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# Stereochemistry of Imine Reduction by a Hydroxycyclopentadienyl Ruthenium Hydride

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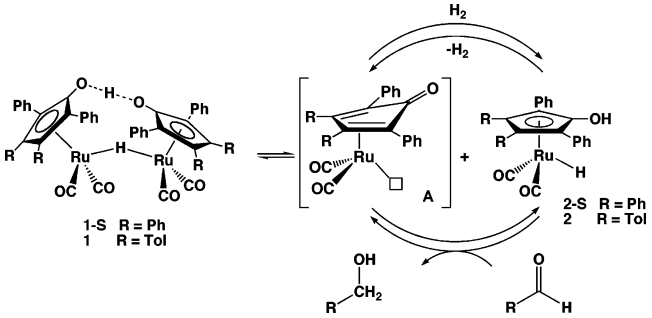
***Abstract:*** The stereochemistry of hydrogen transfer from [2,5-$Ph_2$-3,4-$Tol_2$($\eta^5$-$C_4$COD)]Ru$(CO)_2$D to *N*-aryl imines to give amine complexes was shown to be mostly trans stereospecific. Stereospecific hydrogen transfer is proposed to generate an amine and a coordinatively unsaturated ruthenium intermediate in close proximity. Coordination of the amine is proposed to occur faster than lone pair inversion of the amine. In contrast, hydrogen transfer to *N*-alkyl imines is stereorandom. It is proposed that stereochemistry is lost in part due to the reversibility of the hydrogen transfer being faster than amine coordination.

## Introduction

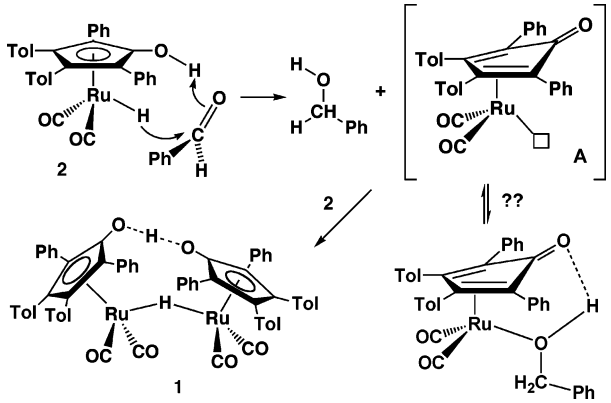
Shvo discovered that the diruthenium bridging hydride complex {[2,3,4,5-$Ph_4$($\eta^5$-$C_4$CO)]$_2$H}$Ru_2(CO)_4$($\mu$-H) **(1-S)** is an efficient catalyst for the hydrogenation of aldehydes and ketones[1] and for transfer hydrogenation of ketones using alcohols as the reducing agent.[2] In the reduction of ketones to alcohols, the mononuclear hydroxycyclopentadienyl ruthenium hydride [2,3,4,5-$Ph_4$($\eta^5$-$C_4$COH)]Ru$(CO)_2$H **(2-S)** was proposed to be the active reducing agent and was shown to reduce aldehydes and ketones (Scheme 1).[1b,1c]

***Scheme 1***



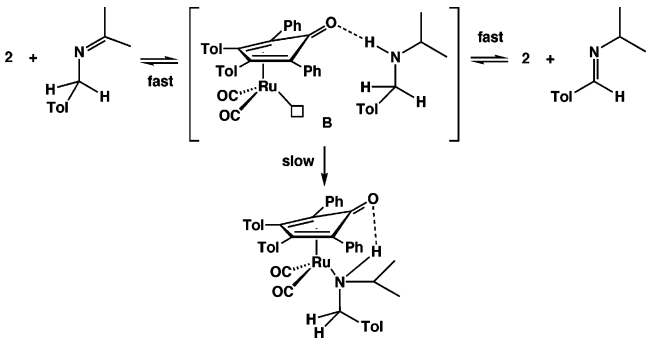

Based on detailed mechanistic studies on the related tolyl complex [2,5-$Ph_2$-3,4-$Tol_2$($\eta^5$-$C_4$COH)]Ru$(CO)_2$H **(2)**, including observation of primary deuterium isotope effects for transfer of both OH and RuH, we proposed a mechanism involving concerted transfer of proton and hydride to aldehyde outside the coordination sphere of the metal (Scheme 2).[3]

***Scheme 2***




More recently, the mechanistic aspects of imine reduction leading to ruthenium amine complexes[3,4] have been investigated.[5,6] We reported detailed mechanistic studies of the reduction of a series of imines having different electronic properties.[5] Reduction of *N*-aryl imines displayed large isotope effects consistent with rate-limiting concerted hydrogen transfer, reactivity that mirrors that of aldehyde and ketone reduction. However, reduction of more electron-rich *N*-alkyl imines showed inverse kinetic isotope effects, imine isomerization, and deuterium scrambling (Scheme 3).[5] These phenomena were ex-

