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J. Am. Chem. Soc., **2005**, 127 (6), 1883-1894• DOI: 10.1021/ja044450t • Publication Date (Web): 20 January 2005

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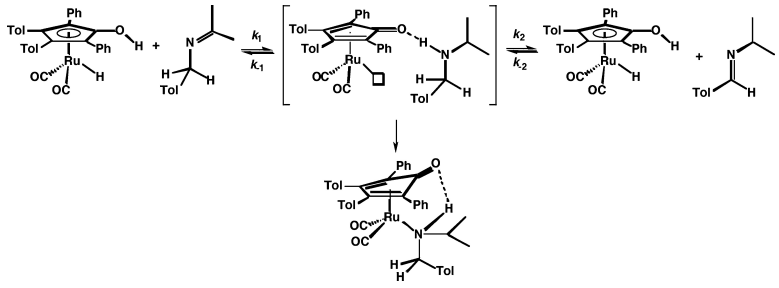

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Isomerization and Deuterium Scrambling Evidence for a Change in the Rate-Limiting Step during Imine Hydrogenation by Shvo's Hydroxycyclopentadienyl Ruthenium Hydride

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Abstract: Hydroxycyclopentadienyl ruthenium hydride **5** efficiently reduces imines below room temperature. Better donor substituents on nitrogen give rise to faster rates and a shift of the rate-determining step from hydrogen transfer to amine coordination. Reduction of electron-deficient *N*-benzilidenepentafluoroaniline (**8**) at 11 °C resulted in free amine and kinetic isotope effects of $k_{OH}/k_{OD} = 1.61 \pm 0.08$, $k_{RuH}/k_{RuD} = 2.05 \pm 0.08$, and $k_{RuHOH}/k_{RuDOD} = 3.32 \pm 0.14$, indicative of rate-limiting concerted hydrogen transfer, a mechanism analogous to that proposed for aldehyde and ketone reduction. Reduction of electron-rich *N*-alkyl-substituted imine, *N*-isopropyl-(4-methyl)benzilidene amine (**9**), was accompanied by facile imine isomerization and scrambling of deuterium labels from reduction with **5**−**RuDOH** into the *N*-alkyl substituent of both the amine complex and into the recovered imine. Inverse equilibrium isotope effects were observed in the reduction of *N*-benzilidene-*tert*-butylamine (**11**) at −48 °C ($k_{OH}/k_{OD} = 0.89 \pm 0.06$, $k_{RuH}/k_{RuD} = 0.64 \pm 0.05$, and $k_{RuHOH}/k_{RuDOD} = 0.56 \pm 0.05$). These results are consistent with a mechanism involving reversible hydrogen transfer followed by rate-limiting amine coordination.

Introduction

The emergence of ligand−metal bifunctional catalysts over the past two decades has revolutionized hydrogenation chemistry. These new catalysts contain electronically coupled acidic and hydridic hydrogens which work in concert to efficiently reduce polar unsaturated compounds under mild conditions. Noyori has led the way in the development of this class of catalysts.[1] His ruthenium(diamine)(BINAP) catalyst (**1**) has displayed extraordinary activity and selectivity in the asymmetric reduction of ketones (Figure 1).[2] Other catalysts having electronically coupled acidic and hydridic hydrogens have been reported by Ikariya,[3] Morris,[4] and others.[5] The first reported bifunctional catalyst was Shvo's hydroxycyclopentadienyl bridging diruthenium hydride (**2**).[6] The majority of our mechanistic studies of bifunctional catalysts have centered on tolyl derivatives of **3**, the active reducing agent in the Shvo system. These new bifunctional catalysts provide attractive alternatives to stoichiometric $NaBH_4$ and $LiAlH_4$ reductions.

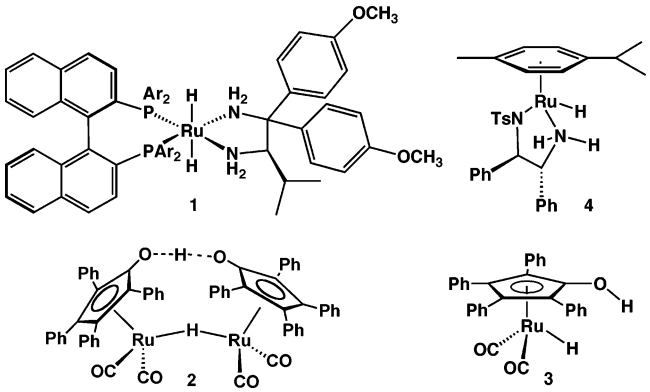

Figure 1. Metal−ligand bifunctional hydrogenation catalysts.

Mechanistic experiments and theoretical calculations are leading to a better understanding of the reduction of carbonyl species with these catalysts. Our group's detailed mechanistic studies employing kinetics and isotope effects have established concerted reduction mechanisms for both Noyori's ruthenium(arene)diamine (**4**) and the tolyl derivative of Shvo's hydroxycyclopentadienyl ruthenium system (**5**) (Figure 1).[7,8] In the concerted mechanism, both the acidic and hydridic hydrogens are simultaneously transferred to the substrate outside the coordination sphere of the metal (Scheme 1). Noyori has provided theoretical support for this type of concerted hydrogen

(1) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (b) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931.
(2) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40.
(3) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1199. (b) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1201. (c) Ito, M.; Hirakawa, M.; Murata, K.; Ikariya, T. *Organometallics* **2001**, *20*, 379.
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(5) Mao, J.; Baker, D. C. *Org. Lett.* **1999**, *1*, 841.
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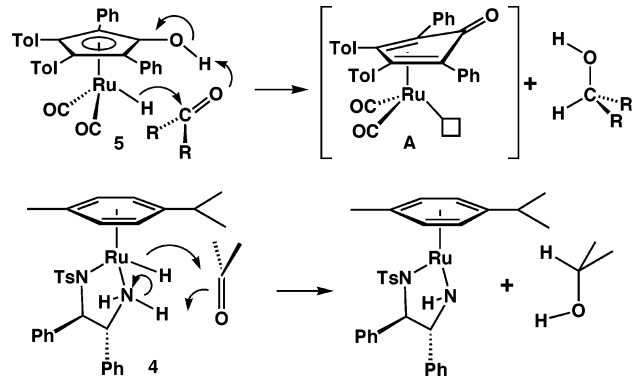
(7) Casey, C. P.; Singer, S. W.; Powell, D. R.; Hayashi, R. K.; Kavana, M. *J. Am. Chem. Soc.* **2001**, *123*, 1090.
(8) Casey, C. P.; Johnson, J. B. *J. Org. Chem.* **2003**, *68*, 1998.

Scheme 1



transfer from his ruthenium(diamine)(BINAP) catalyst to carbonyl compounds.[9]

While the development of new catalysts for ketone and aldehyde reduction is an area of intense study, the study of catalytic imine hydrogenation has lagged behind. Bäckvall used Shvo's hydroxycyclopentadienyl system for the transfer hydrogenation of imines using 2-propanol as the terminal reductant.[10] Asymmetric imine reduction to form chiral amines has met with only limited success. Noyori's ruthenium(arene)diamine system,[11] as well as a rhodium(III) analog published by Baker,[5] has achieved good yields and enantioselectivities utilizing a formic acid/triethylamine solvent system for the transfer hydrogenation of imines.

A detailed study probing the mechanism of imine reduction in these systems is currently lacking. Although one might expect similarities of imine reduction to the well studied carbonyl reduction, there are several factors which might lead to differences in the hydrogen transfer mechanism. The greater basicity of an imine, compared with that of a carbonyl compound, would be expected to influence the transfer of the acidic proton. In addition, the nucleophilicity of the imine or resulting amine may result in coordination issues not displayed during reduction of carbonyls.

Here, we report detailed mechanistic studies of the reduction of a series of imines with different electronic properties. A shift in the rate-determining step was seen as a function of the imine basicity. For imines with electron-withdrawing substituents on nitrogen, significant kinetic isotope effects were observed for concerted transfer of hydride and proton from **5** to the imine. For imines with electron-donating alkyl substituents on nitrogen, we observed imine isomerization, deuterium exchange, and inverse equilibrium isotope effects that established a mechanism involving reversible hydrogen transfer to the imine followed by rate-determining coordination of the amine to ruthenium.

Results

Shvo's catalyst **2** has been reported to catalytically hydrogenate imines and carbonyls at 145 °C under 500 psi of hydrogen.[6] Under typical reaction conditions, the tolyl analogue of **2**, diruthenium hydride **6**, behaves similarly to the parent compound. Dimer **6** dissociates into ruthenium hydride monomer **5**−**RuHOH**, the active reducing species, and a proposed unsaturated species **A**, which quickly reacts with hydrogen to form additional ruthenium hydride monomers or reacts with the hydride monomer to form the bridging diruthenium hydride (Scheme 2).

To better understand the hydrogenation of imines catalyzed by diruthenium catalyst **6**, we studied the stoichiometric reactions of imines with monomeric ruthenium hydride **5**−**RuHOH**, the active reducing agent in the Shvo system. At the low temperatures necessary for convenient monitoring by ^{1}H NMR spectroscopy, the products of most imine reductions are ruthenium amine complexes resulting from coordination of the newly formed amine with the proposed unsaturated ruthenium intermediate formed upon transfer of hydrogen (Scheme 3).

To determine whether the structure of the imine affects the mechanism of imine hydrogenation, kinetic and deuterium isotope effect measurements were carried out on a range of imines from electron-rich alkyl imines to electron-deficient N−C_6F_5-substituted imines. The imines studied include *N*-benzilideneaniline (**7**), *N*-benzilidenepentaflouroaniline (**8**), *N*-isopropyl-(4-methyl)benzylideneamine (**9**), *N*-benzilidene-benzylamine (**10**), and *N*-benzylidine-*tert*-butylamine (**11**) (Figure 2).

