_2$(diphosphine)-(diamine) complex without interaction of the unsaturated moiety and the metallic center. The Ru atom donates a hydride and the NH$_2$ ligand delivers a proton through a pericyclic six-membered TS, giving an alcoholic product directly without forming metal alkoxide. This is contrasted to the conventional $\sigma2 + \pi2$ mechanism involving an M–H and C=O linkage. This mechanistic model well explains the enantioselectivity and high chemoselectivity toward a polar C=O linkage, leaving normally more reactive C=C bonds intact. This asymmetric

catalysis manifests the significance of "kinetic" supramolecular chemistry.[63]

Experimental Section

General. All manipulations were conducted in oven-dried glassware using standard Schlenk techniques employing argon gas (99.998%, purified through a BASF R3-11 catalyst at 80 °C). Toluene, benzene, hexane, THF, and ether were distilled from metal sodium/benzophenone and stored in Schlenk tubes with a sodium mirror; (CH$_3$)$_2$CHOH, (CH$_3$)$_3$COH, and CH$_2$Cl$_2$ were freshly distilled from CaH$_2$; and CH$_3$-OH was distilled from Mg powder. DMF was distilled from CaH$_2$ and stored in a Schlenk flask. All solvents were degassed by three freeze–thaw cycles prior to use. Toluene-*d$_8$*, benzene-*d$_6$*, (CD$_3$)$_2$CDOD, CD$_3$-OD, and (CD$_3$)$_3$COD were purchased from Aldrich, stored in Schlenk tubes (Teflon taps) over CaH$_2$, and freshly distilled and degassed prior to use. NaBH$_4$, a 1.0 M solution of CH$_3$Li in ether, a 54 wt % HBF$_4$ solution in ether, a 1.0 M KO-*t*-C$_4$H$_9$ solution in (CH$_3$)$_3$COH, LiB-(C$_6$H$_5$)$_4$·3CH$_3$OCH$_2$CH$_2$OCH$_3$, and KO-*t*-C$_4$H$_9$ (purified by sublimation) were purchased from Aldrich Chemical Co.. 1-*tert*-Butyl-4,4,4-tris-(dimethylamino)-2,2-bis[tris(dimethylamino)phosphoranylidenamino]-2′,4′-catenadi(phosphazene) (**16**) (1 ± 0.02 M solution in *n*-hexane), potassium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate were purchased from Fluka. Tetra-*n*-butylammonium tetraphenylborate and potassium tetrakis(4-chlorophenyl)borate were purchased from Lancaster. Sodium tetraphenylborate was purchased from Kanto Chemical Co., Inc.. (*R*)-and (*S*)-2,2′-bis(di-4-tolylphosphino)-1,1′-binaphthyl (TolBINAP) were purchased from AZmax. (*R,R*)- and (*S,S*)-1,2-diphenylethylenediamine (DPEN) were also purchased from Kankyo Kagaku Company. Acetophenone, 4′-bromo-, 4′-trifluoromethyl-, and 4′-methoxyacetophenone, and 2-methylbenzophenone were purchased from Aldrich, washed with a 1.0 M KOH solution, and purified by distillation from CaH$_2$ or K$_2$CO$_3$. Hydrogen gas (99.99999%) and deuterium gas (0.4% HD content) were obtained from Nippon Sanso. Unless otherwise stated, all reagents were used without further purification. Syntheses of *trans*-RuCl$_2$[(*R*)-tolbinap][(*R,R*)-dpen],[53a] *trans*-RuH(η^1-BH$_4$)[(*R*)-tolbinap]-[(*R,R*)-dpen],[9] and *trans*-RuH(η^1-BH$_4$)[(*R*)-tolbinap](NH$_2$CH$_2$CH$_2$-NH$_2$)[64] were reported elsewhere.

Gas chromatography (GC) analysis was conducted on a Hewlett-Packard 6890 instrument equipped with a CP-Chirasil-DEX CB (df = 0.25 μm, 0.32 mm i.d. × 25 m, Varian) or HP-INNOWax column (df = 0.25 μm, 0.25 mm i.d. × 30 m, Hewlett-Packard). High-performance liquid chromatography (HPLC) analysis was conducted on a Shimadzu SCL10A instrument equipped with a CHIRALCEL OB-H column (4.6 mm i.d. × 250 mm, Daicel Chemical Industries). ^{1}H, ^{13}C, and ^{31}P{^{1}H} NMR data were collected on a JEOL α-400 FT-NMR, Bruker DMX-500, or AMX-400 spectrometer. Chemical shifts are expressed in parts per million (ppm) relative to Si(CH$_3$)$_4$, benzene, or toluene (δ 0.0, 7.16, and 2.09 ppm for ^{1}H NMR and δ 0.0, 128, and 20.4 ppm for ^{13}C NMR, respectively). All chemical shifts for ^{31}P{^{1}H} NMR data are reported downfield in ppm relative to external 85% H$_3$PO$_4$ at 0.0 ppm. Signal patterns are reported as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; br, broad signal; v br, very broad signal; u, unresolved. The term relative intensity (r.i.) describes the % content of each species present when a mixture of complexes are involved. Standard pulse sequences for two-dimensional (2D) acquisitions were employed for DQF-COSY, ^{1}H–^{31}P HSQC, and ^{1}H–

(61) Ohkuma, T.; Doucet, H.; Pham, T.; Mikami, K.; Korenaga, T.; Terada, M.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 1086–1087.

