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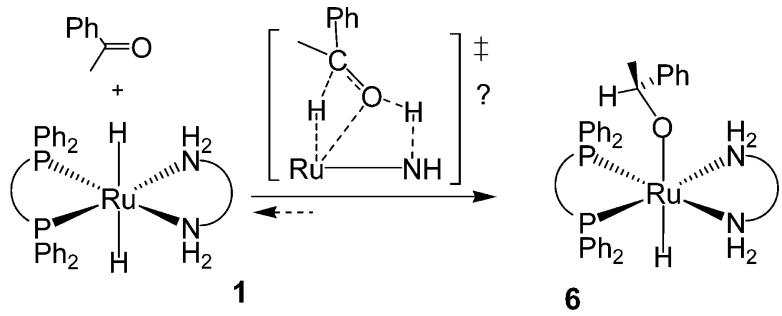

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Direct Observations of the Metal−Ligand Bifunctional Addition Step in an Enantioselective Ketone Hydrogenation

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Abstract: The catalytic intermediate *trans*-[Ru((*R*)-BINAP)(H)$_2$((*R*,*R*)-dpen)] (**1**) reacted on mixing with acetophenone in THF at −80 °C under ∼2 atm H_2 to generate the alkoxide *trans*-Ru((*R*)-BINAP)(H)-((Ph)(Me)CHO)((*R*,*R*)-dpen) (**6**). Contrary to expectations, free Ru-amide and 1-phenylethanol were not the immediate products of this addition reaction. The addition reaction was reversible in THF. 2-Propanol prevents racemization of the alcohol product in THF solvent.

Introduction

Among the most significant advances in enantioselective catalysis is Noyori et al.'s development of the hydrogenation catalyst system *trans*-Ru(diphosphine)Cl_2(diamine) plus base in 2-PrOH.[1,2] The most common diphosphine and diamine ligands in these catalysts are BINAP [(*R* or *S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl], dpen [(*R*,*R* or *S*,*S*)-1,2-diphenylethylenediamine], and their derivatives, respectively. These systems and their variants hydrogenate aryl alkyl, vinyl alkyl, and certain alkyl alkyl ketones with high enantioselectivity, chemoselectivity, turnover numbers, and rates.[2] The mechanism of this hydrogenation is the subject of intense study.[2a,3−9] It has proven difficult to obtain direct experimental information about individual steps in this mechanism because the proposed intermediates rapidly decompose at room temperature in the absence of substrate or hydrogen. Further, the active hydrogen atoms in the system—the Ru−H, Ru−η^2-H_2, and N−H groups—all undergo rapid exchange with 2-PrOH-d_8 at room temperature, thereby hindering direct NMR observations of the steps in the catalytic cycle.[7a] As a result of these limitations, the accepted mechanism has largely been reasoned from model compounds and other catalytic cycles, from isotope labeling studies, kinetics studies of product formation by the catalytic reaction, product distributions, and from theoretical calculations. The accepted best fit with the currently available data is that the enantioselective step is a metal−ligand bifunctional addition reaction involving the dihydride intermediate *trans*-[Ru((*R*)-BINAP)(H)$_2$-((*R*,*R*)-dpen)] (**1**). It is proposed that a nucleophilic hydride on Ru and a protic hydrogen on nitrogen add to the carbon and oxygen atoms of the ketone, respectively (eq 1). This is a concerted addition reaction that proceeds through a pericyclic, six-membered transition state to produce the alcohol product and the amide [Ru((*R*)-BINAP)(H)((*R*,*R*)-NH(CH(Ph))$_2$NH$_2$)] (**2**). The amide **2** then undergoes a turnover-limiting addition of dihydrogen to regenerate **1**.

The literature contains few direct studies of the stoichiometric bifunctional addition step to ketones and related polar double bonds. The one most closely related to the Noyori catalyst system is that reported by Morris et al., in which 1 equiv of

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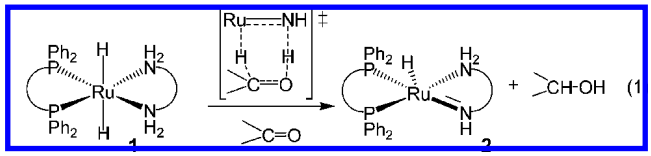
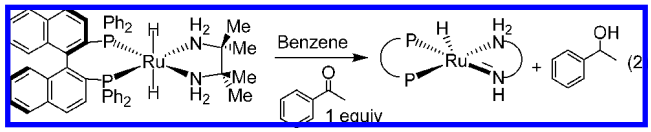
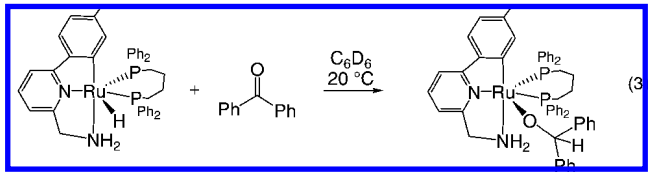


acetophenone adds to the model compounds *trans*-[Ru((*R*)-BINAP)$(H)_2$(tmen)] and *trans*-[Ru$(PPh_3)_2(H)_2$(tmen)] (tmen = tetramethylethylenediamine) at room temperature in benzene to form 1-phenylethanol and the corresponding Ru−amide complexes as predicted by the bifunctional addition reaction (eq 2).[3b] The tmen ligand was incorporated into these model compounds to avoid decomposition under these conditions.

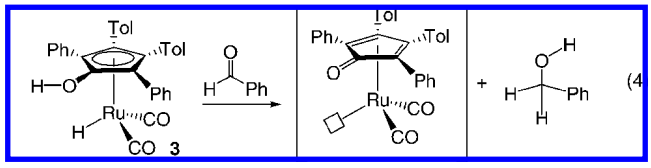


Baratta et al. reported that the compound [Ru(H)(CNN)-(dppb)] (HCNN = 6-(4′-methylphenyl)-2-pyridylmethylamine, dppb = $Ph_2P(CH_2)_4PPh_2$) reacts with ∼1 equiv of benzophenone in benzene solution at 20 °C to form the ruthenium alkoxide product of a net ketone−hydride insertion, rather than the amide compound and free alcohol as predicted by the bifunctional addition reaction (eq 3).[6a] The authors proposed a mechanism



that involves hydrogen-bonding of an N−H group in the CNN ligand to the oxygen in benzophenone, activating the ketone toward nucleophilic attack by the hydride ligand on ruthenium. This nucleophilic attack forms an alkoxide anion that remains hydrogen-bonded to the N−H group. The alkoxide anion then migrates from the N−H group to ruthenium to form the observed product. These authors could not rule out the possibility that this addition reaction occurs by other pathways, including dissociation of the NH_2 functionality to create a vacant coordination site on the metal center.

The groups of Casey[4] and Bäckvall[8] have investigated the addition reactions between polar bonds and the Shvo catalysts [(2,5-Ph_2-3,4-$Tol_2(\eta^5$-C_4COH))Ru$(CO)_2$H] (**3**) and [(2,3,4,5-$Ph_4(\eta^5$-C_4COH))Ru$(CO)_2$H] (**3′**) (eq 4). Deuterium labeling



studies by Casey's group indicate that the stoichiometric reduction of benzaldehyde by **3** in THF proceeds via a concerted, simultaneous transfer of both the hydride and −OH proton to the carbonyl carbon and oxygen of benzaldehyde, respectively. Bäckvall corroborated these findings with an isotope labeling study on the reverse of the addition step, the oxidation of 1-(4-flurophenyl)ethanol. Casey proposed that these reductions occur via a metal−ligand bifunctional addition involving the Ru−H and cyclopentadienyl−OH hydrogen atoms. Bäckvall proposed that these addition reactions commence by coordination of the carbonyl oxygen to ruthenium with a concomitant $\eta^5 \rightarrow \eta^3$-ring slip of the hydroxycyclopentadienyl ligand. The resulting ketone adduct then undergoes simultaneous hydride and OH proton transfer to generate the alcohol product coordinated to ruthenium.