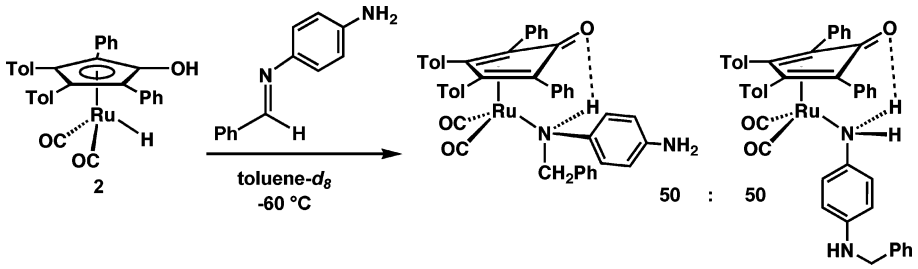
***Scheme 3***



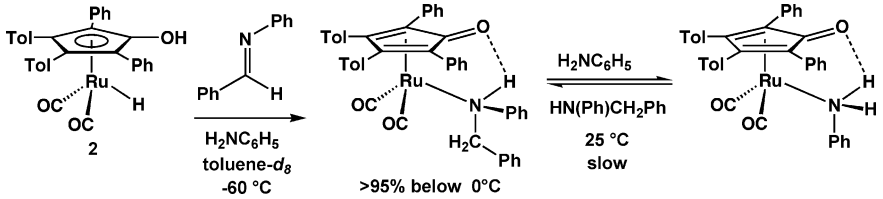

(1) (a) Shvo, Y.; Czarkie, D.; Rahamim, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7400. (b) Menashe, N.; Shvo, Y. *Organometallics* **1991**, *10*, 3885. (c) Menashe, N.; Salant, E.; Shvo, Y. *J. Organomet. Chem.* **1996**, *514*, 97.
(2) (a) Almeida, M. L. S.; Beller, M.; Wang, G.-Z.; Bäckvall, J.-E. *Chem. Eur. J.* **1996**, *2*, 1533. (b) Larsson, A. L. E.; Persson, B. A.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1211. (c) Persson, B. A.; Larsson, A. L. E.; Le Ray, M.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 1645. (d) Persson, B. A.; Huerta, F. F.; Bäckvall, J.-E. *J. Org. Chem.* **1999**, *64*, 5237. (e) Huerta, F. F.; Laxmi, Y. R. S.; Bäckvall, J.-E. *Org. Lett.* **2000**, *2*, 1037. (f) Laxmi, Y. R. S.; Bäckvall, J.-E. *Chem. Commun.* **2000**, 611.
(3) Casey, C. P.; Singer, S. W.; Powell, D. R.; Hayashi, R. K.; Kavana, M. *J. Am. Chem. Soc.* **2001**, *123*, 1090.


**10.1021/ja056402u CCC: $33.50** 

**Scheme 4**




**Scheme 5**




plained by a change in the rate-limiting step from hydrogen transfer to amine coordination.

We also have studied the reduction of imines in the presence of free amines to distinguish between mechanisms involving coordination of nitrogen before reduction (concurrent with Cp ring slippage)[7] and mechanisms involving generation of amines and coordinatively unsaturated ruthenium intermediates.[8] Reduction of an amine-substituted imine resulted in the formation of complexes of both the newly generated amine and the pre-existing amine in a 1:1 ratio (Scheme 4). This combination of products requires transfer of hydrogen from **2** to amine-substituted imine to generate a diamine and coordinatively unsaturated ruthenium intermediate which can be trapped by either amine within the solvent cage.

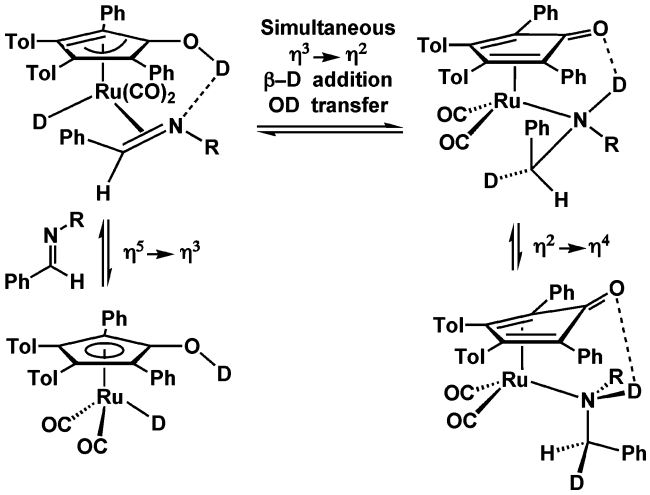
In contrast, reduction of an imine in the presence of an external amine resulted in only the complex formed from complexation of the newly generated amine (Scheme 5). This indicates that even though there may be competition between amines inside the solvent cage, amine diffusion from the solvent cage is much slower than amine coordination to the metal center.

Since trapping of amines by coordination to the ruthenium center is even faster than diffusion from the solvent cage, we thought that amine coordination to ruthenium might be even faster than nitrogen inversion and provide the opportunity for determination of the stereochemistry of imine reduction by **2**. Here we report deuterium labeling experiments that establish the predominant trans stereochemistry of the reduction of *N*-aryl imines by **2**.

## Results

Amine nitrogen inversion is extremely rapid ($\Delta G^{\ddagger} \sim 7.5$ kcal mol$^{-1}$) and has until now precluded determination of the stereochemistry of reduction of imines by any reagent or catalytic system.[9,10] In the reduction of imines by **2**, the amine is generated within a solvent cage and complexation to

**Scheme 6**



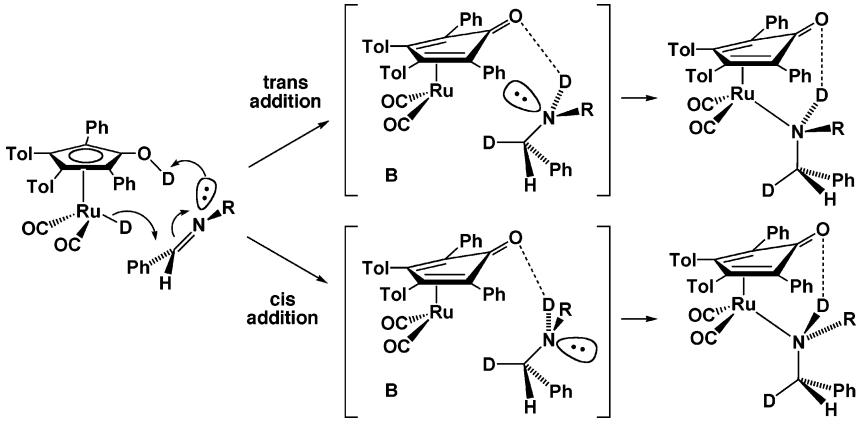

ruthenium occurs before diffusion apart. Since the newly generated amine is so rapidly trapped by coordination and since the amine complex has configurational stability, we set out to determine the stereochemistry of imine reduction by **2**.

Prior to our most recent trapping experiment studies that ruled out a ring slippage mechanism,[8] we were looking for experiments that might distinguish between ring slip mechanisms involving prior coordination of the imine and mechanisms involving transfer of hydrogen without prior imine coordination. We thought that determination of the stereochemistry of imine reduction would provide information to help differentiate between these mechanisms. Cp ring slip and substrate coordination prior to the reduction step, as proposed by Bäckvall, would be expected to lead to trans addition of deuterium (Scheme 6). Hydrogen transfer outside the coordination sphere might lead to either cis or trans addition of deuterium depending on the orientation assumed by the newly generated nitrogen lone pair (Scheme 7).