(62) A similar but alkaline metal-mediated six-membered TS was proposed for reaction using the dichloro Ru complex **5** and alkaline metal alkoxides.[22,23b]

(63) The significance of "thermodynamic" supramolecular chemistry, in which noncovalent interactions including hydrogen bonds are utilized largely for the stabilizing ground-state molecular assemblies, has been well documented over the last two decades. See: Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, 1999.

(64) Absolute assignments were determined by 2D NMR (^{1}H–^{1}H COSY, ^{13}C–^{1}H HMQC, DPFGSE-NOE) analysis and will be described elsewhere: Sandoval, C. A.; Ohkuma, T.; Yamaguchi, Y.; Kato, K.; Noyori, R. Manuscript in preparation.

[13]C HMQC. For NOESY, mixing times of 20 and 40 ms were used. Processing and analyses of the spectra were done using JEOL or Bruker XWINNMR software. Electrospray ionization time-of-flight mass spectroscopy (ESI-TOFMS) was performed on a PE Biosystems Mariner.

Hydrogenations. A. General Procedure. A typical hydrogenation was carried out as follows: An accurately weighed amount of precatalyst (S,SS)- or (R,RR)-**4** (1.8−2.5 mg, 0.33−0.45 mmol) in a pre-oven-dried (120 °C) 100 mL glass autoclave containing a magnetic stirring bar was placed under high vacuum for at least 5 min before purging with argon and placing in a temperature regulated water/oil bath. In a separate flask, a freshly distilled solvent (5.0 mL), a purified substrate (0.375−0.520 mL, 0.59−0.82 mmol), and a 1.0 M KO-t-C$_4$H$_9$ solution in (CH$_3$)$_3$COH (0.10 mL, 18 mM) were mixed. This mixture was degassed by running argon through the solution for 10 min and then transferred to the autoclave under an argon atmosphere. Hydrogen was introduced under 8 atm of pressure with several quick release−fill cycles before being reduced to a desired pressure, typically 4 atm. Temperature and pressure were held constant, unless otherwise stated, during the reaction time (12 or 16 h). For all substrates, the conversion and % ee of products were determined by GC analyses: acetophenone (**1**), CP-Chirasil-DEX CB column, $P = 41$ kPa, $T = 105$ °C, t_R of (R)-1-phenylethanol = 20.9 min, t_R of (S)-1-phenylethanol [(S)-**2**] = 24.6 min; 4′-bromoacetophenone, CP-Chirasil-DEX CB column, $P = 60$ kPa, $T = 135$ °C, t_R of (R)-1-(4-bromophenyl)ethanol = 23.4 min, t_R of (S)-1-(4-bromophenyl)ethanol = 27.0 min; 4′-trifluoromethylacetophenone, CP-Chirasil-DEX CB column, $P = 60$ kPa, $T = 145$ °C, t_R of (R)-1-(4-trifluoromethyl)phenylethanol = 13.5 min, t_R of (S)-1-(4-trifluoromethyl)phenylethanol = 15.9 min.

B. Hydrogenation Profile Determination. (a) Hydrogenations were conducted in a glass autoclave equipped with a sampling needle connected to a three-way stop valve (see Supporting Information). This experimental setup allowed for samples to be taken from the reaction mixture for GC, NMR, and MS analyses and/or for the addition (reinsertion) of substrate aliquots (analyzed samples) at various times during the course of reaction under an H$_2$ or Ar atmosphere. An accurately measured mass of precatalyst (R,RR)-**4** was placed into a predried (120 °C) glass autoclave containing a magnetic stirring bar, which was then maintained under high vacuum for at least 5 min prior to purging with argon. Into a predried Schlenk tube were placed accurately measured amounts of a ketonic substrate, a base (solid KO-t-C$_4$H$_9$, an aliquot from a 1.0 M KO-t-C$_4$H$_9$ solution in (CH$_3$)$_3$COH, or a 1.0 M **16** solution in (CH$_3$)$_2$CHOH), and a solvent such that a desired [catalyst], S/C ratio, and [base] were obtained. The reaction mixture was degassed by three freeze−thaw cycles and added under an argon atmosphere to the autoclave. Hydrogen was introduced under 8 atm of pressure with several quick release−fill cycles before being set to the desired pressure. Stirring and timing ($t = 0$ min) were immediately commenced. Reaction samples were obtained (2 drops into an ether-filled GC sample tube) at specified time intervals (2, 5, or 10 min), and the extent of substrate consumption/product production was determined by GC. **1**, as previously described: 4′-methoxyacetophenone, CP-Chirasil-DEX CB column, $P = 45$ kPa, $T = 130$ °C, t_R of (R)-1-(4-methoxyphenyl)ethanol = 20.3 min, t_R of (S)-1-(4-methoxyphenyl)ethanol = 21.3 min. 2-Methylbenzophenone: conversions determined by GC (HP-INNOWax column), $P = 80$ kPa, $T = 200$ °C, t_R of 2-methylbenzhydrol = 35.9 min. Percent ee was determined by HPLC (CHIRALCEL OB-H column) using a 1:9 (CH$_3$)$_2$CHOH/hexane mixture as eluent, $T = 30$ °C, 0.5 mL/min flow rate, 270 nm detection, t_R of (R)-(2-methylphenyl)phenylmethanol = 19.8 min, t_R of (S)-(2-methylphenyl)phenylmethanol = 22.5 min. Hydrogenations were carried out in (CH$_3$)$_2$CHOH/(CH$_3$)$_3$COH mixtures (Supporting Information). (b) For temperature dependence. The experimental setup and sample preparation are described above. (i) (R,RR)-**4**. Hydrogenation conditions: [(R,RR)-**4**] = 0.41 mM; [**1**] = 0.73 M; P_{H_2} = 4 atm; no added base; S/C ratio = 1800; T = 10−50 °C, (CH$_3$)$_2$CHOH solvent. The