Casey and Bäckvall have also studied the stoichiometric addition reaction between imines and Shvo's catalyst.[4a,b,d−f,8c,d] Both groups report that a ruthenium−amine compound, in which the amine ligand is the reduced imine, is the product of the stoichiometric addition reaction. Bäckvall et al. propose that the ruthenium−amine product results from an inner-sphere mechanism that commences by coordination of the imine nitrogen to ruthenium with a concomitant $\eta^5 \rightarrow \eta^3$-ring slip of the hydroxycyclopentadienyl ligand. Subsequent hydrogen transfer then results in the amine product coordinated to ruthenium. Casey et al. propose that the reaction proceeds via the outer-sphere metal−ligand bifunctional addition mechanism with the product amine hydrogen-bonded to the oxygen on the cyclopentadienone ligand. The amine then coordinates to ruthenium to give the observed product. These research groups carried out intra- and intermolecular trapping experiments to investigate whether the addition reaction proceeds via an inner-sphere mechanism or via an outer-sphere bifunctional addition. Intermolecular experiments failed to trap the coordinatively unsaturated ruthenium product predicted by an outer-sphere bifunctional addition. In the latest of a series of intramolecular trapping experiments carried out by these groups, Casey's group used the pseudosymmetric imine 1,4-$(CH_2Ph)N{=}(c\text{-}C_6H_{10})^{15}NH(CH_2Ph)$ as trapping reagent.[4f] The stoichiometric reduction of this imine at −45 °C in toluene and at −20 °C in CD_2Cl_2 resulted in 85:15 and 91:9 mixtures of the RuN:Ru^{15}N amine complexes, respectively. The presence of the Ru^{15}N isotopomers is interpreted as the reaction proceeding through the outer-sphere bifunctional addition to form the amine product hydrogen-bonded to the cyclopentadienone ligand and trapped within a solvent cage.

Numerous theoretical studies have been carried out on hydrogenations of ketones by the Ru(diphosphine)$(H)_2$(diamine) and related catalyst systems.[3b,e,4d,e,5,8d,9] The predominant conclusion of these studies is that the reaction proceeds via the bifunctional addition pathway, with the activation of hydrogen by the amide complex being the turnover-limiting step. Early calculations were carried out with the steps occurring in the gas phase. Recent studies have investigated the role of the 2-propanol solvent.[3e,5] These recent studies conclude that 2-propanol lowers the activation energy both for the activation of dihydrogen by the ruthenium−amide intermediate and for the bifunctional addition. It is proposed that alcohols lower the activation energy for these processes by acting as a proton acceptor while hydrogen-bonding with the N−H, Ru−η^2-H_2, and product alcohol OH groups, and as a proton donor while hydrogen-bonding with the Ru═N, C═O, and product alcohol C−O groups. Calculations indicate that this hydrogen-bonding can result in pathways that differ from the direct bifunctional

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addition. One such pathway generates the ketone reduction product as an alkoxide that is hydrogen-bonded to alcohol solvent molecules.[9c] The solvent molecules then shuttle a proton from the N−H group to the alkoxide to generate the product alcohol and the ruthenium−amide. In a recent study, calculations by Morris et al. suggest a pathway where the transition state that contains the product alkoxide hydrogen-bonded to the solvent collapses to form a stable ruthenium−product alkoxide compound.[3e] Several other theoretical studies conclude that ruthenium−alkoxides are the most stable of the species considered in the calculations.[9a,b]

We recently reported high-yielding, low-temperature preparations with full NMR characterizations of the majority of the intermediates proposed for the hydrogenation of ketones using *trans*-[Ru((*R*)-BINAP)(H)$_2$((*R*,*R*)-dpen)] as catalyst.[7b] We identified an unexpected pathway whereby base increases the rate of the hydrogenation. Specifically, we found that the amide **2** reacts quickly with 2-PrOH, even at −80 °C, to form the corresponding 2-propoxide compound *trans*-[Ru((*R*)-BINAP)(H)(2-PrO)((*R*,*R*)-dpen)] (**4**). We also found that the dihydride **1** reacts with excess 2-PrOH, albeit at a somewhat lower rate than **2**, to also generate **4**. These observations show that the 2-PrOH solvent competes with hydrogen and ketone for the active catalyst species during these hydrogenations. These observations are also in line with the predictions made by theoretical studies that ruthenium−alkoxide compounds are relatively stable catalyst resting states.[3e,9a,b] The alkoxide **4** did not undergo a net reaction with hydrogen (∼2 atm, 22 °C) over a period of days in the absence of base. Also, **4** is not a catalyst for the hydrogenation in the absence of base under the conditions of our experiments. The alkoxide **4** does react quickly, however, even at −80 °C, via a base-promoted elimination to generate the amide **2**. This elimination proceeds by deprotonation of an N−H group in dpen to form a lone pair on N that displaces the alkoxide ligand in the complex. We also showed that H_2 (∼2 atm) adds quickly to the amide **2** at ∼−80 °C to cleanly generate the dihydride **1**, thereby demonstrating a kinetically feasible route, i.e., **4**→**2**→**1**, whereby added base can increase the rate of these hydrogenations. We now report the results of the first low-temperature, stoichiometric study of the addition reaction between acetophenone and the dihydride **1** as a putative step in the catalytic cycle.

Results and Discussion

Unless stated otherwise, the dihydride **1** was prepared for this study in THF-d_8 by reacting an equilibrium mixture of the cationic compounds *trans*-[Ru((*R*)-BINAP)(H)(η^2-H$_2$)((*R*,*R*)-dpen)](BF$_4$) (**5**) and *trans*-[Ru((*R*)-BINAP)(H)(THF-d_8)((*R*,*R*)-dpen)](BF$_4$) with *t*-BuOK (∼2.5 equiv) under H_2 (∼2 atm) at −80 °C. Complex **5** and the THF adduct were generated from starting materials *in situ*, and stoichiometric quantities of cyclooctene/ane are present. As we showed previously, this route cleanly provides the dihydride **1** in high yields under H_2 in the presence of ∼1.5 equiv of excess base.[10] The use of 2-PrOH-d_8 as solvent was avoided at this stage of the investigation because of rapid and quantitative formation of the 2-propoxide compound **4** under these conditions.[7b] The addition of 1 equiv of acetophenone to **1** was carried out at −80 °C under ∼2 atm H_2 and monitored by NMR spectroscopy. The addition reaction was complete within 60 s of mixing, when the first spectrum

(10) This reaction likely proceeds by loss of η^2-H$_2$, deprotonation of a N−H group to form **2**, and addition of H_2 to form **1**.[7b]

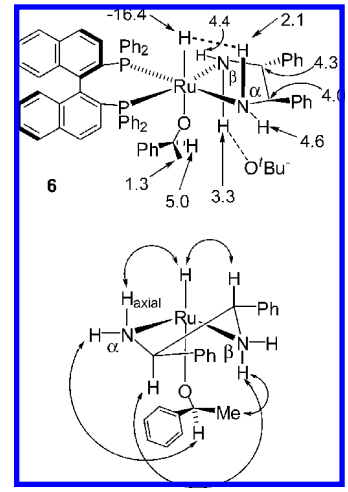
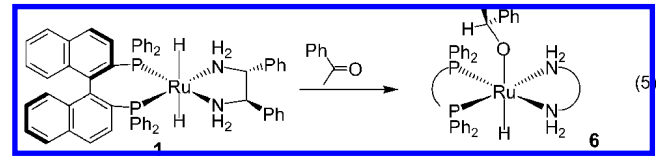


Figure 1. (Top) Assignments of ^{1}H NMR signals in dpen and 1-phenylethoxide ligands in **6**. (Bottom) NOE interactions used to assign axial and equatorial orientations in these groups.

was recorded, demonstrating the high activity of **1** as a reducing agent toward carbonyl compounds. In light of Morris's previous result with the tmen model compounds in benzene at room T (eq 2), we were surprised to find that the addition reaction did not form the amide **2** and 1-phenylethanol, as predicted, by an outer-sphere bifunctional addition. Instead, the product is the 1-phenylethoxide **6**, the net result of ketone−hydride insertion (eq 5). No other intermediates were detected during this rapid



addition reaction at −80 °C. Also, only one set of signals was observed in the NMR spectra of **6**. The difference in activity between the model tmen compounds studied by Morris et al. in benzene at room temperature, and the dpen intermediate studied here in THF at low temperatures, likely arises from the greater electron-donating ability and steric bulk of the tmen ligand relative to dpen. Both of these characteristics would favor the amide over the alkoxide. Although its origins were not investigated further, this difference in activity and reactivity underscores how seemingly minor changes in structure can cause significant changes in the activity of catalytic intermediates, and that caution is warranted when extrapolating the results from model compounds to catalytic cycles.