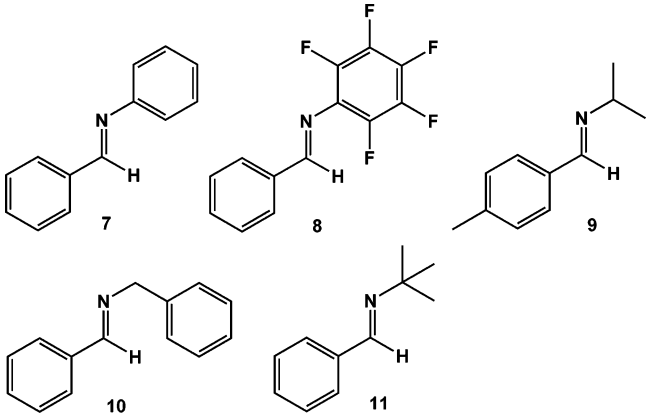


Figure 2. Imines utilized in mechanistic study.

Reduction of imines **7**, **9**, **10**, and **11** by ruthenium hydride **5**−**RuHOH** led to the formation of the corresponding ruthenium amine complexes (Figure 3). The stability of these ruthenium amine complexes depends on the basicity and steric requirements of the complexed amine. While alkylamine complexes **13** and **14** are stable to about 80 °C, the complex of less basic arylamine **12** is stable only to about 50 °C. The complex of the very bulky *tert*-butylamine **15** decomposed above 0 °C. The very nonbasic

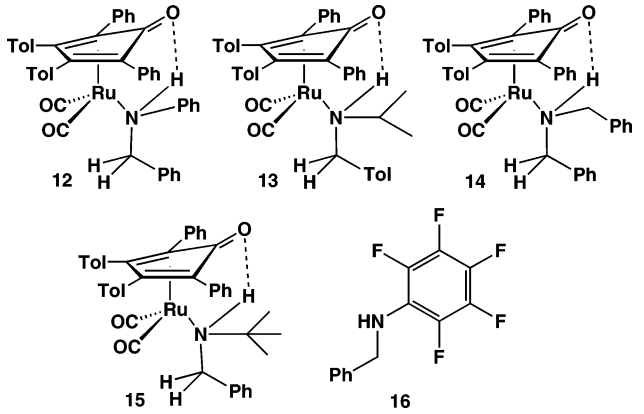


Figure 3. Products formed upon reduction of imines by **5**−**RuHOH**.

(9) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466.
(10) Samec, J. S. M.; Bäckvall, J.-E. *Chem.*−*Eur. J.* **2002**, *8*, 2955.
(11) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916.

Scheme 2

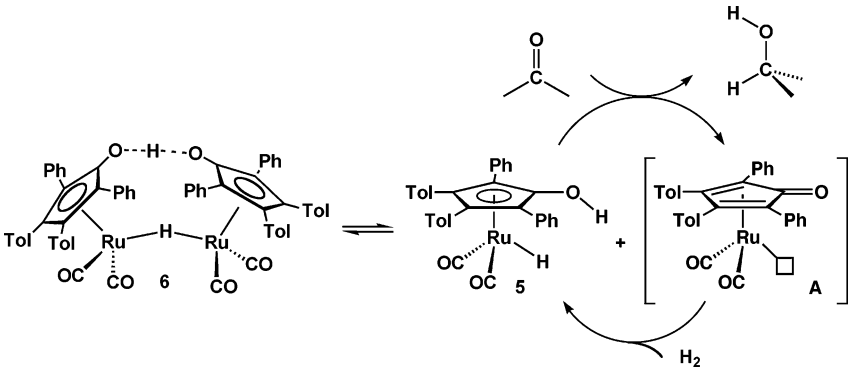
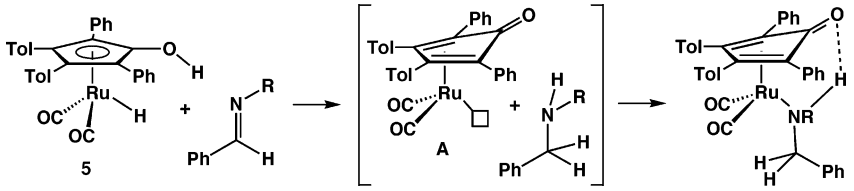


Table 1. Observed Isotope Effects for Reduction of Imines with Isotopologs of **5**

	R = Ph, **7**	R = C_6F_5, **8**	R = *i*-Pr, **9**	R = *t*-Bu, **11**	R = Bn, **10**
k_{RuHOH}/k_{RuHOD}	1.30 ± 0.13	1.57 ± 0.07	0.92 ± 0.09	0.90 ± 0.07	
k_{RuDOH}/k_{RuDOD}	1.31 ± 0.12	1.66 ± 0.08	0.91 ± 0.07	0.88 ± 0.06	
k_{RuHOH}/k_{RuDOH}	1.23 ± 0.12	1.99 ± 0.13	1.03 ± 0.08[a]	0.64 ± 0.05	
k_{RuHOD}/k_{RuDOD}	1.24 ± 0.12	2.11 ± 0.04	1.02 ± 0.07[a]	0.63 ± 0.04	
k_{RuHOH}/k_{RuDOD}	1.60 ± 0.17	3.32 ± 0.14	0.94 ± 0.08[a]	0.56 ± 0.05	1.05 ± 0.05[a]

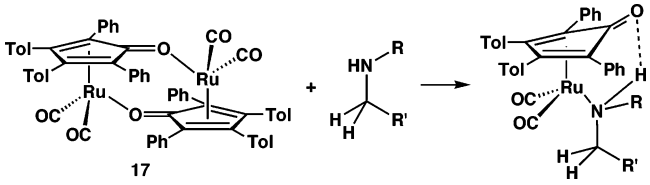
[a] Isotope effects attenuated due to exchange of hydrogen into RuD.

Scheme 3



C_6F_5-substituted amine **16** failed to form an observable amine complex. The amine complexes were also synthesized by reaction of the amines with the cyclopentadienone dimer **17** and were fully characterized (Scheme 4).

Scheme 4



***N*-Benzilideneaniline (7)** was reduced cleanly to **12** by **5**−**RuHOH** in THF-d_8. The rate of reduction of **7** by **5**−**RuHOH** was monitored by ^{1}H NMR spectroscopy at −38 °C under pseudo-first-order conditions, employing a large excess of imine (0.125−0.216 M, 15−20 equiv) and **5**−**RuHOH** concentrations between 0.0106 and 0.0147 M. The first-order disappearance of **5**−**RuHOH** resonances [δ −9.73 (hydride), δ 6.83 (arene)] and the appearance of ruthenium amine complex **12** resonances [δ 6.69 (arene), δ 7.85 (arene)] were monitored over three half-lives. A first-order dependence on ruthenium hydride was indicated by an excellent nonlinear least-squares fit. A linear dependence of the rates on imine concentration between 0.125 and 0.216 M was seen. These experiments established a second-order rate law with $k_7 = (7.02 \pm 0.52) \times 10^{-3}$ M^{-1} s^{-1} (eq 1).[12]

$$-\frac{d[\mathbf{5}]}{dt} = k_7[\mathbf{5}][\mathbf{7}] \qquad (1)$$

Activation parameters for the reduction of *N*-benzilideneaniline were determined from rate constants measured between −48 and −27 °C: $k_7 = 15.7 \times 10^{-3}$ M^{-1} s^{-1} at −27 °C; $k_7 = 10.1 \times 10^{-3}$ M^{-1} s^{-1} at −32 °C; $k_7 = 6.67 \times 10^{-3}$ M^{-1} s^{-1} at −37 °C; $k_7 = 4.45 \times 10^{-3}$ M^{-1} s^{-1} at −41 °C; $k_7 = 2.56 \times 10^{-3}$ M^{-1} s^{-1} at −47 °C. An Eyring plot provided activation parameters of $\Delta H^{\ddagger} = 9.9 \pm 1.2$ kcal mol^{-1} and $\Delta S^{\ddagger} = -26.1 \pm 3.3$ eu (Figure 4).

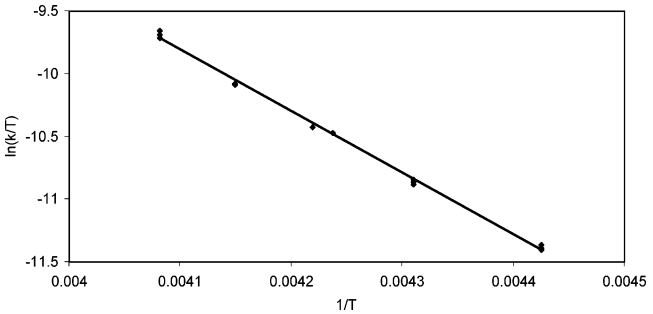
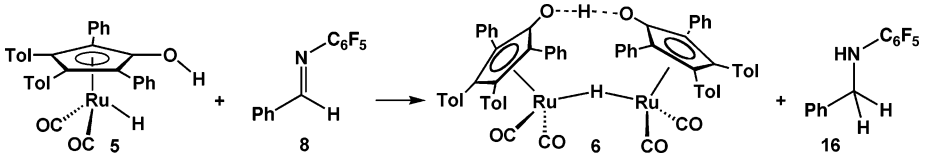


Figure 4. Eyring plot of **5**−**RuHOH** reduction of *N*-benzylideneaniline in THF-d_8 between −27 and −48 °C.

On the basis of the second-order rate law for reduction, in addition to the large negative entropy of activation for reduction ($\Delta S^{\ddagger} = -26.1 \pm 3.3$ eu) of *N*-benzilideneaniline (**7**), it is apparent that an associative process between the imine and the ruthenium hydride occurs prior to reaching the highest energy transition state. A similar associative process is assumed for each imine tested.

(12) Subscripts of rate constants indicate the identity of the imine. The isotopomer of **5**, when not **5**−**RuHOH**, is also noted in the subscript.