initial reaction mixture was degassed by three freeze−thaw cycles and placed in a temperature-controlled water bath (set at desired temperature) together with an autoclave containing **4**. Following a period of 10−15 min, the mixture was added to the autoclave under an argon atmosphere and purged with H$_2$ (several quick release−fill cycles), and then stirring was commenced ($t = 0$ min). Samples were collected at 5 or 10 min intervals, and the conversion and ee were determined by GC. (ii) (R,RR)-**5**. Hydrogenation conditions: [(R,RR)-**5**] = 0.59 mM; [**1**] = 1.16 M; P_{H_2} = 4 atm; [KO-t-C$_4$H$_9$] = 9.1 × 10^{-2} M; S/C ratio = 1800; T = 10−50 °C, (CH$_3$)$_2$CHOH solvent. The same experimental procedure was carried out as that for (R,RR)-**4**. (c) With preheated (R,RR)-**4**. The experimental setup and sample preparation are described above. Hydrogenation conditions: [**4**] = 0.57 mM; [**1**] = 1.10 M; P_{H_2} = 4 atm; no added base; S/C ratio = 1800; T = 30 °C, (CH$_3$)$_2$CHOH/benzene (8:1) solvent. (R,RR)-**4** was dissolved in (CH$_3$)$_2$CHOH/benzene (1:1, 0.5 mL) solution and heated for 15 min at 40 °C. The resulting red mixture was used as precatalyst. Samples were collected at 2 min intervals, and the conversion and ee were determined by GC. Observed TOF at 6 min = 215 min^{-1}, hydrogenation > 95% completed within 14 min (TOF = 7150 h^{-1}), 82% ee. The same procedure allowed for rapid hydrogenation (completion within 6 h) of a mixture with S/C = 20 000 without base addition.[9]

C. General Kinetic k_{obs} Measurement. The experimental setup and sample preparation are described in section B(a). With a similar reaction profile under the same experimental conditions being assumed, a predetermined period of time was allowed such that an estimated >90% substrate was consumed. Following sample collection, an aliquot of substrate was added as follows: a degassed aliquot (three freeze−thaw cycles) of distilled **1** (0.52 mL) and (CH$_3$)$_2$CHOH (0.48 mL) was added to a pre-oven-dried glass autoclave attached to the argon-purged hydrogenation autoclave; this vessel was then purged with hydrogen (ca. 3.1 atm), and the contents were added to the reaction mixture ($t = 0$ min) using a positive pressure flow of H$_2$. For hydrogenations operating at >4 atm, the pressure was reduced to 3 atm immediately prior to aliquot addition and quickly returned to the desired pressure following addition. Samples were obtained at regular time intervals, and the extent of substrate consumption/product production was determined by GC. Unless otherwise indicated, kinetic runs were performed at least in duplicate and the mean value was reported with all errors < ±6%. (a) Base dependence. (i) For KO-t-C$_4$H$_9$ base. Hydrogenation conditions: [(R,RR)-**4**] = 0.44−0.46 mM; [**1**] = 0.89−0.98 M; P_{H_2} = 4 atm; [base] = 0.00−0.13(5) mM KO-t-C$_4$H$_9$; S/C ratio = 2000 ± 50 (S = added + unreacted **1**); T = 30 °C; (CH$_3$)$_2$CHOH solvent. For no base and incubation period = 120 min, samples were collected at 10 min intervals. With added base and incubation period = 40 min, samples were collected at 5 min intervals. (ii) For phosphazene base **16**. Hydrogenation conditions: [(R,RR)-**4**] = 0.42−0.47 mM; [**1**] = 0.90−0.99 M; P_{H_2} = 4 atm; [**16**] = 0.0−130.1 mM (1 M stock solution in (CH$_3$)$_2$CHOH); S/C ratio = 1900 ± 50 (S = added + unreacted **1**); T = 30 °C; (CH$_3$)$_2$CHOH solvent. Stock solution of **16** in (CH$_3$)$_2$CHOH: A 1.0 ± 0.02 M solution of **16** in n-hexane (5 mL) was cooled to −30 °C, and the solvent was removed in vacuo. Then the residue was slowly diluted with (CH$_3$)$_2$CHOH to give a total volume of 5.0 mL. With incubation period = 45 min, samples were collected at 5 min intervals. (b) Hydrogen pressure dependence. Hydrogenation conditions: [(R,RR)-**4**] = 0.41−0.46 mM; [**1**] = 0.89−0.98 M; P_{H_2} = 1−16 atm, [base] = 0.0, 8.2, or 82 mM (1.0 M KO-t-C$_4$H$_9$ in (CH$_3$)$_3$COH or 0.10 M KO-t-C$_4$H$_9$ in (CH$_3$)$_2$CHOH); S/C ratio = 2000 ± 50 (S = added + unreacted **1**); T = 30 °C; (CH$_3$)$_2$CHOH solvent. For no base and incubation period = 120 min, samples were collected at 10 min intervals. For [base] = 82 mM and incubation period = 40 min, samples were collected at 5 min intervals. For [base] = 82 mM and initial incubation period = 30 min, samples were collected at 2 or 5 min intervals. (c) Substrate concentration dependence. Hydrogenation conditions: [(R,RR)-**4**] = 0.41−0.43 mM; [**1**] = 0.15−0.35 M; P_{H_2} = 4 atm, [base] = 0 mM, 70 mM (following aliquot