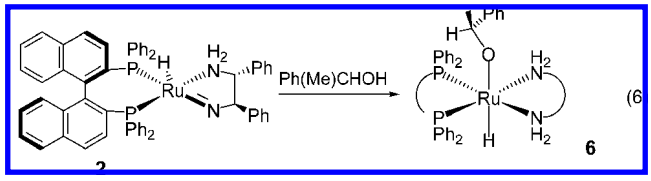
The alkoxide **6** was too unstable to allow a solid-state structure determination by X-ray diffraction. Instead, we identified **6** with ^{1}H, ^{13}C, ^{31}P, HSQC, NOE, and COSY NMR experiments, as well as with ESI mass spectrometry. The assignments of the alkoxy- and methyl-^{13}C signals in the 1-phenylethoxide ligand were confirmed using acetophenone labeled with ^{13}C at C_1 and C_2. One N−H signal (δ 2.1 ppm) was shifted substantially upfield from the others in the ^{1}H NMR spectrum. This upfield shift is believed to arise from a bonding interaction between the Ru−H group and the adjacent (α) N−H$_{axial}$ group. This interaction is shown in Figure 1. We also observed a strong NOE interaction between Ru−H and α-N−H$_{axial}$, confirming the assignment of this ^{1}H NMR signal to the α-N−H$_{axial}$ group. Similar observations were made

previously by the groups of Morris, Bergens, and Noyori with related species.[3a,7,11]

Using this assignment as a starting point and the NMR experiments listed above, ^{1}H and ^{13}C NMR signals were assigned to the remaining C−H and N−H groups in the dpen and 1-phenylethoxide ligands. Figure 1 shows several key assignments as well as the NOE interactions used to assign the axial and equatorial orientations of these groups.

As we reported previously for **4**,[7b] the ∼1.5 equiv of excess *t*-BuOK present from the preparation of **1** formed a weak hydrogen bond with the N−H groups in **6**. To the best of our knowledge, there are no theoretical studies that address such an interaction of base with this or other intermediates in the catalytic cycle. When prepared without excess *t*-BuOK, compound **1** also reacted quickly at −80 °C with acetophenone to form **6**, only without the hydrogen bonds between the N−H groups and *t*-BuOK. A comparison of the ^{1}H NMR chemical shifts for the N−H signals for **6** in the presence and in the absence of base shows that only the signal for the β-N−H$_{axial}$ group shifted substantively (from δ 3.3 to 3.6 ppm) upon removal of the excess base. The alkoxide C−H signal shifted from δ 5.0 to 5.1 ppm upon removal of the base as well. We interpret these differences in chemical shifts as the β-N−H$_{axial}$ group being hydrogen-bonded to the excess base as shown in Figure 1. When the base is removed, the β-N−H$_{axial}$ group engages in intramolecular hydrogen-bonding with the 1-phenylethoxide ligand, as proposed previously for ruthenium−alkoxide compound.[6a,7b]

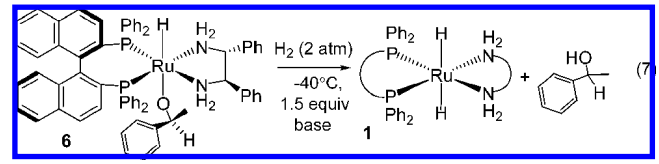
We reported previously that 2-propanol reacts on mixing at −80 °C with the amide **2** to form the alkoxide **4**.[7b] With this reactivity in mind, we carried out an independent preparation of the 1-phenylethoxide **6** by reacting the amide **2** with 1-phenylethanol at −80 °C in THF (eq 6). The 1-phenylethoxide



(6)

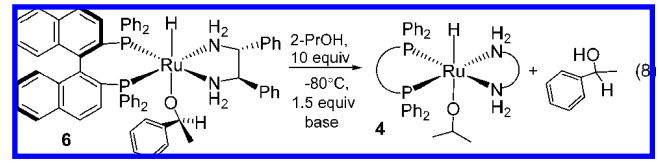
6 formed on mixing, and it was identical to that formed by the addition reaction of acetophenone to the dihydride **1** (eq 5). In contrast, Morris et al. reported previously that the model amide compound [Ru(PPh$_3$)$_2$(H)(NHC(CH$_3$)$_2$C(CH$_3$)$_2$NH$_2$)] (**7**) reacts with 1-phenylethanol at room temperature to slowly form an equilibrium mixture of **7** and the corresponding 1-phenylethoxide [Ru(PPh$_3$)$_2$(H)((Ph)(Me)CHO)(tmen)] (**8**).[3b] The alkoxide **8** was identified by the Ru−H and tmen−CH$_3$ signals in the ^{1}H NMR and signals in the ^{31}P NMR spectrum.

We found that the 1-phenylethoxide **6** reacted in the presence of 1.5 equiv of excess *t*-BuOK and ∼2 atm H$_2$ upon warming to ∼−40 °C to give 1-phenylethanol and to regenerate the dihydride **1**, thereby providing an observation of a complete, kinetically competent catalytic cycle at low temperatures (eq 7). No other intermediates were observed during this transformation. The mechanism for this transformation is discussed below.



(7)

One possible pathway for the addition reaction of acetophenone to **1** is that the alkoxide **6** formed *after* a bifunctional addition of via the rapid reaction between 1-phenylethanol and the amide **2** (Scheme 1, bottom reaction). We showed previously that H$_2$ rapidly adds to the amide **2** to form the dihydride **1** (Scheme 1, middle, reverse) under the conditions for the addition reaction of acetophenone to **1** (−80 °C, ∼2 atm H$_2$).[7b] Thus, the excess H$_2$ present during the addition reaction will act as a trapping agent for the free amide **2**, if it forms. The absence of the trapping product, **1**, after the addition reaction was complete is strong evidence that the free amide **2** did not form as a product of the addition reaction. We also carried out the addition reaction using 2-PrOH to trap the amide **2**. We showed previously that **2** reacts on mixing with 2-PrOH at −80 °C to form the 2-propoxide **4** (Scheme 1, top).[7b] A difficulty encountered with this experiment, however, was the rapid exchange between the 1-phenylethoxide **6** and 2-PrOH in solution. For example, **6** reacts with 10 equiv of 2-PrOH to rapidly form the 2-propoxide **4** at −80 °C in THF-d_8 (eq 8).[12] This complication was



(8)