Scheme 5



Kinetic deuterium isotope effects on the reduction of *N*-benzilideneaniline (**7**) by the isotopologs of ruthenium species **5**−**RuHOH**, **5**−**RuHOD**, **5**−**RuDOH**, and **5**−**RuDOD** were measured at −38 °C. The resulting second-order rate constants, $k_{7-\mathrm{RuHOH}} = (7.02 \pm 0.52) \times 10^{-3}\ \mathrm{M^{-1}\ s^{-1}}$, $k_{7-\mathrm{RuHOD}} = (5.69 \pm 0.74) \times 10^{-3}\ \mathrm{M^{-1}\ s^{-1}}$, $k_{7-\mathrm{RuDOH}} = (5.72 \pm 0.66) \times 10^{-3}\ \mathrm{M^{-1}\ s^{-1}}$, and $k_{7-\mathrm{RuDOD}} = (4.37 \pm 0.65) \times 10^{-3}\ \mathrm{M^{-1}\ s^{-1}}$, were used to determine the kinetic isotope effects (Table 1).

Deuterium Incorporation into Amine Complex 12 was monitored by ^{2}H NMR spectroscopy during the reaction of 5 equiv of imine **7** with **5**−**RuDOH** in THF at −40 °C. The rate of the disappearance of **5**−**RuDOH** was followed by the disappearance of the ruthenium deuteride resonance (δ −9.7, RuD) and matched the rate previously determined using ^{1}H NMR spectroscopy. Resonances corresponding to the diastereotopic benzyl hydrogens were too broad to be readily discerned at −40 °C, but upon raising the temperature to 0 °C, resonances were observed at δ 3.7 (C*D*HPh) and at δ 4.6 (CH*D*Ph), indicating deuterium incorporation into both benzyl positions. No deuterium resonance corresponding to deuterium incorporation onto the imine carbon was observed.

***N*-Benzilidenepentafluoroaniline (8)** was used to study the reduction of an electron-deficient imine. The reaction of **5**−**RuHOH** with an excess of the electron-deficient imine **8** was slower than reduction of **7** and required measurement at a higher temperature (11 °C). The resulting less basic amine **16** did not coordinate to the ruthenium center. Instead, resonances consistent with formation of diruthenium bridging hydride **6** and free *N*-benzylpentafluoroaniline **16** were observed (Scheme 5). The appearance of a resonance corresponding to bridging hydride dimer **6** [δ −18.34 (RuHRu)] was followed in conjunction with the disappearance of resonances corresponding to ruthenium hydride monomer **5**−**RuHOH** [δ −9.73 (RuH), δ 6.83 (arene)]. The rate for **5**−**RuHOH** disappearance corresponds to twice that of imine reduction since each imine reduction consumes 2 equiv of **5**−**RuHOH**, one to reduce the imine and one to form diruthenium complex **6**. The resulting second-order rate constant, $k_8 = (4.78 \pm 0.42) \times 10^{-3}\ \mathrm{M^{-1}\ s^{-1}}$, reflects this relationship (eq 2).

$$-\frac{\mathrm{d}[\mathbf{5}]}{\mathrm{d}t} = -2\frac{\mathrm{d}[\mathbf{8}]}{\mathrm{d}t} = 2k_6[\mathbf{5}][\mathbf{8}] \qquad (2)$$

The isotopologs of ruthenium hydride **5**−**RuHOH** were used to reduce imine **8**, and the resulting rate constants, $k_{8-\mathrm{RuHOH}} = (4.78 \pm 0.42) \times 10^{-3}\ \mathrm{M^{-1}\ s^{-1}}$, $k_{8-\mathrm{RuHOD}} = (3.04 \pm 0.06) \times 10^{-3}\ \mathrm{M^{-1}\ s^{-1}}$, $k_{8-\mathrm{RuDOH}} = (2.40 \pm 0.12) \times 10^{-3}\ \mathrm{M^{-1}\ s^{-1}}$, and $k_{8-\mathrm{RuDOD}} = (1.44 \pm 0.06) \times 10^{-3}\ \mathrm{M^{-1}\ s^{-1}}$, provided the isotope effects listed in Table 1.

***N*-Isopropyl-(4-methyl)benzilideneamine (9)** was used to study the reduction of an electron-rich imine. The reaction of **5**−**RuHOH** with an excess of the electron-rich imine **9** was very fast compared to reduction of **7** and required measurement at a lower temperature (−48 °C). Kinetic analysis was performed for the reaction of excess *N*-isopropyl-(4-methyl)-benzilidene amine with **5**−**RuHOH** and subsequent formation of amine complex **13**. Following the disappearance of ruthenium hydride resonances [δ −9.73 (hydride), δ 6.83 (arene)] and the concurrent appearance of resonances for ruthenium amine complex **13** [δ 7.05 (arene), 1.07 (CH(C*H*$_3$)(CH$_3$))] under pseudo-first-order conditions yielded a second-order rate constant (k_9) at −48 °C of $(8.54 \pm 0.70) \times 10^{-3}\ \mathrm{M^{-1}\ s^{-1}}$.

In addition to ruthenium amine complex **13** and excess free imine **9**, an additional product was observed in small amounts (approximately 15% compared to **13**). The ^{1}H NMR spectrum had three inequivalent methyl resonances (δ 2.22, 1.93, and 1.80) and a new benzyl resonance (δ 4.34). These resonances matched those of independently synthesized *N*-(4-methyl)-benzylisopropylideneamine (**18**). The ketimine **18** is formed by isomerization of aldimine **9** (Figure 5).

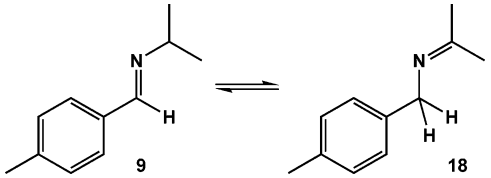


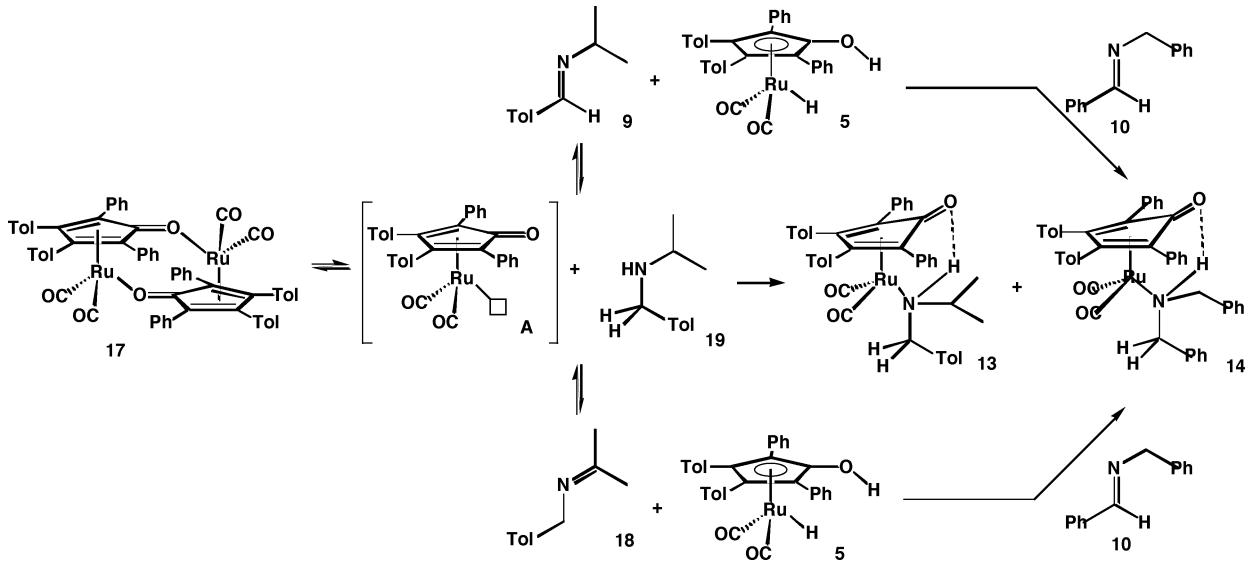
Figure 5. Imine isomerization during reduction of *N*-isopropyl-(4-methyl)-benzilideneamine, **9**.

The determination of the rate constants for reduction of **9** by the isotopologs containing RuD is complicated by fast exchange of the ruthenium deuteride into free imine. Hydrogen quickly exchanges into the hydride position, attenuating these isotope effects, while the acidic proton does not exchange. The resulting rate constants at −48 °C, $k_{9-\mathrm{RuHOD}} = (9.21 \pm 0.51) \times 10^{-3}\ \mathrm{M^{-1}\ s^{-1}}$, $k_{9-\mathrm{RuDOH}} = (8.27 \pm 0.06) \times 10^{-3}\ \mathrm{M^{-1}\ s^{-1}}$, and $k_{9-\mathrm{RuDOD}} = (9.05 \pm 0.07) \times 10^{-3}\ \mathrm{M^{-1}\ s^{-1}}$, provide the observed isotope effects given in Table 1. The isotope effects obtained by labeling the acidic proton ($k_{\mathrm{RuHOH}}/k_{\mathrm{RuHOD}} = 0.92 \pm 0.09$ and $k_{\mathrm{RuDOH}}/k_{\mathrm{RuDOD}} = 0.91 \pm 0.07$) are reliable. The fast exchange into the hydride observed when using **5**−**RuDOH** and **5**−**RuDOD** results in isotope effects that are attenuated toward unity.

Deuterium Incorporation into Products was determined by reacting approximately 5 equiv of imine **9** (0.141 M) with **5**−**RuDOH** (0.0246 M). This reaction was performed at −40 °C and monitored by ^{2}H NMR spectroscopy to identify the concentration of deuterium in the various positions. The resulting ^{2}H NMR spectrum revealed the presence of deuterium in amine complex **13** at the benzyl position (δ 1.3, CHDPh, 44% of D) and deuterium incorporation into residual imine **9** (δ 8.3, DC═N, 24% of D). In addition, a resonance at δ 3.4 (32% of D) indicates deuterium incorporation into the isopropyl sites of amine complex **13** (δ 3.38 in ^{1}H NMR spectrum) and/or residual imine **9** (δ 3.46).