addition, 1.0 M KO-*t*-C$_4$H$_9$ in (CH$_3$)$_3$COH, or 8 mM (following aliquot addition, 0.1 M KO-*t*-C$_4$H$_9$ in (CH$_3$)$_2$CHOH); initial *S/C* ratio = 340 or 700; final *S/C* ratio (following aliquot addition) = 344 to 10 110 ± 100 (*S* = added + unreacted **1**); *T* = 30 °C; (CH$_3$)$_2$CHOH solvent. Following an incubation period = 60 or 30 min for no added base and added base conditions, an aliquot of **1** and (CH$_3$)$_2$CHOH was added (total volume = 3.2 mL), samples were collected at 2 or 5 min intervals. Values for k_{obs} were calculated from [**2**]. (d) For D$_2$/H$_2$ comparison. Hydrogenation conditions: [(*R*,*RR*)-**4**] = 0.41−0.45 mM; [**1**] = 0.98− 1.06 M; $P_{H_2 \text{ or } D_2}$ = 4 atm, [base] = none or 81.6−83.1 mM (CD$_3$)$_2$- CDOK or (CD$_3$)$_3$COK; *S/C* ratio = 1800; *T* = 30 °C, (CH$_3$)$_2$CHOH or (CD$_3$)$_2$CDOD solvent. For no base and incubation period = 120 min, samples were collected at 10 min intervals. For added base and incubation period = 40 min, samples were collected at 5 min intervals.