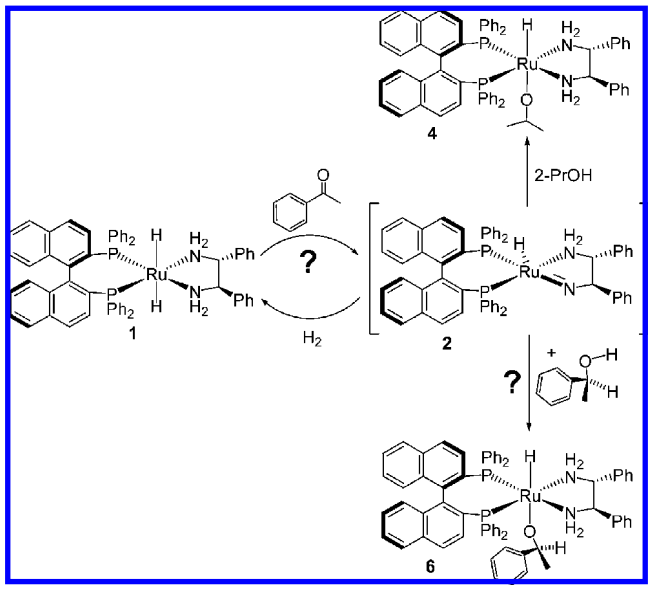
accommodated by preparing frozen THF layers that contained the dihydride **1** in the lower layer and a mixture of acetophenone (2 equiv) and 2-PrOH (∼150 equiv) in the upper layer. The sample was placed in a −80 °C NMR probe, and the first spectrum was recorded once the layers thawed. The addition reaction was complete within 60 s, with the 1-phenylethoxide **6** as the sole species in the bottom product layer. Approximately 5 equiv of 2-PrOH had diffused into the product layer after 60 s, when the addition reaction was complete. Diffusion of more 2-PrOH into the product layer continued thereafter. A preformed mixture of the dihydride **1** and 2-PrOH (5 equiv) was reacted with acetophenone (1 equiv) at −80 °C to THF-d_8 to also give the 1-phenylethoxide **6** as the sole product.[13] In a control competition experiment, the amide **2** was prepared in THF and reacted with a mixture of 2-PrOH (5 equiv) and 1-phenylethanol (1 equiv) at −80 °C. The result was a mixture of the alkoxides **4** and **6** in a ∼1:1 ratio. Thus, a kinetic preference exists for the reaction of **2** with 1-phenylethanol over 2-PrOH, but this preference is insufficient to account for the exclusive formation of **6** by the addition reaction of acetophenone to **1**. These low-temperature addition/trapping experiments prove that the free amide **2** is not the product of the addition reaction between acetophenone and the dihydride **1**. Regardless of the intermediacy of **2**, these experiments show that the net product of the rapid addition reaction at −80 °C is **6** (eq 5). Further, **6** will react quickly during catalytic hydrogenations carried out in 2-PrOH solvent in the presence of base to generate free 1-phenylethanol and the 2-propoxide **4** (eq 8).

(11) Sandoval, C. A.; Yamaguchi, Y.; Ohkuma, T.; Kato, K.; Noyori, R. *Magn. Reson. Chem.* **2006**, *44*, 66–75.

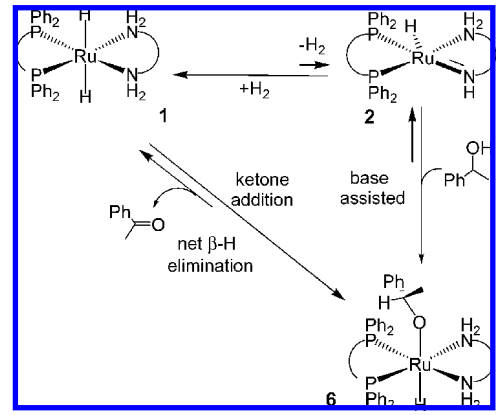
(12) Such exchanges likely proceed via a base-assisted intramolecular elimination of the 1-phenylethoxide ligand, followed by addition of 2-PrOH to **2** (Scheme 3, **6**→**2**→**4**).[7b]

(13) Reaction of a mixture of **1** and 10 equiv of 2-PrOH in the absence of base with acetophenone showed a small amount of **6** in the first spectrum that converted to **4** by the second spectrum.

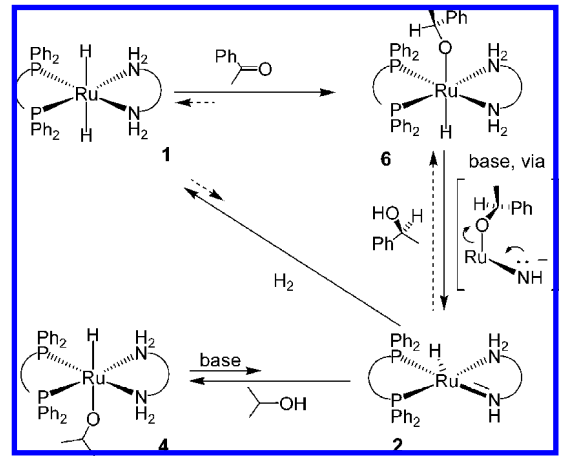
Scheme 1



Scheme 2



Scheme 3



The enantioselectivity of the addition reaction was investigated by reacting the dihydride **1** with 1 equiv of acetophenone in THF at −80 °C, followed by addition of excess 2-PrOH. The 2-PrOH was added to liberate the 1-phenylethanol product via the displacement reaction shown in eq 8. This procedure was adopted because **6** could not be isolated for structure determination, and NMR spectroscopy did not allow us to determine the ratio of diastereomers. The enantiomeric excess (ee) of the liberated 1-phenylethanol was 83% (*S*). Thus, the absolute configuration of the 1-phenylethoxide ligand in the major diastereomer of **6** is *S*, and the minor diastereomer of **6** was present in ∼8.5% abundance.

The initial ee of the catalytic hydrogenation in THF, recorded after six turnovers, was 69% (*S*) (1000 equiv of ketone, 2.5 equiv of *t*-BuOK, 30 °C, 4 atm H_2). The ee of the hydrogenation in 2-PrOH was ∼80% (*S*). Thus, the intrinsic enantioselectivity of the catalytic hydrogenation in THF is less than it is in 2-PrOH. Further, the ee of the catalytic hydrogenation in THF decreased to 59% (*S*) after 94 turnovers. To investigate whether the addition reaction is reversible in THF, 10 equiv of the minor product enantiomer, (*R*)-CH_3(Ph)CHOH (ee ∼99%), was reacted with the dihydride catalyst **1** in THF at 30 °C under ∼2 atm H_2 in the presence of ∼1.5 equiv of *t*-BuOK, conditions similar to those used for the catalytic hydrogenation. The ee was 35% (*R*) after 5 min and 10% (*R*) after 10 min, the alcohol was racemized after 15 min, and it was still racemic after 30 min. The racemization was somewhat faster with the amide **2** in the absence of H_2. We showed previously that the addition reaction of H_2 to the amide **2** to form the dihydride **1** is reversible, it proceeds via elimination of the Ru−H and N−H hydrogen atoms in **1**, and the reaction strongly favors **1** in THF (Scheme 2, top).[7b] Isotope exchange studies with D_2 also showed that the reversible addition proceeds via exchange between D_2 and the Ru−H and N−H_{axial} at −80 °C.[7b] Morris has also reported that the addition reaction of H_2 to *trans*-[Ru((*R*)-BINAP)-$(H)_2$(tmen)] is reversible and that this compound also reacts with excess 1-phenylethanol to generate *trans*-[Ru((*R*)-BINAP)(H)((Ph)(Me)CHO)(tmen)].[3a] We thereby propose that the racemization of CH_3(Ph)CHOH occurs by the sequence shown in Scheme 2: specifically, loss of H_2 from **1** to form **2**, followed by rapid reaction with (*R*)-CH_3(Ph)CHOH to form the alkoxide **6** (see also eq 6), and then a net β-hydride elimination to from **1** and acetophenone. The net β-hydride elimination is the reverse of the addition reaction (eq 5). As discussed below, all of these steps are rapid in the reverse direction in the presence of base. The sequence in Scheme 2 thereby provides a kinetically competent route for the racemization, with the net β-hydride elimination being the slow step in the process.

The sequence of steps in Scheme 2 predicts that a large excess of 2-PrOH would inhibit the racemization reaction by intercepting the amide **2** before it reacts with (*R*)-CH_3(Ph)CHOH. Indeed, carrying out the reaction between 10 equiv of (*R*)-CH_3-(Ph)CHOH and **1** in a 1:1 mixture of THF and 2-PrOH at 30 °C dramatically slowed the rate of racemization. The ee dropped to 84% (*R*) after 10 min but remained at this value for several hours afterward. The initial drop in ee likely resulted from racemization that occurred before complete mixing of the THF and 2-PrOH, or perhaps from local warming by the heat of mixing. These experiments show that one role of 2-PrOH during catalytic hydrogenations carried out in 2-PrOH is to inhibit racemization of the alcohol product by intercepting the amide **2** to form the 2-propoxide **4**, thereby preventing reaction between the product 1-phenylethanol and **2**.