Isomerization and Reduction of Ketimine 18. To further examine the role of ketimine **18** in the formation of the

Scheme 6



ruthenium amine complex **13**, an excess of **18** (0.160 M) was added to a solution of **5**−**RuHOH** in THF-d_8 at −45 °C and was monitored by ^{1}H NMR spectroscopy. Resonances from ketimine **18** [δ 2.22 (Me), 1.93 (Me), 4.34 (CH_2Ar)] quickly disappeared, while resonances for free imine **9** [δ 8.26 CH═N, 1.19 CH(CH_3)$_2$] appeared. The isomerization from **18** to **9** occurred approximately 25 times faster than formation of ruthenium amine complex **13**. As the reaction progressed, the ratio of **18**:**9** reached an equilibrium ratio of 1:23 in favor of aldimine **9**.

Dehydrogenation of Isopropyl-(4-methyl)benzylamine (19) with ruthenium dimer **17** was performed to monitor the relative rates of dehydrogenation to aldimine **9** and ketimine **18**. The dehydrogenation was run in the presence of excess imine **10** which served to trap ruthenium hydride **5** formed upon dehydrogenation. The ratio of imine **9** to ketimine **18** provides a good measure of the relative dehydrogenation rates (Scheme 6).

A solution of dimer **17** with excess imine **10** was cooled to −40 °C, and a solution of amine **19** was added. After several hours, the concentrations of imine **9** [δ 1.19 (*i*-Pr)] and ketimine **18** [δ 4.35 (CH_2Ph)] were determined by ^{1}H NMR spectroscopy. The ratio of resulting aldimine **9** to ketimine **18** was 7:1. Upon completion of the reaction, ruthenium was present as a combination of amine complexes **13** and **14** in a 3:7 ratio favoring amine complex **13**. Amine complex **13** can be formed from direct complexation of amine **19**, while both complexes **13** and **14** are formed from complexation of amine following respective imine reduction.

***N*-Benzilidenebenzylamine (10)** is electronically similar to other *N*-alkyl imines, but provides a symmetrical amine upon reduction, eliminating complications due to isomerization. The reaction of **5**−**RuHOH** with an excess of imine **10** led to the formation of ruthenium amine complex **14**. By following the disappearance of **5**−**RuHOH** resonances and the appearance of characteristic resonances of **14** [δ 3.85 (CH_2Ph) and δ 7.58 (arene)] by ^{1}H NMR spectroscopy, the second-order rate constants were measured with ruthenium hydride **5** and **5**−**RuDOD** ($k_{\mathbf{10}-\mathrm{RuHOH}} = 14.3 \times 10^{-3}$ M^{-1} s^{-1} and $k_{\mathbf{10}-\mathrm{RuDOD}} = 13.6 \times 10^{-3}$ M^{-1} s^{-1}) at −57 °C, providing a kinetic isotope effect of 1.05 ± 0.05.

To determine the extent of deuterium scrambling during reduction, a ~5-fold excess of imine **10** (0.132 M) was reduced by **5**−**RuDOH** (0.0246) in THF at −40 °C and monitored by ^{2}H NMR spectroscopy. The resulting spectrum revealed deuterium resonances at δ 2.9 (CH*D*Ar of amine complex **14**) and δ 4.8 (CH*D*Ar of residual imine **10**) in a 4:1 ratio. No deuterium was detected at the imine carbon of **10**, and 5% of the relative value of deuterium observed in **14** would have been readily detected.

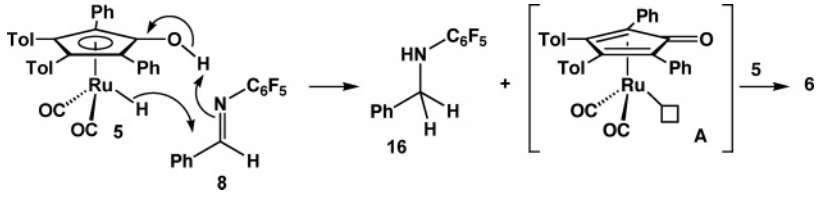
***N*-Benzilidene-*tert*-butylamine (11)** was utilized to study the reduction of an alkyl-substituted imine without complications due to exchange and isomerization. Kinetic analysis was performed for *N*-benzylidene-*tert*-butylamine reduction with an excess of imine to provide pseudo-first-order conditions. The disappearance of resonances for **5**−**RuHOH** and the appearance of resonances consistent with the formation of ruthenium amine complex **15** [δ 0.69 (*t*Bu) and δ 7.65 (arene)] were monitored by ^{1}H NMR spectroscopy at −48 °C to determine the second-order rate constant, $k_{\mathbf{11}-\mathrm{RuHOH}} = (6.19 \pm 0.46) \times 10^{-3}$ M^{-1} s^{-1}. Rate constants for reduction with ruthenium hydride isotopologs are $k_{\mathbf{11}-\mathrm{RuHOD}} = (6.90 \pm 0.26) \times 10^{-3}$ M^{-1} s^{-1}, $k_{\mathbf{11}-\mathrm{RuDOH}} = (9.66 \pm 0.40) \times 10^{-3}$ M^{-1} s^{-1}, and $k_{\mathbf{11}-\mathrm{RuDOD}} = (11.0 \pm 0.62) \times 10^{-3}$ M^{-1} s^{-1}. Inverse isotope effects were observed for this reaction (Table 1). In contrast to the reduction of *N*-isopropyl imine **9** with **5**−**RuDOH** and **5**−**RuDOD**, no ruthenium hydride resonance (δ −9.7) indicating RuD/H exchange was observed by ^{1}H NMR spectroscopy.

Deuterium incorporation into ruthenium amine complex **15** was observed in the reaction of approximately 4 equiv of **9** with **5**−**RuDOH** in THF at −40 °C. ^{2}H NMR spectroscopy showed broad resonances at δ 4.0 and 1.8 due to the presence of deuterium in the diastereotopic benzyl sites. No resonance due to incorporation of deuterium onto the imine carbon (δ 8.3) was observed.

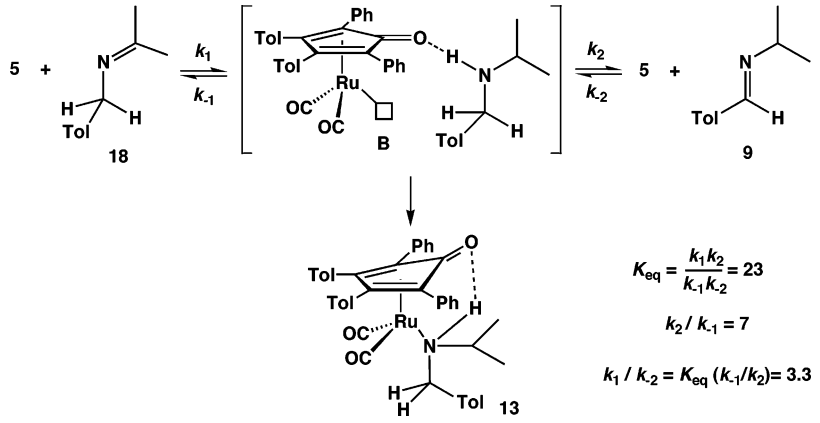
Discussion

Kinetic and isotope effect studies have established that reduction of both aldehydes and ketones by **5** occurs by rate-determining concerted transfer of hydride from ruthenium and proton from oxygen to the carbonyl compound without complexation to the metal. In contrast, imines react with **5** by a

Scheme 7



Scheme 8



variety of mechanisms depending on the electronic properties of the imine. Products, reaction rates, and kinetic isotope effects for the reduction of the electron-deficient imine **8** were very similar to those observed for reduction of carbonyl species. Substitution of the electron-withdrawing substituent with more donating groups led to alteration in reactivity, including the formation of amine complexes as products. This study of imine reduction has led to a greater understanding of the reduction mechanism and its progression as the rate-limiting step changes from the transfer of hydrogen to the complexation of the amine with the increasing electron density on the nitrogen of the imine.

Concerted Hydrogen Transfer to Electron-Deficient Imines. The reduction of the most electron-deficient imine, *N*-benzilidenepentafluoroaniline (**8**), was very similar to that observed for the reduction of ketones and aldehydes. The reduction occurs at a rate close to that of benzaldehyde reduction, results in free amine and diruthenium hydride **6**, and displays comparable isotope effects.

It is presumed that the nucleophilicity of the resulting amine **16** is diminished due to the electron-withdrawing nature of the fluorine substituents and, therefore, does not form a stable amine complex with unsaturated species **A**. Instead, the unsaturated ruthenium species reacts with another equivalent of **5** to form bridging diruthenium hydride **6**.

The kinetic isotope effects for reduction of *N*-pentafluorophenyl imine **8** ($k_{RuHOH}/k_{RuHOD} = 1.62$ and $k_{RuHOH}/k_{RuDOH} = 2.05$) are similar to those observed for the reduction of benzaldehyde (1.30 and 2.60, respectively).[13] The size of these isotope effects is indicative of primary deuterium kinetic isotope effects. The product of the individual isotope effects for the reduction of **8** is within error of the doubly labeled isotope effect, $k_{RuHOH}/k_{RuDOD} = 3.32$ ($1.62 \times 2.05 = 3.32$) and is, therefore, consistent with the concerted transfer of proton and hydride at the highest energy transition state. Subsequent reaction of species **A** with **5** to form product **6** is faster than the hydrogen transfer and does not affect the overall rate of the reaction.

Because ruthenium hydride **5** is an 18 electron species, prior coordination of the imine to the ruthenium center is unlikely, thus suggesting that hydrogen transfer occurs via an outer sphere concerted transfer mechanism, as shown in Scheme 7. The failure of **5** to undergo exchange with ^{13}CO or substitution with phosphines below room temperature also provides evidence for the absence of an available coordination site on **5**.