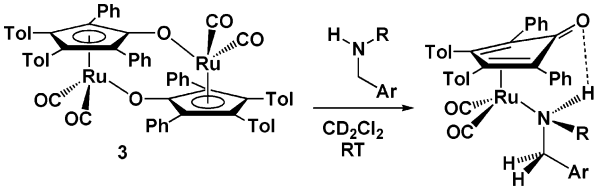
Before examination of the stereochemistry of reduction of imines by **2-RuDOD**, we prepared the unlabeled amine complexes to study their spectral properties (Scheme 8).

(4) Abed, M.; Goldberg, I.; Stein, Z.; Shvo, Y. *Organometallics* **1988**, *7*, 2054.
(5) Casey, C. P.; Johnson, J. B. *J. Am. Chem. Soc*. **2005**, *127*, 1883.
(6) **1-S** is an effective catalyst for the reduction of imines via hydrogen transfer from alcohols. Samec, J. S. M.; Bäckvall, J.-E. *Chem. Eur. J.* **2002**, *8*, 2955.
(7) Csjernyik, G.; Éll, A. H.; Fadini, L.; Pugin, B.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 1657.
(8) Casey, C. P.; Bikzhanova, G. A.; Guzei, I. A. *J. Am. Chem. Soc.* **2005** *127*, 14062.
(9) Rauk, A.; Allen, L. C.; Mislow, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 400.
(10) Bushweller, C. H.; O'Neil, J. W.; Bilofsky, H. S. *Tetrahedron* **1972**, *28*, 2697.

***Scheme 7***




***Scheme 8***




Stereochemistry of hydrogenation of aryl aldimines can be determined by $^1$H NMR spectroscopy since ruthenium benzylamine complexes **4a**−**4d** have diastereotopic benzyl hydrogens. The benzyl hydrogen with large geminal and large vicinal couplings is defined as $\mathbf{H}_A$, and the benzyl hydrogen with large geminal and small vicinal couplings is defined as $\mathbf{H}_B$. The $^1$H NMR resonance of $\mathbf{H}_A$, which is anti to a proton $\mathbf{H}_X$ on nitrogen, is an apparent triplet due to similar couplings to $\mathbf{H}_B$ and $\mathbf{H}_X$. The resonance of $\mathbf{H}_B$, which is gauche to $\mathbf{H}_X$, appears at lower frequency than $\mathbf{H}_A$ as a doublet of doublets with a larger coupling to $\mathbf{H}_A$ and smaller one to $\mathbf{H}_X$. To determine which of the benzylic protons is $\mathbf{H}_A$ and which is $\mathbf{H}_B$, we need to know the major rotamer about the *N*-benzyl bond (Figure 1).

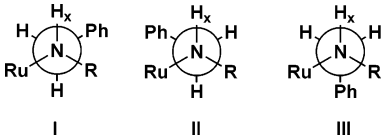



***Figure 1.*** Three rotamers about the *N*-benzyl bond of ruthenium amine complexes.

Rotamer **III**, which has Ph gauche to both Ru and R, would be expected to have similar coupling constants to $\mathbf{H}_X$ and was excluded based on the observation of very different $J_{AX}$ (13 Hz) and $J_{BX}$ (2 Hz). The X-ray crystal structure of **4a** (Figure 1S, Supporting Information) has conformation **I** with Ru anti to Ph. DFT calculations on a simplified analogue of **4a**, $(C_5H_4O)(CO)_2RuNHMe(CH_2Ph)$, at the B3LYP/LANL2DZ level of theory also showed that conformation **I** was 2.3 kcal mol$^{-1}$ more stable than **II** with Ru gauche to Ph.[11]

Conformations **I** and **II** were experimentally distinguished by NOESY 1D NMR spectroscopy. Irradiation of the N-Me resonance of **4c** at $\delta$ 2.39 gave rise to two clear signal enhancements at $\delta$ 1.65 (N$\mathbf{H}_X$, 9% nOe) and 3.57 ($\mathbf{H}_A$, 4% nOe) (Figure 2). Irradiation of the $\mathbf{H}_B$ resonance at $\delta$ 3.77 of **4c** resulted in two significant enhancements at $\delta$ 1.65 (N$\mathbf{H}_X$, 5% nOe) and 3.57 ($\mathbf{H}_A$, 16% nOe). The nOe between the methyl group and $\mathbf{H}_A$ but not $\mathbf{H}_B$ establishes conformation **I** for **4c**.

In a NOESY 1D NMR experiment on **4d**, irradiation of the *o*-methyl resonance at $\delta$ 2.78 gave rise to two clear signal enhancements at $\delta$ 4.15 ($\mathbf{H}_A$, 5% nOe) and 6.62 (*m*-H of mesityl, 4% nOe). Irradiation of the $\mathbf{H}_B$ resonance at $\delta$ 3.85 of **4d** resulted in two significant enhancements at $\delta$ 4.15 ($\mathbf{H}_A$, 16% nOe) and 4.78 (N$\mathbf{H}_X$, 4% nOe). These nOe results require conformation **I** for **4d** (Figure 2).

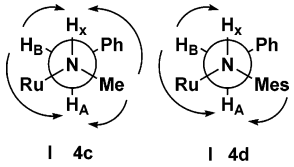



***Figure 2.*** NOESY 1D NMR spectroscopy data for **4c** and **4d**.

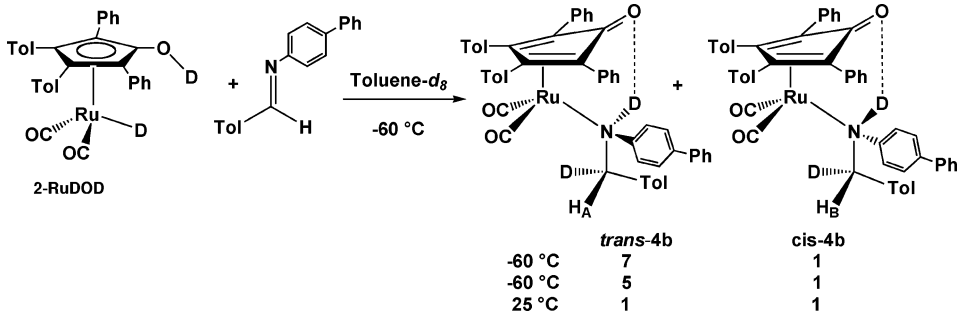
In summary, NOESY 1D NMR spectroscopy on **4c** and **4d**, the X-ray structure of **4a**, and DFT calculations all support the assignment of conformation **I** with phenyl and Ru anti for amine complexes **4a**−**4d**. With the conformation of **4a**−**4d** firmly established, it is possible to determine the stereochemistry of reduction of imines by **2-RuDOD**. *trans*-Addition of deuterium would generate a ruthenium amine complex with deuterium in place of $\mathbf{H}_B$ and the benzyl hydrogen resonance of $\mathbf{H}_A$ would appear as a broad singlet in the $^1$H NMR spectrum. Similarly, *cis*-addition of deuterium would result in the appearance of only the $\mathbf{H}_B$ benzyl hydrogen resonance.