This research is a stoichiometric study of the proposed catalytic intermediates and steps in these catalytic hydrogenations. The sum of the results from this investigation leads to the proposed pathway for the catalytic hydrogenation shown in Scheme 3. The first step is a rapid addition reaction of acetophenone to the dihydride **1** to generate the alkoxide **6** as the net product (Scheme 3 top, and eq 5). This addition

reaction is slowly reversible in THF solution, presumably by a mechanism that is the microscopic reverse of the addition reaction. In THF, the alkoxide **6** eliminates the product alcohol and forms **1** under dihydrogen (Scheme 3 right, and eq 7). On the basis of the reactivity we established previously for the related 2-propoxide **4**,[7b] and the observation of the hydrogen bond between the β-N$-$H$_{axial}$ group and O^{t}Bu in **6** (Figure), we propose that this elimination is promoted by base in THF via deprotonation of an N$-$H group in the dpen ligand, followed by displacement of the alkoxide ligand by the resulting lone pair on nitrogen to form the product alkoxide and the amide **2** (Scheme 3, second step). Either the product alkoxide reacts with the acid form of the base to generate the product alcohol, or a small of amount of the product exists as the alkoxide during the catalytic hydrogenation to act as base promoter. In THF, this elimination is reversible, and the amide **2** reacts with product alcohol to regenerate **6** (Scheme 3, second step reverse, and eq 6). The amide **2** also reacts reversibly with H_2 to generate **1**, thereby completing the catalytic cycle (Scheme 3).

As demonstrated by eq 8, the alkoxide intermediate **6** will undergo rapid exchange with 2-PrOH to generate the 2-propoxide **4** and the product CH_3(Ph)CHOH during hydrogenations carried out in 2-PrOH solvent. As discussed previously, **4** is not a catalyst for the hydrogenation in the absence of base under the conditions of our experiments (30 °C, 4 atm H_2),[7a] but it will react quickly, even at $-$80 °C, via the base-promoted elimination reaction to form the amide **2** and 2-propoxide. The amide **2** then reacts with H_2 to form **1** and complete the catalytic cycle (Scheme 3). Our experiments do not rule out the possibility that **4** or related alkoxides eliminate alcohol and generate the amide **2** under more forcing conditions in the absence of base.

Conclusion

This research provides the most direct experimental insight into the mechanisms of these hydrogenations to date. All of the steps in the proposed catalytic cycle, except the net β-hydride elimination within **6**, are rapid in the presence of base at $-$80 °C, and thereby cannot be ruled out on the basis that they are too slow to account for the reported rates for these catalytic hydrogenations.[2a,3b]

The net product of the addition reaction of acetophenone to **1** is the 1-phenylethoxide **6** (eq 5), without formation of free amide **2**. The addition reaction is rapid even at $-$80 °C. While it is possible that **2** formed trapped in a solvent cage and/or hydrogen-bonded to the CH_3(Ph)CHOH product,[3e,4d] or that ligand arm dissociation generates a vacant site on ruthenium during the addition reaction, our experiments present the possibility that the direct product of the addition reaction is the alkoxide **6**. A possible route for the direct addition reaction **6** begins with formation of the pericyclic six-membered species proposed for the bifunctional addition (eq 1). This process would remove electron density from Ru through the hydride to the carbonyl carbon. This loss of electron density may allow access to the Ru center by the ketone to undergo hydride insertion to form **6**, perhaps with hydrogen-bonding between the alkoxide ligand and the adjacent, axial N$-$H group (*vide supra*). Further kinetic, isotopic, and computational studies are required to obtain more information about the detailed workings of this step, the other steps in the proposed cycle, and their relevance to the catalytic hydrogenation.

Experimental Section

General. All operations were carried out in NMR tubes fitted with a rubber septum under an atmosphere of argon or hydrogen using standard Schlenk and glovebox techniques unless stated otherwise. All solvents were dried and distilled under a dinitrogen atmosphere using standard drying agents unless stated otherwise. Deuterated 2-PrOH was not dried. The deuterated solvents were obtained from Cambridge Isotope Laboratories. Common solvents were obtained from Fisher Scientific. Common chemicals were obtained from Aldrich. (*R*,*R*)-dpen and (*R*)-BINAP [dpen = 1,2-diphenylethylenediamine, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] were obtained from Strem. Potassium *tert*-butoxide was sublimed immediately before use. The acetophenone was distilled, washed with 0.1 M $KOH_{(aq)}$, and distilled again before use. All solids were recrystallized before use. The 1-phenylethanol (Fluka) and acetophenone-α,β-$^{13}C_2$ (Aldrich) were used without further purification. The hydrogen gas was ultra-high-purity grade purchased from Praxair. The reactions were monitored using low-temperature NMR spectroscopy. The reaction times are approximate. If an immediate color change occurred when the reactants were mixed at low temperatures, and if the first NMR spectrum recorded within 5 min of mixing showed the reaction was complete, we report the reaction time as immediate at the temperature at which the NMR spectrum was recorded. If no visible color change occurred upon mixing, and if the first NMR spectrum showed the reaction was complete, we report the reaction time as less than the time period between mixing and when the first NMR spectrum was recorded. ^{1}H, ^{13}C, and ^{31}P NMR spectra were measured using Varian-Inova (400 MHz) spectrometers. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (δ) relative to TMS with the solvent as the internal reference. ^{31}P chemical shifts are reported in parts per million (δ) relative to an 85% H_3PO_4 external reference. NMR peak assignments were made using COSY and ^{13}C$-^1$H HSQC 2D NMR experiments. Some axial and equatorial N$-$H assignments were made using NOESY NMR experiments. The N$-$H$_{axial}$ adjacent to Ru$-$H was $\sim$2 ppm upfield from the other N$-$H signals. The same observation was reported for N$-$H$_{axial}$ adjacent to Ru$-$H in a series of compounds studied by Noyori et al.[11] This observation is used to assign the N$-$H$_{axial}$ adjacent to Ru$-$H in compounds. Masses reported for compounds prepared *in situ* are relative to the initial starting material. Masses for compounds that could be weighed were measured with either a Mettler AE260 DelataRange or AND ER-60A analytical balance. The masses were allowed to stabilize for 5 min before a reading was taken. Air- and moisture-sensitive compounds were weighed in a glovebox. Liquid reagents were added via microliter syringe or 1 and 5 mL gas-tight syringes when appropriate. Stoichiometric amounts of cyclooctane, cyclooctene, KBF_4, HO ^{t}Bu and $((CH_3)_3Si)_2NH$ may be present in solution from the *in situ* preparation of the compounds. Mass spectrometric analyses of organometallic compounds were performed by positive-mode electrospray ionization (ESI-MS (pos)) on a Micromass ZabSpec Hybrid Sector-TOF spectrometer. Calculated *m*/*z* values refer to the isotopes ^{12}C, ^{1}H, ^{14}N, ^{16}O, ^{31}P, and ^{102}Ru. Gas chromatography was performed using a Hewlett-Packard 5890 chromatograph equipped with a flame ionization detector, a 3392A integrator, and a Beta Dex 120 fused silica capillary column (30 m $\times$ 0.25 mm $\times$ 0.25 μm thickness, Supelco) using 20.5 psi He as carrier gas. The standard conditions used to determine the ee of 1-phenylethanol were as follow: initial oven temperature, 70 °C; increased at 1 °C/min to 120 °C; held at 120 °C for 10 min. The retention times were as follow: (*R*)-(+)-1-phenylethanol, $t_R(R)$ = 43.5 min; (*S*)-(−)-1-phenylethanol, $t_R(S)$ = 45.6 min; acetophenone, t_R = 29.9 min. The ee measurements were confirmed against (±)-1-phenylethanol.