NMR Experiments. A. NMR Spectra of (*R*,*RR*)-4 in Various Solvents. (a) ^{1}H NMR (400 MHz, C$_6$D$_6$) δ −13.60 (t, 1, *J* = 22.4 Hz, RuH), −0.40 (v br s, 4, BH$_4$), 1.45 (s, 3, CH$_3$), 1.55 (s, 3, CH$_3$), 1.62 (s, 3, CH$_3$), 1.63 (s, 3, CH$_3$), 1.95 (dd, 1, *J* = 7.2 and 8.4 Hz, N*H*H), 2.38 (d, 1, *J* = 8.2 Hz, N*H*H), 3.82−3.88 (m, 2, 2N*H*H), 3.65 (dd, 1, *J* = 7.9 and 11.2 Hz, C*H*NH$_2$), 4.00 (ddd, 1, *J* = 7.9, 8.4, and 11.6 Hz, C*H*NH$_2$), 6.13−8.12 (m, 38, aromatics).[64] ^{31}P NMR (161.7 MHz, C$_6$D$_6$) δ 71.2 (d, *J* = 41.4 Hz), 75.2 (d, *J* = 41.4 Hz). (b) ^{1}H NMR (400 MHz, 9:1 (CD$_3$)$_2$CDOD/C$_6$D$_6$) δ −14.01 (t, 1, *J* = 23.7 Hz, RuH), −0.89 (br s, 4, BH$_4$), 1.62 (s, 3, CH$_3$), 1.68 (s, 3, CH$_3$), 1.83 (s, 3, CH$_3$), 1.86 (s, 3, CH$_3$), 3.67 (d, 1, *J* = 10.8 Hz, C*H*NH$_2$), 3.90 (d, 1, *J* = 10.8 Hz, C*H*NH$_2$), 6.05−7.93 (m, 38, aromatics). ^{31}P NMR (161.7 MHz, 9:1 (CD$_3$)$_2$CDOD/C$_6$D$_6$) δ 70.28 (d, *J* = 41.5 Hz), 74.75 (d, *J* = 41.5 Hz). (c) ^{1}H NMR (400 MHz, 9:1 CD$_3$OD/C$_6$D$_6$) δ 1.53 (s, 3, CH$_3$), 1.67 (s, 3, CH$_3$), 1.85 (s, 3, CH$_3$), 1.95 (s, 3, CH$_3$), 3.97 (d, 1, *J* = 11.8 Hz, C*H*NH$_2$), ca. 4.21 (u d, 1, C*H*NH$_2$), 5.85−7.90 (m, 38, aromatics). ^{31}P NMR (161.7 MHz, 9:1 CD$_3$OD/C$_6$D$_6$) δ 55.5 (s, r.i. = 35%), 59.9 (s, r.i. = 15%), 67.5 (s, r.i. = 45%). (d) ^{1}H NMR (400 MHz, 9:1 (CD$_3$)$_3$- COH/C$_6$D$_6$) δ −13.89 (t, 1, *J* = 24.4 Hz, RuH), −0.75 (br s, 4, BH$_4$), 1.57 (s, 3, CH$_3$), 1.63 (s, 3, CH$_3$), 1.75 (s, 3, CH$_3$), 1.77 (s, 3, CH$_3$), 3.65 (d, 1, *J* = 12.2 Hz, C*H*NH$_2$), 3.92 (d, 1, *J* = 12.2 Hz, C*H*NH$_2$), 6.08−7.97 (m, 38, aromatics). ^{31}P NMR (161.7 MHz, 9:1 (CD$_3$)$_3$COH/ C$_6$D$_6$) δ 70.28 (d, *J* = 41.5 Hz), 74.75 (d, *J* = 41.5 Hz).

B. H/D Exchange. (a) (i) (*R*,*RR*)-**4** with no added base. First, an ^{1}H NMR spectrum of (*R*,*RR*)-**4** (7.6 mg/0.20 mL benzene-d_6) was obtained. To this solution was added 0.21 mL of (CD$_3$)$_2$CDOD (99.8% deuterated, [(*R*,*RR*)-**4**] = 19 mM), designated *t* = 0 min. ^{1}H NMR spectra were recorded at 5 min intervals, and the declining integration value of the amine protons was monitored relative to the unchanged C*H*NH$_2$ integration (δ 4.01 ppm, defined as 100 H). The RuH and BH$_4$ resonances remained unchanged over 4 days. The remaining mixture was found to hydrogenate **1** ([(*R*,*RR*)-**4**] = 0.38 mM; [**1**] = 0.79 M; $P_{H_2 \text{ or } D_2}$ = 4 atm, [base] = 0.0 M; *S/C* ratio = 1000; *T* = 30 °C, 1:1 benzene-d_6/(CD$_3$)$_2$CDOD as solvent). (ii) (*S*,*SS*)-**5** and (*S*,*SS*)-**6** without added base. The same experimental procedure was followed as that for (*R*,*RR*)-**4**. (iii) (*R*,*RR*)-**4** with base. The ^{1}H NMR spectrum of (*R*,*RR*)-**4** (7.6 mg/0.2 mL benzene-d_6) was first obtained. To this solution was added 0.2 mL of a 10.0 mM (CD$_3$)$_2$CDOK in (CD$_3$)$_2$- CDOD (99.8% deuterated, [base]$_T$ = 5.0 mM) solution, designated *t* = 0 min. ^{1}H NMR spectra were recorded at 2 min intervals, and the declining integration value of the amine protons was monitored relative to the unchanged C*H*NH$_2$ integration (δ 4.04 ppm, defined as 100 H). The RuH resonance intensity steadily decreased to zero over 4 days. However, the BH$_4$ resonance intensity remained unchanged. (iv) (*R*,*RR*)-**5** and (*R*,*RR*)-**6** with base. The ^{1}H NMR spectrum of (*R*,*RR*)-**5** or (*R*,*RR*)-**6** (7.9 mg/0.20 mL benzene-d_6, 19 mM) was obtained. To this solution was added 0.20 mL of a 10.0 mM (CD$_3$)$_2$CDOK solution in (CD$_3$)$_2$CDOD (99.8% deuterated, [base]$_T$ = 5.03 mM), designated *t* = 0 min. ^{1}H NMR spectra were recorded at 5 min intervals, and the declining integration value of the amine protons was monitored relative to the unchanged C*H*NH$_2$ integration (δ 3.4 or 3.97 ppm, defined as 100 H). The RuH resonance intensity remained unchanged over 3 days.