***trans*-Stereochemistry of Reduction of *p*-Ph-$C_6H_4$N═CHTol by 2-RuDOD.** When *p*-Ph-$C_6H_4$N═CHTol was added to a toluene-$d_8$ solution of **2-RuDOD** at −60 °C, broad singlets corresponding to 0.87 $\mathbf{H}_A$ ($\delta$ 4.27) and 0.13 $\mathbf{H}_B$ ($\delta$ 4.08) of **4b** appeared in the $^1$H NMR spectrum within 2 min at −60 °C (Scheme 9).[12] Complete disappearance of the tolyl methyl resonances at $\delta$ 1.85 of **2-RuDOD** and appearance of new resonances for inequivalent tolyl methyl groups of **4b** at $\delta$ 1.77 and 1.80 were also observed in the $^1$H NMR spectrum. The

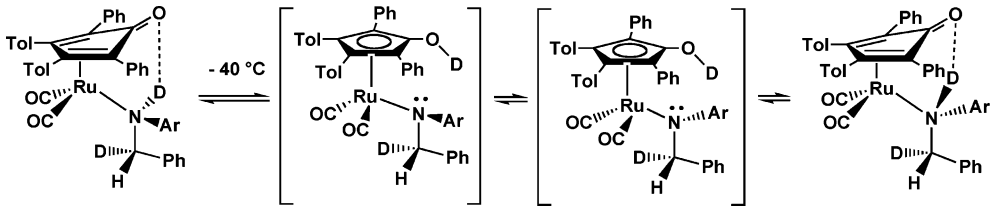
(11) See Supporting Information for details of DFT calculations.

(12) Integrations were measured relative to the tolyl methyl group resonances, were within 5% of 1.00, and normalized to 1.00.

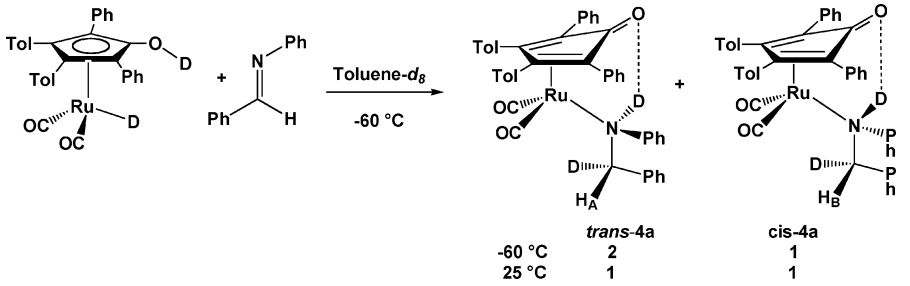
***Scheme 9***




***Scheme 10***




***Scheme 11***




formation of a 7:1 ratio of trans hydrogenation product (***trans*-4b**) : cis hydrogenation product (***cis*-4b**) shows that reduction occurs mainly by trans addition of hydrogen.

In a similar experiment, a 5:1 ratio of $\mathbf{H}_A$:$\mathbf{H}_B$ was observed. Differences may be the result of some product isomerization upon inadvertent warming of samples when NMR tubes are inserted into the pre-cooled spectrometer. No isomerization of ***trans*-4b** was seen at −60 °C and only slow isomerization was seen at −40 °C. Upon warming to room temperature, the mixtures of ***trans*-4b** and ***cis*-4b** equilibrated to a 1:1 ratio probably due to the inversion at the nitrogen. This equilibration presumably occurs through complete transfer of the proton from nitrogen to oxygen, inversion at the nitrogen center,[13] rotation around the ruthenium nitrogen bond, and proton transfer back on nitrogen (Scheme 10).

***trans*-Stereochemistry of Reduction of PhN=CHPh by 2-RuDOD.** When *N*-benzylideneaniline was added to a toluene-$d_8$ solution of **2-RuDOD** at −60 °C, broad singlets corresponding to 0.66 $\mathbf{H}_A$ ($\delta$ 4.16) and 0.34 $\mathbf{H}_B$ ($\delta$ 4.01) appeared in the $^1$H NMR spectrum within 2 min at −60 °C (Scheme 11).[12] Complete disappearance of the tolyl methyl resonances at $\delta$ 1.85 of **2-RuDOD** and appearance of new resonances for inequivalent tolyl methyl groups of **4a** at $\delta$ 1.78 and 1.82 were also observed in the $^1$H NMR spectrum. The observation of a 2:1 ratio of ***trans*-4a**:***cis*-4a** shows that imine reduction occurs by predominant trans addition. Upon warming to room temperature, the mixture of ***trans*-4a** and ***cis*-4a** equilibrated to a 1:1 ratio.

**Stereorandom Products from Reduction of 2,4,6-$Me_3$−$C_6H_2$N=CHPh.** To determine the effect of steric crowding at nitrogen on the stereochemistry of reduction, the reaction of *N*-benzylidene-2,4,6-trimethylaniline by **2-RuDOD** in toluene-$d_8$ was studied. No reduction was seen at −60 °C, but reduction proceeded slowly at −10 °C. Two broad singlets corresponding to 0.53 $\mathbf{H}_A$ ($\delta$ 3.97) and 0.47 $\mathbf{H}_B$ ($\delta$ 3.74) appeared in the $^1$H NMR spectrum at −10 °C (Scheme 12).[12] Complete disappearance of the tolyl methyl resonances at $\delta$ 1.85 of **2-RuDOD** and appearance of new resonances for inequivalent tolyl methyl groups of **4d** at $\delta$ 1.70 and 1.76 were also observed in the $^1$H NMR spectrum. The 1:1 ratio of ***trans*-4d**:***cis*-4d** is likely the result of fast equilibration of trans and cis reduction products at −10 °C. Consequently, no information is obtained about the initial stereochemistry of reduction in this experiment.