Typical Preparation of *trans*-[Ru((*R*)-BINAP)(H)$_2$((*R*,*R*)-dpen)] (1) in THF-d_8. A solution of *trans*-[Ru((*R*)-BINAP)(H)(η^2-H$_2$)((*R*,*R*)-dpen)]BF_4 (9.2 mg, 8.72 $\times$ 10^{-3} mmol) in THF-d_8 (0.7 mL) was prepared under H_2 ($\sim$2 atm) as we described previously[7a]

and kept at −80 °C. The *trans*-[Ru((*R*)-BINAP)(H)(η^2-H_2)((*R*,*R*)-dpen)]BF_4 solution was then quickly canulated using H_2 pressure into a tube containing potassium *tert*-butoxide (2.45 equiv, 2.4 mg, 2.14×10^{-2} mmol) and kept at −80 °C. The pressure of H_2 was replenished after the transfer by injecting 10 mL of H_2 into the tube using a gas-tight syringe. The contents of the tube were then thoroughly mixed by shaking the tube for 10 s outside the −80 °C bath and then returned to the bath. The process was repeated four times in order to mix the contents while maintaining the temperature near −80 °C. A color change from orange to red occurred during the first shake. NMR spectra recorded at −80 °C after ∼5 min showed that the reaction was complete and formed **1** as the sole detectable product.

Typical Preparation of [Ru((*R*)-BINAP)(H)((*R*,*R*)-NH(CH(Ph))$_2$NH$_2$)] (2). A solution of *trans*-[Ru((*R*)-BINAP)(H)(THF-d_8)((*R*,*R*)-dpen)]BF_4 (9.7 mg, 8.72×10^{-3} mmol) in THF-d_8 (0.7 mL) was prepared as we described previously[7b] and kept at −80 °C. The *trans*-[Ru((*R*)-BINAP)(H)(THF-d_8)((*R*,*R*)-dpen)]BF_4 solution was quickly canulated using argon pressure into a tube containing $((CH_3)_3Si)_2NK$ (2.47 equiv, 4.3 mg, 2.16×10^{-2} mmol) and kept at −80. The tube was shaken for 1 s and then returned to the bath. The process was repeated four times in order to mix the contents while maintaining the temperature near −80 °C. A color change from orange to deep red occurred during the first shake. NMR spectra recorded at −80 °C after ∼5 min showed that the reaction was complete and formed two diasteromers of **2** in an approximately 8:2 ratio.

Reaction of 1 with Acetophenone in the Presence of ∼1.5 equiv of Excess Potassium *tert*-Butoxide. A solution **1** (7.6 mg, 7.97×10^{-3} mmol) was prepared in THF-d_8 (0.7 mL) as described above using potassium *tert*-butoxide (2.46 equiv, 2.2 mg, 1.96×10^{-2} mmol) as added base and kept at −80 °C. Acetophenone (1 μL, 1.1 equiv, 1 mg, 8.5×10^{-3} mmol) was injected into the tube containing **1**. The tube was shaken for 1 s and then returned to the bath to mix the contents while maintaining the temperature near −80 °C. NMR spectra recorded at −80 °C after ∼1 min showed that the reaction was complete and formed *trans*-[Ru((*R*)-BINAP)(H)(PhCH(CH_3)O)((*R*,*R*)-(NH_2(CH(Ph))$_2$NH···H···$^-$O-*t*-Bu)] (**6**) as the sole detectable product. ^{1}H NMR (399.95 MHz, THF-d_8, −80 °C): δ −16.4 (1H, t, $^2J_{P-H}$ = 24.0 Hz, Ru−H), 1.3 (1H, PhCH(CH_3)O−Ru, partially obscured), 2.12 (1H, br, C_aH-NH_{axial}H), 3.3 (1H, br, C_bHN*H*H), 4.0 (1H, br, C_b*H*NHH), 4.3 (1H, multiplet, C_a*H*NHH, overlapping with C_bHNH*H*), 4.4 (1H, multiplet, C_bHNH*H*, overlapping with C_a*H*NHH), 4.6 (1H, br, C_aH-NH$H_{equatorial}$), 4.96 (1H, br, PhC *H*(CH_3)O−Ru), 6−10 (overlapping multiplets, aromatic). ^{13}C{^{1}H} NMR (100.6 MHz, THF-d_8, −80 °C): δ 28.0 (PhCH(*C*H_3)O−Ru), 63.0 (C_aHNHH), 69.0 (Ph*C*H(CH_3)O−Ru), 71.1 (C_bHNHH), 123−141 (aromatic). ^{31}P{^{1}H} NMR (161.88 MHz, THF-d_8, −80 °C): δ 68.44 (d, $^2J_{P-P}$ = 40.5 Hz), 73.68 (d, $^2J_{P-P}$ = 40.5 Hz). LRMS (ESI): *m*/*z* calcd for $C_{66}H_{57}N_2OP_2{}^{102}$Ru ([M − 1]$^+$), 1057.3; found, 1057.3.

Reaction of 1 with Acetophenone in the Absence of Excess Potassium *tert*-Butoxide. A solution of *trans*-[Ru((*R*)-BINAP)(H)(η^2-H_2)((*R*,*R*)-dpen)]BF_4 (8.2 mg, 7.96×10^{-3} mmol) in THF-d_8 (0.7 mL) was prepared under H_2 (∼2 atm) as we described previously[7a] and kept at −80 °C. The *trans*-[Ru((*R*)-BINAP)(H)(η^2-H_2)((*R*,*R*)-dpen)]BF_4 solution was then quickly canulated using H_2 pressure into a tube containing potassium *tert*-butoxide (1.23 equiv, 1.1 mg, 9.8×10^{-3} mmol) and kept at −80 °C. The pressure of H_2 was replenished after the transfer by injecting 10 mL of H_2 into the tube using a gas-tight syringe. The contents of the tube were then thoroughly mixed by shaking the tube for 10 s outside the −80 °C bath and then returned to the bath. The process was repeated four times in order to mix the contents while maintaining the temperature near −80 °C. A color change from yellow to orange occurred during the first shake. NMR spectra recorded at −80 °C after ∼5 min showed 70% conversion to **1**. The remaining 30% was *trans*-[Ru((*R*)-BINAP)(H)(OH)((*R*,*R*)-dpen)], indicating the absence of excess base.[7b] Acetophenone (0.6 μL, ∼1 equiv relative to **1**, 0.62 mg, 5.1×10^{-3} mmol) was injected into the tube containing **1**. The tube was shaken for 1 s and then returned to the bath to mix the contents while maintaining the temperature near −80 °C. NMR spectra recorded at −80 °C after ∼1 min showed that **1** reacted with acetophenone to form *trans*-[Ru((*R*)-BINAP)(H)(PhCH(CH_3)O)((*R*,*R*)-dpen)] (**6′**). ^{1}H NMR (399.95 MHz, THF-d_8, −80 °C): δ −16.43 (1H, t, $^2J_{P-H}$ = 22.0 Hz, Ru−H), 1.22 (1H, PhCH(CH_3)O−Ru, partially obscured), 2.12 (1H, br, C_aHNH_{axial}H), 3.6 (1H, br, C_bHN*H*H), 4.05 (1H, br, C_b*H*NHH), 4.28 (1H, multiplet, C_a*H*NHH, overlapping with C_bHNH*H*), 4.45 (1H, multiplet, C_bHNH*H*, overlapping with C_a*H*NHH), 4.6 (1H, br, C_aH-NH$H_{equatorial}$), 5.05 (1H, br, PhC*H*(CH_3)O−Ru), 6−10 (overlapping multiplets, aromatic). ^{13}C{^{1}H} NMR (100.6 MHz, THF-d_8, −80 °C): δ 30.1 (PhCH(*C*H_3)O−Ru), 63.1 (C_aHNHH), 70.0 (Ph*C*H(CH_3)O−Ru), 70.2 (C_bHNHH), 123−141 (aromatic). ^{31}P{^{1}H} NMR (161.88 MHz, THF-d_8, −80 °C): δ 68.4 (d, $^2J_{P-P}$ = 38.86 Hz), 73.66 (d, $^2J_{P-P}$ = 38.86 Hz).