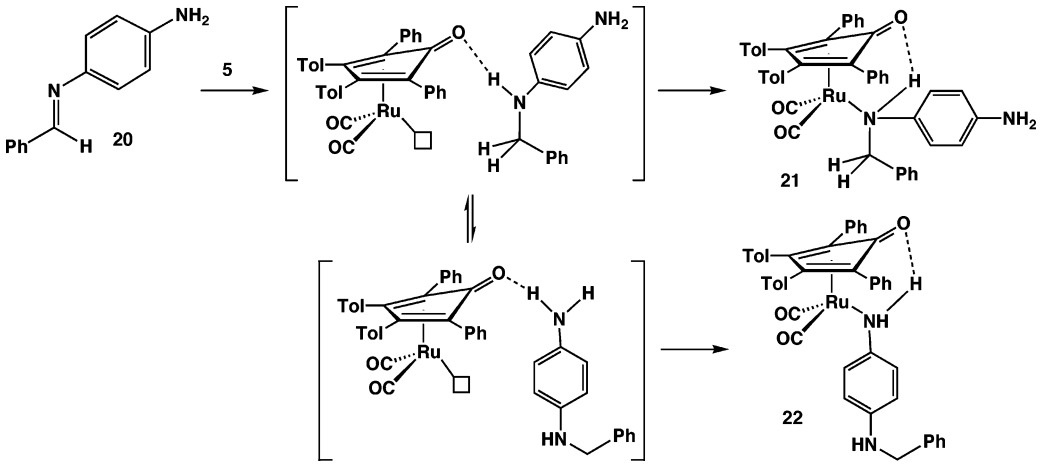
Reversible Hydrogen Transfer to Electron-Rich Imines. More electron-rich alkyl-substituted imines showed marked differences in reactivity patterns. Instead of free amine products from reduction of *N*-isopropyl imine **9**, amine complex **13** was observed. At the temperatures utilized in this study, the formation of the ruthenium amine complex is an irreversible step. During reduction of **9**, the appearance of a small amount of isomerization product, ketimine **18**, was observed. This was attributed to reversible hydrogen transfer to the imine. Reversible hydrogen transfer was conclusively demonstrated by deuterium scrambling into recovered imine **9**, ketimine **18**, and amine complex **13**. In addition, greatly attenuated isotope effects were observed for the reduction of **9** compared with those of aldehydes.

To gain further insight into the apparent interconversion of **9** and **18**, the reduction of ketimine **18** was monitored by ^1H NMR spectroscopy. Isomerization of ketimine **18** to **9** was observed to occur at a rate 25 times faster than formation of ruthenium amine complex **13**. Ultimately, a 23:1 equilibrium ratio of aldimine **9**:ketimine **18** was reached.

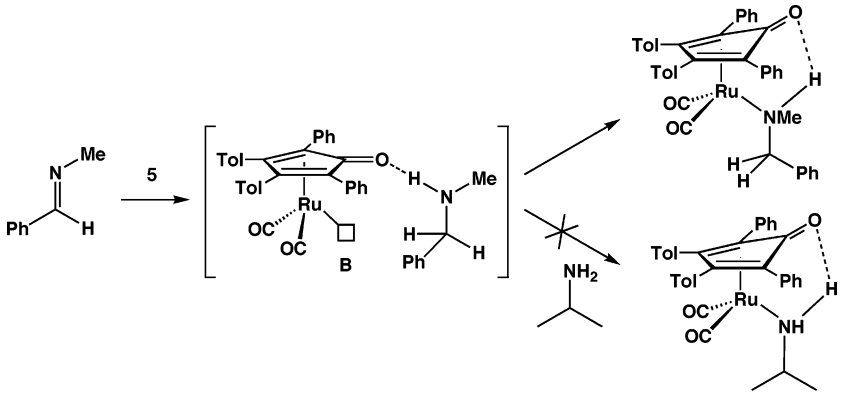
The isomerization of an imine requires that the transfer of hydride be reversible. Upon transfer of hydrogen to imine **9**, the new amine, isopropyl-(4-methyl)benzylamine, and the unsaturated species **A** presumably form and are hydrogen bonded to one another as species **B**. From intermediate **B**, the resulting amine can proceed to form the ruthenium amine

(13) The cited kinetic isotope effects for reduction of benzaldehyde were measured in the absence of water. Those effects provided in ref 8 were determined with 0.1 M H_2O or D_2O: Casey, C. P.; Johnson, J. B. Unpublished results.

Scheme 9



Scheme 10



complex or transfer hydrogen back to the unsaturated ruthenium species. Since β hydrogens are available on both the benzyl and isopropyl substituents, either imine **9** or imine **18** can result from elimination of hydrogen (Scheme 8).

In work that will be reported elsewhere, our group has demonstrated that two amine complexes result from the reduction of amine-substituted imine **20** at −60 °C.[14] Amine complex **21**, formed from coordination of the newly formed amine to the metal center, and amine complex **22**, formed from coordination of the pre-existing amine, are formed in a 1:1 ratio, despite the higher thermodynamic stability of primary amine complex **22**. This combination of products requires that upon transfer of hydrogen from **5** to **20**, the vacant coordination site of intermediate **A** can be trapped by either amine within the solvent cage (Scheme 9).

In contrast, reduction of an imine in the presence of an external amine results in only the complex formed from complexation of the newly formed amine (Scheme 10). This indicates that although there may be competition between amines within the solvent cage, diffusion from the solvent cage is much slower than coordination to the metal center.

We propose that reaction of **5** with imine **9** produces intermediate **B** in which the newly formed amine is hydrogen bonded to the ketone unit of the ruthenium dienone complex (Scheme 8). Two reactions of **B** are more rapid than diffusion apart: (1) coordination of the amine to ruthenium to give amine complex **13**, and (2) hydrogen transfer back to the ruthenium to regenerate **5** and isomerized imine that can diffuse apart. The isomerization requires that hydrogen-bonded intermediate **B** collapses to amine complex **13** 25 times more slowly than dehydrogenation to produce imine **9**.

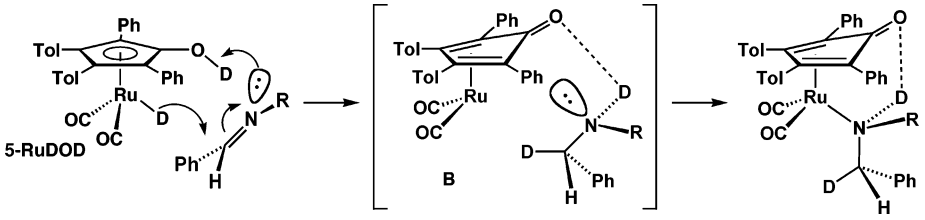
The 23:1 equilibrium ratio of **9**:**18** is determined by the relative rates of reaction of the imines with **5** to produce the intermediate **B** and by the relative rates of reversal of **B** to form **9** and **18**. An independent experiment in which unsaturated intermediate **A** (generated from dienone dimer **17**) dehydrogenated amine **19**, presumably via intermediate **B**, to give a 7:1 ratio of aldimine **9**:ketimine **18**. Therefore, to get an equilibrium constant of 23, the rate of hydrogen transfer from **5** to ketimine **18** must be approximately three times faster than the rate to aldimine **9** (Scheme 8).

Deuterium scrambling into the positions on carbons adjacent to nitrogen provides further evidence for reversible hydrogen transfer. The observation of deuterium in the isopropyl position of both free imine **9** and amine complex **13** supports rapid imine isomerization. From the relative amounts of deuterium in each position, we conclude that the rate of complexation of the amine in intermediate **B** is much slower than that of the dehydrogenation, resulting in extensive deuteration of the benzyl position of **13**, the isopropyl positions of **9** and **13**, and on the imine carbon of **9**.

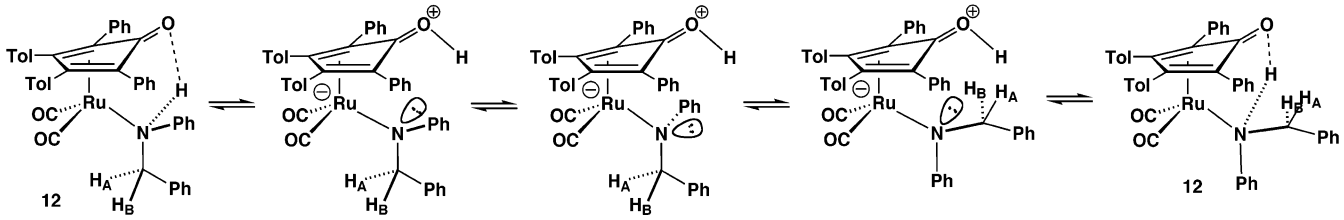
Use of *N*-benzyl imine **10** simplified the reduction experiment as dehydrogenation of the intermediate symmetrical amine results in the same benzyl imine **10**. The results of the deuterium-labeling experiment for the reduction of **10** is also

(14) Casey, C. P.; Bikzhanova, G. A. Unpublished results.

Scheme 11



Scheme 12



consistent with those of reversible hydrogen transfer. As expected, deuterium labels are found in the benzyl position of amine complex **14**. In addition, deuterium is observed in the benzyl position of free imine, indicating similar reversibility to that observed for imines **9** and **18**. Unlike imine **9**, however, deuterium is not observed in the imine position (δ 8.45). The lack of incorporation of deuterium into the imine position of **10** can only be understood by considering the stereospecificity of hydrogen addition to *N*-benzyl imine **10** and the relative rates of dehydrogenation and complexation from intermediate **B**.

Stereospecificity of Hydrogen Transfer. When hydrogen is transferred to an imine, two stereocenters are formed, one at carbon and a second at nitrogen. In unpublished work,[15] our group has used labeling experiments, nOe experiments, crystallographic data, and calculations to establish that hydrogen is transferred via a stereospecific addition of deuterium from **5**−**RuDOD** to imine **7** and related imines, resulting in a trans addition of deuterium (Scheme 11). The observed stereospecificity requires that complexation of the stereospecifically formed amine to ruthenium be much faster than nitrogen inversion, which has a very low barrier ($\sim$7.5 kcal mol^{-1}).[16]

In THF, the reduction of **7** by **5**−**RuDOD** gave equal amounts of deuterium at the two diastereotopic benzyl positions of **12**. We suggest that addition of hydrogen occurs by stereospecific trans addition to the imine, but that the amine complex isomerizes more rapidly than it is formed. Interconversion of diastereomers, and thus scrambling of deuterium in the amine complex, is suggested to occur by transfer of hydrogen from nitrogen to oxygen, inversion at the amido nitrogen, rotation about the ruthenium nitrogen bond, and proton transfer back to nitrogen (Scheme 12). In THF, slower reduction, coupled with faster proton transfer due to assistance from the hydrogen-bonding solvent, results in loss of stereochemistry, but only after formation of the amine complex.