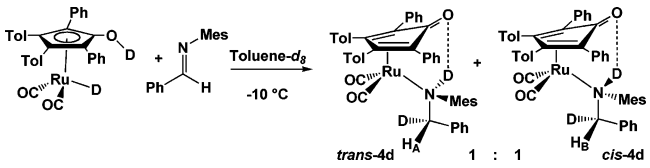
**Low *trans*-Stereospecificity in Reduction of MeN=CHPh by 2-RuDOD.** Since alkylamines are more basic and also have higher inversion barriers than arylamines,[9,14] we thought that reduction of *N*-alkyl imines by **2-RuDOD** might proceed with higher stereospecificity. We reasoned that the initially generated alkylamine would invert more slowly and complex more rapidly to ruthenium and thus retain whatever its initial stereochemistry.

When *N*-benzylidenemethylamine was added to a toluene-$d_8$ solution of **2-RuDOD** at −60 °C, broad singlets corresponding

(13) While the nitrogen center in metal amides is flat for electron-deficient metal species, amide ligands bound to 18e metal centers are often pyramidal. $TpRu(CO)(PPh_3)(NHPh)$ has a pyramidal nitrogen center with the sum of the angles around nitrogen of 346.5°.[a] $Cp(NO)(PPh_3)ReNHPh$ is also pyramidal with the sum of the angles around nitrogen of 345.5°.[b,c] (a) Jayaprakash, K. N.; Gunnoe, T. B.; Boyle, P. D. *Inorg. Chem.* **2001,** *40*, 6481. (b) Dewey, M. A.; Arif, A. M.; Gladysz, J. A. *J. Chem. Soc., Chem. Commun.* **1991**, 712. (c) Dewey, M. A.; Knight, D. A.; Arif, A. M.; Gladysz, J. A. *Chem. Ber.* **1992**, *125*, 815.

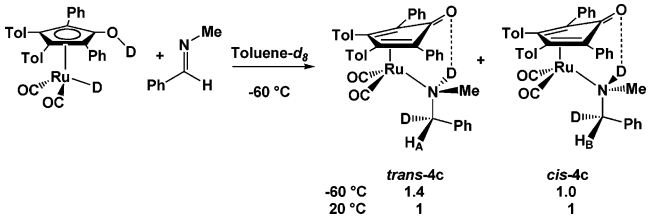
to 0.59 $\mathbf{H}_A$ ($\delta$ 2.95) and 0.41 $\mathbf{H}_B$ ($\delta$ 3.75) of **4c** appeared in the $^1$H NMR spectrum within 2 min at −60 °C (Scheme 13).[12] Complete disappearance of the tolyl methyl resonances at $\delta$ 1.85 of **2-RuDOD** and appearance of new resonances for inequivalent tolyl methyl groups of **4c** at $\delta$ 1.78 and 1.80 were also observed in the $^1$H NMR spectrum. The observation of a 1.4:1 ratio of ***trans*-4c**:***cis*-4c** shows that imine reduction occurs with a slight preference for trans addition. Upon warming to room temperature, the mixture of ***trans*-4c** and ***cis*-4c** equilibrated to a 1:1 ratio. The lower stereospecificity of *N*-alkyl imine reduction compared with *N*-aryl imine reduction was contrary to our expectations.

***Scheme 12***




$^2$H NMR spectroscopy was employed to further investigate the reduction of MeN═CHPh by **2-RuDOD**. The reaction of MeN═CHPh (0.120 M) with **2-RuDOD** (0.018 M) was run at −60 °C in toluene and the product **4c** was examined by $^2$H NMR spectroscopy at room temperature. In addition to approximately equal amounts of deuterium in the two benzyl positions of **4c** ($\delta$ 3.18, $CHD_APh$, 37% of total D; and $\delta$ 3.80, $CD_BHPh$, 43% of D), deuterium was also observed in the *N*-methyl group of **4c** ($\delta$ 1.80, 11% of D). In addition, deuterium was seen in the residual excess imine MeN═CHPh ($\delta$ 7.77, N═CD, 9% of D).

***Scheme 13***




The incorporation of deuterium into MeN═CDPh requires reversible imine reduction and the incorporation of deuterium into a *N*-methyl group of amine complex **4c** requires an isomerization to $CH_2$═NCHDPh and then reduction by **2-RuDOD**. Earlier, we reported evidence for reversible hydrogen transfer from **2** to *N*-alkyl imines.[5] The lack of stereospecificity of *N*-alkyl imine reduction is related to this reversibility which erodes any initial stereospecificity of the process. Further explanation will be provided in the Discussion section.

**Stereorandom Reduction Products from $Me_3CN$═CHPh and 2-RuDOD.** To eliminate complications caused by imine isomerization, we examined reduction of *N*-benzilidene-*tert*-butylamine. When $Me_3CN$═CHPh was added to a toluene-$d_8$ solution of **2-RuDOD** at −60 °C, broad singlets corresponding to 0.48 $\mathbf{H}_A$ ($\delta$ 3.94) and 0.52 $\mathbf{H}_B$ ($\delta$ 4.43) appeared in the $^1$H NMR spectrum within 2 min at −60 °C (Scheme 14).[12] Complete disappearance of the tolyl methyl groups at $\delta$ 1.85 of **2-RuDOD** and appearance of new resonances for inequivalent tolyl methyl groups of **5** at $\delta$ 1.73 and 1.76 were also observed in the $^1$H NMR spectrum. Possible events leading to formation of approximately equal amounts of ***trans*-5**:***cis*-5** will be considered in the Discussion section.

Raising the temperature above 0 °C led to decomposition of **5** generating *N*-benzyl-*tert*-butylamine and ruthenium cyclopentadienone dimer **3** identified by $^1$H NMR spectroscopy as well as other decomposition products.

The reaction of $Me_3CN$═CHPh (0.120 M) with **2-RuDOD** (0.018 M) at −60 °C in toluene was also monitored by $^2$H NMR spectroscopy. No deuterium incorporation into residual excess imine $Me_3CN$═CHPh was seen in the $^2$H NMR spectrum at −60 °C. The deuterium resonances of the benzyl group were broad and could not be resolved at −60 °C. Upon warming of the mixture to room temperature, three deuterium resonances for **5** ($\delta$ 2.39 ND, 4.34 CHDPh, and 3.94 CDHPh) and the CHDPh resonance of *N*-benzyl-*tert*-butylamine ($\delta$ 3.54) were observed. However, all deuterium resonances were too broad for accurate integration.