Reaction of 1 with Acetophenone-α,β-$^{13}C_2$ in the Presence of ∼1.5 equiv of Excess Potassium *tert*-Butoxide. A solution of **1** (7.3 mg, 7.95×10^{-3} mmol) was prepared in THF-d_8 (0.7 mL) as described above using potassium *tert*-butoxide (2.5 equiv, 2.2 mg, 1.96×10^{-2} mmol) as added base and kept at −80 °C. Acetophenone-α,β-$^{13}C_2$ (0.9 μL, 0.97 equiv, 0.94 mg, 7.7×10^{-3} mmol) was injected into the tube containing **1**. The tube was shaken for 1 s and then returned to the bath to mix the contents while maintaining the temperature near −80 °C. NMR spectra recorded at −80 °C after ∼1 min showed that the reaction was complete and formed *trans*-[Ru((*R*)-BINAP)(H)(Ph^{13}CH(^{13}CH$_3$)O((*R*,*R*)-(NH_2(CH(Ph))$_2$NH···H···$^-$O- *t*-Bu)] (**6″**) as the sole detectable product. LRMS (ESI): *m*/*z* calcd for $C_{64}{}^{13}C_2H_{56}N_2OP_2{}^{102}$Ru ([M − 2]$^+$), 1058.3; found, 1058.3.

Reaction of 2 with (±)-1-Phenylethanol To Form 6. A solution of **2** (8.4 mg, 8.97×10^{-3} mmol) was prepared in THF-d_8 (0.7 mL) as described above using $((CH_3)_3Si)_2NK$ (2.46 equiv, 4.4 mg, 2.20×10^{-2} mmol) as added base and kept at −80 °C. (±)-1-Phenylethanol (1.1 μL 1.01 equiv, 1.1 mg, 9.0×10^{-3} mmol) was injected into the tube containing **2**. The tube was shaken for 1 s and then returned to the bath to mix the contents while maintaining the temperature near −80 °C. NMR spectra recorded at −80 °C after ∼1 min showed that the reaction was complete and formed **6** as the sole detectable product.

Reaction of 6 with 2-PrOH To Form *trans*-[Ru((*R*)-BINAP)(H)(2-PrO)((*R*,*R*)-dpen)] (4). Method a: A solution of **6** (8.5 mg, 8.0×10^{-3} mmol) was prepared in THF-d_8 (0.7 mL) as described above using potassium *tert*-butoxide (2.6 equiv, 2.3 mg, 2.05×10^{-2} mmol) as added base and kept at −80 °C. 2-Propanol (48.7 equiv, 23.5 mg, 30 μL, 0.39 mmol) was injected into the tube containing **6**. The tube was shaken for 1 s, frozen in $N_{2(l)}$, and then thawed in the NMR probe at −80 °C. The first spectra upon thawing showed complete conversion to **4**. Method b: A solution of **6** (8.5 mg, 7.8×10^{-2} mmol) was prepared in THF-d_8 (0.7 mL) as described above and kept at −80 °C. 2-Propanol (9.75 equiv, 4.7 mg, 6 μL, 0.39 mmol) was injected into the tube containing **6**. The tube was shaken for 1 s, frozen in $N_{2(l)}$, and thawed in the NMR probe at −80 °C. The first spectra upon thawing showed complete conversion to **4**.

Reaction of 1 with Acetophenone in the Presence of 2-PrOH-d_8. A solution of **1** (7.5 mg, 8.00×10^{-3} mmol) was prepared in THF-d_8 (0.7 mL) as described above using potassium *tert*-butoxide (2.6 equiv, 2.3 mg, 2.05×10^{-2} mmol) as added base and then frozen in $N_{2(l)}$. Acetophenone (2 equiv, 1.9 μL, 1.95 mg, 1.62×10^{-3} mmol) was dissolved in 2-PrOH (0.1 mL) in a NMR tube under argon and cooled to −80 °C. The acetophenone solution was then canulated using H_2 pressure onto the frozen solution of **1** to form a frozen layer on top of the frozen layer of **1**. The sample was then thawed in the NMR probe at −80 °C. The first spectra upon thawing showed conversion to **6** and that approximately 5 equiv of 2-PrOH had diffused into the THF-d_8.

Reaction of 1 with Acetophenone in the Presence of 5 equiv of 2-PrOH. A solution of **1**(7.7 mg, 8.06×10^{-3} mmol) was prepared in THF-d_8 (0.7 mL) as described above using potassium *tert*-butoxide (2.5 equiv, 2.3 mg, 2.05×10^{-2} mmol) as added base and kept at −80 °C. 2-PrOH (5 equiv, 3 μL, 2.4 mg, 3.99×10^{-2} mmol) was injected into the tube containing **1**. The mixture was shaken for 1 s and frozen in $N_{2(l)}$ to prevent the reaction of **1** with 2-PrOH to form **4**. The sample was then thawed in the NMR probe at −80 °C. NMR spectra at −80 °C did not show detectable amounts of **4**. The sample was frozen in $N_{2(l)}$ immediately upon removal from the NMR to ensure that **1** remained in solution. Acetophenone (1.06 equiv, 1 μL, 1 mg, 8.5×10^{-3} mmol) was dissolved in THF-d_8 (0.1 mL) in a NMR tube under argon and cooled to −80 °C. The acetophenone solution was then canulated using H_2 pressure into the tube containing **1** to form a frozen layer on top of the frozen layer of **1**. The sample was then thawed in the NMR probe at −80 °C. The first spectra upon thawing showed complete conversion of acetophenone into **6**.

Reaction of 1 with Acetophenone in the Presence of 10 equiv of 2-PrOH and Excess Base. A solution of **1** (7.7 mg, 8.06 $\times 10^{-3}$ mmol) was prepared in THF-d_8 (0.7 mL) as described above using potassium *tert*-butoxide (2.5 equiv, 2.3 mg, 2.05×10^{-2} mmol) as added base and kept at −80 °C. 2-PrOH (10 equiv, 6 μL, 2.4 mg, 8.0×10^{-2} mmol) was injected into the tube containing **1**. The mixture was shaken for 1 s and frozen in $N_{2(l)}$ to prevent the reaction of **1** with 2-PrOH to form **4**. The sample was then thawed in the NMR probe at −80 °C. NMR spectra at −80 °C showed that approximately 10% of **1** had converted to **4**. The sample was frozen in $N_{2(l)}$ immediately upon removal from the NMR to ensure that **1** remained in solution. Acetophenone (1.06 equiv, 1 μL, 1 mg, 8.5×10^{-3} mmol) was dissolved in THF-d_8 (0.1 mL) in a NMR tube under argon and cooled to −80 °C. The acetophenone solution was then canulated using H_2 pressure into the tube containing **1** and **4** to form a frozen layer on top of the frozen layer of **1** and **4**. The sample was then thawed in the NMR probe at −80 °C. The first spectra upon thawing showed conversion to **4** with no detectable amounts of **6**.

Reaction of 1 with Acetophenone in the Presence of 10 equiv of 2-PrOH in the Absence of Excess Base. A solution of *trans*-[Ru((*R*)-BINAP)(H)(η^2-H_2)((*R*,*R*)-dpen)]BF_4 (8.3 mg, 8.06×10^{-3} mmol) in THF-d_8 (0.7 mL) was prepared under H_2 (∼2 atm) as we described previously[7a] and kept at −80 °C. The *trans*-[Ru((*R*)-BINAP)(H)(η^2-H_2)((*R*,*R*)-dpen)]BF_4 solution was then quickly canulated using H_2 pressure into a tube containing potassium *tert*-butoxide (1.1 equiv, 1 mg, 8.91×10^{-3} mmol) and kept at −80 °C. The pressure of H_2 was replenished after the transfer by injecting 10 mL of H_2 into the tube using a gas-tight syringe. The contents of the tube were then thoroughly mixed by shaking the tube for 10 s outside the −80 °C bath and then returned to the bath. The process was repeated four times in order to mix the contents while maintaining the temperature near −80 °C. A color change from yellow to orange occurred during the first shake. NMR spectra recorded at −80 °C after ∼5 min showed ∼50% conversion to **1**. The remaining 50% was *trans*-[Ru((*R*)-BINAP)(H)(OH)((*R*,*R*)-dpen)], indicating the absence of excess base.[7b] 2-PrOH (∼10 equiv relative to **1**, 3 μL, 2.4 mg, 3.99×10^{-2} mmol) was injected into the tube containing **1**. The mixture was shaken for 1 s and frozen in $N_{2(l)}$ to prevent the reaction of **1** with 2-PrOH to form **4**. The sample was then thawed in the NMR probe at −80 °C. Approximately 5% of **1** had converted to **4**. The sample was frozen in $N_{2(l)}$ immediately upon removal from the NMR to ensure that **1** remained in solution. Acetophenone (0.5 μL, ∼1 equiv relative to **1**, 0.5 mg, 4.2×10^{-3} mmol) was dissolved in THF-d_8 (0.1 mL) in a NMR tube under argon and cooled to −80 °C. The acetophenone solution was then canulated using H_2 pressure into the tube containing **1** and **4** to form a frozen layer on top of the frozen layer of **1** and **4**. The sample was then thawed in the NMR probe at −80 °C. The first spectra upon thawing showed conversion to **4** with approximately 5% of **6**. Complex **6** reacted with 2-PrOH to form **4** within 5 min.