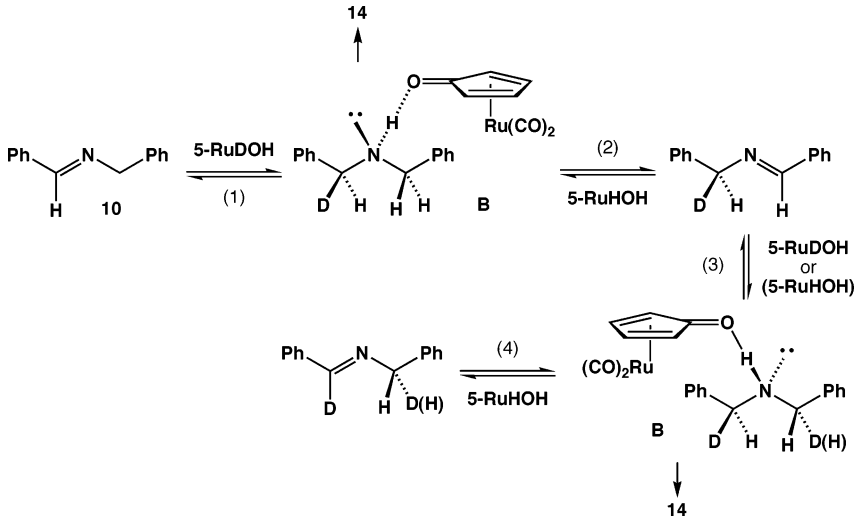
The proposal of stereospecific addition is supported by the lack of deuterium scrambling during reduction of *N*-*tert*-butyl imine **11** by **5**−**RuDOH**. No resonances due to ruthenium hydride are observed when the reaction is monitored by ^{1}H NMR spectroscopy, and no resonances due to deuterium incorporation onto the imine carbon are observed by ^{2}H NMR spectroscopy. Nonspecific addition, or inversion of stereochemistry prior to formation of the ruthenium amine complex, would result in the elimination of either hydrogen or deuterium from the amine intermediate, resulting in a mixture of ruthenium hydride and deuteride, and the presence of both deuterium and hydrogen on the imine carbon.

Exchange of Deuterium into Recovered Imines. In the reaction of *N*-benzyl imine **10** with **5**−**RuDOH**, deuterium was incorporated only into the benzyl position of recovered **10** and not onto the imine carbon, while in the reaction of *N*-isopropyl imine **9** with **5**−**RuDOH**, deuterium was incorporated into the isopropyl group and onto the imine carbon of recovered **9**. This scrambling can be explained by a four step process (Scheme 13). (1) Stereospecific trans addition of **5**−**RuDOH** to one enantioface of the imine to give intermediate **B**, in which the initially formed amine is hydrogen bonded to the ruthenium dienone carbonyl group. (2) Stereospecific trans elimination of **5**−**RuHOH** from **B** to form the other imine regioisomer with deuterium on the *N*-alkyl group. The imine readily diffuses from the solvent cage. (3) Stereospecific trans addition of either **5**−**RuDOH** or **5**−**RuHOH** to the *opposite* enantioface of the regioisomeric imine to form intermediate **B**. (4) Stereospecific trans elimination of **5**−**RuHOH** from this intermediate to reform the initial imine with deuterium on the imine carbon.

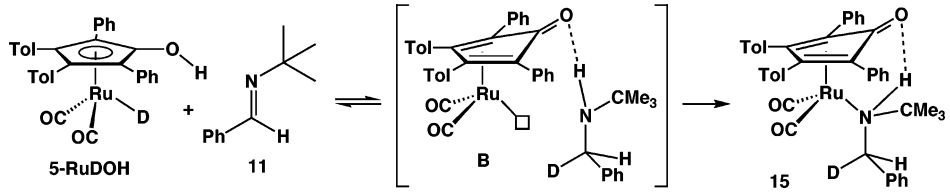
Scheme 13 shows our proposed process for the incorporation of significant amounts of deuterium into the benzyl group of recovered imine **10** but no detectable amounts onto the imine carbon. Only a single addition/elimination sequence is necessary to scramble deuterium into the benzyl position of imine **10**. Since the relative rates of dehydrogenation and amine coordination from intermediate **B** are 1:2,[17] deuterium scrambling into benzyl positions readily occurs. However, since two successive addition/elimination processes are required for scrambling deuterium onto the imine carbon and the chances of this occurring are low, no deuterium was observed on the imine carbon. It should be noted that these results require high stereospecificity of hydrogen transfer from **5**−**RuDOH** to

(15) Casey, C. P.; Bikzhanova, G. A. Unpublished results.
(16) Bushweller, C. H.; O'Neil, J. W.; Bilofsky, H. S. *Tetrahedron* **1972**, *28*, 2697.
(17) Upon the reduction of imine **10** with **5**−**RuDOH**, the ratio of deuterium in the free imine and amine complex is 1:4, indicating that for dibenzylamine, complexation occurs competitively with dehydrogenation. Ignoring isotope effects, this indicates that ruthenium amine complex formation is favored by a factor of 2 over dehydrogenation.

Scheme 13



Scheme 14



imines, dehydrogenation to give only (*E*)- but not (*Z*)-imines, and more rapid amine coordination than inversion at the amine nitrogen.

The reaction of **5**−**RuDOH** with *N*-isopropyl imine **9** led to extensive deuterium incorporation into *both* the isopropyl group *and* onto the imine carbon of recovered **9**. This occurs because the rate of dehydrogenation of **B** is 25 times faster than that of amine coordination. As a result, the likelihood that an imine will undergo multiple addition/elimination processes increases dramatically compared to reduction of **10**, leading to extensive deuterium incorporation both into the isopropyl substituent and onto the imine carbon of **9**.

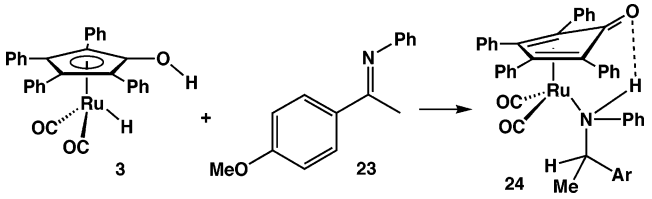
Equilibrium Isotope Effects. In the reduction of *N*-alkyl imines **9** and **10** with ruthenium deuteride, the fast reversible hydrogen transfer results in the scrambling of deuterium into free imine and the production of ruthenium hydride. As a result, the isotope effect on transfer of deuterium from ruthenium cannot be accurately determined. Since the deuterium transferred between oxygen and nitrogen is not exchanged, the isotope effect of the OD can be determined accurately. The observed inverse equilibrium isotope effects ($k_{RuHOH}/k_{RuHOD} = 0.92$ and $k_{RuDOH}/k_{RuDOD} = 0.91$) are consistent with the proposal that transfer does not take place during the rate-limiting step but rather during the equilibrium of the acidic proton between species **5** and the amine prior to the rate-limiting nitrogen coordination.

The *tert*-butyl-substituted imine **11** was employed to obtain accurate RuD isotope effects for reduction of *N*-alkylamines. With no β hydrogens, there is no possibility for isomerization or exchange. As expected, the isotope effects for deuterium labeling of the acidic proton ($k_{RuHOH}/k_{RuHOD} = 0.90$ and $k_{RuDOH}/k_{RuDOD} = 0.88$) are similar to those observed for *N*-isopropyl imine **9**. When *tert*-butyl imine **11** is reduced by **5**−**RuDOH** or **5**−**RuDOD**, isotope effects of $k_{RuHOH}/k_{RuDOH} = 0.64$ and $k_{RuHOD}/k_{RuDOD} = 0.63$ are observed. These values are interpreted as inverse equilibrium isotope effects resulting from rapid reversible deuterium transfer between ruthenium and carbon and rate-determining coordination of the amine. The equilibrium of species **5**−**RuDOH** and **11** with deuterium-labeled intermediate **B** produces an inverse equilibrium isotope effect due to the relative strengths of the ruthenium hydride and carbon hydrogen bonds (Scheme 14). Since the ruthenium hydride bond is weaker than the hydrogen carbon bond in the resulting amine, use of **5**−**RuDOH** results in a shift of the equilibrium favoring **B**, thus resulting in a faster amine complex formation.

In each of these reactions with alkyl-substituted imines, the exact nature of the hydrogen transfer in the reduction of the alkyl-substituted imines remains unknown as the transfer takes place prior to the rate-limiting step in the reaction. The observation of small inverse isotope effects on the acidic proton indicates that the transfer is involved in an equilibrium, but does not provide information to discern between a concerted or stepwise mechanism. The transfer could occur in a reversible concerted step, as with electron-deficient imine and carbonyls, or the transfer could occur via a stepwise mechanism of proton transfer followed by hydride transfer in which both steps are reversible.

Imine of Intermediate Electronic Nature. Electronically, benzilideneaniline (**7**) lies between the electron-deficient pentafluorophenyl-substituted imine and the electron-rich alkyl-substituted imines. The values of the isotope effects observed from reduction of **7** [($k_{RuHOH}/k_{RuHOD} = 1.30$ and $k_{RuDOH}/k_{RuDOD} = 1.31$), ($k_{RuHOH}/k_{RuDOH} = 1.23$ and $k_{RuHOD}/k_{RuDOD} = 1.24$), and ($k_{RuHOH}/k_{RuDOD} = 1.60$)] are smaller than those observed for concerted transfer of hydride and proton in the rate-limiting step for the reduction of electron-deficient imine **8**, but larger than the inverse isotope effects seen for rate-limiting coordination of nitrogen in the reduction of electron-rich imine **11**.

Scheme 15



These isotope effects suggest an intermediate case in the continuum of the imine reduction mechanism where the barriers for transfer of hydrogen from **5** to the imine and formation of the amine complex are of similar energy. A reaction mechanism with similar activation energies for each step would result in observed isotope effects that are smaller than the isotope effects on the first step alone (Figure 6).