## Discussion

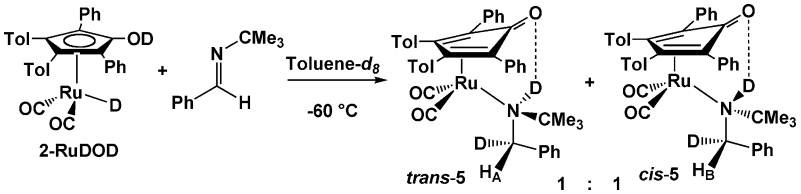
The stereochemistry of imine reduction by any reagent or catalyst system has never been reported since rapid nitrogen inversion scrambles the stereochemistry of the amine product. In this study, the rapid trapping of the newly generated amine by complexation to ruthenium enabled the determination of the stereochemistry of imine reduction by **2-RuDOD**.

***trans*-Stereospecificity of Reduction of *N*-Aryl Imines.** The reduction of *p*-Ph−$C_6H_4$N═CHTol by **2-RuDOD** in toluene produced ruthenium amine complex **4b** with a 5 to 7:1 preference for trans addition of hydrogen; similarly, PhN═CHPh was reduced with a 2:1 preference for trans addition. Previously, we had observed normal deuterium kinetic isotope effects for both RuD and OD in the reaction of *N*-aryl imines with **2-RuDOD** and interpreted this in terms of simultaneous transfer of OH to the imine nitrogen and transfer of RuH to the imine carbon to give intermediate **B** (Scheme 7). Intermediate **B**, which has a vacant site at ruthenium and an amine hydrogen bonded to the dienone carbonyl oxygen, collapses to a ruthenium amine complex faster than amine escapes from the solvent cage (Schemes 4 and 5).

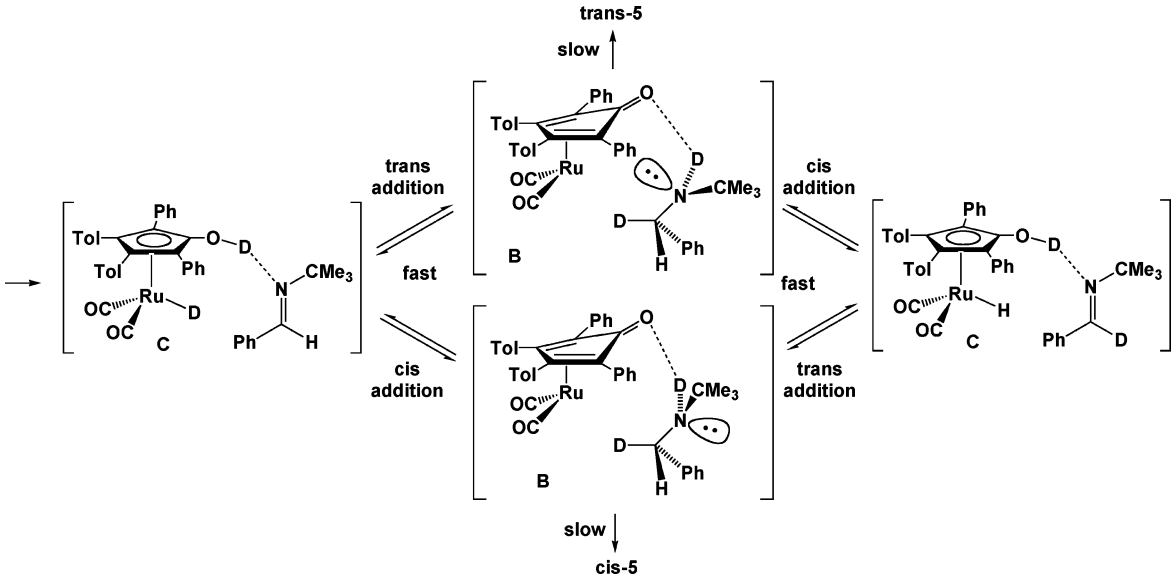
Why should there be a preference for trans addition? Scheme 7 shows protonation of the imine nitrogen lone pair in the C═N plane and, as hydride is transferred from ruthenium to carbon, a new lone pair is generated perpendicular to the C═N plane in one of two orientations. If the amine substituents move toward the sterically crowded dienone ligand, the lone pair goes anti to the new C−H bond and a cis addition results. If the amine substituents move away from the sterically crowded dienone ligand, the lone pair goes syn to the new C−H bond and a trans addition results. The observed trans stereochemistry of *N*-aryl imine reduction is, therefore, attributed to steric effects pushing the amine substituents away from the dienone. The observation of stereospecificity requires that complexation of the stereospecifically formed amine to ruthenium be much faster than nitrogen inversion, which has a very low barrier (~7.5 kcal $mol^{-1}$).[9,10]

(14) Nitrogen inversion is faster for arylamines than for alkylamines. The magnitude of the energy barrier to inversion in amines is correlated by the intergroup bond angle (α, C1−N−C2) and arylamines usually have larger intergroup bond angles (α, C1−N−C2) and are easier to invert. Both the wide angles and lower inversion barrier of arylamines are related to greater resonance stabilization by interaction with the arene π-system as planarity is approached. Koeppl, G. W.; Sagatys, D. S.; Krishnamurthy, G. S.; Miller, S. I. *J. Am. Chem. Soc.* **1967**, *89*, 3396.

***Scheme 14***




***Scheme 15***




If trans hydrogenation predominates, then how do cis products arise? There are three possible ways to form cis products: (1) direct cis addition to the imine; (2) 100% trans addition followed by some amine inversion prior to coordination; (3) partial isomerization of trans addition products.

While a small amount of cis product might result from product isomerization due to slight warming of samples upon transfer to the pre-cooled NMR probe, we do not believe that this is a major source of cis product. The arylamine complexes ***trans*-4** and ***trans*-5** are configurationally stable at −60 °C and slowly isomerize over several hours above ca. −40 °C to 1:1 mixtures of cis and trans isomers. This equilibration presumably occurs through complete transfer of the proton from nitrogen to oxygen, inversion at the nitrogen center, rotation around the ruthenium nitrogen bond, and proton transfer back on nitrogen (Scheme 10).

Amine inversion prior to coordination also seems unlikely. Nitrogen inversion in arylamines is faster than that in alkylamines. Coordination of the less basic arylamines to ruthenium center would be expected to be slower than coordination of the more basic alkylamines. If nitrogen inversion were responsible for loss of stereospecificity, then reduction of *N*-aryl imines would have been expected to be less stereospecific than reduction of *N*-alkyl imines. Since the opposite is observed, it is unlikely that nitrogen inversion before coordination is responsible for loss of stereochemistry.