Competition Reaction of 2 with 1 equiv of (±)-1-Phenylethanol and 5 equiv of 2-PrOH. A solution of **2** (8.4 mg, 8.97×10^{-3} mmol) was prepared in THF-d_8 (0.7 mL) as described above using $((CH_3)_3Si)_2NK$ (2.46 equiv, 4.4 mg, 2.20×10^{-2} mmol) as added base and kept at −80 °C. (±)-1-Phenylethanol (0.93 equiv, 1 μL, 1.01 mg, 8.3×10^{-3} mmol) and 2-PrOH (4.3 equiv, 3 μL, 2.4 mg, 3.9×10^{-2} mmol) were injected into the tube containing **2**, shaken for 1 s outside the bath, and immediately placed in the NMR probe at −80 °C. The first spectra upon thawing showed a 1:1 mixture of **6** and **4**.

Reaction of 1 with Acetophenone Followed by the Addition of a Large Excess of 2-PrOH. A solution of **1** (5.7 mg, 5.99×10^{-3} mmol) was prepared in THF (0.7 mL) as described above using potassium *tert*-butoxide (2.5 equiv, 1.7 mg, 1.51×10^{-2} mmol) and kept at −80 °C. Acetophenone (1 equiv, 0.7 mg, 0.70 μL, 5.99×10^{-3} mmol) was injected into the tube containing **1** and shaken briefly (∼ 1 s) at room temperature, and then 2-PrOH (0.7 mL) was added to halt the reaction. The reaction mixture was then emptied into a vial containing EtOH and passed through a small column of Florosil to remove catalyst residues using EtOH as eluent. Gas chromatography showed that there was ∼50% conversion to 1-phenylethanol with an ee of 83% (*S*).

Reaction of 1 with (*R*)-(+)-1-Phenylethanol. Method a: A solution of **1** (5.7 mg, 5.99×10^{-3} mmol) was prepared in THF (0.7 mL) as described above using potassium *tert*-butoxide (2.5 equiv, 1.7 mg, 1.51×10^{-2} mmol) and kept at −80 °C. (*R*)-(+)-1-Phenylethanol (10 equiv, 7.0 μL, 7.2 mg, 5.99×10^{-2} mmol) was injected into the tube containing **1**, shaken outside the bath for 5 s, and immersed in a room-temperature (21 °C) bath. Aliquots (∼0.05 mL) were taken into a vial containing EtOH and passed through a small column of Florosil to remove catalyst residues using EtOH as eluent. Gas chromatography showed that the ee had dropped to 61% (*R*) after 5 min and to 4% (*R*) after 35 min. Method b: A solution of **1** (5.7 mg, 5.99 $\times 10^{-3}$ mmol) was prepared in THF (0.7 mL) as described above using potassium *tert*-butoxide (2.5 equiv, 1.7 mg, 1.51×10^{-2} mmol) and kept at −80 °C. (*R*)-(+)-1-Phenylethanol (10 equiv, 7.0 μL, 7.2 mg, 5.99×10^{-2} mmol) was injected into the tube containing **1**, shaken outside the bath for 5 s, and immersed in 30 °C bath. Aliquots (∼0.05 mL) were taken into a vial containing EtOH and passed through a small column of Florosil to remove catalyst residues using EtOH as eluent. Gas chromatography showed that the ee had dropped to 35% (*R*) after 5 min and was racemic after 15 min. 1-Phenylethanol was still racemic after 30 min. Method c: A solution of **1** (5.7 mg, 5.99 $\times 10^{-3}$ mmol) was prepared in THF (0.35 mL) as described above using potassium *tert*-butoxide (2.5 equiv, 1.7 mg, 1.51×10^{-2} mmol) and kept at −80 °C. (*R*)-(+)-1-Phenylethanol (10 equiv, 7.0 μL, 7.2 mg, 5.99×10^{-2} mmol) was dissolved in 2-PrOH (0.35 mL), cooled to −80 °C, canulated using H_2 pressure into the tube containing **1**, shaken outside the bath for 5 s, and then immersed in a 30 °C bath. Aliquots (∼0.05 mL) were taken into a vial containing EtOH and passed through a small column of Florosil to remove catalyst residues using EtOH as eluent. Gas chromatography showed that the ee had dropped to 84% (*R*) after 10 min. An aliquot taken after 230 min showed that the ee dropped to 66% (*R*).

Reaction of 2 with (*R*)-(+)-1-Phenylethanol. A solution of **2** (5.7 mg, 5.99×10^{-3} mmol) was prepared in THF (0.7 mL) as described above using $((CH_3)_3Si)_2NK$ (2.5 equiv, 3.0 mg, 1.50 $\times 10^{-2}$ mmol) as added base and kept at −80 °C. (*R*)-(+)-1-Phenylethanol (10 equiv, 7.0 μL, 7.2 mg, 5.99×10^{-2} mmol) was added to the tube containing **2**, shaken outside the bath for 5 s, and then immersed in a 30 °C bath. Aliquots (∼0.05 mL) were taken into a vial containing EtOH and passed through a small column of Florosil to remove catalyst residues using EtOH

as eluent. Gas chromatography showed that the ee had dropped to 14% (*R*) after 5 min and was racemic after 10 min.

Hydrogenation of Acetophenone Using 1 as Catalyst. A solution of **1** (11.4 mg, 1.19×10^{-2} mmol) was prepared in THF (0.7 mL) as described above using potassium *tert*-butoxide (∼2.5 equiv, 3.4 mg, 3.0×10^{-2} mmol) as added base, diluted to 2 mL with THF, and kept at −80 °C. A glass pressure reactor equipped with a magnetic stir bar was fitted with a rubber septum, charged with acetophenone (1.44 g, 1.2×10^{-2} mol, 1000 equiv) in dry, distilled THF (4.8 mL), and then flushed with H_2. Hydrogen gas was bubbled through the solution with stirring for 1 min, and then the solution of **1** was canulated using H_2 pressure into the glass pressure reactor (total THF, 6.8 mL). The septum was replaced with a high-pressure fitting, and the reactor was pressurized to 44 psi (gauge). The mixture was rapidly stirred at 30 °C. Aliquots were taken by first depressurizing the reactor to ∼1.5 atm, removing an aliquot (∼0.1 mL) into a vial containing EtOH, and then repressurizing the reactor to 44 psi. All aliquots were passed through a small column of Florosil to remove catalyst residues using EtOH as eluent. Gas chromatography showed that there were ∼6 turnovers with 69% ee (*S*) after 18 min, ∼22 turnovers with 66% ee (*S*) after 49 min, and ∼94 turnovers with 59% ee (*S*) after 97 min. An aliquot taken at 1198 min indicated that the reaction was complete with 53% ee (*S*). The ee dropped to 47% (*S*) after an additional 428 min under H_2 pressure (44 psi guage).

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Supporting Information Available: NMR spectra of the alkoxide **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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