(b) (*R*,*RR*)-**4** in an 8:1 benzene-d_6/CD$_3$OD mixture. The ^{1}H NMR spectrum of (*R*,*RR*)-**4** (7.8 mg/0.40 mL benzene-d_6, 19.3 mM) was obtained. Then, to this solution was added 50 μL of CD$_3$OD (99.8% deuterated), designated *t* = 0 min. The declining intensity of the amine proton (δ 2.59 ppm) was monitored relative to the unchanged C*H*NH$_2$ integration (δ 3.99 ppm, d, *J* = 11.4 Hz, defined as 100 H) at *t* = 5 (44%), 10 (11%), 15 (5%), 20 (<1%), or 25 (>1%) min. The declining intensity for the RuH signal (δ −13.98 ppm, t, *J* = 22.9 Hz) at *t* = 5 (72%), 10 (22%), 15 (13%), 20 (2%), or 25 (<1%) min. During this experiment new species were formed. The only species observed beyond 3 h were as follows: ^{1}H NMR (400 MHz, 8:1 CD$_3$OD/C$_6$D$_6$) δ 1.53 (s, CH$_3$), 1.67 (s, CH$_3$), 1.85 (s, CH$_3$), 1.95 (s, CH$_3$), 3.61 (d, 1, *J* = 11.4 Hz, C*H*NH$_2$), 3.90 (d, 1, *J* = 11.4 Hz, C*H*NH$_2$), 5.88−7.80 (m, 38, aromatics); ^{31}P NMR (161.7 MHz, 8:1 CD$_3$OD/C$_6$D$_6$) δ 55.5 (s), 67.2 (s). The remaining mixture did not hydrogenate **1** ([(*R*,*RR*)-**4**] = 38.5 mM; [**1**] = 0.93 M; P_{H_2} = 4 atm, [base] = 0.0 M; *S/C* ratio = 500; *T* = 30 °C, 8:1 benzene-d_6/CD$_3$OD as solvent). (c) (*S*,*SS*)-**4** in a 1:1 benzene-d_6/(CD$_3$)$_3$COD mixture. The ^{1}H NMR spectrum of (*R*,*RR*)-**4** (7.7 mg/0.40 mL benzene-d_6, 19.2 mM) was obtained. To this solution was added 0.4 mL of (CD$_3$)$_3$COD (99.0% deuterated), designated *t* = 0 min. The declining intensity of the amine proton (δ 2.49 ppm) was monitored relative to the unchanged C*H*NH$_2$ integration (δ 3.92 ppm, d, *J* = 12.2 Hz, defined as 100 H) at *t* = 5 (89%), 12 (72%), 20 (51%), 30 (38%), 45 (21%), 65 (8%), or 80 (1%) min. The signal intensity for RuH (δ −13.89 ppm) and BH$_4$ (δ −0.75 ppm) remained unchanged over 24 h. The remaining mixture did not hydrogenate **1** in this solvent system ([(*R*,*RR*)-**4**] = 41 mM; [**1**] = 1.82 M; P_{H_2} = 4 atm, no base; *S/C* ratio = 1000; *T* = 30 °C, 1:1 benzene-d_6/(CD$_3$)$_3$COD solvent).

C. Extent of Deuteration in Product. Hydrogenation conditions: [(*R*,*RR*)-**4** or (*S*,*SS*)-**5**] = 0.45 mM; [**1**] = 0.82 M; P_{H_2} = 4 atm; [KO-*t*-C$_4$H$_9$] = none for (*R*,*RR*)-**4** and 18 mM for (*S*,*SS*)-**5**; *S/C* ratio = 1800; *T* = 30 °C, (CH$_3$)$_2$CDOH or (CH$_3$)$_2$CDOD solvent. For all experiments, the conversion was >99% with an ee of 82% for (*S*)-**2**. The extent of deuteration was determined by the relative signal ratios of **2** in ^{1}H and ^{2}H NMR of the crude product mixture as well as the isolated product (in benzene or benzene-d_6) following removal of the solvent under vacuum. For hydrogenation in (CH$_3$)$_2$CDOH with (*R*,*RR*)-**4** and (*S*,*SS*)-**5**, ^{2}H NMR showed no deuteration of **2** within the detection limit. For reaction in (CH$_3$)$_2$CDOD with (*R*,*RR*)-**4**, ^{2}H NMR of **2** showed 4% deuteration at the benzylic position. Reaction with (*R*,*RR*)-**5** gave **2** deuterated 25% at the methyl and also 5% at the benzylic carbon.