The most straightforward explanation—that cis products result from initial cis reduction—is, therefore, the one we favor.

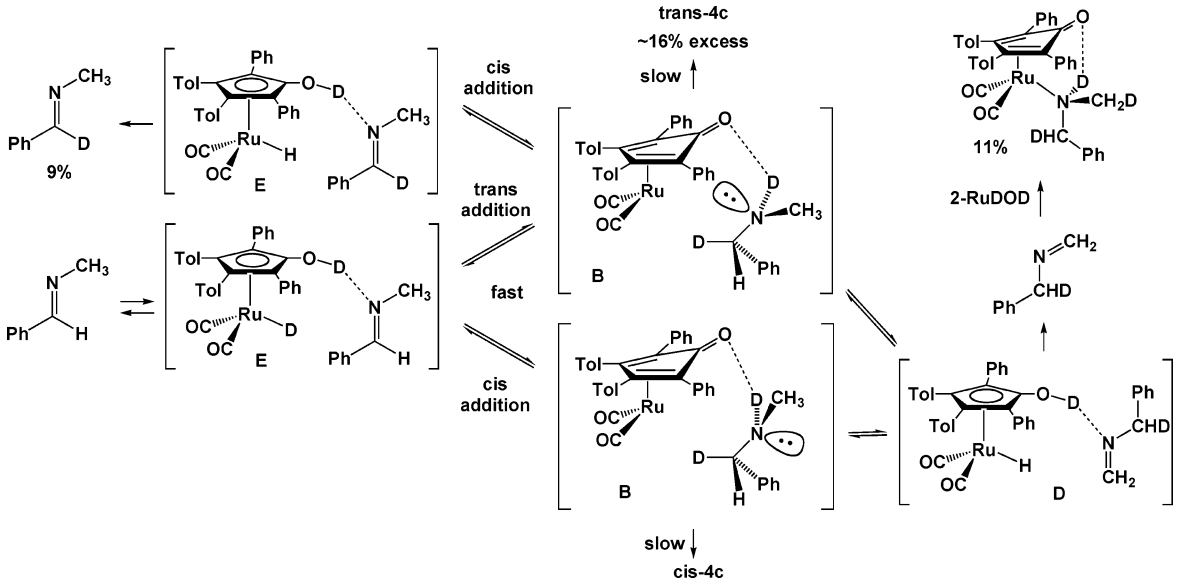
**Stereorandom Reduction of *N*-Alkyl Imines.** Little or no stereospecificity was seen in the reduction of *N*-alkyl imines such by **2-RuDOD** at −60 °C in tolutene-$d_8$. This is a direct consequence of a change in the rate-limiting step from hydrogen transfer to amine coordination for the reduction of *N*-alkyl imines compared with that of *N*-aryl imines.[5] The reversibility of hydrogen transfer to the imine provides additional pathways for loss of stereochemistry. The more electron-rich *N*-alkyl imines showed inverse kinetic isotope effects, imine isomerization, and deuterium scrambling (Scheme 3).[5] Electron donor alkyl substituents on nitrogen are expected to speed up amine dehydrogenation as well as amine coordination. We do not understand why *N*-alkyl groups accelerate back hydrogen transfer more than amine coordination.

No stereospecificity was seen in the reduction of $Me_3CN{=}CHPh$ by **2-RuDOD**. This is not inconsistent with some preference for trans addition over cis addition as in the case of arylamines coupled with reversibility of the hydrogen transfer. With many cycles through an only partially stereospecific process, all stereochemical information will be lost. It is significant that no $Me_3CN{=}CDPh$ was formed in the reduction. This suggests that the reversible addition involves intermediate **C** in which the imine is hydrogen-bonded to the CpOH group and that **C** does not release imine into bulk solution (Scheme 15).[15]

No more than about 16% trans stereospecificity was seen in the reduction of $MeCN{=}CHPh$ by **2-RuDOD**. Significantly, deuterium was found in the *N*-methyl group of amine complex **4c** (11%) and in residual imine $MeN{=}CDPh$ (9%). The presence of the *N*-methyl group provides additional opportunities for loss of stereochemistry since reversible addition of hydrogen to the imine can also lead to isomerized imine $CH_2{=}NCHDPh$

(15) Another process that merits consideration is reversible dehydrogenation of intermediate **B** to give an *anti*-imine. This process, on its own, cannot account for loss of stereochemistry if only trans addition and elimination occur.

*Scheme 16*




(Scheme 16). The intervention of intermediate **D** in which $CH_2$═NCHDPh is hydrogen-bonded to the CpOH group is enough to lose stereochemical information. The incorporation of deuterium into the *N*-methyl group of **4c** requires dissociation of $CH_2$═NCHDPh from **D** and then reaction of free with $CH_2$═NCHDPh with **2-RuDOD**. The formation of MeN═CDPh requires hydrogen transfer to imine with one stereochemistry, reverse of the hydrogen transfer with the opposite stereochemistry, and then dissociation of MeN═CDPh from **E**. We do not understand why imine dissociation occurs from **D** and **E** but not from **C**.

## Conclusion

Our observations of the trans reduction of *N*-aryl imines by **2-RuDOD** constitute the first determination of the stereochemistry of an imine reduction. They also serve to highlight some of the very fast reactions of intermediate **B**: coordination of the aryl-alkyl-amine to Ru is faster than inversion at nitrogen. The stereorandom reduction of *N*-alkyl imines by **2-RuDOD** also requires very fast reactions of intermediate **B**: reversible dehydrogenation of the newly formed dialkylamine is faster than amine coordination to ruthenium. Our earlier studies of successful intramolecular trapping (but failed intermolecular trapping) of **B** showed that breaking the amine hydrogen bond to the dienone carbonyl oxygen of **B** and escape of the amine from the solvent cage is slower than amine coordination to ruthenium. The "slow" reactions of **B** including amine escape from the solvent cage and amine inversion are only slow in comparison with the even faster coordination of nitrogen to ruthenium and reversible dehydrogenation of the amine.