Partitioning of intermediate **B** between the forward and reverse step leads to predicted isotope effects that are a function of both the kinetic isotope effect from initial hydrogen transfer and the equilibrium isotope effect from reversible hydrogen transfer. Our observations of kinetic isotope effects for reduction of electron-deficient imine **8** provide an estimate of the kinetic isotope effects for initial hydrogen transfer (k_{RuHOH}/k_{RuHOD} = 1.61, k_{RuHOH}/k_{RuDOH} = 2.05, and k_{RuHOH}/k_{RuDOD} = 3.32). The equilibrium isotope effects observed for reduction of electron-rich imine **11** provide an estimate of the equilibrium isotope effects for reversible hydrogen transfer (k_{RuHOH}/k_{RuHOD} = 0.89, k_{RuHOH}/k_{RuDOH} = 0.64, and k_{RuHOH}/k_{RuDOD} = 0.56).

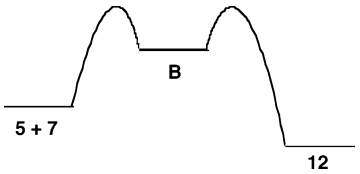


Figure 6. Reaction mechanism results in isotope effects that are smaller than the isotope effects on the first step alone.

Assuming the barrier to the two steps are of exactly the same energy and the isotope effects are similar to those observed for reduction of **8** and **11**, the reaction of **5**−**RuDOD** with *N*-phenyl imine **7** is predicted to result in an observed isotope effect of 1.94. If the rate of dehydrogenation is assumed to be 1.5 times faster than complexation of the amine, the predicted isotope effect drops to k_{RuHOH}/k_{RuDOD} = 1.66, within experimental error of the observed doubly labeled isotope effect for the reduction of **7** by **5**−**RuDOD** (k_{RuHOH}/k_{RuDOD} = 1.60).

With the same ratio between the rate of dehydrogenation and complexation, the predicted and observed isotope effects are within experimental error for reductions by the monodeuterated isotopologs. Reduction of **7** by **5**−**RuHOD** is predicted to display an isotope effect of k_{RuHOH}/k_{RuHOD} = 1.18 (observed 1.30), and reduction by **5**−**RuDOH** is predicted to display an isotope effect of k_{RuHOH}/k_{RuDOH} = 1.20 (observed 1.23).

Since the actual isotope effects from reduction of **7** with these isotopologs of **5** would vary somewhat from those observed from reduction of **8** and **11**, these predicted isotope effects are remarkably close to the observed values. These results support the proposal that the dehydrogenation and amine complexation from intermediate **B** occur at similar rates during the reaction of *N*-phenyl imine **7** with **5**.

Further details regarding the calculation of isotope effects via a mechanism with two steps of similar energy are provided in the Supporting Information.

Ring Slip Mechanism. Bäckvall and co-workers[18] observed negligible kinetic isotope effects (k_{RuHOH}/k_{RuDOD} = 1.05) in the reduction of *N*-phenyl-[1-(4-methoxyphenyl)ethylidene]amine (**23**) by **3**−**RuHOH** and **3**−**RuDOD** (Scheme 15) and concluded that the rate-determining step did not involve hydrogen transfer. We are in full agreement with this conclusion.

Bäckvall proposed rate-limiting imine coordination to reversibly formed η^3-ring-slipped intermediate **C** to form intermediate **D**, which undergoes fast transfer of the hydride and proton to the coordinated imine. Finally, an η^2- to η^4-ring slip leads to the ultimate amine complex (Scheme 16). The transfer of hydrogen occurs following the rate-limiting step, in contrast to our proposal that the transfer occurs prior to slow amine complex formation.

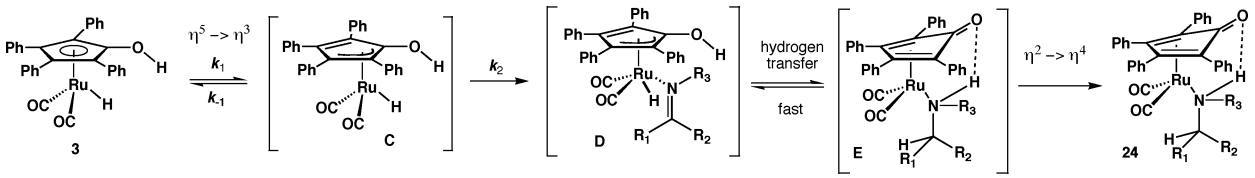
Although Bäckvall's proposal adequately accounts for the isotope effects seen for his single example, it fails to account for our observations on a wider range of imines. In particular, it cannot account for imine isomerization, deuterium scrambling seen in the complexed amine, deuterium incorporation into recovered imine, or observation of inverse equilibrium isotope effects. These phenomena require reversible hydrogen transfer and rate-limiting nitrogen coordination.

A variant of Bäckvall's ring slip mechanism that has all steps reversible prior to η^2- to η^4-ring slippage can account for all of our observations detailed above. However, even this mechanism has two major problems. First, the suggested η^5- to η^3-ring slip without nucleophilic assistance is without precedent. Second and more significantly, if **3** and intermediate **C** are in equilibrium through reversible ring slippage, then ^{13}CO should readily coordinate to the open coordination site and become incorporated into **3**. In contrast, our group has observed that incorporation of ^{13}CO into the tolyl-substituted analogue, **5**, occurs only very slowly over several hours, even at 80 °C.

Rate-Limiting Hydrogen Transfer Versus Rate-Limiting Amine Coordination. The electronic nature of the imine affects both the overall rate of imine reduction and the nature of the rate-determining step. Better donor substituents on nitrogen give rise to faster rates and a shift of the rate-determining step from hydrogen transfer to amine coordination.

Examination of substituent effects on each step in the overall imine reduction reveals a complicated picture. In the case of the C_6F_5-substituted imine **8**, the slower initial concerted transfer

Scheme 16



of hydride and proton from **5** is readily understood in terms of the lower basicity of the nitrogen and the requirement for protonation during hydride transfer. The more basic aryl (**7**) and alkyl-substituted (**9**−**11**) imines are more readily protonated and undergo more rapid hydrogen transfer from **5**. This helps to explain their overall greater kinetic reactivity.

The change in mechanism is related to the partitioning of the reduced hydrogen-bonded amine **B** between coordination to nitrogen to give an amine complex and back hydrogen transfer to ruthenium to regenerate an imine. Electron donor substituents on nitrogen are expected to accelerate both of these processes. For reasons not currently understood, the back transfer of hydrogen is more strongly accelerated by the alkyl substituent, and a mechanistic shift to rate-limiting coordination of nitrogen occurs.

Conclusion

Our mechanistic studies provide a remarkably detailed picture of imine reduction by ruthenium hydride **5** and demonstrate a change in the rate-limiting step as a function of imine basicity. The reaction begins by net trans addition of proton and hydride to the imine and formation of coordinatively unsaturated intermediate **B**. In the case of the electron-deficient C_6F_5-substituted imine **8**, this step is rate-limiting. For electron-rich alkyl-substituted imines, **B** undergoes back hydrogen transfer to ruthenium at a rate competitive with (or faster than) that for coordination of nitrogen. For these electron-rich imines, the rate-limiting step becomes the coordination of nitrogen to ruthenium, and reversible hydrogen transfer leads to imine isomerization, deuterium scrambling, and inverse isotope effects. This study has unmasked the complexity of the reactions of Shvo's hydroxycyclopentadienyl ruthenium hydride **5** with imines and has demonstrated the dependence of the reduction mechanism on the electronic nature of the imine.

Experimental Section

Preparation of Isotopologs of 5. Ruthenium hydrides **5**−**RuHOH** and doubly labeled **5**−**RuDOD** were prepared as described previously.[7] A THF solution of **5**−**RuDOD** was placed in a resealable NMR tube and degassed by three freeze−pump−thaw cycles. Hydrogen gas (1 atm at 77 K) was introduced, and the tube was sealed. When the mixture was warmed to room temperature, the pressure was estimated to be ∼4 atm. The solution was periodically shaken vigorously over 4 h and then degassed by three freeze−pump−thaw cycles to give a solution of **5**−**RuHOD** as the only product seen by ^{1}H NMR spectroscopy. Similarly, **5**−**RuDOH** was obtained in quantitative yield from **5**−**RuHOH** and D_2.

Independent Synthesis of Amine Complexes. [2,5-Ph$_2$-3,4-Tol$_2$-(η^4-C$_4$CO)]Ru(CO)$_2$[NH(CH$_2$C$_6$H$_4$-*p*-CH$_3$)CH(CH$_3$)$_2$] (13). A solution of isopropyl-(4-methylbenzyl)amine (14.3 mg, 0.088 mmol) and {[2,5-Ph$_2$-3,4-Tol$_2$(η^4-C$_4$CO)]Ru(CO)$_2$}$_2$ (**17**) (50.0 mg, 0.044 mmol) in dry CH_2Cl_2 (21 mL) was stirred under nitrogen at room temperature for 4 h. Solvent was evaporated under vacuum to give a brown solid which was recrystallized from hexanes at −30 °C to give **13** (52.0 mg, 81%) as a brown powder. ^{1}H NMR (THF-d_8, 500 MHz): δ 0.11 (d, ^3J = 7.2 Hz, CH(C*H*$_3$)CH$_3$), 0.97 (d, J = 6.2 Hz, C*H*HAr), 1.01 (d, ^3J = 7.2 Hz, CH(CH$_3$)C*H*$_3$), 1.90 (br d, ^3J = 11.4 Hz, CH*H*Ar), 2.12 (s, 6H, CpTolCH$_3$), 2.25 (s, 3H, C*H*$_3$Ar), 3.47 (m, C*H*(CH$_3$)CH$_3$), 6.8−7.7 (m, 22H, aromatics). ^{13}C{^{1}H} NMR (CD_2Cl_2, 75 MHz): δ 19.82 (CpTol*C*H$_3$), 21.39 (CH(*C*H$_3$)$_2$), 22.70 (CH$_2$C$_6$H$_4$*C*H$_3$), 49.41 (*C*HMe$_2$), 61.07 (*C*H$_2$Ar), 83.10, 84.84 (C3,4 of Cp), 103.86, 104.51 (C2,5 of Cp), 126.42, 126.76, 129.22, 132.45, 133.21, 133.92, 135.19, 138.08, 138.12, 138.30 (ipso and para of aromatics), 127.85, 128.28, 128.85, 128.91, 129.45, 129.68, 130.47, 130.71, 132.50, 132.65 (meta and ortho of aromatics), 163.37 (C1 of Cp), 201.39, 203.32 (CO). IR (CH_2Cl_2): ν 1950 (s), 2008 (s) cm^{-1}. HRMS (ESI) calcd (found) for [C$_{44}$H$_{41}$NO$_3$RuNa]$^+$ = 756.2028 (756.2051).