D. [(*S*,*SS*)-7(ROH)]$^+$[(RO)(ROH)$_n$]$^-$ (R = (CH$_3$)$_2$CH). (a) A solution of (*R*,*RR*)-**4** (100 mg, 0.098 mmol) in dried/degassed toluene (1.0 mL) was cooled to −50 °C, and HBF$_4$ (13.6 μL of a 54 wt % ether solution, 1 equiv) was added. The resulting yellow mixture was allowed to warm to room temperature. The temperature was again lowered to −50 °C, and 0.5 mL of NaO-*i*-C$_3$H$_7$/(CH$_3$)$_2$CHOH solution (50 mM) was added. Removal of solvent in vacuo gave a pale reddish solid, which was extracted with benzene (1 mL) and filtered through Celite: ^{1}H NMR (400 MHz, C$_6$D$_6$) δ −17.32 (t, 1, *J* = 25.4 Hz, RuH), 1.89 (s, 3, CH$_3$), 1.75 (s, 3, CH$_3$), 2.02 (s, 3, CH$_3$), 2.07 (s, 3, CH$_3$), 2.26 (m, 1, N*H*H), 3.02 (m, 1, N*H*H), 3.58 (m, 1, N*H*H), 3.78−3.82 (m, 2, C*H*NH$_2$ and N*H*H), 4.51 (m, 1, C*H*NH$_2$), 5.80−8.96 (m, 38, aromatics); ^{31}P NMR (161.7 MHz, C$_6$D$_6$) δ 62.93 (d, *J* = 41.5 Hz), 70.05 (d, *J* = 41.5 Hz); ^{13}C NMR (100.4 MHz, C$_6$D$_6$) δ 20.5−21.2 (*C*H$_3$), 62.2 (*C*HNH$_2$), 69.2 (*C*HNH$_2$), 128.0−144.8 (aromatics). 2D NMR (^{1}H−^{1}H COSY, ^{13}C−^{1}H HMQC, ^{1}H−^{31}P HSQC) measurements aided the assignments listed above. This complex is highly air/moisture-sensitive and decomposes upon removal of benzene unless KO-*i*-C$_3$H$_7$/ (CH$_3$)$_2$CHOH is present. Upon addition of (CD$_3$)$_2$CDOD: ^{1}H NMR (400 MHz, 1:1 (CD$_3$)$_2$CDOD/C$_6$D$_6$) δ −17.82 (t, 1, *J* = 25.3 Hz, RuH), 1.38 (s, 3, CH$_3$), 1.45 (s, 3, CH$_3$), 1.51 (s, 3, CH$_3$), 1.55 (s, 3, CH$_3$), 3.36 (d, 1, *J* = 10.6 Hz, C*H*NH$_2$), 3.99 (d, 1, *J* = 10.6 Hz, C*H*NH$_2$), 5.89−8.36 (m, 38, aromatics); ^{31}P NMR (161.7 MHz, C$_6$D$_6$) δ 62.17 (d, *J* = 41.5 Hz), 70.82 (d, *J* = 41.5 Hz); ^{13}C NMR (100.4 MHz, 1:1

$(CD_3)_2CDOD/C_6D_6)$ δ 20.5$-$21.2 (CH_3), 62.2 ($CHNH_2$), 69.2 ($CHNH_2$), 128.0$-$144.8 (aromatics). Hydrogenation of **1**: [above solution] = 0.50 mM; [**1**] = 1.10 M; P_{H_2} = 4 atm; no added base; S/C ratio = 1800; T = 30 °C, 9:1 $(CH_3)_2CHOH$/benzene as solvent. Observed TOF at 10 min = 192 min^{-1}, hydrogenation > 95% completed within 15 min (TOF = 6950 h^{-1}), (*S*)-**2** in 82% ee. (b) Catalytically active mixed species. A yellow solution of (*R,RR*)-**4** (16.8 mg, 11.9 mM) in 1:1 toluene/$(CD_3)_2CDOD$ (1.4 mL) was heated at 40 °C for 15 min, yielding a red solution. Evaporation of volatiles in vacuo and extraction/Celite filtration with benzene resulted in the formation of a complex indistinguishable from the cationic fragment in part a (^{1}H, ^{31}P, and ^{13}C NMR and MS spectral analysis, r.i. = 80%) and three minor species: (i) r.i. = 10%, ^{31}P NMR δ 51.5 (d, *J* = 41.5 Hz), 60.1 (d, *J* = 41.5 Hz); (ii) r.i. = 5%, ^{31}P NMR δ 68.5 (d, *J* = 41.5 Hz), 75.3 (d, *J* = 41.5 Hz), ^{1}H NMR δ $-$13.01 (t, RuH); (iii) r.i. = 5%, ^{31}P NMR δ 63.6 (d, *J* = 41.5 Hz), 70.0 (d, *J* = 41.5 Hz), ^{1}H NMR δ $-$21.5 (t, RuH). Mixtures obtained in this way hydrogenated **1** efficiently (see section B(c)).