## Experimental Section

**[2,5-Ph$_2$-3,4-Tol$_2$($\eta^4$-C$_4$CO)](CO)$_2$RuNH(C$_6$H$_4$-*p*-Ph)(CH$_2$Tol) (4b).** *Procedure A.* A solution of *N*-(*p*-methylbenzylidene)-*p*-phenylaniline (16.4 mg, 0.06 mmol) in toluene-$d_8$ was added to a solution of **2** (34.2 mg, 0.06 mmol) in toluene-$d_8$ (0.5 mL) at −78 °C. After slow warming to room temperature, solvent was evaporated under vacuum to give a green solid which was recrystallized from hexane at −10 °C to afford **4b** (35 mg, 68% yield) as a yellowish green solid.

*Procedure B. N*-(*p*-Methylbenzyl)-*p*-phenylaniline (54.7 mg, 0.20 mmol) was added via syringe to a $CD_2Cl_2$ suspension of ruthenium cyclopentadienone dimer (**3**) (114 mg, 0.10 mmol) and the mixture was stirred for 30 min, until all the material dissolved. Solvent was evaporated under vacuum to afford **4b** (120 mg, 71% yield) as a yellowish green solid, mp 130−132 °C (dec). IR ($CD_2Cl_2$): 2016 (s), 1957 (s) cm$^{-1}$. $^1$H NMR ($CD_2Cl_2$, 500 MHz): $\delta$ 2.19 (s, tolyl $CH_3$), 2.20 (s, tolyl $CH_3$), 2.27 (s, tolyl $CH_3$), 3.82 (br d, $^3J_{BX}$ = 11.0 Hz, NH), 3.90 (ABX, $^2J_{AB}$ = 13.5 Hz, $^3J_{AX}$ = 2.0 Hz, NC*H*$_A$H), 4.51 (ABX, $^2J_{AB}$ = 13.5 Hz, $^3J_{BX}$ = 11.0 Hz, NCH*H*$_B$), 6.91−7.51 (m, 29 H, aromatic), 7.89 (d, $^3J$ = 8.5 Hz, 2 H, aromatic). $^{13}$C{$^1$H} NMR ($CD_2Cl_2$, 125 MHz): $\delta$ 21.16, 21.23 (tolyl $CH_3$); 63.08 (N*C*H$_2$Tol), 83.45, 85.25 (C 3, 4 of Cp); 103.69, 103.94 (C 2, 5 of Cp); 120.11, 126.63, 126.95, 127.47, 127.53, 127.96, 128.20, 128.63, 128.79, 129.05, 129.36, 130.54, 131.07, 132.20, 132.31, 132.77, 133.14, 134.19, 137.67, 137.95, 138.07, 138.17, 140.25, 149.71 (aromatic),[16] 163.88 (C1 of Cp), 198.97, 201.26 (CO). HRMS (ESI) (M + H)$^+$: Calcd for $C_{53}H_{43}NO_3{}^{102}Ru$, 844.2286; found, 844.2305.

**[2,5-Ph$_2$-3,4-Tol$_2$($\eta^4$-C$_4$CO)](CO)$_2$RuNH(CMe$_3$)(CH$_2$Ph) (5).** A solution of *N*-benzylidene-*tert*-butylamine (3.7 $\mu$L, 0.02 mmol) in toluene-$d_8$ was added to a solution of **2** (11.4 mg, 0.02 mmol) in toluene-$d_8$ (0.5 mL) at −78 °C. The reaction mixture was slowly warmed to −30 °C to yield complex **5**. The complex **5** was spectrally characterized at −30 °C. $^1$H NMR ($CD_2Cl_2$, 500 MHz, −30 °C): $\delta$ 0.77 (s, C(CH$_3$)$_3$), 2.12 (s, tolyl $CH_3$), 2.22 (s, tolyl $CH_3$), 2.68 (br s, NH$_X$), 4.05 (ABX, $^2J_{AB}$ = 14.7 Hz, $^3J_{AX}$ = 11.0 Hz, NC*H*$_A$H), 4.20 (ABX, $^2J_{AB}$ = 14.7 Hz, $^3J_{BX}$ = 2.0 Hz, NCH*H*$_B$), 6.8−7.8 (m, 23 H, aromatics). $^{13}$C{$^1$H} NMR ($CD_2Cl_2$, 125 MHz, −30 °C): $\delta$ 21.1, 21.2 (tolyl $CH_3$); 31.4 (NC(*C*H$_3$)$_3$), 47.6 (N*C*(CH$_3$)$_3$), 63.2 (N*C*H$_2$Ph), 83.5, 84.1 (C 3, 4 of Cp); 103.9, 104.2 (C 2, 5 of Cp); 126.6−135.0 (20 resonances, aromatics), 155.5 (C1 of Cp), 201.8, 201.3 (CO).

Raising the temperature above ~0 °C led to decomposition to ruthenium cyclopentadienone dimer **3** ($\delta$ 1.82, tolyl $CH_3$), *N*-benzyl-*tert*-butylamine ($\delta$ 1.01, C(CH$_3$)$_3$), and other decomposition products.

**Imine Hydrogenation Experiments.** Imine hydrogenation experiments will be illustrated with a specific example. A standard solution of **3** (11.4 mg, 0.01 mmol, 0.022 M) in THF (0.45 mL) in a resealable NMR tube was degassed by three successive freeze−pump−thaw cycles and placed under 1 atm $D_2$ (~0.1 mmol) at −78 °C. The tube was sealed at −78 °C and heated at 90 °C in a constant-temperature bath for 8 h. The THF solvent was evaporated under vacuum to give **2-RuDOD**, which was then dissolved in toluene-$d_8$ (0.5 mL). A 50 $\mu$L aliquot (0.02 mmol) of a standard solution of *N*-benzylideneaniline (36

(16) If none of the aryl resonances were accidentally equivalent, then 28 peaks would be expected; 24 were seen.

mg, 0.2 mmol, in 0.5 mL toluene-$d_8$, 0.400 M) was added via a gastight syringe to the solution of **2-RuDOD** cooled to −78 °C. This sample was inserted into an NMR spectrometer pre-cooled to −60 °C and spectra were acquired.

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**Supporting Information Available:** General experimental information, preparation of (Mes)N═C(H)(Ph), (Mes)(H)N($CH_2$-Ph), (*p*-Ph-$C_6H_4$)N═C(H)(Tol), and HN($CH_2$Tol)($C_6H_4$-*p*-Ph), preparations of **4a**, **4c**, and **4d**, preparation of solutions of **2**, X-ray crystal structure of **4a**, and density functional theory (DFT) studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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