[2,5-Ph$_2$-3,4-Tol$_2$(η^4-C$_4$CO)]Ru(CO)$_2$NH(CH$_2$Ph)(Ph) (12). Reaction of *N*-benzylaniline (36 mg, 0.197 mmol) and **17** (112 mg, 0.098 mmol) in dry CH_2Cl_2 (20 mL) led to the isolation of **12** (106.3 mg, 72%) as a brown crystalline powder. ^{1}H NMR (THF-d_8, 360 MHz): δ 2.14 (s, 3H, CpTolC*H*$_3$), 2.19 (s, 3H, CpTolC*H*$_3$), 2.85 (br s, NH), 3.76 (dd, ^2J = 12.2 Hz, ^3J = 25.6 Hz, C*H*HC$_6$H$_5$), 4.57 (dd, ^3J = 14.7 Hz, ^2J = 12.2 Hz, C*H*HC$_6$H$_5$), 6.8−7.7 (m, 28 H, aromatics). ^{13}C{^{1}H} NMR (CD_2Cl_2, 90 MHz): δ 21.35 (CpTol*C*H$_3$), 21.42 (CpTol*C*H$_3$), 63.51 (*C*H$_2$C$_6$H$_5$), 83.72, 85.33 (C3,4 of Cp), 103.97, 104.06 (C2,5 of Cp), 120−139 (24 resonances, aromatic), 164.02 (C1 of Cp), 199.23, 201.46 (CO). IR (CH_2Cl_2): ν 1957, 2016 cm^{-1}. HRMS (ESI) calcd (found) for [C$_{46}$H$_{38}$NO$_3$Ru]$^+$ = 754.1895 (754.1901).

[2,5-Ph$_2$-3,4-Tol$_2$(η^4-C$_4$CO)]Ru(CO)$_2$NH(CH$_2$Ph)(C(CH$_3$)$_3$) (15). Upon reaction and workup, a solution of benzyl-*tert*-butylamine (14.5 mg, 0.088 mmol) and **17** (50.0 mg, 0.044 mmol) in dry CH_2Cl_2 (20 mL) at −22 °C yielded **15** as a brown solid. Increasing the temperature above ∼0 °C led to imine **15** and ruthenium hydride **5**−**RuHOH**, as identified by ^{1}H NMR spectroscopy as well as decomposition products. ^{1}H NMR (CD_2Cl_2, 360 MHz, −30 °C): δ 0.77 (s, 9H, C(C*H*$_3$)$_3$), 2.12 (s, CpTolC*H*$_3$), 2.22 (s, CpTolC*H*$_3$), 4.05 (dd, ^2J = 14.7 Hz, ^3J = 11.0 Hz, CH*H*C$_6$H$_5$), 4.20 (d, ^2J = 14.7 Hz, C*H*HC$_6$H$_5$), 6.8−7.8 (m, 23 H, aromatics). ^{13}C{^{1}H} NMR (CD_2Cl_2, 75 MHz, −30 °C): δ 21.44 (CpTol*C*H$_3$), 31.43 (C(*C*H$_3$)$_3$), 47.62 (*C*(CH$_3$)$_3$), 63.20 (benzyl), 83.52, 84.10 (C3,4 of Cp), 103.98, 104.02 (C2,5 of Cp), 126−135 (20 resonances, aromatics), 155.48 (C1 of Cp), 201.77, 201.26 (CO). HRMS (ESI) calcd (found) for [C$_{44}$H$_{40}$NO$_3$Ru]$^+$ = 732.2052 (732.2081).

[2,5-Ph$_2$-3,4-Tol$_2$(η^4-C$_4$CO)]Ru(CO)$_2$NH(CH$_2$Ph)$_2$ (14). Upon reaction and workup, a solution of dibenzylamine (17.3 mg, 0.88 mmol) and **17** (50.0 mg, 0.044 mmol) in dry CH_2Cl_2 (20 mL) formed **14** as a light brown solid. Upon recrystallization, reaction yielded 50.1 mg (0.065 mmol, 74%) of **14** as a brown powder. ^{1}H NMR (THF-d_8, 360 MHz): δ 2.13 (s, 6H, CpTolC*H*$_3$), 2.30 (br s, 4H, C*H*$_2$C$_6$H$_5$), 3.75 (br s, NH), 6.80−7.7 (m, 28H, aromatic). ^{13}C{^{1}H} NMR (CD_2Cl_2, 75 MHz): δ 21.34 (CpTol*C*H$_3$), 63.12 (benzyl), 84.15 (C3,4 of Cp), 104.03 (C2,5 of Cp), 126.54, 128.32, 129.29, 133.42, 136.79, 137.95 (ipso and para carbons of aromatics), 128.17, 128.73, 128.83, 129.16, 130.63, 132.46 (meta and ortho carbons of aromatics), 163.30 (C1 of Cp), 201.43 (CO). HRMS (ESI) calcd (found) for [C$_{47}$H$_{40}$NO$_3$Ru]$^+$ = 768.2052 (768.2050).

Kinetics of Imine Reduction. The general kinetic procedure will be illustrated with a specific example. A standard solution of **5**−**RuHOH** was prepared by heating ruthenium dimer **6** (8.4 mg, 7.4 μmol, 9.3 mM) in 0.8 mL of THF-d_8 under 4 atm H_2 at 70 °C overnight. An aliquot of **5**−**RuHOH** (0.25 mL, 4.6 μmol) was added to a resealable NMR tube and degassed by three freeze−pump−thaw cycles. A standard solution of *N*-benzylidene-*tert*-butylamine **11** (35.9 mg, 0.22 mmol, in 0.40 mL of THF-d_8, 0.56 M) was prepared in a glovebox; a 100 μL aliquot (55.7 μmol, 12 equiv) of this solution was added via a 250 μL gastight syringe to the solution of **5**−**RuHOH** and cooled to −78 °C. The cold NMR tube was resealed, inserted into an NMR spin collar, shaken for 2 s, and then inserted into the NMR spectrometer precooled to −47 °C. After locking and shimming (∼1.5 min), data acquisition was begun. The disappearance of the ruthenium hydride [δ −9.75 (RuH), δ 7.24 (arene)] and the appearance of the ruthenium amine complex [δ 7.66 (arene), δ 4.12 (benzyl), δ 0.70 (C(CH$_3$)$_3$] were both followed for over three half-lives. The temperature of the NMR probe was measured before and after each kinetic run via a thermocouple within an NMR tube. The temperature for each run varied less than 0.2 °C. Typically, 16 data points were taken, and a minimum of

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three runs were carried out with each isotopolog at each temperature. Data were plotted as concentration versus time, and the observed rate was determined by a nonlinear least-squares fit to a first-order exponential decay equation.

Procedure for ^{2}H NMR Experiments will be illustrated with a specific example. A standard solution of **5**−**RuDOH** was prepared by heating ruthenium dimer **6** (8.4 mg, 7.4 μmol, 9.3 mM) in 0.8 mL of THF under 4 atm H_2 at 70 °C overnight. An aliquot of the resulting **5**−**RuHOH** (0.25 mL, 4.6 μmol) was added to a resealable NMR tube and degassed by three freeze−pump−thaw cycles and then filled with 1 atm D_2 at −196 °C, warmed to room temperature, and periodically shaken over 6 h for quantitative conversion to **5**−**RuDOH**. This sample was again degassed by three freeze−pump−thaw cycles. A standard solution of *N*-benzylbenzylidene amine **10** (35.9 mg, 0.18 mmol, in 0.40 mL of THF, 0.460 M) was prepared in a glovebox; a 100 μL aliquot (46.0 μmol) of this solution was added via a 250 μL gastight syringe to the solution of **5**−**RuDOH** and cooled to −78 °C. This sample was kept cold until inserted into an NMR spectrometer precooled to −40 °C, and spectra were acquired.

Dehydrogenation of Isopropyl-(4-methyl)benzylamine (18). Standard solutions of ruthenium dimer **17** (20.3 mg in 0.7 mL, 0.0255 M) and *N*-benzyl imine **10** (51.2 mg in 0.4 mL, 0.656 M) in THF-d_8 were prepared in an inert atmosphere glovebox. An aliquot of each solution was added to a resealable NMR tube. The sample was cooled to −40 °C, and an aliquot of amine **19** (9.7 mg in 0.2 mL, 0.0297 M) was added via syringe over blowing nitrogen. The reaction solution contained 0.0145 M **17**, 0.187 M **10**, and 0.0424 M **19**. After reacting for several hours, the concentrations of newly formed imine **9** [δ 1.19 (*i*-Pr)] and imine **18** [δ 4.35 (CH_2Ph)] were measured using ^{1}H NMR spectroscopy.

Acknowledgment. Financial support from the Department of Energy, Office of Basic Energy Sciences, is gratefully acknowledged. J.J. thanks the ACS Organic Division Emmanuil Troyansky Graduate Fellowship for support. Grants from NSF (CHE-962-9688) and NIH (I S10 RR04981-01) for the purchase of NMR spectrometers are acknowledged. We thank Professor Jan-E. Bäckvall and co-workers for many useful discussions.

Supporting Information Available: Preparation of imines and amines, summary of kinetic runs, and Eyring plot. This material is available free of charge via the Internet at http://pubs.acs.org.

JA044450T