E. Detection and Reactivity of the 16e Ru Complex 8. To a solution of (*R,RR*)-**4** in benzene-d_6 (0.04 M, 0.4 mL) was added solid $(CD_3)_2CDOK$ (7.8 mg, 5.3 equiv), followed by $(CD_3)_2CDOD$ (50 μL, [base] = 0.18 M). The solution gradually changed from yellow to deep red with standing for >12 h. ^{1}H and ^{31}P NMR spectra were collected at 2 h and then at 16 h intervals (4 days). The initial (*R,RR*)-**4** resonances decreased with time, coupled with the appearance and increase of a second species (r.i. = 70%): ^{1}H NMR (400 MHz, 8:1 $(CD_3)_2CDOD$/ C_6D_6) δ $-$14.2 (br t, <1, 29.5 Hz, RuH), 1.63 (s, 3, CH_3), 1.67 (s, 3, CH_3), 1.73 (s, 3, CH_3), 1.78 (s, 3, CH_3), 3.36 (d, 1, *J* = 11.5 Hz, C*H*NH$_2$), 4.80 (d, 1, *J* = 11.5 Hz, C*H*NH$_2$), 5.82$-$8.10 (m, 38, aromatics). ^{31}P NMR (161.7 MHz, 8:1 $(CD_3)_2CDOD/C_6D_6$) δ 67.50 (d, *J* = 35.6 Hz), 68.43 (d, *J* = 35.6 Hz). The hydride resonance was observed only when $(CH_3)_2CHOH$ was used due to H/D exchange. Similar results were obtained for 0.36 and 0.54 M basic solutions. This compound assignable to **8** is extremely air and moisture sensitive and unstable in the solid state and in nonbasic solutions and could only be obtained in a mixture with (*R,RR*)-**4**. Attempts to isolate this neutral complex were unsuccessful. Further in situ NMR experiments are described in the Supporting Information. Addition of $(CH_3)_2CHOH$ (0.35 mL) resulted in formation of solvated **7**: ^{1}H NMR δ $-$17.34 (t, 1, *J* = 25.4 Hz, RuH); ^{31}P NMR δ 62.83 (d, *J* = 41.5 Hz), 71.25 (d, *J* = 41.5 Hz), r.i. = 92%.

MS Experiments. The general experimental procedure and setup are described in section B(a). Hydrogenation conditions: [(*R,RR*)-**4**] = 0.48 mM, [**1**] = 0.68 M; P_{H_2} = 4 atm, [KO-*t*-C$_4$H$_9$] = 0.82 mM (1.0 M solution in $(CH_3)_3COH$); S/C ratio = 1400; T = 22 °C; and 1:1 toluene/$(CH_3)_2CHOH$-mixed solvent (5.0 mL). Samples were obtained following the reaction initiation (*t* = 0) for GC and MS analyses. ESI-TOFMS spectra were recorded immediately (within 1 min) for sample aliquots (ca. 0.3 mL) using a 1:1 mixture of predried and degassed toluene and $(CH_3)_2CHOH$ as ionizing solvent: *t* = 0 min, [M]$^+$ = 1007.3 *m/z* (100%), [M]$^+$ = 1025.3 *m/z* (9%); *t* = 40 min, 12% conv, 76% ee, [M]$^+$ = 733 *m/z* (43%), [M]$^+$ = 749 *m/z* (100%), [M]$^+$ = 993.3 *m/z* (10%), [M]$^+$ = 1007.3 *m/z* (20%), [M]$^+$ = 1021.3 *m/z* (10%), [M]$^+$ = 1047 *m/z* (8%); *t* = 60 min, 30% conv, 81% ee, [M]$^+$ = 733 *m/z* (15%), [M]$^+$ = 749 *m/z* (36%), [M]$^+$ = 993.3 *m/z* (100%), [M]$^+$ = 1007.3 *m/z* (15%), [M]$^+$ = 1021.3 *m/z* (17%); *t* = 100 min, 55% conv, 85% ee, [M]$^+$ = 749 *m/z* (24%), [M]$^+$ = 993.3 *m/z* (38%), [M]$^+$ = 1007.3 *m/z* (3%), [M]$^+$ = 1021.3 *m/z* (100%); *t* = 145 min, 78% conv, 83% ee, [M]$^+$ = 749 *m/z* (43%), [M]$^+$ = 993.3 *m/z* (36%), [M]$^+$ = 1021.3 *m/z* (100%). Assignments: (i) [M]$^+$ = 733.3 *m/z*, M = TolBINAP mono-*P*-oxide; (ii) [M]$^+$ = 749.3 *m/z*, M = TolBINAP di-*P*-oxide; (iii) [M]$^+$ = 993.3 *m/z*, M = (*R,RR*)-**7**; (iv) [M]$^+$ = 1007.3 *m/z*, M = (*R,RR*)-**4**; (v) [M]$^+$ = 1021.3 *m/z*, M = (*R,RR*)-**7**(N$_2$). The isotopic distribution of the experimental *m/z* patterns was well matched with the calculated patterns for assigned fragments (See Supporting Information). When only $(CH_3)_2CHOH$ was used as solvent: (i) [M]$^+$ = 733.3 *m/z*, M = TolBINAP mono-*P*-oxide and (ii) [M]$^+$ = 749.3 *m/z*, M = TolBINAP di-*P*-oxide were observed (*t* = 120 min, 98% conv, (*S*)-**2** in 83% ee).

Supporting Information Available: Descriptions of the experimental setup, ESI-TOFMS and miscellaneous NMR/ hydrogenation experiments, rate dependence on substrate concentration, temperature, and *tert*-butyl alcohol. This material is available free of charge via the Internet at http://pubs.acs.org.

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